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Quantitative structure-activity relationship study on affinity profile of a series of 1,8-naphthyridine antagonists toward bovine adenosine receptors

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Abstract

The affinity profiles for the bovine adenosine receptors, A_1 and A_{2A}, of a series of 1,8-naphthyridine derivatives were quantitatively analyzed using physicochemical and structural parameters of the substituents, present at varying positions of the molecules. The derived significant correlation, for bovine A_1 receptor, suggested that a R_1 substituent having a higher van der Waals volume, a R_2 substituent being a hydrogen-bond donor and a R_3 substituent able to transmit a higher field effect are helpful in augmenting the pK_i of a compound. Similarly the study, pertaining to bovine A_{2A} receptor, revealed that a less bulky substituent at R_2 and a strong electron-withdrawing substituent at R_3 are desirable in improving the binding affinity of a compound while substituents at R_1 remain insignificant to any interaction.

Keywords: *Quantitative structure-activity relationship (QSAR), antagonists of bovine adenosine receptors, analogues of 1, 8-naphthyridine, bovine A_1 and A_{2A} receptors, physicochemical parameters*

Introduction

Adenosine is formed from the purine base adenine and the ribose moiety. It is a ubiquitous neuromodulator in the periphery and the central nervous system. The biological activity of adenosine partly occurs through the activation of cell membrane belonging to the family of G-protein coupled receptors [1,2]. Presently, four adenosine receptors, A_1, A_{2A}, A_{2B} and A_3 have been cloned and are characterized pharmacologically. These receptors are associated with different second messenger systems. The adenylate cyclase inhibition is mediated through A_1 and A_3 receptors, whereas adenylate cyclase activity is stimulated by A_{2A} and A_{2B} because of the control of intracellular cyclic AMP levels. The discovery of adenosine receptor subtypes opened up new dimensions for drug treatment of a variety of conditions such as asthma, neurodegenerative disorders, psychosis and anxiety, chronic inflammatory disorders and many other physiopathological states that are believed to be associated with changes in adenosine levels [3–6].

During last few years, a variety of different classes of heterocyclic compounds have been reported to possess the antagonistic activity at adenosine receptors. These include xanthine, 7-deazaadenines, 7-deaza-8-azapurines [7–12], pyrazolo[3,4-c]quinolines [13], pyrazolo[1,5-a]pyridines [14], triazoloquinoxaline [15], triazoloquinazoline, pyrazolotriazolopyrimidine [16,17] and triazinobenzimidazolones [18]. More recently, Ferrarini et al. [19] have undertaken the synthesis and testing of a series of 1,8-naphthyridine derivatives (Figure 1) possessing a phenyl group at position 2 and various substituents at positions 4 and 7. These compounds were evaluated for their affinity for different bovine adenosine receptor subtypes. The initial structure-activity

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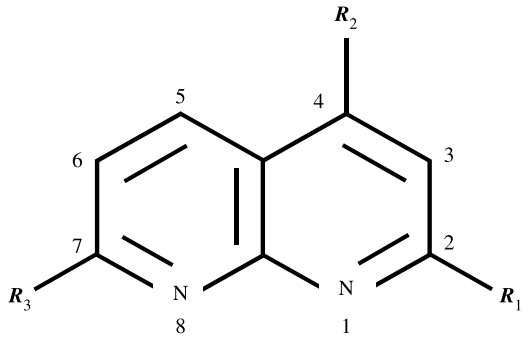

Figure 1. The derivatives of 1,8-naphthyridine.

relationship (SAR) study on these congeners were, however, directed to only alteration of the substituents at different positions of the structure but no rationale has been provided to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) on these analogues was conducted since QSAR not only provides the rationale for drug design but also enlightens the possible mechanism of action at the molecular level.

Materials and methods

The QSAR analysis was carried out on recently reported [19] derivatives of 1,8-naphthyridine. These compounds along with most appropriate quantifying parameters of the substituents and binding affinities for bovine A_1 and A_{2A} receptors are listed in Table I. The quantifying parameters such as hydrogen-bond donor, HD, Field, F, and electronic, σ are taken from the compilation of Hansch et al. [20] whereas the structural parameter, the van der Waals volume Vw for a given substituent was calculated according to the method discussed in one of our publications [21]. The subscripted numerals following the independent variables are indicative of the varying positions of title compounds. The binding affinities were derived from the inhibition of specific [^{3}H]N^6-(cyclohexyl)adenosine ([^{3}H]CHA) binding to bovine brain cortical membranes. For present work, the affinity constants K_i pertaining to bA_1 and bA_{2A} receptor subtypes are expressed as pK_i on molar basis.

The multiple regression analysis (MRA), employing the method of least squares, was used to derive significant correlation equations. The derived QSAR equations were subjected to a validation test such as the leave-one-out (LOO) [22,23] and leave-group-out (LGO) [23] methods. In the LOO method, a number of modified data sets were generated by taking away one compound successively from the parent data set. Then models were developed for each reduced data set and the response values of the deleted observations were predicted from these models. Based on the prediction error sum of squares (PRESS) and sum of squares of deviations of the experimental values from their mean (SSY) statistics, the q^2_{LOO} value was calculated. The value of $q^2_{LOO} > 0.6$ represents a robust QSAR model. In LGO method, three test sets, each representing nearly 25% of total data points, were selected. Of the three test sets, two were obtained from the cluster patterns generated in the SYSTAT [24] using the single linkage hierarchical cluster procedure involving the Euclidean distances of the respective descriptors or the activity as the case may be. The selection of the test set from the cluster tree has been done in such a way to keep the test compounds at a maximum possible distance from each other. The third test set of the compounds corresponds to the random selection procedure. With this, these test sets represent different cross-sections of compounds. The predictions of the test sets have been done with the models developed using remaining compounds in the corresponding training sets. The derived q^2_{EXT} index, for each model equation, is given along with other statistical parameters. Finally, the randomization study was carried out to ensure the robustness and predictive power of derived QSAR model. In this approach, the dependent variable, pK_i is randomly shuffled and a new QSAR model is developed using the original independent variable matrix. After 100 simulations, all new QSAR models are expected to have lower R^2 values compared to the R^2 value obtained for original model equation. If opposite happens then an acceptable QSAR model cannot be obtained for the specific modeling method and data.

Results and discussion

Table I lists a series of 1,8-naphthyridine derivatives (Figure 1) bearing mostly phenyl group at 2-position and different substituents at 4- and 7-positions. In order to account for effects produced by such substituents, a large number of descriptors related to the major interactions namely the hydrophobic, electronic and the steric were initially examined for three varying positions of the 1,8-naphthyridine ring in various possible permutations. The selected parameters for various substituents, for each of these positions were the hydrophobicity, π, hydrogen-bond donor, HD, hydrogen-bond acceptor, HA, electronic (*meta* and *para*), σ, field, F, resonance, R, dipole moment, μ, Taft's steric, Es, molar refraction, MR, molecular weight, MW, and the van der Waals volume, V_w. This resulted into a large number of QSAR equations, which were then subjected to different statistical tests. The correlation equations, which returned the highest correlation coefficient, R and F-statistic and lowest standard deviation, s are finally retained for further discussion. The highest significant correlation that was obtained is shown in

Table I. QSAR parameters and affinities of 1,8-naphthyridine derivatives at the bovine brain A_1 and A_{2A} receptors (Figure 1 for structure).

S No.	R_1	R_2	R_3	Vw_1 (10^2 Å^3)	Vw_2 (10^2 Å^3)	HD_2	F_3	σ_3	pK_i (M)[a] bA_1 Obsd	bA_1 Cald Eq.(2)	bA_1 Prcd	bA_{2A} Obsd	bA_{2A} Cald Eq.(5)	bA_{2A} Prcd
1	Ph	OH	Me	0.785	0.137	1	−0.04	−0.17	8.28	7.66	7.62	6.34	6.28	6.28
2	Ph	SH	Me	0.785	0.260	1	−0.04	−0.17	7.10	7.66	7.69	5.90	5.88	5.87
3	Ph	Cl	Me	0.785	0.244	0	−0.04	−0.17	6.00	5.86	5.84	–[b]	–	–
4	Ph	OMe	Me	0.785	0.304	0	−0.04	−0.17	5.22	5.86	5.96	–[b]	–	–
5	Ph	OPh	Me	0.785	0.844	0	−0.04	−0.17	6.09	5.86	5.83	–[b]	–	–
6	Ph	NH_2	Me	0.785	0.177	1	−0.04	−0.17	7.77	7.66	7.65	6.35	6.15	6.14
7	Ph	NMe_2	Me	0.785	0.551	0	−0.04	−0.17	6.26	5.86	5.80	5.12	4.92	4.64
8	*p*-F-Ph	OH	Me	0.831	0.137	1	−0.04	−0.17	8.28	7.80	7.77	6.20	6.28	6.29
9	*o*-F-Ph	OH	Me	0.831	0.137	1	−0.04	−0.17	7.96	7.80	7.79	6.33	6.28	6.28
10	Ph	OH	Br	0.785	0.137	1	0.44	0.23	9.15	9.01	8.98	7.18	6.91	6.83
11	Ph	OH	Cl	0.785	0.137	1	0.41	0.23	9.82	8.93	8.75	7.00	6.91	6.88
12	Ph	OH	F	0.785	0.137	1	0.43	0.06	8.39	8.99	9.12	6.77	6.64	6.62
13	Ph	OH	H	0.785	0.137	1	0.00	0.00	7.80	7.77	7.77	–[b]	–	–
14	Ph	OH	OPh	0.785	0.137	1	0.34	−0.03	7.59	8.73	8.89	5.72[c]	6.50	–
15	Ph	OH	OEt	0.785	0.137	1	0.22	−0.24	8.28	8.39	8.40	–[b]	–	–
16	Ph	OH	OMe	0.785	0.137	1	0.26	−0.27	8.80	8.50	8.48	5.90	6.13	6.14
17	Ph	H	Me	0.785	0.056	0	−0.04	−0.17	5.16	5.86	5.97	–[b]	–	–
18	*p*-NO_2-Ph	OH	Me	0.972	0.137	1	−0.04	−0.17	8.00	8.26	8.29	6.34	6.28	6.28
19	Ph	$NHNH_2$	Me	0.785	0.286	1	−0.04	−0.17	7.00	7.66	7.70	5.74	5.79	5.80
20	Ph	OH	NH_2	0.785	0.137	1	0.02	−0.66	8.28	7.83	7.80	5.23	5.52	5.61
21	Ph	OH	NMe_2	0.785	0.137	1	0.10	−0.83	9.25	8.05	8.00	5.60	5.25	5.00
22	Ph	OEt	Br	0.785	0.458	0	0.44	0.23	7.30	7.22	7.19	5.58	5.85	6.02
23	Ph	OEt	OEt	0.785	0.458	0	0.22	−0.24	6.54	6.60	6.61	–[b]	–	–
24	Ph	OH	NHAc	0.785	0.137	1	0.28	0.00	6.47[c]	8.56	–	–[b]	–	–
25	Ph	SMe	Me	0.785	0.423	0	−0.04	−0.17	6.42	5.86	5.78	–[b]	–	–
26	*p*-NH_2-Ph	OH	Me	0.884	0.137	1	−0.04	−0.17	8.17	7.98	7.96	6.30	6.28	6.28
27	*p*-AcNH-Ph	OH	Me	1.221	0.137	1	−0.04	−0.17	9.00	9.07	9.10	5.66	6.28	6.32
28	*m*-NO_2-Ph	OH	Me	0.972	0.137	1	−0.04	−0.17	7.82	8.26	8.31	6.28	6.28	6.28
29	*m*-NH_2-Ph	OH	Me	0.884	0.137	1	−0.04	−0.17	7.64	7.98	8.00	6.60	6.28	6.26
30	CH_2Ph	OH	Me	0.945	0.137	1	−0.04	−0.17	5.72[c]	8.17	–	–[b]	–	–
31	H	OH	Me	0.056	0.137	1	−0.04	−0.17	5.15	5.29	5.55	–[b]	–	–
32	n-Pr	OH	Me	0.595	0.137	1	−0.04	−0.17	7.32	7.04	7.01	6.05	6.28	6.30
33	n-Pr	OH	NH_2	0.595	0.137	1	0.02	−0.66	6.68	7.21	7.26	–[b]	–	–

[a]The affinities, determined in terms of binding constant, K_i, for bA_1 and bA_{2A} receptor subtypes and were derived from the inhibition of specific [^{3}H]CHA binding to bovine brain cortical membranes; taken from Ref. (19); [b]affinity value is not reported; [c] 'outlier' compound of present study.

Equation (1)

$$pK_i(bA_1) = 2.839(\pm 1.65)Vw_1 + 1.618(\pm 0.64)HD_2 + 2.682(\pm 1.61)F_3 + 3.754$$

$$n = 33, R = 0.804, s = 0.772, F(3,29) = 17.611,$$

$$FIT = 1.259, AIC = 0.691, q^2_{Loo} = 0.563, LOF = 0.831 \quad (1)$$

As given above, n and F represent respectively the number of data points and the F-ratio between the variances of calculated and observed activities. The ± data within the parentheses are the 95% confidence intervals. FIT is the Kubinyi function [25,26], AIC is the Akaike's information criterion [27,28] and LOF is the Friedman's lack of fit factor [29]. The FIT function is closely related to the F-statistic but proved to be a useful parameter for the assessment of the quality of the models [27,28]. The disadvantage of the F value is its sensitivity to changes in the number of independent variables, k in the equation that describes the model. The F value is more sensitive if k is small, whereas it is less sensitive if k is large. The FIT function, on the other hand, is less sensitive to a lower number k but is more sensitive to a larger number k. The best model would yield the highest value for this function. The AIC takes into account the statistical goodness of fit and the number of parameters that have to be estimated to achieve that degree of fit. The model that produces the lower AIC value should be considered potentially the most useful. The LOF factor takes into account the number of terms used in the equation and is not biased, as are the indicator variables, toward large number of parameters. A statistical sound model will generate the lower value of LOF. In a comparative study, where QSAR models are generated from the descriptors belonging to different categories, the FIT function, the AIC criterion and the LOF factor are very important parameters in explaining the best model equation [30–32]. Even in stepwise development of a QSAR equation, these parameters may play crucial role in ascertaining the overall significance of final model.

From Equation (1), it appears that R_3 substituents are engaged in electronic interaction while R_2 substituents are involved in hydrogen-bond donor interaction. The Vw_1 variable, accounting for molecular bulk, hints at the involvement of R_1 substituents in steric interaction. The derived statistical parameters of this equation, per se, do not account for the significant results as the R^2 value accounted only for 64% of the variance and q^2_{Loo} remained close to a specified level of significance (0.5). However, the F-value is significant at 99% [$F_{3,29}(0.01) = 4.538$]. These findings reflect simply upon the parametric requirements of the substituents in a compound that may lead to binding at bA_1 receptor.

In order to improve upon the significance levels of Equation (1), all data points in Table I, were further analyzed for their deviation from regular trend. Compounds **24** and **30** (Table I) are such congeners whose residuals are large (>1.0). It should be noted that it is not acceptable to remove certain compound from a QSAR analysis simply for improving a correlation. There must be certain reason to treat such a compound as an outlier. The lone compound **24** having a -$NHCOCH_3$ substituent at R_3 seems to behave abnormally due to an acetyl moiety adjacent to nitrogen atom. Comparatively, this moiety reduces electron density from 1,8-naphthyridine scaffold and therefore, elicits lower binding affinity than the expected value. Similarly, the introduction of a methylenic group between the naphthyridine nucleus and the phenyl group (—CH_2Ph at R_1) in compound **30**, renders it to exhibit lower activity possibly due to the mismatch with transmembranal region of bA_1 receptor. At removal of these two compounds from the training set, the next correlation is obtained as in Equation (2)

$$pK_i(bA_1) = 3.244(\pm 1.18)Vw_1 + 1.793(\pm 0.46)HD_2 + 2.831(\pm 1.16)F_3 + 3.429$$

$$n = 31, R = 0.908, s = 0.540, F(3,29) = 42.202,$$

$$FIT = 3.170, AIC = 0.341, \; q^2_{Loo} = 0.778,$$

$$q^2_{EXT} = 0.915, LOF = 0.419 \quad (2)$$

Now both the R- and F-values are increased to account respectively for 82% ($R^2 = 0.824$) of variance in the observed activities and 99% level of significance [$F_{3,27}(0.01) = 4.601$].

In addition, the ± data within parentheses are lowered and the q^2_{Loo} index is increased. The latter index hints at a reasonable robust QSAR model. Compared to Equation (1), the FIT is now increased while the AIC, and the LOF are decreased. Equation (2) is further subjected to external validation and randomization tests. For external validation nearly 25% compounds of total number were selected for a test set while remaining compounds were retained in the training set. Three test sets were generated following the strategy of having the compounds at a maximum possible distance from each other so that they represent different cross-sections of all the data points. Two sets were obtained from the cluster patterns generated in SYSTAT, based on the descriptors and the activity while the third set corresponds to the random selection procedure. The predictions of these test sets were made with the model equations developed using remaining compounds in

the training sets. The compounds selected for test sets, derived correlation equations from data in training set along with statistical parameters and the residuals, pK_i(obsd) – pK_i(prcd), are given in Table II. The statistical parameter q^2_{EXT}, obtained for Equation (2), has accounted for a better robust and predictive QSAR model. Finally, the activity values were randomly shuffled and a new model was developed using the original independent descriptor matrix. The process was repeated 100 times to derive every time a new model equation and associated statistical parameters. None of these models could yield the R^2-values higher than that obtained for Equation (2). This further supported for a statistically sound QSAR model. The required orthogonality conditions, amongst the independent variables of Equation (2), are shown in Table III. The calculated binding activities, using Equation 2 (listed in Table I), were remained in close agreement with the observed ones. The predicted values of the same, obtained from the LOO approach, are also included in Table I for the sake of comparison. The plot of observed versus calculated and predicted pK_i values is shown in Figure 2. Such a plot is useful to understand the goodness of fit and to identify systematic trend. From Equation (2), it appeared that R_1 substituent having higher van der Waals volume, R_2 substituent being a hydrogen-bond donor and R_3 substituent able to transmit higher field effect are helpful in augmenting the pK_i of a compound. Such a strategy may, therefore, be followed in designing new compounds of the series.

The data in Table I show that only 21 compounds have been evaluated for the affinity towards bovine A_{2A} receptor. In order to reveal the possible mechanism of action at this receptor, these data were subsequently subjected to the MRA. A significant correlation that was emerged is shown in Equation (3)

$$\begin{aligned} pK_i(bA_{2A}) &= -3.106(\pm 1.26)Vw_2 + 1.466(\pm 0.58)\sigma_3 \\ &\quad + 6.911 \\ n = 21, R = 0.847, s = 0.301, \\ F(2,18) = 22.872, FIT = 1.827, AIC = 0.104, \\ q^2_{Loo} = 0.583, LOF = 0.150 \end{aligned} \tag{3}$$

where R^2 accounted for 72% of variance in the observed pK_is and F-value remained significant at 99% level [$F_{2,18}(0.01) = 6.013$]. Also, the value obtained for q^2_{LOO} showed that the derived model is statistically sound. Above Equation reflected upon the role of R_2 and R_3 substituents only while the R_1 substituents remain insensitive to any interaction. This implies that the naphthyridine derivatives interact differently at two aforesaid receptors. The same is also apparent from a poor correlation, derived between $pK_i(bA_1)$ and $pK_i(bA_{2A})$, shown in Equation (4)

$$\begin{aligned} pK_i(bA_1) &= 0.747(\pm 0.667)pK_i(bA_{2A}) + 3.494 \\ n = 21, r = 0.474, s = 0.766, F(1,19) = 5.505, \\ FIT = 0.250, AIC = 0.612 \end{aligned} \tag{4}$$

The limited structural differences that exist in the transmembranal region of the two receptors, bA_1AR and $bA_{2A}AR$, perhaps influenced the ability of the title compounds to interact differently with these receptors. Equation (3) was further improved by ignoring a lone compound **14**, bearing a phenoxy group at R_3. This bulky substituent may not be accommodated

Table II. Test sets, derived correlations on training set by external validation method and residuals of compounds of test sets.

Compounds in Test set[a]	Derived equation from data in training set[b]	Residuals [pK_i (Obsd) – pK_i (Prcd)]
	For bA_1 receptor subtype	
4, 8, 13, 16, 22, 27, 28, 31	$pK_i(bA_1) = 3.148(\pm 3.50)Vw_1 + 1.711(\pm 0.61)HD_2 + 2.618(\pm 1.57)F_3 + 3.599$ $n = 23, R = 0.876, s = 0.599, F(3,19) = 20.807$	0.74, 0.46, 0.02, 0.34, 0.08, −0.05, −0.45, −0.23
2, 7, 11, 14, 15, 16, 19, 28, 31	$pK_i(bA_1) = 3.013(\pm 1.90)Vw_1 + 1.936(\pm 0.48)HD_2 + 2.664(\pm 1.35)F_3 + 3.564$ $n = 23, R = 0.917, s = 0.497, F(3,19) = 33.600$	0.44, 0.86, −1.18, −0.17, 0.24, −0.76, −0.50, −0.41
1, 5, 9, 13, 17, 21, 26, 33	$pK_i(bA_1) = 3.100(\pm 1.16)Vw_1 + 1.616(\pm 0.51)HD_2 + 2.877(\pm 1.17)F_3 + 3.617$ $n = 23, R = 0.920, s = 0.509, F(3,19) = 35.044$	0.73, 0.15, 0.27, 0.13, −0.78, 1.30, 0.31, −0.46
	For bA_{2A} receptor subtype	
2, 5, 15, 16, 21	$pK_i(bA_{2A}) = -2.795(\pm 1.17)Vw_2 + 2.122(\pm 0.62)\sigma_3 + 7.003$ $n = 15, R = 0.938, s = 0.221, F(2,12) = 43.930$	−0.02, −0.06, 0.74, −0.63, −0.21
4, 7, 12, 18, 21	$pK_i(bA_{2A}) = -4.149(\pm 1.31)Vw_2 + 1.576(\pm 0.43)\sigma_3 + 7.176$ $n = 15, R = 0.932, s = 0.187, F(2,12) = 39.913$	0.50, 0.21, 0.00, −0.68, −0.29
2, 6, 11, 15, 19	$pK_i(bA_{2A}) = -3.347(\pm 1.18)Vw_2 + 1.877(\pm 0.68)\sigma_3 + 7.030$ $n = 15, R = 0.917, s = 0.262, F(2,12) = 31.634$	0.06, 0.08, −0.16, 0.59, 0.03

[a]See numbering in Table I; [b]only the final Equations (2) and (5) were subjected to external validation.

Table III. Intercorrelation matrix[a] amongst independent variables of Equation (2).

	Vw_1	HD_2	F_3
Vw_1	1.000	0.001	0.012
HD_2		1.000	0.057
F_3			1.000

[a]Matrix elements are the r-values

Table IV. Intercorrelation matrix[a] amongst independent variables of Equation (5).

	Vw_2	σ_3
Vw_2	1.000	0.212
σ_3		1.000

[a]See footnote under Table III.

properly in the narrow binding pocket of $bA_{2A}AR$. Additionally, the poor electron-withdrawing effect revealed by this substituent may further add negatively to activity. The resulting significant correlation is shown in Equation (5)

$$\begin{aligned} pK_i(bA_{2A}) &= -3.296(\pm 1.07)Vw_2 + 1.562(\pm 0.49)\sigma_3 \\ &\quad + 6.999 \\ n = 20, R = 0.900, s = 0.251, F(2,17) &= 36.178, FIT = 3.016, AIC = 0.073 \\ q^2_{Loo} = 0.674, q^2_{EXT} &= 0.833, LOF = 0.121 \end{aligned} \quad (5)$$

Compared to Equation (3), the R^2 value is increased to account for 81% of variance in the observed binding affinities. The F-value, remaining significant at 99% level [$F_{2,17}(0.01) = 6.112$] is also increased and q^2_{LOO} index now reveals a reasonable significant QSAR model. The increased values of FIT and decreased values of AIC and LOF have further supported the strength of this model. Equation (5) was also subjected to external validation method by considering three test sets, each comprising of five compounds. The data for remaining fifteen compounds in each of the corresponding training sets have resulted in to model equations, included in Table II. The residuals obtained for compounds in test sets are also listed in this Table. The q^2_{EXT} statistics, obtained in this way, has further validated the derived model Equation (5). In randomization study, the activity values were shuffled to derive a new model. After 100 such shuffling, all the models were analyzed for the variances accounted by them. None of these models resulted into R^2 values higher than 81%, the variance accounted by model Equation (5).

From Equation (5), it appears that a less bulky substituent at R_2 and a strong electron-withdrawing substituent at R_3 are desirable in improving the binding affinity of a compound at bovine A_{2A} receptor. The calculated and predicted binding activities of compounds, included in Table I, are in analogy with the observed ones. That the variables of Equation (5) are mutually orthogonal is shown in Table IV.

The inferences drawn from present QSAR study for interaction at bovine A_1 and A_{2A} receptors may therefore be used in the synthesis of further similar compounds.

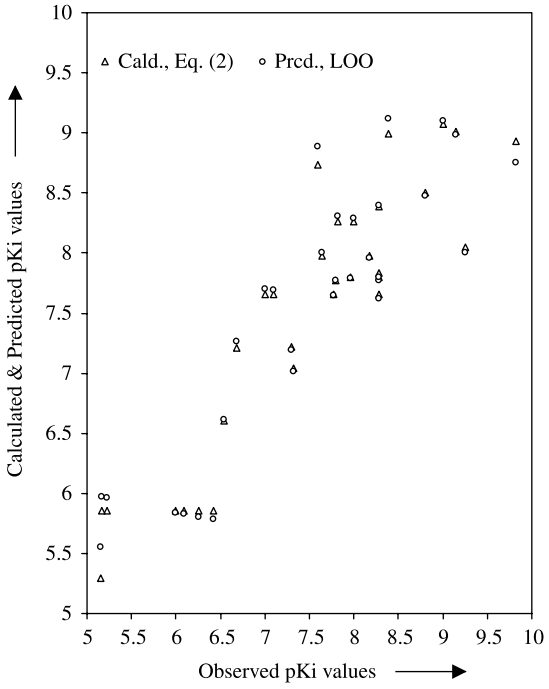

Figure 2. The plot of observed versus calculated and predicted pK_i values.

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