A novel series of non-peptide small molecules for protein-protein interactions: Inhibition of β-amyloid aggregation

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Abstract

Cresset consultants were asked to identify drug-like chemotypes to mimic the activity of a series of peptides. Cresset's field based software was ideal for identifying the key properties of the peptides, providing the seed for a virtual screening experiment. Several novel lead molecules were identified for the client, Senexis. Further collaboration resulted in more ideas and information for Senexis scientists, enabling them to make informed choices about which lead molecules to pursue.

Introduction

The small molecule drug discovery company Senexis had developed a series of 'meptides' (N-methylated peptides) that block the aggregation of β-amyloid. An example 'L-meptide' search molecule is shown in figure 1, below.

Senexis asked Cresset consultants to identify a novel series of non-peptidic small molecules that mimics the activity of the 'meptides'. Cresset's molecular field technology is ideal for such a purpose.

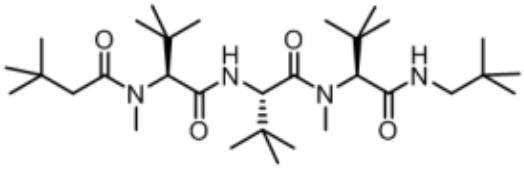

Figure 1: An example 'L-meptide' search molecule from Senexis, used as the basis for finding non-peptide small molecules with similar activity.

Method

Cresset's patented molecular mechanics algorithms describe molecules based on their electrostatic and steric fields, rather than chemical structure. The resulting field point descriptors of molecules give a powerful basis for analyzing and comparing molecules based on their activity.

Once a molecule has been defined according to its field pattern, it is possible to look for compounds with new chemistry that have the same activity, despite being from a different structural class.

The first step was to use Torch to find the best conformation for four of the meptides. A β-sheet conformation was assumed, the molecules were aligned and the field pattern was calculated for each meptide.

The aligned meptides were used as field seeds in Blaze, Cresset's ligand based virtual screening tool. Blaze compared the meptide's fields to Cresset's field database of commercially available molecules. Cresset consultants reviewed and analyzed the hits.

Matches containing interesting and novel chemistry were reported back to Senexis for their review.

Results

Three of the interesting new chemotypes whose fields matched the input seed field are shown in figure 2, below.

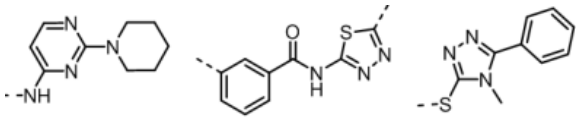

Figure 2: Three of the interesting new chemotypes whose fields matched the meptide seed field, identified using Blaze.

A further field seed from a pyridazine structure derived from RS0406, a known small molecule inhibitor, was then incorporated into the study. Followup Blaze searches were performed using this new query and compared to the results from the original meptide searches.

Discussion

The results from a Blaze field search with the pyridazine seed reinforced our confidence in the validity of the new chemotypes – a consistent field pattern for activity emerged.

Following this study, Senexis embarked on a program of medicinal chemistry and biological testing that resulted in two distinct chemotype sets. Cresset used Forge to produce templates for four active structures (two from each set) to find the common field pattern across all of the conformations and from that deduced the bioactive conformation and pharmacophore for activity (figure 3).

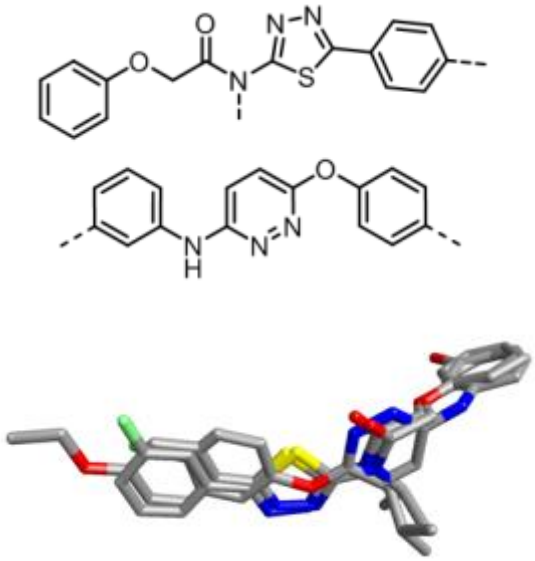

Figure 3: Two active chemotype sets from Senexis and their bioactive conformers, found using Forge.

Further searches using these more reliable field patterns from the bioactive conformations revealed more information and ideas for the Senexis chemists to work with. Their resulting lead molecules were SEN1269 and SEN1186, the core of which is shown in figure 4.

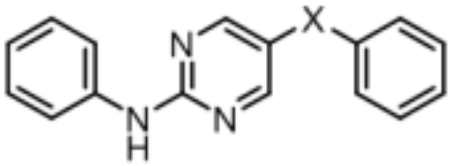

Figure 4: The core of SEN1269 and SEN1186, the lead molecules identified by Cresset.

Conclusion

The use of molecular fields to describe molecules in terms of their steric and electrostatic properties allows sensible comparisons of molecules with very different chemical structures. In this case, a series of active peptides and peptidomimetics were used to locate much more drug like small molecules through molecular field comparisons.

The collaborative nature of the consulting project between Cresset and Senexis resulted in new perspectives for the Senexis chemists, providing them with several possible leads and enabling them to make informed choices about which to pursue.