Calculation of lipophilicity for Pt(II) complexes: experimental comparison of several methods

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Goal: to compare different programs to predict logP of Pt(II) complexes and to provide new methods for on-line prediction of logP for molecules

Analyzed Methods

- CLOGP v. 5.0
- KOWWIN (on-line version)
- ALOGPS 2.1
- 3D Polar Surface Area (3D PSA):[1]

logP = -3.39 + 0.0099TSA – 0.017PSA + 0.054PtSA
n=24, R^2=0.894, RMSE=0.354

- Quantum Chem (QC DFT):[2]

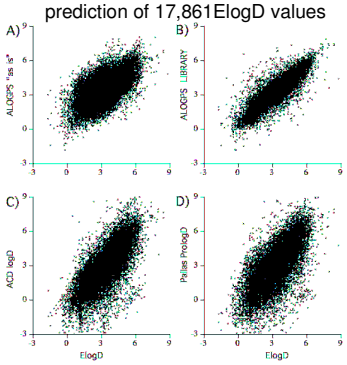
$\log P_{o/w} = 3.06 + 0.012\alpha - 0.14\mu - 9.89I_{S,max} + 1.27\Sigma V^{-}_{S}$
n=24, R^2=0.952, RMSE=0.21

LIBRARY mode:

Corrects model predictions with nearest neighbors and it does not require to re-develop the core model

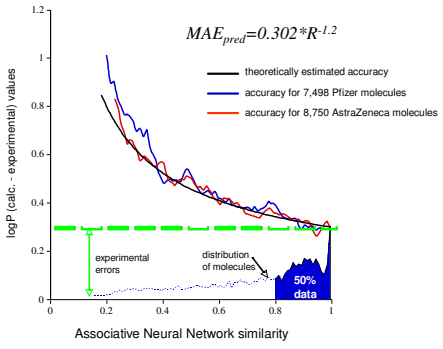
Analysis of Pfizer Dataset[3]

prediction of 17,861 ElogD values



ALOGPS "as is" -> ALOGPS LIBRARY

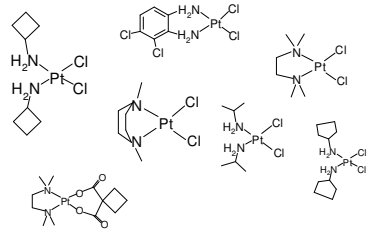
Accuracy of logP predictions[4]



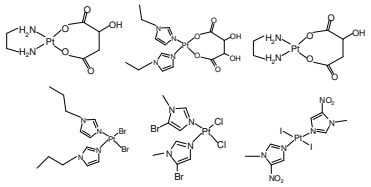
Pt(II) data/complexes

Platinum containing compounds are promising antitumor agents, but must enter cells before reaching their main biological target, namely DNA. Their distribution within the body, and hence their activity is to a large extent determined by their lipophilicity, thus there is a strong interest to develop computational methods to predict this important property

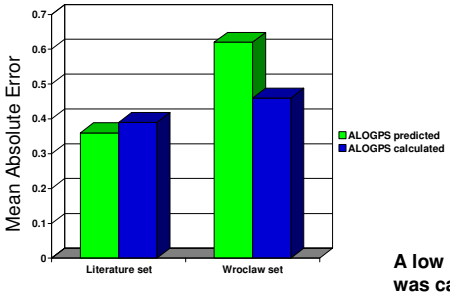
Literature set: N=43 molecules with experimental logP values were collected



Wroclaw set: N=12 new molecules were measured AFTER predictions

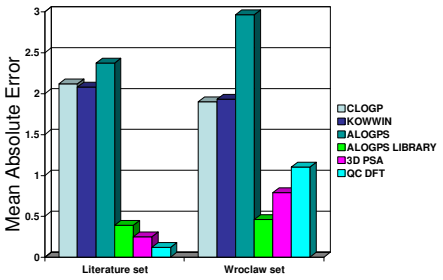


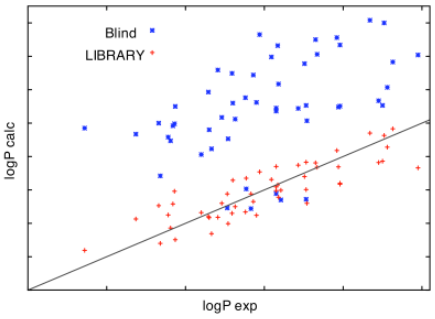
Prediction of errors



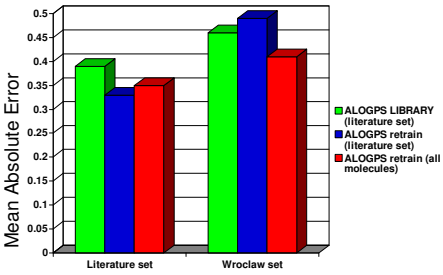
Results

Benchmarking





ALOGPS "reloaded"



Conclusions:

A low logP prediction accuracy of existing methods was calculated
ALOGPS in LIBRARY mode provided the best results and estimated the accuracy of predictions

On-line calculation + error prediction is available at:
http://www.vcclab.org/web/pt/

1) Platts, J. A.; Hibbs, D. E.; Hambley, T. W.; Hall, M. D., Calculation of the hydrophobicity of platinum drugs. J. Med. Chem. 2001, 44, (3), 472-4.
2) Platts, J. A.; Oldfield, S. P.; Reif, M. M.; Palmucci, A.; Gabano, E.; Osella, D., The RP-HPLC measurement and QSPR analysis of logP(o/w) values of several Pt(II) complexes. J. Inorg. Biochem. 2006, 100, (7), 1199-207.
3) Tetko, I. V.; Poda, G. I., Application of ALOGPS 2.1 to predict log D distribution coefficient for Pfizer proprietary compounds. J. Med. Chem. 2004, 47, (23), 5601-5604.
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