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MOLECULAR LIPOPHILICITY POTENTIAL BY CLIP, A RELIABLE TOOL FOR THE DESCRIPTION OF THE 3D DISTRIBUTION OF LIPOPHILICITY : APPLICATION TO 3-PHENYLOXAZOLIDIN-2-ONE, A PROTOTYPE SERIES OF REVERSIBLE MAO_A INHIBITORS

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Abstract : The capacity factor of eleven derivatives belonging to a prototype series of 3-phenyloxazolidin-2-one, reversible MAO inhibitors, was measured and compared to the calculated log P_{calc} using the CLIP package. We demonstrate that this Molecular Lipophilicity Potential (MLP) approach is a valuable tool to estimate log P_{calc} of such compounds.

Introduction

Since lipophilicity has been recognized of importance in QSAR,[1-3] efforts have been made to determine lipohilic indices. Log $P_{oct\text{-}water}$, the logarithm of partition coefficient in 1-octanol/water, is the most commonly used parameter for low molecular weight compounds. This parameter can either be determined experimentally or calculated.

Because experimental methods are time consuming and often enconter problems such as association, adsorption or impurity effects, computational methods are an alternative and attractive way to predict lipophilicity.

Many methods for estimating log P are reported in the litterature. The most common are classified as «fragment constant» methods[4-6] in which a structure is divided into fragments to yield a log P estimate. Recent methods utilizing properties of the entire solute (charge density, molecular surface area, volume weight, shape, and electrostatic potential) to estimate log P[7-8] have been proposed. These methods attempt to overcome various inefficiences of the fragment constant approach such as oversimplification of steric and conformational effects, the need of correction factors and the inability to estimate log P for unknown or uncorrelated fragments.

Moreover, log P values reflect only the overall lipophilicity of a molecule and consequently become insufficient when topochemical or stereochemical features are required to describe intermolecular interactions between a ligand and its target.

In order to overcome such limitations, computational methods based on the concept of Molecular Lipophilicity Potential (MLP) have been developed. Beside the fact that those methods produce good estimated values of log P, [9-11] it has also been demonstrated by the works of Audry et al., [12] Fauchere et al.[13] and Furet et al.[14] that MLP qualitatively describes the 3D distribution of lipophilicity, either in space or on molecular surfaces.

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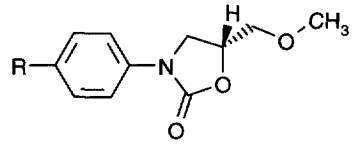
In the present work, the Molecular Lipophilicity Potential (MLP) approach developed at the University of Lausanne by the group of Testa, [11] based on the slightly modified equation by Fauchere and the atomic fragmental system of Broto and Moreau, [4] has been used to study the lipophilicity of a series of substituted 3-phenyloxazolidin-2-ones, a prototype of reversible MAO_A inhibitors.

The experimental determination of log P for this kind of compound is particularly difficult due to their low water solubility. For this reason computational methods became attractive to predict their lipophilic properties.

Eleven compounds were choosen among a series of 3-phenyloxazolidin-2-one that present differences in the size and nature of their side chain on the aromatic moeity (table 1), and for which log k_w (capacity factor) values could be obtained by reversed-phase high-performance liquid chromatography (RP-HPLC).[16-17] The experimental results obtained have been compared to the log P calculated by the MLP approach to check the reliability of the method for this type of molecules. Correlation analysis between log k_w and MAO_A affinity has also been studied to gain insight into the role played by the lipophilicity of the substituent on MAO_A inhibitor potency.



Compound	R	log k_w	log P_{calc}	K_{iA} (μM)	Vol[a] (Å^3)
1	HO-$(CH_2)_2$-	1.00	1.13	0.080	464.88
2	HO-$(CH_2)_2$-O-	1.00	0.77	0.390	479.59
3	(*RS*)-CH_3-CH(OH)-CH_2-O-	1.17	1.17	0.220	514.63
4	HO-$(CH_2)_3$-	1.30	1.27	0.0016	514.62
5	(*S*)-H_3C-CH(OH)-$(CH_2)_2$-O-	1.60	1.71	0.0065	549.67
6	(*R*)-F_3C-CH(OH)-$(CH_2)_2$-O-	2.45	2.48	0.0035	562.45
7	(*S*)-H_3C-CH(OCH_3)-$(CH_2)_2$-O-	2.21	2.70	0.170	584.71
8	HO-$(CH_2)_4$-O-	1.58	1.84	0.029	549.67
9	(*RS*)-H_3C-CH(OH)-$(CH_2)_3$-O-	1.88	2.27	0.013	584.71
10	H_3C-C(O)-$(CH_2)_2$-O-	1.43	1.37	0.046	535.21
11	H_3C-C(CH_2)-$(CH_2)_2$-O	3.08	3.03	0.028	555.54

Table 1 Chemical structures of the 3-phenyloxazolidin-2-one derivatives, capacity factor (log k_w), calculated log P_{calc} and MAO_A inhibitory potency (K_{iA}). [a]Molecular volume calculated by Savol3.[18]

Material and method.

Chromatographic capacity factor (log k_w)

The determination of the retention time t_R of the eleven 3-phenyloxazolidin-2-one derivatives was performed using a Siemens S101 chromatograph equipped with a Orlita DMP-AE 10.4 pump, a Li Chrosorb RP-18 column, a Uvikon 740 LC (λ = 254 nm) detector and a Hewlett-Packard 3390 integrator for the measurement of the peaks and the calculation of the retention time. The eluant is composed by a methanol/water mixture (the percentage of methanol varies from 70 to 20%). A methanol monolayer has been adsorbed on the stationnary phase to confer it a partially polar character similar to *n*-octanol. The capacity factor is defined according to the equation 1. Log k_w were obtained by extrapolation at 100% water[16-17] (values not directly accessible by measurement).

$$k = \frac{t_R - t_0}{t_0}$$

(Equation 1)

Geometry Optimization.

The 3D structure of compound 6 was obtained from X-ray cristallography, and those for which no X-ray data were available (1-5, 7-11) were generated by the builder module of the Insight 95.0 program (Biosym Technologies, MSI Inc.). All the geometries used for the calculation of log P_{calc} and the MLP were optimized by a three steps (Steepest Descent, Conjugate Gradient, Newton-Raphson) molecular mechanics process using the cff91 forcefield[19-20] with the Discover program version 2.9.7 (Biosym Technologies, MSI Inc.).
The calculations and the visualization of the minimized geometries were performed on a Silicon Graphics IndigoII (R4000, IRIX 5.3) computer and on IBM RS-6000 computers.

MLP and Log P calculations

MLP and log P values were calculated using CLIP program developed by the group of Testa at the University of Lausanne. This method is based on the atomic lipophilicity system of Broto and Moreau[4] with a distance function of $e^{-d/2}$. An in-house program has been used to perform the visualization of the MLP with the graphic facilities of Insight (Biosym Technologies, MSI Inc.).

Result and discussion.

Validation of the MLP approach.

The molecules included in the present study were not part of the training set used by Testa. Therefore, the application of the CLIP procedure had to be tested. This was performed on a series of eleven 3-phenyloxazolidin-2-one derivatives for wich experimental results (capacity factors log k_w) were available (Table 1).
Regression analysis was applied for correlating log k_w and log P_{calc}. The predicted log P_{calc} are listed in table 1 and are compared with the capacity factors obtained by RP-HPLC. The individual differences between experimental (log k_w) and calculated log P_{calc} were compared

according to the criteria used by Mannhold at al. to compare 14 calculation procedures for molecular lipophilicity with reliable experimental log P values obtained from literature.[21] All the differences between experiment and calculation are lower than ± 0.5 which corresponds to an acceptable value.[21]

Regression analysis substantiates the results derived from this individual comparison. Correlation coefficient is 0.92 (n = 11, s = 0.22, F = 104, Fig. 1).

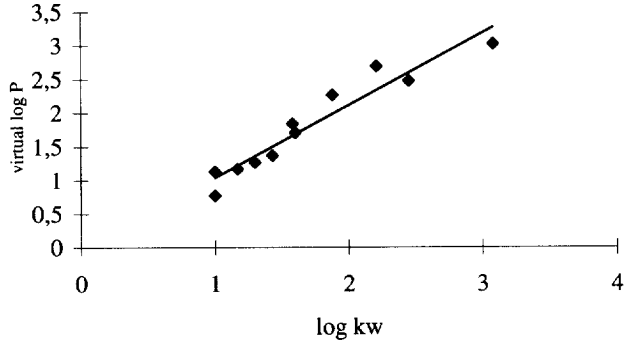


Fig. 1 Plot of log P_{calc} vs log k_w. log P = 1.08 log k_w-0.04

This result demonstrates that the CLIP approach is a valuable tool for estimating log P_{calc} values for a series of the 3-phenyloxazolidin-2-one derivatives.

Influence of lipohilicity on the MAO affinity

Structural variations between the molecules of table 1 are limited to the aryl side chain and allows to study the influence of lipophilicity interaction on MAO_A inhibitory potency of the compounds. A regression analysis has been performed to study the role played by the lipophilicity on MAO_A inhibitory potency. Regression has been done between compound having approximatively the same steric hindrance (5-11, Table 1). No correlation could be found between the lipophilicity of theses compounds and their MAO_A inhibitory activity in contrast with the results obtained with MAO_B inhibitors belonging to different families : various aryl diazoheterocyclic families (oxadiazolones, tetrazoles and oxadiazinones)[22] and 5H-indeno[1,2-c]pyridazines. [23] The representation of the MLP of two compounds (8, 11) presenting a great difference in lipophilicity (1.58 and 3.08 respectively) but having the same inhibitory potency vs MAO_A (0.029 and 0.028 μM respectively) also shows that no correlation exists between lipophilicity and MAO_A inhibitory potency of 3-phenyl-oxazolidin-2-one series (Fig. 2). This analysis revealed that lipophilicity alone is not sufficient to explain the various affinity for MAO_A. Steric and electrostatic field are under study to obtain a better model for the MAO_A inhibition of these compounds.

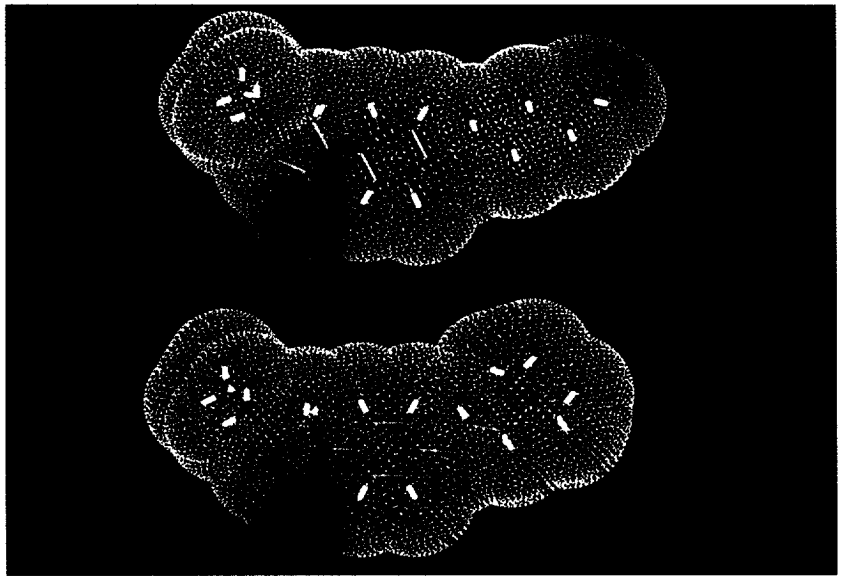


Fig. 2 Representation of the MLP generated on the solvent-accessible surface of compounds 8 (top) and 11 (bottom). Both compounds show the same inhibitory potency vs MAO_A but posses significant differences in their lipophilicity as shown by the MLP. The polar region are represented in red and the nonpolar in blue.

Conclusions.

It has been shown that the CLIP approach used in this study is a valuable tool for estimating log P_{calc} values for a set of compounds not included in the training set of CLIP and belonging to the 3-phenyloxazolidin-2-one family.

No correlation was found between lipophilicity and MAO_A inhibitory potency of 3-phenyl-oxazolidin-2-one series. In addition, MLP approach using CLIP might allow to study in more detail lipophilic properties of other chemicals series and, in particular it might help to have a better understanding of interaction of MAO_A and MAO_B inhibitors with the related enzyme.

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