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

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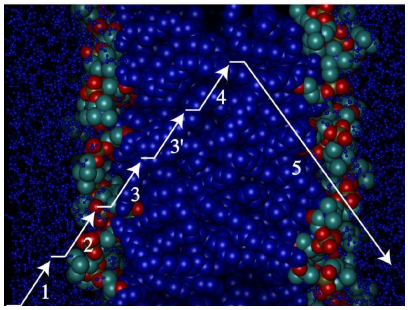
Passive Cell Membrane Permeability

Solubility, *lipophilicity*, *size*, *H-bond donors*, and *charge* are important properties in determining passive membrane permeability of small molecules and macrocycles [1, 3]. The same properties, however, can have opposite effects at different steps of the multi-step process:



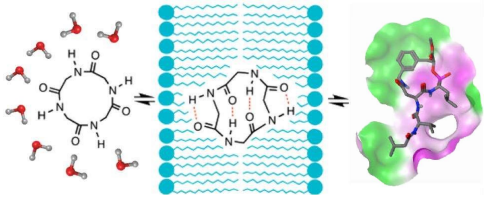
Passive permeation model across a lipid barrier (reproduced from with permission) [2]:

1) diffusion across the aqueous boundary layer;
2) desolvation from the aqueous medium;
3) solute partitioning from aqueous to the lipid environment;
4) diffusion across the lipid bilayer;
5) solute partitioning from the lipid into aqueous environment.

The rate of the passive membrane permeation may be limited by *any of the steps above* depending on the nature of the solute molecule crossing the bilayer.

Intrinsically a 3D problem:

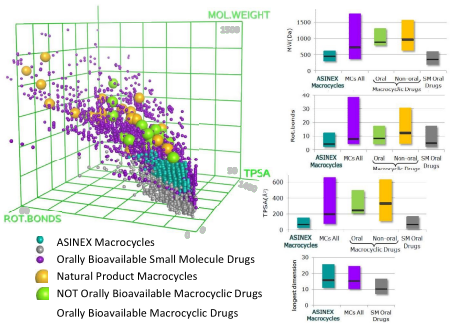
Macrocycles are known to change their 3D conformation depending on environment; for example, from water soluble, to membrane permeable, to target bound:



Water soluble | Low Dielectric Conformer | Target bound

Asinex Macrocycles:

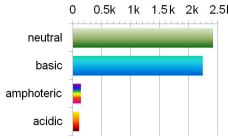
ASINEX has created a library of 32K+ diverse macrocyclic compounds using an extensive tool box of synthetic methods including but not limited to solid phase-supported synthesis, RCM, click-chemistry, and ring expansion. The resulting combinations are novel and have allowed us to generate tremendously diverse, medchem-relevant, macrocyclic frameworks.



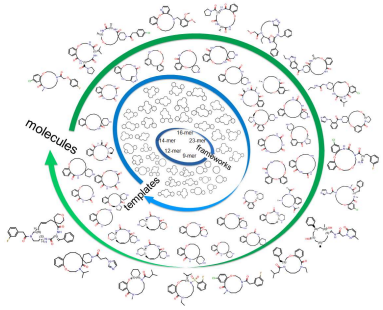
ASINEX Macrocyles tend to be larger than traditional screening molecules which makes them excellent discovery tools for targets with shallow or extended binding sites. Additionally, restricted flexibility and the ability to form intra-molecular hydrogen bonds help optimizing properties such as aqueous solubility and membrane permeability.

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 macrocyles can be divided into 4 major groups based on ability to exist in certain ionizable forms (pKa, pKb values). Two of the most well represented groups, Basic and Neutral macrocyles, were computationally analyzed to create predictive QSPR models..



Macrocycle PAMPA data set:
~ 4000 molecules
- 120 templates
- 50 frameworks
- 100s R-groups



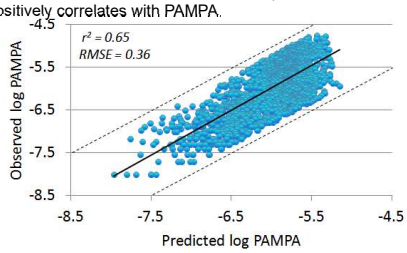
Data preparation

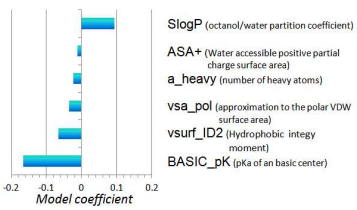
- 3D conformers have been generated using MOE's LowModeMD Method using MMFF94x Force Field with Born Solvation Model
- Low Dielectric Conformer was selected for further analysis

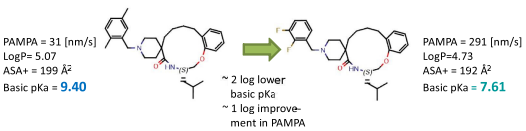
- 100s of 2D & 3D descriptors have been calculated:
  - 2D: Hueckel Theory Descriptors, Subdivided Surface Areas, Atom Counts and Bond Counts, Adjacency and Distance Matrix Descriptors, Pharmacophore Feature Descriptors, Partial Charge Descriptors
  - 3D: Surface, Volume and Shape Descriptors; Conformation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

~2,000 Basic Macrocycles

For Macrocycles with a basic group, we applied two 2D descriptors and four 3D descriptors to build a r^2=0.65 PLS model. We found that the Strength of the basic center, Hydrophobic integy moment, along with size and polar surface properties all correlate negatively with PAMPA whereas the octanol/water partition coefficient (SlogP) positively correlates with PAMPA.

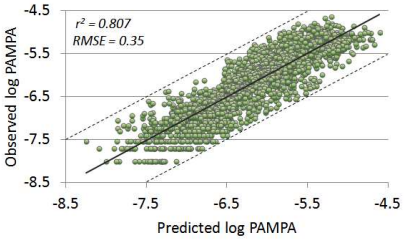


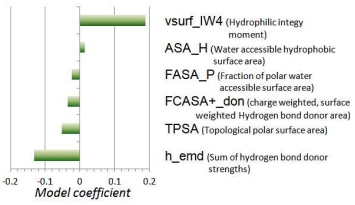


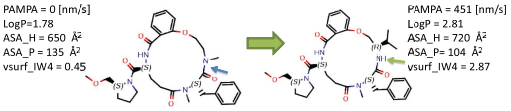


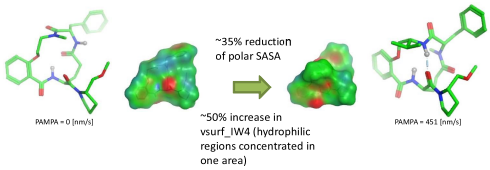
~2,000 Neutral Macrocycles

For neutral Macrocycles, we applied two 2D descriptors & four 3D descriptors to build a r^2=0.807 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 it interesting that the Hydrophilic (and also Hydrophobic) integy moments which indicate that molecules with a concentration of hydrophilic regions in only one part of the molecular surface (and consequently regions predominantly hydrophobic) have better PAMPA .









CONCLUSIONS

- Two QSPR PAMPA models are reported
- As shown before by Oja et al. [3] more predictive and simpler models for PAMPA can be derived if basic / acidic / 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 of PAMPA QSPR models that include 3D variables based on a large experimental data set.
- The proposed QSPR models can be utilized for prioritization of relatively large molecular sets, improving the quality of macrocyclic 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] Valko et al., Expert Opinion 2013; "Predictive approaches to increase absorption of compounds during lead optimization"
[2] Feller et al., Langmuir 1997; "Computer Simulation of a DPPC Phospholipid Bilayer: Structural Changes as a Function of Molecular Surface Area."
[3] Oja et al., SAR and QSAR in Environmental Research, 2016 "QSPR at various pH values for neutral and amphoteric drugs and drug-like compounds"; Oja et al., SAR and QSAR in Environmental Research, 2015 "QSPR at various pH values for acidic and basic drugs and drug-like compounds";
[4] Kancy, M. et al. *(1998) J. Med. Chem., Mar 26; 41(7):1007-10.*

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