



Becoming a power user of Torch

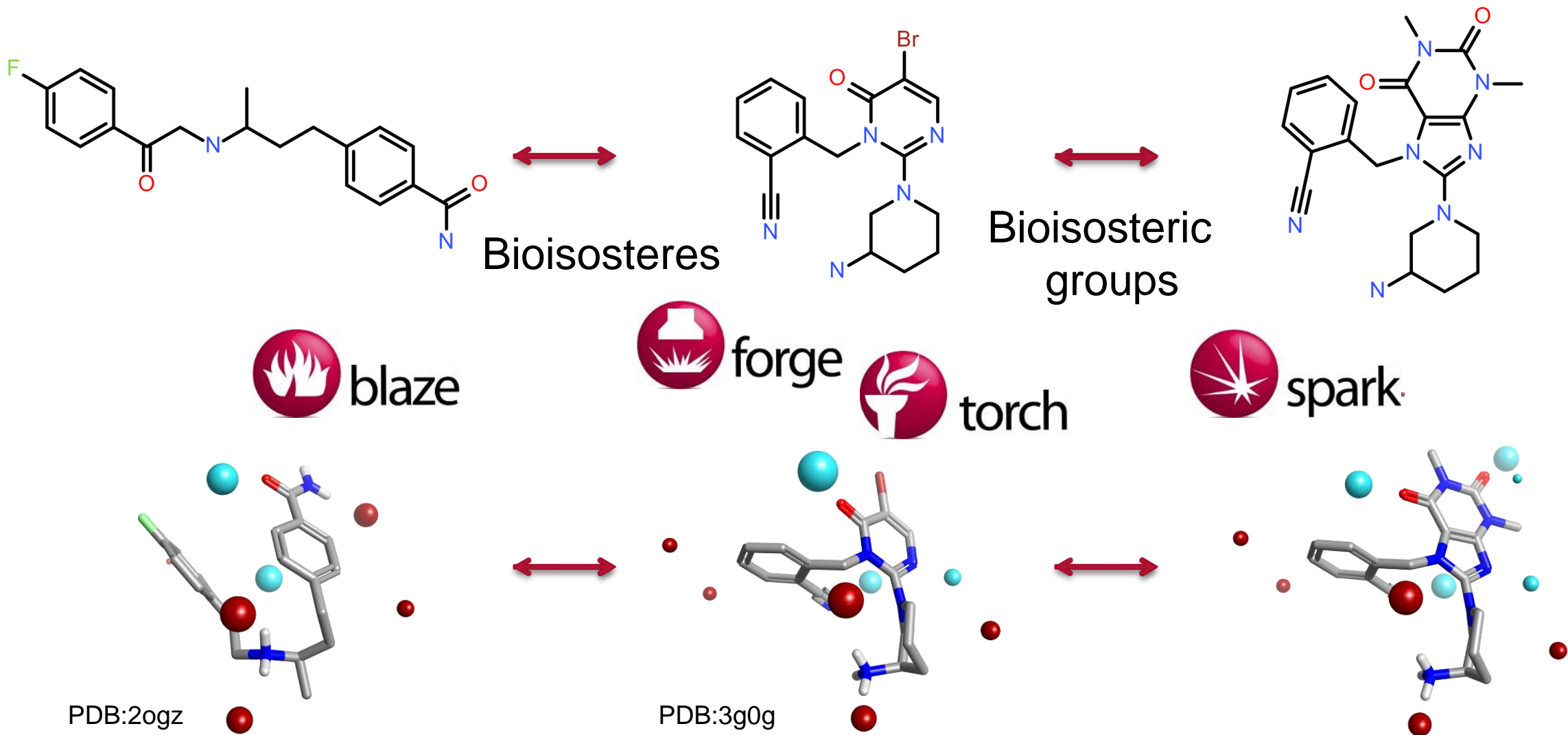
Cresset European User Group Meeting – Workshops

June 2016

Files for this workshop

- > The files used in this workshop are available for download on request
- > Please send an email to enquiries@cresset-group.com stating the name of the workshop

Comparing structurally disparate molecules





Understanding and using SAR to improve molecule design and intellectual property



Using electrostatics and shape to gain new perspectives on molecular design

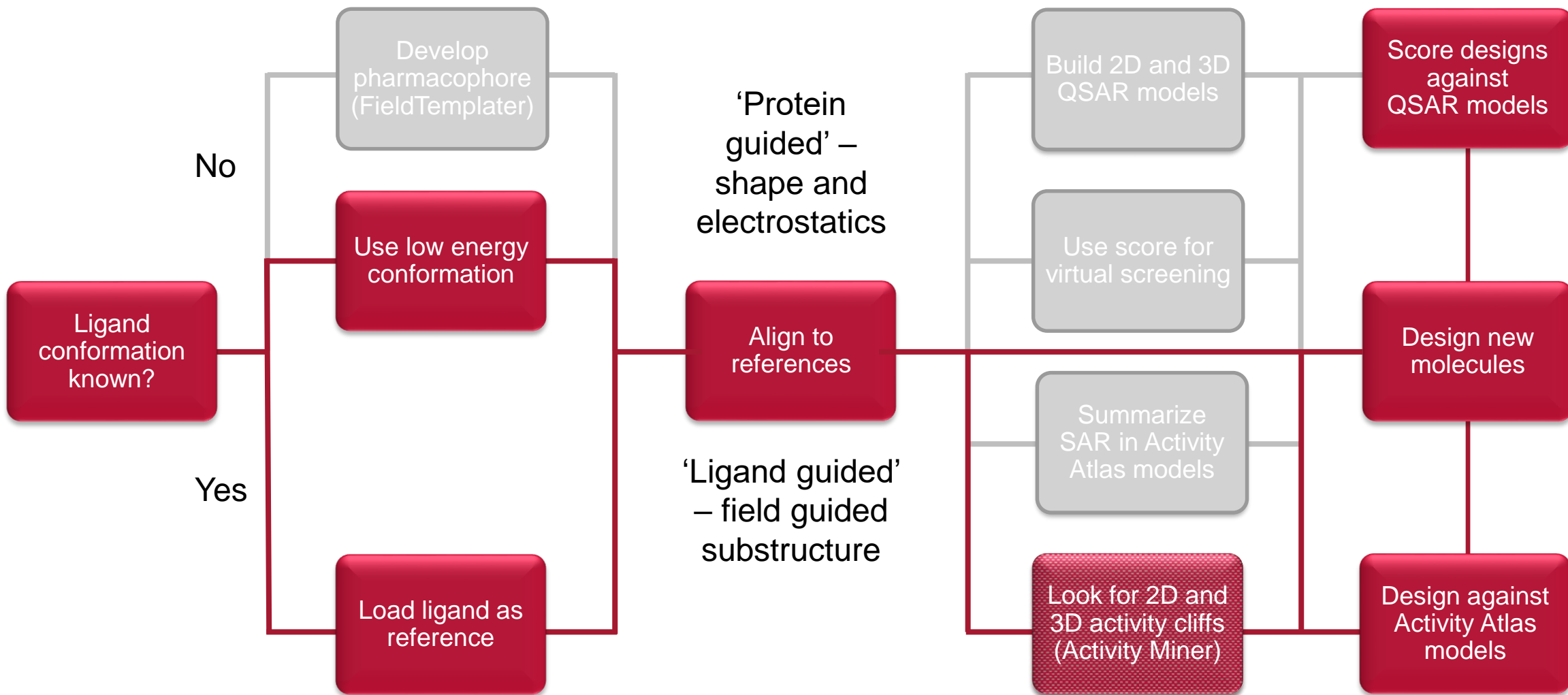
Understand structure-activity using Forge



torch

- > Uses ligand alignment as a basis for design and SAR interpretation
- > Ligands aligned to a reference or 'template' using
 - > Electrostatics and shape
 - > Shape only
 - > Substructure
- > Partner to Forge – create models in Forge, use in Torch
- > Align single chemotype
 - > Understanding design of new molecules
 - > Decipher complex SAR
- > Aligned many chemotypes
 - > Relating activities from different series
 - > SAR transfer

Torch workflow



Torch features

- > Combine multiple numerical properties into a single score
- > Create a project profile for physico-chemical (or other) properties
- > Add properties from external server
- > Color by fit to profile
 - > 2D
 - > 3D
- > Interactive scatter plots and histograms
- > Storyboard to record important 3D views
- > Split datasets into roles
- > Tag molecules across roles
- > Record experiments in Project notes
- > Design in 3D
 - > Reject designs that make no sense in 3D
- > No protein required – wholly ligand based approach
- > Protein can be used data used in visualization
- > Electrostatic focus reveals more detail than available from 2D design
- > Enables hypothesis led design

In this workshop

- > We will be focussing on

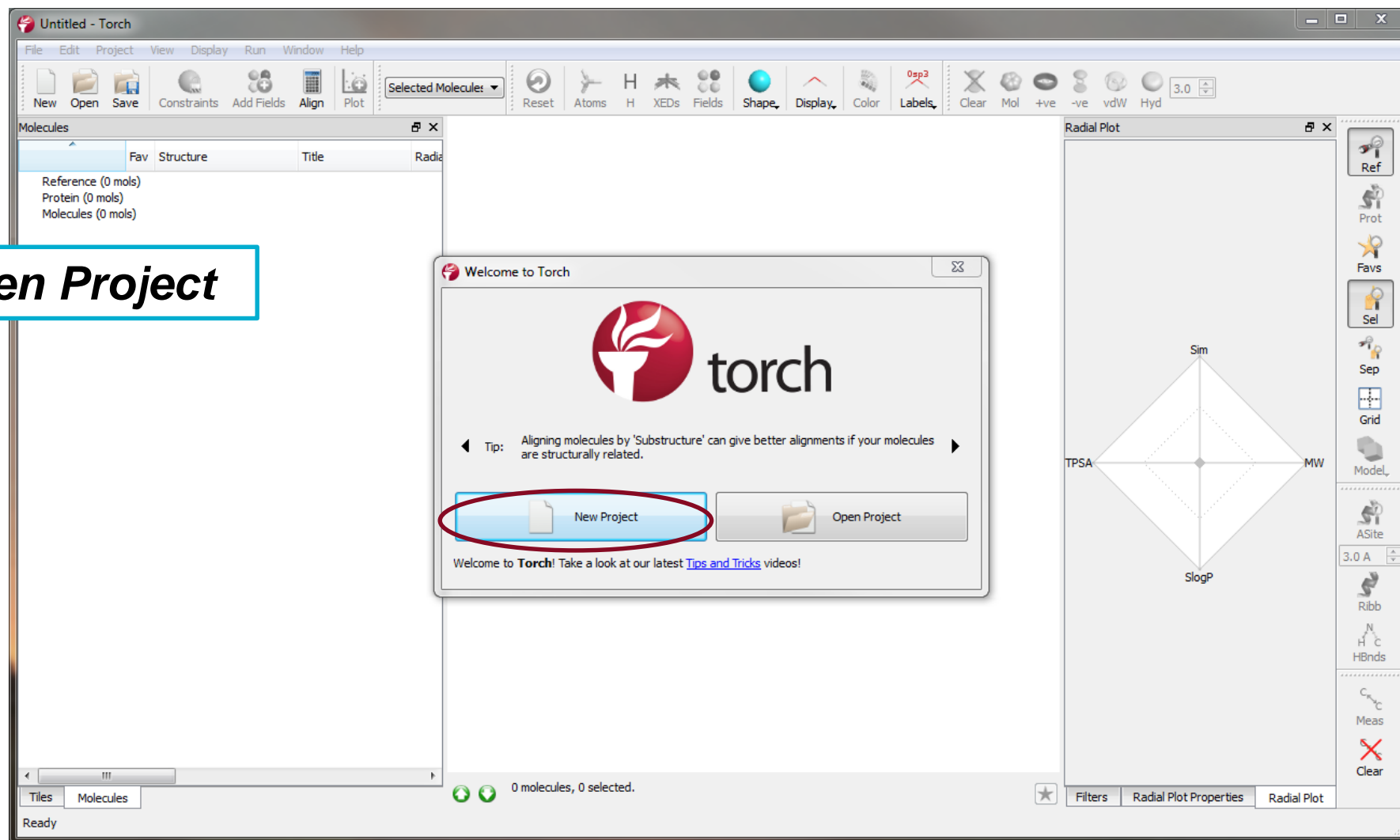
- > Advanced alignment options
- > More advanced parts of the GUI
- > the Activity Miner module for SAR interpretation

- > We will not consider

- > standard alignments
- > standard design tasks

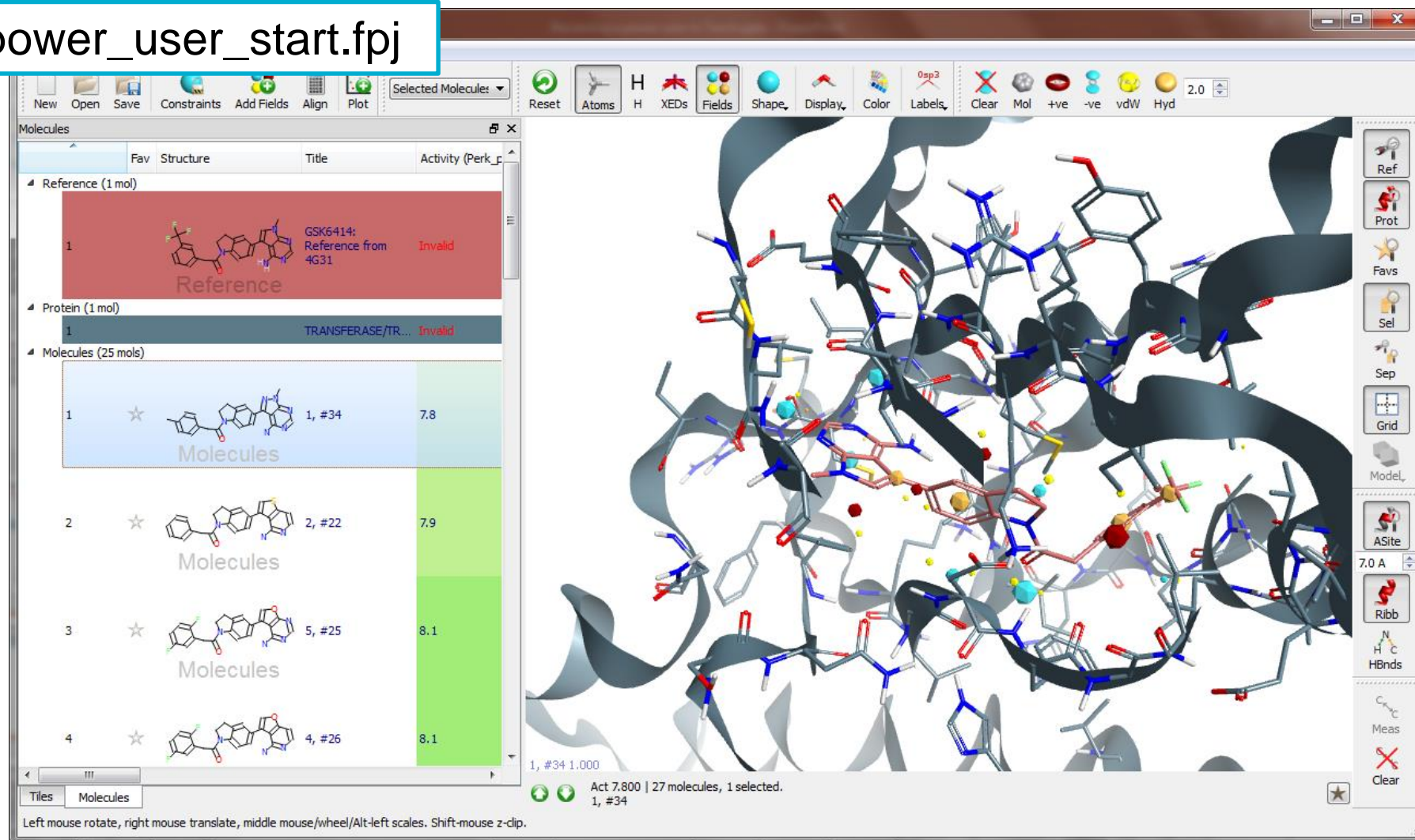
Launch Torch

Click ***Open Project***



Open a Torch project

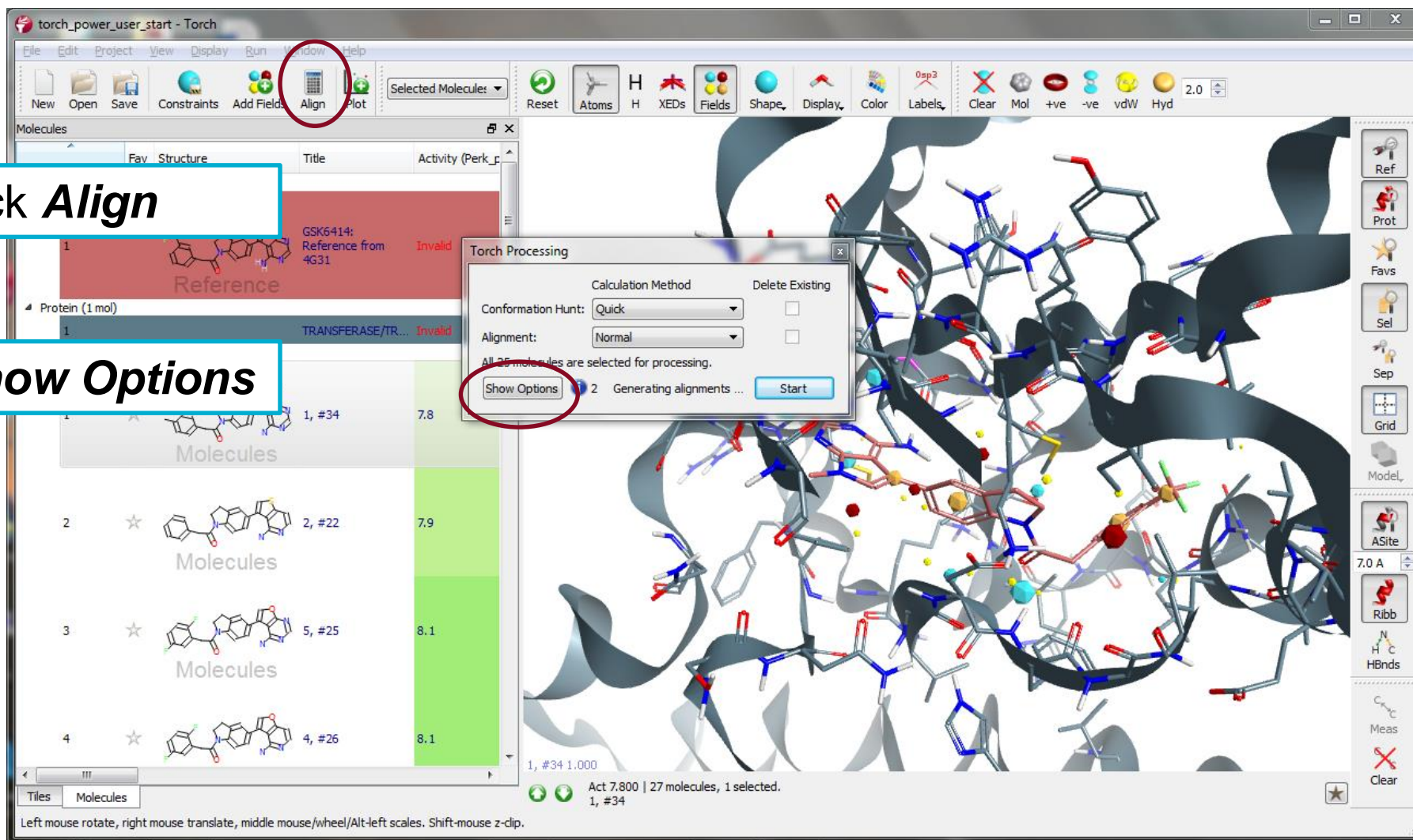
Torch_power_user_start.fpj



Align all ligands using substructure

Click **Align**

Click **Show Options**



Align all ligands using substructure

Conformation Hunt Tab

Torch Processing

Conformation Hunt Alignment

Calculation Method: Normal

Save As... Delete

☐ Delete existing conformations

☒ Perform Conformation Hunt

Maximum number of conformations: 100

No. of high-T dynamics runs for flexible rings: 5

Gradient cutoff for conformer minimization: 0.500 kcal/mol/A

Filter duplicate conformers at RMS: 0.30 A

Energy window: 6.00 kcal/mol

Acyclic secondary amide handling: Force amides trans

Turn off Coulombic and attractive vdW forces: ☒

Use external tool for conformer generation: ☐

Hide Options

2 Generating alignments for 25 molecules

Start

Choose **Accurate**

Choose **Normal**

Alignment Tab

Torch Processing

Conformation Hunt Alignment

Calculation Method: Substructure

Save As... Delete

☐ Delete existing alignments

☒ Perform Alignment

Invert achiral imported confs: ☒

Take shortcuts in alignments: ☐

☒ Maximum-common-substructure conformers and alignment

Matching rules: Normal (element + hybridisation)

Allow conformations to move: ☒

Perform Scoring

Score method for multiple references: Average

Fraction of score from shape similarity: 0.50

Hardness of protein excluded volume: Soft

Add/remove field constraints

Mark field points

Hide Options

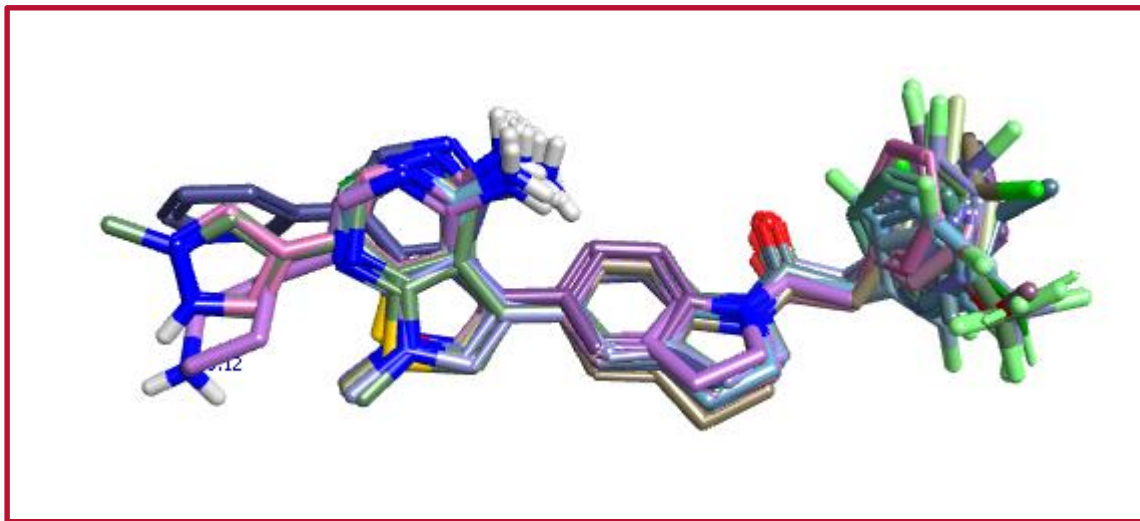
2 Generating conformations for 25 molecules

Start

Choose **Substructure**

Click **Start**

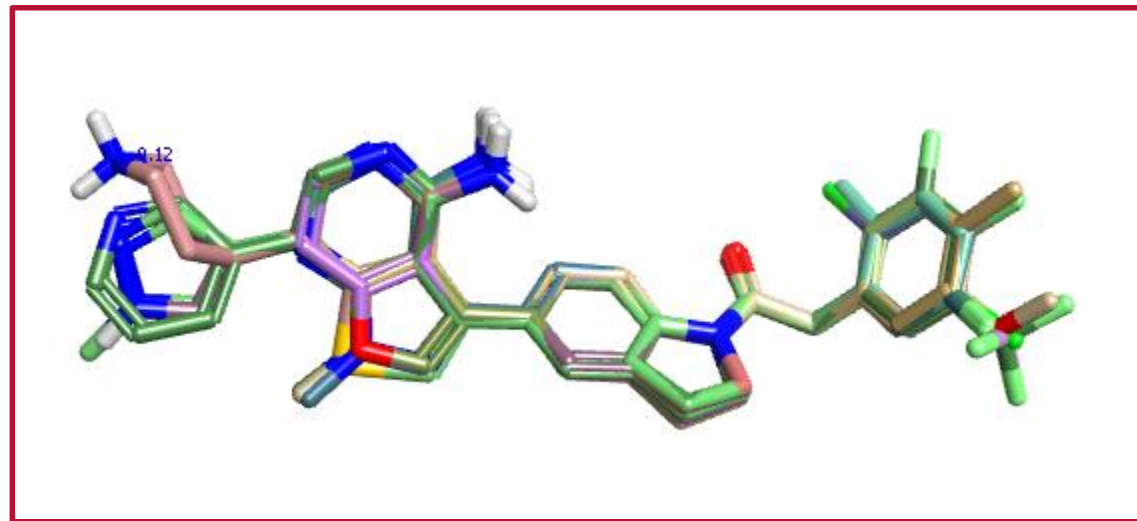
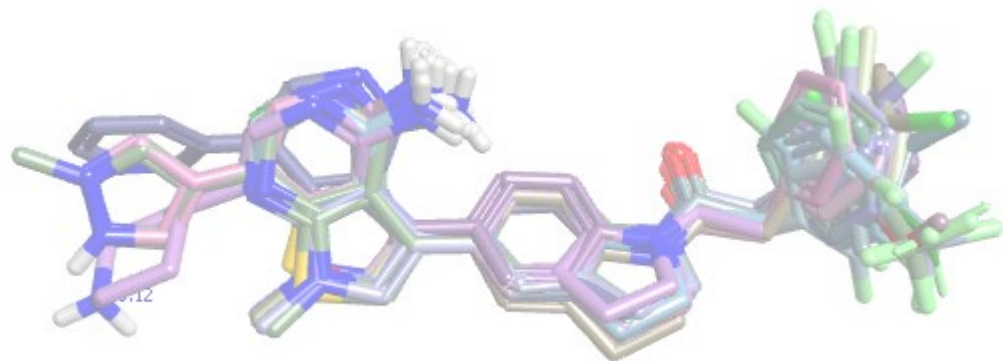
Protein or ligand-based alignment?



> Field-based alignment

- > Uses Cresset electrostatic, shape and hydrophobic field points to align
- > Scored 50% field-based similarity with 50% shape similarity
- > Independent of chemical structure
- > Meaningful score comparisons
- > Better for libraries that have structurally diverse compounds

Protein or ligand-based alignment?

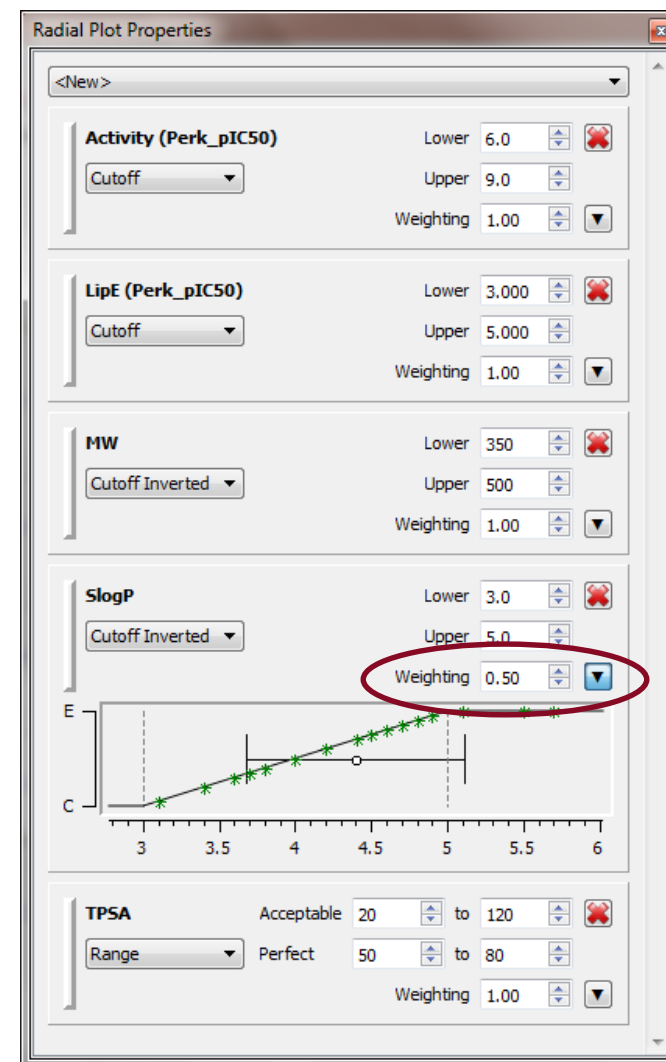
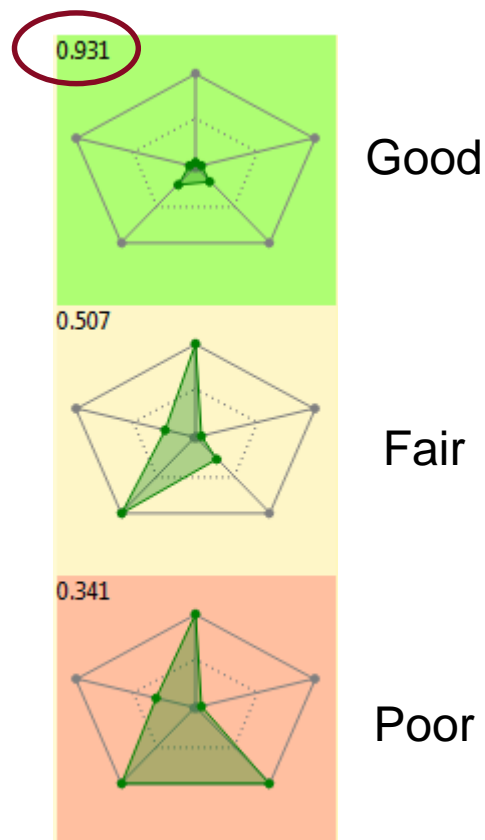


> Maximum common substructure alignment

- > Good for a library with a common core or concentric series
- > Common structural features in database molecules are mapped onto conformation of corresponding features in reference molecule
- > All other parts of the molecule are conformationally hunted
- > Field/shape based scoring
- > Score comparisons between molecules less useful


Radial Plot and multi-parameter optimization


- > Radial plot allows for simultaneous viewing of numerical parameters
- > By default, the smaller the area encased in green, the better the properties
- > Customizable
 - > Many numbers (up to ~15 works ok)
 - > Default and specific profiles
- > Overall fit summarized into a score



Minimize the calculation

Torch Processing

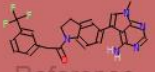
MCS Alignment:  26% - 6 minutes remaining

Scoring:  19% - 7 minutes remaining

[More Details](#) [Cancel](#) [Hide](#)

Click *Hide*

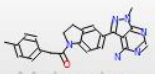
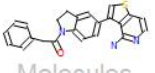
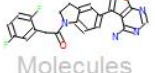
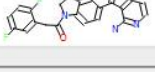
Reference (1 mol)

1  GSK6414: Reference from 4G31

Protein (1 mol)

1 TRANSFERASE/TR... Invalid

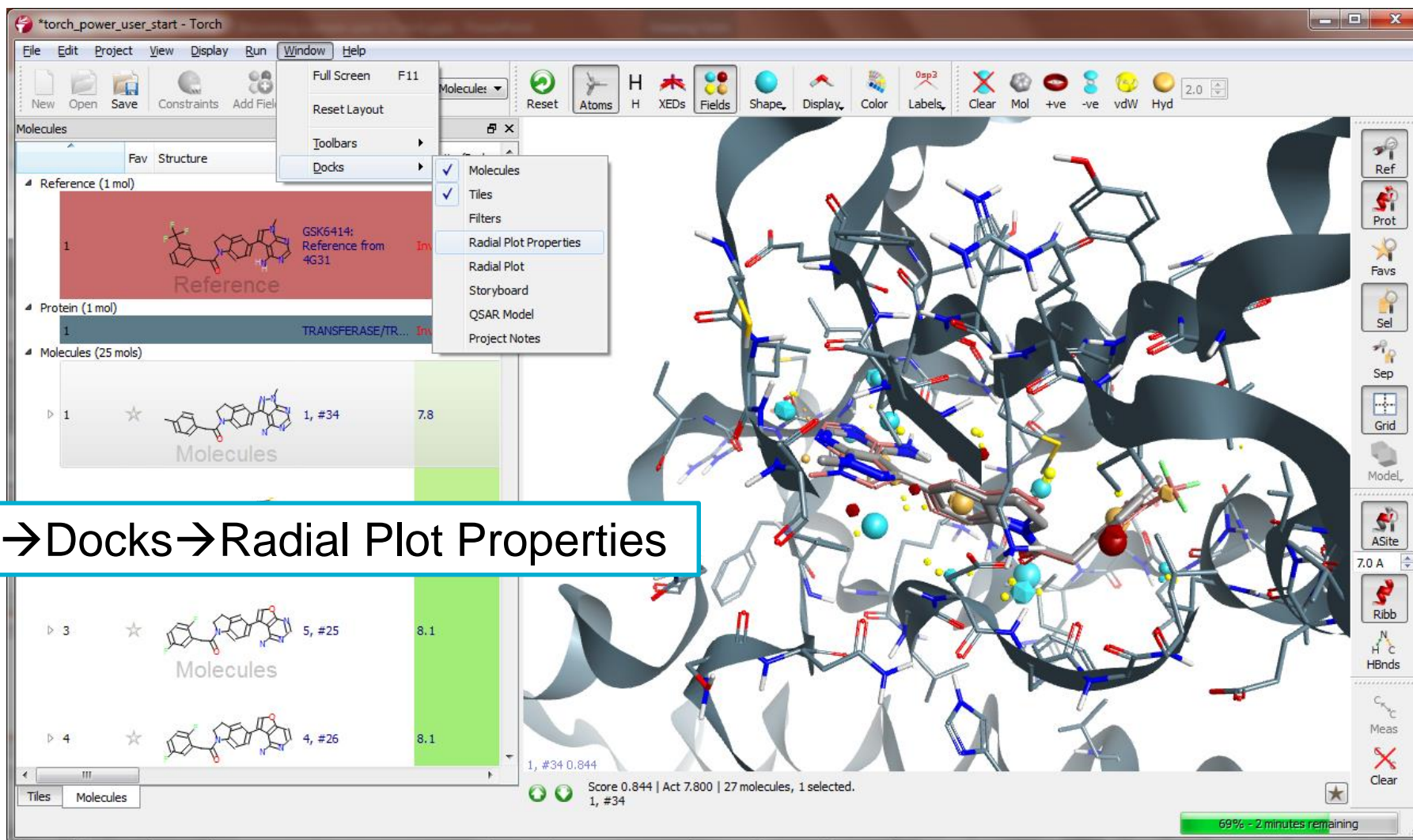
Molecules (25 mols)

1		1, #34	7.8
2		2, #22	7.9
3		5, #25	8.1
4		4, #26	8.1

Score 0.844 | Act 7.800 | 27 molecules, 1 selected.
1, #34

22% - 9 minutes remaining

Show the Radial Plot Properties window



Add flexibility and LE to the radial plot

Use the pull down to choose **Flexibility** and LE (Perk pIC50)

The screenshot displays the Torch software interface. The main window is titled "torch_power_user_start - Torch". The menu bar includes File, Edit, Project, View, Display, Run, Window, and Help. The toolbar contains icons for New, Open, Save, Constraints, Add Fields, Align, Plot, Selected Molecule, Reset, Atoms, H, XEDs, Fields, Shape, Display, Color, Labels, Clear, Mol, +ve, -ve, vdW, and Hyd. The interface is divided into several panels:

- Molecules Panel:** A table listing molecules with columns for Fav, Structure, Title, Activity (Perk_pIC50), and Radial Plot. The table is divided into "Reference (1 mol)" and "Protein (1 mol)" sections.
- Radial Plot Properties Panel:** A panel on the right side of the interface. It contains a list of properties: Confs, Excl Vol Pen, Field Penalty, Flexibility, FScore, FScore+P, FSim, IC50_nM, and LE (Perk_pIC50). The "Flexibility" and "LE (Perk_pIC50)" properties are highlighted. Below this list, there are settings for LipE (Perk_pIC50), MW, SlogP, and TPSA, each with a Cutoff Inverted dropdown and numerical input fields for Lower, Upper, and Weighting.
- Radial Plot:** A 3D visualization of a molecule (GSK6414) bound to a protein (TRANSFERASE/TR...). The plot shows the molecule's position relative to the protein's surface.

Fav	Structure	Title	Activity (Perk_pIC50)	Radial Plot
Reference (1 mol)				
1		GSK6414: Reference from 4G31	Invalid	0.328
Protein (1 mol)				
1		TRANSFERASE/TR...	Invalid	0
1, #34			7.8	0.745
2, #22			7.9	0.571
3		5, #25	8.1	0.698
4		4, #26	8.1	0.612

At the bottom of the interface, there is a status bar showing "Score 0.844 | Act 7.800 | 27 m" and "1, #34".

Set the radial plot order and weighting

Use the vertical bar
to drag properties up
and down

Set the order =
Activity, LiPE, MW,
SlogP, TPSA,
Flexibility

Radial Plot Properties

<New>

Activity (Perk_pIC50) Lower 6.0 Upper 9.0 Weighting 1.00

Cutoff

LipE (Perk_pIC50) Lower 3.000 Upper 5.000 Weighting 1.00

Cutoff

LE (Perk_pIC50) Lower 0.15 Upper 0.00 Weighting 0.00

Cutoff

MW Lower 350 Upper 500 Weighting 1.00

Cutoff Inverted

SlogP Lower 3.0 Upper 5.0 Weighting 0.50

Cutoff Inverted

TPSA Acceptable 20 to 120 Perfect 50 to 80 Weighting 1.00

Range

Flexibility Lower 4.0 Upper 6.0 Weighting 1.00

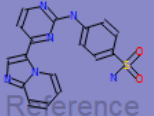
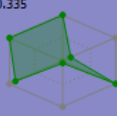
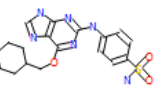
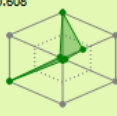
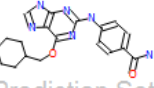
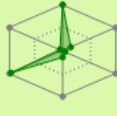
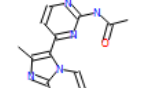
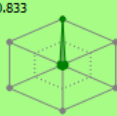
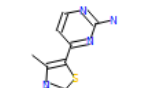
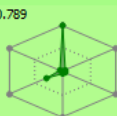
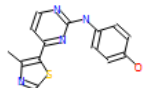
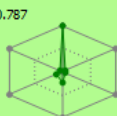

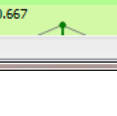
Cutoff Inverted

Set the weight of LE
to zero

Once complete, the
window can be
closed

Coloring in the Molecules Table

Note colours follow the fit to radial plot

	Fav	Structure	Title	Activity (Ki (nM))	LE (Ki (nM))	LipE (Ki (nM))	Radial Plot	Sim	Confs	AIns	MW	#Atoms	2D Sim
Reference (1 mol)													
1			1o1t	Invalid	Invalid	Invalid	 0.335	0	0	0	366.4	26	1
Protein (0 mols) Training Set (0 mols) Test Set (0 mols) Prediction Set (10 mols)													
★			1h1s	8.22	0.411	5.5	 0.608	0	0	0	402.5	28	0.283
Prediction Set													
★			1o1y	7.19	0.373	4.0	 0.637	0	0	0	366.4	27	0.243
Prediction Set													
★			1o1q @1	5.54	0.388	3.5	 0.833	0	0	0	267.3	20	0.341
Prediction Set													
★			1pxo	8.7	0.870	7.6	 0.789	0	0	0	207.3	14	0.118
Prediction Set													
★			1pxn	7.15	0.455	3.8	 0.787	0	0	0	313.4	22	0.299
Prediction Set													
			1pxn				 0.667						

Improve and simplify the view of the protein

The screenshot displays the Cresset software interface. On the left, a panel lists molecules and a protein. The 'Protein (1 mol)' entry is circled in red. Below it, a table lists four molecules with their respective activity values and 3D molecular models. The main window shows a 3D protein structure with a molecule docked. The 'Display' button in the top toolbar is circled in red. On the right, a vertical toolbar contains buttons for 'ASite', '3.5 A', 'Ribb', and 'HBnds', all of which are circled in red. A separate inset shows a detailed view of the 'ASite' button and its associated settings.

Select protein

Select Display → Thin Stick

Select ASite

Select 3.5A

Turn off Ribbons

Turn on HBnds

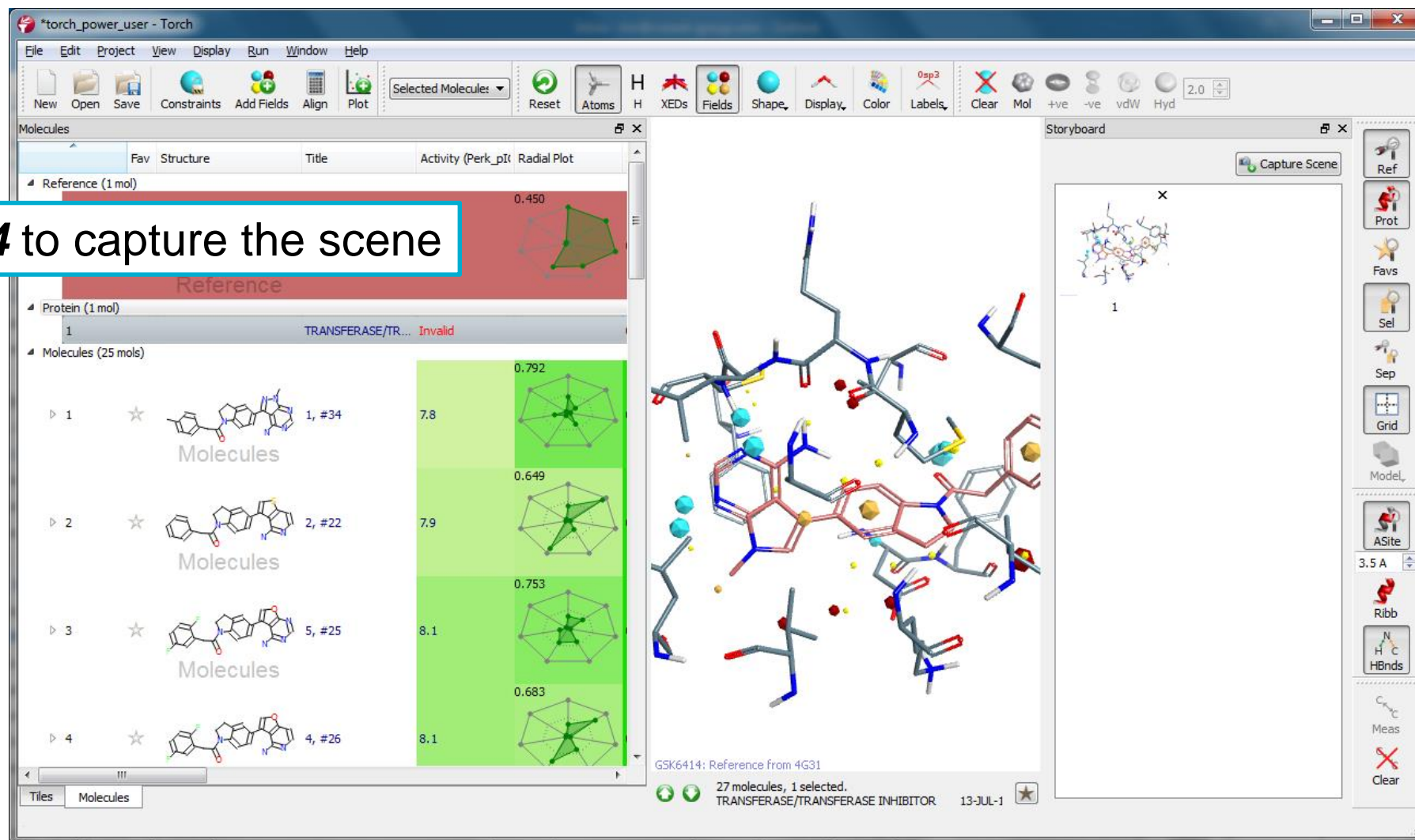
	Title	Activity (Perk_pI)	Radial Plot
Protein (1 mol)	1	TRANSFERASE/TR... Invalid	
Molecules (25 molecules)			
1	★	7.8	0.792
2	★	7.9	0.649
3	★	8.1	0.753
4	★	8.1	0.683

Left mouse rotate, right mouse translate, middle mouse/wheel/Alt-left scales. Shift-mouse z-clip.

© Cresset

Snapshot this view

Press **F4** to capture the scene

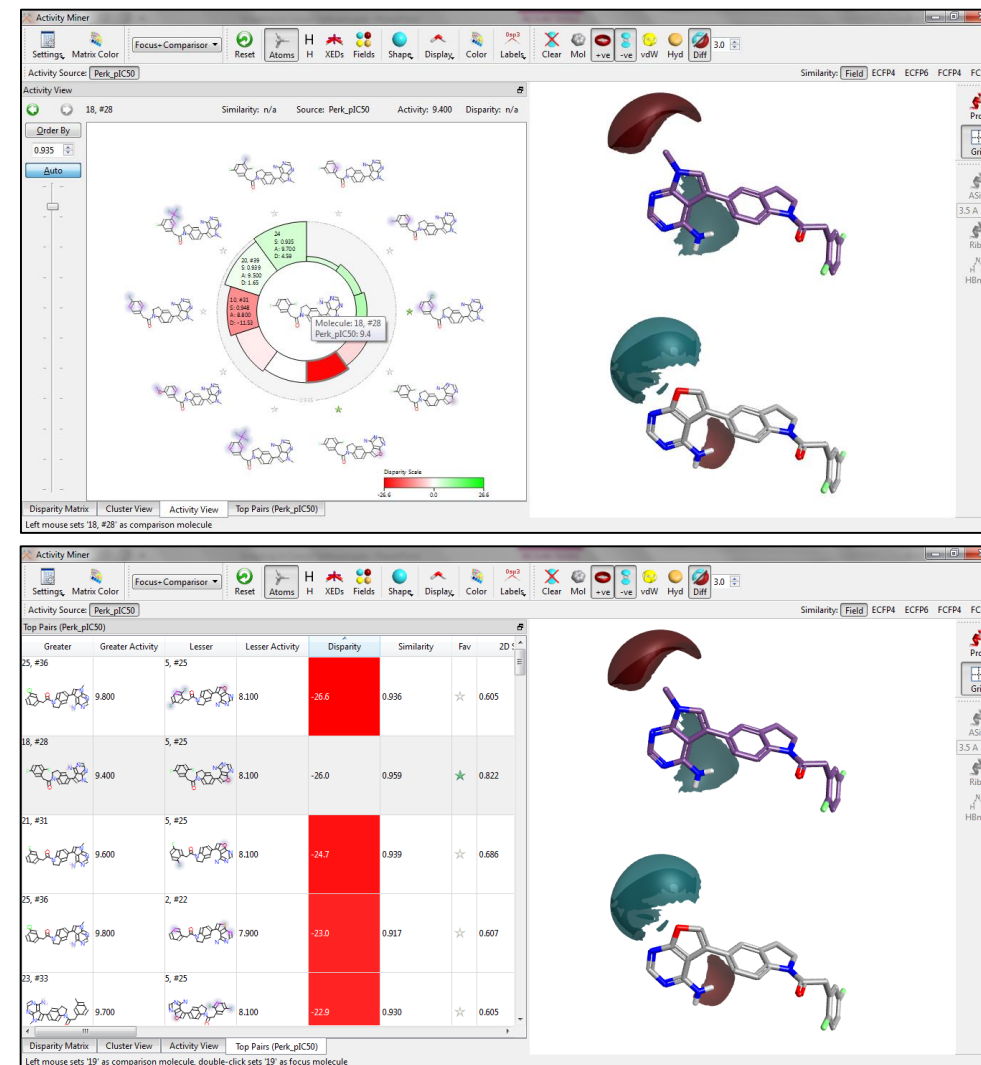


Don't wait for the calculation to finish

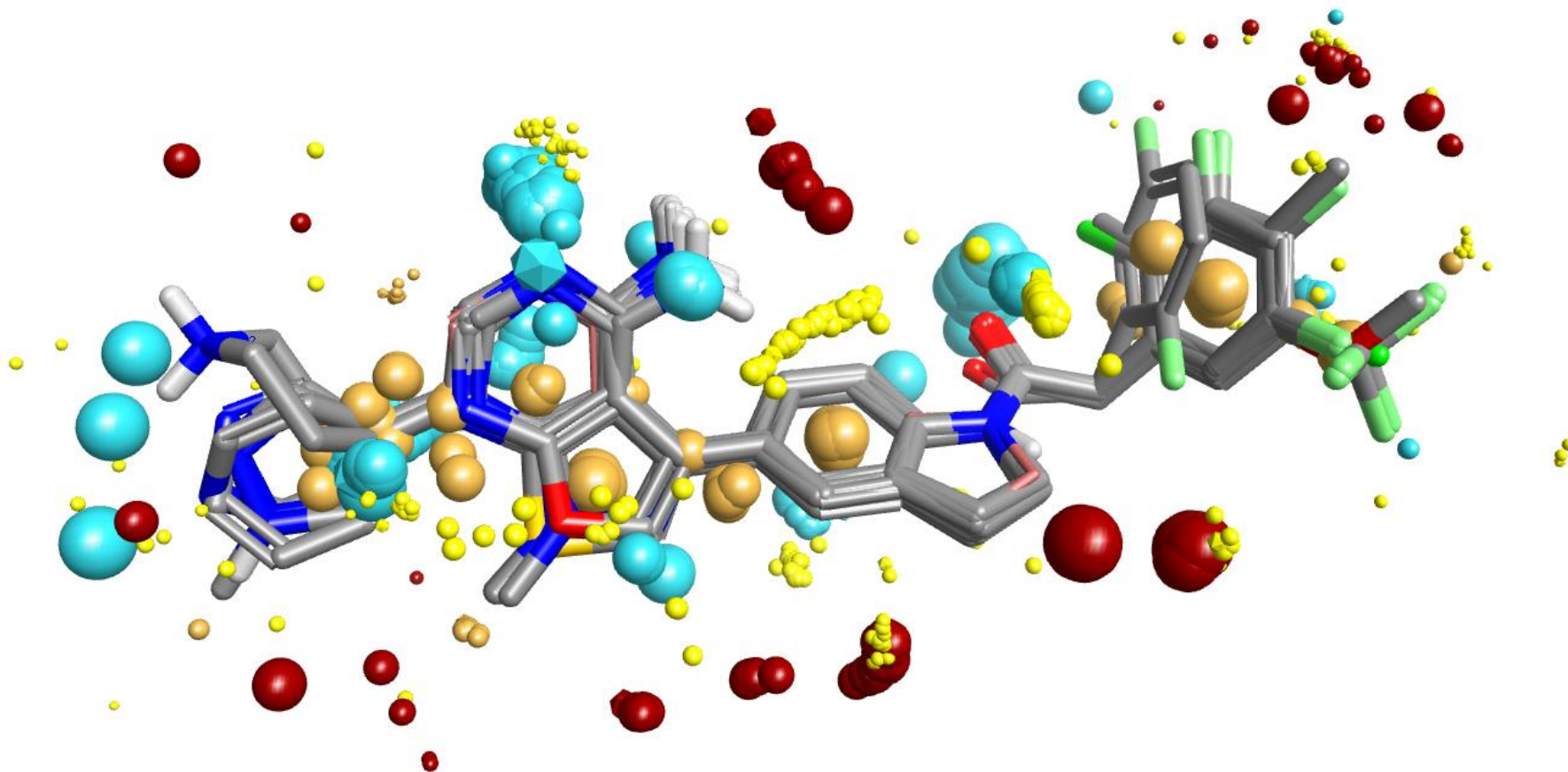
- > If your project has not finished load the completed project
 - > Torch_power_user.fqj

Torch optional module: Activity Miner

- > Activity cliffs reveal regions of acute SAR
- > Activity Miner finds and (tries to) explain activity cliffs
- > Our focus is on understanding, not just detection
 - > Understanding leads to improved hypotheses and designs
- > Data manipulation challenging
 - > Small datasets result in large number of datapoints

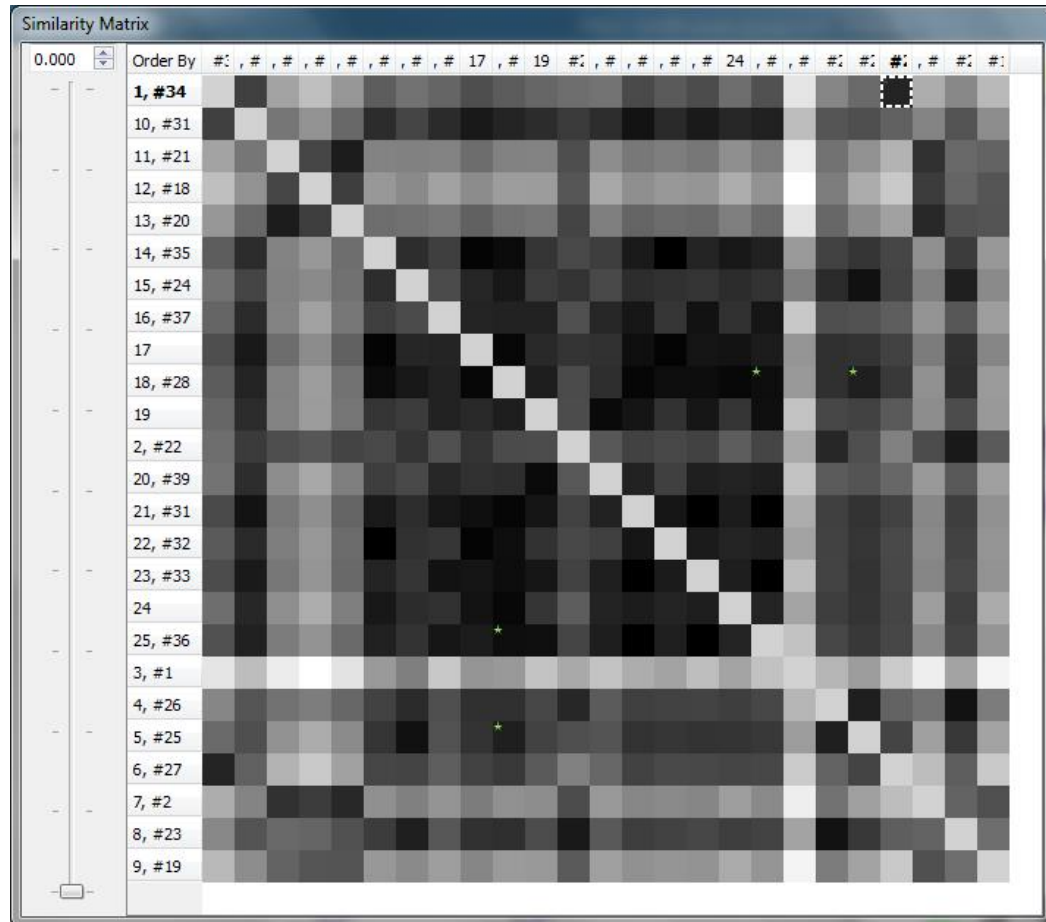


Electrostatic and shape SAR from aligned ligands

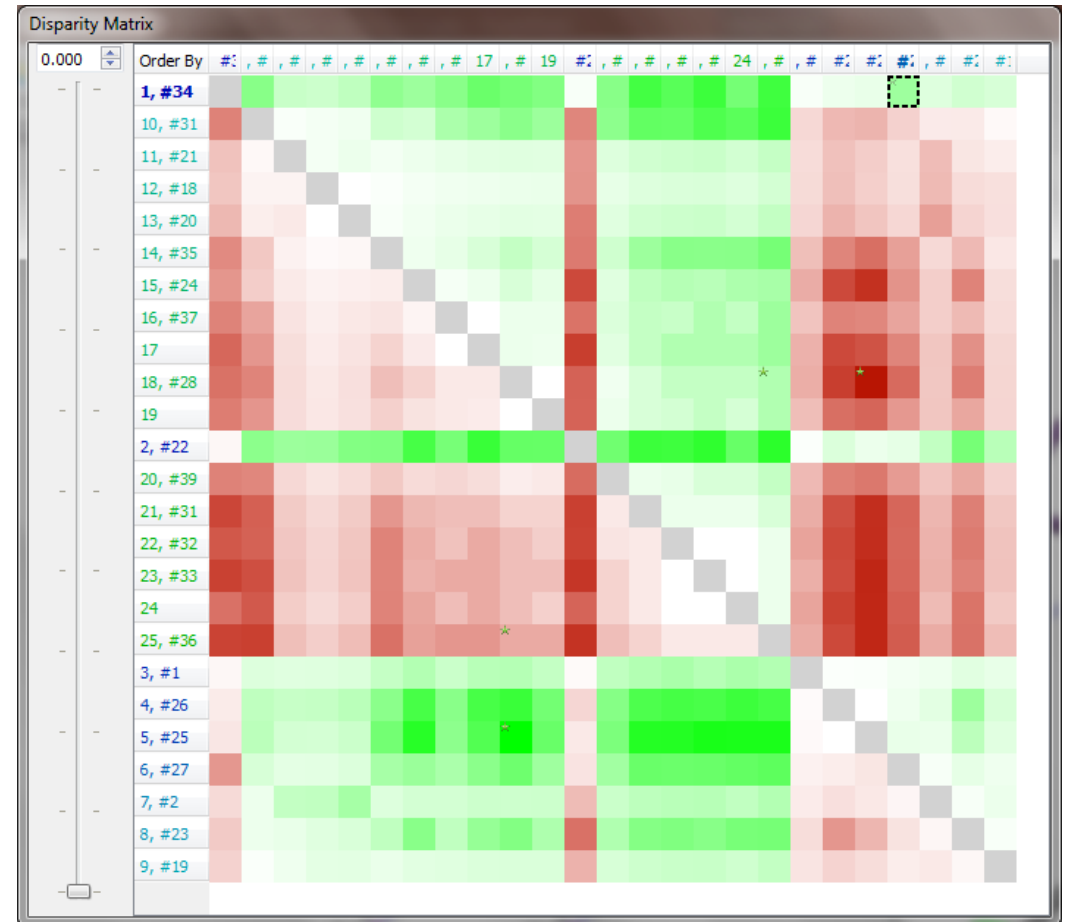


3D Activity Cliffs

Similarity



Disparity ($\Delta\text{activity} / 1\text{-similarity}$)



Launch Activity Miner

Run menu → ***Run Activity Miner***

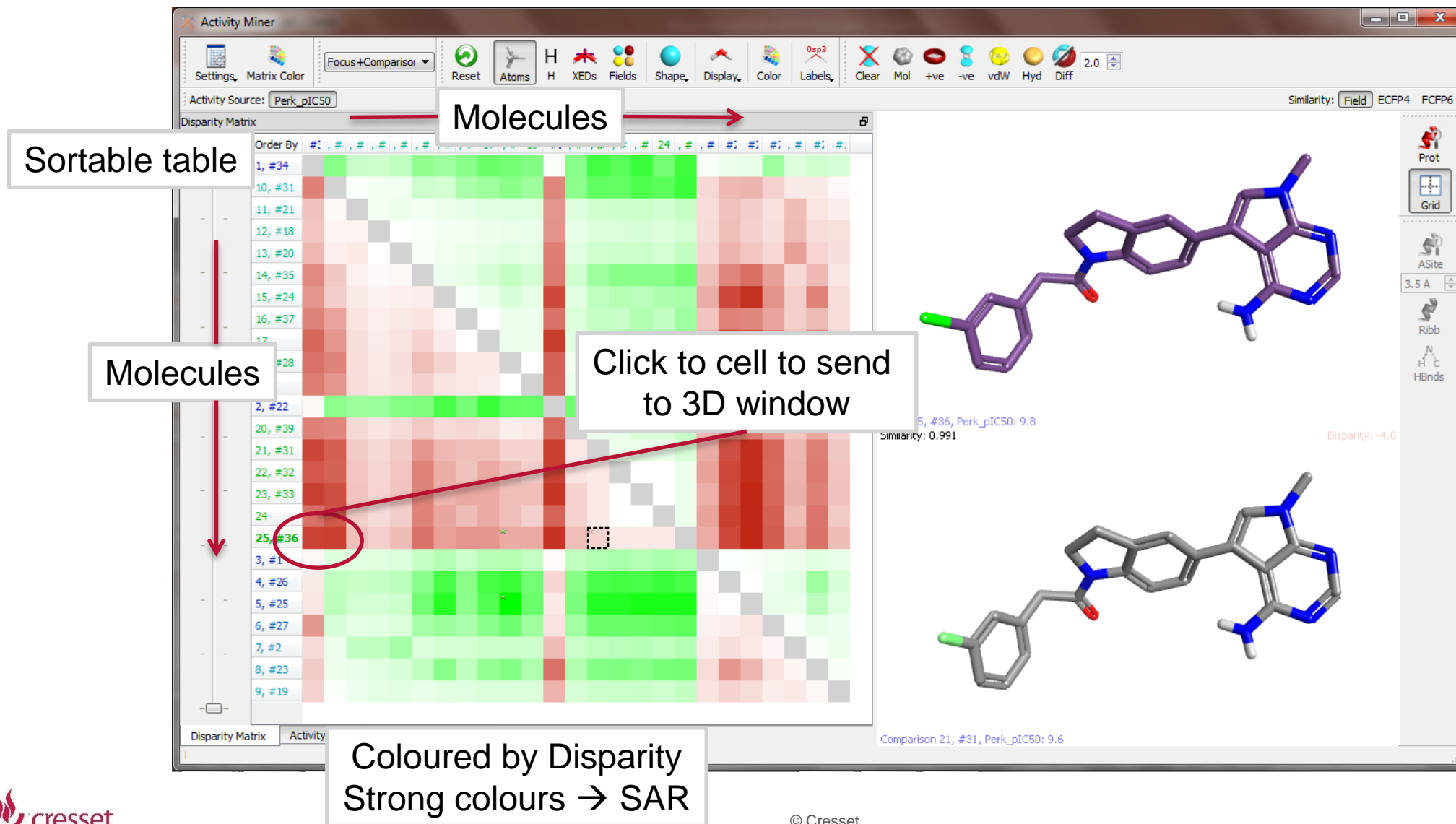
The screenshot shows the Torch software interface. The 'Run' menu is open, highlighting 'Run Activity Miner'. The main window displays a 3D molecular model of a protein-ligand complex. The left panel shows a list of molecules with their IDs and scores.

ID	Score	Structure
1, #34	7.8	<chem>C1=CC=C2C(=C1)N(C(=O)N2)C3=CC=CC=C3</chem>
2, #22	7.9	<chem>C1=CC=C2C(=C1)N(C(=O)N2)C3=CC=CC=C3</chem>
5, #25	8.1	<chem>C1=CC=C2C(=C1)N(C(=O)N2)C3=CC=CC=C3</chem>
4, #26	8.1	<chem>C1=CC=C2C(=C1)N(C(=O)N2)C3=CC=CC=C3</chem>

27 molecules, 25 selected.
1, #34

Run Activity Miner on all the Molecules, there must be at least 2 molecules with alignments.

Disparity Matrix



Sort Disparity Table by activity

The screenshot displays the Activity Miner software interface. The main window is titled "Activity Miner" and features a toolbar with various icons for settings, matrix color, focus+comparison, reset, atoms, H, XEDs, fields, shape, display, color, labels, clear, mol, +ve, -ve, vdW, Hyd, and Diff. The "Activity Source" is set to "Perk_pIC50". The "Disparity Matrix" is shown, with a dropdown menu open for "Order By" showing options: Results Table, Name, Activity (selected), and Favorites. A callout box points to the "Activity" option with the text "Click **Order By**→**Activity**". The matrix is a heatmap where rows are ordered by activity, with the most active molecules at the top. The right panel shows a 3D molecular model of a ligand bound to a protein, with a similarity score of 0.955. The bottom status bar indicates "The molecules are order from highest to lowest activity".

Activity Source: Perk_pIC50

Disparity Matrix

Order By: **Activity**

Click **Order By**→**Activity**

Similarity: Field ECFP4 FCFP6

Focus 4, #26, Perk_pIC50: 8.1
Similarity: 0.955

Comparison 5, #25, Perk_pIC50: 8.1

Disparity Matrix Activity View Top Pairs (Perk_pIC50)

The molecules are order from highest to lowest activity

Filter to show most similar pairs

The screenshot displays the Activity Miner software interface. The 'Disparity Matrix' panel on the left shows a heatmap of similarity scores between various compounds. A slider is set to 0.940, and a specific pair (18, #28) is highlighted with a red dashed box. The main panel on the right shows two chemical structures, one above the other, with their respective activity data: Focus 18, #28, Perk_pIC50: 9.4, Similarity: 0.955, and Disparity: -26.0. The bottom panel shows the 'Top Pairs (Perk_pIC50)' list.

Activity Miner

Settings Matrix Color Focus+Comparison Reset Atoms H XEDs Fields Shape Display Color Labels Osp3 Clear Mol +ve -ve vdW Hyd Diff 1.5

Activity Source: Perk_pIC50

Disparity Matrix

0.940

Order P: 24, 19, 17, 15, 22, 23, 24, 21, 20, 18, 12, 13, 6, 4, 5, 3, 2

18, #28

12, #18

13, #20

6, #27

4, #26

5, #25

3, #1

2, #22

Disparity Matrix Activity View Top Pairs (Perk_pIC50)

Similarity: Field ECFP4 FCFP6

Prot Grid ASite 3.5 A Ribb H C H Binds

Focus 18, #28, Perk_pIC50: 9.4
Similarity: 0.955
Disparity: -26.0

Comparison 5, #25, Perk_pIC50: 8.1

Use the Slider or type in the box **0.940**

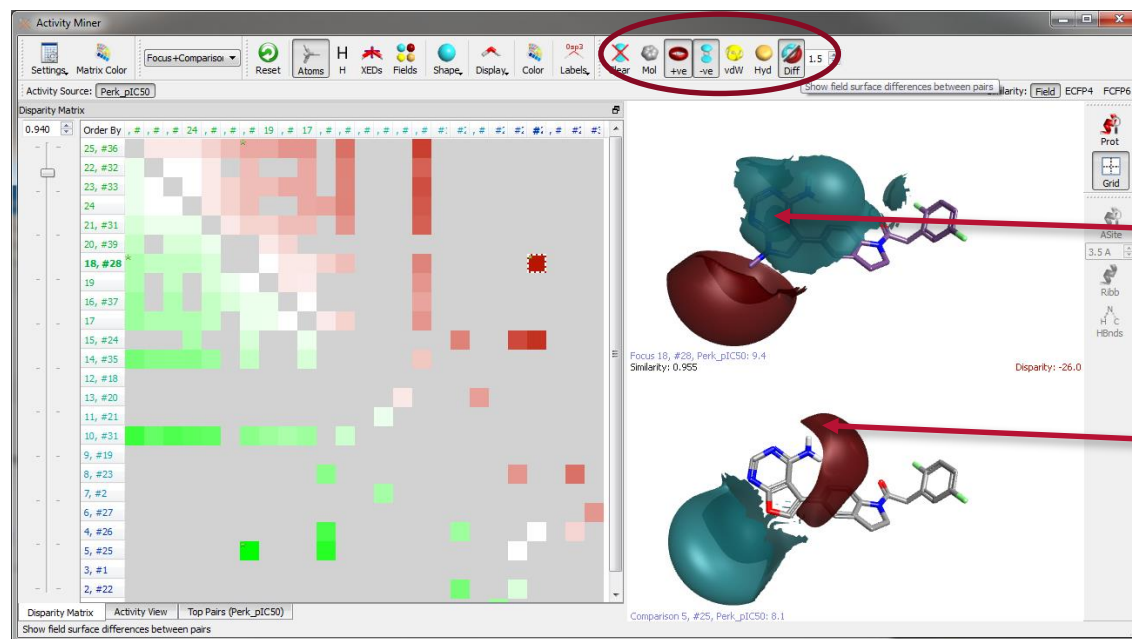
Select the large activity cliff pair

Field differences

Click **+ve**

Click **-ve**

- > Field difference show the higher potential in each pair
- > Always a pairwise comparison



Both have negative rings, but the top is **more** negative

Both have positive NH₂, but the bottom is **more** positive

Click **Diff**

Top Pairs

Activity Miner

Settings Matrix Color Focus+Comparison Reset Atoms H XEDs Fields Shape Display Color Labels Clear Mol +ve -ve vdW Hyd Diff 1.5

Activity Source: Perk_pIC50

Top Pairs (Perk_pIC50)

Greater	Greater Activity	Lesser	Lesser Activity	Disparity	Similarity	Fav	
18, #28	9.400	5, #25	8.100	-26.0	0.955	★	0.822
23, #33		5, #25	8.100	-23.5	0.932	★	0.605
25, #36	9.800	5, #25	8.100	-23.3	0.927	★	0.605
24	9.700	5, #25	8.100	-23.3	0.931	★	0.699
22, #32	9.700	5, #25	8.100	-22.4	0.929	★	0.608

Disparity Matrix Activity View Top Pairs (Perk_pIC50)

Focus 18, #28, Perk_pIC50: 9.4
Similarity: 0.955

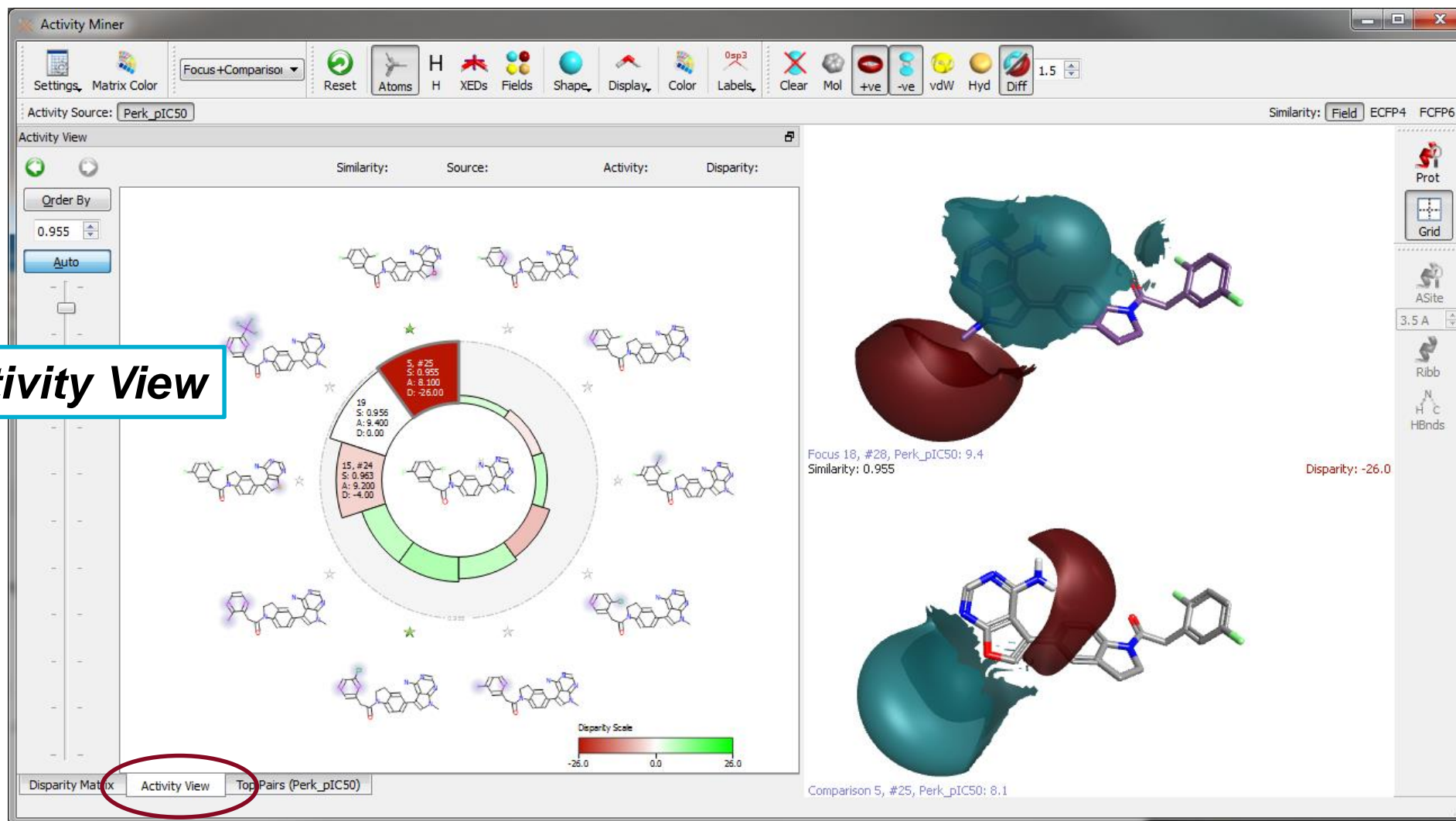
Disparity: -26.0

Comparison 5, #25, Perk_pIC50: 8.1

Prot Grid ASite 3.5 Å Ribb H C H Bnds

Click *Top Pairs*

Activity View: Nearest Neighbors according to 3D



Click **Activity View**

Nearest Neighbors according to 2D

Activity Miner

Settings Matrix Color Focus+Comparison Reset Atoms H XEDs Fields Shape Display Color Labels OSp3 Clear Mol +ve -ve vdW Hyd Diff 1.5

Activity Source: Perk_pIC50

Activity View

Similarity: Source: Activity: Disparity:

Click **ECFP4** to change to 2D similarity

An additional cliff is highlighted

Click **Field** to change back to 3D similarity

Similarity: Field **ECFP4** FCFP6

Prot Grid ASite 3.5 Å Ribb H C HBnds

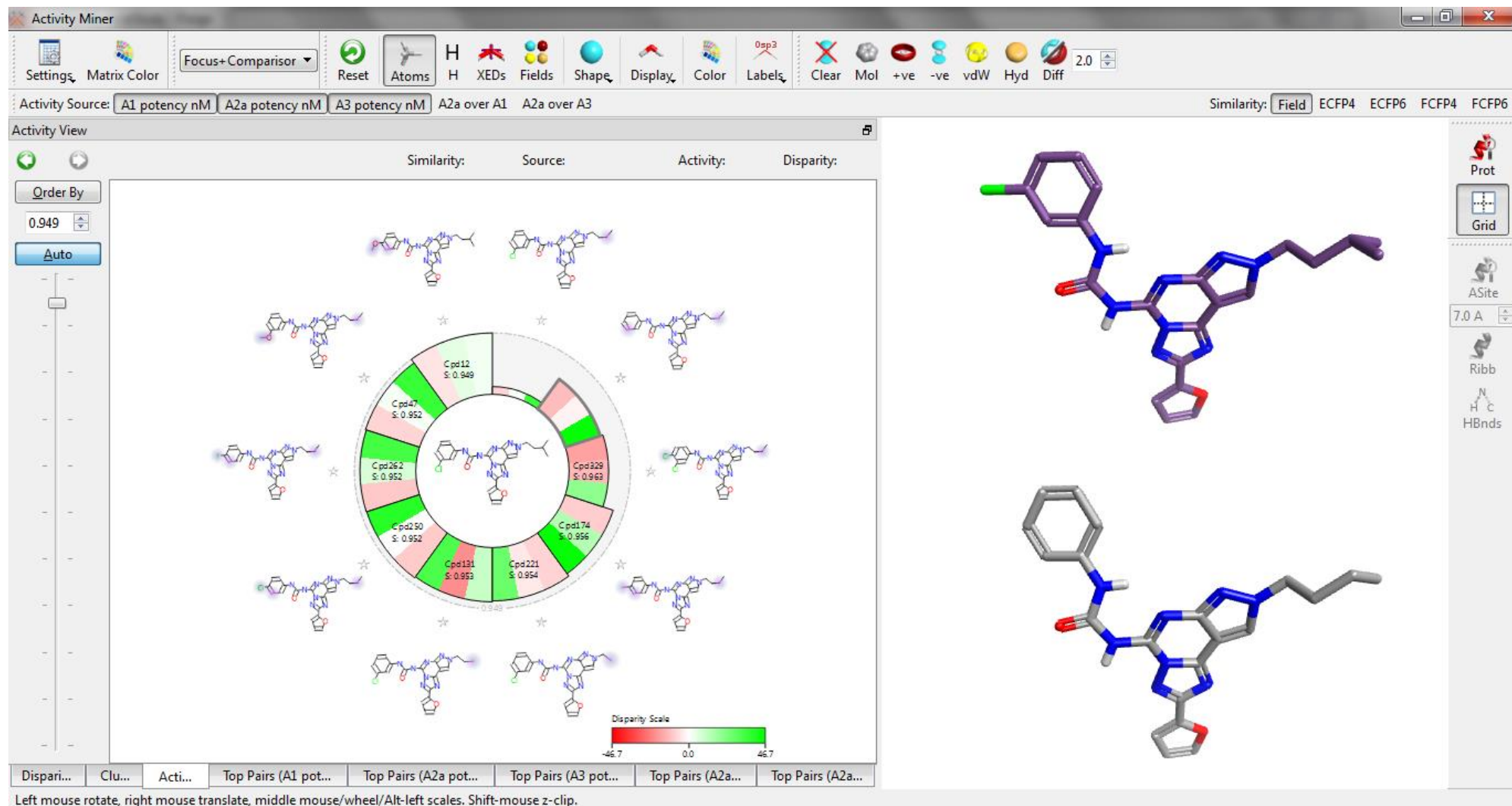
Focus 18, #28, Perk_pIC50: 9.4
Similarity: 0.739
Disparity: -4.2

Comparison 6, #27, Perk_pIC50: 8.3

Disparity Scale -4.8 0.0 4.8

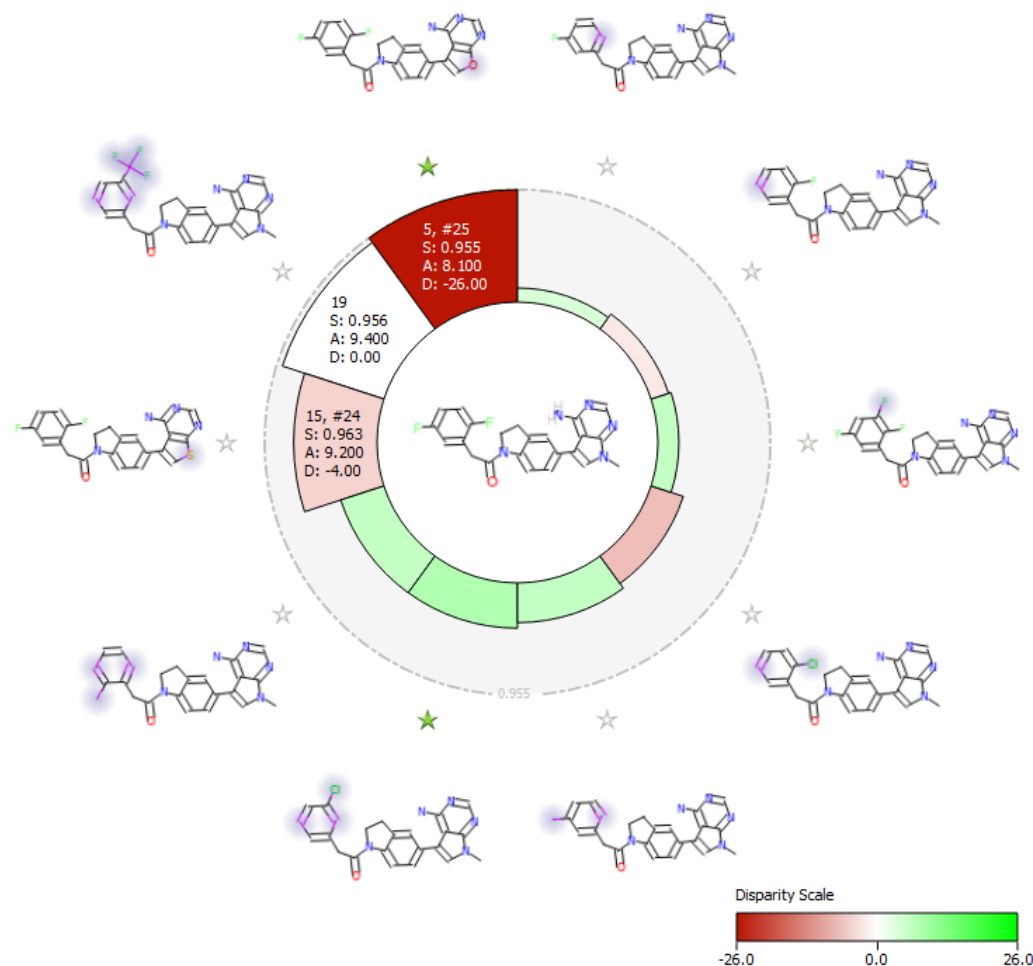
pIC50

Selectivity through multiple activities



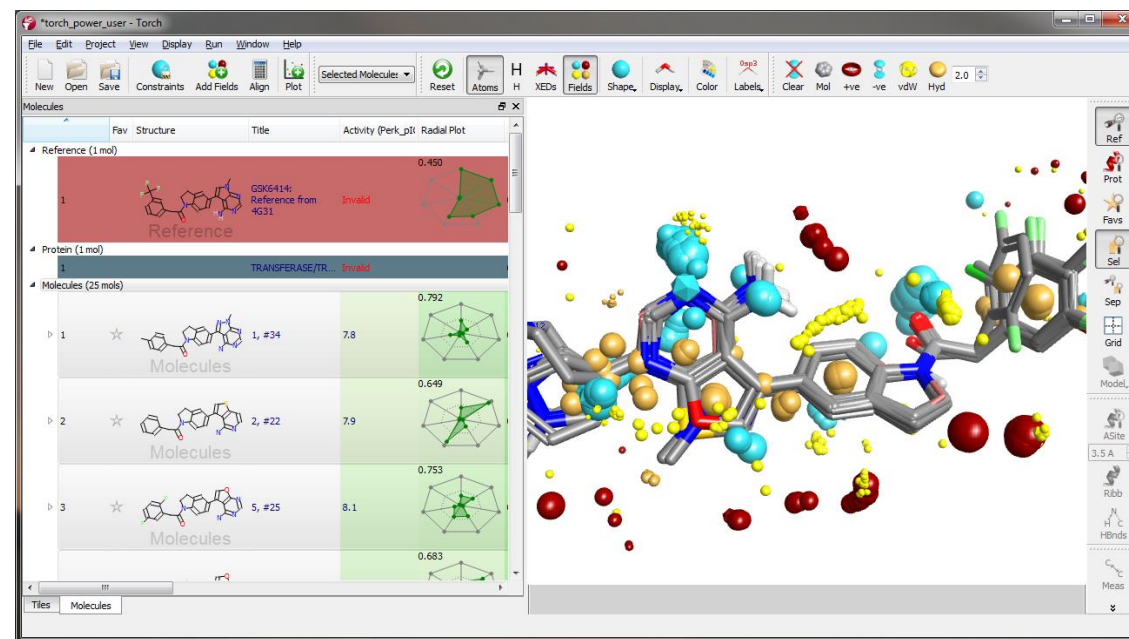
Gross SAR

- > Clearly SAR around the terminal aromatic and its substitution pattern
- > Activity Miner good for investigating this through pair wise comparison
- > Alternatively we could look at the molecules in the main Torch interface



Return to main Torch interface and find a subset of molecules

- > To look at the SAR of the terminal aromatic we need a consistent set of molecules
- > We will get all the molecules with a similar hinge binding group by filtering on substructure or SMARTS
- > We will use tags and Tiles to label and display key details of the molecules
- > We will combine this with a view of the fields of these molecules



Filter on substructure

Right Click **Structure** column header and choose **Add Filter**

The screenshot shows the Torch software interface. The 'Molecules' table is visible with the following columns: Fav, Structure, Title, Activity (Perk_pI), and Radial Plot. The table is divided into two sections: 'Reference (1 mol)' and 'Protein (1 mol)'. The 'Reference (1 mol)' section shows a molecule with a 'Structure' column header highlighted by a red circle and a right-click context menu open, showing the 'Add Filter' option. The 'Protein (1 mol)' section shows a list of molecules with their 'Structure' column headers highlighted in green. A 3D molecular model is displayed on the right side of the interface.

Fav	Structure	Title	Activity (Perk_pI)	Radial Plot
1		Reference	Invalid	0.450
2		Molecules	7.8	0.792
3		Molecules	7.9	0.649
4		Molecules	8.1	0.753
5		Molecules	0.683	0.844

Substructure filter

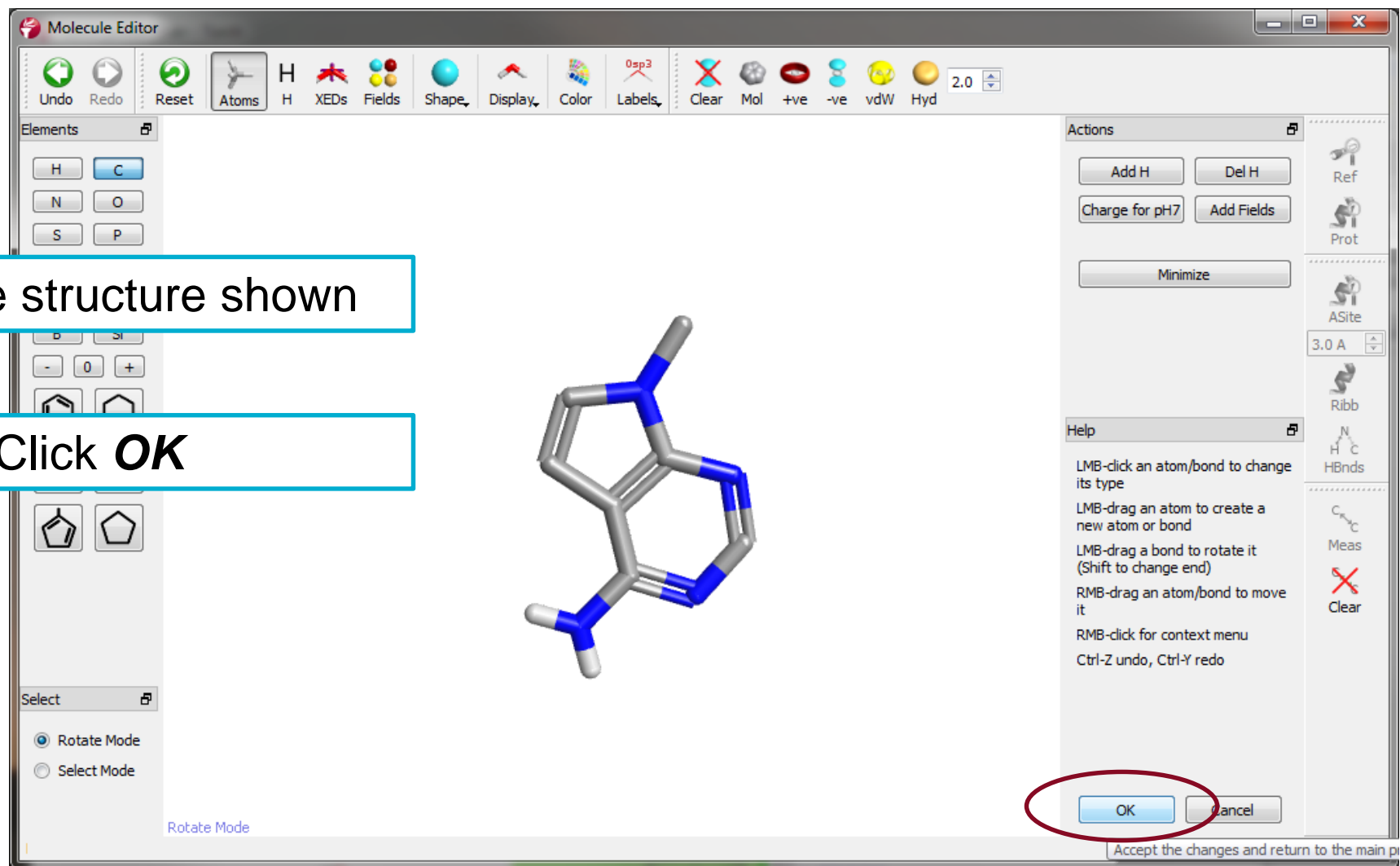
Select **Substructure** then click the button ... to open the editor

The screenshot displays the Torch software interface. The main window is titled '*torch_power_user - Torch'. The menu bar includes File, Edit, Project, View, Display, Run, Window, and Help. The toolbar contains icons for New, Open, Save, Constraints, Add Fields, Align, Plot, Reset, Atoms, H, XEDs, Fields, Shape, Display, Color, Labels, Clear, Mol, +ve, -ve, vdW, and Hyd. The 'Molecules' panel on the left shows a list of molecules with columns for Fav, Structure, Title, Activity (Perk_pI), and Radial Plot. The first molecule is 'Reference (1 mol)' with a structure of GSK6414 and an activity of 0.450. The 'Filters' panel on the right shows a dropdown menu with 'Substructure' selected, and a button with three dots next to it. A tooltip for this button reads: 'Only molecules with structure ONE OR MORE of the "Includes" or NONE of the "Excludes"'. The central 3D view shows a molecular structure with various atoms and bonds.

Draw substructure

Draw the structure shown

Click **OK**



Focus on the terminal aromatic

Check 14 of 27 molecules pass filter

Right click on the *para* carbon

Choose **Center on Picked Atom**

The screenshot shows the Torch software interface. The main window displays a molecular structure with a cyan-colored terminal aromatic ring highlighted by a red circle. A context menu is open over this ring, with the option 'Center on Picked Atom' circled in red. The menu also includes options like 'Full Screen', 'Select', 'Copy This Molecule', 'Export Selected', 'Edit', 'Edit a Copy', 'Rename', 'Delete This Molecule', 'Delete This Alignment', 'Set as Preferred Alignment', 'Re-align This Molecule', 'Send to Blaze', 'View Log', 'Copy as New Reference', 'Reset View Center', 'Save Image As...', and 'Capture Scene'. The background shows a list of molecules with various filters and a 'Picked Molecules' dropdown. The status bar at the bottom indicates 'Score 0.907 | Act 8.800 | 14 of 27 molecules pass filter'.

Electrostatics of terminal aromatic

Select all current molecules

Add Negative surface

Zoom in

View a Grid, no Ref

14 of 27 molecules pass filters. 12 selected.

View 2D, data and 3D at the same time

The screenshot displays the Torch software interface. The main window is titled '*torch_power_user - Torch'. The menu bar includes File, Edit, Project, View, Display, Run, Window, and Help. The toolbar contains icons for New, Open, Save, Constraints, Add Fields, Align, Plot, and a dropdown for Selected Molecules. The Tiles panel on the left shows a list of 25 molecules with their IDs and activity data. A context menu is open over the Tiles panel, showing options like Copy, Export Selected, Delete, Mark as Favorite, Tag Molecules, Align Molecules, Show in Activity Miner, View Log, Copy to new Role, Set Role, Tile Size, Order Tiles by, and Choose Tile Data. The Tile Size submenu is open, showing Small, Medium, and Large options. The Small option is selected. The main display area shows 3D molecular models. The status bar at the bottom indicates '14 of 27 molecules pass filters. 12 selected. 10, #31'.

Choose **Tiles** tab

Right Click on a Tile

Choose **Tile Size** → **Small**

Tiles

Molecules

14 of 27 molecules pass filters. 12 selected. 10, #31

View 2D, data and 3D at the same time

The screenshot shows the Torch software interface. On the left, a grid of molecule tiles is displayed, each showing a chemical structure and associated data (Activity and LE). A right-click context menu is open over one of the tiles, with the 'Choose Tile Data' option highlighted. To the right, the 'Tile Manager' dialog is open, showing a list of visible and hidden data items. The 'Structure', 'Activity (Primary)', and 'LE (Primary)' items are circled in the visible list.

Right Click on a Tile

Choose Tile Data

Include **Structure**, **Activity** and **LE**

Tile Manager

Visible

- Structure
- Activity (Primary)
- LE (Primary)

Hidden

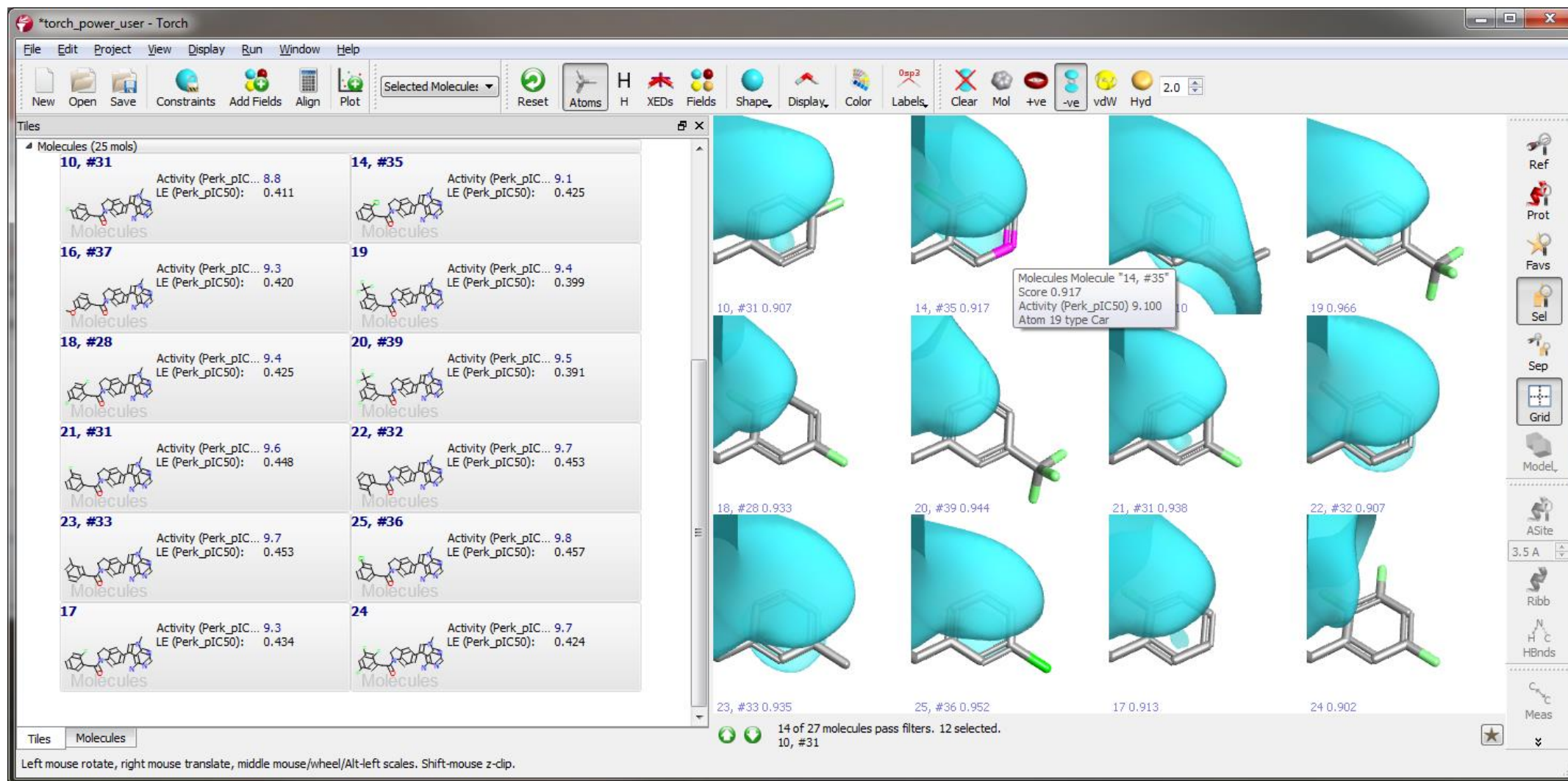
- Fav
- Radial Plot
- LipE (Primary)
- Alignment Chosen
- Sim
- FSim
- FScore
- FScore+P
- SSim
- SScore
- SScore+P
- Exd Vol Pen
- Field Results

Drag and drop to rearrange, hide or show data items. Hover over each item to get a description.

Restore Defaults OK Cancel

14 of 27 molecules pass filters. 12 selected.
10, #31

Conclusion? Capture the Scene to the storyboard



Additional tasks

- > Use tags to label the dataset just created
- > Use substructure filters to find all 3-F substituted aromatics
- > Tag these
- > Change the default data that is used on Tiles
- > Change the defaults to create large high resolution pictures
- > Change the background to grey
- > Create a story of key SAR points
- > Make sure you include protein interactions
- > Which molecule fits the project profile the best?
- > Is it the highest active?



smarter chemistry | smarter decisions

Questions welcomed

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Example files available from
enquiries@cresset-group.com

Contact us for our tailored training courses



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