3D-QSAR COMFA STUDY ON ANNELATED XANTHINE DERIVATIVES - ADENOSINE A_{2A} RECEPTOR ANTAGONISTS

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Adenosine is an endogenous nucleoside that modulates many physiological processes. Its actions are mediated by interaction with specific cell membrane receptors. Four subtypes of adenosine receptors (ARs) have been cloned: A_1, A_{2A}, A_{2B}, and A_3. In our research we are looking for ligands of A_1/A_{2A} ARs among annelated oxygen or nitrogen containing xanthine derivatives. So oxazolo-, oxazino-, oxazepino- and imidazo-, pyrimidino- and diazepinopurindiones were synthesized and evaluated for their affinity to A_1, A_{2A} ARs [1]. Conventional CoMFA [2] was applied to a series of 18 pharmacologically examined derivatives from different structural patterns in order to find activity trend of the molecules analyzed. SYBYL molecular modeling software [3] was used for structure generation. The molecular structures of the investigated compounds were optimized using the DFT (density functional theory) formalism [4]. The 3-21G basis set and the hybrid functionals B3LYP have been applied [5]. The final molecular electronic properties were calculated in a single point using the restricted Hartree-Fock (RHF) method and 6-31++G basis set [6]. Atomic charges were calculated to fit the electrostatic potential at points selected according to the CHelpG scheme [7].

The atom-based RMS alignment yielded good predictive CoMFA model (r2cv=0.752, r2cnv=0.994, F value=285.689) with six components. The 3D-contour maps generated from the above studies were assessed for the activity trend of the molecules analyzed. The interaction of ligand and receptor is under steric and electrostatic control. The steric (contribution of 79%) field is of greater importance for the predictivity than the electrostatic (21%) one.

CoMFA electrostatic contour map and molecular electrostatic potential map for the Connolly surface have been compared. The correlation found proved to be very interesting. The data generated from the present study can be useful in the design of novel compounds with higher predictive abilities.

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