COMPOUNDS FOR CNS DRUG DISCOVERY

CNS-MPO Library

Highlights

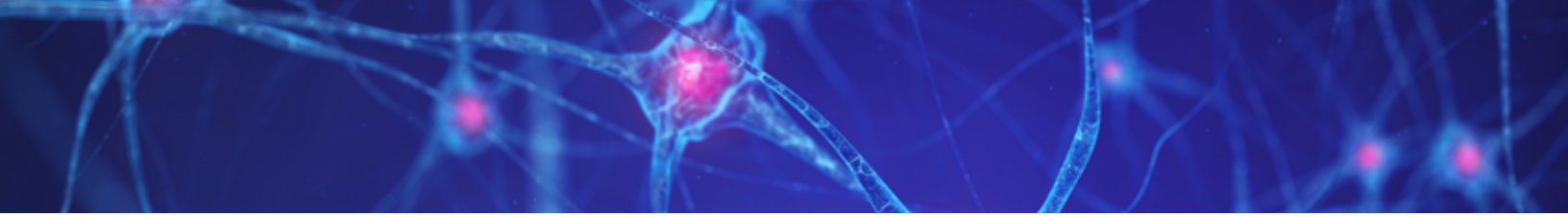
- High quality, PAINS-free, small molecule compounds for CNS drug discovery
- CNS MPO analysis applied to identify compounds with high probability of blood-brain barrier (BBB) penetration and improved clearance and safety profiles
- Custom select from more than 400,000 structures to meet your specific requirements
- Structurally diverse hit-finding and leadlike subsets available
- Includes structural analogs for SAR studies

Introduction

ChemBridge has created a new CNS-focused compound selection, the CNS-MPO Library, to support CNS drug discovery programs. Compounds from the library are predicted to have a higher probability of crossing the BBB based on a multiparameter optimization (MPO) approach. The CNS-MPO Library represents a subset of compounds from ChemBridge's stock of more than 1.1 million leadlike and druglike small molecule screening compounds representing a wide range of different chemotypes.

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.1,2 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 $\geq$ 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.[3]



Selection

The following approach was used to select compounds for inclusion in the CNS-MPO Library:

- Filter to remove compounds with undesirable structural features including PAINS filters
- Remove compounds with carboxylic acid groups due to low probability of BBB permeability[4]
- MW range of 250 to 450 inclusive to allow for hit-finding or lead-like biased selections
- CNS MPO score ≥ 4.0
- Remove compounds with TPSA ≥ 100Å to eliminate high MPO score compounds with less desirable TPSA
- Limit clogD range to 0 to 5.0 inclusive to eliminate high MPO score compounds with less desirable clogD values

The CNS-MPO Library selection can be further refined using methods including structural diversity analysis, focusing on a hit-finding subset (MW range 300 to 450), or focusing on a leadlike subset (MW range 250 to 400; TPSA ≤ 90Å; option to re-score using CNS Lead MPO[5]).

Format

- Download structures and custom select CNS-MPO Library compounds
- Compounds can be provided in 96-well or 384-well format
- Compounds are available dry or as DMSO solutions

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, 435-449.

2. Wager TT et al. Central nervous system multiparameter optimization desirability: Application in drug discovery. ACS Chem. Neurosci. 2016 7, 767-7

3. Rankovic Z CNS drug design: balancing physicochemical properties for optimal brain exposure. J. Med. Chem. 2015 58 (6), 2584–2608

4. Ghose AK et al. Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. ACS Chem. Neurosci. 2012 3, 50–68.

5. Mayol-Llinàs J et al. Assessing molecular scaffolds for CNS drug discovery. Drug Discov. Today. 2017 7, 965-969.

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