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AN EXPLANATION OF THE SUBSTITUENT EFFECT OF 1,3,8-TRISUBSTITUTED XANTHINES ON ADENOSINE A_1/A_2 AFFINITY.

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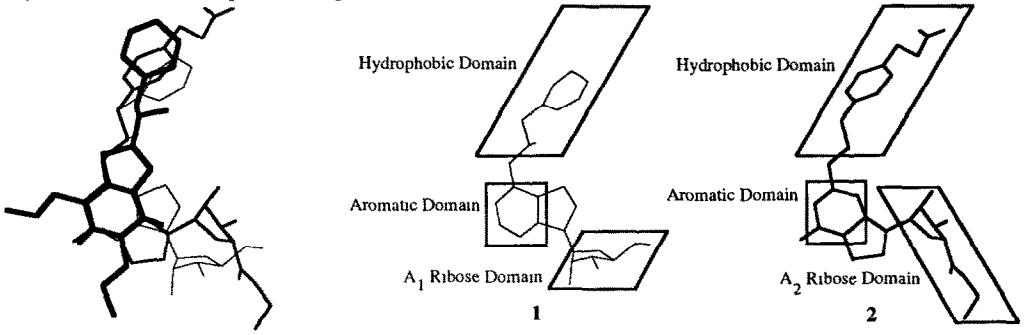
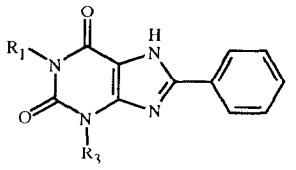
Abstract: Interpretation of recently presented adenosine A_1 and A_2 receptor binding affinity for a series of 1,3,8-trisubstituted xanthines supports a receptor binding model that predicts an orientation of receptor ligands governed by a hydrophobic binding domain, an aromatic binding domain and a ribose binding domain.

We have recently proposed the three binding domain model of adenosine receptors.[1,2] Features of our model are the presence of a ribose binding domain, an aromatic binding domain and a single hydrophobic binding domain in A_1 and A_2 receptors. This is visualized in the figure below showing the overlap of the hydrophobic groups, the common 6-membered ring aromatic and the differential location of the ribose domain of the A_1 selective agonist (R)-N^6-(phenylisopropyl)adenosine (**1**), the A_2 selective agonist 5'-*N*-ethyl-2-[[4-(2-carboxyethyl)phenethyl]amino]-adenosine-5'-uronamide (**2**) and the A_1 selective antagonist 1,3-dipropyl-8(R)-(phenylisopropyl)xanthine (**3**).[2] A recent publication has reported the synthesis and adenosine A_1 and A_2 receptor binding affinities for a large series of 1,3,8-trisubstituted xanthines.[3] It was previously known that changing the 1,3-substituents of theophylline from methyl to propyl increased the potency of the compounds at adenosine receptors[4-7] but until the study by Erikson *et al* [3] it had not been determined whether both propyl groups are needed for activity. We now report that the three binding domain receptor model provides an explanation for the receptor binding results of the 1,3,8-trisubstituted xanthines.



At the adenosine A_1 receptor, in comparison to the parent 8-phenyltheophylline (**4a**), changing either the 1- or 3-methyl group to a propyl, **4b** and **4c** gave a 10-fold increase in potency while changing both positions (**4d**) gave a 20-fold increase in potency. This trend was observed with all eleven different C8 substituents. At the adenosine A_2 receptor, in comparison to 8-phenyltheophylline (**4a**), a change from methyl to propyl at the 3-position (**4c**) gave a 7-fold increase in affinity while the same change at the 1-position (**4b**) caused no increase in A_2 binding . The change in both positions (**4d**) gave no increase over the monosubstitution at the 1-position.

This trend was observed with all eleven different C8 substituents with respect to the 3-position, however while changing the 1-methyl to propyl resulted in no increase in affinity for five of the eleven series of compounds, a 2 to 3-fold increase in affinity was observed for five of the remaining six series of compounds.



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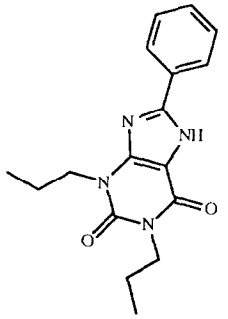
	R_1	R_3	A_1 K_i, nM^3	A_2 K_i nM^3
4a	CH_3	CH_3	60 ± 6	644 ± 144
4b	$CH_2CH_2CH_3$	CH_3	6.96 ± 0.91	553 ± 56
4c	CH_3	$CH_2CH_2CH_3$	6.30 ± 0.17	93 ±10
4d	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	2.75 ± 0.29	116 ±10

At the adenosine A_1 receptor, which is visualized as having a binding domain capable of accepting **1**, superimposition[8] of **4d** is shown in Figure 1. At the adenosine A_2 receptor, which is visualized as having a binding site capable of accepting **2**, superimposition of **4d** is shown in Figure 2. The superimposition of Figure 1 shows that both propyls occupy an unrestricted area and propyl substitution at both positions enhances receptor affinity at the A_1 receptor. On the other hand, Figure 2 shows that the N1 propyl intrudes into the imidazole region and it is only the N3 propyl that can occupy an area that could effectively contribute to receptor affinity at the A_2 receptor.

In summary, the three binding domain model of adenosine receptors has explained the effect on receptor affinity of alkyl substitution in a series of 8-substituted xanthines whereby propyls at both N1 and N3 enhance affinity at A_1 receptors while it is only propyl at N3 which enhances affinity at A_2 receptors.



4d

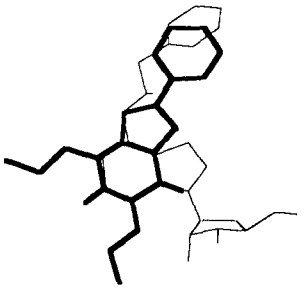


Figure 1 (Adenosine A_1 receptors) superimposition of **1** and **4d**

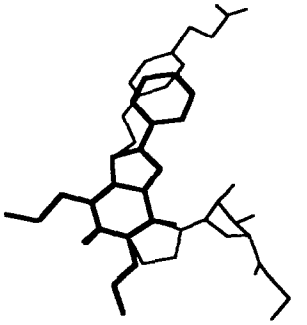


Figure 2 (Adenosine A_2 receptors) superimposition of **2** and **4d**

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