CHEMBRIDGE

Macrocycle CNS Subset

Highlights

- Subset of synthetic macrocycles with potential application for CNS drug discovery
- Extensive conformational analysis performed to identify low energy macrocyclic conformations with internal hydrogen bonds
- 4,000+ macrocycles available; custom select or purchase the full set

Introduction

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 solvent exposed polarity and enhances membrane penetration compared to acyclic molecules of equivalent molecular weight. These attributes make macrocycles a powerful approach for any lead discovery program against challenging targets. However, for CNS drug discovery, macrocyclic leads are not typically thought of as attractive starting points as the TPSA and HBD count tends to be outside of what is considered an acceptable range for blood brain barrier (BBB) penetration. By determining the number of internal hydrogen bonds a macrocyclic molecule makes in a low energy conformation and discounting the HBD count and TPSA (-20Å per HBD) ChemBridge has identified a subset of more than 4,000 macrocyclic compounds from its Macrocycle Library predicted to have a high probability of good BBB penetration based on an MPO scoring approach.

CNS 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. in a 2010 article.[1] The CNS MPO score is now a well-recognized algorithm within 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 score is between 0 and 6.0 with scores $\geq$ 4.0 widely used as a cut-off to select compounds for hit finding in CNS therapeutic area drug discovery programs. A key factor in calculating the CNS MPO score for macrocycles is to predict the number of intramolecular hydrogen bonds in low energy conformations. These conformations are reflective of the macrocycle as it passes through the membrane. Once the internal hydrogen bonds are counted the MPO score is adjusted accordingly.[2]

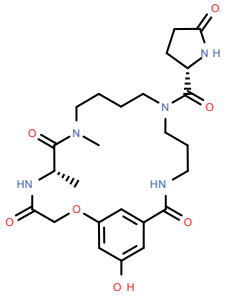
Methodology

A detailed 3D conformational analysis of ChemBridge Macrocycle Library compounds (6,000+ macrocycles) was performed to examine the number of intramolecular hydrogen bonds. Data from the conformational analysis was used to adjust the HBD and TPSA values and resulting MPO score for each compound and identified a subset with an "adjusted MPO" score $\geq$ 4.0.

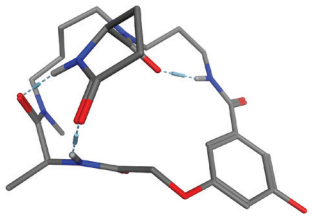
Methodology
continued

Analysis Process

1. Retain all macrocycles with CNS MPO ≥ 4.0 (these meet the MPO cutoff without need to form intramolecular hydrogen bonds)
2. Remove all macrocycles with CNS MPO < 4.0 and without ability to achieve adjusted CNS MPO ≥ 4.0 with all HBD internally hydrated
3. For remaining macrocycles with CNS MPO < 4.0 but with potential to form internal hydrogen bonds and achieve an adjusted CNS MPO ≥ 4.0, perform an extensive conformational search with molecular mechanics minimization, fast implicit vibrational analysis and short molecular dynamics simulation[3]
4. Count maximum number of intramolecular hydrogen bonds predicted from conformational search (conformations analyzed were within 2.8 kcal/mol of minimum)
5. Calculate the adjusted MPO score taking into account the predicted intramolecular hydrogen bonds; retain macrocycles with adjusted CNS MPO of ≥ 4.0
6. Combine macrocycles from step 1 and 5 as CNS Subset (4,000+ macrocycles)



A. 2D representation
(no internal H-bonds)



B. 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

Figure 1: A) Macrocycle ID 14120758 has an MPO score of 3.0 when calculated using standard CNS MPO methodology; B) Detailed conformational analysis shows the macrocycle forms 3 internal hydrogen bonds in a low energy conformation (low energy conformations are defined within 2.8 kcal/mol of minimum). The CNS MPO score is adjusted to count only the solvent exposed hydrogen bond donors and TPSA reduced by 20Å per internal hydrogen bond.

For more details on the Macrocycle CNS Subset or the ChemBridge Macrocycle Library please contact sales@chembridge.com

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References

1. Wager TT et al. Moving beyond Rules: The Development of a Central Nervous System Multiparameter Optimization (CNS MPO) Approach to Enable Alignment of Druglike Properties. ACS Chem. Neurosci. 2010 1(6), 435–449.

2. Hickey JL et al. Passive Membrane Permeability of Macrocycles Can Be Controlled by Exocyclic Amide Bonds. J. Med. Chem. 2016 59(11), 5368–5376

3. Labute P et al. Flexible Alignment of Small Molecules. J. Med. Chem. 2001 44(10), 1483–1490

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