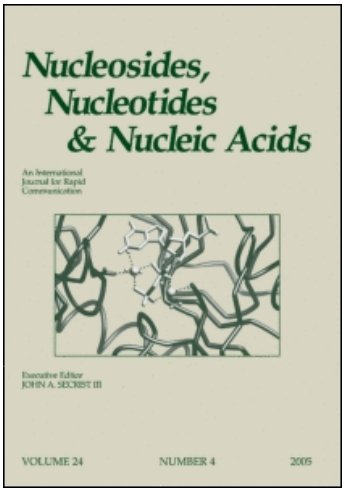

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Mapping the Xanthine CS-Region of the Adenosine A, Receptor with Computer Graphics

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MAPPING THE XANTHINE C8-REGION OF THE ADENOSINE A_1 RECEPTOR WITH COMPUTER GRAPHICS.

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Adenosine A_1 antagonists cause, among other effects, stimulation of the central nervous system, renal vasodilatation and facilitation of the atrio-ventricular conduction. These possible applications call for an examination of the antagonist properties, in order to develop newer and more selective antagonists.

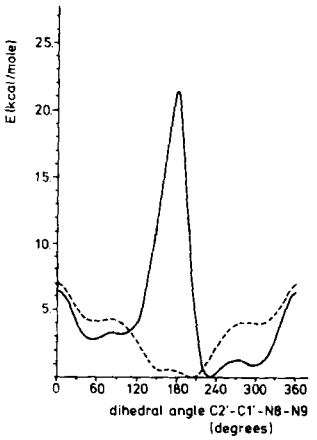

Figure 1. The conformational energy costs vs. dihedral angle of PACPX (drawn) and 8-(o,p-dihydroxyphenyl)DPX (dotted).

C8-substitution of 1,3-dipropylxanthines (DPXs) can lead to potent adenosine A_1 antagonists. The affinities of several C8-substituted DPXs, as determined in radioligand binding studies, have been reported in the literature. These data were used to explore the shape of the xanthine C8-region, employing CAMM (Computer Assisted Molecular Modeling). 30 Compounds were divided in two groups: one which contained the phenyl- and other flat substituents and another which included the cycloalkyl substituted DPXs and other compounds not belonging to the first group.

Energy minimisations and calculations were carried out by the semi-empirical molecular orbital package MOPAC, using the Austin Method 1 Hamiltonian. Conformational searches of the (high affinity) substituents were used to determine the probability of the positions of the C8-substituents. The Chem-X molecular modeling software was applied to map the volume of the xanthine C8-region.

The conformational searches of the ortho substituted 8-phenyl-DPXs, especially those of 8-(2'-amino,4'-chlorophenyl)-DPX (PACPX) and 8-(2',4'-dihydroxyphenyl)-DPX (figure 1), indicated the N9-C8-C1'-C2' dihedral angle to be about 220 degrees (figure 2). The high energy costs of the 7-N-methyl substituted compounds, the caffeine analogs, to accommodate this torsion angle can explain their low affinity. The N9-C8-C1'-C2' dihedral angle for the cycloalkyl substituted compounds, such as 8-cyclopentyl-DPX (DPCPX), was determined likewise to be 330 degrees (figure 3). The volume of the 8-phenyl substituted DPXs, oriented as above, shows considerable overlap with the volume of the 8-cycloalkyl substituted DPXs. Thus, both kinds of substituents bind to the same receptor cavity, each fitting in its own best way. Since the fit in this cavity is one of the aspects which determine affinity, the energy costs to reach the above mentioned dihedral angles affect the affinity.

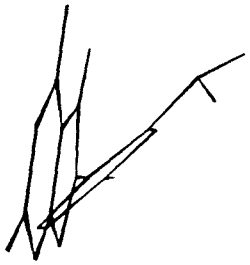

Figure 2. The geometry of PACPX in the N9-C8-C1'-C2' dihedral angle of 220 degrees.

The CAMM gave also some results with regard to the structure-affinity relationship. The affinity of the cycloalkyl substituted DPXs depends mainly on the volume of the substituents and the energy costs to reach the dihedral angle of 330 degrees. The affinity of the phenyl substituted DPXs is dependent on the site of substitution. Para substitution has either no influence, or a positive influence on the affinity, provided that the substituent is not charged, which leads to a strong decrease in affinity. Meta substitution has a negative effect on the affinity, whereas ortho substitution with small substituents can have a positive influence. Large ortho substituents, however, reduce the affinity, by raising the energy costs to reach the dihedral angle of 220 degrees.

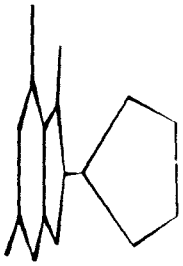

Figure 3. The geometries of DPCPX in the N9-C8-C1'-C2' dihedral angle of 330 degrees.

Thus, the use of CAMM has led to the elucidation of the steric demands, affecting the affinity of 8-DPX substituents.