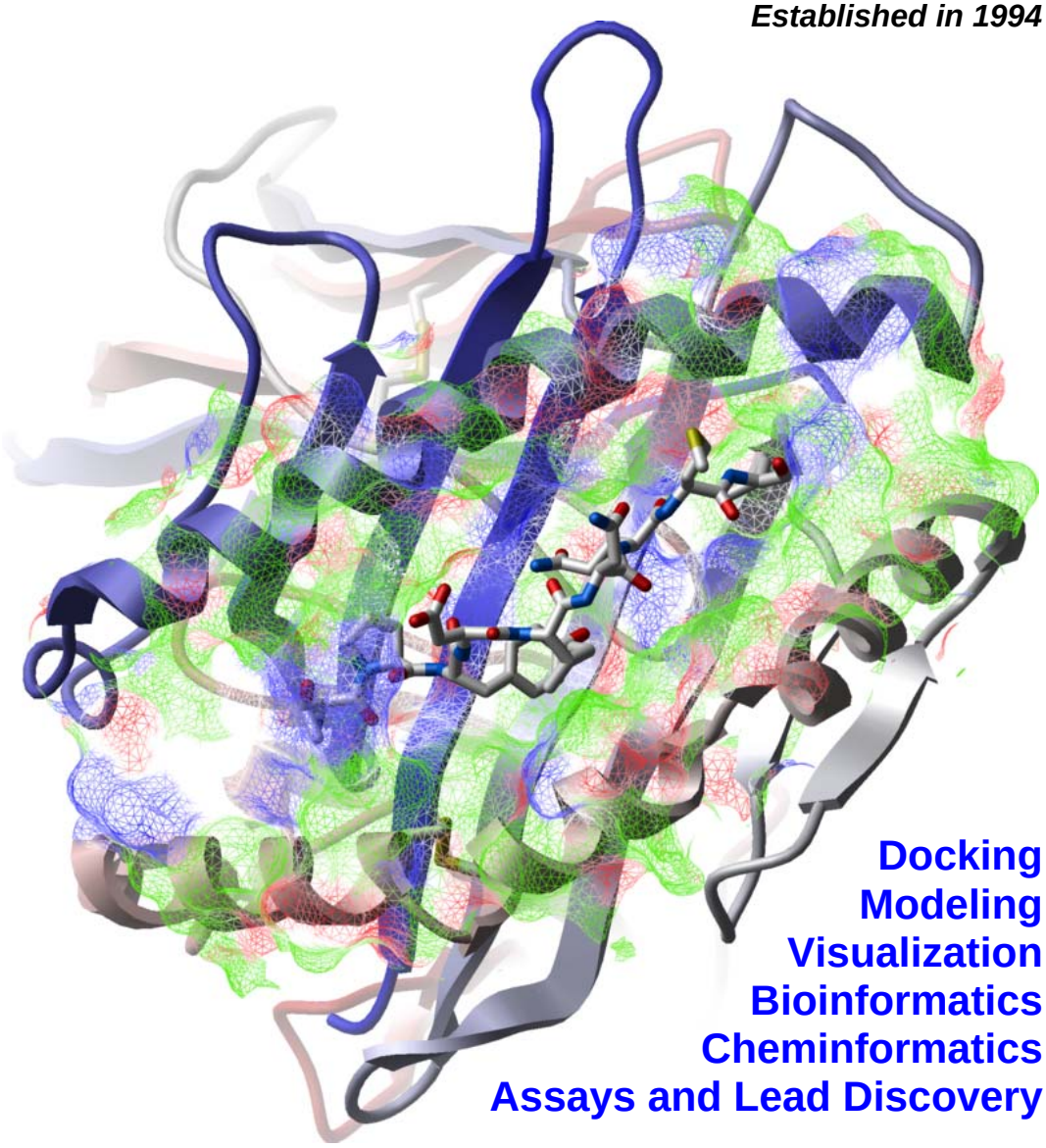
MolSoft

molecules *in silico*

Established in 1994



Docking
Modeling
Visualization
Bioinformatics
Cheminformatics
Assays and Lead Discovery

Products and Services

Products:
ICM-Browser - Powerful Molecular Browser
ICM-Browser-PRO - Upgrade of Browser
ICM-PRO - Main ICM package **>500 tools**
ICM- Homology, VLS, Chemistry
QSAR, MolCart - Chemical Databases

Services:
Drug Target Evaluation
Virtual Ligand Screening and Assays
Software Development
Collaborative Research

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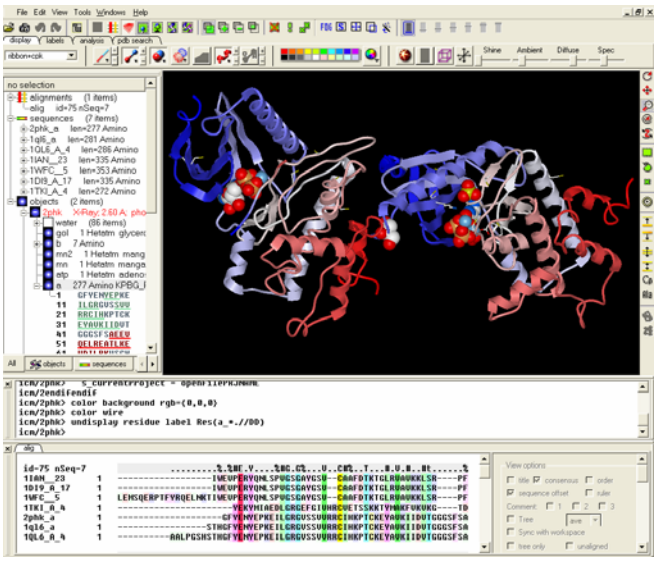
Products

Desktop Molecular Browser



ICM-Browser is a FREE multi-platform program designed for creating quality molecular graphic images, browsing structures from the protein databank, and sharing richly annotated structure, data and chemical information with laboratory scientists (Abagyan *et al* 2006).

High quality molecular graphics

- PDB structure database search
- Structure analysis, annotation and documents
- Manual Docking

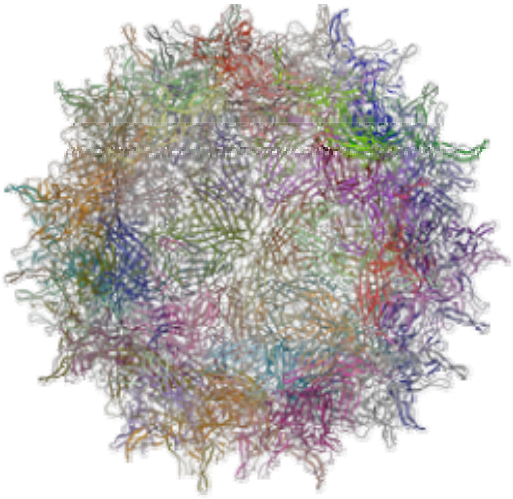
ICM-Browser-PRO is the commercial upgrade of the Browser.

- Hardware stereo
- Create new ICM projects and documents
- Molecular surface representations
- Scripting language for sequence, structure and data analysis

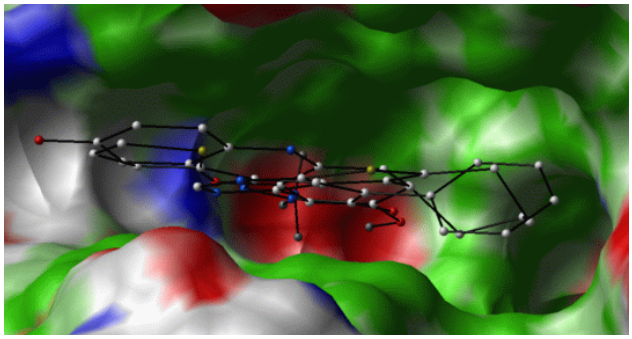
Desktop Molecular Environment - ICM-Pro

ICM-PRO is the main ICM package and contains an all atom internal coordinate force field and efficient algorithm to perform local and global energy optimization of small or large molecules with respect to an arbitrary subset of variables (Abagyan and Totrov 1994 and Abagyan *et al* 1994).

- Makes high quality molecular images and movies
- Read, build, convert, refine, analyze and superimpose molecules
- Sequence analysis and PDB searching
- Multiple alignment: visualization and annotation
- Evolutionary trees
- Symmetry and crystallographic cell generation
- Sensitive structural error detection



1LP3 Adeno-Associated Virus generated using ICM Biomolecule function.

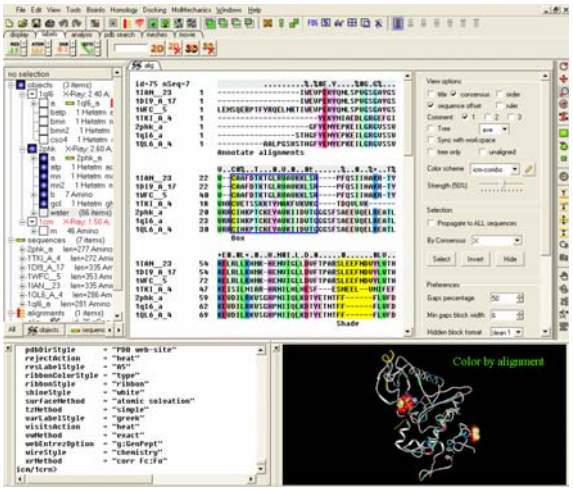


ICM-PRO tools include:

- ICM-REBEL – calculates electrostatic energy surfaces
- Simulations – stochastic global optimization
  - Structure prediction
  - Peptide folding
  - Mutant effect prediction
  - Loop prediction
  - Optimization with electron density and NMR restraints
- Superimpose structures
- XPDB – SwissProt annotated protein structures
- ICMPocketFinder – drug pockets (An et al. 2005)
- Docking
  - Small molecule docking (also see **ICM-VLS**)
  - **Protein-protein docking** (Mendez et al**)**
- Cheminformatics (also see **ICM-MolCart**)
  - Draw and convert compounds to 3D
  - Build Combinatorial Libraries
  - Read large compound databases
  - Chemical spreadsheets
  - Clustering

Products

Molecular Modeling - ICM-HOMOLOGY



ICM- Homology offers a fast routine for building a complete protein model by homology with loops in a matter of seconds. The scripts allow you to refine the backbone and sample the side-chain and loop conformations by global energy optimization.

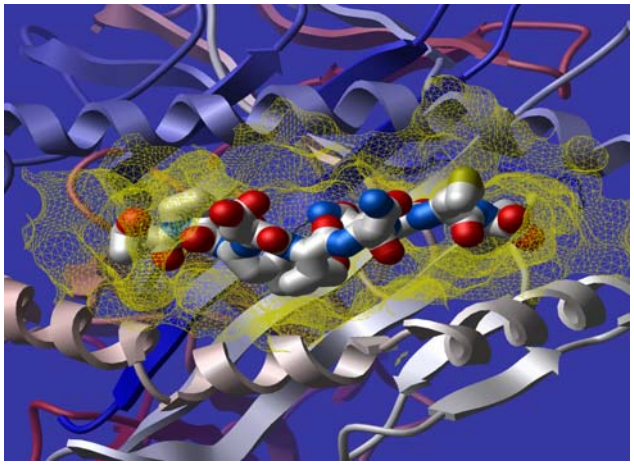
In addition, **ICM-Homology** offers other features to:

- Automate high throughput modeling
- Perform protein health and geometry analysis
- Evaluate local flexibility and potential model errors
- Build loops from a loop database
- Rigorous model refinement algorithms
- Use tethers and distance restraints to build a model

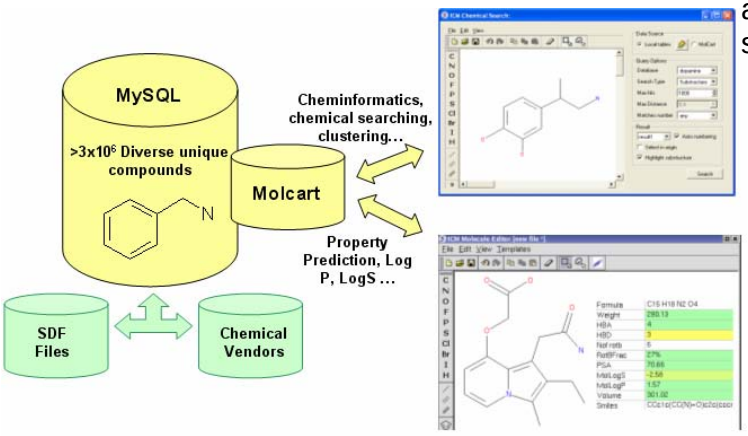
Virtual Screening - ICM-VLS

ICM-VLS provides a unique set of tools for the modeling of protein/ligand interactions. **ICM-VLS** performs fast and accurate docking of fully continuously flexible small molecule ligands to a protein represented by grid interaction potentials. It performs docking by Monte-Carlo minimization procedure by combining pseudo-Brownian positional and torsional steps with fast local gradient minimization (Cavasotto et al. 2006; Chen et al. 2006).

- Fast and accurate docking and scoring procedure
- Incorporates flexibility into the ligand and receptor side chains (Cavasotto and Abagyan 2004).
- Template docking for pharmacophore based design.
- Easy to use graphical user interface for post-docking analysis – graphs tables and display of docking data.



Small Molecule Databases - MolCart

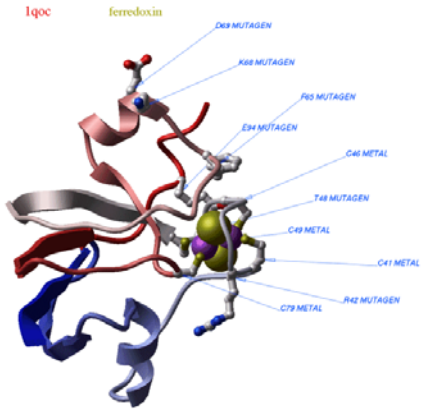


MolCart is a state of the art enterprise wide chemical database management system. Compound databases of any size (>10^6) can be stored in MolCart and analyzed and searched using **ICM-Chemistry** and docking tools.

- Chemical standardization and unification
- Add new or modify existing compounds in your drug databases
- Perform chemical similarity searching
- Perform chemical clustering
- Learn and predict compound properties
- ADME-TOX prediction
- QSAR
- Easily make your own target specific drug databases
- **MolCart Compounds** – An up-to-date collection of compounds from over 40 different chemical vendors.

Contract Research and Consulting Services

Target Evaluation and Preparation

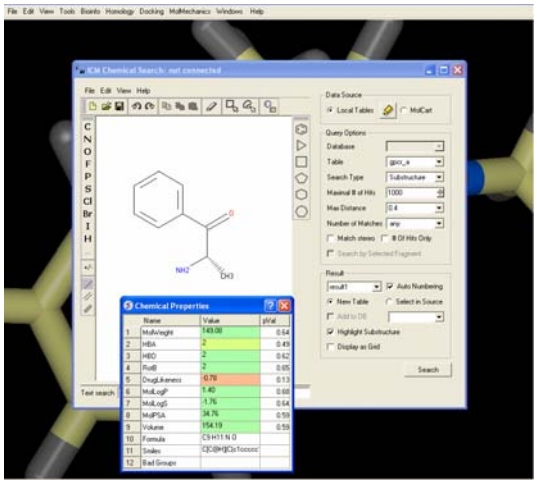


MolSoft provides **target evaluation** services to build three-dimensional models and evaluate candidate target proteins. MolSoft can build and optimize three-dimensional models for each target of interest based on existing homologues with known structures, identify all potential "drugable" sites and predict protein interfaces, evaluate model errors and structural flexibility around the sites of interest, dock all known ligands to the binding sites to validate the models, and re-dock the ligands to fully flexible binding sites if necessary to improve the pocket models for virtual ligand screening.

Virtual Ligand Screening and Assay Service

MolSoft provides **Virtual Ligand Screening (VLS)** services using MolSoft's proprietory molecular modeling tools. MolSoft's VLS technology is based on high-throughput docking of ligands from large databases of compounds using advanced ICM-dock algorithms. Docking is followed by evaluation of the putative complexes with scoring functions, which are tuned for best VLS performance and include sophisticated terms such as solvation electrostatics. Massive screening can be completed in a matter of days thanks to MolSoft's powerful computing facility, which includes several large Linux clusters. Our VLS software is highly ranked by evaluators and is used extensively in the pharmaceutical industry. This service will save your company time and money and will also facilitate the discovery of novel specific drug-compounds which may be missed by more conventional experimental methods. Typically, depending on the receptor, we can screen more than 3 million compounds and test experimentally less than 100 to find a binder. Molsoft can also perform fluorescence, absorbance and luminescence assays depending on the receptor.

Software and Database Development



MolSoft provides custom **software development** using our libraries of routines for scientific data analysis and molecular manipulations. One of MolSoft's recent projects involved the development of interface software and the infrastructure necessary to allow communication between instrumentation controls and the data produced by those controls. The software developed is able to manage the data generated, permit access to the databases of generated data, and permit visualization and analysis of the data. MolSoft provides comprehensive information management for client organizations. MolSoft's universal, cross-platform web-based access tools provide password protected accounts for access to proprietary in-house data.

ICM Training and Support

ICM Workshops are provided regularly throughout the year at our La Jolla offices or onsite training can be requested. The workshops are conducted by Prof. Ruben Abagyan (The Scripps Research Institute) and Maxim Totrov (Principal Scientist – MolSoft) and cover a wide range of topics in the field of computational drug design.

Manuals are available online and technical support is provided over the phone or by e-mail.

World Leader in Computational Drug Design

There are many reasons to use ICM:

Proven Performance and Accuracy

- In the most recent docking evaluation by researchers at Astra-Zeneca, ICM-VLS ranked the best in docking accuracy (see Chen *et al 2006*).
- ICM placed first in the worldwide CAPRI protein-protein docking competition (see Mendez *et al 2003, 2005*).
- There are many published examples of ICM being used successfully in real life drug-discovery problems (e.g. Cavasotto et al 2006).
- ICM is used by the Oxford Structural Genomics Consortium as the main format for exchanging animated structural data.
- We have in-house structure-based drug design expertise in a wide range of drug targets including GPCRs, Kinases and Nuclear Receptors

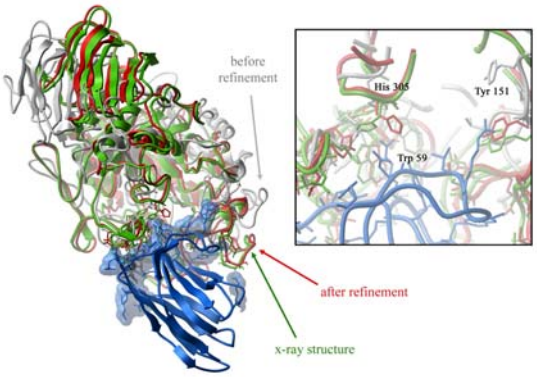
Streamline your Drug Discovery Environment

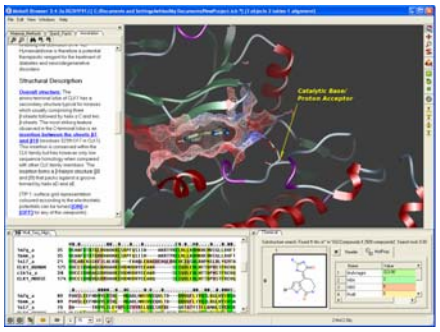
- ICM is an all-in-one package encompassing all the tools you need for a successful structure-based drug discovery program.
- Molsoft supports all major platforms including Windows, Mac, Linux and SGI.
- Share, store and communicate your data in ICM-Projects, Documents and Slides.
- All Files can be stored in a single cross-platform file fully-accessible with the FREE ICM-Browser.

Fast-Track Your Drug Discovery Program

- The ICM software has been rigorously developed for over 10 Years.
- Molsoft's technology has continued to out-perform rival products in both accuracy and performance, which is highlighted in a number of published, independent studies.
- There are many ICM users worldwide in industry and academia.
- Save your company valuable time and money by applying the ICM tools for your drug discovery program. Get accurate results fast.

ICM delivers accurate results in even the most challenging of structure-based problems.





ICM Molecular Documents and Presentations will revolutionize the way you present data to your colleagues. This method represents the future of molecular communication and storage (Abagyan et al 2006). Patent Pending.

Easy-to-use

- Intuitive Graphical User Interface and multi-functional browser with powerful 3D molecular graphics and animations.
- Support available by phone, e-mail, online tools, manuals and regular workshops.

Peer-Reviewed Publications

Selected Publications relating to ICM Methods and Applications

Small Molecule Docking Evaluation

Chen H, Lyne PD, Giordanetto F, Lovell T, Li J. (2006) On evaluating molecular-docking methods for pose prediction and enrichment factors. *J Chem Inf Model. 2006 Jan-Feb;46(1):401-15.* ***Recent evaluation of four of the leading docking algorithms by AstraZeneca researchers. ICM ranked first in all tests including docking accuracy and enrichment factors.***

Drug Discovery Success Stories

Cavasotto CN, Ortiz MA, Abagyan RA, Piedrafita FJ. (2006) In silico identification of novel EGFR inhibitors with antiproliferative activity against cancer cells. *Bioorg Med Chem Lett. 2006 Jan 11.* ***One of many examples of applying ICM-VLS to identify new drug scaffolds and leads.***

Schapira, M., Abagyan, R.A. and Totrov, M.M. (2004) Nuclear Hormone Receptor Targeted Virtual Screening *J. Med. Chem.* 10.1021 ***ICM-VLS can save your company time and money by filtering out non-binders (excellent enrichment factors) and identifying new binders that may have been overlooked by conventional high-throughput screening.***

Flexible Ligand and Receptor Docking

Cavasotto, C., Orry, A.J.W., and Abagyan, R.A. (2003) Structure-Based Identification of Binding Sites, Native Ligands and Potential Inhibitors for G-Protein Coupled Receptors *Proteins: Structure, Function, and Genetics 51(3), 423-433.* ***The first demonstration of fully-flexible ligand and receptor docking into GPCRS.***

Cavasotto, C.N. and Abagyan, R.A. (2004) Protein Flexibility in Ligand Docking and Virtual Screening To Protein Kinases *J. Mol. Biol.* Mar 12; 337(1): 209-25. ***An original approach to incorporate receptor flexibility into ligand docking.***

Drug Binding Pocket Identification

An J, Totrov M, Abagyan R. (2005) Pocketome via comprehensive identification and classification of ligand binding envelopes. *Mol Cell Proteomics. 2005 Jun;4(6):752-61.* ***A new fully-validated algorithm for the prediction of ligand binding sites with high accuracy.***

Fernandez-Recio, J., Totrov, M., Skorodumov, C., Abagyan, R. (2005) Optimal Docking Area: A New Method for Predicting Protein-Protein Interaction Sites. *Proteins* 57:400-13. ***A state-of-the-art method for the prediction of protein-protein interaction sites.***

Protein-Protein Docking

Fernandez-Recio, J., Totrov, M., and Abagyan, R. ICM-DISCO (2003) Docking by Global Energy Optimization with Fully Flexible Side-Chains *Proteins* 52:113-117. ***The ICM Protein-Protein docking method, which ranked highly in the worldwide CAPRI docking competition. See the two papers below by Mendez et al. for evaluation of results.***

Mendez R, Leplae R, Lensink MF, Wodak SJ. (2005) Assessment of CAPRI predictions in rounds 3-5 shows progress in docking procedures. *Proteins. 2005 Aug 1;60(2):150-69.*

Mendez R, Leplae R, De Maria L, Wodak SJ. (2003) Assessment of blind predictions of protein-protein interactions: current status of docking methods. *Proteins. 2003 Jul 1;52(1):51-67.*

ICM Methods

Abagyan, R.A., Totrov, M.M., and Kuznetsov, D.A. (1994) ICM: A New Method For Protein Modeling and Design: Applications To Docking and Structure Prediction From The Distorted Native Conformation *J. Comp. Chem.* 15, 488-506. ***Original ICM methods.***

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. ***Description of the ICM highly efficient global optimization procedure.***

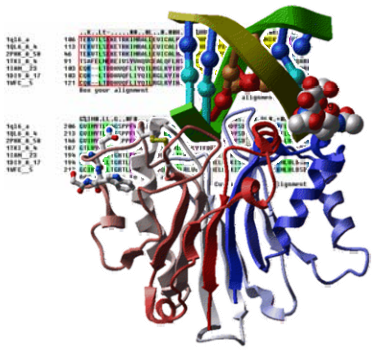
ICM Documents and Presentations

Abagyan R, Lee WH, Raush E, Budagyan L, Totrov M, Sundstrom M, Marsden BD. (2006) Disseminating structural genomics data to the public: from a data dump to an animated story.*Trends Biochem Sci. 2006 Jan 4.* ***New technology for the enterprise-wide exchange and presentation of molecular data.***

Enterprise-Wide Desktop Modeling Software

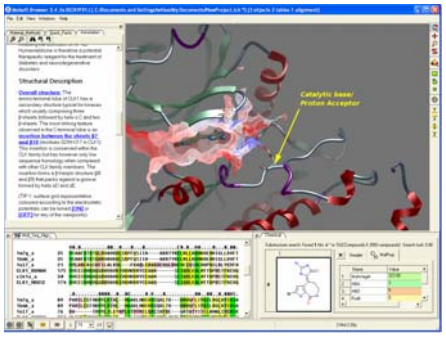
Fast-Track Your Discoveries

ICM- Pro



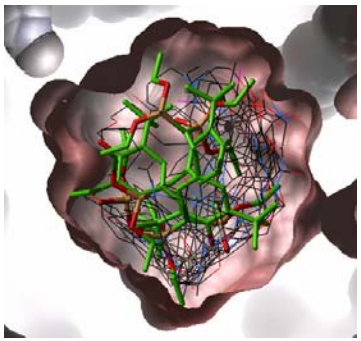
1. Drug Target Selection

ICM-Pro + Homology



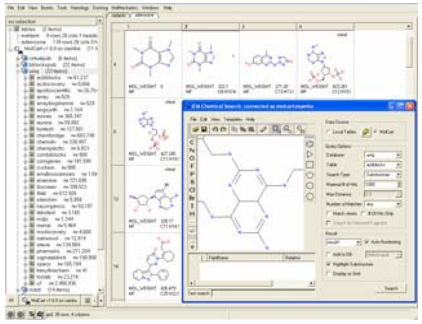
2. Structure Modeling

ICM-Pro +VLS



3a. Docking & Virtual Screening

ICM-MolCart



3b. Cheminformatics & Library Design

Drug Discovery Cycle

ICM-Pro + Chemistry

4. Chemistry & ADME-Tox

ICM-Browser-Pro

5. ICM in the Laboratory

ICM-Browser

Exchange multi-component molecular data with visualization and animation in a single small document

Free Browser Download and Supports Windows, Mac, Linux and SGI

Data Communication & Storage