Designing PAMPA Permeable Macrocycles: Exploring Promising Directions in Early Drug Discovery Research

Passive Cell Membrane Permeability

Solubility, lipophilicity size, H-bond donors, and charge are important properties in determining passive membrane transportability of small molecules and macrocycles [1, 2]. The same properties, however, can have opposite effects at different steps of the multi-step process.

-2,000 Neutral Macrocycles For neutral macrocycles, we applied two 2D descriptors & four 3D descriptors to build a r=0.87 PLS model and found that TPSA and hydrogen bond donor strengths correlate negatively with observed PAMPA. Additionally, a Larger Hydrophobic water accessible surface area correlates positively while higher polar surface area correlates negatively with PAMPA. We found that the Hydrophilic (and also Hydrophobic) intervals which indicate that molecules with a concentration or hydrophobic regions in only one part of the molecule surface (and consequently regions predominantly hydrophobic) have better PAMPA.

PAMPA data set:
A representative set of 4000 ASINEX Macrocycles was experimentally tested in the Parallel Artificial Membrane Permeability Assay (PAMPA) [4]. For the convenience of structure-property analysis all macrocycles can be divided into 4 major groups based on ability to exist in certain ionic forms (pKa, pKb values). Two or the most well represented groups, Basic and Neutral macrocycles, were computationally analyzed to create predictive QSAR models.

Intrinsic a & t processes:
Macrocycles are known to change their 3D conformation depending on environment for example, from water soluble, to membrane permeable, to target bound.

PAMPA

Data preparation

- 3D conformers have been generated using MOE’s LowModeMD
- Method using M0MPP+4x Force Field with Born Solvation Model
- Low Dielectric Conformer was selected for further analysis

-2,000 Basic Macrocycles
For macrocycles with a basic group, we applied two 2D descriptions and four 3D descriptors to build a r=0.65 PLS model. We found the Strength of the basic center, Hydrophobicity moment, along with size and polar surface properties all correlate negatively with PAMPA whereas the octanol/water partition coefficient (LogP)

- 100s of 2D & 3D descriptors have been calculated:
- %2D: Huckel Theory Descriptors, Subdivided Surface Areas, Atom Counts and Bond Counts, Adjacency and Distance Matrix Descriptors, Pharmacaphore Feature Descriptors, Partial Charge Descriptors
- %3D: Surface, Volume and Shape Descriptors; Conformation Dependent Charge Descriptors

CONCLUSIONS:
- Two QSAR PAMPA models are reported
- As shown before by Oja et al. [3] more predictive and simpler models for PAMPA were derived in basic / amphoteric / and neutral compounds are analyzed separately.
- Correlation coefficient of the model for macrocycles with a basic center is still relatively low, presumably because of the quality of pKa predictions.
- Based on our research, this is the first report or PAMPA QSAR models that include 3D variables based on large experimental data set.
- The proposed QSAR models can be utilized for prioritization of relatively large molecular sets, improving the quality of macromolecular library design for pharmaceutical drug discovery.

About ASINEX:
ASINEX is a privately held US-based preclinical stage drug discovery company developing platform solutions to address unmet needs in oncology and infectious disease.

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References:
[1] Velcro et al., Expert Opinion 2013, “Predictive approaches to increase absorption of compounds during lead optimization”
[3] Oja et al., SAR and QSAR in Environmental Research, 2016 “QSAR at various pH values for neutral and amphoteric drugs and diol-glycine compounds”