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# Lipophilicity and Related Molecular Properties as Determinants of Pharmacokinetic Behaviour

Bernard Testa[a]*, Giulia Caron[b], Patrizia Crivori[a], Sébastien Rey[a], Marianne Reist[a], and Pierre Alain Carrupt[a]

*Abstract*: This minireview presents some recent work, mainly from the authors' laboratory, aimed at improving the interpretability and predictivity of structure-pharmacokinetic relationships. The first part of the text discusses the intermolecular forces and intramolecular interactions encoded in lipophilicity, with emphasis on the hydrogen-bonding capacity of bioactive compounds. Three-dimensional molecular fields provide a most informative and relevant description of molecular structure and properties, particularly the Molecular Lipophilicity Potential (MLP) and our novel Molecular Hydrogen Bonding Potentials (MHBPs), both of which are computed from experimentally derived atomic increments.

The second part of the paper discusses selected structure-pharmacokinetic relations, illustrating how permeation processes are influenced by the H-bonding capacity of permeants. Thus, lipophilicity-derived H-bonding parameters are found to correlate with skin permeation and brain penetration. Similarly, the donor MHBP provides a promising correlation with oral absorption data in humans.

Although structure-metabolism relations are not discussed here, we summarise investigations showing how metabolic N-oxygenation modifies the physicochemical properties of pyridines and tertiary arylalkylamines, and hence may influence their distribution and excretion.

**Keywords**: Hydrogen bonding capacity · Intramolecular interactions · Intermolecular forces · Lipophilicity · Pharmaceutical chemistry · Pharmacokinetic behaviour

## 1. Introduction

For decades, biological activity was equated almost exclusively with a *pharmacodynamic (PD) response*, *i.e.* the effects elicited in a biological system by a drug or any other xenobiotic. These effects include among others perturbation of membrane function, activation (agonism) or blockade (antagonism) of receptors, inhibition or induction of enzymes, binding to nucleic acids, stimulation or blockade of a functional biological response, and all manifestations of toxicity.

*Correspondence: Prof. B. Testa[a]
Tel.: +41 21 692 45 21
Fax: +41 21 692 45 25
E-Mail: bernard.testa@ict.unil.ch
[a]Institut de Chimie thérapeutique
Ecole Romande de Pharmacie
Université de Lausanne
CH-1015 Lausanne
[b]Dipartimento di Scienza e Tecnologia del Farmaco
Università di Torino
Via P. Giuria 9
I-10125 Torino, Italy

Progressively, the notion of biological response has been expanded to include also the *pharmacokinetic (PK) response*, *i.e.* all effects and influences a biological system exerts on a xenobiotic [1–3].

- At the *molecular level*, the pharmacokinetic response includes a) low-energy processes such as membrane permeation, reversible binding to circulating and tissular macromolecules, and uptake by transporters, and b) high-energy processes involving the cleavage and formation of covalent bonds, in other words biotransformation (metabolism) to form reactive or stable metabolites.
- At the *organismic level*, the pharmacokinetic response comprises all processes of drug disposition, namely absorption, distribution, storage, metabolism (chemical elimination) and excretion (physical elimination).

For many years, these effects have remained a lesser explored territory of drug design. Recently however, the new armamentarium of drug discovery (combinatorial chemistry, high-throughput screening, molecular modelling, rational drug design, *etc.*) has shifted the bottleneck of drug research from hit and lead discovery to lead optimisation, and more specifically to pharmacokinetic lead optimisation. As a result of this (r)evolution, medicinal chemists now find themselves trying to relate molecular structure to the various components of the pharmacokinetic response, just to discover that what the body does to a drug can be just as varied and complex as what a drug does to the body [4].

In this minireview, we focus on some *relevant physicochemical properties*, and then illustrate how they relate to *pharmacokinetic responses*. Only a few processes of absorption and distribution are considered here. More extensive treatments can be found elsewhere [2][5]. The influence of metabolic oxidation on physicochemical properties is exemplified, but the essentially unsolved problem of pre-

dicting biotransformation is left entirely aside [6].

## 2. Lipophilicity and the Structural Information it Encodes

As exemplified in Section 4, lipophilicity is a molecular property influencing the pharmacokinetic behaviour and pharmacodynamic properties of many classes of drugs [2]. Among the different lipophilicity descriptors, partition coefficients are of particular significance in drug design not only because they allow empirical correlations with many biological data, but also because they encode a wealth of structural information [7]. In this article, the focus is on the structural factors that are expressed in lipophilicity, and how this information can be unveiled to gain insight into structure-disposition relations.

### 2.1. *Intermolecular Forces Expressed in Lipophilicity*

As a ratio of two concentrations at equilibrium, the partition coefficient (expressed as log P) is the net result of all intermolecular forces linking a solute and the two phases between which it partitions. When a given type of interaction elicited by the solute, say H-bond donation, is of equal energy in the two solvents, the two contributions will compensate each other and log P will contain no information about this type of interaction.

The factorisation of log P based on the so-called *solvatochromic parameters* offers a particularly informative interpretation of lipophilicity [8][9]. The major such parameters are:

- $\pi^*$, a measure of the solute's dipolarity/polarisability (orientation and induction forces);
- $\alpha$ and $\beta$, the solute's H-bond donor acidity and H-bond acceptor basicity, respectively;
- in addition to $\pi^*$, $\alpha$ and $\beta$, analyses of this type require a steric parameter such as the molar or molecular volume (V) to assess the solute's capacity to elicit non-polar interactions (*i.e.* hydrophobic bonds, and to some extent dispersive forces).

For example, the octanol/water and the heptane/water partition coefficients can be expressed as shown in Eqn. 1 and Eqn. 2 [8].

As a result of equations of this type, it is now common to factorise lipophilicity into two sets of terms, namely non-polar terms positively related to lipophilicity, and polar terms negatively related to lipophilicity [10] (Eqn. 3).

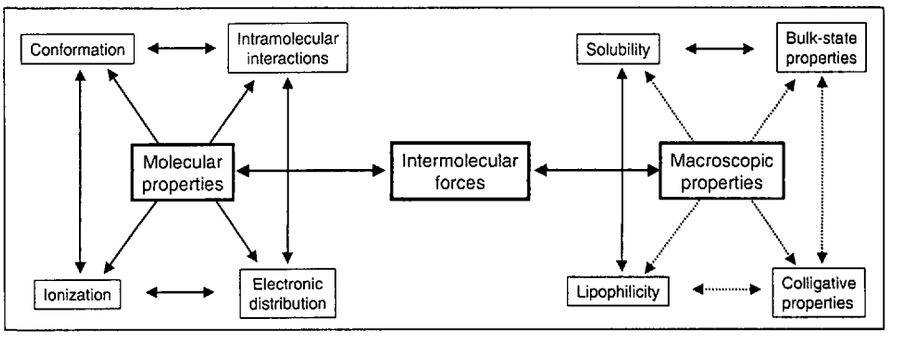


Fig. 1. Intermolecular forces as interface between molecular properties and macroscopic properties. The molecular properties are fully intertwined and mutually influence each other. The properties encountered at the macroscopic level are meaningless at the level of single molecules; they are for example bulk-phase properties (*e.g.* boiling point, melting point, and crystal properties), collogative properties (*i.e.* concentration-dependent properties of solutions, *e.g.* viscosity and vapour tension), solubility and hydration, and lipophilicity. Direct interdependence is indicated by fully arrows, indirect dependence by dotted arrows.

Since the contributions of the volume term in Eqn. 1 and 2 are similar, the difference log $P_{octanol}$ minus log $P_{heptane}$ (noted $\Delta\log P_{oct-hep}$) is a function of the polar terms only, and in fact mostly of the H-bonding donor acidity ($\alpha$) (Eqn. 4 and 5):

The $\Delta\log P$ parameter has found valuable applications in quantitative structure-permeation relationship studies, *e.g.* in relating percutaneous penetration to lipophilicity and H-bonding capacity (Section 4) [2].

### 2.2. *Molecular Factors Influencing Lipophilicity*

Lipophilicity is markedly influenced by a number of *molecular states and structural factors* such as:

- ionisation state,
- conformational and tautomeric states,
- positional isomerism,
- diastereomerism.

Furthermore, the influence of molecular states and structural factors on lipophilicity is itself strongly modulated by *intramolecular interactions* [11], *e.g.*:

- electronic conjugations in aromatic systems and across aliphatic segments,
- proximity effects between polar groups [12], internal H-bonds, internal ionic bonds, and hydrophilic folding,
- steric/hydrophobic effects, such as shielding of polar groups, hydrophobic interactions, and hydrophobic collapse [13].

Such interdependence is schematised in Fig. 1.

$$\log P_{octanol} = 5.83\ (\pm 0.53) \cdot V/100 - 0.74\ (\pm 0.31) \cdot \pi^* - 3.51\ (\pm 0.38) \cdot \beta - 0.15\ (\pm 0.23) \cdot \alpha - 0.02\ (\pm 0.34) \quad \text{(Eqn. 1)}$$

$n = 78;\ r^2 = 0.92;\ s = 0.30;\ F = 248$

$$\log P_{heptane} = 6.78\ (\pm 0.69) \cdot V/100 - 1.02\ (\pm 0.39) \cdot \pi^* - 5.35\ (\pm 0.50) \cdot \beta - 3.54\ (\pm 0.30) \cdot \alpha - 0.06\ (\pm 0.43) \quad \text{(Eqn. 2)}$$

$n = 75;\ r^2 = 0.96;\ s = 0.36;\ F = 438$

$$\text{Lipophilicity} = \text{Hydrophobicity} - \text{Polarity} \quad \text{(Eqn. 3)}$$

$$\Delta\log P_{oct-hep} = 0.12\ (\pm 0.30) \cdot \pi^* + 1.96\ (\pm 0.42) \cdot \beta + 3.40\ (\pm 0.25) \cdot \alpha - 0.43\ (\pm 0.27) \quad \text{(Eqn. 4)}$$

$n = 75;\ r^2 = 0.92;\ s = 0.310;\ F = 288$

$$\Delta\log P_{oct-hep} = 3.54\ (\pm 0.36) \cdot \alpha - 0.37\ (\pm 0.15) \quad \text{(Eqn. 5)}$$

$n = 75;\ r^2 = 0.84;\ s = 0.45;\ F = 325$

$$\log K_p = -1.46\ (\pm 0.23) \cdot \Delta\log P + 0.29\ (\pm 0.14) \cdot \log P - 3.75\ (\pm 0.61) \quad \text{(Eqn. 6)}$$

$n = 21;\ r^2 = 0.91;\ s = 0.35$

$$\log (C_{brain}/C_{plasma}) = -0.48\ (\pm 0.16) \cdot \Delta\log P_{oct-cyc} + 0.89\ (\pm 0.50) \quad \text{(Eqn. 7)}$$

$n = 20;\ r^2 = 0.69;\ s = 0.44$

$$MLP_k = \sum_{i=1}^{N} f_i \bullet fct(d_{ik})$$

*where*

| | |
|---|---|
| ***k*** | a given point in space |
| ***i*** | a given molecular fragment |
| ***N*** | the total number of fragments in the molecule |
| $f_i$ | the lipophilic increment of fragment *i* |
| ***fct*** | a distance function |
| $d_{ik}$ | the distance between fragment *i* and point *k* |

$$MHBP_k = \sum_{i=1}^{N} f_i \bullet fct(d_{ik}) \bullet f(U)$$

*where*

| | |
|---|---|
| ***k*** | a given point in space |
| ***i*** | a given molecular fragment |
| ***N*** | the total number of fragments in the molecule |
| $f_i$ | the HB increment of fragment *i* |
| ***fct*** | a distance function |
| $d_{ik}$ | the distance between fragment *i* and point *k* |
| ***f(U)*** | the angular function |

Fig. 2. Mathematical definition of the Molecular Lipophilicity Potential (MLP, left panel) and the Molecular Hydrogen Bonding Potentials (MHBPs, right panel).

## 3. Molecular fields

Over the years, molecular fields and calculated molecular surface properties have gained ever increased significance in describing pharmacologically relevant molecular properties and behaviour, since they determine how the compound is perceived by its molecular environment. In addition, because of the 3D nature of molecular fields, most of them have been interfaced with algorithms for conformational analysis. In this way it becomes possible to identify families of conformers according to their surface properties (lipophilicity, polarity or H-bonding properties), an approach of distinct interest to rationalise the PD and PK behaviour of flexible drugs.

The best known molecular fields are the *Molecular Electrostatic Potentials* (MEPs), whose interest in modelling electrostatic recognition forces and pharmacophores is well recognised [14]. More complex fields encode information on intermolecular forces obtained by various probes. This is the case with GRID [15][16], which uses probes for hydration, H-bonding, hydrophobicity and other forces.

The *Molecular Lipophilicity Potential* (MLP) created a few years ago in our laboratory is not computed from probes, but from experimentally derived atomic increments to lipophilicity [17]. As a result, it expresses the same entropic component as log P values. One of the major interests of the MLP is that it allows the back-calculation of log P values. And because these calculated log P values are sensitive to the 3D geometry of the molecule, the MLP coupled with an effective method to map conformational spaces (*e.g.* molecular dynamics) allows the virtual lipophilicity of conformers and the lipophilicity range of a solute to be calculated [17].

The information content of the MLP being the same as that of lipophilicity (Section 2), it may fail to yield unambiguous information on the intermolecular forces influencing a given PK response. For this reason, and given the known role of H-bonding in determining membrane permeation, we have recently developed *Molecular Hydrogen Bonding Potentials* (MHBPs) using the same strategy as the MLP [18]. Basically, two components are needed to calculate the MLP as shown in Fig. 2, namely a fragmental system and a distance function. To calculate the MHBPs, an angular function must be added as a third component to take into account the directionality of H-bonds. And to distinguish between H-bond donation and H-bond acceptance, two Molecular Hydrogen-Bonding Potentials have been created, namely a donor potential ($MHBP_{do}$) and an acceptor potential ($MHBP_{ac}$). An application is reported below.

## 4. Applications to Structure-Disposition Relations

A few examples of structure-disposition relations are reported below. Whereas their explicative capacity seems clear, their extrapolative and predictive value should honestly be recognised for what it is, namely modest.

### 4.1. *Lipophilicity Parameters Related to Skin Permeability*

Skin permeability is an active front of pharmaceutical research, transdermal delivery being investigated as an alternative route of administration. There are indeed a number of drugs and therapeutic situations for which non-invasive parenteral administration can afford some ready benefits. In an opposite perspective, skin absorption of industrial and environmental toxins can be highly detrimental and should be prevented. There is therefore a great need to reach a better understanding of the molecular and structural factors that facilitate or hinder the cutaneous penetration of drugs and other xenobiotics [19][20].

In most published studies, quantitative structure-penetration relationships remain of limited scope and predictive value. Thus, the permeability coefficient through excised human skin or nude mouse skin showed fair linear correlations with log P ($r^2$ ranging approximately from 0.7 to 0.9), but only within well-defined chemical series of compounds (*e.g. n*-alkanols, steroids) [21–25]. In contrast, no correlation between skin permeability and log P were found when *n*-alkanols and steroids were examined together. However, $\Delta\log P_{oct-hep}$ yielded a fair correlation ($r^2 = 0.81$) for the two series taken together [21]. The correlation was further improved in a multiple linear relation with log P added (see Eqn. 6).

Here, there is a clear indication that skin permeation is a) markedly favoured by a low H-bond donor capacity (see Eqn. 5), and b) modestly improved by lipophilicity.

### 4.2. *MHBPs in the Prediction of Oral Absorption*

Recently, several theoretical methods have been proposed to predict oral absorption in humans, but the use of molecular fields appears to be one of the most promising ones [18]. Using a set of 20 drugs covering a wide range of values [26], we examined the relations between MHBPs and oral absorption.

The absorption values (Abs%) plotted as a function of H-bonding donor properties ($MHBP_{do}$) are shown in Fig. 3, where the $MHBP_{do}$ of each drug is that of an averaged conformer. The sigmoid represents the best statistical correlation ($r^2 = 0.86$) between absorption and $MHBP_{do}$. In contrast, no correlation was found between absorption and the H-bonding acceptor properties ($MHBP_{ac}$).

Specifically, these results indicate that the H-bond donor capacity is nega-

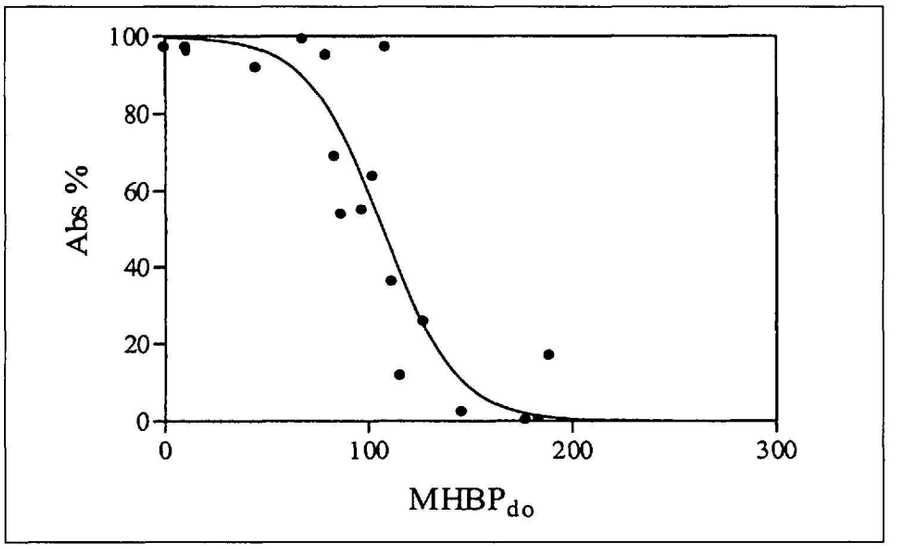


Fig. 3. Human oral absorption data for 20 compounds, taken from [26][39] and expressed as Abs%, plotted as a function of the $MHBP_{do}$.

tively related to oral absorption, whereas the H-bond acceptor capacity does not play a detectable role. More generally, this preliminary study suggests that the MHBPs might be a useful tool to assess some of the surface properties that most influence oral absorption.

### 4.3. *Blood-Brain Barrier Permeation*

For drugs acting in the central nervous system (CNS), permeation through the blood-brain barrier (BBB) is a prerequisite, whereas for other drugs brain penetration may elicit unwanted side-effects and be the cause of low patient compliance. BBB permeation is thus a major issue in drug research, to be favoured or prevented by molecular design depending on site of action [27].

Over the years, many QSAR studies have uncovered relations between CNS activity and lipophilicity. Thus, Hansch found that the ideal lipophilicity of neutral compounds for passive penetration into the brain is around 2 (log $P_{oct}$ scale) [28]. In this context, an illustrative study was carried out in adult baboons with model monofunctional compounds, showing that the more hydrophilic and lipophilic compounds had an incomplete brain extraction, whereas complete brain extraction was the rule for the compounds with a log P in the range 0.9 to 2.5 [29]. This confirms the existence of an optimal log P, or rather a range of optimal lipophilicity for BBB permeation. However, many other molecular factors influence brain penetration, *e.g.* the molecular weight and above all the H-bond donor acidity. This was revealed quite clearly by a seminal paper [30] where the *in vivo* brain penetration (ratio at steady state of brain/plasma concentration ratio) of twenty $H_2$-receptor antagonists was negatively correlated with the $\Delta\log P_{oct-cyc}$ parameter (cyc = cyclohexane) (see Eqn. 7), a parameter which contains the same structural information as the $\Delta\log P_{oct-alk}$ parameter (see Eqn. 4 and 5 above).

The above example should not be interpreted to mean that decent statistical correlations are always found in studies of this type. But even in such cases, more modest qualitative approaches can be used to model permeation. For example, the brain-penetration capacity of histamine $H_1$-antagonists was modelled with a decision tree containing the two main physicochemical parameters influencing brain penetration, namely $\log D^{7.4}_{oct}$ (*i.e.* the distribution coefficient at pH 7.4) and $\Delta\log P_{oct-alk}$ [31]. In this model the potential for brain penetration of antihistamines was first estimated from their $\log D^{7.4}_{oct}$. When this value was < 0 or > 3, penetration was negligible or hindered. For compounds with $\log D^{7.4}_{oct}$ values within the range 0 to 3, penetration could occur if the compound had a weak H-bond donor capacity ($\Delta\log P_{oct-alk} < 2$).

The two antihistamines cetirizine (**1**) and hydroxyzine (**2**) (Fig. 4) offer another example where physicochemical properties can help rationalise the PK behaviour [32][33]. Indeed, the basic hydroxyzine penetrates readily into the brain, whereas the zwitterionic cetirizine has a low brain penetration. The $pK_a$ data (Table 1) show that hydroxyzine **2** exists at physiological pH in the neutral form (50%) and as the cation (50%). In contrast, cetirizine (**1**) is present as the zwitterion (80%) and the anion (20%). The differences in $\log D^{7.4}_{oct-alk}$ (cetirizine is about 1.5 units more hydrophilic than hydroxizine) and in $\Delta\log D^{7.4}_{oct-alk}$ (one unit higher for cetirizine) are in keeping with the molecular factors influencing brain penetration, as exemplified above. Hydrophilic drugs with a high H-bond donor capacity properties have a hindered BBB permeation compared to lipophilic drugs with a low H-bond donor capacity [8][30][34][35]. Furthermore, the information obtained when comparing the lipophilicity of **1** and **2** in isotropic and anisotropic systems is worth noting. The smaller difference in $\log D^{7.4}_{lip}$ (distribution coefficient in a liposomes/water system at pH 7.4) compared to $\log D^{7.4}_{oct}$ is an indicator of the mechanism of interaction of cetirizine with biomembranes. Indeed, as confirmed by NMR studies [33], cetirizine interacts mainly by electrostatic surface forces with phospholipids rather than penetrating into the bilayer.

Table 1. Molecular properties of the antihistaminic drugs cetirizine and hydroxyzine in isotropic and anisotropic systems.

| | cetirizine | hydroxyzine |
|---|---|---|
| $pK_a$ | 2.19; 2.93; 8.00[a] | 1.75; 7.49[a] |
| $\log D^{7.4}_{oct}$ | 1.5[a] | 3.1[a] |
| $\Delta\log D^{7.4}_{oct-alk}$ | 3.1[a] | 2.2[a] |
| $\log D^{7.4}_{lip}$ | 2.46[b] | 3.13[b] |

a) From [32]. b) From [33].

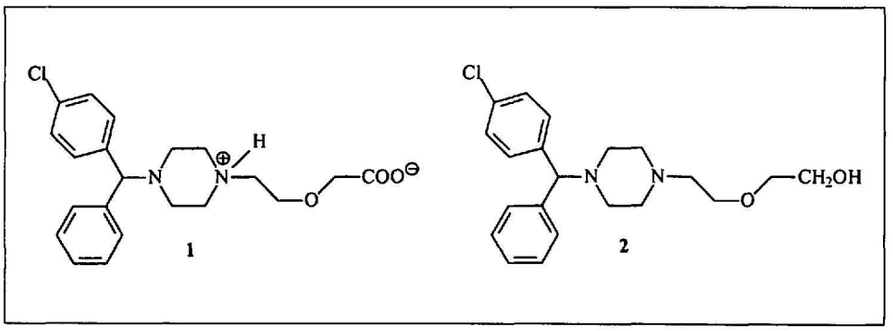


Fig. 4. Chemical structures of zwitterionic cetirizine (**1**) and neutral hydroxyzine (**2**).

### 4.4. *Systematic Studies to Unravel the Effects of Metabolic N-Oxygenation on the Lipophilicity of Tertiary Amines*

N-Oxygenation is one of the major metabolic reactions of tertiary amines [36]. From a physicochemical point of view, the transformation of the parent drug to the correspondent N-oxide is accompanied by a decrease in basicity and lipophilicity, as recently demonstrated with aromatic amines [37] and arylalkylamines [38]. Table 2 summarises the differences in apparent lipophilicity between the tertiary amines and their N-oxides shown in Fig. 5.

Table 2. Decrement in apparent lipophilicity resulting from the N-oxygenation of tertiary amines (structures in Fig. 5).

| Pairs of amines and N-oxides | *diff*(log D) [a] |
|---|---|
| 3; 3a | −1.91 |
| 4; 4a | −2.24 |
| 5; 5a | −0.87 |
| 6-9; 6a-9a | −0.66 ± 0.38 [b] |

a) Difference in log $D_{oct}$ (distribution coefficient at pH 7.4 in octanol/water) between tertiary amines and their N-oxide [37][38]. For the aromatic amines (**3**–**5**) and their N-oxides (**3a**–**5a**), log D = log P.
b) Averaged value (± SD) obtained for the four pairs of compounds reported in Fig. 5B.

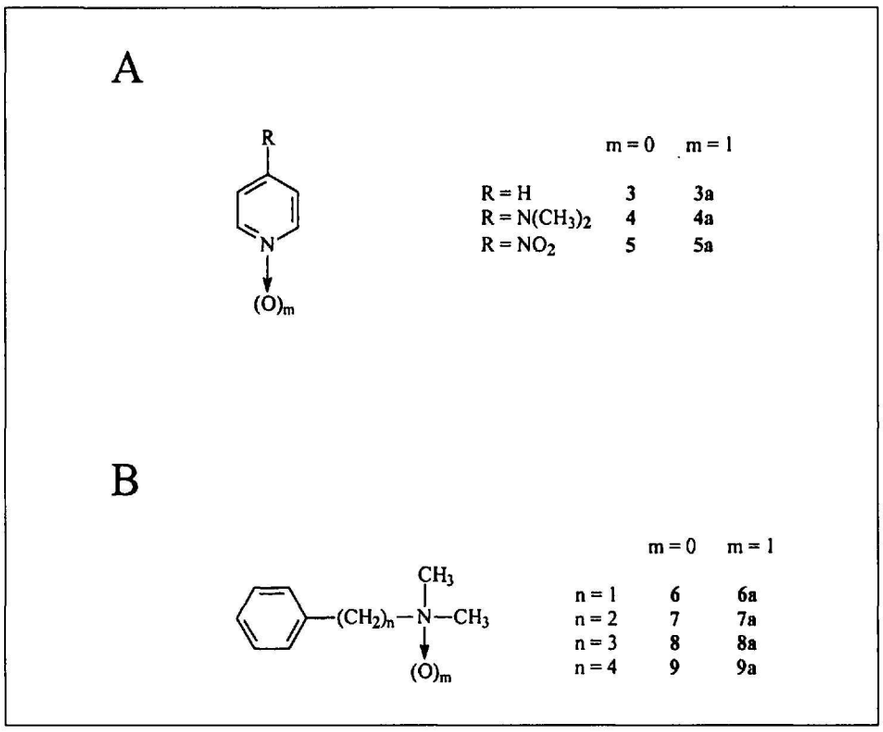


Fig. 5. Chemical structures of the tertiary amines and their N-oxides discussed in the text. A) pyridines; B) aralkyl tertiary amines.

For pyridine N-oxide compared to pyridine, the decrease in log D (equal to log P for these weakly basic amines at the pH used) was −1.91, but the presence of a *para*-substituent markedly affected this value. Indeed, the H-bond acceptor basicity of the oxygen atom has been demonstrated to be the main structural factor influencing the lipophilicity decrement, being maximal in the presence of an electron-donating substituent (compare the pair **4** and **4a** having a 4-dimethylamino substituent) and minimal for electron-withdrawing substituents (compare the pair **5** and **5a** having a 4-nitro substituent).

In contrast to pyridines, the aliphatic amines in Fig. 5B are strong bases ($pK_a$ about 9) and the decrease in lipophilicity for their N-oxides was also strongly sensitive to $pK_a$ variation [38]. The decrease in $pK_a$ resulting from N-oxygenation was close to 4.8 units and almost independent from the structure of the parent amine. The combination of decreased basicity and decreased lipophilicity resulted in decrease in apparent lipophilicity (log D) that was relatively modest and constant along the series (Table 2). These findings have pharmacokinetic implications. For aromatic N-oxides, their decreased lipophilicity and hence ease of urinary excretion will depend on the electronic effects of ring substituents. Conversely, the N-oxygenation of aliphatic tertiary amines may have a smaller effect on their urinary excretion than usually assumed.

## 5. Conclusion

The pharmacokinetic optimisation of lead compounds has become a bottleneck in drug discovery: Technology-based, empirical solutions are needed to improve the situation, but such advances cannot continue for long without parallel progress in fundamental research leading to expanded knowledge, better understanding and improved models. The complexity of interactions between foreign compounds (*e.g.* drug candidates) and biological systems is still poorly understood at a molecular and mechanistic level, not to mention the higher levels of biological regulations and resilience.

A better understanding and description of molecular properties is one of the prerequisites for progress towards structure-pharmacokinetic relationships with greater robustness, improved predictive capacity and broader interpretativity. A molecular property such as lipophilicity, and particularly lipophilicity-derived parameters, have afforded much relevant information on the recognition forces by which a chemical compound and a biological system interact. Recent avenues of research include the development of novel molecular fields such as the Molecular Hydrogen Bonding Potentials. Combined with algorithms to reduce their 3D information into 1D descriptors, these molecular fields have opened a period of fundamental and technological advances.

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