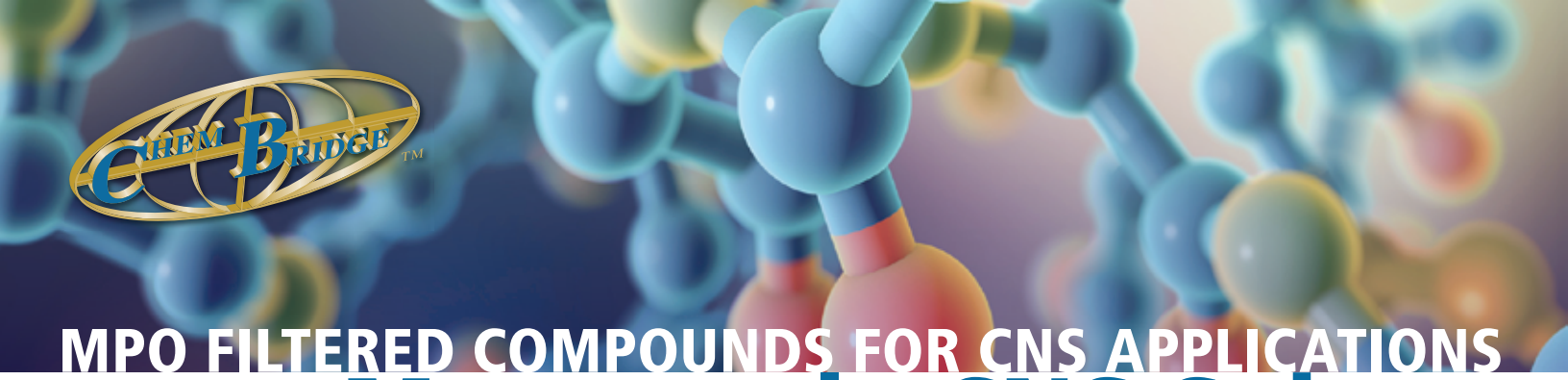


MPO FILTERED COMPOUNDS FOR CNS APPLICATIONS

Macrocycle CNS Subset

Highlights

- Subset of synthetic macrocycles with potential application for CNS drug discovery
- Custom select from more than 4,000 macrocycles

Introduction

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 tend to be outside of the acceptable range for blood brain barrier (BBB) penetration. ChemBridge® has identified a subset of compounds from its Macrocycle Library that are predicted to have a higher probability of good BBB penetration based on use of a CNS MPO (multiparameter optimization) scoring approach combined with a conformational analysis for a subset of macrocycles.

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 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.

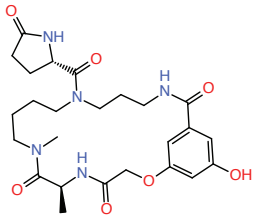
Methodology

For all macrocycles, a CNS MPO (multiparameter optimization) score is calculated, and all macrocycles with a CNS MPO score of 4.0 or higher are included in the Macrocycle CNS Subset. In addition, for 7,000 macrocycles with CNS MPO scores of less than 4.0, a detailed 3D conformational analysis was performed to examine the potential for low energy conformers to form intramolecular hydrogen bonds (H-bonds). A key factor in calculating the CNS MPO score for macrocycles is to predict the number of intramolecular hydrogen bonds in low energy conformations as these conformations are reflective of the macrocycle as it passes through the membrane. Data on the potential to form internal H-bonds was used to adjust the HBD count and TPSA value (-20Å per HBD), and an "adjusted CNS MPO" score was calculated. Macrocycles with an adjusted CNS MPO score of 4.0 or higher were also included in the Macrocycle CNS Subset.

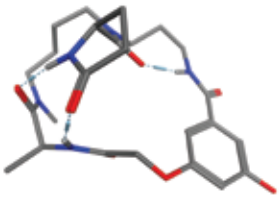
Methodology
continued

A summary of the steps used to analyze the 7,000 macrocycles is provided below:

1. For macrocycles with CNS MPO < 4.0 and 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]
2. Count maximum number of intramolecular hydrogen bonds predicted from conformational search (conformations analyzed were within 2.8 kcal/mol of minimum)
3. Calculate the adjusted MPO score taking into account the predicted intramolecular hydrogen bonds; retain macrocycles with adjusted CNS MPO of ≥ 4.0



2D representation (no internal H-bonds)



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: Macrocycle 14120758 has an initial MPO score of 3.0. Detailed conformational analysis shows it forms 3 internal H-bonds in a low energy conformation (a conformation within 2.8 kcal/mol of minimum). The adjusted MPO score (4.59) counts only solvent exposed H-bond donors and has TPSA reduced by 20Å per internal H-bond.

Format

- Custom select from more than 4,000 Macrocycle CNS Subset compounds
- Available in 384-well and 96-well formats including 384-well acoustic qualified plates
- Amounts as low as 0.25 micromole (25ul of 10mM DMSO solution) available
- Available as DMSO solutions or dry in micromole or mg amounts

Structure File

For a file of structures, please email sales@chembridge.com

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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

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Rev. 20240906