HYDROPATHICITY PROFILE AND LIPOPHILICITY PREDICTION OF WB-4101 ANALOGUES

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INTRODUCTION

It is unanimously accepted that the α-adrenergic receptor be classified into at least three subtypes: α₁a, α₁b, and α₁c. This finding has stimulated several researches highlighting the chemical properties that allow a ligand to selectively bind to each of these subtypes. WB-4101 (1) binds with high affinity both α₁a-adrenergic receptors and 5-HT₂ receptors with an antagonist profile on the latter.

The WB-4101 derivatives were synthesized by replacing the dimethylaminoethyl moiety with several side groups mono- and bis-substituted.

The aim of this work was to study the lipophilicity profile of WB-4101-related compounds and to test the ability of IM (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 (regional and 3D surface based method). A chemical correlation of the delicate balance that exists between hydrophilic and hydrophobic portions in these derivatives has been attempted by the hydropathic index. The hydropathic index contributes to molecular surface to provide not only a global molecular hydrophilic index (IM), but also a detailed intramolecular mapping of the property.

MLP CORRECTION

The virtual logP values obtained using the default MLP atomic parameters (8), have a too high an average error (logP = 0.86) compared to experimental measures. This divergence was probably due to the inaccurate parametrisation of benzodioxane oxgens that are too hydrophilic and/or hydrophobic. The new benzodioxane parametrisation is made comparing the experimental logP values of not-substituted benzodioxane (logP = 2.31) with toluene (logP = 3.45), and calculating the corrected oxygen atomic value with the following equation:

\[ \text{logP}_{\text{corr}} = \logP + \text{correction factor} \]

The correction factor was obtained by subtracting the already known atomic contributions from the value obtained using the default parameters. The correction factor was 0.27 for oxygen.

The resulted logP values obtained for all the compounds are compared with experimental data.

EXAMINED COMPOUNDS

The methyl derivative A15 is less lipophilic because the apolar group create the intramolecular interactions between the two aromatic moieties.

The A8 (WB-4101) hydrophaticy surface shows that the two methoxy groups have a different profile and the interaction between one methoxy group and amine group stabiilized their conformations.

The high hydropathicity of methyl A44 compound A44 is due to strong apolarity of the leaving function, which increases the hydropathic profile of whole phenylethyl.

The A4 not substituted derivative shows a synthetic surface with two hydrophobic aromatic rings and an hydrophobic amine core.

PULSATILE BEHAVIOUR

For A2 (WB-4101) derivative was also performed a long-dalton dynamic (2 nanoseconds) in water in order to highlight how evolve the active-silent interactions and therefore the IM values. The reported plot shows that the active-silent interactions have got a good behaviour in which the attractive and repulsive forces exchange periodically. The axile causes the movement of solvent that go away and go near with a period dependent of axile polarity; the WB 4101 compound the period is equal to 0.85 nanoseconds.

The main factors that determine the conformational profile of WB-4101 derivatives are:

1. Interaction between the benzodioxane ring and the phenylethyl.
2. Electronic effect between the benzodioxane oxygen atoms and electron-rich substituent in phenyl group.
3. Hydrophobic effect between hydrogen atoms and H-acceptor groups.

CONCLUSIONS

The method is based on the principle that at equilibrium the active molecule be more probably found near the hydrophilic regions of the active, while they will be expelled by the more hydrophobic moieties.

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

In the monosubstituted A10 compound the methoxy group interacts with amine hydrogens.

The A9 (WB-4101) hydrophaticy surface shows that the two methoxy groups have a different profile and the interaction between one methoxy group and amine group stabiilized their conformations.

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REFERENCES AND ACKNOWLEDGMENTS

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

The average error is calculated for all examined compounds.

The pH of solutions A12, A14, A16, A15 and A18 is adjusted to maintain the pKa of carboxylate, close to the water stability. According to Watson-Deshpande approach, the logarithmic pH values were calculated using atomic parameters reported in (7). The LogP was calculated as the logarithmic value of the ratio of the partition coefficient.

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