Rapid technique for new scaffold generation II: What is the best source of inspiration?

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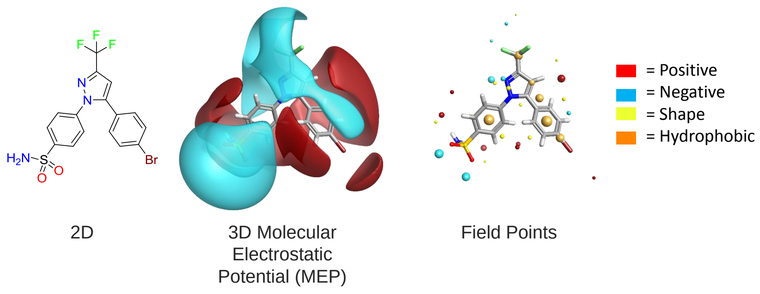
Background

Scaffold hopping and R-group replacement remain central tasks in medicinal chemistry for generating and protecting intellectual property. Spark is a bioisostere replacement tool (available as a desktop software application) for rapidly generating reasonable yet novel scaffold and R-group replacements using Cresset's molecular field points.

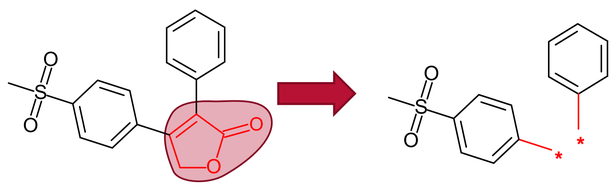
Cresset's field technology condenses the molecular fields down to a set of points around the molecule, termed 'field points'. Field points are the local extrema of the electrostatic, van der Waals and hydrophobic potentials of the molecule.



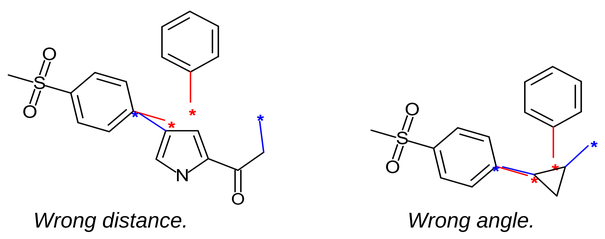
2D | 3D Molecular Electrostatic Potential (MEP) | Field Points

Spark workflow

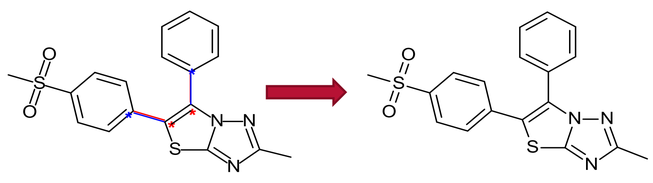
The Spark approach uses a database of molecule fragments, or available reagents, to suggest replacements that maintain the shape and electrostatic character of a known active molecule. The user identifies the region of a known active molecule that they wish to replace, and this piece is removed.



The number of bonds broken is recorded together with the distance and angle between any pair of broken bonds. This information is used to search a database of fragment conformations for replacement moieties.

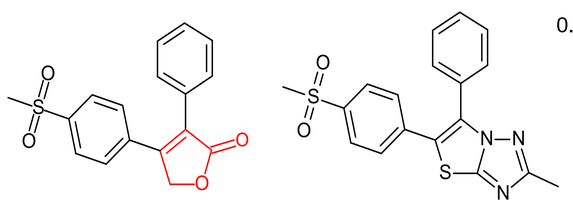


Wrong distance. *Wrong angle.*



Good match. Product is formed, minimized and scored.

The product molecule is energy minimized and then scored as a replacement. Scoring is performed using an average of field and shape similarity on the product molecule. Scoring the product (rather than the fragment) allows the electronic changes induced in the rest of the molecule to be taken into account.



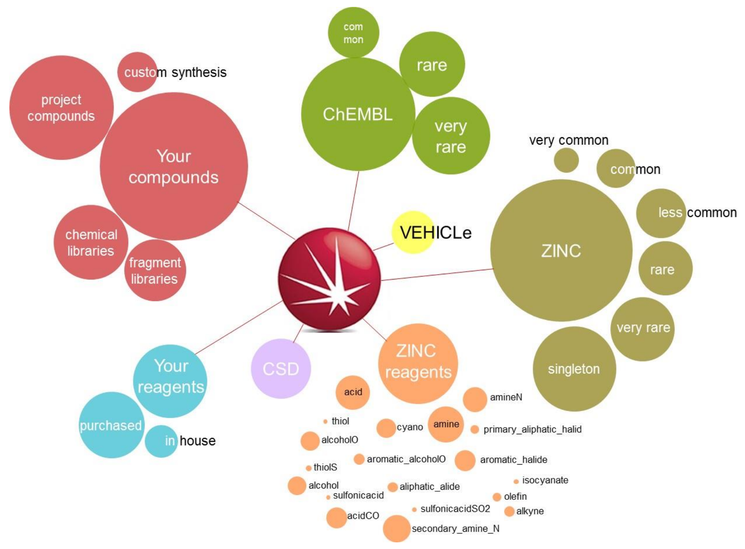
By default, the scoring reflects the change relative to the original molecule, but the user can choose to add other molecules that can be used in the scoring. In this way compounds with sub-optimal interactions can be improved by mimicking other known actives.

Fragment Sources in Spark

Spark generates bioisosteres from databases of fragments derived from:

- commercially available, real compounds and reagents (ZINC)
- theoretical aromatic rings (VEHICLe)
- literature reports of bioactive compounds (ChEMBL)
- fragments from the Cambridge Structural Database (CSD) of small molecule crystal structures

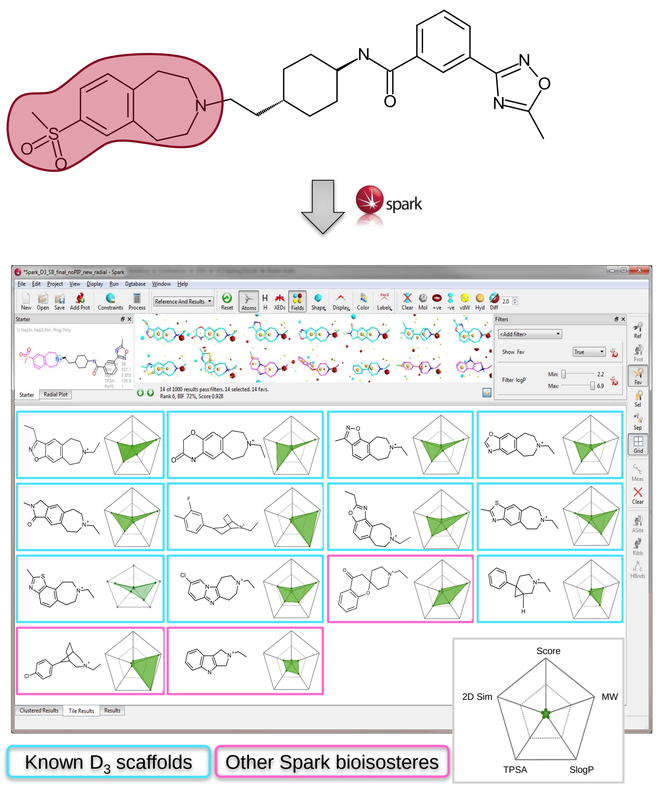
In this case study we investigate which of the fragment sources available in Spark is the best source of inspiration.



If you have access to significant proprietary chemistry, to specialized reagents, or want to consider fragments from reagents that you have in stock, then the creation of custom databases with the Spark Database Generator will enable you to exploit your own proprietary chemistry to generate and protect intellectual property.

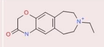
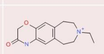
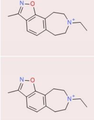
R-group replacement to D_3 antagonists

The ChEMBL 'common', 'rare' and 'very rare', ZINC 'very common', 'common', 'less common', 'rare', 'very rare', 'singleton' and the VEHICLe fragment databases were searched using 'Accurate But Slow' calculation settings. Compounds with piperazine scaffolds were filtered out as these are very well known in the literature.



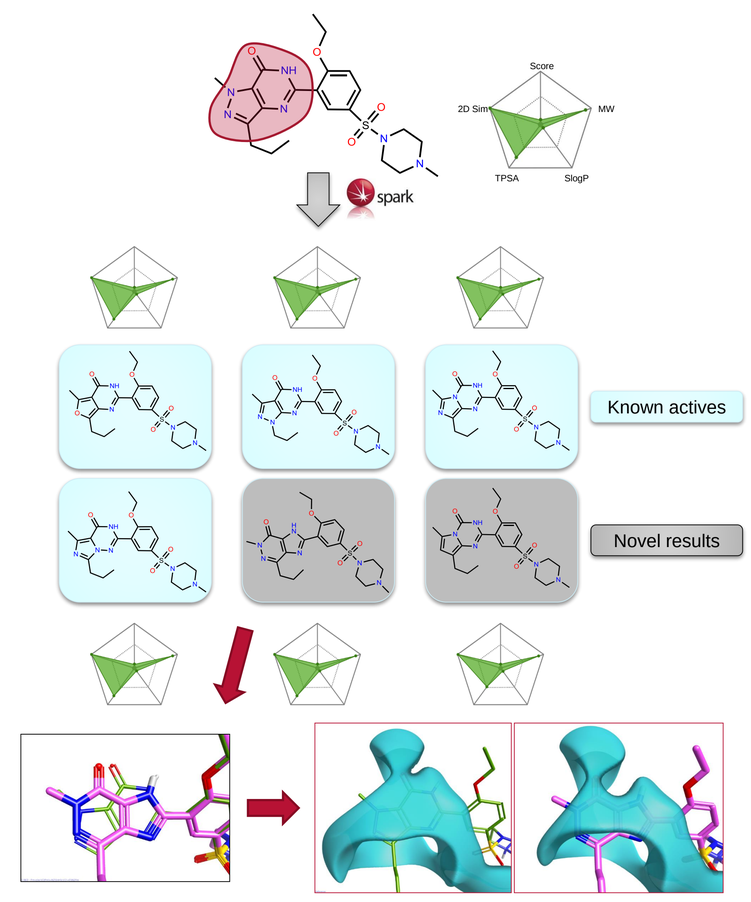
Known D_3 scaffolds were found in ChEMBL or Zinc (commercially available compounds) databases. Novel solutions were found in the ChEMBL database.

An analysis of the chemical diversity of the known D_3 scaffolds retrieved from each database clearly shows that the less common fragments derived from the literature database are a precious source of potentially useful chemical diversity. Note that these less common fragments may be associated with more complex and less documented synthetic routes.

Database	BAZ	*[h]*-fused	*[g]*-fused	[4.1.0]	[3.2.1]	Heterofused
Zinc						
ChEMBL common						
ChEMBL rare						
ChEMBL very rare						

Scaffold hopping application to Sildenafil

The ChEMBL and VEHICLe fragment databases were searched using 'Accurate But Slow' calculation settings. The protein structure for 1UDT was used as an excluded volume, constraining the field points associated with the interaction with glutamine (Gln^{817}) in the 1UDT protein.



Known actives were found in ChEMBL and VEHICLe databases. Novel but highly plausible solutions were found in the VEHICLe database.

Conclusion

Spark provides both known active scaffolds and novel solutions that represent opportunities for scaffold hopping and R-group replacement.

The nature of the experiment appears to dictate the best source of fragments. It is therefore important to have a wide range of fragment sources to choose from for each experiment, to provide a balance between novelty and synthetic accessibility.

The creation of fragment databases from proprietary collections of compounds can be a powerful way of increasing the chemical diversity available to Spark.

References

J. Chem. Inf. Mod. **2006**,*46,* 665-676*; J. Med. Chem.* **2007,** *50,* 5076-5089; *Bioorg. Med. Chem. Lett.* **2008**, *18*, 901–907; *Bioorg. Med. Chem. Lett.* **2008**, *18*, 908–912; *J. Med. Chem.* **2010**, *53*, 7129–7139; http://www.cresset-group.com/spark