

ASINEX PROTEIN-PROTEIN INTERACTION LIBRARY

7000 compounds / 76 scaffolds

Exploring New Areas of Chemical Space to Find PPI Inhibitors

For the protein-protein interaction (PPI) group of targets, it has proved particularly challenging to find significantly active hit compounds [1,2]. Screening experiences have so far has been typified by very low hit rates.

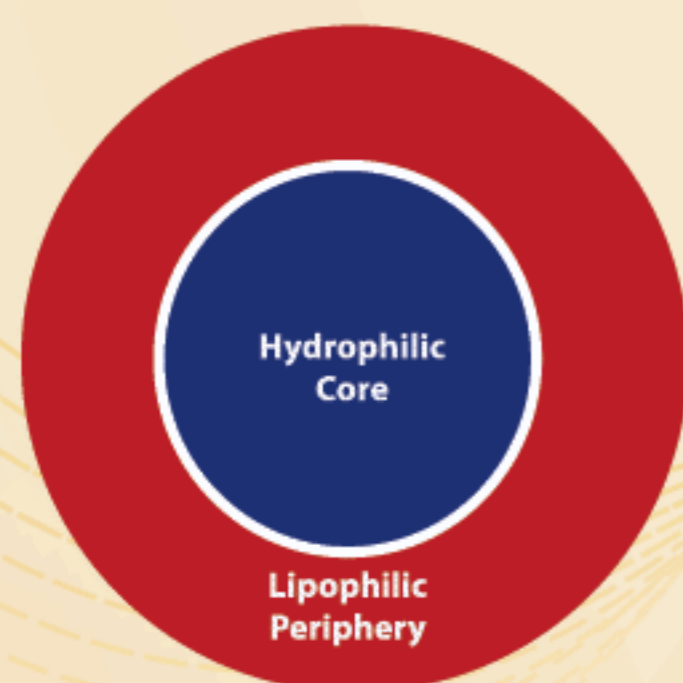
Accordingly very little data has been garnered in order to enable rational medchem design of PPI-disrupting compounds. The few hits and leads found to date have been relatively hydrophobic, rigid, often contain multiple aromatic residues and in general are not drug-like [3].

Asinex is committed to tackling the problem of designing compounds that are likely to produce higher valid hit rates when screened against pharmacologically relevant PPI targets, but at the same time lacking potential ADMET and solubility liabilities.

To address these issues, we have devised an algorithm that combines **highly hydrophilic 3D-like scaffold cores** that are enriched in H-bond acceptors and donors, with PPI-specific **lipophilic peripheries**. The algorithm involves an extensive retro-synthetic analysis of known PPI hits from the literature and in-silico property filtering, including shape analysis.

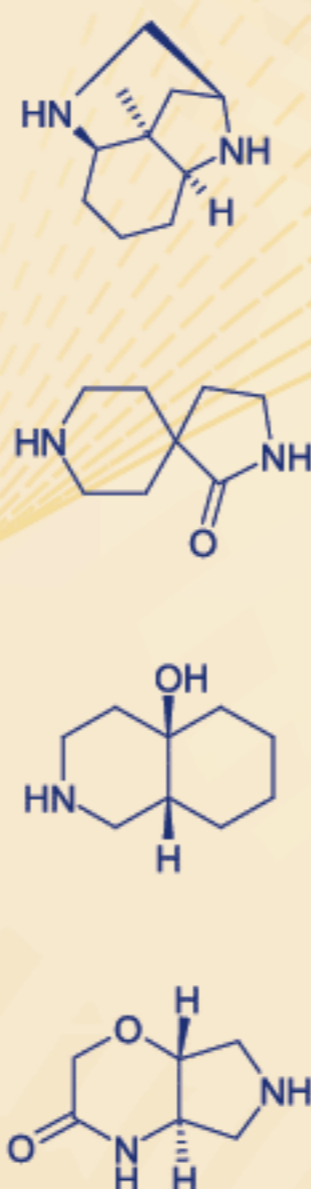
In total, **7000** unique final compounds have been produced using a range of coupling reactions, utilizing the 2-3 available synthetic handles of the **25 selected saturated scaffold cores**. Despite having relatively high clogP values, all compounds have proved to be soluble at standard screening concentrations both in DMSO and PBS.

MW ≤ 475
ClogP: 1.5-4.5
RotBonds: 2-9
HBD: 0-4, HBA: 4-9
TPSA: 75-120

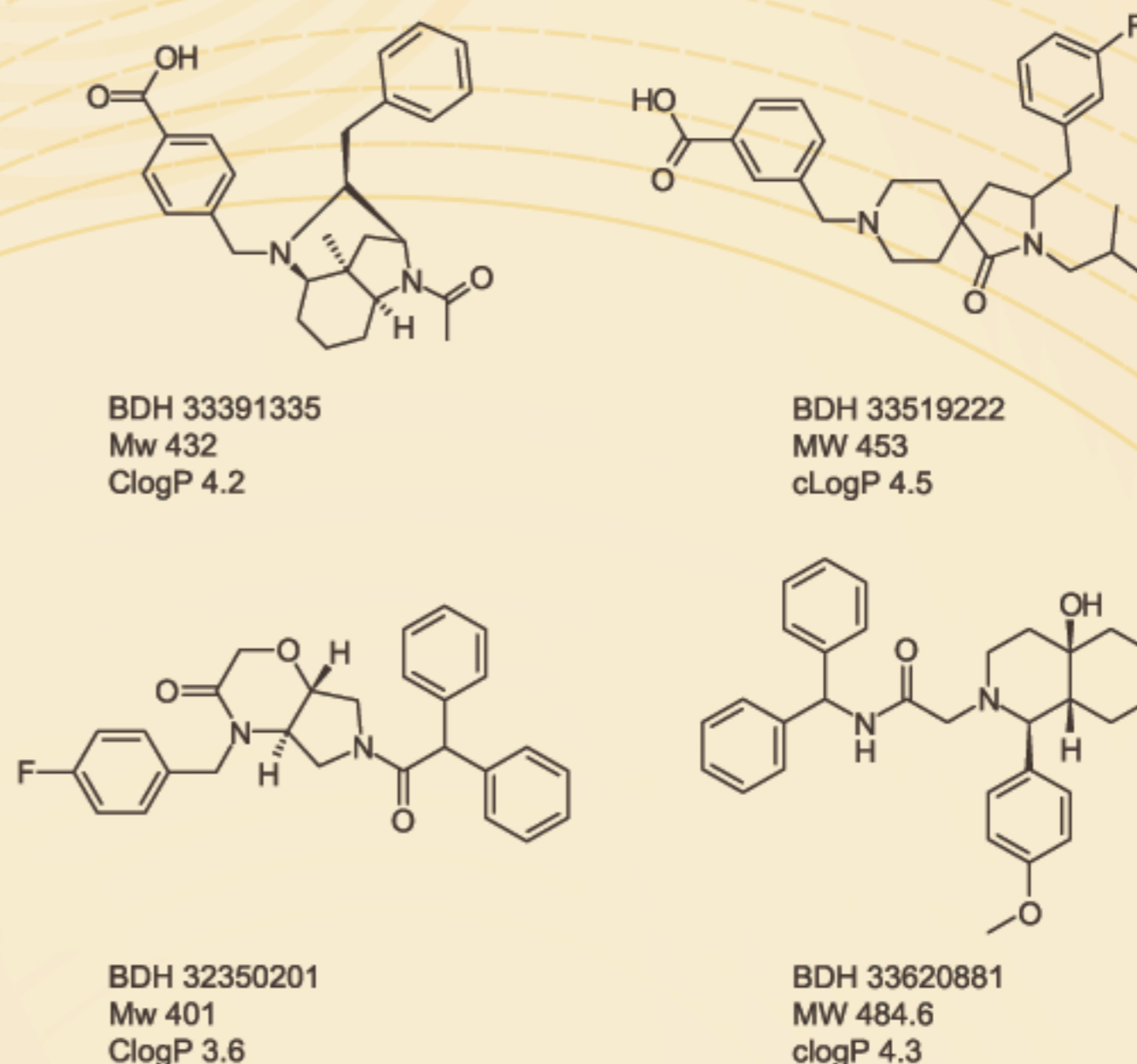


SHP2 ≤ 0.30
Mor11m > -0.10
RDF070m ≥ 12.0
Dipole Moment ≥ 0.5

Core



Final Molecule



By refining the design of the library, it is possible to select appropriate cores and periphery for creating more focused compounds, thus increasing the likelihood of binding to a specific target. For example, we have identified **several molecules** that were predicted to bind well in the MDM2 pocket and have consequently been found **active in the in-vitro screening assay** afterwards.

Library specifics:

Measured Solubility: 100% of compounds soluble in DMSO at 10 mM, and in PBS at 50 μ M

Quality: min.purity of 90%, avg. of 95% (LC-MS, NMR), stored as dry powder

ASINEX's PROTEIN-PROTEIN INTERACTION LIBRARY is only available upon request, please contact us at:

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1. María J. Vicent, Enrique Pérez-Payá and Mar Orzáez, Discovery of inhibitors of protein-protein interactions from combinatorial libraries, *Curr Top Med Chem*. 2007, 7(1):83-95
2. Zinzalla G, Thurston D., Targeting protein-protein interactions for therapeutic intervention: a challenge for the future, *Future Med Chem*. 2009 Apr;1(1):65-93
3. Olivier Sperandio et al., Rationalizing the chemical space of protein-protein interaction inhibitors, *Drug Discovery Today*, Volume 15, Issues 5-6, March 2010, pp 220-229