Using Spark to Identify New Cores for PDE5 Inhibitors: Scaffold-Hopping Sildenafil

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Abstract

This case study demonstrates how Cresset's Spark software can be used to explore the bioisosteric space of the heteroaryl scaffold of Pfizer's Sildenafil to provide substitutions with low 2D similarity. The scaffold-hopping technique employs molecular fields, and identified other known PDE5 inhibitors, as well as a large number of new chemical entities (NCEs) that are potentially active and in open intellectual property space.

Introduction

PDE5 (phosphodiesterase type 5) inhibitors are used in the treatment of erectile dysfunction, and due to their ability to relax the smooth muscle tissue of the pulmonary arteries, have also been investigated for treating pulmonary hypertension. Indeed, sildenafil was discovered during the search for a treatment for angina.

A recent publication[1] from Pfizer reported the results of a QM method used develop a database of heteroaromatic fragments derived from the GDB database, then searching this database for replacements for the core of sildenafil. This case study conducts the same scaffold-hopping experiment using Spark and the Spark fragment databases to replace the heteroaryl core of sildenafil.

As sildenafil is a potent and selective inhibitor of PDE5, other compounds with similar shape and field properties should have similar activity and selectivity.

Computational exploration of chemical space around existing compounds to ascertain structural changes that result in new compounds that retain the activity of the parent compound and potentially improve on ADME/Tox effects is known as scaffold-hopping. *In silico* scaffold-hopping experiments can reduce both the time and financial cost of discovering new leads by traditional medicinal chemistry or high-throughput screening methods.

Scaffold-Hopping with Spark

Spark's approach to scaffold-hopping uses Cresset's field-based technology[2] to identify viable replacements for a selected fragment from a reference compound. The workflow proceeds as:

1. Take reference compound in its bioactive conformation (if available) and circle the moiety that will be replaced.
2. The number of attachment points, as well as the vector for the distance(s) and angle(s) between them are recorded.
3. Conformationally populated fragment databases[3] are searched for fragments that have the correct number of attachment points and correct geometry.
4. Acceptable fragments are used to form a new molecule which is minimized to the nearest local minimum and aligned on field points to the reference molecule for scoring (default 50% fields, 50% shape).

Scoring whole molecule to whole molecule allows circumvention of fragment-to-fragment scoring limitations. As one could imagine, it is possible to find fragments that work well at the fragment level, however, when placed into the context of the whole molecule, the electrostatics may be altered such that potency is lost. The whole molecule scoring in Spark is underpinned by Cresset's XED force field, and takes into account neighbor-group effects and electronic influences between groups.

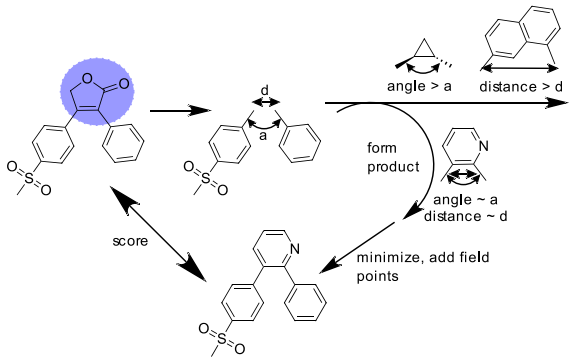


Figure 1: Pictorial representation of Spark bioisostere substitution workflow.

Method

The bioactive conformation of sildenafil and the PDE5 target structure were obtained from PDB:1UDT[4], and waters deleted. The ligand and protein structures were loaded into the Spark wizard when prompted.

Using Spark's wizard, the 3D structure of Sildenafil was selected as the "Starter" molecule and the moiety shown in Figure 2 selected for replacement. During the Spark experiment, 3 bonds are broken (3 connection points).

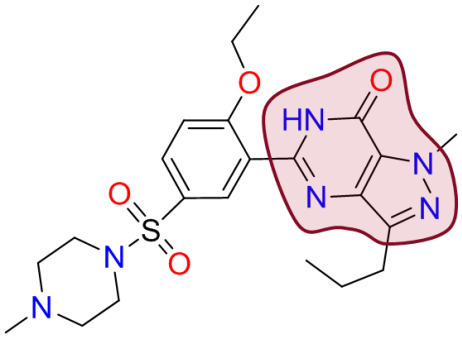


Figure 2: Sildenafil with the moiety to be replaced during the Spark experiment.

The protein structure for 1UDT was included as an excluded volume around the ligand to specify regions where replacement bioisosteric fragments should not enter.

Further, the pyrimidinone structure forms two hydrogen bonds to a glutamine (Gln^{817}) in the protein which are important for activity. To encode these important interactions, the field points associated with that group were constrained (figure 3), such that those field points must be matched in any result, otherwise, the scores are down-weighted.

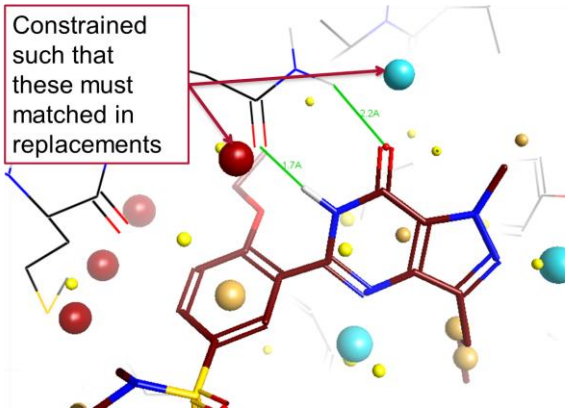


Figure 3: Sildenafil with field points, showing constrained field points associated with hydrogen bonds to Gln^{817}.

Initially the Spark fragment databases derived from commercial compounds were selected for searching. However the results showed only one known PDE5 core together with fragments that were poor bioisosteres for the chosen moiety.

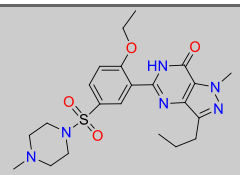
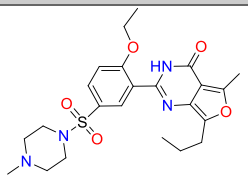
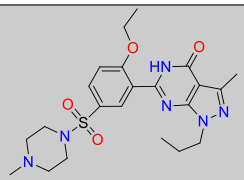
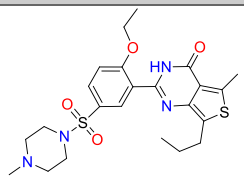
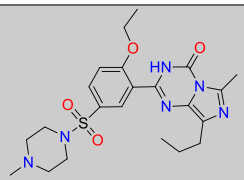
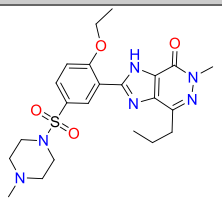
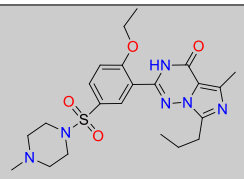
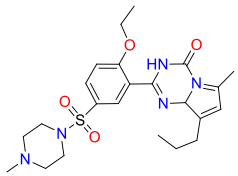
A second experiment was performed that was identical to the original except that the fragment databases derived from ChEMBL, and VEHICLe. were searched. In the calculation settings, the 'Accurate But Slow' pre-set conditions were used, but with the number of rotatable bonds that are allowed in replacement fragments decreased to zero to ensure that only ring replacements were found. Additionally, any replacements were filtered so that only aromatic rings were acceptable.

Results and Discussion

The results were visualized overlaid with the reference or side by side. The first compound reported was Sildenafil itself. The next several hits (Table 1) are very similar to known PDE5 inhibitors, including one with a Levitra-like core. However, the Spark experiment also produces scaffold suggestions that have not appeared in literature/patents.

A comparison of the negative electrostatics of the sildenafil core with that of Spark result #6 is shown in figure 5. Despite the 6-5 ring in sildenafil being replaced by a 5-6 ring, the electrostatics are largely the same, which suggests that Spark #6 could likely be active against PDE5.

Table 1: Top 8 hits from Spark.

Result	Structure	Comment
1		Sildenafil
2		New IP
3		Known active
4		Unknown
5		Known active
6		New IP
7		Levitra-like core
8		New IP

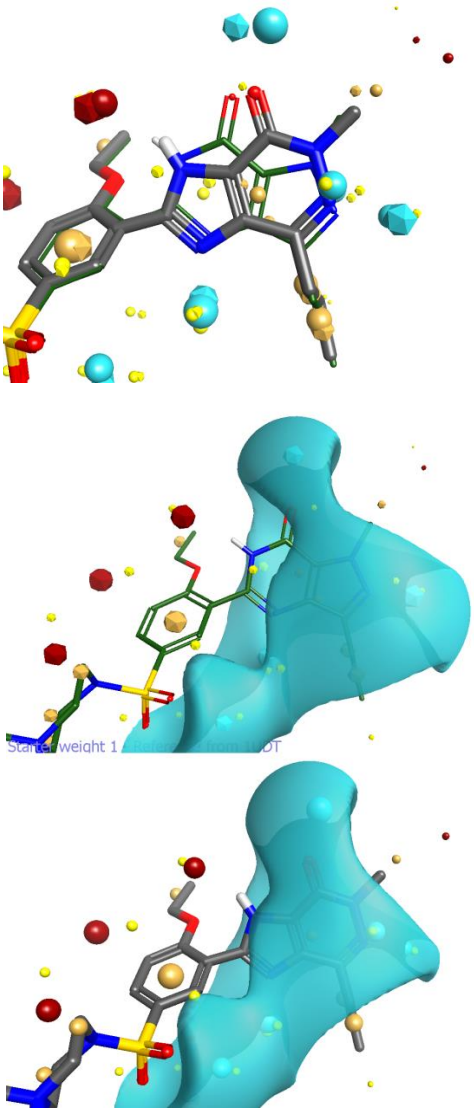


Figure 5: Comparison of sildenafil (top) and Spark result #6 overlaid (top) and of the negative electrostatic surfaces (Sildenafil middle, #6 bottom).

Conclusion

A simple scaffold-hopping experiment conducted in Cresset's Spark software provided a significant number of known inhibitors for PDE5. Pleasingly it also produced a significant number of results with no reported PDE5 activity but that have significant shape and electrostatic similarities to known actives.

Interestingly the results compare very favorable with the previously reported QM based method for the scoring of replacements. In contrast to that report, the Spark experiment was completed in minutes on a desktop computer rather than over many hours on a Linux cluster.

References

1. *J. Chem. Inf. Model.*, **2012**, *52(5)*, 1114-1123.
2. *J. Chem. Inf. Model.*, **2006**, *46*, 665-676.
3. The fragment databases within Spark come from various sources, including commercial compounds, ChEMBL, ZINC, and VEHICLe.
4. *Nature*, **2003**, *425*, 98-102.
5. *J. Med. Chem.*, **2009**, *52(9)*, 2952-2963.