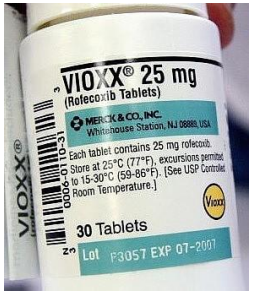
Building a Chemical Database

In this tutorial we will build a database of COX-2 Inhibitors, perform chemical searching and clustering.

Background COX-2 selective inhibitor is a form of non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, an enzyme responsible for inflammation and pain. Targeting selectivity for COX-2 reduces the risk of peptic ulceration, and is the main feature of celecoxib, rofecoxib and other members of this drug class.

Controversy After several COX-2 inhibiting drugs were approved for marketing, data from clinical trials revealed that COX-2 inhibitors caused a significant increase in heart attacks and strokes, with some drugs in the class having worse risks than others. Rofecoxib (commonly known as Vioxx) was taken off the market in 2004 because of these concerns and celecoxib (Celebrex) and traditional NSAIDS received boxed warnings on their labels.

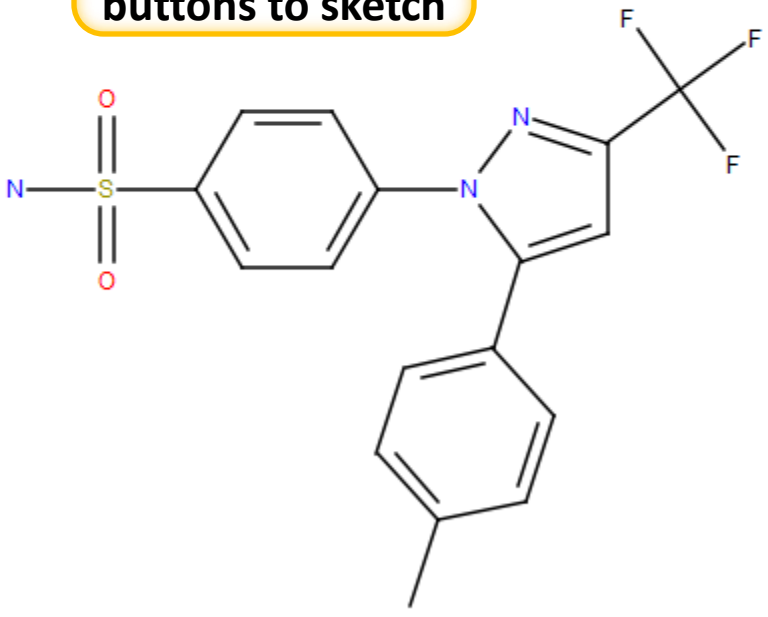


Sketch the COX-2 inhibitor Celebrex

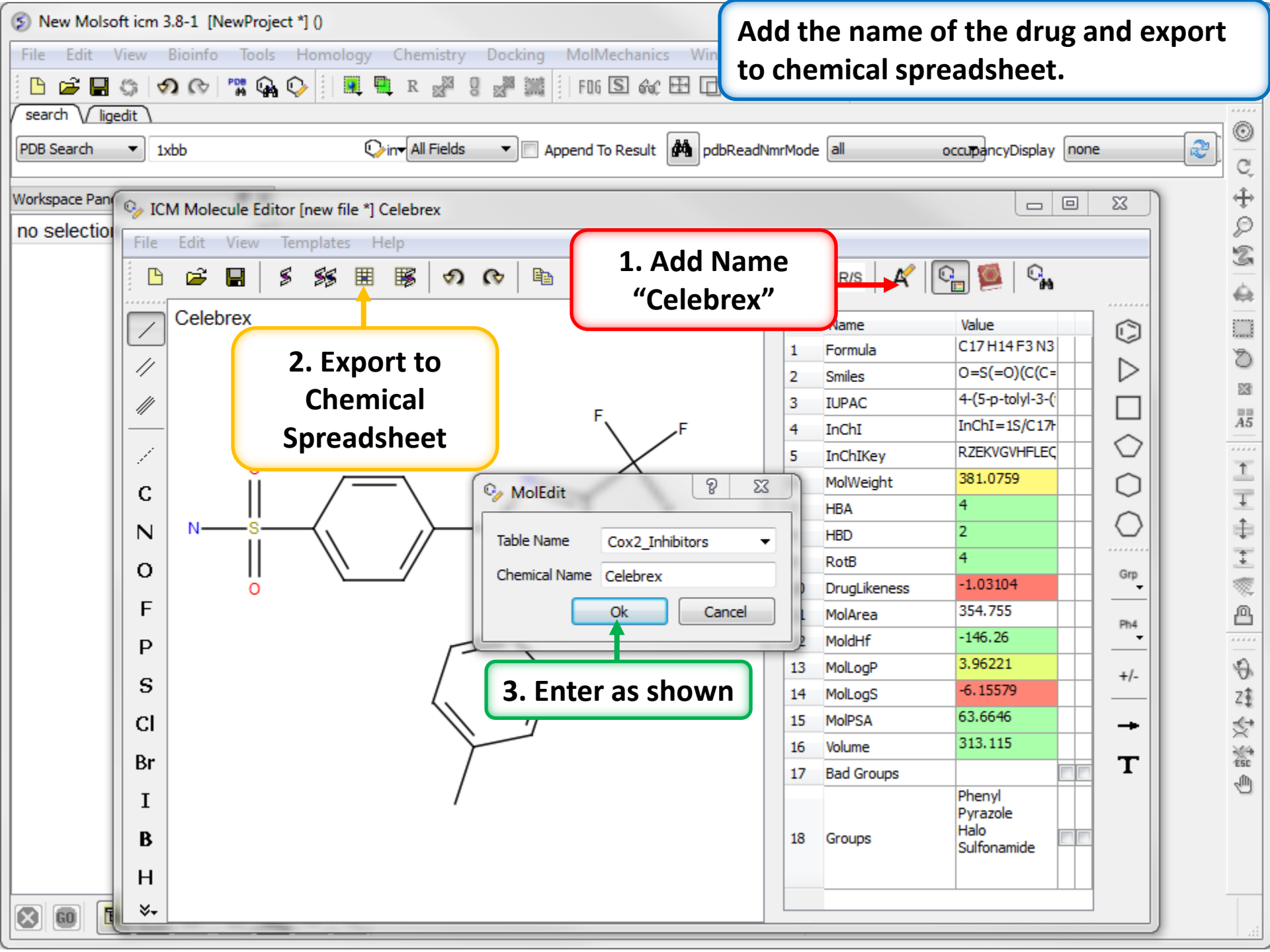
1. Click on the Molecular Editor button

2. Use the bond and atom buttons to sketch

3. Monitor Properties



	Name	Value
1	Formula	C17 H14 F3 N3
2	Smiles	O=S(=O)(C(C=
3	IUPAC	4-(5-p-tolyl-3-(
4	InChI	InChI=1S/C17H
5	InChIKey	RZEKVGVHFLEQ
6	MolWeight	381.0759
7	HBA	4
8	HBD	2
9	RotB	4
10	DrugLikeness	-1.03104
11	MolArea	354.755
12	MolHf	-146.26
13	MolLogP	3.96221
14	MolLogS	-6.15579
15	MolPSA	63.6646
16	Volume	313.115
17	Bad Groups	
18	Groups	Phenyl Pyrazole Halo Sulfonamide


New Molsoft icm 3.8-1 [NewProject *] ()
Add the name of the drug and export to chemical spreadsheet.
ICM Molecule Editor [new file *] Celebrex
1. Add Name "Celebrex"
2. Export to Chemical Spreadsheet
3. Enter as shown
MolEdit
Table Name
Cox2_Inhibitors
Chemical Name
Celebrex
Ok
Cancel
Name
Value
Formula
C17 H14 F3 N3
Smiles
IUPAC
InChI
InChIKey
MolWeight
381.0759
HBA
4
HBD
2
RotB
4
DrugLikeness
-1.03104
MolArea
354.755
MoldHf
-146.26
MolLogP
3.96221
MolLogS
-6.15579
MolPSA
63.6646
Volume
313.115
Bad Groups
Groups
Phenyl
Pyrazole
Halo
Sulfonamide

Cox2_Inhibitors Molsoft icm 3.8-1 [NewProject *] (1 table)

Observe new chemical spreadsheet.

File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics Wind

search ligedit

PDB Search 1xbb in All Fields Append To Result pdbReadNmrMode all occupancyDisplay none

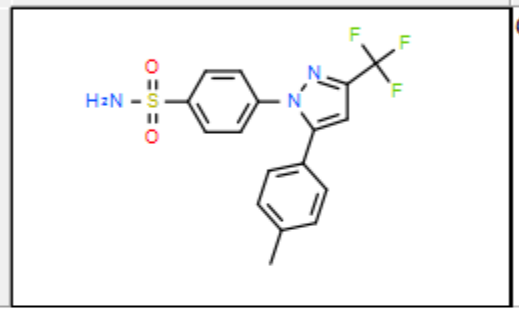
Workspace...

no selection

tables

Cox2_I

Cox2_Inhibitors

	mol	Molecule Name
1		Celebrex

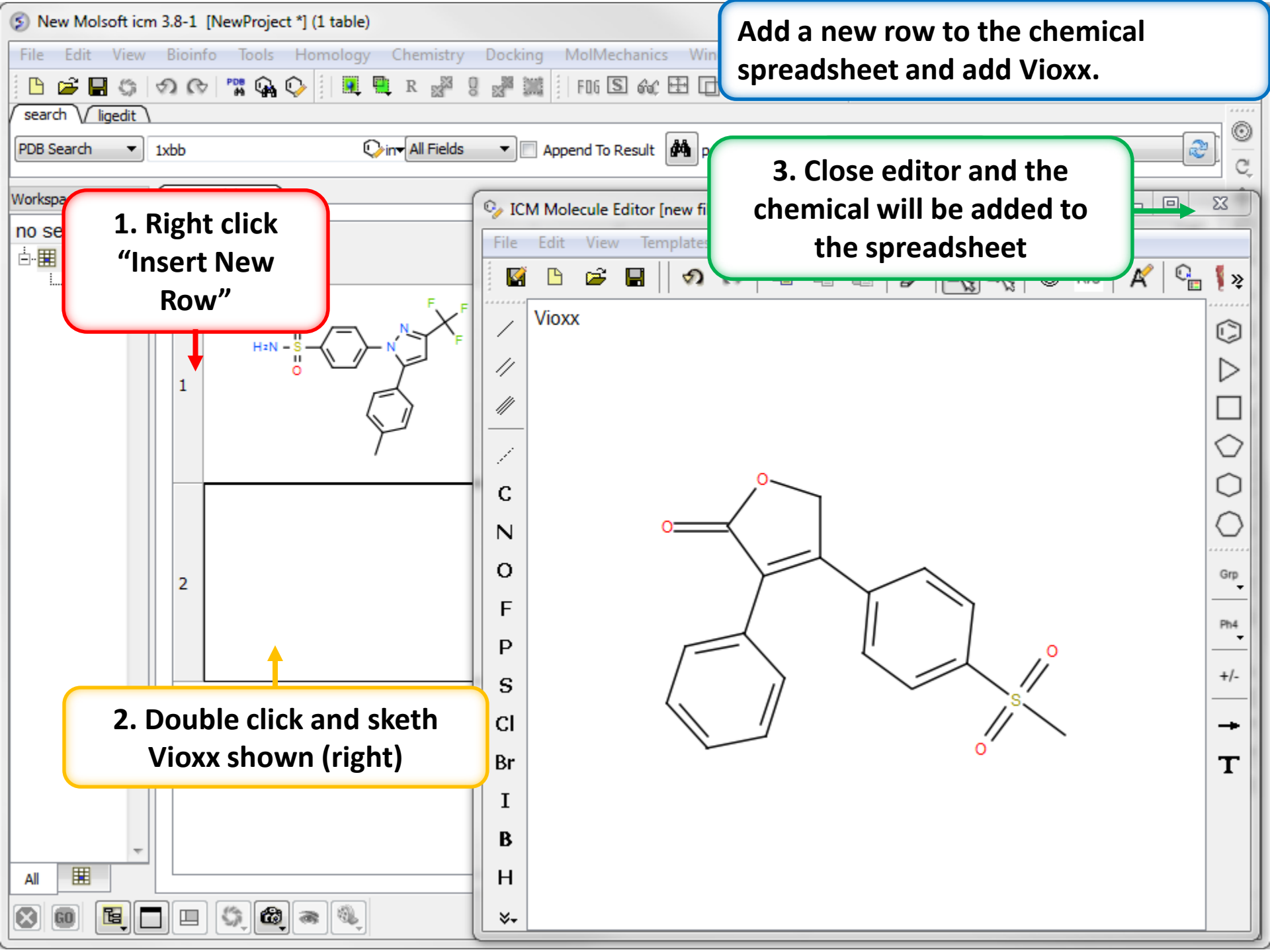
All

Add a new row to the chemical spreadsheet and add Vioxx.

1. Right click "Insert New Row"

2. Double click and sketh Vioxx shown (right)

3. Close editor and the chemical will be added to the spreadsheet



Now you should have two chemicals in your spreadsheet.

New Molsoft icm 3.8-1 [NewProject *] (1 table)

File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics Win

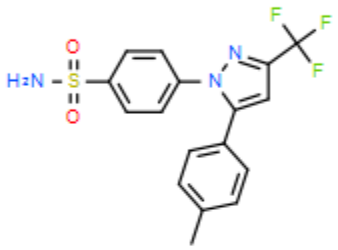
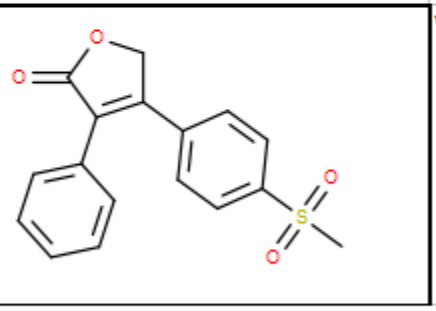
search ligedit

PDB Search 1xbb in All Fields Append To Result pdbReadNmrMode all occupancyDisplay none

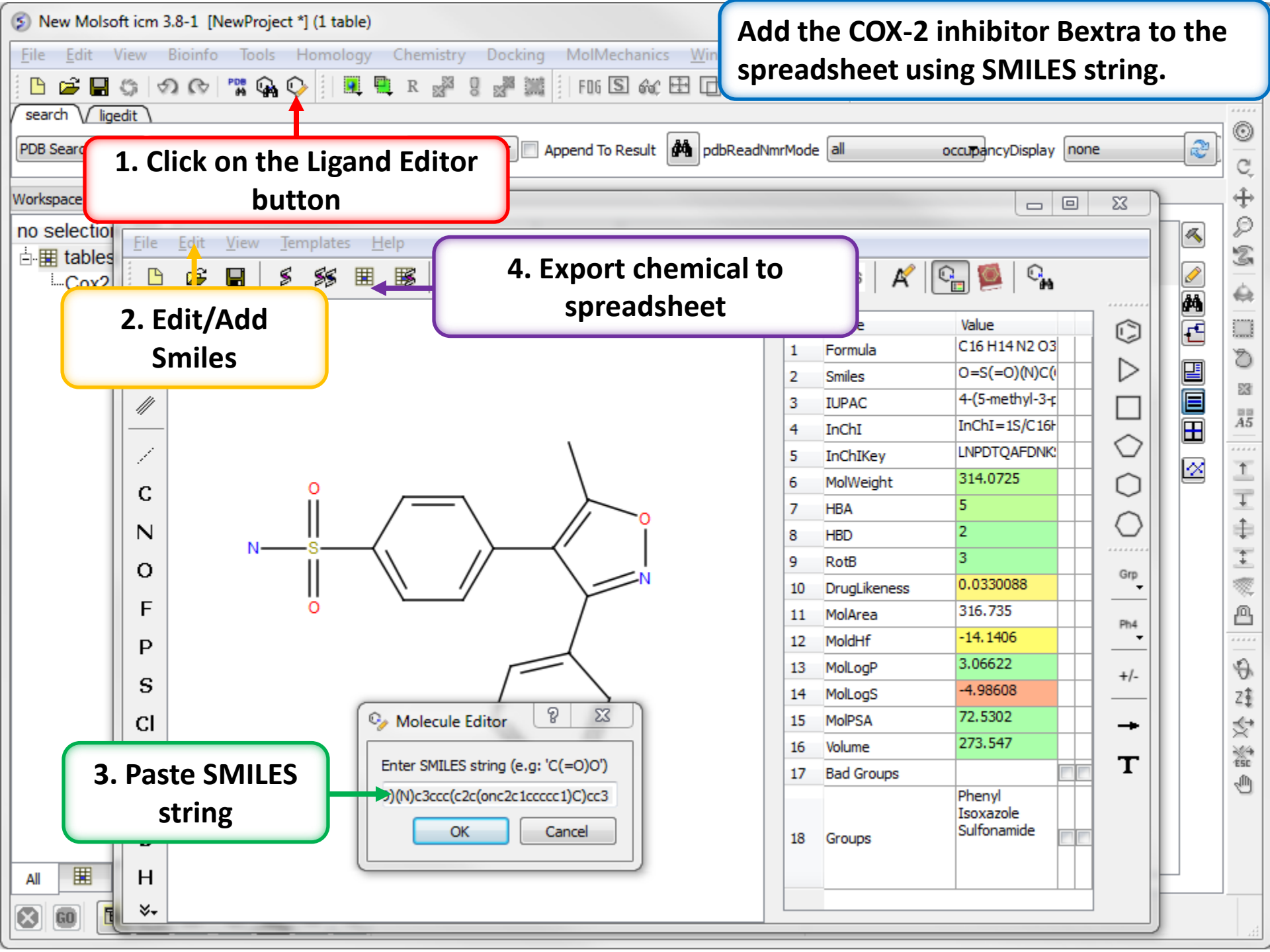
Workspace...

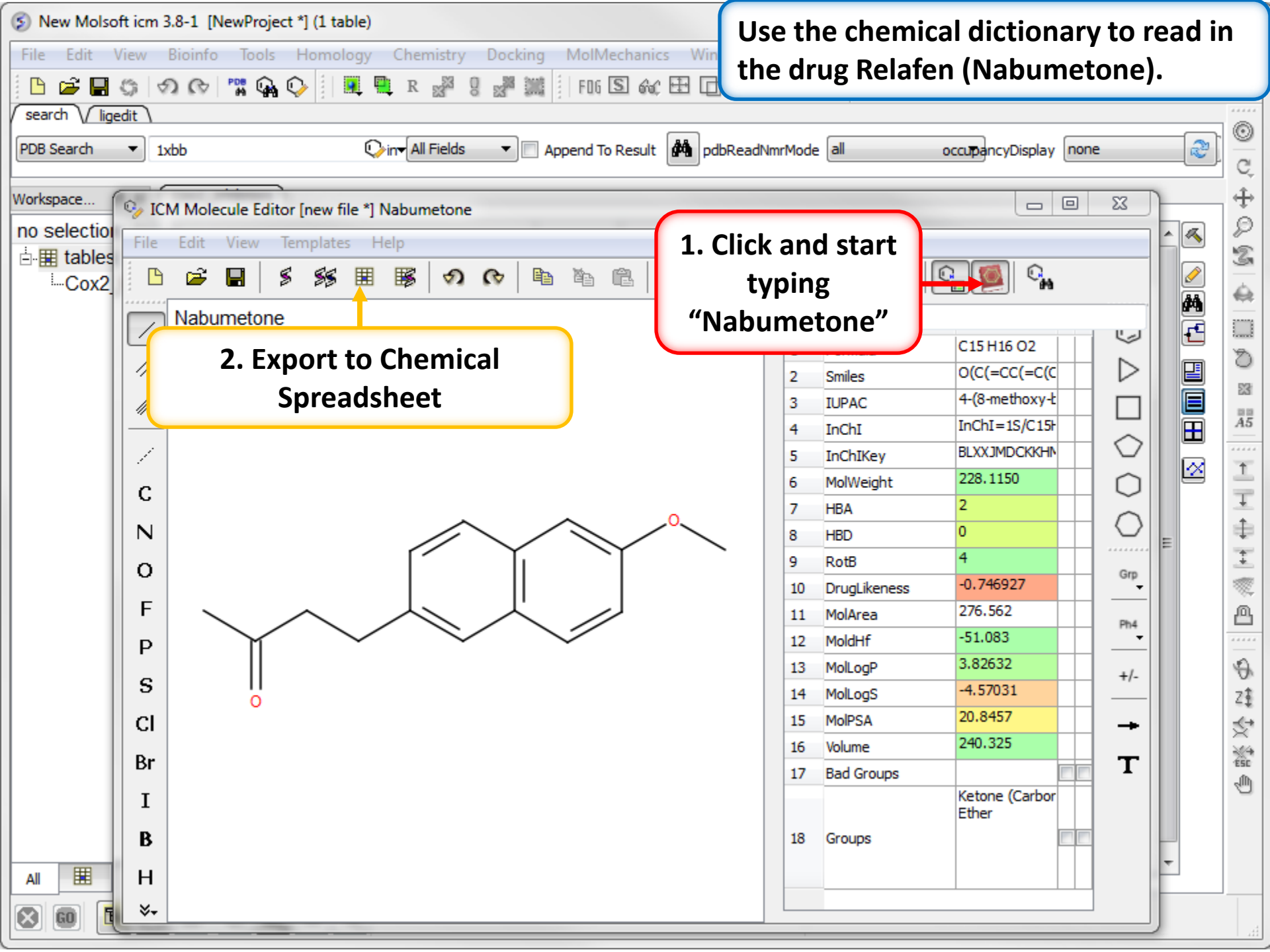
no selection
tables
Cox2_I

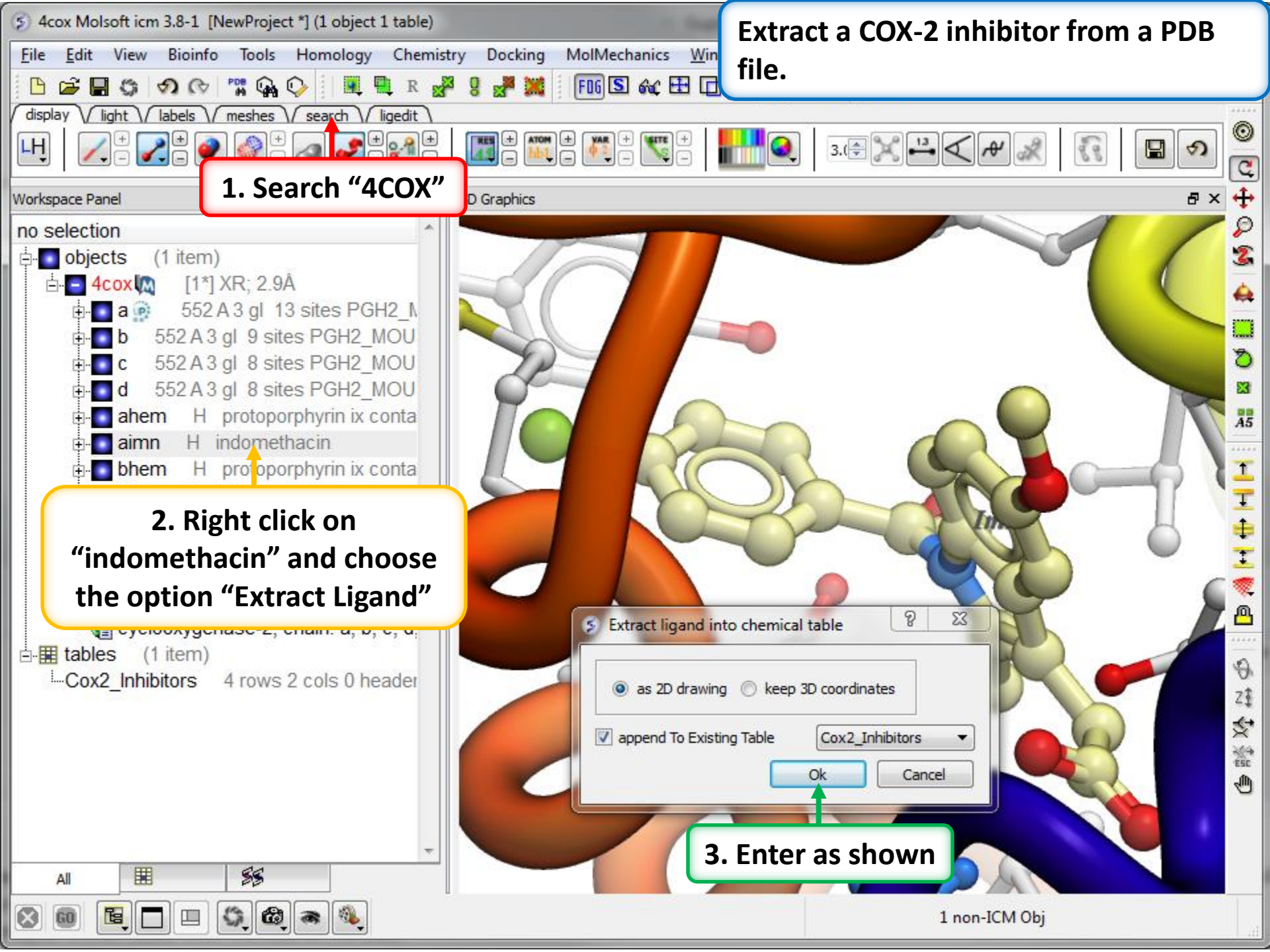
Cox2_Inhibitors

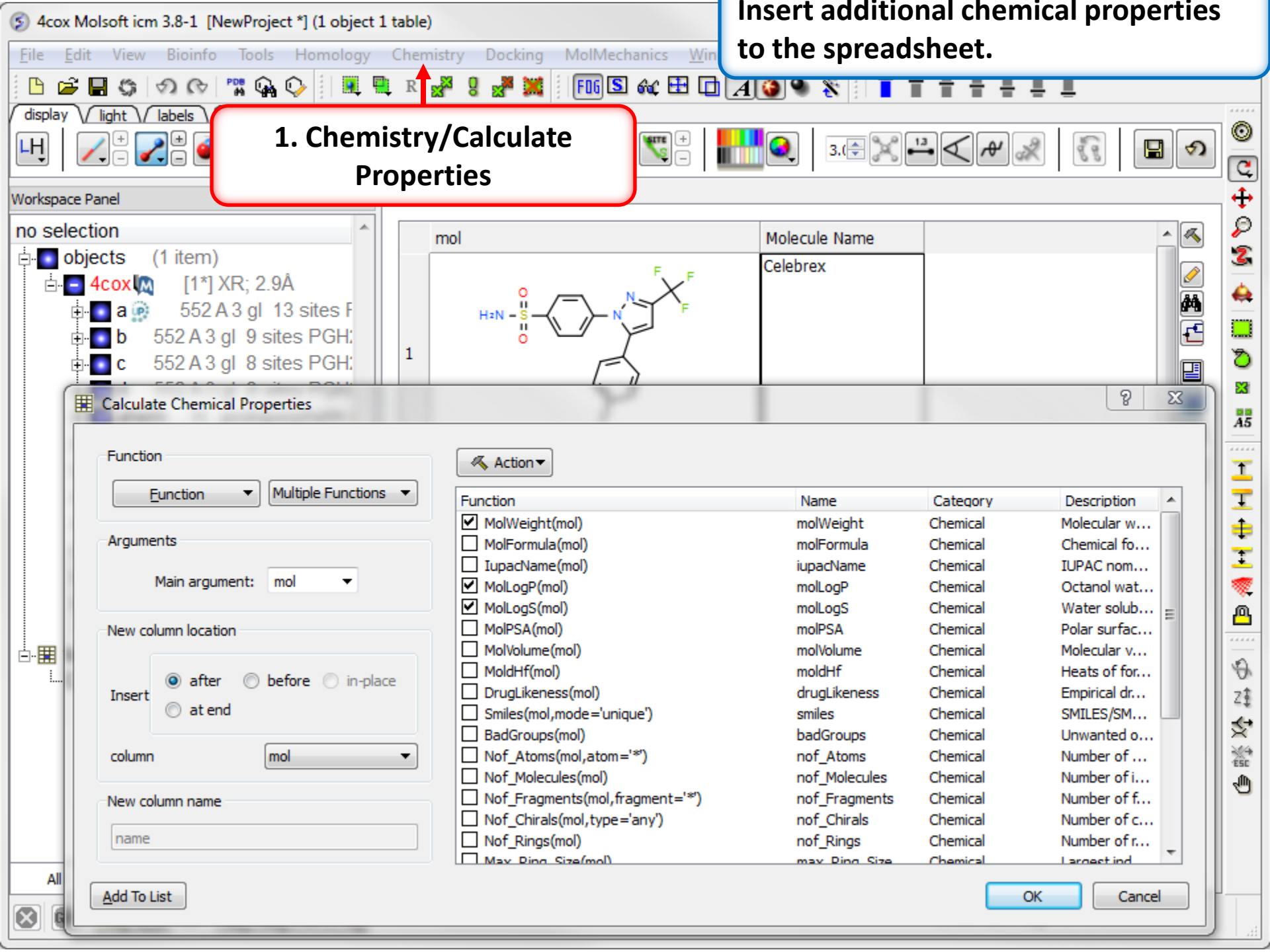
	mol	Molecule Name
1		Celebrex
2		Vioxx

All

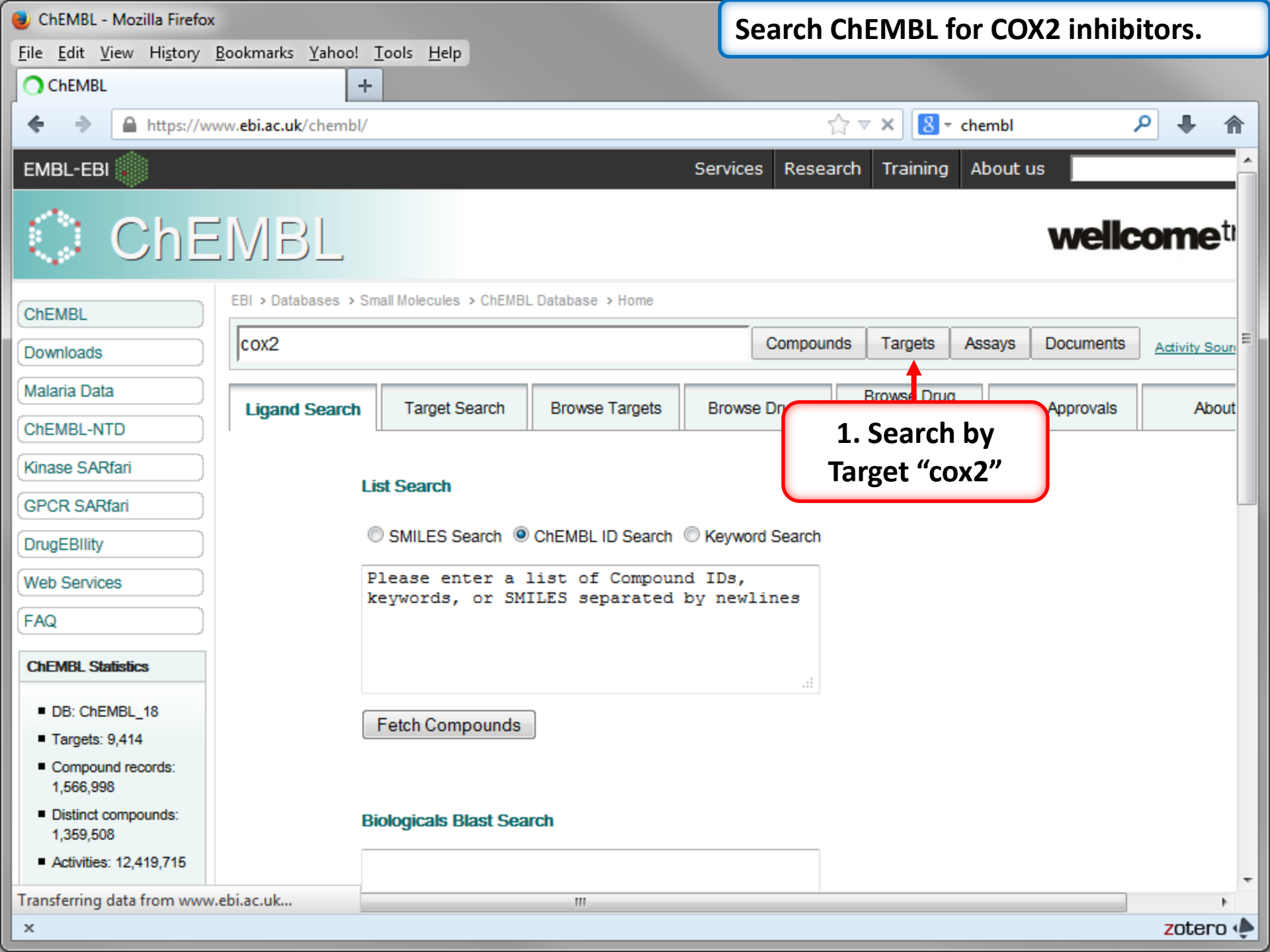

Add the COX-2 inhibitor Bextra to the spreadsheet using SMILES string.
New Molsoft icm 3.8-1 [NewProject *] (1 table)
1. Click on the Ligand Editor button
2. Edit/Add Smiles
3. Paste SMILES string
4. Export chemical to spreadsheet
Molecule Editor
Enter SMILES string (e.g: 'C(=O)O')
OK
Cancel
Value
Formula
Smiles
IUPAC
InChI
InChIKey
MolWeight
HBA
HBD
RotB
DrugLikeness
MolArea
MoldHf
MolLogP
MolLogS
MolPSA
Volume
Bad Groups
Groups
Phenyl
Isoxazole
Sulfonamide


New Molsoft icm 3.8-1 [NewProject *] (1 table)
Use the chemical dictionary to read in the drug Relafen (Nabumetone).
ICM Molecule Editor [new file *] Nabumetone
1. Click and start typing "Nabumetone"
2. Export to Chemical Spreadsheet
Nabumetone
C15 H16 O2
O(C(=CC(=C(C
4-(8-methoxy-t
InChI=1S/C15H
BLXXJMDCKKHN
228.1150
-0.746927
276.562
-51.083
3.82632
-4.57031
20.8457
240.325
Ketone (Carbor
Ether

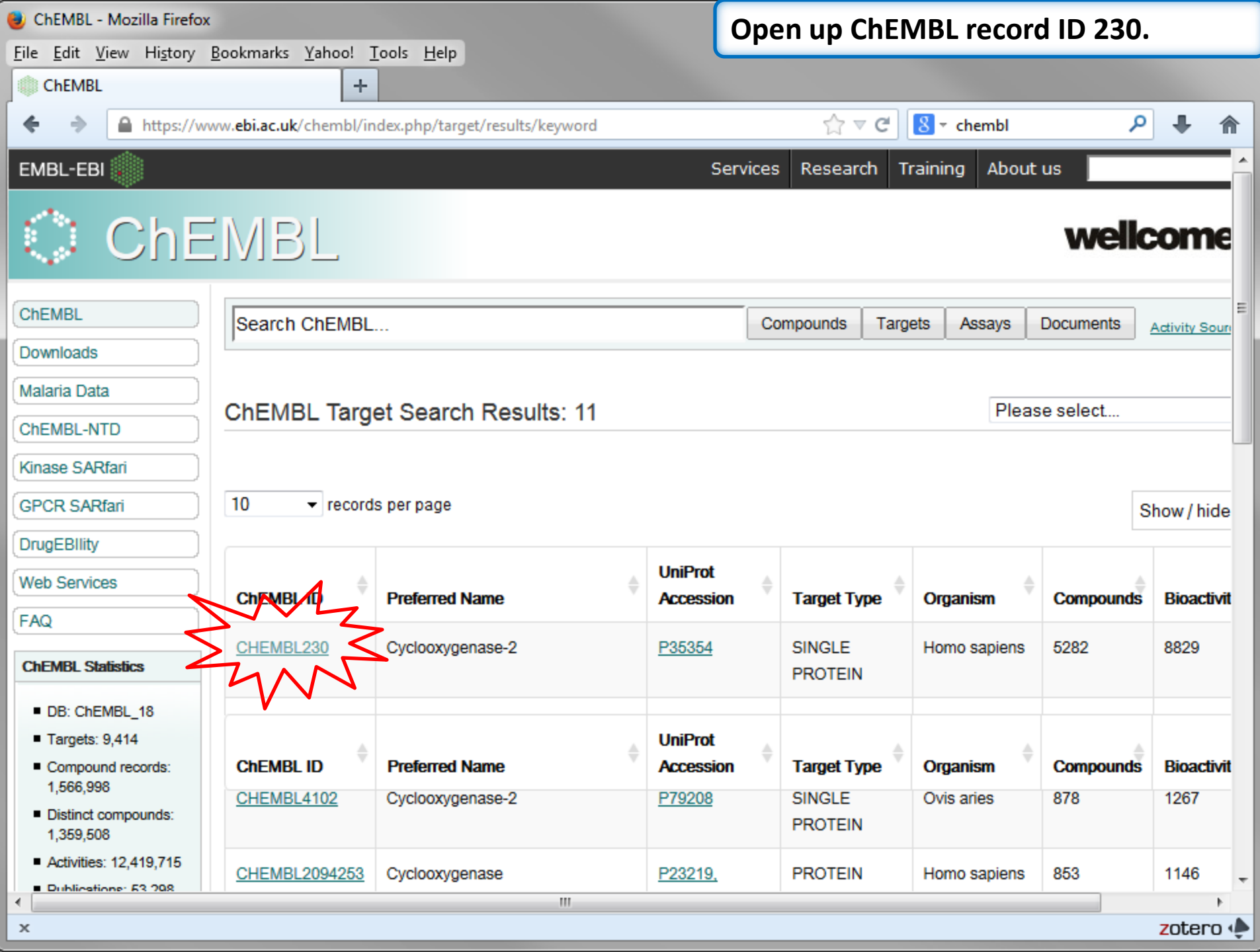

Extract a COX-2 inhibitor from a PDB file.
4cox Molsoft icm 3.8-1 [NewProject *] (1 object 1 table)
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics Win
display light labels meshes search ligedit
1. Search “4COX”
Workspace Panel
D Graphics
no selection
objects (1 item)
4cox [1*] XR; 2.9Å
a 552 A 3 gl 13 sites PGH2_M
b 552 A 3 gl 9 sites PGH2_MOU
c 552 A 3 gl 8 sites PGH2_MOU
d 552 A 3 gl 8 sites PGH2_MOU
ahem H protoporphyrin ix conta
aimn H indomethacin
bhem H protoporphyrin ix conta
2. Right click on “indomethacin” and choose the option “Extract Ligand”
tables (1 item)
Cox2_Inhibitors 4 rows 2 cols 0 header
All
Extract ligand into chemical table
as 2D drawing
keep 3D coordinates
append To Existing Table
Cox2_Inhibitors
Ok
Cancel
3. Enter as shown
1 non-ICM Obj


Insert additional chemical properties to the spreadsheet.
1. Chemistry/Calculate Properties
4cox Molsoft icm 3.8-1 [NewProject *] (1 object 1 table)
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels
Workspace Panel
no selection
objects (1 item)
4cox [1*] XR; 2.9Å
a 552 A 3 gl 13 sites
b 552 A 3 gl 9 sites PGH
c 552 A 3 gl 8 sites PGH
mol
Molecule Name
Celebrex
Calculate Chemical Properties
Function
Function
Multiple Functions
Arguments
Main argument: mol
New column location
Insert after before in-place at end
column mol
New column name
name
Action
Function Name Category Description
MolWeight(mol) molWeight Chemical Molecular w...
MolFormula(mol) molFormula Chemical Chemical fo...
IupacName(mol) iupacName Chemical IUPAC nom...
MolLogP(mol) molLogP Chemical Octanol wat...
MolLogS(mol) molLogS Chemical Water solub...
MolPSA(mol) molPSA Chemical Polar surfac...
MolVolume(mol) molVolume Chemical Molecular v...
MoldHf(mol) moldHf Chemical Heats of for...
DrugLikeness(mol) drugLikeness Chemical Empirical dr...
Smiles(mol,mode='unique') smiles Chemical SMILES/SM...
BadGroups(mol) badGroups Chemical Unwanted o...
Nof_Atoms(mol,atom='*') nof_Atoms Chemical Number of ...
Nof_Molecules(mol) nof_Molecules Chemical Number of i...
Nof_Fragments(mol,fragment='*') nof_Fragments Chemical Number of f...
Nof_Chirals(mol,type='any') nof_Chirals Chemical Number of c...
Nof_Rings(mol) nof_Rings Chemical Number of r...
Add To List
OK
Cancel

Search ChEMBL for COX2 inhibitors.



Open up ChEMBL record ID 230.



Open up the records containing IC50 data

CHEMBL230 Target Report Card - Mozilla Firefox

File Edit View History Bookmarks Yahoo! Tools Help

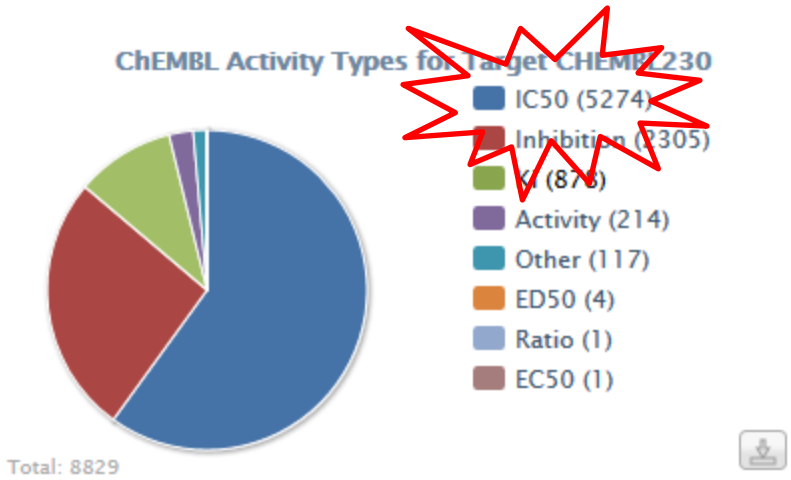
CHEMBL230 Target Report Card

https://www.ebi.ac.uk/chembl/target/inspect/CHEMBL230

chembl

CHEMBL622	ETODOLAC	Cyclooxygenase-2 inhibitor	PubMed
CHEMBL599	MELOXICAM	Cyclooxygenase-2 inhibitor	PubMed
CHEMBL1070	NABUMETONE	Cyclooxygenase-2 inhibitor	DailyMed
CHEMBL122	ROFECOXIB	Cyclooxygenase-2 inhibitor	FDA
CHEMBL865	VALDECOXIB	Cyclooxygenase-2 inhibitor	DailyMed

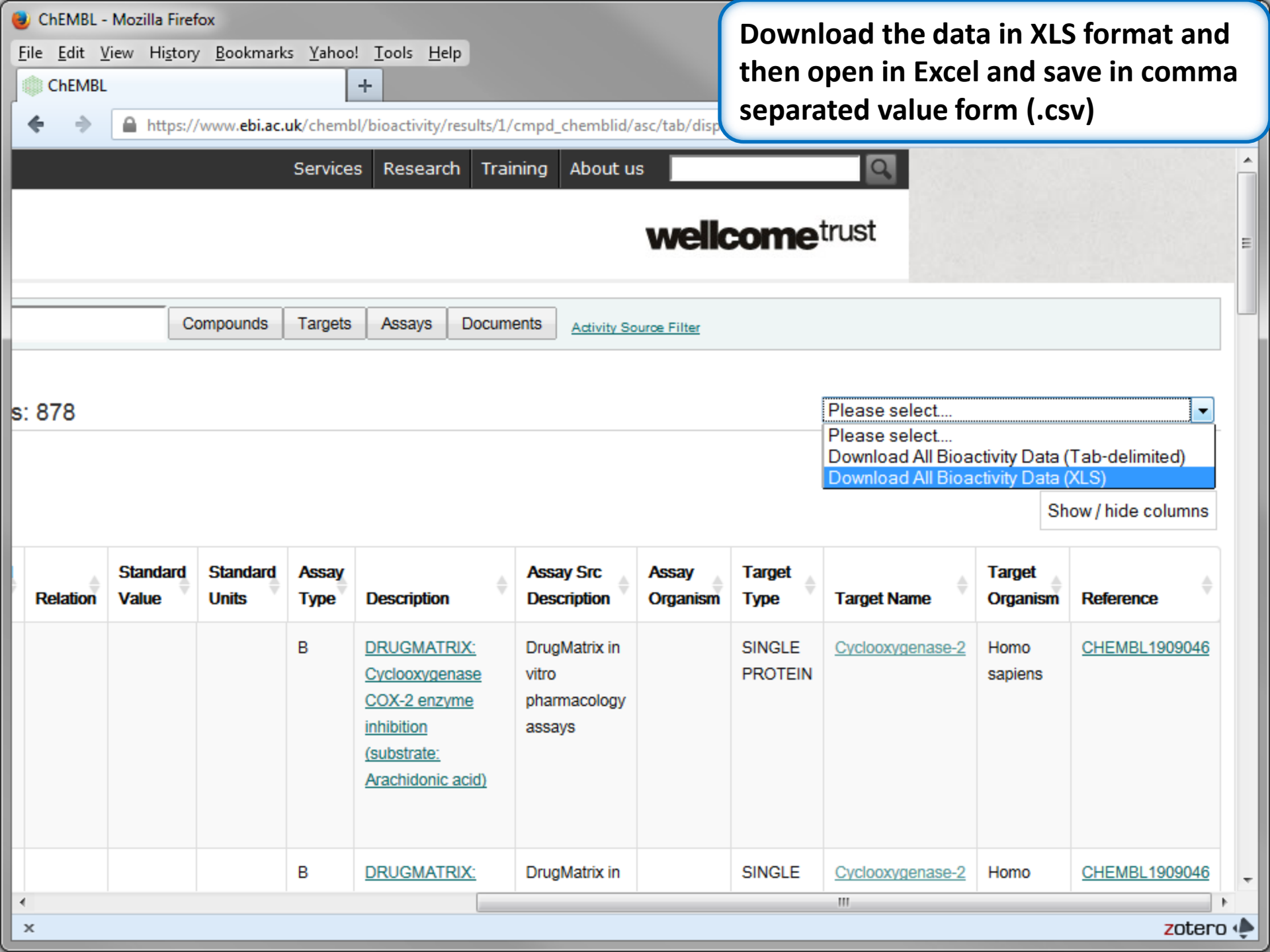
Target Associated Bioactivities

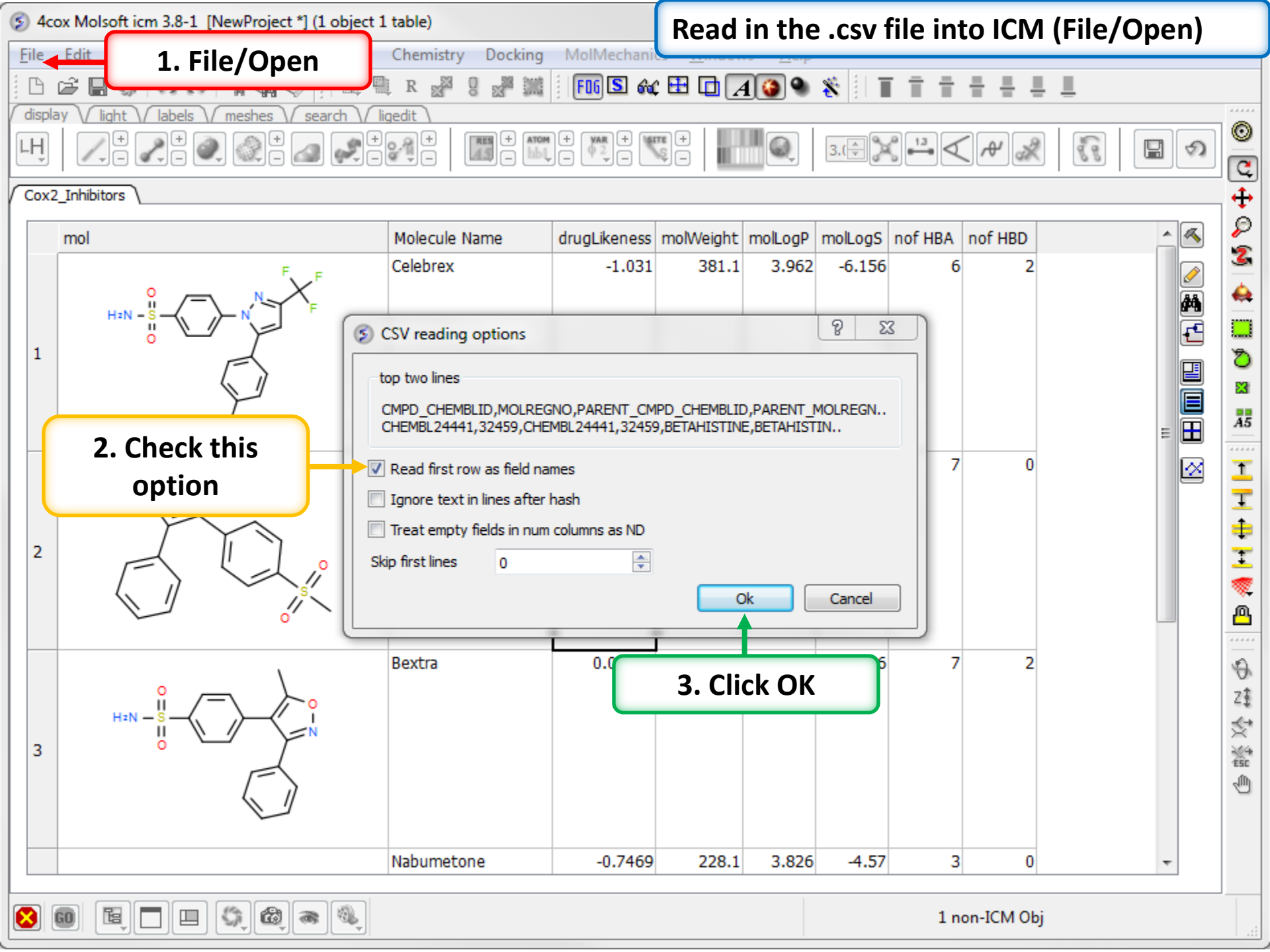


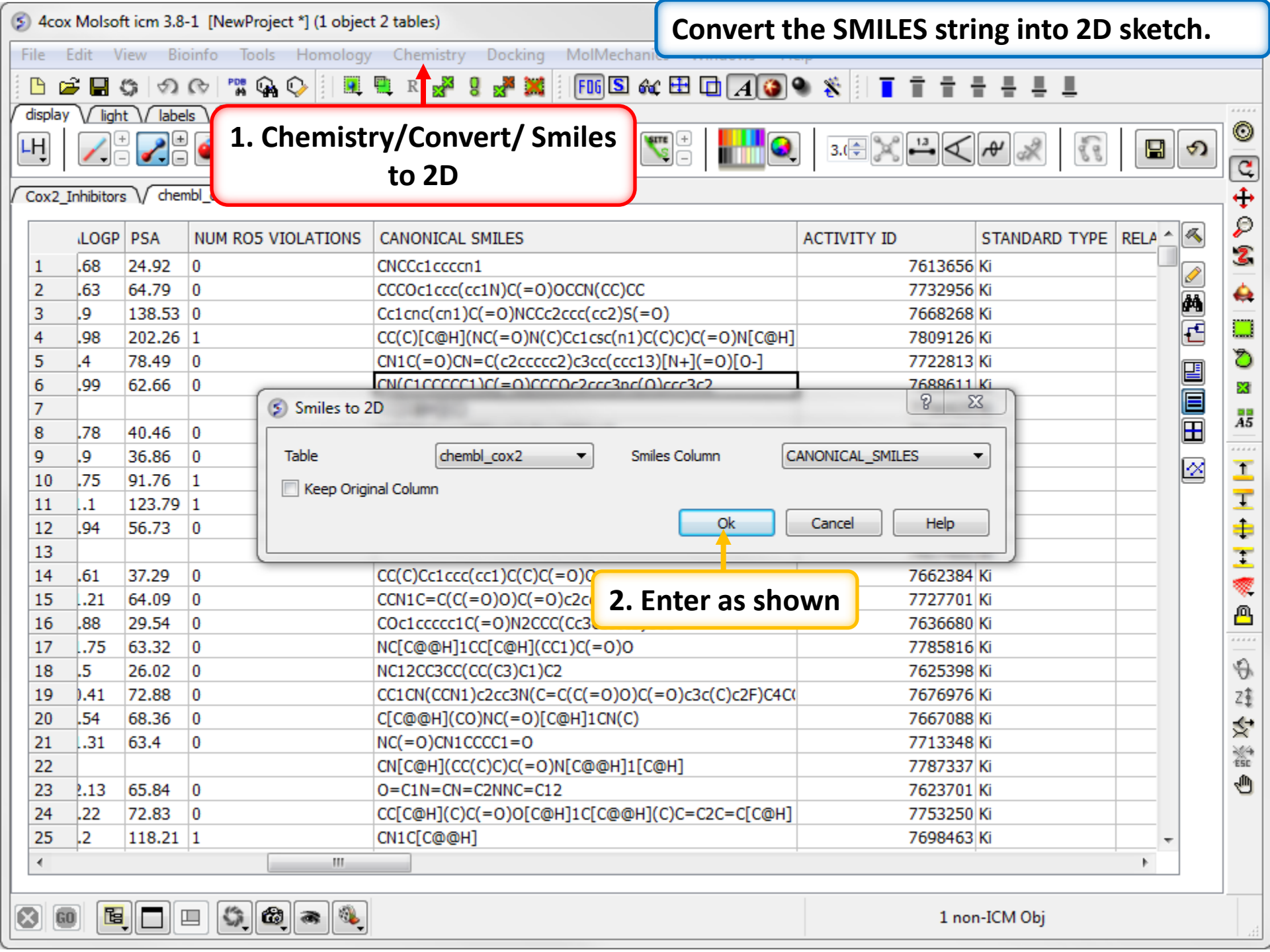
Target Associated Assays

Transferring data from www.ebi.ac.uk...

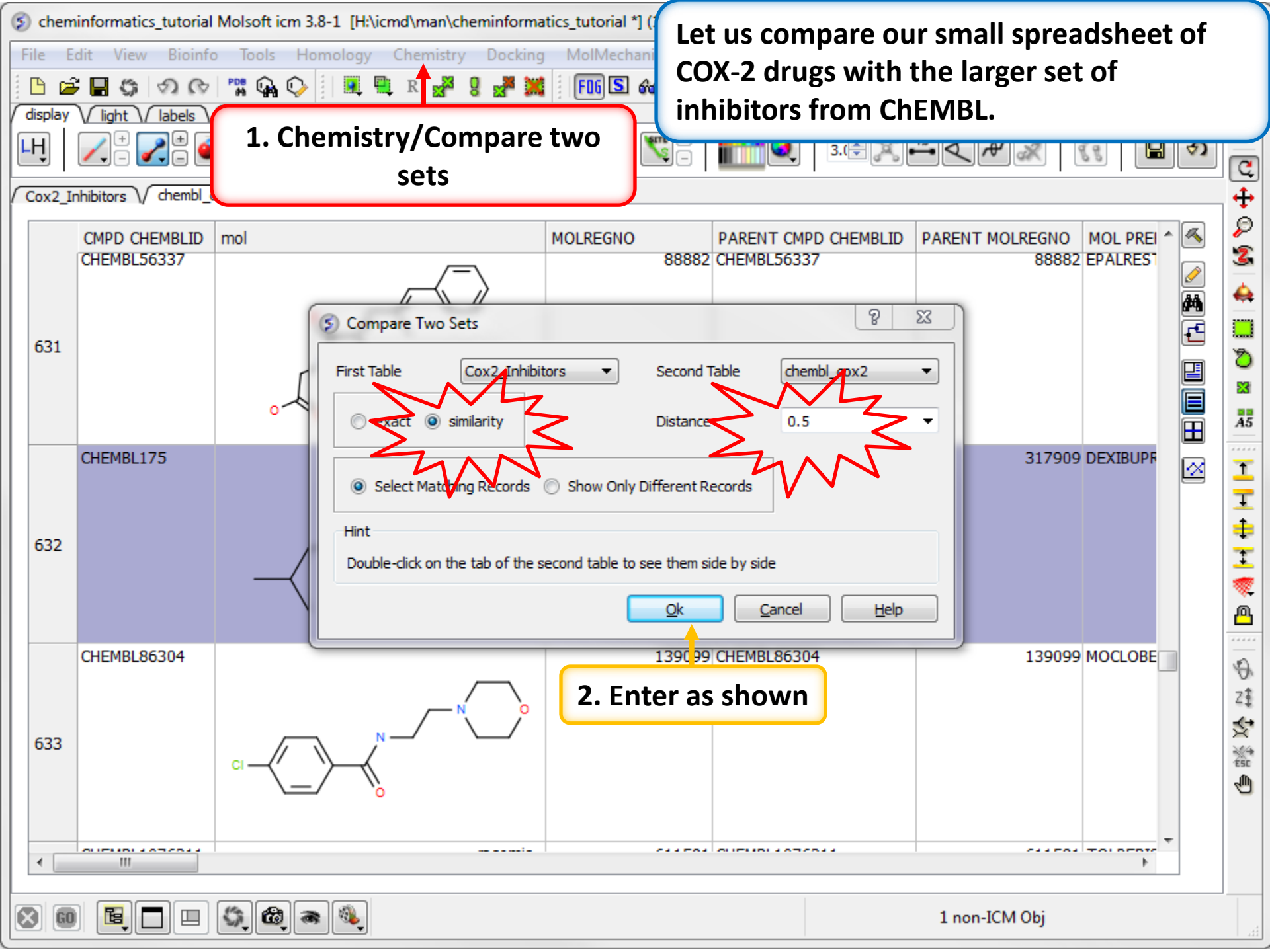
zotero


Download the data in XLS format and then open in Excel and save in comma separated value form (.csv)
ChEMBL - Mozilla Firefox
File Edit View History Bookmarks Yahoo! Tools Help
ChEMBL
https://www.ebi.ac.uk/chembl/bioactivity/results/1/cmpd_chemblid/asc/tab/disp
Services Research Training About us
wellcome trust
Compounds Targets Assays Documents
Activity Source Filter
s: 878
Please select...
Please select...
Download All Bioactivity Data (Tab-delimited)
Download All Bioactivity Data (XLS)
Show / hide columns
Relation
Standard Value
Standard Units
Assay Type
Description
Assay Src Description
Assay Organism
Target Type
Target Name
Target Organism
Reference
B
DRUGMATRIX: Cyclooxygenase COX-2 enzyme inhibition (substrate: Arachidonic acid)
DrugMatrix in vitro pharmacology assays
SINGLE PROTEIN
Cyclooxygenase-2
Homo sapiens
CHEMBL1909046
B
DRUGMATRIX:
DrugMatrix in
SINGLE
Cyclooxygenase-2
Homo
CHEMBL1909046
zotero


Read in the .csv file into ICM (File/Open)
4cox Molsoft icm 3.8-1 [NewProject *] (1 object 1 table)
File
Edit
Chemistry
Docking
1. File/Open
display
light
labels
meshes
search
ligedit
Cox2_Inhibitors
mol
Molecule Name
drugLikeness
molWeight
molLogP
molLogS
nof HBA
nof HBD
Celebrex
-1.031
381.1
3.962
-6.156
6
2
7
0
Bextra
7
2
Nabumetone
-0.7469
228.1
3.826
-4.57
3
0
CSV reading options
top two lines
CMPD_CHEMBLID,MOLREGNO,PARENT_CMPD_CHEMBLID,PARENT_MOLREGN..
CHEMBL24441,32459,CHEMBL24441,32459,BETAHISTINE,BETAHISTIN..
Read first row as field names
Ignore text in lines after hash
Treat empty fields in num columns as ND
Skip first lines
0
Ok
Cancel
2. Check this option
3. Click OK
1 non-ICM Obj


4cox Molsoft icm 3.8-1 [NewProject *] (1 object 2 tables)
Convert the SMILES string into 2D sketch.
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics
display light labels
1. Chemistry/Convert/ Smiles to 2D
Cox2_Inhibitors
chembl_
LOGP PSA NUM RO5 VIOLATIONS CANONICAL SMILES ACTIVITY ID STANDARD TYPE RELA
1 .68 24.92 0 CNCCc1ccccn1 7613656 Ki
2 .63 64.79 0 CCCOc1ccc(cc1N)C(=O)OCCN(CC)CC 7732956 Ki
3 .9 138.53 0 Cc1cnc(cn1)C(=O)NCCc2ccc(cc2)S(=O) 7668268 Ki
4 .98 202.26 1 CC(C)[C@H](NC(=O)N(C)Cc1csc(n1)C(C)C)C(=O)N[C@H] 7809126 Ki
5 .4 78.49 0 CN1C(=O)CN=C(c2ccccc2)c3cc(ccc13)[N+](=O)[O-] 7722813 Ki
6 .99 62.66 0 7688611 Ki
7
8 .78 40.46 0
9 .9 36.86 0
10 .75 91.76 1
11 .1 123.79 1
12 .94 56.73 0
13
14 .61 37.29 0 CC(C)Cc1ccc(cc1)C(C)C(=O)O 7662384 Ki
15 .21 64.09 0 CCN1C=C(C(=O)O)C(=O)c2c 7727701 Ki
16 .88 29.54 0 COc1ccccc1C(=O)N2CCC(Cc3 7636680 Ki
17 .75 63.32 0 NC[C@@H]1CC[C@H](CC1)C(=O)O 7785816 Ki
18 .5 26.02 0 NC12CC3CC(CC(C3)C1)C2 7625398 Ki
19 .41 72.88 0 CC1CN(CCN1)c2cc3N(C=C(C(=O)O)C(=O)c3c(C)c2F)C4C 7676976 Ki
20 .54 68.36 0 C[C@@H](CO)NC(=O)[C@H]1CN(C) 7667088 Ki
21 .31 63.4 0 NC(=O)CN1CCCC1=O 7713348 Ki
22 CN[C@H](CC(C)C)C(=O)N[C@@H]1[C@H] 7787337 Ki
23 .13 65.84 0 O=C1N=CN=C2NNC=C12 7623701 Ki
24 .22 72.83 0 CC[C@H](C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H] 7753250 Ki
25 .2 118.21 1 CN1C[C@@H] 7698463 Ki
Smiles to 2D
Table chembl_cox2
Smiles Column CANONICAL_SMILES
Keep Original Column
Ok
Cancel
Help
2. Enter as shown
1 non-ICM Obj

Chemical Searching


cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutorial *]
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechani
display light labels
Let us compare our small spreadsheet of COX-2 drugs with the larger set of inhibitors from ChEMBL.
1. Chemistry/Compare two sets
Cox2_Inhibitors
chembl_
CMPD CHEMBLID
mol
MOLREGNO
PARENT CMPD CHEMBLID
PARENT MOLREGNO
MOL PREI
631
CHEMBL56337
88882
CHEMBL56337
88882
EPALRES
632
CHEMBL175
317909
DEXIBUPR
633
CHEMBL86304
139099
CHEMBL86304
139099
MOCLOBE
Compare Two Sets
First Table
Cox2_Inhibitors
Second Table
chembl_cox2
exact
similarity
Distance
0.5
Select Matching Records
Show Only Different Records
Hint
Double-click on the tab of the second table to see them side by side
Ok
Cancel
Help
2. Enter as shown
1 non-ICM Obj

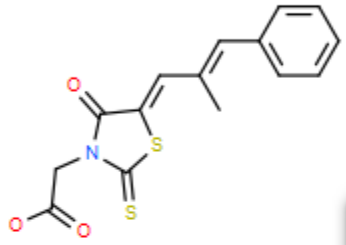
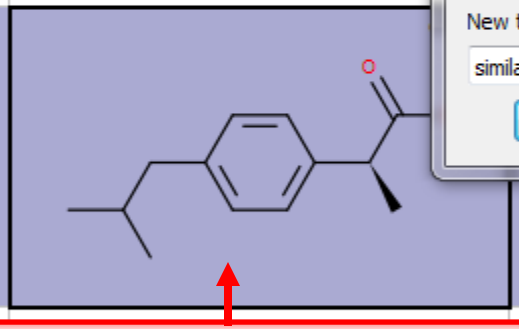
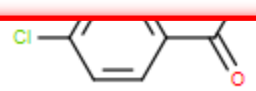
Let us make a new spreadsheet from the comparison hits. Selected compounds will be highlighted in blue.

cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutorial *]

File Edit View Bioinfo Tools Homology Chemistry Docking MolMechani

display light labels meshes search ligedit

Cox2_Inhibitors chembl_cox2 similar_0_5

	CMPD CHEMBLID	mol	MOLREGNO	PARENT CMPD CHEMBLID	PARENT MOLREGNO	MOL PREI
631	CHEMBL56337		88882	CHEMBL56337	88882	EPALRES
632	CHEMBL175					09 DEXIBUPR
633	CHEMBL8		139099	CHEMBL86304	139099	MOCLOBE

Table

New table name:

similar_0.5

OK Cancel

2. Enter a new table name for the similar compounds

1. Right click and choose Copy rows to ICM Table

1 non-ICM Obj

Save the spreadsheets in SDF format and delete Cox2_Inhibitors and similar_0_5

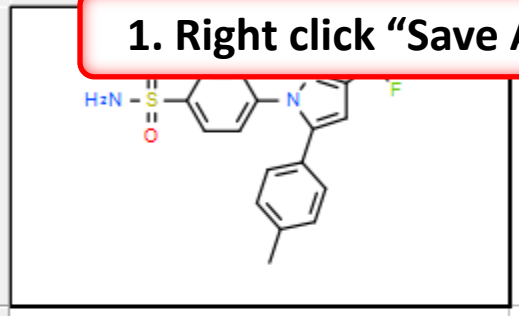
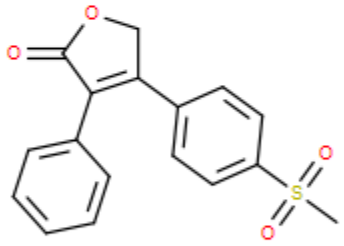
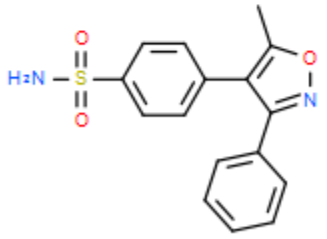
cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutorial *]

File Edit View Bioinfo Tools Homology Chemistry Docking MolMechani

display light labels meshes search ligedit

Cox2_Inhibitors chembl_cox2 similar_0_5

1. Right click "Save As" .sdf.

	mol	Molecule_Name	drugLikeness	molWeight	molLogP	molLogS	nof HBA	nof HBD
1			-1.031	381.1	3.962	-6.156	6	2
2		Vioxx	-0.7455	314.1	2.205	-4.957	7	0
3		Bextra	0.03301	314.1	3.066	-4.986	7	2
		Nabumetone	-0.7469	228.1	3.826	-4.57	3	0

1 non-ICM Obj

Chemical Searching

cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutorial *] (1 object 1 table)

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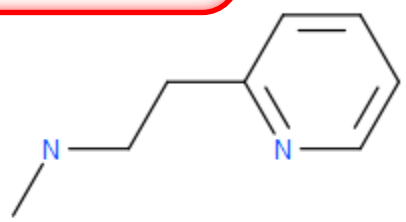
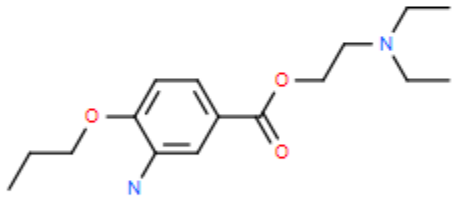
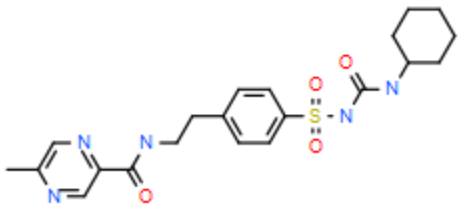
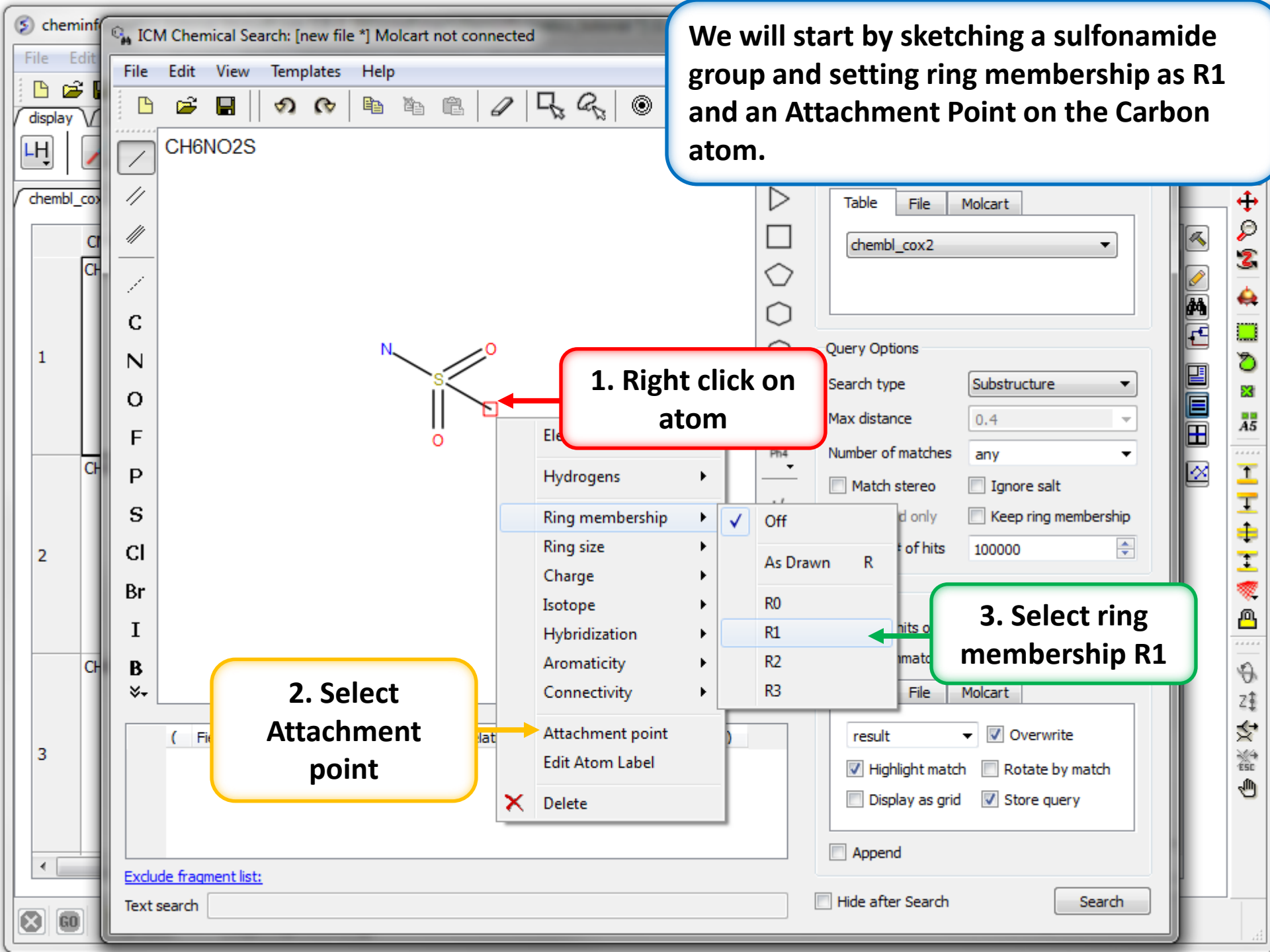
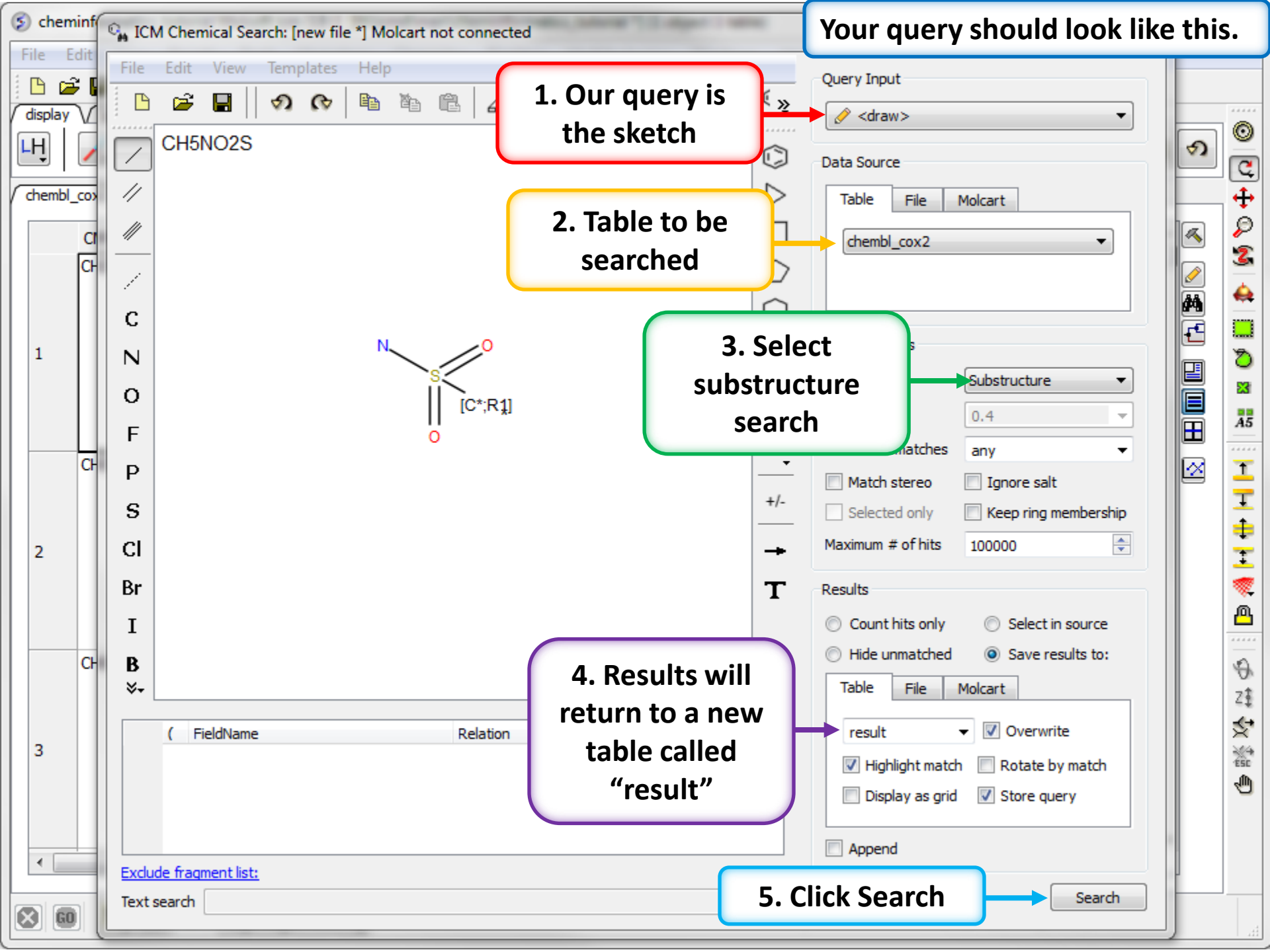
1. Click here to open Chemical Search window

chembl_cox2

	CMPD C		MOLREGNO	PARENT CMPD CHEMBLID	PARENT MOLREGNO	MOL PREI
1	CHEMBL		32459	CHEMBL24441	32459	BETAHIST
2	CHEMBL1196		209007	CHEMBL1196	209007	PROPARA
3	CHEMBL1073		139286	CHEMBL1073	139286	GLIPIZIDE

1 non-ICM Obj


We will start by sketching a sulfonamide group and setting ring membership as R1 and an Attachment Point on the Carbon atom.
ICM Chemical Search: [new file *] Molcart not connected
File Edit View Templates Help
CH6NO2S
1. Right click on atom
Hydrogens
Ring membership
Ring size
Charge
Isotope
Hybridization
Aromaticity
Connectivity
Attachment point
Edit Atom Label
Delete
Off
As Drawn R
R0
R1
R2
R3
3. Select ring membership R1
2. Select Attachment point
Table File Molcart
chembl_cox2
Query Options
Search type Substructure
Max distance 0.4
Number of matches any
Match stereo
Ignore salt
Keep ring membership
100000
result
Overwrite
Highlight match
Rotate by match
Display as grid
Store query
Append
Exclude fragment list:
Text search
Hide after Search
Search


Your query should look like this.
1. Our query is the sketch
2. Table to be searched
3. Select substructure search
4. Results will return to a new table called “result”
5. Click Search
ICM Chemical Search: [new file *] Molcart not connected
File Edit View Templates Help
CH5NO2S
Query Input
<draw>
Data Source
Table File Molcart
chembl_cox2
Substructure
0.4
any
Match stereo
Ignore salt
Selected only
Keep ring membership
Maximum # of hits
100000
Results
Count hits only
Select in source
Hide unmatched
Save results to:
Table File Molcart
result
Overwrite
Highlight match
Rotate by match
Display as grid
Store query
Append
FieldName
Relation
Exclude fragment list:
Text search
Search

Results are shown with the query highlighted in green. We are finding chemicals with sulfonamide linked between two substituents e.g Phenyl-Sulfonaminde-Thiazole shown - let us filter these out (next step).

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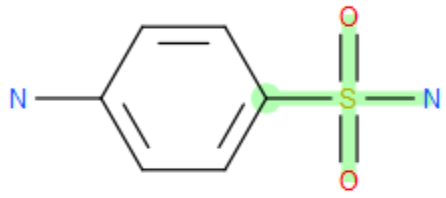
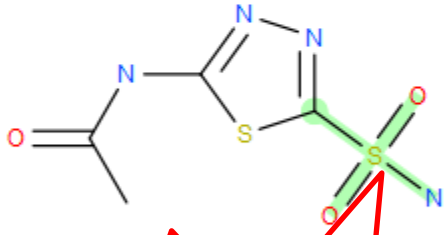
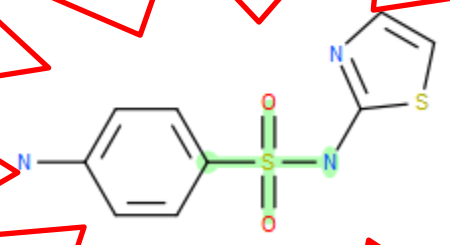
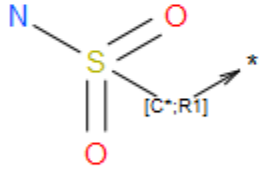
chembl_cox2 result

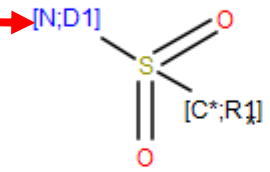
	CMPD CHEMBLID	mol	MOLREGNO
1	CHEMBL21		
2	CHEMBL20		1125 CHEI
3	CHEMBL437		2095 CHEI



1 non-ICM Obj

By changing the connectivity of the Nitrogen we can find only terminal sulfonamide groups similar to the drug Celebrex.

1. Right click on the Nitrogen atom and choose Connectivity "As Drawn"



ICM Chemical Search: [new file *] Molcart not connected

File Edit View Templates Help

CH5NO2S

S Cl Br I B

(FieldName Relation Value)

Exclude fragment list:

Text search

Data Source

Table File Molcart

chembl_cox2

Query Options

Search type: Substructure

Max distance: 0.4

Number of matches: any

Match stereo Ignore salt

Selected only Keep ring membership

Maximum # of hits: 100000

Results

Count hits only Select in source

Hide unmatched Save results to:

Table File Molcart

result Overwrite

Highlight match Rotate by match

Display as grid Store query

Append

Hide after Search Search

By changing the connectivity of the Nitrogen we can find only terminal sulfonamide groups similar to the drug Celebrex.

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chembl_cox2 result

	CMPD CHEMBLID	mol	MOLREGNO	PAR
10	CHEMBL406	racemic	619	CHEI
11	CHEMBL878	racemic	73548	CHEI
12	CHEMBL118		18694	CHEI

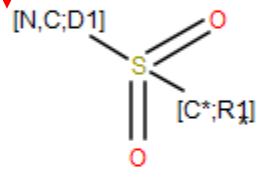
Header Filter Tree Scaffold

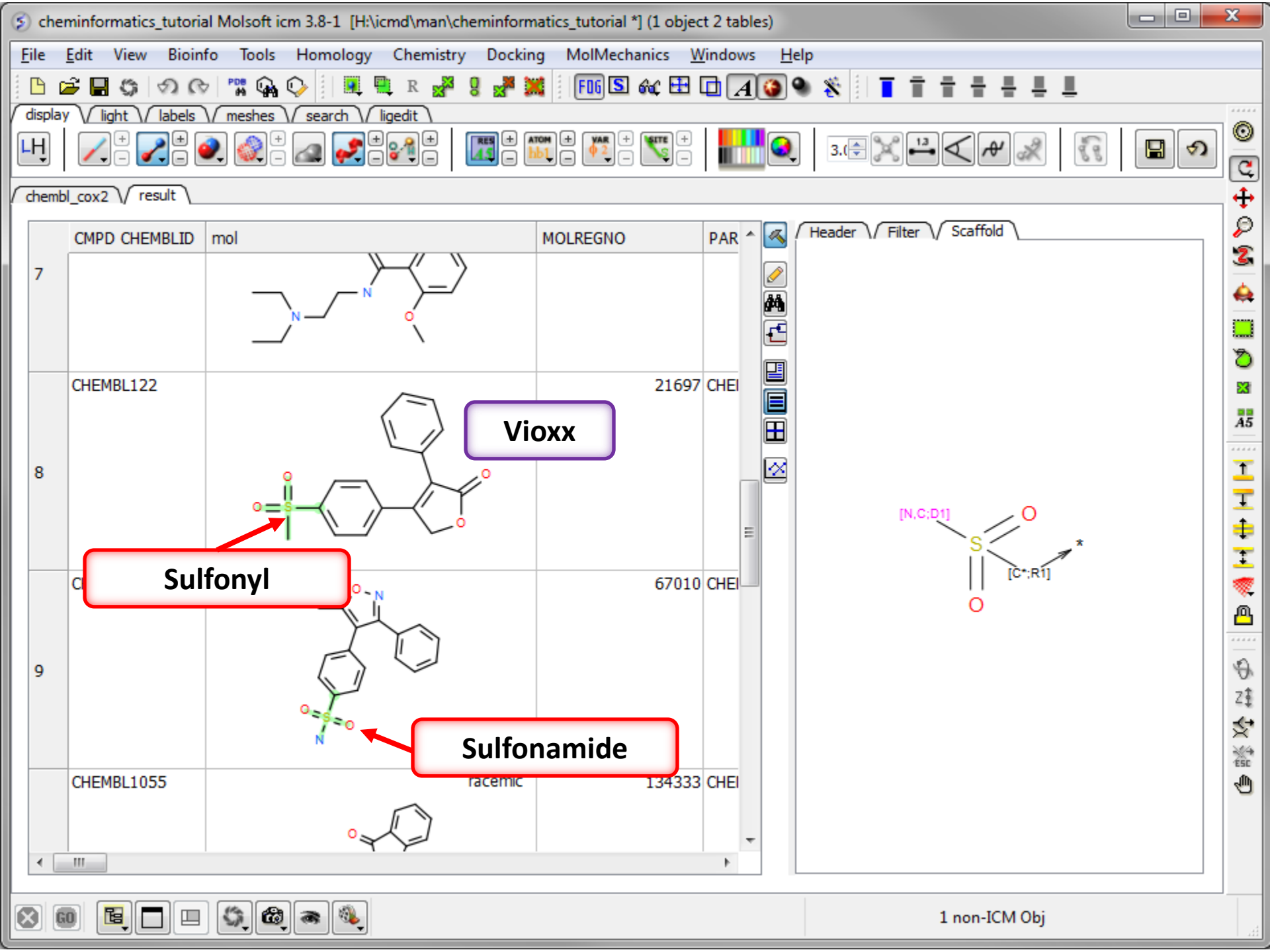
[N;D1] [C*;R1]

1 non-ICM Obj

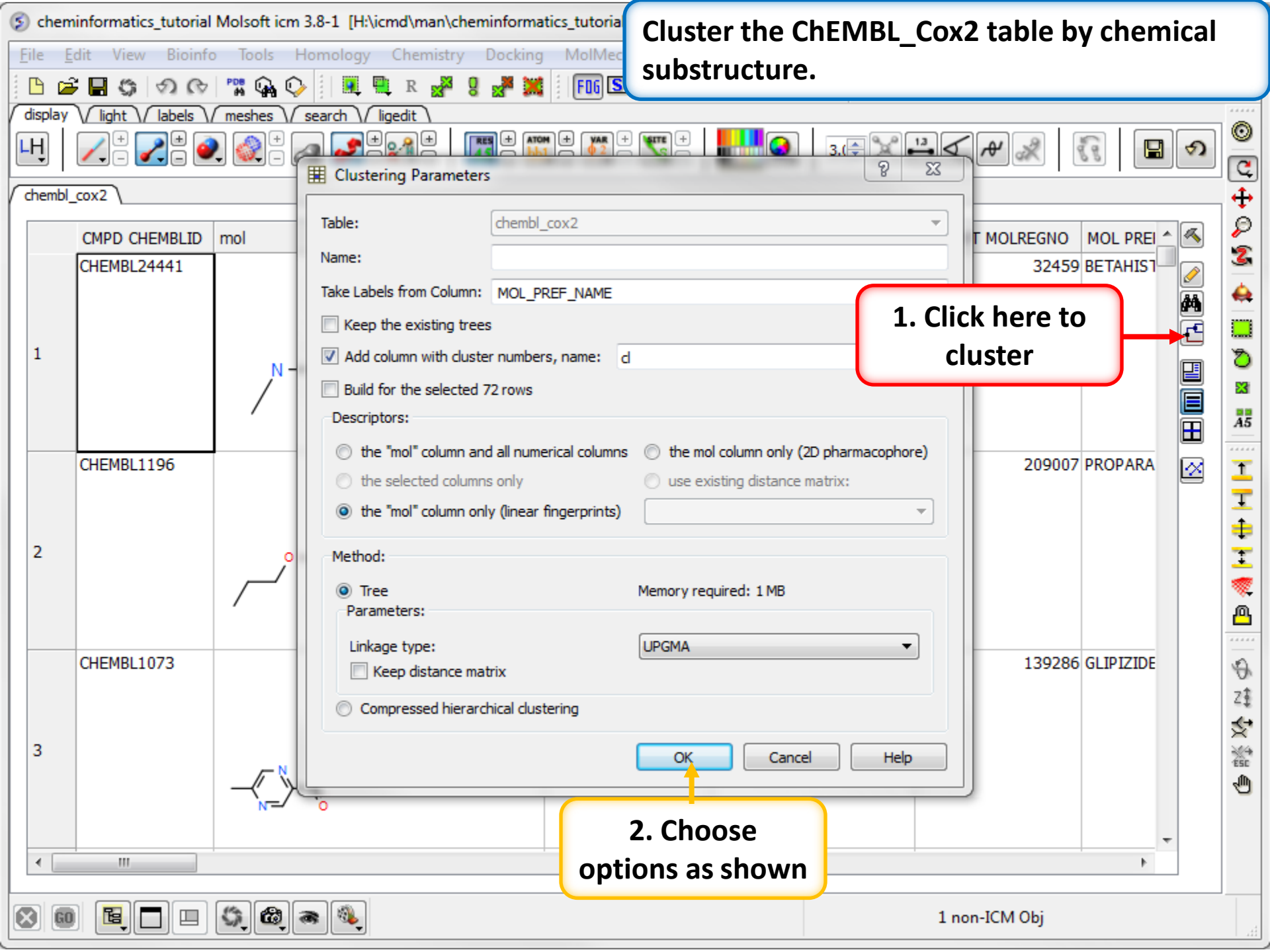
Now let us expand the search a bit by including sulfonyl groups as well as sulfonamides – this will identify Vioxx like molecules as well.

1. Right click on the Nitrogen atom and choose Element/Custom and add “N,C”



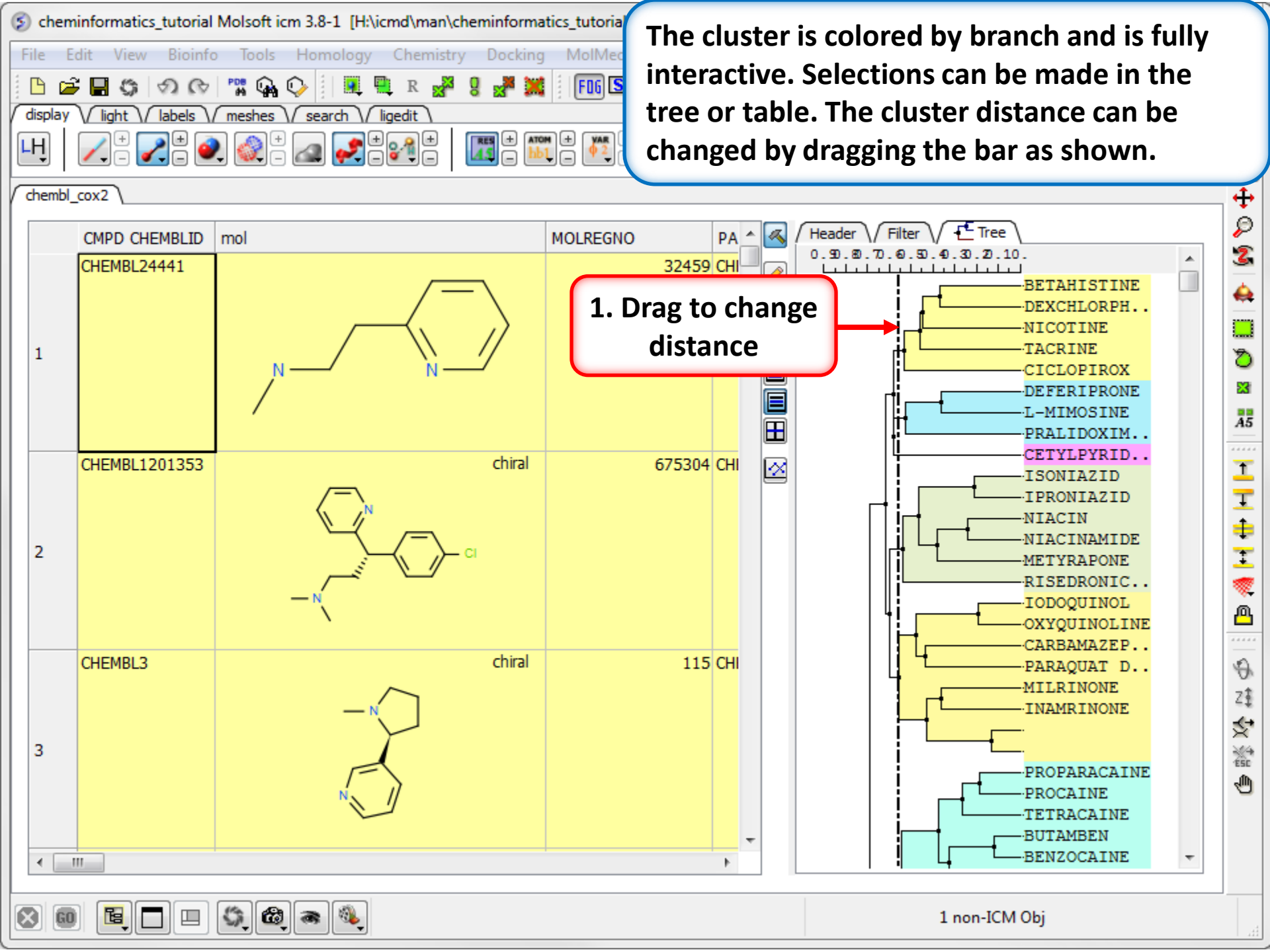

cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutorial *] (1 object 2 tables)
File Edit View Bioinfo Tools Homology Chemistry Docking MolMechanics Windows Help
display light labels meshes search ligedit
chembl_cox2 result
CMPD CHEMBLID
mol
MOLREGNO
PAR
7
CHEMBL122
21697
CHEI
8
Vioxx
Sulfonyl
67010
CHEI
9
Sulfonamide
CHEMBL1055
racemic
134333
CHEI
Header Filter Scaffold
[N,C;D1]
[C*;R1]
1 non-ICM Obj

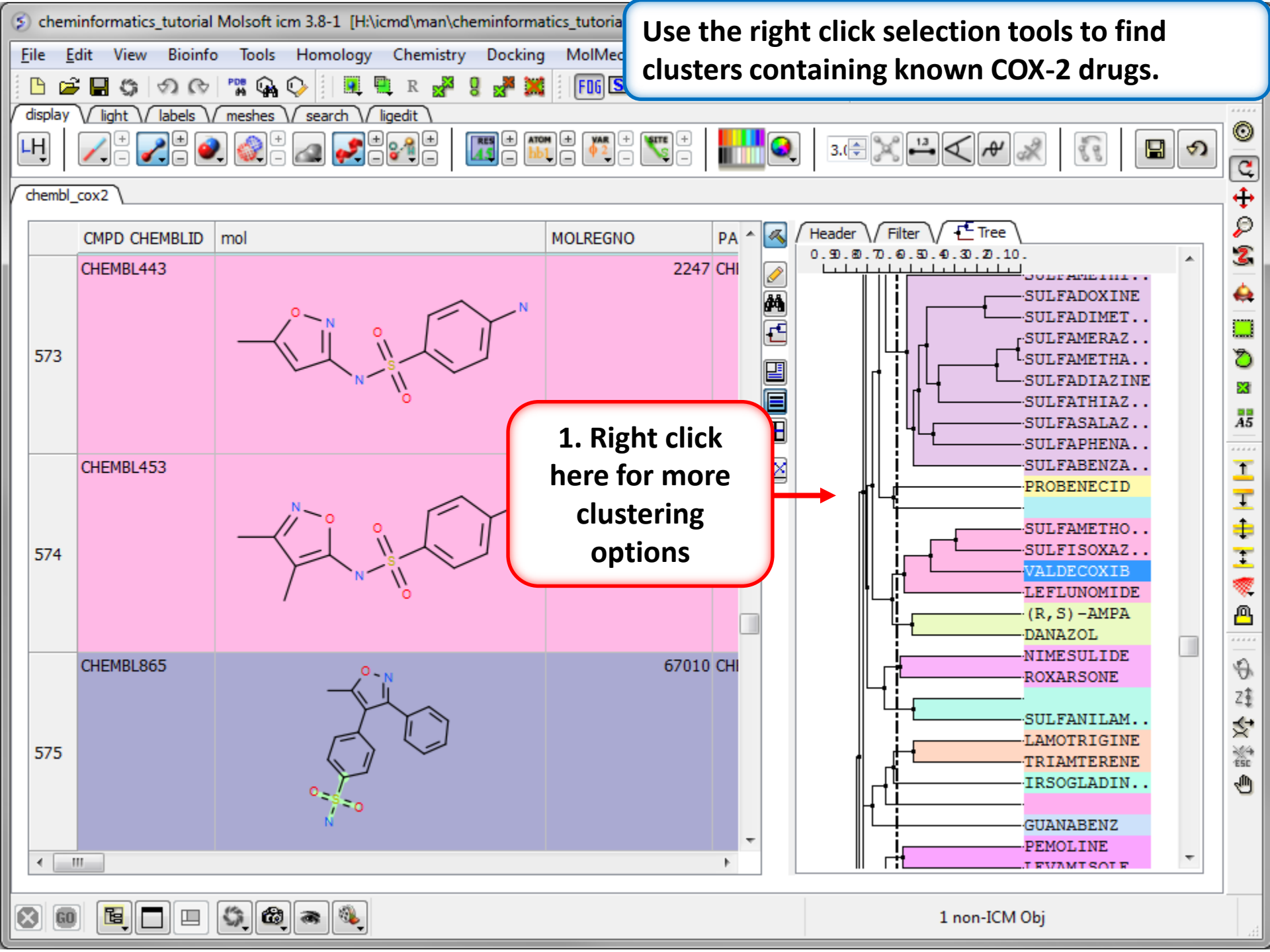
Chemical Clustering


Cluster the ChEMBL_Cox2 table by chemical substructure.
Clustering Parameters
Table:
chembl_cox2
Name:
Take Labels from Column:
MOL_PREF_NAME
Keep the existing trees
Add column with cluster numbers, name:
cl
Build for the selected 72 rows
Descriptors:
the "mol" column and all numerical columns
the mol column only (2D pharmacophore)
the selected columns only
use existing distance matrix:
the "mol" column only (linear fingerprints)
Method:
Tree
Memory required: 1 MB
Parameters:
Linkage type:
UPGMA
Keep distance matrix
Compressed hierarchical clustering
OK
Cancel
Help
1. Click here to cluster
2. Choose options as shown
chembl_cox2
CMPD CHEMBLID
mol
MOLREGNO
MOL PREI
CHEMBL24441
32459
BETAHIST
CHEMBL1196
209007
PROPARA
CHEMBL1073
139286
GLIPIZIDE
1 non-ICM Obj

The cluster is colored by branch and is fully interactive. Selections can be made in the tree or table. The cluster distance can be changed by dragging the bar as shown.

1. Drag to change distance




cheminformatics_tutorial Molsoft icm 3.8-1 [H:\icmd\man\cheminformatics_tutoria
Use the right click selection tools to find clusters containing known COX-2 drugs.
File Edit View Bioinfo Tools Homology Chemistry Docking MolMec
display light labels meshes search ligedit
chembl_cox2
CMPD CHEMBLID
mol
MOLREGNO
PA
573
CHEMBL443
2247
574
CHEMBL453
575
CHEMBL865
67010
1. Right click here for more clustering options
Header
Filter
Tree
SULFADOXINE
SULFADIMET..
SULFAMERAZ..
SULFAMETHA..
SULFADIAZINE
SULFATHIAZ..
SULFASALAZ..
SULFAPHENA..
SULFABENZA..
PROBENECID
SULFAMETHO..
SULFISOXAZ..
VALDECOXIB
LEFLUNOMIDE
(R,S)-AMPA
DANAZOL
NIMESULIDE
ROXARSONE
SULFANILAM..
LAMOTRIGINE
TRIAMTERENE
IRSOGLADIN..
GUANABENZ
PEMOLINE
1 non-ICM Obj