RECEPTOR DEPENDENT 3D-LQTA-QSAR OF A SERIES OF SUBSTITUTED AMPHETAMINES

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The amphetamine family of drugs is the most common group of psycho-stimulant drugs. Amphetamines inhibit the monoamine oxidase enzyme (MAO, isoforms A and B) which catalyzes the oxidation of neurotransmitters. Two different amphetamines derivatives, selegiline and rasagiline are of particular interest. They are selective irreversible inhibitors of type B monoamine oxidase (MAO-B), that is used primarily in the form of a covalent adduct with the isolloxazone moiety of the FAD cofactor in the treatment of Parkinson's and Alzheimer's diseases and depression.

Docking studies were performed with GOLD program [1] on 30 selegiline and rasagiline derivatives [2] and according to the results the most potent compounds had the propargyl group in an orientation suitable for their reaction with the FAD cofactor placed at the receptor binding site. However, this orientation was not obtained for some compounds, so, a manual docking was done to obtain the best orientation to form such FAD-ligands adducts as suggest by Potashman [3].

Docked reactive poses from the superimposed ligands at the binding site provided aligned conformations for receptor dependent 3D-LQTA-QSAR [4], where electrostatics and Lennard-Jones interaction energies were calculated using (NH_3^+) as probe in a grid box of 1 Å and used as descriptors for modelling.

Regression models were built employing the ordered predictor selection [5] algorithm for variable selection and multiple linear regression (MLR). The y–randomization and leave–N–out cross-validation procedures were carried out in addition to the external validation. MLR models provided the following statistics: $Q^2 = 0.64$, $R^2 = 0.77$ for 6 variables selected. The selected descriptors illustrated in Figure 1 provide information regarding the interaction of the derivatives with FAD and two isoleucines (172,199). These preliminary results are promising and useful for further receptor dependent studies with adduct formed from these selected selegiline and rasagiline derivatives.

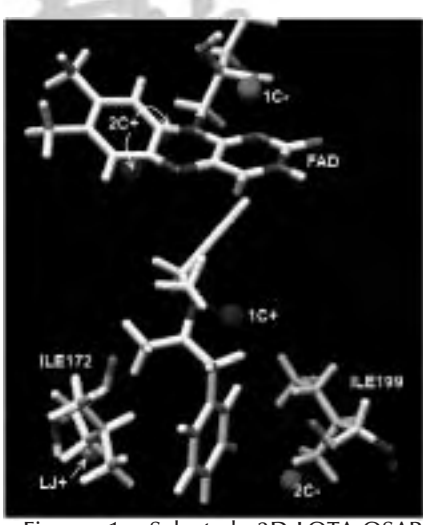

Figure 1: Selected 3D-LQTA-QSAR descriptors (ball) and the interaction of the derivatives with FAD and isoleucines 172 and 199.

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