CNS Focused Library

8 850 compounds for cherry picking

The success of drug discovery projects on CNS targets significantly depends on quality of the initial screening hits. Choice of the selection criteria in design of a screening library against CNS-targets plays a crucial role for the whole CNS-drug discovery process [1, 2].

We employed a well-balanced set of versatile approaches used in CNS-drug discovery to identify 9,219 diverse and structurally related compounds from our entire over 2,000,000-compound screening collection.

BBB Permeability and Molecular Properties

Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. To assure that our library compounds move across the blood-brain barrier (BBB) we selected molecules with low polar surface area (TPSA < 100Å^2, mean value 35Å^2, *cf.* 47Å^2 for the top 25 known CNS drugs), with low degree of possible hydrogen bond formation (total number of nitrogen and oxygen atoms less than 6), and only such compounds for which cLogP - (N+O) > 0.

Other important molecular properties criteria that are widely exploited to distinguish CNS-targeted compounds [1, 2] and that have been used by us in the design of CNS-Targeted Library include:

MW < 350 (mean value 286, *cf.* 293 for the top 25 known CNS drugs),

ClogP < 5 (mean value 3.13, *cf.* 2.8 for the top 25 known CNS drugs),

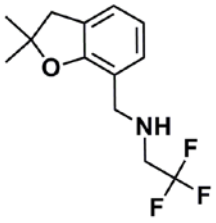
HBD / HBA < 3 / 7 (mean HBD 0.74, *cf.* 0.8 for the top 25 known CNS drugs),

RotBonds < 8 (mean value 3.36).

Parameter	Range	Parameter	Range
MW	180 ... 350	RotBonds	≤ 4
ClogP	1.3 ... 3.0	ClogP-(N+O)	> 0
PSA	≤ 65 Å^2	Fsp^3	0.15 ... 0.8
Hbond Donor	≤ 3	Ring count	1 ... 4
Hbond Acceptor	≤ 6	Basic N	≤ 2
Total H-bonding	< 8	Carboxylic acid group	≤ 1
Carboxylic acid group	≤ 1	Diversity	≤ 85%
S atoms	≤ 2	No NO_2, Br, I, P, C#N,	
Cl atoms	≤ 2	No quaternary Nitrogen	

Structural features

The recent trends suggest conformational constrains and rigidity of the molecules as important structural characteristics of the CNS-targeted compounds. We have focused our selection of the library compounds on the recently synthesized molecular arrays having sp^3-rich saturated ring cores of various architecture including spirocyclic (1,341 compounds, 14.5%), and bridged & fused scaffolds (4,106 compounds, 44.5%).



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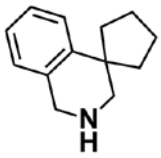

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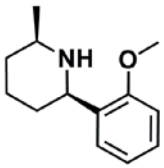

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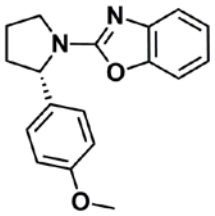

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Novelty

The CNS-Targeted Library compounds have been selected from the HTS, Advanced and Premium collection compounds synthesized within the last 5 years on the basis of innovative scaffolds and with the use of advanced building blocks widely modulating their physicochemical properties. The compounds are representatives of the new chemical space discovered by Enamine researchers.

Diversity

Structures of Enamine CNS-target library were analyzed using similarity scoring to identify the most diverse compounds.

MedChem filtering and hit follow-up opportunities

Toxicity and PAINS filters were applied to remove all high reactive and toxic motifs.
All compounds were synthesized at Enamine and are available on stock in over 10 mg quantities and scale-up is guaranteed. Further rapid and non-expensive lead generation and optimization can be performed at Enamine.

1. Pardridge W. M. Blood–brain barrier delivery. *Drug Discovery Today*. **2007**, 12 (1/2); 54–61.
2. Pajouhesh H., Lenz G. R. *NeuroRx*., **2005**, 2; 541–553.
3. Vlieghe1 P., Khrestchatisky M. *Medicinal Research Reviews*, **2012**, 00; 1–60.