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Short communication

In silico analysis of monoamine oxidase B inhibitory activity of 8-substituted xanthine derivatives

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Introduction

The monoamine oxidase B (MAOB) is a mitochondrial enzyme that catalyzes degradation of neurotransmitter amines. MAOB inhibitors increase the dopamine levels and are frequently used as a supplement treatment of levodopa therapy in Parkinson's disease. They also exert a neuroprotective effect by reducing the excess formation of hydrogen peroxide and aldehydes that are neurotoxic (Youdim and Bakhle, 2006). In last decades there is a steady interest in the design of inhibitors by modification of naturally occurring compounds, including caffeine (Dhiman et al., 2018). Although it is a weak MAOB inhibitor, 8-substituted xanthines have shown improved inhibitory profiles (Booysen et al., 2011). In the current study we developed quantitative structure-activity relationships (QSAR), based on literature data for MAOB inhibitory properties of 95 derivatives (Mostert et al., 2012; Okaecwe et al., 2012; Strydom et al., 2010, 2011).

The aim was to reveal the structural characteristics, most relevant for MAOB potency of compounds and to guide a future synthesis.

Materials and methods

Biological activities of compounds

MAOB inhibitory activities of compounds were collected from the literature. They were measured as 50% inhibition concentration (IC_{50}) in the same laboratory, following the same experimental protocol, which is necessary condition for reliable analysis. For the purposes of QSAR, activity was expressed in pIC_{50} units (pIC_{50} = -log IC_{50}) thus stronger inhibitors acquired higher pIC_{50} values and vice versa.

Descriptors of the molecular structure

Four domains for structural modifications were distinguished in the molecules of investigated compounds. The first is located in the xanthine -N1 and N3 atoms. The rest three concern the side chain – atom connected at C8 position, terminal substituent, opposed to xanthine and the bridge in between. Altogether 36 different fragments were identified and they served as molecular descriptors. Structures were binary coded by indicator variables – 1 for presence and 0 for absence of the respective fragment.

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Model development and validation

The descriptors most relevant to MAOB inhibitory activity of compounds were selected by genetic algorithm, as implemented in the package MDL QSAR v.2.0. Multiple linear regression models were derived and estimated on the basis of determination coefficient (r^2), standard error of estimate (SEE) and Fisher coefficient (F). The ability of models to predict activity of non-synthesized compounds was checked by cross-validation and y-scrambling procedures.

Results and discussion

The best linear regression model for structure-activity relationships outlined modifications in the side chain as more significant for MAOB inhibition compared to these in the xanthine ring. It showed positive correlation between the presence of oxygen or sulfur atoms connected to xanthine C8-atom and MAOB inhibitory activity. Two descriptors, accounting for properties of the linker, participate in the equation. These are bridge, consisted of four methylene groups and inclusion of additional oxygen atom. Both are favorable for the antagonistic activity, because possesses positive correlation coefficients. Six descriptors describe the contribution of the terminal fragments. Meta and para, chloro- or bromo-substituted phenyls cause the greatest improvement in MAOB inhibition, while saturated aliphatic (isopropyl) cyclic (cyclopentyl) derivatives are among the weakest inhibitors.

The correlation plot between experimental and predicted pIC_{50} values for investigated compounds revealed four outliers, for which a deviation of more than one logarithmic unit of the predicted pIC_{50} is detected. These are compounds with short or missing linker, containing also cyclohexyl or unsubstituted phenyl rings and the model poorly predicts their activity.

Results of the cross-validation and randomization procedures showed the model is able to reliably predict MAOB inhibitory activity of non synthesized compounds.

Conclusion

The present study revealed the structural features of 8-substituted xanthines favorable for their MAOB inhibitory activitiy, namely sulfur and oxygen atoms, directly connected to the C8 atom from the xanthine ring, meta and para chloro- and bromophenyl terminal substituents, elongation of the linker as well as introduction of second oxygen atom in the side chain. Ten new xanthine derivatives were designed, synthesized and submitted to an *in vitro* testing for MAOB inhibition.

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