Finding Potential New IP with Novel Bioisosteres of mGluR5 Modulators

T. Cheeseright[†]

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

Abstract

This case study shows how Cresset's Spark software was used to find novel bioisosteres for mGluR5 modulators. The scaffold hopping technique using molecular fields identified existing and potential new intellectual property in this busy therapeutic space.

Method

The metabotropic glutamate receptors (mGluR) have become popular and important targets in small molecule drug discovery. In particular, there is increasing interest in mGluR5 antagonists in the treatment of anxiety, depression, pain, gastro-esophageal acid reflux disease (GERD), Parkinson's disease, epilepsy, and Fragile X Syndrome (FXS). Several mGluR5 antagonists have entered clinical trials.

The allosteric binding site of mGluR5, located within the transmembrane region, is generally considered to be more likely to lead to effective medicines than other binding sites. One of the prototypical small molecule mGluR5 allosteric antagonists is MPEP (2-methyl-6-(phenylethynyl) pyridine).

Using MPEP as a starting point, Cresset scientists used Spark to search for bioisosteric replacements that would introduce novel IP into this well worked area. Spark uses Cresset's field technology to find biologically equivalent replacements for key moieties in a molecule. Using the molecular field descriptors as the basis for the search makes it possible to find new structures in new chemical space while retaining similar biological activity.

Firstly, the 3D molecular field descriptors were calculated for MPEP, as shown in figure 1. Then two different moieties were identified as candidates for fragment swapping – the central alkyne or the complete pyrido-alkyne group.

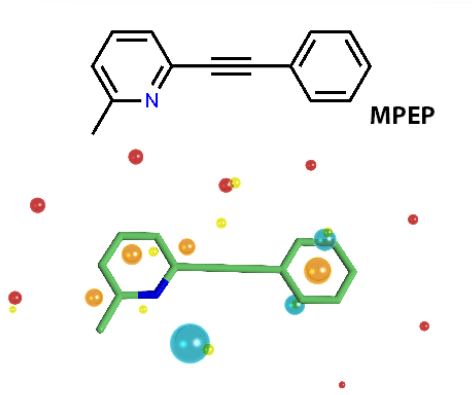

Figure 1. The 2D structure of MPEP, above, and the 3D structure with molecular field descriptors, below, as shown in Spark.

Two separate experiments were performed reflecting these two candidates. Firstly, Spark was used to search for replacements for the central alkyne. Spark searches a database of up to 600,000 fragments for bioisosteres that exhibit similar shape and electronic properties when placed in the context of the final molecule. Spark uses molecular interaction fields to represent the key binding interactions of a molecule giving a close approximation to the protein's view of a potential ligand. The results are shown in the left column of figure 2, below.

Secondly, a search was carried out for replacements for the entire pyrido-alkyne section of the molecule. The results are shown in the right column of figure 2, below.

In both experiments results were returned that show significant similarity to known mGluR5 ligands. Pleasingly, a number of suggestions were as yet unreported inhibitors of mGluR5 yet show excellent potential when compared to other active chemotypes.

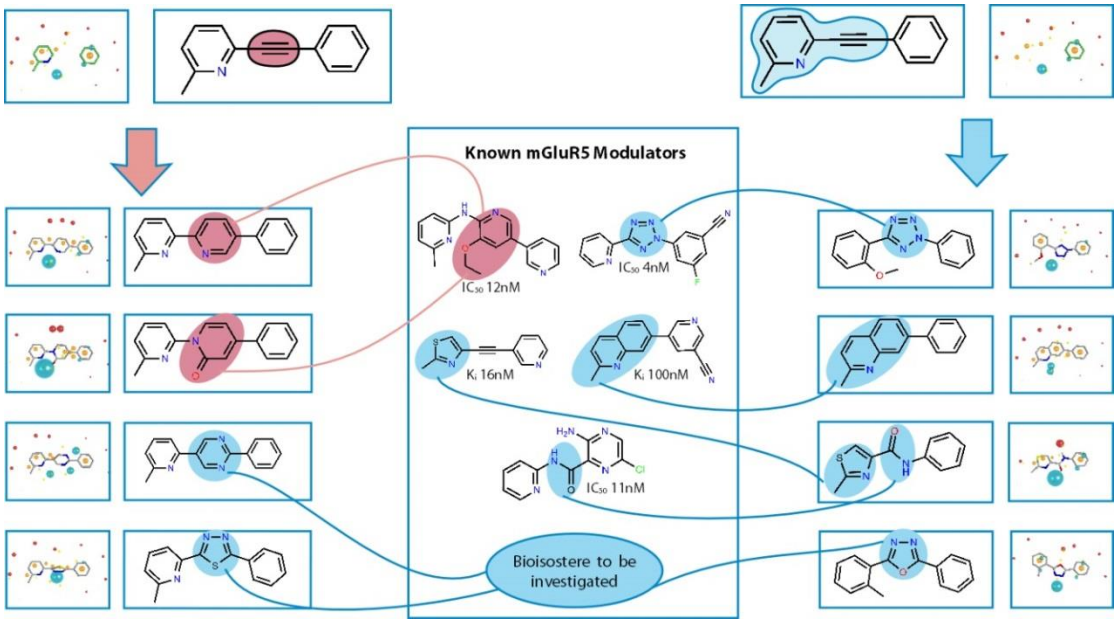

Figure 2. The results of the fragment swapping experiments performed on the mGluR5 modulator MPEP using Spark.

Conclusion

Both experiments resulted in unreported, novel structures, along with a significant number of previously reported actives. The position of the identified actives was irrespective of the 2D similarity of the final molecule to MPEP.

This example demonstrates the power of bioisosteric fragment swapping to generate new leads and potential new IP, even in crowded therapeutic areas.