Identifying Bioisosteres of the Benzazepine scaffold

T. Cheeseright[†]

[†] Cresset, New Cambridge House, Bassingbourn Road, Litlington, Cambridgeshire, SG8 0SS, UK

Abstract

Drug discovery projects continuously explore novel and diverse structures with the objective of optimizing existing leads, improving IP position, or identifying new leads by switching scaffolds completely. The identification of novel chemotypes can be particularly difficult for those targets where the crystallographic information is scarce or unavailable (for example GPCRs, ion channels and novel targets). In this case study, working from just a 2D structure of a known active D_3 antagonist, we show how Spark[1] was able to quickly identify a variety of alternative scaffolds, some of which have proven D_3 activity.

Introduction

Spark is an exciting and powerful way of generating novel and diverse structures for drug discovery projects. Used by synthetic, medicinal and computational chemists, Spark makes use of Cresset's field technology to find biologically equivalent replacements for key moieties in a reference compound. Thus leading to the identification of new structures in new chemical space.

Selective antagonists of the dopamine D_3 receptor (a GPCR 7TM target) are reported as a potential approach for the treatment of substance dependence and addiction. In recent years, a significant part of the research work towards to the discovery of novel potent and selective D_3 antagonist was dedicated to the exploration of novel chemical scaffolds.

In this case study, Spark searches were carried out starting from the 2D structure of a benzazepine compound (SB-414796[2], Figure 1), to assess whether the software was able to correctly identify, among the top-scoring results, alternative interesting scaffolds potentially active on D_3.

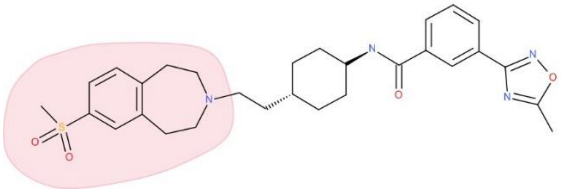

Figure 1. 2D structure of SB-414796, a D_3 antagonist[2]. The benzazepine fragment is shown in the pink circle.

Method

In the standard Spark workflow, it is recommended that the moiety to be replaced is selected (by circling it, see Figure 1) from the bioactive conformation of a reference compound, if available.

In this case, the absence of crystallographic information for SB-414796 bound to the D_3 target and the flexibility of the compound make it difficult to determine the bioactive conformation. For this reason the lowest energy

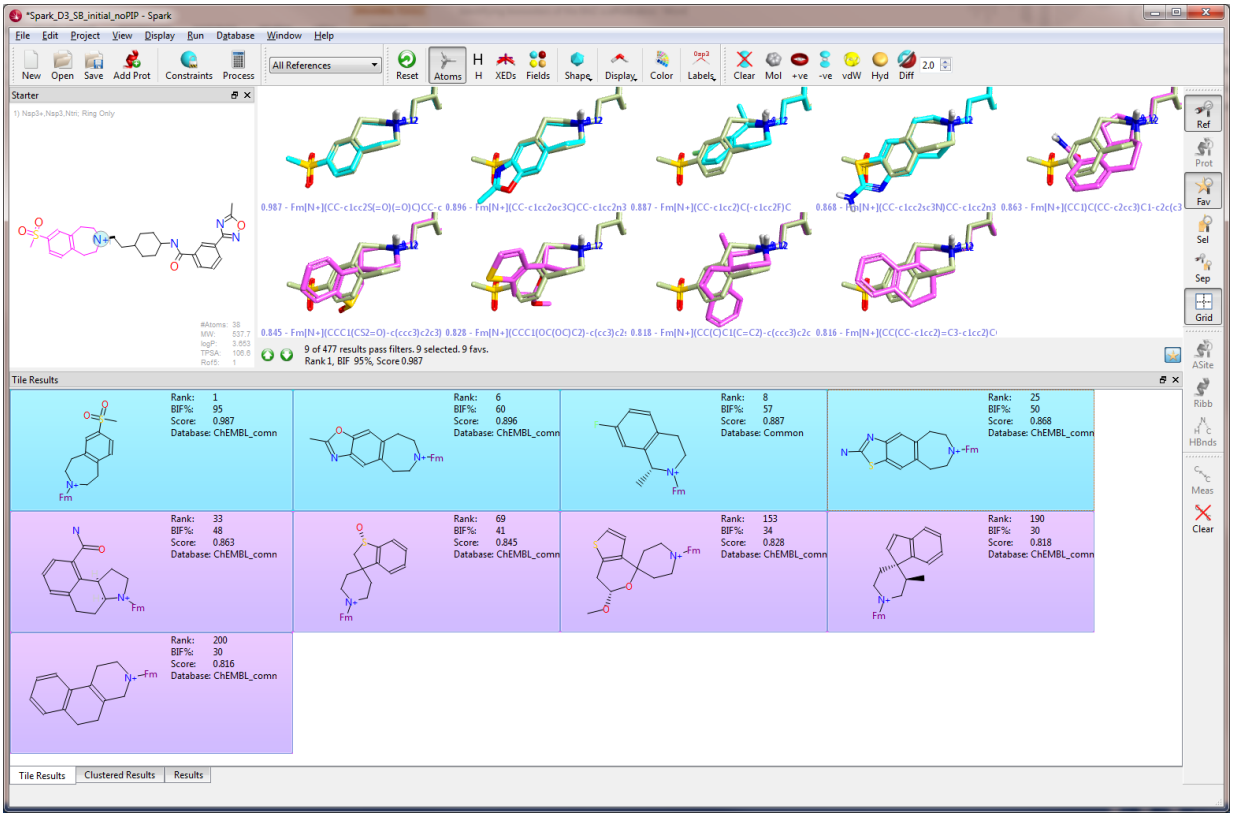

Figure 2. Results for the first run of Spark searches.
Lime green: SB-414796; cyan: known D_3 scaffolds; magenta: other Spark bioisosteres.

conformer of SB-414796 from a ('Very accurate but slow') conformation hunt carried out with Forge[3] was instead used in Spark as the reference compound.

The benzazepine moiety to be replaced is shown circled in Figure 1 and in magenta on the left hand side of Figure 2. The search was constrained in order to retrieve only fragments:

- having as an attachment point a positively charged sp3 Nitrogen ring atom
- containing at least one aromatic ring
- not belonging to the piperazine scaffold.

Piperazines were discarded using a SMARTS filter in the Spark 'Advanced Filters' panel as aryl-piperazines are a widely explored class of D_3 antagonists, of no special interest for the purposes of this case study. All the other conditions were left as in the 'Accurate but slow' default, in particular, the default ratio of 50% field and 50% shape similarity was used to score the replacement fragments.

The Spark searches were carried out in two runs. In the first run (see results in Figure 2), only the default databases were searched, namely the 'common' fragments from ChEMBL (database of literature reports) and the 'very common' and 'common' fragments from ZINC (database of commercial compounds).

In the second run (see results in Figure 3) it was explored whether more interesting (if possibly less synthetically accessible) scaffolds could be

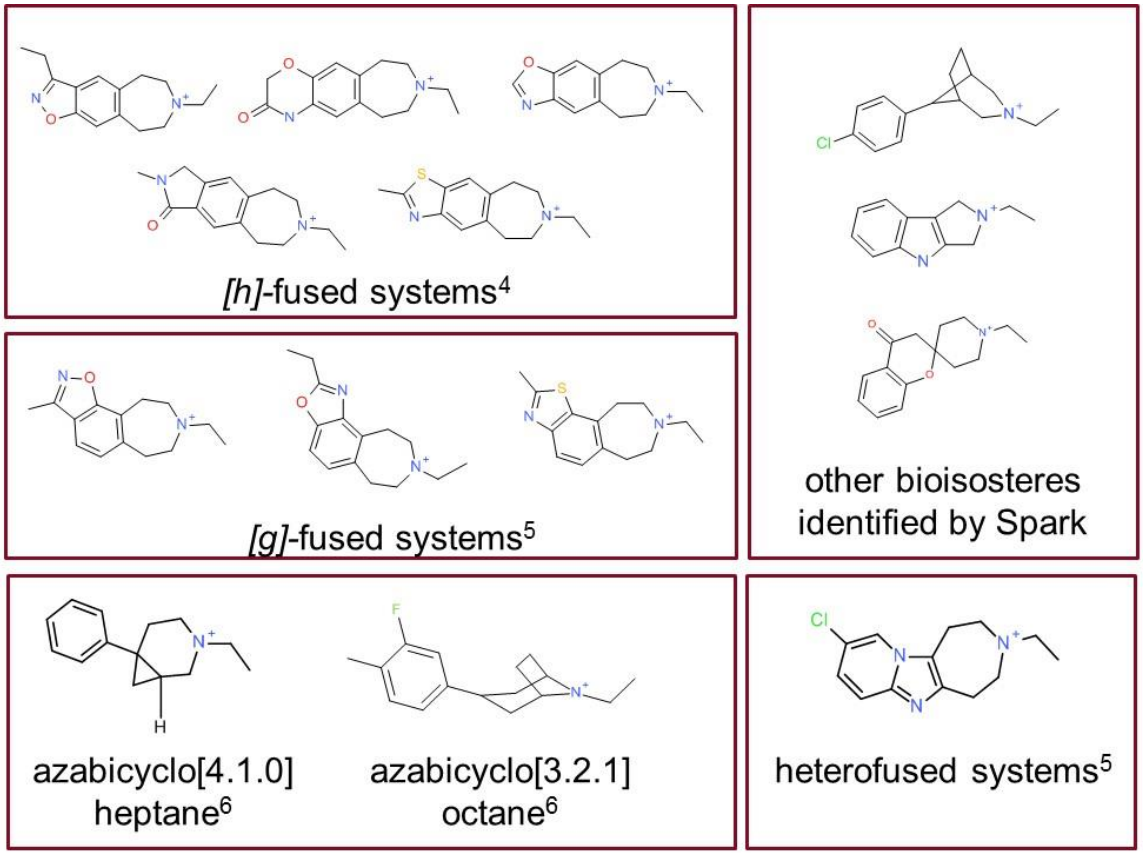

Figure 3. Results for the second run of Spark searches.

retrieved by searching the other databases available in Spark. The ChEMBL 'rare' and 'very rare', ZINC 'less common', 'rare', 'very rare' and 'singleton' databases, together with the VEHICLe database of theoretical ring systems were selected at this purpose.

Results

The results of the first Spark search (Figure 2), show that some known D_3 scaffolds (benzazepine[2], tetrahydroisoquinoline[2], *[h]*-fused tricyclic systems[4]) can be found among the 50 top scoring clusters of results. In addition other fused systems (in magenta in Figure 2), closely resembling other D_3 scaffolds published by GSK (*[g]*-fused systems[5] and spyro[6]) were also retrieved.

As expected, the second Spark search offers more interesting results. Many published D_3 scaffolds can be found among the 50 top scoring clusters of results (azabicyclo[4.1.0]heptane and azabicyclo[3.2.1]octanes[6], *[h]*- and *[g]*-fused systems[4,5], heterofused systems[5], see Figure 3) spanning a larger chemical diversity. Other interesting possible replacements were also identified by Spark and are shown on the top right side of Figure 3.

Conclusion

Spark searches were able to identify a large number of known D_3 scaffolds starting from a fragment of an earlier benzazepine scaffold, in a particularly difficult case where the absence of

crystallographic information and the flexibility of the ligands makes it difficult to determine the bioactive conformation of these antagonists.

Spark has an easy to use interface that in a matter of minutes generates a range of lead molecules from an initial 2D structure and helps the scientist choose the most innovative and tractable leads with the properties required.

Filters can be applied to find the result with the right mix of physicochemical properties and biological activity. The results can be tailored by selecting the chemistry allowed for the replacement moieties. Visualization of results is made easy by clustering similar chemical scaffolds, and by means of tile views that allow a side-by-side comparison of selected replacement scaffolds.

Custom databases can be created starting from the reagents available in house or the customer's proprietary chemistry.

References and Links

1. http://www.cresset-group.com/products/spark/
2. *J. Med. Chem.* **2007,** *50,* 5076-5089
3. http://www.cresset-group.com/products/forge/
4. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 901–907
5. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 908–912
6. *J. Med. Chem.* **2010**, *53*, 7129–7139