CNS-Targeted Library

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CNS activity

It is patently obvious that CNS activity (and trans-cellular permeability in general) is a complex function of physical/chemical properties of molecules such as size, lipophilicity, hydrogen-bonding potential, charge, and conformation[i]. For any given molecule, one of these factors may dominate others[ii]. Drugs with the brain as the site of action should, in general, be able to cross the BBB. Drug delivery to the brain can be enhanced by increasing the lipophilicity of the molecule, by using prodrugs that dissociate after crossing the BBB, or by using passive or active drug targeting that utilizes transport systems at the BBB in the normal or disease states[iii]. In general, the trans-endothelial transport of compounds can depend on binding to constituents of the plasma, ionization state, time-dependent plasma concentration, and cerebral flow. It is possible to modify many of these properties with changes in chemical structure.

Previous attempts at understanding CNS activity have resulted in certain rules-of-thumb. For example, Andrews et al.[iv] have shown that an aromatic ring-tertiary nitrogen pharmacophore is important for CNS activity. Levin[v] has successfully correlated octanol/water partition coefficient (LogP) and brain capillary permeability for compounds with molecular weight less than 400. However other, more recent attempts conclude that the octanol/water partition coefficient does not correlate well with blood-brain transport[vi]. Other criteria, like a limit of 8-10 hydrogen bonding groups per molecule, have also been proposed[vii].

Blood-brain barrier permeability

Blood-brain barrier permeability (BBB) is a metabolically active tissue that facilitates and controls the brain uptake of certain solutes while helping to maintain homeostasis within the central nervous system. The BBB consists of a monolayer of polarized cerebral endothelial cells1 (CEC) that exhibit various functional and morphological differences in comparison with endothelial cells derived from peripheral organs. CEC possess narrow intercellular tight junctional structures. The tight junctions are composed of a complex of belt-like zonula occludens, which is localized close to the lumen of the capillary[viii]. These tight junctions hinder paracellular transport of hydrophilic compounds across the cerebral endothelium and protect the brain from blood-borne compounds, since a strict homeostasis of the neuronal environment and an intact barrier are essential for optimal brain functioning.

Optimizing the distribution of therapeutic compounds between brain and blood is one of the key issues in the design of novel CNS-active drugs[ix]. Given the problem's importance, reliable new methods of effective pre-synthetic assessment of BBB permeability are needed for the discovery of CNS-active agents. This problem is especially important in the early stages of the drug discovery process, where high-throughput and efficient estimation of BBB permeability represents a serious bottleneck in the design of CNS-targeted or non-CNS

targeted compound libraries. There have been many published computational models for this property using a variety of techniques (for example,[x]).

Concept and Applications

CNS-targeted library design at CDL involves:

• *A combined profiling methodology that provides a consensus score and decision based on various advanced computational tools and theoretical knowledge*:

1. Targeted diversity concept applied for the targeted library design

2. Various Artificial Neural Network (ANN) tools for BBB assessment, in particular back-propagation ANN and Self-organizing Kohonen Maps, performed in SmartMining Software. We have also used Sammon mapping as a more accurate computational approach to predict BBB permeability.

3. Computational-based `*in silico*` ADME/Tox assessment for novel compounds includes prediction of human CYP P450-mediated metabolism and toxicity as well as many pharmacokinetic parameters, such as Human Intestinal Absorption (HIA), Plasma Protein binding (PPB), Plasma half-life time ($T_{1/2}$), Volume of distribution in human plasma (V_d), etc.

The fundamentals for these applications are described in a series of our recent articles on the design of exploratory small molecule chemistry for bioscreening [for related data visit ChemDiv. Inc. online source: www.chemdiv.com].

• *Synthesis, biological evaluation and SAR study for the selected structures*:

1. High-throughput synthesis with multiple parallel library validation. Synthetic protocols, building blocks and chemical strategies are available.

2. Library activity validation via bioscreening. SAR is implemented in the next library generation.

CNS-targeted library design

1. *Concept of Targeted Diversity*

ChemDiv introduces the concept of Targeted Diversity which is intended for the design of high quality libraries of drug-like compounds that have been focused against various biological targets. Targeted diversity signifies the superposition of highly diverse chemical space on the assortment of divergent families or sub-families of targets and unique biomolecules. These targets may be congener or “orthogonal” (non-overlapping) and include:

(a) Different classes of targets.

(b) Distinct, structurally unrelated branches of the same target class.

(c) Independent targets.

The different classes of biomolecules are represented by G-protein coupled receptors (GPCR), nuclear hormone receptors (NHR), ligand- and voltage-gated ion channels (LGICh and VGICh), transporters (TR), various enzymes (kinases, proteases, phosphodiesterases, etc.), effector proteins and others. Examples of the branches of related proteins include serine/threonine protein kinases (STPK) and tyrosine kinases (TK) as sub-families of the kinome. An example of independent targets is GPCR-like Smo receptors. The current edition of the Targeted Diversity Library (TDL) is based on approximately 100 small molecule sets. Each of these sets is

focused against distinct biological targets belonging to the different classes and sub-families of targets (list of targets selected is shown below) and includes about 5000 individual drug-like molecules. The selection process for these sets involves identifying active ligands/inhibitors as prototypes existing in the patent and research literature or databases and performing bioisosteric replacement strategies, e.g. a known peptide ligand may be substituted with a small non-peptide peptidomimetic. Then a similarity search based on these strategies is conducted within ChemDiv's collection for possible augmentation of the rational set. Other techniques include computer-assisted 3-D pharmacophore matching and when possible, in silico docking experiments. The directed synthesis of new chemotypes with functionality mimicking recognition elements (shapes, "warheads") of known active ligands/inhibitors has also been performed. In some cases, proof of concept has been established with in-house biological data. A special effort has been made to select respective compounds and synthetic templates with good IP potential, as deduced from Beilstein, SciFinder and Markush sub-structure searches. The special rules of ChemDiv's medchem filters (MCF) ensure the high quality and drug-like properties of selected molecules. The first edition of the TDL includes the most diverse compounds (250-750 members) from each of 100 target-specific sets. The current TDL is built around 1,000 diverse chemical templates to yield a library of about 50,000 individual drug-like molecules. Embellishment of the library is an ongoing effort at ChemDiv. Regular updates are being made as newly synthesized compounds become available and pass our QA specifications (>90% purity as established by LC/MS with UV and ELSD). Additionally, new proposals for target-specific sets are being evaluated, tested and made available.

Thus, the TDL may provide high-quality hits in screening against "difficult" targets with limited or no structure/ligand information, as well as "eclectic" biological targets, including cellular processes (e.g. apoptosis and cell cycle), signaling pathways (e.g. WNT, Hh, RTK and Ras) or protein-protein interactions (e.g. XIAP, pGPCRs).

2. *Neural Network Tools for BBB Assessment*

The second step towards our CNS-focused library includes several computational models which can be effectively used for the prediction of BBB permeability. This approach is schematically illustrated in Fig. 1.

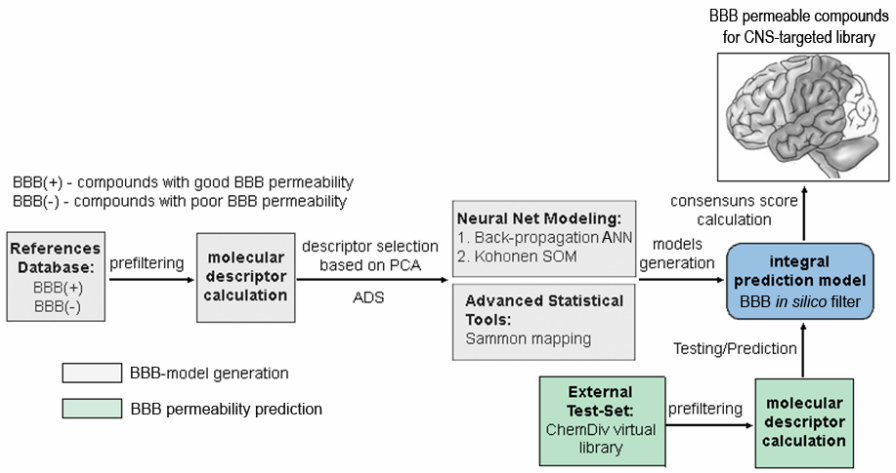

Fig. 1. Integral computational approach for the prediction of BBB permeability

We have built a robust qualitative model for the early assessment of the BBB permeability (passive diffusion) of small, therapeutically relevant molecules using the same unsupervised Kohonen learning approach. A comprehensive set of experimental data on BBB permeation of 502 compounds (197 compounds with poor (BBB(-)) and 305 compounds with good BBB permeation (BBB(+)) was collected with key assumption that only passive diffusion is involved in BBB transport of these compounds. Statistical analysis enabled the selection of an optimal set of molecular descriptors for the effective prediction of BBB penetration.

The combined data set of BBB(+) and BBB(-) compounds was projected onto Kohonen map. The data set of BBB(+) compounds occupies distinct area on the map substantially different from the regions of localization of BBB(-) compounds (Figure 2)[xi]. Therefore, the sites of compound's localization on the Kohonen map can be used for the assessment of its BBB-permeability. The constructed learning model is useful in constraining the size of libraries of potential CNS active agents, as an *in silico* filter, to assist in the synthetic design and planning of novel combinatorial libraries.

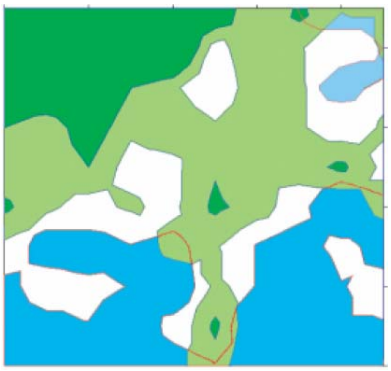

Figure 2. Smoothed contour plots of the occurrences of BBB(+) (green area) and BBB(-) (blue area) compounds within the Kohonen map. The contours correspond to at least 1.5% of compounds, from a particular category, per node

For the BBB consensus score generation we also have developed the neural-based and non-linear Sammon computational models. All the models constructed were successfully validated using external test sets; the average prediction accuracy was found to be more than 90%, and it is quite statistically significant.

Conclusion

Here we provide an efficient approach for the design of novel CNS-active compounds. Based on the accumulated knowledgebase, concept of target diversity as well as unique structure-based computational models for the BBB assessment we have been designed CNS-targeted library of more than 35K small molecule compounds. As a result, the library is renewed each year, proprietary compounds comprising 50-75% of the entire set. Clients are invited to participate in the template selection process prior to launch of our synthetic effort.

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