Rapid Technique For New Scaffold Generation

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Introduction

Scaffold hopping remains a central task in medicinal chemistry for generating and protecting intellectual property. We present **spark**V10, an application for rapidly generating reasonable yet novel scaffold replacements.

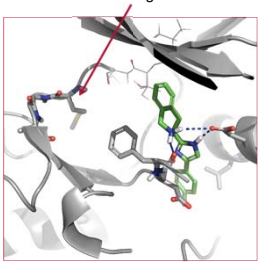
Our technique uses the molecular interaction fields of the parent molecule and assesses replacements in the context in which they will be synthesized. This enables the differing steric and electronic effects of potential new scaffolds to be used. An added bonus of our method is that replacements for 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 (bottom) together with applications to core replacement (right) and to fragment growing/optimization (below).

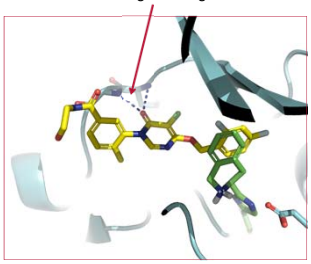
Application to Fragment Growth

Search fragments from commercial compounds for moieties that create interactions with hinge region of p38, starting with a DFG-out binding fragment.

PDB 3K3I - no hinge interaction

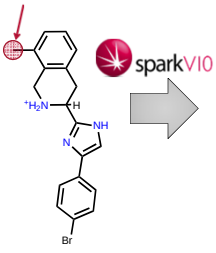


Add PDB 3ROC - good hinge interaction



Experiment - grow 3K3I ligand to make interactions of 3ROC ligand - score replacements against both ligands (80% weight 3ROC, 20% weight 3K3I). Search fragments from commercial compounds. Only consider replacements with < 3 rotable bonds and attached through N or O, must contain Ar ring.

Match N,O only;
Frags < 3 rot. Bonds;
Frags must contain Ar



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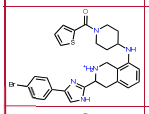
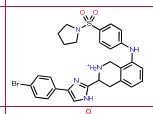
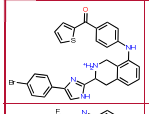
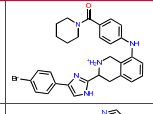
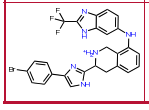
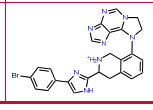
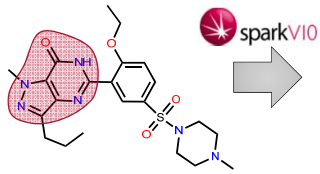
	1		11
	4		13
	6		53

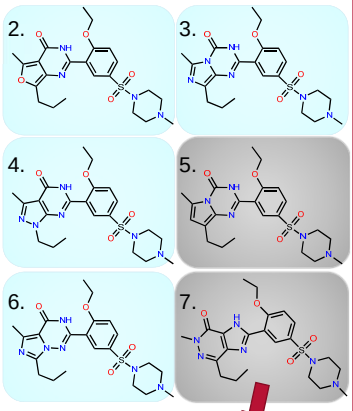
Application to Sildenafil

Search GDB derived database[3] for Sildenafil core replacements. Results limited to 0 rotable bonds, must contain Ar ring. Compare with published quantum mechanics based method.



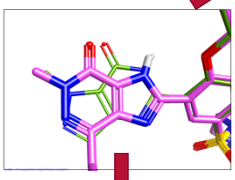
Known actives

Novel results

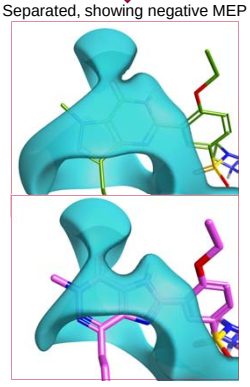


Comparison to NEAT:[3]
NR = Not Reported, NF = Not Found

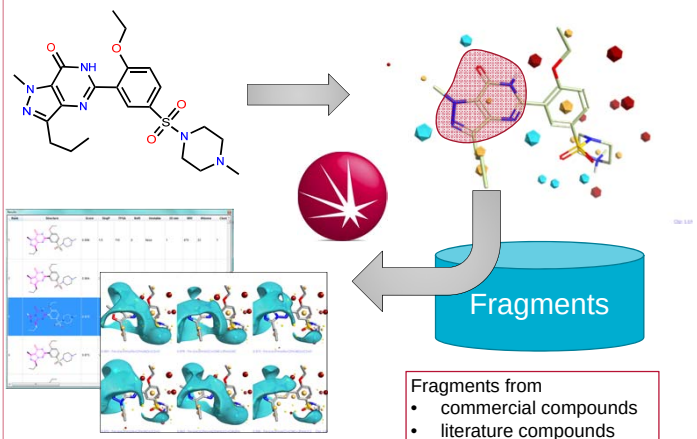
Compound	NEAT rank	**spark**V10 rank
Sildenafil	1	1
Shown above	2	3
Shown above	3	2
Shown above	4	4
Shown above	5	5
Shown above	6	9
	7	48
	8	NF
	9	NF
	10	6
	11	NF
	12	17
	NR	7
	NR	8
	NR	10
	NR	11



Separated, showing negative MEP



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, Mackey M, Rose S, Vinter A. "Molecular field extrema as descriptors of biological activity: definition and validation.", *J. Chem Inf. Mod.*, 2006, 665. Cheeseright TJ, Mackey MD, Scoffin RA. "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. Tu M, Rai BK, Mathiowetz AM, Didiuk M, Pfefferkorn JA, Guzman-Perez A, Benbow J, Guimarães CR, Mente S, Hayward MM, Liras S. "Exploring Aromatic Chemical Space with NEAT: Novel and Electronically Equivalent Aromatic Template.", *J. Chem Inf. Mod.*, **2012**, 52(5), 1114-23.