What's new in Spark 10.4:
Exploring the new features and enhancements

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

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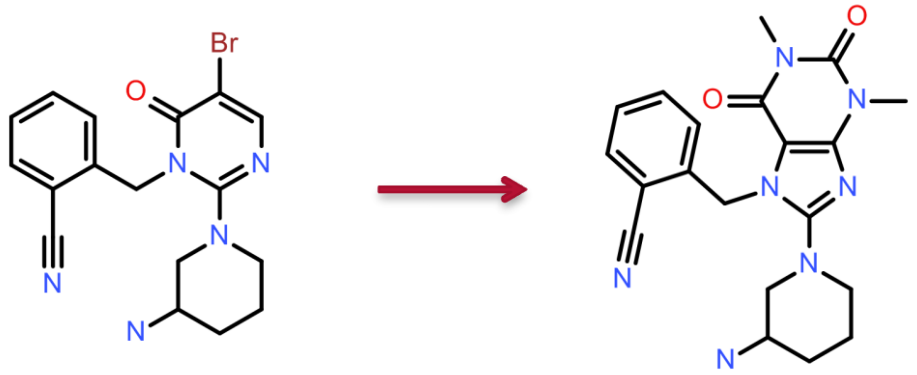
Scaffold hopping from Spark



- > 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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Why Spark?

- Great results
  - Obvious
  - Less obvious
  - Completely novel
- Easy to use
  - Few clicks for an experiment
- Property profile not just activity
  - Radial plot properties
- Designed to share
  - Result tagging
- Get the best IP position
  - Find freedom to operate even in congested space
  - Map out larger chemistry spaces – deny freedom to competitors
  - Get the best properties
- Find a back up series
  - Avoid your own IP
- Generate leads from patents
- Quickly step through LO
  - Avoid the ‘obvious’
  - Link ideas to available reagents

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Spark 10.4 improvements

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Overview of Spark 10.4 enhancements

- Experimental set-up
  - Cleaner, more efficient experiment set up dialogue
  - eMolecules reagent databases replacing Zinc
  - Pre-run fragment filtering on substructure

- Results interface
  - Color-coding
  - MPO score in radial plot
  - Substructure filtering
  - Attachment point type
  - Torsion frequency analysis

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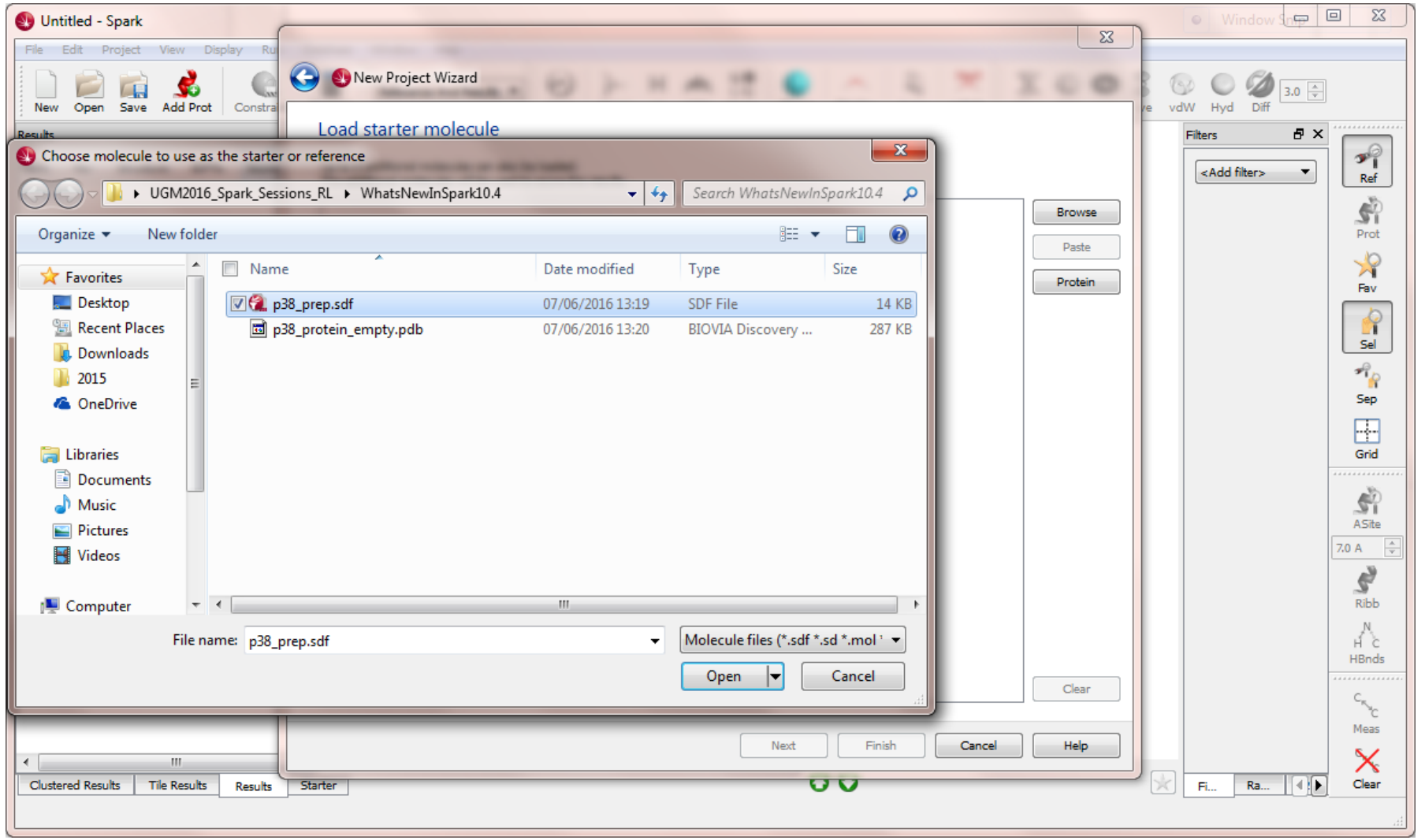
Show p38 growing experiment



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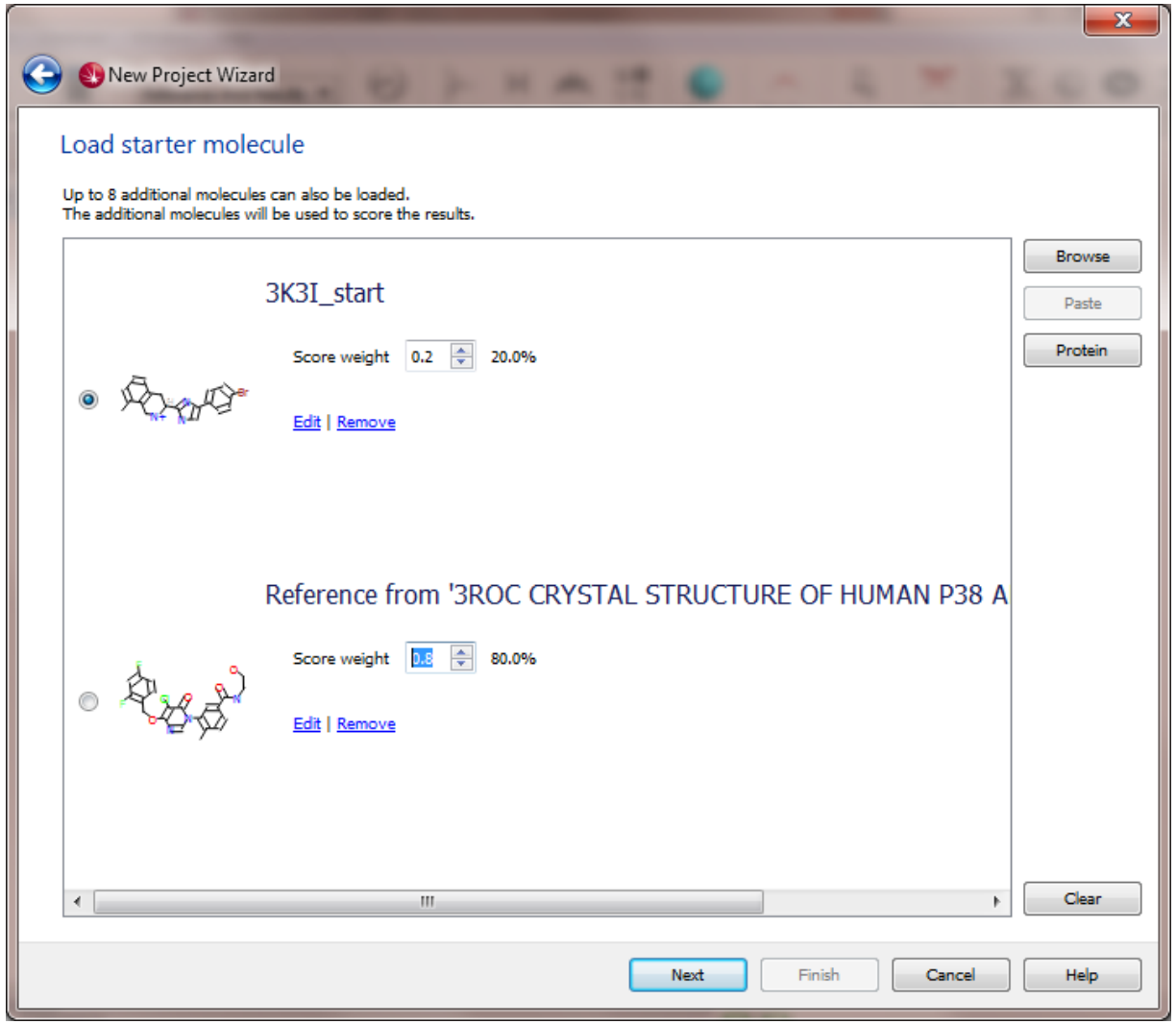
Change the scoring weights



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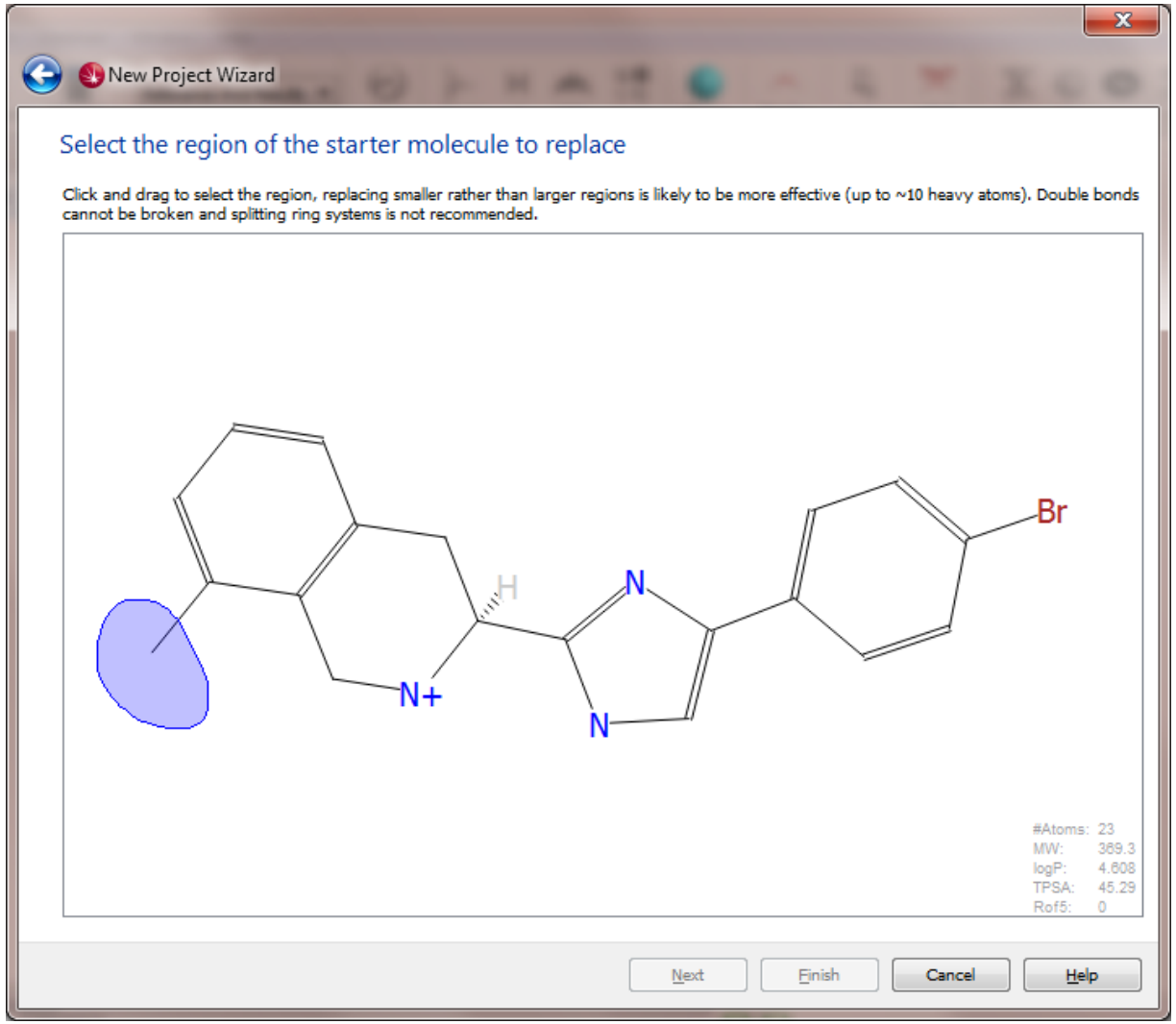
Circle the methyl



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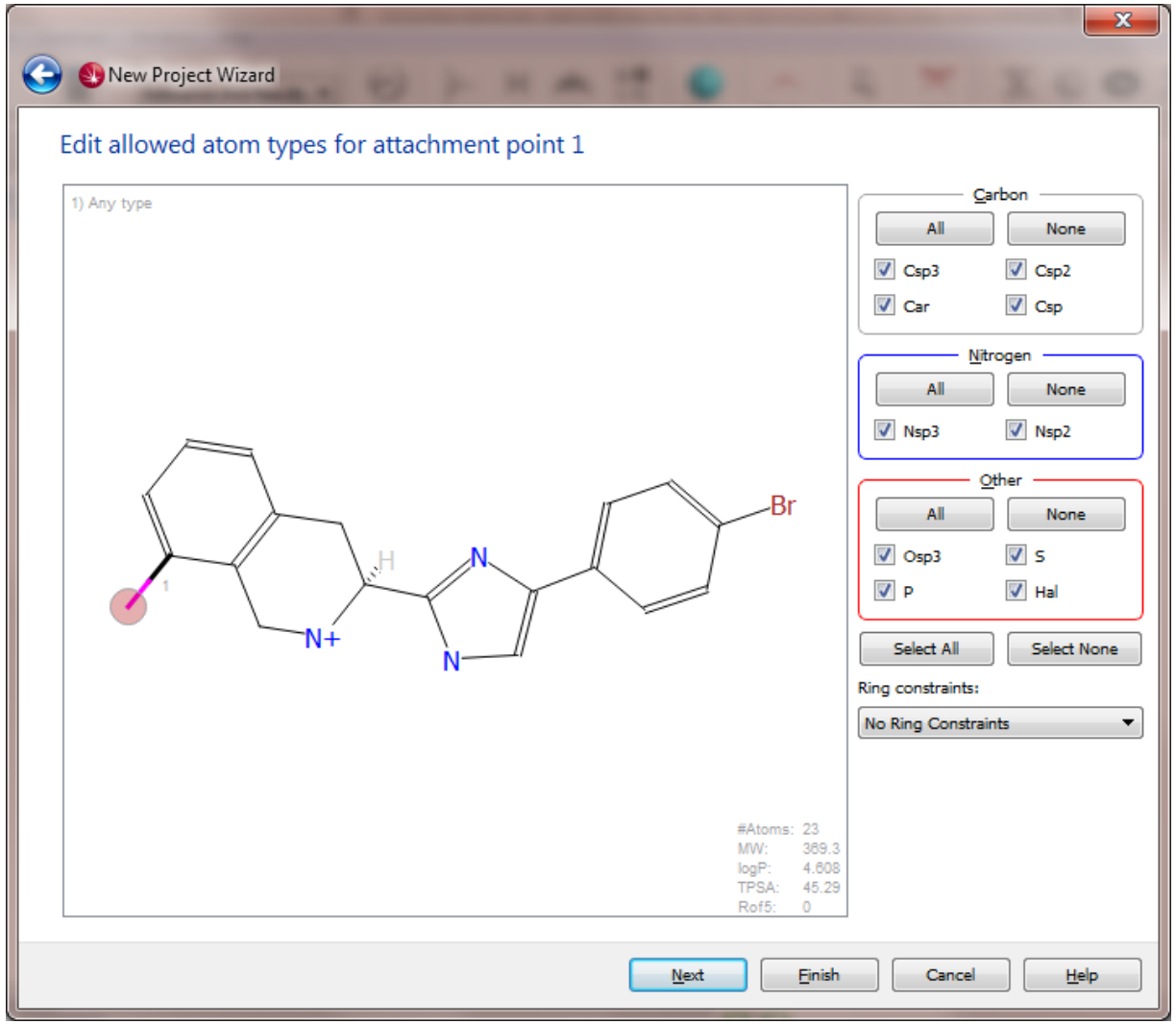
No conditions for allowed atom types



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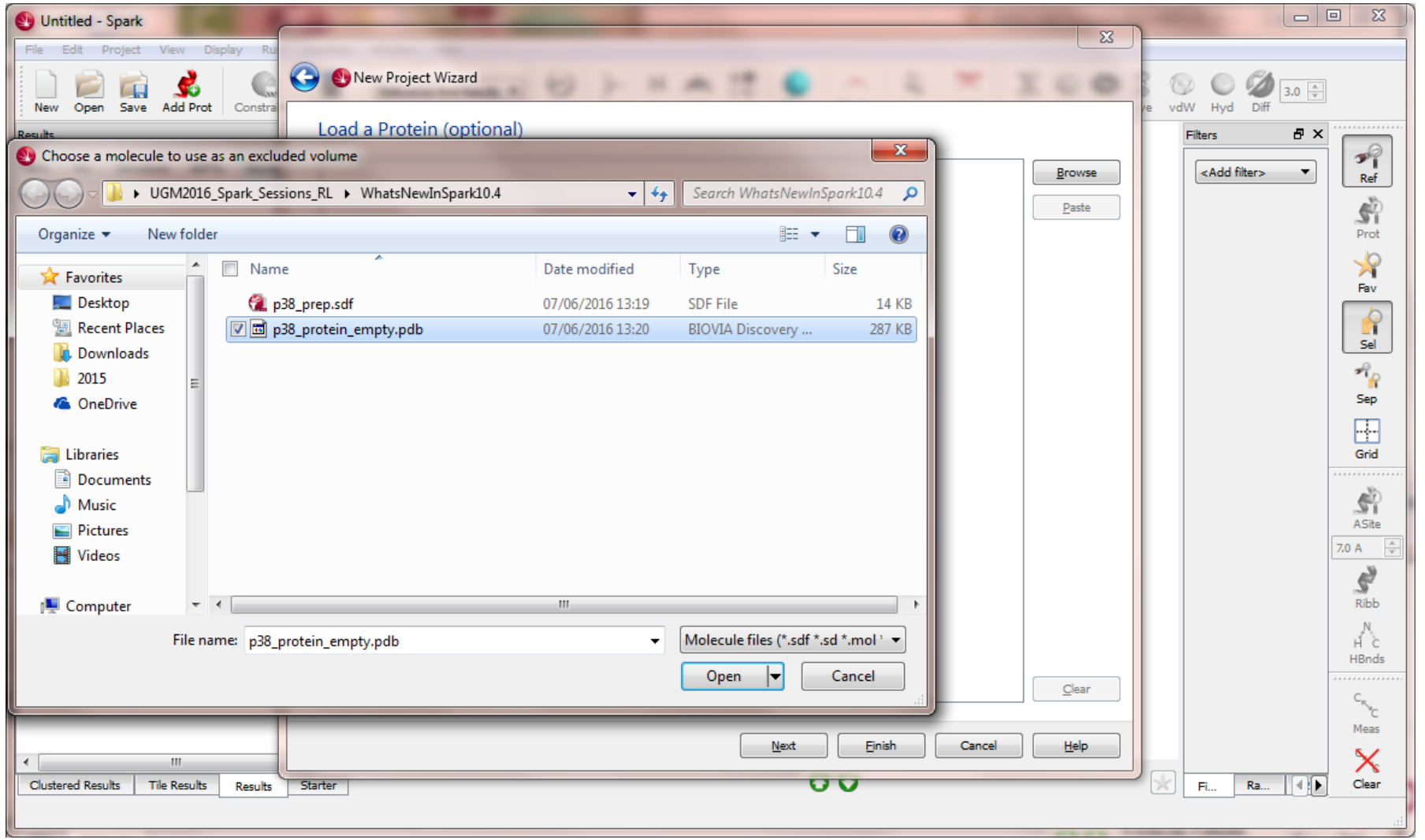
Load the protein from a PDB



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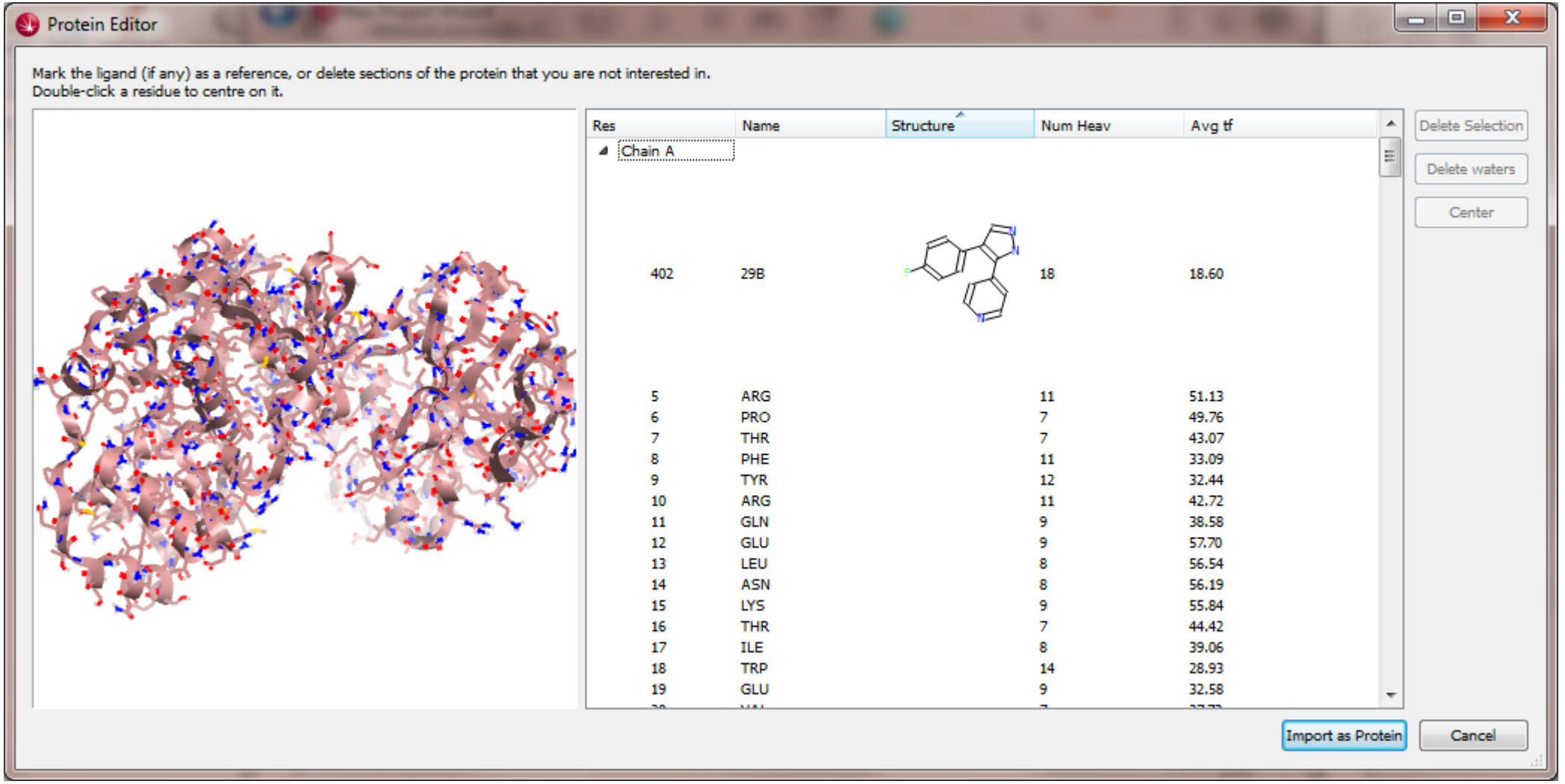
Import as a protein



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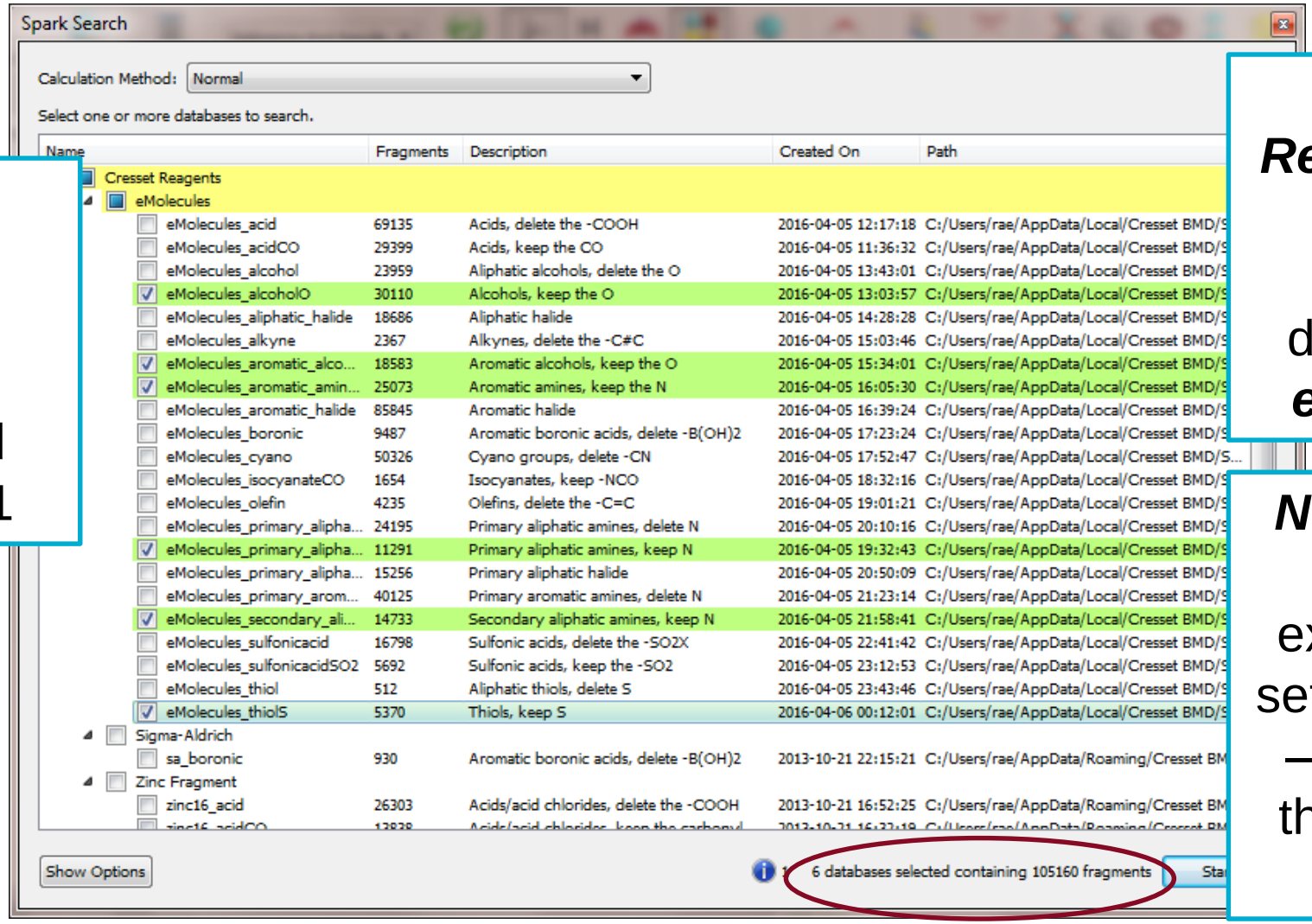
Choose the eMolecules databases as shown

Zinc and ***CHEMBL*** fragments updated to Zinc15 and CHEMBL21



Cresset Reagents now contain fragments derived from ***eMolecules***

Notifications ensure experiment is set up correctly – suggests if there are any errors

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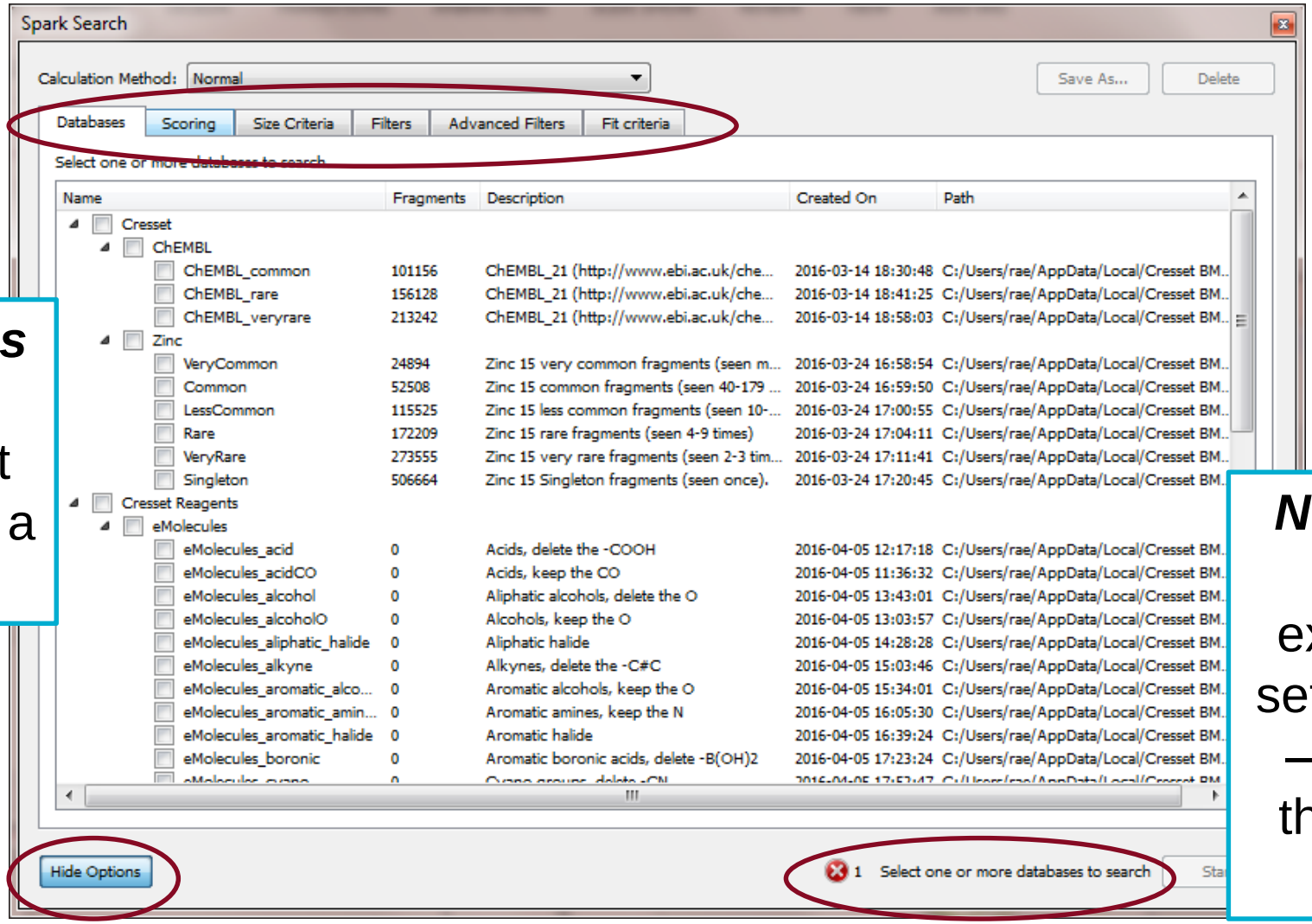
Experiment set up: Combined panel and notifications

Show Options expands the rest of the set up into tabs in a single panel



Notifications ensure experiment is set up correctly – suggests if there are any errors

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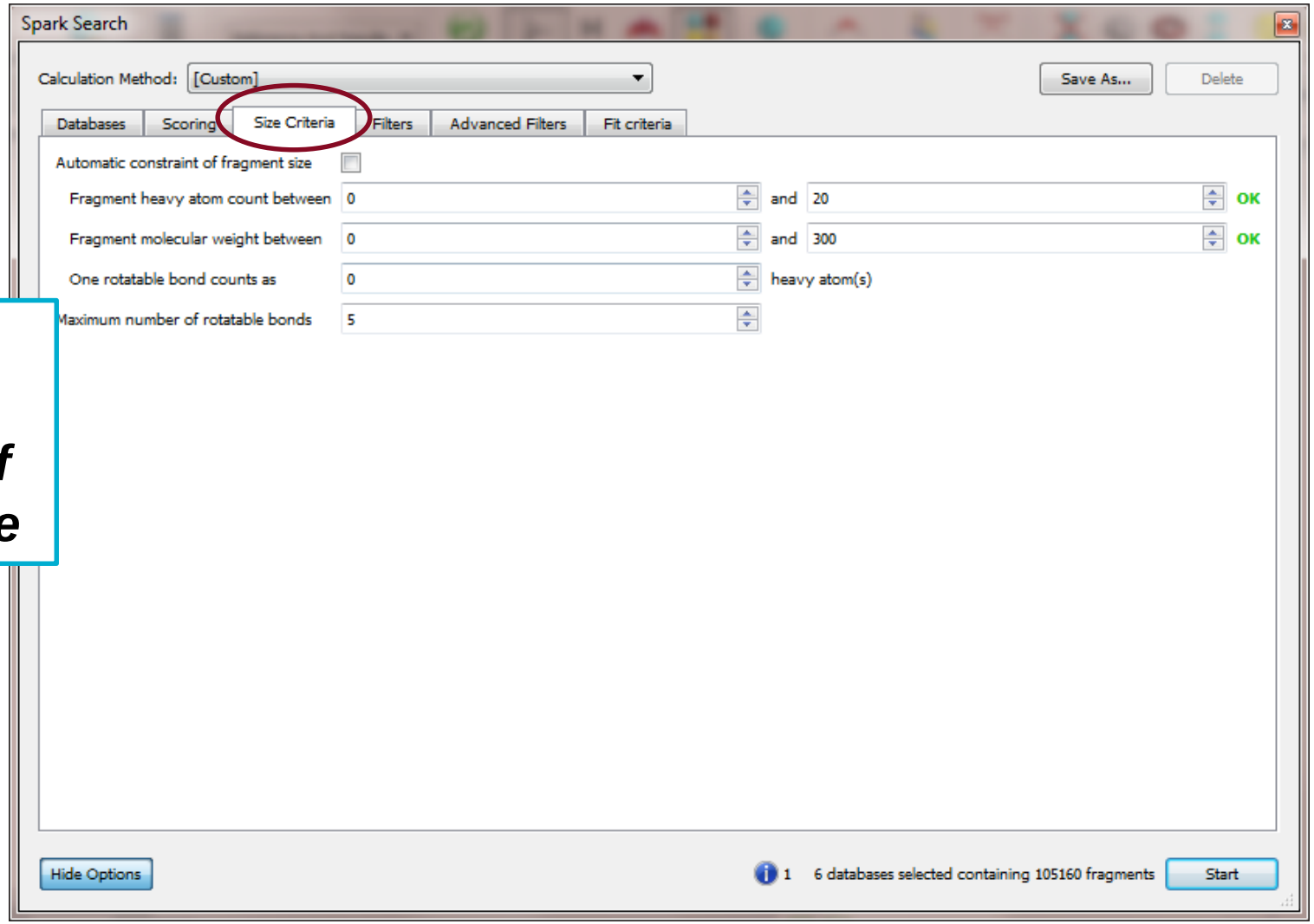
Streamlined set up: Change fragment size constraint

Turn off the automatic constraint of fragment size



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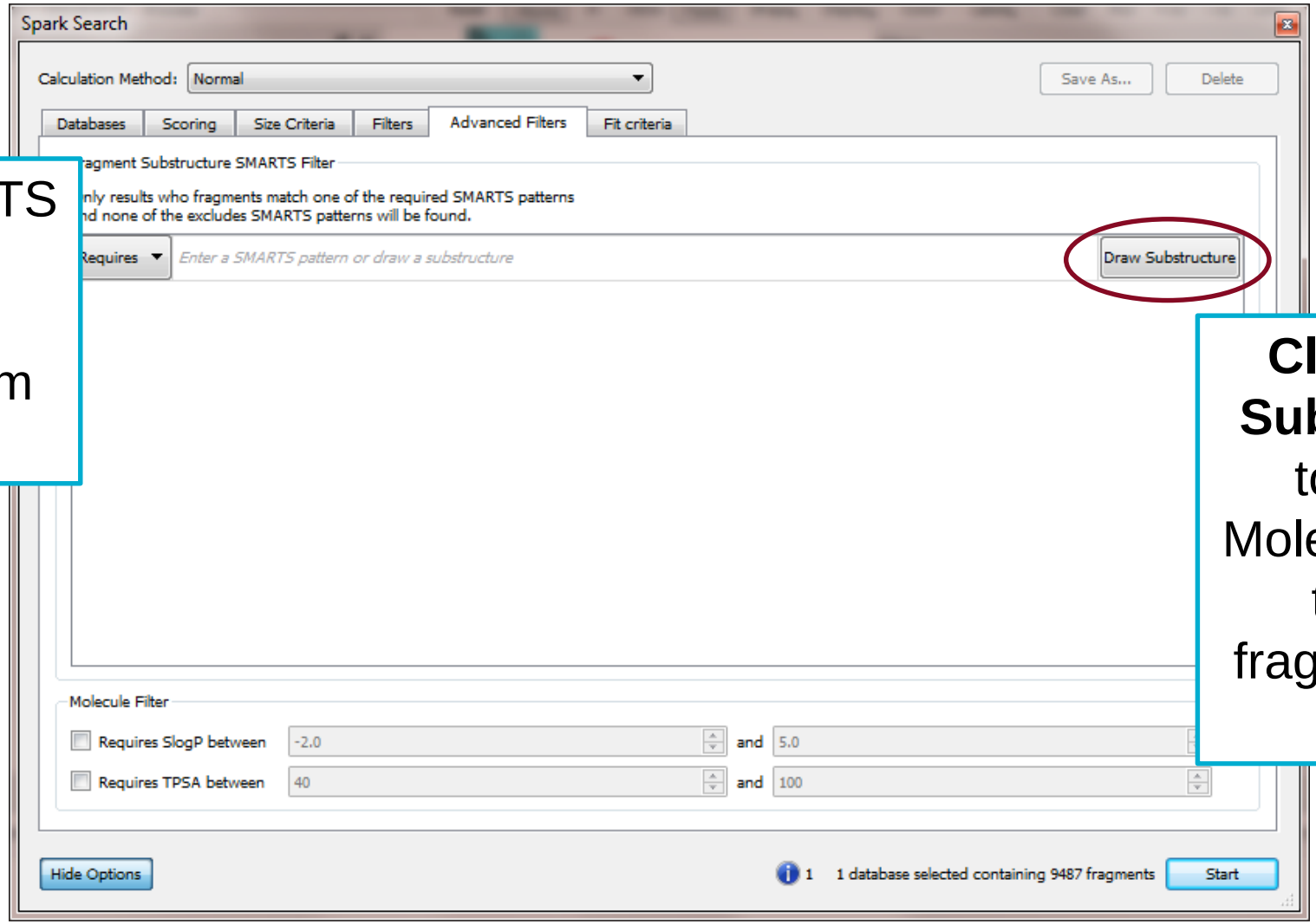
Advanced Filters: Pre-filtering fragments

Enter SMARTS pattern to **require** or **exclude** from fragments



Click Draw Substructure to launch Molecule Editor to enter fragment to be filtered

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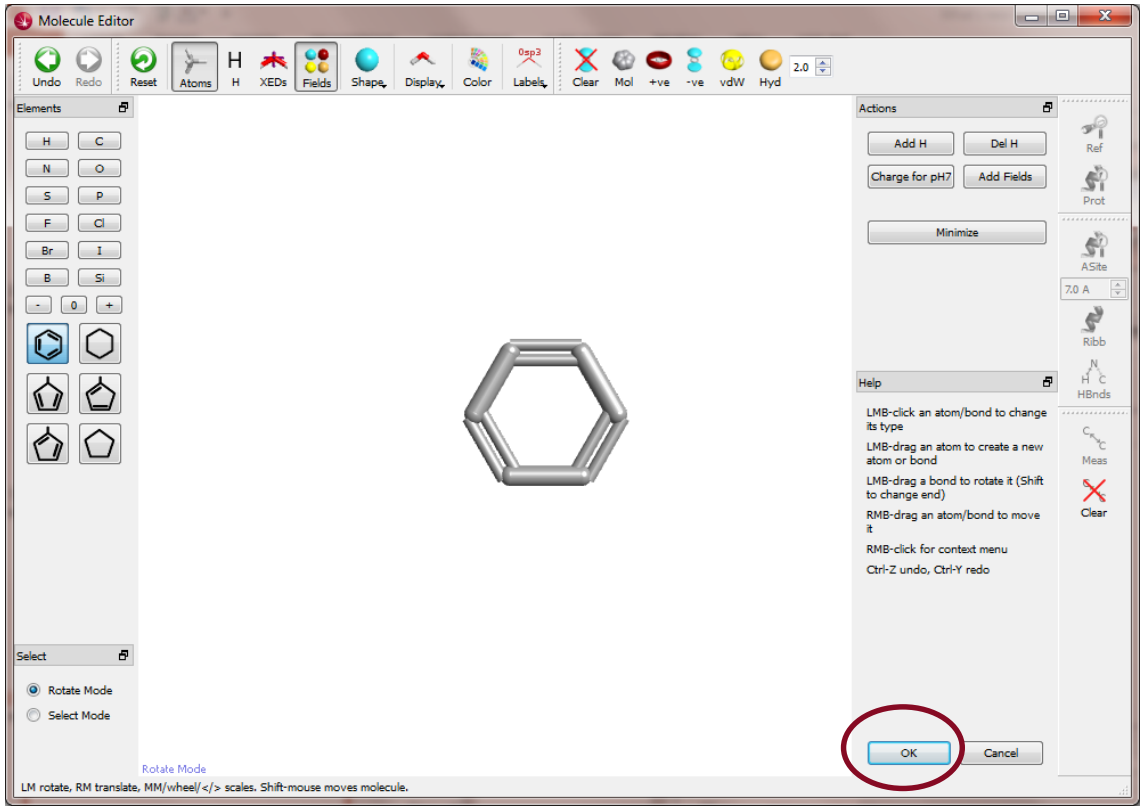
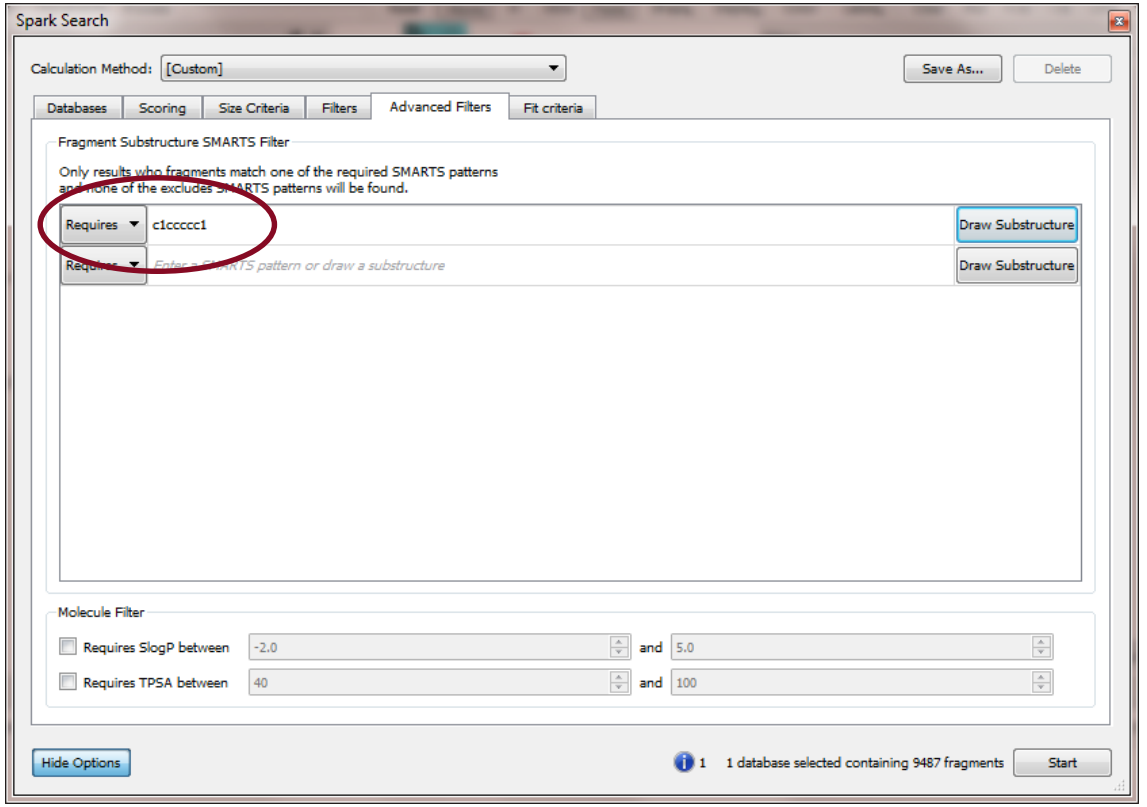
Advanced Filters: Substructure drawing





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Press Start

> DON’T WAIT – go to the one that was cooked earlier!

> Run took about 7 minutes on a laptop

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eMolecules information in results table

Results

#RB	RoF5	Radial Plot	2D Sim	Tags	Notes	rmsAng	rmsDist	Parent Title	Parent Aux1	Database	Frag ID	Frequency	Unstable	Attachment Point 1 Type	Attachment types	Cluster SMILES	Setting	Total formal char
6	2	0.447	0.347					54659881	Tier 3 - Ships within 4 weeks	eMolecules_thiolS	3387	1	false	S		[Fm]Sc1ccccc1	[Custom]	0.125
6	2	0.427	0.339					32179332	Tier 1 - Ships in 1-5 business days	eMolecules_alcoholO	3519	1	false	Osp3		[Fm]Oc1ccccc1	[Custom]	0.125
6	2	0.427	0.367					53961943	Tier 3 - Ships within 4 weeks	eMolecules_alcoholO	18994	1	false	Osp3		[Fm]Oc1ccccc1	[Custom]	0.125
6	2	0.407	0.36													cccn1	[Custom]	0.125

Parent title is the eMolecules ID. These can be copy/pasted to eMolecules, or favorites exported to CSV, then copy/pasted as a list

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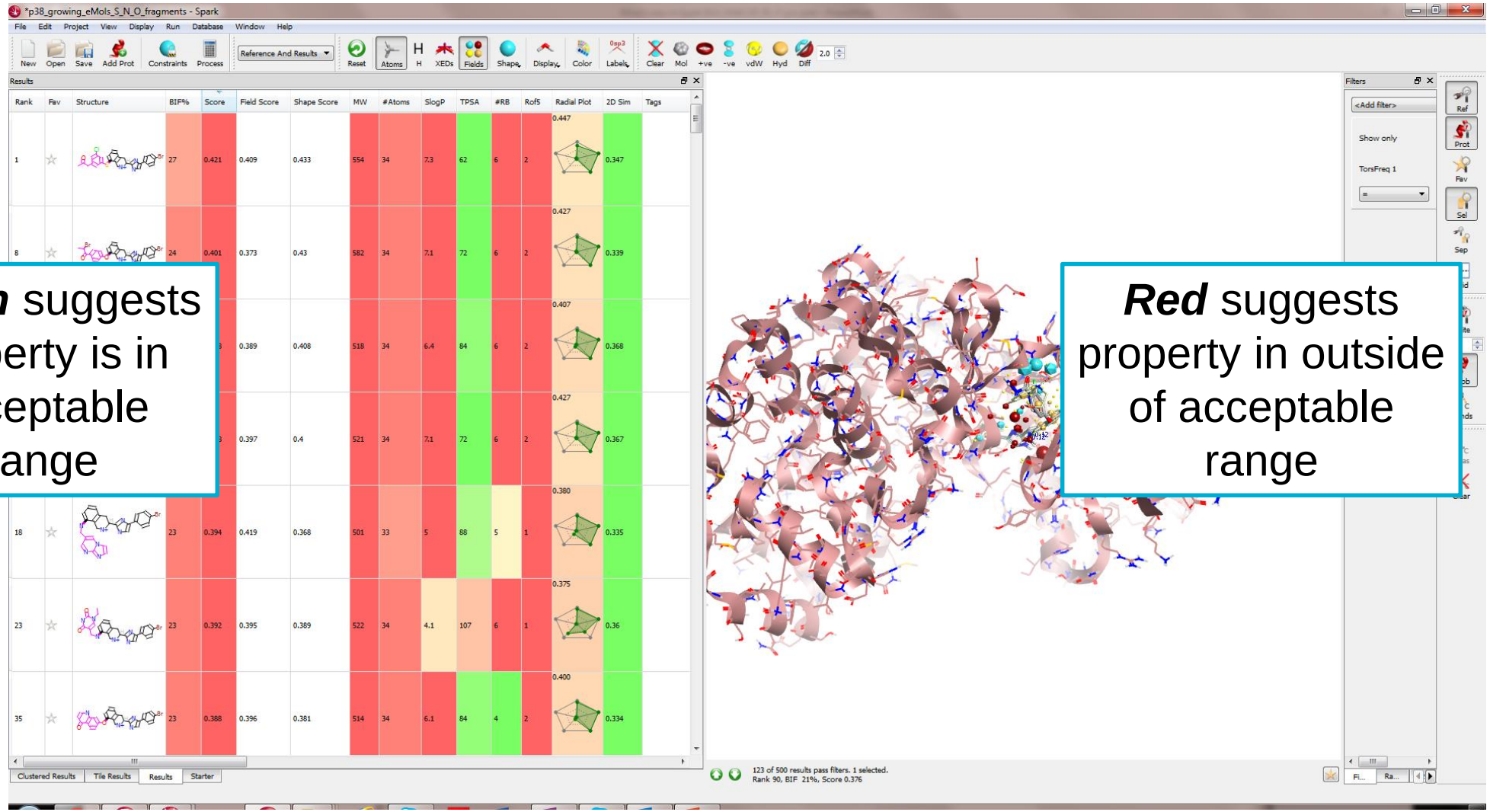
Results interface: Property-based colouring in Molecules Table

Green suggests property is in acceptable range



Red suggests property in outside of acceptable range

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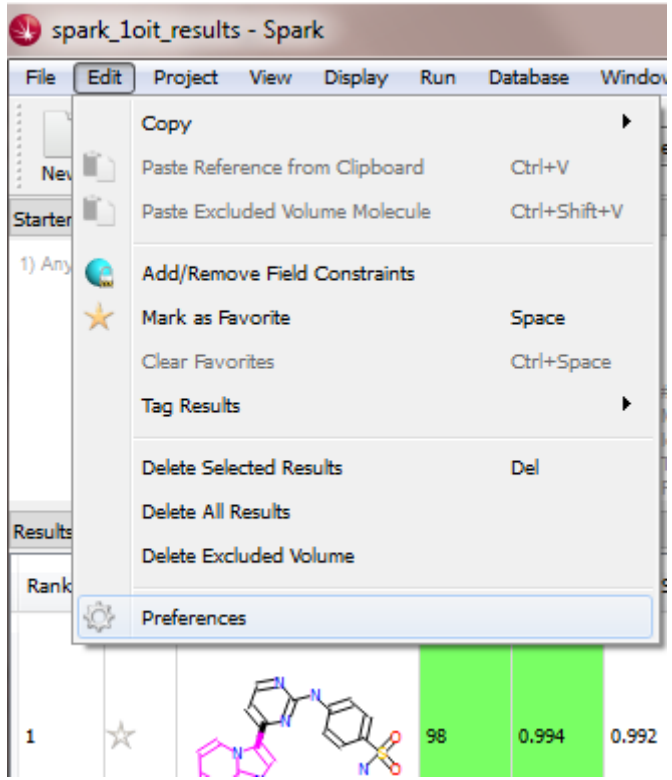
Defining acceptable ranges for properties and coloring

- Edit / Preferences
  - Control appearance
  - Control property ranges in Radial Plot properties
  - Control how results are displayed
  - Control how processing is done



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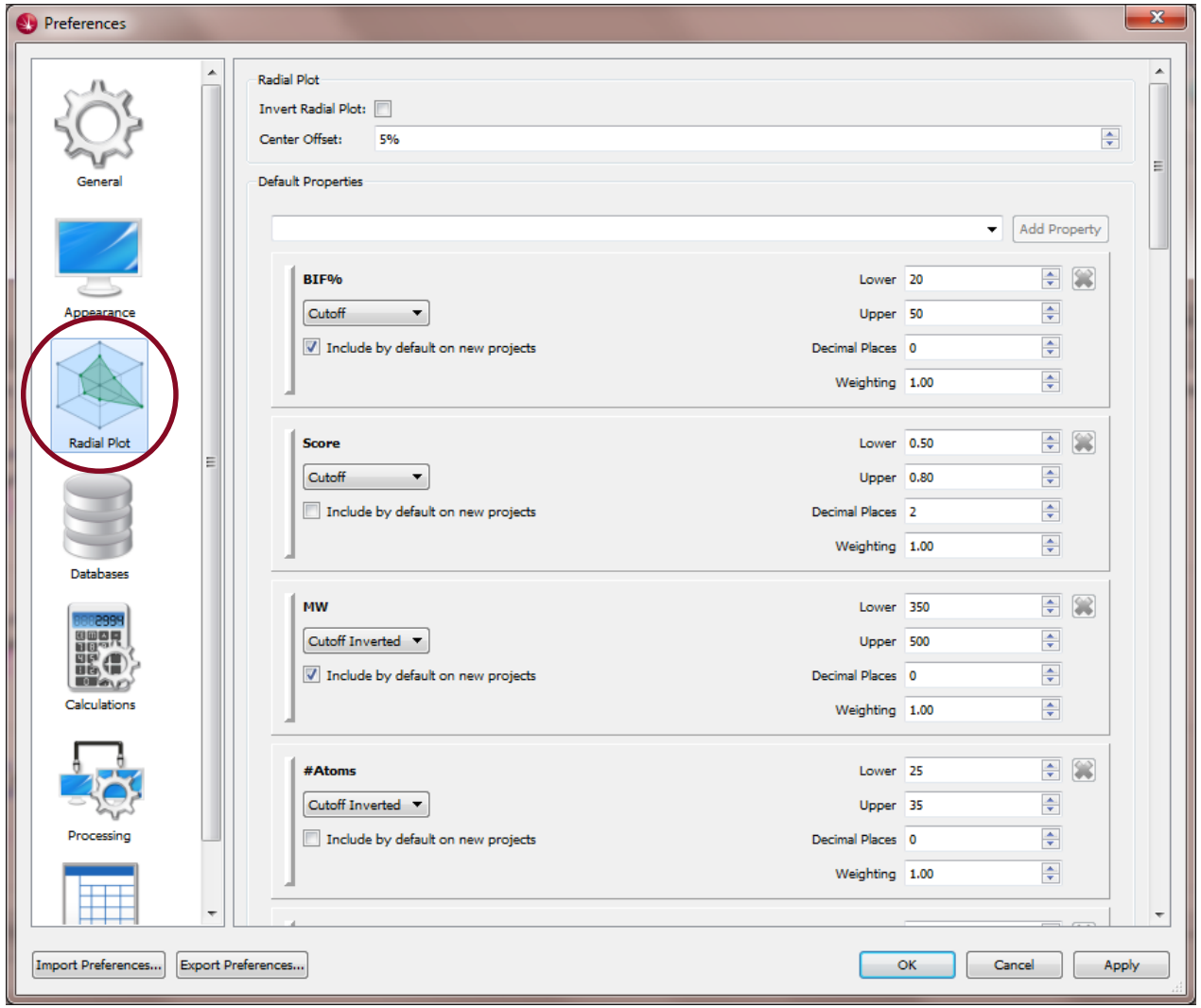
Preferences: Radial Plot

***Radial Plot** tab opens section to control acceptable ranges and cut-offs for column properties*



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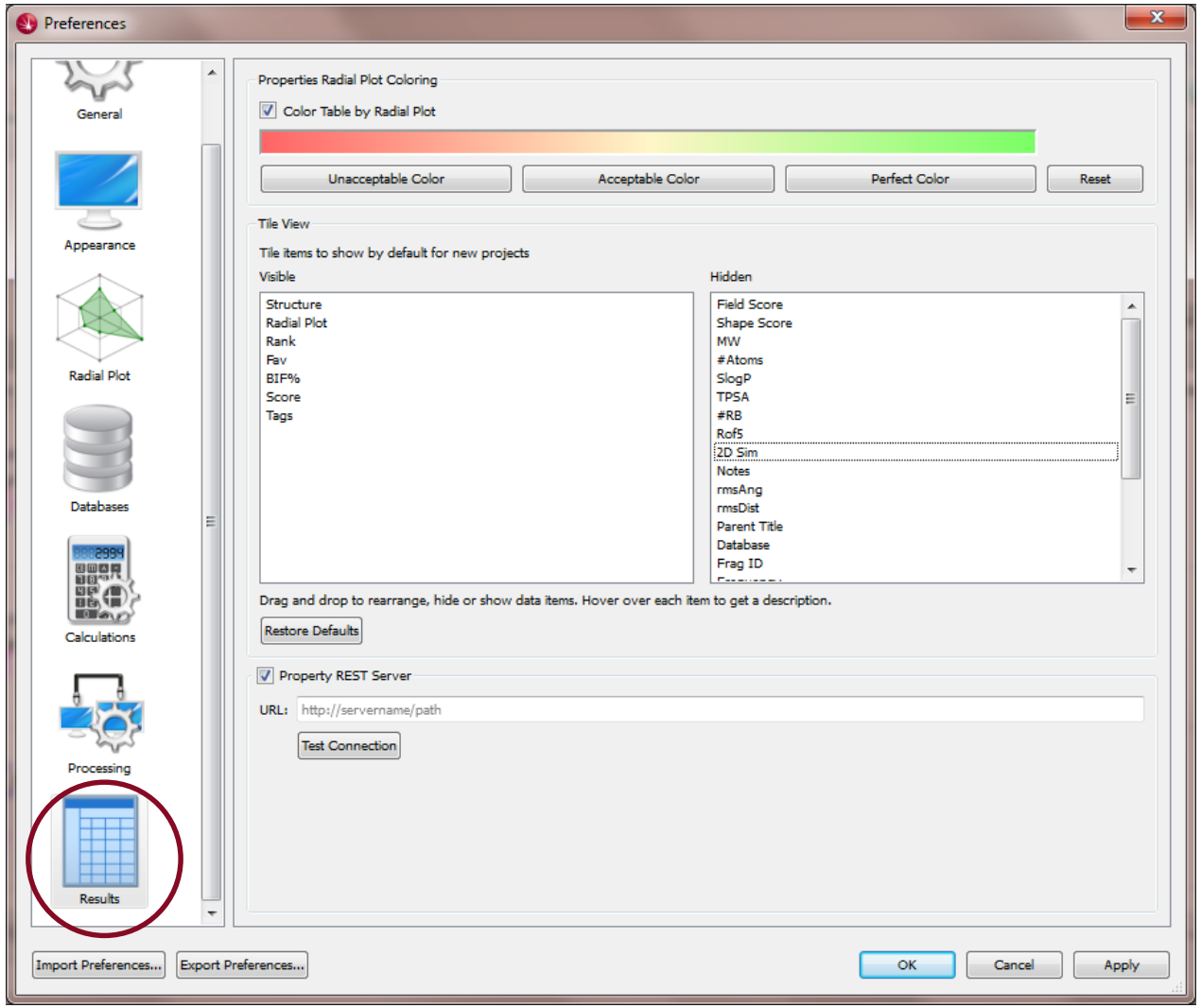
Preferences: Results

***Results** tab opens section to control how results are displayed in the Molecules Table*



***Coloring** can be modified or turned on/off*

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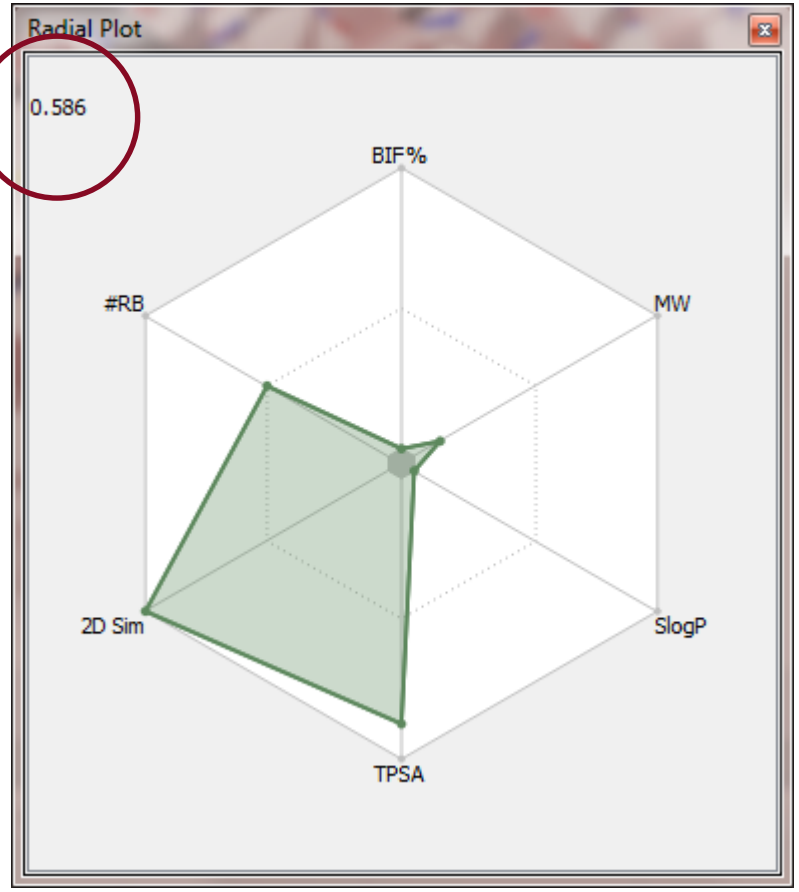
Multi-parameter optimization score in radial plot

MPO score *in top left corner of Radial Plot dock is a number between 0 and 1 which correlates how close a molecule is to having "ideal" properties*



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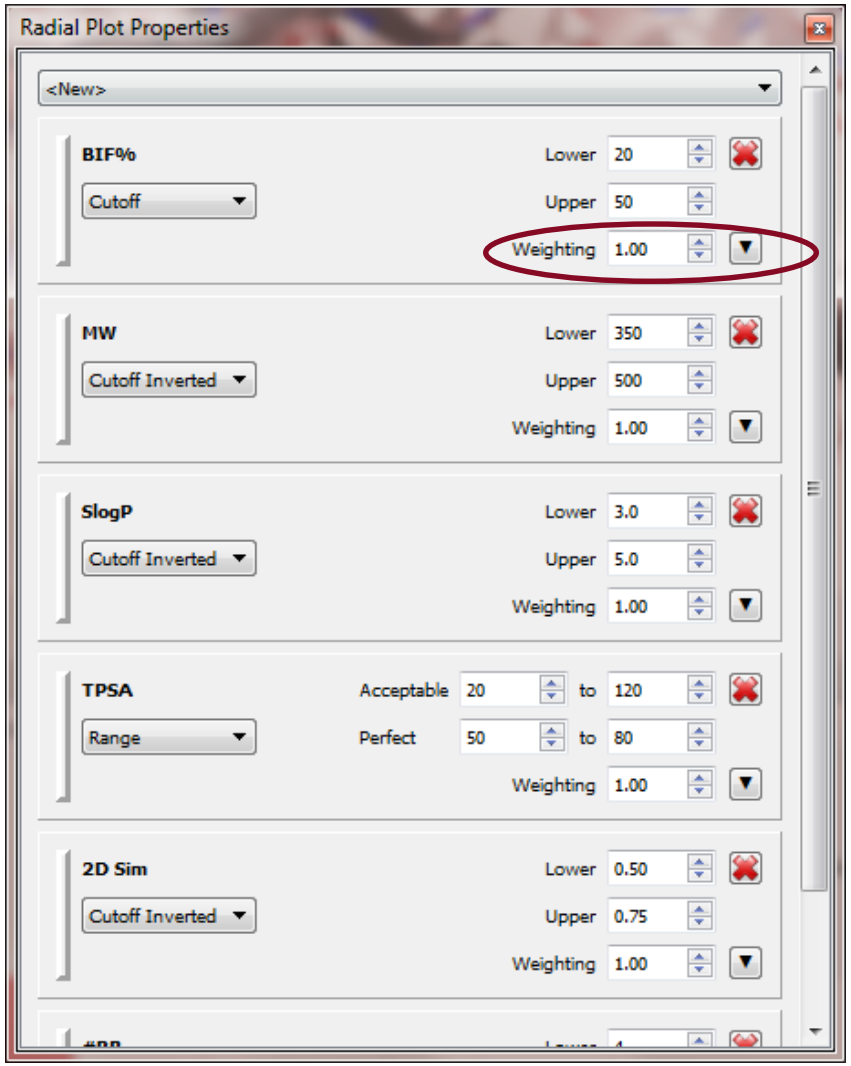
Weighting properties for MPO scoring

Radial Plot Properties *dock allows different properties to be weighted differently when calculating the MPO score*



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Sorting results on MPO score

***Sort** the results by MPO score by clicking on the **Radial Plot** column header*

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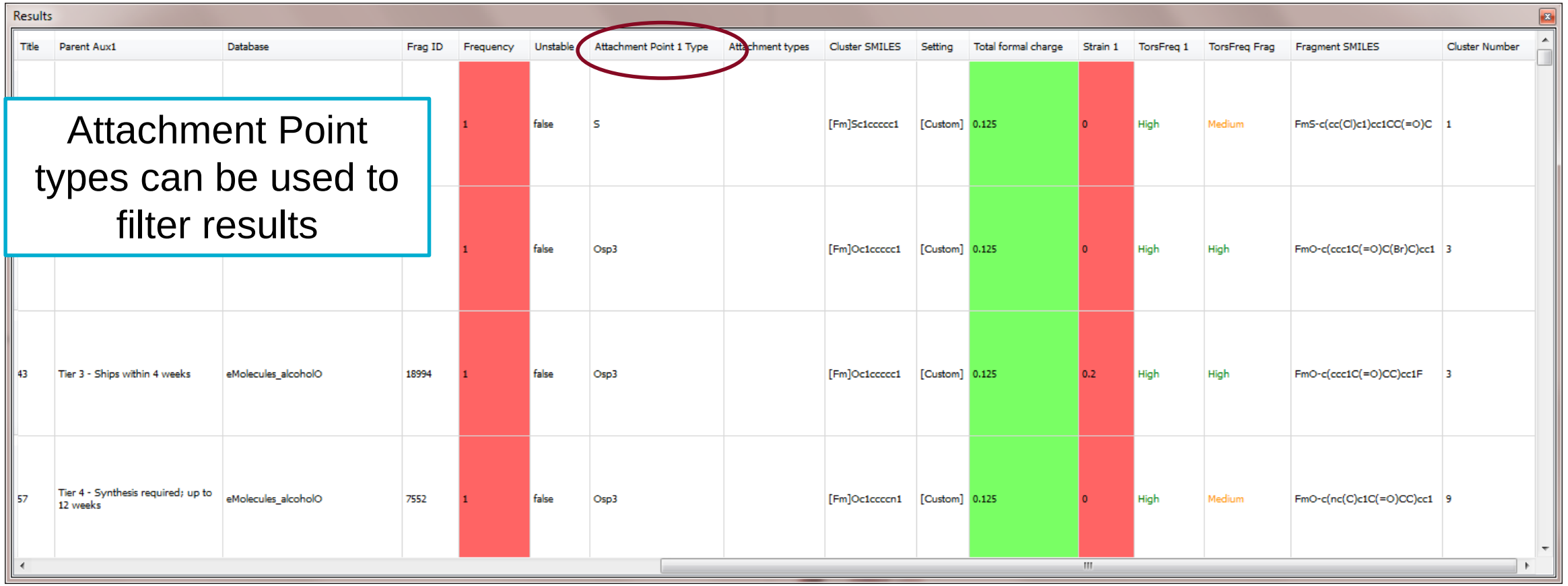
New results columns: Attachment point atom types

Attachment Point types can be used to filter results


Results

Title	Parent Aux1	Database	Frag ID	Frequency	Unstable	Attachment Point 1 Type	Attachment types	Cluster SMILES	Setting	Total formal charge	Strain 1	TorsFreq 1	TorsFreq Frag	Fragment SMILES	Cluster Number
				1	false	S		[Fm]Sc1ccccc1	[Custom]	0.125	0	High	Medium	FmS-c(cc(Cl)c1)cc1CC(=O)C	1
				1	false	Osp3		[Fm]Oc1ccccc1	[Custom]	0.125	0	High	High	FmO-c(ccc1C(=O)C(Br)C)cc1	3
43	Tier 3 - Ships within 4 weeks	eMolecules_alcoholO	18994	1	false	Osp3		[Fm]Oc1ccccc1	[Custom]	0.125	0.2	High	High	FmO-c(ccc1C(=O)CC)cc1F	3
57	Tier 4 - Synthesis required; up to 12 weeks	eMolecules_alcoholO	7552	1	false	Osp3		[Fm]Oc1ccccn1	[Custom]	0.125	0	High	Medium	FmO-c(nc(C)c1C(=O)CC)cc1	9

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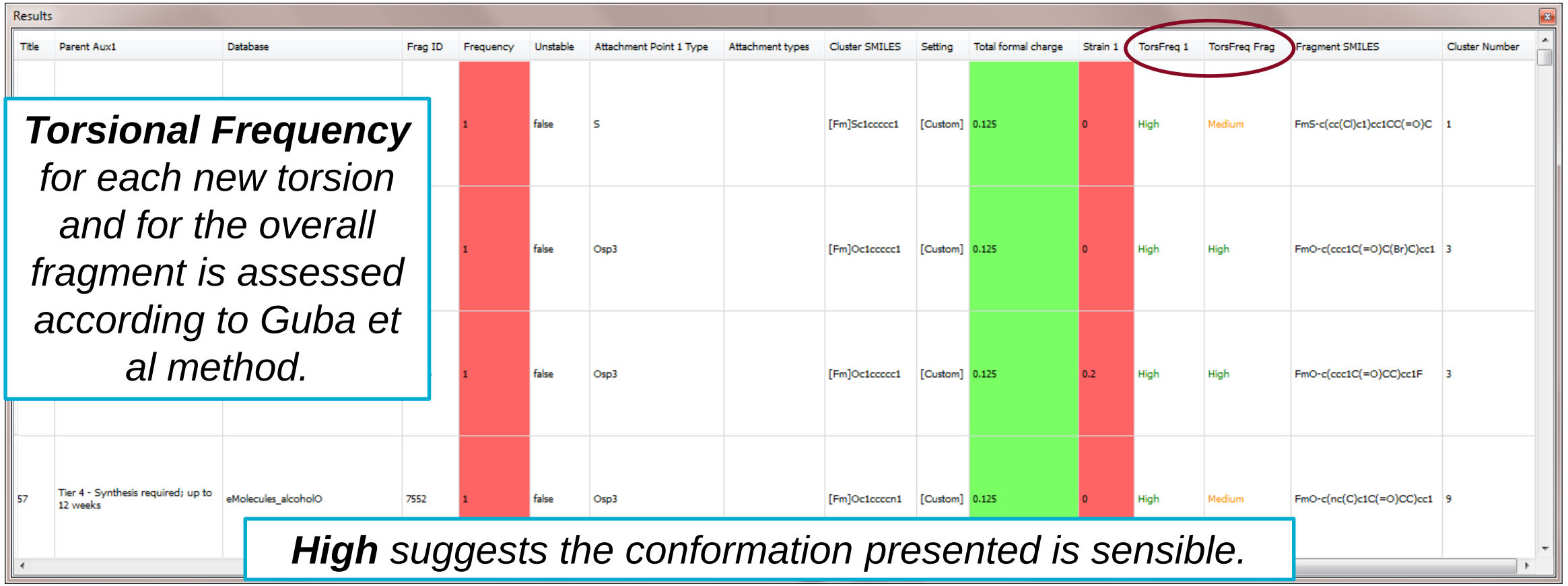
New results columns: Torsional frequency 1, 2, 3, etc.



Torsional Frequency *for each new torsion and for the overall fragment is assessed according to Guba et al method.*

High *suggests the conformation presented is sensible.*

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Depending on time…

> Use filters to filter on each atom attachment point and torsional freq 1 to see how many pass.

> Sulfur – 17 total; 13 high; 2 med; 2 low.
> Nitrogen – 369 total; 34 high; 335 med; 1 low.
> Oxygen – 114 total; 76 high; 23 med; 15 low.

> S – 76% high; N – 9%; 66%
> Appears that S as the linker has a better chance of adopting an appropriate geometry.

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- Results interface
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