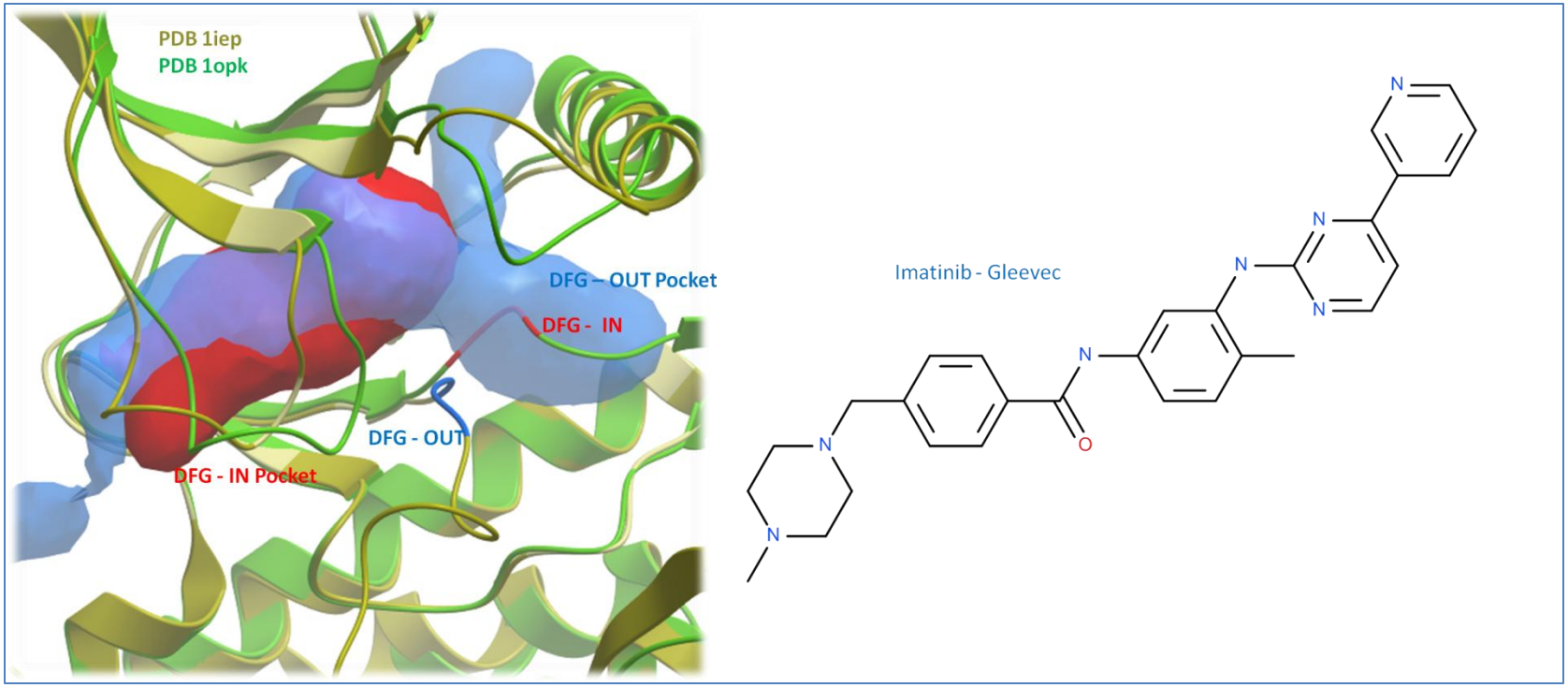
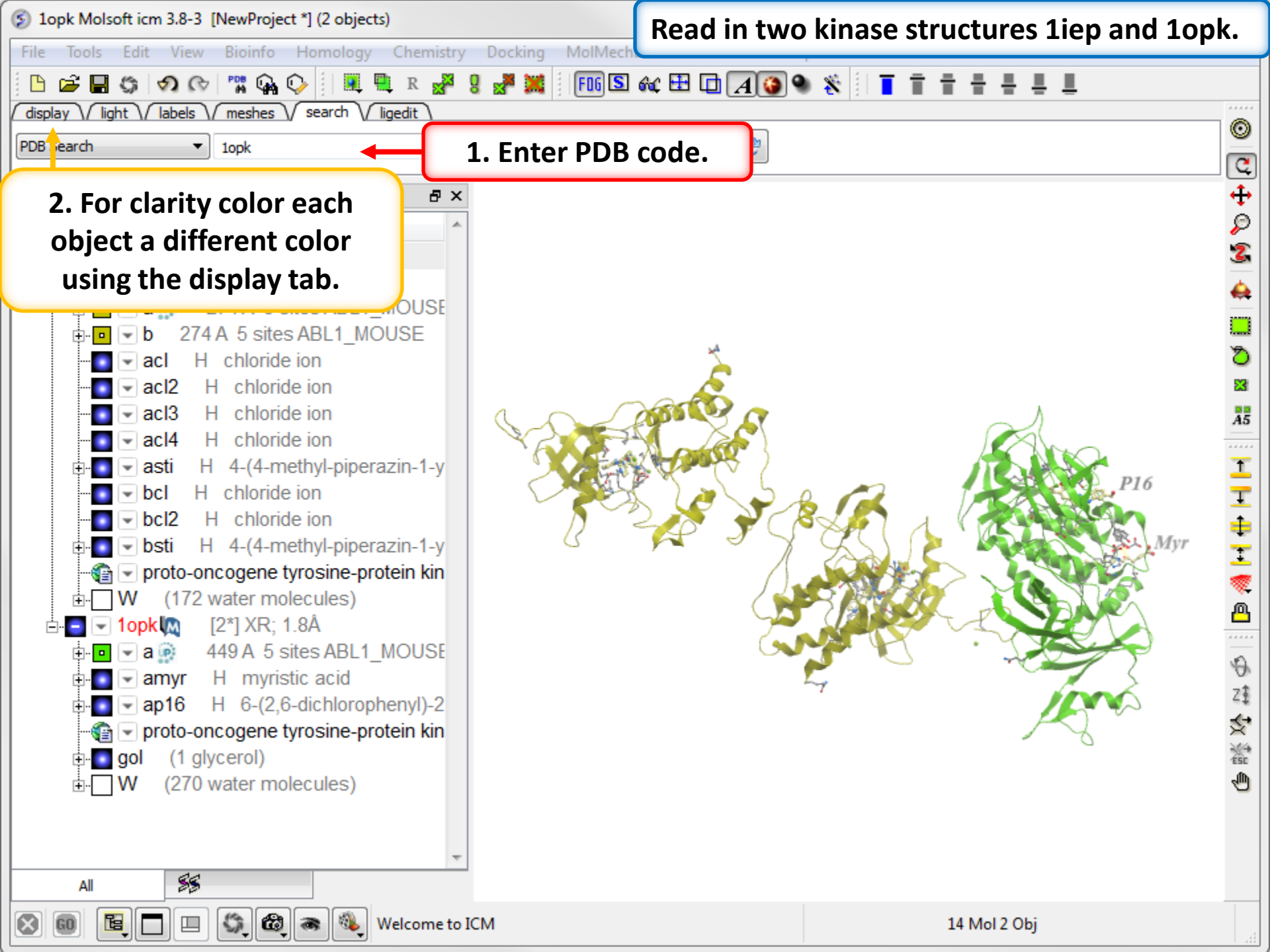
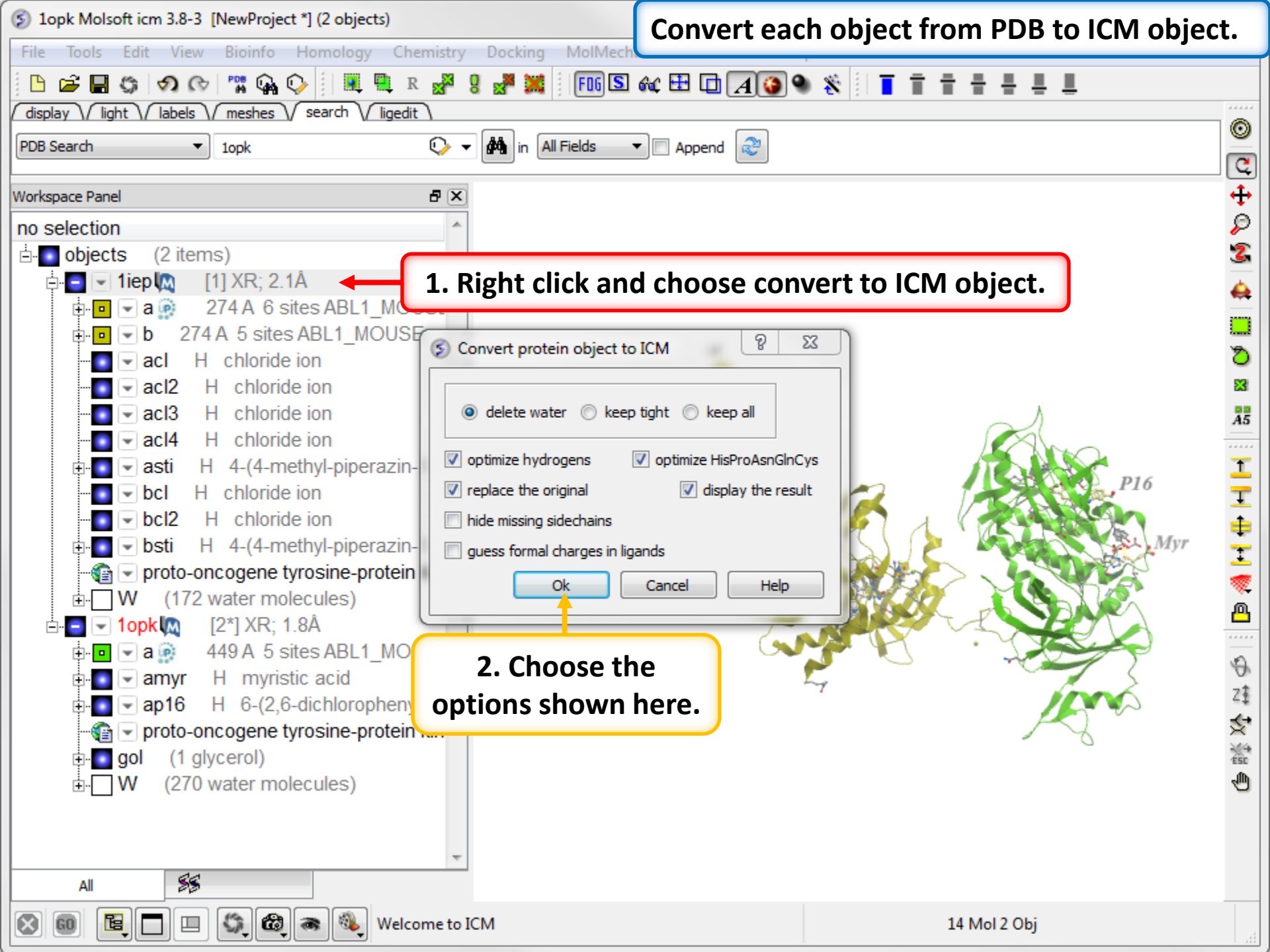
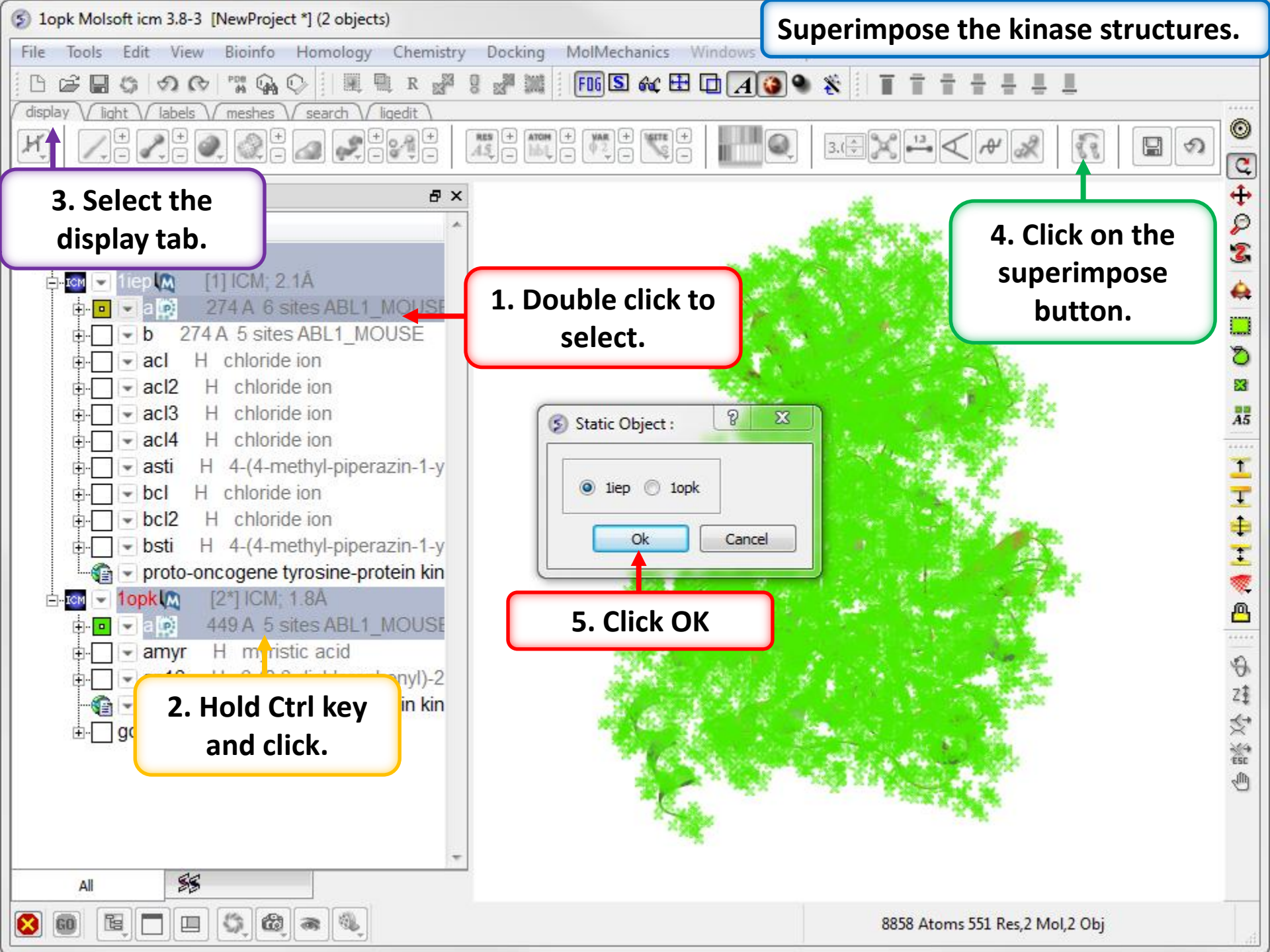
Protein Structure Analysis

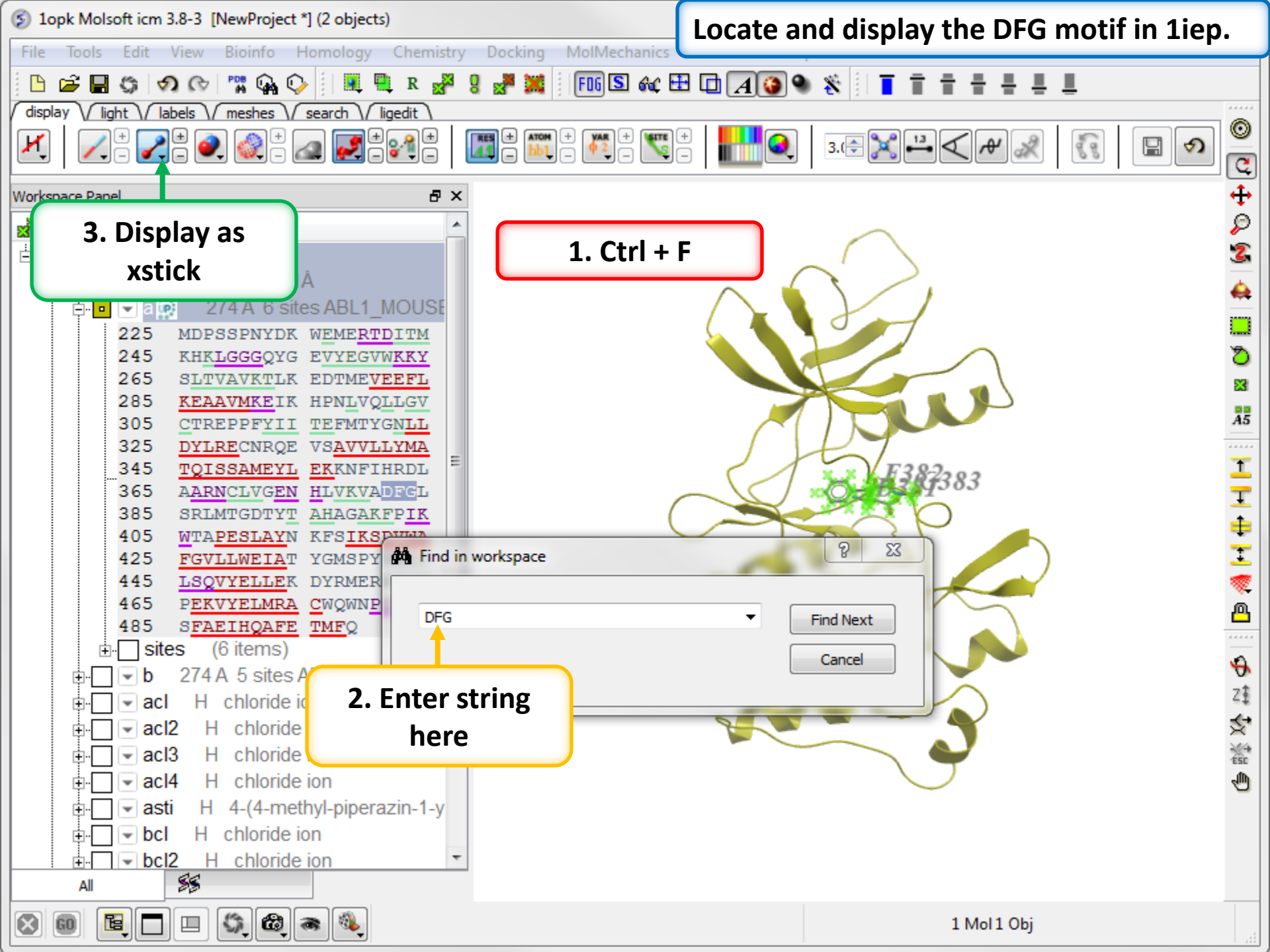


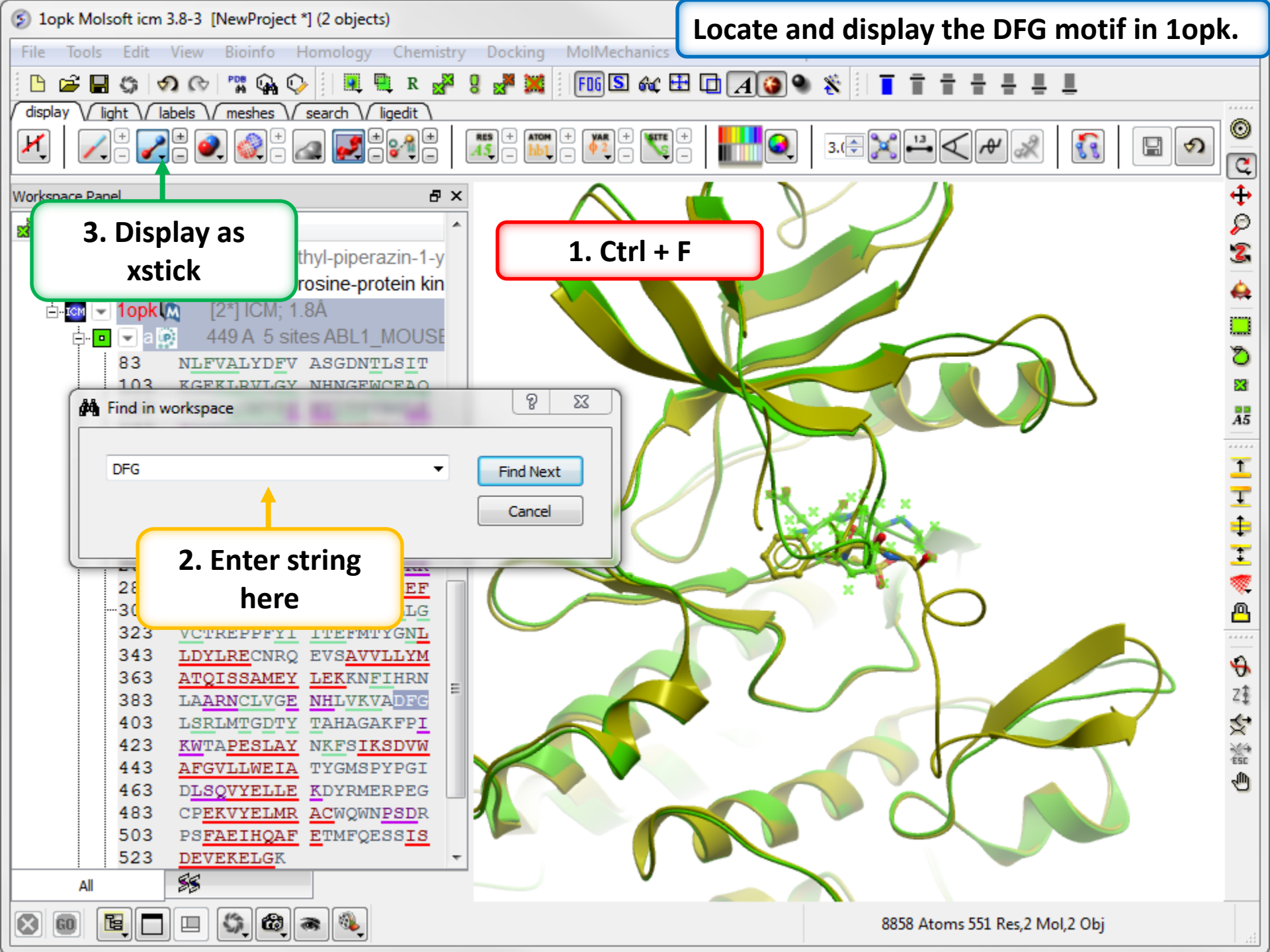
The positioning of the DFG motif in the activation loop of a protein kinase has an effect on the size and properties of the ATP binding pocket. Most kinase inhibitors target the kinase with the DFG inwards to the ATP binding site. Type-II inhibitors target the site where the DFG motif is in the out position which opens up the pocket and provides additional hydrophobic binding sites. Targeting DFG-out conformations can improve inhibitor specificity and slower-off rates.

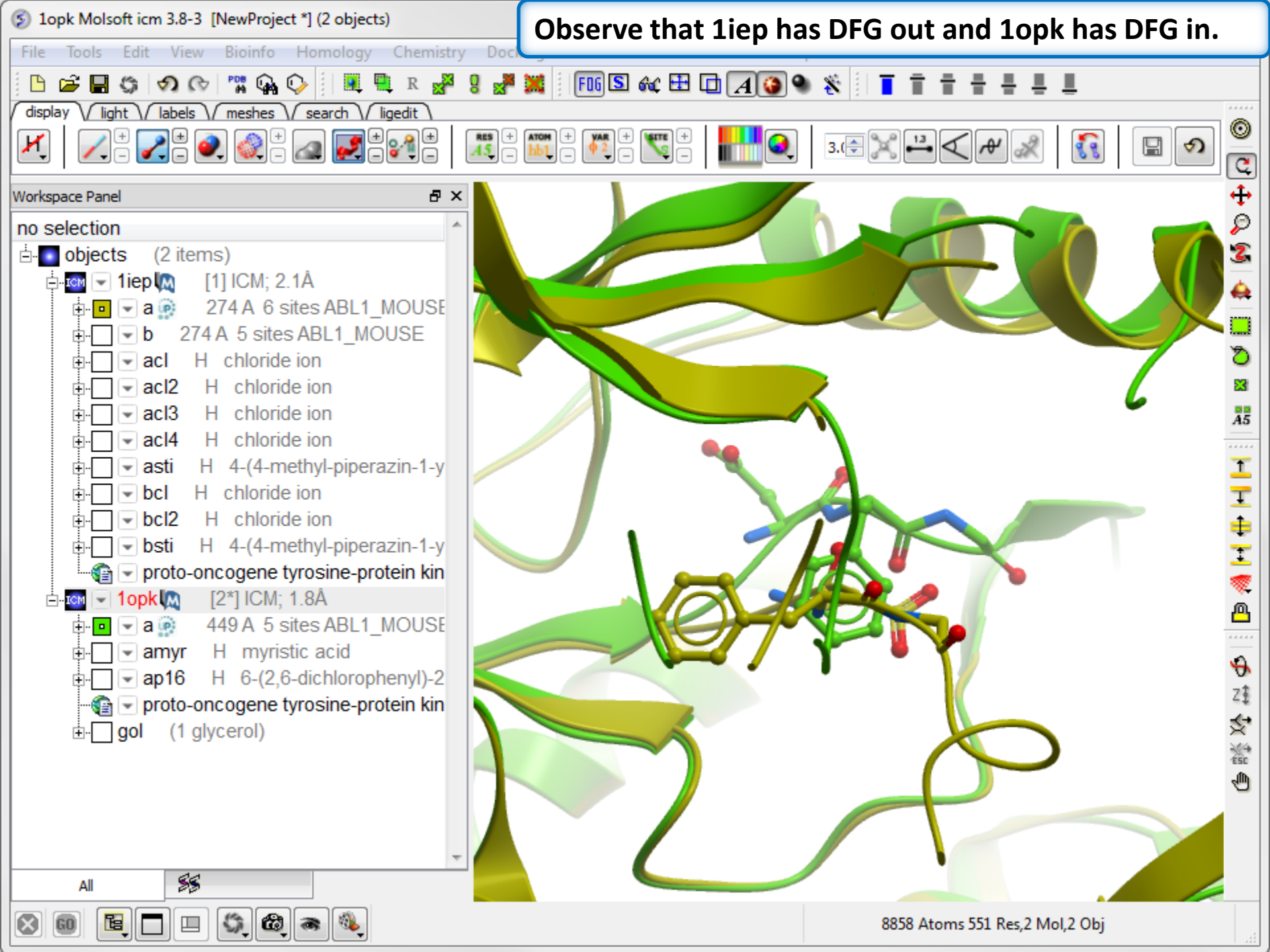

1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Read in two kinase structures 1iep and 1opk.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMech
display light labels meshes search ligedit
PDB search
1opk
1. Enter PDB code.
2. For clarity color each object a different color using the display tab.
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
bcl2 H chloride ion
bsti H 4-(4-methyl-piperazin-1-y
proto-oncogene tyrosine-protein kin
W (172 water molecules)
1opk [2*] XR; 1.8Å
a 449 A 5 sites ABL1_MOUSE
amyr H myristic acid
ap16 H 6-(2,6-dichlorophenyl)-2
proto-oncogene tyrosine-protein kin
gol (1 glycerol)
W (270 water molecules)
P16
Myr
All
Welcome to ICM
14 Mol 2 Obj

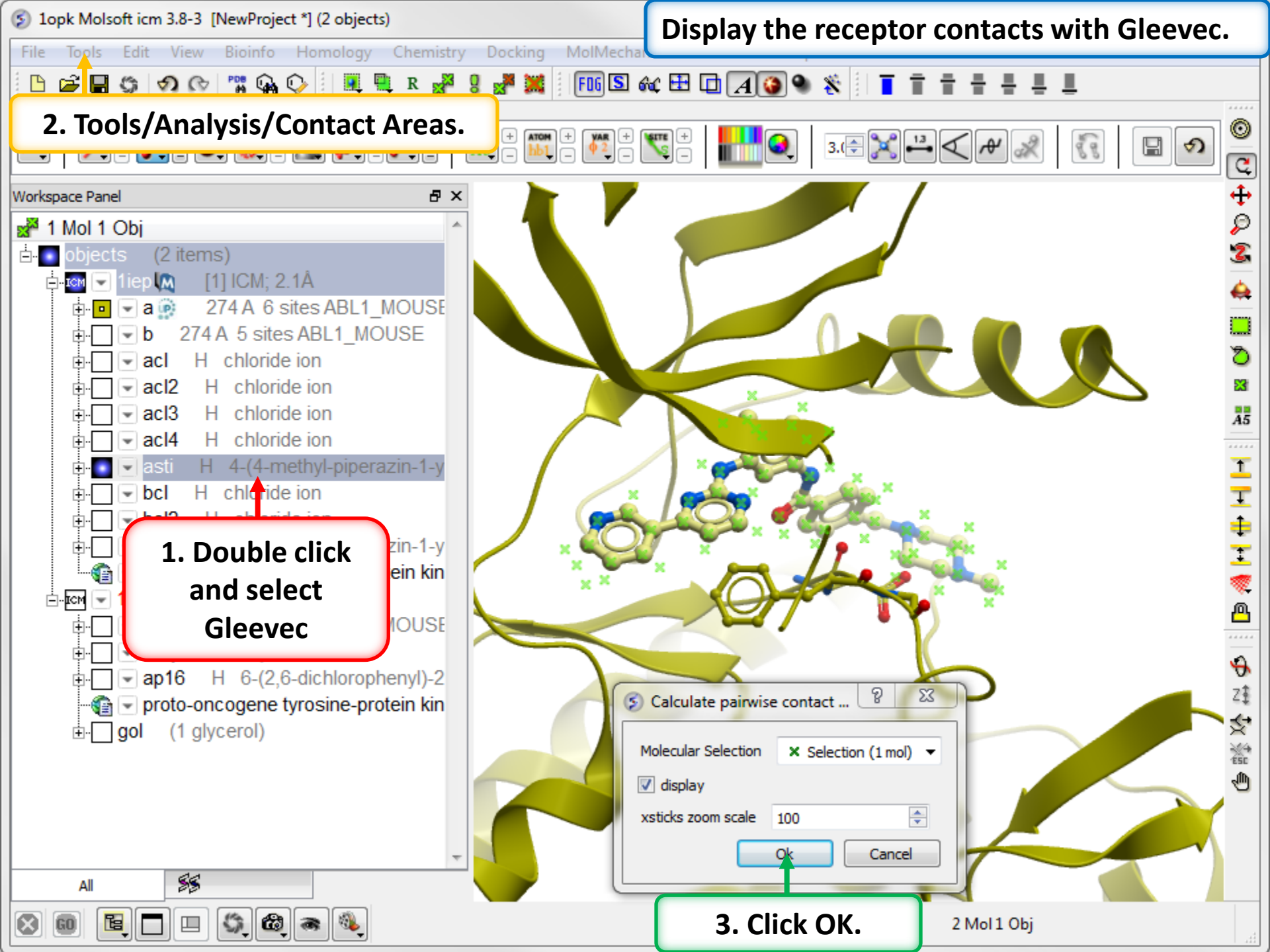

1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Convert each object from PDB to ICM object.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMech
display light labels meshes search ligedit
PDB Search
1opk
in
All Fields
Append
Workspace Panel
no selection
objects (2 items)
1iep [1] XR; 2.1Å
a 274 A 6 sites ABL1_MO
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-
bcl H chloride ion
bcl2 H chloride ion
bsti H 4-(4-methyl-piperazin-
proto-oncogene tyrosine-protein
W (172 water molecules)
1opk [2*] XR; 1.8Å
a 449 A 5 sites ABL1_MO
amyr H myristic acid
ap16 H 6-(2,6-dichlorophen
proto-oncogene tyrosine-protein
gol (1 glycerol)
W (270 water molecules)
1. Right click and choose convert to ICM object.
Convert protein object to ICM
delete water
keep tight
keep all
optimize hydrogens
optimize HisProAsnGlnCys
replace the original
display the result
hide missing sidechains
guess formal charges in ligands
Ok
Cancel
Help
2. Choose the options shown here.
P16
Myr
All
Welcome to ICM
14 Mol 2 Obj

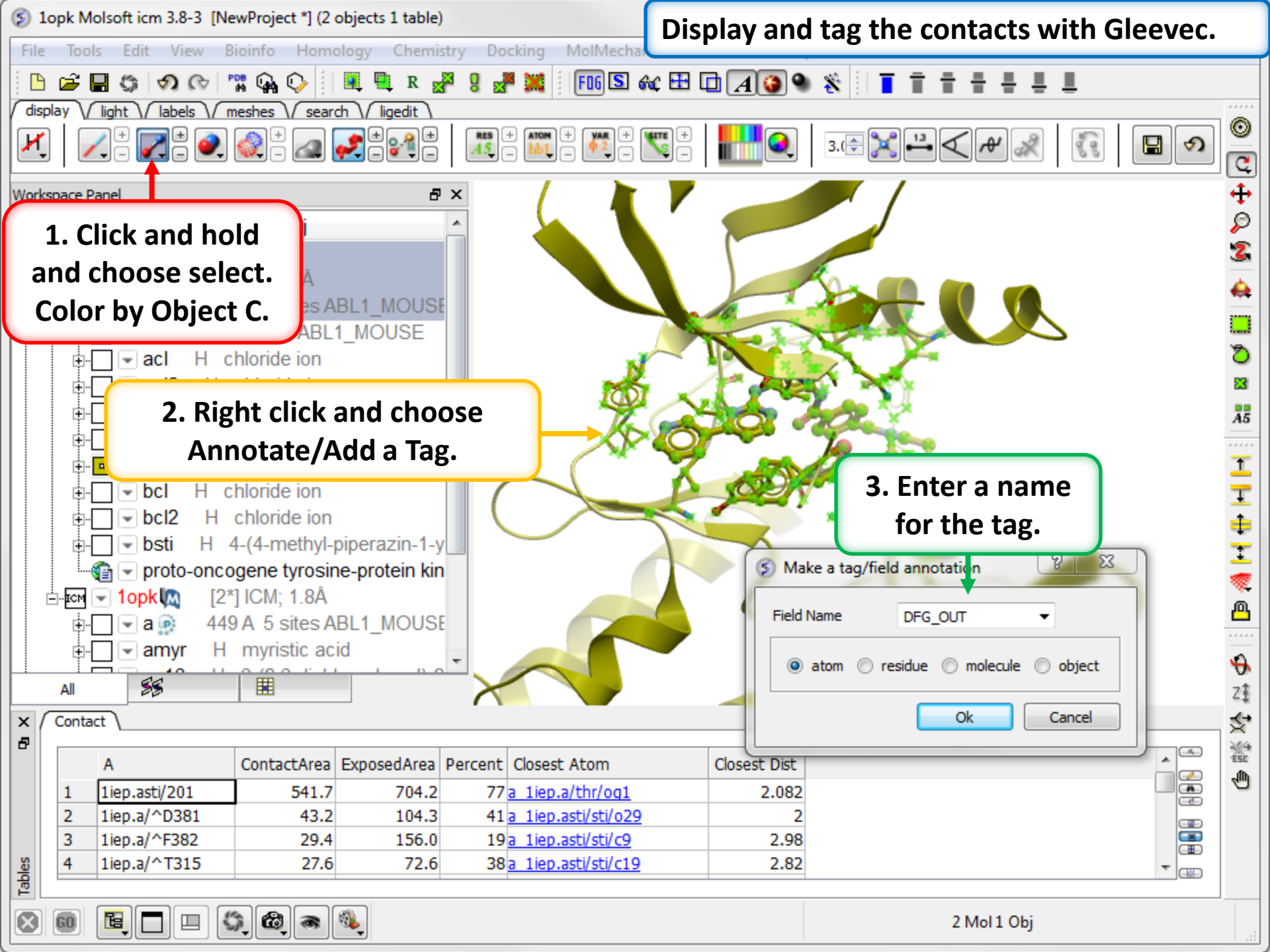

1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Superimpose the kinase structures.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMechanics Windows
display light labels meshes search ligedit
3. Select the display tab.
1iep [1] ICM; 2.1Å
a 274 A 6 sites ABL1_MOUSE
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
bcl2 H chloride ion
bsti H 4-(4-methyl-piperazin-1-y
proto-oncogene tyrosine-protein kin
1opk [2*] ICM; 1.8Å
a 449 A 5 sites ABL1_MOUSE
amyr H myristic acid
1. Double click to select.
2. Hold Ctrl key and click.
4. Click on the superimpose button.
Static Object :
1iep 1opk
Ok Cancel
5. Click OK
All
8858 Atoms 551 Res,2 Mol,2 Obj


1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Locate and display the DFG motif in 1iep.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit
Workspace Panel
3. Display as xstick
1. Ctrl + F
274 A 6 sites ABL1_MOUSE
225 MDPSSPNYDK WEMERTDITM
245 KHKLGGGQYG EVYEGVWKKY
265 SLTVAVKTLK EDTMEVEEFL
285 KEAAVMKEIK HPNLVQLLGV
305 CTREPPFYII TEFMTYGNLL
325 DYLRECNRQE VSAVVLLYMA
345 TQISSAMEYL EKKNFIHRDL
365 AARNCLVGEN HLVKVADFGL
385 SRLMTGDTYT AHAGAKFPIK
405 WTAPESLAYN KFSIKSDVWA
425 FGVLLWEIAT YGMSPY
445 LSQVYELLEK DYRMER
465 PEKVYELMRA CWQWNP
485 SFAEIHQAFE TMFQ
sites (6 items)
b 274 A 5 sites A
acl H chloride i
acl2 H chloride
acl3 H chloride
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
bcl2 H chloride ion
All
Find in workspace
DFG
Find Next
Cancel
2. Enter string here
F382
G383
1 Mol 1 Obj

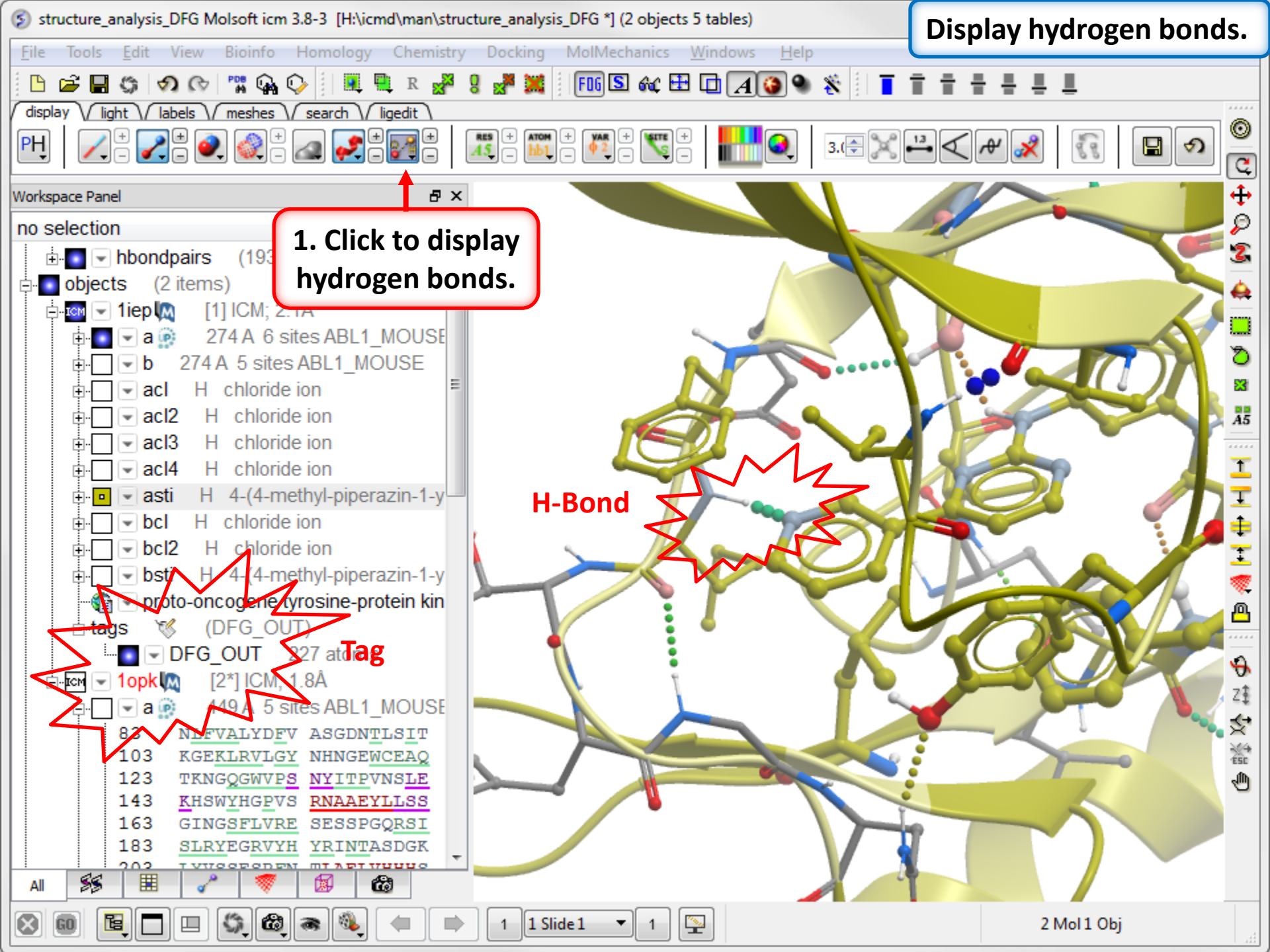

1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Locate and display the DFG motif in 1opk.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMechanics
display light labels meshes search ligedit
Workspace Panel
3. Display as xstick
1. Ctrl + F
1opk [2*] ICM; 1.8Å
449 A 5 sites ABL1_MOUSE
83 NLFVALYDFV ASGDNTLSIT
Find in workspace
DFG
Find Next
Cancel
2. Enter string here
323 VCTREPPFYI TTEFMTYGNL
343 LDYLRECNRQ EVSAVVLLYM
363 ATQISSAMEY LEKKNFIHRN
383 LAARNCLVGE NHLVKVADFG
403 LSRLMTGDTY TAHAGAKFPI
423 KWTAPESLAY NKFSIKSDVW
443 AFGVLLWEIA TYGMSPYPGI
463 DLSQVYELLE KDYRMERPEG
483 CPEKVYELMR ACWQWNPSDR
503 PSFAEIHQAF ETMFQESSIS
523 DEVEKELGK
All
8858 Atoms 551 Res,2 Mol,2 Obj

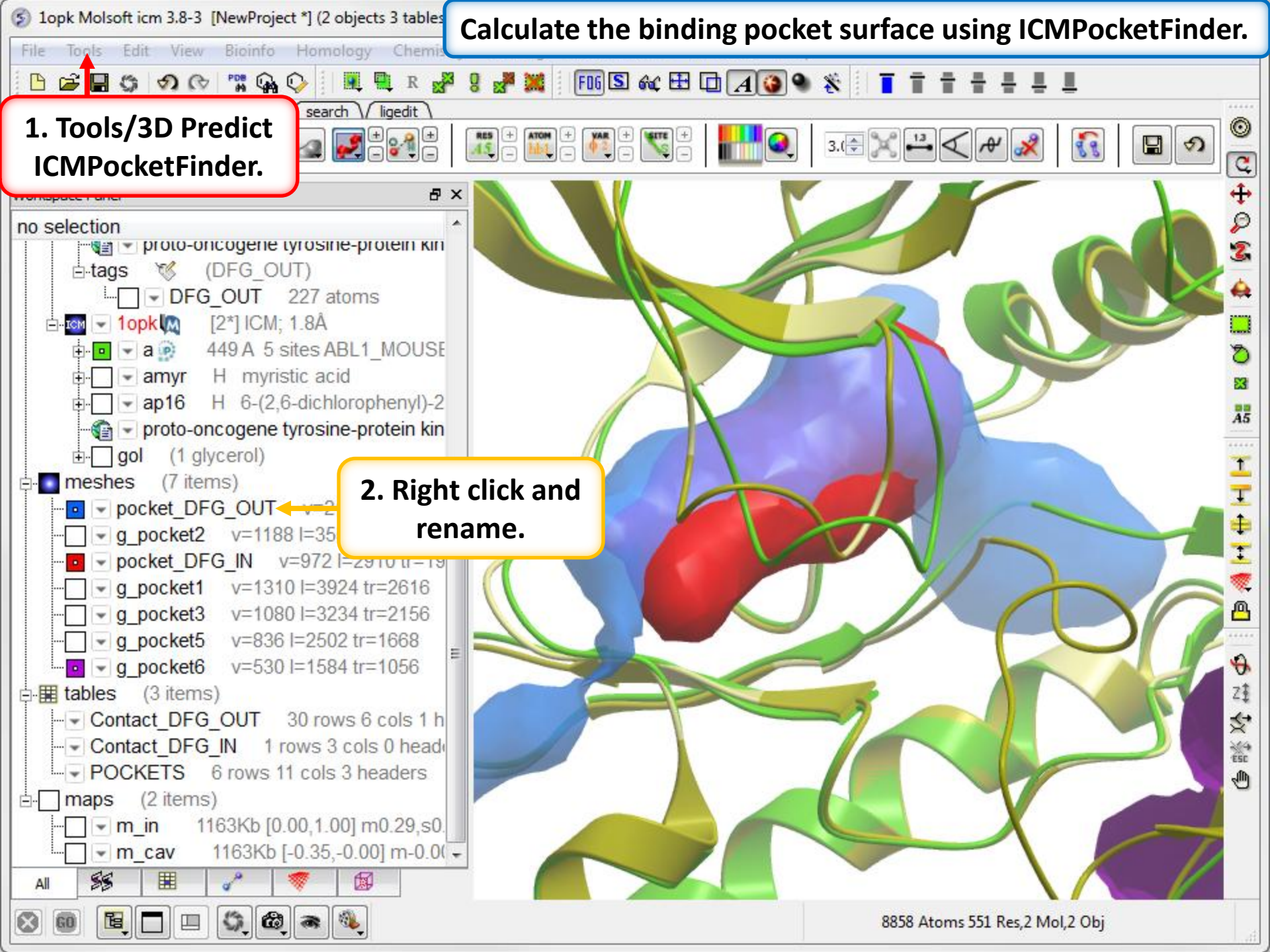

1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Observe that 1iep has DFG out and 1opk has DFG in.
File Tools Edit View Bioinfo Homology Chemistry
display light labels meshes search ligedit
Workspace Panel
no selection
objects (2 items)
1iep [1] ICM; 2.1Å
a 274 A 6 sites ABL1_MOUSE
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
bcl2 H chloride ion
bsti H 4-(4-methyl-piperazin-1-y
proto-oncogene tyrosine-protein kin
1opk [2*] ICM; 1.8Å
a 449 A 5 sites ABL1_MOUSE
amyr H myristic acid
ap16 H 6-(2,6-dichlorophenyl)-2
proto-oncogene tyrosine-protein kin
gol (1 glycerol)
All
8858 Atoms 551 Res,2 Mol,2 Obj


1opk Molsoft icm 3.8-3 [NewProject *] (2 objects)
Display the receptor contacts with Gleevec.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMecha
2. Tools/Analysis/Contact Areas.
Workspace Panel
1 Mol 1 Obj
objects (2 items)
1iep [1] ICM; 2.1Å
a 274 A 6 sites ABL1_MOUSE
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
ap16 H 6-(2,6-dichlorophenyl)-2
proto-oncogene tyrosine-protein kin
gol (1 glycerol)
1. Double click and select Gleevec
Calculate pairwise contact ...
Molecular Selection
Selection (1 mol)
display
xsticks zoom scale
100
Ok
Cancel
3. Click OK.
All
2 Mol 1 Obj



	A	ContactArea	ExposedArea	Percent	Closest Atom	Closest Dist
1	1iep.asti/201	541.7	704.2	77	a 1iep.a/thr/oq1	2.082
2	1iep.a/^D381	43.2	104.3	41	a 1iep.asti/sti/o29	2
3	1iep.a/^F382	29.4	156.0	19	a 1iep.asti/sti/c9	2.98
4	1iep.a/^T315	27.6	72.6	38	a 1iep.asti/sti/c19	2.82


structure_analysis_DFG Molsoft icm 3.8-3 [H:\icmd\man\structure_analysis_DFG *] (2 objects 5 tables)
Display hydrogen bonds.
File Tools Edit View Bioinfo Homology Chemistry Docking MolMechanics Windows Help
display light labels meshes search ligedit
Workspace Panel
no selection
hbondpairs
objects (2 items)
1iep [1] ICM;
a 274 A 6 sites ABL1_MOUSE
b 274 A 5 sites ABL1_MOUSE
acl H chloride ion
acl2 H chloride ion
acl3 H chloride ion
acl4 H chloride ion
asti H 4-(4-methyl-piperazin-1-y
bcl H chloride ion
bcl2 H chloride ion
proto-oncogene tyrosine-protein kin
tags (DFG_OUT)
DFG_OUT
1opk [2*] ICM; 1.8Å
a 449 A 5 sites ABL1_MOUSE
1. Click to display hydrogen bonds.
H-Bond
Tag
All
1 Slide 1
2 Mol 1 Obj


Calculate the binding pocket surface using ICMPocketFinder.
1. Tools/3D Predict ICMPocketFinder.
2. Right click and rename.
1opk Molsoft icm 3.8-3 [NewProject *] (2 objects 3 tables
File Tools Edit View Bioinfo Homology
search ligedit
no selection
tags (DFG_OUT)
DFG_OUT 227 atoms
1opk [2*] ICM; 1.8Å
a 449 A 5 sites ABL1_MOUSE
amyr H myristic acid
ap16 H 6-(2,6-dichlorophenyl)-2
proto-oncogene tyrosine-protein kin
gol (1 glycerol)
meshes (7 items)
pocket_DFG_OUT
g_pocket2 v=1188 l=35
pocket_DFG_IN v=972
g_pocket1 v=1310 l=3924 tr=2616
g_pocket3 v=1080 l=3234 tr=2156
g_pocket5 v=836 l=2502 tr=1668
g_pocket6 v=530 l=1584 tr=1056
tables (3 items)
Contact_DFG_OUT 30 rows 6 cols 1 h
Contact_DFG_IN 1 rows 3 cols 0 head
POCKETS 6 rows 11 cols 3 headers
maps (2 items)
m_in 1163Kb [0.00,1.00] m0.29,s0
m_cav 1163Kb [-0.35,-0.00] m-0.0
All
8858 Atoms 551 Res,2 Mol,2 Obj