Synthetic Macrocycle Library with Potential to Find Hits for CNS Drug Discovery Programs

Sergey Sviridov, Duncan Beniston, Reg Richardson, Dmitriy Lvovskiy • ChemBridge Corporation | duncan@chembridge.com | San Diego, CA, USA

ABSTRACT

Topologically, macrocycles have the unique ability to span large surface areas while remaining conformationally restricted compared to acyclic molecules of equivalent molecular weight. Macrocyclization also reduces overall polarity and enhances membrane penetration compared to acyclic versions of similar structure. These attributes make macrocycles a powerful tool for any lead discovery program working with challenging targets.

For CNS drug discovery, macrocyclic leads are not typically thought of as attractive starting points for the TPSA and HBD count tends to be outside of what is considered an acceptable range for blood brain barrier penetration (BBB). By determining the number of internal hydrogen bonds a macrocyclic molecule makes in a solvent with a low dielectric constant and discounting the HBD count and TPSA ChemBridge has identified a subset of more than 4,000 macrocyclic compounds from its Macrocycle Library predicted to have a high probability of achieving good BBB penetration based on an MPO scoring approach. This poster will describe the analysis, the results and provide examples of macrocyclic molecules with modified MPO scores > 4.0.

CONCEPT OF MACROCYCLIZATION

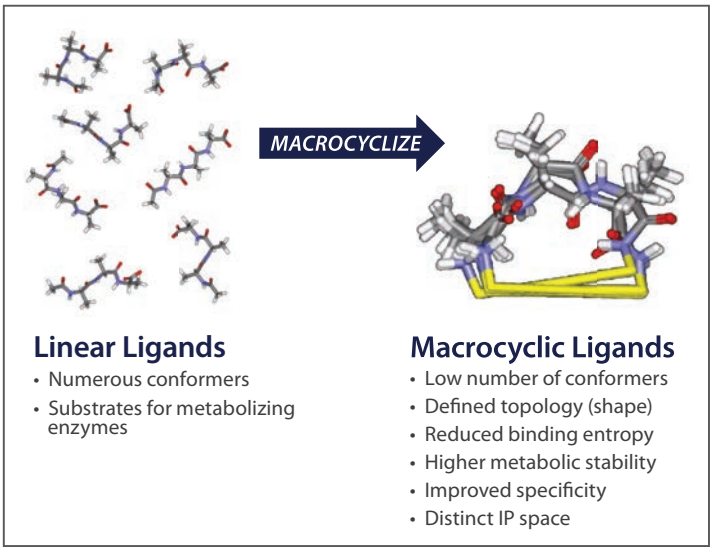


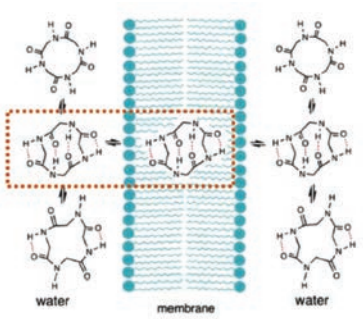
Figure taken from lecture given by Eric Marsault and Mark L. Peterson; Macrocycles Drug Discovery: Opportunities, Challenges and Challenges.

CHAMELEONIC PROPERTIES OF MACROCYCLES - Enhanced Membrane Permeability

Chameleonic macrocycles can access low energy conformers in which their H-bond donors are either solvated by water or internally solvated with H-bond acceptors.

From the perspective of a lipophilic membrane the apparent tPSA of a macrocycle conformer with internally solvated H-bond donors is lower than the conformer with water solvated H-bond donors.

The macrocycle with access to a low energy conformer with a lower apparent tPSA has a higher probability of crossing a lipophilic membrane.



Rezai, *et al., J. Am. Chem. Soc.* **2006**, *128*, 14073-14080.
Beck, *et al., J. Am. Chem. Soc.* **2012**, *134*, 12125-12133.

CNS MULTIPARAMETER OPTIMIZATION (MPO) SCORE

A fundamental challenge for the design of CNS penetrant drugs is the need to cross the BBB. Physiochemical parameters for BBB permeable compounds form a smaller subset within the property space of oral drugs. To best define the physicochemical properties for CNS library design ChemBridge selected a weighted scoring approach described by Wager et al.

The CNS MPO score is now a well-recognized algorithm in the CNS focused medicinal chemistry community. The algorithm uses a weighted scoring function assessing 6 key physicochemical properties (clogP, clogD, MW, TPSA, HBD, and pKa) for BBB penetration, CYP mediated metabolism and inhibition of dofetilide binding. The CNS MPO score is between 0 and 6.0 with scores ≥ 4.0 widely used as a cut-off to select compounds for hit finding in CNS therapeutic area drug discovery programs.

A recent article assessing 616 compounds with measured unbound concentrations in the brain confirmed increasing CNS MPO score correlates with increased unbound concentration in the brain.

ANALYSIS OF CHEMBRIDGE MACROCYCLE LIBRARY FOR CNS DRUG LIKENESS

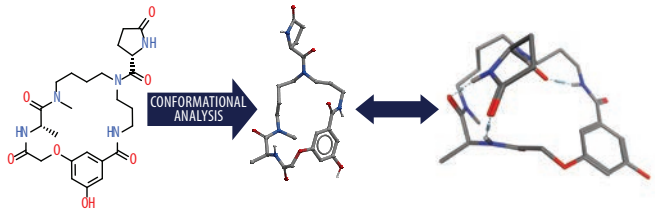
The ChemBridge Macrocycle library (n=6995) was analyzed to determine what percentage of the molecules might be suitable for screening in CNS projects. The CNS-MPO score (Wager 2010) was used to predict drug-likeness for CNS indications.

A key factor in calculating the CNS MPO score was to predict the possibility of forming intramolecular hydrogen bonds when passing through the membrane and to adjust the MPO score with apparent TPSA values and reduced H-bond donor (HBD) count.

Adjusted MPO Score
For each internal H-bond
- HBD count is reduced by 1
- Apparent TPSA: ΔTPSA = -20 Å2 per internal H-bond

EXAMPLE OF AN ADJUSTED MPO SCORE

The MPO score of ChemBridge macrocycle D 14120758 is increased to 4.59 when adjusting for its chameleonic properties.



ChemBridge Example ID 14120758 | Open form A low energy conformation* zero internal H-bonds | Closed form A low energy conformation* 3 internal H-bonds

MPO method	MPO score	MW	clogP	clogD	Basic pKa	TPSA Å	HBD
Standard MPO	3.0	517	-1.0	0.0	< 6	157	4
Adjusted MPO	4.59	517	-1.0	0.0	< 6	97	1

METHODS

1. Carboxylic acids removed (Lassalas 2016): 210, 3%, as non CNS druglike
2. Calculate CNS MPO score for remaining macrocycles
3. Keep macrocycles with CNS MPO > 4.0: 1269, 18%, as CNS druglike
4. Calculate Max CNS MPO with the assumption that every HBD could form an intramolecular hydrogen bond (ΔTPSA = 20Å2 per HBD)
5. Remove Max CNS MPO < 4.0: 592, 8%, as non CNS druglike
6. For Max CNS MPO > 4.0, run extensive conformational search with molecular mechanics minimization, fast implicit vibrational analysis and short molecular dynamics simulation (Labute 2001)
7. Count maximum number of intramolecular hydrogen bonds predicted from conformational search (conformations analyzed were within 2.8 kcal/mol of minimum)
8. Calculate the estimated score (Est CNS MPO) taking into account the predicted intramolecular hydrogen bonds
9. Keep Est CNS MPO > 4.0: 3129, 45%, as CNS druglike
10. Remove Est CNS MPO < 4.0: 1796, 26%, as non CNS druglike

RESULTS

GROUP	NUMBER	PERCENT
Carboxylic acids	210	3%
CNS-MPO ≥ 4	1269	18%
Max-MPO < 4	592	8%
Est-MPO ≥ 4	3129	45%
Est-MPO < 4	1795	26%
TOTAL	6995	100%

CONCLUSION

ChemBridge has identified a subset of 4398 macrocycles with an MPO score > 4.0. By exploiting the chamelionic properties of macrocycles and through a process of detailed conformational analysis, macrocycles were identified with internal H-bonds present in their low energy conformation. The tPSA and HBD count was then adjusted to calculate the MPO score. This library of macrocycles is an attractive screening library for the identification of macrocyclic hits for a CNS program.

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