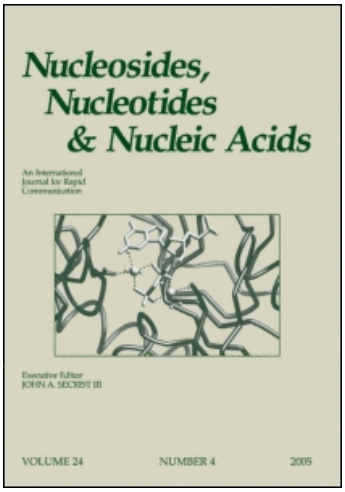

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article van Galen, P. J. M. , Ijzerman, A. P. and Soudijn, W.(1991) 'Xanthine-7-Ribosides as Adenosine Receptor Antagonists: Further Evidence for Adenosine'S *Anti* Mode Of Binding', Nucleosides, Nucleotides and Nucleic Acids, 10: 5, 1191 — 1193
To link to this Article: DOI: 10.1080/07328319108047272
URL: http://dx.doi.org/10.1080/07328319108047272

NUCLEOSIDES & NUCLEOTIDES, 10(5), 1191-1193 (1991)

XANTHINE-7-RIBOSIDES AS ADENOSINE RECEPTOR ANTAGONISTS: FURTHER EVIDENCE FOR ADENOSINE'S *ANTI* MODE OF BINDING

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With the aid of computer graphics methods, we recently developed a model for the antagonist binding site of the adenosine A_1 receptor (J. Med. Chem. **1990**, 33, 1708-1713). According to this model, xanthines should bind to the receptor in a flipped orientation, i.e. the ring atoms N1, N3, N7 and N9 in adenosine coincide with C2, C6, N9 and N7 respectively in theophylline (FIG. 1a and 1 b). This implicates that the domain where the ribose moiety of adenosine binds must be adjacent to N7 in xanthines, and furthermore that xanthine-7-ribosides should have affinity for the receptor. To further explore the role of the orientation of the ribose moiety in binding to the receptor, we have synthesized and determined the A_1 affinity of the 7-ribosides of theophylline, 1,3-dipropylxanthine and 1,3-dibutylxanthine (FIG. 1c). The orientation of the ribose moiety was studied with ^{1}H-NMR spectroscopy and theoretical chemical calculations.

Although A_1 receptor affinies (TABLE 1) of xanthine-7-ribosides are somewhat lower than those of the parent xanthines, the N7 region can obviously accomodate the bulky ribose moiety, quite unlike many other N7-substituents, which are usually badly tolerated. K_i-values and Hill-coefficients are not altered by the addition of 500 µM GTP, indicating that these compounds are antagonists rather than agonists.

The ^{1}H-NMR spectra (in DMSO-solution) of the ribose part of adenosine and theophylline-7-riboside show considerable differences, which reflect a different orientation about the glycosidic bond. Especially $\delta_{H2'}$ is a good indicator of this orientation. In purine nucleosides and nucleotides, typical values for $\delta_{H2'}$ are 5.2 ppm for compounds that are restricted to the *syn* conformation (e.g. 8-bromoadenosine) and 4.2 ppm for compounds that exist exclusively in the *anti* conformation (e.g. 8,5'-cyclo-8-oxoadenosine). The intermediate value found for adenosine (4.62 ppm) indicates that an equilibrium exists between both rotamers. The low values found for xanthine-7-ribosides (4.30 ppm), on the other hand, show that these compounds exist predominantly in the *anti* conformation.

The results of an AM1-calculation of the dependence of the intramolecular energy upon the glycosidic torsion angle (χ) (FIG. 2) again indicate that - for adenosine - there is little difference between the *syn* and the *anti* conformations (< 1 kcal/mol), with a slight preference for the *syn* conformation. Theophylline-7-riboside however has a distinct preference for the *anti* conformation (3 kcal/mol), with a rather large energy barrier between

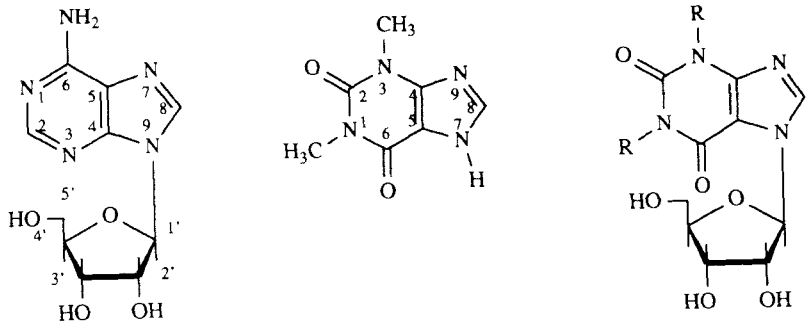

FIG. 1 Structure and relative orientation of (a) adenosine, (b) theophylline, (c) xanthine-7-ribosides.

TABLE 1. A_1 receptor affinities and pseudo-Hill coefficients of tested compounds in the absence and presence of 500 μM GTP. Displacement of [^{3}H]DPCPX binding from calf brain membranes.

Compound	- GTP		+ GTP	
	K_i (μM)	n_H	K_i (μM)	n_H
Theophylline	6.0	1.03	7.2	0.99
Dipropylxanthine	0.26	1.01	0.27	1.00
Dibutylxanthine	0.14	0.91	0.14	0.95
Theophylline-7-riboside	58	0.91	95	1.04
Dipropylxanthine-7-riboside	1.7	0.98	1.8	0.94
Dibutylxanthine-7-riboside	0.45	0.99	0.51	0.93
R-PIA	0.00076	0.74	0.0073	0.92

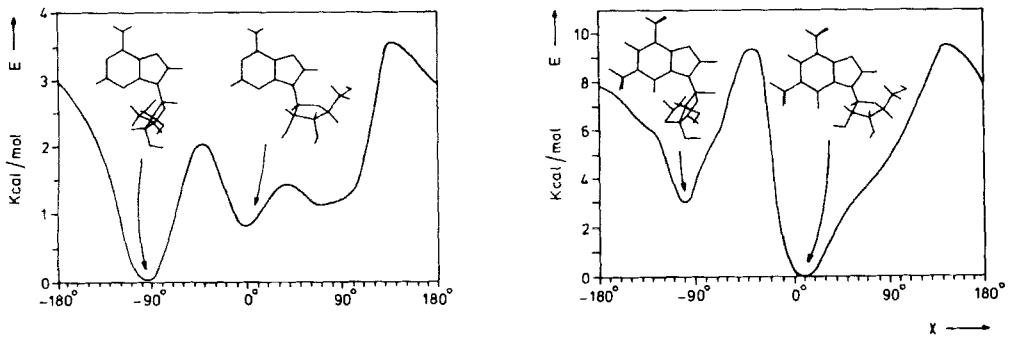

FIG. 2. Dependence of intramolecular energy, relative to the global minimum, upon variation of χ for (a) adenosine and (b) theophylline-7-riboside. Note the different scales on the abscissa.

both rotamers. In conclusion, both NMR and AM1-data indicate that xanthine-7-ribosides have a distinct preference for the *anti* conformation, whereas adenosine can readily adopt both conformations. Since both classes most probably bind to the receptor with the same orientation of the ribose moiety, these results provide further evidence in favor of the concept that adenosine binds to the receptor in the *anti* conformation.