Electronic Structure of Some Adenosine Receptor Antagonists. VQSAR Investigation

Sabry El-Taher,† K. M. El-sawy,‡ and Rifaat Hilal*,†

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt, and
National Center for Drug Control and Research, Giza, Egypt

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A QSAR model has been developed for 1,3-dimethylxanthines as adenosine receptor antagonists. The model is capable of predicting the affinity toward both the A1 and A2 receptors. Constitutional, geometrical, topological, electronic descriptors (computed at the ab initio 6-31G level), and some empirical descriptors related to the hypophilicitywere computed and analyzed. A two step computational strategy was adopted to select the descriptors relevant to the A1 or the A2 affinity. In the first step, each of the four main groups of descriptors is treated independently. Multiple regression analysis lead to a set of equations that reflect the weight of each of the studied descriptors. The most relevant of these descriptors were grouped, and a new multiple regression analysis has been carried out and arrived at the final QSAR model. These QSAR equations account for almost all the A2 and an appreciable part of the A1 affinity. The proposed model has been examined as a general tool of predicting the activity toward the adenosine receptor sites. Avalidation set of 22 xanthines were selected, and their activities were computed using the proposed QSAR model. The correspondence between the predicted and observed activities is excellent. Anova statistical analysis on the data of the validation set elaborates on the quality of these fits.

INTRODUCTION

The ultimate aim of any structure−activity relationship is to pinpoint those structure-related properties that underlie the biological activity of a certain series of biomolecules. Since first introduced by Hansch,[1] QSAR investigations of several series of drugs, enzymes and biologically active compounds had been performed, and the predictive power of QSAR equations is now well-appreciated.[2]

Caffeine or more generally 1,3-dimethylxanthines are the most widely ingested mood-altering compounds.[3] The mode of action is within the central nervous system where it acts as a stimulant, perhaps by competitive blockade of endogenous adenosine at A1 and/or A2 receptors.[4]

Extensive structure−activity studies have been made using xanthine derivatives seeking high selectivity toward A1 or A2 receptor antagonism. The analysis of individual group contributions shows, for both A1 and A2 receptors, the importance of the presence of bulky substituents at position 8.[5] Several computer models for adenosine receptors have been proposed[6−8] where steric and hydrophobic features of A1 adenosine receptor antagonists have been used to develop some of these models.[8] Despite these several structure−activity studies, the literature does not seem to contain any systematic and quantitative study to relate the activity of xanthines to their electronic structural parameters and to compare it with the corresponding parameters of adenosine.

The aim of the present work is to develop a quantitative electronic structure−activity relationship forxanthines. Our QSAR is intended to be comprehensive, in the sense that structural parameters such as constitutional, topological, geometrical, and empirical descriptors, will be thoroughly investigated. However, the merit of the present investigation is to assess the impact of electronic structural descriptors on the biological activity of alkyl xanthines. The important feature of the present QSAR study is its comparative nature where all studied descriptors are compared and related to the corresponding ones in adenosine.

METHOD OF CALCULATION

Full geometry optimizations were performed at the ab initio HF−SCF level.[9] Equilibrium geometries are identified, and correlation energies and zero-point energies were computed for the two sets of xanthines studied (cf. Figure 1) at the MP2 level. All computations were carried out using the Gamess ab initio computer software package.[10]

The choice of the appropriate basis set is of prime importance. The size of molecules studied in the present work is medium to large and hence a cost-effective study of basis sets, taking into account the consistency of the computed observables, is in order. Such a study[10] revealed that the 6-31G basis set provides the minimum acceptable level of accuracy. This basis set is thus adopted throughout the present work.

The Dragon software package[12] is used to compute all constitutional,[13] topological,[14] geometrical,[15] and empirical[16] descriptors.[17] Dragon generates over 800 descriptors, and no QSAR treatment can handle such huge number of descriptors. Therefore, limitation of this number is essential from the statistical point of view.

To select the set of descriptors that are most relevant to the bioactivity of xanthines, a two step computational strategy

* Corresponding author phone: 00202-567-6615; fax: 00202-572-8843; e-mail: hilal@chem-sci.cairo.eun.eg.
† University of Cairo.
‡ National Center for Drug Control and Research.

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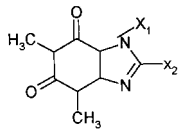
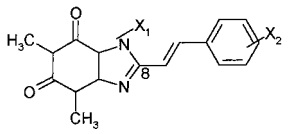
Working Set



Drug	X1	X2	Drug	X1	X2
Xan01	H	CF3			
Xan02	H	H			
Xan03	H	CH3			
Xan04	H	Cl	Xan12	CH3	H
Xan05	H	NH2	Xan13	CH3	CH3
Xan06	H	ph	Xan14	CH3	CF3
Xan07	H	styryl	Xan15	CH3	Br
Xan08	H	3Fstyryl	Xan16	CH3	NH2
Xan09	H	Butyl	Xan17	CH3	Ph
Xan10	H	NO2	Xan18	CH3	Styryl
Xan11	H	Br	Xan19	CH3	3Fstyryl

Validation Set



Drug	X1	X2	Drug	X1	X2
Xan20	H	H	Xan29	CH3	H
Xan21	H	2-MeO	Xan30	CH3	2-MO
Xan22	H	3-hydroxy	Xan31	H	3-MeO
Xan24	H	3-CF3	Xan32	CH3	3-CF3
Xan25	H	3-NO2	Xan33	CH3	3-NO2
Xan26	H	3-NH2	Xan34	CH3	3-NH2
Xan27	H	3-F	Xan35	CH3	3-F
Xan28	H	4-MeO	Xan36	CH3	4-MeO
Xan23	H	3-MeO			
Xan37	H	8-(CH2)COOH			
Xan38	(CH2)2CH3	8-(p-SO3Hphenyl)			
Xan39	(CH2)2CH3	8-(p-COOHphenyl)			
Xan40	(CH2)2CH3	CH=CH-COOH			
Xan41	(CH2)2CH3	OCH2-COOH			

Figure 1. Working and validation sets of alkylxanthines studied in the present work.

was adopted. Each of the four main groups of descriptors is considered independently in the first step. A nonlinear regression analysis of each group of descriptors against the A1 or the A2 activity is performed. This is followed by a factor impact analysis to evaluate the weight of each descriptor. The second step is to collect all relevant descriptors emerged in step 1 in the final QSAR analysis.

Statistical treatment of the data, multiple-regression analysis, and polynomial fits were carried out using two computer software packages namely, CurveExpert *1.3 and WINKS* evaluation copy. Both operate under Windows environment and employ a large number of regression models (both linear and nonlinear) as well as various interpolation schemes to represent the data in the most precise and convenient way.

RESULTS AND DISCUSSION

Structural Correlations. Table 1 presents the 11 constitutional descriptors computed for a representative set of 19 1,3-dimethylxanthines (cf. Figure 1). Attempts were made to correlate the individual constitutional descriptors with both the A1 and the A2 activities. Multiple regression analysis on all 11 constitutional descriptors versus the A1 activity results in an excellent correlation ($r^2 = 0.96$) which is given in Table 2. Out of the 11 descriptors involved in the regression, the A1 activity seems to be governed by only three, namely the Mv (mean atomic van der Waals volume), Me (mean atomic Sanderson electronegativity), and Mp (mean atomic polarizability). This correlation suggests that the activity toward the A1 receptor sites is governed to a large extent by constitutional factors. On the other hand, a less satisfactory correlation is obtained for the A2 activities versus the constitutional descriptors (cf. Table 2). Thus, constitutional factors cannot account for more than 60% of the A2 activity. The QSAR equations and the corresponding statistical data are given in Table 2.

Table 3 presents the geometrical, topological, and empirical descriptors computed for the set of xanthines studied in the present work. Multiple regression analysis on the A1 activity versus topological or empirical descriptors failed to result in any satisfactory correlation. Geometrical descriptors correlate to a better extent, however, with the A1 activity. The FDI (folding degree index) seems to be the only geometrical descriptor relevant to the A1 activity. Better correlations have been obtained for the A2 activity versus the set of geometrical descriptors versus the set of empirical descriptors and versus the topological descriptors. These three correlations indicate that the A2 activity is determined to a large extent by the degree of flexibility (as measured by the FDI and SPAM descriptors) and by the hydrophilic nature of the drug. The QSAR equations and the corresponding data are given in Table 2.

In summary, the A1 activity seems constitution dependent, whereas the A2 activity is much more involving and depends on the geometrical and topological properties of the drug. Furthermore, both the A1 and the A2 activities are highly dependent on the hydrophilic nature of the drug as measured by the Hy empirical descriptor.

Energy Correlations. Table 4 presents some energy descriptors for 15 1,3-dimethylxanthine derivatives computed at the HF-6-31G level of theory. Also, presented in Table 4 is the activity toward the A2 receptor for the studied series. Figure 2 presents the variation of the HOMO and of the LUMO energies with the A2 activity. Biomolecules are arranged in an ascending order of increasing A2 activity. Solid lines correspond to the HOMO or LUMO of adenosine. The general features of these figures reveal the following:

(1) There is a general trend of increasing the A2 activity by increasing the donation capacity. Thus, 8-(trifluoromethyl)-theophylline has the highest I.P. (9.66 ev) and is completely inactive as far as A2 receptor is concerned. On the other hand, 8-(3-chlorostyryl)caffeine has the highest A2 activity (I.P = 8.19 ev) of the studied drugs.

(2) There seams to be a maximum value of the I.P above which the biomolecule is no longer active. This value is very close to the I.P of adenosine (~8.85 ev).

The trend with electron-affinity is more involving. Thus, the A2 activity increases, at first, with decreasing the electron affinity. Biomolecules in this group seems to maximize electron-affinity by approaching the electron-affinity of adenosine. Another set of drugs, however, shows a completely different trend, and their bioactivities seem to show second order dependence of the LUMO energy.

Attempt to correlate the A2 activity with the E_{homo}, E_{lumo}, and the ΔE_{gap} resulted in polynomial fits of moderate correlation coefficients. However, these correlations suggest that the A2 activity involve a charge-transfer interaction where the LUMO of the drug plays a pronounced role. To investigate this mechanism a little bit further, several functions were examined to better explain

Table 1. Constitutional Descriptors[a] Computed for the Working Set of Alkylxanthines

drug	nHA	nHD	Mp	Me	Mv	Ss	Sp	Se	Sv	MW	AMW	1/EC50(A2)	1/EC50(A1
Xan01	6	1	0.63	1.1	0.63	61.08	15.01	26.29	15.13	248.19	10.34	0.0a	0
Xan02	6	1	0.64	1.04	0.63	36.17	13.44	21.87	13.19	180.19	8.58	0.045c	0.071
Xan03	6	1	0.63	1.03	0.62	37.83	15.2	24.75	14.79	194.22	8.09	nd	nda
Xan04	6	1	0.68	1.06	0.66	39.94	14.3	22.19	13.93	214.63	10.22	nd	nda
Xan05	7	2	0.63	1.04	0.62	39.83	14.45	23.97	14.19	195.21	8.49	nd	nda
Xan06	6	1	0.68	1.02	0.66	47.5	20.96	31.64	20.39	256.29	8.27	1.031a	13.158a
Xan07	6	1	0.68	1.02	0.66	51.5	23.72	35.53	22.99	282.33	8.07	3.438b	1.529b
Xan08	6	1	0.68	1.03	0.66	59.17	23.65	36.04	23.1	300.32	8.58	1.838b	0.368b
Xan09	6	1	0.62	1.01	0.59	42.33	20.48	33.42	19.59	236.31	7.16	0.357a	5.263a
Xan10	9	1	0.63	1.08	0.64	51.83	14.6	24.75	14.61	225.19	9.79	nd	nda
Xan11	6	1	0.7	1.05	0.68	38.58	14.8	22.09	14.28	259.08	12.34	nd	nda
Xan12	6	0	0.63	1.03	0.62	37.67	15.2	24.75	14.79	194.22	8.09	0.106c	0.024d
Xan13	6	0	0.63	1.02	0.61	39.33	16.96	27.64	16.39	208.25	7.71	0.132a	0.204a
Xan14	6	0	0.62	1.08	0.62	62.58	16.77	29.18	16.72	262.22	9.71	0.034a	nda
Xan15	6	0	0.69	1.04	0.66	40.08	16.56	24.98	15.88	273.11	11.38	0.083a	0.020a
Xan16	7	1	0.62	1.03	0.61	41.33	16.21	26.86	15.79	209.24	8.05	nd	nda
Xan17	6	0	0.67	1.02	0.65	49	22.72	34.53	21.99	270.32	7.95	0.057c	0.067a
Xan18	6	0	0.67	1.01	0.65	53	25.48	38.42	24.59	296.36	7.8	10.638b	0.257b
Xan19	6	0	0.67	1.02	0.65	60.67	25.41	38.93	24.7	314.35	8.27	12.048b	0.035b

[a] AMW, average molecular weight; MW, molecular weight, Sv, sum of atomic van der Waals volumes; Se, sum of atomic Sanderson electronegativities; Sp, sum of atomic polarizabilities; Ss, sum of Kier-Hall electrotopological states; Mv, mean atomic van der Waals volume; Me, mean atomic Sanderson electronegativities, Mp, mean atomic polarizability; nHD, number for donor atoms for H-bonds; nHA, number of acceptor atoms for H-bonds.

Table 2. QSAR Equations and the Corresponding Statistical Data ($n = 19$)

activity	descriptor	QSAR equation	r^2	Anova prob. F
A1	constitutional	−13.6768 − 0.27339MW + −53.3602Sv + 8.8784Se + 37.00212Sp + 1.727337Ss + 802.1085Mv − 330.34Me − 222.669Mp + 2.575558nHD − 1.62571nHA	0.96	0.46
A2	constitutional	96.57332 − 0.06327MW − 10.5893Sv − 2.53267Se + 12.94952Sp + 0.739027Ss − 44.5912Mv − 1.9054Me − 13.5048Mp − 0.20899nHD + 0.023918nHA	0.44	0.99
A2	geometrical	−93.9928 + 0.000104W3D + 0.114687DDDA − 31.5277SPAM + 104.3909FDI + 1.252644SHP2	0.54	0.26
A2	topological	21.82956 + 0.022182ISIZ − 7.62001IDE + 10.89395IC − 47.4174SIC − 0.50906AECC + 0.37472MSDI	0.59	0.33
A2	empirical	0.816606 − 0.73023VI − 3.27746Hy − 0.03283LogP	0.66	0.18
A1	geometrical	819.8423 − 0.00435W3D + 0.590666DDDA + 28.61744SPAM − 840.999FDI − 0.36003SHP2	0.48	0.36
A1	topological	26.38818 + 0.017223ISIZ − 16.3552IDE + 28.52585IC − 94.9062SIC + 0.557763 − 1.59155SDI	0.51	0.47
A1	empirical	−0.78295 − 0.02011VI − 0.61237Hy + 0.07488LogP	0.05	0.97

the dependence ofthe A2 activity on the frontier orbital energies. The best correlation is obtained with a rational function of the form:

$$Y = (a + bx)/(1 + cx + dx^2)$$

This statistical function reflects the fact that at $E_{HOMO} < -0.31$, and no A2 activity is detected. The excellent correlation of the LUMO ($r = 0.906$) with the A2 activity shoots very high for a relatively narrow range of E_{LUMO}. Outside the range $0.057 > E_{LUMO} > 0.038$ the A2 activity seems independent of the electron affinity of the drug.

The best possible correlation has been obtained, however, using the HOMO−LUMO energy gap. Using the same rational function a correlation coefficient of $r = 0.96$ has been obtained. As is reflected from the dependence of the A2 activity on the HOMO−LUMO energy gap, the maximum activity is obtained at a gap of 0.346 ev. A very small variation in the magnitude of the gap causes dramatic drop in A2 activity. Trends with respect to A1 activity is different from that presented for the A2 affinities. Several attempts have been made to correlate the A1 affinity with HOMO−LUMO energy gap yet the trend observed indicates that A1 affinities are not governed, in first principle, by the energetics of the gap. The mechanism for drug−receptor interaction seems to proceed via two different routes for the two cases of A1 and A2. For the later, charge-transfer interactions between the HOMO of the drug and the LUMO of the receptor (or vice versa) seems to be a dominating route. For the A1 case, this route does not seem to have any potential impact.

Charge Density Correlation. 8-(Trifluoromethyl)theophylline shows no biological activity as adenosine receptor antagonist, and as such, we have taken it as the reference point in our discussion of the charge density-activity relationship. The dependence of the A1 or A2 affinities on the charge density redistribution will be discussed along two main lines, viz., variations in bond orders and variations on the net atomic charges. Table 5 presents the percent change in bond order relative to the reference compound. Inspection of the figures cited in this table indicates a considerable redistribution of the charge density upon substitution in the 8-position. The most pronounced changes are those in the

Table 3. Topological, Geometrical, and Empirical Descriptors Computed for the Working Set of Alkylxanthines[a]

drug	logP	Hy	Ui	SHP2	FDI	SPAM	DDDA	W3D	MSDI	AECC	SIC	IC	IDE	ISIZ
Xan01	1.007	0.039	2.322	0.515	1	0.448	24.449	1149.409	3.797	5.765	0.845	3.455	2.671	110.039
Xan02	−0.522	0.031	2.322	0.568	1	0.441	21.078	781.82	2.946	4.538	0.875	3.239	2.192	92.239
Xan03		−0.019	2.322	0.593	1	0.45	24.445	1149.269	3.159	4.929	0.887	3.379	2.351	110.039
Xan04		0.051	2.322	0.596	1	0.451	21.381	793.3	3.159	4.929	0.887	3.379	2.351	92.239
Xan05		0.767	2.322	0.589	1	0.437	22.98	1009.58	3.159	4.929	0.887	3.379	2.351	104.042
Xan06	−1.674	−0.192	3	0.459	1	0.498	30.986	2307.703	4.383	7.158	0.867	3.682	2.946	153.58
Xan07	2.341	−0.24	3.17	0.423	1	0.52	34.887	3382.769	5.34	8.857	0.832	3.654	3.261	179.525
Xan08	2.481	−0.216	3.17	0.426	1	0.52	34.904	3385.442	5.559	8.955	0.87	3.88	3.311	179.525
Xan09	1.431	−0.134	2.322	0.498	1	0.494	32.815	2700.09	4.214	7.118	0.914	3.735	2.902	166.465
Xan10		0.083	2.585	0.56	1	0.451	23.336	1026.3	3.658	5.688	0.863	3.453	2.626	104.042
Xan11		0.051	2.322	0.598	1	0.469	21.43	795.07	3.159	4.929	0.887	3.379	2.351	92.239
Xan12	−0.275	−0.557	2.322	0.585	1	0.427	23.886	1098.621	3.096	4.786	0.836	3.182	2.294	110.039
Xan13	5.057	−0.586	2.322	0.606	0.997	0.412	26.788	1486.461	3.254	5	0.804	3.14	2.384	128.382
Xan14	4.272	−0.491	2.322	0.521	1	0.422	27.094	1500.839	3.803	5.778	0.783	3.266	2.658	128.382
Xan15		−0.521	2.322	0.612	1	0.44	24.237	1113.32	3.254	5	0.804	3.14	2.384	110.039
Xan16		0.003	2.322	0.604	0.993	0.409	25.682	1347.21	3.254	5	0.804	3.14	2.384	122.211
Xan17	1.921	−0.689	3	0.461	0.986	0.474	33.345	2757.443	4.357	7.1	0.789	3.409	2.929	172.974
Xan18	2.588	−0.717	3.17	0.425	0.989	0.498	37.403	3958.711	5.292	8.818	0.765	3.413	3.25	199.421
Xan19	2.727	−0.686	3.17	0.428	0.991	0.497	37.466	3963.963	5.51	8.913	0.805	3.642	3.301	199.421

[a] Geometrical descriptors: W3D, 3D-Wiener index; DDDA, distance-distance degree average; SPAM, average span R; FDI, folding degree index; SHP2, average shape profile index of order 2. Empirical descriptors: VI, unsaturation index; Hy, hydrophilic factor; LogP, log of isooctane/water. Topological descriptors: ISIZ, molecular size index; IDE, mean information content on the distance equality; IC, information content index; SIC, structural information content; MSDI, mean square distance index.

Table 4. Electronic Descriptors[a] Computed for the Working Set of Alkylxanthines at the 6-31G/HF Level

A1 activity	E,HOMO	E,LUMO	E,gap	A2 activity
0	0.4148	0.0596	−0.3552	0
−1.34679	0.4269	0.0948	−0.3321	−1.14874
0.01326	0.3725	0.0644	−0.3081	1.11919
0.53631	0.3493	0.049	−0.3003	0.18441
0.26435	0.3507	0.0416	−0.3091	−0.43415
−0.44733	0.4245	0.1038	−0.3207	0.72123
−0.97469	0.423	0.0972	−0.3258	−1.61979
−0.87943	0.4221	0.1039	−0.3182	−0.69037
−1.46852	0.4215	0.0909	−0.3308	−1.69897
−1.08092	0.3901	0.0788	−0.3113	−1.17393
−1.24413	0.349	0.0553	−0.2937	−0.59007
1.02686	0.348	0.0462	−0.3018	−1.45593
0.035	0.346	0.0447	−0.3013	0.035
0.072	0.343	0.057	−0.286	0.072

[a] In atomic units.

four bonds C8−N7, C8−N9, C2−O11, and C6−O13. These four bonds are the most polar, and analysis of the charge density variations in these four regions would thus be instructive. Inspection of A2 vs percent change in bond order reveals the following:

1. The percent change in bond order of N7−C8 is not discriminative for biological affinity toward A2 receptor but it is necessary. That is to say, the seven highest biologically active members are distinguishable from the others in view of percent change in bond order but are indistinguishable from each other.

2. A decrease of almost −4% in bond order of C8−N9 and C6−O13 is the same for the highest four members. These four members are different with respect to percent change in C2−O11 bond order; the highest has the lowest percent change.

Up to this point, it can be concluded that C8−N9 and C6−O13 play, somehow, a role in receptor binding in a cooperative binary way. Increase of C2−O11 is necessary to decrease its competition with C8−N9 and C6−O13.

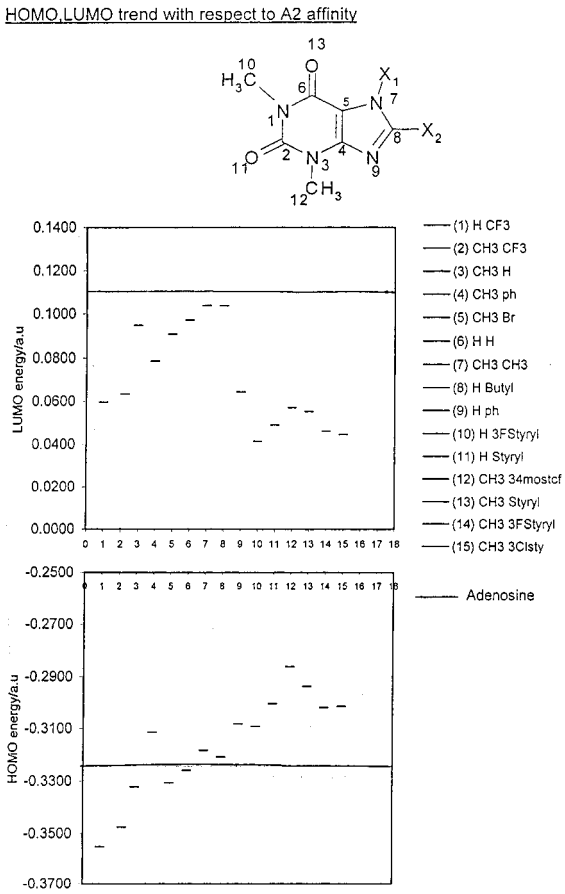
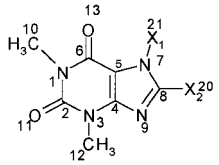


Figure 2. The variation of the HOMO and LUMO energies of 1,3-dimethylxanthines computed at the 6-31G level. Each drug is assigned a number at the horizontal axis and the substituents X1 and X2 are shown to the right of this number in the legend.

3. The fifth highest member is low in biological affinity although it shows a large decrease in C8−N9 bond order; this can be explained in view of the small decrease in C6−O13 bond order. This ascertains that C8−N9 and C6−O13 working cooperative manner toward interaction with A2 receptor.

Table 5. Comparison of Bond Order for Theophylline Derivatives at the HF/6-31G Level



substituent																
X1	X2	N1−C2	C2−N3	N3−C4	C4−C5	C5−C6	C6−N1	C5−N7	N7−C8	C8−N9	N9−C4	C8−X	N7−H21	C6−O13	C2−O11
H	H	0.833	0.879	0.764	1.430	0.998	0.745	0.746	1.060	1.438	1.271	0.920	0.801	1.812	1.803
H	CH3	0.839	0.878	0.754	1.446	1.009	0.740	0.720	1.014	1.433	1.242	0.916	0.806	1.809	1.798
H	CF3	0.828	0.874	0.759	1.450	0.971	0.754	0.756	0.997	1.431	1.237	0.928	0.780	1.838	1.808
H	CL	0.831	0.867	0.775	1.450	0.993	0.747	0.742	1.034	1.408	1.249	1.107	0.790	1.821	1.813
H	NH2	0.850	0.870	0.758	1.443	1.038	0.729	0.681	1.017	1.400	1.225	0.948	0.806	1.794	1.791
H	ph	0.827	0.877	0.735	1.455	1.011	0.751	0.712	0.952	1.409	1.202	1.057	0.798	1.810	1.798
H	styryl	0.834	0.886	0.738	1.453	1.004	0.742	0.710	0.952	1.366	1.218	1.068	0.800	1.812	1.800
H	3FStyryl	0.835	0.873	0.743	1.458	0.999	0.743	0.719	0.952	1.374	1.223	1.065	0.801	1.816	1.802
H	butyl	0.840	0.877	0.747	1.444	1.009	0.740	0.715	1.008	1.402	1.237	0.905	0.802	1.807	1.793
H	NO2	0.822	0.869	0.765	1.435	0.965	0.758	0.784	1.020	1.486	1.221	0.530	0.772	1.842	1.820
H	Br	0.835	0.871	0.778	1.445	0.992	0.742	0.733	1.022	1.402	1.257	1.074	0.790	1.827	1.807
CH3	H	0.832	0.883	0.763	1.413	1.009	0.750	0.725	1.102	1.408	1.286	0.926		1.766	1.799
CH3	CH3	0.836	0.883	0.753	1.426	1.021	0.744	0.701	1.045	1.411	1.256	0.929		1.760	1.798
CH3	CF3	0.823	0.879	0.756	1.436	0.983	0.760	0.758	1.022	1.420	1.243	0.935		1.785	1.813
CH3	Br	0.831	0.878	0.770	1.426	1.002	0.749	0.723	1.069	1.372	1.273	1.085		1.776	1.803
CH3	NH2	0.849	0.872	0.761	1.422	1.055	0.729	0.658	1.028	1.372	1.238	0.944		1.744	1.796
CH3	ph	0.839	0.881	0.742	1.433	1.011	0.745	0.715	1.013	1.394	1.236	1.028		1.768	1.790
CH3	Styryl	0.840	0.880	0.743	1.423	1.023	0.744	0.700	0.956	1.360	1.251	1.060		1.755	1.792
CH3	3FStyryl	0.839	0.878	0.743	1.426	1.018	0.746	0.704	0.957	1.364	1.249	1.060		1.759	1.795
CH3	3clsty	0.837	0.877	0.744	1.426	1.019	0.746	0.703	0.957	1.365	1.245	1.061		1.758	1.798
CH3	34mostcf	0.842	0.879	0.743	1.428	1.021	0.742	0.703	0.954	1.363	1.244	1.063		1.762	1.789

To summarize, to have a high A2-affinity a compound should possess, relative to CF3Th, lower bond orders in the N7−C8, C8−N9, and C6−O13 region. This decrease in bond order should not be less than −4% provided that the bond order in C2−O11 region is essentially nondiminished.

By the same token inspection of A1 vs percent change in bond order relative to CF3Th reveals the following:

1. Small decrease in C6−O13 is necessary but not discriminative.

2. Large decrease in C8−N9 decreases affinity toward A1 receptor.

This implies that C6−O13 is not cooperatively involved with C8−N9 in A1 receptor binding.

3. Decrease in C2−O11 bond order inhibits biological affinity toward A1 receptor.

It can be concluded from the above-mentioned remarks that C6−O13 is responsible alone for interaction with the A1 receptor

A multiple regression correlation between the A2 affinity and bond orders was obtained

$$\text{A2 affinity} = 0.4315 + 0.2052X_1 - 0.1797X_2 - 0.8601X_3; \quad r^2 = 0.77$$

$X_1 =$ sum of bond orders at (1,2), (2,3), (1,6), (6,13), (2,11)

$X_2 =$ sum of bond orders at (7,8), (8,9)

$X_3 =$ bond order at (4,5)

The previous correlation accounts for only 77% of the variance in data and elaborates upon the involvement of the two ring-system in interaction with A2 receptor. The bond order in the C4−C5 bond region accounts alone for 74% of this correlation. This complies with the qualitative picture developed for the cooperative interaction through C6−O13 and C8−N9. The small value of r^2 reveals the limited power of this correlation model and its inability to give a direct picture of the drug- receptor interaction since the competitive behavior of C2−O11 predicted qualitatively is not straightforward and the discriminative role of C8−N9 is obscured. Use of a larger number of descriptors may reveal the trend predicted qualitatively but this would require a larger number of data series.

The QSAR Model. The present study presents a comprehensive QSAR analysis for 1,3-dimethylxanthines as adenosine receptor antagonists.The activity toward both the A1 and A2 receptor sites were investigated. Constitutional, geometrical, topological, electronic descriptors, and some empirical descriptors related to the hypophilicitywere computed and analyzed. Multiple regression analysis lead to a set of equations that reflect the weight of each of the studied descriptors. The most relevant of these descriptors are grouped, and a new multiple regression analysis has been carried out and arrived at the final QSAR equation for the A2 activity as

$$\text{A2 activity} = 0.71278 + 0.013113\text{IDE} - 0.00979\text{IC} + 0.005615\text{SIC} - 0.09843\text{SPAM} + 0.692891\text{FDI} + 0.692891\text{SHP2} - 0.0081\text{Hy}$$

$$r^2 = 0.807; \text{ Anova probability of } F = 0.123 \qquad (1)$$

Although, this equation is statistically acceptable, yet it accounts for only 80% of the A2 activity. This can be greatly improved if the Egap has been taken into account.

Table 6. Some Molecular Descriptors Computed for the Validation Set

name	Hy	Ui	SHP2	FDI	SPAM	DDDA	W3D	MSDI	AECC	SIC	TIC	IC	IDE	ISIZ
xan20	−0.24	3.17	0.423	1	0.525	34.898	3384.344	5.34	8.857	0.832	76.729	3.654	3.261	179.525
xan21	−0.236	3.17	0.4	0.982	0.498	38.092	4376.683	5.655	9	0.885	92.042	4.002	3.321	206.131
xan22	0.399	3.17	0.427	1	0.518	35.937	3671.24	5.559	8.955	0.87	85.353	3.88	3.311	186.117
xan23	−0.236	3.17	0.409	1	0.521	38.911	4628.29	5.827	9.652	0.858	89.287	3.882	3.392	206.131
xan24	−0.195	3.17	0.389	1	0.518	38.089	4234.683	6.193	9.84	0.849	98.587	3.943	3.463	199.421
xan25	−0.173	3.322	0.408	1	0.515	36.905	3940.89	6.033	9.75	0.859	94.529	3.939	3.436	192.75
xan26	0.399	3.17	0.427	0.998	0.511	36.756	3929.636	5.559	8.955	0.87	85.353	3.88	3.311	192.75
xan27	−0.216	3.17	0.427	1	0.525	34.999	3392.961	5.559	8.955	0.87	85.353	3.88	3.311	179.525
xan28	−0.236	3.17	0.41	0.99	0.545	38.437	4646.202	6.014	10.348	0.827	86.042	3.741	3.465	206.131
xan29	−0.717	3.17	0.424	0.98	0.503	37.027	3926.662	5.292	8.818	0.765	75.088	3.413	3.25	199.421
xan30	−0.699	3.17	0.4	0.964	0.479	40.244	5010.602	5.609	8.958	0.841	92.529	3.855	3.314	226.477
xan31	−0.699	3.17	0.409	0.982	0.499	41.048	5282.422	5.778	9.625	0.816	89.774	3.741	3.382	226.477
xan32	−0.646	3.17	0.389	0.986	0.497	40.202	4852.897	6.15	9.808	0.795	97.192	3.738	3.456	219.66
xan33	−0.632	3.322	0.409	0.981	0.494	39.034	4534.491	5.987	9.72	0.802	93.077	3.723	3.427	212.877
xan34	−0.236	3.17	0.427	0.978	0.49	38.924	4527.031	5.51	8.913	0.805	83.777	3.642	3.301	212.877
xan35	−0.686	3.17	0.428	0.982	0.503	37.114	3934.45	5.51	8.913	0.805	83.777	3.642	3.301	199.421
xan36	−0.699	3.17	0.411	0.971	0.525	40.593	5306.058	5.962	10.333	0.786	86.529	3.605	3.454	226.477
xan37	0.556	2.585	0.475	1	0.518	33.06	2756.291	4.94	8.053	0.867	69.956	3.682	3.144	166.465
xan38	0.37	3.17	0.368	0.975	0.458	44.613	6312.792	5.877	10	0.847	103.457	3.979	3.431	254.084
xan39	0.332	3.17	0.368	0.974	0.458	44.594	6307.887	5.877	10	0.847	103.457	3.979	3.431	254.084
xan40	0.287	3.322	0.346	0.972	0.488	48.393	8191.446	6.659	11.571	0.831	111.851	3.995	3.636	282.193
xan41	0.322	3.17	0.346	0.972	0.482	48.383	8213.108	6.659	11.571	0.861	115.851	4.138	3.636	282.193

Table 7. Final Set of Descriptors Relevant to the A1 Activity Computed for the Working Data Set of 1,3-Dialkylxanthines Studied

drug	Log1/EC50	nHA	nHD	Mp	Me	Mv	Ss	Sp	Se	Sv	MW	1/EC50
Xan01	0	6	1	0.63	1.1	0.63	61.08	15.01	26.29	15.13	248.19	0
Xan02	−1.148741	6	1	0.64	1.04	0.63	36.17	13.44	21.87	13.19	180.19	0.071
Xan03	1.119189	6	1	0.63	1.03	0.62	37.83	15.2	24.75	14.79	194.22	13.158
Xan04	0.184407	6	1	0.68	1.06	0.66	39.94	14.3	22.19	13.93	214.63	1.529
Xan05	−0.434152	7	2	0.63	1.04	0.62	39.83	14.45	23.97	14.19	195.21	0.368
Xan06	0.721233	6	1	0.68	1.02	0.66	47.5	20.96	31.64	20.39	256.29	5.263
Xan07	−1.619788	6	1	0.68	1.02	0.66	51.5	23.72	35.53	22.99	282.33	0.024
Xan08	−0.690369	6	1	0.68	1.03	0.66	59.17	23.65	36.04	23.1	300.32	0.204
Xan09	−1.698970	6	1	0.62	1.01	0.59	42.33	20.48	33.42	19.59	236.31	0.02
Xan10	−1.173925	9	1	0.63	1.08	0.64	51.83	14.6	24.75	14.61	225.19	0.067
Xan11	−0.590066	6	1	0.7	1.05	0.68	38.58	14.8	22.09	14.28	259.08	0.257
Xan12	−1.455931	6	0	0.63	1.03	0.62	37.67	15.2	24.75	14.79	194.22	0.035

Equation 2 presents the final QSAR equation for the A2 activity.

$$\text{A2 activity} = 0.734094 + 0.003099\,\text{IDE} - 0.01161\,\text{IC} + 0.062631\,\text{SIC} - 0.069897\,\text{SPAM} - 0.66695\,\text{FDI} - 0.06208\,\text{SHP2} - 0.00296\,\text{Hy} - 0.05889\,\text{Egap}$$

$$r^2 = 0.98966;\ \text{Anova probability of } F = 0.00105 \quad (2)$$

This QSAR equation accounts for almost all the A2 activity and represents the weight of all relevant descriptors.

The A1 activity, on the other hand, can be described to a very satisfactory degree by the constitutional equation given in Table 2. Any attempt to incorporate additional geometrical, electronic, ... etc. descriptors lead to a lower correlation coefficient, and hence eq 3 is the final QSAR equation which accounts for the A1 activity.

$$\text{A1 activity} = 0.028 - 0.0018\text{MW} - 0.0614\text{SV} + 0.0069\text{Se} + 0.0.474\text{Sp} + 0.0019\text{Ss} + 0.8691\text{Mv} - 0.3179\text{Me} - 0.3697\text{Mp} + 0.0027\text{nHD} \quad (3)$$

$$r^2 = 0.96;\ \text{Anova probability of } F = 0.46$$

Validation and Conclusions. To examine the validity of the proposed model as a general tool for predicting the activity toward the adenosine receptor sites, a validation set of 22 xanthines is selected. Compounds selected in this set are known[18−20] to be selective to either the A1 or the A2 receptor sites. Figure 1 presents this validation set. Notice that this set spans the structure−property space explored and

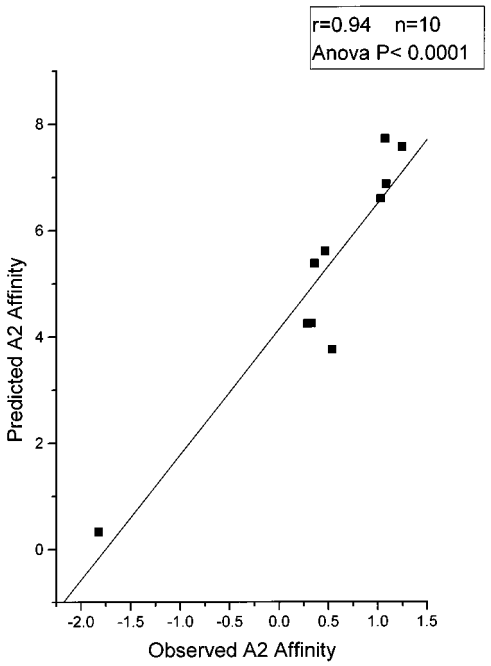


Figure 3. Correlation between observed and predicted A2 activity.

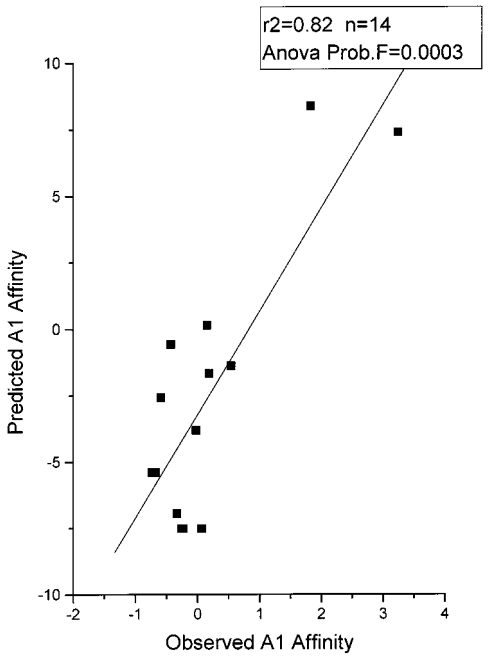


Figure 4. Correlation between observed and predicted A1 activity.

examined by the working set. In fact compounds 7, 8, 17, and 18 represent the parant structures of all elements of the validation set. Table 6 presents the molecular descriptors computed for the validation set. The correspondence between the predicted and observed A2 activity is excellent and the fit is given in Figure 3. The data presented in this figure were subjected to an Anova statistical analysis where the variance, and the probability of *F* were quite satisfactory. The correspondence between the predicted and observed A1 activity although shows a lower correlation coefficient, yet still acceptable and is shown in Figure 4.

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