Macrocycles for CNS Drug Discovery

ASINEX

An effective CNS drug must be potent, selective, and have the ability to penetrate the blood-brain barrier in therapeutic concentrations. Passive diffusion through the cellular membrane and P-glycoprotein-mediated efflux can be limiting factors for blood-brain barrier penetration (BBB). It is, therefore, generally recognized that the physicochemical features of CNS drugs are related to their ability to penetrate the BBB.

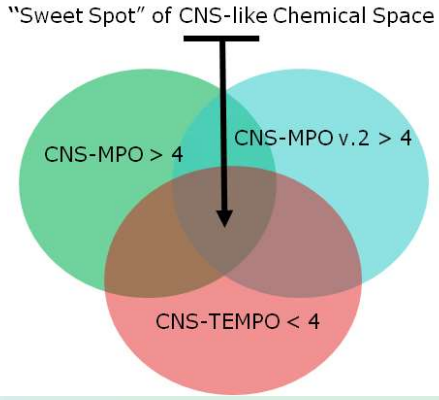
Differences in the in vitro permeability, Pgp substrate profiles, and physicochemical properties of CNS drugs have resulted in the creation of a set of rules defining the attributes of successful drug candidates [1-3]. In creating these rules, it was found that CNS drugs are generally smaller, more lipophilic, with fewer hydrogen bond donors (HBDs) and a lower topological polar surface area (TPSA) than oral non-CNS drugs.

However, many emerging CNS targets require larger and more polar ligands, conflicting with the aforementioned BBB-permeability requirements. To address this challenge, several macrocyclization strategies have been suggested to organize and stabilize bioactive conformations as well as to improve membrane permeability and reduce Pgp susceptibility. These macrocyclization strategies have been actively developed at ASINEX resulting in a30K+ library of diverse macrocycles.

Several CNS multi-parameter scoring approaches have been reported: CNS-MPO [1], CNS-MPO v.2 [2], CNS-TEMPO [3] suggesting an algorithm to predict CNS-like properties of new chemical entities. At ASINEX, we have applied these scoring algorithms to select macrocycles satisfying multiple cut-offs and structural desirability criteria (Figure). The resulting set consists of 2300 macrocyclic compounds for CNS-related drug discovery and research

2300 CNS-like Macrocycles

Preferred values:
MW < 500
cLogP = 2.6 – 4.5
TPSA 40 – 100 Å;
pKa = 8
Number of basic N: 1
Rotatable bonds: 1 - 4
Aromatic rings: 1 - 2
Number of H-acceptors: 2 - 3
Number of H-donors <= 1
Carbon/Heteroatom ratio: 2.1 - 4.5



References:

1. ACS Chem.Neurosci. 2010 Jun 16; 1(6): 435–449. doi: 10.1021/cn100008c
2. J Med Chem. 2017 Jul 27;60(14):5943-5954. doi: 10.1021/acs.jmedchem.6b01469.
3. ACS Chem. Neurosci., 2017, 8 (1), pp 147–154. doi: 10.1021/acschemneuro.6b00273