Fast Computational Method for Growing and Joining Fragments Using Molecular Fields

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Introduction

Cresset's field point descriptors are widely used for molecular alignment and similarity scoring[1,2]. The similarity scoring uses a field sampling technique, in which the field extrema from one molecule are used as sampling points into the analytically-calculated field of the other molecule.

One of the many benefits of this approach is that it provides a very compact information rich representation of molecules. More importantly, in moving from drug sized molecules to fragments this information content does not degrade as quickly as other 3D or 2D methods.

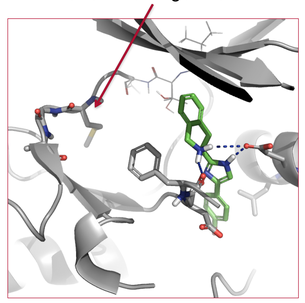
Our technique uses the molecular interaction fields of the parent molecule and assesses replacements in the context in which they will be synthesized. This enables the differing steric and electronic effects of potential new scaffolds to be used. An added bonus of our method is that replacements for terminal substituents can be considered alongside more central moieties enabling its use in growing fragments and lead optimization as well as lead generation.

We present the methodology, together with applications to core replacement and to fragment growing/optimization.

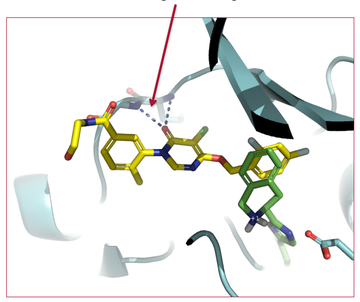
Application of **spark**V10 to Fragment Growth

Purpose - grow a fragment binding to DFG-out conformation of p38 kinase to make interactions with hinge region.

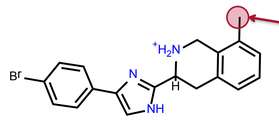
PDB:3K3I - no hinge interaction



Add PDB:3ROC - good hinge interaction



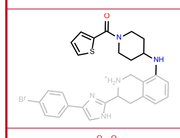
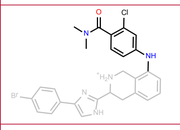
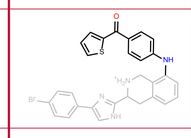
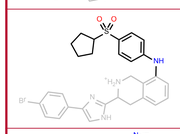
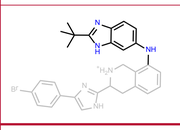
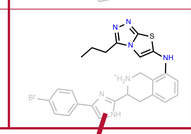
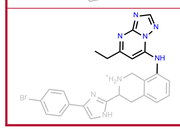
Experiment - Start with K3I "fragment", use 3ROC ligand to describe new interactions.
Search for new moieties from commercial compounds. Only consider replacements with < 3 rotable bonds and attached through N or O, must contain Ar ring. Score replacements against both ligands (80% weight 3ROC, 20% weight 3K3I).



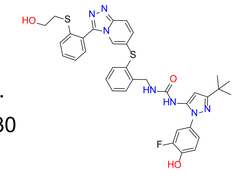
Replace Me group with new moieties
Replacement must have N or O at this point;
Moieties < 3 rot. bonds;
Moieties must contain a ring

sparkV10

Search all moieties derived from commercial catalogs

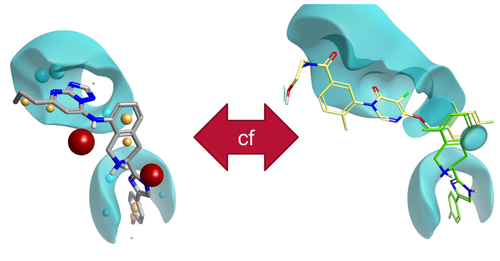
Structure	Rank	Structure	Rank	Structure	Rank
	1		4		8
	10		11		30
	128				

Shortly after this work was completed, Pfizer scientists published a crystal structure[3] (PDB: 2YIS, ligand right) that contained a COPD drug candidate that took advantage of both regions of the p38 kinase active site.

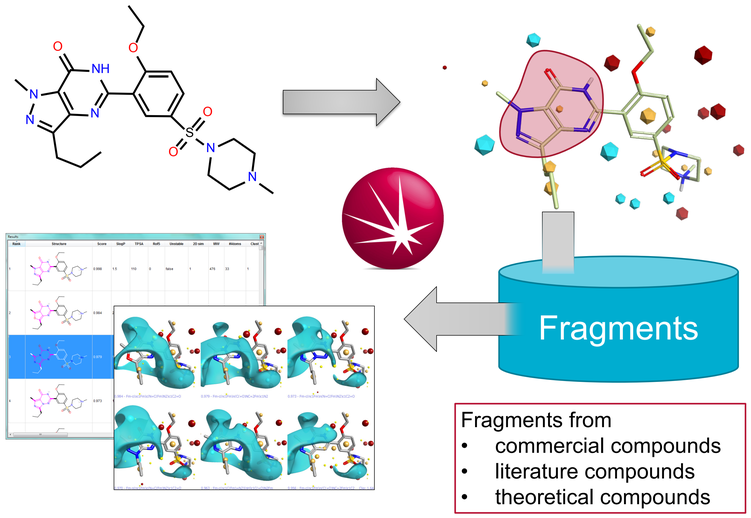


The hinge binding motif is remarkably similar to result 30 found during our mid-summer 2011 experiments.

However, the **spark**V10 results still contain a number of novel suggestions for growing the original fragment towards the hinge binding region (e.g. 128 above 2D and 3D below left compared to starting points below right).



sparkV10 Methodology



Fragments from
- commercial compounds
- literature compounds
- theoretical compounds

Our approach is encoded in a desktop software application "**spark**V10". Using **spark**V10, a user identifies a region of a known active molecule that they wish to replace. The number of bonds broken by removing this piece is recorded together with the distance (d_1 - d_n) and angle (a_1 - a_n) between any pair of broken bonds.

The angle and distance criteria are used, together with the number of connection points, to search a database of fragment conformations for replacement moieties. Matching fragment conformations are merged with the retained portions of the starter molecule to create a new "product" molecule. The product molecule is energy minimised and then scored as a replacement.

Scoring is performed using an average of field similarity[1] and shape similarity[2] on the product molecule. By default the scoring reflects the change relative to the original starter 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.

References

1. Cheeseright T, *et al*. "Molecular field extrema as descriptors of biological activity: definition and validation.", *J. Chem Inf. Mod.*, **2006**, 665. Cheeseright TJ, *et al*. "High content pharmacophores from molecular fields: a biologically relevant method for comparing and understanding ligands.", *Curr. Comput. Aided Drug Des.* **2011**, 7(3), 190-205.
2. Grant JA, Pickup BT. "A Gaussian Description of Molecular Shape.", *J. Phys. Chem.* **1995**, *99*, 3503-3510.
3. Millan, DS, *et al.* "Design and synthesis of inhaled p38 inhibitors for the treatment of chronic obstructive pulmonary disease.", *J. Med. Chem.*, **2011**, *54*, 7797.

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