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A TOPS-MODE approach to predict affinity for A_1 adenosine receptors. 2-(Arylamino)adenosine analogues

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Abstract—The TOPological Sub-Structural Molecular Design (TOPS-MODE) approach has been applied to the study of the affinity of A_1 adenosine receptor of different 2-(arylamino)adenosine analogues. A model able to describe closed to 79% of the variance in the values for binding experiments of 32 analogues of these compounds through multilinear regression analysis (MRA) was developed with the use of the mentioned approach. In contrast, no one of seven different approaches, including the use of Constitutional, Topological, Molecular walk counts, BCUT, Randic Molecular profiles, Geometrical, and RDF descriptors was able to explain more than 70% of the variance in the mentioned property with the same number of descriptors. In addition, the TOPS-MODE approach permitted to find the contribution of different fragments to the biological property giving to the model a straightforward structural interpretability.

1. Introduction

Endogenously produced adenosine serves a number of roles in the body, but it is especially important as an extracellular messenger where it acts at specific receptors on the cell surface to modulate neuronal activity and inflammation.[1,2] Adenosine (ADO) acts via extracellular receptors, of which there are four subtypes (termed A_1, A_{2A}, A_{2B}, and A_3), that are coupled by G-proteins to secondary messenger systems such as the enzyme, adenylate cyclase, and ion channels.[3–6]

The A_1 ADO receptor is the best known and the most comprehensively studied ADO receptors subtype.[7–10] It has been cloned from different species, including humans.[11] During the past 20 years a large number of A_1 adenosine receptor agonists have been developed.[12,13] The A_1 agonists have therapeutic potential, for example, as analgesic, antiepileptic, and neuroprotective agents.[13]

In spite of extensive effort, the direct pharmacological modulation of adenosine receptors with agonists has not yielded useful drug candidates for human use, due to the prevalence of mechanism based side effects (prominently hemodynamic effects). A rationale for a therapeutic approach targeting an indirect modulation of ADO receptors has been proposed as providing 'site and event selectivity', with an enhanced therapeutic window.[14]

For this reason, novels A_1 agonist compounds with more selectivity are needed for the future.[15] Many researchers worldwide have been worked in the synthesis and evaluation of novel compounds.[4–6]

On the other hand, Graph–Theoretical methods have shown to be very useful in QSAR problems in order to perform a rational analysis of different pharmacological activities.[16,17] In the context of the Graph–Theoretical and Topological methods for modeling physicochemical and biological properties of chemical there has been introduced the TOPological Sub-structural MOlecular DEsign (TOPS-MODE) approach. Several applications for the design of biologically active compounds have been described.[18–20]

The successful applications of this theoretical approach to the modeling of biological properties have inspired us to perform a more exhaustive study in order to test and/

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or validate the TOPS-MODE applicability in this area. Here we will investigate the role that TOPS-MODE and other molecular descriptors calculated from the molecular structure play on the explanation of such property using a data set of 32 adenosine agonists.

2. The TOPS-MODE approach

The TOPS-MODE approach is based on the computation of the spectral moments of the bond adjacency matrix, and its mathematical basis has been described in previous reports.[21–23] In addition, a methodological explanation about the use of this approach as well as a software description[24] has been recently published.[25]

The application of TOPS-MODE approach to the study of quantitative structure–toxicity relationships can be resumed in the following set of steps:

1. To draw the hydrogen-depleted molecular graphs for each molecule of the data set.
2. To use appropriated bond weights in order to differentiate the molecular bonds, for example, bond distance, bond dipoles, bond polarizabilities, etc.
3. To compute the spectral moments of the bond matrix with the appropriated weights for each molecule in the data set generating a table in which rows correspond to the compounds and columns correspond to the spectral moments of the bond matrix. Spectral moments are defined as the trace of the different powers of the bond matrix.
4. To find a quantitative structure–activity relationship (QSAR) by using any appropriated linear or nonlinear multivariate statistical technique, such as multilinear regression analysis (MRA), etc.:

$$P = a_0\mu_0 + a_1\mu_1 + a_2\mu_2 + a_3\mu_3 + \cdots + a_k\mu_k + b \quad (1)$$

   where P is the measurement of biological activity, μ_k is the kth spectral moment, and the a_k's are the coefficients obtained by the MRA.
5. To test the predictive capability of the QSAR model by using cross-validation techniques.
6. To compute the contribution of the different fragments of interest in order to determine their quantitative contribution to the biological activity of the molecules under study.

The computation of fragment contributions to the biological property under study is probably the most important advance of the TOPS-MODE approach to the study of biological variables compared to the traditional QSAR method. This procedure can be useful for the identification of possible entity that can be further studied by using different theoretical and experimental techniques. The procedure consists of calculating the spectral moment for all the fragments contained in a given substructure, and by difference of these moments we obtain the contribution of the substructure. The general algorithm for this computational approach is as follows:

First, we select the substructure whose contribution to the moments we would like to determine. Then, we generate all the fragments, which are contained in the corresponding substructure, and calculate the spectral moments for both, the substructure and all their fragments. The contribution of the substructure to the spectral moments is finally obtained as the difference between the spectral moments of the substructure and all those from their fragments. Once, the contributions of the different structural fragments are obtained, we only need to substitute these contributions into the quantitative model developed to describe the property studied.

3. Data sets and computational strategies

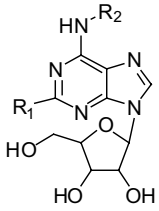
A data set of 32 adenosine agonists for which their affinities A_1 adenosine receptors were reported in the literature was selected.[1] The parameter studied is the $-\log(K_i)$ where K_i is the values for binding experiments given in nM. The names of the compounds, as well as the experimental values of K_i and $-\log(K_i)$ are shown in Table 1.

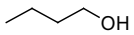
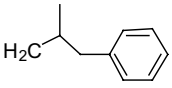
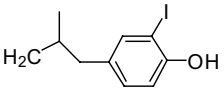
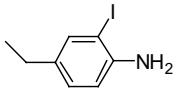
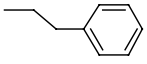
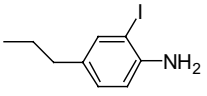
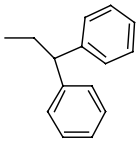
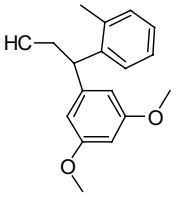
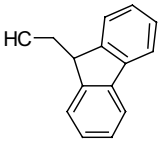
TOPS-MODE[25] and DRAGON[26] computer softwares were employed to calculate the molecular descriptors. In the case of TOPS-MODE software, the hydrophobicity, the molecular refractivity and the atom polarizability were used as bond weight for making differentiations of heteroatom. The selection of only these types of descriptors from the whole pool of nine types included in TOPS-MODE methodology was carried out on the sake of simplicity and on the belief that polarity and hydrophobic parameters influence the interaction of these adenosine analogues with the A_1 subtype receptor. We also used multiplications of spectral moments as independent variables for describing biological characteristics.[27] In this case we only multiplied μ_0 for the first seven spectral moments obtaining eight new variables. The total number of descriptors used in this model was 69 (45 spectral moments + 24 multiplications of moments).

On the other hand, we carry out geometry optimization calculations for each compound used in this study using the quantum chemical semi-empirical method AM1[28] included in MOPAC 6.0.[29] Other seven models were developed using the computer software Dragon,[26] calculating the Constitutional, Topological, Molecular walk counts, BCUT, Randic Molecular profiles, Geometrical, and RDF descriptors were.[30] All statistical analysis and data exploration was carried out using the STATISTICA 6.0 software.[31] The statistical processing to obtain the QSAR models was carried out by using the forward stepwise regression methods. Analysis of residuals from the regression equations was used to identify outliers.

In addition to the models considering one specific family of descriptors mixed models with the entire pool of

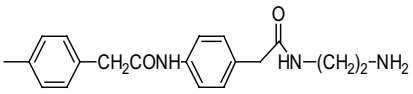
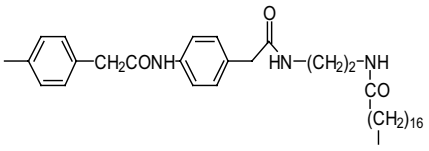
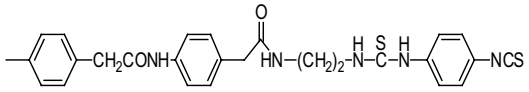
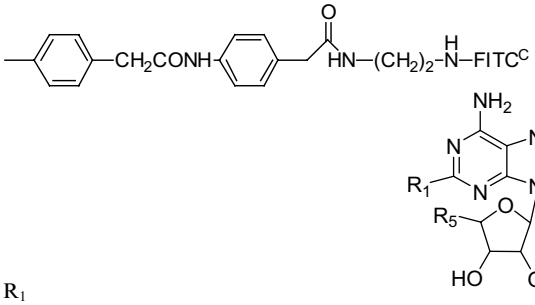
Table 1. Structures of adenosine agonists and their affinities at A_1 adenosine receptors[a]

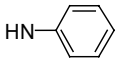
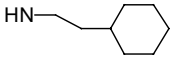
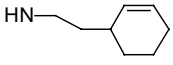
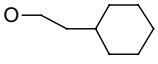
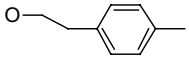
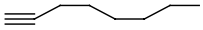
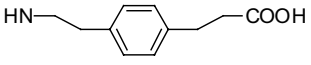
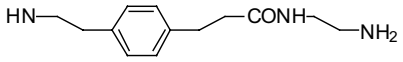


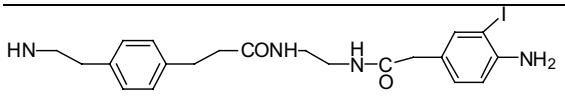
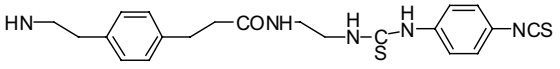
Compound	R_2	R_1	$K_i(A_1)$	$-\log(K_i)$
1		H	0.59	0.23
2		Cl	0.6	0.22
3		NH_2	8.3	−0.92
4		H	1.3	−0.11
5		H	0.3	0.52
6		H	7.0	−0.85
7		H	1.2	−0.08
8		H	0.94	0.03
9		H	4.6	−0.66
10		H	0.7	0.15
11		H	4.1	−0.61
12		H	2.0	−0.30
13		H	6.8	−0.83
14		H	142	−2.15
15		H	5.2	−0.72

(*Continued on next page*)

Table 1 (*continued*)

Compound	R_2	R_1	$K_i(A_1)$	$-\log(K_i)$
16		H	0.85	0.07
17		H	0.22	0.66
18		H	0.47	0.33
19		H	7.1	−0.85

	R_1	R_5		
20	Cl	CH_2OH	9.3	−0.97
21		CH_2OH	560	−2.75
22		CH_2OH	12,000	−4.08
23		CH_2OH	2700	−3.43
24		CH_2OH	1500	−3.18
25		CH_2OH	48	−1.68
26		CH_2OH	147	−2.17
27		CH_2OH	211	−2.32
28	H	$CONHCH_2CH_3$	6.3	−0.80
29		$CONHCH_2CH_3$	2600	−3.41
30		$CONHCH_2CH_3$	240	−2.38

	R_1	R_5		
31		$CONHCH_2CH_3$	212	−2.33
32		$CONHCH_2CH_3$	280	−2.45

[a] K_i values for binding experiments are given in nM; data is from Ref. 1.

descriptors were seek. In this experiment feature selection was carry out by means of genetic algorithm. All the parameters such as population size mutation probabilities, cross-over probabilities, smoothing and so on where fixed at their default values.[30]

The statistical significance of the models was determined by examining the regression coefficient, the standard deviation, the number of variables, the cross-validation leave-one-out statistics, and the proportion between the cases and variables in the equation.

4. Results and discussion

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

$$\begin{aligned} -\log(K_i) &= 7.751 - 0.001 \cdot \mu_5^H - 3.92 \times 10^{-9} \\ &\quad \cdot \mu_0\mu_7^{MR} - 0.058 \cdot \mu_2^{MR} + 5.53 \times 10^{-6} \\ &\quad \cdot \mu_0\mu_4^{MR} + 0.001 \cdot \mu_5^P \\ N &= 32,\ S = 0.786,\ R^2 = 0.789, \\ F &= 19.482,\ p = 0.000,\ q^2 = 0.753,\ S_{cv} = 0.824 \end{aligned} \quad (2)$$

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, p is the significance of the variables in the model, and S_{cv} is the standard deviation of the cross-validation.

The variables included in the model are the designed as follow: the sub-index represents the order of the spectral moment and the super-index the type of bond weight used, that is, H for hydrophobicity, P for polarizability and MR for molar refractivity.

The selection of this model as the best obtained with the TOPS-MODE approach was due to that present the highest explanation of the variance experimental (R^2) with the minor number of parameters (variables), the biggest Fischer ration (F), and the lowest standard deviation (S) of the models obtained with this approach.

The structural significance of this model will be more evident later when we analyze the contribution of the different structural fragments to the affinity of A_1 adenosine receptor. From the statistical point of view this model is a robust one as can be seen from the statistical parameters of the cross-validation.

Consideration of the outliers removed from a QSAR is essential. An outlier to a QSAR is identified normally by having a large standard residual.[32] There are several reasons for their occurrence in QSAR studies, for example, chemicals might be acting by a mechanism different from that of the majority of the data set. It is also likely that outliers might be a result of random experimental error that might be significant when analyzing large data sets. Although it is acceptable to remove a small number of outliers from a QSAR[33–36] it is noted that it is not acceptable to remove outlier repeatedly from a QSAR analysis simply to improve a correlation. In the current work the compound 22 present a large residual and should be consider as outlier.

Nevertheless, the regression coefficient of the model represent by Eq. 2 not improve significantly when this compounds is removed of the model ($R^2 = 0.796$). For this reason, here any compound was considered as a potential outlier.

As we advance previously one of the objectives of the current work is to compare the reliability of the TOPS-MODE approach to describe the property under study as compared with other different descriptors and methods. Consequently, we have developed seven other models using the same data set and the same number of variables that was included in the TOPS-MODE QSAR model. The results obtained with the use of Constitutional, Topological, Molecular walk counts, BCUT, Randic Molecular profiles, Geometrical, and RDF descriptors are given in Table 2. In addition the meaning of the variables used in Table 2 are given in Table 3.

Table 2. The statistical parameters of the lineal regressions models obtained whit five variables for the eight kinds of descriptors

Descriptors	Variables[a]	S	R^2	F	p	q^2
Spectral moments	μ_5^H, $\mu_0\mu_7^{MR}$, μ_2^{MR}, $\mu_0\mu_4^{MR}$, μ_5^P	0.736	0.789	19.482	0.000	0.753
Constitutional	Mp, nCIR, nR05, nN, nBnz	1.110	0.421	3.638	0.013	0.378
Topological	IVDE, BIC0, T(N..I), CIC1, PJI2	0.982	0.546	6.034	0.000	0.517
Molecular walk counts	MWC02, MWC04, MWC06, SRW07, SRW10	1.317	0.384	1.129	0.040	0.156
BCUT	BELm1, BEHv3, BELv5, BEHp2, BEHp3	1.019	0.511	5.239	0.002	0.425
Randic Molecular profiles	DP05, DP18, SP05, SP12, SP20	1.128	0.401	3.357	0.018	0.302
Geometrical	L\BW,ASP, SPH, G(O..S), G(N..Cl)	0.905	0.614	7.977	0.000	0.513
RDF	RDF030m, RDF075m, RDF020m, RDF090m, RDF035u	0.786	0.709	12.229	0.000	0.658
Mixed model	μ_5^H, $\mu_0\mu_7^{MR}$, μ_2^{MR}, $\mu_0\mu_4^{MR}$, μ_5^P	0.736	0.789	19.482	0.000	0.753

[a] The definition of the terms appears largely explained in Ref. 30.

Table 3. Symbols of the descriptors used in the models and their definitions

Mp	Mean atomic polarizability (scaled on Carbon atom)
nCIR	Number of circuits
nR05	Number of five-membered rings
nN	Number of nitrogen atoms
nBnz	Number of benzene-like rings
IVDE	Mean information content vertex degree equality
BIC0	Bond information content (neighborhood symmetry of 0-order)
T(N..I)	Sum of topological distance between N..I
CIC1	Complementary information content (neighborhood symmetry of 1-order)
PJI2	2D Petitjean shape index
MWC02	Molecular walk count of order 01
MWC04	Molecular walk count of order 04
MWC06	Molecular walk count of order 06
SRW07	Self-returning walk count of order 07
SRW10	Self-returning walk count of order 10
BELm1	Lowest eigenvalue n.1 of burden matrix/weighted by atomic masses
BEHv3	Highest eigenvalue n.3 of burden matrix/weighted by atomic van der waals volumes
BELv5	Lowest eigenvalue n.5 of burden matrix/weighted by atomic van der waals volumes
BEHp2	Highest eigenvalue n.2 of burden matrix/weighted by atomic polarizabilities
BEHp3	Highest eigenvalue n.3 of burden matrix/weighted by atomic polarizabilities
DP05	Molecular profile no. 05
DP18	Molecular profile no. 18
SP05	Shape profile no. 05
SP12	Shape profile no. 12
SP20	Shape profile no. 20
L\Bw	Length-to-breadth ratio by WHIM
ASP	Asphericity
SPH	Spherosity
G(O..S)	Sum of geometrical distances between O..S
G(N..Cl)	Sum of geometrical distances between O..S
RDF030m	Radial distribution function—3.0/weighted by atomic masses
RDF075m	Radial distribution function—7.5/weighted by atomic masses
RDF020m	Radial distribution function—2.0/weighted by atomic masses
RDF090m	Radial distribution function—9.0/weighted by atomic masses
RDF035u	Radial distribution function—3.5/unweighted
μ_5^H	Spectral moment of order 5 weighted by hydrophobicity
$\mu_0\mu_7^{\mathrm{MR}}$	Multiply of spectral moment of order 0 and spectral moment of order 7 weighted by molar refractivity
μ_2^{MR}	Spectral moment of order 2 weighted by molar refractivity
$\mu_0\mu_4^{\mathrm{MR}}$	Multiply of spectral moment of order 0 and spectral moment of order 4 weighted by molar refractivity
μ_5^P	Spectral moment of order 5 weighted by polarizability

As can be seen all the models present five variables, its is due to that best models with minor number of variables from statistical point of view not were found for any kind of descriptors. In addition, if found some model with more variables (six, seven, or more) then the statistical restriction in the number of variables that should be used as compared to the number of observation is violated. The ratio of observation to variables should be as high as possible and at least 5:1.[40] In this sense, biological activity is certainly a multivariate process, there are not infinite numbers of controlling factor, and a QSAR would be expected to have no more variables than factors controlling biological activity under study.

On the other hand, there are remarkable differences concerning the explanation of the experimental variance given by these models compared to the TOPS-MODE one. While the TOPS-MODE QSAR model explains more than 78.5% of the properties the rest of the models are unable to explain more than 70% of such variance.

The TOPS-MODE model not only overtakes the other seven models in the statistical parameters of the regression but more importantly in the stability to the inclusion–exclusion of compounds as measured by the correlation coefficient and standard deviation of the cross-validation. Because in the data set these statistics of the leave-one-out cross-validation might be considered as a good measurement of the predictability of the models. As can be seen in Table 2 the value of the determination coefficient of leave-one-out cross-validation for the model obtained with the spectral moments ($q^2 = 0.753$) was the highest for the all analyses model proving the high predict power of this approach and the high stability of the model.

However, in all previous studies we only consider models with a specified family of molecular descriptors. Thence, in order to complete the demonstration of the potentialities of TOPS-MODE over the remnant ones mixed models considering all the molecular descriptors at the same time must be developed. The total number of molecular descriptors considered here is higher than 1000. Thus, a strategy for feature selection is necessary. In this sense, we performed a genetic algorithm previous to forward stepwise regression analysis. Table 2 depicts

the result of this study. In our opinion the most interesting result is that the best model found coincides with the one reported in Eq. 2. These results have shown that the TOPS-MODE approach not only explains the experimental data, but seems to be the best one in doing so.

5. Fragments contributions

One of the most important advantages that TOPS-MODE brings for the study of QSAR and QSPR is that concerned with the structural interpretability of the models. This interpretability comes from the fact that the spectral moments can be expressed as linear combinations of structural fragments. In such a way, we can learn what fragments are making a positive or negative contribution to the property under study, which can be interpreted in terms of the physicochemical or biological processes influencing it. In Table 4 and Figure 1 we show the fragments and their contributions to the affinity at A_1 adenosine receptors as were calculated from Eq. 2.

Table 4. Contribution of different groups to the affinity at A_1 adenosine receptors.

Studied fragments	Group contribution
F_1	1.413
F_2	1.005
F_3	0.631
F_4	0.277
F_5	0.901
F_6	0.264
F_7	−0.148
F_8	−0.514
F_9	−0.861
F_{10}	0.947
F_{11}	1.336
F_{12}	0.541
F_{13}	0.142
F_{14}	−2.783
F_{15}	6.773
F_{16}	−3.068
F_{17}	−2.661
F_{18}	1.590
F_{19}	0.836
F_{20}	0.612
F_{21}	−2.160
F_{22}	−0.663
F_{23}	−2.345
F_{24}	0.675
F_{25}	0.485
F_{26}	−0.797
F_{27}	−1.245
F_{28}	−3.900
F_{29}	3.733
F_{30}	−1.532
F_{31}	−0.157
F_{32}	−3.366
F_{33}	4.701
F_{34}	1.126

Here we have only study some small fragments present in the structures of the compounds in the data set. However, the extension of this study to other fragments in such molecules or even to fragments in molecules not contained in this data set is straightforward and it has been shown for other particular cases elsewhere.[18,19,27]

According to the contributions of the fragments from F_1 to F_4 (see Fig. 1) an increase of the carbon lineal chain leads to decreases the affinity of the compound for the A_1 adenosine receptors, where an increasing of methyl group in each fragment decreasing the contribution to the property from 1.412 to 0.277.

Nevertheless, when the branching of the fragments is increased, the contribution to the property is higher as was observed in the fragments F_3, F_{10}, and F_{11} where the contribution is higher from 0.631 to 1.336. Müller[13] report that this type of contribution associate to the branching of the carbon chain increases the A_1 selectivity and the potency of the receptors agonist.

As have been observed there are a suddenly increase to the activity by ramification of the groups of the lineal aliphatic chain, each one of these fragment have the same number of carbon (Almost the same hydrophobicity), but their contribution are different, but if we compare aliphatic groups with different in ramification and different number of methyl group we could be able to appreciate higher changes in their contributions. In this case an increase of the hydrophobicity leads to enlarge the analyzed property.

TOPS-MODE by the substructural analysis provides a more exact approach to the phenomena under study. By using other descriptors could be achieve wrong conclusion about the influent of the hydrophobicity on the property without to concern another particularity as we have mentioned before.

In the same way, when a saturated cyclic fragment is inserted in a determinate structure the affinity for the A_1 receptors decreases when the number of carbon overcome the five members. This behavior can be appreciated in the contribution that presents the fragments from F_5 to F_9, where an increasing of methyl group in each group decreasing the contribution to the property from 0.901 to −0.861. Recently, different authors have been reported the inclusion of aliphatic rings in different new adenosine receptor agonist, in special in position N^6 of this adenosine structure.[12–15,37] Nonetheless, Müller[13] in an excellent review reported that N^6-cycloalkyl-substituted 1-deaza adenosine derivates were about 10-fold less active than the corresponding adenosine counterparts. Thence, this demonstrated the interesting conclusion about the influence of the aliphatic rings in the property under study.

On the other hand, an example of predominance of the electronic interactions of compounds in this series was observed by the fragments F_{20}, F_{22}, F_{23} where could be appreciated an arrangement of the contribution $F_{20} > F_{22} > F_{23}$. This behavior obeys to ability of these

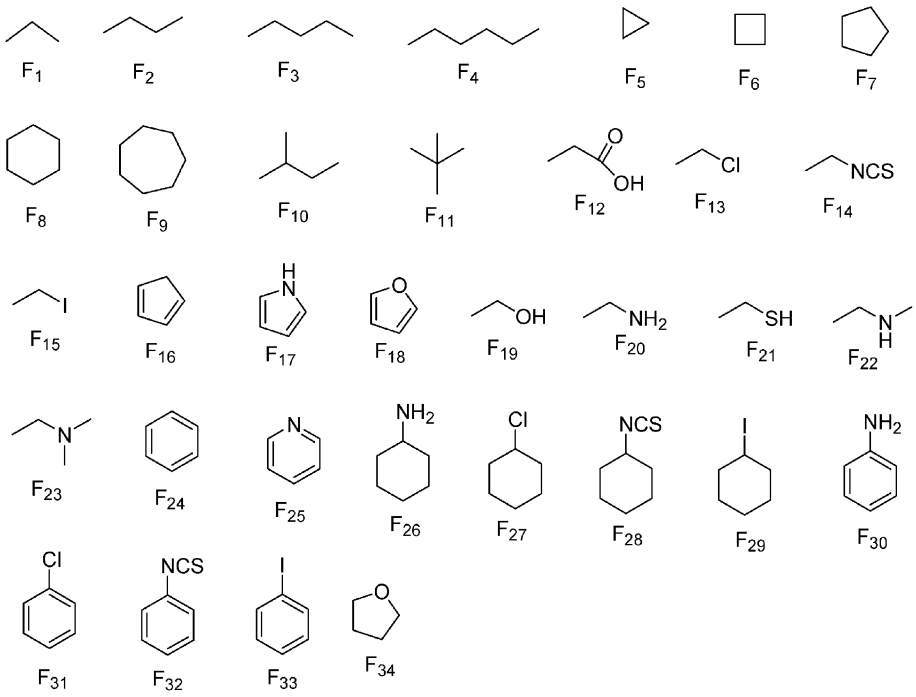


Figure 1. Structures of selected fragments for which their contributions to the affinity at A_1 adenosine receptors were calculated using Eq. 2.

amines to form hydrogen bonding. The fragment F_{23} corresponds to tertiary amine, which not has available hydrogen to form this kind of interaction. Thus it is clearly the negative contribution of F_{23} to the property under study. Therefore, we can conclude that the ability to the formation of hydrogen bonds is very important in the linkage of adenosine analogues with A_1 receptors. This phenomenon has been largely demonstrated by Lohse et al.[38] and Tao et al.[39] in excellent papers where affirm that removal of the 2′- and 3′-hydroxyl groups of adenosine led to a large decrease in affinity and a loss of intrinsic activity. In addition, Müller[13] establish that a double substitution in the N^6 led to a loss of activity too.

Therefore, this study demonstrated that the affinity of these adenosine analogues for A_1 receptors is controlled mainly by the polarity, hydrophobicity, and the ability to the formation of hydrogen bonds of these molecules.

6. Concluding remarks

We have shown that the TOPS-MODE approach is able to describe the affinity for A_1 adenosine receptors of different adenosine analogues. In fact, we have developed a model for predicting this activity of a data set of 32 compounds, which is both statistically and chemically sounded. This model explains more than 78.5% of the variance in the values for binding experiments with a good predictive power. These features are significantly better than that obtained from seven other different methodologies.

On the other hand, the main advantage of using TOPS-MODE approach in QSAR/QSPR has been confirmed again in this work. This approach is able to derive group contributions and gives simultaneously a valuable capability of interpretation, contributing to understanding the physicochemical or biological processes involved.

Finally, this study demonstrated that the affinity of these adenosine analogues for A_1 receptors is controlled mainly by the polarity, hydrophobicity, and the ability to the formation of hydrogen bonds of these molecules.

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