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IAM chromatography: information provided and relevance in the prediction of permeability

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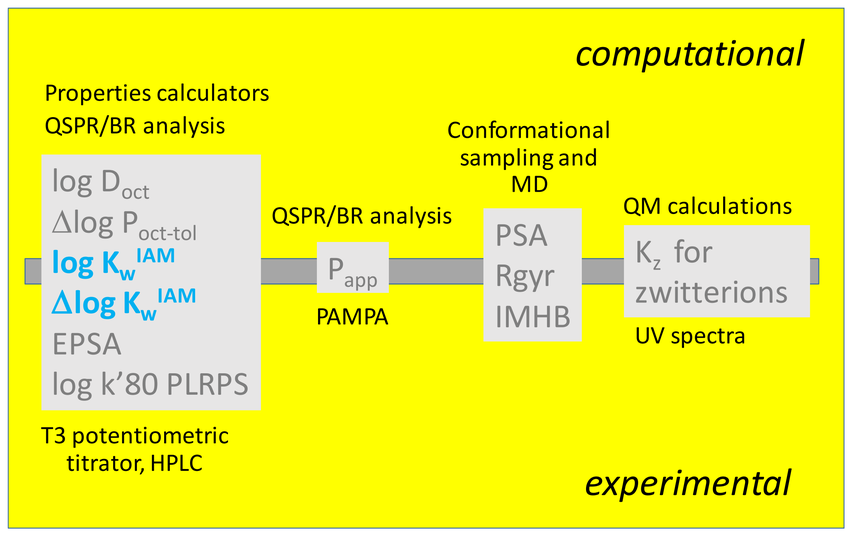
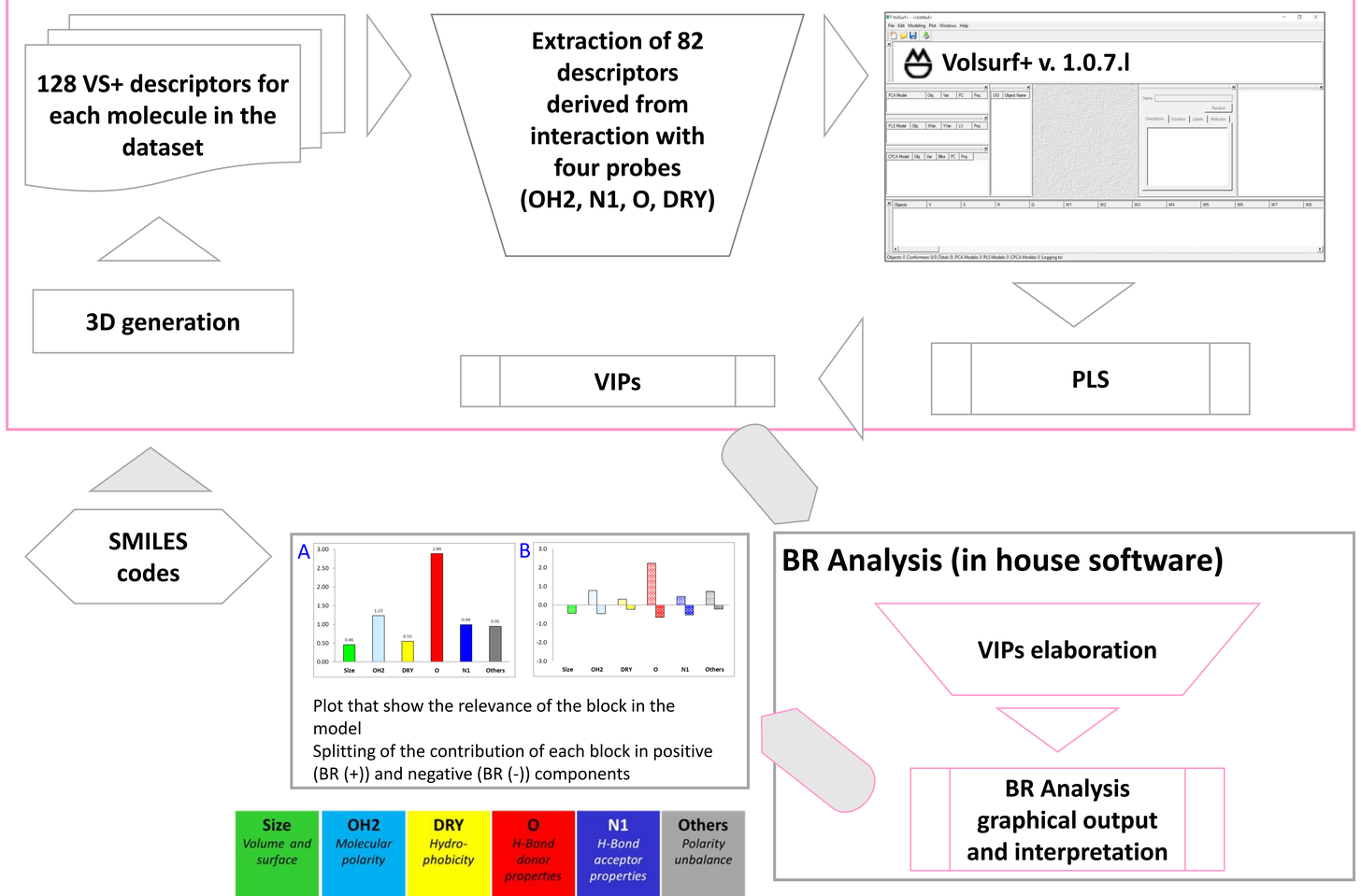


In silico method: BR Analysis [2, 3]



Size	OH2	DRY	O	N1	Others
Volume and surface	*Molecular polarity*	*Hydro-phobicity*	*H-Bond donor properties*	*H-Bond acceptor properties*	*Polarity unbalance*
molecular hydrophobic interaction with the system mainly of entropic nature	mostly the enthalpic contribution to solvation	the enthalpic and the entropic contribution to solvation	specific HB interactions between solute and system	specific HB interactions between solute and system	difference in interactions of solutes and system due to different location of polar and apolar regions

Setting the scene

The interest for IAM (Immobilized Artificial Membranes) chromatography in the prediction of drug permeability is increasing [1].

Here we firstly collected IAM.PC.DD2 log K^W_{IAM} data for a dataset of 253 molecules.

Then we applied block relevance (BR) analysis [2, 3] to extract the relative contribution of intermolecular forces governing log K^W_{IAM} and Δlog K^W_{IAM} (a new combined descriptor [4] calculated from log K^W_{IAM}).

Finally, the relationship between log K^W_{IAM} , Δlog K^W_{IAM} and passive permeability determined in both PAMPA [5] and MDCK-LE [6] systems was looked for.

Experimental method: IAM chromatography

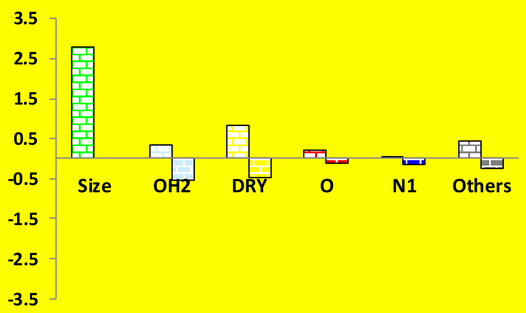
The analyses were performed at 30°C with 20 mM ammonium/acetate at pH 7.0 (when mixtures with acetonitrile at various percentages were used then extrapolation at 100% buffer was performed to obtain log K^W_{IAM}). The stationary phase was IAM.PC.DD.2. (Regis, 10cmx4.6cm 10um packing 300Å pore size). The flow rate was 1.0 ml/min.

Results

BR analysis showed that log K^W_{IAM} is mainly a descriptor of the molecular dimensions and shape whereas Δlog K^W_{IAM} mostly describes polarity of neutral compounds

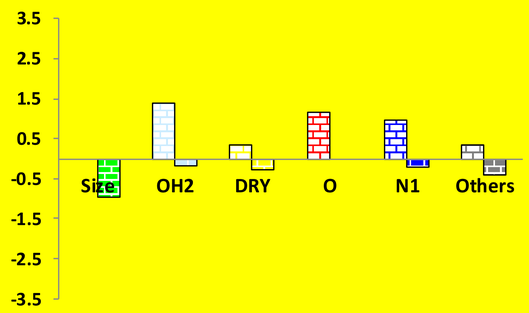
Models provided the basis for a rational application of IAM chromatography in permeability prediction.

log K_w^{IAM}



All compounds

Δlog K_w^{IAM}



Neutral compounds

PAMPA log P_{eff}

log P_{eff} = 1.67(±0.44) log K_w^{IAM} - 2.16(±0.45)*PSA -5.92(±0.33)*

N = 47, R^2 = 0.65 Q^2 = 0.59

All compounds

MDCK-LE log P_{app}

log P_{app} = -1.04(±0.17) Δlog K_w^{IAM} - 3.80(±0.20)*

N = 17, R^2 = 0.71, Q^2 = 0.62

Neutral compounds

References

[1] Tsopelas, F., *et al*., Expert Opin. Drug Discov. **2016**, 441, 1–16.
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[3] Caron, G *et al.* Mol. Pharmaceutics **2016**, 13, 1100−1110.
[4] Grumetto, L. et al. Int. J. Pharm. **2016**, 500, 275–290.
[5] Oja, M. *et a*l. SAR QSAR Environ. Res. **2016**, 27, 813–832.
[6] Varma, M. *et al*. J. Med. Chem. **2010**, 53, 1098–1108.

The poster can be downloaded from https://sites.google.com/site/cassmedchem/home