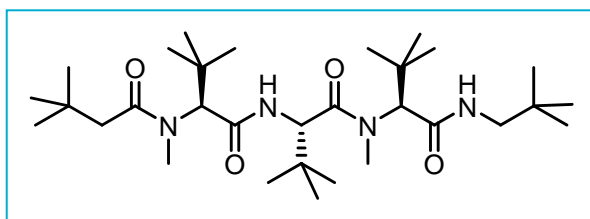


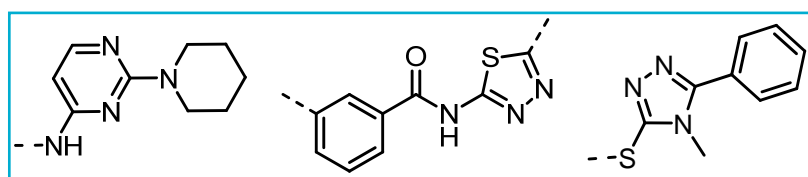
Protein-Protein Interactions - Inhibition of β -Amyloid Aggregation

Senexis Ltd has developed a series of 'meptides' (N-methylated peptides) that block the aggregation of β -amyloid. An example 'L-meptide' search molecule is shown opposite.



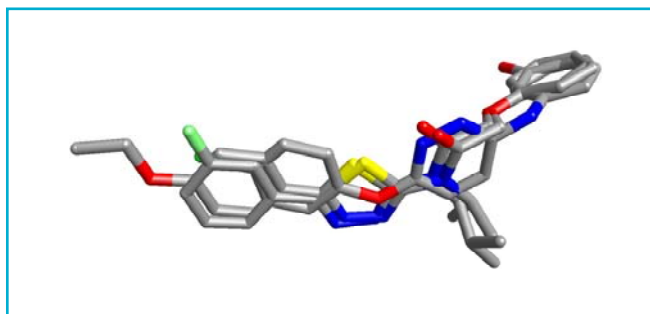
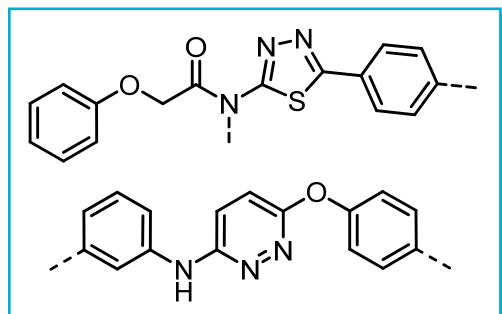
Cresset was asked to find novel series of non-peptide small molecules with different physico-chemical properties from the 'meptides'.

A β -sheet conformation for four of the meptides was assumed and each was used as a Field seed to search a Cresset's Field database which at the time contained 1M commercially available molecules. Matches containing interesting and novel chemistry were reported back to Senexis for their assessment.



Three of the interesting new chemotypes whose Fields matched the input seed Field are shown opposite.

A further Field seed from a pyridazine structure (see below left) derived from RS0406, a known small molecule inhibitor, was then incorporated into the study. Results from a Field search with this seed reinforced confidence in the validity of the chemotypes above. Senexis embarked on a programme of medicinal chemistry and biological testing that resulted in two distinct chemotype sets. Cresset templated 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.



Two active chemotype sets from Senexis and their bioactive conformers using FieldTemplater

Further searches using the more reliable Field patterns from these bioactive conformations revealed more information and ideas for the Senexis chemists to work with. Their current lead molecules are SEN1269 and SEN1186, the core of which is shown opposite.

