HYDROPATHICITY PROFILE AND LIPOPHILICITY PREDICTION OF WB-4101 ANALOGUES

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INTRODUCTION

It's unanimously accepted that the α_1 adrenoreceptors can be classified into at least three subtypes named: α_{1a}, α_{1b} and α_{1d}. This finding has stimulated several researches to highlight the chemical properties that allow a ligand to selectively bind to one receptor subtype.
WB-4101 (1) binds with high affinity both α_1 adrenoreceptors and 5-HT1$_A$ receptors, while not showing any antagonism at α_2 adrenoreceptors.
The WB-4101 derivatives were synthesized by replacing the dimethoxyphenyl moiety with several aril groups mono- and bi-substituted.

The aim of this work was to study the lipophilicity profile of WB-4101- related compounds and to test the ability of *ILM* (*Molecular Hydropathicity Index*) approach to predict the experimental logP values.

The predicted values obtained with this computational approach were compared with the logP values calculated by other theoretical methods (fragmental and 3D surface based methods). A nearer characterization of the delicate balance that exists between hydrophilic and hydrophobic portions in these derivatives has been attempted projecting the hydropathicity local contributes on to molecular surface to provide not only a *global molecular hydropathicity index (ILM)*, but also a detailed *tridimensional mapping* of this property (2).

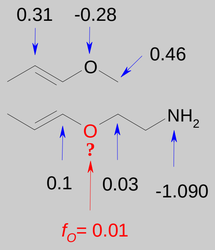
MLP CORRECTION

The virtual logP values obtained using the default MLP atomic parameters (8), have a too high an average error (ΔlogP = 0.66) compared to experimental measures. This divergence was probably due to the inaccurate parametrization of benzodioxane oxygens that are too hydrophilic and/or methoxylic oxygens that are too hydrophobic. The new benzodioxane parametrization is made comparing the experimental logP values of not-substituted benzodioxane (logP = 2.01) with tetraline (logP = 3.49) and calculating the correct oxygen atomic value with the following equation:

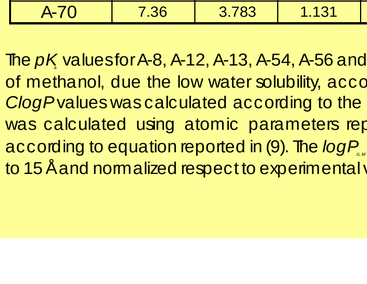
$$f(O_{Bdz}) = -\frac{\log P}{2} - \frac{2\, f(CH_2)}{2} = -0.28$$

The different contribution of benzodioxane oxygen α-substituted is obtained subtracting the already known atomic contributions from experimental logP of the A2 (logP = 1.325).

The comparison of experimental logP for A3, A8 and A10 derivatives shows that the contribution of methoxylic group is not constant and can be neglected in approximation. For this reason the oxygen atomic value is made equal to CH_3 contribution with opposite sign (f_O = -0.63).
The new parametrization gives a lower average error (ΔlogP = 0.3) and shows the good enhancement of corrected oxygen contributions.



PULSATILE BEHAVIOUR



For A3 (WB-4101) derivative was also performed a long-duration dynamic (2 nanoseconds) in water in order to highlight how evolve the solute-solvent interactions and therefore the ILM values.
The reported plot shows that the solvent-solute interactions have got a pulsatile behaviour in which the attractive and repulsive forces exchange periodically. The solute causes the movement of solvent that go away and go near with a period dependent of solute polarity. For WB-4101 compound this period is equal to 0.85 nanoseconds.

FINAL TABLE

Comparing the $logP_{neutral}$ and $logP_{ion}$, you can observe the constant difference between each pair of values. This $\Delta logP$ (2.75 ± 0.2) suggests that the contribution of protonated nitrogen is significantly independent from the whole structure.

Compound	pK_a	$logP_{neutral}$	$logP_{ion}$	ClogP	$logP_{Moreau}$	$logP_{MLP}$	$logP_{ILM}$
A-3	7.62	3.330	0.801	2.301	2.40	3.084	3.32
A-8	7.46	3.131	0.782	2.885	2.60	3.112	3.17
A-10	7.36	3.074	0.522	2.321	2.40	3.010	3.14
A-12	7.06	4.140	1.304	3.042	3.20	3.606	3.46
A-13	6.82	3.684	0.815	3.042	3.20	3.541	3.70
A-15	7.62	3.553	0.874	2.630	2.70	3.533	3.42
A-16	7.79	3.602	0.792	2.630	2.70	3.487	3.59
A-23	7.51	3.379	0.661	3.194	2.90	3.582	3.29
A-25	7.45	3.461	0.758	3.194	2.90	3.508	3.37
A-38	8.53	3.158	0.484	2.474	2.50	3.472	3.19
A-40	8.41	3.068	0.311	2.474	2.50	3.476	3.18
A-42	8.56	3.580	0.847	2.783	2.80	3.800	3.57
A-43	8.46	3.342	0.600	2.783	2.80	3.776	3.36
A-54	7.25	4.295	1.623	3.905	3.30	3.721	4.14
A-56	7.49	3.691	0.831	3.346	2.80	3.214	3.67
A-58	7.73	3.709	1.381	3.429	3.20	3.722	3.44
A-60	7.82	3.350	0.243	3.429	3.20	3.765	3.07
A-63	7.19	3.172	0.414	3.016	2.00	2.505	3.19
A-70	7.36	3.783	1.131	3.429	2.90	3.401	3.76

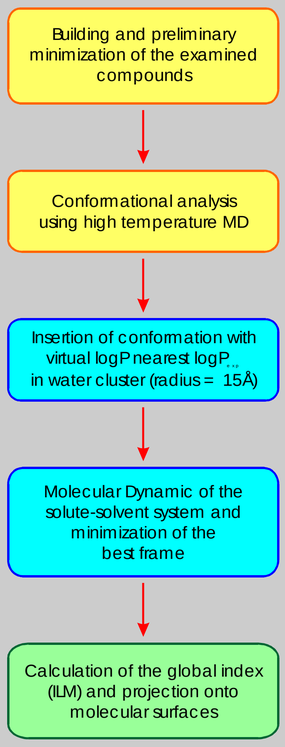
The *pK*$_a$ values for A-8, A-12, A-13, A-54, A-56 and A-58 derivatives was measured in presence of methanol, due the low water solubility, according to Yasuda-Shedlovsky approach. The *ClogP* values was calculated according to the method of Leo and Hansh (7). The $logP_{Moreau}$ was calculated using atomic parameters reported in (8). The $logP_{MLP}$ was determined according to equation reported in (9). The $logP_{ILM}$ was calculated using a cut-off radius equal to 15 Å and normalized respect to experimental values.

THE ILM APPROACH

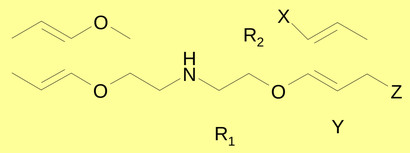
This method is based on the principle that at equilibrium the solvent molecules will be more probably found near the hydrophilic regions of the solute, while they will be repelled by the more hydrophobic moieties (3).
This allows the calculation of a global hydropathicity index (*ILM*) and this property can also be projected onto a molecular surface, giving rise to a very detailed local hydropathicity mapping. The ILM calculation comprised the correction of the values by exclusion of the contributions of the water molecules which, at the end of the simulation, were found at more than 15 Å from the solute atoms. This correction is allowed because at such a distance the sum of the contributions of the solvent tends to average out the details in the local hydropathicity profile (4).

$$ILM = \frac{d_{ij}}{n_a n_s}$$

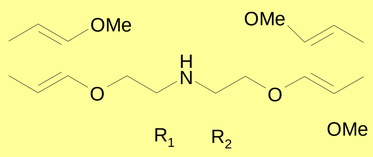
d_{ij} is the distance between the solute atom *i* and the center of mass of water molecule *j*.
N_a is the number of solute atoms and N_s is the number of water molecules.



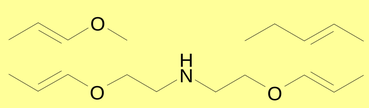
EXAMINED COMPOUNDS



Compound	*Configuration*	R_1	R_2	*X*	*Y*	*Z*
A-3 (WB4101)	R	H	H	OMe	OMe	H
A-8	R	H	H	OMe	H	H
A-10	R	H	H	OMe	H	OMe
A-15	R,R	Me	H	OMe	OMe	H
A-16	S,R	Me	H	OMe	OMe	H
A-23	S,R	Me	H	OMe	H	H
A-25	R,R	Me	H	OMe	H	H
A-54	R	H	H	SMe	H	H
A-56	R	H	H	H	H	H
A-58	S,S	H	Me	OMe	OMe	H
A-60	R,S	H	Me	OMe	OMe	H
A-61	R	H	H	CN	H	H
A-63	R	H	H	COMe	H	H
A-70	R	H	H	F	H	H



Compound	*Configuration*	R_1	R_2
A-38	R	Me	H
A-40	R	H	Me
A-42	R,R	Me	Me
A-43	R,S	Me	Me

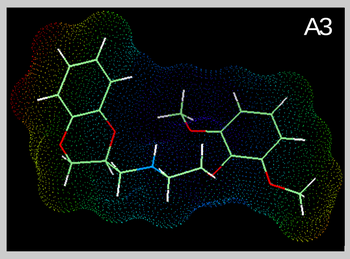


A-12 (R,R), A-13 (meso)

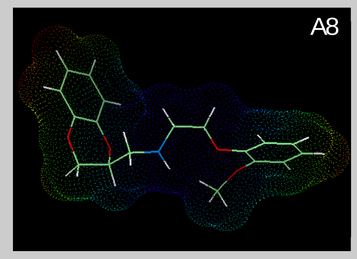
EXPERIMENTAL RESULTS

The pK_a and $logP_{octt}$ of WB-4101 related compounds were measured, using potentiometric determination with Sirius PCA-101 instrument (5). The detailed experimental method can be found elsewhere (6).
The presence of five diastereoisomers pairs in the examined compounds lets us highlight the influence of stereoisomerism on lipophilicity. The following table reports the two logP values for neutral forms with the corresponding ΔlogP for each pair. The ΔlogP values, that are significant only for the pairs A12/A13 and A58/A60, suggest that the stereoisomerism effect on logP is strictly dependent on the conformational rigidity of examined diastereoisomers.

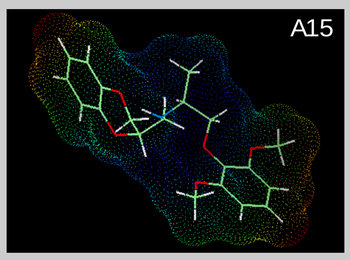
Compound	Chirality	$LogP_{neutral}$	ΔlogP
A12	R-R	4.140	0.456
A13	meso	3.684	
A15	R-R	3.553	0.049
A16	R-S	3.602	
A23	S-R	3.379	0.082
A25	R-R	3.461	
A42	R-R	3.580	0.238
A43	R-S	3.342	
A58	S-S	3.709	0.359
A60	R-S	3.350	



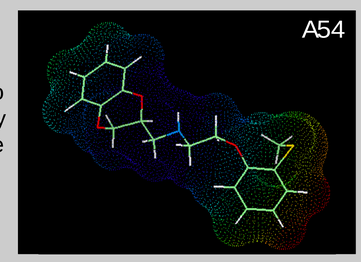
The *A3 (WB-4101)* hydropathicity surface shows that the two methoxyl groups have a different profile and the interaction between one methoxyl moiety and amino group stabilizes folded conformations.



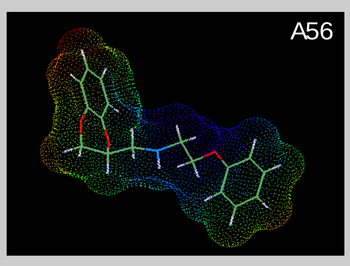
In the monosubstitued *A8* compound the methoxyl group interacts with aminic hydrogens.



The methyl derivative *A15* is less hydrophilic because this apolar group breaks the intramolecular interactions between the two aromatic moieties.



The high hydropathicity of methyltio compound *A54* is due to strong apolarity of tioether function, that increases the hydropathic profile of whole phenyl ring.



The *A56* not-substituted derivative shows a symmetrical surface with two hydropathic aromatic rings and an hydrophilic aminic core.

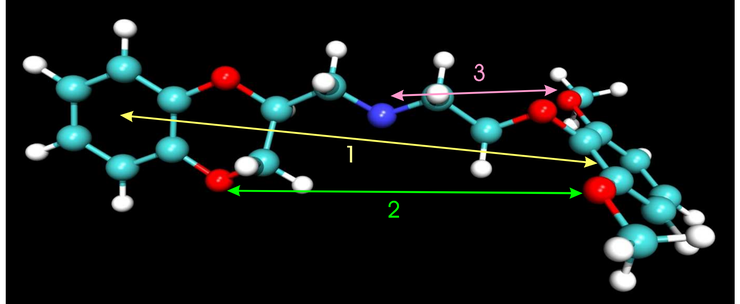
DISCUSSION

Predictive approach	ClogP	$logP_{MLP}$	$logP_{ILM}$
Average error	0.37	0.30	0.12

The average error is calculated for all examined compounds

Also considering the structural similarity of examined derivatives, the very low average error of ILM approach shows that this method is able to evaluate the dynamic behaviour of solute-solvent interaction at the equilibrium, highlighting the its influence on the partition coefficients. On the other hands, this method, based only on molecular dynamic simulations, is disconnected from knowledge of appropriate fragmental parameters.

CONFORMATIONAL PROPERTIES



The main factors that determine the conformational profile of WB-4101 derivatives are showed in this figure:

1 π-π interaction between the benzodioxane ring and the phenil Moiety;
2 electronic repulsion between the benzodioxane oxygen atoms and electron rich substituents in phenil group;
3 H-bonds between aminic hydrogen atoms and H-acceptor groups.

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