Becoming a power user of Torch

Cresset European User Group Meeting – Workshops

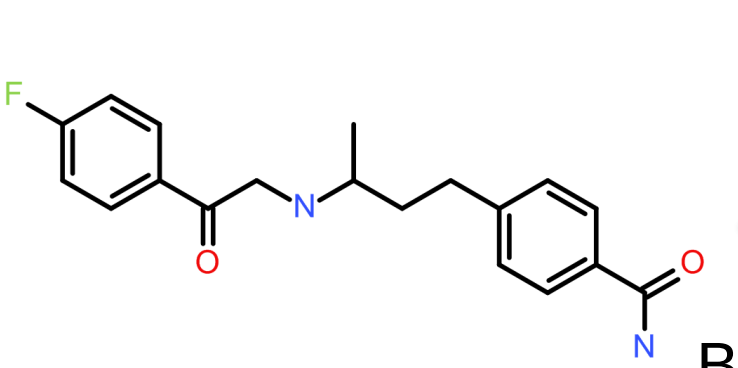
June 2016

Files for this workshop

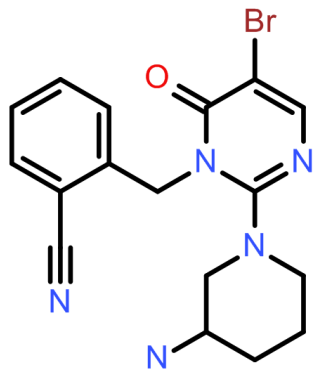
> The files used in this workshop are available for download on request

> Please send an email to enquiries@cresset-group.com stating the name of the workshop

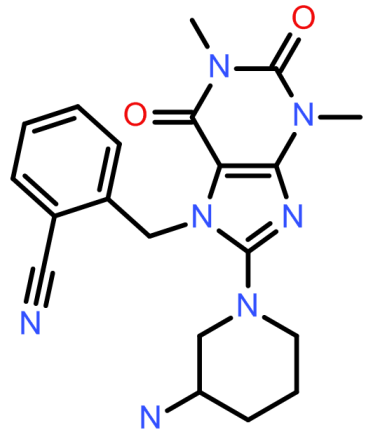
Comparing structurally disparate molecules



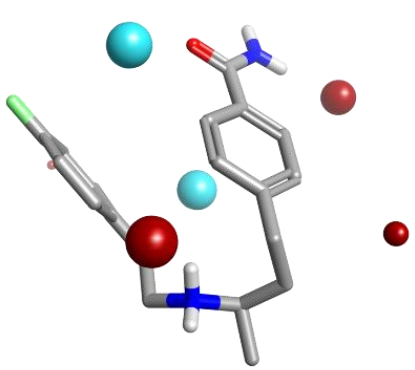
Bioisosteres



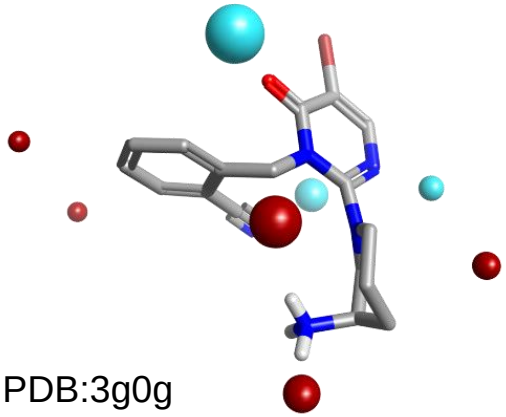
Bioisosteric groups



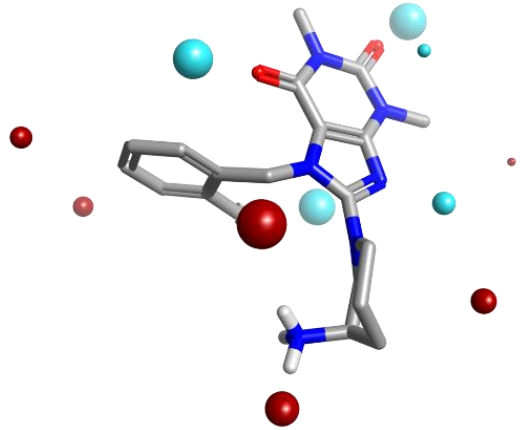
blaze forge torch spark



PDB:2ogz



PDB:3g0g



Understanding and using SAR to improve molecule design and intellectual property

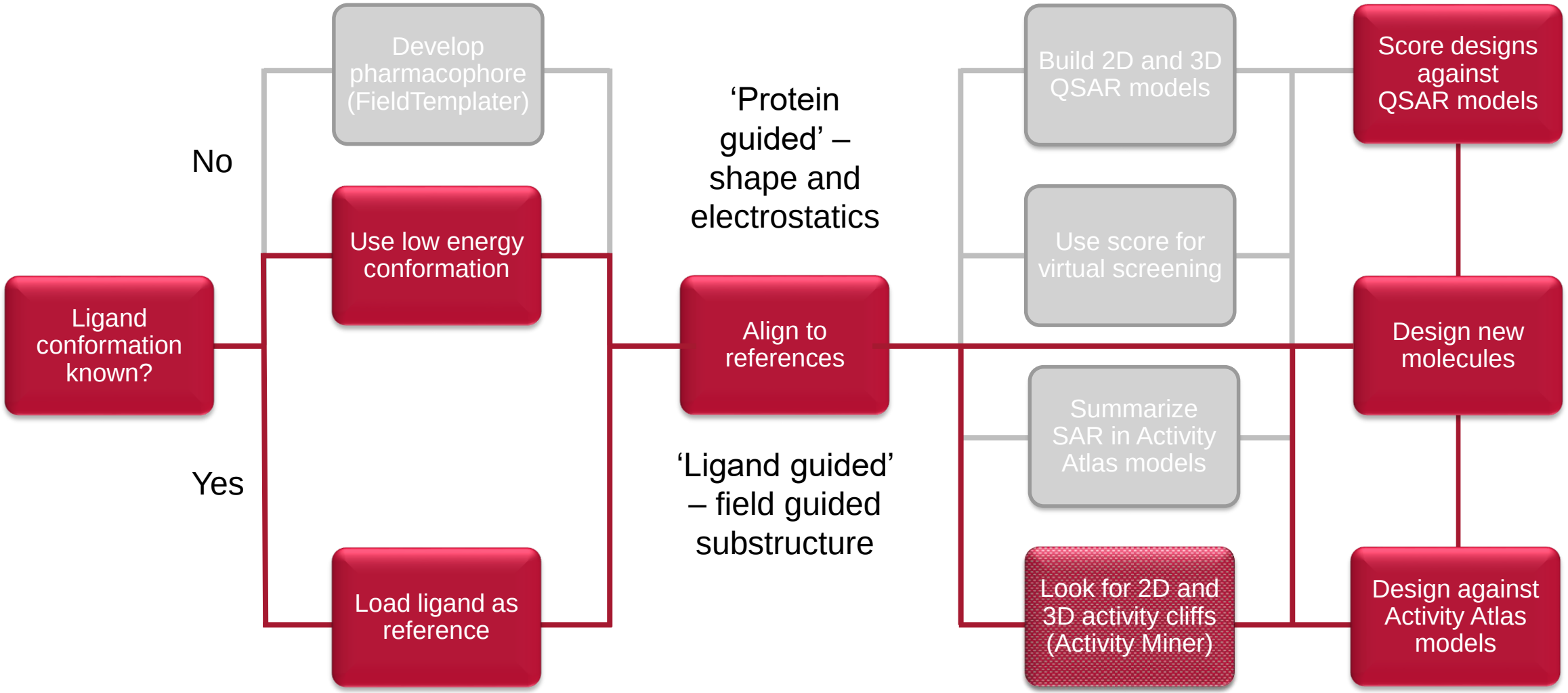
Using electrostatics and shape to gain new perspectives on molecular design

Understand structure-activity using Forge

- 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

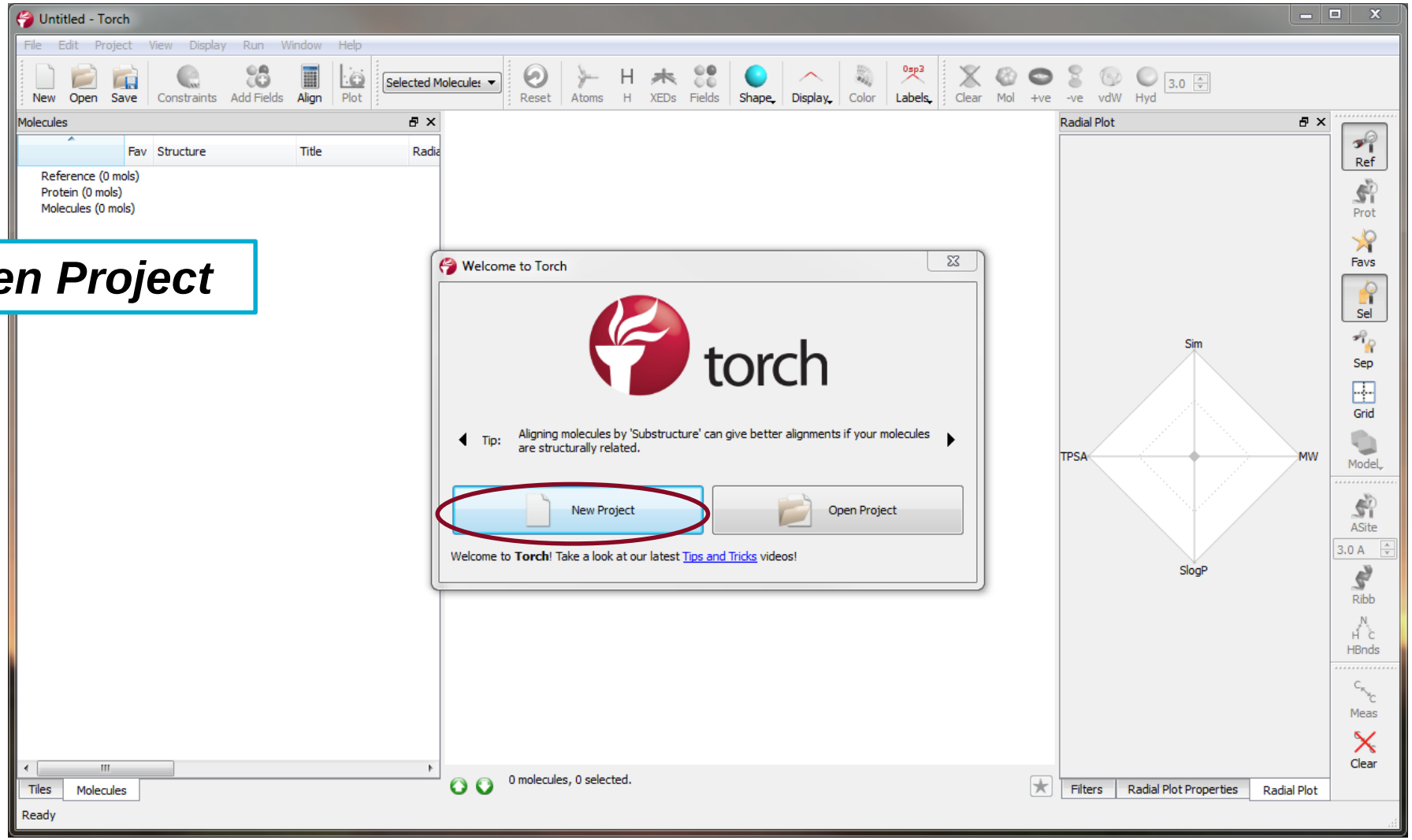
- Combine multiple numerical properties into a single score
- Create a project profile for physico-chemical (or other) properties
- Add properties from external server
- Color by fit to profile
  - 2D
  - 3D
- Interactive scatter plots and histograms
- Storyboard to record important 3D views
- Split 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

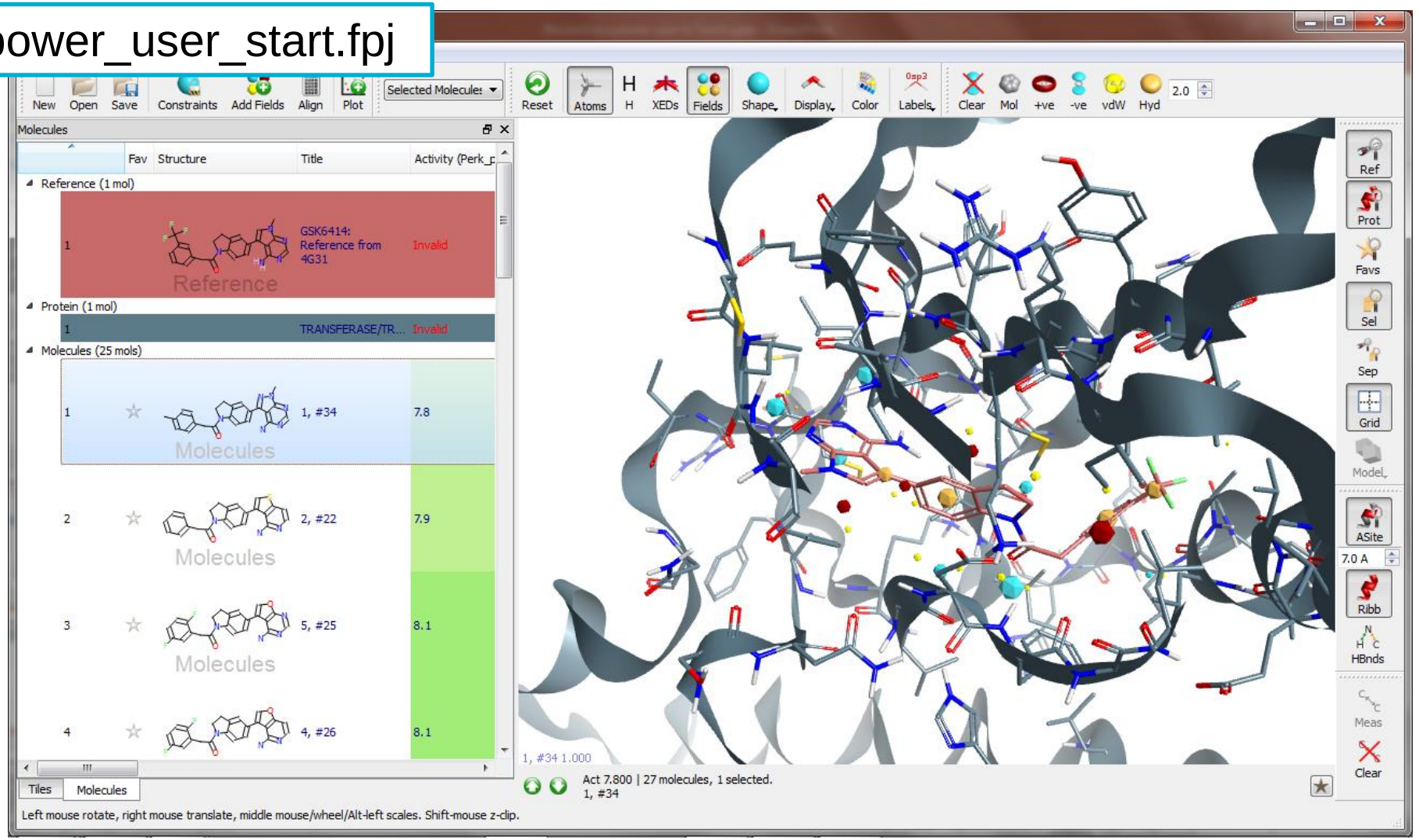
Launch Torch

Click ***Open Project***



Open a Torch project

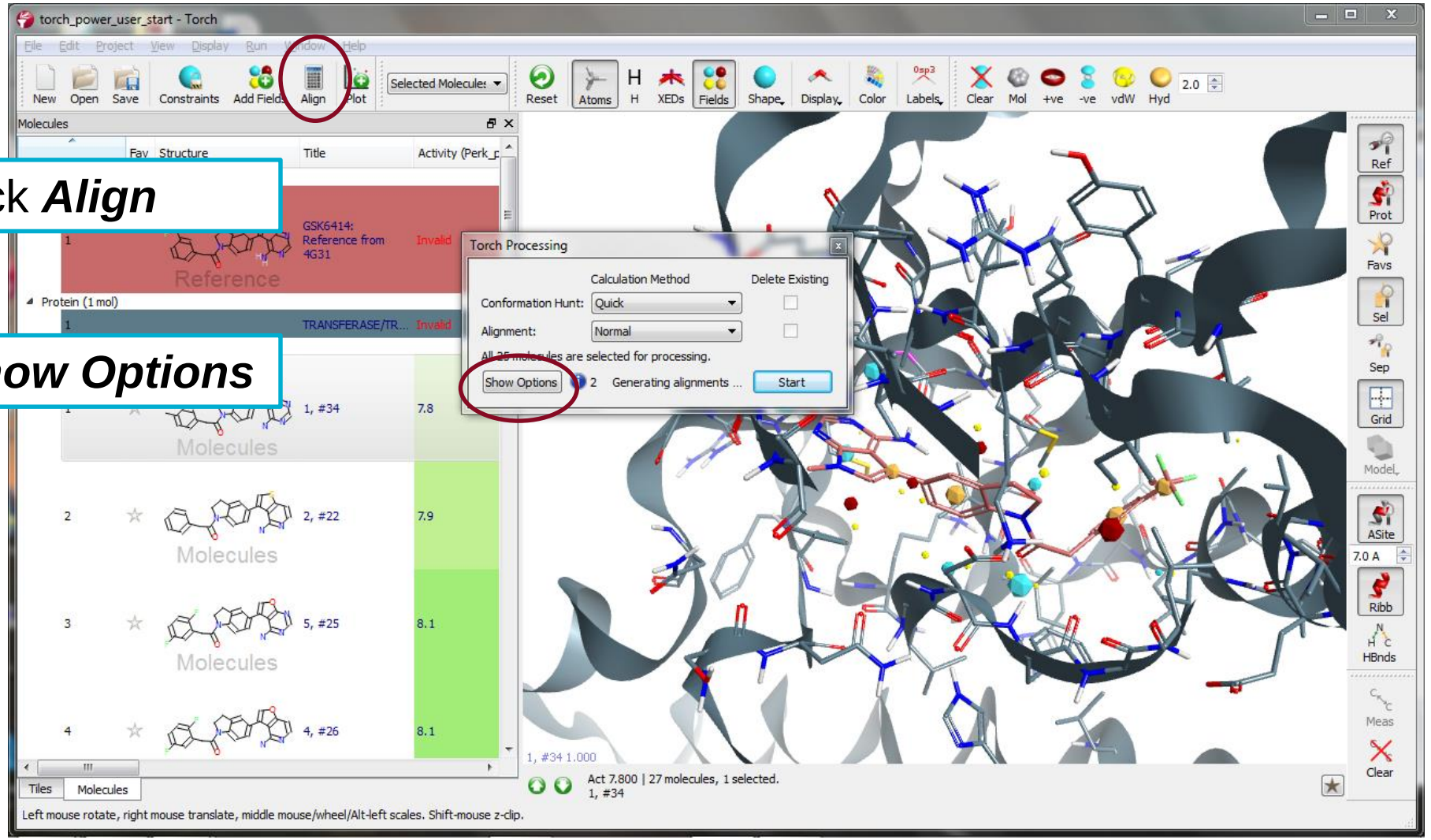
Torch_power_user_start.fpj



Align all ligands using substructure

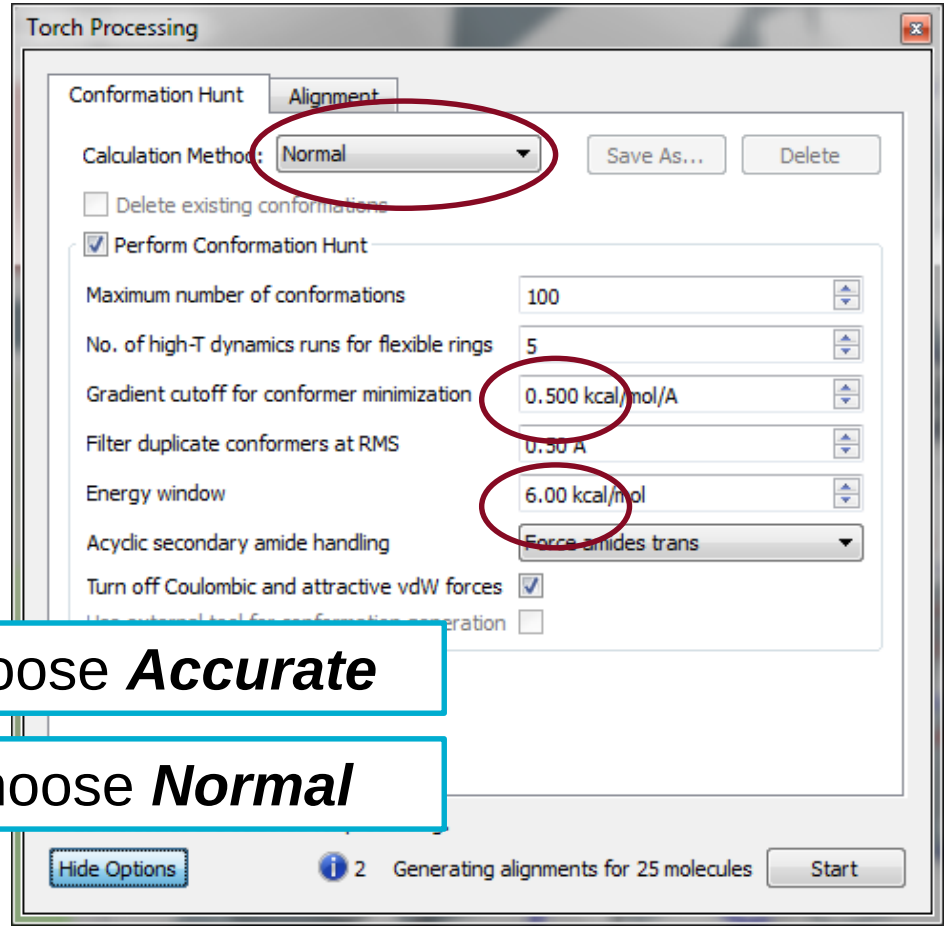
Click ***Align***

Click ***Show Options***



Align all ligands using substructure

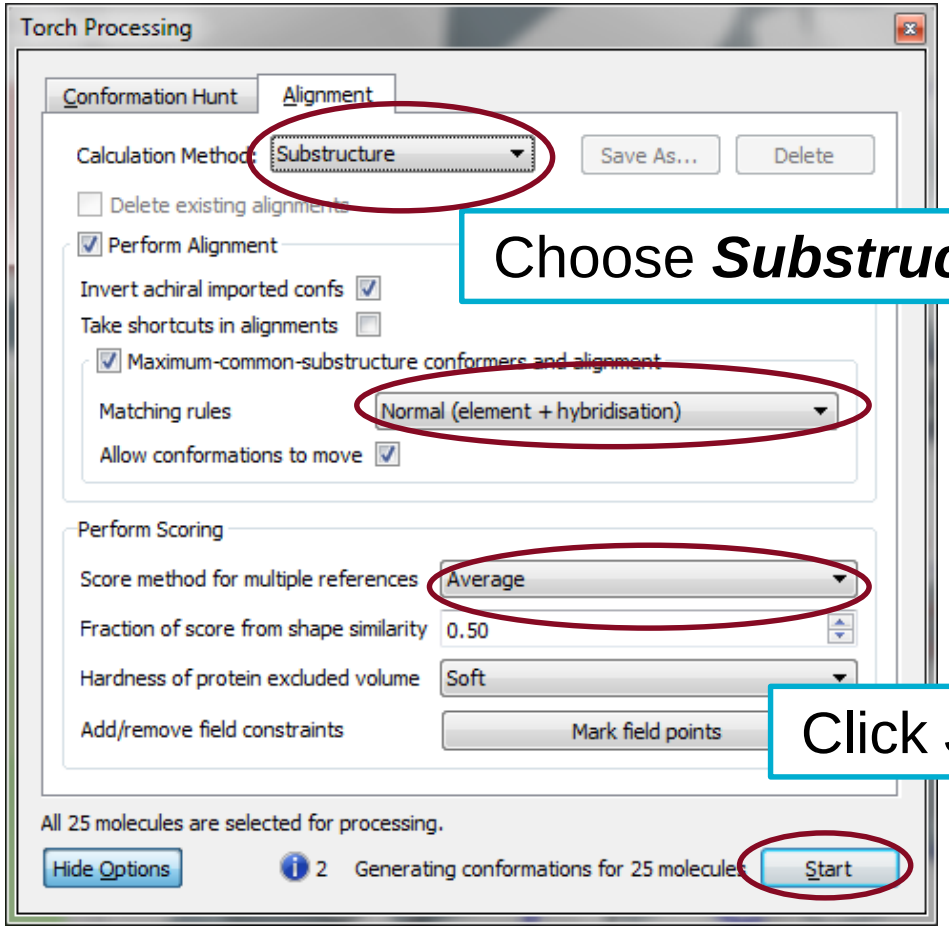
Conformation Hunt Tab



Choose ***Accurate***

Choose ***Normal***

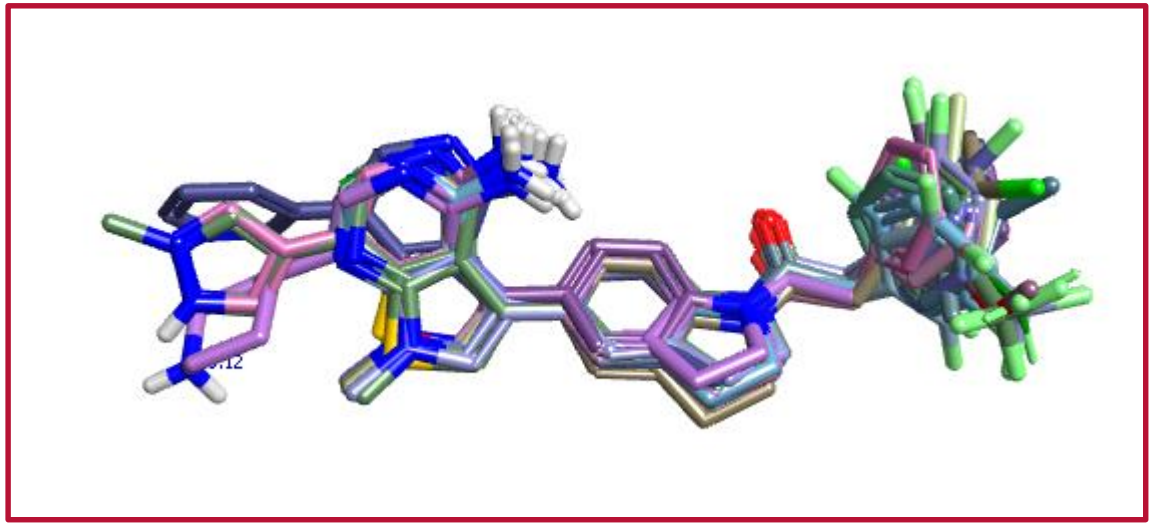
Alignment Tab

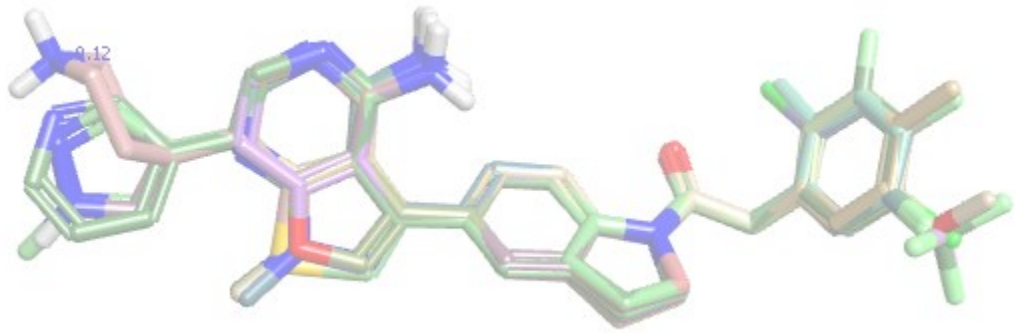


Choose ***Substructure***

Click ***Start***

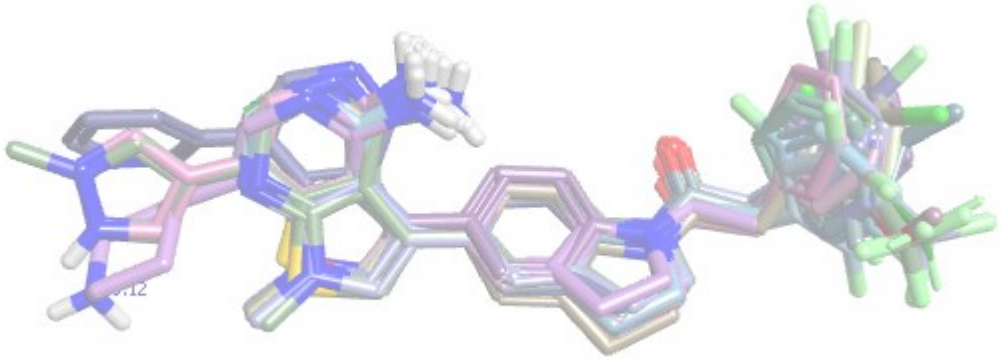
Protein or ligand-based alignment?

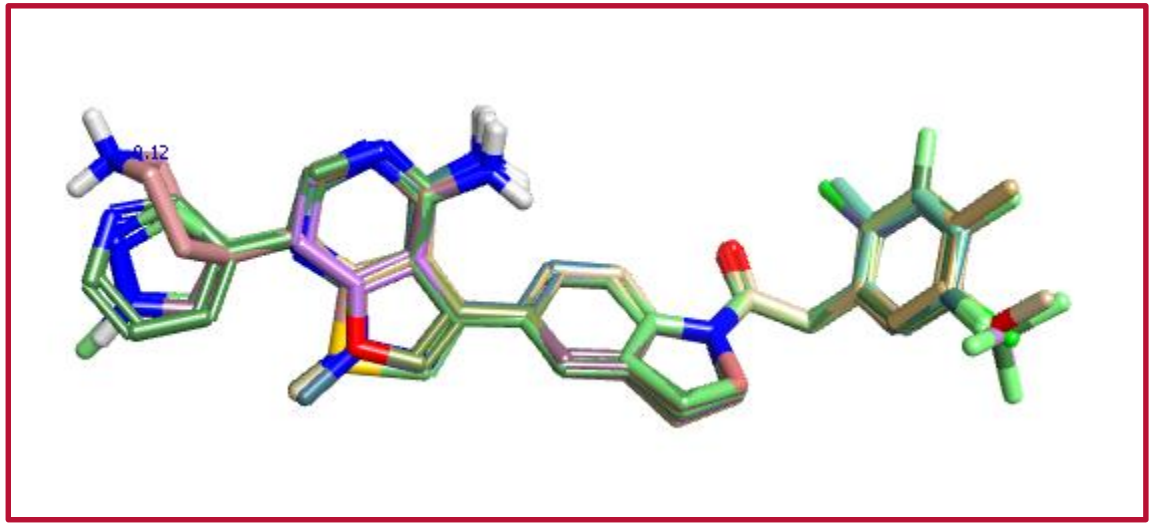




- Field-based alignment
  - Uses Cresset electrostatic, shape and hydrophobic field points to align
  - Scored 50% field-based similarity with 50% shape similarity
  - Independent of chemical structure
  - Meaningful score comparisons
  - Better for libraries that have structurally diverse compounds

Protein or ligand-based alignment?

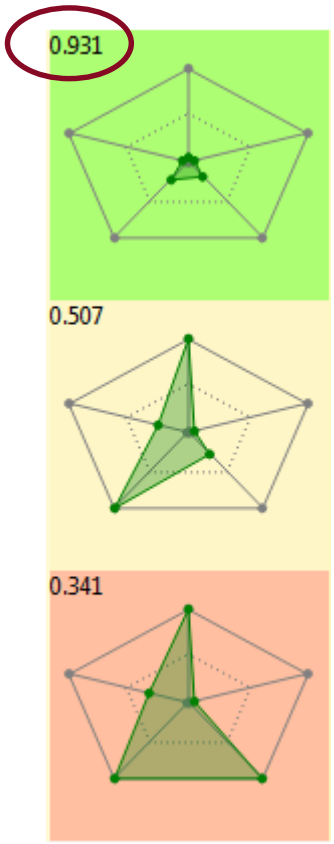




- Maximum common substructure alignment
  - Good for a library with a common core or concentric series
  - Common structural features in database molecules are mapped onto conformation of corresponding features in reference molecule
  - All other parts of the molecule are conformationally hunted
  -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

Radial Plot and multi-parameter optimization

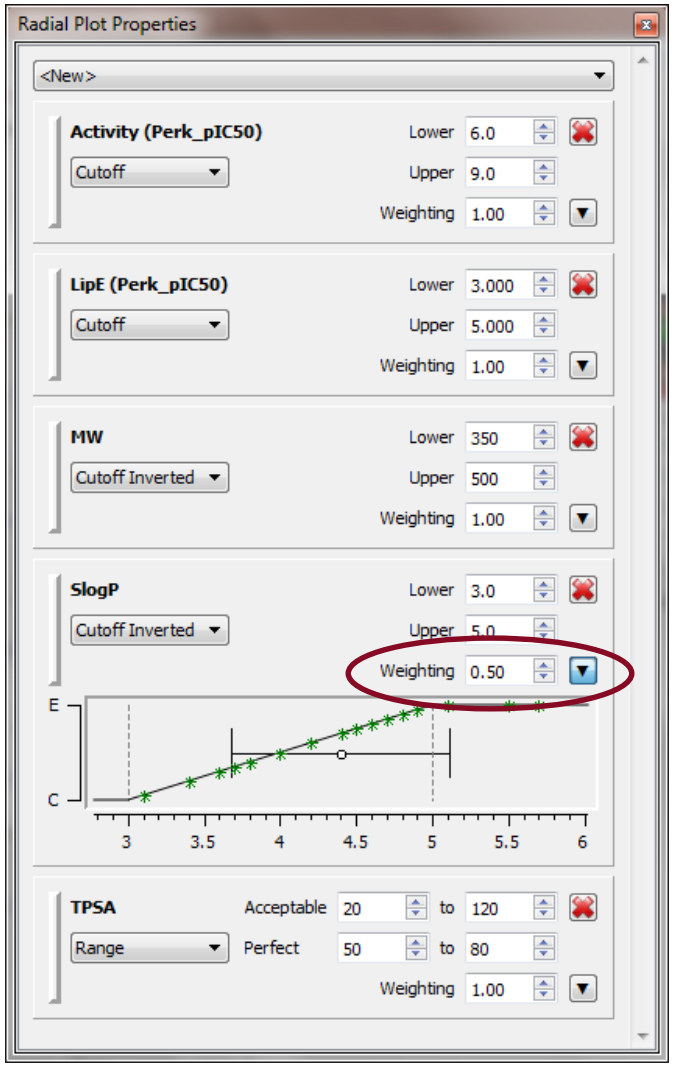
- Radial plot allows for simultaneous viewing of numerical parameters
- By default, the smaller the area encased in green, the better the properties
- Customizable
  - Many numbers (up to ~15 works ok)
  - Default and specific profiles
- Overall fit summarized into a score



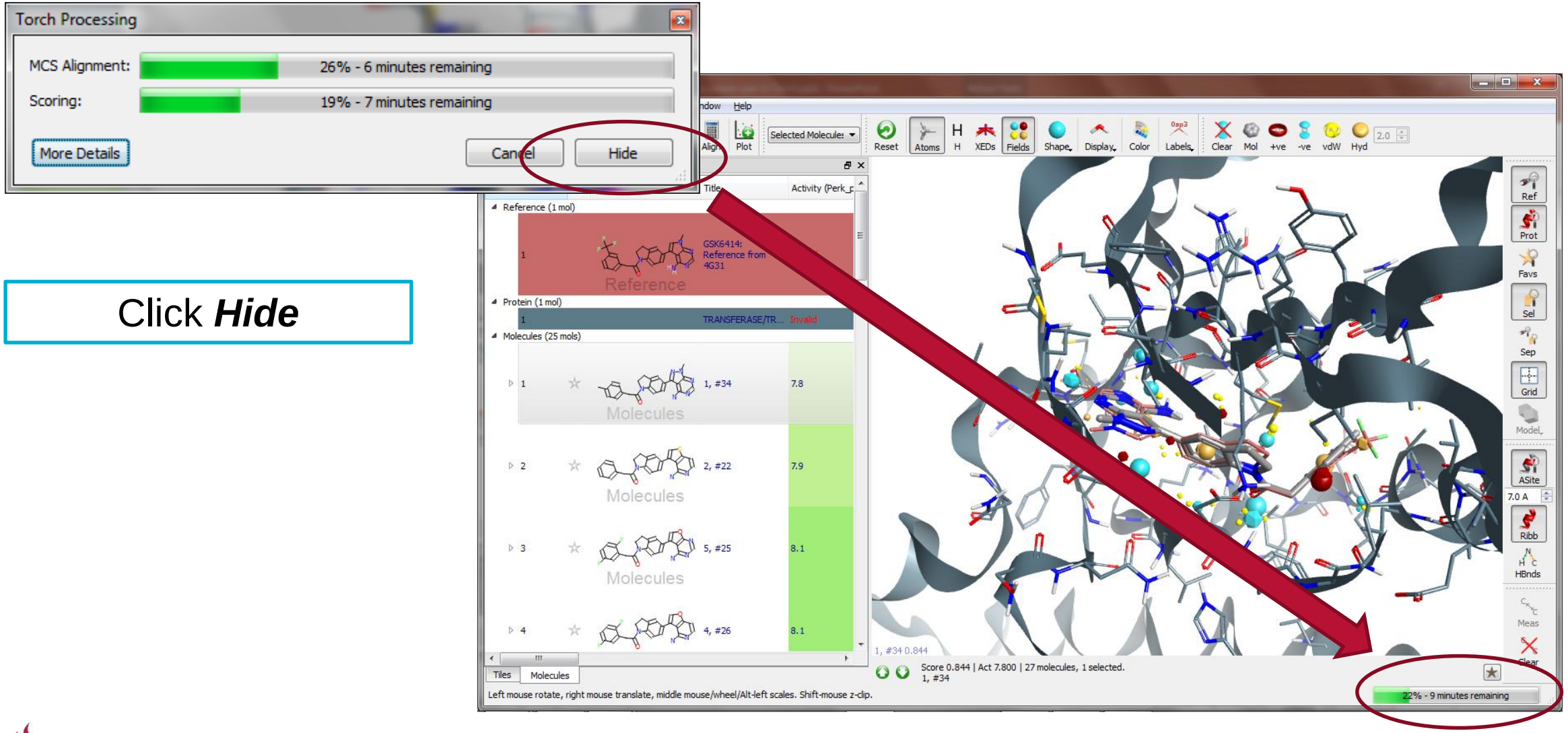
Good

Fair

Poor

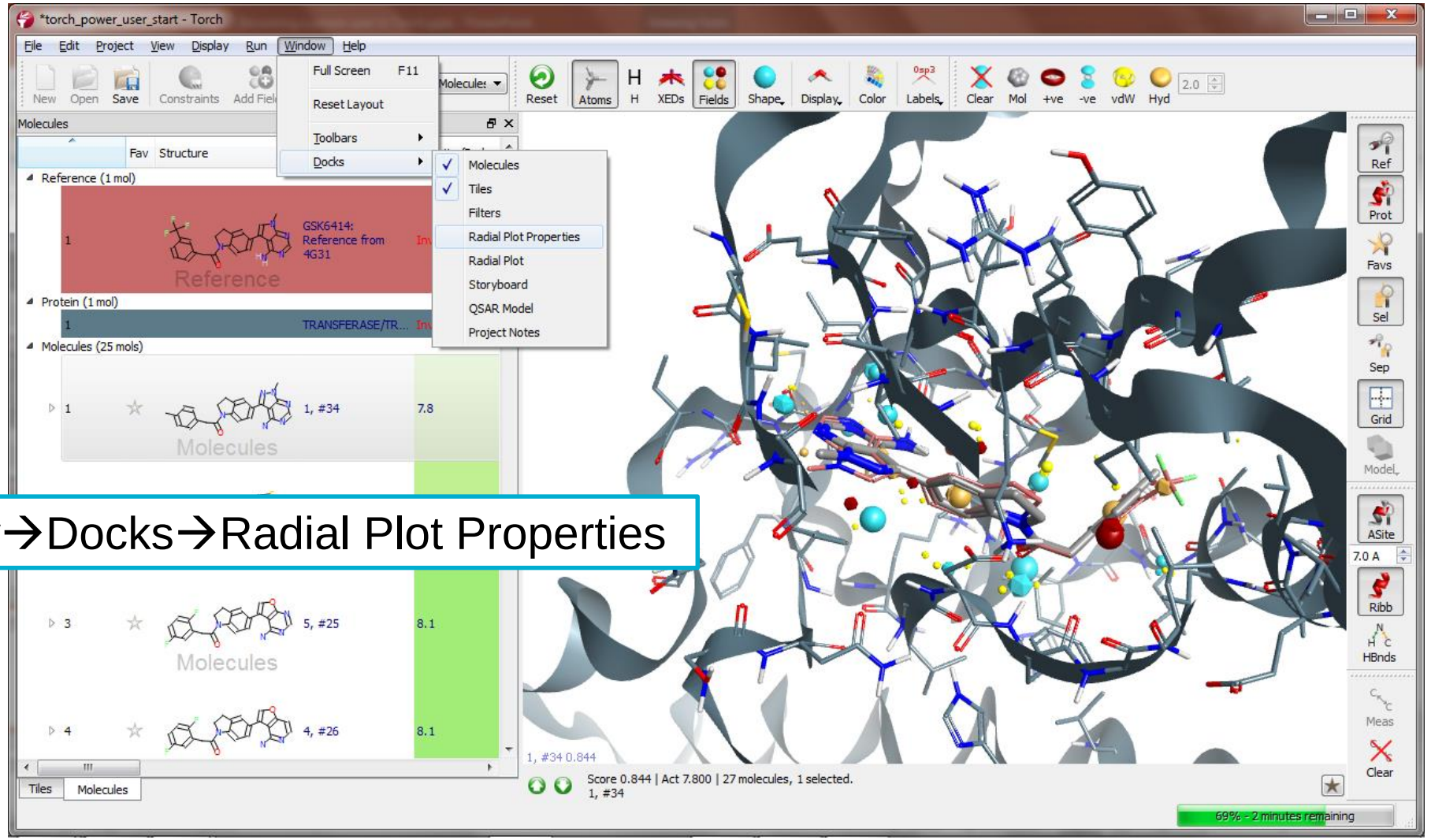


Minimize the calculation



Click ***Hide***

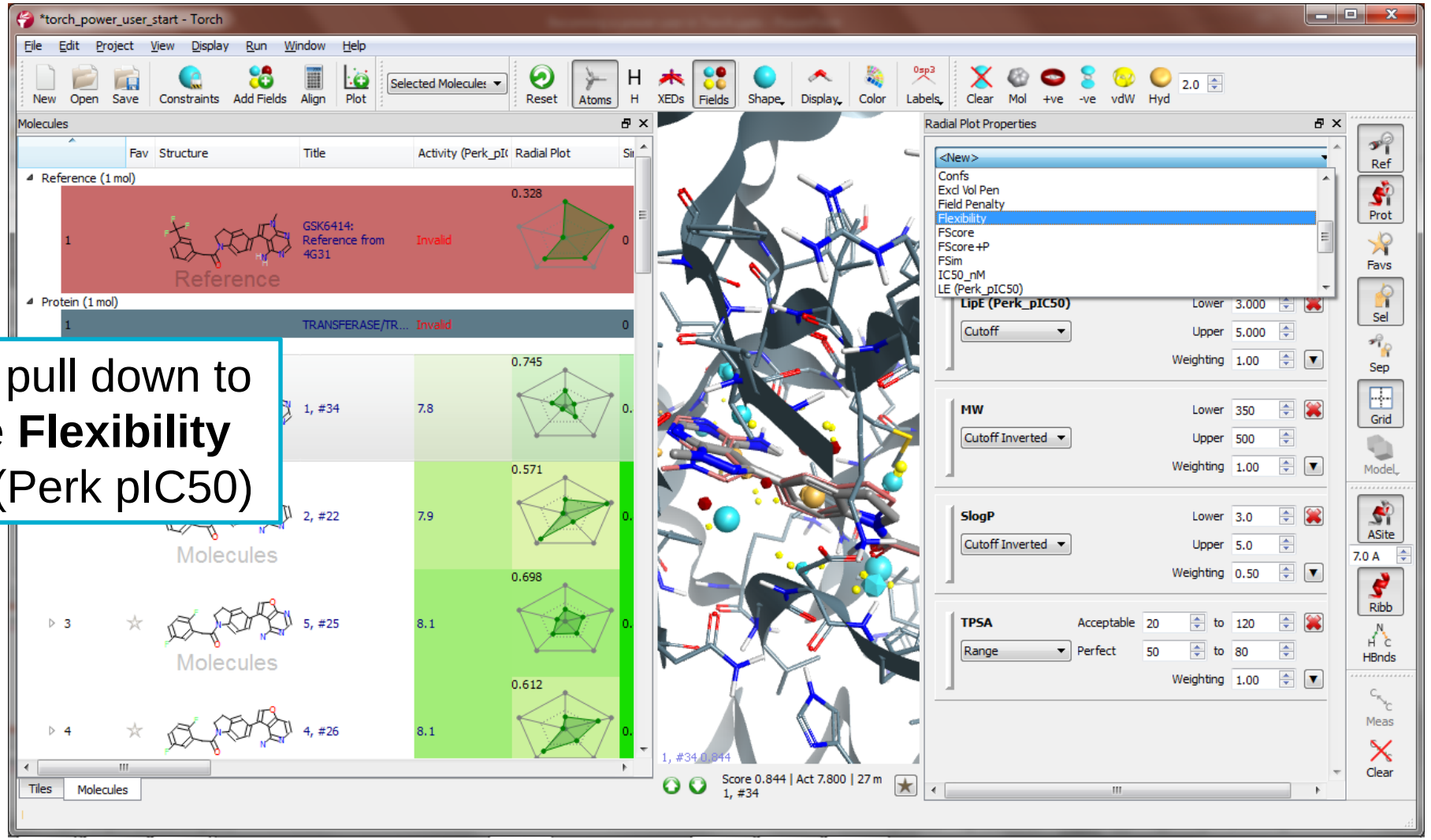
Show the Radial Plot Properties window



Window→Docks→Radial Plot Properties

Add flexibility and LE to the radial plot

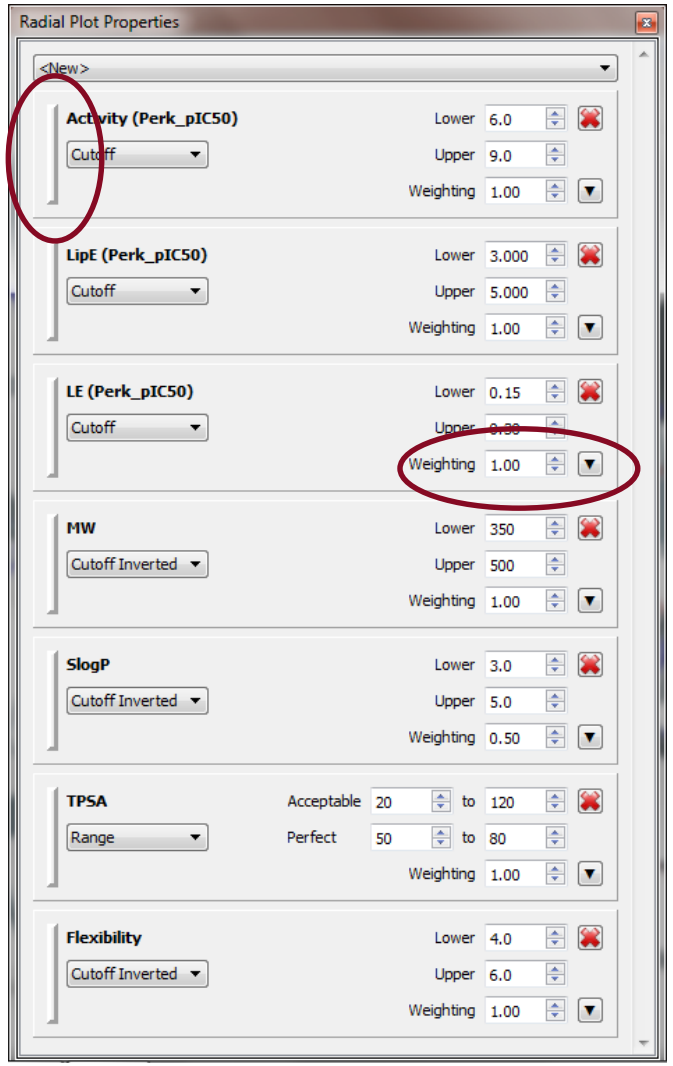
Use the pull down to choose **Flexibility** and LE (Perk pIC50)



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

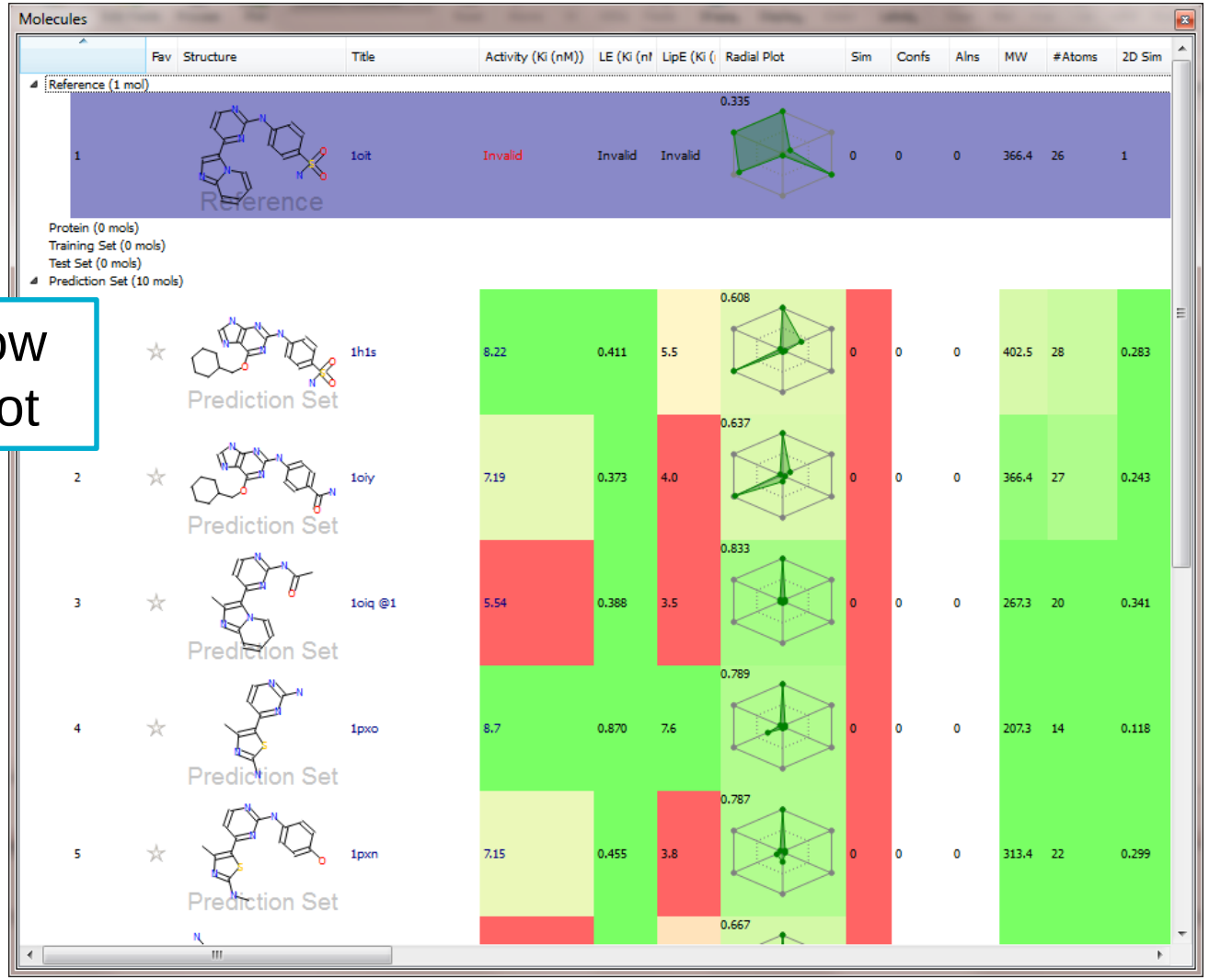


Set the weight of LE to zero

Once complete, the window can be closed

Coloring in the Molecules Table

Note colours follow the fit to radial plot



Improve and simplify the view of the protein

Select protein

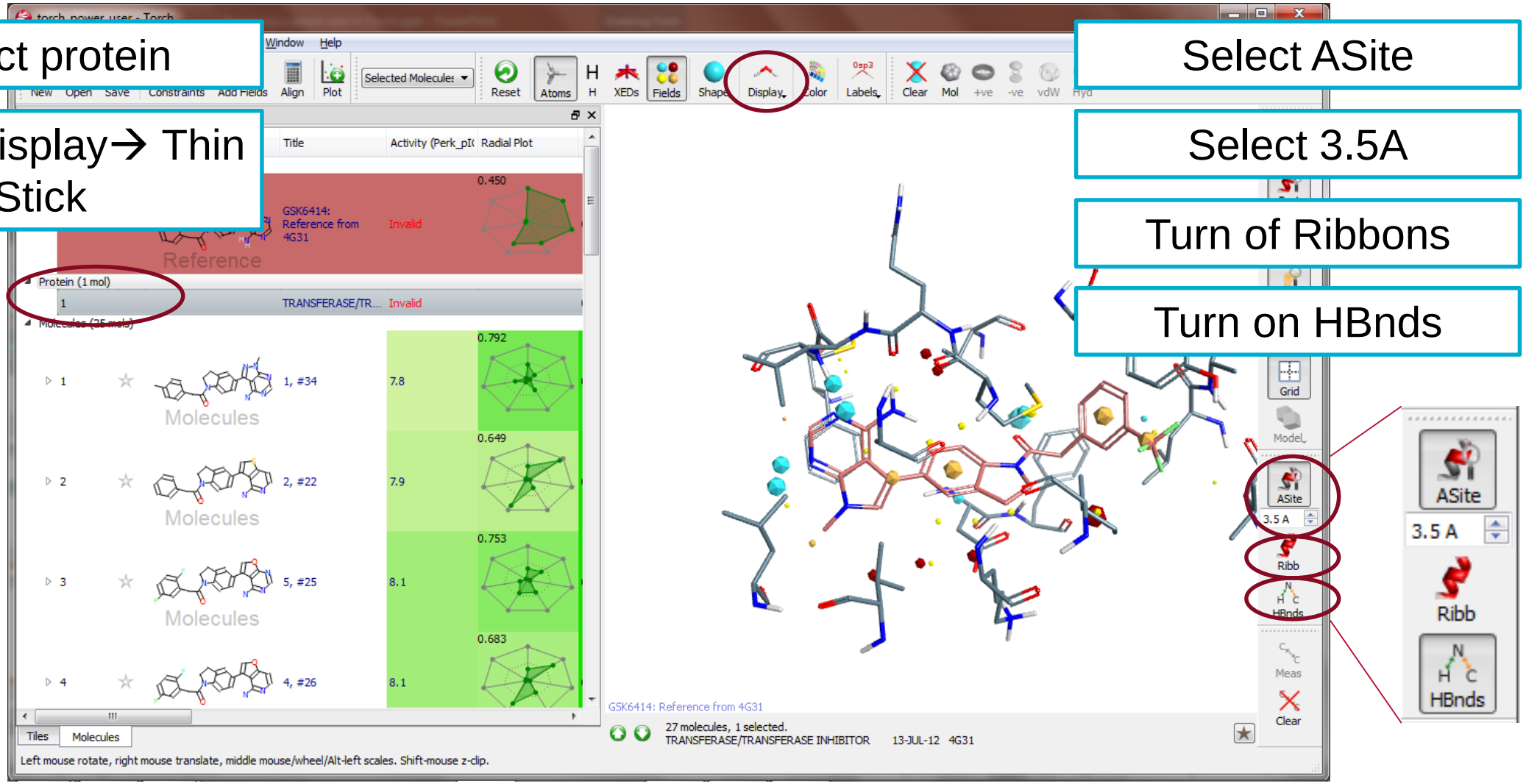
Select Display→ Thin Stick

Select ASite

Select 3.5A

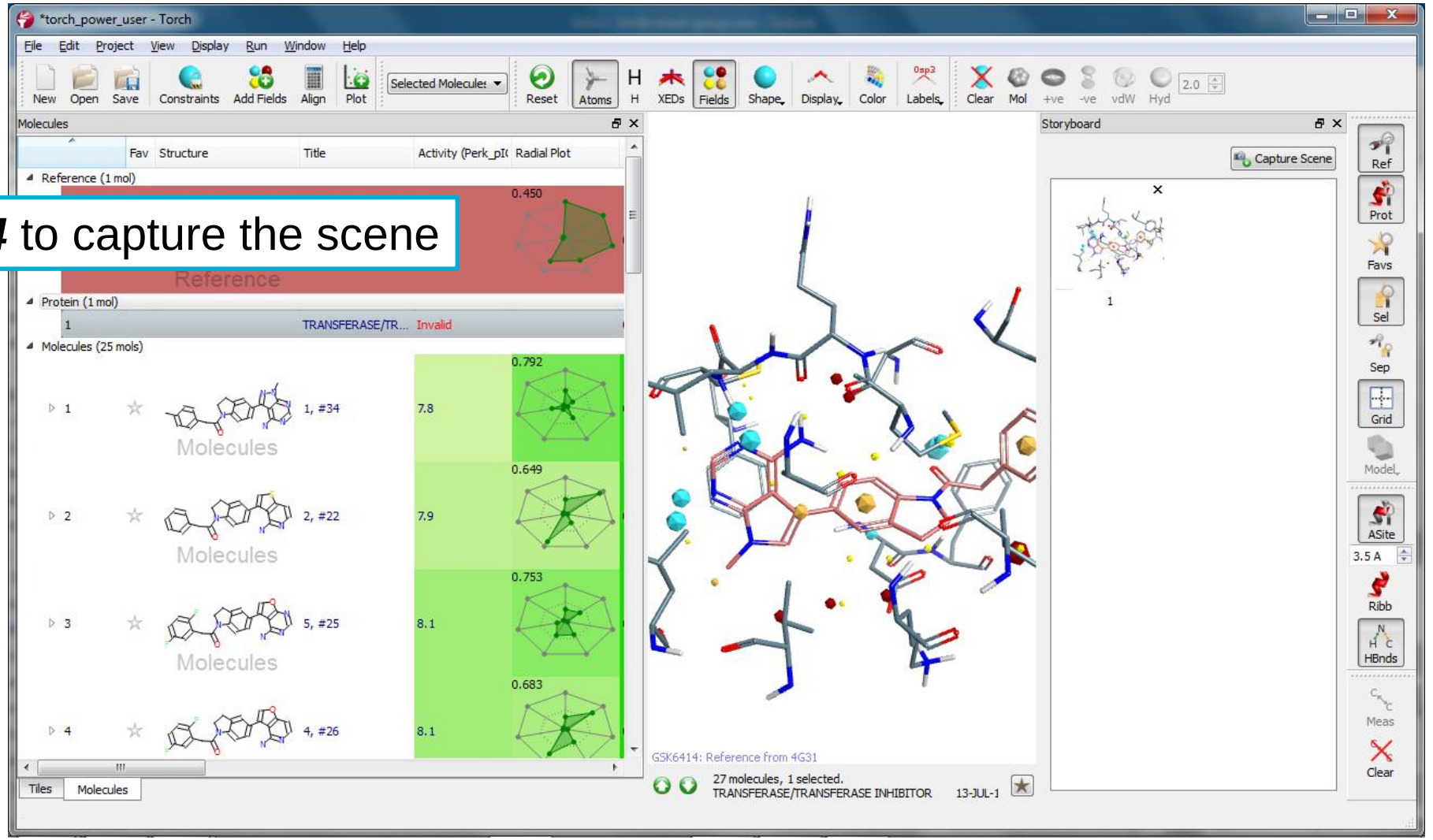
Turn of Ribbons

Turn on HBnds



Snapshot this view

Press ***F4*** to capture the scene

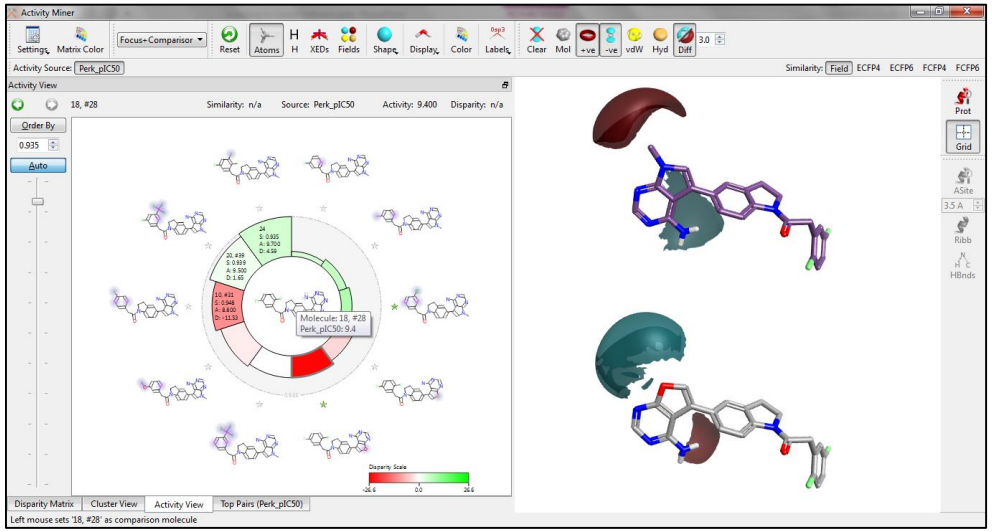


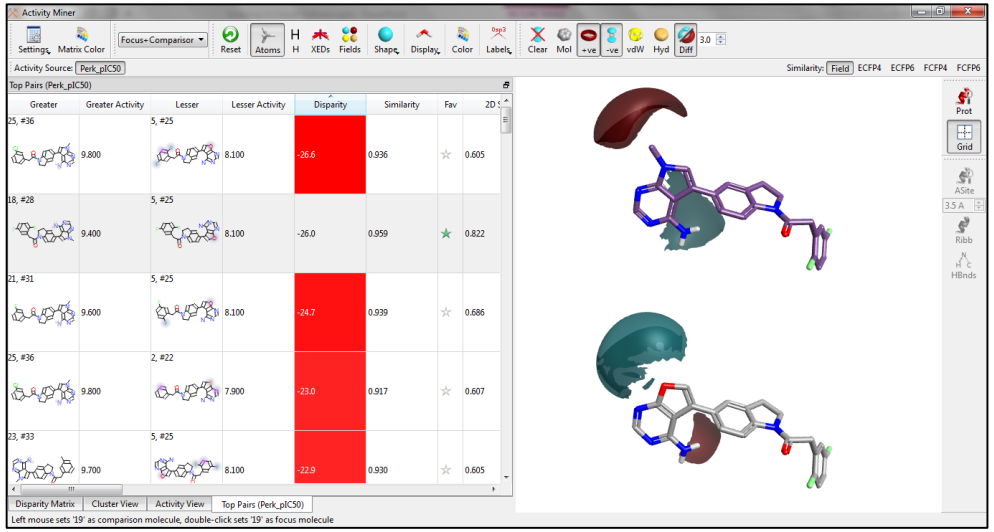
Don’t wait for the calculation to finish

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

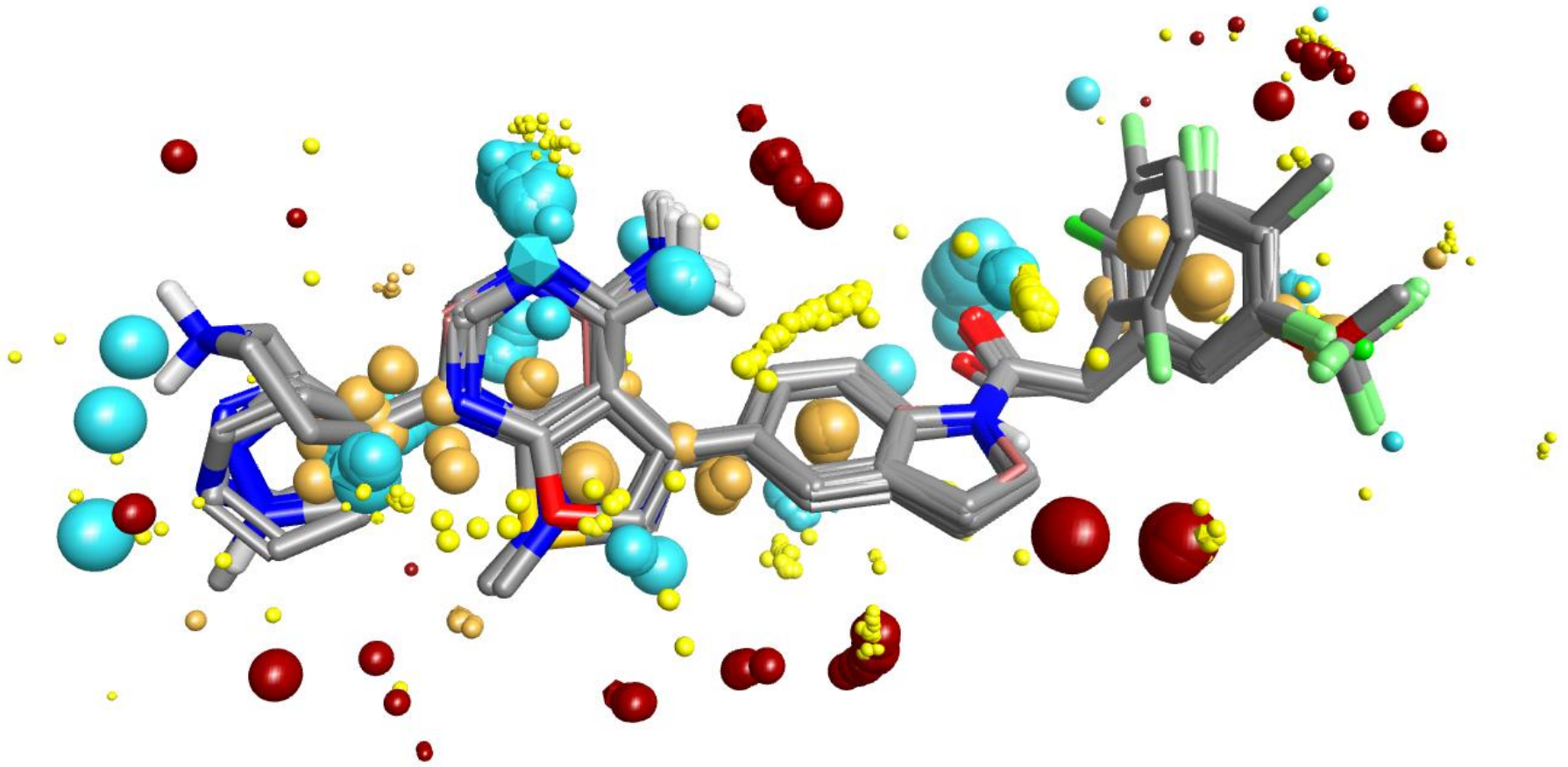
Torch optional module: Activity Miner

- 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





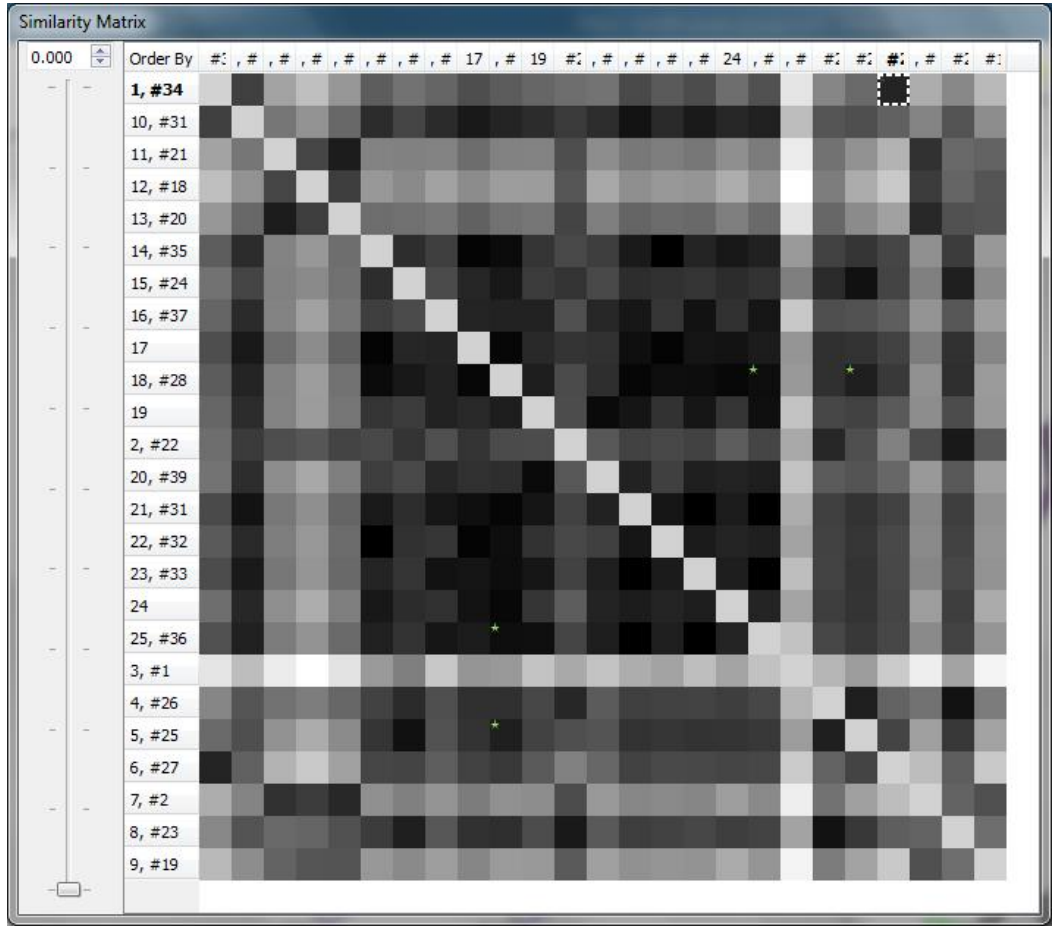
Electrostatic and shape SAR from aligned ligands



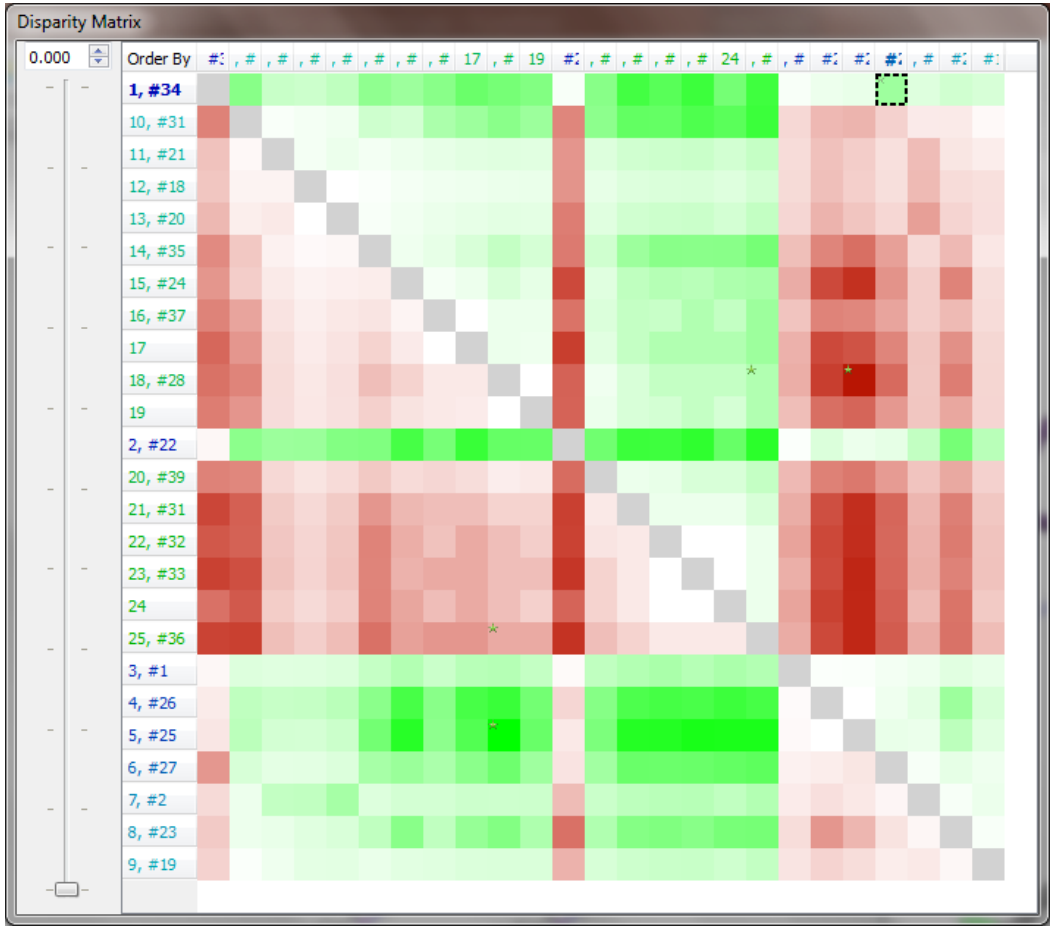
cresset

3D Activity Cliffs

Similarity

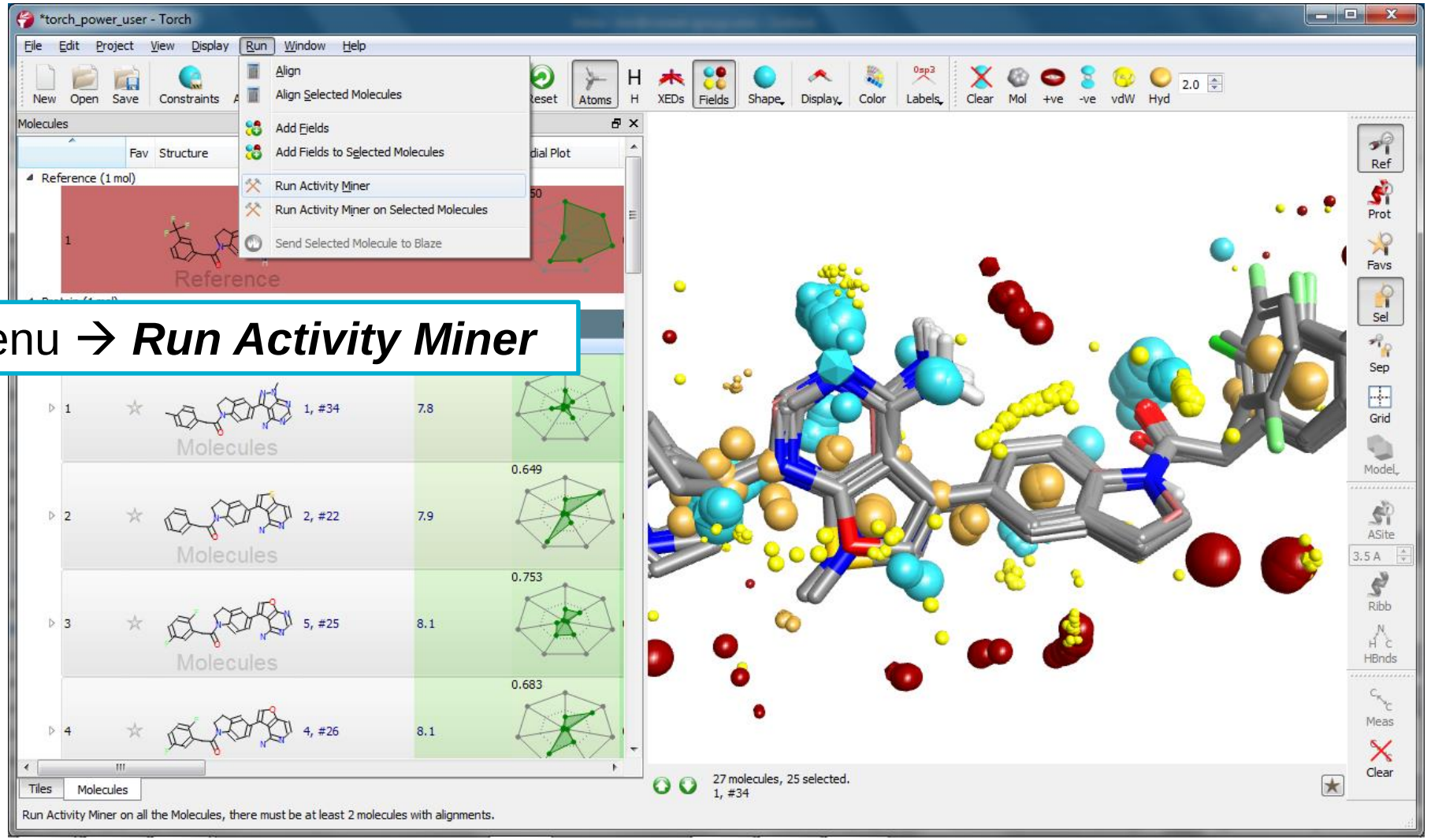


Disparity (Δactivity / 1-similarity)

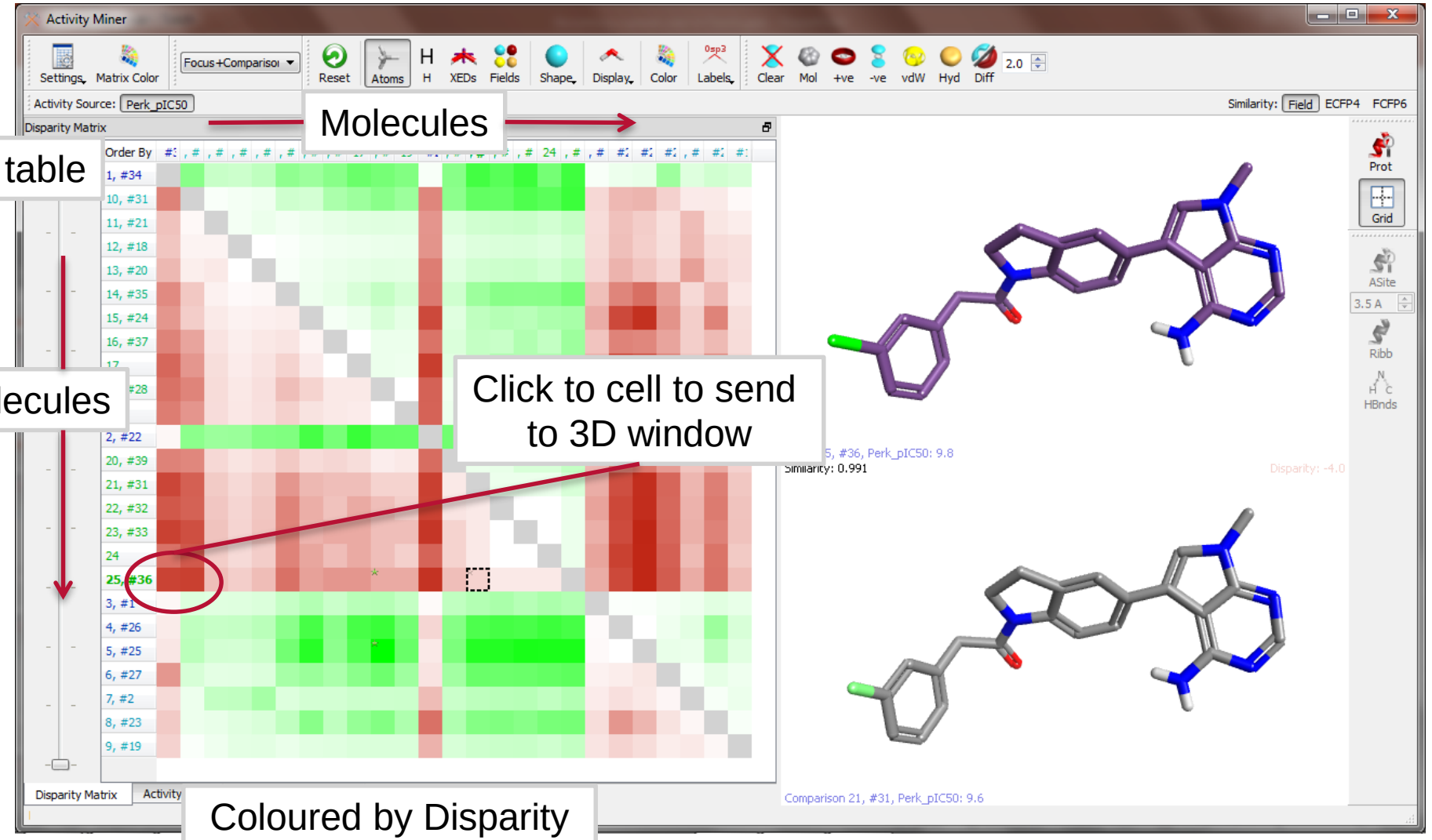


Launch Activity Miner

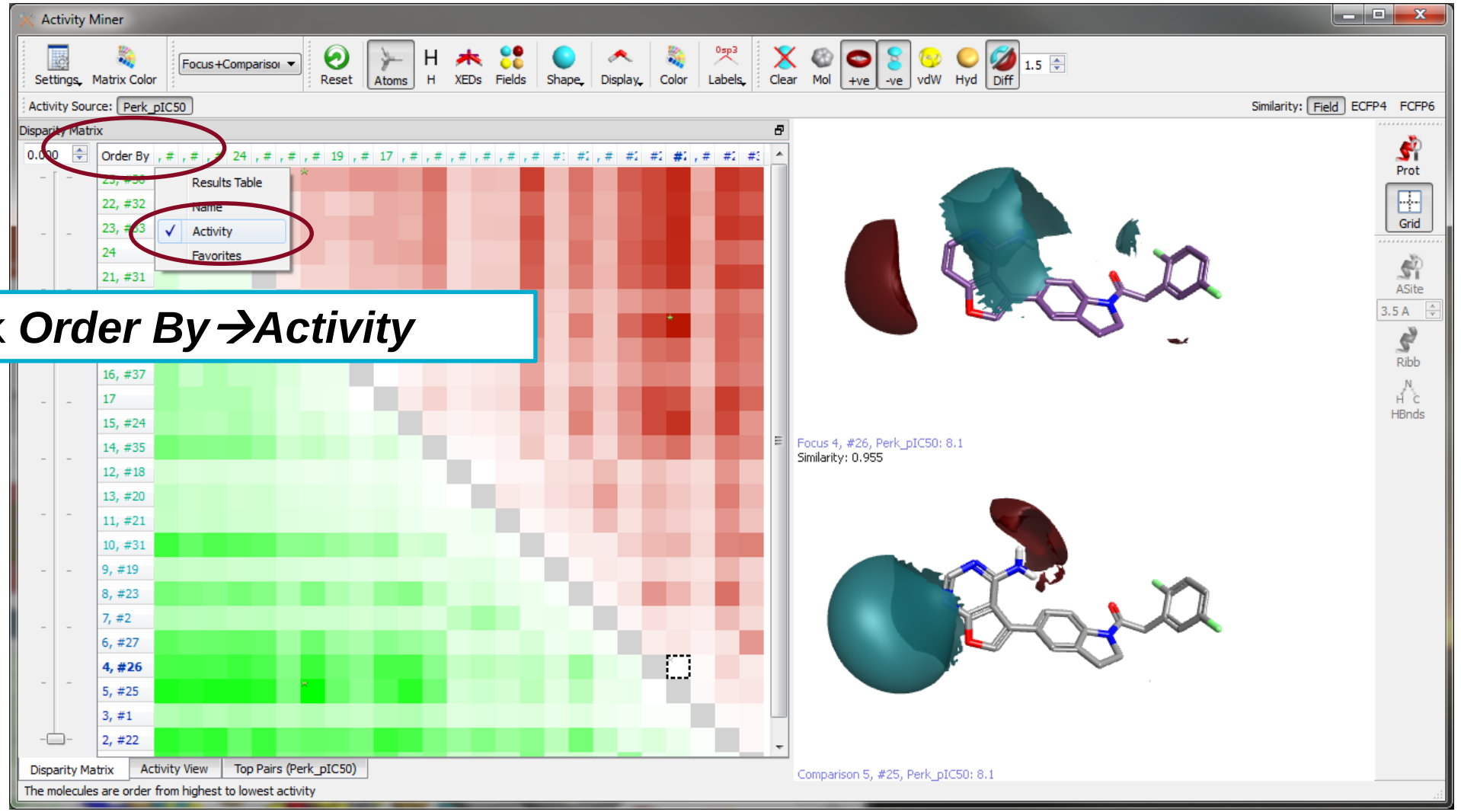
Run menu → ***Run Activity Miner***



Disparity Matrix

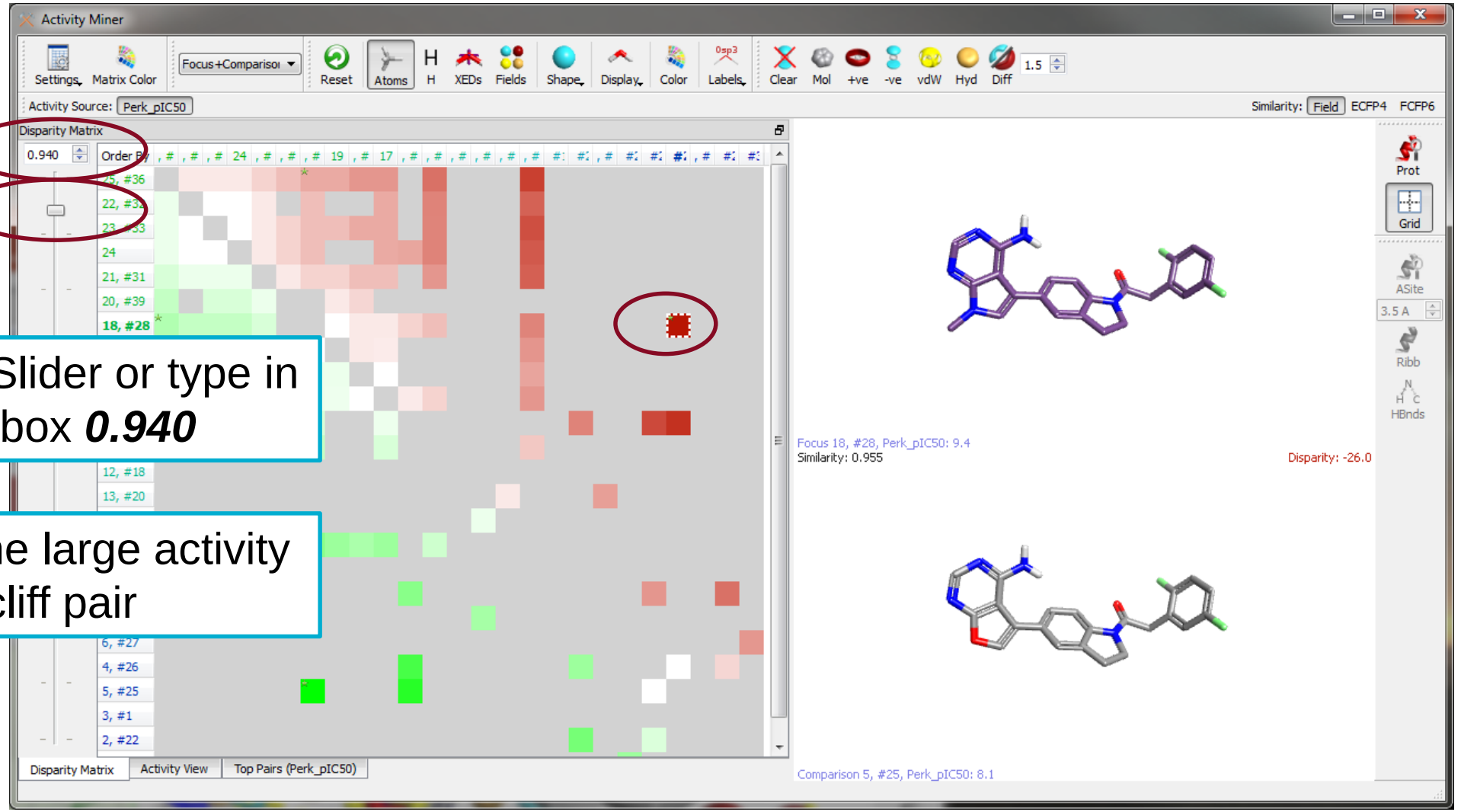


Sort Disparity Table by activity



Click ***Order By→Activity***

Filter to show most similar pairs



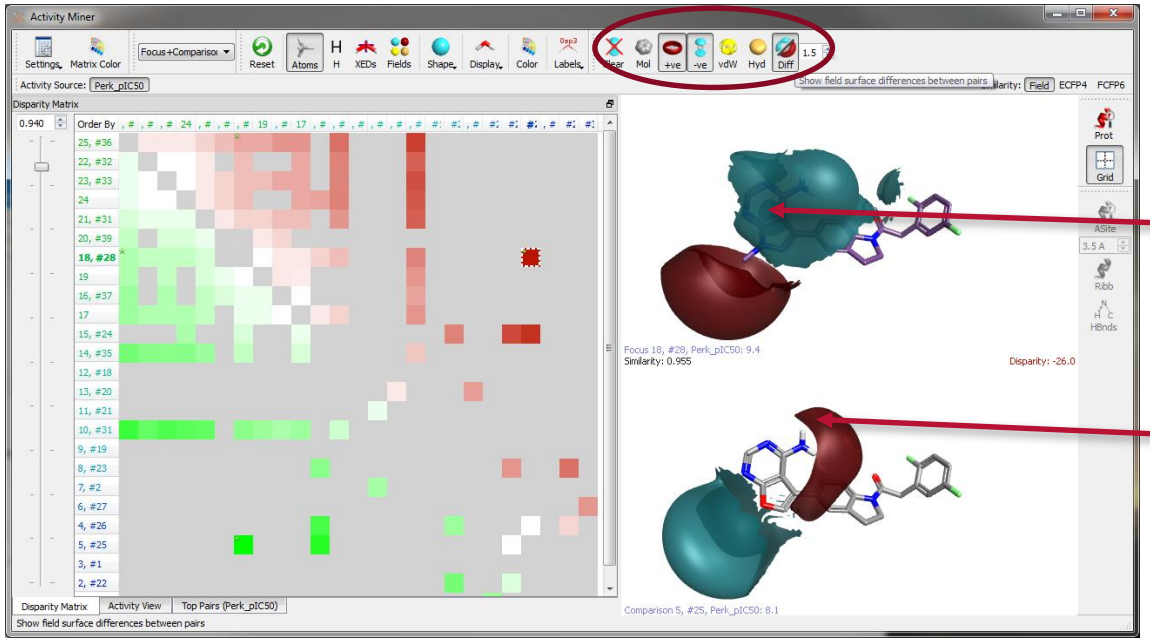
Use the Slider or type in the box ***0.940***

Select the large activity cliff pair

Field differences

Click ***+ve***

Click ***-ve***



Click ***Diff***

> Field difference show the higher potential in each pair

> Always a pairwise comparison

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

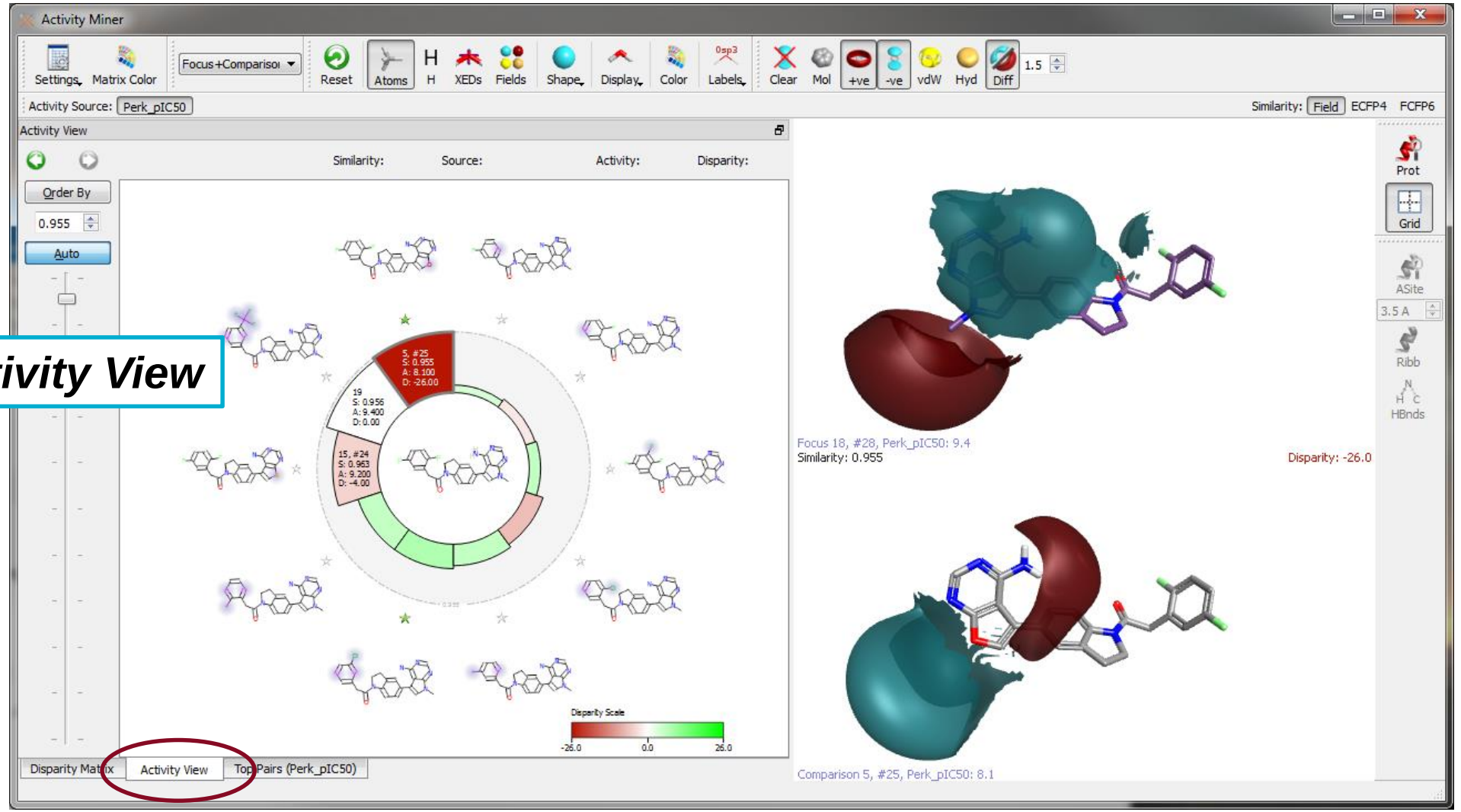
Both have positve NH_2, but the bottom is ***more*** positive

Top Pairs

Click ***Top Pairs***

Activity View: Nearest Neighbors according to 3D

Click ***Activity View***

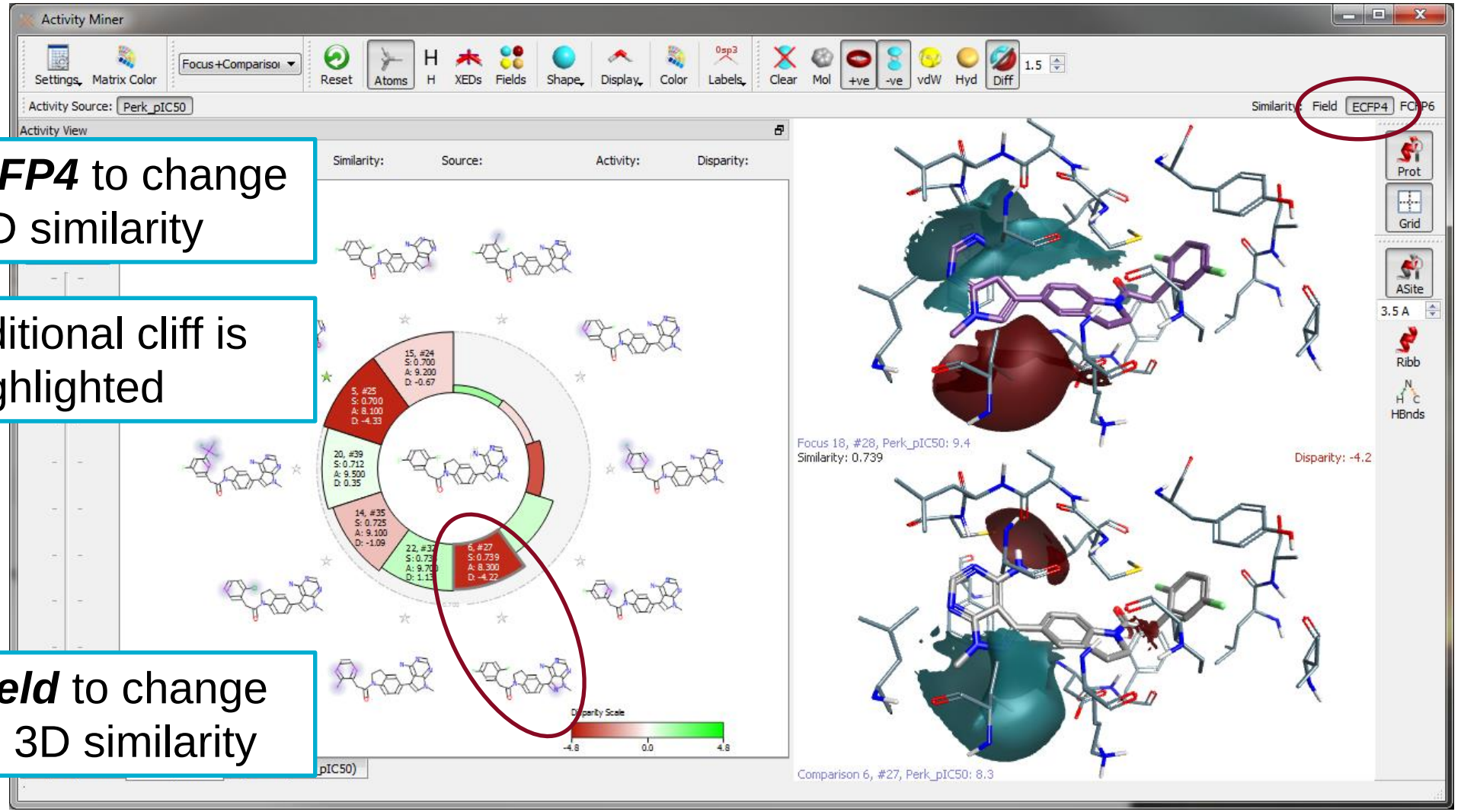


Nearest Neighbors according to 2D

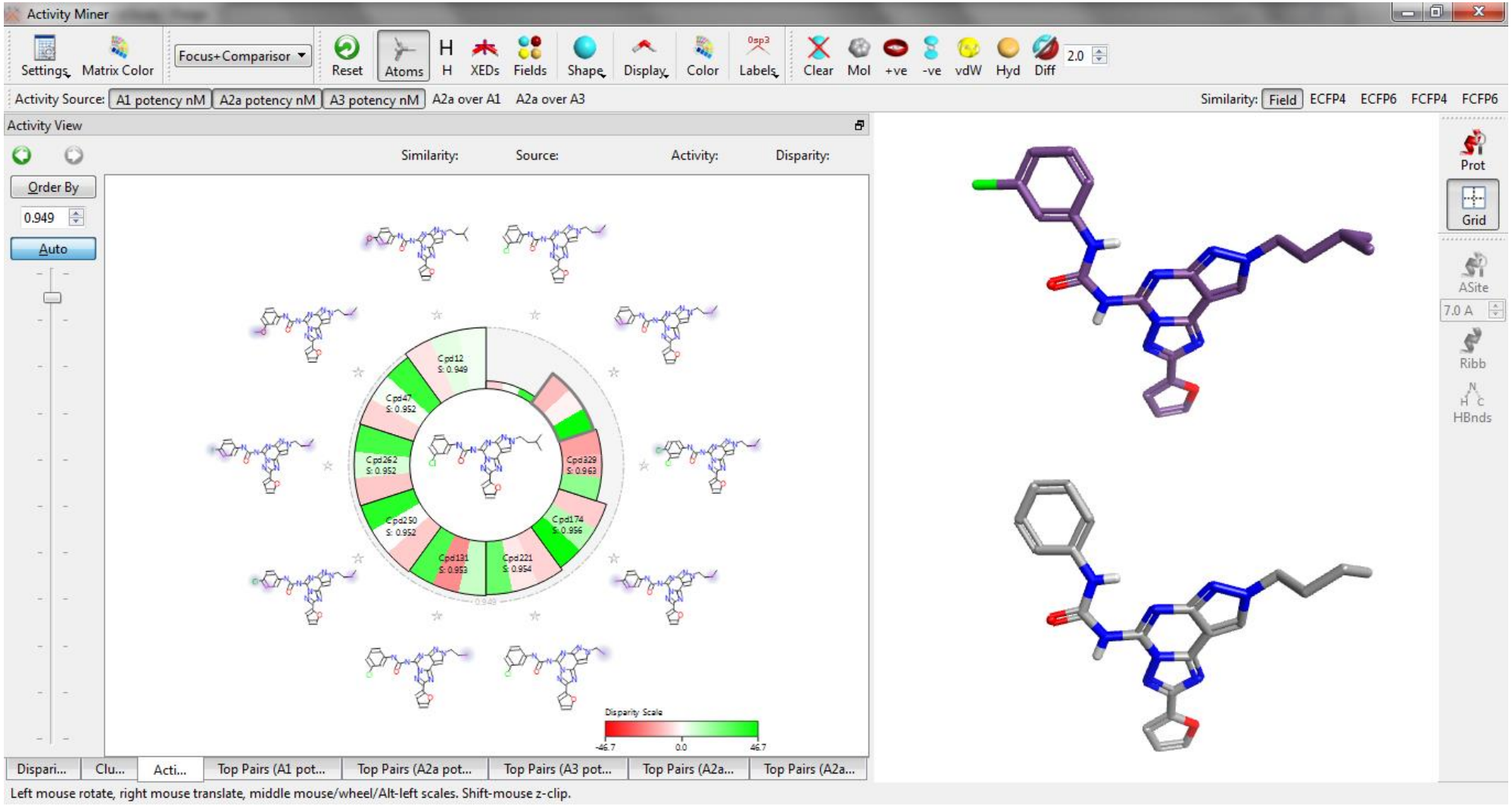
Click ***ECFP4*** to change to 2D similarity

An additional cliff is highlighted

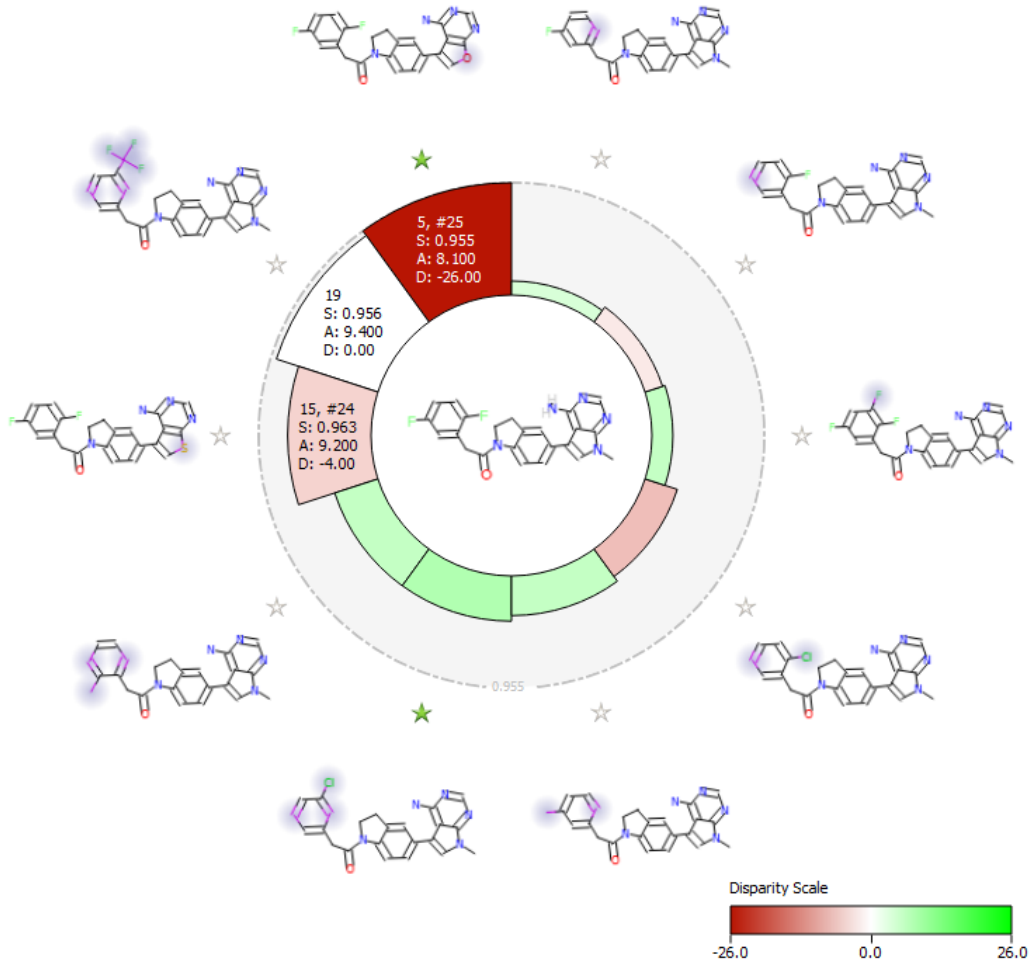
Click ***Field*** to change back to 3D similarity



Selectivity through multiple activities



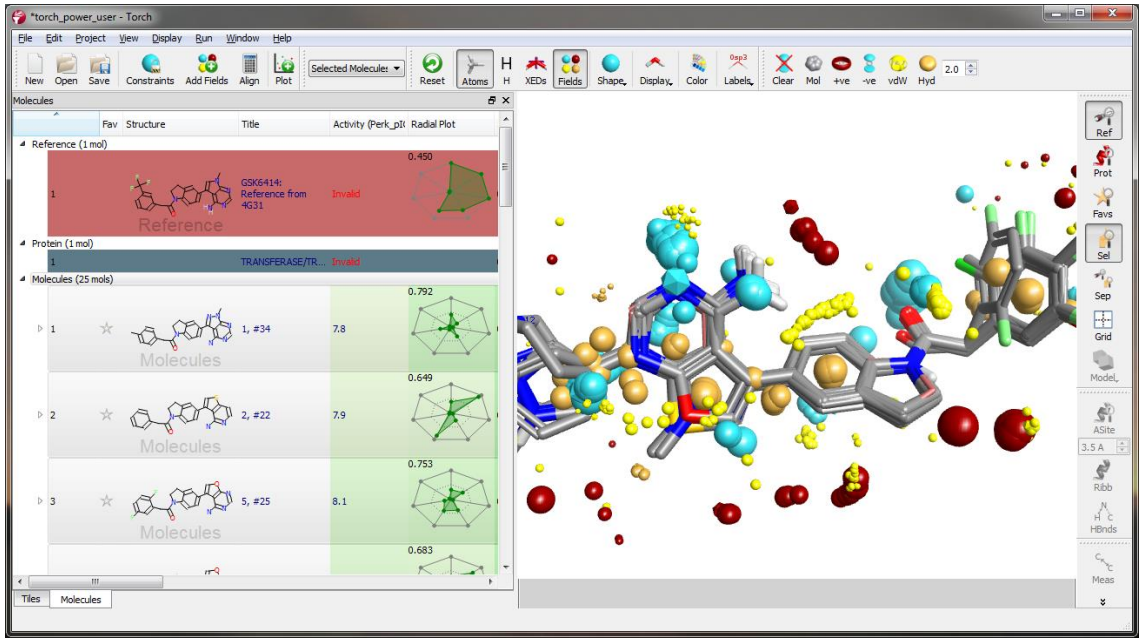
Gross SAR



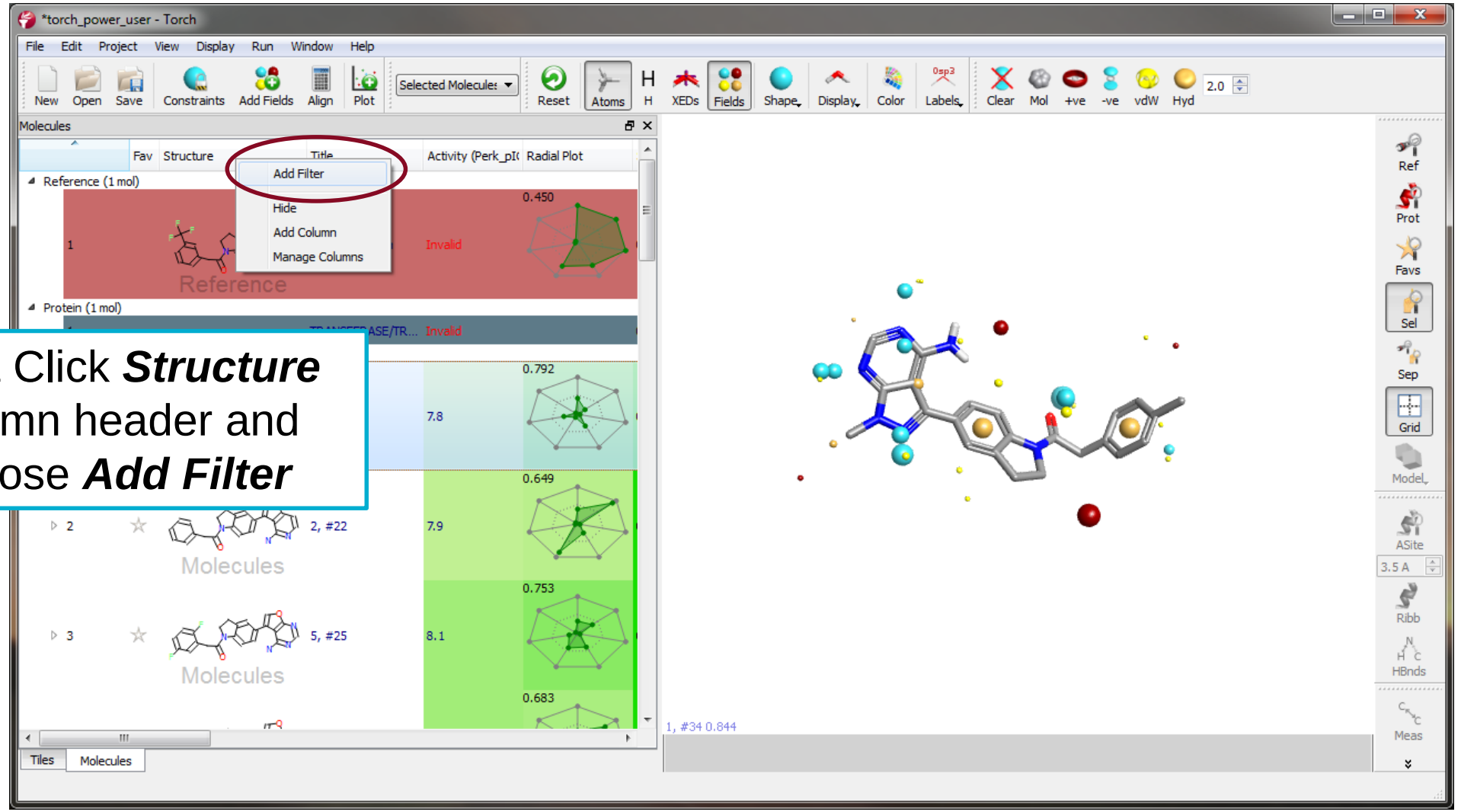
- Clearly SAR around the terminal aromatic and its substitution pattern
- Activity Miner good for investigating this through pair wise comparison
- Alternatively we could look at the molecules in the main Torch interface

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

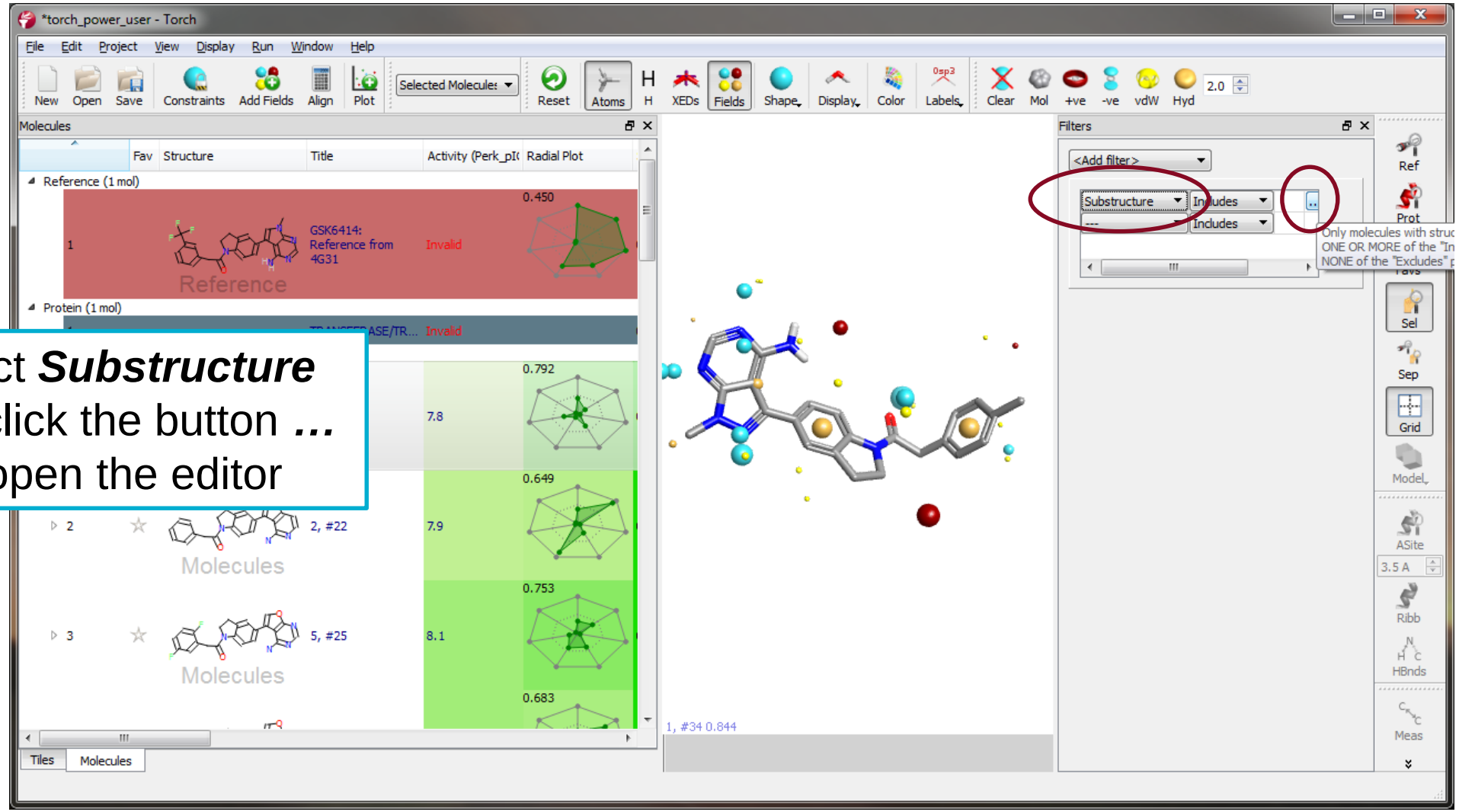


Filter on substructure



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

Substructure filter

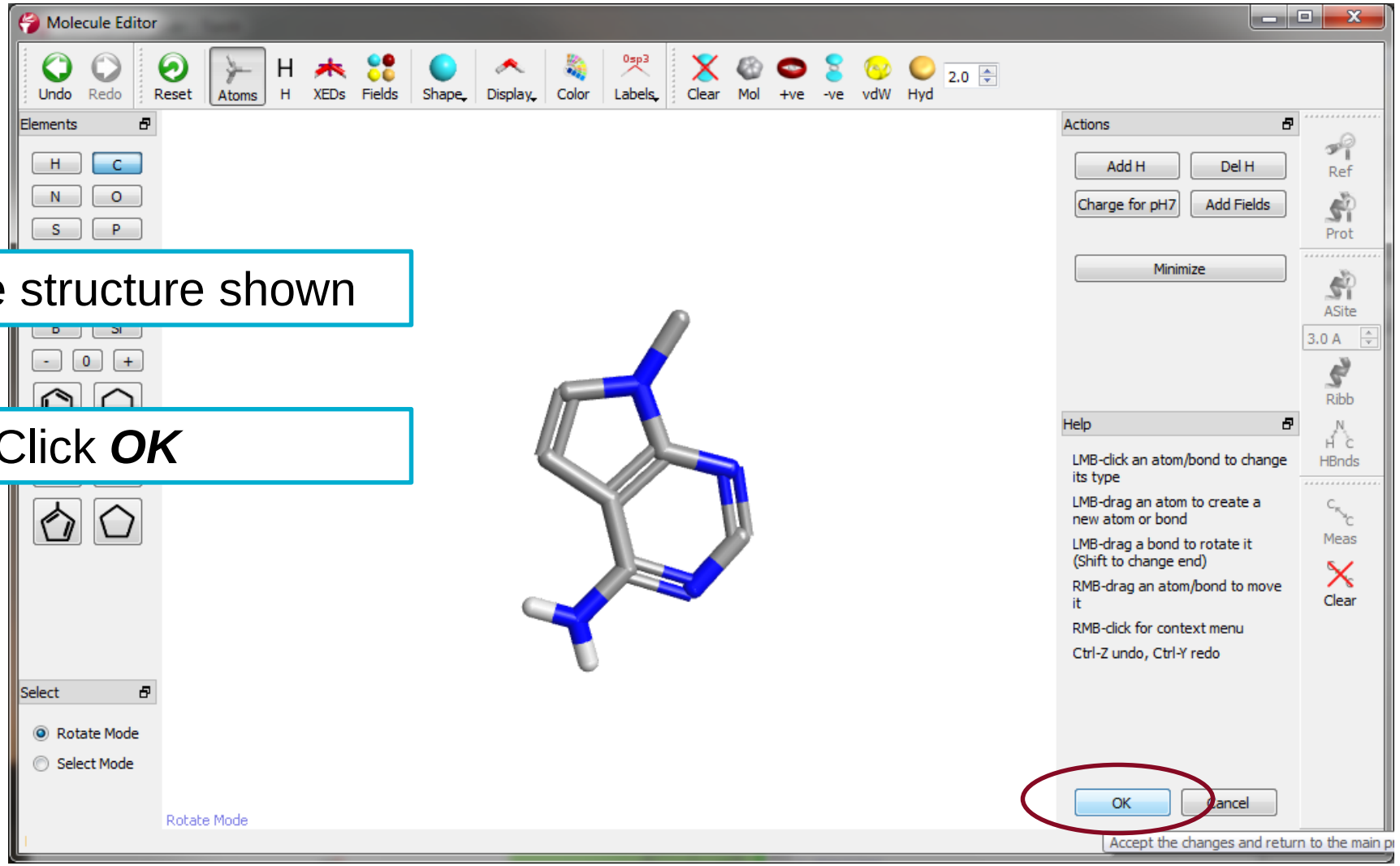


Select ***Substructure*** then click the button **…** to open the editor

Draw substructure

Draw the structure shown

Click ***OK***

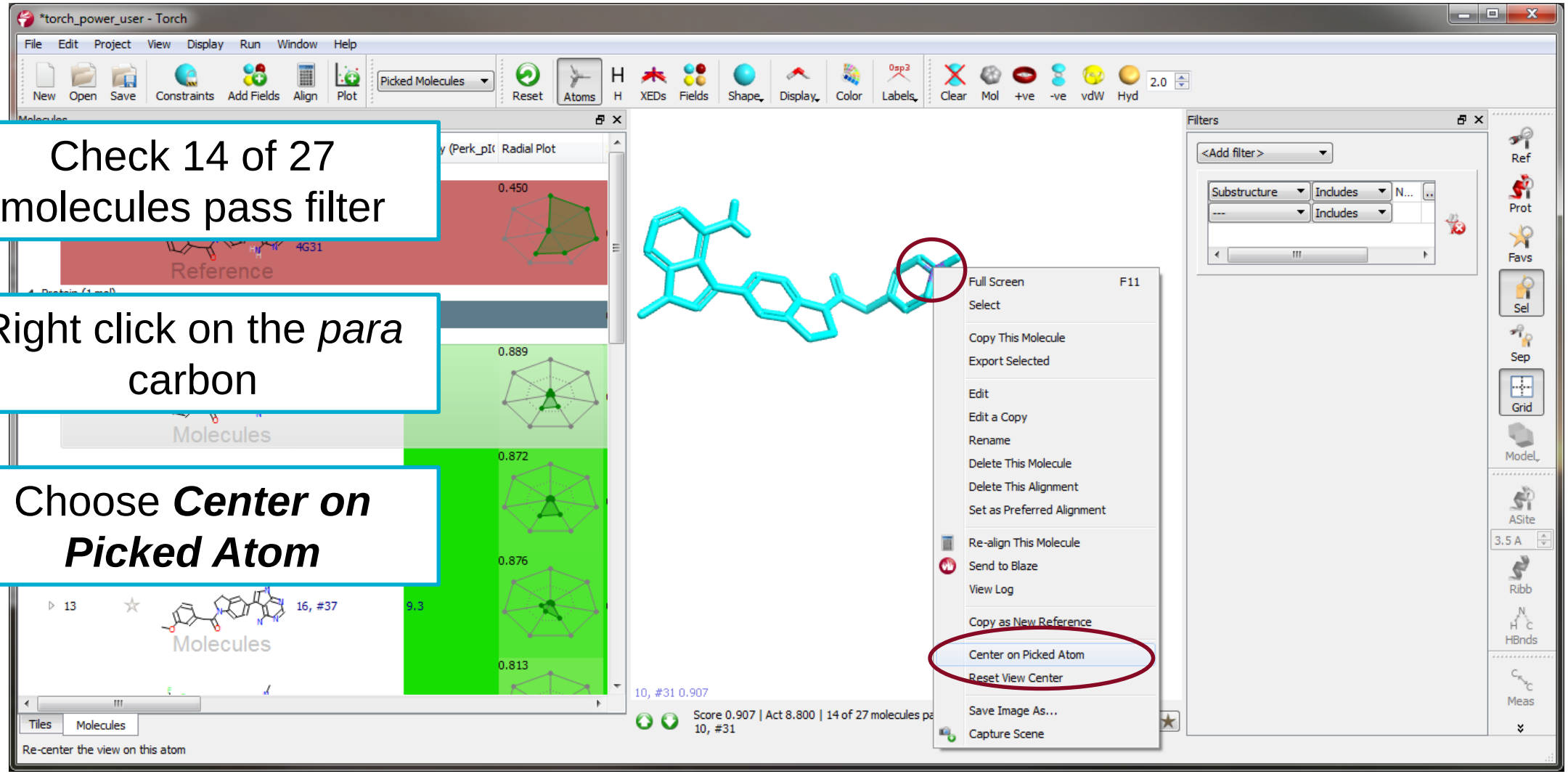


Focus on the terminal aromatic

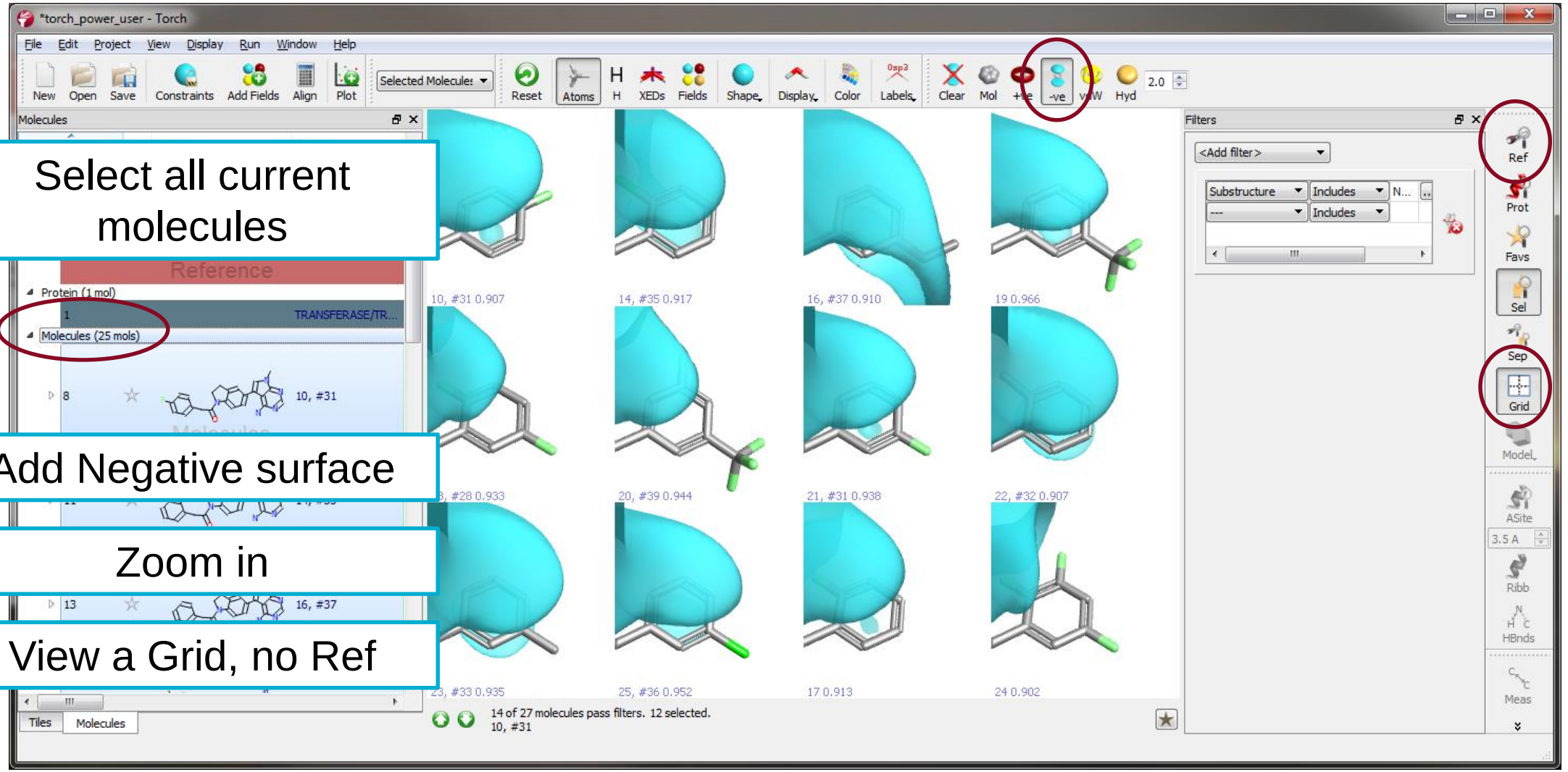
Check 14 of 27 molecules pass filter

Right click on the *para* carbon

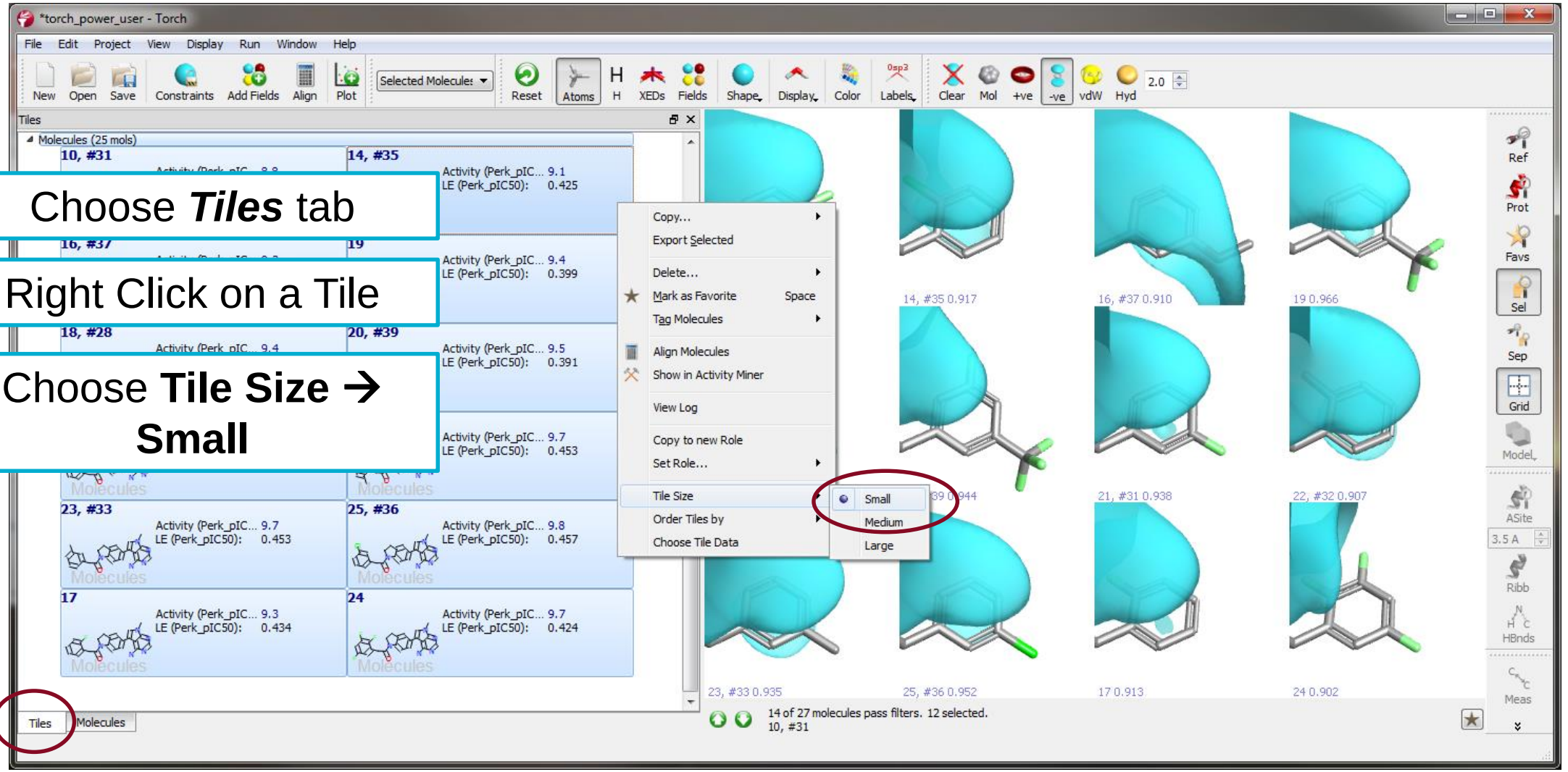
Choose ***Center on Picked Atom***



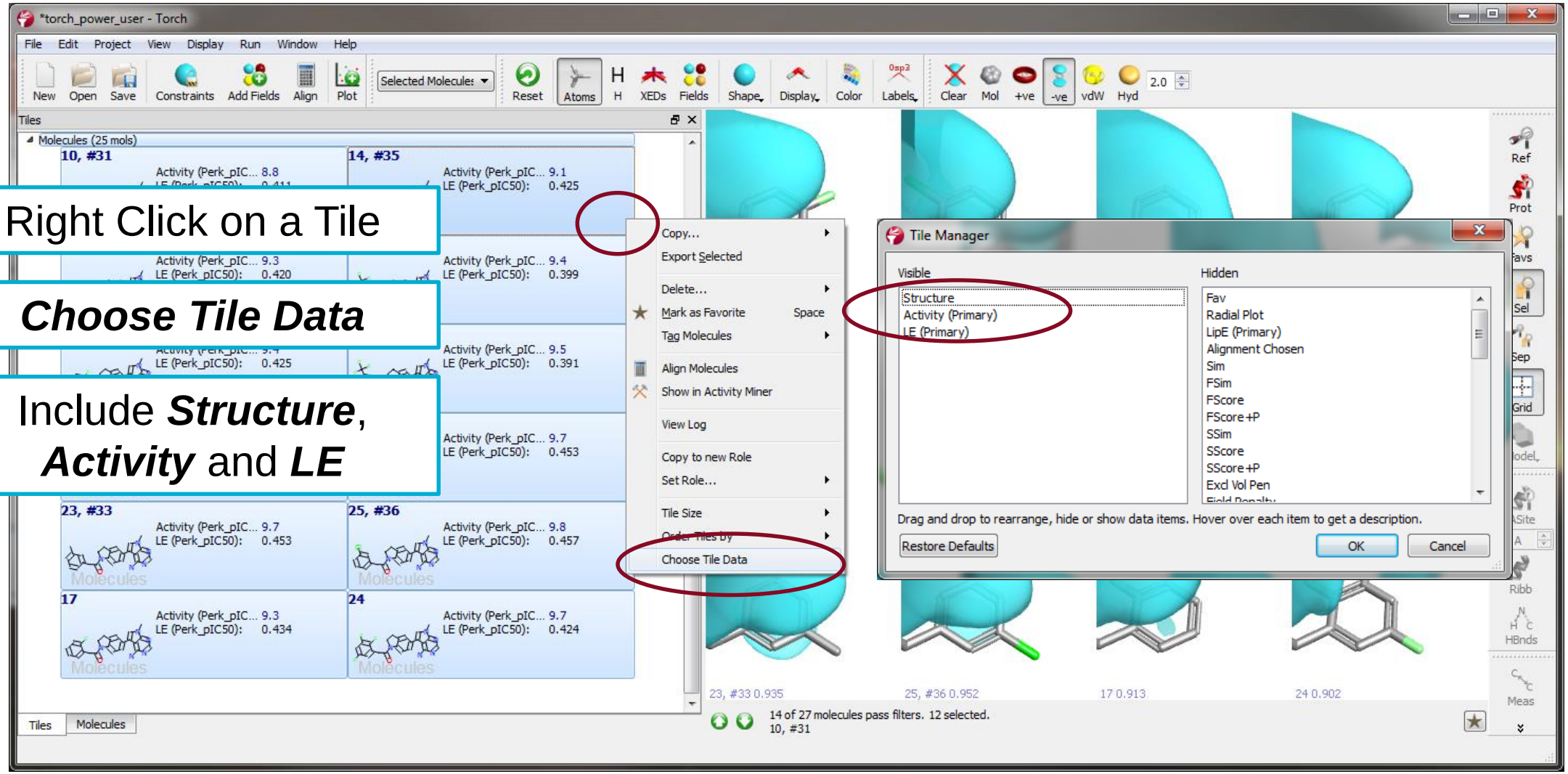
Electrostatics of terminal aromatic



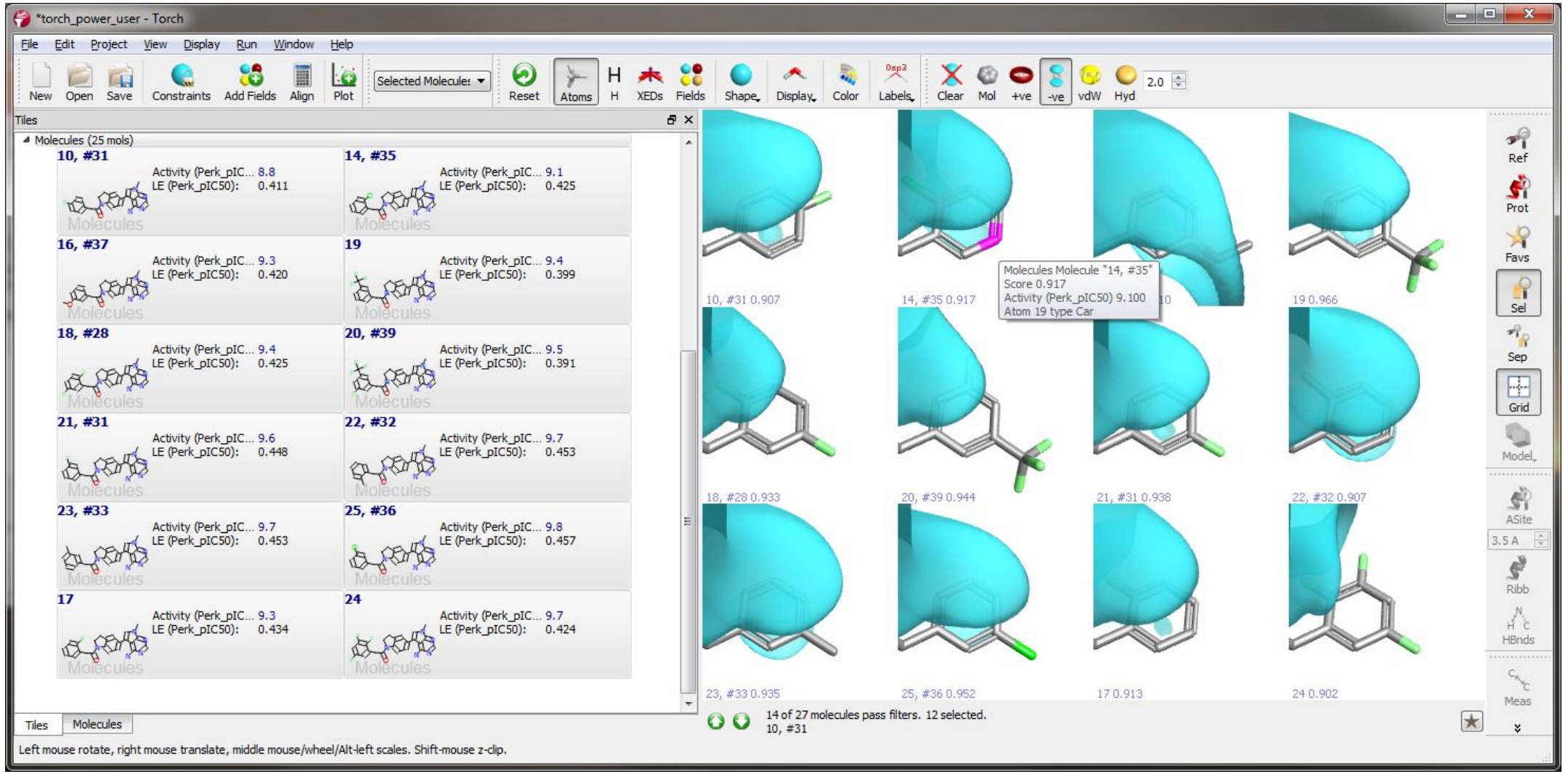
View 2D, data and 3D at the same time



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



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

- Create a story of key SAR points
- Make sure you include protein interactions

- Change the default data that is used on Tiles
- Change the defaults to create large high resolution pictures
- Change the background to grey

- Which molecule fits the project profile the best?
- Is it the highest active?

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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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