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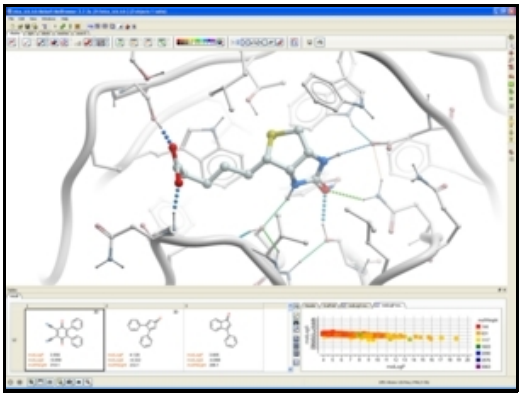
ICM−Browser ActiveICM Guide v.3.7−2a

#else

ICM−Pro User Guide v.3.7−2a

#endif

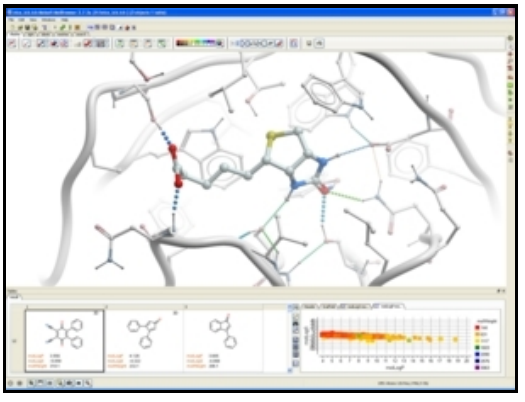
by Ruben Abagyan, Andrew Orry, Eugene Raush, and Maxim Totrov



Dec 9 2010
Feedback.

1 Introduction

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



Welcome to the ICM−Browser and ActiveICM manual. ICM−Browser provides a biologist or a chemist with direct access to the treasures of structural biology and protein families. It reads a variety of file formats directly from the database web−sites including: PDB, chemical, electron density maps, sequence and alignment files. ICM−Browser provides a rich professional molecular graphics environment with powerful representations of proteins, DNA and RNA, and multiple sequence alignments.

With the free ActiveICM plugin you can save fully interactive 3D files to display on the web or in Windows PowerPoint. You can also add and optimize hyrogens to PDB files, display hydrogen bonds, and display transparent ligand binding pocket property surfaces as well as other molecule sufaces.

Features

Please visit our product web pages for a full description of all the features in `ICM−Browser` and `ActiveICM`.

Download

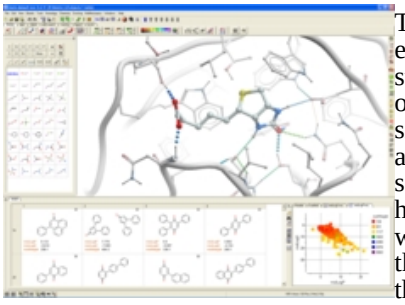
Please follow the links below to download the software.

Getting Started: Download and Install ICM−Browser and ActiveICM.	
Download ICM−Browser Distribution.	`Download`
Install ICM−Browser Instructions.	`Windows` `Linux` `Mac`
Download ActiveICM Distribution.	`Download`
Install ActiveICM.	`Windows` `Linux` `Mac`

#else

2 Introduction

Background



The **ICM Suite of Software** provides an easy to use general environment for a biologist or chemist who is curious about protein structure. In just a few seconds you can browse hundreds of structures of interest, analyze and visualize sequences, alignments and binding sites. Also you can perform molecular modeling, fully−flexible ligand and receptor docking, virtual ligand screening, chemical similarity searching, chemical clustering and much more... This book describes how to use the program via the **Graphical User Interface** (GUI) without the knowledge of the commands and functions running through your terminal window. After reading this book you may read the full **ICM Language Reference Manual** (www.molsoft.com/man) for the dying breed of command line users and occasional programmers. This is a separate document which is provided with a full ICM distribution or can be obtained from Molsoft in a printed form.

ICM is constantly updated with new features and so it is always a good idea to keep an eye on the `release notes`. Most of the things you will read in this manual are sort of natural or can be figured out by common sense and trial−and−error. However, if you like to read a "structured" description of the material, go ahead and read this.Since this book is intended for basically anyone who is even remotely interested in molecules, some basic knowledge of biology and chemistry is implied. Do not try to find definitions of "atom" or "sequence" here, but most terms beyond that will be explained. A keyword search of this manual is available on the online version which is located at (`www.molsoft.com/gui`). For detailed information regarding ICM programming please consult the separate ICM language reference guide (`www.molsoft.com/man`).If you want to have a more hands−on introduction to ICM you are always more than welcome to join us at one of our ICM workshops which are held periodically throughout the year (`click here for training information`).

ICM Specifications and Recomendations

Minimum specification for Windows, Mac, SGI and Linux:

55 Mb of disk space and 256Mb or more of memory. 512Mb of memory is good enough. Our databases such as XPDB require another 1Gb of disk space.

The Graphic card should have Hardware OpenGL acceleration and 64Mb or more memory. (128Mb or more is recommended)

We recommend NVIDIA (http://www.nvidia.com) brand.

- *GeForce* models are good if you do not plan to use hardware stereo.
- *Quadro* models can be used with hardware stereo

If you need Stereo Glasses we can recommend CrystalEyes:
`http://reald−corporate.com/scientific/crystaleyes.asp`

Before you can begin you need to download and install ICM−Browser, ICM−Browser−Pro, or ICM−Pro. See below for instructions on how to do this.

Requesting an ICM license and Installation

To obtain an **ICM license** (either trial of full) please follow these steps:

You can choose either a nodelocked or floating license. A nodelocked license will be for a single machine whereas a floating license will be placed on a server and can be accessed from any machine connected to that server.

1. Go to our `support page`.
2. Enter your login information or go here to `register` with us.
3. Click on downloads
4. Select which platform
5. Select ICM (Full Package) − follow the download instructions and remember to generate the hostid (see below).
6. Click on the hostid link − the first instruction in the installation guide (windows) or follow the instructions on the website (Linux/SGI). If you would like a floating license follow the instructions for floating license and send the IP address or name of the server in addition to the FlexLM id.
7. Send key to andy@molsoft.com or info@molsoft.com. **IMPORTANT** Please let us know 1) Your full name. 2) Institution 3) If you want a trial or want to purchase 4) If you want a trial please let us know the full contact details (name, address and phone number) of the person responsible for signing software license agreements at your institution or company.
8. A license will be sent to you by E mail usually as an attachment. Follow the instructions on www.molsoft.com/support on where to save the license.

Install ICM

Full installation instructions are provided at our support site www.molsoft.com/support

How to Start ICM

Starting ICM in Windows

There are several ways to start ICM under Windows, including the following:

1. Click the **Start** button on the taskbar, then select **Programs/Molsoft/ICM**
2. Double−click the file with one of the ICM extensions, including pdb files (−−*.pdb) icm projects and binaries (`*.icb`), and other ICM file types.
3. Create a shortcut to the ICM binary and click the
4. Start a command prompt window and type the path the ICM binary, usually it is `C:\Program Files\Molsoft LLC\ICM\icm.exe −g` . In this case you can start ICM with different options.

Starting ICM in Unix or Mac

Mac users can start icm as described below in unix or click on the ICM icon.

Under a **UNIX** platform your executables will reside in the `$ICMHOME` directory.

`$ICMHOME` is an environmental variable of your UNIX shell and it needs to be set to the actual location of the icm files. The installation procedure does tell you to what value the ICMHOME variable needs to be set.

Examples:

```
/usr/icm/icm −X   # returns

/usr/icm/icm −g   # −g GUI interface will be displayed

/usr/icm/icm −h   # help

/usr/icm/icm −bio −g # starts ICM−bio program with gui

/usr/icm/icm −G  # GUI interface will be displayed with a separate window for the ICM command
```

Once you are in ICM you can spawn another window by choosing **File/New** ICM Window .

In this case if you close the main ICM window, all the children will be closed too.

Activating the Graphical User Interface

If you are running ICM in Windows then the graphical user interface will be displayed automatically.

However in Unix the GUI version of ICM can be activated by typing icm −g or icm −G and hitting RETURN. Or, to start the graphical user interface from the ICM command line, simply type gui.

#endif

3 How To Guides and Videos

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

ICM−Browser How To Guide

ICM−Browser−Pro How To Guide #endif

ActiveICM How To Guide − Create 3D Molecular Documents for the Web and PowerPoint

ICM−Chemist How To Guide

ICM−Chemist−Pro How To Guide

#endif

3.1 ICM−Browser How To Guide

For instructions on how to use ICM−Browser to make fully−interactive 3D slides and publish them in PowerPoint and the web please see the ActiveICM User Guide. ActiveICM is a free plugin for Windows PowerPoint and web browsers. Other related tutorials include:

- Graphical Display: Molecule Representation, Coloring, Labeling and Annotation
- Graphical Selections Tutorial
- Generating Fully Interactive Slides for PowerPoint and the Web Tutorial

3.1.1 Download and Install ICM−Browser

Getting Started: Download and Install ICM−Browser and ActiveICM.		
Download ICM−Browser Distribution.	Download	video
Install ICM−Browser Instructions.	Windows Linux Mac	
Download ActiveICM Distribution.	Download	video
Install ActiveICM.	Windows Linux Mac	

3.1.2 How to use the Graphical Display

'; winRef.document.write(str); }

How to use the Graphical Display		
How to search the PDB.	HTML GUI Manual	video

How to Move a Structure in the Graphical Display.	HTML GUI Manual	video
How to use the Graphics window controls.	HTML GUI Manual	
How to use the ICM Workspace Panel	HTML GUI Manual	video
How to Display a Molecule.	HTML GUI Manual	video
How to Change Protein Representation.	HTML GUI Manual	video
How to Change Ribbon Representation.	HTML GUI Manual	video
How to color wire or xstick carbon atoms.	HTML GUI Manual	video
How to Display the Residues Surrounding the Ligand Binding Pocket.	HTML GUI Manual	video
How to remove chain breaks (dotted lines).	HTML GUI Manual	video
How to Color.	HTML GUI Manual	video
How to Change the Color of Molecule Representations.	HTML GUI Manual	video
How to Change the Background Color.	HTML GUI Manual	video
How to Display a Binding Pocket Surface	HTML GUI Manual	video
How to (Un)Display Hydrogens.	HTML GUI Manual	video
How to Save an ICM Object.	HTML GUI Manual	video
How to Save an ICM Project File.	HTML GUI Manual	video
How to Drag and Drop.	HTML GUI Manual	
How to: Right Click Options.	HTML GUI Manual	
How to Move Windows.	HTML GUI Manual	video
How to Arrange Windows	HTML GUI Manual	video

3.1.3 How to make Graphical Selections

How to Make Selections.	HTML GUI Manual	
How to Select an Object	HTML GUI Manual	video
How to Select a Molecule	HTML GUI Manual	video
How to Select Residues	HTML GUI Manual	video
How to Select Atoms	HTML GUI Manual	video
How to Make a Spherical Selection.	HTML GUI Manual	video
How to Invert a Selection.	HTML GUI Manual	video
How to Remove a Selection.	HTML GUI Manual	video
How to Change the Selection Level and Mode.	HTML GUI Manual	video
How to Check What is Selected.	HTML GUI Manual	

3.1.4 How to Convert Proteins, Display Hydrogens and Ligand Binding Pocket.

Convert Protein, Display Hydrogens and Ligand Binding Pocket.		
How to Convert a PDB Structure into an ICM Object.	HTML GUI Manual	video
How to Display Ligand Binding Pocket.	HTML GUI Manual	video
How to Display Hydrogen Bonds.	HTML GUI Manual	video

3.1.5 How to change Graphics Effects

How to change Graphics Effects		
How to display the FOG effect.	HTML GUI Manual	video
How to display side−by−side stereo.	HTML GUI Manual	
How to toggle full screen mode.	HTML GUI Manual	video
How to adjust perspective.	HTML GUI Manual	
How to change the lighting.	HTML GUI Manual	video
How to display sketch accents.	HTML GUI Manual	video
How to display elegant ribbon and ligand sketch.	HTML GUI Manual	video

3.1.6 How to add Labels and Annotations

How to add Labels and Annotations		
How to Label Residues.	HTML GUI Manual	video
How to Label Atoms.	HTML GUI Manual	video
How to Label Variables.	HTML GUI Manual	video
How to Display and Undisplay Sites.	HTML GUI Manual	
How to Make and Display Annotations.	HTML GUI Manual	
How to Make and Display 2D and 3D Labels.	HTML GUI Manual	video

3.1.7 How to Make High Quality Publication Images

How to Make High Quality Publication Images		
How to Toggle High Quality Display	HTML GUI Manual	video
How to Toggle Antialiasing.	HTML GUI Manual	video
How to Copy Image to ClipBoard	HTML GUI Manual	video
How to Write an Image.	HTML GUI Manual	video
How to Use the Advanced Write Image Options.	HTML GUI Manual	video
How to Add an Image to the ICM Photo Album.	HTML GUI Manual	video

3.1.8 How to Superimpose Protein Structures.

How to Superimpose Protein Structures.		
How to Superimpose Two or More Protein Structures.	HTML GUI Manual	video

3.1.9 How to Measure Distances and Angles.

How to Measure Distances and Angles.		
How to Measure Distances Between Two Atoms.	HTML GUI Manual	video
How to Measure Distances From One Atom to Many.	HTML GUI Manual	video
How to Show Corresponding Distances in Two Objects.	HTML GUI Manual	video
How to Display the Ruler Bar.	HTML GUI Manual	video

3.2 ICM−Browser−Pro How To Guide

NOTE: ICM−Browser−Pro contains all the features in ICM−Browser. Click here for the ICM−Browser How To Guide.

3.2.1 Download and Install ICM−Browser−Pro

Getting Started: Download and Install ICM−Browser−Pro	
Download ICM−Browser−Pro Distribution.	Download
Install ICM−Browser−Pro.	Windows Linux Mac

3.2.2 Graphics

Graphics and Movie Making	
How to generate the shadow effect.	HTML GUI Manual
How to make a screenshot movie	HTML GUI Manual
How to make a view−defined movie	HTML GUI Manual
How to move a molecule independently of the other display objects (Connect).	HTML GUI Manual

3.2.3 Protein Structure Analysis

Protein Structure Analysis	
How to calculate contact areas between molecules.	HTML GUI Manual
How to identify closed cavities.	HTML GUI Manual
How to calculate surface area.	HTML GUI Manual
How to generate interactive Ramachandran plots.	HTML GUI Manual

3.2.4 Surfaces

Surfaces	
How to generate electrostatic and binding property surfaces.	HTML GUI Manual
How to connect and rotate/translate surface (mesh).	HTML GUI Manual
How to crop a mesh/surface.	HTML GUI Manual
How to save a mesh/surface.	HTML GUI Manual

3.2.5 Superimpose Proteins

Superimpose Proteins	
How to superimpose proteins based on 3D by visible atoms, C−alpha, backbone or heavy atoms.	HTML GUI Manual
How to superimpose multiple proteins based on aligned residues..	HTML GUI Manual
How to superimpose by specific interatomic pairs.	HTML GUI Manual

3.2.6 Crystallographic Tools

Crystallographic Tools	
How to contour electron density.	HTML GUI Manual
How to display crystallographic cell.	HTML GUI Manual
How to display crystallographic symmetry.	HTML GUI Manual
How to convert x−ray density to a grid.	HTML GUI Manual

3.2.7 Sequence Analysis

Sequence Analysis	
How to annotate an alignment − box and shade.	HTML GUI Manual
How to annotate an alignment with text.	HTML GUI Manual
How to display secondary structure in an alignment.	HTML GUI Manual
How to extract sequences from pdb files.	HTML GUI Manual
How to assign secondary structure.	HTML GUI Manual
How to link sequence, alignments, and structures.	HTML GUI Manual
How to save as image, print, and delete sequences and alignments.	HTML GUI Manual

3.2.8 Plotting Tools

Plotting Tools	
Make fully interactive colorful X−Y plots and histograms with up to 4 dimensions.	HTML GUI Manual
Save plot and histogram as image.	HTML GUI Manual

#endif

3.3 ActiveICM How To Guide − Create 3D Molecular Documents for the Web and PowerPoint

This guide is focused on how to make fully interactive 3D documents for Windows PowerPoint and the Web. For more information on the other features in ICM−Browser please see the `ICM−Browser User Guide.`

Creating 3D Documents Is Straightforward

Creating fully interactive 3D documents for PowerPoint, the web, and standalone browser is straightforward.

1. `Download` ICM−Browser and the ActiveICM plugin. They are completely free! [`video`]
2. Open the ICM−Browser and make a series of animated `fully−interactive slides` showing different colored and rendered views of your molecules. [`video`]
3. Add hyperlinked `HTML text` to annotate and link to your slides. [`video`]
4. Save your file in ICM−Browser and then insert into `PowerPoint` or the `web` using the ActiveICM plugin. You can also share your documents in the standalone ICM−Browser. [`video − powerpoint`][`video −web browser`]

'; winRef.document.write(str); }

3.3.1 Getting Started

Getting Started: Download and Install ICM−Browser and ActiveICM.		
Download ICM−Browser Distribution.	`Download`	`video`
Install ICM−Browser Instructions.	`Windows Linux Mac`	
Download ActiveICM Distribution.	`Download`	`video`
Install ActiveICM.	`Windows Linux Mac`	

3.3.2 How to Create a Series of Fully−Interactive 3D Slides.

Creating Slides How to Create a Series of Fully−Interactive 3D Slides.	`video`
How to Make Fully Interactive 3D Slides	`HTML GUI Manual`
How to Animate Slides	`HTML GUI Manual`
How to View and Navigate Slides in the ICM−Browser.	`HTML GUI Manual`
How to Edit Slides.	`HTML GUI Manual`
How to Add Smooth Blending and Transition Effects Between Slides.	`HTML GUI Manual`

3.3.3 How to Create Molecular Documents

How to Create Molecular Documents: Linking Slides to HTML Text.	`video`

How to Create an HTML Document.	HTML GUI Manual
How to Edit an HTML Document.	HTML GUI Manual
How to Make a Hyperlink Between HTML Text and a Slide.	HTML GUI Manual

3.3.4 How to Display Molecular Documents in PowerPoint

How to Display Molecular Documents in PowerPoint	video
How to Embed in Microsoft PowerPoint 2003	HTML GUI Manual
How to Embed in Microsoft PowerPoint 2007	HTML GUI Manual
How to Use ActiveICM in PowerPoint	HTML GUI Manual
How to Change ActiveICM Component Properties in PowerPoint	HTML GUI Manual
Advanced use of ActiveICM: Macros to direct visualisation changes.	HTML GUI Manual

3.3.5 How to Display Molecular Documents on the Web

How to Display Molecular Documents in Web Browsers	video
How to Display Molecular Documents in Web Browsers	HTML GUI Manual

3.4 ICM−Chemist How To Guide

3.4.1 How to Import, Sketch, and Edit Chemicals

How to Import, Sketch, and Edit Chemicals		
How to access the ICM Molecular Editor.	HTML GUI Manual	video
How to sketch chemicals in the ICM Molecular Editor.	HTML GUI Manual	video
How to save a 2D sketch into a chemical spreadsheet.	HTML GUI Manual	video
How to save a 2D sketch in mol format.	HTML GUI Manual	video
How to use SMILES strings to sketch a chemical.	HTML GUI Manual	video
How to load a mol, sdf or mol2 file.	HTML GUI Manual	video
How to extract a 2D sketch of a ligand in complex with a PDB structure.	HTML GUI Manual	video

3.4.2 How to Work with Chemical Spreadsheets

Working with Chemical Spreadsheets		
How to add columns into a chemical spreadsheet.	HTML GUI Manual	video
How to sort a column(s) in a chemical spreadsheet.	HTML GUI Manual	video
How to change the view of a chemical spreadsheet − form, table and grid.	HTML GUI Manual	video
How to copy, cut and paste columns and rows in a chemical spreadsheet.	HTML GUI Manual	video
How to show and hide columns and rows in a chemical spreadsheet.	HTML GUI Manual	video
How to save a chemical spreadsheet in sdf format.	HTML GUI Manual	video
How to export your chemical spreadsheet into Excel.	HTML GUI Manual	video
How to print a chemical spreadsheet.	HTML GUI Manual	video
How to filter columns in a chemical spreadsheet.	HTML GUI Manual	video
How to use find and replace in a chemical spreadsheet.	HTML GUI Manual	video
How to mark and label rows in a chemical spreadsheet.	HTML GUI Manual	video
How to insert hyperlinks to the PDB, PubMed, and Uniprot.	HTML GUI Manual	video
How to copy and paste 2D chemicals.	HTML GUI Manual	video
How to edit data inside a chemical spreadsheet.	HTML GUI Manual	video
How to remove salts, explicit hydrogens and standardize chemical groups.	HTML GUI Manual	video
How to calculate chemical properties in a chemical spreadsheet.	HTML GUI Manual	video
How to identify duplicate chemicals in a chemical spreadsheet.	HTML GUI Manual	video
How to compare two chemical spreadsheets.	HTML GUI Manual	video

How to merge two chemical spreadsheets.	HTML GUI Manual	video

3.4.3 How to Undertake a Chemical Search

How to Perform Chemical Searching		
How to setup a chemical search.	HTML GUI Manual	video
How to draw a chemical search query.	HTML GUI Manual	video
How to add conditions to your chemical search.	HTML GUI Manual	video
How to search chemical spreadsheets, local databases and MolCart.	HTML GUI Manual	video
How to send a chemical search query.	HTML GUI Manual	video

3.4.4 How to Work with Pharmacophores

How to Work with Pharmacophores		
How to draw 2D pharmacophore.	HTML GUI Manual	video
How to search a 2D pharmacophore.	HTML GUI Manual	video
How to draw 3D pharmacophore.	HTML GUI Manual	video
How to extract a 3D pharmacophore from a ligand.	HTML GUI Manual	video
How to edit a 3D pharmacophore.	HTML GUI Manual	video
How to send a 3D pharmacophore search query.	HTML GUI Manual	video
How to color a 2D chemical sketch by pharmacophore feature.	HTML GUI Manual	video

3.4.5 How to Perform Chemical Clustering

How to Perform Chemical Clustering		
How to perform chemical clustering.	HTML GUI Manual	video
How to select representative centers from a tree.	HTML GUI Manual	video
How to reorder branches and change the distance of trees.	HTML GUI Manual	video
How to edit the tree − labels, spacing and coloring.	HTML GUI Manual	video

3.4.6 How to Generate Stereoisomers and Tautomers

How to Generate Stereoisomers and Tautomers		
How to generate stereoisomers.	HTML GUI Manual	video
How to generate tautomers.	HTML GUI Manual	video

3.4.7 How to Generate Combinatorial Libraries

How to Generate Combinatorial Libraries		
How to enumerate a Markush library.	HTML GUI Manual	video
How to decompose a library based on a Markush structure.	HTML GUI Manual	video
How to create a Markush structure.	HTML GUI Manual	video
How to enumerate a chemical library by reaction.	HTML GUI Manual	video

3.4.8 How to Generate Plots and Histograms

How to Generate Plots and Histograms		
How to make a histogram.	HTML GUI Manual	video
How to make an X−Y scatter plot.	HTML GUI Manual	video

#endif

3.5 ICM−Chemist−Pro How To Guide

'; winRef.document.write(str); }

3.5.1 How to use the ICM 3D Ligand Editor

'; winRef.document.write(str); }

ICM Chemist−Pro Contains All the Tools in ICM−Chemist	ICM−Chemist Tutorials	
ICM 3D Ligand Editor: Setup		
How to setup the ligand in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to setup the receptor in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to change the 3D Ligand Editor preferences.	HTML GUI Manual	video
How to configure the default display in the ICM 3D Ligand Editor.	HTML GUI Manual	video
ICM 3D Ligand Editor: Display		

How to display and undisplay the ligand surface representation in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to display hydrogen bonds in the ICM 3D ligand editor.	HTML GUI Manual	video
How to display energy atomic circles in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to display and undisplay hydrogen atoms in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to display unsatisfied hydrogen bonds in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to center on a ligand in the ICM 3D Ligand Editor.	HTML GUI Manual	video
ICM 3D Ligand Editor: Edit Ligand		
How to begin editing your ligand in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to undo and redo changes in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to add and sample new substiutents to your ligand in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to sample more than one substituent at a time in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to edit the ligand in 2D in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to evaluate the SCORE and ligand strain.	HTML GUI Manual	video
How to add an edited ligand to a chemical spreadsheet (table).	HTML GUI Manual	video
How to change the size of the ligand binding pocket − change purple box size.	HTML GUI Manual	video
ICM 3D Ligand Editor: Docking and Minimization		
How to perform ligand minimization in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to re−dock a ligand in the ICM 3D Ligand Editor.	HTML GUI Manual	video
How to restrain (tether) atoms during docking.	HTML GUI Manual	video
How to screen databases of chemical substituents.	HTML GUI Manual	video
How to sample linkers between two chemical fragments.	HTML GUI Manual	video

3.5.2 How to Convert Chemicals to 3D

Convert Chemicals to 3D		
How to convert 2D sketches in the molecule editor into 3D.	`HTML GUI Manual`	`video`
How to convert 2D chemical sketches to 3D.	`HTML GUI Manual`	`video`
How to generate 3D ligand conformers.	`HTML GUI Manual`	`video`

3.5.3 How to Superimpose Chemicals

How to Superimpose Chemicals		
How to Perform Rigid and Flexible Chemical Substructure Superposition.	`HTML GUI Manual`	`video`
How to use Atomic Property Fields for Chemical Superposition	`HTML GUI Manual`	`video`

3.5.4 How to Perform QSAR

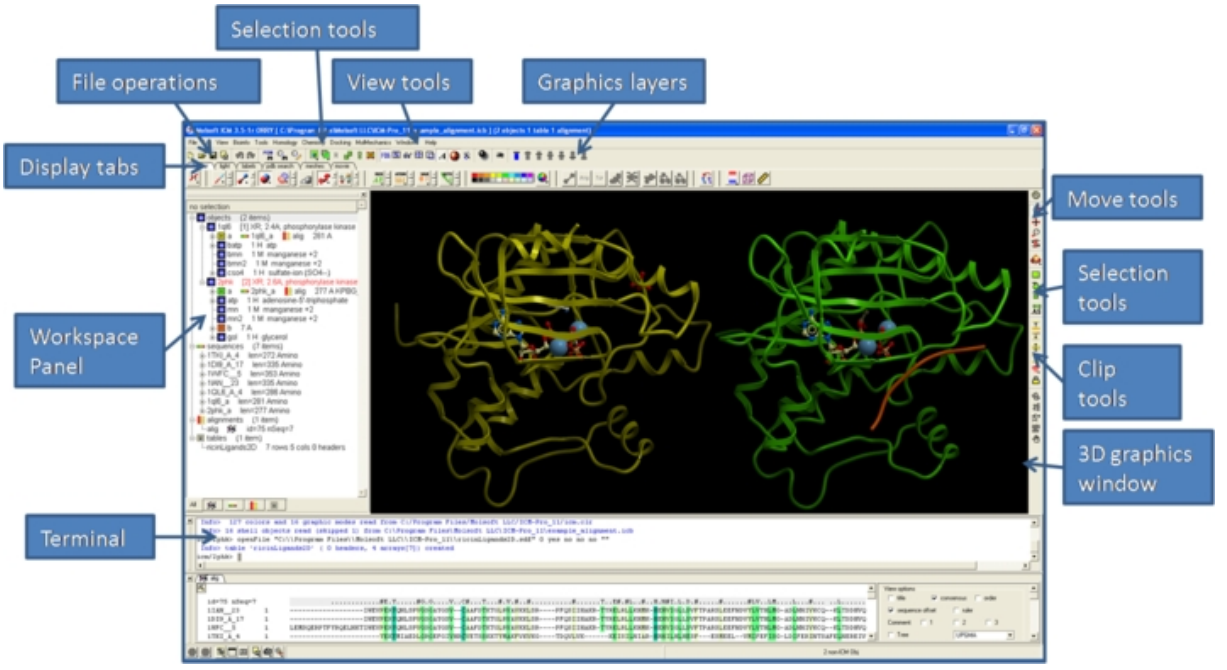
QSAR		
How to build a QSAR prediction model.	`HTML GUI Manual`	`video`
How to apply a QSAR prediction model.	`HTML GUI Manual`	`video`

#endif

4 Getting Started

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

The **Graphical User Interface** (GUI) has many components. When you first use the GUI the default window layout is displayed as shown below.



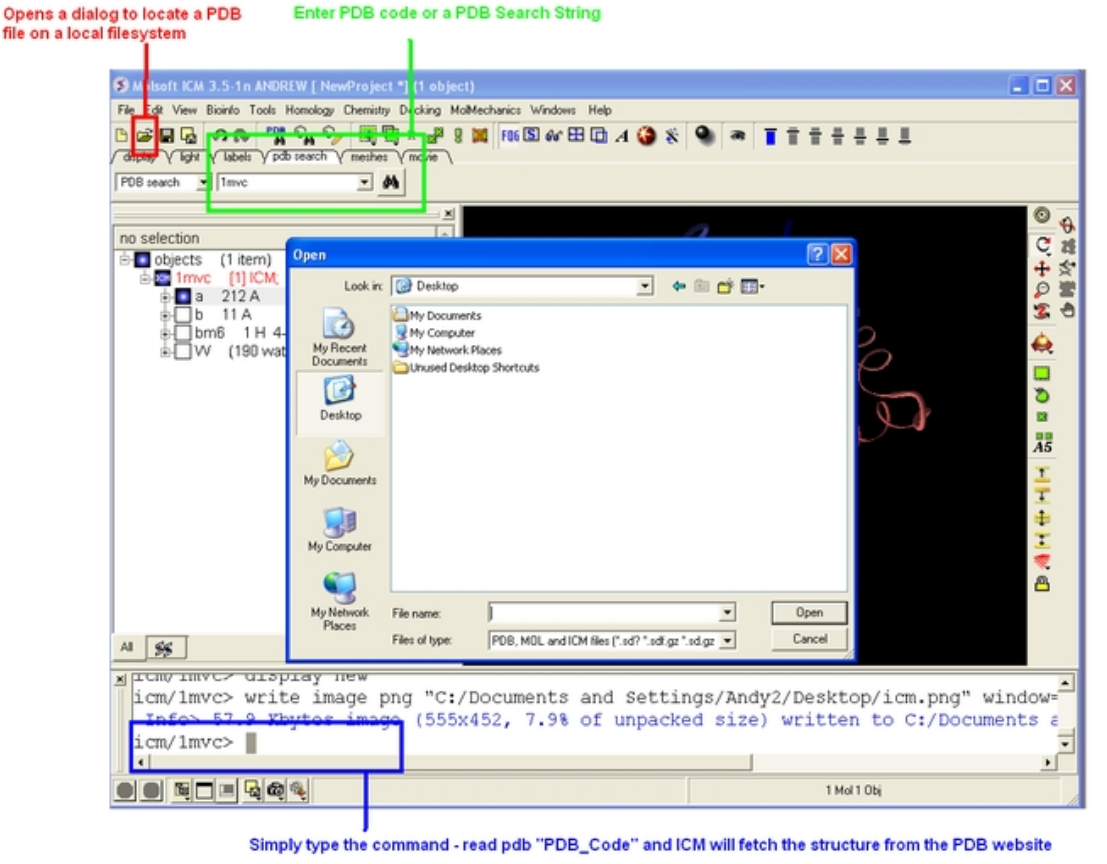
4.1 How to Use the Graphical Display

4.1.1 How to load a PDB Structure

There are three main ways to read in a PDB file.

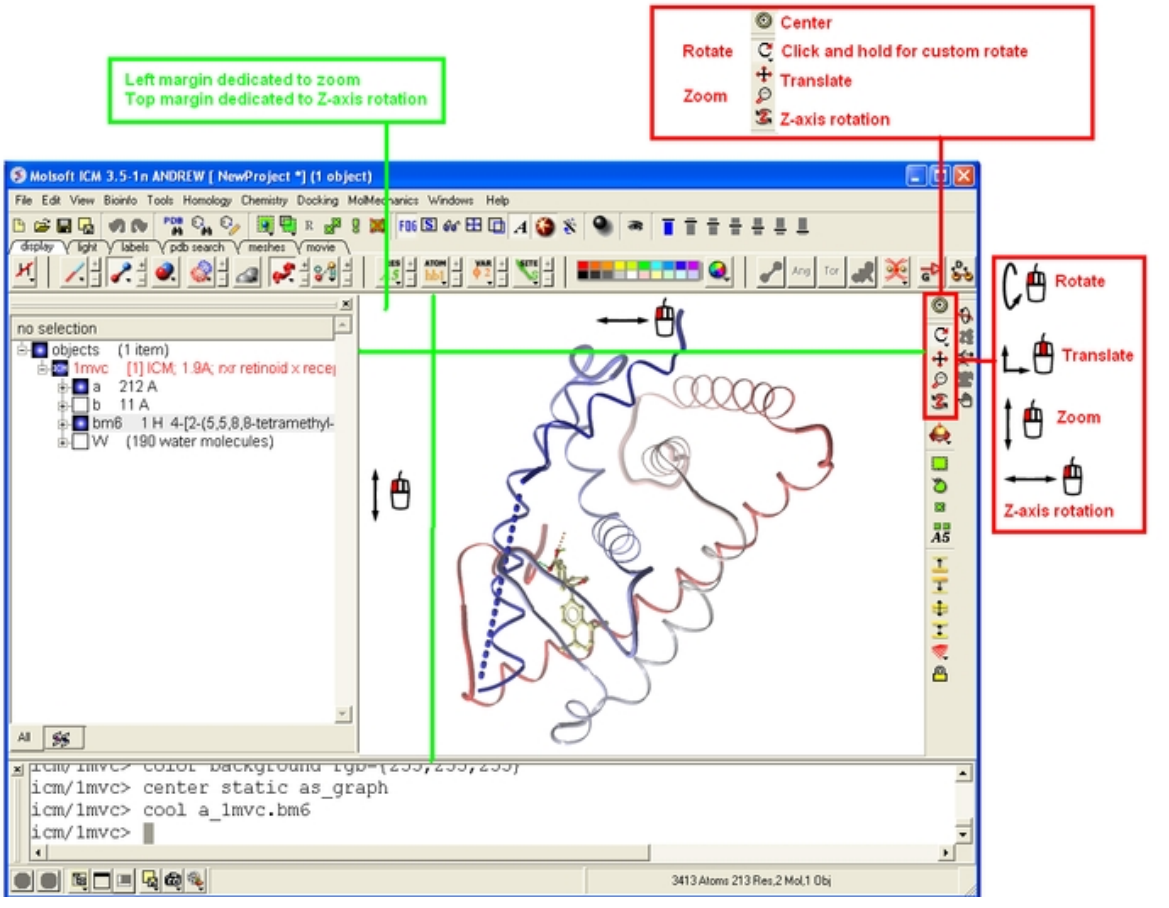
1. Using the command line.
2. Using File/Open button
3. Using the PDB Search tab

Other PDB search options are described in more detail in the `PDB Search` section of this manual.



4.1.2 How to Move a Structure in the Graphical Display

Available buttons and options for moving molecules around the graphical display window. This is described in more detail in the section entitled Move Buttons.



4.1.3 How to use the Graphics window controls

In the graphics window you can use various `tools` described elsewhere but it is helpful to know the following things:

- **Picking a tool**: the left mouse button will function according to the selected tool
- **Popup menus**: right click on an atom gives a pop−up menu
- **Selecting in the rotation mode**: the right mouse button will select atoms
- **Translating in the rotation mode**: the middle mouse button will translate the scene
- **Zooming and moving clipping planes in the rotation mode**: the left, top and right margins of the graphics window are reserved for other actions, zoom, z−rotation, and clipping plains, respectively. That means that even if you are picking atoms, by pressing control you can still rotate your molecule with the left−mouse−button.
- **Rotating in any non−rotation mode**: if you press **Control** in any mouse mode, e.g. zoom, pick etc., it will temporarily switch to **rotation**
- **Escaping from the connect and continuous movement modes**: pressing **Escape** helps to get out of certain modes, such as Full Screen, Continuous rotation or rocking, the Connect mode.
- **Global rotation in the Connected mode**: pressing **Shift** will temporarily switch to the global rotation/translation mode.

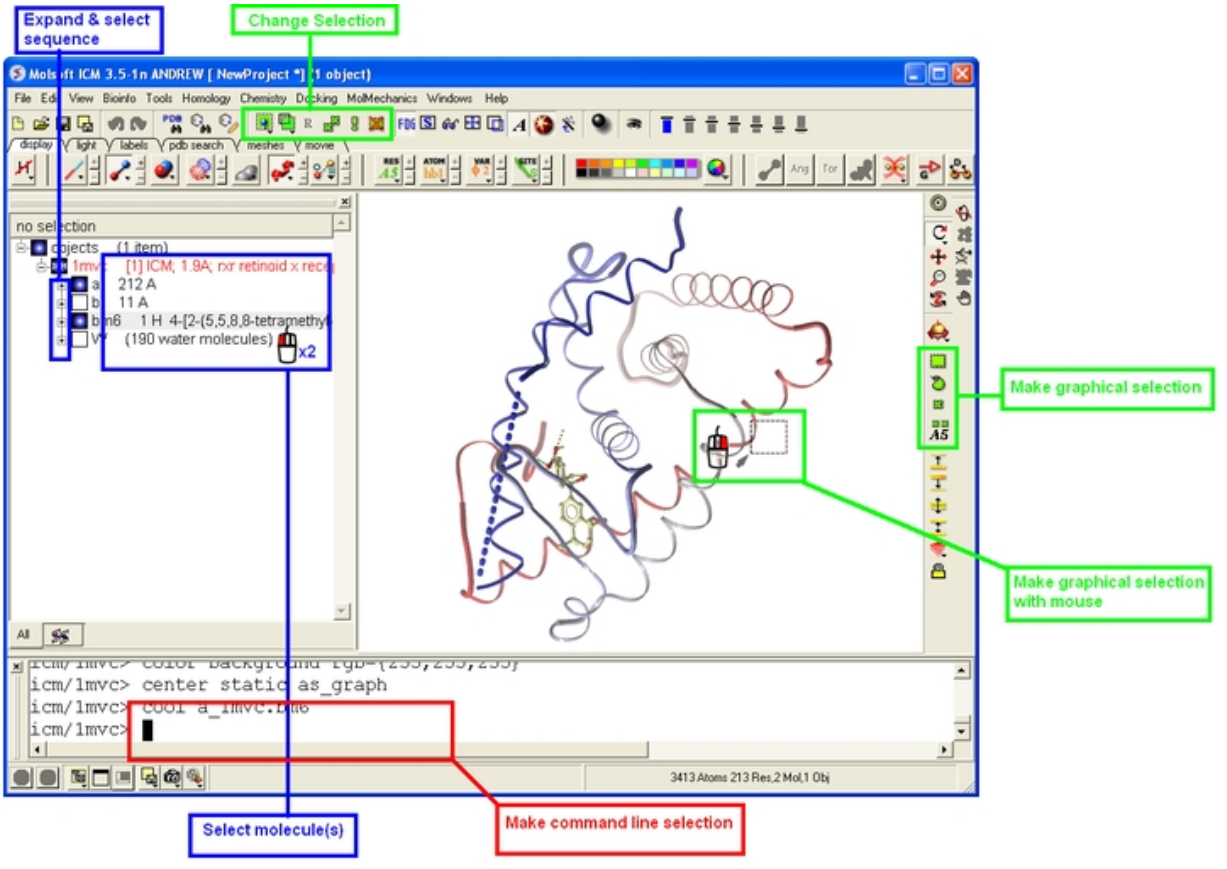
4.1.4 How to Make Selections

Making selections in ICM is an important skill to master (e.g. you may want to select a binding pocket for docking or a region of a molecule for coloring). The four levels of selection are:

1. Atoms
2. Residues
3. Molecules
4. Objects (multiple molecules comprising a PDB entry)

There are several ways of making selection in ICM. The simplest is to interact directly with the graphics window − **right−click, hold and drag** around the area of the screen you want to select. Alternatively, in the workspace window, expand the tree of molecules and chains until the relevant protein sequences is displayed. Then left click and drag to mark residues to form a selection.

See the chapter entitled `Making Selections` for more information.



4.1.5 How to Change the Selection Level and Mode

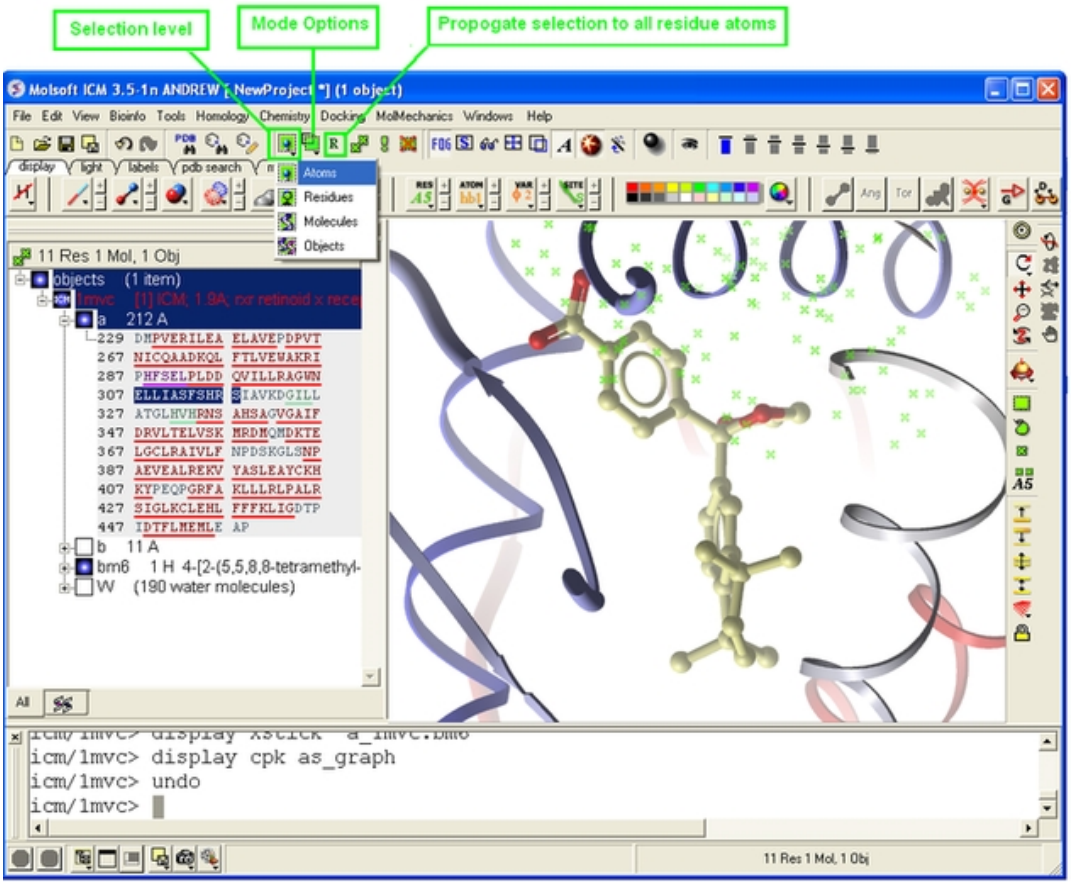
It is possible to change the level of selection before or during the building of a selection. The selection level drop−down button can be used to do this (see image below).

For example, a C−alpha of a residue is selected but one would like to select all atoms in the residue. You can change the level to **Residues.** This selection can then be changed into all atoms of the residue by then selecting the **Atoms** level again. Or you can use the **Propagate Selection to all Atoms** button (see image below).

It is also important to observe the selection mode that is being used. There are four modes:

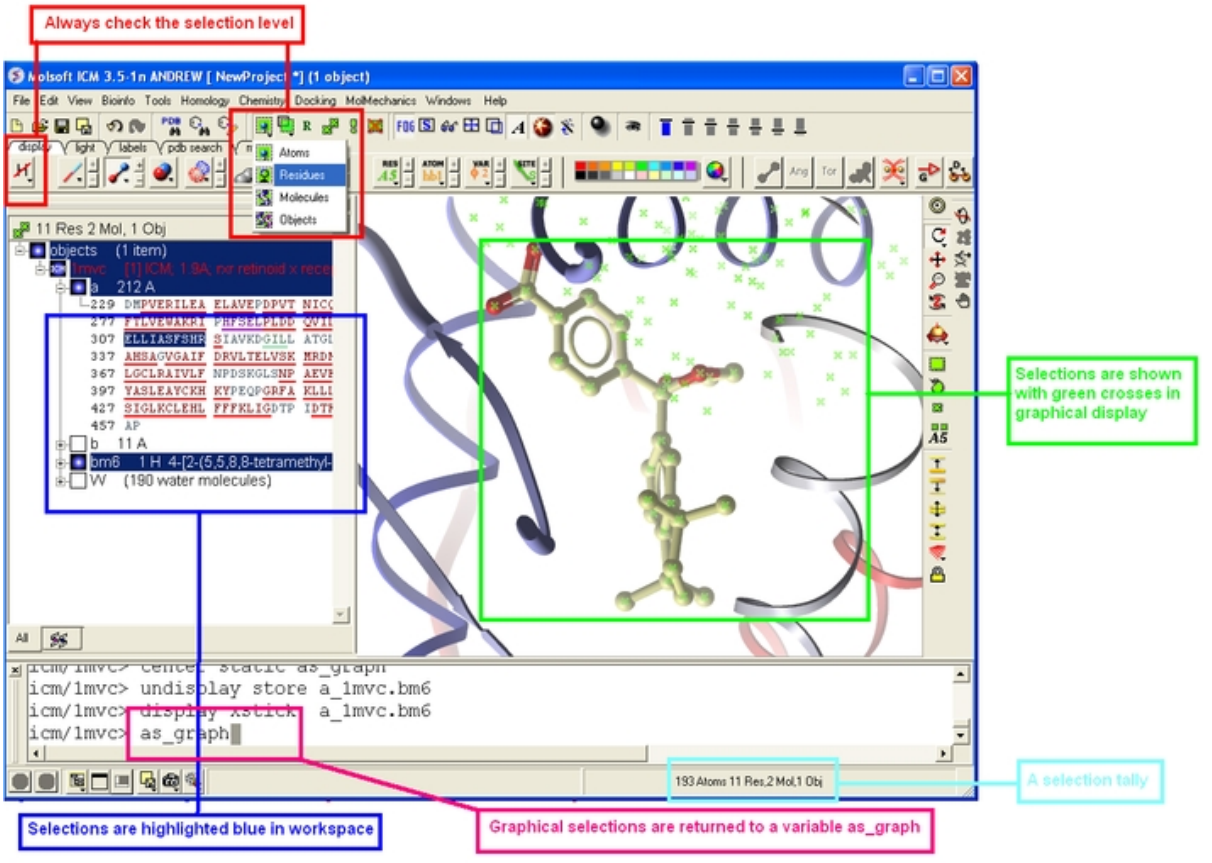
- New: new selection replaces everything selected before
- Add: new selection is added to previous selection(s), if any
- Remove: previously selection (part or whole of it), if included in the new selection will be unselected.
- Toggle: within the new selection, everything that has been selected is unselected and everything that hasnï¿½t been selected, will be selected

See the chapter entitled `Making Selections` for more information.



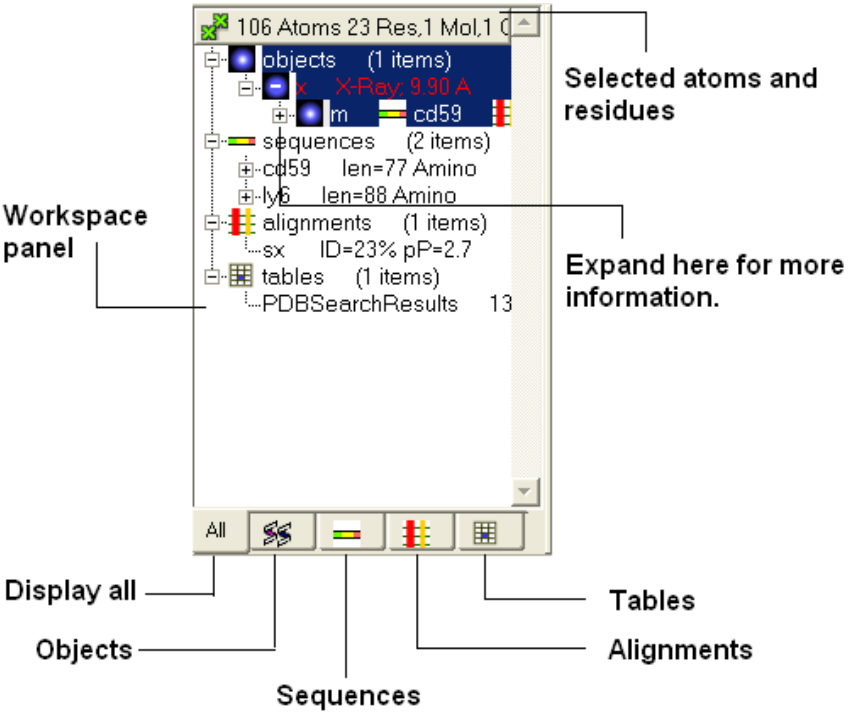
4.1.6 How to Check What is Selected

Once you have made your selection − how can you be sure you have made it and what exactly have you selected. See the chapter entitled `Making Selections` for more information.



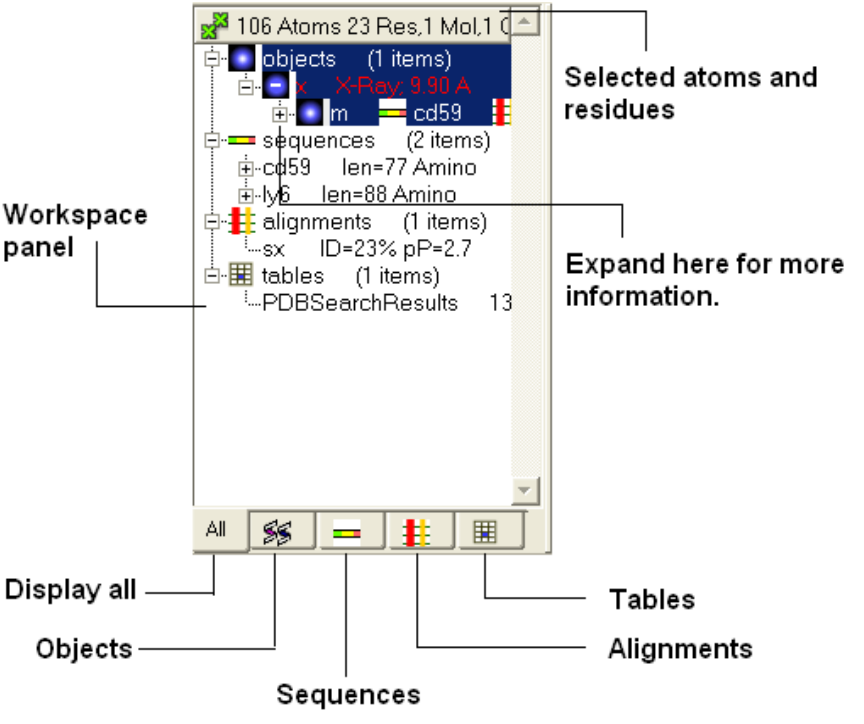
4.1.7 How to use the ICM Workspace Panel

The workspace panel (located on the left hand side panel of the gui) is an important place within the graphical user interface because it displays which sequences, structures, objects, tables and alignments are currently loaded into ICM. Also, from this panel you can make graphical selections and drag and drop objects and sequences to other locations within the GUI. More details about how to use the ICM Workspace Panel for displaying structures can be found here.



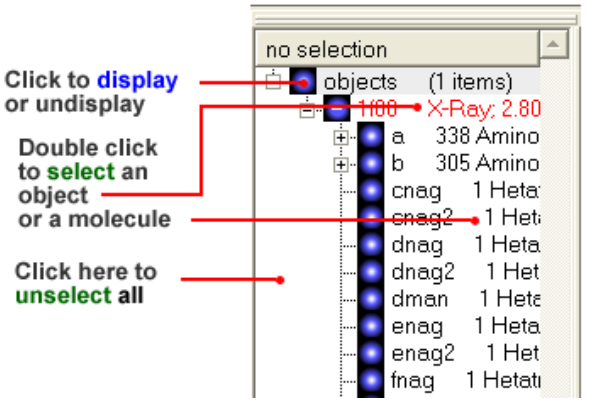
4.1.8 How to Display a Molecule

Once a structure has been loaded into ICM the individual components of that structure (i.e. amino acids, metal ions, binding sites etc) are listed in the ICM workspace.



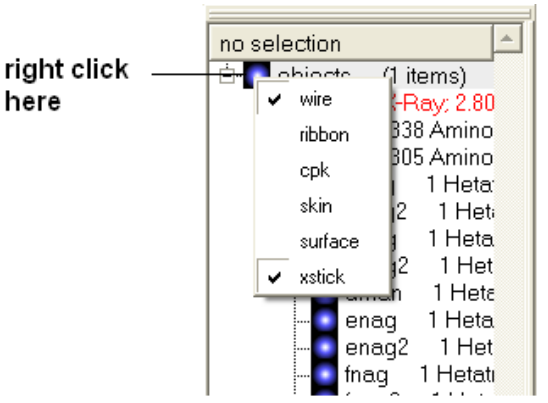
To display every component of the object except for binding sites and water atoms:

- Click on the white box next to the word object at the top of the ICM workspace. This box will be colored blue once the structure is displayed



To display the whole structure in wire, ribbon, cpk, skin, surface and xstick representations:

- Right click on the blue box next to the word object. A menu will be displayed.



- Select which representation you desire for your structure by clicking on the appropriate word. A check mark indicates the representation currently displayed. To un−display a particular representation click on the word again.

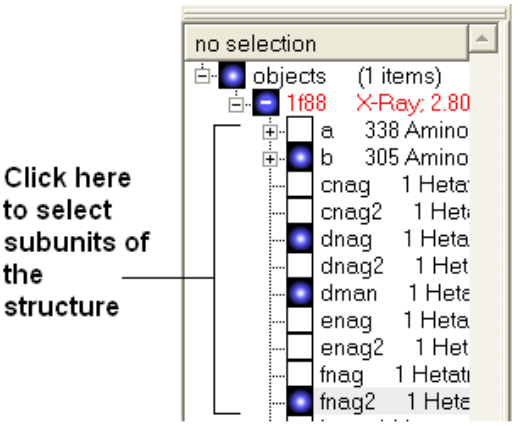
In order to clear your graphical display:

- Select **View/Undisplay All**

If you only wish to display part of the structure then click in the boxes further down the tree in the ICM workspace.

To display the selected regions of the structure in wire, ribbon, cpk, skin, surface and xstick representations:

- Right click on the appropriate box in the **ICM** workspace. A menu will be displayed.
- Select which representation you desire for your structure by clicking on the appropriate word. A check mark indicates the representation currently displayed. To un−display a particular representation click on the word again.

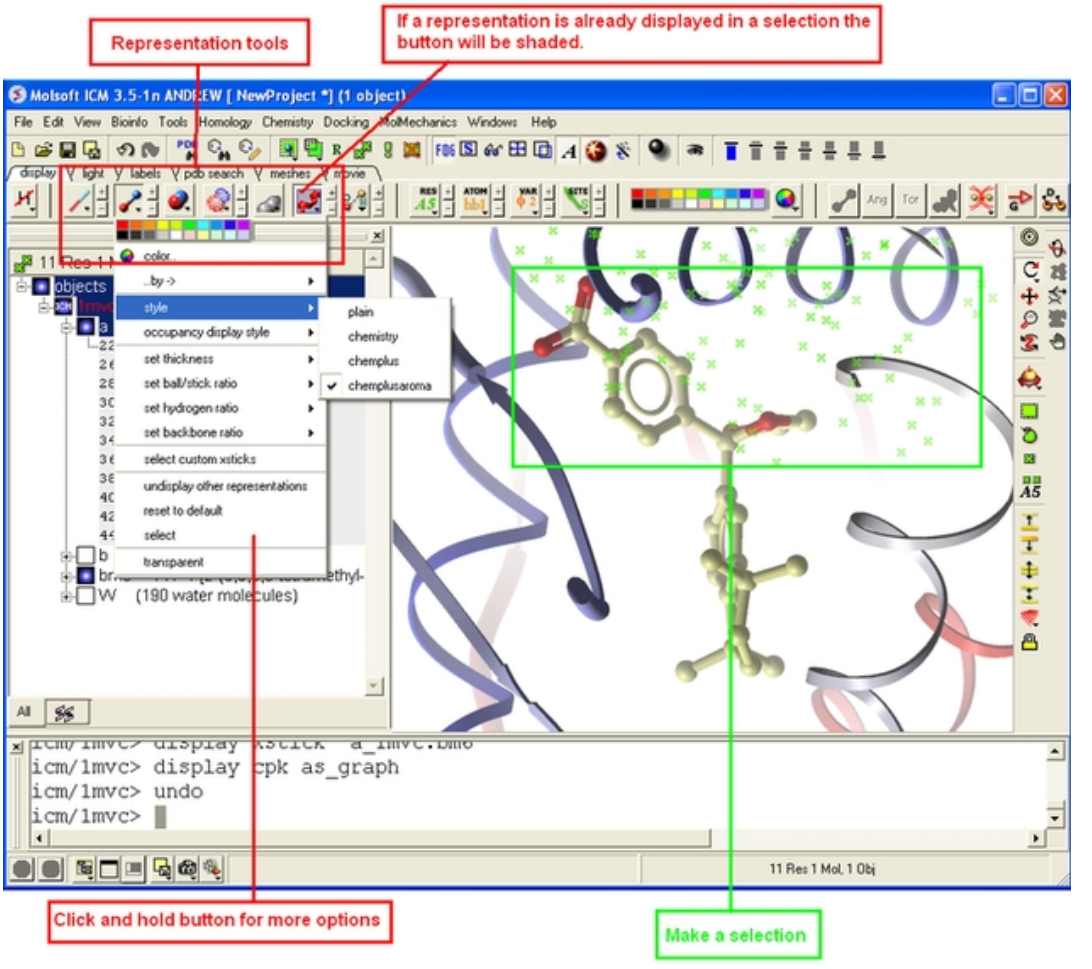


4.1.9 How to Change Protein Representation

To change the representation of the protein, make a make−selection{selection} and then use the tools in the `display tab.`

There are 6 main types of representation:

- **Wire:** Wires connecting covalently bound atoms of a molecule. This representation has no defined thickness as such will not make shadows. Useful for showing the chemical structure of a small molecule.
- **Xstick:** Covalent bonds are represented as cylinders whilst atoms are represented as small spheres.
- **CPK:** Atoms are represented as spheres with their respective van der Waals radius and coloured according to a standard defined by Corey, Pauling and Kultun.
- **Surface:** Solvent accessible surface. This is the center of water sphere as a water probe rolls over the molecule.
- **Skin:** A Connolly molecular surface over the selection. This is a smooth envelope touching the van der Waals surface of atoms as a water probe rolls over the molecule.
- **Ribbons:** Cartoon representation of protein and DNA secondary structure. Protein residues marked as alpha−helices ('H') are shown as a flat, helical ribbon, those marked as beta−sheets ('E') are shown as a flat ribbon with an arrow−head, and the rest are shown as a cylindrical "worm". If secondary elements are not defined everything will be shown as a cylindrical worm. ICM can automatically assign secondary structure: Tools/3D predict /Assign Helices and Strands



4.1.10 How to remove chain breaks (dotted lines)

Chain breaks in a protein structure are represented by dotted lines. To remove them use

```
GRAPHICS.chainBreakStyle =1
```

e.g.

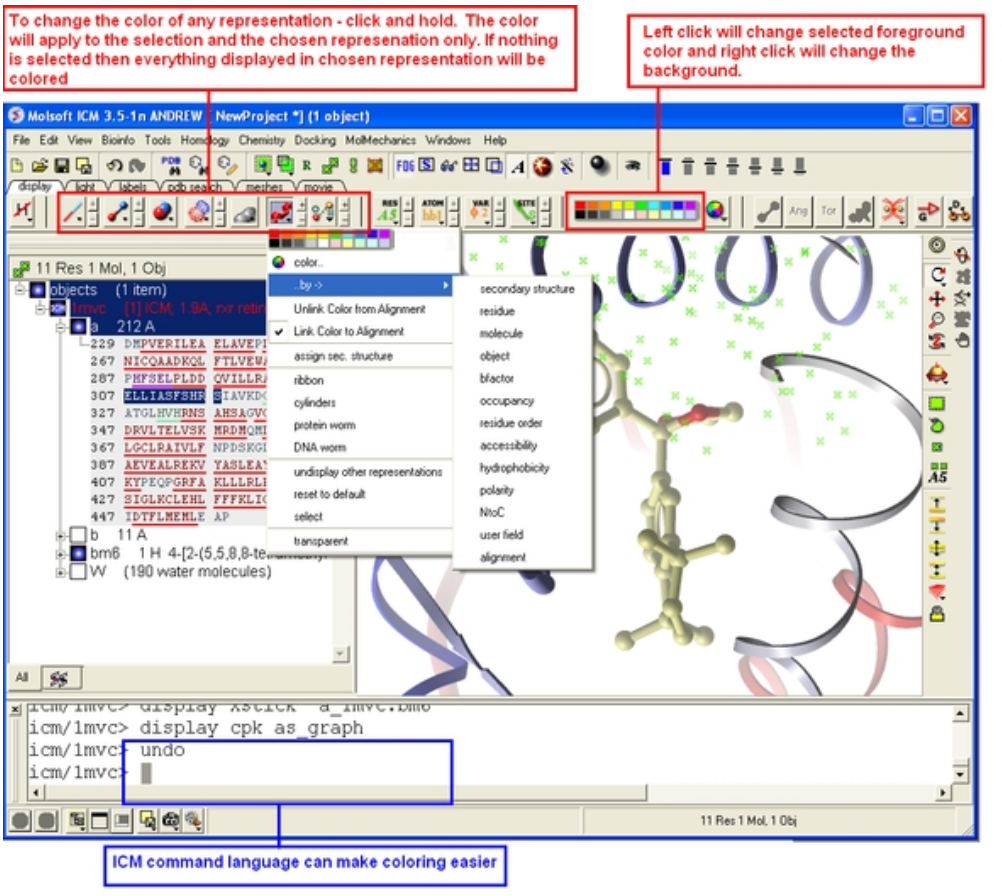
```
read pdb "1xbb"
cool a_
GRAPHICS.chainBreakStyle = 1  # this removes the dotted lines between chain breaks
```

In version 3.6−1a and above you can use the options in the display tab. Click and hold on the ribbon button and then select **Display Chain Breaks/ None**.

4.1.11 How to Color

To change the color of the representation you need to use the buttons in the `display tab.`

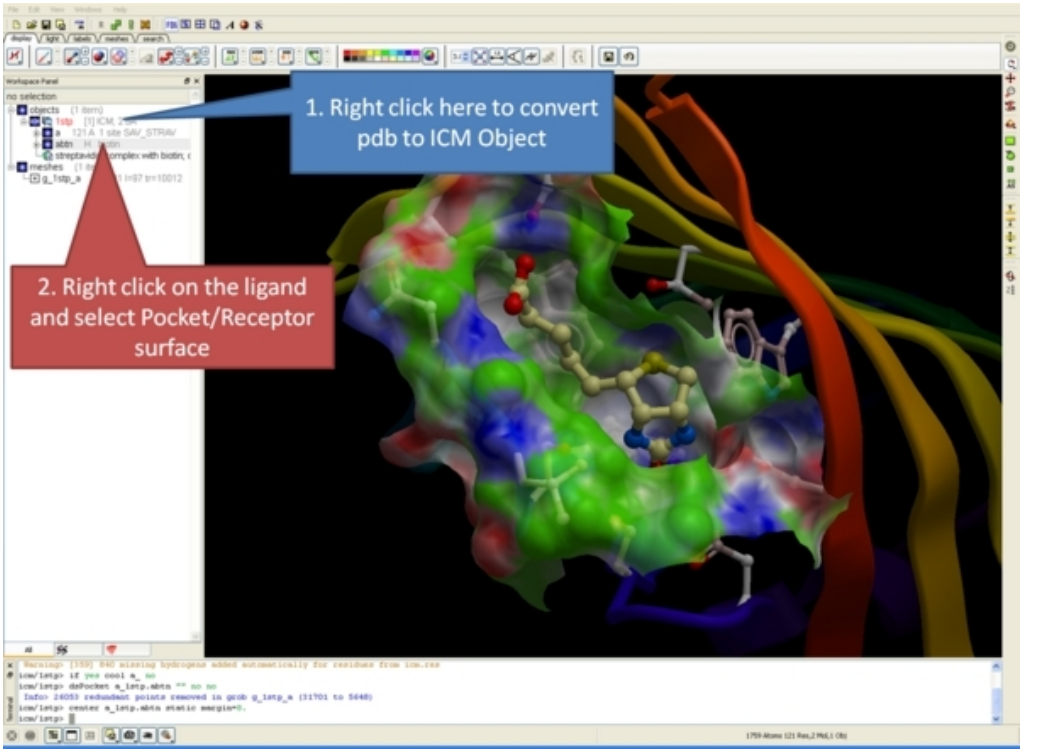
Changing the colour of a representation works in much the same way as displaying the representation itself. The selection rationale is the same followed by clicking on a colour in the palette. It is also possible to colour different representations of the same selection independently (e.g. when displaying a loop (selection series of residues), represented as ribbon and xsticks; colour the ribbons of that selection in cyan and the xsticks in red).



4.1.12 How to Display a Binding Pocket Surface

To display the surface of a small molecule ligand or peptide binding pocket:

- `Load` the PDB of interest.
- `Convert` PDB to ICM object. If you do not convert you will not get the properties of the pocket displayed on the surface.
- Right click on the small molecule or peptide in the ICM Workspace and select **Ligand Pocket**.

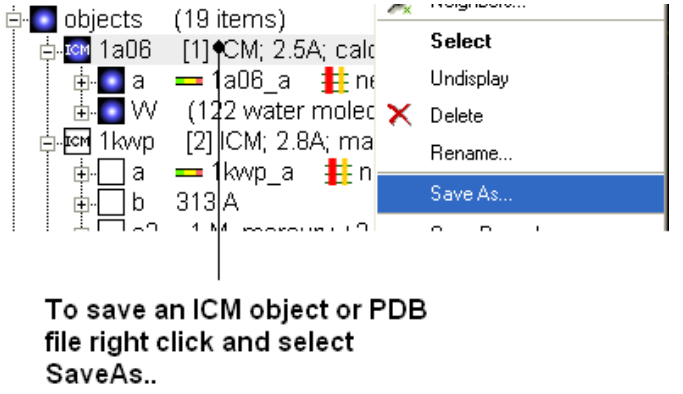


4.1.13 How to Save an ICM Object

Any ICM object such as a structure, sequence, or alignment, can be saved for use at a later time.

To save an object:

- Right click on the object name in the ICM workspace or ICM alignment editor and a menu will be displayed.
- Click on the **Save As...** option.
- Enter the unique name you wish to call your object in the box labeled **File name:**
- Choose which folder or directory you wish to save your object by clicking scrolling down in the box labeled **Save in:**
- Choose which file type you would like to save your object as by scrolling down in the box labeled **Save as type** . ICM structure objects should have the file ending yourfilename.ob and alignments yourfilename.ali
- Once the appropriate information has been entered click on the **Save** button in the bottom right hand section of the window.
- The object is now saved.



4.1.14 How to Save an ICM Project File

All objects contained within an ICM session can be saved in a single file with the extension .icb. The file can then be read into ICM and the exact layout of the file will be preserved. To save a project file go to the **File** menu and select **Save Project**.

4.1.15 How to Drag and Drop

> **NOTE:** "Drag and Drop" is a useful way of moving objects and sequences around the graphical user interface.

Sequences and objects can be moved around the graphical user interface by dragging and dropping them. All loaded sequences and objects are always displayed in the workspace panel. Select the desired object or sequence from the workspace panel by clicking and holding, move the selection to the desired location and release.

This is a useful application in the graphical user interface. For example, you may have an alignment displayed and you wish to add another sequence to the alignment. This can simply be accomplished by dragging a loaded sequence from the workspace panel into the alignment display panel. Or, you can quickly view an object by dragging and dropping it from the workspace panel into the 3D graphics window.

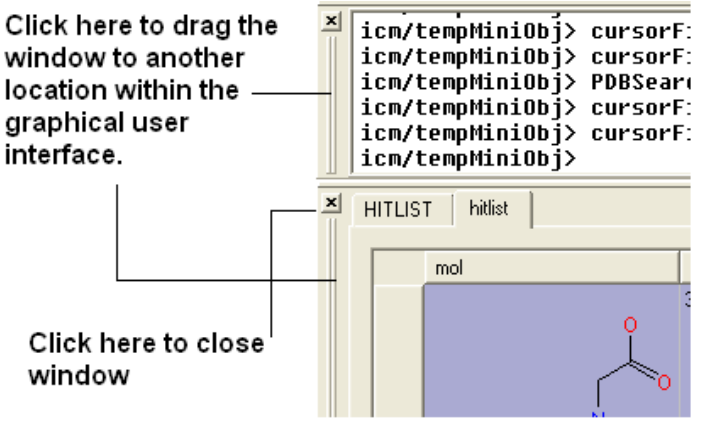
4.1.16 How to: Right Click Options

> **NOTE:** If you right click on any object you will see a new menu of options related to that object.

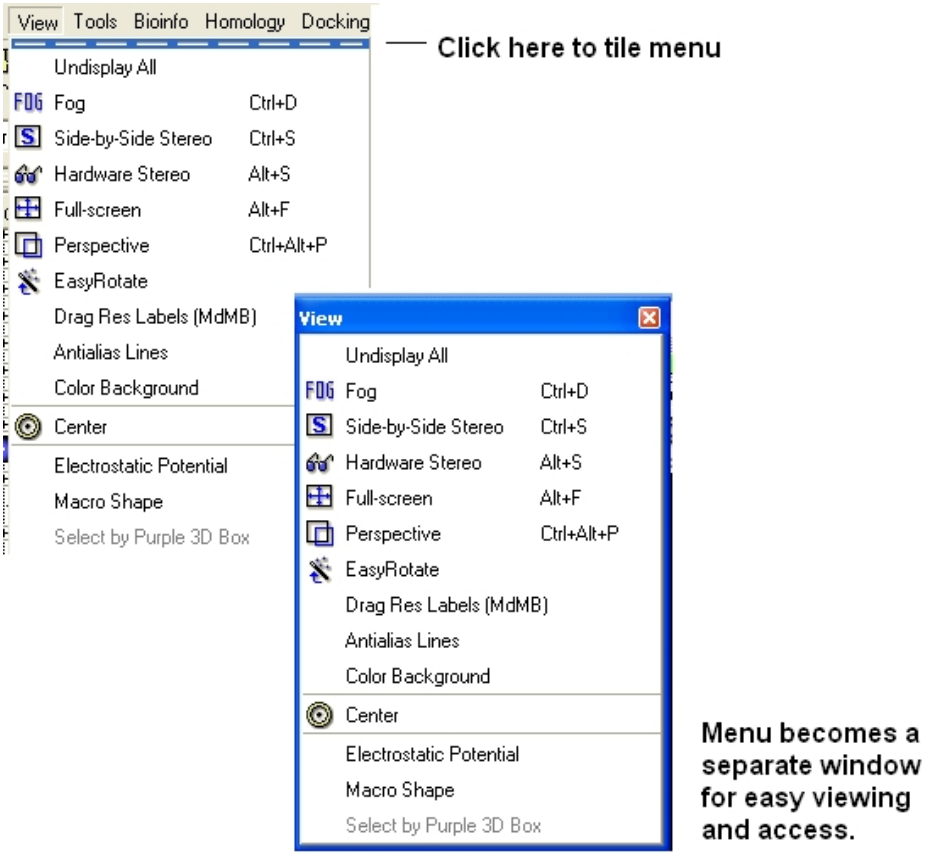
The right click mouse option can be used throughout the graphical user interface. It is a very useful means of opening up a whole new world of menus and options. Most of these options are described in this book. However, when using the graphical user interface it is always a good idea to try right clicking the mouse on an object and seeing which extra options that are available for you to use.

4.1.17 How to Move Windows

It is possible to move some windows around the graphical user interface to make viewing easier.



It is also possible to separate menus from the GUI.



NOTE: To return to the default display option select the 'Default layout' option in the windows menu.

OR

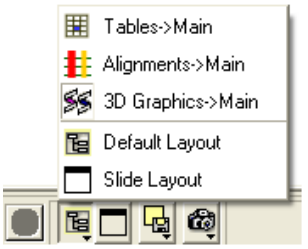
Click the default layout icon.

OR

Double click on the window header.

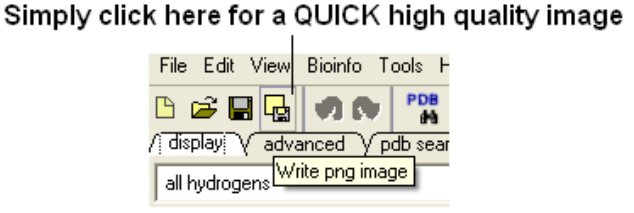
4.1.18 How to Arrange Windows

Sometimes when using ICM you may have many items displayed such as structures, alignments and tables. As a default the graphical display is the largest and centered in the middle of the ICM graphical user interface. However if you wish to work on an alignment or table you can place the alignment or table as the main display by clicking on the buttons shown below. The larger display generally makes it easier to manipulate the alignment or table. There are ofcourse other ways to alter the layout such as `tier` the windows but this option is just a simple click and can sometimes come in useful.



4.1.19 How to Make a Picture

There are several ways of taking a picture of the contents of the 3D graphical display window `see the write image section`. However the easiest way is to simply click on the button in the view tools panel (see image below).



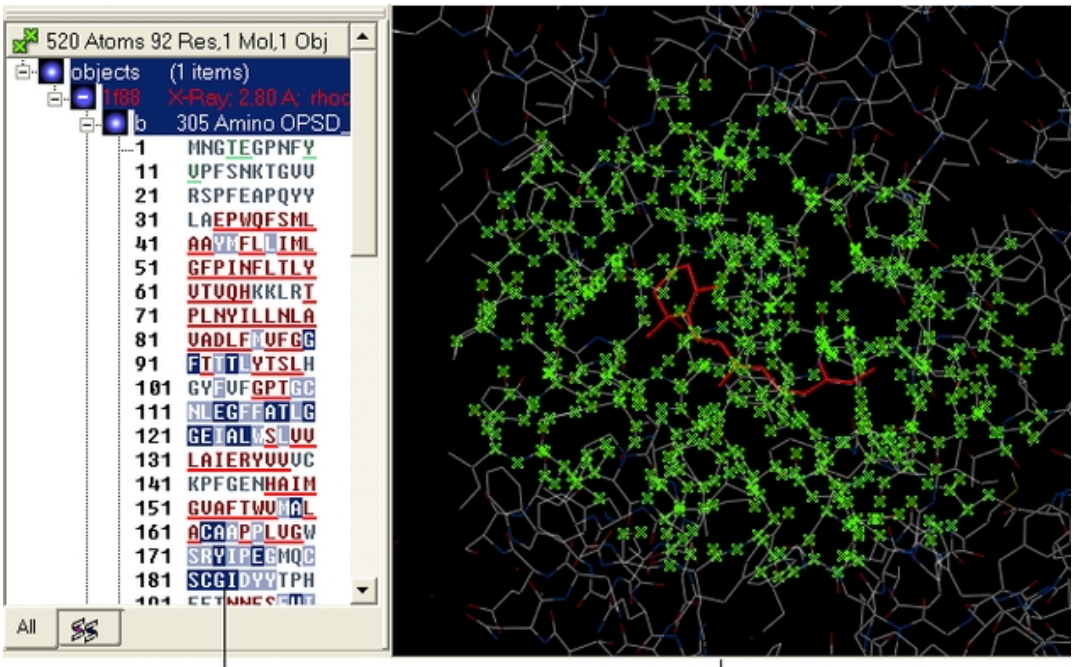
Or select /File/Quick Image

The picture will be automatically saved as a PNG file in the directory from which you loaded ICM. The default picture name is icm[n].png, where n is the number of pictures taken in one ICM session. To save in other picture formats and to change the file name `see the write image section`.

4.2 Making Selections

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

There will be many occasions when you will have to make selections. For example, if you want to display a particular region or molecule contained within your protein structure or if you want to select residues around a binding pocket. If you have a molecule displayed in the graphics window, then selections will be displayed as green crosses. The selection you have made is also displayed at the top of the ICM Workspace. It is always a good idea to keep an eye on what is selected and what isnt.



There are four basic levels of selection

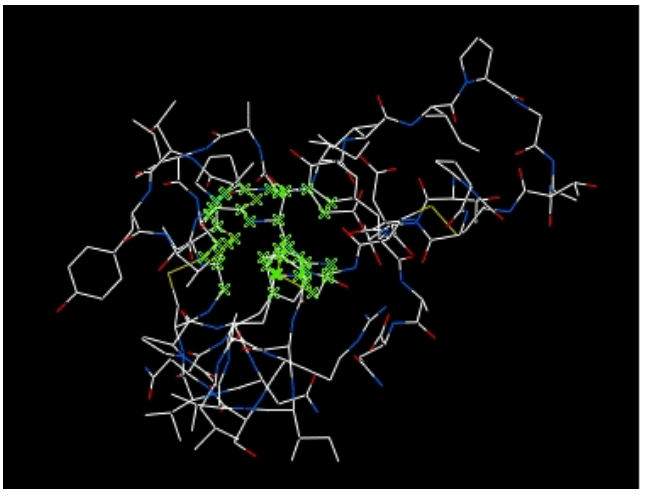
1. Object (eg a PDB structure or ICM object)
2. Molecule
3. Residue
4. Atom

You can make selections in:

- The Graphics Display
- The ICM Workspace (Selections are highlighted in blue)
- Tables
- Sequences
- Plots
- Alignments

4.2.1 Graphical Selections

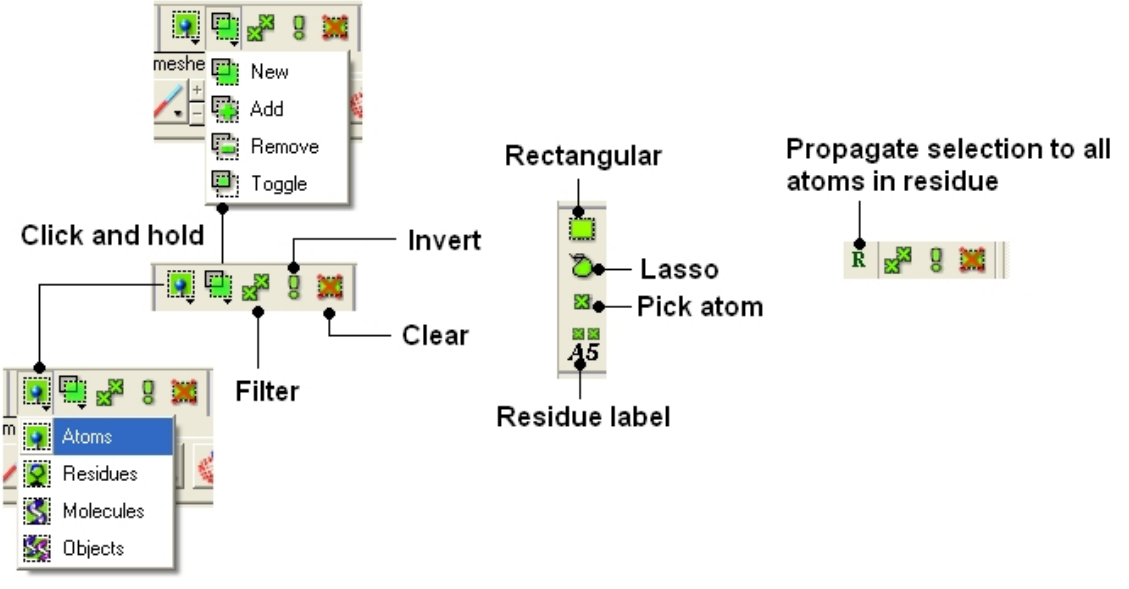
In this section you will learn how to select parts and certain regions of molecules from the 3D graphical display. Graphical and molecule selections are required for many operations within ICM. For example, if you wanted to display graphically part of a molecule or if you wanted to perform a minimization of residues within a sphere of an imporant atom.



Selection shown in green.

4.2.2 Selection Tools

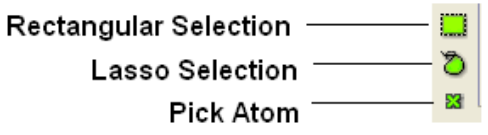
The following buttons can be used to make a selection once a structure is displayed.



NOTE: All selection tool buttons are colored green. Graphical selections are represented as green crosses.

4.2.3 Basic Selections

To make a basic selection (ie nothing too complicated!) the following buttons can be used.



To select parts of your structure:

- Click on the **Rectangular selection icon** and click and drag around the part of the structure you wish to select.

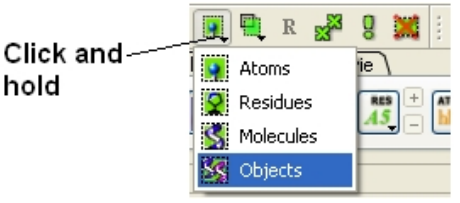
OR

- Click on the **Lasso selection icon** and click and drag your mouse around the area of the structure you wish to select, forming a lasso around it.

To pick individual atoms:

- Click on the 'pick atom' button

You can also change the level of a selection using the button shown below. Click and hold the button to choose the level of selection. For example, if you have selected atoms you can convert the selection to all atoms at the residue level by choosing the Residues option.



- Click on the **Select** objects , **Select molecules**, **Select residues**, or **Select atoms** icon, depending on which part of the structure you wish to be highlighted.

NOTE: The selection you have made is always recorded at the top of the ICM workplace. If you are familiar with using the ICM terminal (See language manual) the atoms, residues, molecules or objects selected interactively in the graphics window are automatically stored in the as_graph variable.

4.2.4 Clear Selection

To unselect everything you have previously selected:

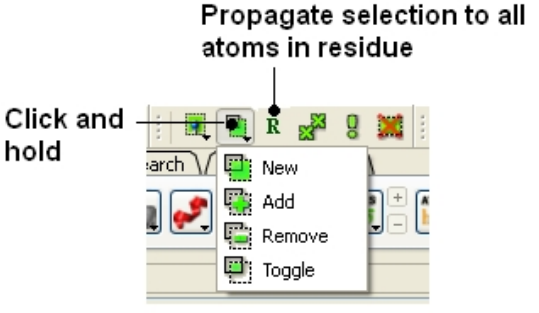
- Simply click on the **Clear Selection** button on the selection toolbar.

OR

- Right click and drag away from the displayed structure.

4.2.5 Altering a Selection

Once you have made a selection you may wish to add or remove parts of the selection. The buttons shown below allow you to accomplish this.



To add or remove from your current selection:

- Click on the **Selection mode: add** or **Selection mode: remove** icon on the toolbar.
- Click and drag around the part of your structure you wish to add or remove.

You may also wish to invert your selection in a specific part of the structure.

The parts that are currently selected will become unselected, and the unselected parts will become selected.

In order to invert a selection:

- Click on the **Invert** icon on the toolbar.

If you wish to select and unselect certain regions of a selection the toggle selection button is very useful.

- Click on the Toggle selection button.
- Right click around the selections you wish to select or unselect.

NOTE: The selection you have made is recorded at the top of the ICM workplace. Any selection is stored in the variable as_graph.

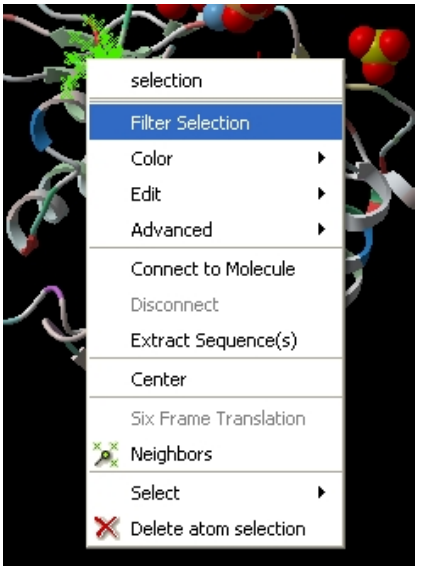
4.2.6 Filter Selection

You may want to be very specific about a selection you want to make. For example you may only want to select protein backbone atoms.

The button shown below enables you to filter your selection:

Or

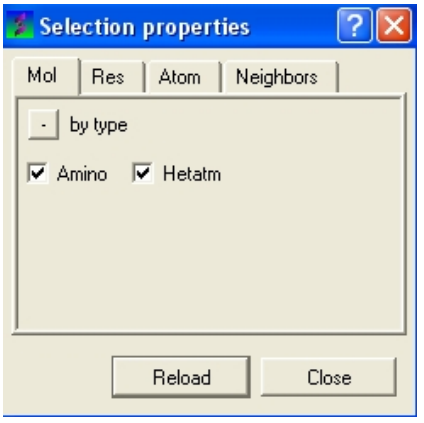
Right click on a selection and a menu as shown below will be displayed.



- Select the Filter Selection option.

If you wish to filter and select by residue or atom type:

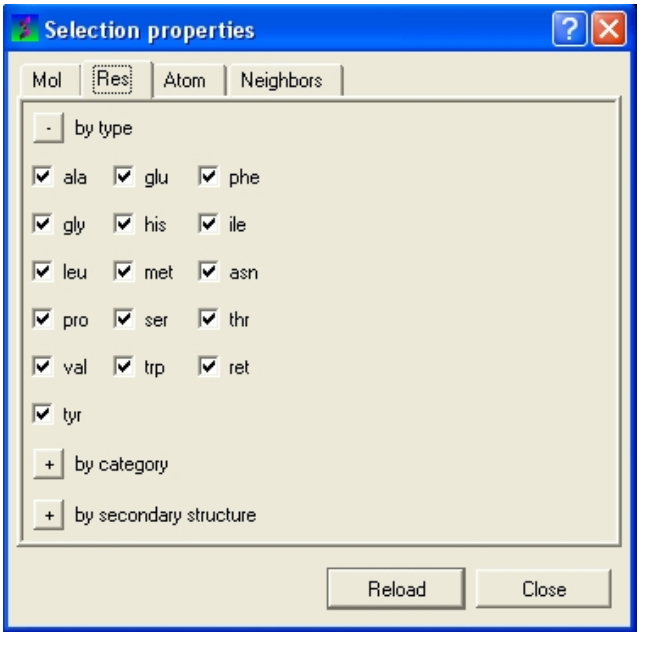
- Click on the Filter graphical selection icon on the toolbar and a data entry box as shown below will be displayed.



To select just the protein or just the hetatoms as well:

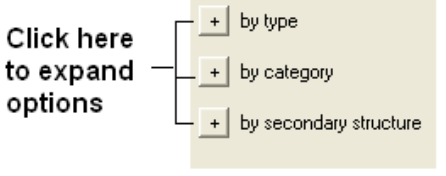
- Click on the Mol tab.
- Check the appropriate boxes depending on your desired selection.

To filter by residue type or secondary structure:

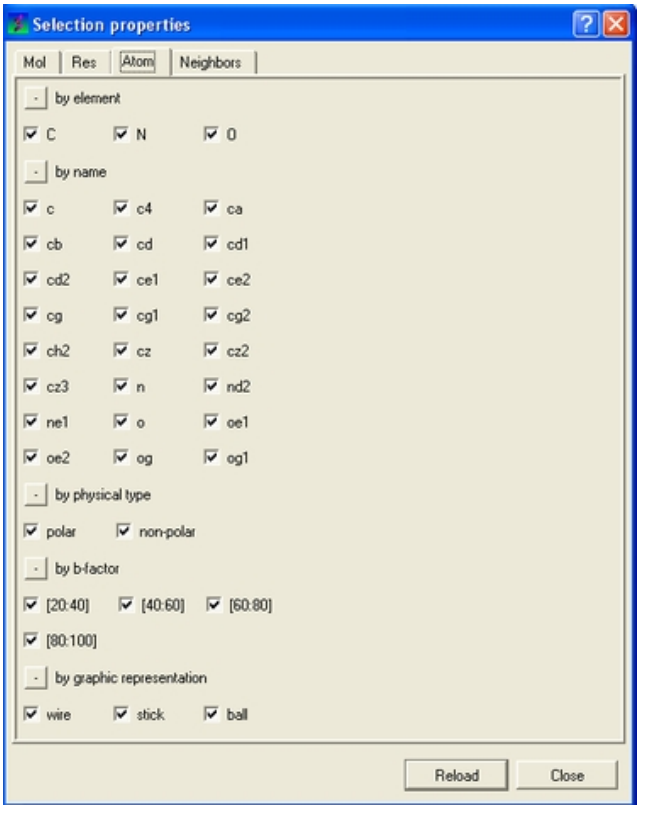


- Click on the Res tab.
- Check the appropriate boxes.

NOTE: You may need to click on the button marked with a '+' symbol to expand the options.

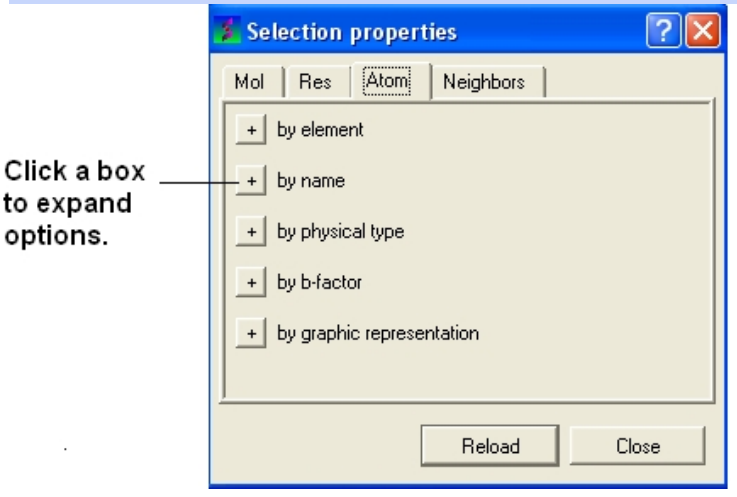


To filter by atom type.



- Click on the Atom tab.
- Check the appropriate boxes.

NOTE: You may need to click on the button marked with a '+' symbol to expand the options.



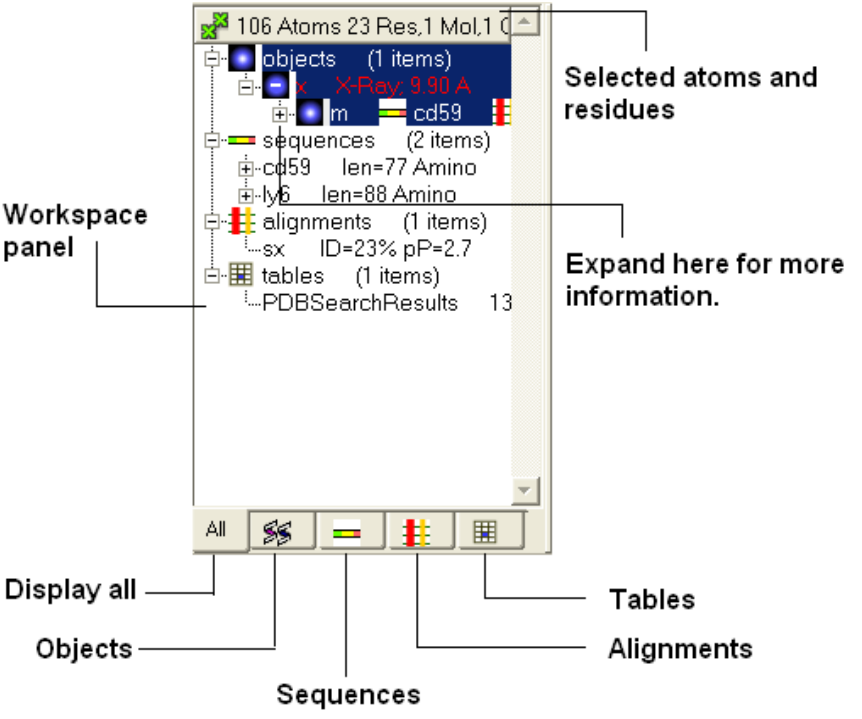
To select neighbors to a particular selection.

- See the `select neighbours` section for detailed instructions.

NOTE: The selection you have made is always recorded at the top of the ICM workplace. If you are familiar with using the ICM terminal (See language manual) the atoms, residues, molecules or objects selected interactively in the graphics window are automatically s

4.2.7 Workspace Selections

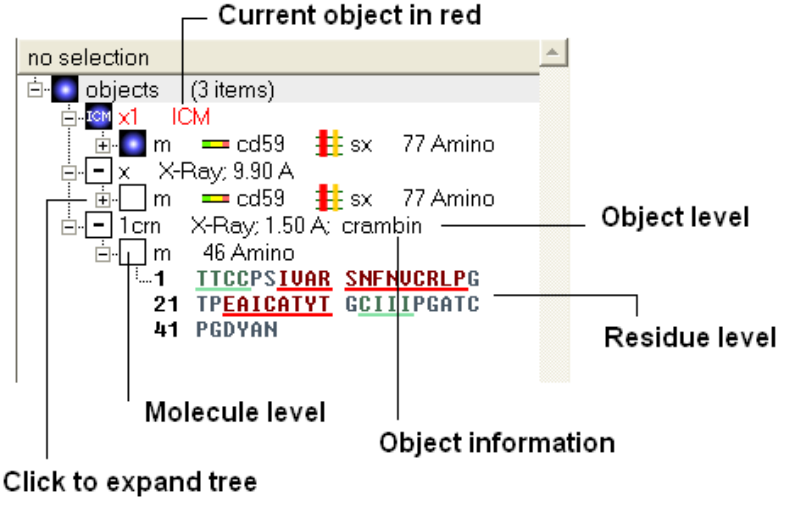
In the default GUI layout the workspace panel is located to the left of the 3D graphics display. It is a great tool for keeping track of all your sequences, pdb structures, objects, tables and alignments. As you will see in this section it also provides a way of making selections.



4.2.8 Workspace Navigation

Once you have mastered how to navigate the ICM workspace making a selection will become easier. Each object is divided into 3 levels:

1. Object Level − Shown in red if it is the current object. Holds details about the structure − name, X−ray, NMR, resolution etc. Importantly it will state whether the structure is an ICM object or a structure straight from the PDB. To learn how to convert a PDB into an ICM object go to the section on `converting a PDB`.
2. Molecular Level − Shows the individual subunits, ligands and hetatoms of a molecule.
3. Residue Level − Shows the sequence.

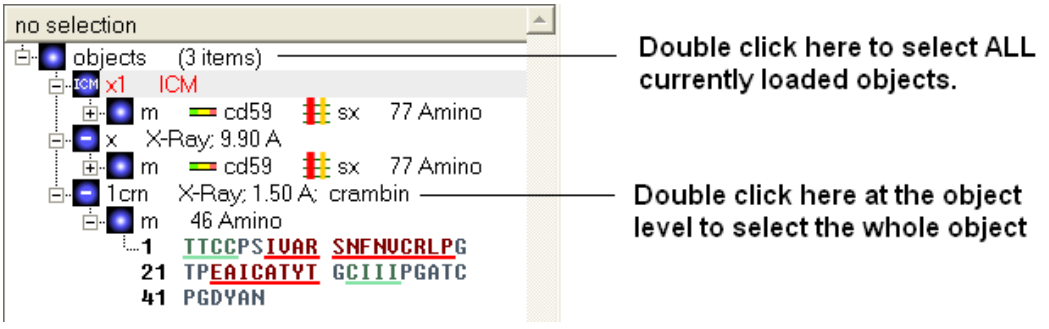


NOTE: You can expand each level of the ICM workspace by clicking the "+" button as shown above.

4.2.9 Selecting the Whole Object

To select the whole object:

- Double click on the object level.

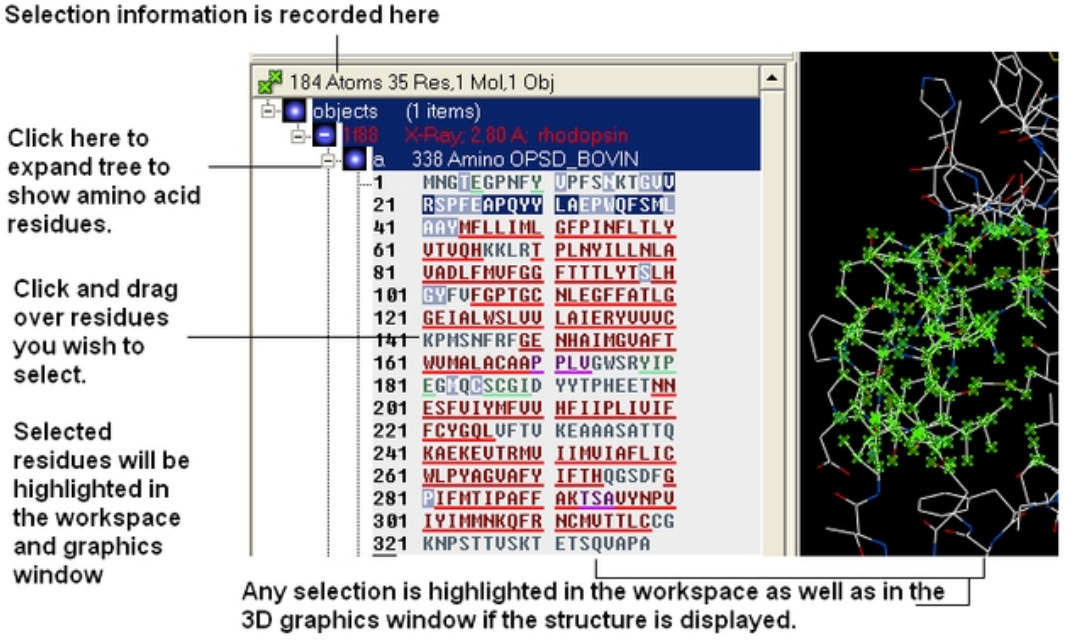


4.2.10 Selecting Amino Acids

There are three options to select individual amino acid residues:

OPTION 1:

- Click and drag over the residues you wish to select in the ICM workspace. Selected residues will be highlighted in dark blue in the workspace and with green crosses in the graphical display.

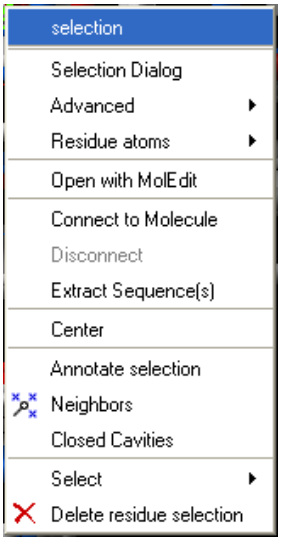


OPTION 2:

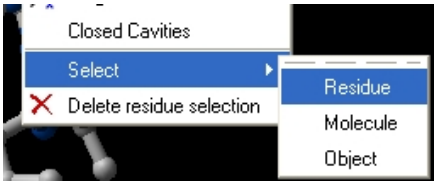
- Click on the **rectangular selection** icon or **lasso selection** icon on the toolbar.
- Click and drag around the residues you wish to select. Selected residues will be displayed by green crosses on the graphical display and blue in the ICM workspace.
- Click on the Pick Atom button.

OPTION 3:

- Right click on the selected residue in the graphical display and a menu as shown here will be displayed.



- Click on **Select** and a further menu will be displayed.
- Click on **Residue**, **Molecule** or **Object.**



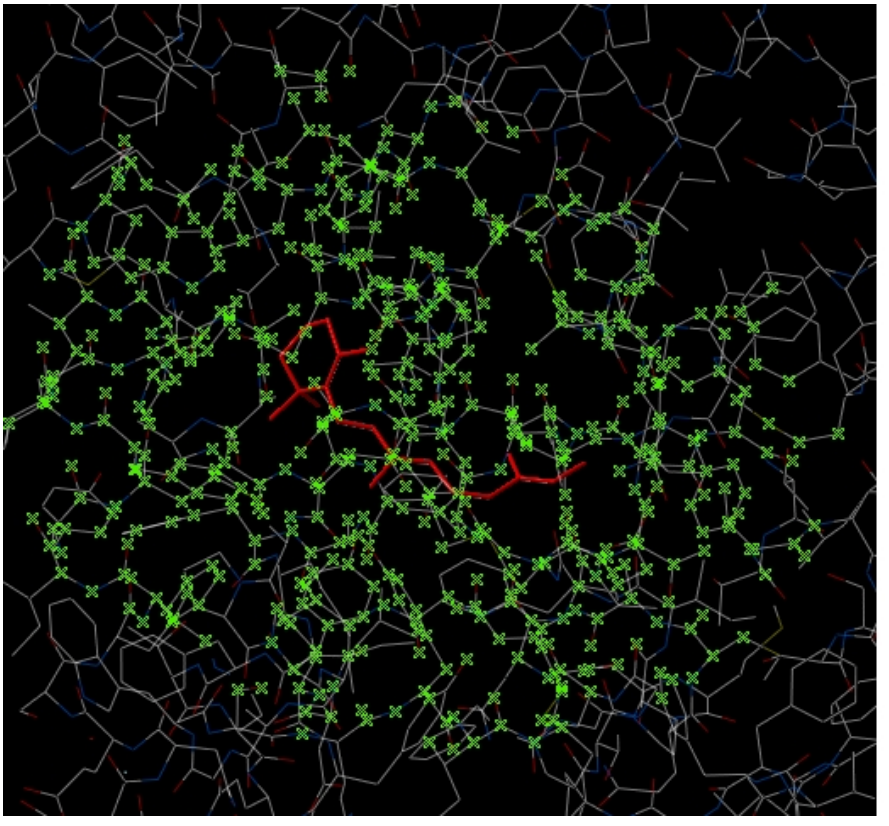
NOTE: Ctrl + A will select everything in the ICM workspace, and Ctrl + Shift + A will unselect your objects.

NOTE: The selection you have made is always recorded at the top of the ICM workplace. If you are familiar with using the ICM terminal (See language manual) the atoms, residues, molecules or objects selected interactively in the graphics window are automatically s

4.2.11 Selecting Neighbors

In some instances you may only want to display or select only a subset of a structure. For example you may only wish to display the residues surrounding a ligand (as shown below (ligand red; graphical selection green crosses). The "Selecting Neighbors" option selects the residues within a shpere of a defined radius.

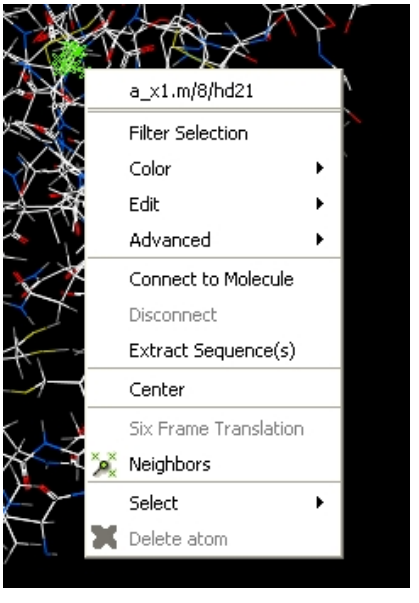
There are two ways of selecting neighbours to a particular atom or residue in ICM. Either by right clicking on the atom or residue in the graphical display or by right clicking in the ICM workspace.



4.2.12 Selecting Neighbors: Graphical

To select neighboring atoms or residues around a sphere of a certain radius:

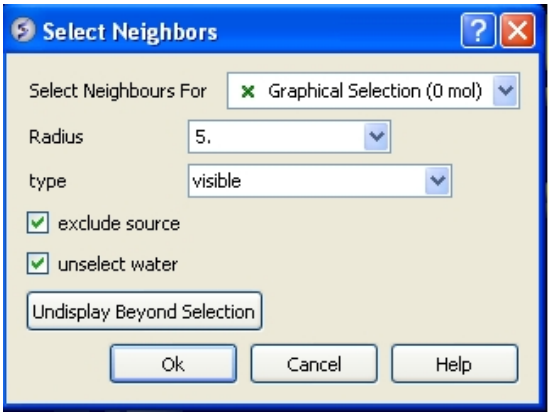
- First select the residue(s) or atom(s) around which you wish to select neighbors. (See the `Selection Toolbar Section`)
- Right click on the selection and a menu as shown below will be displayed or choose Tools/Geometry/Neighbors.



- Select the Neigbors option and a data entry box as shown below will be displayed.

This option will allow you to make a spherical selection.

The window will open as displayed as below:



- Select the molecule you wish to select neighbors around. For example you can `select` a ligand in the `ICM Workspace` and then choose the **Graphical Selection** option in the "Select Neighbors For" dialog entry box. Or alternatively you can select the object by clicking on the drop down button next to the "Select Neighbors For" dialog entry box.
- Enter the radius in Angstroms for the neighbor selection. e.g. 5.
- **Type** − this option is **important.** This option relates to what is going to be selected. For example if you leave this option as **visible** and you only have ribbon representation displayed for your receptor (e.g. when selecting neighbors for a ligand) then only backbone atoms will be selected.

Selection **Type** option includes:

- **visible** − will select all atoms displayed within the radius selected.
- **visible sidechains** will select all visible side−chains − not backbone atoms.
- **same_object_other_chains** will select all atoms in other chains in the same object as the original selection.
- **other objects** will select atoms in objects other than the original selection.
- **same object** will select atoms in the same object as the original selection.
- **all_objects** will select atoms in all objects
- **choose_from_list** will allow you to select the object you wish to include in the neighbors selection.

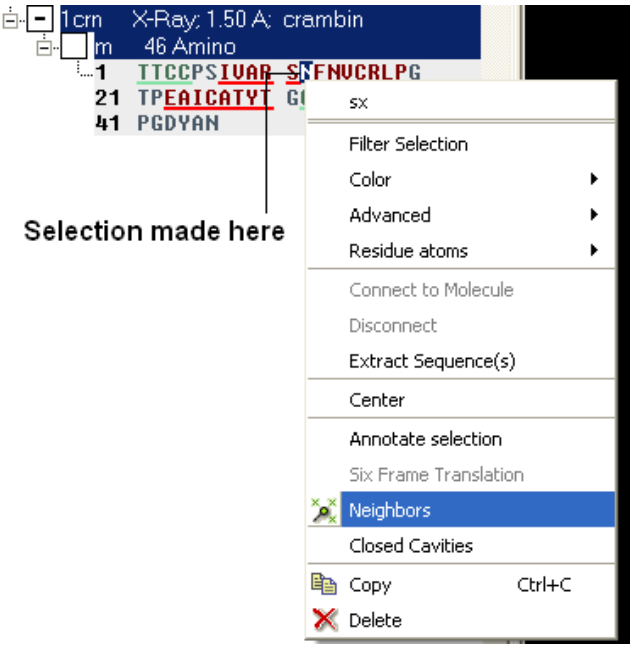
- **exclude source** if checked will not include your original selection in the spherical selection.
- **unselect water** if checked will not select water molecules
- **Undisplay Beyond Selection** will only display the atoms selected.

NOTE: The selection you have made is always recorded at the top of the ICM workplace. If you are familiar with using the ICM terminal (See language manual) the atoms, residues, molecules or objects selected interactively in the graphics window are automatically saved in the variable as_graph. Graphical selections are shown in green (crosses) or highlighted in blue in the ICM Workspace.

4.2.13 Selecting Neighbors: Workspace

To select neighboring atoms or residues around a sphere of a certain radius from a residue in the ICM workspace:

- First select the residue in the ICM workspace around which you wish to select neighbors. (See the `Residue Selection`)
- Right click on the selection and a menu as shown below will be displayed.



- Select the Neigbors option and a data entry box as shown below will be displayed.
- Follow the instructions in the `previous section`.

NOTE: The selection you have made is always recorded at the top of the ICM workplace. If you are familiar with using the ICM terminal (See language manual) the atoms, residues, molecules or objects selected interactively in the graphics window are automatically s

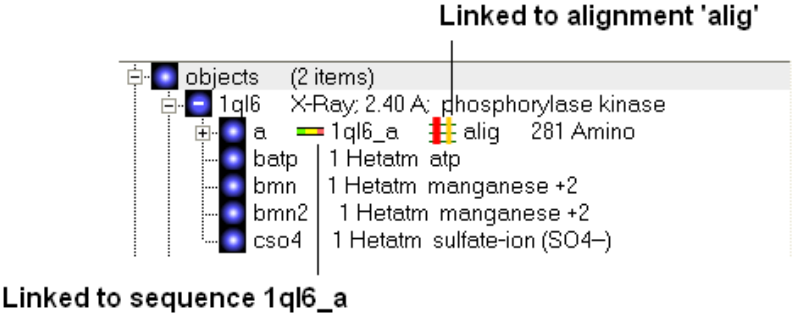
4.2.14 Alignment and Table Selections

Descriptions on how to make selections in Alignments and Tables are in the sections entitled `Making Selections in Alignments` and `Making Table Selections`.

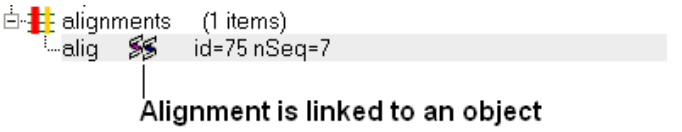
4.2.15 Making Links

It is sometimes necesary to make links between sequences objects and alignments. A link enables you to make selections in one environment such as an alignment and then these selections are transfered to the object such as the PDB structure displayed.

If a link is made then a symbol will be displayed next to the object in the ICM workspace. In the example shown below subunit_a of the X−ray structure 1ql6 is linked to the sequence 1ql6_a and the alignment called 'alig'.



If an object is linked to an alignment a symbol as shown below will be displayed.



To link a sequence from an object − extract the sequence from the object.

- Right click on the object in the ICM workspace.
- Select extract sequence.

To link a sequence and object to an alignment.

Use the extracted sequence as described above to build your alignment.

In addition a link can be made between a structure and alignment by:

- Bioinfo/Link to Structure.
- Enter alignment name.
- OK

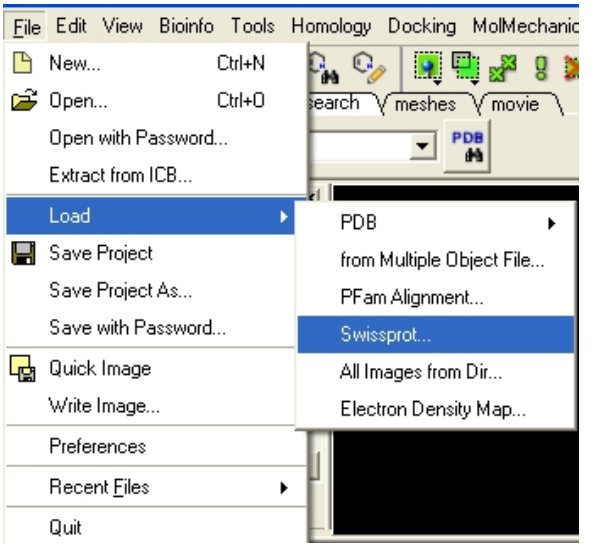
4.3 How to Work With Sequences and Alignments

A quick start guide on how to search for, read in, analyze sequences and build alignments.

4.3.1 How to Download a SwissProt sequence

To download a SWISSPROT sequence into ICM

- Select File/Load/SwissProt
- The sequence will be loaded into the ICM Workspace.



4.3.2 How to Load a FASTA Format File

To read a FASTA file:

- Select File/Open and look for file type "Sequence Format"
- The sequence will be loaded into the ICM Workspace.

4.3.3 How to Make a New Sequence

- File/New
- Select "sequence" tab.
- Cut and Paste or type sequence
- Click OK and the sequence will be loaded into the ICM Workspace.

4.3.4 How to Extract a Sequence from a PDB Structure.

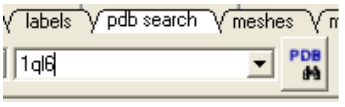
- As an example we will use the PDB structure 1STP. Type 1STP in the pdb search tab and press return.
- Right click on the protein molecule "m" and select "Extract Sequences"
- The sequence will be loaded into the ICM Workspace.

4.3.5 How to Make a Sequence Alignment

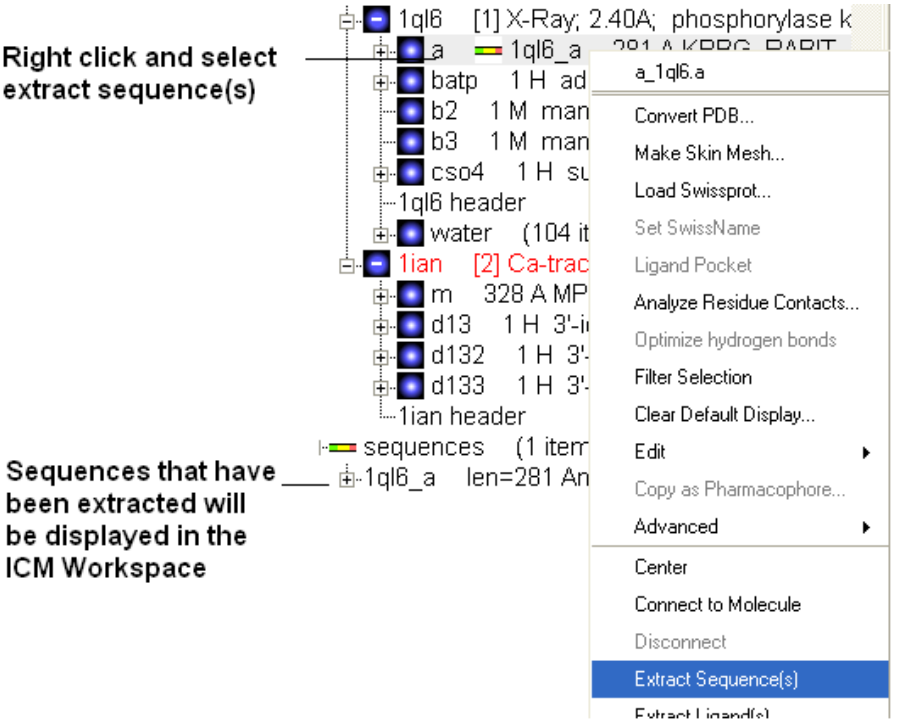
An example of how to perform an alignment between two sequences.

PDB Search:

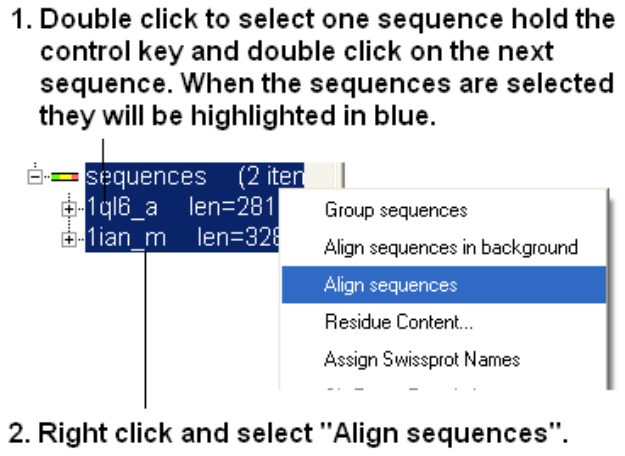
- PDB Search Tab 1ql6
- PDB Search Tab 1ian



- Now extract the sequence information from each protein. To do this right click on the molecule "a" of 1ql6 and molecule "m" of 1ian. and select extract sequences. Once the sequences have been extracted you should see the sequence in the ICM Workspace entitled 1ql6_a and 1ian_m



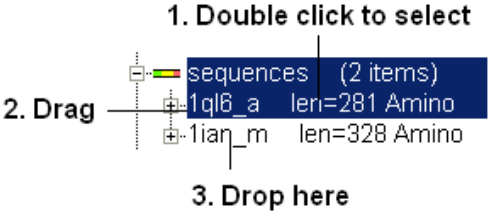
- Now align the sequences by selecting both sequences right clicking and selecting Align sequences. An alignment will be displayed at the bottom of the graphical user interface.



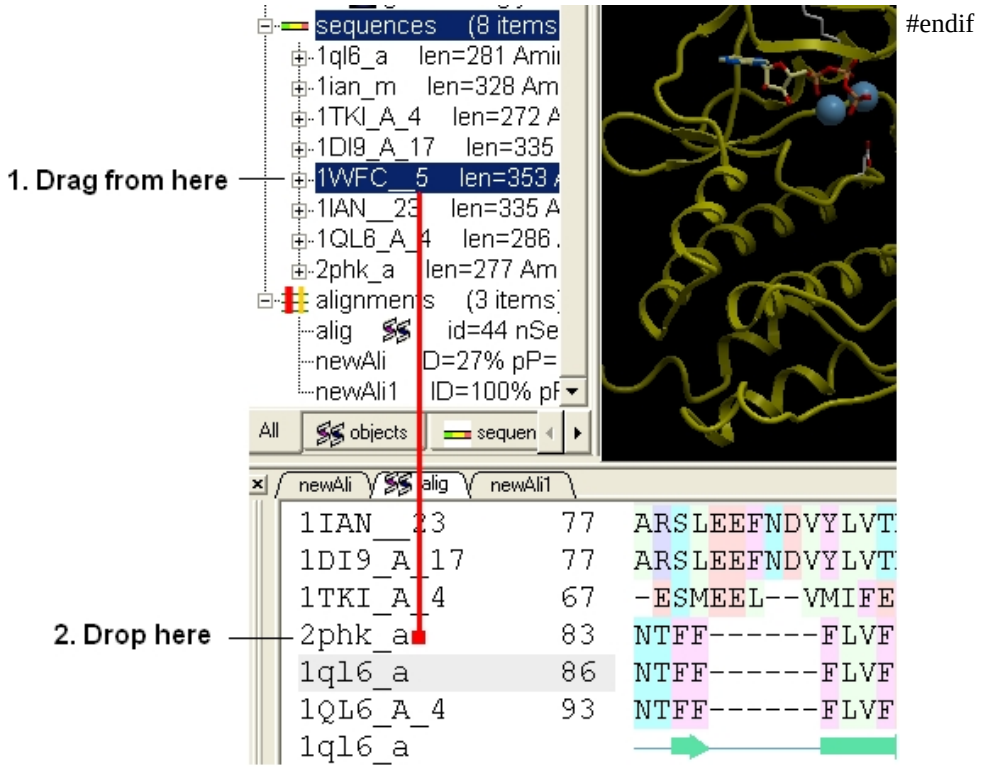
NOTE: To build a multiple alignment just select more sequences right click and align sequences. Or you can drag and drop sequences into an already made alignment.

4.3.6 How to Make an Alignment using Drag and Drop

(An easier way to build an alignment is to drop one sequence onto another in the ICM Workspace}



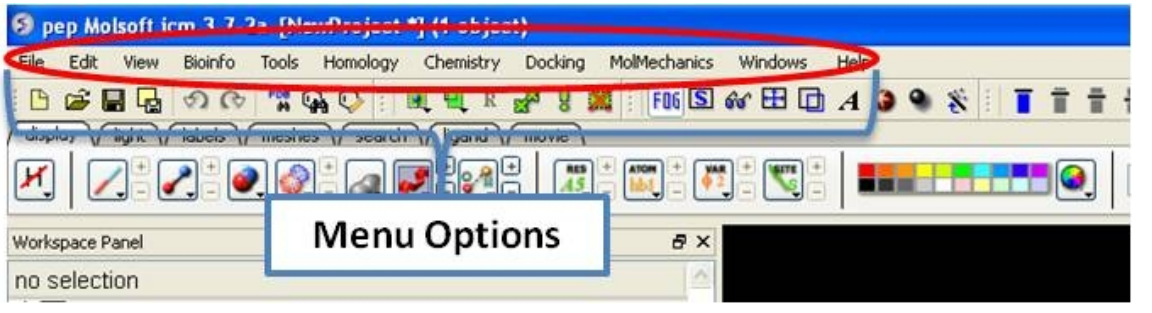
You can add sequences to an alignment by dragging and dropping them into the alignment.



4.4 Menu Option Guide

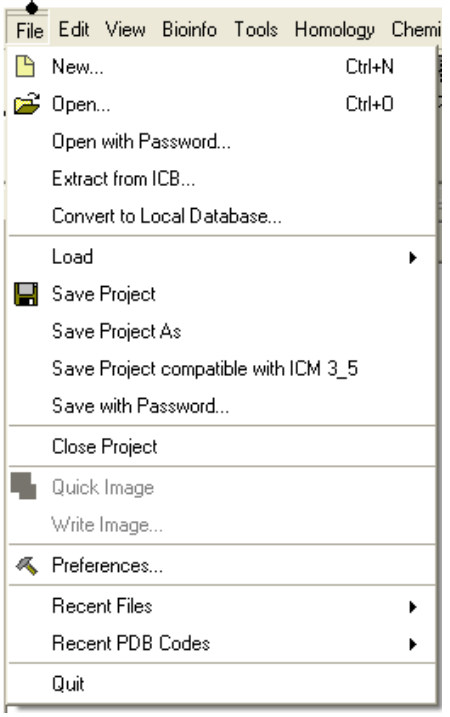
Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

Here we describe all the options in the drop down graphical user interface menus.



4.4.1 File Menu

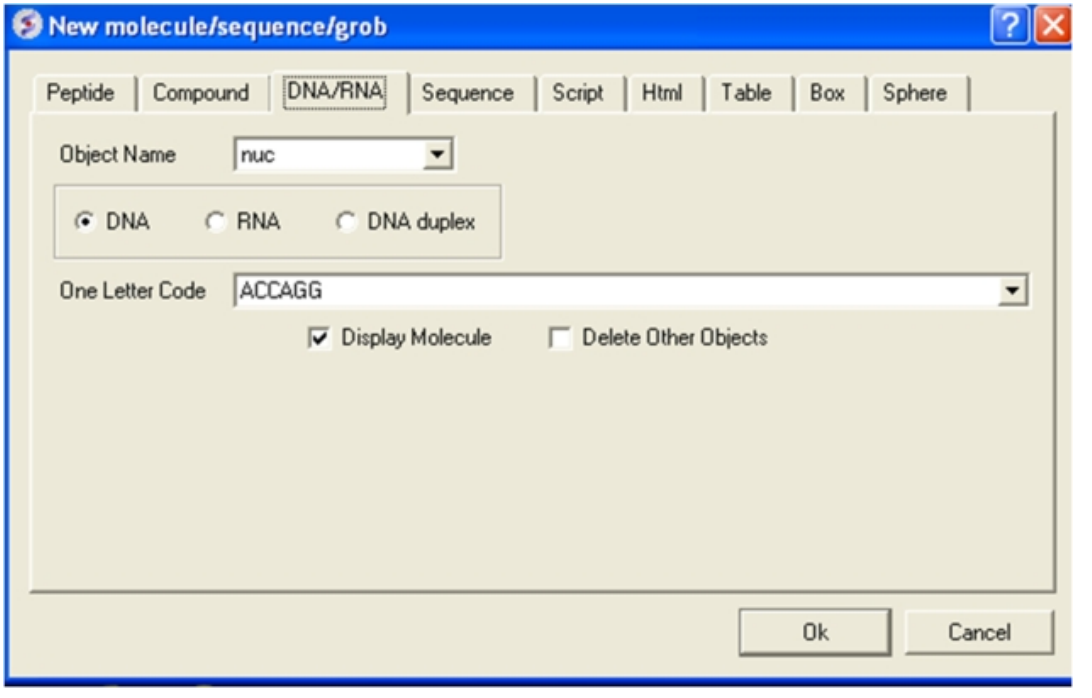
File Menu



4.4.1.1 New

ICM can read as well as create several different entities. This dialog box helps you to create new entities from scratch:

All the processes in this section can be found under **File/New**, in the **New molecule/sequence/grob window**

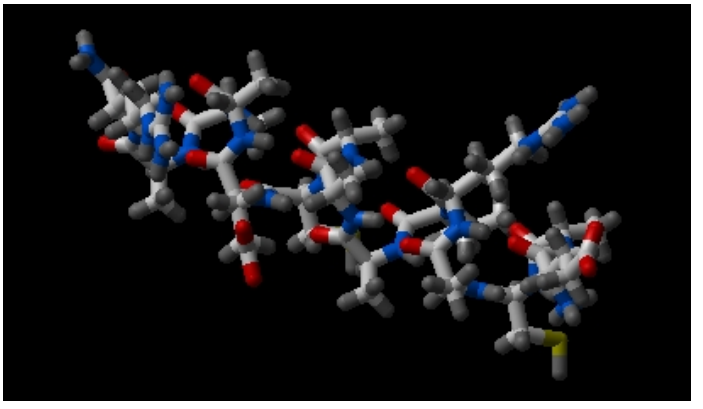


4.4.1.1.1 Constructing a New Peptide

Creates a peptide as a new ICM Object, named after the string entered in the 'Object name' field. The residue composition of the new peptide is the string entered in the 'One Letter Code' field. The chemical property of the peptide ends will be created according to the type of terminus choosen from the 'N−terminus' and 'C−terminus' drop−down list.

The peptide can be displayed immediately after creation (check the 'Display molecule' option). The new peptide can be folded as an alfa−helix (phi= −62 deg.; psi= −41 deg.), instead of a linear stretch of residues (phi,psi = 180 deg.) (check the 'Assign A−helix' option).

Please note that the created peptide will not be in its most favorable energetic conformation.



To construct a new peptide:

- Select **File/New** and the **New molecule/sequence/grob window** will appear.
- Type the peptide sequence into the One letter code data entry box. Remember to delete the previous entry if it is in the box.

NOTE: If the peptide you wish to make has been made previously then it will be in the drop down menu in the One letter code box.

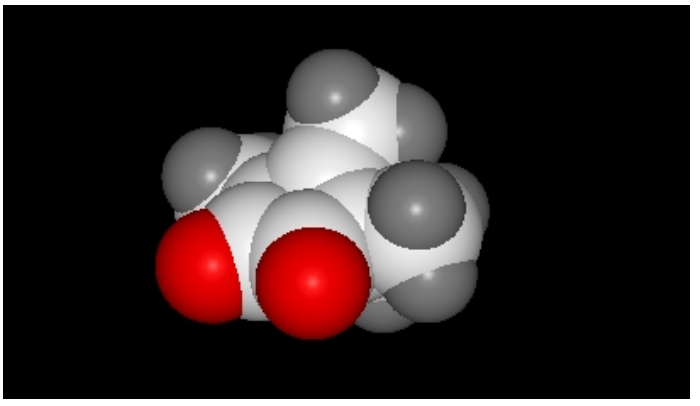
- Select the appropriate N−terminal and C−terminal from the drop down menu.
- Check the boxes **Display Molecule** or **Assign A−Helix** according to your particular preference.
- Click the **OK** button.

4.4.1.1.2 Constructing a New Compound

Creates a compound/ small chemical molecule, based on the SMILES − Simplified Molecular Input Line Entry Specification − string supplied. The name of the compound can be specified on the 'Object name' field. For further information on SMILES syntax
`http://www.daylight.com/dayhtml/smiles.`

The new compound can be displayed immediately after creation (check the 'Display molecule' option). All other objects can be deleted before the creation of the new object (check the 'Delete other objects' option).

Please note that the created compound will not be in its most favorable energetic conformation.



To construct a new compound:

- Select **File/New** and the New molecule/sequence/grob window will appear.
- Click the **Compound** tab at the top of the window.

OPTION 1:

- Type in the Smiles String in the Smiles String data entry box. Remember to delete the previous string. If a string has been entered previously it will be available by clicking on the drop−down button.
- Check the boxes **Display Molecule** or **Delete Other Objects** according to your preference.
- Click the **OK** button.

OPTION 2:

- Click the Launch Molecule Editor button.

Please refer to the `Molecule Editor` section of this manual for instructions.

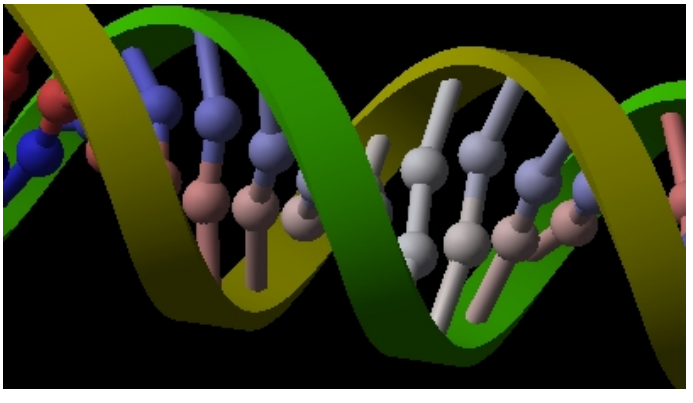
4.4.1.1.3 Constructing New DNA or RNA

Creates a nucleic acid chain object − either DNA or RNA, according to the selection and the nucleotide sequence. The sequence should be supplied in one−letter code (ATCG) format, starting from 5' end. The name of the DNA/ RNA object can be specified on the 'Object name' field.

If the 'DNA duplex' option is selected, the complementary strand will be created automatically as a separate molecule in the same object.

The new DNA/ RNA can be displayed immediately after creation (check the 'Display molecule' option). All other objects can be deleted before the creation of the new object (check the 'Delete other objects' option).

Please note that the DNA/ RNA will be created as adopting the canonical B−DNA conformation.



To construct new strand of DNA or RNA:

- Select **File/New** and the **New molecule/sequence/grob** window will appear.

- Click the **Nucleotide** tab at the top of the window.
- Check the appropriate box for the nucleotide you are constructing, either DNA RNA or DNA Duplex
- Enter the nucleotide sequence into the **One Letter Code** data entry box. Remember to delete the previous nucleotide sequence. If a sequence has been entered previously it will be available by clicking on the drop−down button.
- Check the boxes **Display Molecule** or **Delete Other Objects** according to your preference.
- Click the **OK** button.

4.4.1.1.4 Constructing New Protein and Nucleic Acid Sequences

Creates a new Sequence using the information supplied by the user in FASTA format. The sequence type can be defined as protein or nucleic acid by the user, or automatically detected by ICM. Simply choose one of the options on the dialog box. The sequence name can be specified in the 'Sequence name'.

To construct a new protein and nucleic acid sequence:

- Select **File/New** and the **New molecule/sequence/grob** window will appear.
- Click the **Sequence** tab at the top of the window.
- Copy and paste a Fasta−format sequence into the Sequence data entry box.
- ICM will automatically determine what kind of sequence you have constructed but if you wish to specify then you can check either the protein or nucleic acid box.
- Click the **OK** button.

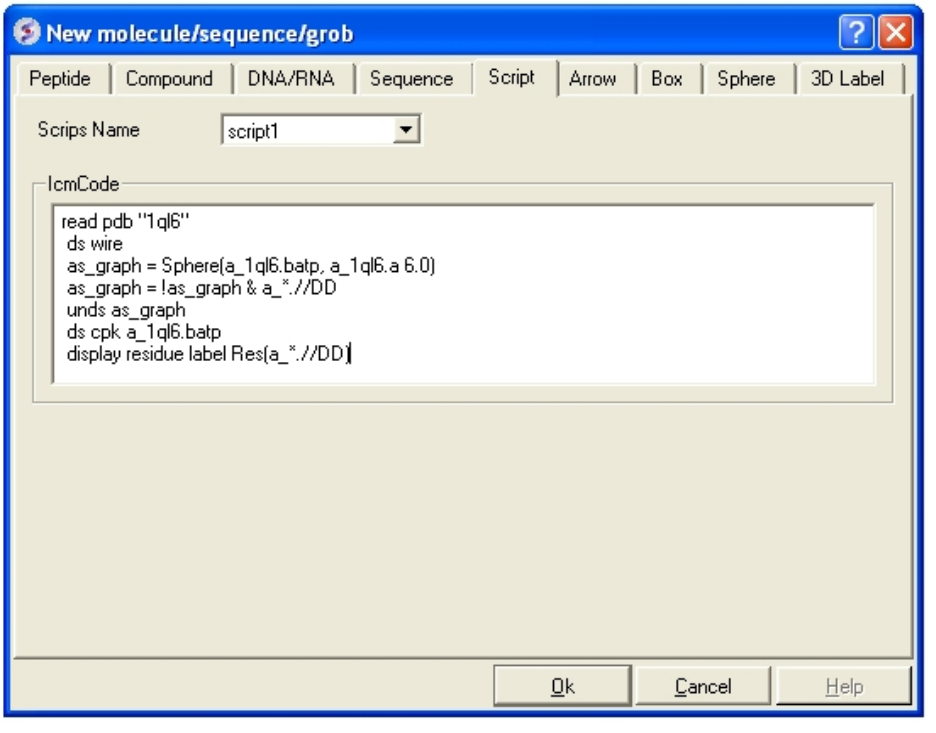
4.4.1.1.5 Writing a Script in GUI.

Creates a clickable link on the workspace that launches scripts written using ICM language. The link is named after the 'Script Name'.

There are two ways of defining the script to be associated with the link. The first is to input the ICM script directly into the 'IcmCode' field. Alternatively, a file containing an ICM macro can also be associated with the link.

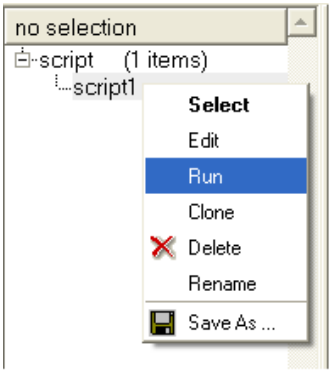
To write a script in the graphical user interface:

- Select **File/New** and the **New molecule/sequence/grob** window will be displayed.
- Click the Script tab at the top of the window.
- Write your ICM script in the text box provided (see below) and click OK.



To run or edit your script:

- Right click on the script name in the ICM workspace.



NOTE: For more details regarding the ICM scripting language please see the separate ICM language manual.

#endif

4.4.1.1.6 HTML

- File/New HTML tab provides a window to enter HTML code. This window is a good starting point for generating new `molecular documents`.

4.4.1.1.7 New Table

To generate a new empty table:

- File/New and select the **Table** tab and a window as shown below will be displayed.
- Enter the number of rows and columns you wish to include in your table and whether you wish to add a column with chemical data.

4.4.1.1.8 arrow

Creates a 3D arrow as a new graphical object ('grob' or 'mesh'). This arrow can be generated both as a solid object or as a simpler line representation. The name of the object can be defined in the 'Arrow Name' field.

The start (StartXYZ) and end (End XYZ) points of the arrow are defined in cartesian coordinates (X, Y, Z). The quality of the arrow can be adjusted (the higher the value, the smoother the arrow will be). Color can be assigned by simply clicking on the desired one or using rgb scale (eg. for red: rgb={1. 0. 0.}).

The Arrow Radius is defined in Angstroms. The size of the head, shown as a solid cone is defined as a fraction of the whole lenght of the arrow. Thus 0.1 means that the height of the head will take 10% of the total size of the arrow, while 1.0 means that the head will take the whole arrow (resulting in a shaftless arrow). The width of the head refers to the diameter of the head cone and it is defined as a multiplier of the Arrow Radius.

Tip: the arrow can be moved independently using 'connect'

4.4.1.1.9 Box

Creates a 3D box as a new graphical object ('grob' or 'mesh'). This box can be generated both as a solid object or as a simpler wire representation. The name of the box can be defined in the 'BoxName' field.

Dimensions of the box (X, Y, Z) are given in Angstroms and the angles connecting the sides are given in degrees. Color can be assigned by simply clicking on the desired one or using rgb scale (eg. for red: rgb={1. 0. 0.}).

Tip: the box can be moved independently using 'connect'

4.4.1.1.10 sphere

Creates a 3D sphere as a new graphical object ('grob' or 'mesh'). This sphere can be generated both as a solid object or as a simpler wire representation. The name of the sphere can be defined in the 'BoxName' field.

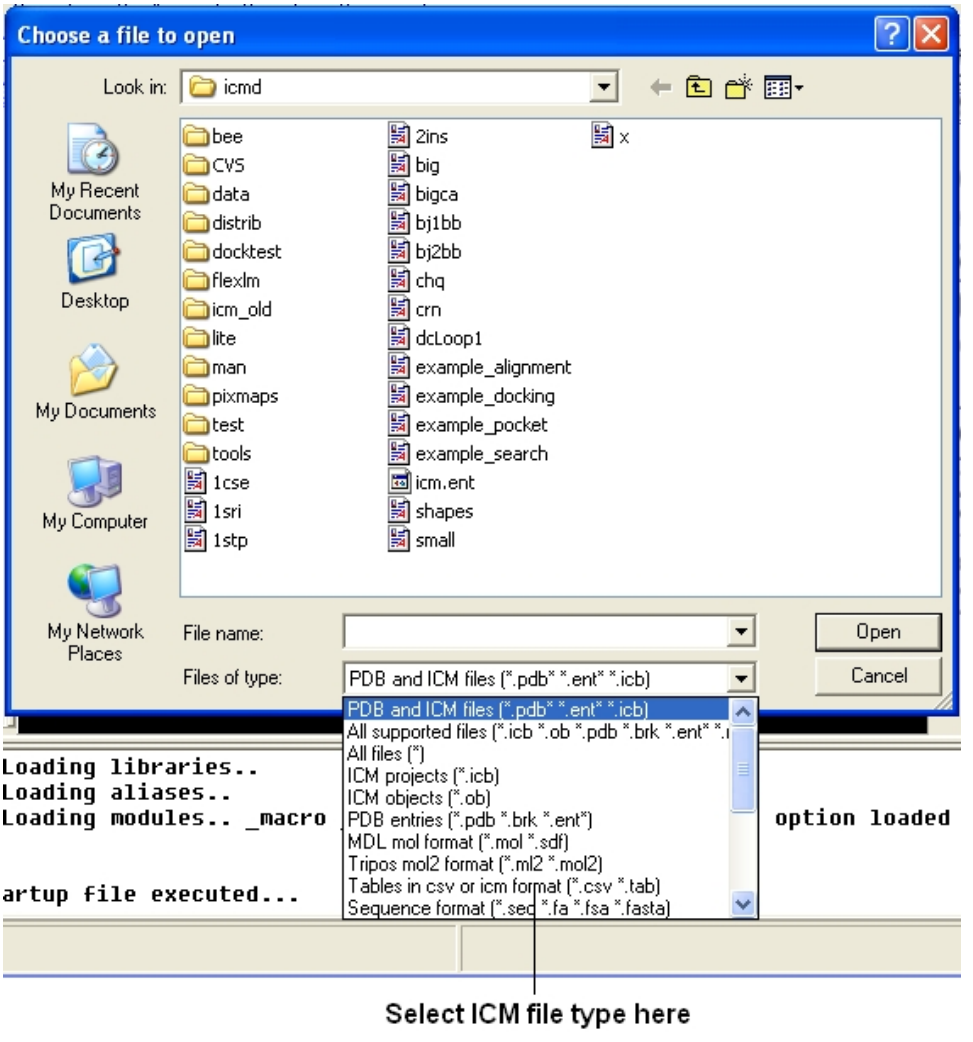
Dimensions of the sphere (X, Y, Z) are given in Angstroms and the angles connecting the sides are given in degrees. Color can be assigned by simply clicking on the desired one or using rgb scale (eg. for red: rgb={1. 0. 0.}).

Tip: the arrow can be moved independently using 'connect'

4.4.1.2 Open

Any file that ICM can understand can be opened by:

- Selecting File/Open.



4.4.1.3 Open with Password

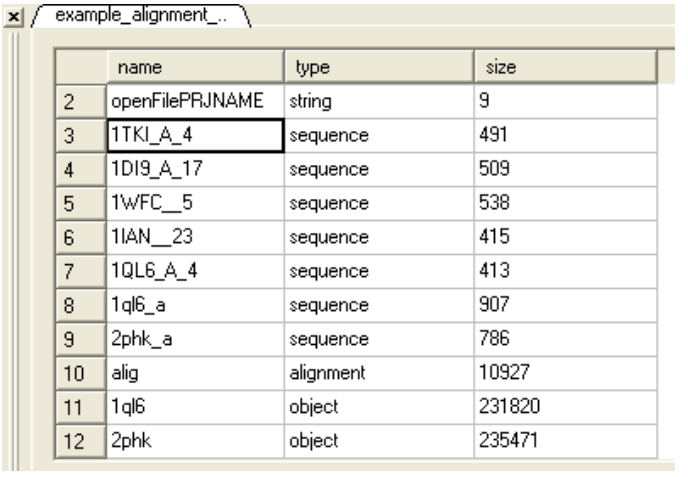
To open a file that is password `protected`:

- File/Open with Password

4.4.1.4 Extract from ICB

An **icb** file is an `icm project file` and this option allows you to view a tabulated list of what the icb file contains.

- File/ Extract from ICB
- Locate the saved icb file.
- A table as shown below will be displayed
- Double−click on any of the entry to extract that item from ICB



	name	type	size
2	openFilePRJNAME	string	9
3	1TKI_A_4	sequence	491
4	1DI9_A_17	sequence	509
5	1WFC__5	sequence	538
6	1IAN__23	sequence	415
7	1QL6_A_4	sequence	413
8	1ql6_a	sequence	907
9	2phk_a	sequence	786
10	alig	alignment	10927
11	1ql6	object	231820
12	2phk	object	235471

4.4.1.5 Convert to Local Database

Please see the `Local Databases` chapter for more information about this option.

#endif

4.4.1.6 Load

Options contained within the menu File/Load

PDB − read PDB from FTP, http, and local PDB

From Multiple Object File − A multiple object file will have a file extension *.ob and you can select which member of the multiple object is displayed.

PFam Alignment − PFam is a collection of multiple sequence alignments − enter FASTA ID

SwissProt − Download SwissProt sequence.

All Images from Dir − Read into ICM multiple image files png or jpg.

Electron Density Map − Download electron density map from Uppsala electron density server `http://eds.bmc.uu.se/eds/`

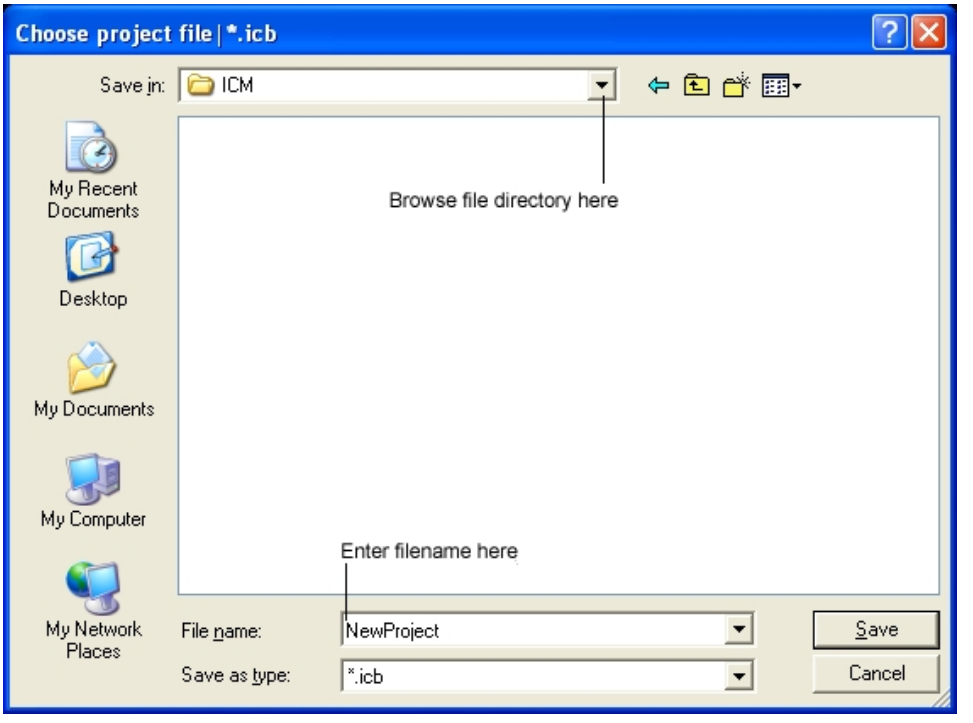
3D Mesh in KMZ or COLLADA Format from Google − see `http://sketchup.google.com/3dwarehouse/` to download KMZ or COLLADA.

4.4.1.7 Save Project

Saving a project will allow you to quit from ICM and then return to the exact set−up and display at which you left off at a later date. The projects are saved in files with the extension *.icb

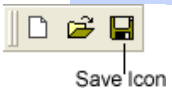
To save a project:

- Select **File/Save Project** and a data entry window will be displayed. This window will only appear if this is the first time you have saved a project.
- Enter the unique name you wish to call your project in the box labeled **File name:**



- Choose which folder or directory you wish to save your project in by scrolling down in the box labeled **Save** in:
- Once the appropriate information has been entered click on the **Save** button in the bottom right hand section of the window.
- The project is now saved as yourfilename.icb.

NOTE: An alternative way to save a project is to click on the save icon on the toolbar.



4.4.1.8 Save Project As

If you wish to re−name the project or save different versions of the same project use the **Save Project As** option.

To rename a project:

- Click on the **File/Save Project** option and a data entry window will be displayed. This window will only appear if this is the first time you have saved a project.
- Enter the unique name you wish to call your project in the box labeled **File name:**
- Choose which folder or directory you wish to save your project by scrolling down in the box labeled **Save in:**
- Once the appropriate information has been entered click on the **Save** button in the bottom right hand section of the window.
- The project is now saved as yourfilename.icb.

4.4.1.8.1 Reloading a Saved ICM Object when ICM is Running

Once an ICM object has been saved you can re−read it by:

- Click on **File/Open** and a data entry window will be displayed (below).

- Locate your saved ICM Object by clicking on the **Browse** button in the bottom right hand section of the window.

NOTE: To make your search easier you can limit the number of files you search through by scrolling down in the Open as section and selecting the appropriate file ending.

- Click on the **OK** button when the file has been located and your saved ICM Object will load.

NOTE: If the file you wish to load has been viewed recently then it will be in the drop down menu in the Open box.

4.4.1.8.2 Reloading a Saved ICM Object in Windows when ICM is not Running

To reload a saved project in Windows simply find the file in the "My Computer" file store and double−click on the icon.

4.4.1.9 Save Project Compatible with ICM 3_5

File/Save Project Compatible with ICM 3_5

Use this option to save a version of your ICM project compatible with an older version of ICM. Version 3.5 or older. If you have an ICM license you can update your version of ICM by visiting our support site at www.molsft.com/support

4.4.1.10 Save with Password

To save a project which is protected by a password:

- File/Save with Password
- Enter a file name or browse for a previously saved project.
- Enter a password
- Determine whether you want the file to be **Fully Protected**, **read only** or **Read Only and Allow Comments** .

4.4.1.11 Export as ActiceICM Html

To embed in a web browser.

1. Download ActiveICM from here `http://www.molsoft.com/getbrowser.cgi?product=activeicm(it is free!).`
2. `Create` an HTML page in ICM (File/New/Html).
3. Add a series of `slides`.
4. File/Export As ActiveICM Html..

4.4.1.12 Close Project

To close a project:

File/Close Project

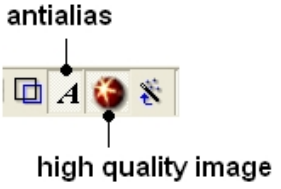
4.4.1.13 Quick Image

A quick image can be saved using this option. The image will be saved as icm1.png in the current directory in which you are working. Each subsequent image produced will be incrementally numbered.

This option is also available via a button as shown below:

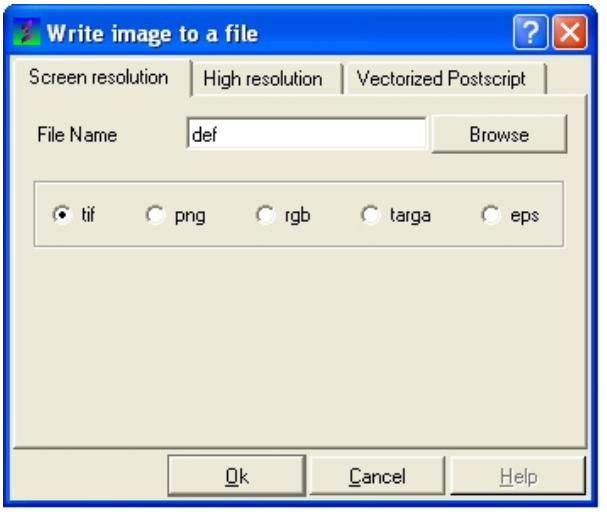
4.4.1.14 Write Image

Before saving an image it is best to improve the quality of the image using the "High Quality Image" and antialias buttons shown below.



To save and write an image:

- Select **File/Write Image** and the following window will be displayed:



- Enter the name for the picture in the **File name** data entry box.
- Select which file format you would like to save the picture in by clicking in the circular selection button next to the file types. The options are .tif; .png; .rgb; .targa .eps.
- To specify which resolution you wish the picture to be saved click on the **High resolution** button at the top of the panel.
- Click the drop down arrow in the **Resolution Increase** data entry box and select which resolution you require the picture to be. Alternatively you can type the resolution you require into this box.

NOTE: A quick way to save an image is to use the Quick Capture Graphics button on the toolbar which is described in the `Picture Tips` section of this manual.

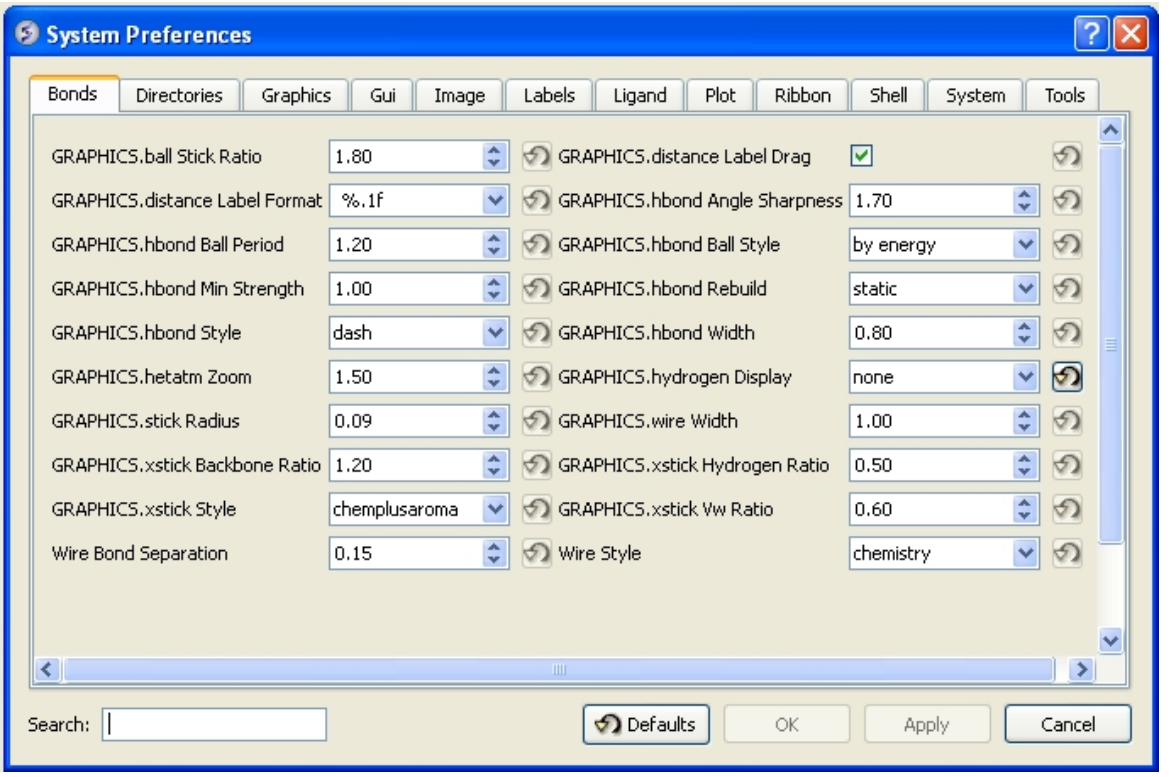
4.4.1.15 Preferences

Your ICM preferences can be changed by:

- Select File/Preferences.

NOTE: There is a "Reset to Default" button in case you make any changes you are not happy with.

4.4.1.15.1 Bonds Preferences



GRAPHICS.ballStickRatio − A default ratio of ball and stick radii. This ratio is applied when the styles are switched from the GUI xstick toolbar. Default (1.4)

GRAPHICS.hbond Ball Period − Default (3)

GRAPHICS.hbondMinStrength − parameter determines the hbond strength threshold for hbond display. The strength value is between 0. and 2. By changing 1. to 0.2 you will see more weak hydrogen bonds. Default: (1).

GRAPHICS.hbondStyle − determines the style in which hydrogen bonds are displayed. Here hbond−Donor, Hydrogen, and hbond−Acceptor atoms will be referred to as D, H and A, respectively,

GRAPHICS.hetatmZoom − The default ball and stick radii of a ligand can be different by the GRAPHICS.hetatmZoom factor. This makes a better ligand view since the ligand stands out from the surrounding protein atoms.

GRAPHICS.stickRadius − radius (in Angstroms) of a cylinder displayed as a part of stick or xstick graphical representation of a molecule. Individual (residue−wide) control of stick radii.

GRAPHICS.xstick Backbone Ratio − Default (1.2)

GRAPHICS.xstick Style − `xstick` style

wireBondSeparation the distance between two parallel lines representing a chemical double bond if wireStyle = "chemistry". Default (0.2 Angstroms).

GRAPHICS.distance Label Drag − enable distance label dragging

GRAPHICS.hbondAngleSharpness determines how the strength depends on the D−H...A(lone pair) angle. The preference can be found the general Preferences menu Default (1.7)

GRAPHICS.hbond Ball Style even, by atom size, by energy or telescopic

GRAPHICS.hbond Rebuild

GRAPHICS.hbondWidth relative width of a displayed hbond .

GRAPHICS.hydrogenDisplay determines the default hydrogen display mode for the display command.

```
GRAPHICS.hydrogenDisplay = "polar"
       1 = "all"   # all hydrogens are shown
       2 = "polar" <-- current choice  # polar displayed, the non-polar hidden
       3 = "none"  # no hydrogens are displayed
```

GRAPHICS.wire Width − relative width of wire Default (1)

GRAPHICS.xstick Hydrogen Ratio − Default (0.5)

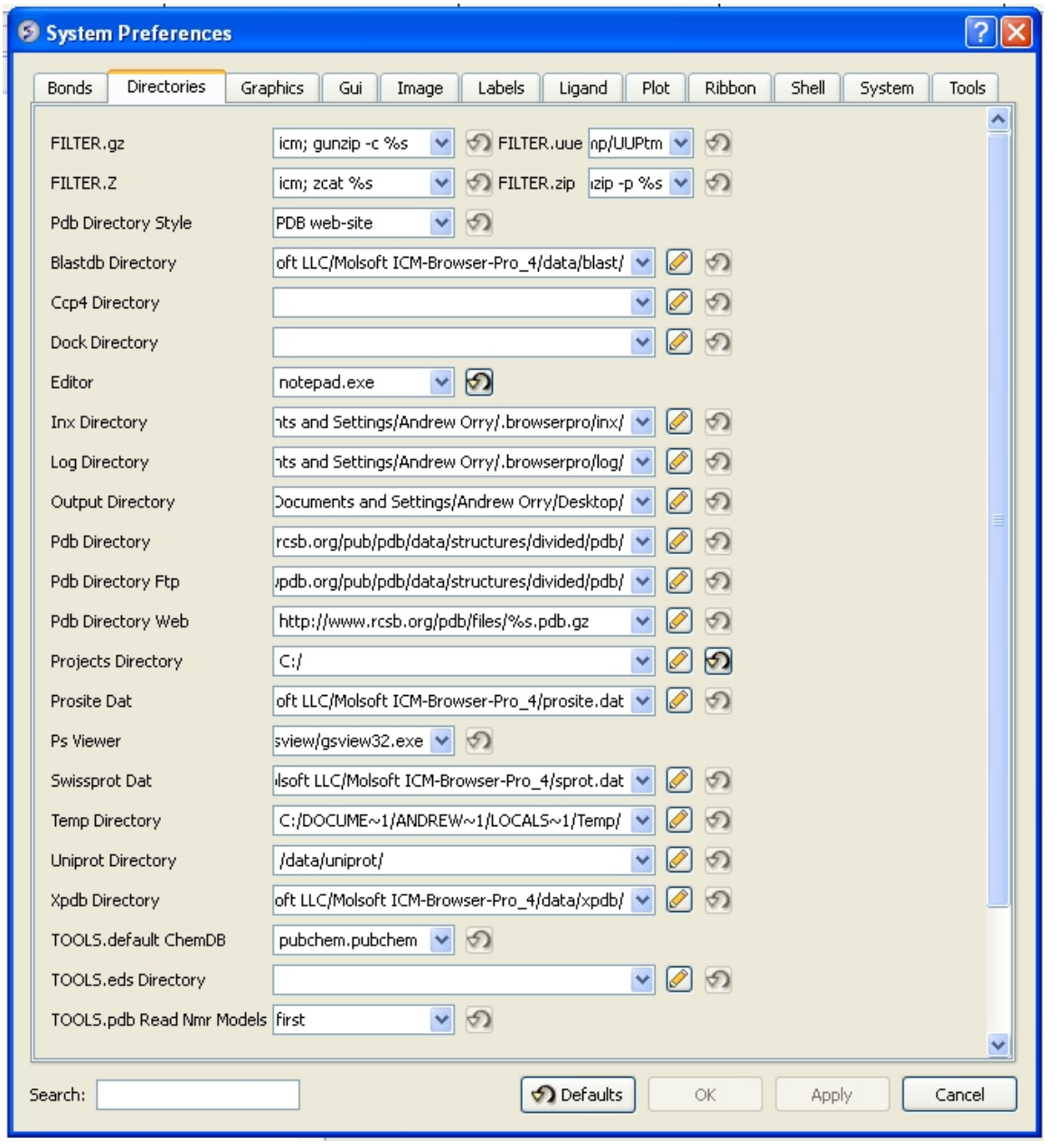
GRAPHICS.xstick Vw Ratio − Default (0.6)

Wire Style − change the default `wire` style

```
GRAPHICS.hbondStyle = "dash"
       1 = "wire"      # Just a line
       2 = "chemistry"    # shows different types of chemical bonds.
       3 = "tree"  # shows a directed graph of the ICM-molecular tree
       4 = "aromatic"  #
```

4.4.1.15.2 Directories Preferences

DIRECTORIES TAB:



Within this tab you can select the default directories for:

FILTER.gz, FILTER.uue, FILTER.Z, Filter.zip allows you to read compressed files .gz, .uue, .Z, and, .zip files automatically leaving the compressed file intact.

PDB Directory Style − The style of your Protein Data Bank directory/directories. ICM will understand all of the listed styles, including distributions with compressed *.gz , *.bz2 and *.Z fil es

BlastDB Directory − return directory with Blast−formatted sequence files for ICM sequence searches.You can download Blast formatted databases from here `ftp://ftp.ncbi.nih.gov/blast/db/`

Dock Directory − Default directory for storing docking files.

CCP4 Directory

Editor − Select a default text editor

Inx Directory − location of stored index (*.inx) files.

Log Directory − when you quit an icm−session, a _seslog.icm file is automatically stored. If the s_logDir variable is empty, it is stored to the s_userDir + "/log/" directory. However one can redirect it to the current working directory (".") or any other directory.

Output Directory −

PDB Directory − directory containing the PDB database of 3D structures. These files can also be easily downloaded directly from the PDB site if the variables are set as in the example below. PDB distributions can exist in several styles (all files in the same directory, or divided etc.).

PDB Directory FTP

PDB Directory Web

Projects Directory − Select the default location for storing ICM projects. Save your data in an ICM project. It is a convenient way of keeping all your structures, alignments, tables, docking results etc... in one place. A description on how to save an ICM project is described in the `GUI Basics` section of this manual.

Prosite Dat − location of the prosite.dat file a dictionary of protein sites and patterns, (Copyright by Amos Bairoch, Medical Biochemistry Department, University of Geneva, Switzerland).

Ps Viewer − Select a postscript viewer

Swissprot Dat − location of swissprot.dat file

Temp Directory − scratch directory for temporary files (some montecarlo files will be saved there).

Uniprot Dat − location of uniprot.dat file

XPDB Directory − Path to the ICM XPDB database of compact binary ICM objects which are annotated with the site information. The advantage of the XPDB database is the speed of reading and smaller size than PDB. XPDB entries are read about 80 times faster!

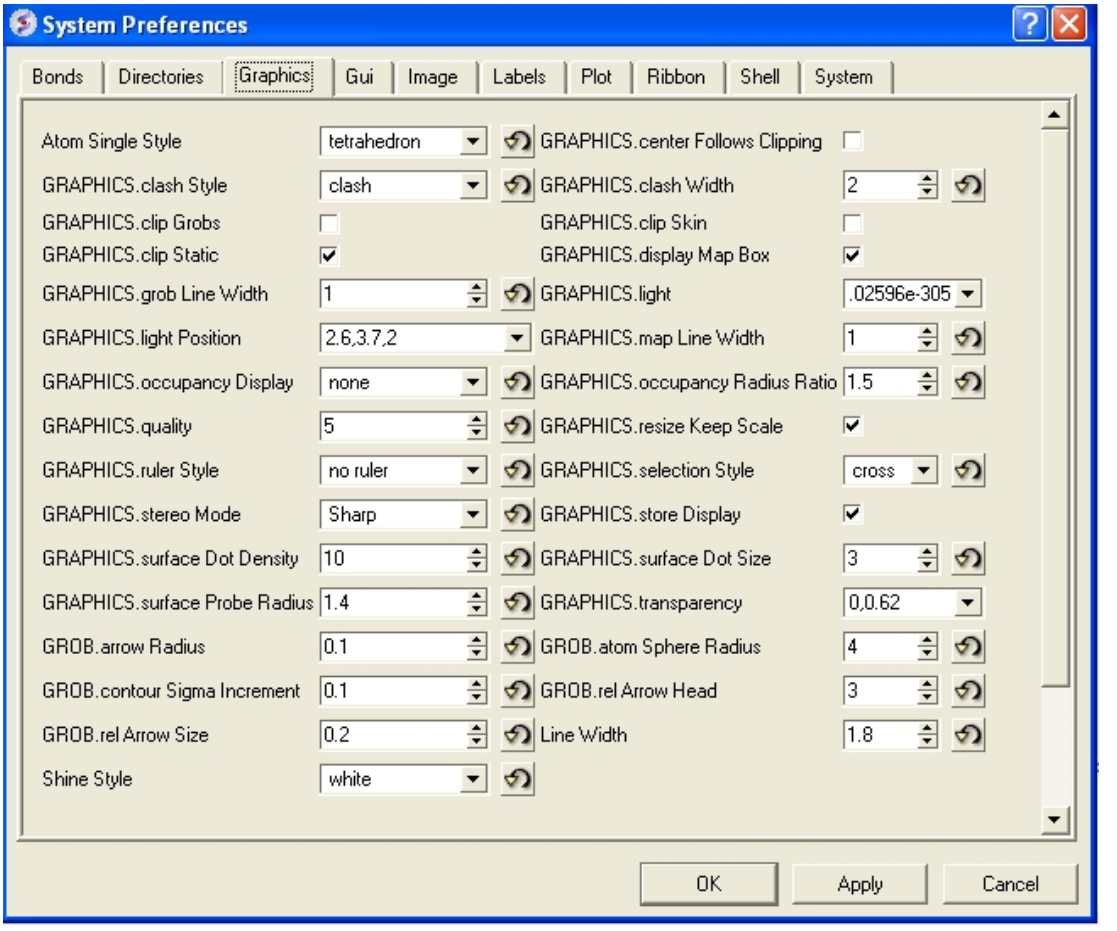
TOOLS.default ChemDB

TOOLS.eds Directory

TOOLS.pdb Read Nmr Models

```
1. = "first" : reads only one model from a multi−model (e.g. NMR) pdb file
2. = "all" : reads all models from a multi−model (e.g. NMR) pdb file and creates a separate
3. = "all stack" : creates one object and loads all other models as a stored cartesian stac
```

4.4.1.15.3 Graphics Preferences



Atom Single Style − display style of isolated atoms in the wire mode.

1. "tetrahedron"
2. "cross"
3. "dot"

GRAPHICS.clash Style − choose clash length, strain or length.

GRAPHICS.clip Grobs − enable grob clipping.

GRAPHICS.clip Static −

GRAPHICS.grobLineWidth − relative width of displayed lines of 3D meshes (grobs). Also affects the interatomic distance display.

GRAPHICS.lightPosition − X ,Y and Z posiion of the light source in the graphics window. The X and Y coordinates are usually slightly@@ beyond the [−1. 1] range where [−1.,1.] is the size of the window, and the Z position is perpendicular to the screen and is set to 2. (do not make it negative).

GRAPHICS.occupancyDisplay preference controlling if and how the partical or zero atom occupancies are displayed. The abnormal occupanices are shown as circles around atoms. These following values are allowed.

1. = "none" # nothing is displayed
2. = "circle" # a circle is displayed
3. = "label" # a circle and a lable with the value (zero values are not shown)

GRAPHICS.quality − integer parameter controlling quality (density of graphical elements) of such representations as cpk, ball, stick, ribbon . Do not make it larger than about 20 or smaller than 1.

GRAPHICS.ruler Style − change ruler from center to side

GRAPHICS.stereoMode − 1. "up−and−down", 2. "line interleaved" 3. "in−a−window"

*a simple hardware stereo mode for workstations with a horizontal frame splitter. *In the "up−and−down" mode a longer frame with two stereo images on top of each other is generated and the two halves are then superimposed with the splitter. This mode does not require anything from a graphics card, but does require a frame splitter. A frame splitter box was connected between a monitor and a graphics card output. This mode has an unpleasant side effect, the rest of the screen (beyond the OpenGl window) becomes stretched and the lower part of the screen is superimposed on the top half. *The "line interleaved" mode can be used with a new type of frame splitter at the line level. In this case the odd lines from one stereo−image are interleaved with the even lines of another. The side−effect of this mode is that the intensity is reduced in half since at each moment one sees only one half of the lines. The splitter device for this mode can be purchased from Virex (www.virex.com). This mode produces a dark stereo image but is easily available (requires stereo goggles, e.g. from Virex). *The "in−a−window" mode is used in SGI workstations and in a Linux workstation with an advanced graphics card supporting a quad graphics buffer. In this mode the hardware stereo regime applies only to an OpenGl window. This is the best mode but it requires an expensive graphics card (plus the stereo goggles).

GRAPHICS.surfaceDotDensity − Determines the number of dots per square Angstrom on the graphical solvent accessible surface.

GRAPHICS.surfaceProbeRadius − An increment to the van der Waals radii of atoms at thich the dotted atomic surface is calculated. It is used by the display surface command to display dotted van der Waals surface. If the GRAPHICS.surfaceProbeRadius is set to 1.4 the surface becames equivalent to the solvent accessible surface with a probe of 1.4A

GROB.arrowRadius − a real arrow radius in Angstoms used by the Grob("ARROW", R_) function. Default: 0.5.

GROB.contourSigmaIncrement − a real increment in the sigma level used to re−contour an electron density map using the make grob m_eds add r_increment command. This parameter is used in the GUI when plus and minus are pressed.

GROB.relArrow Size − a real ratio of the arrow head radius to the arrow radius. This parameter is used by the Grob("ARROW", R_) function. Default: 3.0.

shineStyle − defines how solid surfaces of cpk , skin and grobs reflect light. Possibilities:

1. "white" <- default
2. "color"

The first option gives a more shiny and greasy look.

GRAPHICS.center Follows Clipping − determine the function of center button.

GRAPHICS.clashWidth − relative width of a displayed clash .

GRAPHICS.clip Skin − enable skin clipping.

GRAPHICS.displayMapBox − controls if the bounding box of a map is displayed

GRAPHICS.light − a rarray of 13 elements between 0. and 1. which controls the main properties of lighting model in GL.

GRAPHICS.mapLineWidth − relative width of lines and dots of a displayed map.

GRAPHICS.occupancy Radius Ratio − preference controlling the radius of the partical or zero atom occupancies

GRAPHICS.resize Keep Scale

GRAPHICS.selectionStyle − preference for the style in which the graphical selection is shown. The preference may have the following values.

GRAPHIC.store Display − maintains representation and coloring for an object.

GRAPHICS.surfaceDotSize − Determines the size of the dot on the solvent accessible graphical surface.

GRAPHICS.transparency − Two parameters regulating the transparency of grobs.

GROB.atomSphereRadius − default radius (in Angstroms) which is used to select a patch on the surface of a grob.

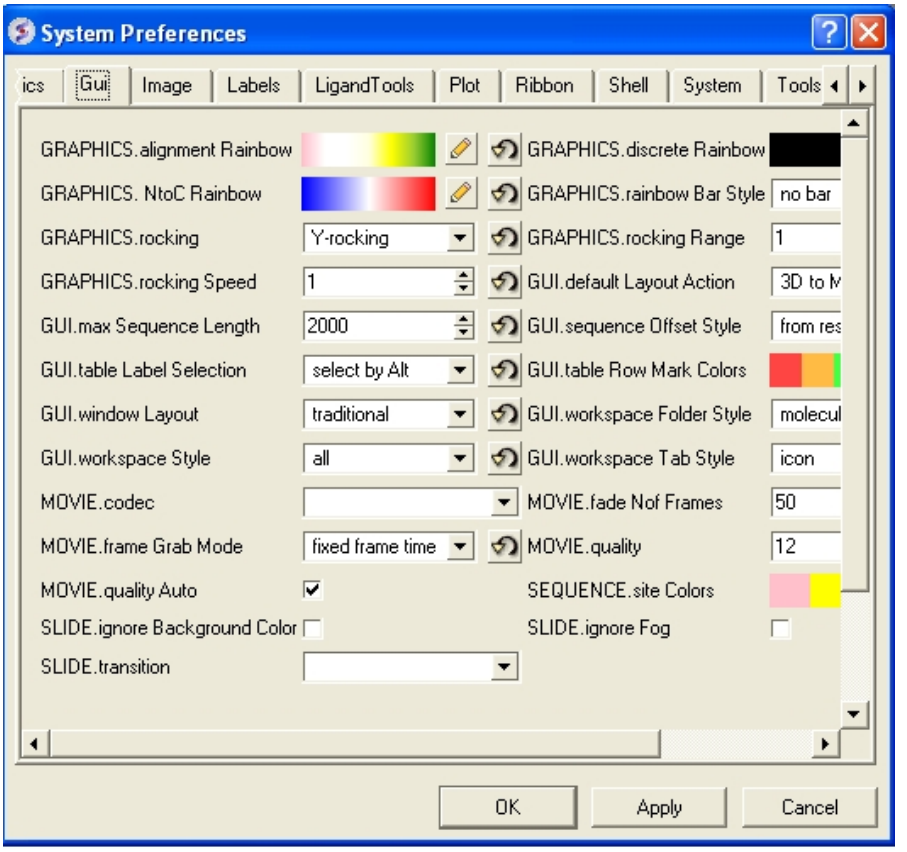
GROB.relArrowHead − a real ratio of the arrow head radius to the arrow radius.

lineWidth − the real width of lines used to display the wire representation of chemical bonds.

4.4.1.15.4 GUI Preferences

GUI TAB:

The options contained within the Preferences/Gui tab are described below.



GRAPHICS.alignment Rainbow − This option controls how alignments are colored by default.

GRAPHICS.NtoC Rainbow − Controls the coloring of structural representation from the N−terminal to the C−terminal

GRAPHICS.rocking − Controls default `rocking motion`.

GRAPHICS.rocking Speed − Controls rocking or rotation `speed`.

GUI.auto Save Interval − Controls auto save period (minutes)

GUI.table Row Mark Colors − Controls colors used for `marking tables`.

GUI.workspaceTabStyle − Controls the style of ICM−object tabs created in the `workspace panel` of ICM GUI.

Movie.fade Nof Frames − Controls number of frames for the fade out option in `screenshot movie` making.

Movie.quality − Controls the resoltuion of the movie

SEQUENCE.site Colors − Controls coloring of squence sites.

SLIDE.ignore Fog − Fog representations can be ignored in `slide` preparation if desired.

GRAPHICS.discrete Rainbow −

GRAPHICS.rainbow Bar Style − determines if and where the color bar will appear after a molecule is colored by an array.

GRAPHICS.rocking Range − real value of rocking range.

GUI.auto Save − auto save on or off

GUI.max Sequence Length − maximum sequence length displayed in ICM

GUI.workspace Folder Style − `Workspace` folder style.

MOVIE.frame Grab Mode − with `screenshot movie` making you can choose either fixed frame time or real time.

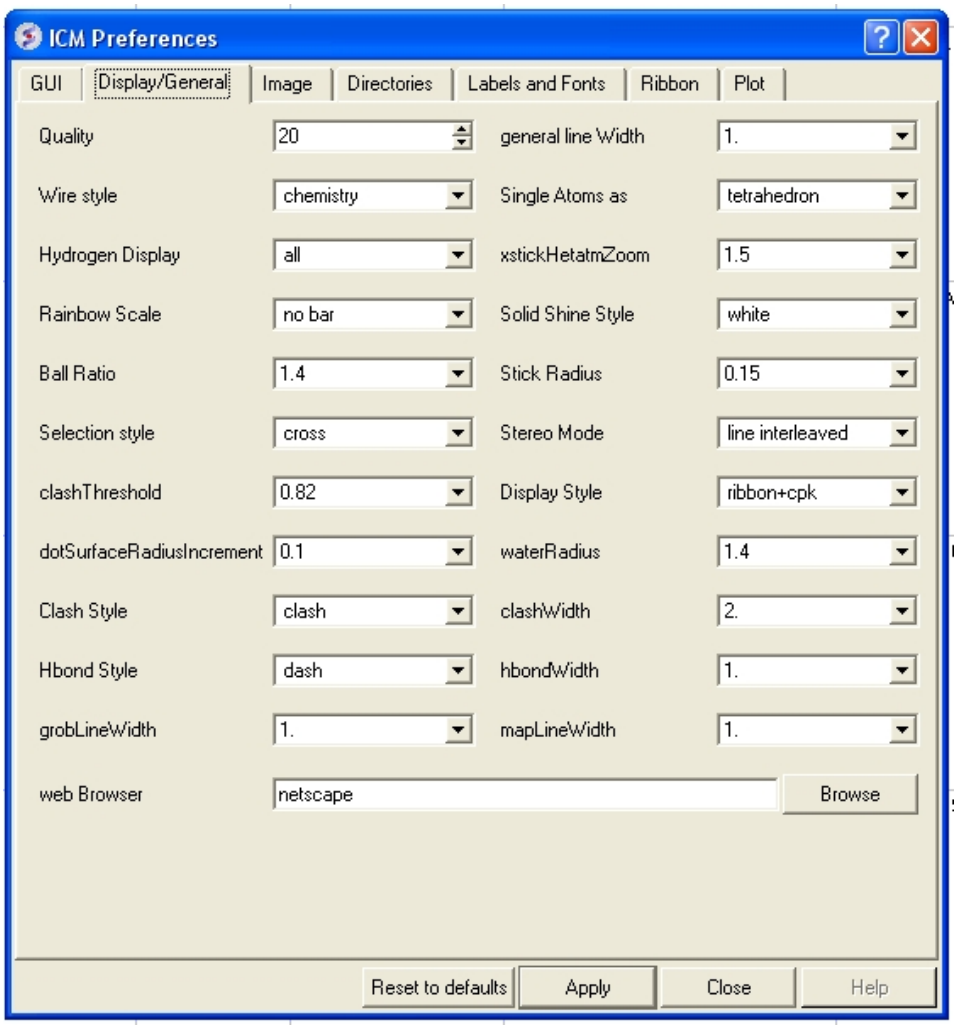
Movie.quality Auto − with `screenshot movie` making you can allow ICM to control the movie resolution.

SLIDE.ignore Background Color − Ignore background color when you are making a `slide`.

4.4.1.15.5 General Preferences

DISPLAY/GENERAL TAB:

Here is a summary of the important options in the DISPLAY/GENERAL Preferences Tab.



Quality − controls the quality (density of graphical elements) of such representations as cpk, ball, stick, ribbon . Do not make it larger than about 20 or smaller than 1. We recommend to make this parameter at least 15 if you want to make a high quality image. You can also increase the number of image resolution by making the image window 2,3,4 times larger (in the example below it is 2 times larger) than the displayed window.

Wire Style − Four different wire styles are available.

Hydrogen Display − Select whether you always want all hydorgens displayed or just−polar hydrogens or no hydrogens at all.

Rainbow Scale − determines if and where the color bar will appear after a molecule is colored by an array. Coloring by an array is one of the options of the display and color commands.

```
1. = "left" <- default choice
2. = "right"
3. = "no text"
4. = "no bar"
```

Ball Ratio − The ratio of ball and stick radii. This ratio is applied when the styles are switched to xstick from the GUI xstick toolbar.

Selection Style − Change the graphical display of your selections. Default is a green cross.

Clash Threshold − a clash is defined as an interatomic distance less than a sum of van der Waals radii of two atoms of interest multiplied by the clashThreshold parameter. For hydrogen bonded atoms, the distance threshold is additionally reduced by 20% . Default = 0.82

DotSurfaceRadiusIncrement − adius of a probe sphere used to display a dotted surface of a molecule. All van der Waals radii are expanded by this value. vwExpand=0 corresponds to the CPK surface, vwExpand=1.4 corresponds to the water−accessible surface. Be aware of the difference between the waterRadius and vwExpand parameters: waterRadius is used in

- show energy "sf"
- show [area|volume] skin
- display skin while vwExpand is used in
- show [area|volume] surface
- display surface

Default (1.4).

H Bond Style − How do you wish your H−Bonds to be displayed by default? Dashes, Bond Length, Bond Lenght and Angle.

grobLineWidth − relative width of displayed lines of 3D meshes (grobs). Also affects the interatomic distance display.

general line with − the real width of lines used to display the wire representation of chemical bonds. See also IMAGE.lineWidth parameter which controls line thickness in molecular images generated by the write postscript command, and the PLOT.lineWidth which controls the width for the plot command. Default (1.0)

single atom as − display style of isolated atoms in the wire mode.

```
1. "tetrahedron"
2. "cross"
3. "dot"
The size of the first two representation is controlled by the GRAPHICS.ballRadius parameter an
```

xstickhetatomzZoom − The default ball and stick radii of a ligand can be different. This makes a better ligand view since the ligand stands out from the surrounding protein atoms.

solid shine style − choose either white or color

Stick Radius − radius (in Angstroms) of a cylinder displayed as a part of stick or xstick graphical representation of a molecule. Individual (residue−wide) control of stick radii.

Stereo Mode − Select a default stereo mode

Display Style − A default display style can be chosen using a combination of styles.

Water Radius − radius of water sphere which is used to calculate an analytical molecular surface (referred to as skin) as well as the solvent−accessible surface (centers of water spheres).

clashWidth − relative width of a displayed clash.

hbondWidth − relative width of hydrogen bond display

mapLineWidth − relative width of lines and dots of a displayed map.

4.4.1.15.6 Image Preferences

IMAGE TAB:

Here is a summary of the important options in the IMAGE Preferences Tab.

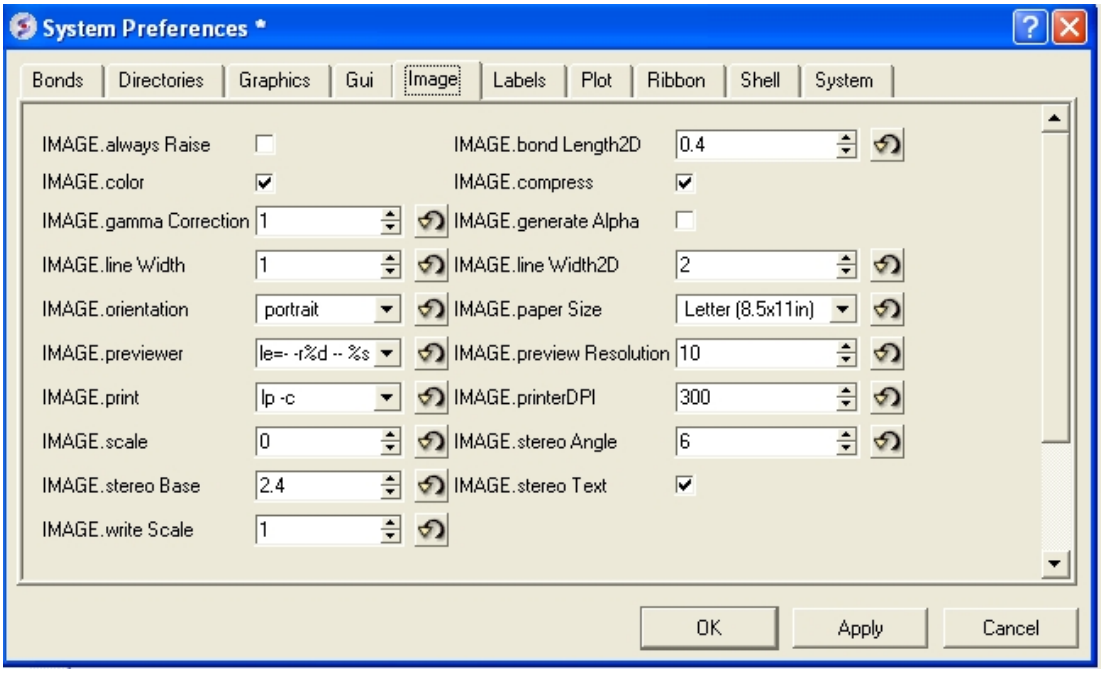


IMAGE.color − logical to save color or black_and_white ('bw') images.

IMAGE.gammaCorrection − real variable to to lighten or darken the image by changing the gamma parameter. A gamma value that is greater than 1.0 will lighten the printed picture, while a gamma value that is less that 1.0 will darken it.

IMAGE.lineWidth − this real parameter specifies the default line width for the postscript lines.

IMAGE.orientation − image orientation.

IMAGE.previewer − a string parameter to specify the external filter which creates a rough binary (pixmap) postscript preview and adds it to the header of the ICM−generated high resolution bitmap or vectorized postscript files saved by the write image postscript, and write postscript , respectively .

IMAGE.print − unix command for printer.

IMAGE.scale − real variable. If non zero, controls the image scale with respect to the screen image size.

IMAGE.stereoBase − real variable to define the stereo base (separation between two stereo panels) in the write image postscript and write postscript command.

IMAGE.writeScale − an integer parameter used to increase the image resolution in the `Quick Image Write tool`.

IMAGE.bondLength2D − real length of a chemical bond (in inches) in chemical 2D drawings upon the Copy Image command.

IMAGE.compress − logical to toggle simple lossless compression, standard for .tif files. This compression is required to be implemented in all TIFF−reading programs.

IMAGE.generateAlpha − logical to toggle generation of the alpha (opacity) channel for the SGI rgb, tif and png image files to make the pixels of the background color transparent.

IMAGE.lineWidth2D − integer thickness of bonds in chemical 2D drawing upon the Copy Image command. This is useful for cutting and pasting from ICM to external documnents.

IMAGE.paper Size − specify paper size.

IMAGE.previewResolution − integer resolution of the rough bitmap preview added to the vectorized postscript file in lines per inch.

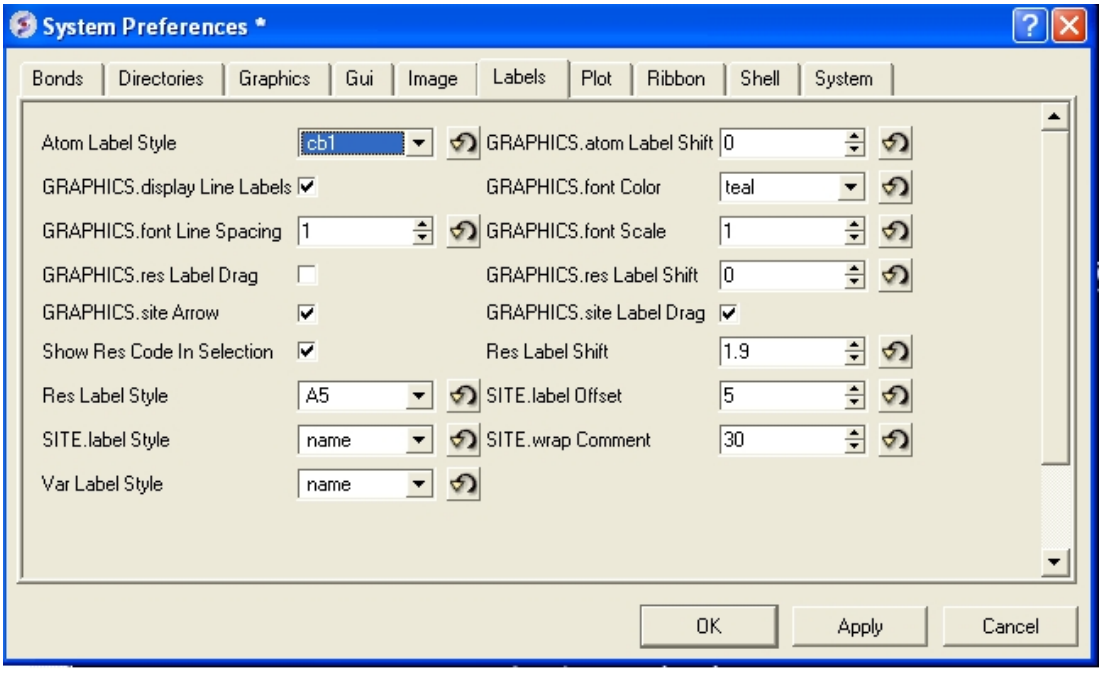
IMAGE.printerDPI − this integer parameter the printer resolution in Dot Per Inch (DPI). Important for the write image postscript command.

IMAGE.stereoAngle − real variable to define stereo angle (relative rotation of two stereo images) in the write image postscript and write postscript command.

IMAGE.stereoText − logical to make text labels for only one panel or both panels of the stereo diagram.

4.4.1.15.7 Font Preferences

LABEL FONT TAB:



atomLabelStyle style of atom labels invoked by clicking on an the `atom label button`.

GRAPHICS.displayLineLabels − enables/disables the display of edge lengths (inter−point distances) of a grob generated with the Grob("distance" ..) function.

GRAPHICS.font Line Spacing − Change the spacing between lines in labels.

GRAPHICS.resLabelDrag − if yes, enables dragging of the displayed residue labels with the middle mouse button.

GRAPHICS. site Arrow − Highlight sites with an arrow yes or no.

Show Res Code In Selection − When you make a selection the icm selection language will be displayed when you right click on the selection.

Res Label Style − Default `residue label` style.

SITE.label Style − Default `label sites` style.

Var Label Style − Default `label variable` style.

GRAPHICS.atomLabelShift − a non−negative integer number of spaces preceding an atom label. This parameter is useful for displaying labels next to a solid representation,

GRAPHICS.fontColor − set font color

GRAPHICS.font Scale − set font size

GRAPHICS.site Label Shift − GRAPHICS.resLabelShift a non−negative integer number of spaces preceding a site label.

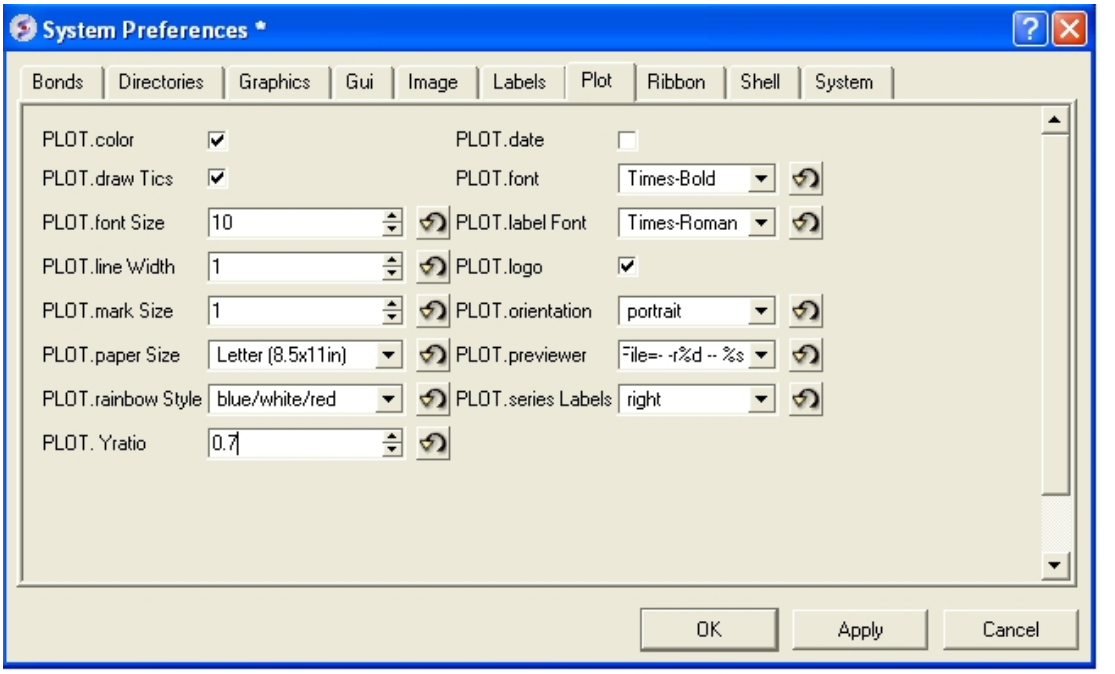
GRAPHICS. site Label Drag − if yes, enables dragging of the displayed site labels with the middle mouse button.

Res Label Shift − a non−negative integer number of spaces preceding a residue label. This parameter is useful for displaying residue labels next to a solid

SITE.labelOffset − (default 5. A) the real offset of the site label with respect to the residue label atom.

SITE.wrap Comment − Number of characters per comment line.

4.4.1.15.8 Plot Preferences



PLOT.color − logical to generate a color plot. Usually it does not make sense to switch it off because your b/w printer will interpret the color postscript just fine anyway.

PLOT.draw Tics logical yes or no

PLOT.fontSize real font size. Any reasonable number from 3. (1 mm, use a magnifying glass then) to 96.

PLOT.lineWidth − real line width for graphs (not the frame and tics)

PLOT.markSize − real mark size in points. Allowed mark types: line, cross, square, triangle, diamond, circle, star, dstar, bar, dot, SQUARE, TRIANGLE, DIAMOND, CIRCLE, STAR, DSTAR, BAR. Uppercase words indicate filled marks.

PLOT.paper Size − preference to specify plor paper size

PLOT.rainbowStyle − preference defining the color spectrum used by the plot area command.

PLOT.Yratio − real aspect ratio of the ICM plot frame. Using link option of the plot command is equivalent to setting this variable to 1.0. If PLOT.Yratio is set to 0. , the ratio will be set automatically to fill out the available box optimally.

[PLOT.date} − display date on plot

PLOT.font − preference for the title/legend font.

PLOT.labelFont − preference for the data point label font.

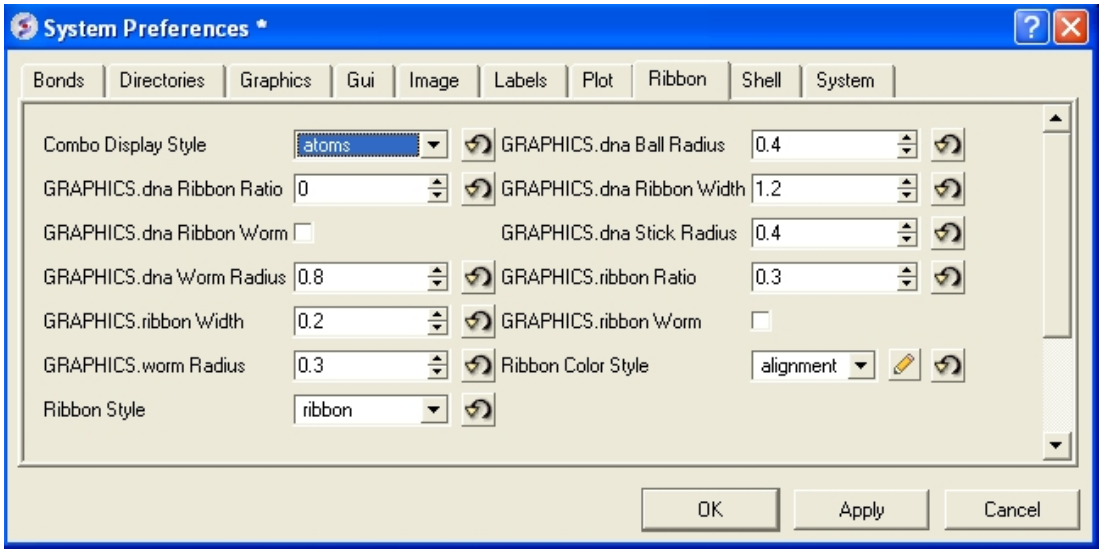
PLOT.logo − logical switch for the ICM−logo on the plot.

PLOT.orientation − preference for the plot orientation.

PLOT.previewer − command to local ps viewer

PLOT.seriesLabels − preference to indicate position of a series/color legend inside the plot frame.

4.4.1.15.9 Ribbon Preferences



Combo Display Style − select ribbon−cpk, atoms, ribbon−ligand, chemical

GRAPHICS.dnaRibbonRatio − real ratio of depth to width for the DNA ribbon .

GRAPHICS.dnaRibbonWorm − logical which, if yes, makes the DNA backbone ribbon round, rather than rectangular. Default: no

GRAPHICS.dnaWormRadius − real radius of the worm representing bases in DNA ribbon .

GRAPHICS.ribbonWidth − real width of the protein ribbon .

GRAPHICS.wormRadius − radius of coiled segments (i.e. those where the secondary structure is marked as "_") of a polypeptide chain in ribbon representation. Default (0.3).

Ribbon Style − specifies default style when `ribbon` is displayed.

GRAPHICS.dnaBallRadius − DNA bases in ribbon representation are shown as balls controlled by this real parameter.

GRAPHICS.dnaRibbonWidth − real width (in Angstroms) of the DNA ribbon .

GRAPHICS.dnaStickRadius − real radius of the sticks representing bases in DNA ribbon .

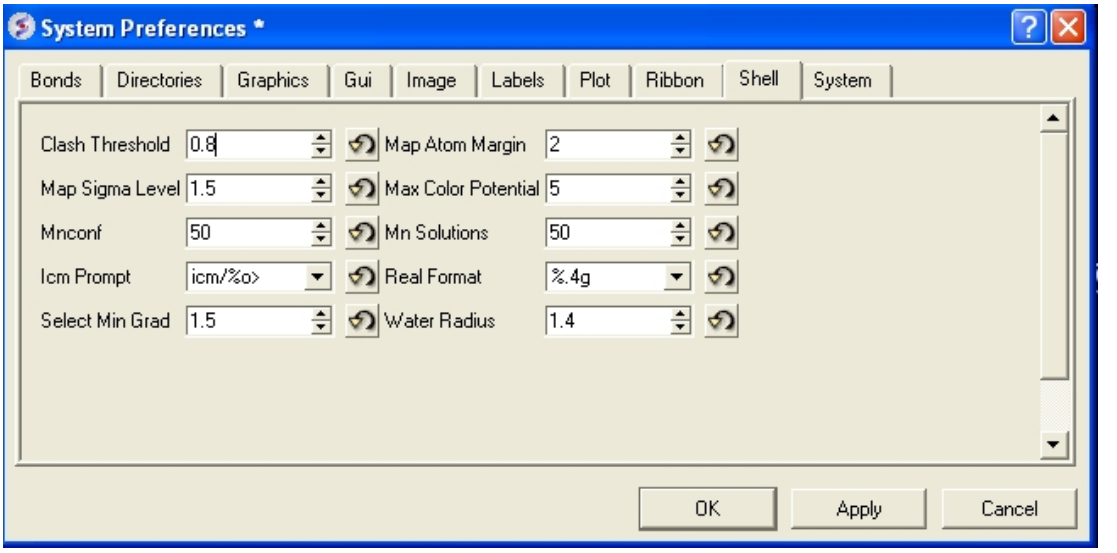
GRAPHICS.ribbonRatio − real ratio of depth to width for the protein ribbon .

GRAPHICS.ribbonWorm − logical parameter, if yes, makes the ribbon round, rather than rectangular.

ribbonColorStyle −

```
- sets the ribbon coloring scheme.
1 = "type"      default. colors by secondary structure type or explicit color
2 = "NtoC"      colors each chain gradually blue-to-red from N- to C- (or from 5' to 3' for DN
3 = "alignment" if there is an alignment linked to a protein, color gapped backbone regions gr
4 = "reliability"       3D gaussian averaging with selectSphereRadius of alignment strength in
If ribbonColorStyle equals to 4, the conserved areas will be colored blue, while the most dive
```

4.4.1.15.10 Shell Preferences



Clash Threshold − a clash is defined as an interatomic distance less than a sum of van der Waals radii of two atoms of interest multiplied by the clashThreshold parameter.

Map Sigma Level − (in Rmsd values over the mean value). Margin value used for making graphical objects contouring the 3D density map .

Mnconf − maximal number of conformations in the conformational stack . The stack stops growing after this number is achieved and starts replacing representative conformations with higher energy values by new conformations with superior energies, if the latter are found.

Icm Prompt − defines the ICM−prompt string.

Select Min Grad − default minimal gradient vector length for gradient atom selection (a_//G). This parameter is also used by the montecarlo fast command, which requires a value of 2. to 10. for optimal performance.

Map Atom Margin − Margin in Angstoms around selected atoms. The margin is added to the positional boundaries to define a submap index box in the Map (map_source , as_) function.

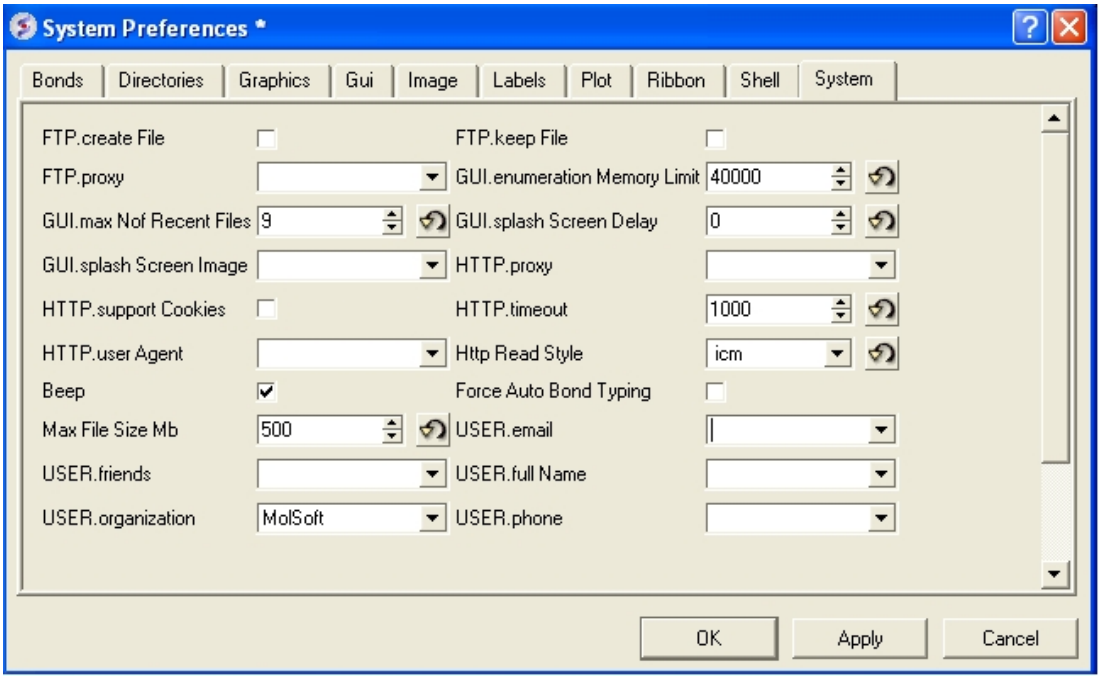
maxColorPotential − local electrostatic potential in kcal/e.u.charge units at which the surface element is colored by extreme red or extreme blue. All higher values will have the same color. This absolute scaling is convenient to develop a feeling of electrostatic properties of molecular surfaces.

mnSolutions − this parameter limits the number of hits retained by the program after a search.

Real Format − format of real numbers

Water Radius − radius of water sphere which is used to calculate an analytical molecular surface

system−preferences{FTP.createFile, FTP.proxy, GUI.max Nof Recent Files, GUI.splash Screen Image, HTTP.support Cookies, HTTP.user Agent, Beep, Max File Size Mb, USER.friends, USER.organization, FTP.keep File, GUI.enumberation Memory Limit, GUI.splash Screen Delay, HTTP.proxy, Http Read Style, Force Auto Bond Typing, USER.email, USER.full Name, USER.phone} h4−− System Preferences {System Preferences}



FTP.createFile −

FTP.proxy − string path to the proxy server for connections through firewall. Default: "" (empty string).

GUI.max Nof Recent Files − maximum number of `recent files` stored.

GUI.splash Screen Image − path to splash image displayed on startup

HTTP. support Cookies − http support cookies yes or no

HTTP.user Agent − client application used within a particular network protocol for www

Beep − warning beep yes or no

Max File Size Mb − Maximu file size in MegaBytes that can be loaded into ICM.

USER.friends

USER.organization

FTP.keep File − (default no). If yes, the temporary file is kept in the s_tempDir directory. Otherwise the file is deleted.

GUI.enumberation Memory Limit − memory limit for enumeration operations.

GUI.splash Screen Delay

HTTP.proxy − string for HTTP server for connection through firewall

HTTP.timeout − timeout in seconds

Http Read Style icm or lynx

Force Auto Bond Typing − yes/no

USER.email, USER.full Name, USER.phone

4.4.1.16 Recent Files

Recently viewed projects and files can be easily downloaded from the "Recent Files" option. To access this:

- Select File/Recent Files.
- Select the desired project by clicking on it once.

4.4.1.17 Recent PDB Codes

Quickly retrieve and display PDB structures that have recently been viewed.

- Select File/Recent PDB Codes
- Select desired PDB code by clicking on it once and it will be loaded into the graphical display.

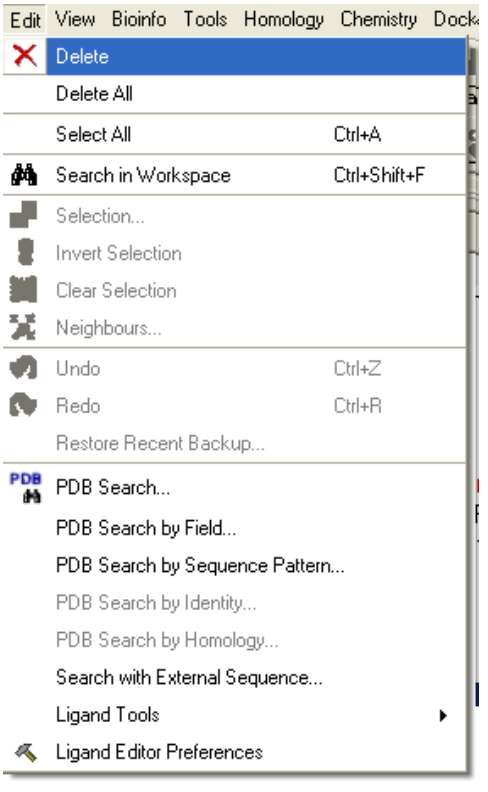
4.4.1.18 Quit

Need to close down ICM − no problem. You do one of the following:

1. Select **File/Quit.** ICM will quit without saving files.
2. Save and Click **X** at the upper right corner of the ICM window.
3. Type `quit` in the terminal window.

> **NOTE:** You may want to save the icm session as an `ICM Project file` before quiting.

4.4.2 Edit Menu



4.4.2.1 Delete

This option will delete anything that is `selected`.

4.4.2.2 Delete All

This option will delete everything e.g. sequences, structures, tables ... Use with care!

4.4.2.3 Select All

This option will select everything e.g. sequences, structures, tables...

4.4.2.4 Search in Workspace

This option allow you to search for a particular text in the workspace

4.4.2.5 Selection

This option allows you to make a precise selection either by neighbors or specifying a particular atom or neighbor. Click on the tabs to jump between selection levels.

4.4.2.6 Invert Selection

This option will select everything that is not currently selected.

4.4.2.7 Clear Selection

This option will remove all selections. For more information on selections see the `Making Selections Chapter`.

4.4.2.8 Neighbor Selection

This option will allow you to select neighboring atoms. For more information see the `Select Neighbors` section in the Selections Chapter.

4.4.2.9 Undo

Due to the complexities of working in an internal coordinates environment not everything can be undone or redone. Certain things like coloring and representations can be undone or redone.

4.4.2.10 Redo

Due to the complexities of working in an internal coordinates environment not everything can be undone or redone. Certain things like coloring and representations can be undone or redone.

4.4.2.11 Restore Recent Backup

ICM periodically makes a backup of your ICM project. If for whatever reason you lose an ICM session and you want to load the backup for the file use:

Edit/Restore Recent Backup

4.4.2.12 PDB Search

See `PDB Search Tab`

4.4.2.13 PDB Search by Field

See `PDB Search Tab`

4.4.2.14 PDB Search by Identity

See `PDB Search Tab`

4.4.2.15 PDB Search by Homology

See `PDB Search Tab`

4.4.2.16 PDB Search with External Seqeuence

See `PDB Search Tab`

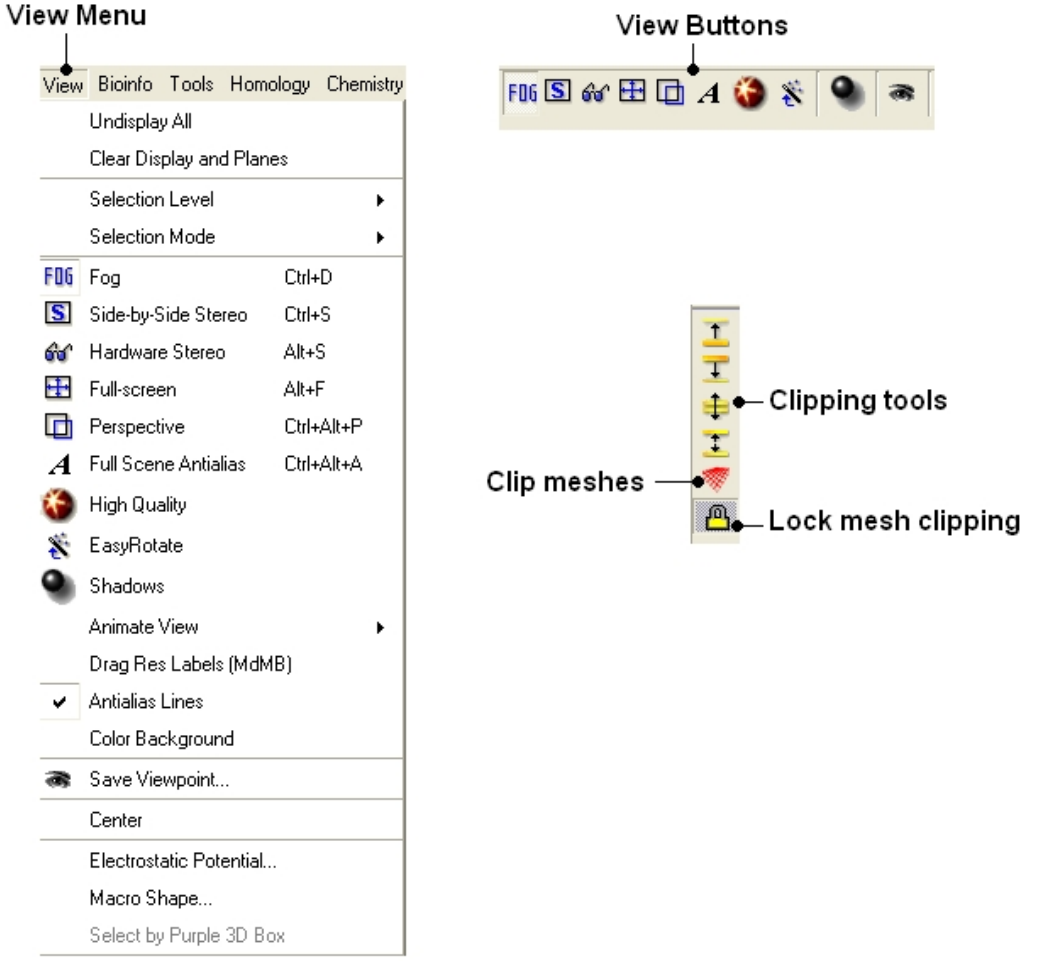
4.4.2.17 Ligand Tools

See the `ligand editor` section of the manual.

4.4.2.18 Ligand Editor Preferences

See the `ligand editor` section of the manual.

4.4.3 View Menu



4.4.3.1 Undisplay All

To undisplay everything currently displayed in the graphical display

- View/Undisplay All

> **Note** For more details on displaying structures please see the `GUI Overview` chapter.

4.4.3.2 Clear Display Planes

To clear the display and planes

- View/Clear Display and Planes

> **NOTE:** For more details on planes please see the sections on `clipping tools` and `mesh clipping`.

4.4.3.3 Selection Level

There are four levels of selection − atom, residue, molecule and object. For more details on selections please see the `Making Selections` section.

4.4.3.4 Selection Mode

There are four different ways to make selections − new, add, remove and toggle. For more details on selections please see the `Making Selections` section.

4.4.3.5 Fog

Fog Toggle(Ctrl + D) : this feature creates a fog−like environment for your object, so that the part of your structure that is closer appears clear and the distant parts are faded as if they are in fog. The `clipping planes` control the point at which the fog begins.

- View/Fog

4.4.3.6 Side−by−Side Stereo

Side−by−side stereo toggle(Ctrl + S) : this feature allows you to view your structure in 3D form without any 3D goggles.

- View/Side−by−Side Stereo

4.4.3.7 Hardware Stereo

Hardware stereo toggle(Alt + S) − if you have 3D goggles and you wish to view your structure in 3D form, this feature will allow you to do so.

- View/Hardware Stereo

4.4.3.8 Full Screen

Full screen toggle Alt_F − this makes your graphical display fill the entire screen. If you wish to exit this mode, press escape.

- View/Full Screen

4.4.3.9 Perspective

Toggle perspective Ctrl_P this will add perspective to your structure, enhancing depth in the graphical display.

- View/Perspective

4.4.3.10 Full Scene Antialias

Anti−aliasing is the technique of minimizing the distortion artifacts known as aliasing when representing a high−resolution signal at a lower resolution. Always use this option before making `high resolution images`.

- View/Full Scene Antialias

4.4.3.11 High Quality

Toggle High Quality: this option will give your ICM object better resolution and higher quality. The change in quality is most visible at a high magnification. However, if your object is very large, this feature could slow down your program.

Always use this option before making `high resolution images`.

- View/High Quality

4.4.3.12 Easy Rotate

Toggle easy rotation: this feature is necessary if your structure is very large or perhaps your computer cannot quickly `rotate` it. It will prevent your structure from fully loading each time you rotate it, therefore speeding up the process.

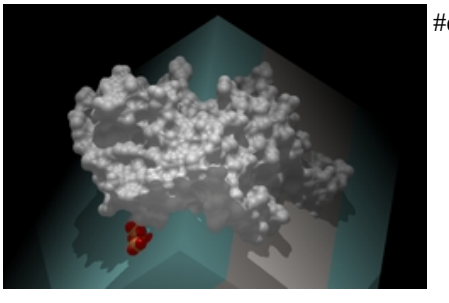
- View/Easy Rotate

4.4.3.13 Shadows

- View/Shadows

OR

select the shadow button shown below.

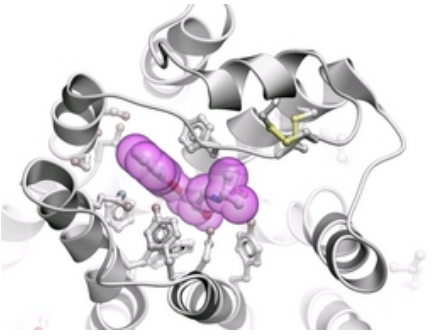


#endif

4.4.3.14 Sketch Accents

To make images as shown below use:

- View/Sketch Accents



4.4.3.15 Animate View

This tool is described in more detail in the `Molecular Animations and Transitions` section.

4.4.3.16 Drag Res Labels

To change the location of your residue label:

- Select View/Drag res labels.
- If your mouse has a middle mouse button, then click on handle (as shown) of the label you wish to move, and drag it to your desired area.

- If your mouse has no middle mouse button, then click on the Translation icon on the toolbar, and click on the handle (as shown) of the label you wish to move, and drag it to your desired area.

The +/− buttons on the side of the Residue and Atom buttons will shift the label. There are also other **residue label move** options available when you click and hold the residue label button. These options include **Shift to Sidechain Tips**, **Shift to Calphas**, and **Restore Positions**

4.4.3.17 Antialias Lines

Use this option to activate antialias lines. It is recommended to leave this option selected.

- View/Antialias Lines

4.4.3.18 Color Background

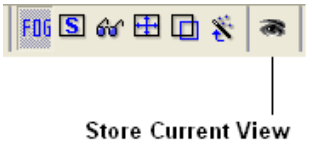
To change the background color

- View/Color Background
- Select a color from the panel and press OK.

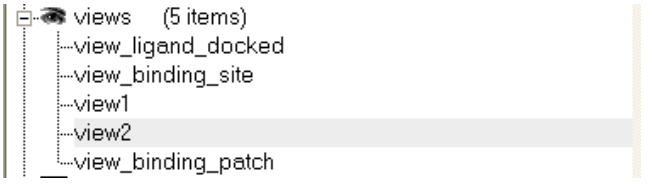
This option is also in the more convenient `display tab`.

4.4.3.19 Save Viewpoint

It is possible to store a current view using the button shown below.

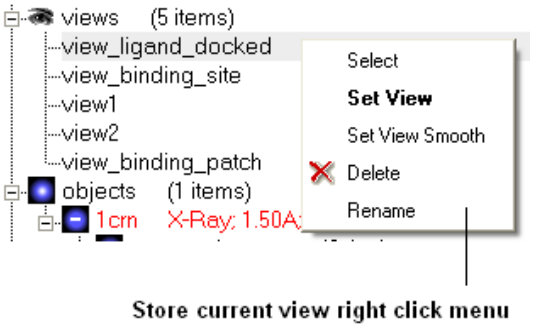


Click on the button and the current view will be stored so that you can view it later. A data entry box will be displayed asking you to name the view. All stored views can be found in the ICM workspace as shown below.



- Double click on the view in the ICM Workspace to display it.

A number of view display options are available by right clicking on the view in the ICM workspace as shown below.



The option in the right click menu called "set view smooth" returns to the view slowly showing the trajectory between the original view and the current one.

4.4.3.20 Center

To center on an object displayed in the graphical display

- Make a selection on the region on which you wish to center on.
- Tools/Center (or use the `center` button on the right hand−side of the graphical display).

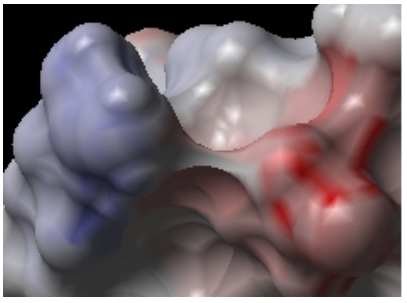
4.4.3.21 Electrostatic potential

This option generates the skin representation of the molecular surface colored according to the electrostatic potential calculated by the REBEL method (hydrogen atoms are ignored). REBEL is a method to solve the Poisson equation for a molecule. REBEL is a powerful implementation of the boundary element method with analytical molecular surface as dielectric boundary. This method is fast (takes seconds for a protein) and accurate. REBEL stands for Rapid Exact−Boundary ELectrostatics. The energy calculated by this method consists of the Coulomb energy and the solvation energy

In order to color the skin of your molecule by electrostatic potential:

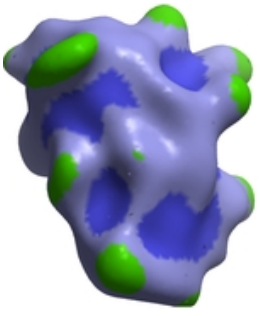
- Select **View/Electrostatic** potential.
- Enter the potential scale value. This is the local electrostatic potential in kcal/e.u.charge units at which the surface element is colored by extreme red or extreme blue. All higher values will have

the same color. This absolute scaling is convenient to develop a feeling of electrostatic properties of molecular surfaces.
- Areas colored blue represent positive areas and red represents negative areas.



4.4.3.22 Macro Shape

A macroshape allows easy viewing and manipulation of a structure. A macroshape representation is ideal for large structures which allows the user to easily identify important regions of the structure and facilitate the return to the 'standard' view of a particular molecule. The level of detail displayed in the macroshape can be controled by changing the number of harmonics, gridStep, and, contour level.



- View/Macro Shape

#endif

4.4.3.23 Select by Purple 3D Box

An alternative way to make a make−selection{selection} is to use the purple 3D box. To do this:

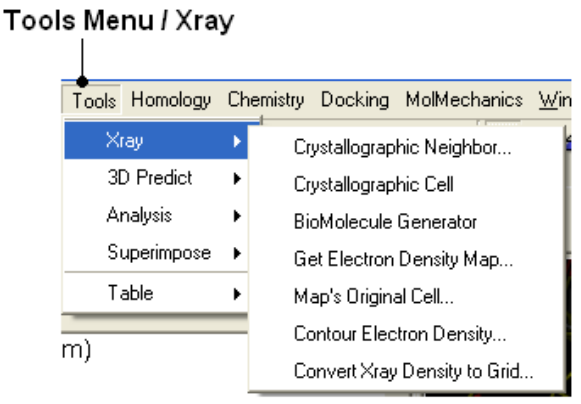
- Select the **display** tab and the purple box button
- View/ Select by Purple 3D Box
- The atoms contained within the purple box will be selected.

4.4.4 Bioinfo Menu

The tools in the Bioinfo Menu are described `here`

4.4.5 Tools Menu − Xray

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



4.4.5.1 Crystallographic Neighbor

See `Crystallographic Neighbor`

4.4.5.2 Crystallographic Cell

See `Crystallographic Cell`

4.4.5.3 Biomolecule Generator

See `Biomolecule`

4.4.5.4 Get Electron Density Map

See `Load Electron Density Map`

4.4.5.5 Map's Original Cell

See `Load Map's Original Cell`

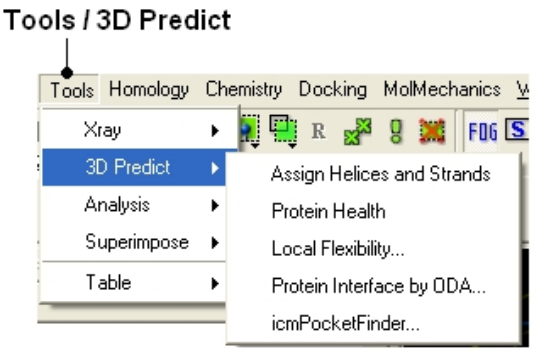
4.4.5.6 Contour Electron Density Map

See `Contour Electron Density Map`

4.4.5.7 Convert Xray Density to Grid

See `Convert Xray Density to Grid`

4.4.6 Tools Menu − 3D Predict



4.4.6.1 Assign Helices and Strands

See `Assign Helices and Strands`

4.4.6.2 Protein Health

See `Protein Health`

4.4.6.3 Local Flexibility

See `Local Flexibility`

4.4.6.4 Protein Interface by ODA

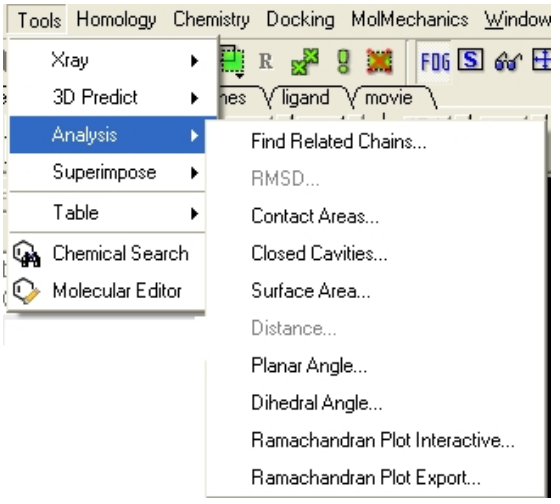
See `Predict Protein−Protein Interfaces`

4.4.6.5 icmPocketFinder

See `Identify Ligand Binding Pockets`

4.4.7 Tools Menu − Analysis

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



4.4.7.1 Find Related Chains

See `Find Related Chains`

4.4.7.2 RMSD

See `Calculate RMSD`

4.4.7.3 Contact Areas

See `Calculate Contact Areas`

4.4.7.4 Closed Cavities

See `Closed Cavities`

4.4.7.5 Surface Area

See `Surface Area`

4.4.7.6 Distance

See `Measure Distances`

4.4.7.7 Planar Angle

See `Measure Planar Angle`

4.4.7.8 Dihedral Angle

See `Measure Dihedral Angle`

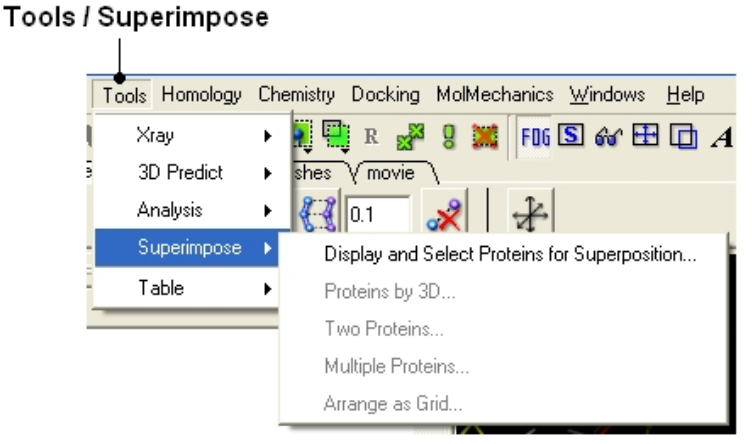
h4 −− Ramachandran Plot Interactive {Ramachandran Plot} __REQUIRES(P)

See `Ramachandran Plot`

4.4.7.9 Export Ramachandran Plot

See `Ramachandran Plot Export`

4.4.8 Tools Menu − Superimpose



4.4.8.1 Display and Select Proteins for Superposition

See `Protein Superposition`

4.4.8.2 Proteins by 3D

See `Superimpose Proteins by 3D`

4.4.8.3 Multiple Proteins

See `Superimpose Proteins by 3D`

4.4.8.4 Arrange as Grid

See `Superimpose Proteins by 3D`

4.4.9 Tools Menu − Extras

4.4.9.1 Plot Function

To plot a function:

- Tools/Extras/Plot Function
- Enter the Function(x) eg Sin(x)
- Enter the starting value of x (From).
- Enter the end point of x (To).
- Enter the number of points (N points).
- Click OK and your plot will be displayed next to a table of values for your function.

4.4.10 Tools Menu − Table

4.4.10.1 Build Prediction Model

Learn and Predict tools are described `here`.

4.4.10.2 Predict

Learn and Predict tools are described `here`.

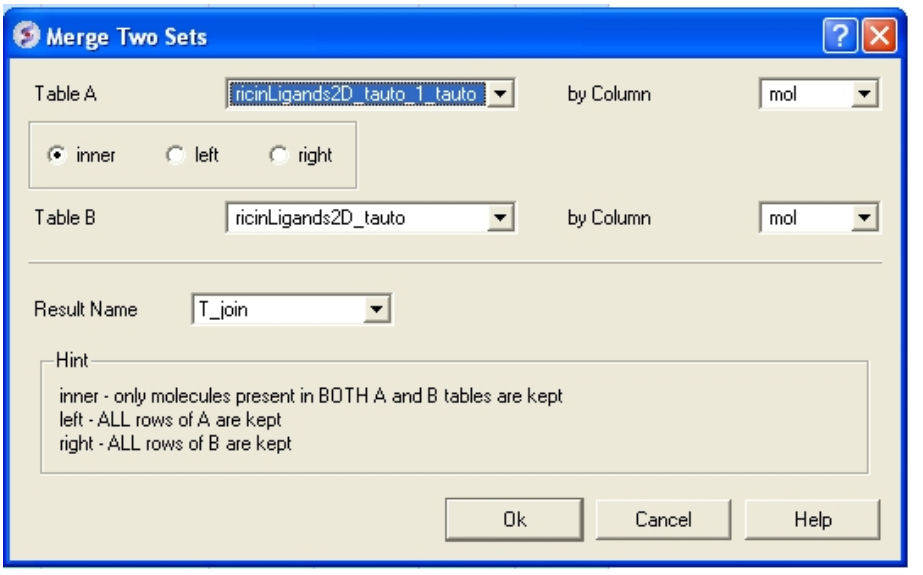
4.4.10.3 Cluster Set

This is described in the `cluster` section of the Working with Tables Chapter.

4.4.10.4 Merge Two Sets

To merge two tables:

- `Read` the two tables into ICM.
- Tools/Table/Merge Two Sets
- Select the first table from the drop down list (Table A) and the column you wish to use to merge the table by.
- Select merge method 1. **inner** − only molecules present in BOTH A and B tables are kept; or 2. **left** ALL rows of A are kept ; or 3. **right** ALL rows of B are kept.
- Select the second table from the drop down list (Table B) and the column you wish to use to mergethe table by.
- Enter a name for the output table.
- Click OK and a new table will be displayed.



4.4.10.5 Add External Columns

To add external columns to a table:

- `Read` at least two tables into ICM − the table you want to add to and the table you want to add the column from.
- Tools/Table/Add External Columns
- Enter the target table name and the column you wish to match each table by.
- Enter the source of the new column (Other table and column name)
- Choose to add "all the columns" from the source or "overwrite matching columns" or select the columns you want to add by selecting the "choose column" option.

4.4.10.6 Append Rows

To append rows from one table to another one:

- `Read` at least two tables into ICM − the table you want to add to and the table you want to add the column from.
- Tools/Table/Append Rows
- Enter the name of the Target Table (where you will append).
- Enter the name of the Source Table (where you will append from).

4.4.11 Tools Menu − Chemical Search

Chemical searching is described in the Chemistry chapter `here`.

4.4.12 Tools Menu − Molecular Editor

The molecular editor is described in the Chemistry chapter `here`.

4.4.13 Homology Menu

The options in this menu are described in the `Homology Modeling Chapter`.

4.4.14 Chemistry Menu

The tools in the **Chemistry** menu are described `here`.

4.4.15 Docking Menu

The tools in the **Docking** menu are described in the `Docking` chapter.

4.4.16 MolMechanics Menu

4.4.16.1 ICM Convert

See `Molecular Mechanics` Chapter.

4.4.16.2 Optimize H,His,Asn,Gln,Pro

See `Molecular Mechanics` Chapter.

4.4.16.3 Regularization

See `Molecular Mechanics` Chapter.

4.4.16.4 Impose Conformation

See `Molecular Mechanics` Chapter.

4.4.16.5 Edit Structure

See `Molecular Mechanics` Chapter.

4.4.16.6 MMFF

See `Molecular Mechanics` Chapter.

4.4.16.7 Minimize

See `Molecular Mechanics` Chapter.

4.4.16.8 Sample Loop

This option is described in the `Loop Modeling` section.

4.4.16.9 Generate Normal Mode Stack

See `Molecular Mechanics` Chapter.

4.4.16.10 Stack

See `Molecular Mechanics` Chapter.

4.4.16.11 GAMESS

See `Molecular Mechanics` Chapter.

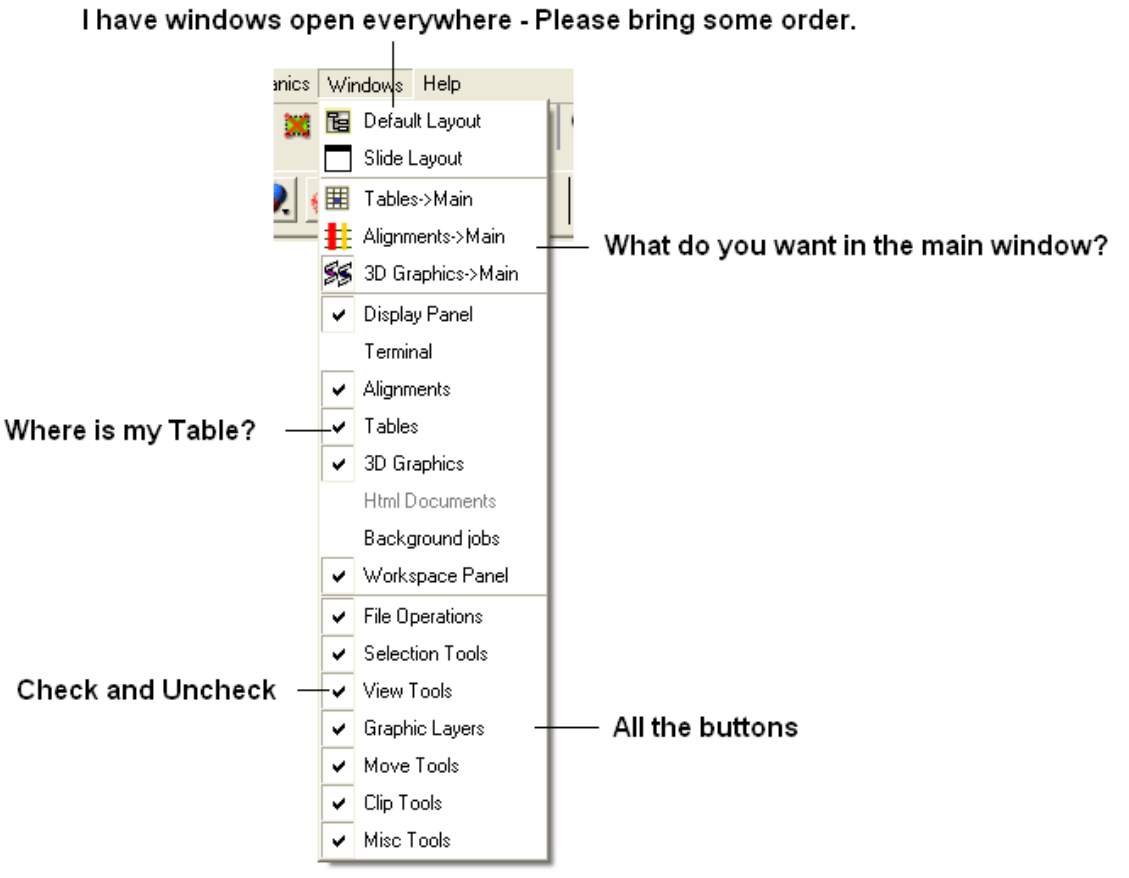
4.4.16.12 Energy Terms

See `Molecular Mechanics` Chapter. #endif

4.4.17 Windows Menu

This menu allows you to choose the windows you wish to display. The windows which open automatically when you first open GUI are shown in the Default GUI section. Other windows can be displayed by selecting the windows menu. For example, if you have loaded a table but cannot see it in the GUI it may be because the Tables option in the window menu hasnt been selected.

To add or remove windows from the GUI display select the 'window menu'. Other windows not included in the default display such as tables and alignments can be added.



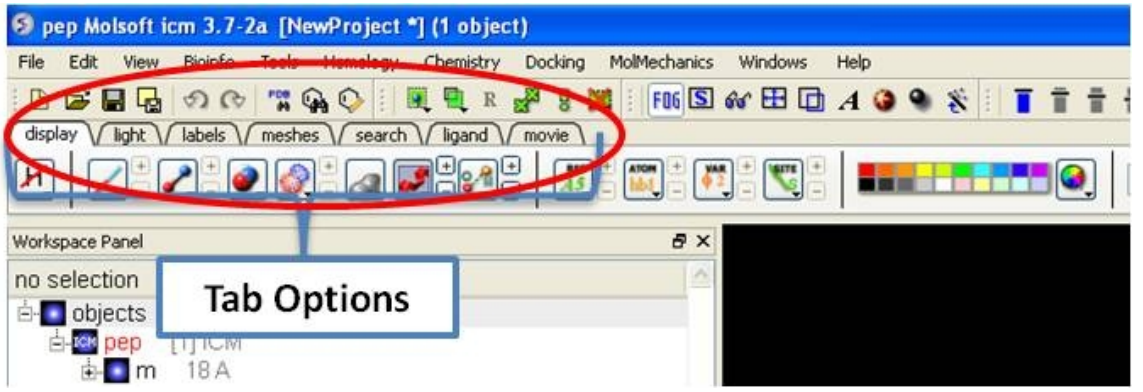
To return to the default display option select the 'Default layout' option in the windows menu.

OR

Click the default layout icon.

4.5 Tab Guide

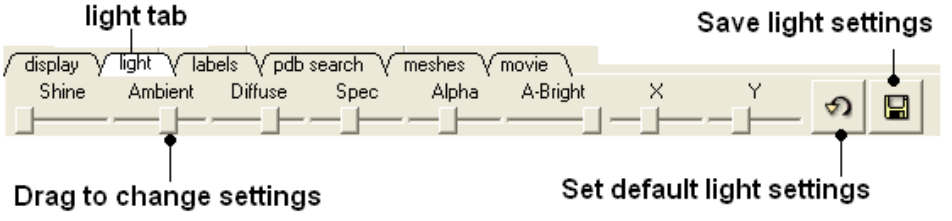
In this section we describe the contents of the tabs in the graphical user interface.



4.5.1 Display Tab

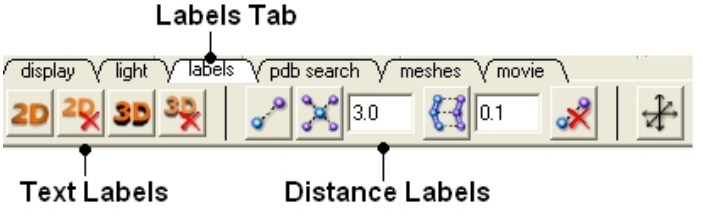
The display tab contains tools for a variety of functions including − structural `representations`, `coloring`, `labeling` and superposition. This tab is shown below.

4.5.2 Light Tab



The options in this tab are described in the `Lighting Section`.

4.5.3 Labels Tab



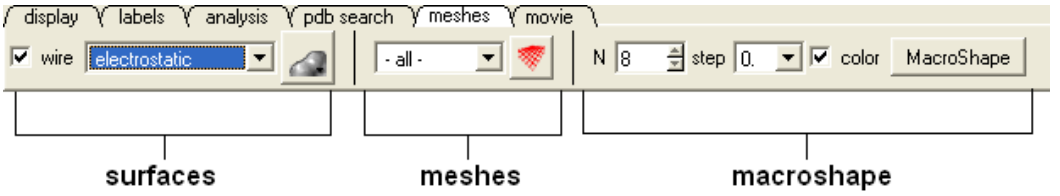
The options in this tab are described in the `labels` section of this manual.

4.5.4 PDB Search Tab

Instructions on how to use this tab can be found in the `Search PDB section.`

4.5.5 Meshes Tab

Click on the tab button entitled '**meshes**' and three different graphical display tools are available for you to use. The three displays are surface, meshes and macroshape and are collectively referred to as meshes.



The benefits and applications of each display are described in the `section`.

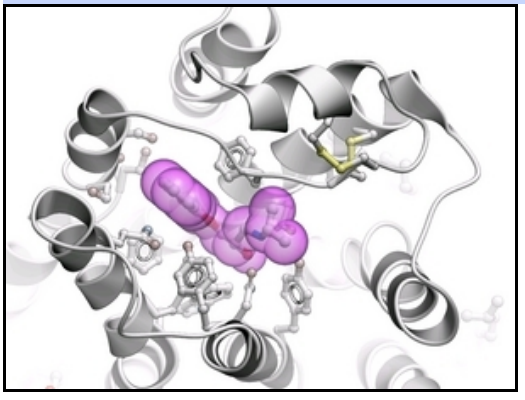
4.5.6 Movie Tab

The options in this tab are described in the `View Defined Movie Making` section of the Movie Making Chapter.

#endif

5 Working with Protein Structures

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



In this chapter we describe how to work with protein structures. We describe how to read them into ICM and display key features of the structure such as the ligand binding pocket and hydrogen bonds. We also teach how to convert a PDB file into an ICM object which is a critical operation if you want to perform any energy related task such as docking, displaying h−bonds etc...

5.1 Searching the PDB

The **PDB search tab** provides easy access to the PDB database. You can use keyword searching or type in the PDB code you are interested in. An asterisk (*) wildcard can be used to list all the pdb files currently available in the protein databank. Different fields can be searched by using the drop down arrow as shown below. More advanced PDB search tools and how to use the PDB search result table are described in the section entititled `Searching the PDB`.

Once a search is complete a table of PDB files relating to your search query will be displayed. To view the PDB file in 3D in the graphical display double click on a row in the `PDBSearchResults` table.

NOTE: If you have a PDB structure already saved you can read it into ICM by going to the File Menu and selecting Open. PDB files that have been viewed previously can be loaded using File/ Recent PDB Codes.

5.1.1 Searching the PDB

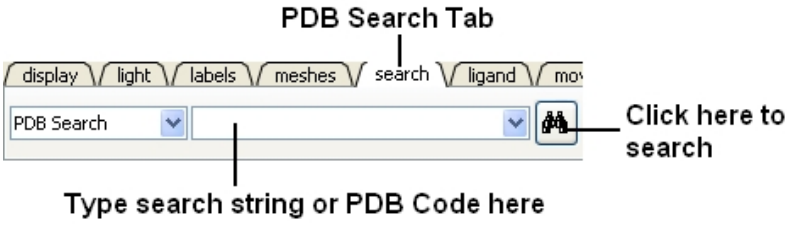
Protein structures solved by X−ray crystallography, NMR or other experimental methods are stored in the Protein Data Bank (PDB). These structures can be easily accessed, displayed and analyzed using ICM.

There are a number of different ways to find a structure from the PDB database and load it into ICM: You can query the PDB using the following options:

5.1.1.1 Query PDB by Keyword or PDB Code

Query by Keyword of PDB Code

- Click on the PDB search tab.
- Enter the PDB code or search string.
- Click on the search button to run the search.
- A list of related PDB entries based on your search will be displayed in the `PDBSearchResults table` of the graphical user interface.



Or

- Select **Edit/PDB** search and the "Find PDB Entries by Keyword" data entry window will be displayed.
- Enter a keyword or PDB code into the Keywords data entry field.
- Click the **OK** button and a list of related PDB entries based on your search will be displayed in the `PDBSearchResults table` of the graphical user interface.

NOTE: If a keyword has been entered previously it will be available by clicking on the drop−down button.

5.1.1.2 Query PDB by Sequence

To query the PDB by sequence:

- Click on the PDB search tab.
- Select the drop down arrow and select one of the following options

Seq Pattern− Enter a protein sequence and this option will tell you whether a protein structure exists in the PDB for that sequence.

Close Match− Enter a protein sequence and this option will tell you which sequences are similar to your entered sequence.

Homology− Enter a protein sequence and homologous proteins in the PDB will be displayed in a table.

- Click the **Search** button and a list of related PDB entries based on your search will be displayed in the `PDBSearchResults table` of the graphical user interface.

#endif

5.1.1.3 Query PDB by Ligand Code

To query the PDB by ligand code:

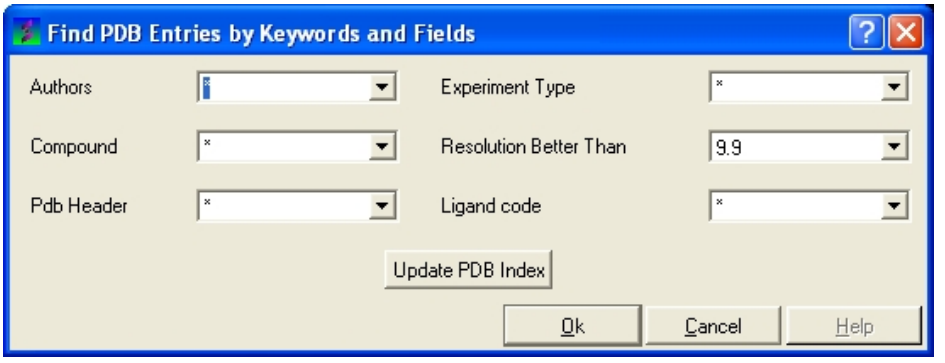
- Click on the PDB search tab.
- Select the drop down arrow and select ligand code option from the list.
- Enter the ligand code and press the search button.
- Click the **Search** button and a list of related PDB entries based on your search will be displayed in the `PDBSearchResults table` of the graphical user interface.

5.1.1.4 Query PDB by PDB Field

To query the PDB by field (Author, Compound, PDB Header, Experiment Type, Resolution or Ligand Code

- Select **Edit/PDB** search by field.
- Enter the search string or value

- Click **OK** and a list of related PDB entries based on your search will be displayed in the `PDBSearchResults table` of the graphical user interface.



5.1.2 Sensitive PDB Similarity Searches

There are two ways to search a sequence against the PDB database.

OPTION 1:

If your sequence is already loaded into ICM:

- Select **Edit/PDB Search by sensitive similarity**
- Type the sequence name into the **Sequence name** field. Sequences which are already loaded into ICM can be seen by clicking the drop−down button
- Select the number of hits you wish to see by typing the number into the Limit field. A number can also be selected by clicking on the up and down arrows. (Default is 50)
- Select the sensitivity of your search by typing a value into the Expect field. This value is a database−size error estimate and the default value is 0.01.
- Choose whether you wish to display All entries or Entries with unique sequence by checking the appropriate button.
- If you wish to load the sequences leave the Load Sequences box checked.
- If you merely want to see the PDB codes which are similar to your sequence then un−check the Load Sequences box.
- Click the **OK** button.

OPTION 2:

If your PDB sequence is not loaded into ICM:

- Select **Edit/Search with external sequence**
- Cut and paste or type (shown below) your sequence into the **Sequence** data entry field.
- Select the number of hits you wish to see by typing the number into the **Limit** field. A number can also be selected by clicking on the up and down arrows. (Default is 50)
- Select the sensitivity of your search by typing a value into the **Expect** field. This value is a database−size error estimate and the default value is 0.01.
- Choose whether you wish to display **All entries** or ** Entries with unique sequence ** by checking the appropriate button.
- If you wish to load the sequences leave the **Load Sequences** box checked.

NOTE: If you merely want to see the PDB codes which are similar to your sequence then un−check the Load Sequences box.

- Click the **OK** button.

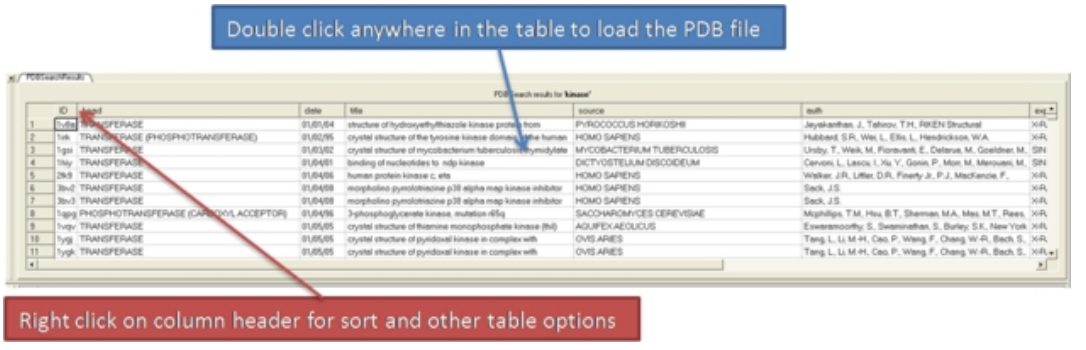
NOTE: You can also use the toolbar search option by homology if you wish.

#endif

5.1.3 PDB Search Results Table

Once you have searched for a PDB structure, a table with the search results will be displayed on the bottom of the ICM window. See the `Tables` section for more information on how to use ICM tables. See the next section `loading your PDB file` for information how to view the PDB file. More information about working with tables can be found in the `Tables Section` of this manual.

- To load a pdb file double click on the search results table.
- Sort the table by right clicking on the column header. Other table manipulation options are described in the `Working with Tables` chapter.



NOTE: In the table there are blue hyperlinks directing you to the PDB and Uniprot websites.

5.1.4 Loading Your PDB File

- To load a pdb file double click on the search results table.
- Sort the table by right clicking on the column header. Other table manipulatio n options are described in the `Working with Tables` chapter.

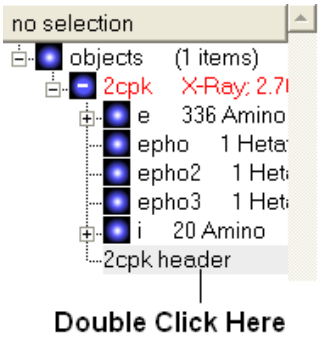
5.1.5 Hyperlinks to PDB Website and UniProt

In the PDB Search Results Table you will see blue hyperlinks that will take you directly to the PDB website or Uniprot website.

5.1.6 Display PDB Header

To display the PDB Header for a PDB file.

- First load a PDB file into ICM (see `Load PDB`)
- Double click on the word header in the ICM Workspace.



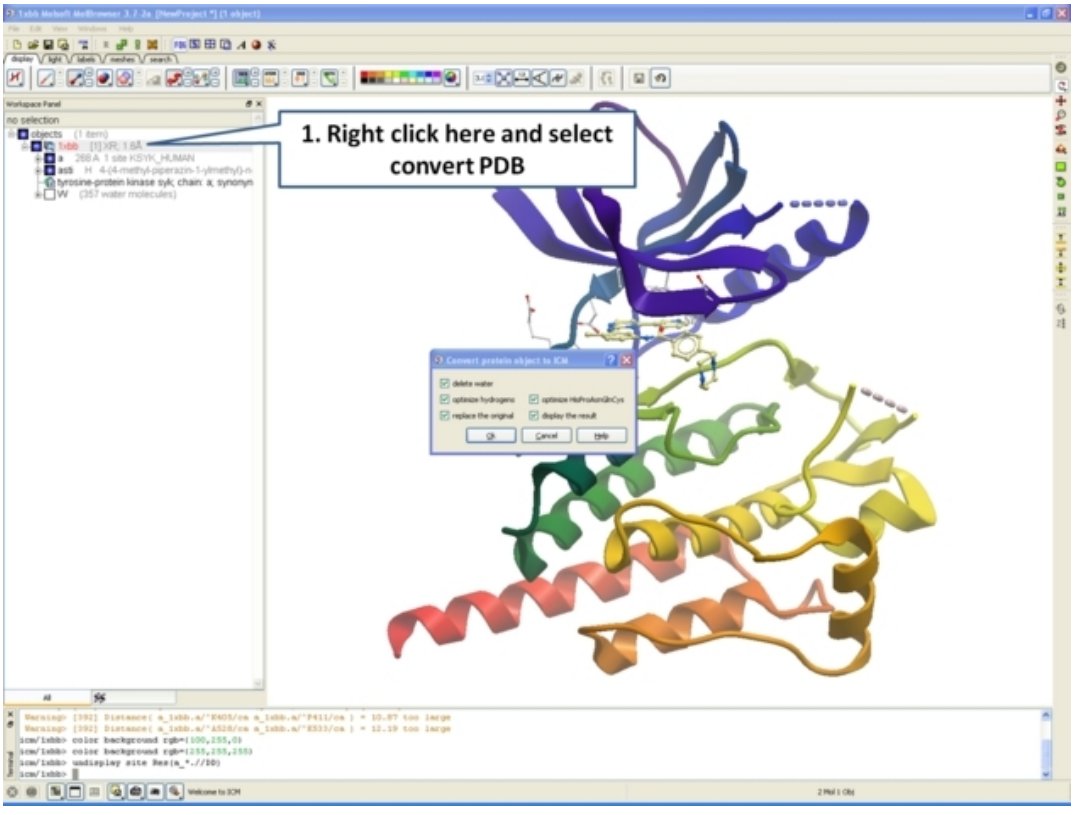
- The PDB Header information will be displayed.
- Click on the blue hyperlinked text to link to external web pages for additional information if needed.

5.2 Converting PDB Files Into ICM Objects

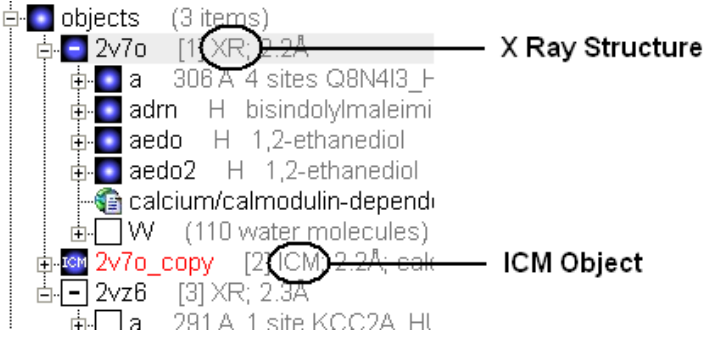
If you are going to make any energy calculation in ICM (eg docking, display H−bonds, display electrostatic and binding property surfaces etc..) it is necesary to convert a protein or chemical into an ICM object.

To convert a PDB structure into an ICM object follow the steps shown below:

- Right click on the name of the protein you wish to convert in the ICM Workspace.
- A dialog box will be displayed.Check the boxes as desired. If you are performing important calculations then it is necessary to optimize all hydrogens and ASN, GLU, PRO, and CYS.



If your object is an ICM object it will tell you in the ICM Workspace:



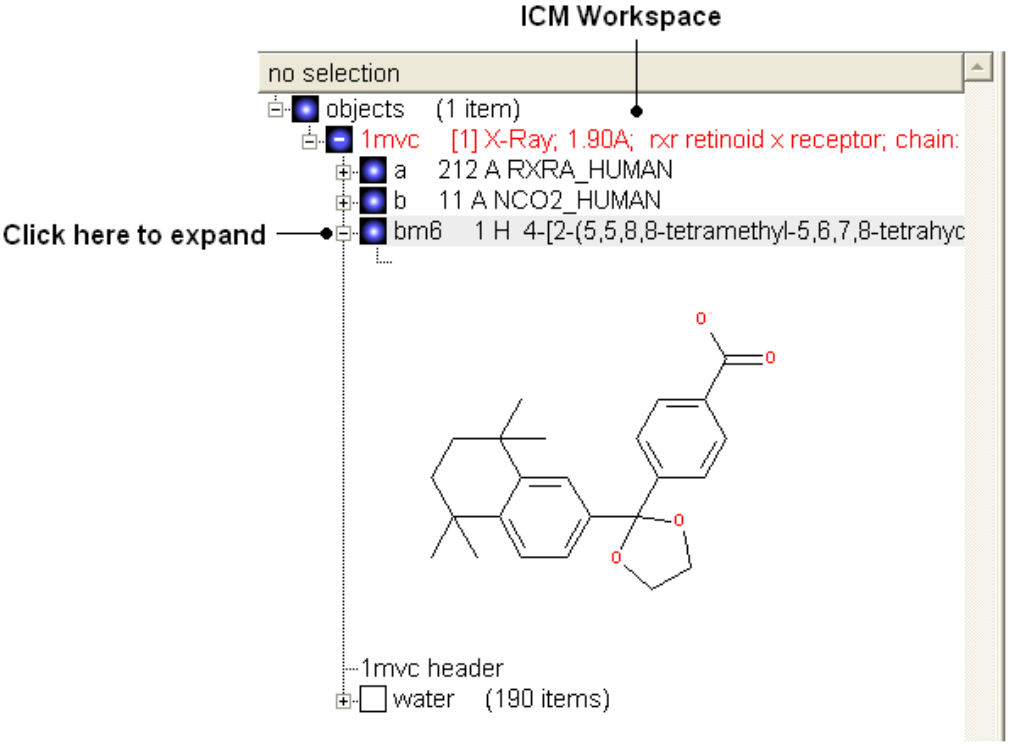
h2−− How to Convert a Chemical from the PDB {Convert Chemical} __REQUIRES(E)

The protein data bank has not been storing any information about covalent bond types and formal charges of the chemical compounds interacting with proteins! This oversight makes it impossible to automatically convert those molecules to anything sensible and requires your manual interactive assignment of bond types and formal charges for each compound in a pdb−entry. Therefore, if you apply the convert command to a pdb−entry with ligands, the ligands will just become some crippled incomplete molecules that can not be further conformationally optimized.

Therefore, follow these steps to convert a chemical properly from a pdb form to a correct icm object. There are two ways to do this either via the `ICM Workspace` (recommended) or via the `Graphical Display`.

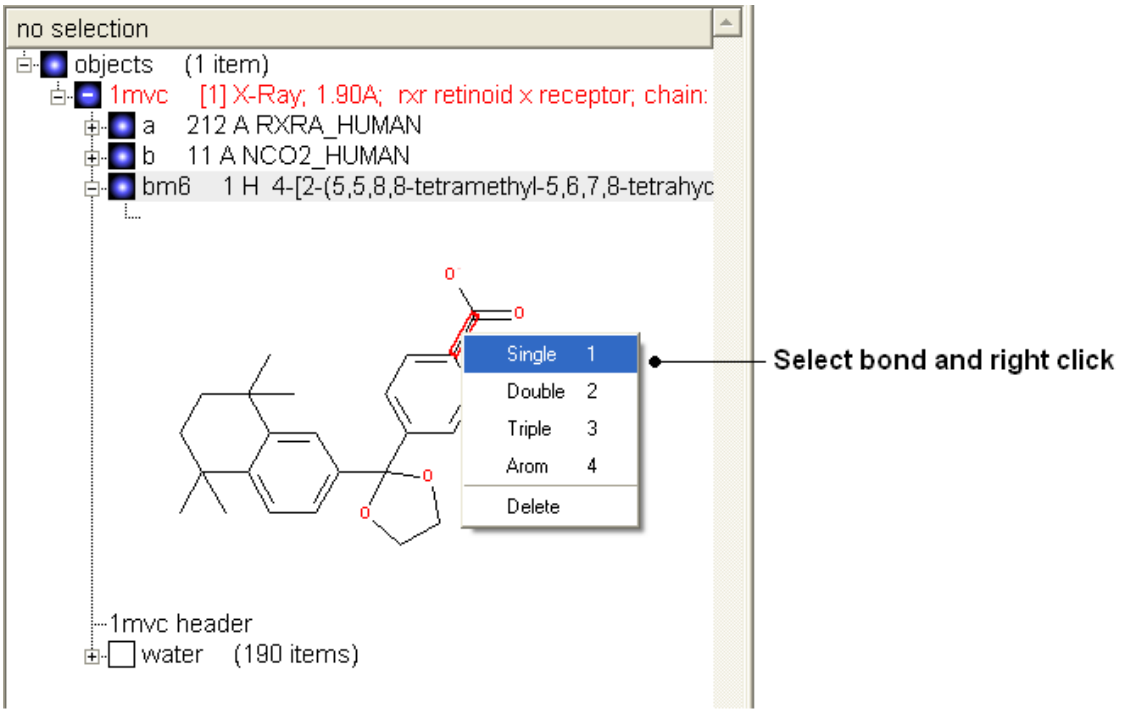
5.2.1 Converting a Chemical from the PDB using the ICM Workspace

- **File/Open** PDB
- View the ligand in the ICM Workspace by expanding the molecule tree (see below).



Change bond orders:

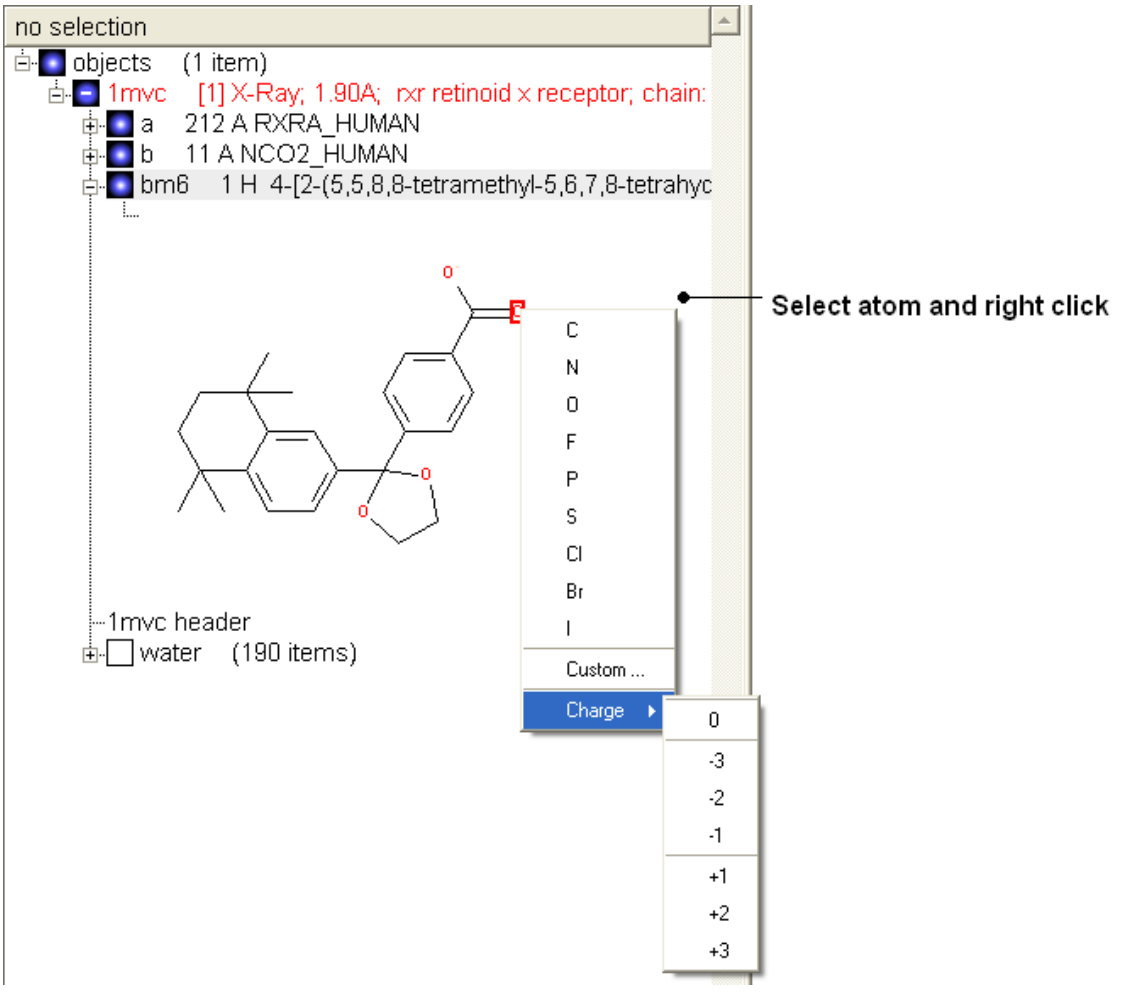
- Change the bond orders by selecting the bond (highlighted in red).
- Right click and select the desired bond as shown below.



NOTE: Keyboard `shortcuts` are provided to make editing faster.

Change atom and charge:

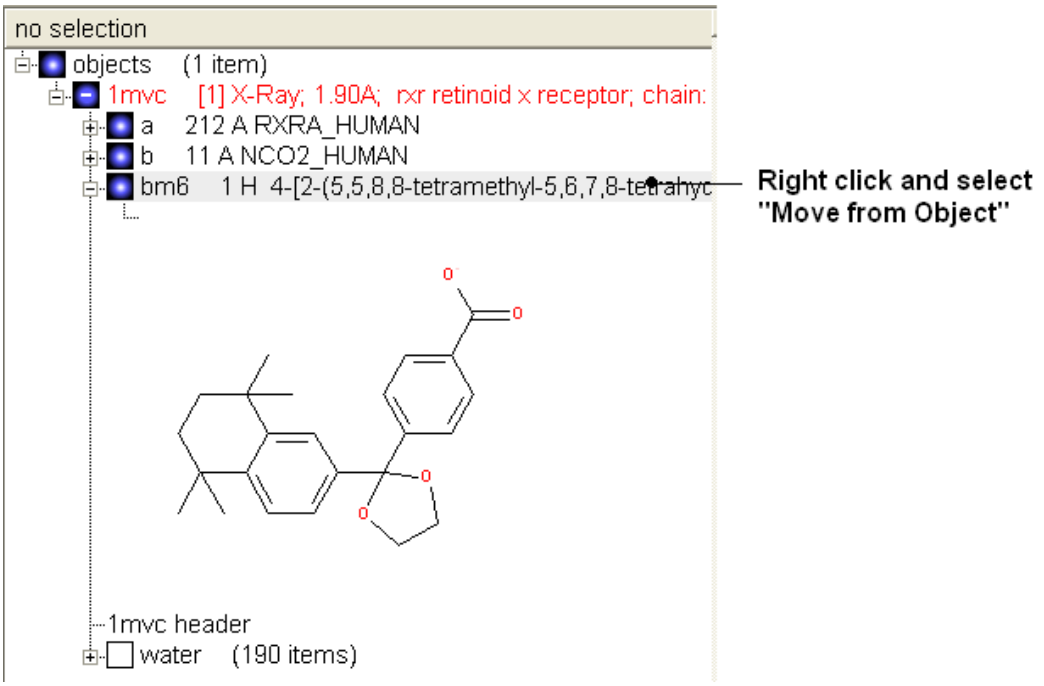
- Change the atom or charge by selecting the atom (highlighted in red).
- Right ckick and select the desired atom or charge as shown below.



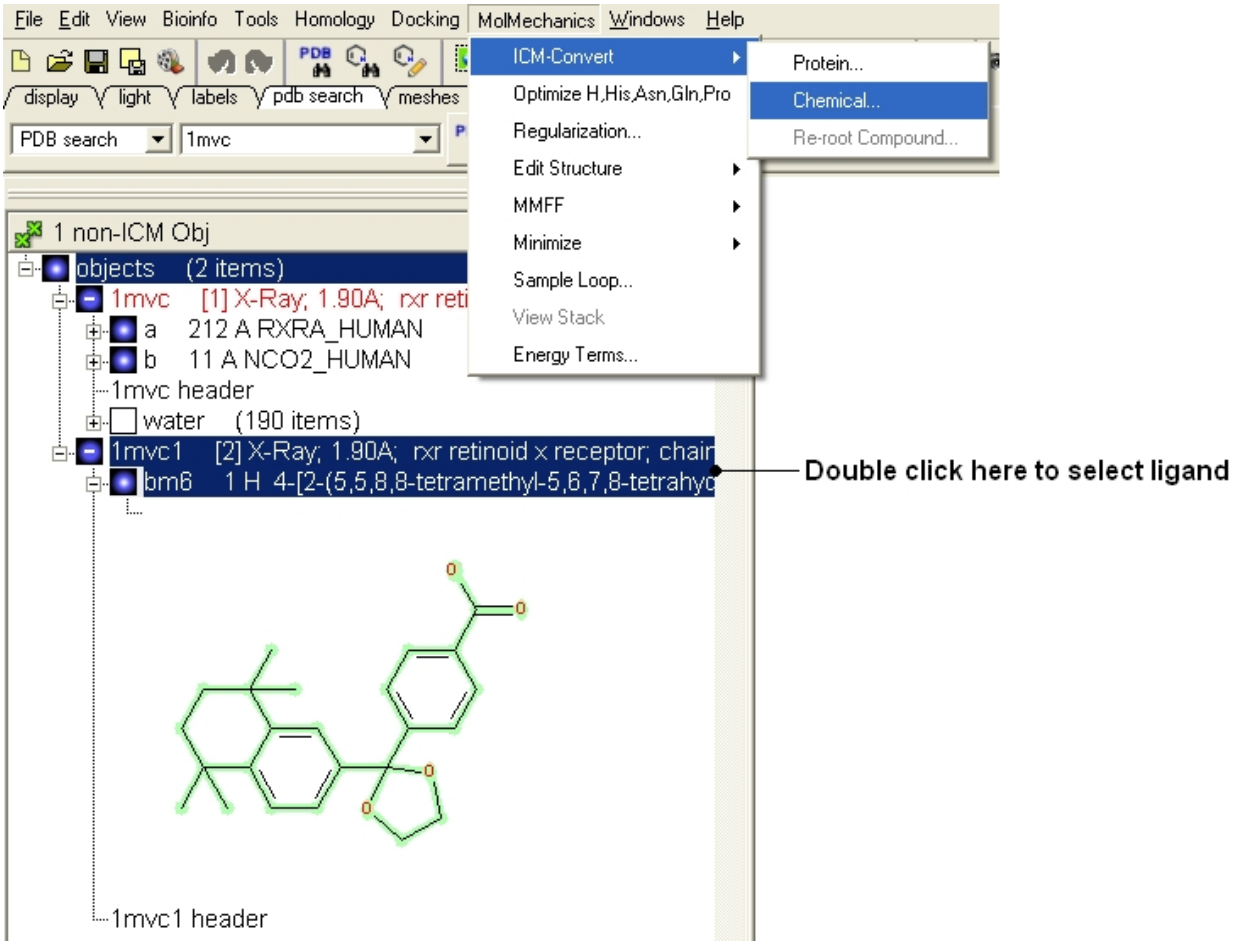
NOTE: Keyboard `shortcuts` are provided to make editing faster.

Convert to 3D in MMFF force field:

- Once you have made the changes to the ligand − right click on the name of the ligand in the ICM Workspace and select **Move from Object**.



- Select the ligand by double clicking on it in the ICM Workspace.
- Select **MolMechanics/ICM−Convert/Chemical**



NOTE: If you need to add an extra bond you will need to use the full molecular editor. Right click on the name of the ligand in the ICM Workspace and select **Edit/Edit Compound**.

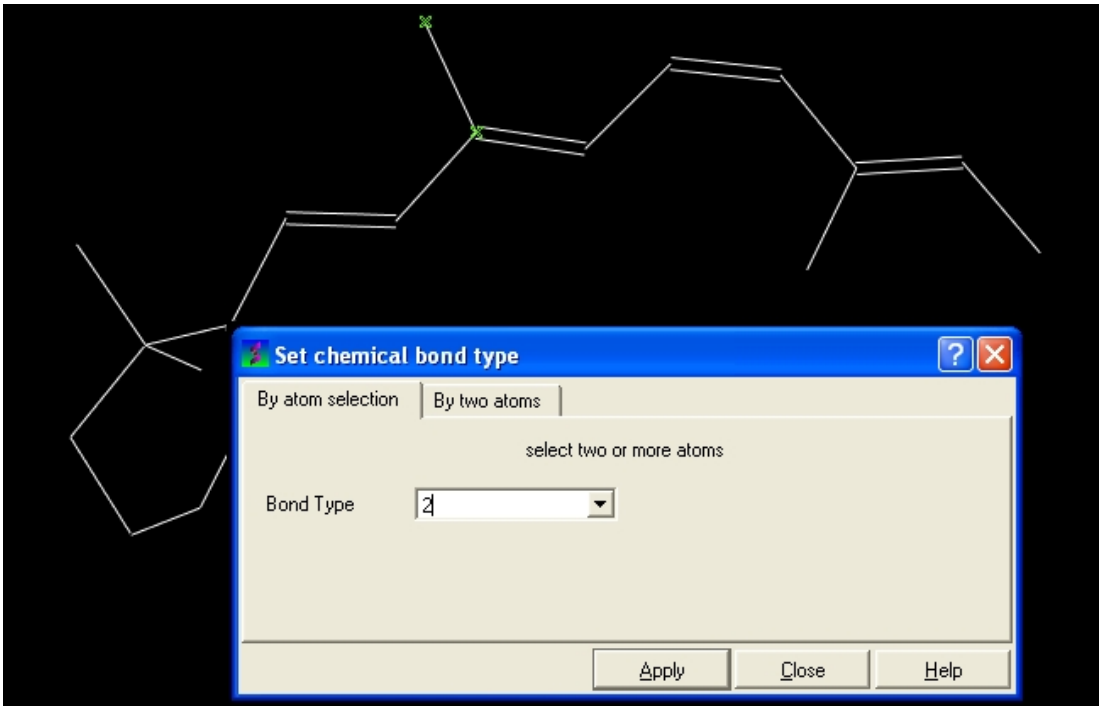
5.2.2 How to Convert a Chemical from the PDB using the Graphical Display

- Display the molecule in wire chemistry style mode by right clicking on the Wire Representation button (see `Wire Representation section`).

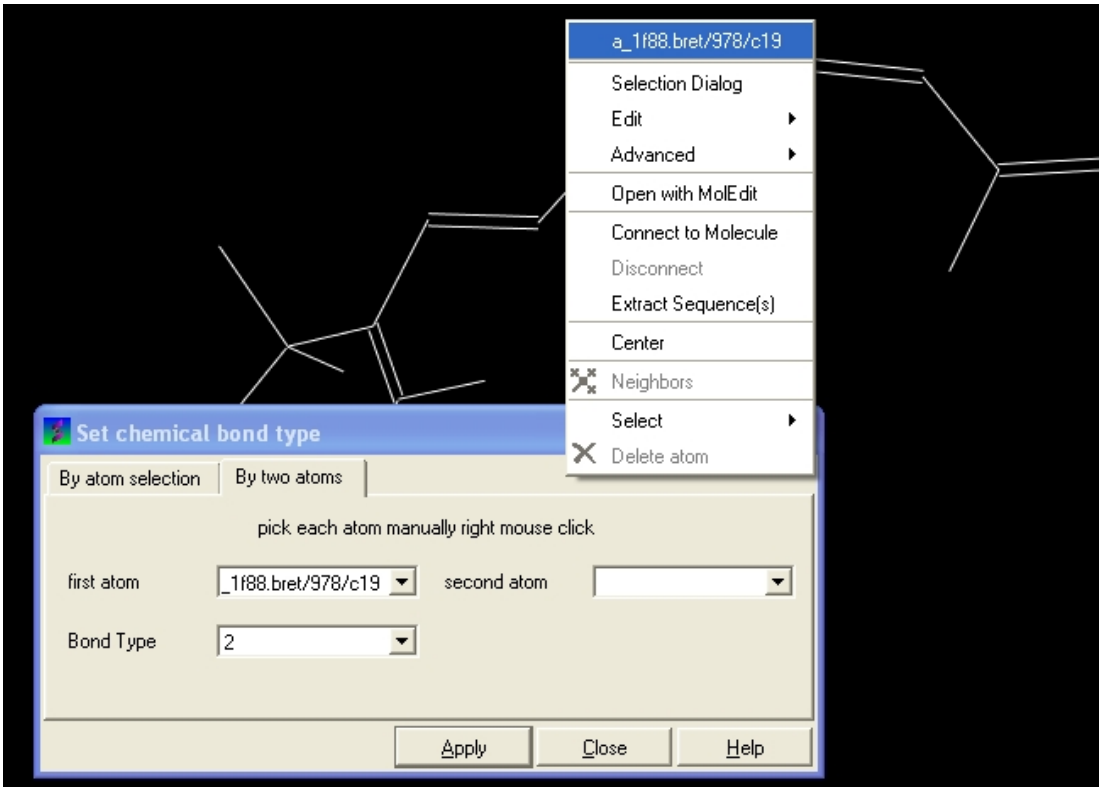
To change the bond types in your ligand:

- Click on MolMechanics/Edit Structure/Set Bond Type and the Set chemical bond type data entry box will be displayed.

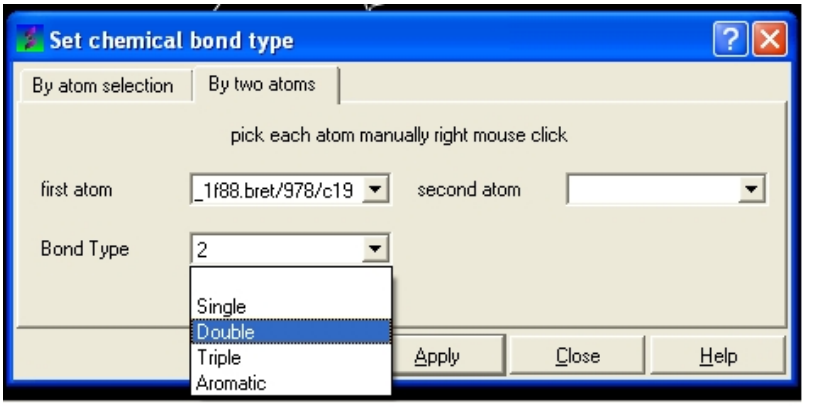
You can either select (see `selection menu section`)the atoms you wish to change graphically using the rectangular or lasoo selection button OR



You can select the **By two atoms** tabs and right click on the atoms you wish to change and then selecting the atom descriptor with the left mouse button as shown below.

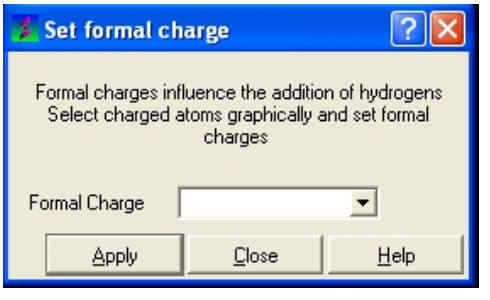


- Select the desired bond type either single, double, triple or aromatic.



To set the formal charge of a compound:

Click on MolMechanics/Edit Structure/Set Formal Charge and then select the appropriate charge.



The final step is to convert the compound into an ICM object:

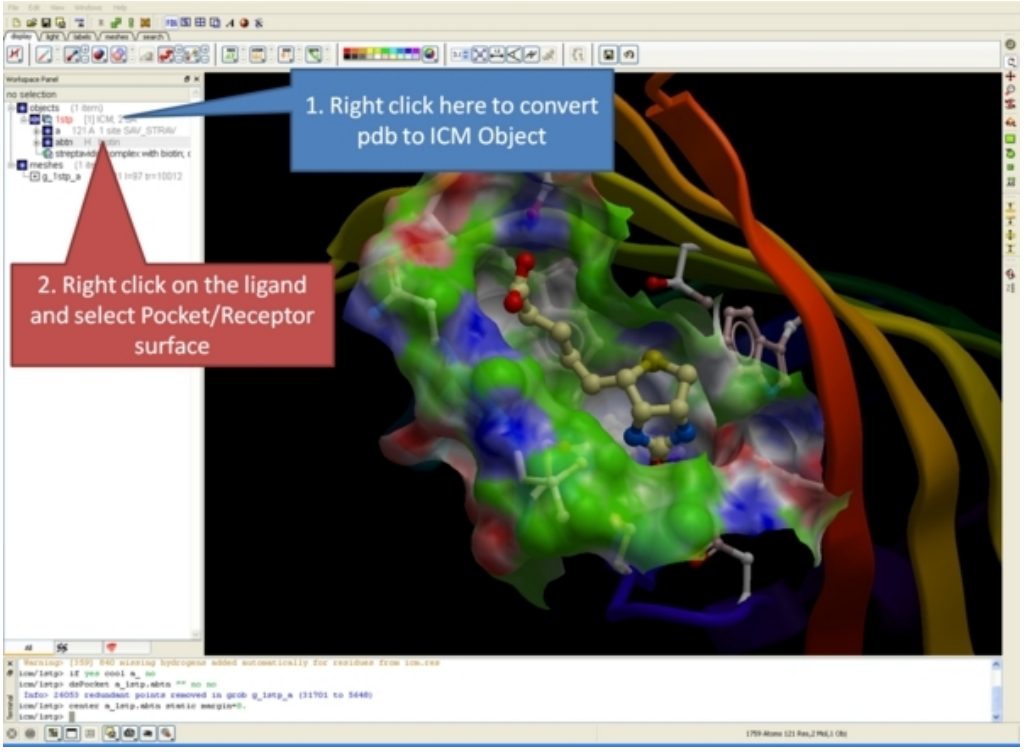
- `Select` the chemical (green crosses in graphical display).

- MolMechanics/ICM−Convert/Chemical

#endif

5.3 How to Display the Ligand Binding Pocket Surface and Neighboring Residues.

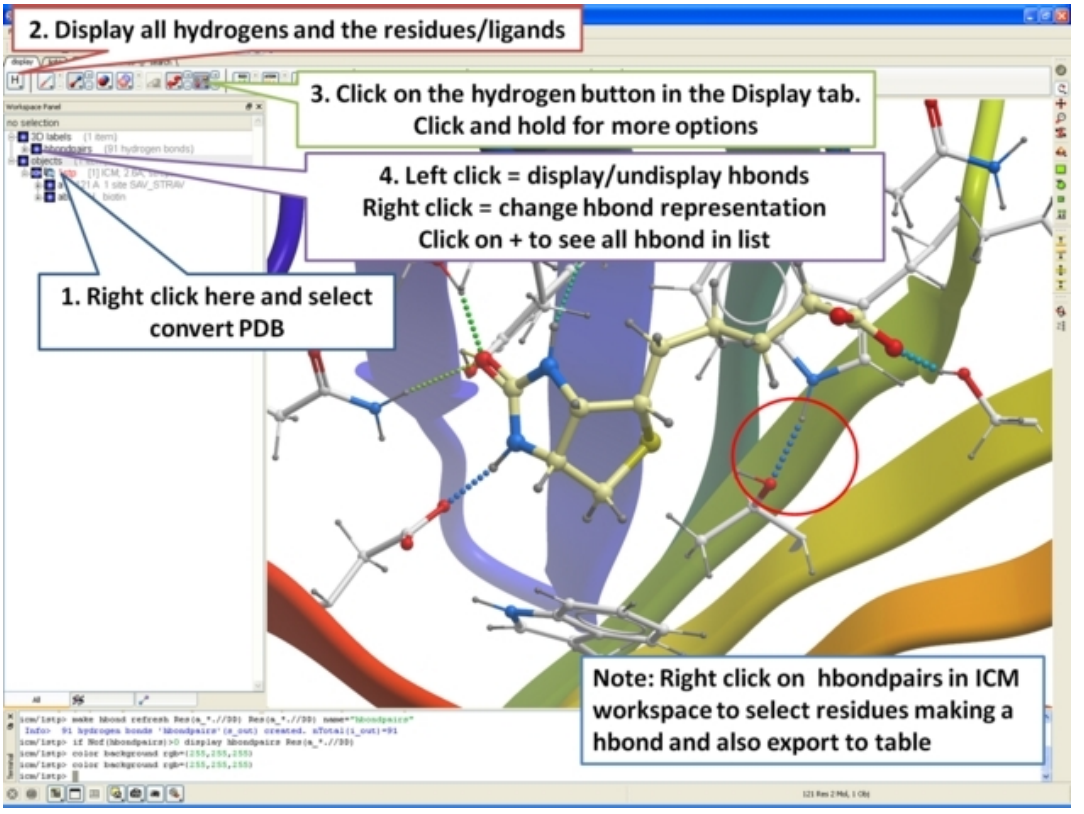
- As an example we will use the PDB structure 1STP. Type 1STP in the pdb search tab and press return.
- `Convert` the protein to an ICM object.
- Right click on the ligand "btn" and select "Ligand Pocket"
- To remove the ribbon display and display only the residues in the pocket. Select the "display" tab and click on the ribbon button which will undisplay the ribbon representation and leave only the residues surrounding the pocket.



5.4 How to Display Hydrogen Bonds

NOTE: The method by which hydrogen bonds are calculated is described `here` in the command line manual. The GRAPHICS.hbondMinStrength parameter determines the hbond strength threshold for hbond display. The strength value is between 0. and 2. By changing 1. to 0.2 you will see more weak hydrogen bonds.

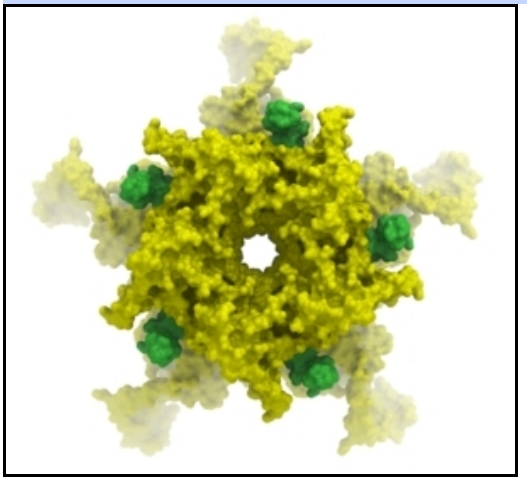
- As an example we will use the PDB structure 1STP. Type 1STP in the pdb search tab and press return.
- In order to display energy related properties we need to convert the PDB file into an ICM object. `Convert` 1STP into an ICM object. In this example, the option "Replace the Original" was selected.
- Display the receptor in wire format and the ligand in xstick.
- Right click on the ligand and select "Neighbors" − Enter 3 Angstroms and Type = Visible. Do not exclude source (the ligand) therefore remove tick from box entitled "exclude source".
- Select the display tab and then select the Display H−Bond button.



NOTE: Different options for displaying the H−bond can be accessed by clicking and holding on the H−bond button in the "Display" tab. The coloring of the H−bonds are red (strong − thick spheres) to blue (weak − thin spheres). Once the hydrogen bonds have been displayed they can be displayed and undisplayed in the 3D labels section of the ICM Workspace (left hand side of graphical window).

6 Molecular Graphics

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



In this chapter we describe how to make beautiful graphical representations of molecules and manipulate them in the 3D graphics window. This includes how to change color, light, represenations, clipping planes, and how to use built in graphics effects. We also teach how to label and annotate molecules displayed in the graphical user interface.

6.1 Molecule Representation

To change the molecule display representation:

- `Select` the atoms, residues, molecules, or objects you wish to change in the graphical display or in the ICM Workspace.
- Then use the molecule representation (e.g. wire, ribbon) options in the `Display Tab`.

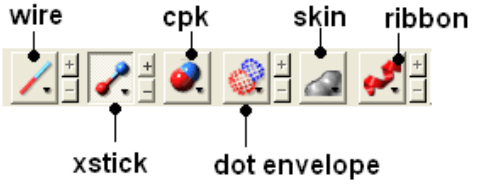
The display tab contains tools for a variety of functions including − structural representations, coloring, labeling and superposition. This tab is shown below.

6.1.1 Structure Representation

There are six main types of structural representation in ICM. They are wire, ball and stick (Xstick), ribbon, skin, CPK and dot envelope (surface).

To display one of these representations:

- Click on the representation button you desire in the **display** tab.

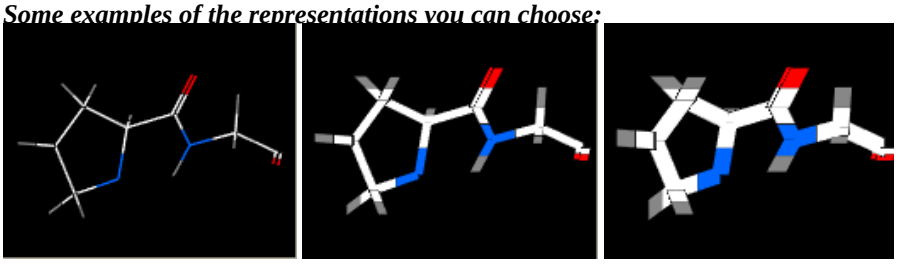


To remove a displayed representation or to toggle between display and undisplay:

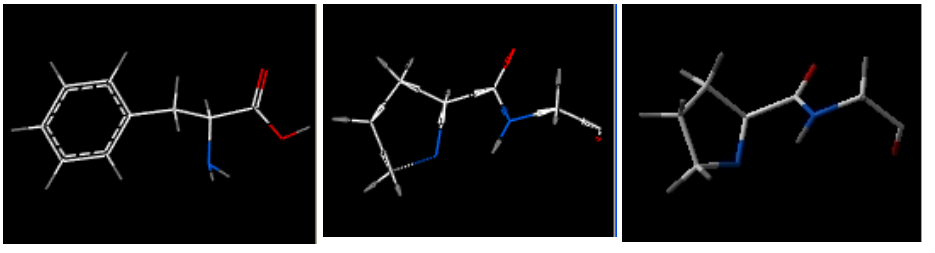
- Click on the corresponding representation button in the **display** tab.

NOTE: The button display will change appearance (shaded) when pressed. This makes it easier to identify which representations are currently being displayed. Many characteristics of the graphical representation such as color can be changed by clicking and holding on the button or by cliking the plus(+) and minus(−) buttons next to them.

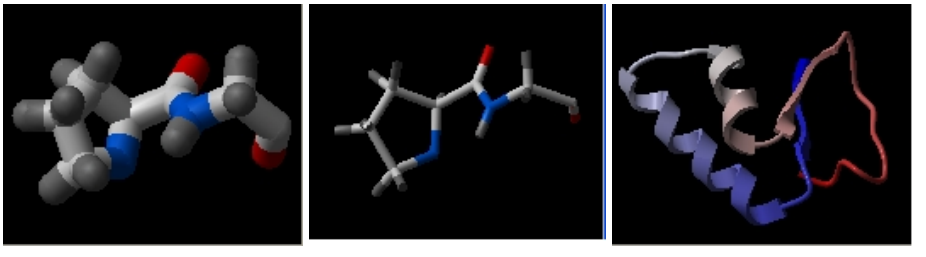
Some examples of the representations you can choose:



Wire : Thin Wire : Normal Wire : Thick

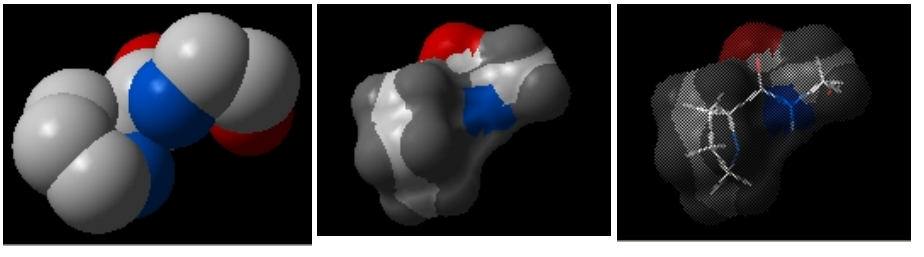


Wire : Chemistry Wire : Tree Xstick− Thin

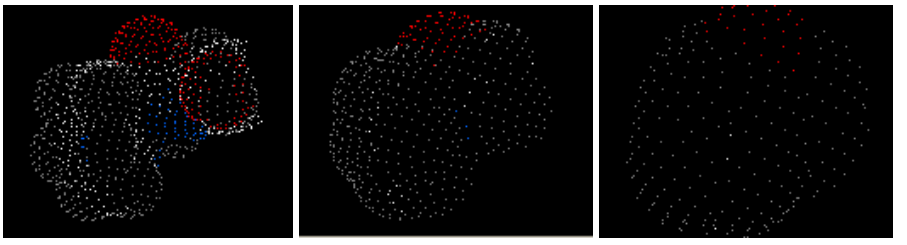


Xstick : Thick Xstick : Stick / Ball Ribbon : Ribbon

Ribbon : Segment Ribbon : Protein Worm Ribbon : Transparent



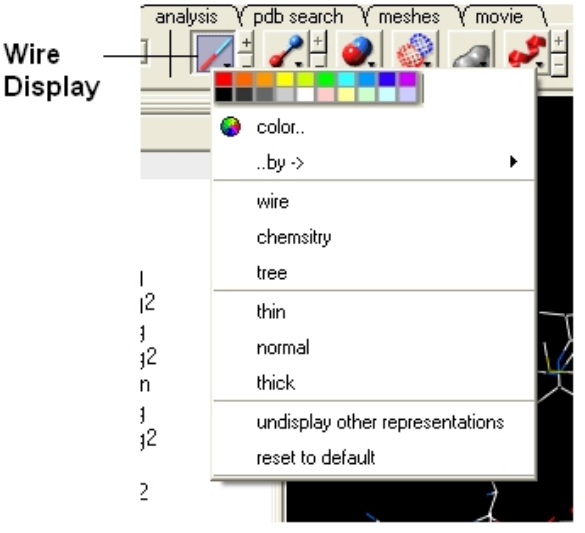
CPK : Default Skin : Default Skin : Transparent



Surface : Tight Surface : Normal Surface − Sparse

6.1.2 Wire Representation

Click and hold on the **wire representation** button. A menu will be displayed as shown below.



To change the wire style:

- Click and hold on the **wire representation** button and then click on **wire**, **chemistry** or **tree.**

To change the size of the wire representation:

- Click and hold on the **wire representation** button and then click on **thin**, **normal** or **thick.**

NOTE: Clicking on the +/− next to the **wire representation** button also changes the thickness of the wire representation.

To undisplay representations other than wire:

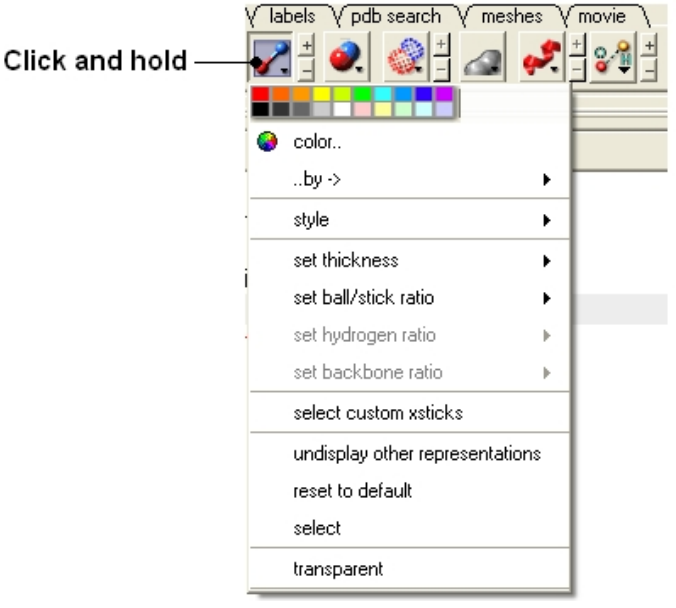
- Click and hold on the **wire representation** button and then click on undisplay other representations.

If you make a mistake or you are not happy with the way your structure is displayed with the wire representation:

- Click and hold on the **wire representation** button and then click on reset to default.

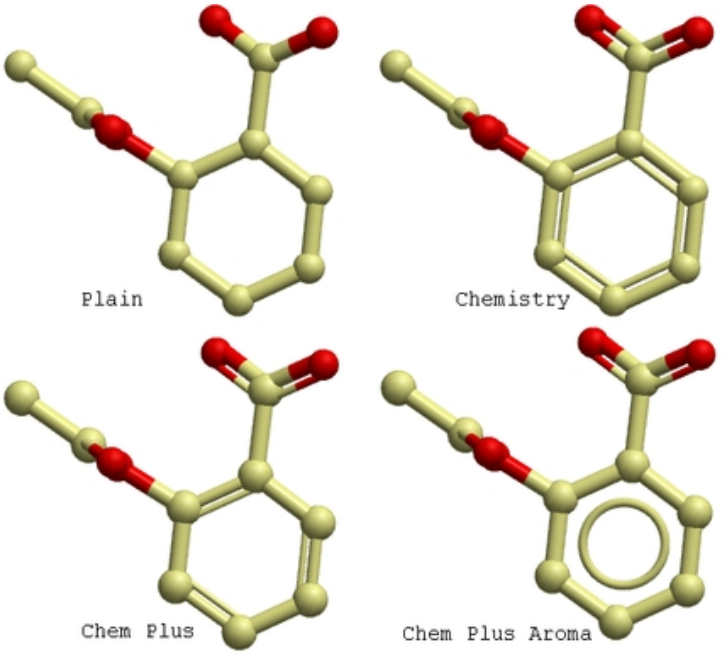
6.1.3 Stick and Ball (Xstick) Representation

Click and hold on the **stick and ball representation** button. A menu will be displayed as shown below.



To change the style of the Xstick representation:

- Click and hold on the **stick and ball representation** button and then click on style. Choose a style as shown below.



To change the size of the Xstick representation:

- Click and hold on the **stick and ball representation** button and then click on **set thickness** , **set ball/stick ratio**, **set hydrogen ratio**, and **set backbone ration**.

NOTE: Clicking on the +/− next to the **xstick representation** button also changes the thickness of the xstick representation.

In order to make some parts of your picture clearer, the xstick representation can be set to transparent:

- Click and hold on the **stick and ball representation** button and then click on transparent.

To undisplay representations other than xstick:

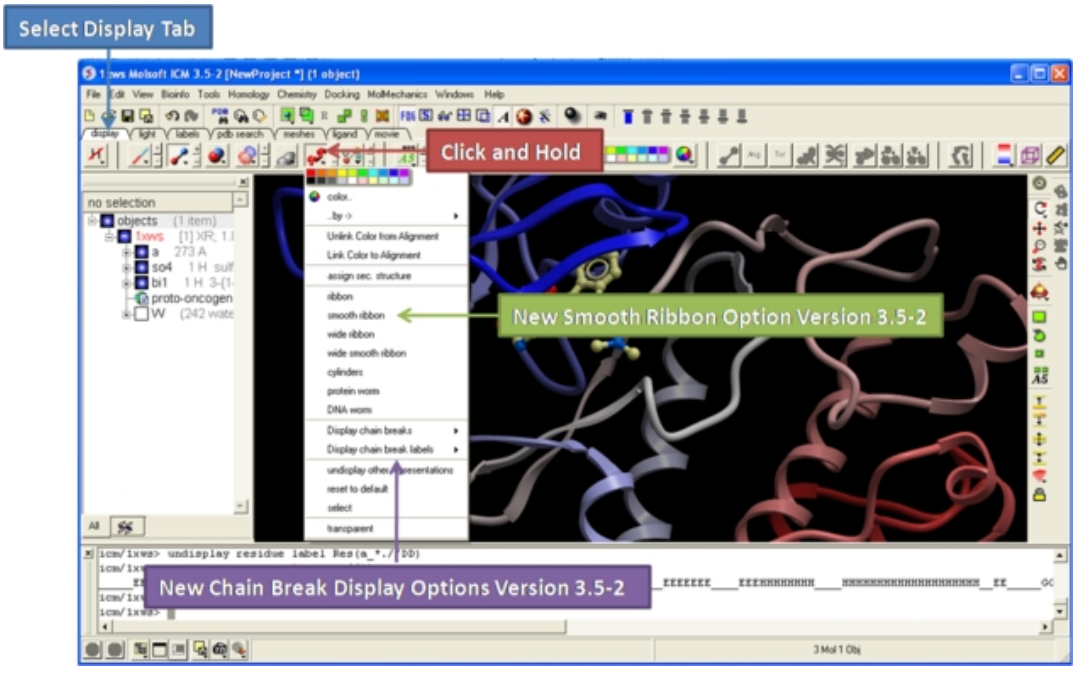
- Click and hold on the **stick and ball representation button** and then click on undisplay other representations.

If you make a mistake or you are not happy with the way your structure is displayed with the xstick representation:

- Click and hold on the **stick and ball representation** button and then click on reset to default.

6.1.4 Ribbon Representation

Click and hold on the ribbon representation button. A menu will be displayed as shown below.



To change the style of the Ribbon representation:

- Click and hold on the **ribbon representation button** and then click on a style option.

To accurately represent the secondary structure of the molecule in ribbon representation you may wish to assign secondary structure:

- Click and hold on the **ribbon representation** button and then click on **assign sec. structure**. New in version 3.5−2 is they smooth ribbon style.

To make some parts of your picture clearer, the ribbon representation can be set to transparent:

- Click and hold on the **ribbon representation button** and then click on **transparent.**

To undisplay representations other than ribbon:

- Click and hold on the **ribbon representation** button and then click on undisplay other representations.

If you make a mistake or you are not happy with the way your structure is displayed with the ribbon representation:

- Click and hold on the **ribbon representation button** and then click on **reset to default**.

NOTE: Always use the **ICM** assign sec.** structure tool in the ribbon right click menu to get accurate secondary structure assignment. This is particularly important when studying helices which may have non−cannonical elements within them such as 3/10 or pi. To view non−cannonical helix segments use

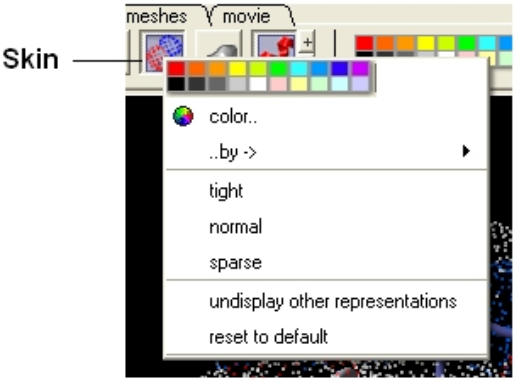
the segment option in the ribbon right click menu.

To change the display of chain breaks (dotted lines):

- Click and hold on the ribbon represenation button.
- Select the options Display Chain Breaks or Display Chain Break label.

6.1.5 Skin Representation

Click and hold on the **skin representation button**. A menu will be displayed as shown below.



To make some parts of your picture clearer, the skin representation can be set to tight, normal or sparse:

- Click and hold on the **skin representation button** and then click on either tight, normal or sparse.

To undisplay representations other than skin:

- Click and hold on the **skin representation button** and then click on **undisplay other representations**.

If you make a mistake or you are not happy with the way your structure is displayed with the skin representation:

- Click and hold on the **skin representation button** and then click on ** reset to default**.

NOTE: Sometimes due to singularity problems holes may appear within the skin surface. To cure this infliction select atoms nearby and right click select Advanced−>RandomizeAtoms

6.1.6 CPK Representation

Click and hold on the **CPK representation button**. A menu will be displayed as shown below.

To undisplay representations other than CPK:

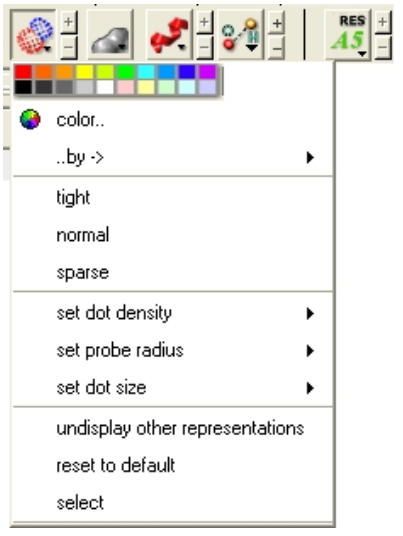
- Click and hold on the **CPK representation button** and then click on **undisplay other representations**.

If you make a mistake or you are not happy with the way your structure is displayed with the cpk representation.

- Click and hold on the **CPK representation button** and then click on **reset to default**.

6.1.7 Surface Representation

Click and hold on the surface representation button. A menu will be displayed as shown below.



To change the style of the surface representation:

- Click and hold on the **surface representation button** and then click on **tight**, **normal**, or **surface.**

To undisplay representations other than surface:

- Click and hold on the **surface representation button** and then click on undisplay other representations.

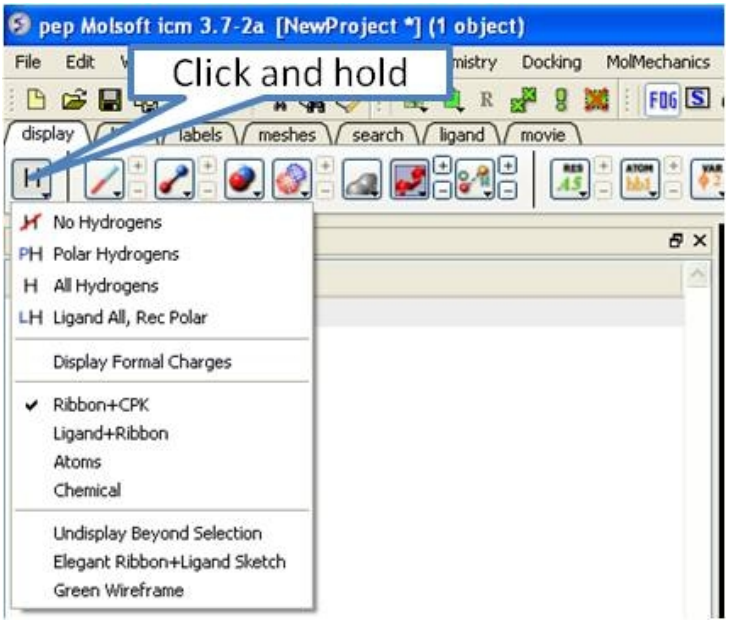
If you make a mistake or you are not happy with the way your structure is displayed with the surface representation:

- Click and hold on the **surface representation button** and then click on **reset to default**.

6.1.8 Display and Undisplay Hydrogens

To display and undisplay hydrogens. Click and hold on the **"Change Hydrogen Display"** button shown below. Multiple single clicks will toggle through the hyrogen display options.

- Display Tab
- Click and hold on the **"Change Hydrogen Display"** button shown below.

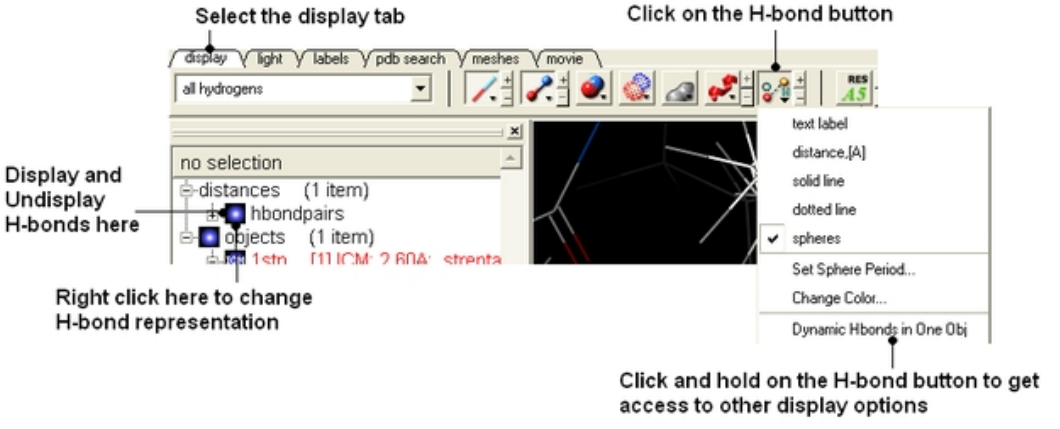


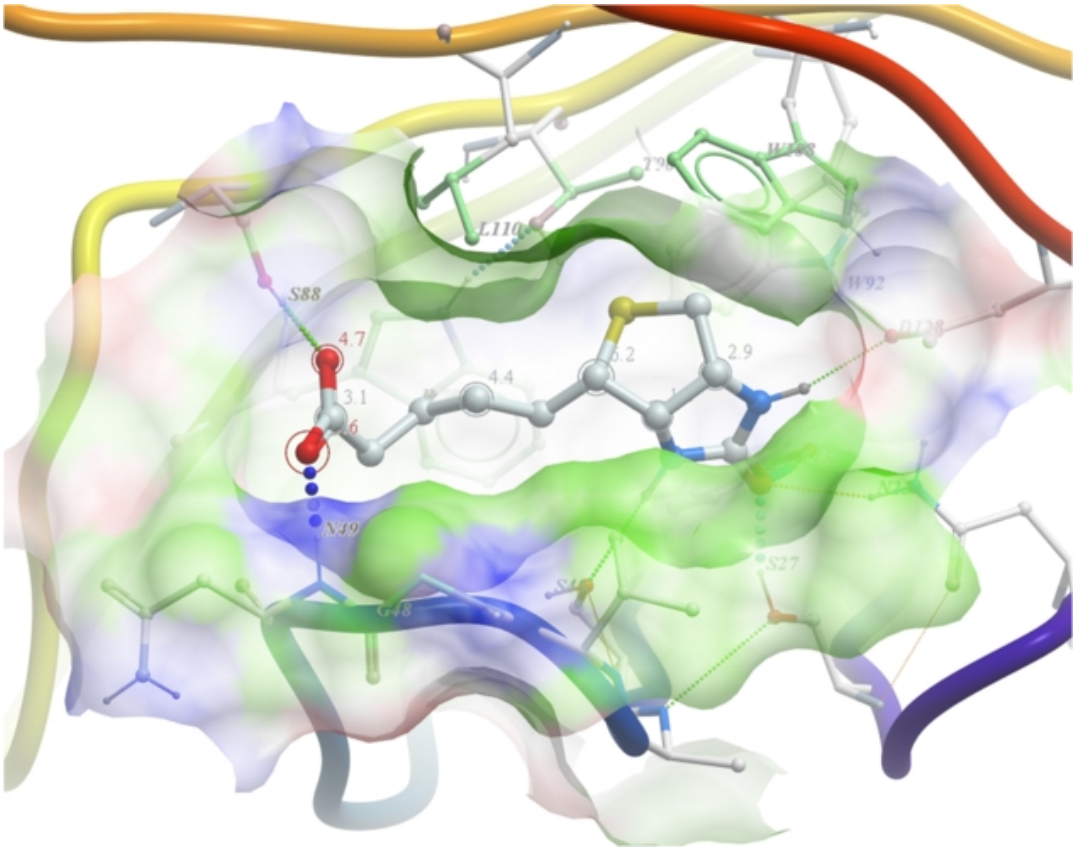
6.1.9 Display Hydrogen Bond

NOTE: The method by which hydrogen bonds are calculated is described `here` in the command line manual. The GRAPHICS.hbondMinStrength parameter determines the hbond strength threshold for hbond display. The strength value is between 0. and 2. By changing 1. to 0.2 you will see more weak hydrogen bonds.

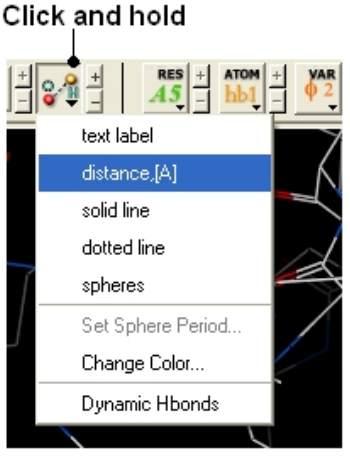
In order to display potential hydrogen bonds in your structure:

- Convert to an ICM Object
- Make a selection − if you are trying to display the H−bonds between a ligand and the receptor make sure the ligand is part of the selection.
- Click the Display Tab.
- Click on the **Toggle H−bonds** icon in the **display** tab.





- Click the +/− on the right of the H−Bond button to change thickness of H−bond representation.
- Click and hold the button to change representation or use the **hbondpairs** option in the ICM Workspace.



What do the default coloring of the H−bond represent?

Longer and shorter H−X distances in the hydrogen bond are color−coded, from red to blue, respectively.

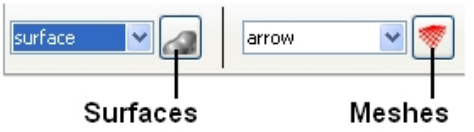
NOTE Dynamic hydrogen bonds can be set by clicking and holding on the **H−bond toggle** button in the **Display** tab. Hydrogen bonds will then respond to any changes made to the ligand.

6.1.10 Display Formal Charges

You can display formal charges by clicking and holding on the **"Change Hydrogen Display"** button in the **Display tab**.

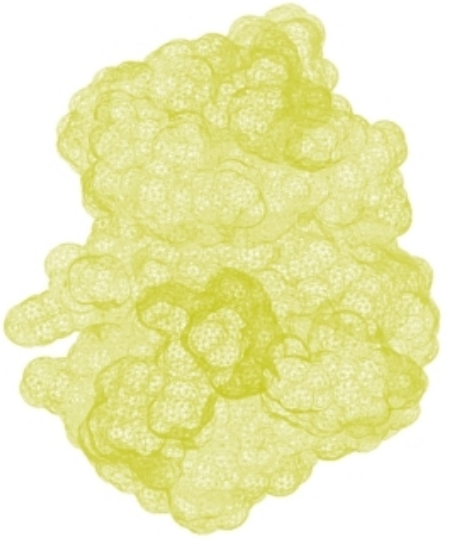
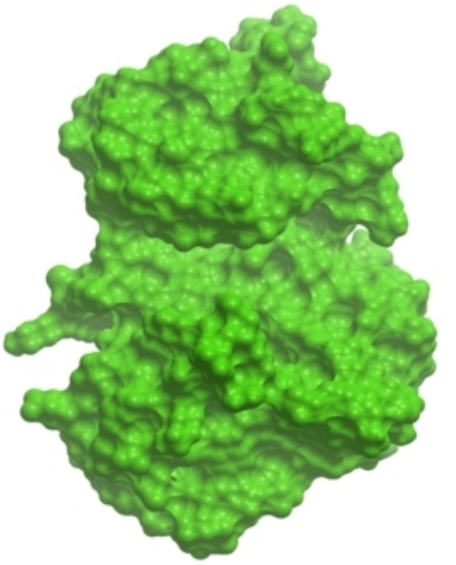
6.2 Meshes − Surface − Grobs

Click on the tab button entitled '**meshes**' and more graphics tools for surfaces are available. In ICM surfaces are sometimes referred to as meshes or graphical objects (Grobs).

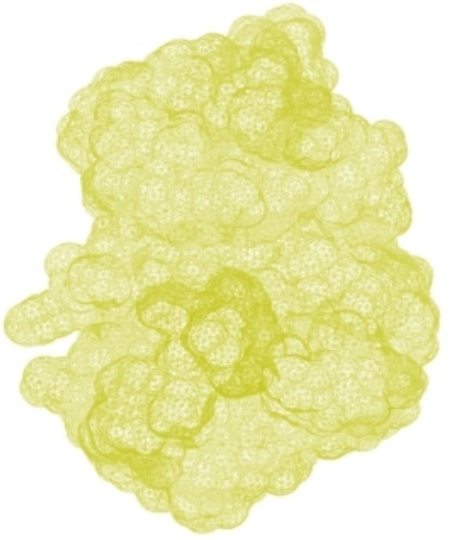
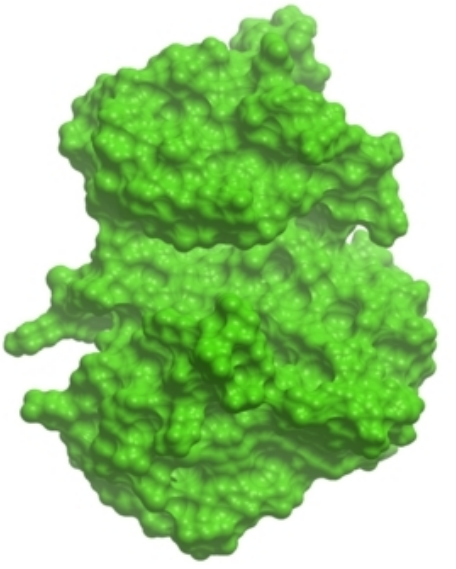
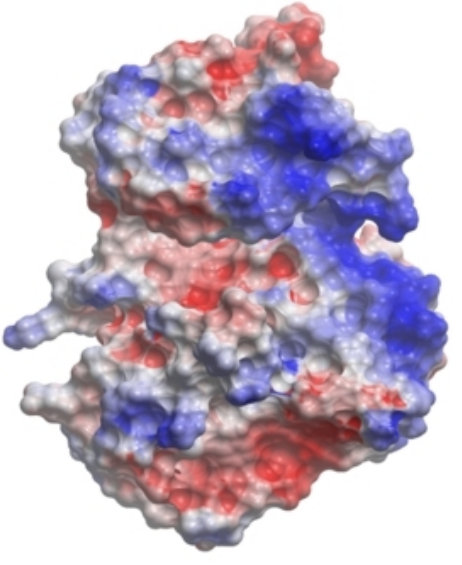
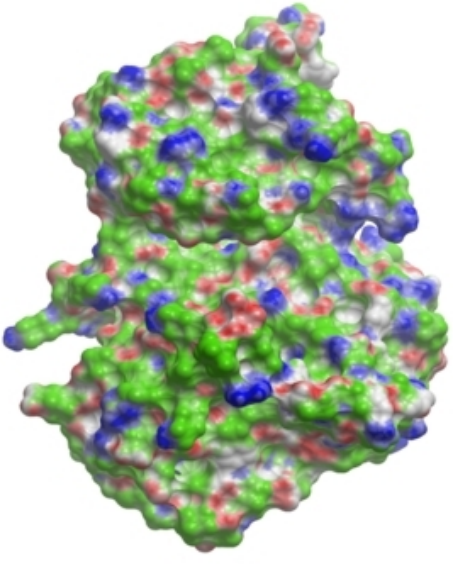


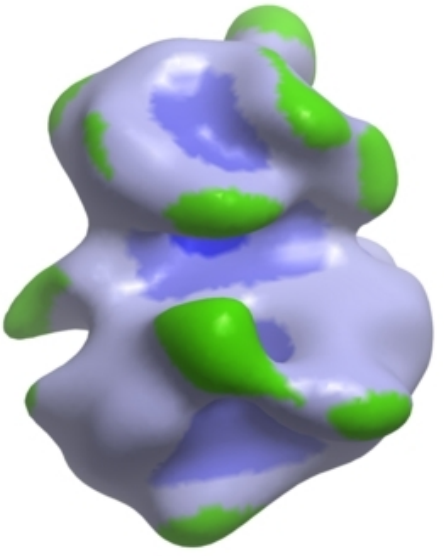
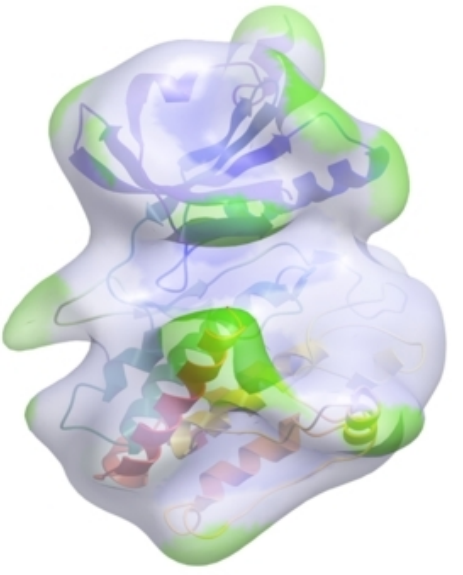
#endif

#endif

	
Surface	Plain Solid

#endif

	
Surface	Plain Solid
	
Electrostatic Surface	Binding Property Surface

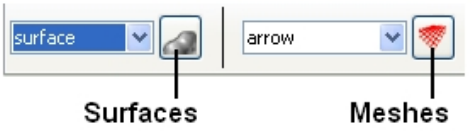
	
Macroshape Solid	Macroshape Transparent

#endif

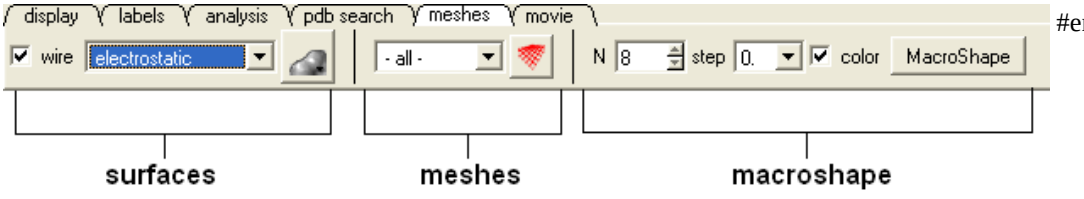
6.2.1 Surfaces

The surface of your structure can be displayed and colored by **electrostatics** or **binding** properties. To do this:

- Load a structure into ICM `File/Open` or tab−pdb{PDB Search}
- `Convert` the structure into an ICM object.
- Select the 'meshes' tab button.
- Click on the drop down arrow menu shown below and select which surface you wish to generate.
- Click on the generate surface button next to the drop down arrow.



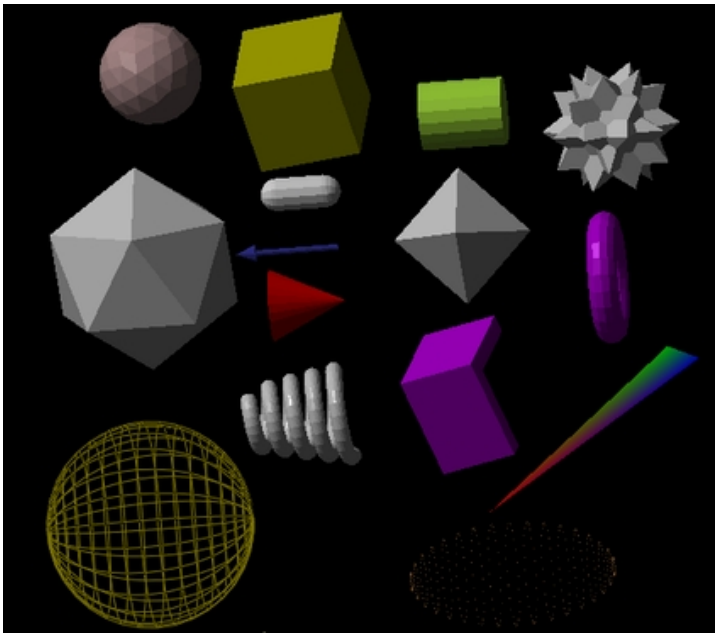
#endif



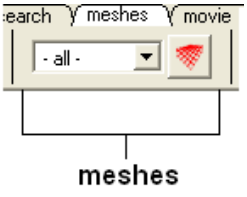
#endif

6.2.2 Meshes

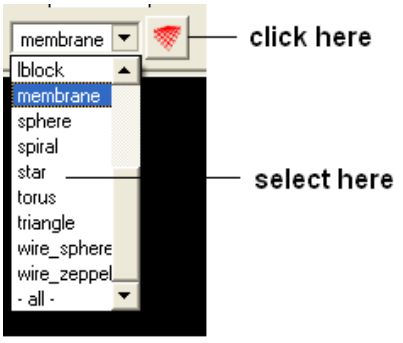
A variety of shapes can be constructed automatically using ICM. These shapes are referred to as meshes. The types of shapes you can build are shown below:



All the buttons for creating these shapes are shown here:

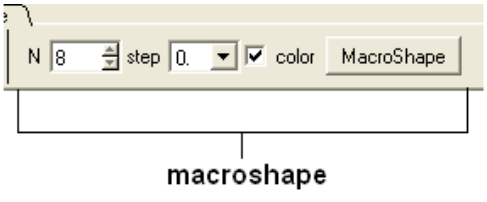


To make a shape select it from the menu by clicking on the down arrow and then click the button next to the menu. The shape will then be displayed in the 3D graphics window.



6.2.3 Macroshape

A macroshape can be constructed and allows easy viewing and manipulation of the structural representation. A macroshape representation is ideal for large structures which allows the user to easily identify important regions of the structure and facilitate the return to the 'standard' view of a particular molecule. All the buttons needed to display a macroshape structure are shown below in the 'meshes' tab.



To construct a macroshape:

- Load a molecule into ICM `File/Open` or tab−pdb{PDB Search}
- Select the amount of detail required in the shape by increasing the values in 'N' or 'step' data entry box (note the default values are usually sufficient).
- Check the 'color' if you wish your molecule to be colored.
- Click the button labeled 'MacroShape'.

Macroshape can also be used from the View menu: View/Macro Shape #endif

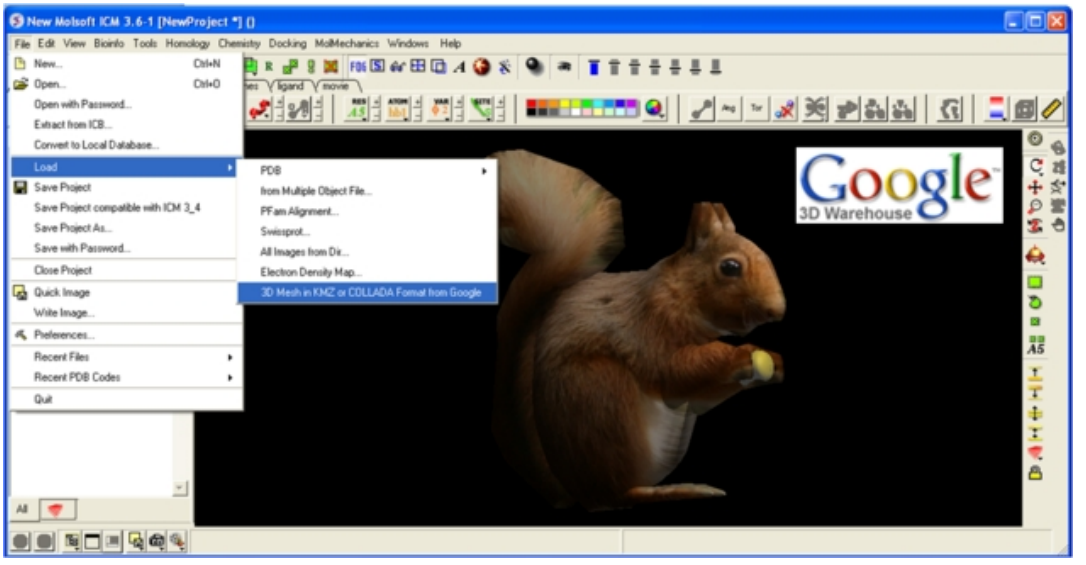
6.2.4 Google 3D Objects (Sketchup)

To read in a 3D Mesh from Google in KMZ or COLLADA format:

- File/Load/ 3D Mesh in KMZ or COLLADA Format from Google
- Search for the object you would like to view and download it.
- To read the file go to File/Open

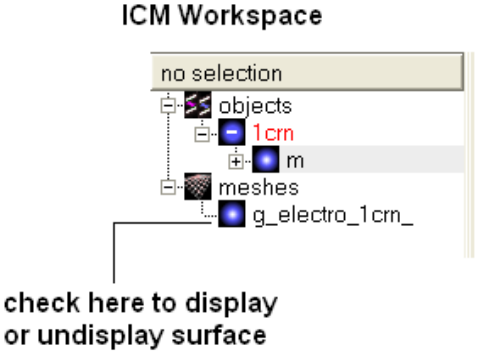
An example of a KMZ file can be found in the distribution (a squirrel model by **ilikipie**, provided with author's permission).

- File/Open, and choose the squirrel.kmz file



6.2.5 Display or Undisplay Meshes or Surfaces

To display or undisplay the surface click in the box in the ICM workspace as shown below:



NOTE: All surfaces, meshes and macroshapes come under the one heading of **meshes** in the workspace panel.

6.2.6 Mesh Options.

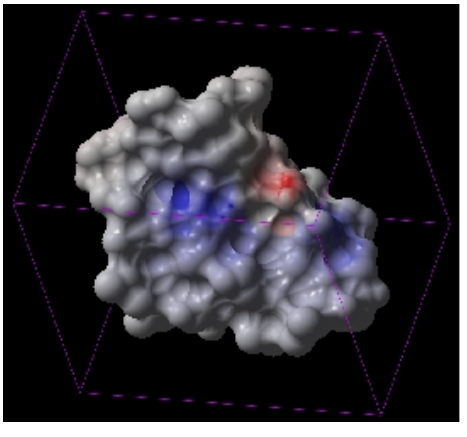
A number of options relating to meshes can be used by right clicking on the mesh in the ICM Workspace. This section describes some of these options.

6.2.7 Move and Resize Mesh

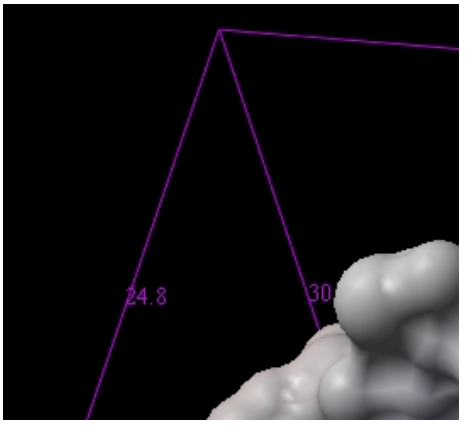
Once a mesh has been created you can move it and resize it. To do this, locate the mesh you wish to either move or resize in the ICM Workspace and right click on it as shown below.

- Select the **Resize/Move Mode** in the menu.

A purple box as shown below will surround the molecule.



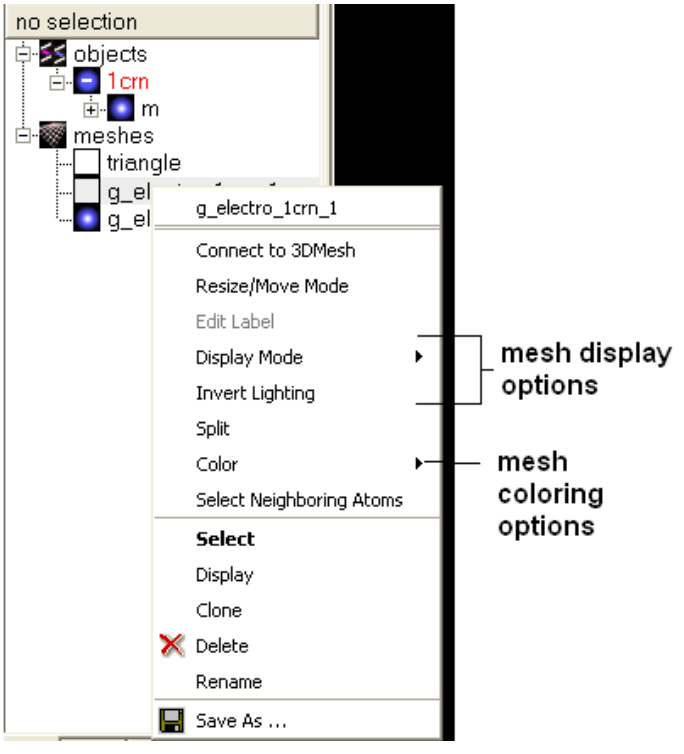
To resize the mesh click on one of the corners of the box and drag to the required size. The number displayed on the edges of the box represent the dimensions.



To move the mesh click on it with the center mouse button or selct the connect option.

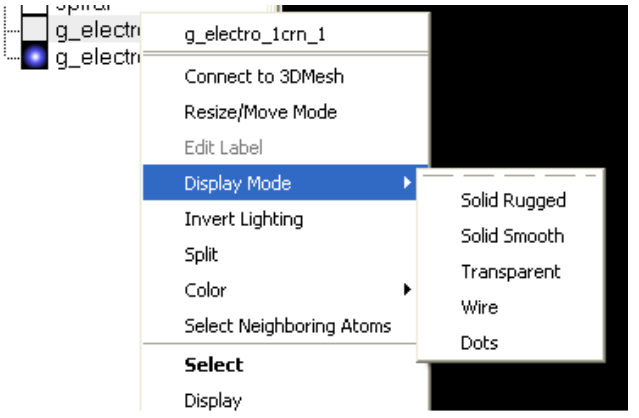
6.2.8 Color and Mesh Display

There are a number of options to color and change the display of the mesh. These options can be accessed simply by right clicking on the mesh name in the ICM Workspace as shown below.



The lighting and display can be changed by selecting the options 'Display Mode' or 'Invert Lighting'.

There are five different display modes as shown below:



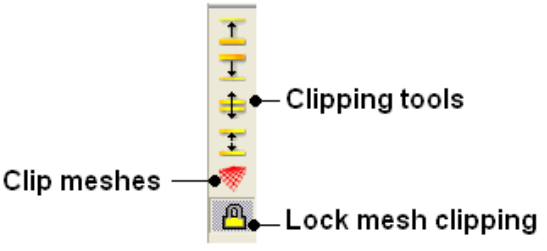
To change the lighting effects select 'Invert Lighting'.

The mesh colors can be changed by using the 'Color' option in the menu.

6.2.9 Mesh Clipping

Clipping tools can be used to adjust the frames of the mesh independently of other objects.

The buttons shown below can be used for this purpose.



The buttons used for clipping are described in the section entitled `Clipping Tools`.

6.2.10 Save Mesh

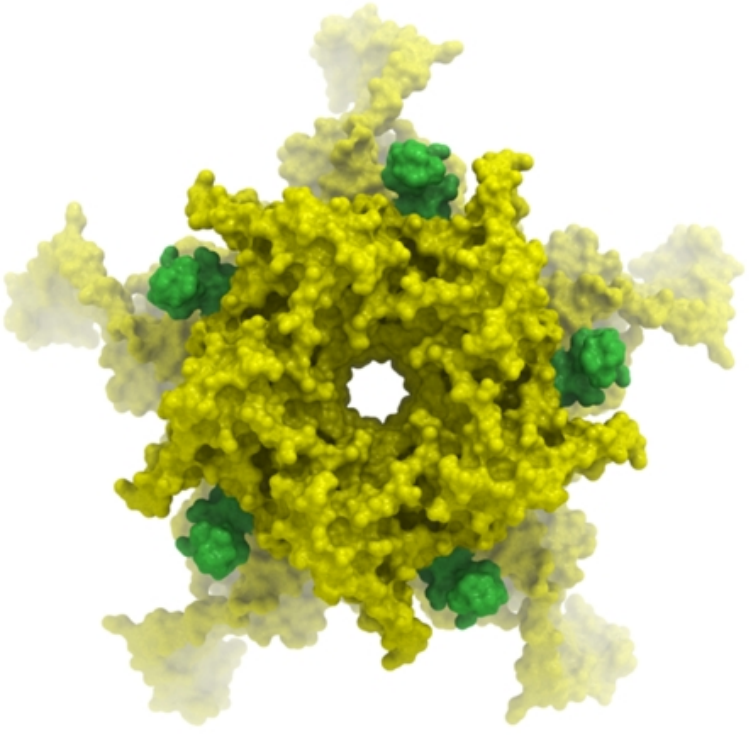
You can save a mesh as a wavefront object by right clicking on the mesh in the ICM Workspace and selecting **SaveAs.**

6.2.11 Occlusion Shading

The occulusion shading option provides better representation of depth within a cavity. The color of each surface element of a grob (mesh) is changed by mixing its own color with the background depending on the burial of the surface element

To add occlusion shading:

- Right click on the mesh in the ICM Workspace and select **Occlusion Shading**.
- Enter a depth value − default is 0.8. Higher values will generate a more dramatic shading.



6.3 Coloring

To change the coloring of the molecules:

- `Select` the atoms, residues, molecules, or objects you wish to color in the graphical display or in the ICM Workspace.
- Then use the color options in the `Display Tab`.

6.3.1 Coloring

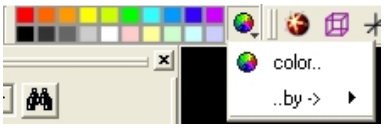
To change the color of a structural representation such as CPK, Xstick, wire or ribbon.

- Click and hold on the structural representation button for the representation you wish to color (e.g. wire, ribbon etc...) in the **Display** tab.
- Select a color by clicking color.

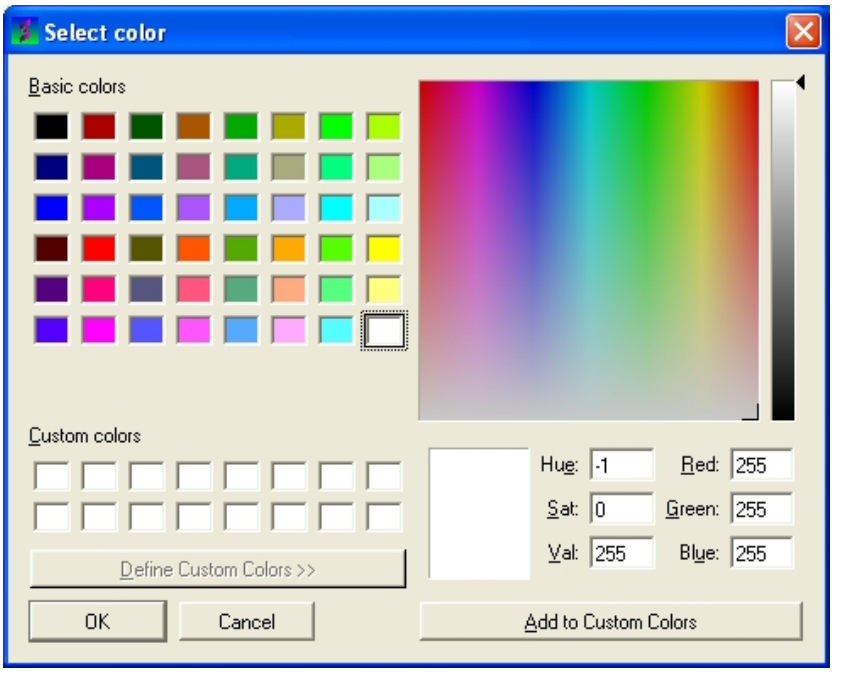
To color by a particular parameter such as atom type, b−factor, secondary structure etc...

- Click and hold on the structural representation button for the representation you wish to color (e.g. wire, ribbon etc...) in the **Display** tab.
- Select ..by−> option

To change the color of the whole of your displayed structure:



- Click on the color palate displayed on the toolbar.
- If you are not satisfied with these colors, click on the color wheel on the toolbar. A window as shown below will be displayed. Select the desired color by either clicking on one of the basic colors or by selecting the desired color on the right hand side of the window.

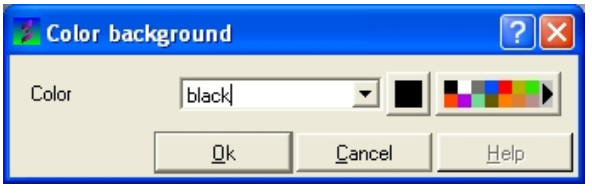


- Once the desired color has been selected it can be added to custom colors for future use by clicking on the Add to Custom Colors button.
- Click the **OK** button and the color will be applied to the structure.

6.3.2 Color Background

To change the color of the background:

- Select **View/Color** background.



- Click on the square of your desired color. If you are not satisfied with the color palate, click on the arrow next to the colors to customize a color.

OR

- Right click on a color in the colors panel in the display tab.

6.3.3 Background Image

NOTE: this functionality is only available in versions 3.6 and above.

A background image can be added to the graphical display. This can be useful for making cool images or for comparing structures (e.g.compare displayed object with background image of object).

To add a background image from an image file (png or jpeg):

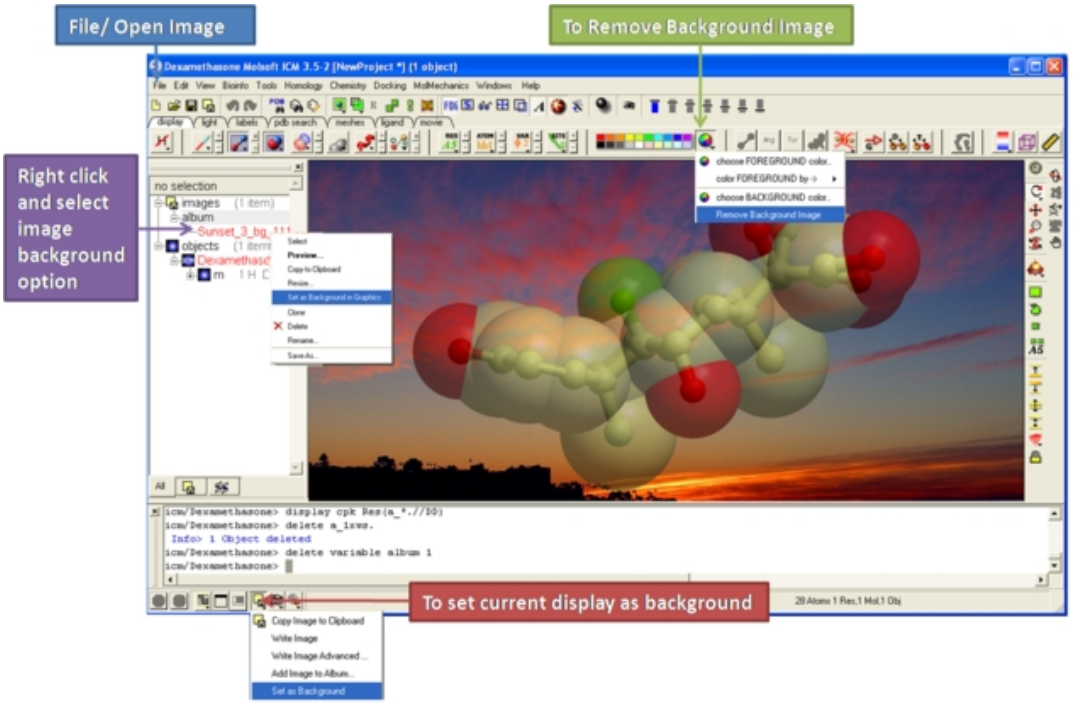
- File/Open Image
- Right click on the image in the ICM Workspace and select "Set as Background in Graphics."

To set currently display as background image:

- Click and hold on the "Copy Image to Clipboard" button at the bottom of the gui and select the "Set as Background" option.

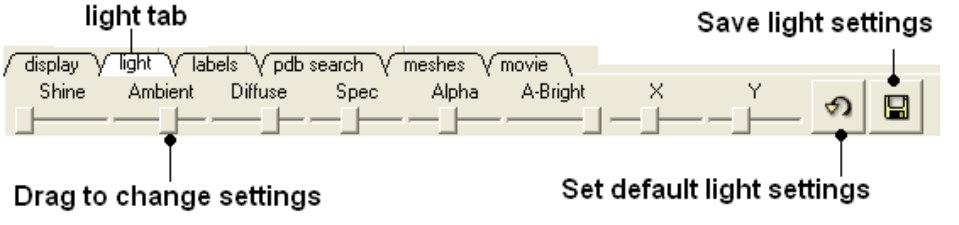
To remove a background image:

- Select the **display** tab and then click and hold on the color sphere button and select "Remove Background Image".



6.4 Lighting

These options are in the light−tab{light tab}



CLick and drag the sliders to change the lighting. You can also save your preferred lighting settings and return to default.

Shine − shininess property of the solid material

Ambient − ambient light intensity of RGB for ambient light

Diffuse − diffuse light intensity of RGB for diffuse light

Spec − specular light intensity of RGB for specular light

Alpha − transparency setting for grob

A−Bright − light intensity shinning on grob

X and Y − Change the position of the light source in the graphics window

6.5 Labeling and Annotation

To add labels or display or undisplay pre−defined annotation:

- `Select` the atoms, residues, molecules, or objects you wish to label in the graphical display or in the ICM Workspace.
- Then use the label options in the `Display Tab`.

To add new user−defined annotation:

- `Select` the atoms, residues, molecules, or objects you wish to label in the graphical display or in the ICM Workspace.
- Right click on the selection and choose "Annotate Selection".

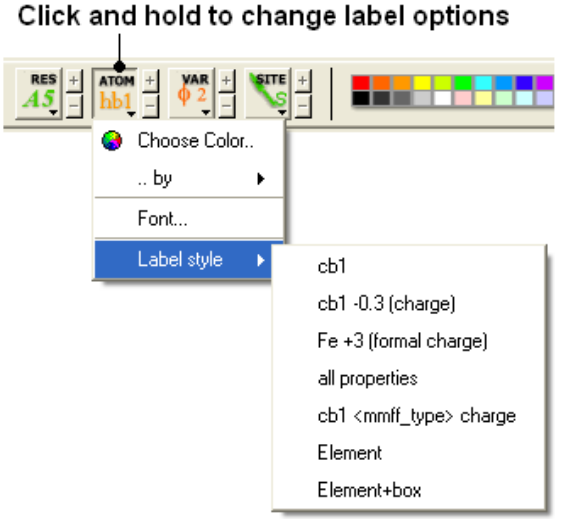
6.5.1 Labeling

Labeling options are contained within the Labels or Display Tab. In many cases clicking and holding a label button will allow you to view more options.

6.5.2 Labeling Atoms

Select the atoms you wish to label (see `display structure` or `selection toolbar`).

- Select the **display** tab.
- Click the **label ATOM** button.



To change the level of label detail:

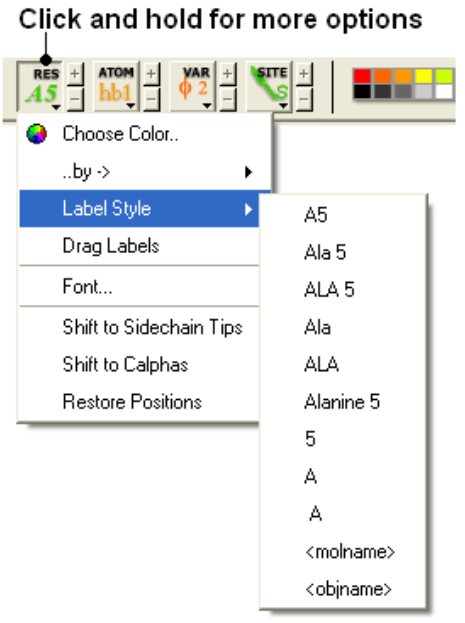
- Click and hold the **label ATOM** button and select the desired level of label detail, color or style.

6.5.3 Labeling Residues

To label residues:

- Select the **display** tab.
- Select the residues you wish to label (see `display structure` or `selection toolbar`).

- Click the **label RES** button.



To change the level of label detail:

- Click and hold the **label RES** button and select the desired level of label detail or style.

6.5.4 Move Residue Label

To change the location of your residue label:

- Select View/Drag res labels.
- If your mouse has a middle mouse button, then click on handle (as shown) of the label you wish to move, and drag it to your desired area.

- If your mouse has no middle mouse button, then click on the Translation icon on the toolbar, and click on the handle (as shown) of the label you wish to move, and drag it to your desired area.

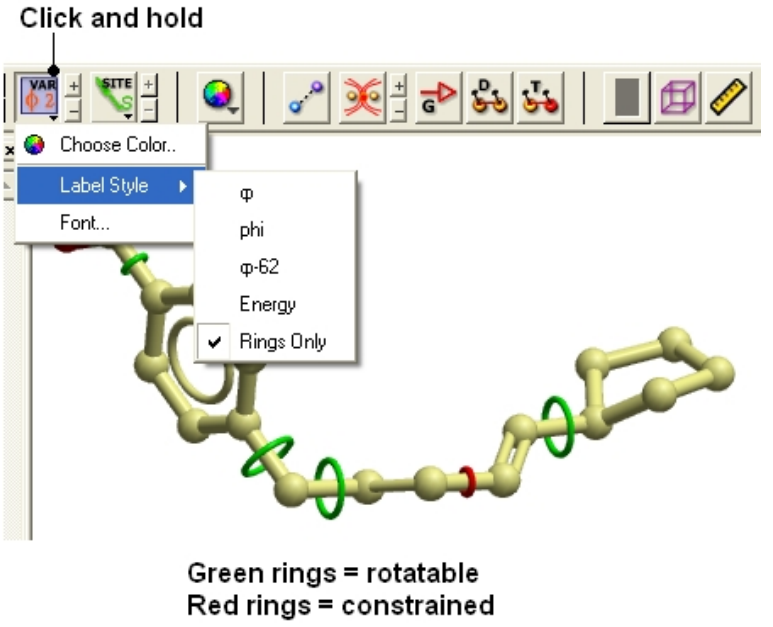
The +/− buttons on the side of the Residue and Atom buttons will shift the label. There are also other **residue label move** options available when you click and hold the residue label button. These options include **Shift to Sidechain Tips**, **Shift to Calphas**, and **Restore Positions**

6.5.5 Label Variables

To label variable angles (dihedral−torsion, planar and phase angle) the molecule needs to be converted into an `ICM object`.

- Convert the molecule to an `ICM object`.
- Select the atoms for which you would like to display the variables (see `display structure` or `selection toolbar`).
- Click on the **toggle variable label** button shown above located in the **display** tab.
- Change the font size by using the +/− buttons.
- Change the font and color by clicking and holding on the variable atom label button.

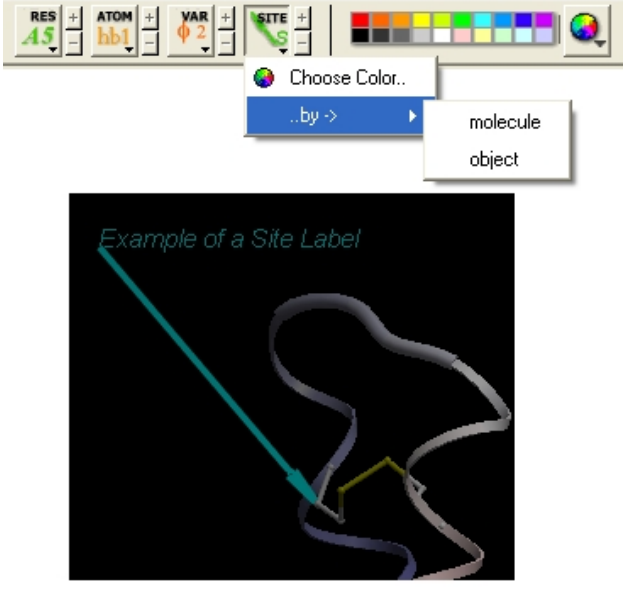
To change the variable label style click and hold the variable atom label button as shown below.



Rings of varying diameter and color are superimiposed on rotatable bonds. Green rings with large diameter are considered less constrained than rings with small green rings. Red rings are highly constrained and non−rotatable. When the **Label Style/Energy** option is selected the first number displayed represents the bond angle, the second the energy and the third the worst energy that could be achieved by rotating the bond.

6.5.6 Labeling Sites

To display and undisplay sites use the Toggle Site Label button shown below



- Click the **label SITE** button.

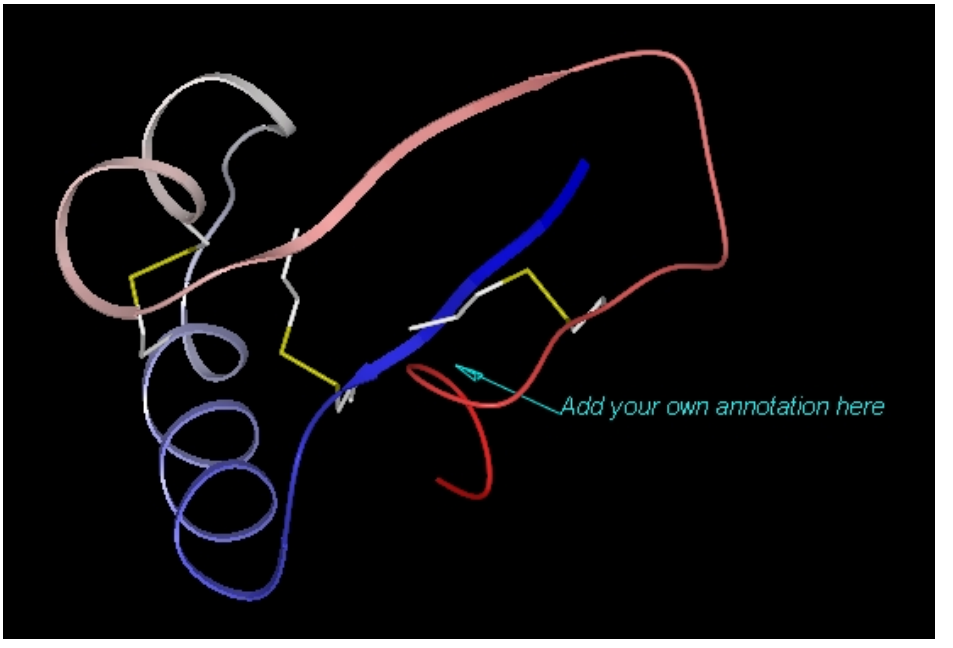
To change the level of label detail:

- Click and hold the **label SITE** button and select the desired level of label detail or style.

NOTE: To create your own site labels see the `Label Annotation` section.

6.5.7 Annotation

To annotate a protein structure. Select the region you wish to annotate (see `Selection Toolbar`).



- Right click on the selection.
- Select the option **Annotate Selection**.
- Enter the annotation into the text box and select ok

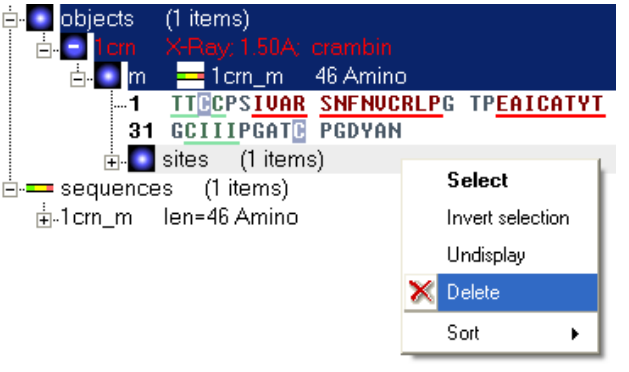
To change the detail (such as residue number) contained within the annotation.

- Click in the bottom left hand corner of your annotation.

To undisplay an annotation click on the site button in the Display tab.

To permanently delete an annotation.

- Right click on the Sites box in the ICM Workspace and select delete (see below).



To change the direction the arrow is pointing or move the arrow.

- Click on the `translation button` (or use the middle mouse button).
- Click on the end of the arrow and drag to the desired position.

6.5.8 Changing Label Colors

To change the color of any label:

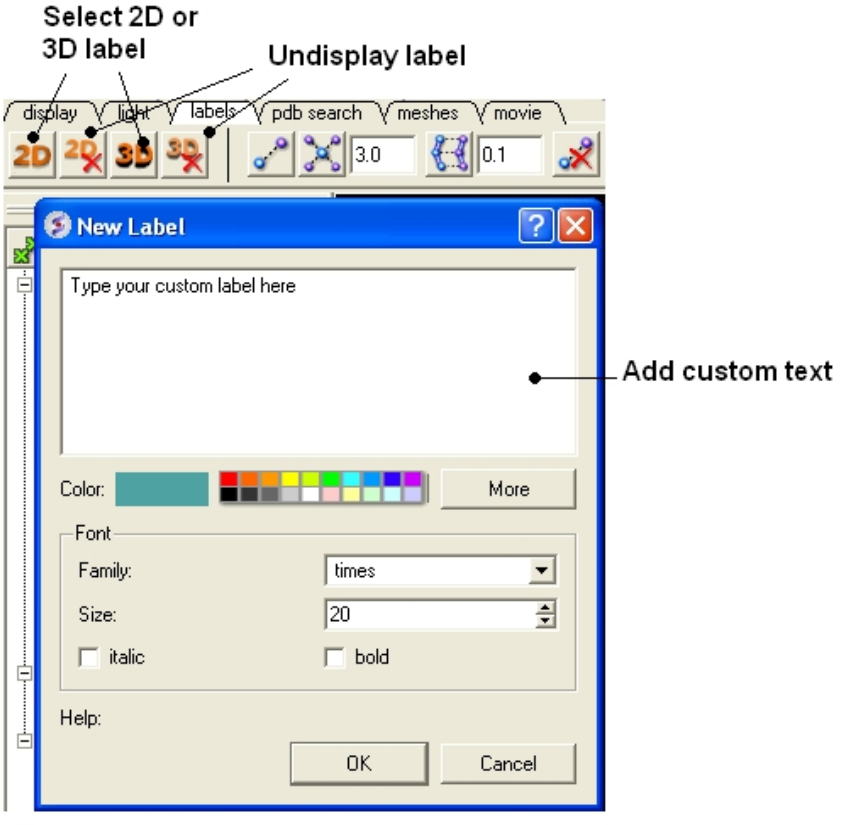
- Click and hold down the required label button and a menu as shown below will be displayed.

- Select **color.**

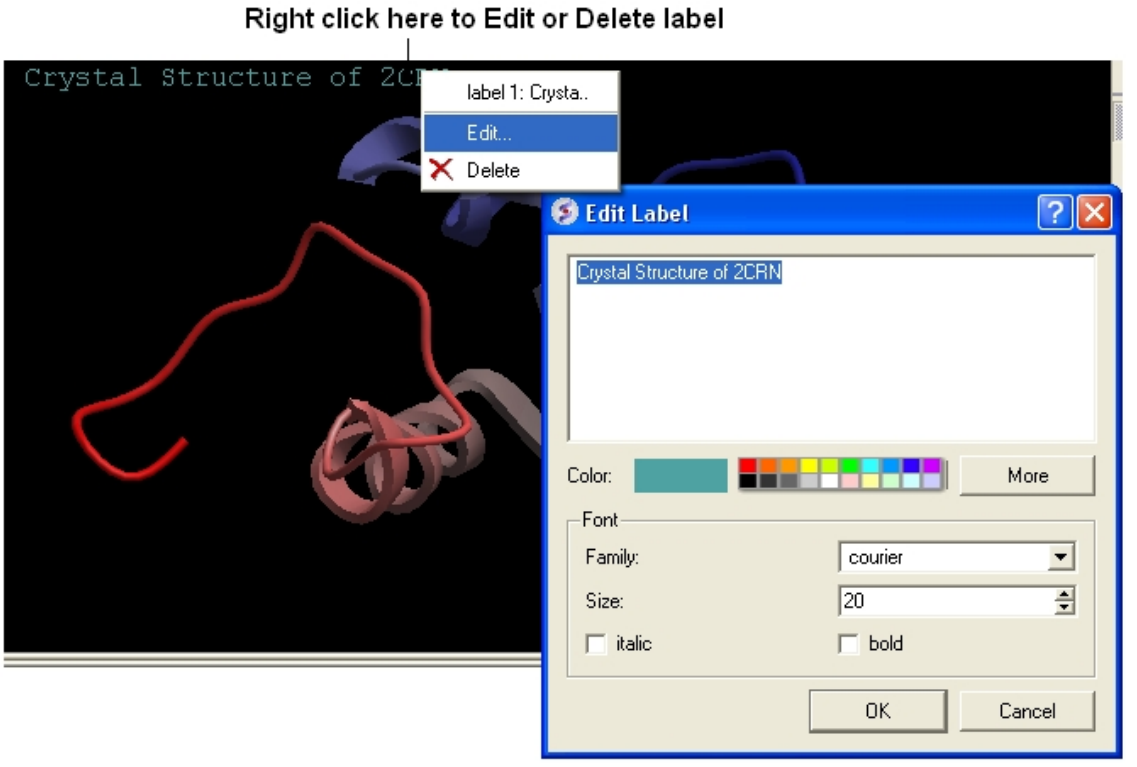
6.5.9 Customized Label 2D or 3D

To generate a customized a label:

- Select the **labels** tab.
- Select either 2D or 3D button.
- Enter your label and select the desired color, font and size.



To **edit** or **delete** a label − right click on the label in the graphical display as shown below.



6.5.10 Undisplay Customized Label

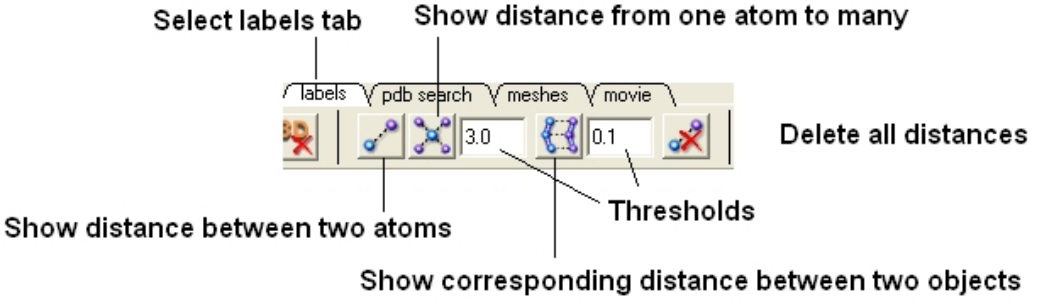
Undisplay Residue, Atom, and Variable Label Any label that is displayed can be undisplayed by selecting the region of the molecule related to the label and clicking on the corresponding label button in the labels tab. For example if you wish to undisplay an atom label − click the atom label button. If a label is displayed the coresponding button in the **display** tab will be shaded blue. When you delete the button will return to grey. 2D and 3D labels have an undisplay button (red cross on the button see `customized label section`).

Undisplay 2D or 3D label Click onthe undisplay label button in **labels** tab.

NOTE: A label can also be deleted by right clicking on the label in the graphical display and selecting **delete.**

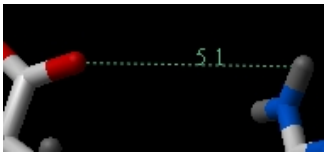
6.5.11 Labeling Distances

Within the **labels** tab there are tools for calculating and displaying distances. These tools can also be found in the `Tools/Analysis` menu.



To display distance between two atoms:

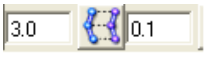
- Click on the labels tab (previously called advanced tab).
- Select the atoms between which you would like to find the distance. (See `selection toolbar`)
- Click on the 'Show Distances Between Two Atoms' Button
- The distance will be displayed in angstroms, in green.



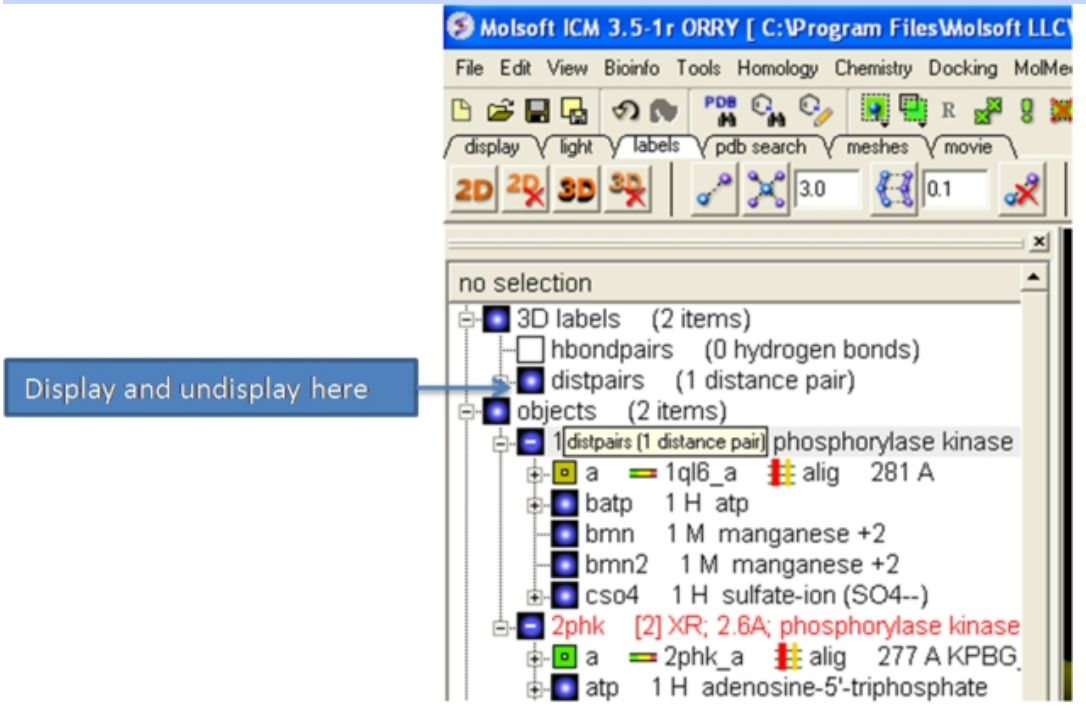
To find the distance from one atom to many:

- Click on the labels tab (previously called advanced tab).
- Select the atom from which you wish to measure the distance from (See `selection toolbar`)
- Click on the 'Show Distances From One Atom To Many' button.
- The distances will be displayed in green.

The maximal and minimal distances can be selected by entering values in the boxes shown here (below) in the labels tab (previously called Advanced tab).



NOTE: Distances can be displayed and undisplayed in the 3D labels section of the ICM Workspace. See image below.



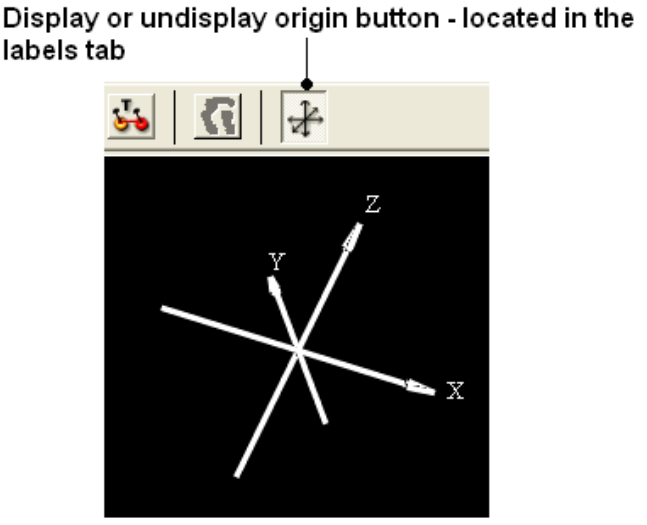
To change the color of the distance label

- Right click on the **distpairs** under the **3D labels** section of the ICM workspace and select **Change Color**.

6.5.12 (Un)display Origin

To display and undisplay the axis of the coordinate frame (origin):

- Select the **labels** tab and select the **toggle origin** button.



6.5.13 Displaying Tethers

Theory

A tether is a harmonic restraint pulling an atom in the current object to a static point in space. This point is represented by an atom in another object. Typically, it is used to relate the geometry of an ICM molecular object with that of, say, an X−ray structure whose geometry is considered as a target. Tethers can be imposed between atoms of an ICM−object and atoms belonging to another object, which is static and may be a non−ICM−object. You cannot create tethers in ICM−Browser, however, if the project that you have loaded contains tethers between two objects, then they can be displayed:

- Click on the **display tab** (previously called advanced tab).
- Click on the 'Toggle Tethers' button.

6.5.14 Displaying Distance Restraints

Theory

A distance restraint imposes a penalty function on the distance between two atoms in the same object. You cannot create distance restraints in ICM−Browser, however, if the project that you have loaded contains distance restraints, then they can be displayed:

- Click on the **display tab** (previously called advanced tab).
- Click on the 'Toggle distance restraints' button.

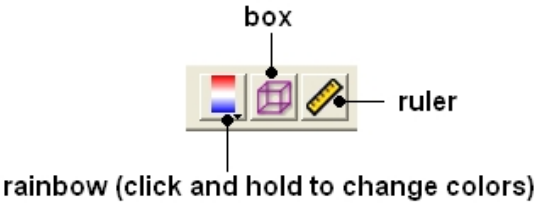
6.5.15 Display Clash

To display a clash the file needs to be an ICM Object.

- `Select` the region around which you would like to identify clashes.
- Select the display tabs and the "toggle clashes" button shown below.

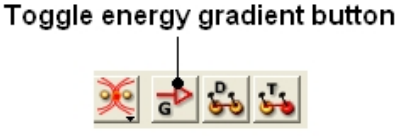
6.5.16 Display Rainbow, Box, Ruler

To (un)display a rainbow key, box or ruler use the buttons shown below located i n the **display** tab.



6.5.17 Display Gradient

This button is located in the **display** tab.



This option is described in detail in the language manual
`http://www.molsoft.com/man/icm-commands.html#display-gradient` #endif

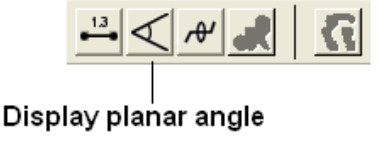
6.6 Display Distances and Angles

6.6.1 Display Distance Between Two Atoms − the quick way

- Click on the **Display** tab
- Click on the **Distance between two atoms** button shown below.
- Click on the atoms you wish to measure.
- Distance will be displayed in the graphical display. You can turn this on and off in the ICM Workspace panel under the heading **3D labels**.

6.6.2 Display Planar Angle

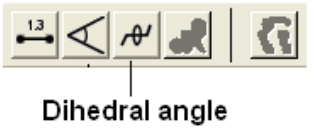
- Select the **display** tab.
- `Select` three atoms.
- Select the button shown below.



NOTE: This option is also available in the `Tools/Analysis` menu.

6.6.3 Display Dihedral Angle

- Select the **display** tab.
- `Select` four atoms.
- Select the button shown below.



NOTE: This option is also available in the `Tools/Analysi s` menu.

6.6.4 Delete Label

To delete distance or angle labels

- Select the **display** tab.
- Select the delete distance or angle label button shown below.

Delete distance or angle labels button in display tab

6.7 Graphics Effects

All the visual effects tools can be accesed by the `View Menu` or click on the corresponding button in the View Tools panel shown below.

6.7.1 Fog

Fog Toggle(Ctrl + D) : this feature creates a fog−like environment for your object, so that the part of your structure that is closer appears clear and the distant parts are faded as if they are in fog. The `clipping planes` control the point at which the fog begins.

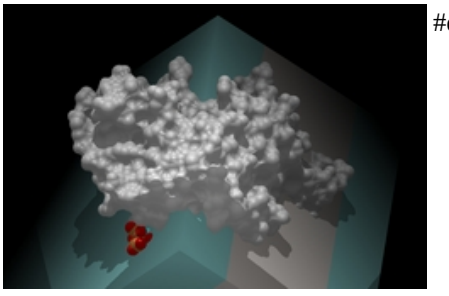
- View/Fog

6.7.2 Shadows

- View/Shadows

OR

select the shadow button shown below.



#endif

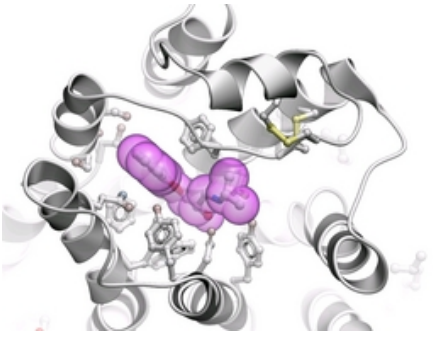
6.7.3 Sketch Accents

To make images as shown below use:

- View/Sketch Accents

6.7.4 Elegant Ribbon Ligand Sketch

- Display Tab
- Click and hold Hydrogen button
- Select Elegant Ribbon+Sketch



6.7.5 Perspective

Toggle perspective Ctrl_P this will add perspective to your structure, enhancing depth in the graphical display.

- View/Perspective

6.7.6 Animate View

This tool is described in more detail in the `Molecular Animations and Transitions` section.

6.8 Graphics Shortcuts

The left mouse button can be mapped onto different graphics tools which can be selected from the right hand tool bar.

Note: (1) You can access many non−rotation modes directly from the rotation mode by using Middle and Right−mouse buttons, as well as by using the right, top and left margins of the graphics window. (2) You can access the rotation mode from non−rotation modes by pressing Ctrl.

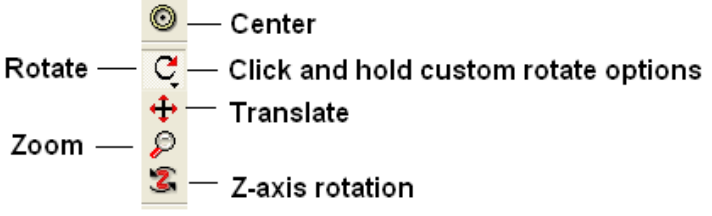
- rotation (**the default** , press Ctrl if you in the non−rotation modes)
- translation (the middle mouse button in the rotation mode)
- zooming in and out by dragging the mouse up and down (the left margin in the rotation mode, or use the mouse **wheel)**
- Z−rotation (the top margin in the rotation mode)
- selecting by box (the right mouse click in the rotation mode)
- selecting by lasso (Ctrl−draw lasso in the rotation mode)
- picking out atoms (a toggle)
- picking out and labeling residues (a toggle)
- moving the front clipping plane (the top section of the right margin in the rotation mode)
- moving the rear clipping plane (the bottom section of the right margin in the rotation mode)
- moving the slab (the middle section of right margin in the rotation mode)
- unclipping (Ctrl−U)
- rotating torsions (Ctrl−left−mouse−click in the rotation mode)
- connect and unconnect separate molecules to movement controls

Many useful graphics tips are summarized `here`.

NOTE: Key mouse controls are summarized in the command line manual here `http://www.molsoft.com/man/graphics-controls.html`

6.9 Molecule Move Buttons

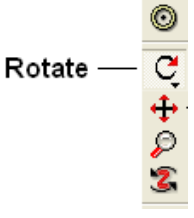
To move your structure it must first be displayed in the graphics window (for instructions on how to display a structure see the `Display Tab`). All of the following options are displayed in the Move Tools toolbar (shown below).



6.9.1 Rotation

In order to achieve the best pose for a picture or to enable the study of a certain region of your structure in more detail you may need to rotate the structure:

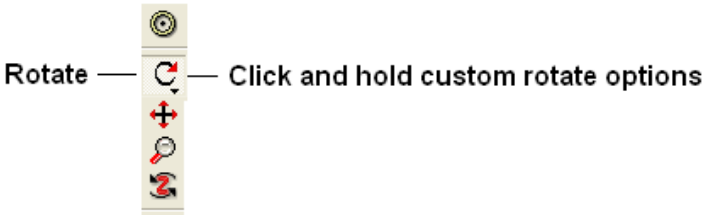
- Click on the **rotation** icon on the toolbar.



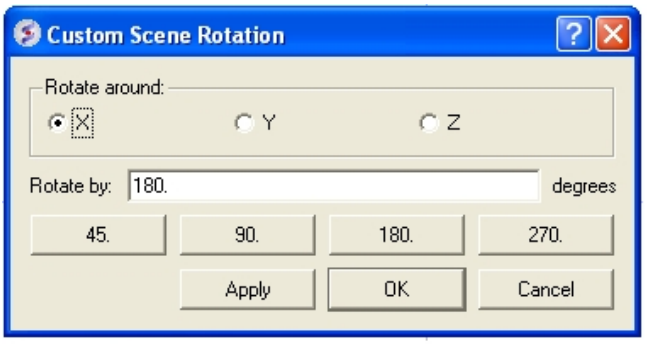
- Click and drag on your structure in the display window until it is in the desired position.

6.9.2 Custom Rotation

An option is provided to customize the rotation of the molecule. This allows exact rotation by a specified number of degrees.



- Click and hold down the rotation button and a data entry box as shown below will be displayed.
- Enter the number of degrees of rotation you require and in which X, Y or Z coordinate.

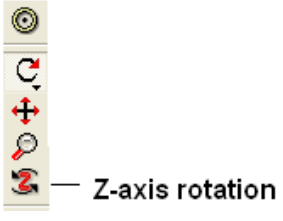


To continuously rotate the picture:

- Click on the **continuous rotation** icon on the toolbar.
- Click, hold, and slightly move your mouse anywhere on the graphical display window. The point at which you hold your mouse, is the direction to which the object will turn.
- Positioning the mouse towards the center of the display will move the object slower than if the mouse is positioned towards the edge of the graphical display.

In order to rotate your picture around the Z−axis:

- Click on the **Z−axis rotation** icon on the toolbar.



- Click and drag your object around the Z−axis until it is in the desired position.

6.9.3 Translation

To translate your structure up, down, left, or right:

- Click on the **translation** icon on the toolbar.

- Click and drag on your structure in the display window until it is in the desired position.

When you are displaying more than one object and you wish to translate one object in relation to the other on the Z−axis:

- Right click on the name of the object you wish to move in the ICM workspace and select connect to object. This object is now independent from the other object and can now be manipulated separately.
- Click on the **Z translate** icon on the toolbar.
- Click and drag your structure along the Z−axis, moving it closer or further from your unconnected structure.
- Once you are finished, right click on the name of the object which is connected, and click on disconnect.

6.9.4 Zoom

To zoom in or out of your structure:

- Click on the **zoom** icon on the toolbar.

- Click and drag your mouse up to zoom in and down to zoom out.

You can also zoom in and out directly with the right−mouse−button *without* explicitly switching to the zoom tool, if you use the **left 5%−margin** of the graphics window.

6.9.5 Center

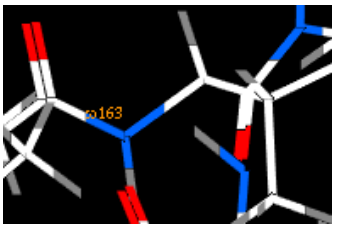
To restore your picture to the center of the graphical display window or to center on a selection:

- Make a `selection` of the region you wish to zoom into − if no selection is made the whole structure will be centered.
- Click on the **center** icon on the toolbar.

6.9.6 Torsion Angles

To alter the torsion angle of certain residues of your structure:

- `Convert` your pdb structure into an ICM object.
- Click on the **change torsion angles** icon on the toolbar (see button key above).
- Click and drag on the atom around which you wish to rotate a residue. The changing angle will be displayed in orange.



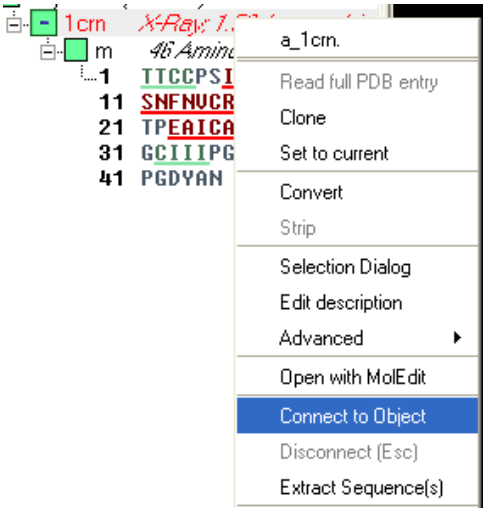
NOTE: This option can be used more effectively in conjunction with the `variable label` option.

6.9.7 Connect (Move)

When there is more than one object displayed in the graphical display window the objects are connected to one another. If you wish to move or manipulate one object independently from the others you need to **connect** to it

To do this from the ICM Workspace:

- Right click on the name of the object you wish to move in the ICM workspace and select **Connect to Object**. The object will now be colored yellow.

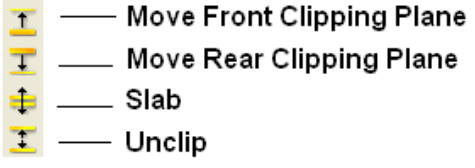


- The object is now controlled separately from the rest of your objects by your mouse.
- Disconnect your object by once again right clicking on the name of the object in the ICM Workspace and selecting disconnect in the drop down menu or **Press the ESCAPE key**.

Note: you can temporarily switch to the global rotation in the connected state if you press Shift

Note: use the Escape button to disconnect

6.10 Clipping Tools



The clipping tools allow you to adjust the frames of the ICM window, changing the clipping planes.

Clipping planes can also be moved *without* switching to the clipping tool, if you click the right hand margin of the graphics window:

- The top section of the right 5% margin of the graphics window: moves the back clipping plane
- The middle section of the right 5% margin of the graphics window: moves the slab (both clipping planes)
- The bottom section of the right 5% margin of the graphics window: moves the front clipping plane

In order to move the front or rear clipping planes of your screen:

- Click on the **Move front clipping plane** or **Move rear clipping plane** icons on the toolbar.
- Click and drag the respective plane frontward or backward, depending on how you wish to clip it.

You can also move the **slab** of viewing window, keeping the distance between the front and back clipping planes. In order to adjust the area of the structure where your viewing window is located:

- Click on the **Slab** icon on the toolbar.
- Click and drag the slab frontward or backward, depending on the desired area of the structure you wish to see.

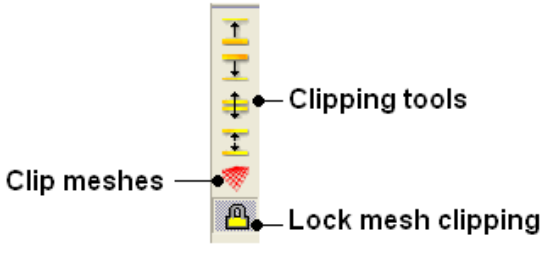
If you have made changes to the clipping planes which you do not wish to keep or you wish to automatically fit your entire structure within the clipping planes:

- Click on the **Unclip** icon on the toolbar. This will automatically set the clipping planes to fit your object.

6.10.1 Mesh Clipping

Clipping tools can be used to adjust the frames of the mesh independently of other objects.

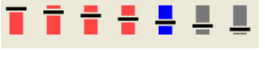
The buttons shown below can be used for this purpose.



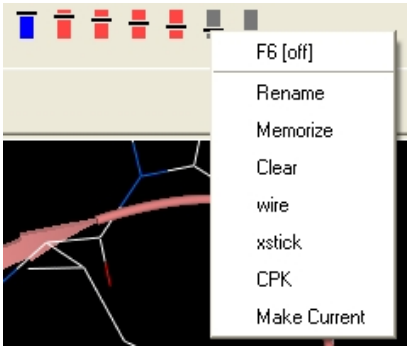
The buttons used for clipping are described in the section entitled `Clipping Tools`.

6.11 Graphic Layers

To display and undisplay layers of a structure you can use the buttons shown below. Seven layers can be created and within each layer different structural representations can be displayed.



Right click on one of the layer buttons and a number of options can be chosen as shown below.



To change the display in one of the layers:

- Right click on one of the layer buttons.
- Select a representation wire, xstick or CPK.
- You can do this for each of the seven layer buttons.
- Click on the layer button to display and undisplay. If the layer button is shaded red then the layer is not displayed. If the layer button is shaded light blue then it is displayed. You can switch between layers by clicking on the button or using the. You can use the **memorize** button to store a particular representation and **clear** to remove a memorized representation.

6.12 Make High Quality Publication Images

6.12.1 Write Image

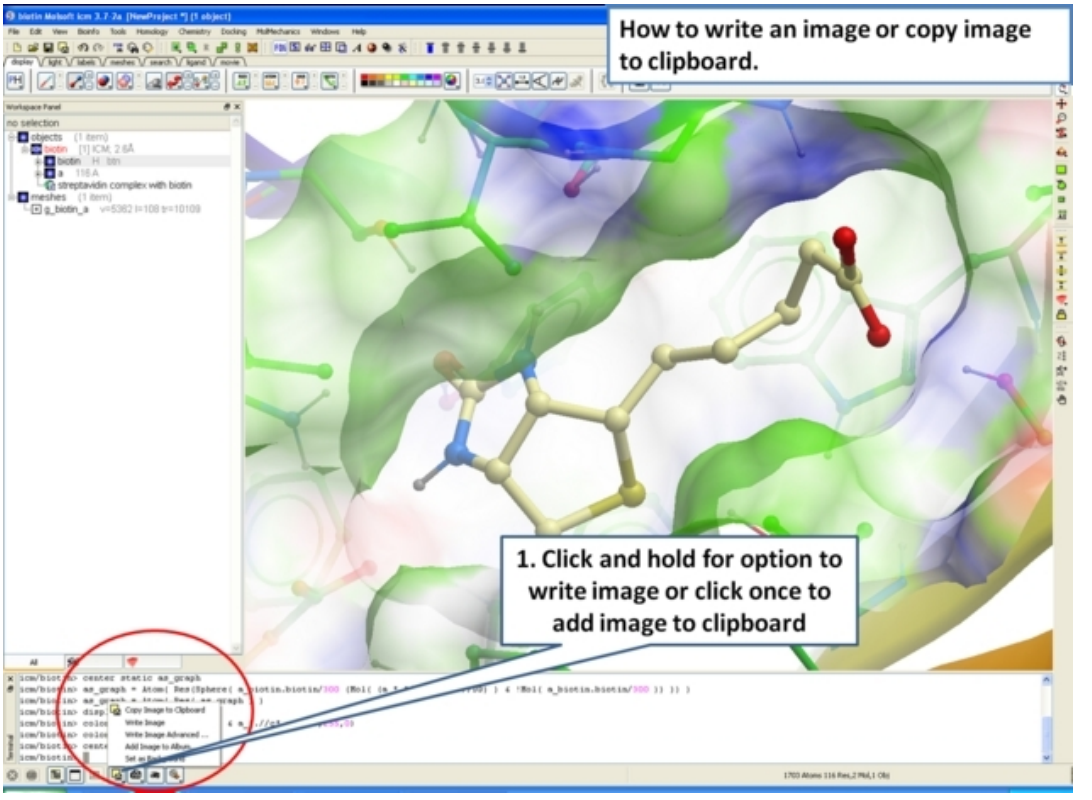
To make high quality publication images:

- File/Write Image

This is described in more detail `here`.

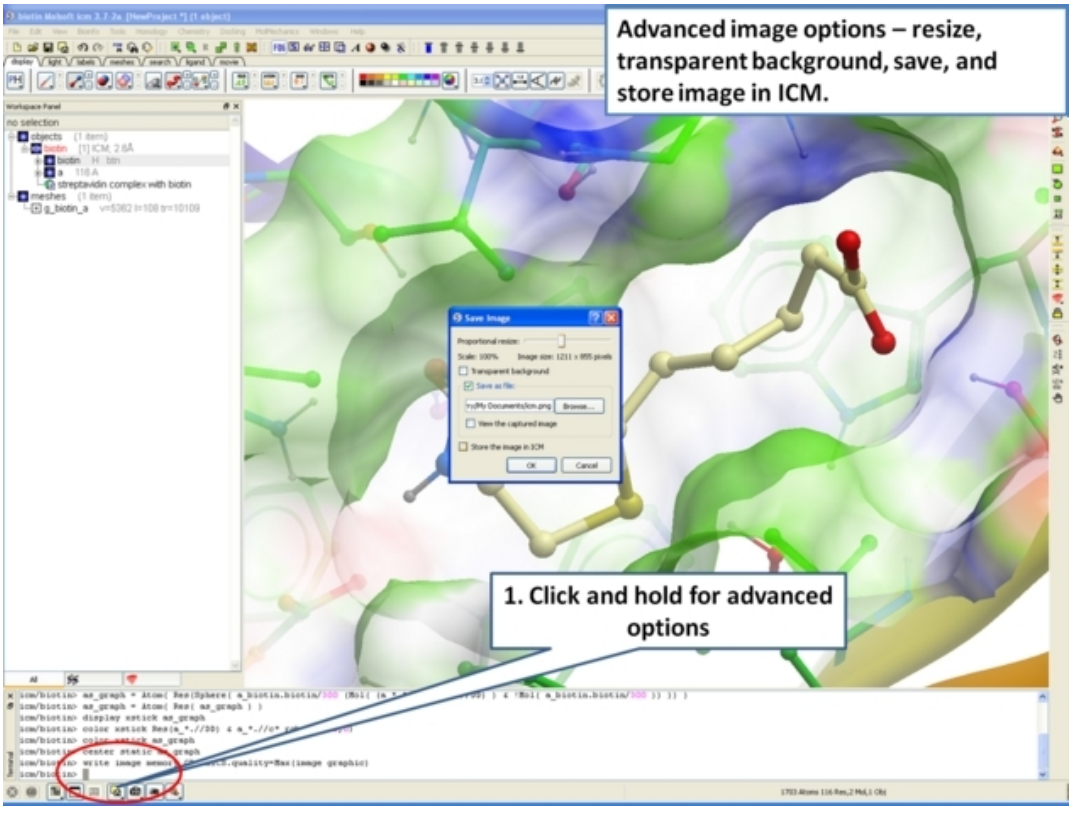
Or, use the button at the bottom of the graphical user interface (see images below).

6.12.2 How to Save an Image to the Clipboard



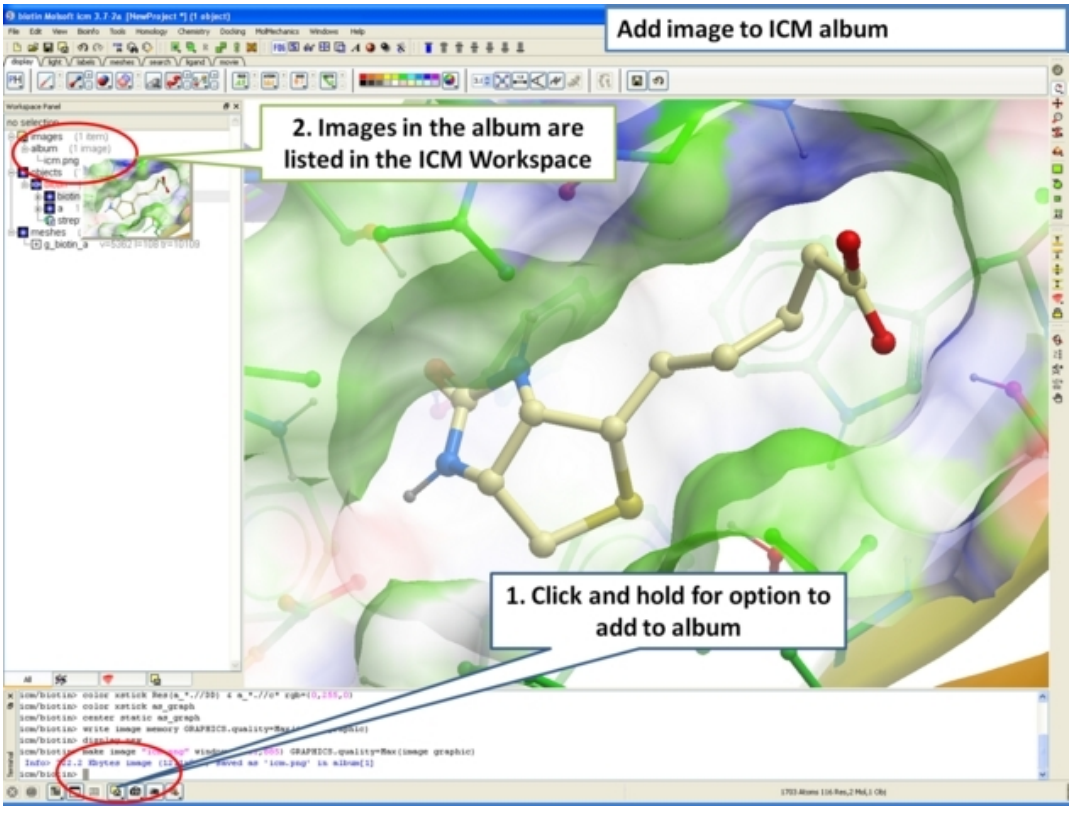
6.12.3 Advanced Image Options.

Click and hold the button shown below for options for resizing, transparent background , and storing an image in ICM.



6.12.4 Add Image to Album

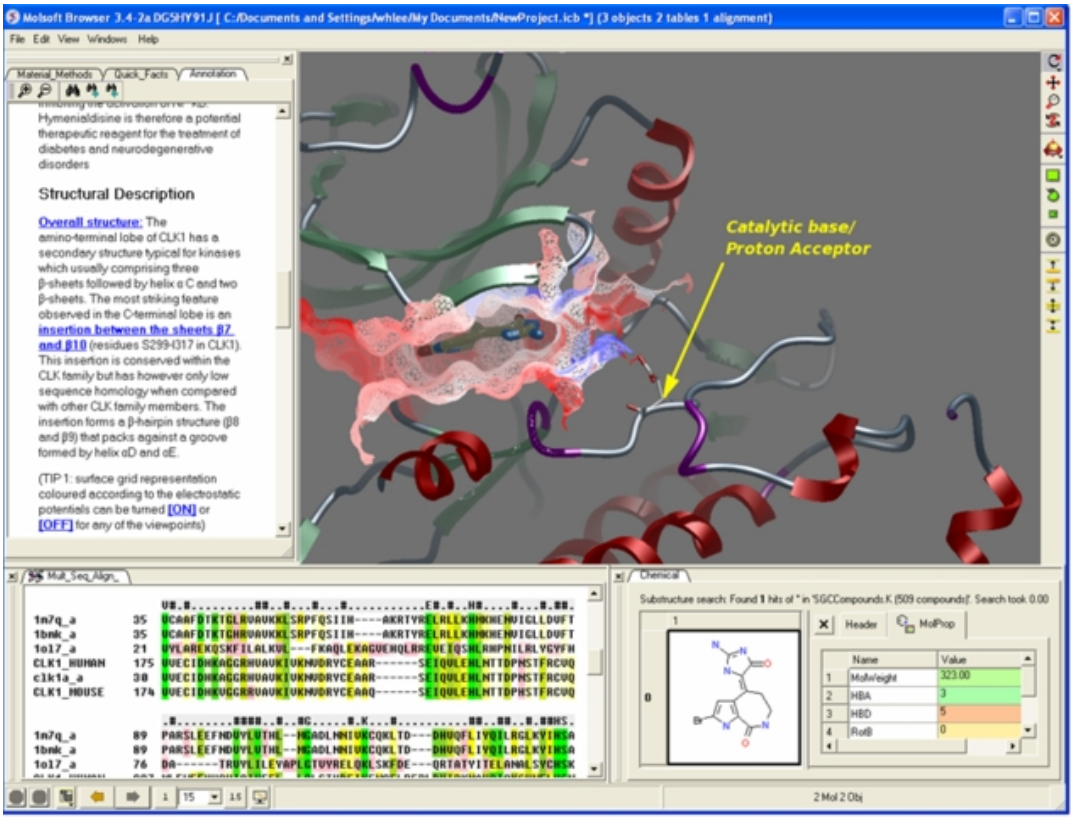
If you are making an `ICM document` you may want to store images inside ICM.



7 Molecular Animations, Slides, and Documents

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

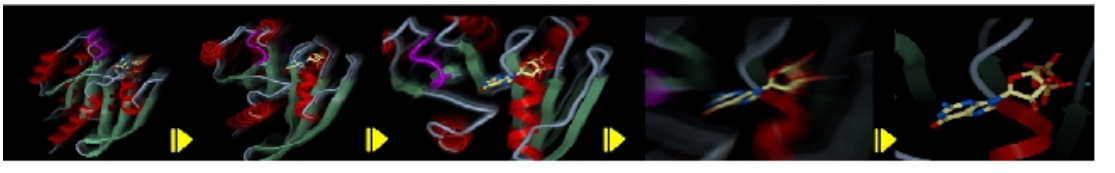
In this chapter you will find a description of the tools available to create files (.icb) containing fully−interactive three−dimensional (3D) molecules and two−dimensional (2D) data. These files can contain multiple interactive views and animations of molecular structures and objects in conjunction with related hyperlinked text, chemical, biological sequence, alignment and data views. The files are small and easily transferable and downloadable. The files can be used for Molecular Presentation and Documents inside the ICM browser or displayed on the web and in PowerPoint using the `ActiveICM` plugin.



For examples of ICM Molecular Documents please see MolSoft's ActiveICM product page at www.molsoft.com/activeicm.html

7.1 Molecular Animations and Transitions

Learn how to build fully interactive and interruptable animations.

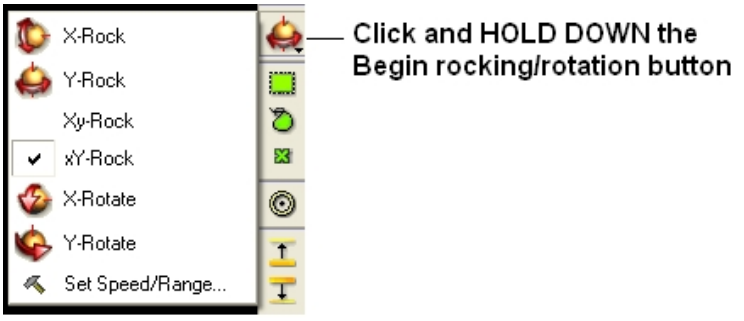


Smooth Animated Transitions

7.1.1 Make Animation

To quickly produce an ICM Molecular Animation:

- Click and hold down the "Begin rocking/rotation" button shown in the picture below.
- Choose from the following options − X−Rock, Y−Rock, Xy−Rock, xY−Rock, X−Rotate, and Y−Rotate.

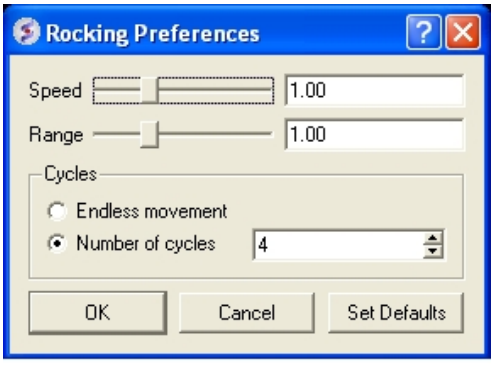


NOTE: Default rocking representation can be changed in the `File/Preferences/Gui` menu.

7.1.2 Change Speed, Range and Cycle Length of Animation

To change the speed, range and cycle length of the animation:

- Click and hold down the "Begin rocking/rotation" button shown in the picture above.
- Choose the set speed range option and change the speed and range using the drag bars. Any change will appear in the graphical display behind this box.
- If desired you can change the number of cycles of the animation. This is an ideal tool for `screen−shot movie making`.



NOTE: There is a return to default button in the Rocking Preferences dialog box shown above and defaut values can be changed in `File/Preferences/Gui`.

NOTE: Default rocking speed can be changed in the `File/Preferences/Gui` menu.

7.1.3 Interrupt Animation

An ICM Animation or Transition is fully interactive and is interrupted by a single click of the mouse.

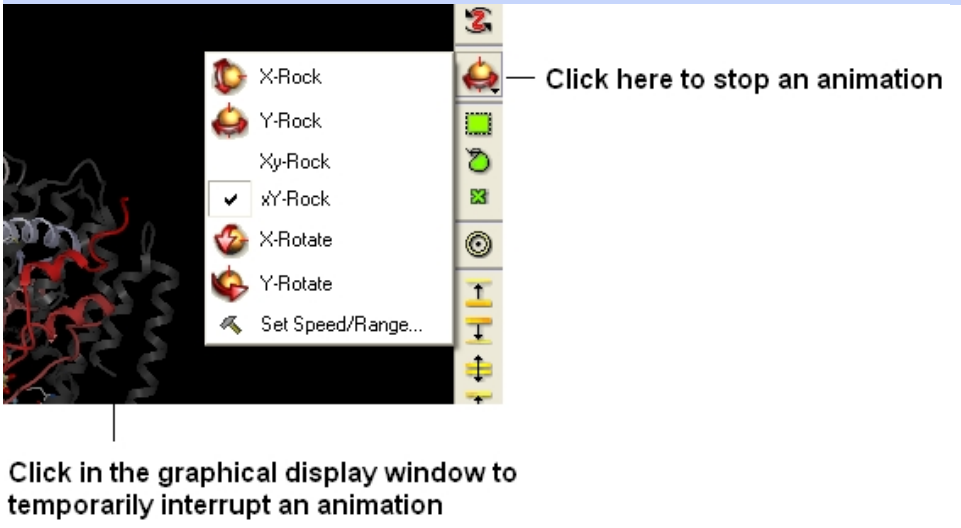
To stop or change an animation or transition:

- Click the "Begin rocking/rotation" button shown in the picture below.

To temporarily halt an animation or transition:

- Click in the graphical display. Once you release the mouse button the animation will start again.

NOTE: If you click on the graphical display during an animation the animation will be interrupted. Whilst clicking and holding the mouse button other operations can be performed such as zooming and selections.



7.1.4 Saving an Animation

An animation can be saved in an ICM project:

`File/Save Project`

Or

as a `slide`.

7.2 Making Molecular Slides

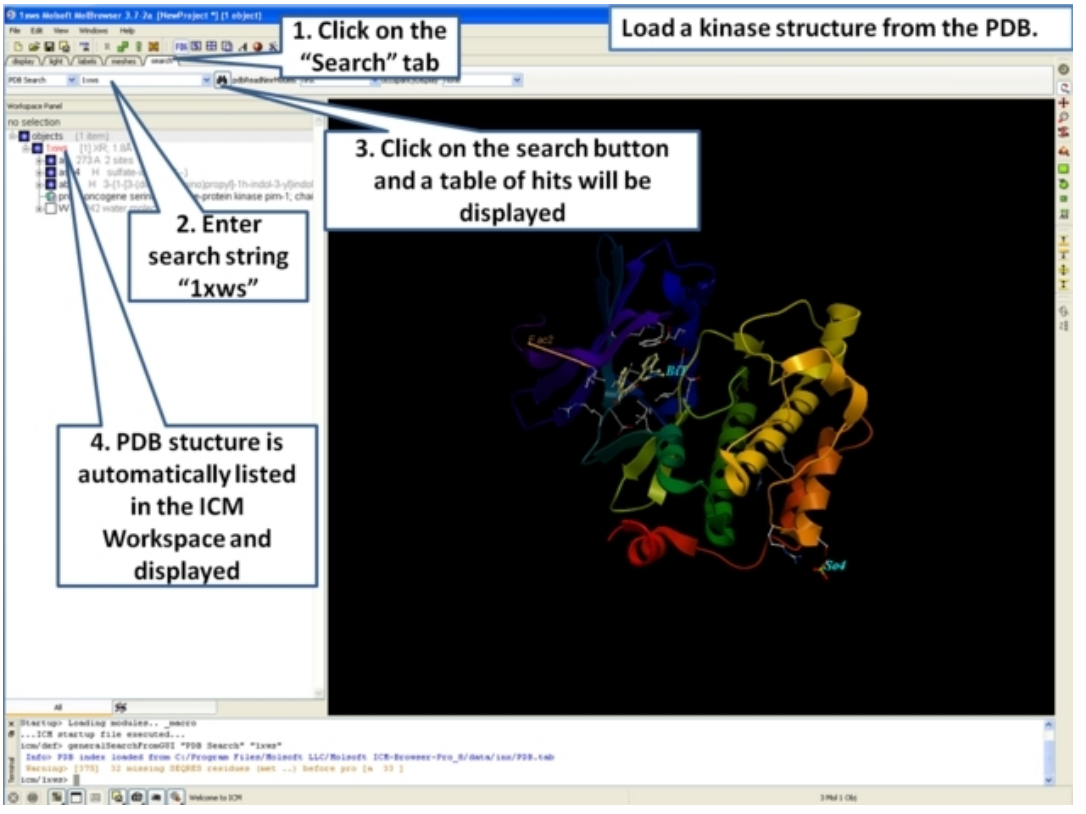
The following information can be stored in a slide.

- Viewpoint
- Window layout
- Current table(s)
- Alignments
- Annotations, labels, user−defined
- HTML
- Preferences for GRAPHICS.quality, ruler style, rocking state information
- For each (mol.) object: representations and their colors, sites
- For each grob (mesh): representation and colors.

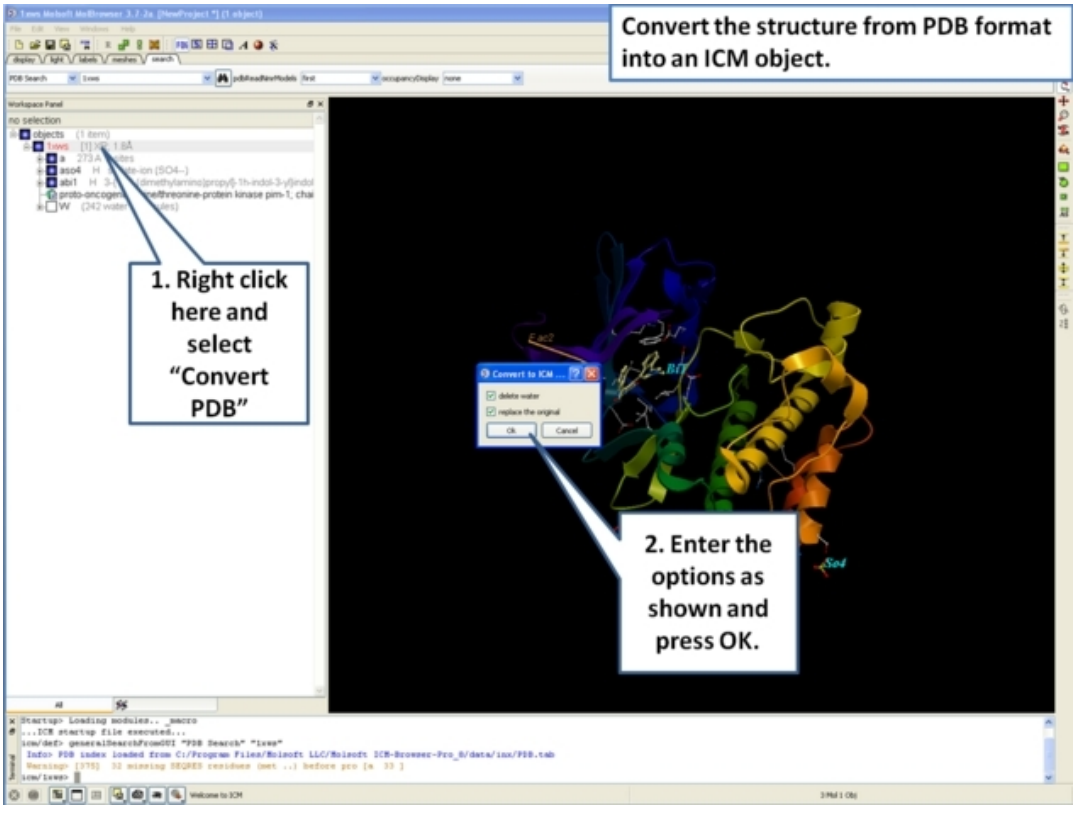
This tutorial takes you through the steps to create a series of fully interactive 3D slides. The slides can then be embedded into the web, or PowerPoint using ActiveICM or viewed in ICM−Browser (or ICM−Pro).

To begin making ICM Molecular Slides:

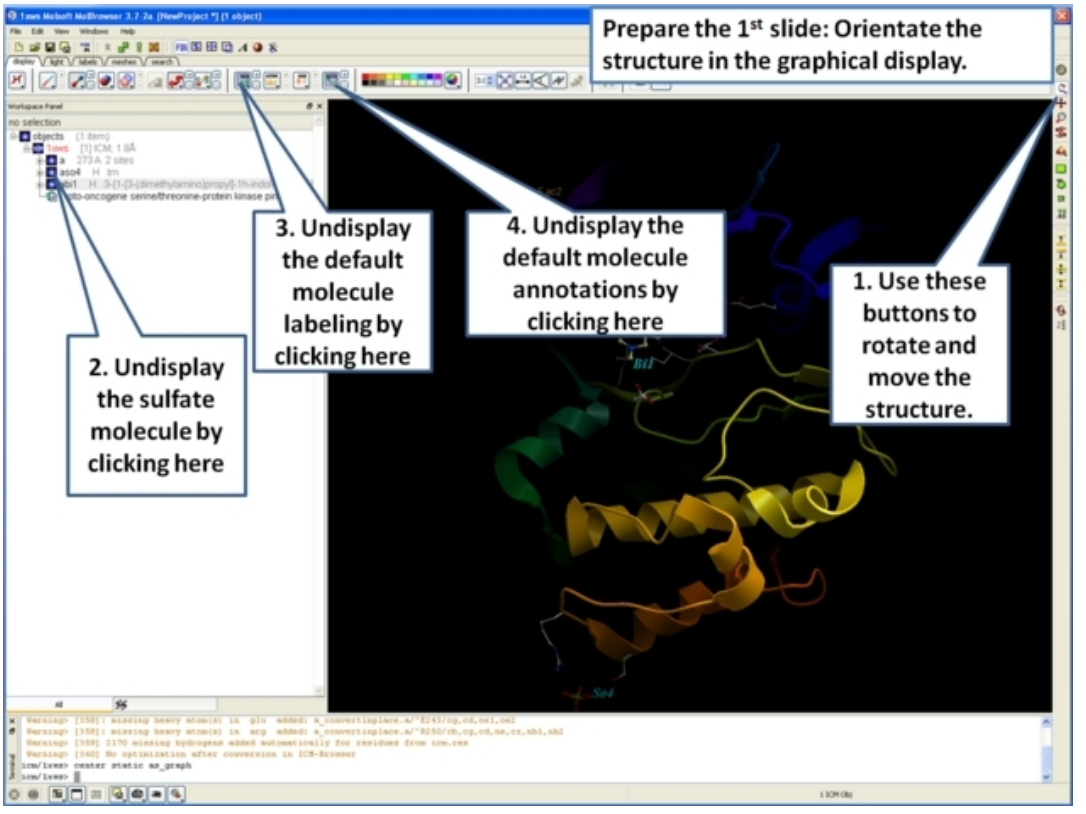
- First load the structure or structures you wish to display in your first slide. Additional structures, labels etc and text can be added at any point during the slide making process. In this example we will load the PDB file 1XWS a PIM1 kinase.



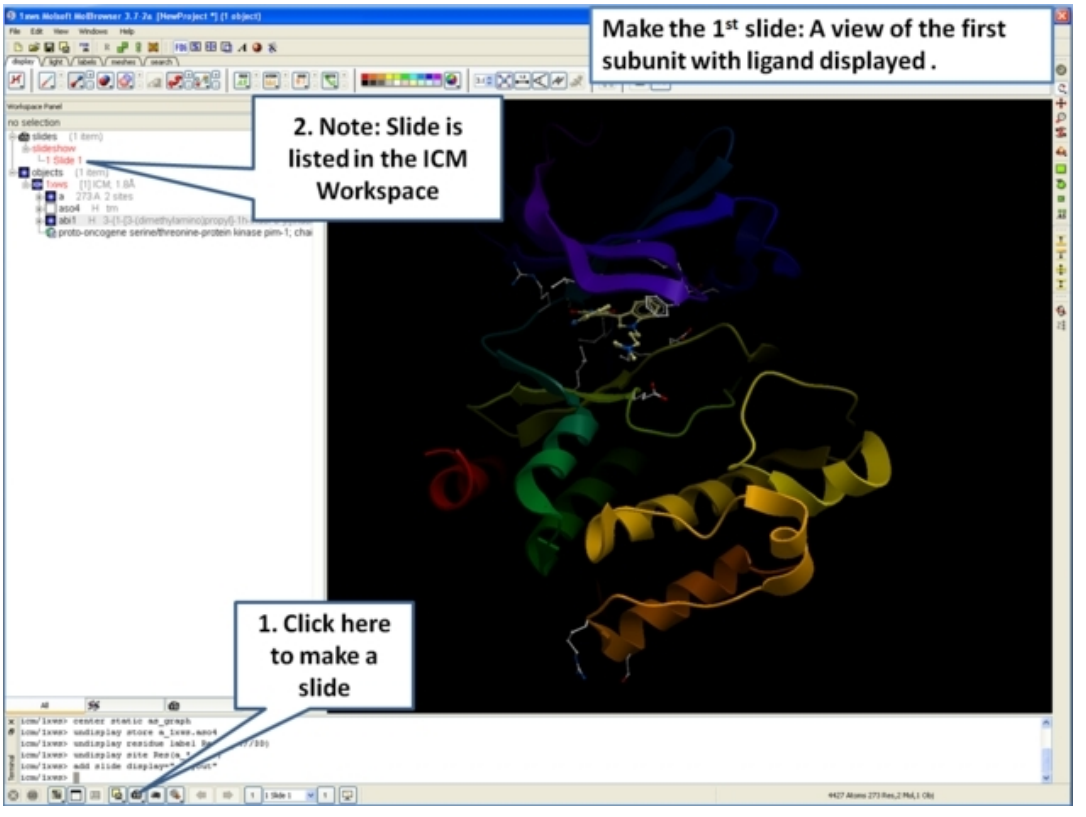
- Next, we will convert the PDB file to an ICM object so we can make slides of the ligand−receptor hydrogen bonds and binding pocket surface.



- Now we are going to prepare the first slide by rotating the protein structure to an orientation which allows the viewer to see the key features of the kinase. For example the bulge in the hinge region (between the N− and C− lobes) which is unique to PIM proteins.

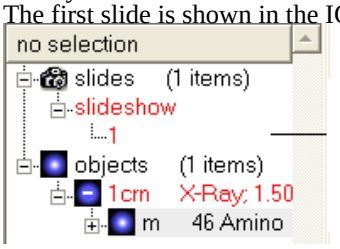


- Next, make the first slide by clicking on the camera button at the bottom of the graphical user interface.



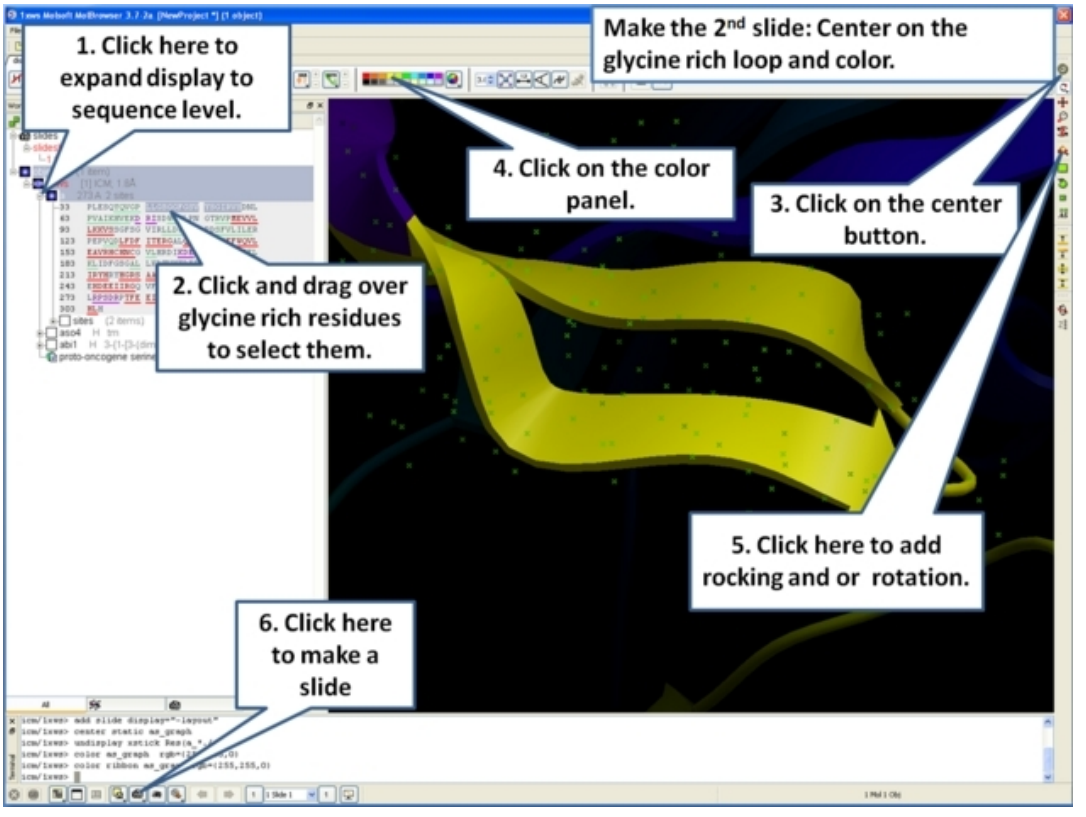
Click to add slide

- Once you have clicked on the camera button you will see that the first slide has been generated. The first slide is shown in the ICM Workspace window as shown below.

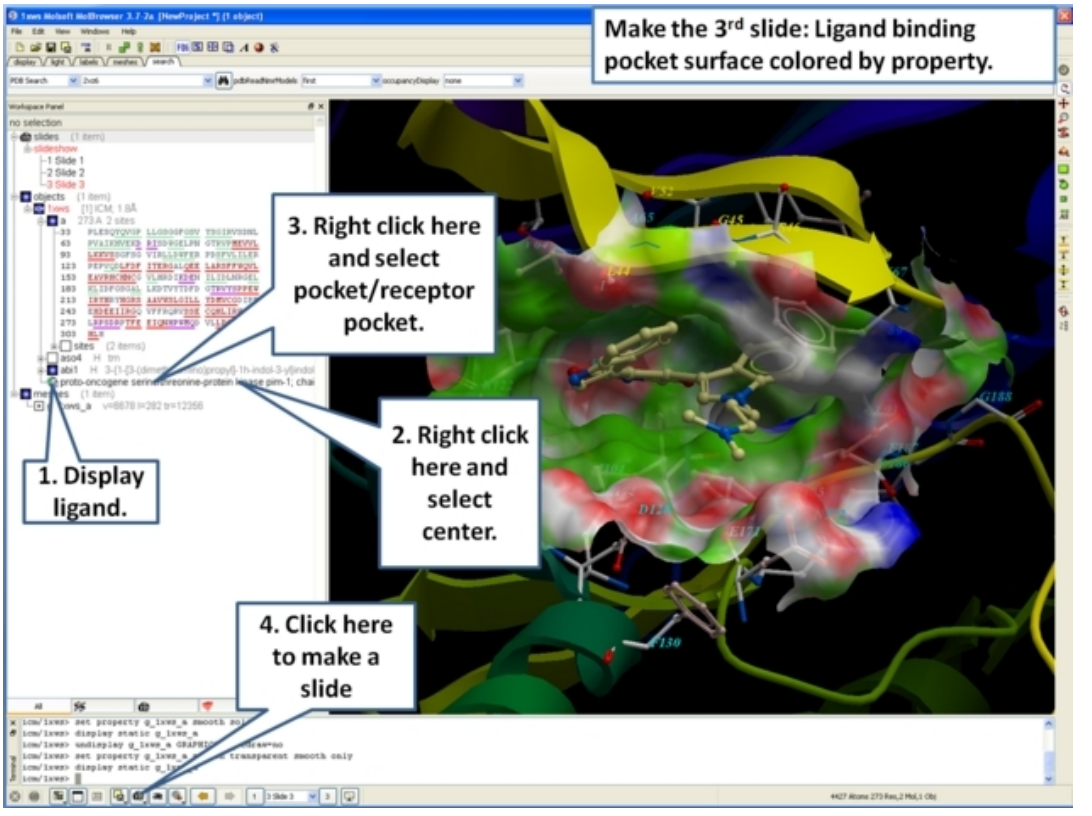


The number and name of the first slide is displayed in the ICM Workspace

- Slides can consist of Static views or `Transitions and Animations`. Here we will zoom into the flexible glycine rich region of the kinase which lays across the roof of the ATP−binding pocket. Click on the camera button and make the second slide



- Next, we will make a slide of the surface of the ligand binding pocket colored by binding property.

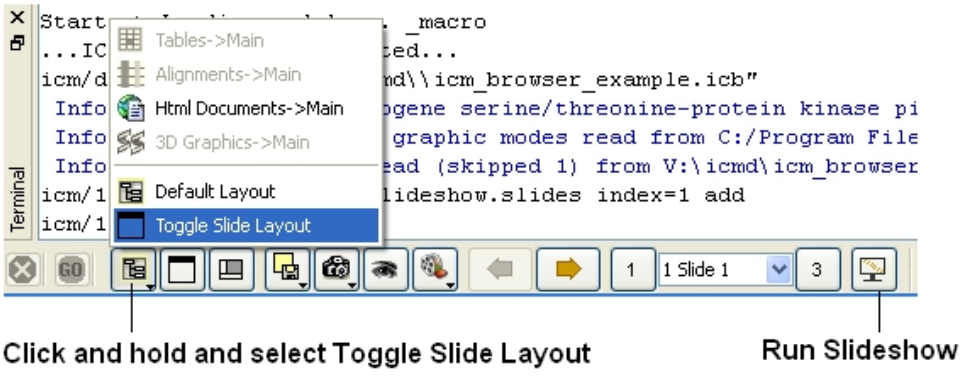


- Now save the document as an icb file. Go to File/Save as...

7.3 How to View and Navigate Slides

7.3.1 View Slide Show

To view a slide show select the buttons shown below:



NOTE: Slides are associated with the objects currently loaded into ICM. Therefore if you delete an object then the slides will not work. However if you delete an object and then re−read the same object with the same name and structure the slides will be ok.

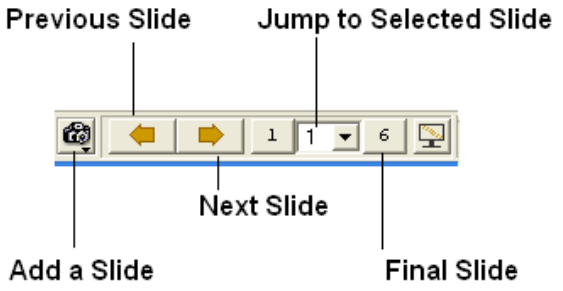
To save a slide show

- File/Save Project

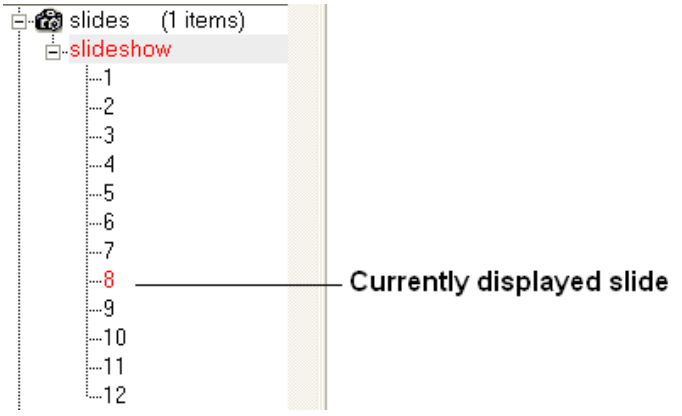
7.3.2 Slide Navigation

You can make as many slides as you wish as described in the `Making Molecular Slides section`.

To navigate through the slides you can use the buttons shown below, the cursor keys for some operations or the right click options in the ICM Workspace.



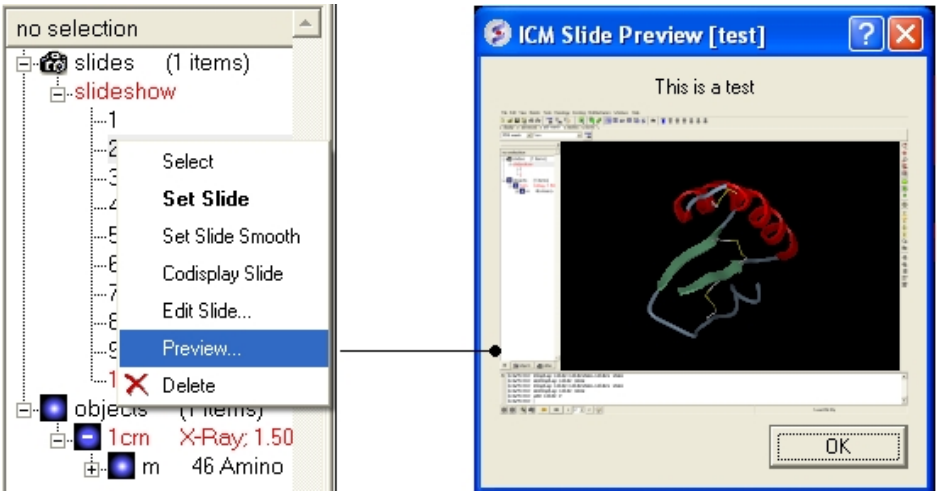
The slide currently displayed is highlighted in red in the ICM Workspace.



To jump to another slide right click and select "Set Slide".

All slides are displayed in the ICM Workspace. You can hover the mouse over a slide name in the ICM Workspace and a thumbnail sketch of the slide is displayed as shown below. This can be used for slide navigation purposes.

Or you can right click on the name of the slide in the ICM Workspace and select the option "Preview".



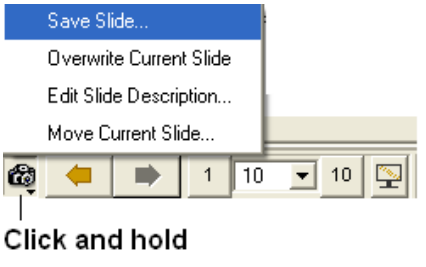
7.4 How to Edit Slides

You can jump to the slide you wish to edit by following the `slide navigation instructions`.

7.4.1 Edit Slide

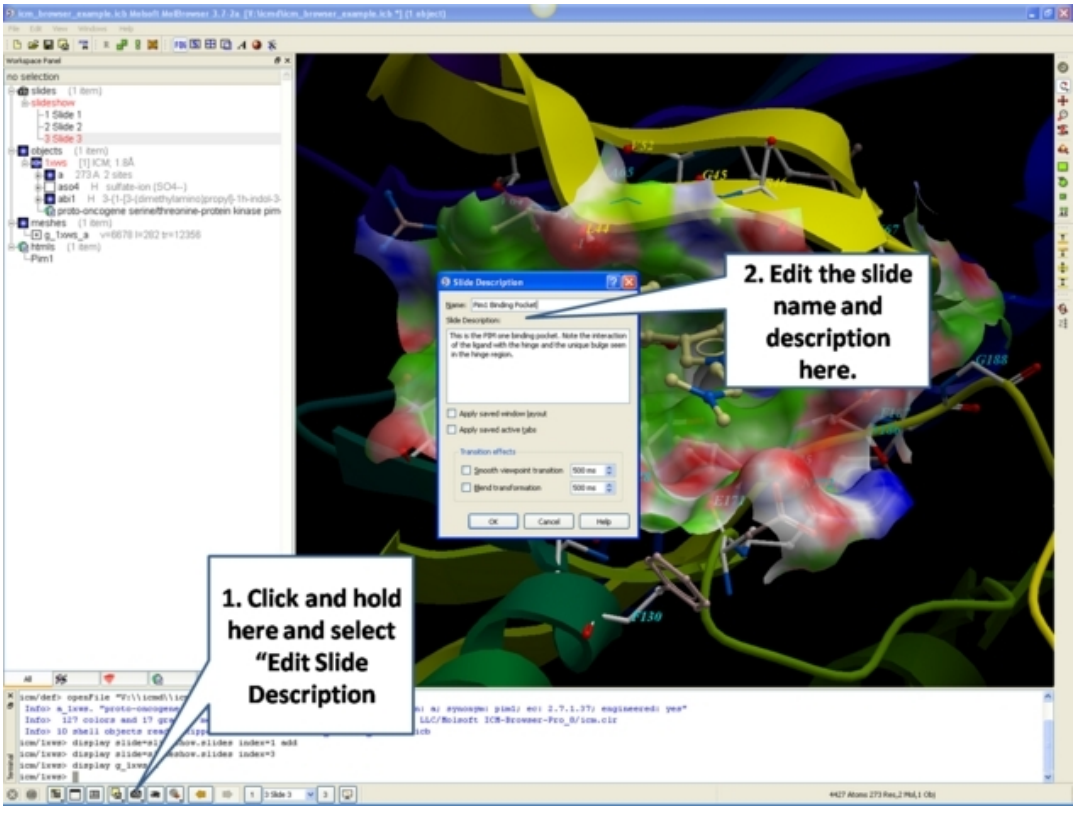
Edit slide contents: To edit the content of a slide the procedure is to add a new slide and then delete the old one or use the "overwrite current slide" option as shown below:

- Click and hold down on the camera button.



To edit a slide description.

- Click and hold down on the camera button and select the option "Edit Slide Description".



- Enter the name of the slide
- Enter a description of the slide.
- If you wish to keep the current window layout or active tabs check the boxes provided

---

To delete a slide:

- Right click on the name of the slide in the ICM Workspace and select Delete.

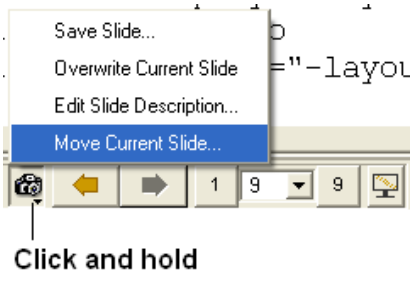
To change the name of a slide

- Right click on the name of the slide in the ICM Workspace and select Edit Slide.

7.4.2 Move Slide

To change the slide's position in the slideshow use the Move Current Slide option and select the new position from the list.

- Click and hold on the "make slide button".
- Select Move Current Slide.



- Select the position in the slide show where you want to move the slide to.

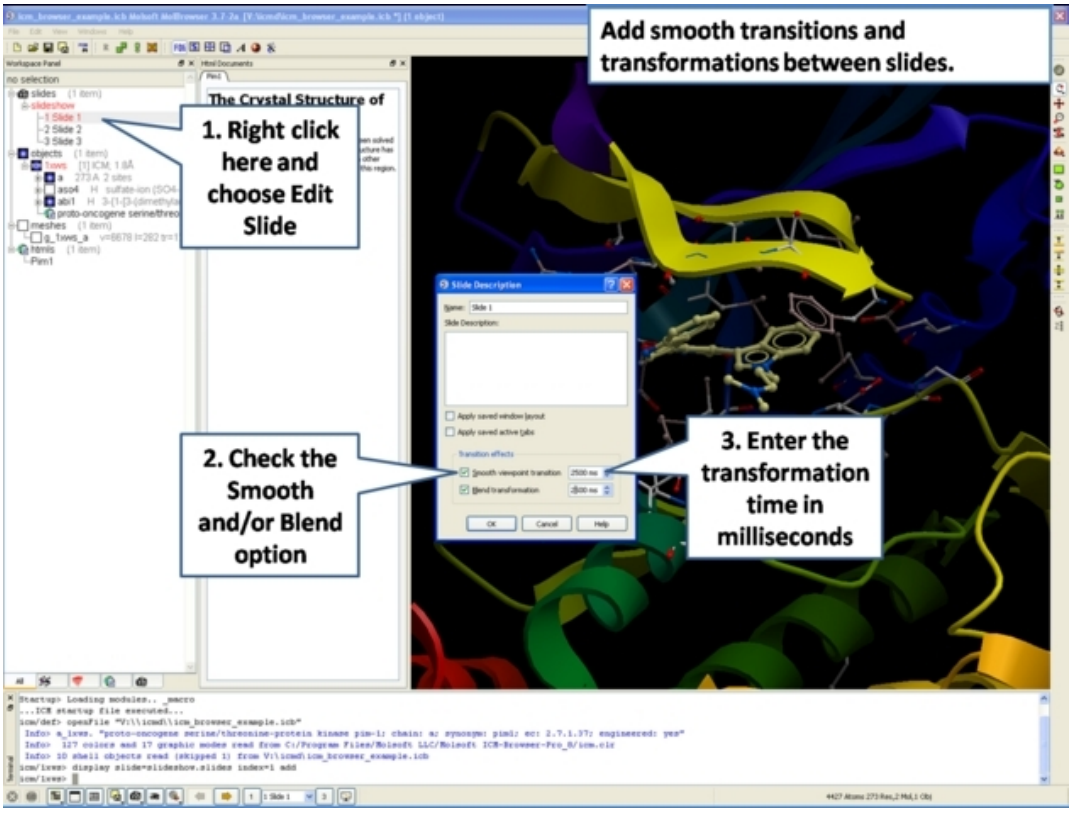
Co−display more than one slide

- Right click on the name of the slide in the ICM Workspace you wish to co−display with the curently displayed slide.
- Select the option co−display slide.

7.5 How to Add Smooth Blending and Transition Effects Between Slides

How to add smooth and blend transitions to a slide.

- Right click on the name of the slide in the ICM Workspace.
- Select **Edit Slide**.
- Select the desired transition effect − **smooth** or **blend** as shown below.
- Select the length of the transition in milli seconds.

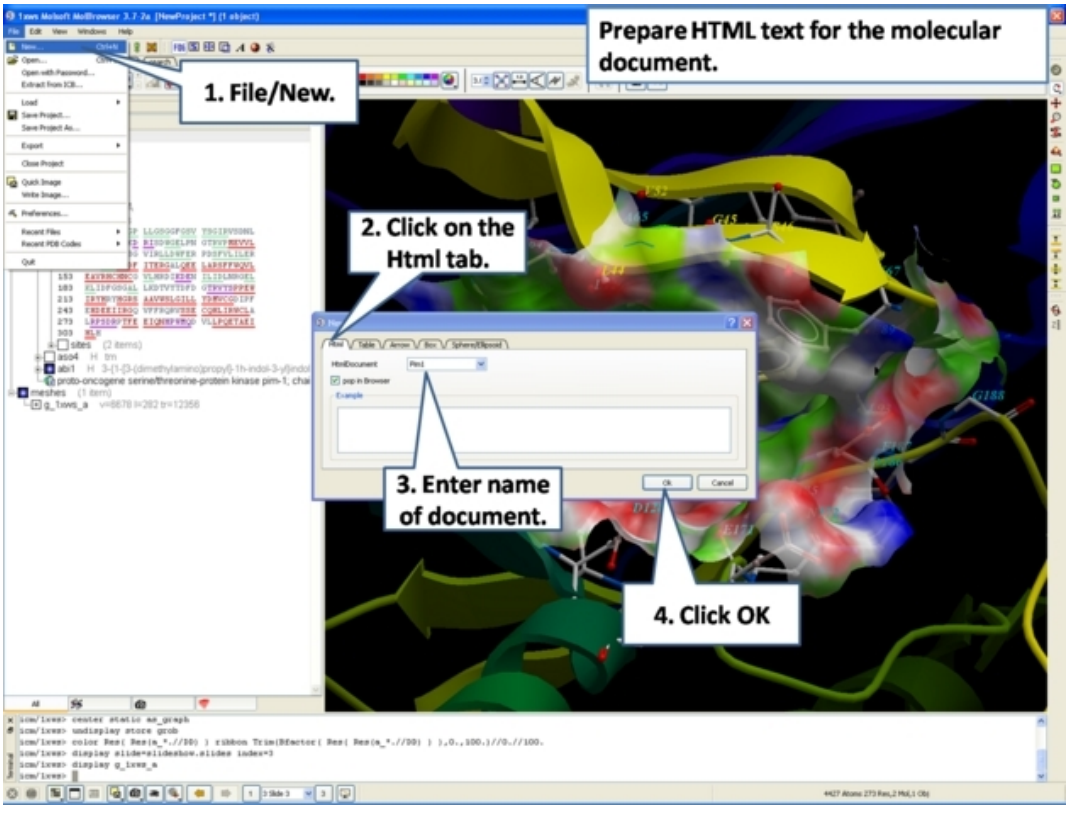


7.6 How to Make Molecular Documents − Link HTML Text to Slides

An ICM Molecular Document contains text and images which can be hyperlinked to the graphical display. Click on the hyperlinked text and then a fully−interactive 3D slide will be displayed. The hyperlinks are usually linked to a set of slides but can also be linked to a series of commands in a script, a web page, a table or alignment. Once a molecular document has been made you can view it in the ICM−Browser (File/Save Project .icb file) or download `ActiveICM` and view it in a web page or Powerpoint.

To begin creating an ICM document

- File/New/ and click on the HTML tab.
- Enter some text. E.g the Name of the HTML document. Formatting can be changed as described in the `edit` section below.
- Click OK



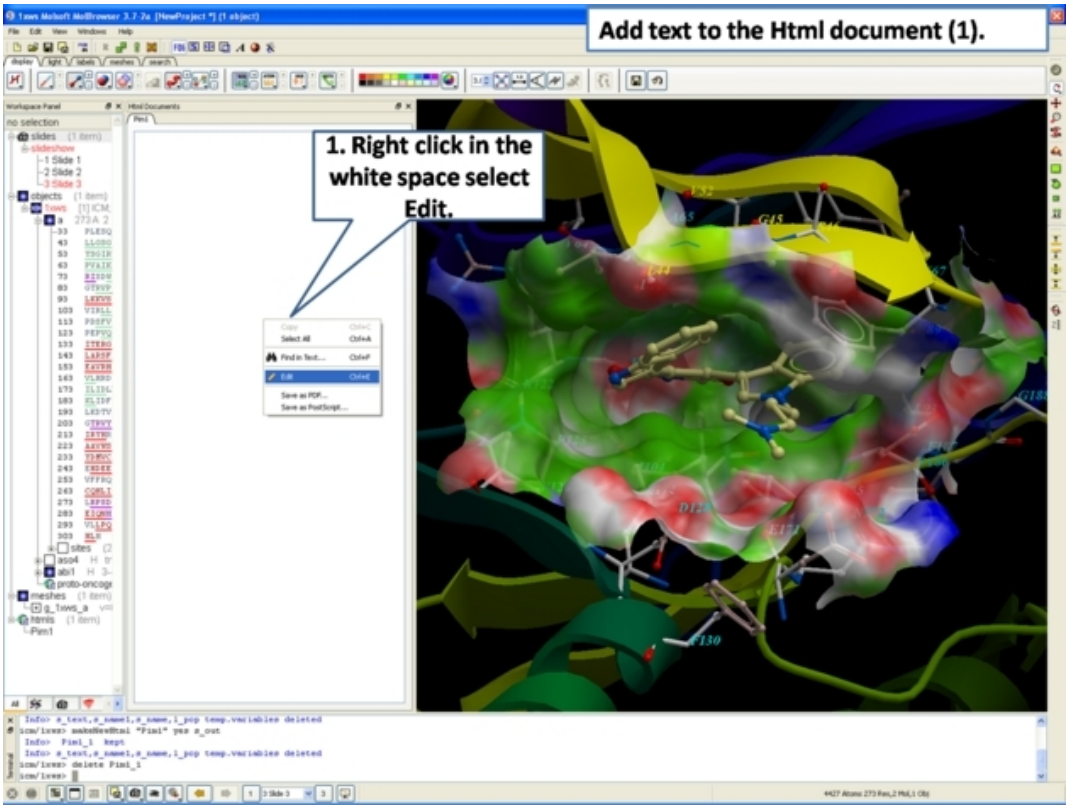
- A HTML text panel will be displayed in the graphical user interface.

NOTE: You can add multiple documents into a single file. The documents will be accessible via tabs at the top of the HTML panel.

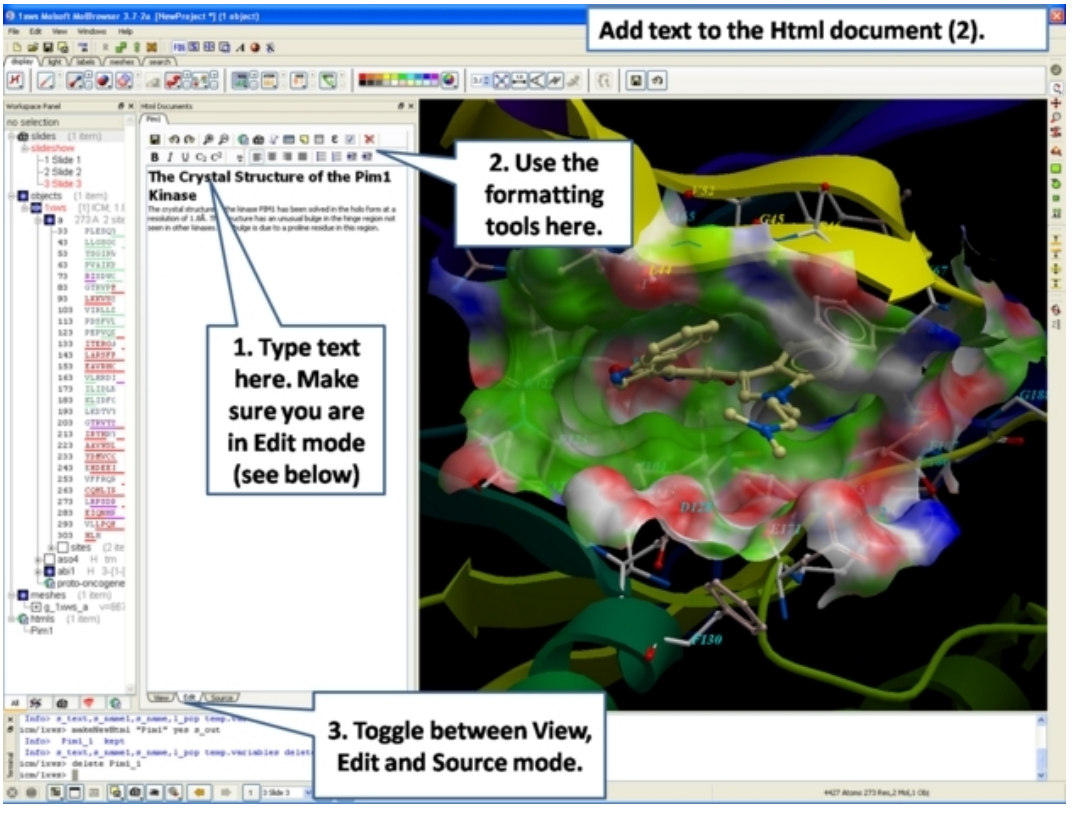
7.6.1 How to Add Text or Edit a Molecular Document

To edit the HTML text in the graphical display

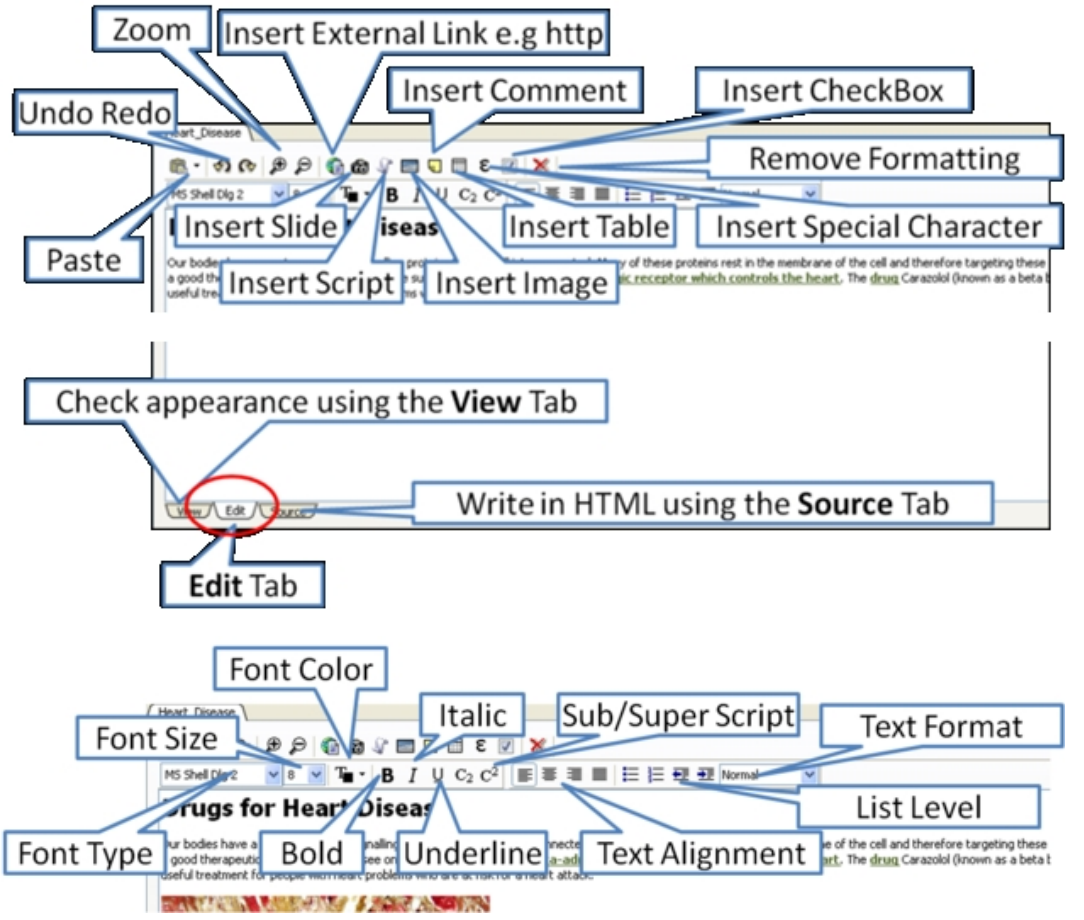
- First `create` an HTML document and the text panel will be displayed in the graphical user interface.
- Right click in the body of the text display panel and select **Edit.**



- Enter text and use the formatting tools provided in the panel above the text editor. Make sure you have selected the **Edit** tab in the HTML editor. You can see your page in the **View** tab or write directly in HTML in the **Source** tab.



The key formatting tools in the HTML editor are shown below.

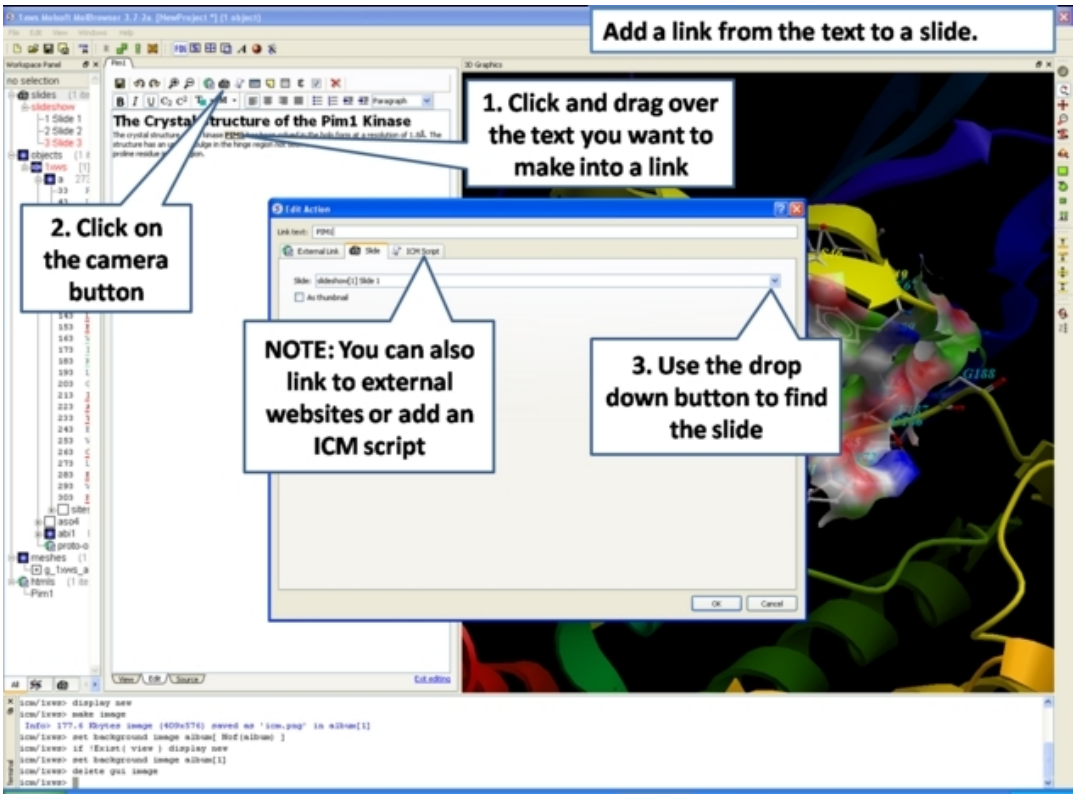


7.6.2 How to Make a Hyperlink Between Text and a Slide

To make a hyperlink between the text and the graphical display (slide)

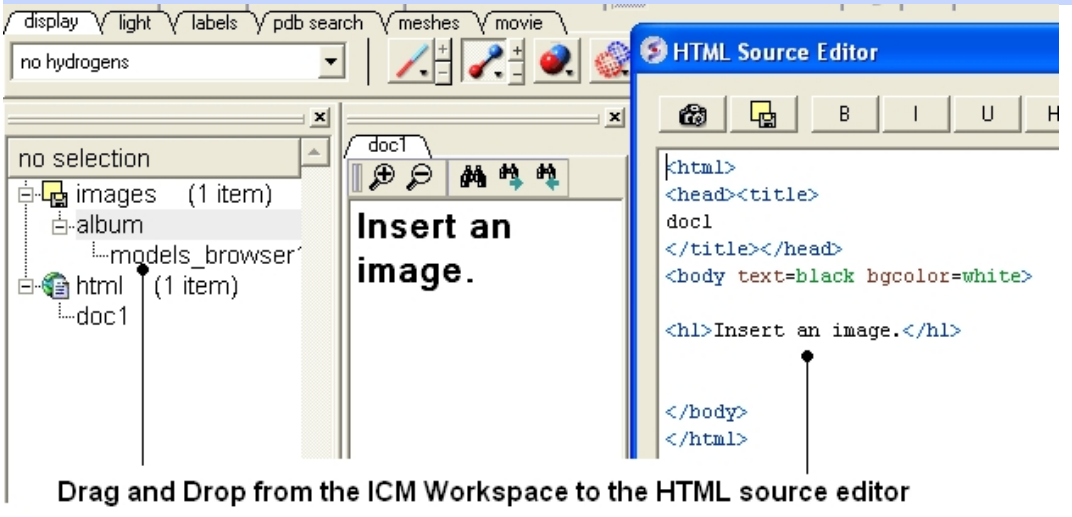
Make a slide or set of slides of the graphical display you wish to link to. See `Making Molecular Slides` for help on this.Once slides have been created:

- File/New/Html
- Right click in the body of the text display panel.
- Select Edit.
- Highlight the text you wish to link to a graphical display − you can do this by left clicking and dragging over the text (selected text will be highlighted in blue).
- Click on the "Camera button" in the HTML editor formatting tool panel.
- Select the **Slide** tab.
- Select which number slide you wish the text to be linked to from the drop down menu.
- There is an option to display the slide as a thumbnail image in the text document panel. Check if appropriate.



7.6.3 Insert Image

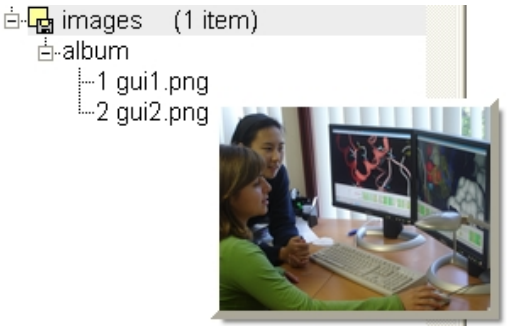
NOTE: The easiest way to add images (PNG or JPEG) into an ICM Document is to use drag and drop. You can drag and drop the image into the ICM Workspace or go to File/Open. Once the image is in the album in the ICM Workspace you can then drag it from the ICM workspace into tthe HTML editor.



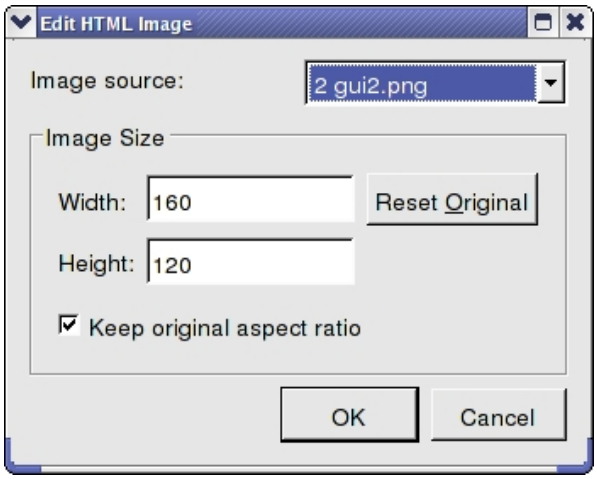
Another way to insert a picture into the HTML text panel

- First read the image into the ICM photo album File/Open OR Drag and Drop from directory into the ICM Workspace.

The image name and preview will then be displayed in the ICM Workspace.



- Create HTML text − File/New/HTML. Add text.
- Right click in the HTML window and select 'Edit Source'.
- Right click on the position in the ICM Script Editor where you would like to insert the image.
- Select 'Insert Image'



- Select the image name source.
- Choose the desired Width and Height.
- Click OK.
- Click Save in the ICM Script Editor.

7.6.4 Insert Script

How to insert a script to the text panel

There are 3 ways to add a script − described in more detail below

1. Drag and drop script from ICM Workspace

2. In the HTML Source Editor − right click and select Insert Slide or Action

3. Create an "inline" script

These methods are described below:

Drag and Drop Method

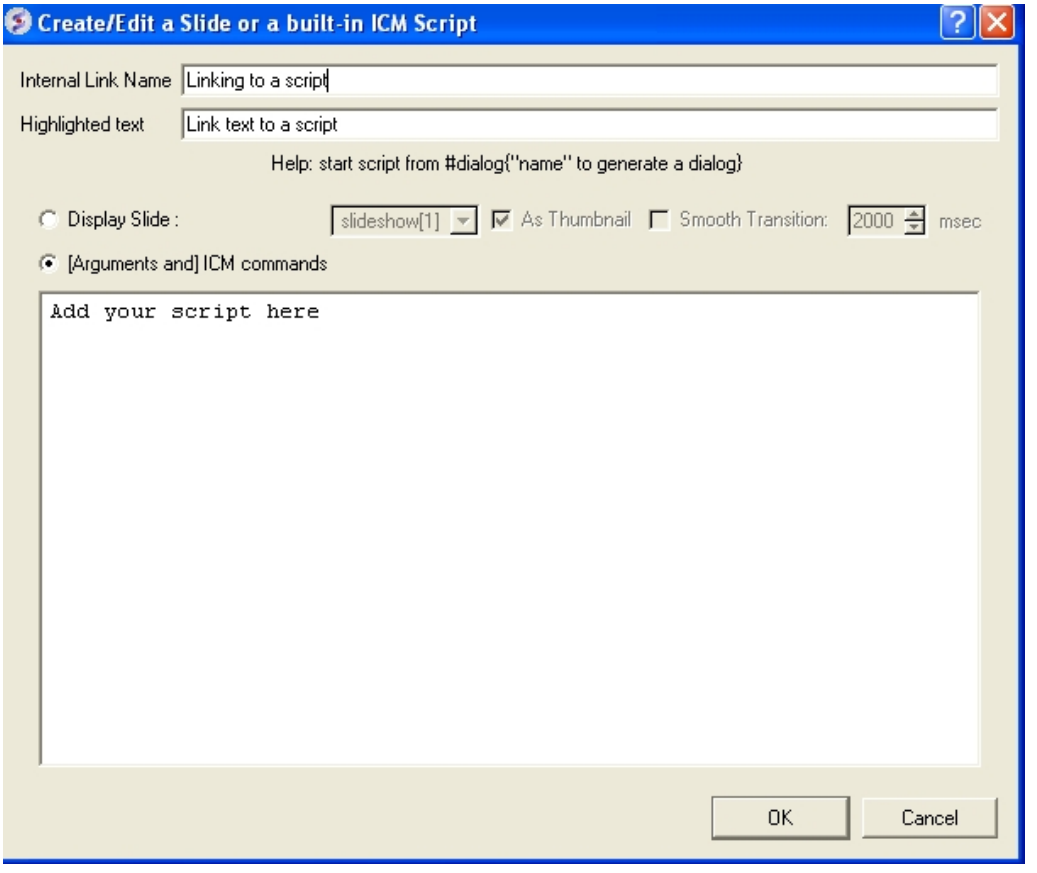
- Create a script File/New/Script
- The script will be displayed in the ICM Workspace.
- Right click in the HTML Text Panel (for instructions on how to create this panel see create molecular document) and select edit source and the HTML Source Editor will be displayed.
- Click−Drag and Drop the script into the HTML Source Editor

A line as shown below will be added.

```
<a href="#icm/script/script1">text placed here will be displayed as a link in the document</a>
```

Another way to add a script to the document is to Insert Action:

- Right click in the body of the text display panel.
- Select Edit Source
- Highlight the text you wish to link to a graphical display − you can do this by left clicking and dragging over the text (selected text will be highlighted in blue).
- Right click and select 'Insert Slide or Action' or select the button in the HTML Source Editor and a window as shown below will be displayed.



- Select the option [Arguments and] ICM commands
- Add script in the editor provided
- Select ok

Inline Script

A script can be added to the HTML text in the following way

- Right click in the body of the text display panel.
- Select Edit Source
- Enter script in the format as shown below.

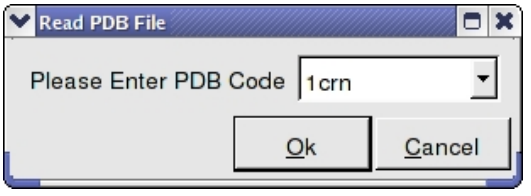
```
<!--icmscript name="script2"
#dialog{"Test"}
# i_number1 (2)
# i_number2 (3)
print $1 + $2
--><a name="script2" href="#_">script2</a>
```

7.6.5 Insert a Dialog Box

Dialog boxes are provided to enable a viewer to interact with a presentation or document file. The dialog box will be a gui data entry box. For an example here is a script to prompt the user of the file to enter a pdb

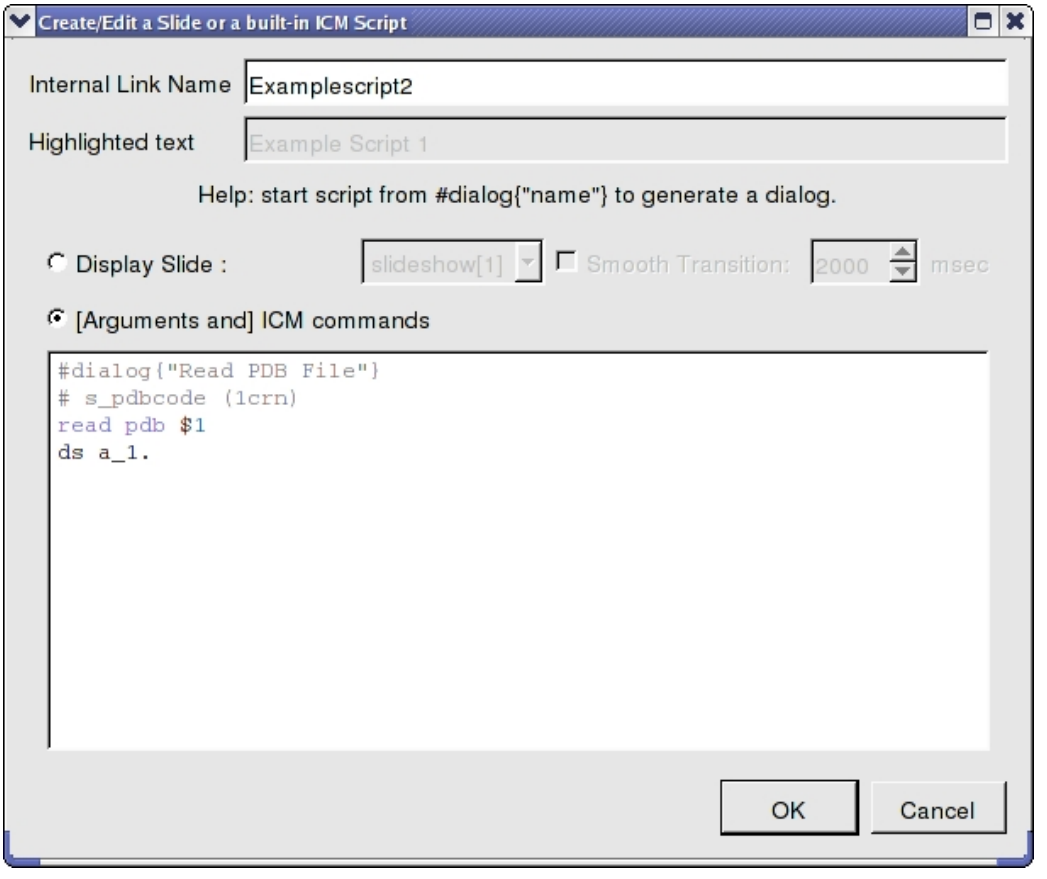
code:

```
#dialog{"Read PDB File"}
# s_pdbcode (1crn)
read pdb $1
ds a_1.
```



The code above can be saved as a script or inside the html text. To do this:

1. Right click on the HTML text display and select "Edit Source".
2. Highlight the text you wish to link to a dialog box and then select the right click and select 'Insert Slide or Action' or select the button in the HTML Source Editor and a window as shown below will be displayed.



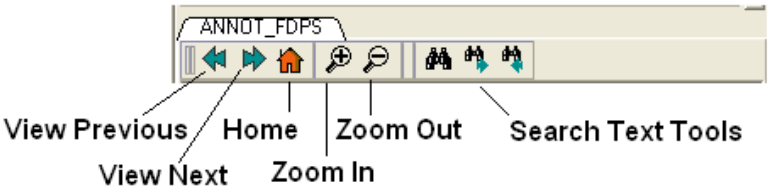
OR.

1. Right click on the HTML text display and select "Edit Source".
2. Add a link to a `script` as shown below.

```
<a href="#icm/script/script1">Example Script 2</a>
```

7.6.6 Document Navigation

The following buttons shown below aid document navigation. Also remember that more than one document can be stored and the header of each document file will be displayed in multiple tabs in the text panel window.



7.6.7 Protect Shell Objects From Deletion

When making a molecular document you can protect objects from deletion by the person who reads your document by:

- Right click on the object in the ICM Workspace.
- Select the **Protect** option.

8 ActiveICM

`ActiveICM` enables you to view and display ICM graphical `slides` and `animations` interactively inside Windows Microsoft PowerPoint and web browsers such as Internet Exporler and Mozilla Firefox.

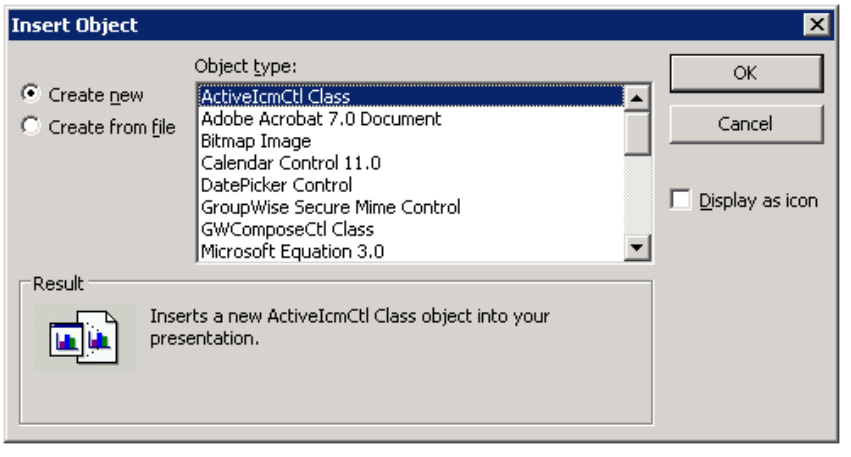
8.1 How to Embed in Microsoft PowerPoint 2003

Setup

- Download ActiveICM from www.molsoft.com/support
- Save an ICM file (.icb) containing slides. Click `here` to see how to make slides.

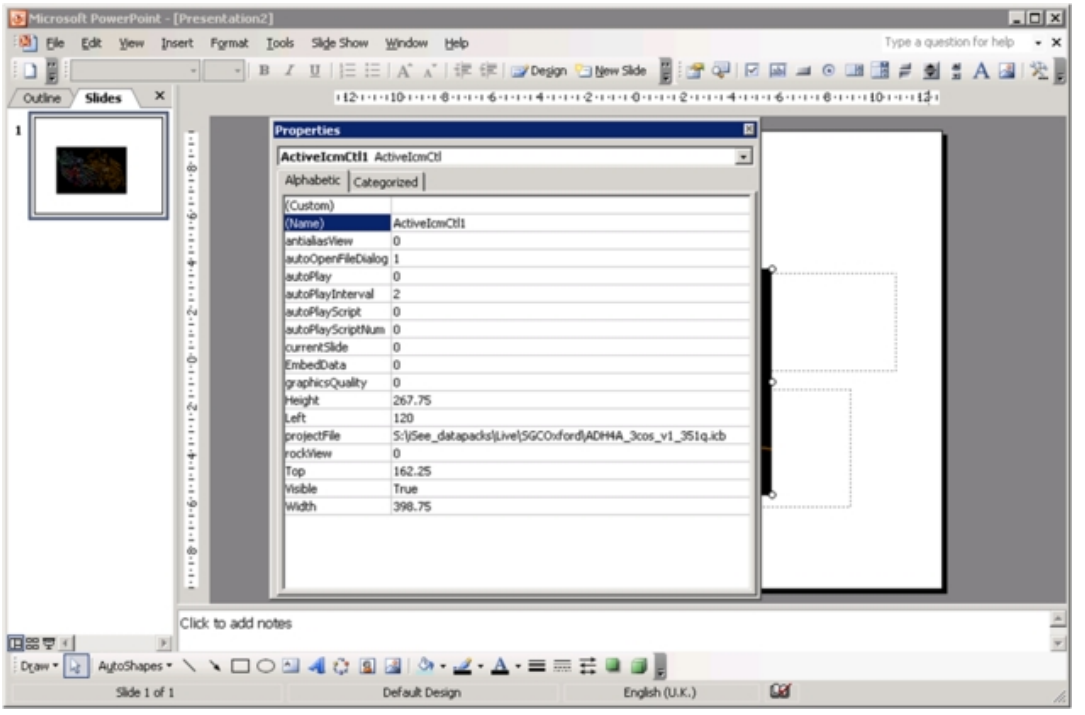
Embed icb file

- Open the Insert menu from the top bar of PowerPoint and select **Object**
- This opens up the Object dialogue. Select **ActiveIcmCtlClass:**



- Click on OK. A file dialogue will then be opened. Open the ICB file you wish to use via this dialogue. IMPORTANT: To avoid later problems, make sure the ICB file is in the same folder as the PowerPoint file.

- A low−resolution snapshot of the first slide in the ICB file will be shown in the activeICM control you created. You can change the shape of the control by dragging the corners of the control with the mouse, once selected.
- Right−click on the activeICM control and select the Properties menu item



- Save the PowerPoint presentation

8.2 How to Embed in Microsoft PowerPoint 2007

Setup

- Download ActiveICM from www.molsoft.com/support
- Save an ICM file (.icb) containing slides. Click `here` to see how to make slides.

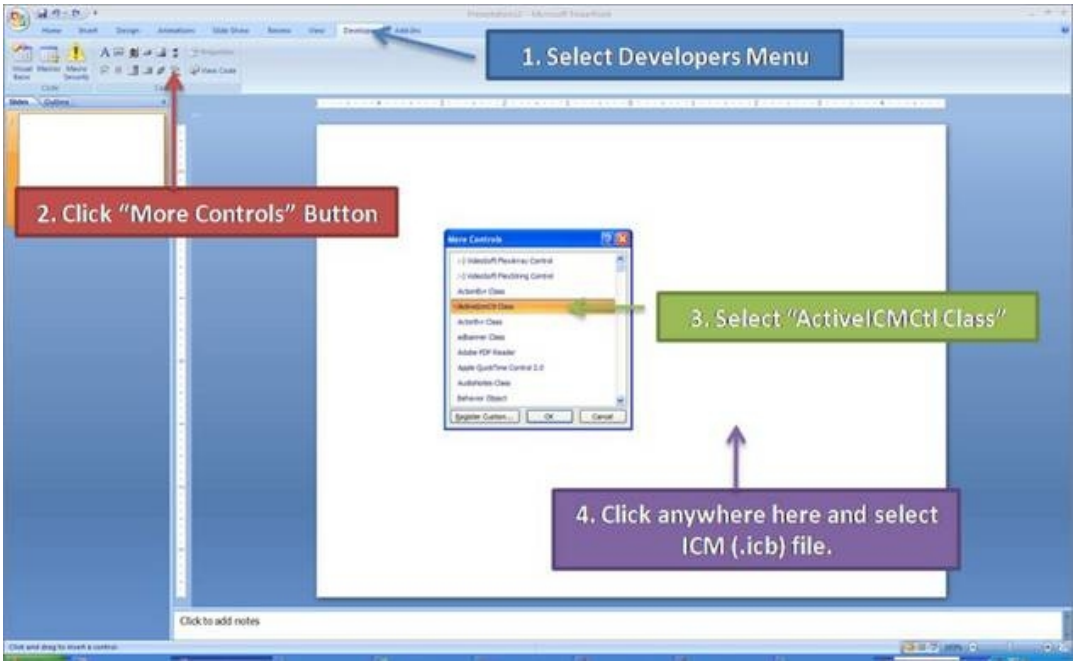
NOTE: Here are the instructions for ActiveICM in Microsoft Office 2007, for older versions of PowerPoint see `here`.

Enable the Developer Menu:

- Click the **Microsoft Office Button** (button top left), and then click **PowerPoint Options**.
- In the **PowerPoint Options** dialog box, click Popular.
- Under **Top options for working with PowerPoint**, selet the **Show Developer tab in the Ribbon** check box, and then click **OK.**

Insert ActiveICM into PowerPoint:

- Select the **Developer** menu.
- Select the **More Controls** button in the **Controls** field.
- Select **ActiveICMCtl Class** from the list of controls and click **OK.**
- Click the mouse anywhere in the white PowerPoint space and a dialog box will be displayed asking you to select your ICM (.icb) file.
- Click and drag at the corners of the image to resize the normal way you would resize an object in PowerPoint.



8.3 Embed in Web Browser

To embed in a web browser.

1. Download ActiveICM from here `http://www.molsoft.com/getbrowser.cgi?product=activeicm(it is free!).`
2. `Create` an HTML page in ICM (File/New/Html).
3. Add a series of `slides`.
4. File/Export As ActiveICM Html..

8.4 How to Use ActiveICM in PowerPoint

*****IMPORTANT There are two ways to open a presentation:***

- Double click on the ppt file in windows folder. (in this case PowerPoint will set the current directory to the one which contains the file and there should be no problems with both relative and absolute paths)
- Open ppt through the "File−Open" or recent files. (in this case PowerPoint DOES NOT SET the current directory to the one which contains the file −> relative path might not work and user will be prompted to locate the ICB file unless file is found in absolute location)

To view the slides you must be in Slide Show mode

- Press the **F5** button to start the **Slide Show**. In edit mode (i.e. not presentation mode), the control is shown as a static image ï¿½ it is not possible to interact with the ICB file. Therefore, to prepare the presentation so that the control shows the correct initial visualisations it is necessary to run the PowerPoint slide(s) in presentation mode

Change Slides

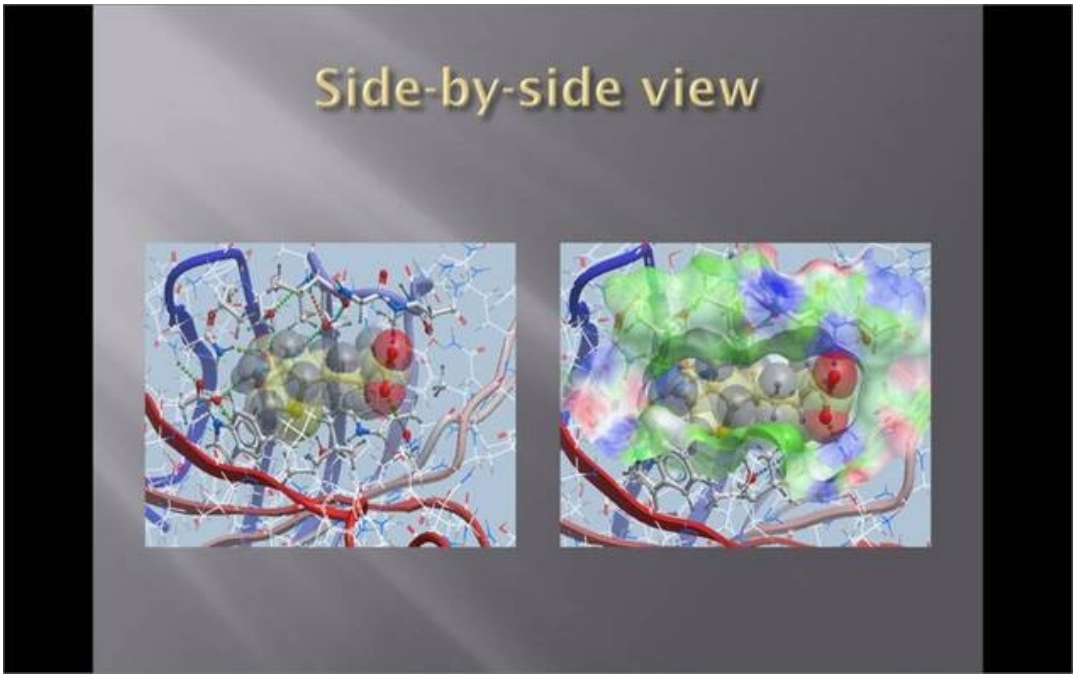
- Use the left and right cursor keys to change slides.

A number of other options can be accessed by right clicking on the slide. These options include:

- Select Slide
- Auto Play
- Set on/off rocking
- Center
- Load a new ICM File

You can also add multiple ActiveICM 3D displays in one slide:

- To display mutliple ActiveICM 3D displays in one slide just copy the original display or repeat the steps described above. All powerpoint slides should point to the same ICM file (.icb) but they can point to different slides.



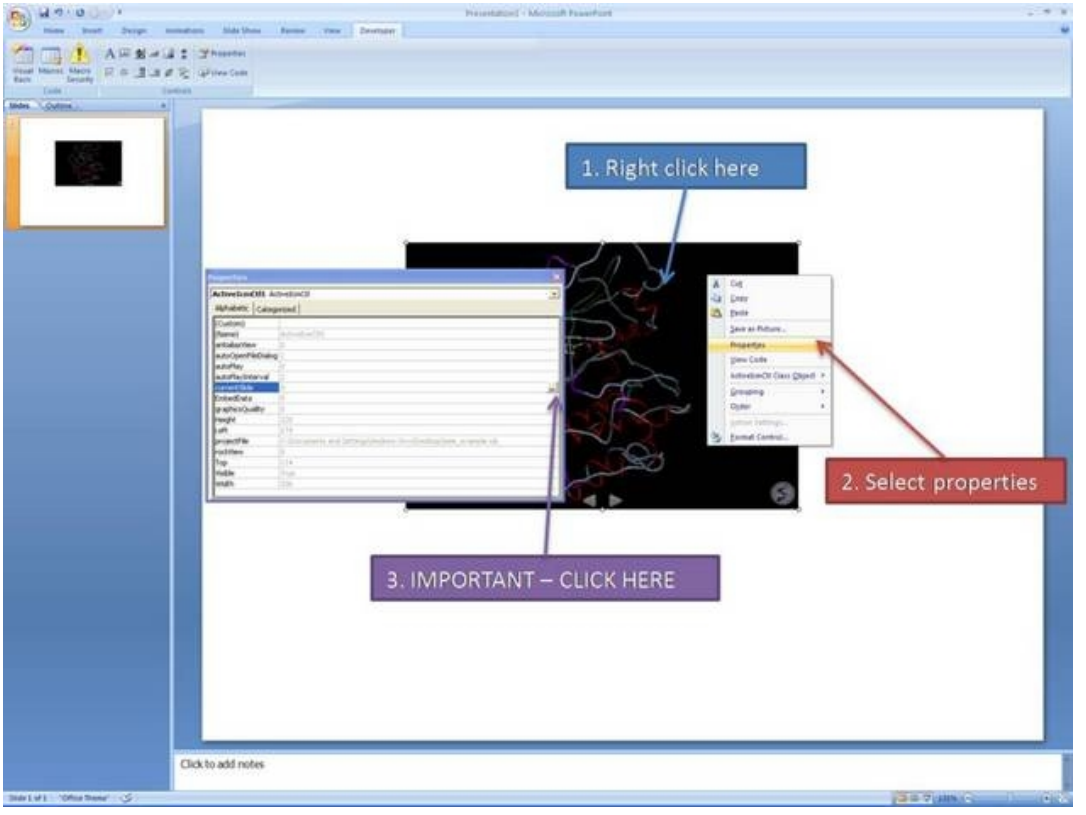
8.5 How to Change ActiveICM Component Properties

A number of properties of ActiveICM can be changed once embedded in powerpoint. The options include:

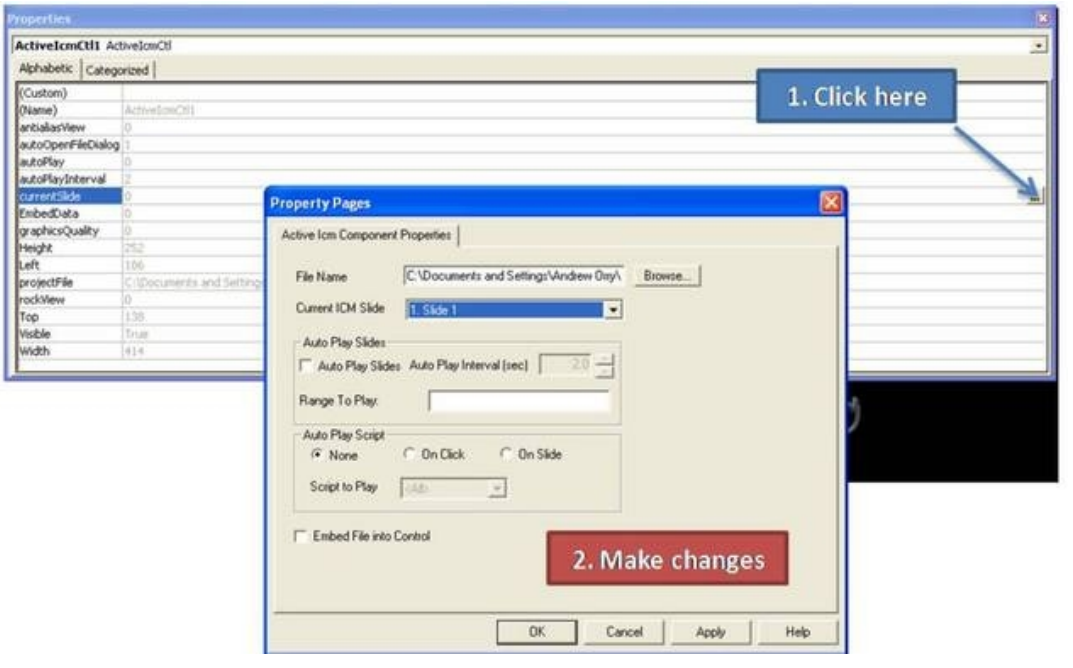
- Select the first slide to be displayed.
- Set slide auto play.
- Set auto play of a script.
- Embed the powerpoint file and the icb file all into one file.

To change these options:

- Right click on your embedded activeICM in Powerpoint.
- Select **Properties** and click on the button shown below.



- A **Property Pages** window will then be displayed as shown below.



To change the file name of the icb file linked to activeICM: Simply type in the path to the file or use the browse option.

To change the current ICM slide: Use the drop down button next to **Current ICM Slide** to select the slide you wish to display first in your presentation.

To auto play slides: Check the **Auto Play Slides** box and select the interval between slides option. A range of slides can be played by entering the number of the slides separated by a comma.

To auto play a script: Select whether you want the script to run **On Click** or **On Slide** then select the script from the **script to play** drop down button. You should first save your `script` in the icb file.

To embed the icb file in the ppt file Click the **Embed File into Control** option. **Important** − Please save your PowerPoint file in the t 1997−2003 ppt format not pptx.

8.6 Advanced use of activeICM: Macros to direct visualisation changes

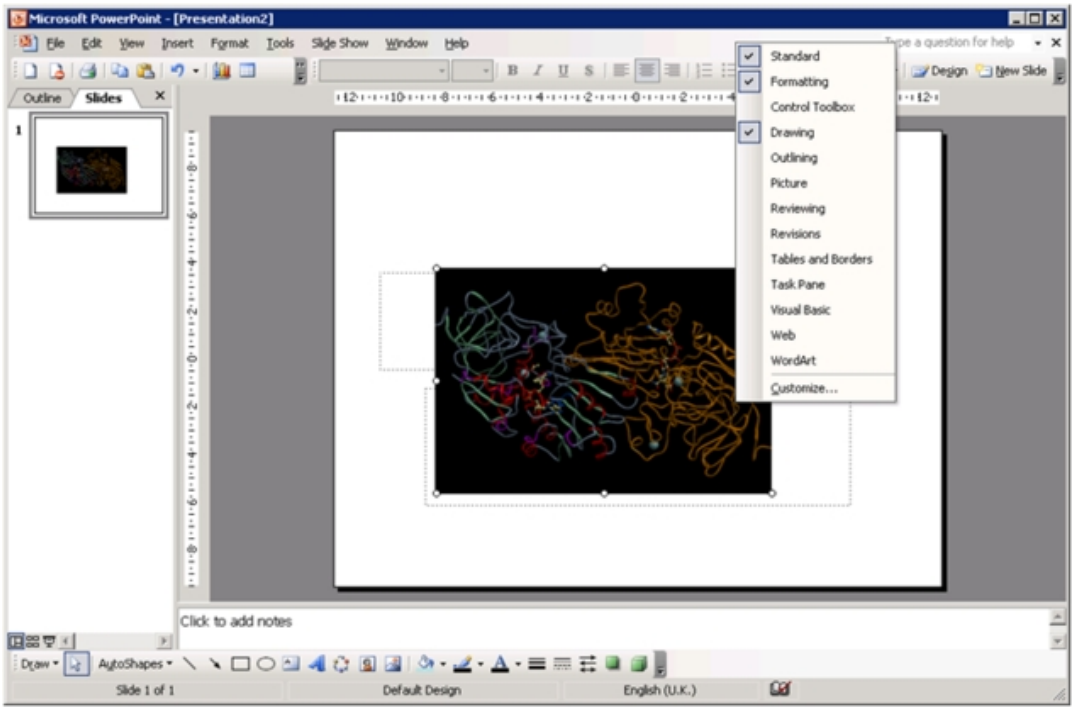
Documentation kindly provided by Dr. Brian Marsden (SGC Oxford `http://www.sgc.ox.ac.uk/people/brian/`)

It is possible to write simple VisualBasic scripts to avoid having to use the right−click menu approach to changing activeICM control slides within the control itself. This allows one to place buttons outside of the activeICM control, but in the same PowerPoint slide, which controls the control's behaviour. Below are a couple of useful examples of this approach.

Creating a button to set the control's active slide:

Insert a button Office 2003

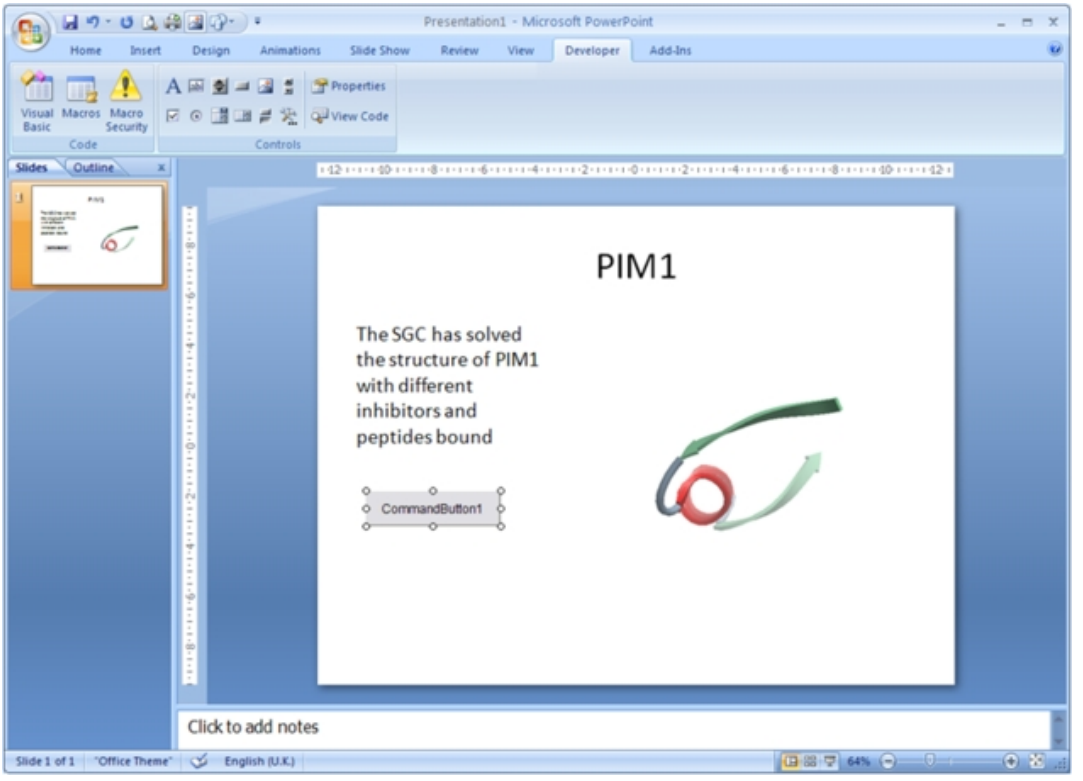
- In edit mode, make sure the control toolbox toolbar is shown by right−clicking the blank area at the top of the top bar and ensuring **Control Toolbox** is ticked.



- Click on an icon in the Control Toolbox which corresponds to the sort of button you wish to use. Then click and drag in the PowerPoint slide to generate the button.

Insert a button Office 2007:

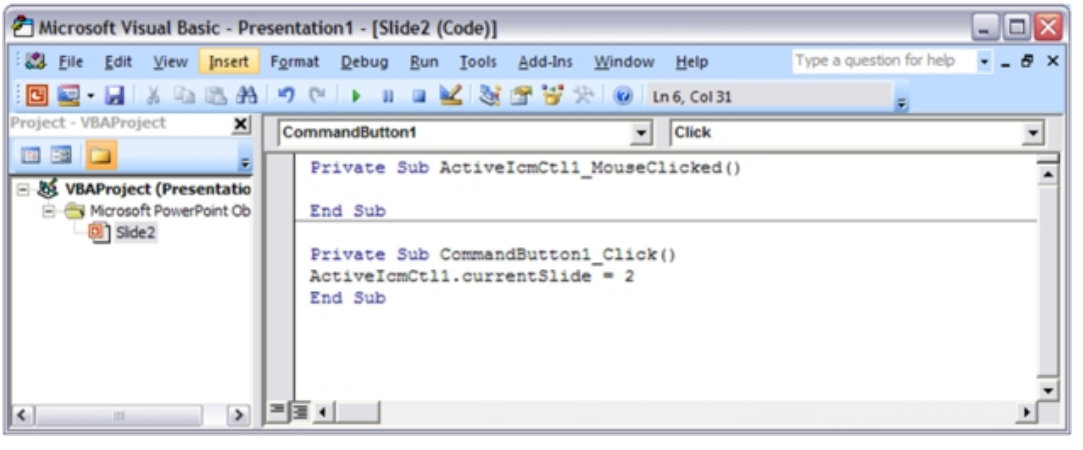
- In edit mode, click on an icon in the Developer menu or ribbon which corresponds to the sort of button you wish to use. Then click and drag in the PowerPoint slide to generate the button.



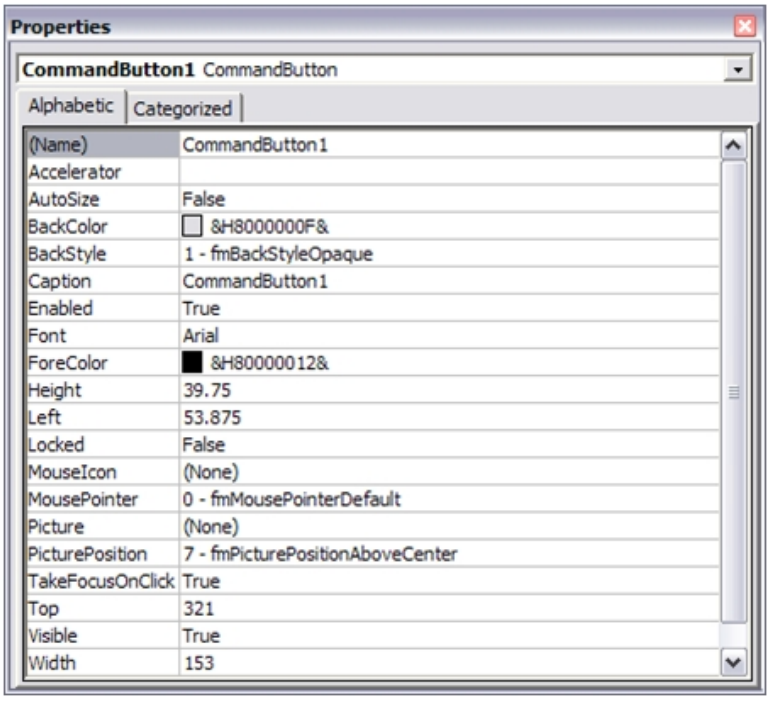
- Double−click on the new button to open the VisualBasic editor with two empty functions pre−defined. The first one pertains to the control itself and can be ignored in this context *For the second function (which is for the newly−created button), copy the following into the editor, between the two lines of function code:

```
ActiveIcmCtl1.currentSlide = 2
```

- This sets the current activeICM control's slide to be number 3 **note** that the value placed in this code needs to be 1 less than the actual slide number (confusing, no?). Obviously, use a value here that makes sense in the context of your ICB file.
- This should leave the editor looking like this:



- Close the Visual Basic editor
- To change the physical properties of the button e.g. text, colour e.t.c.right−click on the button and select the Properties menu option. This opens up a dialogue as below, where many properties of the button can be changed:



- Using this dialogue, it should be possible to disguise the button to look like normal text (for example) which can be clicked on during the presentation to change the visualisation of the control, apparently magically. Note that the button will only work in presentation mode.
- IMPORTANT: In Office 2007, remember to save the PowerPoint presentation now as a pptm file that is, a macro−enabled PowerPoint file otherwise the macros will not work next time you load the presentation.

Other code examples: Just copy and paste the example of interest inside the function for the button in the Visual Basic editor. Code that enables a button to cycle through the ICB files slides in order (including wrap−around)

```
currentSlide = ActiveIcmCtl1.currentSlide
numSlides = ActiveIcmCtl1.nofSlides
If currentSlide = numSlides − 1 Then
ActiveIcmCtl1.currentSlide = 0
Else
ActiveIcmCtl1.currentSlide = currentSlide + 1
End If
```

8.6.1 PowerPoint Cache Errors

PowerPoint caches some information about active controls. Sometimes after an ActiveICM upgrade you may get an error when trying to access some property or method: "Wrong number of arguments or invalid property assignment" or something similar.

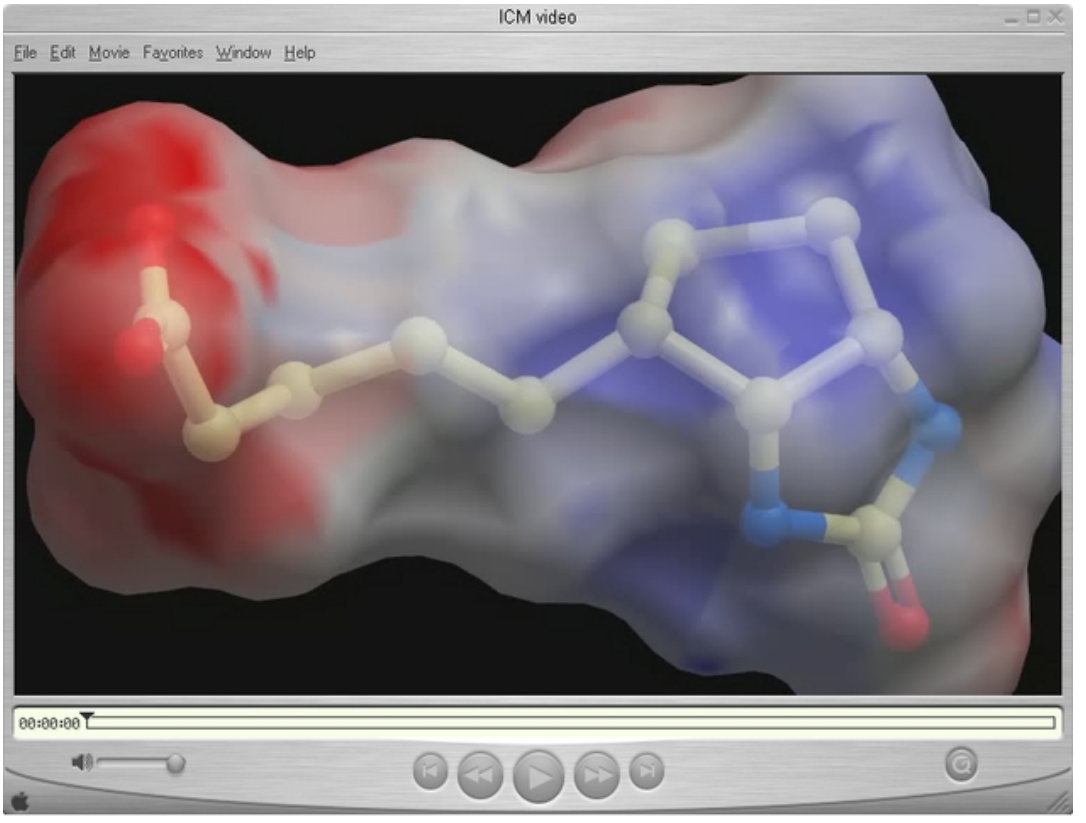
In this case you need to close PowerPoint and remove all files from the location below:

C:\Documents and Settings\seva\Local Settings\Temp\PPT11.0

9 Movie Making

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

ICM enables users to easily make a movie. Here we will describe how to make and convert a series of frames and scenes into a movie. A movie is an excellent means of communicating results obtained in ICM such as Monte Carlo and docking simulations. The resulting movie can easily be transfered into other applications such as Microsoft Powerpoint.

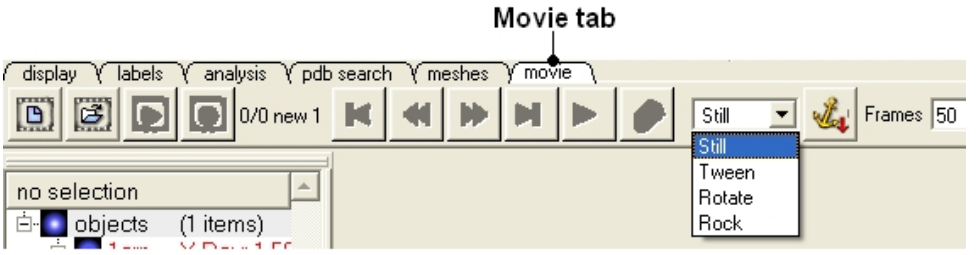


9.1 Movie Making Options

From version 3.4−9 onwards there are two ways to make a movie.

1. **`Screenshot Movie Making`**

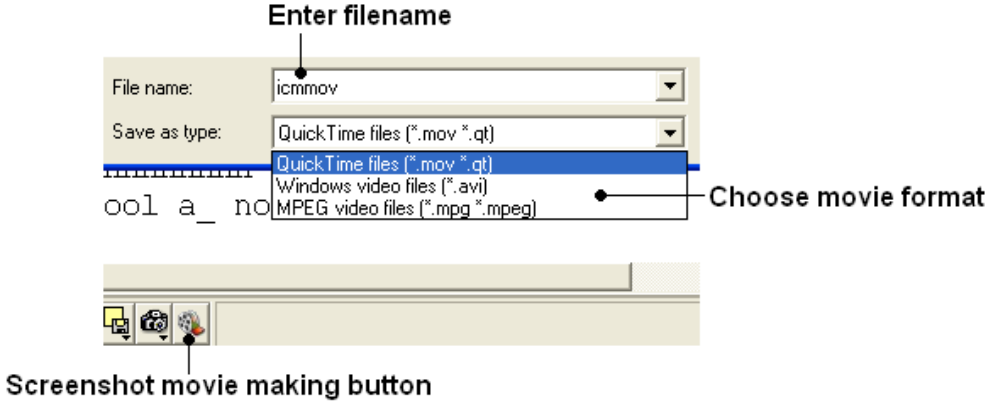
2. **`View−Defined Movie Making`**



9.2 Screen−grabbing Movie

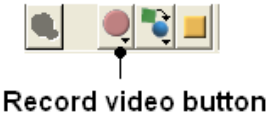
To make a **Screen−grabbing Movie** follow these steps:

- Resize the graphical display to the screen size/resolution you need. You may also want to select the `high quality` image button and antialiasing to improve the quality of the movie or add visual effects such as `shadows`.
- To begin making a movie click on the movie making button at the bottom of the graphical user interface (as shown below).
- Enter a file name for your movie and select the movie format (.mov, .avi, mpeg).



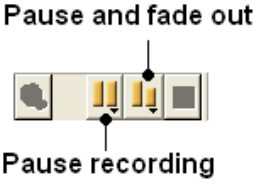
NOTE: If you want to make a movie to include in a PowerPoint presentation you need to save the movie in AVI format.

- To begin recording the screenshot movie click on the red **Record video** button. Anything displayed in the graphical display will be recorded, for example you can record `animations and transitions`. Specifying the `number of cycles` in the animation (rocking, rotation) is an ideal tool for screen−shot movie making. If you have a fast computer you can use **Realtime screen grabbing** which can be selected by clicking and holding the **Record video** button. The real time option can also be set in `File/Preferences/Gui` menu.



- The length of the movie in minutes, seconds and milliseconds is displayed in the top right hand corner of the graphical display.

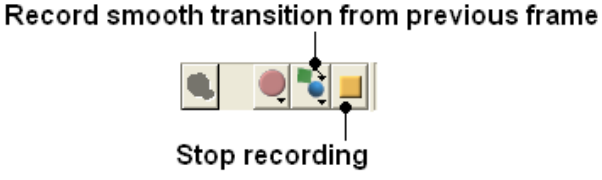
- You can pause the movie and fade out by clicking on the button shown below. The number of frames for the fading out option can be controled using the option in `File/Preferences/Gui`



- You can record a smooth transition from a previous frame by clicking on the button shown below.

NOTE: Anything you do in the graphical display will be recorded in the movie. For example you can change representations, lighting, add new molecules etc. This can be achieved in a more controled manner using the **pause** and **record smooth transition** button.

- Once you have paused the recording the viewpoint and representation of the molecules can be changed and a smooth transition from the previous frame can be generated by selecting the **Record smooth transition from previous frame** button.
- To stop recording a video press the button shown below.



9.3 View−Defined Movie Making

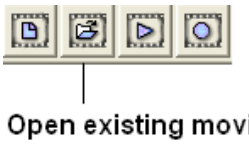
Before starting to make a movie:

1. First set up and make a directory into which you wish to store the movie.

2. Read the PDB files and objects you wish to include in the movie

A previously saved movie can be opened by:

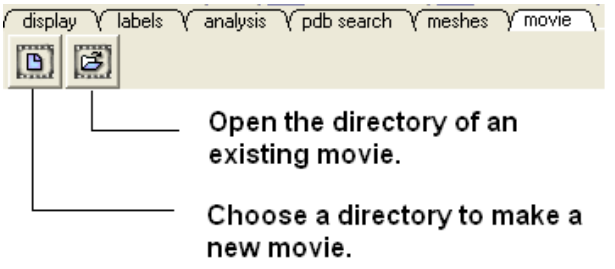
- Clicking on the movie open button shown below.



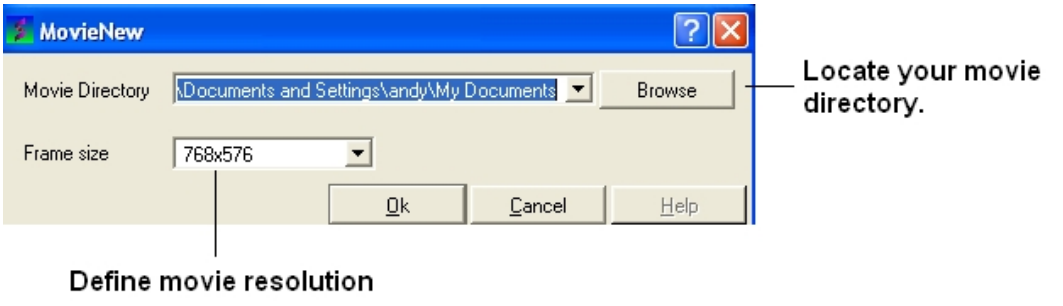
9.3.1 Movie Files and Resolution Setup

To start making a movie:

- Select the movie tab.



- Click the button to choose a new movie directory (See Figure Above).



- Browse for your movie directory.
- Select which resolution you desire for your movie by selecting the appropriate frame size.
- Click OK.

9.3.2 Defining a Movie Scene

The first step is to make the first scene.

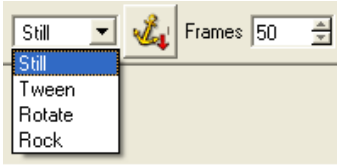
There are four choices of scene – `still`, `tween`, `rotate` or `rock`.

Select which scene you would like to start your movie with and follow the instructions for whichever one of the four scenes you choose.

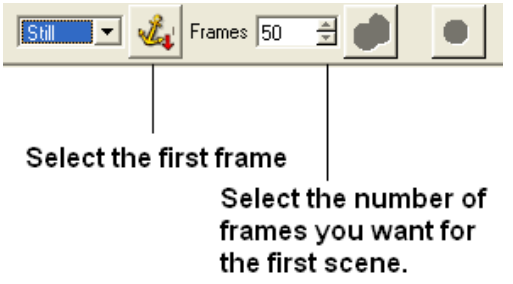
9.3.3 Still

To make a still scene:

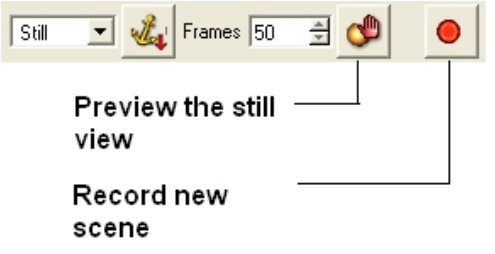
- Select the still option from the drop down list shown below.



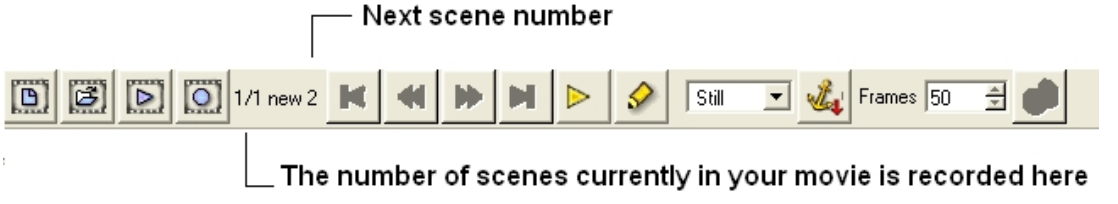
- Move the object to the starting position.
- Click on the "Define first view" button (see figure below).
- Type in the data entry box how many frames you desire for the scene.



- If you wish to preview the still view click the "preview" button (see figure below)
- If you are happy with the scene, click the red record button.



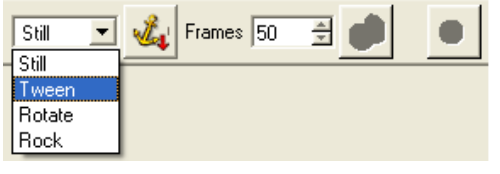
The number of scenes you have recorded so far is displayed in the video panel (see figure below).



9.3.4 Tween

To make a "tween" scene (moving your object from one point to another):

- Select the tween option from the drop down list shown below.



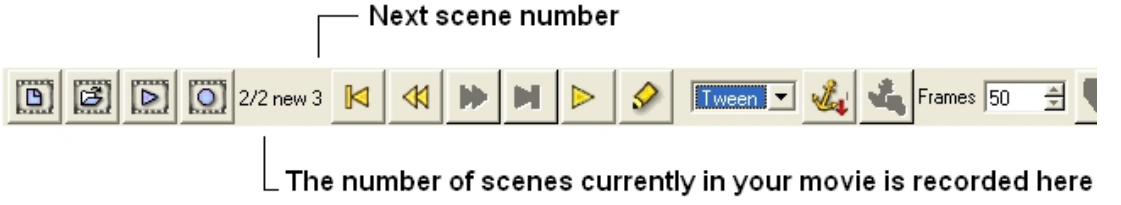
- Move the object to the starting position.
- Click on the "Define first view" button (see figure below).
- Type in the data entry box how many frames you desire for the scene.

- Move the object to the place you wish it to be translated to..
- Click on the "Define second view" button (see figure below).

- Click on the button shown below to preview the interpolation between the two views.

- If you are happy with the scene, click the red record button.

The number of scenes you have recorded so far is displayed in the video panel (see figure below).



9.3.5 Rotate

To make a "rotation" scene:

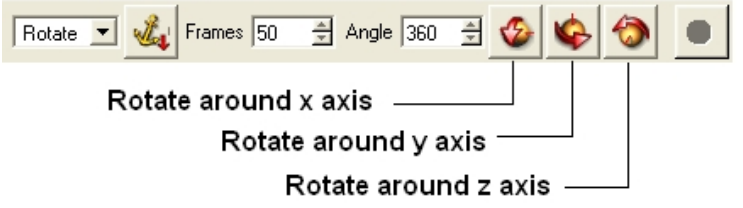
- Select the rotate option from the drop down list shown below.

- Move the object to the starting position.
- Click on the "Define first view" button (see figure below).
- Type in the data entry box how many frames you desire for the scene.

Now you have **three** preview options

1. Rotate around the x axis.
2. Rotate around the y axis.
3. Rotate around the z axis.

The buttons for each of the three options are shown below:



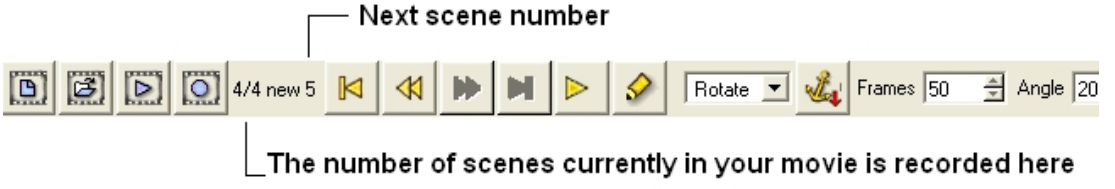
- Enter by how many degrees you wish your object to be rotated.
- Click one of the three preview options − rotate x, rotate y and rotate around the z axis.

NOTE You can play with and change the number of degree option and which kind of rotation as many times as you wish until you are satisfied with your scene.

Once you are satisfied with your scene:

- Click the red record button.

The number of scenes you have recorded so far is displayed in the video panel (see below).



9.3.6 Rock

To make your object perform a "rock" motion:

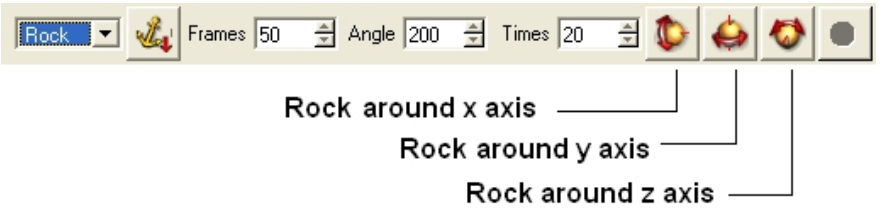
- Select the rock option from the drop down list shown below.

- Move the object to the starting position.
- Click on the "Define first view" button (see figure below).
- Type in the data entry box how many frames you desire for the scene.

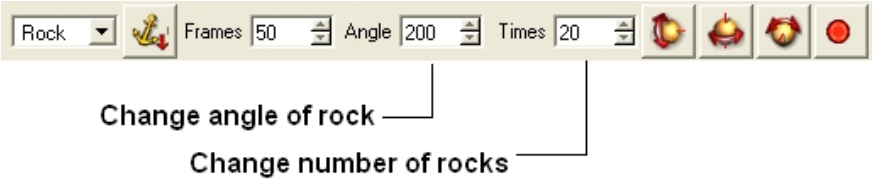
Now you have **three** preview options

1. Rock around the x axis.
2. Rock around the y axis.
3. Rock around the z axis.

The buttons for each of the three preview options are shown below:

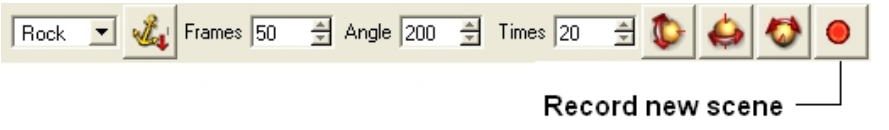


To change the angle and the number of times the rock occurs, enter the desired numbers in the data entry boxes shown below.



Once you are satisfied with your scene:

- Click the red record button.

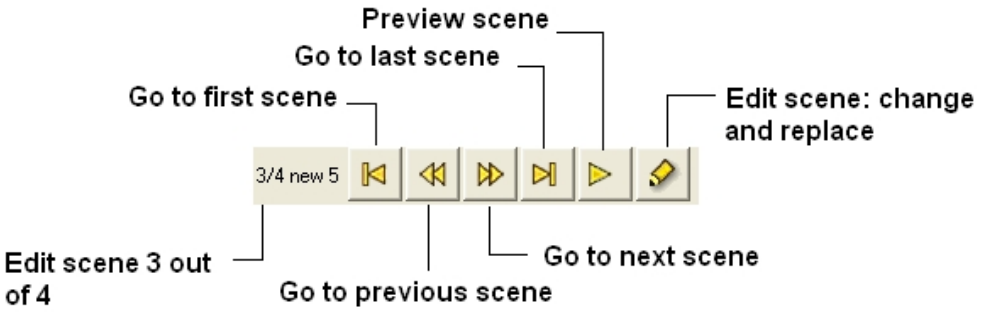


The number of scenes you have recorded so far is displayed in the video panel (see below).

9.3.7 Edit a Movie

To edit a movie:

- Select the scene you wish to edit by using the buttons shown below. The scene number is displayed in the movie panel.



- Click the "Edit scene: Change or replace scene" button.
- Make changes to the scene as described in the `Movie Making` section of this manual.

9.3.8 Preview and Export

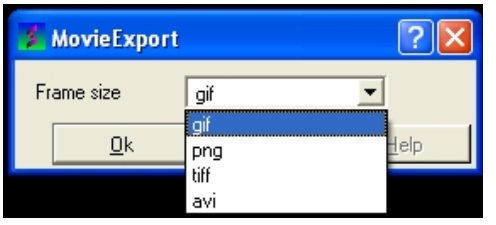
To preview a movie:

- Click on the preview movie button shown below.

To export a movie to a series of png,gif,tiff files or an avi file:

- Click on the export movie button shown below.

- Select which format you wish to save your movie.



If you select avi a window as shown below will be displayed:

- Select which windows compression software you wish to use to make the movie.

#endif

10 Working with Sequences and Alignments

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

Many powerful sequence manipulation tools are contained within ICM. In this section we will describe some of the bioinformatic manipulations you can perform with sequences and in the following chapter we describe sequence `alignments`.

10.1 Load Sequence

There are a number of different ways to load a sequence into ICM via the Graphical User Interface.

10.1.1 Read a Sequence from SwissProt

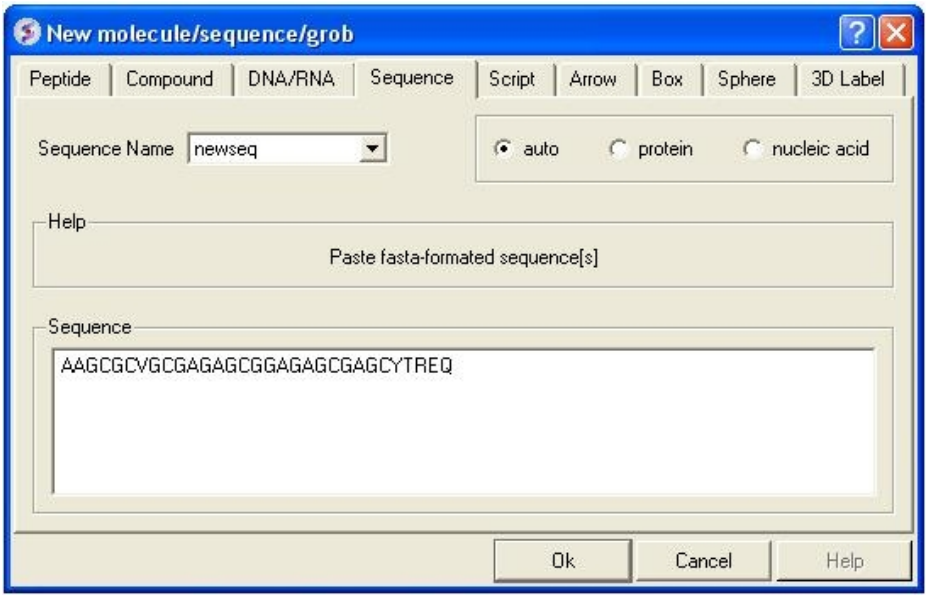
Swissprot is a curated protein sequence database which provides a high level of annotation (such as the description of the function of a protein, its domains structure, post−translational modifications, variants, etc.). Each protein entry has an unique SwissID code associated. To retrieve a Swissprot annotated protein sequence enter the SwissID code and click 'OK'. The annotation can be transferred to a protein structure, providing that the structure has the same sequence (or has been aligned to the retrieved Swissprot sequence)

- File/Load/SWISSPROT
- Enter SWISSPROT ID

10.1.2 Cut and Paste a Sequence

Paste your own sequence into ICM

- File/New/Sequence
- Paste the Sequence into the box provided.



10.1.3 Extract a Sequence from a PDB File

Extract a Sequence from a PDB file

- Right click on a loaded PDB file in the ICM Workspace.
- Select Extract Sequence(s)

10.1.4 Read directly from a Sequence File

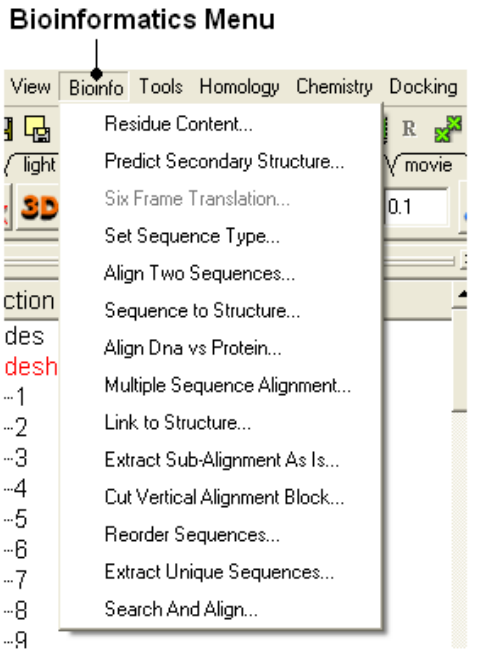
Read from file

If you have a sequence file saved in FASTA format it can be read into ICM by:

- File/Open

10.2 Bioinfo Menu

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



10.2.1 Residue Content

To determine the residue content of a sequence.

- Bioinfo/Residue Content and a data entry box as shown below will be displayed.
- Enter the sequence name. (Go to the `Load Sequence` section for more information on how to load a sequence into ICM using the Graphical User Interface)
- A table and graph of residue frequencies will be displayed.

10.2.2 Predict Secondary Structure

To predict the secondary structure of a sequence:

- Bioinfo/Predict Secondary Structure
- Enter the sequence name. (Go to the `Load Sequence` section for more information on how to load a sequence into ICM using the Graphical User
- An option is provided to ignore currently assigned secondary structure.

To view the secondary structure prediction click on and expand the sequence in the ICM workspace. Regions underlined in red are helices and green represents beta sheet.

10.2.3 Six Frame Translation

This options returns the translated DNA or RNA sequence ('−' for a Stop codon, 'X' for an ambiguous codon) using the standard genetic code.

- Read into ICM a DNA sequence from a file (eg File/Open FASTA) or use the File/New option and cut and paste a DNA sequence.
- Bioinfo/Six Frame Translation
- Translate all frames or use start codon.

10.2.4 Set Sequence Type

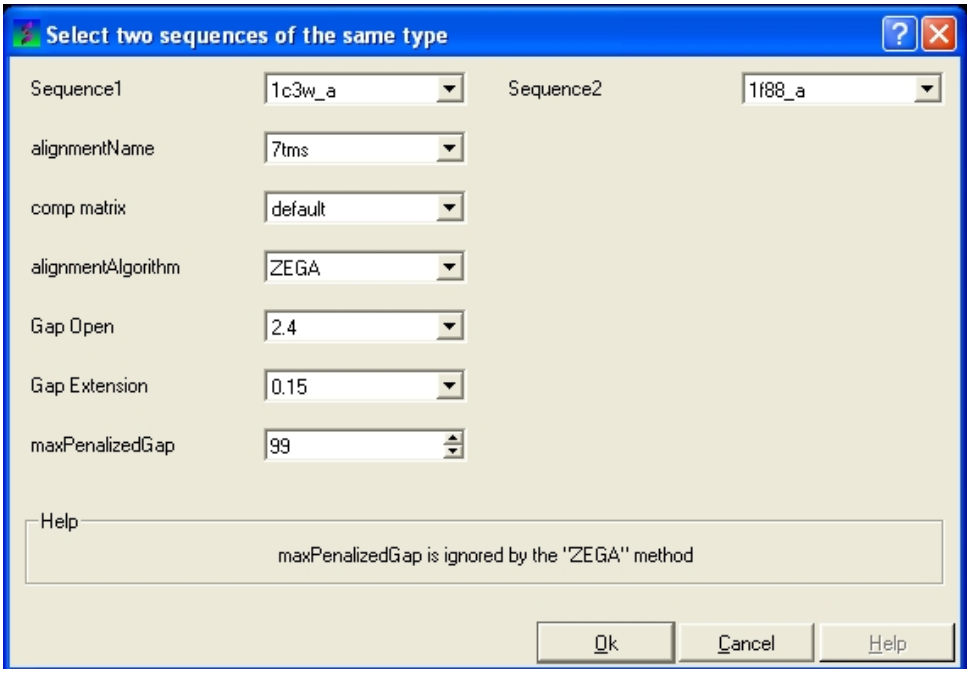
This option allows you to define whether a sequence that is read into ICM is a protein or nucleotide sequence.

- Read into ICM a sequence (eg File/New and cut and paste sequence or File/Open FASTA)
- Bioinfo/Set Sequence Type
- Select the sequence name using the drop down button
- Select sequence type protein or DNA.

10.2.5 Align Two Sequences

To align two sequences:

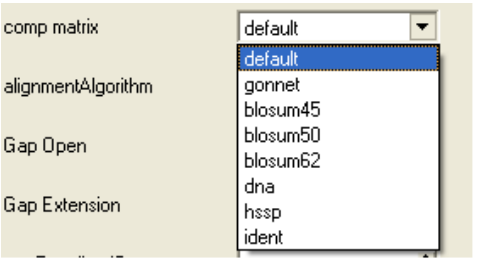
- Read into ICM two or more sequences.
- Bioinfo/Align Two Sequences



- Enter the name of your first sequence in the 'Sequence 1' data entry box.
- Enter the name of your second sequence in the 'Sequence 2' data entry box.

NOTE: Any sequences already loaded into ICM can be seen by clicking on the down arrow next to the 'Sequence 1 and 2' data entry boxes. This can save typing and trying to remember what you called your sequence.

- Enter a unique alignment name in the 'alignmentName' data entry box.
- Select a comparison matrix from the list shown below by clicking on the arrow next to the 'comp matrix' data entry box.



- Select the alignment algorithm you wish to use from the list shown below by clicking on the arrow next to the 'alignmentAlgorithm' data aentry box.

ZEGA − a Zero End−gap Global Alignment, that is a pairwise alignment method based on the Needleman and Wunsch algorithm modified to use zero gap end penalties. This type of alignment was first described by Michael Waterman, who called it the "fit" alignment. The paper of Abagyan and Batalov, 1997 describes the statistics of the structural significance of the alignment score and optimization of the alignment parameters for the best recognition of structurally related proteins.

H−Align − alignment method used in the Align and Score functions and find database command (as described in Batalov and Abagyan, 1999)

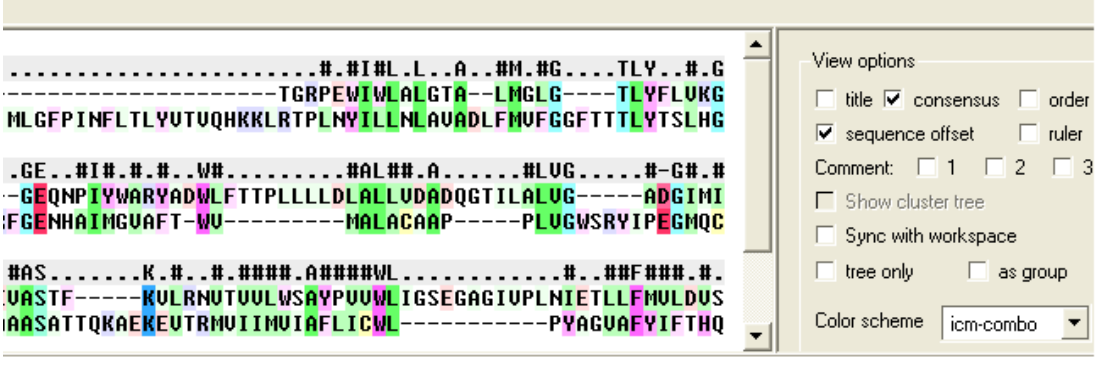
- Enter the values you wish to use for Gap Open, Gap Extension and the maximum penalized gap penalty.

Gap Open The absolute gap penalty is calculated as a product of gapOpen and the average diagonal element of the residue comparison table You may vary gapOpen between 1.8 and 2.8 to analyze dependence of your alignment on this parameter. Lower pairwise similarity may require somewhat lower gapOpen parameter. A value of 2.4 (gapExtension=0.15) was shown to be optimal for structural similarity recognition with the Gonnet et. al.) matrix, while a value of 2.0 was optimal for the Blosum50) matrix (Abagyan and Batalov, 1997).

Gap Extension The absolute gap penalty is calculated as a product of gapExtension and the average diagonal element of the residue comparison table.

maxPenalizedGap The maximum penalized gap which is used for Gap Open and Extension

- Click OK and the alignment will be displayed in the alignment editor window at the bottom of the graphical user interface.
- Remember to save the project or write the alignment if you wish to keep the alignment for use at another time.



10.2.6 Sequence to Structure alignment

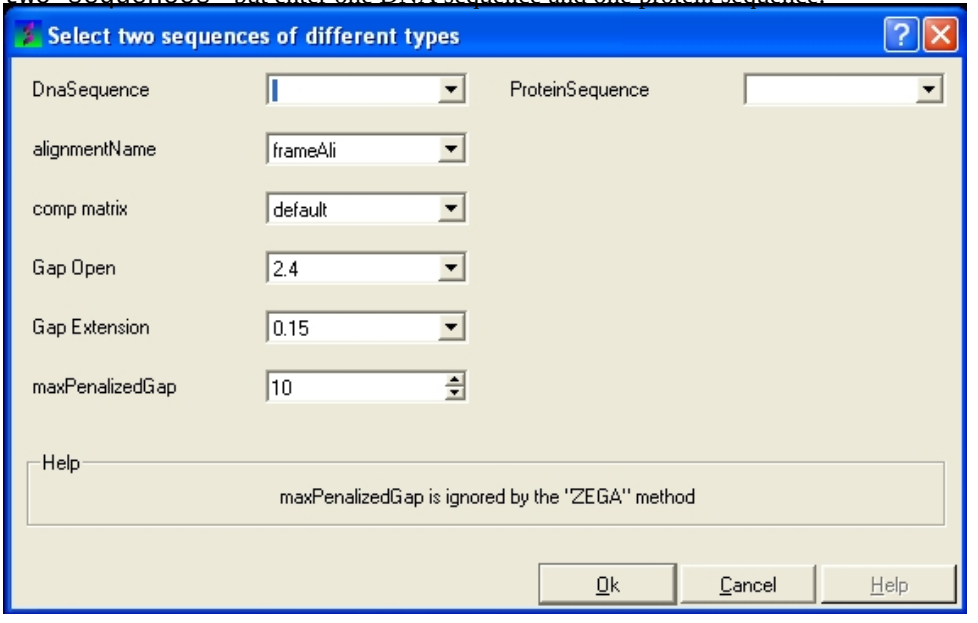
This option allows you to align a sequence to a template structure sequence using secondary structure weighting.

- Read into ICM the sequence (ModelSeq) you wish to align to the template sequence.
- Read in the template (TemplateSeq) structure and extract the sequence from this structure
- Bioinfo/Sequence to Structure Alignment
- Enter the ModelSeq and the TemplateSeq name
- Enter the name you wish to call the alignment.
- Enter the weights you wish to use for apha and beta secondary structure. The default values have been very well tested.
- This function uses a dynamic algorithm to find the alignment of the locally structurally similar backbone conformations. The RMSD is calculated within a certain residue window. The default is 3.
- Press OK and the alignement will be displayed in the bottom of the gui interface.

10.2.7 Align DNA vs Protein

To align DNA to protein:

- Select the 'Bioinfo' menu.
- Select the option Align DNA vs Protein
- Follow the data entry instructions shown in the previous section entitled "align two sequences" but enter one DNA sequence and one protein sequence.



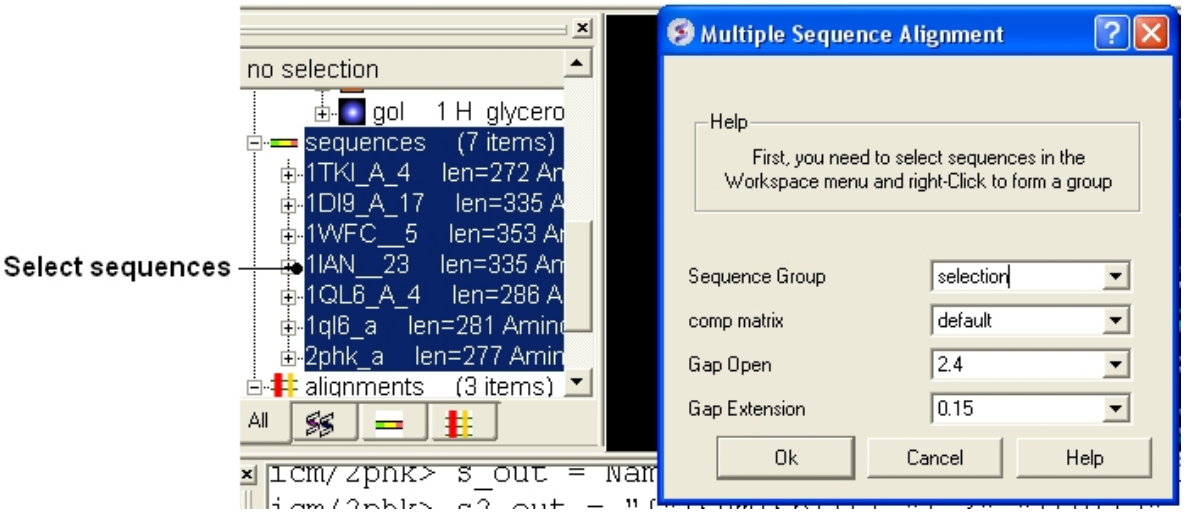
10.2.8 Multiple Sequence Alignment

To align more than 2 sequences:

- Read into ICM the sequences you wish to align.
- Select the sequences you wish to align in the ICM workspace. A sequence can be selected by double clicking (highlighted blue in ICM workspace) − a range of sequences in the ICM Worskpace can be selected by holding down the SHIFT button and double clicking. A non−contiguous selection can be made by holding down the CTRL button and double clicking.
- Bioinfo/Multiple Sequence Alignment
- Enter the name of the sequence group. If you selected the sequences as described above then the name of the group is **selection.** Other named groups of sequences can be made by right clicking on the sequence selection.
- Select the comparison matrix you would like to use.
- Enter Gap open and extension values.

Gap Open The absolute gap penalty is calculated as a product of gapOpen and the average diagonal element of the residue comparison table You may vary gapOpen between 1.8 and 2.8 to analyze dependence of your alignment on this parameter. Lower pairwise similarity may require somewhat lower gapOpen parameter. A value of 2.4 (gapExtension=0.15) was shown to be optimal for structural similarity recognition with the Gonnet et. al.) matrix, while a value of 2.0 was optimal for the Blosum50) matrix (Abagyan and Batalov, 1997).

Gap Extension The absolute gap penalty is calculated as a product of gapExtension and the average diagonal element of the residue comparison table.



10.2.9 Link to Structure

To link a structure to an alignment:

- Double click on the structure in the ICM workspace to select it.
- Bioinfo/Link to Structure

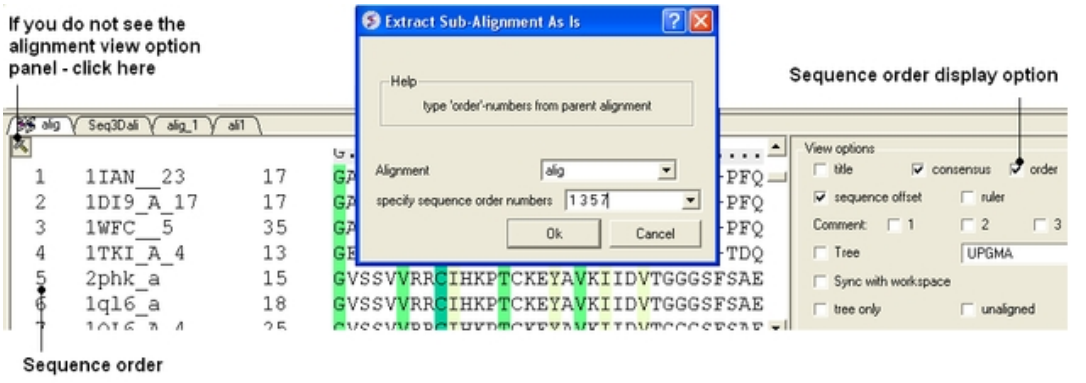
NOTE Links are described in more depth in the `Making Links Section` of the manual.

10.2.10 Extract Sub−Alignment As Is

On occasion you may want to extract a sub alignment from a bigger alignment. For example you wmay only wanto extract the alignment for the sequences linked to a structure.

To extract a sub−alignment:

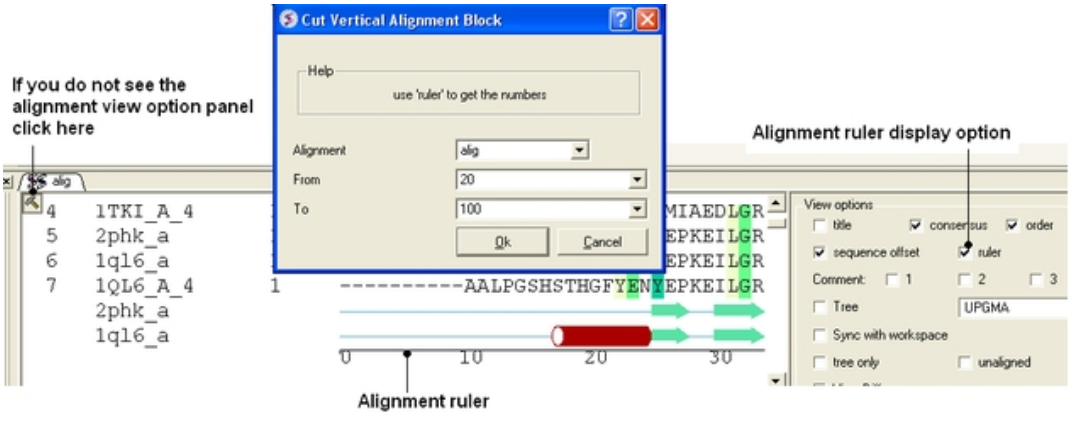
- An initial `multiple sequence alignment` must first be displayed in the graphical user interface.
- Bioinfo/Extract Sub−Alignment As Is
- Enter the name of the algienment from which you wish to extract a sub−alignment from.
- Specify the sequence order numbers you wish to extract − enter each number separated by a space.You can see the sequence order alignment number by selecting the **order** option in the alignment view options panel. See image below below.
- Click OK and the extracted sequence alignment will be displayed in a separate alignment tab.



10.2.11 Cut Vertical Alignment Block

To cut a vertical alignment block:

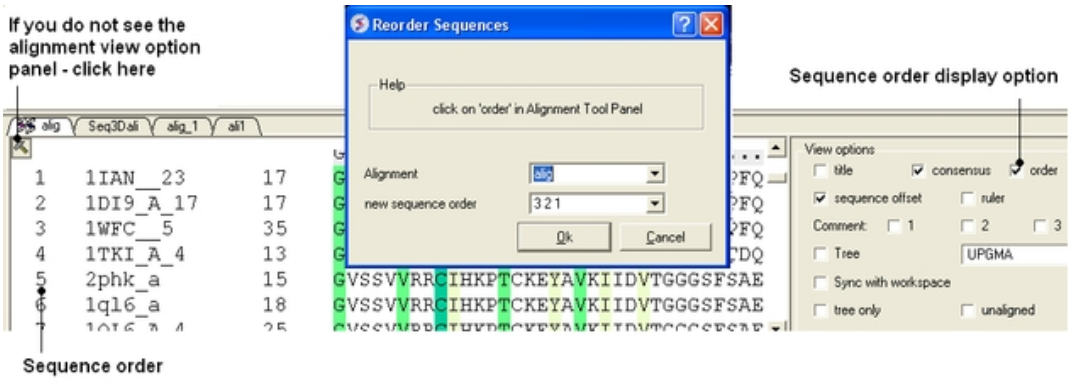
- An initial `alignment` must first be displayed in the graphical user interface.
- Bioinfo/Cut Vertical Alignment Block
- Enter the alignment from which you wish to cut from.
- Enter the region of the alignment you wish to cut (from: to:). The easiest way to determine the region to cut is to display the ruler in the alignment. This is an option in the alignemtn view panel − see image below.
- Click OK and the cut section will be displayed in a new alignment.



10.2.12 Reorder Sequences

To reorder sequences in an alignement

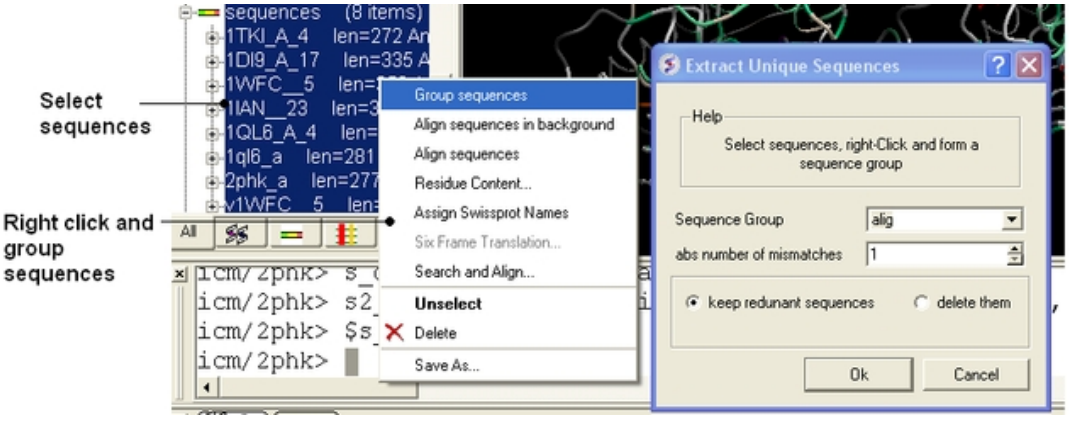
- An initial `multiple sequence alignment` must first be displayed in the graphical user interface.
- Bioinfo/Reorder Sequences
- Enter the alignment name
- Enter the new sequence order.You can see the sequence order alignment number by selecting the **order** option in the alignment view options panel. See image below below.



10.2.13 Extract Unique Sequences

To extract unique sequences from a group of sequences:

- `Read` into ICM the sequences you wish to make unique.
- Select the sequences. A sequence can be selected by double clicking (highlighted blue in ICM workspace) − a range of sequences in the ICM Worskpace can be selected by holding down the SHIFT button and double clicking. A non−contiguous selection can be made by holding down the CTRL button and double clicking.
- Right click on the sequence selection in the ICM Workspace and select Group sequences
- Bioinfo/Extract Unique Sequences
- Enter the name of the sequence group.
- Enter the number of residue mismatches necesary to determine that a sequence is unique or not.
- Select whether you want to keep the redundant sequences or delete them from ICM.



10.2.14 Load Example Alignment

To see an example of an alignment select:

- Bioinfo/Load Example Alignment

10.3 Sequence Search and Align

ICM provides a fast tool to search any Blast−formatted database with a query sequence and generate an alignment on the fly. For example you can use this option to find template structures for homology modeling.

1. Select Bioinfo/Search and Align (or right click on a sequence)
2. Enter the sequence name you wish to search against the database with.
3. Locate the blast−formatted database to search. You can download Blast formatted databases from here `ftp://ftp.ncbi.nih.gov/blast/db/` eg. pdbaa − PDB sequence database.

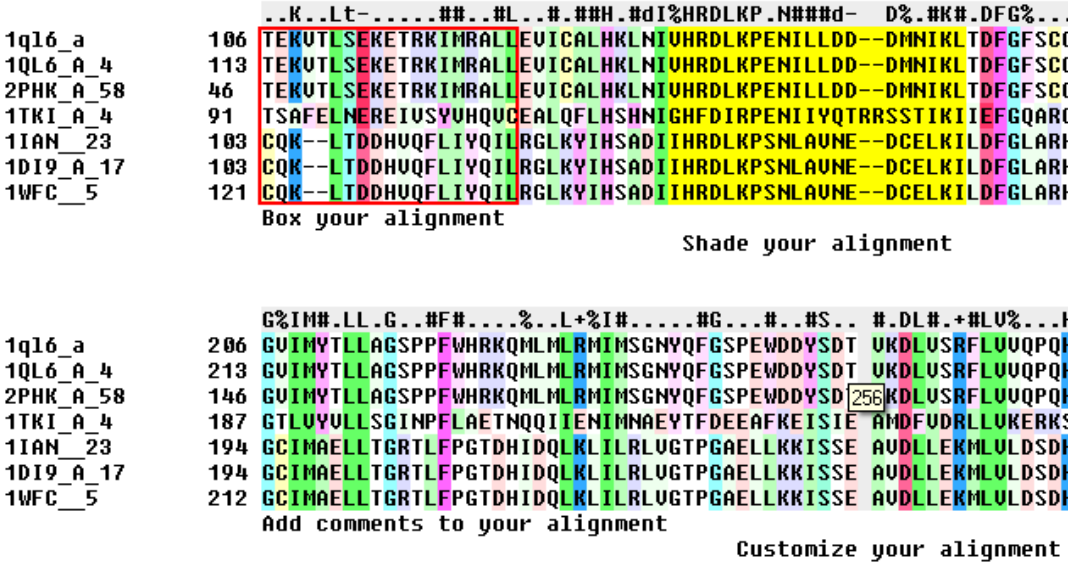
4. Specify the speed parameter (0 is the slowest, but the most detailed, 100 is the fastest search for nearly identical sequences).
5. Enter the number of hits you would like to view
6. Enter an identity threshold filter to narrow down the number of hits.
7. The top hits will be displayed in a table.

10.4 Sequence Alignments

ICM provides a powerful sequence alignment editing tool.

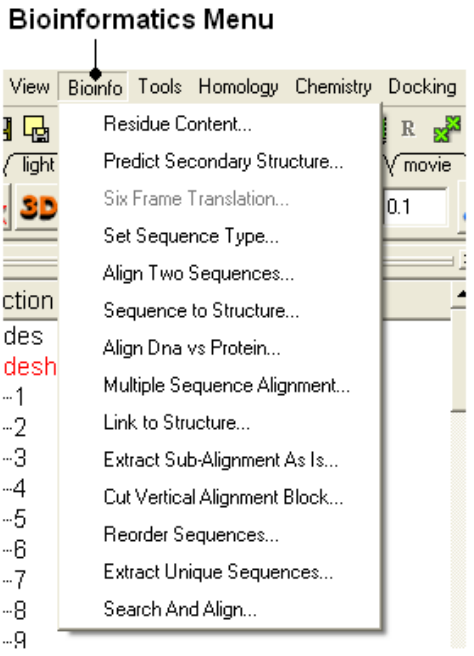
You can customize your sequence alignments in a number of ways:

1. Coloring according to a number of different consensus schemes.
2. Customizing your own consensus tables.
3. Shading areas of interest.
4. Boxing areas of interest.
5. Adding comments to an alignment.
6. Saving an alignment as a high quality image for publication.
7. Displaying and analyzing phylogenetic trees.
8. Direct selection from the alignment to the 3D object.



10.4.1 Alignment Introduction

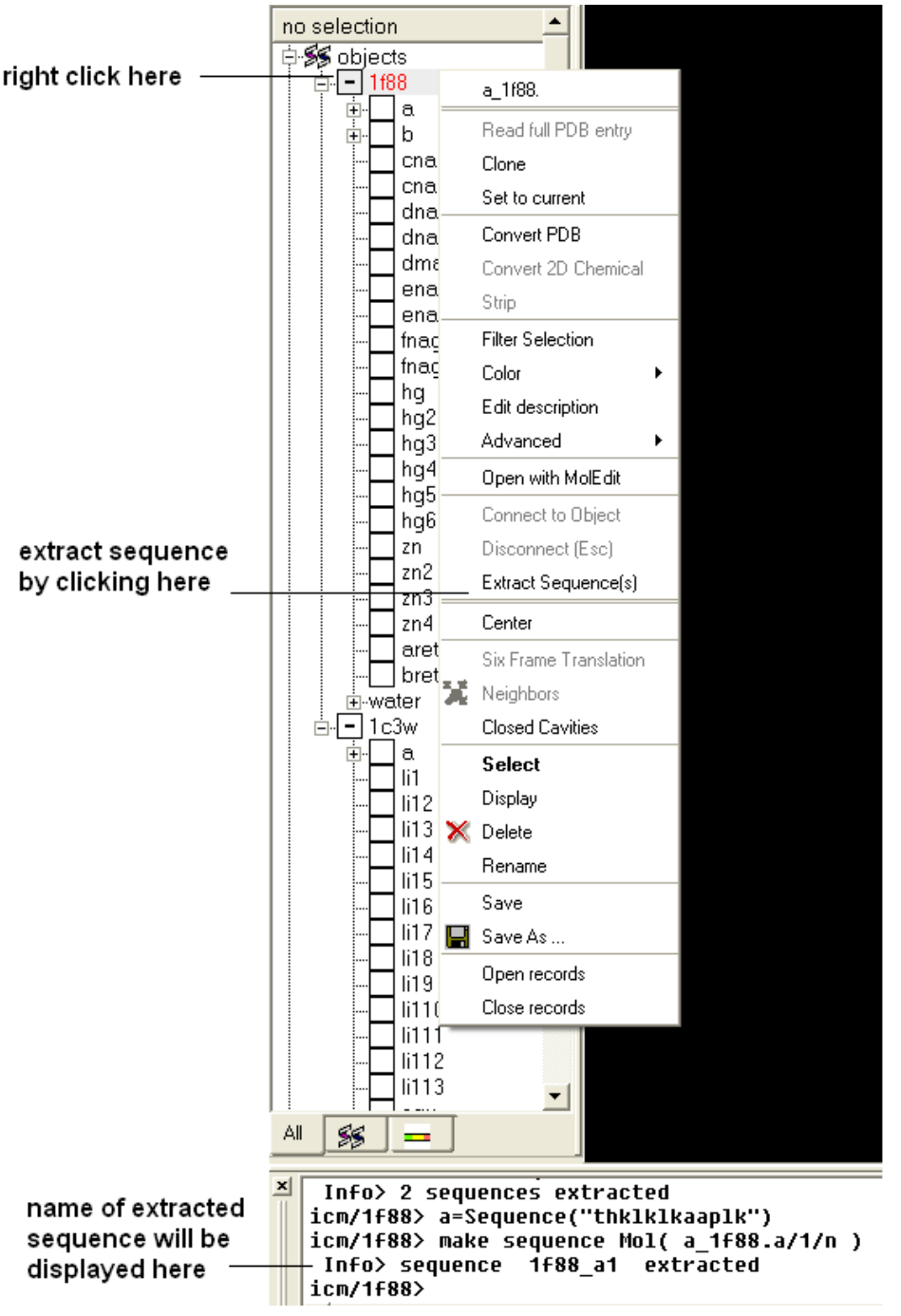
To align two or more sequences you need to use the options in the 'Bioinfo' menu shown below.



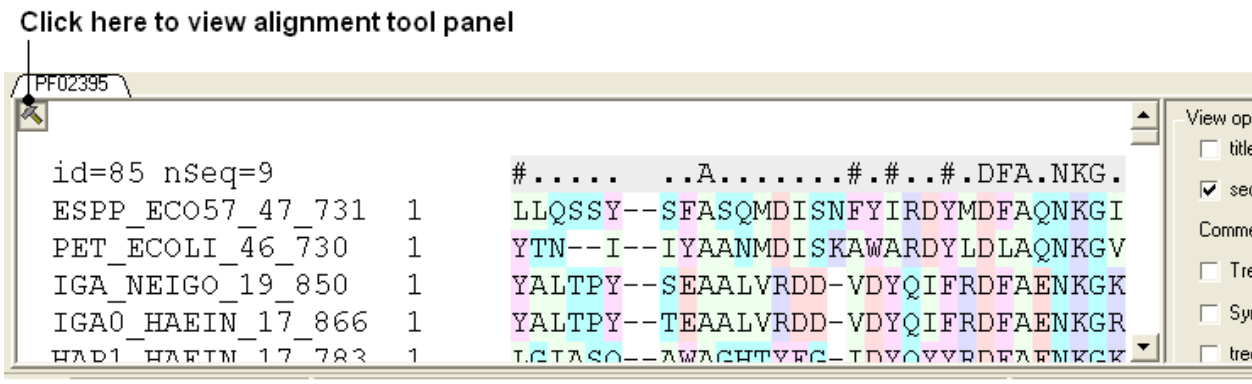
To construct an alignment, two or more sequences need to be loaded into ICM. This can be done be done in one of the following ways:

1. Constructing your own sequence see `new sequence section.`
2. Extracting the sequence from a loaded PDB sequence by:
3. File/Open sequence in FASTA seq format.
4. File/Load SwissProt

- Right clicking on the object name in the workspace panel
- Select 'extract sequence' and the name of the extracted sequence will be displayed in the terminal window.



Once the alignment has been constructed it will be displayed at the bottom of the graphical user interface (see below). If you cannot see the alignment try the **Windows** menu and select alignments.

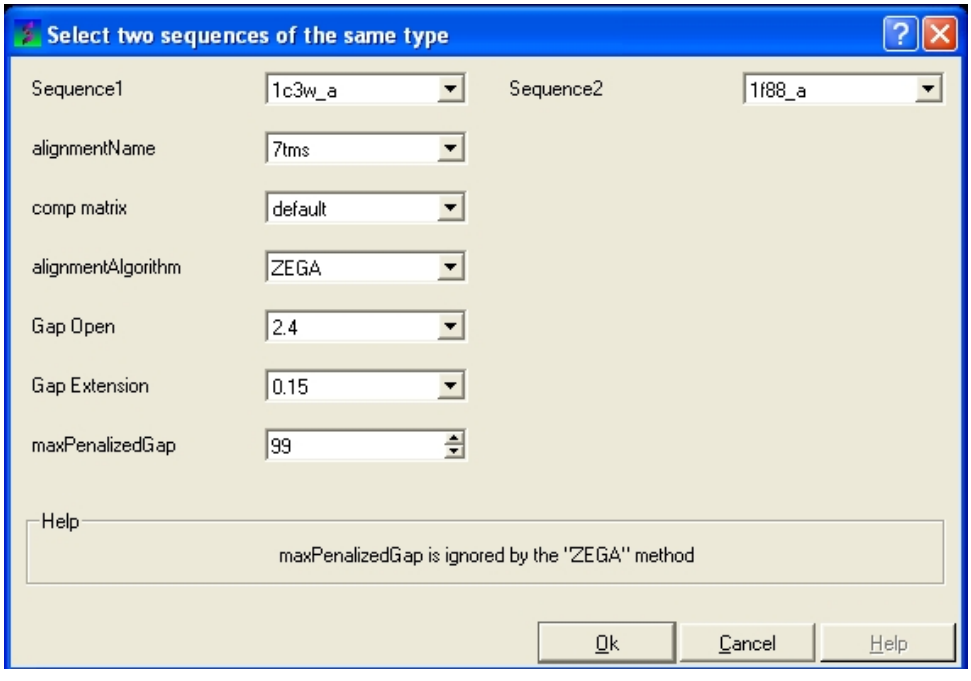


Alig

10.4.2 Align Two Sequences

To align two sequences:

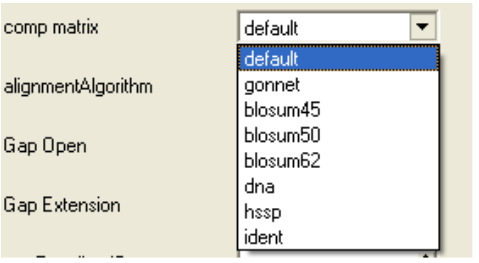
- Select the 'Bioinfo' menu.
- Click on 'Align Two Sequences' and the following data entry box will be displayed.



- Enter the name of your first sequence in the 'Sequence 1' data entry box.
- Enter the name of your second sequence in the 'Sequence 2' data entry box.

NOTE: Any sequences already loaded into ICM can be seen by clicking on the down arrow next to the 'Sequence 1 and 2' data entry boxes. This can save typing and trying to remember what you called your sequence.

- Enter a unique alignment name in the 'alignmentName' data entry box.
- Select a comparison matrix from the list shown below by clicking on the arrow next to the 'comp matrix' data entry box.



- Select the alignment algorithm you wish to use from the list shown below by clicking on the arrow next to the 'alignmentAlgorithm' data aentry box.

ZEGA − a Zero End−gap Global Alignment, that is a pairwise alignment method based on the Needleman and Wunsch algorithm modified to use zero gap end penalties. This type of alignment was first described by Michael Waterman, who called it the "fit" alignment. The paper of Abagyan and Batalov, 1997 describes the statistics of the structural significance of the alignment score and optimization of the alignment parameters for the best recognition of structurally related proteins.

H−Align − alignment method used in the Align and Score functions and find database command (as described in Batalov and Abagyan, 1999)

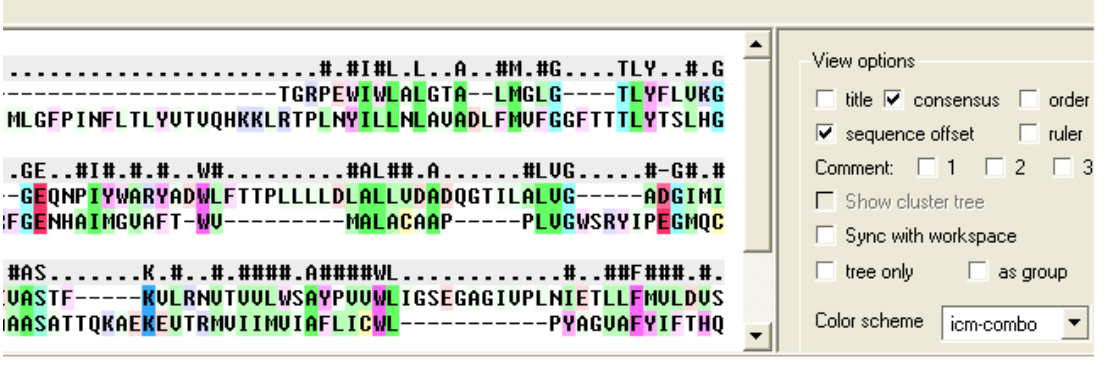
- Enter the values you wish to use for Gap Open, Gap Extension and the maximum penalized gap penalty.

Gap Open The absolute gap penalty is calculated as a product of gapOpen and the average diagonal element of the residue comparison table You may vary gapOpen between 1.8 and 2.8 to analyze dependence of your alignment on this parameter. Lower pairwise similarity may require somewhat lower gapOpen parameter. A value of 2.4 (gapExtension=0.15) was shown to be optimal for structural similarity recognition with the Gonnet et. al.) matrix, while a value of 2.0 was optimal for the Blosum50) matrix (Abagyan and Batalov, 1997).

Gap Extension The absolute gap penalty is calculated as a product of gapExtension and the average diagonal element of the residue comparison table.

maxPenalizedGap The maximum penalized gap which is used for Gap Open and Extension

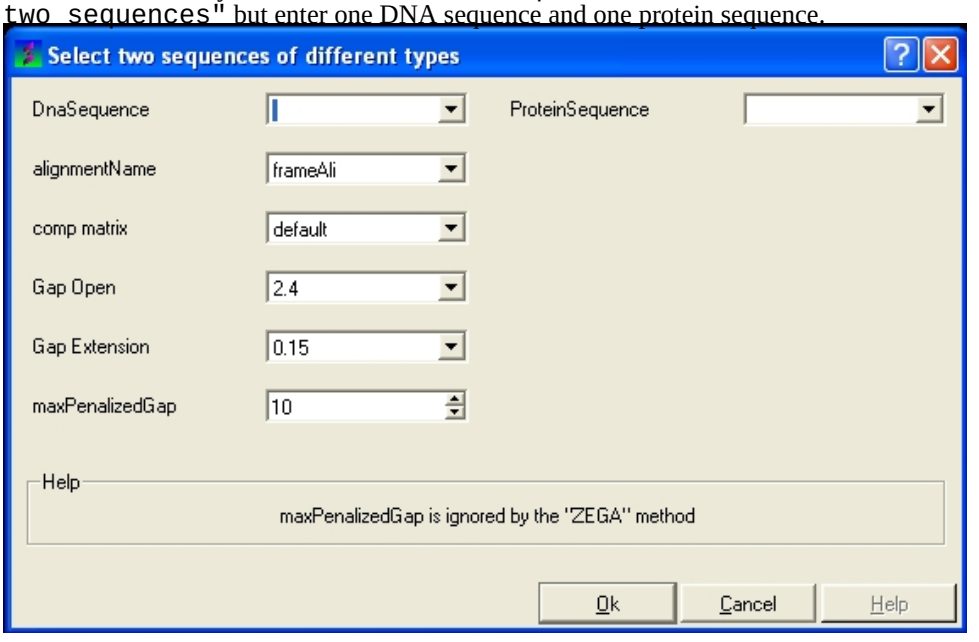
- Click OK and the alignment will be displayed in the alignment editor window at the bottom of the graphical user interface.
- Remember to save the project or write the alignment if you wish to keep the alignment for use at another time.



10.4.3 Align DNA to Protein

To align DNA to protein:

- Select the 'Bioinfo' menu.
- Select the option Align DNA vs Protein
- Follow the data entry instructions shown in `the previous section entitled "align two sequences"` but enter one DNA sequence and one protein sequence.

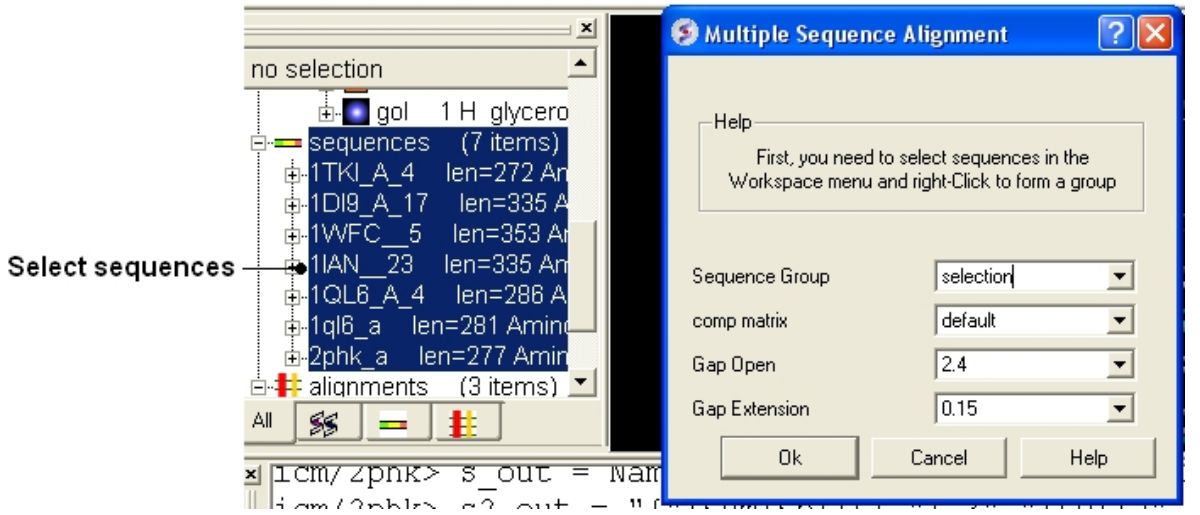


10.4.4 Align Multiple Sequences

- `Read` into ICM the sequences you wish to align.
- Select the sequences you wish to align in the ICM workspace. A sequence can be selected by double clicking (highlighted blue in ICM workspace) − a range of sequences in the ICM Worskpace can be selected by holding down the SHIFT button and double clicking. A non−contiguous selection can be made by holding down the CTRL button and double clicking.
- Bioinfo/Multiple Sequence Alignment
- Enter the name of the sequence group. If you selected the sequences as described above then the name of the group is **selection.** Other named groups of sequences can be made by right clicking on the sequence selection.
- Select the comparison matrix you would like to use.
- Enter Gap open and extension values.

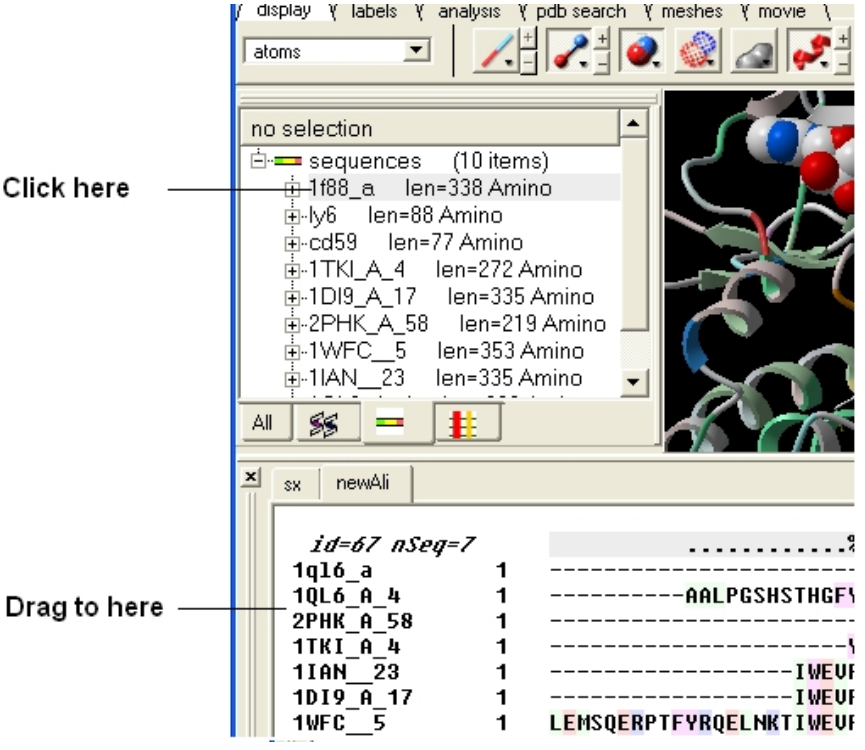
Gap Open The absolute gap penalty is calculated as a product of gapOpen and the average diagonal element of the residue comparison table You may vary gapOpen between 1.8 and 2.8 to analyze dependence of your alignment on this parameter. Lower pairwise similarity may require somewhat lower gapOpen parameter. A value of 2.4 (gapExtension=0.15) was shown to be optimal for structural similarity recognition with the Gonnet et. al.) matrix, while a value of 2.0 was optimal for the Blosum50) matrix (Abagyan and Batalov, 1997).

Gap Extension The absolute gap penalty is calculated as a product of gapExtension and the average diagonal element of the residue comparison table.



10.4.5 Drag and Drop

An easy way to add another sequence to an alignment is to drag and drop a loaded sequence from the ICM workspace panel to the alignment window. The sequence automatically becomes part of the alignment.



10.5 Alignment Editor

The default position for the alignment editor is at the bottom of the graphical user interface. If you have made an alignment and you cannot see the alignment you can select Window/Alignments (`See Window Menu section of this manual`) and it will be displayed.

ICM has an easy to use editor for pairwise and multiple alignments. ICM alignment editor is robust and always protects the integrity of your alignment by protecting you from making unintended changes in the alignment.

NOTE: To increase or decrease the size of the font in the Alignment Editor press the CTRL key and the '+' or '−' keys.

10.5.1 Edit an Alignment

To edit an alignment one only needs four types of operations:

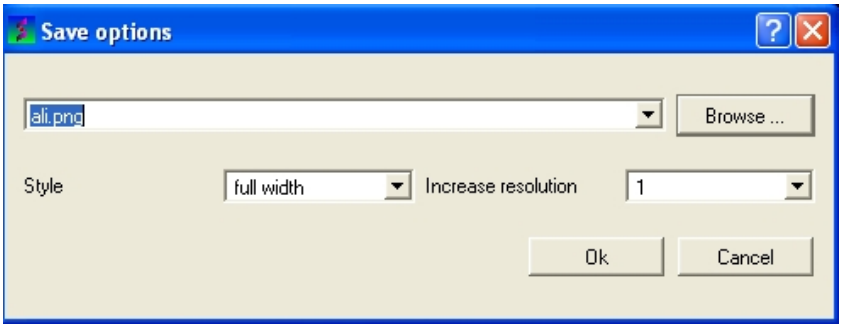
- select a block with one or several sequences to be moved (press Ctrl to add blocks). **Important:** since you can only move the selection **to the gapped space** , the moving front of the selection must be next to the gaps.
- (optional) create space on both sides around a vertical section of the alignment
- use the keyboard *arrows* to move the selected block with respect to the other sequences
- squeeze out the excessive gaps (an item in the alignment popup menu)

OPERATION	KEYS
set a vertical selection for ALL sequences in the alignment	**Double−Click**
add white space by hitting the Space bar	**SpaceBar**
remove white space	**Backspace**
select a sub−block for shifting	**Drag Left−Mouse−Button**
shift the selected block next to a gapped area	**Right and Left Arrows**

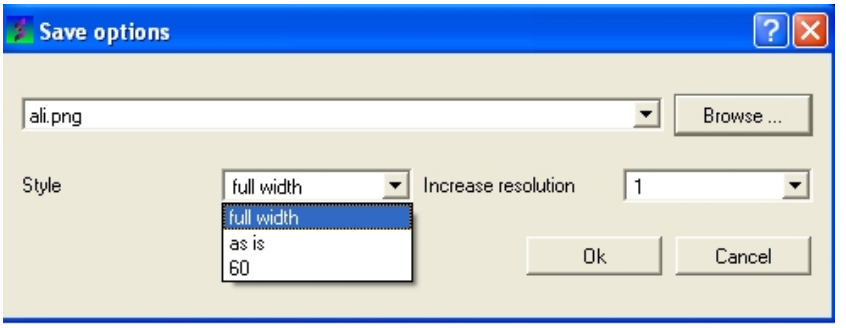
10.5.2 Save, Print and Delete

To save your alignment as a picture:

- Right click on the alignment and select the Save as image option.
- A data entry box as shown below will be displayed.



- Enter the filename you wish to call your alignment. We advice you to keep the .png file extensions.
- Select the drop down arrow next to the Style data entry box as shown below.



- Select the style you desire from full−width, as is, or 60.

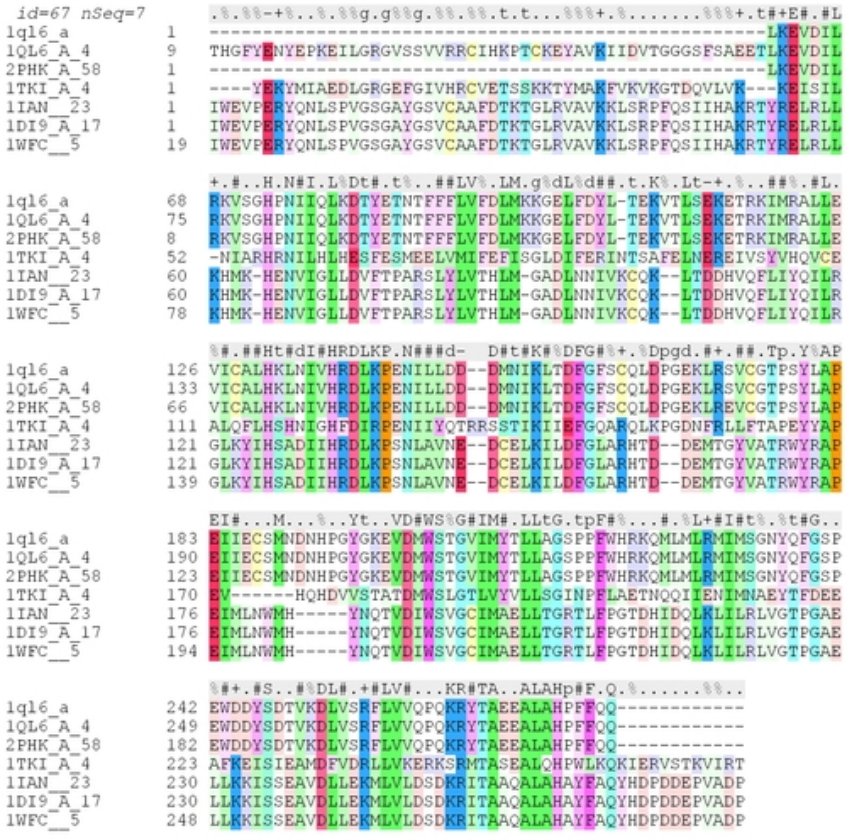
Full−width:

```
 id=67 nSeq=7          .%.%%-+%..%.%%g.g%%g.%%.%%.t.t...%%
1ql6_a           1     ------------------------------------
1QL6_A_4         9     THGFYENYEPKEILGRGVSSVVRRCIHKPTCKEYA
2PHK_A_58        1     ------------------------------------
1TKI_A_4         1     ----YEKYMIAEDLGRGEFGIVHRCVETSSKKTYM
1IAN__23         1     IWEVPERYQNLSPVGSGAYGSVCAAFDTKTGLRVA
1DI9_A_17        1     IWEVPERYQNLSPVGSGAYGSVCAAFDTKTGLRVA
1WFC__5          19    IWEVPERYQNLSPVGSGAYGSVCAAFDTKTGLRVA
```

Asis: As displayed in GUI.

```
 id=67 nSeq=7          .%.%%-+%..%.%%g.g%%g.
1ql6_a           1     ----------------------
1QL6_A_4         9     THGFYENYEPKEILGRGVSSV
2PHK_A_58        1     ----------------------
1TKI_A_4         1     ----YEKYMIAEDLGRGEFGI
1IAN__23         1     IWEVPERYQNLSPVGSGAYGS
1DI9_A_17        1     IWEVPERYQNLSPVGSGAYGS
1WFC__5          19    IWEVPERYQNLSPVGSGAYGS

                       %%.%%.t.t...%%%+.%...
1ql6_a           1     ----------------------
1QL6_A_4         30    VRRCIHKPTCKEYAVKIIDVT
2PHK_A_58        1     ----------------------
1TKI_A_4         18    VHRCVETSSKKTYMAKFVKVK
1IAN__23         22    VCAAFDTKTGLRVAVKKLSRP
1DI9_A_17        22    VCAAFDTKTGLRVAVKKLSRP
1WFC__5          40    VCAAFDTKTGLRVAVKKLSRP
```

60: 60 residues width



- Select the resolution for the image. We recomend 3.0.
- Select the browse button if you wish to save the picture in a directory other than the one you are running ICM in. If you decide to change directories you will have to reenter the desired file name and click ok. The path of the file will then be entered in the save options data entry box.
- Click OK.

To save an alignment or tree:

- Right click on the alignment or tree and a menu will be displayed.
- Select the save as option.

To print an alignment or tree:

- Right click on the alignment or tree and a menu will be displayed.
- Select the print option.

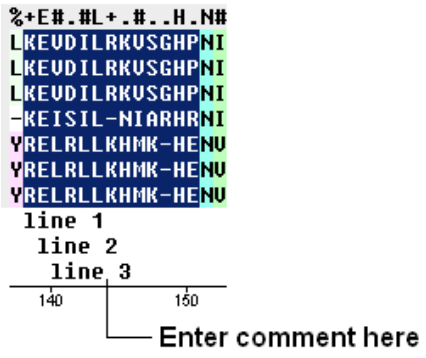
To delete an alignment or tree:

- Right click on the alignment or tree and a menu will be displayed.
- Select the delete option.

10.5.3 Add a Comment

To add a comment to an alignment:

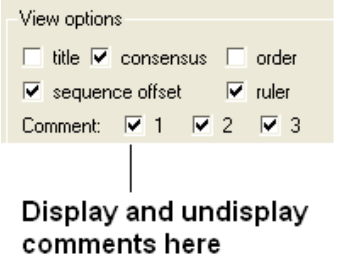
- Click and drag over the region of the alignment under which you wish to add a comment. The selected region will be highlighted in blue.
- Right click on the blue selected region and select 'Edit Comment' and either Line 1 ,2 or 3.
- Enter your comment text.
- Unselect by clicking away from the selection.



NOTE: The length of text added in a comment line can only be as long as the selected region in the alignment. However, there are up to 3 comment lines which you can add.

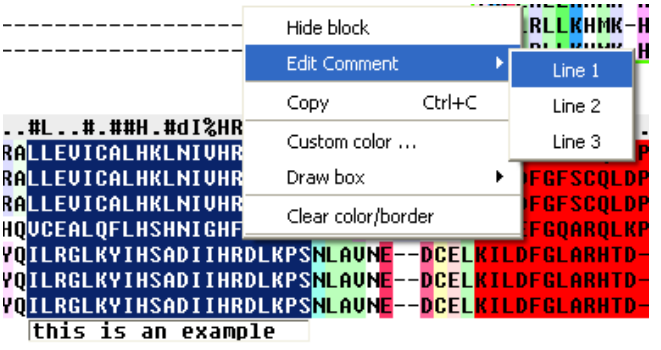
To display and undisplay comments:

- Check and un−check the comment boxes in the view options section of the alignment editor shown below.



To edit a comment:

- Select the comment in the alignment window.
- Right click and a menu will be displayed as shown below.



- Select edit comment and the line number you wish to edit.
- Type the new comment.

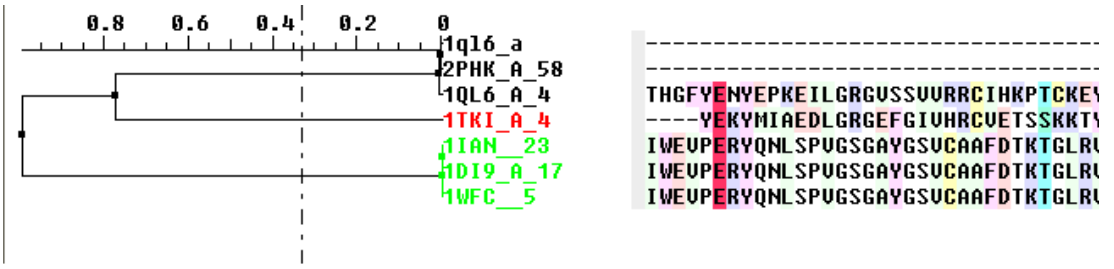
10.5.4 Phylogenetic Trees

NOTE: Before constructing a phylogenetic tree you need to align the sequences as described in the `alignment section`

To view a tree:

- Check the 'Tree' option in the alignment editor.

The tree will be displayed in the editor as shown below:



To display the tree alone without the alignment:

- Check the 'tree only' option in the alignment editor.

Tree functionality:

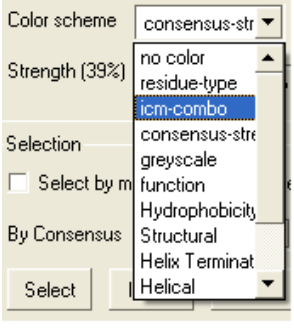
- the tree−section in the alignment is **resizeable**, just grab the rightmost end of the top ruler and drag it
- **branch swapping** : the sequences can be reordered by swapping the tree branches. Just do the following:
  - ♦ **Right−click** on a tree−node to get a popup−menu
  - ♦ **swap** the branches
- **selecting a branch**: double click on a tree−node to select the sequences belonging to it.

10.5.5 Coloring an Alignment.

To color an alignment:

There are a number of ways to color an alignment in ICM. ICM offers a wide range of default coloring options to choose from in the Alignment Editor.

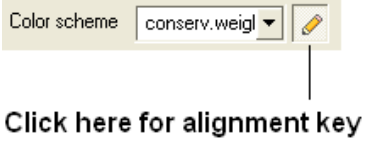
- Click on the drop down arrow beside the "Color scheme" data entry box and a number of color schemes will be displayed.
- Select the color scheme.



NOTE: You can keep selecting from the list until you find an appropriate color scheme. See the ICM language manual for other ways of coloring, definitions of color schemes and customizing the color. The colors are shaded from pale to bright where the brighter color represents higher conservation at that point in a multiple alignment.

To see the alignment color key:

- Click the pencil icon next to the color scheme selection tools and a table as shown below will be displayed.

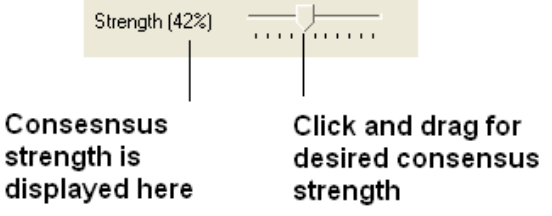


	residue	color	symbols	comment
39	DE			acidic, hydrophilic
40	RKH			basic hydrophilic
41	GAVILM			neutral, hydrophobic, aliphatic
42	FYW			neutral, hydrophobic, aromatic
43	STNQ			neutral, hydrophilic
44	C			thiol containing
45	P			imino acid
46	**Hydrophobicity**			
47	DE			acidic
48	RKH			basic
49	AVILMFWP			hydrophobic
50	GSTNQCY			hydrophilic
51	**Structural**			
52	RNDQEHK			external
53	ACGPSTWY			ambivalent
54	ILMFV			internal
55	**Helix**			
56	GTMRKHF			start
57	SNDELWP			end
58	CQAVIY			ambivalent
59	**Helical**			(consensus from several scales)
60	AMLEQK			likely to form helix
61	VIFW			weak formers
62	CSTNDHR			ambivalent
63	PGY			helix breaking
64	**Beta**			
65	VILMTFWY			likely to form strand
66	ACSNQHR			ambivalent
67	DEKGP			beta sheet breaking
68	**Turn**			
69	GSDNP			likely to form turn
70	EQTKRY			ambivalent
71	AVLIMHFWC			turn breaking
72	**Steric**			(order of increasing side chain length) (color by sp

To color by strength of consensus:

To color your multiple alignment by the strength of consensus at each point in an alignment:

- Click and drag on the consensus strength button shown below:

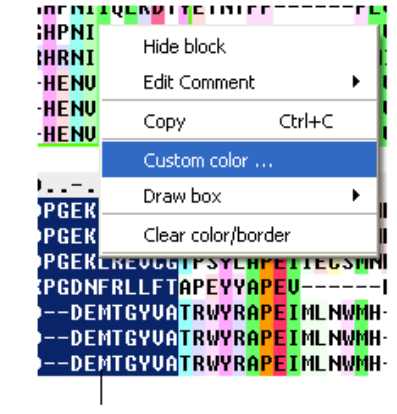


10.5.6 Shading and Boxing an Alignment

To shade an alignment:

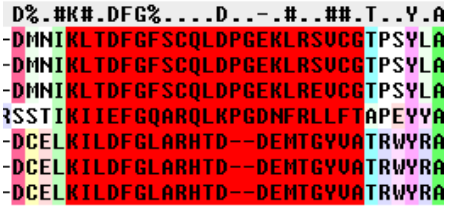
- Click and drag over the region of the alignment you wish to shade. It should be highlighted in blue.

- Right click and a menu will be displayed as shown below.
- Select the Custom color... option



Selected region to be shaded is highlighted in blue.

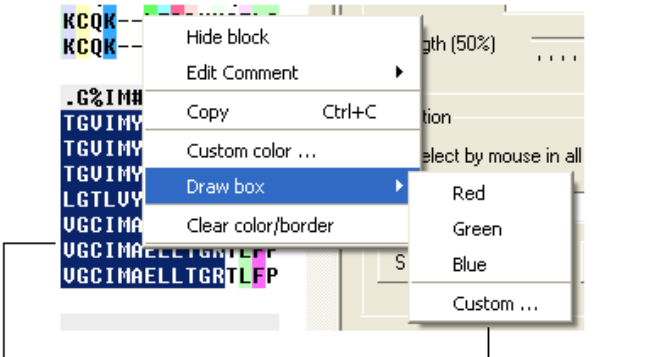
- Select your desired shading color.



A shaded alignment

To box an alignment

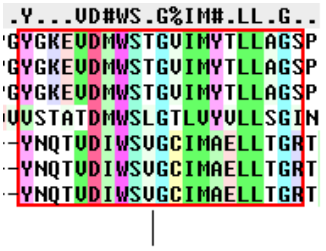
- Click and drag over the region of the alignment you wish to shade. It should be highlighted in blue.
- Right click and a menu will be displayed as shown below.
- Select the Draw box option.



Selected alignment region shown in blue

Select box color here

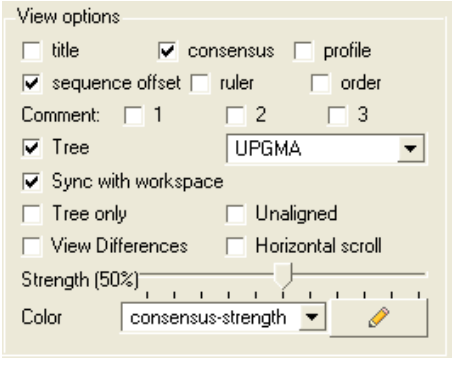
- Select which color you wish to box your alignment in.



A boxed alignment

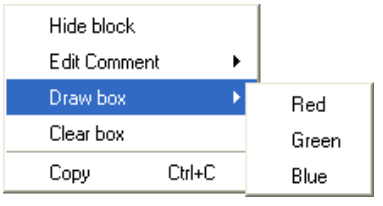
10.5.7 Alignment View Options

The alignment view options are located on the right hand side of the alignment editor.



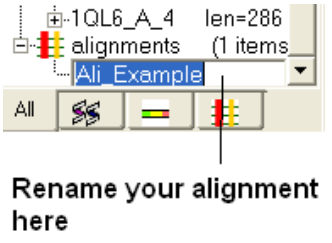
To add or remove the alignment title:

- Check the title box in the view options.



To rename an alignment:

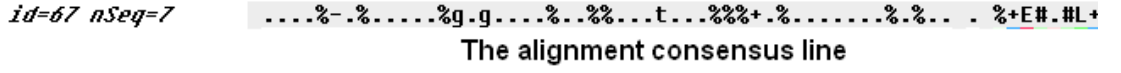
- Right click anywhere in the alignment or on the alignment tab and a menu will be displayed.
- Select the 'Rename' option.
- Type the new name for your alignment in the data entry box which becomes activated in the ICM workspace (See below).



Rename your alignment here

To add or remove the alignment consensus display.

- Check the box labeled 'consensus' in the view options.

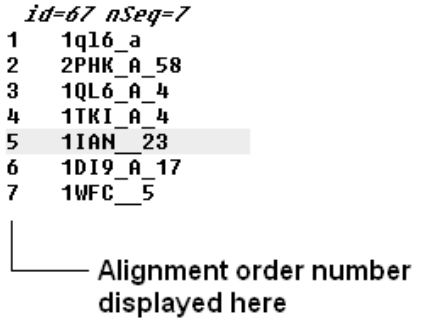


The alignment consensus line

If you have a large alignment it may be convenient to show the number of each sequence

To number your alignment:

- Check the 'order' box in the view options.

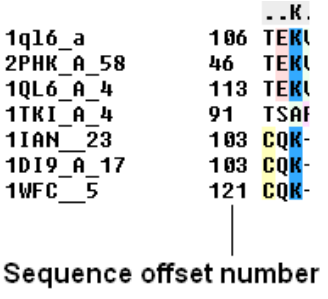


Horizontal Scroll

To view the alignment in **Horizontal scroll** click on the "Horizontal scroll" button in the **View Options** panel in the Alignment tool bar.

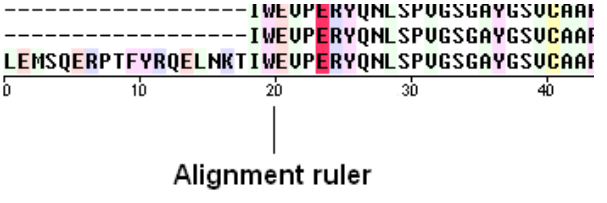
To view the sequence offset number for each of your sequences in an alignment:

- Check the 'offset' box in the view options.



To view the sequence ruler:

- Check the 'ruler' box in the view options.

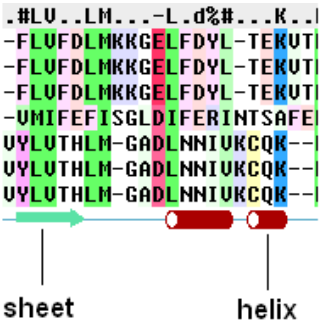


To view secondary structure.

If one of the sequences of the alignment is linked to a structure then you can display the secondary structure by:

- Check the "show secondary structure for" box.

The secondary structure will be displayed at the bottom of the alignment.

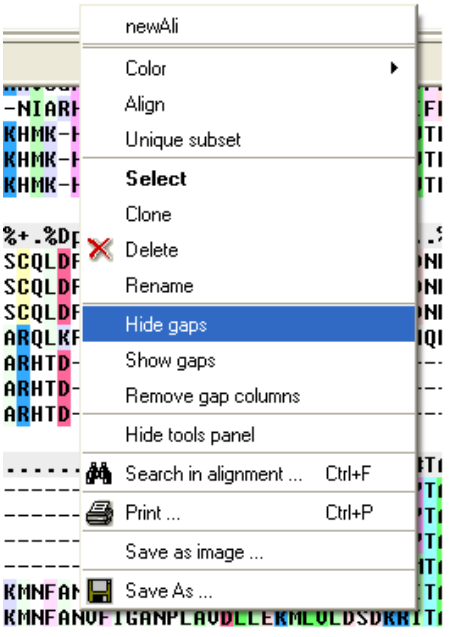


10.5.8 Alignment Gaps

To make an alignment clearer you may wish to HIDE gap regions.

To hide all gap regions:

- Right click on the alignment and a menu as shown below will be displayed.



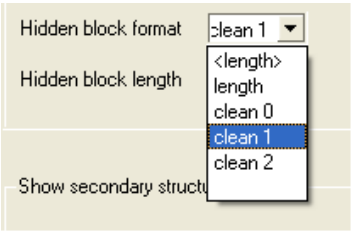
- Select the "Hide gaps" option.

The gaps in your alignment will be hidden according to the preference made in the alignment tools panel shown below. Click on the drop down arrow in the "Hidden block format" data entry box.

Two parameters can be specified directly from the Tools Panel in the alignment window:

1. the `"Hidden Block Format` can use the following special symbols:
   - ♦ %l number of hidden chars
   - ♦ %L length of the hidden block
   - ♦ %f hidden from
   - ♦ %t hidden to

   e.g. `" %f .. %t "` or `" %L "`
2. the `"Hidden block width"` which defines the total length of the hidden section.



Some predefined hidden block formats are shown here:

length: displays the length of the gap

```
S.. 27 #%D
SDT    VKD
SDT    VKD
SDT    VKD
SIE    AMD
SSE 27 AVD
SSE 27 AVD
SSE 27 AVD
```

length: displays the length of the gap in .

```
S..< 27 >#%D
SDT<    >VKD
SDT<    >VKD
SDT<    >VKD
SIE<    >AMD
SSE< 27 >AVD
SSE< 27 >AVD
SSE< 27 >AVD
```

clean0: displays no indication of a gap

```
S..#%D
SDTVKD
SDTVKD
SDTVKD
SIEAMD
SSEAVD
SSEAVD
SSEAVD
```

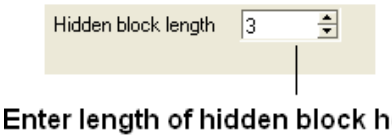
clean1: displays grey panel in the gap position.

```
S.. #%DI
SDT VKDI
SDT VKDI
SDT VKDI
SIE AMDI
SSE AVDI
SSE AVDI
SSE AVDI
```

clean2: displays a wider grey panel in the gap position

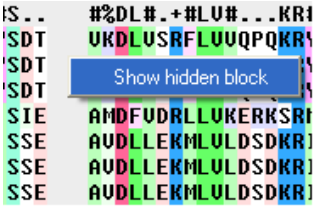
```
S..   #%DI
SDT   VKDI
SDT   VKDI
SDT   VKDI
SIE   AMDI
SSE   AVDI
SSE   AVDI
SSE   AVDI
```

NOTE: The width of the hidden panel can be changed as shown below.



If you have hidden all the gaps individual gaps (or blocks) can be displayed by:

- Right clicking on the gap and select "Show hidden block" option.



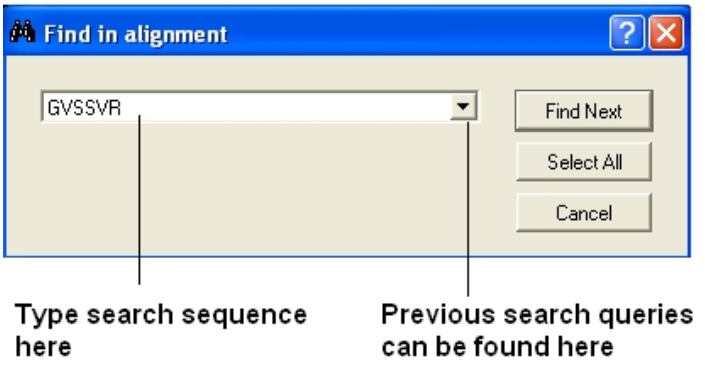
To show all gaps:

- Right click on the alignment away from a gap region and a menu will be displayed.
- Select the "Show gaps option.

10.5.9 Searching an Alignment

If you have a large alignment and you wish to find a specific group of amino acids within that residue the you can use the Alignment search tool.

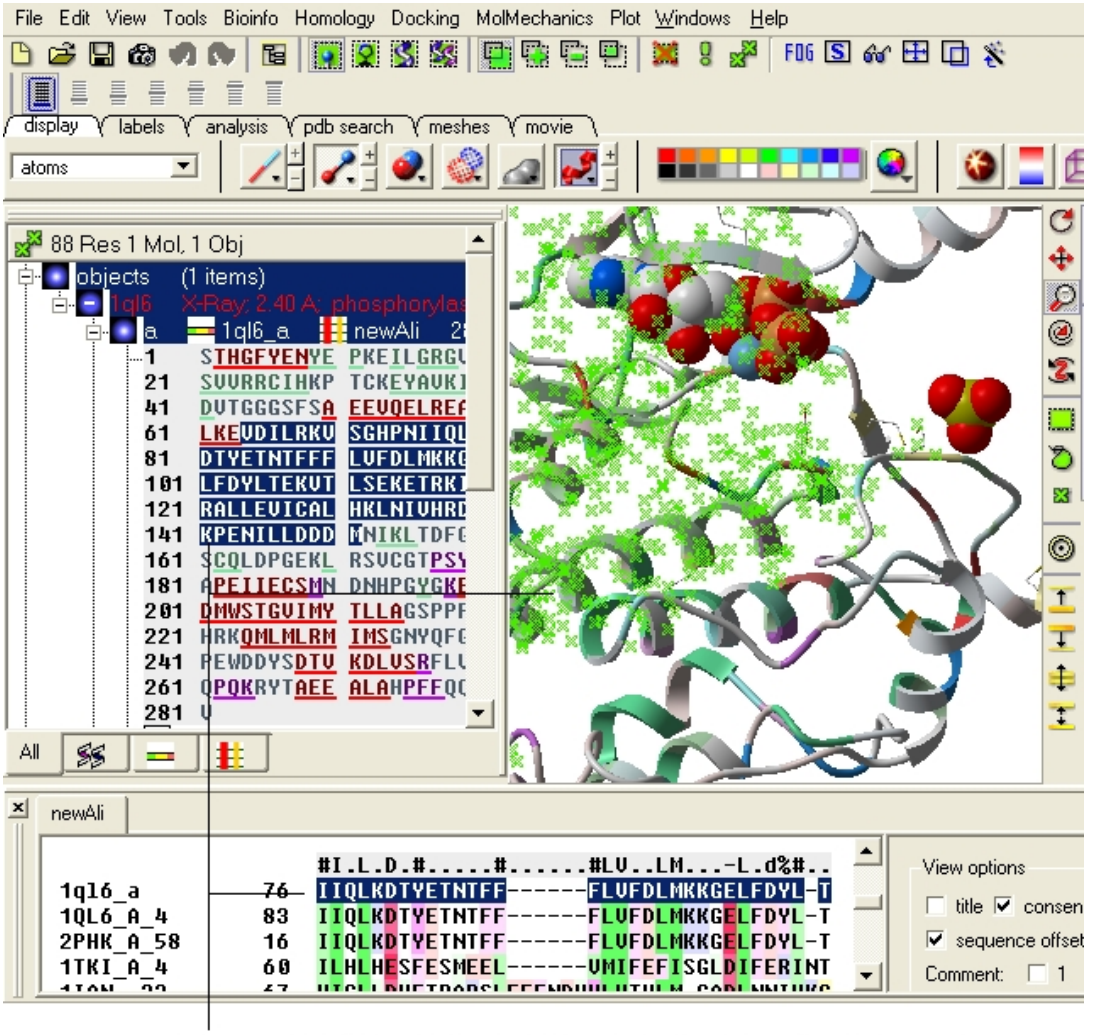
- Right click on the alignment away from any hidden gaps and a menu will be displayed.
- Select the "Search in alignment option" and a data entry box as shown below will be displayed.



NOTE: Another way of searching an alignment is to use the alignment selection tools which are linked to the ICM workspace and 3D graphical window. This is described in the section entitled `Making Selections in Alignments`.

10.5.10 Making Alignment Selections

ICM has a very powerful alignment selection tool which enables sequences and structures to be interlinked with the 3D graphical window, the alignment window and the ICM workspace.

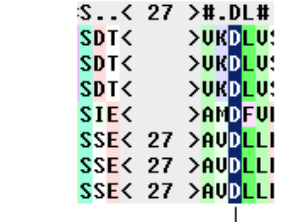


Selection is displayed in the ICM workspace (blue) the alignment window (blue) and the 3D graphics display (green cross).

10.5.11 Basic Alignment Selections

To select a single column of an alignment:

- Double click.



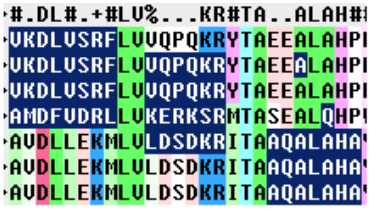
One column selected by double clicking

To select parts of an alignment:

- Click and drag over the region you wish to select.

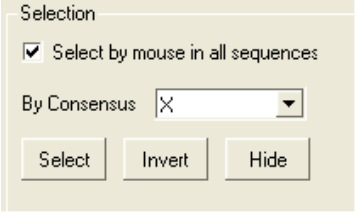
To select multiple discontinuous parts of an alignment:

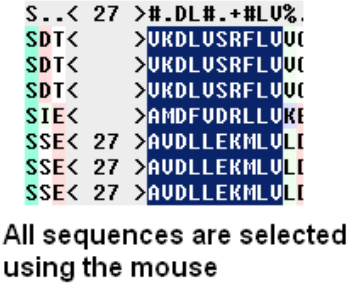
- Click and drag whilst holding down the control key.



To enable the easy selection of all sequences in an alignment:

- Check the box labeled "Select by mouse in all sequences".



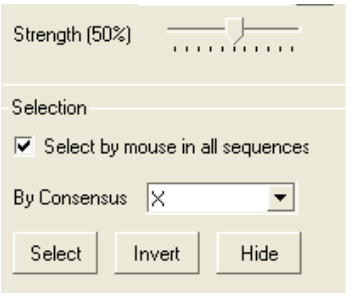


NOTE: All selections made in the alignment window are linked to the 3D graphics window and the ICM workspace if a structure is in the alignment.

10.5.12 Select by Consensus

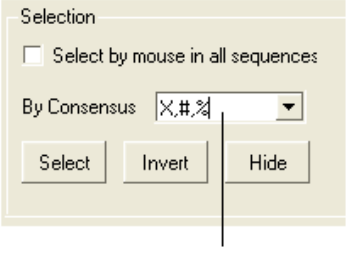
This is a very useful tool, for example, you may want to color the consrved regions of your structure in the 3D display windowa different color to the rest of the structure. This tool allows you to select the conserved regions in the sequence alignment. Once the selection has been made it can be used for a number of different ICM operations such as `coloring` and `displaying secondary structure`.

A selection can be made based on the alignment consensus. The buttons relating to this are in the alignment tool panel.



Before selecting by consensus you first need to define a consensus strength:

- Click and drag on the bar labelled "Strength" and select your desired percentage.
- Enter which elements of the consensus you wish to select separated by comma. Refer to the language manual for definition of each consensus symbol.



Enter which elements of the consensus you wish to select seperated by a comma.

- Click the Select button and your selection will be highlighted in blue in the alignment windown and ICM workspace and as green crosses in the 3D graphical display window.

Once the selection has been made it can be used for a number of different ICM operations such as `coloring` and `displaying secondary structure`.

To invert a selection:

- Click on the invert button.

To hide a selection.

- Click on the Hide button

NOTE: All selections made in the alignment window are linked to the 3D graphics window and the ICM workspace if a structure is in the alignment.

#endif

11 Protein Structure Analysis

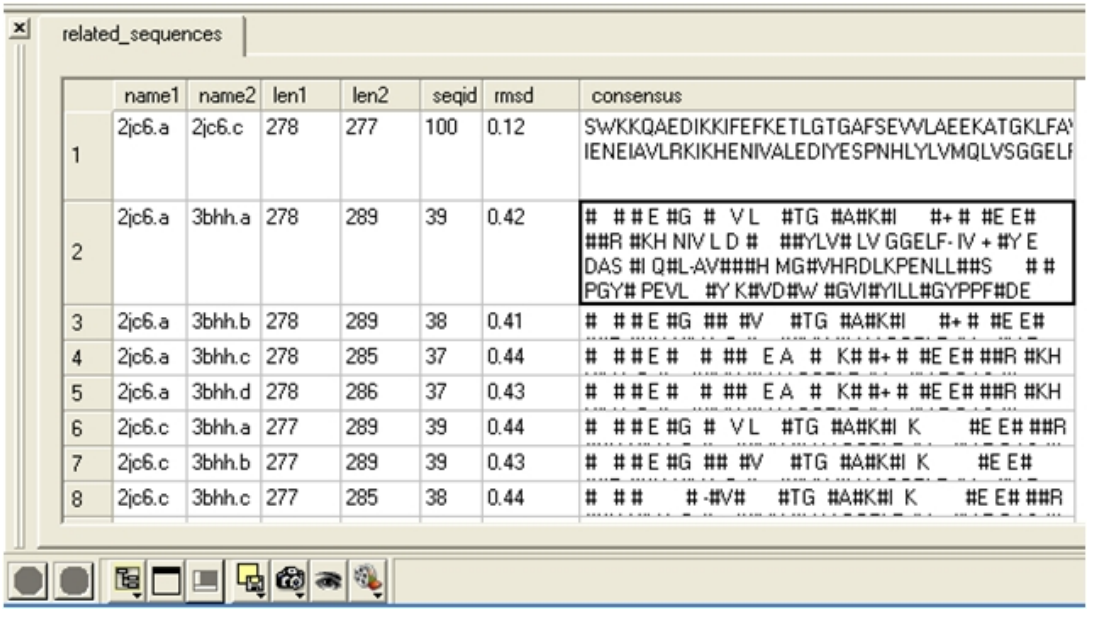
Note: Click **Next** (top right hand corner) to navigate through this chapter or click on the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

11.1 Find Related Chains

This option allows you to search the currently loaded PDB files or ICM objects and identify chains which are similar and/or related.

You can do this by:

- `Select` the objects or pdb files you want to compare.
- Tools/Analysis/Find Related Chains
- Click OK to confirm the selection you made
- A table as shown below will be displayed.



	name1	name2	len1	len2	seqid	rmsd	consensus
1	2jc6.a	2jc6.c	278	277	100	0.12	SWKKQAEDIKKIFEFKETLGTGAFSEVVLAEEKATGKLFA IENEIAVLRKIKHENIVALEDIYESPNHLYLVMQLVSGGELF
2	2jc6.a	3bhh.a	278	289	39	0.42	# ##E #G # VL #TG #A#K#I #+# #E E# ##R #KH NIV L D # ##YLV# LV GGELF- IV + #Y E DAS #I Q#L-AV####H MG#VHRDLKPENLL##S # # PGY# PEVL #Y K#VD#W #GVI#YILL#GYPPF#DE
3	2jc6.a	3bhh.b	278	289	38	0.41	# ##E #G ## #V #TG #A#K#I #+# #E E#
4	2jc6.a	3bhh.c	278	285	37	0.44	# ##E # # ## EA # K# #+# #E E# ##R #KH
5	2jc6.a	3bhh.d	278	286	37	0.43	# ##E # # ## EA # K# #+# #E E# ##R #KH
6	2jc6.c	3bhh.a	277	289	39	0.44	# ##E #G # VL #TG #A#K#I K #E E# ##R
7	2jc6.c	3bhh.b	277	289	39	0.43	# ##E #G ## #V #TG #A#K#I K #E E#
8	2jc6.c	3bhh.c	277	285	38	0.44	# ## #-#V# #TG #A#K#I K #E E# ##R

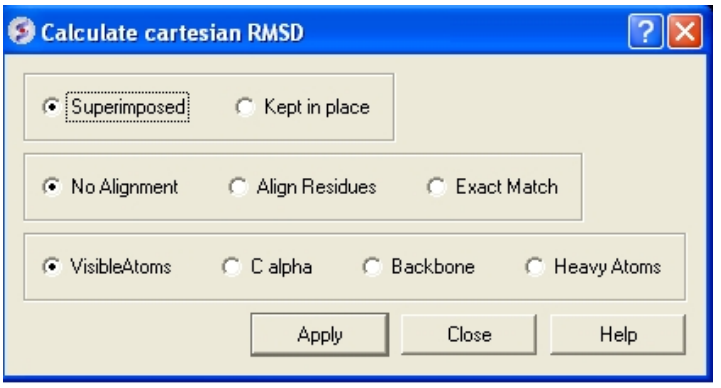
name1 = Name of query structure molecule **name2** = Name of hit **len1** = length of query **len2** = length of hit **seqid** = Sequence identity percentage **consensus** = Consensus sequence

11.2 Calculate RMSD

NOTE: This option is for protein structures only not for chemical compounds. You can use the command line options RMSD and SRmsd for chemicals.

To calculate RMSD between two structure:

- Read into ICM the two structures (File/Open or PDB Search or `Read in Chemical`)
- Select the two structures you wish to superimpose. You can do this by double clicking on the name of the structure in the ICM Workspace (a selection is highlighted blue in the ICM Workspace and green crosses in the graphical display} or you can use the right−click button and drag it over the whole structure in the graphical display. Use the CTRL key to select more than one object in the ICM Workspace or use the **add** selection button if `selecting` more than one object in the graphical display.
- Tools/Analysis/RMSD and a window as shown below will be displayed.

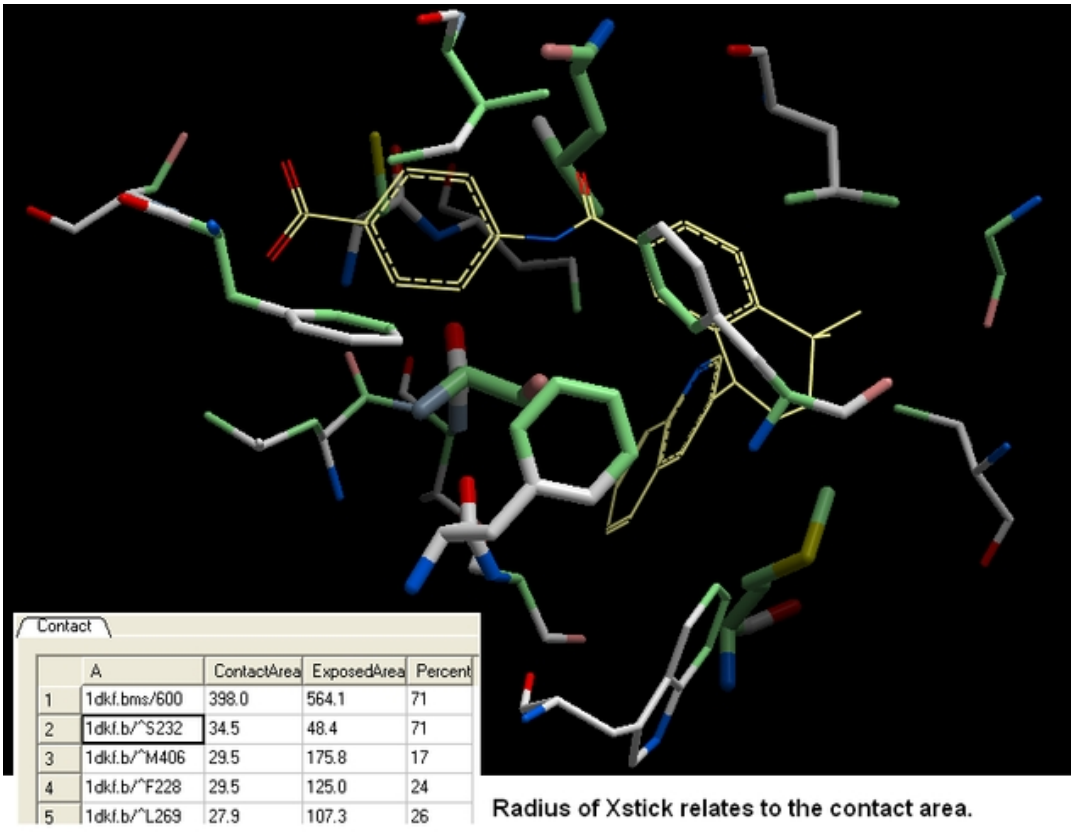


- Select whether you wish the atoms to be superimiposed onto one another or kept in place. The kept in place option would be ideal for compating docked structures.
- Choose whether you wish to make the superposition by alignment or exactly matching the atom names.
- Select which atom types you wish to superimpose.

The **RMSD** value will be displayed in the terminal window.

11.3 Contact Areas

- Read in a protein structure (File/Open or PDB Search)
- `Select` the region you wish to analyse.
- Tools/Analyze/Contact Areas
- The xstick display in the region will be scaled according to the atom/residue contact area. For example, residues making large contacts with a ligand will be displayed in thicker xstick representation than those making small contacts.
- A table as shown below will be displayed. Residues making key contacts will be displayed in xstick (radius represents contribution size). Carbon atoms are colored light green, nitrogen atoms are colored light blue and oxygen atoms are colored light red. The table lists the contact area, exposed area and the percentage of contact area compared to exposed.



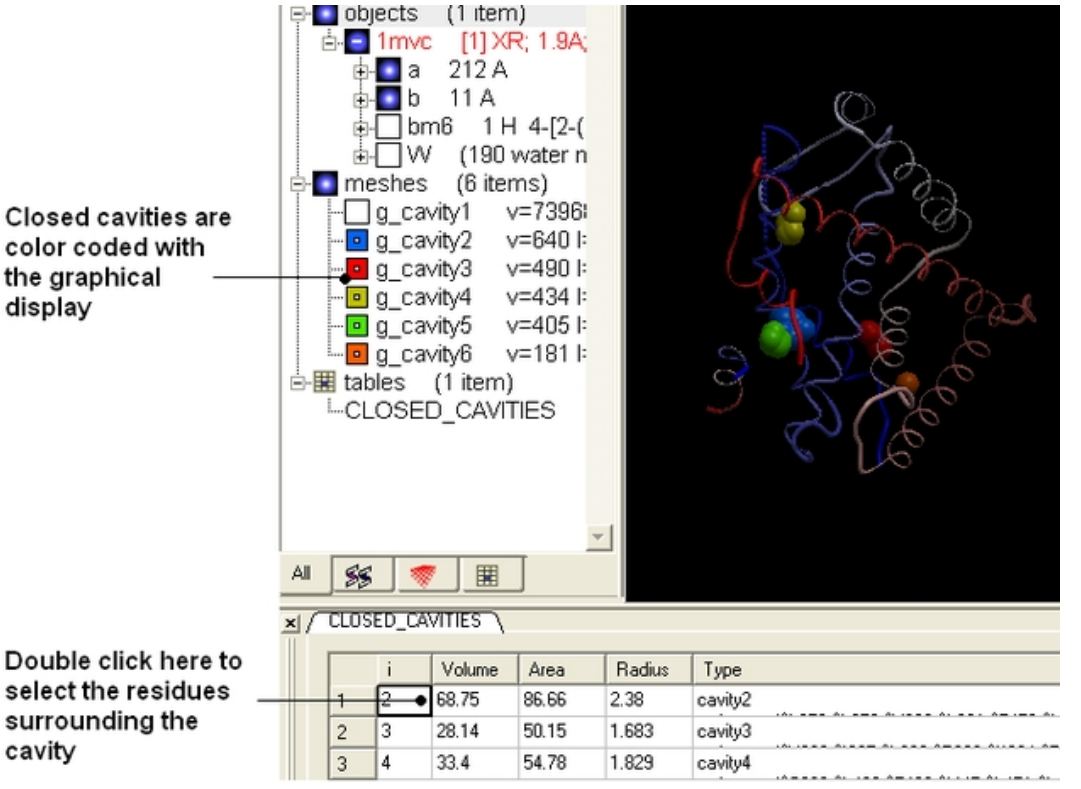
Radius of Xstick relates to the contact area.

NOTE: You can slso right click on the molecule in the ICM Workspace and select "Analyze Residue Contacts"

11.4 Identify Closed Cavities

This tool will identify cavities within a molecule which are completely closed,. If you are looking for buried and open pockets then use `icmPocketFinder`.

- Read in a protein structure (File/Open or PDB Search)
- Tools/Analysis/Closed Cavities
- Use the drop down arrow to locate the receptor you are interested in.
- Enter the minimum volume of the cavities you wish to identify.
- Click OK
- The closed cavities will be displayed in the meshes section of the ICM Workspace and a table of the cavities will be displayed. Double click on a row in the table to jump to a particular closed cavity and select the residues surrounding it.



11.5 Surface Area

This option calculates solvent accessible area of each selection in multiple objects and stores it in a table. If a molecule is specified in a multi−molecular object, the surface area of an isolated molecule is calculated and other molecules are ignored. The area is reported in square Anstroms and the probe radius is assumed to be the value set in the variable waterRadius.

Output: the macro creates table AREA . The empty comment field is added for user's future use. If the table exists, new rows are appended.

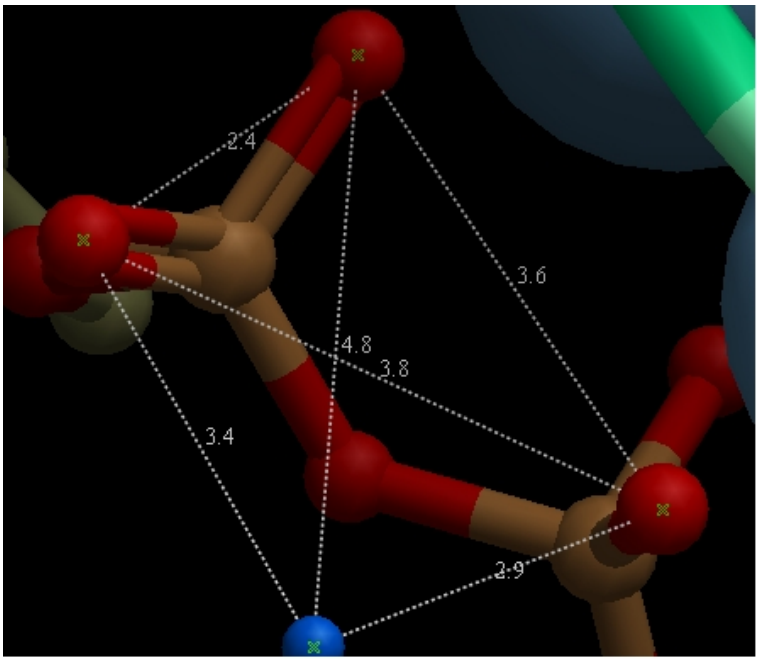
To calculate a surface area:

- Read in a protein structure (File/Open or PDB Search)
- `Select` the region you wish to analyse.
- Tools/Analysis/Surface Area
- A table will be displayed listing the residues in the selection along with the corresponding total surface area.

11.6 Measure Distances

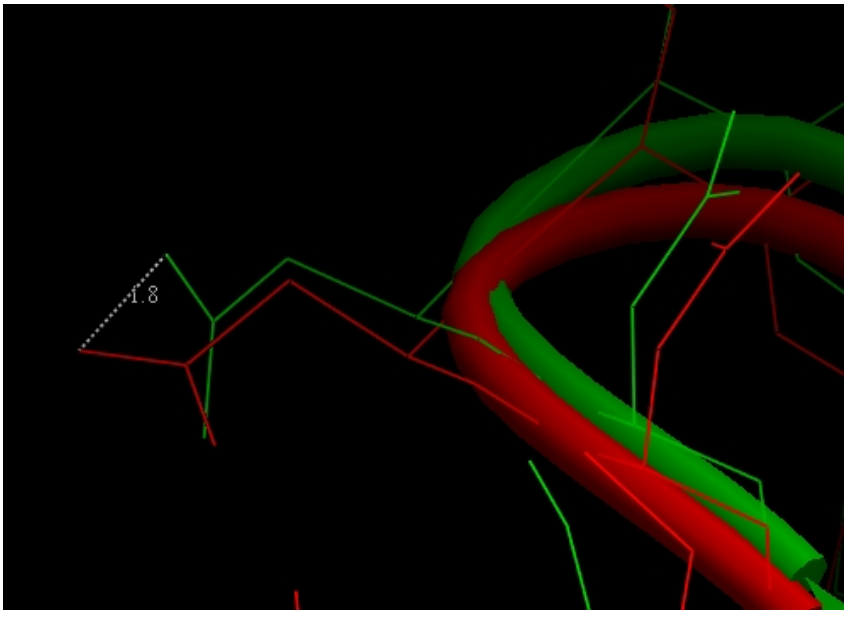
There are two approaches to calculating and displaying distances between atoms. You can either use the options in the Labels tab or use Tools/Analysis/Distance

To display **all to all** distances:



- Select the atoms between which you would like to find the distance. (See `selection toolbar`)
- Tools/Analysis/Distance
- Select all to all

To display **intermolecular** distances



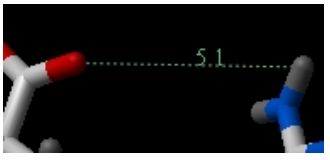
- Select the atoms between which you would like to find the distance. (See `selection toolbar`)
- Tools/Analysis/Distance
- Select **intermolecular**

To display the distances between the same atoms in two objects.

- Select the atoms between which you would like to find the distance. (See `selection toolbar`)
- Tools/Analysis/Distance
- Select **same atoms in two objects**

You can also use the buttons in the **label** tab to display the distance between two atoms:

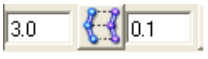
- Click on the labels tab (previously called advanced tab).
- Select the atoms between which you would like to find the distance. (See `selection toolbar`)
- Click on the 'Show Distances Between Two Atoms' Button
- The distance will be displayed in angstroms, in green.



To find the distance from one atom to many:

- Click on the labels tab (previously called advanced tab).
- Select the atom from which you wish to measure the distance from (See `selection toolbar`)
- Click on the 'Show Distances From One Atom To Many' button.
- The distances will be displayed in green.

The maximal and minimal distances can be selected by entering values in the boxes shown here (below) in the labels tab (previously called Advanced tab).

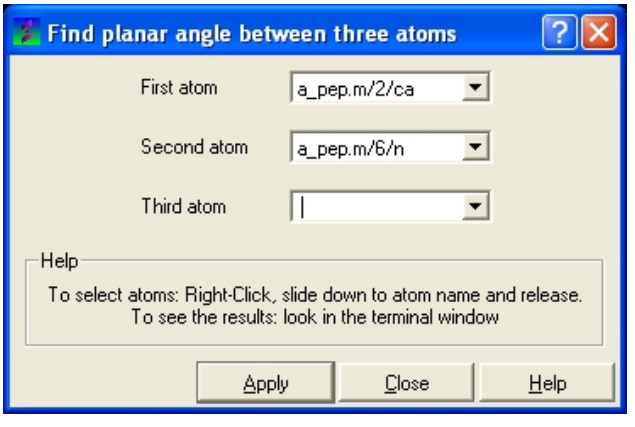


NOTE: Distances can be displayed and undisplayed in the 3D labesl section of the ICM Worskapce (left hand side of graphical user interface). You can change the color of a distance label by right clicking on it in the ICM Workspace. You can alse export the distance to a table.

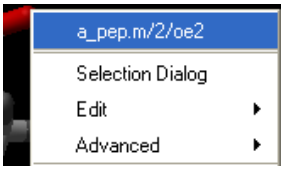
11.7 Planar Angle

If you wish to find the planar angle between three atoms:

- Select **Tools/Analysis/PlanarAngle**



- Right click on the each of the three atoms which you wish to use, and select their name. The spaces next to **First atom**, **Second atom**, and **Third atom** should now contain the name of your atoms.



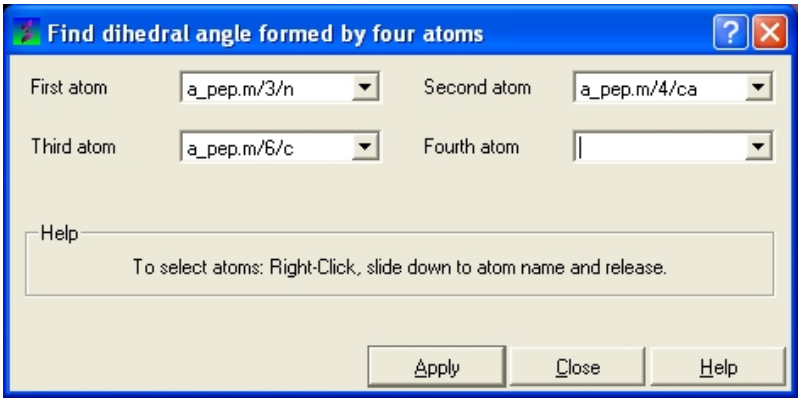
- Click **Apply** to display the angle measure in the terminal window.

```
Angle ( a_pep.m/6/hh21 a_pep.m/2/oe2 a_pep.m/3/o ) = 74.72 deg.
```

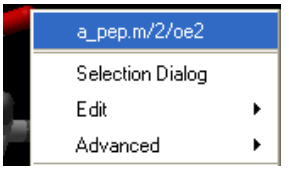
11.8 Dihedral Angle

In order to find the angle dihedral angle between two sets of atoms:

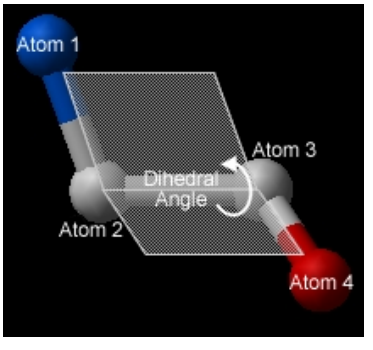
- Select **Tools/Analysis/Dihedral Angles.**



- Right click on each of the four atoms which you wish to use, and select the name of the atoms. The spaces next to **Atom 1**, **Atom 2**, **Atom 3**, and **Atom 4** should now contain the names of your atoms.



- To find the correct angle, select your atoms according to the following diagram:



- Click **Apply** to display your dihedral angle measure in the terminal window.

11.9 Ramachandran Plot Interactive

To make an interactive ramachandran plot:

- Read in a protein structure (File/Open or PDB Search)
- Select the structure you wish to build the plot for. You can do this by double clicking on the name of the structure in the ICM Workspace (a selection is highlighted blue in the ICM Workspace and green crosses in the graphical display) or you can use the right−click button and drag it over the whole structure in the graphical display.

- Tools/Analysis/Ramachandran Plot Interactive
- The interactive ramachandran plot will be displayed in table called **RAMA.**
- You can view the **Omega**, **Phi/Psi** (Gly) or Phi/Psi angles by clicking on the tabs at the top of the plot. Each point is linked to the data in the table **RAMA** and also to the graphical display. Soby clickin on a point in the plot will highlight the corresponding angles in the table and also center on this region in the 3D display.

11.10 Export Ramachandran Plot

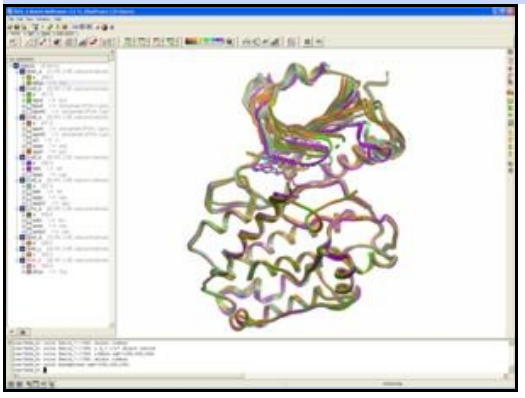
- Read in a protein structure (File/Open or PDB Search)
- Select the structure you wish to build the plot for. You can do this by double clicking on the name of the structure in the ICM Workspace (a selection is highlighted blue in the ICM Workspace and green crosses in the graphical display) or you can use the right−click button anddrag it over the whole structure in the graphical display.
- **Tools/Analysis/Ramachandran Plot Export**

A postscript viewer needs to be downloaded onto your machine in order to view the plot. This can be downloaded from `http://www.cs.wisc.edu/~ghost/.` Once this software is downloaded you need to tell ICM where it is located by typing the pathname into File/Preferences.

NOTE: You can always export the plot as an image directly in ICM without exporting. You can do this by right clicking on the plot and select **save as image**. Another approach could be to export the RAMA table to Excel and use the plotting tools there. You can do this by right clicking on the table name tab and selecting "Export to Excel" or save as ".csv".

12 Proteins Superposition

Note: Click **Next** (top right hand corner) to navigate through this chapter or click on the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.



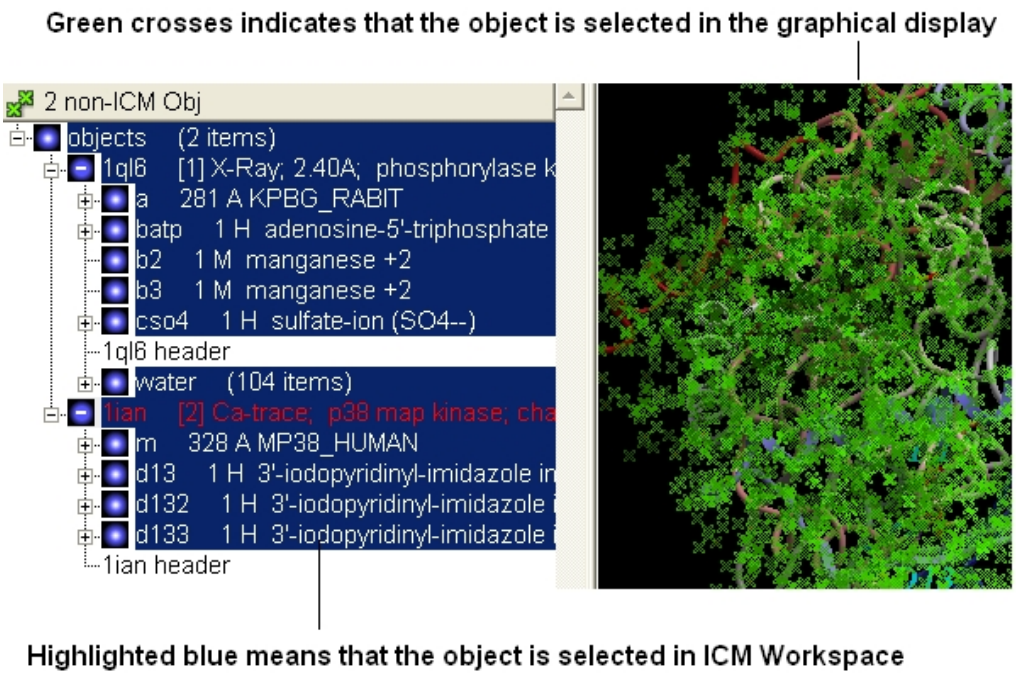
One or more proteins can be superimposed. Simply select the molecules or parts of the molecules you wish to superimpose and then use the selection of protein superimpose tools described in this section. For example a convenient superimpose button can be found in the display tab (see below).

12.1 Select Proteins for Superposition

Before any superposition operation can be undertaken you need to select the protein structures you wish to superimpose.

One way to do this is by selecting in the ICM workspace. For other selection tools please see the `Making Selections` section of the manual.

- Select both receptors by double clicking on the name of the receptor in the ICM Workspace.To select two receptors use the Ctrl button or use the shift button to select a range of objects in the ICM Workspace. A receptor which is selected will be highlighted in blue in the ICM Workspace and with green crosses in the graphical display.



Once the molecules are selected you can then superimpose them using the options described in the next section of this manual.

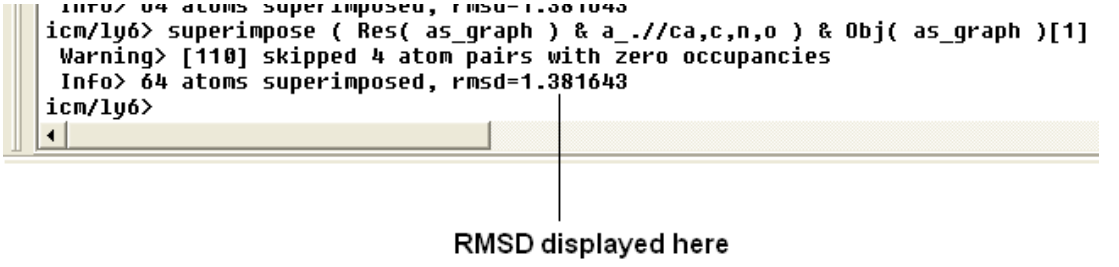
12.2 Superimpose Button

In order to calculate the root mean square deviation (RMSD) between two structures it is necesary to superimpose them. By using the superimpose button in the **display** tab, ICM will calculate the Ca−atom, backbone atom and heavy atom differences between the two structures. More advanced superimpose options can be found in the **Tools/Superimpose** menu.

To superimpose two structures which have the same number of residues and atoms:

- First load the two structures into ICM.
- Select which parts or all of the two structure you wish to superimpose (see `selection toolbar`).
- Select the **display** tab (previously called Advanced tab) at the top of the GUI.
- Select the superimpose button.

The rmsd will be displayed in the terminal window as shown below:

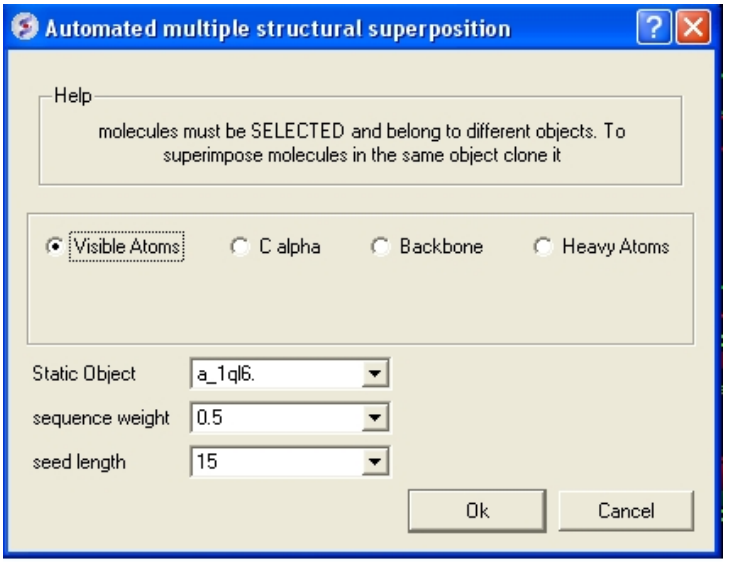


#endif

12.3 Superimpose by 3D

To superimpose proteins by 3D:

- First `display and select` the proteins you wish to superimpose by 3D.
- Tools/Superimpose/Proteins by 3D
- A window as shown below will be displayed.

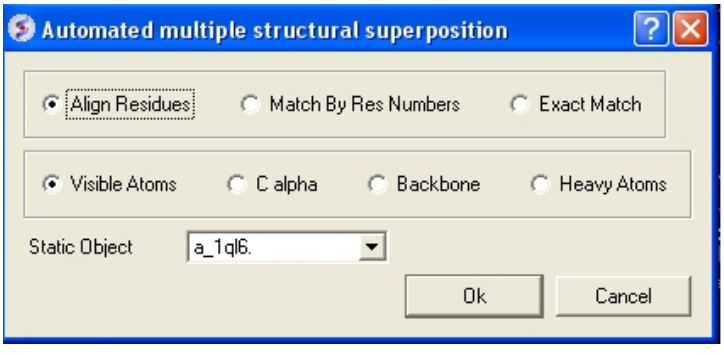


- Select by which atoms you wish to superimpose.
- Enter the ICM selection language description for the protein structure you wish to remain static. You can also use the drop down arrow button to select it.
- Enter the **sequence weight** Average local sequence alignment score.
- Enter the **seed length** This is the similarity window size.

12.4 Superimpose Multiple Proteins

To superimpoe multiple proteins:

- First `display and select` the proteins you wish to superimpose by 3D.
- Tools/Superimpose/Multiple Proteins
- A window as shown below will be displayed.



- Select by which method you would like to superimpose

Align Residues − Residue correspondence is established by sequence alignment using the ICM ZEGA alignment Abagyan, Batalov, 1997. Atom alignment: by atom name.

Match by Res Numbers − Residue alignment by residue number.Atom alignment: by atom name for pairs of identical residues or pairs of close residues (F with Y; B with D,N; D with N; E with Q or Z, Q with Z),

for other residue pairs only the backbone atoms ca,c,n,o,hn,ha are aligned.

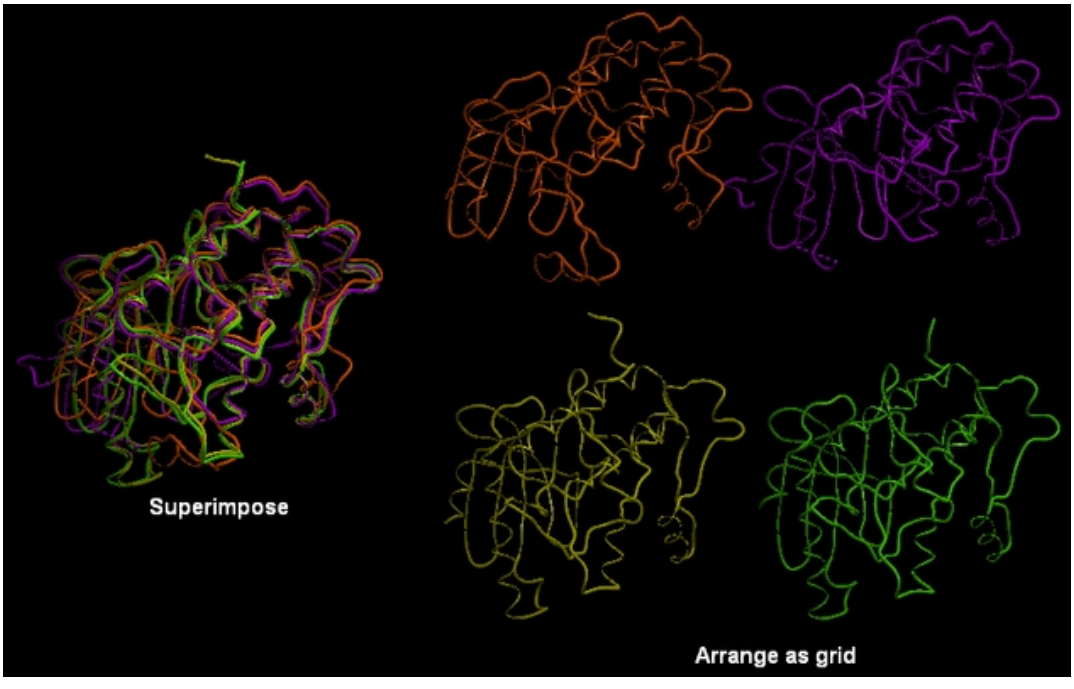
Exact Match − Residue alignment is by the Needleman and Wunsch method. Inside residue atoms are aligned sequentially and regardless of the name.

- Select which atoms you would like to superimpose. Visible Atoms, C alpha, Backbone, or Heavy Atoms.

12.5 Arrange as Grid

To separate superimposed proteins:

- Tools/Superimpose/Arrange as Grid



#endif

13 Crystallographic Analysis

Note: Click **Next** (top right hand corner) to navigate through this chapter or click on the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

13.1 Crystallographic Neighbor

Theory

Molecular objects and 3D density maps may contain information about crystallographic symmetry. It consists of the following parameters:

1. Crystallographic group eg. P2121 that determine N (depends on a group) transformations for the atoms in the asymetric unit.
2. Crystallographic cell parameters A, B, C, Alpha, Beta and Gamma

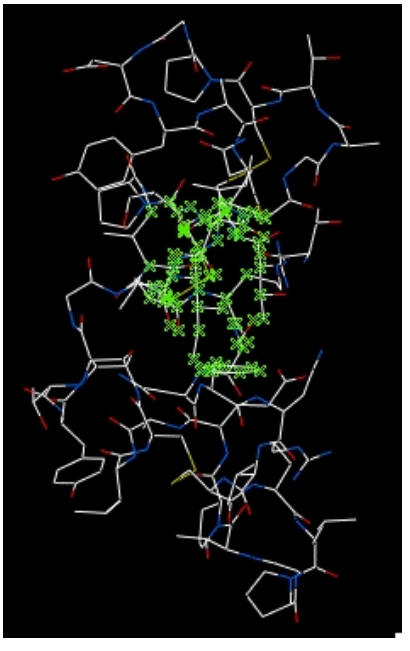
To generate the coordinates within one cell one needs to apply N transformations and then to generate neigboring cells the content of one cell needs to be translated in space according to the cell position.

ICM has a function which generates crystallographic neighbors for the selected atoms. For large proteins it is impractical to generate neighbors for the whole molecule due to the high number of atoms in all neighboring molecules.

This information allows to generate symmetry related parts of the density or molecular objects.

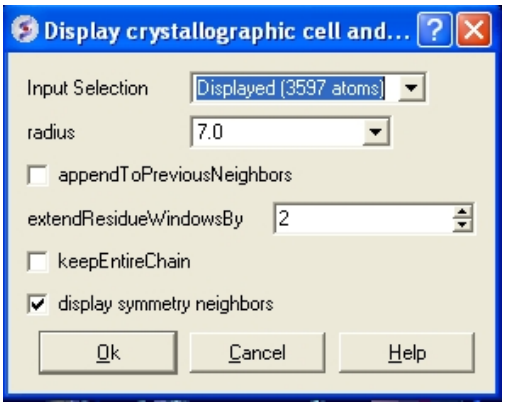
To generate symmetry related molecules around a selection of atoms:

- Read a PDB file into ICM. For instruction see the section entitled `Finding a PDB Structure`.
- Display the structure and select the residues around which the symmetry will be generated. For information on how to select residues see the `Making Graphical Selections` section.



- Select the menu Tools/Xray/Crystallograhic Neighbors.

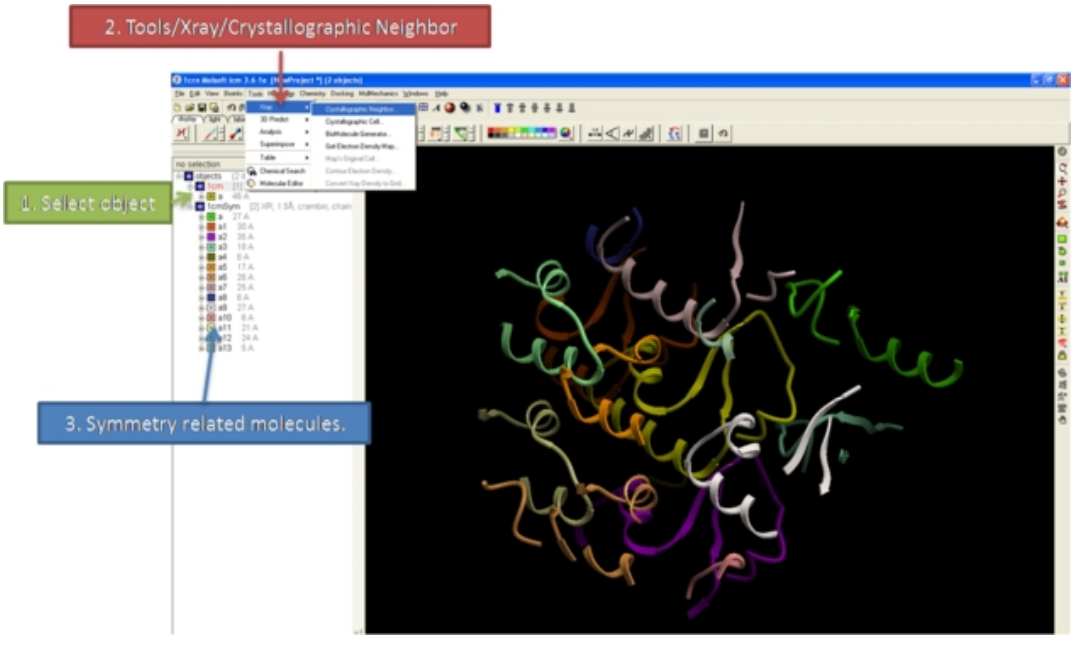
A data entry box as shown below will be displayed.



- Select the object.
- Enter the radius around your selction from which you wish to construct the symmetry related molecules.
- If you have made symmetry related molecules previously you can select **appendToPreviousNeighbors** otherwise leave unchecked.
- The **extendResidueWindowsBy** option will allow a window of residues outside of the selection radius selected above to be displayed
- If you leave the **keepEntireChain** unchecked then a fragment of each neighbor will be created. If you check this box the full neighbor will be generated
- Check display symmmetry neighbors to display them in the graphics window. The nearest neighbor residues will be displayed in xstick representation and the each neighbor colored by molecule.
- Click OK.

The crystallographic symmetry neighbors will be displayed in the Workspace. By default the object will have the object name + "Sym" and each of the neighbors will be individual molecules.

For packing analysis and display you can color each symmetry unit a different color as described in the `Structural Representations Color section`. This is shown in the picture below.



13.2 Crystallographic Cell

Theory

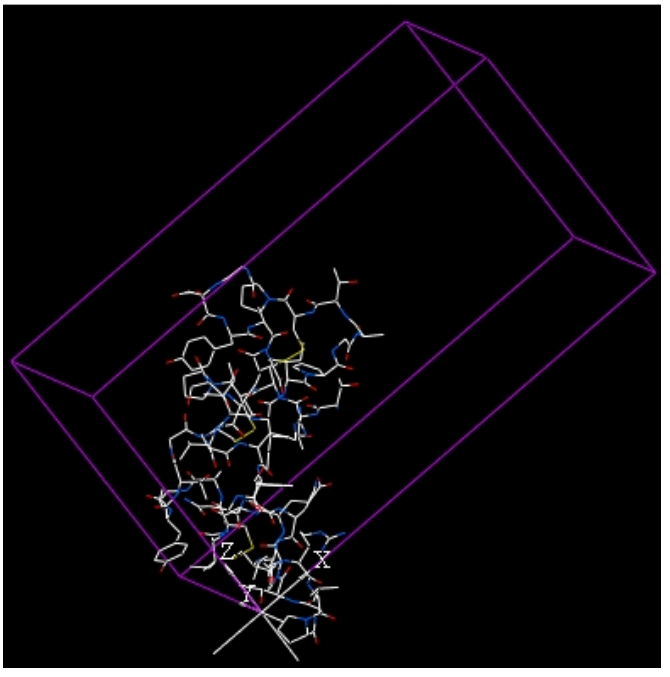
The crystal structure of a protein is often discussed in terms of its unit cell. The unit cell is a box containing one or more motifs, a spatial arrangement of atoms. The units cells are tiled in three−dimensional space to

describe the crystal. The unit cell is given by its lattice parameters, the length of the cell edges and the angles between them, while the positions of the atoms inside the unit cell are described by the set of atomic positions measured from a lattice point.

To display the crystal cell of a PDB structure:

- Read a PDB file into ICM. For instruction see the section entitled `Finding a PDB Structure`.
- Select the whole object. You can do this by double clicking on the name of the structure in the ICM Workspace (a selection is highlighted blue in the ICM Workspace and green crosses in the graphical display) or you can use the right−click button and drag it over the whole structure in the graphical display.
- Select the menu Tools/Xray/Crystallograhic Cell and a data entry box will be displayed.
- Click OK

The crystallographic cell will be displayed as a box as shown below.



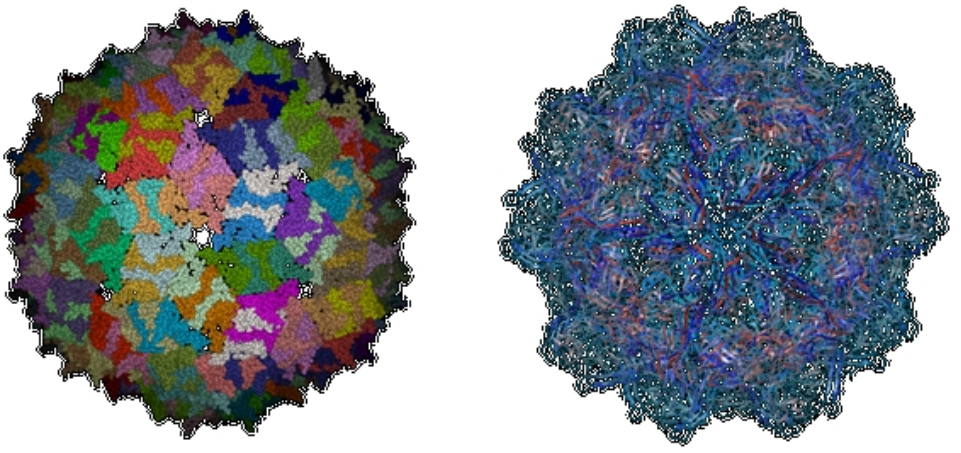
13.3 Biomolecule Generator

Theory

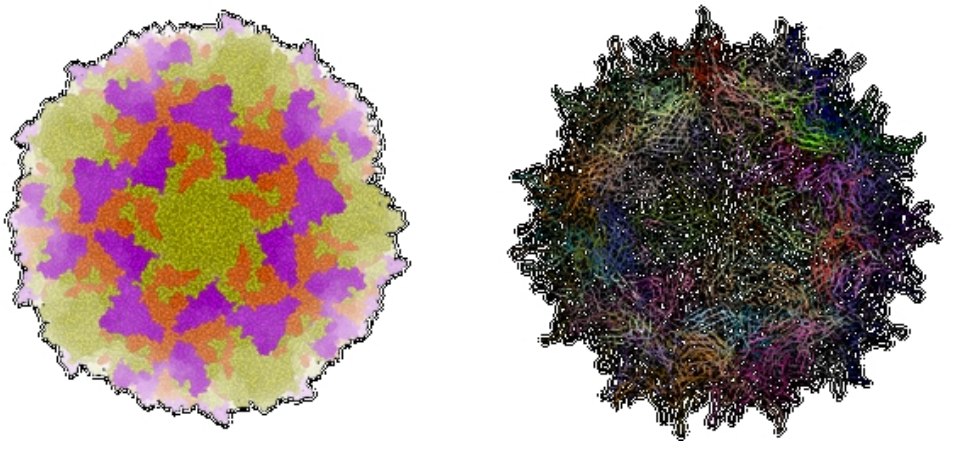
It is very useful to know how a protein from the PDB may look in a biological environment. The PDB entries solved by X−ray crystallography and deposited in the PDB contain the information about the crystal structure rather than the biologically relevant structure. For example, for a viral capsid only one instance of capsid protein complex will be deposited and only one or two molecules of haemoglobin that is a tetramer in solution maybe deposited.

In some other cases the asymetric unit may contain more than one copy of a biologically monomeric protein. ICM reads the biological unit information and has a tool to generate a biological unit. Not every PDB entry has the biological unit information.

A gallery of images created using the ICM Biomolecule generator is shown below:



Left: PDB: 1DWN Bacteriophage Pp7 From Pseudomonas Aeruginosa At 3.7 A Resolution **Right:** PDB: 1C8E Feline Panleukopenia Virus Empty Capsid Structure At 3.0 A Resolution



Left: PDB: 1AL2 P1/Mahoney Poliovirus, Single Site Mutant V1160I At 2.9 A Resolution **Right:** PDB: 1LP3 Adeno−Associated Virus (Aav−2), A Vector For Human Gene Therapy At 3.0 A Resolution

NOTE: Right click on a PDB structure in the ICM workspace to determine whether a structure from the PDB has biological unit information. If it does have this information then there will be an option in the menu entitiled "Generate Biomolecules" if not the option will be blanked out.

To generate a biological unit with ICM:

- `Select` the object or PDB file.
- Select the menu Tools/Xray/Biomolecule Generator.

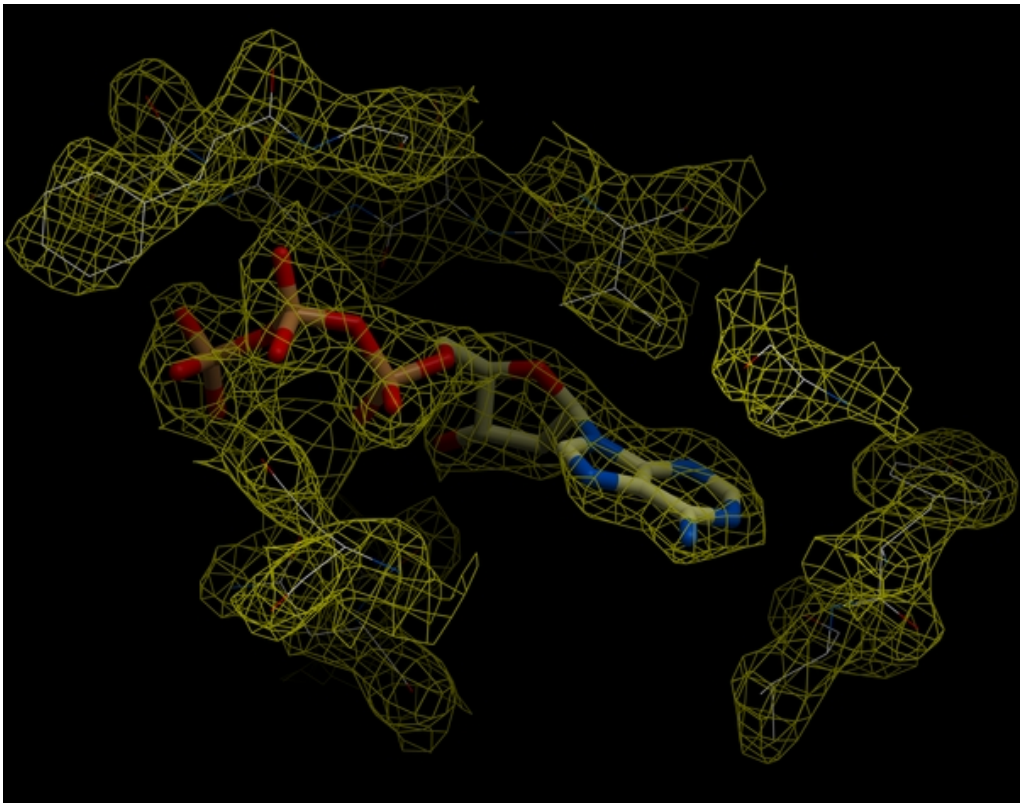
- Tick the **makeAllBiomolecules** box.
- Click OK − with very large molecules the biomolecule generation may take some time.

13.4 Get Electron Density Map

Theory

An electron density map is a representation of a crystal structure based on the diffraction data. The map is constructed by a summation of waves of known phase, amplitude and frequency using Fourier transform. The electron density map of a protein can be viewed along with the pdb structure. The easiest way to view the electron density map is to contour and convert it into a graphical object (mesh).

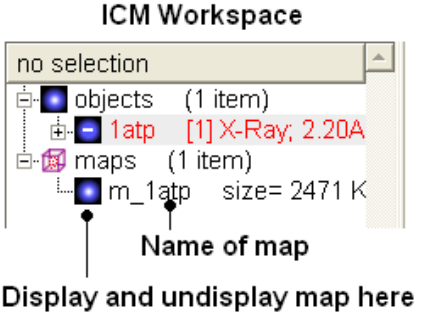
A figure showing the electron density contours surrounding the ATP molecule in pdb entry 1ATP.



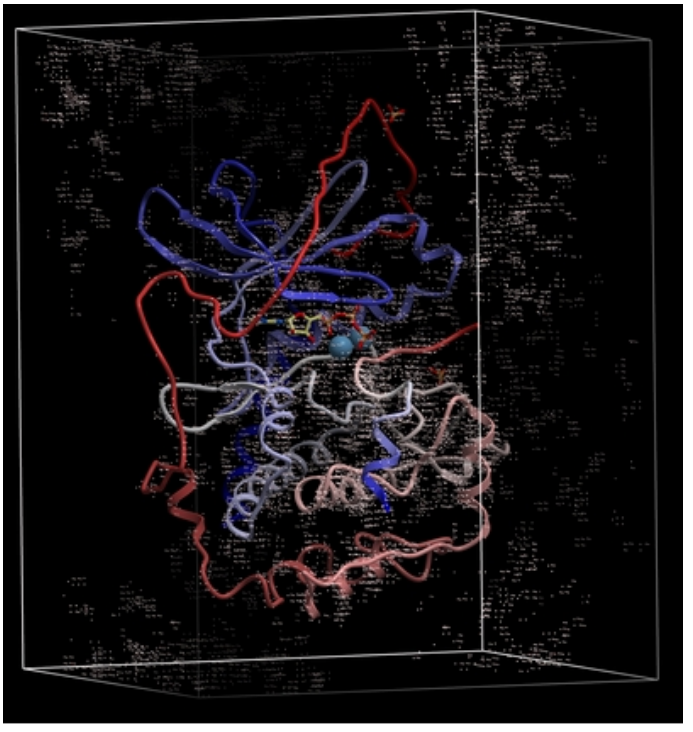
To load an electron density map:

- Tools/Xray/Get Electron Density Map
- Enter the PDB code of the map you would like to view.
- Click OK and the map will be downloaded from the Uppsala Electron Density Server.

The map will be represented in the ICM Workspace as shown below.



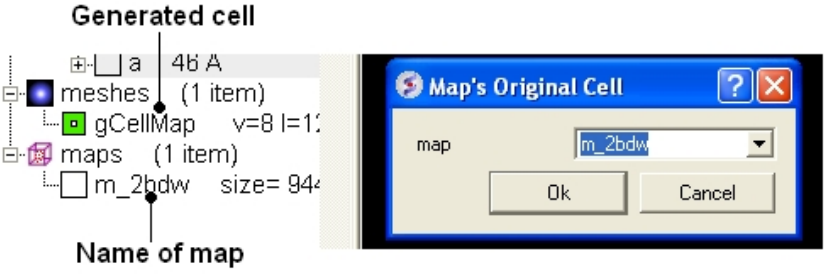
The map can be displayed as shown below however a clearer way of representing the density is to contour the map into a graphical object (mesh) as described in the following section.



13.5 Map's Original Cell

To display the original `crystallographic cell` of an electron density map:

- Tools/Xray/Map's Original Cell
- Enter the name of the map or use the drop−down button to locate it. If you do not know the name of the map the name can be located in the ICM Workspace.
- Click OK and the cell will be displayed. The map can be displayed and undisplayed in the **meshes** section of the ICM Workspace.



13.6 Contour Electron Density Map

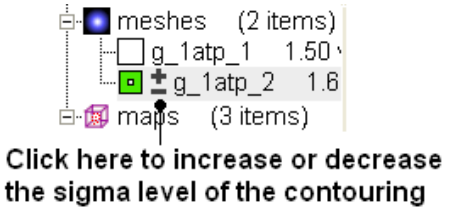
To contour an electron density map and display as a graphical object:

- Load an electron density map as described earlier in the `Load Map` section.
- Read in the PDB file − File/Load PDB or use the PDB search tab.
- Tools/Xray/Contour Electron Density.

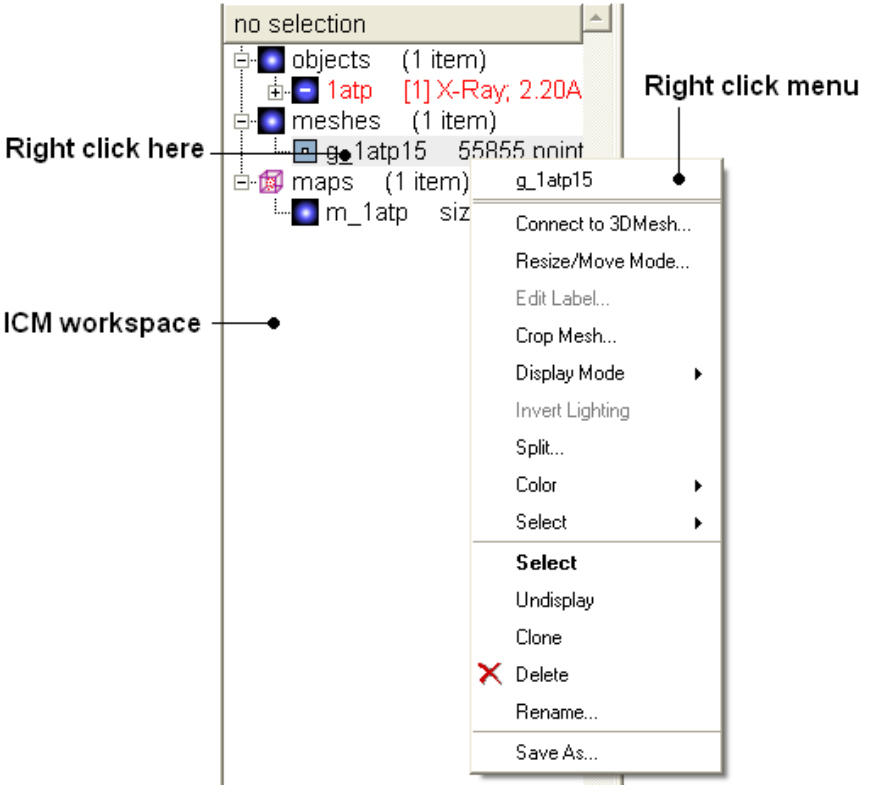
- Enter the name of the map e.g. m_1atp − the name of the map is displayed in the ICM Workspace or use the drop down arrow to locate it.
- If nothing is displayed then the whole map will be contoured. If you only want to contour a particular region of the map then you need to display that region of the PDB structure. Eg the binding pocket.
- Enter a sigmaLevel value for more information see: `http://www.molsoft.com/man/reals.html#mapSigmaLevel.` Once the contoured

map has been created the sigma level can be changed manually using the +/− buttons in the ICM workspace.

- In ICM versions 3.6−1f and above there is an option to **Keep All Density in Box**. If this option is checked the density will be contoured around a box surrounding your selection if you do not check this box only the atoms selected will be contoured.



- Click OK and the mesh will be displayed. Right click on the mesh in the ICM Workspace for display options (see below).



NOTE: Meshes can be cut away using the `mesh clipping tools`.

13.7 Convert Xray Density to Grid

For some applications, such as trying to fit a structure to a density map, you may want to extract a sub map and convert to a grid. You can do this by

- First read into ICM a map (eg File/Open or Tools/X−ray/Get Electron Density Map)
- Tools/X−ray/Convert Xray Density to Grid
- Enter the map name or use the drop down list
- Enter a grid size
- Click OK

#endif

14 Homology Menu and Modelling Tools

Note: Click **Next** (top right hand corner) to navigate through this chapter or click on the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

In this Chapter:

14.1 Homology Modeling Introduction

The basis behind molecular modeling is to use as much information as possible derived from solved structures in the PDB and apply them to the wealth of newly generated gene sequences, derived from many genome programs. All the available parameters are considered. Whenever there are variables that are too uncertain to derive from experimental data, you can use powerful prediction algorithms such as the ICM program to find the most probable solution. With today's need for high−throughput, molecular modeling is often one of the best approaches to define priorities for researchers and corporations.

ICM has an excellent record in building accurate models by homology. The procedure will build the framework and shake up the side−chains and loops by global energy optimization. You can also color the model by local reliability to identify potential errors in your model.

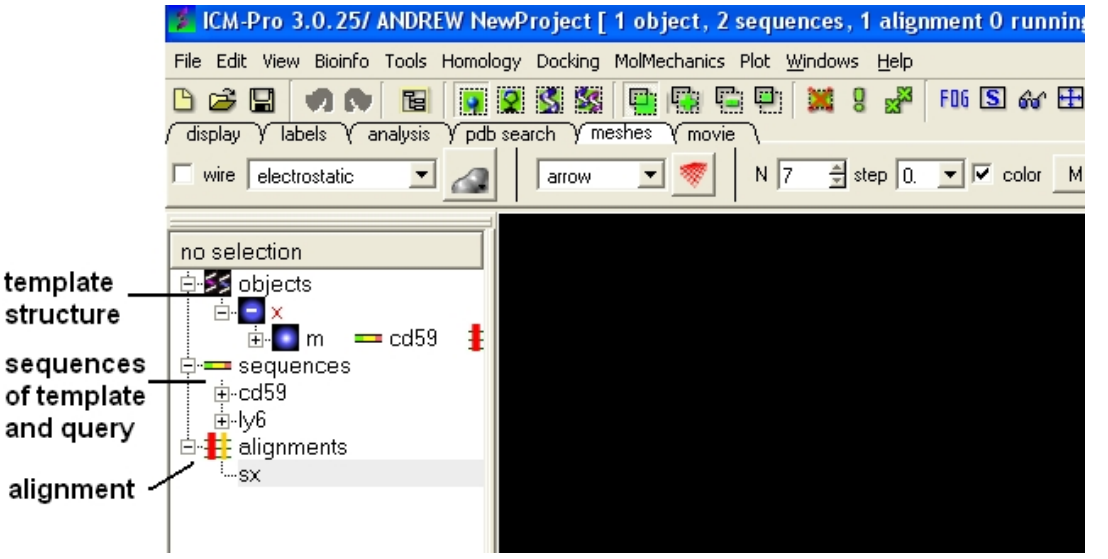
ICM also offers a fast and completely automated method to build a model by homology and extract the best fitting loops from a database of all known loops. It just takes a few seconds to build a complete model by homology with loops.

14.2 Getting Started

The three items you need for ICM protein molecular modeling are:

1. An alignment (see `alignment section`) of your query sequence against a template sequence from the PDB. This is a *.ali file in ICM.
2. A template structure from the PDB converted (See `convert object`) into an ICM object.
3. A sequence file of your query sequence for the structure you wish to allographic−construct and a sequence file for your template. Note ICM automatically extracts this information from the alignment or template structure.

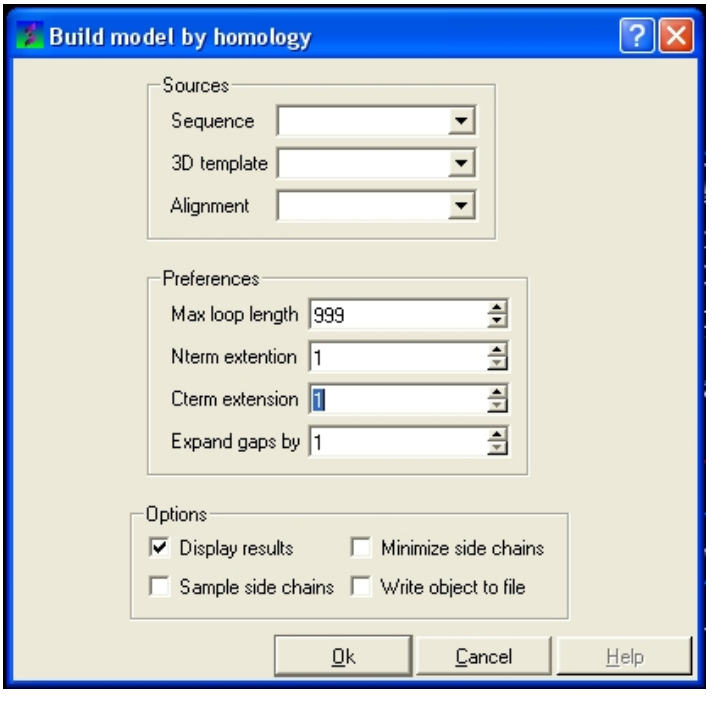
Your graphical user interface window should look something like this:



14.3 Build Model

To build a molecular model:

- Click on the 'Homology' menu at the top of the graphical user interface.
- Select Build Model and a data entry box will be displayed as shown below.



This data entry box is split into 3 sections, the first is 'sources' where you need to specify your query sequence, template and alignment. The second section is called 'preferences where penalty information for the model needs to be entered and the third section is called 'Options'. Each will be described in detail below.

To construct your model follow these steps:

- Enter the name of your QUERY (ie the sequence of the model you wish to build − NOT the template) sequence in the data entry box labeled 'sequence. If you click on the arrow next to this box a list of sequences loaded in ICM will be displayed click on your QUERY sequence. The names of the sequences are also listed in the workspace panel on the left of the graphical user

interface.
- Enter the name of your template structure in the '3D template' data entry box. Once again the name of your template structure can be found by clicking the down arrow or in the workspace panel.
- Enter the name of your alignment in the 'Alignment' data entry box.

You could build your model now as ICM has enough infromation but it may be wise to take a look at some of the preferences and change them accordingly. However in most cases the default values provided are sufficient to produce a good quality model.

To change the preferences either type the number you wish or use the up and down arrows next to the data entry boxes.

Max loop length (default= 999) − loops longer than this value are not modeled

Nterm extension (default=1) − the maximal length of the N−terminal model sequence which extends beyond the template

Cterm extension (default=1) − the maximal length of the C−terminal model sequence which extends beyond the template

Expand gaps by (default=1) − additional widening of the gaps in the alignment. End gaps are not expanded

Now all you need to do to build your model is to select some options. Check the box if you would like ICM to perform that option.

The options are:

Display results − displays your model in the 3D graphics window

Minimize side chains − performs minimization on the side−chains

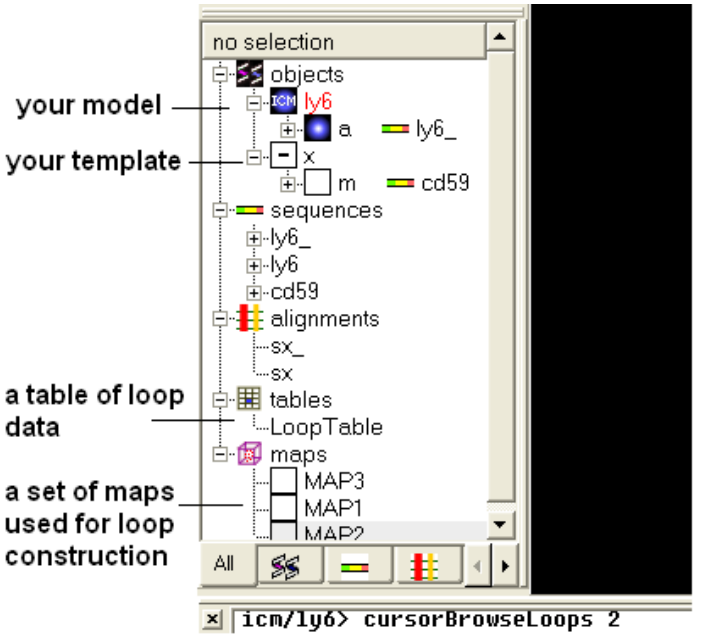
Sample side chains − performs monte−carlo optimization on the side chains

Write object to file − writes your new model as an ICM object

To build your model:

- Click OK

Once your model is built a new object will be seen in your workspace panel. This is your model (see below).



A table of the loop data will also be displayed showing the RMSD from the template.

LoopTable

	1_Loop	2_Conf	3_Rmsd	4_Nof	5_Type
1	a_ly6.a/57:58	1RRR	0.46	3	1
2	a_ly6.a/9:10	RRR3	0.58	3	1
3	a_ly6.a/32:33	L1R322LLR2	0.54	2	1
4					

14.4 Interactive Modeling

How to perform interactive modeling:

What you need before you can undertake interactive modeling:

- A template structure from the PDB converted (See `convert object`) into an ICM object.
- A `sequence file` of your query sequence.

You can use an alignment you have constructed yourself or allow ICM to generate one (referred to as **automatic)**

- An alignment (see `alignment section`) of your query sequence against the template structure from the PDB. This is a *.ali file in ICM.

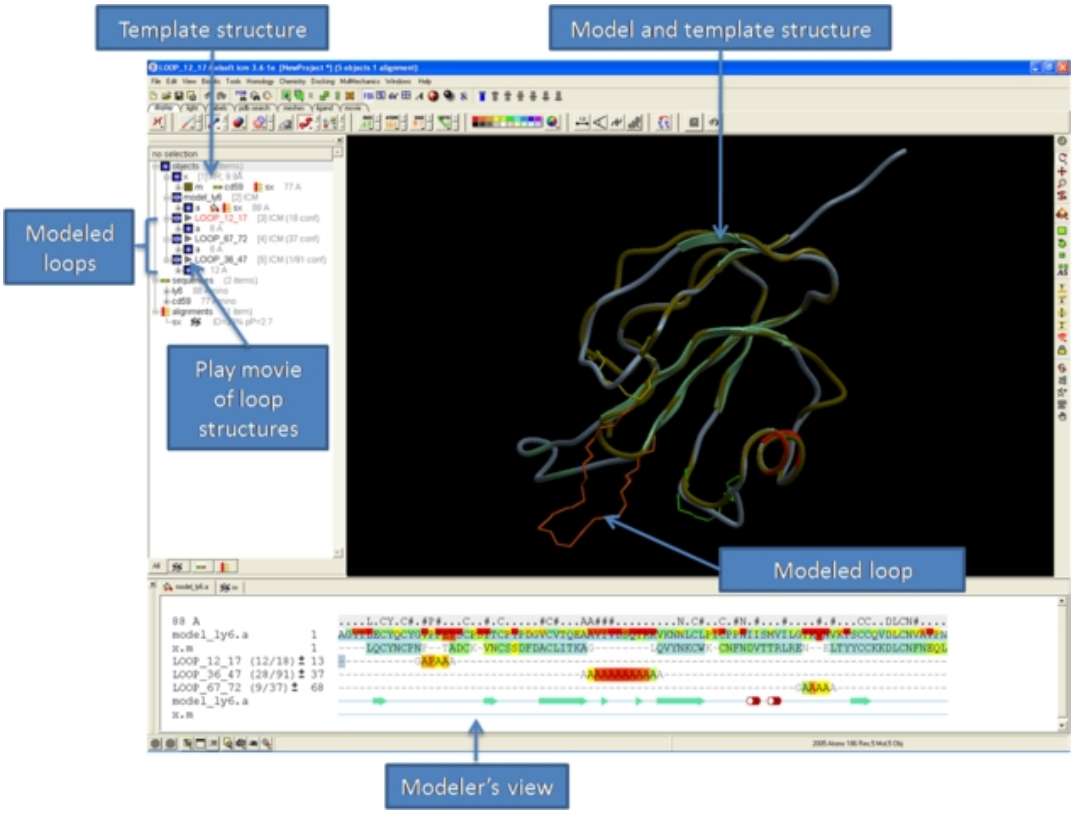
14.4.1 Making an interactive model.

- Homology/Interactive Modeling
- Enter the name of your loaded sequence.
- Enter the name of your loaded 3D template
- Enter the name of your alignment or allow ICM to generate an alignment by selecting automatic
- Check whether you wish ICM to sample the loop regions of your model or not

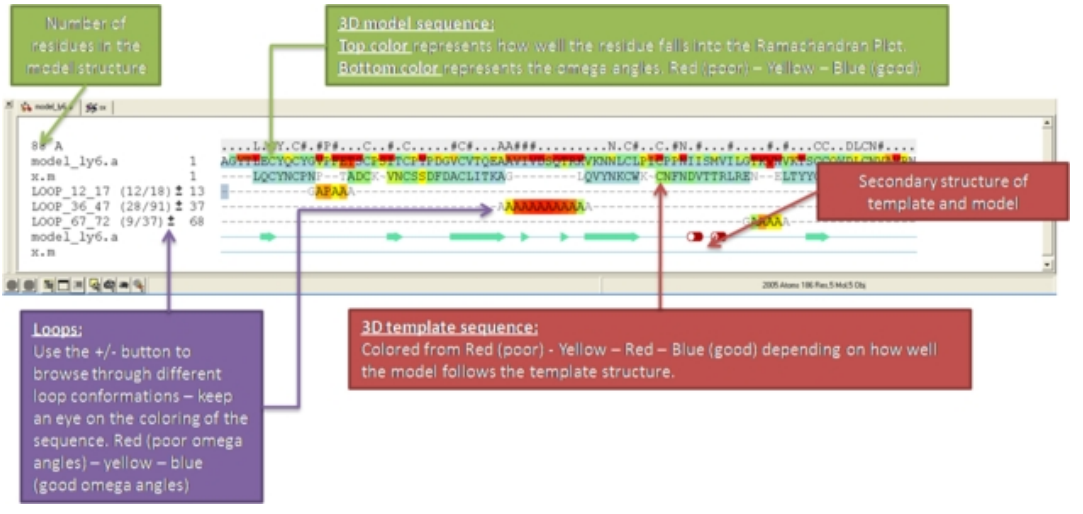
An Interactive Modeler's View of the alignment will then be displayed.

14.4.2 Modeler's View

Once you have made your interactive model your graphical user interface should look something like this:



What do all the elements of the **Modeler's View** mean?



14.4.3 Interactive Loop Modeling

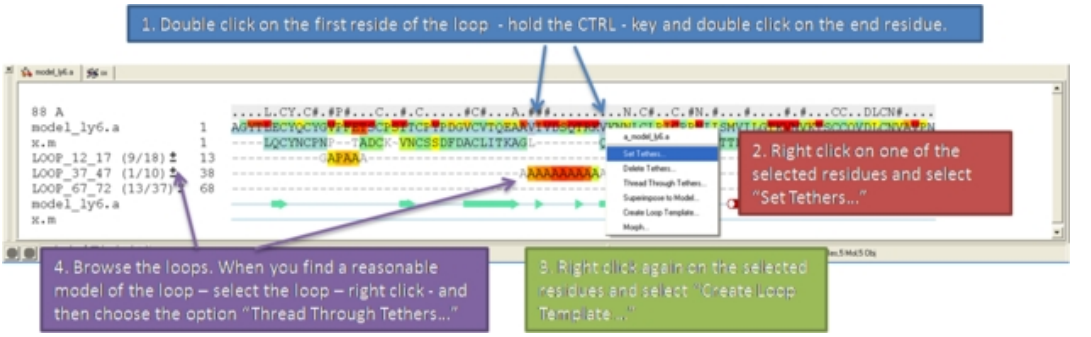
You can browse a number of different loop conformations by clicking on the +/− button next to the loop in the `modeler view's` window. Keep an eye on the colors of the loop residues in the alignment − they are colored red (poor) −yellow − blue (good) depending on how good the omega angles are. The residues in the loops are represented by Alanines for every residue other than Glycine or Proline.

If you want to remodel the loop.

- Set tethers at the residue at the start and end of the loop. To set a tether double click on the two residues whilst holding down the CTRL key. Right click and select **Set tethers**. Selecthow you want to tether to the template either by **alignment**, **residue numbering** or **selection.** Select the **alignment** − automatic represents the **Moldeler's View**. Select the **Template Molecule** which is

the object you built the model on.

- Select the loop you wish to model including the tethered residues at the start and end of the loop and then right click and select **Create Loop Template**
- Once the simulation has finised you can once again browse the solutions by clicking on the +/− button next to the loop in the `modeler view's` window.
- When you have identified a reasonable conformation of the loop you can re−thread it onto the model structure by selecting the loop region in the **Modeler's View**. You can do this by clicking and dragging over the loop. Right click and select **Thread Through Tethers**.

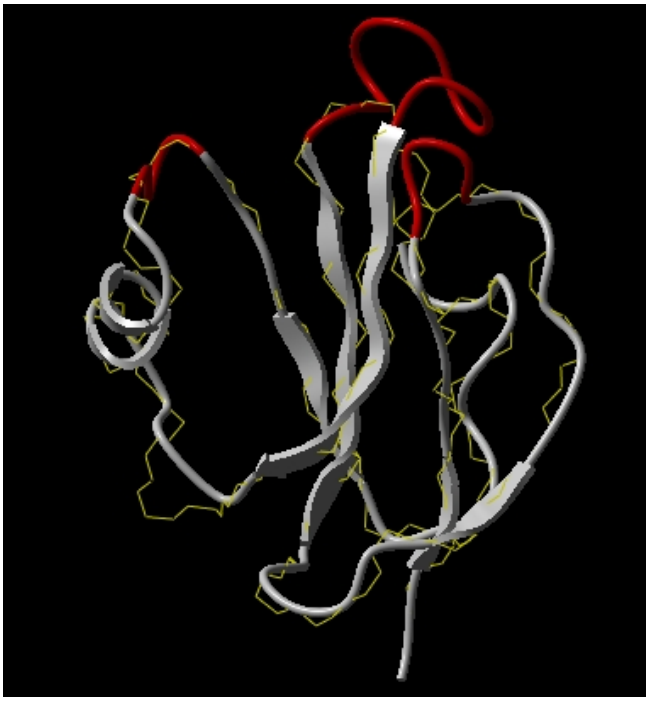


14.5 Display Loops

Once you have built a model (see section `Build Model`) the loop regions or (inserted fragments) can be viewed by:

- Click on the 'Homology' menu.
- Select 'Display Loops'

The loop regions in the model will be displayed in red. Information regarding the RMSD in the loops are displayed in the Loop Table. If your template structure is still loaded this will be displayed in yellow as shown below.

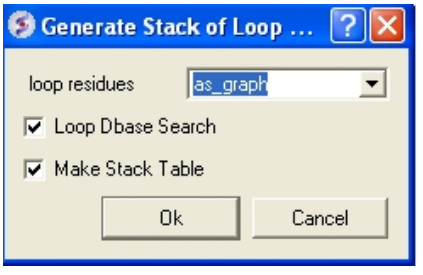


14.6 Loop Modeling

Building an accurate model of a loop is very tough. However with small loops ICM has been very succesful. ICM was used to design two new 7 residue loops and in both cases the designs were successful. Moreover, the predicted conformations turned out to be exactly right (accuracy of 0.5ï¿½) after the crystallographic structures of the designed proteins were determined in Rik Wierenga's lab.

To build a new loop to an existing structure or to improve your already modeled loops:

- Read your modeled structure into ICM. Or continue immediately after using build model.
- Select the loop region you wish to model (green crosses in the graphical display).
- MolMechanics/Sample Loop.
- MolMechanics/View Stack A table will then be displayed with the optimized structures ranked by energy. To view each structure double click on the table. The first row is the loop with the best energy.



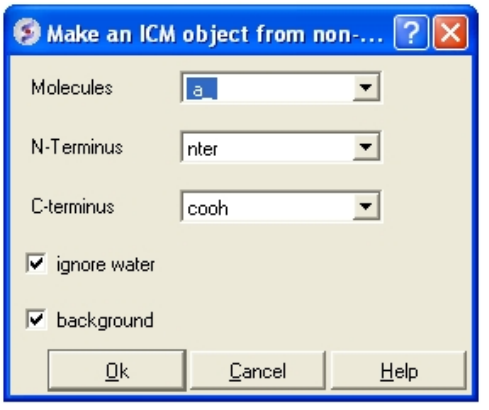
14.7 Regularization

Once a molecular model has been constructed it is generally a good idea to analyze it using the `Protein Health` macro. The results from protein health will indicate which part of the molecule is strained or has unusual geometry. A way of solving these problems is to use the Regul option after modeling. Regul stands for Regularization which is a procedure for fitting a protein model with the ideal covalent geometry of residues (as represented in the icm.res residue library) to the atom positions of a target PDB structure.

Regularization is a procedure for fitting a protein model with the ideal covalent geometry of residues (as represented in the icm.res residue library) to the atom positions of a target PDB structure (usually provided by X−ray crystallography or NMR). Regularization is required because the experimentally determined PDB−structures often lack hydrogen atoms and positional errors may result in the unrealistic van der Waals energy even if these structures were energetically refined (since the refinement of the crystallographic structures typically ignores hydrogen atoms and employs different force fields). The following steps are required to create the regularized and energy refined ICM−model of an experimental structure.

To use the regularization protocol:

- MolMechanics/Regularization and a data entry box as shown below will be displayed.
- Enter the molecule you wish to refine.
- Choose which kind of N and C− terminus
- Choose whether you wish to include water molecules.
- Choose to run in background if the structure is very large.

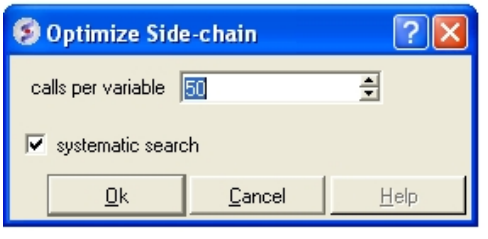


Once the refinement is complete a new ICM object will be displayed in the ICM workspace called object_name_reg

14.8 Refine Side Chains

To refine or optimize a selection of side chains the structure needs to be an ICM object.

- Make a selection of the side chains you wish to optimize. See `how to make selections` section.
- Right click on the selection in the graphical display. A selection will be displayed as green crosses.
- Select from the right click menu Advanced/Optimize Side Chains and a data entry box as shown below will be displayed.
- Enter the number of calls per variable you wish to use for the simulation. For more details on this please see the ICM language manual.

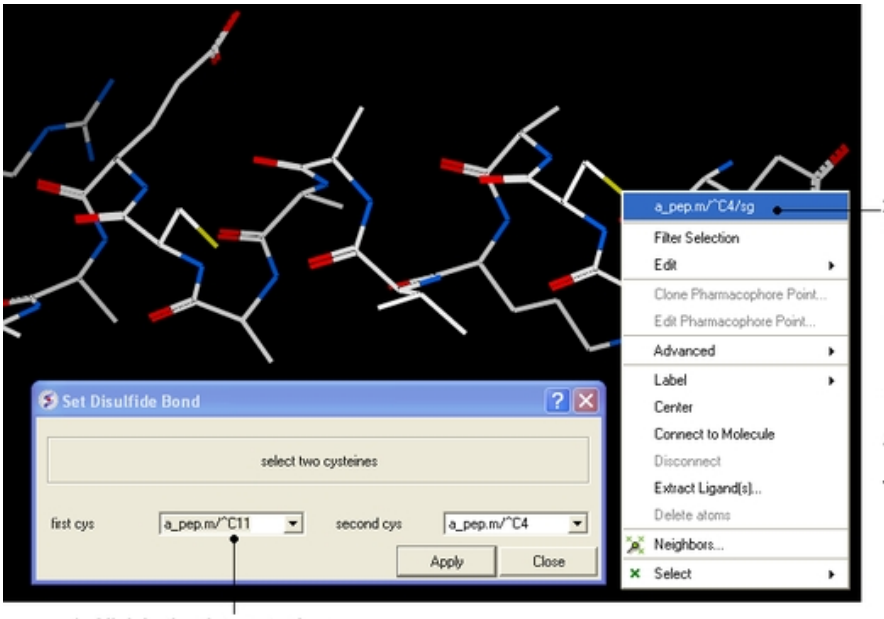


A stack of energy conformations will be displayed in a table. Each conformation can be viewed simply by clicking in the table.

14.9 Making a disulfide bond.

To make a disulfide bond:

- **MolMechanics/Edit Structure/Set Disulfide Bond...**
- Click in the "first cys" data entry box and right click on the cys residue or type in the ICM selection language for the first cysteine.
- Click in the "second cys" data entry box and right click on the cys residue ortype in the ICM selection language for the second cysteine.
- Click on the **Apply** button



1. Click in the data entry box

2. Right click on the CYS residue and select the selection language description of the atom. This will then be added to the Set Disulfide Bond data entry box.

An alternative method is to type the selection language directly.

15 3D Predict

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

15.1 Assign Helices and Strands

Theory

The **Assign helices and Strands** option will manually reassign secondary structure to a protein structure. This command does not change the geometry of the model, it only formally assigns secondary structure symbols to residues. f the secondary structure string is not specified, apply ICM modification of the DSSP algorithm of automatic secondary structure assignment (Kabsch and Sander, 1983) based on the observed pattern of hydrogen bonds in a three dimensional structure. The DSSP algorithm in its original form overassigns the helical regions. For example, in the structure of T4 lysozyme (PDB code 103l) DSSP assigns to one helix the whole region a_/93:112 which actually consists of two helices a_/93:105 and a_/108:112 forming a sharp angle of 64 degrees. ICM employs a modified algorithm which patches the above problem of the original DSSP algorithm. Assigned secondary structure types are the following: "H" − alpha helix, "G" − 3/10 helix, "I" − pi helix, "E" − beta strand, "B" − beta−bridge, "_" or "C" − coil.

To assign secondary structure:

- Load the pdb structure (File/Open or PDB Search}
- Select the structure. You can do this by double clicking on the name of the structure in the ICM Workspace (a selection is highlighted blue in the ICM Workspace and green crosses in the graphical display) or you can use the right−click button and drag it over the whole structure in the graphical display.
- Tools/3D Predict/Assign helices and Strands

15.2 Protein Health

Theory

The protein health option calculates the energy strain of a structure in ICM. It is generally a good idea to investigate the energy strain of any protein structure before undertaking such processes as docking. It is also essential to use this tool after making a model (see `Molecular Modeling`) to identify strained regions within your model and then some optimization procedure can be undertaken to rectify the problems.

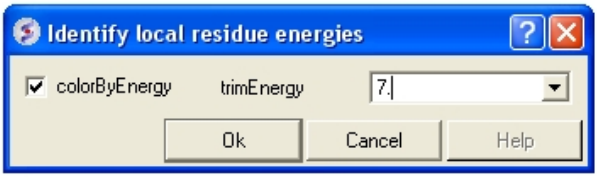
The protein health option calculates the relative energy of each residue for a selection and colors the selected residues by strain.

This macro uses statistics obtained in the following paper Maiorov, V.N. and Abagyan, R.A. (1998) Energy strain in three−dimensional protein structures Folding and Design, 3 , 259−269.

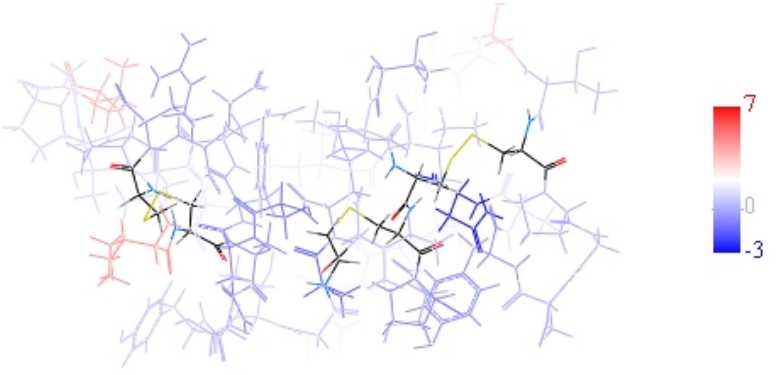
To use the Protein Health option your structure must be converted into an ICM object (see `Converting to ICM Object`)

Next, make a selection of which residues you wish to analyze (see `Making Selections`).

- Tools/3D Predict/Protein Health and a window as shown below will be displayed.



- The scale of the coloring can be changed by altering the value within the trimEnergy data entry box.
- Click OK and the structure will be colored according to energy strain (red − high) and a table of residue energy will be displayed in a table.
- To reactivate the screen click the Go button in the bottom left hand corner of the GUI display.

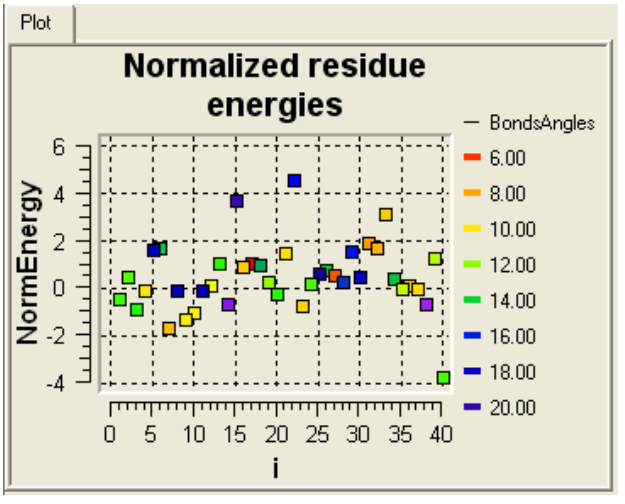


The Protein Health option returns a table of energies for each amino acid in the selection:

ENERGY_STRAIN

	i	Sel	Res	sec_str	NormEnergy	BondsAngles	Bonds	Angles	Phi	Psi
1	22	1crn.m/25	ile	H	4.55	16.51	2.07	14.44	-75.00	-38.00
2	15	1crn.m/18	leu	_	3.71	20.15	3.35	16.80	-53.00	-46.00
3	33	1crn.m/38	ala	_	3.14	9.13	0.36	8.77	-121.00	1.00
4	31	1crn.m/36	pro	_	1.92	7.75	3.26	4.49	116.00	-24.00
5	6	1crn.m/8	val	H	1.74	14.12	1.17	12.96	-56.00	-45.00
6	32	1crn.m/37	gly	_	1.71	8.43	1.16	7.27	-90.00	-162.00
7	5	1crn.m/7	ile	H	1.65	17.87	2.22	15.65	-64.00	-42.00
8	29	1crn.m/34	ile	E	1.59	16.16	1.87	14.29	-112.00	130.00
9	21	1crn.m/24	ala	H	1.46	9.84	1.24	8.60	-63.00	-35.00
10	39	1crn.m/45	ala	_	1.28	11.54	1.24	10.30	-89.00	-3.00
11	17	1crn.m/20	gly	_	1.08	5.11	0.40	4.72	106.00	7.00
12	13	1crn.m/15	val	H	1.04	13.13	1.01	12.12	-69.00	-41.00
13	18	1crn.m/21	thr	_	1.03	14.51	3.61	10.90	-53.00	136.00

The Protein Health option returns a plot of energies for each amino acid in the selection:



15.3 Local Flexibility

This option systematically samples rotamers for each residue side−chain in the input selection and uses resulting conformational ensembles to evaluate energy−weighted RMSDs for every side−chain atom. These are stored in the 'field' values on atoms and can be used for example to color the structure by side−chain flexibility. Conformational entropy for each residue side−chain is also calculated and stored in a table. If l_entropyBfactor flag is on, the atom rmsds are normalized within the residue to reflect its total conformational entropy. If l_bfactor flag is set, the bfactors are reset to the same values that are placed in the atom 'field', and occupancy is set to be inversely proportional to it (O=1/(1+2*rmsd))

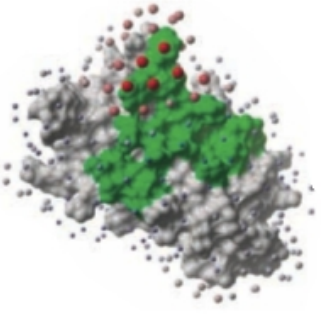
- Read pdb file (File/Open or PDB Search Tab).
- `Convert` to an ICM Object.
- Tools/3D Predict/Local Flexibility

15.4 Protein−Protein Interface Prediction

The ICM Optimal Docking Area method is a useful way of prediciting likely protein−protein interaction interfaces. If you do not have mutational data or other experimental data which indicates the likely protein−protein docking site this method will be useful. This procedure can save you time during the docking procedure by focusing your docking only on areas on the receptor and ligand most likely to interact.

Theory

ODA (Optimal Docking Areas) is a new method to predict protein−protein interaction sites on protein surfaces. It identifies optimal surface patches with the lowest docking desolvation energy values as calculated by atomic solvation parameters (ASP) derived from octanol/water transfer experiments and adjusted for protein−protein docking. The predictor has been benchmarked on 66 non−homologous unbound structures, and the identified interactions points (top 10 ODA hot−spots) are correctly located in 70% of the cases (80% if we disregard NMR structures). For a description of the method see *Fernandez−Recio et al Proteins (2005) 127: 9632*.



To display the optimal docking area.

- Convert the PDB file to an ICM object.
- Tools/3D Predict/Protein Interface by ODA
- If you select the **Residue Table** option the average ODA score for each residue will be displayed in a table. The lower the number the higher the chance the residue will be involved in protein−protein interactions. Regions colored red represent low ODA score and blue represents a high score.

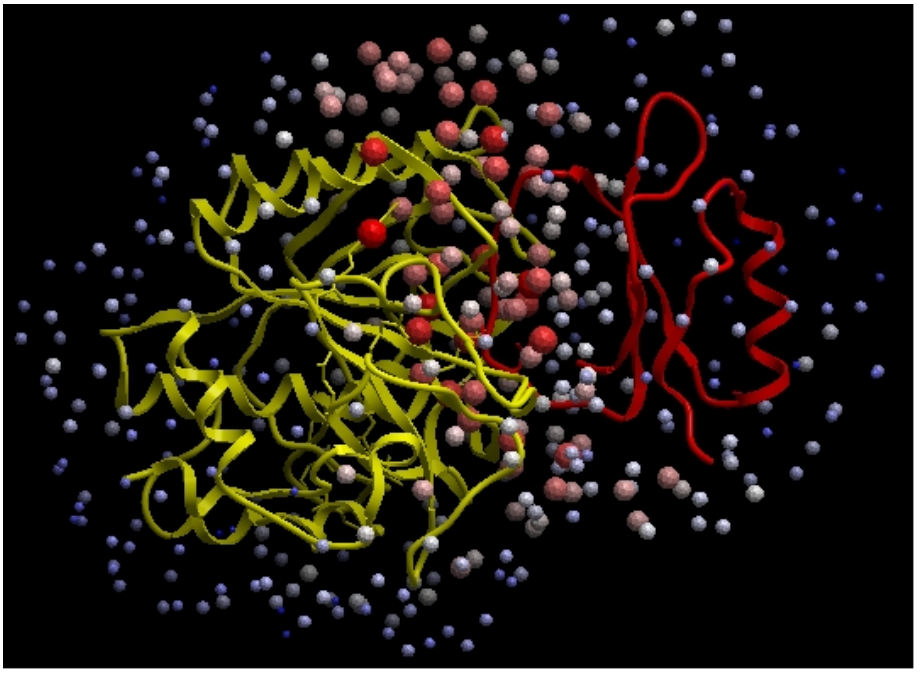
ODA Example with a subtilisin−chymotrypsin complex.

As an example we will determine whether the ICM−ODA method can accurately predict the binding surface of the complex between subtilisin and chymotrypsin. This example is used in the protein−protein docking tutorial below as well.

This complex has been solved experimentally and has PDB id 2sni.

Calculate the ODA for each subunit (Tools/3D Predict / Protein Interface by ODA).

ODA for subtilisin and ODA for chymotrypsin − red colored spheres indicate a region highly likely to be involved in protein−protein interaction, blue coloring is unlikely to be involved in protein−protein interaction. A clickable table is also displayed with ODA values.

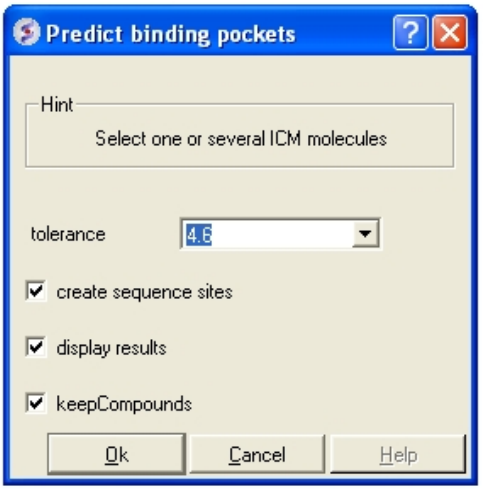


15.5 Identfy Ligand Pockets

If a binding pocket is not known in advance, use icmPocketFinder or icmCavityFinder (for closed pockets). The protein needs to be `converted` to an ICM object in order to use icmPocketFinder.

icmPocketFinder can be accessed by

- Click on the menu **Tools/3D Predict/icmPocketFinder**

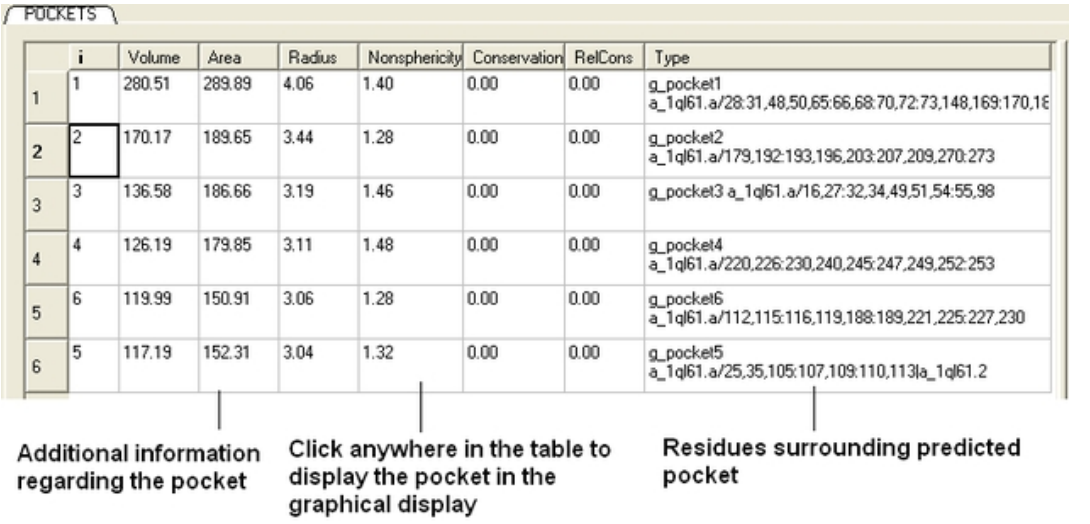


- Enter a tolerance level (4.6 is the default value and we recommended you to use this). The lower the tolerance value the more pockets predicted and the higher the tolerance the less pockets predicted.
- Check the box **create sequence sites** if you wish the site to be labeled.
- Check the box **display results** to see the predicted pockets as grobs in the display panel.
- Check the box **keep compounds** if you wish the compounds (ligands) in the receptor to be included in the prediction. If you dont check this box the pockets will be calculated based on the receptor without ligands.

- Click OK to run icmPocketFinder

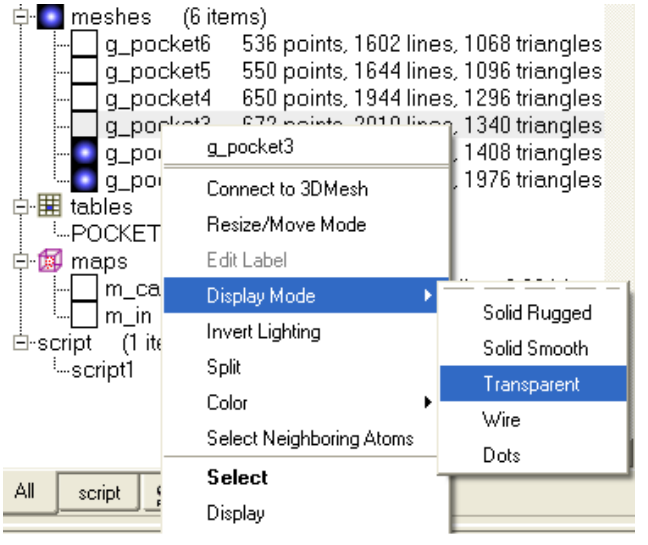
NOTE: A button for icmPocketFinder can be found on the Setup Receptor option in the docking menu. It performs the same function as **Tools/3D Predict/icmPocketFinder**

The results from icmPocketFinder will be displayed in a table.



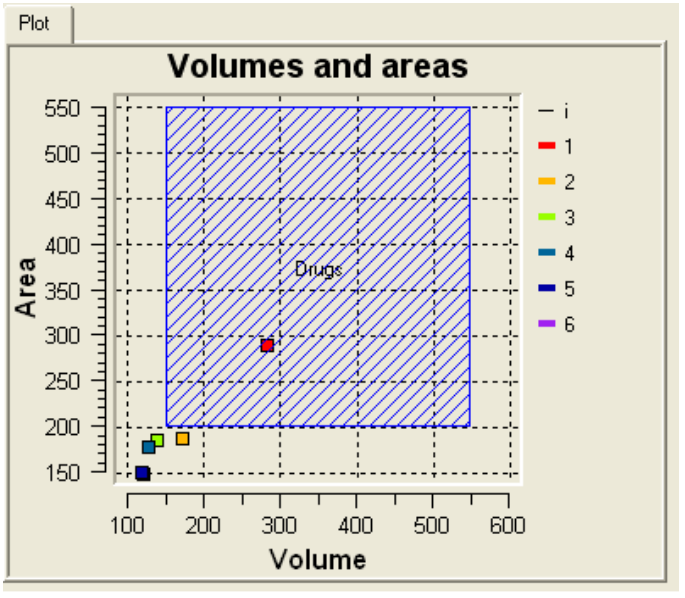
To view the pocket in the graphical display:

- Click on the pocket in the table or select the pocket from the meshes section of the ICM workspace. Right click on the pocket mesh in the ICM Workspace to retrieve more display options.



Right click on the mesh in the ICM workspace to retrieve more display options

The results from icmPocketFinder are also plotted graphically (Area vs Volume). A blue square highlights potential drug binding pockets based on typical area and volume values − this is only a guide on what constitutes a pocket likely to be involved in ligand binding. Selections can also be made from the plot by clicking and dragging around a point in the graph.



To identify ligand binding pockets which are completely enclosed in the receptor:

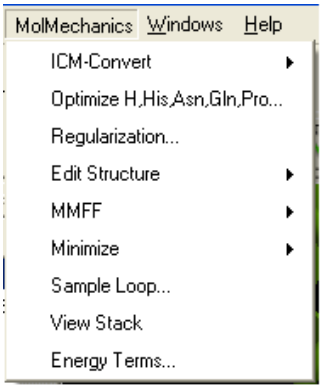
- Click on the menu Tools/Analysis/Closed Cavities and a window as shown below will be displayed.

A similar output to that generated by ICMPocketFinder will be displayed. This output includes a plot and a table. By clicking on the table or plot graphical selections can be made.

16 Molecular Mechanics

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

All of the options in this chapter can be found in the MolMechanics Menu.



16.1 ICM Convert

To calculate energy, build a molecular surface and for all energy operations you need to convert a PDB file into an ICM object.

- MolMechanics/ICM−Convert/Protein
- Select the object you want to convert from the drop down list.
- Check or uncheck the options, delete water, optimize hydrogens, replace the original, and/or display the result.

To convert a small molecule into an ICM object.

- MolMechanics/ICM−Convert/Chemical
- `Select` the ligand.
- Choose whether you want to keep the current geometry of the ligand or not.
- Check or uncheck the options build hydrogens, fix amide bonds, and/or overwrite geometry.

16.2 Optimize H,His,Asn,Gln,Pro

This option optimizes H, His, Asn, Gln, and Pro by maximizing hydrogen bonds and other interactions with the rest of the protein and/or with the ligand.

To perform this optimization

- Convert your protein to an ICM Object.
- Select MolMechanics/Optimize, H, His,Asn,Gln and Pro
- Choose whether you want to sample rotatable hydrogens or optimize His, Asn and Gln.

16.3 Regularization

This option is described in detail in the modeling chapter `here`.

16.4 Impose Conformation

If you have two protein structures with the same atom namse and ALTER records but with different conformations you can impose the conformation of one of the protein structures onto the other.

You can do this by:

- Convert the structures into ICM Objects.
- MolMechanics/Impose Conformation
- Select the source molecule (the conformation you wish to impose).
- Optional: superimpose the structures
- Optional: re−optimize hydrogens

16.5 Edit Structure

Set Bond Type

- `Select` the two atoms forming the bond.
- MolMechanics/Edit Structure/Set Bond Type
- Choose the **Bond Type** from the drop down arrow.
- Press Apply button

Set Formal Charge

- `Select` the atom.
- MolMechanics/Edit Structure/Set Formal Chage
- Choose the **Charge** from the drop down arrow.
- Press Apply button

Set Chirality

- `Select` the atom.
- MolMechanics/Edit Structure/Set Chirality
- Choose the **Chirality** from the drop down arrow.
- Press Apply button

Build Hydrogens

- `Select` the atoms.
- MolMechanics/Edit Structure/Build Hydrogens
- Press Apply button

Set Tether

Theory

A tether is a harmonic restraint pulling an atom in the current object to a static point in space. This point is represented by an atom in another object. Typically, it is used to relate the geometry of an ICM molecular object with that of, say, an X−ray structure whose geometry is considered as a target. Tethers can be imposed between atoms of an ICM−object and atoms belonging to another object, which is static and may be a non−ICM−object. You cannot create tethers in ICM−Browser, however, if the project that you have loaded contains tethers between two objects, then they can be displayed:

- `Convert` the two structures you wish to tether to an ICM object.
- MolMechanices/Edit Structure/Set Tether
- Right click on the first atom you wish to tether and click on the first option which is the selection language for the atom. This information will automatically be placed in the **first atom** dialog box. Alternatively you can type in the ICM selection language into the dialog box.
- Right click on the second atom (in a different object) you wish to tether and click on the first option which is the selection language for the atom. This information will automatically be placed in the **second atom** dialog box. Alternatively you can type in the ICM selection language into the dialog box.
- Press Apply button

Delete Tether

- `Select` the atoms you wish to delete the tethers from.
- MolMechanices/Edit Structure/Delete Tether

16.6 MMFF

Set Types This option is described in detail here in the command line manual
`http://www.molsoft.com/man/icm-commands.html#set-type-mmff`

Set Charges This option is described in detail here in the command line manual
`http://www.molsoft.com/man/icm-commands.html#set-chargemmff`

Read Libraries This option is described in detail here in the command line manual
`http://www.molsoft.com/man/icm-commands.html#read-librarymmff`

16.7 Minimize

Cartesian This option is described in detail here in the command line manual
`http://www.molsoft.com/man/icm-commands.html#minimize-cartesian`

Local This option is described in detail here in the command line manual
`http://www.molsoft.com/man/icm-commands.html#minimize`

16.8 Sample Loop

This option is described in the `Loop Modeling` section.

16.9 Generate Normal Mode Stack

Normal modes can be used to generate an ensemble of protein structures. For example the method can be used to represent flexibility in the pocket.

To generate an ensemble of structures using normal modes.

- Convert your protein to an ICM object.
- MolMechanics/Generate NM stack
- Enter the number of normal modes to sample
- Enter the relative amplitude of the normal modes.
- Optional: select to make random combination of modes.
- Optional: select Fast GAP model only.
- Optional: run the normal mode generation locally.

16.10 Stack

Operations which use the ICM Biased Probability Monte Carlo method e.g. docking and loop modeling generate a stack of energy conformations.

MolMechanics/Stack/View will display the conformations of a stack in a table ranked by energy. Each conformation can be viewed by double clicking on the table. A stack file will have the extension .cnf. For example, after running the `sample loop` algorithm a stack of different loop conformations will be generated.

MolMechanics/Stack/Play This option will play the elements of the stack as a movie. You can set the number of frames for the movie and also select whether you would like ICM to interpolate between each frame. You can save this movie in avi, mpeg format using the `Screen-Grabbing Movie` options.

MolMechanics/Stack/Add current conformation This option will add the currently displayed conformation to the stack. This is useful for experiments such as `multiple receptor` docking whereby you dock to a stack of conformations.

MolMechanics/Stack/Store Stack in Object This option takes the current stack and stores it in a compressed form inside the specified object. The compressed stack can then be extracted with the load stack object command. Option stack of the montecarlo command stores the generated stack inside the current object automatically.

MolMechanics/Stack/Delete Deletes the current stack.

MolMechanics/Stack/Set conf Comparison This option compares the stack as described here: `http://www.molsoft.com/man/preference.html#compareMethod` and `http://www.molsoft.com/man/icm-commands.html#compare`

MolMechanics/Stack/Recalculate Energies Recaluclates the energy of a current stack if changes have been made.

16.11 GAMESS

This option is described in detail here in the command line manual `http://www.molsoft.com/man/gamess.html`

16.12 Energy Terms

The energy function calculated for any conformation of an ICM molecular object consists of individual terms described which can be turned on and off using **MolMechanics/Energy Terms**. These terms are described in more detail here `http://www.molsoft.com/man/terms.html` #endif

17 Cheminformatics

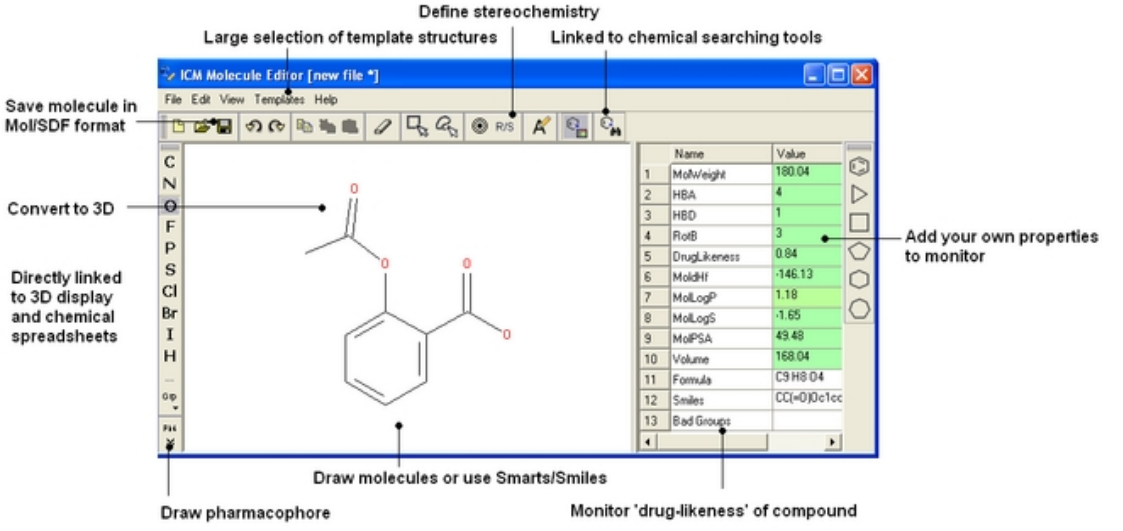
Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

The cheminformatics tools provide an environment in which chemicals can be constructed, manipulated, stored an analyzed in one easy to use graphical interface.

Some of the features include:

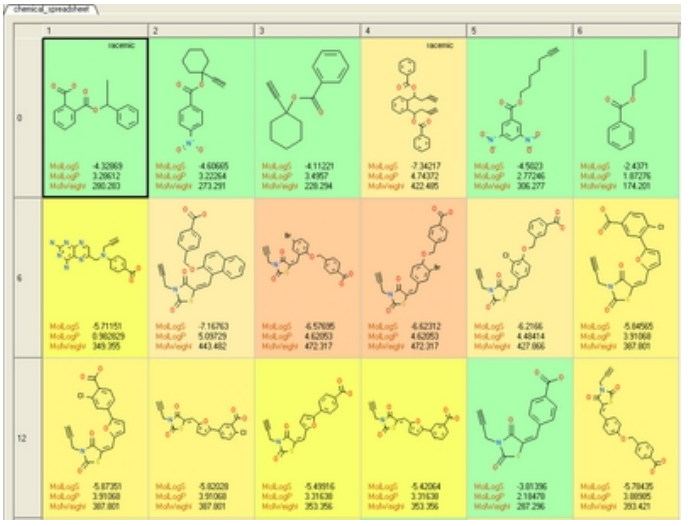
Chemical Drawing

- `Draw` compounds using an easy−to−use molecular editor
- `Keyboard shortcuts` for fast molecule sketching
- Large selection of annotated templates
- Full support for smiles and smarts
- Automated 2D drawing from 0D or 3D sdf files
- Draw compounds whilst `monitoring key properties` (eg Log P, drug−likeness etc..)
- `Save` files in mol, sdf and smiles format.



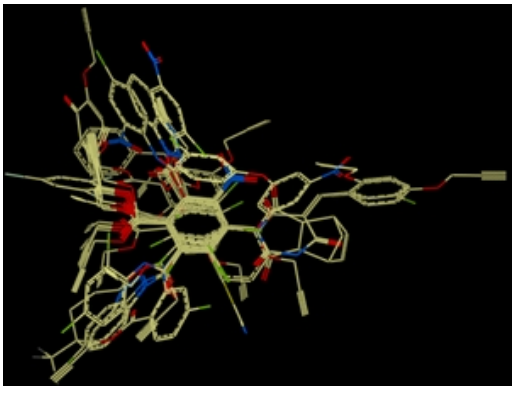
Chemical Display

- `Chemical spreadsheets` − molecular tables − add columns, predict properties, annotate, edit
- `3D Browsing` − quickly browse through a collection of 3D structures
- `Browse and Lock` − lock compounds in 3D display
- `Highlight substructure` − color chemical drawings by substructure
- `Color by properties` − color chemical drawings by properties



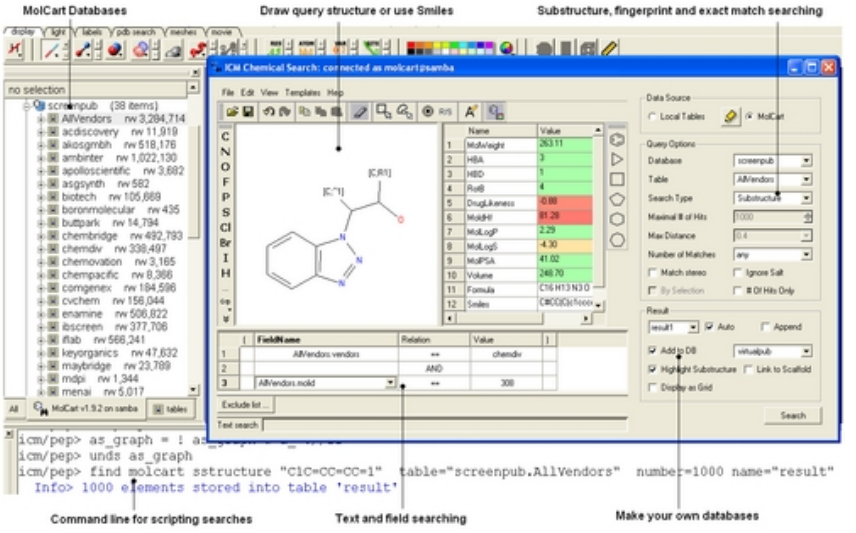
3D Chemistry

- `Convert chemicals` to 3D using the Merck Molecular Force Field (MMFF)
- Generate `stereoisomers`
- Generate `tautomers`
- Easy `modification` of a ligand in a 3D protein structure.
- Chemical `superposition`
- Flexible compound 3D overlay



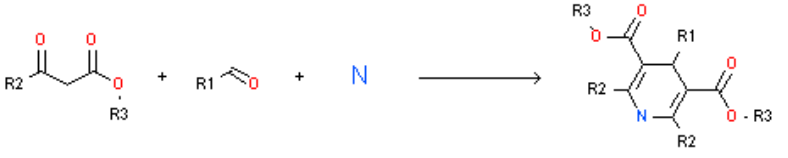
Chemical Searching

- Chemical similarity `searching` − substructure, fingerprint similarity and exact match
- Search local tables (SDF, Mol Files) or `MolCart`
- Pharmacophore searching in conformer databases or files
- 2D pharmacophore searching in compound databases



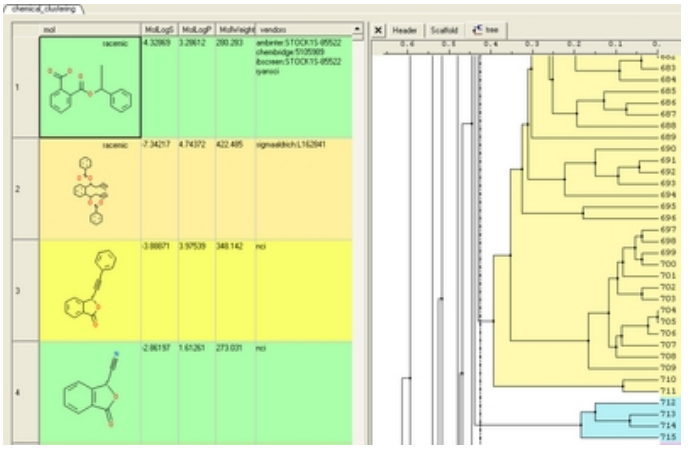
Library Generation

- Virtual chemistry library generation using `reactions`
- Conformation `generator`
- Split into `fragments` to generate a series of R groups.
- `Find and replace` chemical editing
- Focused `library` generation
- Structure−based and ligand−based virtual screening using `MolCart`



Chemical clustering

- Fast chemical `clustering` with a variety of Linkage Types
- Extract representative "center" structures from each node.
- Branch reordering and distance changing



QSAR

- `Predict` compound properties − LogP, LogS, PSA, hERG, aggregation, CYP3A4, druglikeness, reactive chemical groups, Heats of Formation, Lipinski, etc..
- Various methods for linear and non−linear QSAR including, both regression and classification methods PLS, pcR and PC regression methods

- PC regression or classification with the following kernels radial, scalar products, polynomial, sigmoid and tanimoto
- Cross `validation` and boot−strapping
- Save models and data plotting

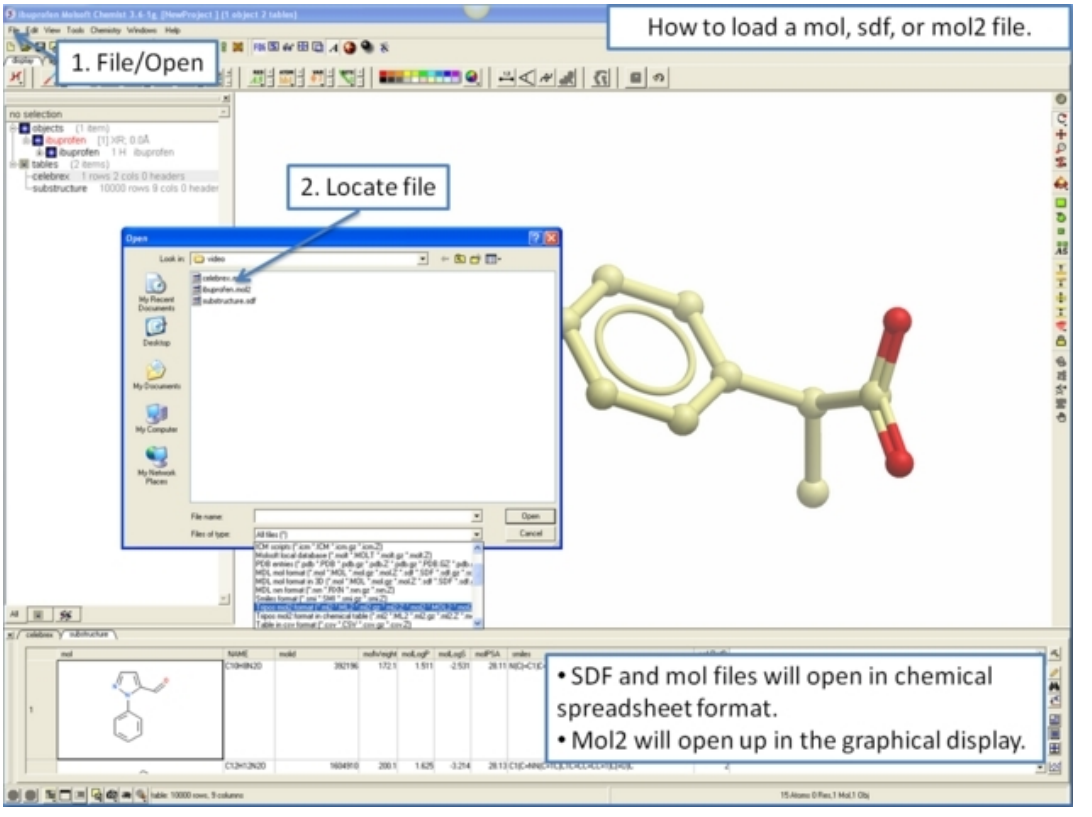
17.1 Reading Chemical Structures

Chemical structures can be read into ICM from MOL/MOL2, SMILES, and SDF files OR you can construct your own structures by drawing them in the ICM molecular editor.

17.1.1 Loading Chemical Structures

Chemical structures from pre−existing molecular files such as MOL, MOL2 or SDF can be read into ICM by:

- Select File/Open and the window as shown below will be displayed.
- Select the chemical structure file you wish to open: MOL, MOL2 or SDF
- Once selected the file will be displayed as a chemical table (See `ICM molecular tables` section).



17.1.2 Chemical Smiles

If you know the chemical smiles string for the compound you can build it by:

- Select **File/New**.
- Click the **Compound** tab at the top of the window.
- Enter a name for the compound.
- Type in the **Smiles String** in the Smiles String data entry box. Remember to delete the previous string.
- Check the boxes Display Molecule Delete Other Objects according to your preference.
- Click the OK button.

Smiles can be read from a text file into a `chemical table` by:

- **File/Open** and select **Files of type:** Smiles format

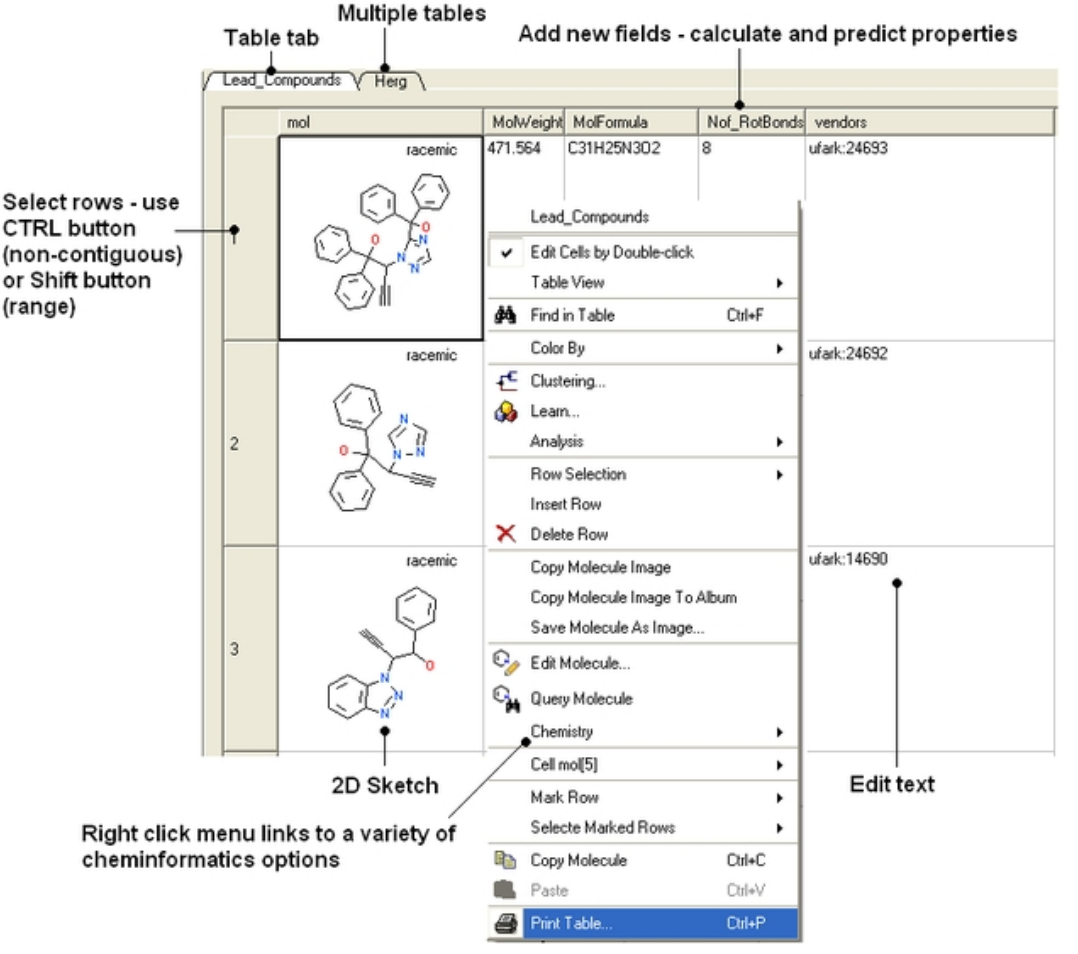
Smiles can be read directly into the `ICM Molecular Editor`:

- Open the `ICM Molecular Editor` window.
- Select **Edit/Add Smiles**

17.2 Working with Chemical Spreadsheets.

When an sdf file is read into ICM it is displayed as a chemical spreadsheet. Many of the operations you can perform on chemical spreadsheets (Molecular Tables) are described in the `table` section of this manual. Some useful chemical−only options are described in this section.

An example of an ICM molecular table:

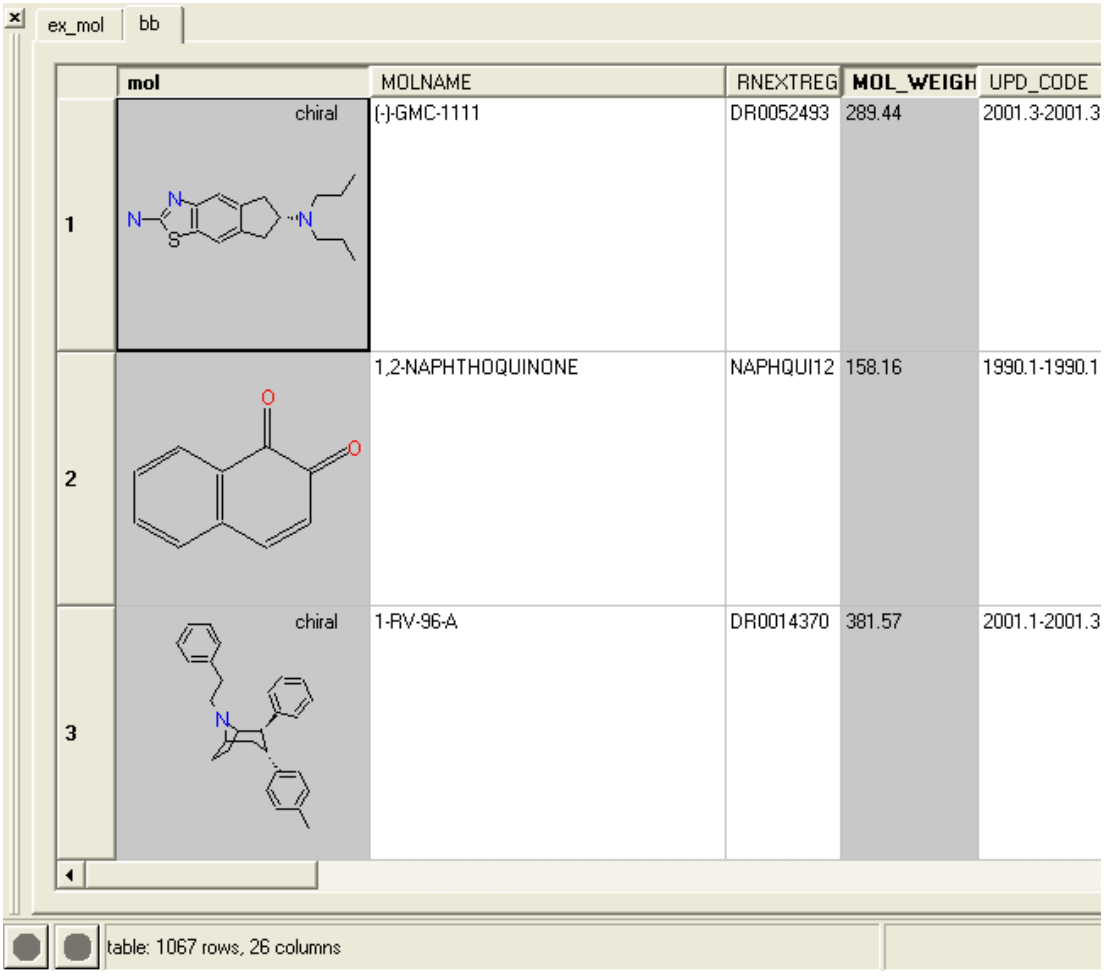


17.2.1 Molecular Table Display

There are many ways in which a molecular table can be displayed. For example you can select whether you want to have just the structure displayed or maybe you want to display the structure with a lot of other important information such as molecular weight, docking score, energy etc...

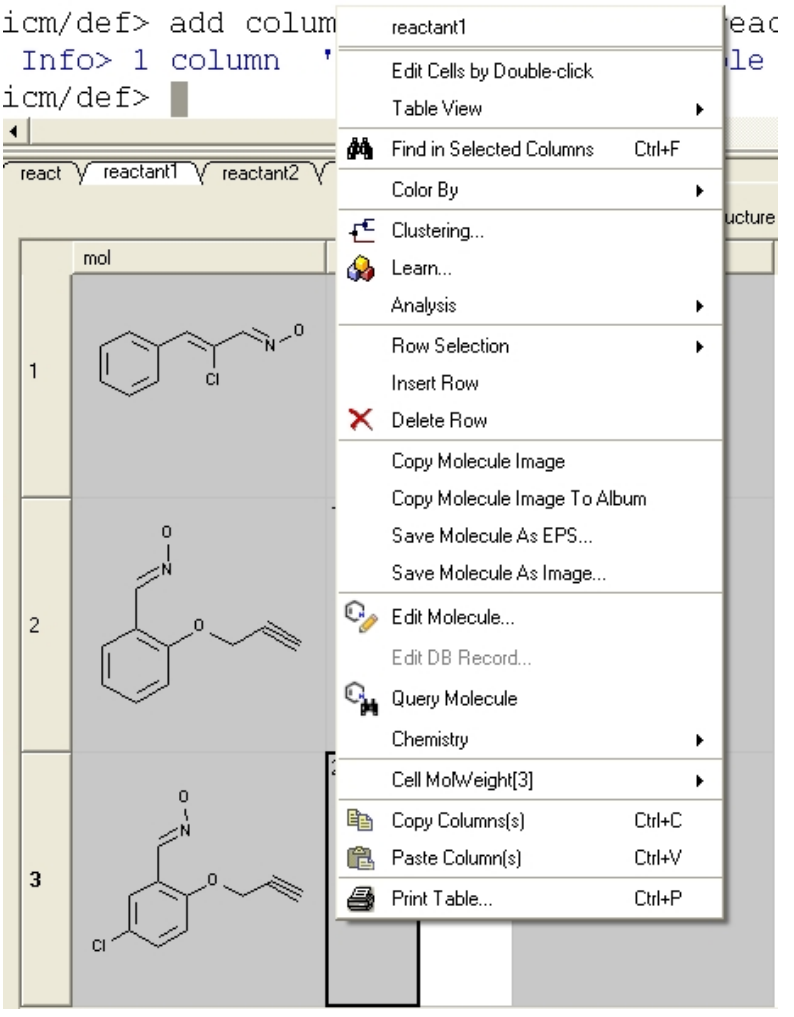
The default layout displays all the columns and tables. However using the table selection tools described in the previous section `Standard ICM Table` you can customize the display.

- First select which columns you wish to display.

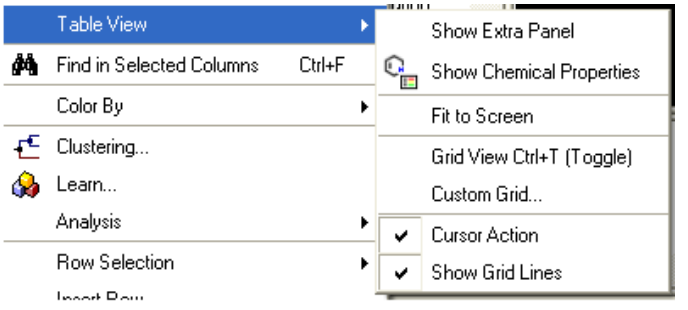


Next,

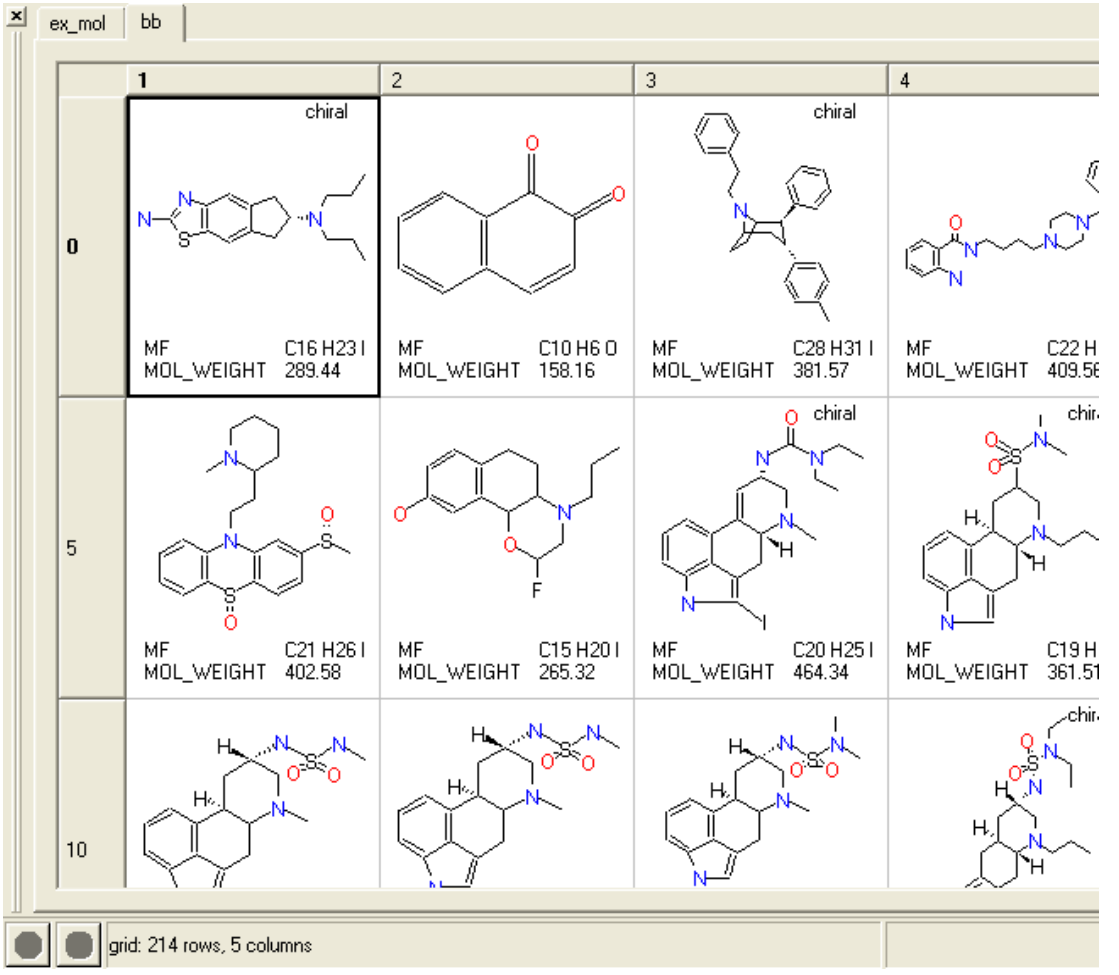
- Right click on the selection and the following menu will be displayed



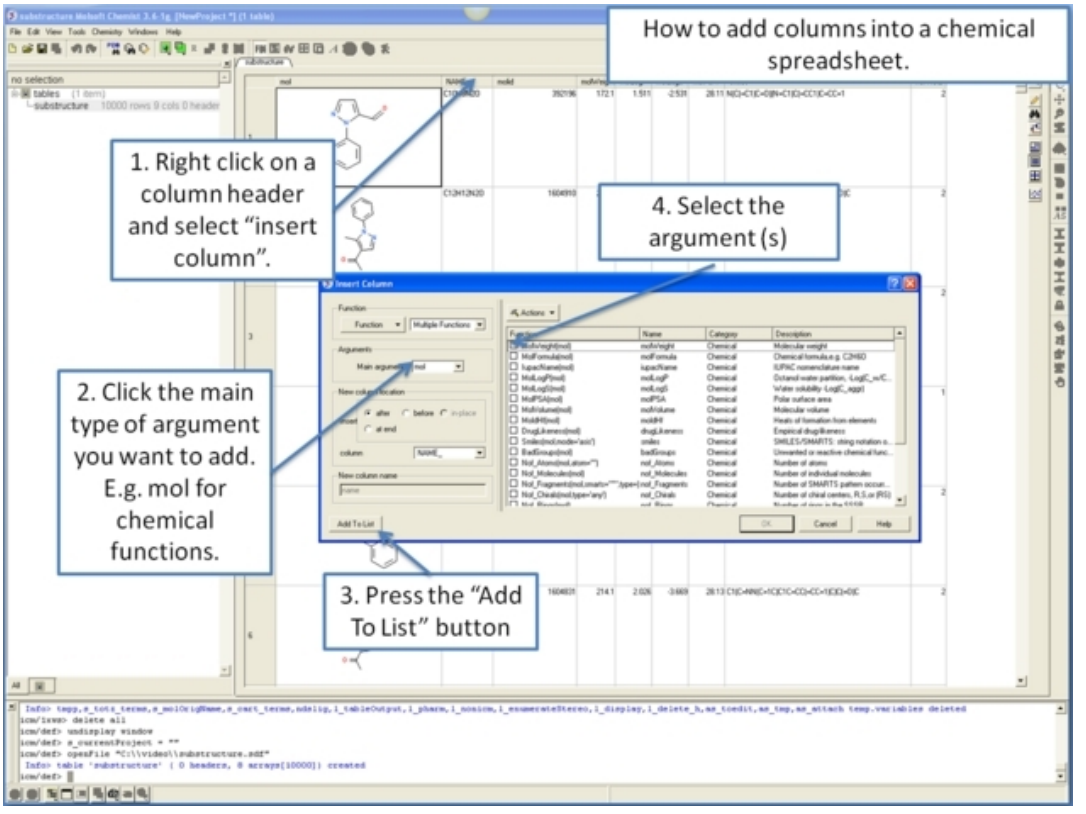
- Select Table View and either grid view or custom grid..



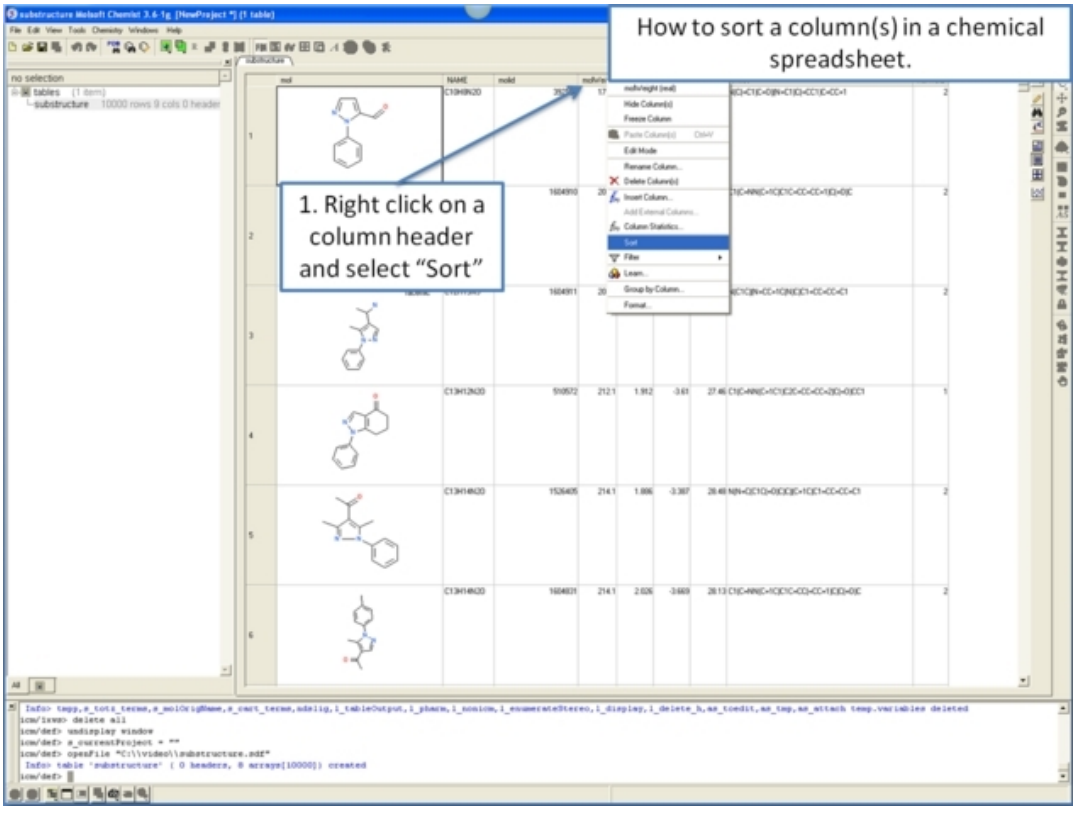
- If you select "custom grid" you will be asked the number of columns you wish to display in a grid view (eg 5 column grid view is shown below).



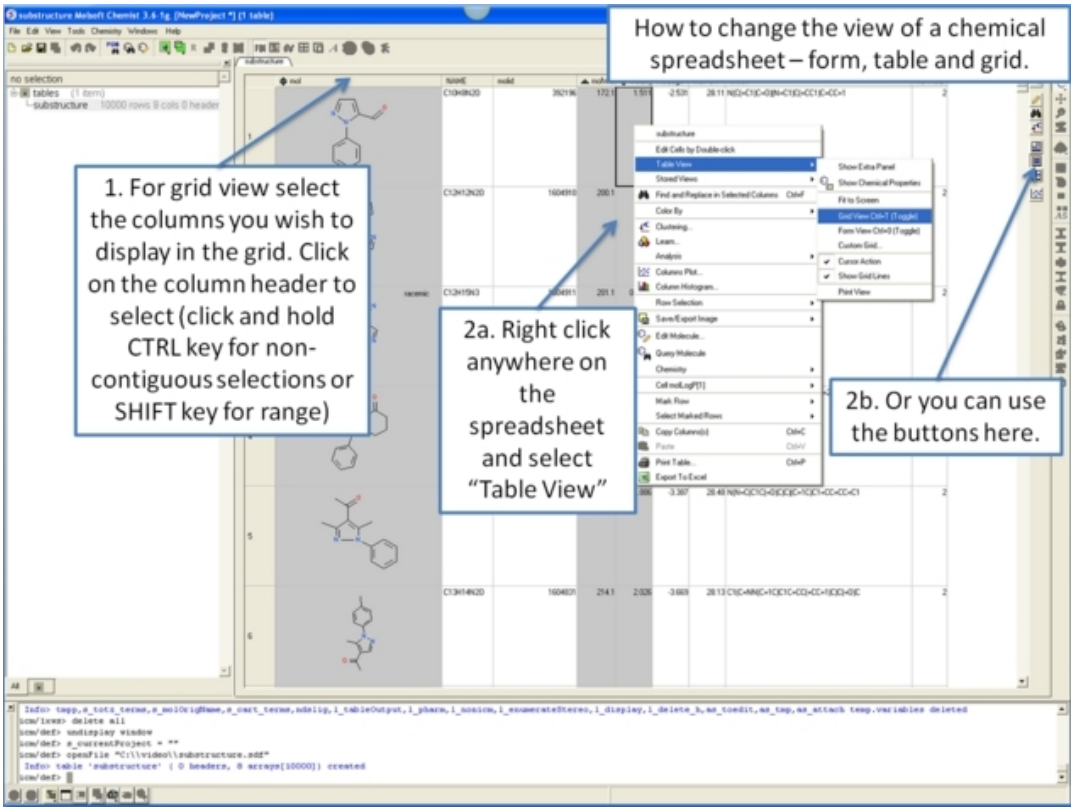
17.2.2 How to add columns into a chemical spreadsheet.



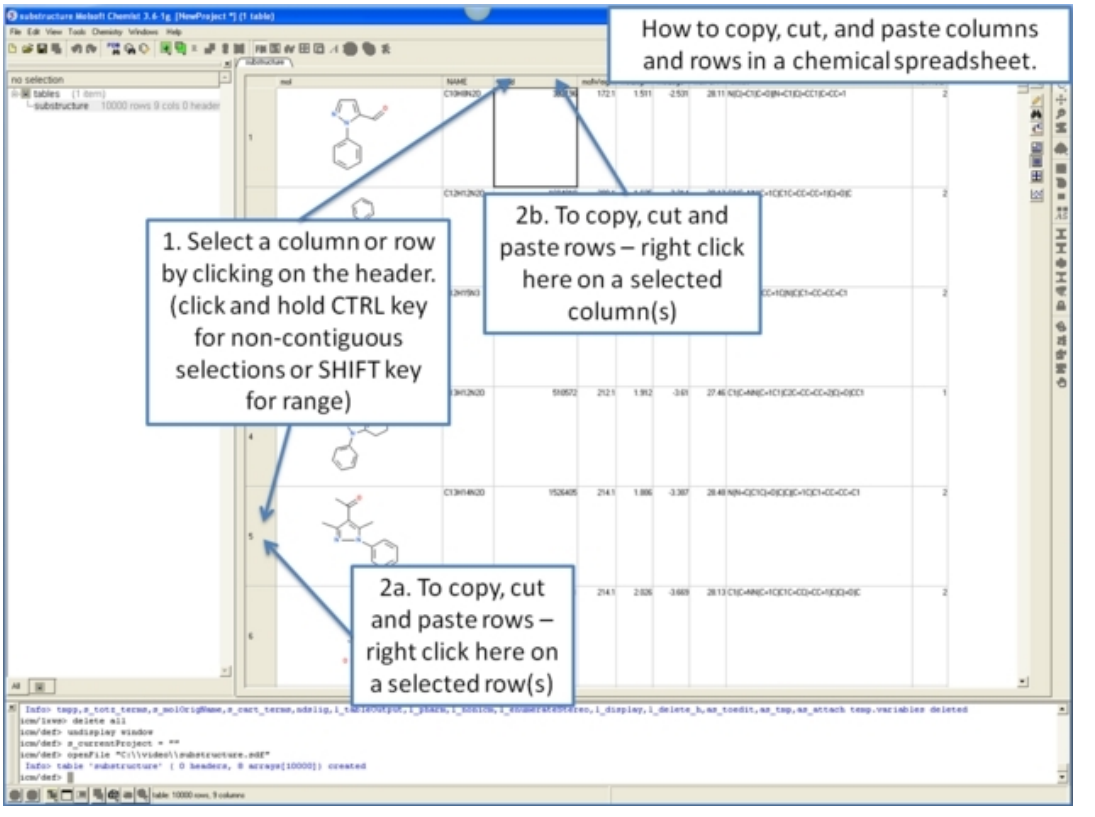
17.2.3 How to sort a column(s) in a chemical spreadsheet.



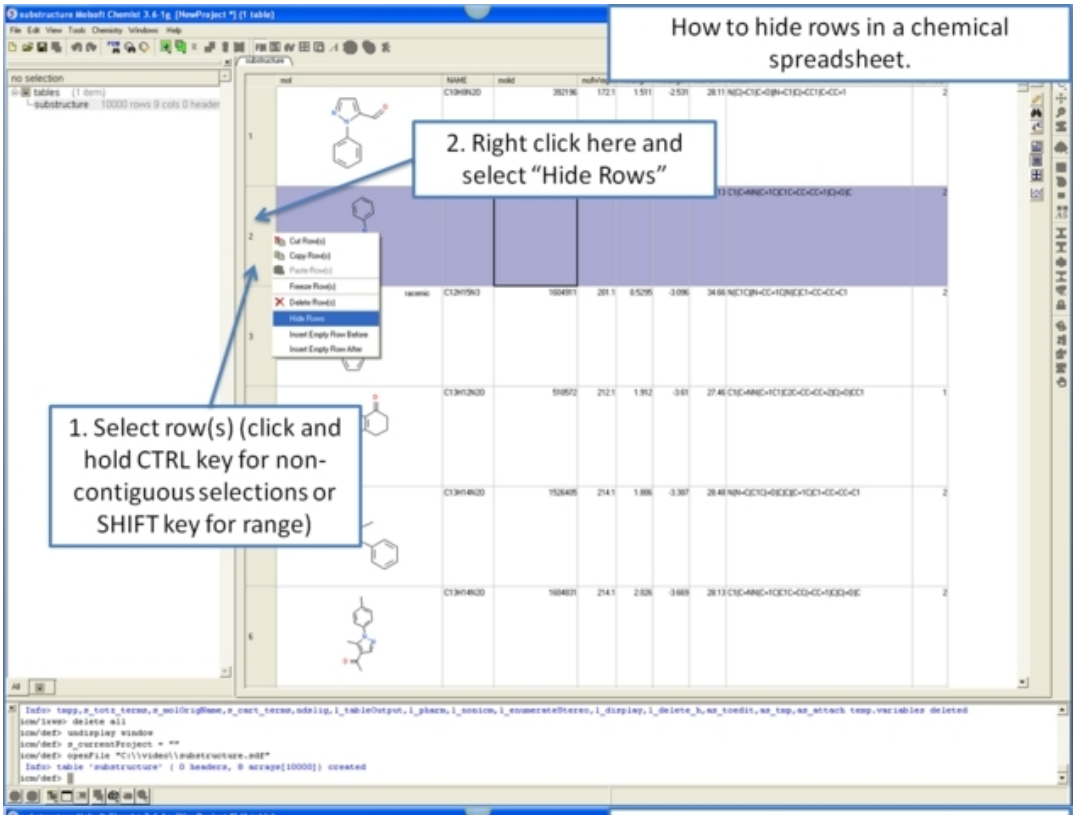
17.2.4 How to change the view of a chemical spreadsheet − form, table and grid.

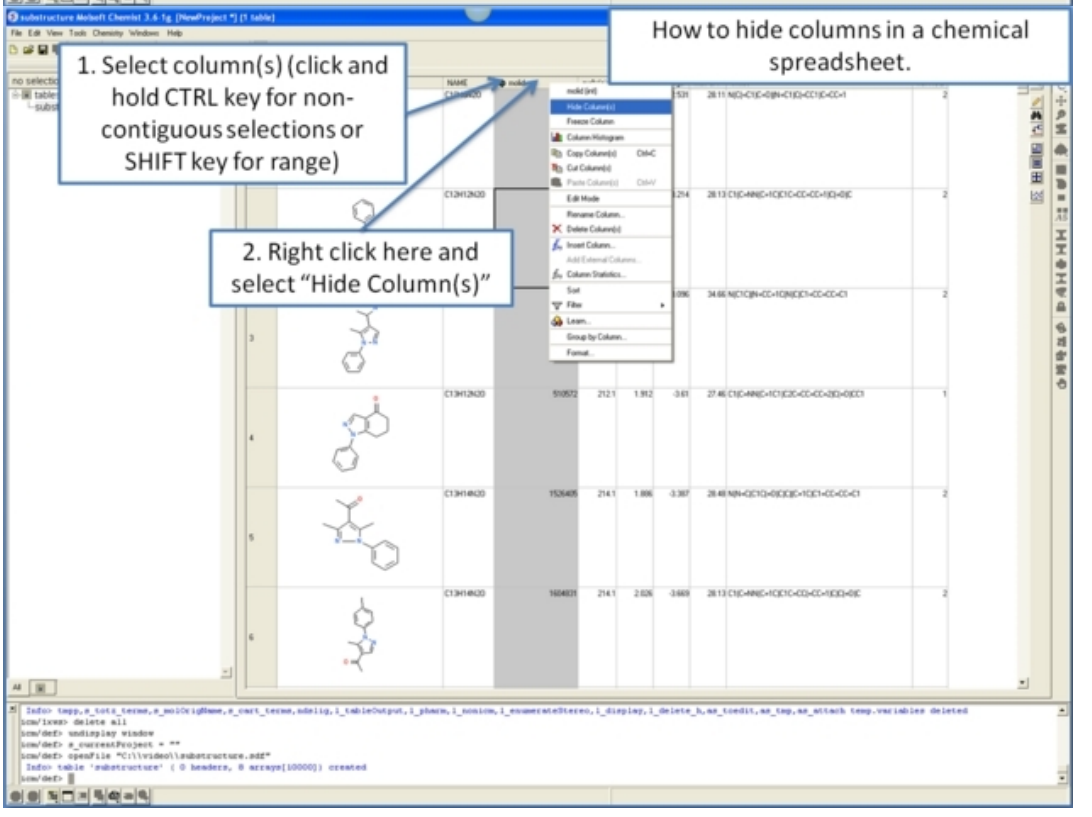


17.2.5 How to copy, cut and paste columns and rows in a chemical spreadsheet.

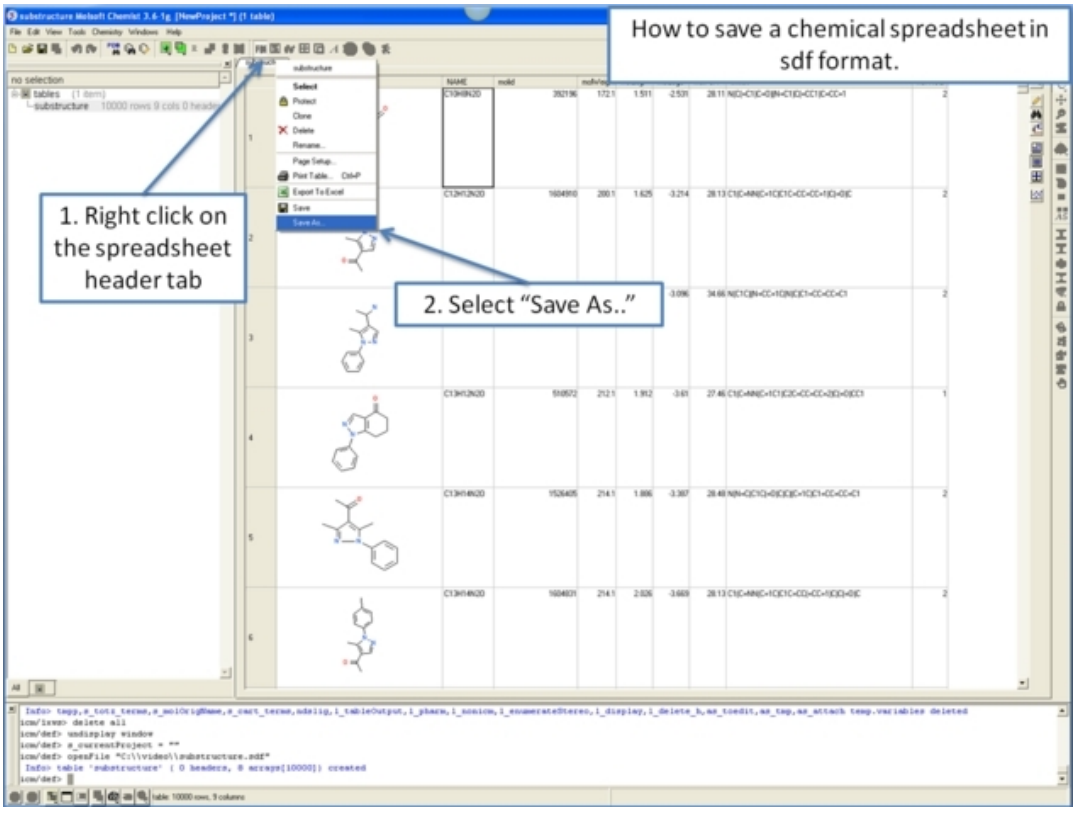


17.2.6 How to show and hide columns and rows in a chemical spreadsheet.

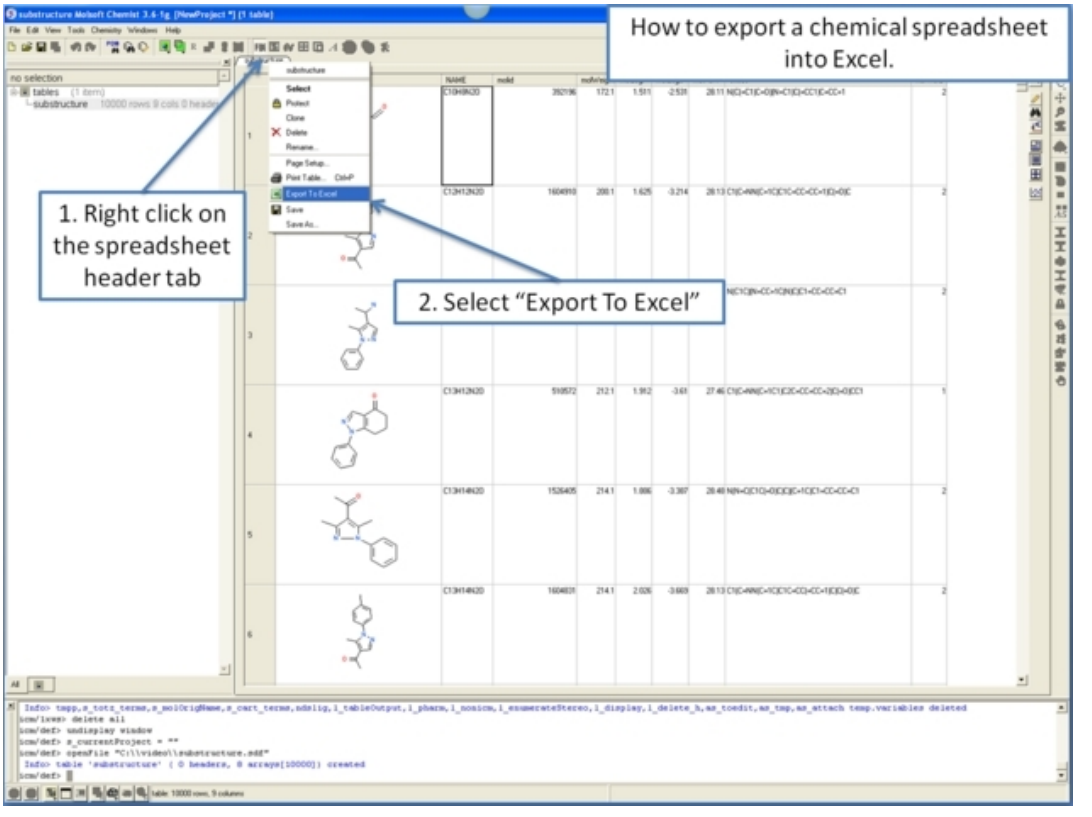




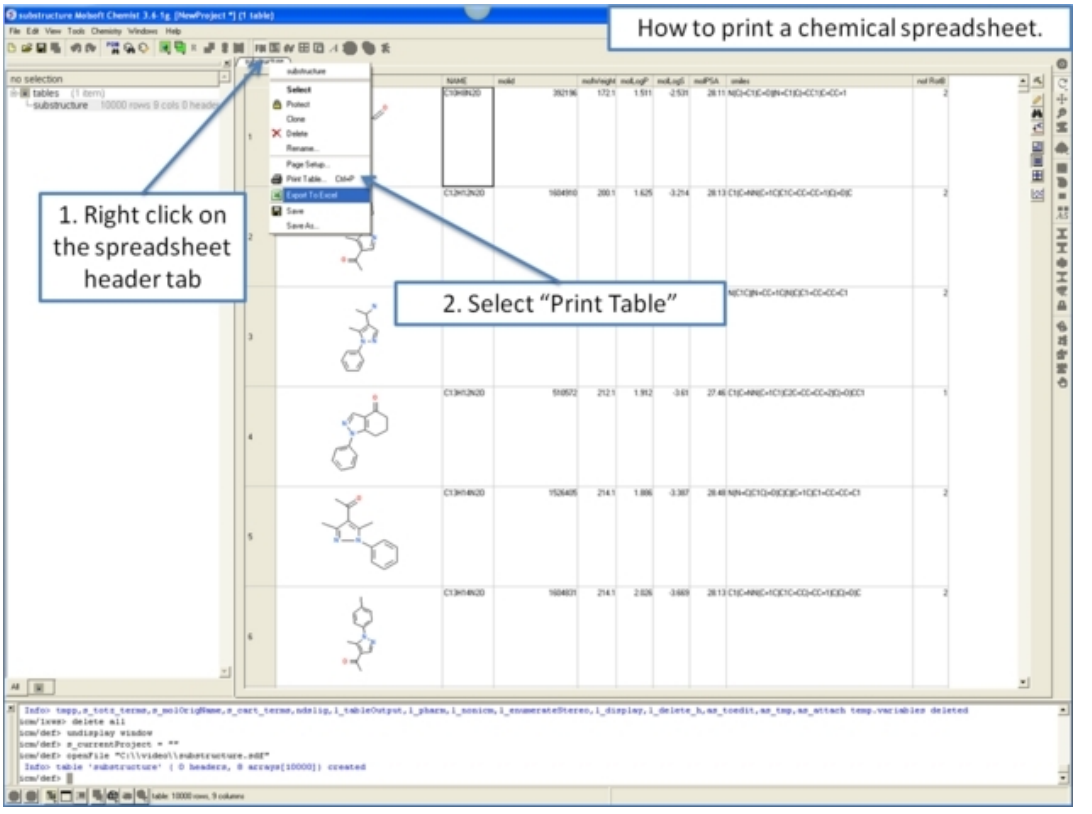
17.2.7 How to save a chemical spreadsheet in sdf format.



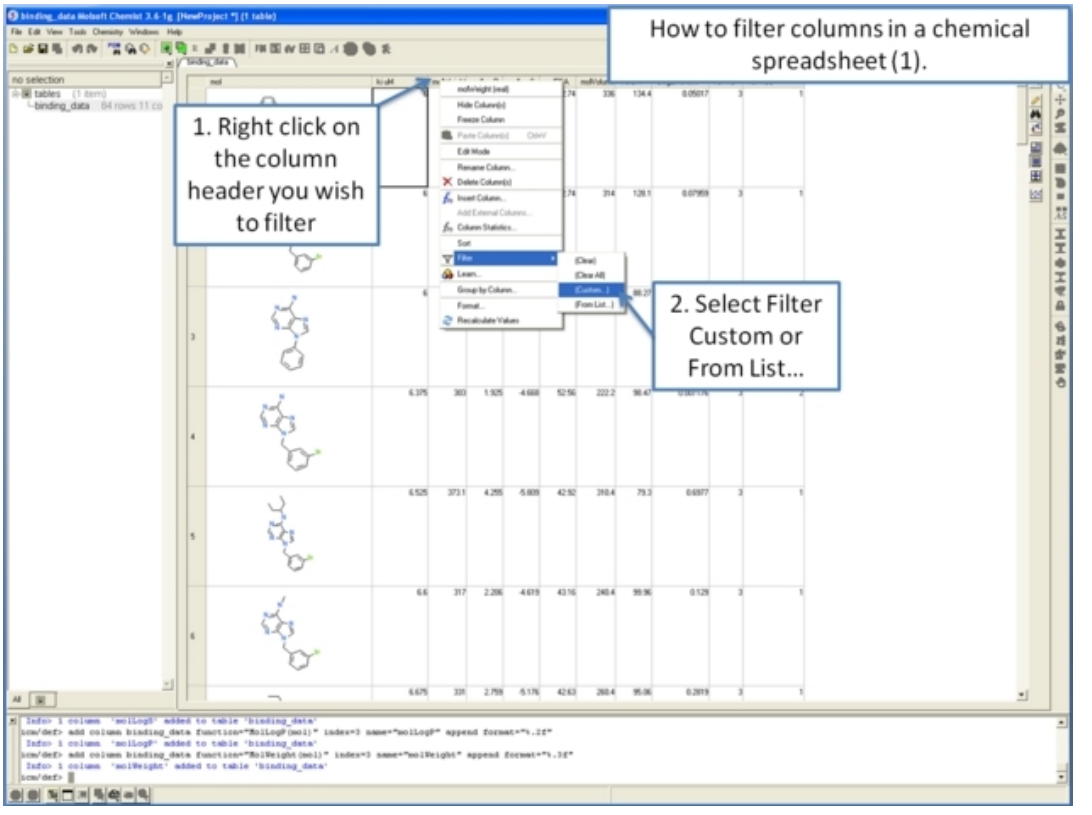
17.2.8 How to export your chemical spreadsheet into Excel.

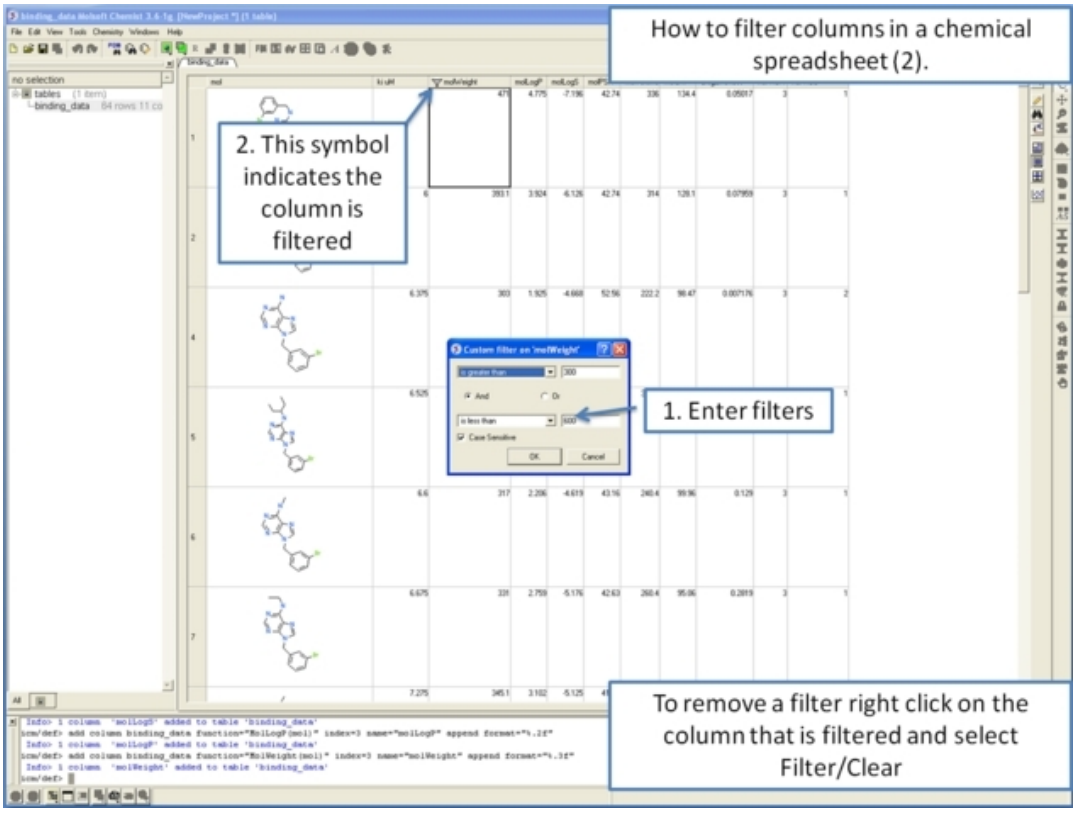


17.2.9 How to print a chemical spreadsheet.

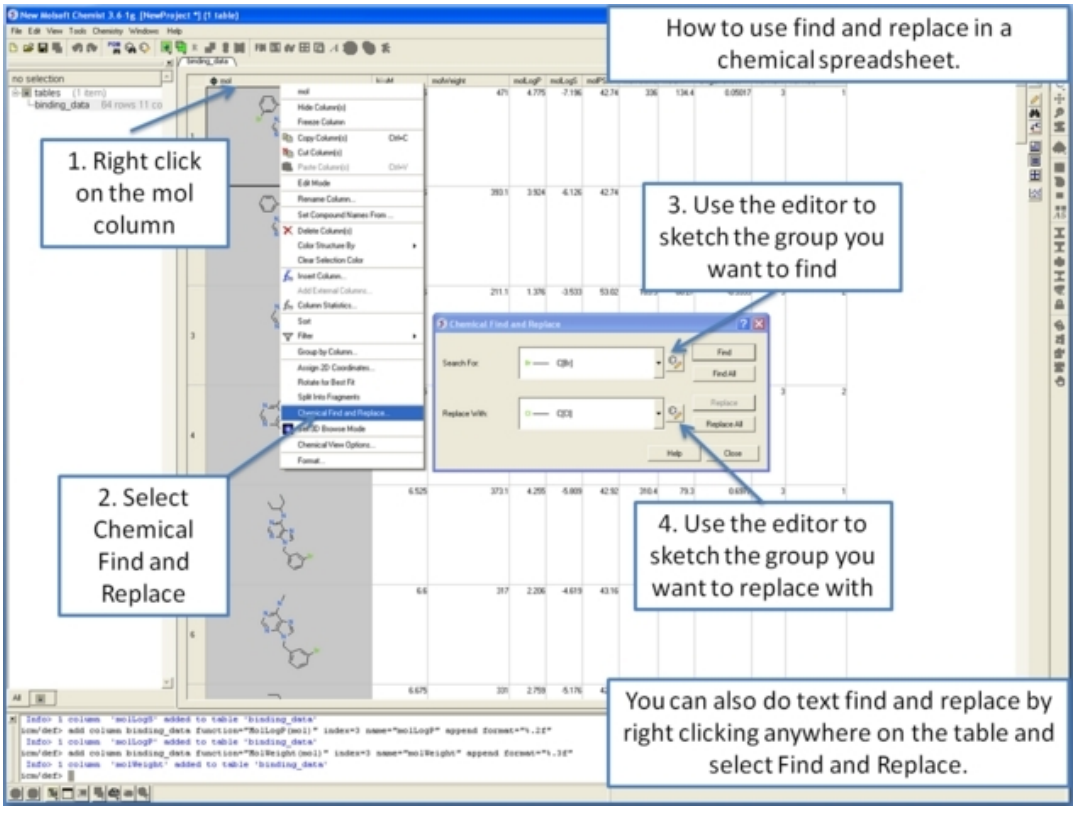


17.2.10 How to filter columns in a chemical spreadsheet.

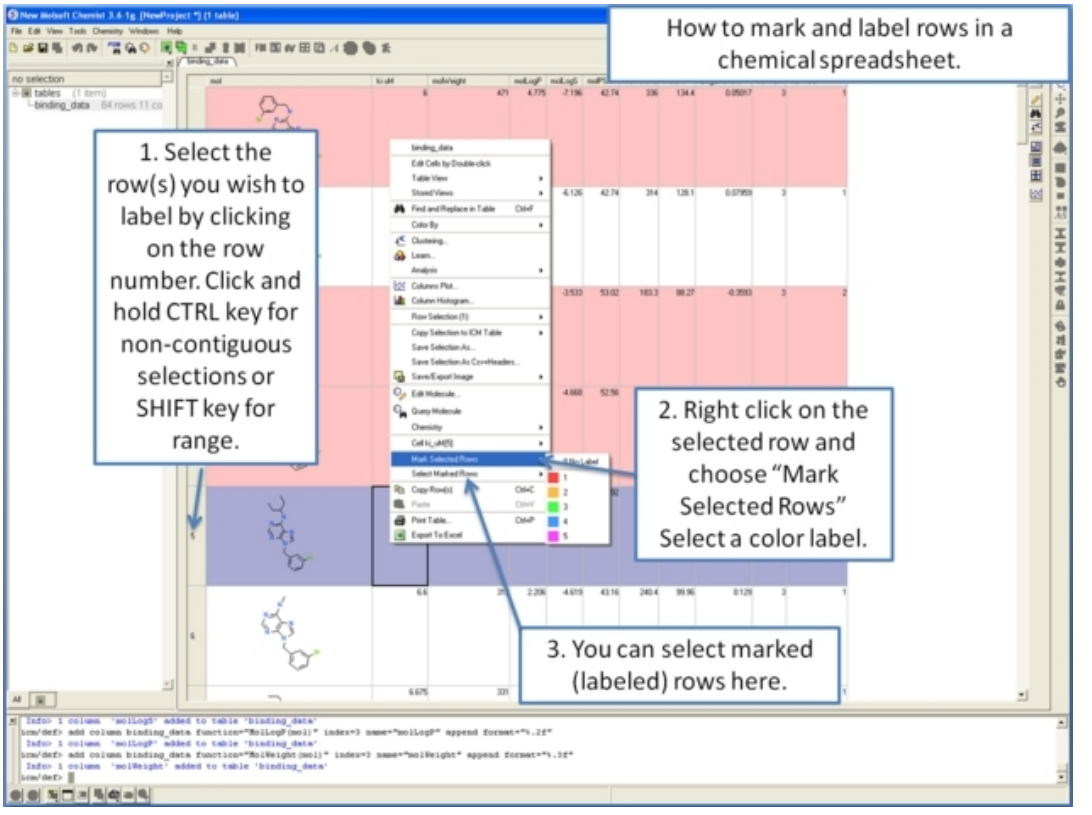




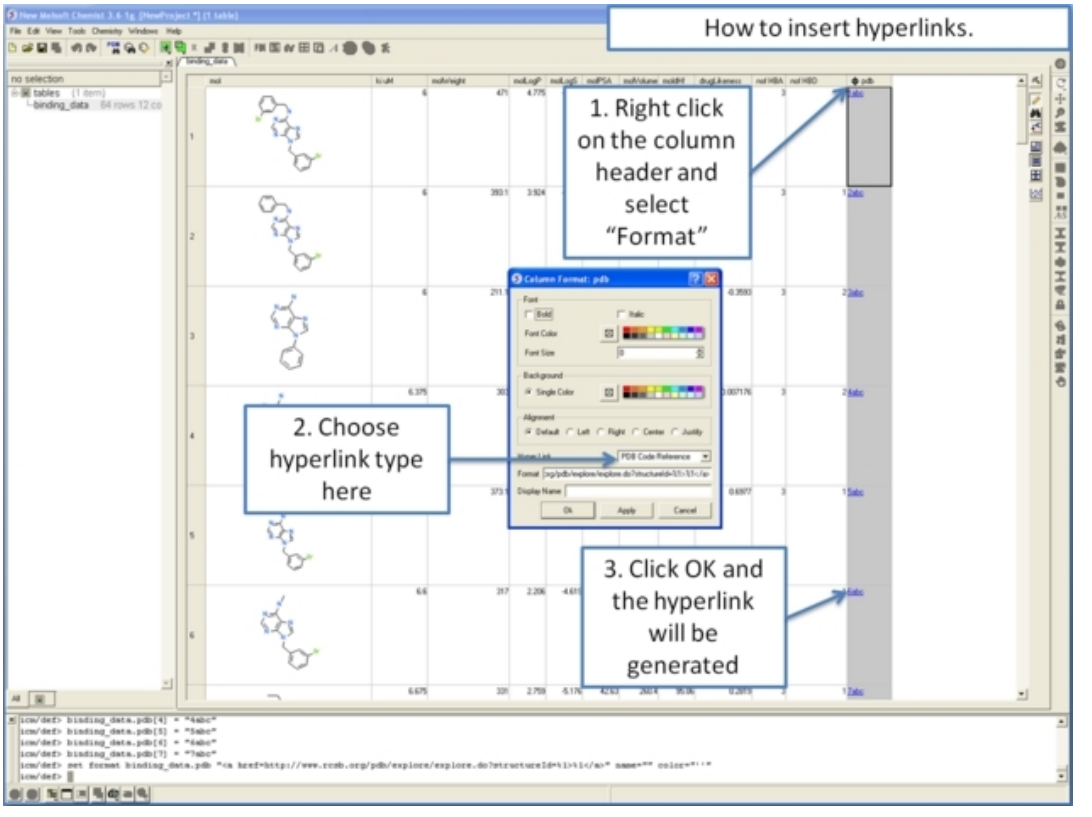
17.2.11 How to use find and replace in a chemical spreadsheet.



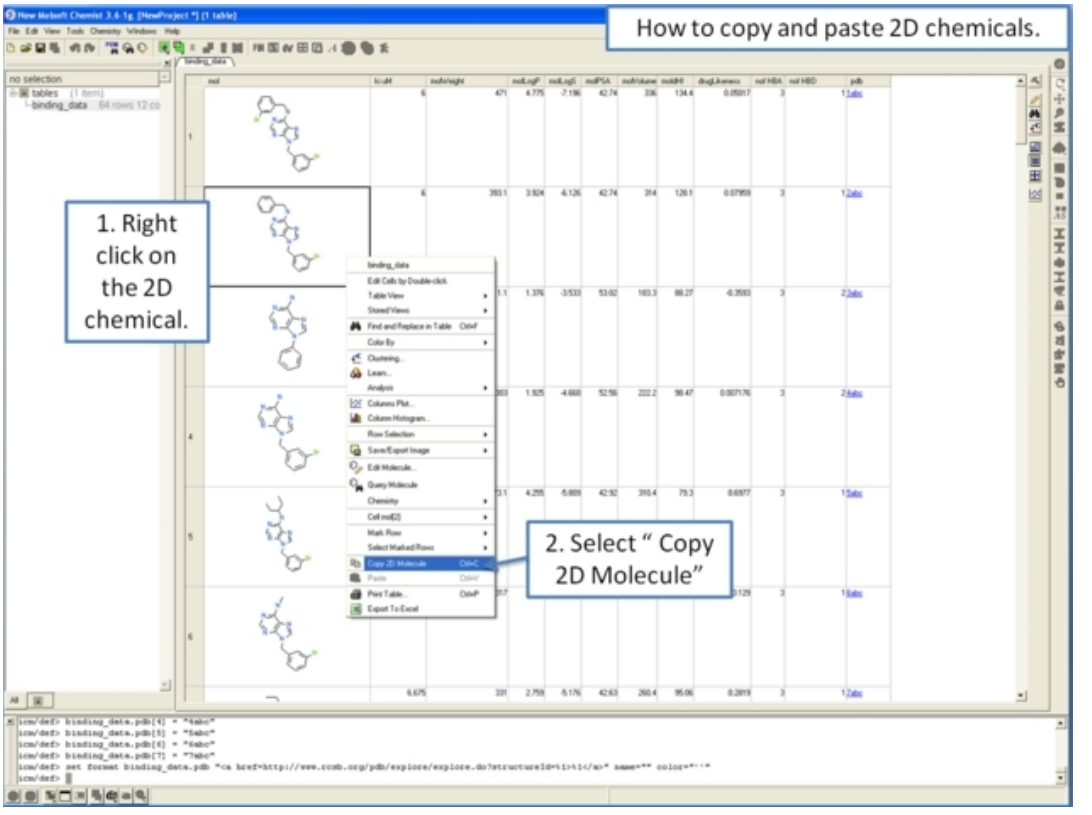
17.2.12 How to mark and label rows in a chemical spreadsheet.



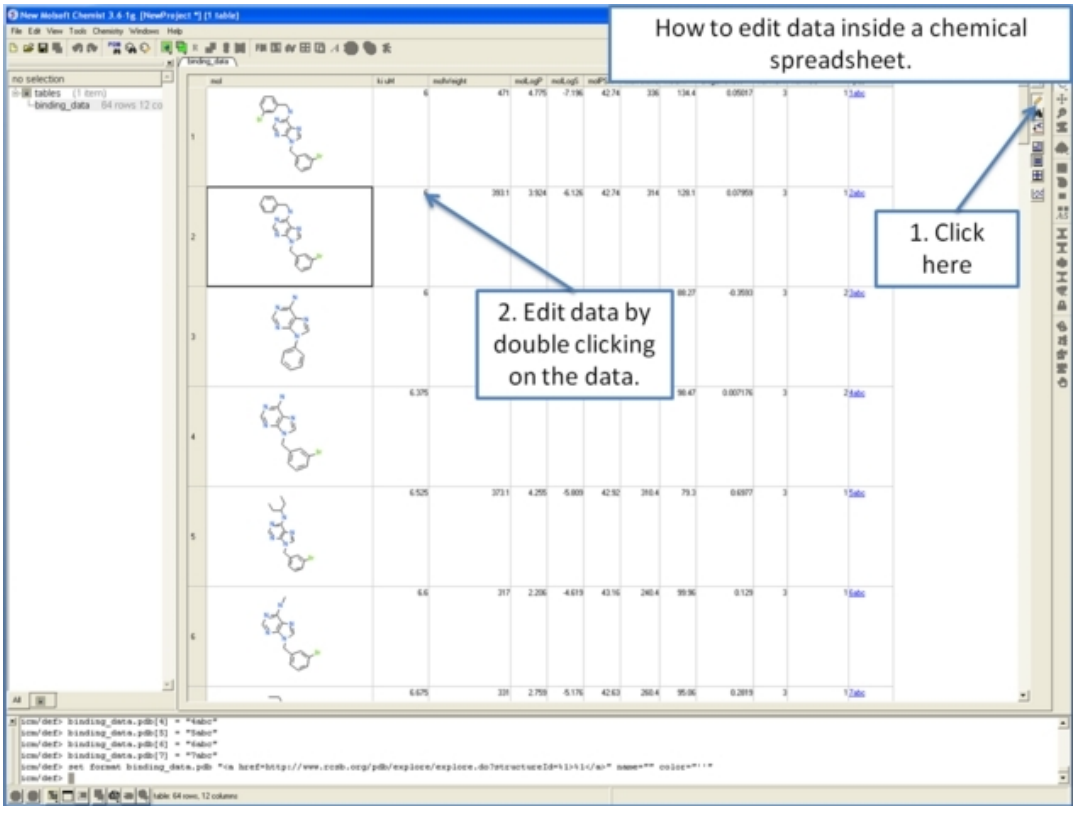
17.2.13 How to insert hyperlinks to the PDB, PubMed, and Uniprot.



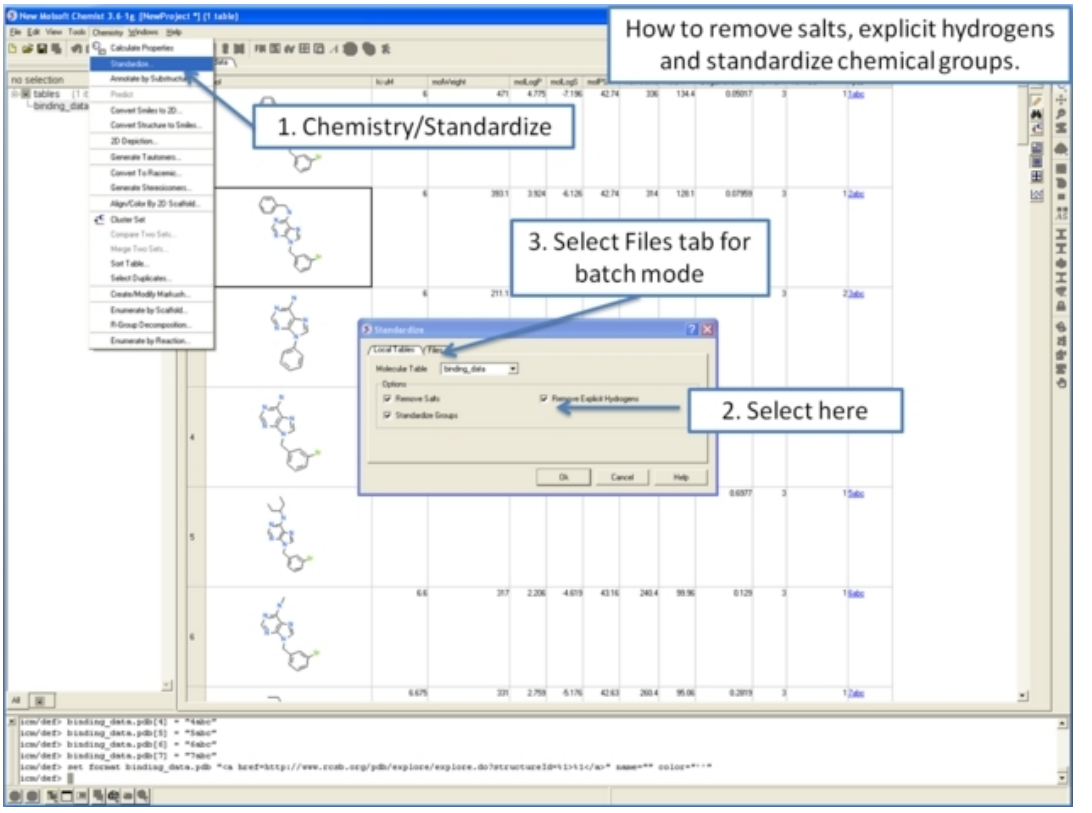
17.2.14 How to copy and paste 2D chemicals.



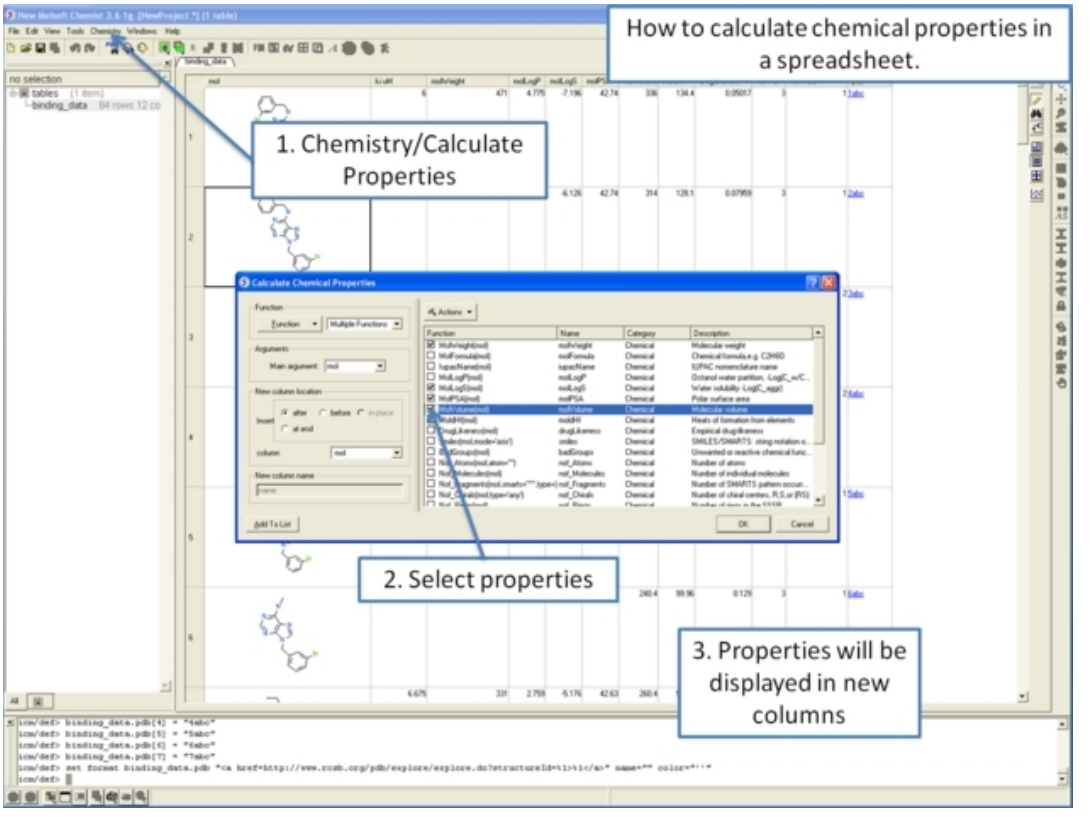
17.2.15 How to edit data inside a chemical spreadsheet.



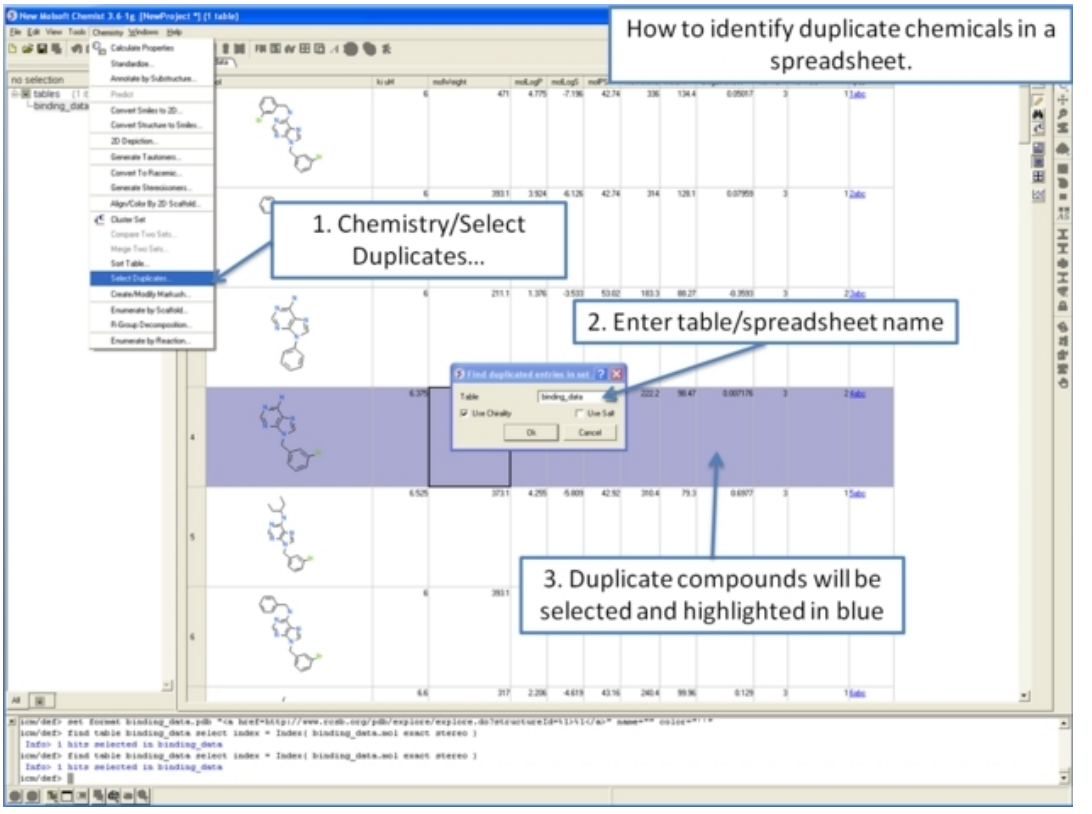
17.2.16 How to remove salts, explicit hydrogens and standardize chemical groups.



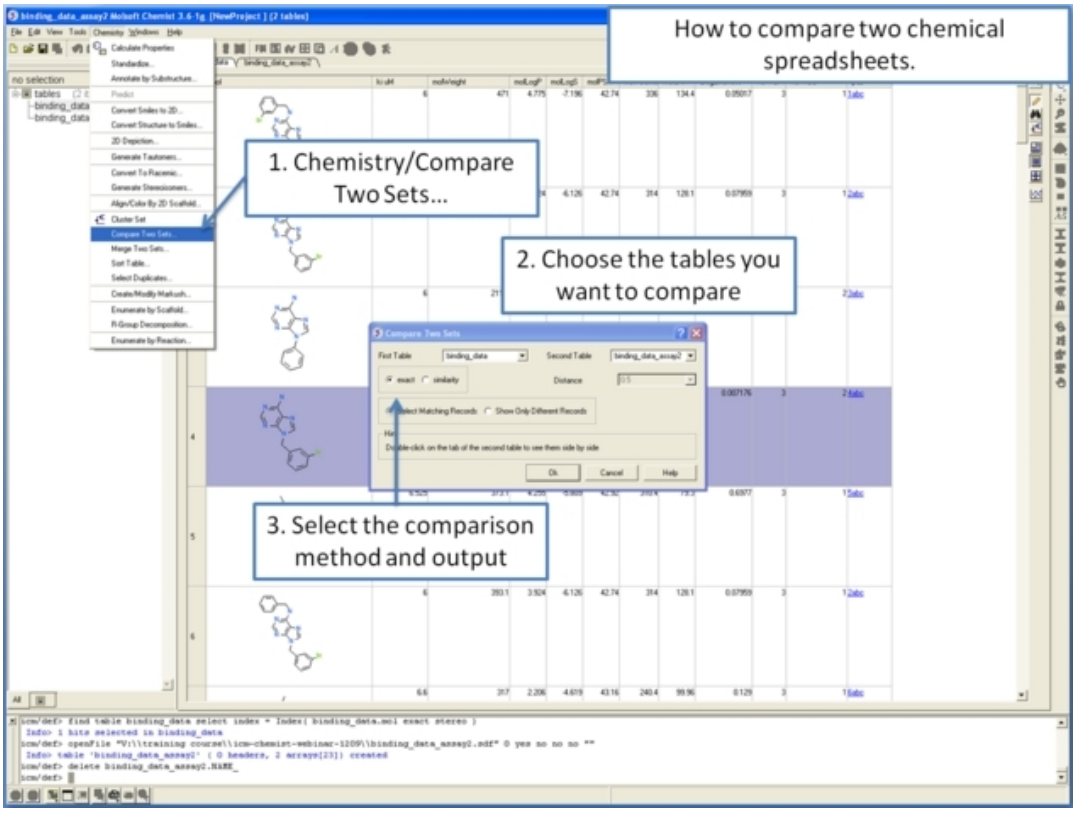
17.2.17 How to calculate chemical properties in a chemical spreadsheet.



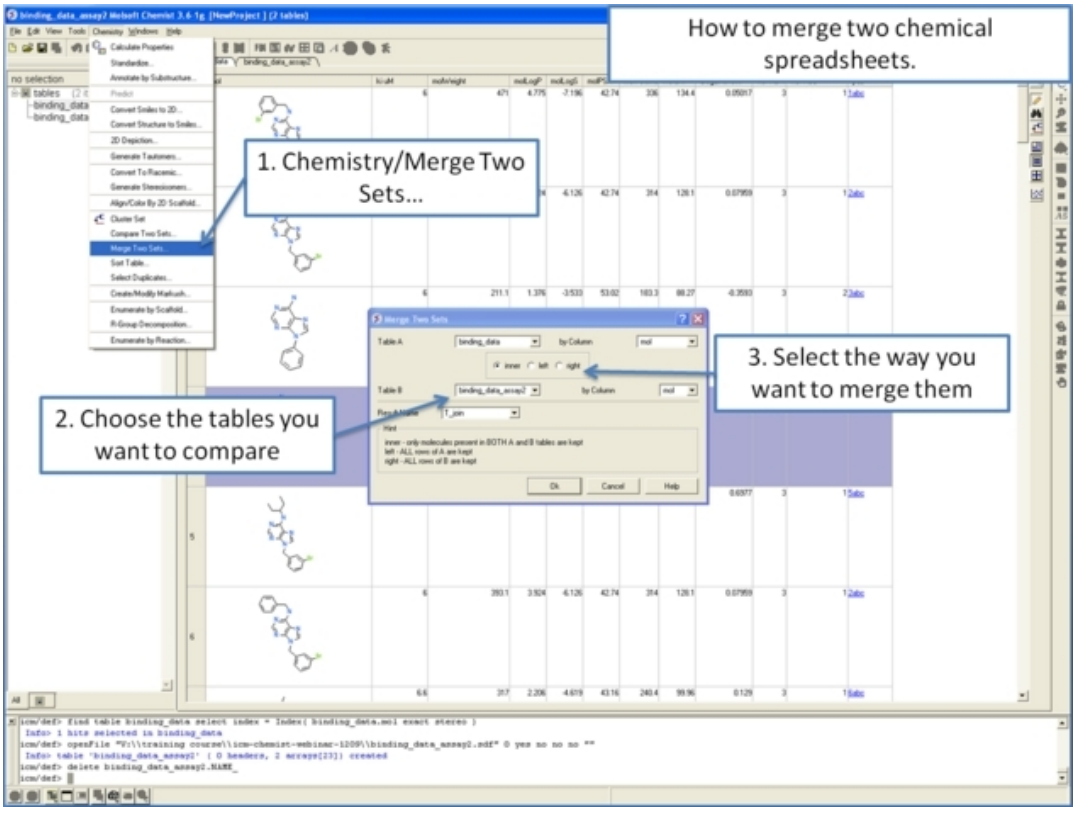
17.2.18 How to identify duplicate chemicals in a chemical spreadsheet.



17.2.19 How to compare two chemical spreadsheets.



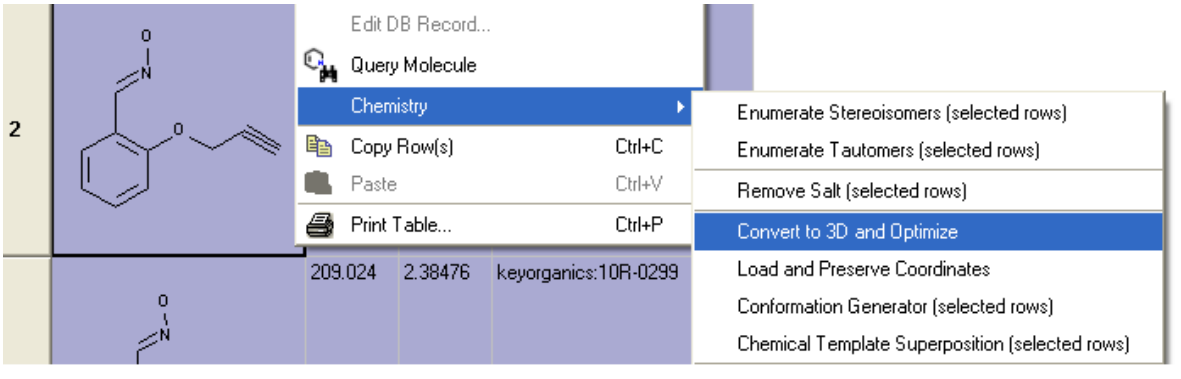
17.2.20 How to merge two chemical spreadsheets.



17.2.21 Display and Convert Molecule

To display and convert a molecule from a molecular table in the 3D graphics display window:

- Select the molecule image or images in the molecular table.
- Right click and select the Chemistry/ Convert to 3D option.



17.2.22 Copy Molecule

To copy a molecule to paste into another application or into the ICM Molecular Editor:

- Right click on the molecule and a menu will be displayed.
- Select the option "Copy Molecule"

To copy a molecule or image to paste into another row within an ICM table or into the ICM Molecular editor:

- Right click on the molecule and a menu will be displayed.
- Select the option "Copy Molecule"
- Right click in the cell into which you wish to paste the molecule.
- Select the option "Paste Molecule"

> **NOTE:** To learn how to insert a row read the `insert row` section.

Molecules drawn in ICM can be cut and pasted into ISIS−Draw and molecules from ISIS−Draw can be cut and pasted into ICM.

To perform thes functions the correct settings need to be turned on in ISIS−Draw so that the compound drawing is saved in the clipboard.

IN ISIS−DRAW − Go to Options/Settings/General/Copy Mol Rxn file to the clipboard.

Compounds drawn in ISIS Draw can be cut and pasted into the `ICM Molecular Editor` and into ICM tables. Compounds can be copied in ICM by:

- Right click on the compound in the chemical table and select Copy Molecule.

17.2.23 Edit Molecule

To edit a molecule:

- Right click on the molecule and a menu will be displayed.
- Select the option **Edit Molecule** and the `ICM Molecular Editor` will be displayed.
- Edit the molecule.
- Click Exit in the ICM molecular editor.

17.2.24 Color Table Column

You can color your table based on values within a column by: You can also color the compound according to specific values see `Color Chemical Structure`.

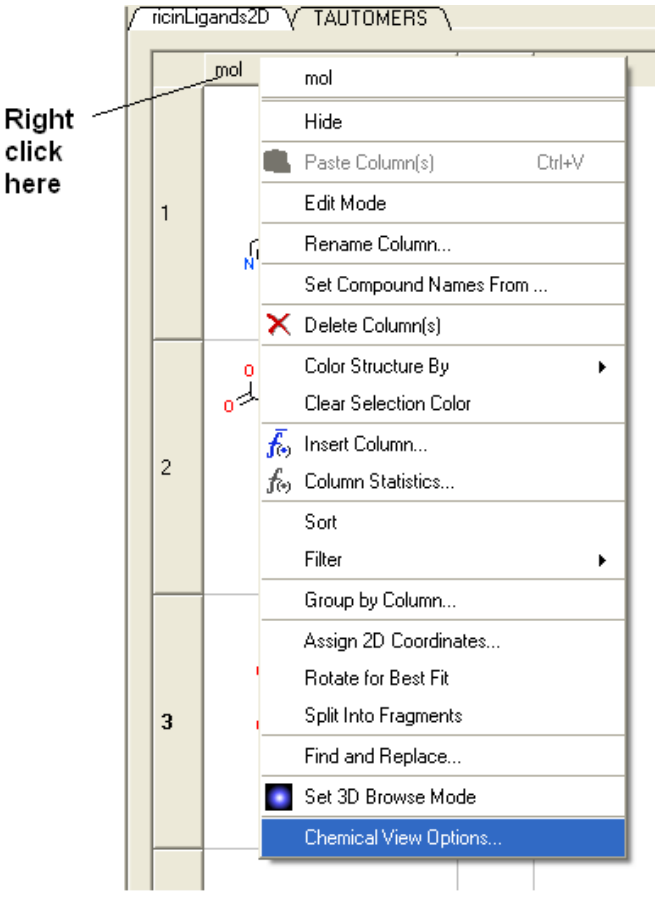
- Selecting the column.
- Right click on the column header and a menu will be displayed.
- Select the option "Color By"

> **NOTE:** You can remove the color from the table by right clicking on the column header selecting **Clear Selection Color**.

Rows can be colored by marking them as described `here`

17.2.25 Chemical Display

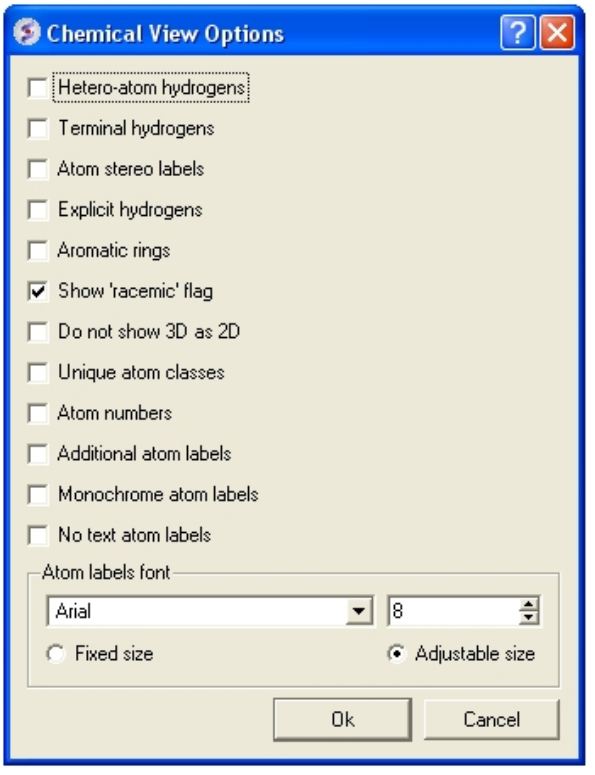
There are various display options for chemicals contained in `ICM molecular tables`. Most of these options are accessed by right clicking on the table column header "mol".



17.2.26 Chemical View Options

Different chemical view options in the `ICM molecular table` can be set.

- Right click on the "mol" column header.
- Select Chemical view options... and the following data entry box will be displayed

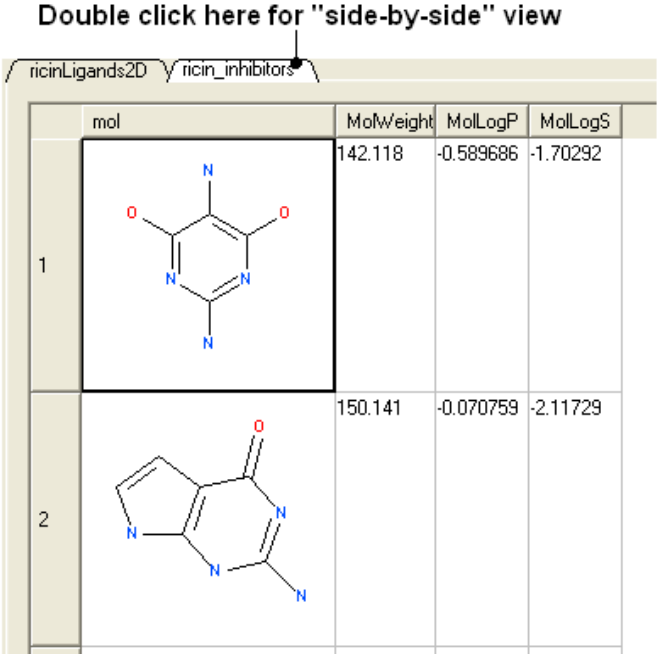


Options can be changed by checking the appropriate boxes or by entering the desired font and size.

17.2.27 Chemical Table Side−by−Side View

Chemical tables can be visually compared by placing them side−by−side. This can be done by:

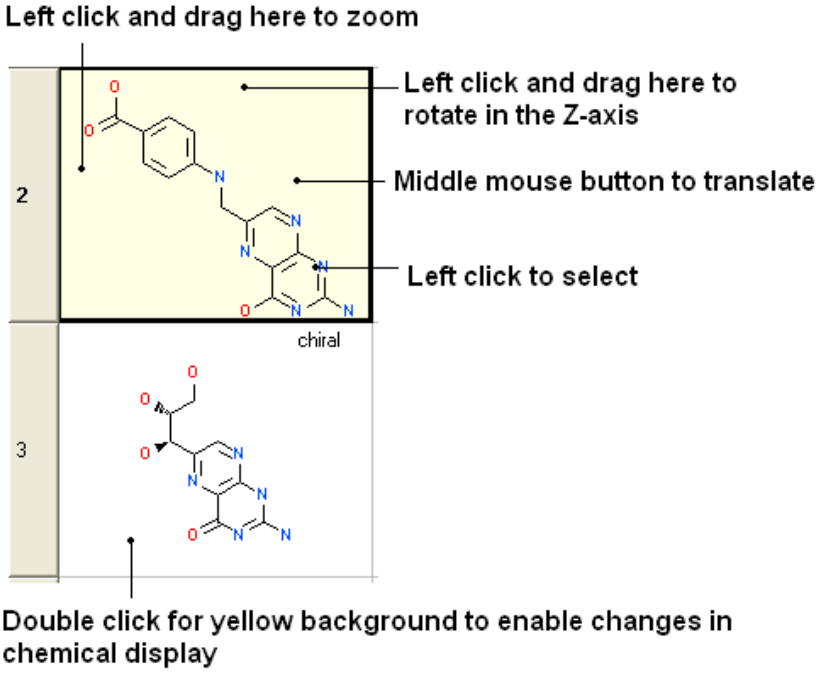
- Double click on the table header for side−by−side view.
- Double click on the table header again to remove side−by−side view.



17.2.28 Zoom, Translate and Z−rotate a Chemical in a table.

Sometimes you may want to get a better view of a chemical in a an `ICM molecular table` you can do this inside the chemical table by:

- Double clicking on the chemical drawing and the background will turn yellow.

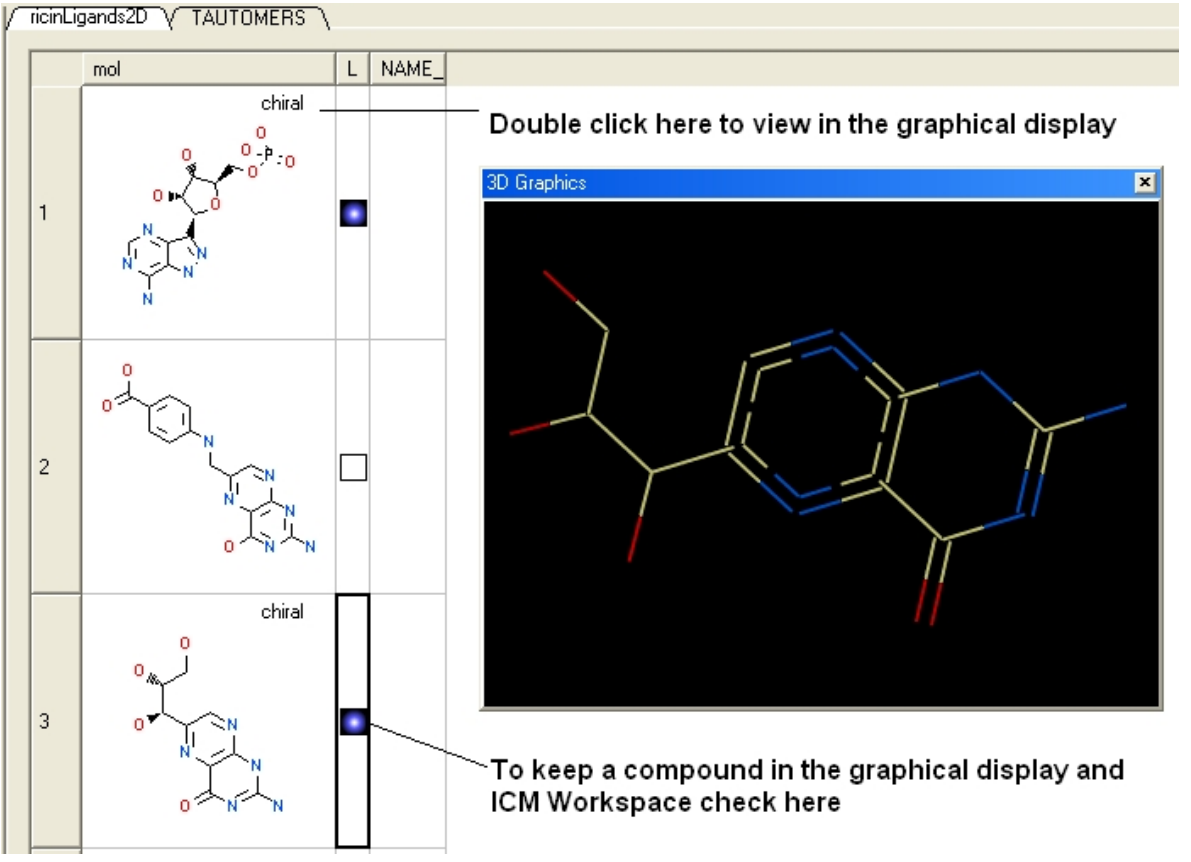


NOTE: You can also browse your structures in 3D. See section entitled `"Set Chemical Table 3D Browse Mode"`.

17.2.29 Set Chemical Table 3D Browse Mode

To browse the chemicals contained within an `ICM molecular table` in the graphical display:

- Right click on the "mol" column header.
- Select Set 3D Browse Mode



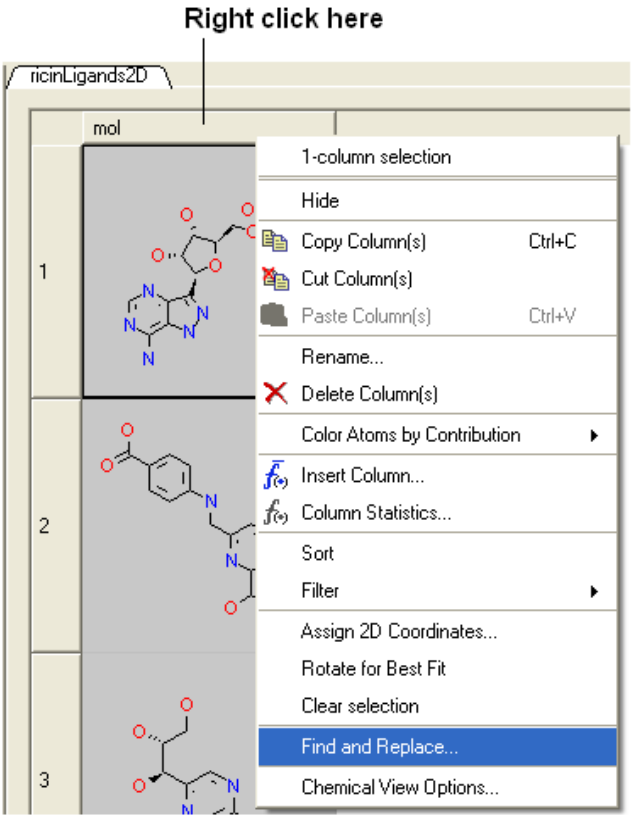
To remove 3D browse:

- Right click on the "mol" column header.
- Select UnSet 3D Browse Mode

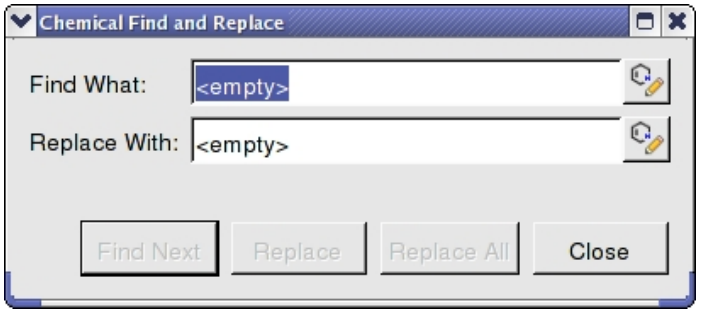
17.2.30 Chemical Find and Replace

Chemical Findtool allows you to find an arbitrary chemical fragment with one or more attachment point(s) and replace it with another fragment with the same number of attachment points.

To find a substructure and replace it with something else:



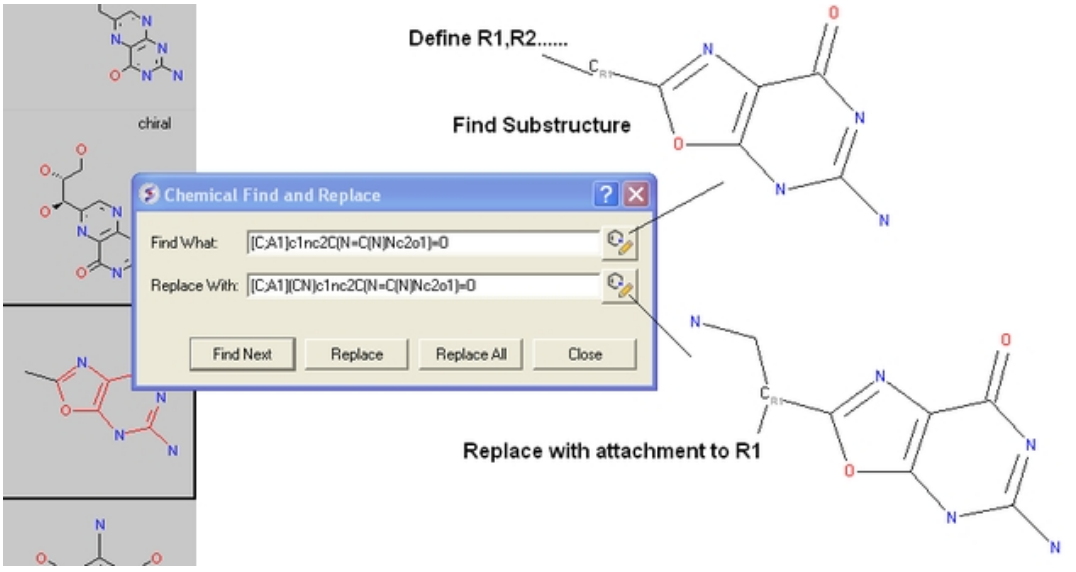
- Select the column in which the molecular structures are displayed. The column is usually called "mol".
- Right click on the "mol" column header and select Find and Replace. A data entry box as shown below will be displayed.



- Click on the Molecular Editor button at the end of the Find What: data entry box.
- The ICM Molecular Editor will be displayed. Draw the substructure you wish to search for and replaced.
- Draw the pattern and mark attachment points with R1,R2.... R−groups can be added by right clicking at the attachment point and selecting the R−group from the drop down options.
- Close the ICM Molecular Editor and the string will be displayed.
- Repeat with the "Replace With:" data entry box. Make sure the same number of R1,R2... labels are drawn.
- Click the Find Next button and then Replace or Replace All. When a substructure to replace is identified it will be colored red.

NOTE: There are a number of `keyboard shortcuts` which can be used to draw chemicals. Also please note that an aromatic bond in the source molecule will not match a double bond in the replacement pattern.

Here is an example:

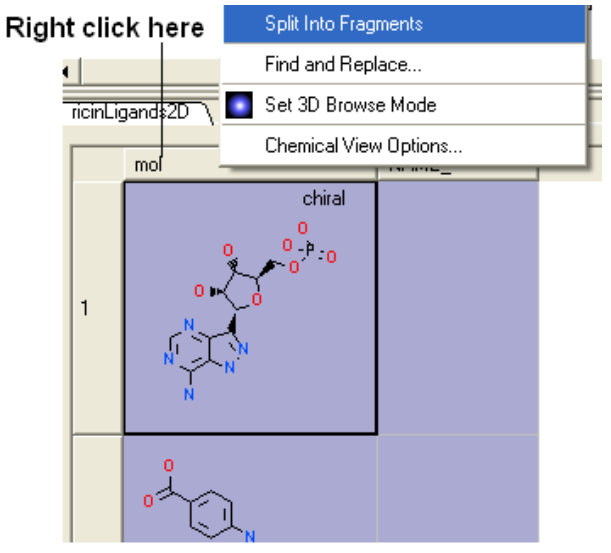


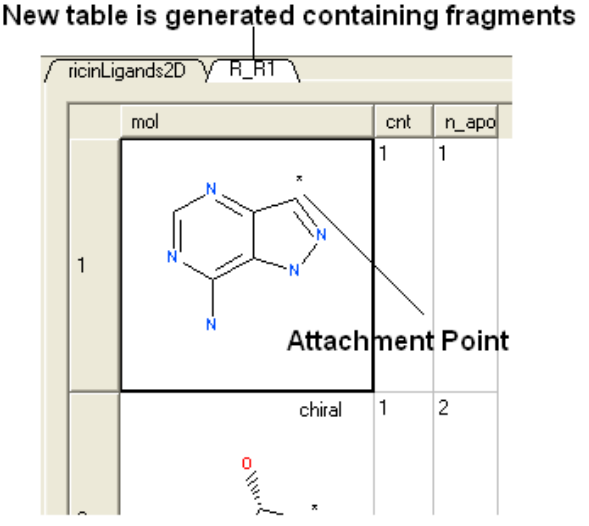
17.2.31 Split Chemical(s) into Fragments

Chemicals displayed in an `ICM Molecular Table` can be split into fragments. This is useful for generating a series of R−groups to be added to a scaffold (See `section describing reactions`.

To generate fragments:

- `Select` the column or row(s) you wish to generate the fragment from.
- Right click on the "mol" column header and select "Split Into Fragments".
- A new table of chemical fragments will be displayed. Each fragment is assigned an attachment point which is flagged with an asterisk (*).





17.2.32 Rotate Chemical for Best−Fit

To improve the display of a chemical within an `ICM molecular table` you can choose an option called "Rotate for best fit".

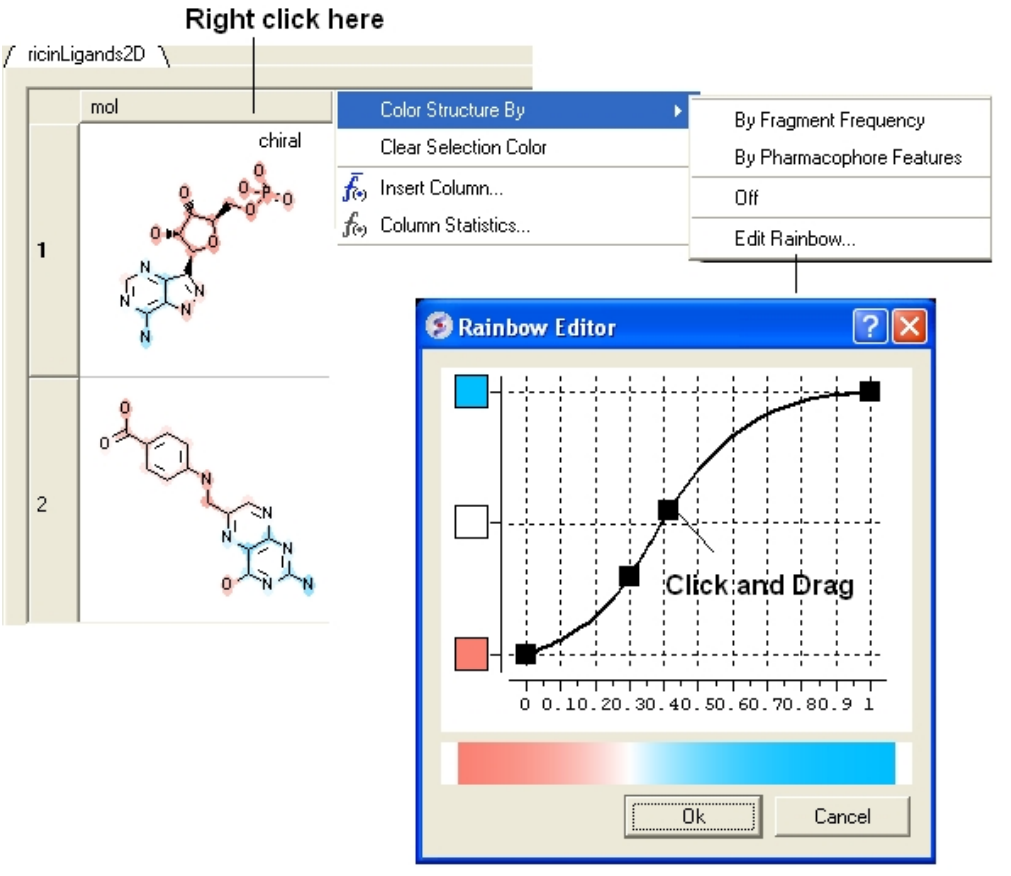
This option can be found by:

- Right click on the "mol" column header.
- Select "Rotate for Best Fit"

17.2.33 Color Chemical Structure

To color the structure of a chemical in an `ICM molecular table` by fragment of pharmacophore frequency:

- Right click on the "mol" column header.
- Select Color Structure By
- Select "By Fragment Frequence" or "By Pharmacophore Features"



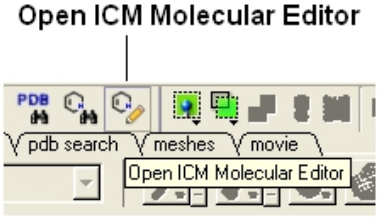
NOTE: The coloring can be controled using the "Edit Rainbow" option and the coloring can be removed using the "Off" option

17.3 Molecular Editor

Draw new compounds by using the ICM Molecular Editor.

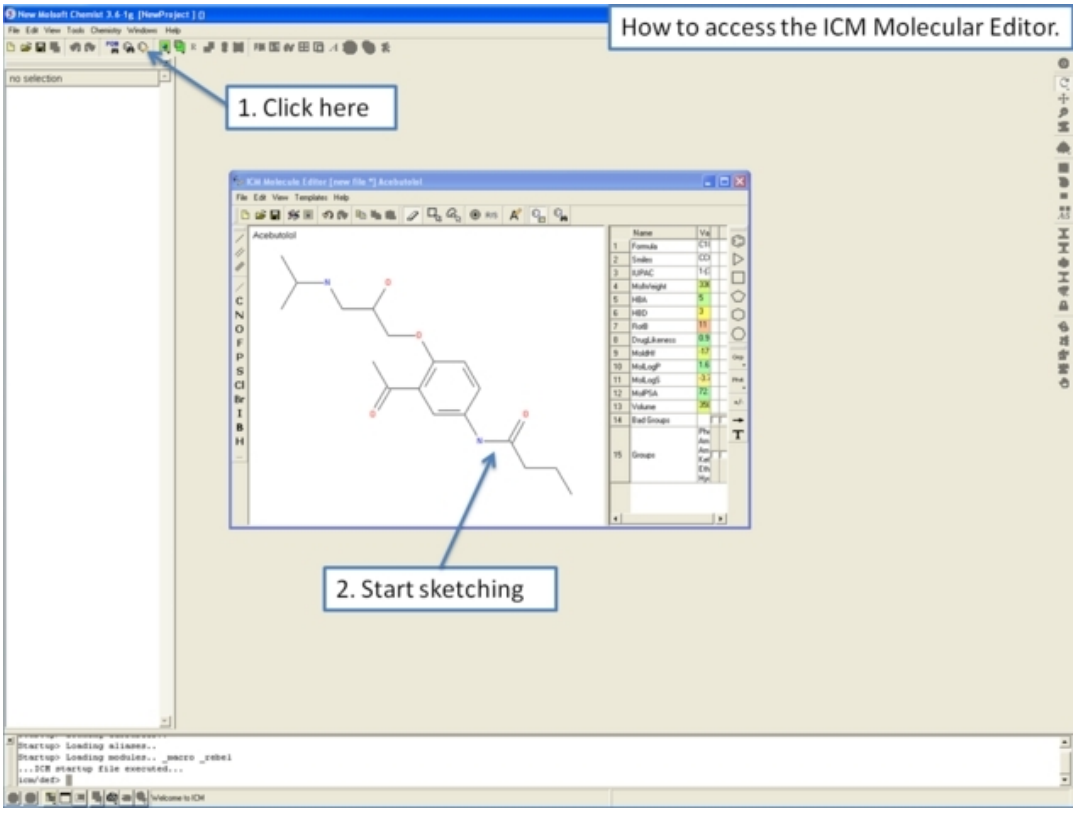
The molecular editor can be activated by:

- Clicking on the Open ICM Molecular Editor button shown below.



OR

- Select Chemistry/Molecular Editor and the editor as shown below will be displayed.



17.3.1 Drawing a New Chemical Structure

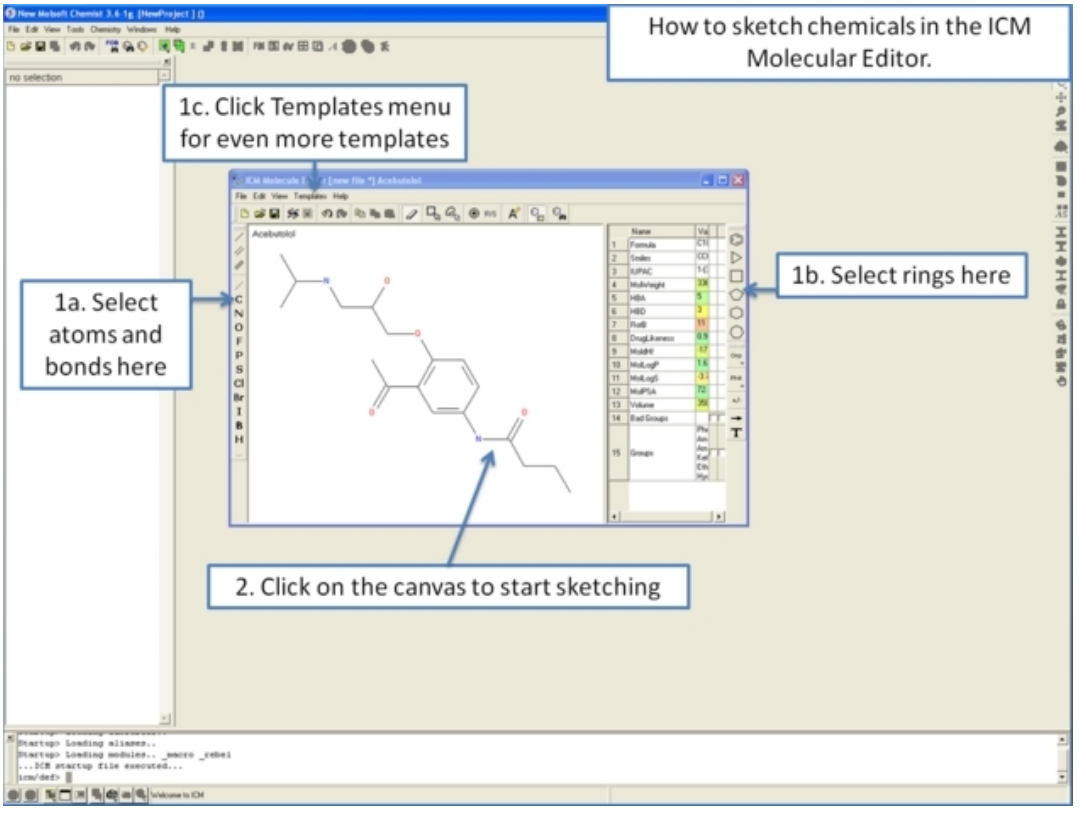
To draw a new chemical structure the ICM Molecular Editor should be loaded.

To do this:

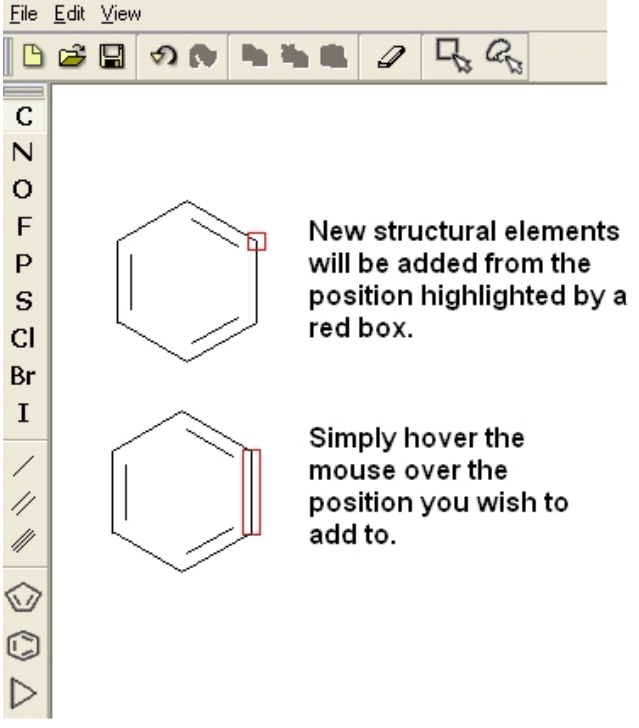
- Select Chemistry/Molecular Editor

Now you can start drawing your structure.

- First select one of the appropriate buttons on the left hand side of the molecular editor.
- Then click in the white Molecular Editor Workspace and your element, ring or bond will be displayed.

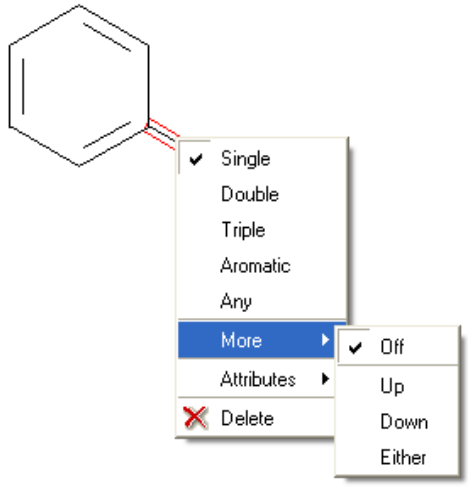


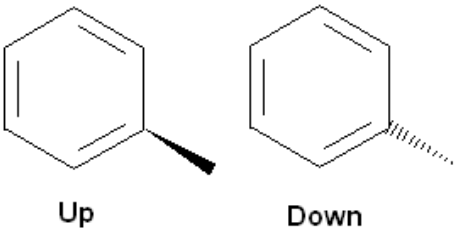
- You can extend your structure by selecting another button from the left hand−side as before.
- Select where on the structure you would like to add the new group by hovering the mouse over the desired position. The position you will add to will be highlighted in a red box.

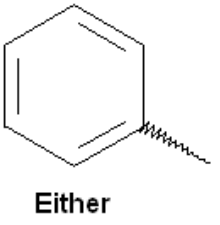


To change the direction of a bond:

- Right click on the bond and a menu as shown below will be displayed.
- Select which bond direction you desire from up, down or either.

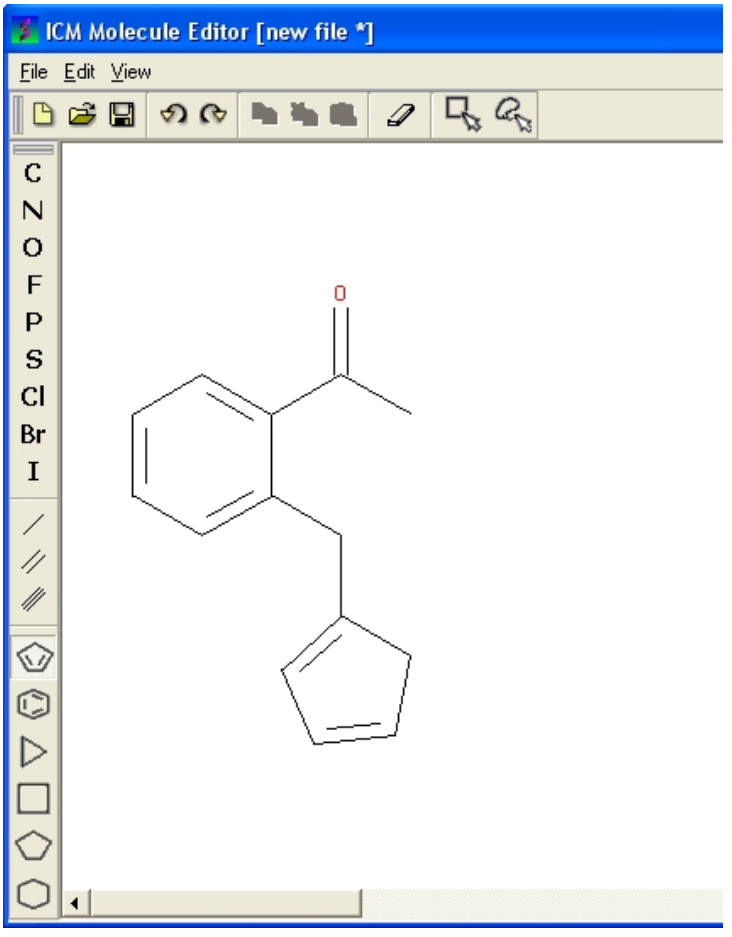






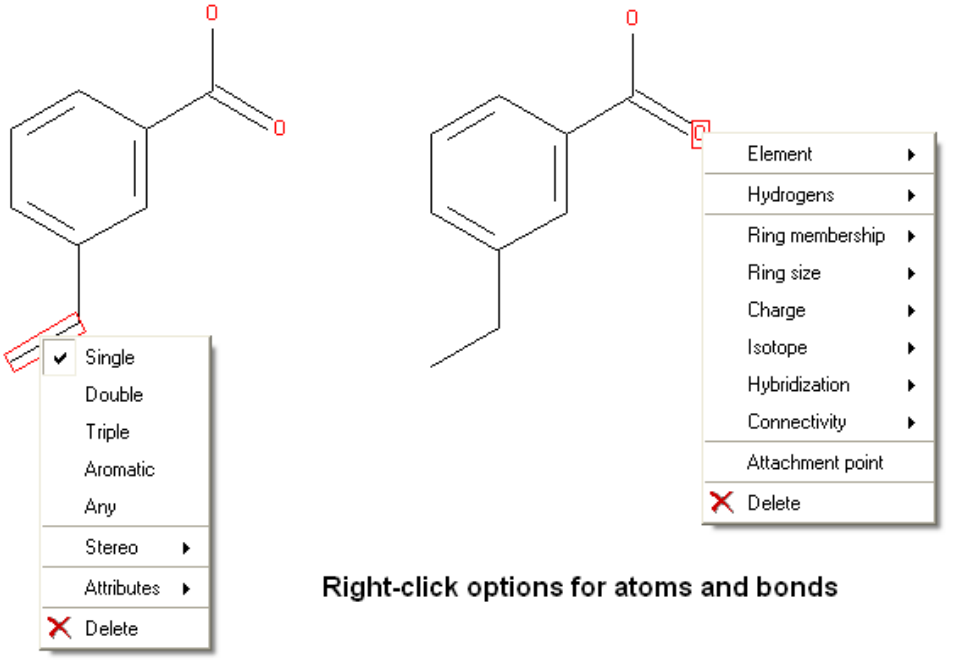
Carry on drawing until your structure is complete! See the other sections in this chapter.

1. To save your structure read the `save and append chemical structure` section.
2. To append your structure to an existing SDF file read the `save and append chemical structure` section.
3. To save your structure to an ICM table read the `save and append chemical structure` section.
4. To edit your structure read the `edit your structure` section.



17.3.2 Right Click Options

There are a number of different options available when you **right click** on a **bond** or **atom.** These options are described in detail in the `Chemical Searching` part of the manual.



Right-click options for atoms and bonds

17.3.3 A dictionary of chemical groups.

The ICM Chemical Editor has a dictionary of chemical groups. These groups are stored in a table stored in `CHEM_GROUPS.csv` file. This file can be manually edited to remove or add new definitions. The group can be selected using the `Grp` button of the Editor.

17.3.4 Adding and rotating a fragment in molecular editor by clicking−holding−and−dragging.

The Chemical Editor allows one to add bonds (click the `bond` button), or chemical groups (the `Grp` button), Often one needs to re−orient the added bond or fragment. In this case press on the atom to which you are going to append the bond or the fragment and **hold−and−drag** the mouse it until you see added fragment rotating around the attachment point. While you keep the mouse button pressed you can **rotate** by dragging in the preferred direction.

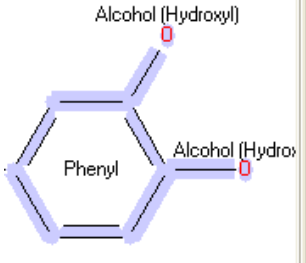
If you add templates (the `Templates` menu, or **paste** fragments, the mechanism is somewhat different because the group is added in its default orientation. In this case you can press **Ctrl** to rotate the fragment to to be able to attach the fragment in the desired orientation.

17.3.5 Property Monitor

When drawing a compound in ICM you can monitor important ADME−Tox and drug−likeness properties.

To view the drug−likeness monitor

- ICM Molecular Editor/View/Chemical Monitor and a window as shown below will be displayed.



	Name	Value
1	Formula	C9 H13 I
2	Smiles	CNCC(C
3	MolWeight	183.089
4	HBA	4
5	HBD	4
6	RotB	3
7	DrugLikeness	1.91
8	MolHf	-110.33
9	MolLogP	-0.11
10	MolLogS	-1.54
11	MolPSA	61.46
12	Volume	173.62
13	Bad Groups	
14	Groups	Phenyl Amine Alcohol (

Click here to label and highlight groups

The following properties are monitored.

- Molecular Weight (MolWeight)
- Number of Hydrogen Bond Acceptors (HBA)
- Number of Hydrogen Bond Donators (HBD)
- Number of Rotatable Bonds (RotB)
- DrugLikeness value Druglikeness is not based on other properties, this is separate model built using Bayesian Classifier. `http://www.molsoft.com/mpropdesc.html` − Normaly Bayesian classifier returns either 1 ot −1 (positive ot negative) So, roughly speaking: positive values means drug−like, negative − not.
- Preidction model build for 'delta Hf in gas' property. using public NIST database. Description can be found: `http://webbook.nist.gov` A low dHf value means that the compound is more 'stable'.
- LogP
- LogS

- Polar Surface Area (PSA)
- Volume
- Formula
- Smiles String
- Bad ADME−Tox Groups

The rows in the monitor window are colored from green (good) to red (poor) ADME−Tox properties.

17.3.6 Editing structure using keyboard

You can select a fragment or simply position your mouse cursor over a bond or atom and use the following keystrokes for editing:

- **Changing atom properties**
- `d` set/unset heavy *atom* **connectivity** as drawn to avoid additional branches in chemical searches. Toggle.
- `r` set/unset the **"in−ring"** property of *atoms.* Toggle.
- `y` set/unset *atom* h**y**bridization type (*sp1*,sp2,sp3). Toggle.
- `A` set *atomic* property to be **aliphatic**
- `a` set *atomic* property to be **aromatic**
- `*` (asterisk) set *atomic* property to be **any atom**
- `C` Carbon
- `H` Hydrogen
- `N` Nitrogen
- `O` Oxygen
- `F` Fluorine
- `P` Phosphorus
- `S` Sulfur
- `I` Iodine
- **Changing chemical bonds**
- `1`,− (dash) **single** *bond.*
- `2`,= (equal) **double** *bond.*
- `3`,# (hash) **triple** *bond.*
- `4`,: (column) **aromatic** *bond.*
- `0`,~ (tilde) **any** *bond*
- **Changing R−Groups**
- `Press` 1 to mark an atom as R1
- `Press` Ctrl−1 to preserve its type and create [C;R1]
- `Press` Ctrl−0 to remove the mark.

17.3.7 Save and Append Chemical Structures

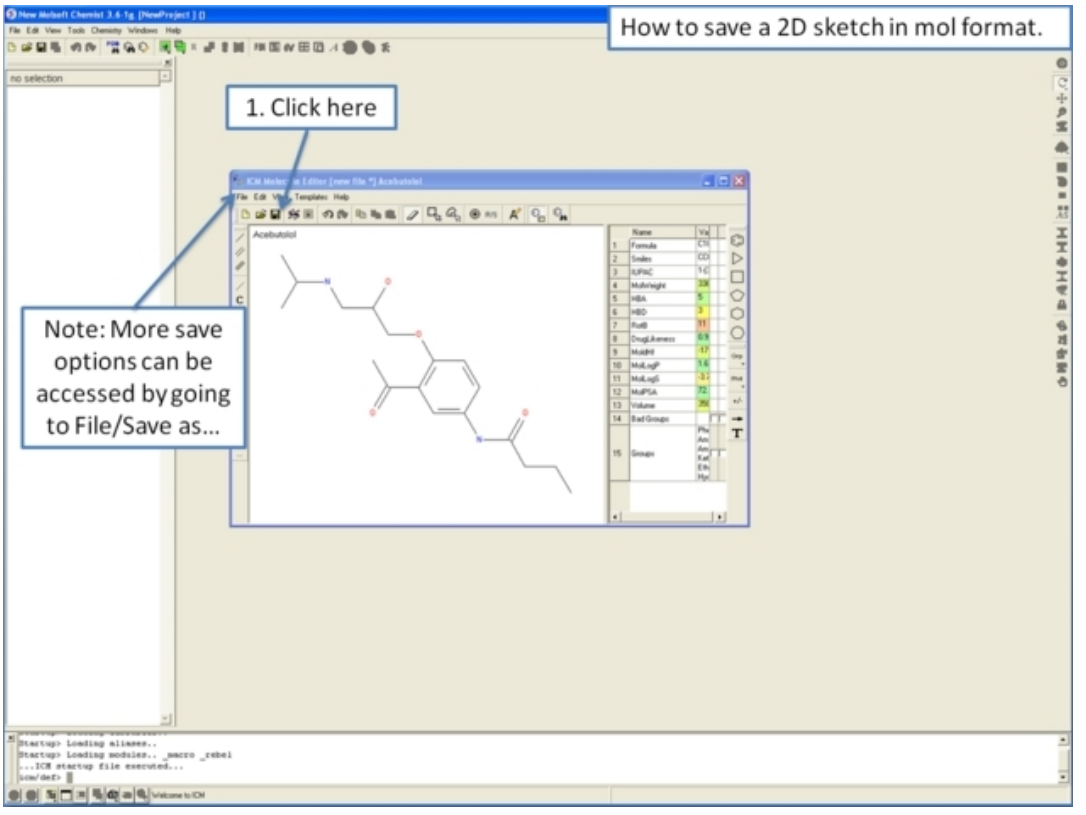
Once you have drawn a chemical structure `(see Drawing a New Chemical Structure)` then you can save the structure in the following ways:

1. By saving the structure as a MOL file or SDF file on your machine or server.
2. Appending the structure to an already created SDF file.
3. Appending the structure to an ICM Molecular table.

To save the structure as a MOL or SDF file on your machine or server.

- In the Molecular Editor window select File/Save
- Enter a filename and select where you wish to save the file.

> **NOTE:** Other save options can be found on the ICM Molecular Editor Toolbar.



To append the structure to an already created sdf file.

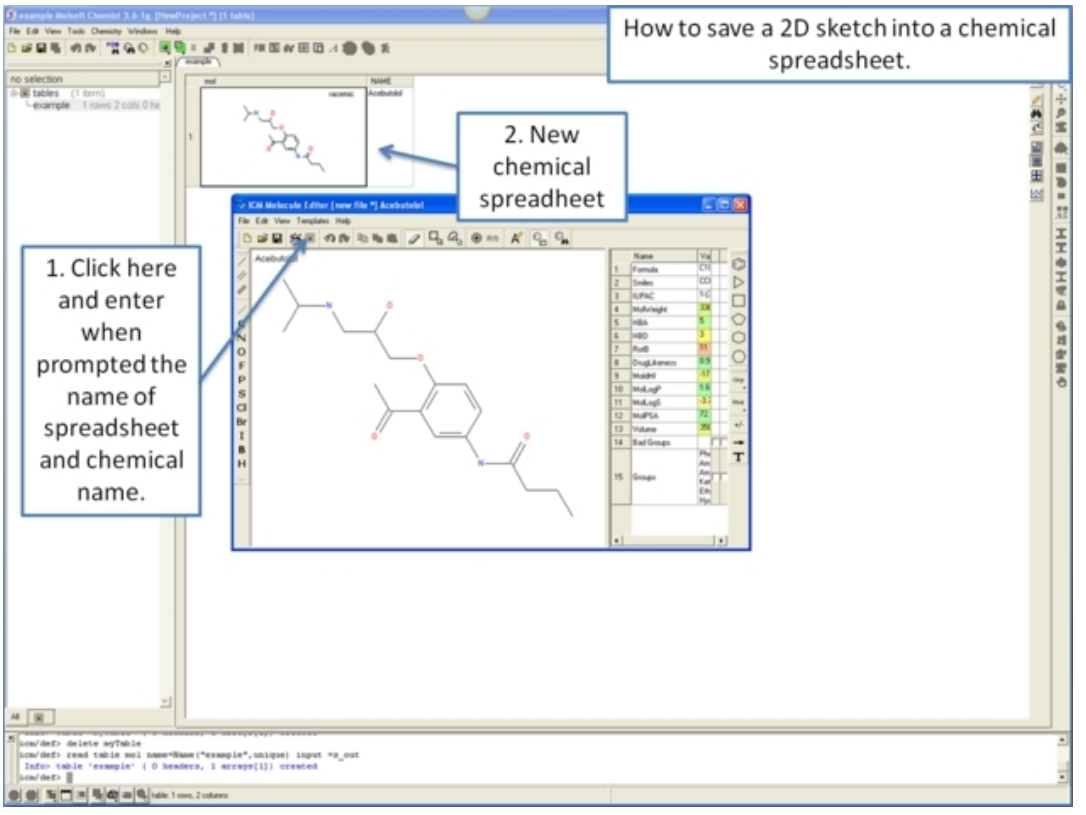
- In the Molecular Editor window select File/Append to SD file...
- Search for the SDF file you wish to append to and select OK. This SDF file can be read into ICM as described in `Read Chemical Structure` section of this manual.

To append your structure to an ICM table:

- In the Molecular Editor window select File/Append to table
- A list of loaded ICM tables will be displayed as shown below. If you dont have any ICM table loaded or you wish to add the structure to a new table select the "new" option.
- The structure will be automatically added to an ICM table and displayed in the GUI.

OR

- Click click on the append to table button in the editor (see below).



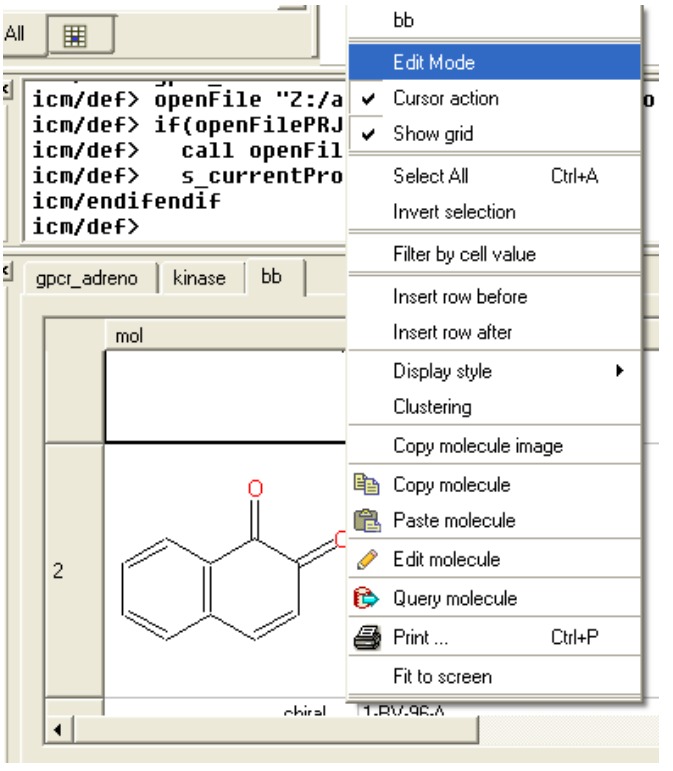
NOTE: For more information on how to manipulate standard ICM Tables and Molecular Tables see the `Table` section of this manual.

17.3.8 Editing a Chemical Structure

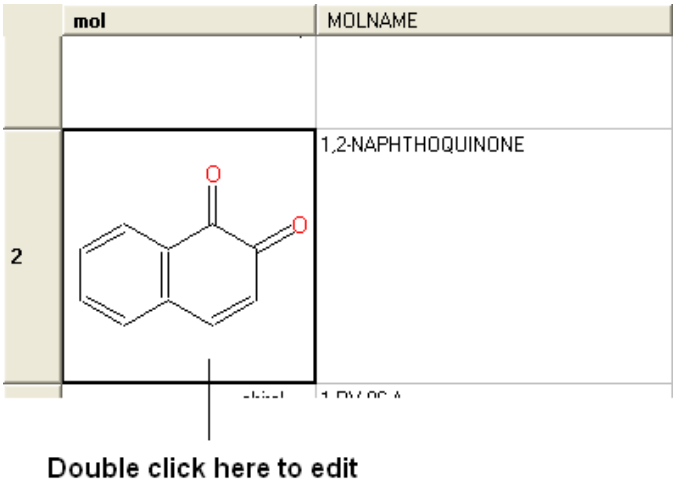
If you make a mistake whilst drawing a chemical structure or if you wish to change an already saved and loaded structure there are a number of editing tools and techniques which can be used.

To edit a structure which is in a loaded ICM molecular table:

- Right click on the structure in the table and a menu as shown below will be displayed.

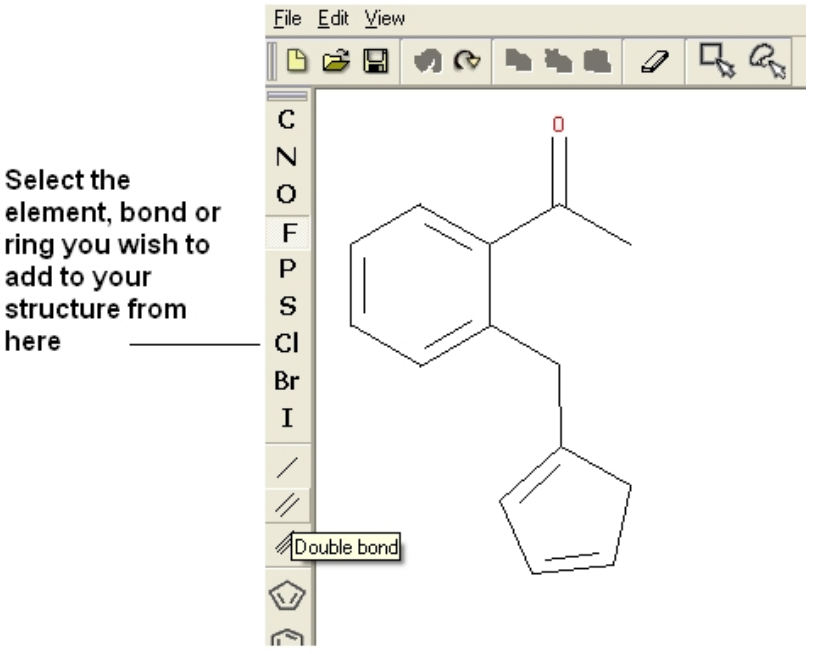


- Select the Edit Mode and a black square will be displayed around the chemical you wish to edit.
- Double click on the structure and the ICM Molecular Editor will be activated.

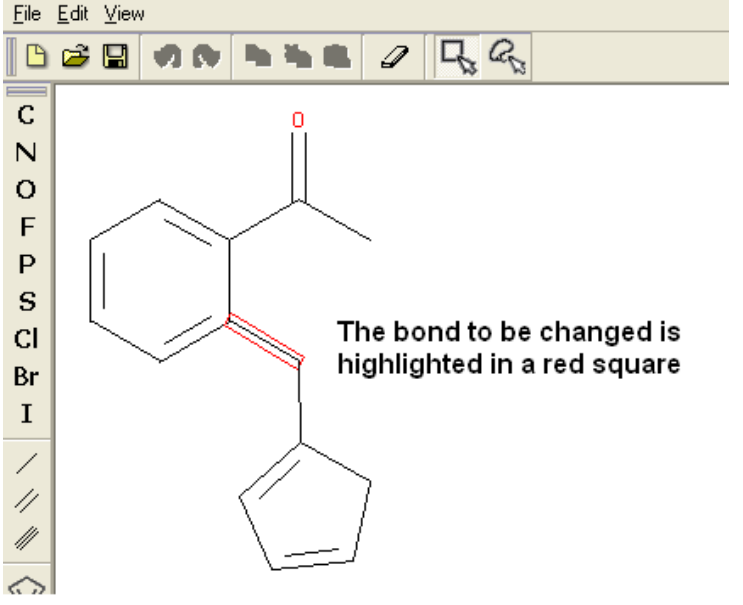


To edit a bond or atom in the structure:

- First select the new bond, atom or ring from the buttons on the left of the ICM Molecular Editor.



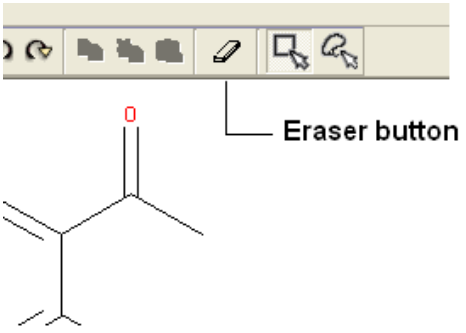
- Hover over the element or bond you wish to change in the ICM Molecular Editor workspace. A red square will be displayed over the bond or element you select as shown below.



- Click on the bond or element and it will automatically change to your selection.

To delete parts of a structure:

- Select the eraser button on the ICM Molecular Editor Toolbar.



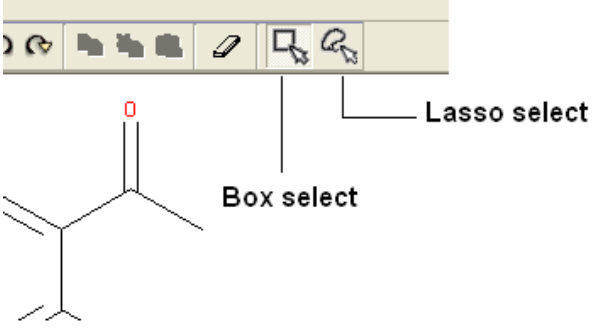
- Click on the regions you wish to delete.

Alternatively you can select the delete option in the ICM Molecular Editor "Edit" menu.

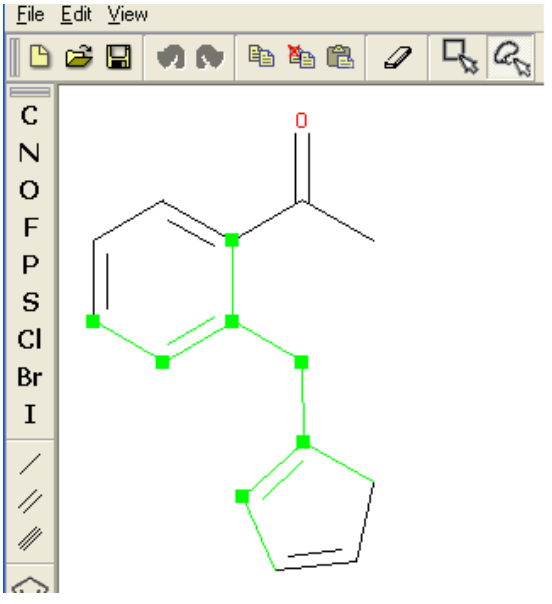
NOTE: A quick image can be constructed using the camera button A quick image can be constructed using the camera button as described in the TIPS section of this manual .

17.3.9 Molecular Editor Selections

Selections can be made in the ICM Molecular Editor using the two buttons shown below.



Selections are displayed in green.

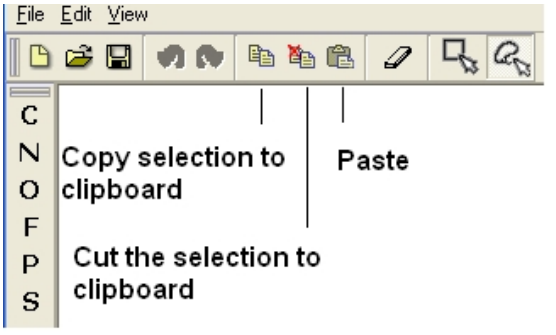


17.3.10 Copy, Cut and Paste

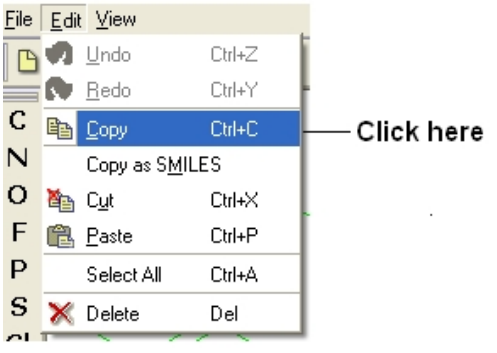
To copy, cut and paste part or all of your structure.

- First select the parts you wish to copy or cut by reading the instructions in the `Molecular Editor Selections` section of this manual.
- Select copy or cut from the ICM Molecular Editor "Edit" menu.
- The selected regions will then be placed on the copy clipboard and can be pasted into the ICM Molecular Editor or any other program.

The copy and paste buttons and menus are shown below:



OR



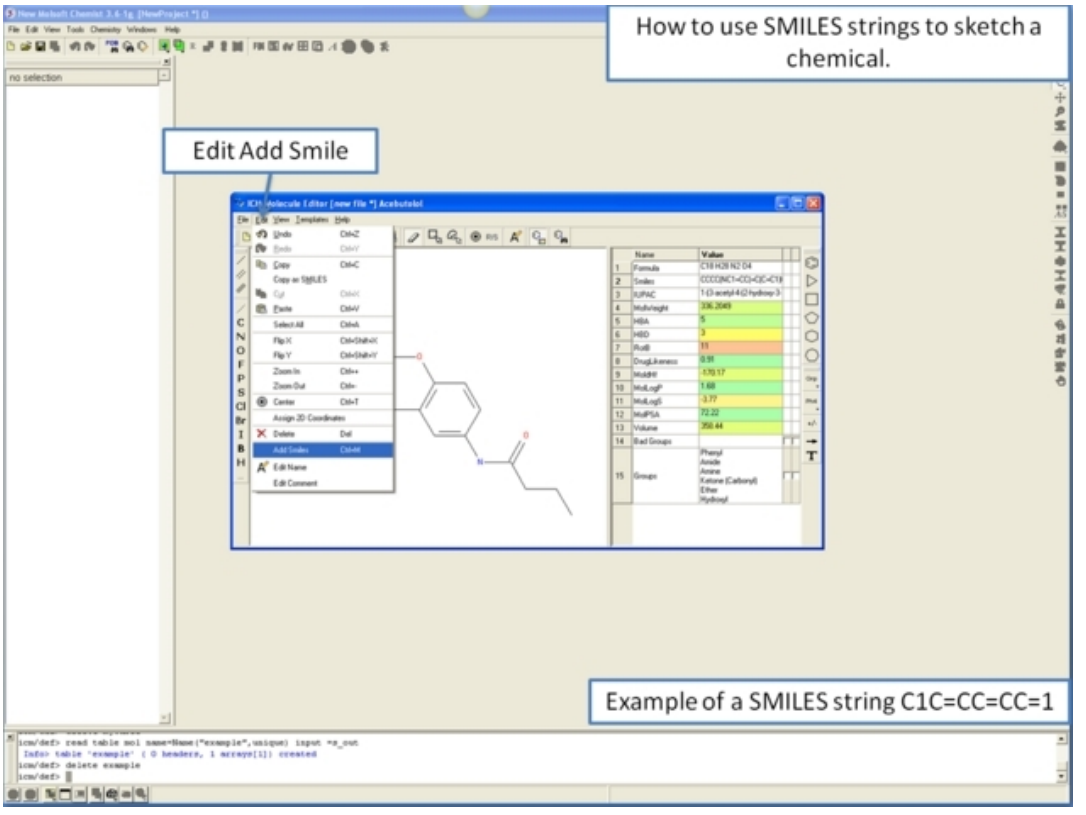
To copy your structure as a smiles string:

C1C=CC=C(C=1C(C)=O)CC(CC=C1)=C1

- Select the "Copy as SMILES" option in the ICM Molecular Editor "Edit" menu.

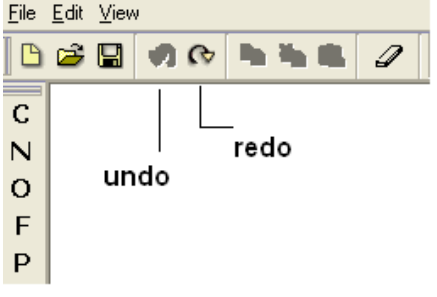
This will place the SMILES string on the clipboard which can then be pasted into any application.

17.3.11 How to use SMILES strings to sketch a chemical.

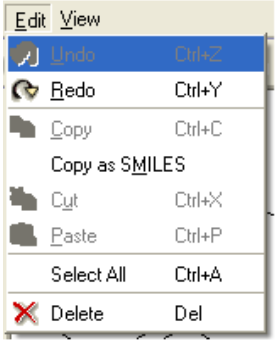


17.3.12 Undo and Redo

The undo and redo options for the ICM Molecular Editor are located in the Edit menu and on the toolbar as shown below.



OR



17.3.13 Isis Draw Copy and Paste

Molecules drawn in ICM can be cut and pasted into ISIS−Draw and vice−versa molecules from ISIS−Draw can be cut and pasted into ICM.

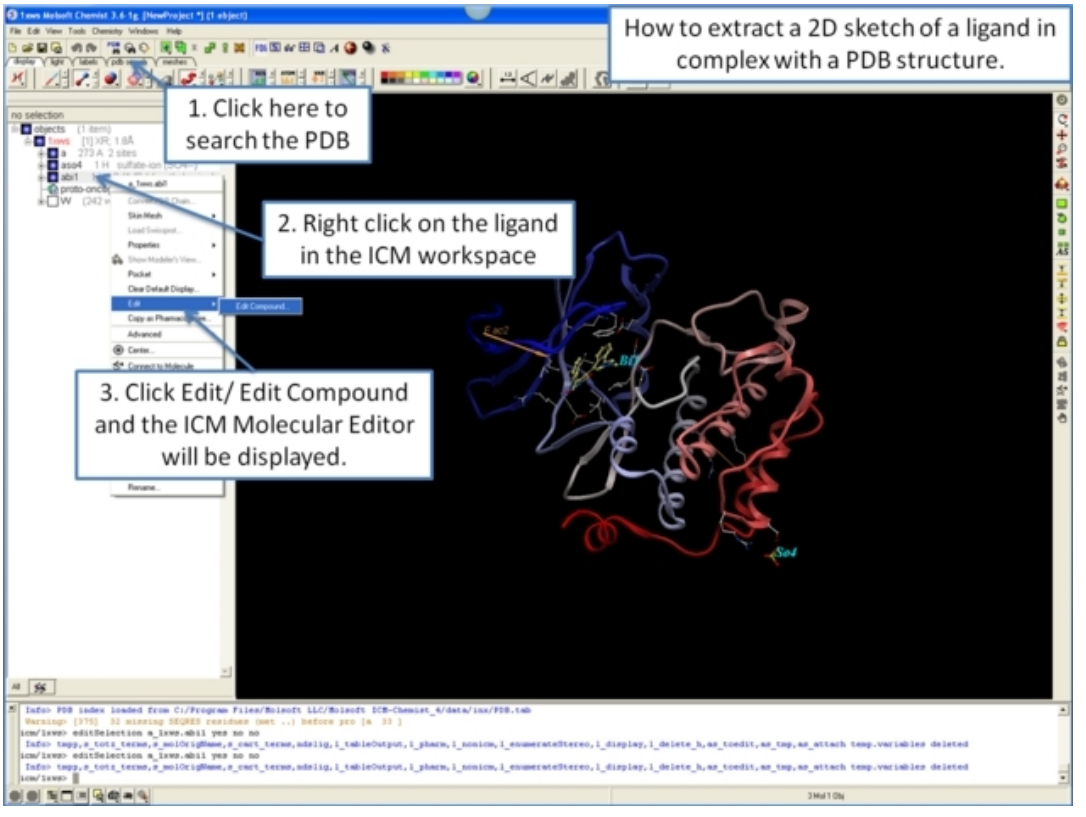
To perform these functions the correct settings need to be turned on in ISIS−Draw so that the compound drawing is saved in the clipboard.

IN ISIS−DRAW − Go to Options/Settings/General/Copy Mol Rxn file to the clipboard.

Compounds drawn in ISIS Draw can be cut and pasted into the `ICM Molecular Editor` and into ICM tables. Compounds can be copied in ICM by:

- Right click on the compound in the chemical table and select Copy Molecule.

17.4 How to extract a 2D sketch of a ligand in complex with a PDB strcture.



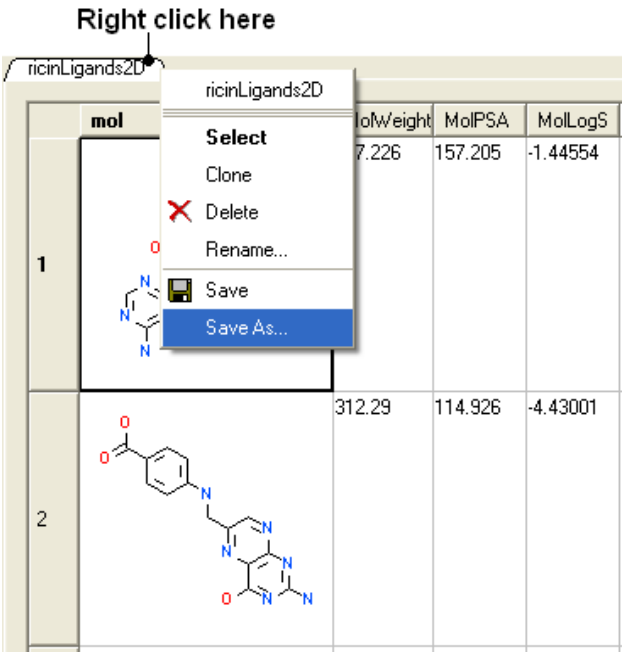
17.5 Saving Chemical Structures and Images

There are a variety of ways to save chemical structures. Chemicals can be saved in mol, sdf and smiles format from a `chemical table` (spreadsheet), `molecular edior` or from the `ICM−Workspace`. An `image` of the 2D sketch can be saved as an image from a chemical table.

17.5.1 Saving from a chemical table.

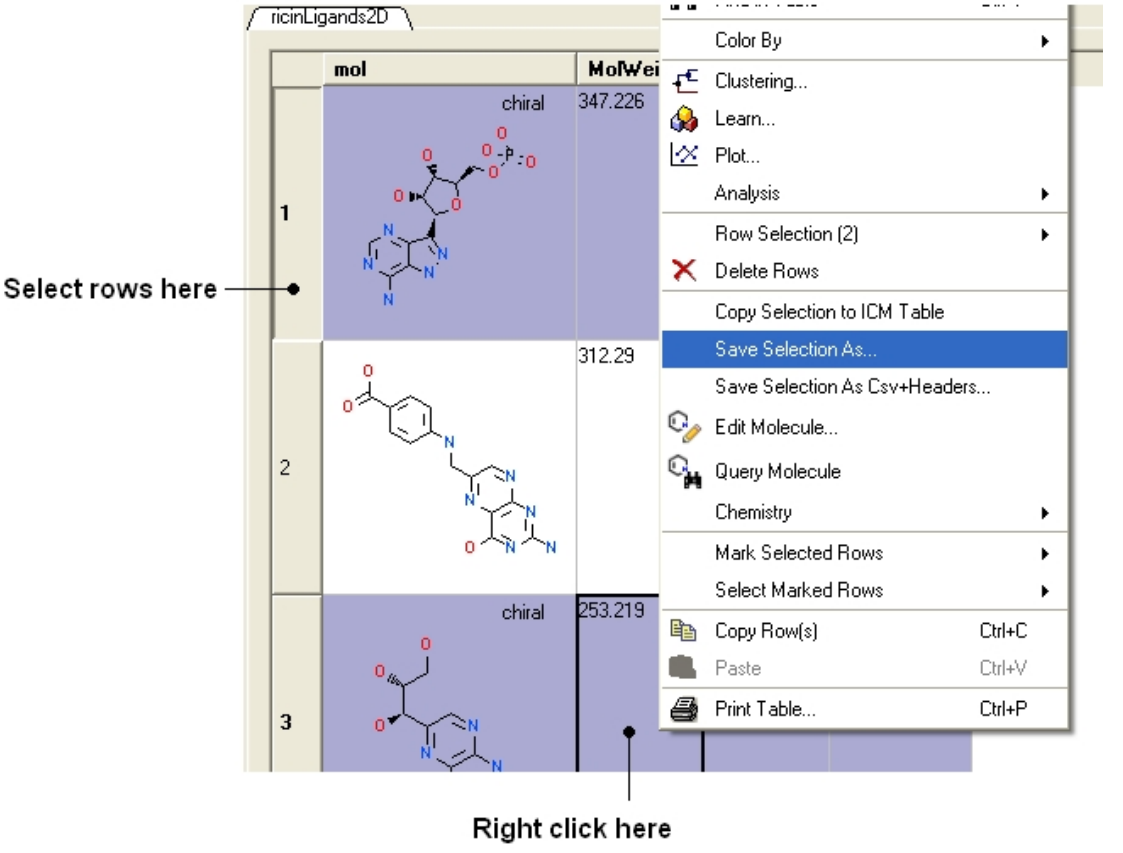
To save all the chemicals in a table as an SDF file:

- Right click on the chemical table header.
- Select **Save as..**
- Select **Save as type:** (SD file or Mol file_



To save selected chemicals in a table as an SDF file:

- Select the row(s) of the chemicals you wish to save in SDF format. Row selections in tables is described in the `Tables` chapter.
- Right click on any of the selected rows and select **Save Selection As...**.



17.5.2 Saving in the Molecular Editor

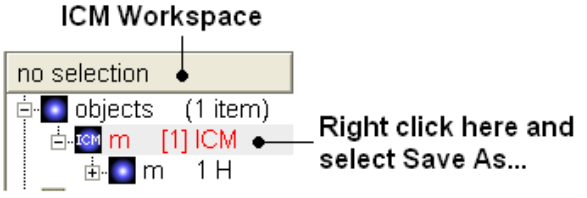
Chemicals drawn in the `ICM Molecular Editor` can be saved:

- **File/Save** or **File/Save As...** or **Edit/Copy as SMILES**

17.5.3 Saving in the ICM Workspace

If you have `converted` a chemical sketch into 3D, the 3D structure will be displayed in the ICM Workspace. To save this structure in mol format:

- Right click on the name of the chemical in the ICM Workspace.
- Select **Save As..**

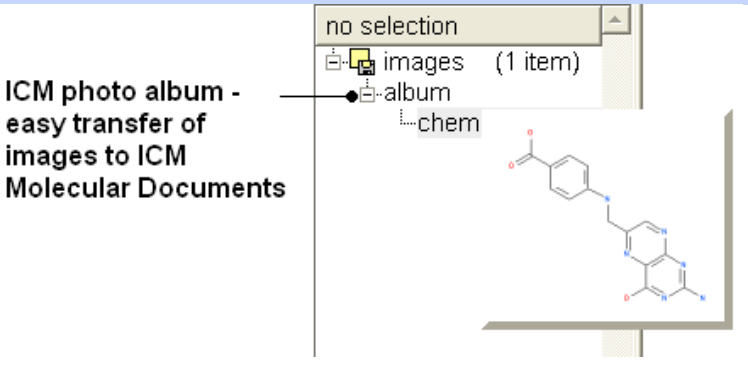


17.5.4 Saving Chemical Images

To save an image of a chemical sketch:

- The chemical needs to be displayed in a `chemical table`.
- Right click on the 2D image
- Select **Save Molecule As Image**

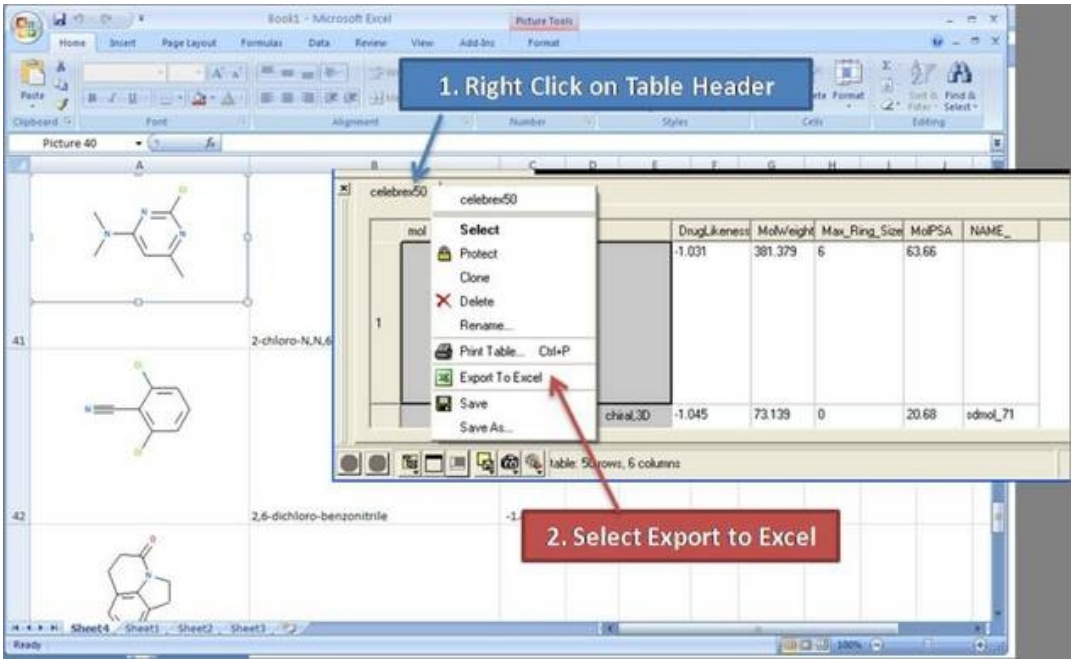
NOTE Using the right click options you can also save the image to the **clipboard** or copy the molecule to the `ICM Image Album` for use in `Molecular Documents`.



17.6 Export to Excel

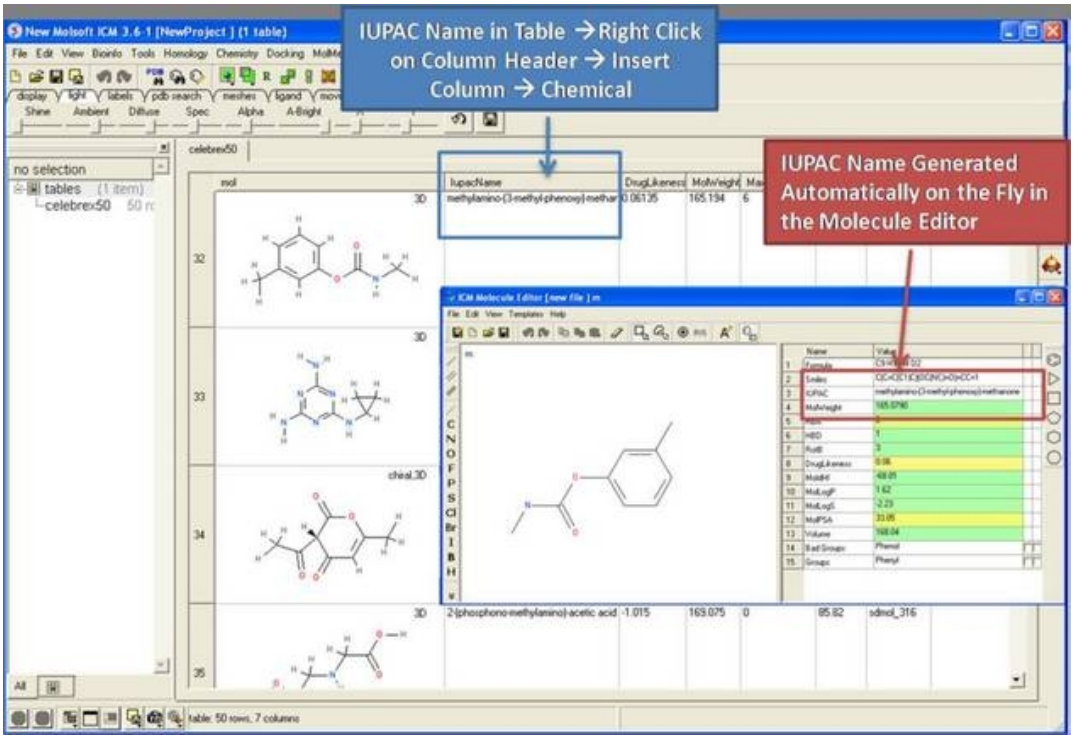
To export a chemical spreadsheet to MS Excel:

- Right click on the chemical spreadsheet header in ICM.
- Select **Export to Excel**



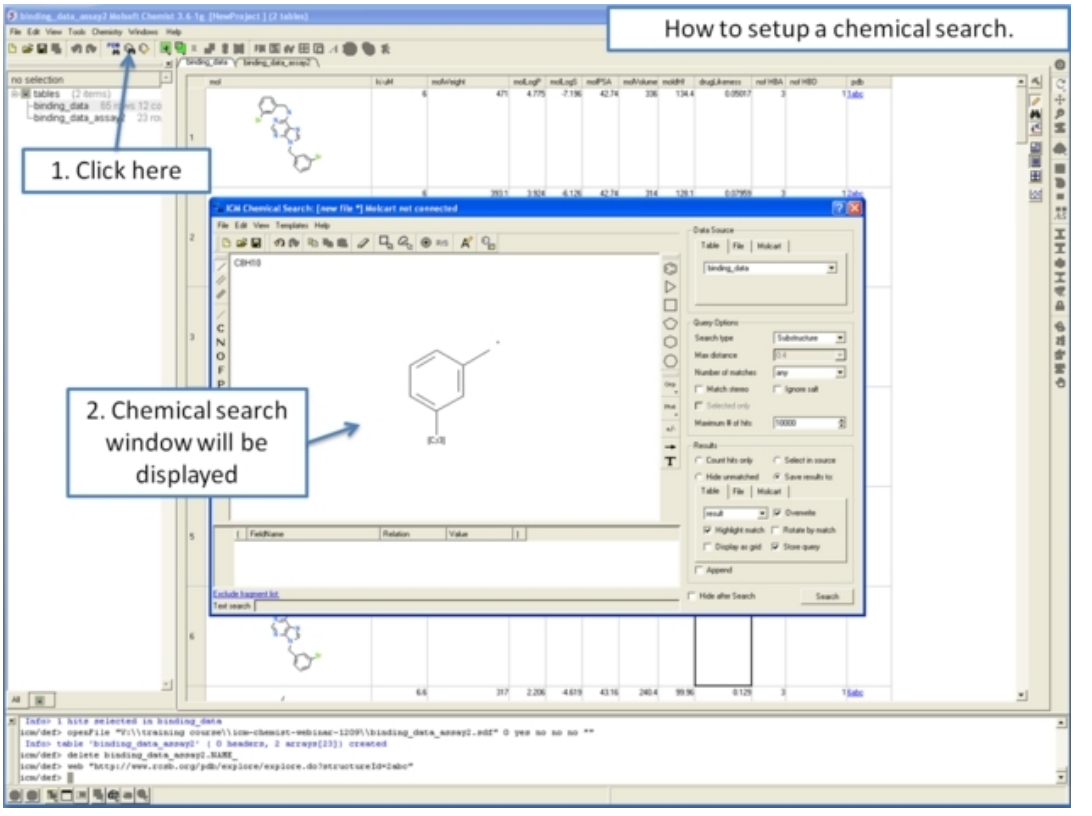
17.7 IUPAC Chemical Nomenclature

The `IUPAC` nomenclature for a compound can be generated on the fly for a chemical. You can view the IUPAC name in the `Molecule Editor` or you can `insert` a column into a chemical spreadsheet with the IUPAC name.

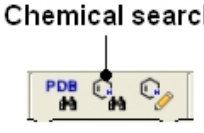


17.8 Chemical Search

Chemical similarity searching can be used to screen a database of compounds for structural similarity to a query chemical structure. The chemical similarity search window is shown below.



To access this window use the Tools/Chemical Search menu or select the button shown below.



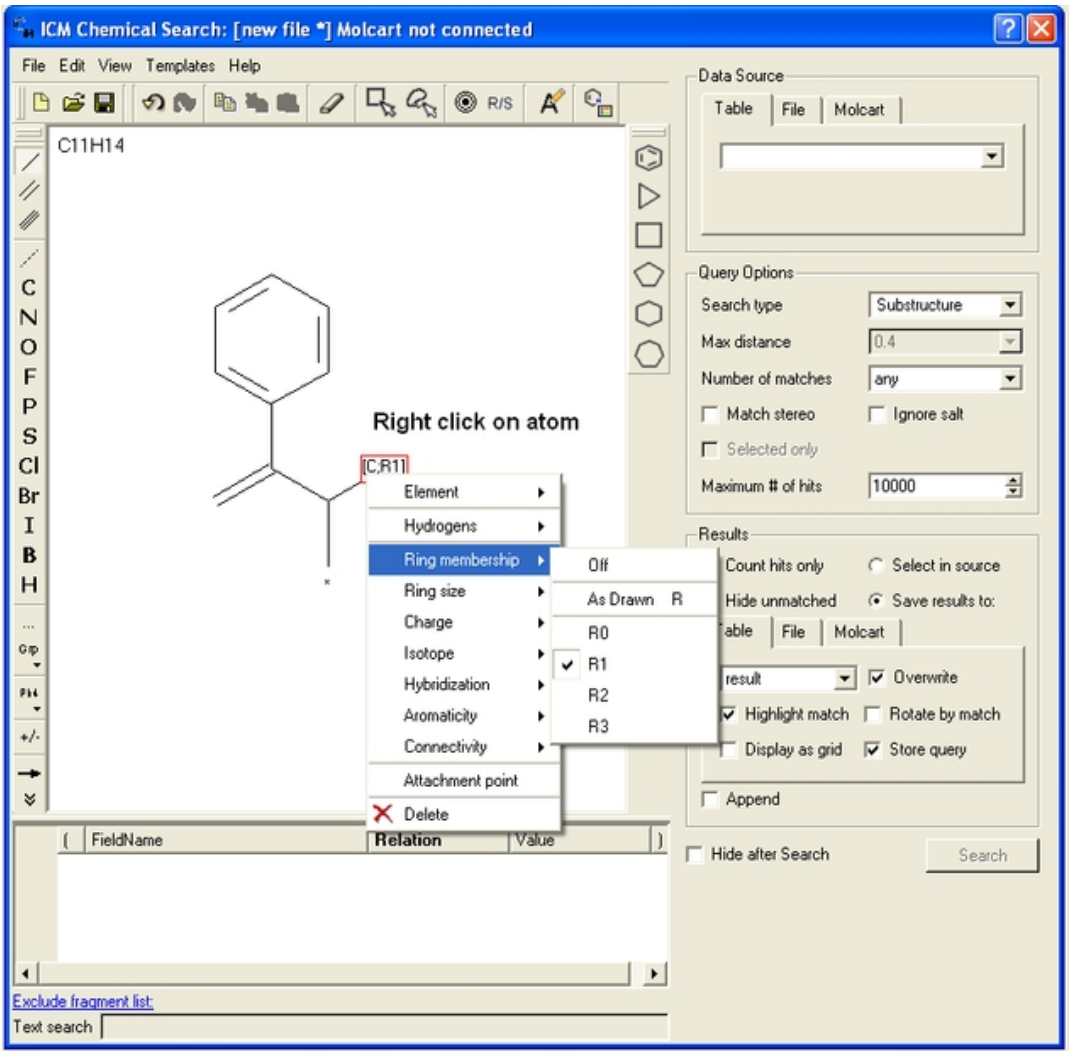
17.8.1 Query Setup

To set up a query first you must have either drawn or loaded a chemical structure into ICM. Instructions for this are described in the `Reading Chemical Structures` and `Molecular Editor` sections of this manual. If for example the query molecule you want to search is in a chemical spreadsheet you can right click on chemical in the spreadsheet and select **Query Molecule**.

At this point your query can be modified as described in the `Molecular Editor` sections of this manual. **However**, there are a number of ways to specifically modify your query and filter your search. The way to accomplish this is to right click on a bond or atom and a menu as displayed below will be displayed. The menus differ depending on whether you right click on a bond or atom.

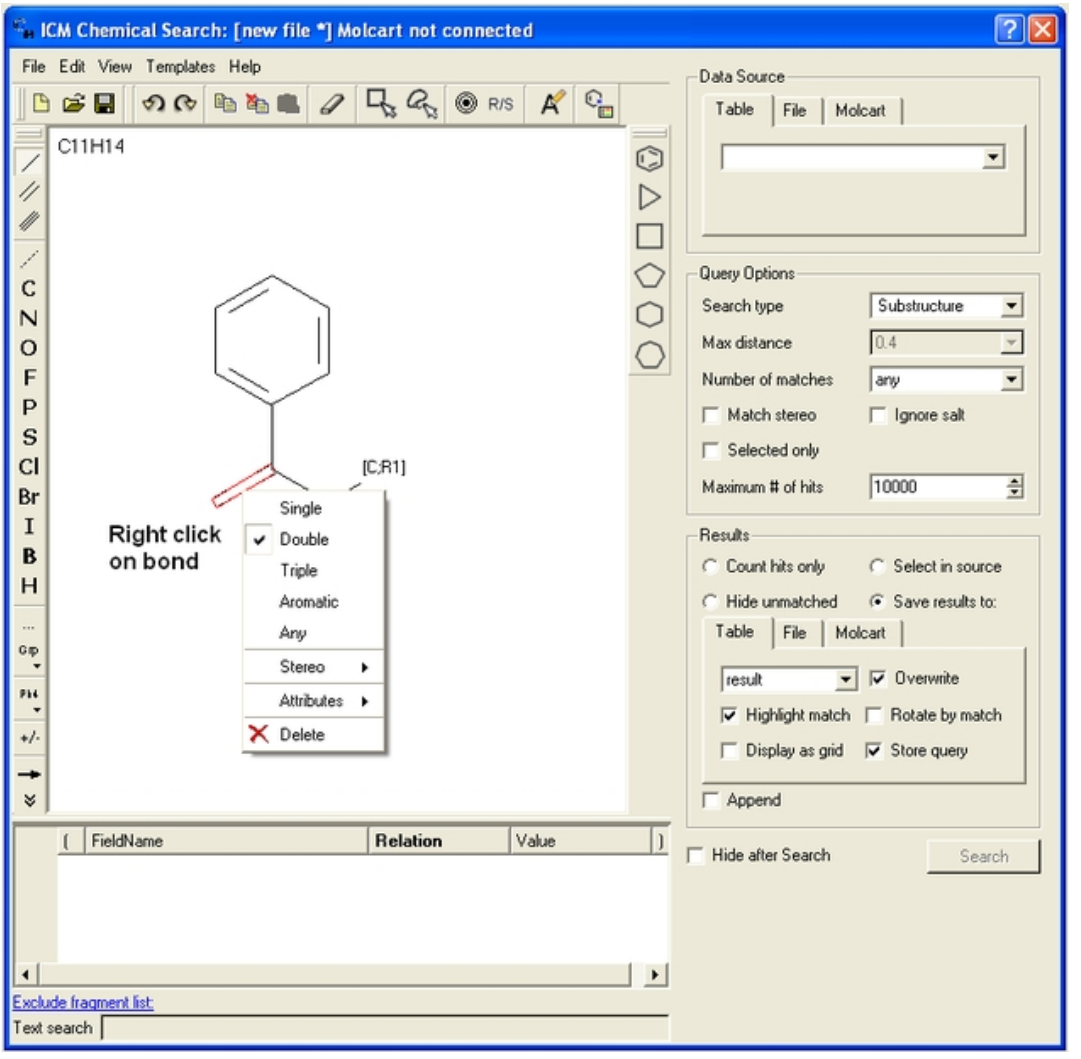
If you wish to specify a filter at an atom.

- Right click on the atom and the menu shown below will be displayed.



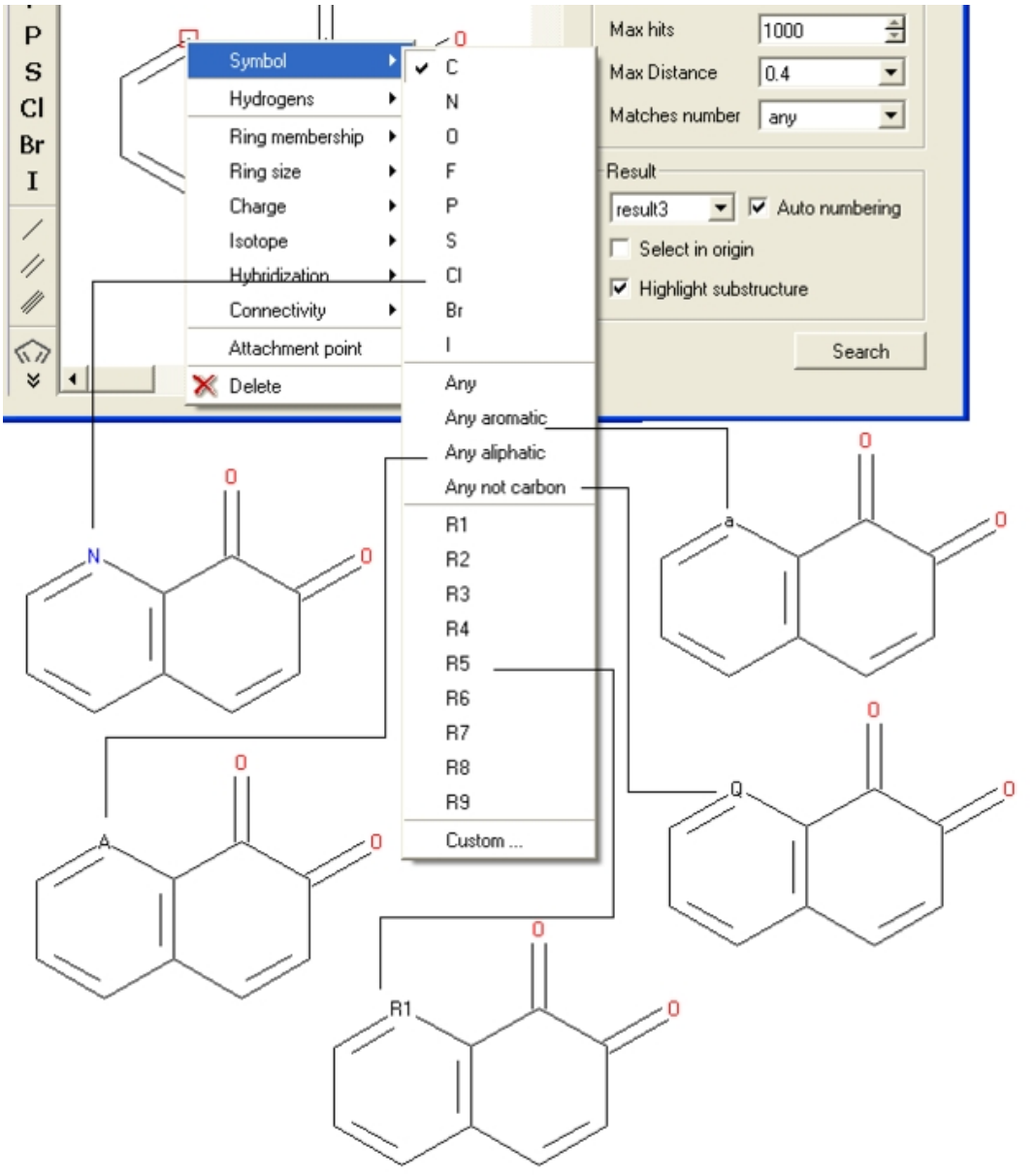
If you wish to specify a filter at a bond.

- Right click on the bond and the menu shown below will be displayed.



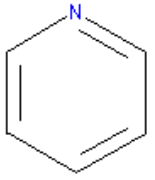
To specify a particular atom type, aromatic, aliphatic or R−group at a particular atom site.

- Right click on the atom and select the "symbol" option as shown below.
- Select the desired atom type, aromatic, aliphatic or R−group and a symbol will be displayed as shown below.


P
S
Cl
Br
I
Symbol
Hydrogens
Ring membership
Ring size
Charge
Isotope
Hybridization
Connectivity
Attachment point
Delete
C
N
O
F
P
S
Cl
Br
I
Any
Any aromatic
Any aliphatic
Any not carbon
R1
R2
R3
R4
R5
R6
R7
R8
R9
Custom ...
Max hits
1000
Max Distance
0.4
Matches number
any
Result
result3
Auto numbering
Select in origin
Highlight substructure
Search
N
A
a
Q
R1

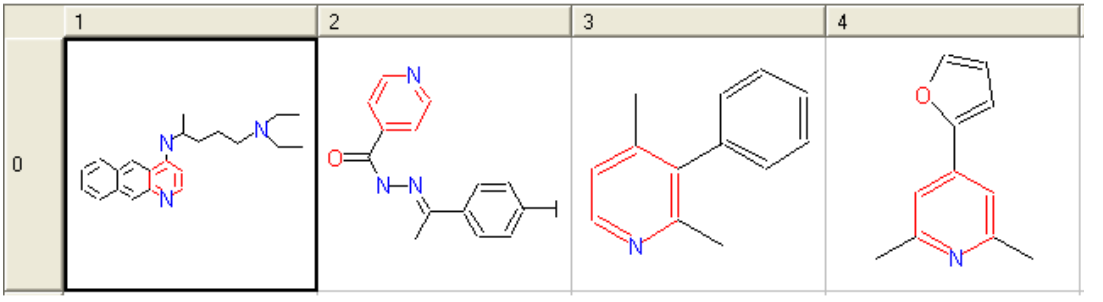
For example:

Query:



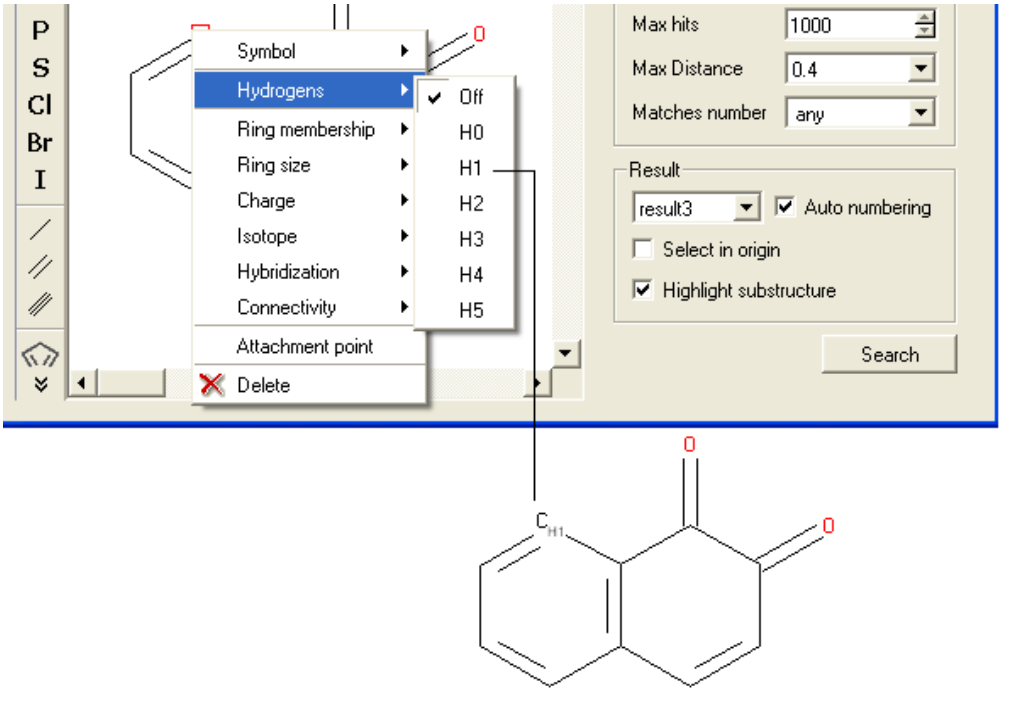
Right click atom - Symbol - N

Selection of chemical substructure search results



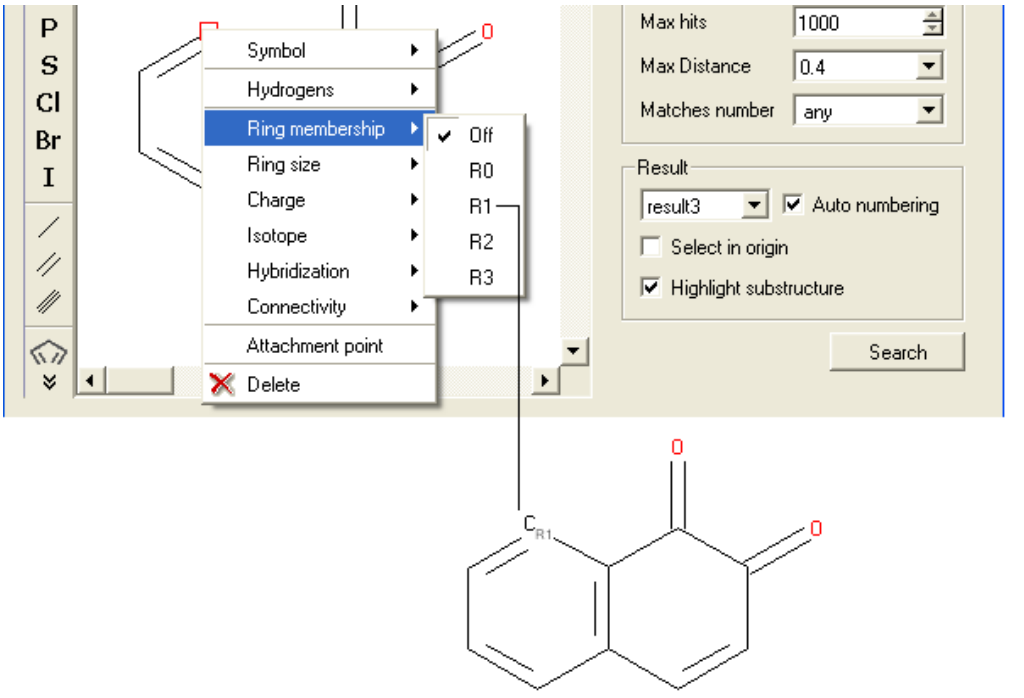
To specify a particular number of hydrogen atoms at a particular site:

- Right click on the atom and select the "Hydrogens" option as shown below.
- Select how many hydrogens you wish to specify and a symbol will be displayed as shown below.



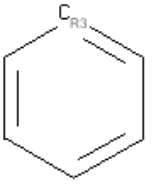
To specify the number of rings a particular atom will be a member of:

- Right click on the atom and select the "Ring membership" option as shown below.
- Select whether the atom should be part of 1, 2 or 3 rings.



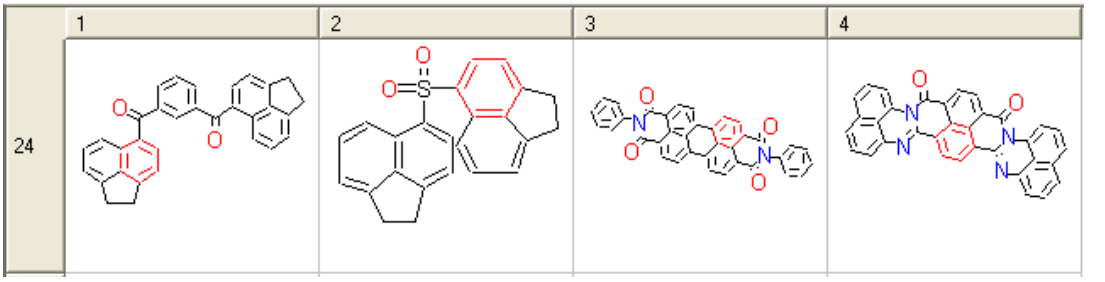
For example:

Query:



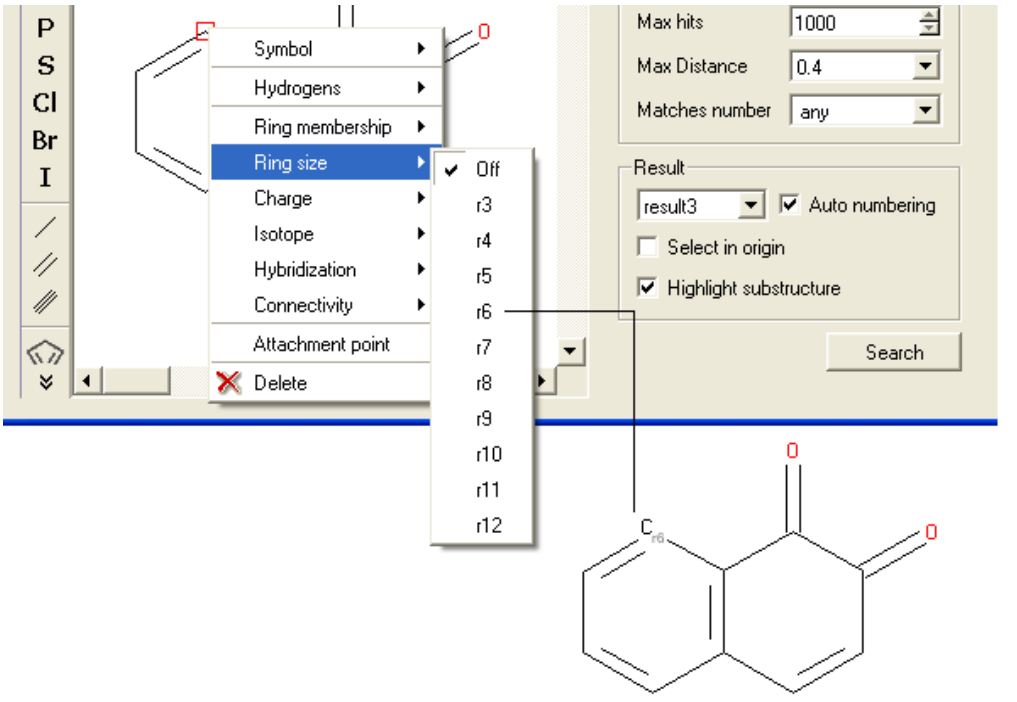
Right click atom - Ring Membership - R3

Selection of chemical substructure search results



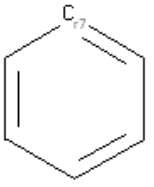
To specify the ring size connected to an atom:

- Right click on the atom and select the "Ring size" option as shown below.
- Select the size of the ring the atom should be connected to and a symbol will be displayed as shown below.



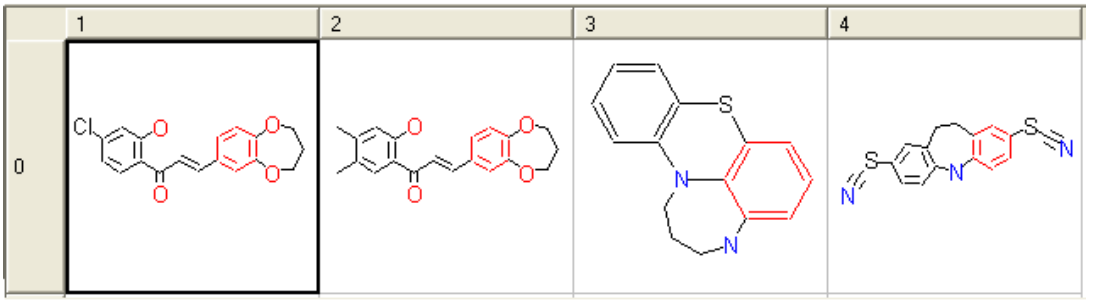
For example:

Query:



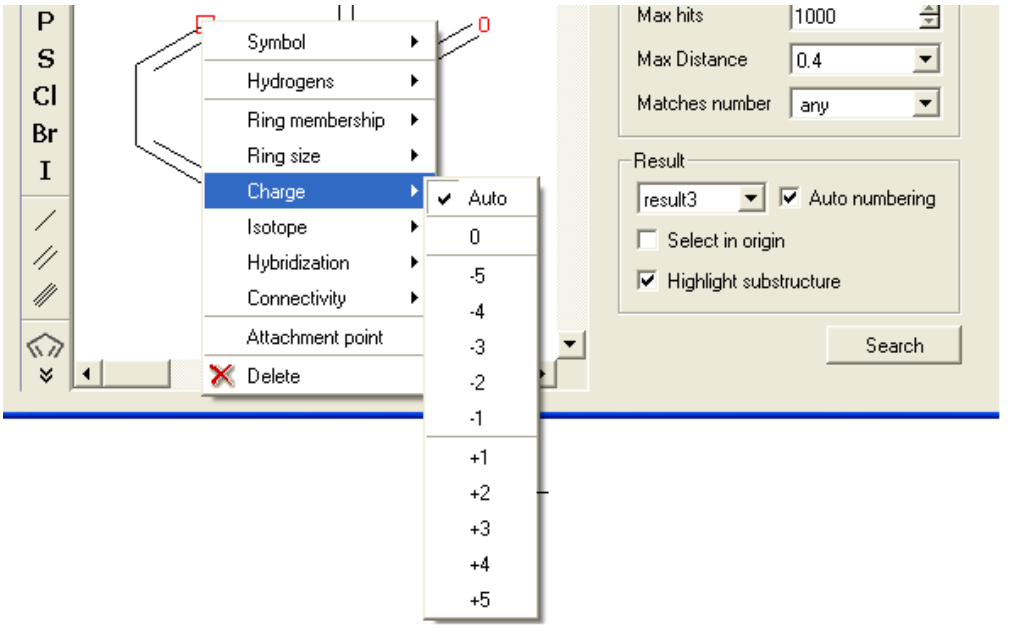
Right click atom - Ring size - R7

Selection of chemical substructure search results



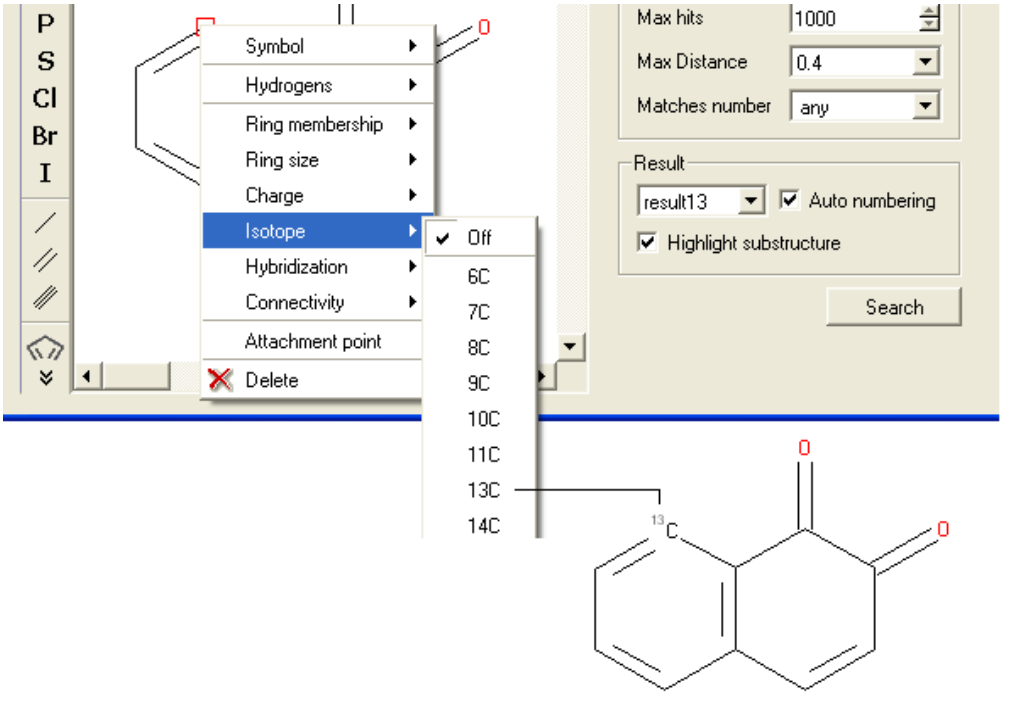
To specify the charge at a particular point:

- Right click on the atom and select the "Charge" option as shown below.
- Select the desired charge and a symbol will be displayed as shown below.



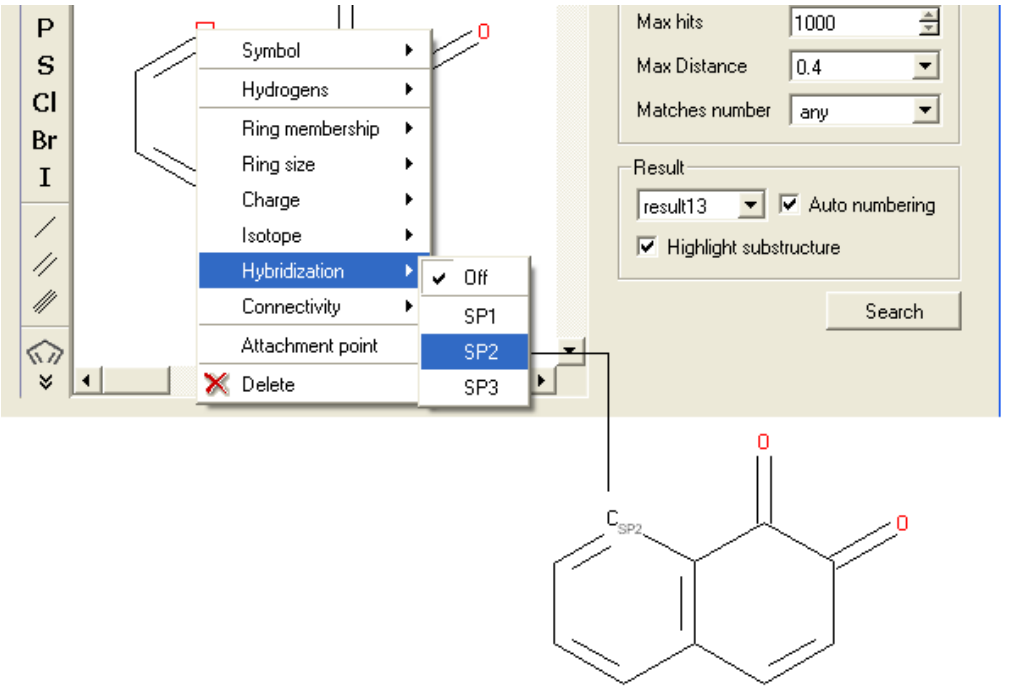
To specify an isotope at a particular atom

- Right click on the atom and select the "Isotope" option as shown below.
- Select the desired isotope from the list and a symbol as shown below will be displayed.



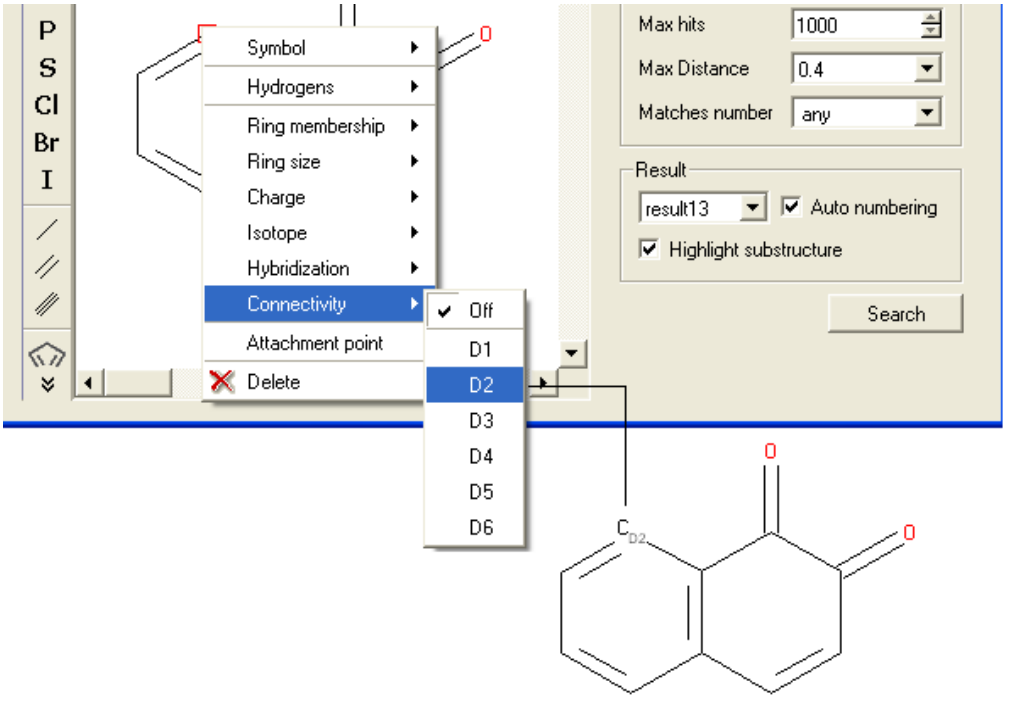
To specify the hybridization state of the atom:

- Right click on the atom and select the "Hybridization" option as shown below.
- Select the desired hybrization state and a symbol will be displayed as shown below.



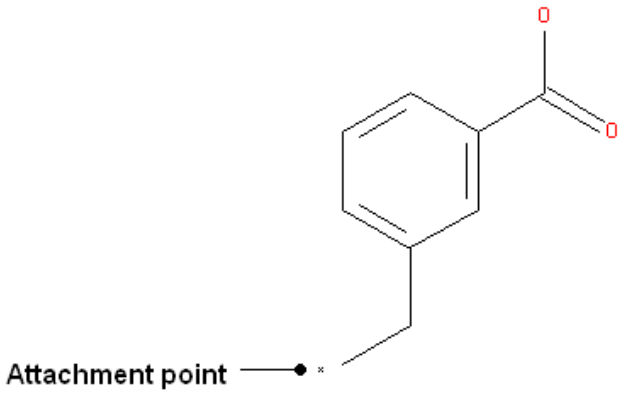
To specify the number of atoms you wish an atom to be connected to:

- Right click on the atom and select the "Connectivity" option as shown below.
- Select the number of atoms you wish the atom to be connected to and a symbol will be displayed as shown below.



To specify an attachment point − ie the position at which substituents will be added

- Right click on the atom and select the "Attachment point" option as shown below.
- An asterisk representing the attachment point will be displayed next to the atom.



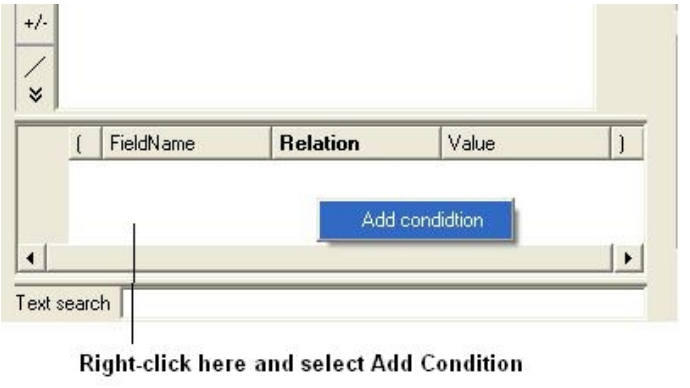
An attachment point means that the atom can be attached to zero or more bonds to heavy atoms.

17.8.2 Filter Search

How to filter your query

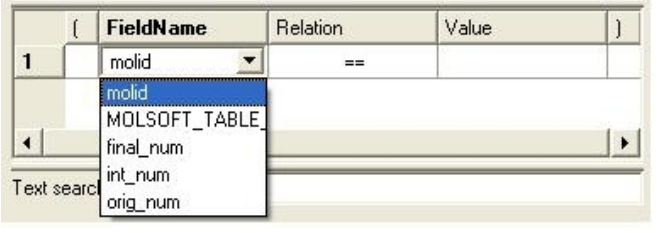
To filter your query:

- Right click in the box shown below and select 'Add Condition'



To add conditions to your filter:

- Double click in the fields labeled "Name" and "Relation" and select the options from the drop down arrow or type in values.

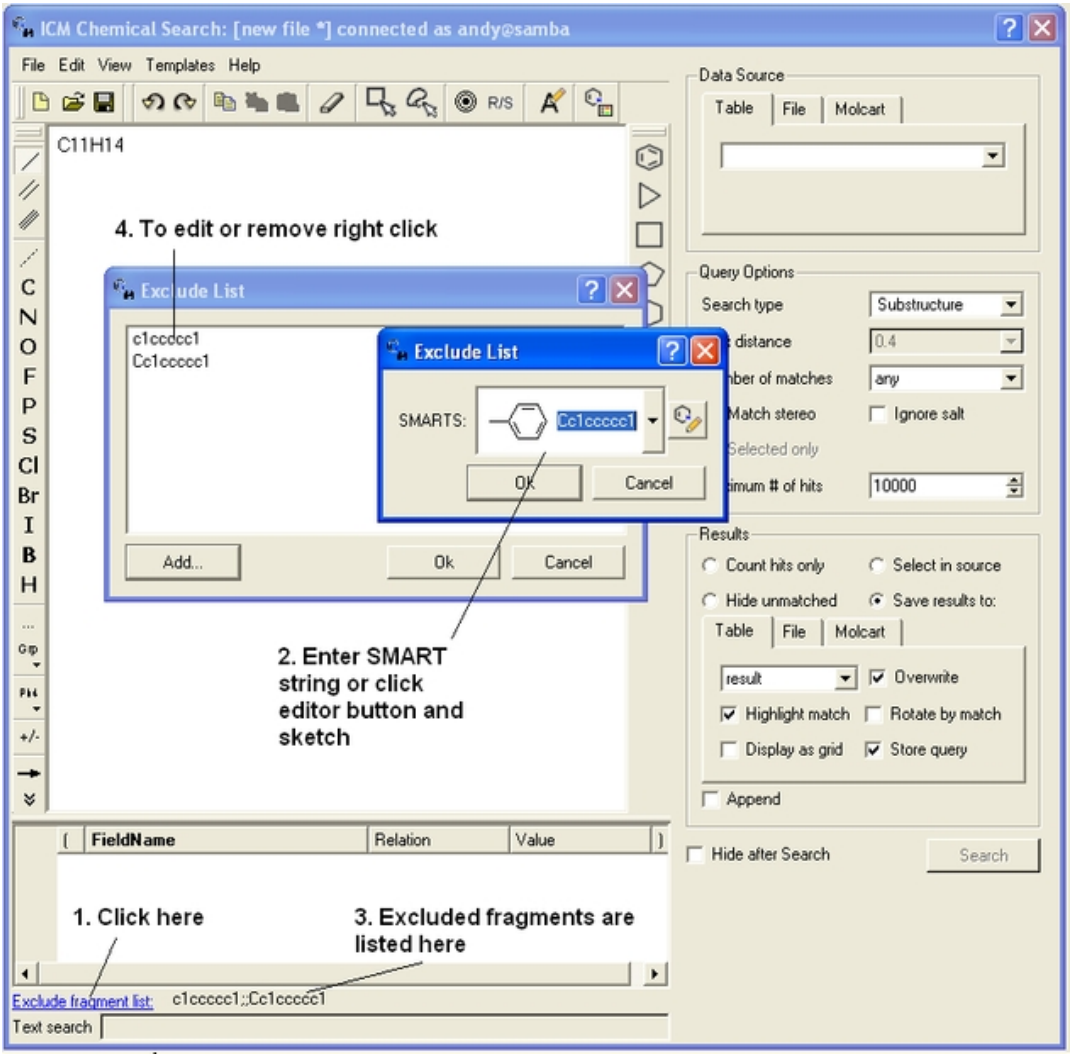


To remove a filter, right click on the filter and select 'Remove Filter'.

To exclude a fragment from your search

Click on the option **Exclude fragment list**:

- Enter the SMART string of the fragment or use the Molecular Editor option to sketch the fragment.
- Click OK and the fragment will be listed at the bottom of the chemical search window as shown below.



17.8.3 Query Processing

To begin processing your query first you need to decide which database to search. The options are listed in the **Data Source** section of the ICM chemical search window.

Data Source

You can either search a `Table– Chemical Spreadsheet` a `File – Local Database` or `MolCart`.

If you select **MolCart** you first need to setup the link to the correct database.

- Enter the Server Name in which the database is stored.
- Enter the database name.
- Enter your username and password for the server.
- You can save these details so you dont have to re−enter this information each time you use the chemical similarity search.

If you are searching a **Table**, click on the **Table** tab and then select the drop down button where the names of your currently loaded tables are stored.

If you are searching a **File** click on the **File** tab and then locate your `local database` file .molt or if it is already loaded into ICM you can locate it with the drop down button.

Query Options

Now select a search type:

- Click on the drop down arrow next to the "Search Type" option in the Query Options panel.
- Select the search type you want to use.

A **substructure** search is a search whereby only the defined molecule in the query will be searched against the database. Whereas, a **FP similarity** search which stands for fingerprint search enables any fingerprint within a structure to be searched for in the database.

The **Max distance** option is available for use with the FP search and the **Matches number** option is for use with the substructure search. The option you do not require based on your search method will be blanked out. A "Max distance" value of 0 means that the search will only identify matches exactly the same as the fingerprint − the default is 0.4. The "Matches number" option allows you to stipulate how many times within a structure in the database your query can be found.

You can match stereo by selecting the **Match stereo** option and **ignore salts**. If you make a selection of your query ICM can use that selection to search. How to make selections in the Molecular Editor are described `here`. Enter the Maximum number(#) of hits you would like returned.

Results

Before processing the query determine how you would like your results displayed in the **Results** section of the **Chemical Search** window.

Count hits only − this option will count the number of hits and display this number in a window once the searching has been completed.

Select in source − If you are searching a table you can select and highlight the query in the source table that you are searching.

Hide unmatched − Hide unmatched will hide the compounds that were not matched from view.

Save results to: − this option gives you the option to save the output results to a `Table− Chemical Spreadsheet` a `File −Local Database` or `MolCart`.

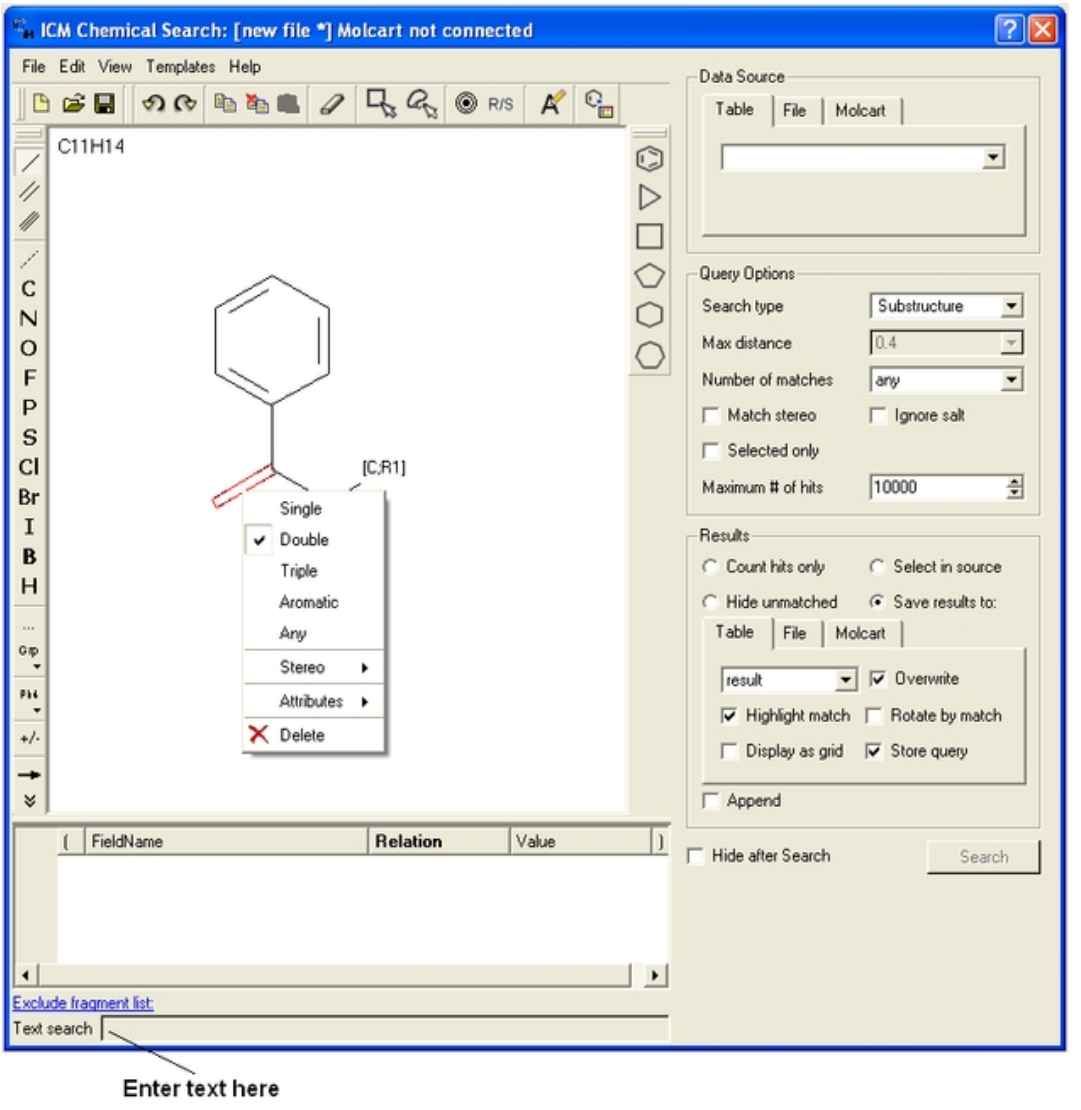
Append − this option will allow you to append to current table, file or Molcart database.

Search

- Click on the **Search** button to execute the search. You can choose to hide the window after the search.

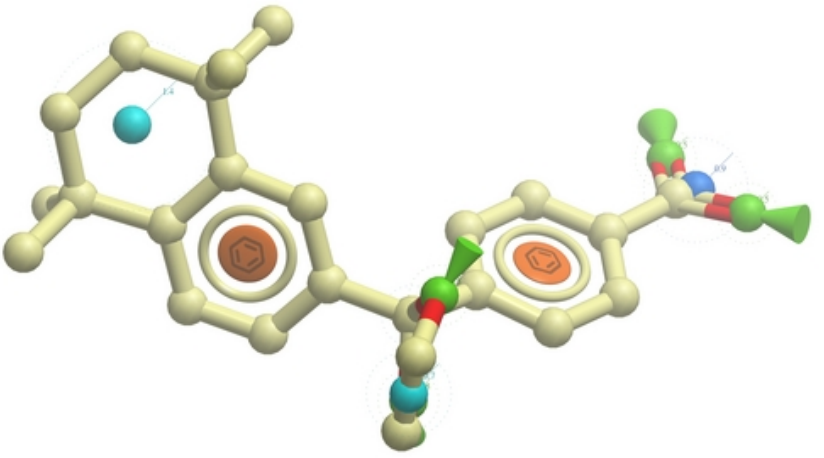
17.8.4 Search a Database by Text

To search a database by text enter the text you wish to search in the **Text Search** data entry box at the bottom of the ICM Chemical Search window.



17.9 Pharmacophore Drawing and Searching

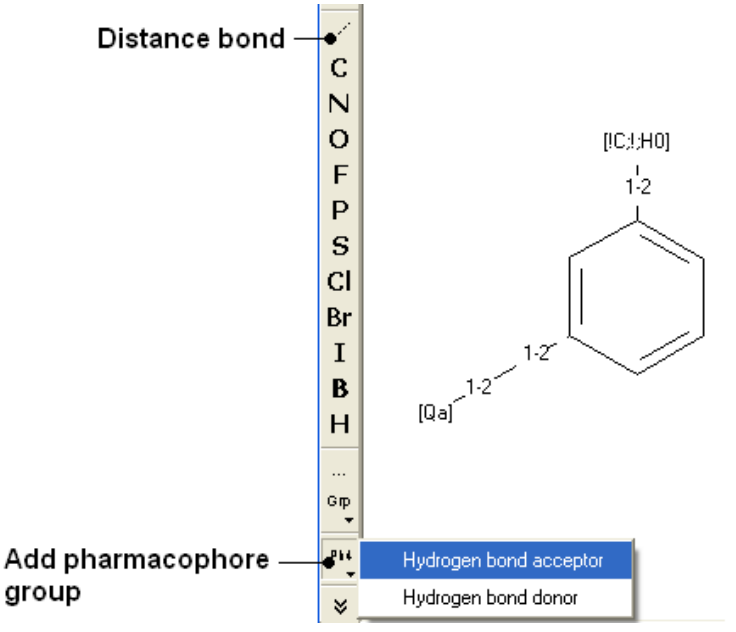
Pharmacophores can be drawn in 2D in the ICM Molecular Editor or in 3D in the Graphical Display. 2D pharmacophore sketches can be used to search chemical tables (spreadsheets) containing 2D or 3D coordinates. A 3D pharmacophore can be used to search chemical tables containing 3D coordinates only.



17.9.1 Pharmacophore Draw 2D

A 2D pharmacophore can be drawn using the `ICM Molecular Editor`or if you are going to use the drawing to search it is more efficient if you draw it in the `Chemical Search` window.

Use the distance bond button and the add pharmacophore group button to sketch the pharmacophore. The distance bond button represents the number of bonds between each pharmacophore point. You can edit the distance by right clicking on the bond and selecting edit. Other groups such as aromatic can be added using the standard molecular editor buttons.



NOTE: Do not mix the 2D and 3D pharmacophore environment. For example do not edit a 3D pharmacophore in the 2D editor.

17.9.2 Pharmacophore Draw 3D

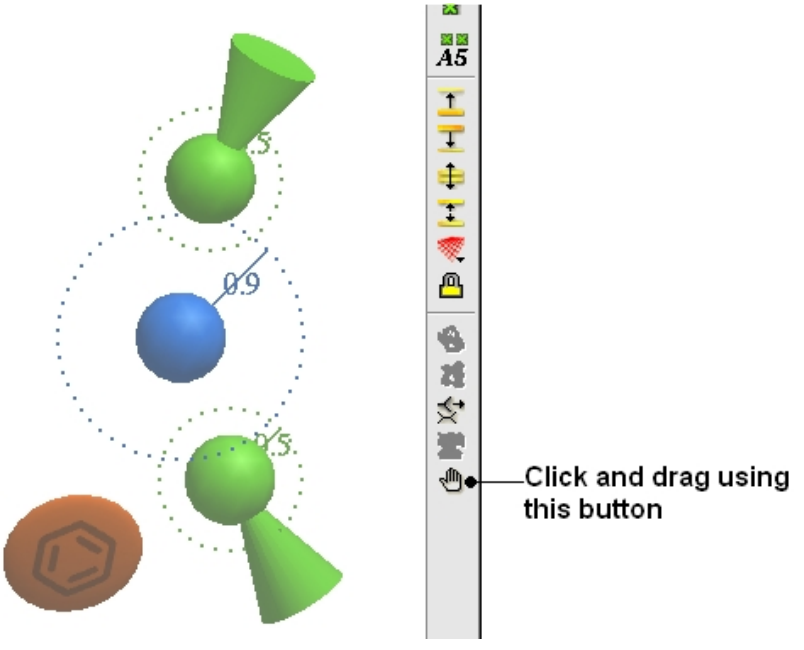
The easiest way to begin drawing a 3D pharmacophore is to draw a chemical in the `ICM Molecular Editor` which contains the key pharmacophore groups you want and then `convert to 3D` and extract the pharmacophore groups.

To draw a 3D pharmacophore this:

- Once the ligand is converted to 3D, right click on the ligand in the ICM Workspace.
- Select the option **Copy as Pharmacophore** and choose the **pharm centers** option.
- The pharmacophore groups or centers will then be displayed in the graphical display and can be displayed and undisplayed in the ICM workspace.

To move a pharmacophore group:

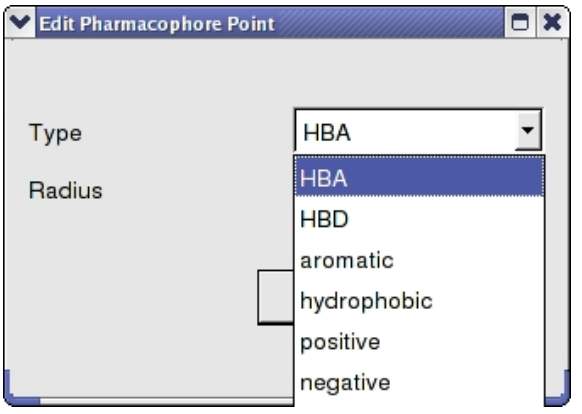
- Use the **drag atom** button (picture of a hand. See below)
- Click on the pharmacophore group and then drag.



NOTE: Distances between groups can be monitored using the atom distance measurement tool. See Calculating the distance between two atoms.

To change a pharmacophore group:

- Right click on the pharmacophore group in the ICM Workspace or in the Graphical Display.
- Select **Pharmacophore/Edit Point**
- Choose the group from the drop−down list shown below.
- Enter the desired radius.



To make a new pharmacophore group:

The easiest way to make a new pharmacophore group is to clone a pre−exisiting one. To do this:

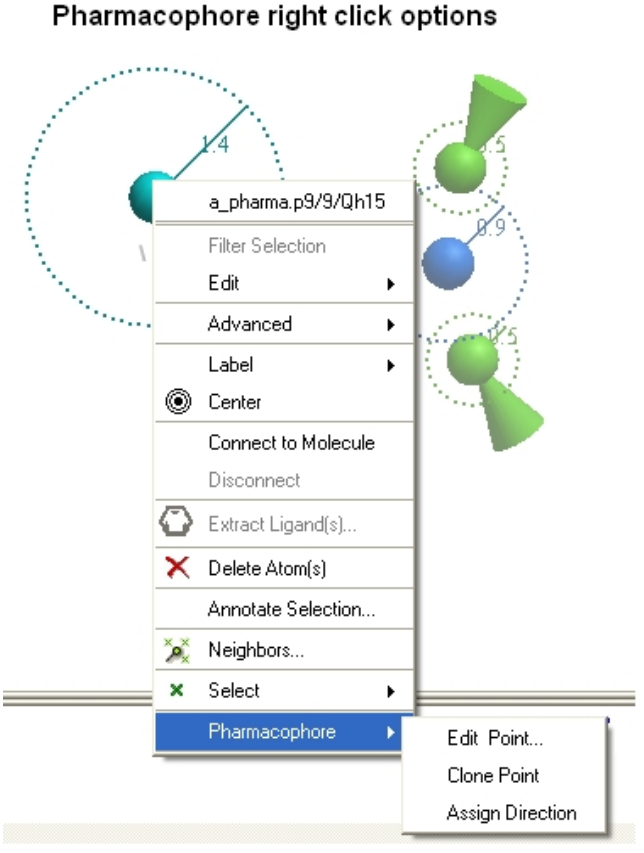
- Right click on the pharmacophore group in the ICM Workspace or in the Graphical Display.
- Select **Pharmacophore/Clone Point**
- You can then move the new group as described above.

To change the direction of a pharmacophore group:

- Right click on the pharmacophore group in the ICM Workspace or in the Graphical Display.
- Select **Pharmacophore/Assign Direction**
- You can then move the new group using the drag atom button described above.

To remove the direction of a pharmacophore group:

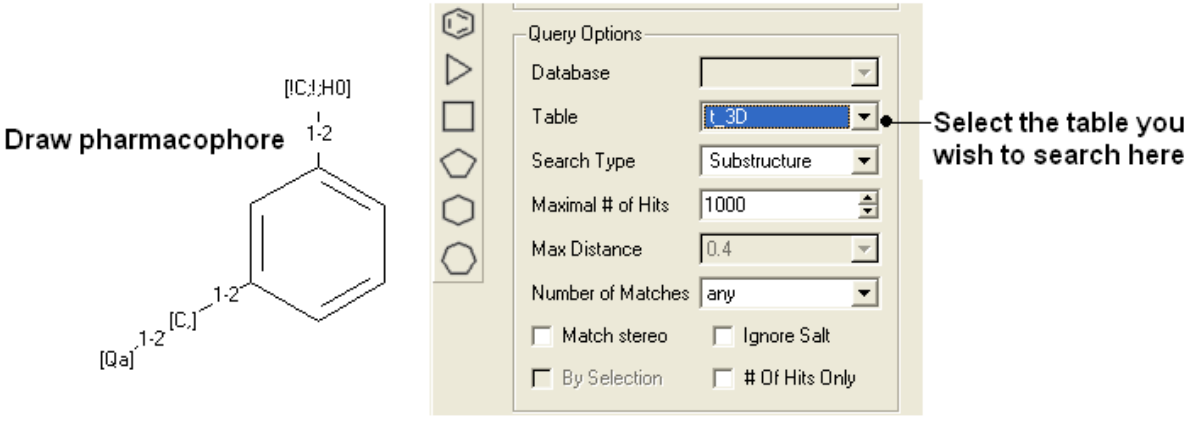
- Right click on the pharmacophore group in the ICM Workspace or in the Graphical Display.
- Select **Pharmacophore/Remove Direction**



17.9.3 Pharmacophore Search

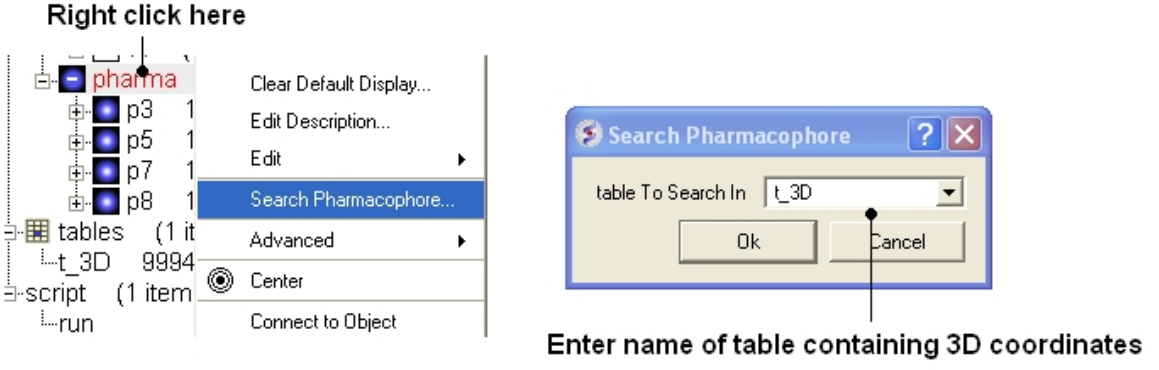
To perform a pharmacophore search using a 2D pharmacophore:

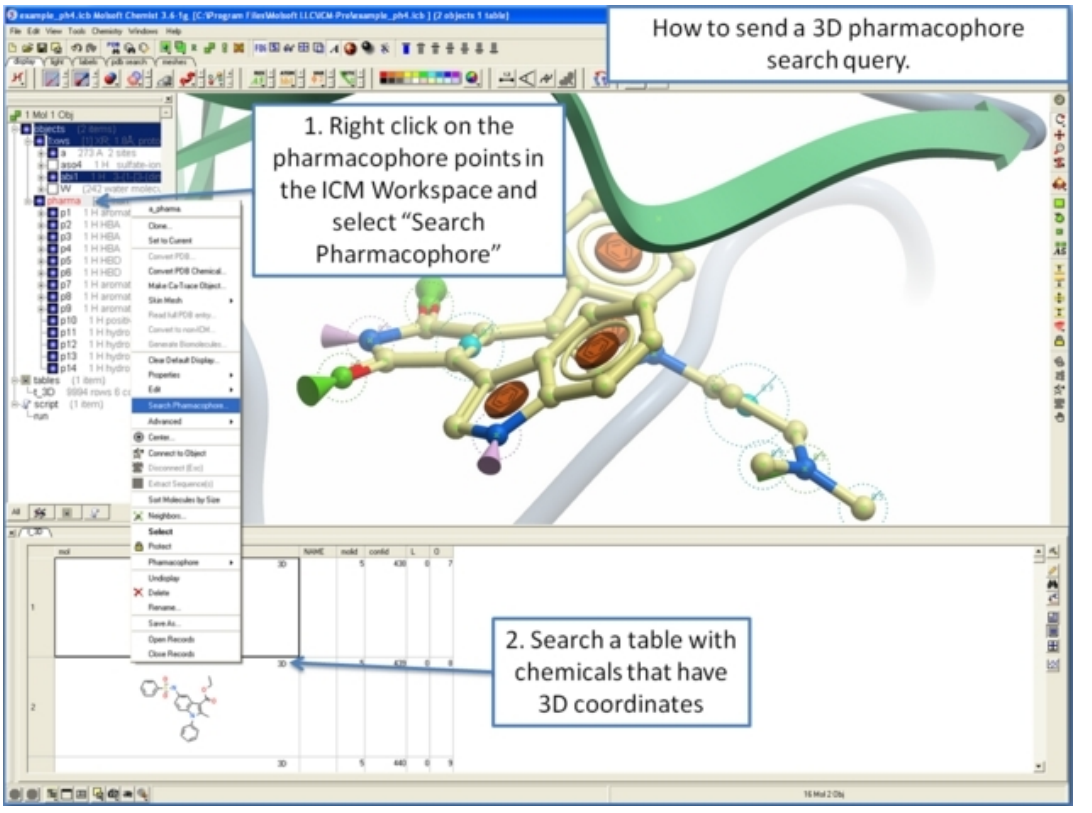
- `Draw` the 2D pharmacophore as described earlier in the Chemical Search window.
- Read in a molecular table to search or search a table in MOLCART.
- Select the chemical search options as shown below.
- Once the search has completed a new table with the results will be displayed.



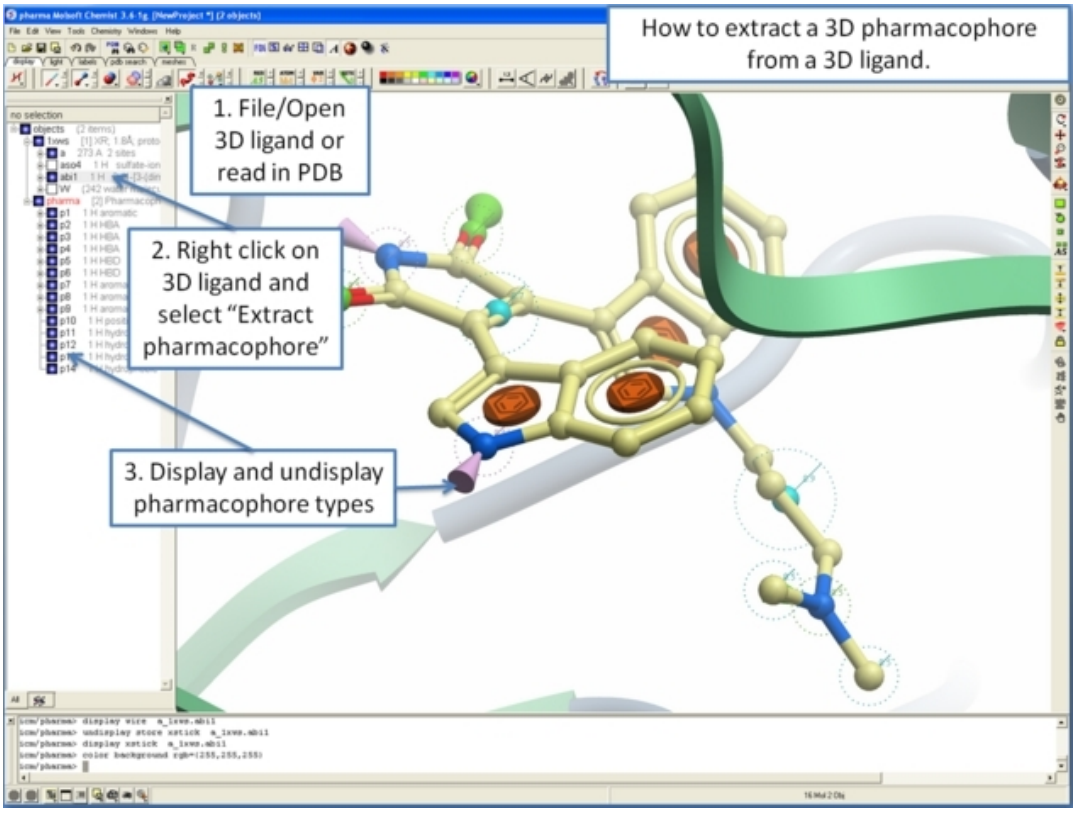
To perform a pharmacophore search using a 3D pharmacophore:

- Right click on the pharmacophore in the ICM Workspace
- Select **Search** Pharmacophore
- Use the drop−down button to select the table you wish to search. The table must contain 3D coordinates.

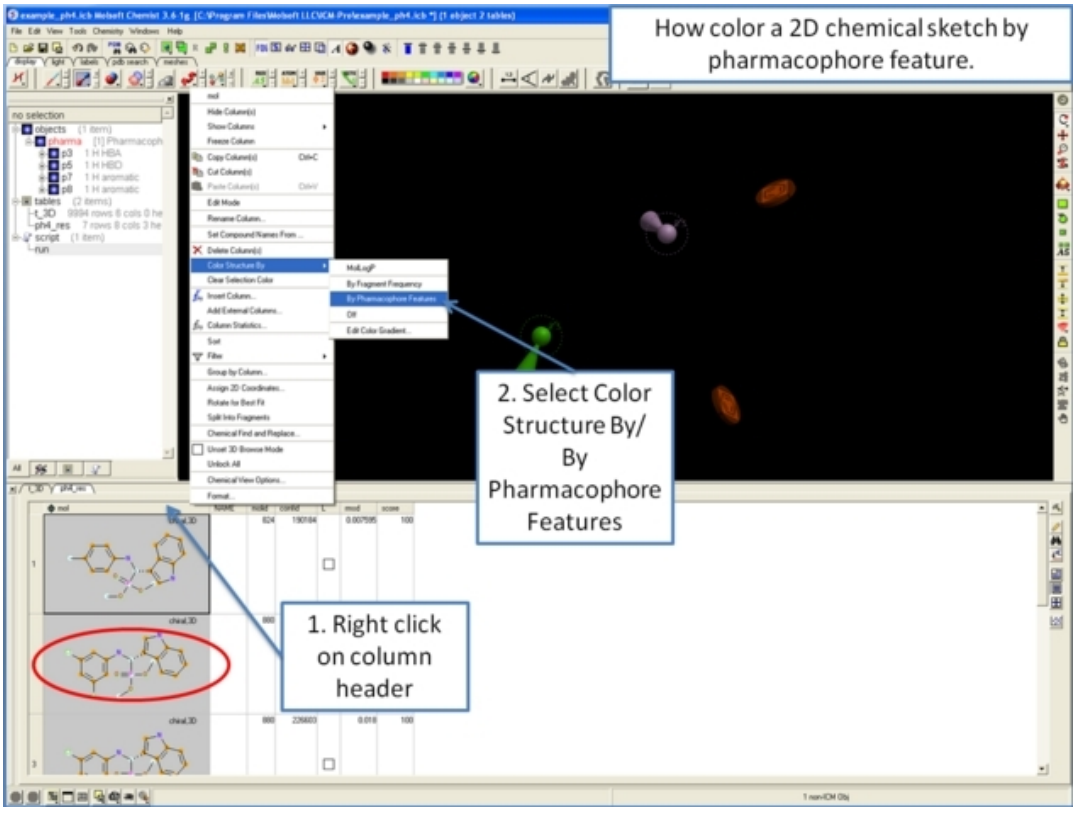




17.9.4 How to extract a 3D pharmacophore from a ligand.



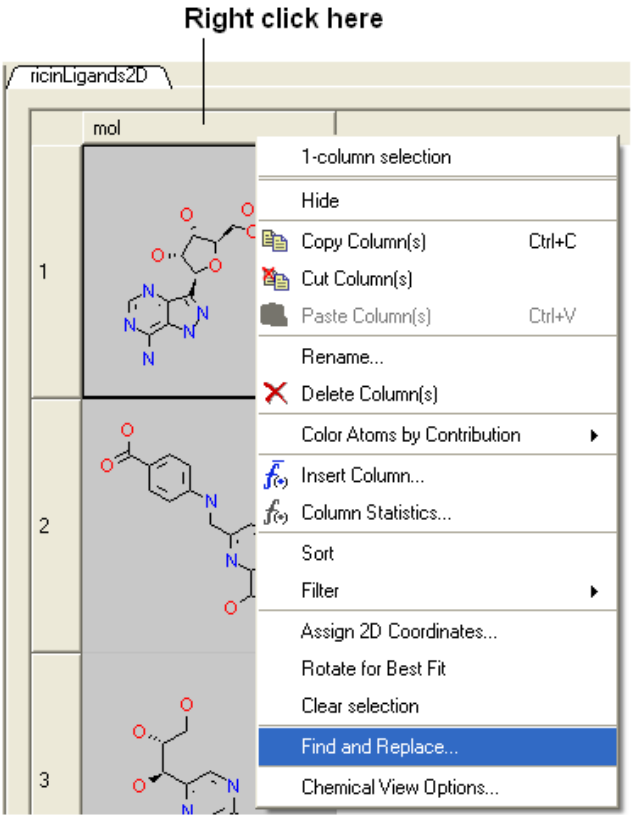
17.9.5 How to color a 2D chemical sketch by pharmacophore feature.



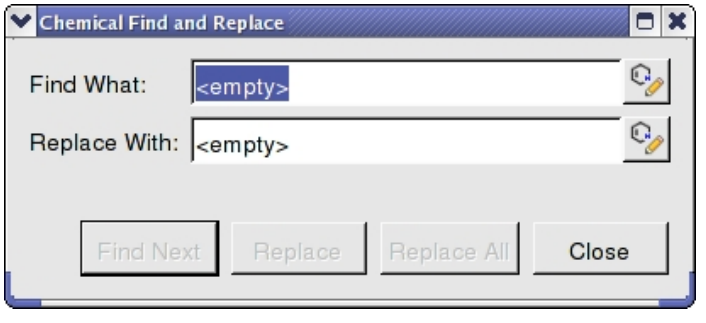
17.10 Find and Replace

Chemical Findtool allows you to find an arbitrary chemical fragment with one or more attachment point(s) and replace it with another fragment with the same number of attachment points.

To find a substructure and replace it with something else:



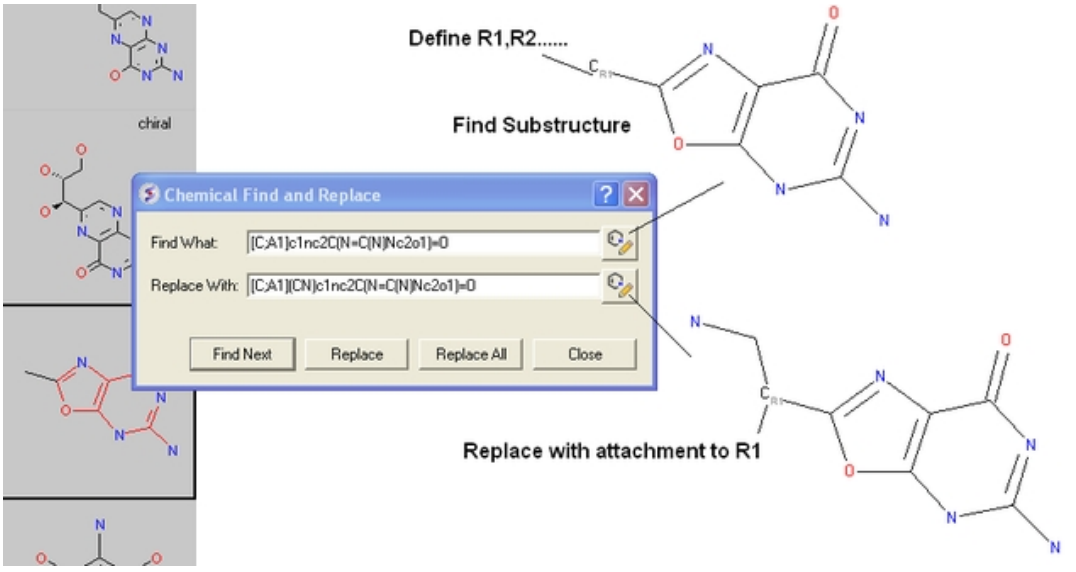
- Select the column in which the molecular structures are displayed. The column is usually called "mol".
- Right click on the "mol" column header and select Find and Replace. A data entry box as shown below will be displayed.



- Click on the Molecular Editor button at the end of the Find What: data entry box.
- The ICM Molecular Editor will be displayed. Draw the substructure you wish to search for and replaced.
- Draw the pattern and mark attachment points with R1,R2.... R−groups can be added by right clicking at the attachment point and selecting the R−group from the drop down options.
- Close the ICM Molecular Editor and the string will be displayed.
- Repeat with the "Replace With:" data entry box. Make sure the same number of R1,R2... labels are drawn.
- Click the Find Next button and then Replace or Replace All. When a substructure to replace is identified it will be colored red.

NOTE: There are a number of `keyboard shortcuts` which can be used to draw chemicals. Also please note that an aromatic bond in the source molecule will not match a double bond in the replacement pattern.

Here is an example:

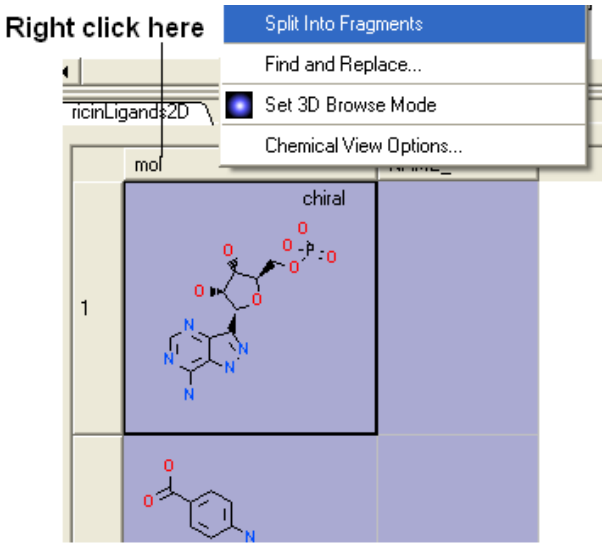


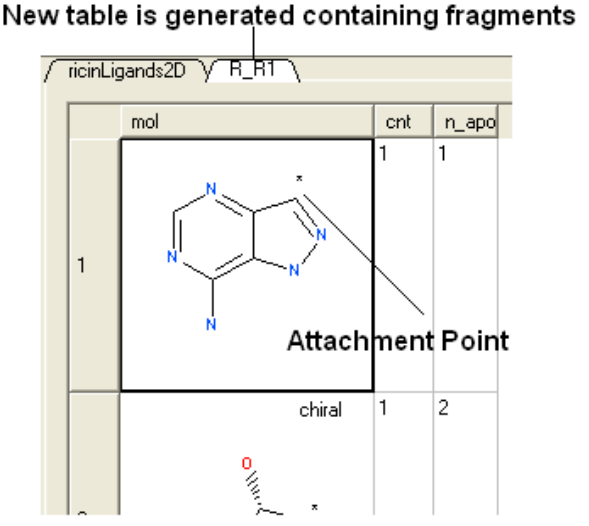
17.11 Generating Chemical Fragments

Chemicals displayed in an `ICM Molecular Table` can be split into fragments. This is useful for generating a series of R−groups to be added to a scaffold (See `section describing reactions`.

To generate fragments:

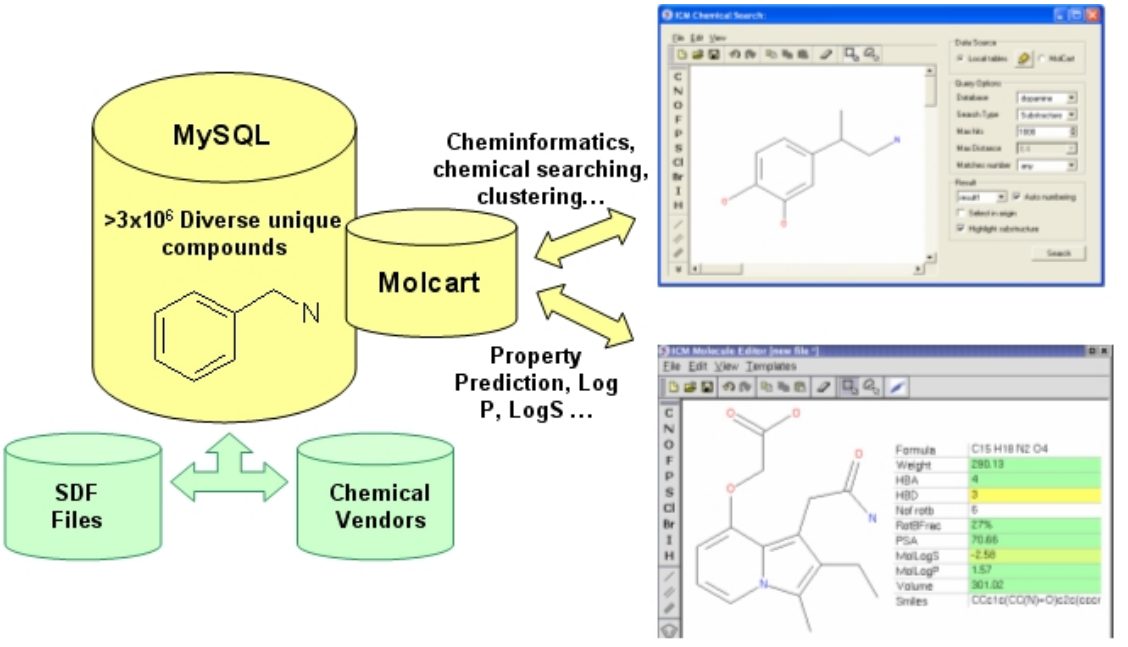
- `Select` the column or row(s) you wish to generate the fragment from.
- Right click on the "mol" column header and select "Split Into Fragments".
- A new table of chemical fragments will be displayed. Each fragment is assigned an attachment point which is flagged with an asterisk (*).





17.12 Molcart

Molcart is an enterprise wide chemical management system. Compound databases of any size can be stored in MolCart and analyzed and searched using ICM cheminformatic tools.



17.12.1 Molcart Installation

In order to run MolCart it is necesary to install the FREE OPEN SOURCE MySQL database on your machine. Please see your systems administrator or see `http://dev.mysql.com/downloads/`

Linux Installation

Mysql: Check if `mysql` daemon is running :

```
/etc/init.d/mysql status
```

If you see that the MYSQL service is `unused` (not `running`), you need to start the `mysql` deamon. Become `root` and do the following:

```
/etc/init.d/mysql start
```

Download and install Molcart files.

The MolCart package is a self−extracting executable file.

Installation Instructions:

- Download the MolCart file (molcart−*version*−*platform*.sh) from the Molsoft website.
- Type in a shell window: `./molcart-version-platform.sh -p=`*THE_PATH_YOU_WANT_TO_DOWNLOAD* (NOTE: You must be logged in as 'root' to install the 'molcart−version−platform.sh` to '/usr/molcart−version−platform'
- The following question will be displayed: Do you want to install the molcart−1.6−6 to "/usr/molcart−1.6−6" now? (y/n) [y]
- Answer YES and the unpacking process will begin
- You will now be prompted for a password.
- Select which default databases you wish to install.
- Make a note of the HOSTNAME, DATABASE NAME and USER NAME
- MolCart is now fully installed.

Mac Installation

System requirements: * Mac OS 10.3 * MySQL server for Mac OS 10.3

To install Molcart on the Mac just run this:

sudo /some/path/molcart−1.6−6−darwin.sh

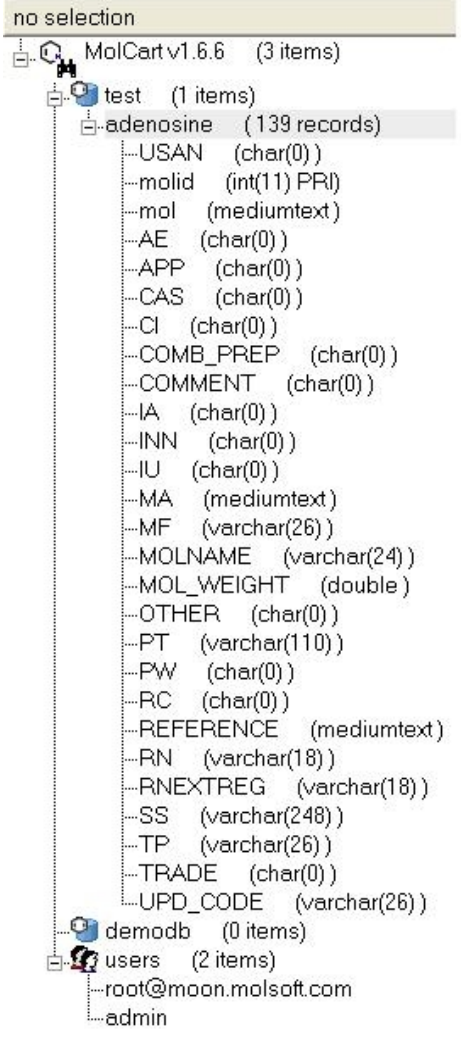
17.12.2 Molcart Getting Started

To start Molcart

Tools/Connect Molcart

Once you have activated MolCart the loaded databases and users will be shown in the ICM Workspace as shown below.

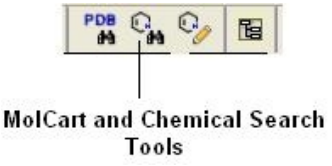
All the records and fields contained within each database can be viewed by expanding the tree structure in the ICM Workspace.



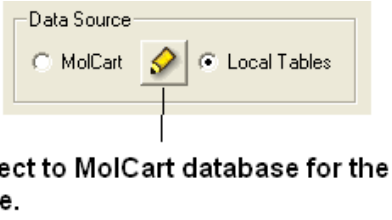
17.12.3 Molcart Search

How to search the databases contained within MolCart

Click on the button shown below.

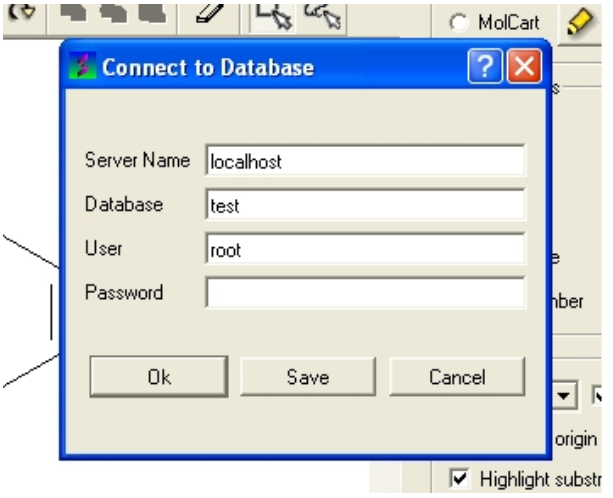


To begin processing your query first you need to decide which database to search. The options are listed in the "Data Source" section of the ICM chemical search window.



You can either search a local table (molecular table) or you can search MolCart.

If you select MolCart you first need to setup the link to the correct database − described earlier. Click on the button shown above (yellow pencil) and the Connect to Molcart window will be displayed as shown below.



- Enter the Server Name in which the database is stored.
- Enter the database name.
- Enter your username and password for the server.
- You can save these details so you dont have to re−enter this information each time you use the chemical similarity search.

See the `Chemical Search` section of this manual on the many different search procedures.

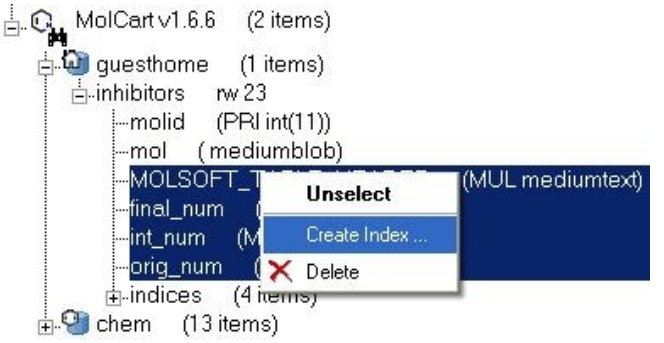
How to perform a text search

To perform a text search on one of the databases contained within Molcart you first need to index the text within the database and then search using the query option.

To make the database index, see text and picture below:

- Expand the tree of the database in the ICM Workspace.
- Select the column headers you wish to search which contain Full Text or Partial Text(the data type for each column is listed next to the column name). Multiple column headers can be selected by clicking and holding down the CTRL key. A range of column headers can be selected by holding down the shift key and clicking to select.
- Next, right click and select Create Index.

- Select 'Full Text' and you will notice an additional header in the ICM Workspace called 'indices'. The value in the items category represents the number of columns you have chosen to text search.



To perform the text search:

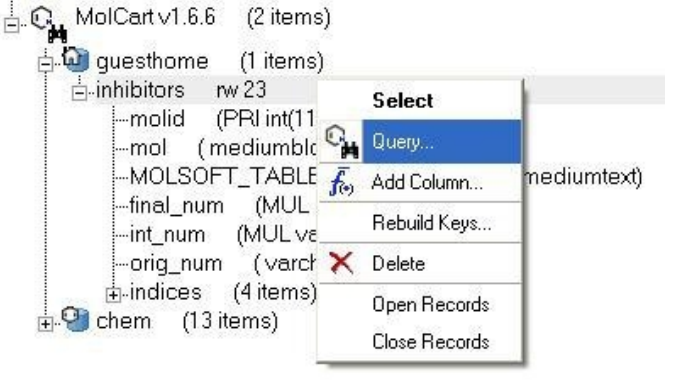
- Right click on the database name in the ICM Workspace.
- Select 'Query' as shown below.

The options are:

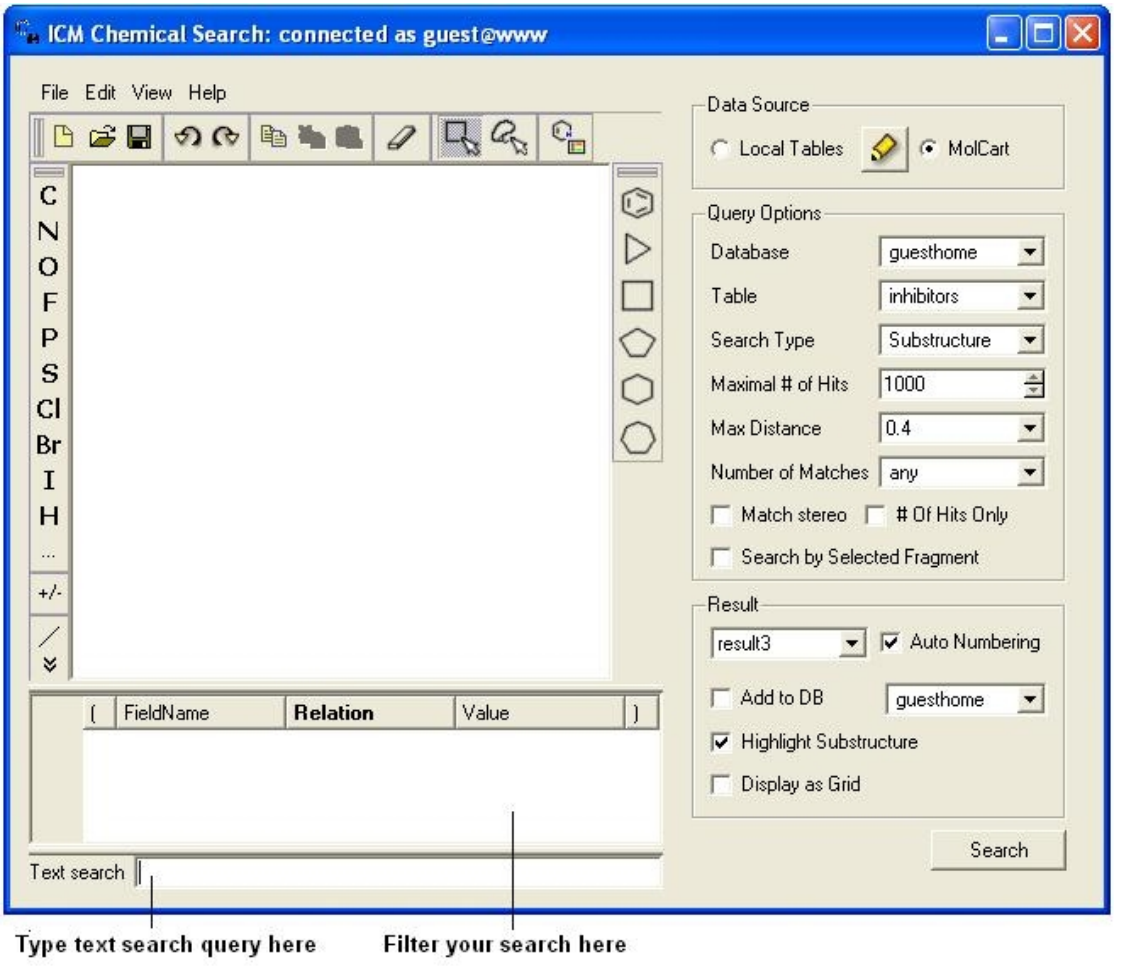
- Display results − displays your model in the 3D graphics window
- Minimize side chains − performs minimization on the side−chains
- Sample side chains − performs monte−carlo optimization on the side chains
- Write object to file − writes your new model as an ICM object

To build your model:

- Click OK

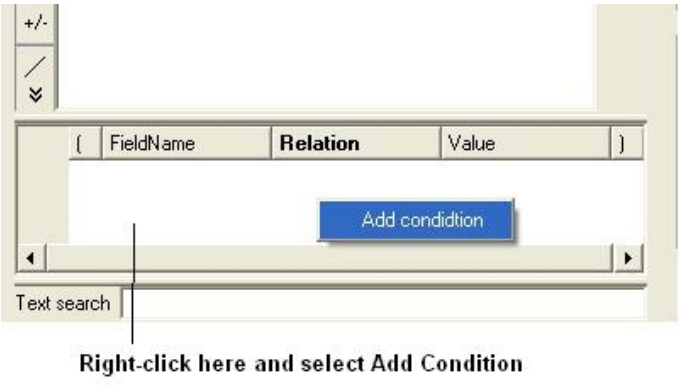


The ICM Chemical Search query window will be displayed as shown below. Type your query text in the space provided and hit the enter key or click on the search button.

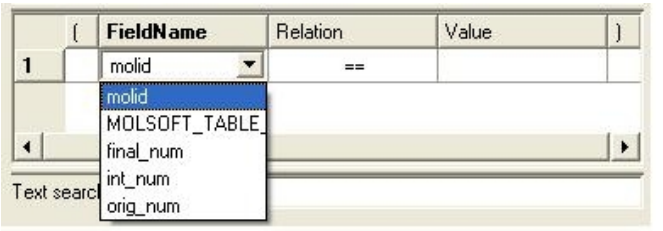


How to add conditions to your query

- Right click in the box shown below and select 'Add Condition'. You can add as many conditions as you like.



- Double click in the fields labeled "Name" and "Relation" and select the options from the drop down arrow or type in values.



To remove a condition, right click on the filter and select 'Remove Filter'.

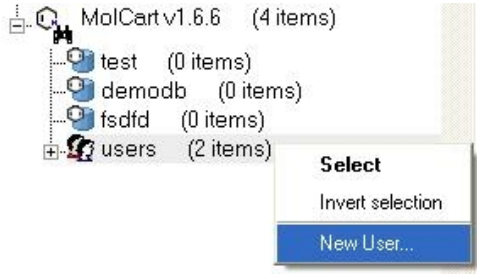
17.12.4 Molcart Administration

Edit Password

- Right click on the MolCart header in the ICM Workspace and select Change Password.

Add a New MolCart User − Root Only

- Right click on the User Section of MolCart in the ICM Workspace as shown below.



- Select the New User Option.
- Add new username and password in the data entry box.
- New user will be displayed in the ICM Workspace.

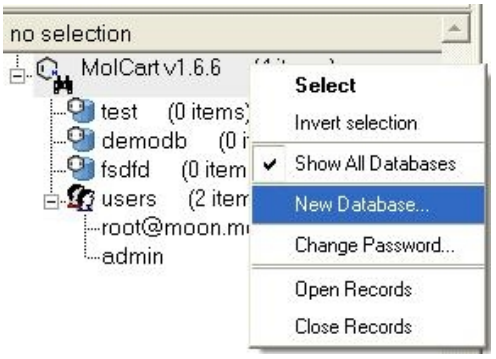
Edit User Privileges − Root Only

- Right click on the user in the ICM Workspace.
- Select Edit Privileges and a data entry box as shown below will be displayed.

- Select the database name.
- Edit the privileges by checking or unchecking the appropriate boxes.

Add a New Database

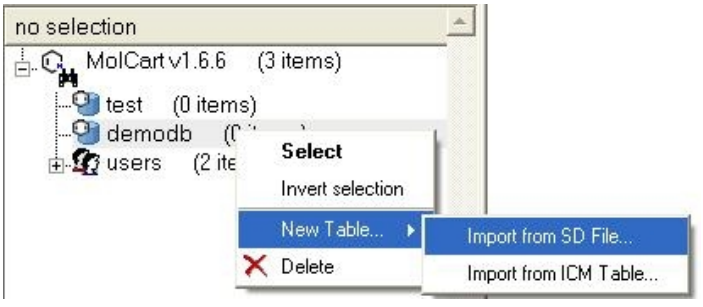
- Right click on the MolCart Header in the ICM Workspace as shown below.



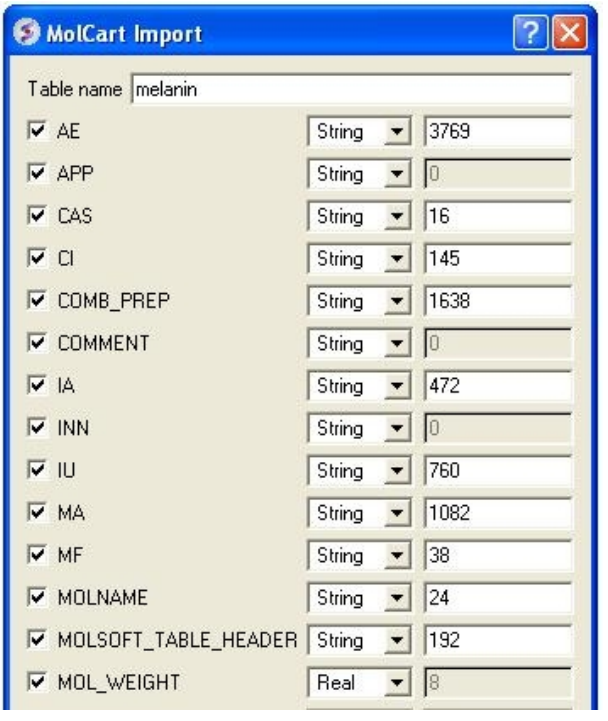
- Select the New Database option.
- Enter a unique name for your new database.
- The new database name will appear in the ICM Workspace.
- Now you need to add data to your new database (See Instructions Below).

Add New Data to Database

- Right click on the database name in the ICM Workspace as shown below.



- Select New Table.
- Select either Import from SD file or Import from ICM table.
- Select the appropriate file and the records structure of your sdf or ICM table will be displayed as shown below.



- The database name can be changed at this point and the fields contained within the database can be altered. Certain fields can be excluded by checking the boxes − this will help in minimizing the size of a database. Caution must be taken if you want to change the field type or length.
- Click OK and your sdf file or ICM table will be added to the database. This can be seen by expanding the tree structure in the ICM Workspace.

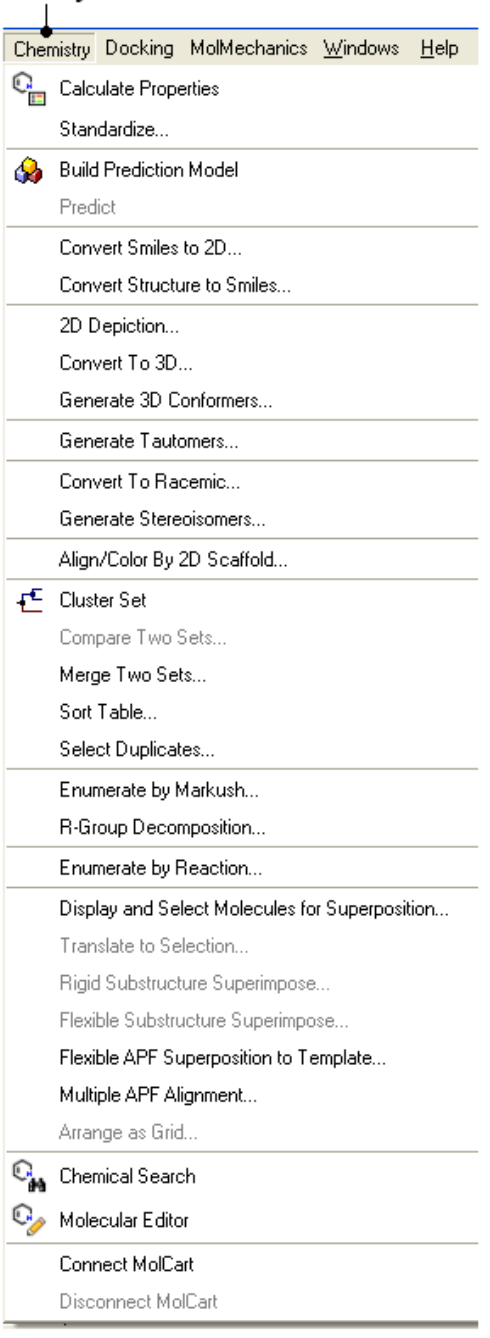
Delete a Database or User

- Right click on either the database or user in the ICM Workspace.
- Select Delete.

18 Chemistry Menu

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

Chemistry Menu

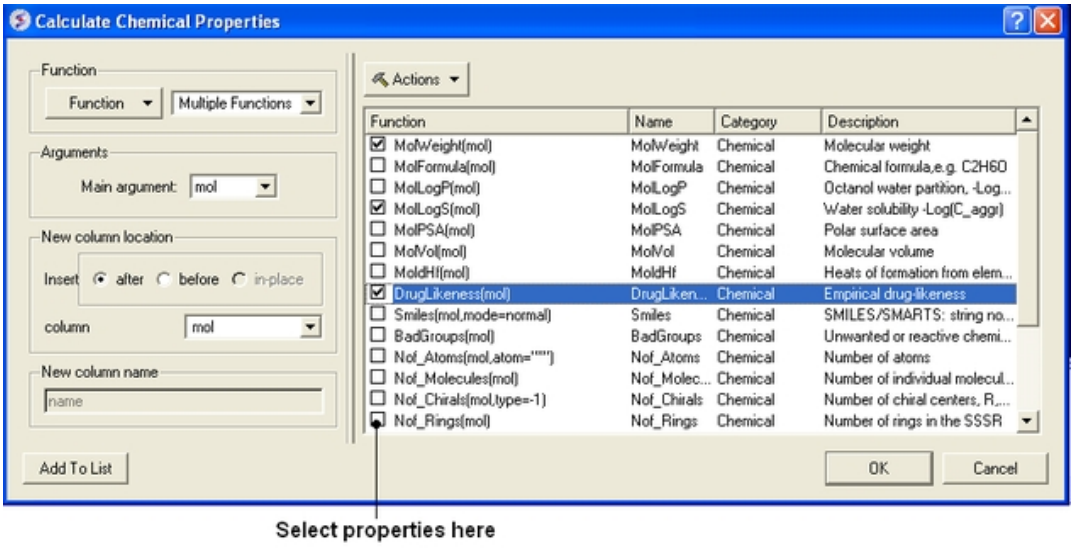


18.1 Calculate Properties

To calculate chemical properties for compounds within a chemical table:

- Read in the chemical table.

- Select **Chemistry/Calculate Properties** and a window as shown below will be displayed.
- Select the properties you wish to calculate using the 'tick' check boxes.
- Click OK and the properties will be added as new columns in the chemical table.

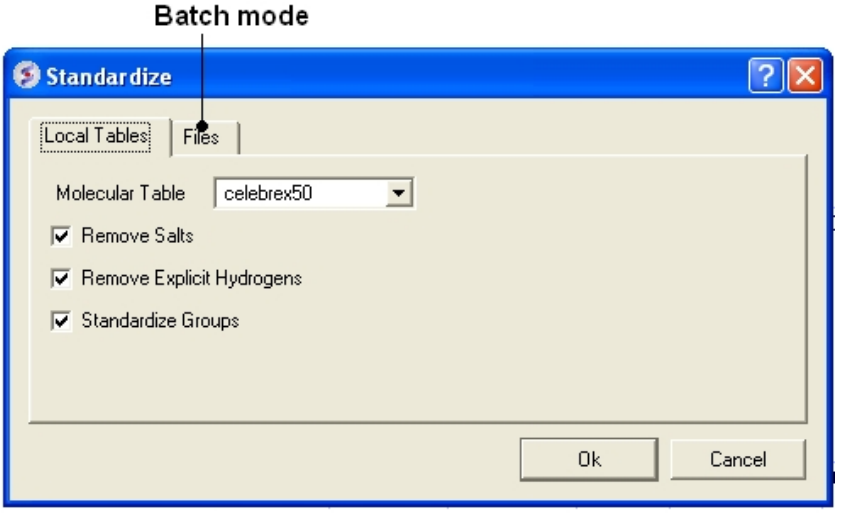


18.2 Standardize Table

NOTE: Before standardizing a chemical you may want to make a copy of the original so you do not lose any information. You can do this by right clicking on the name tab of the table and selecting **clone** or **save as**.

To remove salts, explicit hydrogens and standardize groups in a chemical table:

- Chemistry/Standardize
- Select the table from the drop−down list. This will also work for selections made on the table.
- Select option − Remove Salts, Remove Explicit Hydrogens or Standardize Groups
- Click OK.



Standardize chemical groups will apply rules from ICMHOME/CHEMNORMRULES.tab For example some chemical groups may have different representations e.g. [N+] (=O)O versus N(=O)=O

To run in batch mode:

- Chemistry/Standardize

- Select the **Files** tab
- Enter the path and name of the sdf file you wish to standardize or use the browse button.
- Enter the path and name of the output file or use the browse button.

To remove a salt from an individual row in a chemical table:

- Select the `row or rows`.
- Right click − Chemistry/Remove Salt (Selected Row)

18.3 Annotate By Substructure

This feature allows you to annotate a `chemical spreadsheet` according to functional group. It also allows you to flag substructures which may have poor ADME properties.

First read in a chemical spreadsheet or sdf file you wish to annotate. To do this:

- File Open. More information on the chemical structures can be found `here`.

To annotate functional groups:

- Chemistry/Annotate by Substructure.
- Enter the name of the Molecular Table (Chemical Spreadsheet) or use the drop down button to locate it.
- Check the **Functional Groups** option.
- The functional groups will be listed in a new column in your chemical spreadsheet called **funcgroup.** The default table with functional group will be used for annotation called FUNCGROUPS.sdf in ICMHOME.

To annotate potentially poor ADME groups (Substructure Alert).

- Chemistry/Annotate by Substructure.
- Enter the name of the Molecular Table (Chemical Spreadsheet) or use the drop down button to locate it.
- Check the **Substructure Alerts** option.
- The alerts will be listed in a new column of your chemical spreadsheet called **alerts.** The default table with substructure alerts will be used for annotation called CHEMFILTER.sdf

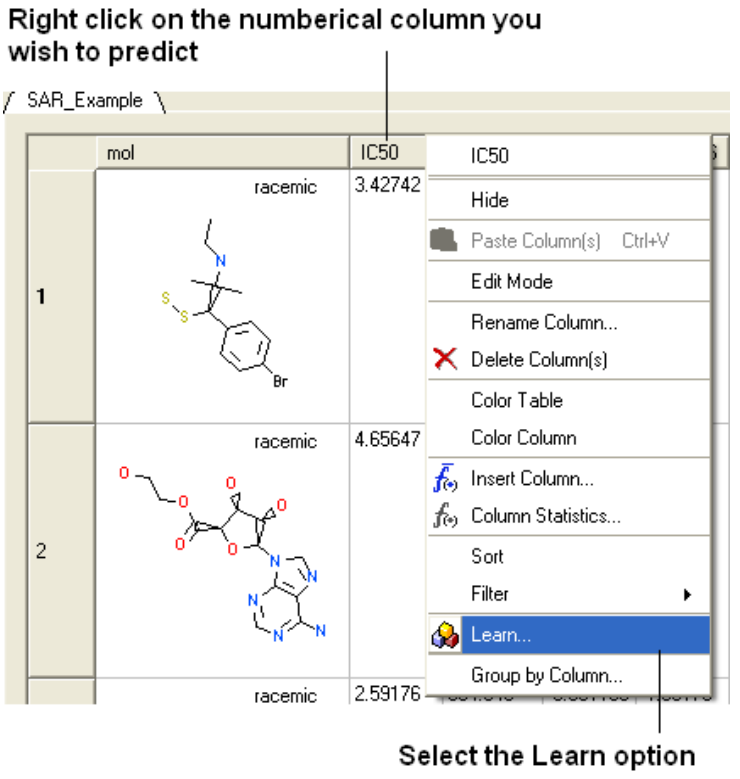
18.4 Build Prediction Model

Structure−Activity Relationship (SAR) is a process by which the activity of a molecule is related to its molecular structure. If a significant ammount of structural and activity data is available a model can be made which can be used to predict the activity of a molecule or series of molecules.

In ICM SAR is undertaken using the `Learn and Predict tools` in a `Molecular Table`.

Learn

Step 1: Select the column you wish to predict and then Tools/Table/Learn or use the right click option shown below.



Step 2: Fill in the Learn options as shown below.

- Enter the name of table with which you want to perform the predictions. You may locate your table from the drop down arrow menu.
- Select the column from which you wish to learn. Use the drop down arrow to select.

NOTE If the table does not contain any numeric (integer or real) columns, there is nothing to predict, so the "Learn" button will be disabled.

- Enter a name for the learn model.
- Select which regression method you wish to use from the drop down menu. See the `theory` section to determine which method and parameters to use.
- Select which columns (descriptors) of your table you wish to use to 'learn'.
- If you are using chemical descriptors to produce your model select the maximal chain length.
- Select the number of cross−validation groups you wish to use or selected rows can be used for cross validation. The number of iterations will impact the speed of the calculation. 5 is the default number of groups but 2 would be the least rigorous and selecting the 'Leave−1−out' would be the most rigorous calculation.
- Click on the learn button and a table summarizing your model will be displayed as shown below.

18.5 Predict

To make a prediction using a `model`.

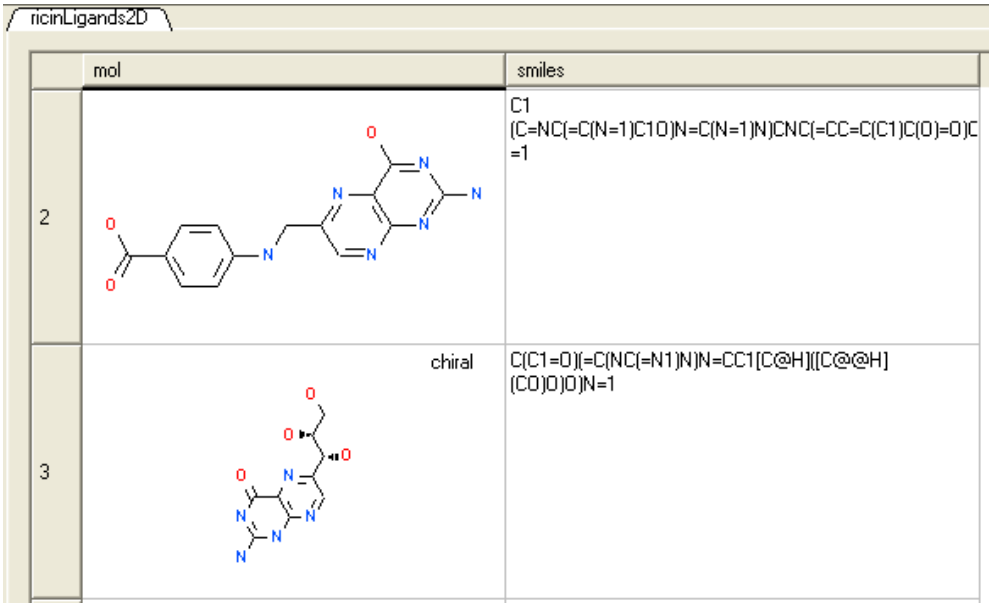
Read the table of data into ICM from which you wish to predict. Make sure the table contains the same columns used for the `learn` model.

- Tools/Table/Predict
- Select which table you wish to make the prediction on.
- Select which model you wish to use.
- Check that the required columns are in the table. If they are absent a red mark will appear against the column that is missing.
- Click Predict.

18.6 Convert Smiles to 2D

To convert smiles strings to 2D sketches

- Read in a table containing the smiles strings in separate rows. For example the smiles strings maybe in an Excel file and you can load this into ICM by saving the Excel file as comma−separated (csv).
- Select **Chemistry/Convert Smiles to 2D**.
- Select the table you want to convert using the drop down arrow and the name of the column containing the smiles string.
- Select whether you wish to keep the smiles column in the new table.
- Click OK and a table will be displayed containing the 2D structure.



18.7 Convert Structure to Smiles

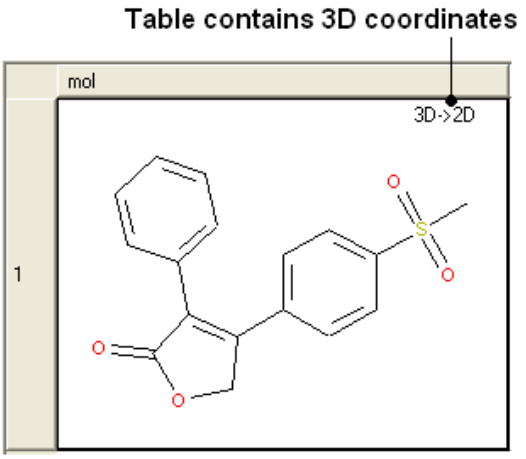
To convert an sdf file of 2D or 3D chemical coordinate in Smiles:

- `Read` a chemical table (sdf file) into ICM.
- Select **Chemistry/Convert Structure to Smiles**.
- Select the table you want to convert using the drop down arrow and the name of the column containing the 2D sketch.
- Select whether you wish to keep the 2D sketch column in the new table.
- Click OK and a table will be displayed containing the smiles string.

18.8 2D Depiction

If you have a chemical table displayed containing 3D coordinates or you wish to reassign the 2D cooridnates in an sdf file you can use this option.

- Chemistry/2D Depiction
- Enter name of loaded chemical table.
- Choose **In Place** if you want to overwrite the table.
- Choose the **Files** tab to run in batch mode.



18.9 Convert to 3D

To convert a chemical structure from 2D to 3D:

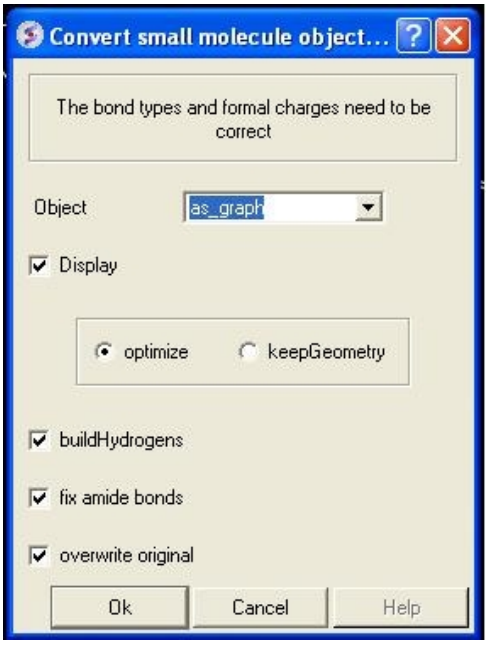
There are three ways in which to do this depending on whether you have a chemical in a chemical table or in the ICM workspace.

From the Chemistry/Convert To 3D option from a table.

- Select the table from the drop down list.
- Select to keep hydrogens and/or fix amide bonds.
- Keep current table or overwrite.

If the compound is in the ICM Workspace:

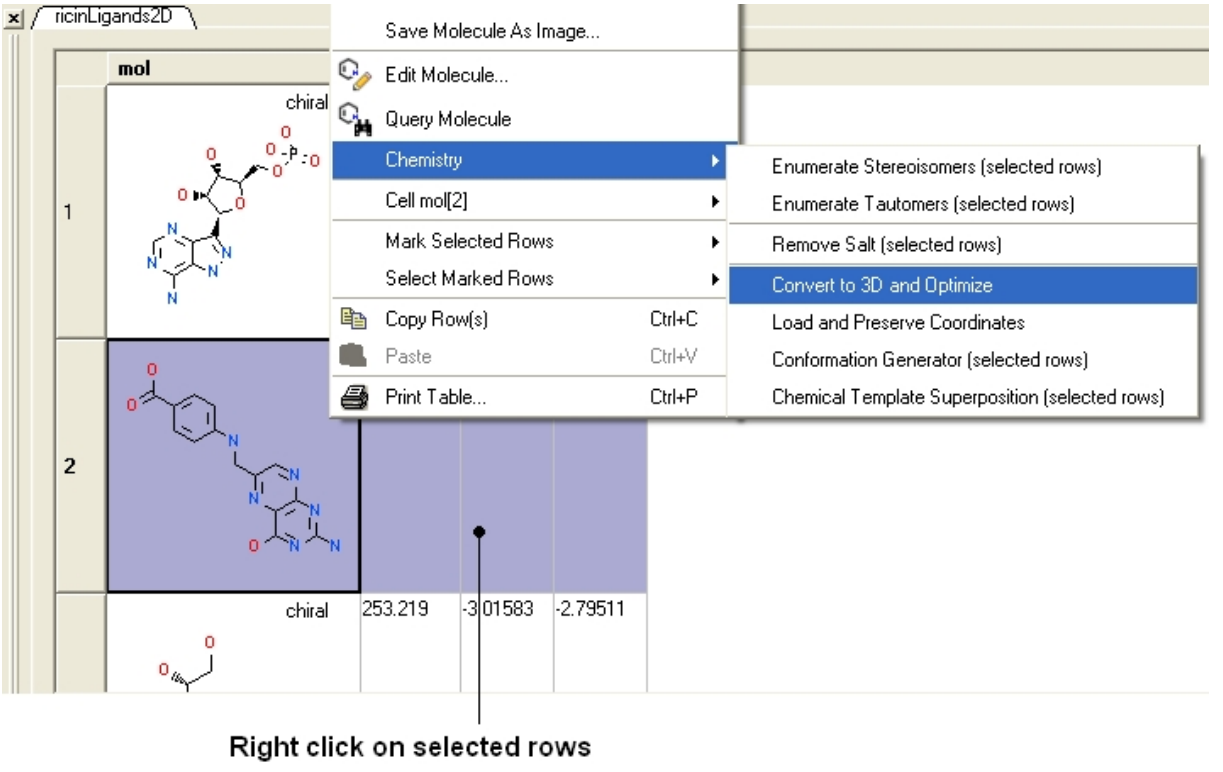
- Select all of the structure to be converted by double clicking on it in the ICM workspace or by using other selection tools described in the `Selection Toolbar Section` of this manual.
- MolMechanics/ICM−Convert/Chemical and a data entry box as shown below will be displayed.



If you have selected the compound as described above the "as_graph" option in the Object data entry box will suffice. You can decide whether you wish to keep the chemical geometry or optimize it in a force−field. Other options include whether you wish to add hydrogens and fix amide bonds.

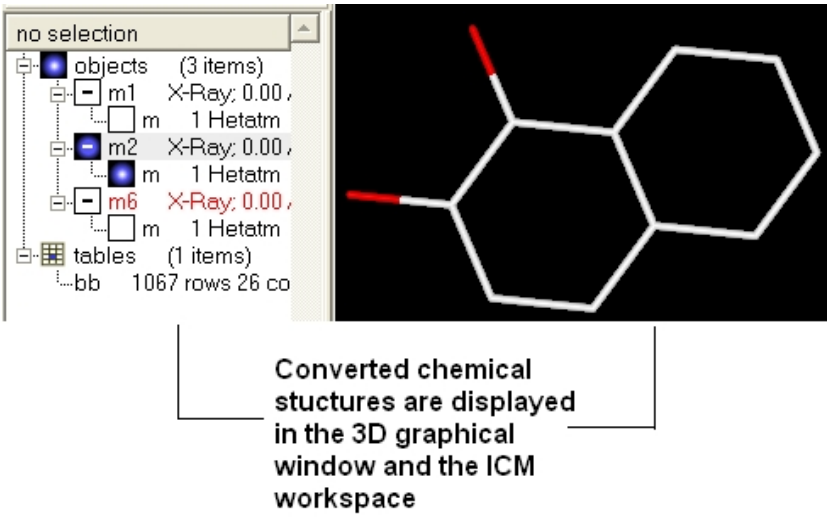
From an ICM chemical table:

- Select which structures you wish to convert in the molecular table. For instructions on making selections within tables see the `Making Table Selections` part of this manual.
- Right click on one of the selections you have made and a menu as shown below will be displayed. Or use the Chemistry menu and select **Convert To 3D**.



- Select the **Chemistry/Convert to 3D and Optimize** option and you will see the compounds being converted and minimized in the 3D graphical display window.

Once converted the compounds will be displayed in the 3D graphical display window and also in the ICM workspace.



Another way to convert all the ligands contained within a table (or a selection) into 3D coordinates :

- Chemistry/Convert to 3D..
- Use the drop down list to select the Molecular Table.

- Select whether you want to **Keep Hydrogens**, **Fix Omegas** and **In Place**. Select **In Place** if you want to overwrite current table.
- Click OK
- If you wish to run in **Batch** mode select the **Files** option.

> **NOTE:** Use the `3D-Browse mode` to view the chemicals in the graphical display.

To convert 3D representation in a molecular table back to 2D:

- Chemistry/2D depiction
- Use the drop down list to select the Molecular Table.
- Select **In Place** if you want to overwrite the current table.
- Click OK.

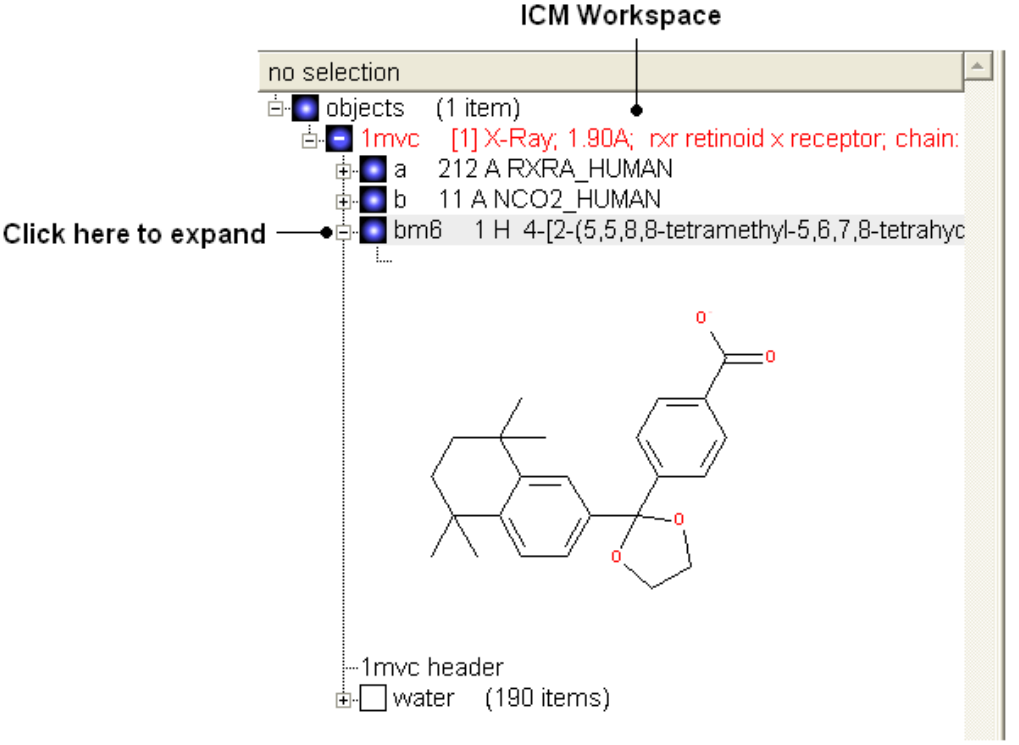
18.9.1 Converting a Chemical from the PDB

The protein data bank has not been storing any information about covalent bond types and formal charges of the chemical compounds interacting with proteins! This oversight makes it impossible to automatically convert those molecules to anything sensible and requires your manual interactive assignment of bond types and formal charges for each compound in a pdb−entry. Therefore, if you apply the convert command to a pdb−entry with ligands, the ligands will just become some crippled incomplete molecules that can not be further conformationally optimized.

Therefore, follow these steps to convert a chemical properly from a pdb form to a correct icm object. There are two ways to do this either via the `ICM Workspace` (recommended) or via the `Graphical Display`.

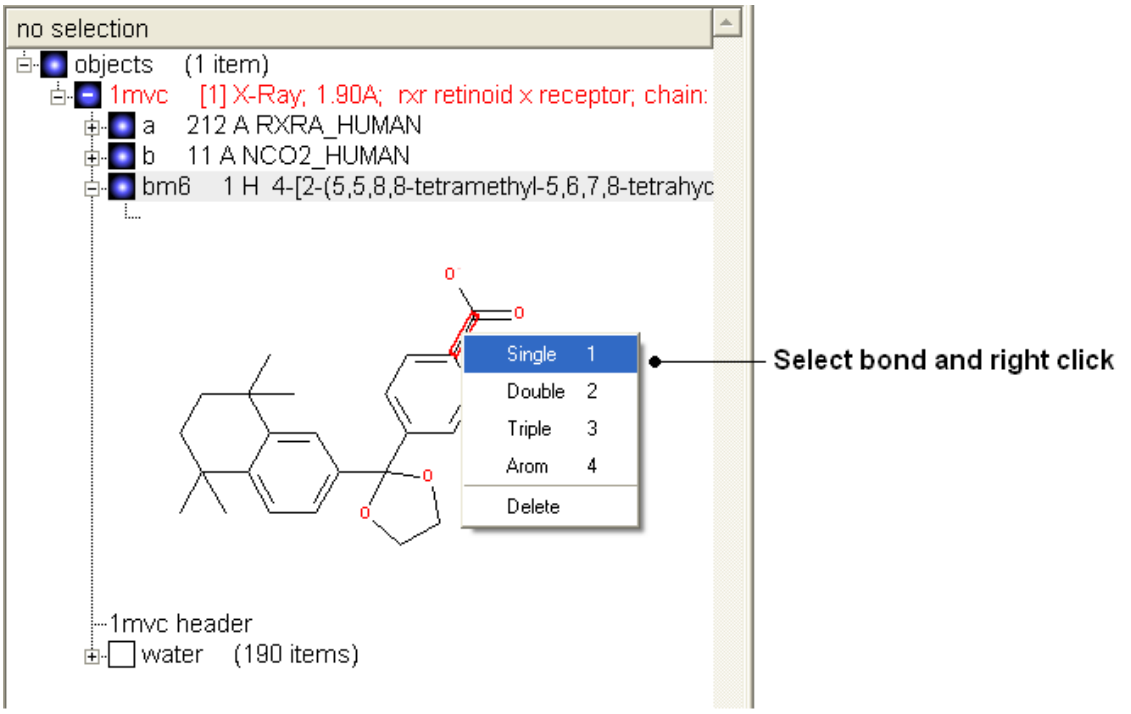
18.9.2 Converting a Chemical from the PDB using the ICM Workspace

- **File/Open** PDB
- View the ligand in the ICM Workspace by expanding the molecule tree (see below).



Change bond orders:

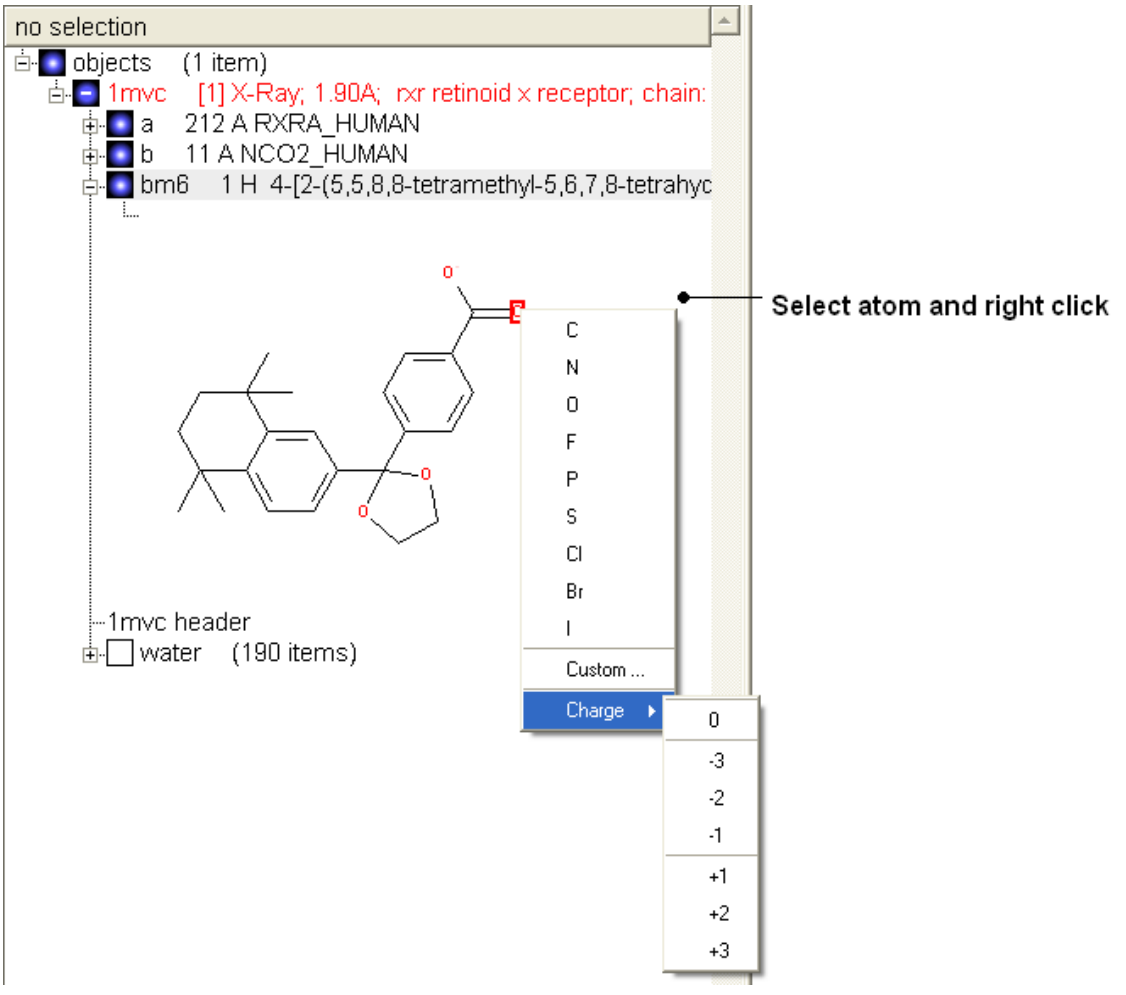
- Change the bond orders by selecting the bond (highlighted in red).
- Right click and select the desired bond as shown below.



NOTE: Keyboard `shortcuts` are provided to make editing faster.

Change atom and charge:

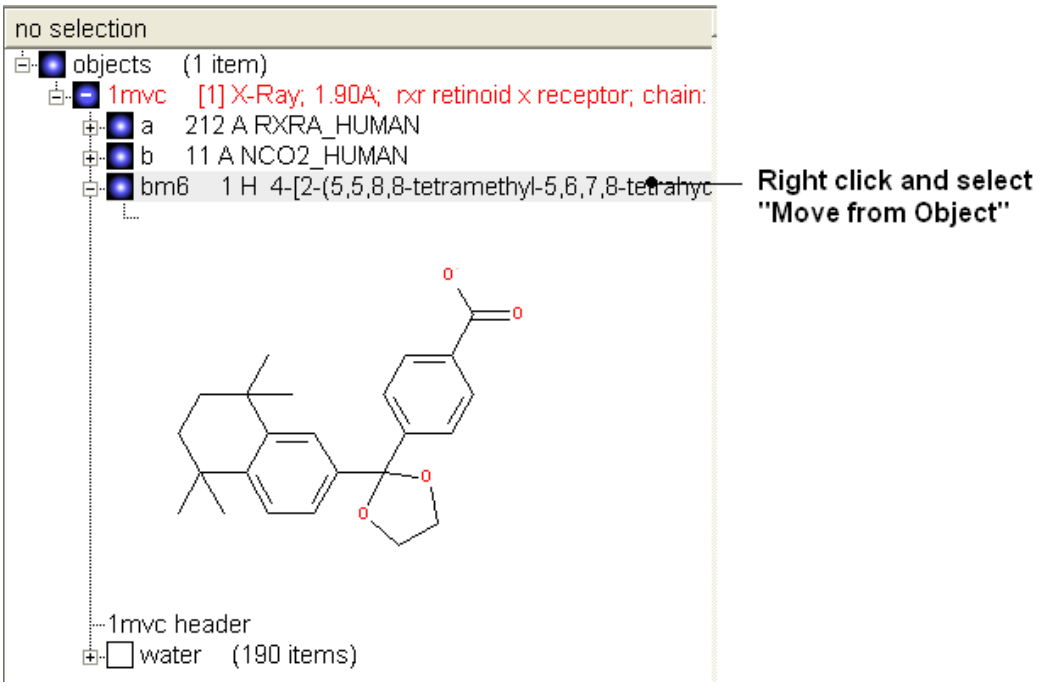
- Change the atom or charge by selecting the atom (highlighted in red).
- Right ckick and select the desired atom or charge as shown below.



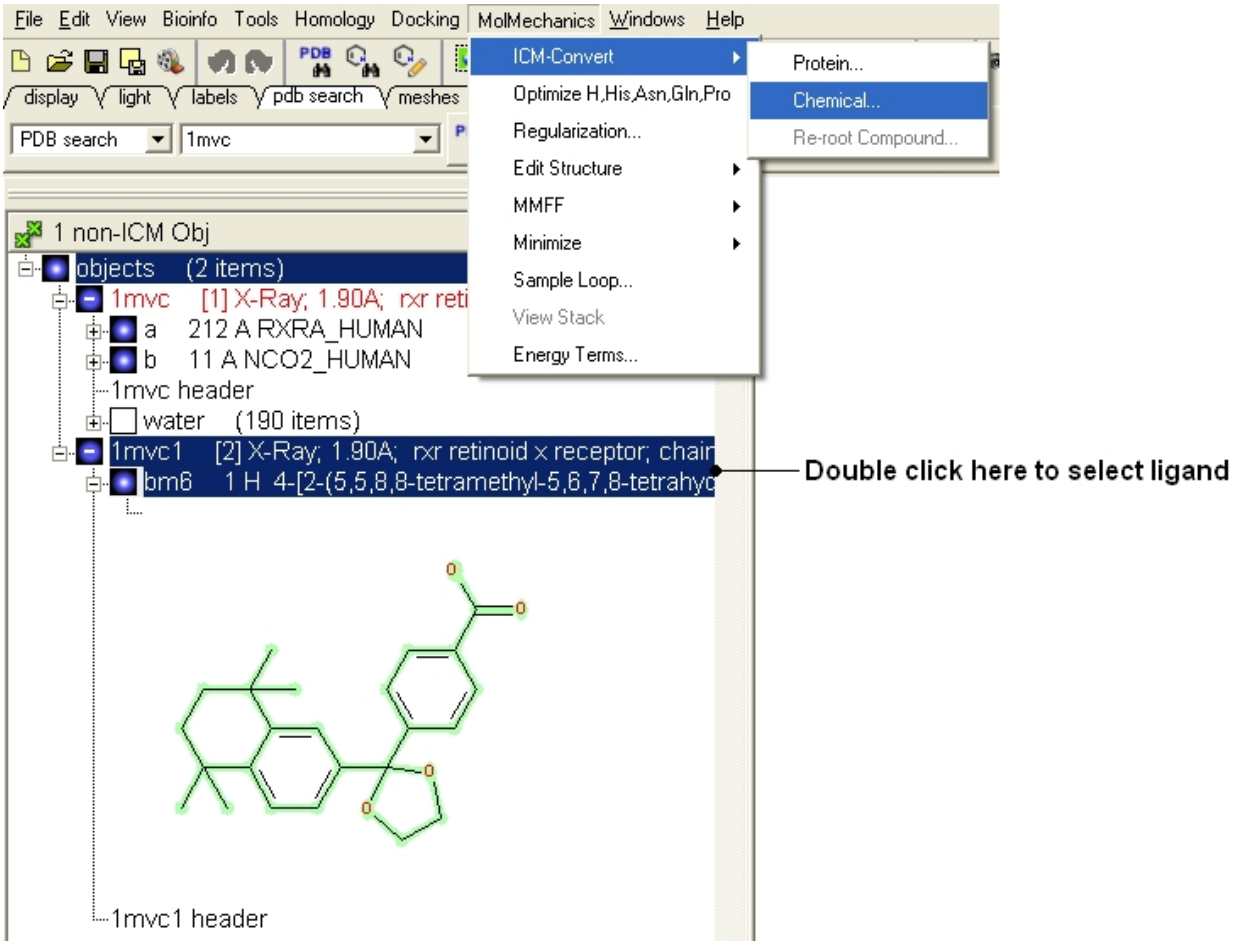
NOTE: Keyboard `shortcuts` are provided to make editing faster.

Convert to 3D in MMFF force field:

- Once you have made the changes to the ligand − right click on the name of the ligand in the ICM Workspace and select **Move from Object**.



- Select the ligand by double clicking on it in the ICM Workspace.
- Select **MolMechanics/ICM−Convert/Chemical**



NOTE: If you need to add an extra bond you will need to use the full molecular editor. Right click on the name of the ligand in the ICM Workspace and select **Edit/Edit Compound**.

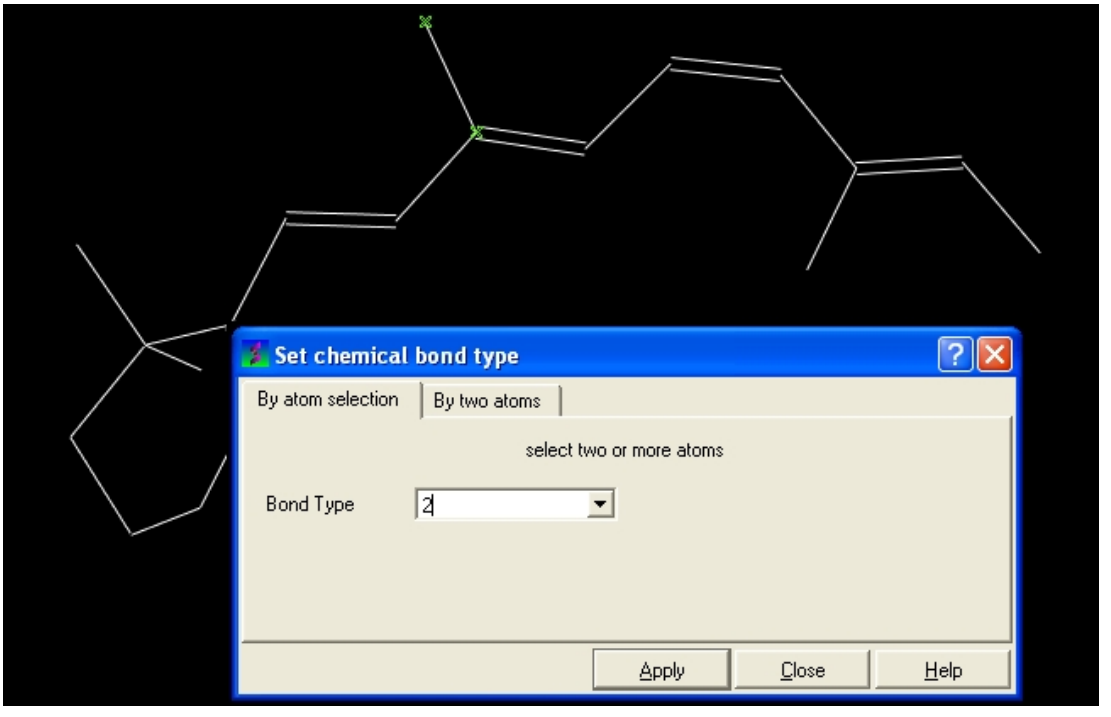
18.9.3 Converting a Chemical from the PDB using the Graphical Display

- Display the molecule in wire chemistry style mode by right clicking on the Wire Representation button (see `Wire Representation section`).

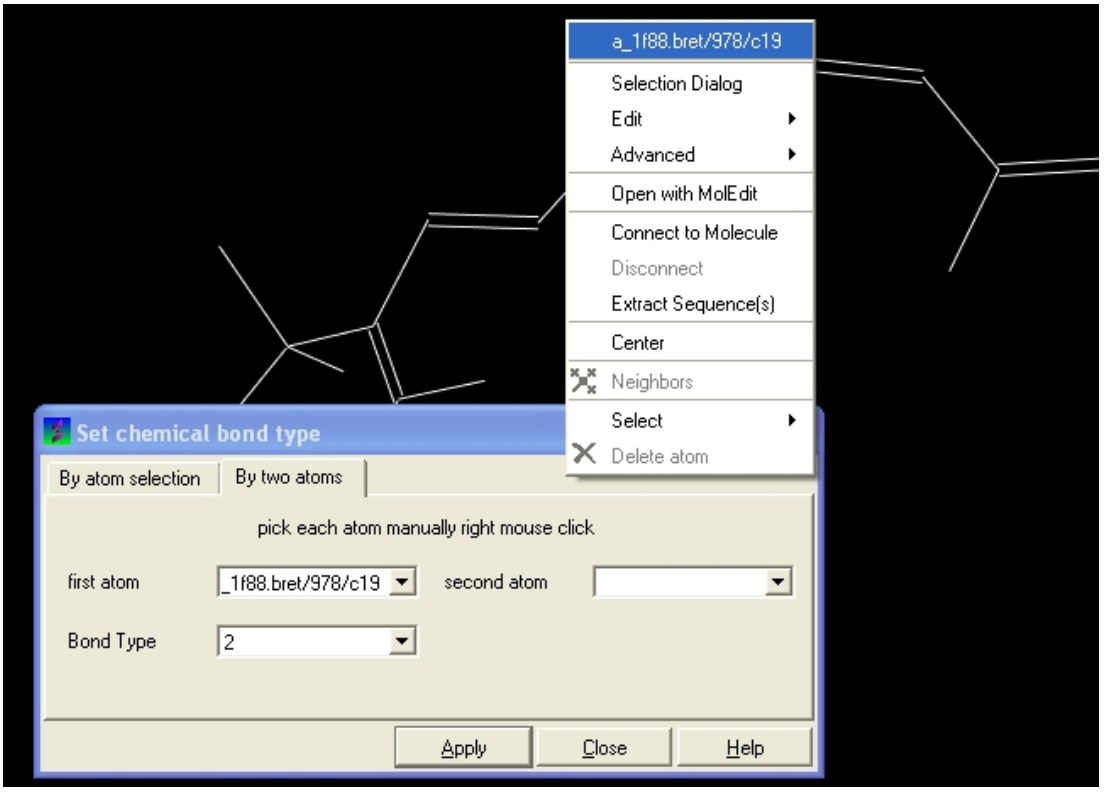
To change the bond types in your ligand:

- Click on MolMechanics/Edit Structure/Set Bond Type and the Set chemical bond type data entry box will be displayed.

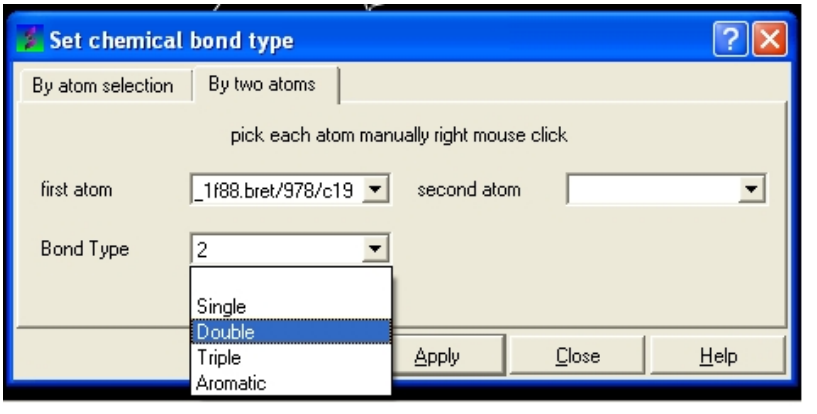
You can either select (see `selection menu section`)the atoms you wish to change graphically using the rectangular or lasoo selection button OR



You can select the **By two atoms** tabs and right click on the atoms you wish to change and then selecting the atom descriptor with the left mouse button as shown below.

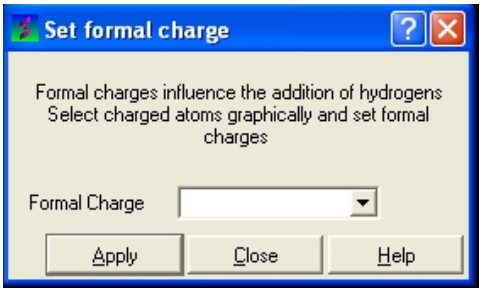


- Select the desired bond type either single, double, triple or aromatic.



To set the formal charge of a compound:

Click on MolMechanics/Edit Structure/Set Formal Charge and then select the appropriate charge.



The final step is to convert the compound into an ICM object:

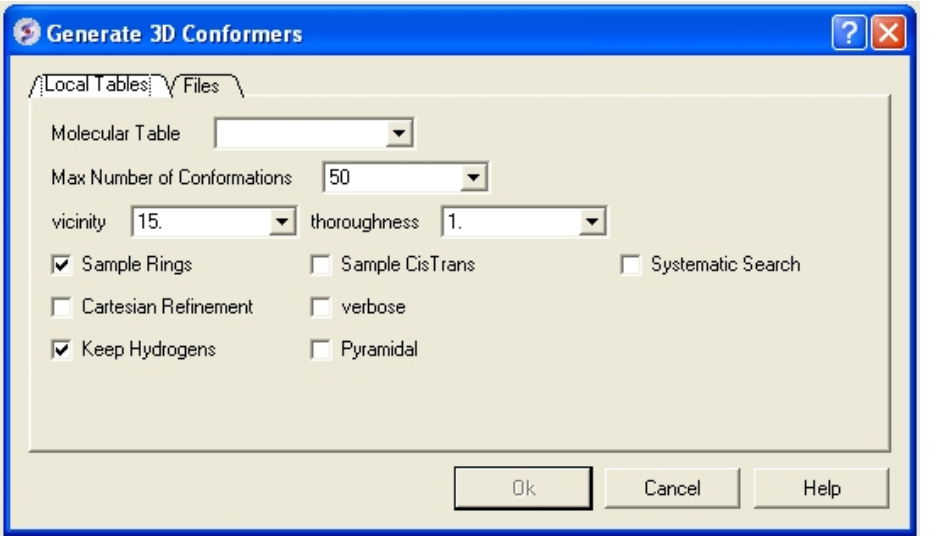
- `Select` the chemical (green crosses in graphical display).

- MolMechanics/ICM−Convert/Chemical

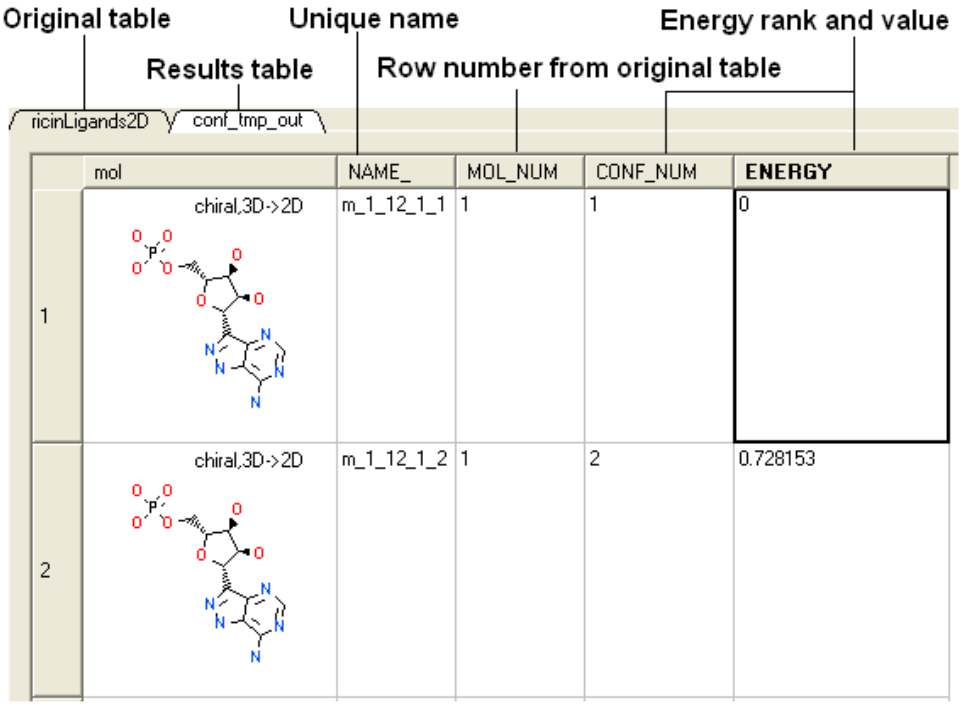
18.10 Generate 3D Conformers

To generate a series of conformers for a ligand(s):

- `Select` the compounds (row(s)) you wish to generate conformers for in an `ICM Molecular Table` . Or to convert a whole table of compounds select **Chemisty/Generate 3D Conformers** menu.
- Right click on the selected row(s) and Chemistry/Conformation Generator (selected rows) and a data entry window as shown below will be displayed.



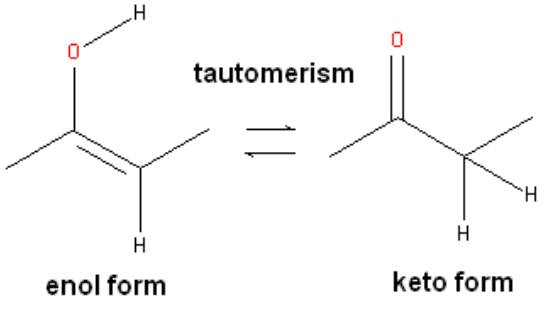
- Enter the maximum number of conformations you wish to generate.
- Enter a vicinity value. For more information on vicinity please see the command language manual `http://www.molsoft.com/man/reals.html#vicinity`
- Enter a thoroughness value. This relates to the length of sampling time.
- Check boxes for Sampling Rings, Systematic Search, Cartesian Refinement (http://www.molsoft.com/man/reals.html#vicinity),Sample Cis and Trans, sample Pyramidal and Verbose (Display Warnings).
- Click OK and the sampling will be undertaken in the background − see Windows/Background Jobs
- Once the sampling has finished a table as shown below will be displayed. To view the compounds in 3D − Right Click Menu Chemistry/Load and Preserve Coordinates



18.11 Generate Tautomers

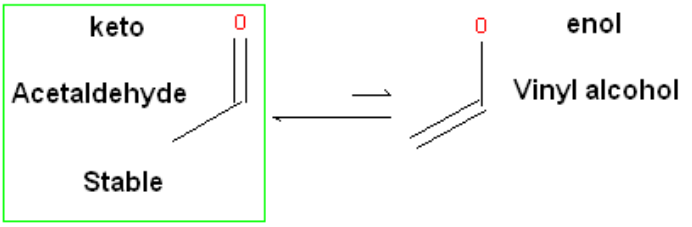
Theory

Tautomers are formed by an interconvertible reaction called tautomerization whereby there is a formal migration of a hydrogen atom along with a switch of a single bond and an adjacent double bond. A common example is the keto to enol tautomerism:



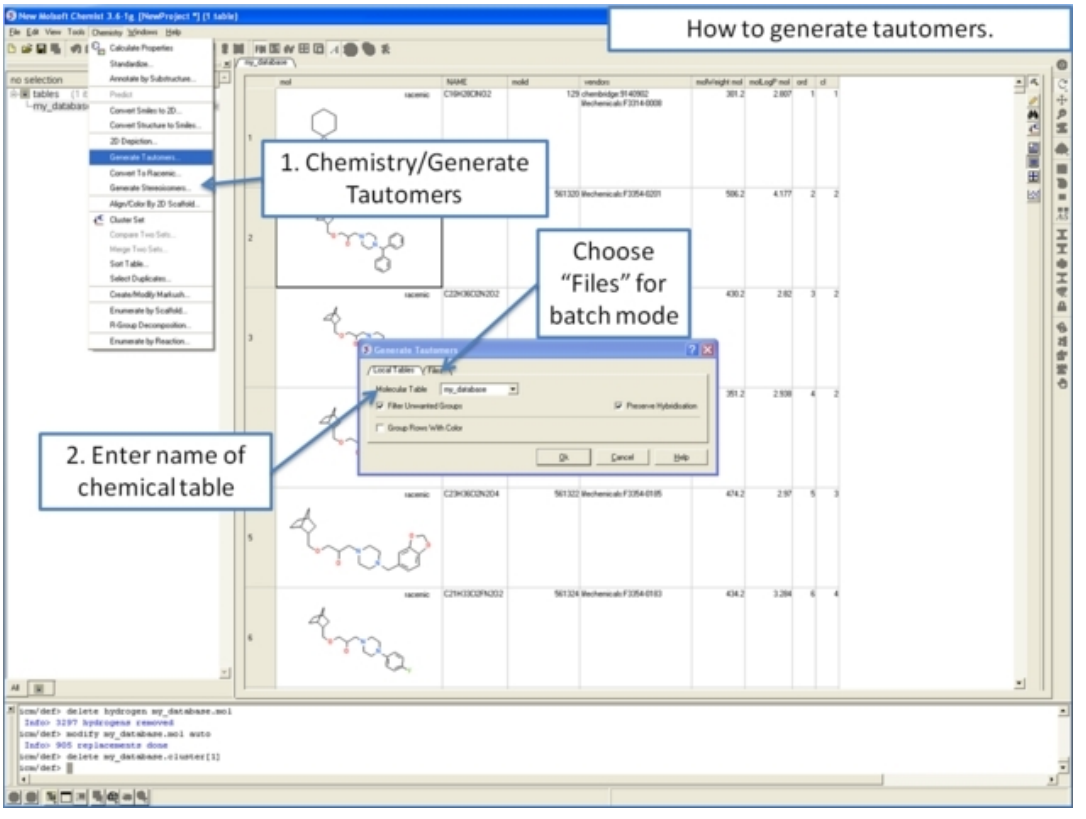
During tautomerization a chemical equilibrium of the tautomers will be reached based on several factors, including, pH, temperature and solvent. Tautomerizations are catalyzed by: bases (deprotonation, formation of a delocalized anion, and, protonation at a different position of the anion; and acids (protonation, formation of a delocalized cation, and deprotonation at a different position adjacent to the cation).

ICM will only generate energetically favorable tautomers. Generally tautomers that have a change in hybridization state are less stable and so ICM will not generate these thus reducing the number of scaffolds generated. For example the keto form shown below is more stable by ~14 kcal.mol than the enol therefore ICM will not generate the enol form.



To generate tautomeric conformations of your compound:

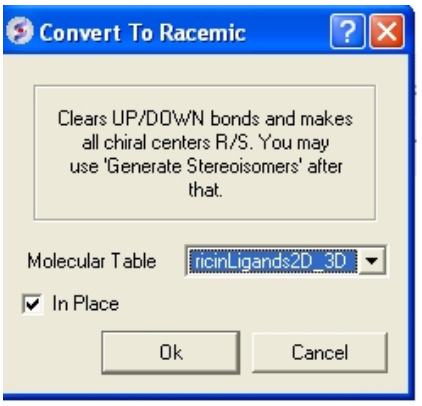
- Select the compound(s) in the molecular table. Selected compounds are highlighted in blue.
- Right click in the table and select the option Chemistry/ Enumerate Tautomers. Or select the Chemistry menu/Generate Tautomers.
- If you select Chemistry/Generate Tautomers a dialog box will be displayed. There is also an option to run in batch mode (click the **Files** Tab).
- Choose the table containing the compounds using the drop−down list.
- **Filter Unwanted Groups** option will filter results from patterns in the TAUTOFILTER.tab file provided in the distribution. If results match any row from that table then the it will be excluded.
- **Preserve Hybridisation** Although generally a change in hybridisation state will generate less stable compounds in some cases this is not the case and so you can choose to change hybridisation for a single atom.
- **Group Rows With Color** option will color tautomers from the same compound with the same color to visually highlight groups.
- The compounds will be displayed in a separate molecular table called TAUTOMERS.



18.12 Convert to Racemic

To remove stereo bonds and make all chemical centers R/S in a chemical table:

- **Chemistry/Convert to Racemic**
- Select the Molecular Table
- Select **In Place** if you wish to overwrite the table.



NOTE: To reassign stereo bonds use the `Generate Stereoisomers option`

18.13 Generate Stereoismers

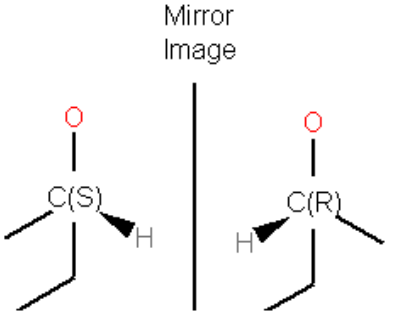
Theory

Isomers are molecules which have the same chemical formula and sometimes the same kind of bonds but in which the atoms are arranged differently.

Structural isomers have different atom−to−atom connections e.g. propanol (C3H8O or C3H7OH) has two isomers Propan−1−ol and Propan−2−ol.

Diastereomers are not mirror images and have different internal dimensions (e.g. dihedral angles and distances between non−bonded atoms). They can be configurational diastereomers (which can be interconverted only by breaking bonds or by changing the configurations of stereocenters) or conformational diastereomers (which can be interconverted by rotation about bonds − including chair flips or by lone pair inversion .

Enantiomers have identical internal dimensions, and are nonsuperimposable mirror images. Enantiomers can be configurational and conformational.

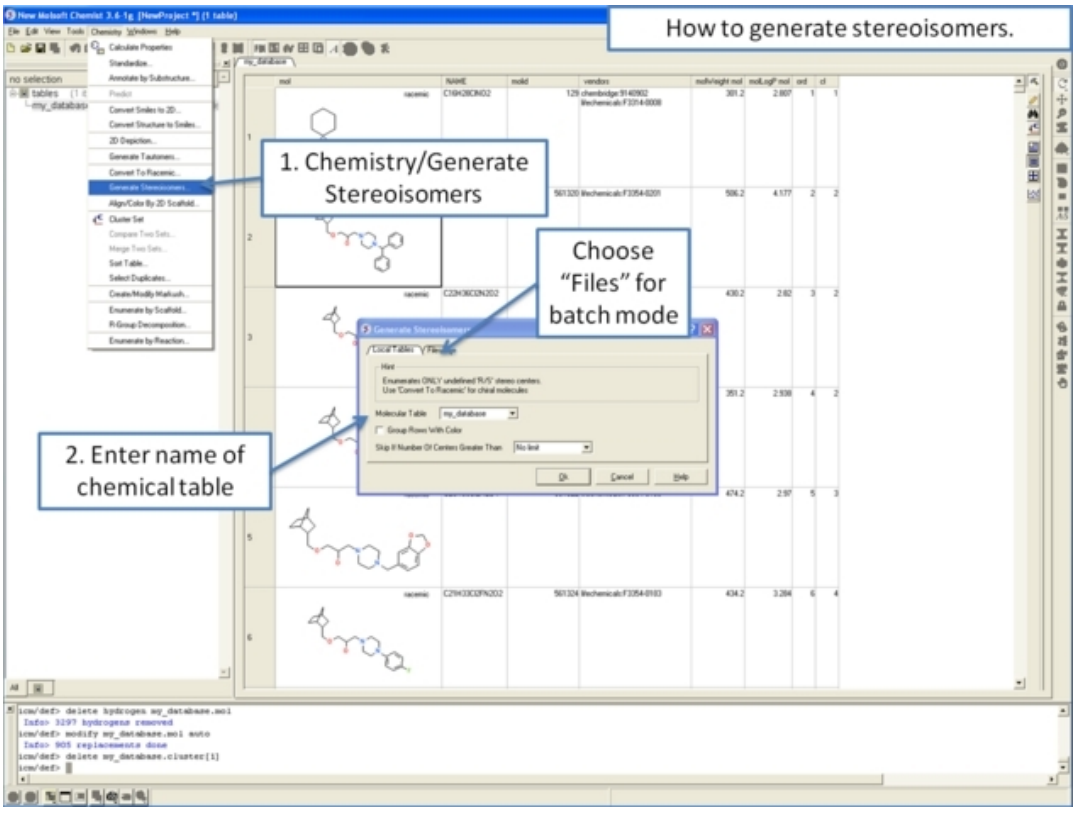


Enatiomers are distinguished based on the Latin terms for left (sinister) and right (rectus). In some cases where the handedness is unknown a chiral center can be labeled "RS"or unknown.

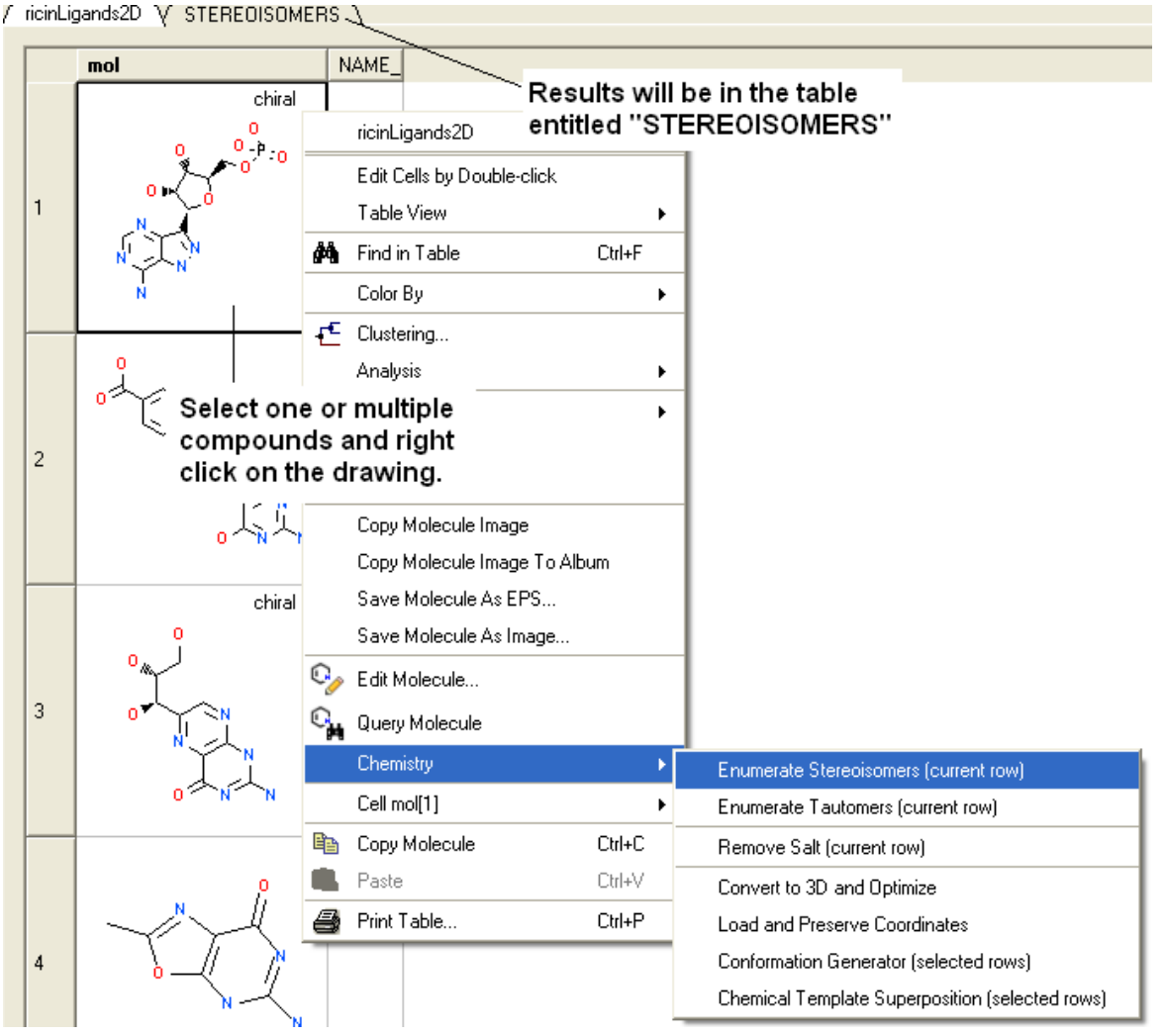
To enumerate and display in a separate table the stereoisomers of selected compounds.

- Select the compound(s) in the molecular table. Selected compounds are highlighted in blue.
- Right click in the table and select the option **Chemistry/ Enumerate stereoisomers**. Or select the Chemistry menu and choose **Generate Stereoisomers**. If you generate stereoisomers via the Chemistry menu you will get a dialog box whereby you can run the process in batch mode. There is also an option to color stereoisomers from the same compound with the same color.
- The compounds will be displayed in a separate molecular table called STEREOISOMERS.

From the Chemistry Menu:



From a chemical spreadsheet:}

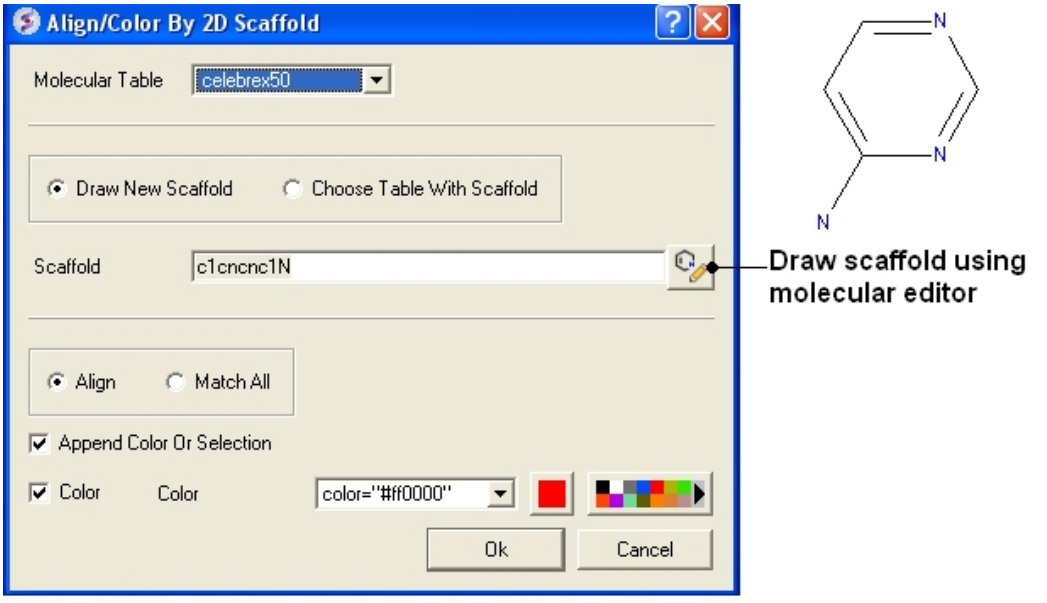


NOTE: Only centers with unknown chirality will be enumerated.

18.14 Align/Color by 2D Scaffold

This option **aligns** a set of sketches in a chemical table in the same orientation according to a defined scaffold or **color** by a common substructure.

- Chemistry/Align−Color by 2D Scaffold
- Choose a loaded molecular table from the drop−down arrow.
- Draw a new scaffold using the molecular editor or choose the scaffold from a table (Index = row number).
- You can then **Align** or **Match All** the substructure and color.
- If coloring has already applied to the molecule then this new coloring by scaffold can be appended.
- Select **color** for common scaffold.

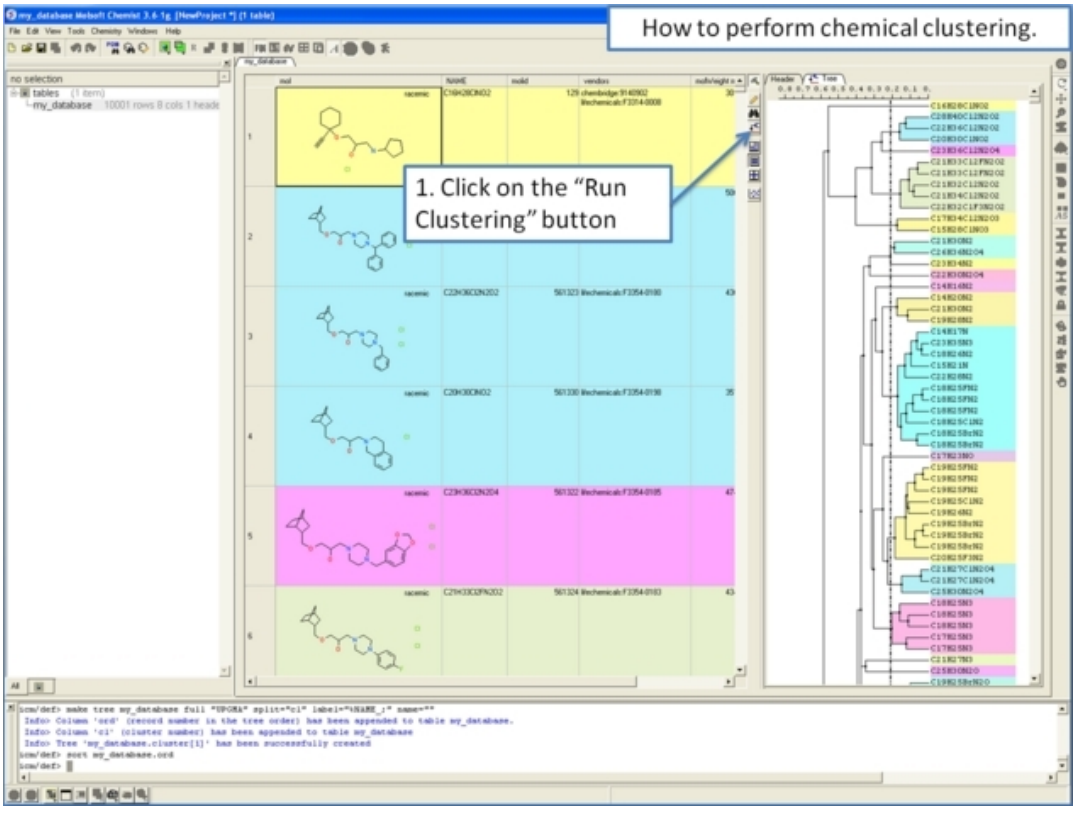


18.15 Cluster Set

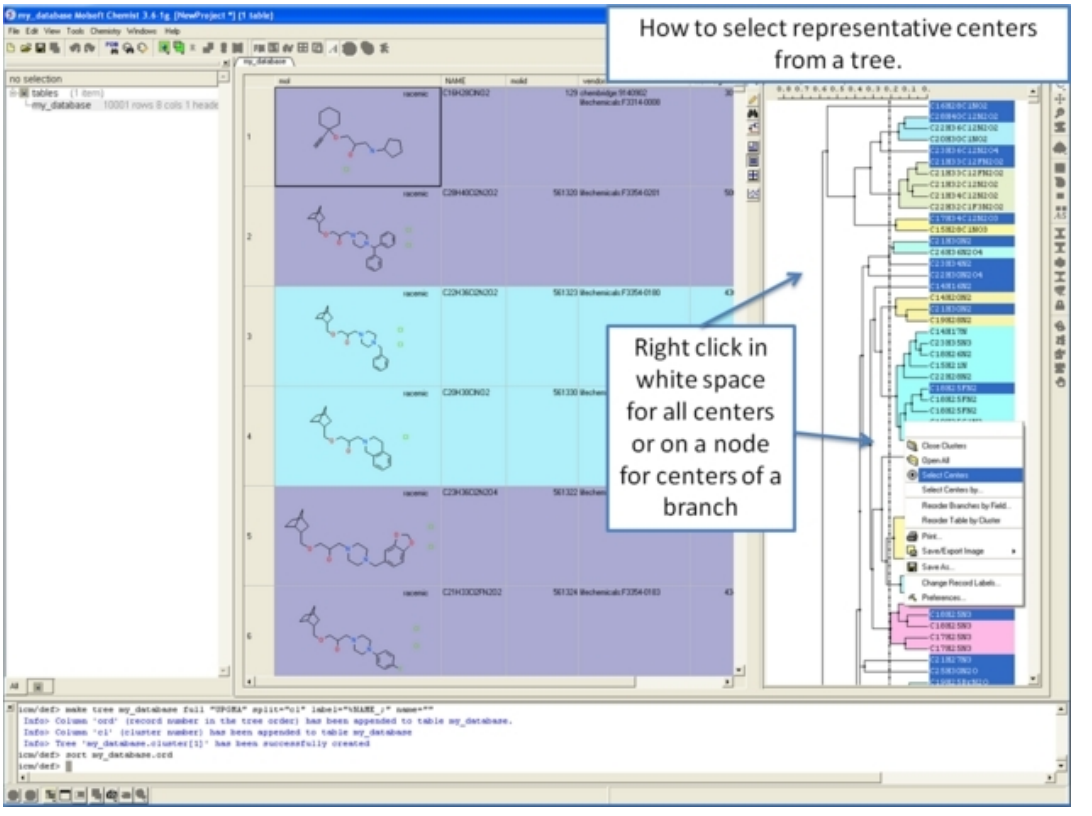
Clustering is described in more detail in the `Tables Clustering` section of this manual. To undertake chemical clustering choose:

- Chemistry/Cluster Set

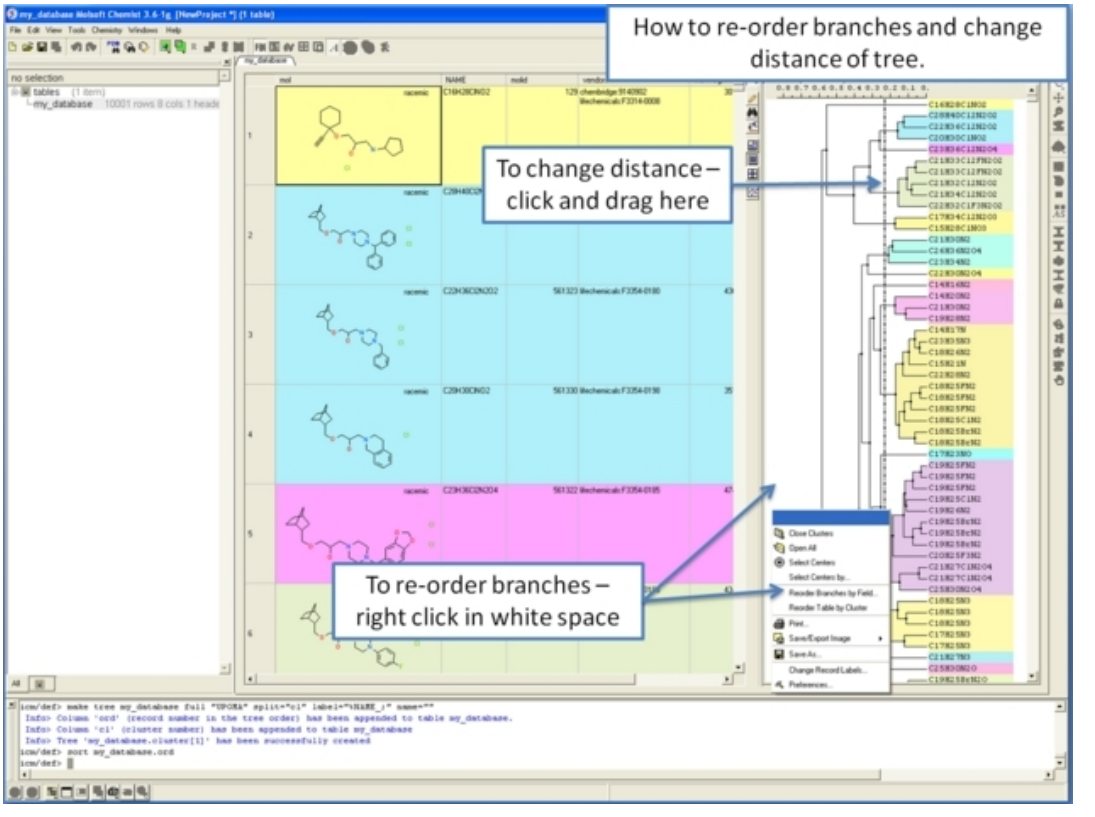
18.15.1 How to perform chemical clustering.



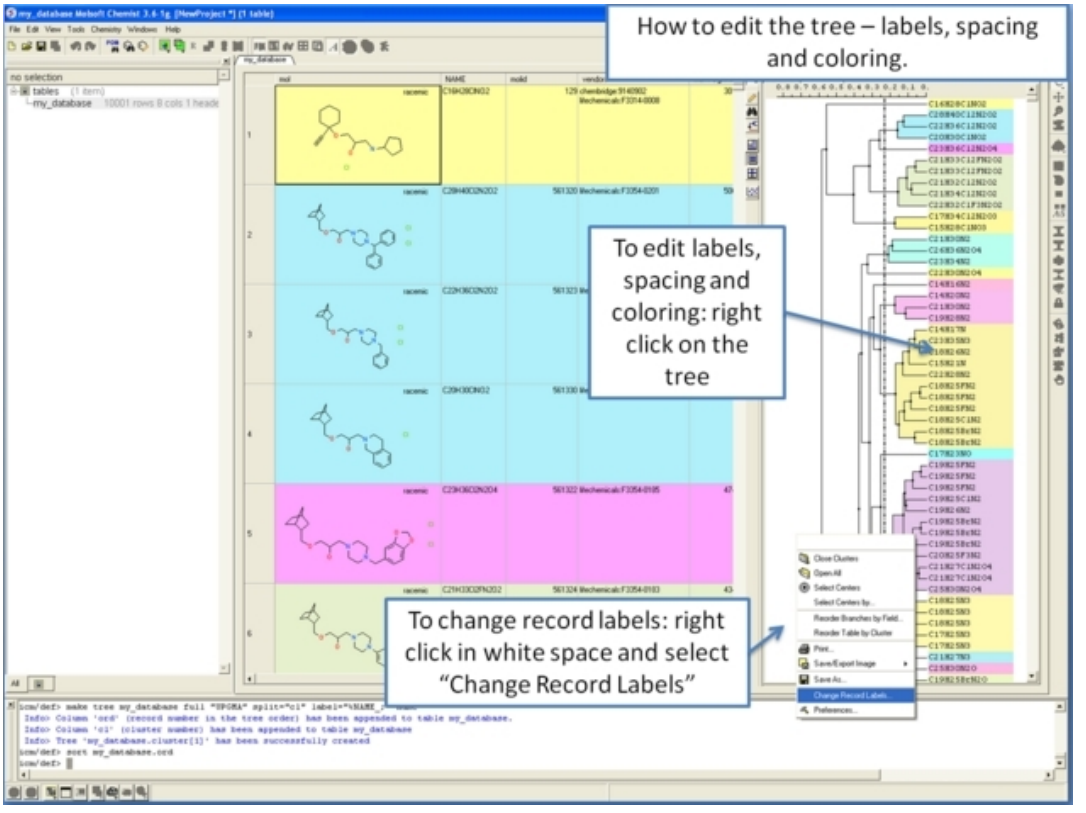
18.15.2 How to select representative centers from a tree.



18.15.3 How to reorder branches and change the distance of trees.



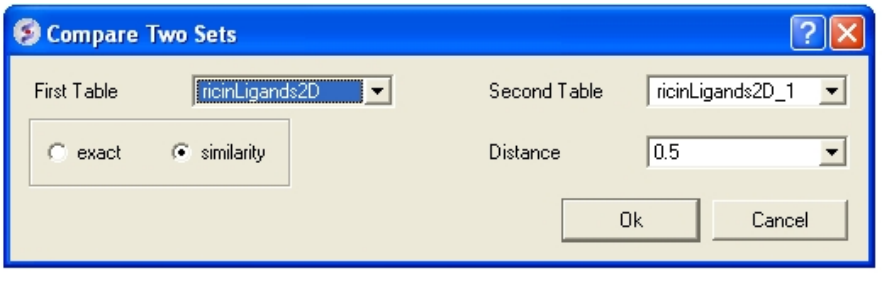
18.15.4 How to edit the tree − labels, spacing and coloring.



18.16 Compare Two Sets

To compare two chemical tables for similar compounds:

- `Read` the two tables into ICM.
- **Chemistry/Compare Two Sets...**
- Select the first table from the drop−down list and then select the second table.
- Choose whether you want to use **exact** or **similarity** comparison. If the **similarity** option is selected a **Distance** value needs to be entered.
- Select OK
- Similar compounds will be highlighted blue (selected). A selection can be transferred to a new table by right−clicking on the table and select **Copy Selection to ICM Table**.

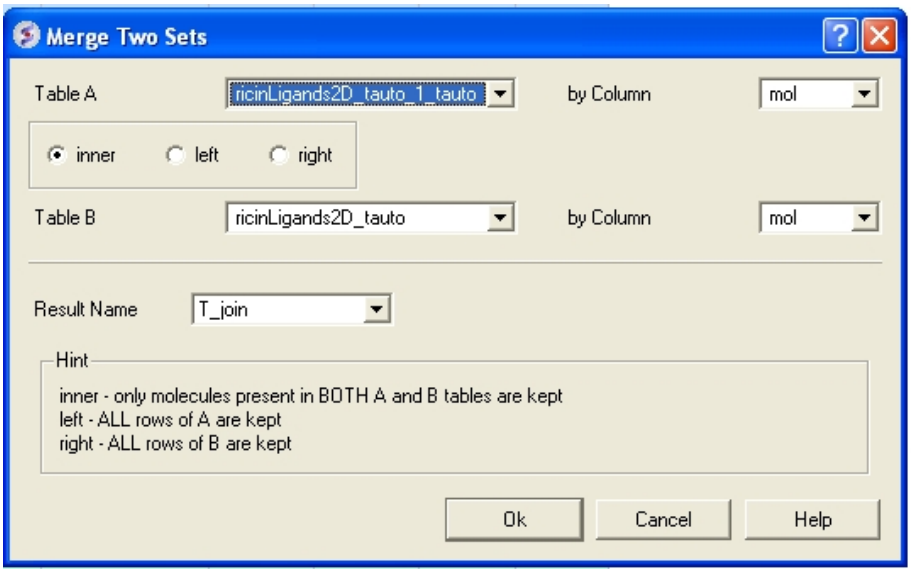


18.17 Merge Two Sets

To merge two tables:

- `Read` the two tables into ICM.
- Chemistry/Merge Two Sets

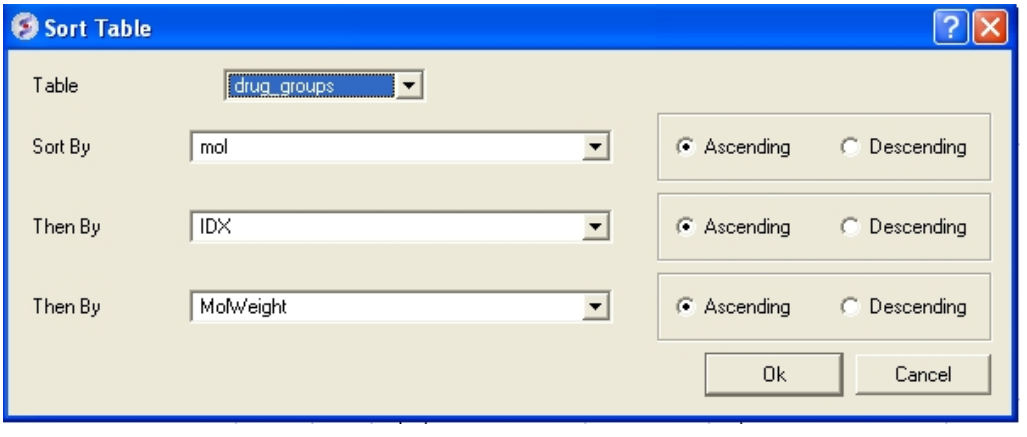
- Select the first table from the drop down list (Table A) and the column you wish to use to merge the table by.
- Select merge method 1. **inner** − only molecules present in BOTH A and B tables are kept; or 2. **left** ALL rows of A are kept ; or 3. **right** ALL rows of B are kept.
- Select the second table from the drop down list (Table B) and the column you wish to use to merge the table by.
- Enter a name for the output table.
- Click OK and a new table will be displayed.



18.18 Sort Table

There are a couple of ways to sort a chemical table. You can right click on the a column header and select `sort` or you can use the option in the menu Chemistry/Sort Table.

- `Read` a chemical table into ICM.
- Select the columns by which you wish to sort by as shown below.
- Select **Ascending** or **Descending** and for each **sort by** option and then click OK

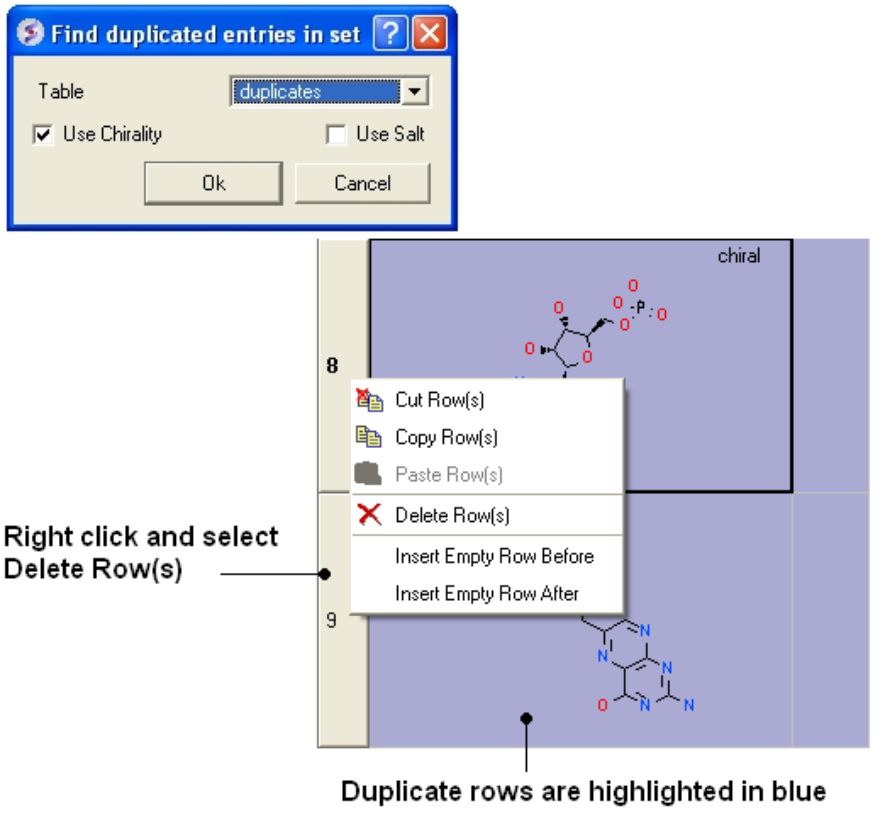


18.19 Select Duplicates

NOTE: Gui option is available in versions 3.5−1o and higher. The command line options for this function are described in the ICM Command Language manual at `http://www.molsoft.com/man/icm-functions.html#Index-chemical`

This option allows you to select and remove duplicate chemicals in a table.

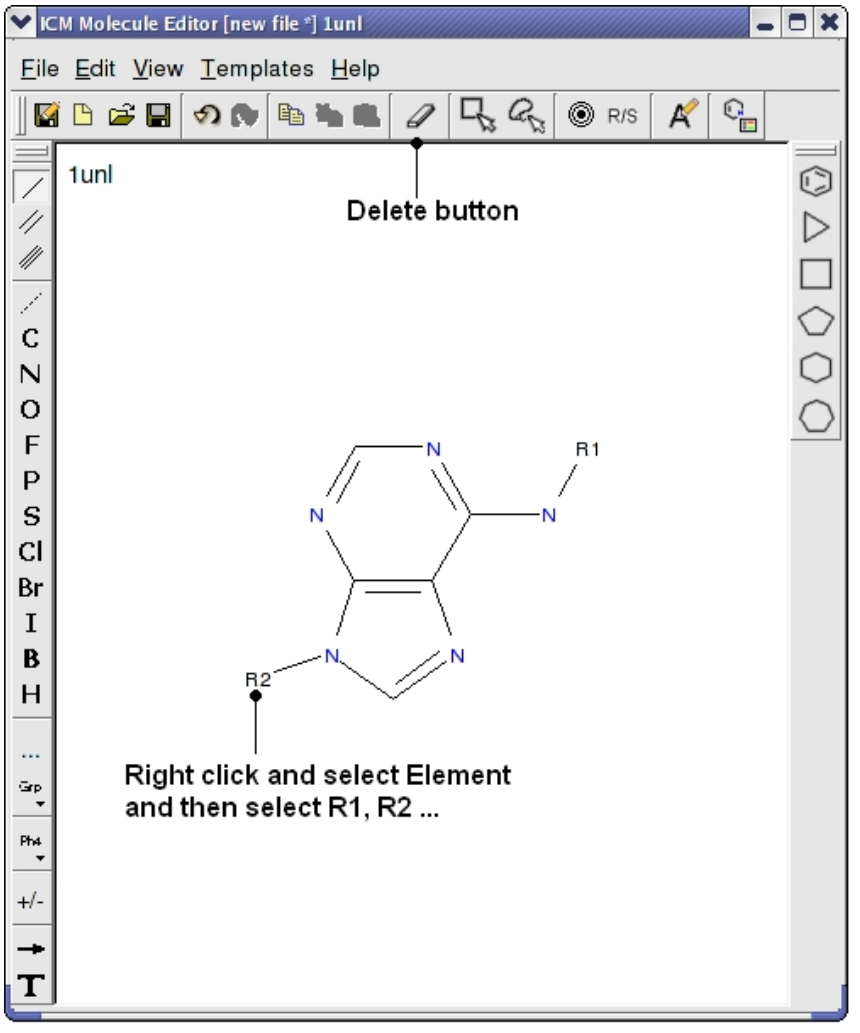
- `Read` a chemical table into ICM.
- Chemistry/Select Duplicates
- Enter the table name you want to check for duplicates
- Enter whether you want chirality or the salts included in the analysis.
- Press OK
- Duplicate compounds will be **highlighted** blue in the table. You can delete them by right clicking on the row header ans selecing **Delete Rows(s)**



18.20 Create/Modify Markush

To create or modify a Markush Structure:

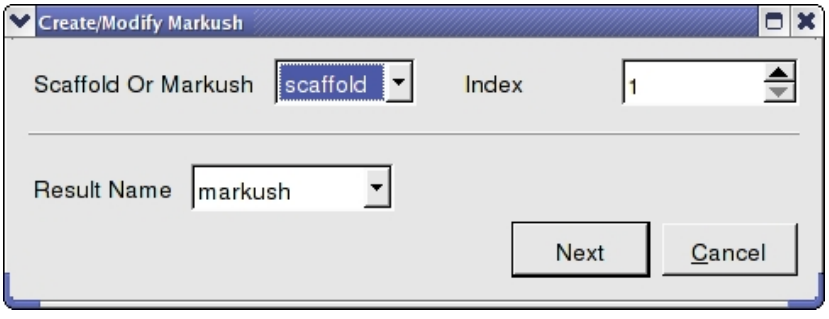
- Use the `Molecular Editor` to edit the scaffold as shown below.



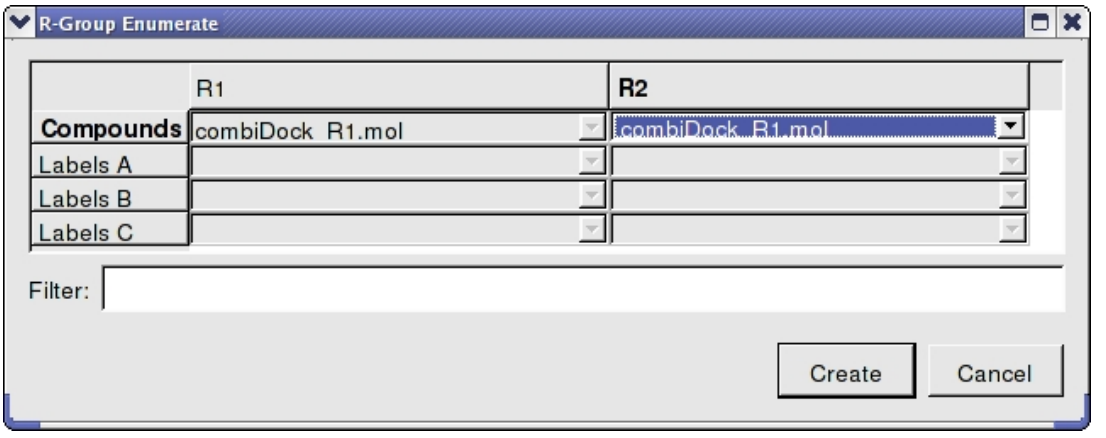
- Close the `Molecular Editor` window by clicking on the cross in the top right hand corner and the changes will be submitted to the table.
- The sketch in the chemical spreadsheet is named "chem" by default. For this example we will rename it "scaffold". You can rename it by right clicking on the table tab and selecting rename.

Step 4: Create Markush Combinatorial Library

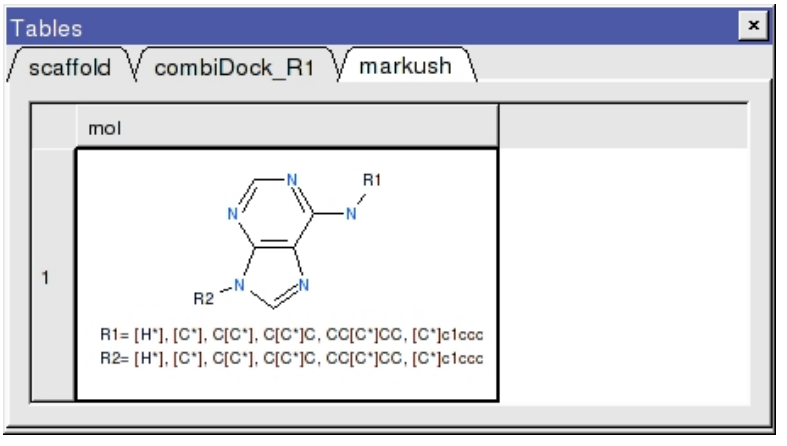
- Read in a table of substituents. For this example we will use an sdf file called combiDock_R1.sdf − this can be found in the ICM distribution (File/Open). If you cannot find this file please E mail support@molsoft.com and we will send it to you.
- Chemistry/Create Modify Markush and enter the data as shown below and press next.



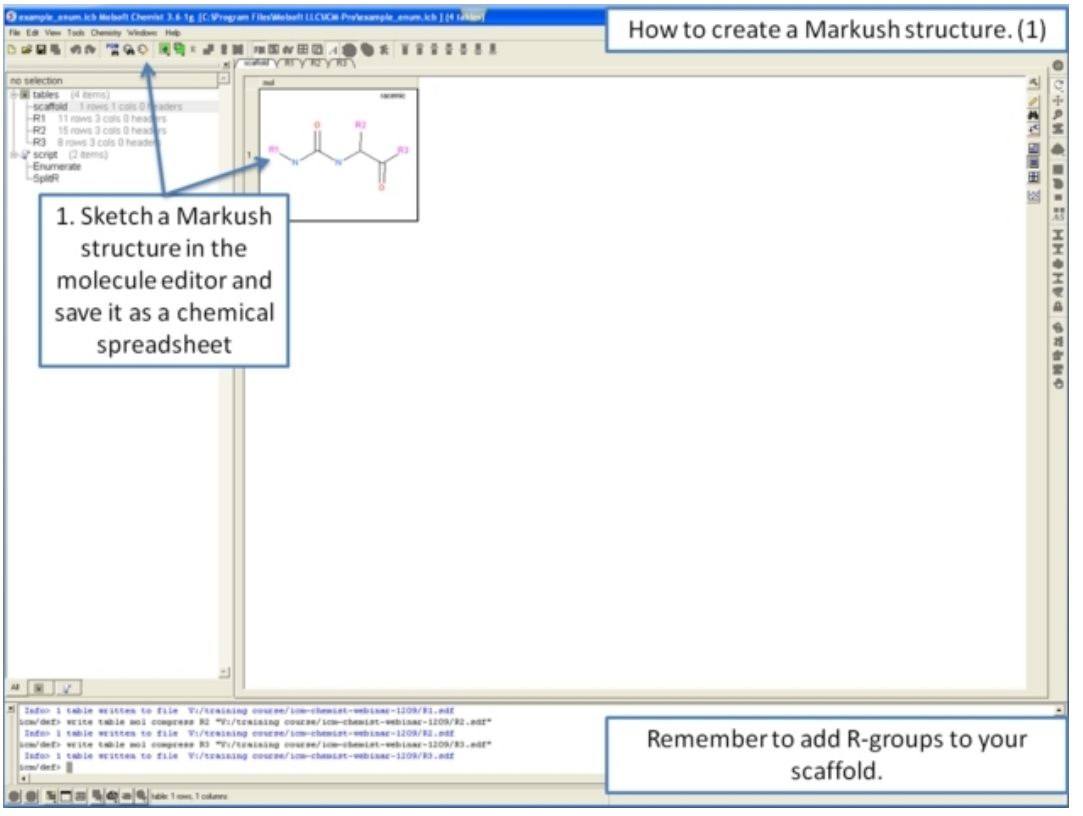
- Enter the name of the table containing substituents for R1 and R2. In this example we will use the same table **combiDock_R1** for R1 and R2 as shown below. You can use the drop down arrows to select the table you require.

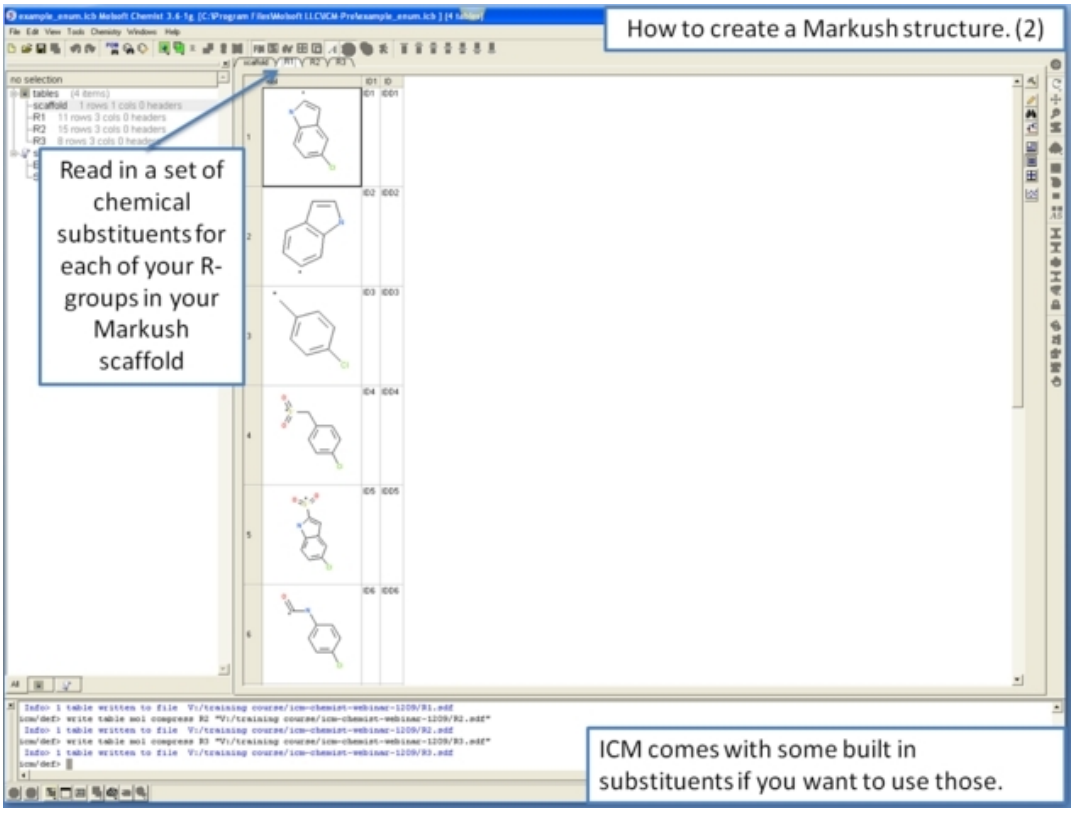


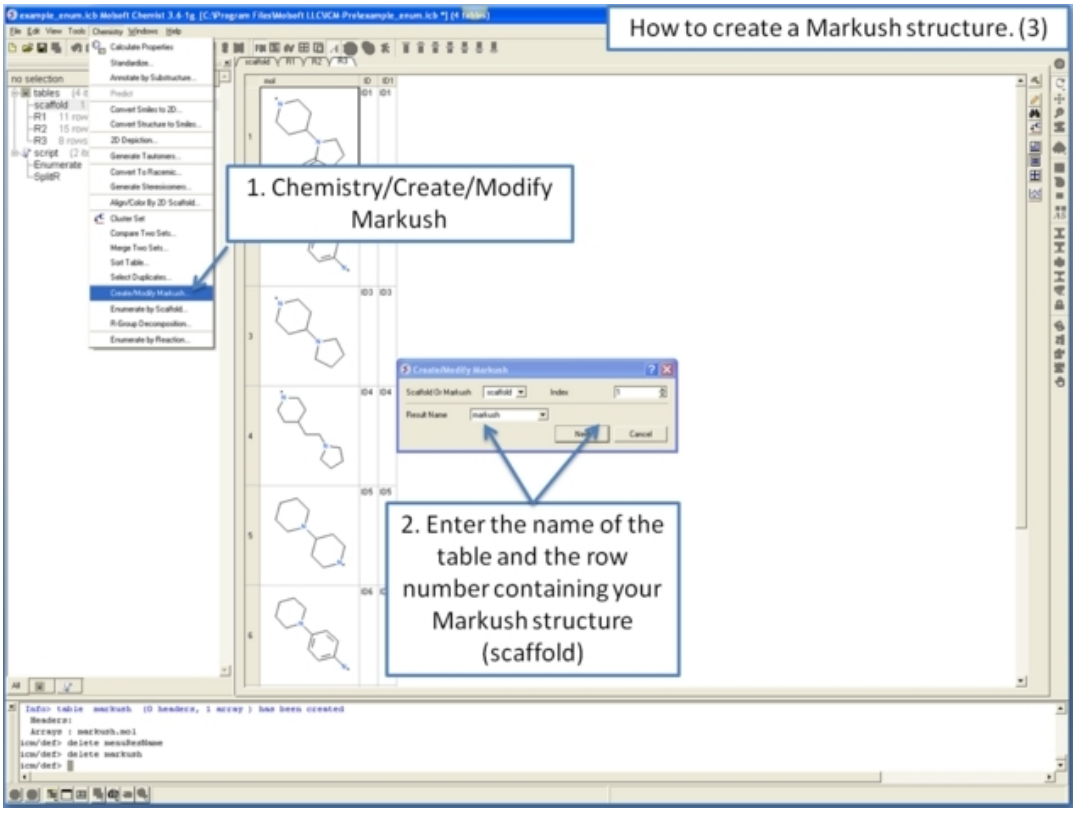
- Once the tables are selected press **Create** and a new chemical table will be displayed with the markush structure annotated with the substituents for R1 and R2 as shown below.

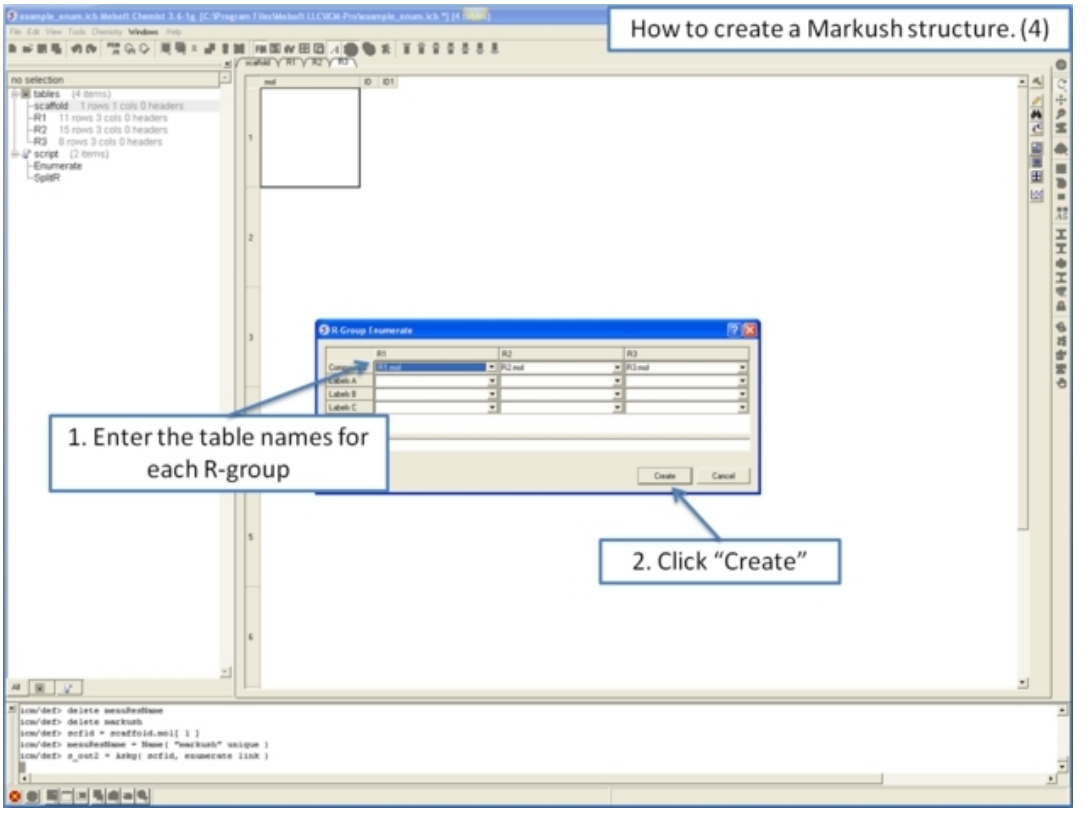


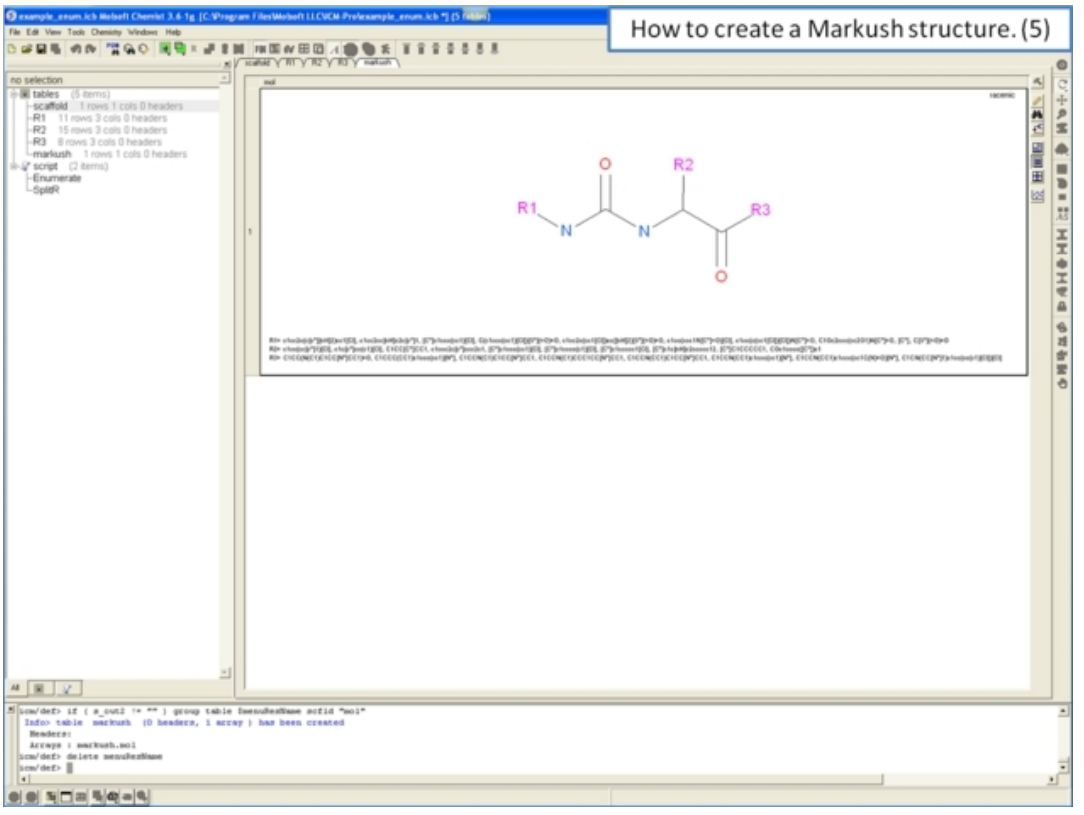
18.20.1 How to create a Markush structure.


How to create a Markush structure. (1)
1. Sketch a Markush structure in the molecule editor and save it as a chemical spreadsheet
Remember to add R-groups to your scaffold.


How to create a Markush structure. (2)
Read in a set of chemical substituents for each of your R-groups in your Markush scaffold
ICM comes with some built in substituents if you want to use those.


How to create a Markush structure. (3)
1. Chemistry/Create/Modify Markush
2. Enter the name of the table and the row number containing your Markush structure (scaffold)

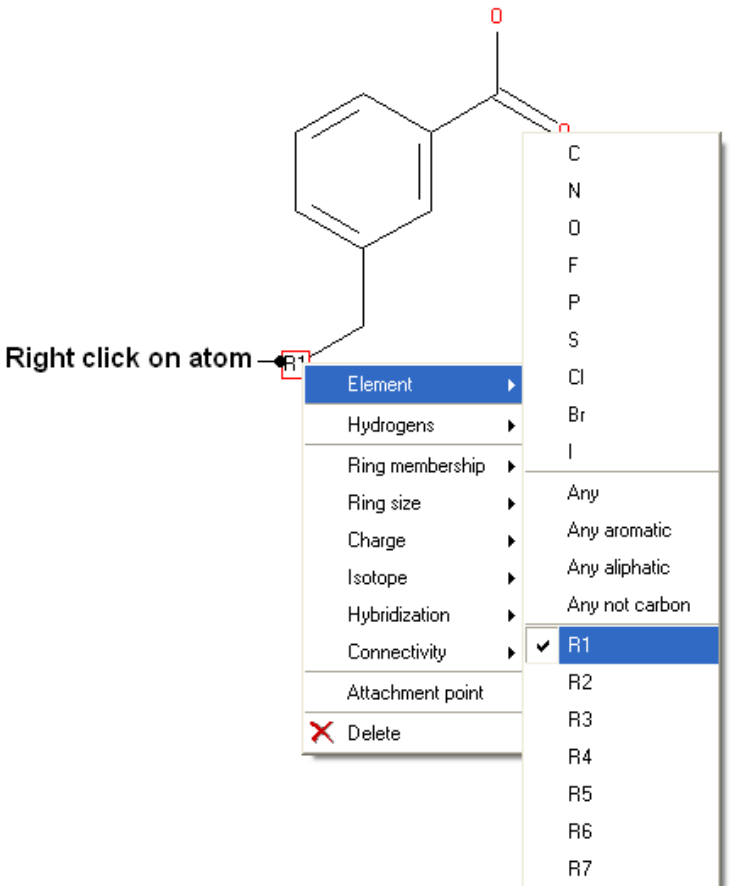

How to create a Markush structure. (4)
1. Enter the table names for each R-group
2. Click “Create”



18.21 Enumerate by Scaffold

To enumerate a library based on R−groups you first need to draw a sketch of the structure and display it in a `chemical spreadsheet`. To do this:

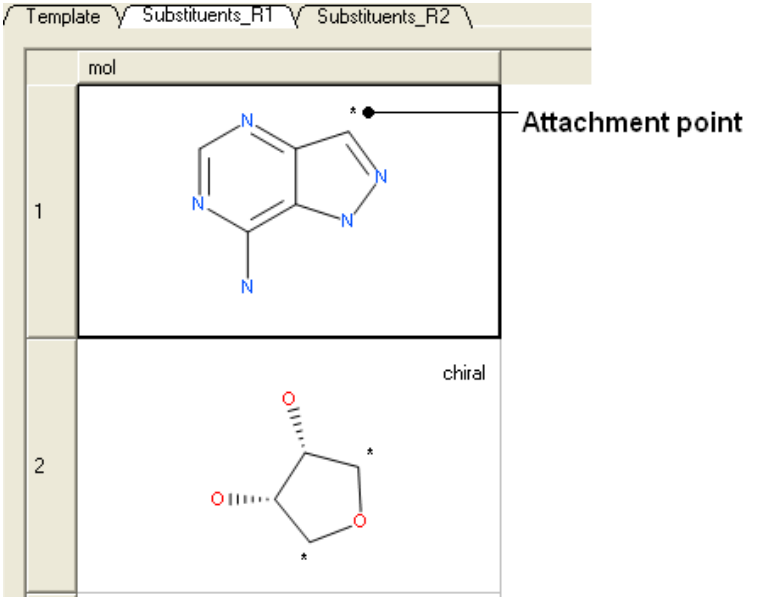
- Open up the `ICM Molecular Editor`.
- Draw the template structure with R−groups attached. Right click on an atom and select Element/R1, R2 ...



- In the Molecular Editor select File/Append to Table/New

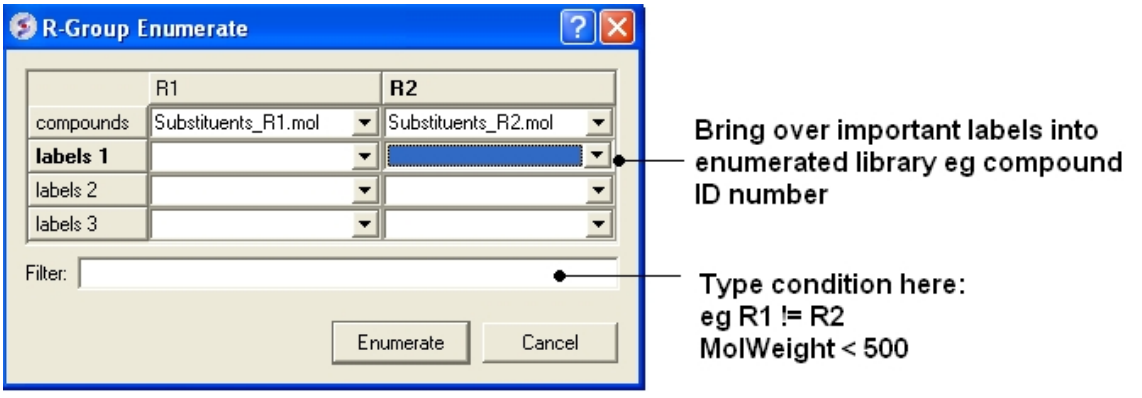
The next step is to read into ICM or construct a table of substituents. You can read in an SDF, mol, smiles file or `extract fragments`. If you do not want the first atom of the substituents to be the attachment point you need to define the attachment point. Attachment points are automatically assigned when you `extract fragments` or you can define them manually by:

- Right click on the substituent sketch and select **Edit Molecule**
- Right click on the atom and select **Attachment point**.

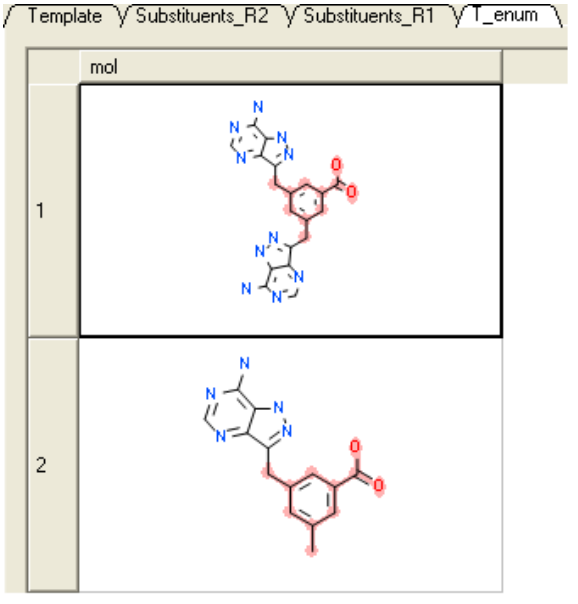


Next enumerate the library

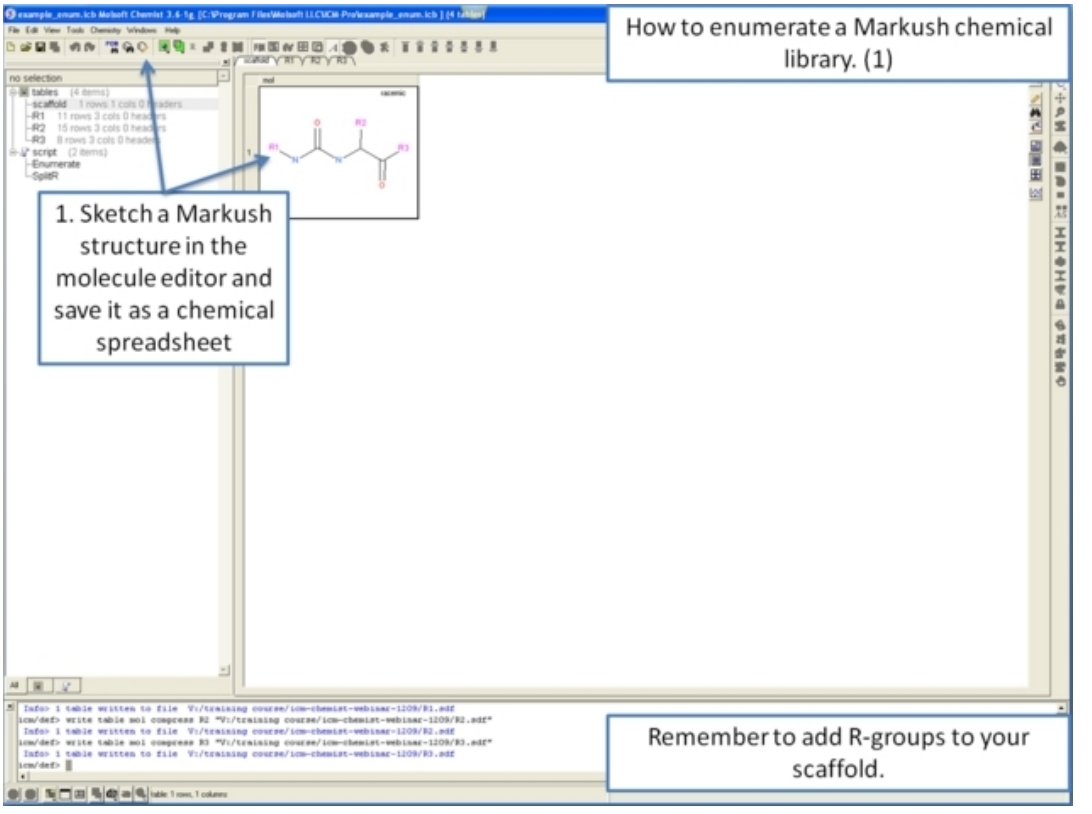
- Select the template structure (highlighted blue).
- Right click on the structure and select Chemistry/Enumerate R−groups or use the Chemistry menu and select Enumerate by Markush. If you use the menu option you will need to choose the table containing the scaffold from the drop down list of currently loaded tables. The index number refers to the row number in the scaffold table. In this example we only have one row containing the scaffold so the index number is 1.
- Select the R1, R2... table , labels and filters if necesary.

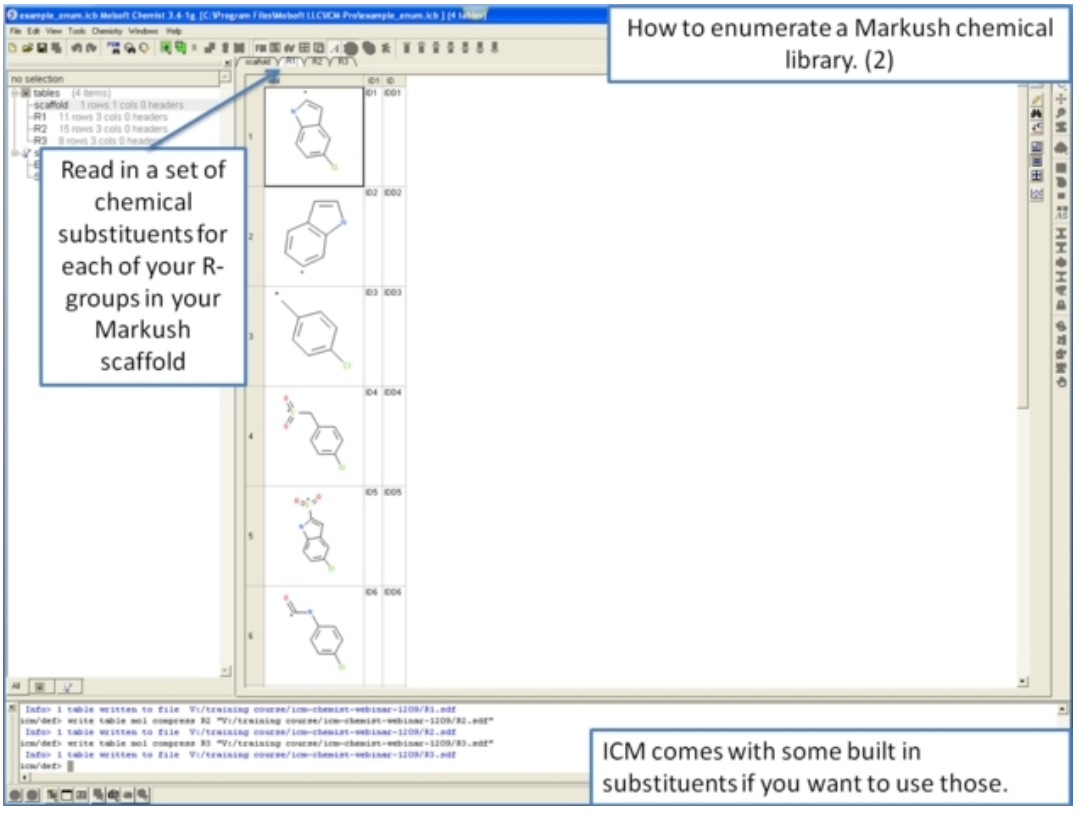


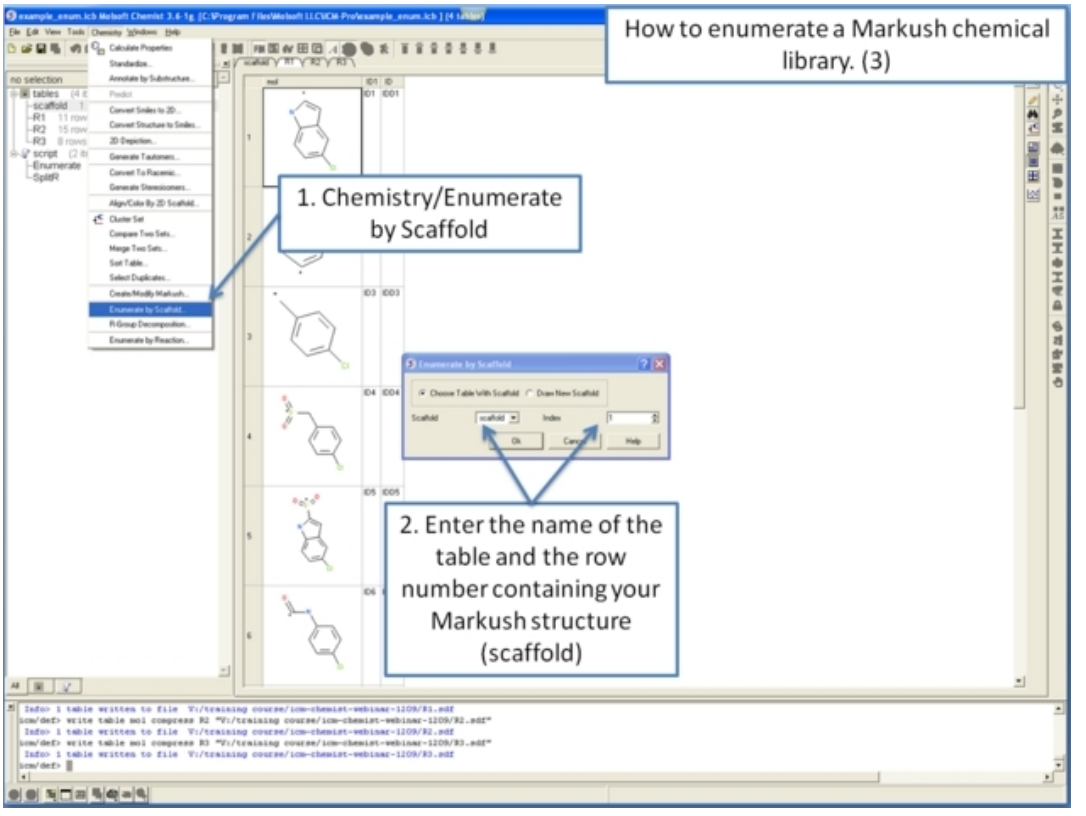
A new table will be produced called **T_enum** with the Template structure highlighted in red.

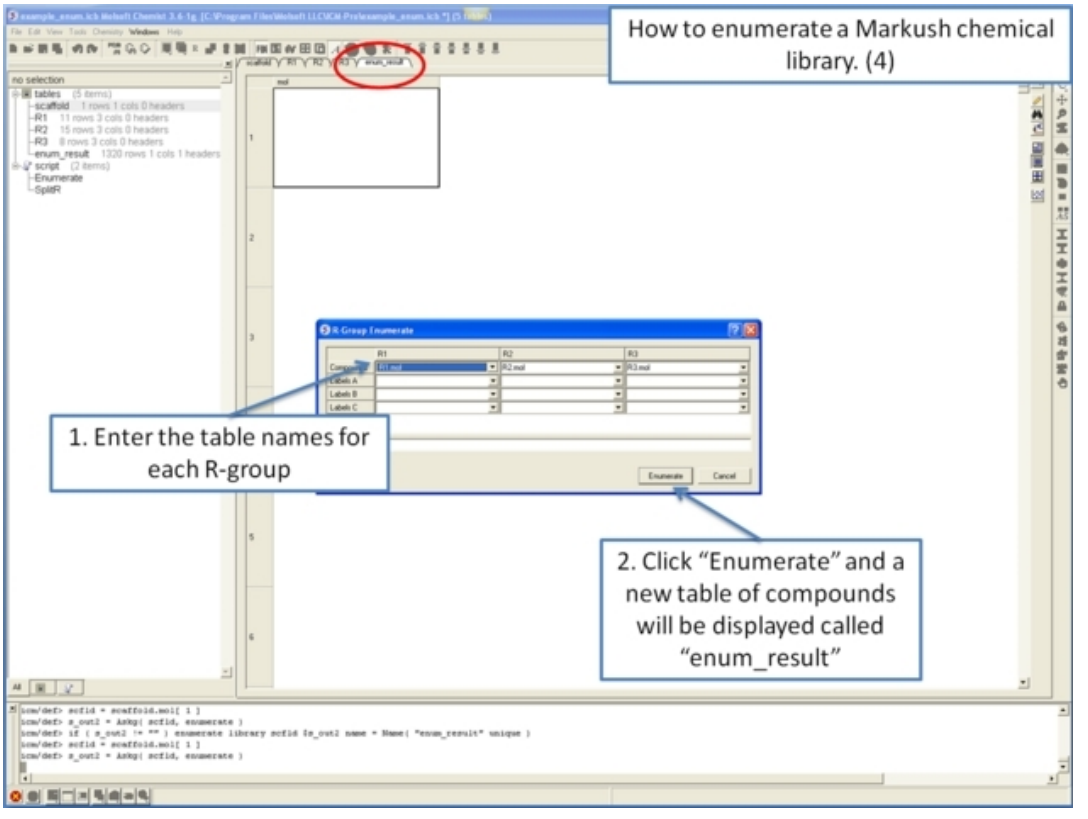


18.21.1 How to enumerate a Markush library.


How to enumerate a Markush chemical library. (1)
1. Sketch a Markush structure in the molecule editor and save it as a chemical spreadsheet
Remember to add R-groups to your scaffold.


How to enumerate a Markush chemical library. (2)
Read in a set of chemical substituents for each of your R-groups in your Markush scaffold
ICM comes with some built in substituents if you want to use those.

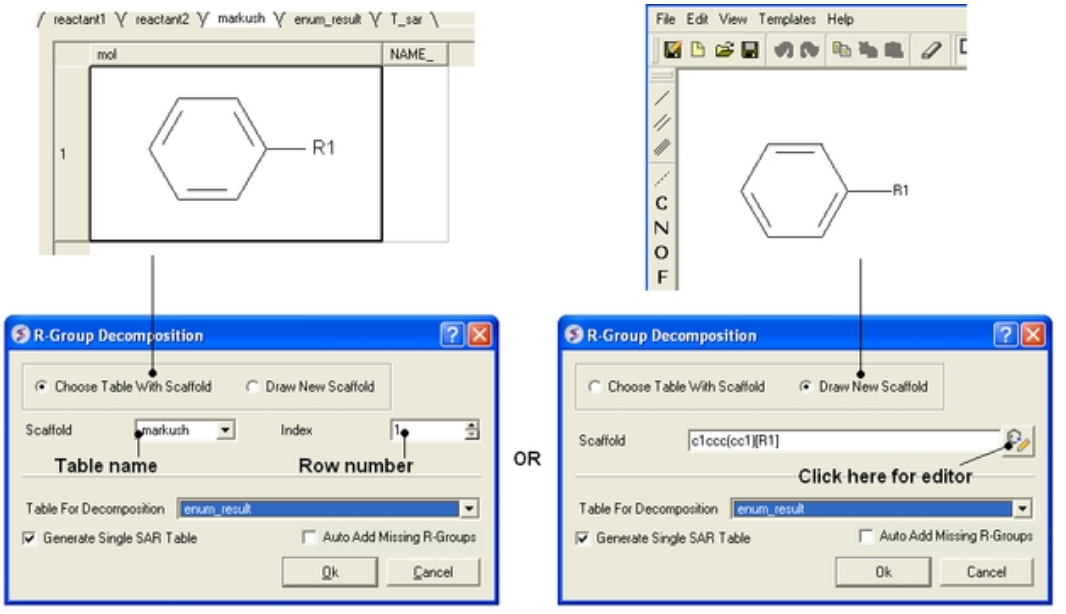




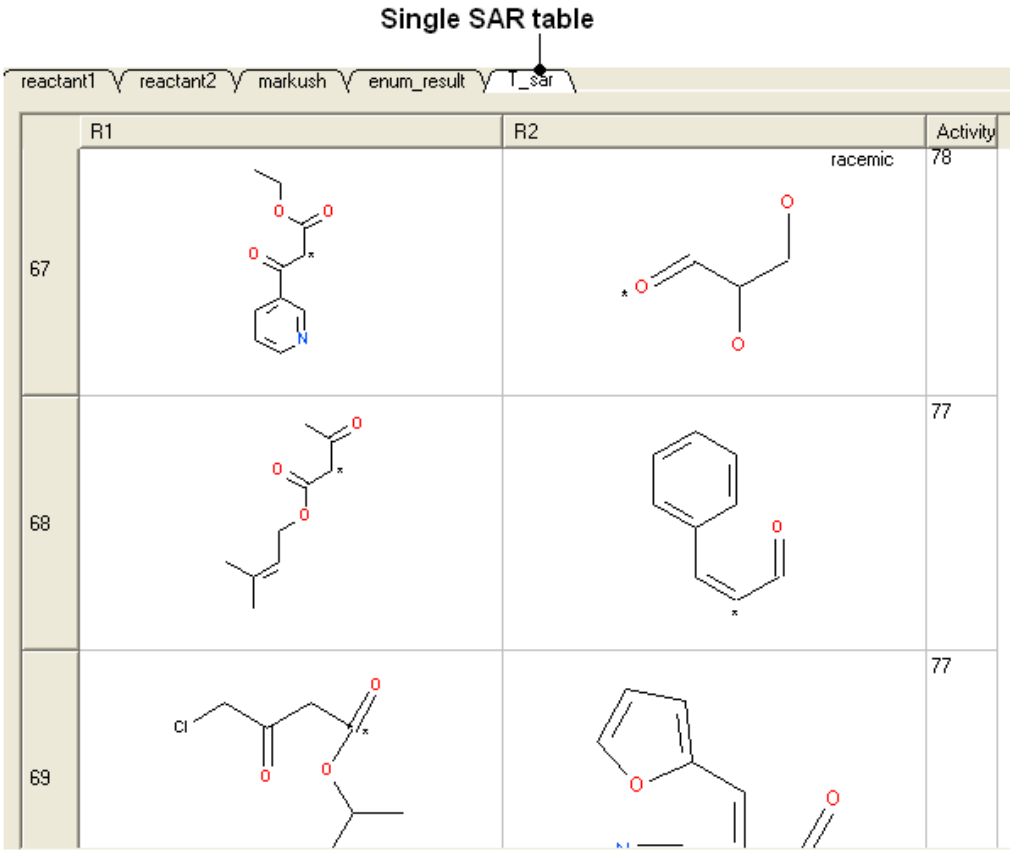
18.22 R−Group Decomposition

To decompose a library into fragments based on a Markush scaffold (opposite of `R-group (Markush) enumeration`):

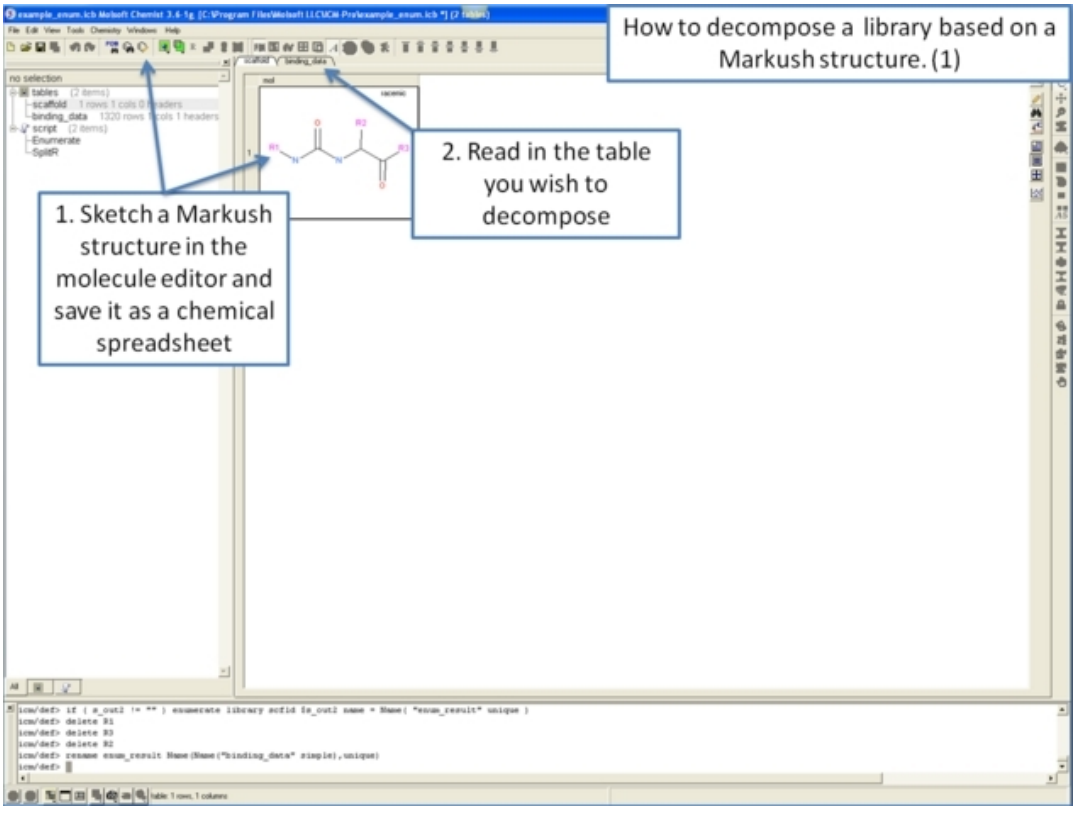
- Read the sdf file you wish to decompose into ICM and it will be displayed as a molecular table.
- **Chemistry/R−Group Decomposition** and a window as shown below will be displayed.
- You now have two options on how to define the Markush scaffold. You can either 1). Draw it using the molecular editor and the smiles string will be added to the window shown below or 2). select a row of a prexisting table.

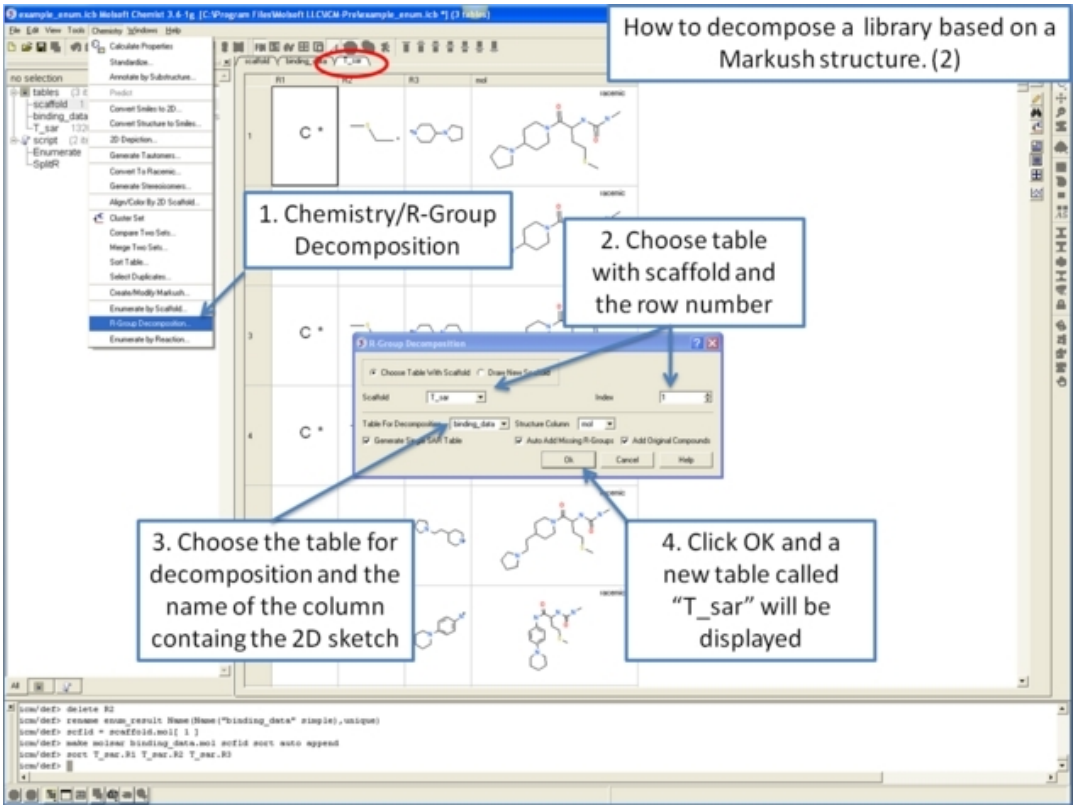


- Use the drop−down option to select the table you wish to decompose.
- If you have more than one R−group ICM can either generate a different table for each R−group or it can merge it into one single table whereby column will represent R1 and column two R2 .... This option is useful if you want to generate a SAR table with a column of activity data next to the R1 and R2 columns (see below).
- If you check the box "Auto Add Missing R Groups" then unique R−groups will be extracted from the scaffold where hydrogens can be attached.



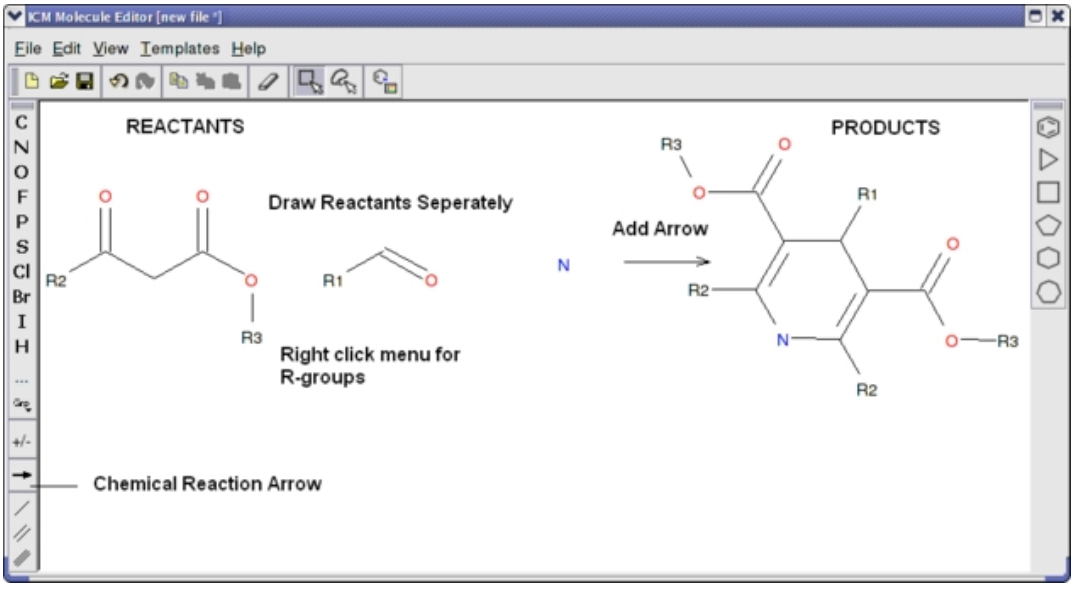
18.22.1 How to decompose a library based on a Markush structure.





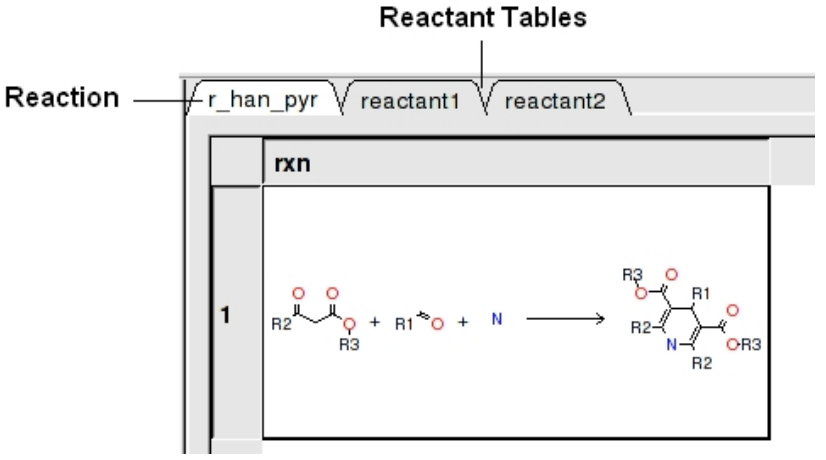
18.23 Enumerate by Reaction

Reactions can be drawn using the `ICM Molecular Editor`. Reactants should be drawn side−by−side (no + sign is necesary) and separated from the product using the arrow. See example shown below:



This example is available in the ICM distribution as example_reaction1.icb. The reaction is the Hantzsch Dihydropyridine (Pyridine) Synthesis. This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a ï¿½−ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine−3,5−dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

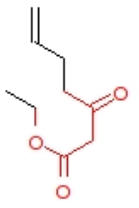
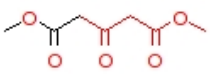
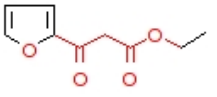
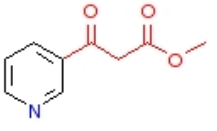
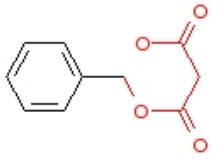
In this example we have two reactants therefore it is necesary to have two reactant substructure tables loaded into ICM. ICM will match the substructure drawn in the reaction with the chemicals in thereactant table.



reactant 1 table:

r_han_pyr | reactant1 | reactant2

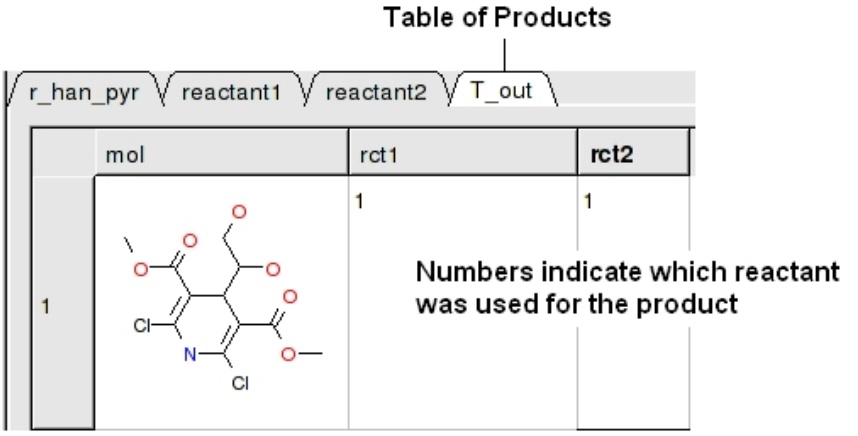
Substructure search: Found **88** hits of 'O=C([C;D2]C(=O)O[R3])[

	molid	MolW	mol	vendors
18	65236	170.094		asdi:500028335
19	87804	174.053		apolloscientific:12582 asdi:500014701
20	65360	182.058		apolloscientific:13718 keyorganics:11X-0925
21	87822	179.058		apolloscientific:2965 interchim:616
22	3341	194.058		asdi:500016383

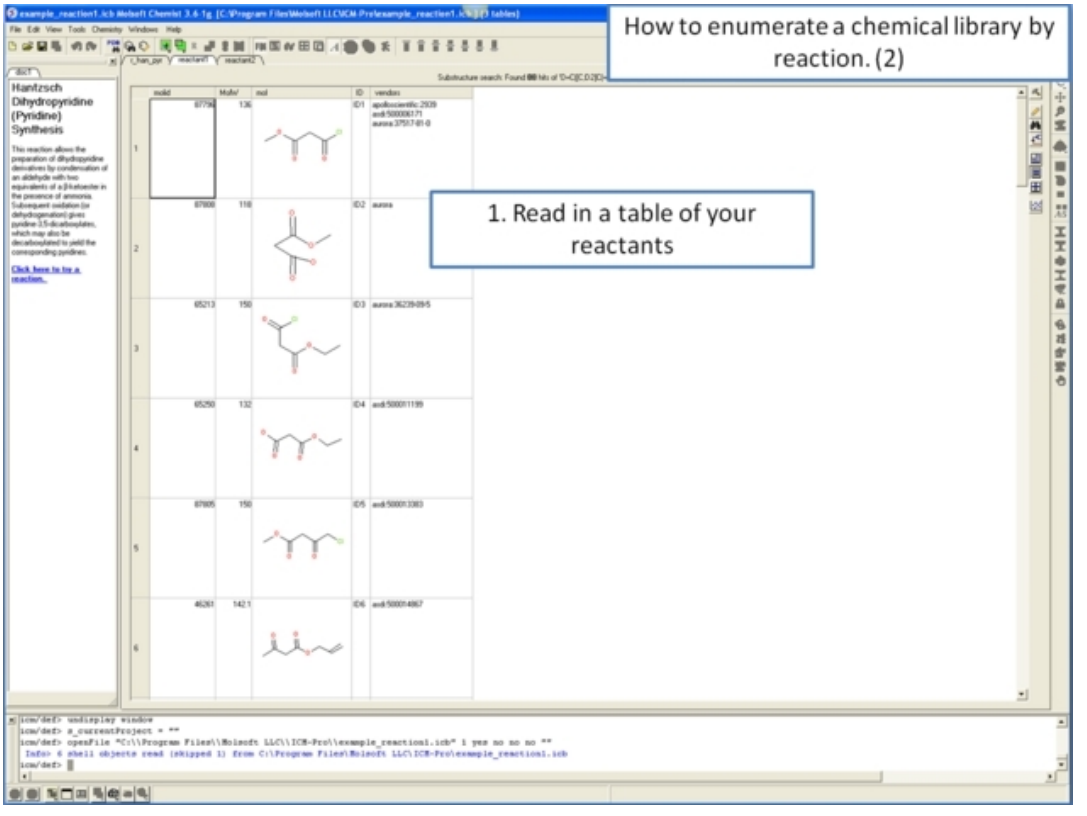
To apply a reaction:

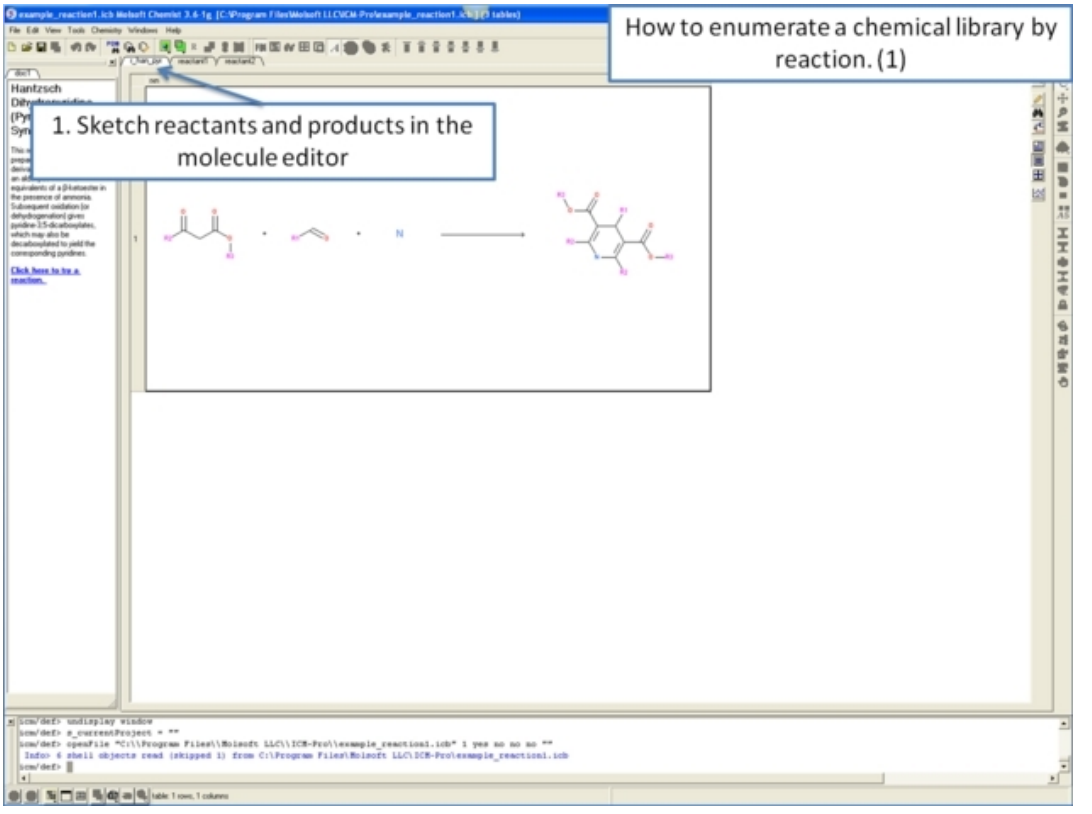
- Chemistry/Enumerate by Reaction.
- In this example (example_reaction1.icb) we already have the reaction drawn in a chemical table. Therefore select the **Choose Table With Reaction**. If you would like to draw a new reaction select **Draw New Reaction**.
- Enter the name of the table containing the reaction. If you have more than one reaction drawn you can select the row using the index option.
- Click OK and then you will be asked to enter the Reactants. Select the reactant tables from the drop down arrow for Reactant 1 and Reactant 2.
- You can transfer information to the reactant table by selecting columns in the **Labels** section.
- Unused reactants can be marked.
- Select what you want to do with multiple matches.

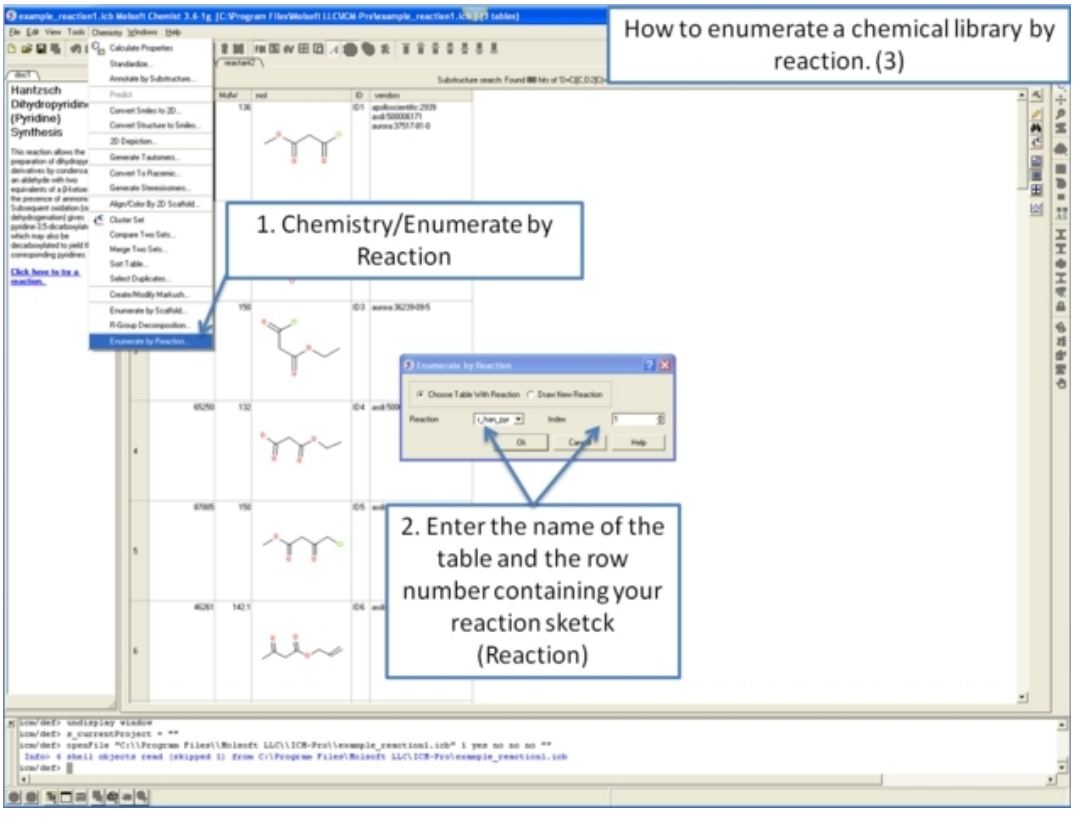
A table of Products will be then displayed in a table called T_out. Columns in T_out labeled "rct" display which reactants were used to build the product.

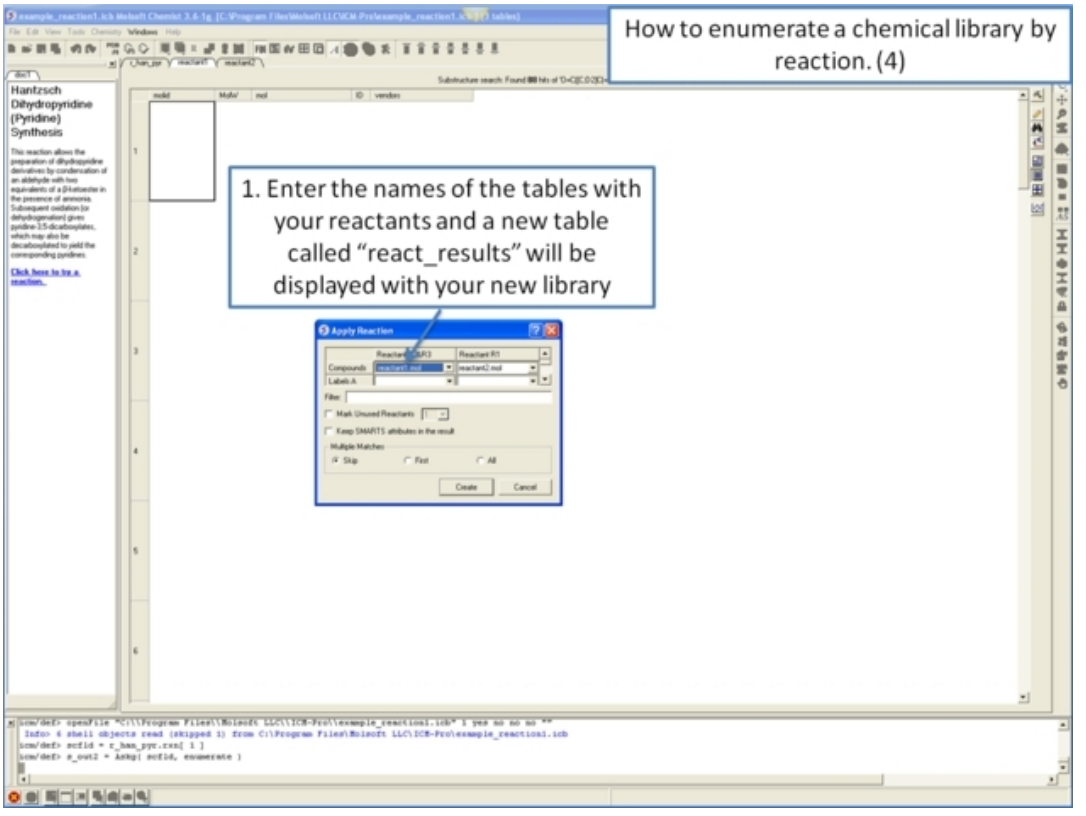


18.23.1 How to enumerate a chemical library by reaction.




How to enumerate a chemical library by reaction. (1)
1. Sketch reactants and products in the molecule editor

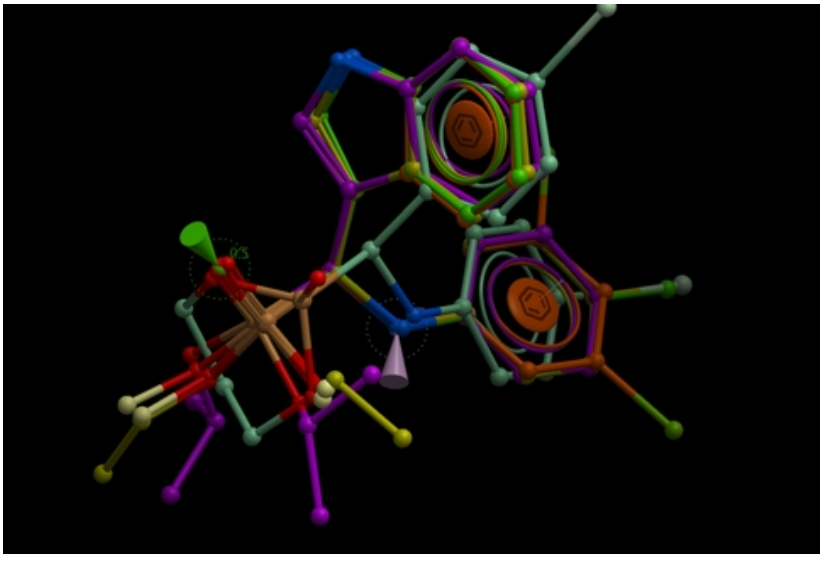

How to enumerate a chemical library by reaction. (3)
1. Chemistry/Enumerate by Reaction
2. Enter the name of the table and the row number containing your reaction sketck (Reaction)



18.24 Superposition

Chemical superposition can be undertaken in the following ways.

- `Rigid Superposition of Compounds in a Table onto a Template in The Graphical Display`
- `Rigid Substructure Superposition of Chemicals in the Graphical Display`
- `Flexible Substructure Superposition`
- `Flexible APF Superposition to Template from Table`
- `Multiple APF Alignment of Compounds in a Table`

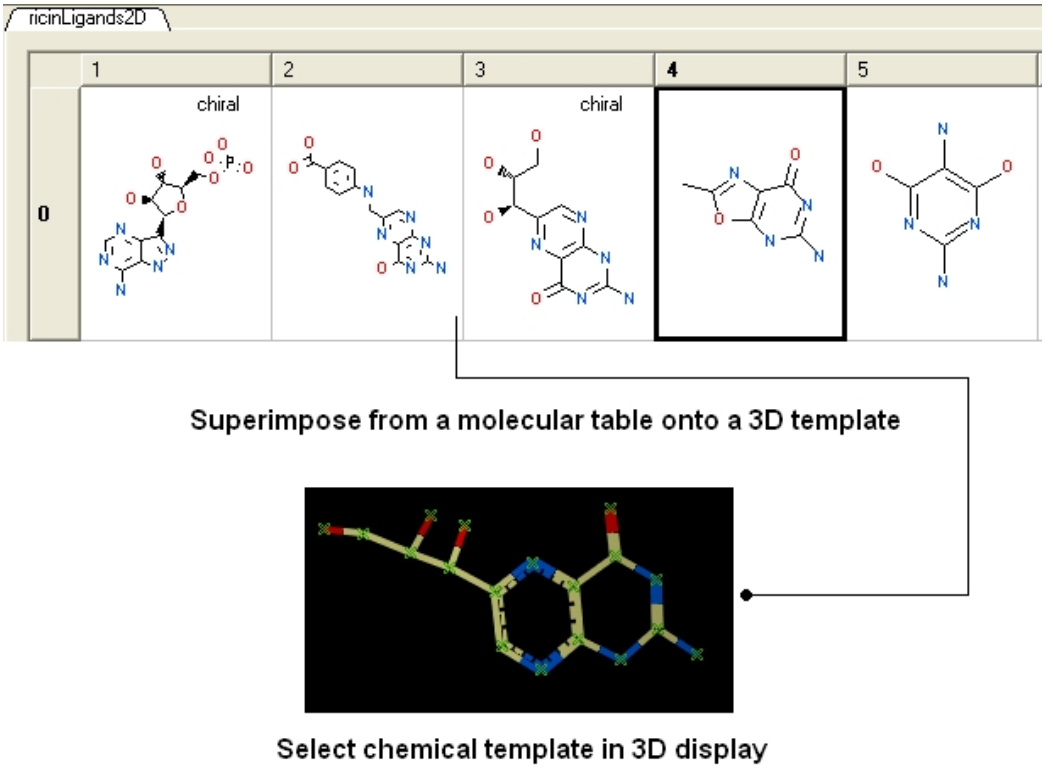


The substructure superposition requires topologically exact match with the template. As long as there is a large consistent scaffold then the substructure superposition is the best approach. In cases where the structures differ topologically then the APF methods should be used to superimpose moieties which have similar properties.

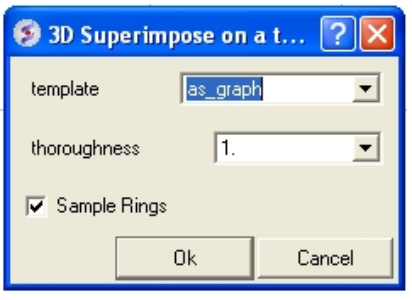
18.24.1 Rigid Superposition of Compounds in a Table onto a Template in The Graphical Display

NOTE: The substructure superposition requires topologically exact match with the template. As long as there is a large consistent scaffold then the substructure superposition is the best approach. In cases where the structures differ topologically then the APF methods should be used to superimpose moieties which have similar properties.

Here we describe how to superimpose chemicals from an `ICM Molecular Table` onto a 3D template displayed in the graphical display.



- Load the template chemical into the 3D display.
- Select the chemical template. One way to do this is to double click on the chemical name in the ICM Workspace (selected=blue in ICM Workspace and green crosses in graphical display).
- Select the chemical(s) (row(s)) in an `ICM Molecular Table`.
- Right click on the table and select Chemistry/Chemical Template Superposition and a table a data entry window as shown below will be displayed.



- Enter the name of the template or use as_graph if you selected the template as described above.
- The thoroughness value represents the sampling length. The higher the value the longer the sampling takes.
- Select whether or not you wish the rings to be sampled.
- Click OK and the selected chemicals will be superimposed on the template in the chemical display.

18.24.2 Rigid Substructure Superposition

NOTE: The substructure superposition requires topologically exact match with the template. As long as there is a large consistent scaffold then the substructure superposition is the best approach. In cases where the structures differ topologically then the APF methods should be used to superimpose moieties which have similar properties.

Here we describe how to perform a rigid−superposition of chemical structures in the graphical display:

- Select the chemicals you wish to superimpose.One way to do this is to double click on the chemical names in the ICM Workspace whilst holding down the control button (selected=blue in ICM Workspace and green crosses in graphical display) or hold the right mouse button and drag over the chemicals in the graphical display.
- Chemistry/Rigid Substructure Superimpose
- A window will be displayed. Enter the name of the template structure using the ICM selection language. The ICM selection language can be found by right clicking on the molecule in the ICM Workspace − first line of right click menu.
- Click OK

NOTE: Superimposed chemicals can be separated easily using the Arrange as grid option. This option can be found in the Chemisty menu Chemistry/Arrange as Grid.

18.24.3 Flexible Substructure Superposition

NOTE: The substructure superposition requires topologically exact match with the template. As long as there is a large consistent scaffold then the substructure superposition is the best approach. In cases where the structures differ topologically then the APF methods should be used to superimpose moieties which have similar properties.

Here we describe how to perform a flexible−superposition of chemical structures in the graphical display:

- Select the chemicals you wish to superimpose.One way to do this is to double click on the chemical names in the ICM Workspace whilst holding down the control button (selected=blue in ICM Workspa ce and green crosses in graphical display) or hold the right mouse button and drag over the chemicals in the graphical display.
- Chemistry/Flexible Substructure Superimpose
- A window will be displayed. Enter the name of the template structure using the ICM selection language. The ICM selection language can be found by right clicking on the molecule in the ICM Workspace − first line of right click menu.
- Click OK

NOTE: Superimposed chemicals can be separated easily using the Arrange as grid option. This option can be found in the Chemisty menu Chemistry/Arrange as Grid.

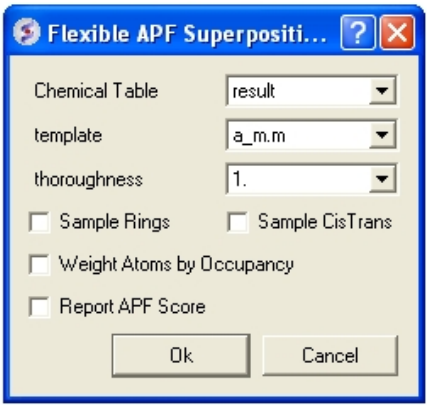
18.24.4 Flexible APF Superposition to Template from Table

NOTE: The APF superposition method should be used when there is no common substructure between the chemicals that are being superimposed. If a common substructure is present then the substructure superposition methods described earlier should be used. The APF method will superimpose moieties that similar properties.

The Atomic Property Fields (APF) superposition/alignment method was reported by Maxim Totrov PhD (Principal Scientist − MolSoft) at the 2007 233rd American Chemical Society National Meeting, Chicago, IL USA (see: `http://oasys2.confex.com/acs/233nm/techprogram/P1057814.HTM`). APF is a 3D pharmacophoric potential implemented on a grid. APF can be generated from one or multiple ligands and seven properties are assigned from empiric physico−chemical components (hydrogen bond donors, acceptors, Sp2 hybridization, lipophilicity, size, electropositive/negative and charge).Here we describe template APF superposition whereby the APF is generated from a single or multiple template and is then globally optimized with the internal force−field energy of the ligand. The optimization is undertaken using the ICM Biased Probability Monte−Carlo method described in Abagyan and Totrov JMB 1994.

To perform Flexible APF Superposition:

- `Read` a chemical table into ICM containing the compounds you wish to superimpose.
- Display in 3D the template structure you wish to superimpose on. See `convert to 3D` for instructions on how to generate a 3D template structure.
- Select **Chemistry/Flexible APF Superposition** and a window as shown below will be displayed.



- Use the drop−down arrow to select the chemical table containing the chemicals you wish to superimpose.
- Enter the template structure name using the ICM command language. You can determine the correct selection for a molecule displayed in ICM by looking at the label in the ICM Workspace.
- Enter a thoroughness value. This represents how long the simulation will run for. A value of 1 has been validated as being a suitable length for this kind of superposition.
- Select whether you want flexible rings to be sampled by checking the appropriate box.
- Select whether you want cis and trans conformations of double bonds to be sampled by checking the appropriate box.
- Select whether you want the superposition to be weighted by occupancy of the atoms by checking the appropriate box. It is often desirable to preferentially superimpose parts of a ligand while ignoring other regions. This can be achieved by setting the occupancy to zero for regions you are not focusing on.
- Select whether you want the superposition to be scored in order to rank solutions by checking the appropriate box.
- Click OK and the simulation will run in the background. Once the superposition is complete the molecules will be displayed in the graphical display.

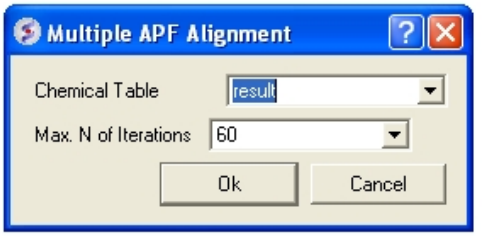
18.24.5 Multiple APF Alignment of Compounds in a Table

NOTE: The APF superposition method should be used when there is no common substructure between the chemicals that are being superimposed. If a common substructure is present then the substructure superposition methods described earlier should be used. The APF method will superimpose moieties that similar properties.

APF is briefly described in the previous section describing flexible APF superposition to a template. In the Multiple APF alignment method an initial superposition is generated by superimposing the inertia ellipsoids of all ligands in random conformations and then the total APF is generated on a grid. Each molecule is then optimized in the APF fields by ICM Biased Probability Monte−Carlo method described in Abagyan and Totrov JMB 1994. The procedure is repeated until a self−consistent field is acheieved.

To superimpose multiple chemicals in a chemical table by the APF method:

- Read a chemical table into ICM containing the compounds you wish to superimpose.
- Select Chemistry/Multiple APF Alignment and a window as shown below will be displayed.
- Use the drop down arrow to select the chemical table.
- Select the number of iterations for the simulation. This represents how long the simulation will run for. A value of 60 has been validated as being a suitable length for this kind of superposition.
- Click OK and the simulation will run in the background. Once the superposition is complete the molecules will be displayed in the graphical display.



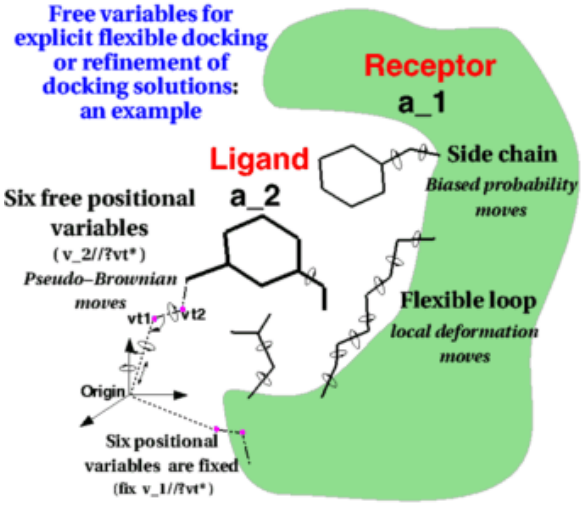
#endif

19 Docking

Note: Click **Next** (top right hand corner) to navigate through this chapter or use the links below. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

In this chapter we describe:

- Small Molecule Docking
- Flexible Receptor Docking
- Template Docking
- Virtual Screening of Small Molecules (>100 compounds and ICM Scoring Function)
- Automated Model Building into Density
- Protein−Protein Docking



19.1 Small Molecule Docking

This section is concerned with predictions of interactions of drugs or small biological substrates (less than about 600−700 Da) to pockets of larger, more rigid, receptors (typically, protein molecules, DNA or RNA).

For accurate ligand docking, the goal is to have an adequate three−dimensional model of the receptor pocket you are planning to dock ligands to. If this is the case then ICM docking has been shown to be very accurate in a number of independent assesments.

However, there are a number of pitfalls which need to be overcome to achieve accurate ligand docking. The pitfalls are that your model is not accurate overall, does not reflect the induced fit, or alternative conformations of the receptor binding pocket are missed.

Some facts about ICM docking:

- An average docking time is 20 seconds to 3 minutes per ligand per processor.
- ICM docking is probably the most accurate predictive tool of the binding geometry today. ICM ranked first place compared to other leading docking software in terms of accuracy in a recent analysis undertaken by Astra Zeneca scientists. See: On Evaluating Molecular−Docking Methods for Pose Prediction and Enrichment Factors. Hongming Chen, Paul D. Lyne, Fabrizio Giordanetto, Timothy Lovell, and Jin Li *J. Chem. Inf. Model.; 2006; 46(1) pp 401 − 415*
- The time per ligand was chosen to be the smallest possible to allow screening of very large data sets. To increase the time spent per ligand, change the Docking_thoroughness parameter.

19.1.1 Receptor Considerations

If you have only a single PDB entry for your receptor, `convert` the protein to an ICM object, delete water molecules and irrelevant chains. However, if you have a choice between several templates, take the following into account:

- X−ray structure is preferable to an NMR structure
- High resolution X−ray structure (less than 2.1A) is much better than, say 2.5A . Watch out for high−B−factor regions and avoid them; sometimes crystallographers deposit fantasy coordinates with high−B−factors.
- Place polar hydrogens and choose correct form of histidine.
- A bound conformation of the receptor is preferable, however if you use an apo−model, an NMR structure or a model by homology, the side−chains in a pocket may be incorrect. Frequently they stick out and prevent a ligand from binding. Those stubborn side−chains can be 'tamed', (i) manually; (ii) by a side chain simulation with elevated surfaceTension; or (iii) by an explicit flexible docking calculation with a known ligand.
- A model by homology can be built with the build model command (see `molecular modeling` section of this manual) and used for docking.

19.1.2 Ligand Considerations

Usually a good start is to try to dock the known ligand(s) to the receptor model. You may also want to dock a library of compounds in order to identify lead candidates. In this case the main pitfall is that the library is too restricted, molecules are not chemically feasible or not drug−like.

NOTE: If you are docking a ligand directly from the PDB please check the bond types and formal charges of the ligand. This is discussed in the section entitled `Converting a Chemical from the PDB`

19.1.3 Setting up the Docking Project

ICM ligand docking procedure performs docking of the fully flexible small−molecule ligand to a known receptor 3D structure. The goal of the flexible docking calculation is prediction of correct binding geometry for each binder. ICM stochastic global optimization algorithm attempts to find the global minimum of the energy function that includes five grid potentials describing interaction of the flexible ligand with the receptor and internal conformational energy of the ligand. During this process a stack of alternative low energy conformations is saved (one of the choices in the Docking menu). Before setting up the docking project, an ICM object of the receptor has to be created. In most cases, x−ray structure of the receptor is initially in the PDB format. Thus, it has to be converted to the ICM format. This process involves addition of the hydrogen atoms, assignment of atom types and charges from the residue templates (icm.res) and imposition of internal coordinates tree (icm−tree) on the original pdb coordinates. To convert a pdb structure into icm object is through GUI as follows:

- Load receptor pdb file into ICM by clicking **File/Open/PDB**.
- `Convert` loaded structure into an ICM object by clicking MolMechanics/ICM−convert/Protein. Remember to select the options to optimize all hydrogens and Optimize HisProAsnGlnCys. If you do not select "replace original" just make sure you understand which of your objects is an ICM Object and which one is in PDB format. You can only dock to an ICM object.

NOTE: It is recommended that "optimize hydrogens" option is selected. To accelerate the procedure, disable the 3D graphics window (type in the terminal window unds window) When the procedure finishes, converted object is the 'current' object in icm. You can check the results by displaying the converted structure.**REMEMBER!! If you are redocking a ligand please remember to remove the ligand from the ligand binding pocket otherwise the ligand will be included in the docking maps and you will not be able to re−dock it correctly. To remove a ligand from an object − right click on the ligand in the ICM Workspace and select "remove from object". Simply undisplaying the ligand is NOT sufficient.

Follow these instructions in order:

1. `Set Project Name`
2. `Setup Receptor`

3. Setup Ligand ***Note:Version 3.4−7f and higher does not have this option − ligand setup is selected at interactive docking or batch setup step (See Start Docking Simulation)***
4. `Review and Adjust Binding Site`
5. `Make Receptor Maps`
6. `Start Docking Simulation`
7. `View Docking Results`

19.1.4 Set Project Name

Start the docking project setup by defining the project name:

- Click on Docking/Set project name
- Enter a unique name into the Project name data entry box. Avoid spaces and leading digits in the name. All files related to the docking project will be stored under names, which start from the project name. Most customized parameters will be saved in the table file under the project name as well:

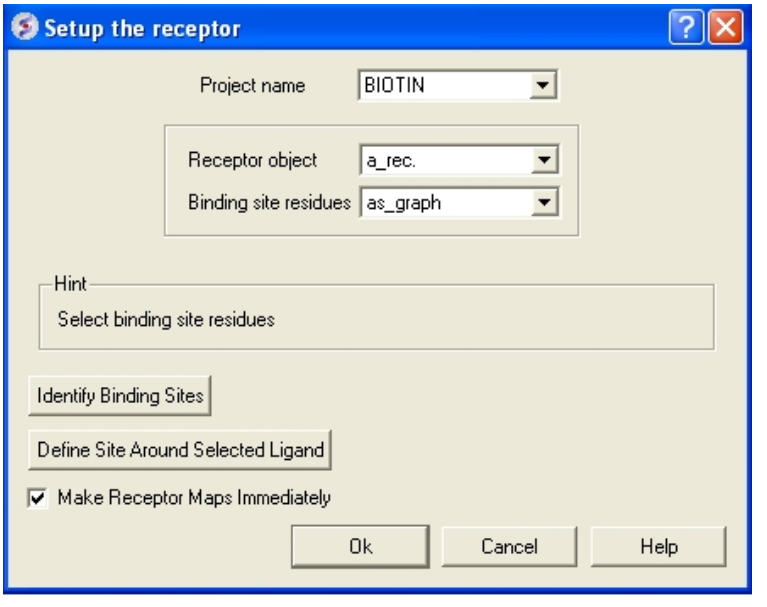
- Click on the 'OK' button.

Now set up the receptor. Go to `Receptor Setup`

19.1.5 Setup Receptor

The next step is to set up the receptor for docking.

- Click on Docking/Receptor setup



- Enter the project name in the Project name data entry box. If the project name was established in the same ICM session then it should automatically appear in this box.

NOTE: Other docking project names that you have entered can be found by clicking on the arrow besides the Project name data entry box.

- Enter the receptor molecule(s) in the Receptor object data entry box. In most cases a_* will do − all molecules in the current object will be included. The receptor molecule can also be found by clicking on the arrow next to the data entry box. A list of potential receptors will be displayed. Click on the receptor you wish to use for your docking experiment.

There are different ways to enter the binding site residues

1. Define the binding site residues, either manually e.g. a_/123,144,152 for selection by residue numbers.
2. Graphically using `the graphical selection tools` such as the lasso tool (don't forget to set selection level to residue) or the `icmPocketFinder` function. If the residues are selected using the lasso tool or icmPocketFinder there should be green crosses surrounding the ligand binding pocket. The green crosses represent a graphical selection and are returned to a variable called as_graph type as_graph in the Binding site residues data entry box.
3. Or possibly the easiest way (if you have a ligand in the correct place already) is to select the ligand in the icm workspace (double click on it) and then press the "Define Site Around Selected Ligand" button. This will make a graphical selection (green crosses) of the residues surrounding the ligand.

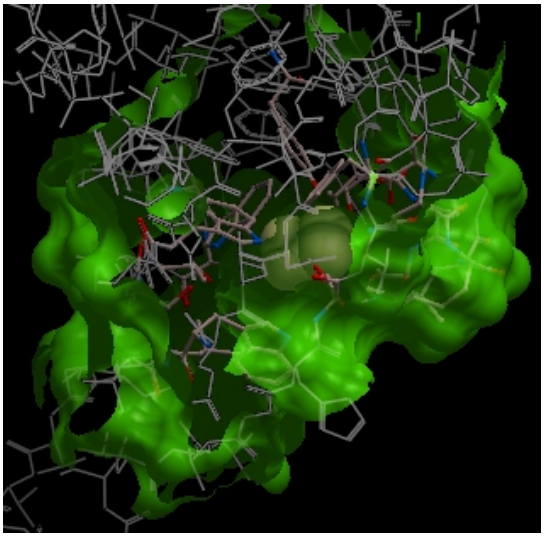
This selection is used solely to define boundaries of the docking search and the size of the grids and doesn't have to be complete, selecting some 4 residues delimiting the binding site is sufficient. Receptor setup dialog also lets you run binding site identification routine to quickly locate putative binding sites on your receptor.

- If you do not select the option **Make Receptor Maps Immediately** you can make the maps by using the option `Docking/(Re)Make Receptor Maps`.

NOTE: Potential ligand binding pockets can be identified using `ICMPocketFinder` or by clicking on the **Identify Binding Sites** button in the **Docking/Receptor Setup..** data entry window. These two methods for identifying pockets are identical.

- Click on the **OK** button.

After the receptor setup is complete, the program normally displays the receptor with the selected binding site residues highlighted in xstick representation surrounded by a surface representation.

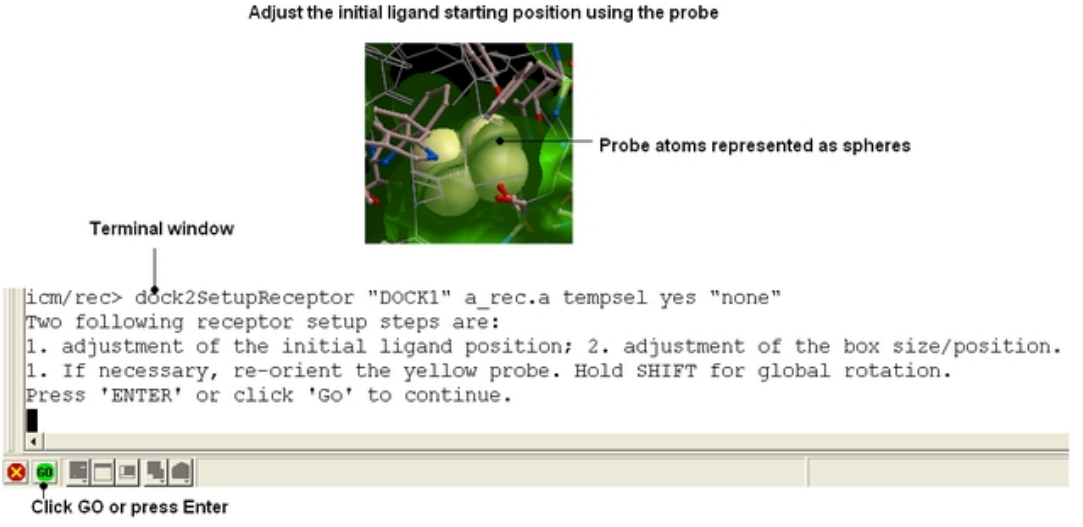


NOTE: At this stage of the docking setup it is a good idea to keep an eye on the terminal window. Instructions and any error messages will be displayed in the terminal window. If you do not see the terminal window select **Windows/Terminal Window**.

To complete the receptor setup there are **two more steps:**

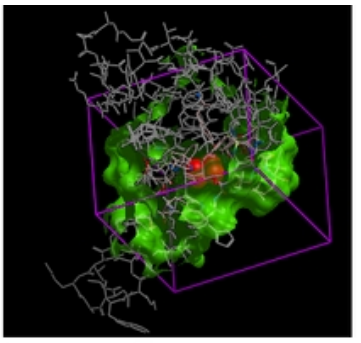
Adjust the position of the probe (initial ligand starting position

The position of the probe (usually represented as 4 spheres in the center of the pocket) represents the initial position where sampling will begin. The default probe position is generally OK for most purposes but if you would like to move it to a critical part of the receptor so that sampling initially concentrates in that region you can do so using the middle mouse button and holding the SHIFT button for global rotation. Once you are happy with the position of the box press the enter key or click on "GO".

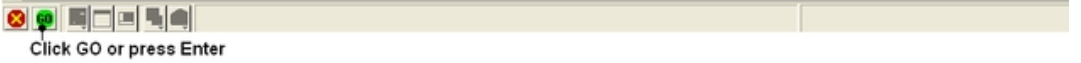


NOTE The probe position can be changed again using the **Docking/Review/Adjust Ligand/Box..** option.

Adjust the size and/or position of the box The purple box represents the region in which maps will be generated. The box needs to be large enough to encompass the binding pocket but not too large and including regions of the receptor which are not relevant for the ligand to bind. If the binding site is correctly defined in the earlier **Receptor setup** then the default box size is usually fine. If it is necesary to change the box size you can use the left mouse button with the cursor at any corner of the purple box to change it.




```
icm/rec> dock2SetupReceptor "DOCK1" a_rec.a tempsel yes "none"
Two following receptor setup steps are:
1. adjustment of the initial ligand position; 2. adjustment of the box size/position.
1. If necessary, re-orient the yellow probe. Hold SHIFT for global rotation.
Press 'ENTER' or click 'Go' to continue.
If necessary, adjust the size/position of the box around the binding site
(hold LEFT MOUSE BUTTON with the cursor at any corner of the box).
Press 'ENTER' or click 'Go' to continue.
```



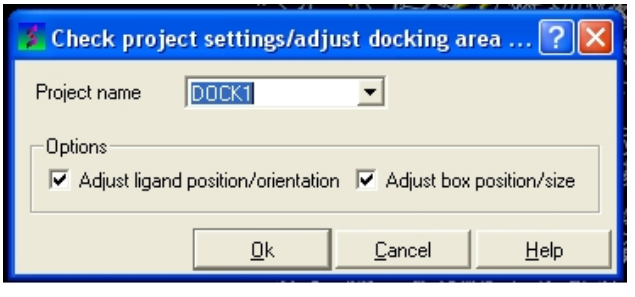
NOTE The size of the box can be changed again using the `Docking/Review/Adjust Ligand/Box..` option.

19.1.6 Review and adjust binding site

NOTE: Generally the default box ICM generates in the receptor setup stage is adequate. It is usually a good idea to double check the box encompasses all the residues you want to dock to.

ICM makes a box around the ligand binding site based on the information entered in the receptor setup section. The position of the box encompasses the residues expected to be involved in ligand binding, however you may wish to alter the size of the purple box or the position of the ligand probe (red spot).

- Click on the menu Docking/Review/Adjust Ligand/Box
- A data entry window will be displayed as shown below.



- Select the option Adjust/ligand position/orientation and/or Adjust box position/size

Follow the instructions in the command line display.

NOTE: Always check that the correct project name is displayed in the data entry window.

Now go to `Make Receptor Maps`.

19.1.7 (Re)Make Receptor Maps

NOTE: You need to use this option if you have changed the size of the box (Review/Adjust Ligand/Box). You also need to use this option if you did not select the **Make Receptor Maps Immediately** option in Docking/Receptor Setup.

The next step is to construct energy maps of the environment within the docking box.

- Click on the menu Docking/Make Receptor Maps

NOTE: Always check the correct project name is displayed in the data entry window.

- Select the resolution of the map by entering a value into the grid cell size data entry box. We recommend a value of 0.5 for both accuracy and speed of calculation.

NOTE: Calculation of the maps may take a few minutes.

Now begin the `docking procedure`.

19.1.8 Begin the Docking Simulation

Once the receptor and maps have been correctly set up then the docking procedure can begin.

There are two options `INTERACTIVE` or `BATCH` docking (Please note some of the options may be limited for users without ICM−VLS)

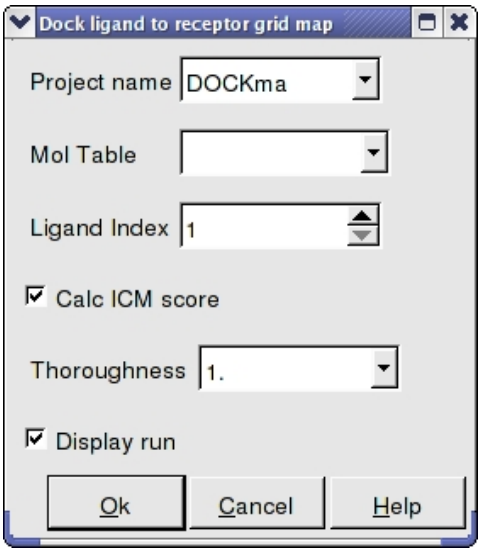
19.1.9 Interactive Docking

Use interactive docking to dock one ligand at a time in the foreground. It is ideal to use this option for small−scale docking.

- Click on the menu Docking/Interactive Docking

Choose either Mol Table Ligand or Loaded Ligand

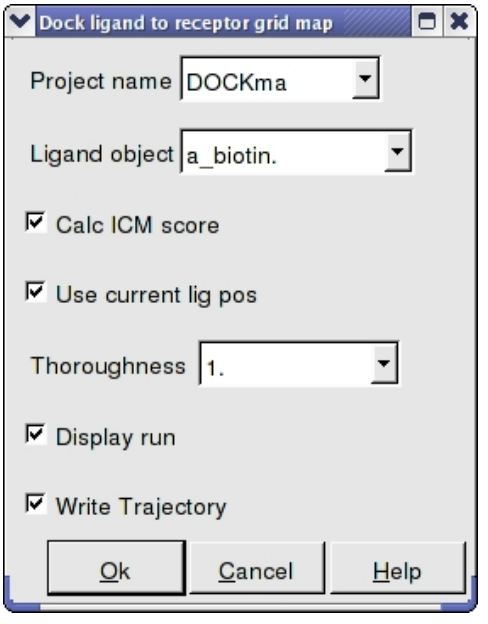
Interactive Docking − Mol Table Ligand If you have a chemical table already loaded into ICM you can use this option to dock them. You can read mol/mol2 or sdf files into ICM by using File/Open. They will be displayed in a table.



- Enter the Docking Project Name
- Use the drop down arrow to find the table of ligands you wish to dock.
- Enter the number of the ligand in the table you wish to dock. Eg if the ligand is in row 6 enter 6.
- If you have ICM−VLS you can retrieve an ICM docking score for the docked ligand.
- Thoroughness represents the length of the simulation. Generally 1 is a reasonable value for buried hydrophobic pockets. If you are docking to solvent exposed pockets or pockets containing metal ions you may wish to increase this slightly.
- Display run will display the ligand sampling the energy in the ligand binding pocket. Although this is fun to watch this significantly slows down the docking operation.

Interactive Docking − Loaded Ligand

If you have a ligand as an ICM object you can use this option.



- Enter the Docking Project Name
- Use the drop down arrow to find the ligand.
- If you have ICM−VLS you can retrieve an ICM docking score for the docked ligand.
- If the ligand is already located in the pocket you can use this option. However by default the ligand will start sampling in the center of the pocket so this option does not need to be used.
- Thoroughness represents the length of the simulation. Generally 1 is a reasonable value for buried hydrophobic pockets. If you are docking to solvent exposed pockets or pockets containing metal ions you may wish to increase this slightly.

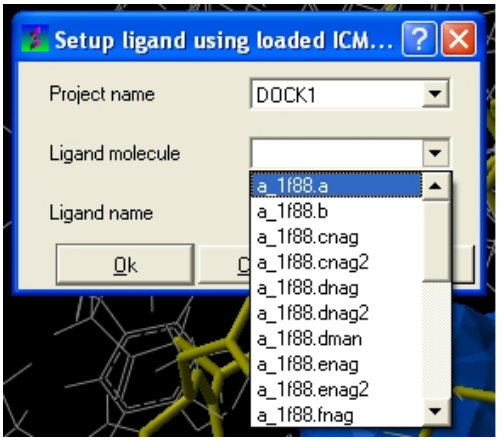
- Display run will display the ligand sampling the energy in the ligand binding pocket. Although this is fun to watch this significantly slows down the docking operation.
- You can write the docking simulation to a trajectory file. Please see the command language manual for more information on this.

19.1.10 Batch Docking

Batch Docking is used for running docking jobs in the background. It is ideal for large−scale docking jobs.

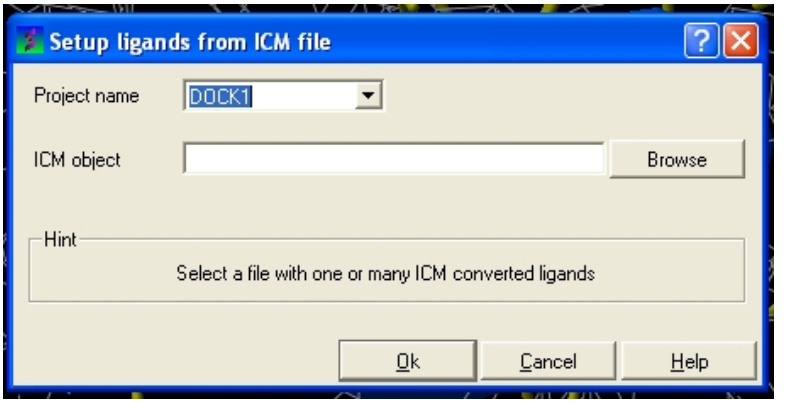
- Docking/Batch Ligand Setup
- Select which format (see below) your ligand is in − object−loaded or file, mol/mol2, inx, MolCart.

From Loaded ICM Object Your ligand will have been converted to an ICM object and loaded into ICM (File/Open) Your object will be displayed in the ICM Workspace.



- Enter the name of the docking project followed by the ligand molecule name and you can also change the name of the ligand if you wish.

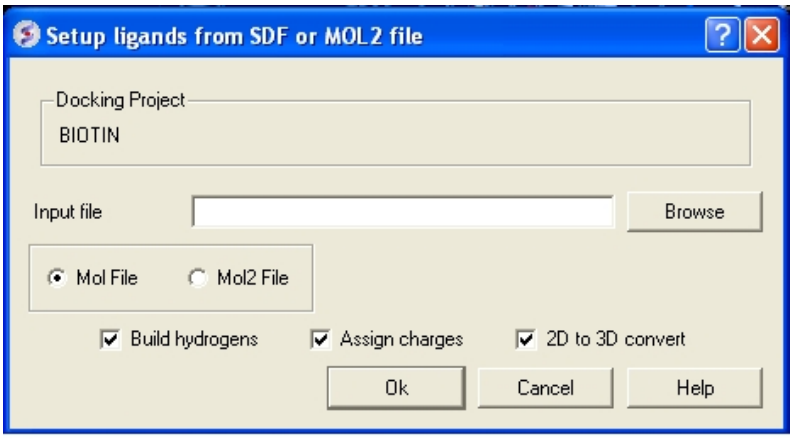
From File: ICM If your ligand (s) is saved and converted to an ICM object but is not yet loaded into ICM then you need to use this option.



- Enter the name of the docking project.
- Click OK

From File:MOL/MOL2

If your ligand is a MOL or MOL2 file then



- Browse for your MOL/MOL2 file.
- Select whether your ligand is in MOL or MOL2 format.
- If you wish hydrogens to be added to your compound or charges to be assigned then click on the appropriate boxes in the display panel.
- Click OK

File Formats:

MOL Format

```
name
jscorina  12209406473DS
LongName
  7  6
   -0.0187    1.5258    0.0104 C   0  0  0  0  0
    0.0021   -0.0041    0.0020 C   0  0  0  0  0
    1.6831    2.1537   -0.0024 S   0  0  0  0  0
   -1.4333   -0.5336    0.0129 C   0  0  0  0  0
    2.0692    1.9811   -1.7665 C   0  0  0  0  0
   -1.4126   -2.0635    0.0045 C   0  0  0  0  0
    1.4620    3.1542   -2.5386 C   0  0  0  0  0
  2  1  1  0  0  0
  3  1  1  0  0  0
  4  2  1  0  0  0
  5  3  1  0  0  0
  6  4  1  0  0  0
  7  5  1  0  0  0

> <NSC>
19

> <CAS_RN>
638-46-0

$$$$
```

MOL2 Format

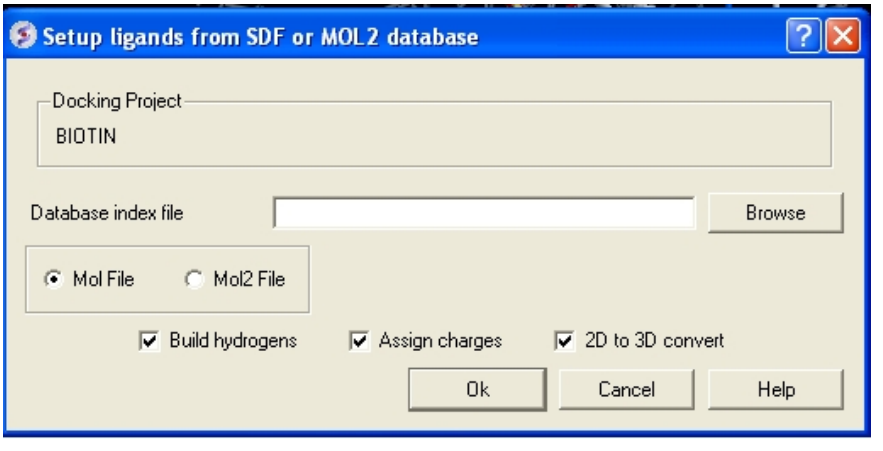
```
@<TRIPOS> MOLECULE
a1
     3     2
SMALL
USER_CHARGES

@<TRIPOS>ATOM
      1  ho1     -2.0000    0.0000   -1.0000    H         1  hoh     0.3280
      2  o       -2.4944    0.0000   -1.8229    O         1  hoh    -0.6550
      3  ho2     -3.4149    0.0000   -1.5503    H         1  hoh     0.3280

@<TRIPOS>BOND
      1      1      2    1
      2      2      3    1
```

From Indexed Database − only available with ICM−VLS

In most cases the ligand input file will be an SDF or MOL2 file. These files need to be indexed by ICM before they can be used in VLS runs (see next section of this manual). The index is used to allow fast access to an arbitrary molecular record in a large file such as an SDF file which in some cases contains over one million compounds.

To index an sdf file:

- Click on the menu Docking/Tools/Index Mol/Mol2 File/Database to generate the index. The following data entry box will be displayed.



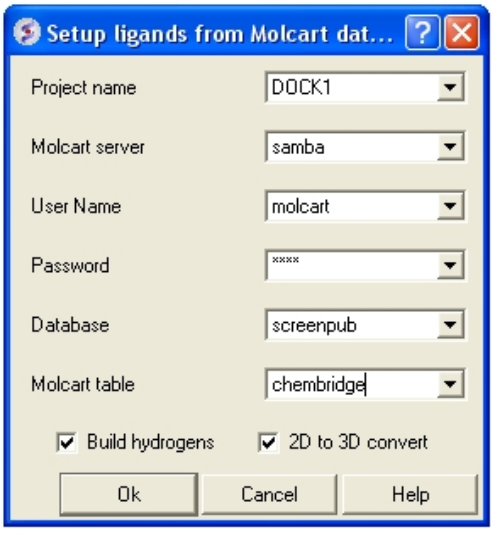
- Enter the name of your Mol/Mol2 file and enter the name you wish to call your index file.
- Select whether your file is in Mol or Mol2 format.

- Browse for your Index file.
- Select whether your ligand is in MOL or MOL2 format.
- If you wish hydrogens to be added to your compound or charges to be assigned then click on the appropriate boxes in the display panel.
- Click OK

From MolCart − only available with ICM−VLS

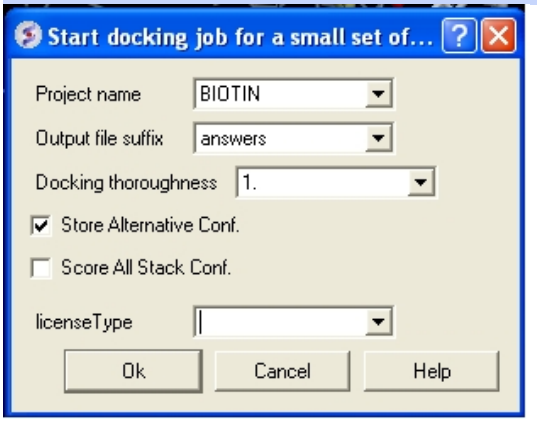
NOTE A separate license is required for MolCart

- Enter docking project name.
- Enter the MolCart server
- Enter your username
- Enter Password
- Enter the Database Name
- Enter the name of the MolCart table within the Database
- Select whether you would like to build hydrogens or convert the compounds from 2D to 3D.



IMPORTANT − NOW SET YOUR BATCH JOB RUNNING USING DOCKING/SMALL SET DOCKING BATCH

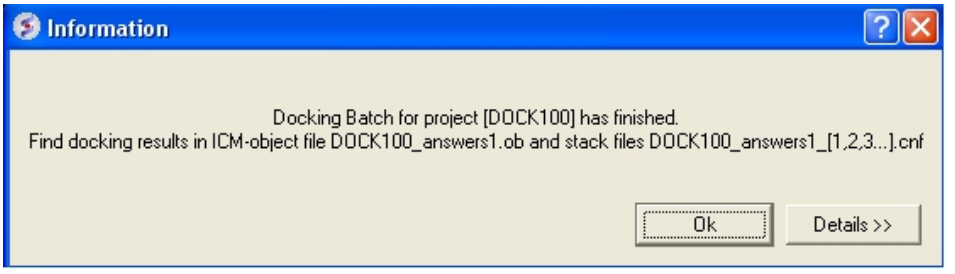
NOTE: NOW SET YOUR BATCH JOB RUNNING USING DOCKING/SMALL SET DOCKING BATCH}



- Docking/ Run Docking Batch
- Enter the Docking Project Name
- Batch docking will generate an output file − enter the name you wish to call this file here.
- Thoroughness represents the length of the simulation. Generally 1 is a reasonable value for buried hydrophobic pockets. If you are docking to solvent exposed pockets or pockets containing metal ions you may wish to increase this slightly.
- Selecting Store Alternative Conf will allow you to look at all conformations in the energy stack.
- Score All Stack Conf. will allow you to determine an ICM docking Score for all members of the stack − this will slow the docking down.
- License type: For nearly all license (e.g. standard ICM−VLS licenses) types you need to **leave this entry blank**. If you have a −vlscluster license or a molvls license (−vls) then select the option from the drop down list. Any questions first check your license.dat file or Email support@molsoft.com.
- Click OK ***IMPORTANT − IF THE JOB IS RUNNING IT WILL TELL YOU bgrnd job AT THE TOP OF THE GUI − SEE BELOW***

Docking simulation is running

Docking simulation has ended message



To check the status of your docking simulation

- Windows/Background Jobs

19.1.11 Viewing Your Docking Results

Docking results can be visualized and browsed in one of the following ways.

- `Docking/Browse/Scan Hits` − If you have docked a multi−ligand file (eg SDF) or if you want to go back and see a single docked structure you can scan the structures using this option.
- `Docking/Browse/Stack Conformation` − View other possible conformations for the docked ligand ranked by energy.
- `Docking/Make Hit List` − Rank docked compounds by ICM Docking Score **Only available with ICM−VLS**

The results of the docking are saved in the following files

PROJECTNAME_LIGANDNAME.ob #icm−object file with best solutions for each ligand
PROJECTNAME_*.cnf # icm conformational stack files with multiple docked conf.

The results of the docking job using ICM−VLS (separate license required) are saved in the folling files:

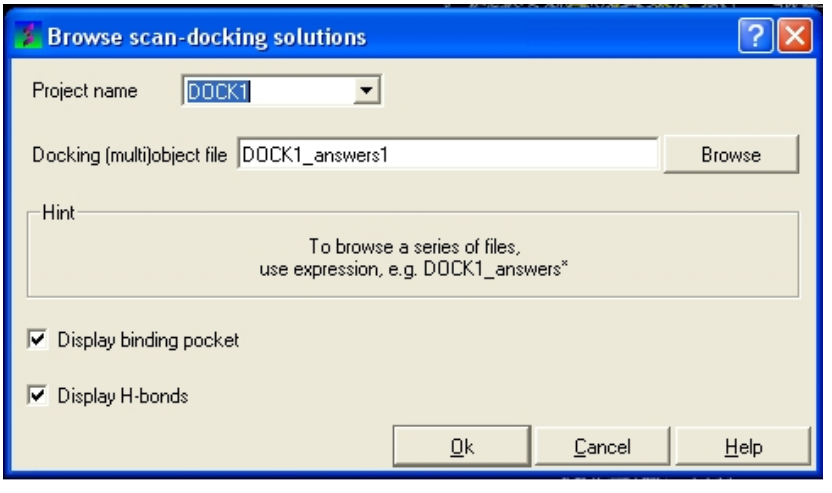
PROJECTNAME_answers*a.ob #icm−object file with best solutions for each ligand

PROJECTNAME_*.cnf # icm conformational stack files with multiple docked conf.

PROJECTNAME_*.ou # output file where various messages are stored eg.SCORE

19.1.12 Results − Scan Hits

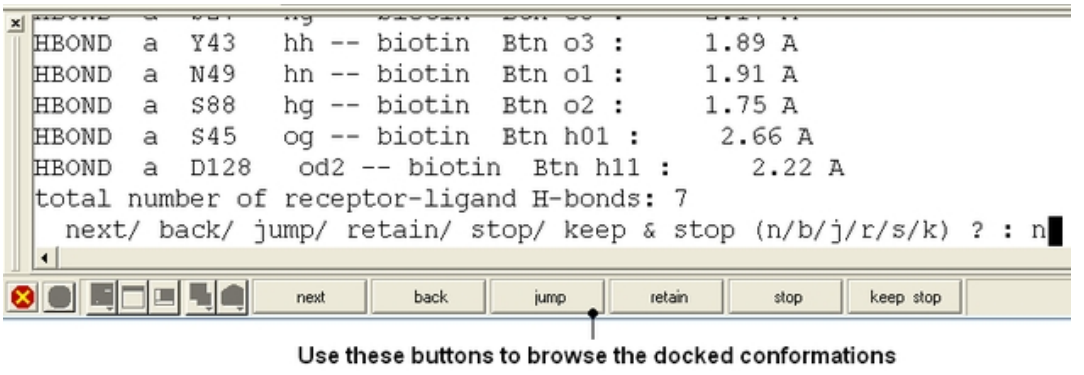
- Select **Docking/Browse/Scan Hits** and a data entry box as shown below will be displayed.



- Select the correct project name for the docking simulation results you wish to browse.
- Enter the name of the icm object file in the Docking (multi)object data entry field. This file will be called PROJECTNAME_answers*.ob or LIGAND_NAME.ob The browse button can be used to

search for the correct file.

- You can display the binding pocket or the H−bonds by selecting the appropriate boxes in the Browse scan−solutions data entry window (shown above).
- Use the buttons at the bottom of the graphical user interface to browse the docked conformations. **NEXT(or** type ï¿½nï¿½), **BACK** (or type ï¿½bï¿½), **JUMP** (or type ï¿½jï¿½), **RETAIN** (or type ï¿½rï¿½), **STOP** (or type ï¿½sï¿½), **KEEP_STOP** (or type ï¿½kï¿½).



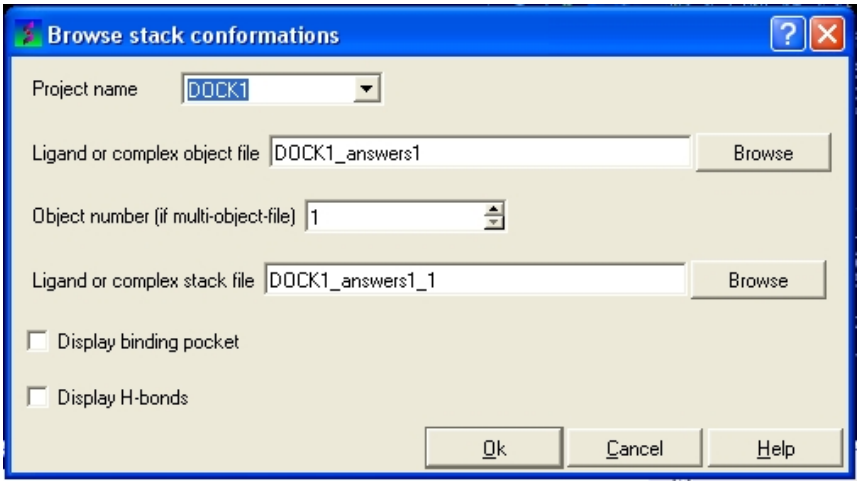
- The options **keep and stop** and **retain** will retain the displayed ligand in the graphical user interface. If you want to export the docked complex as a PDB file you will need to move the ligand and receptor into one ICM object. Moving objects is described in the FAQ section entitled `How can I merge two objects into one?`

19.1.13 Docking Results − View Stack Conformations

To view the multiple positions of a single ligand in the docking simulation ranked by energy.

- Select menu Docking/Browse/Stack Conformations

The Browse Stack Conformation data entry window will be displayed.



- Select the correct project name for the docking simulation results you wish to browse.
- Enter the name of the icm object file in the Docking (multi)object data entry field. This file will be called PROJECTNAME_answers*.ob .The browse button can be used to search for the correct file.
- Enter the name of the icm conformational stack files with multiple docked conformations into the Ligand or complex stack file data entry box. This file will be called PROJECTNAME1_1.cnf . The browse button can be used to search for the correct file. The second solution in the stack can be viewed by changing the number 1 at the end of the file name to 2 (PROJECTNAME1_2.cnf) and so on for each solution in the stack.
- You can display the binding pocket or the H−bonds by selecting the appropriate boxes in the Browse scan−solutions data entry window (shown above).

- Use the buttons at the bottom of the graphical user interface to browse the docked conformations. **NEXT(or** type ï¿½nï¿½), **BACK** (or type ï¿½bï¿½), **JUMP** (or type ï¿½jï¿½), **RETAIN** (or type ï¿½rï¿½), **STOP** (or type ï¿½sï¿½), **KEEP_STOP** (or type ï¿½kï¿½).

- The options **keep and stop** and **retain** will retain the displayed ligand in the graphical user interface. If you want to export the docked complex as a PDB file you will need to move the ligand and receptor into one ICM object. Moving objects is described in the FAQ section entitled `How can I merge two objects into one?`

Columns in the Stack Table

i rank in stack

ener Energy kcal/mol

gvw van der Waals grid potential

gb hydrogen bonding grid potential

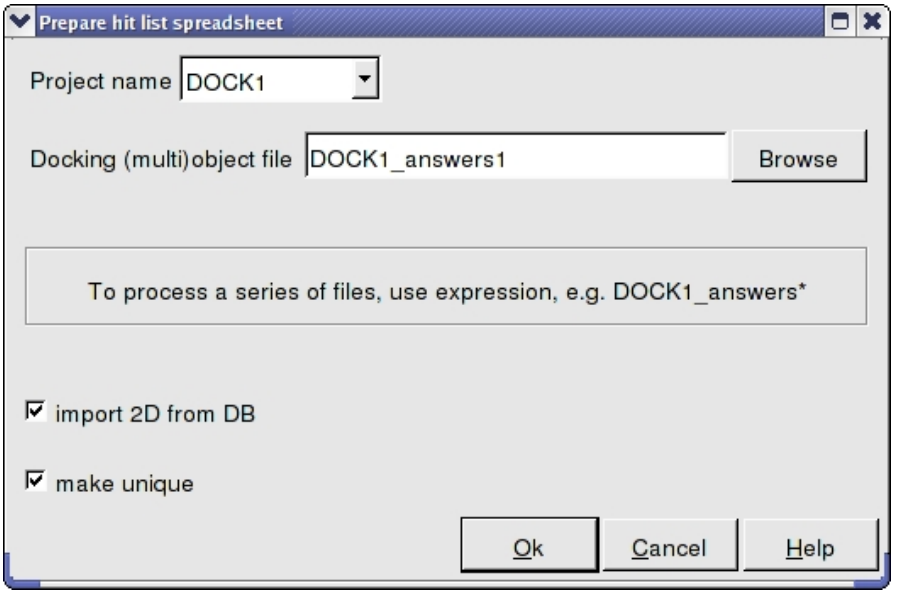
ge electrostatic grid potential

gs hydrophobic grid potential

Einternal is internal conformation energy of the ligand

19.1.14 Make a HIT LIST − Only available with ICM−VLS

- Docking/Make Hit List



- Enter project name
- Use the browse button to locate DockingProjectName_answers.ob file
- You can include a 2D image into the HITLIST
- Select **Unique** if you have made multiple docking runs the best docking score will be taken to make the hitlist unique.
- A HITLIST table will be displayed. Each docked ligand can be viewed by double clicking in the HITLIST table. A stack of conformations for each ligand will also be displayed in a table.

Columns in the HitList Table

IX is the index number from the docked database

Score is the ICM score −32 and lower are generally considered good scores − but depends on the receptor (e.g. exposed pockets or pockets with metal ions mayhave higher scores than −32).

Natom is the number of atoms in docked ligand

Nflex is the number of rotatable torsions.

Hbond is Hydrogen Bond energy

Hphob is the hydrophobic energy in exposing a surface to water

VwInt is the van der Waals interaction energy (sum of gc and gh van der waals). Current version of the score uses explicit van der Waals interaction energy calculation (no grids)

Eintl is internal conformation energy of the ligand

Dsolv is the desolvation of exposed h−bond donors and acceptors.

SolEl is the solvation electrostatics energy change upon binding.

mfScore is the potential of mean force score

RecConf − if multiple receptor conformations was used Docking/Flexible Receptor/Setup 4D grid and represents the receptor conformation number.

19.1.15 Reload a Docking Project

To reload a docking project.

/Docking/Set Project − Type in the Docking Project Name (Case Sensitive)

Now you can browse scan solutions etc.... and use the maps to dock another ligand.

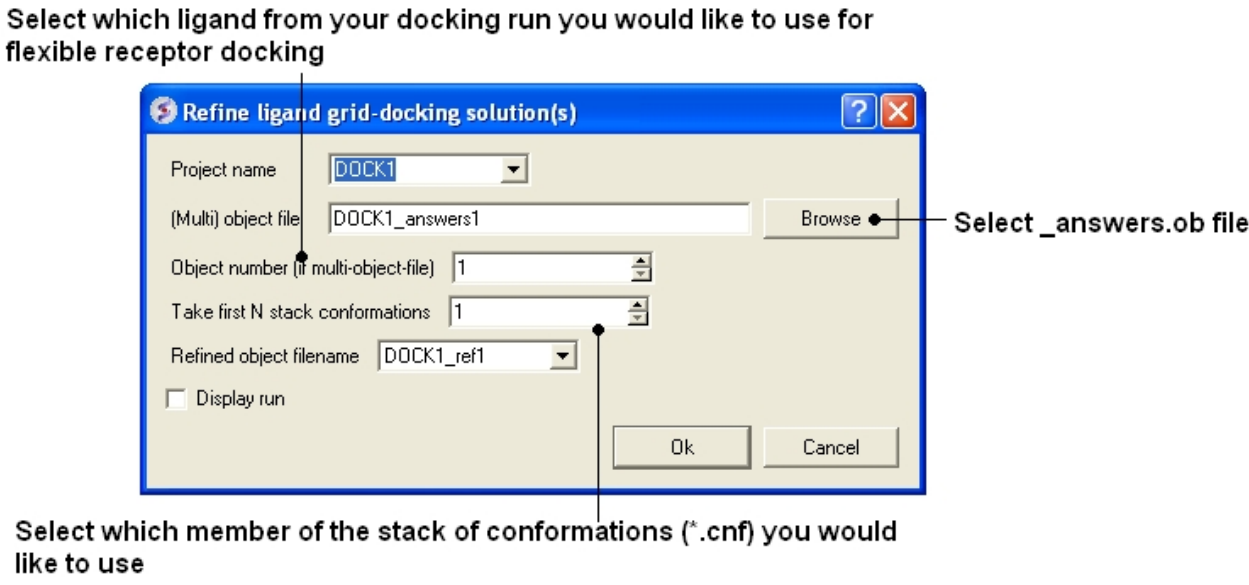
19.2 Flexible Receptor Docking and Multiple Receptor Conformations

The standard ICM docking procedure desribed in the previous section incorporates a flexible ligand and a semi−rigid receptor wherby flexibility is incorporated by including soft van der Waals potential maps. However due to ligand induced−fit there is sometimes a need to incorporate flexibility more `explicitly` by allowing the side−chains of the receptor to be fully flexible or by using multiple−rec{multiple conformations} of a receptor in the docking procedure.

19.2.1 Fully Flexible Ligand and Receptor Docking

To undertake fully−flexible ligand and receptor docking you first need to dock the ligand into the receptor using the procedures described in the previous section entitled `Small Molecule Docking`. The next step is to select the pose from your docking experiment you wish to use for flexible docking.

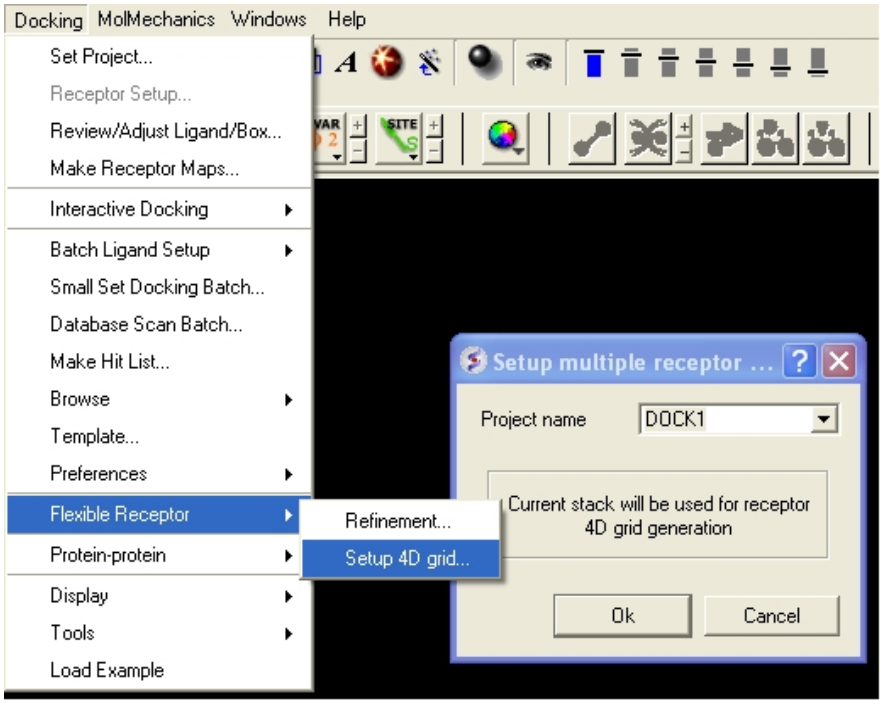
- Docking/Flexible−Receptor/Refinement and a window as shown below will be displayed.
- Enter the name of the initial docking project.
- Select the answers.ob file from the docking experiment.
- If you docked more than one ligands you need to select which ligand you want to use for the flexible receptor docking. For example if you want to refine the 3rd ligand in your docked database you would enter 3 in the **Object number** data entry box.
- Select which member of the stack of docking solutions you wish to use. In most cases it will be the first member of the stack and therefore you will enter "1".
- Enter a name for the refined complex.
- You can display the run in the graphical display but this will slow the process down.



19.2.2 Multiple Receptor Conformation Docking

To dock to more than one conformation of a receptor you must first generate a stack of conformations. One way to do this is to select a number of side−chains and right click on the graphical selection and choose **Advanced/Optimize Side Chains** or right click on the ligand in the binding pocket and select **Advanced/Optimize Ligand Vicinity**. Other methods of generating a stack of conformations involve using the command line (see: `http://www.molsoft.com/man/icm-commands.html#store-conf).` A stack can be viewed using the **MolMechanics/View Stack** option and a table is generated which can be clicked on to view the different conformations. If there are too many elements in the stack redundant conformations can be deleted using the delete conf command (See: `http://www.molsoft.com/man/icm-commands.html#delete-conf).`

The docking procedure is the same as described in the `Small Molecule Docking` section. The only difference is **before** generating the maps you need to select **Flexible Receptor/ Setup 4D grid**.



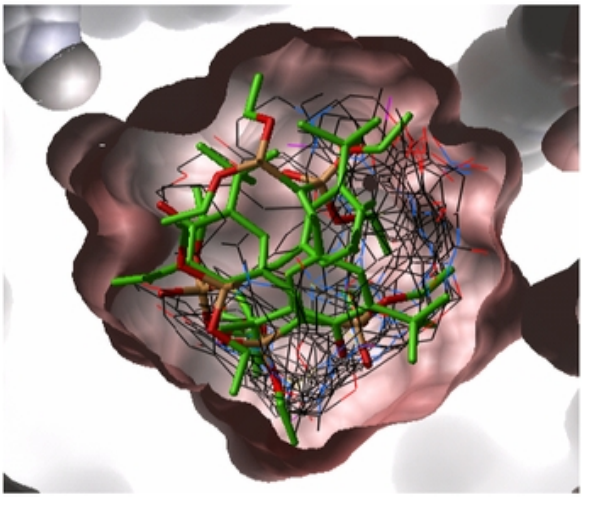
19.3 Template Docking

To perform constrained docking to a template structure you need to position the template in the desired position in the receptor − this can be done by docking or using the `connect` option if the template is not already in the correct position. Make sure the template contains only the atoms you wish to match − a template can be edited by right clicking on it in the ICM Workspace and select Edit/ Edit Compound.

- Setup the docking project as described in the `Small Molecule Docking` chapter.
- Before starting the docking select Docking/Template
- Select the template object name.
- Select the template match method. Match by atom name, substructure, fuzzy or `APF`.
- Click OK
- Set the docking job running − Docking/Interactive or Docking/Run Docking Batch

19.4 Virtual Ligand Screening

Virtual Ligand Screening can be used for screening as many compounds as you desire depending on the amount of computer power you have available. ICM−VLS has been successfully used by the pharmaceutical industry and academia for identifing drugs and inhibitors for a wide variety of disease.



19.4.1 Virtual Ligand Screening

Virtual Ligand Screening (VLS) in ICM is performed by docking a database of ligands to a receptor structure followed by an evaluation of the docked conformation with a binding−score function. Best−scoring ligands are then stored in the multiple icm−object file. The set−up of the VLS process is largely identical to the set−up for the small molecule docking simulation (see `Small Molecule Docking section`).

19.4.2 VLS Getting Started

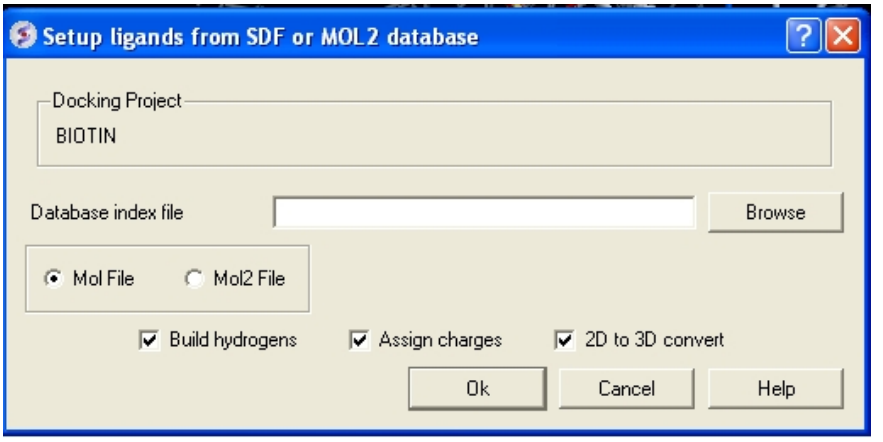
Follow the instructions in the `small molecule docking section` manual from `docking project setup option` to the `calculate maps option`. Use Docking/Setup Batch Ligand option to select the database you wish to dock.

19.4.3 Database File Format

In most cases the ligand input file will be an SDF or MOL2 file. These files need to be indexed by ICM before they can be used in VLS runs. The index is used to allow fast access to an arbitrary molecular record in a large file such as an SDF file which in some cases contains over one million compounds.

To index an sdf file:

- Click on the menu Docking/Tools/Index Mol/Mol2 File/Database to generate the index. The following data entry box will be displayed.



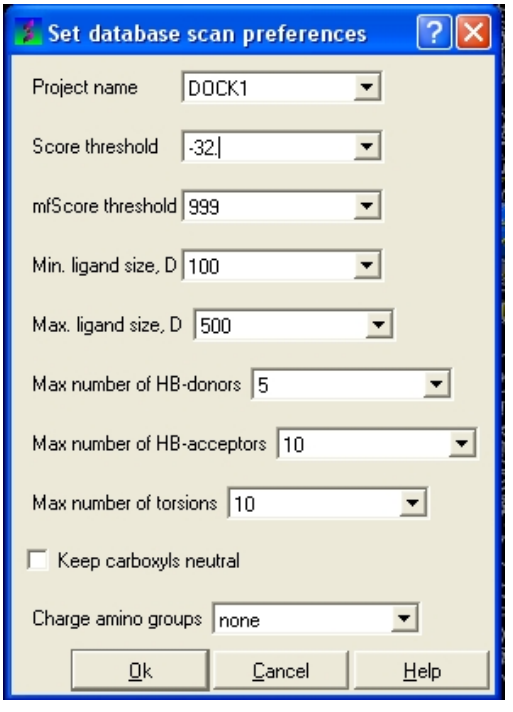
- Enter the name of your Mol/Mol2 file and enter the name you wish to call your index file.
- Select whether your file is in Mol or Mol2 format.

19.4.4 VLS Preferences

NOTE: It is important to setup the VLS preferences before undertaking VLS run.

VLS preferences can be setup by:

- Selecting the menu Docking/Preferences/Database Scan



Different options are available to select by clicking the down arrow next to the data entry field. These options are described here:

Score Threshold:

An important parameter of the VLS run is the score threshold. Docked conformations for a particular ligand will only be stored by ICM VLS procedure if its binding−score is below the threshold. The choice of the threshold can be done in two ways: based on the scores calculated by docking known ligands. Generally, a

value somewhat above typical score observed for known ligands is a good guess. If no ligands are known, a pre−simulation can be run using ~1000 compounds from the target database. Using the resulting statistics for the scores, the threshold should be set to retain ~1% of the ligands.

Potential of mean force score:

Potential of mean force calculation (pmf) provides an independent score of the strength of ligand−receptor interaction. The pmf−parameters are stored in the icm.pmf file.

Other selection criteria:

Other selection criteria which can be changed include

Minimum/Maximum Ligand Size you wish to be screened.

Maximum number of H−bond donors

Maximum number of H−bond acceptors

Maximum number of torsions

19.4.5 Run VLS in the Graphical User Interface

First `setup` the docking project (From Set Project to Setup Batch Ligand)

To start the vls job:

- Docking/Run Docking Batch

19.4.6 Running VLS Jobs in PBS UNIX Cluster Environment

Before VLS jobs can be run make sure you follow the instructions in the manual entitled `Small Molecule Docking` from docking `project setup menu` to the `calculate maps menu`. Select the "From indexed database", "From MolCart" or "From File: SDF/Mol2" option in the `Setup Batch Ligand`. Docking setup can be scripted see the terminal output from the GUI options to view the commands. Jobs on the Linux cluster are run through PBS queuing system. Several scripts are provided to facilitate submission of vls jobs. To submit a single job, use pbs script 'pbsrun', which is a pbs wrapper for rundock qsub $ICMHOME/pbsrun −v"JOBARGS=−f 1 −t 1000 −o MYPROJECT"

NOTE: The rundock arguments go in the quotes after JOBARGS= . The qsub command is a part of PBS.

Other rundock arguments are:

−l # change the length of MC docking, default is 1.

−L # dock selected compounds from the database

−n # change the run name in the output files

−a # force docking and saving of all compounds

−s # save stack conformations

−j # dock several ligands in parallel

−o # redirect output to _from−to.ou

To submit multiple jobs, there is a simple shell script 'pbsscan' which executes multiple qsub's for database stripes: $ICMHOME/pbsscan MYPROJECT 1 6000 1000 −submits 6 jobs, 1 to 1000; 1001 to 2000 ... 5001 to 6000. Currently this script only supports default rundock arguments, copy/edit to change. The command qstat is a part of PBS and can be used to check the status of the jobs. In addition, $ICMHOME/scanstat script can be used to monitor the progress of the VLS jobs. It analyses the *.ou rundock output files. $ICMHOME/scanstat *.ou

To delete the jobs, use PBS command qdel: qdel 1234 # deletes job number 1234

19.4.7 Parallelization

If the database size exceeds several thousand compounds, it is desirable to run a number of VLS jobs in parallel to speed up calculations. Use −f and −t options of rundock to start multiple jobs on different parts of the database, e.g.

rundock −f 1 −t 10000 −o rundock −f 10001 −t 20000 −o rundock −f 20001 −t 30000 −o ..

19.4.8 VLS Results

The easiest way to view the results of a VLS run is to make a hitlist. This was described earlier in the `hitlist` section of the small molecule docking chapter of the manual. Other ways of manipulating VLS data are described here:

19.4.9 Sorting the compounds in your HITLIST

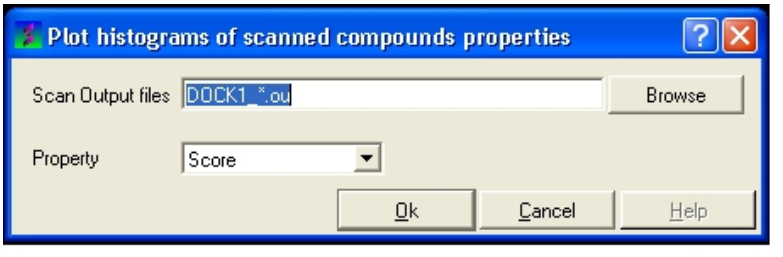
Compounds can be sorted according to their SCORE etc. See the `tables section` of this manual for more information about manipulating tables.

19.4.10 How to Plot Histograms and Scatterplots of VLS Data

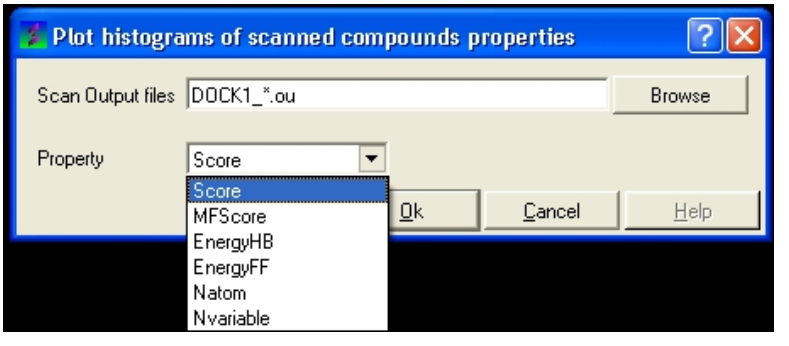
The hitlist contains many columns with numerical data. ICM can build interactive plots with the table columns `(See Tables section)`. However, there are some easy to use plotting options in the docking menu which is described here.

19.4.11 To construct a histogram of your VLS data

- Select the menu Docking/Tools/Scan Results Histogram



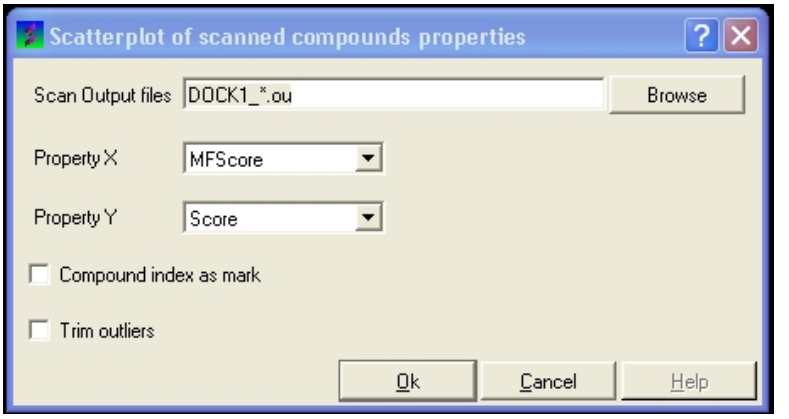
- Enter the name of the VLS output file (*.ou) you wish to construct a histogram for.
- Select which paramater you wish to plot against frequency (see below).



- Click OK and a def.eps file will be saved with a picture of your histogram.

19.4.12 To construct a scatterplot of your VLS data

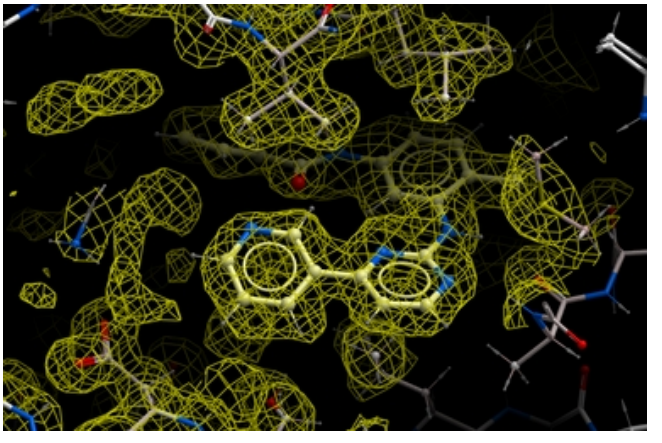
- Select the menu Docking/Tools/Scan Results Scatterplot



- Enter the name of the VLS output file (*.ou) you wish to construct a scatterplot for.
- Select which paramater you wish to on the X axis.
- Select which paramater you wish to on the Y axis.
- Click OK and a def.eps file will be saved with a picture of your scatterplot.

19.5 ICM X−Ray AutoFit − Automated Model Building into Density

The **ICM X−Ray AutoFit** is an automated method to fit a ligand into electron density. The tool combines the powerful ICM docking algorithm with an electron density fitting function.

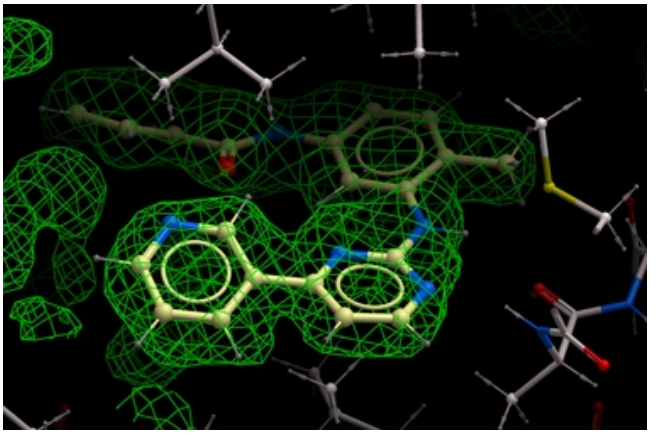


The input for **ICM X−Ray AutoFit** is an electron density map in CCP4 format, the protein recpeptor and ligand which can either be `drawn` or `imported` into ICM.

Theory

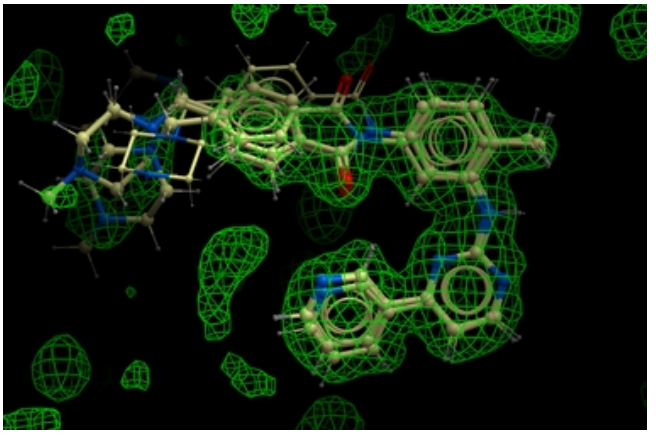
The **ICM X−Ray AutoFit** method includes the following features:

- Soft docking energy function.
- Intra and inter ligand interaction energy function.
- Weighted electron density contributions.
- The electron density for the fit function is filtered to exclude areas occcupied by the protein receptor atoms.

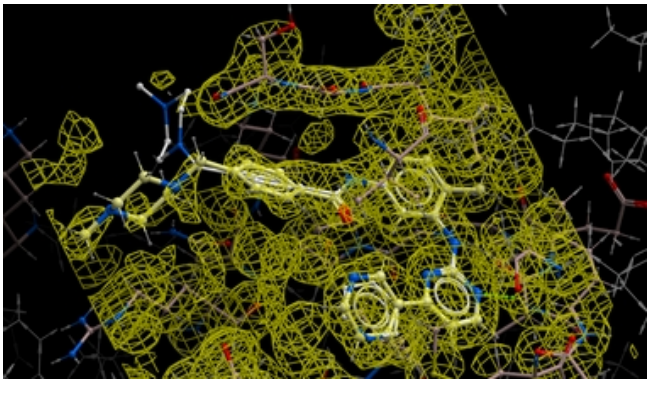


NOTE: Density from the receptor is automatically filtered out from the analysis. In the picture shown above the green map represents attractive potential.

The method generates multiple hits for each ligand with a score assigned. It has been demonstrated that improved ligand receptor interactions can be determined by the **ICM X−Ray AutoFit** method compared to published crystal structures.



In the figure shown below the interaction between Gleevec and Syk kinase is shown. The white carbon atoms are the published ligand pose and the yellow carbon ligand is the result of ICM which gives a better fit to the density.



Instructions

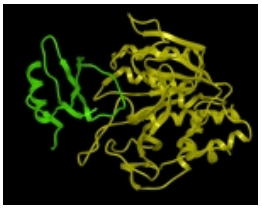
How to run the **ICM X−Ray AutoFit**.

- Load the receptor structure and `convert` to an ICM object.
- Load the CCP4 map (File/Open)
- Load the ligand and `convert` to an ICM object.

- Follow the small molecule docking `procedure` but **after** generating maps select Docking/X−Ray Density and then undertake docking in the standard way.

19.6 Protein−Protein Docking

Here we describe the steps for protein−protein docking. An example is described using a complex of subtilisin and chymotrypsin (PDB code:2sni). The example will re−dock the ligand (PDB code entry 2ci2) into the receptor molecule (PDB code 2st1) and then determine how accurately the molecules are docked by comparison with the complex 2sni. The structure of 2sni is shown below with the ligand displayed in green and the receptor in yellow.

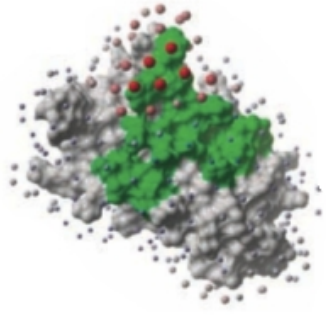


19.6.1 Optimal Docking Area

The ICM Optimal Docking Area method is a useful way of prediciting likely protein−protein interaction interfaces. If you do not have mutational data or other experimental data which indicates the likely protein−protein docking site this method will be useful. This procedure can save you time during the docking procedure by focusing your docking only on areas on the receptor and ligand most likely to interact.

Theory

ODA (Optimal Docking Areas) is a new method to predict protein−protein interaction sites on protein surfaces. It identifies optimal surface patches with the lowest docking desolvation energy values as calculated by atomic solvation parameters (ASP) derived from octanol/water transfer experiments and adjusted for protein−protein docking. The predictor has been benchmarked on 66 non−homologous unbound structures, and the identified interactions points (top 10 ODA hot−spots) are correctly located in 70% of the cases (80% if we disregard NMR structures).



To display the optimal docking area.

- Convert the PDB file to an ICM object.
- Tools/3D Predict/Protein Interface by ODA

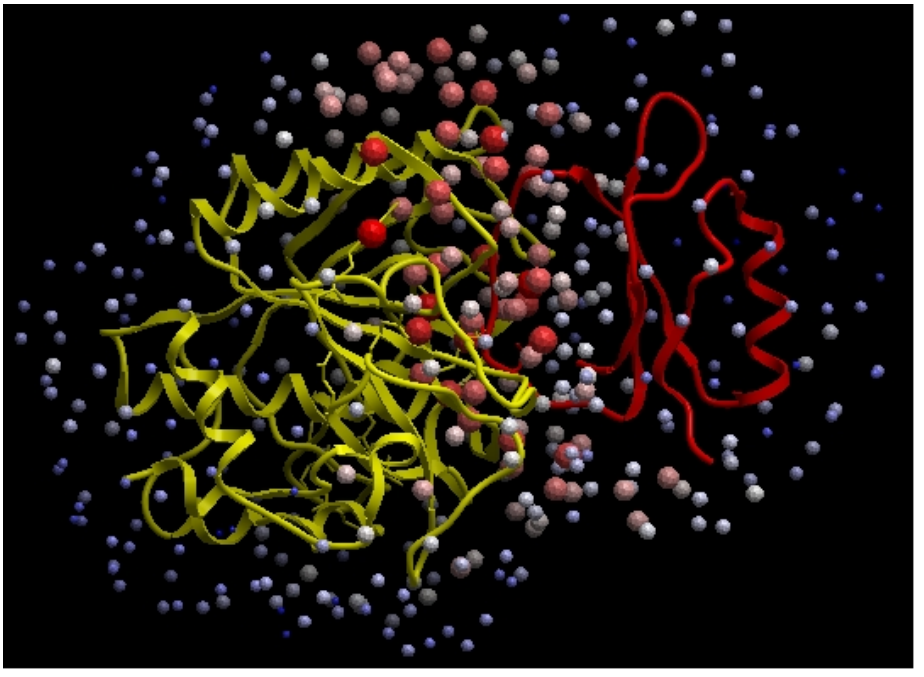
ODA Example with a subtilisin−chymotrypsin complex.

As an example we will determine whether the ICM−ODA method can accurately predict the binding surface of the complex between subtilisin and chymotrypsin. This example is used in the protein−protein docking tutorial below as well.

This complex has been solved experimentally and has PDB id 2sni.

Calculate the ODA for each subunit (Tools/3D Predict / Protein Interface by ODA).

ODA for subtilisin and ODA for chymotrypsin − red colored spheres indicate a region highly likely to be involved in protein−protein interaction, blue coloring is unlikely to be involved in protein−protein interaction. A clickable table is also displayed with ODA values.



19.6.2 Protein−Protein Docking Procedure

To begin the protein−protein docking procedure:

1. Read in the PDB files for 2ci2 (ligand) 2st1 (receptor) and 2sni (complex for comparison). For instructions on how to load a PDB structure into ICM `please click here`.
2. Convert all three PDB files into `ICM objects`.
3. Delete all waters and sulfate ions, you can keep the calcium ions if you wish.

Now go onto the first step of the protein−protein docking protocol which is to `Set Project` name.

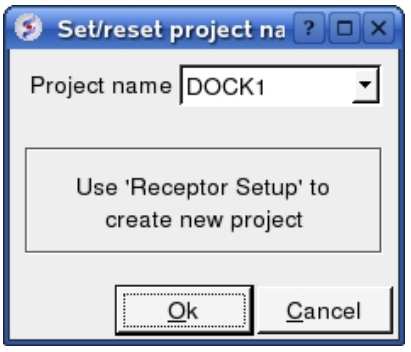
NOTE: All the protein−proteing docking options can be found in the GUI menu Docking/Protein−Protein.

19.6.3 Protein−Protein Set Project

Docking/Protein−protein/Set Project

Start the protein−protein docking project setup by defining the project name:

- Click on Docking/Protein−protein/Set project
- Enter a unique name into the Project name data entry box. Avoid spaces and leading digits in the name. All files related to the docking project will be stored under names, which start from the project name.

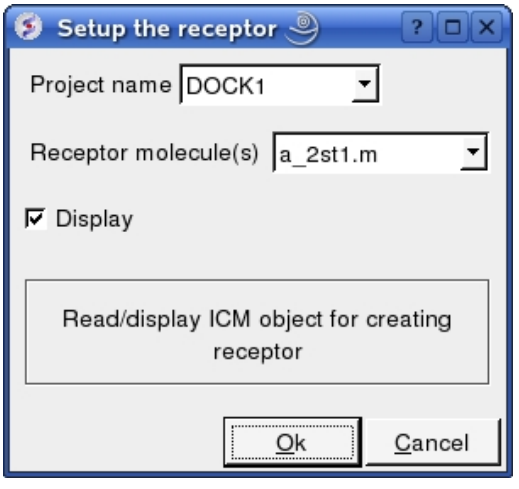


Now setup the `receptor`.

19.6.4 Protein−Protein Receptor Setup

Docking/Protein−protein/Receptor setup

- Enter the Docking Project name e.g. DOCK1
- Enter the receptor molecule e.g. a_2st1.m (use a_2st1.* if you want to include all molecules such as Calcium ions)
- Click OK

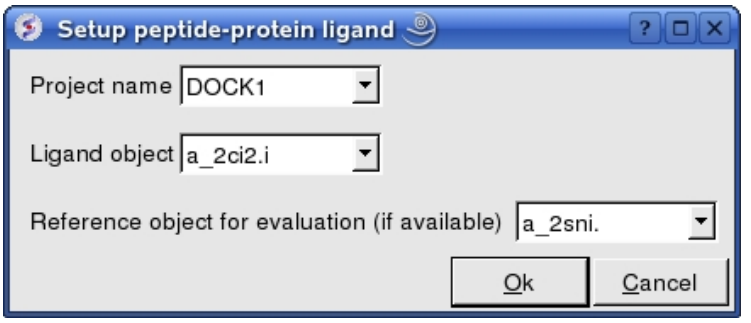


Now setup the `ligand`.

19.6.5 Protein−Protein Ligand Setup

Docking/Protein−protein/Ligand setup

- Enter the project name e.g. DOCK1
- Enter the ligand molecule e.g. a_2ci2.i
- If you wish to compare your docking data with a solved structure enter the name of the converted reference object in the "Reference Object" data entry box e.g. a_2sni.
- Click OK



Now select an initial point of interest on the receptor referred to as `epitope` selection (NOTE: This step is optional. If you do not wish to select an initial point of interest junp to the `make maps` section.

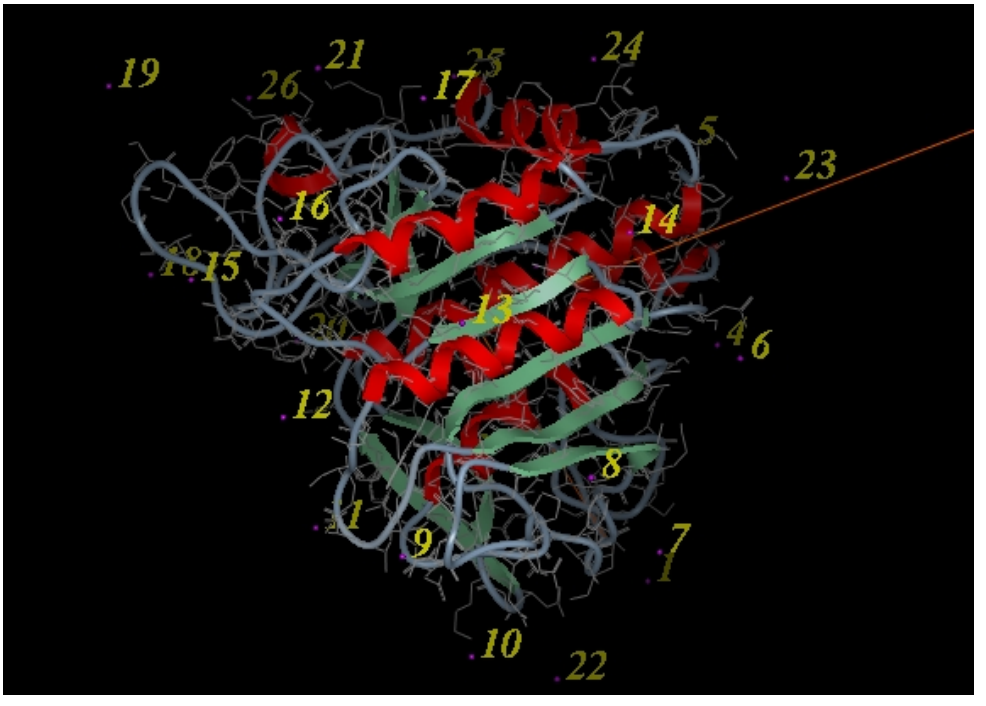
19.6.6 Epitope Selection

Docking/Protein−protein/Epitope selection

Select an initial point of interest on the receptor for the docking simulation. You may want to check biological data or a reference complex before doing this step.

NOTE: This step can be left out completely if you dont know or dont want to select an initial point of interest.

- You can make selections on either the ligand or receptor or both the ligand and receptor. Check the appropriate box(es).
- A display as shown below will be displayed.
- Using the right button of the mouse select a numbered sphere surrounding the receptor or ligand that you wish to dock to by clicking and dragging the mouse over the sphere. The spheres are numbered and change color from purple to yellow when they are selected. If you are happy with the selection type 'a' or press the apply button. The selected numbered regions will change from purple to yellow. The easiest way to select multiple epitopes is to use the `pick atom` button (green cross button).
- When you have finished selecting the epitoples type 'q' or select the quit button in the terminal window.



NOTE: If you are unsure which epitopes you have selected they are listed in the DOCKING_PROJECT_NAME.tab file in the first two fields eg here epitope 1 and 3 have been selected in both the ligand and the receptor:

```
#>I test2.I_selLigPos
  1
  3
#>I test2.I_selLigRot
  1
```

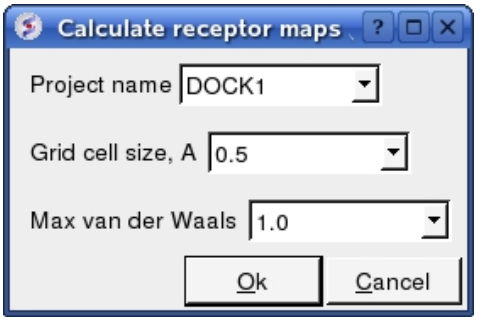
You can also select epitopes by editing this field in the .tab file.

The next step is to make the `maps` of the receptor.

19.6.7 Protein−Protein Make Receptor Maps

Docking/Protein−protein/Make Receptor Maps

- Enter the Project name e.g. DOCK1
- Enter the grid size e.g. how detailed you want your maps − the default value of 0.5 is generally ok.
- Enter the Max van der Waals value which gives the receptor an element of 'softness' to incoporate some induced fit − the default value of 1.0 is generally ok.



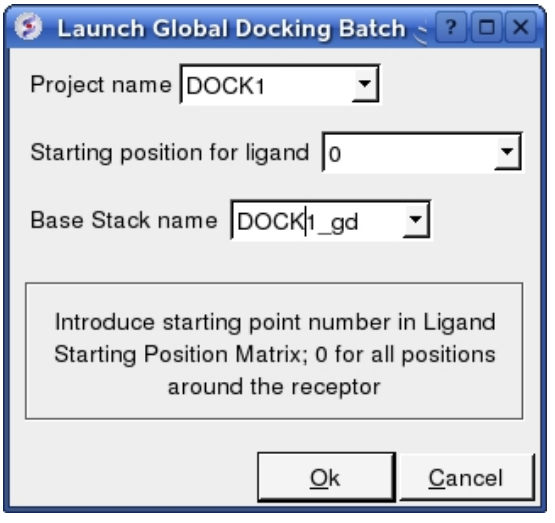
Now run the `docking simulation`.

19.6.8 Protein−Protein Docking Batch

The docking can be run on your local machine or in PBS.

To run on your local machine:

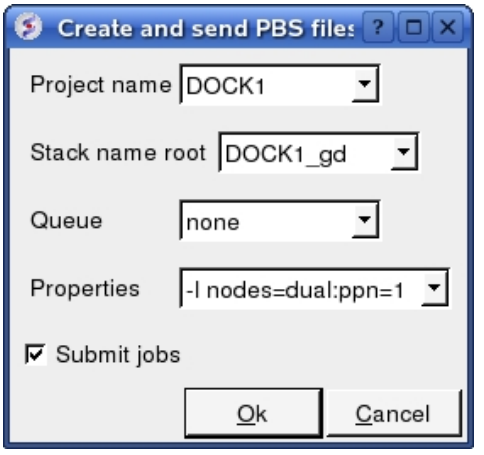
Docking/Protein−protein/Docking Batch/Local Machine



- Enter the Project Name
- Starting Position for Ligand − if you select 0 it will sample all the points on the receptor you selected in the epitope step of the docking project setup. If however you want to break your jobs down into smaller chunks you can enter the number of a position on the receptor you chose in the epitope selection step and it will sample that point.
- Enter a name for the conformational stack which will be saved.

To run in PBS:

Docking/Protein−protein/Docking Batch/PBS



19.6.9 Display Grid Docking Results

A window will be displayed once the docking has finished or you can check the docking progress by going to Windows/Background Jobs. To display the grid−docking ligand conformations :

1. Read object "DOCK1_rec" # read receptor (if not read yet)
2. Display a_DOCK1_rec. # display receptor (if not displayed yet)
3. Read object "DOCK1_lig" # read ligand object
4. Display a_ # display this ligand
5. Read table "DOCK1_gd.Var" # read table of the ligand conformations
6. Click on table rows to view ligand conformations
7. Check the R_Srmsd column for the difference between docked and the crystal structure complex for comparison (if selected).

Or in gui go to:

- Docking/Protein−protein/Docking Batch/Process Global Docking Solutions.

A table as shown below will be displayed. You can sort the table by Energy (ener) by right clicking on the column header and select sort.

DOCK1_gd

	i	ener	rmsd	naft	nvis	v1	v2	v3	v4	v5	v6	Ey_gh	Ey_gc	Ey_gb	Ey_ge	Ey_gs	Ey_sfl
1	1	-41.391	0	2	6	0.04483	90.9106	524.007	92.0525	49.7742	83.8696	-7.8806	-35.857	-5.8146	-1.2662	-6.2756	11.168
2	2	-40.565	0	2	2	0.19569	91.2981	520.773	-8.9542	86.9122	79.9324	-9.0676	-34.638	-3.9748	-1.7934	-11.620	13.840
3	3	-38.606	0	2	4	1.02538	91.1309	522.608	171.737	101.824	81.2009	-5.5076	-36.427	-3.9280	0.35496	-7.8400	11.038
4	4	-37.223	0	2	2	-0.2911	90.6959	527.715	-168.89	106.47	16.6569	-7.7926	-26.602	-6.7522	-0.8824	-7.4796	8.4756
5	5	-36.899	0	2	5	-1.8815	88.37	522.204	178.837	103.21	40.3486	-4.1510	-33.382	-6.2505	-1.2081	-8.5090	11.532
6	12	-34.038	0	2	8	-1.6260	89.4907	528.356	72.7411	74.769	66.6841	-1.4804	-29.692	-6.3669	-1.0912	-8.6190	9.6204
7	15	-33.743	0	2	3	-0.9527	90.0158	528.304	-160.48	89.2895	72.3303	-6.0312	-27.820	-3.3335	-2.1168	-8.5995	10.073
8	16	-33.086	0	2	2	-0.9266	91.388	521.931	-36.119	116.206	77.6997	2.43218	-39.036	-5.2885	-0.6586	-11.599	15.206
9	21	-30.652	0	2	2	-1.7173	88.3469	523.435	153.731	124.097	68.3627	-5.8456	-27.796	-3.8465	-1.4351	-5.8874	9.8432

The output columns represent:

- i − a slot number in the stack of conformations
- ener − total energy as calculated before the conformation was stored

- rmsd − the distance (either Cartesian or angular RMSD) between the current conformation of the object and the stack conformation calculated according to the comparecommand.
- naft − the number of visits AFTER the last improvement of energy
- nvis − the total number of visits to this slot; since new conformation are only compared with the last stack conformation the conformations may drift and cover a large area than described by the vicinityparameter
- v1 to v6 − are the virtual variables defining position and rotation of the ligand molecule.
- ey gh − van der Waals grid potential − hydrogen probe
- ey gc − van der Waals grid potential − carbon probe
- ey gb hydrogen bonding grid potential
- ey ge electrobstatics grid potential
- hydrophobic potential
- ey sfPola − polar terms of the solvation energy
- Ey_sfAl − aliphatic terms of the solvation energy
- Ey_sfAr − aromatic terms of the solvation energy
- Ey_compSol − weighted total of the solvation energy terms

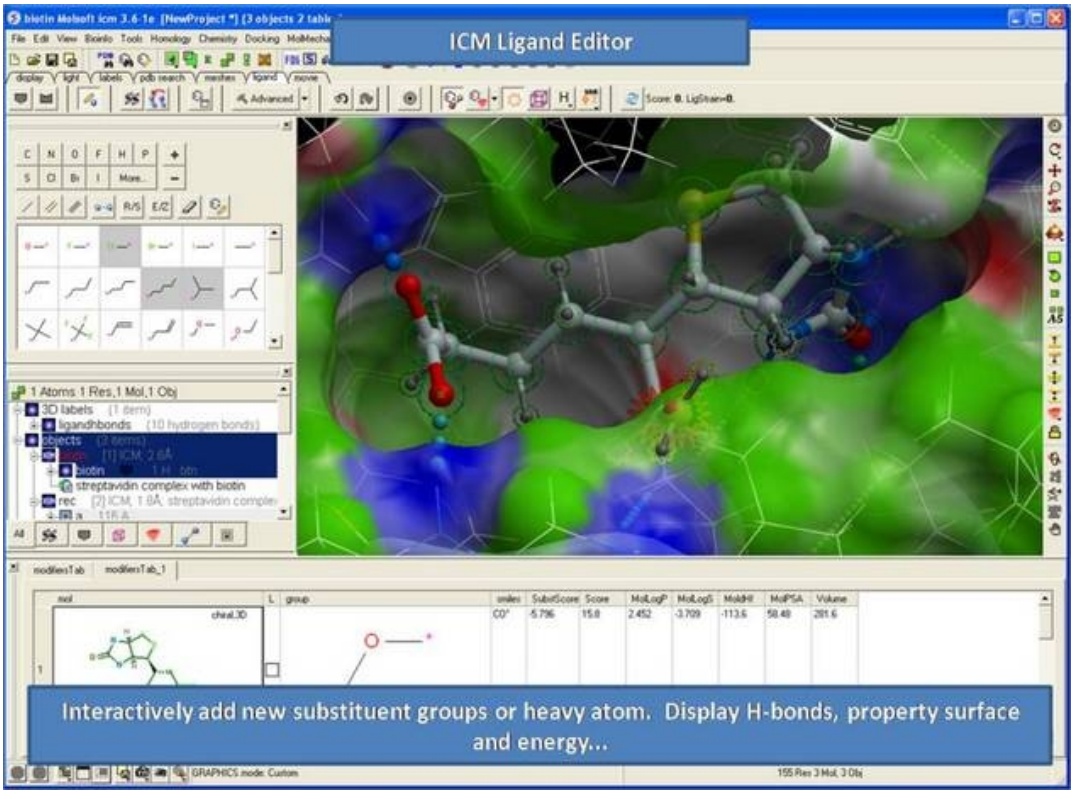
To display the complexes:

- **Single** click on a row of the table shown above. The ligand will be displayed in the ICM workspace and named according to the project name followed by "_lig" (e.g. DOCK1_lig).
- To view interactions between the receptor and the ligand each moleucule needs to be in the same object. See the FAQ section: `How do I merge two separate objects into one.`

20 How To Use The Ligand Editor

NOTE: this functionality is only available in versions 3.6 and above.

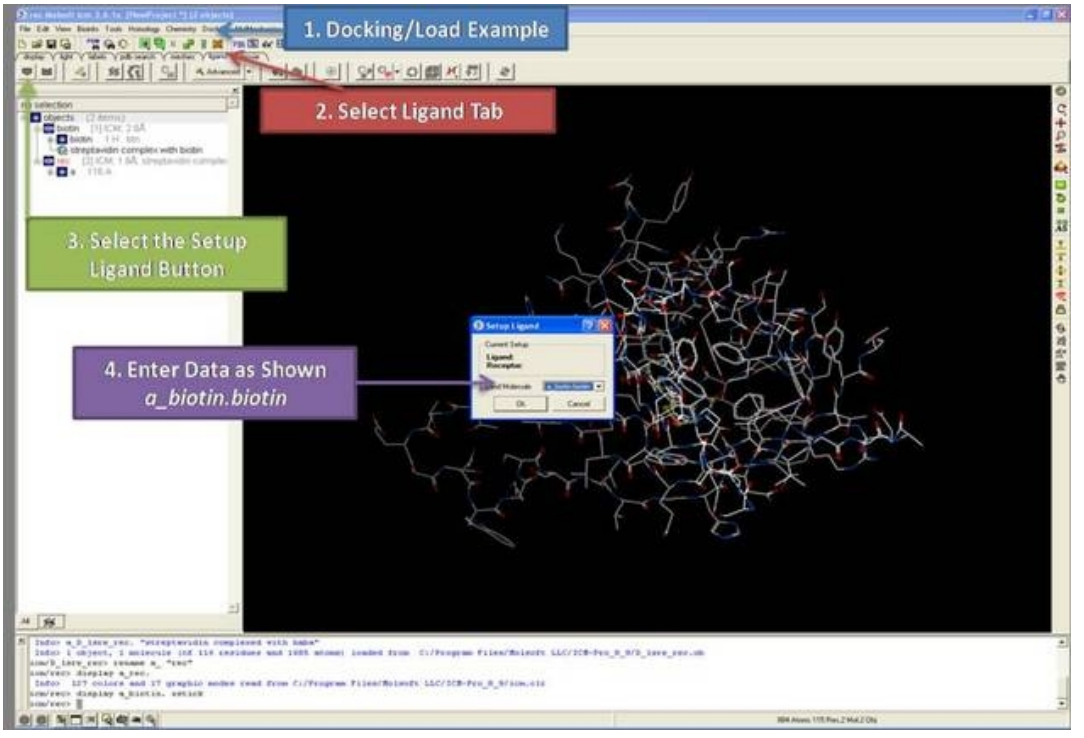
The ligand editor is a powerful tool for the interactive design of new lead compounds in 3D. It allows you to make modifications to the ligand and see the affect of the modification on the ligand binding energy and interaction with the receptor.



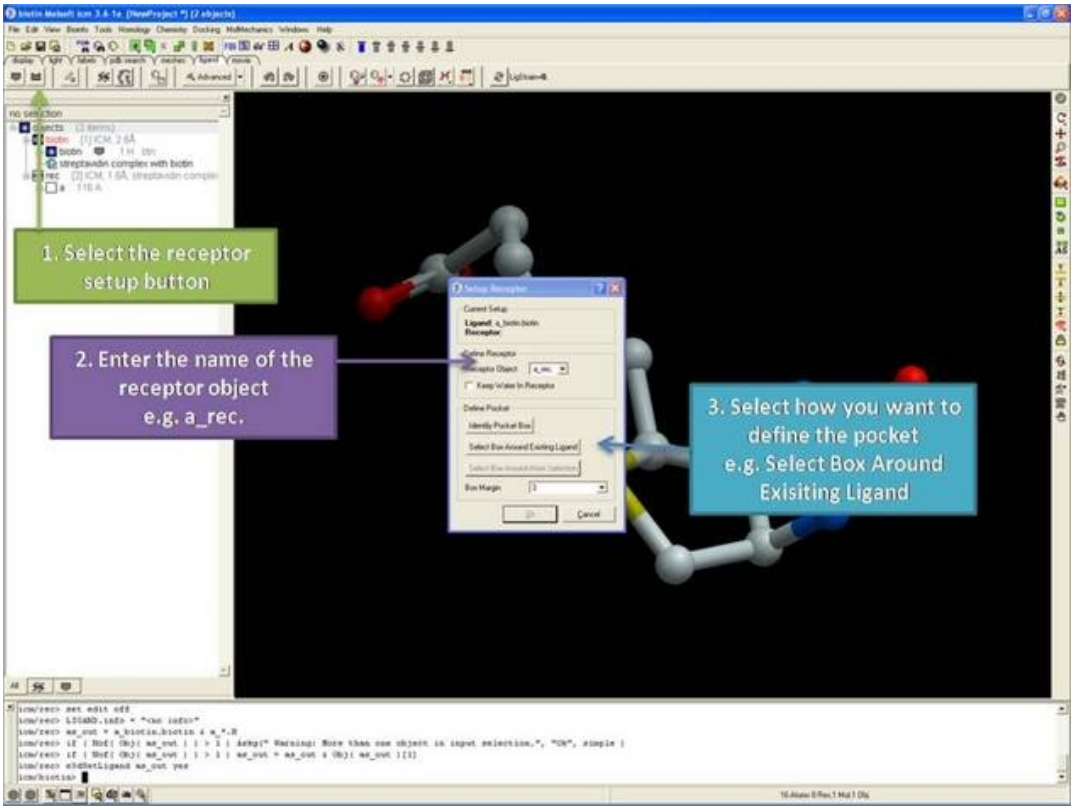
20.1 Setup Ligand and Receptor

As an example we will use the streptavidin−biotin complex which can be found by clicking on the Docking menu and selecting Load Example.

- Docking/Load Example − NOTE: The molecule needs to be an ICM object. In this example the receptor and ligand have already been converted into an ICM object.
- Click on the **ligand** tab
- Click on the **Setup Ligand** button.
- Enter the ICM selection language for the **Ligand Molecule** (a_biotin.biotin) or use the drop down button to locate it.

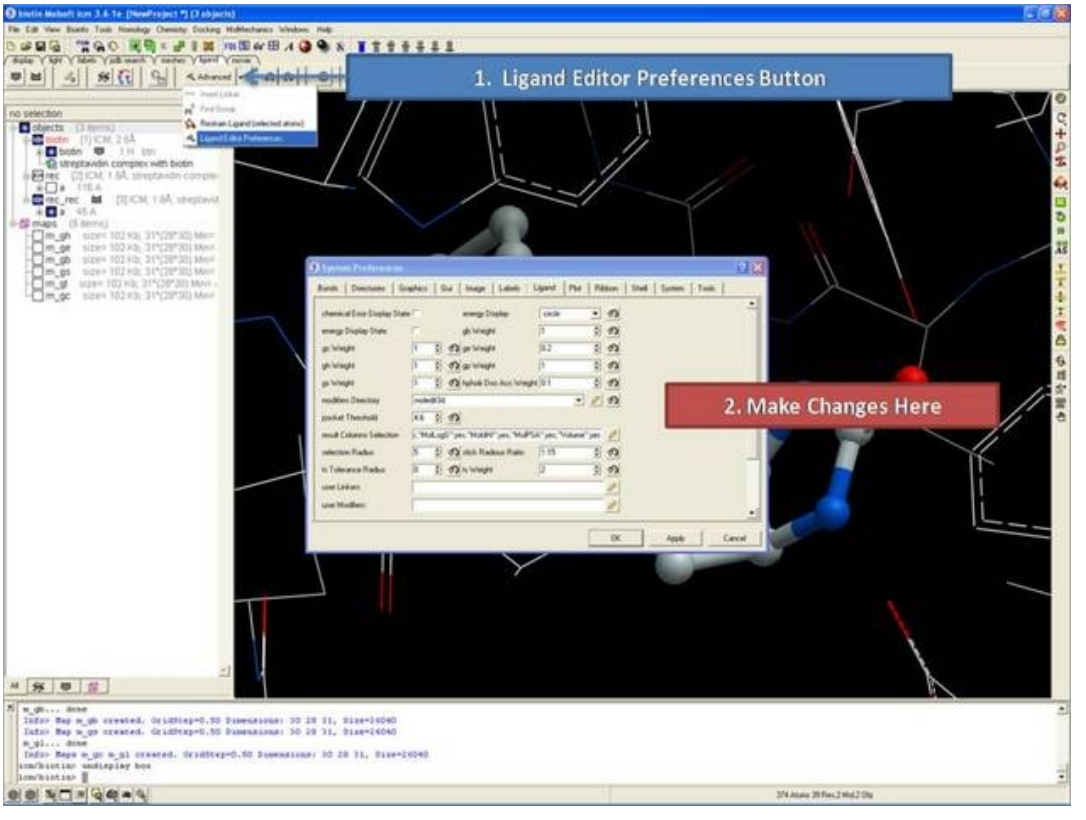


- Select the **Receptor Setup** button .
- Enter the ICM selection language for **Receptor Object** (a_rec.) or use the drop down button to locate it.
- There are no waters in this example but if you have key water molecules in the binding pocket then select the box entitled **Keep Water in Receptor**.
- Click on the option to select **Box Around Existing Ligand**. There are other options: **Identify Pocekt Box** will run ICMpocketFinder and return a table of pockets. Click on the table to select the pocket you want and then press OK. You can also**{Select Box Around Atom Selection}.
- Enter a box margin of 3. This option defines the size of the energy maps around the ligand. The value of 3. should encompass the whole site but if you have a binding pocket that is very elongated or unusual in any way it is recomended that you check that the purple box covers the site you are interested in.
- Click OK and the energy maps will be generated.



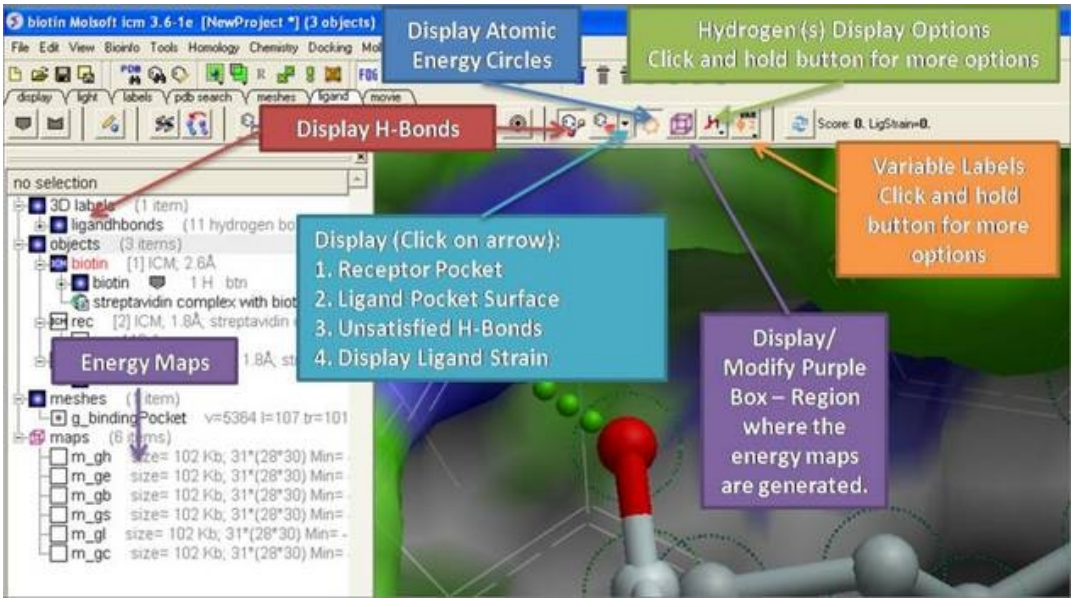
20.2 Ligand−Editor−Preferences

This step is optional but you may want to tweak the default preferences a bit. You can change the display preferences by clicking on the **"Setup Ligand Editor Preferences"** button as shown below.



20.3 Pocket Display Options

Our first step is to display the binding pocket property surface, ligand and receptor hydrogen bonds, and atomic energy circles. To do this click on the buttons highlighted below. You can also select to display or undisplay hydrogens and variable labels. During the ligand editing process these display options are very useful to guide your ligand design.



About Hydrogen Bonds: The coloring of the H−bonds are red (strong − thick spheres) to blue (weak − thin spheres). Once the hydrogen bonds have been displayed they can be displayed and undisplayed in the **3D labels** section of the ICM Workspace (left hand side of graphical window).

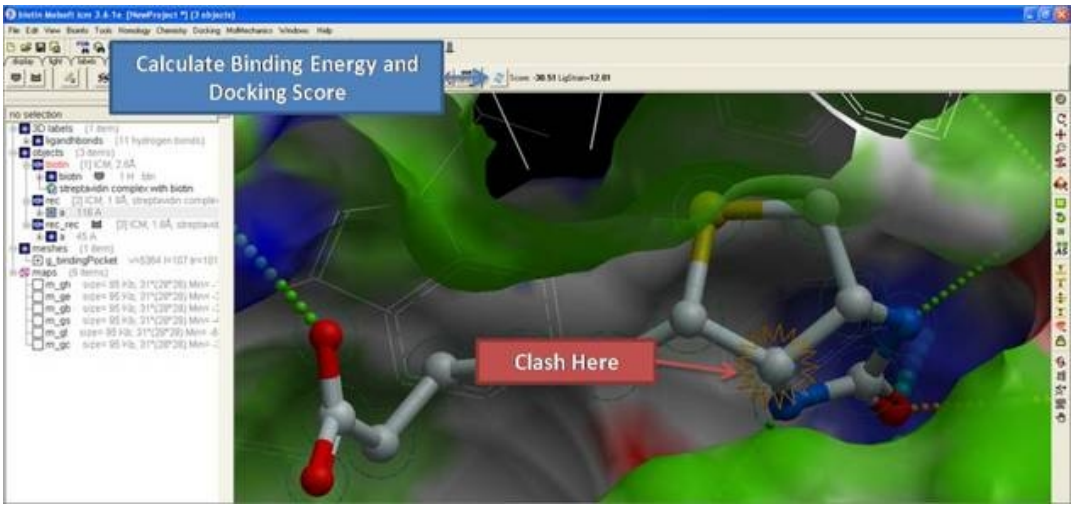
About the Receptor and Ligand Pocket Surface: White=neutral surface Green=hydrophobic surface Red=hydrogen bonding acceptor potential Blue=hydrogen bond donor potential

About the Atomic Energy Circles: Good ligand−receptor interactions are highlighted by green spheres. Poor energy interactions are displayed as orange−−>red stars − red being a major clash and a very poor energy contribution. Each stom is given an energy value relating to its contribution to the total receptor−ligand interaction energy. Low values colored green are considered favorable.

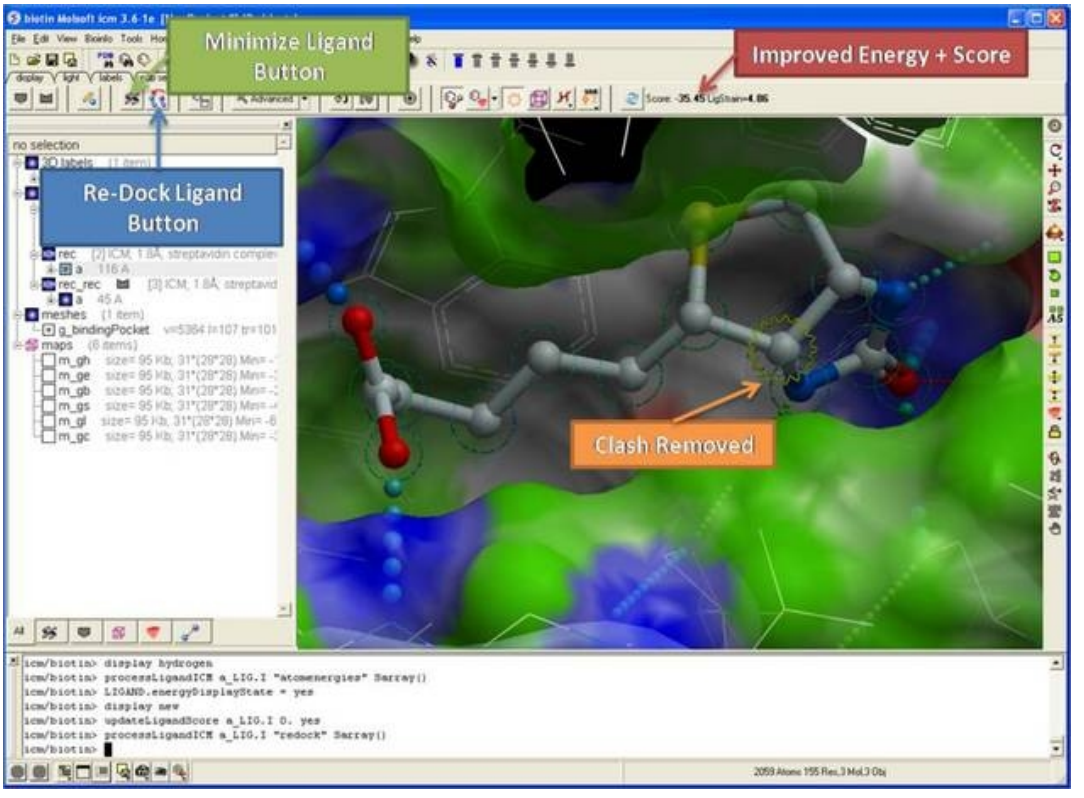
@About Purple Box The purple box represents the region in which the energy maps are generated. If you want to change the size of this region you can do so by clicking and dragging on the corners of the puprle box. You will then have to remake the maps by re−clicking the display/modify pocket box.

20.4 Re−Dock and Minimize Ligand

In the Docking/Load Example the ligand is not optimally bound to the receptor. A clash between one of the atoms and the receptor is highlighted by an orange star (see below). We can also calculate the binding energy of the receptor complex and Score.



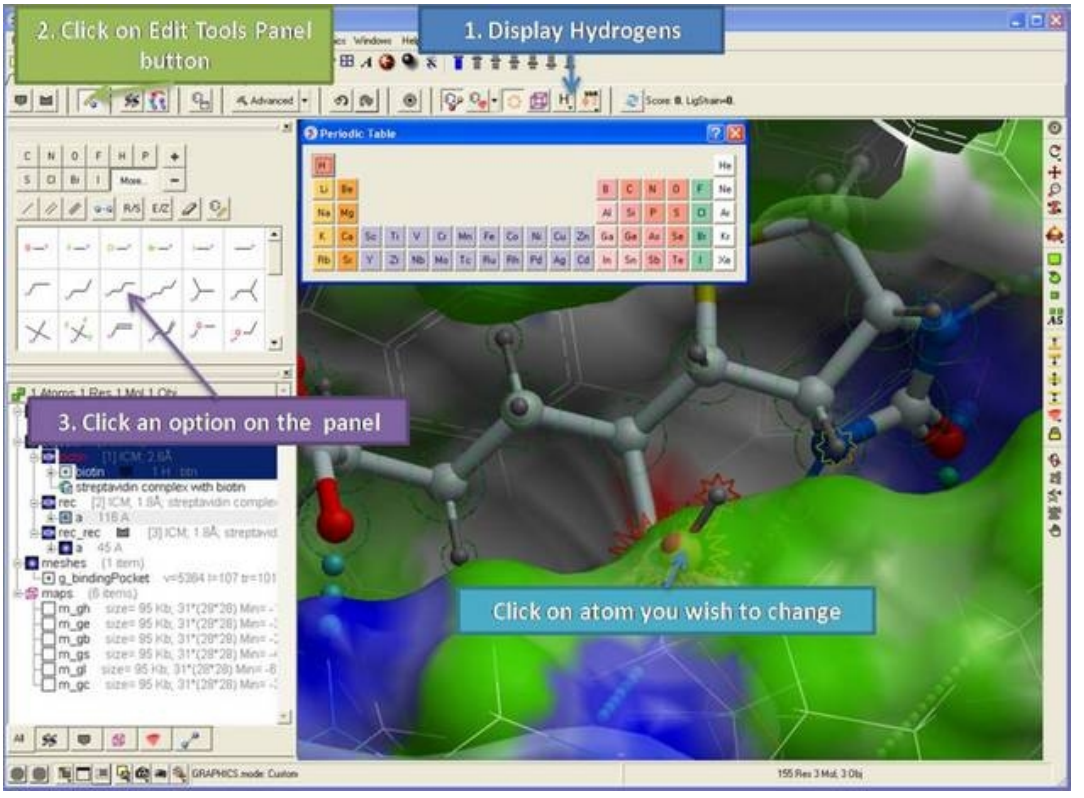
To remove this clash we can re−dock or minimize the biotin ligand. To do this click the **"Re−Dock"** ligand button.



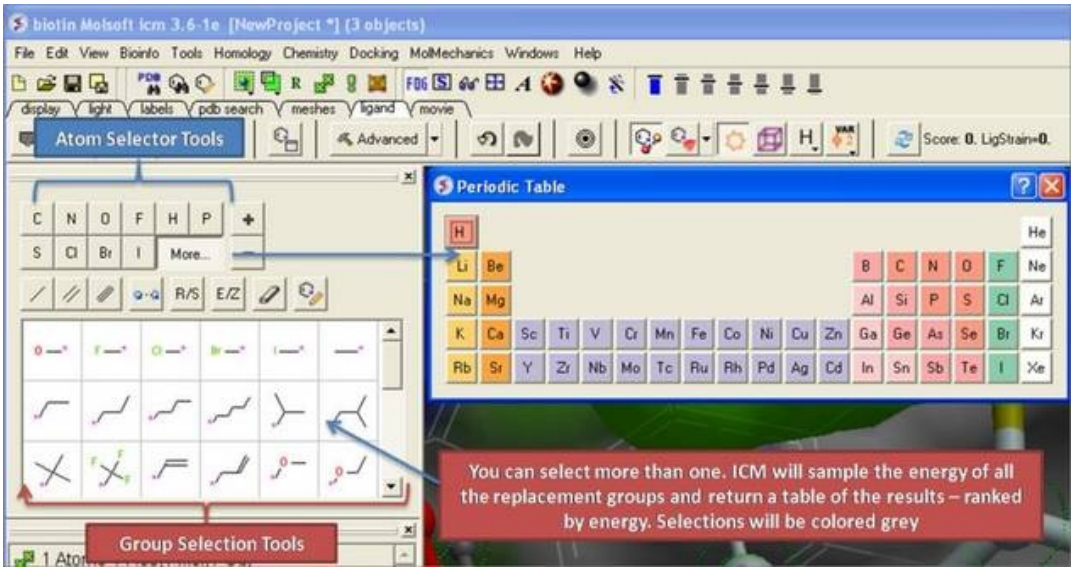
20.5 Edit Ligand

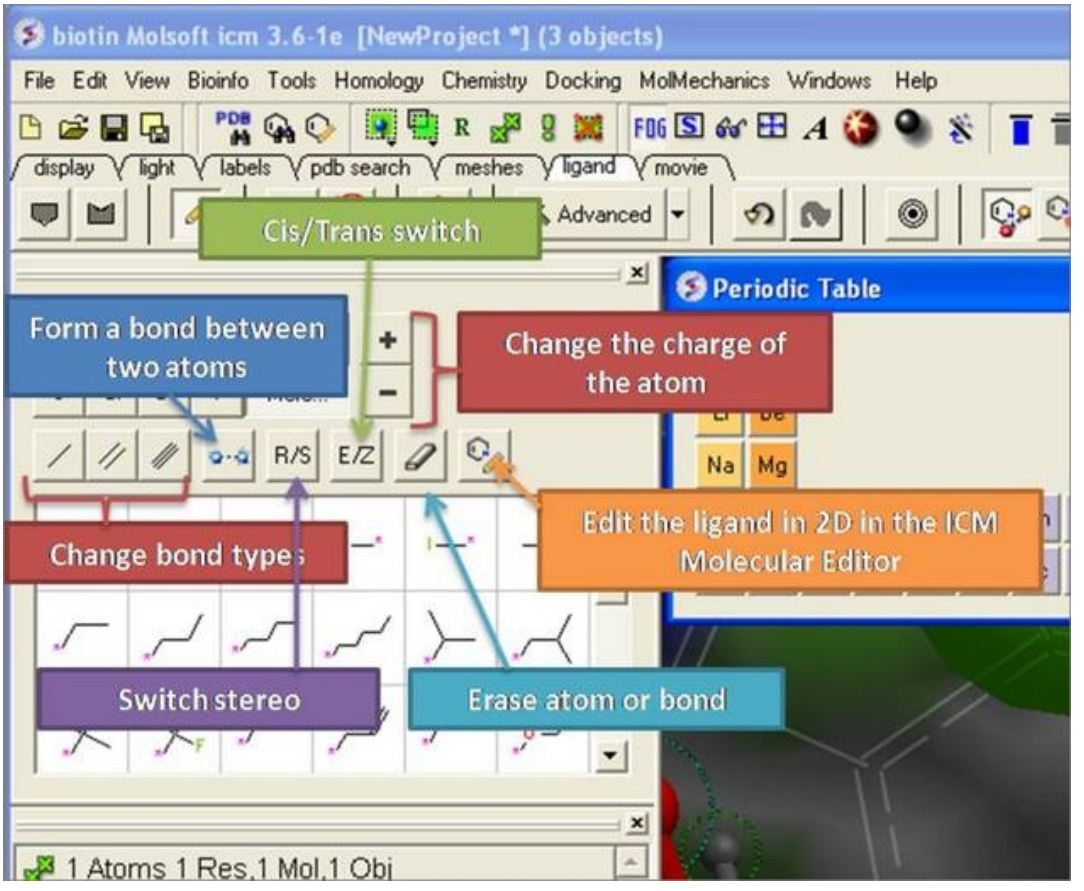
To edit a ligand:

- Display hydrogens using the hydrogen `display button`.
- Click on the **Edit Tools Button** and a panel of buttons will be displayed as shown below.
- To edit an atom or bond, first click on the desired atom, group or bond in the panel and the click on the atom or bond which you want to modify in the graphical display.

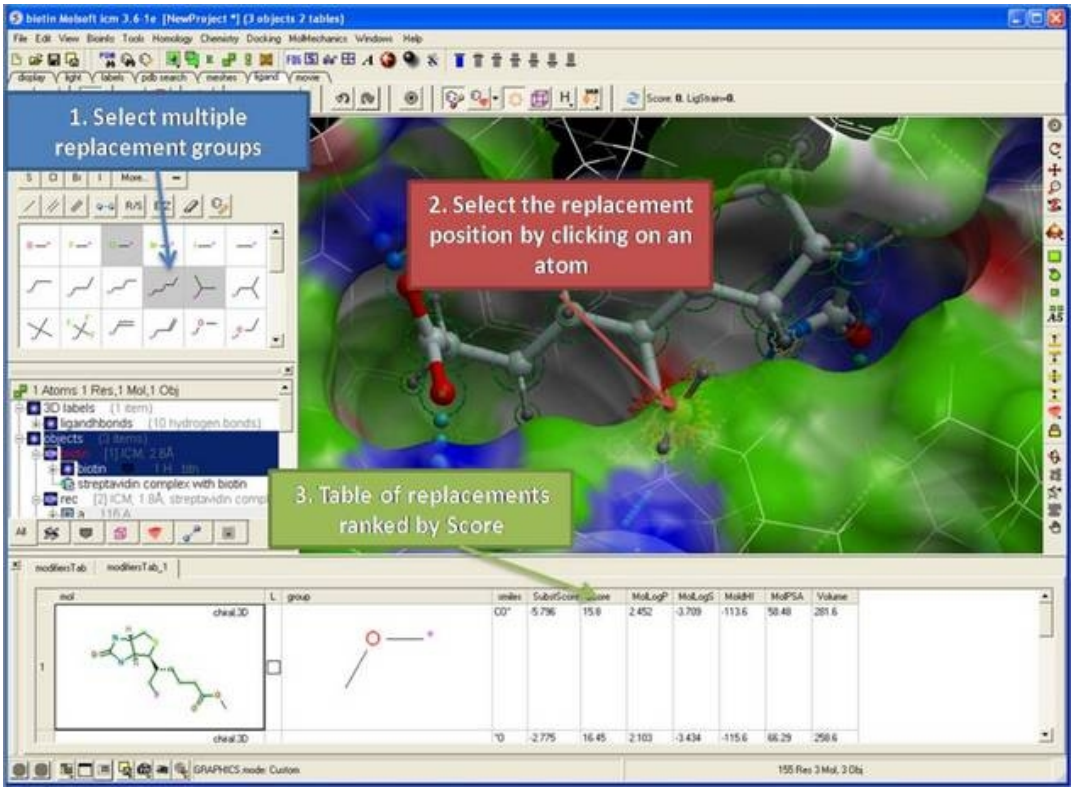


- See graphic below to understand what each button does.





- You can select more than one group. ICM will sample the energy of each group and return a table of the results ranked by binding score.



About the modifiers tabel

mol = 2D sketch of ligand with core substructure highlighted in green. Modifier group is not highlighted in green.

L = Click in box to display ligand with modifier group.

smiles = smiles string of modifier group

SubstScore = Score for modifier group only

Score = Score of whole ligand including modifier group

MolLogP = Predicted LogP

MolLogS = Predicted LogPredicted LogSS

MoldHf = Preidction model build for 'delta Hf in gas' property. using public NIST database. Description can be found: `http://webbook.nist.gov` A low dHf value means that the compound is more 'stable'.

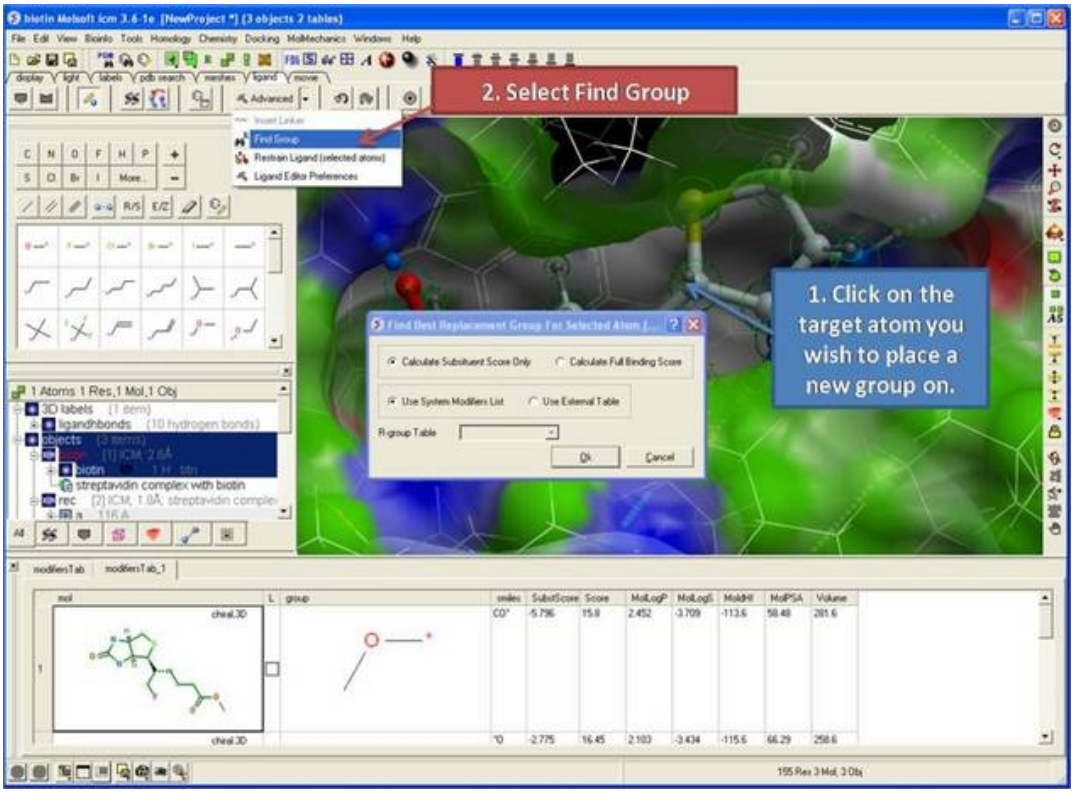
MolPSA = Polar Surface Area

Volume = Volume of ligand.

20.6 Insert a linker

To insert a linker between two fragments

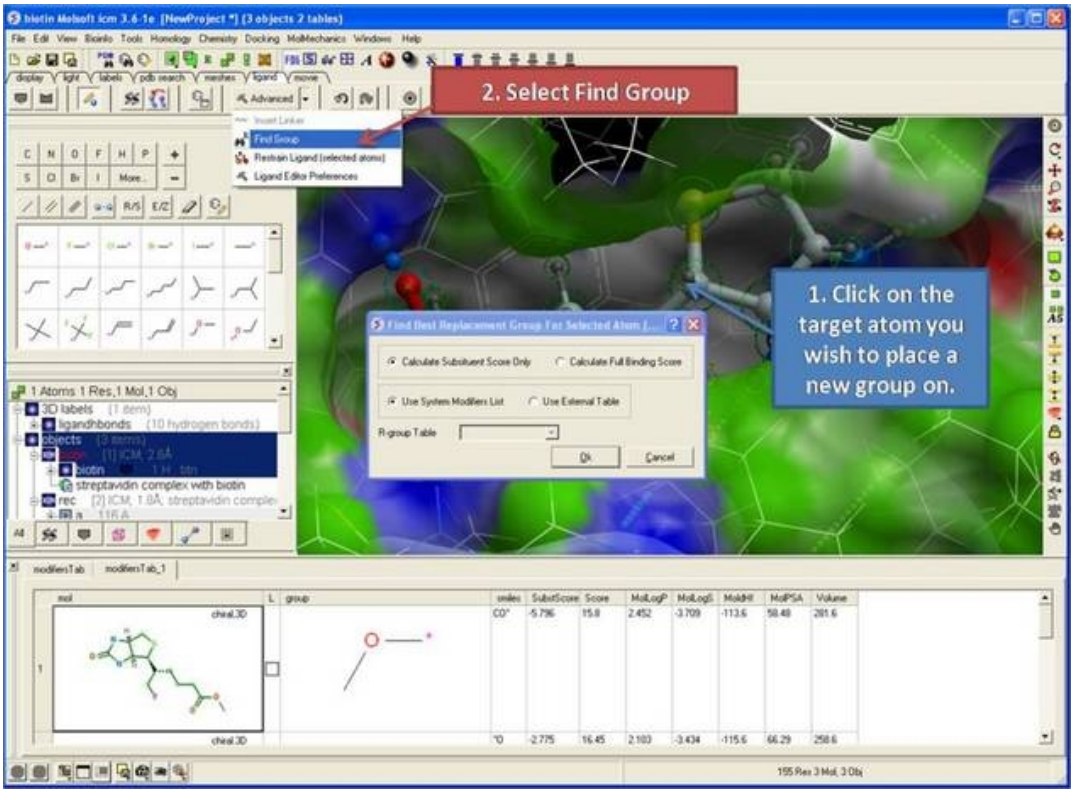
- Select two atoms in the ligand using the atom pick button.
- Click on the **Advanced/"Insert Linker Fragment"** button.
- Select linker.
- Click OK



20.7 Find Best Replacement Group

Find best replacement group for selected atom

- Select the atom you want to add a new replacement group to.
- Click on the **Advanced/Find Group** button.
- A dialog box as shown below will be displayed. Select whether you want the **substituent score only** to be evaluated (quick) or the **full binding** score.
- Select whether you want to screen the modifying groups built into ICM (see sarray of smiles called LIGAND.modifiers) or a table of your own modifier groups. If you choose your own table you will need to load the table (sdf file) into ICM and enter the name of the table into this dialog box or you can add modifiers to the sarray of smiles called LIGAND.userModifiers.

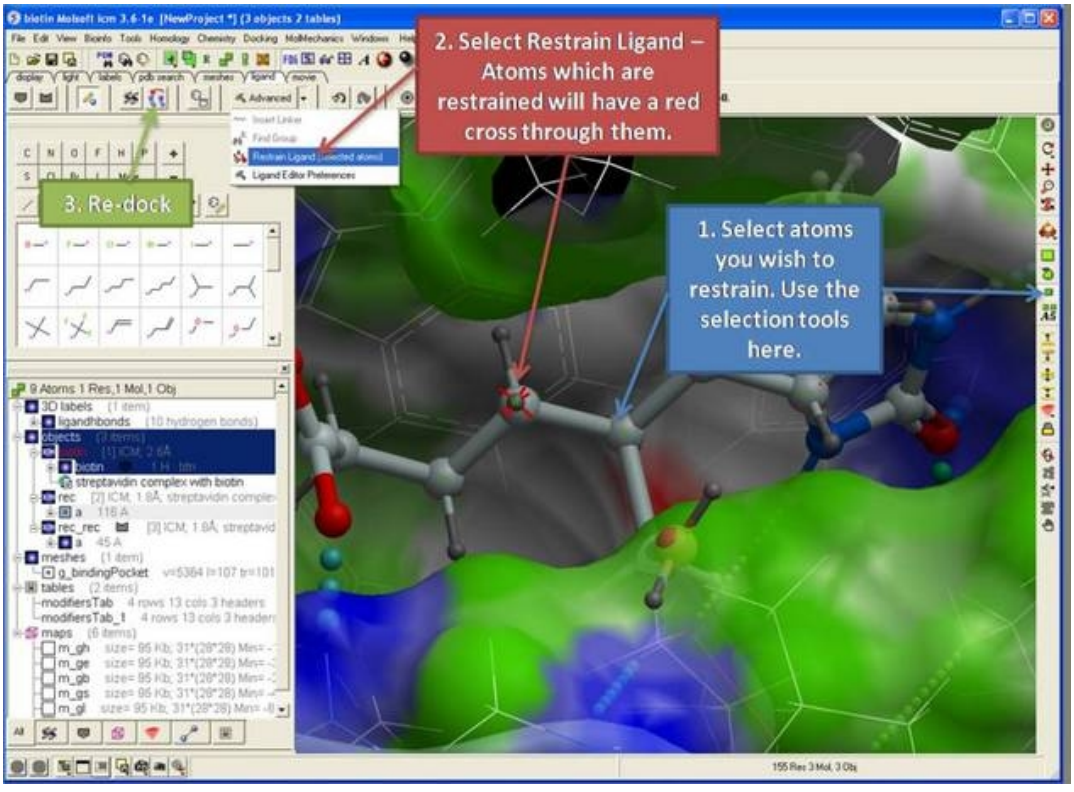


- ICM will add each fragment to the target atom and sample the energy and return a table ranked by score (see below).

20.8 Impose Restraint (tethers) To Ligand Atoms

To impose tethers to selected atoms of the ligand before redocking.

- Select the atoms you wish to tehter in the ligand. You can do this using the selection tools in gui or right click and drag over the atoms.
- Click on the **Advanced/ Restrain Ligand (selected atoms)** button. Tethered atoms will be highlighted by red−crosses.
- Click on the re−dock button and the atoms selected will remain tethered in place.


2. Select Restrain Ligand – Atoms which are restrained will have a red cross through them.
3. Re-dock
1. Select atoms you wish to restrain. Use the selection tools here.

#endif

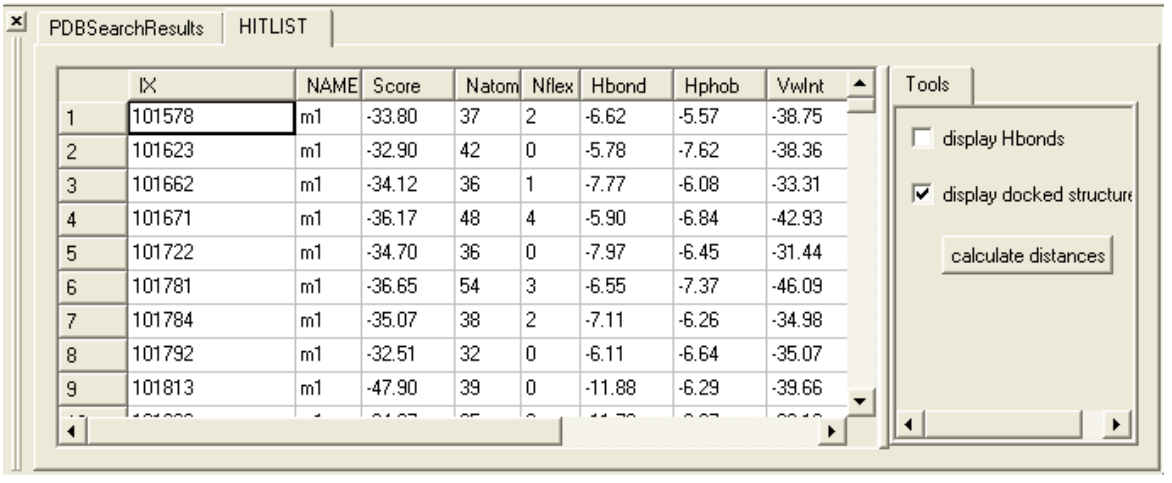
21 Working with Tables

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

One of the easiest ways to store, sort and display data in ICM is by the use of a table. In most cases tables are automatically created, for example, if you search for a PDB file or when you load a compound database (SDF file). It is also possible for you to create your own table. Once a table is created, ICM provides easy to use tools to sort, add, edit and plot data.

Here we will concentrate on describing the actions you can perform on a table once it has been read into ICM. We will start by describing a simple table. Actions which can be performed on chemicalmolecular tables are described in the section entitled `Working with Chemical Spreadsheets`.

A standard ICM table:



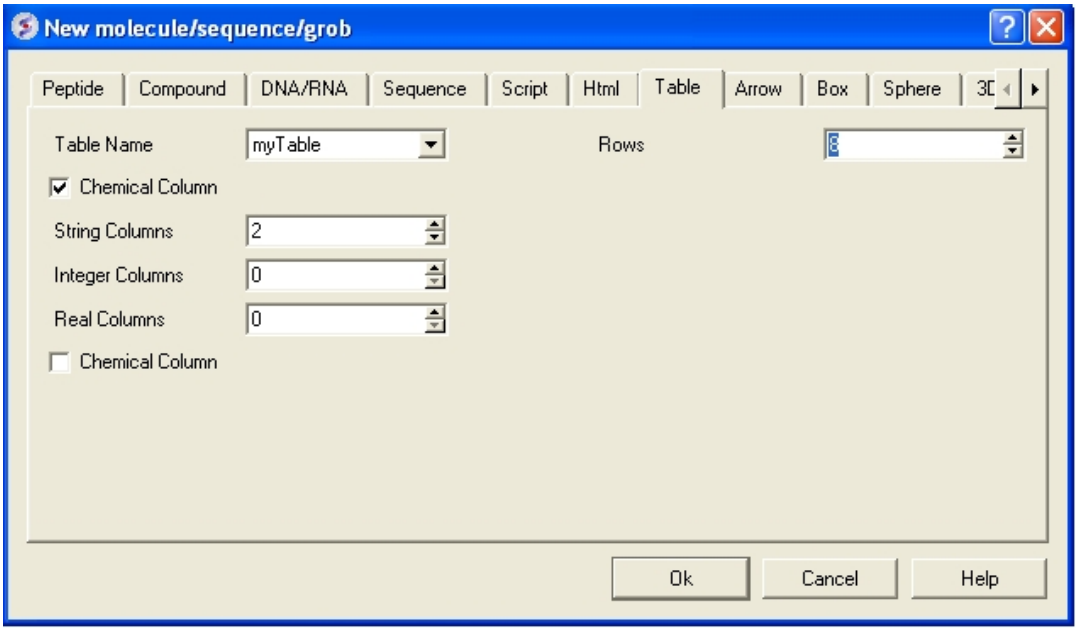
	IX	NAME	Score	Natom	Nflex	Hbond	Hphob	VwInt
1	101578	m1	-33.80	37	2	-6.62	-5.57	-38.75
2	101623	m1	-32.90	42	0	-5.78	-7.62	-38.36
3	101662	m1	-34.12	36	1	-7.77	-6.08	-33.31
4	101671	m1	-36.17	48	4	-5.90	-6.84	-42.93
5	101722	m1	-34.70	36	0	-7.97	-6.45	-31.44
6	101781	m1	-36.65	54	3	-6.55	-7.37	-46.09
7	101784	m1	-35.07	38	2	-7.11	-6.26	-34.98
8	101792	m1	-32.51	32	0	-6.11	-6.64	-35.07
9	101813	m1	-47.90	39	0	-11.88	-6.29	-39.66

21.1 Standard ICM Tables

21.1.1 Generate New Table

To generate a new empty table:

- File/New and select the **Table** tab and a window as shown below will be displayed.
- Enter the number of rows and columns you wish to include in your table and whether you wish to add a column with chemical data.
- If you wish to make a `chemical table` (chemical spreadsheet) select the **Chemical Column** box.



21.1.2 Reading a Table

A table can be read and saved as a .csv file or a .tab file. Saving or reading your table as a csv (comma separated value) file enables the table to be transfered or loaded from other applications such as Microsoft Excel. A compound database such as an .sdf file can also be viewed as a table in ICM, additional details on how to manipulate a `molecular table` is explained in the next section.

A table can be read into ICM by selecting:

- File/Open and then selecting the table you have saved.

OR

Sometimes data is naturally stored and displayed in a table − e.g. PDB data. A common use of tables is for compound data. An explanation of how to use compound molecular tables is in the next section entitled `ICM Molecular Tables`.

For an example of a table try the following:

- Select PDB search tab.
- Type * into data entry box.
- Click on the button next to the data entry box.

A table of all the PDB structures will be displayed at the bottom of the GUI.

NOTE: If you have loaded a table and it is not displayed it may be because the table window is hidden. To display the table, select the window menu and select table see the `Window Menu Section`.

21.1.3 Saving a table

To save the whole table:

- To save a table right click on the table header tab and select Save As..

To save a row selection:

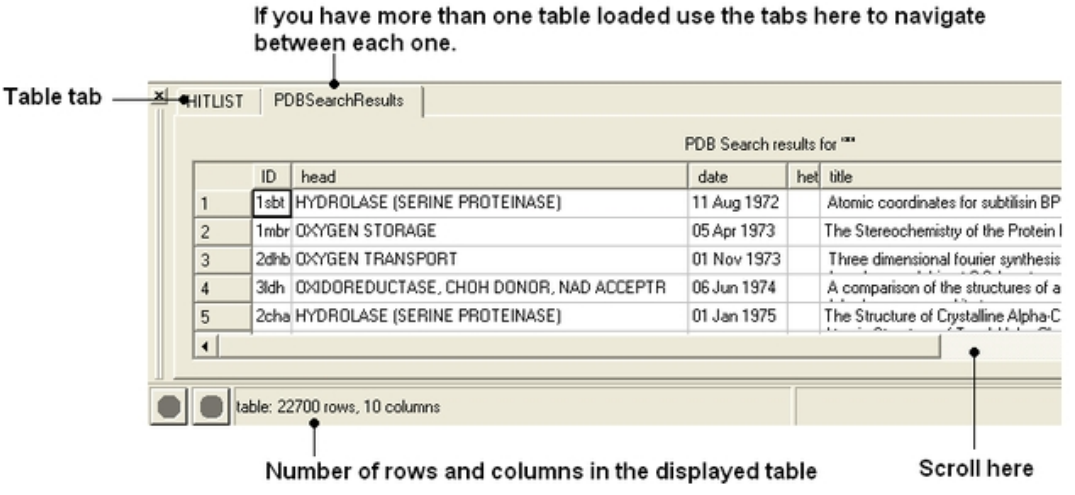
- `Select` a row(s)
- Right click and choose **Save Selection As** or **Save Selection As Csv + Headers**

21.1.4 Basic Table Navigation

To view the contents of a table you can move the table up and down using the scroll bars on the side and bottom of the display.

NOTE: If you have loaded a table and it isnt displayed it may be because the table display isnt selected. To select the table display, select the window menu and select table (See `Window Menu Section`).

If you have read more than one table in ICM you can select a table by clicking the tab on the top of the table (See Below).



NOTE: Double clicking on the tab allows two tables to be displayed at once. Double clicking again returns to the default table layout.

NOTE: Information regarding the number of rows and columns within a table is displayed at the bottom of the table.

If you would like the table to be the main window in the graphical user interface:

- Select Windows/Table−>Main

21.1.5 Table View (Grid Layout)

To change the table view (layout):

- Select the columns you wish to display in grid view. No selection will place all columns in grid view
- Right click on a table row and select **Table View**
- You can view the table in **Grid View** and toggle between grid and standard view. You can define your own grid using the **Custon Grid** option or display the table in **Form View**.

NOTE: You can `save` a table view.

21.1.6 Table View Save

Once you have a `table view` that you want to keep. You can save it by:

- Right click on a table row and select **Store Views**
- Select **Save Current View**

- Enter a name for the table view and you can return to that view by repeating the first two steps above.
- You can rename, delete or restore view by right clicking on the name of the table view.

21.1.7 Table Search

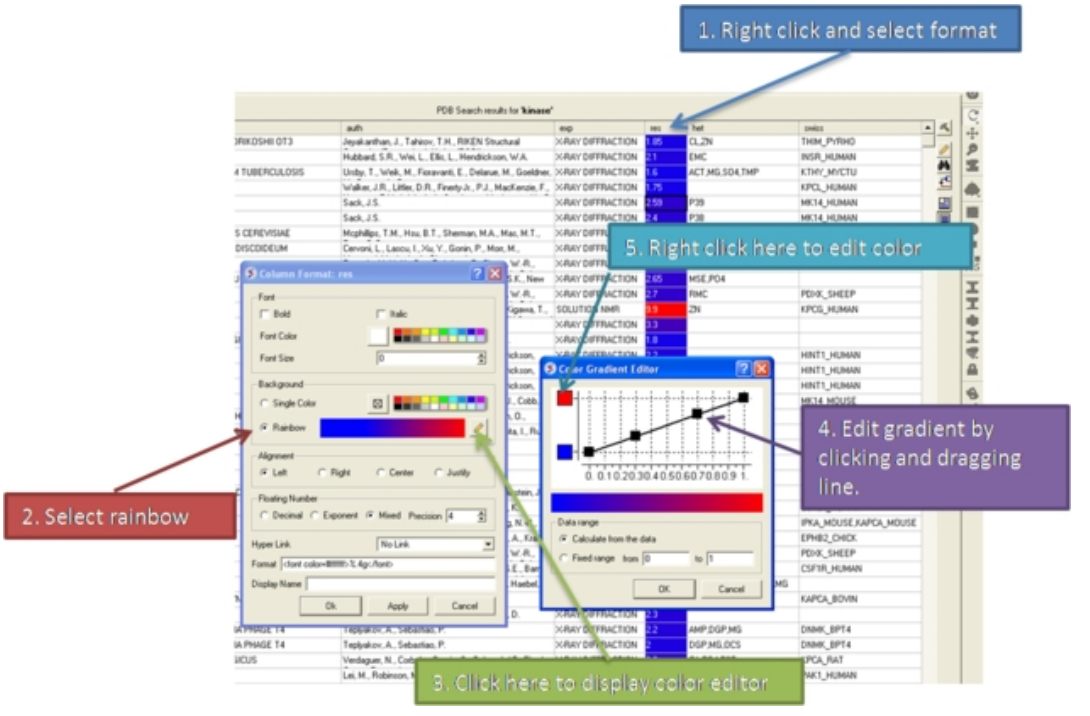
To search a table:

- Right click on a table row and select **Find and Replace**. You can also use CTRL F.
- Enter a search string.
- Press the **Find** button.

21.1.8 Table Color

You can color your table based on values within a column by:

- Right click on the column header and select **Format.**
- In the **Background** panel select the color you desire eg **Single Color** or you can by a rainbow according to the data in the column. To edit the range of values relating to each color click on the pencil (edit) button as shown below.



21.1.9 Table Font

- Right click on the column header and select **Format.**
- Change the font using the options in the **Font** panel.

21.1.10 Table Alignment

- Right click on the column header and select **Format.**
- Change the font using the options in the **Alignment** panel.

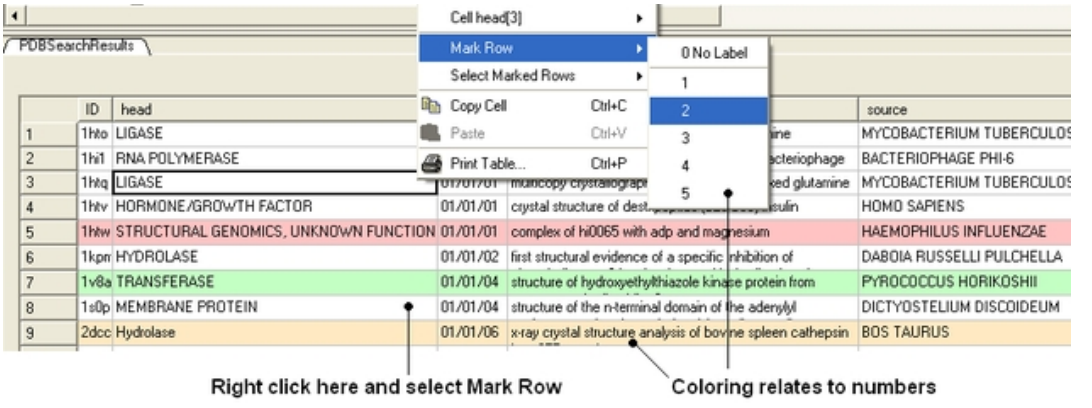
Rows can be colored by marking them as described `here`

21.1.11 Mark a Row

A row in a table can be marked and grouped by a label which enables the row(s) to be selected easily at a later time.

To mark a row

- Right click on the row in the table you wish to **mark.** Or `select` multiple rows and then right click.
- Select **Mark Row/** and then choose a number. In the GUI the number of rows that can be marked is limited to 5 but this can be increased using the command line command.
- A row that is marked will be colored − each number is assigned a color. The coloring can be changed in the `gui tab in preferences`.



To select marked rows

- Right click on the table and choose **Select Marked Rows** and choose a number which relates to the marked rows as described earlier.
- Selected rows will be highlighted blue − once rows are selected a number of right click options are activated such as copy selection to new ICM table.

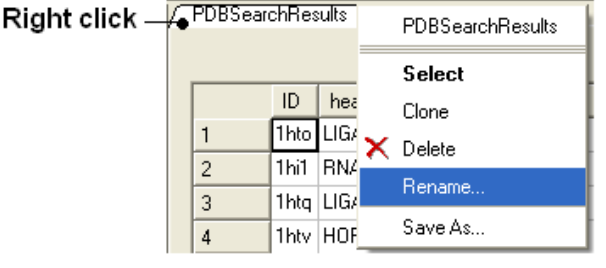
21.1.12 Table right click options

Right−click options vary according to where you click and what is selected. The options are intuitive, for example options that are performed on the whole table (eg Save and Delete) are performed by right−clicking on the Table tab. Other right−click options vary according to whether the row or column is `selected` or not.

21.1.13 Rename a Table

To rename a table:

- Right click on the table tab and select rename.
- Enter a new name and select OK.



21.1.14 Clone a Table

- Right click on the table tab and select clone.

21.1.15 Delete a Table

- Right click on the table tab and select delete.

21.1.16 Page Setup

Before `printing a table` you can change the orientation and scale.

To do this:

- Right click on the table header and select **Page Setup**.

21.1.17 Print a Table

A table can be printed by:

- Right click on the table and a menu will be displayed.
- Select the "Print" option. You may want to change the setup of the table (eg orientation and scale. You can do this using `Page Setup` option.

21.1.18 Export to Excel

To export a table to excel.

- Right click on the table header.
- Select the option to **Export to Excel**.

21.1.19 Save a Table

- Right click on the table tab and select Save As..

NOTE: You can save your table in comma separated format if you want to read it into another program such as Microsoft Excel.

21.1.20 Change Column and Row Width

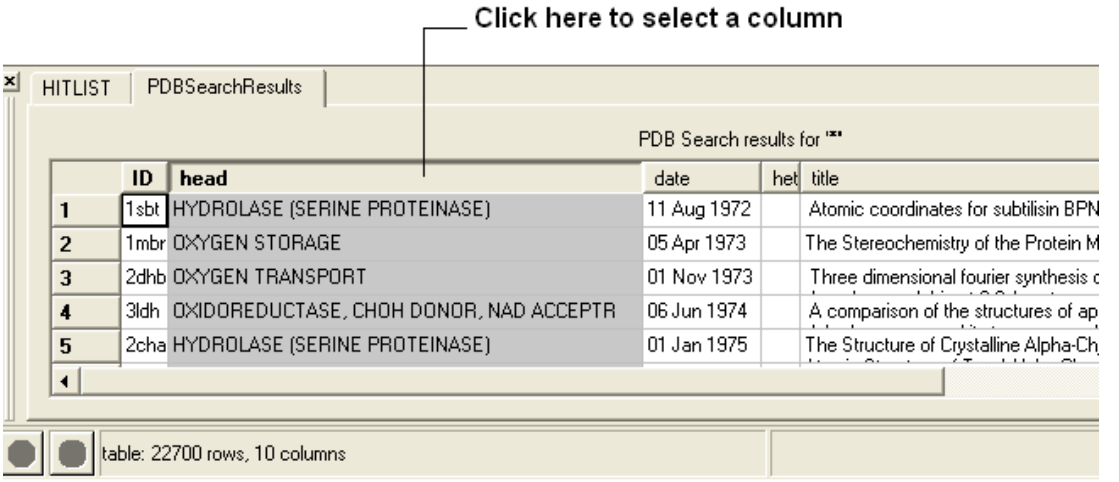
To change the width of column and rows:

You can change the width of a row or column by clicking on the separating line and dragging. You can make each row the same width by holding down the **Shift** key and dragging one of the row edges.

21.1.21 Making Table Selections

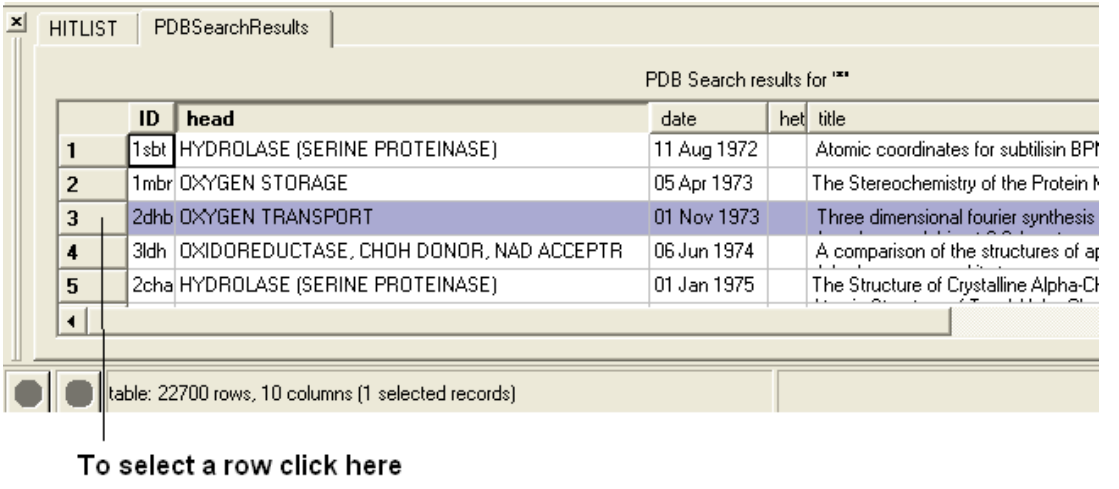
To select one column of a table:

- Click on the column header



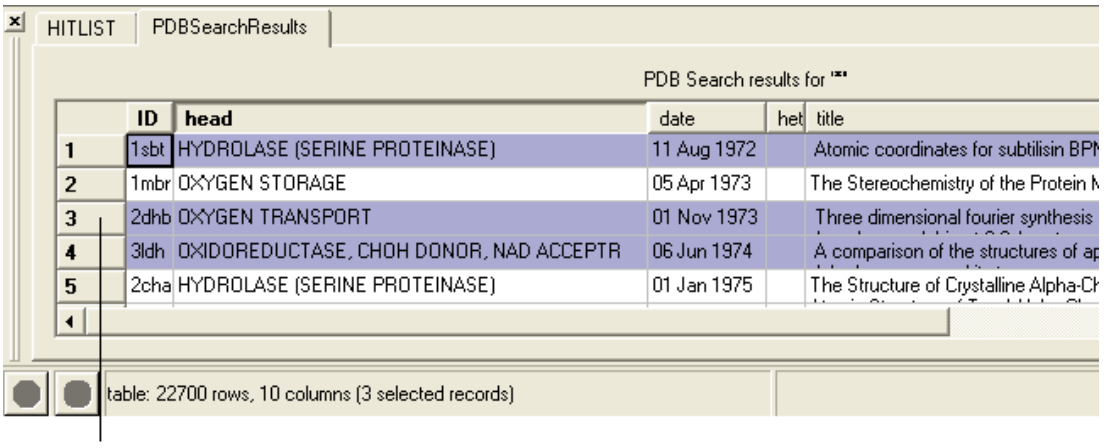
To select one row of a table:

- Click on the row header



To select more than one row or column:

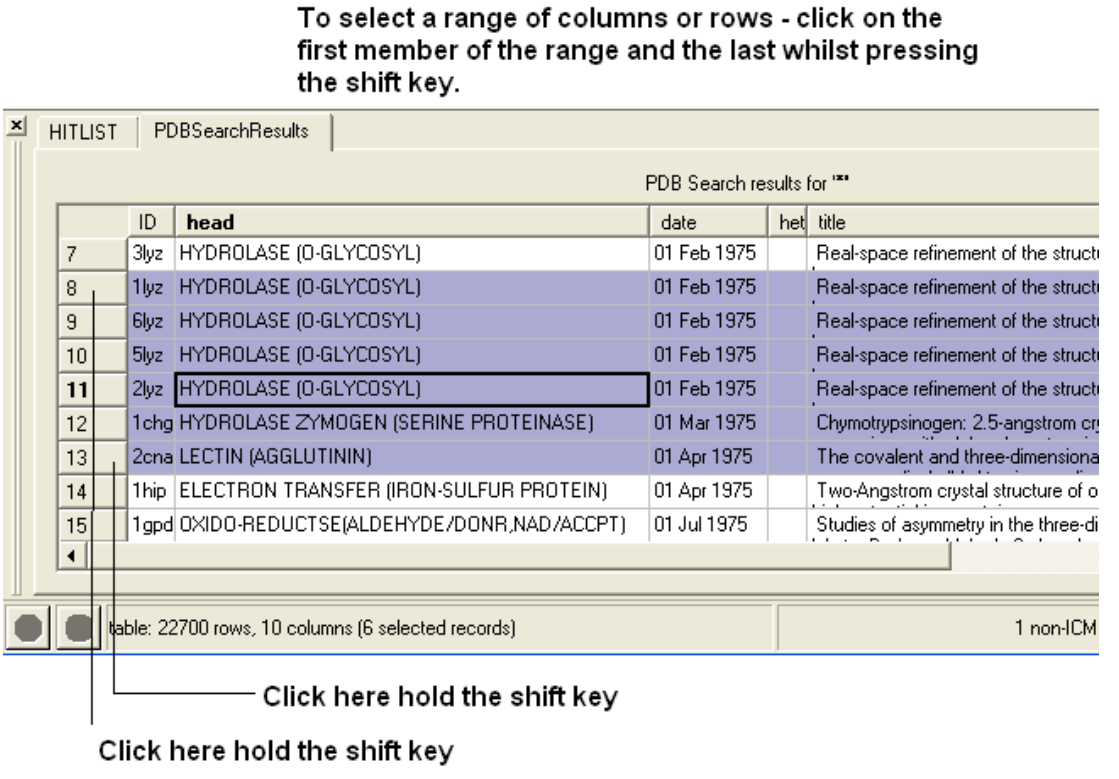
- Click on one row or column whilst pressing the Ctrl key
- Select multiple number of rows or columns whilst still pressing the Ctrl key



NOTE: The Ctrl key acts as a toggle enabling select and unselect.

To select a range of columns or rows:

- Click on the first row or column in the range whilst pressing the Shift key.
- Click on the last row or column in the range whilst pressing the Shift key.



To invert a selection:

- Right click on the original selection and a menu will be displayed.
- Select the Row Selection/Invert selection option.

NOTE: Invert selection can only be used on rows.

To select the whole table:

- Right click in the table and a menu will be displayed.

- Select the Row Selection/Select All option.

To remove a selection:

- Click anywhere within the table.

A selection can also be made from a plot select(`table−plot{See Select plot section}).

21.1.22 Editing a Table

To edit the contents of a table column:

- `Select` the column and then right−click on a column header and a menu will be displayed.
- Select the "Edit Mode" option. A tick will be displayed if it is selected.

OR

To edit the text or values within a cell:

- Right click on the table and select **Edit Cells by Double−click** .

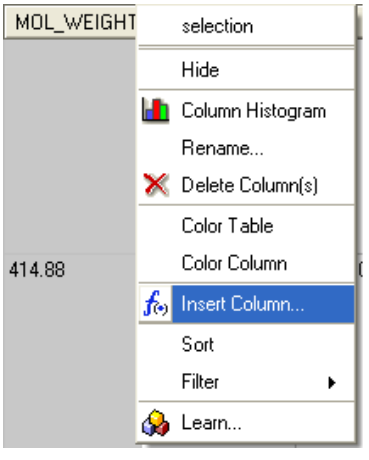
To edit the name of a column:

- Right click on the column header and a menu will be displayed.
- Select the option "Rename Column..." and enter the appropriate new text.

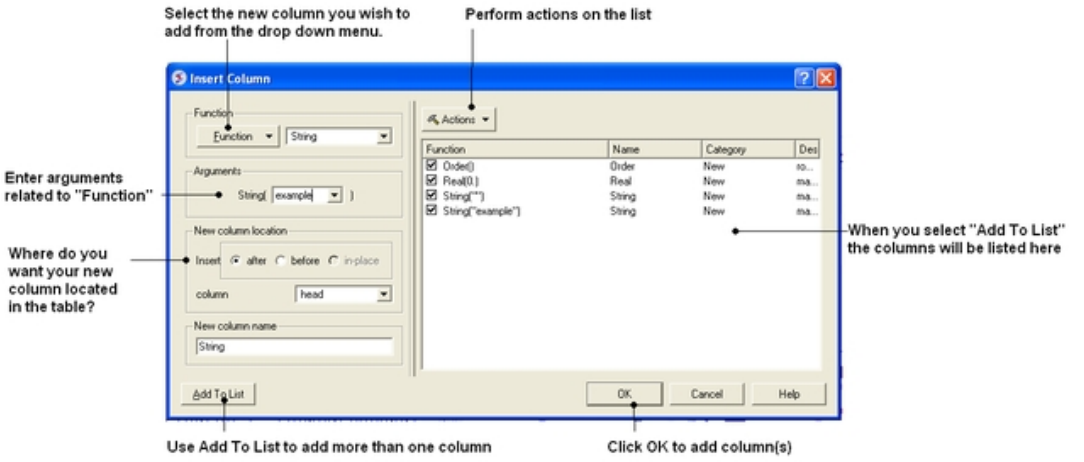
21.1.23 Inserting Columns

To insert a column:

- Identify the position within the table where you wish the column to be inserted.
- Right click on the column header and a menu will be displayed.
- Select "Insert Column"



A dialog box will then be displayed as shown below.



- Select the function you wish to add to the new column. Functions can be applied to many columns e.g. add etc..
- A set of arguments related to the function selected will then be displayed.
- Enter the appropriate arguments related to the function selected.
- Select where you want the new column to be located in the table.
- Enter the new column name
- If you wish to add multiple columns then use the **Add to List** option.

Many different functions are available:

- ***New*** Add a new column containing a real number, integer, string,or random number.
- ***Transformations*** A number of transformations can be selected and applied to a table column as shown below.
- ***Mathematical*** A number of mathematical functions
- ***Text*** Apply a number of different functions to the text in a column.
- ***Chemical*** Calculate a number of different chemical properties.
- ***Convert Units*** Radian to Degrees and Degree to Radian

Once the function and the correct arguments have been entered:

- Select whether you wish the new column to be added before,after or in place of this column.
- Enter the name of the new column.

NOTE: If you want to add more than one column choose **Add to List** and the action will be added to a list on the right hand side of the dialog box.

21.1.24 Column Statistics

To calculate various statistics describing columns and inter−column relationship:

- Right click on the column header and a menu will be displayed.
- Select "Column Statistics"

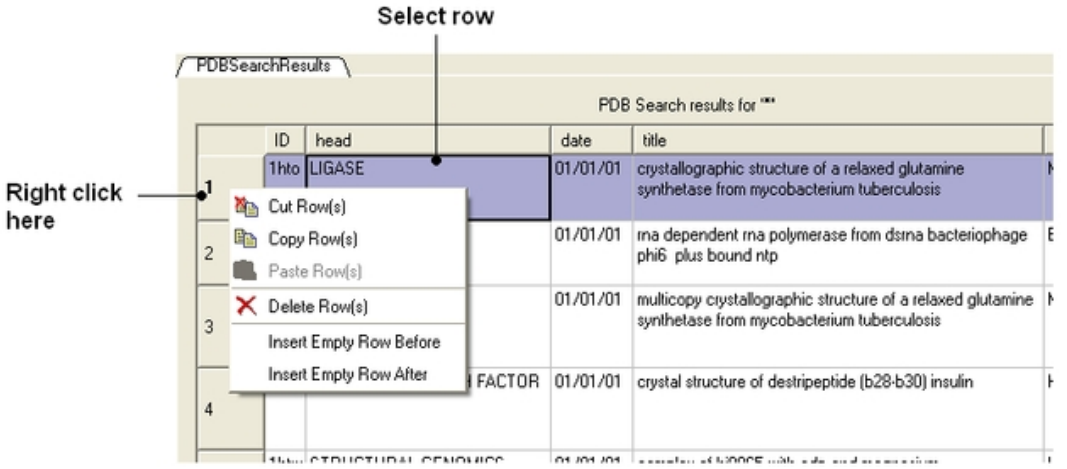
The output is printed into the ICM Terminal window and the Column Statistics Window.

21.1.25 Inserting Rows

To insert a row:

- Identify the position within the table where you wish the row to be inserted and `select` the row.
- Right click on the row name (eg the number of the row) and a menu will be displayed.
- Select **Insert Row Before or Insert Row After**.

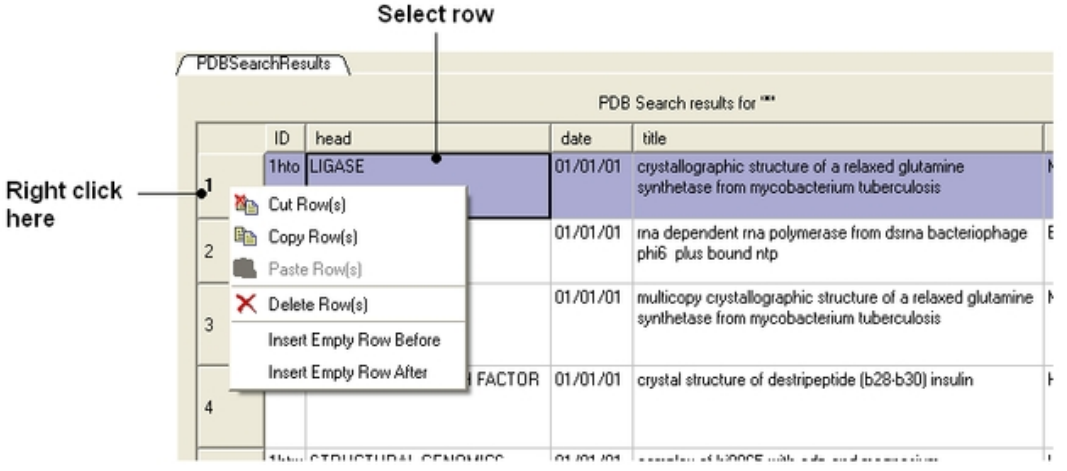
A blank row will be inserted. You can add data to this row by following the instructions in the `edit table section`.



21.1.26 Copy Cut and Paste Row

Copy, Cut and Paste Row:

- Select the row(s) `See table selection section`.
- Right click on the row header
- Select **Copy Row(s)**.
- To paste a row select the row header under which you wish to paste the row. Right click and select **Paste Row(s)**



21.1.27 Copy Cell

To copy a table cell:

- Right click on cell.
- Select Copy Cell − you can then paste it into a new table.

21.1.28 Copy Selection to an ICM Table

To copy a selection to a new table:

- Select the row(s) `See table selection section`.
- Right click on the row header
- Select **Copy Selection to ICM Table** and then choose Auto (ICM will name the table or New and you can enter a new table name.

21.1.29 Deleting Columns and Rows

To delete a column or row:

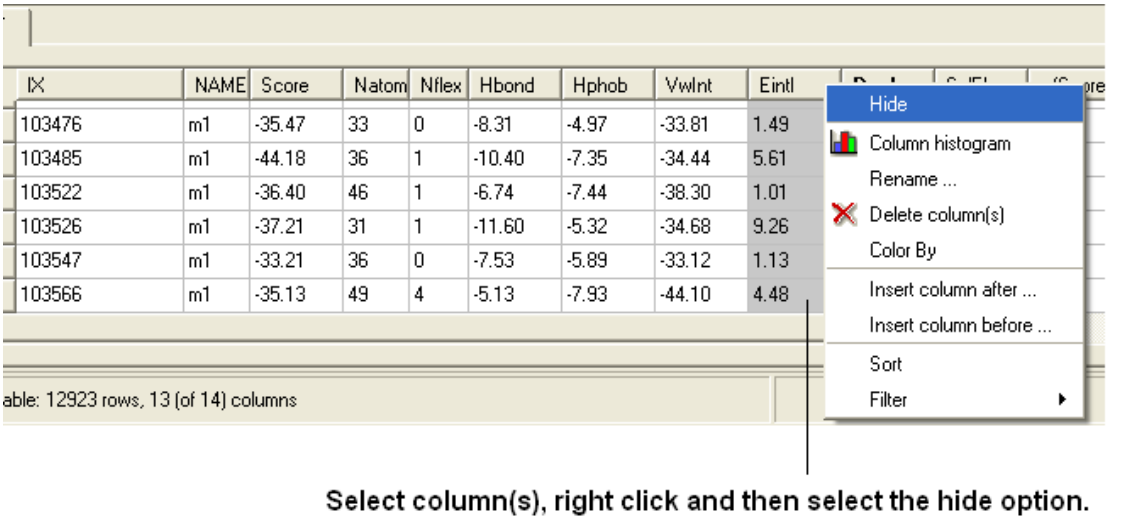
- Select the column(s) or row(s) you wish to delete. See the `select table` section for information on how to make table selections.
- Right click on the row to delete a row or right click on the column header to delete a column and select the delete option from the menu.

21.1.30 Hide and Show Columns

If you have a large table you may wish to only show and display certain columns and hide others. By default any loaded table will have all the columns displayed.

To select which columns you wish to hide:

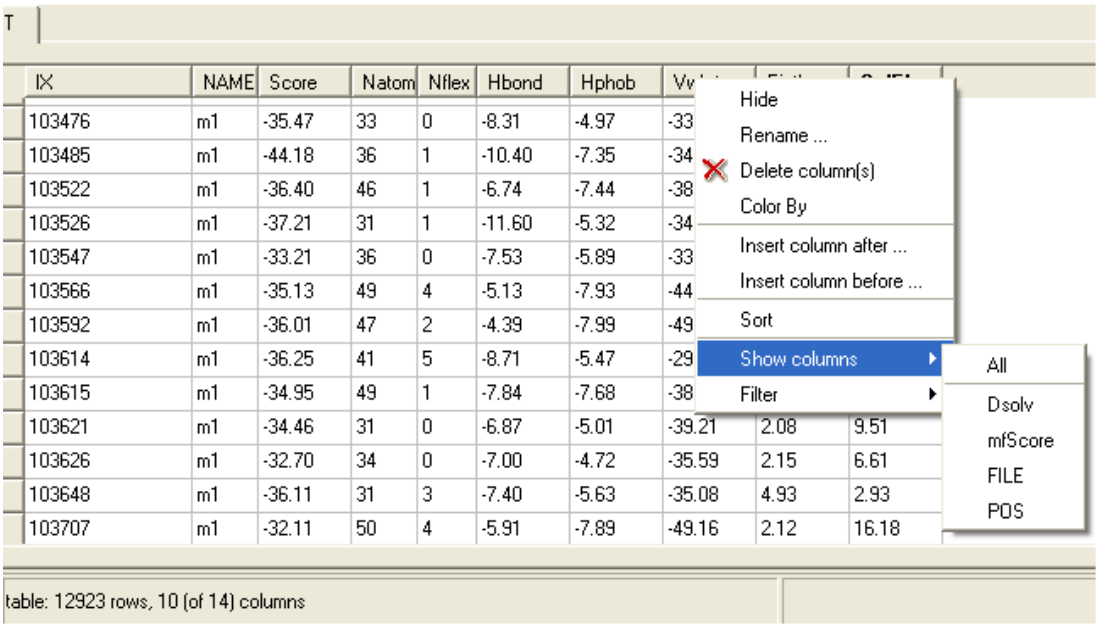
- Select the column(s) you wish to hide. See the `select table` section for information on how to make table selections.
- Right click and select the hide option from the menu.



Select column(s), right click and then select the hide option.

To show hidden columns:

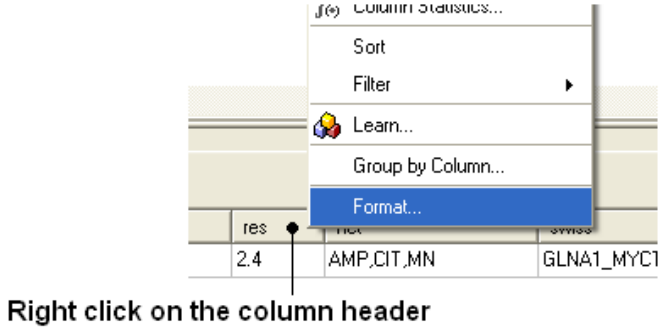
- Right click on the column header and a menu will be displayed.
- Select the **Show Columns** options.
- Select which column you wish to show from the drop down list.



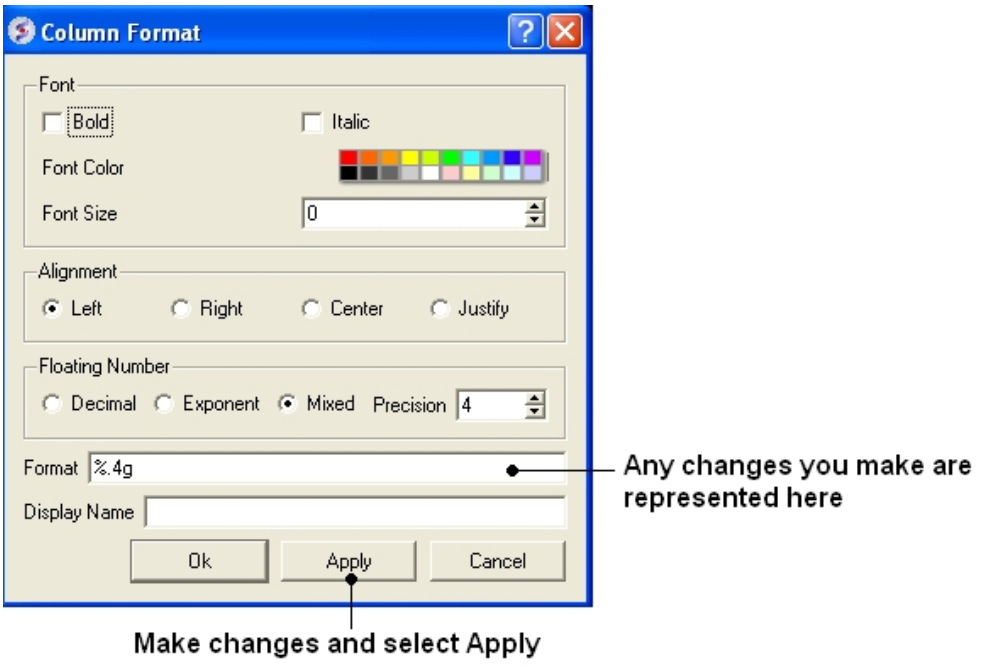
21.1.31 Change Column Format

To change the **font** color or size, the **alignment** of the column data, the **floating** point number or **column name**.

- Right click on the column header and select **Format**



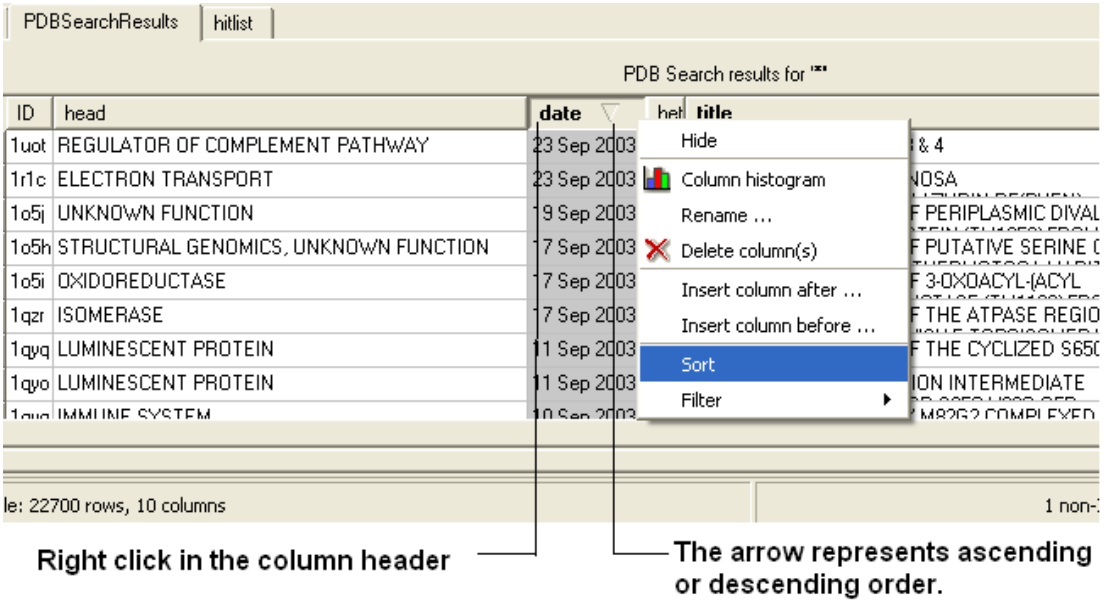
- A window as shown below will be displayed.
- Make the desired changes and click **Apply**



21.1.32 Table Sorting

To sort a table by a column value:

- Right click on the column header.
- Select the **Sort** option.

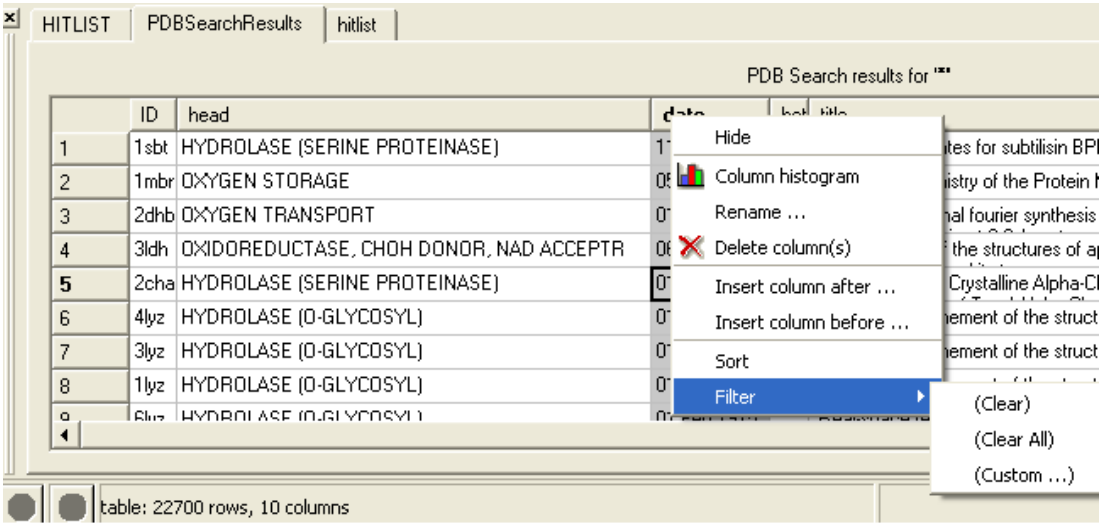


21.1.33 Table Filtering and Appending

Here we will describe how you can filter your table so that you can then append the filtered data to a new table or display only relevant information to your filter query.

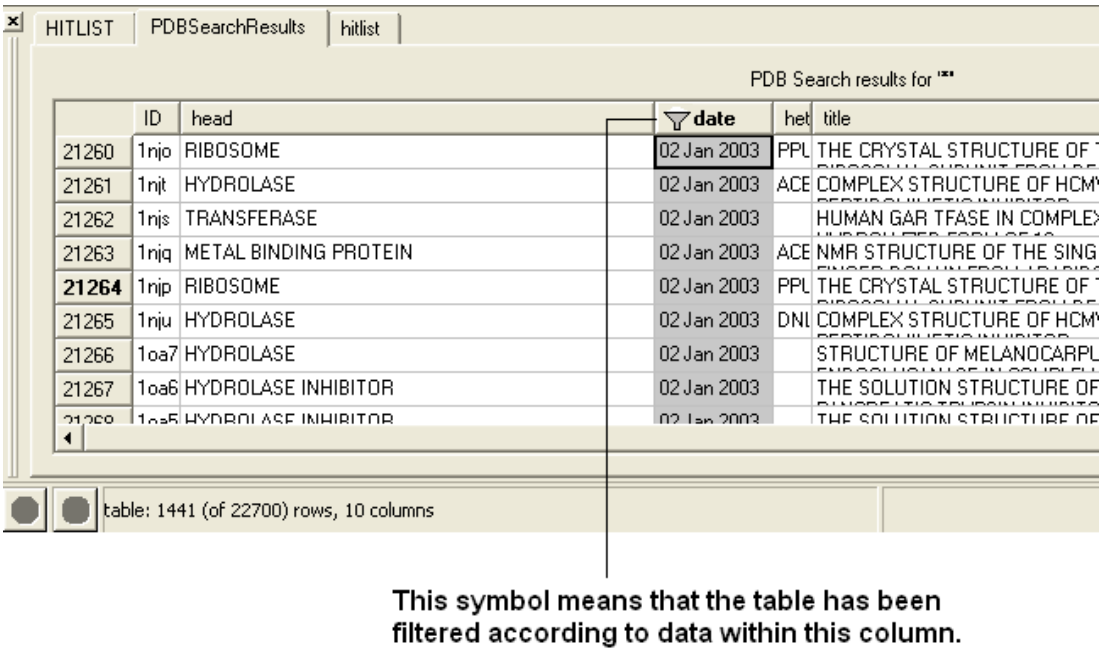
To filter a table:

- Select the column you wish to filter. See the `select table` section for information on how to make table selections.
- Right click on the column header.
- Select the **Filter** option.



- Select the "Custom" option and a data entry box as shown below will be displayed.
- Enter the appropriate operations and filter values for your search.
- Click OK.

NOTE: When a column has been filtered a symbol as shown below will appear in the header of the column.



To append the filtered information into a new table:

- Select the whole table either by right clicking or pressing Ctrl A.
- Right click on the table and select "Append to other table".
- Enter a new name for the table you are appending with your filter results.

OR

Selected rows can be appended to a new table by:

- Right clicking on the selected rows and a menu will be displayed.
- Selecting the "copy selection to ICM table" option.

A table can be filtered by a cell value:

- By clicking once in a cell.
- Right click and a menu will be displayed.
- Select the option "Filter by cell value".

A filter can be cleared by:

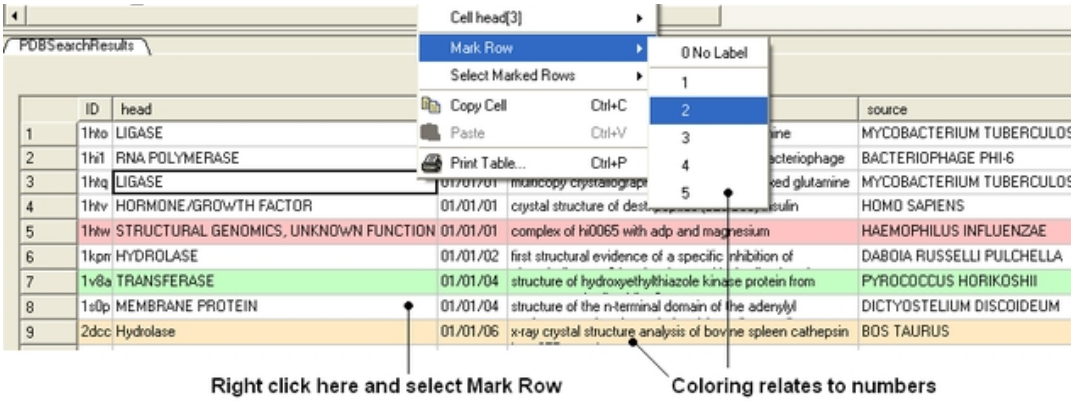
- Right clicking on the column selection and selecting Filter/Clear or Filter/Clear All

21.1.34 Mark and Select Rows

A row in a table can be marked and grouped by a label which enables the row(s) to be selected easily at a later time.

To mark a row

- Right click on the row in the table you wish to **mark.**
- Select **Mark Row/** and then choose a number. In the GUI the number of rows that can be marked is limited to 5 but this can be increased using the command line command.
- A row that is marked will be colored − each number is assigned a color. The coloring can be changed in the `gui tab in preferences`.



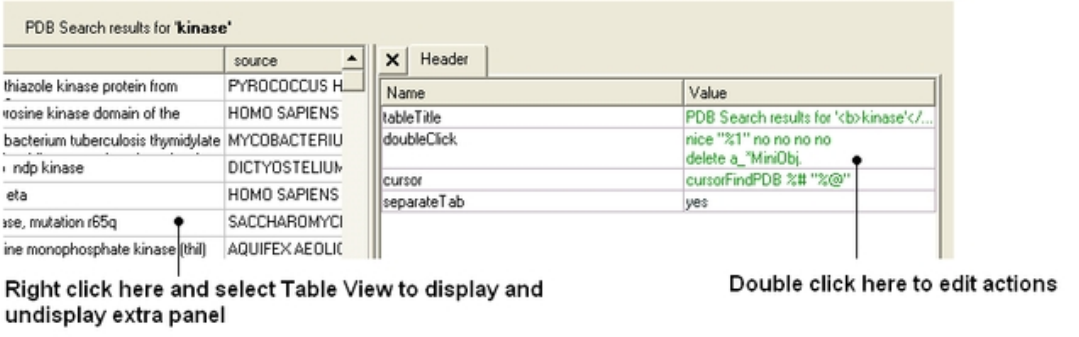
To select marked rows

- Right click on the table and choose **Select Marked Rows** and choose a number which relates to the marked rows as described earlier.
- Selected rows will be highlighted blue − once rows are selected a number of right click options are activated such as copy selection to new ICM table.

21.1.35 Mouse and Cursor Actions on a Table

The actions resulting from a mouse click or cursor on a table can be changed by:

- Right click on a table and select Table View/Show Extra Panel
- A panel as shown below will be displayed.



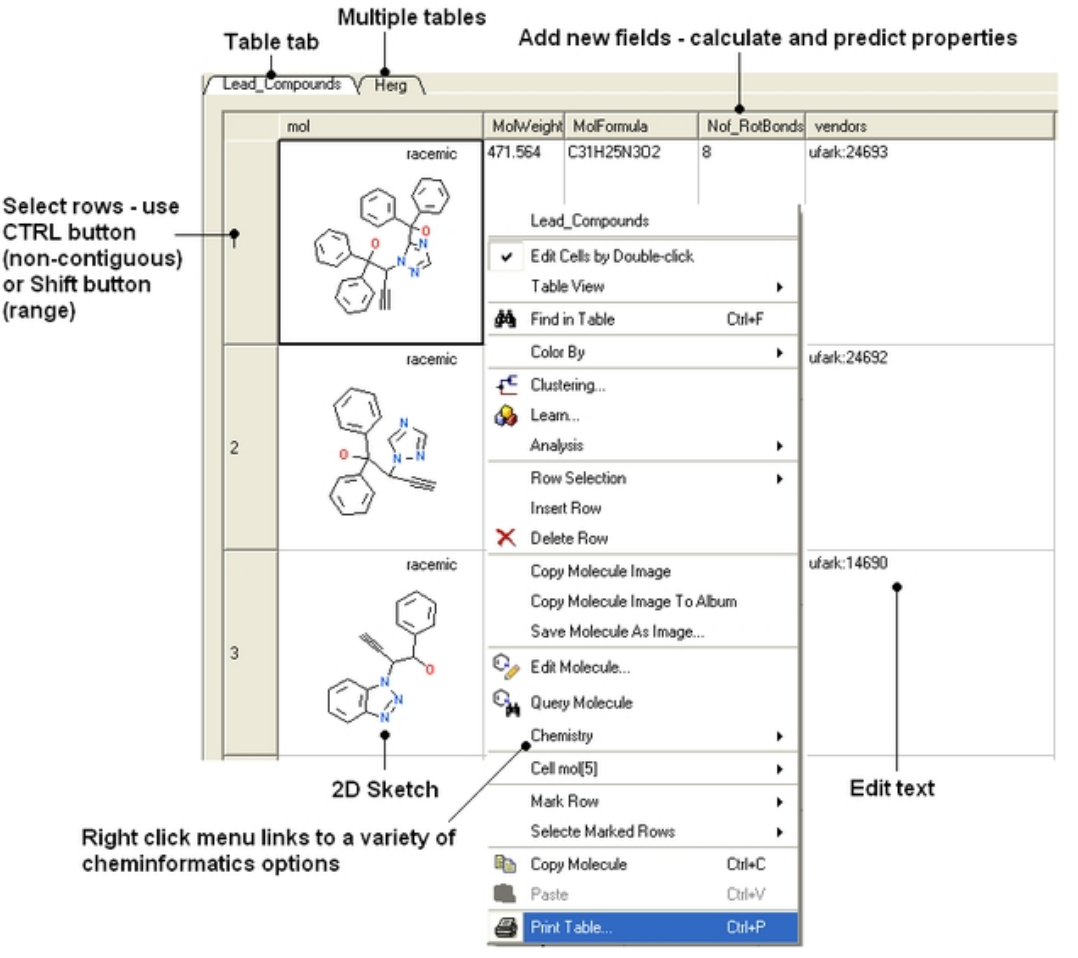
- Double click in the **Value** column and the column can be edited. Add ICM commands for the action you want. A value in a column can be referred to using "%" e.g. column two would be referred to as "%2". In the example shown above the function nice is acting on the contents of column one for the double click action.

NOTE: The action associated with cursor and double click is placed in a variable name TableName.cursor and TableName.doubleClick

21.2 Molecular Tables

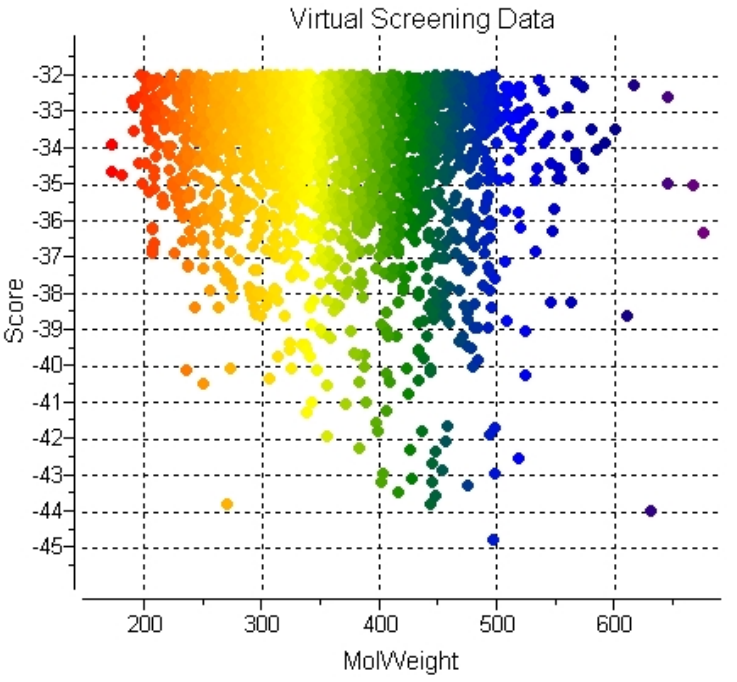
An ICM molecular table is created when an SDF or Mol file is read into ICM. To read and open a mol or sdf file go to File/Open `(See Open an ICM file section)` All of the table functions described in the previous section `Standard ICM Table` can be applied to molecular tables. Molecular tables are described in more detail in the `Cheminformatics` chapter.

An example of an ICM molecular table:



21.3 Plotting Table Data

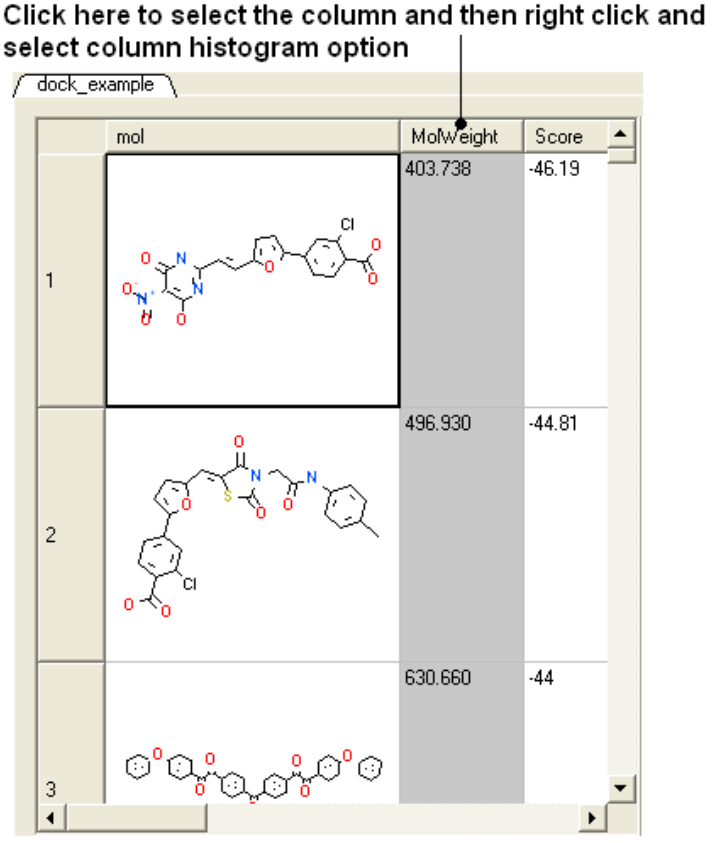
The data within a table can be plotted graphically. A histogram can be made for the data within one column or a plot can be constructed for the data within two columns.



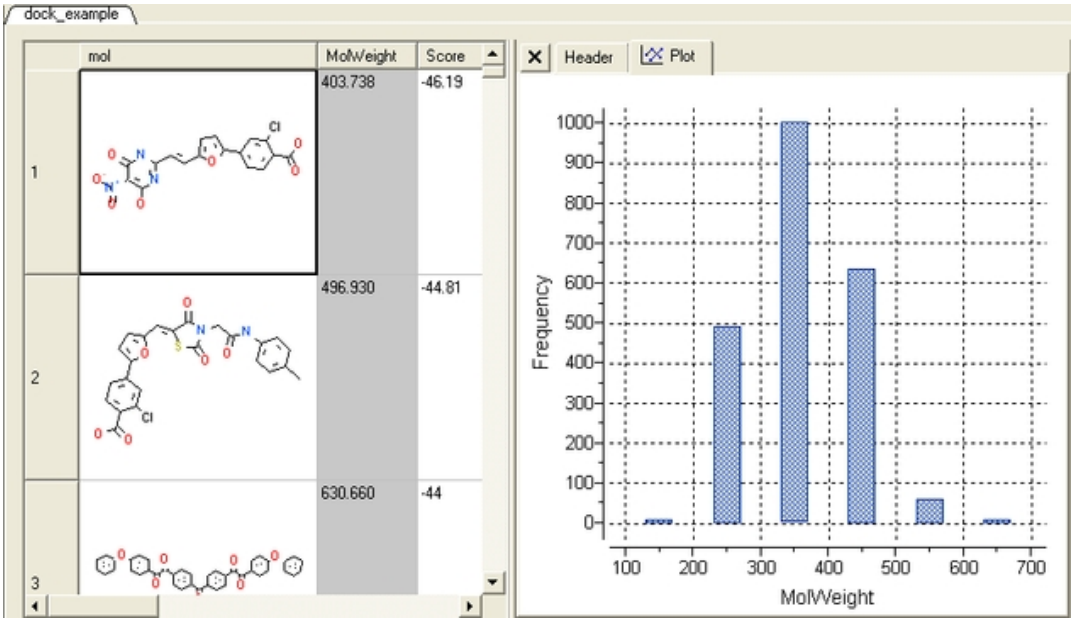
21.3.1 Column Histogram

To plot a histogram of the data within one column:

- Select the column by clicking on the column header.
- Right click on the column header.
- Select the **Column histogram** option.



A plot will then be displayed next to the table.

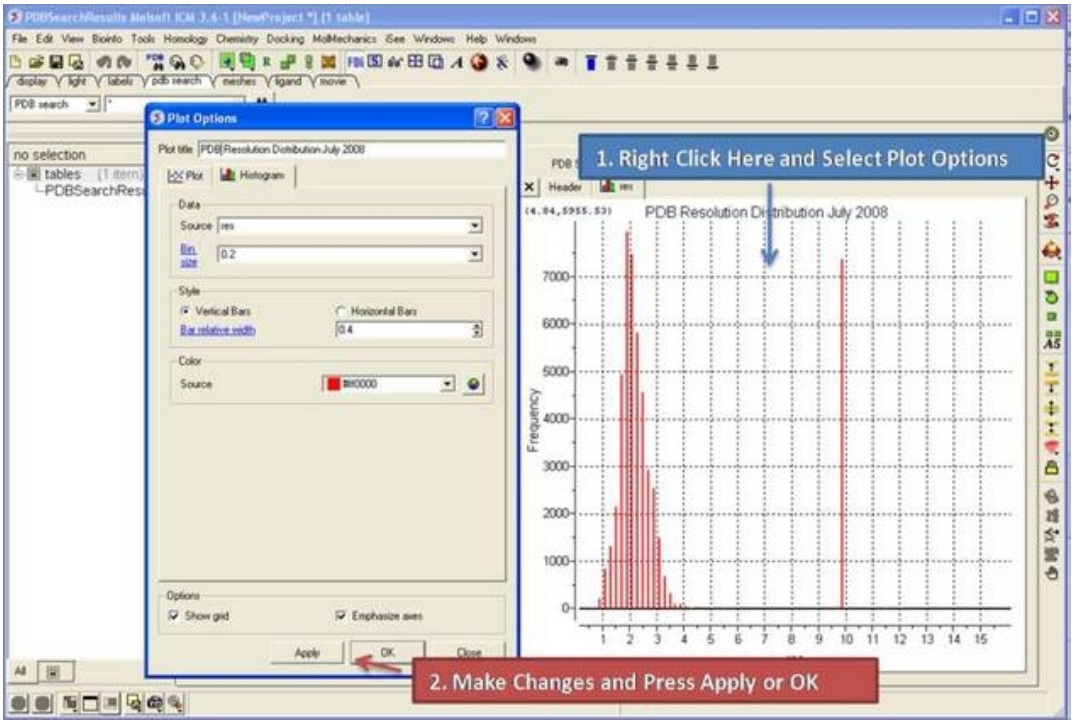


21.3.2 Histogram Options

Once you have created a histogram you can change the following parameters by right clicking on the plot and selecting options

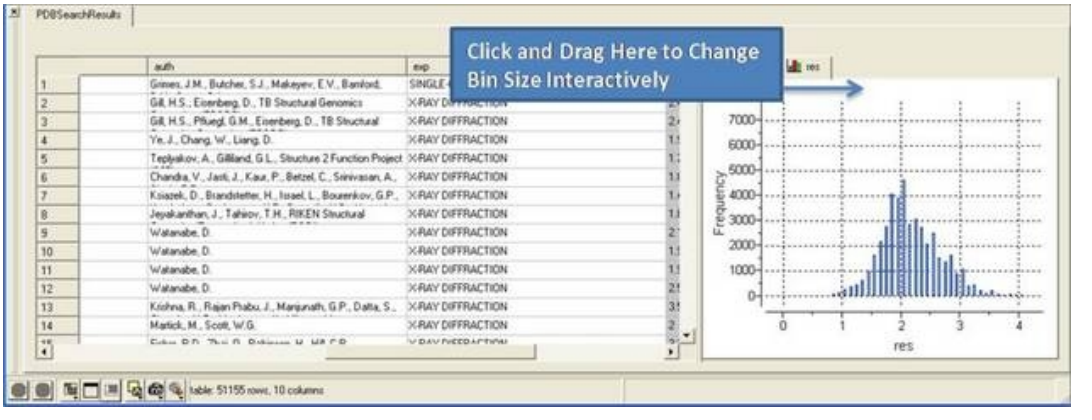
Options:

- Change plot title.
- Change the data source using the drop down button and select another column in the table.
- Change the histogram bin size.
- Change the bars positioning from vertical to horizontal.
- Change the bar relative width compared to bin size. Bigger values give thicker bars.
- Color the bars



21.3.3 Histogram Bins

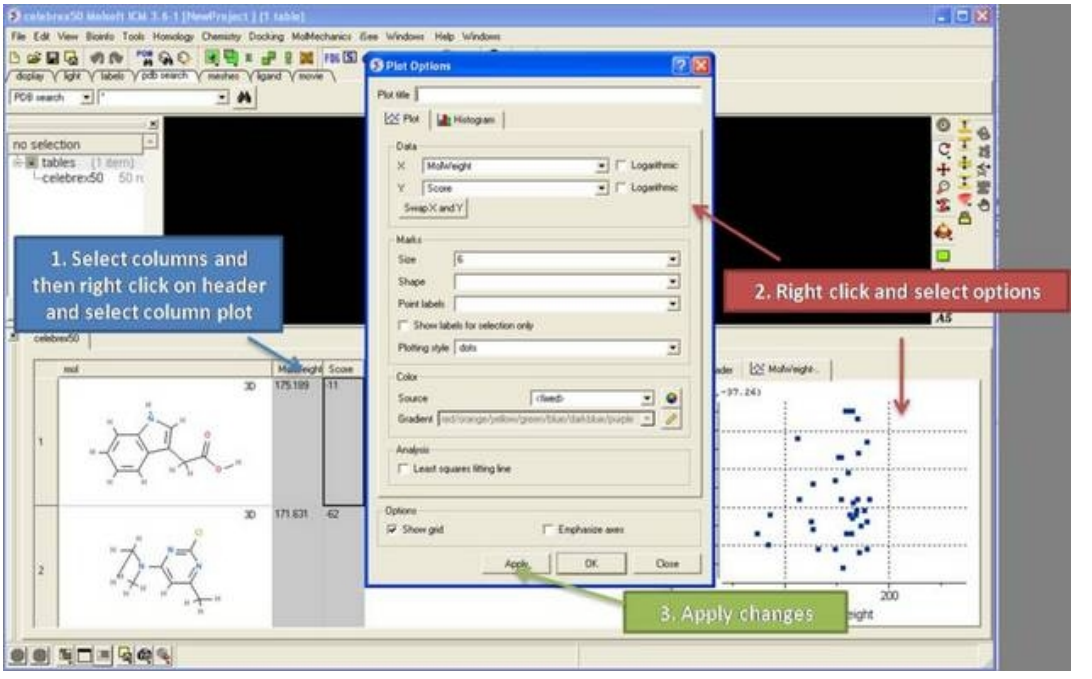
There are two ways to change the bin size. 1. Using the **options** dialog box or 2. interactively by left clicking and dragging at the top of the plot as shown below − this will allow you to find the best density estimation picture.



21.3.4 Plotting two columns

To construct a plot from data within two columns:

- Select the two columns.
- Right click on the column header.
- Select the **Columns plot** option.



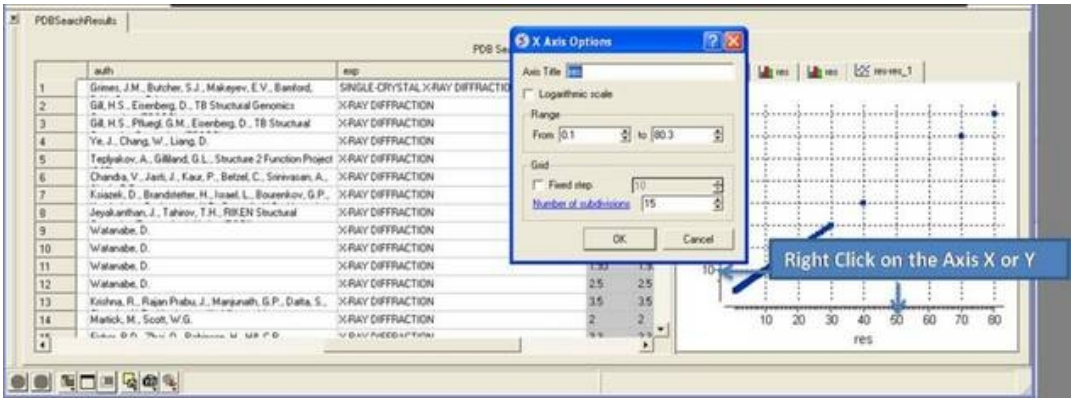
21.3.5 Add a title to a plot

To add a title to a plot:

- Right click on the plot and select **Edit Title** or choose **Options**

21.3.6 Axis Options

Each axis has a set of options which can be accessed by right clicking on the axis and selecting **Options.**



To change the title of the X or Y Axis:

- Right click on the axis and select **options**

To change the data range:

- Right click on the axis and select **options**
- Change the **From** and **to** values in the **Range** box

To change the Grid steps (ticks) on the X or Y axis:

- Select either a fixed step e.g. 10 and you can define the number of subdivisions (ticks) in each step. Choosing 1 will display zero ticks between divisions.

To change the axis to logarithmic

- Right click on the axis and select **options**
- Select the Logarithmic scale check box

21.3.7 Change Axis Data

To swap the X and Y axis:

- Right click on the plot and select **Options**.
- Select the **Swap X and Y** button.
- Click OK.

To change the data source for either the X or Y axis:

- Right click on the plot and select **Options**.
- Select the drop down arrow as shown below and select a different column from the table.
- Click OK.

21.3.8 Logarithmic Plots

To change the scale of the axis to logaritmic:

- Right click on the plot and select **Options**.
- Select the **Logarithmic** check box.

21.3.9 Change Mark Shape or Size

To change the plot mark, shape, style or label:

- Right click on the plot and select **Options**.
- Select the desired size and shape using the drop−down buttons in the **Marks** section of the window.

To add point labels:

- Right click on the plot and select **Options**.
- Select the drop down arrow in the **Point labels** dialog box
- If you only want to label selected points check the **Show labels for selection only** option. Making plot selections is described `here`.

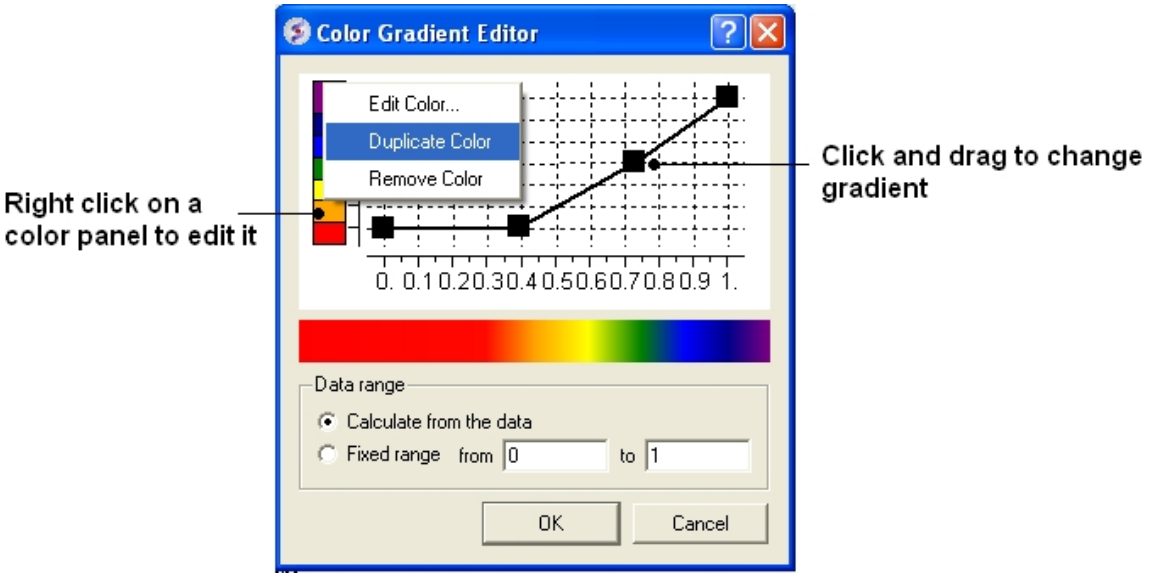
21.3.10 Change Mark Color

To change the color of the plot marks:

- Right click on the plot and select **Options**.
- In the **Color** section of the window select the **Source** (column name plotted as X or Y) you wish to color.
- Select the color palette and choose the desired color or you can choose a Gradient of colors.

To edit the color gradient

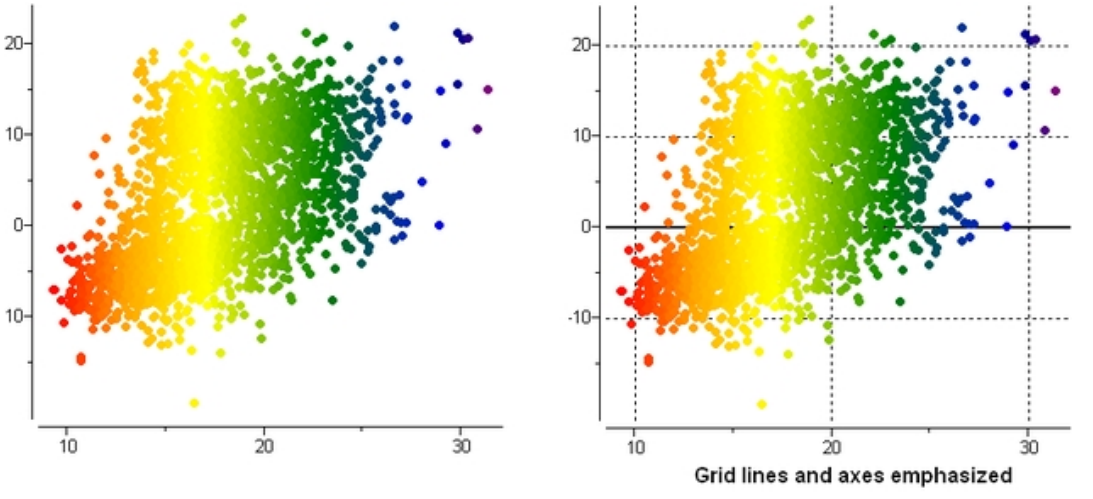
- Click on the **Color gradient editor** button and a window as shown below will be displayed.
- Click and drag on a mark in the gradient plot to change the color gradient.
- Right click on a color in the Y−axis to − **Edit, Duplicate or Remove Color**.
- The color gradient can be applied to all points in the data or for a fixed range.



21.3.11 Grid and Axis Display

To remove the grid display and/or highlight the axes:

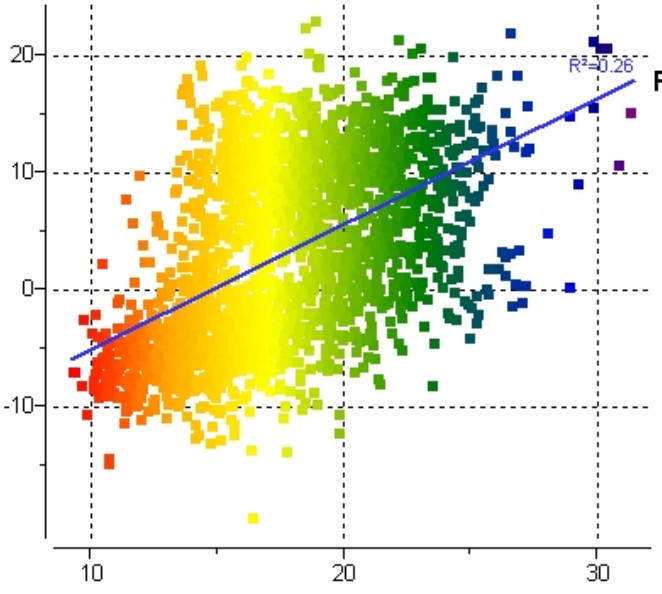
- Right click on the plot and select **Options**.
- Check the **Show grid** or **Emphasize axes** options.



21.3.12 Least Squares Fitting

To fit the data to a straight line using least square fitting

- Right click on the plot and select **Options**.
- Select the check box for **Least squares fitting line**.



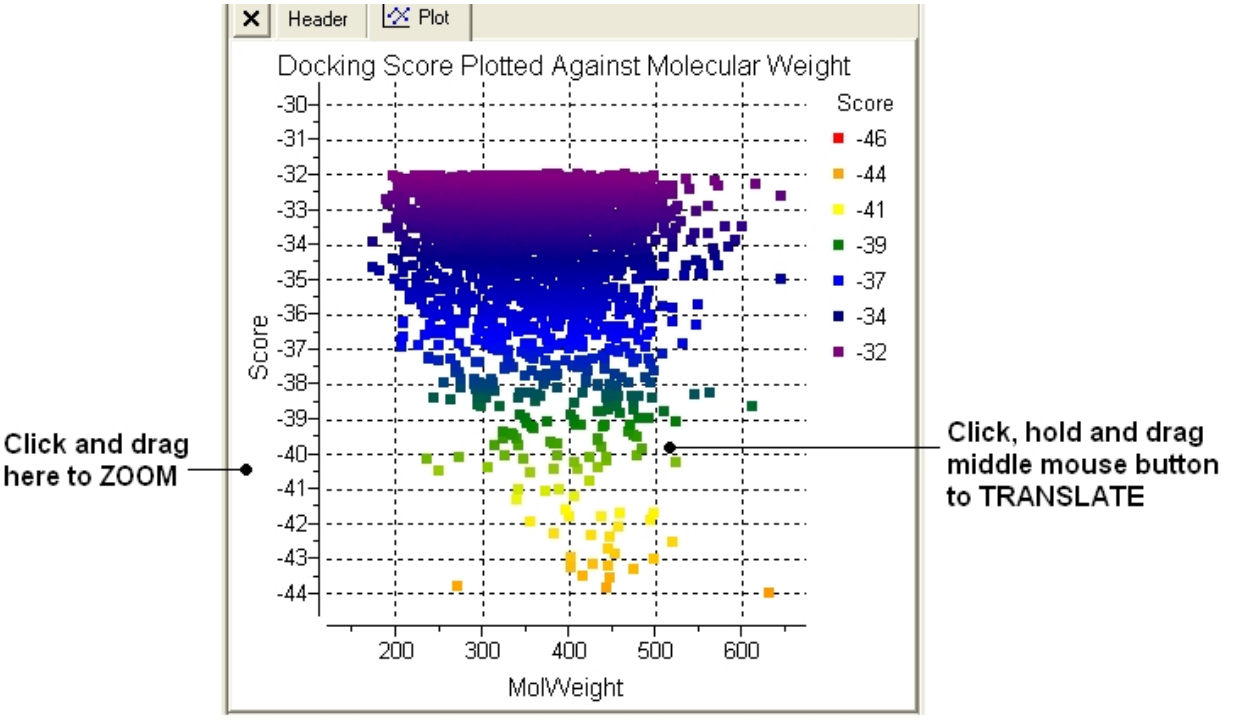
21.3.13 Zoom, Translate and Center

To zoom into a plot:

- Click outside the plot on the left−hand−side and drag the mouse or use the middle mouse wheel to zoom in and out.

To translate a plot

- Click, hold and drag using the middle mouse button on the plot.



To center onto a plot

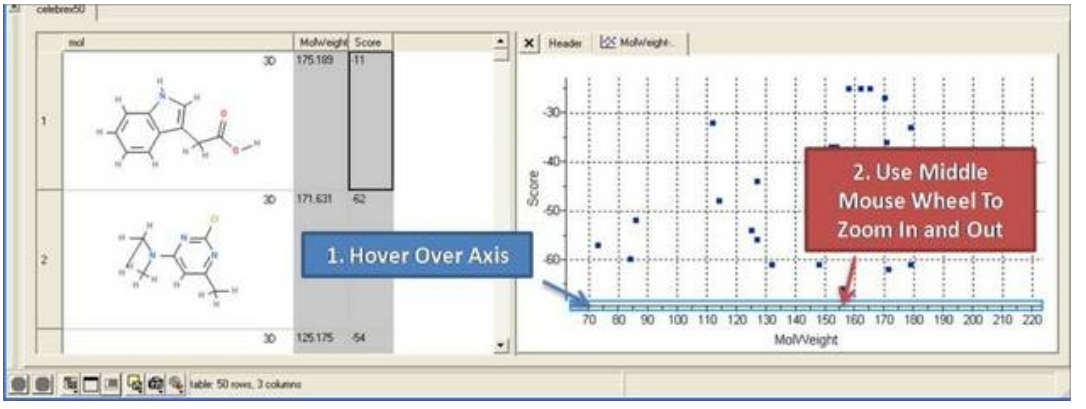
- Right click on the plot and select **Center all** or **Center Selection**. Making selections in a plot is described in the next section.

To center into an axis

- Right click on the axis and select **center.**

To zoom into an axis

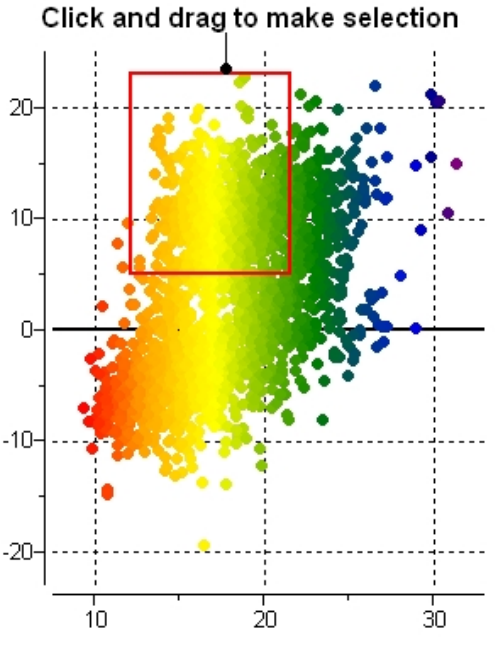
- Hover the mouse over the axis until you see a blue rectangle surrounding the axis.
- User the middle mouse wheel to zoom in and out as shown below.

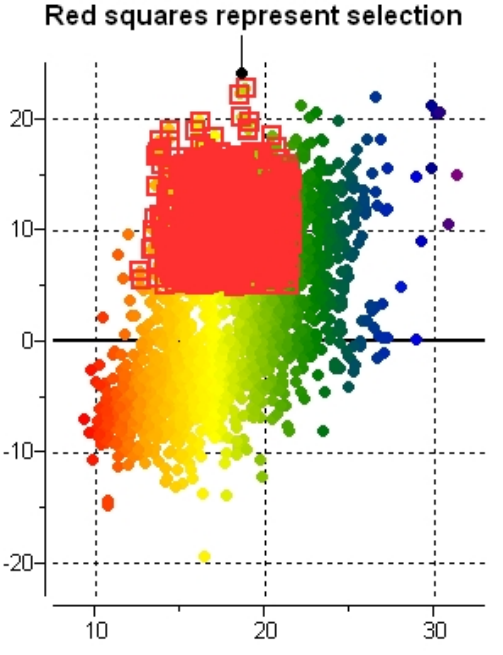


21.3.14 Plot Selection

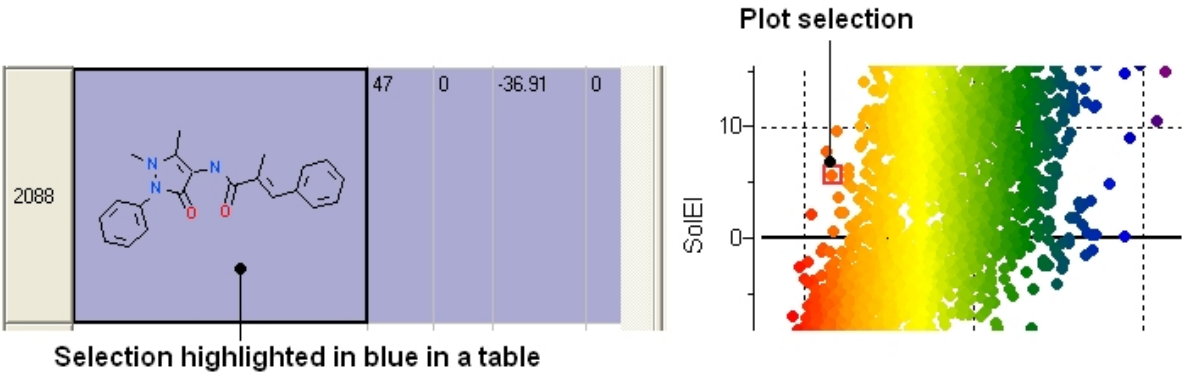
To make a selection in a plot:

- Click and drag in the plot to make a selection. Individual points can be selected with a single click.

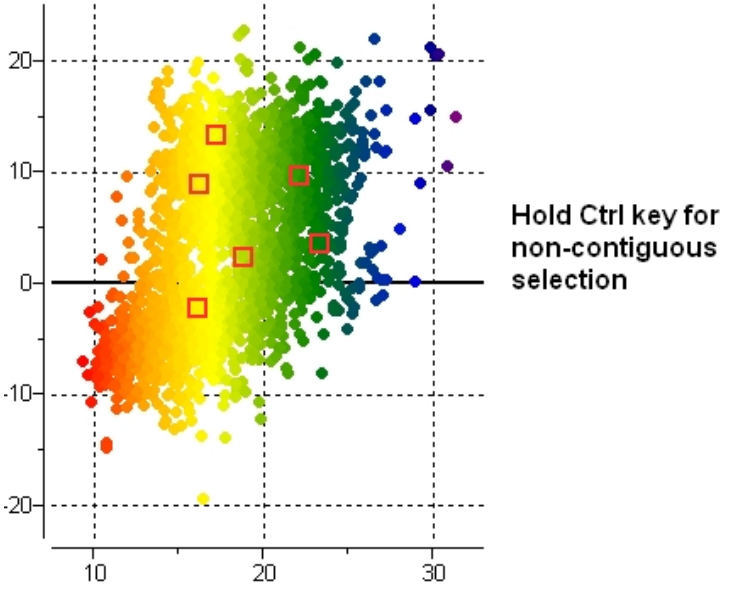




All selections are directly linked to the table from which the plot was made. Selections in the table are highlighted in blue.



Non−contiguous selections in the plot can be made by holding the CTRL key.



21.3.15 Print Plot

To print a plot:

- Right click on the plot and a menu will be displayed.
- Select the print option.

21.3.16 Saving a Plot Image

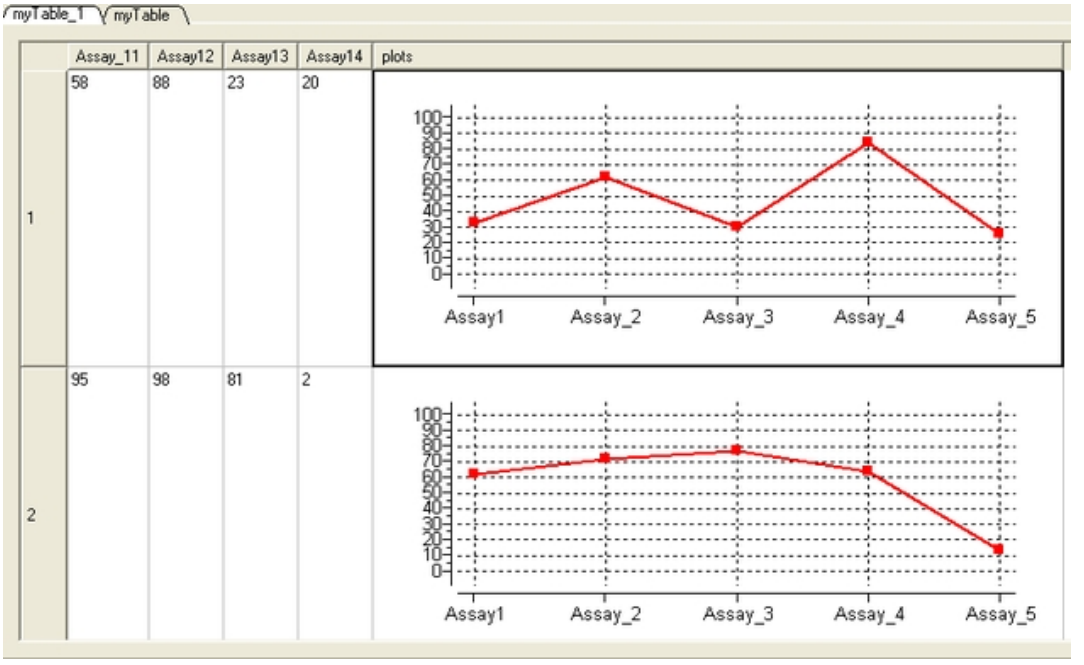
To save a plot image or copy to clipboard:

- Right click on the plot and a menu will be displayed.
- Select the **Save/Export Image** option.

21.3.17 Table Inline Plots

Plots can be inserted into a table row by:

- Select the columns you wish to plot.
- Right click on the column header and select **Inline Plots**
- The plot will then be displayed in each row of the table.



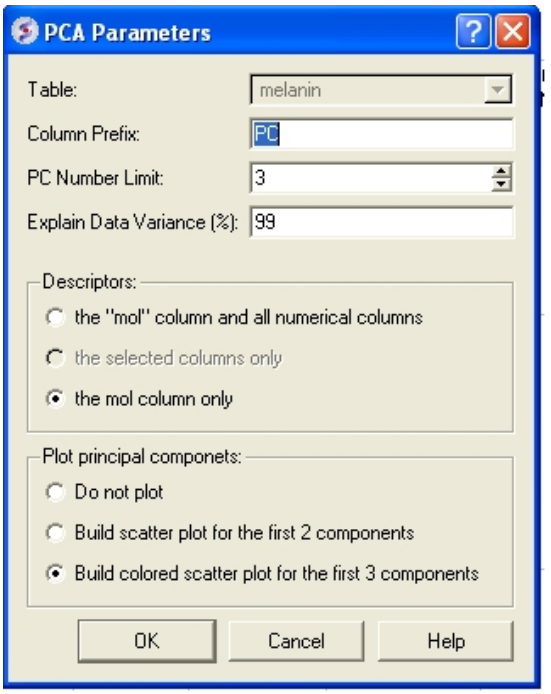
21.4 Principal Component Analysis

Principal Component Analysis (PCA) is the younger brother of ICM's more powerful data analysis tools, like `property prediction` and `clustering`, though it still may give a good description of the data with a few columns or even chemical compounds. PCA is a mathematical procedure that transforms a number of correlated variables into a number of smaller uncorrelated variables known as Principal Components The first component accounts for as much of the variability as possible with the rest of the components accounting for the remainder. PCA may be very helpful when you believe the data actually contains only a few meaningful components. Principal components are linear combinations of the provided data columns.

To perform a PCA analysis a table (either chemical or standard ICM table) needs to loaded into ICM. For information regarding `ICM Tables` and `ICM Chemical` Tables please follow these links.

To begin the PCA procedure

- Right click on a `ICM Tables` and `ICM Chemical Table` and select the PCA option. It is important to right click inside the data table and not on a column or row header in order to see the correct menu on which pca is listed.
- Select which columns you wish to incorporate into the PCA analysis.



- Enter the table name on which you wish to perform the PCA analysis. If only one table is loaded this option will be greyed out.
- Enter the number of Principal Components (PC number limit) you wish to generate. Generally 3 principal components may be effectively visualized and it will be enough often to fulfil the data variance percentage requirement (see next option). The value displayed in the terminal window under the heading "cumulative explained data variance" will show what percentage of data relates to each PC.
- Enter a value in the "Explain Data Variance (%)" data entry box (99% is the default value) if you prefer this indirect way of limiting number of PC. The algorithm will stop when either PC number or explained variance limit is reached, so if you want only one of this criteria to work, make sure that the other limit is weak (by assigning accordingly the number of PC limit a high value, e.g. 50, or setting data variance to 100%).
- Select which descriptors you would like to include in the PCA analysis.
- Select which plot you would like to display. If you choose to display a plot use the color key on the side of the plot and the information contained within the ICM terminal window to relate which axes and points relates to which PC. PC3 is usually the color in the plot with the values displayed in the plot key.
- Click OK and if selected a plot will be displayed on the right−hand−side of the table. Points within a plot are linked to the table and can manipulated as other `plots contained within a table`.

21.5 Learn and Predict

Partial Least Squares (PLS) and Principal Components are commonly used methods which are implemented in ICM to predict compound properties or any other variable. There are many tutorials in the web available for free download. For the details of ICM implementation and the explanation of our terminolgy see the `theory` section below.

In order to perform 'learn and predict' in ICM information must be stored in a table, molecular table or csv file. See the `tables` chapter for more information on ICM tables. Both chemical compounds and numeric data can be source for building prediction models.

All molecular property predictors are calculated using fragment−based contributions. We developed an original method for splitting a molecule into a set of linear or non−linear fragments of different length and representation levels and then each chemical pattern found is converted into a descriptor.

21.5.1 Learn

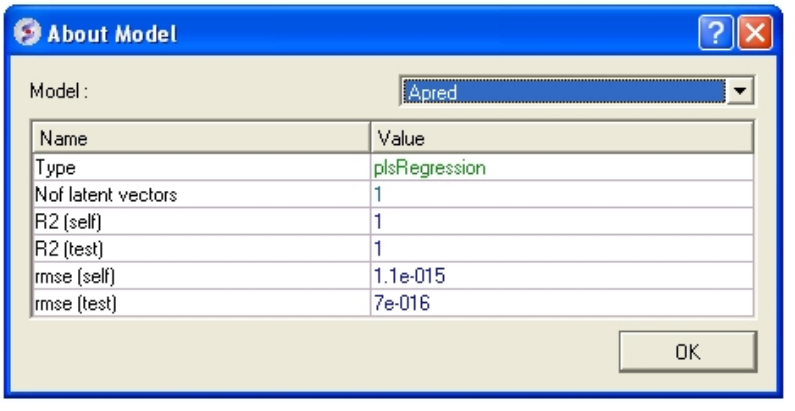
First load in a table of data on which you wish to perform the learn and predict functions. See the `tables` chapter for more information on ICM tables.

- Select Tools/Table/Learn and a window as shown below will be displayed. Or use the Chemistry/Build Prediction Model option.

- Enter the name of table with which you want to perform the predictions. You may locate your table from the drop down arrow menu.
- Select the column from which you wish to learn. Use the drop down arrow to select.

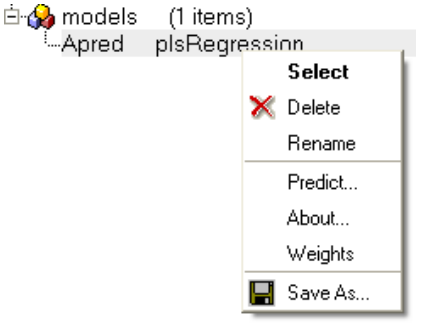
> **NOTE** If the table does not contain any numeric (integer or real) columns, there is nothing to predict, so the "Learn" button will be disabled.

- Enter a name for the learn model.
- Select which regression method you wish to use from the drop down menu. See the `theory` section to determine which method and parameters to use.
- Select which columns (descriptors) of your table you wish to use to 'learn'.
- If you are using chemical descriptors to produce your model select the maximal chain length.
- Select the number of cross−validation groups you wish to use or selected rows can be used for cross validation. The number of iterations will impact the speed of the calculation. 5 is the default number of groups but 2 would be the least rigorous and selecting the 'Leave−1−out' would be the most rigorous calculation.
- Click on the learn button and a table summarizing your model will be displayed as shown below.



- Click OK and this table will be removed.

All models are then stored in the ICM workspace as shown below. A number of options are displayed in the right click menu.



21.5.2 Predict

To make a prediction using a `created` model.

Read the table of data into ICM from which you wish to predict. Make sure the table contains the same columns used for the `learn` model.

- Tools/Table/Predict or Chemistry/Predict
- Select which table you wish to make the prediction on.
- Select which model you wish to use.
- Check that the required columns are in the table. If they are absent a red mark will appear against the column that is missing.
- Click Predict.

21.5.3 A little theory on learning

For a more detailed explanation of the theory behind Partial Least Squares (PLS) we suggest you read Geladi et al Analytica Chimica Acta (1986) 1−17.

PLS (Partial Least Squares) Regression PLS regression algorithm builds linear prediction model: in format `y=(w,x)+b`, where `b` is the **bias** − a real number, and `w` is the weights vector, which is scalarly multiplied by the data vector `x.` PLS uses the given learning `y` values very actively which allows it to produce fairly good models with respect to constraint of being linear. Although linear regression models have an advantage of weights for each descriptor which gives a useful information and allows feature selection in many cases.

The linear model simply is not able to predict higher order dependencies.

There are different ways to deal with it. By adding the second order columns into the descriptor set you can let PLS predict them. Actually if you have a lot of columns derived from basic data, the linear model built will be able to make a high−quality linear approximations of the actual functions. ICM has a powerful tool for automatical generation of such descriptors based on compound data −− molecule fingerprints generation algorithm. It generates hundreds of columns based on initial data. The withdraw is that analysing the weights given by PLS to generated descriptors is almost senseless. You will need a *mol* column in your table to use this feature.

ICM has built−in models for prediction of several significant molecule properties, like logP, logS, PSA based on fingerprints+PLS symbiosis, which have proven their quality.

PC (Principal Component) Regression

PCR also builds linear model in its simplest form, as PLS does, though it sets other weights to descriptors, and built models are usually worse in sense of predicting, because PCR uses *value* information of the *training data* only in secondary way. We recommend you to use PCR, when you want to build an ordinary regression (MLR − Multiple Linear Regression) model by using only some number of first principal components of X data matrix (ordered by decreasing eigenvalues) or even builing the full MLR model (by setting the number of PCs to value higher than the number of rows in matrix).

21.5.4 Data Clustering

ICM allows you to create hierarchical clusters for chemical and other objects. Cluster trees can be used for:

- Navigation through large data sets.
- Selecting group representatives (taxons).
- Filtering tables to exclude redundancy.
- Finding similar elements, and more.
- Creating hierarchical views of data sets in many different styles, with subsequent image export/printing ability.

21.6 Cluster

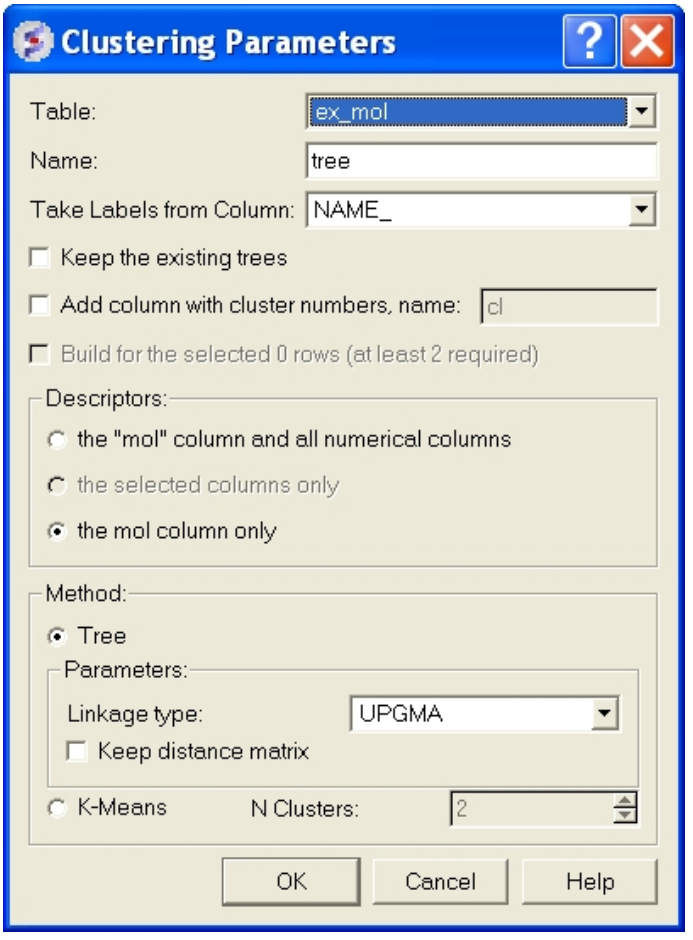
To perform clustering based on chemical similarity or any other data you must have an SDF file or table loaded into ICM.

- Right click on the table and select the Clustering option OR select the Chemistry menu and choose the option entitled **Cluster Set**.

OR

- Tools/Table/Clustering.

A data entry box as shown below will be displayed.



- Select which table from the drop down menu you wish to cluster.

There are two clustering methods:

1. A rigorous tree approach (advice to use this with 10000 compounds or less). This clustering algorithm consists of 2 steps: calculation of distance matrix (based on chemical fingerprints for chemical data) and the hiearchical clustering itself. Usually most time is being spent on first step.
2. A less rigorous K−means approach. This option is quicker but the generated tree is not detalized down to the level of table rows. The elements within the table are colored and numbered according to their clustered group.

If your computer has enough memory we recomend you use the TREE method. It takes ~6 minutes to cluster 10000 compounds on a standard computer with 512Mb of memory.

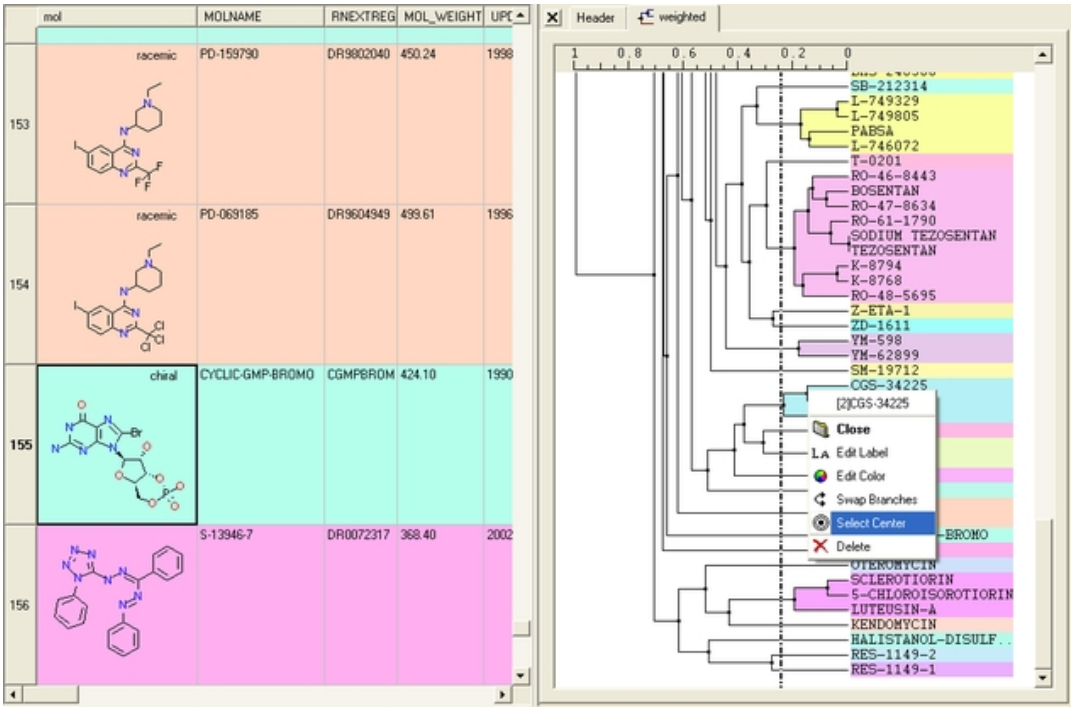
NOTE If you wish to cluster a selection of a table; first select the compounds you wish to cluster (Ctrl A will select all or see the section of the manual entitled `making table selections`.

When using the TREE method select which linkage type you wish to use:

- UPGMA (unweighted pair group method using averages): Distance calculated is the average of all elements (recommended).
- Single linkage: Nearest neighbour linkage
- Complete linkage: Furthest neighbour linkage
- WPGMA (weighted pair group method using averages): Rough approximation of weighted (slightly faster)

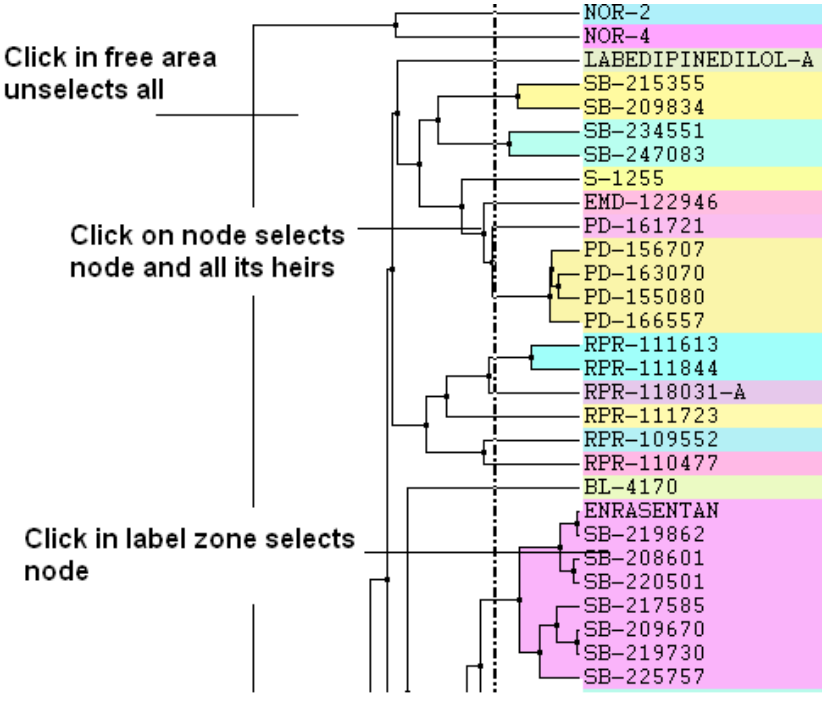
Check the option "Keep Distance Matrix" if you wish the Distance Matrix to be saved.

- Click the RUN button and the tree and table will be displayed as shown below.



21.6.1 Tree Selection

A number of different selections can be made once the tree has been created.



- Click in free area unselects all.
- Click on node selects node and all its heirs.
- Ctrl+click adds to (if not selected yet) or removes from (if already in selection) current selection.
- Shift plus click allows a range to be selected.

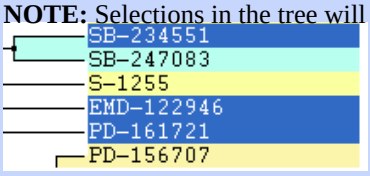
- Click in label zone selects node.
- Keyboard "Up"/"Down" cursor keys move selected node up/down in the tree. With Shift held the selection expands in the according direction.
- Keyboard "Escape" unselects all.

Select Center Representatives From a Node.

To select the "center" representative compound or value from a cluster.

- Right click in the free area of the tree and select the option "Select Centers".

NOTE: Selections in the tree will be highlighted in blue in the tree and in the table.



Copy selection to new table.

All selections can be copied to a new table by:

- Right clicking on the selected rows in table and a menu will be displayed.
- Selecting the "copy selection to ICM table" option.

21.6.2 Save and Print Tree

To save a tree

Option 1:

- Save the whole session as an ICM project. See `Saving an ICM project`

Option 2:

- Save the table as an .icb file. Right click on table header and select "save as".

To save a tree as a picture

- Right click in the "free area".
- Select "Save Image..."

The image of the tree can also be saved to the clipboard.

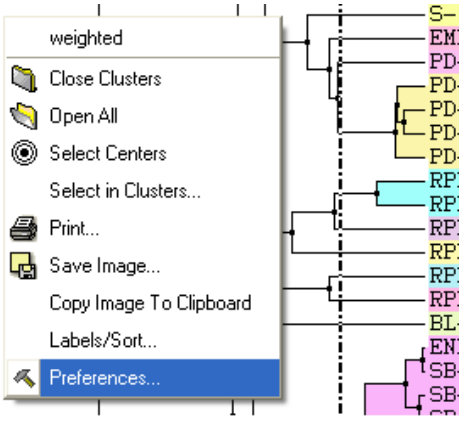
- Right click in the "free area".
- Select "Copy Image to Clipboard"

To print the tree

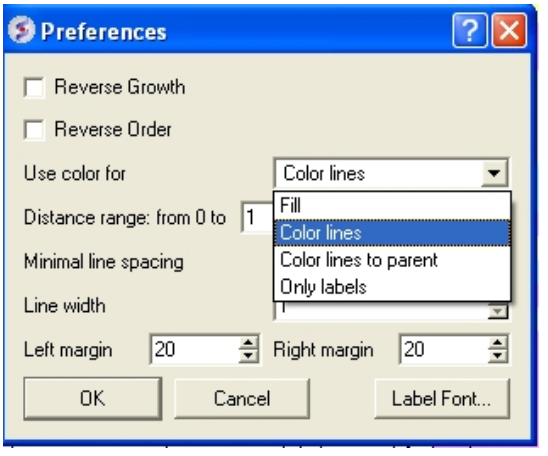
- Right click in the "free area".
- Select "Print"

21.6.3 Tree View

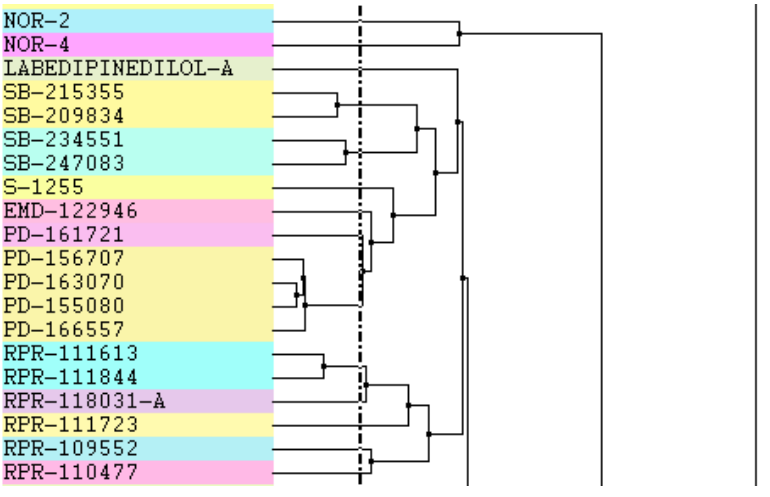
A number of changes to the tree view can be made by right clicking in the tree "free area" and selecting preferences as shown below.



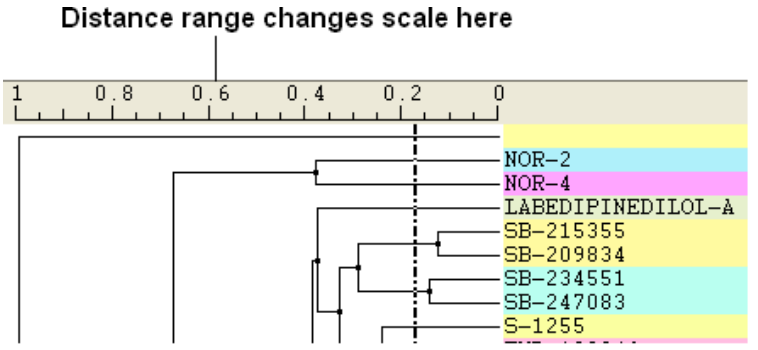
A preferences window as shown below will be displayed.



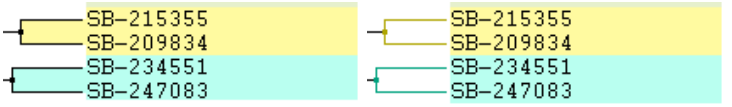
Reverse Growth:



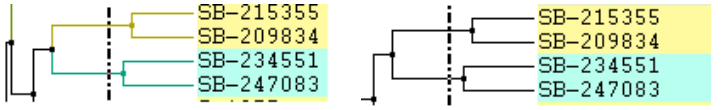
Distance Range:



Color Preferences:

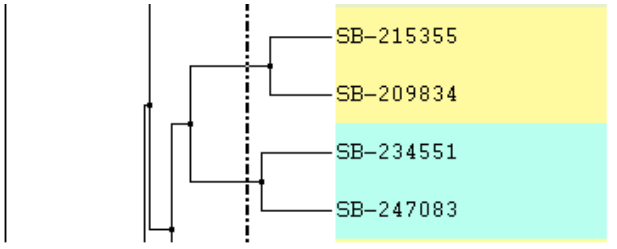


Left: Fill **Right:** Color Lines

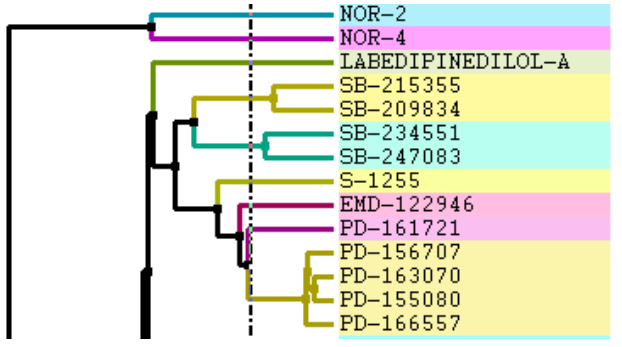


Left: Color lines to parent **Right:** Only labels

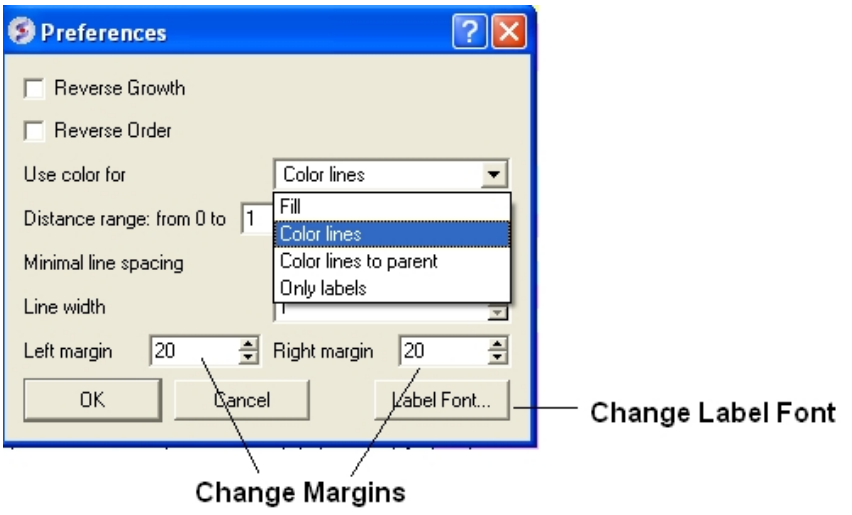
Increase or Decrease Line Spacing:



Increase or Decrease Line Width:



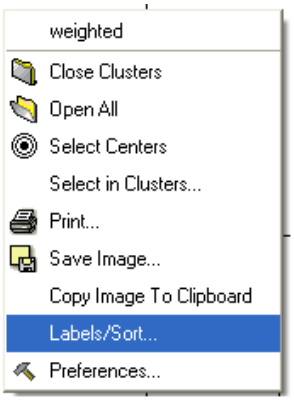
Change Font and Margins:



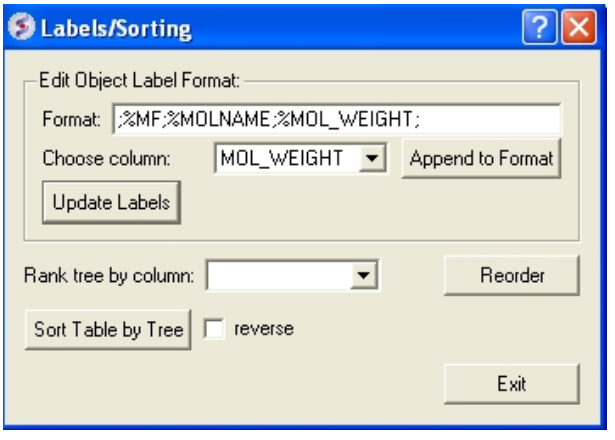
Change Label

To change the tree labeling (GLOBAL):

* Right click in the "free area" and select the Label/Sort option.



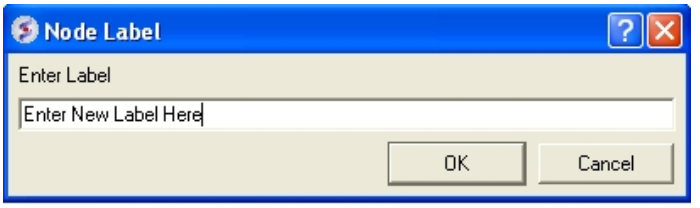
A window as shown below will be displayed:



- Choose the column name you wish to label the elements of your tree.
- Click the Append to Format button. You may wish to delete some of the information in the Format data entry box if you do not wish that column header to be displayed. Note more than one column header can be used as a label.
- Click the update labels button to view the changes.

To change the tree labeling (NODE):

- Right click on the node you wish to change the label of and select "Edit Label" and a data entry box as shown below will be displayed.



- Enter the new label.

Change Node Coloring

To change the color of a node:

- Right click on the node you wish to change the color of and select "Edit Color".
- Select the desired color and click OK.

22 Working with Local Databases

`ICM tables` are capable of storing tens of thousands records. However, some problems operate with data sets so large that they do not fit in computer's memory. To work with such large amounts of data ICM uses the concept of Molsoft database (MOLT) files. Unlike many other table file formats, such as SDF, CSV and others, database files are optimized for fast search and other operations, like unique entry addition and diverse subset selection.

Database files do not provide all the functionality available for tables but they allow the user to organize large amounts of data, search data using various advanced criteria and share created data collections with other users. For large amounts of chemical data database files provide specialized chemical functionality.

ICM provides the following database file operations:

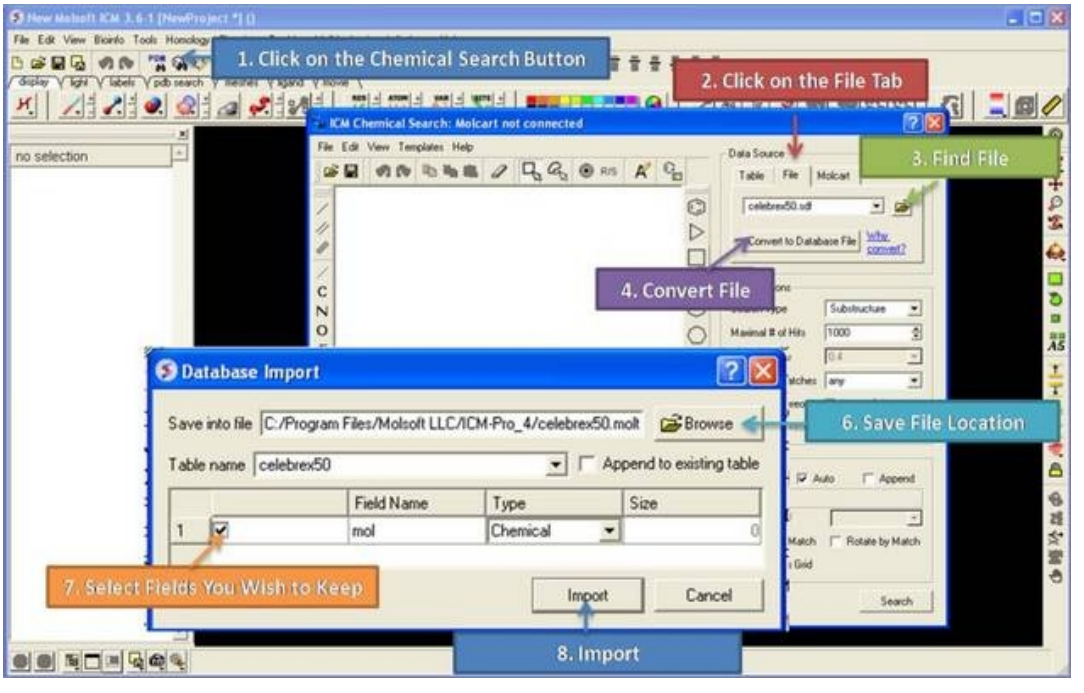
- `create database files` from SDF, CSV/TSV, SMILES files and from ICM tables;
- impose unique constraints on certain columns upon table creation to avoid redundancy;
- store multiple tables in a single file; rename, delete tables in a database file;
- `search fast` using advanced conditions, including advanced `chemical search`;
- `select diverse subsets` from chemical database files;
- `browse database tables` using flexible filtering and sorting conditions;
- `directly edit/delete/insert entries` in the database;
- export in popular formats, such as SDF (for chemistry) and CSV;
- export and import tables to and from `Molcart`.

22.1 How to make a local database.

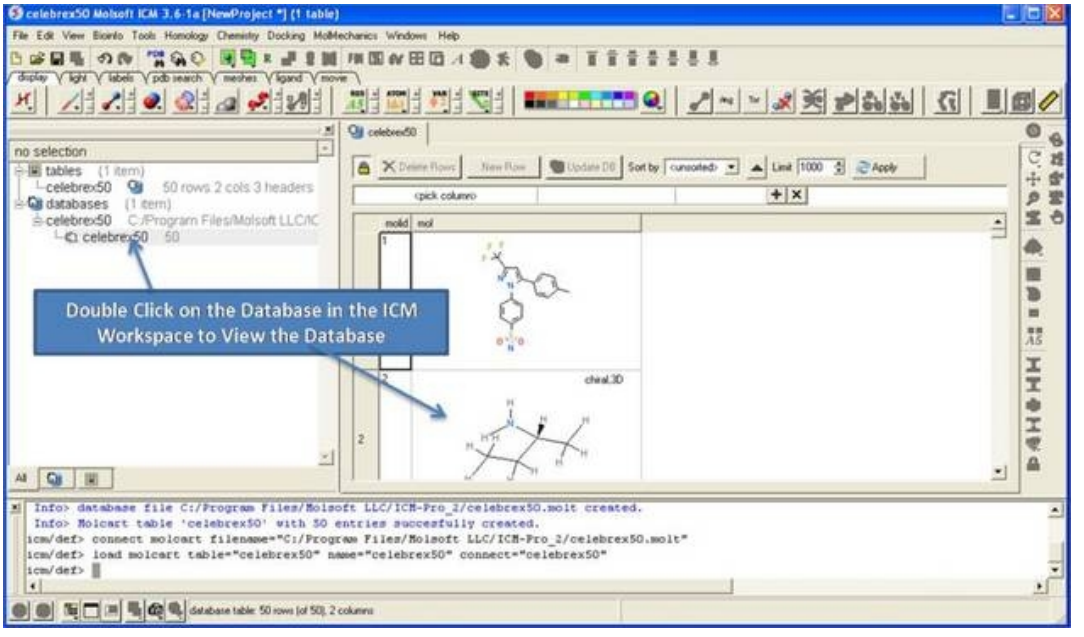
There are two ways to convert a file into MOLT format.

1. File/Convert to Local Database
2. In the ICM Chemical Search window as shown below.

Both approaches will display the **Database Import** dialog box.



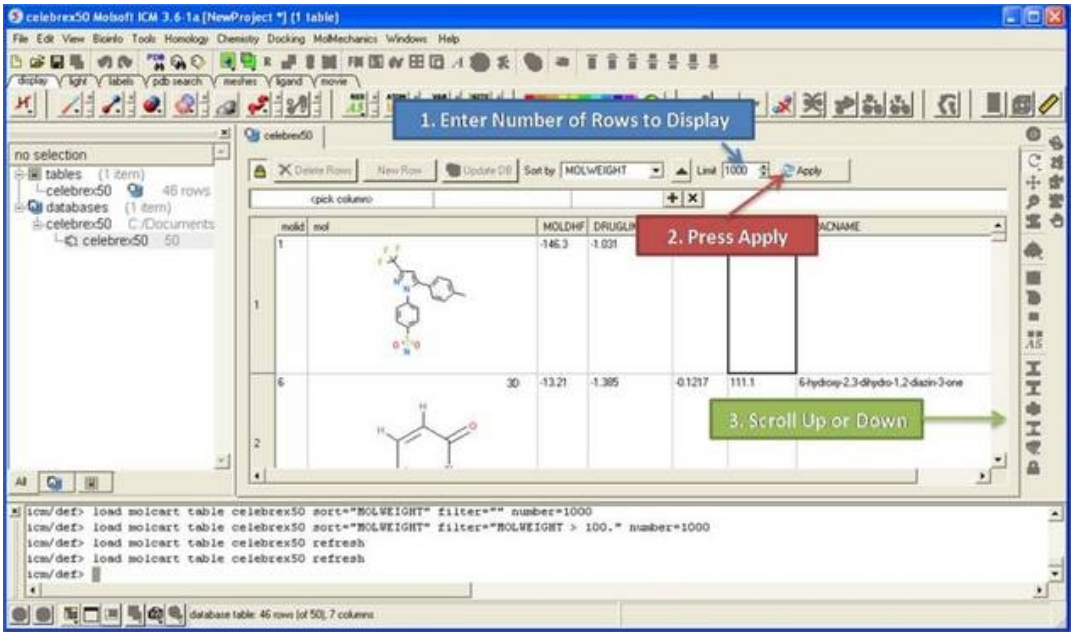
- Once the file has been converted to MOLT and imported then it will be displayed in the ICM Workspace.
- Double click on the file name in the ICM workspace and the database browse mode will activated.



22.2 Browse Database

To browse a database first decide how many rows of your database you wish to view

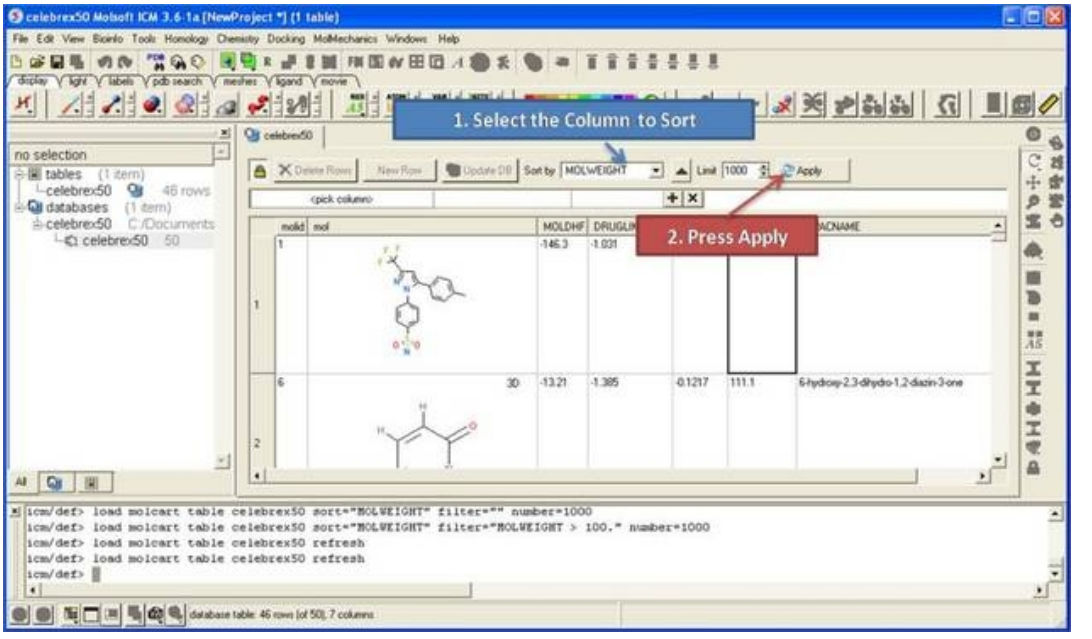
- Double click on the file name in the ICM workspace and the database browse mode will activated.
- Select the number of rows you wish to be displayed in the **Limit** data entry box.
- Click on the **Apply** button.
- Scroll up and down the displayed rows using the scroll bar on the right hand side of the table.



To sort a database by a value in a column

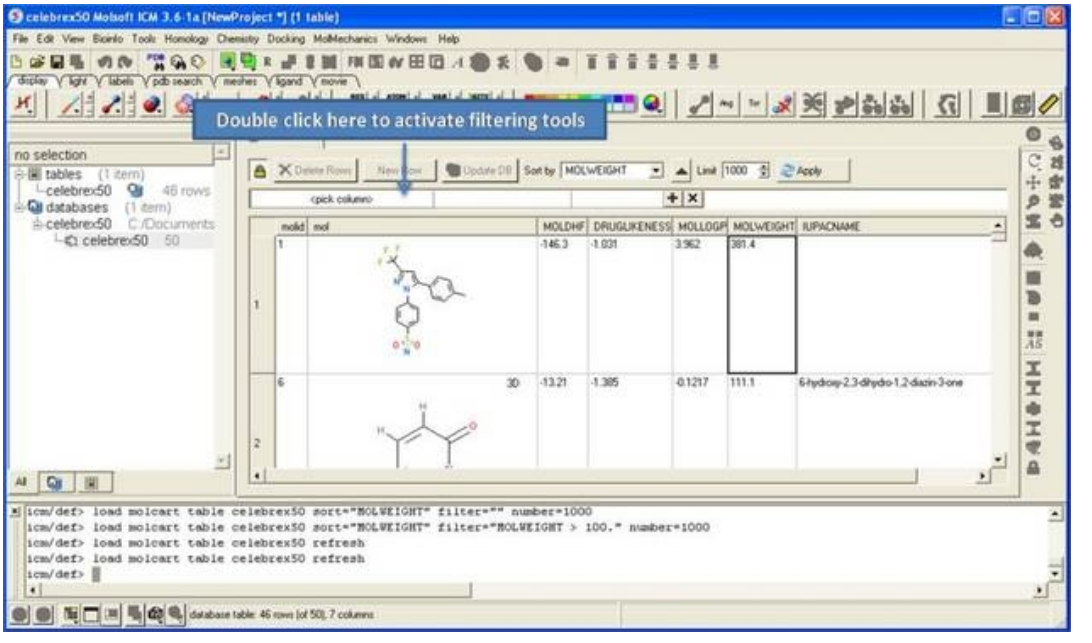
- Click on the drop down arrow next to the **Sort by** data entry box and select a column.
- Click on the **Apply** button.

NOTE: The database will be sorted globally not just the displayed rows.

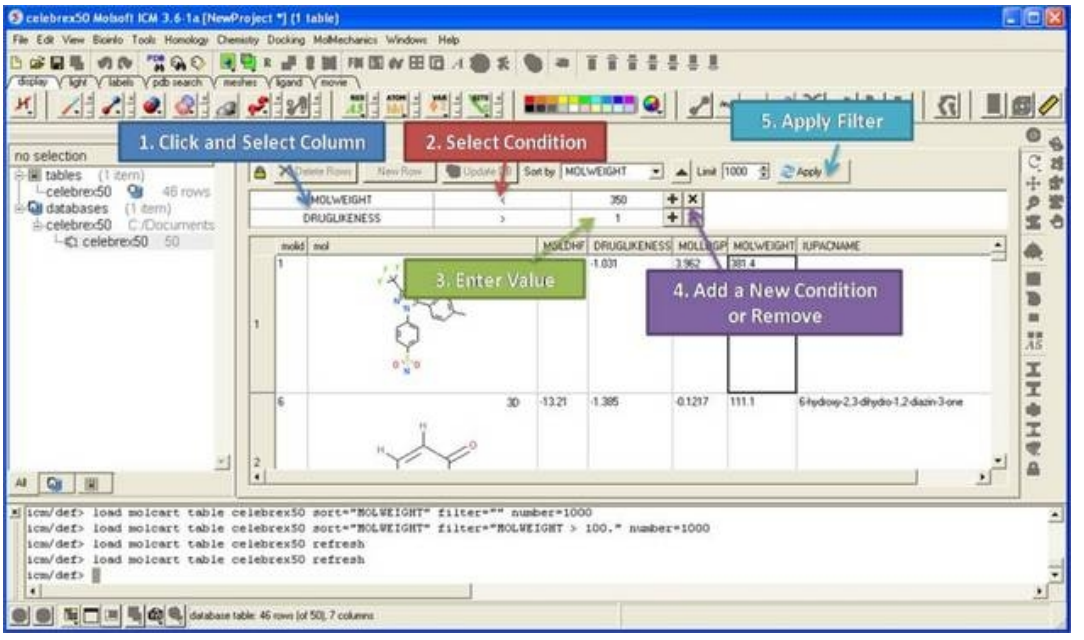


To filter a database:

- Double click on the panel labeled and the filtering tools will be activated.



- Click and select a column to filter (as shown below).
- Enter a condition.
- Enter a value.
- Add or remove another condition
- Click the **Apply** button



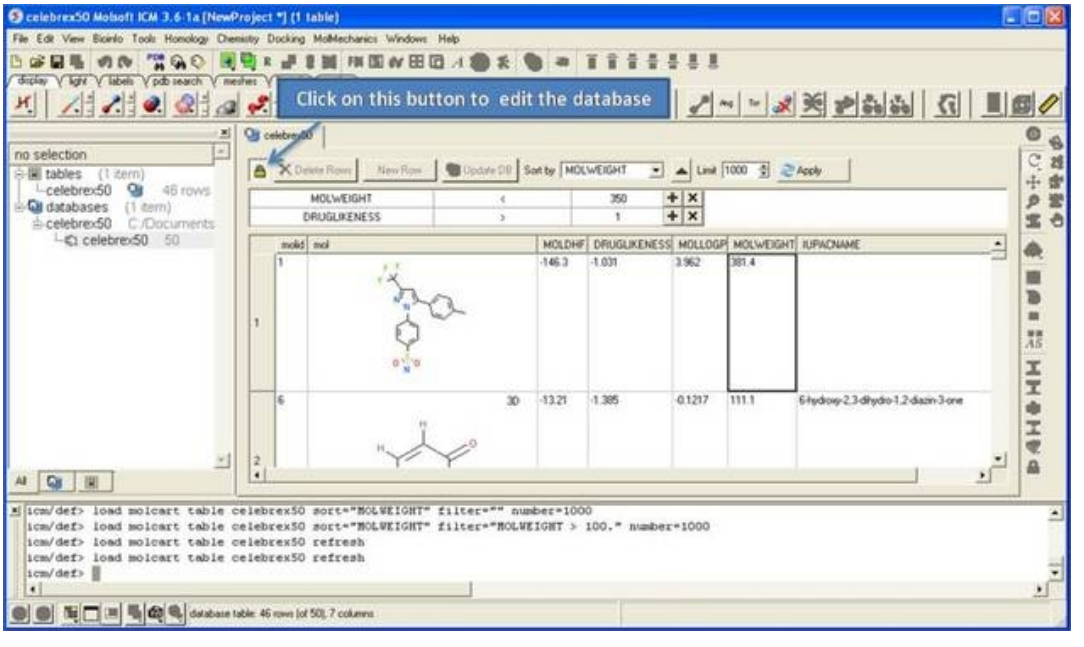
To view a diverse set of rows from your database:

- Right click on the database in the ICM Workspace and select **Select Diverse Set**.

22.3 Edit Database

To make any changes to a database you must first unlock it:

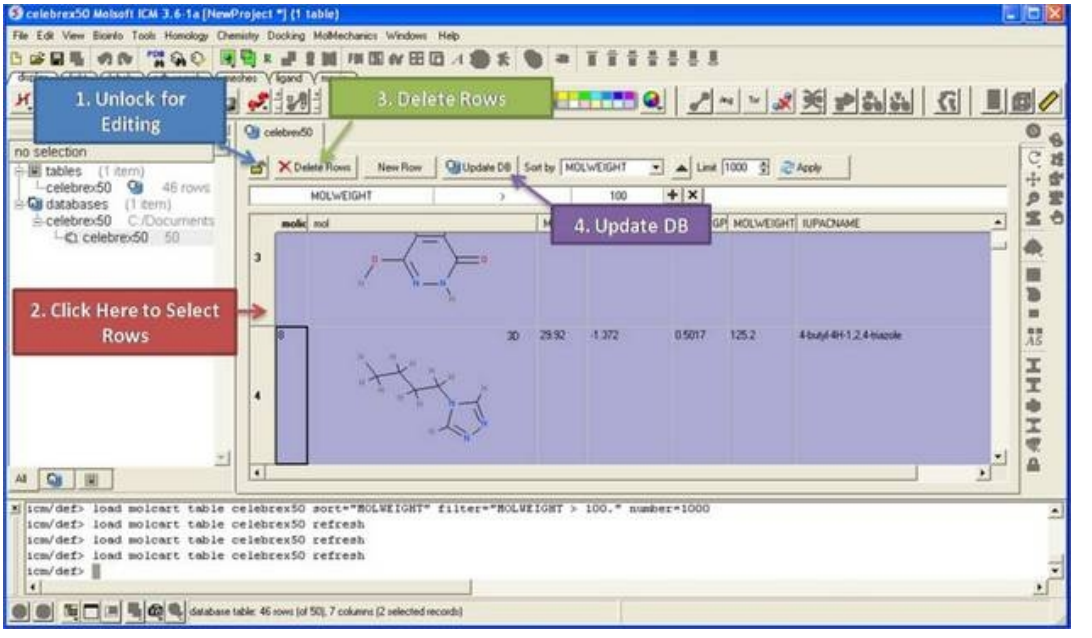
- Click on the **Allow editing rows** button which has a picture of a lock on it.
- Once this button has been selected the **Delete Rows**, **New Row**, and **Update DB** buttons will become activate.



To delete rows

- Select the row(s) by clicking on the row numbers. A range of rows can be selected by holding the shift key and clicking a non−contiguous set of rows can be selected by holding down the control key.

- Click the **Delete Rows** button.



To insert a new row

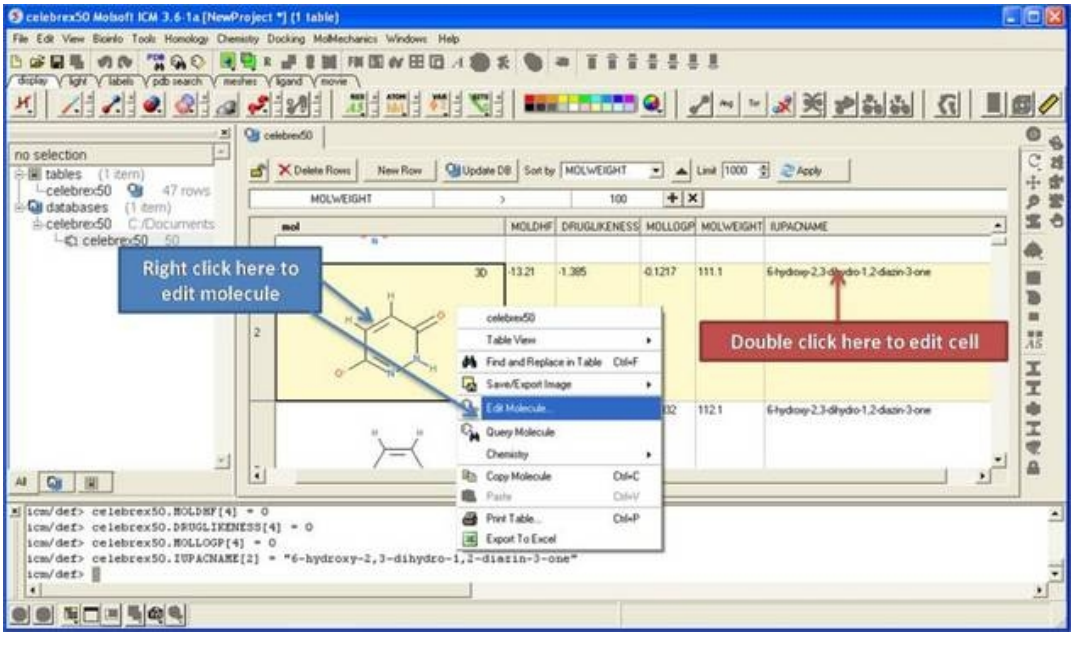
- Select a row.
- Click on the **New Row** button. A new row will be inserted underneath the selected row.
- Click **Update DB**

To edit strings and numbers in a row

- Double click on the cell you wish to edit and then enter a new value.
- Click **Update DB**

To edit a chemical (2D sketch):

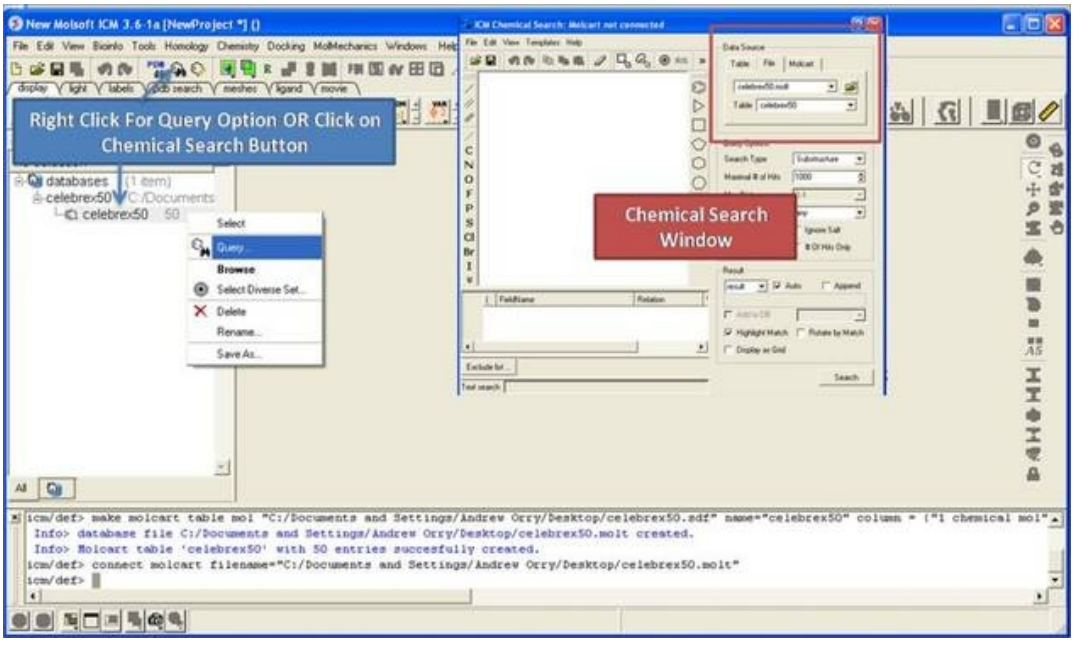
- Right click on the cell and select **Edit Molecule**
- Make changes using the `Molecular Editor`
- Click **Update DB**



22.4 Query Local Database

To query a local database:

- Right click on the database in the ICM Workspace and select **Query.**
- Query using the `chemical search` tools.



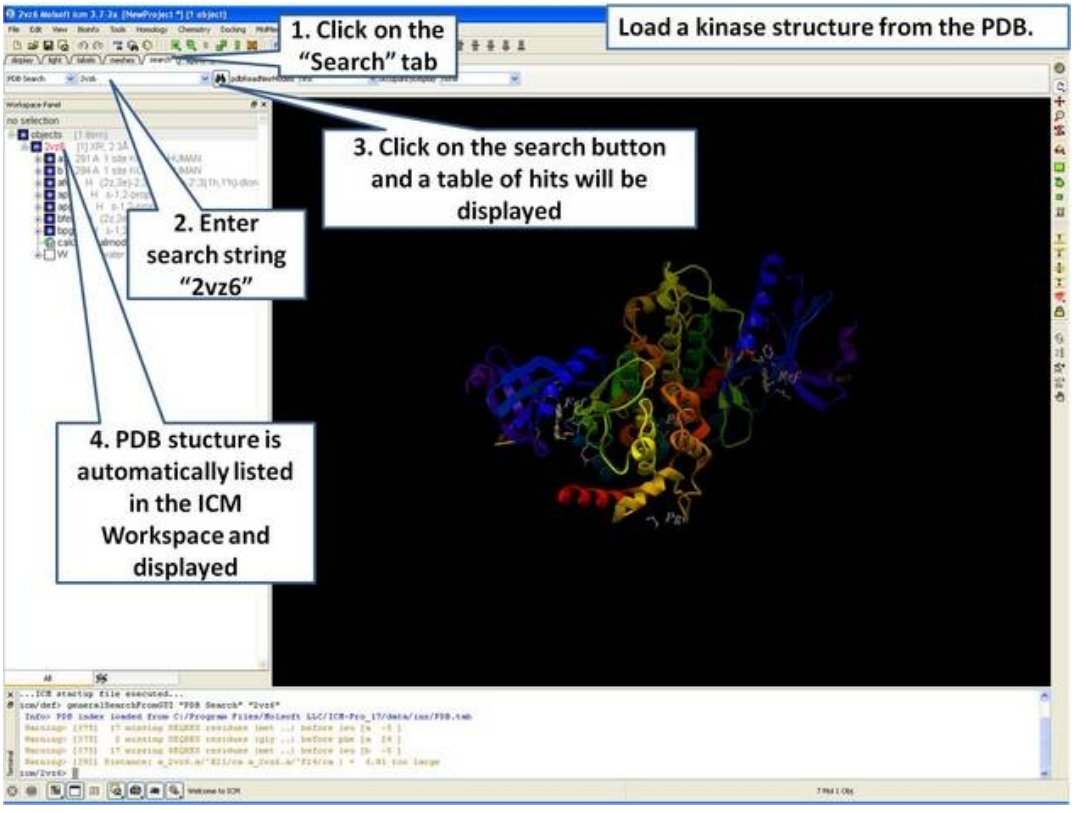
#endif

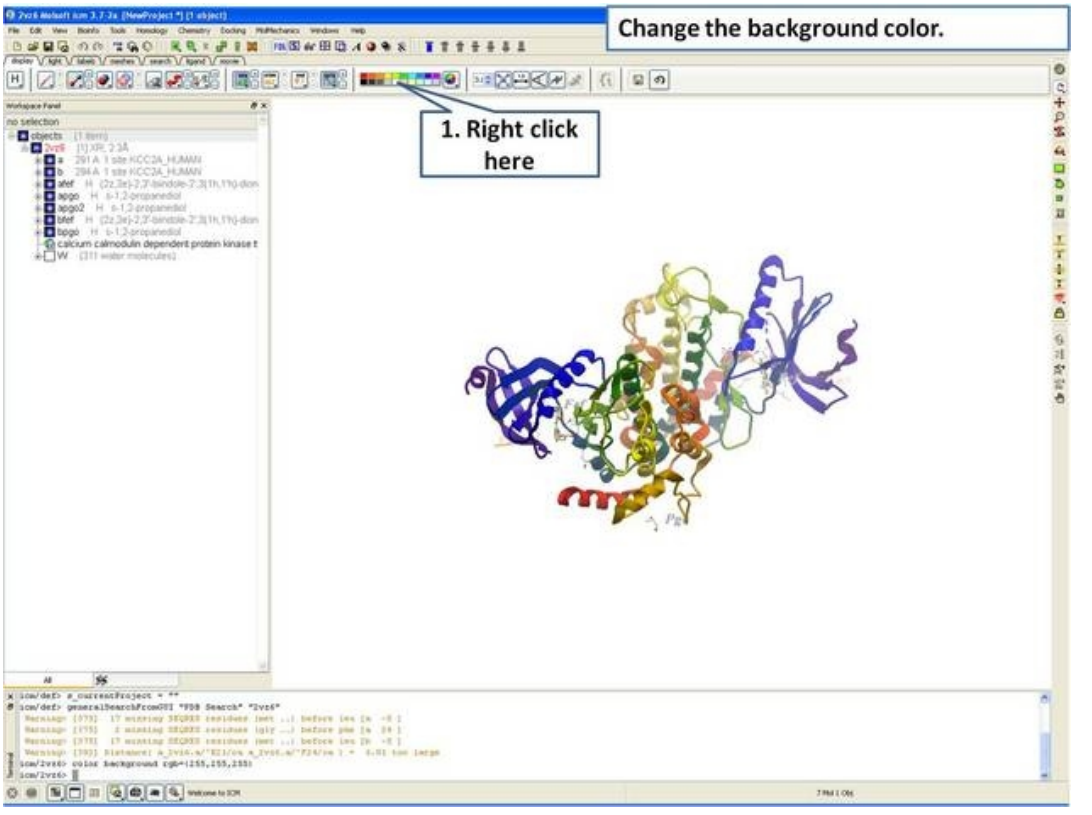
23 Tutorials

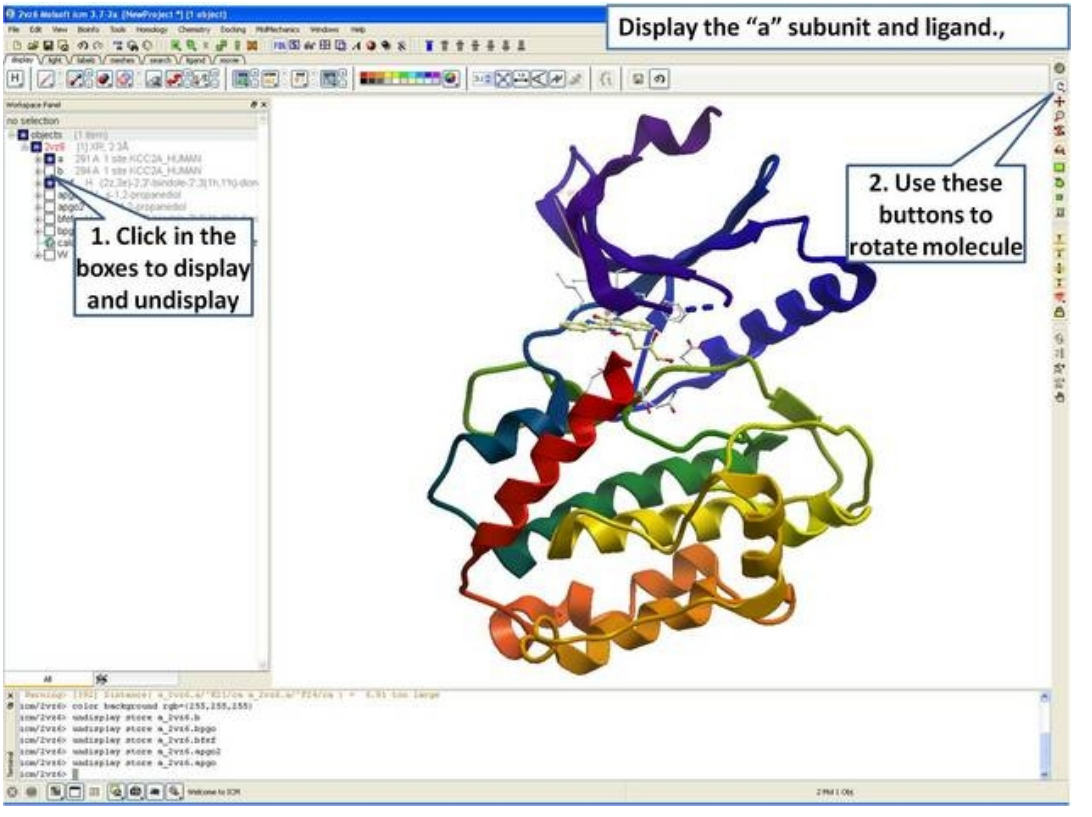
Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

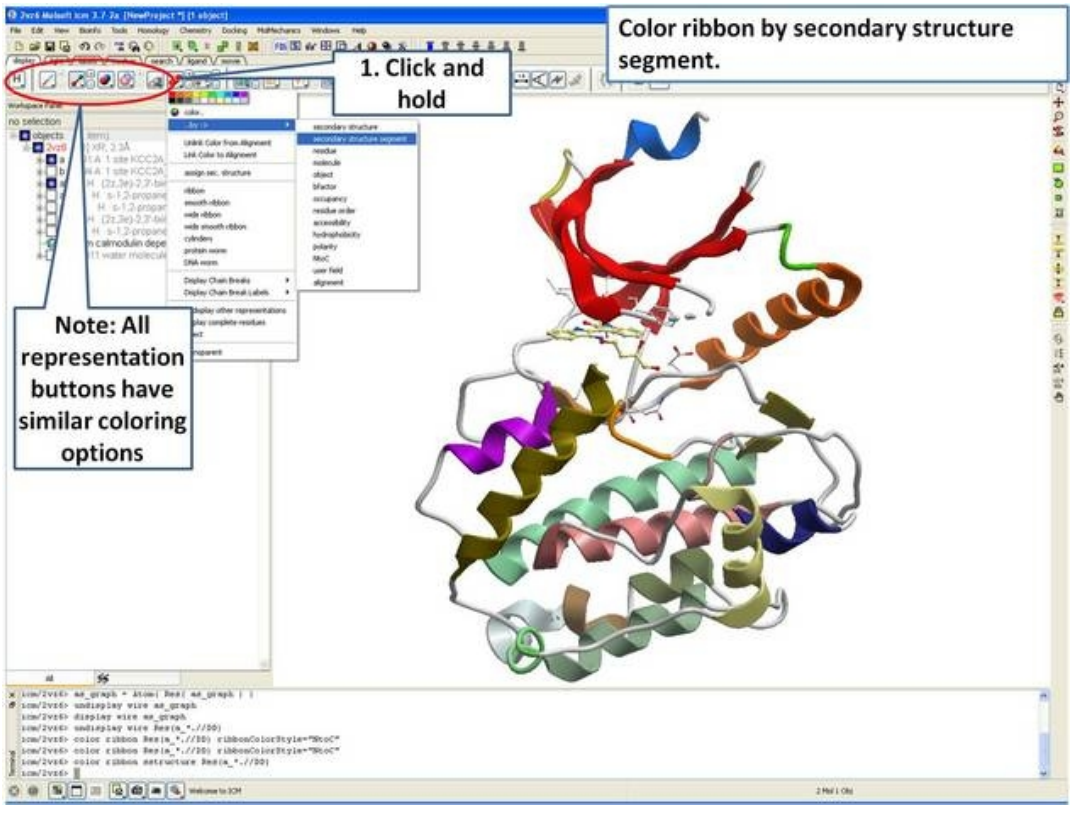
23.1 Graphical Display Tutorial: Molecule Representation, Coloring, Labeling and Annotation

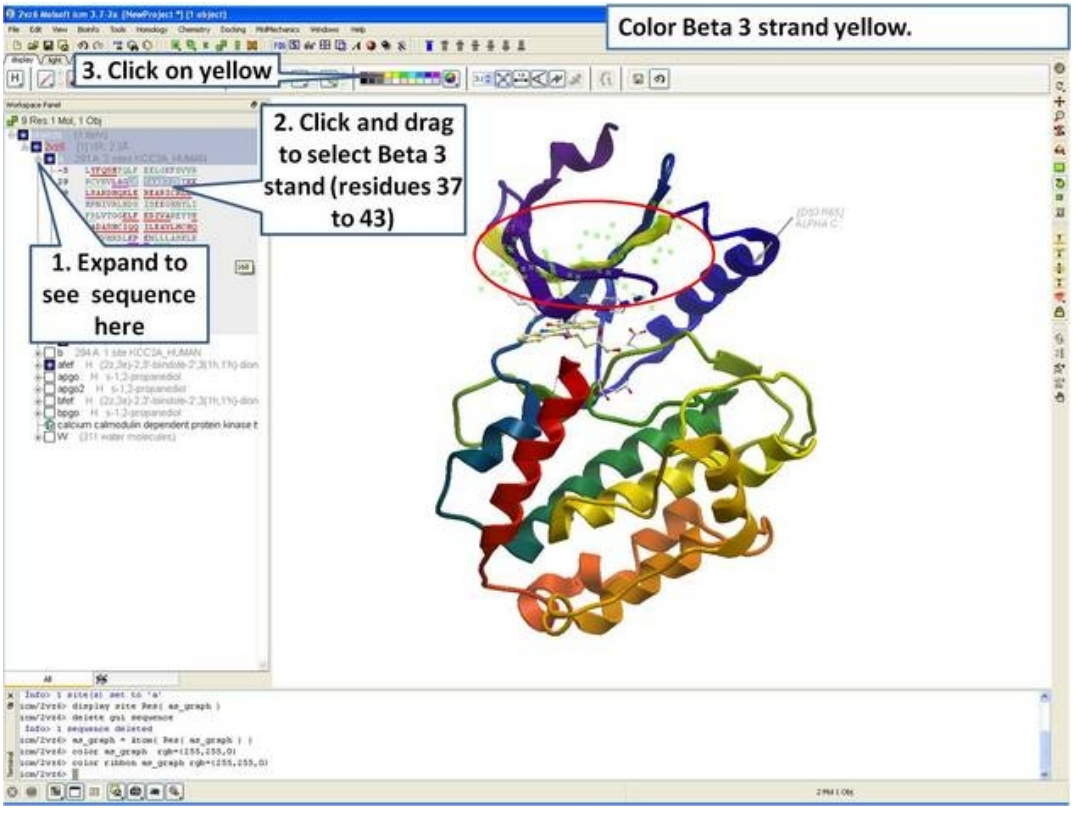
23.1.1 Change Molecule Representation and Color



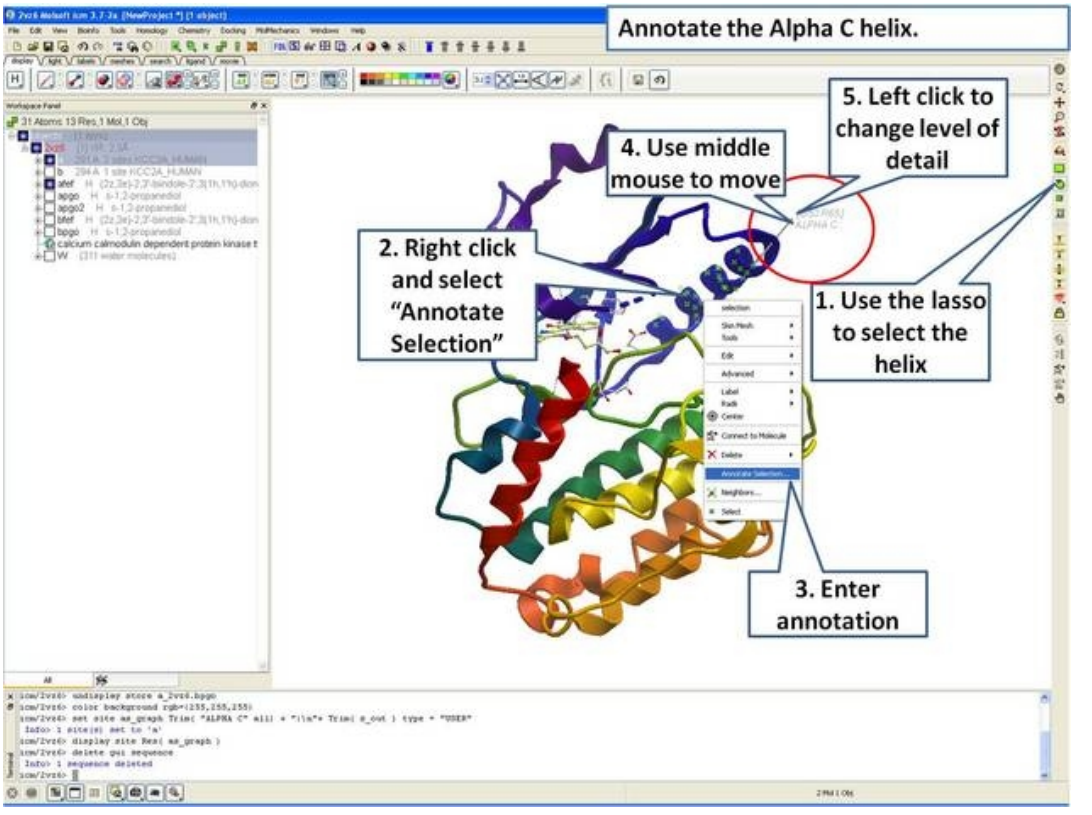

Change the background color.
1. Right click here


Display the “a” subunit and ligand.,
1. Click in the boxes to display and undisplay
2. Use these buttons to rotate molecule

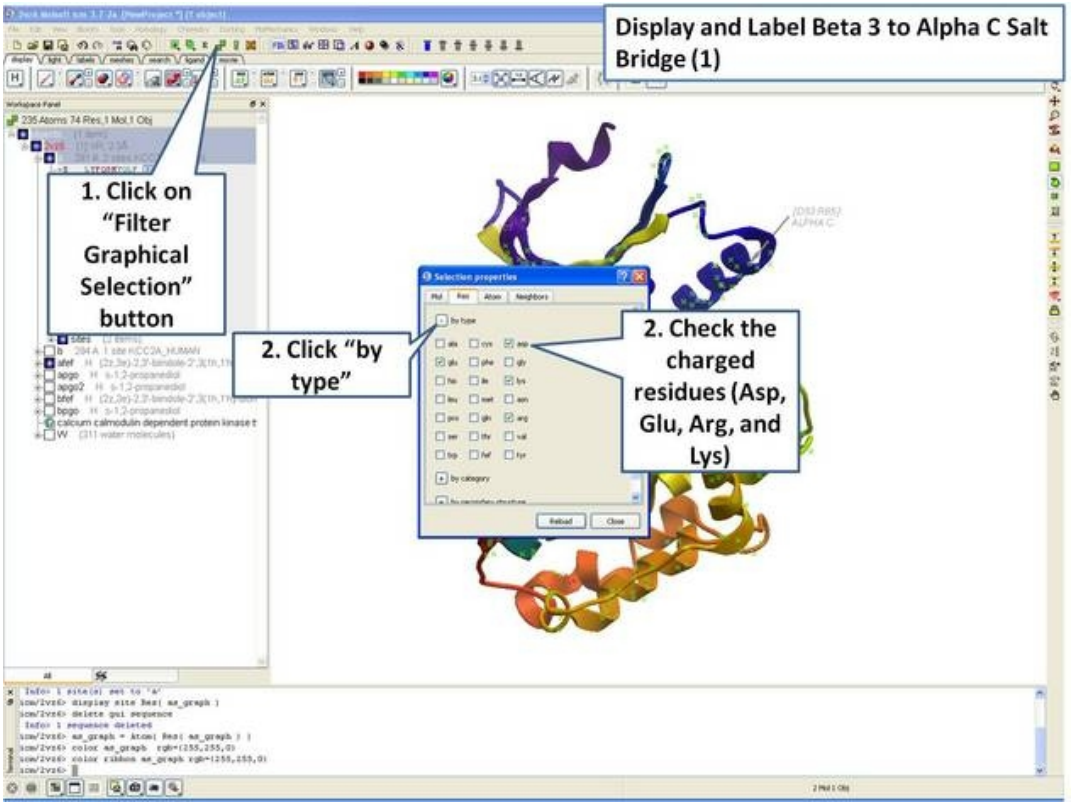


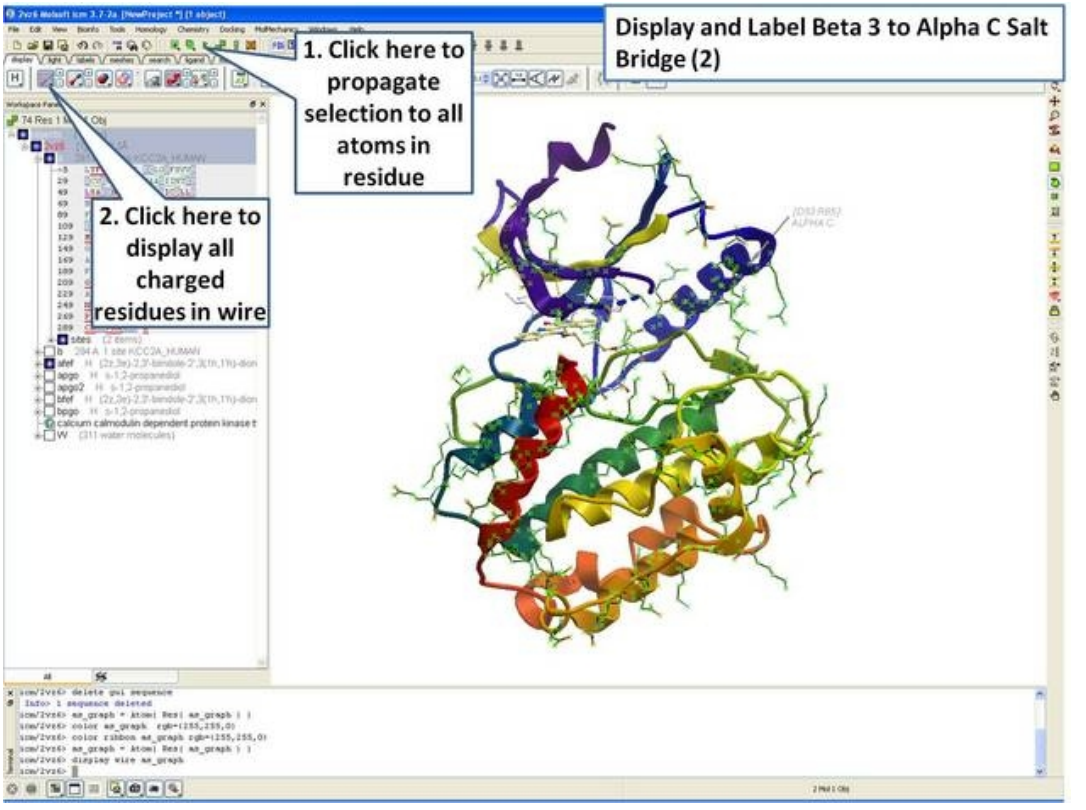


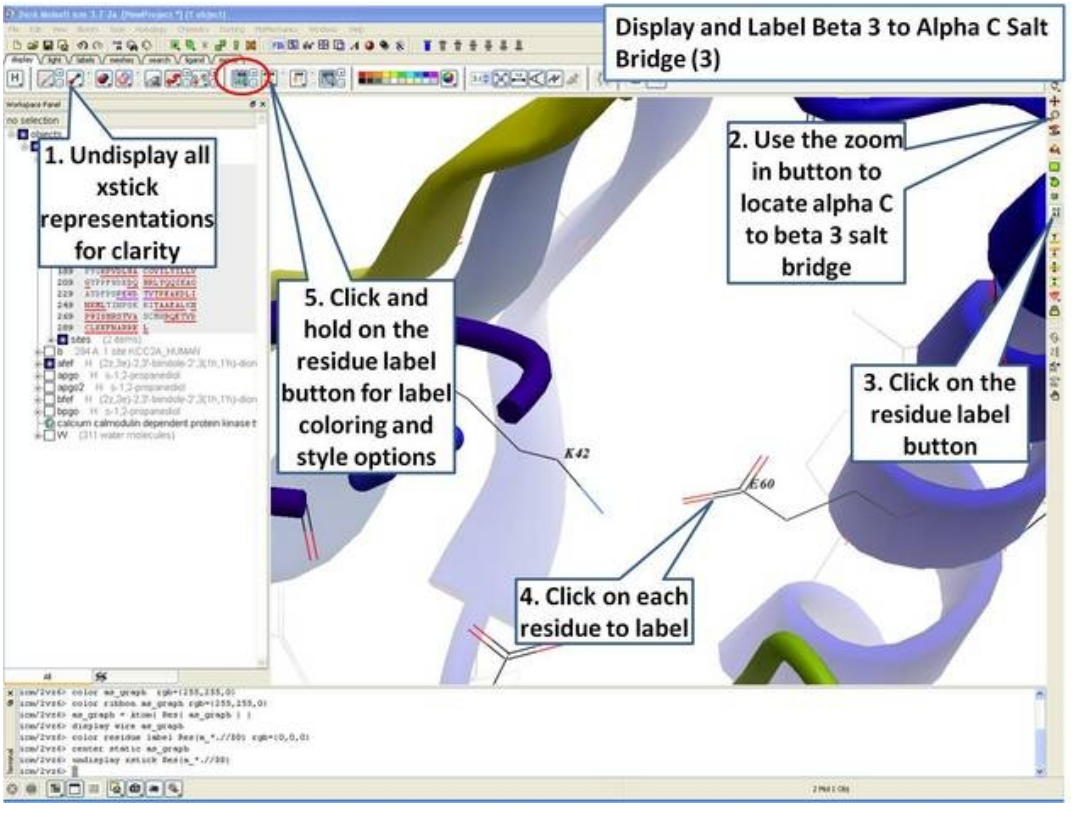
23.1.2 Annotation

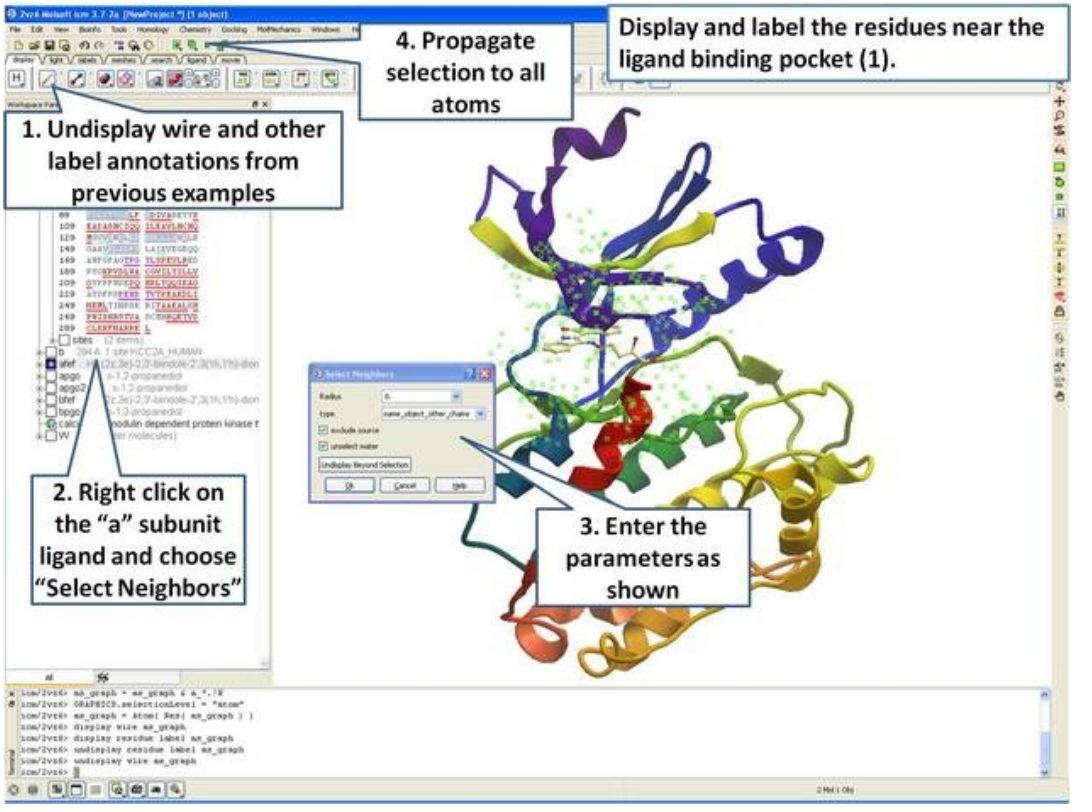

Annotate the Alpha C helix.
5. Left click to change level of detail
4. Use middle mouse to move
2. Right click and select "Annotate Selection"
1. Use the lasso to select the helix
3. Enter annotation

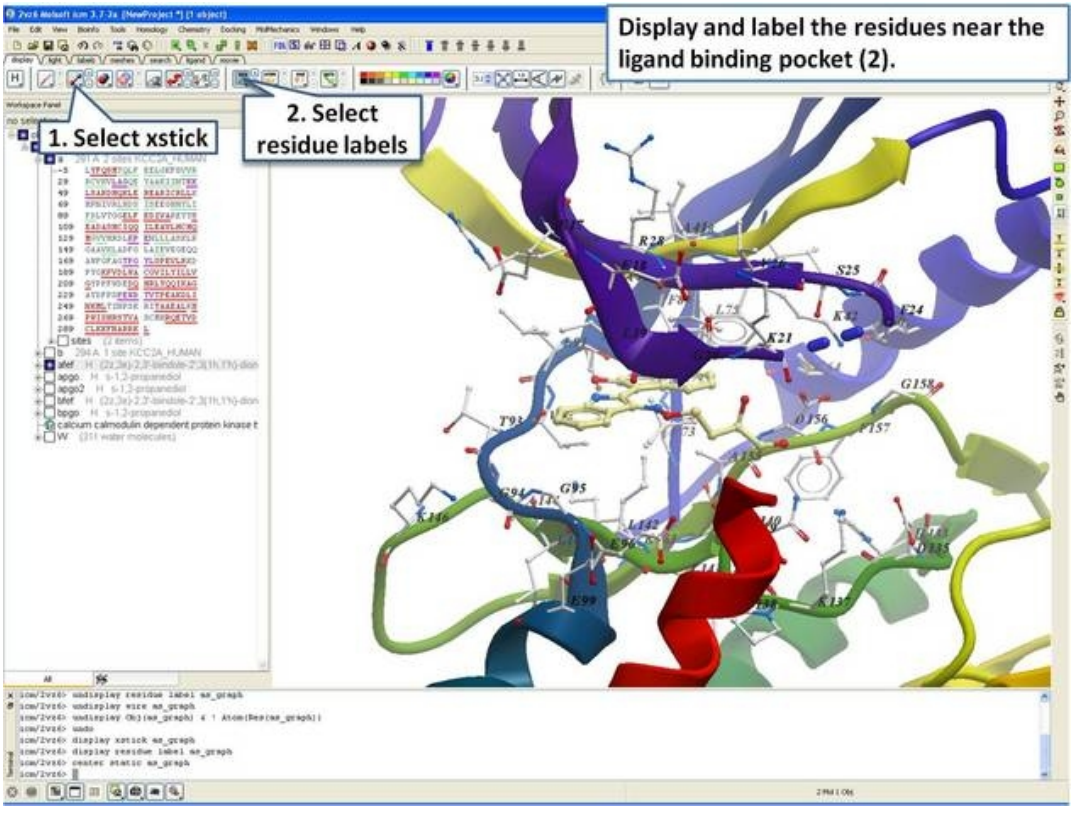
23.1.3 Labels


Display and Label Beta 3 to Alpha C Salt Bridge (1)
1. Click on "Filter Graphical Selection" button
2. Click "by type"
2. Check the charged residues (Asp, Glu, Arg, and Lys)

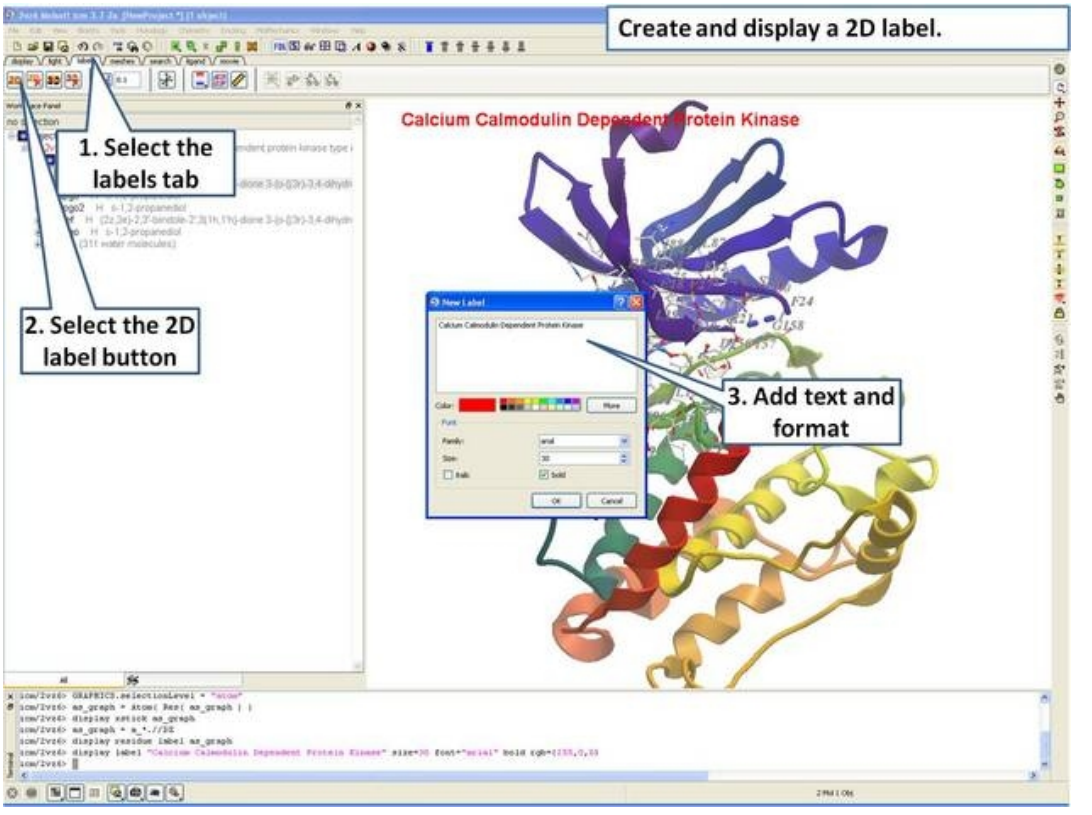

Display and Label Beta 3 to Alpha C Salt Bridge (2)
1. Click here to propagate selection to all atoms in residue
2. Click here to display all charged residues in wire

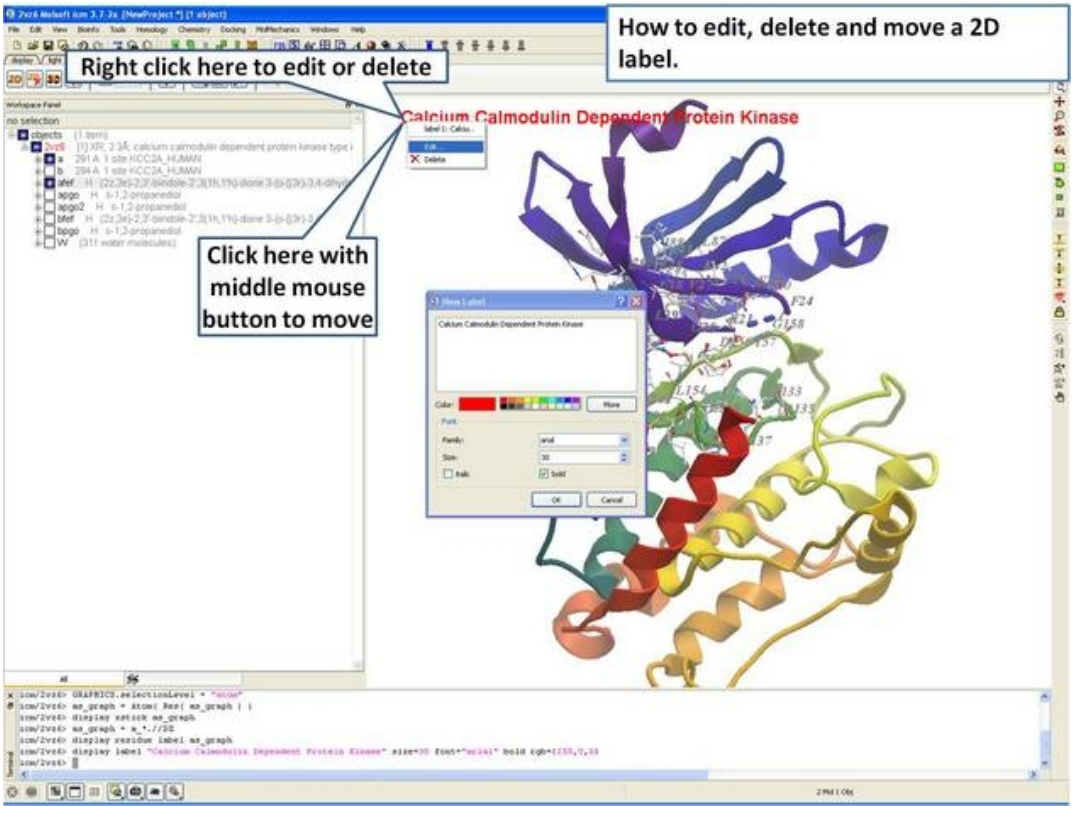

Display and Label Beta 3 to Alpha C Salt Bridge (3)
1. Undisplay all xstick representations for clarity
2. Use the zoom in button to locate alpha C to beta 3 salt bridge
3. Click on the residue label button
4. Click on each residue to label
5. Click and hold on the residue label button for label coloring and style options
K42
E60

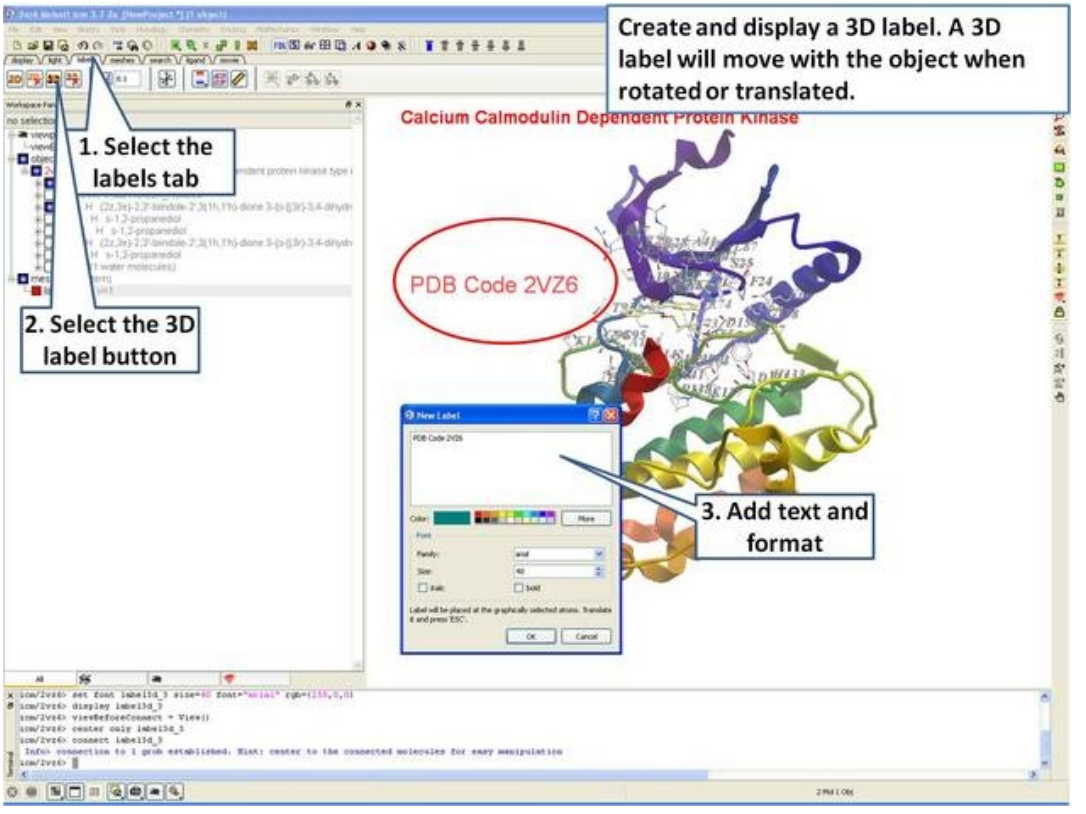


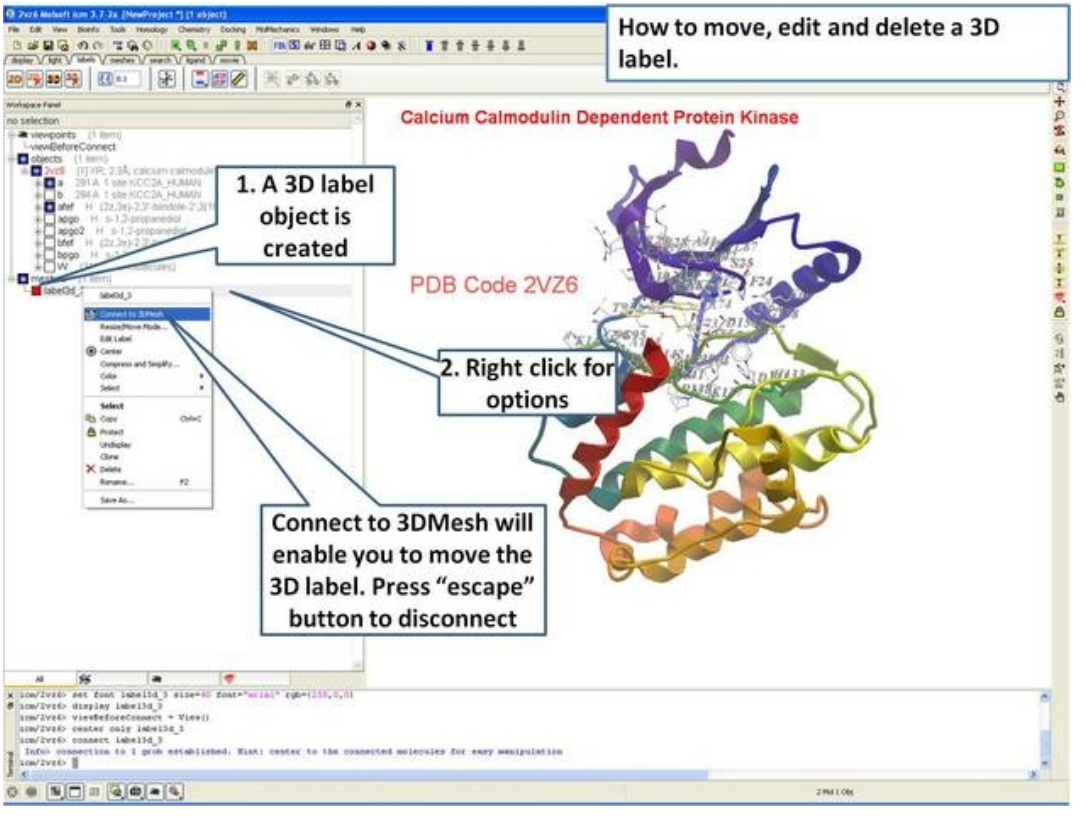


23.1.4 2D and 3D Labels


Create and display a 2D label.
1. Select the labels tab
2. Select the 2D label button
3. Add text and format
Calcium Calmodulin Dependent Protein Kinase

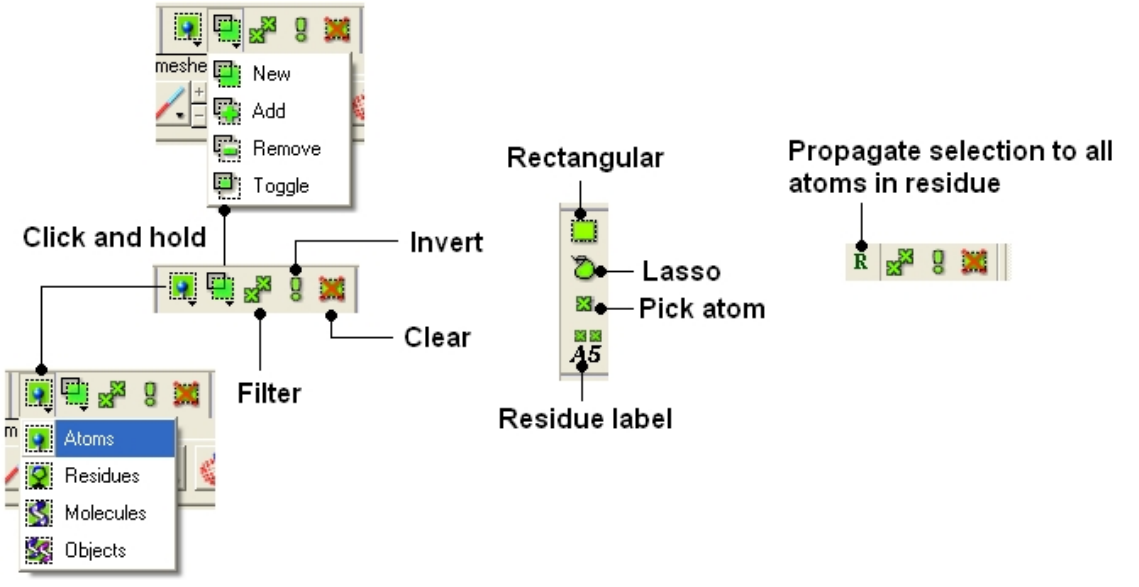

How to edit, delete and move a 2D label.
Right click here to edit or delete
Click here with middle mouse button to move
Calcium Calmodulin Dependent Protein Kinase



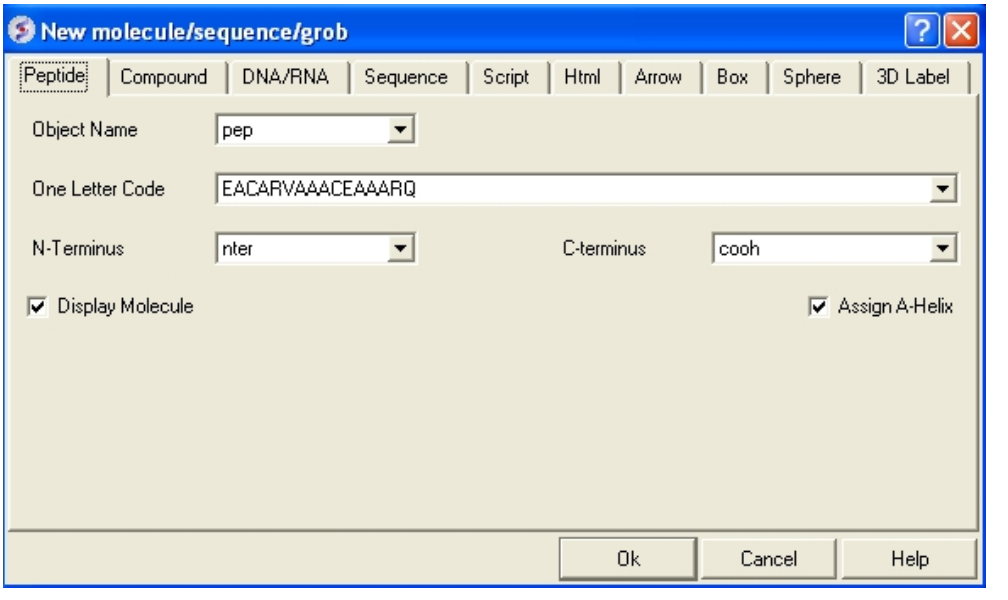


23.2 Graphical Selections Tutorial

All buttons relating to graphical selections are shaded green. These buttons are shown here and are located at the top of the graphical user interface and along the side.



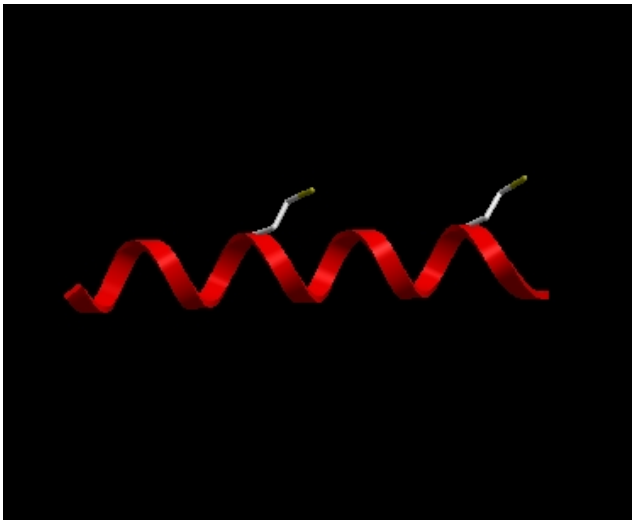
The **File/New window** is a great place to start learning how to use ICM as it provides a quick and easy way to generate new peptides, compounds, DNA/RNA, sequences and graphical objects.



The examples in this section will take you through the basics of making selections in the graphical user interface using objects generated from File/new.

23.2.1 Making Basic Selections

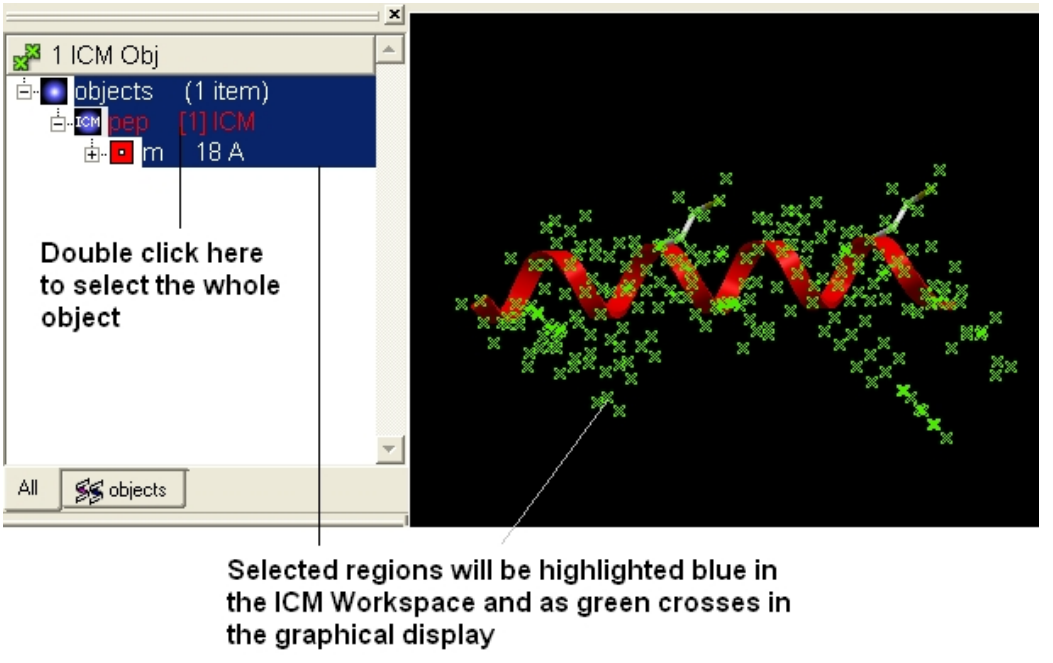
- File/New − Select Peptide Tab and use the default peptide entries and select OK. A peptide as shown below will be displayed in ribbon format and the cysteine side−chains in xstick.



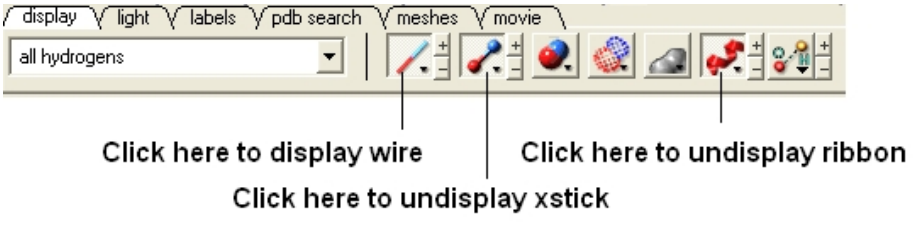
Now let us display the peptide in wire format and remove the ribbon and xstick representation

To do this:

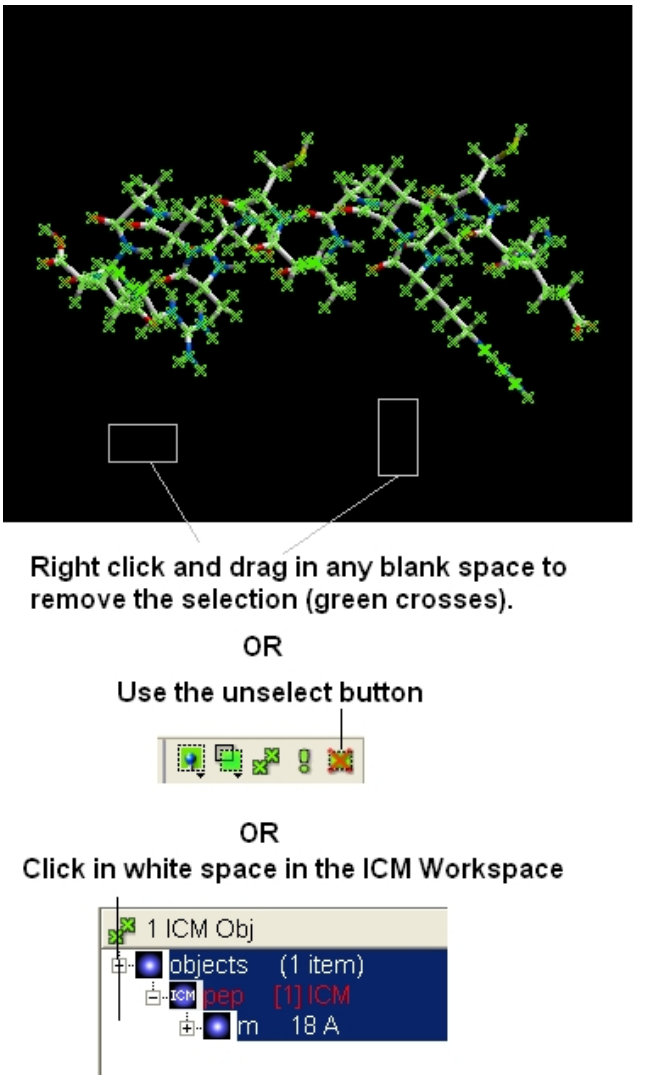
- Select the whole object by double clicking on the name of the object "pep" in the ICM Workspace. When selected it will be highlighted in blue in the ICM Workspace and green crosses in the graphical display.



- Select the "Display Tab" and select the wire button to display wire representation. Select the ribbon button and xstick button to undisplay ribbon and xstick.

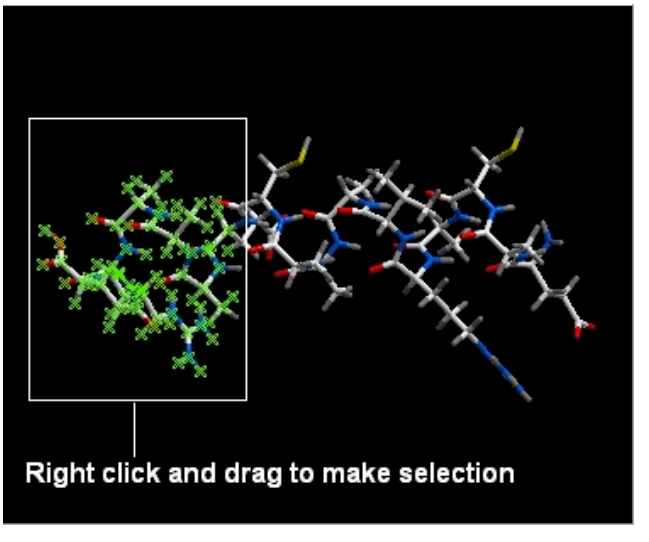


- Your peptide will still be selected. See below on how to remove selections.

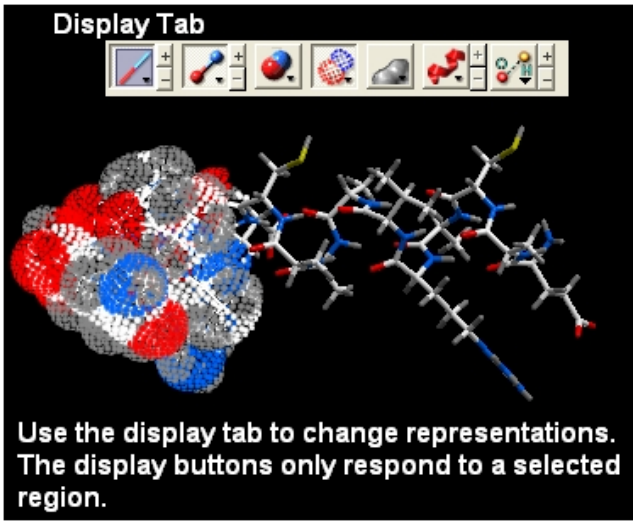


Now we will display different parts of the peptide in different representations.

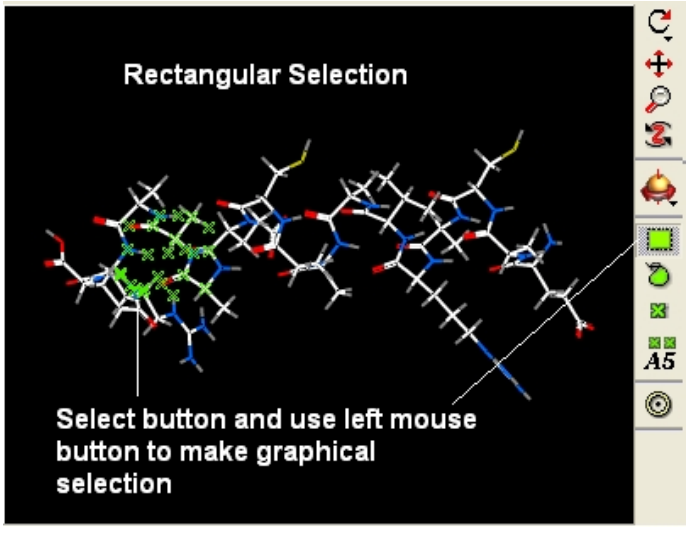
- Right click and drag over a region of the peptide you would like to change.

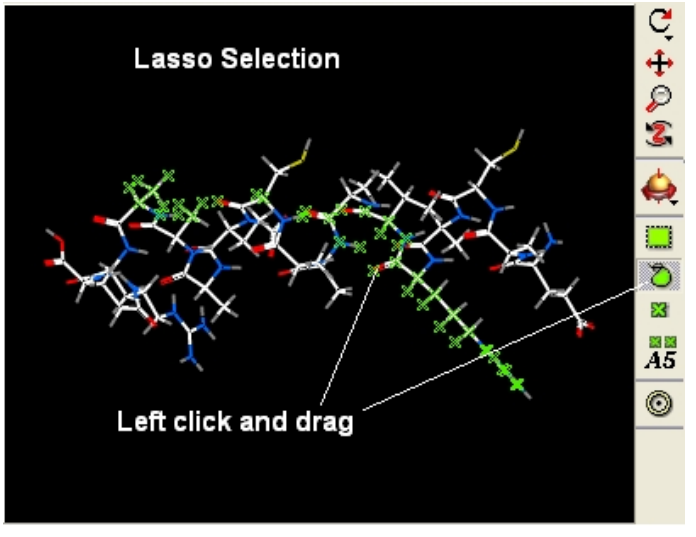


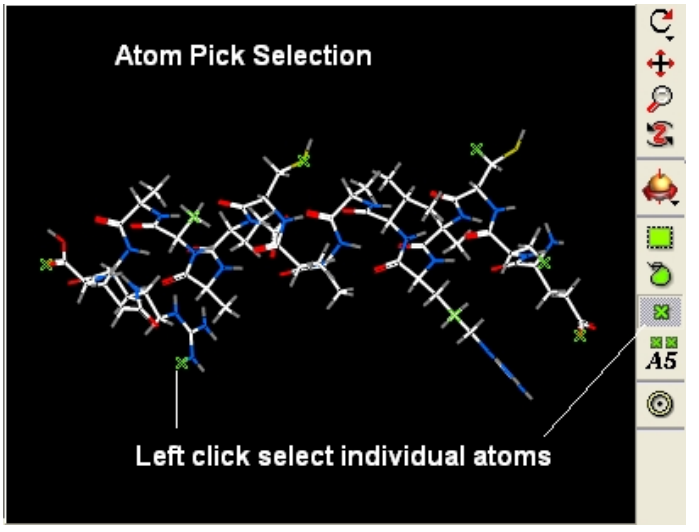
- Use the display panel to select the represenation you would like to display.



Other ways of making selections.



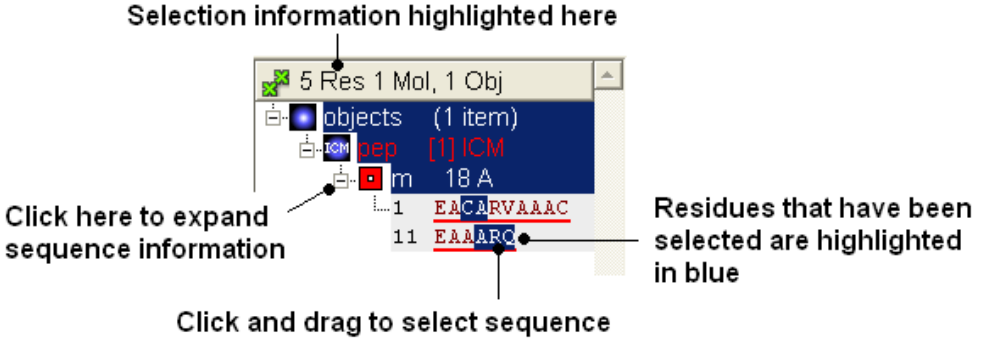




23.2.2 Making Sequence Selections in the ICM Workspace

- File/New − Select Peptide Tab and use the default peptide entries and select OK. A peptide as shown below will be displayed in ribbon format.

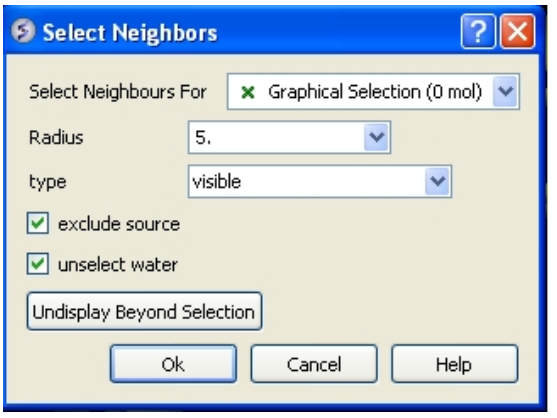
Selections can be made on the sequence of the peptide. This can be done by expanding the sequence display in the ICM Workspace and clicking and dragging on the sequence as shown below.
Non−contiguous selections can be made by clicking/dragging over the sequence whilst holding down the Ctrl key.



23.2.3 Making a Spherical Selection.

In this example we will select the residues surrounding a ligand.

- PDB Search tab (PDB code **1MVC)**
- Right click on the ligand **bm6** in the ICM Workspace.
- Select the **Neighbors** option

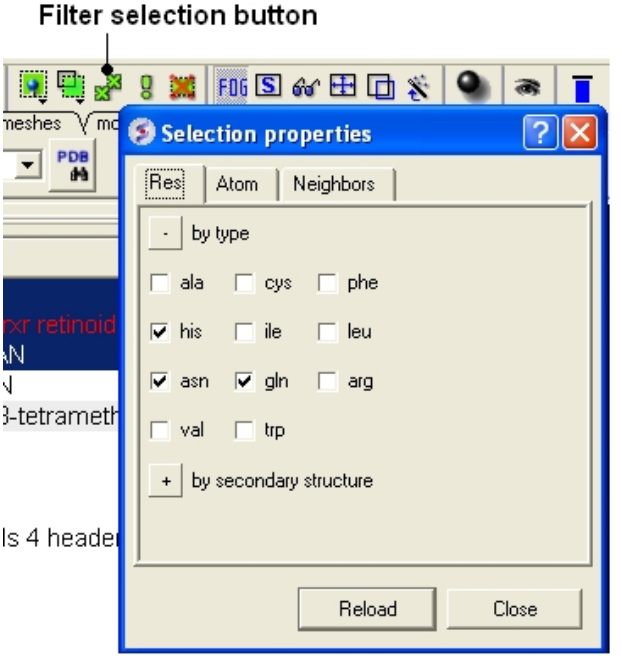


- In the "Select Neighbors For" box leave as Graphical Selection (1 mol)
- Enter Radius 5.
- Enter type **same_object_other_chains**
- Choose **exclude source** and **unselect water**.
- You will see green crosses surrounding the ligand binding pocket.

23.2.4 Filtering a Selection.

In this example we will filter the selection made in the previous `example` and select only His, Asn, Gln and Pro residues surrounding the ligand.

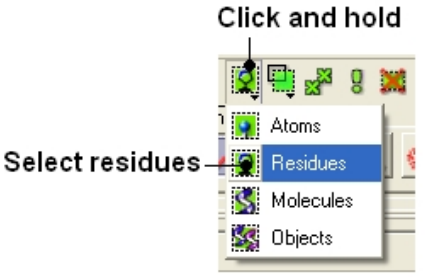
- Make a spherical selection surrounding the ligand in PDB structure *1MVC (See earlier `example`).
- Click on the **Filter graphical selection button**.
- Click on the **Res** tab
- Select His, Asn, Gln and Pro residues.



NOTE: Only amino acid residues in the current selection will be available in the **Filter.**

Display the selected residues in wire format.

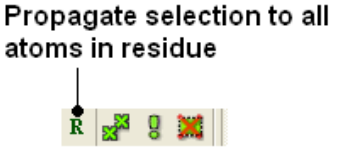
- Change the selection from **Atom** to **Residue.**



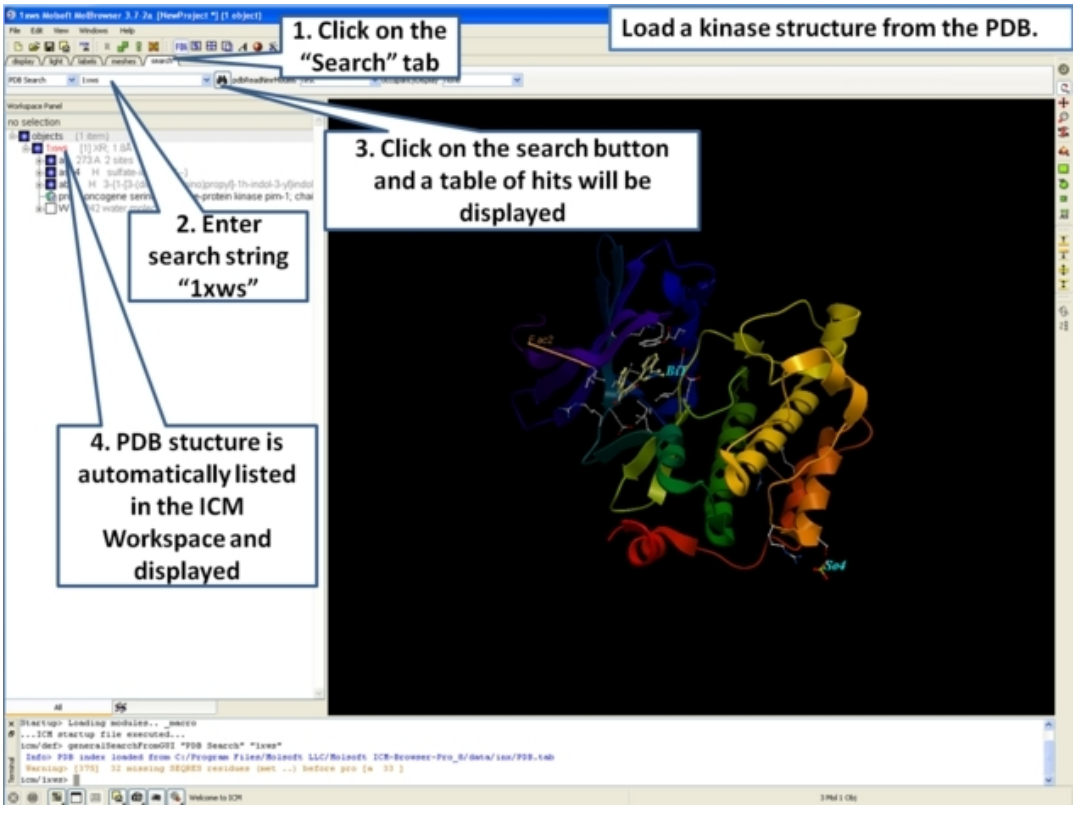
- Select the wire representation button in the **display** tab.

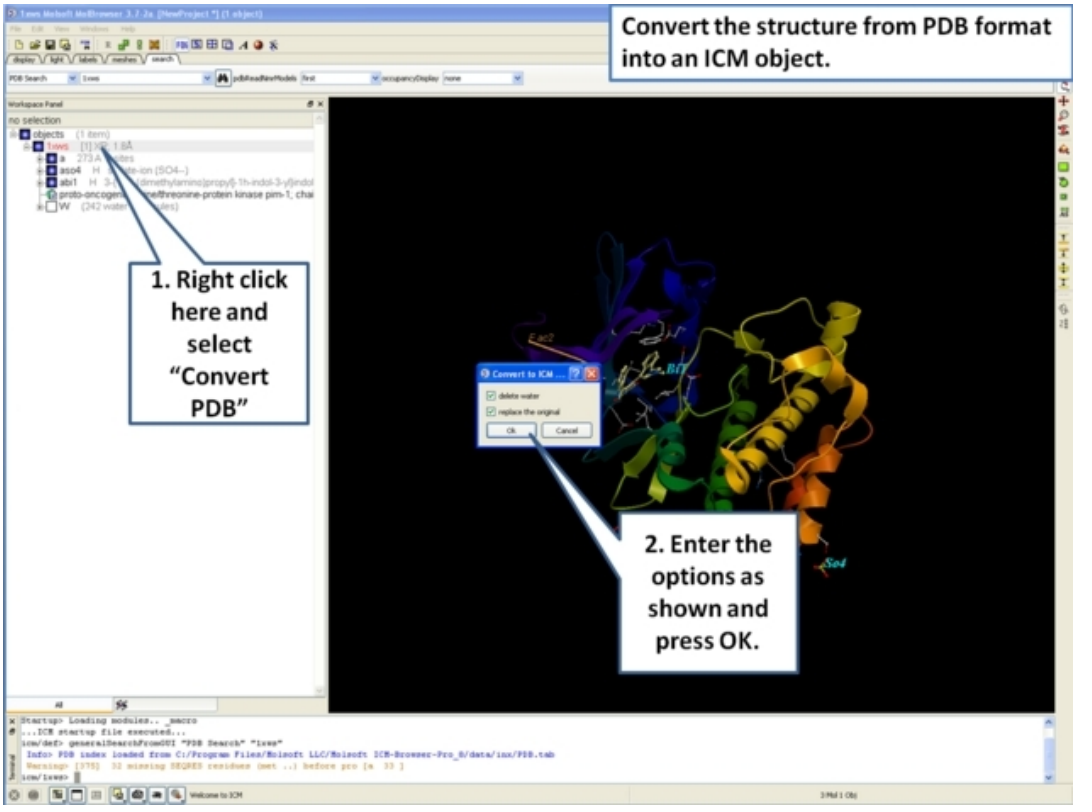
23.2.5 Propogating a selection to all atoms in a residue.

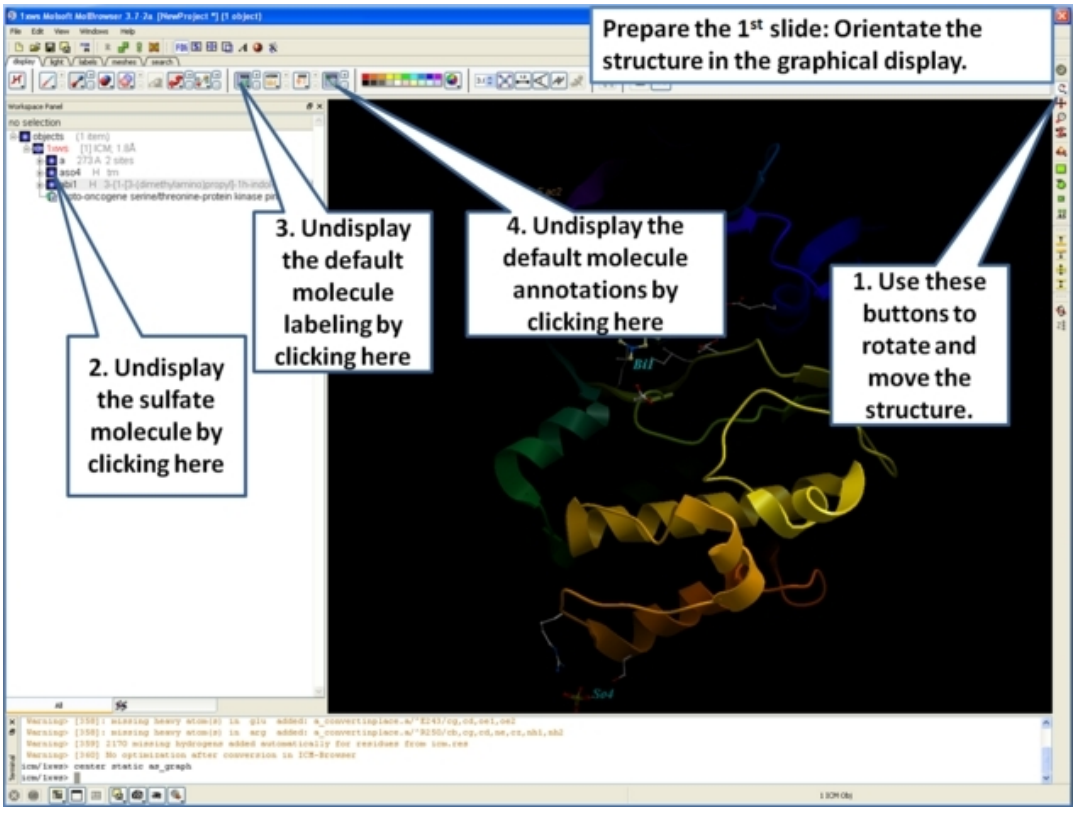
Sometimes it is useful to propogate a selection to all atoms in a residue. For example when selecting the residues surrounding a ligand within a certain angstrom radius the selection will only pick up certain atoms of a residue. The button shown below can be used to propogate the selection to all atoms in a residue.

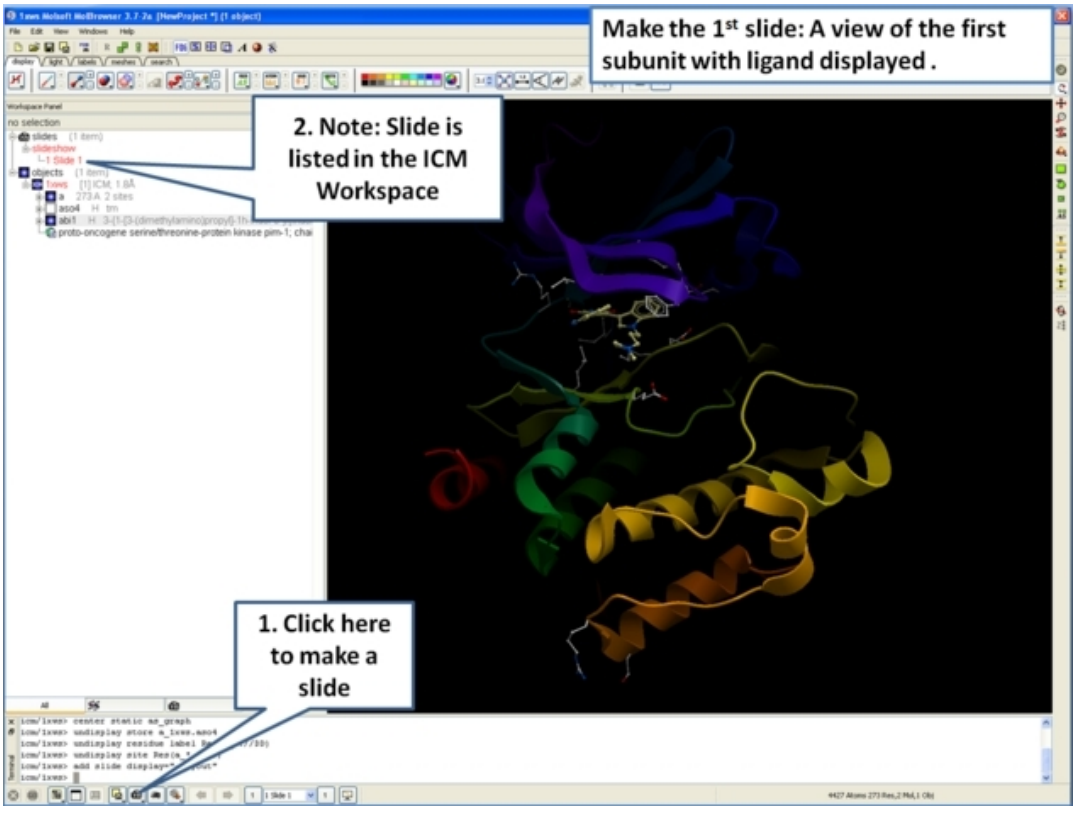


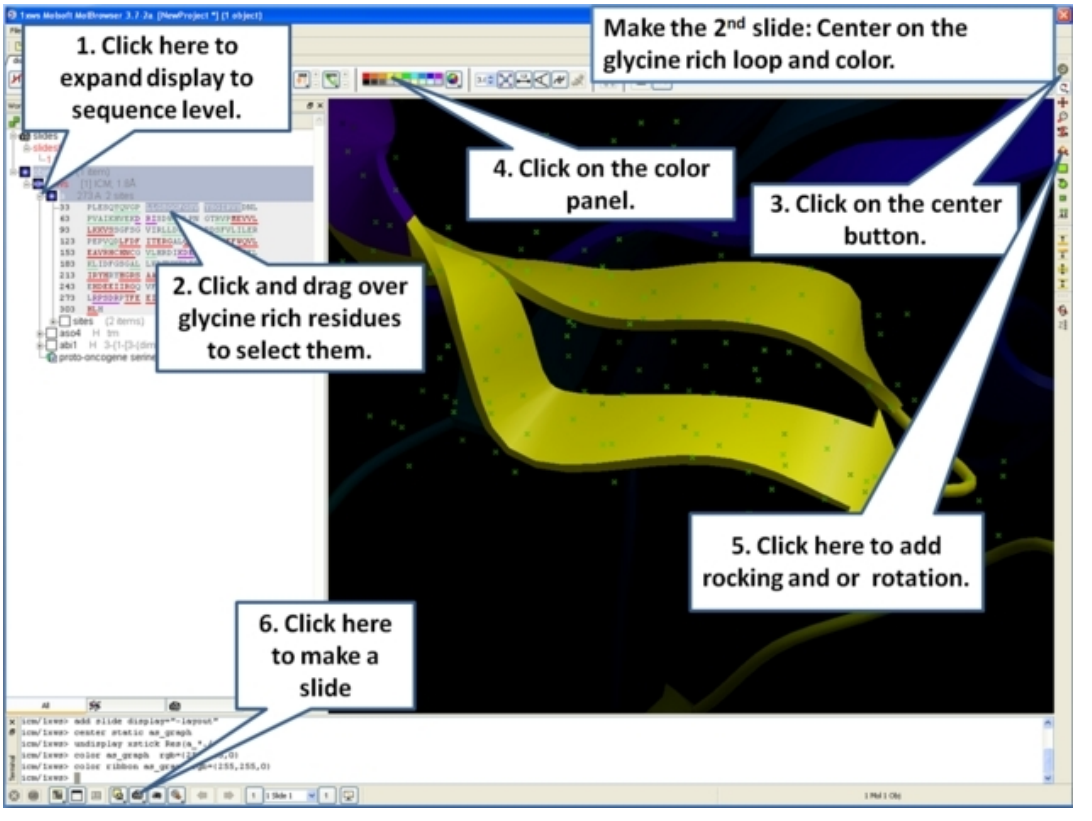
23.3 Generating Fully Interactive Slides for PowerPoint and the Web Tutorial

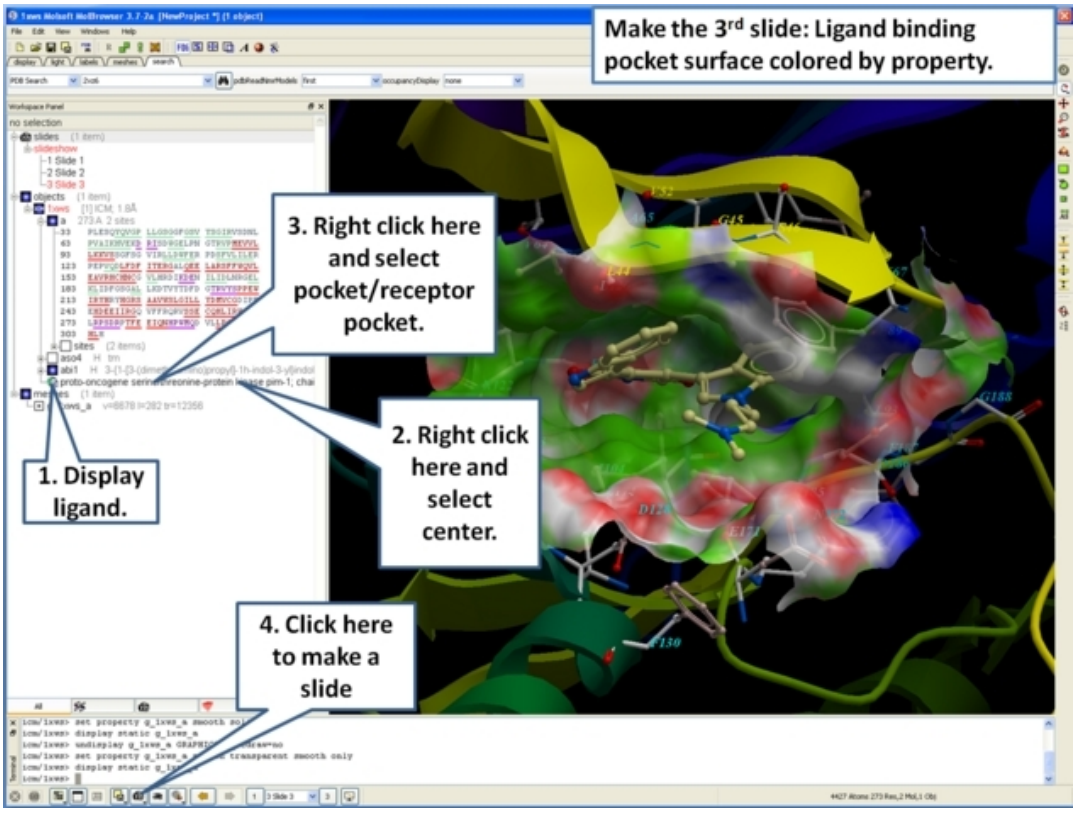


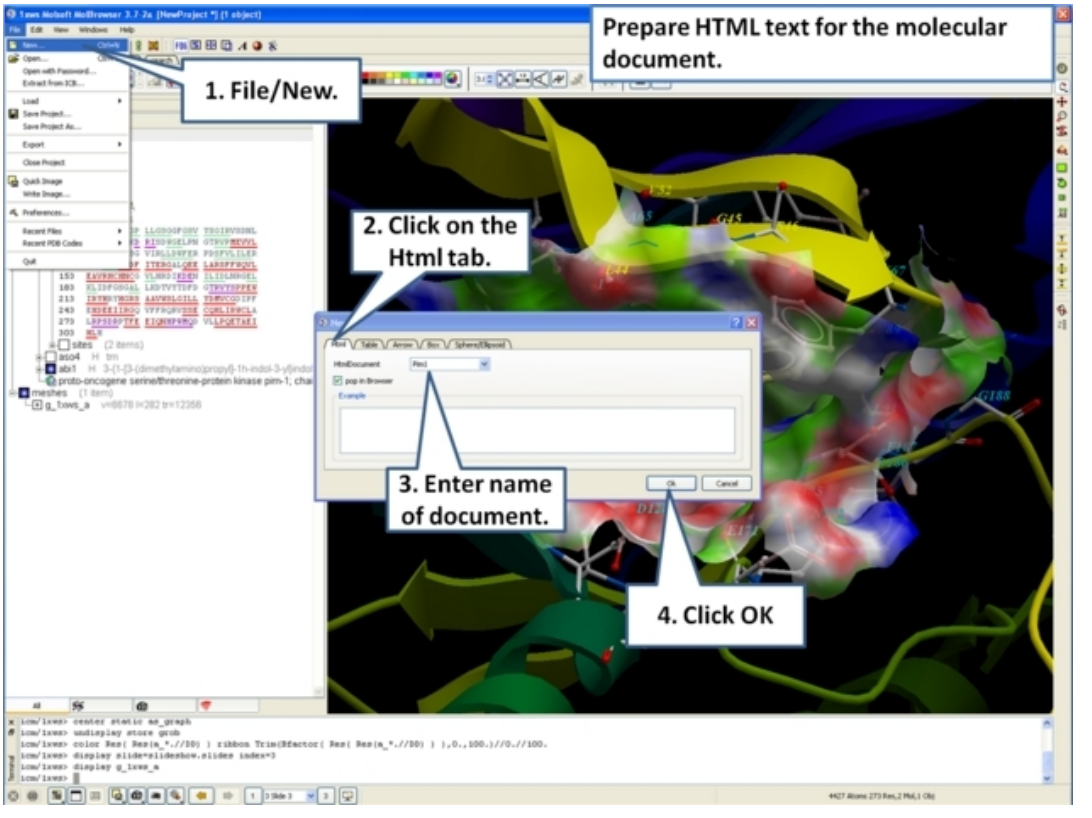

Convert the structure from PDB format into an ICM object.
1. Right click here and select "Convert PDB"
2. Enter the options as shown and press OK.

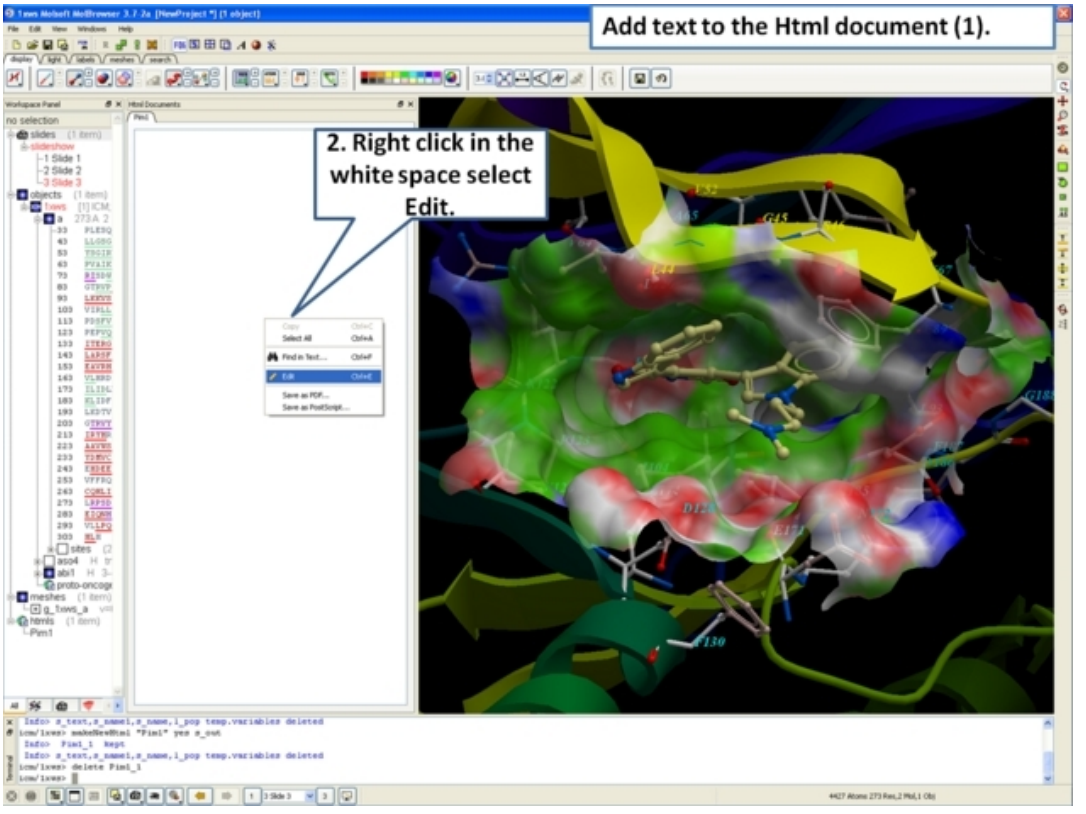

Prepare the 1st slide: Orientate the structure in the graphical display.
1. Use these buttons to rotate and move the structure.
2. Undisplay the sulfate molecule by clicking here
3. Undisplay the default molecule labeling by clicking here
4. Undisplay the default molecule annotations by clicking here

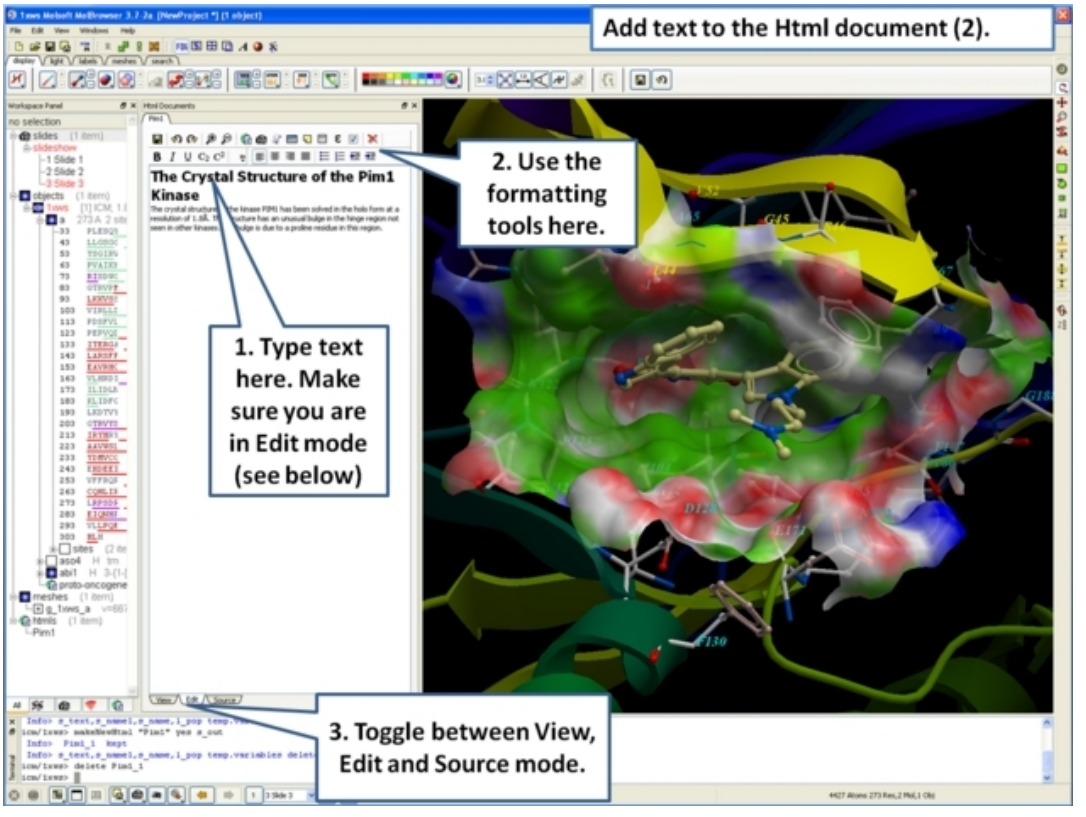

Make the 1st slide: A view of the first subunit with ligand displayed .
2. Note: Slide is listed in the ICM Workspace
1. Click here to make a slide

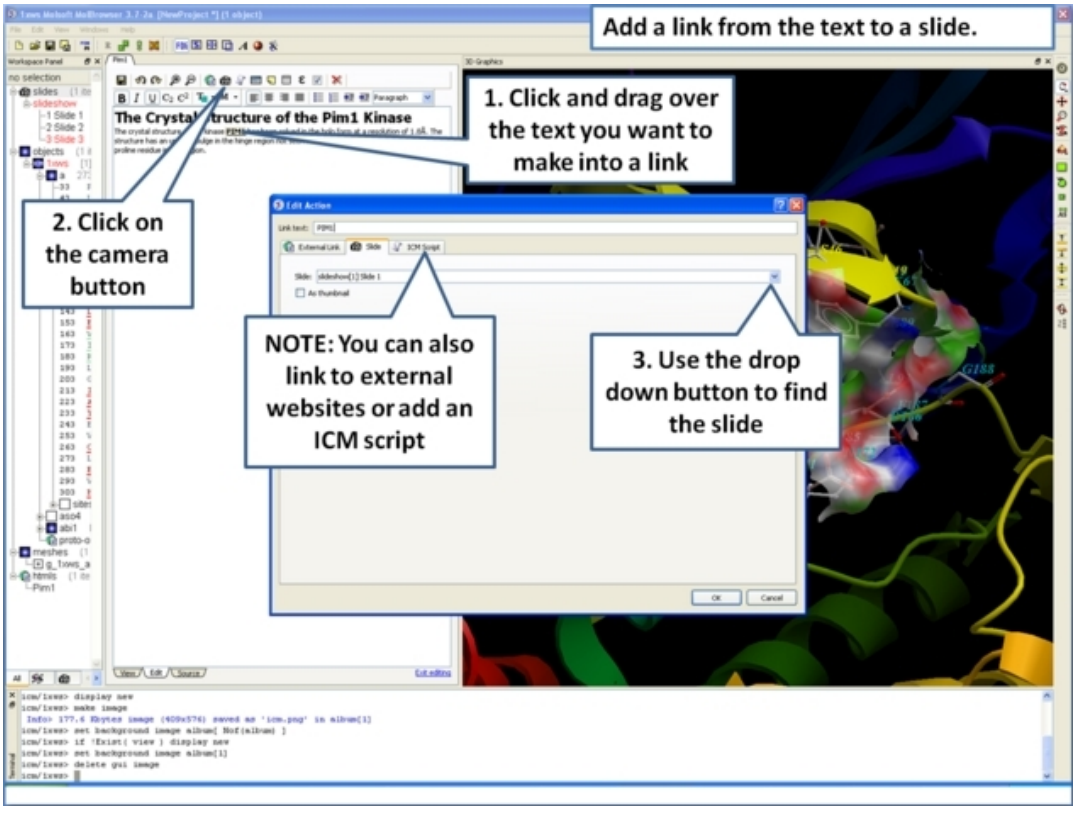

Make the 2nd slide: Center on the glycine rich loop and color.
1. Click here to expand display to sequence level.
4. Click on the color panel.
3. Click on the center button.
2. Click and drag over glycine rich residues to select them.
5. Click here to add rocking and or rotation.
6. Click here to make a slide


Make the 3rd slide: Ligand binding pocket surface colored by property.
3. Right click here and select pocket/receptor pocket.
2. Right click here and select center.
1. Display ligand.
4. Click here to make a slide


Prepare HTML text for the molecular document.
1. File/New.
2. Click on the Html tab.
3. Enter name of document.
4. Click OK


Add text to the Html document (1).
2. Right click in the white space select Edit.


Add text to the Html document (2).
2. Use the formatting tools here.
The Crystal Structure of the Pim1 Kinase
1. Type text here. Make sure you are in Edit mode (see below)
3. Toggle between View, Edit and Source mode.



#endif

23.4 Working with PDB Structures

Overview

This lesson will take you through the basics of reading and displaying PDB structures and their conversion into ICM objects. Topics covered include:

- `Loading a PDB structure.`
- `Converting a PDB structure into an ICM object.`

23.4.1 PDB Searching

Objective

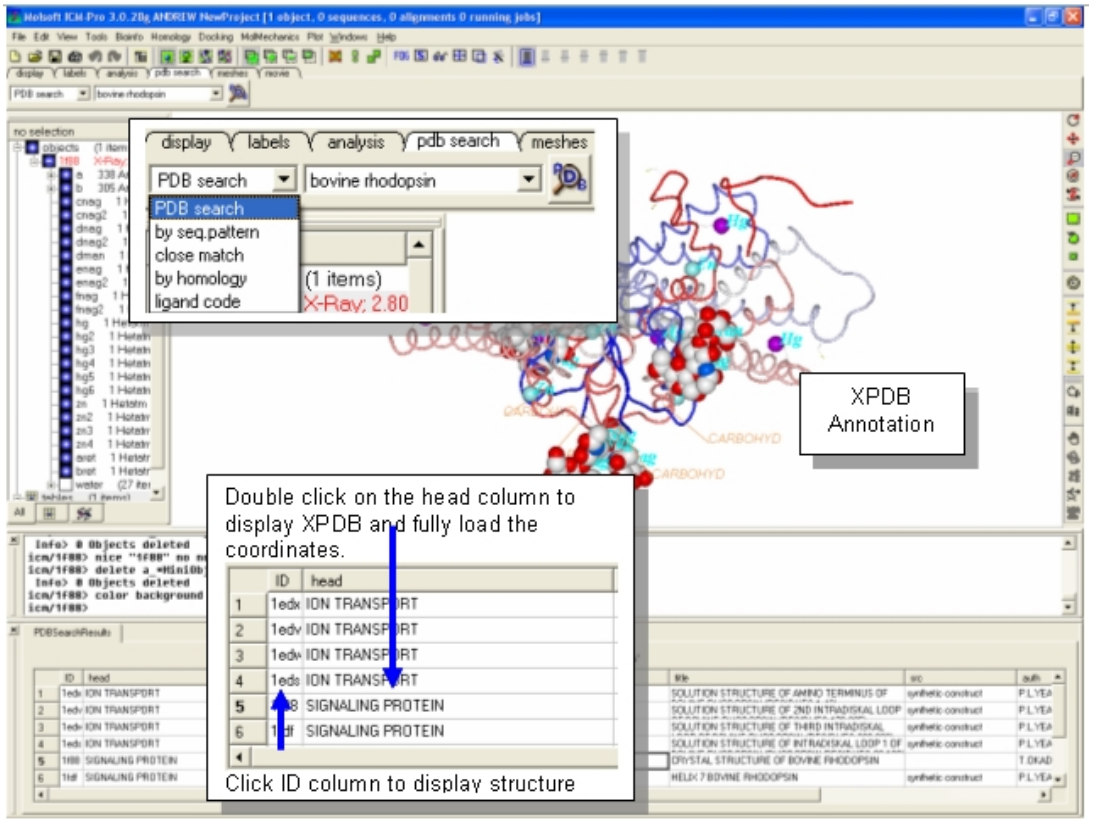
To display the crystal structure of a G−Protein Coupled Receptor (GPCR).

Background

Using ICM it is easy to quickly search and download PDB files using the .pdb search. tab.

Instructions

1. Click on the PDB Search Tab
2. Type **bovine rhodopsin** into the search box and click the button next to it. A table of hits will be displayed at the bottom of the GUI.
3. Double click on the ID field of structure 1F88 to display the structure.



Notes and things to try:

- Try searching for a PDB file by sequence or homology. Use the drop down menu next to the PDB search box to define which kind of search you are undertaking.

Manual References (Web Links)

`Finding a PDB Structure`

23.4.2 Converting a PDB File into an ICM Object

Objective

To convert a PDB file into an ICM object.

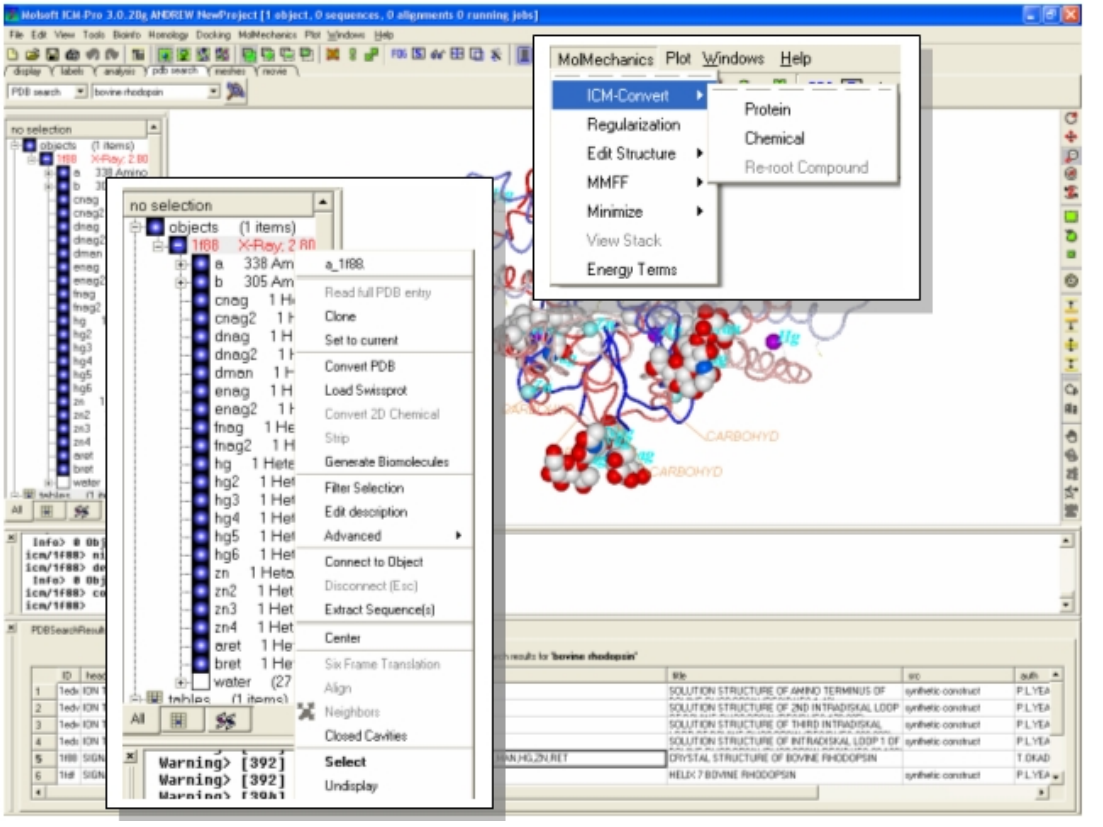
Background

Sometimes it is necessary to have a PDB file in the form of an ICM molecular object. For example, it's a convenient way to list and/or to change a torsion angle (or a series of them). It is also necessary to convert PDB files into ICM objects for ICM functions such as docking. There are two principally different modes of conversion. In the default mode the program looks at the residue name and tries to find a full−atom description of this residue in the icm.res file. This search is suppressed with the exact option. Hydrogen atoms will be added if the converted residues are known to the program and described in the icm.res library.

Instructions

To convert a PDB file into an ICM object (**IMPORTANT Do not use this method for small molecules (sdf, mol, mol2) use MolMechanics/ICM−Convert/Chemical) :

- Right click on the PDB file name in the ICM Workspace and select **Convert PDB** OR select **MolMechanics/ICM−Convert/Protein**

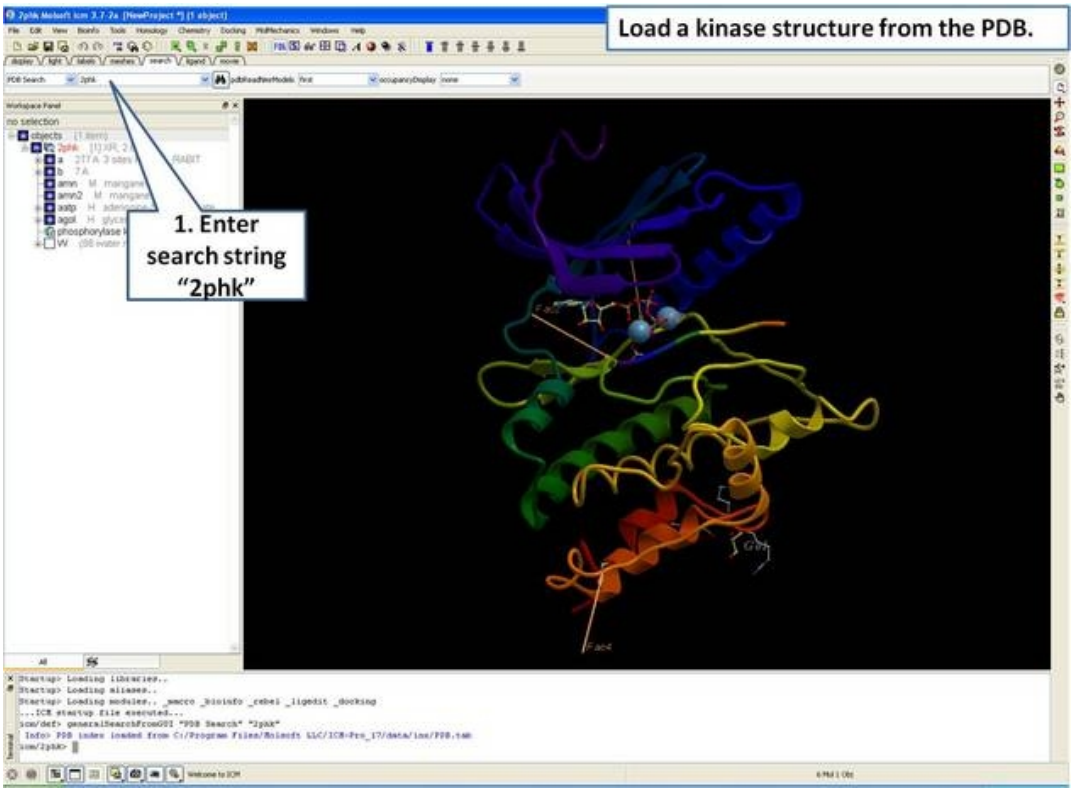


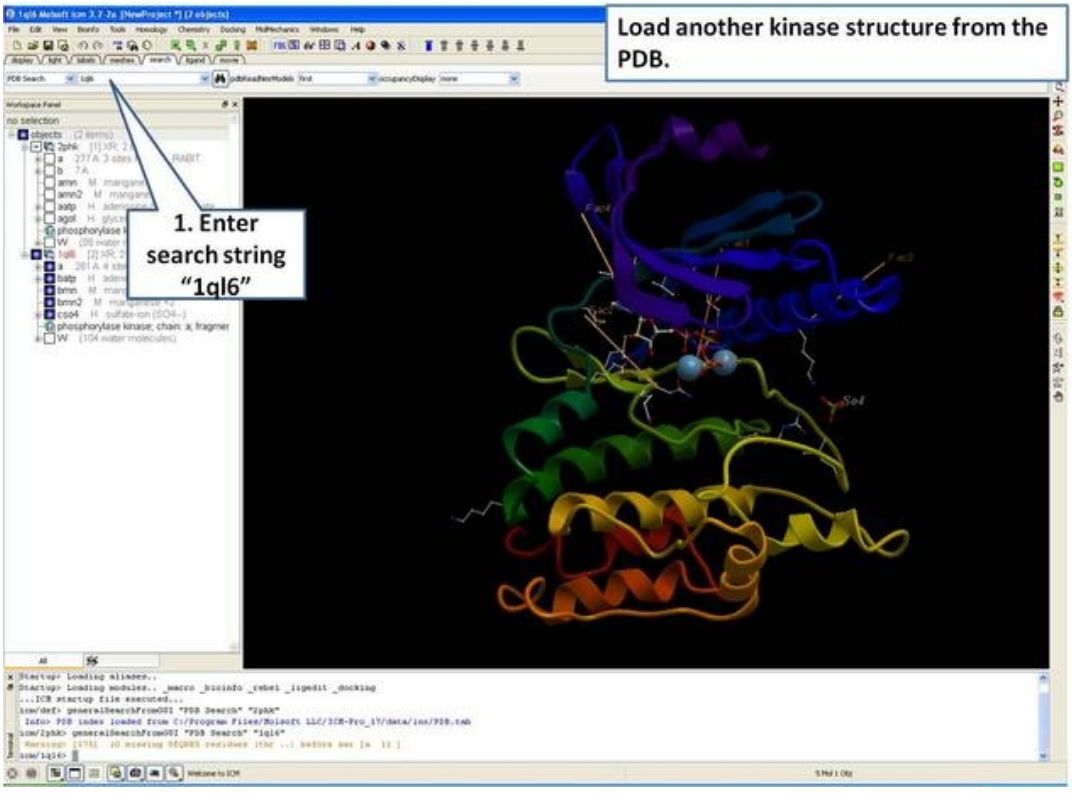
Notes and things to try:

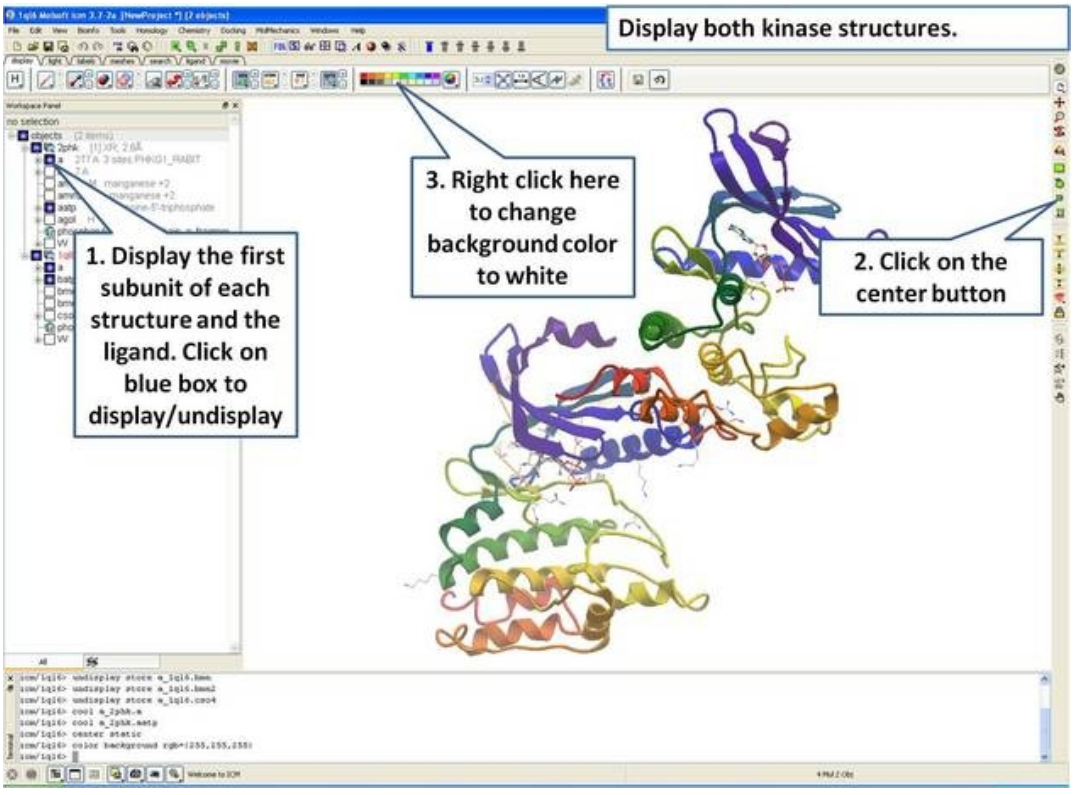
- Within the right click menu there are many other useful options such as: clone− which copies the current object; set to current − if multiple structures are loaded you can set this object to be the current one; Extract Sequence(s) . extracts the sequence of the whole object or the subunit depending where you click. Experiment with some of these options.
- The ICM workspace will tell you whether a structure is an X−Ray or an ICM object.

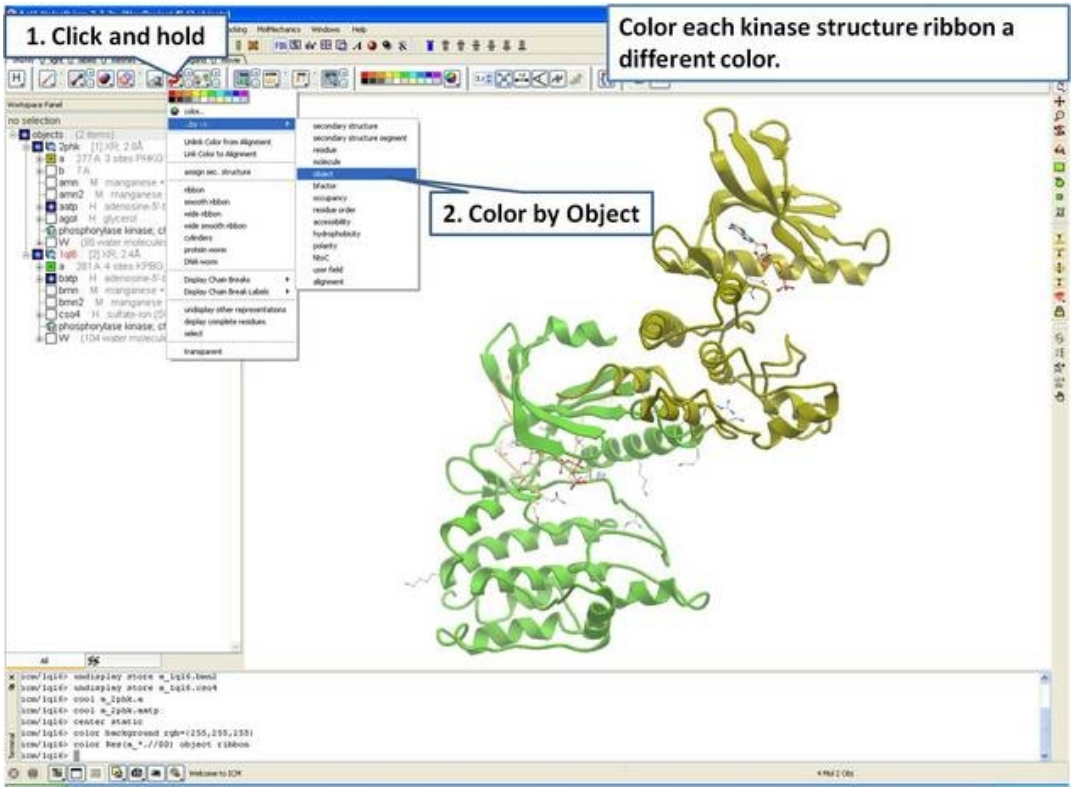
23.5 Sequence and Alignment Tutorial

23.5.1 Load and Display Protein Kinase Structures

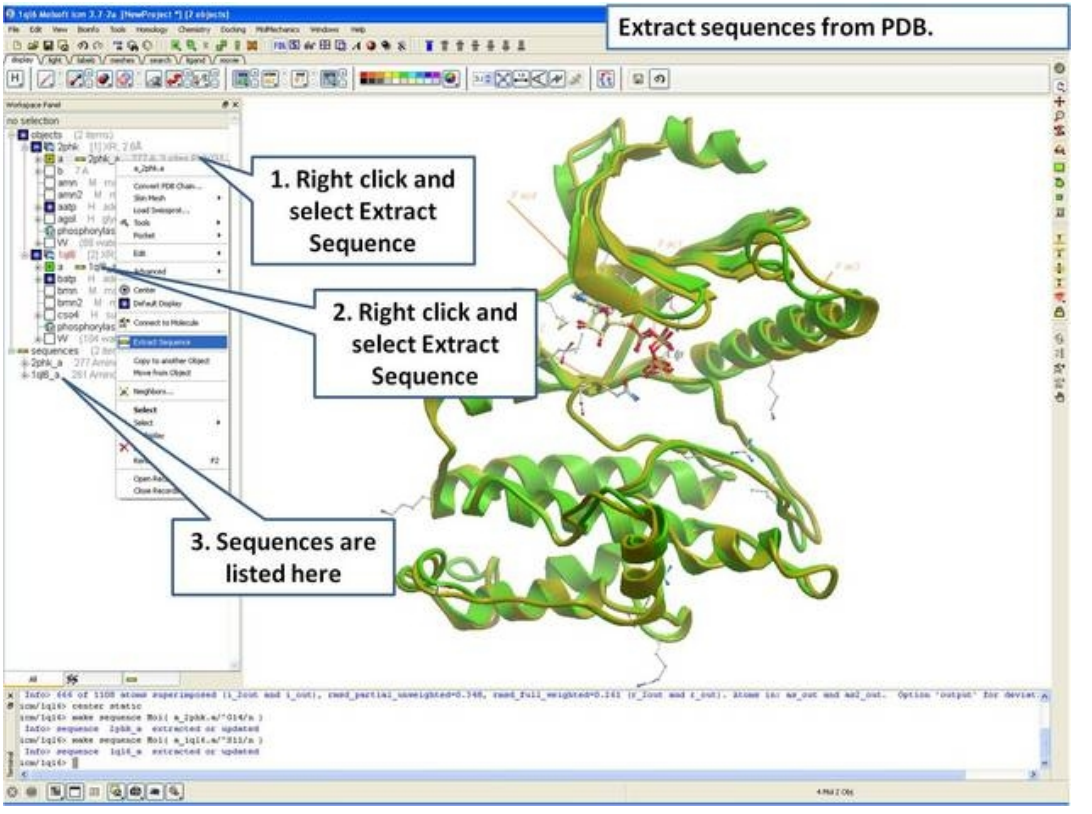

Load a kinase structure from the PDB.
1. Enter search string "2phk"

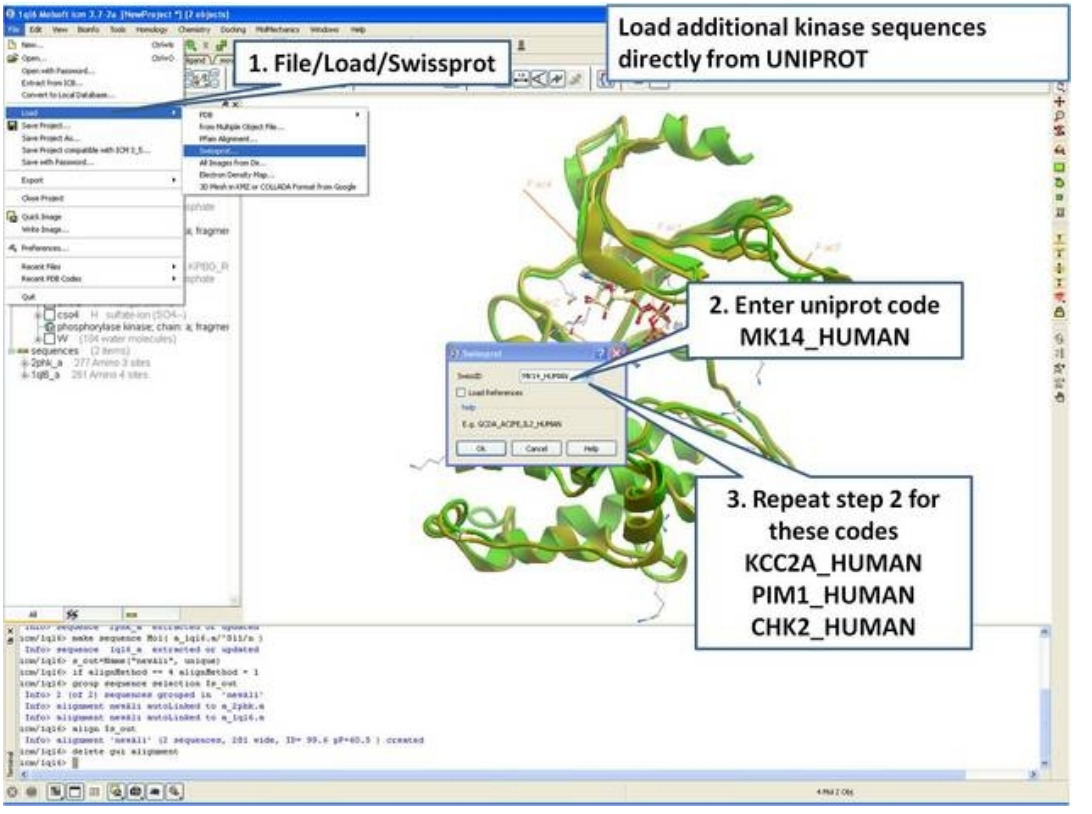

Load another kinase structure from the PDB.
1. Enter search string "1ql6"

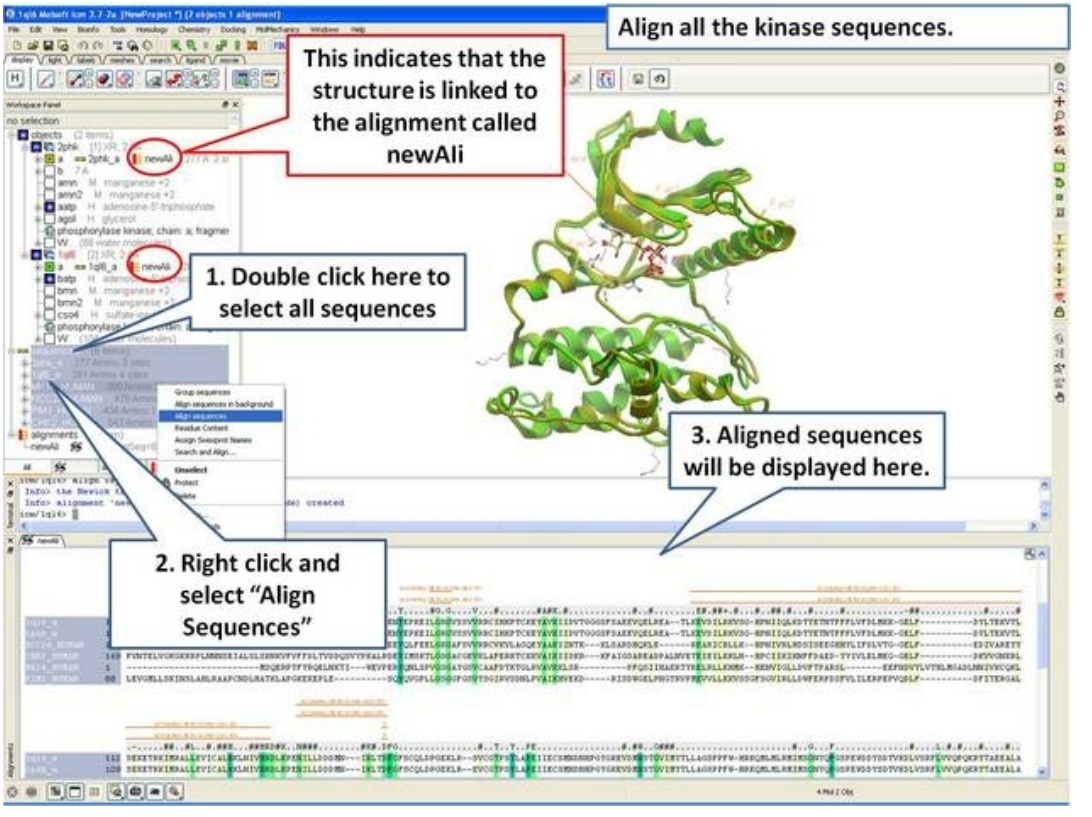

Display both kinase structures.
3. Right click here to change background color to white
1. Display the first subunit of each structure and the ligand. Click on blue box to display/undisplay
2. Click on the center button


1. Click and hold
Color each kinase structure ribbon a different color.
2. Color by Object

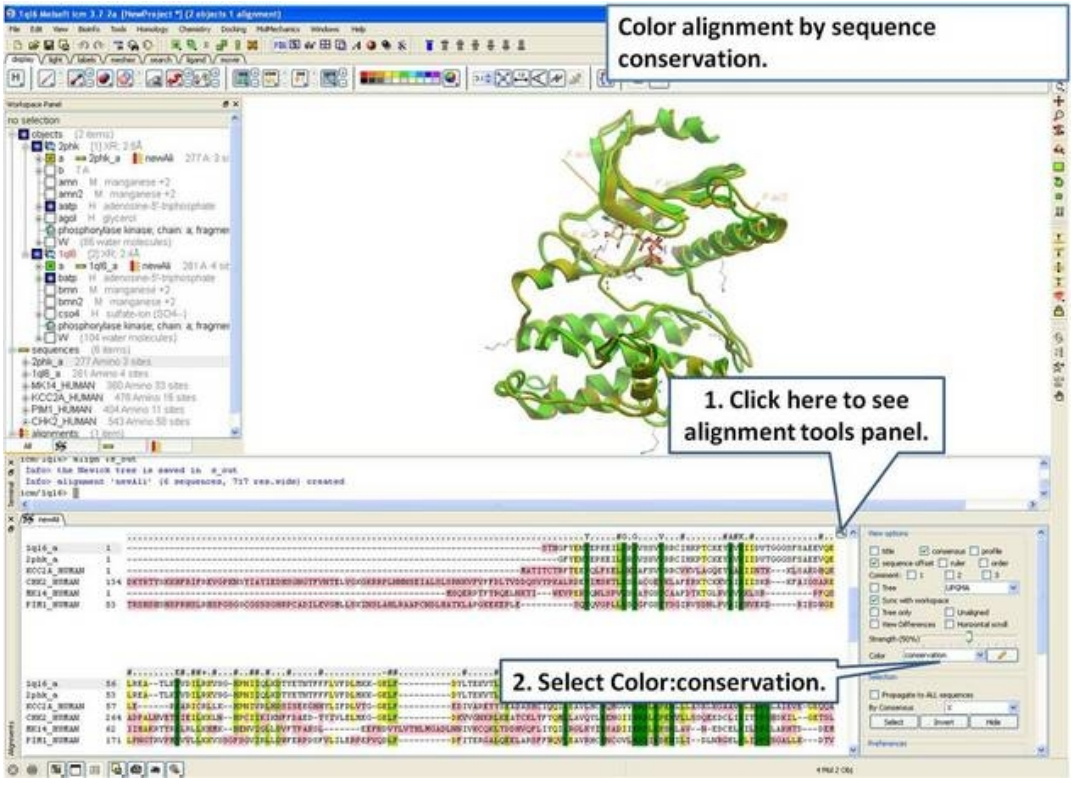
23.5.2 Extract Sequences from PDB Structures and Load New Sequences from UniProt

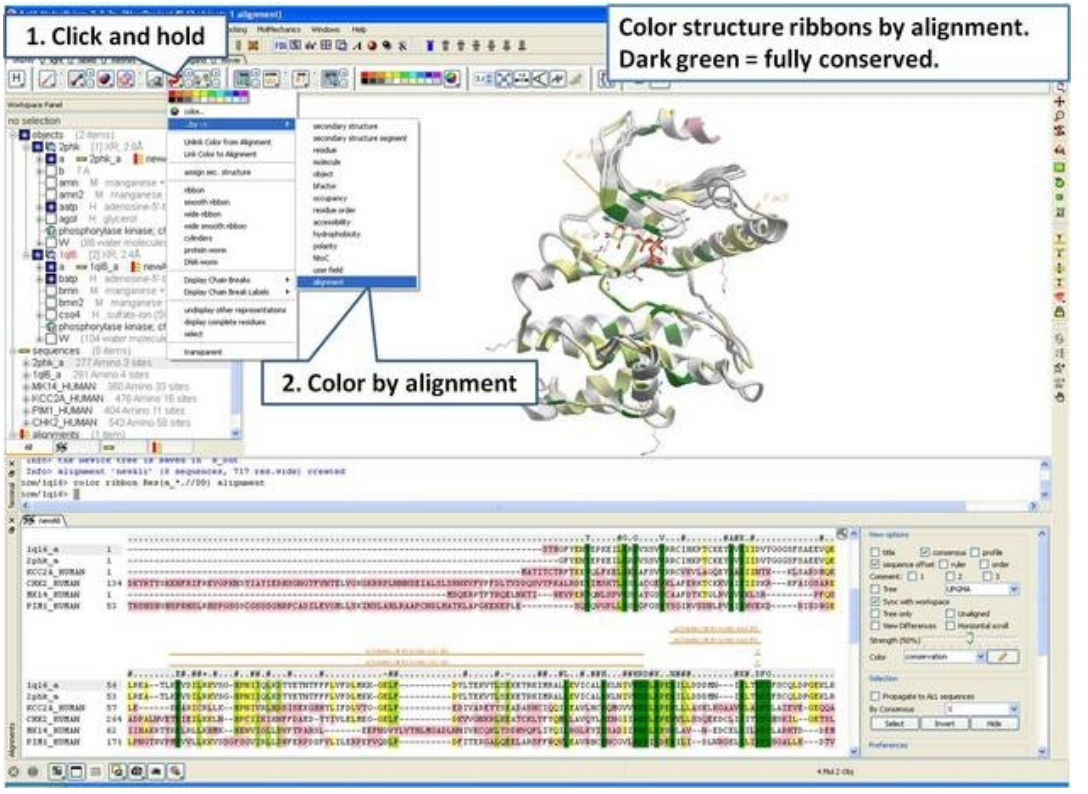




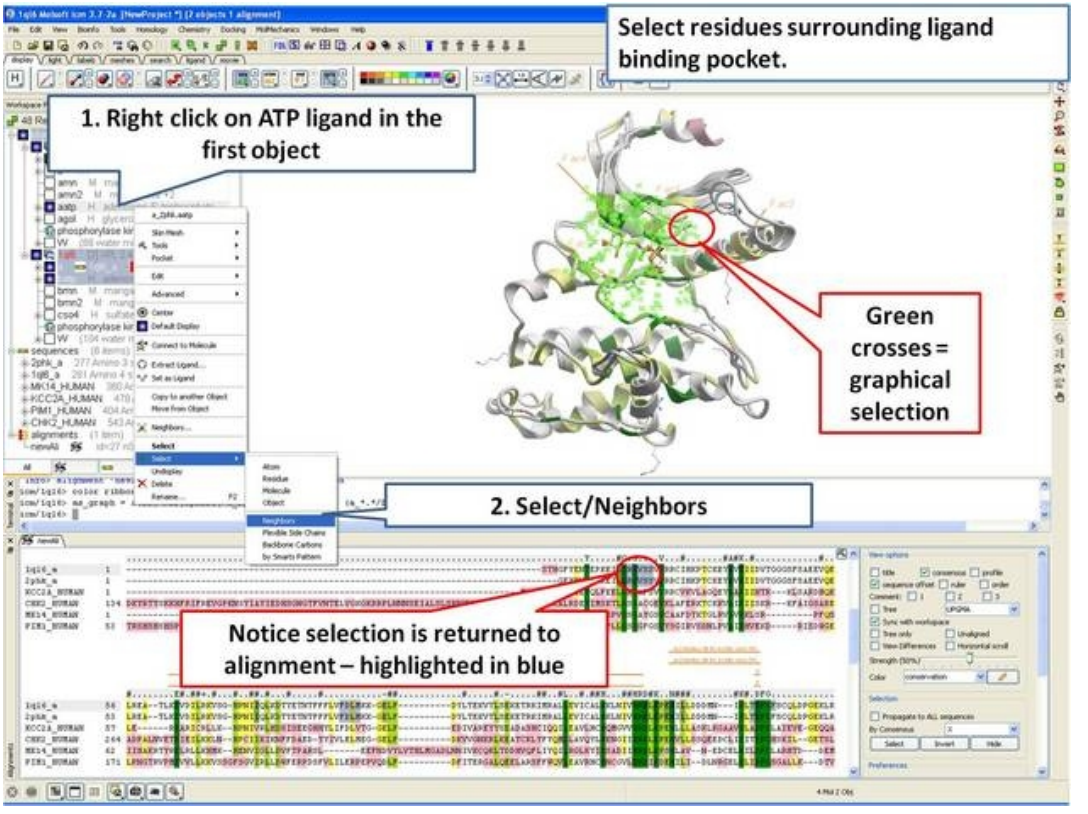


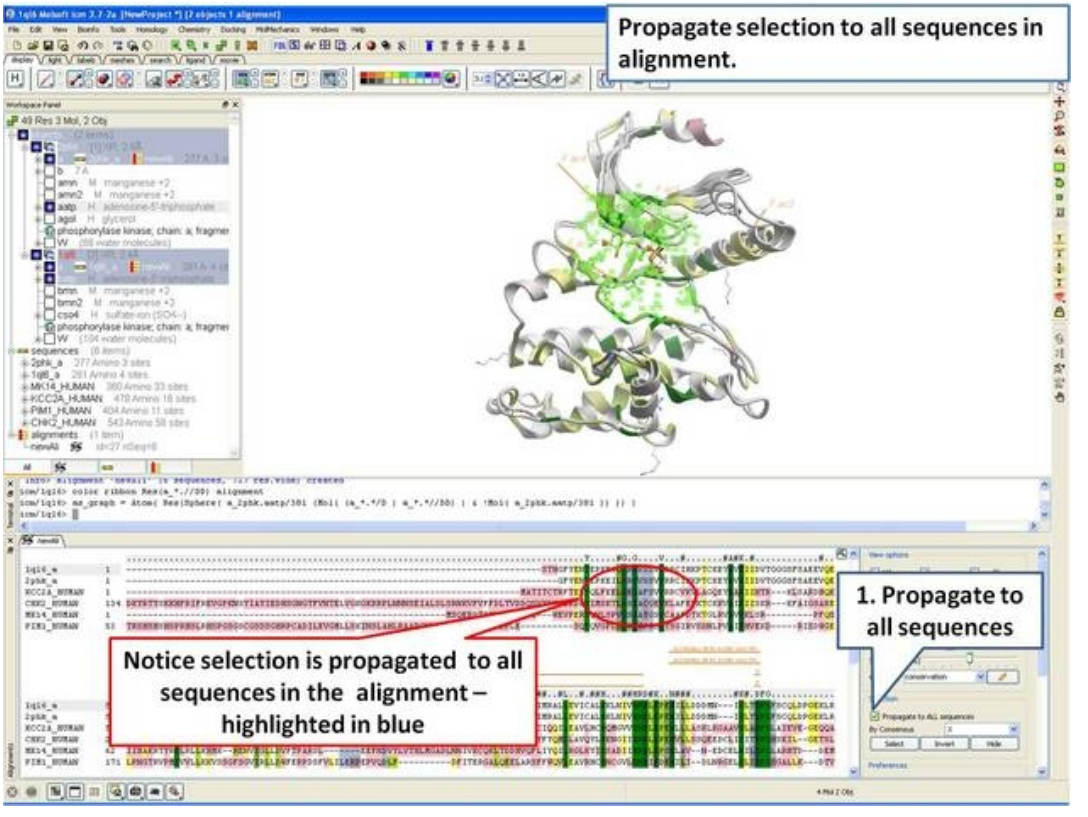
23.5.3 Linking Sequence Alignment to Structure

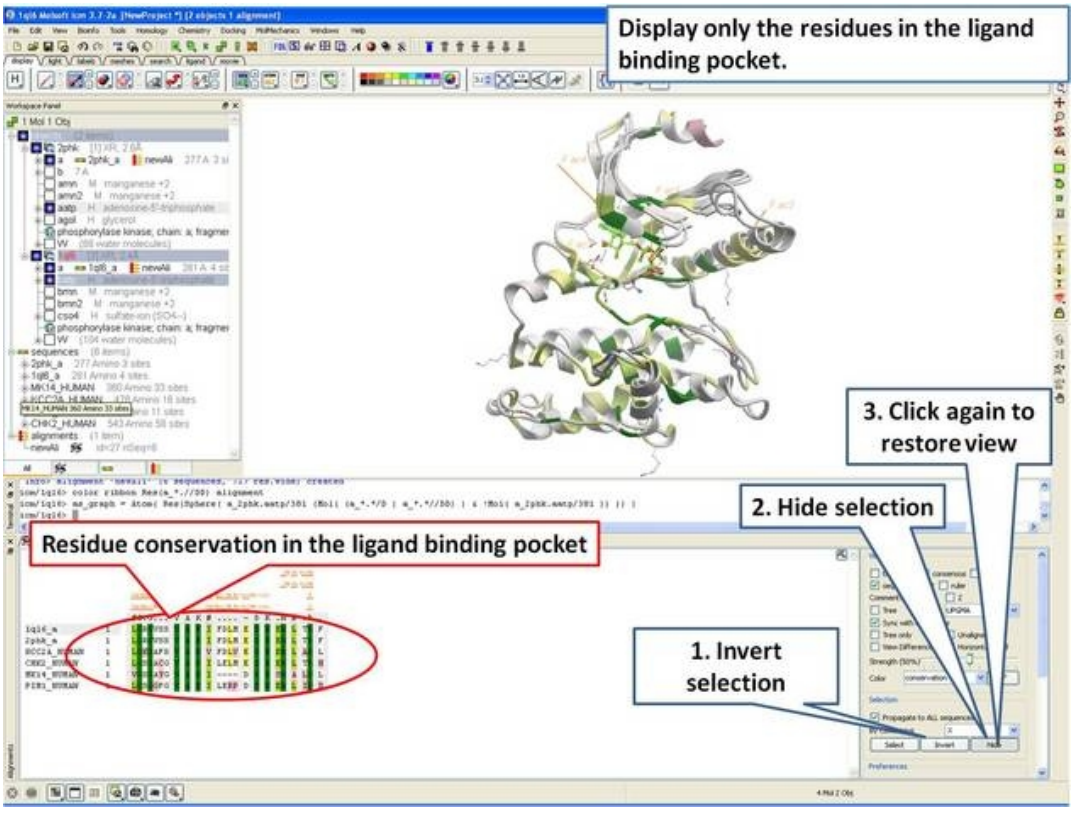


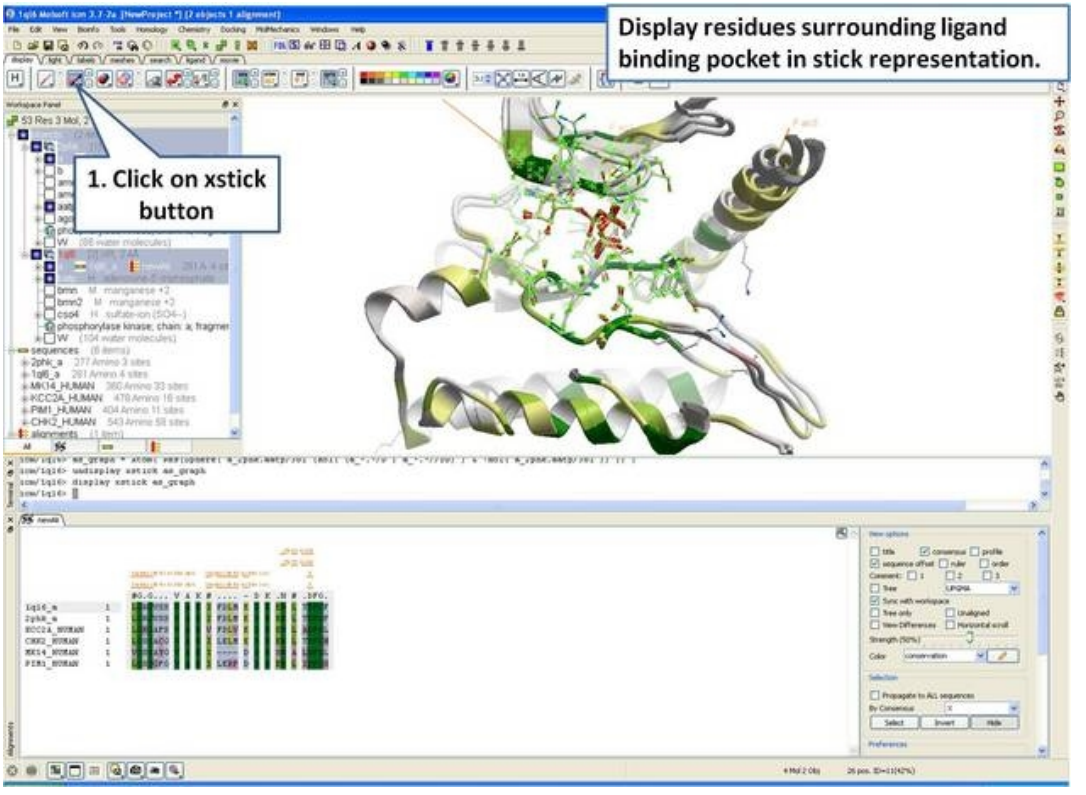


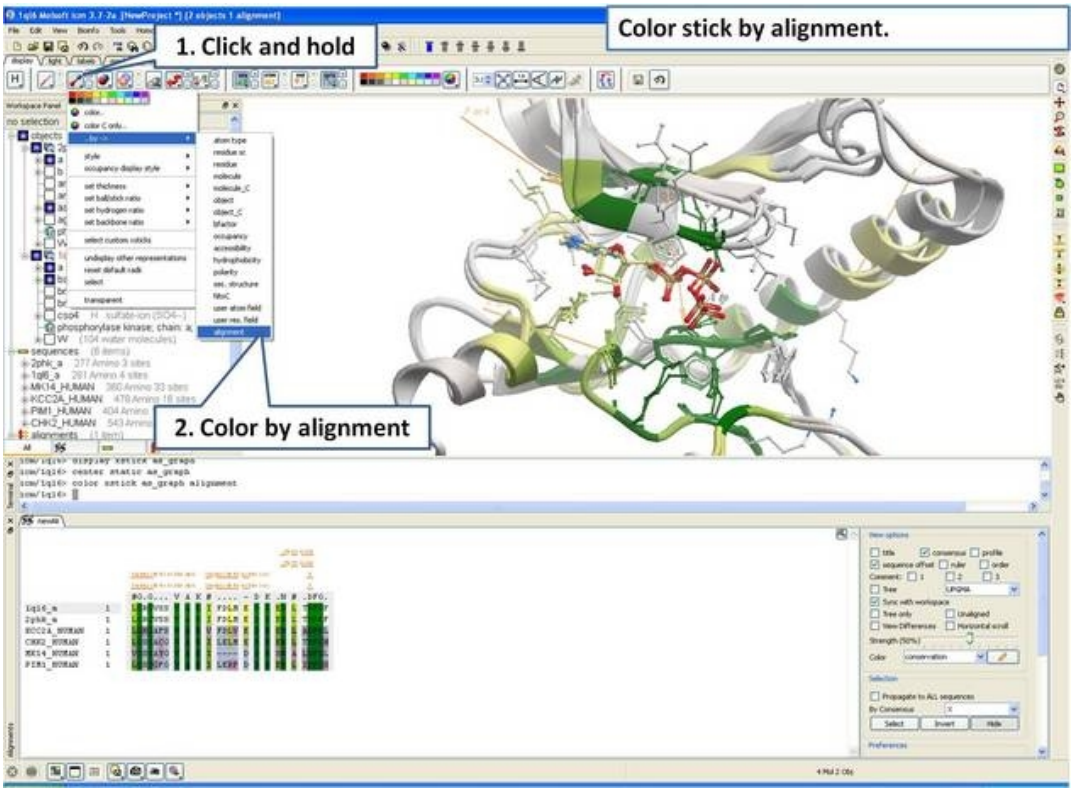
23.5.4 Identify Sequence Conservation in Ligand Binding Pocket


Select residues surrounding ligand binding pocket.
1. Right click on ATP ligand in the first object
Green crosses = graphical selection
2. Select/Neighbors
Notice selection is returned to alignment – highlighted in blue


Propagate selection to all sequences in alignment.
1. Propagate to all sequences
Notice selection is propagated to all sequences in the alignment – highlighted in blue


Display only the residues in the ligand binding pocket.
3. Click again to restore view
2. Hide selection
Residue conservation in the ligand binding pocket
1. Invert selection


Display residues surrounding ligand binding pocket in stick representation.
1. Click on xstick button



23.6 Ligand Binding Pocket Analysis Examples

The examples covered here include:

`Displaying only the residues that surround the ligand binding pocket.`

`Displaying sequence conservation around the ligand binding pocket`

`Displaying hydrogen bonds between a ligand and the receptor`

23.6.1 Displaying only the residues that surround the ligand binding pocket.

There is a quick and easy way to do this as described in the Tips section of the manual entitled `"Quick Binding Pocket Display"` or you may want to follow the instructions below for a more user−defined method.

- Double click on the ligand name in the ICM workspace and it will be highlighted in blue.
- Right click on the name and select the Neighbors option.
- Enter 6ï¿½ (or whatever distance is appropriate for the ligand) for the sphere radius selection. Green crosses represent selected residues.
- Select type from the drop down menu "same_object_other_chains".
- Convert your selection to a residue selection if you wish using the button shown in the example below.
- Go to the display tab and select the representation you would like for the residues surrounding the pocket. Next use the "Invert Graphical Selection" `button` to select everything else other than the residues around the pocket and undisplay them by clicking on the representation buttons in the display tab.

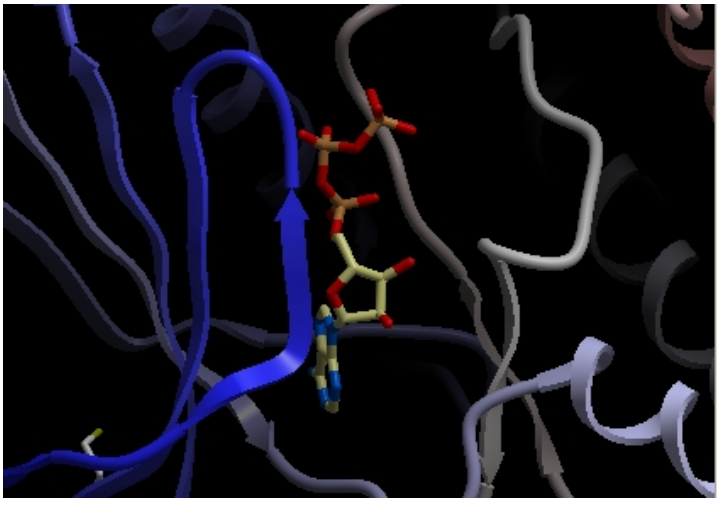
For example if your structure is shown in ribbon you and you wanted to display the surrounding residues in xstick and udisplay the rest of the structure you would do the following.

- Select the residues around the pocket using the spherical selection method as described above.
- Select the xstick representation button in the display panel

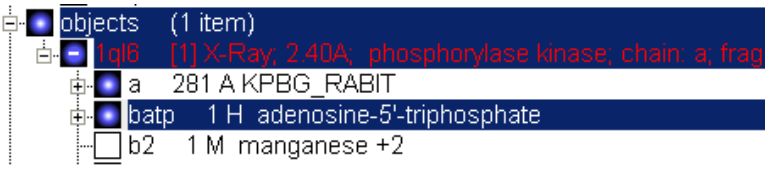
- Select the invert selection button
- Select the ribbon display button and the ribbon display will be removed from outside the pocket.

Steps shown graphically below for the kinase 1ql6 and the atp ligand.

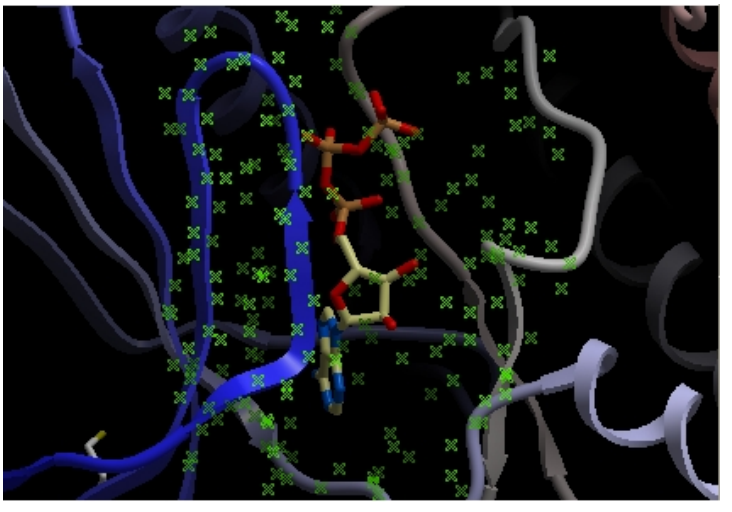
Step 1: Receptor (1ql6.a) is in ribbon display:



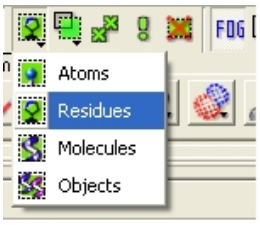
Step 2: Double click and select the atp molecule in the ICM Workspace



Step 3: Right click on the selected atp molecule in the ICM Workspace and select Neighbors. Enter radius and type of selection. Click OK and you will see a graphical selection of green crosses around the pocket.

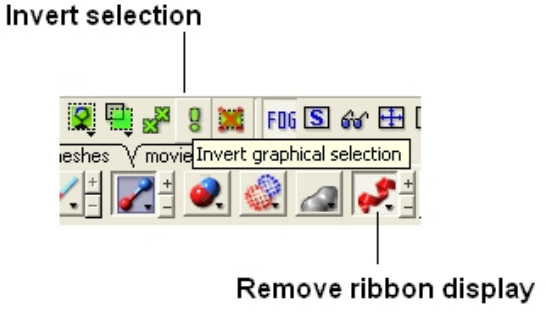


Step 4: Convert your selection to a residue selection if you wish. You will then see green "R" in the graphical selection rather than green crosses.



Step 5: Select the xstick representation and the residues around the ligand will be displayed.

Step:6: If you want to undisplay the rest of the receptor outside the pocket use the invert selection button and then click the ribbon representation button.

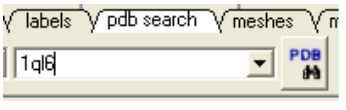


23.6.2 Displaying the sequence conservation around the ligand binding site.

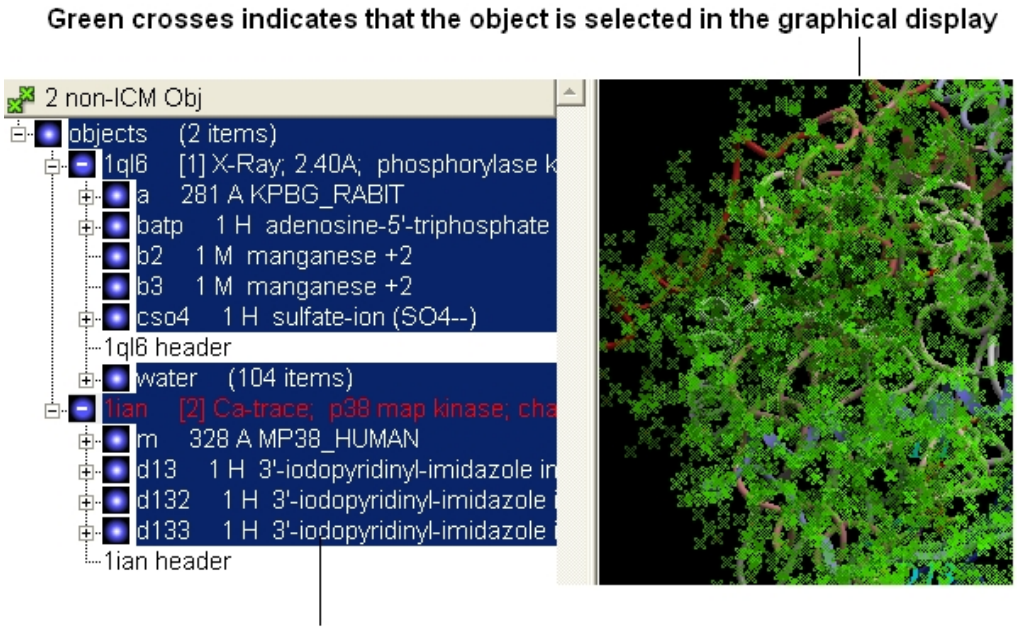
Here is an example on how to superimpose the structures of two proteins and display the sequence conservation around the ligand binding pocket.

PDB Search

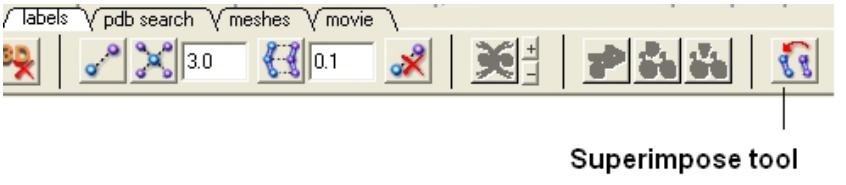
- PDB Search Tab 1ql6
- PDB Search Tab 1ian



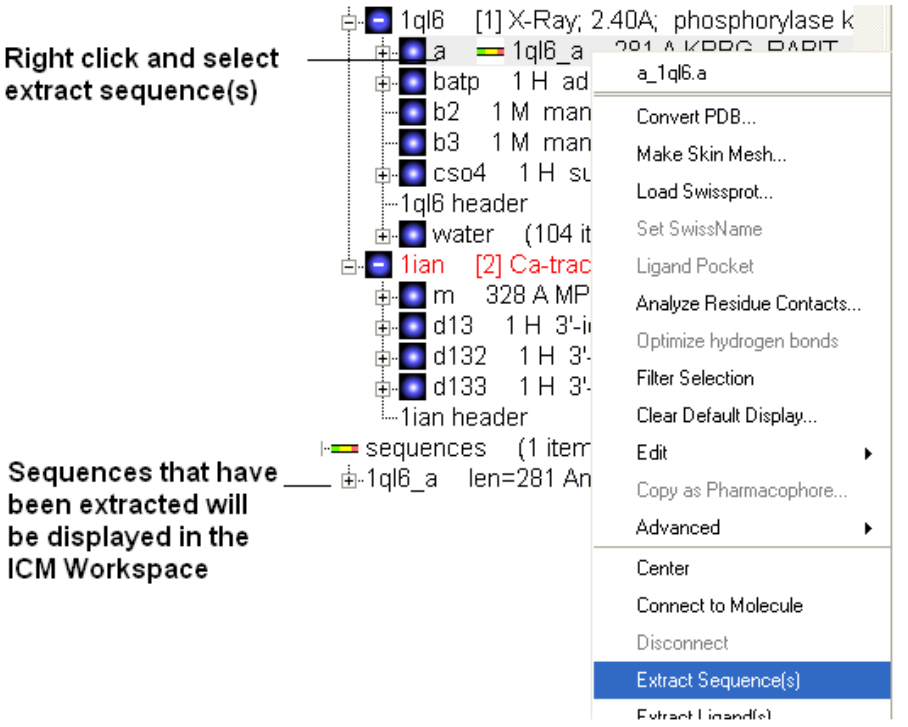
- Select both receptors by double clicking on the name of the receptor in the ICM Workspace. To select two receptors use the Ctrl button or use the shift button to select a range of objects in the ICM Workspace. A receptor which is selected will be highlighted in blue in the ICM Workspace and with green crosses in the graphical display.



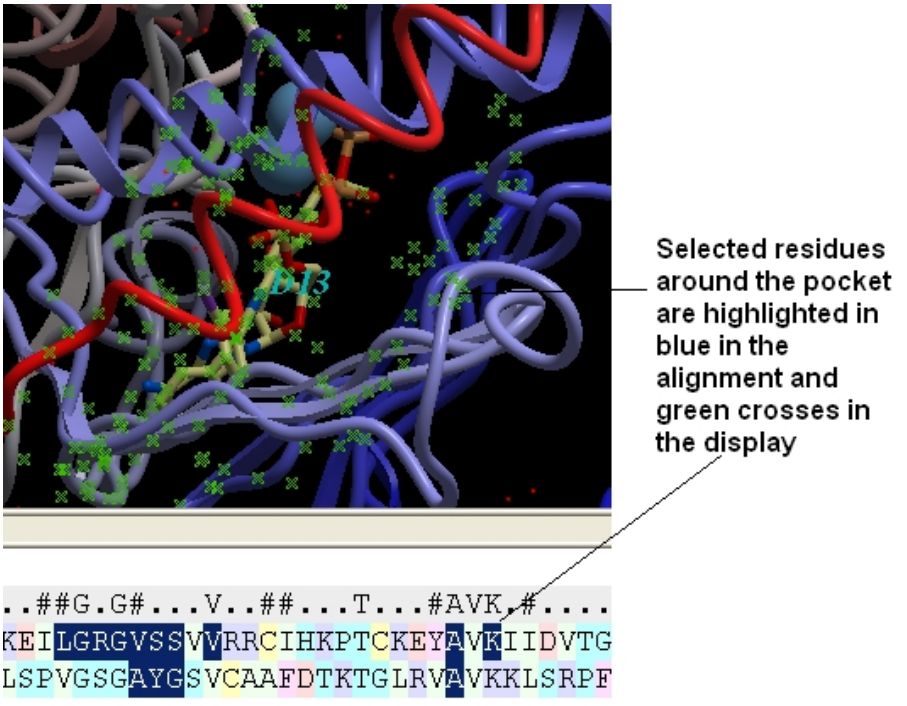
- Superimpose both structures by clicking on the **display** tab and selecting the superimpose button.



- Now that the structures are superimposed we can unselect everything − to do this right click and drag in blank space in the graphical display or double click in white space in the ICM Workspace or use the `unselect button` green box with red cross through it.
- Now extract the sequence information from each protein. To do this right click on the molecule "a" of 1ql6 and molecule "m" of 1ian. and select extract sequences. Once the sequences have been extracted you should see the sequence in the ICM Workspace entitled 1ql6_a and 1ian_m

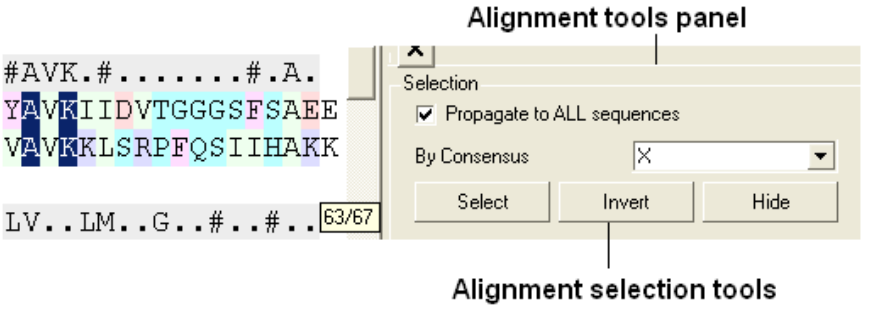


- Now align the sequences by selecting both sequences right clicking and selecting Align sequences. An alignment will be displayed at the bottom of the graphical user interface.
- Next we need to select the ligand ATP and select a sphere of residues around the ligand. To do this double click on the ATP molecule in 1ql6 (batp) in the ICM Workspace. You should see green crosses in the graphical display. Right click on the ATP molecule in the ICM Workspace and select neighbors. Enter a value of 6A for the radius. Select all_objects for the type of selection. Click ok and you should see a cluster of green crosses in the two proteins around the ligand and selected residues will be highlighted in blue in the alignment.



- Right click in white space in the alignment and select display tools panel.
- In the alignment tools panel select propogate to all sequences.
- Select the "invert" button to invert the current selection.

- Select the "hide" button to hide the current selection and you will be left with the residues surrounding the binding pocket in the alignment.

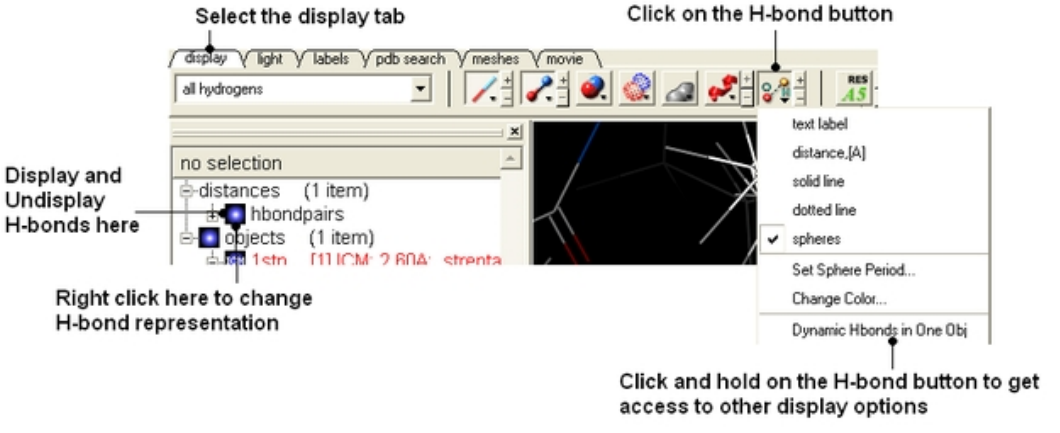


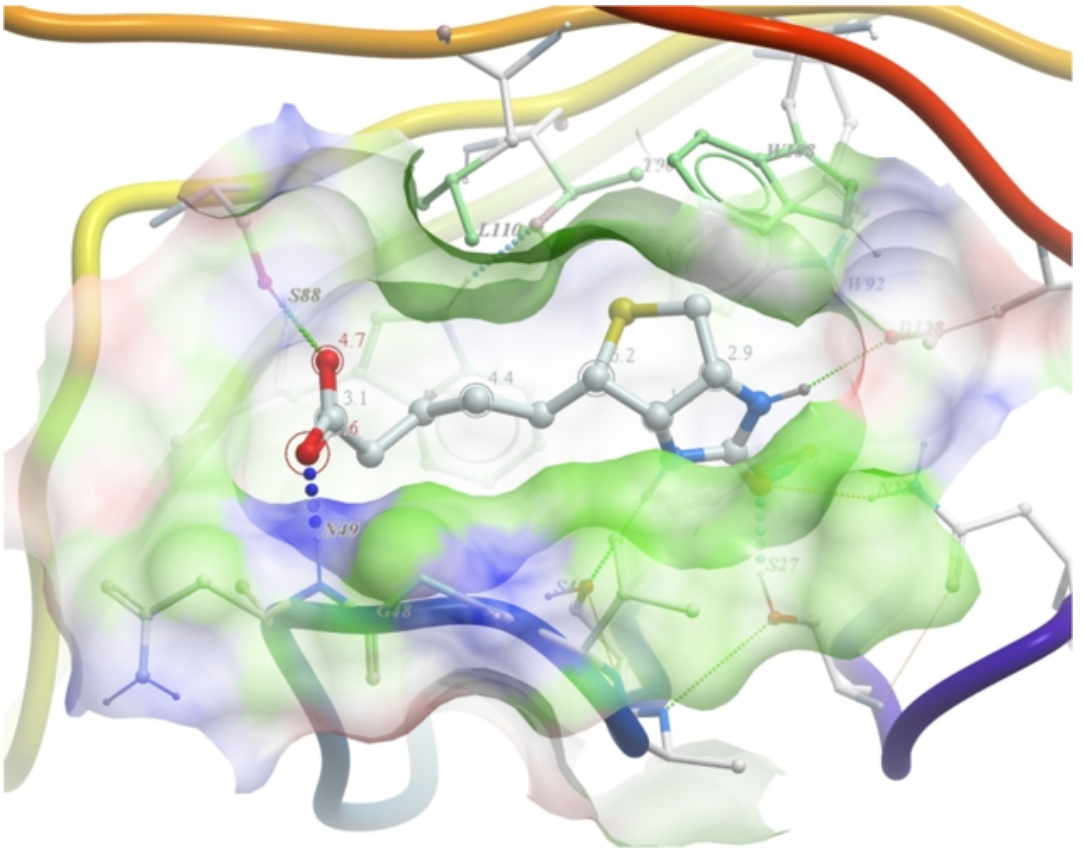
NOTE: Please note that all alignments are linked with structure therefore selections can be made in the alignment. Also as an example structure can be colored according to the color in the alignment which is useful for identifying conserved regions.

23.6.3 Displaying hydrogen bonds between a ligand and receptor.

NOTE: The method by which hydrogen bonds are calculated is described `here` in the command line manual. The GRAPHICS.hbondMinStrength parameter determines the hbond strength threshold for hbond display. The strength value is between 0. and 2. By changing 1. to 0.2 you will see more weak hydrogen bonds.

- As an example we will use the PDB structure 1STP. Type 1STP in the pdb search tab and press return.
- In order to display energy related properties we need to convert the PDB file into an ICM object. To convert 1STP into an ICM object follow the instructions Converting a Protein into an ICM Object. In this example, the option "Replace the Original" was selected.
- Display the receptor in wire format and the ligand in xstick.
- Right click on the ligand and select "Neighbors" − Enter 3 Angstroms and Type = Visible. Do not exclude source (the ligand) therefore remove tick from box entitled "exclude source".
- Select the display tab and then select the Display H−Bond button.





NOTE: Different options for displaying the H−bond can be accessed by clicking and holding on the H−bond button in the "Display" tab.

23.7 Homology Modeling and Structure Analysis Tools

Overview

This lesson will take you through the basics of protein modeling. Topics include:

- Building a homology model.
- Linked alignments and structures.
- Protein health and regularization.
- Protein folding and structure prediction.

Background

ICM has an excellent record in building accurate models by homology. The ICM modeling procedure builds the framework, shakes up the side−chains and loops by global energy optimization. You can also color the model by local reliability to identify the potentially wrong parts of the model. ICM also offers a fast and completely automated method to build a model by homology and extract the best fitting loops from a database of all known loops. It just takes a few seconds to build a complete model by homology with loops. Some selected publications related to modeling and structure determination are listed here.

Abagyan, R.A., and Totrov, M.M. (1994). Biased Probability Monte Carlo Conformational Searches and Electrostatic Calculations for Peptides and Proteins. J. Mol. Biol., 235, 983−1002

Cardozo, T., Totrov, M., and Abagyan, R. (1995). Homology modeling by the ICM method. Proteins: Structure, Function, Genetics, 23, 403−414

Abagyan, R., and Totrov, M. (1999). Ab initio folding of peptides by the optimal−bias Monte Carlo minimization procedure. Journal of Computational Physics, 151, 402−421

Maiorov, V.N., and Abagyan, R.A. (1997). A new method for modeling large−scale rearrangements of protein domains. Proteins, 27, 410−424

Schapira, M., Totrov, M. and Abagyan, R. (2002). Structural Model of Nicotinic Acetylcholine Receptor Isotypes Bound to cetylcholine and Nicotine. BMC Structural Biology 2:1

ICM also provides powerful tools for determining crystallographic symmetry and neighbors which allows the biological environment of a protein to be viewed and understood.

23.7.1 Homology Modeling

Objective

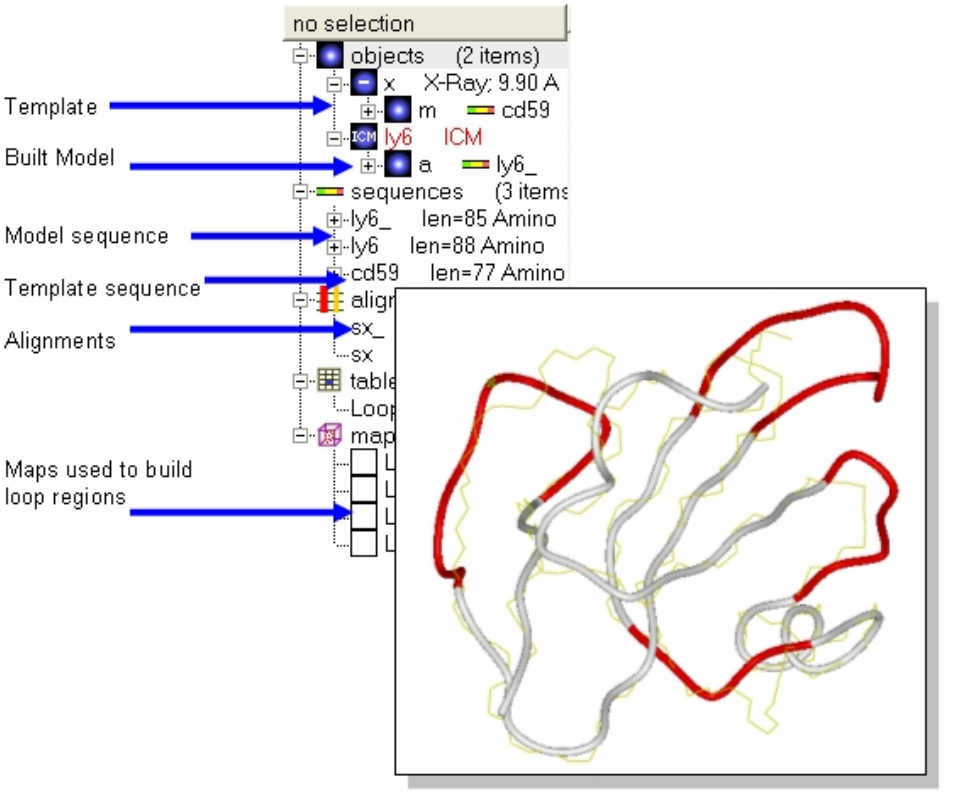
To make a protein model based on sequence homology.

Background

ICM has an excellent record in building accurate models by homology. The procedure will build the framework, shake up the side−chains and loops by global energy optimization. You can also color the model by local reliability to identify the potentially wrong parts of the model.

Instructions

1. Edit/Delete All . let us begin with a clear ICM session!
2. Homology/Load Example
3. Two sequences (ly6,CD59), one template structure (x) and an alignment (sx) should be loaded. Sequence CD59 is the sequence of the template structure called x.
4. Homology/Build Model and fill in the table using the drop down options. Warning minimize side−chains may take a few minutes.



Notes and things to try:

- The four built in loops are shown in red as default.
- Try displaying the model and the template in different colors or representations to observe any siginificant deviations between template and model.

Manual References (Web Links)

`Homology Modeling`

23.7.2 Linked Alignments and Structures

Objective

To select, display and label the conserved regions of the model.

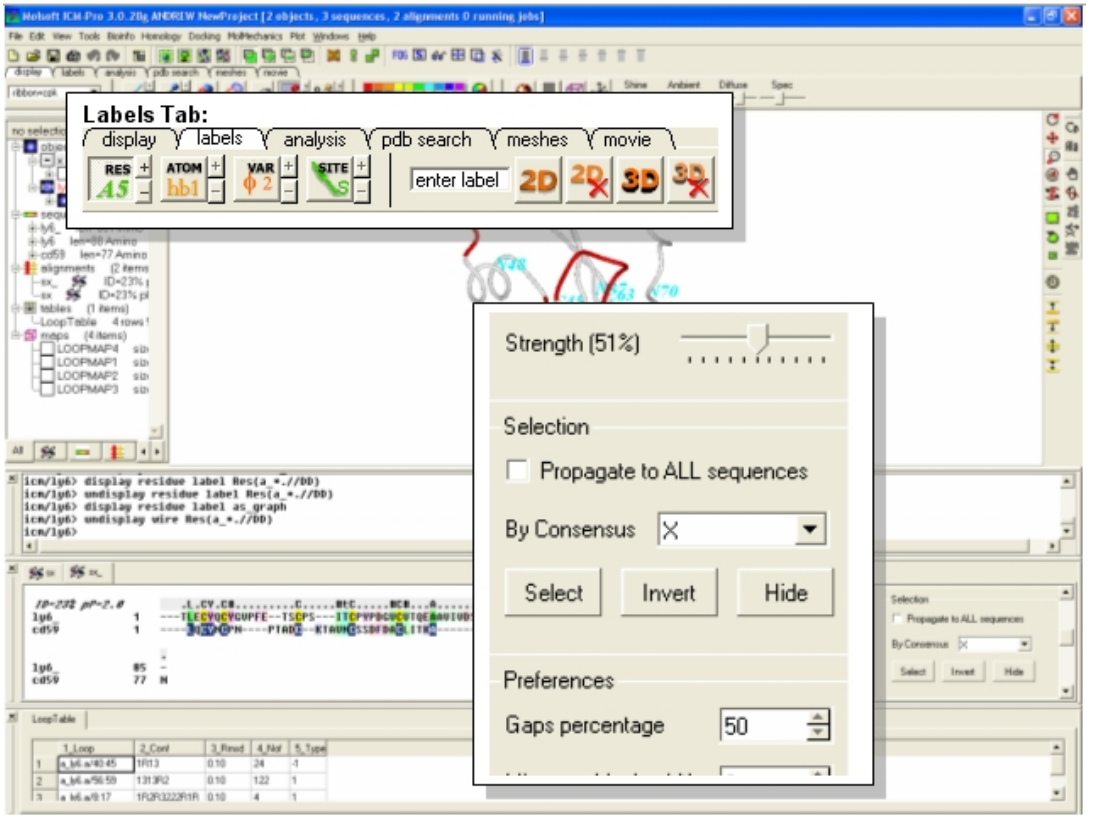
Background

Within the ICM Alignment Editor there is a rich array of tools. Some of these tools allow selections between a linked alignment and a structure. The strength of consensus can be changed and selections can be made according to a variety of criteria. There will be an alignment symbol next to a structure in the ICM Workspace if the structure is aligned.

Instructions

Using the alignment from the previous lesson we will display and label the conserved residues between our model and the template in CPK format.

1. Change the strength of the alignment consensus to 50% in the ICM Alignment Editor.
2. Type in the consensus you wish to select. For example if you only want to select identical residues between the template and model type in X. Other symbols (such as #) from the alignment consensus line can be entered here if desired. You may wish to play with this and the alignment consensus value.
3. Click on the Select button and the residues selected will be highlighted with green crosses.
4. To label the residues select the **display** tab and select the label residue button.



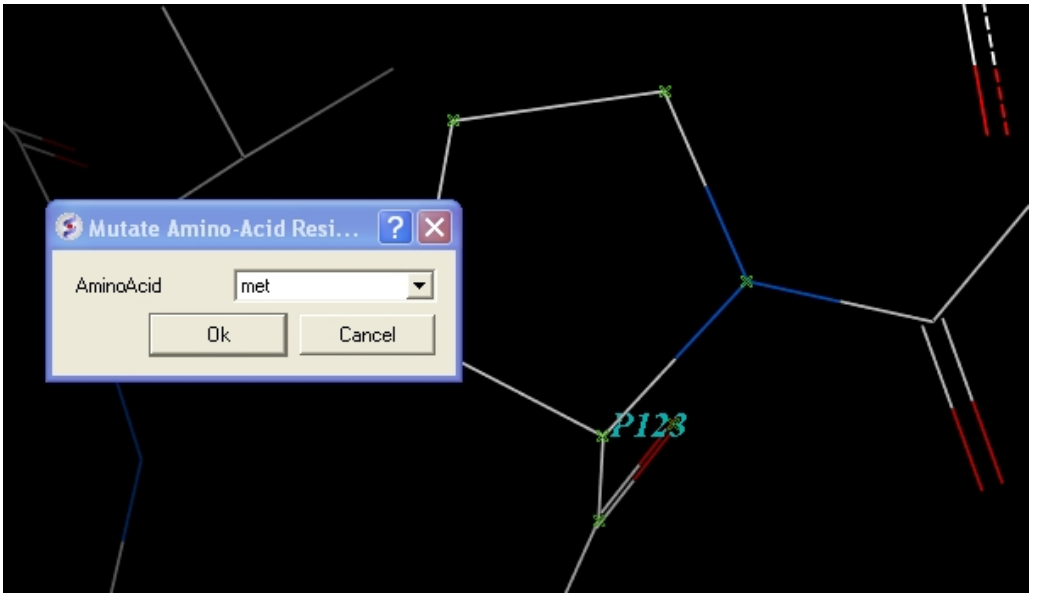
Manual References (Web Links)

`Alignment Editor`

23.7.3 Making an amino acid mutation

Background Pim1 is a unique protein kinase because it has a proline residue located in the hinge region which precludes the canonical second hydrogen bond between the hinge backbone and the adenine moiety of ATP. Mutants of Pim1 have been crystallized to see if mutating the proline residue can restore the ATP binding pocketed to that of a typical kinase. As an example we will make a P123M mutation of PIM1.

- Type pdb code **1yxu** into the PDB search tab.
- `Convert` the PDB file into an ICM object.
- `Select` residue number 123 in the "a" subunit
- Right click on the selection in the graphical workspace or ICM workspace and select Advanced/Mutate Amino−Acid
- Select Methionine from the drop down list.



- Now optimize the side chains surrounding the residue.
- Right click on Methionine 123 and select Neigbors/5A > Same Object `>include` source
- Right click on the selection and choose Advanced/Optimize Side Chains
- The higher the number of calls per variable the longer the simulation. The default number has been shown to provide an ideal simulation length. Press OK.
- MolMechanics/View Stack and look at the solutions ranked by energy by double clicking through the table.
- Compare your mutated structure with the crystal structure of PIM1 with the P123M mutation (PDB code 1yxs)

23.7.4 Protein Health

Objective

To remove clashes from a PDB structure.

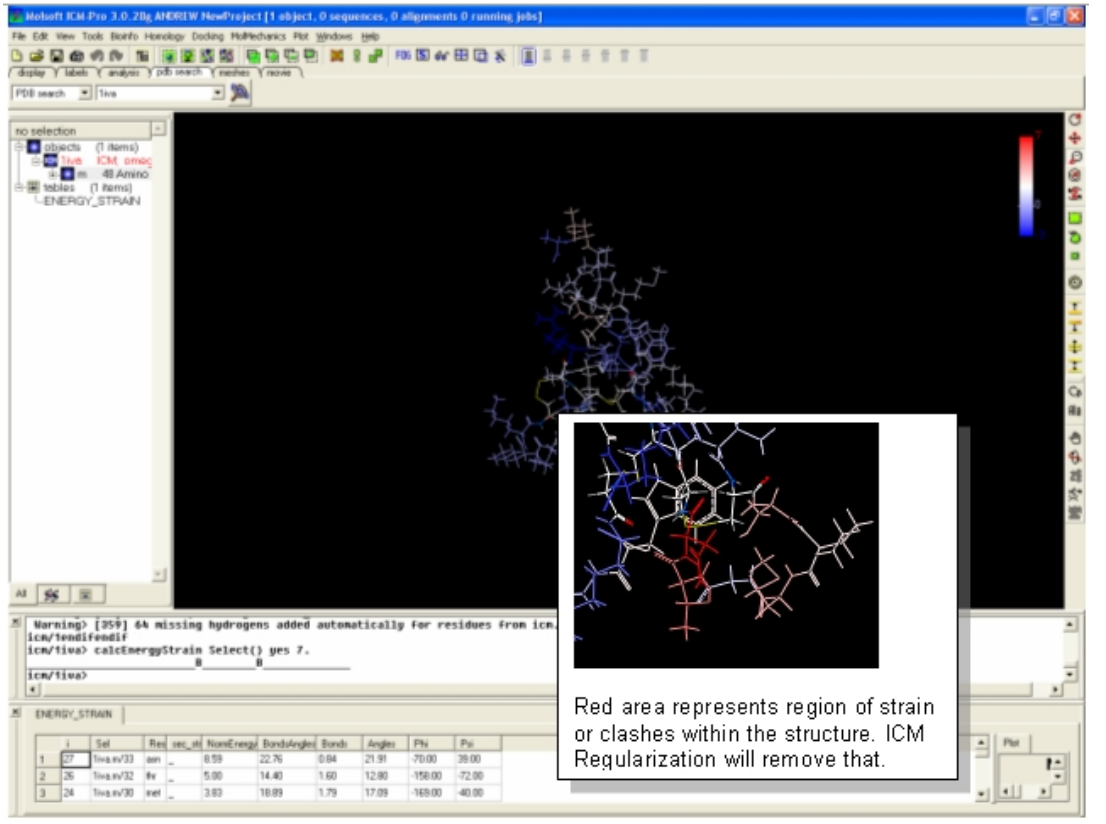
Background

Here we will use a macro that calculates the energy strain (Protein Health) within a protein structure. The macro is based on a paper by Maiorov and Abagyan (1998). The regularization macro will remove any clashes and improve the energy of the structure.

Instructions

1. Edit/Delete All . let us begin with a clear ICM session!
2. Search FOR and display the PDB structure 1iva (use PDB search tab).
3. Convert 1iva into an ICM object (see previous lesson or search for "convert")

4. Tools/3D Predict/Protein Health Note red coloring indicates clashes or high strain. Lets remove these clashes using the ICM regularization tool.
5. MolMechanics/Regularization
6. Color and display in wire − all clashes should have been removed.



Notes and Things To Try:

- Always use the Protein Health tool and ICM Regularization after you have constructed a protein model.
- It is always wise to check a protein structure from the PDB with the Protein Health tool and then use ICM Regularization to remove any potential problems you may identify.

23.7.5 Superimpose Structures

Objective

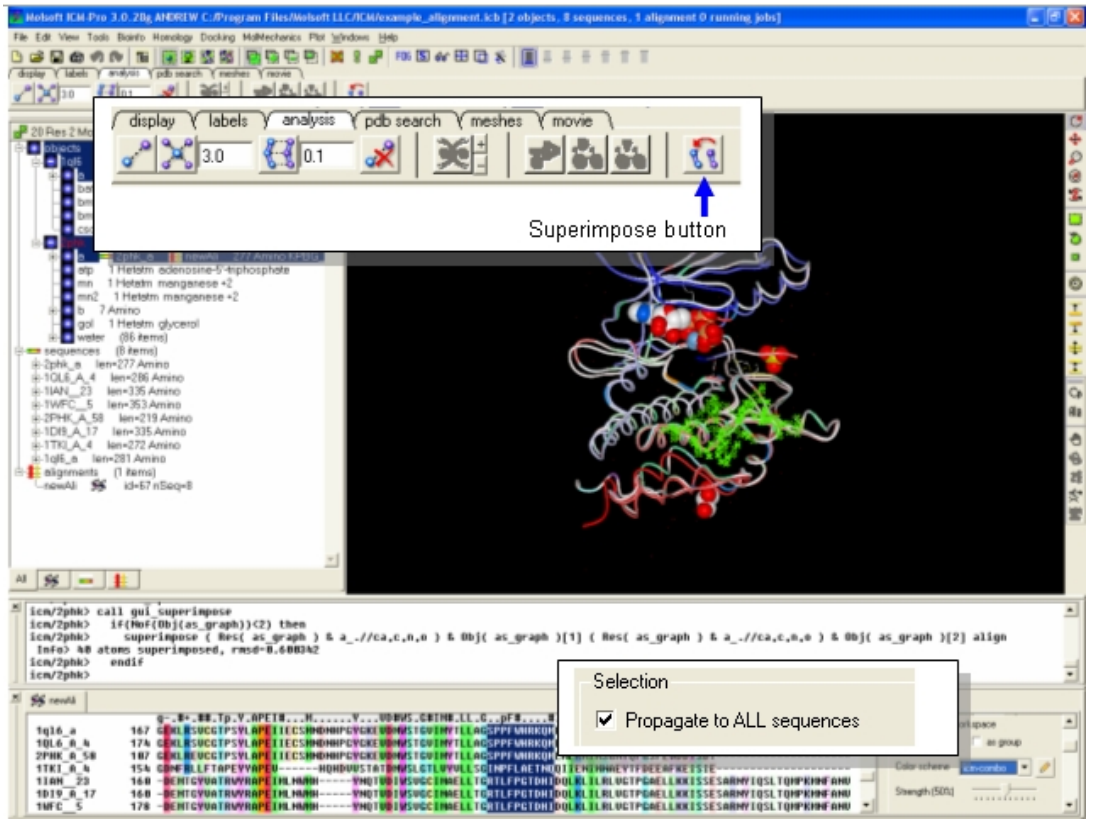
To superimpose two structures.

Background

In this lesson we demonstrate the use of a superposition based upon a sequence alignment. All superposition analyzes can be performed using the button available within the Analyses tab. The example here uses protein kinase structures to superimpose.

Instructions

1. File/Open/Example_Alignment.icb
2. Read PDB 2PHK
3. Extract the sequence from 2PHK and then drag it and drop it into the alignment.
4. Select a region of the alignment around which you wish to superimpose. You can use the propogate to all sequences in the Alignment Editor to make this selection.
5. Select the **display** tab and click on the superimpose button.



Notes and Things To Try:

- Try making a superposition around the ligand binding pocket only by selecting the ligand.
- Try improving poorly superimposed regions such as loops.

Manual References (Web Links)

`How to Superimpose Two Structures`

h3− Protein Folding and Structure Prediction {Folding}

Objective

To use a script to perform protein folding / structure prediction.

Instructions

```
                    # Example folding script. Use as directed.
read libraries
build "pep16"       # your peptide sequence is in pep16.se file.
rename a_*. "f2"    # specifies current name.
                    # Several runs (f2,f3, etc.) are recommended
nvar = Nof( v_//* ) # number of variables

nProc=4             # if you are using parallel version.

mncallsMC    = nvar*50000  # maximal number of energy evaluations
mncalls      = 170+nvar*3  # maximal n_of minimization calls after
                           # each random change
temperature  = 600   # optimal temperature for the simulation
tolGrad      = 0.01  # exit minimization when gradient is < 0.01
mcBell       = 1.0   # the default width of the MC probability distributions
mnconf       = 40    # maximal n_of low-energy conformations saved
                     # in the stack (f2.cnf file)
mnvisits     = 25    # if stuck for >= 25 times, push it out
mnreject     = 10
mnhighEnergy = 30
l_bpmc       = yes   # use biased probability
electroMethod = "MIMEL"
surfaceMethod = "constant tension"
```

```
set terms "vw,14,hb,el,to,sf,en"
                    # ECEPP/2 energy + solvation + entropy (see icm.hdt file)

fix v_//?vt*        # exclude irrelevant virtual variables specifying
                    # absolute molecular position
set vrestraint a_/*  # load preferred backbone and side-chain angle zones
                    # for the  biased probability MC
randomize v_//!omg 180.0  # create random starting conformation
vicinity = 15.0
compare v_//phi,psi  # use these variables to compare structure
montecarlo trajectory # run it and record a trajectory file.
                    # watch the movie later by:
                    # read trajectory "f2"; display ribbon
                    # display trajectory "f2" 4. 8.
                    # analyze the best conf. in the stack by:
                    # build "pep16"; read stack; show stack all
                    # load conf 1
quit
```

23.8 Protein Preparation and Crystallographic Analysis Tutorial

Note: Click **Next** (top right hand corner) to navigate through this chapter. Headings are listed on the left hand side (web version) or by clicking the **Contents** button on the left−hand−side of the help window in the graphical user interface.

23.8.1 PDB Preparation − Symmetry

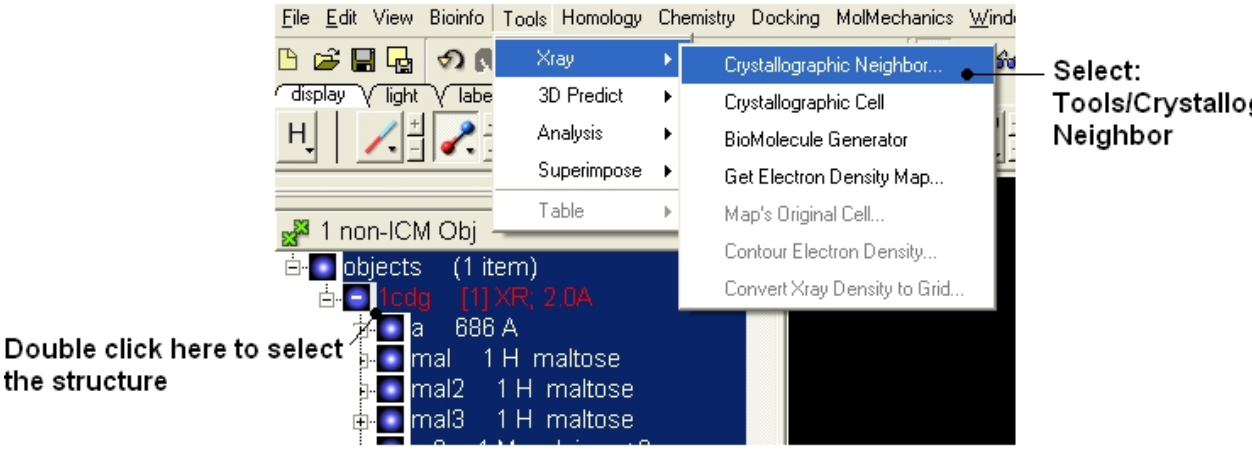
Background When inspecting a ligand binding pocket it is important to check that the true pocket is formed by chains which are not explicitely present in a PDB entry. Therefore it is necesary to use **Tools/X Ray/Crystallographic Neighbor** to find all molecules/subunits or chains involved in the interaction with the ligand. Molecular objects and 3D density maps may contain information about crystallographic symmetry. It consists of the following parameters:

1. Crystallographic group eg. P2121 that determine N (depends on a group) transformations for the atoms in the asymetric unit.
2. Crystallographic cell parameters A, B, C, Alpha, Beta and Gamma

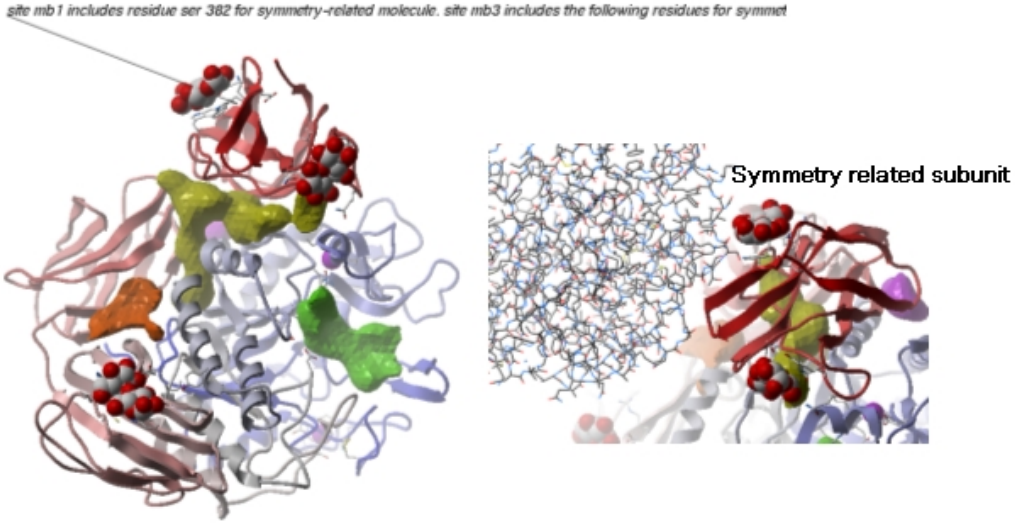
To generate the coordinates within one cell one needs to apply N transformations and then to generate neigboring cells the content of one cell needs to be translated in space according to the cell position.

Example As an example let us look at Cycloldextrin glycosyltransferase (PDB Code: 1CDG). The problem with docking to this receptor is that the true pocket is formed by chains which are not explicitly present in the PDB entry. Site mb1 includes serine 382. This cannot be predicted just by looking at the structure. Therefore we need to identify symmetry related molecules to this protein.

- Use the PDB search tab to load the crystal structure 1cdg.
- Inspect the ligand binding pocket of **maltose** (mal)
- To identify if there are any other chains involved in the interaction with the ligand select the whole structure in the ICM Workspace.



- Tools/Crystallographic Neighbor
- Select a 7A radius
- Check "create symmetry related molecules" and "display symmetry neighbors".
- Inspect the neighbors surrounding **maltose(mal).** Each symmetry related subunit can be colored by object by clicking and holding the representation button in the display tab and selecting color−by.



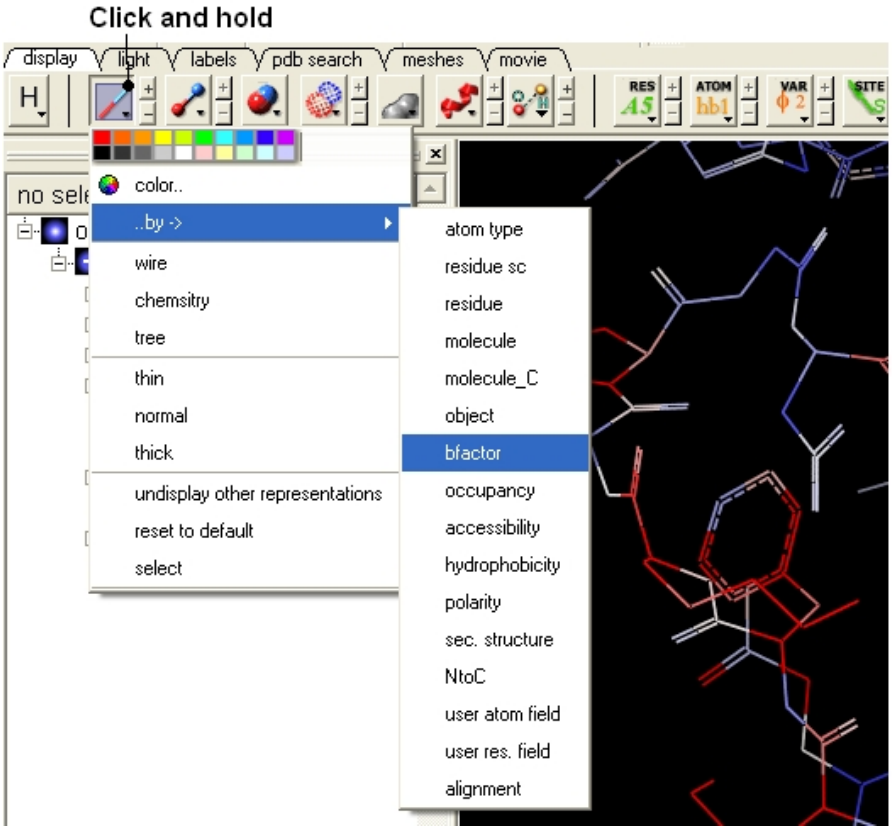
23.8.2 PDB Preparation − Occupancy and B−Factors

Background When preparing a PDB for analysis (eg docking or modeling) it is important to check the reported occupancies and b−factors. The occupancy is a fraction of atimic density at a given center. If there are two eqally occupied conformers both will have an occupancy of 0.5 − the normal value is 1 range 0−1. The *{B−Factor} is the mean−square displacement of atom from its position in the model − the normal range is 5−50.

One way of visualizing the occupancy and b−factor is by coloring the structure by these values. You can do this by clicking and holding on a representation button in the **display** panel and selecting Color−by.

As an example let us look at the crystal structure 1ATP

- Type in the PDB search tab 1atp and the structure will be displayed in the graphical display.
- Use the ICM workspace to undisplay everything except for the "e" subunit. You can do this by clicking in the blue boxes in the ICM Workspace.
- Display the "e" subunit in wire representation using the wire button in the **display** tab.
- Click and hold on the wire button and select Color−by B−Factor. Regions of high B−factor are colored red.

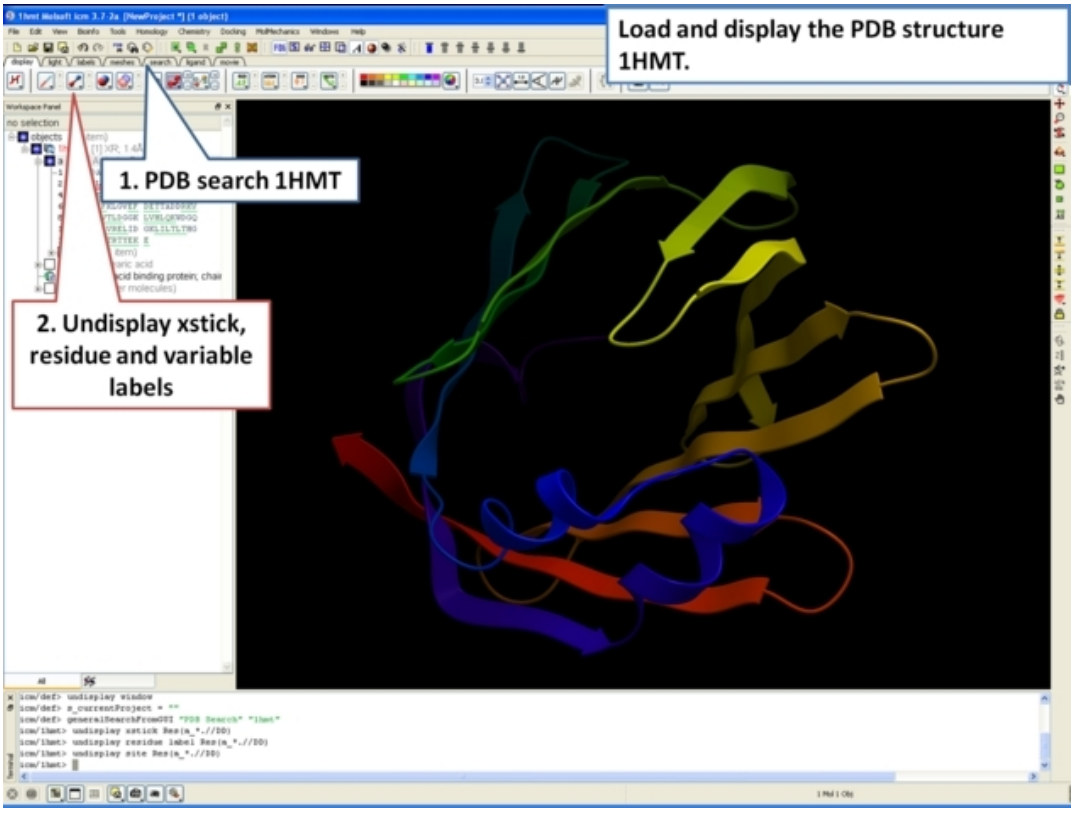


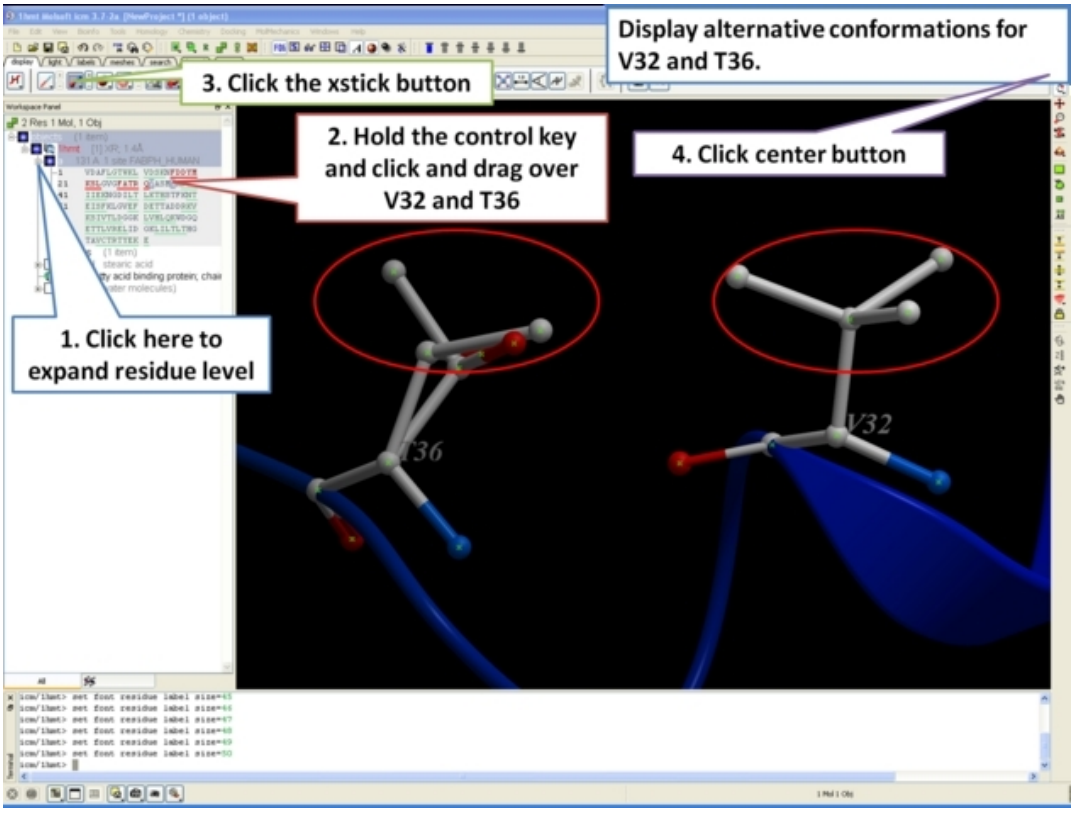
Residues with high B-Factor are colored red

23.8.3 PDB Preparation − Residue Alternative Orientation

For some very high resolution structures two alternative conformations for a residue are provided. Therefore for docking you need to decide to use one conformation of the residue or generate seveal separate docking models. This could be performed using `multiple receptor conformation docking`.

Here is an example of alternative residue orientations found in a crystal structure of a Fatty Acid Binding protein in complex with stearic acid.





23.8.4 Biomolecule Generator

Objective

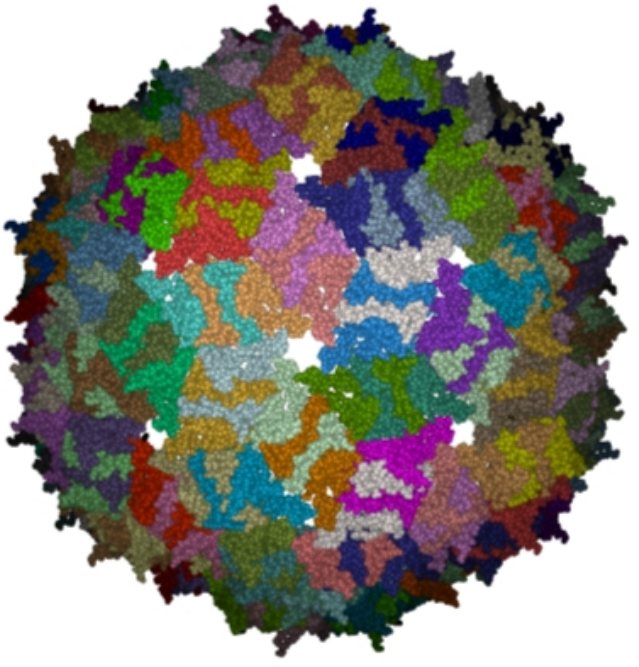
Here we will investigate the biological environment of a virus protein . PDB code 1DWN.

Background

It is very useful to know how a protein from the PDB may look in a biological environment. The PDB entries solved by X−ray crystallography and deposited in the PDB contain the information about the crystal structure rather than the biologically relevant structure. For example, for a viral capsid only one instance of capsid protein complex will be deposited and only one or two molecules of haemoglobin that is a tetramer in solution maybe deposited. In some other cases the asymmetric unit may contain more than one copy of a biologically monomeric protein. ICM reads the biological unit information and has a tool to generate a biological unit. Not every PDB entry has the biological unit information.

Instructions

- Read and load the PDB file 1DWN
- Tools/Xray/Biomolecule Generator
- Tick the makeAllBiomolecules box (Warning this may take a few minutes to generate)
- The generated molecules will be listed in the ICM Workspace. Each one can be selected and displayed. The biomolecule is shown below.



NOTE: Please note that right clicking on a PDB file in the ICM Workspace will tell you whether there is any **Biomolecule** information available for the structure. If this information is not present then the option will be greyed out.

Manual References (Web Links)

`Biomolecule Generator`

23.9 Working with the Molecular Editor

23.9.1 Draw Chemical

Objective

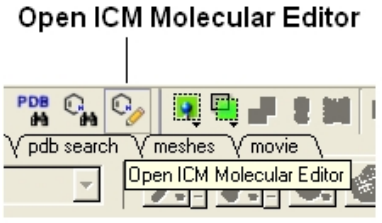
To sketch the chemical structure of Celebrex a COX−2 inhibitor and save it in an ICM Molecular Table.

Background

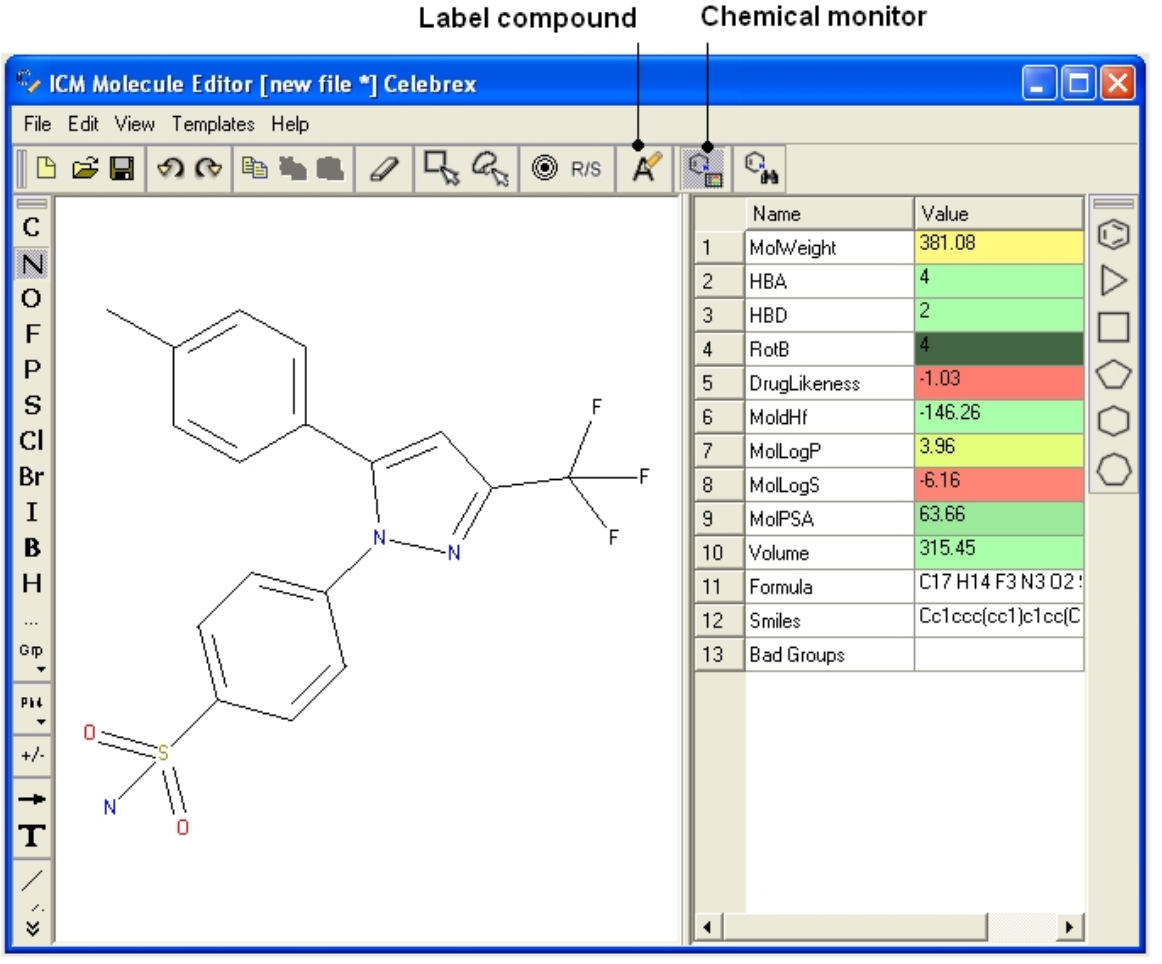
In ICM it is possible to not only edit structures that you have read into ICM but also create your own and append them to a table, file or a database of structures. All these actions take place in the ICM Molecular Editor.

Instructions

- **Chemistry/Molecular Editor** and the editor will automatically be displayed or click on the button shown below.

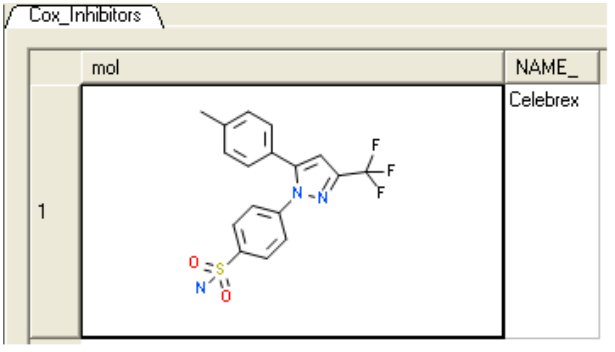


- Draw the Celebrex compound (shown below) within the editor using the rings, atoms and bonds on the left hand side of the editor. Note more advanced options can be found by right clicking on either a bond or an atom.



- You can monitor the properties of the molecule whilst drawing it by clicking on the **Chemical Monitor** button.
- Label the compound "Celebrex" (see below)
- Once you have finished drawing you can either save the compound as a separate file, convert to 3D in the graphical display, append it to an already existing compound database in 2D or 3D, or you can save it into a new ICM table.
- In this example we will save it to an ICM table by selecting **File/Append to Table** and then select **New.** Give the table a name such as **Cox Inhibitors**. A molecular table as shown below will be

displayed.
- **File/Quit**



Manual References (Web Links)

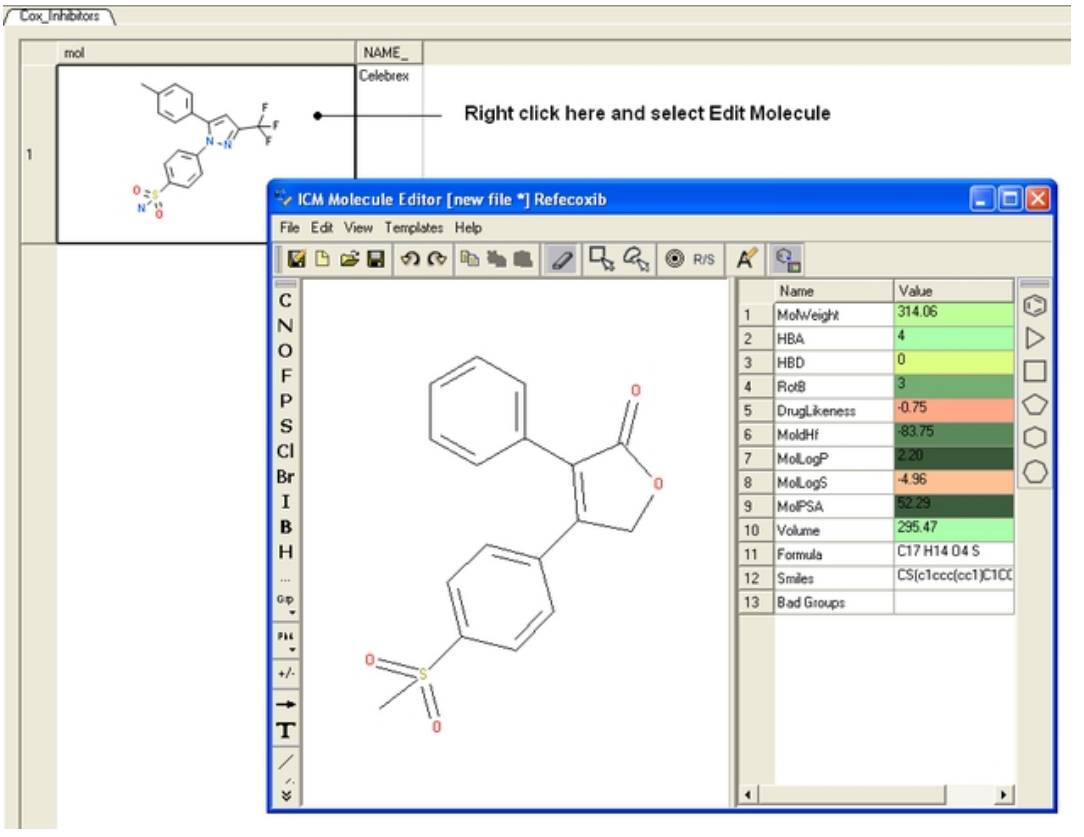
`Molecular Editor`

23.9.2 Edit Chemical

Objective

To edit the **Celebrex** compound (drawn in the previous `example`) into a newer C0X−2 drug called **Rofecoxib** which maintains the Celebrex backbone but with many changes in functionality.

- To edit the Celebrex compound − right click on the sketch of Celebrex in the Molecular Table and select **Edit molecule**.
- You can submit the changes to the table by clicking on the red cross (close window button) in the molecular editor.
- Alternatively you can append the Rofecoxib molecule to a saved sdf file or save as a separate mol file by using the **File Menu** in the ICM Molecular Editor.
- If you would like to try the chemical search example below append the file to celebrex50.sdf in the distribution



Manual References (Web Links)

`Molecular Editor`

23.10 Chemical Searching

23.10.1 Chemical Similarity Searching

Objective

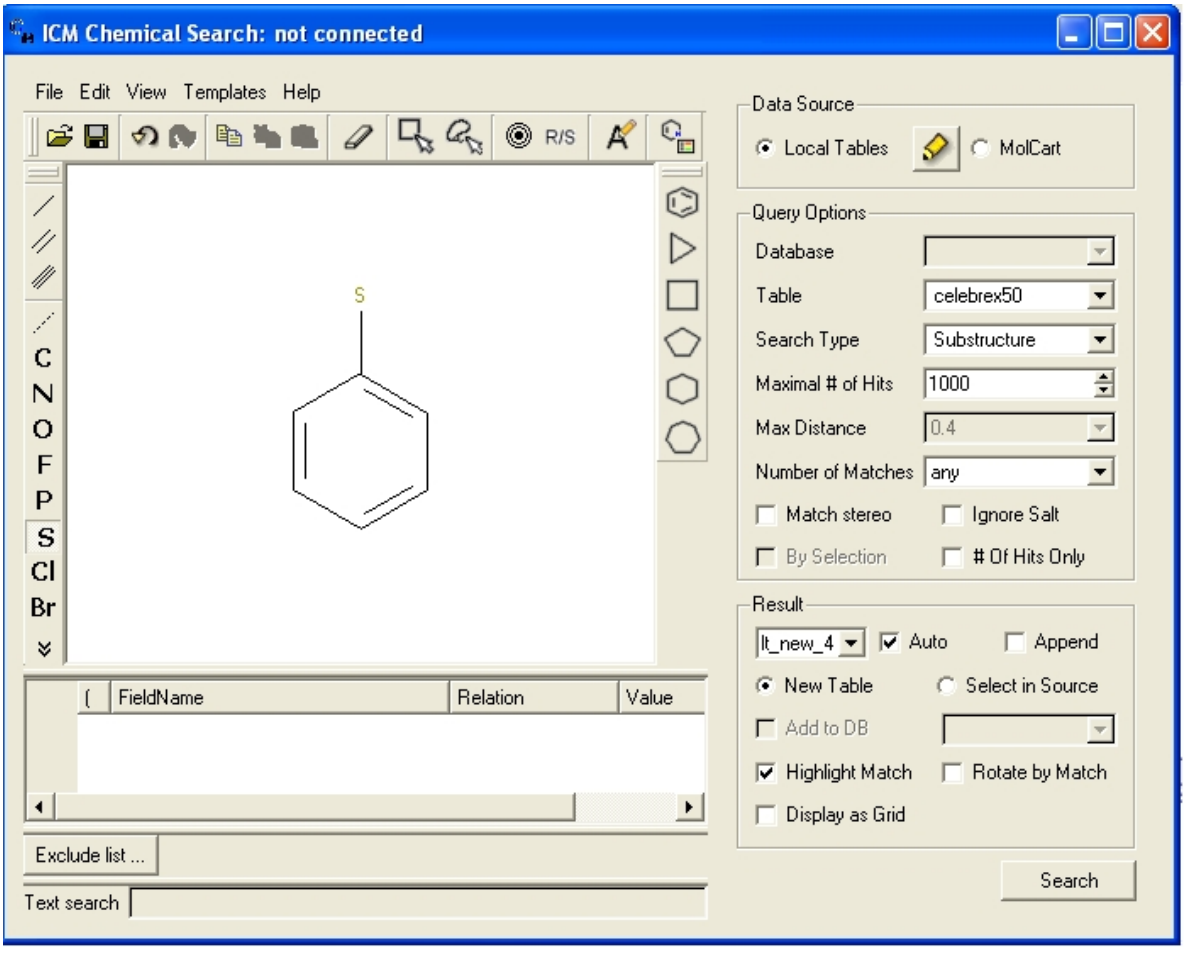
To find the drugs celebrex and rofecoxib in the chemical table **celebrex50.sdf** by performing a substructure chemical similarity search.

Background

Using ICM you can perform a compound similarity search whereby a query structure will be searched against a database of compounds. The database can be a compound database already loaded into ICM such as an SDF file or Molsoft's very own compound database called MOLCART.

Instructions

1. Load the celebrex50.sdf file into ICM (File/Open). This file is provided in the ICM distribution.
2. Chemistry/Chemical Search
3. The ICM Molecular Editor and another menu for query search (on the right) will be displayed.
4. If a molecule is already displayed in the editor you can delete it by Edit/Select All to delete
5. We will start by seeing if we can identify celebrex and refecoxib from the common substructure shown below. Draw the substructure query using the `Molecular Editor` buttons. In this example you will draw a benzene ring with a single bond to a Sulfur atom.



* Select the option Local Tables

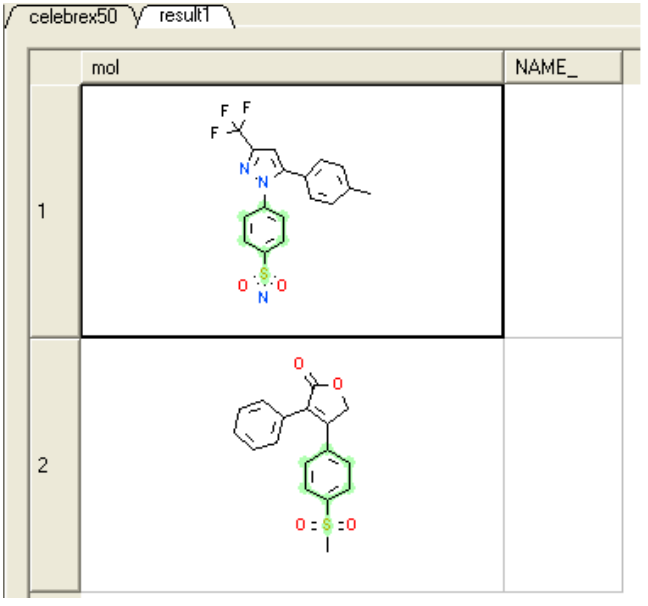
* Select Celebrex50 as your database.

* Select substructure search

* Select the other options as shown in the figure above. You can experiment with different values from the drop down menu.

* Select the Search button.

* A new table will be constructed called result1 with your substructure search results contained in it. If you added Rofecoxib to the celebrex50.sdf in the `previous example` your results table should contain 2 hits − celebrex and rofecoxib.



Notes and Things to Try:

- Note your substructure is highlighted in green in the results table.
- Try using the FP finger print option from the drop down **Search Type** button. A substructure search is a search whereby only the defined molecule in the query will be searched against the database. Whereas, a FP search which stands for fingerprint search enables any fingerprint within a structure to be searched for in the database. The "Max distance" option is available for use with the FP search and the "Matches number" option is for use with the substructure search. The option you do not require based on your search method will be blanked out. A "Max distance" value of 0 means that the search will only identify matches exactly the same as the fingerprint − the default is 0.4. The "Matches number" option allows you to stipulate how many times within a structure in the database your query can be found.

Manual References (Web Links)

`Chemical Substructure/Similarity Searching`

23.10.2 Advanced Chemical Similarity Searching

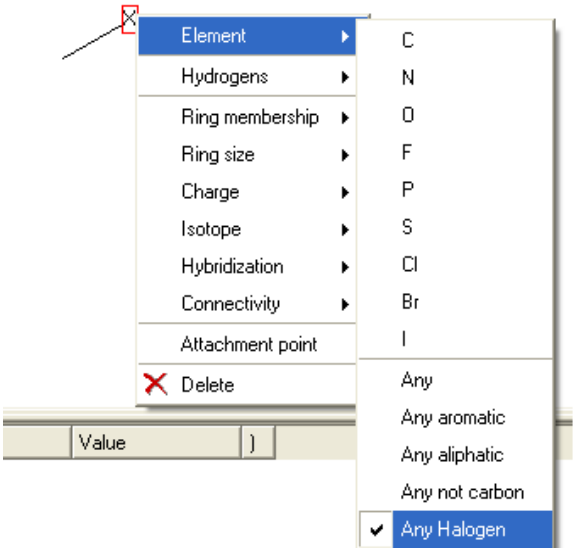
Objective

To use the right click options in the chemical search window to add additional search criteria and find ways to distinguish Celebrex from Rofecoxib.

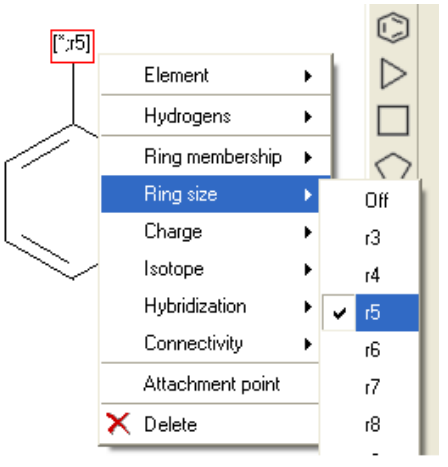
Instructions

1. Load the celebrex50.sdf file into ICM (File/Open). This file is provided in the ICM distribution. Add Rofecoxib to the celebrex50.sdf file as described in the `chemical-edit` tutorial.
2. Chemistry/Chemical Search
3. The ICM Molecular Editor and another menu for query search (on the right) will be displayed.
4. If a molecule is already displayed in the editor you can delete it by Edit/Select All to delete
5. Follow the search instructions described in the `previous example` with the following chemical search substructures:

Celebrex contains halogen atoms and Rofecoxib does not − therefore one way to distinguish the two would be a simple filter as shown below.



One of the key features between Celebrex and Rofecoxib is a benzene ring connected to a five−membered ring. The difference is that in celebrex the connection point is with a nitrogen atom and in Rofecoxib the connection point is with a carbon atom. Therefore to retrieve both Celebrex and Rofecoxib in the results table you would need to right click and select **Element/Any** (*) and select **Ring Size 5** (r5) or to retrieve only one you would need to specify nitrogen or carbon at the connection point.



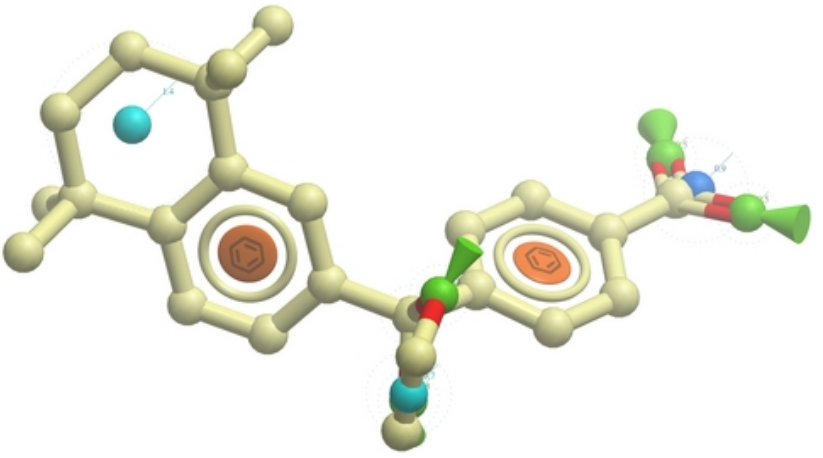
You can also perform the same query using Ring Membership (R1) or Attachment Point.

Manual References (Web Links)

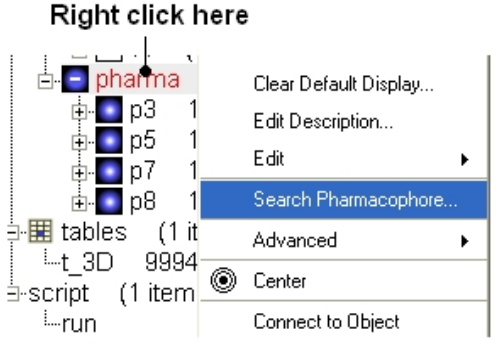
`Chemical Similarity Searching`

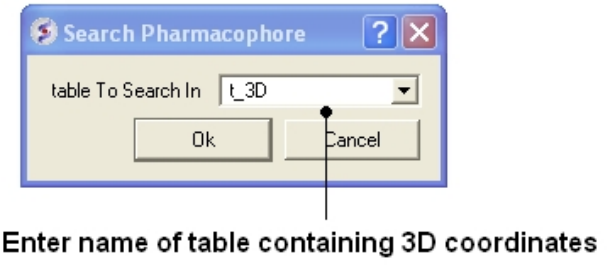
23.10.3 3D Pharmacophore Searching

Objective Undertake a 3D pharmacophore search of a table containing 3D coordinates.

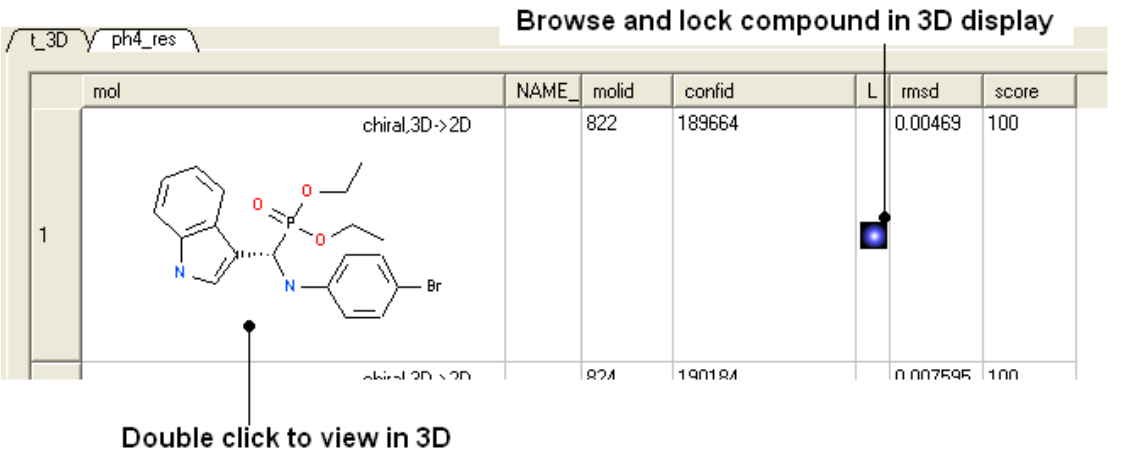


- File/Open **example_ph4.icb** (this file is provided in the ICM distribution and therefore can be found in $ICMHOME or in Windows Program Files/MolSoft
- In this example the 3D pharmacophore has already been extracted from a ligand. To find out how to generate a 3D pharmacophore see the section entitled `Pharmacophore Draw 3D`.
- In this example a table containing 3D coordinates is already provided containing 3D coordinates. The table is called t_3D.
- To run 3D pharmacophore searching right click on the name of the pharmacophore object in the ICM Workspace and select **Search Pharmacophore**.
- Select the table t_3D from the drop down list and click OK.
- A table of search results will be displayed.





- You can browse the results by clicking on the table and the ligand will be displayed in the graphical display.
- Remember you can use the check boxes in column L to `lock` compounds and overlay them.



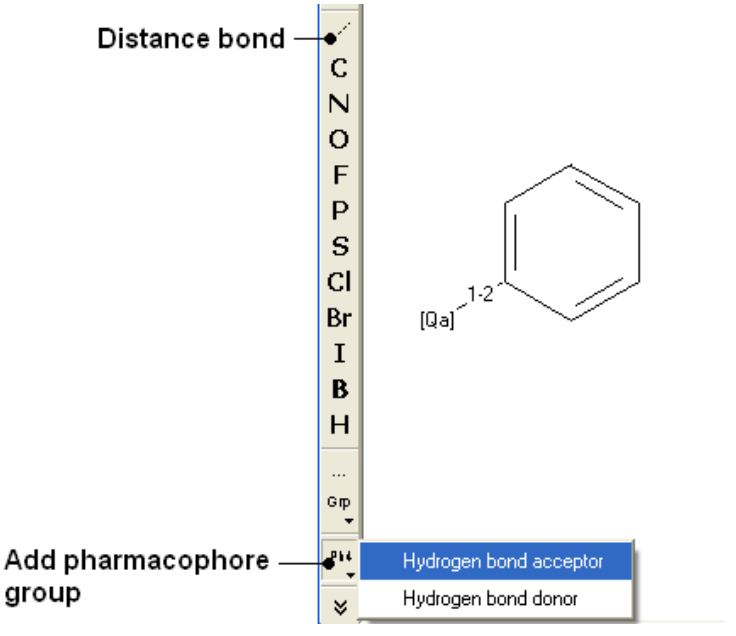
Manual References (Web Links)

`3D Pharmacophore Search`

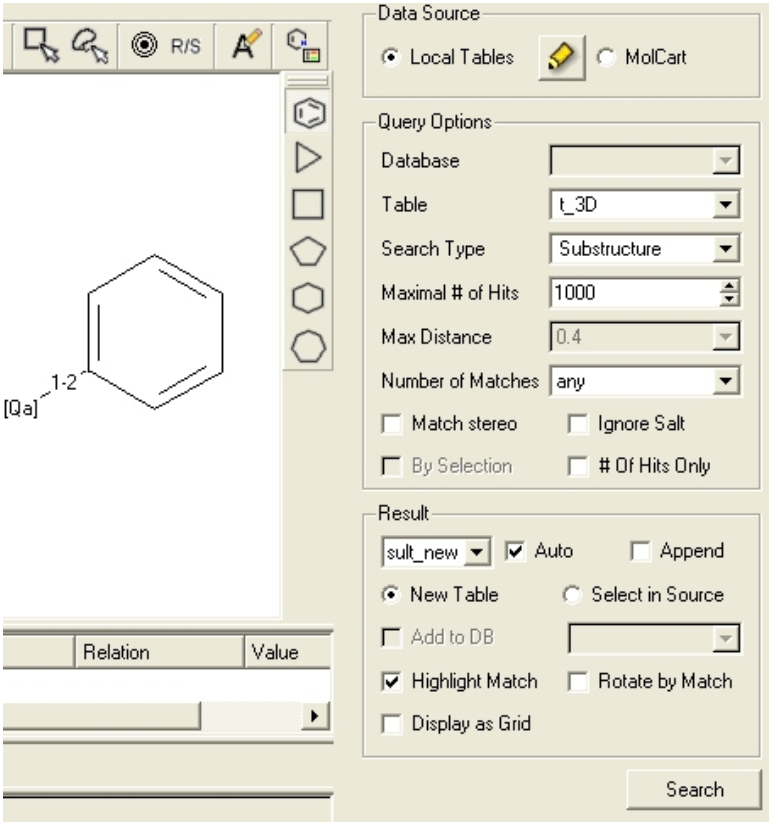
23.10.4 2D Pharmacophore Searching

Objective Undertake a 2D pharmacophore search of a `chemical spreadsheet`.

- File/Open **example_ph4.icb** (this file is provided in the ICM distribution and therefore can be found in $ICMHOME or in Windows Program Files/MolSoft
- Chemistry/Chemical Search
- Draw the query as shown below using the



- Fill in the query and results option as shown below.

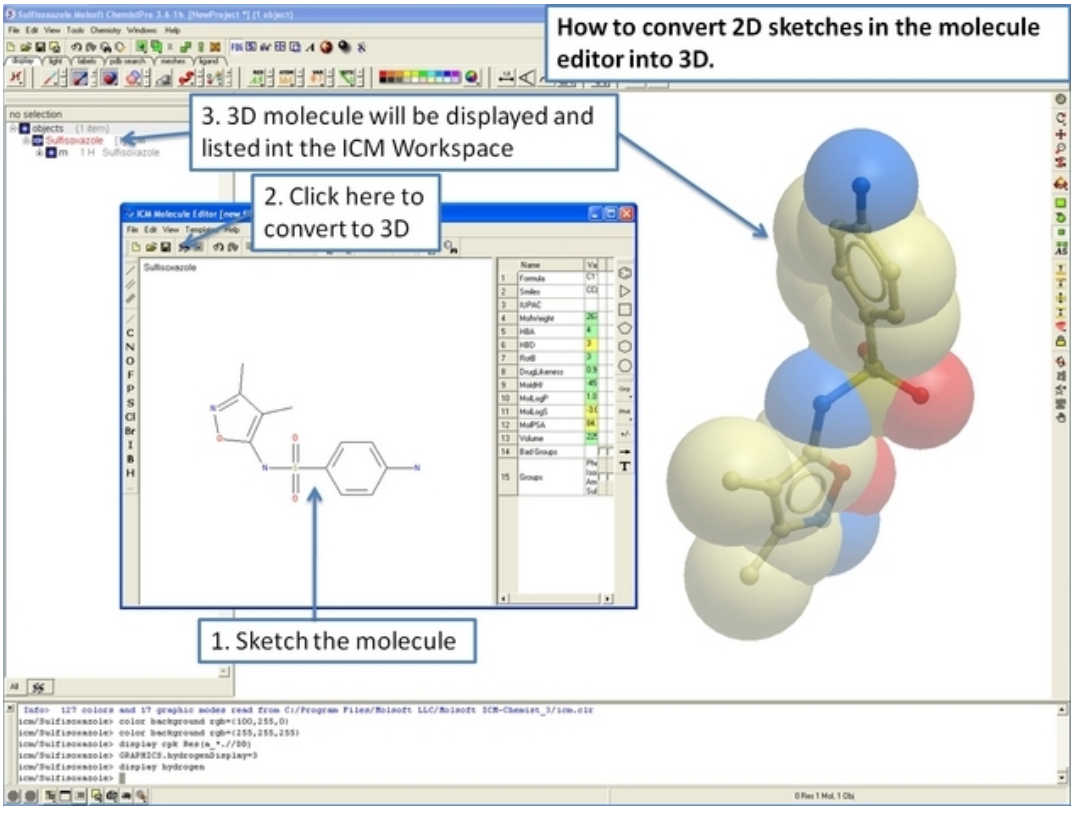


Manual References (Web Links)

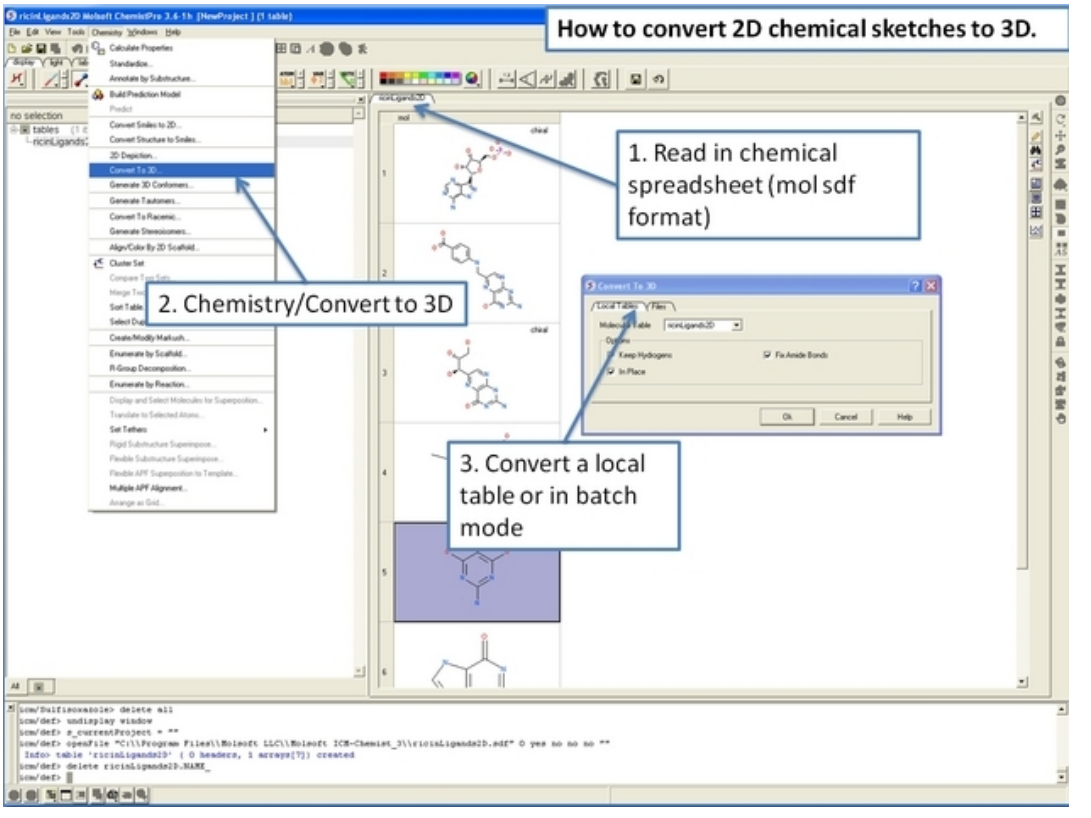
`2D Pharmacophore Search`

23.11 How to Convert Chemicals from 2D to 3D

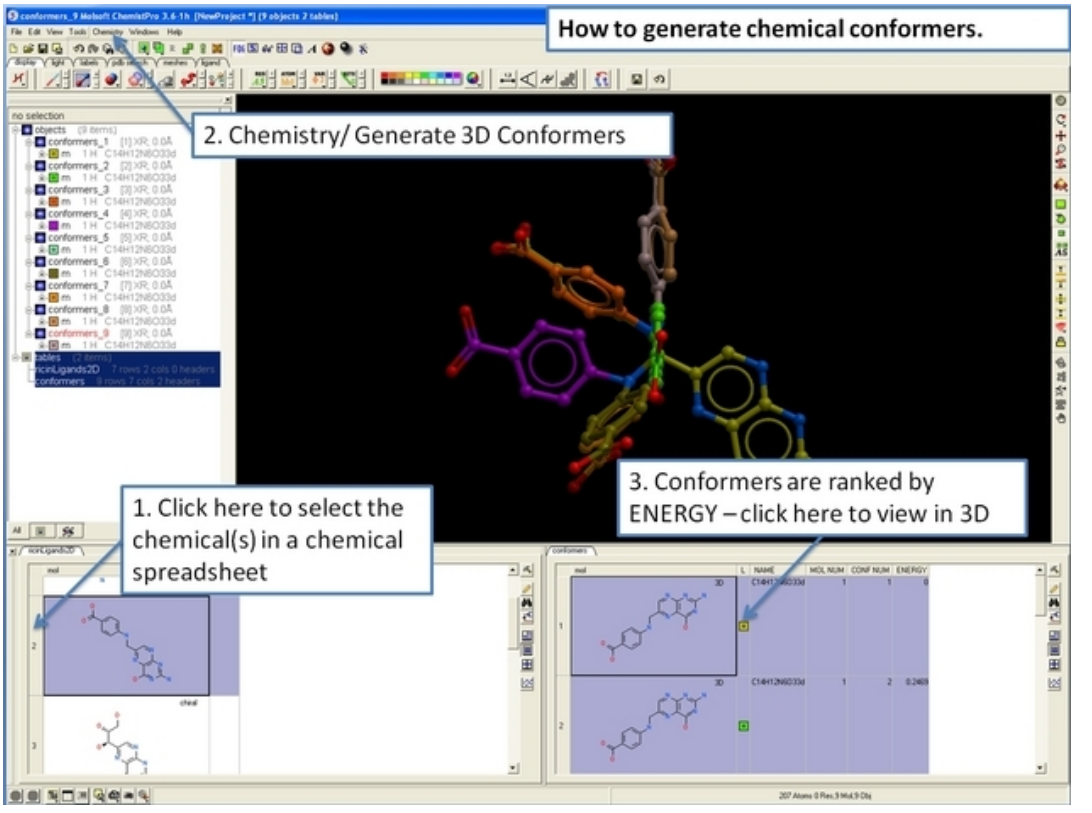
23.11.1 How to convert 2D sketches in the molecule editor into 3D.



23.11.2 How to convert 2D chemical sketches to 3D.

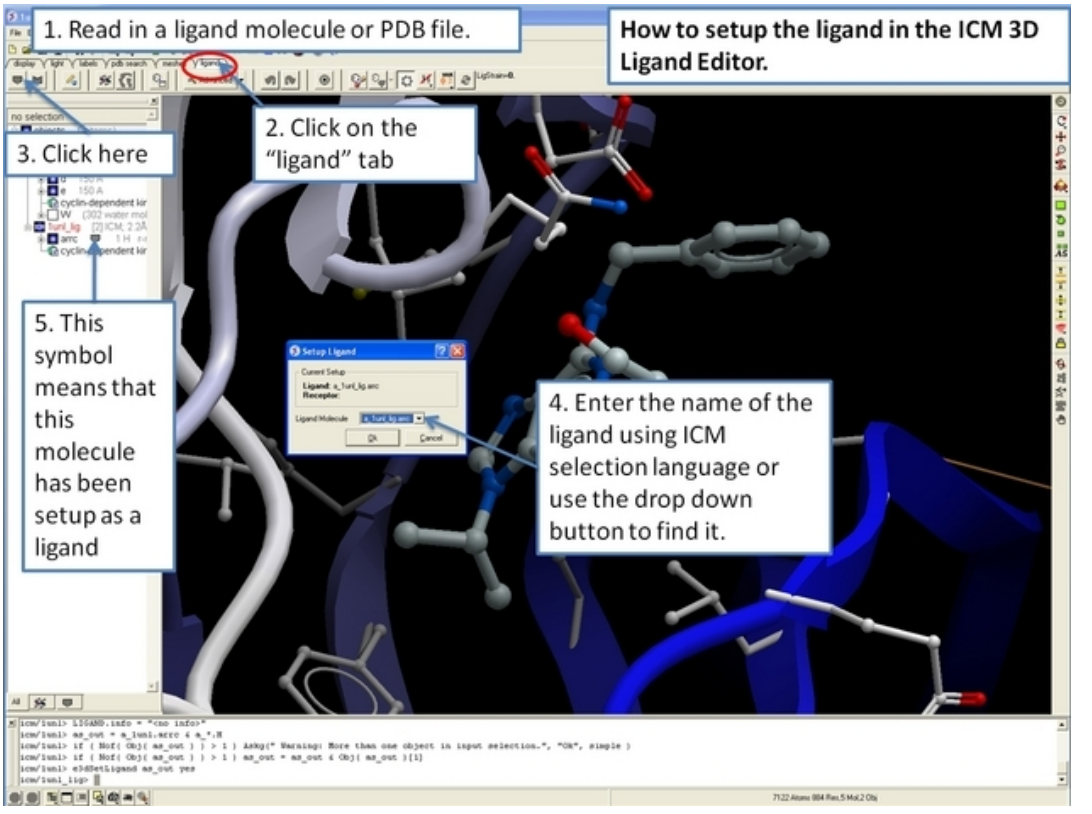


23.11.3 How to generate 3D ligand conformers.

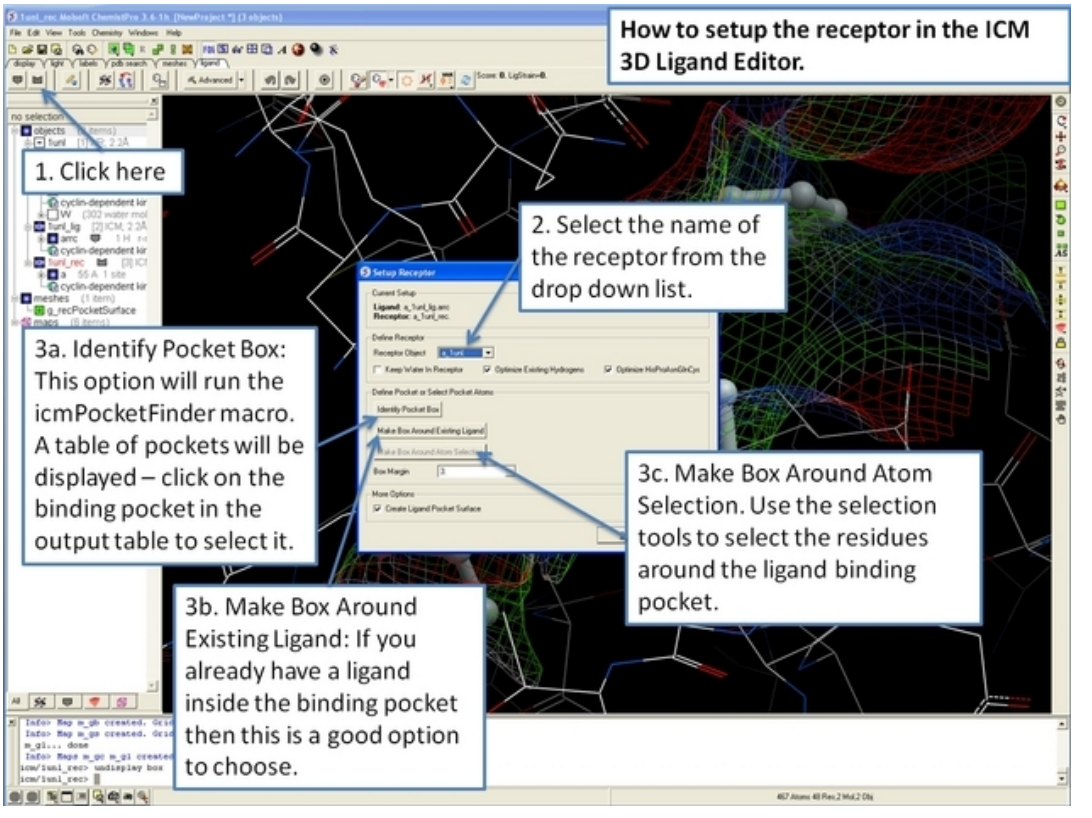


23.12 How to Work with the ICM 3D Ligand Editor

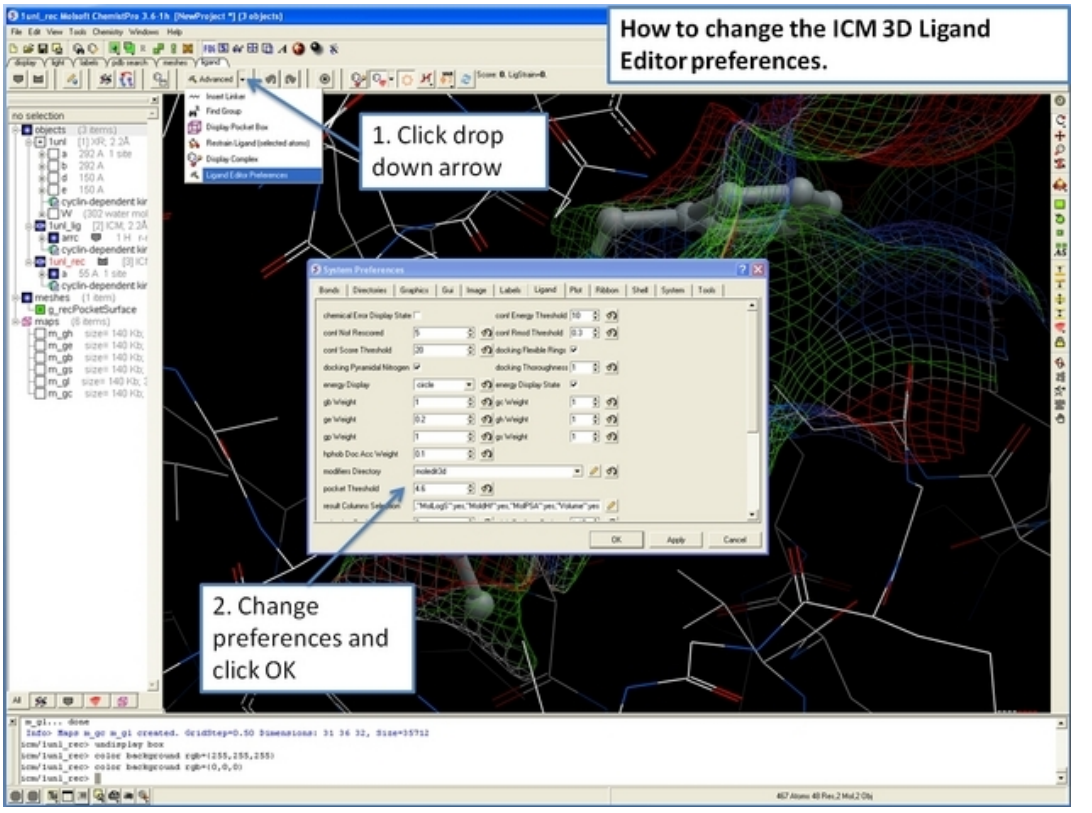
23.12.1 How to setup the ligand in the ICM 3D Ligand Editor.



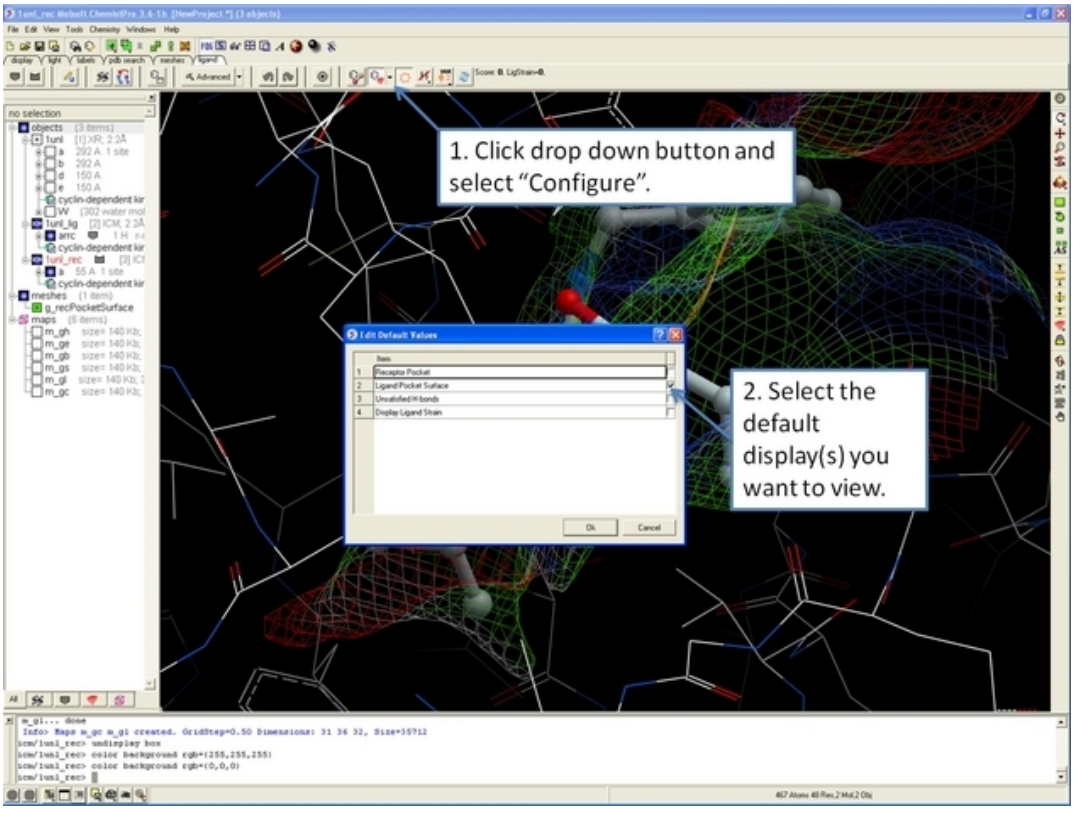
23.12.2 How to setup the receptor in the ICM 3D Ligand Editor.



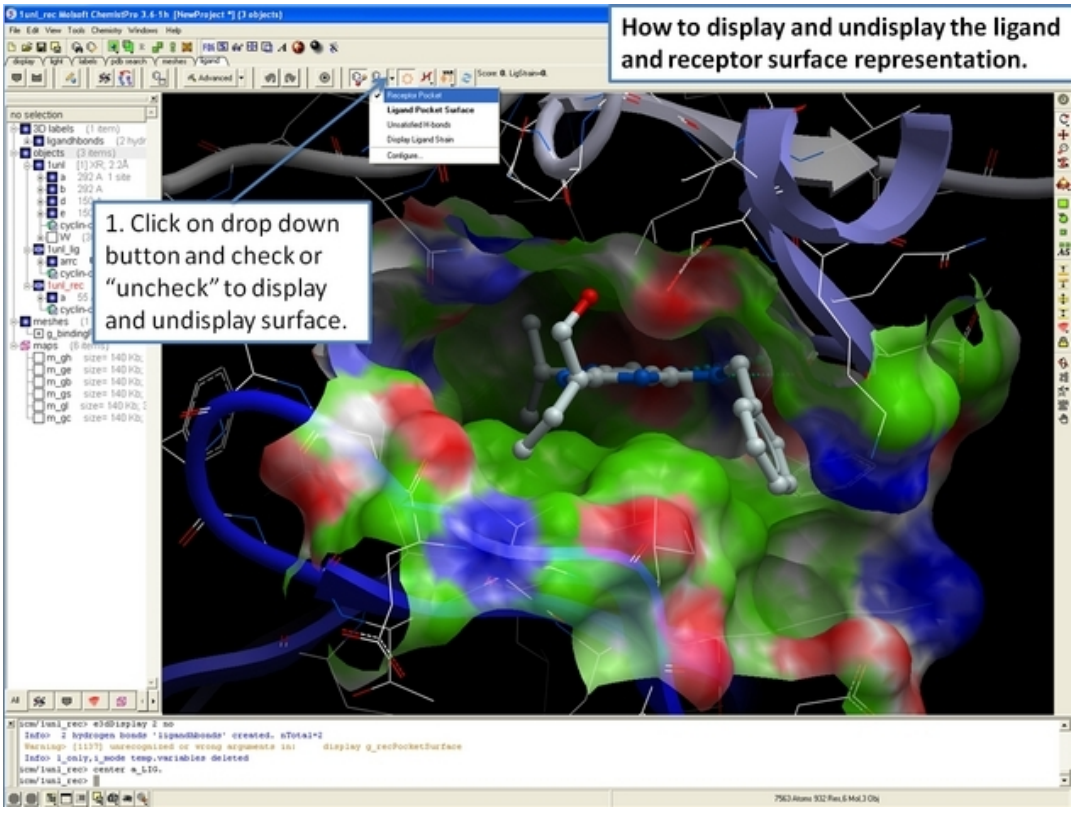
23.12.3 How to change the 3D Ligand Editor preferences.



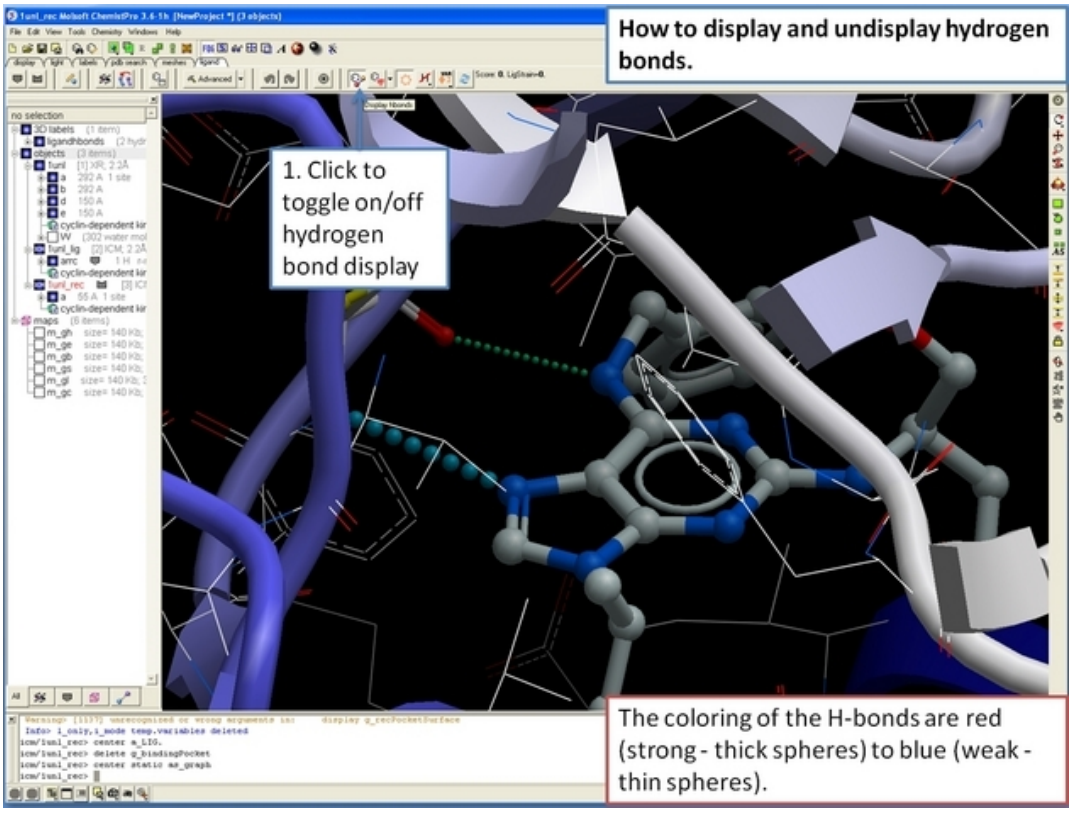
23.12.4 How to configure the default display in the ICM 3D Ligand Editor.



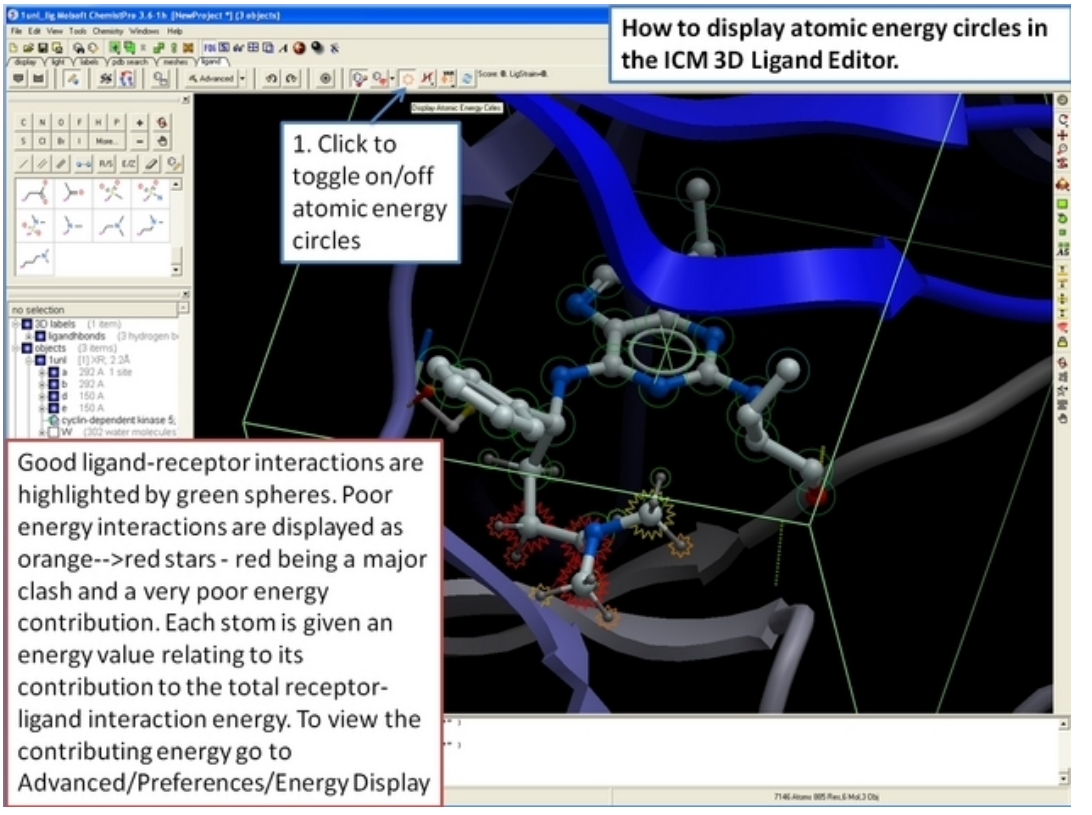
23.12.5 How to display and undisplay the ligand surface representation in the ICM 3D Ligand Editor.



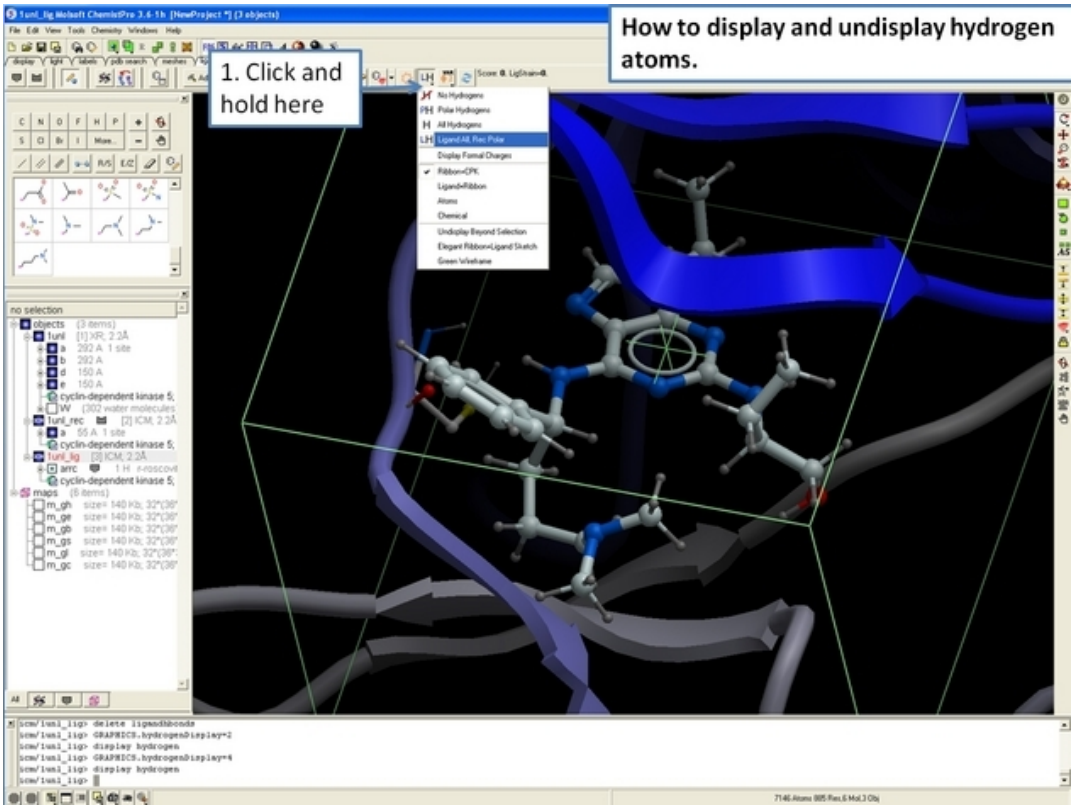
23.12.6 How to display hydrogen bonds in the ICM 3D ligand editor.



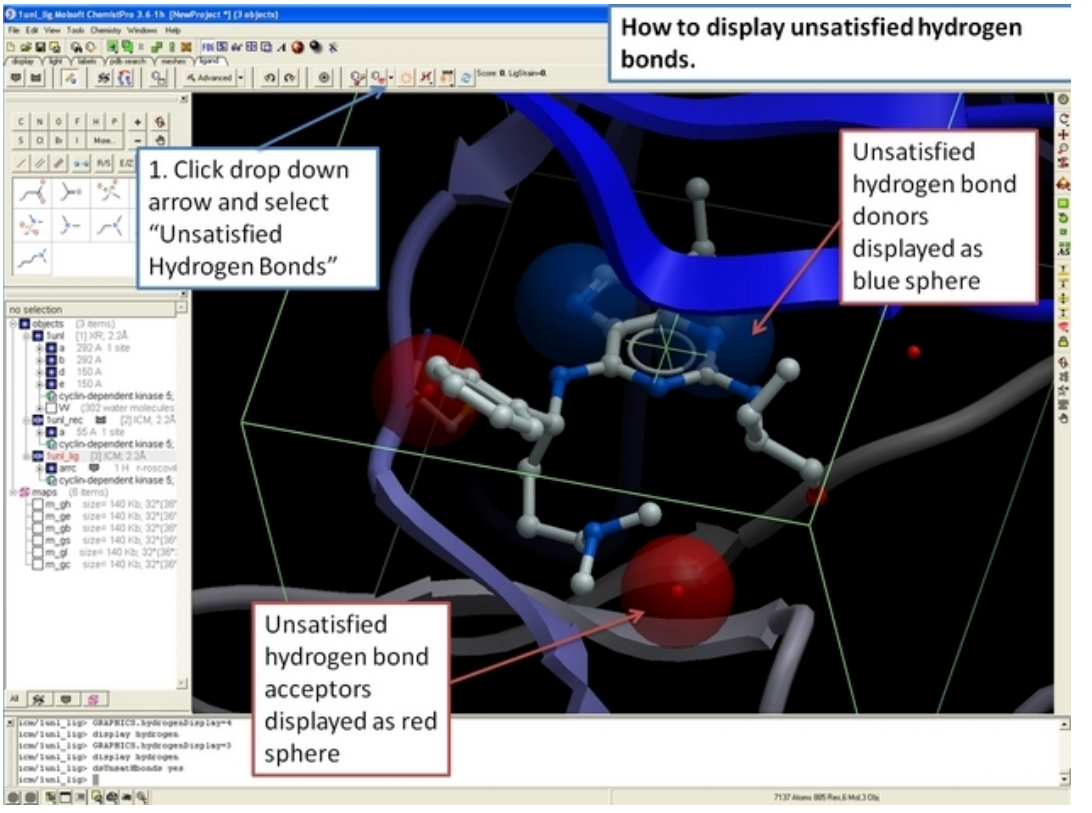
23.12.7 How to display energy atomic circles in the ICM 3D Ligand Editor.



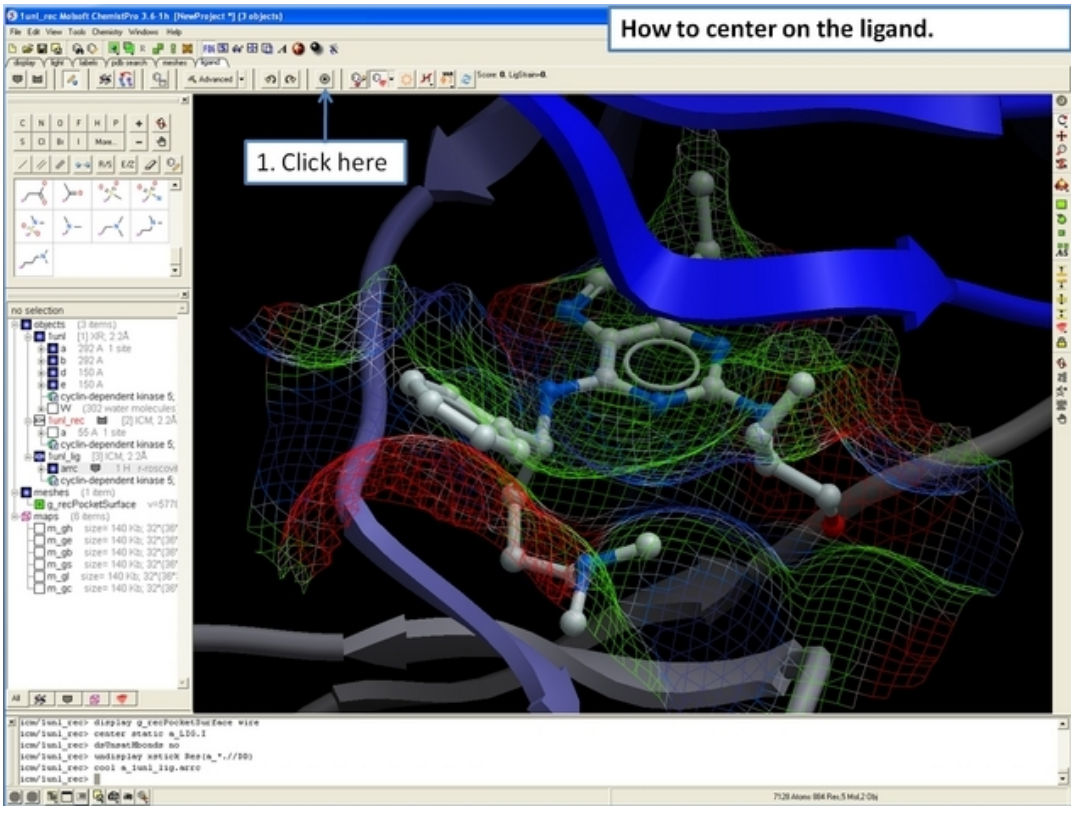
23.12.8 How to display and undisplay hydrogen atoms in the ICM 3D Ligand Editor.



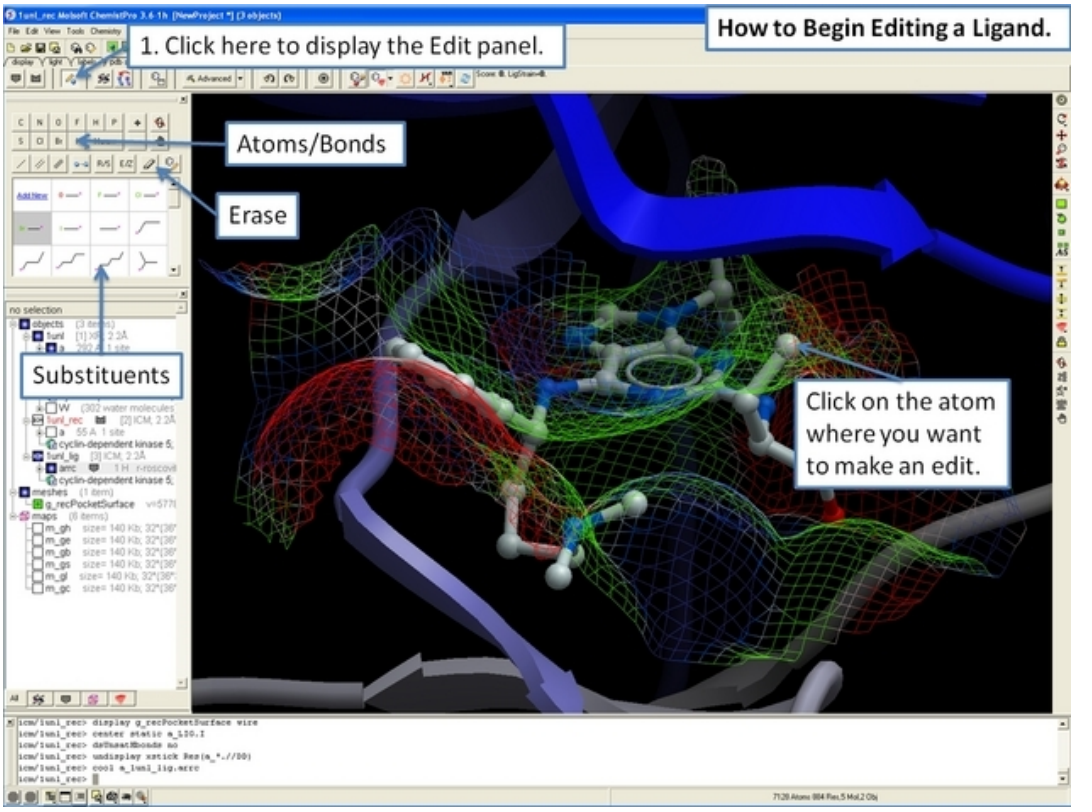
23.12.9 How to display unsatisfied hydrogen bonds in the ICM 3D Ligand Editor.



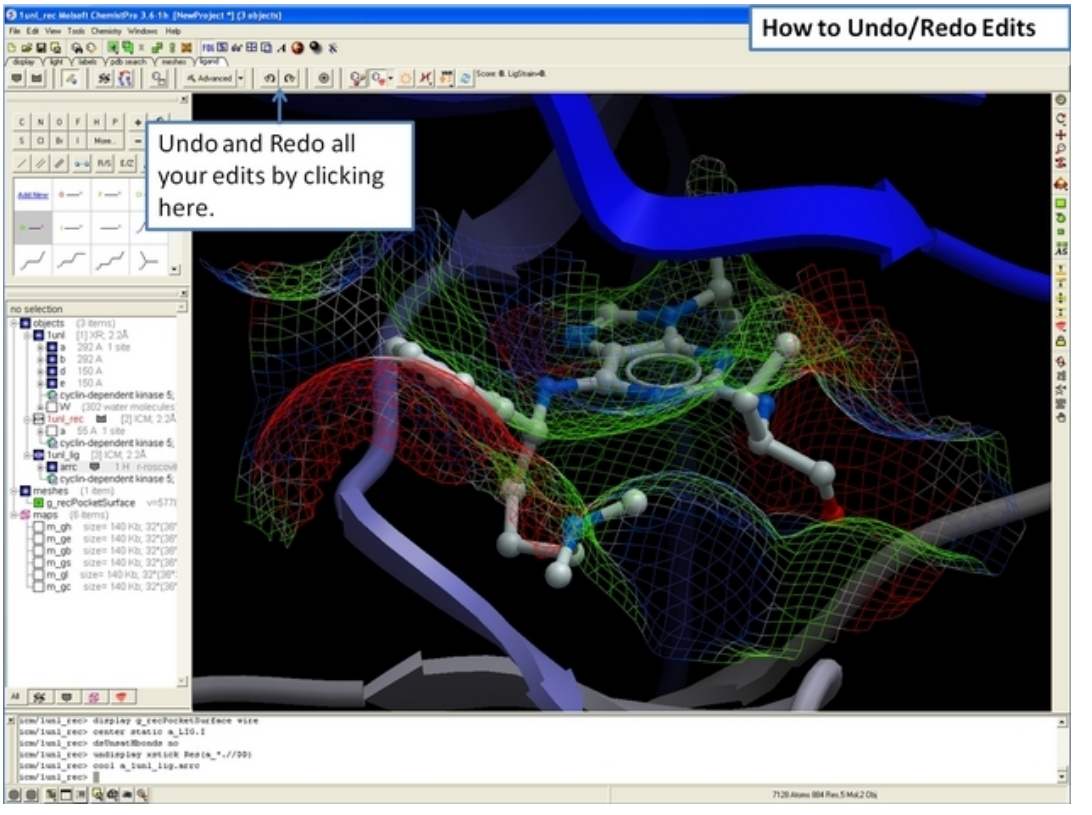
23.12.10 How to center on a ligand in the ICM 3D Ligand Editor.



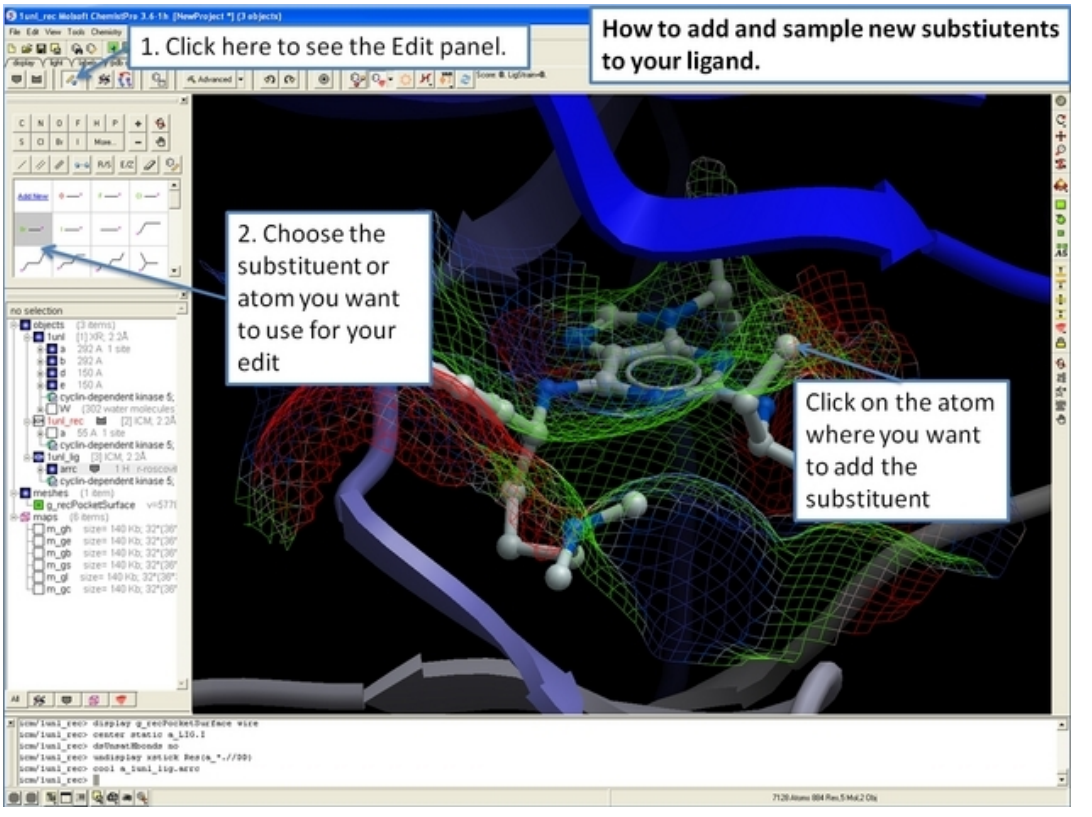
23.12.11 How to begin editing your ligand in the ICM 3D Ligand Editor.



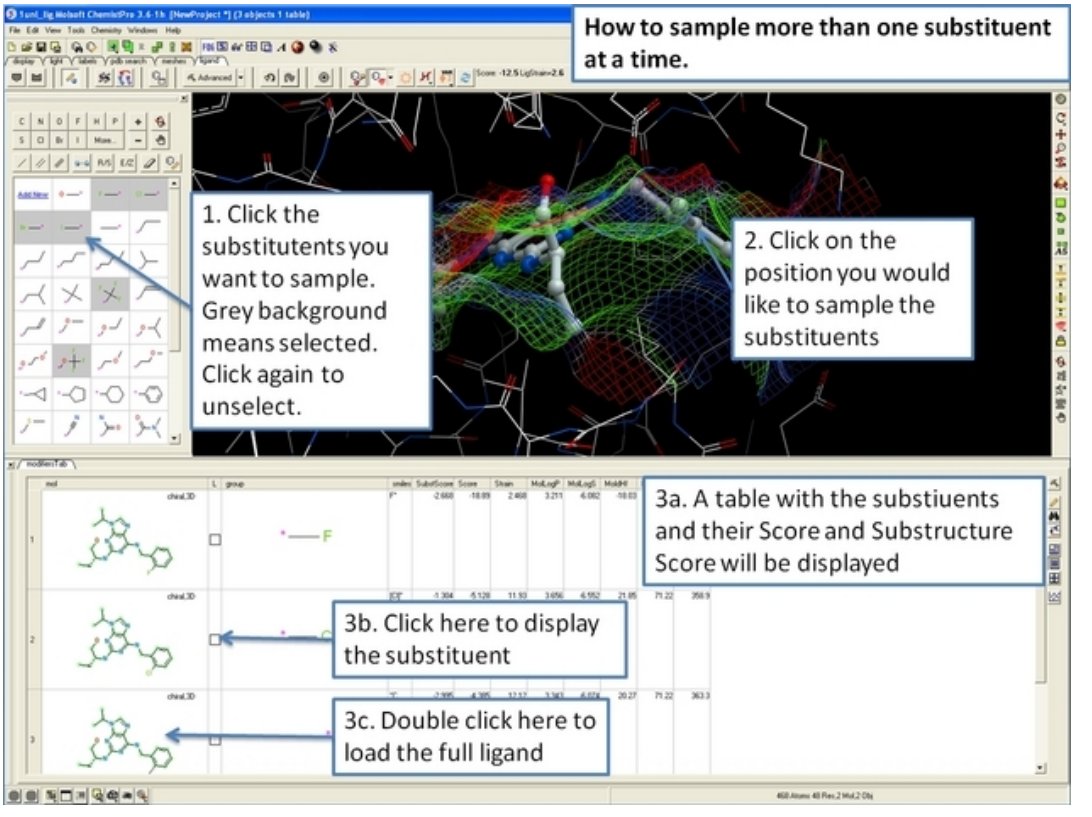
23.12.12 How to undo and redo changes in the ICM 3D Ligand Editor.



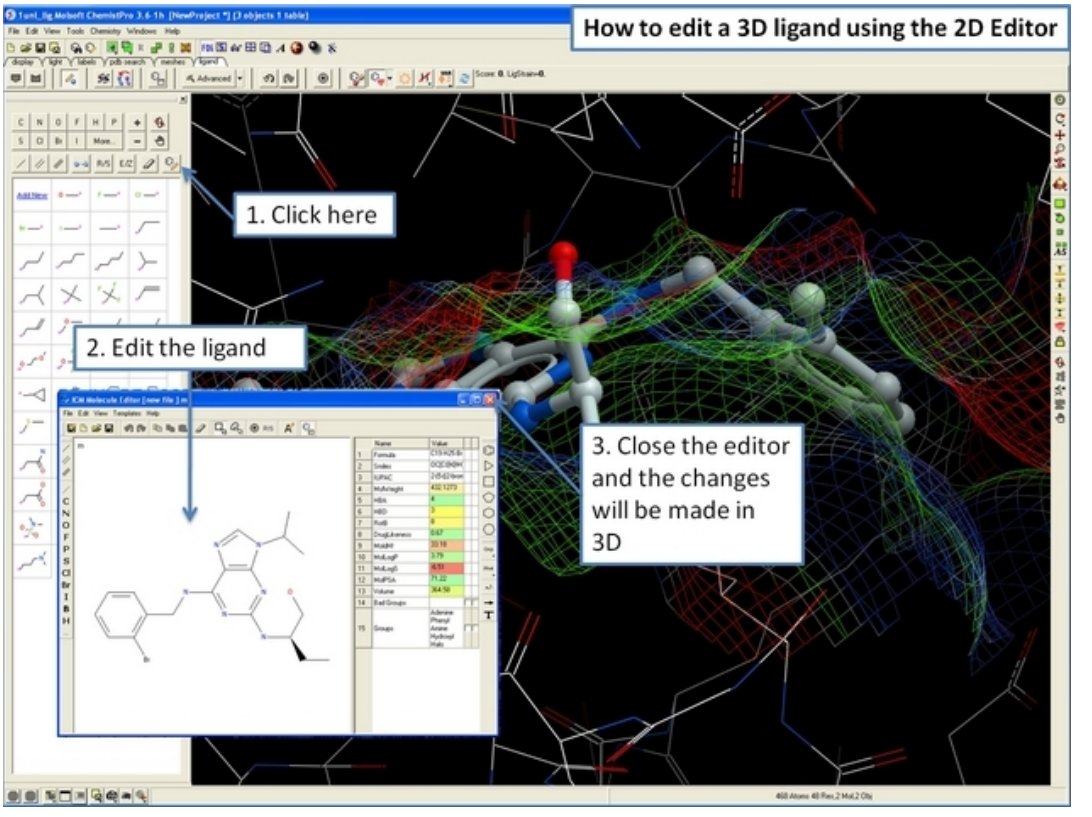
23.12.13 How to add and sample new substiutents to your ligand in the ICM 3D Ligand Editor.



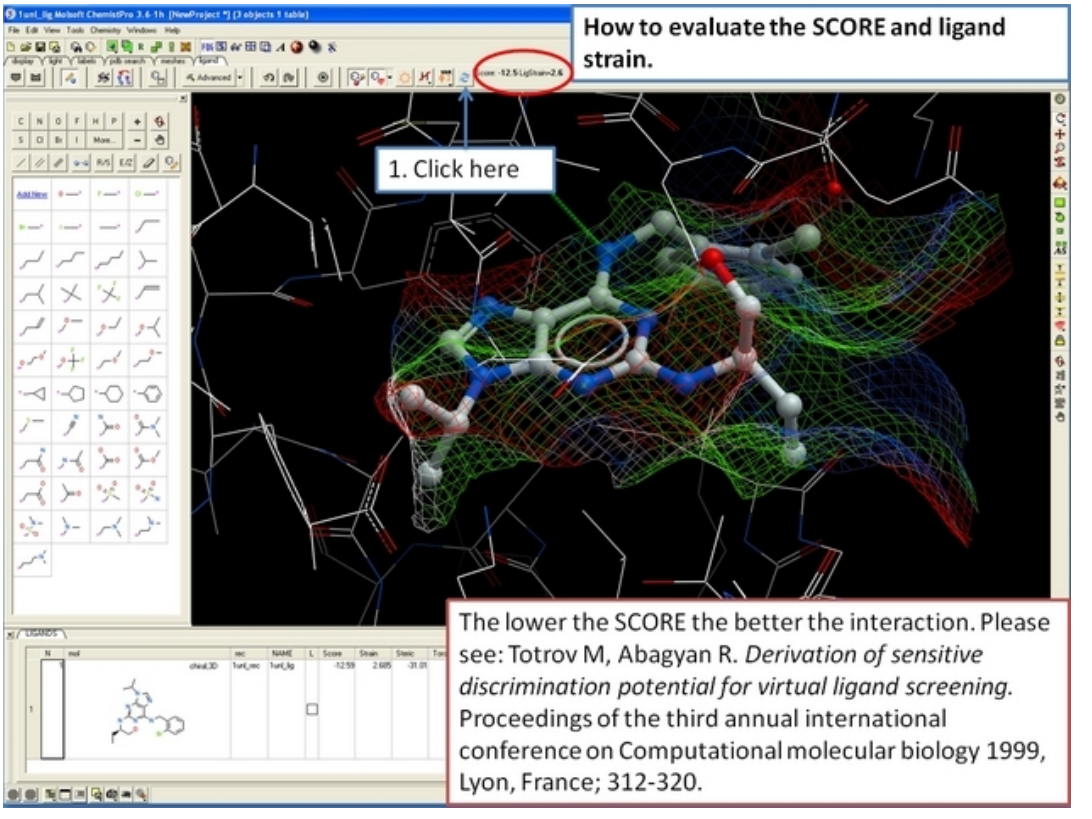
23.12.14 How to sample more than one substituent at a time in the ICM 3D Ligand Editor.



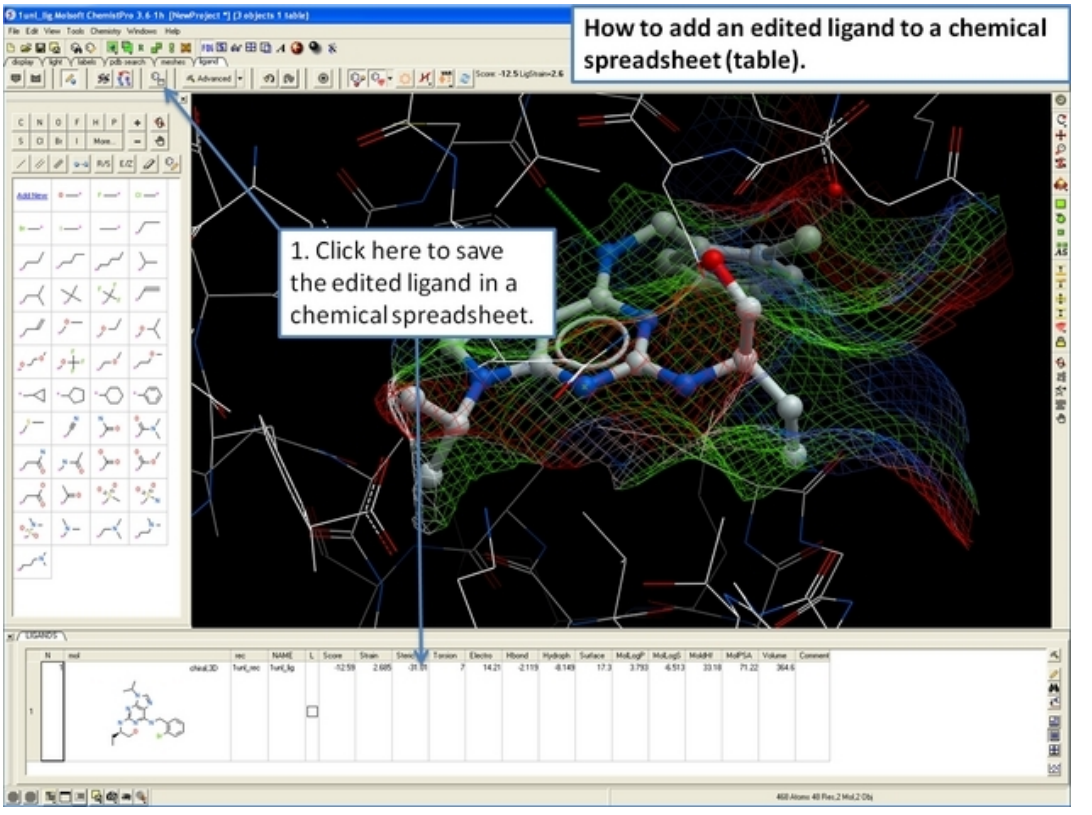
23.12.15 How to edit the ligand in 2D in the ICM 3D Ligand Editor.



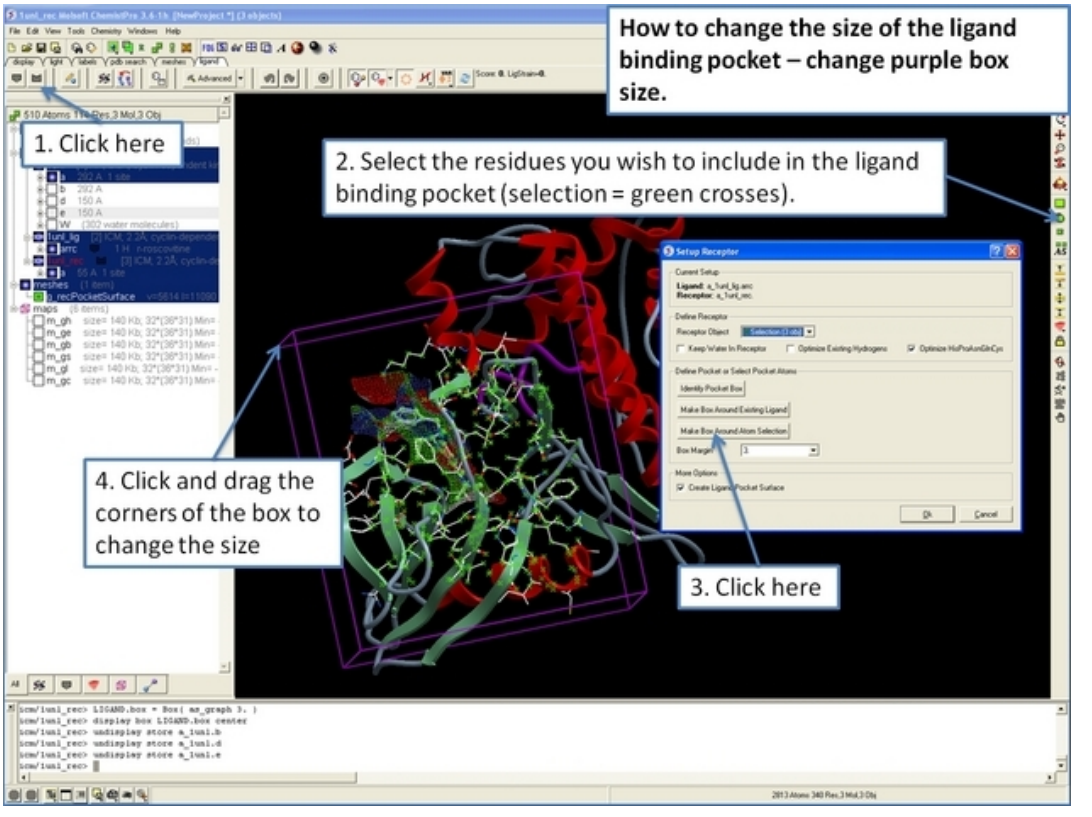
23.12.16 How to evaluate the SCORE and ligand strain..



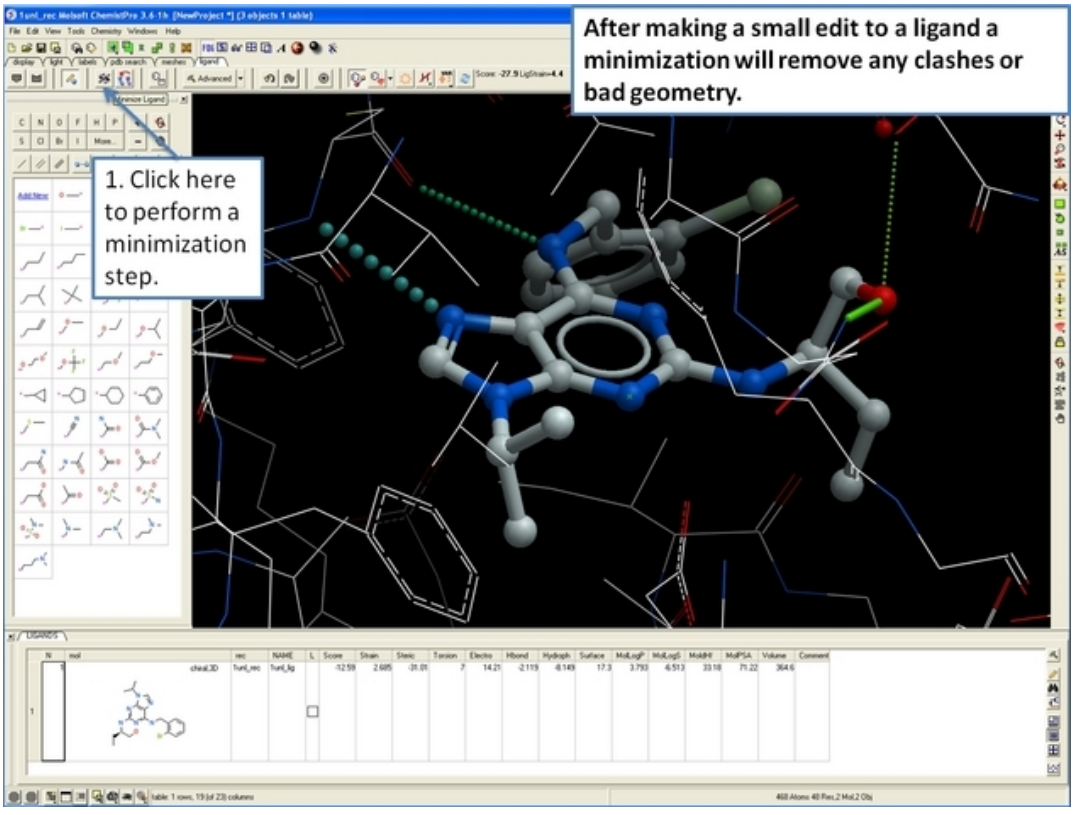
23.12.17 How to add an edited ligand to a chemical spreadsheet (table).



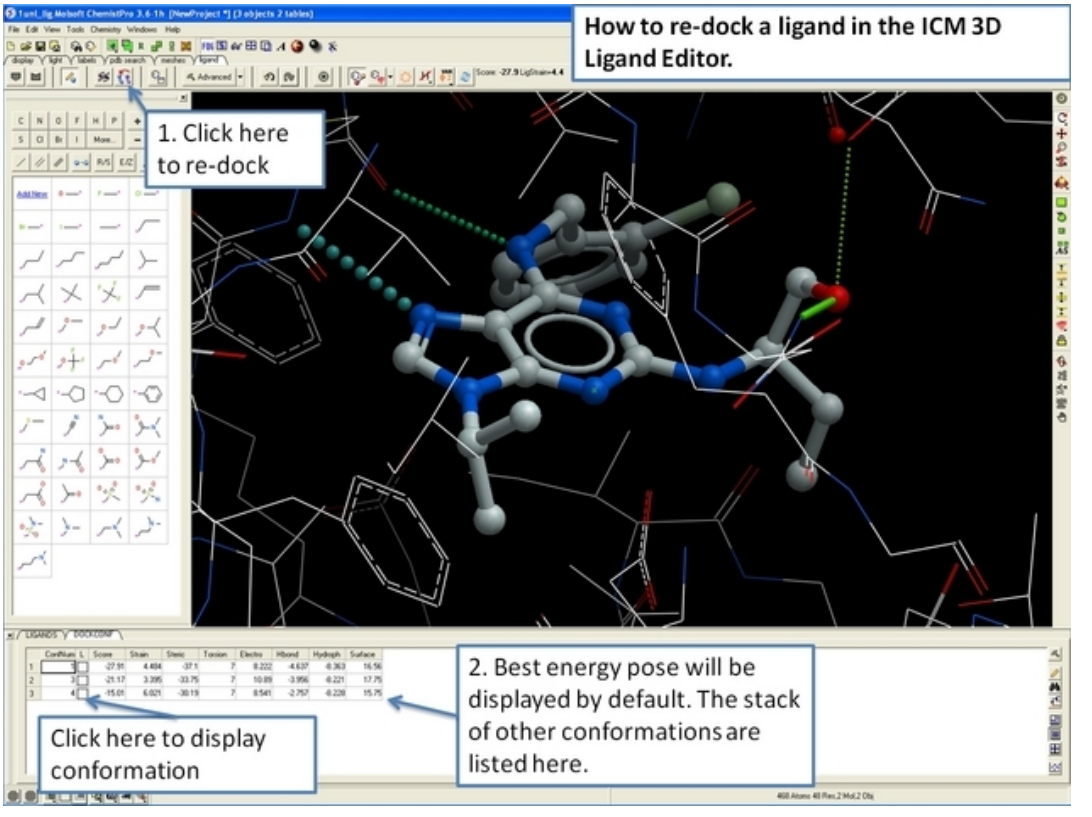
23.12.18 How to change the size of the ligand binding pocket − change purple box size.



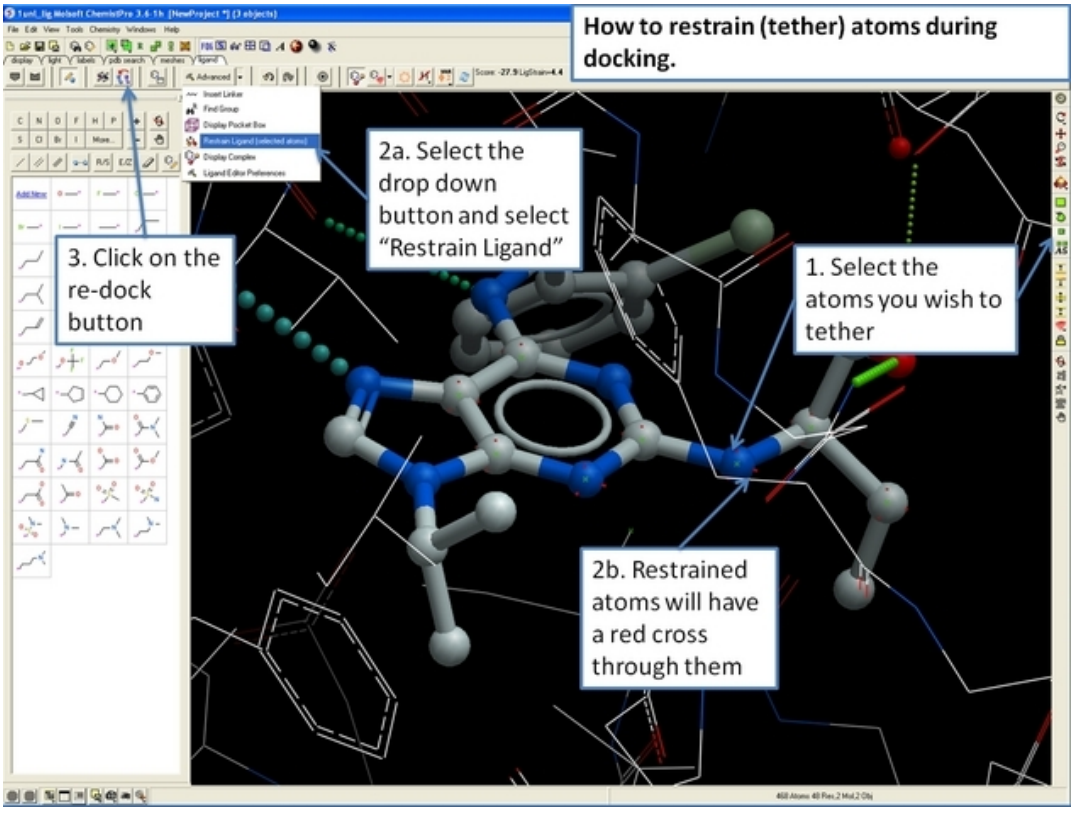
23.12.19 How to perform ligand minimization in the ICM 3D Ligand Editor.



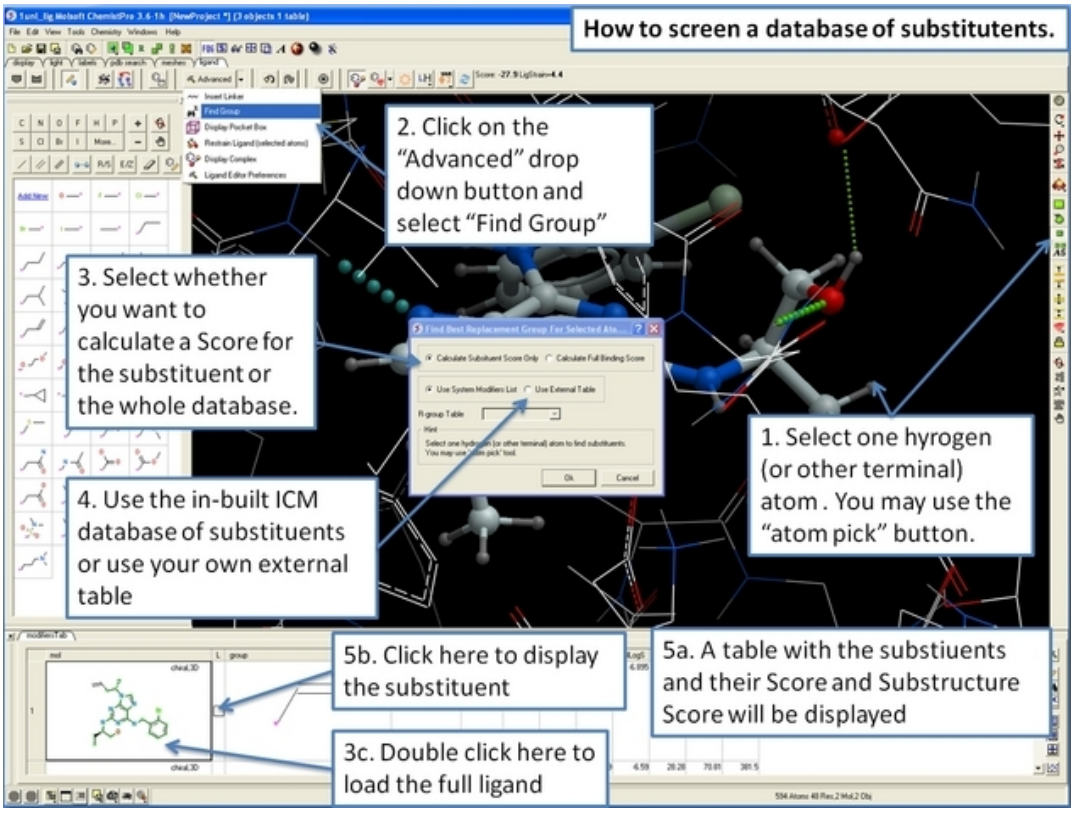
23.12.20 How to re−dock a ligand in the ICM 3D Ligand Editor.



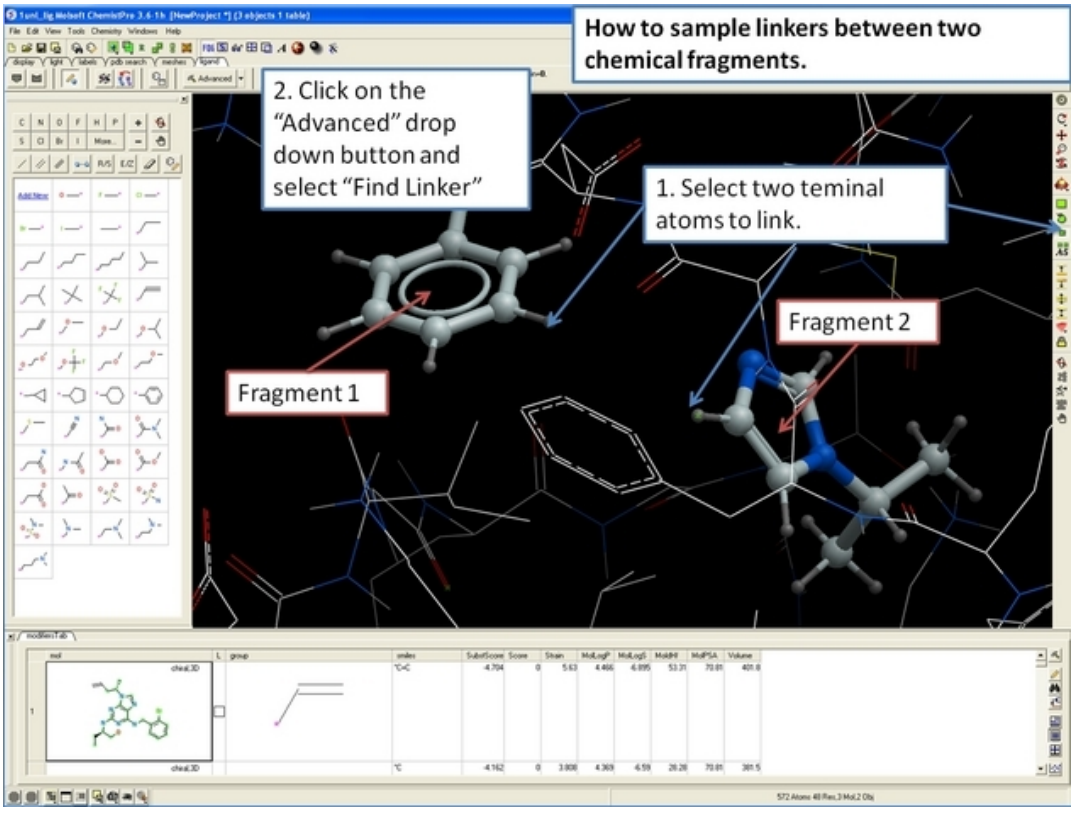
23.12.21 How to restrain (tether) atoms during docking.



23.12.22 How to screen databases of chemical substituents.

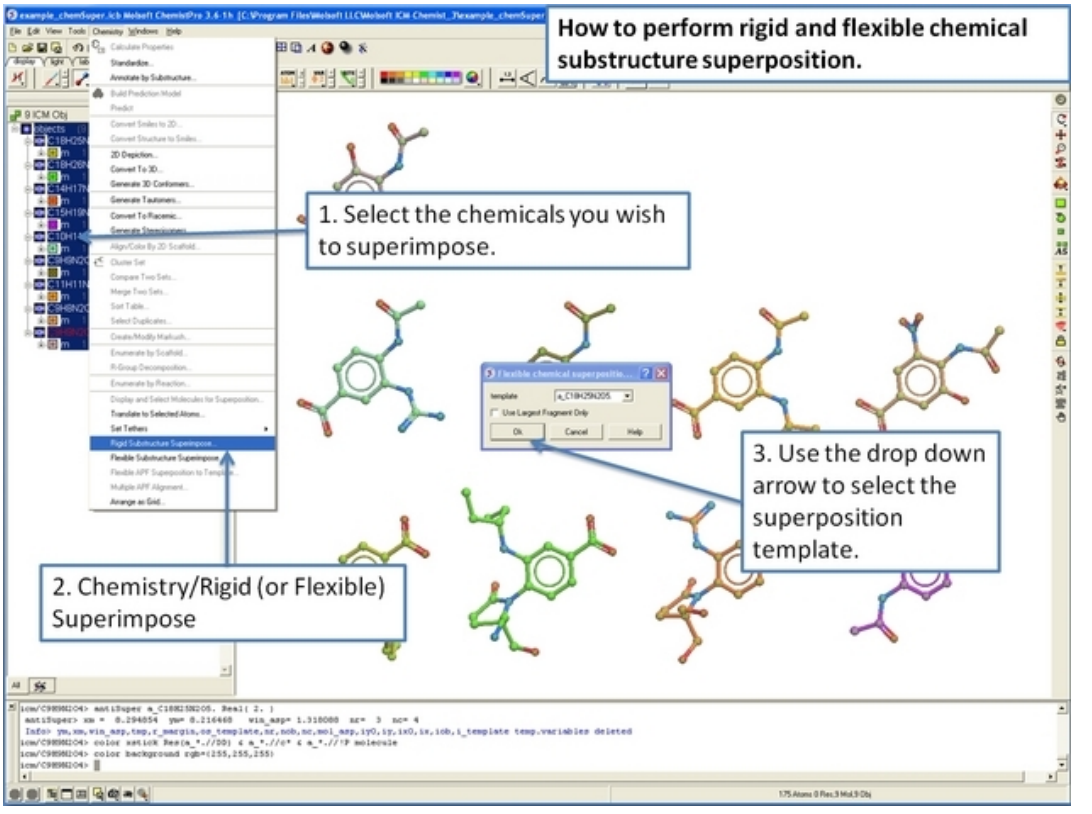


23.12.23 How to sample linkers between two chemical fragments.

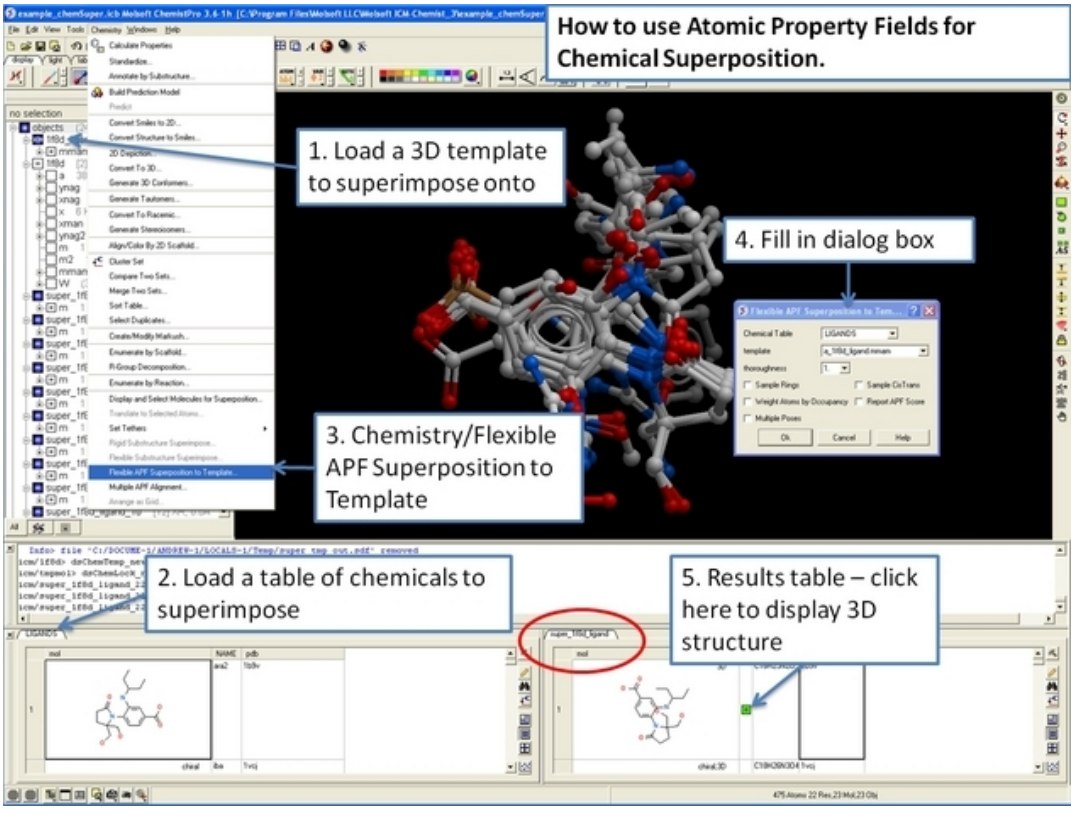


23.13 How to Superimpose Chemicals

23.13.1 How to Perform Rigid and Flexible Chemical Substructure Superposition.

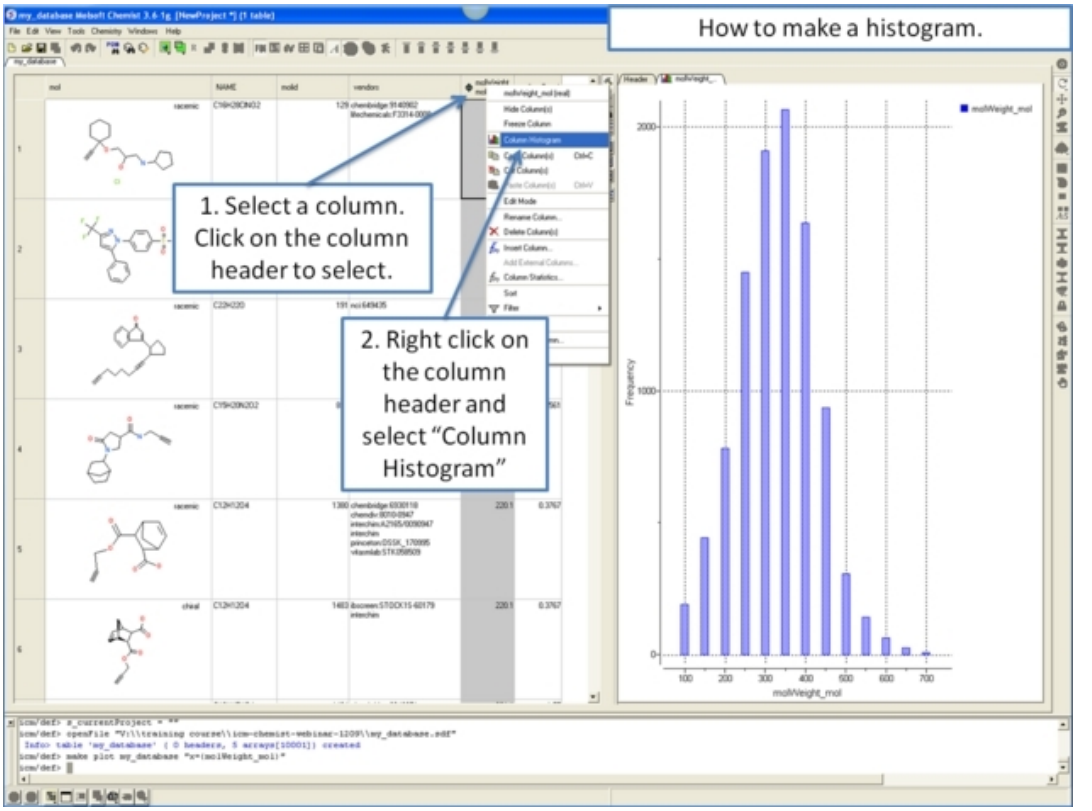


23.13.2 How to use Atomic Property Fields for Chemical Superposition

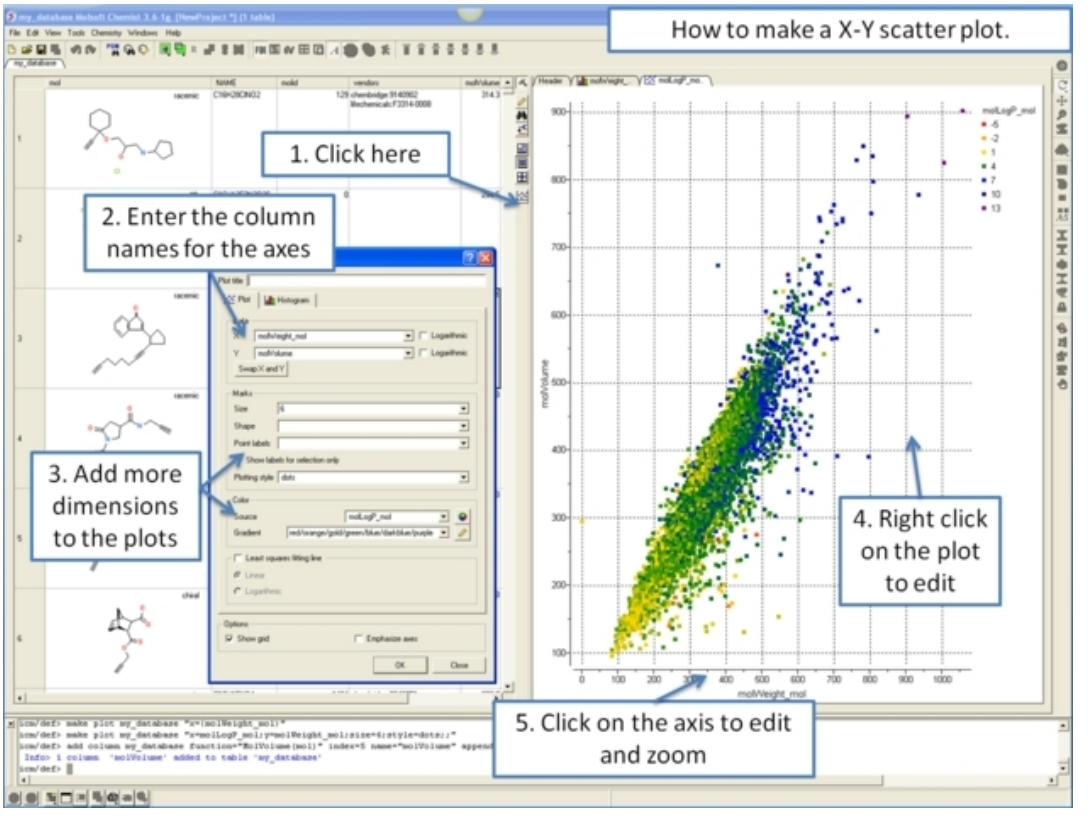


23.14 How to Generate Plots and Histograms

23.14.1 How to make a histogram.

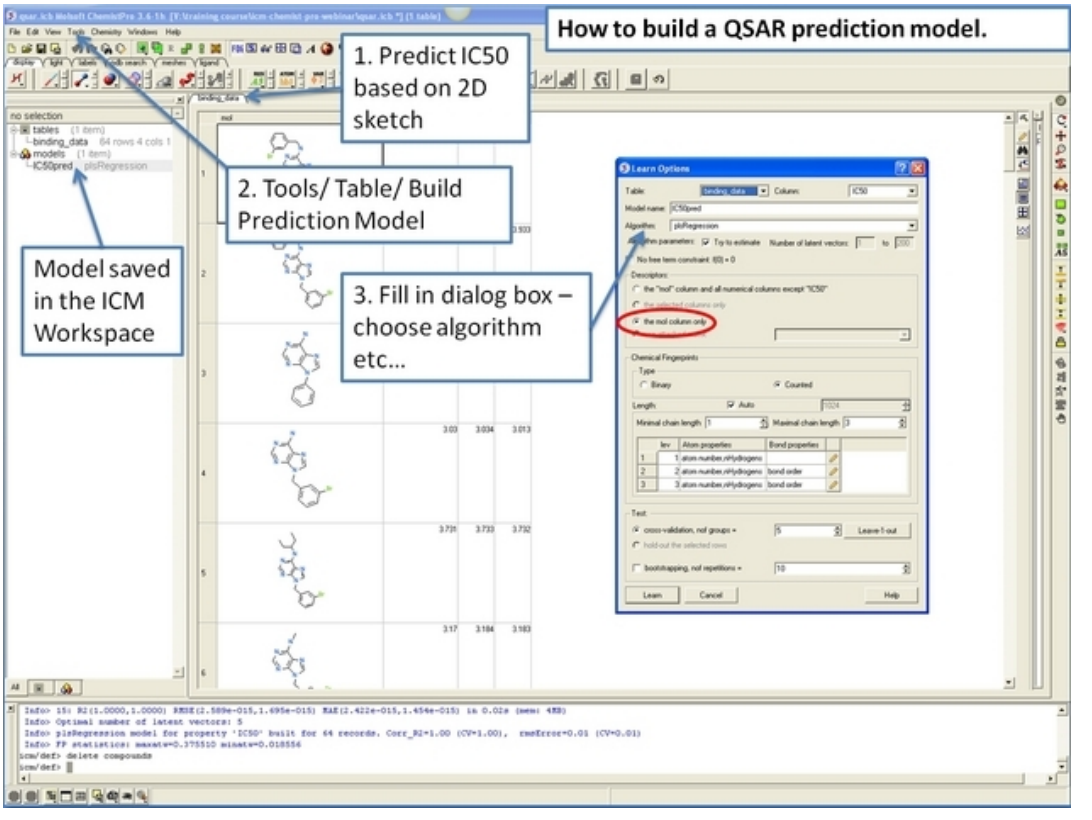


23.14.2 How to make an X−Y scatter plot.

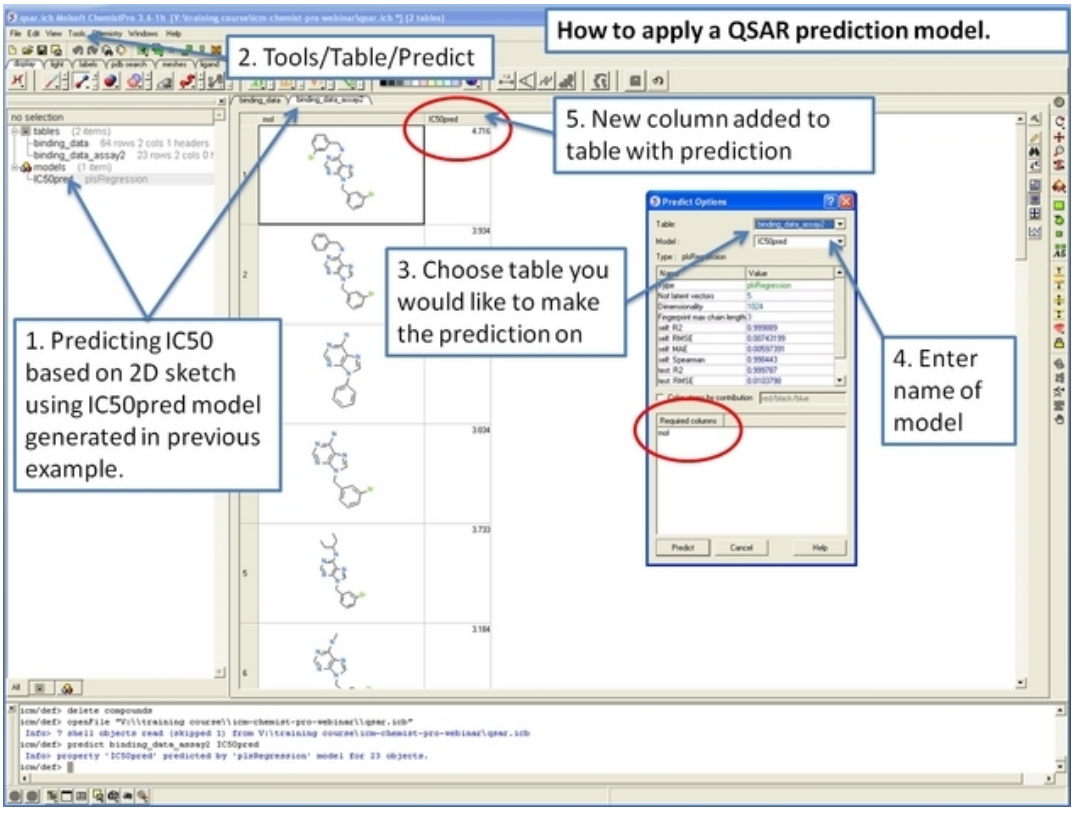


23.15 How to Build and Apply QSAR Prediction Models

23.15.1 How to build a QSAR prediction model.



23.15.2 How to apply a QSAR prediction model.



23.16 Docking Examples

23.16.1 Re−Dock Biotin to the Streptavidin Receptor

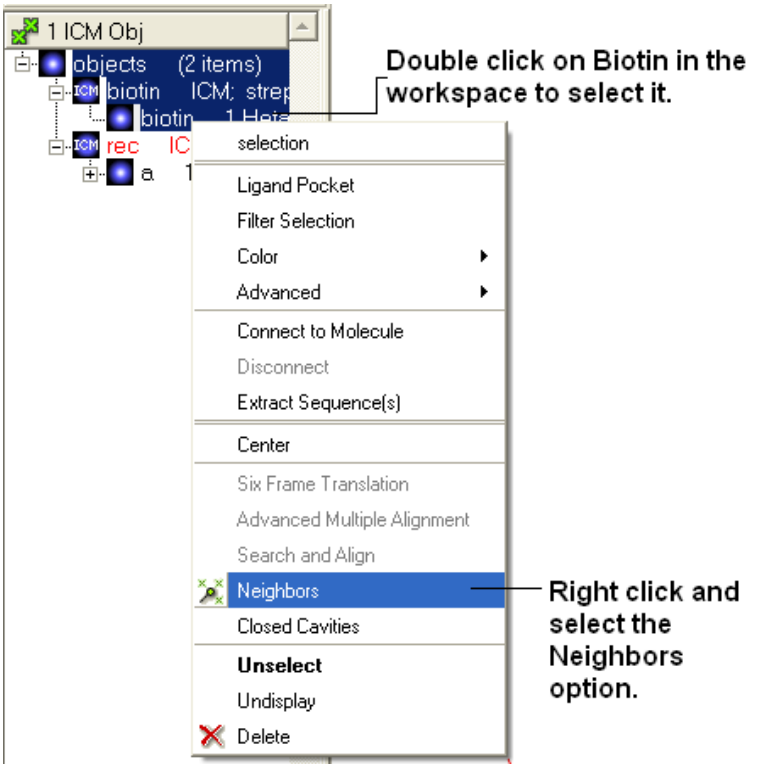
Objective

To dock biotin into the streptavidin receptor.

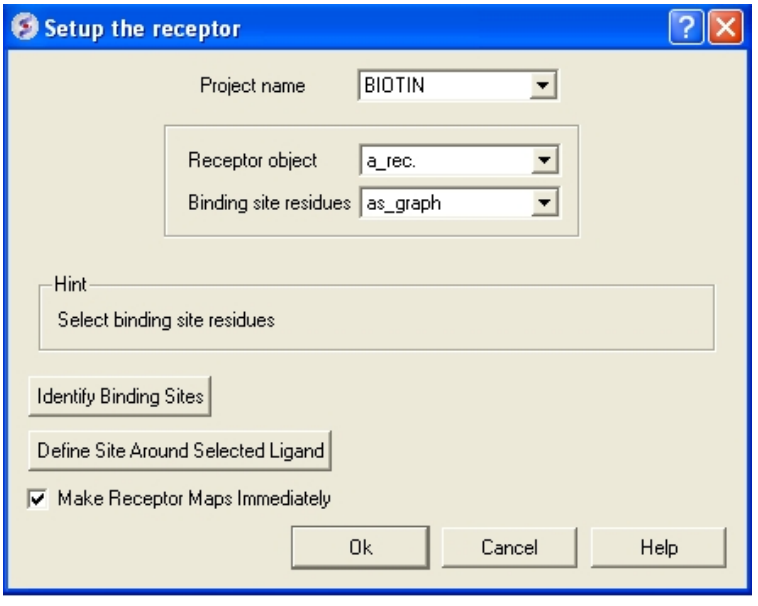
Instructions

- Docking/Set Project Name (BIOTIN)

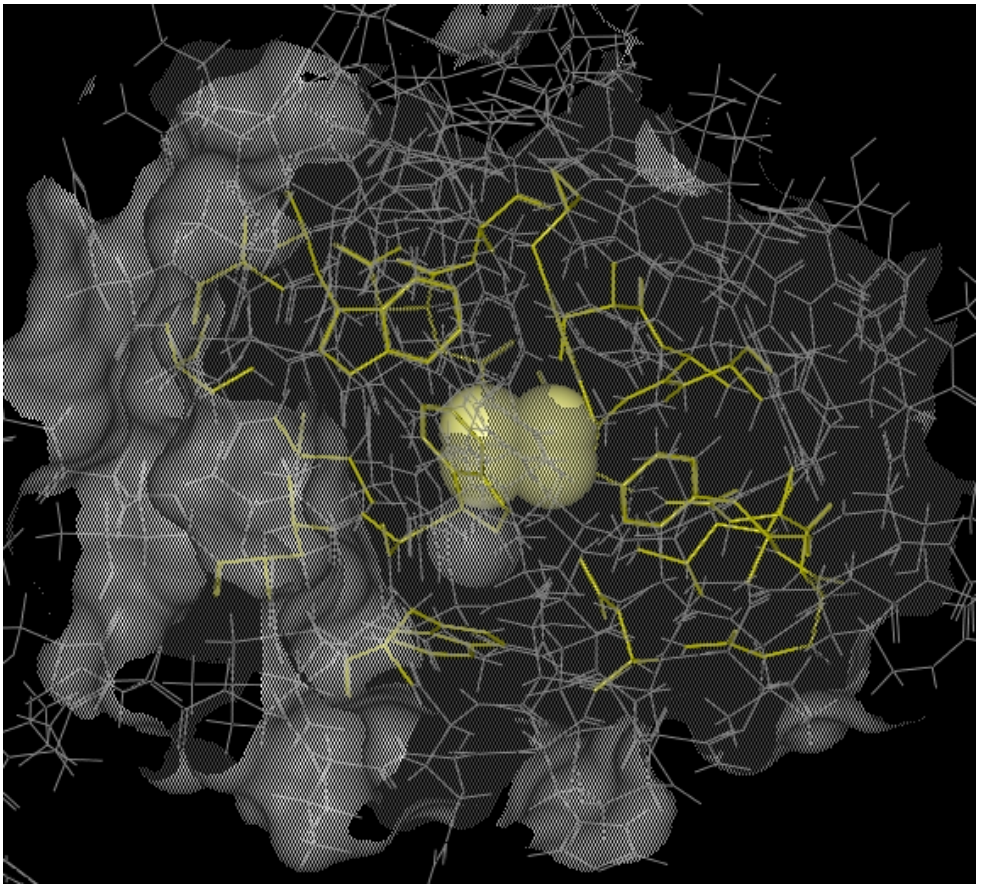
- Docking/Load Example (streptavidin complexed with haba)
- Select biotin in workspace window and right click and select neighbors.



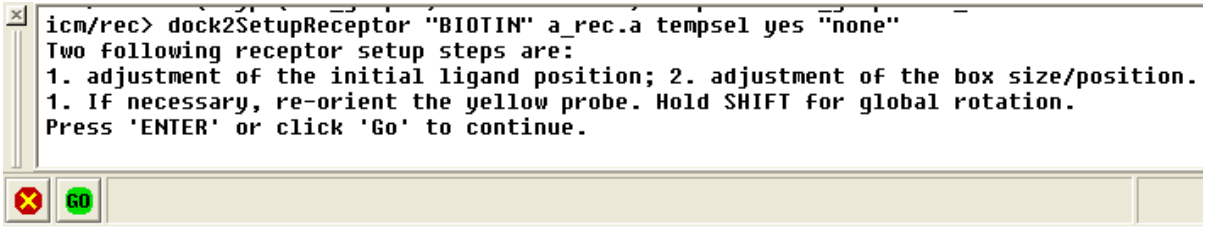
- Select atoms on other objects in a 5 A radius.
- Docking/Receptor setup (Receptor molecules: a_rec.a)



The binding pocket should be displayed something like as shown below:



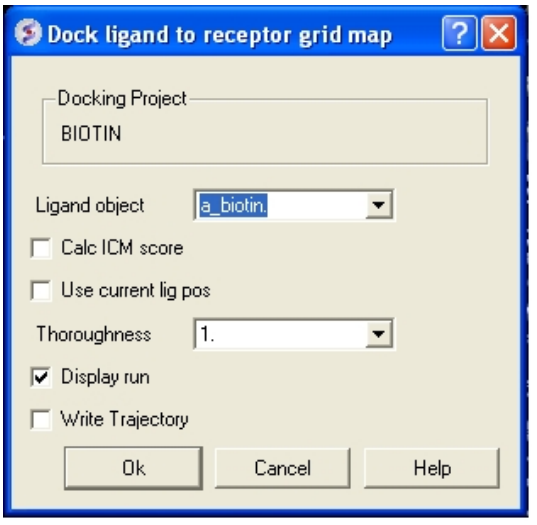
In the terminal window instructions will be given telling you how to alter the initial starting position of the ligand and how to change the size of the box in which the maps will be generated.



Adjust box size / probe position and press return or use the green GO button in the bottom left hand corner.

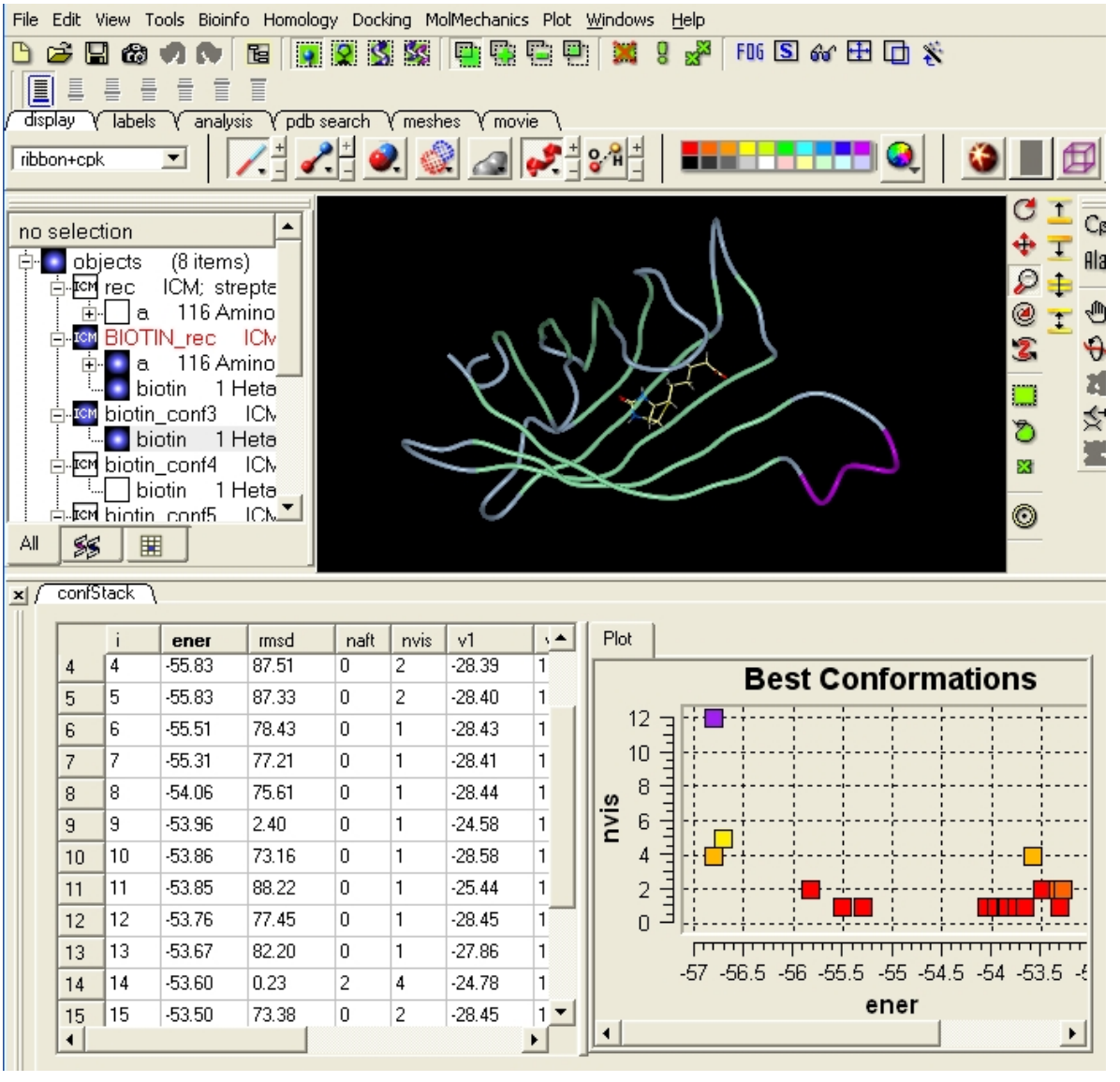
Now let us set up the ligand and start the simulation:

- Docking/Interactive Docking/From Loaded ICM object (Ligand molecule: a_biotin.biotin)



Once the simualtion has finished select

- MolMechanics > View Stack
- Double click on each element of the stack and the ligand will be displayed in the graphical display. Each ligand position can be displayed or undisplayed using the ICM workspace.



	i	ener	rmsd	naft	nvis	v1	
4	4	-55.83	87.51	0	2	-28.39	1
5	5	-55.83	87.33	0	2	-28.40	1
6	6	-55.51	78.43	0	1	-28.43	1
7	7	-55.31	77.21	0	1	-28.41	1
8	8	-54.06	75.61	0	1	-28.44	1
9	9	-53.96	2.40	0	1	-24.58	1
10	10	-53.86	73.16	0	1	-28.58	1
11	11	-53.85	88.22	0	1	-25.44	1
12	12	-53.76	77.45	0	1	-28.45	1
13	13	-53.67	82.20	0	1	-27.86	1
14	14	-53.60	0.23	2	4	-24.78	1
15	15	-53.50	73.38	0	2	-28.45	1

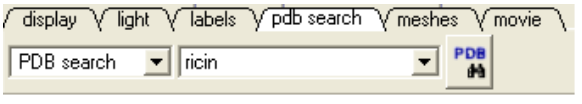
23.16.2 Re−Dock an Inhibitor to Ricin Crystal Structure

Objective

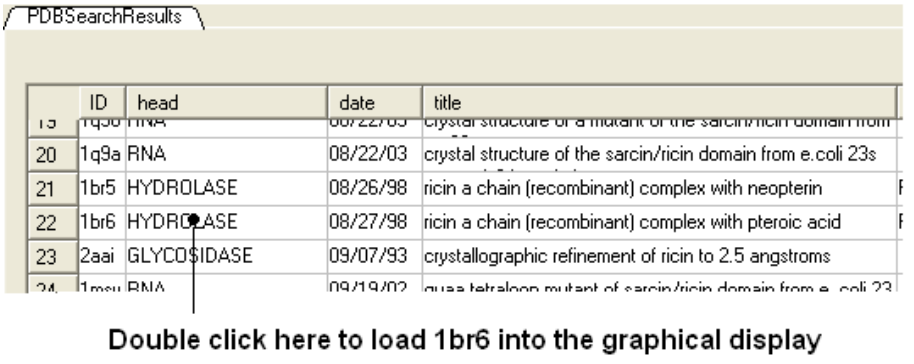
To re−dock a ricin inhibitor into the ricin crystal structure (1br6).

Instructions

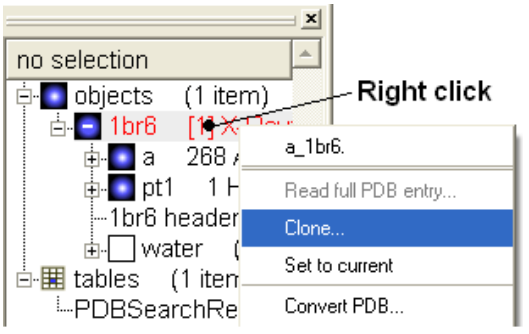
- Select the Pdb Search tab and type ricin followed by the 'Enter" key.



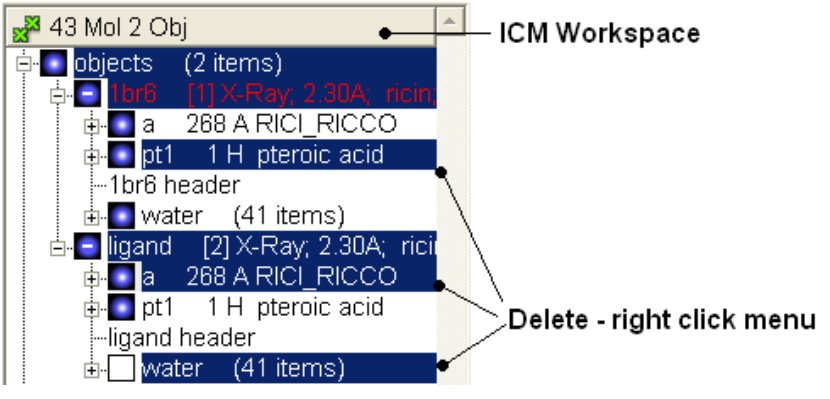
- A table as shown below will be displayed. Double−click on 1br6



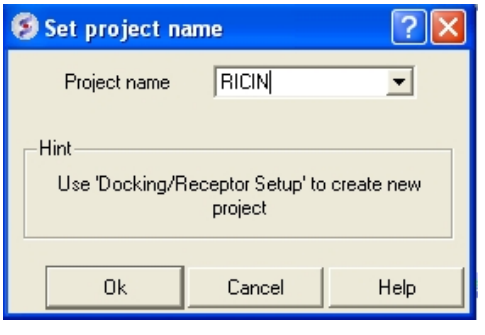
- Right click on 1br6 in the ICM Workspace and select Clone and call it ligand.



- From the first object delete the small molecule (pt1) by right clicking on it in the ICM workspace. From the clone, delete the receptor (a), and water

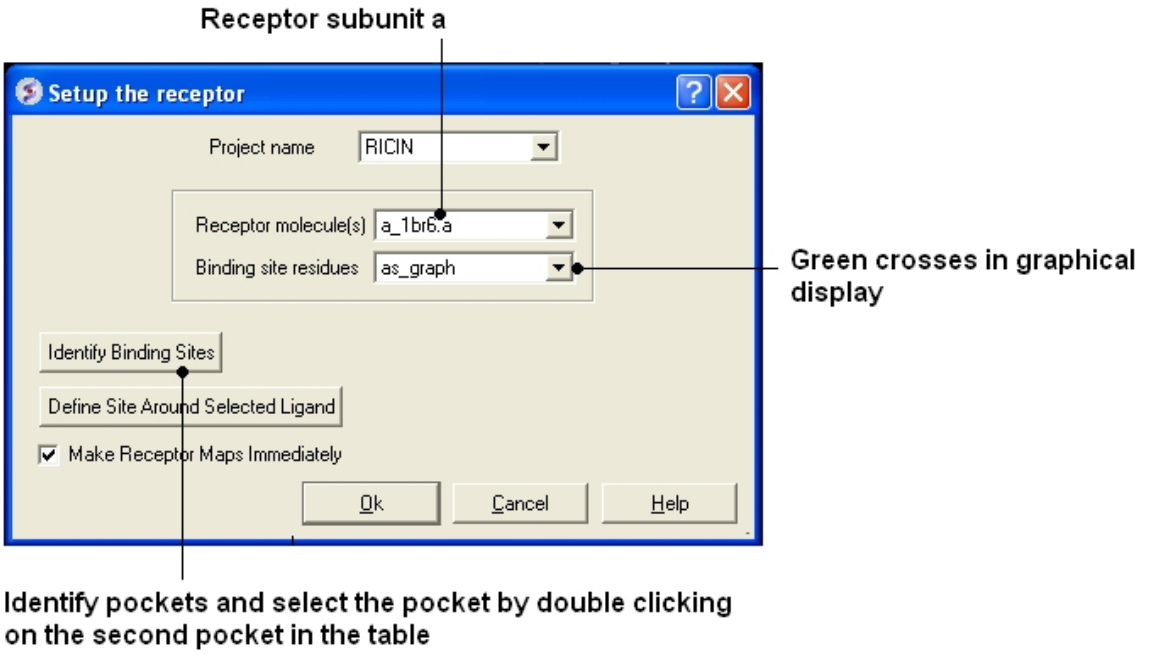


- MolMechanics >ICM−Convert >Protein (Object: a_1br6., replace the original)
- MolMechanics >ICM−Convert >Chemical (Object: a_ligand.)
- Docking > Set Project Name (RICIN)

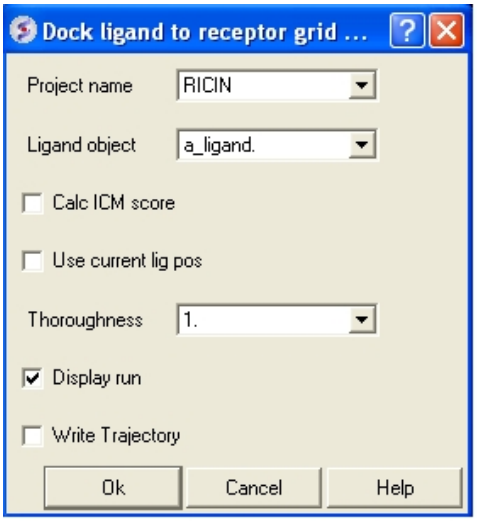


- Docking > Receptor Setup. Fill in the boxes as shown below and select the Identify binding sites button Select second pocket in the table, Click OK. Press Enter or click on the "GO" button. In

this example there is no need to change the box size or probe position.

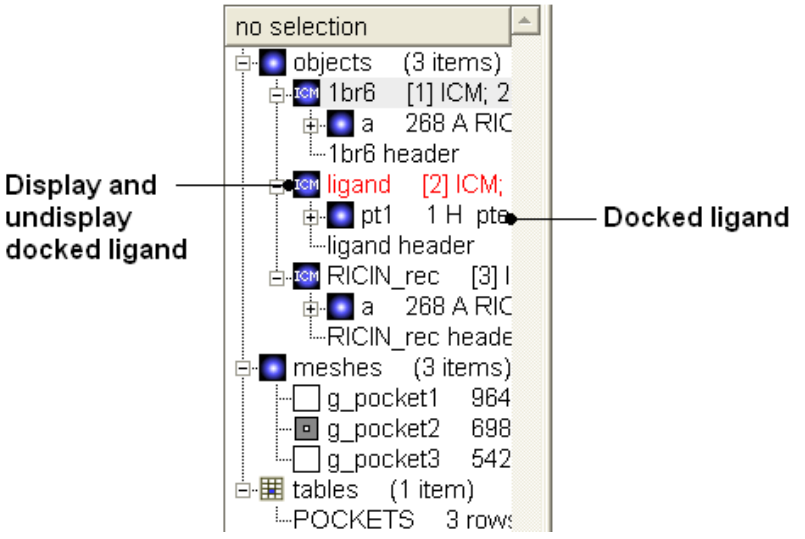


- Docking/Review/Adjust Ligand/Box (Box can be resized)
- Docking/Make receptor maps
- Docking > Interactive docking > Loaded Ligand (Ligand: a_ligand.)



NOTE: The simulation may take longer if you are displaying the ligand during docking.

Once the docking has finished you can display the best energy solution



Compare with crystal structure

- Read in 1br6 and display ligand. Note docking pose for this example can be improved by including the water molecules w37 and w41 which are inside the binding pocket. To include water molecules remember not to delete water in the pdb conversion to object and type the following in the receptor setup stage a_1br6.a,w37,w41
- You can drag and drop the docked ligand into the receptor inside the ICM Workspace resulting in a single complex (see `FAQ section` "How can I merge two separate objects into one?")

23.17 Virtual Screening Examples

23.17.1 Virtual Ligand Screening to Ricin Receptor

Objective

To perform virtual screening into the ricin receptor.

Instructions

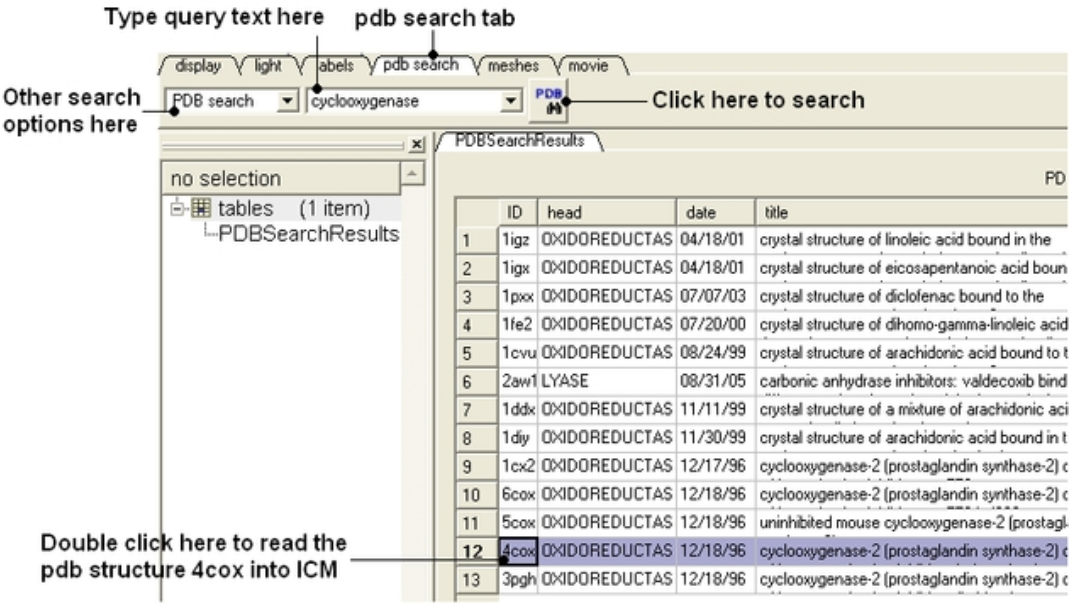
- Docking> Set Project (select RICIN) see previous lesson `Re-Dock an Inhibitor to Ricin Crystal Structure`.
- Docking> Tools> Index Mol/Mol2 file/database (Input file . select ricinLigands2D.sdf,)
- Docking> Ligand Setup> From Database (select mydb.inx, check .mol., .build hydrogens. .assign charges. and .2D to 3D. convert)
- Docking > Run Docking Batch
- Docking > Make Hit List (select import 2D from DB)
- Browse HITLIST table

23.17.2 Virtual Ligand Screening to Cyclooxygenase

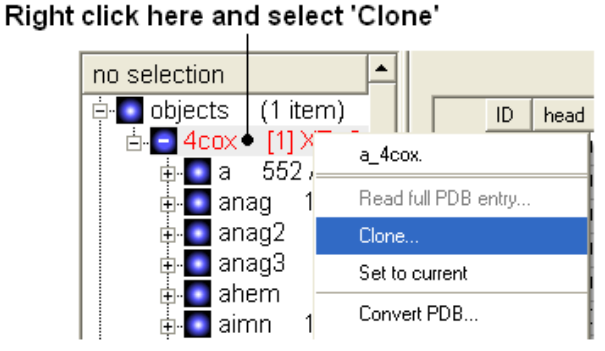
Objective: To dock **indomethacin** and perform virtual screening of a database of **COX inhibitors** into the **Cyclooxygenase** receptor.

Retrieve the Cyclooxygenase receptor 4cox from the protein databank.

- Select the **PDB Search tab** and type 'Cyclooxygenase' and hit the PDB button.
- Find the pdb entry **4cox** in the table and double click on the row to load it into ICM.



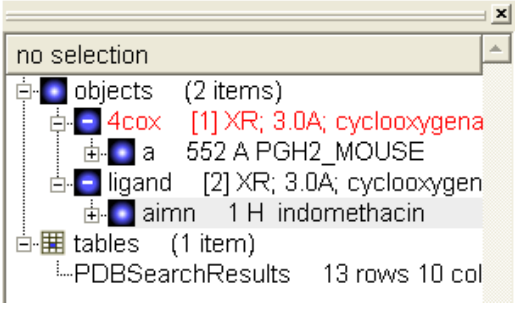
- Right click on the pdb file **4cox** in the ICM Workspace and select clone − use the default options and select OK.



- Enter object name **ligand.**
- From the first object (**4cox) delete everything except for the first molecule '**a**'
- From the second object (**ligand) delete everything except for **aimn**

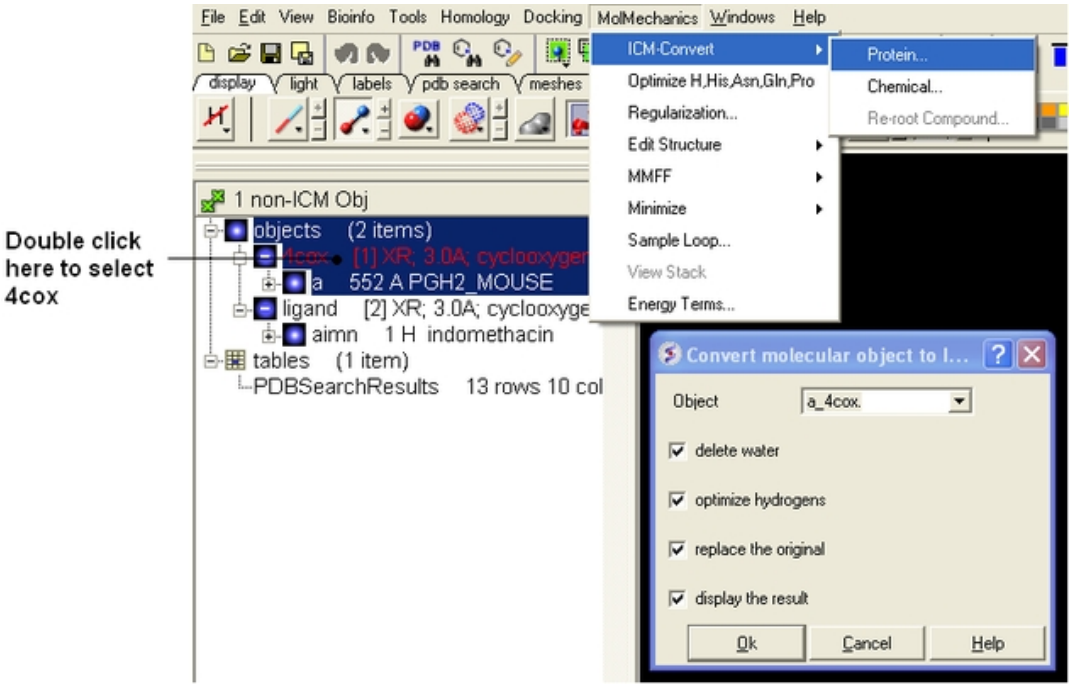
NOTE: To delete molecules you need to select them in the ICM Workspace and then right click and select **delete.** A range of molecules can be selected by clicking on one and whilst holding the **Shift** button click on the last molecule. Non−contiguous selections can be made using the **Ctrl** button.

- The ICM Workspace should now look something like this:

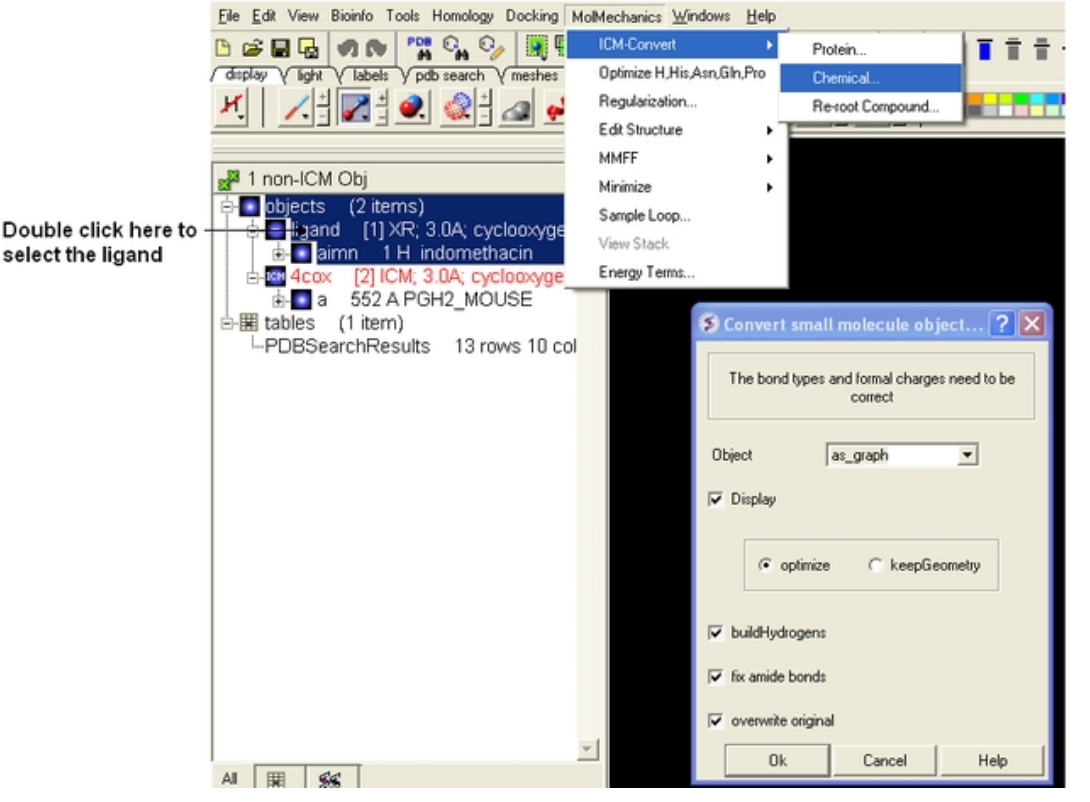


Converting the Ligand and Receptor into an ICM Object.

- Double click on the first object **4COX** and select **MolMechanics/ICM−Convert/Protein** − choose the options shown below



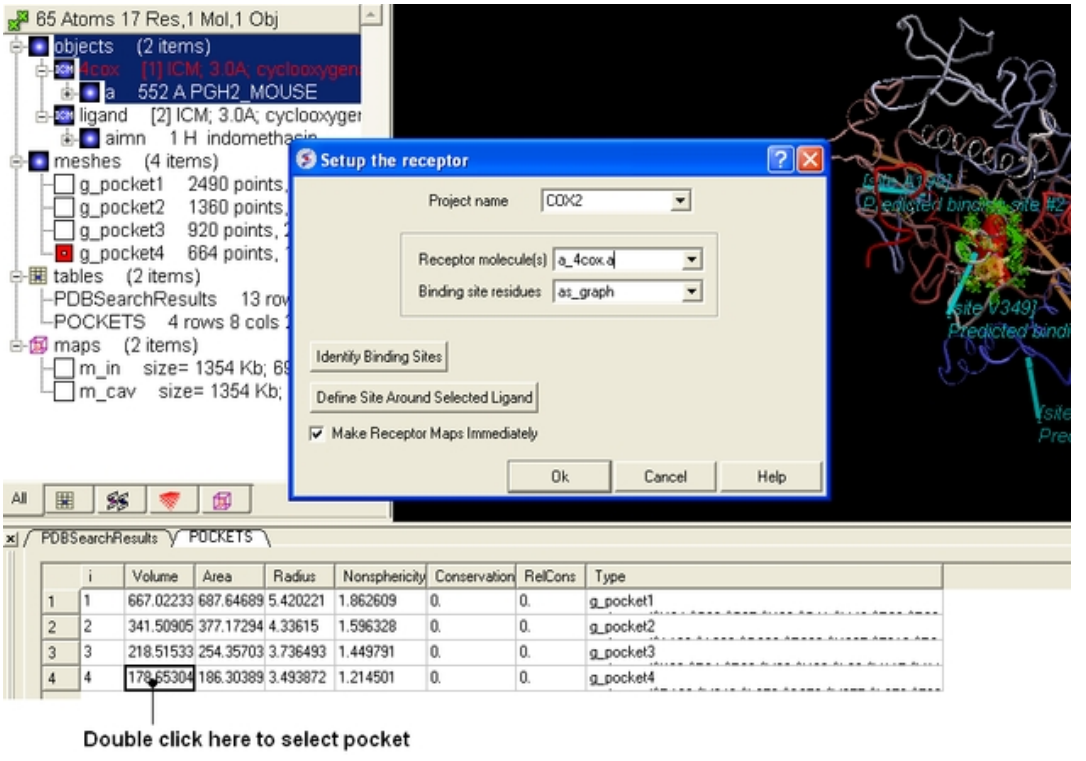
- Double click on the second object **ligand** and select **MolMechanics/ICM−Convert/Chemical** − choose the options shown below



Setting up the docking experiment

- **Docking/Set Project** enter COX2

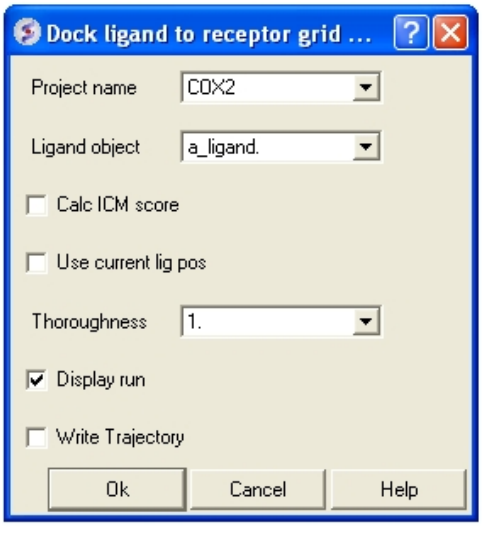
- Select **4cox** in the ICM Workspace (double click in the ICM Workspace on 4cox − should be highlighted blue in the ICM Workspace and green crosses in the graphical display).
- **Docking/Receptor Setup** and select the **Identify Binding Sites** button.
- Select the 4th pocket in the **POCKETS table** and you should see green selection crosses around the binding site as shown below.
- Fill in the **Setup the receptor** windows as shown below and press OK.



- Press the *GO button in the button left hand corner of the GUI twice. In this example there is no need to change the position of the probe or the box.

- **Docking/Make Receptor Maps** and press the **OK** button.

- **Docking/Interactive Docking/Loaded Ligand** − (see below)



- The ligand will be seen on the screen sampling the pocket.
- The final docked ligand pose will be displayed and is in the ICM Workspace

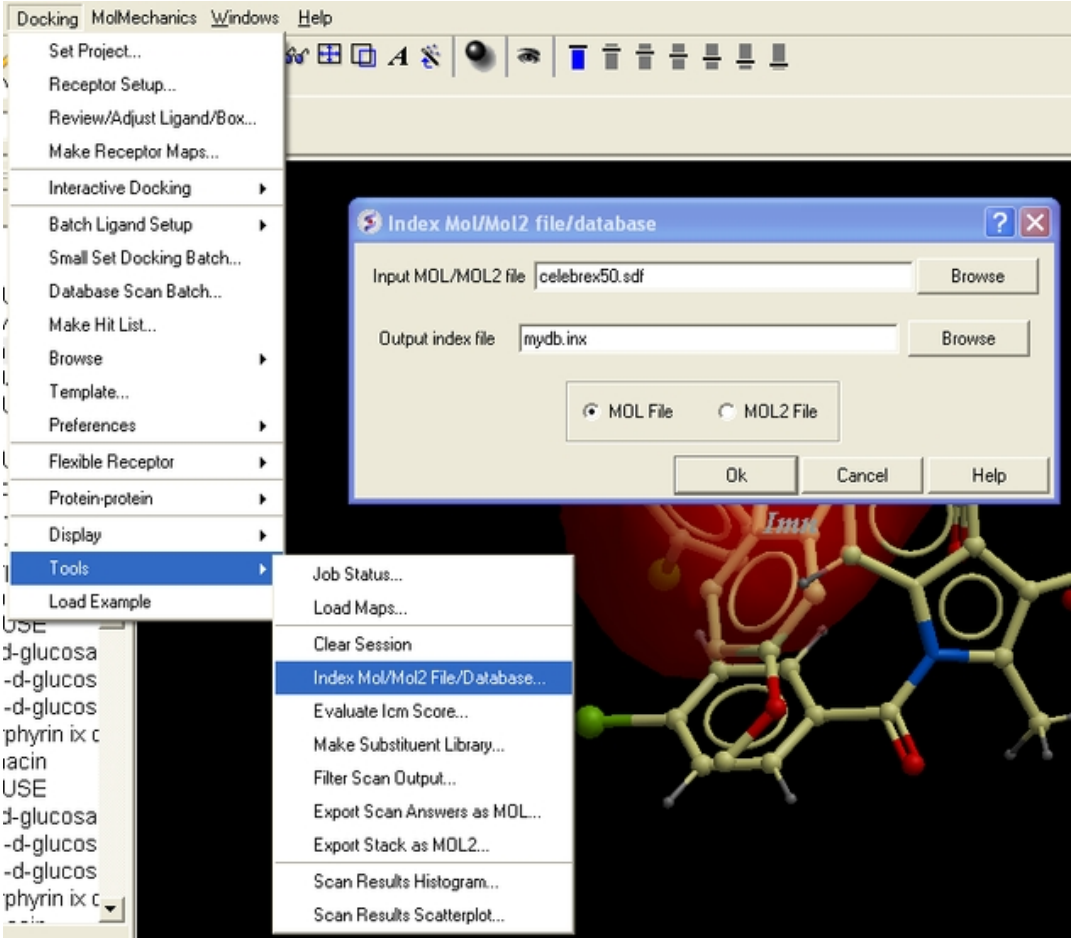
To compare the docked pose with the crystal structure − we need to rename the first object **4cox** to **4cox_receptor** (or just delete the first object) and then double click on **4cox** in the PDBSearchResults table we used earlier.

Now we will dock Vioxx into the Cox receptor

- In the ICM distribution (cd $ICMHOME or C:Project Files/MolSoft LLC) you can find a file called **vioxx.sdf.** If you cannot find this file please E mail support@molsoft.com and we can send it to you.
- **File/Open** and find the **vioxx.sdf** file
- **Docking/Interactive Docking/Mol Table Ligand**
- Compare the docked pose of Vioxx with the crystal structure **1cx2** (pdb search **1cx2)**

Now let us perform a virtual screen of a database of COX inhibitors

- **Docking/Set Project** enter COX2
- **Docking/Tools/Index Mol/Mol2/ file/database** and select celebrex50.sdf . If you cannot find this file please E mail support@molsoft.com and we can send it to you (cd $ICMHOME or C:Project Files/MolSoft LLC).



- **Docking/Ligand Setup/From Database** and select mydb.inx − check mol,build hydrogens, assign charges and 2D to 3D convert
- **Docking/Run Docking Batch**

You can check up on the progress of the docking by selecting Windows/Background Jobs. A messsage will be displayed on the screen when the docking is finished.

- **Docking/Make Hitlist** select import 2D from DB
- Browse Hitlist table to view docked complexes.

23.18 Docking a Markush Library

NOTE: this functionality is only available in versions 3.6 and above.

Background Once a lead compound has been identified by virtual screening, experimentally tested for activity and crystallized to confirm the docked pose then you may want to try and optimize the compound by modifying the scaffold and improve the ligand−receptor interactions. One way to do this is to enumerate a `Markush library` and dock that **but** a more direct and quicker method is to generate a focused Markush library and then dock on the fly. In this example we will use the roscovitine ligand bound to CDK5 as a scaffold to generate a focused Markush library and then identify compounds which may have better receptor interactions than roscovitine.

Step 1: Load the PDB File and Convert to ICM Object

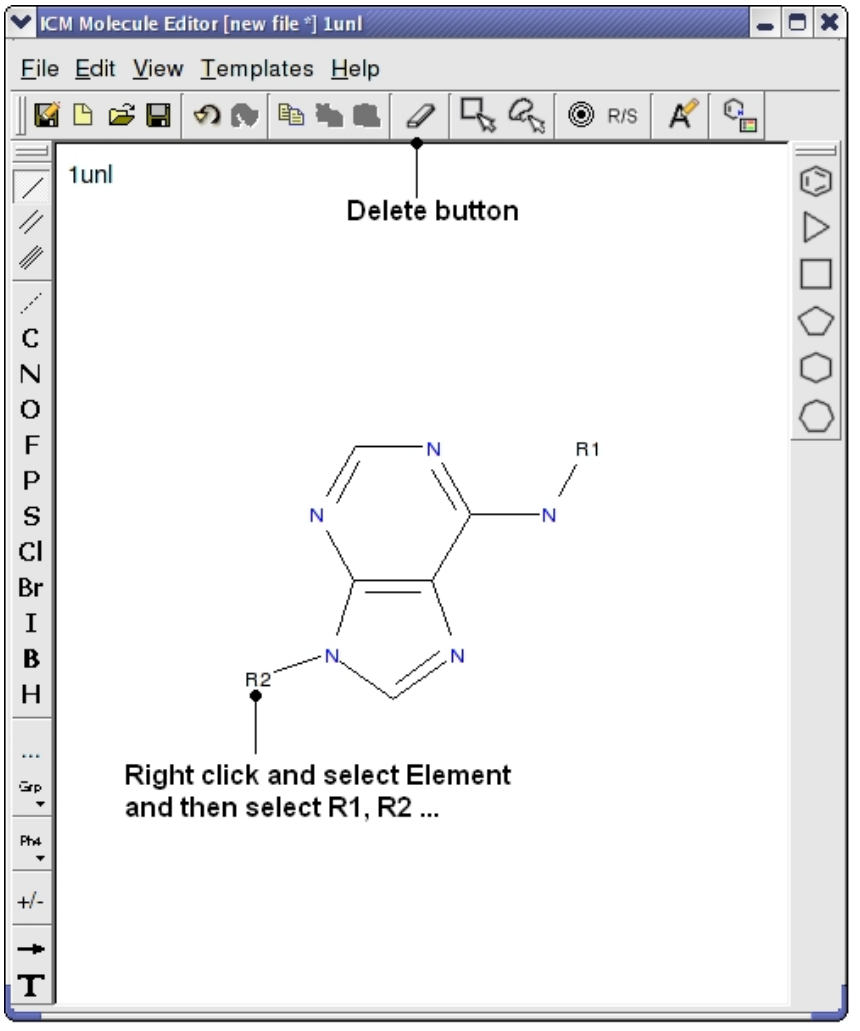
- Select the PDB Search tab and enter pdb code **1UNL.**
- Delete the subunits we are not interested in. Delete "b", "d","e" and "W" (water) by double−clicking on the subunits in the ICM Workspace whilst holding the CTRL key. This will select the subunits (highlighted blue in the ICM workspace and green crosses in the graphical display) and then right click and select **Delete.**
- MolMechanics/ICM Convert/Protein select optimize hydrogens and display the result.

Step 2: Inspect the ligand binding pose and identify positions to add new substituents.

- Right click on the ligand which is abbreviated to **"arrc"** in the converted object in the ICM workspace and select **Ligand Pocket**.
- The ligand roscovitine has a purine scaffold and there are a couple of places where substituents could be placed in order to improve ligand−receptor interactions.
- In this example we will add two R−groups (see next step).

Step 3: Extract the ligand and draw Markush structure

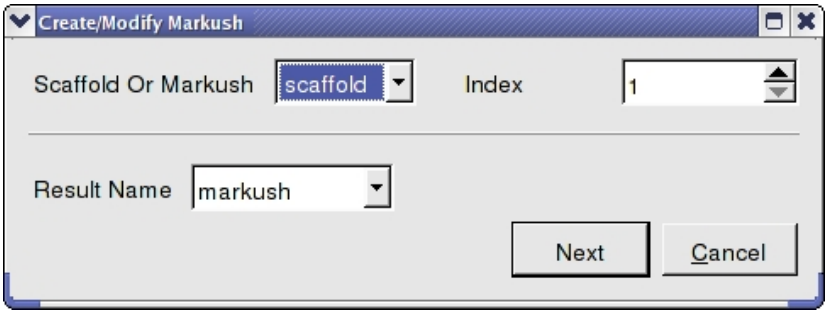
- Right click on the ligand "arrc" in the converted object in the ICM workspace and select **Extract Ligand** and choose the extract 2D drawing option. The sketch will now be displayed in an `ICM chemical spreadsheet`.
- Right click on the sketch of the compound and select **Edit Molecule**
- Use the delete button and add R groups options in the `Molecular Editor` to edit the scaffold as shown below.



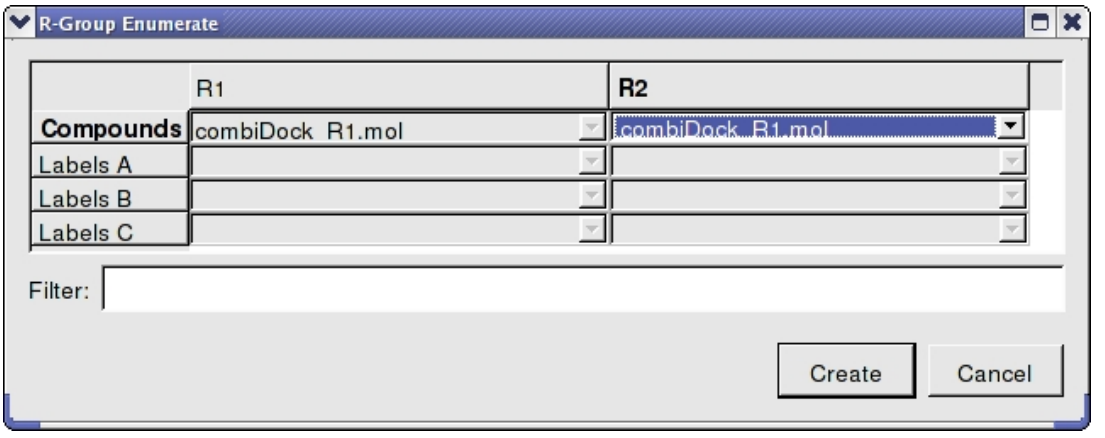
- Close the `Molecular Editor` window by clicking on the cross in the top right hand corner and the changes will be submitted to the table.
- The sketch in the chemical spreadsheet is named "chem" by default. For this example we will rename it "scaffold". You can rename it by right clicking on the table tab and selecting rename.

Step 4: Create Markush Combinatorial Library

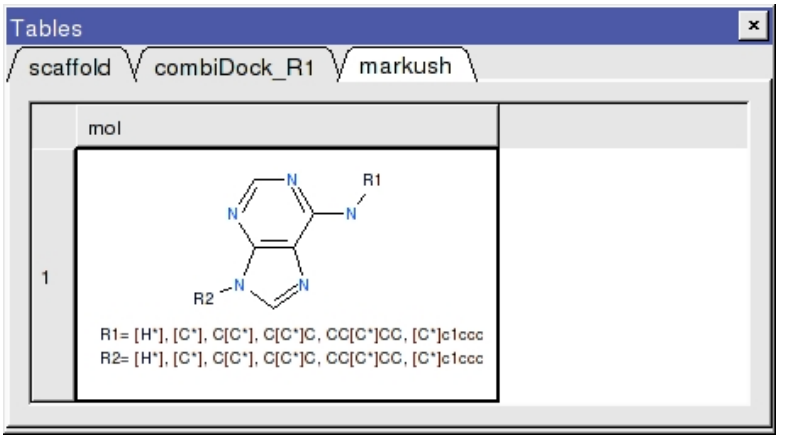
- Read in a table of substituents. For this example we will use an sdf file called combiDock_R1.sdf − this can be found in the ICM distribution (File/Open). If you cannot find this file please E mail support@molsoft.com and we will send it to you.
- Chemistry/Create Modify Markush and enter the data as shown below and press next.



- Enter the name of the table containing substituents for R1 and R2. In this example we will use the same table **combiDock_R1** for R1 and R2 as shown below. You can use the drop down arrows to select the table you require.

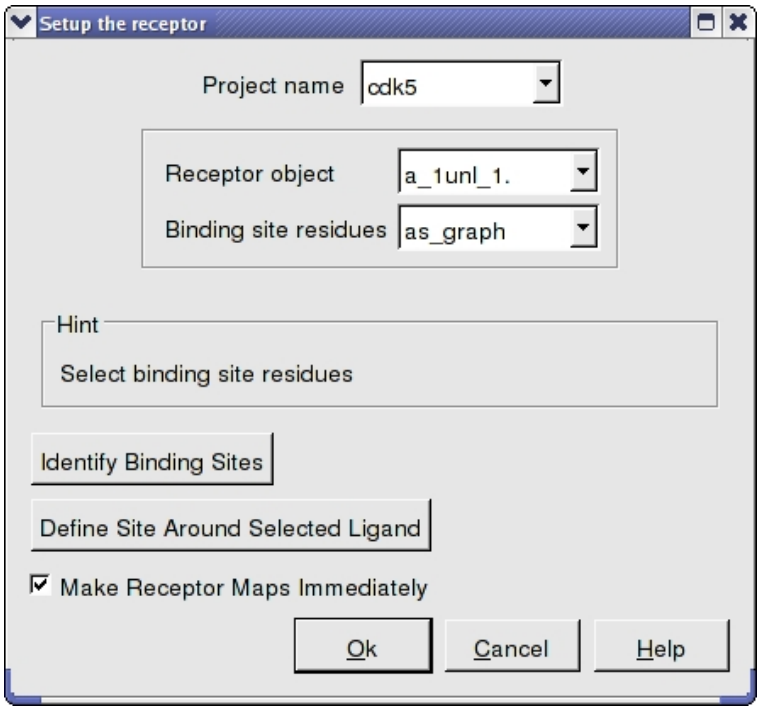


- Once the tables are selected press **Create** and a new chemical table will be displayed with the markush structure annotated with the substituents for R1 and R2 as shown below.

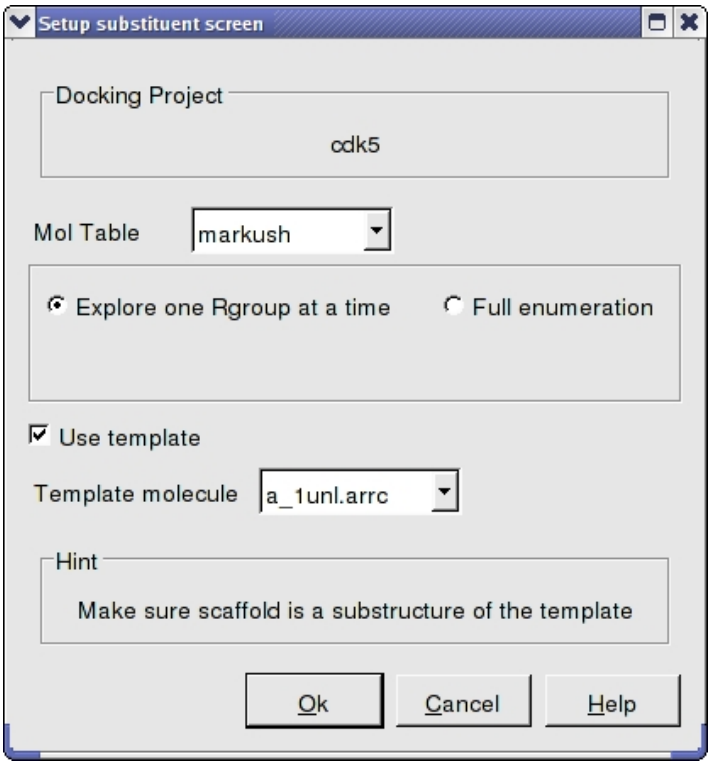


Step 5: Dock Markush Combinatorial Library

- Move the ligand from the converted object so that we can dock in that position. To do this right click on the ligand (arrc) in the converted object and select "move from object".
- Docking/Project Name Enter a name for the project e.g. cdk5
- Docking/Receptor Setup − enter the data as shown below. To select the residues around the ligand. Double click on the converted ligand in the ICM Workspace to select it and then press the button labeled **Define Site Around Selected Ligand**.
- Click OK.

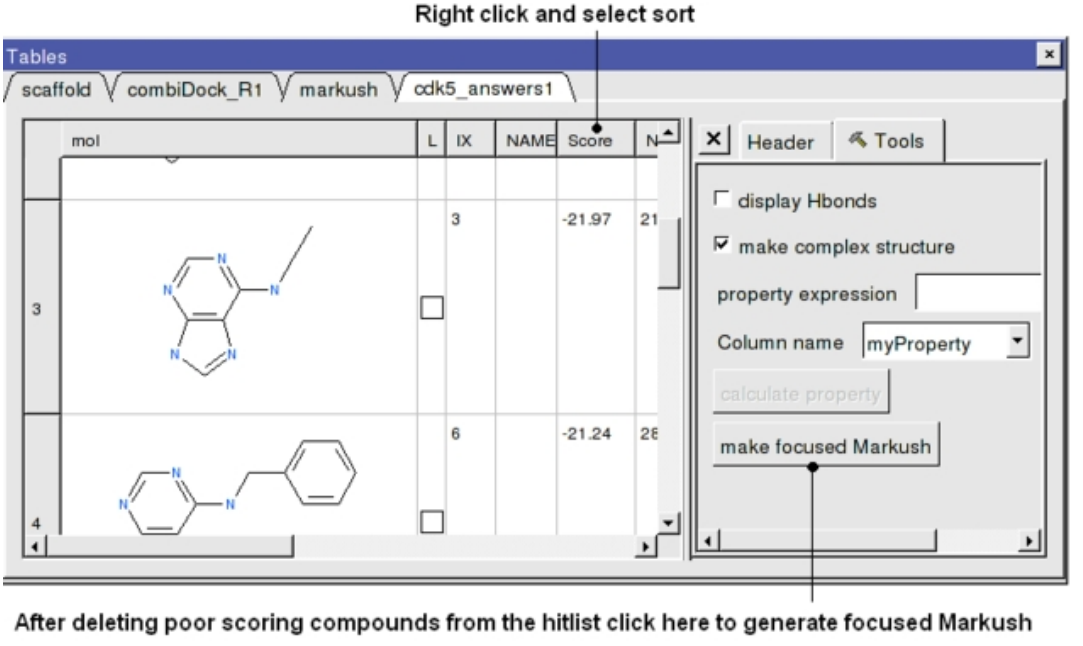


- In this example there is no need to change the position of the probe or the size of the purple box. Click on the **GO** button (bottom left hand corner) to proceed to the preparation of maps. The generation of maps usually takes a couple of minutes.
- Docking/Setup Batch Ligand/ Markush Combinatorial Library
- Enter the name of the table containing the Markush structure.
- In this example we are going to first enumerate the Markush library by exploring one Rgroup at a time rather than a full enumeration. The substituent table (combiDock_R1) has 8 groups and with the "one at a time" option a hydrogen will be placed on one Rgroup whilst the other 8 groups are substituted on the other R group. Therefore in this case we will dock 16 compounds rather than 64 with the full enumeration. This option is particularly useful if you have many hundreds of substituents and this is a shortcut to save you from docking all of them. You will see in the next steps that docking score will be used to evaluate which substituents have good receptor interaction and then only the good substituents are used for full enumeration.
- We know the correct binding pose of the main scaffold of our Markush structure and therefore we will select the docking to template option (**{Use template}). The template option will match the substructure of the Markush and use this as a template. To choose the template select the original ligand from the drop down menu. In this example the ligand is defined in the ICM selection language as − **a_1unl.arrc** (see screenshot below).
- Click OK.
- Docking/Run Docking Batch

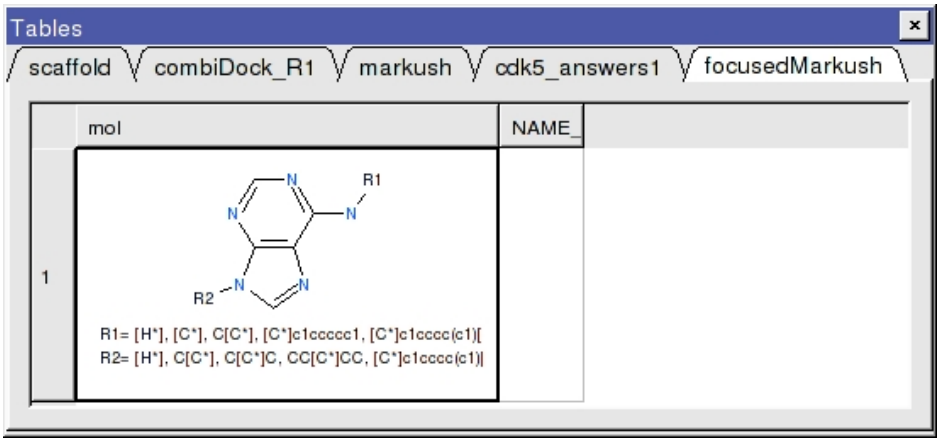


Step 6: Make a focused Markush library

- When the docking is complete make a **hitlist** Docking/Make Hit List.
- Sort the hitlist by Score. You can sort a column by right cliking on the column header and selecting sort.
- In this example we will delete all compounds that scored higher than −15. To delete a row select it by clicking on the row header and then right click on the row header and select **Delete Row**. At this point you should be left with ~9 compounds.
- Click on the button on the right hand side of the hitlist labeled **make focused Markush** (see below). If you do not see this panel − Right click on the table and select Table View/ View Extra Panel.

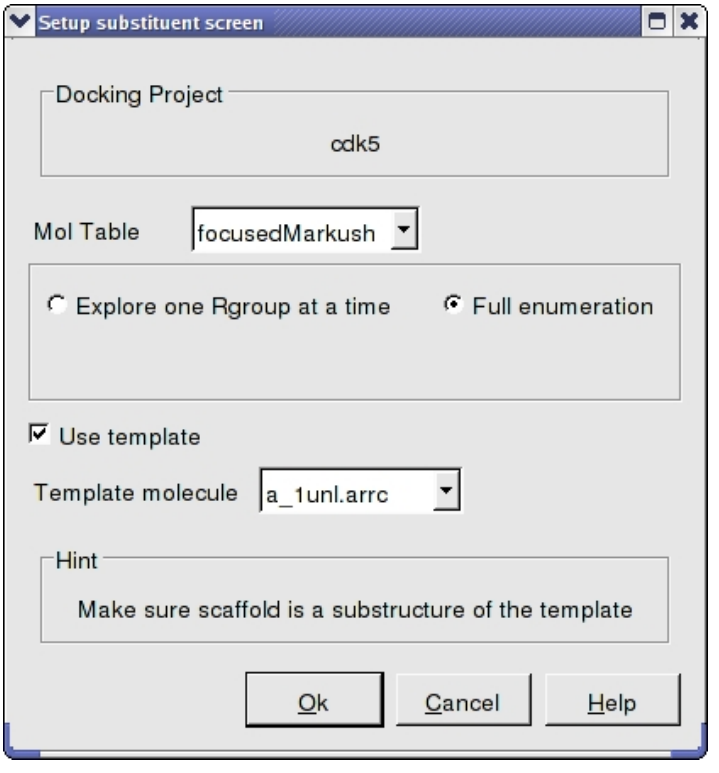


- A focused library based on the substituents contained within the top−scoring hits will be generated and displayed in a chemical table entitled **focusedMarkush** as shown below.



Step 7: Dock focused Markush library

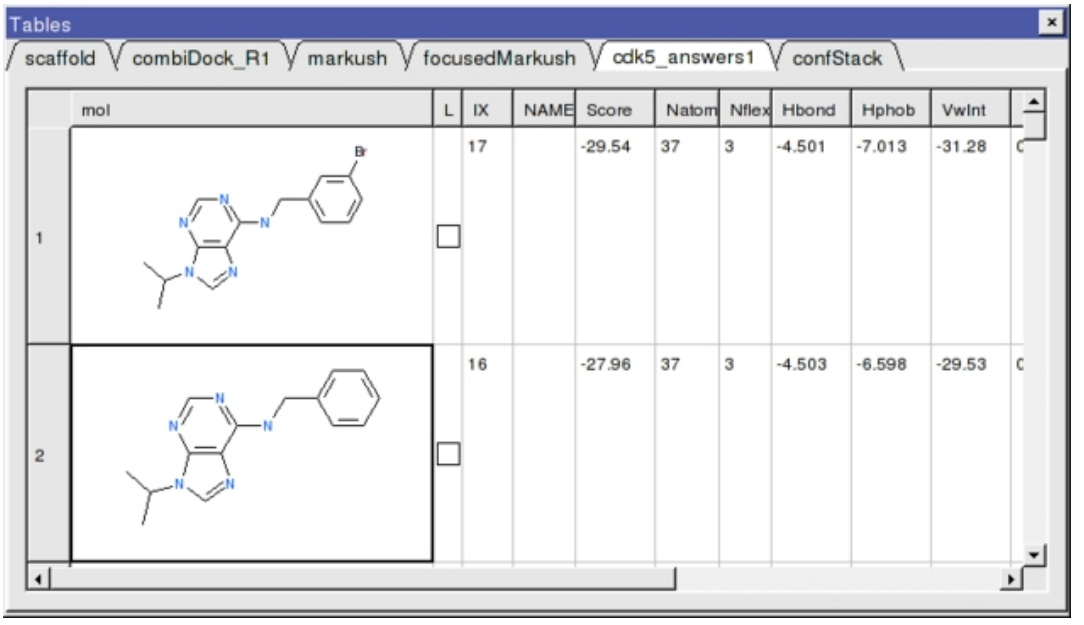
- Docking/Setup Batch Ligand/ Markush Combinatorial Library
- Enter the name of the table containing the **focused** Markush structure.
- Select **Full** Enummeration this time for the focused Markush library.
- Select the template as before.



- Docking/Run Docking Batch

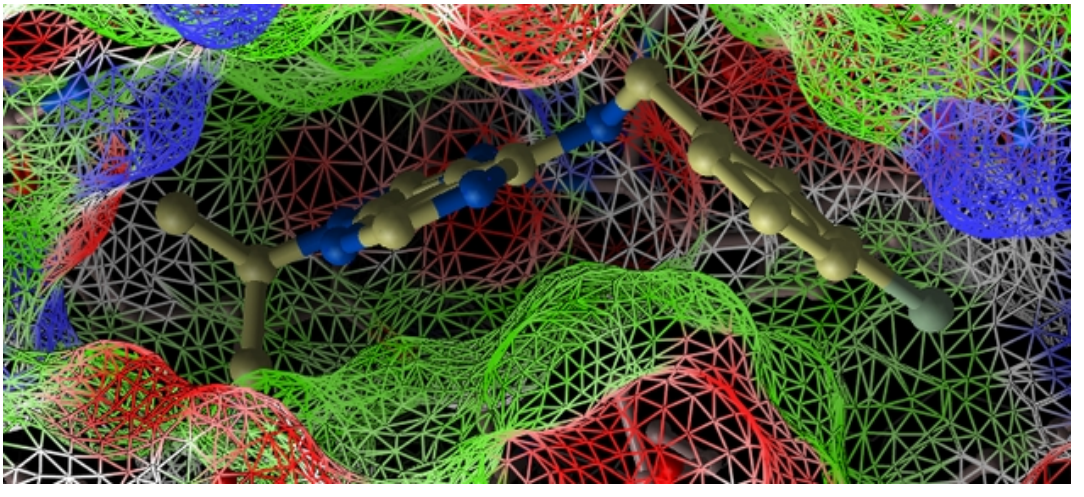
Step 7: Evaluate results

- When the docking is complete make a **hitlist** Docking/Make Hit List.
- Sort the hitlist by Score. You can sort a column by right cliking on the column header and selecting sort.
- If everything went well the top two hits should be as shown below.



The 2nd compound on the list is the original ligand in the 1UNL structure of CDK5 whilst the generation and screening of a Markush based library has led to the identification of a better binder in terms of ICM score. The compound ranked one has a bromine attached to a ring in the R1 position.

- Let us view how the bromine is interacting with the receptor.
- Docking/Display/Property Skin
- Click OK and a skin surrounding the pocket will be displayed.
- Double click on the top−scoring compound in the hitlist and it will be displayed in the pocket. To zoom into the pocket click on the ligand in the ICM Workspace and then press the center button. You will see that the bromine is making a contact with the hydrophobic part of the pocket (colored green) and thus improving the interactions with the receptor compared to the original ligand scaffold.



23.19 Multiple Receptor Conformation Ensemble Docking Example

Background

Here we will demonstrate multiple receptor conformation docking in ICM using Aldose Reductase as an example. Aldose Reductase has a flexible loop in the ligand binding pocket vicinity which enables a variety of inhibitors to bind therefore in order to identify these ligands via docking it is necessary to sample the conformations of this loop and dock to an ensemble of structures. **Step 1** to **Step 3** takes you through the standard re−docking procedure and highlights the accuracy of re−docking a ligand to the receptor

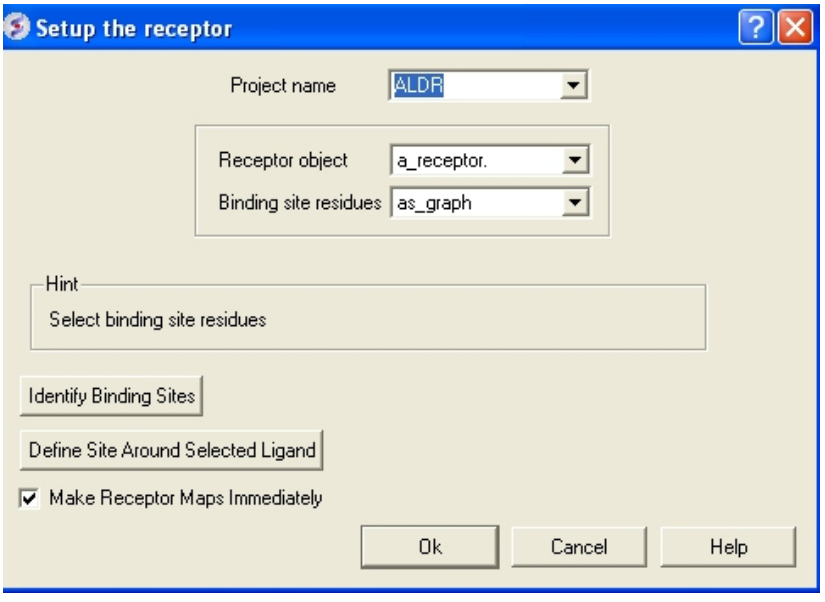
conformation from which it was crystallized. **Step 4** demonstrates that a single conformation of the Aldose Reductase receptor cannot account for the binding of all known aldose reductase inhibitors. **Step 5** outlines the steps for sampling the conformation of the flexible loop regions and generating a series of conformations (stack). **Step 6** is the multiple receptor docking stage (4D docking) and the results are viewed in a hitlist with an additional column which reports the receptor conformation that the highest scoring ligand is bound to.

Step1: Prepare the Receptor

- `Load` PDB file 1pwm. You can search for a PDB file using the PDB Search tab.
- Delete the chlorine atom. This can be done by right clicking on the chlorine in the ICM Workspace and selecting delete.
- Move the ligand (fid) out of the receptor. You can do this by right clicking on the ligand (fid) in the ICM Workspace and select **Move From Object**.
- `Convert` 1pwm into an ICM object. MolMechanics/ICM−Convert/Protein
- Rename the small molecule (fid) object "ligand" and the receptor object "receptor". You can rename an object by right clicking on the name of the object in the ICM Workspace and select **rename.**

Step2: Setup the Docking Project

- Docking/Set Project and enter the project name **ALDR**
- Docking/Setup Recptor Enter the data as shown below. Double click on the ligand in the ICM Workspace and then select the **Define Site Around Selected Ligand** button (you should see green crosses surrounding the ligand on the receptor).
- Click OK and then the green GO button twice and wait for the maps to be generated.



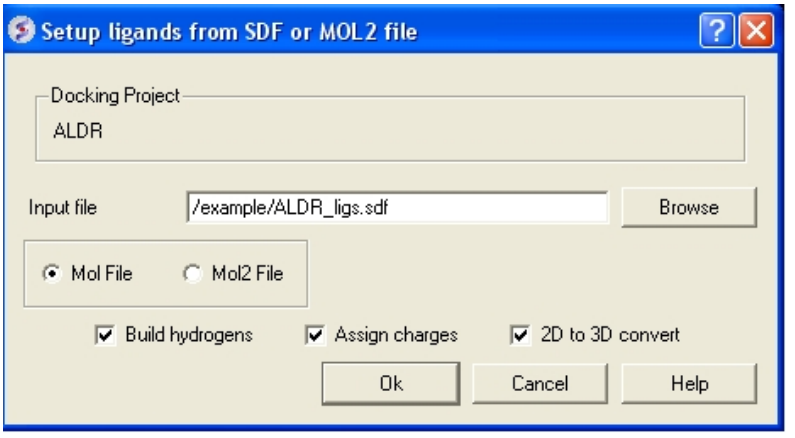
Step 3: Optional: Re−Docking the X−ray Ligand

- Drag the ligand out of the pocket so that we can re−dock it. You can do this using the `CONNECT` option. Right click on the ligand and select **Connect to Object** and then use the middle mouse button to drag the ligand. Once you have moved the ligand press the escape button.
- `Convert` ligand into an ICM object. MolMechanics/ICM−Convert/Chemical − select or enter a_ligand.
- Docking/Setup Batch Ligand/From loaded ICM object − enter a_ligand.
- Click OK
- Docking/Run Docking Batch
- Once the docking has finished select Docking/Make Hitlist. Compare the docked ligand to the crystal structure ligand in 1PWM. The ligand should be accurately re−docked and overlay nicely with the crystal structure ligand. In the next part of this exercise we will try to determine if other inhibitors to this receptor could be identified using this one crystal structure or if more than one representation of the receptor is needed.

Step 4: Docking a Set of Known Inhibtors

In the next part of this exercise we will try to determine if other inhibitors to this receptor could be correctly docked using this one crystal structure or if more than one representation of the receptor is needed. We have already setup the docking project and made all the required maps (Steps 1 to 3) so now let us dock a set of inhibitors to the receptor. We will dock a database called ALDR_ligs.sdf which should be present in your ICM distribution if you cannot find this example sdf file then please E mail support@molsoft.com and we will E mail it to you.

- Docking/Setup Batch Ligand/ From FIle: SDF/MOL2 − Select Mol and Check All boxes

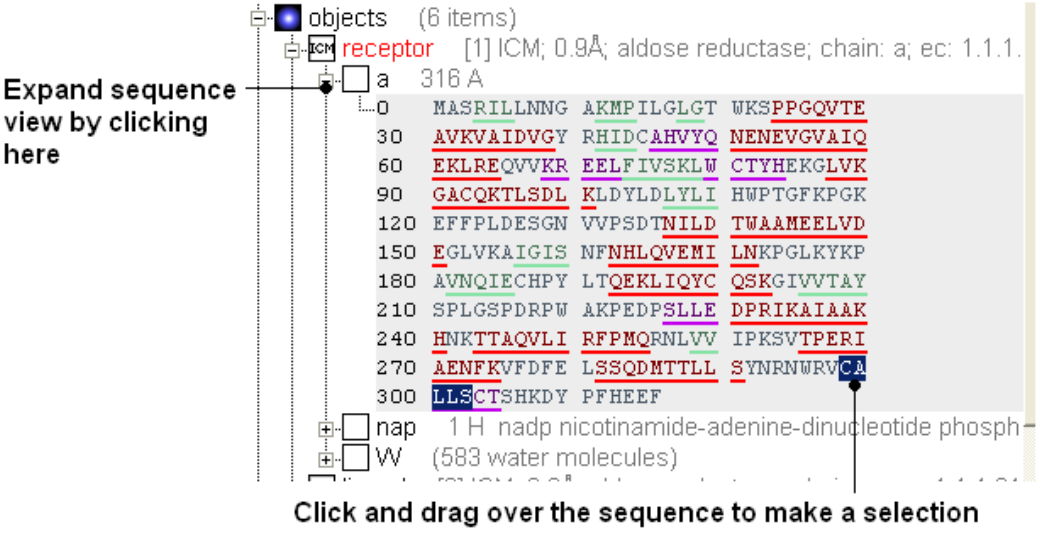


- Docking/Run Docking Batch
- Once the docking has finished select Docking/Make Hitlist. Notice the poor poses and scores for some of the inhibitors − can these be improved by incorporating multiple receptor conformations?

Step 5: Generating Multiple Receptor Conformations

Here we will generate multiple receptor conformations of a flexible loop in the binding pocket of 1PWM.

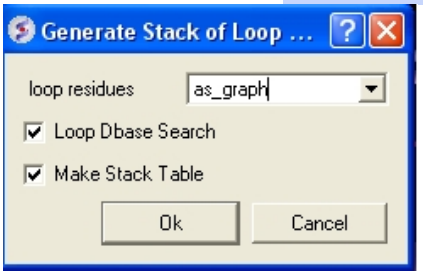
- If you have viewed some previous docking results make sure the ligand is deleted from the object called ALDR_rec. You can do this by right click on the ligand name (most likely the third molecule in the object ALDR_rec).
- Expand the sequence display for the **receptor** in the ICM Workspace and select the loop region "CALLSC" (it is located towards the C−terminal). See screenshot below. You can select the region by clicking and dragging over the sequence in the ICM Workspace.



- MolMechanics/Sample Loop and check the boxes as shown below. If the option is greyed out and you cannot click on it this means the selection you have made is not in the current object. You can

fix this by right clicking on the object in the ICM Workspace (in this example the object is called **receptor)** and select "Set to Current".
- Choose the option Loop Dbase Search.
- Choose the option Make Stack Table.

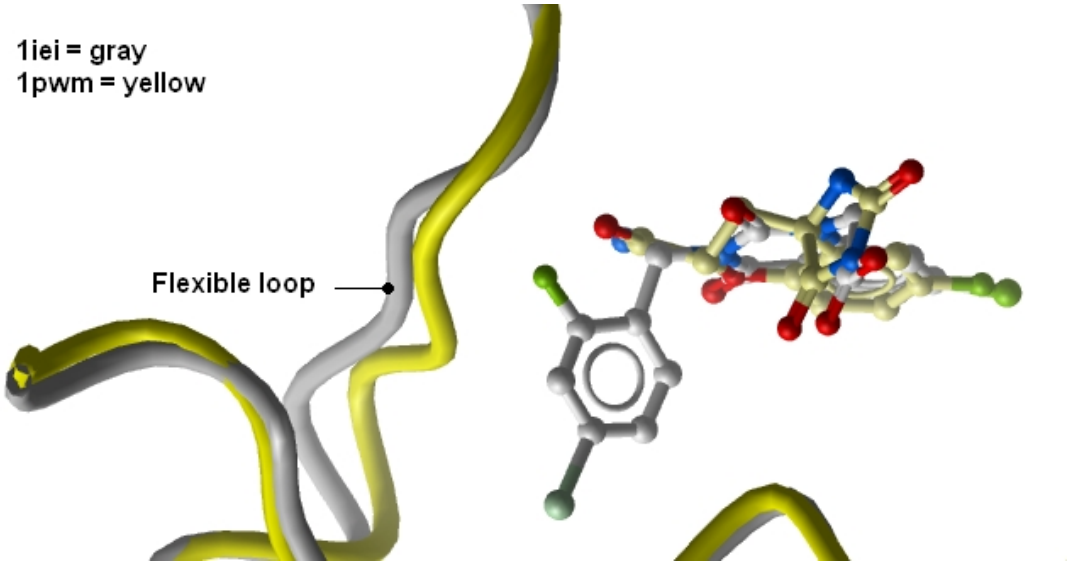
Warning sampling the loop may take some time.



- Once the loop sampling has finished a table called **confStack** will be displayed. You can view the loop conformations by clicking on the rows.

Step 6: Docking to Multiple Receptor Conformations

- Delete all but the top 4 conformations in **confStack.** This can be done by clicking on the row header (5) and this will highlight the row in blue and then whilst holding the **Shift key** click on the header of the final row. Next right click on the row header and select and select **Delete Rows**.
- If you have viewed some previous docking results make sure the ligand is deleted from the object called ALDR_rec. You can do this by right click on the ligand name (most likely the third molecule in the object ALDR_rec).
- Docking/Flexible Receptor/Setup 4D grid and click OK.
- Docking/(Re)Make Receptor Maps
- Re−run docking batch /Docking/Run Docking Batch but change output file suffix to something different such as **flex3conf.**
- Once the docking has finished make the hitlist Docking/Make Hitlist.
- Browse the hitlist by clicking on the hitlist table and watch the receptor conformation switching along wih the ligand and note the additional column rec.conformation in the list. This column indicates which receptor in the stack the ligand is docked to.
- Load PDB entry 1iei and compare the pose of the first ligand in the hit list and the corresponding receptor conformation to the experimental data.
- You will see that the flexibility in the loop region is accounted for by multiple receptor conformation docking and therefore inhibitors which scored poorly in Step 4 now score well and the corresponding receptor loop conformation for a ligand is identified.

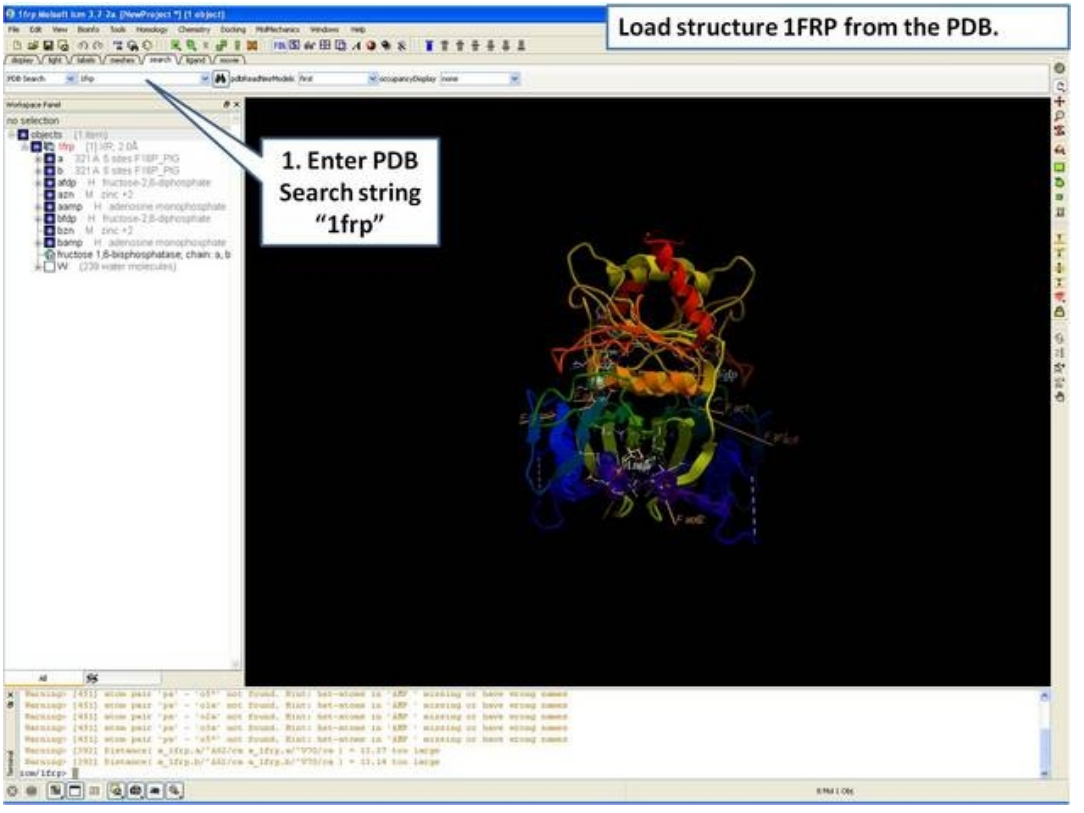


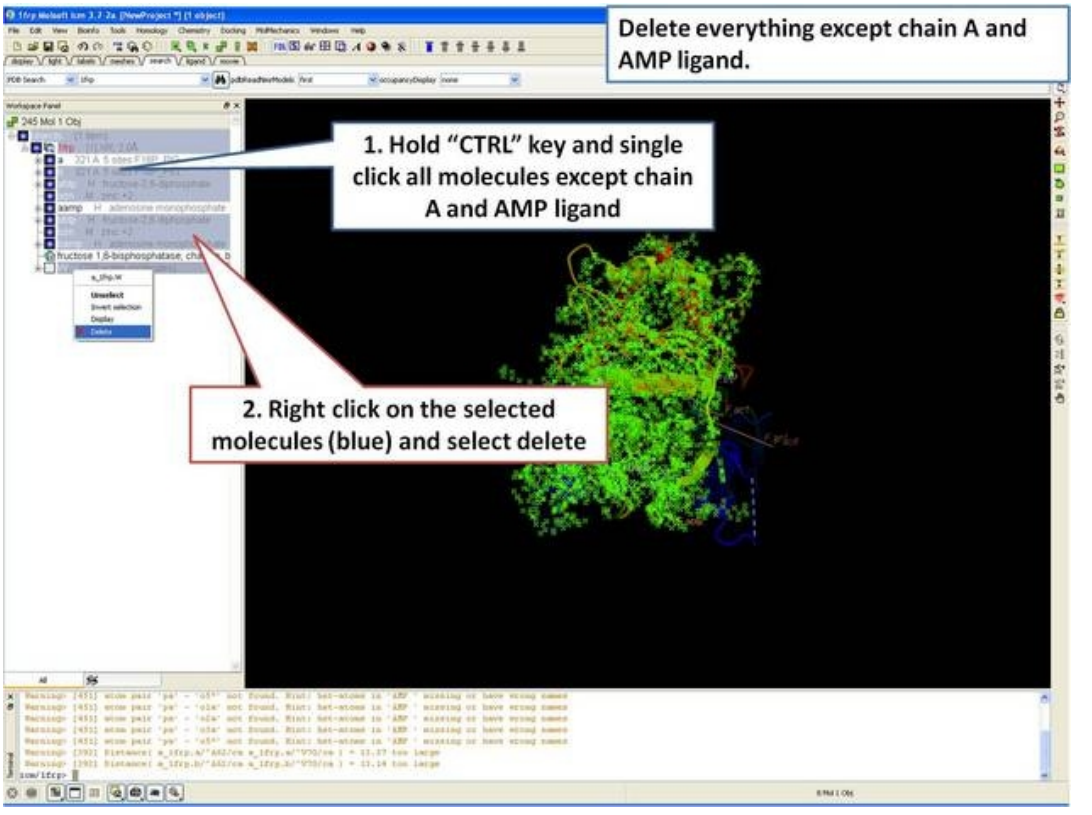
23.20 Explicit Group Docking

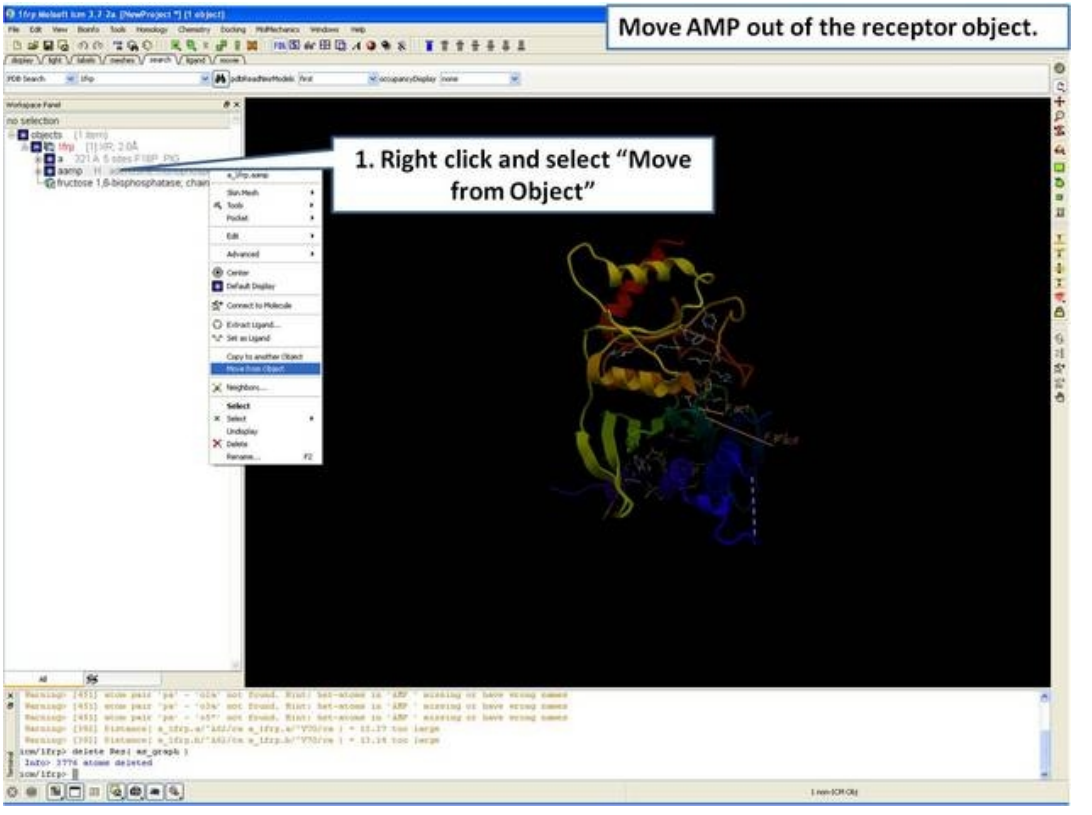
This example demonstrates how to keep certain residues as explicit during grid docking. Hydroxyls of Ser, Thr, and Tyr can be treated explicitly during docking.

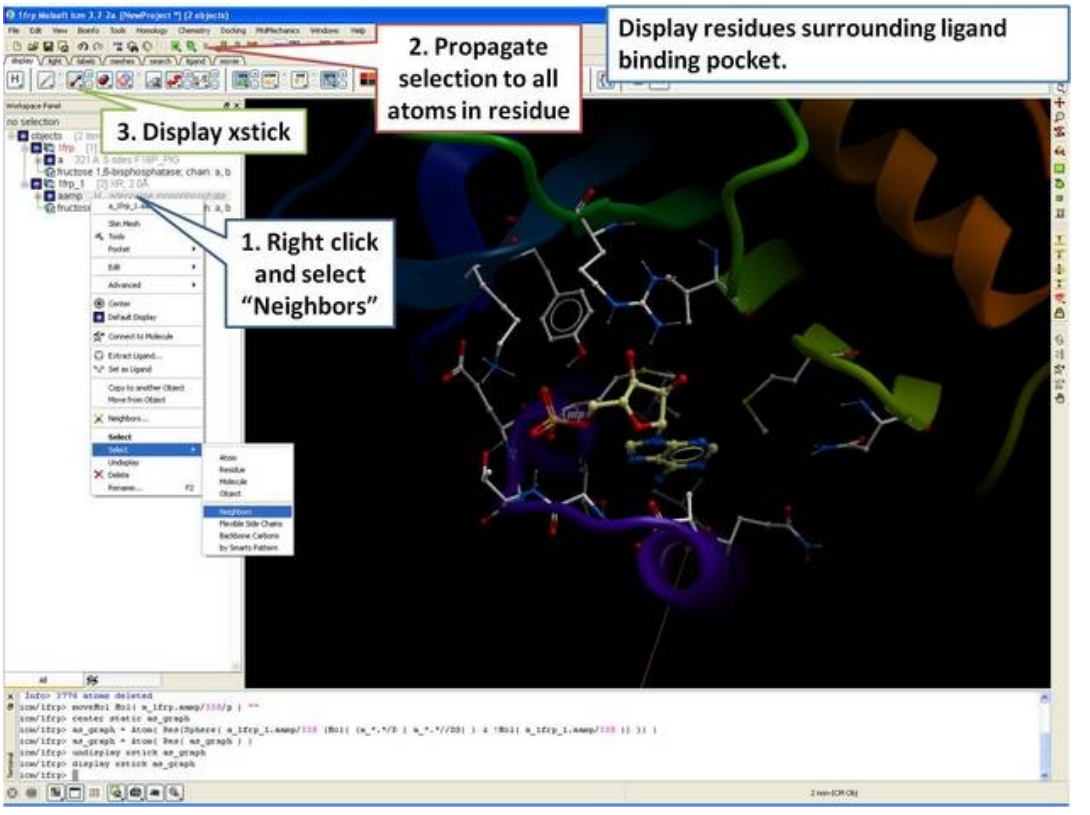
NOTE Feature only available in version 3.7−2a or higher

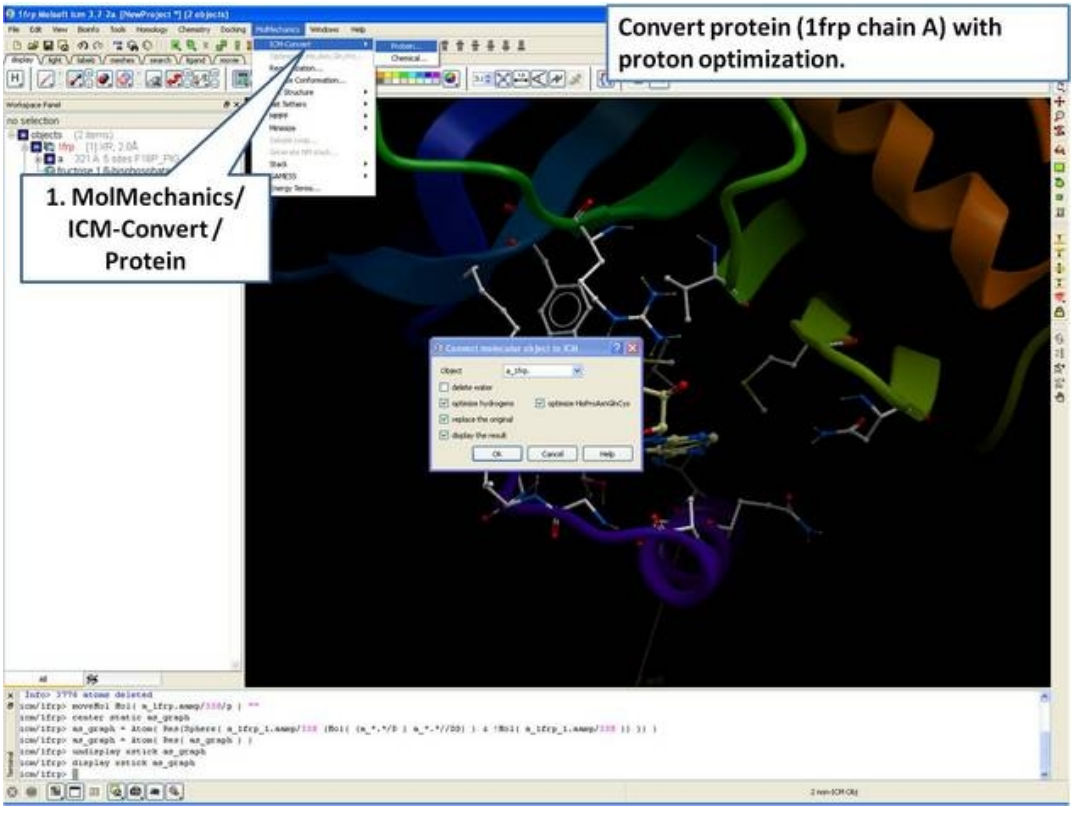
23.20.1 Receptor Setup



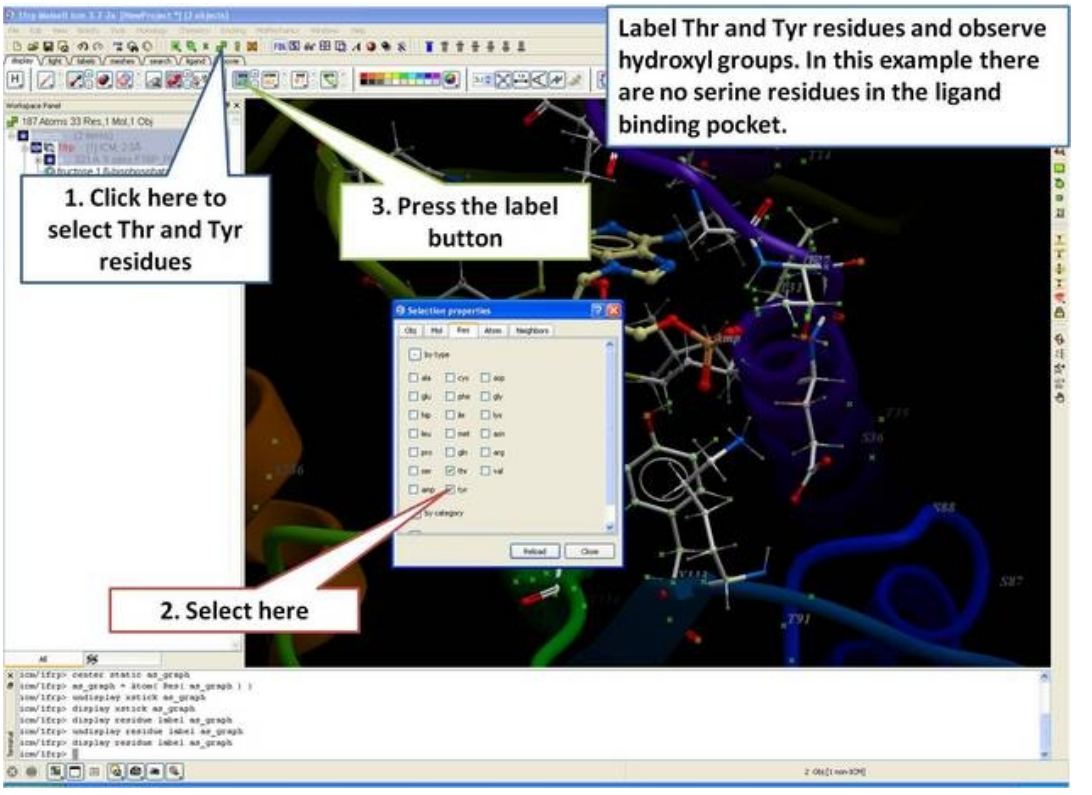

Delete everything except chain A and AMP ligand.
1. Hold “CTRL” key and single click all molecules except chain A and AMP ligand
2. Right click on the selected molecules (blue) and select delete

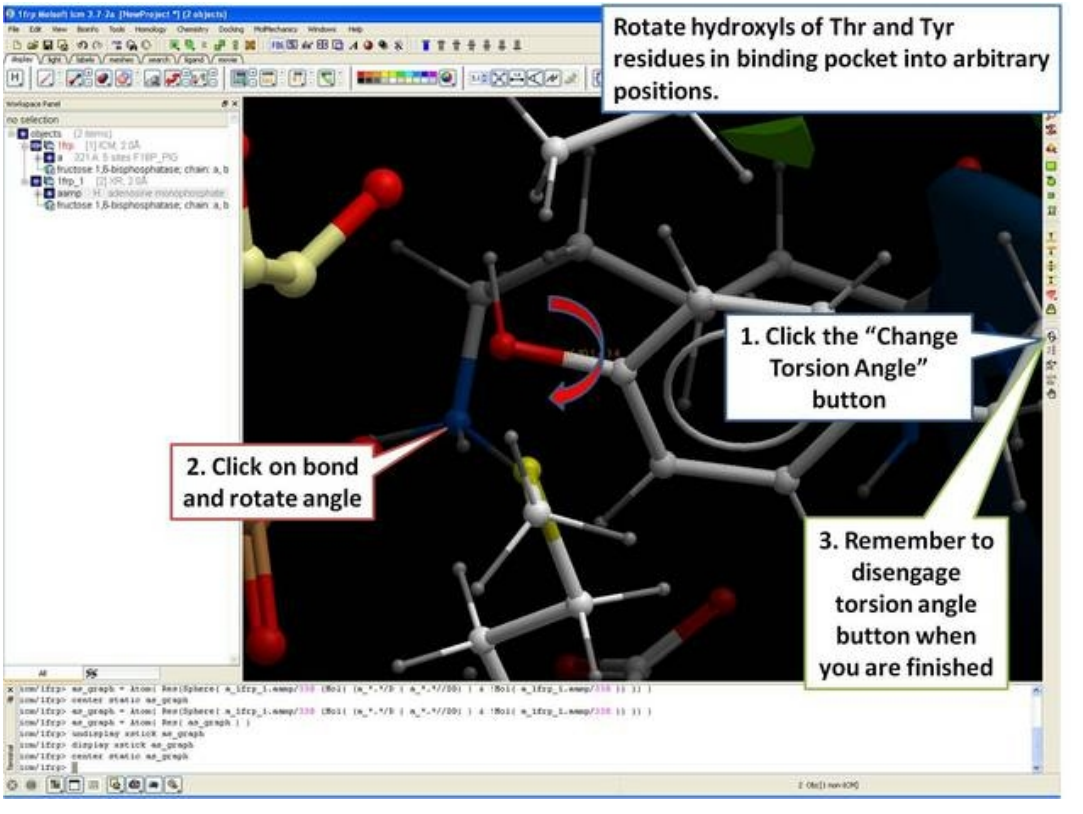

Move AMP out of the receptor object.
1. Right click and select “Move from Object”



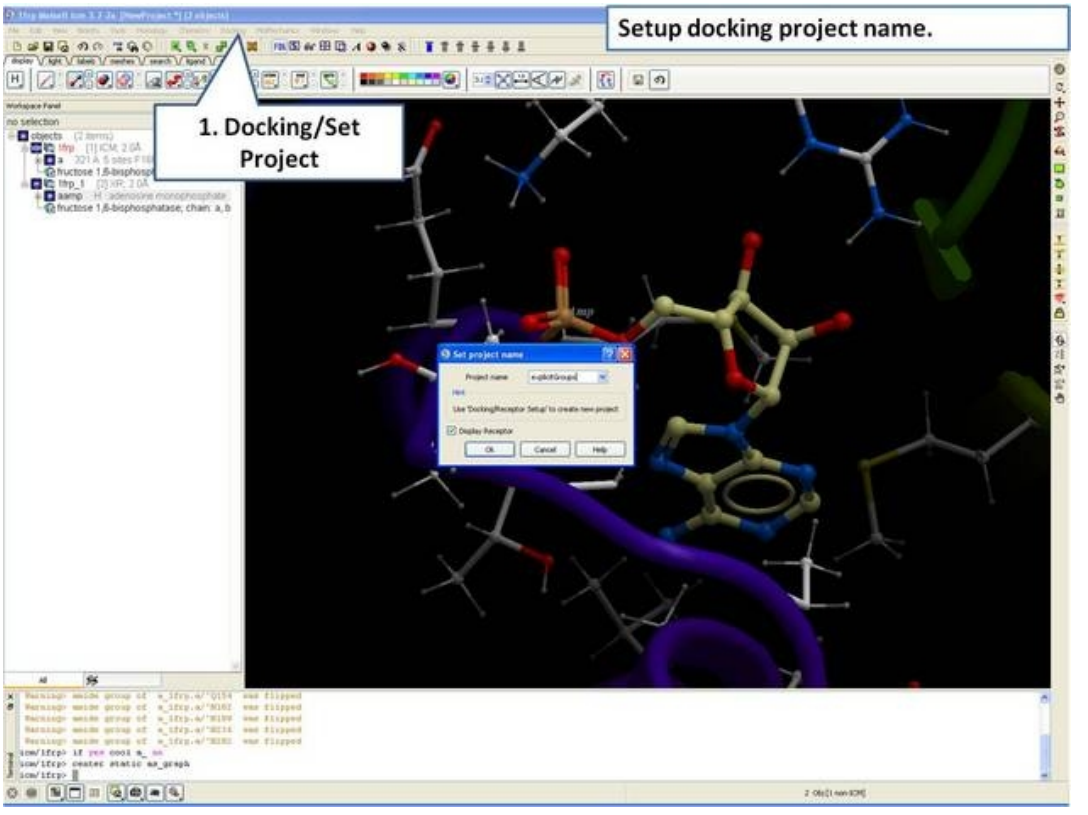


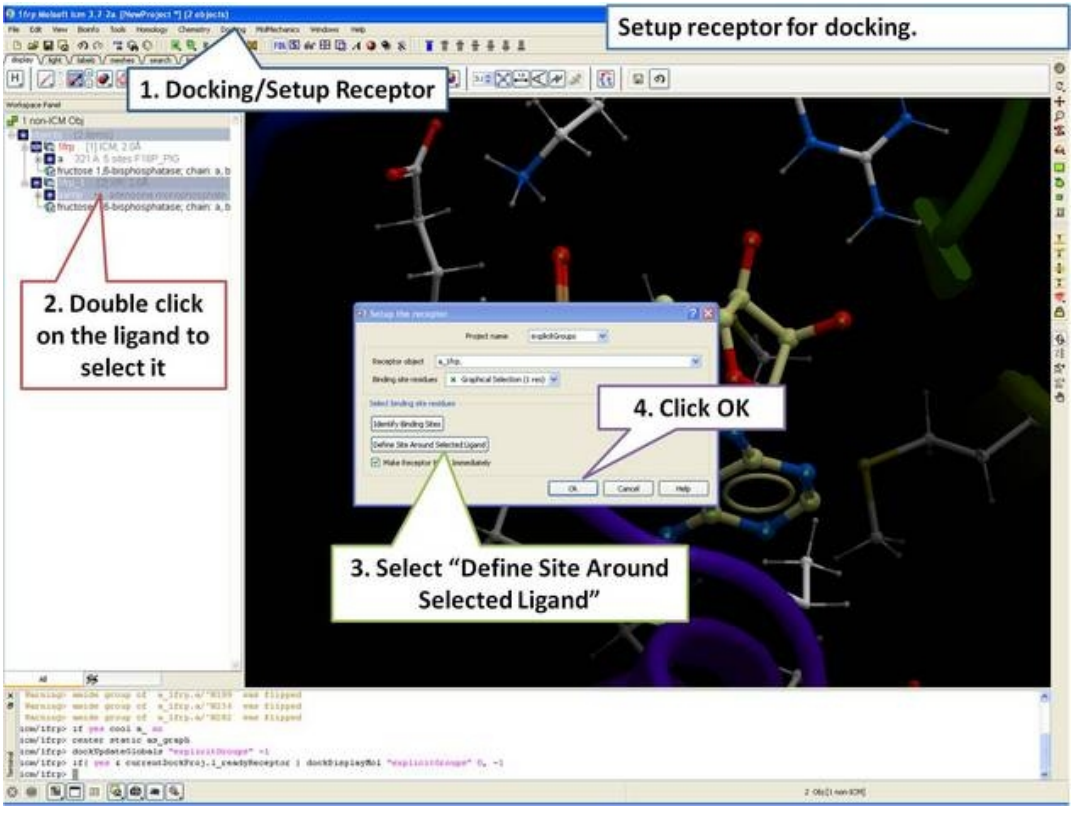
23.20.2 Rotate Hydroxyls

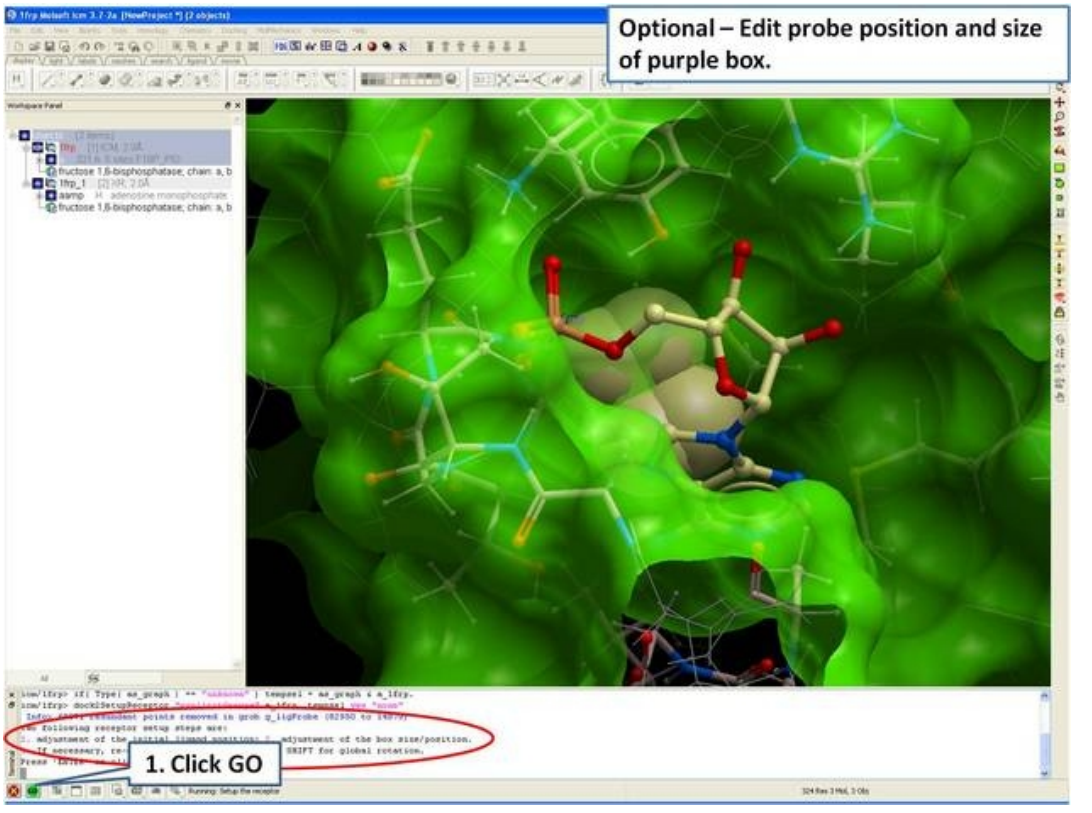


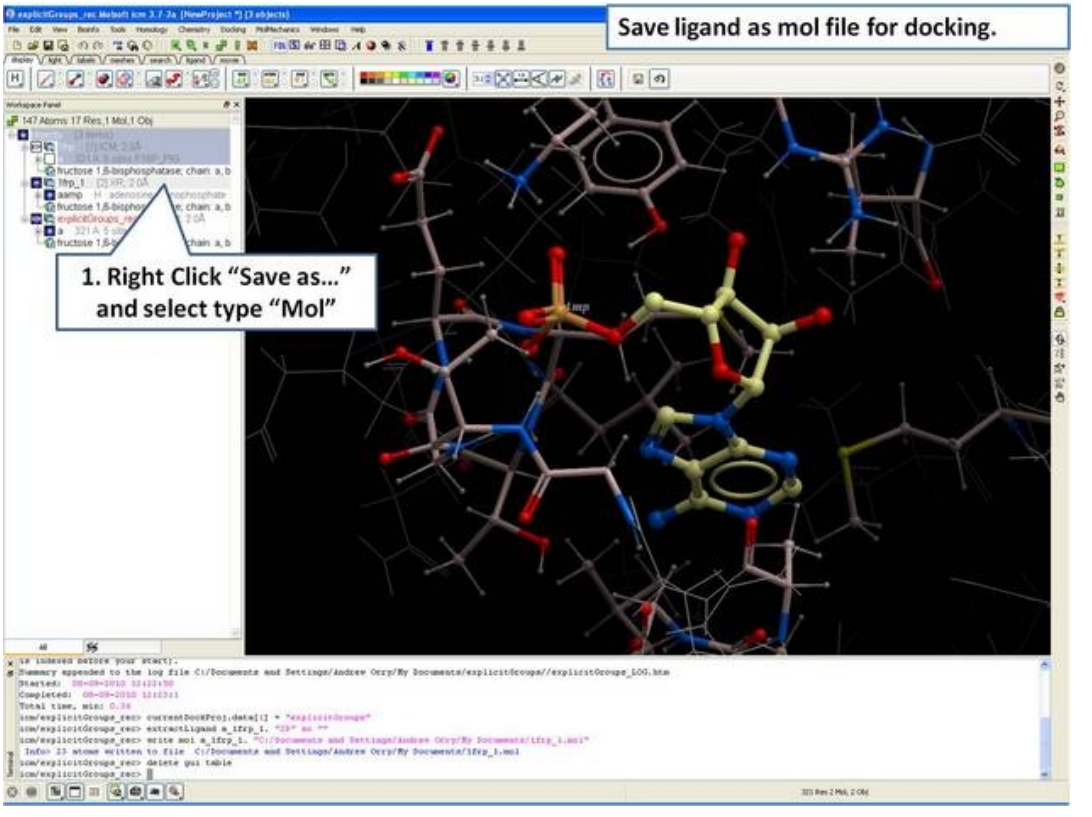


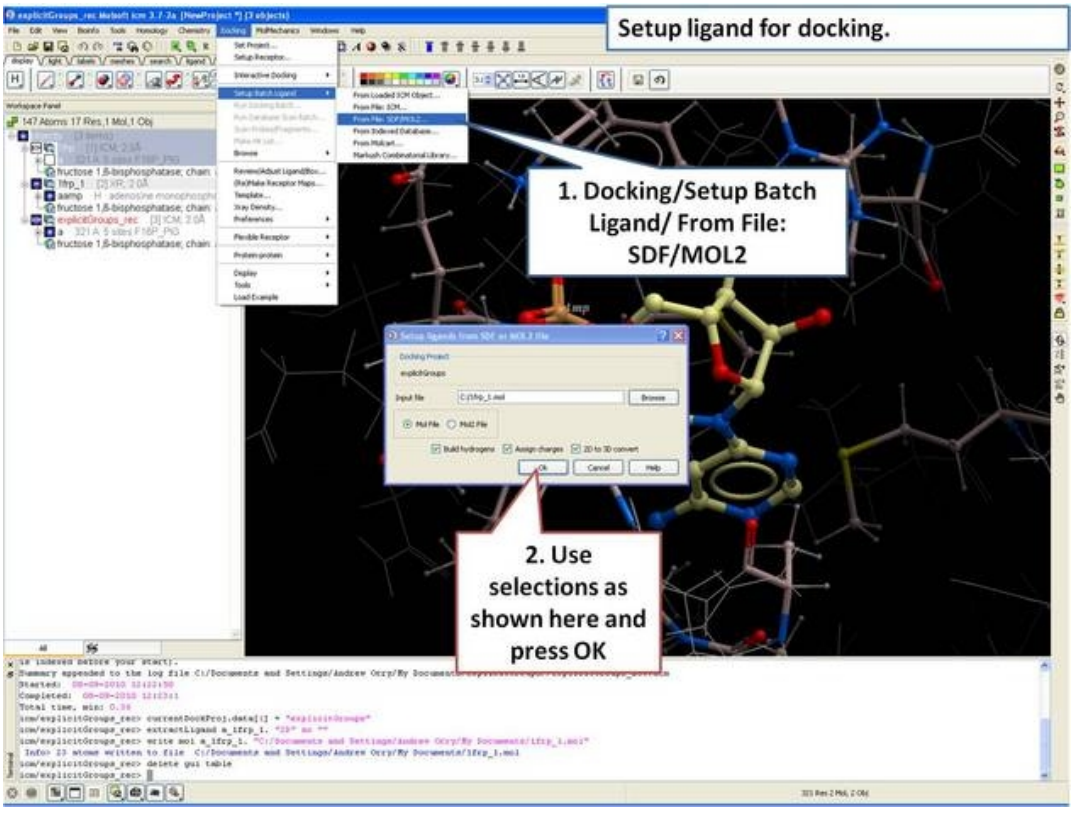
23.20.3 Setup Docking


Setup docking project name.
1. Docking/Set Project

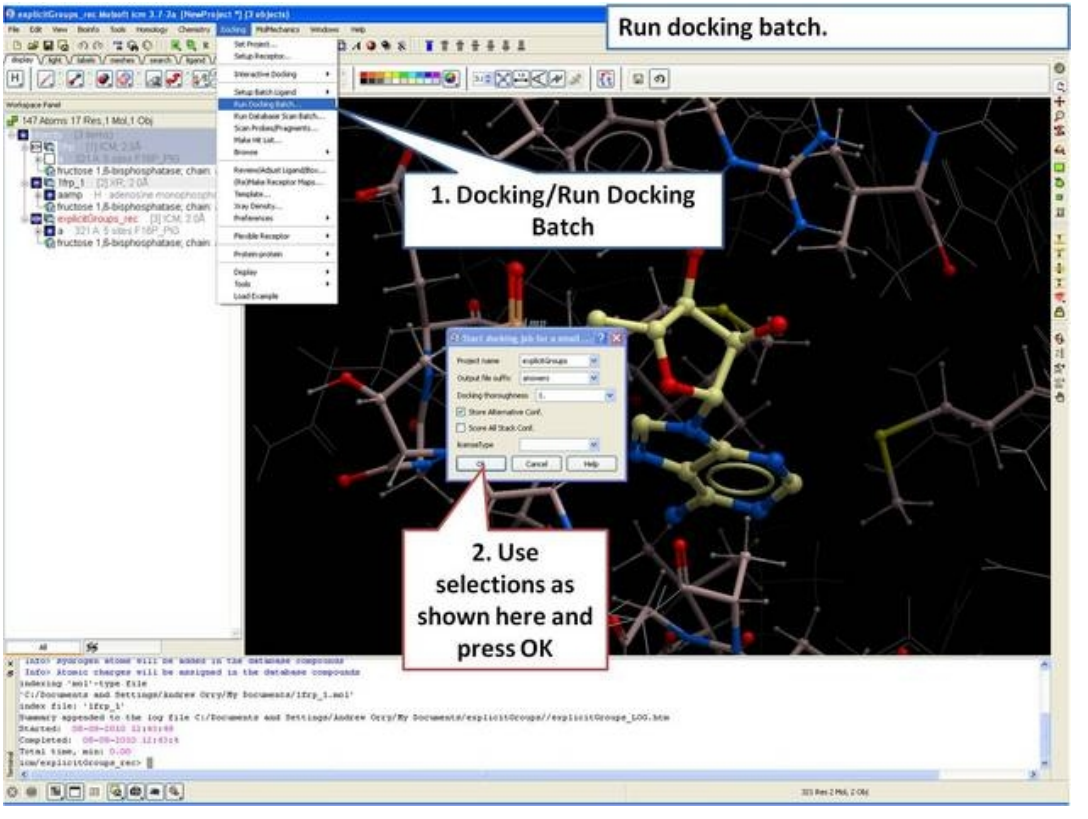

Setup receptor for docking.
1. Docking/Setup Receptor
2. Double click on the ligand to select it
4. Click OK
3. Select "Define Site Around Selected Ligand"

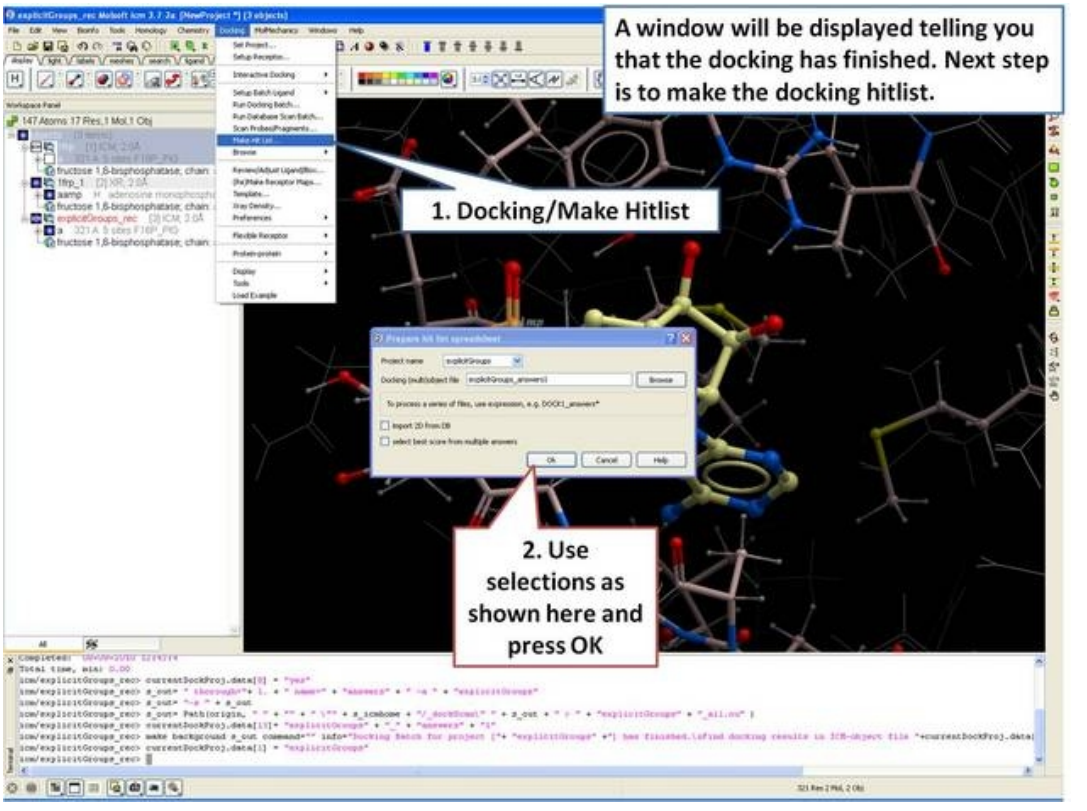

Optional – Edit probe position and size of purple box.
1. Click GO

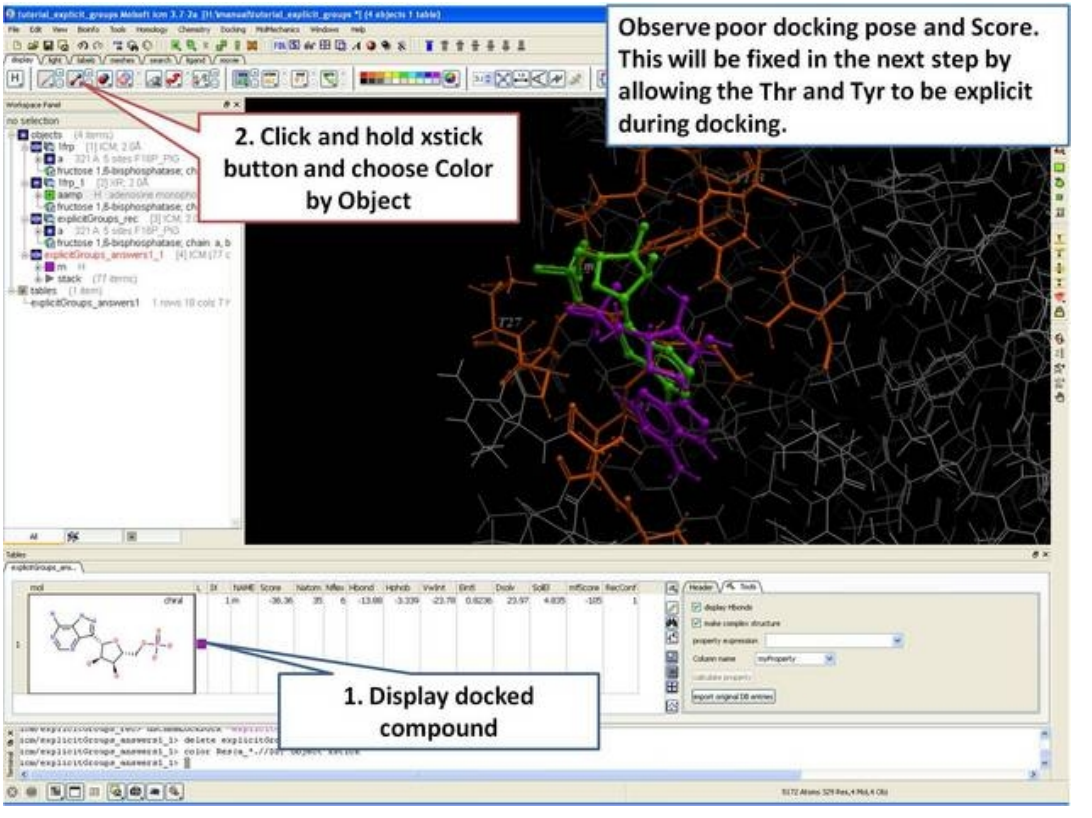

Save ligand as mol file for docking.
1. Right Click “Save as…” and select type “Mol”



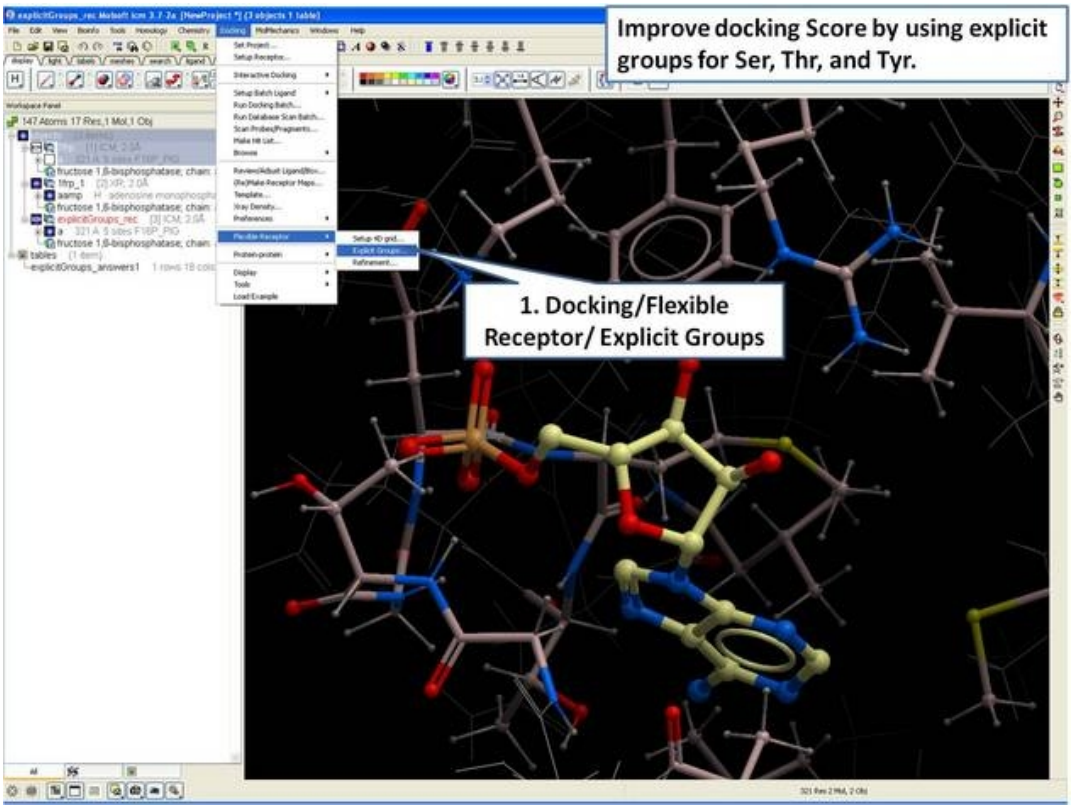
23.20.4 Run Docking

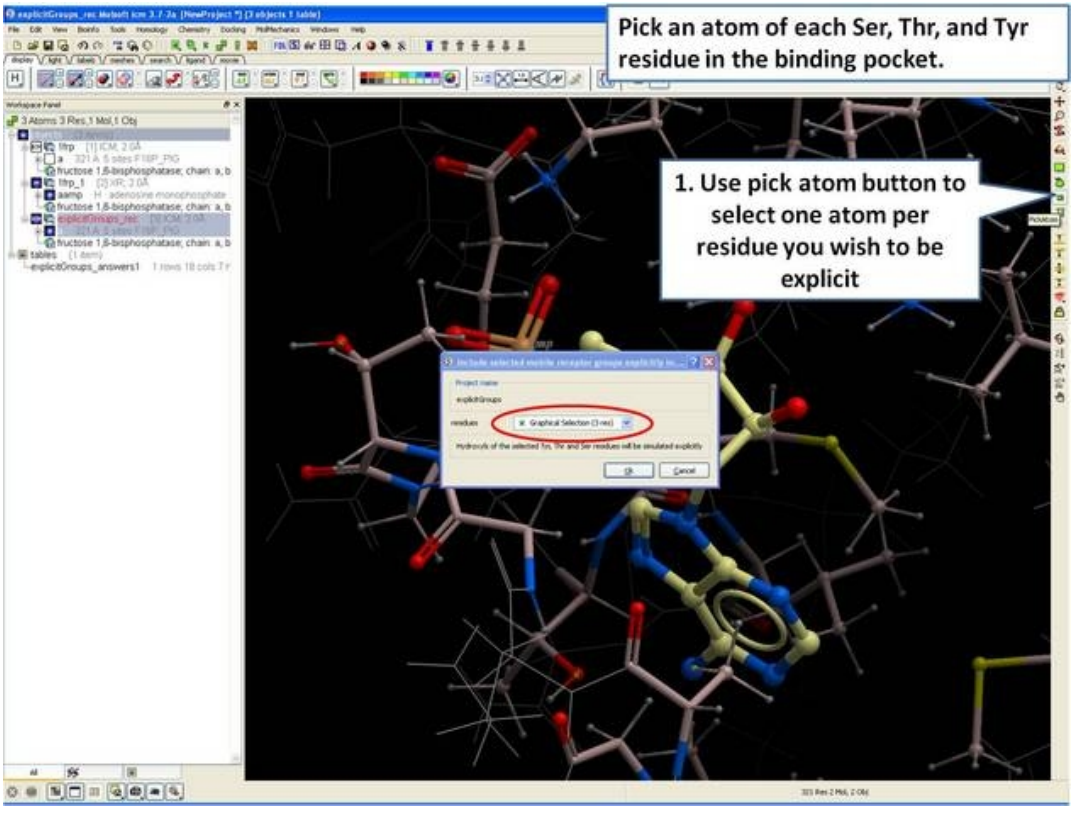


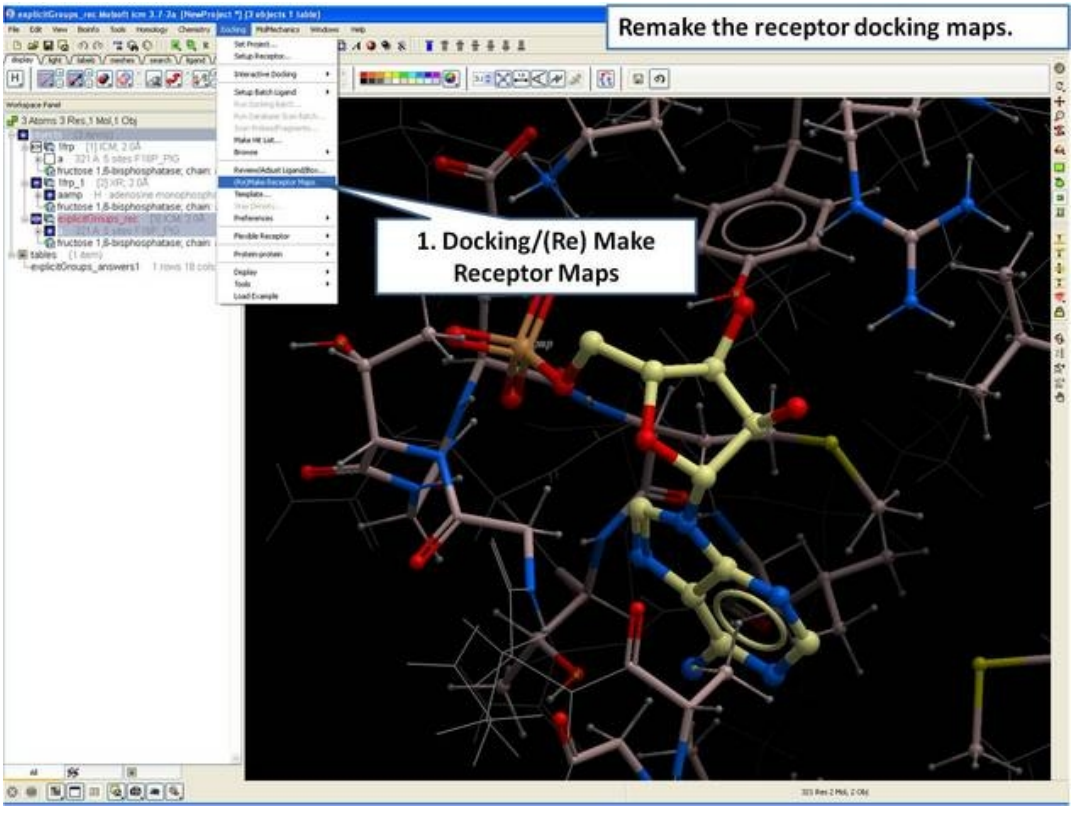


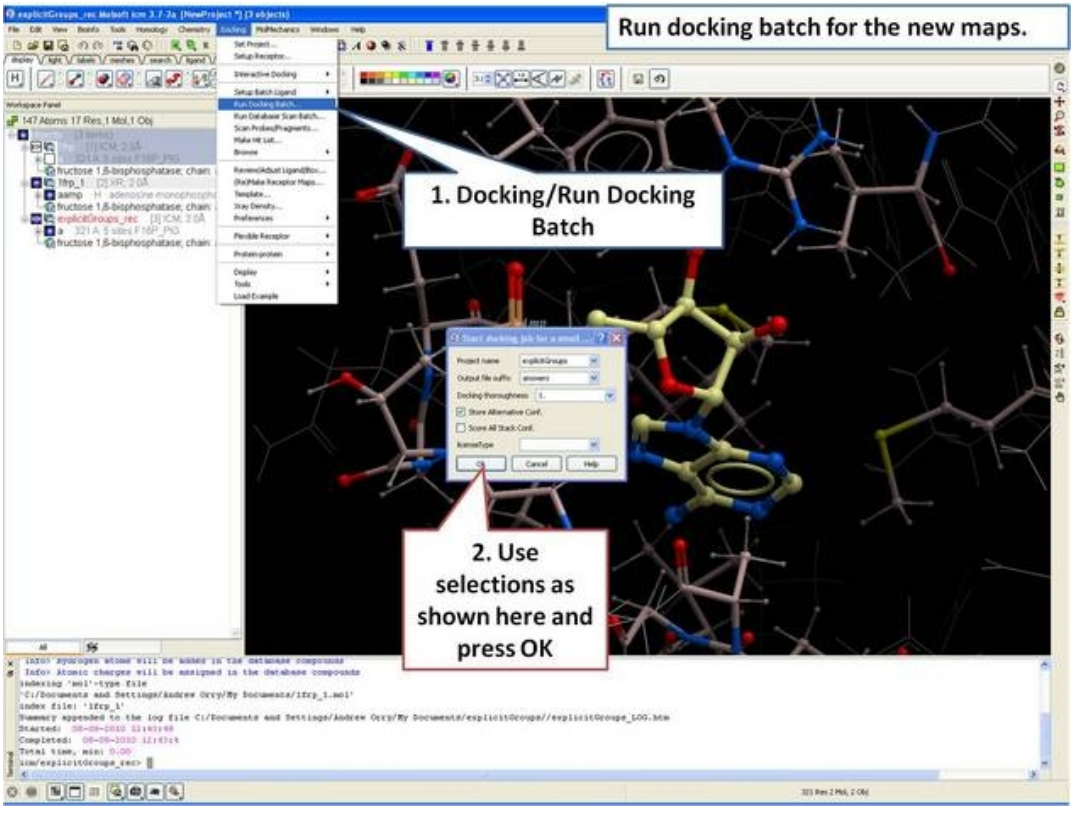


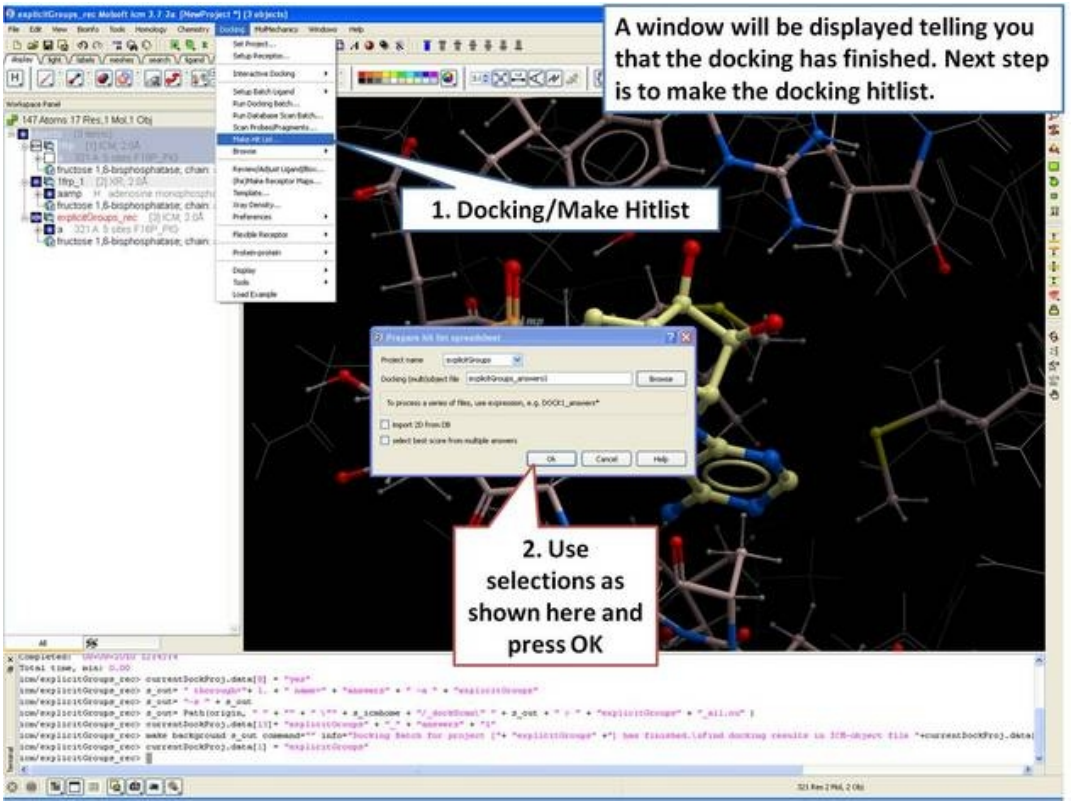
23.20.5 Explicit Docking

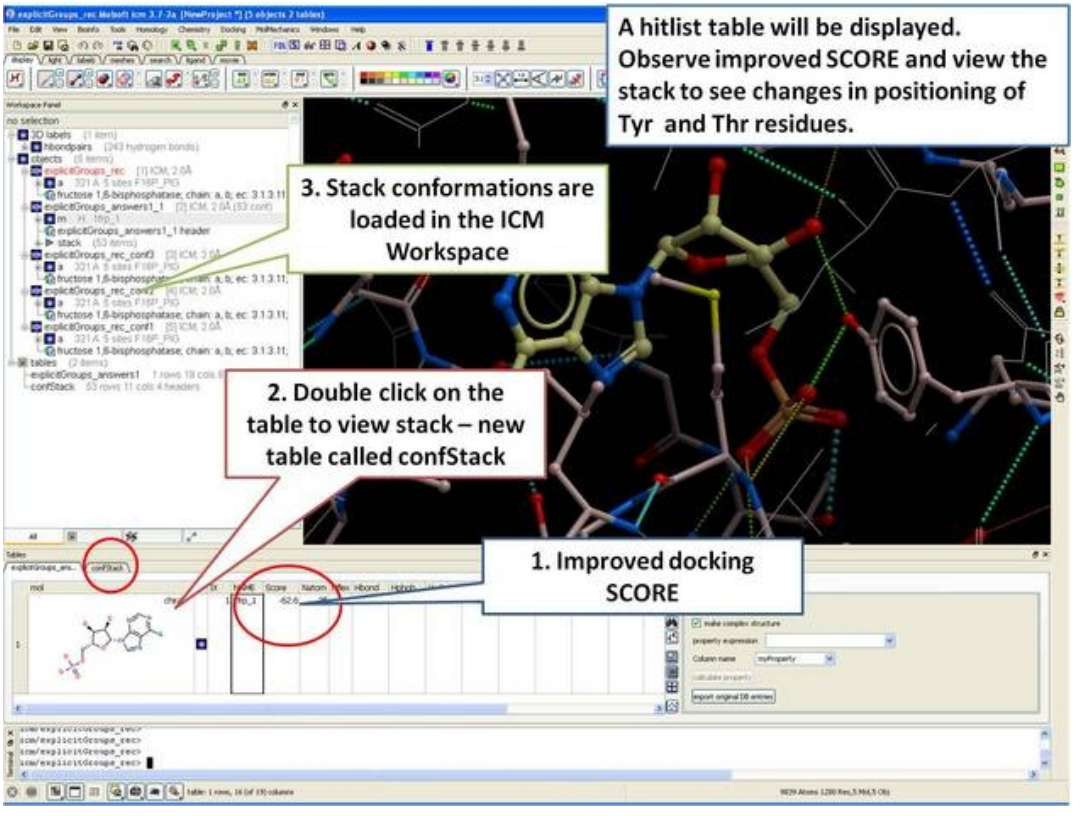

Improve docking Score by using explicit groups for Ser, Thr, and Tyr.
1. Docking/Flexible Receptor/ Explicit Groups


Pick an atom of each Ser, Thr, and Tyr residue in the binding pocket.
1. Use pick atom button to select one atom per residue you wish to be explicit


Remake the receptor docking maps.
1. Docking/(Re) Make Receptor Maps


Run docking batch for the new maps.
1. Docking/Run Docking Batch
2. Use selections as shown here and press OK


A window will be displayed telling you that the docking has finished. Next step is to make the docking hitlist.
1. Docking/Make Hitlist
2. Use selections as shown here and press OK


A hitlist table will be displayed. Observe improved SCORE and view the stack to see changes in positioning of Tyr and Thr residues.
3. Stack conformations are loaded in the ICM Workspace
2. Double click on the table to view stack – new table called confStack
1. Improved docking SCORE

24 Frequently Asked Questions

Do you have a question regarding ICM? See if it is already answered in our FAQ section.

FAQ−Installation

FAQ−Hardware

FAQ−Graphics and Display

FAQ−Structure

FAQ−Docking

FAQ−Cheminformatics

FAQ−Simulations

FAQ−Script Writing

Troubleshooting

24.1 FAQ Installation

Installation FAQ:

- I downloaded and installed ICM. It seems to start fine. However it dies every time I try to open something, giving an NVIDIA error. NVIDIA: Could not open the device file /dev/nvidiactl (Permission denied).
- I get chemlib.so erron:22 error when I install MolCart on 64Bit machines.
- I am having problems installing ICM on SGI.
- Where do I save my MolCart license?

24.1.1 I downloaded and installed ICM. It seems to start fine. However it dies every time I try to open something, giving an NVIDIA error. NVIDIA: Could not open the device file /dev/nvidiactl (Permission denied).

To permanently fix this problem you need to add the following line to /etc/logindevperm file

0 0666 /dev/nvidiactl:/dev/nvidia0:/dev/nvidia1:/dev/nvidia2:/dev/nvidia3

24.1.2 MolCart installation error on 64Bit machines

If you are installing MolCart and you come across this error:

```
Error> Can't open shared library 'chemlib.so' (errno: 22 chemlib.so: canno
t open shared object file: No such file or dire) (/usr/molcart−1.9−1/regmol
cart:52)
Error> error while running 'ExecSql(string("CREATE FUNCTION molcart_versi.
..))' (/usr/molcart−1.9−1/regmolcart:52)
Error> error while running 'regFunction(string("molcart_version"),string("
STRING"),)' (/usr/molcart−1.9−1/regmolcart:96)
```

Solution−− For 64 bit platforms molcart−1.9−1−linux64.sh should be used instead of molcart−1.9−1−linux.sh

24.1.3 Where do I save my MolCart license?

Save the MolCart license in:

/var/lib/mysql/license.dat

24.2 FAQ Hardware

24.2.1 What are the minimum specifications to run ICM on my computer?

The minimum specifications to run ICM are described in the `introduction`.

24.2.2 Stereo Hardware Questions

Hardware stereo for SGI (in−window)

Question:

In the Stereo mode, the ICM window is bigger than the actual screen size; thus, many items are not displayed within the screen. Is there a way to fix that?

Answer:

This is the way SGI handles the Stereo mode. Depending on the type of graphics card, the additional memory necessary for the left/right screen buffers is obtained by lowering the actual resolution. The XP Windows system however remains unaware of lesser amount of visible pixels − for instance, you can move the mouse beyond the screen. As the size (in pixels) of all (not just ICM) windows remains the same, their apparent size is bigger at a lower resolution. Normally we would just resize the window.

Hardware stereo for Windows (in−window)

Question:

I have ***NVIDIA Quadro4*** 750 (or 800/890) installed on my Windows machine but the ***hardware stereo*** does not work in ICM. What do I do ?

Answer:

The settings for your graphics card need to be changed. Perform the following steps to check and correct the problem:
1. Go to Start −> Control Panel.

2. Double click the icon labeled 'Display'.
3. Choose the 'Settings' tab.
4. Click the button labeled 'Advanced'.
5. Choose the tab labeled 'Quadro4'.
6. From the menu on the left, choose the OpenGL settings.
7. In the dialog that appears, find and enable the option labeled "Enable quadrobuffered stereo API".

8. Click the OK button to save your changes.

24.2.3 Does ICM support quad−buffer stereo?

Yes − change the stereo mode to in−a−window. To do this File/Preferences/Graphics Tab and change stereo Mode.

24.3 FAQ Graphics and Display

Questions and answers relating to displaying molecules in the graphical user interface.

- How to change font size in html−documents, alignments, terminal, table, graphics?
- How to change the background color with one click?
- How to make a transparent ribbon?
- How do I specify a particular color for only the carbon atoms of a molecules?
- I have multiple proteins overlayed and I would like to color the carbon atoms of each molecule uniquely − how can I do this?
- If I have multiple graphical selections how can I remove one without losing the others?
- Can you suggest some ways to remove a graphical selection completely?
- What does as_graph mean?
- I have the XYZ origin cross displayed − How can I undisplay this?
- The front and back part of my structure have been clipped away how do I restore these regions in my display.
- Is it possible to draw dashed lines between atoms without displaying the corresponding bond length. I would like to do this to show which atoms are making key intermolecular interactions?
- How can I select only the backbone atoms?
- How can I find out which residues are surrounding a ligand binding pocket?
- How to truncate a mesh object?
- How can I change the color of a grob atom based surface according to the underlying atom coloring scheme?
- How can I display more information regarding an atom such as mmff type and charge?
- How can I display the dihedral angle?
- Which stereo glasses?
- I have made a H−Bond displayed in ICM−Browser−Pro which I would like someone to see in ICM−Browser − how do I do this?
- I would like to create a movie wherein I "walk" through the molecule by moving the front clipping plane to the end. Can I write a loop that moves the clipping and generates an image after every step to generate my movie afterwards?
- How do I color a structure by secondary structure?
- How can I display a structure in many different representations simultaneously?
- How can I store a view and return to it later?
- Some structures are displayed as noodles (the "worm" representation). Why are they displayed improperly?
- I would like to have a local copy of the PDB − any advice?
- I would like to have a local copy of the NCBI Blast database− any advice?
- How do I color ribbon models according to Optimal Docking Area (ODA)
- How do I load an electron density map into ICM?
- How can I contour an electron density map and adjust contour levels and color?
- I want to visualize weak hydrogen bonds how can I change the H−bond cutoff parameter
- What is an iSee File?
- How do I set a blend transition effect in a slide?
- How to check on the display status of an object in the command line.
- How to check on the display status of an object in the command line.
- ICM and Autosaving
- How to remove the dotted lines in chain breaks?
- When using ActiveICM is there a way to set a RELATIVE path to an icb file rath than ABSOLUTE?
- How do I turn off the annoying beep?

24.3.1 How to change font size in html−documents, alignments, terminal, table, graphics?

First, click on this window of interest. Then just press `Ctrl−+` (Ctrl−plus) to increase the font size and `Ctrl−−` (Ctrl−minus) to descrease the font size.

Here is a more complete list of methods to change the font size:

location	how to change
tables	Ctrl +/−
alignment	Ctrl +/−
terminal	Ctrl +/−
html−documents	Button + and −
residue, atom and variable labels	change icm.clr file in $ICMHOME
graphics: 2D labels	right−click on a label and modify the font size/color
graphics: 3D labels	right−click **at the lower left corner** of a 3D label and modify the font size/color
graphics: distances and hbonds	right−click on a line modify the font size/color

The sizes will also be preserved between sessions.

24.3.2 How to change the background color with one click?

To change the background color with one mouse click, go to the Display toolbar and **right click** on the color you like. Warning: the *left click* on the same palette will color all the object, but will preserve the background color. The ICM command for changing the background is

```
color background red # or any other color
```

24.3.3 How to make a transparent ribbon?

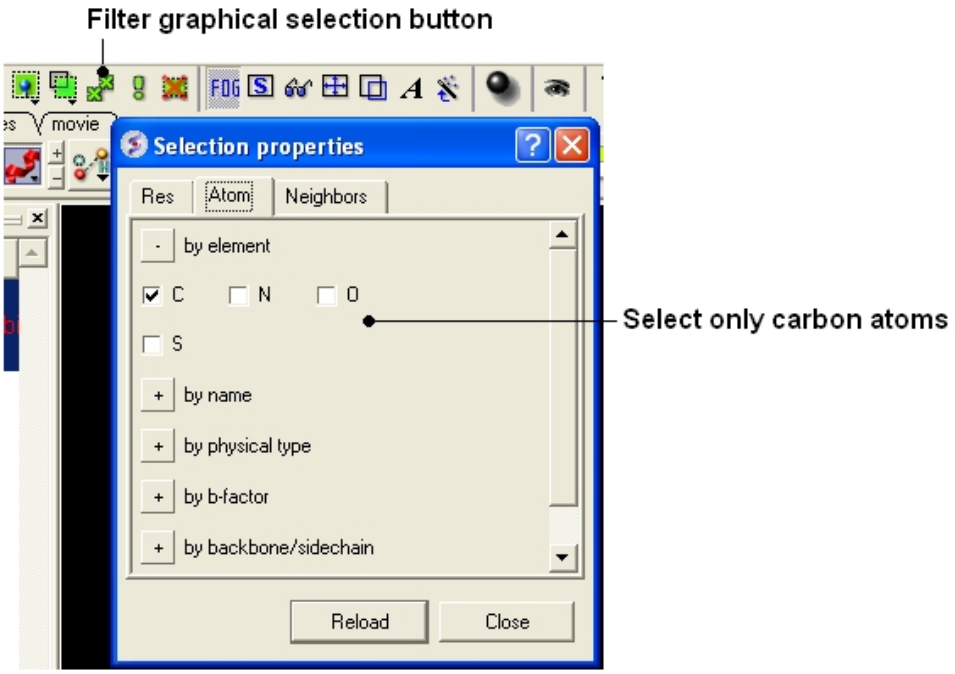
To make a transparent ribbon follow these steps:

- display only the ribbon of interest, undisplay all other objects and molecular representations
- color the ribbon as you like, and change its thickness by pressing on little "plus" and "minus" icons in the *Display* toolbar
- go to the *Mesh* toolbar
- select `"from display"` and click the mesh button
- undisplay the original ribbon (the mesh−ribbon will stay)
- right click on the newly created ribbon−mesh either in the workpanel or in the graphics
- select the type of representation from the popup menu for this mesh object (e.g. `transparent`, `wire`, etc.)

24.3.4 How do I specify a particular color for only the carbon atoms of a molecules?

In this example we will display PDB 1CRN with yellow carbon atoms

- Select the **pdb search Tab** and enter 1crn and press enter.
- Double click on 1CRN in the ICM Workspace to select the molecule.
- Select the **Wire** representation button in the **display panel**.
- Select the **Filter Graphical Selection** button and select the **Atom** tab as shown below.
- Select only carbon atoms.

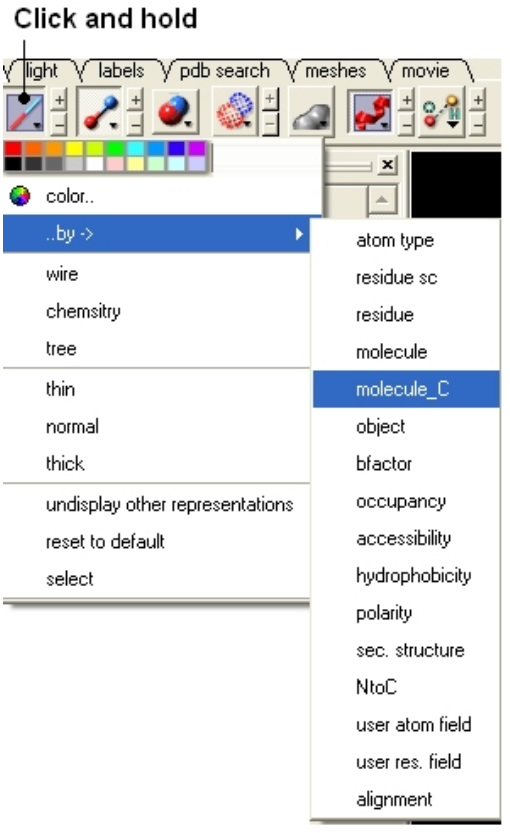


- Click and hold on the **wire** button in the **display panel**.
- Select the color.

24.3.5 I have multiple proteins overlayed and I would like to color the carbon atoms of each molecule uniquely − how can I do this?

{Color −C}

- Click and hold on the representation button (eg wire, ribbon, xstick etc..) and select **Color ..by−> molecule_C**.

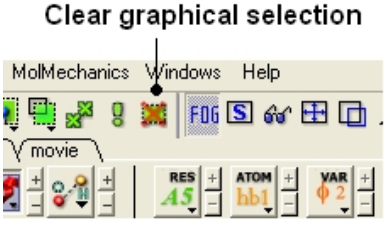


24.3.6 If I have multiple graphical selections how can I remove one without losing the others?

One way to do this is to use the **Remove** selection button shown below and then drag over the region you would like to remove using the right−click mouse button.

24.3.7 Can you suggest some ways to remove a selection completely?

- Use the **Clear graphical selection** button shown below.



Some other ways include:

- Right click and drag in empty space in the graphical display.

- Double click in white space in the ICM Workspace.

24.3.8 What does as_graph mean?

By default anything (object, molecule, residue, atom) is returned to a variable called as_graph. If you type as_graph in the terminal window you will see all the atoms, residues, molecules or objects contained in as_graph. You can also rename as_graph to a different variable name in order to save it for other functions. For example:

```
my_binding_pocket=as_graph
```

```
ds wire my_binding_pocket
```

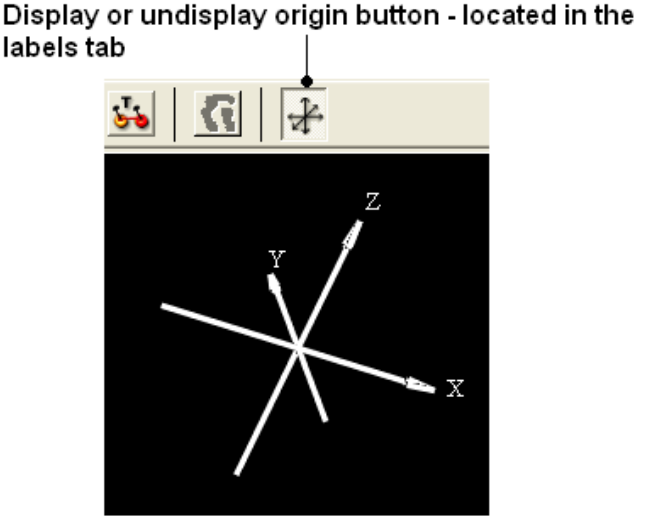
To list the residues surrounding the pocket type:

```
String(as_graph)
```

24.3.9 I have the XYZ origin cross displayed − How can I undisplay this?

To undisplay the origin shown below:

- Select the **labels** tab and select the **toggle origin** button.



24.3.10 The front and back part of my structure have been clipped away how do I restore these regions in my display.

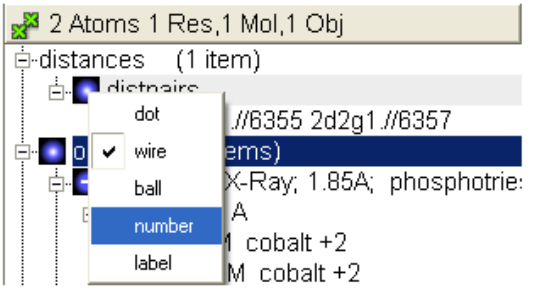
It looks like the clipping tools have been used to clip away the front and back planes. Use the "unclip" button (See the section entitled `Clipping Tools`).

24.3.11 Is it possible to draw dashed lines between atoms without displaying the corresponding bond length. I would like to do this to show which atoms are

making key intermolecular interactions?

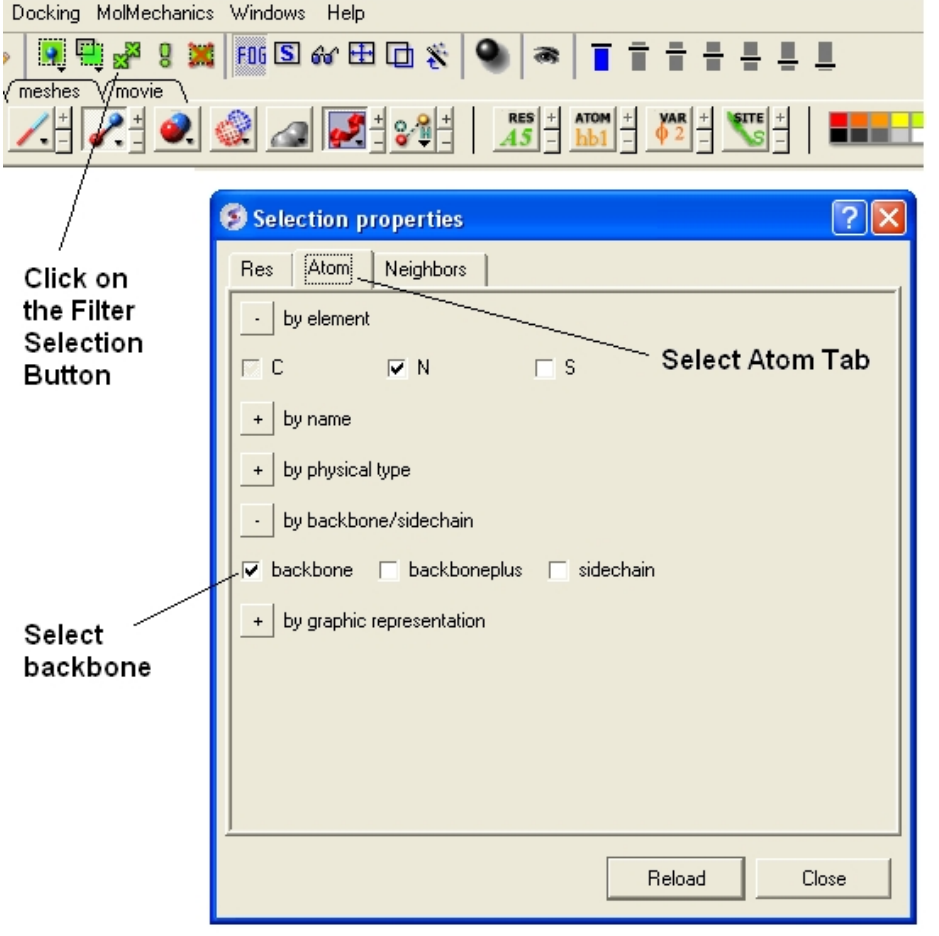
To do this first you need to display the distance.

- Use the atom pick tool (See `Selection Tools`) to select the two atoms you wish to measure the distance between.
- Labels tab − measure distance (See `Measuring distance between atoms section`.
- When the distance label is displayed you will see a new section in the ICM Workspace entitled "distances−distpairs".
- Right click in the blue box next to the word distpairs as shown below.



24.3.12 How can I select only the backbone atoms?

- Select the Filter Selection Button (see below).
- Select the Atom Tab
- Select backbone.



24.3.13 How can I find out which residues are surrounding a ligand binding pocket?

Use icmPocketFinder

- Tools/3D Predict/ icmPocketFinder
- Select the option to creat sequence sites.
- The residues surrounding the pocket will then be displayed in the table of pockets output that icmPocketFinder produces.

24.3.14 How to truncate a mesh object?

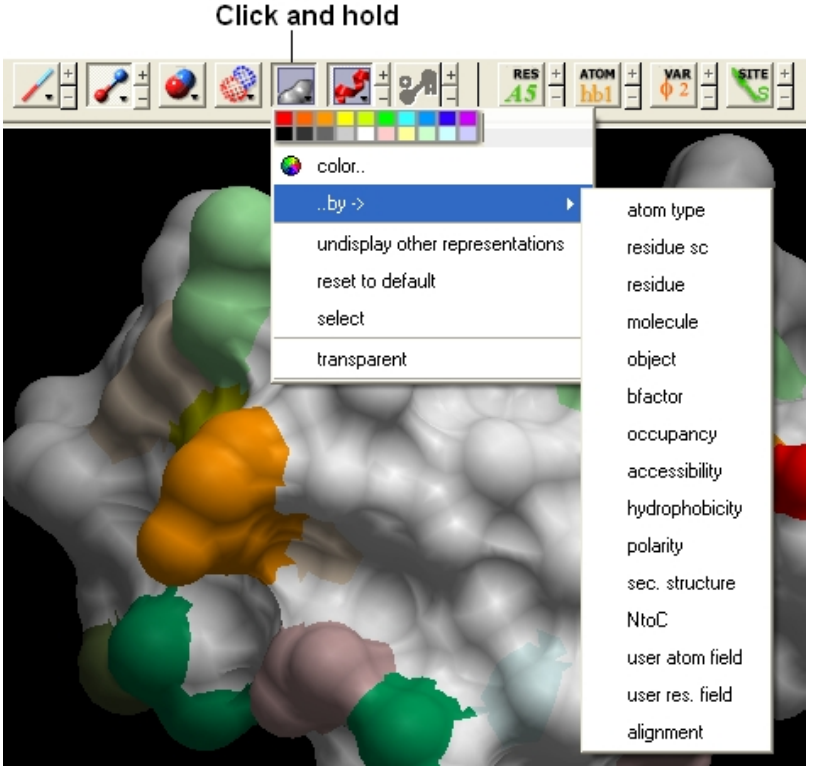
Sometimes you have a mesh object (a.k.a. *grob* in ICM language) and you want to crop it. This can be achieved with the "make mesh from display"−tool (the `"Mesh"` toolbar) that creates a mesh object from the all visible objects in the Graphics window. The trick is to use the *window* border as a trimming device by moving the unwanted parts of the mesh outside the Display window. Follow these steps:

- Undisplay everything and display only the object(s) you need. They will form a single mesh−object at the end of your operation
- Use the right mouse click to rotate and the middle mouse button to translate the mesh object so that only the parts you want to retain are visible and the unwanted parts are outside the window
- Go to the `Mesh` toolbar and select `"from display"` tool
- Click on the mesh button and create a new truncated object with an even flat border
- rename it if needed

24.3.15 How can I change the color of a grob atom based surface according to the underlying atom coloring scheme?

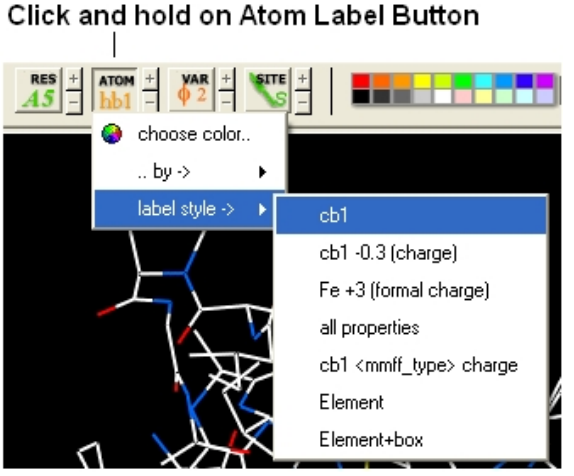
To do this:

- Clicking and hold down on the skin representation button in the Display tab and choose the "color by option". You can then color by atom type and a number of other parameters.



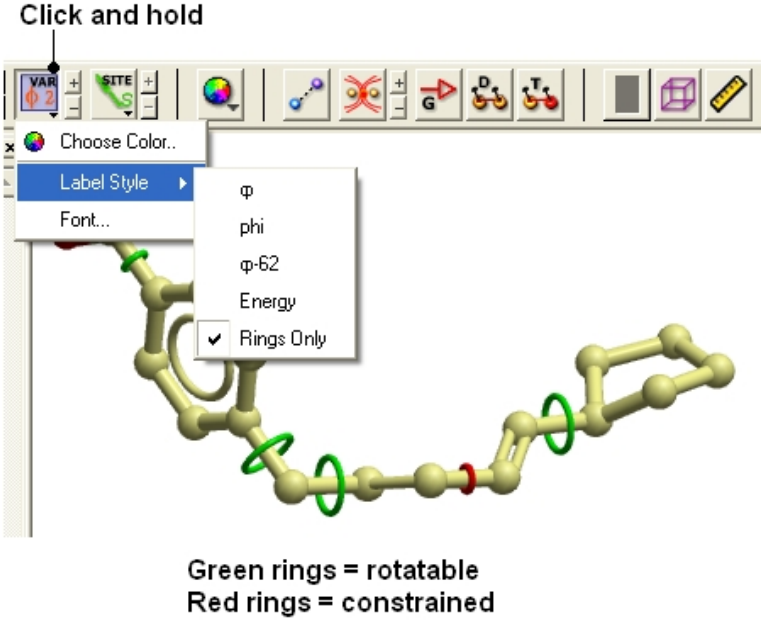
24.3.16 How can I display more information regarding an atom such as mmff type and charge?

- Select an atom
- Select the Display tab
- Click and hold down on the label atom button
- Select Label Style
- Choose the mmff option or formal charge.



24.3.17 How can I display the dihedral angle?

To label the dihedral angle the molecule needs to be converted into an `ICM object`.



- Convert the molecle to an `ICM object`.
- Select the atoms for which you would like to display the dihedral angle (see `display structure` or `selection toolbar`).
- Click on the **toggle variable label** button shown above located in the **display** tab.
- Change the level of detail displayed by using the +/− buttons.

24.3.18 Which stereo glasses?

Stereo Support for Any PC under NT/2000/XP (not available in ICM Browser).

As of version 2.7.060, we have introduced support for viewing of icm graphics in stereo on nearly any PC using Above−and−Below format and CrystalEyes for PC from StereoGraphics, which was previously only available on the SGI platform.

Hardware requirements:

CrystalEyes or CrystalEyes II eyewear + emitter, version for the PC (Important! workstation emitter will not work), available from QualixDirect (StereoGraphics doesn't seem to sell their products directly. Practically any graphics card would work, though higher resolutions and support for hardware OpenGL acceleration is desirable. However, your monitor has to be able to support high vertical refresh frequencies (120Hz or better).

Currently, stereo is only supported under Windows NT/2000/XP. Due to an apparent bug in Windows 95 implementaion of OpenGL, switching ICM to stereo mode may cause a program crash unless you have a graphics card which supports OpenGL stereo directly. We are working on a workaround to this problem.

You may always try to press Alt−S in your graphics window and see what happens. It should toggle the stereo mode. Unless you have built−in stereo, the main graphics window should get squeezed by half and a second window appears below. Close or minimize all other windows on your desktop to avoid confusing displays. At this point, you should press the button on your emitter to change the mode of the monitor. The two windows will stretch and overlap, producing a double picture. Try to view it with the glasses − you should see stereo! If the two pictures do not align vertically, you might need to adjust stereoWinOffset parameter in ICM.

PC's with built−in stereo support: A limited number of graphics cards provide built−in stereo modes. You would need a different emitter (the workstation type). Generally, ICM will try to utilize such built−in capabilities if they are accessible through OpenGL graphics driver. We know that hardware stereo in ICM works fine on the Integraph graphics workstations (see www.intergraph.com). A caveat: to switch to the hardware stereo mode on an Intergraph machine you need to reboot. Please report the results to us.

24.3.19 I have made a H−Bond displayed in ICM−Browser−Pro which I would like someone to see in ICM−Browser − how do I do this?

ICM−Browser does not have energy functions and therefore H−Bonds are disabled. If you are using ICM−Pro or ICM−Browser−Pro and you know that someone with only browser will need to see theH−Bonds that you have displayed you need to make a mesh of the H−bonds. To do this:

- display h−bonds
- click on the meshes tab
- click on the first drop down arrow and select from display
- click on the build surface for an object button (grey blob button) next to drop down menu
- a graphical object should be built − may look a bit strange at first but you can change the view by right clicking on the mesh in the ICM workspace
- only whatever is currently being viewed in the display will be converted

24.3.20 I would like to create a movie wherein I "walk" through the molecule by moving the front clipping plane to the end. Can I write a loop that moves the clipping and generates an image after every step to generate my movie afterwards?

The easiest way is to interpolate between front and back clipping plane

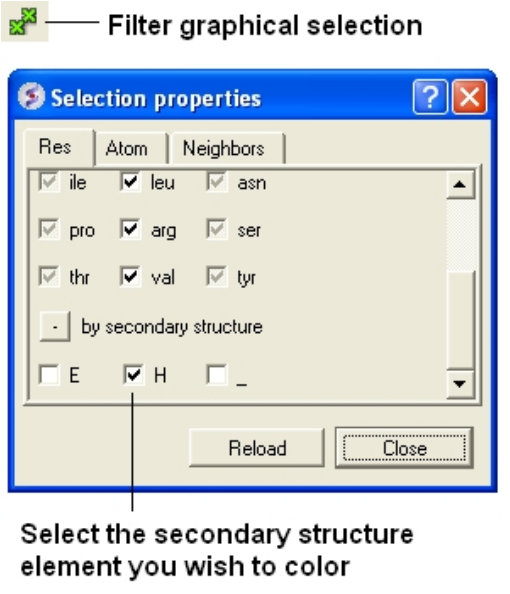
```
v1=View()  # define the 1st view   # v2=View()  # cut through clipping plane

for i=1,100   set view View(v1,v2,i*0.01) # interpolation

write image String(i) png

endfor
```

24.3.21 How do I color a structure by secondary structure?

You may wish to color your structure accordingly:

Helix: Red Beta Sheet: Green Loops: White

To do this you should use the filter graphical selection button and then select either H, E or _ for helix, sheet or loop. Then click on the color panel in the display tab.



24.3.22 How can I display a structure in many different representations simultaneously?

Use the slide button and make a series of `slides`.

24.3.23 How can I store a view and return to it later?

To store multiple views of an object and quickly change between each one use the "eye" button shown below.

For more information see the section entitled `Store Current View`

24.3.24 Some structures are displayed as noodles (the "worm" representation). Why are they displayed improperly?

Question : Some structures are displayed as noodles (the "worm" representation). Why are they displayed improperly?

Answer: There are several possible reasons:

- The ribbon display preferences are incorrect
- PDB entry lacks the secondary structure description
- PDB entry is incomplete (e.g. Ca− only, or an ICM mini−xpdb object); therefore, the secondary structure cannot be assigned

1. Perform the following steps to fix your display preferences: Go to File.Preferences and click on the Ribbon tab. Then uncheck the Ribbon worm checkbox. Alternatively left−click on the ribbon icon in the Display dialog and select Ribbon .
2. If the above manipulations do not fix the problem, the problem could be attributed to the PDB entry's lack of the secondary structure information. The secondary structure can be assigned with the Tools.Assign Helices and Strands menu.
3. It is possible that you are looking at an ICM mini−xpdb entry or a PDB entry with incomplete information about atom coordinates (could be a Calpha only entry). In this case the secondary structure could not be assigned.

24.3.25 I would like to have a local copy of the PDB − any advice?

Accessing PDB files locally

The simplest way to access pdb files locally, is to **download** the compressed pdb files in the old pdb format (not the mmcif files!) from the PDB ftp site and reset the values in **File/Preferences/Directories** .

By default ICM will set the s_pdbDir and `pdbDirStyle` variables to download each file from the PDB web site. In this case to update the PDB table of entry headers and the blast files with PDB sequences, select **Edit/PDBSearch** and click on the "Update PDB Table" button for the headers and the "Update PDB Sequences button for the sequences.

24.3.26 I would like to have a local copy of the NCBI Blast database− any advice?

Accessing the NCBI sequence databases locally

To enable ICM sequence search simply dowload NCBI blast database files to the local `s_blastdbDir` directory (see **File/Preferences/Directories**). Download only three file types for the databases of interest: `*.pin, *.phr, *.psq` , e.g. `nr.pin,nr.phr,nr.psq` to your `s_blastdbDirectory` (**File/Preferences/Directories**) or anywhere else. You can download Blast formatted databases from here `ftp://ftp.ncbi.nih.gov/blast/db/` eg. pdbaa − PDB sequence database.

ICM command `find database` and the `Bioinfo/Find_and_Align` macro can then use the blast files for both fast searches and ZEGA searches.

24.3.27 How do I color ribbon models according to Optimal Docking Area (ODA)

The Optimal Docking Area (ODA) tool is used to predict protein−protein interaction sites.

Tools/3Dpredict/ODA/3D−Mesh−Envelope

24.3.28 How do I load an electron density map into ICM?

You can load CCP4 maps into ICM

- File/Open
- File type = ICM maps

24.3.29 How can I contour an electron density map and adjust contour levels and color?

Load the electron density map into ICM and then follow the instructions in the section entitled `Contour Electron Density Map.`

24.3.30 I want to visualize weak hydrogen bonds how can I change the H−bond cutoff parameter?

GRAPHICS.hbondMinStrength parameter determines the hbond strength threshold for hbond display. The strength value is between 0. and 2. By changing 1. to 0.2 you will see more weak hydrogen bonds.

- In the command line type GRAPHICS.hbondMinStrength = 0.2

24.3.31 What is an iSee File?

A common question is − what is an iSee file? An iSee file is a term coined by scientists at the Structural Genomics Consortium at Oxford University for ICM molecular documents saved in .icb format.

>From the SGC website:

"Different from PDF files and paper manuscripts, iSee files allow total interactivity with the scene/ image by the user. Also, real−time rendered movies enable smooth transition of a viewpoint to another, helping to convey the sense of depth and inter−relationship of different structural features in space. iSee files also permit non− linear navigation through the expert annotation, thus not restraining the user to the sequencial explanation of traditional molecular movies."

See: `http://www.sgc.ox.ac.uk/iSee/` `http://www.molsoft.com/sgc.html`

How to make an iSee file? `http://www.molsoft.com/gui/tut6.html`

24.3.32 How do I set a blend transition effect between two slides?

In ICM version 3.5−1l a new blending transition effect between slides is available. To see this in action download the latest version of ICM or the free ICM−Browser and view this icb file:

`http://www.molsoft.com/~andy/blend.icb`

To generate this transition effect:

1. Make a couple of slides − click camera button at bottom of the gui − Note: to see the blending transition the transition needs to be made between different representations e.g. wire to ribbon 2. Right click on the name of the slide in the ICM workspace and select edit slide 3. At the bottom of this window you will see options for the currently available transitions − blend and smooth − check which one you would like to use and the transition time in ms.

24.3.33 How to check on the display status of an object in the command line.

You can check if molecule is displayed by using 'DD' selector.

For example:

```
Mol(a_1xbb.a//DD) == a_1xbb.a # returns 'yes' if at least one atom in the molecule is displaye

Res(a_1xbb.a//DD) == Res(a_1xbb.a) # returns 'yes' if at least one atom in each residue is dis

Atom(a_1xbb.a//DD) == Atom(a_1xbb.a) # returns 'yes' if every single atom is displayed
```

24.3.34 ICM and AutoSave

There are two preferences controlling 'autosave/restore behaviour'

```
GUI.autoSave  # toggles autosave on/off
GUI.autoSaveInterval  # autosave interval in min.
```

NOTE: that ICM will not perform autosave when idle. autosave is only preformed if autoSaveInterval was expired AND some command was executed.

ICM writes autosaved session into s_tempDir directory (it usually points to some locally mounted directory) The filename starts with 'icmauto' prefix.

If ICM crashes it renames the last autosaved file to 'icmcrash' prefix. On startup ICM checkes if s_tempDir directory contains at least one file with prefix = 'icmcrash' and offers to restore session from it. 'icmautoXXXX' and 'icmcrashXXXX' are normal icm files and can be copied/renamed and read directly with 'read binary' or through GUI.

ICM deletes 'icmautoXXXX' file before normal exit. Note that in certain cases these files will be kept. E.g: if you press "Ctrl+C" on linux will not receive crash signal −> 'icmauto' will not be renamed to the 'icmcrash' and will be kept.

NOTE: autoSavePeriod is used to periodically store stack in montecarlo simulations. It has nothing to do with save/restore functionality

24.3.35 How to remove the dotted lines in chain breaks.

See the how to `section` entitled "How to remove chainbreaks (dotted lines)".

In version 3.6−1a and above you can use the options in the display tab. Click an d hold on the ribbon button. You can then select **Display Chain Breaks/ None**.

24.3.36 When using ActiveICM is there a way to set a RELATIVE path to an icb file rath than ABSOLUTE?

When you open ppt with embedded activeICM it actually tries original absolute location and then (if not found) looks for that file in the current directory.

Unfortunately the meaning of "current directory" is not well defined in Power Point. For example if you double click on ppt file it sets the current directory to the folder which conatains that ppt file, but if you open the same file from the PowerPoint it does not set current directory accordingly.

So, let's say you have aaa.ppt which has c:\some\location\aaa.icb embedded. Nowyou want to copy that presentation to your laptop. You need to put these two files in the same directory. After that on you laptop you can just double click on aaa.ppt. Note, if you open aaa.ppt from "File−Open" it'll popup open file dialog where you should locate aaa.icb.

24.3.37 How do I turn off the annoying beep?

To turn off the **beep** noise when an error is made in the command line type:

```
l_beep = no
write system preferences # if you want to store this permanently
```

You can also remove it in the system preferences tab in File/Preferences

24.4 FAQ Structure

Questions and answers relating to protein and DNA structures, objects and the PDB

- How do I make a covalent bond between a ligand and a receptor?
- How do I convert a Chemical from the PDB into an ICM object?
- How to write a pdb file?
- How do I renumber the residues in a PDB file
- How can I merge two separate objects into one?
- How do I superimpose two proteins?
- How can I calculate the RMSD between two protein structures?
- Can you give me some tips on which options to use for RMSD calculations?
- I would like to delete all the residues in my protein except for the ones surrounding the ligand binding pocket.
- How do I display the distance between two atoms?
- How do I display only the residues that surround the ligand binding pocket?
- How do I show the sequence conservation around the ligand binding site?
- How do I mutate a residue?
- How do I mutate a terminal N or C residue?
- How do I change the tautomeric form of Histidine in a structure?
- How can I change the torsion angle?
- How do I make a disulfide bond?
- How do I read in all the structures in a PDB file of a protein solved by NMR?
- How do I write a script to calculate solvent−accessible surface and tabulate the results to show area for each residue in a protein?
- How do I display weak hydrogen bonds?
- How do I set a formal charge?
- How can I select the closest residue from the center of mass of a selected residue?

24.4.1 How do I change the bond types and add formal charges to a ligand from the PDB?

Please see the section in the cheminformatics chapter entitled Converting a Chemical from the PDB.

24.4.2 How do I make a covalent bond between a ligand and a receptor?

To make a covalent bond between a ligand and receptor:

Step one − place the ligand and receptor into the same object − how to move into one object is described here.

Step two − you can only make bonds in non−icm objects so you will need to "strip" the ICM object back to PDB Right click on the object name in the ICM Workspace and select Convert to non−ICM ...

Step three − use the ICM selection language to select the two atoms you would like to select and use the make bond command.

eg in 1f88 there is a covalent bond between the ligand retinal and K296 − zoom into it and see the bond − first we will delete this bond and then we will remake it like this:

```
delete bond a_1f88.aret/977/c15 a_1f88.a/^K296/nz

make bond as_graph

make bond  a_1f88.aret/977/c15 a_1f88.a/^K296/nz
```

If you right click on an atom it will give you the icm selection language for each atom.

24.4.3 How to write a pdb file?

- Right−click on the molecular object name in the ICM Workspace Panel
- Select −− Save as −−
- Choose the file type `pdb`

24.4.4 How Do I renumber the residues in a PDB file

To renumber the residues in a PDB file you need to use the command line option

align number rs_residuesToBeRenumbered [i_firstNumber]

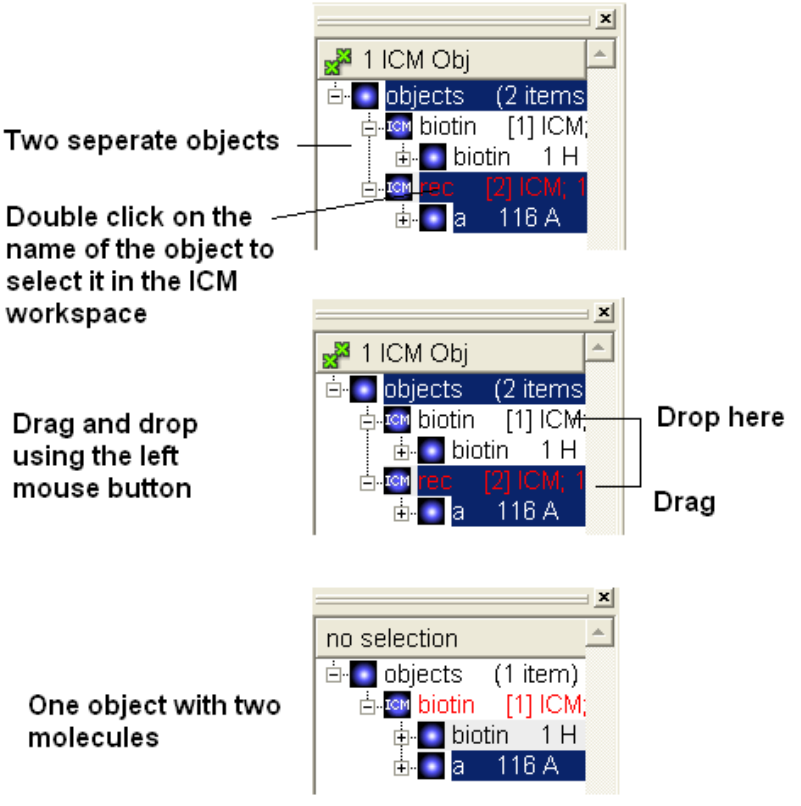
More details here:

`http://www.molsoft.com/man/icm-commands.html#align-res-numbers`

24.4.5 How can I merge two separate objects into one?

To merge two objects into one you can use drag and drop.

- Double click on the object you want to move in the ICM workspace (should be highlighted in blue).
- Click on the object you want to move and drag it to the name of the object (in the ICM workspace) you wish to move it to and then drop.



24.4.6 How do I superimpose two proteins?

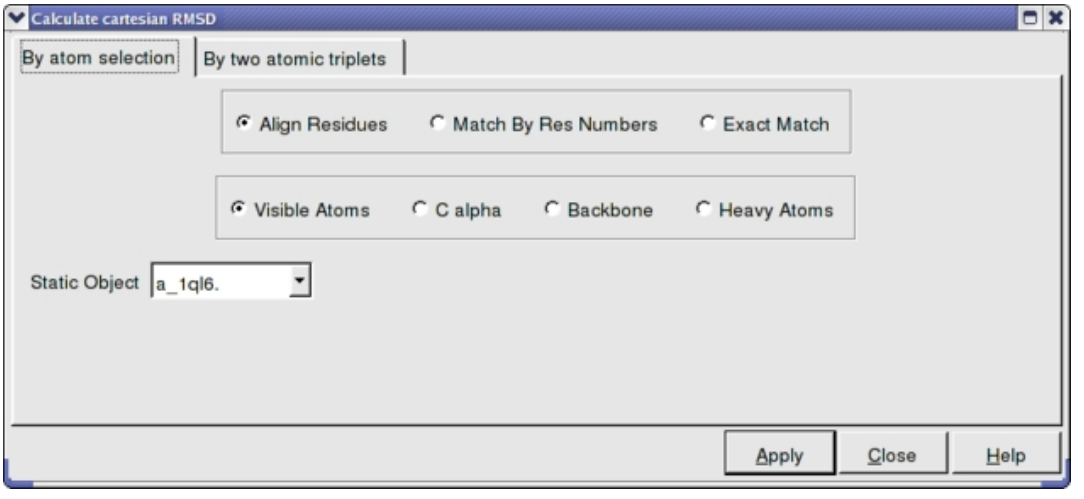
The quick way to do this is described in the section entitled `"How to Superimpose Two Structures"`. However more superimpose options are found in the Tools/Superimpose menu.

- Display and select the proteins you wish to superimpose. You can select the whole protein simply by doublo−clicking on the name of the protein in the ICM Workspace. When selected there will be green−crosses on the protein in the graphical display and the protein molecules will be highlighted in blue in the ICM Workspace.
- Tools/Superimpose

There are three options

1. Superimpose two proteins by 3D only
2. Superimpose two proteins
3. Superimpose multiple proteins.

In option 2 and 3 above you can select exactly what you would like to superimpose e.g. backbone, Calpha. See the image below. Also you can select which protein you want to remain static.



24.4.7 How can I calculate the RMSD between two protein structures?

To calculate RMSD.

- First select the two molecules you wish to calculate the RMSD difference of. For example you can double click on the name of the ligand in the ICM Workspace (shaded blue when selected) and then whilst holding the CTRL key select the other ligand in the same way.
- Tools/Analysis/RMSD
- Select which parameters such as "Kept in Place" or "superimipose" and which atoms you wish to superimpose.
- The RMSD value will be displayed in the terminal window.

24.4.8 Can you give me some tips on which options to use for RMSD calcu

lations? {RMSD tips}

There are a number of ways to calculate RMSD and the method you use depends on the problem you wish to solve. For example you need to use different approaches when calculating the RMSD of proteins and ligands.

There are two options in GUI:

1. Tools/Analysis/RMSD # For protein structures only.
`http://www.molsoft.com/gui/rmsd.html` 2. Superimpose Button # will work for chemicals and protein structures but beware the ligand is superimposed and therefore not useful for comparing docked structures `http://www.molsoft.com/gui/superimpose.html`

Command Line:

1. RMSD command `http://www.molsoft.com/man/icm-functions.html#Rmsd` 2. Static RMSD command # the way to compare two docked structures − use the chemical parameter and beware of how many atoms have been compared when comparing non−identical chemical structures.

http://www.molsoft.com/man/icm-functions.html#Srmsd

24.4.9 I would like to delete all the residues in my protein except for the ones surrounding the ligand binding pocket.

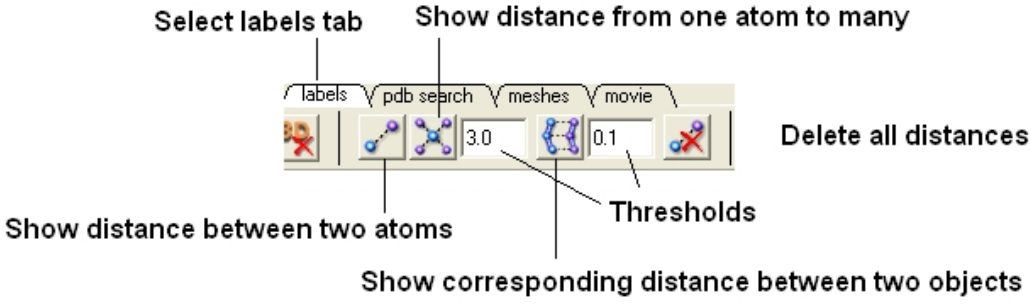
You cannot delete from an ICM Object. You can delete from a model or PDB structure. So if the structure is an ICM object strip it to a model by right−clicking on the name of the object in the ICM Workspace and selecting "strip". Now follow these instructions.

- Double click (select) on ligand in the icm workspace and it will be colored dark blue and green crosses in the display
- Right click on the ligand in ICM workspace and select neighbors
- Enter 7 (Angstroms) and Type "Same Object Other Chains" − now you should see greeen crosses around ligand.
- If you want the whole residues surrounding the pocket select the Residue selection and you should see Rs rather than green crosses
- Now select the exclamation mark button which `inverts` selection − now everything but the surrounding residues are selected
- All selections are placed in the variable name `as_graph`.
- Type in the terminal window delete Res(as_graph)

24.4.10 How do I display the distance between two atoms?

One way to do this is to use the atom select button on the right hand side of the graphical user interface.

- The atom selection button has a green cross displayed on it see `the selection buttons`.
- Next select two atoms using this tool. Selected atoms will have green crosses on them in the graphical display.
- Select the labels tab (in older versions of ICM this is called the Advanced tab) and select the "Show distance between two atoms button".



More instructions on how to display distances can be found in the section of the manual entitled `"Finding the Distance Between Atoms"`

24.4.11 How do I display only the residues that surround the ligand binding pocket?

There is a quick and easy way to do this as described in the Tips section of the manual entitled `"Quick Binding Pocket Display"` or you may want to follow the instructions below for a more user−defined method.

- Double click on the ligand name in the ICM workspace and it will be highlighted in blue.
- Right click on the name and select the Neighbors option.
- Enter 6ï¿½ (or whatever distance is appropriate for the ligand) for the sphere radius selection. Green crosses represent selected residues.
- Select type from the drop down menu "same_object_other_chains".
- Convert your selection to a residue selection if you wish using the button shown in the example below.
- Go to the display tab and select the representation you would like for the residues surrounding the pocket. Next use the "Invert Graphical Selection" `button` to select everything else other than the

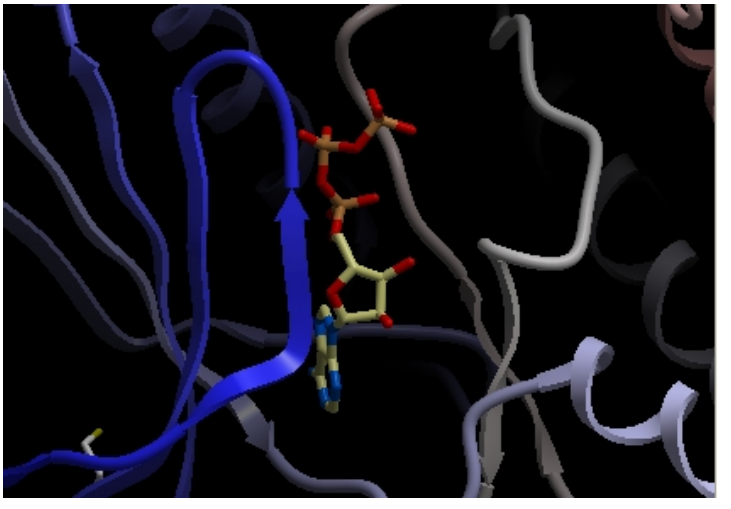
residues around the pocket and undisplay them by clicking on the representation buttons in the display tab.

For example if your structure is shown in ribbon you and you wanted to display the surrounding residues in xstick and udisplay the rest of the structure you would do the following.

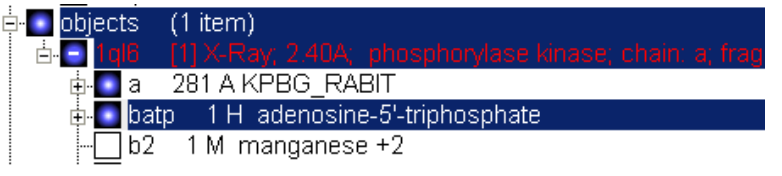
- Select the residues around the pocket using the spherical selection method as described above.
- Select the xstick representation button in the display panel
- Select the invert selection button
- Select the ribbon display button and the ribbon display will be removed from outside the pocket.

Steps shown graphically below for the kinase 1ql6 and the atp ligand.

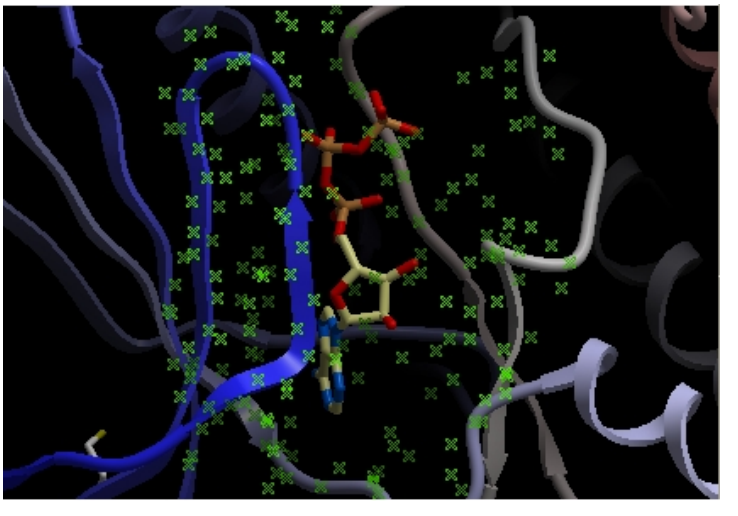
Step 1: Receptor (1ql6.a) is in ribbon display:



Step 2: Double click and select the atp molecule in the ICM Workspace

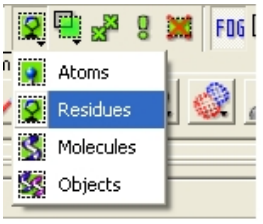


Step 3: Right click on the selected atp molecule in the ICM Workspace and select Neighbors. Enter radius and type of selection. Click OK and you will see a graphical selection of green crosses around the pocket.

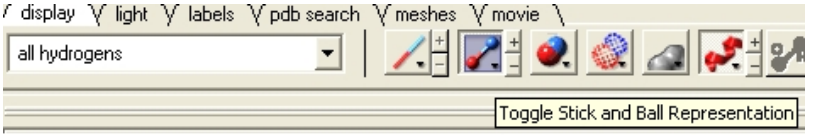


24.4.9 I would like to delete all the residues in my protein except for the ones surrounding the ligand binding pocket.

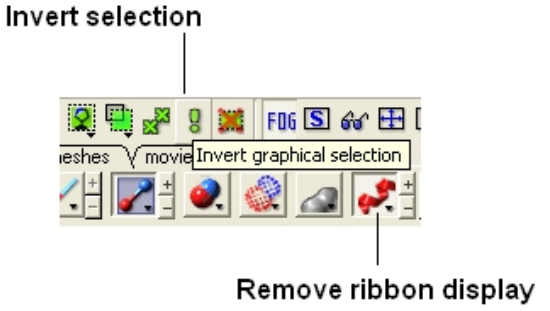
Step 4: Convert your selection to a residue selection if you wish. You will then see green "R" in the graphical selection rather than green crosses.



Step 5: Select the xstick representation and the residues around the ligand will be displayed.



Step:6: If you want to undisplay the rest of the receptor outside the pocket use the invert selection button and then click the ribbon representation button.

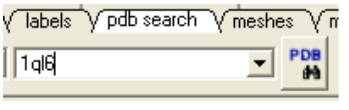


24.4.12 How do I show the sequence conservation around the ligand binding site?

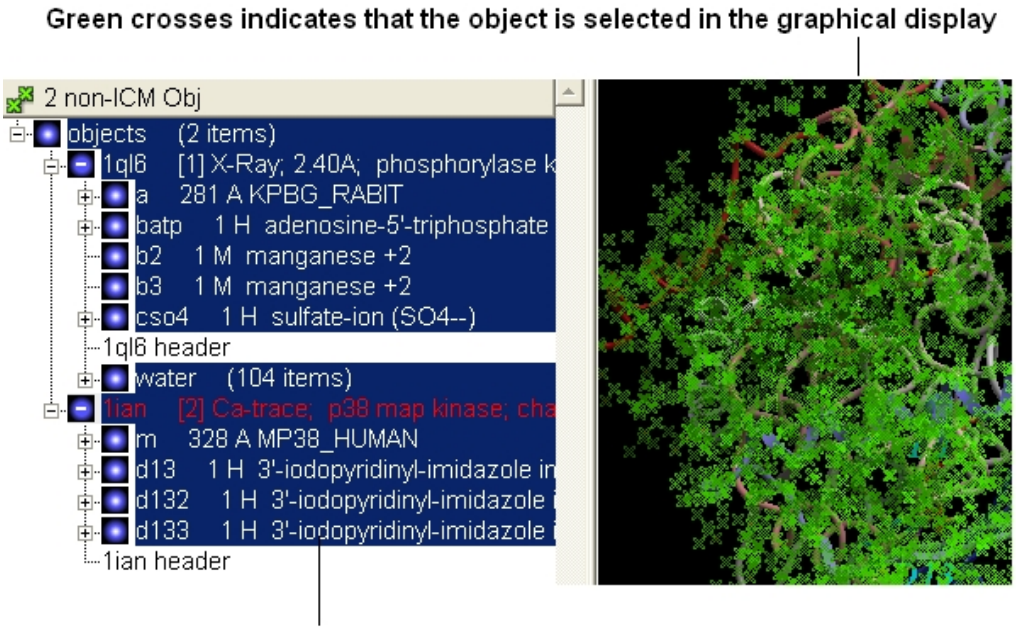
Here is an example of how to superimpose the structures of two proteins and display the sequence conservation around the ligand binding pocket.

PDB Search

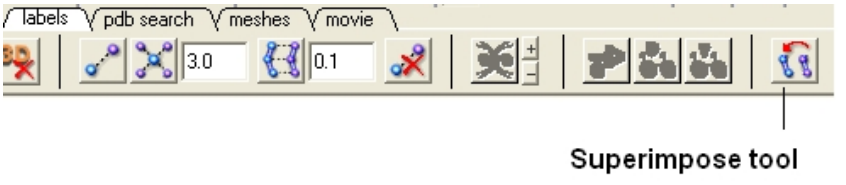
- PDB Search Tab 1ql6
- PDB Search Tab 1ian



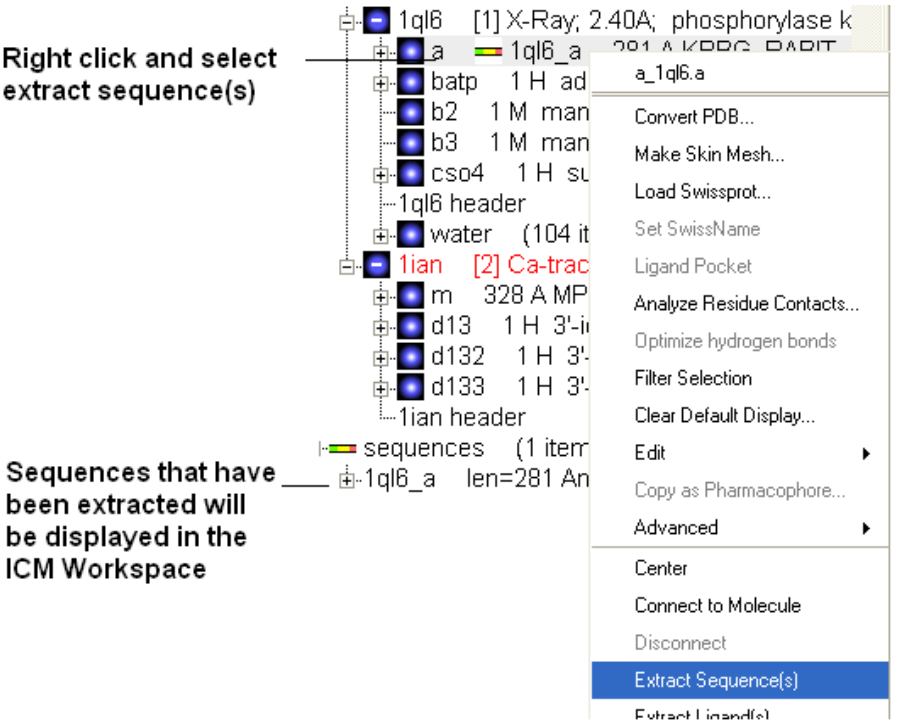
- Select both receptors by double clicking on the name of the receptor in the ICM Workspace. To select two receptors use the Ctrl button or use the shift button to select a range of objects in the ICM Workspace. A receptor which is selected will be highlighted in blue in the ICM Workspace and with green crosses in the graphical display.



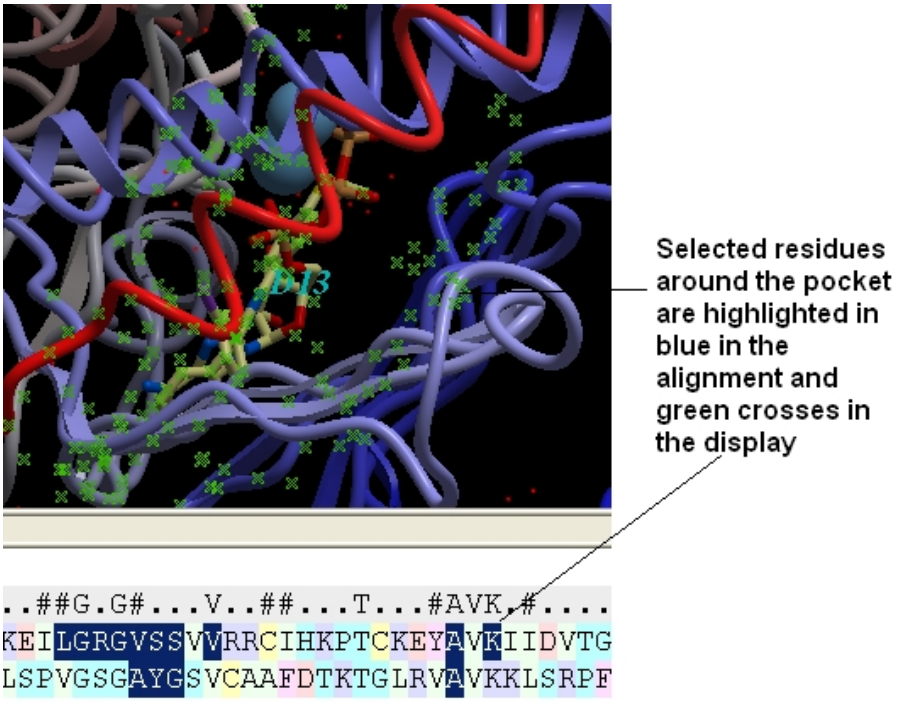
- Superimpose both structures by clicking on the **display** tab and selecting the superimpose button.



- Now that the structures are superimposed we can unselect everything − to do this right click and drag in blank space in the graphical display or double click in white space in the ICM Workspace or use the `unselect button` green box with red cross through it.
- Now extract the sequence information from each protein. To do this right click on the molecule "a" of 1ql6 and molecule "m" of 1ian. and select extract sequences. Once the sequences have been extracted you should see the sequence in the ICM Workspace entitled 1ql6_a and 1ian_m

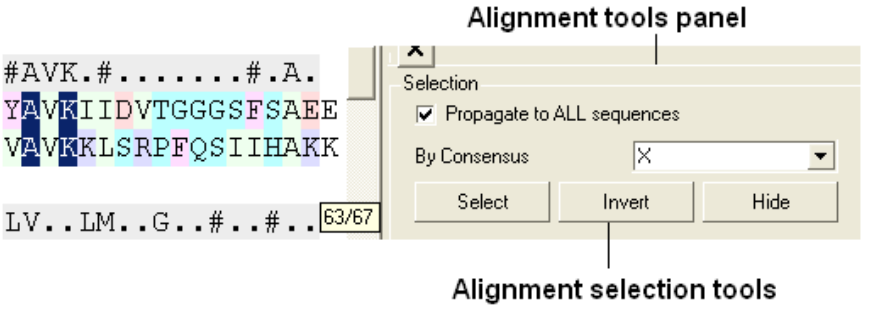


- Now align the sequences by selecting both sequences right clicking and selecting Align sequences. An alignment will be displayed at the bottom of the graphical user interface.
- Next we need to select the ligand ATP and select a sphere of residues around the ligand. To do this double click on the ATP molecule in 1ql6 (batp) in the ICM Workspace. You should see green crosses in the graphical display. Right click on the ATP molecule in the ICM Workspace and select neighbors. Enter a value of 6A for the radius. Select all_objects for the type of selection. Click ok and you should see a cluster of green crosses in the two proteins around the ligand and selected residues will be highlighted in blue in the alignment.



- Right click in white space in the alignment and select display tools panel.
- In the alignment tools panel select propogate to all sequences.
- Select the "invert" button to invert the current selection.

- Select the "hide" button to hide the current selection and you will be left with the residues surrounding the binding pocket in the alignment.



NOTE: Please note that all alignments are linked with structure therefore selections can be made in the alignment. Also as an example structure can be colored according to the color in the alignment which is useful for identifying conserved regions.

24.4.13 How do I mutate a residue?

- Display protein.
- `Convert` to ICM Object.
- Right click on the residue you wish to mutate. If you wish to mutate the C or N terminal please see the next question.
- Select Advanced/Mutate Amino Acid
- Select amino acid from drop down menu

24.4.14 How do I mutate a terminal N or C residue?

Unfortunately with Internal Coordinates it is very difficult to re−route the first residue and last residue by using modify However there is a way around it which is a bit long but here it is:

For example we want to change the first and last residue of "1crn"

- Read pdb "1crn" or use the PDB search tab
- `Convert pdb` to an ICM object and select replace original − you can do this by right clicking on the name of the object in the icm workspace and select convert object.
- Extract sequence by right clicking on 1crn in the ICM Workspace and select extract sequence
- Right click on sequence and select edit sequeuce − double click on it and copy the sequence
- File New − select peptide and copy sequence into data entry box entitled one letter code
- Edit the first and last residue to the one you want
- Select ok and then you should have a long elongated unfolded peptide
- Type in terminal window

```
set tether a_2. a_1.
```

- click on the advanced tab and select the button Toggle Tethers − to check tethers have been set − should see lots of red lines
- Type in terminal window

```
mncalls=10000

minimize "tz"
```

you should see the unfolded peptide thread onto the structure − if it is not 100% perfect repeate mn calls and minimize command

24.4.15 How do I change the tautomeric form of Histidine in a structure?

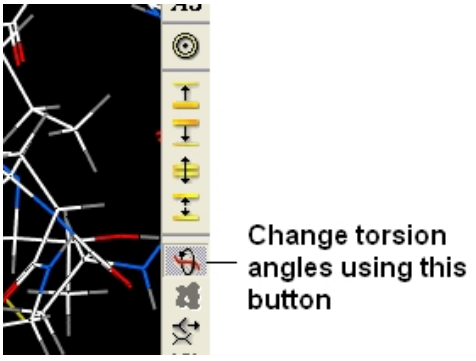
- Display protein.
- Convert to `ICM Object`.

- Right click on the residue you wish to mutate. If you wish to mutate the C or N terminal please see the next question.
- Select Advanced/Mutate Amino Acid
- Select one of the following: Hip(histidine protonated), Hie (histidine epsilon tautomer)

24.4.16 How can I change the torsion angle?

To do this:

- Convert your pdb file into an ICM object.
- Change the torsion angle using the button below.



24.4.17 How do I make a disulfide bond?

Use **MolMechanics/Edit Structure/Set Disulfide Bond.** More description of this can be found in the section entitled `Making a disulfide bond`.

24.4.18 How do I read in all the structures in a PDB file of a protein solved by NMR?

- In the terminal window type the following.

```
read pdb pdb_FileName all
```

e.g.

```
read pdb 1sgg all
```

24.4.19 How do I write a script to calculate solvent−accessible surface and tabulate the results to show area for each residue in a protein?

Here is a script to calculate solvent−accessible surface and tabulate the results to show area for each residue in a protein:

```
read pdb "1crn"
show surface area mute # compute surface areas
res = a_/1:18 # residue range of interest
n = Nof(res)  # the number of residues.
add column t Sarray(n, Name(Obj(res))[1]),Trim(Label(res),all),Area(res)

write t_1 separator="," "t.csv"  # read into Excel or something else similar
```

24.4.20 How do I display weak hydrogen bonds?

To display a weak hydrogen bond you may have to change the ICM parameter which controls the hbond strength threshold for hbond display. This parameter is called:

```
GRAPHICS.hbondMinStrength
```

By default it is set to 1 but the strength value can be set between 0. and 2. e.g By changing 1. to 0.2 you will see more weak hydrogen bonds.

24.4.21 How do I set a formal charge?

To set a formal charge:

1. Display the molecule
2. Simply right click on the atom and choose Edit−−−> Set formal charge.

24.4.22 How can I select the closest residue from the center of mass of a selected residue?

See the ICM language manual here :

`http://www.molsoft.com/man/icm-functions.html#select-by-center-of-mass`

24.5 FAQ−Docking

Frequently asked questions regarding small molecule and protein−protein docking.

- What are the units of the energy values displayed after docking?
- I do not have ICM−VLS but I would like to calculate the binding energy of my docked complex − how can I do this?
- How do I sample conformations of flexible rings in docked ligands, for example, a "chair−boat" transition?
- How can I guide my docking to a known conformation of a smilar ligand?
- How do I reload a docking project?
- During a Virtual Ligand Screening experiment how many times should I re−run the docking?
- Which score value should I use for analysis?
- Some compounds are missing from my HITLIST.
- What constitutes a good docking score?
- When I view my docking run my ligand never jumps into the box − what did I do wrong?
- How do I identify the binding pockets in my receptor?
- How long does it take to dock one ligand using ICM−VLS?
- What does thoroughness mean?
- When I setup the receptor I am asked to move a probe − what is this?
- I want to dock to the receptor and include other molecules in the receptor such as a tightly bound water molecule − how can I do this?
- How can I run docking with a flexible receptor?
- How can I run the docking simulation from the UNIX command line?
- I have a complex I wish to generate an ICM VLS Score for, however I did not dock it using VLS. How can I do this?
- Why is there always a small difference between the score calculated interactively by scanScoreExternal and that obtained by docking (VLS)?
- How do I monitor and terminate a background docking job?
- How do I sample flexible ring conformations (boat, chair etc..) during docking?
- I am docking a racemic compound how can I sample both R and S states during docking?

24.5.1 What are the units of the energy values displayed after docking?

The energy units are kcal/mol

24.5.2 I do not have ICM−VLS but I would like to calculate the binding energy of my docked complex − how can I do this?

For more in depth information on this topic please see the command line manual www.molsoft.com/man however the basic approach is this: Calculuate the energy of the receptor (e1, a_1), energy of the ligand (e2, a_2) and the energy of the complex (e12) then the binding energy = e12 − e1 − e2

Here is a script to do this whereby the ligand is a_2 and the receptor is a_1:

```
electroMethod="boundary element"

surfaceMethod="constant tension"

surfaceTension=0.020

dielConst = 12.7

set terms "sf,el,en"

read object s_icmhome+"2ptc"

show energy a_1 a_1 mute

e1  =Energy("el,sf,en")

show energy a_2 a_2 mute

e2  =Energy("el,sf,en")

show energy mute

e12 =Energy("el,sf,en")

print "Binding energy = ", e12 − e1 − e2
```

There are many different approaches to the evaluation of binding energy. One of the reasonable approximations has the following features: van der Waals/hydrogen bonding interaction is excluded since it has close magnitudes for protein−protein and for protein−solvent interactions; electrostatic free energy change is calculated by the REBEL method (see also the section "How to calculate the electrostatic free energy ... ") above); side−chain entropy change is calculated by standard ICM entropic term based on exposed surface area of flexible side−chains; hydrophobic energy change is calculated using surface term with constant surface tension of 20. cal/Angstrom.

24.5.3 How do I sample conformations of flexible rings in docked ligands, for example, a "chair−boat" transition?

Find your docking project file (*yourDockingProjectName.tab*) and set the `ringFlexibilityLevel` to 1 or 2.

In GUI, this parameter can be reset in the "Docking Preferences" dialog. It is called "Flexible ring sampling level".

24.5.4 How can I guide my docking to a known conformation of a smilar ligand?

Use Docking/Template as described `here`.

24.5.5 How do I reload a docking project?

To reload a docking project.

/Docking/Set Project − Type in the Docking Project Name (Case Sensitive)

Now you can browse scan solutions etc.... and use the maps to dock another ligand.

24.5.6 In a VLS run how many times should I run the docking?

Generally we suggest the docking should be repeated 2−3 times and the lowest ICM score pose should be taken.

24.5.7 Which score value should I use for analysis.

The value under the heading SCORE relates to the ICM docking score and is the best one to use for docking result analysis. The other score we provide − potential of mean force score (mfscore − `http://www.molsoft.com/man/terms.html#term-mf`) provides an independent score of the strength of ligand−receptor interaction.

24.5.8 Some compounds are missing from my HITLIST.

The hitlist is filtered according to a score cutoff defined in the PROJECTNAME.TAB file. Therefore poor scoring compounds are not reported in the HITLIST − this can be changed by opening the .tab file in a suitable text editor e.g. notepad in windows or vi and changing the DOCK1.r_ScoreThreshold value (by default it is −32). The scores for all compounds in a VLS screen are available in the PROJECTNAME.OU file.

You can also change this value in Graphical User Interface:

- Docking/Preference/Database Scan
- Change the Score Threshold Value

24.5.9 What constitutes a good docking score?

Generally a score below −32 is regarded as a good docking score. A good score depends on the system into which you are docking. For example is the pocket open or closed and are there metal ions interacting with the ligand. If the pocket is open scores higher than −32 may indicate potential binders. If a crystal structure is available remove the ligand and re−dock it to get an indication of approximately what is a good score for the receptor you are interested in.

24.5.10 When I view my docking run my ligand never jumps into the box − what did I do wrong?

Here are some reasons and some solutions for why your ligand is sampling outside of the binding pocket:

1. On Receptor Setup when it asks to move the initial probe − did you accidently move the probe outside the box?
2. Double check exactly where you built the maps (read one map in) in command line type read map "DOCK1_gl" ds map or check Docking/Review Adjust Ligand binding box
3. On the Docking/Interactive Docking/ LoadedLigand − did you check the box Use Current Ligand position? If so remove this option.

24.5.11 How do I identify the binding pockets in my receptor?

To do this go to:

- Tools/3D Predict/ICMPocketFinder

More information can be found in the section entitled `Identifying Binding Pockets`

24.5.12 How long does it take to dock one ligand using ICM−VLS?

It takes approximately 30−60 seconds per ligand depending on the size of the ligand and the nature of the pocket. ICM ranked first place compared to other leading docking software in terms of accuracy in a recent analysis undertaken by Astra Zeneca scientists.

See: On Evaluating Molecular−Docking Methods for Pose Prediction and Enrichment Factors Hongming Chen, Paul D. Lyne, Fabrizio Giordanetto, Timothy Lovell, and Jin Li J. Chem. Inf. Model.; 2006; 46(1) pp 401 − 415

24.5.13 What does thoroughness mean?

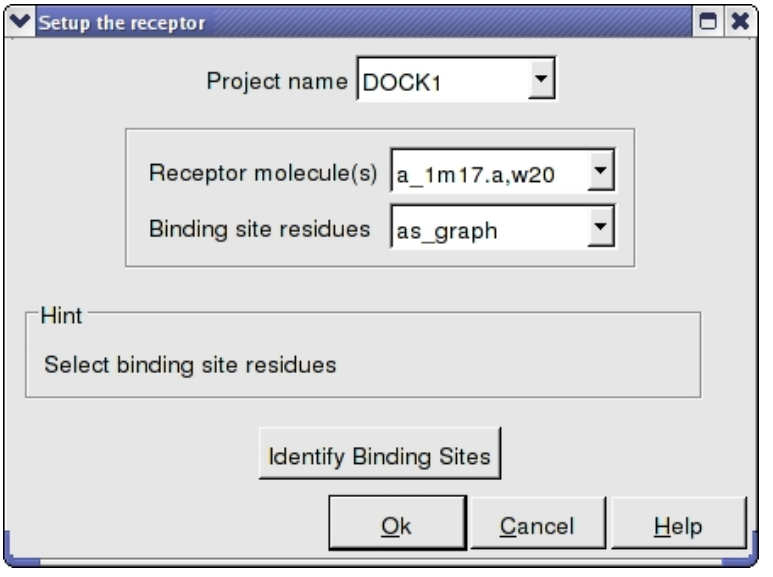
When you send a docking job either using Docking/Interactive or Docking/Run Docking Batch you are asked to enter a thoroughness value. This value represents the length of the docking simulation. The default value is 1. and this works well with nearly every kind of docking scenario, however in certain circumstances such as if you have a very large pocket this value should be increased slightly to a range of between 5. and 10.

24.5.14 When I setup the receptor I am asked to move a probe − what is this?

The probe which you see after Receptor Setup (Docking/ Receptor Setup) represents the initial starting position for the ligand. Usually this does not have to be changed as ICM by default places it into the center of the pocket. However if you do wish to move it to position closer to a critical region of the pocket you can do this using the middle mouse button when prompted in receptor setup.

24.5.15 I want to dock to the receptor and include other molecules in the receptor such as a tightly bound water molecule − how can I do this?

All molecules that you wish to dock to need to be stated in the Docking/Receptor Setup/ Receptor molecule (s) data entry box using the ICM selection language. For example if you wish to dock to the protein with PDB code 1m17 and water molecule number 20 you need to enter the information as shown below:



24.5.16 How can I run docking with a flexible receptor?

- First dock the ligand in the standard way (flexible ligand, rigid receptor).
- Then use Docking/Flexible Receptor /Refinement. This will allow the ligand and the receptor to be flexible during docking.

24.5.17 How can I run the docking simulation from the UNIX command line?

- Set your docking project up (eg, Set Project, Receptor Setup, Ligand Setup, Maps}

In the unix command line type:

```
/icm/rundock "DOCK1"
```

Where DOCK1 is the name of your docking project.

A variety of flags can be used with rundock:

```
 echo $prog": usage:   " $prog " <options> <project name> "
    -f <db entry from>"
    -t <db entry to>"
    -l <thoroughness> # change the length of MC docking, default is 1."
    -L <ligand list>  # dock selected compounds from the database"
    -i <ligand sdf>   # dock compounds from an SDF supplied"
    -n <scanName>     # change the run name in the output files"
    -a                # force docking and saving of all compounds"
    -s                # save stack conformations"
    -S                # evaluate score for all stack conformations (slow)"
    -d                # dock only (no scoring)"
    -j <nprocess>     # dock several ligands in parallel"
    -o                # redirect output to <project name>_from-to.ou"
    -c <output file>  # continue interrupted job with <output file>"
    -r                # dock rigid (no ligand flexibility)"
    -R <rand. seed>   # set random seed"
    -h                # show brief help"
```

24.5.18 I have a complex I wish to generate an ICM VLS Score for, however I did not dock it using VLS. How can I do this?

type in the command line:

```
scanScoreExternal
```

OR

- Docking/Tools/Evaluate ICM Score...

24.5.19 Why is there always a small difference between the score calculated interactively by scanScoreExternal and that obtained by docking (VLS)?

The reason for this is that ICM score has terms that require calculations on the reference 'free' state of the ligand, in particular solvation electrostatics and internal force−field strain energy change are calculated as a difference between free and bound state. VLS uses as a free state the lowest energy conformation found by MC search for the unbound ligand. Interactive score just minimizes the ligand locally. To ensure consistency we recomend you use one method or the other for scoring or you could recalculate the interactive score for your ligand from VLS before modifying/minimizing.

24.5.20 How do I monitor and terminate a background docking job?

If a background job is running you will see a message saying "1 bgrnd job" at the top of the gui interface (gui blue title panel).

To monitor the progress of the job:

1. Windows/Background Jobs
2. A panel will be displayed with information such as running time and percentage completed.

To terminate a background job:

1. Windows/Background Jobs
2. Right click on the job ID number and select "Terminate".

To view the current output of a background job:

1. Windows/Background Jobs
2. Right click on the job ID number and select "View Output"

When a background job has finished a message will appear in the graphical user interface

24.5.21 How do I sample flexible ring conformations (boat, chair etc..) during docking?

MolSoft's ICM docking algorithm has flexible ring sampling included on the fly. Just set ring sampling level to 1 (flex ring only in pre−sampling step) or 2 (throughout the simulation).

To do this:

- Set up the docking project (http://www.molsoft.com/gui/start− dock.html#docking−start)
- Before running the docking simulation go to Docking/Preferences/ General and change the flexible ring sampling level to 1 or 2.
- Now run the docking simulation (http://www.molsoft.com/gui/start−dock.html#begin−docking−simulation)

OR,

If you want to generate the conformations before docking and you have ICM−Pro + ICM−Chemistry then you can use the conformation generator algorithm described here:
`http://www.molsoft.com/gui/conf−gen.html`

24.5.22 I am docking a racemic compound how can I sample both R andS states during docking?

To sample both R and S states of a compound during docking. Edit the project_name.tab file and edit l_sampleRacemin to yes

If l_sampleRacemic is 'yes', R and S states are sampled for racemic centers and best−fitting one is chosen. If it is 'no', they are kept fixed (in an aribtrary R or S state). Note that stereo centers that centers with pre−assigned R or S state are never sampled, if sampling is desired they need to be reassigned as racemic.

24.6 FAQ−Cheminformatics

Frequently asked questions regarding small molecules, ICM−Chemistry tools and MolCart

- How do I generate the hostid for my MolCart license?
- How do I connect to Molcart?
- How can I download the MolCart vendor compounds provided by MolSoft?
- I have a database in MolCart and I want to save it in SDF format − how can I do this?
- How do I perform a chemical search?
- How do I make a new molcart database from a query search?
- How can I draw small molecules?
- How do I read in a small molecule from ISIS draw and convert it to 3D?
- How can I change the layout of a chemical table?
- How can I convert a chemical in a chemical table into 3D?
- I have a small molecule which already has the 3D coordinates defined. How can I load the molecule and not optimize it so as to preserve the assigned 3D coordinates?
- I have a chemical table displayed − how can I add columns of chemical properties associated with each chemical in my table?
- I have a small molecule displayed in 3D in a loaded PDB file. How can I extract this molecule into an ICM Chemical Table?
- What is considered a good druglikeness value?
- I do not see the chemical property monitor in the molecular editor. Where is it?
- How do I perform a text query on a database in MolCart?
- How do I convert SMILES string into a 2D structure
- Is there a way to build a classification model using the APF output?

- How to rotate a 2D chemical sketch so it fits nicely in its cell in a chemical table?

24.6.1 How do I generate the hostid for my MolCart license?

- Download MolCart from www.molsoft.com/support and unpack it.
- run run /usr/molcart−1.9−5/sysid and send the number to support@molsoft.com

24.6.2 How do I connect to Molcart?

When you unpack the MolCart distribution from www.molsoft.com/support you will be given a unique number (which you need to send to support@molsoft.com to get a MolCart license) along with MolCart login details such as Server Name, UserName and Password.

Once you have the MolCart distribution loaded you can connect to MolCart by going to Tools/Chemistry/Connect to Molcart

24.6.3 How can I download the MolCart vendor compounds provided by MolSoft?

MolCart Compound Database is an up−to−date collection of vendor compound databases. This database is divided into three collections:

- Screening Compounds for cherry picking.
- Building blocks for combinatorial chemistry

Each collection consists of two components:

- a single non−redundant set of compounds, with a list vendors and vendor−IDs for each unique compound
- the original files with the full set of fields as provided by each vendor

The Molcart Compounds can be uploaded to a relational database using MolCart and can be further enhanced and annotated with the Molsoft ICM−Chemistry tools.

The MolCart compounds can be downloaded from `http://www.molsoft.com/screening.html` then to unpack them type:

```
zcat vendor.gz | mysql −h<hostname> −u<user> −p<password> molcart_database_name
```

24.6.4 I have a database in MolCart and I want to save it in SDF format − how can I do this?

In the terminal window type:

```
write molcart table="molcart_table_name" "name_of_sdf"
```

24.6.5 How do I perform a chemical search

You can search MolCart or Chemical Tables using the ICM Chemical Search Window. This window can be displayed by going to:

- Tools/Chemistry/Chemical Search

OR

- Click on this icon

OR

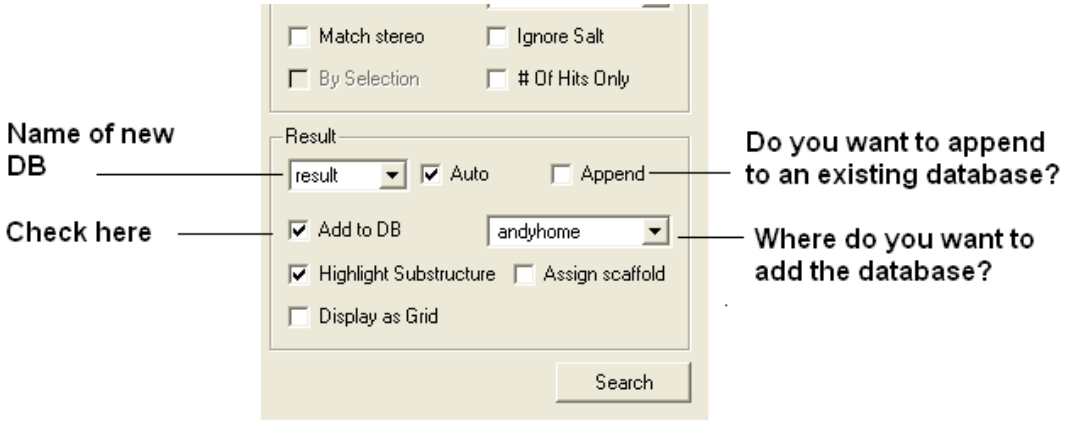
- Right click on a structure in a chemical table and select Query Molecule.

OR

- Or right click on a database in MolCart you wish to search and select Query...

24.6.6 How do I make a new molcart database from a query search?

To write the data from a query to a new MolCart database table use the Add to DB option in the Chemical Search window.

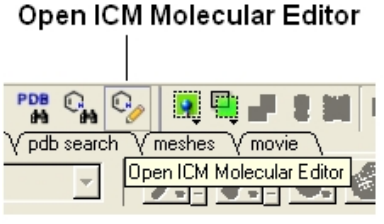


24.6.7 How can I draw small molecules?

Use the molecule editor

Chemistry/Molecular Editor

or look for the ICM molecular editor button at the top of the graphical user interface.



24.6.8 How do I read in a small molecule from ISIS draw and convert it to 3D?

- Save the molecule in mol format and then read into ICM (File/Open).
- The molecule should be displayed in 2D in a molecular table.
- Right click on the molecule in the table and select chemistry/convert to 3D and optimize.

NOTE: There is no need to use an external chemistry drawing software when you can use the ICM molecular editor which is fully integrated into the ICM software.

24.6.9 How can I change the layout of a chemical table?

To change the layout of a chemical table (eg converting a table to grid view).

- Select the columns you wish to display in grid view. You can do this by clicking on the column headers with the CTRL key pressed down.
- Once the columns are selected right click inside the table and select Table View
- Select Custom Grid...

24.6.10 How can I convert a chemical in a chemical table into 3D?

To do this:

- Select the chemical or chemicals you wish to convert to 3D. You can do this by clicking on the row number whilst keeping the CTRL key pressed down.
- Right click on the chemical table and select Chemistry/Convert 3D and Optimize

24.6.11 I have a small molecule which already has the 3D coordinates defined. How can I load the molecule and not optimize it so as to preserve the assigned 3D coordinates?

- File/Open and read in the molecule − it should be then displayed in a molecular table
- Right click on the molecule in the table and select Chemistry/ Load and Preserve Coordinates.

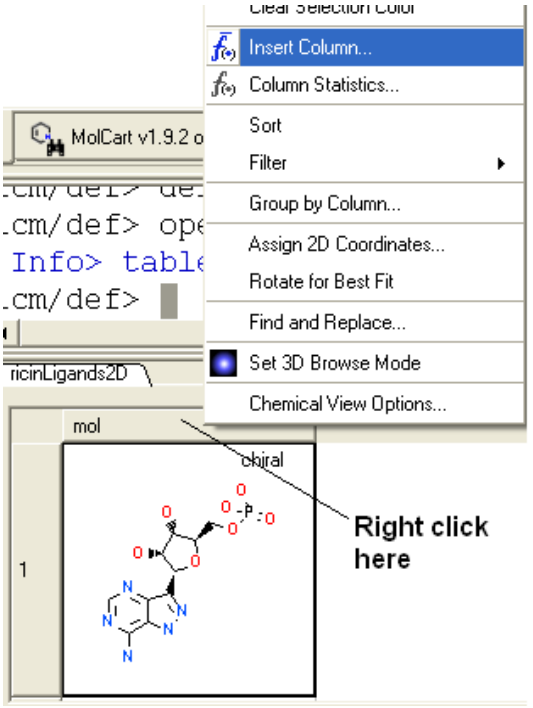
24.6.12 I have a chemical table displayed − how can I add columns of chemical properties associated with each chemical in my table?

To read a chemical table into ICM:

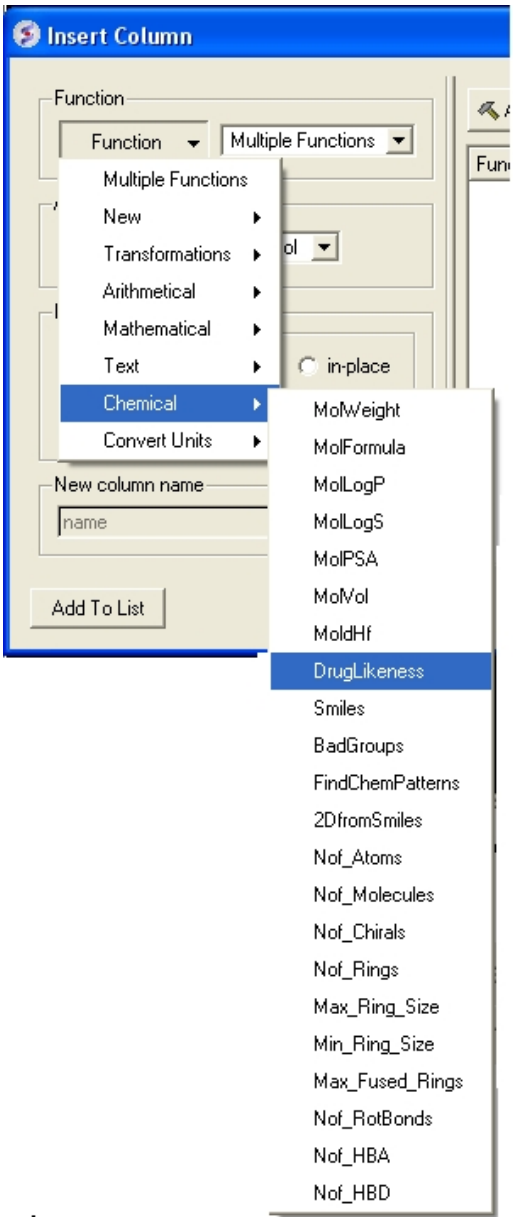
- File/Open and look for sdf files.

To add a chemical property to the table.

- Right click on the 'mol' column header and select Insert Column...



- Click on the drop down 'Function' button and select chemical.
- Select which property you wouls like to add and click OK.
- The property you selected will be displayed in the table.



24.6.13 I have a small molecule displayed in 3D in a loaded PDB file. How can I extract this molecule into an ICM Chemical Table?

You can extract a ligand from an ICM object or PDB file by:

- Right click on the ligand in the ICM Workspace.=
- Select Extract Ligand.
- Choose to extract either 2D or 3D coordinates and the molecule will be placed in a chemical table.

24.6.14 What is considered a good druglikeness value?

When building a molecule in the ICM Molecular Editor (Tools/Chemistry) properties such as druglikeness are calculated on the fly. The properties can also be added by inserting a column into a chemical table (right click on column header/ insert column/ Function = Chemical). These values should be used as a guide and druglikeness is a prediction based on drug−like properties. A druglikeness value less than zero indicates that the compound may have some non−drug−like properties.

24.6.15 I do not see the chemical property monitor in the molecular editor. Where is it?

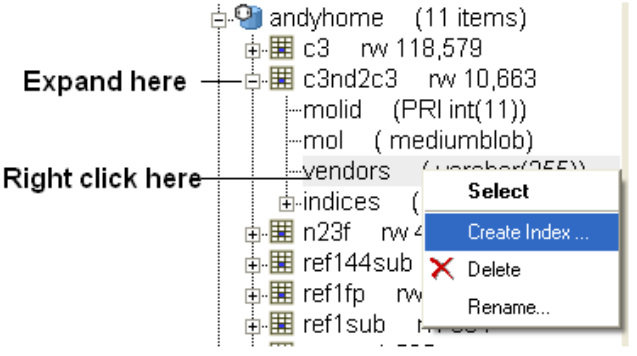
If you do not see the chemical monitor in the ICM Molecule Editor − Go to:

- Go to Molecular Editor
- View/Chemical Monitor

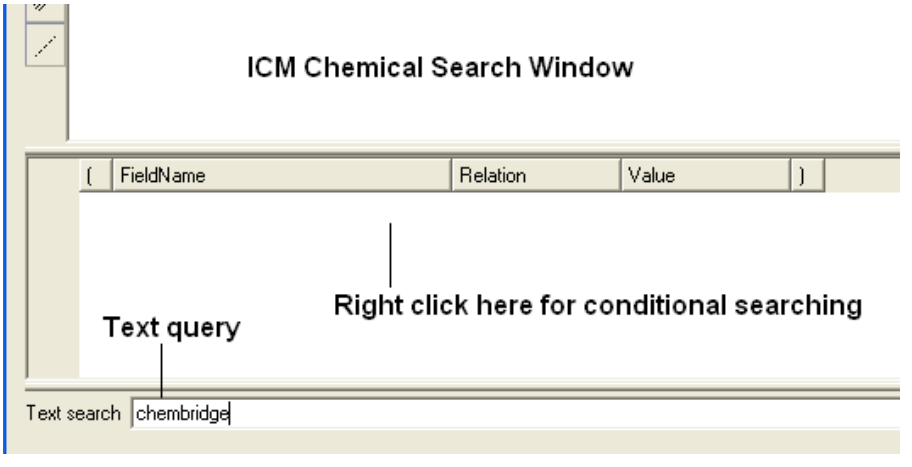
24.6.16 How do I perform a text query on a database in MolCart?

To perform a text search an index needs to be made on the field you wish to search. To do this:

- Expand the contents of the database in the ICM workspace by clicking on the '+' sign.
- Right click on the field you wish to text search.
- Select Create Index
- Select Keyword Search



- Once the index has been created you should see the text query box appear next time you perform a query.



NOTE: Queries can also be made in the window above the text search window (see above). If you right click you will see fields that you can fill in and use conditional based queries.

24.6.17 How to convert SMILES strings to 2D

See How To section.

24.6.18 Is there a way to build a classification model using the APF output?

_setAPFparams is in the distribution since 3.6−0;

The usage:

icm _apf3Dqsar train=trainingSet.sdf activity=LogIC50 table=testSet.sdf

Training and test set compounds should be all pre−aligned, for example by aligning training set actives using APF multiple chemical alignment, and then superimposing the test compounds onto aligned actives using APF superposition. Any external alignment method can be used as well. The field containing activity data in the training set SDF is specified by activity= argument.

The script also can take alignments in icm multiple object format *.ob, in which case SDFs are only used for input/output of activity data and can be just 2D:

icm _apf3Dqsar train=trainingSet.sdf align=trainingSet3Daligned.ob activity=LogIC50 predict=testSet3Daligned.ob table=testSet.sdf

The results are written to testSet_predict.sdf output file. Some statistics is reported along the way. If testSet.sdf contains activity (i.e. LogIC50) column like the training set, RMSD and R2 will be reported as well.

24.6.19 How to rotate a 2D chemical sketch so it fits nicely in its cell in a chemical table?

See this description in the command line manual:

`http://www.molsoft.com/man/icm−commands.html#make−flat`

24.7 FAQ−Simulations

Frequently asked questions regarding simulations, BPMC ....

- `How do I make a movie of my montecarlo simulation and write all output?`
- `How do I view a stack of solutions after a simulations?`

24.7.1 How do I make a movie of my montecarlo simulation and write all output.

To make a movie simply use the command :

montecarlo movie

To write all the buffered output to a file

On your UNIX command line

icm < montecarlo.scr > output.icm

where montecarlo.scr is your montecarlo ICM script

For an example of an mc script see the `tutorial` below.

24.7.2 How do I view a stack of solutions after a simulations?

Once any monte−carlo simulation is complete a stack of the most energetically favorable solutions is generated along with the associated energy for each element of the stack. To view this stack:

- MolMechanics/View Stack.
- Double click on each element in the stack (table) to load it into ICM.

24.8 FAQ−Script

Are you having problems with an ICM script? See if your question is answered here

- `How can I write a script in the Graphical User Interface?`
- `I am having problems with my ICM script when running from the unix command line.`
- `How do I use the Dollar $ in ICM Scripts`
- `Is there a way to determine the name of the current table displayed GUI?`

24.8.1 How can I write a script in the Graphical User Interface?

- File/New and select the **Script** tab.

For more details see the section entitled `Writing a Script in GUI`

24.8.2 I am having problems with my ICM script when running from the unix command line.

A common problem when running an ICM script from the command line is that people forget to call the startup file and therefore common commands in ICM are not recognized (eg the output says "convertObject: unknown word") The start of your ICM script should look something like this with call _startup included:

```
#!/usr/bin/icm

call _startup
```

24.8.3 How do I use the Dollar $ in ICM Scripts?

In ICM you need to use '$' ONLY before string variable which contains the name of the OTHER variable or expression. (that different from Perl)

Using dollar in most other cases won't hurt (e.g: $a (where a is an integer variable) but will have no effect and only will make parsing/execution heavier. For example: a = 1 # the two lines below are equivalent print $a print a

Example of dollar usage:

```
a = 1
s = "a"
print $s   # will print the content of 'a' variable
#
for i=1,10
  s = "a" + i
  $s = i
endfor
```

Will create a1,a2,...a10 variable with corresponding values.

So you should consider '$' as a substitution of the content of the string variable after it.

```
build string "AAA"
s = String( a_ )
print s
$s
```

24.8.4 Is there a way to determine the name of the current table displayed GUI?

To determine the name of the current active table in GUI:

```
Name( foreground table )
```

This will return a sarray because there might by two active tables (when you double click on the tab and for side−by side view). To access the table using $ sign:

```
s_tableName = Name( foreground table )[1]
$s_tableName.mol
```

24.9 Troubleshooting

Here is a collection of known problems and workarounds.

- ICM graphics crashes − any tips?
- Defective graphics on a laptop or Windows computer with a low end graphics card.
- ICM crashes, or hangs if you are trying to start the Chemical Editor, or a Query window
- Problem with stereo?

Installation

24.9.1 ICM graphics crashes.

Some Linux installations need extra setup to permit the use of the GL graphics.

Description of the problem

ICM starts, GUI is launched and works OK, however ICM crashes after the first attempt to display any 3D object in the GL window. System issues an error message stating:

"Error: Could not open /dev/nvidiactl because the permissions are too restrictive. Please see the FREQUENTLY ASKED QUESTIONS section of /usr/share/doc/NVIDIA_GLX−1.0/README for steps to correct."

Solution

(tested only for the Suse Linux): do not follow the instructions contained in the `/usr/share/doc/NVIDIA_GLX−1.0/README` document. Instead do the following:

1. find `/etc/logindevperm` file
2. edit the file by changing/uncommenting the line containing `'/dev/nvidiactl...'` to this:
   `0 0666 /dev/nvidiactl:/dev/nvidia0:/dev/nvidia1:/dev/nvidia2:/dev/nvidia3`
3. `logout` and `login` again

24.9.2 Defective graphics on a laptop or Windows computer with a low end graphics card.

This problem can manifest itself in multiple ways, but always with the **FOG** depth−cueing effect on. Usually graphics behaves strangely, for example:

- the selection crosses have the color of the background, or
- the skin representation appears to be damaged, or
- 3D Labels and site annotations disappear with when FOG is on

The solution is to reduce the level and the OpenGL acceleration from the maximal one to some intermediate.

Some inexpensive graphics cards (e.g. Intel 82915G/GV910GL Express Chipset Family) have a problem with high level of hardware acceleration. 3D labels or site labels disappear when you press a **FOG** button. We found that the problem is due to the hardware acceleration. By switching to the lower levels of hardware acceleration one can avoid the problem.

Solution: switch the FOG effect off, or change the settings of OpenGL acceleration.

- Right−click on the screen, get the main pop−up menu
- Go to *Properties* (the last item)
- Go to the *Settings* tab
- Click on the *Advanced* button
- Choose the *Troubleshoot* tab
- Reset Hardware acceleration to the **3rd** level or lower

24.9.3 ICM crashes, or hangs if you are trying to start the Chemical Editor, or a Query window

Platform under which this problem had been detected: Linux

ICM may hang of crash when you are trying to start an new window with a Chemical editor, or a Query. One possible reason is that for some reason the molsoft preference file in the `~/.qt` directory is locked. In this case there is the `.lock` file which need to be deleted.

Recovery under Unix/Linux. Delete the file called `.molsoftrc.lock` in the `.qt` directory

```
rm .qt/.molsoftrc.lock
```

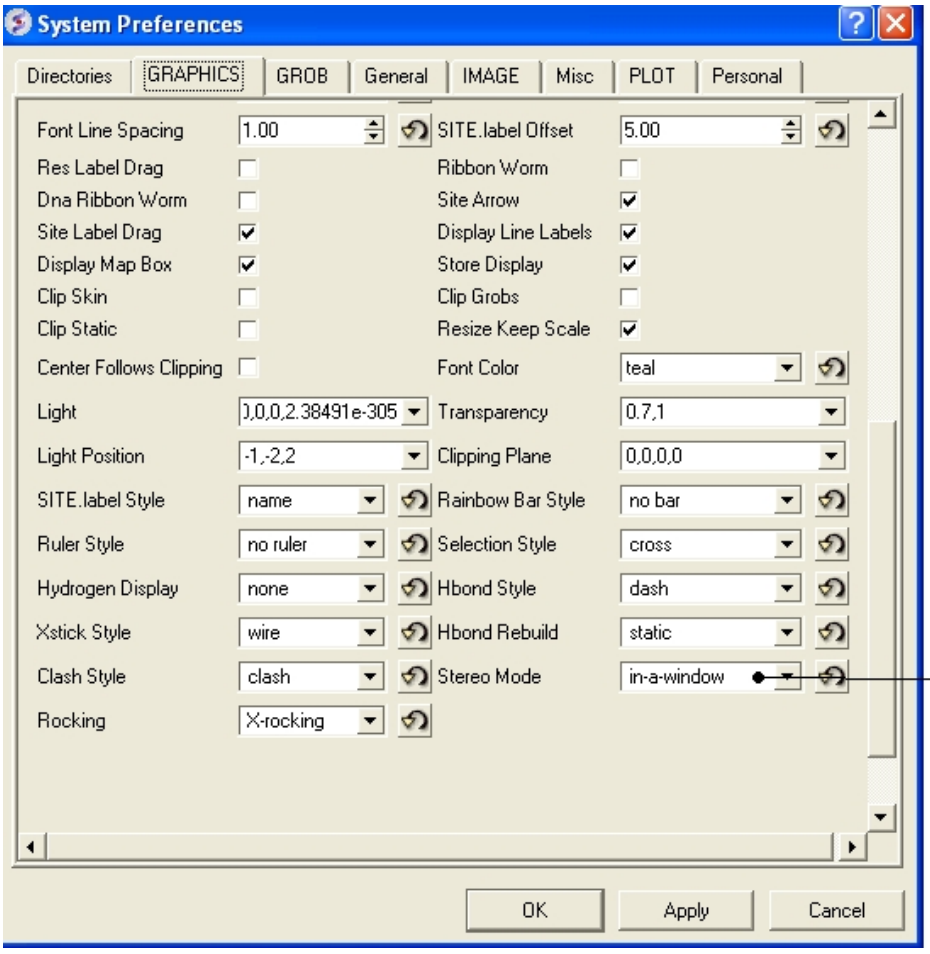
24.9.4 Problem with stereo?

ICM is working fine but for some reason your stereo is not working.

Check if "Stereo Mode" preference is set to "in−a−window" in ICM.

To do this :

- Go to **File/Preferences** menu.
- select the **Graphics** tab
- Set the "Stereo Mode" combo box to "in−a−window"
- Then press "Apply " button to write preferences and* restart ICM.


System Preferences
Directories
GRAPHICS
GROB
General
IMAGE
Misc
PLOT
Personal
Font Line Spacing
1.00
SITE.label Offset
5.00
Res Label Drag
Ribbon Worm
Dna Ribbon Worm
Site Arrow
Site Label Drag
Display Line Labels
Display Map Box
Store Display
Clip Skin
Clip Grobs
Clip Static
Resize Keep Scale
Center Follows Clipping
Font Color
teal
Light
),0,0,2.38491e-305
Transparency
0.7,1
Light Position
-1,-2,2
Clipping Plane
0,0,0,0
SITE.label Style
name
Rainbow Bar Style
no bar
Ruler Style
no ruler
Selection Style
cross
Hydrogen Display
none
Hbond Style
dash
Xstick Style
wire
Hbond Rebuild
static
Clash Style
clash
Stereo Mode
in-a-window
Rocking
X-rocking
OK
Apply
Cancel
Select "in-a-window"

#endif

Index

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