Alpha-helix peptidomimetics

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Protein–protein interactions

- Protein–protein interactions (PPIs) play a central role in many cellular processes and are involved in numerous pathways, including different stages of cancer development, host–pathogen interactions, and other diseases.
- PPIs have shown increasing potential as new therapeutic targets over the last 10 years.
- Modulators of these original interactions are likely to lead to the next generation of highly innovative drugs that should reach the market in the next decade.*
- α-helices are one of the key recognition elements of protein secondary structure.

*2014, J. R. Soc. Interface 11: 20130860

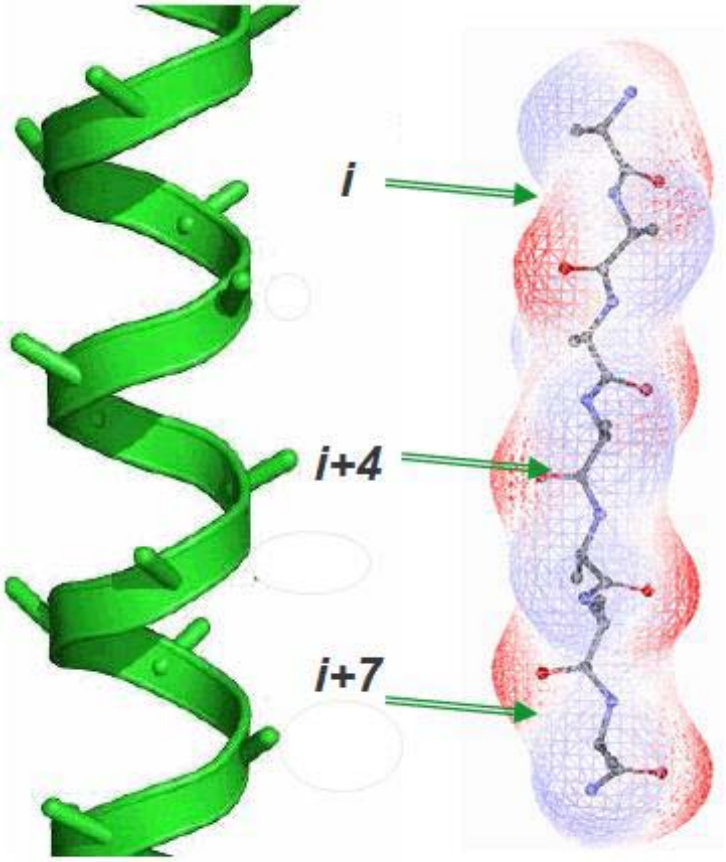
α-Helix 3D-Mimetics Library Design

Preferable scaffolds selection:

- ***sp3 – enriched (Fsp3 ≥ 0.4) to ensure their complexity and therefore 3D-diversity;***
- ***Contain at least 2 points of diversification;***
- ***Contain moieties of "privileged structures" such as piperazines, piperidines (including 3- or 4-amines, carboxamides etc.), pyrrolidines (including 3- amines, carboxamides etc.), (benz)-1.4-diazepines, prolines (including unusual) and others;***
- ***Contain moieties of naturally occurring compounds;***
- ***Lipophilitciy / hydrophilicity balanced;***
- ***Conformationally constrained (e.g. spiro- and bridged heterocyclic systems).***

α-Helix 3D-Mimetics Library Design

Our strategy for the design of helix-mimetics involves:



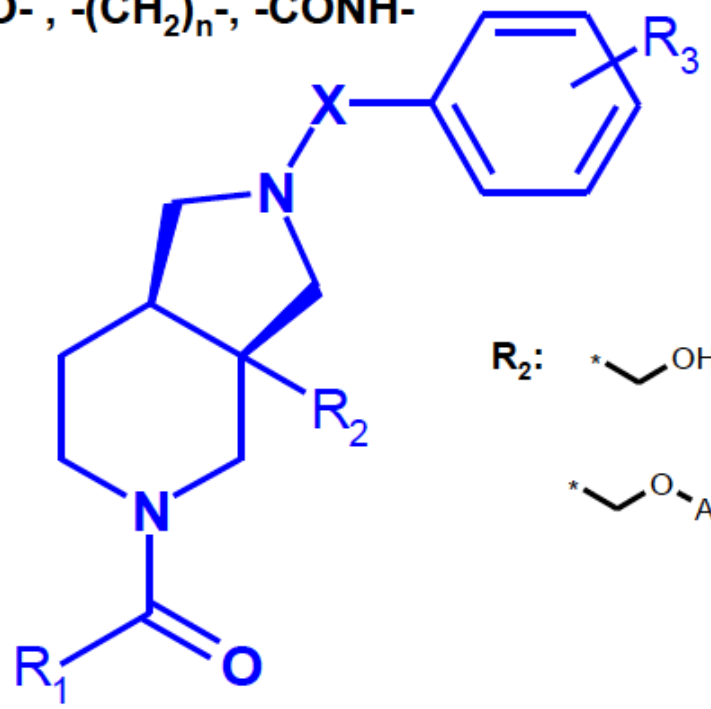
Energy minimized poly- and 7-alanine α-helix displaying *i*, *i* + 4, and *i* + 7 positions

- **Mimicry of helix by the structure of polycyclic small molecule scaffolds**
- **Mimicry of side-chain residues on one face of the α-helix**
- **At least three points of interaction with 7-ala helix at I, i+4 (or i+3) and i+7 positions**
- **Possible H-bond, hydrophobic, electrostatic or π-π-interaction (not electrophilic or redox!!!)**
- **Include hydrophilic and lipophilic regions in the scaffolds**
- **Avoidance of polycyclic aromatics (such as terphenyls and their hetero-analogs, oligo-benzamides and their hetero-analogs etc.)**
- **High Fsp3 for core scaffolds**

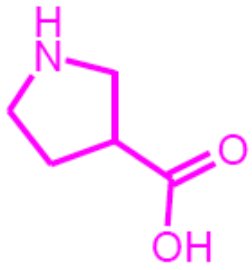
Example of selected scaffold

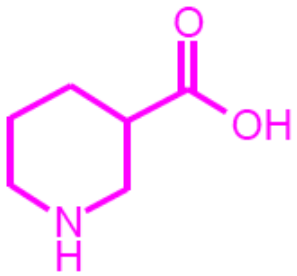
R_3: H, Alk (including bulky), OAlk, OAr, any other substituents, hydrophilic or lipophilic

X = -CO- , $-(CH_2)_n-$, -CONH-

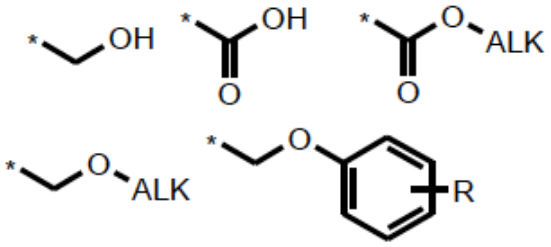


Privileged structures:



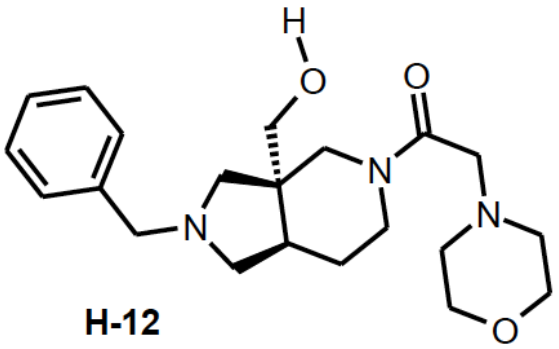


R_2:

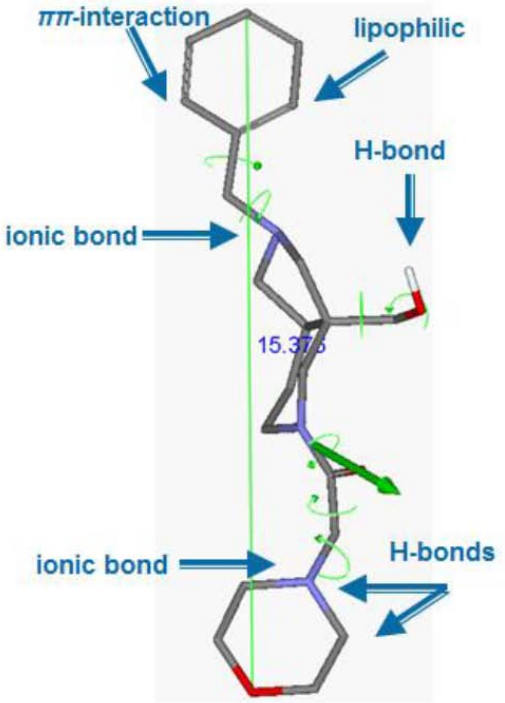


R_3: Diverse set of hydrophilic or lipophilic Aryl, Alkyl, Hetaryl, attached directly or using various linkers (e.g. NH, $(CH_2)_n$ etc.

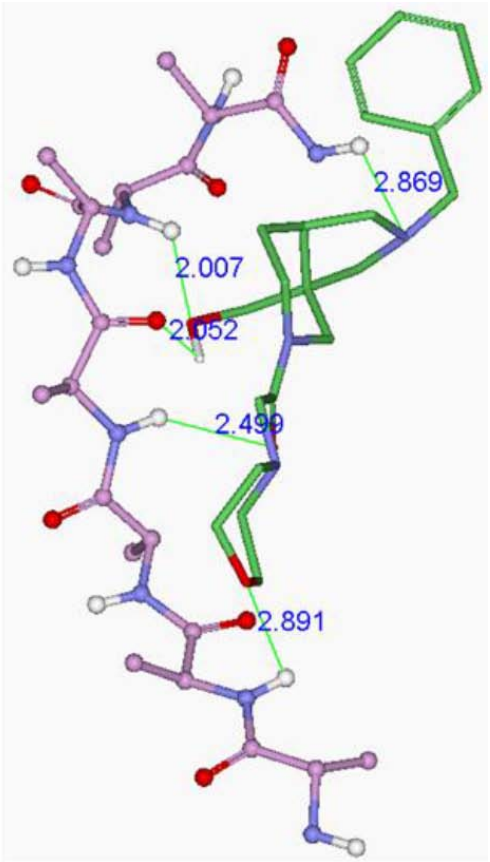
Example of modeling: interaction of H12 with 7-Ala



H-12

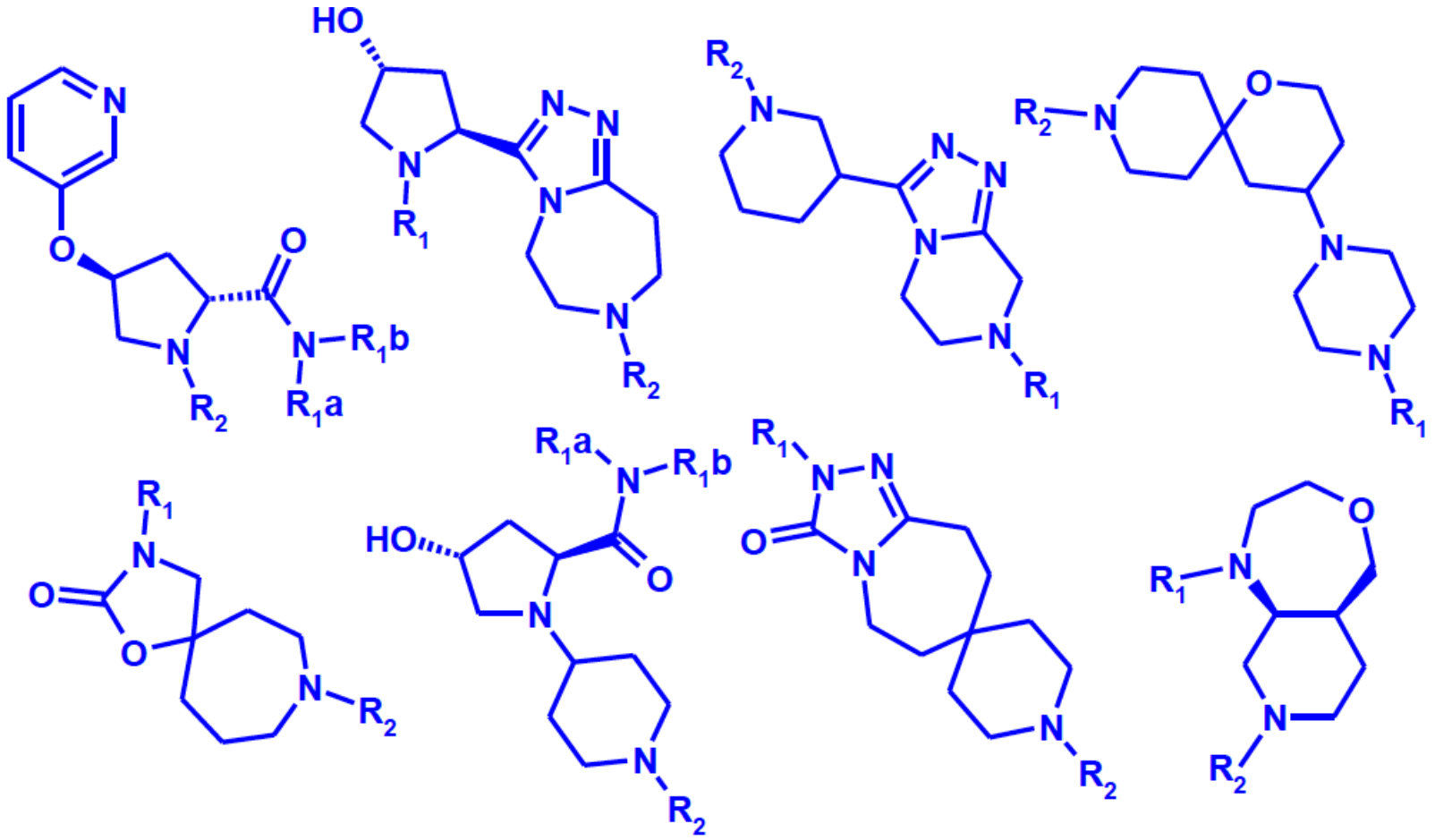


Energy minimized structure of H-12 and possible regions of interaction

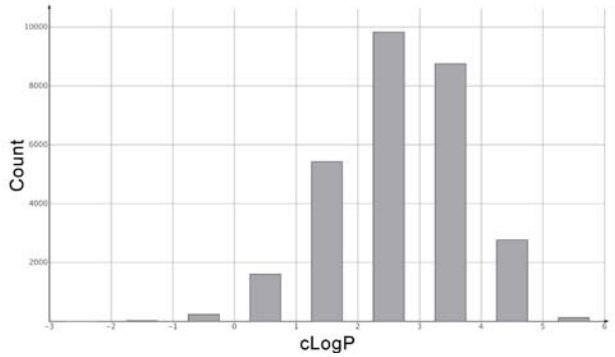


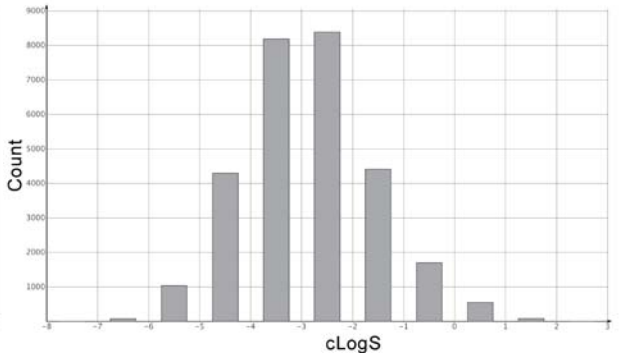
Energy minimized three-dimensional interaction of H-12 with 7-ala. Intermolecular forces were taken into account.Favorable H-bonds are pointed out by green lines.

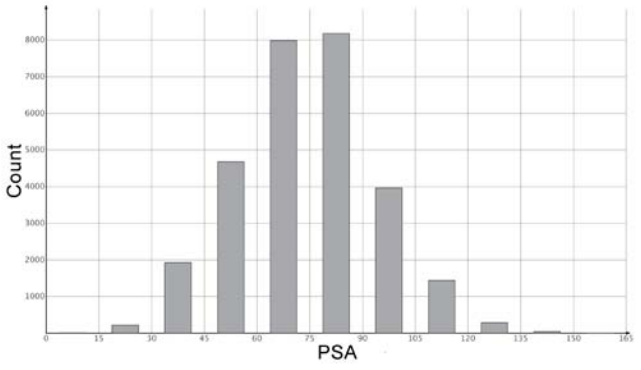
More examples of α-Helix-mimetic scaffolds

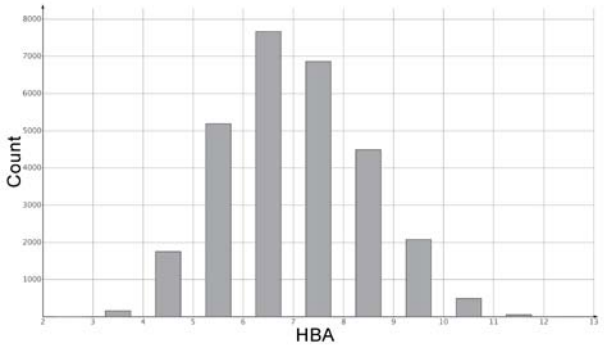


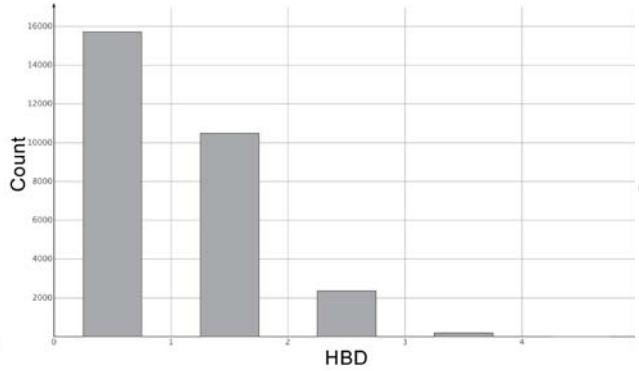
Key properties of compounds in the library

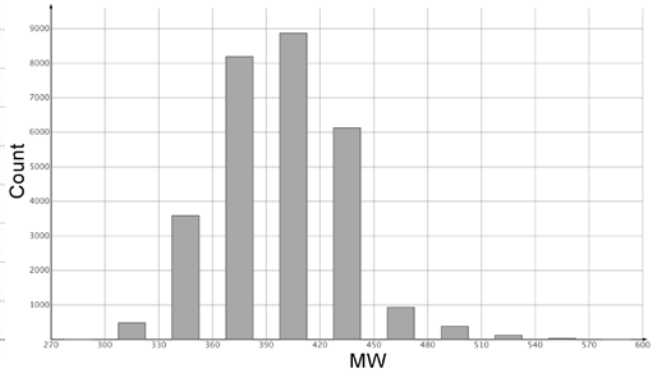






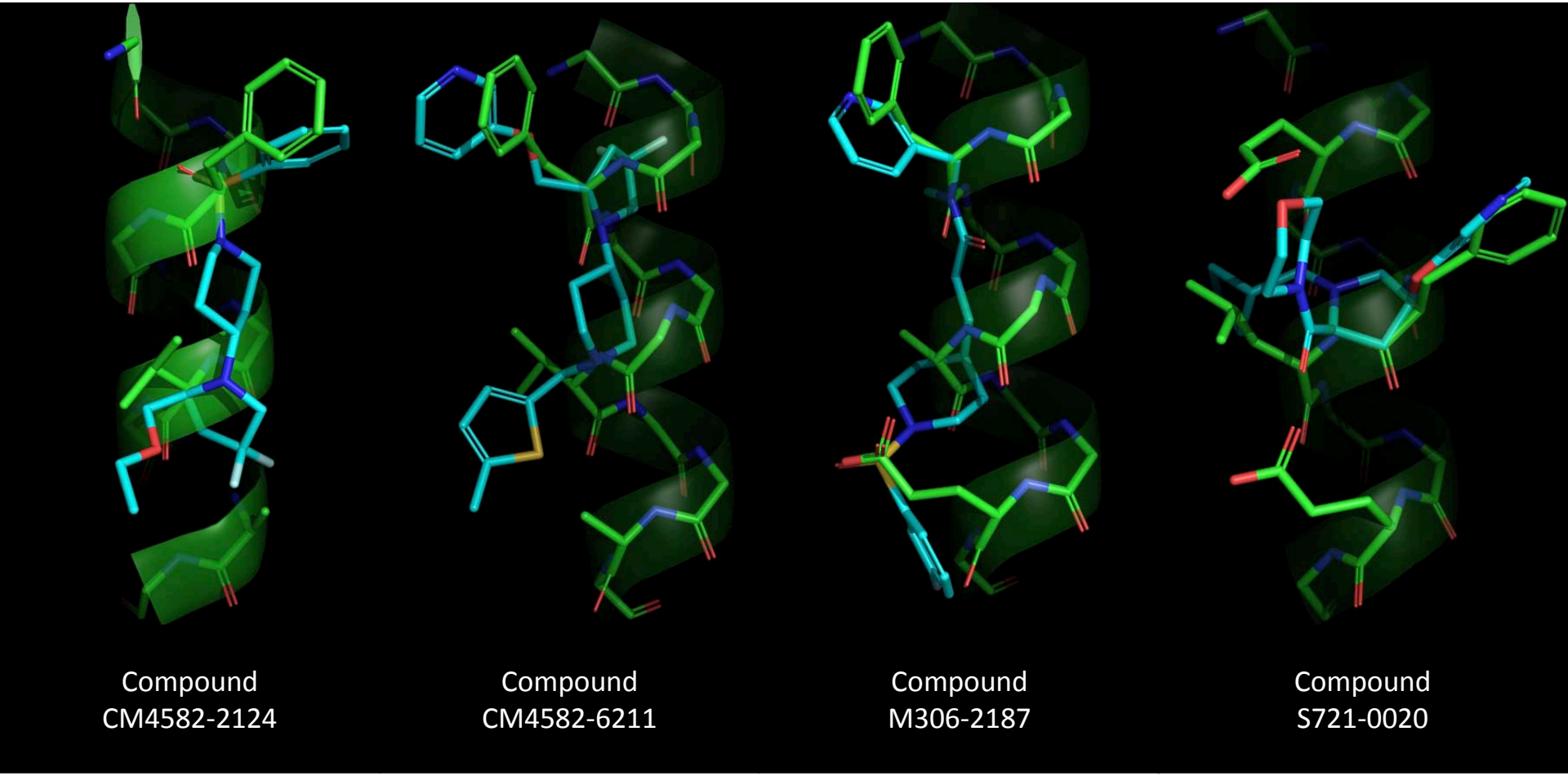






- Number of compounds: 28740

3D conformations for selected molecules



Ligand molecular structures are superimposed over the alpha-helical motif

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Examples of molecules