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QSAR of adenosine receptor antagonists. Part 3: Exploring physicochemical requirements for selective binding of 1,2,4-triazolo[5,1-*i*]purine derivatives with human adenosine A_3 receptor subtype

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Abstract—Considering potential of selective adenosine A_3 receptor antagonists in the development of prospective therapeutic agents, an attempt has been made to explore selectivity requirements of 1,2,4-triazolo[5,1-*i*]purine derivatives for binding with cloned human adenosine A_3 receptor subtype. In this study, partition coefficient ($\log P$) values of the molecules (calculated by Crippen's fragmentation method) and Wang–Ford charges of the common atoms of the triazolopurine nucleus (calculated from molecular electrostatic potential surface of energy minimized geometry using AM1 technique) were used as independent variables along with suitable dummy parameters. The best equation describing A_3 binding affinity [$n = 29$, $Q^2 = 0.796$, $R^2_a = 0.853$, $R^2 = 0.874$, $R = 0.935$, $s = 0.342$, $F = 41.5$ (df 4, 24), SDEP = 0.396] showed parabolic relation with $\log P$ (optimum value being 4.134). Further, it was found that an aromatic substituent conjugated with the triazole nucleus should be present at R_2 position for A_3 binding affinity. Again, high negative charges on N^2 and N^4 are conducive to the binding affinity. While exploring selectivity requirements of the compounds for binding with A_3 receptor over that with A_{2A} receptor, the selectivity relation [$n = 23$, $Q^2 = 0.909$, $R^2_a = 0.918$, $R^2 = 0.933$, $R = 0.966$, $s = 0.401$, $F = 62.4$ (df 4, 18), SDEP = 0.412] showed that an aromatic R_2 substituent conjugated with the triazole nucleus contributes significantly to the selectivity. Again, presence of a 4-substituted-phenyl ring (except 4-OH–phenyl and 4-CH_3–phenyl) at R_2 position also increases selectivity. Further, charge difference between N^2 and N^{11} (negative charge on the former should be higher and that on the latter should be less) contributes significantly to the selectivity. In addition, negative charge on N^7 is conducive while presence of substituents like propyl, butyl, pentyl or phenyl at R_1 position is detrimental for the A_3 selectivity.

Adenosine is a physiological purine nucleoside, which acts as an autacoid and activates G protein-coupled membrane receptors (GPCRs), designated as A_1, A_{2A}, A_{2B} and A_3. Adenosine receptors are present on virtually every cell. However, receptor subtype distribution and densities vary greatly. Adenosine plays an important role in many pathophysiological conditions in the CNS as well as in peripheral organs and tissues.[1] The multiple effects of extracellular adenosine observed in many tissues are dependent on its ability to bind and activate GPCRs. Adenosine can mediate diverse physiological effects including bronchoconstriction, inhibition of platelet aggregation, inhibition of lipolysis, induction of sedation, vasodilation, suppression of cardiac rate and contractility,[2] and stimulation of gluconeogenesis.[1]

A_1 adenosine receptor activation inhibits inflammation, necrosis, and apoptosis after renal ischaemia-reperfusion injury in mice.[3] Its activation in CNS leads to neuroprotective effects through the blockade of neurotransmitter release, whereas, in heart, it is a potential target for cardioprotective and anti-infarct agents.[4] Some A_1 antagonists are undergoing clinical trials as renal protective agents.[4]

Specific A_{2A} agonists promote wound healing in both normal animals and in animals with impaired wound

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healing.[5] A_{2A} antagonists are being developed as novel therapeutic agents for Parkinson disease based on their capacity to enhance motor function.[6] A_{2B} receptor has been found to mediate vasodilation in some vascular beds, inhibit vascular smooth muscle growth and collagenase expression, stimulate cytokine synthesis, modulate intestinal functions and neurosecretions.[7] The presence of adenosine A_{2B} receptors in human lung mast cells mediates adenosine-induced bronchoconstriction in asthmatics.[7]

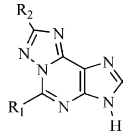
Activation of A_3 agonists also causes stimulation of phospholipase D and the release of inflammatory mediators, such as histamine from mast cells, which are responsible for inflammation and hypotension.[8] Moreover, A_3 adenosine receptor blocks ultraviolet (UV)-irradiation-induced apoptosis in mast-like cells.[5]

Quantitative structure–activity relationship (QSAR) studies have been done on various derivatives acting on different adenosine receptors. Comparative molecular field analysis (CoMFA) has been used on xanthines,[9,10] styryl-xanthines[11] and oxyadenosines[12] to study the affinity for adenosine receptors. Multiple regression analysis was used on 1,3-dimethylxanthines,[13] quinazolines[14] and quinoline derivatives[15] for the QSAR study of the binding affinity on various adenosine receptors.

The present paper attempts QSAR modelling of A_3 and A_{2A} receptor binding and explores selectivity requirements for A_3 versus A_{2A} binding of 1,2,4-triazolo[5,1-*i*]purine derivatives[16] using lipophilicity, quantum chemical and indicator parameters.

Adenosine receptor binding affinity data[16] of 1,2,4-triazolo[5,1-*i*]purine derivatives (Table 1) have been used

Table 1. Structural features, log *P* values and adenosine receptor binding affinities of 1,2,4-triazolo[5,1-*i*]purine derivatives



1-29

Sl. no	Structural features		log *P*	Adenosine receptor binding affinity								
	R_1	R_2		A_3 binding affinity (pC_3)			A_{2A} binding affinity (pC_{2A})			Selectivity ($pC_3 - pC_{2A}$)		
				Obsd[a]	Calcd[b]	Pred.[b]	Obsd[a]	Calcd[c]	Pred.[c]	Obsd[a]	Calcd[d]	Pred.[d]
1	CH_3	Ph	2.82	3.000	3.044	3.061	0.260	0.315	0.368	2.740	2.816	2.867
2	C_2H_5	Ph	3.39	3.347	3.434	3.451	0.444	0.300	0.208	2.903	2.839	2.797
3	*n*-C_3H_7	Ph	3.81	3.638	3.216	3.175	0.921	0.311	−0.032	2.717	2.990	3.094
4	*n*-C_4H_9	Ph	4.23	3.602	3.470	3.460	1.149	1.123	1.121	2.453	2.413	2.409
5	*n*-C_5H_{11}	Ph	4.64	3.523	3.427	3.421	0.699	1.102	1.134	2.824	2.448	2.408
6	*n*-C_6H_{13}	Ph	5.06	3.215	3.008	2.984	−0.892	−0.803	−0.669	4.107	4.095	4.077
7	Ph	Ph	4.20	3.387	3.399	3.399	1.638	1.345	0.655	1.749	2.076	2.111
8	*n*-C_4H_9	CH_3	2.57	0.215	0.060	−0.277	1.337	1.410	1.421	−1.122	−1.277	−1.437
9	*n*-C_4H_9	$PhCH_2$	4.33	0.167	0.322	0.659	1.328	1.281	1.275	−1.161	−1.006	−0.846
10	*n*-C_4H_9	3-Pyridyl	2.89	2.921	2.527	2.248	0.046	0.383	0.507	2.875	2.168	2.100
11	*n*-C_4H_9	2-Furyl	2.84	2.229	2.603	2.794	0.678	0.782	0.796	1.551	1.828	1.879
12	*n*-C_4H_9	Ph(2-Cl)	4.78	3.538	3.322	3.311	1.745	1.581	1.528	1.793	1.981	2.006
13	*n*-C_4H_9	Ph(3-Cl)	4.78	2.959	3.025	3.036	1.252	1.051	1.035	1.707	1.811	1.831
14	*n*-C_4H_9	Ph(4-Cl)	4.78	3.387	3.166	3.149	−0.415	−0.180	−0.131	3.802	3.385	3.279
15	*n*-C_4H_9	Ph(4-F)	4.38	3.602	3.424	3.413	0.292	−0.216	−0.320	3.310	3.613	3.675
16	*n*-C_4H_9	Ph(4-Br)	5.05	2.721	3.063	3.094	−0.519	−0.155	−0.078	3.240	3.415	3.458
17	*n*-C_4H_9	Ph(3-CH_3)	4.71	3.569	3.328	3.315	0.726	1.059	1.086	2.843	2.301	2.252
18	*n*-C_4H_9	Ph(4-CH_3)	4.71	3.481	3.333	3.325	0.745	1.012	1.033	2.736	2.393	2.359
19	*n*-C_4H_9	Ph(4-*t*-C_4H_9)	5.93	2.921	2.653	2.461	—	—	—	—	—	—
20	*n*-C_4H_9	Ph(4-CF_3)	5.15	3.215	3.140	3.134	—	—	—	—	—	—
21	*n*-C_4H_9	Ph(4-Ph)	5.90	2.309	2.689	2.934	—	—	—	—	—	—
22	*n*-C_4H_9	Ph(4-OH)	3.84	2.745	3.500	3.578	1.237	1.145	1.137	1.508	2.481	2.589
23	*n*-C_4H_9	Ph(3-OCH_3)	4.10	3.658	3.378	3.360	1.174	1.089	1.082	2.484	2.351	2.338
24	*n*-C_4H_9	Ph(4-OCH_3)	4.10	4.000	3.590	3.537	−0.204	−0.363	−0.396	4.204	4.079	4.043
25	*n*-C_4H_9	Ph(4-OC_2H_5)	4.44	3.678	3.561	3.548	−0.580	−0.389	−0.350	4.258	3.978	3.909
26	*n*-C_4H_9	Ph(4-*n*-OC_3H_7)	4.92	3.523	3.381	3.369	—	—	—	—	—	—
27	*n*-C_4H_9	Ph(3,4,5-OCH_3)$_3$	3.85	2.959	3.381	3.411	−0.398	−0.520	−0.548	3.357	3.702	3.771
28	*n*-C_4H_9	Ph(4-SCH_3)	4.66	2.481	3.189	3.247	—	—	—	—	—	—
29	*n*-C_4H_9	Ph(4-N(CH_3)$_2$)	4.51	3.174	3.532	3.567	—	—	—	—	—	—

[a] Obsd = Observed (Ref. 16), Calcd = Calculated, Pred. = Predicted.
[b] From Eq. 1.
[c] From Eq. 2.
[d] From Eq. 3.

for the present QSAR study. The biological activity data [IC_{50} (nM)] were converted to logarithmic scale [pC (μM)] and then used for subsequent QSAR analyses as the response variable. The biological activity values and structural features of the compounds are presented in Table 1. Quantum chemical calculations were done according to AM1 (Austin Model 1)[17–19] method using Chem 3D Pro[20] package. The general structure of the compounds (Fig. 1) was drawn in Chem Draw Ultra ver 5.0[20] and it was saved as the template structure. For every compound, the template structure was suitably changed considering its structural features, copied to Chem 3D ver 5.0[20] to create the 3-D model and finally the model was 'cleaned up'. The nonhydrogen common atoms of the compounds were given a serial number so that these maintain same serials in all the models (Fig. 1). Energy minimization was done under MOPAC module using RHF (restricted Hartree–Fock: closed shell) wave function.[21,22] The energy minimized geometry was used for calculation of Wang–Ford charges (obtained from molecular electrostatic potential surface) of different atoms. Lipophilicity ($\log P$) values of the compounds (Table 1) were calculated according to Ghose and Crippen's fragmentation method[23] using Chem Draw Ultra ver 5.0.[20] The biological activity data of the compounds [pC (μM)] were subjected to stepwise multiple regression with different combinations of charges of common atoms, lipophilicity and appropriate indicator parameters (defined in Table 2) to obtain the best relations using the program AUTOREG[24] developed by one of the authors.

The regression analyses were carried out using a GW-BASIC program RRR98.[24] The statistical quality of the equations[25] was judged by the parameters like explained variance (R^2_a, i.e., adjusted R^2), correlation coefficient (r or R), standard error of estimate (s), average of absolute values of the residuals (AVRES), variance ratio (F) at specified degrees of freedom (df), 95% confidence intervals of the regression coefficients, cross-validation R^2 (Q^2),[26] predicted residual sum of squares (PRESS),[26] standard deviation based on PRESS (S_{RESS})[27] standard deviation of error of prediction (SDEP)[27] and average absolute predicted residual ($Pres_{av}$). PRESS (leave-one-out) statistics[26,27] were calculated using the programs KRPRES1 and KRPRES2.[24] All the accepted equations have regression constants and F ratios significant at 95% and 99% levels, respectively, if not stated otherwise. For convenience, definitions of different variables appearing in the reported equations are given in Table 2.

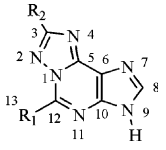


Figure 1. General structure of 1,2,4-triazolo[5,1-*i*]purine derivatives: the common atoms have been numbered 1 through 13.

Table 2. Definitions of variables

Variables	Definition
q_{2+4}	Sum of Wang–Ford charges of atoms 2 and 4
q_8	Wang–Ford charge of atom 8
q_{13}	Wang–Ford charge of atom 13
q_{2-11}	(Signed) Difference of Wang–Ford charges of atoms 2 and 11
q_7	Wang–Ford charge of atom 7
I_{aro}	Indicator variable having value 1 if the atom C_3 is not directly connected to an aromatic nucleus, value 0 otherwise
I_{R_1}	Indicator variable having value 1 if $R_1 =$ propyl, butyl, pentyl or phenyl, value 0 otherwise
I'_{4-R_2}	Indicator variable having value 1 if $R_2 =$ 4-substituted phenyl except 4-Me–Ph and 4-OH–Ph, value 0 otherwise

In case of A_3 binding activity, the best relation involving all 29 compounds was the following:

$$\begin{aligned} pC_3 &= 2.174(\pm 1.257)\log P - 0.263(\pm 0.148)\log P^2 \\ &\quad - 14.058(\pm 11.281)q_{2+4} - 3.396(\pm 0.710)I_{aro} \\ &\quad - 16.562 \\ n &= 29, \quad Q^2 = 0.796, \quad R^2_a = 0.853, \\ R^2 &= 0.874, \quad R = 0.935, \quad F = 41.5(4, 24), \\ s &= 0.342, \quad AVRES = 0.255, \quad SDEP = 0.396, \\ S_{PRESS} &= 0.435, \quad PRESS = 4.5, \quad Pres_{av} = 0.328 \end{aligned} \tag{1}$$

The 95% confidence intervals of the regression coefficients are shown within parentheses. Eq. 1 could predict 79.6% and explain 85.3% of the variance of A_3 binding affinity. Eq. 1 shows parabolic relation of the A_3 receptor binding affinity with lipophilicity ($\log P$). The optimum $\log P$ value calculated from Eq. 1 is 4.134. Further, the negative coefficient of I_{aro} suggests that an aromatic substituent conjugated with the triazole nucleus should be present at R_2 position for the A_3 binding affinity. Again, high negative charges on N^2 and N^4 are conducive to the binding affinity as evidenced by the negative coefficient of q_{2+4}. The calculated and predicted A_3 binding affinity values according to Eq. 1 are given in Table 1.

In case of A_{2A} binding activity, the best relation involving 23 compounds was the following:

$$\begin{aligned} pC_{2A} &= -76.138(\pm 30.602)q_8 + 2.642(\pm 2.142)q_{13} \\ &\quad + 0.884(\pm 0.463)I_{R_1} - 1.385(\pm 0.306)I'_{4-R_2} \\ &\quad + 11.220 \\ n &= 23, \quad Q^2 = 0.733, \quad R^2_a = 0.854, \\ R^2 &= 0.880, \quad R = 0.938, \quad F = 33.1(4, 18), \\ s &= 0.295, \quad AVRES = 0.213, \quad SDEP = 0.390, \\ S_{PRESS} &= 0.441, \quad PRESS = 3.5, \quad Pres_{av} = 0.299 \end{aligned} \tag{2}$$

Eq. 2 could predict 73.3% and explain 85.4% of the variance of A_{2A} binding affinity. Though an equation with four predictor variables derived from 23 data

points may not be statistically highly interesting, it still maintains the recommended ratio of 1:5 for number of predictor variables and data points. The variables q_8 and q_{13} in Eq. 2 indicate the importance of charge distribution in different regions of the triazolopurine nucleus for the A_{2A} binding affinity. The positive coefficient of the variable I_{R_1} indicates that groups like propyl, butyl, pentyl and phenyl are suited at R_1 position. Further, the negative coefficient of I'_{4-R_2} indicates that a 4-substituted phenyl ring (except 4-methylphenyl and 4-hydroxyphenyl) would be detrimental for the A_{2A} binding affinity. The calculated and predicted A_{2A} binding affinity values according to Eq. 2 are given in Table 1.

While exploring selectivity relations, the following best relation was obtained:

$$\begin{aligned} pC_3 - pC_{2A} &= -21.470(\pm 11.020)q_{2-11} \\ &\quad - 4.238(\pm 0.770)I_{aro} - 0.589(\pm 0.579)I_{R_1} \\ &\quad + 1.280(\pm 0.428)I'_{4-R_2} + 3.254 \\ n &= 23, \quad Q^2 = 0.909, \quad R^2_a = 0.918, \\ R^2 &= 0.933, \quad R = 0.966, \quad F = 62.4(4, 18), \\ s &= 0.401, \quad \text{AVRES} = 0.278, \quad \text{SDEP} = 0.412, \\ S_{\text{PRESS}} &= 0.465, \quad \text{PRESS} = 3.9, \quad \text{Pres}_{\text{av}} = 0.337 \end{aligned} \tag{3}$$

Eq. 3 could predict 90.9% and explain 91.8% of the variance of the selectivity. Another relation, which is statistically comparable to Eq. 3, is the following:

$$\begin{aligned} pC_3 - pC_{2A} &= -54.108(\pm 31.534)q_7 - 3.067(\pm 0.710)I_{aro} \\ &\quad - 0.873(\pm 0.579)I_{R_1} + 1.289(\pm 0.453)I'_{4-R_2} \\ &\quad - 19.158 \\ n &= 23, \quad Q^2 = 0.880, \quad R^2_a = 0.908, \\ R^2 &= 0.925, \quad R = 0.962, \quad F = 55.1(4, 18), \\ s &= 0.424, \quad \text{AVRES} = 0.316, \quad \text{SDEP} = 0.473, \\ S_{\text{PRESS}} &= 0.535, \quad \text{PRESS} = 5.1, \quad \text{Pres}_{\text{av}} = 0.407 \end{aligned} \tag{4}$$

The predictor variables of Eqs. 3 and 4 are not much intercorrelated [intercorrelation (r^2) values among predictor variables of Eqs. 3 and 4 are given in Table 3]. The negative coefficient of the variable q_{2-11} in Eq. 3 indicates that charge difference between N^2 and N^{11} (negative charge on the former should be higher and that on the latter should be less) contributes significantly to the selectivity. Again, the negative coefficient of q_7 in Eq. 4 indicates that negative charge on N^7 is conducive for the A_3 selectivity. Further, the negative coefficient of variable I_{aro} shows that that an aromatic R_2 substituent conjugated with the triazole nucleus contributes positively to the selectivity. Again, presence of a 4-substituted-phenyl ring (except 4-OH–phenyl and 4-CH_3–phenyl) at R_2 position also increases selectivity as evidenced from the positive coefficient of I'_{4-R_2}. Further, the negative coefficient of I_{R_1} indicates that presence of substituents like propyl, butyl, pentyl or phenyl at R_1 is detrimental for the A_3 selectivity. The calculated and predicted selectivity values according to Eq. 3 are given in Table 1.

Table 3. Intercorrelation (r^2) among different predictor variables for the selectivity relations ($n = 23$)

	q_7	I_{aro}	I_{R_1}	I'_{4-R_2}
q_{2-11}	0.263	0.240	0.045	0.000
q_7		0.107	0.010	0.041
I_{aro}			0.014	0.033
I_{R_1}				0.053

The present QSAR study could throw some light on the physicochemical requirements of 1,2,4-triazolo[5,1-*i*]-purine derivatives for selectively binding with A_3 receptor over A_{2A} receptor. However, more data points covering wider features of substitution pattern need to be considered to reach a conclusion.

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