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COMPUTER AIDED DRUG DESIGN (CADD)

POSTER PRESENTATIONS

POSTER PRESENTATION I.
(CADD)

Molecular Modelling of N-Substituted Phenylacetamidines As MAO-Inhibitors

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Monoamine oxidase (MAO) is a flavoenzyme located on the outer wall of mithochondria. Two forms, MAO-A and MAO-B have been identified. MAO inhibitors type A are used as antidepressant drugs. As depression is a very widespread menthal disease in the adult population, during the last ten years efforts have been directed to the design, synthesis, and study of new reversible and potent MAO-A inhibitors.

Recently, we have reported the synthesis and the MAO inhibitory activity of a series of N-substituted phenylacetamidines, which general molecular structure is not similar to the one of the MAO-A inhibitors described already in literature.

The present study is based on the idea that the size and shape of these molecules reflect their reversible interaction with the MAO enzyme. After geometry optimization (the Fletcher - Reeves method) we have calculated and compared the molecular size, volumes and surfaces of the test amidines. For a better and wider definition of the optimal molecular size and shape some antidepressant drugs have been also analyzed in the study as reference models of highly potent MAO-A inhibitors.

The linear sizes of all tested compounds have been calculated using molecular modeling system HyperChem™, Hypercube Inc., Ver. 2, 1991, by constructing boxes around the molecules. The modeling package Chem-X (Chemical Design Ltd.), updated to the July 1999, version have been used for computation, visualization and comparison of the Van der Waals volumes of all studied compounds. The comparison of the volumes has been performed using logical operations (EOR, OR, AND). The output data have been expressed as excluded and common volumes of the compared molecules.

Thus, applying the molecular modeling technique on our phenylacetamidines we have designed new N-substituted amidines which would better have satisfied the steric requirements of the MAO-A enzyme and would be more active as reversible MAO-A inhibitors.

POSTER PRESENTATION II.
(CADD)
A CoMFA Based Selection Of The Active Conformation For Binding To A2a Adenosine Receptor

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A 3D-QSAR analysis has been performed with a series of twenty three 2-alkylethoxy, 2-arylethoxy and 2-aralkylethoxy adenosines, as inhibitors of the binding of [^{3}H]5'-N-ethylcarboxamidoadenosine (NECA) to A2a adenosine receptor in rat striatal membranes.

The aim of the study was among all the possible conformers to select these ones which show the best correlation with the affinity to A2a adenosine receptor and have the highest predictive significance. As a criterion for a good correlation was used the parameter R^2 (multiple correlation coefficient). As a criterion for a good prediciton were used Q^2 (cross-validated R^2 from the PLS analysis) and E^{press} (error of predicition).

For this purpose, conformers were generated by a stepwise rotation around the bonds in the side chain at 2nd position. The conformers obtained after rotation around the first torsion were arranged in subsets according to the degrees of the torsion angles and a CoMFA on each subset was performed. The subset with the highest Q^2 was chosen as "parent" for the second torsion. This procedure was repeated for the next three torsion angles. The conformation, for which the model shows the best predictive ability (the highest value of Q^2) was defined as the "active conformations", or very close to it.

In conclusion, the conformational requirements for new active A2a adenosine agonists are proposed.

POSTER PRESENTATION III.
(CADD)

Quantum Mechanical Claculations In Gas Phase And Polar Medium And QSAR Analysis Of A Series 2- And 4-[(hydroxy-imino) - methyl] pyridium Derivatives

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This theoretical study was performed with a series of twenty five 2- and 4- [(hydroxy-imino) - methyl] - pyridinium derivatives, called for briefness bis-pyridinium oximes, as inhibitors and reactivators of inhibited with sarin, VX and paraoxon AChE. The aim of the study was to suggest the most important structural features, responsible for both the activities.

For this purpose, topological indices were calculated as well as electronic indices in gas phase (AM1) and in polar medium (COSMO).

According to the best QSAR models it was suggested that for the inhibitory activity the most important atoms are the carbon atom from the oxime group in the first pyridinium ring and the oxygen atoms from the substituent in the first and the secondpyridinium rings. The influence of the oxygen atom in the second pyridinium ring would not be identified without calculations in polar medium. For the reactivatory potency, it was determined that the significant atoms are the carbon and the oxygen atoms of the oxime group only in the first pyridinium ring.

In conclusion, there exists a strong dependency of the QSAR models from the position of the oxime group in the first pyridinium ring.