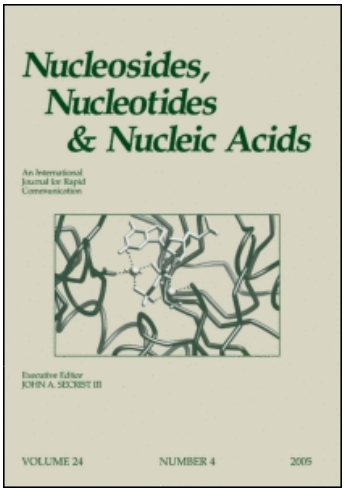

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A Computer Generated Model of Adenosine Receptors Rationalising Binding and Selectivity of Receptor Ligands

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A COMPUTER GENERATED MODEL OF ADENOSINE RECEPTORS RATIONALISING BINDING AND SELECTIVITY OF RECEPTOR LIGANDS.

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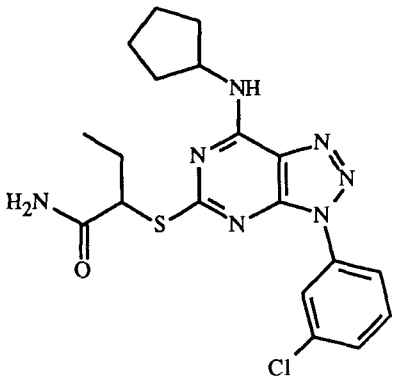
Abstract Computer graphic analyses on a broad spectrum of adenosine receptor ligands has shown that both the A1 and A2 adenosine receptors have three binding sites. The spatial relationship of these three binding sites has been defined. Adenosine orientation at A1 and A2 is different.

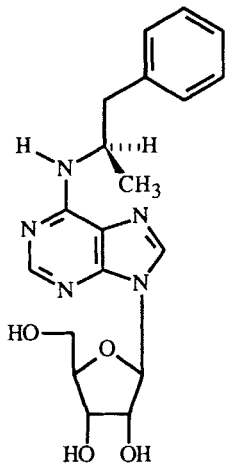
Over the last several years we have been exploring the role of the heterocyclic rings in affecting affinity to adenosine receptors by synthesis and radioligand binding assay of a variety of adenosine analogues where the heterocyclic ring has been modified. In particular our work, in addition to purine systems, has involved pyrazolo[3,4-*d*]pyrimidines, triazolo[4,5-*d*]pyrimidines and thiadiazolo[4,5-*d*]pyrimidines. During the course of this work we observed a lack of additivity in the substituents, typified by 3-(3-chlorophenyl)-7-(N-cyclopentylamino)-5-(2-butanamidyl-thio)[1,2,3]triazolo[4,5-*d*]pyrimidine (1), which showed a decreased affinity for the A1 receptor compared to analogous mono-substituted compounds. At the same time, similar observations were reported on substituting adenosine at both the C2 and N^6 positions. For example, 2-(phenylamino) substitution of the A2-selective agonist N^6-[2-(3,5-



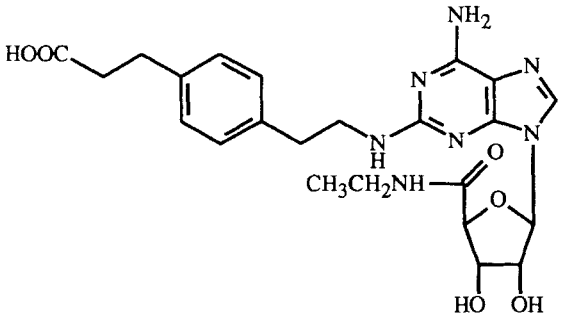
(1)

dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine resulted in no change in A2 selectivity but about a 75-fold loss of affinity at both receptors, while the same substitution on the A1-selective agonist N^6-cyclopentyladenosine resulted in a 67-fold shift in selectivity in favour of the A2 receptor by a 3.2-fold increase in A2 affinity and a 21 fold decrease in A1 affinity.[1] Two possible explanations have been advanced, the direct steric interference between the two side chains due to partial overlap between the C2 and N^6 aryl binding pockets or an indirect interaction resulting in an allosteric change in the receptor when one of the pockets is occupied resulting in closure of the other pocket.[1]

An alternate explanation for both our results and the literature observations is that there is only one hydrophobic binding site at both the A1 and A2 receptors. We firstly overlaid a series of N^6-substituted adenosine analogues by fitting[2] the analogues which had been relaxed to their global minima using MM2 optimization in order to minimize the RMS distance between selected pairs of atoms. The same procedure was applied to a group of antagonists and this group then fitted to the former group in order to visualise the N^6-binding domain. Once these parameters were obtained an hypothesis of a single hydrophobic domain was examined. Aligning the hydrophobic groups of PIA (2) and CGS 21680 (3) within the previously defined hydrophobic binding domain and maximising correlations between atoms of the heterocycle gave a fit in which the



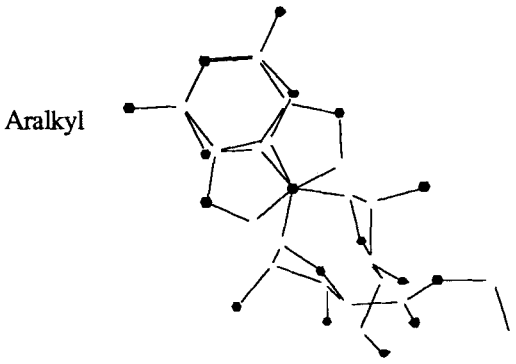
(2)



(3)

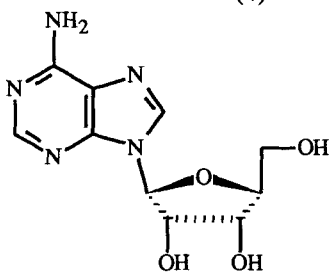
superimposition of the purine ring and the ribose are shown in (4) (the aralkyl side chains occupy the area indicated). For adenosine, itself, the superimposition (4) consists of (5)

and (6) thereby allowing determination of how adenosine binds at A1 and A2 receptors. The orientation of adenosine in (5) can undergo a 180° rotation about the 4,5-bond, so that the ring oxygen of the ribose is now into the page and a rotation of the purine ring through about 130° anti-clockwise would give adenosine oriented as in (6).

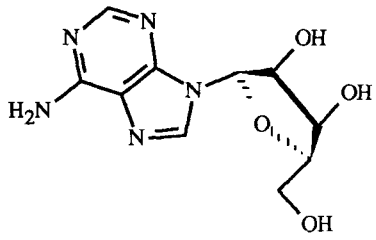


(4)

In (4) the 2' hydroxyls are 5.88Å apart, the 3' hydroxyls are 5.54Å apart

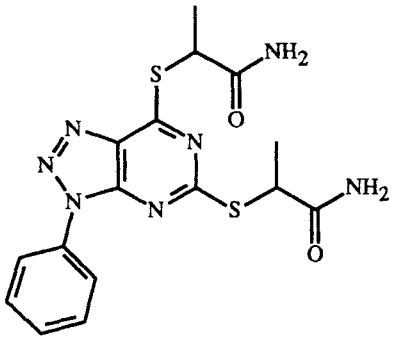


(5)

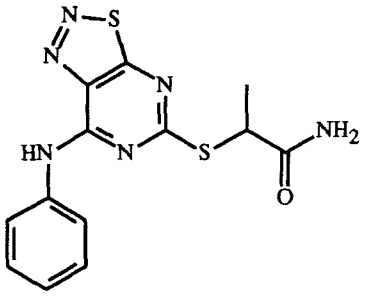


(6)

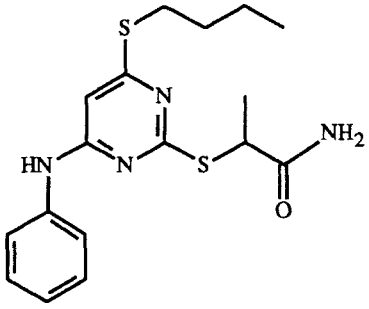
This model is further substantiated by examples (7), (8), (9) from a series of heterocyclic compounds which have the same order of A1 binding (IC_{50}'s around 10^{-5}M) such that when the phenyl ring occupies the hydrophobic domain, the other chains occupy a common region, confirming that it is the relationship of the phenyl and amide that is important in binding. Fitting of these compounds against NECA has shown that both amides are in close proximity. (10) shows the fitting of the ribose of NECA to the amide side chains where the O - O' distance was 1.0074 Å , the C - C' distance was 1.0443 Å and the N - N' distance was 0.8917 Å. Consistent with the six-membered ring of the heterocycle being conserved, (9) has a similar affinity for the A1 receptor. Lack of additivity has been reported with N^6,5' doubly modified agonists.[3,4] N^6 substitution forces the ribose into the A1 ribose binding pocket so that NECA type substitution in the ribose would be expected to lower affinity.



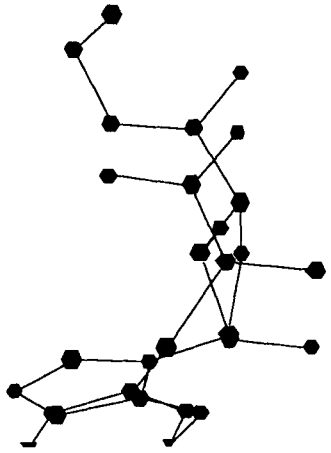
(7)



(8)



(9)



(10)

Adenosine receptors have three binding pockets:- a hydrophobic binding domain, a central aromatic binding domain and a ribose binding domain. The spatial relationship of these three binding sites has been defined. The different orientation of adenosine at the A1 and A2 receptors could be explained by a hydrogen bonding interaction between the respective receptor proteins and a N^6 hydrogen.

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