The lipophilicity mirage: logD as an endpoint in drug discovery

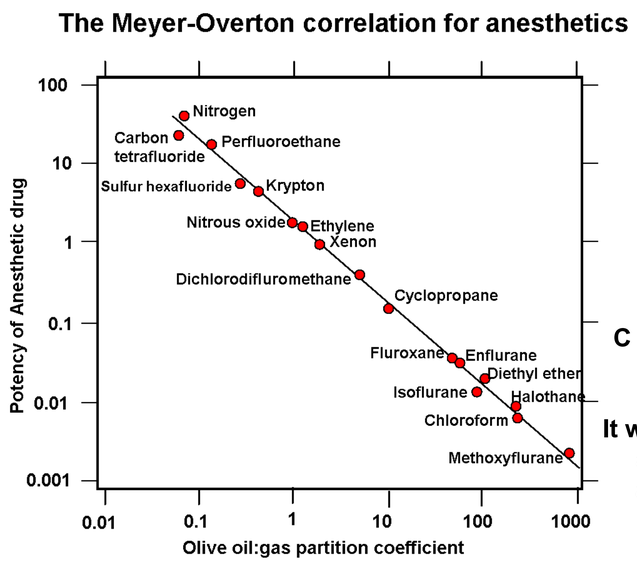
Christian Tyrchan, Fredrik Bergström, Johan Ulander

RIA Medicinal Chemistry, CVMD DMPK, CVMD Medicinal Chemistry, AstraZeneca R&D Mölndal, Sweden

(email: christian.tyrchan@astrazeneca.com, johan.ulander@astrazeneca.com)

Introduction

Several metrics and rules such as LLE or Lipinski rules incorporate lipophilicity and are often seen as valid endpoints in drug discovery, which is in fact a Fata Morgana (eng. Mirage). This italian phrase is derived from Latin meaning "fairy", from the belief that these mirages were fairy castles in the air to lure sailors to their death. These mirages distort the object which they are based on significantly, often such that the object is completely unrecognizable [1]. The use of distribution and partition coefficients to explain biological potency ranges back into the first half of the 20th century [2,3,4] and was further developed by Hansch [5]. The octanol water partition coefficient ($logD_{octanol/water}$) is defined as the logarithm of the ratio of the concentration of all ionized and un-ionized forms at a specific pH in the two phases. The conceptual simplicity and appealing correlations between $logD_{octanol/water}$ and e.g. potency and pharmacokinetic parameters has put it in focus for many discussions with tremendous impact in drug discovery.



$$\log\left(\frac{1}{C}\right) = k_i\pi + k_2\sigma + k_3$$

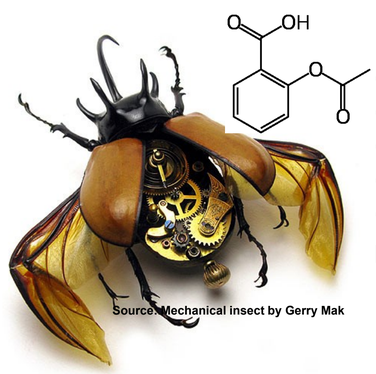
Hansch, Muir and Fujita
C is the molar concentration of compound, pi: lipophilicity, sigma: Hammett's electronic parameter;
It was noted that the prediction of the biological activity did not improved while using logP alone, but in combination with Hammett' s sigma.

Figure1: Meyer-Overton correlation with olive oil (Source: Wikipedia)

logD and the chemical potential

To identify specific interactions or highlight possible sweet spots for optimisation, a reference point needs to be defined. To account for specific interactions it has become popular to use LLE defined as –log(potency)-logD. In biological systems it is natural to use as reference the chemical potential in aqueous phase of pharmacological active compounds. Differences in logD have become a surrogate measure for the difference in the chemical potential between compounds, but the choice of $logD_{octanol/water}$ is arbitrary. Several other solvents (e.g. hexadecane, cyclohexane) or Reverse-phase high-performance liquid chromatography were used with success in the past depending on the system under research.

$$\mu_i = \mu_i^{std} + RT\ln a_i$$



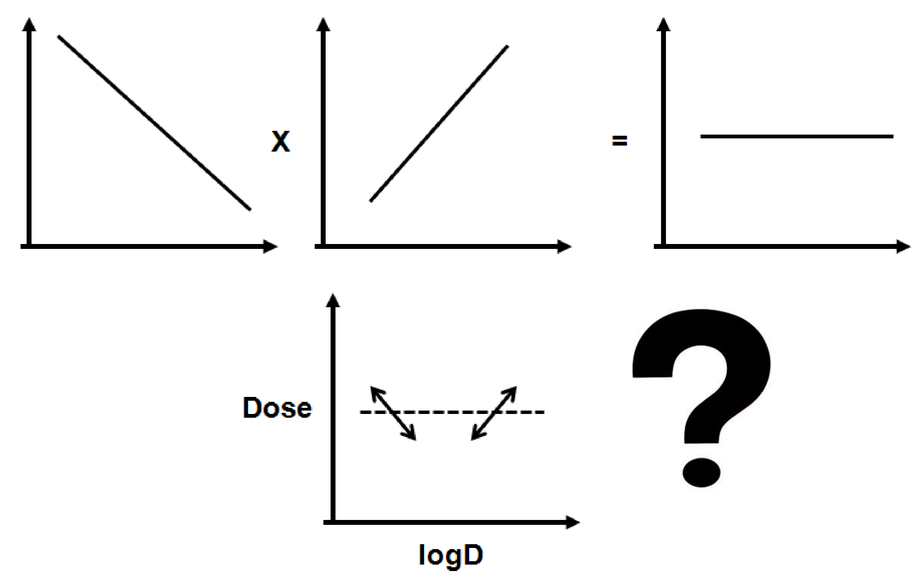
- **Chemical structure (chemical work)**
- **Electrostatics (electrical work)**
- **Concentration (osmotic work)**
- **Mass (gravitational work)**
- **Volume (work against applied pressure)**

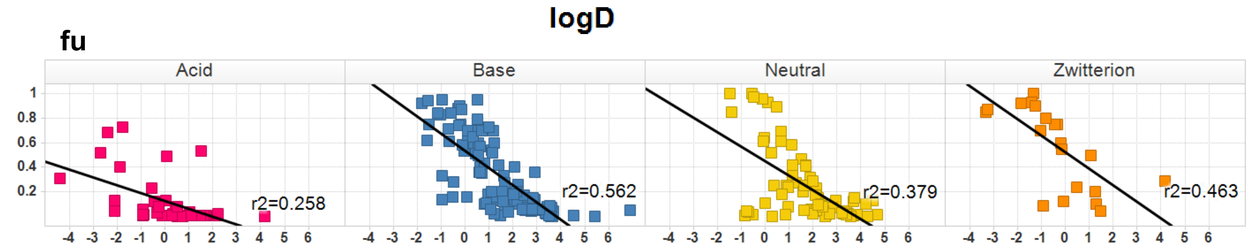
$$\log D_{\text{octanol/water}} \propto K_{\text{octanol/water}} = e^{\frac{\mu_{j,\text{water}}^{std} - \mu_{j,\text{octanol}}^{std}}{RT}}$$

logD and dose related parameters

Lipophilicity can be strongly correlated to physico-chemical parameters like solubility or permeability which are related to bioavailability. The same is true for the most important complex endpoint in medicinal chemistry the dose to man. logD may influence simultaneously in a non-linear way all dose dependent parameters such as potency, clearance (CL), fraction unbound (fu) and volume of distribution (Vss). Any optimisation strategy based on bulk properties such as logD does not capture the underlying complexity [6,7].

$$Dose \sim \frac{IC50_u \bullet Cl\,\text{int}_u}{f_{abs}} \qquad Halflife_{(t_{1/2})} = \ln(2)\cdot\frac{V}{CL}$$





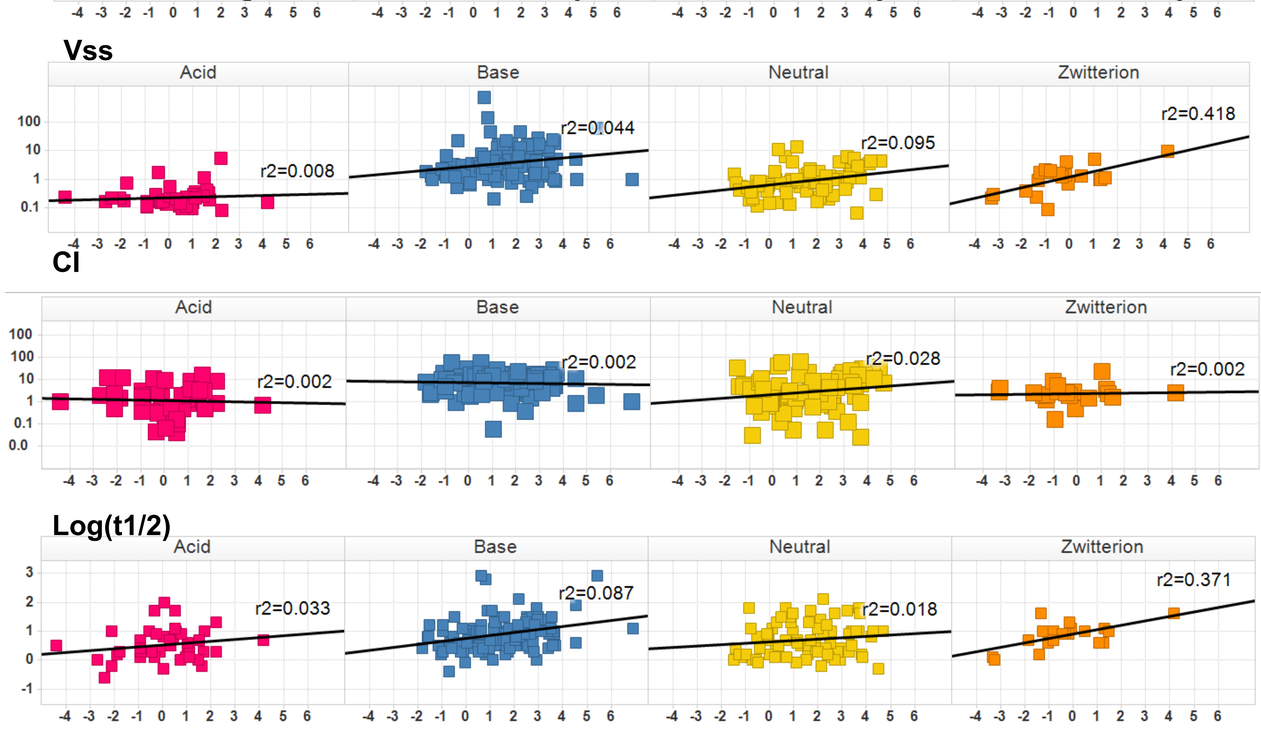


Figure2: Correlation of $logD_{octanol/water}$ measured with shake flask for 246 compounds with different dose relevant PK parameters [8]

Summary

The lipophilic/hydrophobic character of a molecule will influence most parameters used in drug design. This influence should be carefully studied and accounted for in interpretation of experimental signals. Failure to do so will lead to driving design on non-relevant signals.

Therefore it should not be expected to find linear correlations of logD to complex, composite parameters. Bulk properties such as logD does not capture the underlying complexity and the net contribution of lipophilicity to in-vivo endpoints can be considerably smaller than often assumed.

With LLE as one way to attempt to separate bulk effects from more relevant specific signals, the choice of octanol as reference system and pIC50-values should be used with care and specific limits are to be avoided.

References

[1] Wikipedia, http://en.wikipedia.org/wiki/Fata_Morgana_(mirage), Feb. 2014.
[2] Overton E. Studien ueber die Narkose; Jena: Gustav Fischer Verlag, Germany, 1901.
[3] Meyer H. Zur Theorie der Alkoholnarkose, Arch Exp Pathol Pharmakol, 1899, 42, 109-118.
[4] Fieser L., Ettlinger M., Fawaz G. Naphthoquinone Antimalarials; Distribution between Organic Solvents and Aqueous Buffers, J. Am. Chem. Soc., 1948, 70, 3228– 3232.
[5] Hansch C., Maloney P., Fujita T., Muir R. Correlation of Biological Activity of Phenoxyacetic Acids with Hammett Substituent Constants and Partition Coefficients, Nature, 1962, 194, 178– 180.
[6] van de Waterbeemd H., Smith D.A., Barry C.J. Lipophilicity in PK design: methyl, ethyl, futile, J. Computer-Aided Molecular Design, 2001, 15, 273-286.
[7] Grime K. H., Barton P., and McGinnity D. F. Application of In Silico, In Vitro and Preclinical Pharmacokinetic Data for the Effective and Efficient Prediction of Human Pharmacokinetics, Molecular Pharmaceutics, 2013, 10(4), 1191-1206.
[8] Obach R.S., Lombardo F., Waters N.J. Trend Analysis of a Database of Intravenous Pharmacokinetic Parameters in Humans for 670 Drug Compounds, Drug Metabolism and Disposition, 2008, 36(7), 1385-1405.

AstraZeneca