innovative science • intuitive software

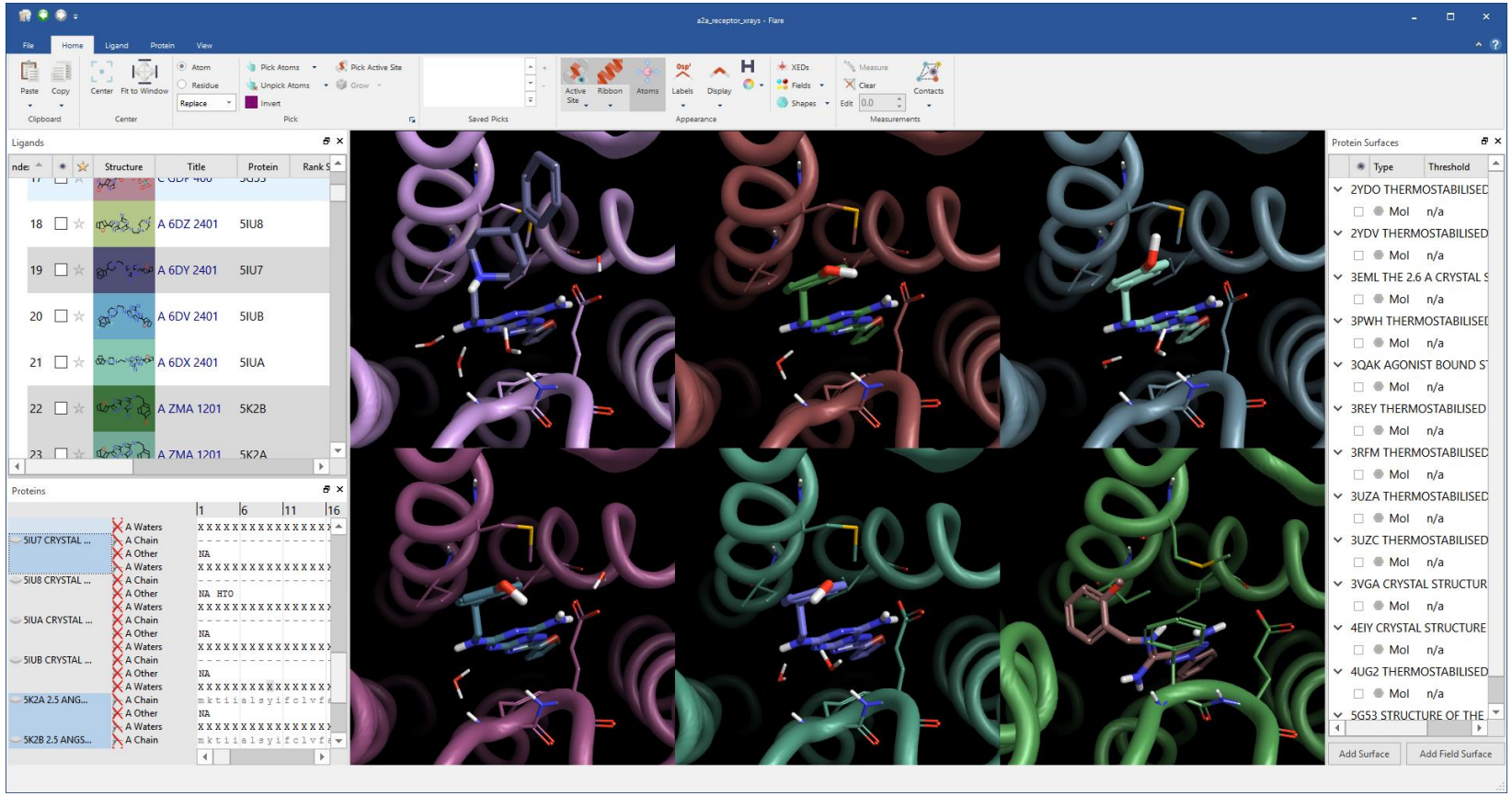
Flare V2:
Raising the Bar in Structure-based Design

Mark Mackey

Flare: Providing new insights for structure based design

Last year we launched Flare™ 1.0

- > New foray for Cresset into SBDD
- > New methods
- > New look
- > Easy to use



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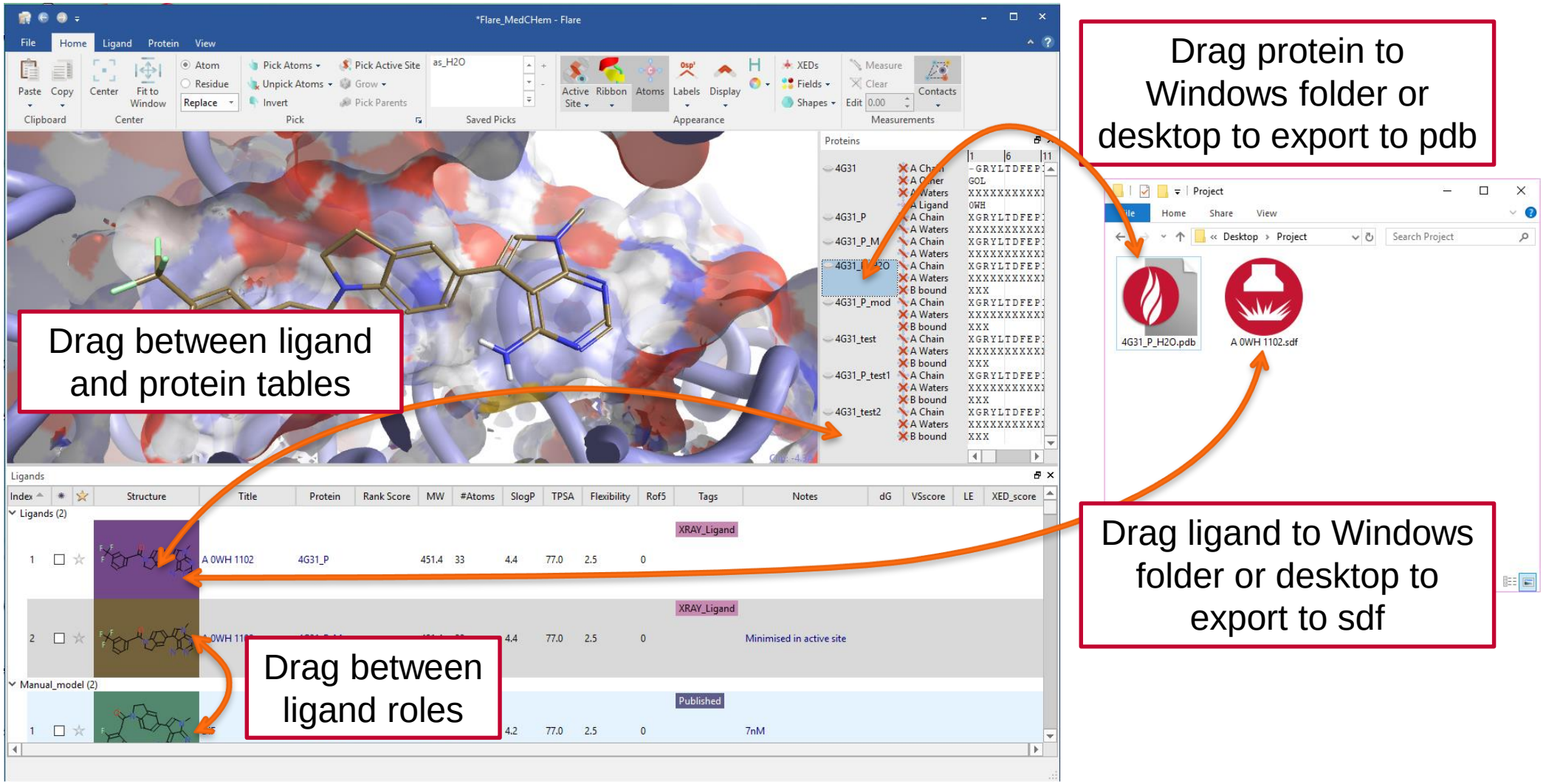
Extensive drag and drop support



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Flare: Providing new insights for structure based design

Cresset are now proud to announce the release of Flare 2.0

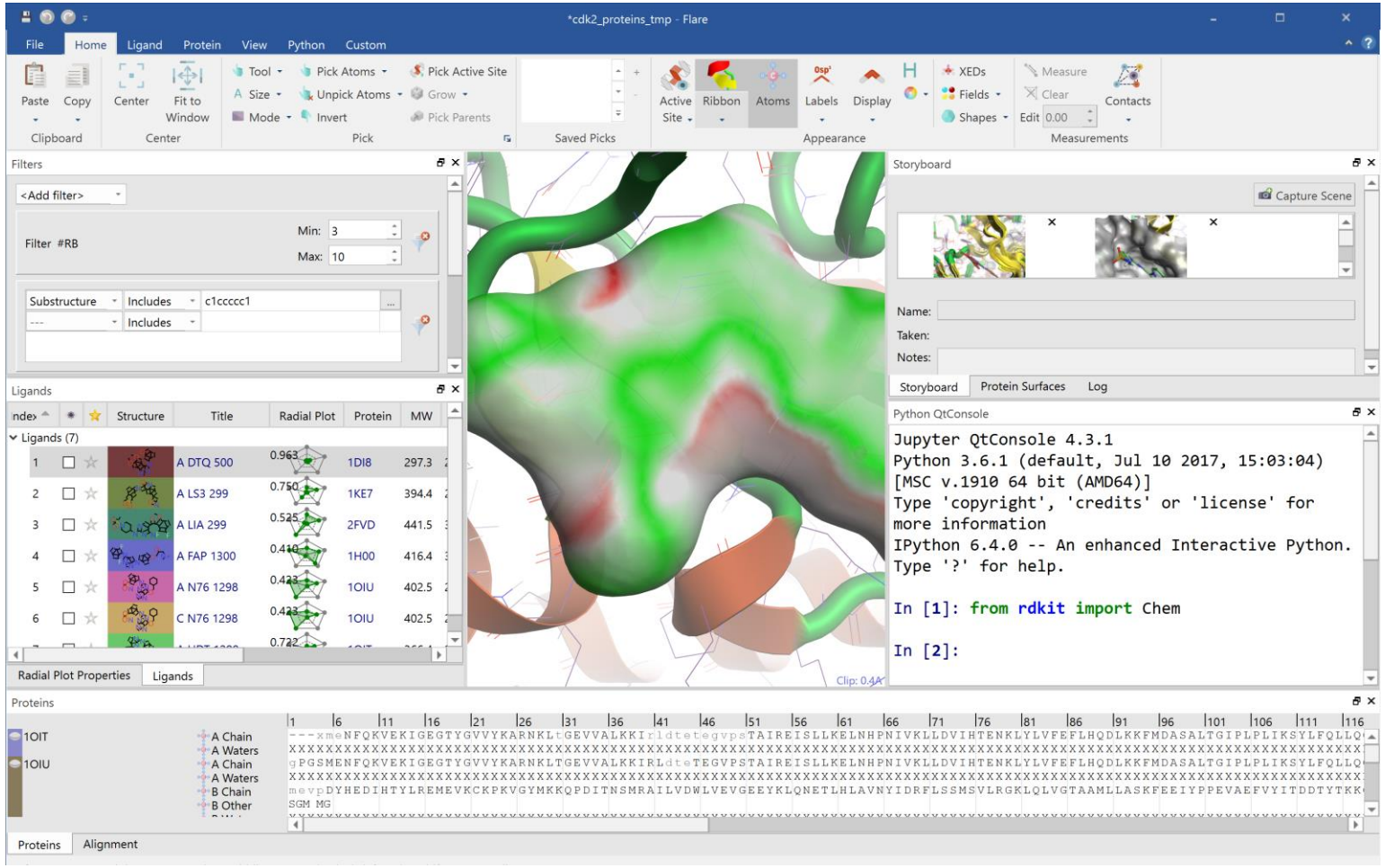
> More science

> More features

> Looks better

> Still easy to use!

Focus on designing better ligands



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Why use Flare?

Cutting edge science

- Electrostatic Complementarity™ (EC)
  - Scoring
  - Visualization
- Protein interaction potentials
  - Gain vital knowledge of protein and ligand electrostatics to improve new molecule design
- 3D-RISM using XED or AMBER force fields
  - Understand the locations and stability of water in your protein
- WaterSwap analysis
  - Find the energetic hotspots in your protein

Easy workflows

- Ligand focus with phys-chem properties and multi-parametric scoring
  - Tagging of ligands
  - Filtering using properties or sub-structure
- Accurate docking using Lead Finder
  - Excellent reproduction of protein-ligand poses
  - Ensemble docking for handling active site flexibility
- Storyboard to capture important scenes
- Python scripting
- UI customizations

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Electrostatics

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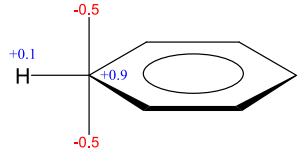
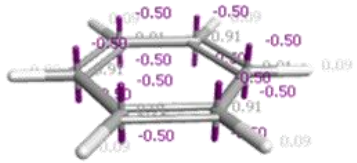
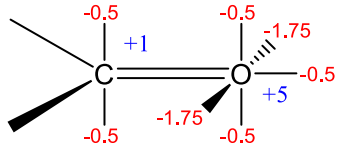
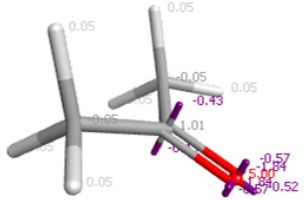
The Cresset difference - the XED force field

- XED force field – eXtended Electron Distribution
  - Multipoles via additional monopoles

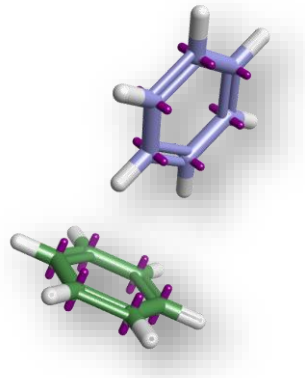








  - Huckel
    - separation of π and σ components of partial charges
      - π charges added to ‘xed’ atoms
      - σ charges added to nuclei
      - Excellent modeling of substituent effects
    - find bond orders and assign hybridization
      - Analogue N(sp^3) atoms – pyramidal to planar



  - Full molecular mechanics force field with excellent coverage of organic chemistry, water and proteins
    - Minimization, conformations etc.
    - Not a dynamics force field

Vinter, *J. Comput.-Aided Mol. Des.*, **1994**, 8, 653-668

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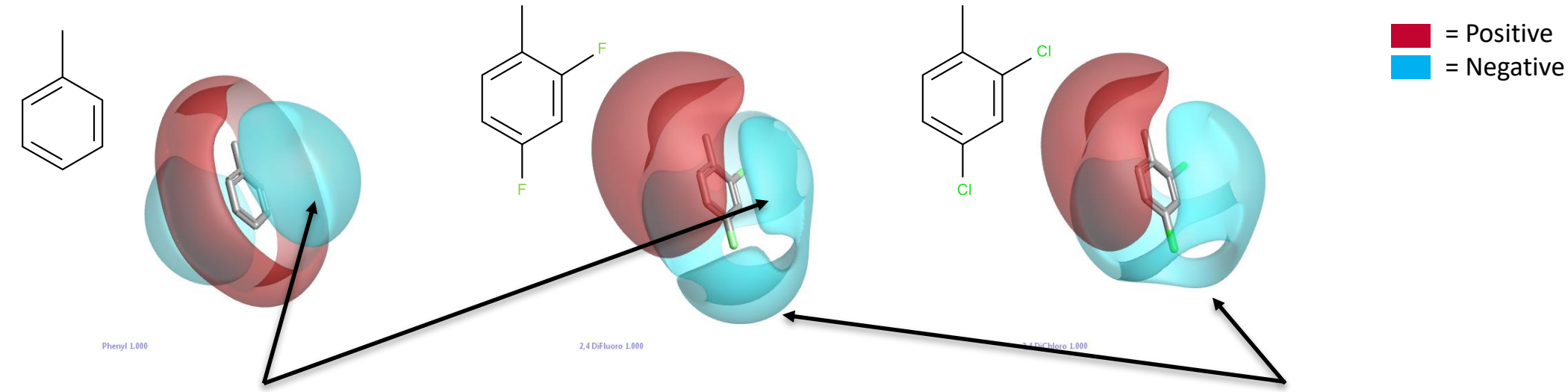
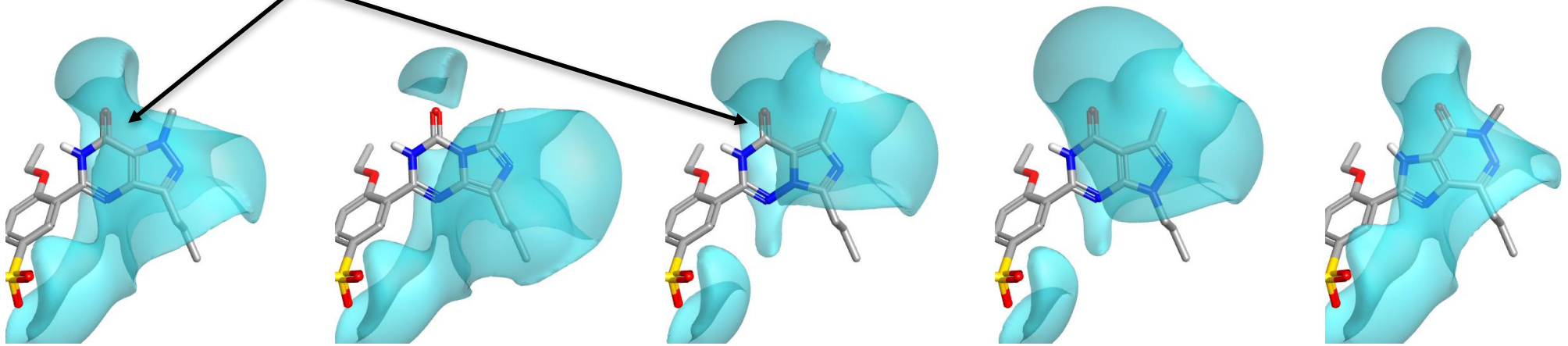
XED electrostatics generate detailed ligand interaction patterns



Detailed simulation of electrostatics

Detailed description of halogens



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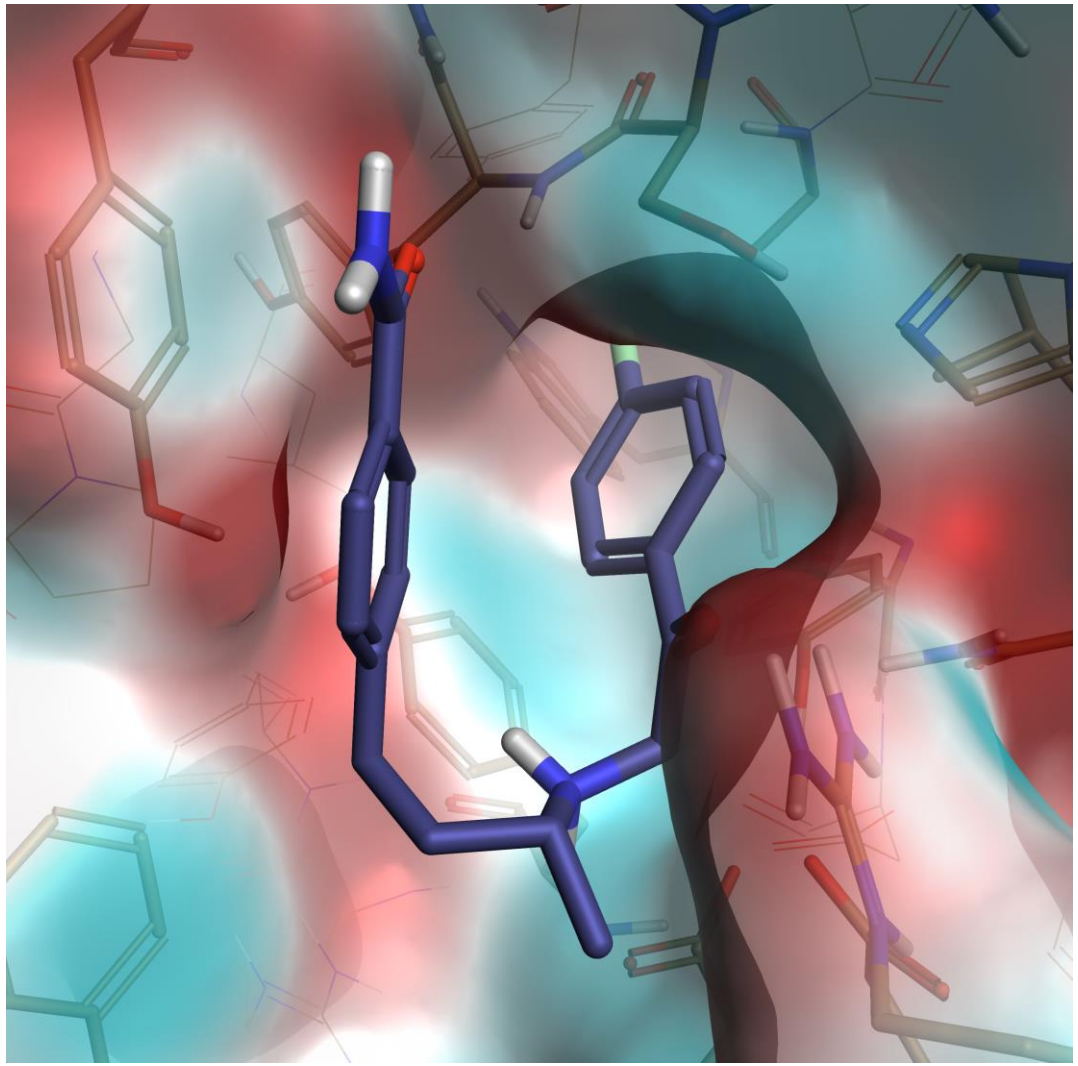
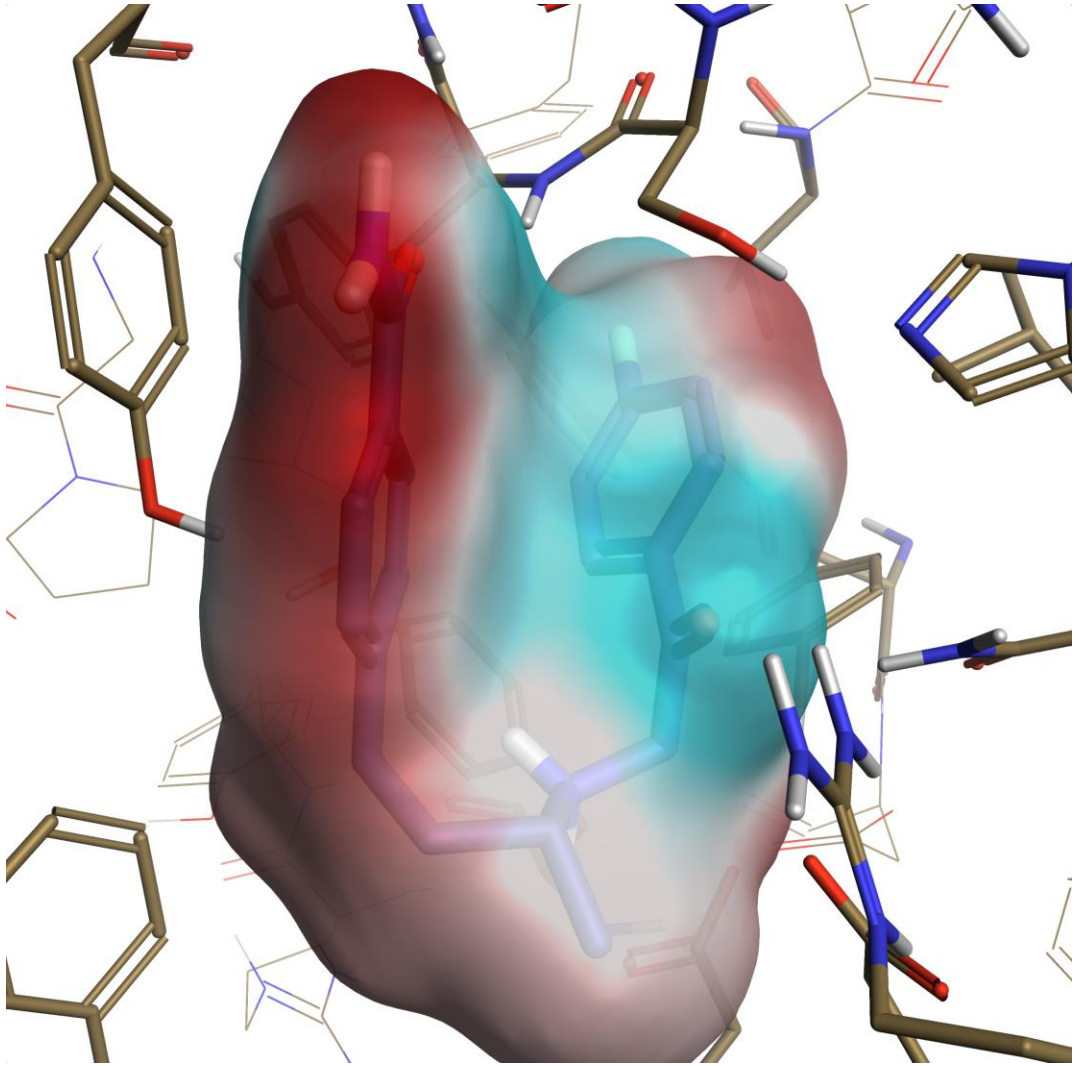
Electrostatics mapped to surfaces





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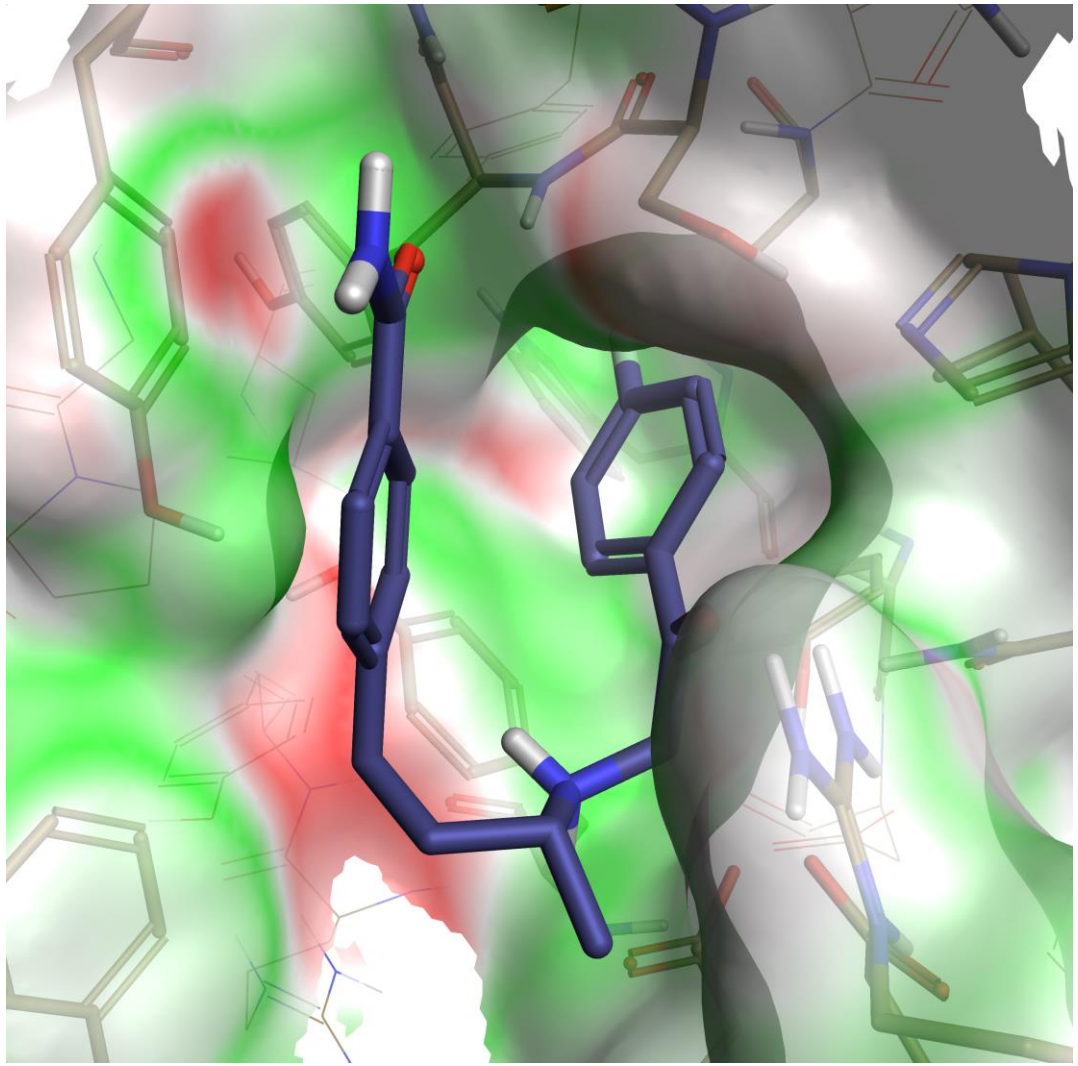
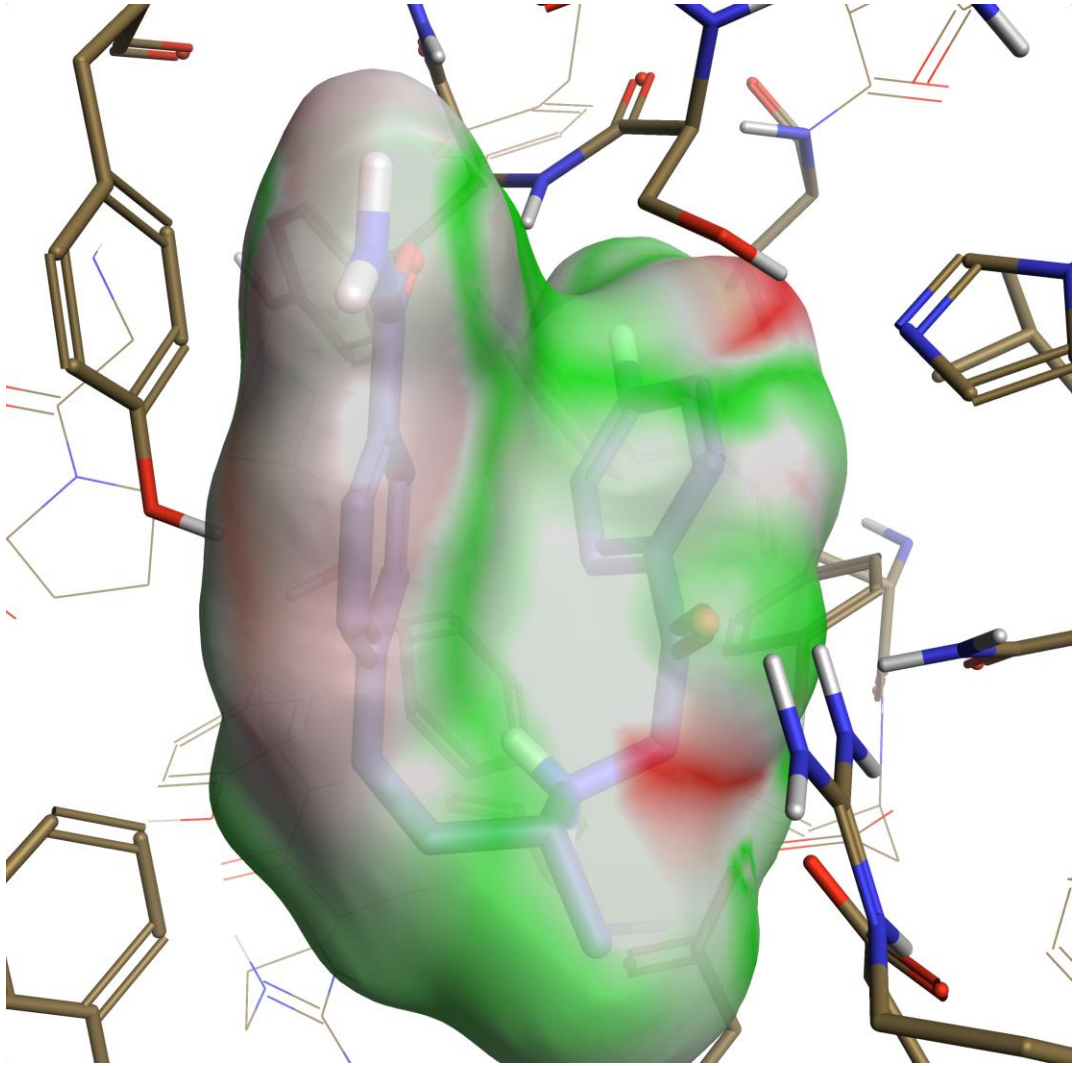
Electrostatic Complementarity





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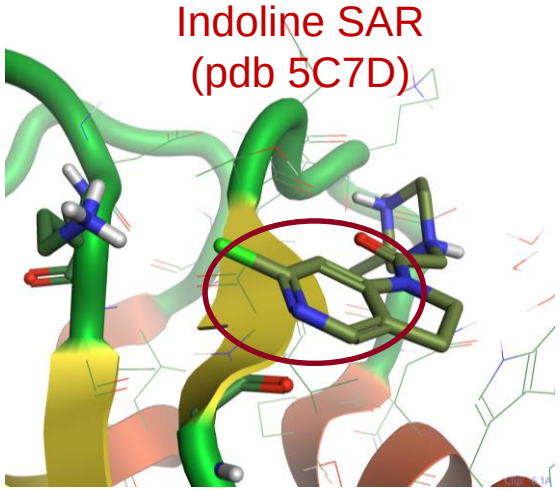
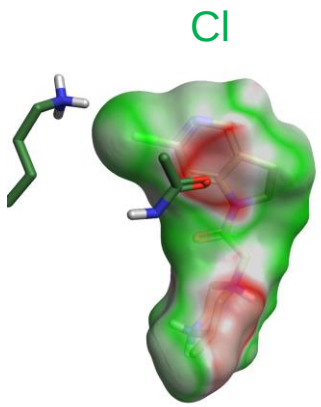
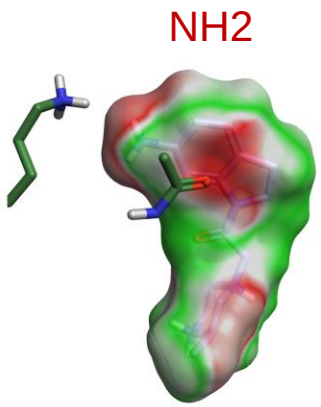
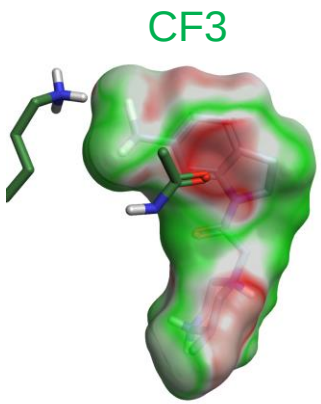
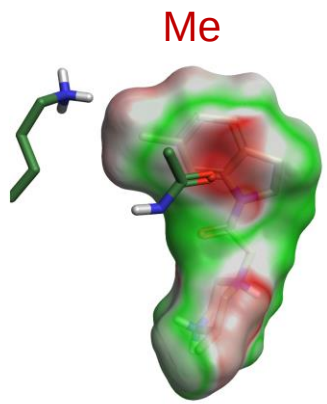
Electrostatic Complementarity (EC) scoring



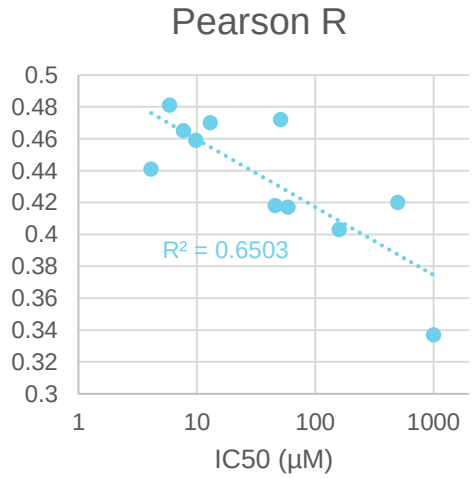








> Bioactivity correlates with electrostatic complementarity



Chessari et al. JMC 2015

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Electrostatic Complementarity

> For full details see Matthias' talk, coming soon!

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Ensemble Docking

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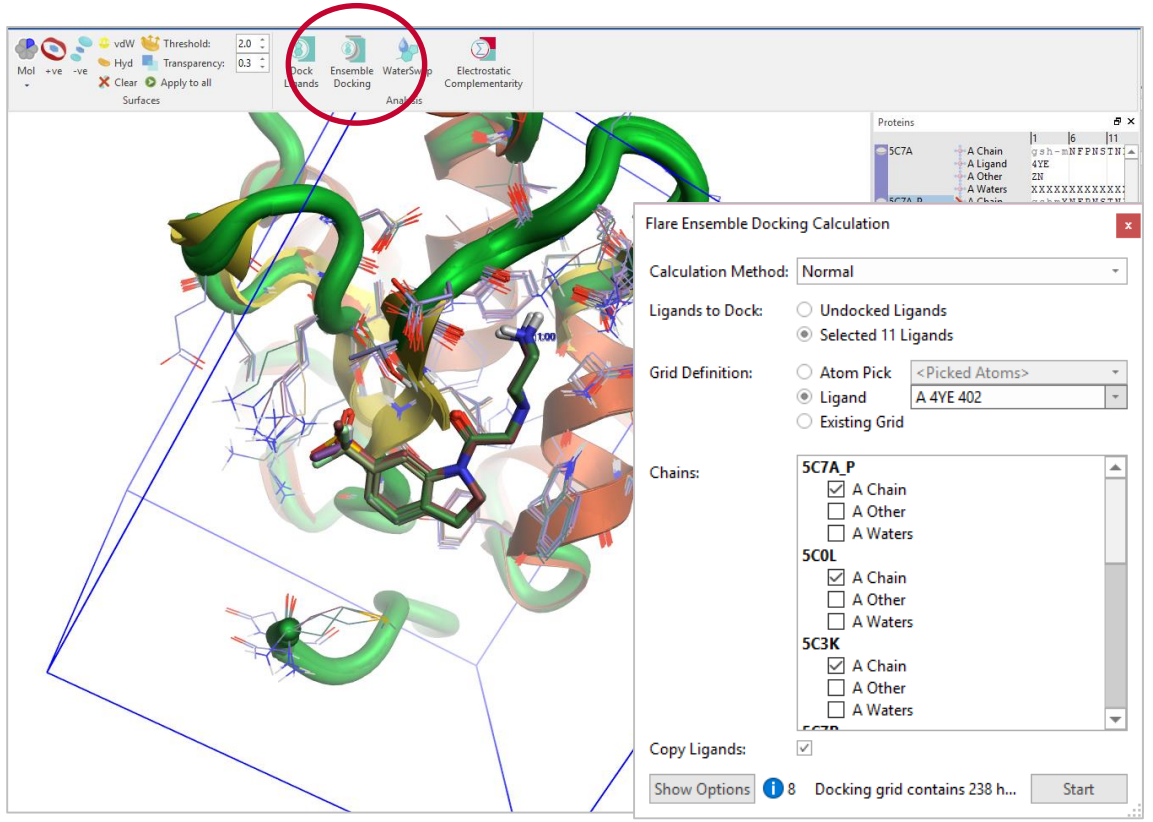
Ensemble docking: considering active site flexibility in docking

- Many docking algorithms assume a rigid active site
  - Unrealistic
- ‘Flexible’ docking algorithm do not always give the expected results
  - User feedback
- Ensemble docking: considering active site flexibility when alternative active site conformations of the same protein are available

© Cresset

Ensemble docking: workflow

- Select the ligands you want to dock
- Choose docking method
- Define the active site
  - Manual atom pick
  - Ligand
  - Existing grid
- Choose proteins to dock into
  - Same protein, alternative conformations for the active site
  - Choose chains to include in docking for each protein



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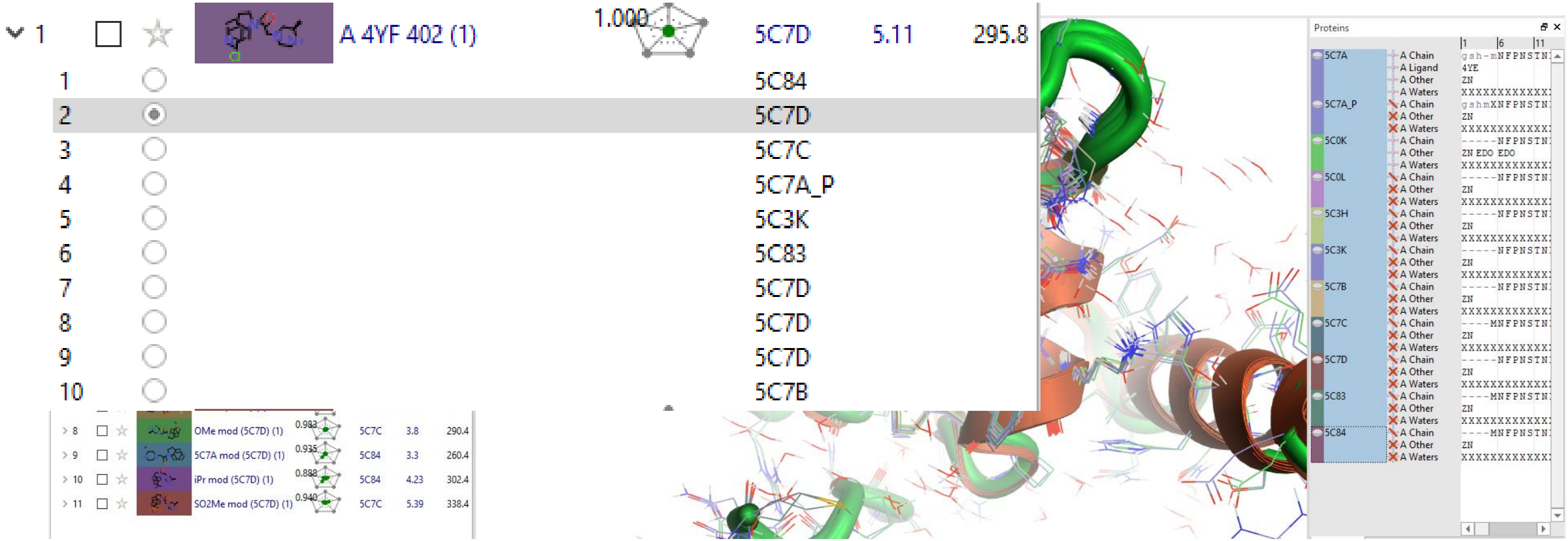
Ensemble docking: results

> Best poses across all protein conformations saved as docked results



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Python

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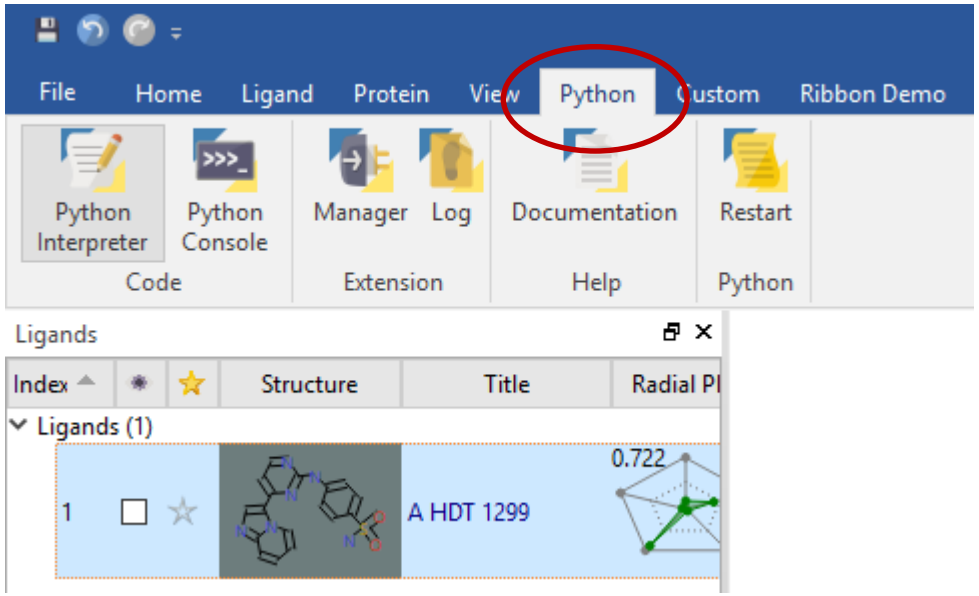
Python API for Flare

- The vast majority of Flare's functions are now scriptable using Python
  - File I/O
  - Docking
  - GUI
  - Waterswap
  - 3D-RISM
  - Protein prep, alignment, superposition
  - etc
- New "pyflare" executable provides command-line access

© Cresset

New Python tab

- Python Interpreter
  - Write/Paste, Load, Run, Save a script
- Python Console
  - Run one command at a time
- Manager
  - Manage Python extension
- Built-in Python documentation



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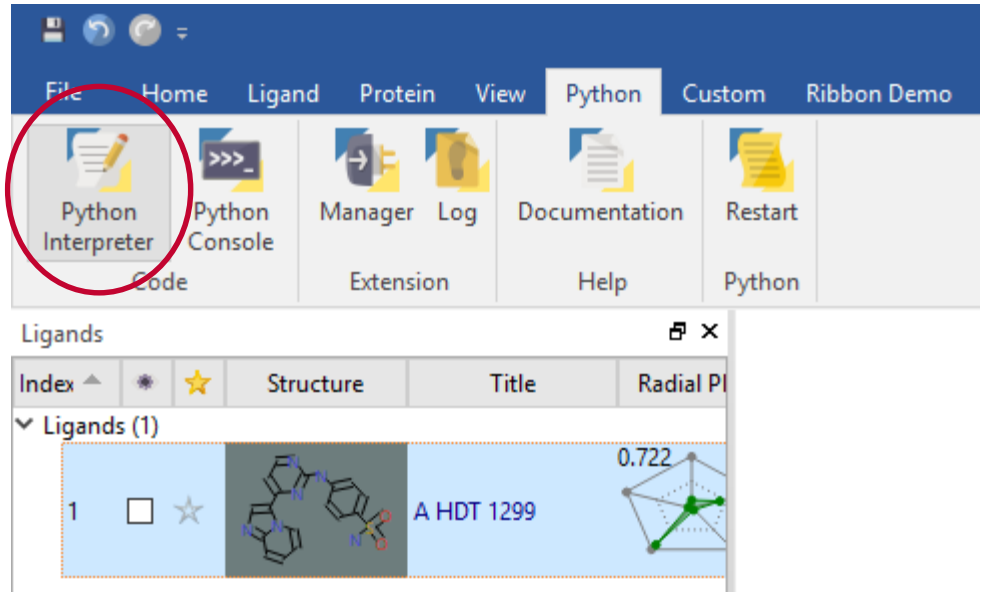
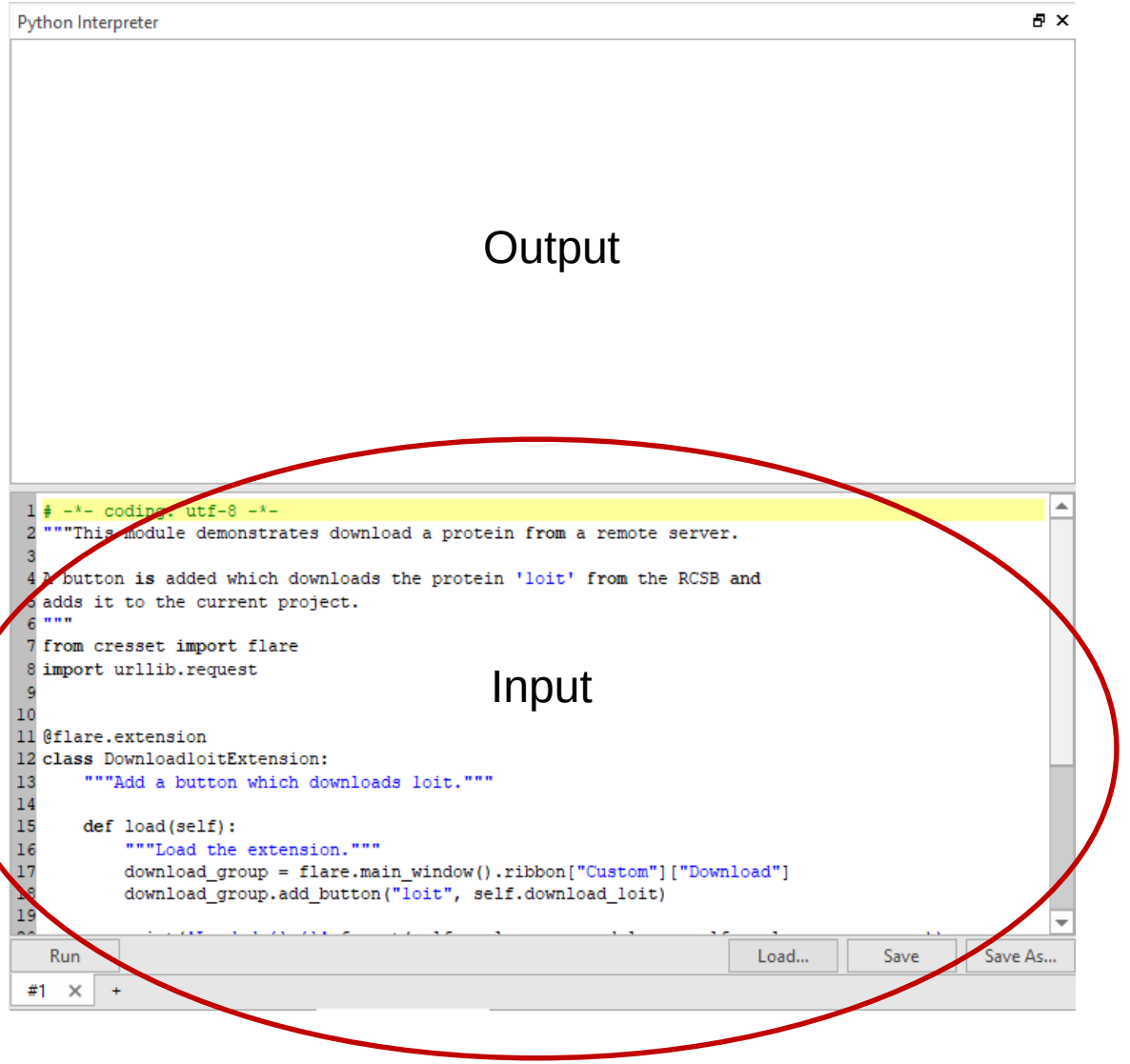
The Python Interpreter window





- Write, Copy/Paste, Load a script
- Run the loaded Python script
- Save/Save as your script
- Multiple tabs to work with multiple scripts in the same Flare session

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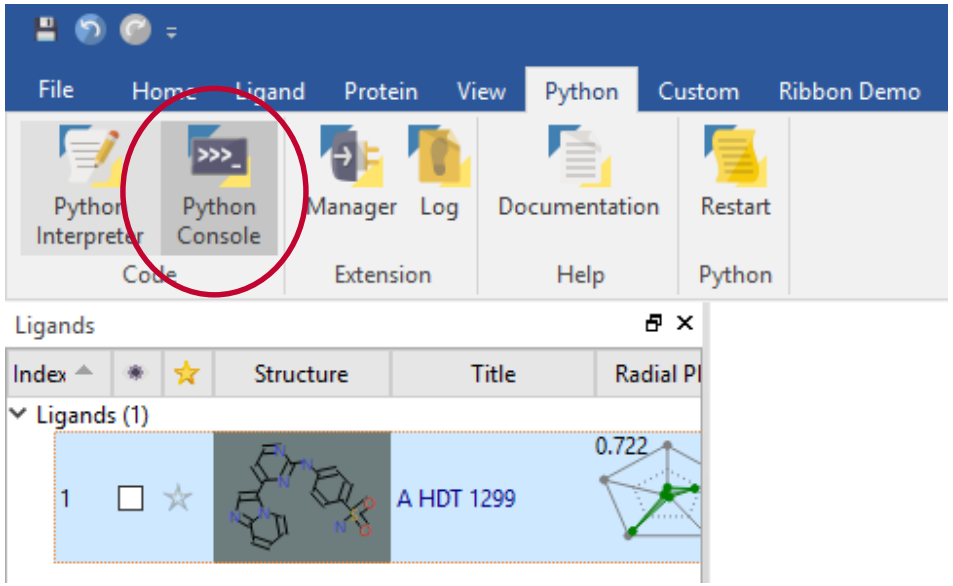
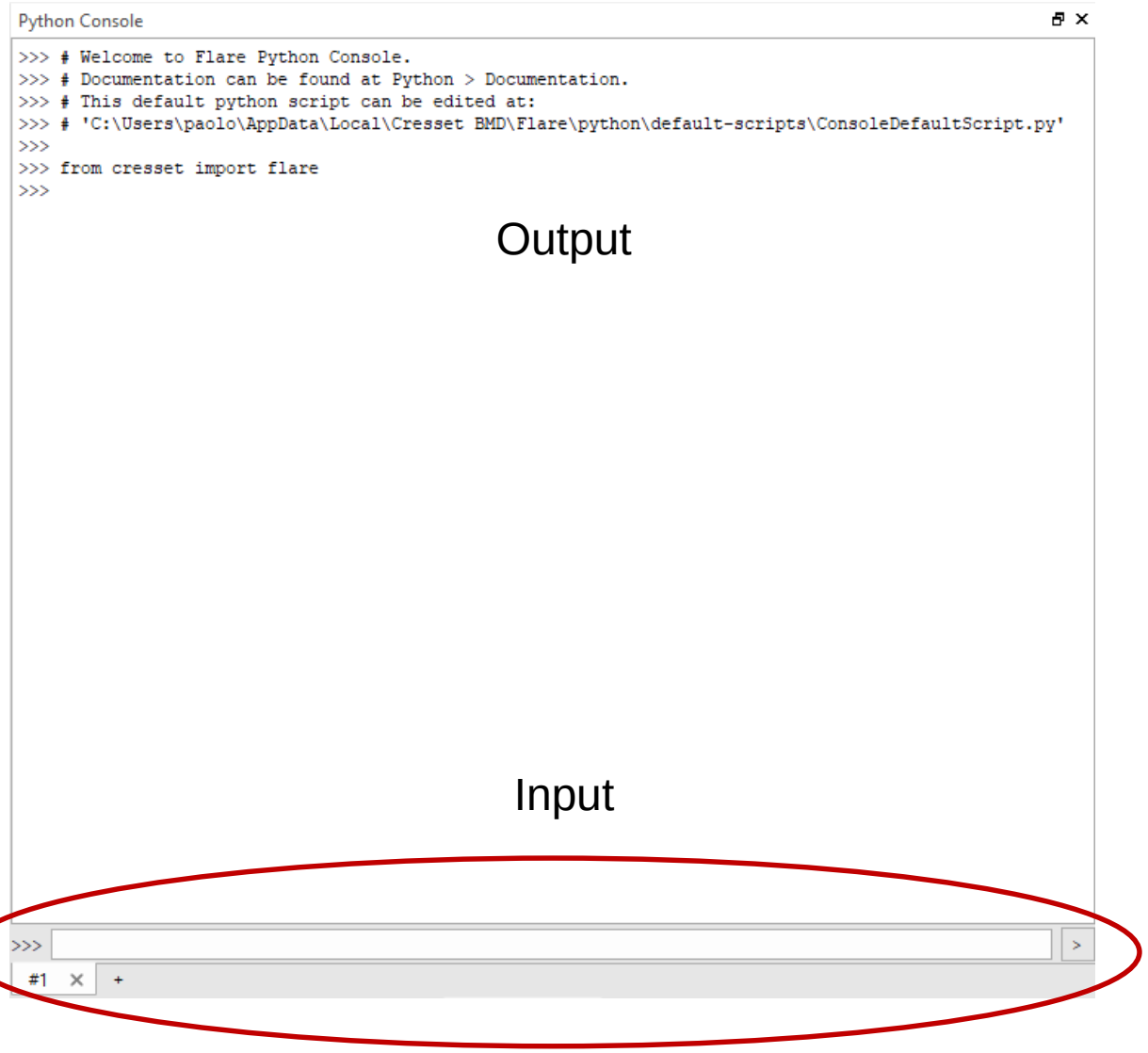
The Python Console window





- Write or Copy/Paste simple Python commands
- Ideal for one-liners, but it also supports multi-line loops
- Multiple tabs to work with in the same Flare session

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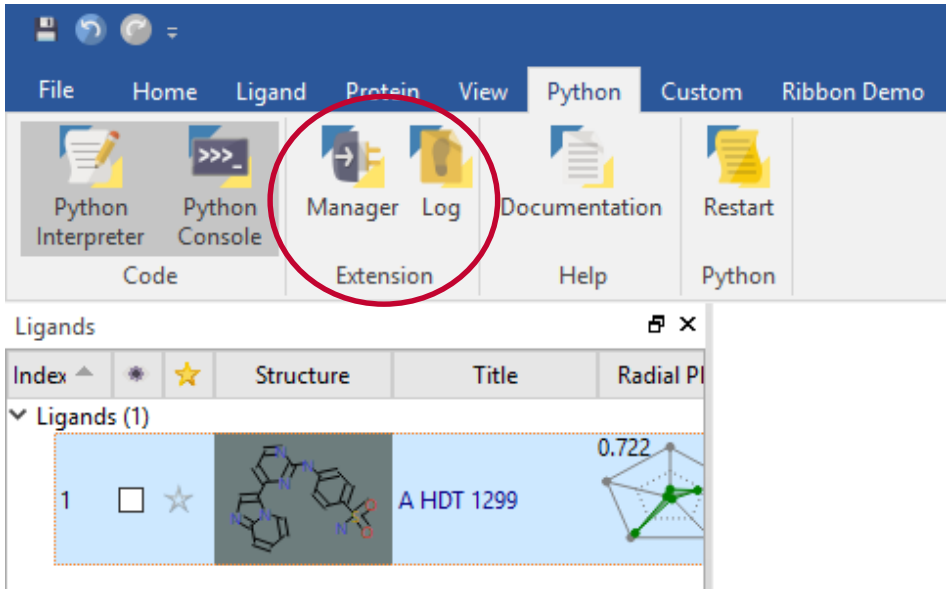
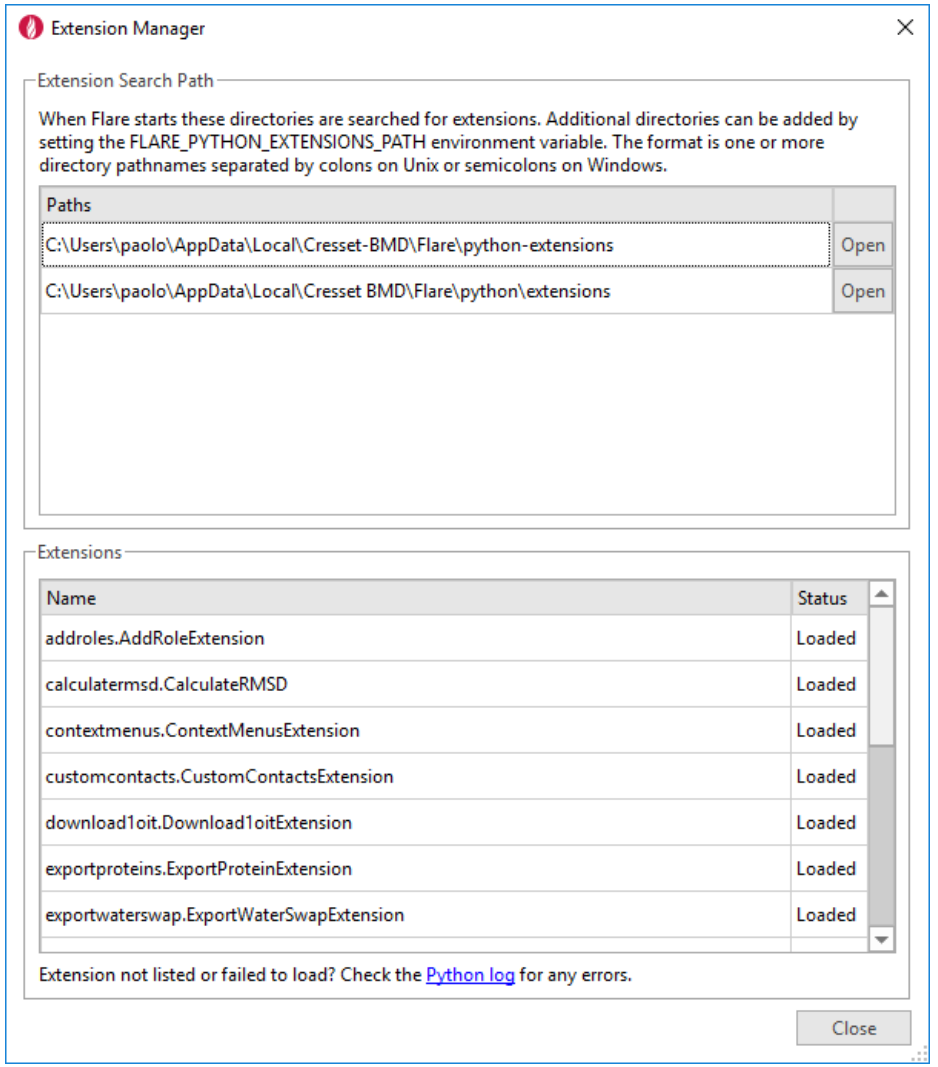
Python Extension Manager





> Manage your Python extensions

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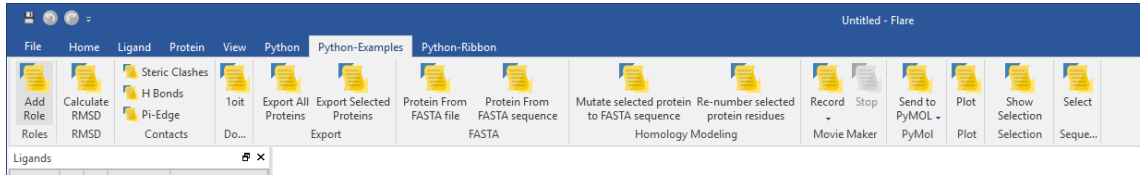
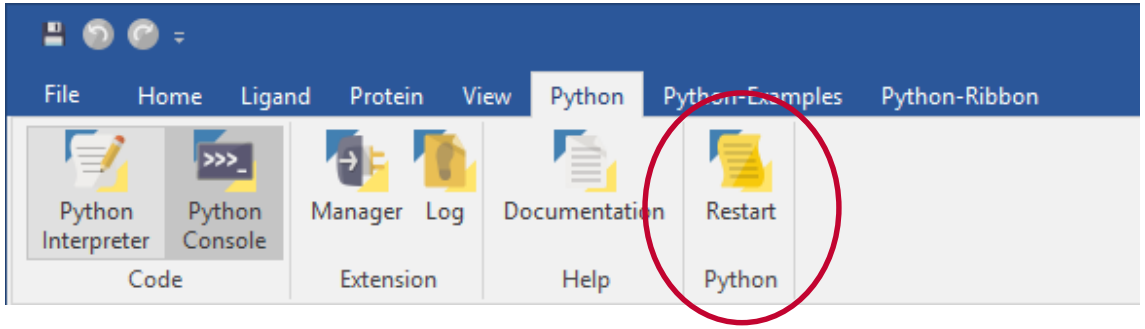
Playing with ribbons

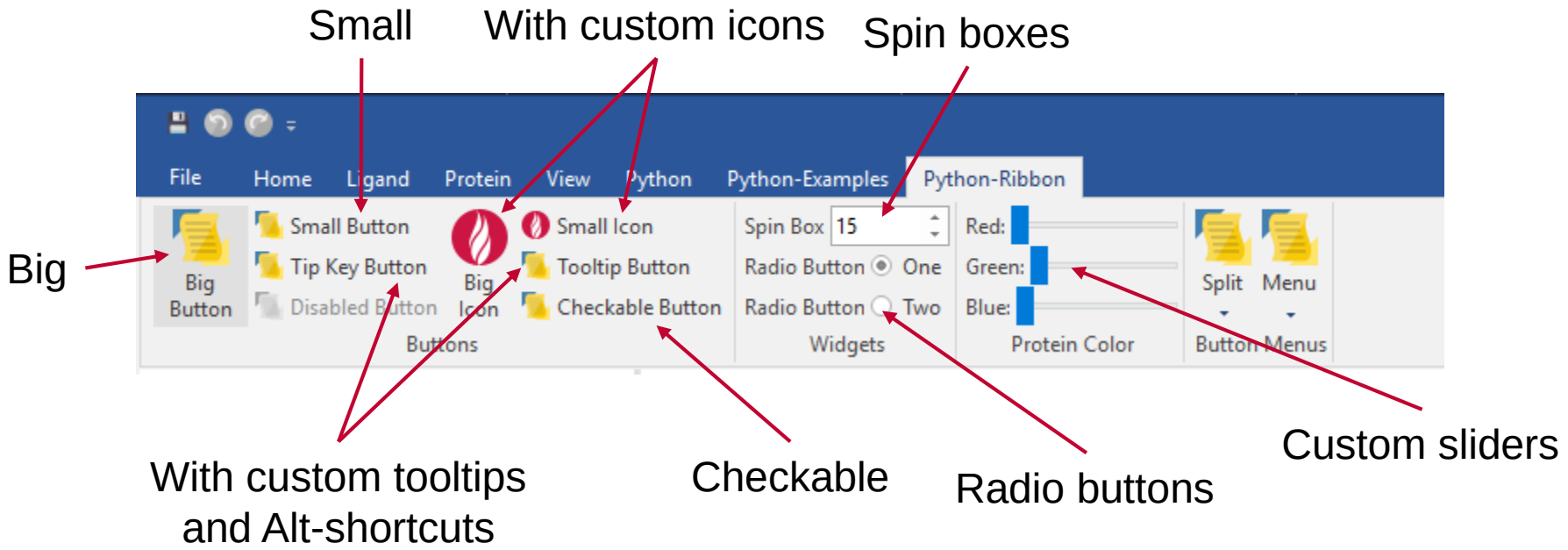
Create a new ribbon for your scripts



Add buttons to a existing ribbon



Create buttons



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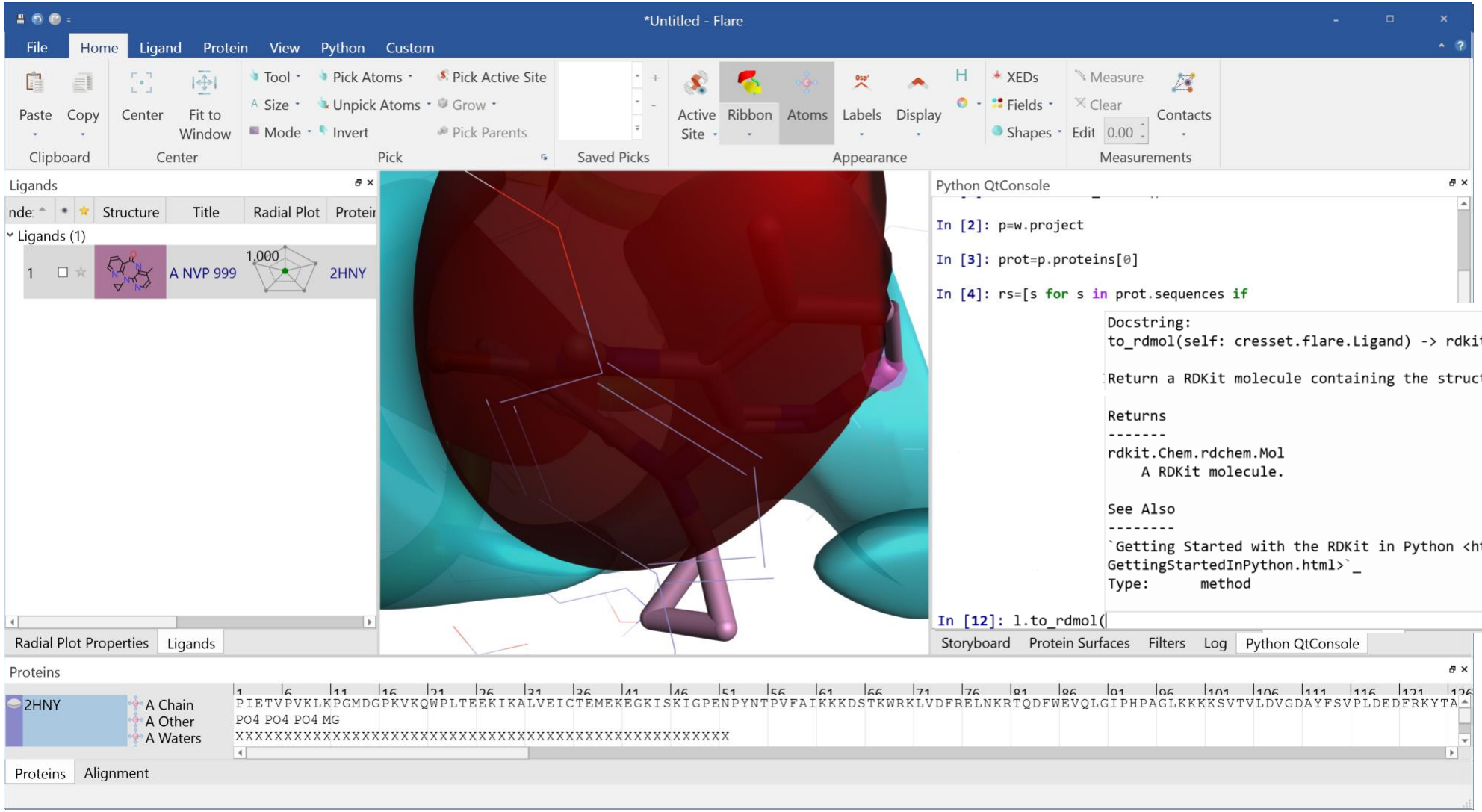
IPython console

IP[y]: IPython
Interactive Computing



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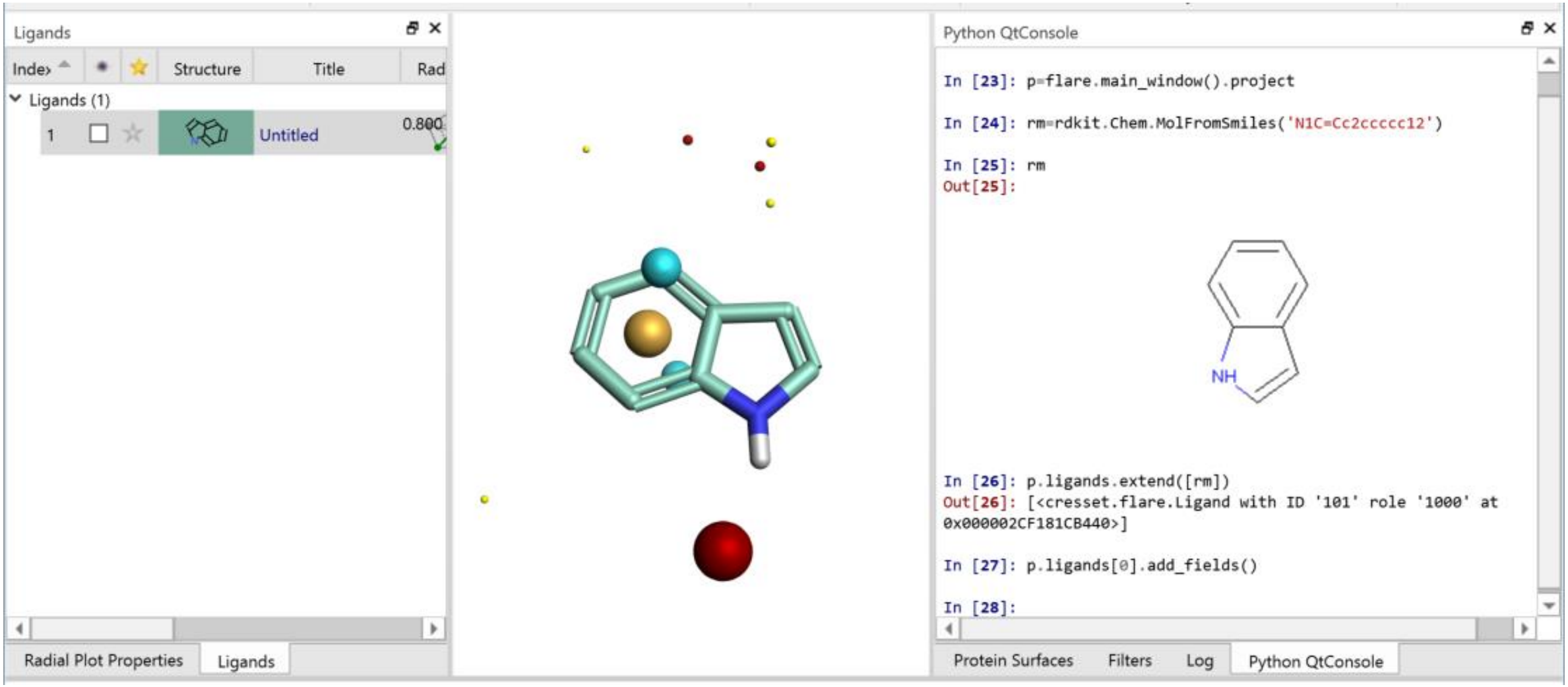
RDKit integration



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Python – not just for developers

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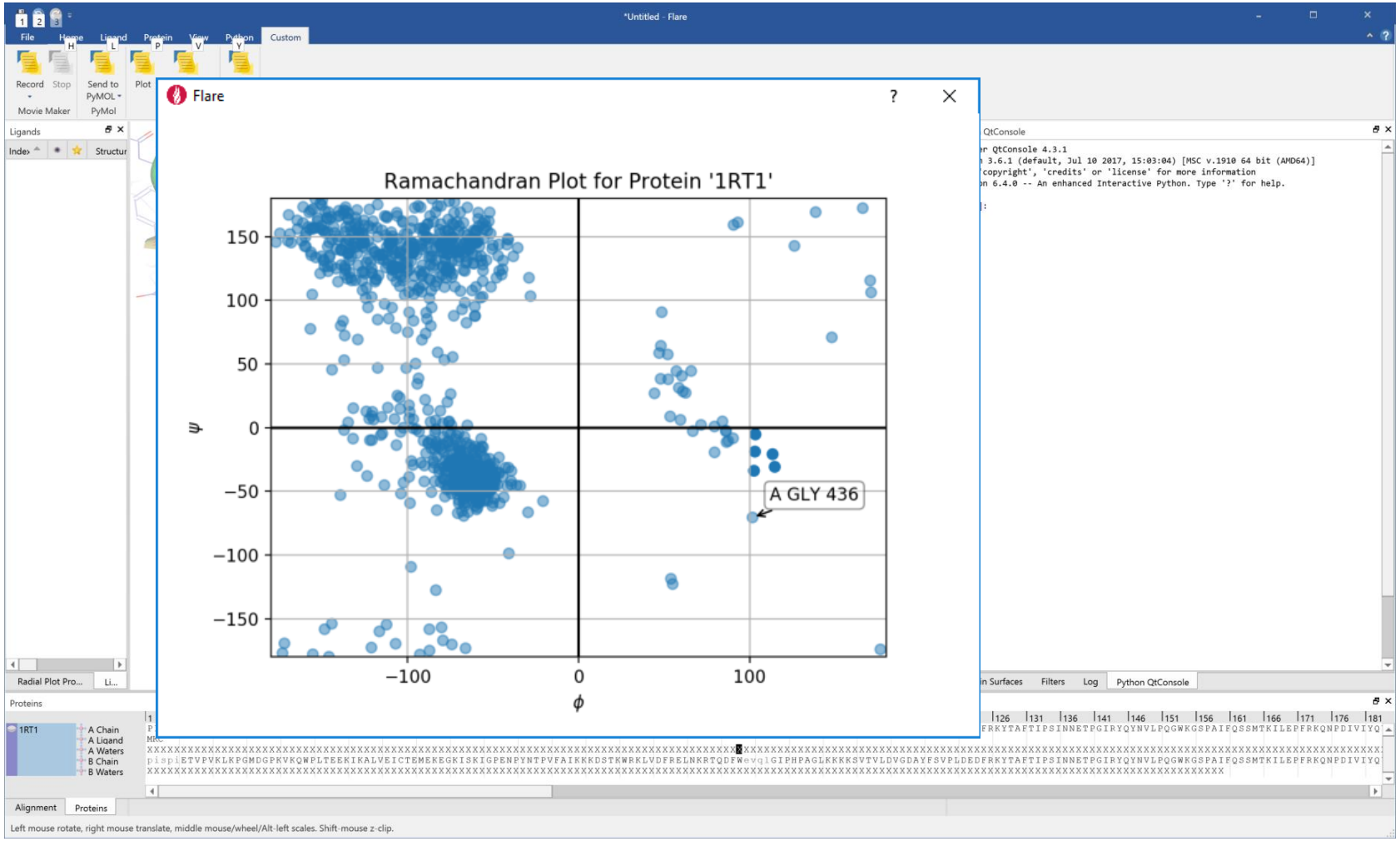
Ramachandran plots



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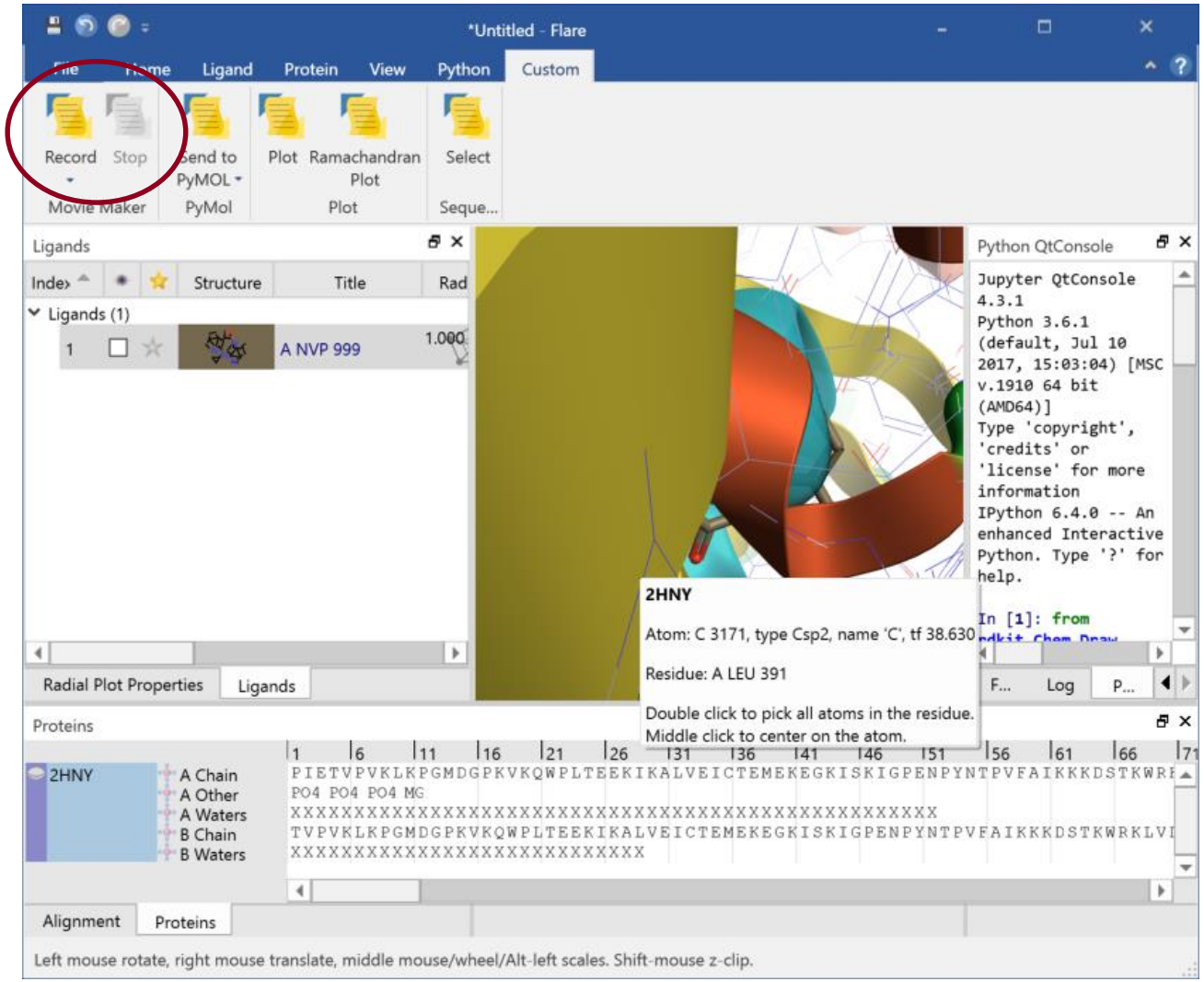
Export movies



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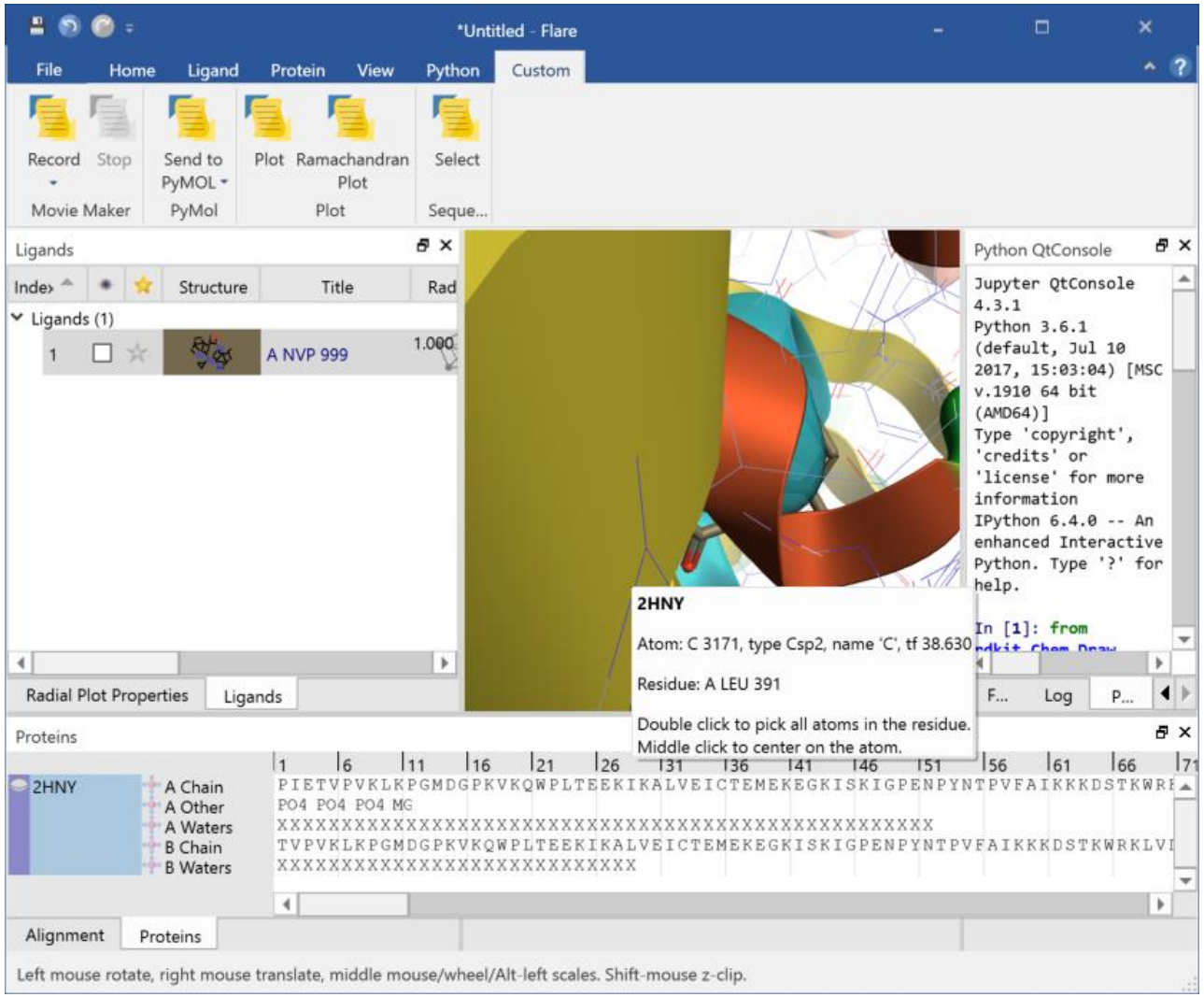
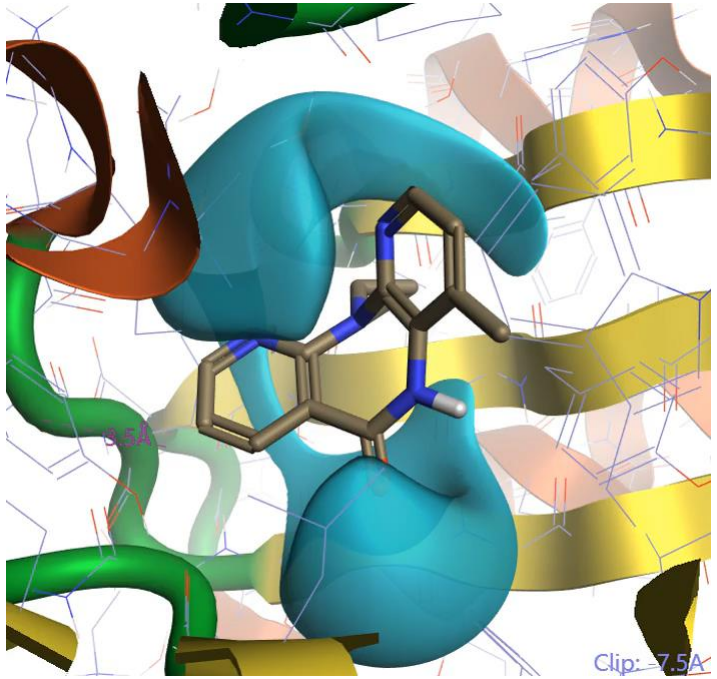
Export movies





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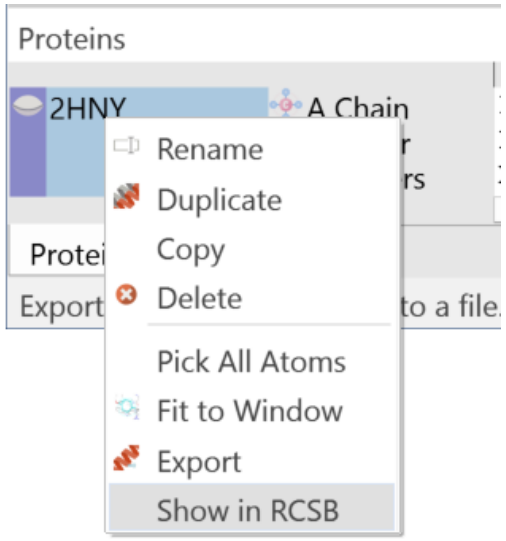
Web access



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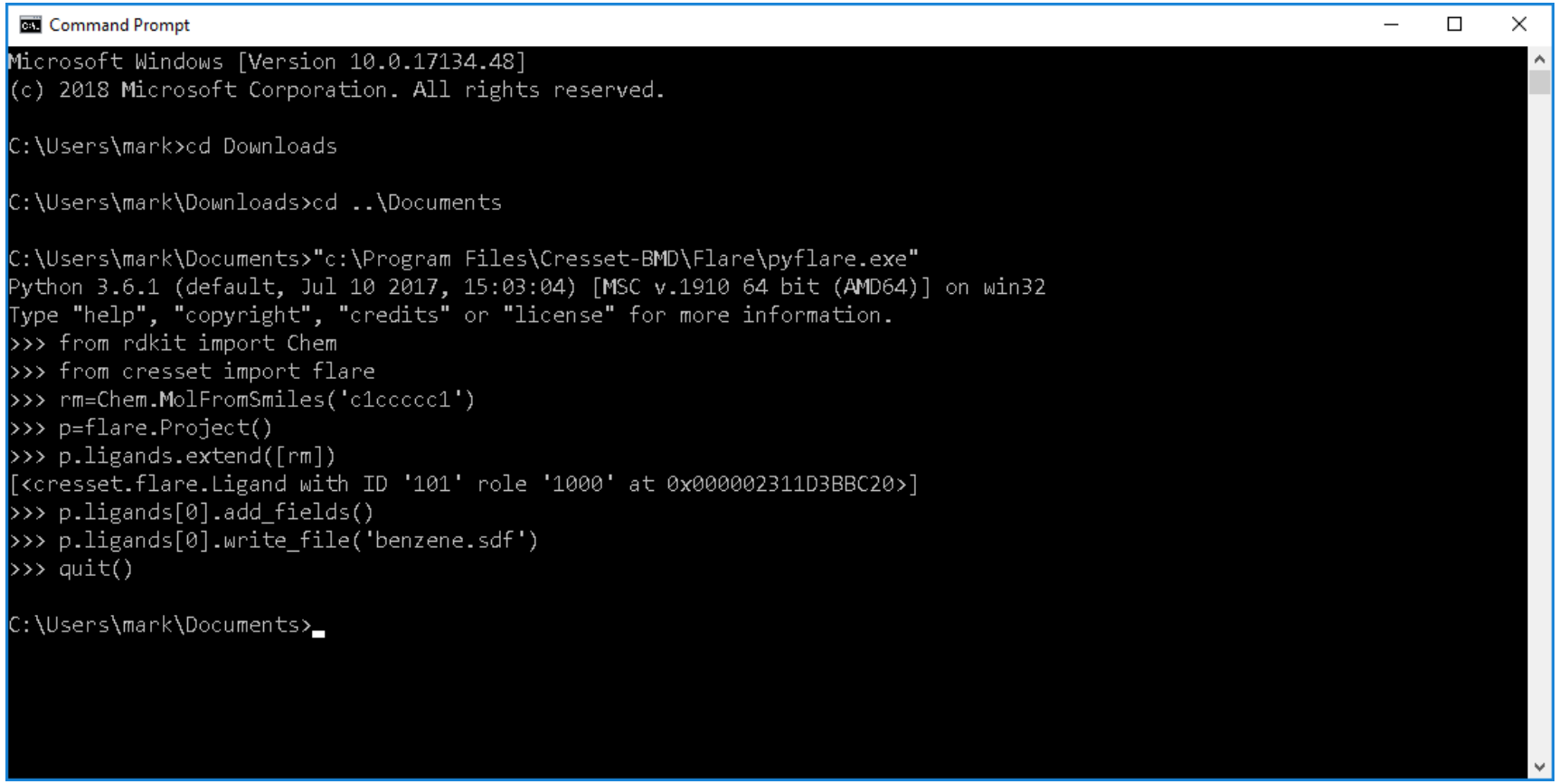
Pyflare

The new “pyflare” executable allows you to script all Flare functions from the command-line



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Easy, flexible, informed ligand design

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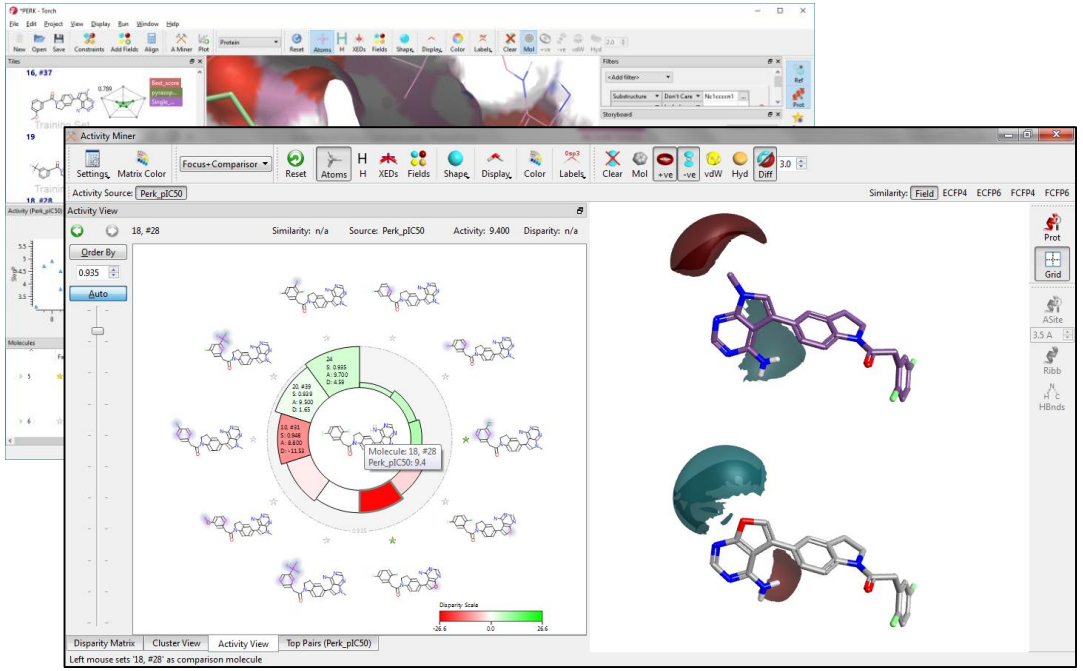
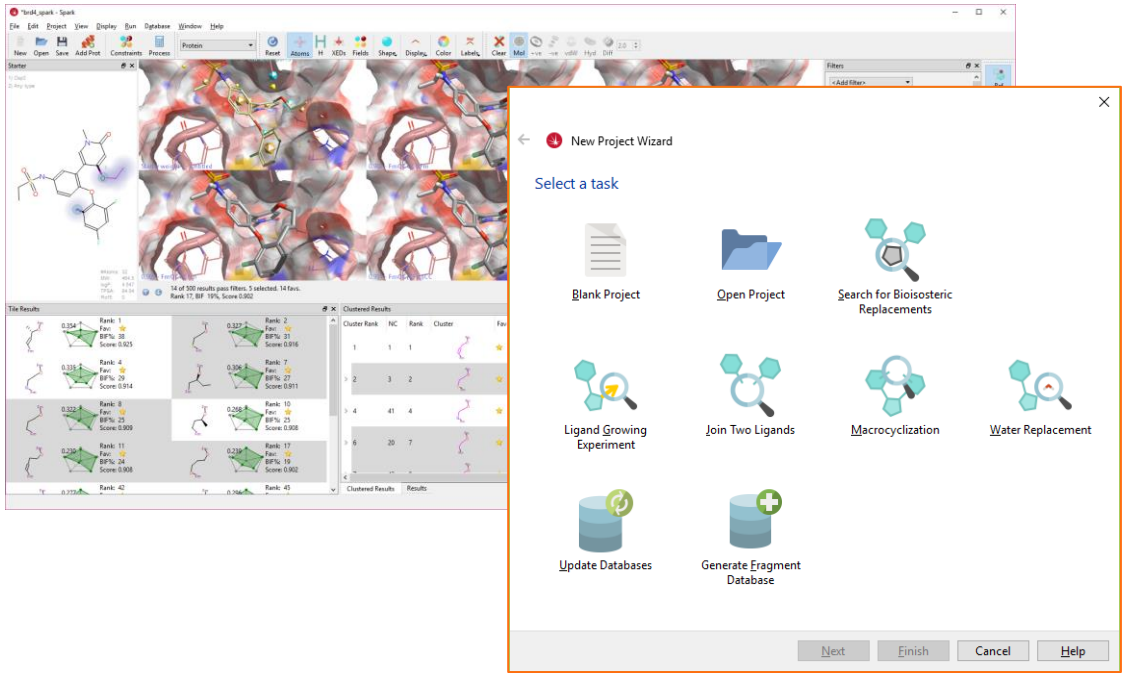
UI improvements

Cresset has always been great at making ligand-based drug design easy





and with Flare we aim to bring the same simplicity and power to SBDD

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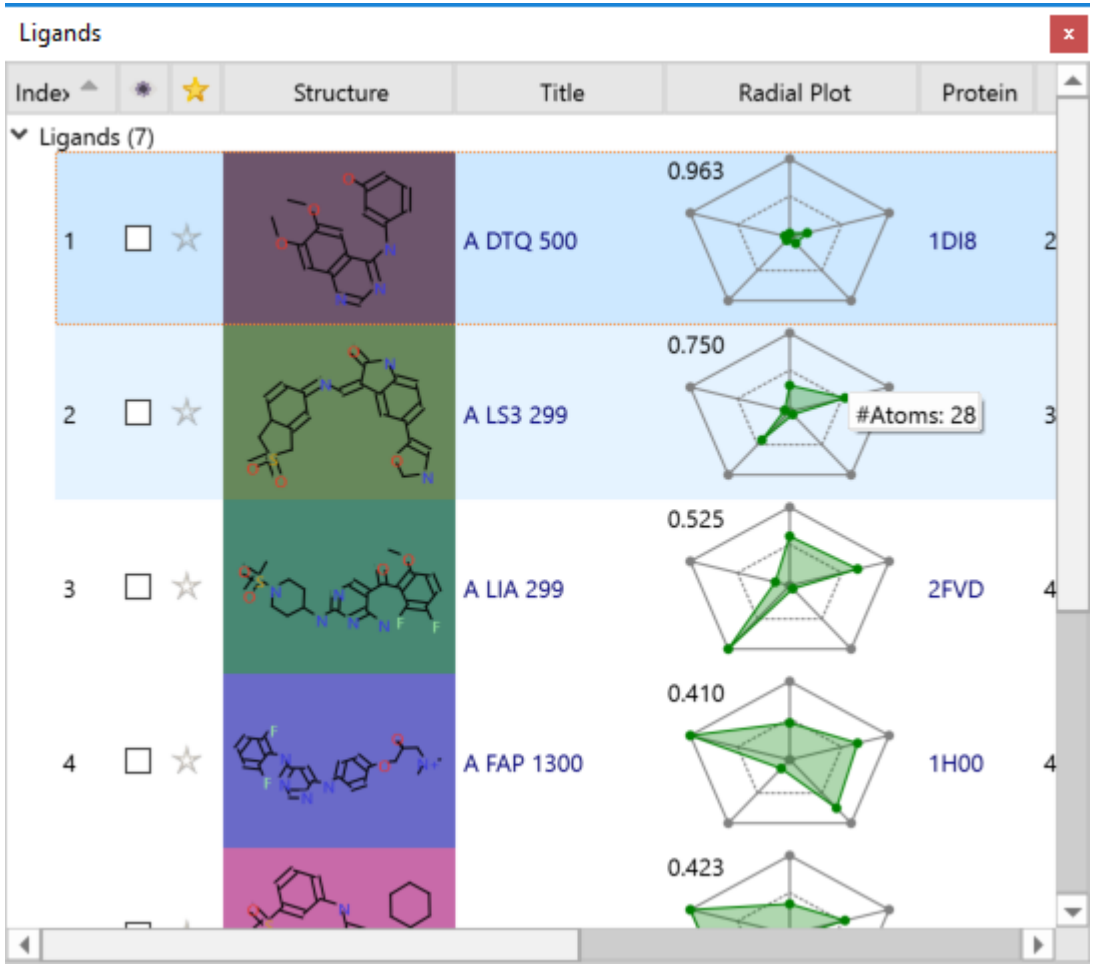
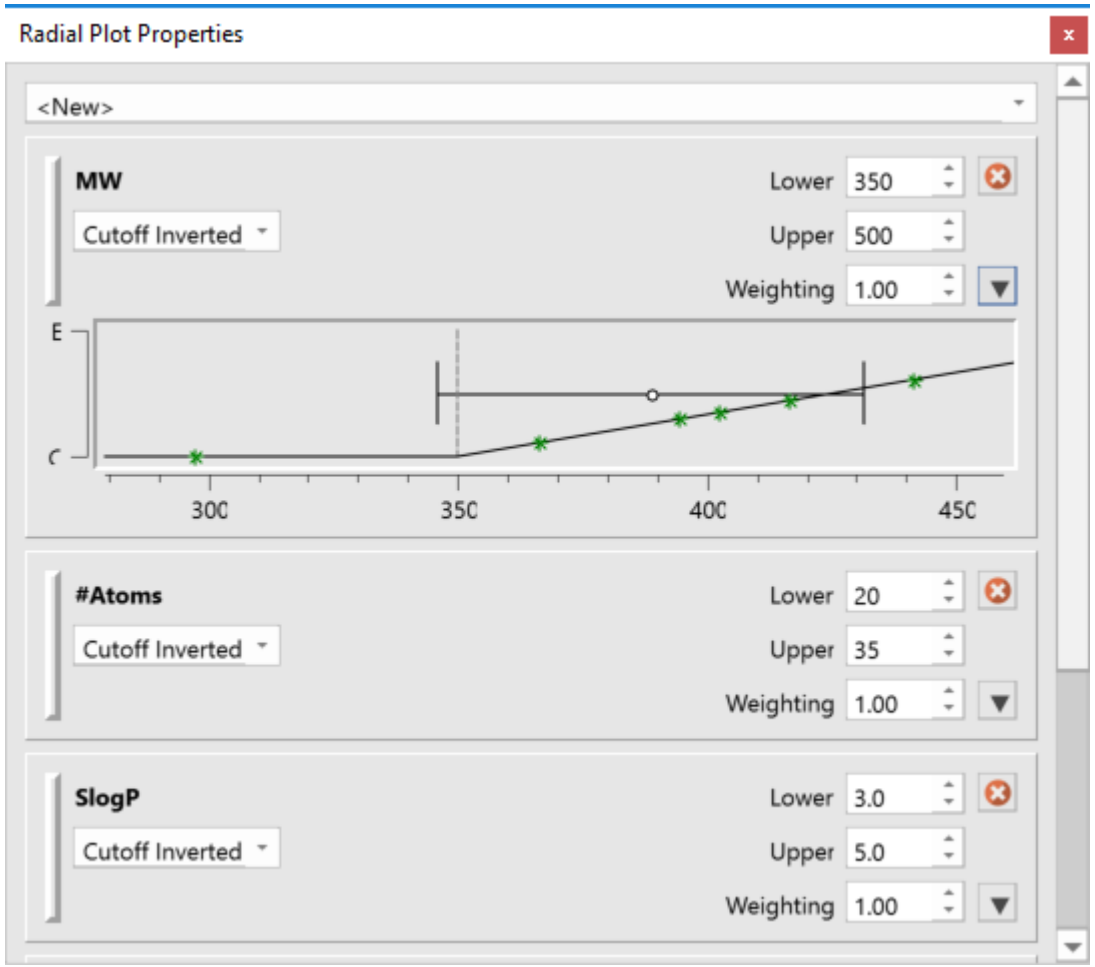
Multi-parameter optimization with radial plots





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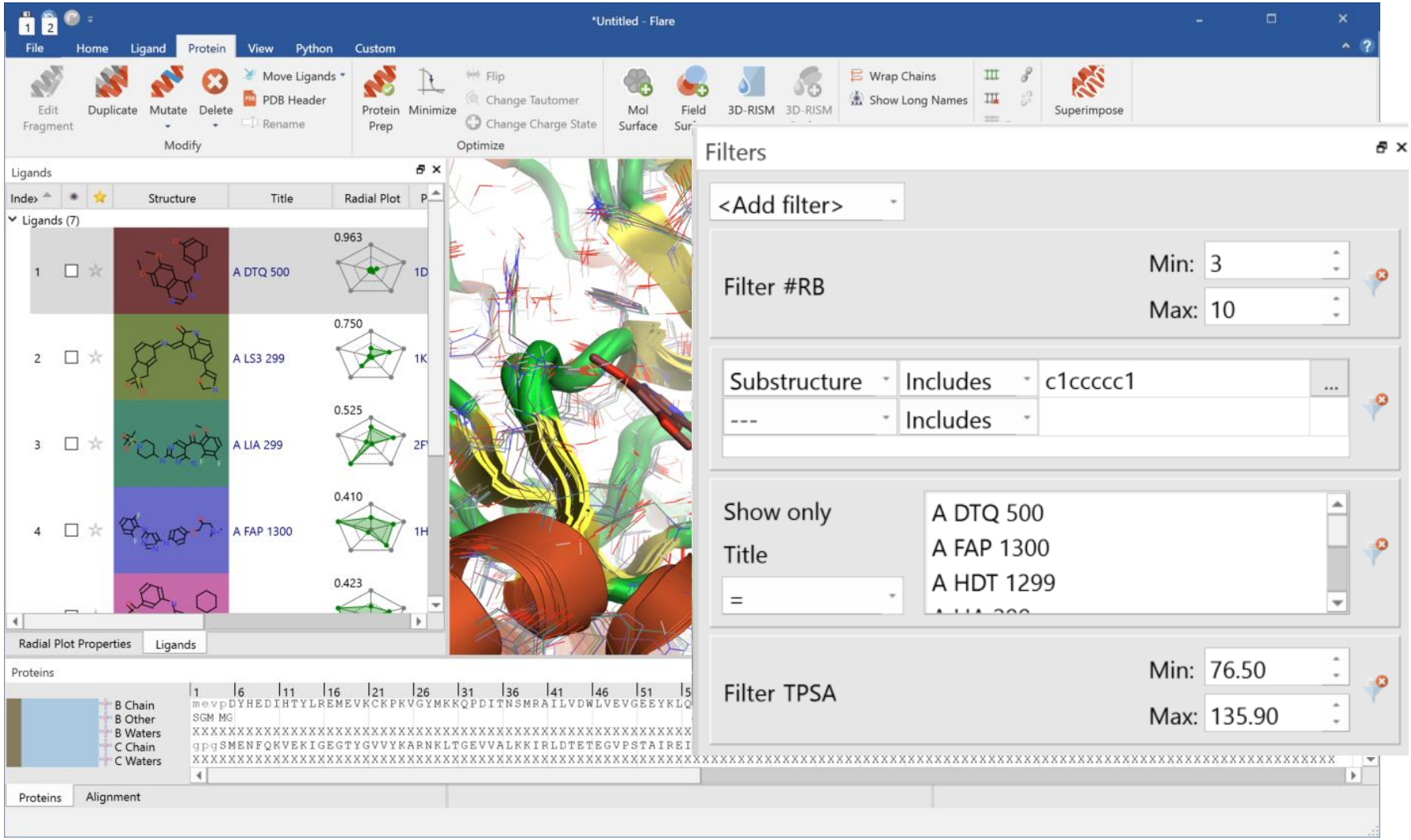
Filters



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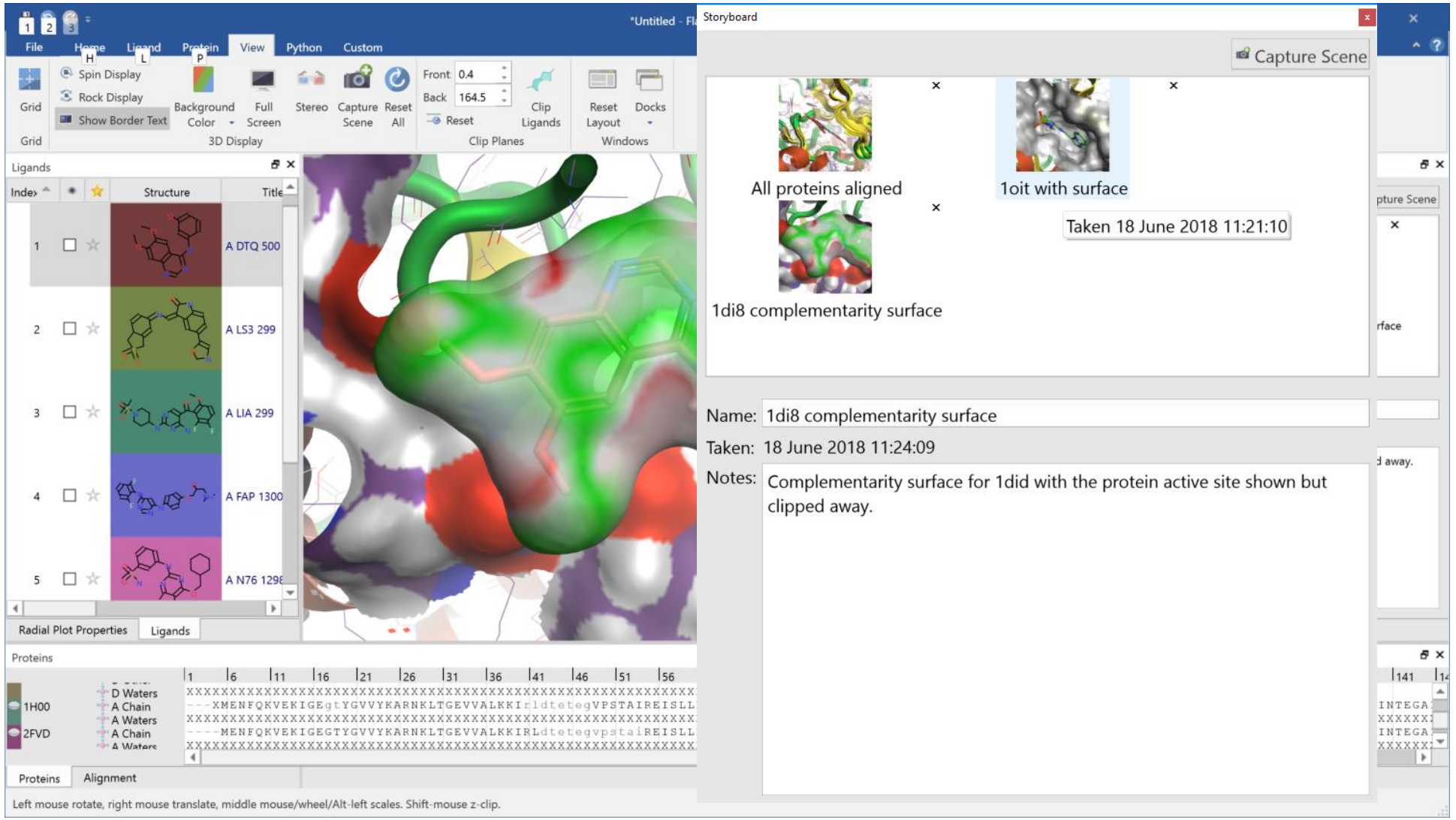
Storyboards



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Loads of other improvements

>200 new features and improvements

Updated AmberTools to ver

Updated Lead Finder a

Model algorithms

Improved clipping of front and back Z-planes in the 3D windo

now allowing to choose whether the ligands should be affect

by the clip planes

Improved ligand minimization, protein preparation dialogs

New 'Delete Dock

Proteins' funct

energy grids, r

space in the sa

g the superimposition of

s. selected proteins

Improved Wate

analysis – filter

by bind

Update

mproved performance of multi-

hreaded docking runs

ventions

'Move to protein' me

to merge a ligand to

protein structure

Coloring of crystallographic water molecules according to calculated 3D-RISM dG

Improved display

protein name is n

name column is resizable; background color for the 'visibility'

icon matches the c

ng relevant

edge of the

3D window

Export all proteins' functionality

Improved definitions for ligand-protein interactions

The FieldEngine binary now enables the setting of the

mum number of cores the process should use

Export ligand field surfaces

Improved import of peptides as ligands

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Flare 2.0

- A fully-featured SBDD application
  - Aim to help you design better ligands, simply and effectively
- Extensible and customisable
- Keeps the Cresset focus on electrostatics
- More to come!

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Thank you!

Questions welcomed

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