PROCEEDING

Determination of solute lipophilicity by reversed-phase high-performance liquid chromatography (RP-HPLC)

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Abstract : Lipophilicity was evaluated by the high-throughput RP-HPLC method. A set of 40 solutes with well-defined solvatochromic parameters were selected in this study. The chromatographic results show that, under the conditions of study, the lipophilicity index log k_w was highly correlated with the experimental log P_{oct}. J. Med. Invest. 52Suppl. :293-294, November, 2005

Keywords **:** *lipophilicity, log k_w, log P_{oct}, LC*

THE IMPORTANCE OF LIPOPHILICITY

Lipophilicity is well-known as a prime physicochemical descriptor of xenobiotics with relevance to their biological properties. It plays an essential role in the control of pharmacokinetic and pharmacodynamic properties of drugs. Lipophilicity is mostly defined in terms of the 1-octanol/water partition coefficient (log P_{oct}).

Recent advances in automated synthesis and combinatorial chemistry have led to the production of a vast number of potential drug candidates. The vital role of lipophilicity in ADMET (absorption, distribution, metabolism, elimination and toxicity) predictions has been demonstrated by the early identification of potential pharmacokinetic problems. The high throughput methods to measure lipophilicity parameters are highly demanded in modern drug development.

The reversed-phase HPLC is a very popular surrogate to the traditional shake-flask method in log P_{oct} measurement due to its high-throughput, small amount of solutes needed and a wide applicable range (1). In this method, the lipophilicity index is derived from the retention factor log k. The extrapolated log k_w values (at 100% water as mobile phase) was used as the lipophilicity parameter. Currently the main limitation of the RP-HPLC method is that it can only predict log P_{oct} for structurally related compounds (2, 3). It is a very big challenge to find the optimal stationary and mobile phase conditions in order to predict log P_{oct} for a wide range of noncongeneric compounds.

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THE RESULT OF THIS STUDY

In this study, we investigated log P_{oct} measurement on a novel RP-HPLC stationary phase, namely Discovery-RP-Amide-C 16 phase. A set of 40 model solutes and drugs with well-defined solvatochromic parameters were selected to allow a broad distribution of property spaces. Linear solvation free-energy relationship (LSER) analyses have shown that the retention of the solutes under the experimental conditions and partitioning in 1-octanol/water are controlled by the same balance of intermolecular forces (van der Waals volume V_w, H-bond acceptor basicity β and dipolarity/polarizability π^*) as reflected by equations 1 and 2.

$\log k_w = 2.57 \bullet 10^{-2} (\pm 0.46 \bullet 10^{-2}) \bullet V_w - 0.46 (\pm 0.45) \bullet \pi^* - 2.59 (\pm 0.58) \bullet \beta + 0.29 (\pm 0.64) \bullet \alpha - 0.17 (\pm 0.64)$ (1)

$n=40$; $q^2=0.86$; $r^2=0.88$; $s=0.50$; $F=62$

$\log P_{oct} = 2.43 \bullet 10^{-2} (\pm 0.42 \bullet 10^{-2}) \bullet V_w - 0.43 (\pm 0.40) \bullet \pi^* - 2.40 (\pm 0.52) \bullet \beta + 0.01 (\pm 0.64) \bullet \alpha + 0.38 (\pm 0.57)$ (2)

$n=40$; $q^2=0.87$; $r^2=0.88$; $s=0.45$; $F=64$

As a result, the chromatographic lipophilicity index log k_w obtained from this stationary phase was highly correlated with the experimental log P_{oct} values (equation 3 and Figure 1).

$\log P_{oct}=0.90 (\pm 0.06) \log k_w + 0.54 (\pm 0.12)$ (3)

$n=40$; $q^2=0.96$; $r^2=0.97$; $s=0.22$; $F=1267$

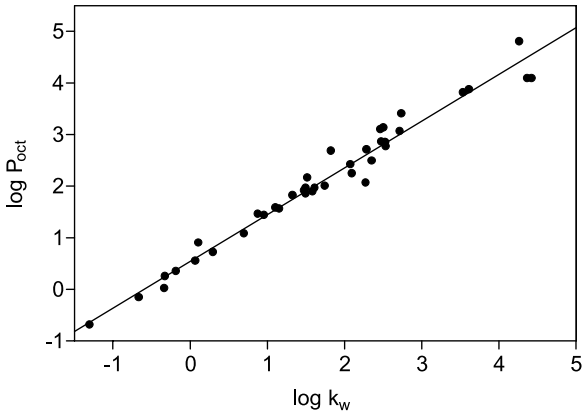

Figure 1 Relationship between log P_{oct} and log k_w obtained from Discovery-RP-Amide-C16 stationary phase.

A test set of 25 drugs and flavonoids with a broad structural diversity was used to validate the log k_w/log P_{oct} relationship. The validation equation is shown by equation 4.

$\log P_{oct}=1.04 (\pm 0.02) \log P$ (est. From log k_w) $-0.07 (\pm 0.04)$ (4)

$n=25$; $q^2=0.99$; $r^2=0.99$; $s=0.07$; $F=8465$

The results obtained from this study implies that the RP-HPLC method is very promising to derive log P_{oct} values for wide range of compounds, including drugs and nutritional compounds.

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