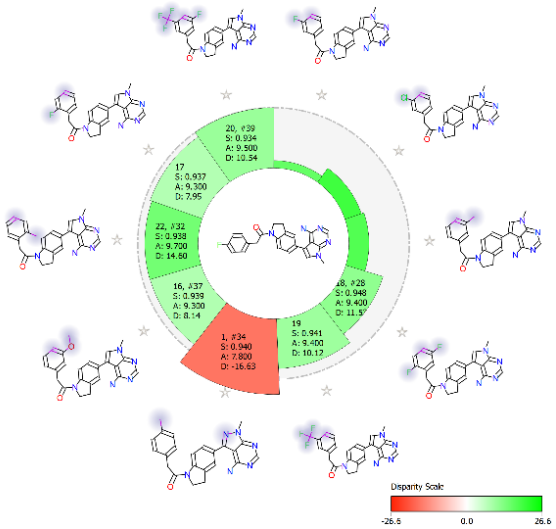
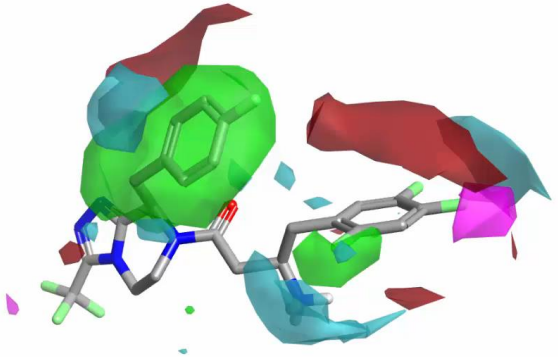
What's New in Cresset Software
Including Our Upcoming Structure-based Design Application

Cresset application philosophy

- Find new ways to discover or view compounds and data that provide results that would otherwise be missed
- Deliver this new science in easy-to-use interfaces with minimal learning curves
  - GUIs, command lines, Pipeline Pilot components, KNIME nodes ….
- Ligand based applications
  - Forge, Spark, Blaze, Torch





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Understanding and using SAR to improve molecule design and intellectual property

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Forge 10.4 main new features

- New (Q)SAR analysis methods
  - Activity Atlas, kNN
- QSAR Model dock: save, analyze, visualize multiple (Q)SAR models in the same Forge project
- Multi-parameter optimization
- Storyboards
- Data from an external server via web service API
- Improved interface to Blaze for virtual screening
- Updated processing dialogue

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(Q)SAR analysis in Forge

- Quantitative SAR (3D)
  - Requires alignments
  - Fields/shape similarity
  - Field Based 3D-QSAR
  - kNN
- Qualitative SAR (3D)
  - Requires alignments
  - Fields/shape similarity
  - Activity Miner
  - Activity Atlas
- Quantitative SAR (2D)
  - Does not require alignments
  - 2D fingerprints and pharmacophore fps available
  - kNN
- Qualitative SAR (2D)
  - Does not require alignments
  - 2D fingerprints and pharmacophore fps available
  - Activity Miner

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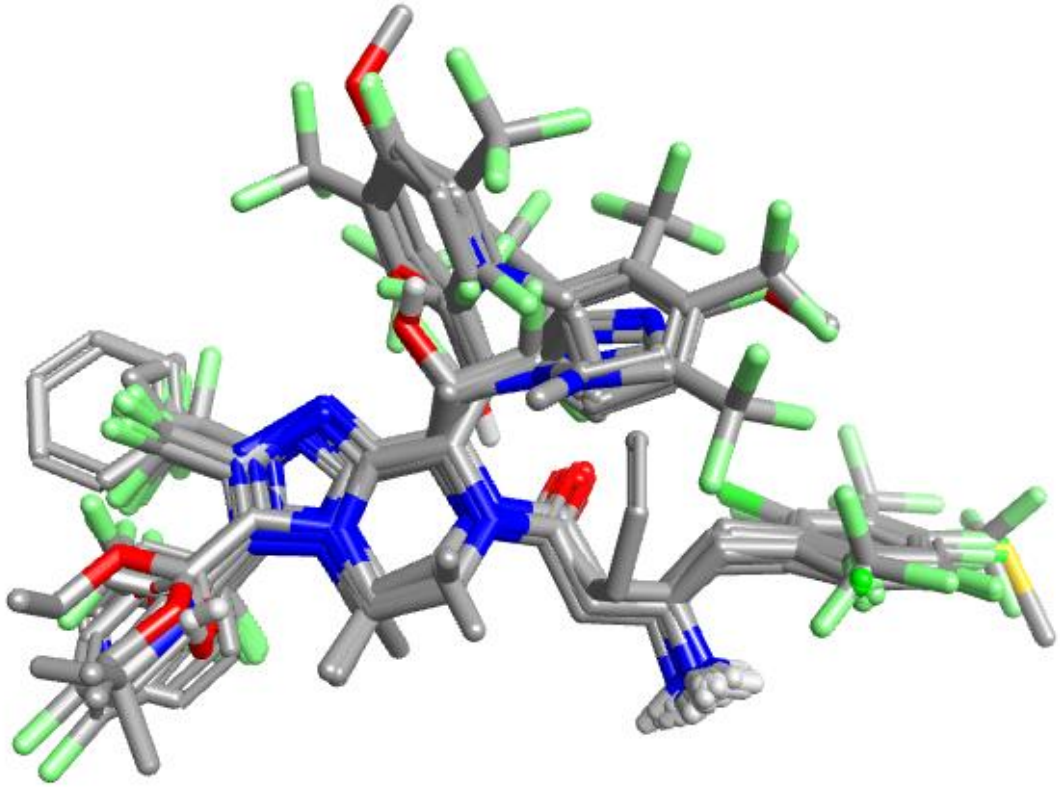
Electrostatic and shape SAR from aligned ligands



What now?

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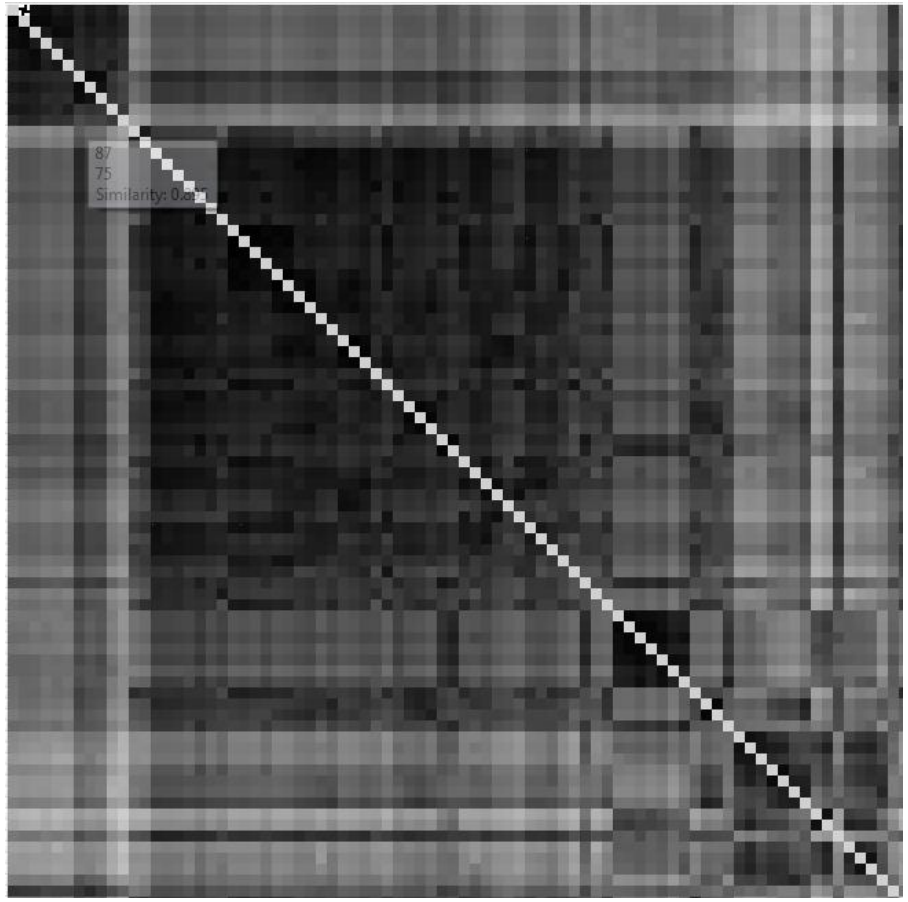
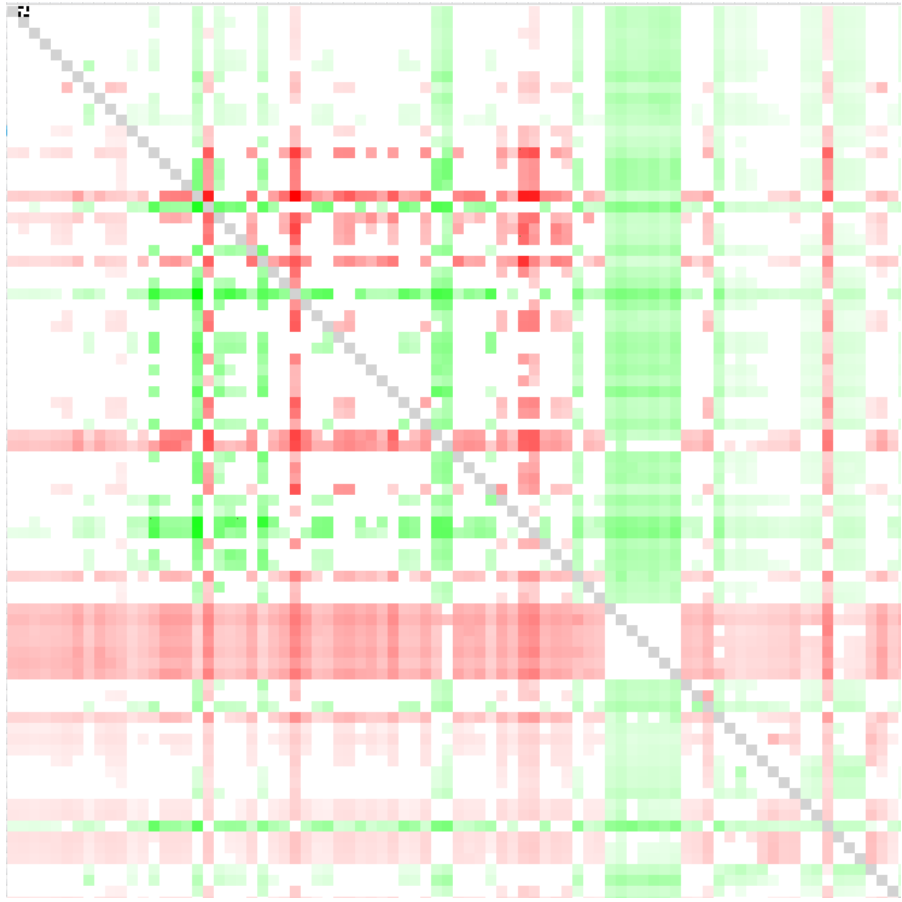
3D pairwise similarity and disparity

3D pairwise similarity



Disparity (Δactivity / 1-similarity)



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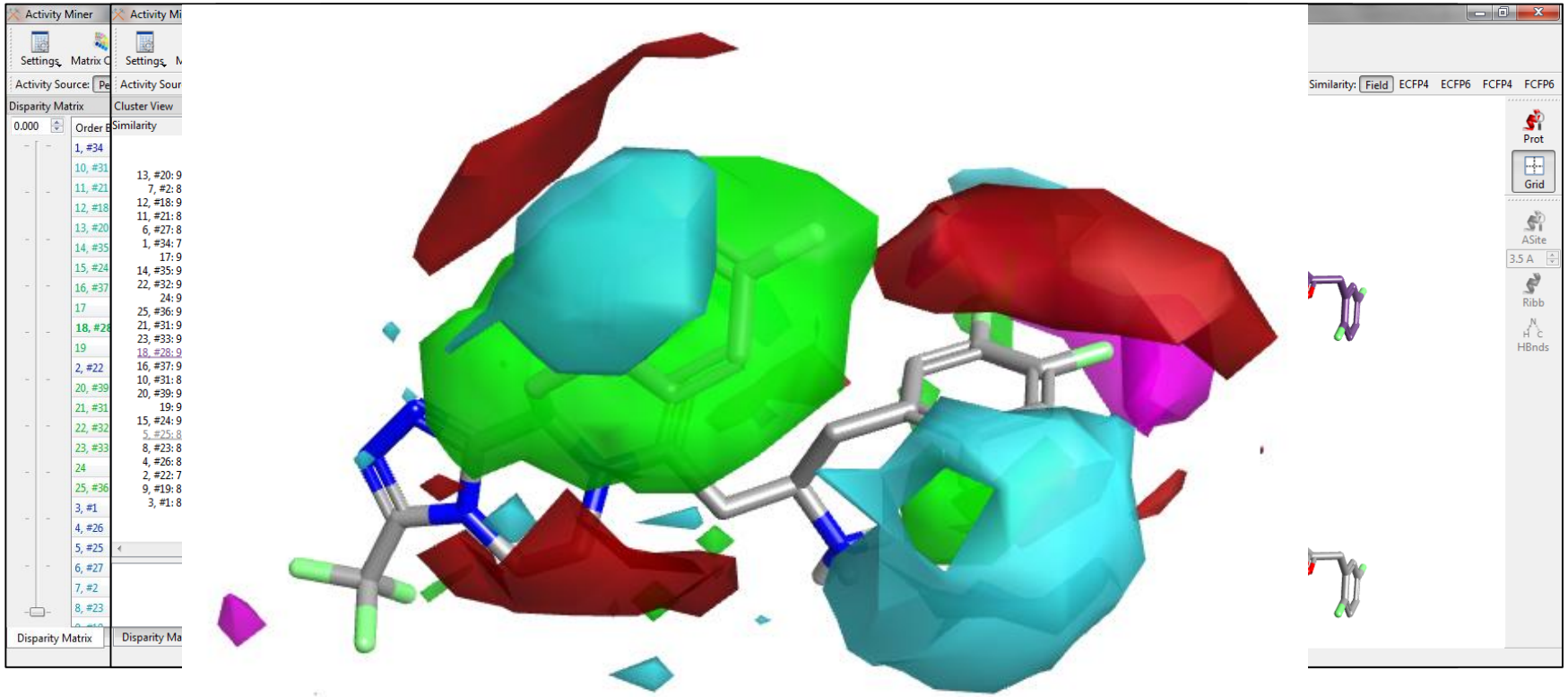
Electrostatic and shape SAR from aligned ligands



Activity Miner

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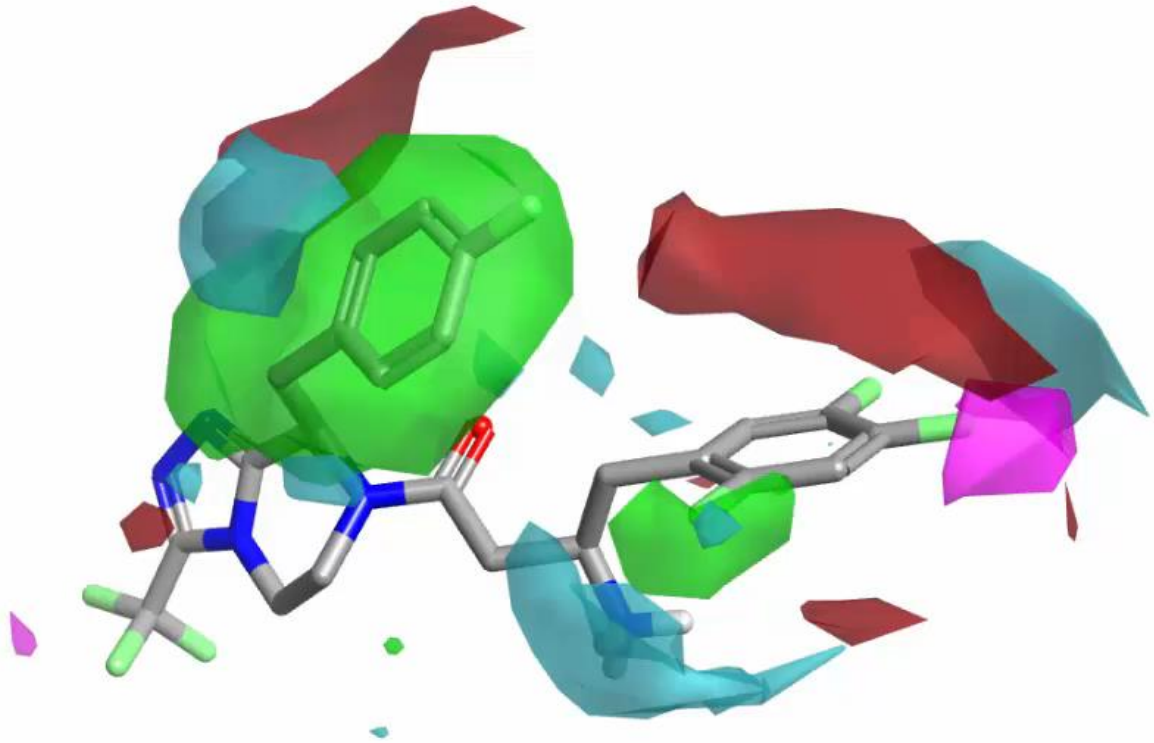
Activity Atlas: Summary of activity cliff data

Look at each pair of molecules

Weight the grid difference by the activity difference

→ Summary of activity cliff data (acute SAR)



= Positive

= Negative

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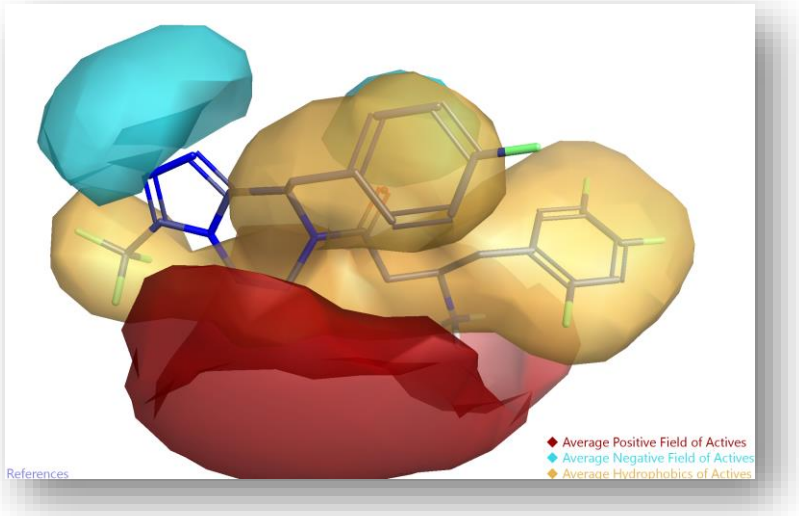
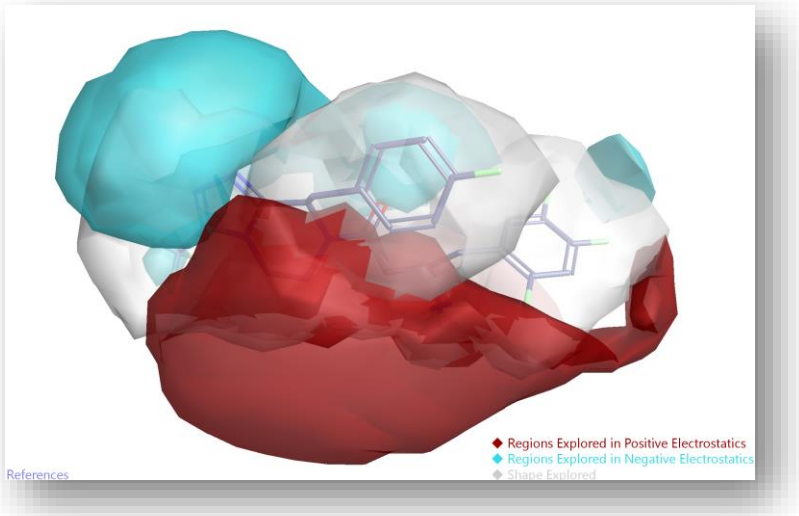
Activity Atlas: Average of actives and regions explored





- Look at the high actives
  - What grid points are in common?
  - → Average electrostatic and shape pattern on actives (gross SAR)

- Look at all molecules
  - What is the nature of each grid point?
  - → Exploration map in electrostatic and shape space

= Positive
= Negative

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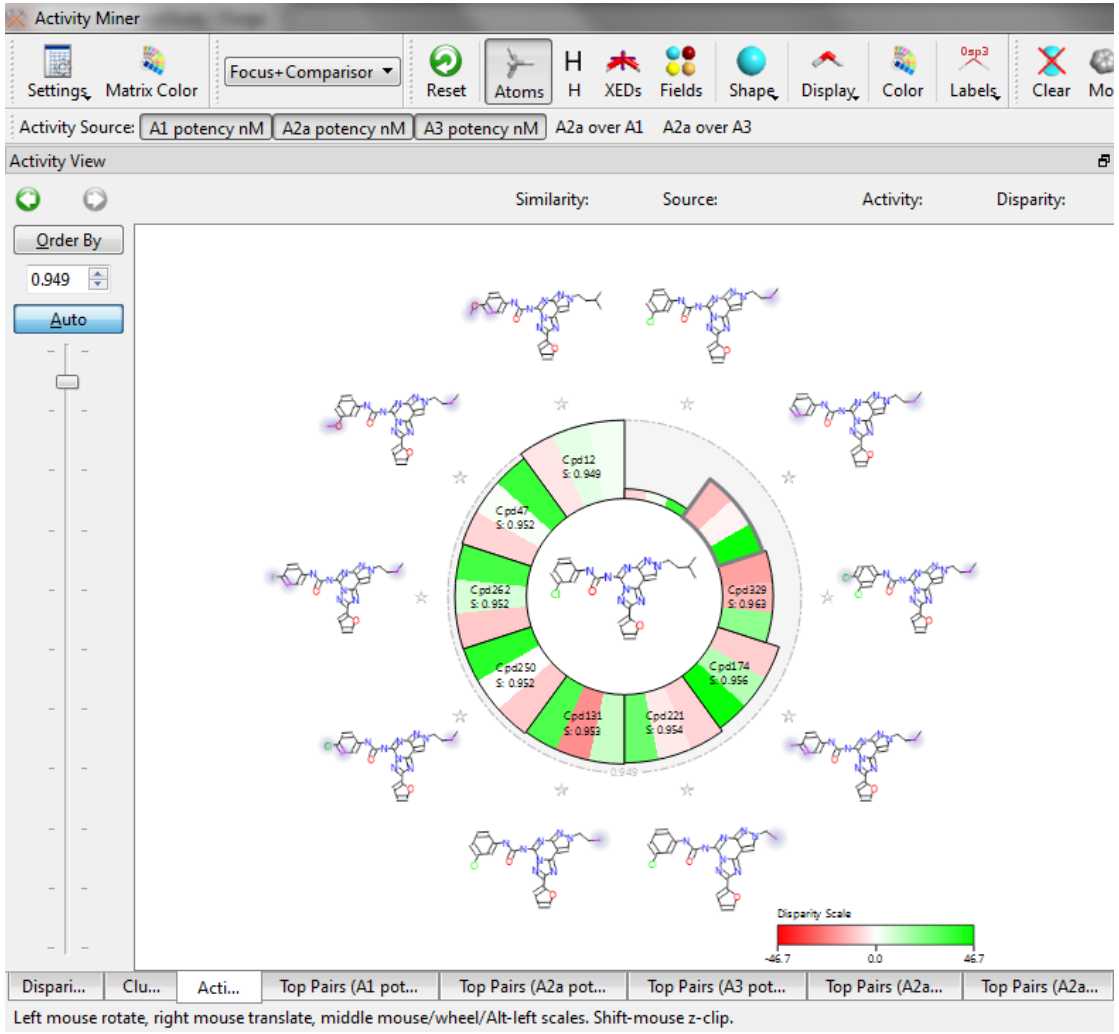
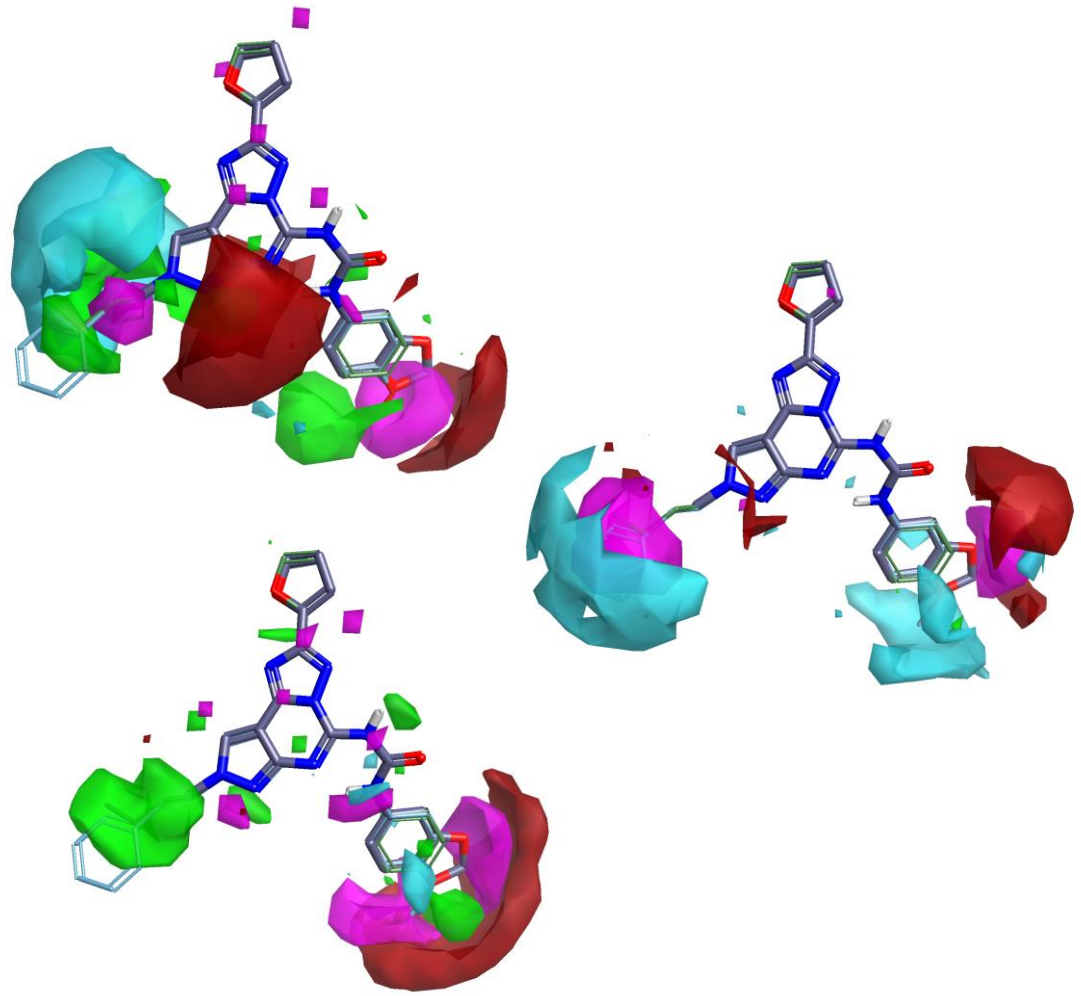
Selectivity mining





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Discover new directions for your project using bioisosteres

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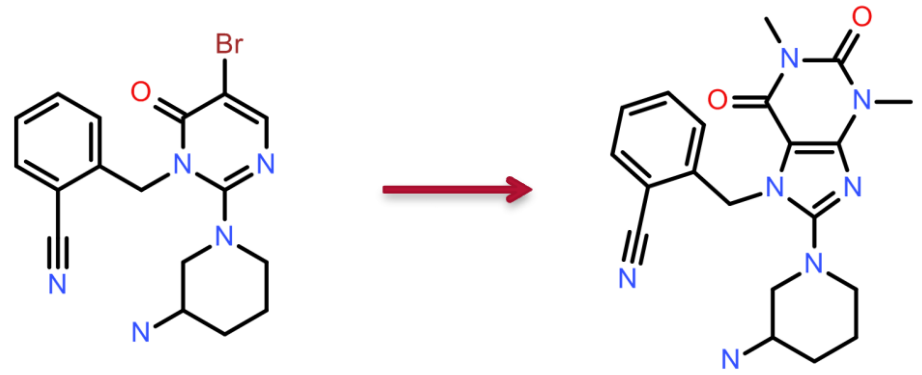
Scaffold hopping from Spark



- > Scaffold hop using a db of fragments
- > Find new R groups from db of available reagents
- > New ideas
- > Fragment growing

- > Increased novelty
- > Find gaps in patents
- > Rapid assessment of available chemistry space
- > Protect your Patents

"The best bioisostere application on the market"

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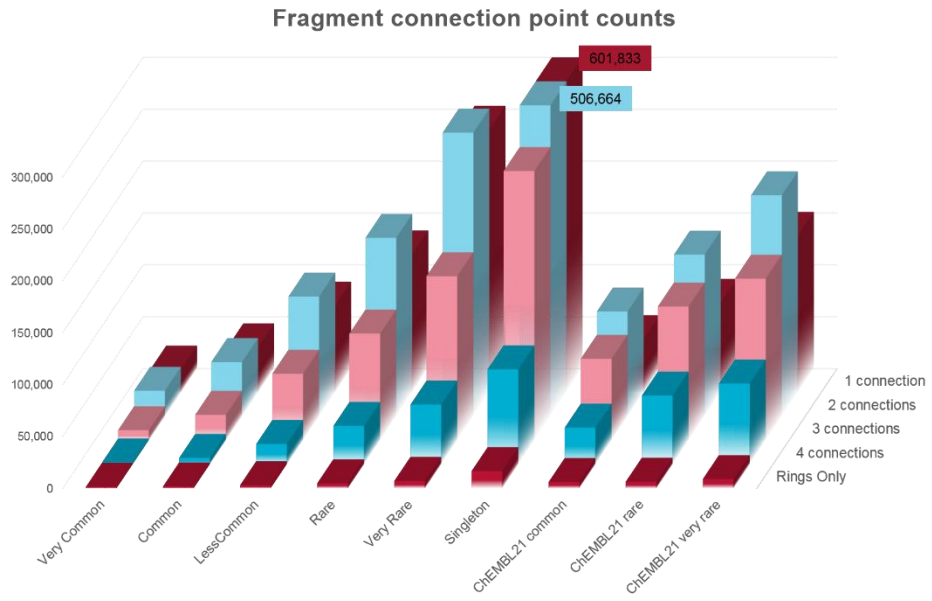
Spark 10.4: April 2016

- Updated fragment and reagent databases
  - New/updated chemical diversity from ChEMBL and ZINC
  - Improved reagent categories (e.g., separated primary/secondary amine databases)
  - Reagents from eMolecules



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Spark 10.4: April 2016

- Multi-parameter optimization
  - Add a weighting to each property and combine into a single score
  - Color columns and molecules by radial plot score
  - Color columns and molecules by any property (e.g., activity)

- Additional information in results table
  - Attachment point type
  - Frequency of torsions

- Data from an external server
- Filtering using multiple SMARTS/drawn substructure during the search
- Filtering of results on drawn substructure
- Lots of GUI improvements and tweaks

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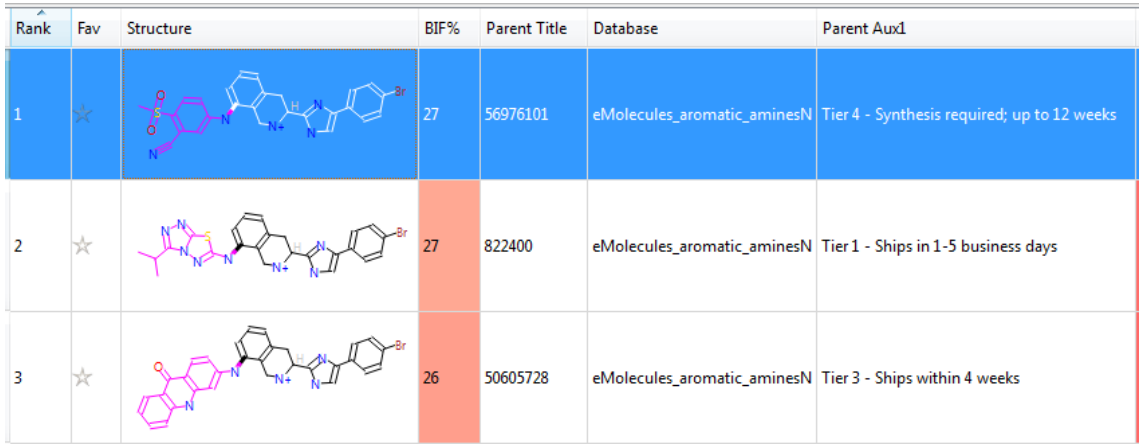
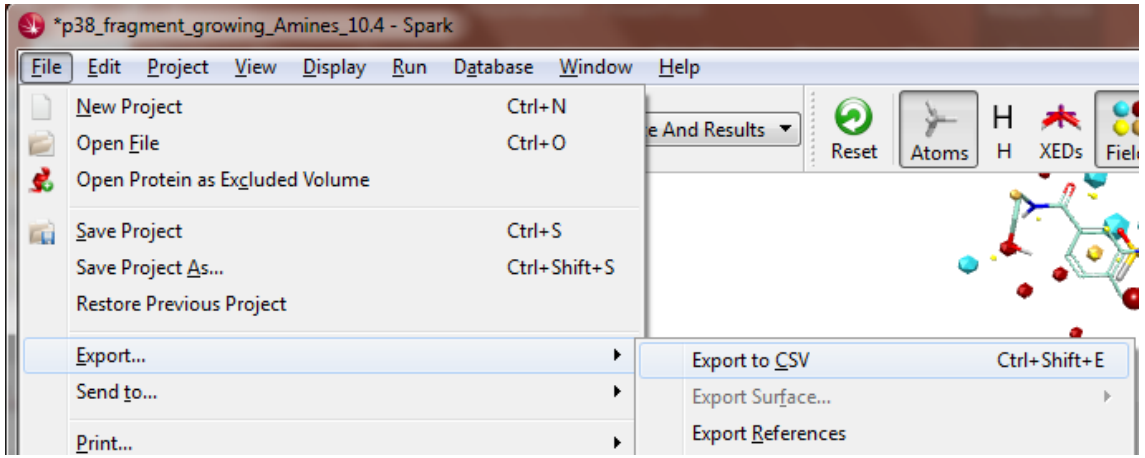
Reagents from eMolecules

- Improved availability
  - Regular updates (3-4 monthly)
  - Availability tier present in results



Rank	Fav	Structure	BIF%	Parent Title	Database	Parent Aux1
1	☆		27	56976101	eMolecules_aromatic_aminesN	Tier 4 - Synthesis required; up to 12 weeks
2	☆		27	822400	eMolecules_aromatic_aminesN	Tier 1 - Ships in 1-5 business days
3	☆		26	50605728	eMolecules_aromatic_aminesN	Tier 3 - Ships within 4 weeks

- Easier to bulk order from results
  - Export favorites to CSV
  - Extract eMolecules ID



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Torsion analysis

JOURNAL OF CHEMICAL INFORMATION AND MODELING
Application Note
pubs.acs.org/jcim

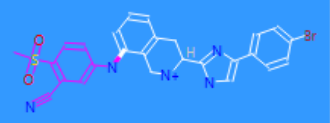
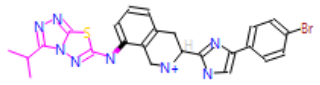
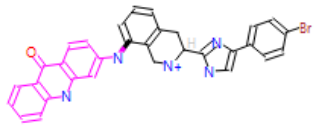
Torsion Library Reloaded: A New Version of Expert-Derived SMARTS Rules for Assessing Conformations of Small Molecules

Wolfgang Guba,*,† Agnes Meyder,‡ Matthias Rarey,*,‡ and Jérôme Hert†

†Molecular Design and Chemical Biology, Roche Pharma Research and Early Development (pRED), Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland

‡Center for Bioinformatics, University of Hamburg, Bundesstrasse 43, D-20146 Hamburg, Germany

- Implemented in Spark
- Applied to
  - New bonds
  - Fragment conformation
- Augments existing Strain calculation

Rank	Fav	Structure	BIF%	Database	Strain 1	TorsFreq 1	TorsFreq Frag
1	☆		27	eMolecules_aromatic_aminesN	0.5	Medium	Medium
2	☆		27	eMolecules_aromatic_aminesN	0.6	Medium	High
3	☆		26	eMolecules_aromatic_aminesN	0.4	Medium	High

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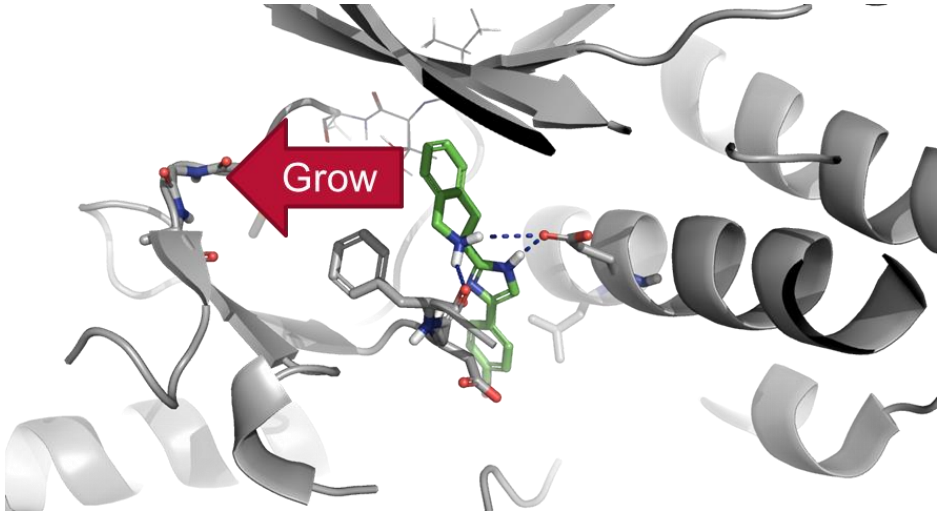
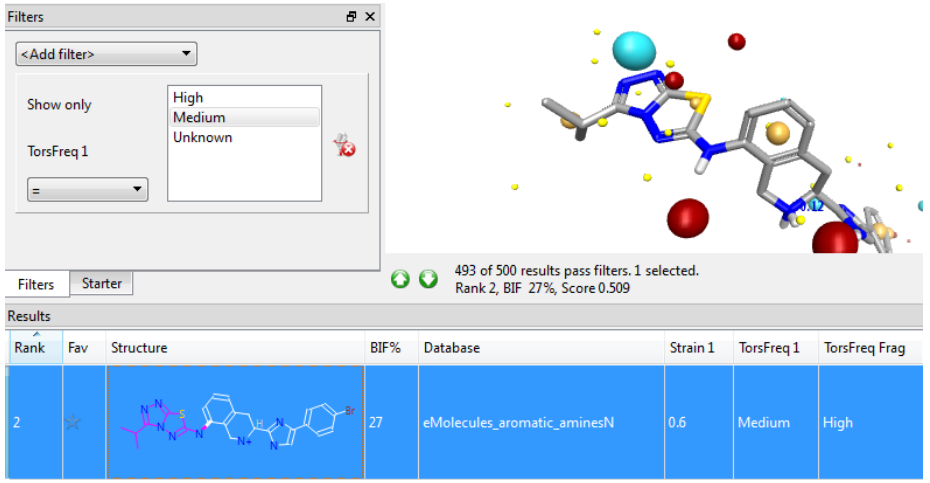
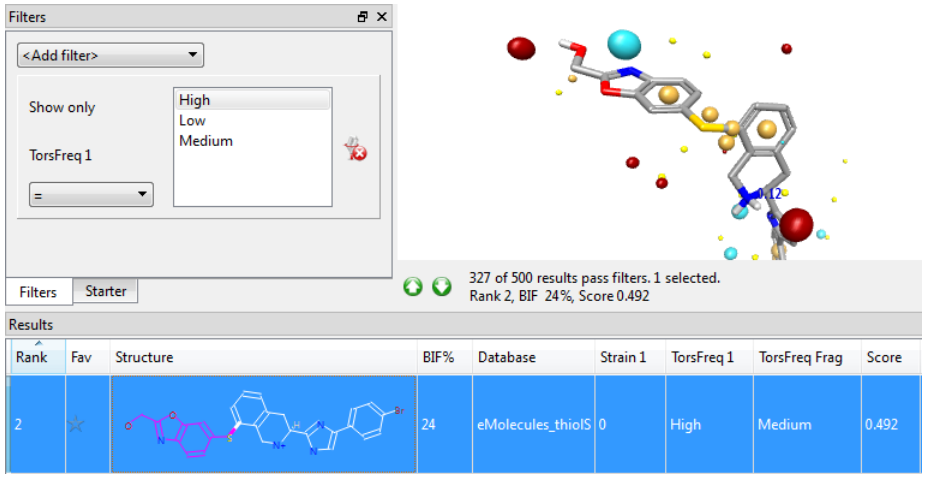
Torsion example

- Fragment growing in p38 case study
- Search for amine based reagent
- Search for thiol based reagent







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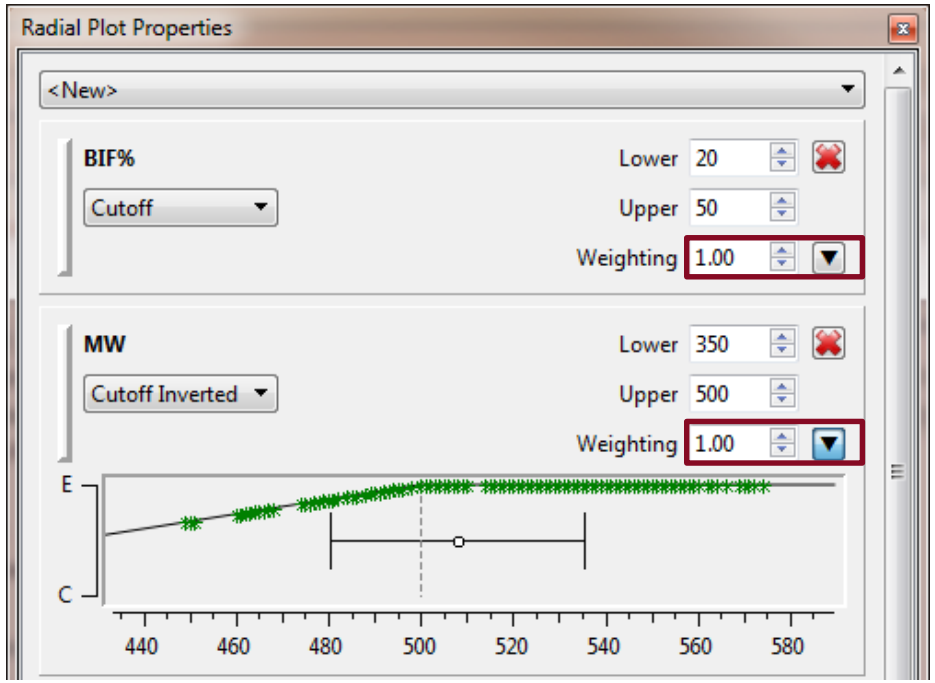
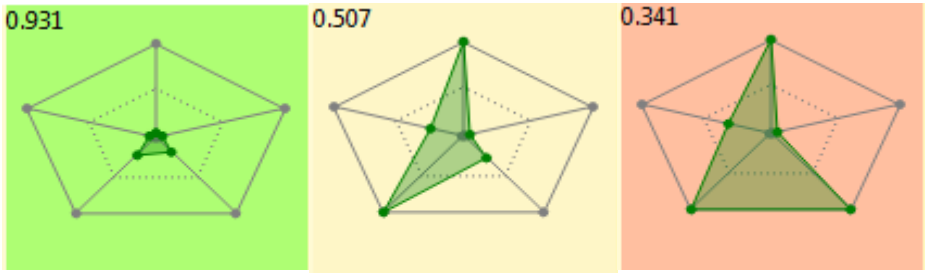
Radial plot and Multi-Parameter Optimization





- Radial Plot shows a graphical representation of properties and their fit to the project profile
- In this release we complement the graphics with a single numerical score
  - Do not always want the properties to be weighted evenly
  - Different importance of different properties in different projects
  - Graphical representation and numerical scoring may differ
- Color molecules, columns, radial plot by score

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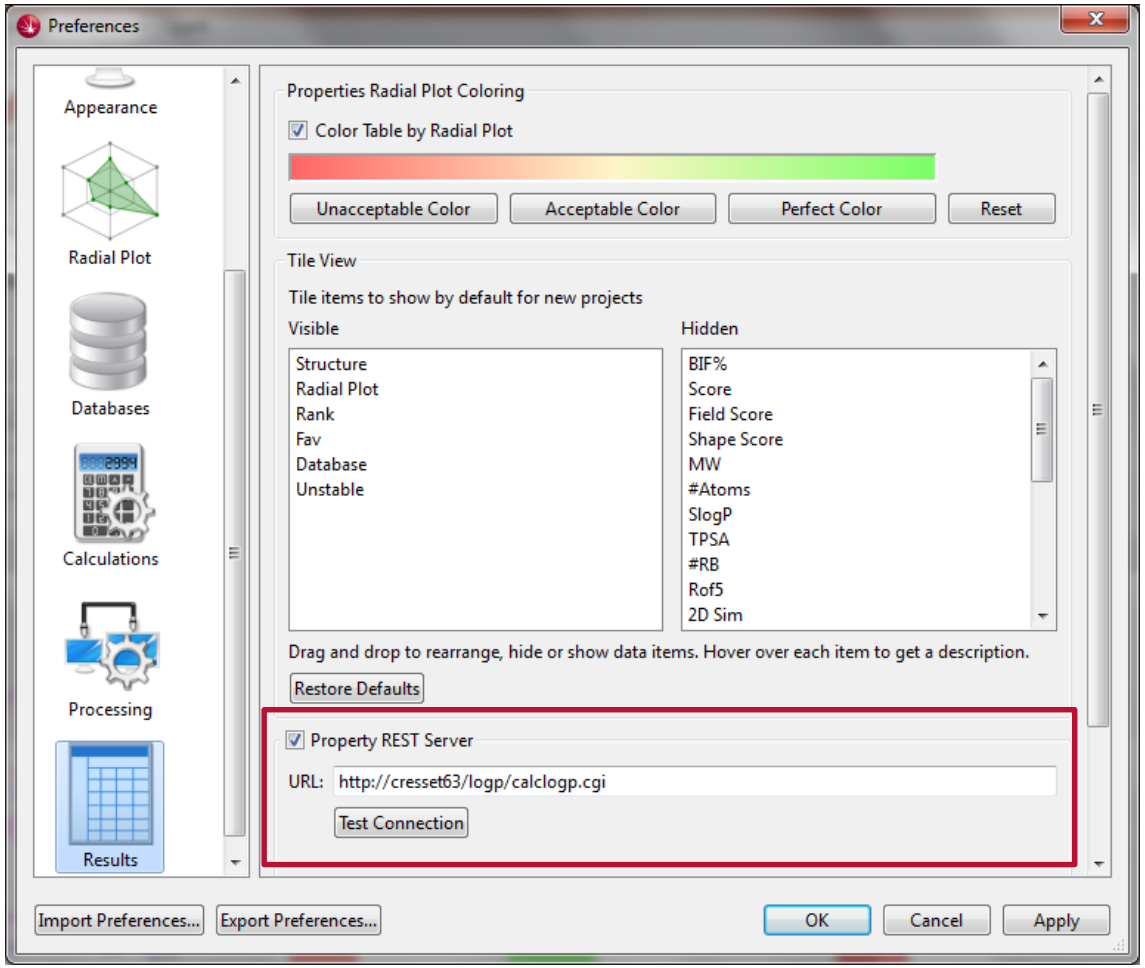
Data from external server



> Each result sent to server as smiles

> Properties received as Property/Value pairs in JSON

> More complex queries possible by passing parameters (e.g., project or username)

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Blaze on Amazon

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Blaze Cloud

- New deployment option for Blaze
- Cresset provide an Amazon Web Services AMI
  - Full installation of Blaze and all prerequisites
  - Can run in an Amazon private cloud for security
  - Automatically starts/stops Amazon spot instances to do the calculations
  - Highly scalable and cost-effective

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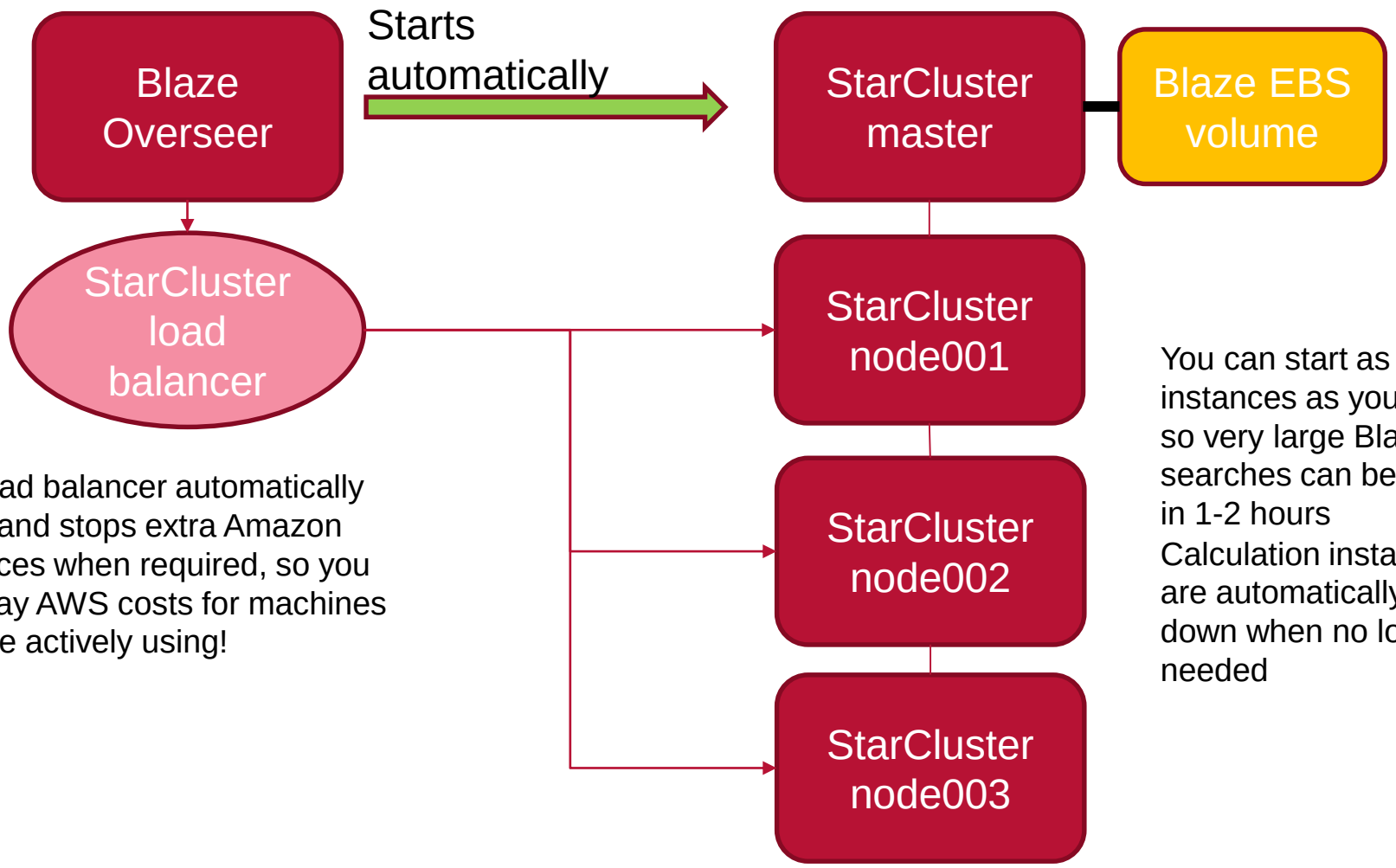
Architecture

The Blaze overseer manages the entire Blaze cluster



This is the actual Blaze installation, and provides the same web front end you are used to!

The load balancer automatically starts and stops extra Amazon instances when required, so you only pay AWS costs for machines you are actively using!

You can start as many instances as you like, so very large Blaze searches can be done in 1-2 hours
Calculation instances are automatically shut down when no longer needed

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Structure-based design

Cresset's next step

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Philosophy (again)

- Find new ways to discover or view compounds and data that provide results that would otherwise be missed
- Deliver this new science in easy-to-use interfaces with minimal learning curves
  - GUIs, command lines, Pipeline Pilot components, KNIME nodes ….
  - APIs and plugin modules

- Cresset science
  - Protein Interaction Potentials
  - 3D RISM
  - Minimization

- Interesting academic methods
  - WaterSwap
  - Ligand Swap
  - …

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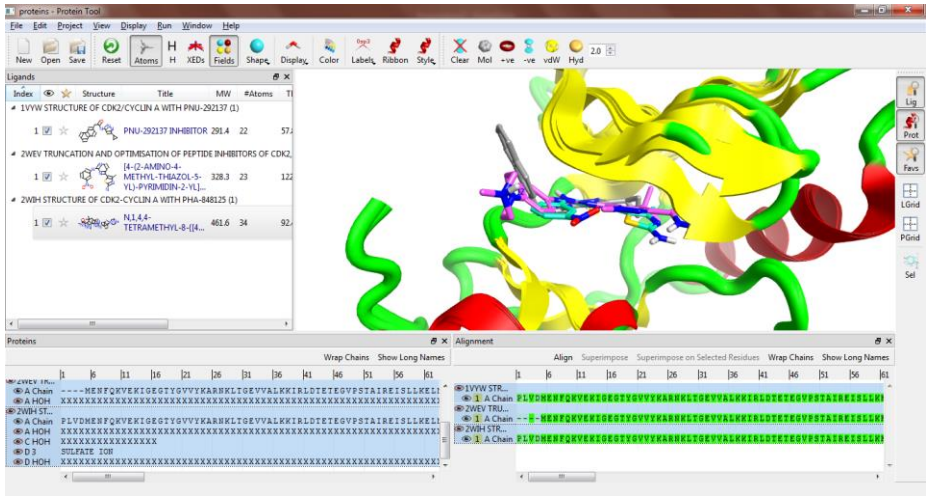
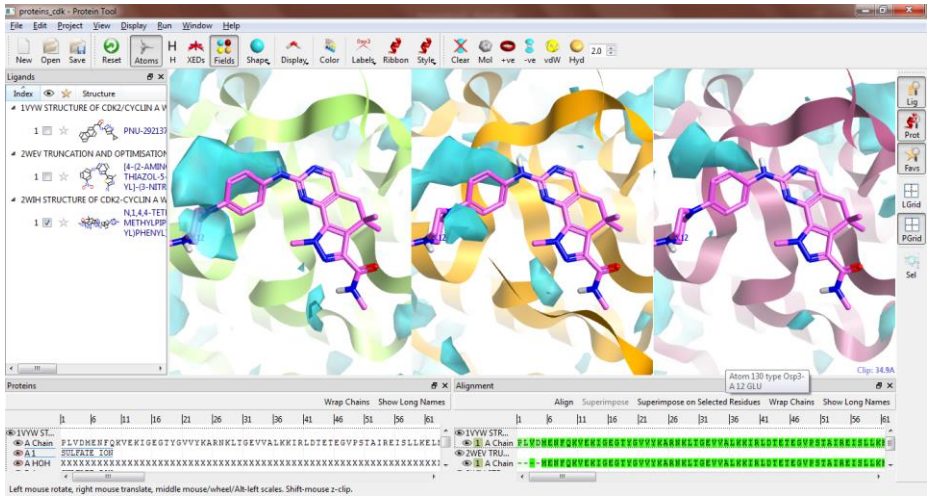
New protein application

- Currently in development
- Launch in March 2017
- Extensive alpha and beta testing through summer, fall and winter 2016
  - Let us know if you want to give it a try





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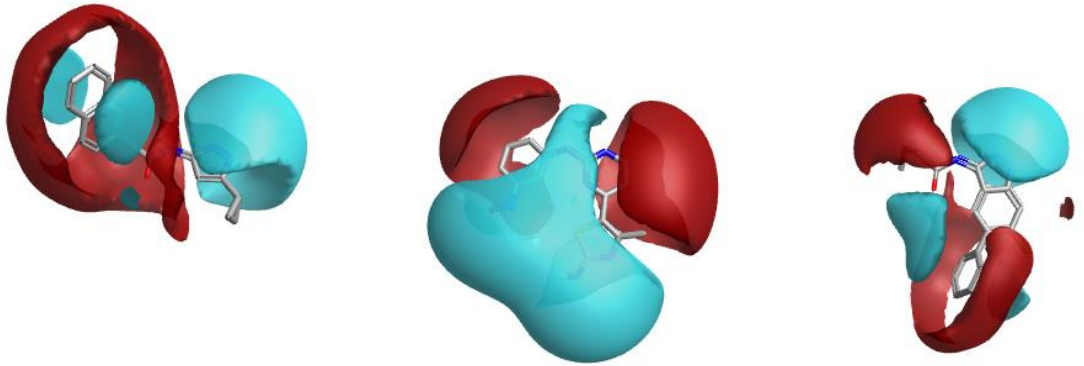
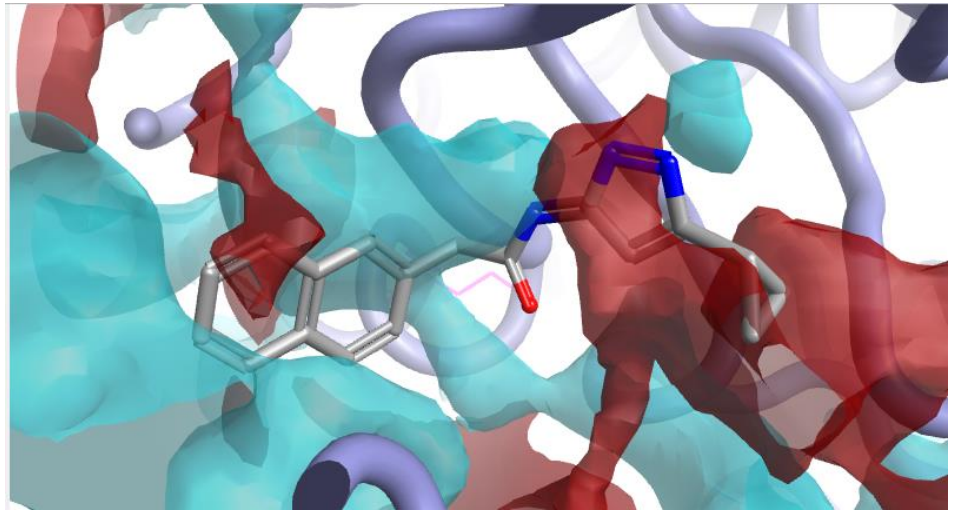
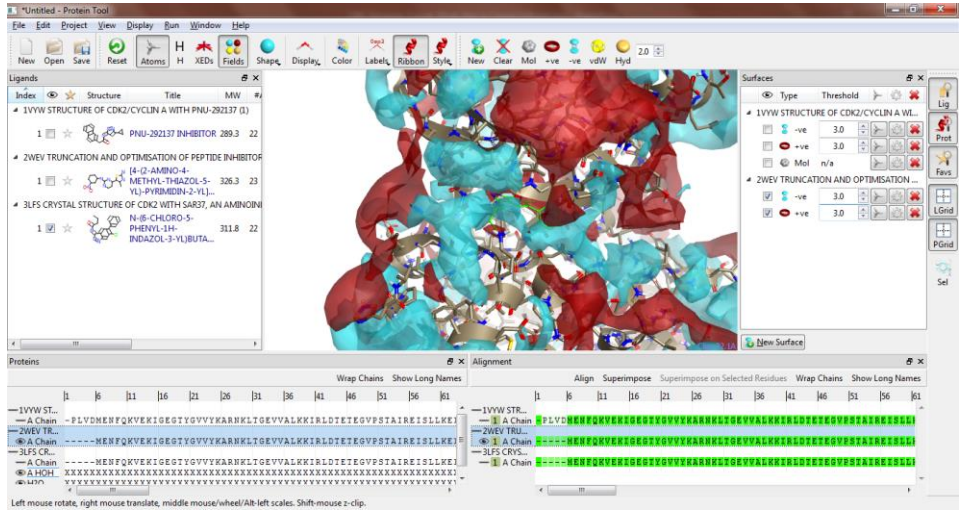
Current Status

- Rapidly evolving
- Aiming for first alpha in the next few weeks







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Architecture

- C++ backend
  - Performs all heavy lifting
  - Interfaces to Fortran force field
  - Distributes calculations to FieldEngines
- RDKit core
  - Built on and around RDKit to enable wide selection of cheminformatics methods
- Python front end
  - Customizable
  - API
  - Scripting

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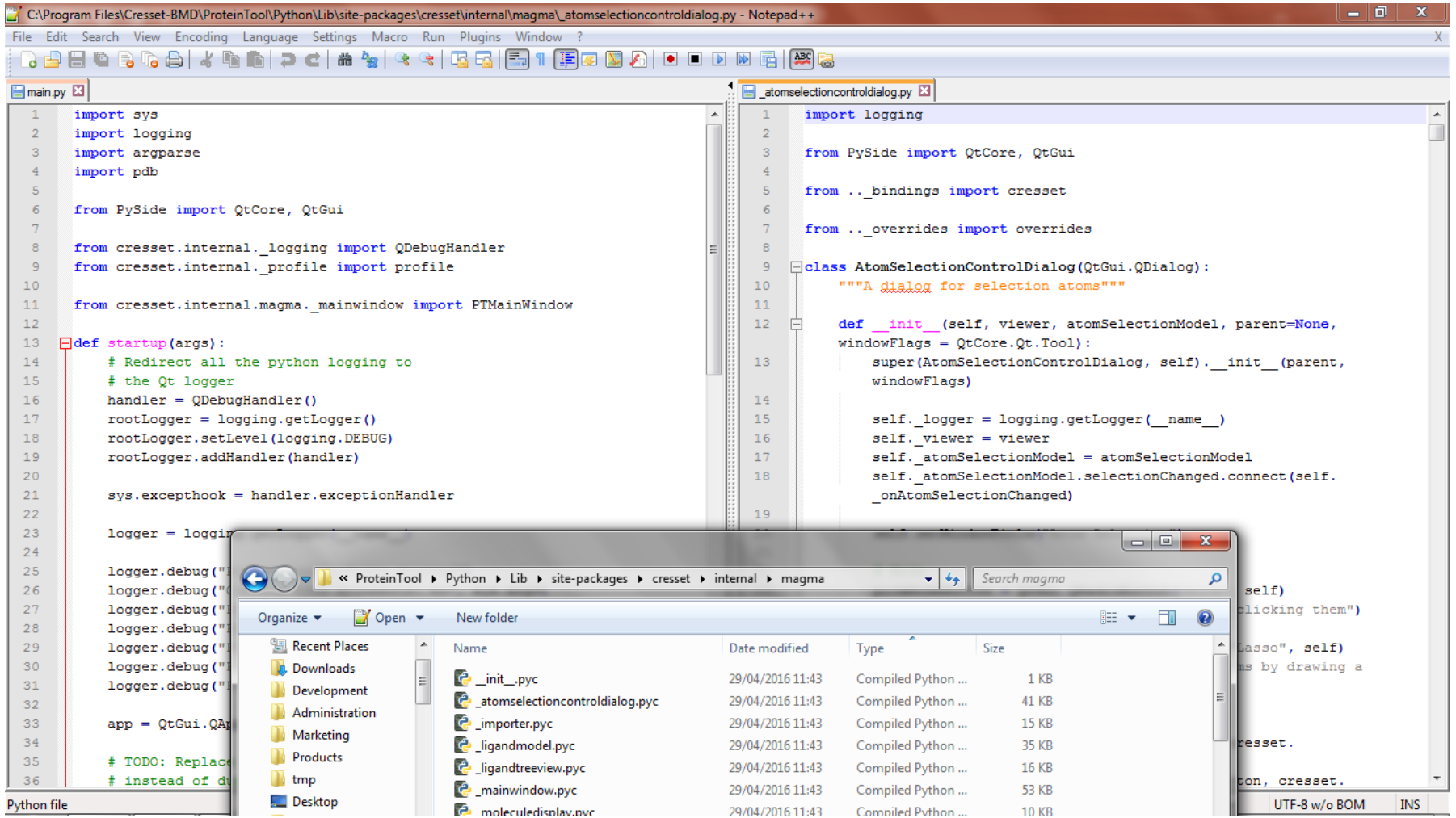
Protein tool



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smarter chemistry | smarter decisions

Thank you

Questions welcome

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