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QSAR Study on Malate Dehydrogenase Inhibitors

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Heat of formation, HOMO energy, total energy, absolute hardness, chemical potential, global hardness and energy of LUMO have been used as descriptors in different combinations, to develop quantitative structure activity relationship (QSAR) models of inhibitors of enzyme malate dehydrogenase. The inhibitors are derivatives of 7-substituted-4-hydroxyquinoline-3-carboxylic acids. Thirty QSAR models have been found to have high degree of predictive power with regression coefficient above 0.8 and six models above 0.876. The combination of descriptors providing best models are heat of formation, total energy alongwith any of two descriptors *viz*., HOMO energy, LUMO energy, absolute hardness and chemical potential.

Key Words: Quantitative structure activity relationship, PM3, Malate dehydrogenase, Quantum chemical descriptors.

INTRODUCTION

Quantitative structure activity relationship (QSAR) is a predictive tool 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. Quantitative structure activity relationship techniques increase the probability of success and reduce time and costs involvement in drug discovery process. The main objective of this paper is to make PM3 based QSAR study of inhibitors of enzyme malate dehydrogenase[1-4] which catalyzes the dehydrogenation of malate to oxaloacetate. Recently, Coats *et al.*[5] synthesized a series of 7-substituted-4-hydroxyquinoline-3-carboxylic acids and studied their inhibition activities against malate dehydrogenase. This paper presents the QSAR study of 31 derivatives of 7-substituted-4-hydroxyquinoline-3-carboxylic acid, with the help of new set of descriptors: ΔH_f (heat of formation)[6], GH (global hardness), HOMO energy[7], LUMO energy[8], TE (total energy)[9], AH (absolute hardness)[10,11], μ (chemical potential)[12], these descriptors have been successfully employed for QSAR study recently[13-15].

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EXPERIMENTAL

The study materials of this paper are derivatives of 7-substituted-4-hydroxy-quinoline-3-carboxylic acids (inhibitors of enzyme malate dehydrogenase) and are presented in Table-1. The biological activity of the derivatives has been measured in term of inhibitory activity I_{50}. For QSAR prediction, the 3D modeling and geometry optimization of all the compounds have been done with the help of PCMODEL software using the semiemperical PM3 Hamiltonian. All calculations have been performed with Win MOPAC 7.21 software by applying key words PM3 charge = 0 Gnorm = 0.1, Bonds, Geo-OK, Vectors density. The values of heat of formation (ΔH_f), energy of highest occupied molecular orbital (εHOMO), energy of lowest unoccupied molecular orbital (εLUMO), total energy (TE), absolute hardness (η) and chemical potential (μ) have been obtained from this software by solving the equations given below and result are reported in the Table-2.

Parr *et al.*[11,12] defined electronegativity as the negative of chemical potential:

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

The absolute hardness, η, is defined as

$$\eta = 1/2\cdot(\delta\mu/\delta N)_{v(r)}$$

$$\eta = 1/2\cdot(\delta^2 E/\delta N^2)_{v(r)} \quad (2)$$

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

The operational definition of absolute hardness and electronegativity 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[12] and the EA is the eigen value of the LUMO with change of sign hence the eqns. 5 and 6 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

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

where P is the density matrix and H is the one-electron matrix. These parameters and the charges on atoms were obtained from PM3 calculations.

TABLE-1
m-MDH CELL RESPIRATION INHIBITION ACTIVITIES OF
4-HYDROXYQUINOLINE-3-CARBOXYLIC ACIDS

Compd. No.	R	I_{50}
1C	H	2.98
2C	SO_2CH_3	3.18
3C	OCH_3	3.28
4C	OH	3.31
5C	CI	2.44
6C	F	1.98
7C	$CONH_2$	3.13
8C	COOH	2.97
9C	SO_3^-	2.67
10C	SO_2NH_2	3.02
11C	$COCH_3$	3.04
12C	NO_2	2.72
13C	$N(CH_3)_2$	3.32
14C	$OCH_2C_6H_5$	4.49
15C	$OCH_2C_6H_3$-3,4-Cl_2	5.32
16C	$OCH_2C_6Cl_5$	5.32
17C	OCH_2-α-$C_{10}H_7$	4.48
18C	$OCH_2C_6H_4$-4-F	4.40
19C	$OCH_2C_6H_4$-4-Br	5.17
20C	OCH_2-β-$C_{10}H_7$	5.39
21C	$OCH_2C_6H_4$-4-C_6H_5	5.83
22C	$O(CH_2)_2C_6H_5$	4.42
23C	$O(CH_2)_2C_6H_4$-4-F	4.83
24C	$O(CH_2)_2C_6H_4$-4-Br	5.60
25C	$O(CH_2)_2$-β-$C_{10}H_7$	5.66
26C	$O(CH_2)_2C_6H_4$-4-OC_6H_5	5.74
27C	$O(CH_2)_2OC_6H_5$	4.22
28C	$O(CH_2)_2OC_6H_4$-4-F	4.74
29C	$O(CH_2)_2OC_6H_4$-4-Br	5.29
30C	$O(CH_2)_2O$-β-$C_{10}H_7$	5.80
31C	$O(CH_2)_2OC_6H_4$-4-OC_6H_5	5.61

RESULTS AND DISCUSSION

The skeleton structure of 4-hydroxyquinoline-3-carboxylic acid is shown in Fig. 1 and the derivatives are listed in Table-1 alongwith their observed activity in term of inhibitory concentration (I_{50}). The values of various descriptors of the derivatives listed in Table-1 have been evaluated and are presented in Table-2.

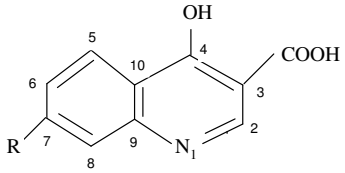

Fig. 1. 7-Substituted-4 hydroxyquinoline-3-carboxylic acid

TABLE-2
VALUES OF DESCRIPTORS OF 31 DERIVATIVES OF
4- HYDROXYQUINOLINE-3-CARBOXYLIC ACID

Compd. No.	ΔH_f	GH	TE	εHOMO	εLUMO	AH	μ	I_{50}
1C	-84.315	-8.255	-105.373	-9.381	-1.125	4.128	5.253	2.980
2C	-105.356	-7.816	-145.720	-9.076	-1.260	3.908	5.168	3.180
3C	-124.177	-8.292	-124.759	-9.259	-0.966	4.146	5.113	3.280
4C	-131.107	-8.280	-117.609	-9.302	-1.021	4.140	5.162	3.310
5C	-91.563	-8.236	-117.147	-9.424	-1.187	4.118	5.306	2.440
6C	-128.205	-8.327	-121.293	-9.576	-1.249	4.163	5.413	1.980
7C	-121.267	-8.079	-132.321	-9.593	-1.513	4.040	5.553	3.130
8C	-173.669	-8.182	-135.104	-9.637	-1.455	4.091	5.546	2.970
9C	-144.432	-5.635	-149.657	-3.832	1.803	2.818	1.014	2.670
10C	-96.093	-6.809	-147.969	-8.004	-1.195	3.404	4.599	3.020
11C	-126.349	-8.284	-130.035	-9.554	-1.270	4.142	5.412	3.040
12C	-4.261	-7.417	-137.061	-9.781	-2.365	3.708	6.073	2.720
13C	-89.487	-7.845	-129.076	-8.744	-0.899	3.922	4.821	3.320
14C	-94.495	-8.287	-160.923	-9.238	-0.951	4.144	5.095	4.490
15C	-106.424	-8.281	-184.456	-9.312	-1.031	4.141	5.172	5.320
16C	-119.730	-8.299	-219.755	-9.318	-1.018	4.150	5.168	5.320
17C	-76.278	-8.041	-184.597	-9.000	-0.959	4.020	4.980	4.480
18C	-137.959	-8.294	-176.834	-9.307	-1.013	4.147	5.160	4.400
19C	-88.178	-8.281	-170.809	-9.297	-1.016	4.140	5.156	5.170
20C	-78.855	-8.061	-184.601	-8.993	-0.932	4.031	4.962	5.390
21C	-70.441	-8.122	-197.130	-9.074	-0.952	4.061	5.013	5.310
22C	-100.429	-8.288	-168.088	-9.241	-0.953	4.144	5.097	3.810
23C	-143.877	-8.293	-183.999	-9.294	-1.001	4.146	5.148	4.830
24C	-92.627	-8.293	-177.977	-9.288	-0.995	4.146	5.142	5.600
25C	-83.139	-7.924	-191.766	-8.916	-0.992	3.962	4.954	5.660
26C	-103.505	-8.193	-216.476	-9.160	-0.967	4.097	5.063	5.740
27C	-127.266	-8.194	-180.250	-9.296	-1.102	4.097	5.199	4.220
28C	-171.441	-8.259	-196.166	-9.350	-1.090	4.130	5.220	4.740
29C	-120.529	-8.279	-190.146	-9.363	-1.084	4.139	5.224	5.290
30C	-111.271	-7.814	-203.936	-8.827	-1.013	3.907	4.920	5.800
31C	-121.045	-8.094	-228.641	-9.166	-1.073	4.047	5.119	5.610

The quantities of descriptors in a number of combinations have been used for MLR analysis and for QSAR models. Six 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.

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

RE-1 = 0.00711829*ΔH_f-0.0294163*TE-1.99716*εHOMO-2.44073*CP-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-1 involves heat of formation as first descriptor, total energy as the second descriptor, HOMO energy as thirrd descriptor and chemical potential as fourth descriptor. Correlation and cross validation coefficient indicate that this model

has high degree of predictive power as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{1}P_{Activity}$ of compounds number1C-31C are listed in Table-3.

TABLE-3
PREDICTED ACTIVITY OBTAINED FROM REGRESSION EQUATION-RE-1-RE-6

Compd. No.	Observed I_{50}	$^{1}P_{Activity}$	$^{2}P_{Activity}$	$^{3}P_{Activity}$	$^{4}P_{Activity}$	$^{5}P_{Activity}$	$^{6}P_{Activity}$
1C	2.98	2.729	2.729	2.729	2.729	2.729	2.729
2C	3.18	3.364	3.364	3.364	3.364	3.364	3.364
3C	3.28	3.114	3.114	3.114	3.114	3.114	3.114
4C	3.31	2.821	2.821	2.821	2.821	2.821	2.821
5C	2.44	2.981	2.981	2.981	2.981	2.981	2.981
6C	1.98	2.885	2.885	2.885	2.885	2.885	2.885
7C	3.13	2.949	2.949	2.949	2.949	2.949	2.949
8C	2.97	2.764	2.764	2.764	2.764	2.764	2.764
9C	2.67	2.867	2.867	2.867	2.867	2.867	2.867
10C	3.02	2.743	2.743	2.743	2.743	2.743	2.743
11C	3.04	3.113	3.113	3.113	3.113	3.113	3.113
12C	2.72	3.030	3.030	3.030	3.030	3.030	3.030
13C	3.32	3.171	3.171	3.171	3.171	3.171	3.171
14C	4.49	4.392	4.392	4.392	4.392	4.392	4.392
15C	5.32	4.960	4.960	4.960	4.960	4.960	4.960
16C	5.32	5.923	5.923	5.923	5.923	5.923	5.923
17C	4.48	5.023	5.023	5.023	5.023	5.023	5.023
18C	4.40	4.529	4.529	4.529	4.529	4.529	4.529
19C	5.17	4.694	4.694	4.694	4.694	4.694	4.694
20C	5.39	5.033	5.033	5.033	5.033	5.033	5.033
21C	5.31	5.500	5.500	5.500	5.500	5.500	5.500
22C	3.81	4.560	4.560	4.560	4.560	4.560	4.560
23C	4.83	4.701	4.701	4.701	4.701	4.701	4.701
24C	5.60	4.892	4.892	4.892	4.892	4.892	4.892
25C	5.66	5.080	5.080	5.080	5.080	5.080	5.080
26C	5.74	5.882	5.882	5.882	5.882	5.882	5.882
27C	4.22	4.588	4.588	4.588	4.588	4.588	4.588
28C	4.74	4.798	4.798	4.798	4.798	4.798	4.798
29C	5.29	5.001	5.001	5.001	5.001	5.001	5.001
30C	5.80	5.143	5.143	5.143	5.143	5.143	5.143
31C	5.61	5.991	5.991	5.991	5.991	5.991	5.991

Where observed I_{50} is observed activity; $^{1}P_{Activity}$ is first predicted activity, $^{2}P_{Activity}$ is second predicted activity, $^{3}P_{Activity}$ is third predicted activity, $^{4}P_{Activity}$ is fourth predicted activity, $^{5}P_{Activity}$ is fifth predicted activity and $^{6}P_{Activity}$ is sixth predicted activity.

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

RE-2 = 0.00711829*ΔH_f-1.22036*GH-0.0294163*TE+0.443564*εHOMO-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-2 involves heat of formation as first descriptor, global hardness as the second descriptor, total energy as third descriptor and HOMO energy as

fourth descriptor. Correlation and cross validation coefficient indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{2}P_{Activity}$ of compounds number 1C-31C are listed in Table-3.

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

RE-3 = 0.00711829*ΔH_f-0.7768*GH-0.0294163*TE+0.443564*εLUMO-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-3 involves heat of formation as first descriptor, global hardness as the second descriptor, total energy as third descriptor and LUMO energy as fourth descriptor. Correlation and cross validation coefficient indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{3}P_{Activity}$ of compounds number 1C-31C are listed in Table-3.

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

RE-4 = 0.00711829*ΔH_f-0.998582*GH-0.0294163*TE-0.443564*CP-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-4 involves heat of formation as first descriptor, global hardness as the second descriptor, total energy as third descriptor and chemical potential as fourth descriptor. Correlation and cross validation coefficient indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{4}P_{Activity}$ of compounds number 1C-31C are listed in Table-3.

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

RE-5=0.00711829*ΔH_f-0.0294163*TE-0.7768*εHOMO+1.22036*εLUMO-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-5 involves heat of formation as first descriptor, total energy as the second descriptor, HOMO energy as third descriptor and LUMO energy as fourth descriptor. Correlation and cross validation coefficient indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{5}P_{Activity}$ of compounds number 1C-31C are listed in Table-3.

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

RE-6=0.00711829*ΔH_f-0.0294163*TE+0.443564*εHOMO+2.44073*Ah-5.68456

rCV^2 = 0.659994

r^2 = 0.876067

Equation RE-6 involves heat of formation as first descriptor, total energy as the second descriptor, HOMO energy as third descriptor and absolute hardness as fourth descriptor. Correlation and cross validation coefficient indicate that this regression gives very good regression results as the value of rCV^2 and r^2 are 0.659994 and 0.876067, respectively. The values of $^{6}P_{Activity}$ of compounds number 1C-31C are listed in Table-3. With the help of above MLR equations the activity of any inhibitors can be best predicted.

The predicted activities, calculated by regression equation RE-1 to RE-6 give best QSAR models with regression coefficient 0.876067 and cross validation coefficient 0.659994. With the help of these MLR equations, the activity of any inhibitor can be best predicted. Figure for the observed activity and $^{1}P_{Activity}$-$^{6}P_{Avtivity}$ is shown in the Figs. 1-6.

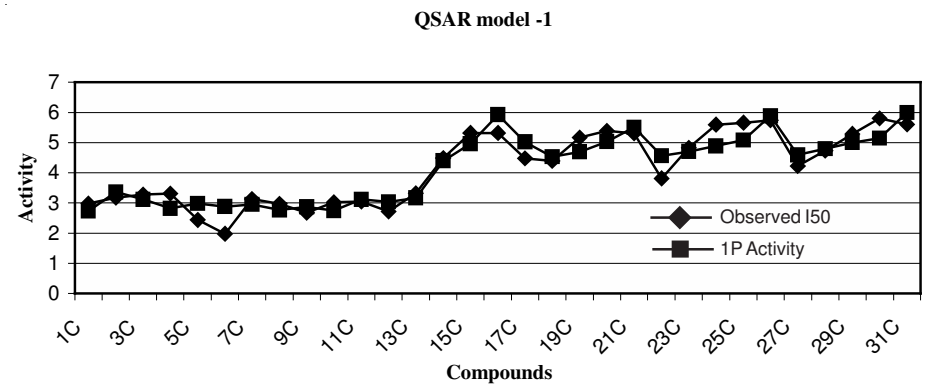

Fig. 1. Graph between predicted activity $^{1}P_{Activity}$ and observed activity

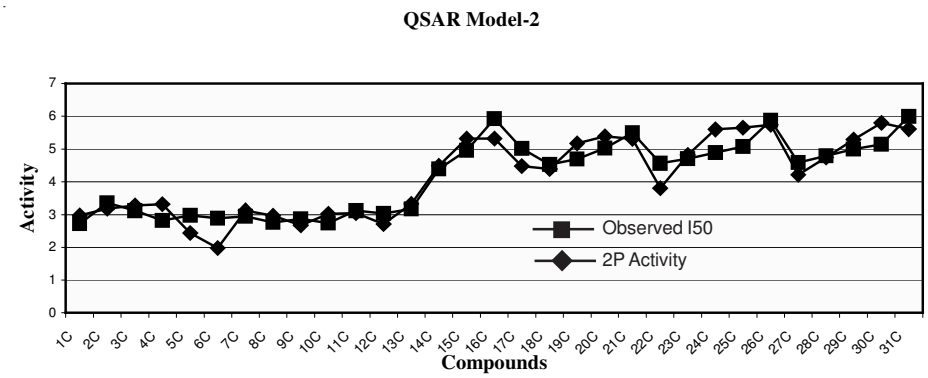

Fig. 2. Graph between predicted activity $^{2}P_{Activity}$ and observed activity

In all the above QSAR models, the first descriptor heat of formation is supported to be prime descriptor for QSAR models.

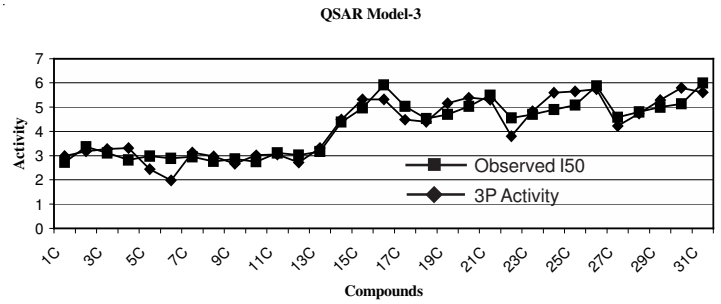

Fig. 3. Graph between predicted activity $^{3}P_{Activity}$ and observed activity

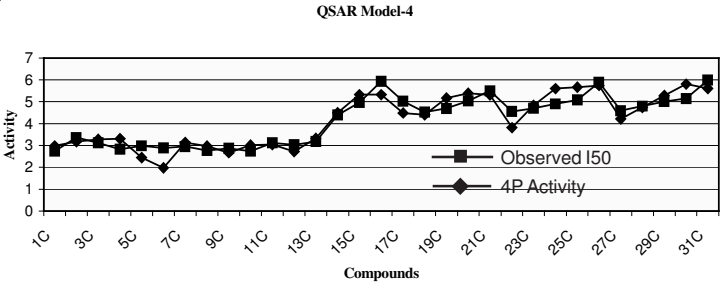

Fig. 4. Graph between predicted activity $^{4}P_{Activity}$ and observed activity

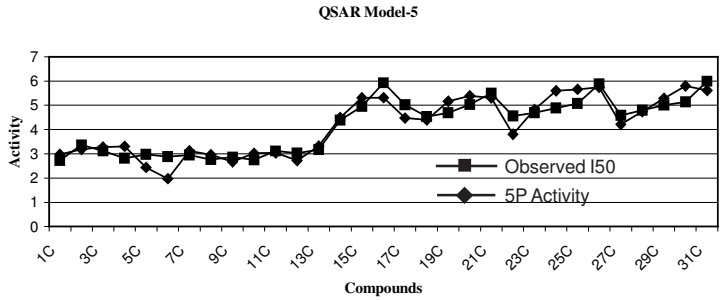

Fig. 5. Graph between predicted activity $^{5}P_{Activity}$ and observed activity

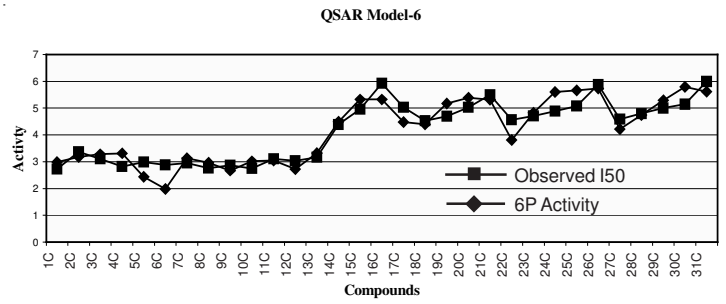

Fig. 6. Graph between predicted activity $^{6}P_{Activity}$ and observed activity

Conclusion

The quality of prediction of QSAR model is adjudged by the values of cross validation and correlation coefficient. Collectively these values are presented in Table-4. The combinations 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 0.87. The prime of descriptors providing the model are heat of formation, total energy and HOMO energy. No single descriptor has been noticed to provide any direct relationship with the activity of any 4-hydroquinoline-3-carboxylic acids derivatives. Quantum chemical descriptors, such as absolute hardness, chemical potential and global hardness have provided little contribution in preparing QSAR model.

TABLE-4
VALUES OF CORRELATION COEFFICIENT AND COMBINATION OF DESCRIPTORS

rCV^2	r^2	Descriptors used in the predicted activity
0.659994	0.876067	Heat of formation, total energy, HOMO energy, chemical potential
0.659994	0.876067	Heat of formation, global hardness, total energy, HOMO energy
0.659994	0.876067	Heat of formation, global hardness, total energy, LUMO energy
0.659994	0.876067	Heat of formation, global hardness, total energy, chemical potential
0.659994	0.876067	Heat of formation, total energy, HOMO energy, LUMO energy
0.659994	0.876067	Heat of formation, total energy, HOMO energy, absolute hardness

Where: RE is regression equation, rCV^2 is cross validation coefficient and r^2 is correlation coefficient.

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