Asian Journal of Chemistry Vol. 20, No. 8 (2008), 6067-6074

PM3 Based Quantitative Structure Activity Relationship (QSAR) Study on 9-Benzyladenines Derivatives

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With the help of PM3 calculations using Cache software QSAR study has been made on 9-benzyladenines derivatives as adenosine deaminase inhibitors. For QSAR prediction, the 3D modelling and geometry optimization of all the derivatives of 9-benzyladenines have been done with the help of PC Model software using the semi-emperical PM3 Hamiltonian. The MOPAC calculations have been performed with Win MOPAC 7.21 software by applying key words Charge=0, Gnorm-0.1, Bonds, Geo-ok, vector density. The values of descriptors: heat of formation (ΔH_f); molecular weight (m.w.); total energy (TE); eigen value of highest occupied molecular orbital (εHOMO); eigen value of lowest unoccupied molecular orbital (εLUMO); absolute hardness (η) and electronegativity (χ), have been evaluated by PM3 methods. The correlation and cross validation coefficient values of the QSAR models are above 0.89 and 0.69, respectively. The combination of descriptors providing the best coefficient values are ΔH_f, m.w., TE and εHOMO.

Key Words: PM3, QSAR, 9-Benzyladenine derivatives, Adenosine deaminase.

INTRODUCTION

Quantitative structure activity relationships (QSARs)[1,2] are predictive tools for a preliminary evaluation of the activity of chemical compounds by using computer-aided models. PM3 based calculations are in general capable of generating a variety of isolated molecular properties[3-10]. QSAR techniques increase the probability of success and reduce time and cost involvement in drug discovery process[11,12]. The main objective of this paper is to make QSAR study of inhibitors of enzyme adenosine deaminase, which catalyses the hydrolytic deamination of purine nucleoside adenosine to inosine, that results in mutation and which in turn forms tumours. The selective inhibition of this enzyme would, therefore, be important for the treatment of tumours. Schaeffer *et al.* studied 9-alkyladenines[13], 9-(1-hydroxy-2-alkyl)adenines[14] and 9-benzyladenines[15] for their adenosine deaminase inhibition activity. QSAR study of 17 derivatives of 9-benzyladenine has been made with the reactivity indices: Heat of formation (ΔH_f), molecular weight (m.w.), total energy (TE), eigen value of HOMO (εHOMO), eigen value of LUMO (εLUMO), absolute hardness (η) and electronegativity (χ).

EXPERIMENTAL

For QSAR prediction, the 3D modelling and geometry optimization of all the derivatives of 9-benzyladenines have been performed with the help of PC Model software using the semi-emperical PM3 Hamiltonian. The MOPAC calculations have been performed with Win MOPAC 7.21 software by applying key words Charge=0, Gnorm-0.1, Bonds, Geo-ok, vector density. The values of descriptors that have been used for QSAR models have been evaluated using the same software by same methods.

TABLE-1
DERIVATIVES OF 9-BENZYLADENINES AND THEIR BIOLOGICAL ACTIVITY IN TERMS OF INHIBITORY ACTIVITY[15] log $(S/I)_{50}$

Compd. no.	X	$O_{Activity}$
1	3-COOEt	0.69
2	3-NO_2	0.52
3	3-CN	0.48
4	3-COOMe	0.44
5	3-CH_2Br	0.32
6	3-NHAc	-0.16
7	3-CH_2OH	-0.27
8	3-NH_2	-0.48
9	3-Ac	0.61
10	H	-0.20
11	4-NHAc	0.32
12	4-COOMe	0.08
13	4-CH_2Br	-0.15
14	4-NH_2	-0.33
15	4-CN	-0.55
16	4-NO_2	-0.56
17	4-CH_2OH	-0.59

X = substituents and $O_{Activity}$ = observed activity.

The values of descriptors have been derived by solving the relevant equation given below: Parr *et al.*[16] defined electronegativity as the negative of chemical potential:

$$\chi = -\mu = -(\partial E/\partial N)_{\nu(r)} \quad (1)$$

The absolute hardness, η, is defined as[17]

$$\eta = 1/2.\ (\delta\mu/\delta N)_{\nu(r)}$$
$$= 1/2.\ (\delta^2E/\delta N^2)_{\nu(r)} \quad (2)$$

where E = the total energy, N = number of electrons of the chemical species and ν(r) = the external potential.

The operational definition of absolute hardness and electronegativity[18] is defined as:

$$\eta = (IP-EA)/2 \quad (3)$$

$$\chi = -\mu = (IP+EA)/2 \quad (4)$$

where IP and EA are the ionization potential and electron affinity, respectively of the chemical species.

According to the Koopman's theorem, the IP is simply the eigen value of the HOMO with change of sign[19] and the EA is the eigen value of the LUMO with change of sign. Hence the eqns. 3 and 4 can be written as

$$\eta = (\varepsilon LUMO - \varepsilon HOMO)/2 \quad (5)$$

$$\chi = (\varepsilon LUMO + \varepsilon HOMO)/2 \quad (6)$$

The heat of formation is defined as:

$$\Delta H_f = E_{elect.} + E_{nuc.} - E_{isol.} + E_{atom} \quad (7)$$

where $E_{elect.}$ is the electronic energy, $E_{nuc.}$ is the nuclear-nuclear repulsion energy, E_{isol} is the energy required to strip all the valence electrons of all the atoms in the system and E_{atom} is the total heat of atomization of all the atoms in the system.

Total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of internuclear repulsion, E_{nr}.

The total electronic energy of the system is given by[20]

$$E = P (H + F)/2 \quad (8)$$

where P = the density matrix and H = the one-electron matrix.

Finally a more general but important property of a molecular system is the molecular weight (m.w.) which has been tested as descriptor.

RESULTS AND DISCUSSION

The observed biological activity ($O_{Activity}$) in term of log $(S/I)_{50}$ of 9-benzyladenines derivatives are given in Table-1. The values of various descriptors of the derivatives have been evaluated (Table-2).

The quantities of descriptors in a number of combinations have been used for MLR analysis and for QSAR models. Out of them only 6 QSAR models, presented below, have been found to have very high predictive power. The predicted activities of these QSAR models are presented in Table-3.

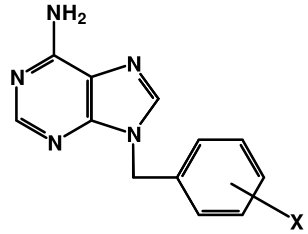

Fig. 1. Structure of 9-benzyladenines derivatives

TABLE-2
VALUES OF DESCRIPTORS OF 17 DERIVATIVES OF 9-BENZYLADENINES

Compd.	ΔH_f	m.w.	TE	εHOMO	εLUMO	η	χ	$O_{Activity}$
1	146.120	297.32	-0.007	-8.783	-0.692	4.045	-4.737	0.69
2	162.710	270.25	0.259	-8.883	-2.059	3.412	-5.471	0.52
3	117.280	250.26	0.187	-8.877	-0.864	4.007	-4.870	0.48
4	110.100	283.29	0.004	-8.815	-0.636	4.089	-4.726	0.44
5	80.347	318.18	0.128	-8.799	-0.752	4.023	-4.775	0.32
6	18.697	298.30	0.288	-8.824	-1.119	3.853	-4.972	-0.16
7	11.354	255.28	0.315	-8.783	-1.076	3.854	-4.929	-0.27
8	19.430	240.27	0.127	-8.713	-0.325	4.194	-4.519	-0.48
9	172.510	283.29	0.275	-8.748	-1.051	3.849	-4.900	0.61
10	25.407	225.25	0.374	-8.767	-1.065	3.851	-4.916	-0.20
11	122.040	298.30	0.290	-8.734	-1.003	3.866	-4.868	0.32
12	110.790	283.29	0.001	-8.845	-0.840	4.003	-4.843	0.08
13	38.029	318.18	0.379	-8.786	-1.097	3.845	-4.942	-0.15
14	46.598	240.27	0.393	-8.564	-0.996	3.784	-4.780	-0.33
15	17.199	250.26	0.187	-8.900	-0.965	3.968	-4.933	-0.55
16	8.419	270.25	0.268	-8.700	-2.114	3.293	-5.407	-0.56
17	25.548	255.28	0.057	-8.716	-0.333	4.191	-4.525	-0.59

ΔH_f = heat of formation, m.w. = molecular weight, TE = total energy, εHOMO = eigen value of highest occupied molecular orbital, εLUMO = eigen value of lowest unoccupied molecular orbital, η = absolute hardness, χ= electronegativity and $O_{Activity}$ = observed activity of compounds.

1st QSAR model: The $^{1}P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE1

RE1 = 0.00668133*ΔH_f
+0.0023642*m.w.+0.200352*TE-
0.576776* εHOMO-6.2242
rCV^2 = 0.717791
r^2 = 0.891653

Equation-RE1 involves heat of formation as first descriptor, molecular weight as second descriptor, total energy as third descriptor and eigen value of HOMO as fourth descriptor. Correlation and cross validation coefficients indicate that this model has high degree of predictive power as the value of rCV^2 and r^2 are 0.717791 and 0.891653, respectively. The values of $^{1}P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

2nd QSAR model: The $^{2}P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE2

RE2 = 0.00658986*ΔH_f
+0.00233995*m.w.-0.521497*εHOMO
+0.0448873*εLUMO -5.63933
rCV^2 = 0.694538
r^2 = 0.890764

TABLE-3
PREDICTED ACTIVITY OBTAINED FROM REGRESSION EQUATIONS, RE1-RE6

Compd.	$O_{Activity}$	$^1P_{Activity}$	$^2P_{Activity}$	$^3P_{Activity}$	$^4P_{Activity}$	$^5P_{Activity}$	$^6P_{Activity}$
1	0.69	0.519	0.568	0.568	0.568	0.568	0.568
2	0.52	0.677	0.605	0.605	0.605	0.605	0.605
3	0.48	0.309	0.310	0.310	0.310	0.310	0.310
4	0.44	0.265	0.318	0.318	0.318	0.318	0.318
5	0.32	0.165	0.189	0.189	0.189	0.189	0.189
6	-0.16	-0.247	-0.266	-0.266	-0.266	-0.266	-0.266
7	-0.27	-0.416	-0.435	-0.435	-0.435	-0.435	-0.435
8	-0.48	-0.476	-0.420	-0.420	-0.420	-0.420	-0.420
9	0.61	0.699	0.675	0.675	0.675	0.675	0.675
10	-0.20	-0.390	-0.420	-0.420	-0.420	-0.420	-0.420
11	0.32	0.392	0.373	0.373	0.373	0.373	0.373
12	0.08	0.288	0.329	0.329	0.329	0.329	0.329
13	-0.15	-0.074	-0.111	-0.111	-0.111	-0.111	-0.111
14	-0.33	-0.327	-0.349	-0.349	-0.349	-0.349	-0.349
15	-0.55	-0.347	-0.342	-0.342	-0.342	-0.342	-0.342
16	-0.56	-0.457	-0.509	-0.509	-0.509	-0.509	-0.509
17	-0.59	-0.411	-0.343	-0.343	-0.343	-0.343	-0.343

$O_{Activity}$ = Observed activity; $^1P_{Activity}$ = First predicted activity, $^2P_{Activity}$ = Second predicted activity, $^3P_{Activity}$ = Third predicted activity, $^4P_{Activity}$ = Fourth predicted activity, $^5P_{Activity}$ = Fifth predicted activity and $^6P_{Activity}$ = Sixth predicted activity.

Equation-RE2 involves heat of formation as first descriptor, molecular weight as second descriptor, eigen value of HOMO as third descriptor and eigen value of LUMO as fourth descriptor. Correlation and cross validation coefficients indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.694538 and 0.890764, respevtively. The values $^2P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

3rd QSAR model: The $^3P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE3

$$RE3 = 0.00658986*\Delta H_f$$
$$+0.00233995*m.w.-0.47661*\varepsilon HOMO$$
$$+0.0897745*\eta-5.63933$$
$$rCV\hat{}2 = 0.694538$$
$$r\hat{}2 = 0.890764$$

Equation-RE3 involves heat of formation as first descriptor, molecular weight as second descriptor, eigen value of HOMO as third descriptor and absolute hardness as fourth descriptor. Correlation and cross validation coefficients indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.694538 and 0.890764, respevtively. The values $^3P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

4th QSAR model: The ${}^{4}P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE4

RE4 = 0.00658986*ΔH_f
+0.00233995*m.w.-0.566385*εHOMO
+0.0897745*χ-5.63933
rCV^2 = 0.694538
r^2 = 0.890764

Equation-RE4 involves heat of formation as first descriptor, molecular weight as second descriptor, eigen value of HOMO as third descriptor and electronegativity as fourth descriptor. Correlation and cross validation coefficients indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.694538 and 0.890764, respevtively. The values ${}^{4}P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

5th QSAR model: The ${}^{5}P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE5

RE5 = 0.00658986*ΔH_f
+0.00233995*m.w.-0.47661*εLUMO
+1.04299*η-5.63933
rCV^2 = 0.694538
r^2 = 0.890764

Equation-RE2 involves heat of formation as first descriptor, molecular weight as second descriptor, eigen value of LUMO as third descriptor and absolute hardness as fourth descriptor. Correlation and cross validation coefficients indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.694538 and 0.890764, respevtively. The values ${}^{4}P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

6th QSAR model: The ${}^{6}P_{Activity}$ of compounds of Table-1 is calculated by solving regression equation-RE6

RE6 = 0.00658986*ΔH_f
+0.00233995*m.w.+0.566385*εLUMO
-1.04299*χ-5.63933
rCV^2 = 0.694538
r^2 = 0.890764

Equation-RE6 involves heat of formation as first descriptor, molecular weight as second descriptor, eigen value of LUMO as third descriptor and electronegativity as fourth descriptor. Correlation and cross validation coefficients indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.694538 and 0.890764, respevtively. The values ${}^{6}P_{Activity}$ of compound numbers 1-17 are listed in Table-3.

Conclusion

The quality of prediction of QSAR model is adjudged by the values of corss-validation and correlation coefficients. Collectively these values are presented in Table-4, in order of their decreasing order of creditability. The combination of descriptors providing the various models are also included in the same table. It is clearly indicated that all the QSAR models provide high degree of dependability as they have correlation value above 0.89. The best among them is 1st QSAR model, which has correlation coefficient value above 0.89 and also the cross validation coefficient above 0.71.

The combination of descriptors providing best model is heat of formation, molecular weight, total energy and eigen value of HOMO.

TABLE-4
CORRELATION COEFFICIENT (r^2) AND CROSS-VALIDATION COEFFICIENT (rCV^2) OF VARIOUS MODELS IN DECREASING ORDER OF PREDICTIVE POWER ALONGWITH THE COMBINATION OF DESCRIPTORS

RE	rCV^2	r^2	Descriptors used in the predicted activity
1	0.717791	0.891653	Heat of Formation, Molecular Weight, Total Energy, HOMO Energy
2	0.694538	0.890764	Heat of Formation, Molecular Weight, HOMO Energy, LUMO Energy
3	0.694538	0.890764	Heat of Formation, Molecular Weight, HOMO Energy, Absolute Hardness
4	0.694538	0.890764	Heat of Formation, Molecular Weight, HOMO Energy, Electronegativity
5	0.694538	0.890764	Heat of Formation, Molecular Weight, LUMO Energy, Absolute Hardness
6	0.694538	0.890764	Heat of Formation, Molecular Weight, LUMO Energy, Electronegativity

RE = Regression equation, rCV^2 = Cross-validation coefficient and r^2 = correlation coefficient.

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(*Received*: 6 November 2007; *Accepted*: 1 July 2008) AJC-6649

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