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Original article

GETAWAY descriptors to predicting A_{2A} adenosine receptors agonists

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Abstract

The GEometry, Topology and Atom-Weights AssemblY approach has been applied to the study of the A_{2A} adenosine receptors agonist effect of 29 adenosine analogues: N^6-arylcarbamoyl, 2-arylalkynyl-N^6-arylcarbamoyl, and N^6-carboxamido derivatives. A model able to describe more than 77% of the variance in the experimental activity was developed with the use of the mentioned approach. In contrast, no one of four different approaches, including the use of Topological, Galvez Topological Charges indexes, Geometrical and WHIM descriptors were able to explain more than 70% of the variance in the mentioned property with the same number of variables in the equation.

Keywords: QSAR; A_{2A} adenosine receptors agonists; GETAWAY descriptors

1. Introduction

Adenosine regulates a great variety of physiological functions in nervous, cardiovascular, renal, immune, and other organism systems through specific cell membrane receptors [1]. Four different adenosine receptors subtypes (A_1, A_{2A}, A_{2B} and A_3) have been defined on the basis of biological experiments and receptor cloning, and all may be coupled to the enzyme adenylate cyclase [2]. Activation of the A_1 and A_3 adenosine receptors inhibit the adenylate cyclase, diminishing the production of the second messenger cyclic AMP, whereas activation of A_{2A} and A_{2B} subtypes stimulate adenylate cyclase to produce cyclic AMP [3,4].

A_1 and A_{2A} receptors ("high affinity" receptors) are activated by nanomolar concentrations of adenosine. However, A_{2B} and A_3 receptors ("low affinity" receptors) are activated only when adenosine levels increase into the micromolar range during periods of inflammation, hipoxia or ischemia [5–7].

Adenosine is a nonselective agonist of these four receptors subtypes, is rapidly degraded in circulation, and produces a high incidence of side effects such as: chest pain, dyspnea, facial flushing, heart block, and bronchoconstriction in asthmatic patients. The negative dromotropic action and the chest pain are due to activation of A_1 adenosine receptor [8]. The A_3 adenosine receptor activation may be responsible for the bronchoconstriction that occurs in asthmatic patients [9]. On the other hand, it is known that the coronary vasodilation induced by adenosine is mediated by activation of A_{2A} subtype [10]. Hence, a compound capable of producing coronary vasodilation through activation of A_{2A} adenosine receptor, but that it is devoid of A_1 and A_3 agonist activity, would have advantage over adenosine, for the use in myocardial perfusion imaging studies [11,12]. Selective A_{2A} agonist have also potential therapeutic applications as anti-aggregatory, anti-inflammatory, anti-psychotic and anti-Huntington's disease agents [12].

Although a large number of adenosine derivatives have been synthesized and tested at the adenosine A_{2A} receptor, none of them exhibits high affinity and selectivity at the same time for this receptor subtype. So, there is a strong need for more potent and selective ligands.

Much effort has been spent trying to elucidate Structure–Activity Relationships (SARs) for adenosine analogues. However, a limited number of QSAR models have been developed about this topic [13–15]. On the other hand, 3D molecular descriptors have shown to be very useful in QSAR problems in order to perform a rational analysis of different

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pharmacological activities [16]. In this sense, a new kind of 3D molecular descriptors named Geometry, Topology and Atom-Weights AssemblY (GETAWAY) have been introduced to model physicochemical and biological properties of organic compounds [17]. This approach has been used to describe several applications for the design of biologically active compounds [18,19]. The successful results obtained by this theoretical approach in the modeling of biological properties have attracted our interest. As a result, we decided to perform a more exhaustive study, in order to test and/or validate the applicability of the GETAWAY descriptors in this area and, in particular, for the prediction of A_{2A} agonist effect of different series of adenosine analogues.

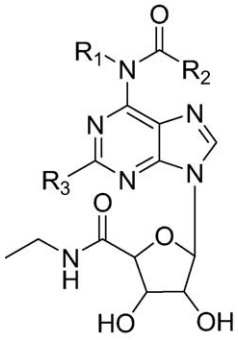
2. Materials and methods

2.1. Data set

In the present study a data set of 29 adenosine derivatives, which activities are reported in the literature by Baraldi et al. [20] was used. Molecular structure, numbering of the substituents and activities of the adenosine derivatives are summarized in Table 1.

Binding of [^{3}H]CGS 21680 to A_{2A} receptors from rat striatal membranes was performed as described previously [21]. The displacement of specified [^{3}H]CGS 21680 binding (A_{2A}) were measured in rat striatal membranes expressed as K_i in nM (n = 3–6).

Table 1
Structures and affinities in radioligand binding assays at rat brain A_{2A} adenosine receptors used in the current work



Compounds	R_1	R_2	R_3	log(K_i(A_{2A}))[a]nm
1	H	4-biphenyl	H	3.554
2	H	2,4-Cl-Ph-CH_2	H	1.425
3	H	4-CH_3O-Ph	H	2.375
4	H	2-Cl-Ph	H	3.292
5	H	Ph	H	2.826
6	H	PhCH_2NH	H	3.254
7	H	4-SO_2NH_2PhNH	H	3.072
8	H	4-CH_3CO-PhNH	H	3.021
9	H	(*R*)-α-phenylethyl-NH	H	2.446
10	H	(*S*)-α-phenylethyl-NH	H	3.473
11	H	5-Me-isoxazol-3-yl-NH	H	2.946
12	H	1,3,4-thiadiazol-2-yl-NH	H	2.962
13	H	4-n-C_3H_7O-PhNH	H	2.407
14	H	Ph-CH_2CH_2NH	H	3.423
15	H	3,4-MeO-Ph-CH_2CH_2NH	H	3.196
16	H	Fur-2-yl-CH_2NH	H	3.270
17	H	4-(pyridin-2-yl-$NHSO_2$)PhNH	H	2.869
18	H	4-(5-Me-isoxazol-3-yl-$NHSO_2$)PhNH	H	2.990
19	H	4-(pyrimidin-2-yl-$NHSO_2$)PhNH	H	1.225
20	4-NO_2-Ph-NH-CO	4-NO_2-Ph-NH	H	3.403
21	5-Cl-pyridin-2-yl-NH-CO	5-Cl-pyridin-2-yl-NH	H	2.903
22	H	3-Cl-Ph-NH	Cl	2.746
23	H	4-MeO-Ph-NH	Cl	1.771
24	H	3-Cl-Ph-NH	I	4.025
25	H	4-MeO-Ph-NH	I	2.415
26	H	3-Cl-Ph-NH	n-C_4H_9–C≡C	3.853
27	H	3-Cl-Ph-NH	Ph–C≡C	4.688
28	H	4-MeO-Ph-NH	n-C_4H_9–C≡C	3.367
29	H	4-MeO-Ph-NH	Ph$(CH_2)_3$–C≡C	3.223

[a] Displacement of specified [^{3}H]CGS 21680 binding (A_{2A}) in rat striatal membranes expressed as K_i in nM (n = 3–6).

2.2. Molecular descriptors

In this way we carry out geometry optimization calculations for each compound of this study using the quantum chemical semi-empirical method AM1 included in Mopac 6.0 computer software [22]. Dragon [23] computer software was employed to calculate the GETAWAY molecular descriptors and other four kinds of descriptors such as Topological indexes, Galvez topological charge indexes, Geometrical descriptors, and Weighted Holistic Invariant Molecular (WHIM) descriptors.

Descriptors with constant values inside each group of descriptors were discarded. For the remaining descriptors, pairwise correlation analysis (see below) for all kinds of descriptors was performed. The following descriptors exclusion methods were used to reduce, in a first step, the collinearity and correlation among descriptors.

2.3. GETAWAY approach

The GETAWAY descriptors [17] are recently proposed molecular descriptors derived from a new representation of molecular structure, the *molecular influence matrix* (MIM), denoted by H and defined as the following

$$H = M \cdot (M^T \cdot M)^{-1} \cdot M^T$$

where M is the molecular matrix constituted by the centered Cartesian coordinates x, y, z of the molecule atoms (hydrogens included) in a chosen conformation, and the superscript T refers to the transposed matrix.

The diagonal elements h_{ii} of the MIM, called *leverages*, encode atomic information and represent the "influence" of each molecule atom in determining the whole shape of the molecule. In fact, mantle atoms always have higher h_{ii} values than atoms near the molecule center. Moreover, the magnitude of the maximum leverage in a molecule depends on the size and shape of the molecule itself. Each off-diagonal element h_{ij} represents the degree of accessibility of the jth atom to interactions with the ith atom or, in other words, the attitude of the two considered atoms to interact themselves. A negative sign for the off-diagonal elements means that the two atoms occupy opposite molecular regions with respect to the center, hence the degree of their mutual accessibility should be low.

Two sets of theoretically closely related molecular descriptors have been devised: H-GETAWAY descriptors have been calculated from the MIM **H**, while R-GETAWAY descriptors are from the *influence/distance matrix* **R** where the elements of the MIM are combined with those of the geometry matrix. With the aim of catching relevant chemical information, these new descriptors have been defined applying: some traditional matrix operators, concepts of the theoretical information and spatial autocorrelation formulas, and weighting the molecule atoms accounting atomic mass, polarizability, van der Waals volume, and electronegativity.

2.4. Pairwise correlation analysis

The procedure consists on the elimination of the descriptor from each pair with the modulus of the correlation coefficients higher than a predefined value R_{max} (0.90). The procedure must be carried out with care. First let $R_{ij} = R(d_i, d_j)$ be the correlation coefficient between descriptors d_i and d_j. Then, from $R_{ij} > R_{max}$ and $R_{jk} > R_{max}$ does not follow that $R_{ik} > R_{max}$. So, in this case, if d_j is eliminated, d_k must be retained.

In this work, we have used the following algorithm of the pairwise correlation analysis:

- Sort descriptors by variance and exclude all descriptors with the variance lower than the predefined value. Let D be the descriptor with the highest variance.
- Calculate correlation coefficient between D and all other descriptors.
- Exclude descriptor having the modulus of the correlation coefficient with D higher than R_{max}.
- Let D be the next descriptor with the highest variance. Go to step (2). If there are no descriptors left, stop.

2.5. Orthogonalization of molecular descriptors

Although the pairwise correlation analysis is a good method to eliminate the collinearity, in this case the correlation among the variables persist. For that reason, other method of elimination of the collinearity is necessary.

In order to avoid collinearity, Randić orthogonalization procedure was carried out [24–27]. The main philosophy of this approach is to avoid the exclusion of descriptors on the basis of collinearity with other variables previously included in the model. It is known that the interrelatedness among the different descriptors can result in highly unstable regression coefficients, which makes impossible to know the relative importance of an index and underestimates the utility of the regression coefficients in a model.

The Randić method of orthogonalization has been described in detail in several publications [24–27]. Thus, we will only give a general overview here. The first step in orthogonalizing the molecular descriptors is to select the appropriated order of orthogonalization. In this case it is the order in which the variables were selected in the forward stepwise search procedure of the linear regression analysis.

In this sense, we used $R6u+ = {}^1\Omega(R6u+)$ as the first orthogonal variable. Afterwards, the successive residuals of the step-by-step regressions between each variable selected in the model and the others in order of statistical significance were calculated [28,29]. All these residuals were used as the remnant orthogonal variables in the Eq. (3) [28,29]. In this analysis, the least-squares method selected all orthogonal analogs of collinear variables. It ensured us that, in spite of variables collinearity, each variable have an amount of information do not encoded in the others [28,29].

2.6. Statistical methods

2.6.1. Genetic algorithm (GA) analysis

Five models were developed using the descriptors obtained by Dragon computer software. All statistical analysis and data exploration was carrying out using the Statistic 6.0 [30]. The most significative parameters were identified from the data set using GA analysis [31,32].

GA is a class of methods based on biological evolution rules. The first step is to create a population of linear regression models. These regression models mate with each other, mutate, crossover, reproduce, and then evolve through successive generations toward an optimum solution. The GA simulation conditions were 10000 generations and 300 populations. The models were linear combinations of five descriptors. The GA procedure was repeated *n*-times to confirm that the selected descriptors are the most optimal descriptor set for describing the modeled property.

The exam of the regression coefficients, the standard deviations, the significances, and the number of variables in the equation determined the quality of the models.

2.6.2. Validation of the models

Lineal models were validated by calculating q^2 values. The q^2 values are calculated from "leave-one-out" (LOO) test, also known as cross-validation. A data point is removed from the set, and the regression recalculated; the predicted value for that point is then compared to its actual value. This is repeated until each datum has been omitted once; the sum of squares of these deletion residuals can then be used to calculate q^2, an equivalent statistic to R^2. The q^2 values can be considered a measure of the predictive power of a regression equation: whereas R^2 can always be increased artificially by adding more parameters (descriptors), q^2 decreases if a model is overparameterized [33] and, therefore, it is a more meaningful summary statistic for QSAR models.

3. Results and discussion

3.1. Quantitative SARs models

The model selection was subjected to the principle of parsimony. Then, we chose a function with high statistical signification, but having as few parameters (b_k) as possible. The five-dimensional models are characterized by the best compromise between predictive power and model complexity. The addition of another variable does not lead to such an increase in predictive power such that the complexity increase is counterbalanced.

The best QSAR model obtained with the GETAWAY descriptors is given below together with the statistical parameters of the regression.

$$\log(K_i) = 1.038 - 54.677 \cdot (R6u+) + 1.793 \cdot \mathrm{HGM} - 23.814 \cdot (R5e+) + 15.137 \cdot (\mathrm{HATS}\,3u) - 14.396 \cdot (R1v+) \quad \text{(Eq. 1)}$$

$N = 29$ $S = 0.375$ $R^2 = 0.778$ $F = 16.149$ $p < 10^{-5}$ $q^2 = 0.681$

where N is the number of compounds included in the model, R^2 is the correlation coefficient, S the standard deviation of the regression, F the Fisher ratio, q^2 the correlation coefficient of the cross-validation and p is the significance of the variables in the model.

The meaning of the variables included in the model and the total of the other descriptors used in the current work appear in Table 2.

However, one outlier (compounds **15**) has been removed from the complete data set; these compounds present a large residual and deleted residual (Table 3). It is not appropriate to remove compounds from a data set simply to improve a correlation because some important information may be eliminated and the model overfitting.

Analysis of the residuals and deleted residual for Eq. (1) identified to compound **15** as significant outlier.

In this sense, the compound **15** is one of the two cases in the whole data set that present two methylene groups between the aromatic ring, in common for the whole data, and the amine group at position R_2.

Removal of these compounds and subsequent re-analysis of the data set produced a following QSAR.

$$\log(K_i) = 0.2124 - 55.480 \cdot (R6u+) + 1.772 \cdot \mathrm{HGM} - 24.249 \cdot (R5e+) + 18.802 \cdot (\mathrm{HATS}\,3u) - 14.807 \cdot (R1v+) \quad \text{(Eq. 2)}$$

$N = 28$ $S = 0.331$ $R^2 = 0.831$ $F = 21.658$ $p < 10^{-5}$ $q^2 = 0.793$

In this case, the improvement of statistical parameters of Eq. (2) (standard deviation, regression coefficient and q^2 of the cross validation) justified broadly, from statistical point of view, the removal of this compounds.

However, in spite of carrying out a Pairwise Correlation Analysis of the variables, the correlation among the descriptors persists. So, due to the high intercorrelation existing among some of the descriptors (shown in Table 4), before making the interpretation of the model we need to orthogonalize the ones included in the models.

The process is repeated until all variables are completely orthogonalized, and the orthogonal variables are then used to obtain the new model.

Table 2
Topological, Galvez topological charges indexes, geometrical, whim and GETAWAY descriptors of the QSAR regression reported in this study

HGM	Geometric mean on the leverage magnitude
HATS3u	Leverage-weighted autocorrelation of lag 3/unweighted
R6u+	R maximal autocorrelation of lag 6/unweighted
R5e+	R maximal autocorrelation of lag 5/weighted by atomic Sanderson electronegativities
GGI4	Topological charge index of order 4
GGI6	Topological charge index of order 6
GGI7	Topological charge index of order 7
JGI4	Mean topological charge index of order 4
JGI6	Mean topological charge index of order 6
SPAN	Span R
G(O..O)	Sum of geometrical distances between O..O
G(Cl..Cl)	Sum of geometrical distances between Cl..Cl
G3v	3rd component symmetry directional WHIM index/weighted by atomic van der Waals volumes
G3e	3rd component symmetry directional WHIM index/weighted by atomic Sanderson electronegativities
G1p	1st component symmetry directional WHIM index/weighted by atomic polarizabilities
Tv	T total size index/weighted by atomic van der Waals volumes
Ds	D total accessibility index/weighted by atomic electrotopological states
X5A	Average connectivity index γ-5
PW5	Path/walk 5–Randić shape index
IC2	Information content index (neighborhood symmetry of 2-order)
IC5	Information content index (neighborhood symmetry of 5-order)
R1v+	R maximal autocorrelation of lag 1/weighted by atomic van der Waals volumes
AGDD	Average geometric distance degree
FDI	Folding degree index
T(N..I)	Sum of topological distance between N..I

As a result of the orthogonalization process of the Eq. (2), we obtain:

$$\log(K_i) = 0.001 - 0.371 \cdot {}^{1}\Omega R6u^{+} + 0.604 \cdot {}^{2}\Omega\mathrm{HGM} - 0.307 \cdot {}^{3}\Omega R5e^{+} + 0.392 \cdot {}^{4}\Omega\mathrm{HATS3}u - 0.280 \cdot {}^{5}\Omega R1v^{+} \quad \text{(Eq. 3)}$$

$N = 28 \quad S = 0.331 \quad R^2 = 0.831 \quad F = 21.658 \quad p < 10^{-5}$
$q^2 = 0.793$

The most important variable in this equation is ${}^{2}\Omega$(HGM), because it presents the highest coefficient. This descriptor has a positive influence in the studied property, the reason why the affinity of the adenosine analogues for the A_{2A} receptors decreases.

The HGM descriptor is defined as the geometric mean on the leverage magnitude in study. This descriptors in the isomeric series of hydrocarbons increases from linear, to more branched molecules. It is also inversely related to molecule size, decreasing when the number of atoms in the molecule increases [17]. Therefore, according to this behavior, analogues of adenosine with branched groups might possess little affinity for this type of receptors.

This behavior was observed some years ago by van Tilburg et al. [34] in a set of 2, 5′-disubstituted adenosine derivatives. These authors reported that the adenosine A_{2A} receptor accommodate only 2-substituents with a restrained spacer. This explains the rather low affinities of the 2-iodo derivatives for this receptor, and the good affinities of the compounds with larger 2-substituents that contain a relatively rigid spacer. In this sense, in a set of 2-aralkynyl and 2-heteroalkynyl derivates of adenosine-5′-*N*-ethyluronamide, Cris-

Table 3
Observed and predicted activity, residual and deleted residual of the compounds used in this study according to the Eq. (1)

Compounds	Observed activity	Predicted activity	Residual	Deleted residual
1	3.554	3.163	0.390	0.419
2	1.425	1.548	–0.123	–0.174
3	2.375	2.769	–0.394	–0.486
4	3.292	2.830	0.462	0.555
5	2.826	2.635	0.191	0.294
6	3.254	3.542	–0.289	–0.385
7	3.072	3.070	0.002	0.002
8	3.021	2.835	0.186	0.198
9	2.446	2.773	–0.328	–0.388
10	3.473	3.536	–0.064	–0.077
11	2.946	3.027	–0.081	–0.092
12	2.962	3.021	–0.058	–0.070
13	2.407	2.822	–0.415	–0.517
14	3.423	3.585	–0.162	–0.221
15	3.196	2.437	0.759	1.028
16	3.270	3.208	0.061	0.084
17	2.869	2.233	0.636	0.715
18	2.990	2.432	0.558	0.657
19	1.225	1.843	–0.617	–0.791
20	3.403	3.319	0.084	0.132
21	2.903	2.894	0.008	0.015
22	2.746	2.774	–0.028	–0.033
23	1.771	2.365	–0.594	–0.708
24	4.025	3.707	0.319	0.383
25	2.415	2.530	–0.115	–0.135
26	3.853	3.854	–0.001	–0.001
27	4.688	4.694	–0.007	–0.010
28	3.367	3.562	–0.195	–0.248
29	3.223	3.409	–0.187	–0.234

Table 4
Correlation Matrix of the variables in the model 2

	R6u+	HGM	R5e+	HATS3u	R1v+
R6u+	1.00	0.92	0.60	0.49	0.18
HGM		1.00	0.66	0.56	0.28
R5e+			1.00	0.57	0.09
HATS3u				1.00	0.52
R1v+					1.00

talli et al. reported that the affinity was reduced by introducing the bulkier naphthyl ring in position C2. Viziano et al., at the same position, reported that the presence of a bulky chain as diphenyl derivatives is detrimental for A_{2A} affinity [35,36].

A similar report was introduced by Gungor et al. in a set of N6-substituted adenosine receptor agonists, where they noticed that the size of 2-position substituent may influence the activity on A_2 receptors. In this region, hydrogen was the most effective substituent for A_2 binding affinities. For the *2*-methyl group, a slight decrease was observed, while for the *2*-phenyl substituent the binding affinity decreased dramatically. It can be assumed that the steric hindrance caused by a phenyl group placed the indolyl moiety in an unfavorable position for binding to the receptor [37].

Therefore, according to the model, the previous report and the criterion of Homma et al. one of the major determinants for the affinity at A_{2A} adenosine receptors would be bulkiness of substituents attached at the 2 and 5′ positions of the adenosine derivatives [38].

On the other hand, a group of three variables $R1v^+$, $R5e^+$ and $R6u^+$ decreases the $\log(K_i)$ and, for that reason, increases the affinity for A_{2A} adenosine receptor subtype. Especially, terms $R5e^+$ and $R6u^+$ are expected to have a high dependence on conformational changes as encoding information on pairs of atoms near each other. Jacobson et al. [39] prepared a pair of methanocarba-adenosine analogues for exploring the role of sugar puckering in ligand recognition. The (*S*)-methanocarba analogue of adenosine was only weakly active in binding to A_{2A} adenosine receptors, presumably because of an unfavorable conformation that decreases receptor binding. In contrast, the methanocarba analogues constrained in the (N)-conformation, displayed high receptor affinity. PHP-NECA possesses an asymmetrical carbon in the side chain in 2-position. For that reason, Klotz et al. investigated the stereoselectivity of the respective diastereomers [40]. These authors demonstrated that the *S*-diastereomer are about 20-fold more potent at A_{2A}-receptor than the *R*-form. For this reason, accordingly to our model and the previous reports, the stereoselectivity plays an important role for the affinity at A_{2A} adenosine receptors.

3.2. Comparison with other approaches

As we previously pointed out, one of the objectives of the current work is to compare the reliability of the GETAWAY descriptors to describe the property under study as compared with other different descriptors and methods. Consequently, we have developed other four models using the same data set that was included in the GETAWAY QSAR model. The results obtained with the use of Topological, Galvez topological charge indices, Geometrical, WHIM and GETAWAY descriptors are given in Table 5.

As it can be seen, there are remarkable differences concerning the explanation of the experimental variance given by these models compared to the GETAWAY one. While the GETAWAY QSAR model explains more than 77% of activities, the rest of the models are unable to explain more than 71% of such variance. Moreover, important statistic parameters such as the Fischer ratio (*F*) and the standard deviation (*S*) have higher quality in the case of GETAWAY model.

The GETAWAY model not only overtakes the other four models in the statistical parameters of the regression, but more significantly, in the stability to the inclusion–exclusion of compounds as measured by the correlation coefficient and standard deviation of the cross-validation. Because of that, these statistics of the leave-one-out cross validation might be considered as a good measurement of the predictability of the models. As it is shown in Table 5, the value of the determination coefficient of leave-one-out cross validation for the model obtained with the GETAWAY ($q^2 = 0.681$) was the highest for the all analyzed models, proving the predicted power of this approach and the stability of the model. These results have shown that the GETAWAY descriptors not only explain the experimental data, but seem to be the best one in doing so.

4. Concluding remarks

We have shown that the GETAWAY approach is able to describe the A_{2A} agonist activity of different N^6-arylcarbamoyl, 2-arylalkynyl-N^6-arylcarbamoyl, and N^6-carboxamide adenosine derivatives. In fact, we have developed a model to predict this effect from a data set of 29 compounds, which is both statistically and chemically sounded. This model explains more than 77% of the variance in the experimental activity with an acceptable predictive power. These features are significantly better than that obtained from four other different methodologies. In addition, accordingly to the inter-

Table 5
The statistical parameters of the lineal regressions models obtained for the five kinds of descriptors

Descriptors	Variables	S	R^2	F	q^2	S_{cv}
Topological	X5A, PW5, IC2, IC5, T(N..I)	0.474	0.646	8.396	0.391	0.621
Galvez Topological Charges indexes	GGI4, GGI6, GGI7, JGI4, JGI6	0.591	0.450	3.759	0.011	0.801
Geometrical	AGDD, SPAN, FDI, G(O..O), G(Cl..Cl)	0.436	0.701	10.760	0.515	0.555
WHIM	G3v, G3e, G1p, Tv, Ds	0.570	0.487	4.381	0.130	0.743
GETAWAY	**HGM, HATS3u, R6u+, R1v+, R5e+**	**0.375**	**0.778**	**16.149**	**0.681**	**0.464**

pretation model, the major determinants for the affinity at A_{2A} adenosine receptors would be bulkiness of substituents attached at the 2 and 5′ position and the stereoselectivity of the adenosine derivatives.

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