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Quantative Structure Activity Relationship Of Inhibitors Of Glycolic Acid Oxidase

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ABSTRACT

In order to avoid trial and error method in selecting a suitable drug, QSAR methods have provided a rational basis to the design of enzyme inhibitors. 90 derivatives of enzyme inhibitors, whose inhibitory potencies in term of PI_{50} are reported, have been used as study material for QSAR study. These derivatives are divided into five groups 1.Substituted glycolic acids, 2. Substituted oxyacetic acids, 3.Substituted glyoxylic acids, 4. Substituted-3-hydroxy-1H pyrrole-2,5-diones derivatives, 5. 4-Heterocyclic substituted 3-hydroxy-1H-pyrrole-2,5-diones derivatives. The QSAR study and MLR analysis have been collectively made, because the potency is reported in one unit and the target enzyme glycolic acid oxidase (GAO) is common to all. The study has been made with the help of seven descriptors in different combinations. 1.Heat of formation (ΔH_f), 2.HOMO energy3. LUMO energy, 4. Absolute hardness (η) 5. Molecular weight (MW), 6.Electronegativity (χ) 7.Total energy (TE). This is perhaps for the first time when inhibitory potency has been related with quantum mechanical parameters, without any significance to structure of compounds. The values of descriptors have been obtained with the help of PC MODEL software using the semiempirical PM3 Hamiltonian. 32 multi linear regression models using different combinations of descriptors have been developed using the project leader program associated with CAChe software. The predicted activity is close to the observed activity and the correlation coefficient is above 0.80. The best QSAR models are obtained by MLR analysis using the combinations, (i) heat of formation, molecular weight and electronegativity, (ii) molecular weight, total energy and electronegativity.

KEYWORDS

QSAR;
Glycolic acid oxidase;
Enzyme inhibitors;
Quantum chemical descriptors;
Multi linear regression analysis.

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INTRODUCTION

Inhibition of enzyme reaction has acquired a very vast dimension in biochemical, biophysical, medical and pharmaceutical research and in treatment of large number of diseases[1]. The enzyme catalyzes the production of such chemicals, which are harmful and are responsible for diseases. The enzyme if inhibited will produce the desired, therapeutic effect without causing toxicity to the host. After the target enzyme has been identified, the attempts are made to find an effective inhibitor. The drugs, which are enzyme inhibitors, were actually found by trial and error methods, but now QSAR studies have provided a rational basis to the design of enzyme inhibitors. The enzymes whose inhibitions have undergone QSAR studies have been classified into 14 groups according to the similarity in chemical process involved in catalyzing biochemical phenomenon[1]. We shall however, confine our study to enzyme of oxidoreductase group, where O_2 is the acceptor. Such enzymes are better-known as oxidases, and the relevant example is glycolic acid oxidase (GAO). This catalyzes the production of glyoxylate from glycolate. Oxalates are predominant component of kidney stone[2,3]. Inhibitors of GAO may serve as useful drug for treatment. In order to avoid trial error method QSAR study on inhibitors of GAO was made[4,5] with the help of two descriptors, molar refractivity (MR) and hydrophobic constant (π). The inhibitory potency was measured in terms of PI_{50} [6]. Last decade has seen a tremendous advancement in the development of several descriptors for QSAR study[7]. Important studies on QSAR are compiled in two recent reviews one on carcinogenicity of amines[8] and the other on anti HIV drugs[9].

In our latest communication[10-14] we have used a number of descriptors for QSAR study of 75 derivatives of testosterone, 105 derivative of estrogen, 50 derivatives of phenols. The predicted activities have been found very close to observed activities. In this paper we present the QSAR prediction of GAO inhibitors, of ninety compounds with the help of MLR analysis. For MLR analyses a number of descriptors in different combinations have been tried and the result are discussed accordingly.

MATERIAL AND METHOD

The study materials of this paper are inhibitors of glycolic acid oxidase (GAO). They are listed in five TABLES 1-5[15].

TABLE 1: Substituted glycolic acids and their GAO inhibitory potencies RCH (OH) COOH (d,l)

Compound	R	PI_{50}
1	C_6H_5	2.40
2	4-ClC_6H_4	3.23
3	4-(C_6H_5O) C_6H_4	3.80
4	4-(C_6H_5) C_6H_5	4.40
5	4-FC_6H_4	2.40
6	4-(1-c C_6H_4N) C_6H_4	4.16
7	4-BrC_6H_4	3.39
8	4-(c-C_6H_{11}) C_6H_4	4.52
9	2-Cl C_6H_4	2.77
10	$CH_3CH_2SCH_2$	2.72
11	$C_6H_5CH=CH$	3.33
12	C- C_6H_{11}	2.40
13	$(CH_3)_2CHCH_2$	2.60
14	4-(C_6H_5) $C_6H_4SCH_2$	5.00
15	$CH_3SCH_2CH_2$	2.30

TABLE 2: Substituted oxyacetic acids and their GAO inhibitory potencies $ROCH_2COOH$

Compound	R	PI_{50}
16	C_6H_5	2.74
17	4-$NO_2C_6H_4$	2.96
18	4-$(CH_3)_3CC_6H_4$	3.64
19	4-HOC_6H_4	2.64
20	4-ClC_6H_4	3.80
21	4-$CH_3OC_6H_4$	2.64
22	4-(C_6H_5)C_6H_4	3.80
23	4-($CH_3COCH=CH$) C_6H_4	3.85
24	4-$NH_2C_6H_4$	2.09
25	$NO_2CH=CHC_6H_4$	3.14
26	4-[$C(CH_3)_2CH_2C(CH_3)_3$] C_6H_4	3.27
27	2-$NH_2COC_6H_4$	2.57
28	2-$CH_3C_6H_4$	3.55
29	2-ClC_6H_4	3.27
30	2-$CH_3OC_6H_4$	2.80
31	2-HOC_6H_4	2.62
32	2-($CH_2=CHCH_2$) C_6H_4	3.80
33	2-($CH_3CH=CHCH_2$) C_6H_4	3.82
34	3-$CH_3OC_6H_4$	3.00
35	3-ClC_6H_4	343
36	3-$CH_3C_6H_4$	3.57
37	3-$NO_2C_6H_4$	3.09
38	3-$CF_3C_6H_4$	3.46
39	3-$C_2H_5OC_6H_4$	3.09
40	$C_6H_5CH=CHCH_2$	2.57
41	2-naphthyl	3.09
42	$C_6H_5CH_2$	3.10

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TABLE 3: Substituted glyoxylic acids and their GAO inhibitory potencies RC (O) COOH

Compound	R	PI_{50}
43	4-(C_6H_5) C_6H_4	3.21
44	C_6H_5	2.64
45	2-NO_2-6-$CH_3C_6H_3CH_2$	4.02
46	3,4-$(CH_3O)_2C_6H_3CH_2$	3.85
47	2-$NO_2C_6H_4CH_2$	4.37
48	3-HO-4-$(CH_3O)C_6H_3CH_2$	3.64
49	4-Cl C_6H_4CH=CH	3.57
50	3-CH_3O C_6H_4CH=CH	3.40
51	3,4-$Cl_2C_6H_3CH$=CH	4.10
52	2,4-$Cl_2C_6H_3CH$=CH	4.10
53	2-Cl C_6H_4CH=CH	3.80
54	5- C_6H_5-2-(c-C_4H_3S)	4.52
55	5-$C_6H_5CH_2$-2--(c-C_4H_3S)	4.70
56	5-(4-ClC_6H_4)-2--(c-C_4H_3S)	5.05

The inhibitors or substrates act at a particular site on the enzyme, known as enzyme- substrate interaction[15]. The enzymatic binding sites are usually composed of a combination of very polar and very nonpolar amino acid[16]. The binding affinities were determined by the measurement of inhibitory potency pI_{50}.

For QSAR prediction the 3D modeling and geometry optimization of all the derivatives have been done with the help of PC MODEL software using the semiempirical PM3 Hamiltonian. The MOPAC calculations have been performed with Win MOPAC 7.21 software by applying keywords PM3 charge = O Gnorm = 0.1 GEO-OK vector density. The descriptors that have been used for QSAR modeling are: -

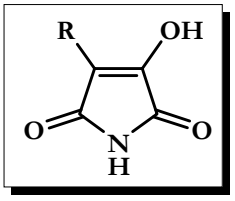
Heat of Formation (ΔH_f)
Molecular Weight (MW)
Total Energy (TE)
HOMO Energy ($\in$HOMO)
LUMO Energy ($\in$LUMO)
Electronegativity (χ)
Absolute Hardness (η)

The values of these descriptors have been calculated with the help of equations 1-7 using the above software.

Theory

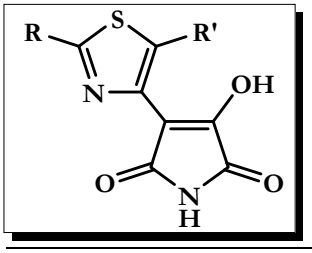
In DFT the electronegativity, commonly known to a chemist, is defined as the negative of a partial derivative of energy E of an atomic or molecular system with respect to the number of electrons N

TABLE 4: 4-Substituted 3-hydroxy-1H-pyrrole-2, 5-dione derivatives and their GAO inhibitory potencies



Compound	R	PI_{50}
57	C_6H_5	4.87
58	4-BrC_6H_4	5.60
59	4-IC_6H_4	5.70
60	4-$NO_2C_6H_4$	5.10
61	4-(c- C_6H_{11})C_6H_4	5.98
62	4-(C_6H_5)C_6H_4	6.38
63	4-(4-Br C_6H_4)C_6H_4	7.06
64	4-(3,4-Cl_2 $C_6H_3CH_2$) C_6H_4	6.66
65	4-(1,2,3,4-H_4-1-$C_{10}H_7$) C_6H_4	5.89
66	4-(2- C_6H_5-1-C_8H_6N) C_6H_4	6.30
67	4-(C_6H_5) C_6H_4CO	4.76
68	4-(C_6H_5) C_6H_4O	6.57
69	4-(C_6H_5) C_6H_4S	5.52
70	6-OCH_3-2-$C_{10}H_7$	5.66
71	n-$C_{10}H_{21}$	7.23
72	4-$(CH_3)_2CH$ C_6H_4	5.34
73	4-(4-Br C_6H_4)-2-C_3H_2NS	6.63
74	5-(4-Cl C_6H_4)-2-C_4H_3S	6.58

TABLE 5: 4-Heterocyclic-substituted 3-Hydroxy-1H-pyrrole-2,5-dione derivatives and their GAO inhibitory potencies



R' = CH_3 for 77; for all others R' = H.

Compound	R	PI_{50}
75	4-FC_6H_4	6.75
76	4-Br C_6H_4	7.00
77	2-Br C_6H_4	4.58
78	3-Br C_6H_4	6.82
79	4-Cl C_6H_4	6.86
80	3-CF_3 C_6H_4	6.57
81	4-Br $C_6H_4CH_2$	6.18
82	2,6-Cl_2 C_6H_3	7.07
83	2,3-Cl_2 C_6H_3	6.77
84	3,4-Cl_2 C_6H_3	7.11
85	3-Cl-4-CH_3 C_6H_3	6.92
86	2,6-$(CH_3)_2$ C_6H_3	6.92
87	4-CH_3O-2,6-Cl_2 C_6H_2	6.77
88	4-C_5H_4N	6.48
89	3-C_5H_4N	6.16
90	2,6-$(CH_3)_2$-4-C_5H_2N	6.26

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with a constant external potential $\nu(\gamma)$ [17].

$$\mu = -\chi = -(\delta E / \delta N)v(r) \quad (1)$$

In accordance with the earlier work of Iczkowski and Margrave[18], it should be stated that when assuming a quadratic relationship between E and N a finite difference approximation Eq. 1 may be rewritten as:

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

Where IE and EA are the vertical ionization energy and electron affinity, respectively, thereby recovering the electronegativity definition of Mullken [19]. Moreover, a theoretical justification was provided for Sanderson's principle of electronegativity equalization, which states that when two are more atoms come together to form a molecule, their electronegativities become adjusted to the same intermediate value[20-22]. The absolute hardness η is defined as [23].

$$\eta = 1/2\,(\delta\mu / \delta N)v(\Upsilon) = 1/2\,(\delta 2E / \delta N2)v(\Upsilon) \quad (3)$$

Where E is the total energy, N is the number of electrons of the chemical species, and $\nu(\Upsilon)$ is the external potential. The operational definition of absolute hardness and electronegativity is given as:

$$\eta = 1/2(IP - EA) \quad (4)$$

Where IP and EA are the ionization potential and electron affinity, respectively, of the chemical species. According to Koopman's theorem, the IP is simply the eigenvalue of the HOMO with change of sign and the EA is the eigenvalue of the LUMO with change of sign[24]; hence, Eqs. 4-6 can be written as:

$$\eta = 1/2(\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (5)$$

$$\chi = -\mu = 1/2(\varepsilon_{LUMO} + \varepsilon_{HOMO}) \quad (6)$$

With regard to QSAR of a chemical system, the total energy also played an important role. The total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of the internuclear repulsion, E_{nr}. The total electronic energy of the system is given by [25].

$$E = 1/2\,P(H+F) \quad (7)$$

Where P is the density matrix and H is the one-electron matrix.

Finally, a more general, but important, property of a molecular system, the molecular weight has also been tested as a descriptor.

RESULT AND DISCUSSION

Ninty inhibitors of glycolic acid oxidase (GOA) have been studied which are divided into five groups. (i) Substituted glycolic acid (ii) Substituted oxyacetic acid (iii) Substituted glyoxylic acid (iv) 4-Substituted 3-hydroxy-1H-pyrrole,2,5-dione derivatives (v) 3-Hetrocyclic Substituted-3-hydroxy-1H-pyrrole 2.5-dione. These inhibitors are included in TABLE-1-5 alongwith their GAO inhibitory potencies in terms of PI_{50}. Though the inhibitors belong to five groups of compound, yet we have drawn QSAR models collectively of all the 90 inhibitors because their inhibitory potencies have been measured in terms of PI_{50} and their target enzyme is glycolic acid oxidase (GAO). For QSAR study the descriptors such as heat of formation, molecular weight, total energy, LUMO, HUMO, electronegativity and absolute hardness, have been evaluated by solving the various equations given in method with the help of PC MODEL software using semiempirical PM3 Hamiltonian and the results are included in TABLE-6. 32 QSAR models using different combinations of descriptors have been developed, which are presented below : -

PA1=0.0040466*ΔH_f+0.019423*MW+0.0788982
rCV^2=0.803299 r^2=0.82099
PA2=0.019423*MW+2.53928*TE+0.0788982
rCV^2=0.803299 r^2=0.82099
PA3=0.0215891*MW+0.0100181*$\in$HOMO -0.667238
rCV^2=0.781199 r^2=0.807438
PA4=0.0186795*MW-0.333075*$\in$LUMO -0.335389
rCV^2=0.795021 r^2=0.824334
PA5=0.0185779*MW-0.562411*χ+2.35763
rCV^2=0.798292 r^2=0.821889
PA6=0.0202717*MW-0.392656*η-2.43895
rCV^2=0.783835 r^2=0.817263
PA7=0.00404753*ΔH_f+0.0194294*MW-0.00346442*
$\in$HOMO +0.0450888
rCV^2=0.800451 r^2=0.820991
PA8=0.00227694*ΔH_f+0.0182423*MW-0.242936*$\in$LUMO
+0.0233555
rCV^2=0.80016 r^2=0.827389
PA9=0.00259249*ΔH_f+0.0181332*MW-0.385072*χ+1.91384
rCV^2=0.80544 r^2=0.826017
PA10=0.00317672*ΔH_f+0.0190485*MW-0.247951*η-1.15933
rCV^2=0.795433 r^2=0.824284

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TABLE 6: Values of descriptors of 90 compounds and their observed activity

Compound inhibitors	Heat of formation (kcal/mole) (ΔH_f)	Molecular weight (MW)	Total energy (Hartree) (TE)	HOMO energy (eV) ($\in$HOMO)	LUMO energy (eV) ($\in$LUMO)	Electro negativity (χ)	Absolute hardness (η)	Activity observed
1	-105.733	152.149	-0.168	-9.720	0.192	4.956	-4.764	2.400
2	-112.386	186.595	-0.179	-9.377	-0.041	4.668	-4.709	3.230
3	-107.847	244.246	-0.172	-9.484	0.050	4.767	-4.717	3.800
4	-81.470	228.247	-0.130	-8.909	-0.354	4.277	-4.632	4.400
5	-149.181	170.140	-0.238	-9.779	-0.130	4.824	-4.954	2.400
6	-74.587	229.235	-0.119	-9.138	-0.613	4.262	-4.876	4.160
7	-98.063	231.046	-0.156	-9.783	-0.106	4.839	-4.944	3.390
8	-109.232	234.294	-0.174	-9.421	0.208	4.815	-4.607	4.520
9	-112.290	186.595	-0.179	-9.321	-0.042	4.640	-4.681	2.770
10	-141.987	150.192	-0.226	-9.378	-0.197	4.591	-4.787	2.720
11	-93.730	178.187	-0.149	-9.328	-0.485	4.422	-4.907	3.330
12	-140.473	158.197	-0.224	-10.339	0.899	5.619	-4.720	2.400
13	-160.519	132.159	-0.256	-11.019	0.955	5.987	-5.032	2.600
14	0.800	274.334	0.001	-7.761	-1.715	3.023	-4.738	5.000
15	-142.946	150.192	-0.228	-9.161	0.040	4.600	-4.560	2.300
16	-98.818	152.149	-0.157	-9.380	0.140	4.760	-4.620	2.740
17	-7.911	197.147	-0.013	-10.091	-2.082	4.005	-6.087	2.960
18	-120.952	208.257	-0.193	-9.340	0.160	4.750	-4.590	3.640
19	-144.290	168.149	-0.230	-9.253	0.110	4.682	-4.572	2.640
20	-105.321	186.595	-0.168	-9.450	-0.162	4.644	-4.806	3.800
21	-137.178	182.176	-0.219	-9.187	0.175	4.681	-4.506	2.640
22	-74.619	228.247	-0.119	-9.049	-0.518	4.265	-4.783	3.800
23	-126.963	220.224	-0.202	-9.446	-0.872	4.287	-5.159	3.850
24	-101.296	167.164	-0.161	-8.771	0.191	4.481	-4.290	2.090
25	-5.523	223.185	-0.009	-9.337	-1.995	3.671	-5.666	3.140
26	-137.876	264.364	-0.220	-9.273	0.186	4.730	-4.543	3.270
27	-138.024	195.174	-0.220	-9.676	-0.594	4.541	-5.135	2.570
28	-108.196	166.176	-0.172	-9.281	0.142	4.712	-4.569	3.550
29	-100.437	186.595	-0.160	-9.293	-0.054	4.620	-4.674	3.270
30	-137.196	182.176	-0.219	-9.173	0.158	4.665	-4.508	2.800
31	-144.341	168.149	-0.230	-9.219	0.107	4.663	-4.556	2.620
32	-86.625	192.214	-0.138	-9.386	0.104	4.745	-4.641	3.800
33	-96.210	206.241	-0.153	-9.241	0.148	4.694	-4.546	3.820
34	-128.316	182.176	-0.204	-8.998	0.087	4.543	-4.456	3.000
35	-105.379	186.595	-0.168	-9.181	-0.105	4.538	-4.643	3.430
36	-108.148	166.176	-0.172	-9.153	0.173	4.663	-4.490	3.570
37	-10.575	197.147	-0.017	-9.785	-2.040	3.873	-5.912	3.090
38	-249.930	220.148	-0.398	-10.031	-0.557	4.737	-5.294	3.460
39	-140.813	196.202	-0.224	-8.987	0.095	4.541	-4.446	3.090
40	-89.282	192.214	-0.142	-9.076	-0.252	4.412	-4.664	2.570
41	-81.871	202.209	-0.130	-8.893	-0.569	4.162	-4.731	3.090
42	-102.727	166.176	-0.164	-9.571	0.252	4.912	-4.660	3.100
43	-81.413	228.247	-0.130	-8.855	-0.312	4.272	-4.584	3.210
44	-105.734	152.149	-0.168	-9.728	0.185	4.957	-4.772	2.640
45	-26.168	225.201	-0.042	-9.779	-2.012	3.884	-5.896	4.020
46	-188.580	226.229	-0.301	-9.743	-0.301	4.721	-5.022	3.850
47	-20.945	211.174	-0.033	-10.136	-2.142	3.997	-6.139	4.370
48	-191.421	212.202	-0.305	-9.080	0.006	4.543	-4.537	3.640
49	-105.260	212.632	-0.168	-9.400	-0.701	4.349	-5.050	3.570
50	-137.053	208.213	-0.218	-8.954	-0.473	4.240	-4.713	3.400
51	-106.613	247.077	-0.170	-9.215	-0.851	4.182	-5.033	4.100
52	-107.482	247.077	-0.171	-9.314	-0.958	4.178	-5.136	4.100

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TABLE 6 cont...

Compound inhibitors	Heat of formation (kcal/mole) (ΔH_f)	Molecular weight (MW)	Total energy (Hartree) (TE)	HOMO energy (eV) (∈HOMO)	LUMO energy (eV) (∈LUMO)	Electro negativity (χ)	Absolute hardness (η)	Activity observed
53	-104.527	212.632	-0.167	-9.321	-0.708	4.307	-5.014	3.800
54	-71.185	234.269	-0.113	-9.011	-0.897	4.057	-4.954	4.520
55	-76.615	248.296	-0.122	-9.587	-0.446	4.570	-5.017	4.700
56	-75.341	268.714	-0.120	-8.930	-1.013	3.958	-4.972	5.050
57	-70.162	189.170	-0.112	-9.300	-1.439	3.931	-5.370	4.870
58	-61.918	268.066	-0.099	-9.403	-1.585	3.909	-5.494	5.600
59	-48.303	315.066	-0.077	-9.046	-1.530	3.758	-5.288	5.700
60	18.970	234.168	0.030	-9.990	-2.458	3.766	-6.224	5.100
61	-73.829	271.315	-0.118	-9.107	-1.407	3.850	-5.257	5.980
62	-46.147	265.268	-0.074	-8.849	-1.498	3.676	-5.174	6.380
63	-38.243	344.164	-0.061	-8.969	-1.583	3.693	-5.276	7.060
64	-5.495	348.185	-0.009	-9.033	-1.394	3.819	-5.213	6.660
65	87.100	315.328	0.139	-9.040	-1.456	3.792	-5.248	5.890
66	29.507	382.418	0.047	-9.344	-1.463	3.941	-5.404	6.300
67	-77.739	293.278	-0.124	-9.598	-2.048	3.775	-5.823	4.760
68	-72.585	281.267	-0.116	-9.177	-1.305	3.936	-5.241	6.570
69	-35.066	297.328	-0.056	-9.050	-1.497	3.776	-5.273	5.520
70	32.094	269.256	0.051	-9.911	-1.309	4.301	-5.610	5.660
71	-130.974	156.098	-0.209	-10.676	-1.698	4.489	-6.187	2.190
72	-88.923	231.251	-0.142	-9.161	-1.411	3.875	-5.286	5.340
73	-31.425	353.190	-0.050	-9.842	-1.220	4.311	-5.531	6.630
74	37.328	305.735	0.059	-8.915	-2.268	3.324	-5.592	6.580
75	-51.693	290.268	-0.082	-9.373	-1.696	3.838	-5.534	6.750
76	-0.155	351.174	0.000	-9.338	-1.682	3.828	-5.510	7.000
77	-28.798	365.201	-0.046	-9.015	-1.501	3.757	-5.258	4.580
78	-21.557	351.174	-0.034	-9.203	-1.580	3.812	-5.392	6.820
79	-11.846	306.723	-0.019	-9.299	-1.673	3.813	-5.486	6.860
80	-151.840	340.276	-0.242	-9.498	-1.815	3.842	-5.657	6.570
81	-25.233	365.201	-0.040	-9.306	-1.533	3.886	-5.419	6.180
82	-35.191	341.168	-0.056	-9.090	-1.486	3.802	-5.288	7.070
83	-37.504	341.168	-0.060	-9.172	-1.525	3.824	-5.349	6.770
84	-30.053	341.168	-0.048	-9.273	-1.727	3.773	-5.500	7.110
85	-30.946	320.750	-0.049	-9.214	-1.610	3.802	-5.412	6.920
86	-40.717	300.331	-0.065	-9.019	-1.425	3.797	-5.222	6.920
87	-75.821	371.194	-0.121	-8.985	-1.440	3.773	-5.213	6.770
88	-22.582	273.266	-0.036	-9.310	-1.668	3.821	-5.489	6.480
89	-23.607	273.266	-0.038	-9.268	-1.632	3.818	-5.450	6.160
90	-34.666	301.319	-0.055	-9.230	-1.623	3.803	-5.426	6.260

PA24=0.00216205*ΔH_f +0.0180457*MW-0.183793*∈LUMO - 0.144514*χ+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA25=0.00216205*ΔH_f +0.0180457*MW-0.328307*∈LUMO +0.144514*η+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA26=0.00216205*ΔH_f +0.0180457*MW-0.328307*χ- 0.183793*η+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA27=0.0180457*MW+1.35671*TE+0.0722569*∈HOMO - 0.25605*∈LUMO + 0.725514
rCV^2=0.799647 r^2=0.827717
PA28=0.0180457*MW+1.35671*TE-0.183793*∈HOMO - 0.512101*χ+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA29=0.0180457*MW+1.35671*TE+0.328307*∈HOMO - 0.512101*η+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA30=0.0180457*MW+1.35671*TE-0.183793*∈LUMO - 0.144514*χ+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA31=0.0180457*MW+1.35671*TE-0.328307*∈LUMO +0.144514*η+ 0.725514
rCV^2=0.799647 r^2=0.827717
PA32=0.021609*MW-0.765565
rCV^2=0.783708 r^2=0.807431

TABLE 7: Observed activities and the predicted activities PA1 to PA8

Compound	Obsd. Activity	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8
1	2.400	2.606	2.606	2.520	2.443	2.397	2.516	2.607	2.512
2	3.230	3.248	3.248	3.267	3.164	3.199	3.193	3.248	3.181
3	3.800	4.386	4.386	4.511	4.210	4.214	4.365	4.387	4.221
4	4.400	4.182	4.182	4.171	4.046	4.192	4.007	4.181	4.088
5	2.400	2.780	2.780	2.908	2.886	2.805	2.955	2.781	2.819
6	4.160	4.230	4.230	4.190	4.151	4.219	4.122	4.229	4.184
7	3.390	4.170	4.170	4.223	4.016	3.929	4.186	4.171	4.041
8	4.520	4.188	4.188	4.297	3.972	4.002	4.119	4.188	3.998
9	2.770	3.249	3.249	3.268	3.164	3.215	3.182	3.248	3.182
10	2.720	2.422	2.422	2.481	2.536	2.566	2.486	2.421	2.488
11	3.330	3.161	3.161	3.086	3.155	3.181	3.100	3.160	3.178
12	2.400	2.583	2.583	2.645	2.320	2.136	2.621	2.586	2.371
13	2.600	1.996	1.996	2.076	1.815	1.446	2.216	2.001	1.837
14	5.000	5.411	5.411	5.178	5.360	5.754	4.983	5.405	5.446
15	2.300	2.418	2.418	2.484	2.457	2.561	2.396	2.416	2.428
16	2.740	2.634	2.634	2.524	2.460	2.507	2.459	2.634	2.540
17	2.960	3.876	3.876	3.488	4.041	3.768	3.947	3.878	4.107
18	3.640	3.634	3.634	3.735	3.501	3.555	3.585	3.634	3.508
19	2.640	2.761	2.761	2.870	2.769	2.848	2.765	2.760	2.736
20	3.800	3.277	3.277	3.267	3.204	3.212	3.231	3.277	3.227
21	2.640	3.062	3.062	3.174	3.009	3.109	3.024	3.061	2.992
22	3.800	4.210	4.210	4.170	4.101	4.199	4.066	4.209	4.143
23	3.850	3.843	3.843	3.993	4.069	4.038	4.051	3.843	3.963
24	2.090	2.916	2.916	2.854	2.723	2.943	2.634	2.913	2.796
25	3.140	4.391	4.391	4.058	4.498	4.439	4.310	4.391	4.567
26	3.270	4.656	4.656	4.947	4.541	4.609	4.704	4.656	4.487
27	2.570	3.311	3.311	3.449	3.508	3.430	3.534	3.312	3.414
28	3.550	2.869	2.869	2.827	2.721	2.795	2.724	2.868	2.774
29	3.270	3.297	3.297	3.268	3.168	3.226	3.179	3.296	3.212
30	2.800	3.062	3.062	3.174	3.015	3.118	3.024	3.061	2.996
31	2.620	2.761	2.761	2.871	2.770	2.859	2.759	2.760	2.736
32	3.800	3.462	3.462	3.388	3.220	3.260	3.280	3.462	3.307
33	3.820	3.695	3.695	3.693	3.468	3.549	3.527	3.695	3.531
34	3.000	3.098	3.098	3.176	3.039	3.187	3.004	3.096	3.033
35	3.430	3.277	3.277	3.269	3.185	3.272	3.167	3.276	3.213
36	3.570	2.869	2.869	2.829	2.711	2.822	2.693	2.868	2.767
37	3.090	3.865	3.865	3.491	4.027	3.842	3.879	3.867	4.091
38	3.460	3.343	3.343	3.985	3.962	3.783	4.103	3.346	3.606
39	3.090	3.320	3.320	3.479	3.298	3.449	3.284	3.318	3.259
40	2.570	3.451	3.451	3.392	3.339	3.447	3.289	3.450	3.388
41	3.090	3.675	3.675	3.609	3.631	3.774	3.518	3.673	3.664
42	3.100	2.891	2.891	2.824	2.685	2.682	2.759	2.891	2.760
43	3.210	4.183	4.183	4.172	4.032	4.196	3.988	4.181	4.078
44	2.640	2.606	2.606	2.520	2.445	2.397	2.519	2.607	2.513
45	4.020	4.347	4.347	4.097	4.541	4.357	4.441	4.349	4.561
46	3.850	3.710	3.710	4.119	3.991	3.905	4.119	3.711	3.794
47	4.370	4.096	4.096	3.790	4.323	4.033	4.253	4.098	4.348
48	3.640	3.426	3.426	3.823	3.627	3.745	3.644	3.425	3.457
49	3.570	3.783	3.783	3.829	3.870	3.862	3.855	3.783	3.833
50	3.400	3.568	3.568	3.738	3.711	3.841	3.633	3.567	3.624
51	4.100	4.446	4.446	4.575	4.563	4.596	4.546	4.446	4.495
52	4.100	4.443	4.443	4.574	4.599	4.598	4.586	4.443	4.519
53	3.800	3.786	3.786	3.830	3.872	3.886	3.840	3.786	3.836
54	4.520	4.341	4.341	4.300	4.339	4.428	4.255	4.340	4.353
55	4.700	4.592	4.592	4.597	4.451	4.400	4.564	4.592	4.487

Full Paper

TABLE 7 cont...

Compound	Obsd. Activity	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8
56	5.050	4.993	4.993	5.045	5.022	5.124	4.961	4.992	5.000
57	4.870	3.469	3.469	3.324	3.678	3.661	3.504	3.469	3.664
58	5.600	5.035	5.035	5.026	5.200	5.139	5.152	5.035	5.158
59	5.700	6.003	6.003	6.044	6.060	6.098	6.024	6.002	6.033
60	5.100	4.704	4.704	4.288	4.858	4.590	4.752	4.706	4.936
61	5.980	5.050	5.050	5.099	5.201	5.233	5.125	5.049	5.146
62	6.380	5.044	5.044	4.971	5.119	5.218	4.970	5.043	5.121
63	7.060	6.609	6.609	6.673	6.621	6.675	6.609	6.608	6.599
64	6.660	6.819	6.819	6.759	6.633	6.678	6.666	6.819	6.701
65	5.890	6.556	6.556	6.050	6.040	6.083	6.014	6.556	6.328
66	6.300	7.626	7.626	7.495	7.295	7.246	7.435	7.627	7.422
67	4.760	5.461	5.461	5.568	5.825	5.683	5.793	5.462	5.694
68	6.570	5.248	5.248	5.313	5.353	5.369	5.321	5.248	5.306
69	5.520	5.712	5.712	5.661	5.717	5.757	5.659	5.711	5.731
70	5.660	5.439	5.439	5.046	5.130	4.941	5.222	5.441	5.326
71	2.190	2.581	2.581	2.596	3.146	2.733	3.155	2.585	2.985
72	5.340	4.211	4.211	4.233	4.454	4.474	4.325	4.210	4.382
73	6.630	6.812	6.812	6.859	6.668	6.495	6.893	6.814	6.691
74	6.580	6.168	6.168	5.844	6.131	6.168	5.954	6.167	6.237
75	6.750	5.508	5.508	5.505	5.652	5.591	5.618	5.508	5.613
76	7.000	6.899	6.899	6.821	6.785	6.729	6.844	6.900	6.838
77	4.580	7.056	7.056	7.127	6.986	7.029	7.029	7.055	6.984
78	6.820	6.813	6.813	6.822	6.751	6.738	6.797	6.813	6.764
79	6.860	5.988	5.988	5.861	5.951	5.912	5.933	5.989	5.998
80	6.570	6.074	6.074	6.584	6.625	6.519	6.680	6.075	6.326
81	6.180	7.070	7.070	7.124	6.997	6.956	7.092	7.071	7.000
82	7.070	6.563	6.563	6.607	6.532	6.557	6.554	6.563	6.528
83	6.770	6.554	6.554	6.606	6.545	6.545	6.577	6.554	6.532
84	7.110	6.584	6.584	6.605	6.613	6.574	6.637	6.584	6.598
85	6.920	6.184	6.184	6.165	6.192	6.178	6.188	6.184	6.195
86	6.920	5.747	5.747	5.726	5.749	5.802	5.700	5.747	5.756
87	6.770	6.982	6.982	7.256	7.078	7.132	7.133	6.981	6.972
88	6.480	5.295	5.295	5.139	5.325	5.285	5.256	5.295	5.362
89	6.160	5.291	5.291	5.139	5.313	5.287	5.241	5.291	5.351
90	6.260	5.791	5.791	5.746	5.834	5.816	5.800	5.791	5.835

PA11=0.0194294*MW+2.53987*TE-0.00346442*∈HOMO +0.0450888
rCV^2=0.800451 r^2=0.820991
PA12=0.0182423*MW+1.4288*TE-0.242936*∈LUMO +0.0233555
rCV^2=0.80016 r^2=0.827389
PA13=0.0181332*MW+1.62681*TE-0.385072*χ+1.91384
rCV^2=0.80544 r^2=0.826017
PA14=0.0190485*MW+1.99342*TE-0.247951*η-1.15933
rCV^2=0.795433 r^2=0.824284
PA15=0.0183657*MW+0.103681*∈HOMO -0.345366*∈LUMO +0.69811
rCV^2=0.795112 r^2=0.825027
PA16=0.0183657*MW-0.241685*∈HOMO -0.690733*χ+0.69811
rCV^2=0.795112 r^2=0.825027
PA17=0.0183657*MW+0.449048*∈HOMO -0.690733*η+0.69811
rCV^2=0.795112 r^2=0.825027
PA18=0.0183657*MW-0.241685*∈LUMO -0.207362*χ+0.69811
rCV^2=0.795112 r^2=0.825027
PA19=0.0183657*MW-0.449048*∈LUMO +0.207362*η+0.69811
rCV^2=0.795112 r^2=0.825027
PA20=0.0183657*MW-0.449048*χ-0.241685*η+0.69811
rCV^2=0.795112 r^2=0.825027
PA21=0.00216205*ΔH_f +0.0180457*MW+0.0722569*∈HOMO -0.25605*∈LUMO +0.725514
rCV^2=0.799647 r^2=0.827717
PA22=0.00216205*ΔH_f +0.0180457*MW-0.183793*∈HOMO -0.512101*χ + 0.725514
rCV^2=0.799647 r^2=0.827717
PA23=0.00216205*ΔH_f +0.0180457*MW+0.328307*∈HOMO -0.512101*η +0.725514
rCV^2=0.799647 r^2=0.827717

TABLE 8: Observed activites and the predicted activities PA8 to PA16

Compound	Obsd. Activity	PA9	PA10	PA11	PA12	PA13	PA14	PA15	PA16
1	2.400	2.490	2.584	2.607	2.512	2.490	2.584	2.418	2.418
2	3.230	3.209	3.206	3.248	3.181	3.209	3.206	3.167	3.167
3	3.800	4.228	4.320	4.387	4.221	4.228	4.320	4.183	4.183
4	4.400	4.194	4.078	4.181	4.088	4.194	4.078	4.089	4.089
5	2.400	2.754	2.836	2.781	2.819	2.754	2.836	2.854	2.854
6	4.160	4.236	4.179	4.229	4.184	4.236	4.179	4.173	4.173
7	3.390	3.986	4.156	4.171	4.041	3.986	4.156	3.964	3.964
8	4.520	4.025	4.099	4.188	3.998	4.025	4.099	3.952	3.952
9	2.770	3.220	3.199	3.248	3.182	3.220	3.199	3.173	3.173
10	2.720	2.501	2.438	2.421	2.488	2.501	2.438	2.552	2.552
11	3.330	3.199	3.154	3.160	3.178	3.199	3.154	3.171	3.171
12	2.400	2.254	2.578	2.586	2.371	2.254	2.578	2.221	2.221
13	2.600	1.589	2.096	2.001	1.837	1.589	2.096	1.653	1.653
14	5.000	5.726	5.244	5.405	5.446	5.726	5.244	5.524	5.524
15	2.300	2.495	2.378	2.416	2.428	2.495	2.378	2.493	2.493
16	2.740	2.584	2.570	2.634	2.540	2.584	2.570	2.472	2.472
17	2.960	3.926	4.080	3.878	4.107	3.926	4.080	3.992	3.992
18	3.640	3.548	3.562	3.634	3.508	3.548	3.562	3.499	3.499
19	2.640	2.786	2.719	2.760	2.736	2.786	2.719	2.789	2.789
20	3.800	3.236	3.252	3.277	3.227	3.236	3.252	3.201	3.201
21	2.640	3.059	2.992	3.061	2.992	3.059	2.992	3.031	3.031
22	3.800	4.217	4.137	4.209	4.143	4.217	4.137	4.131	4.131
23	3.850	3.927	3.911	3.843	3.963	3.927	3.911	4.064	4.064
24	2.090	2.957	2.767	2.913	2.796	2.957	2.767	2.793	2.793
25	3.140	4.533	4.479	4.391	4.567	4.533	4.479	4.518	4.518
26	3.270	4.529	4.565	4.656	4.487	4.529	4.565	4.528	4.528
27	2.570	3.347	3.393	3.312	3.414	3.347	3.393	3.485	3.485
28	3.550	2.832	2.795	2.868	2.774	2.832	2.795	2.739	2.739
29	3.270	3.258	3.235	3.296	3.212	3.258	3.235	3.180	3.180
30	2.800	3.065	2.993	3.061	2.996	3.065	2.993	3.038	3.038
31	2.620	2.793	2.715	2.760	2.736	2.793	2.715	2.794	2.794
32	3.800	3.348	3.378	3.462	3.307	3.348	3.378	3.219	3.219
33	3.820	3.597	3.591	3.695	3.531	3.597	3.591	3.477	3.477
34	3.000	3.135	3.008	3.096	3.033	3.135	3.008	3.081	3.081
35	3.430	3.277	3.211	3.276	3.213	3.277	3.211	3.209	3.209
36	3.570	2.851	2.776	2.868	2.767	2.851	2.776	2.741	2.741
37	3.090	3.970	4.028	3.867	4.091	3.970	4.028	4.009	4.009
38	3.460	3.434	3.553	3.346	3.606	3.434	3.553	3.894	3.894
39	3.090	3.358	3.233	3.318	3.259	3.358	3.233	3.337	3.337
40	2.570	3.469	3.375	3.450	3.388	3.469	3.375	3.374	3.374
41	3.090	3.766	3.605	3.673	3.664	3.766	3.605	3.686	3.686
42	3.100	2.769	2.835	2.891	2.760	2.769	2.835	2.671	2.671
43	3.210	4.197	4.066	4.181	4.078	4.197	4.066	4.080	4.080
44	2.640	2.490	2.586	2.607	2.513	2.490	2.586	2.420	2.420
45	4.020	4.434	4.509	4.349	4.561	4.434	4.509	4.515	4.515
46	3.850	3.709	3.796	3.711	3.794	3.709	3.796	3.947	3.947
47	4.370	4.150	4.319	4.098	4.348	4.150	4.319	4.265	4.265
48	3.640	3.516	3.400	3.425	3.457	3.516	3.400	3.652	3.652
49	3.570	3.822	3.809	3.783	3.833	3.822	3.809	3.871	3.871
50	3.400	3.701	3.540	3.567	3.624	3.701	3.540	3.757	3.757
51	4.100	4.507	4.456	4.446	4.495	4.507	4.456	4.574	4.574
52	4.100	4.507	4.479	4.443	4.519	4.507	4.479	4.601	4.601
53	3.800	3.840	3.802	3.786	3.836	3.840	3.802	3.881	3.881
54	4.520	4.415	4.305	4.340	4.353	4.415	4.305	4.376	4.376
55	4.700	4.458	4.571	4.592	4.487	4.458	4.571	4.418	4.418

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TABLE 8 cont...

Compound	Obsd. Activity	PA9	PA10	PA11	PA12	PA13	PA14	PA15	PA16
56	5.050	5.067	4.953	4.992	5.000	5.067	4.953	5.057	5.057
57	4.870	3.649	3.553	3.469	3.664	3.649	3.553	3.705	3.705
58	5.600	5.109	5.112	5.035	5.158	5.109	5.112	5.194	5.194
59	5.700	6.055	6.000	6.002	6.033	6.055	6.000	6.075	6.075
60	5.100	4.759	4.905	4.706	4.936	4.759	4.905	4.812	4.812
61	5.980	5.160	5.078	5.049	5.146	5.160	5.078	5.223	5.223
62	6.380	5.189	5.030	5.043	5.121	5.189	5.030	5.170	5.170
63	7.060	6.633	6.583	6.608	6.599	6.633	6.583	6.636	6.636
64	6.660	6.743	6.748	6.819	6.701	6.743	6.748	6.638	6.638
65	5.890	6.397	6.425	6.556	6.328	6.397	6.425	6.055	6.055
66	6.300	7.407	7.559	7.627	7.422	7.407	7.559	7.258	7.258
67	4.760	5.577	5.624	5.462	5.694	5.577	5.624	5.797	5.797
68	6.570	5.310	5.267	5.248	5.306	5.310	5.267	5.363	5.363
69	5.520	5.760	5.700	5.711	5.731	5.760	5.700	5.737	5.737
70	5.660	5.223	5.463	5.441	5.326	5.223	5.463	5.068	5.068
71	2.190	2.676	2.932	2.585	2.985	2.676	2.932	3.045	3.045
72	5.340	4.384	4.274	4.210	4.382	4.384	4.274	4.483	4.483
73	6.630	6.577	6.840	6.814	6.691	6.577	6.840	6.586	6.586
74	6.580	6.275	6.170	6.167	6.237	6.275	6.170	6.172	6.172
75	6.750	5.565	5.578	5.508	5.613	5.565	5.578	5.643	5.643
76	7.000	6.807	6.896	6.900	6.838	6.807	6.896	6.760	6.760
77	4.580	7.015	7.009	7.055	6.984	7.015	7.009	6.989	6.989
78	6.820	6.758	6.798	6.813	6.764	6.758	6.798	6.739	6.739
79	6.860	5.977	6.006	5.989	5.998	5.977	6.006	5.945	5.945
80	6.570	6.211	6.243	6.075	6.326	6.211	6.243	6.590	6.590
81	6.180	6.974	7.061	7.071	7.000	6.974	7.061	6.970	6.970
82	7.070	6.545	6.539	6.563	6.528	6.545	6.539	6.535	6.535
83	6.770	6.531	6.546	6.554	6.532	6.531	6.546	6.540	6.540
84	7.110	6.570	6.608	6.584	6.598	6.570	6.608	6.599	6.599
85	6.920	6.186	6.194	6.184	6.195	6.186	6.194	6.190	6.190
86	6.920	5.792	5.727	5.747	5.756	5.792	5.727	5.771	5.771
87	6.770	6.995	6.963	6.981	6.972	6.995	6.963	7.081	7.081
88	6.480	5.339	5.335	5.295	5.362	5.339	5.335	5.328	5.328
89	6.160	5.338	5.322	5.291	5.351	5.338	5.322	5.319	5.319
90	6.260	5.823	5.816	5.791	5.835	5.823	5.816	5.836	5.836

TABLE 9: Observed activities and the predicted activities PA17 to PA24

Compound	Obsd. Activity	PA17	PA18	PA19	PA20	PA21	PA22	PA23	PA24
1	2.400	2.418	2.418	2.418	2.418	2.491	2.491	2.491	2.491
2	3.230	3.167	3.167	3.167	3.167	3.183	3.183	3.183	3.183
3	3.800	4.183	4.183	4.183	4.183	4.202	4.202	4.202	4.202
4	4.400	4.089	4.089	4.089	4.089	4.115	4.115	4.115	4.115
5	2.400	2.854	2.854	2.854	2.854	2.800	2.800	2.800	2.800
6	4.160	4.173	4.173	4.173	4.173	4.198	4.198	4.198	4.198
7	3.390	3.964	3.964	3.964	3.964	4.003	4.003	4.003	4.003
8	4.520	3.952	3.952	3.952	3.952	3.983	3.983	3.983	3.983
9	2.770	3.173	3.173	3.173	3.173	3.187	3.187	3.187	3.187
10	2.720	2.552	2.552	2.552	2.552	2.502	2.502	2.502	2.502
11	3.330	3.171	3.171	3.171	3.171	3.189	3.189	3.189	3.189
12	2.400	2.221	2.221	2.221	2.221	2.299	2.299	2.299	2.299
13	2.600	1.653	1.653	1.653	1.653	1.723	1.723	1.723	1.723
14	5.000	5.524	5.524	5.524	5.524	5.556	5.556	5.556	5.556
15	2.300	2.493	2.493	2.493	2.493	2.455	2.455	2.455	2.455
16	2.740	2.472	2.472	2.472	2.472	2.544	2.544	2.544	2.544
17	2.960	3.992	3.992	3.992	3.992	4.070	4.070	4.070	4.070
18	3.640	3.499	3.499	3.499	3.499	3.506	3.506	3.506	3.506

TABLE 9 cont...

Compound	Obsd. Activity	PA17	PA18	PA19	PA20	PA21	PA22	PA23	PA24
19	2.640	2.789	2.789	2.789	2.789	2.751	2.751	2.751	2.751
20	3.800	3.201	3.201	3.201	3.201	3.224	3.224	3.224	3.224
21	2.640	3.031	3.031	3.031	3.031	3.008	3.008	3.008	3.008
22	3.800	4.131	4.131	4.131	4.131	4.162	4.162	4.162	4.162
23	3.850	4.064	4.064	4.064	4.064	3.966	3.966	3.966	3.966
24	2.090	2.793	2.793	2.793	2.793	2.840	2.840	2.840	2.840
25	3.140	4.518	4.518	4.518	4.518	4.577	4.577	4.577	4.577
26	3.270	4.528	4.528	4.528	4.528	4.480	4.480	4.480	4.480
27	2.570	3.485	3.485	3.485	3.485	3.402	3.402	3.402	3.402
28	3.550	2.739	2.739	2.739	2.739	2.783	2.783	2.783	2.783
29	3.270	3.180	3.180	3.180	3.180	3.218	3.218	3.218	3.218
30	2.800	3.038	3.038	3.038	3.038	3.013	3.013	3.013	3.013
31	2.620	2.794	2.794	2.794	2.794	2.754	2.754	2.754	2.754
32	3.800	3.219	3.219	3.219	3.219	3.302	3.302	3.302	3.302
33	3.820	3.477	3.477	3.477	3.477	3.534	3.534	3.534	3.534
34	3.000	3.081	3.081	3.081	3.081	3.063	3.063	3.063	3.063
35	3.430	3.209	3.209	3.209	3.209	3.228	3.228	3.228	3.228
36	3.570	2.741	2.741	2.741	2.741	2.785	2.785	2.785	2.785
37	3.090	4.009	4.009	4.009	4.009	4.076	4.076	4.076	4.076
38	3.460	3.894	3.894	3.894	3.894	3.576	3.576	3.576	3.576
39	3.090	3.337	3.337	3.337	3.337	3.288	3.288	3.288	3.288
40	2.570	3.374	3.374	3.374	3.374	3.410	3.410	3.410	3.410
41	3.090	3.686	3.686	3.686	3.686	3.701	3.701	3.701	3.701
42	3.100	2.671	2.671	2.671	2.671	2.746	2.746	2.746	2.746
43	3.210	4.080	4.080	4.080	4.080	4.108	4.108	4.108	4.108
44	2.640	2.420	2.420	2.420	2.420	2.492	2.492	2.492	2.492
45	4.020	4.515	4.515	4.515	4.515	4.541	4.541	4.541	4.541
46	3.850	3.947	3.947	3.947	3.947	3.773	3.773	3.773	3.773
47	4.370	4.265	4.265	4.265	4.265	4.307	4.307	4.307	4.307
48	3.640	3.652	3.652	3.652	3.652	3.483	3.483	3.483	3.483
49	3.570	3.871	3.871	3.871	3.871	3.835	3.835	3.835	3.835
50	3.400	3.757	3.757	3.757	3.757	3.661	3.661	3.661	3.661
51	4.100	4.574	4.574	4.574	4.574	4.506	4.506	4.506	4.506
52	4.100	4.601	4.601	4.601	4.601	4.524	4.524	4.524	4.524
53	3.800	3.881	3.881	3.881	3.881	3.844	3.844	3.844	3.844
54	4.520	4.376	4.376	4.376	4.376	4.378	4.378	4.378	4.378
55	4.700	4.418	4.418	4.418	4.418	4.462	4.462	4.462	4.462
56	5.050	5.057	5.057	5.057	5.057	5.026	5.026	5.026	5.026
57	4.870	3.705	3.705	3.705	3.705	3.684	3.684	3.684	3.684
58	5.600	5.194	5.194	5.194	5.194	5.156	5.156	5.156	5.156
59	5.700	6.075	6.075	6.075	6.075	6.045	6.045	6.045	6.045
60	5.100	4.812	4.812	4.812	4.812	4.900	4.900	4.900	4.900
61	5.980	5.223	5.223	5.223	5.223	5.164	5.164	5.164	5.164
62	6.380	5.170	5.170	5.170	5.170	5.157	5.157	5.157	5.157
63	7.060	6.636	6.636	6.636	6.636	6.611	6.611	6.611	6.611
64	6.660	6.638	6.638	6.638	6.638	6.701	6.701	6.701	6.701
65	5.890	6.055	6.055	6.055	6.055	6.324	6.324	6.324	6.324
66	6.300	7.258	7.258	7.258	7.258	7.390	7.390	7.390	7.390
67	4.760	5.797	5.797	5.797	5.797	5.681	5.681	5.681	5.681
68	6.570	5.363	5.363	5.363	5.363	5.315	5.315	5.315	5.315
69	5.520	5.737	5.737	5.737	5.737	5.744	5.744	5.744	5.744
70	5.660	5.068	5.068	5.068	5.068	5.273	5.273	5.273	5.273
71	2.190	3.045	3.045	3.045	3.045	2.923	2.923	2.923	2.923
72	5.340	4.483	4.483	4.483	4.483	4.406	4.406	4.406	4.406
73	6.630	6.586	6.586	6.586	6.586	6.632	6.632	6.632	6.632
74	6.580	6.172	6.172	6.172	6.172	6.260	6.260	6.260	6.260

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TABLE 9 cont...

Compound	Obsd. Activity	PA17	PA18	PA19	PA20	PA21	PA22	PA23	PA24
75	6.750	5.643	5.643	5.643	5.643	5.609	5.609	5.609	5.609
76	7.000	6.760	6.760	6.760	6.760	6.818	6.818	6.818	6.818
77	4.580	6.989	6.989	6.989	6.989	6.986	6.986	6.986	6.986
78	6.820	6.739	6.739	6.739	6.739	6.756	6.756	6.756	6.756
79	6.860	5.945	5.945	5.945	5.945	5.991	5.991	5.991	5.991
80	6.570	6.590	6.590	6.590	6.590	6.316	6.316	6.316	6.316
81	6.180	6.970	6.970	6.970	6.970	6.981	6.981	6.981	6.981
82	7.070	6.535	6.535	6.535	6.535	6.530	6.530	6.530	6.530
83	6.770	6.540	6.540	6.540	6.540	6.529	6.529	6.529	6.529
84	7.110	6.599	6.599	6.599	6.599	6.589	6.589	6.589	6.589
85	6.920	6.190	6.190	6.190	6.190	6.193	6.193	6.193	6.193
86	6.920	5.771	5.771	5.771	5.771	5.770	5.770	5.770	5.770
87	6.770	7.081	7.081	7.081	7.081	6.979	6.979	6.979	6.979
88	6.480	5.328	5.328	5.328	5.328	5.362	5.362	5.362	5.362
89	6.160	5.319	5.319	5.319	5.319	5.354	5.354	5.354	5.354
90	6.260	5.836	5.836	5.836	5.836	5.837	5.837	5.837	5.837

TABLE 10: Observed activities and the predicted activities PA25 to PA32

Compound	Obsd. Activity	PA25	PA26	PA27	PA28	PA29	PA30	PA31	PA32
1	2.400	2.491	2.491	2.491	2.491	2.491	2.491	2.491	2.522
2	3.230	3.183	3.183	3.183	3.183	3.183	3.183	3.183	3.267
3	3.800	4.202	4.202	4.202	4.202	4.202	4.202	4.202	4.512
4	4.400	4.115	4.115	4.115	4.115	4.115	4.115	4.115	4.167
5	2.400	2.800	2.800	2.800	2.800	2.800	2.800	2.800	2.911
6	4.160	4.198	4.198	4.198	4.198	4.198	4.198	4.198	4.188
7	3.390	4.003	4.003	4.003	4.003	4.003	4.003	4.003	4.227
8	4.520	3.983	3.983	3.983	3.983	3.983	3.983	3.983	4.297
9	2.770	3.187	3.187	3.187	3.187	3.187	3.187	3.187	3.267
10	2.720	2.502	2.502	2.502	2.502	2.502	2.502	2.502	2.480
11	3.330	3.189	3.189	3.189	3.189	3.189	3.189	3.189	3.085
12	2.400	2.299	2.299	2.299	2.299	2.299	2.299	2.299	2.653
13	2.600	1.723	1.723	1.723	1.723	1.723	1.723	1.723	2.090
14	5.000	5.556	5.556	5.556	5.556	5.556	5.556	5.556	5.163
15	2.300	2.455	2.455	2.455	2.455	2.455	2.455	2.455	2.480
16	2.740	2.544	2.544	2.544	2.544	2.544	2.544	2.544	2.522
17	2.960	4.070	4.070	4.070	4.070	4.070	4.070	4.070	3.495
18	3.640	3.506	3.506	3.506	3.506	3.506	3.506	3.506	3.735
19	2.640	2.751	2.751	2.751	2.751	2.751	2.751	2.751	2.868
20	3.800	3.224	3.224	3.224	3.224	3.224	3.224	3.224	3.267
21	2.640	3.008	3.008	3.008	3.008	3.008	3.008	3.008	3.171
22	3.800	4.162	4.162	4.162	4.162	4.162	4.162	4.162	4.167
23	3.850	3.966	3.966	3.966	3.966	3.966	3.966	3.966	3.993
24	2.090	2.840	2.840	2.840	2.840	2.840	2.840	2.840	2.847
25	3.140	4.577	4.577	4.577	4.577	4.577	4.577	4.577	4.057
26	3.270	4.480	4.480	4.480	4.480	4.480	4.480	4.480	4.947
27	2.570	3.402	3.402	3.402	3.402	3.402	3.402	3.402	3.452
28	3.550	2.783	2.783	2.783	2.783	2.783	2.783	2.783	2.825
29	3.270	3.218	3.218	3.218	3.218	3.218	3.218	3.218	3.267
30	2.800	3.013	3.013	3.013	3.013	3.013	3.013	3.013	3.171
31	2.620	2.754	2.754	2.754	2.754	2.754	2.754	2.754	2.868
32	3.800	3.302	3.302	3.302	3.302	3.302	3.302	3.302	3.388
33	3.820	3.534	3.534	3.534	3.534	3.534	3.534	3.534	3.691
34	3.000	3.063	3.063	3.063	3.063	3.063	3.063	3.063	3.171
35	3.430	3.228	3.228	3.228	3.228	3.228	3.228	3.228	3.267
36	3.570	2.785	2.785	2.785	2.785	2.785	2.785	2.785	2.825

TABLE 10 cont...

Compound	Obsd. Activity	PA25	PA26	PA27	PA28	PA29	PA30	PA31	PA32
37	3.090	4.076	4.076	4.076	4.076	4.076	4.076	4.076	3.495
38	3.460	3.576	3.576	3.576	3.576	3.576	3.576	3.576	3.992
39	3.090	3.288	3.288	3.288	3.288	3.288	3.288	3.288	3.474
40	2.570	3.410	3.410	3.410	3.410	3.410	3.410	3.410	3.388
41	3.090	3.701	3.701	3.701	3.701	3.701	3.701	3.701	3.604
42	3.100	2.746	2.746	2.746	2.746	2.746	2.746	2.746	2.825
43	3.210	4.108	4.108	4.108	4.108	4.108	4.108	4.108	4.167
44	2.640	2.492	2.492	2.492	2.492	2.492	2.492	2.492	2.522
45	4.020	4.541	4.541	4.541	4.541	4.541	4.541	4.541	4.101
46	3.850	3.773	3.773	3.773	3.773	3.773	3.773	3.773	4.123
47	4.370	4.307	4.307	4.307	4.307	4.307	4.307	4.307	3.798
48	3.640	3.483	3.483	3.483	3.483	3.483	3.483	3.483	3.820
49	3.570	3.835	3.835	3.835	3.835	3.835	3.835	3.835	3.829
50	3.400	3.661	3.661	3.661	3.661	3.661	3.661	3.661	3.734
51	4.100	4.506	4.506	4.506	4.506	4.506	4.506	4.506	4.574
52	4.100	4.524	4.524	4.524	4.524	4.524	4.524	4.524	4.574
53	3.800	3.844	3.844	3.844	3.844	3.844	3.844	3.844	3.829
54	4.520	4.378	4.378	4.378	4.378	4.378	4.378	4.378	4.297
55	4.700	4.462	4.462	4.462	4.462	4.462	4.462	4.462	4.600
56	5.050	5.026	5.026	5.026	5.026	5.026	5.026	5.026	5.041
57	4.870	3.684	3.684	3.684	3.684	3.684	3.684	3.684	3.322
58	5.600	5.156	5.156	5.156	5.156	5.156	5.156	5.156	5.027
59	5.700	6.045	6.045	6.045	6.045	6.045	6.045	6.045	6.043
60	5.100	4.900	4.900	4.900	4.900	4.900	4.900	4.900	4.295
61	5.980	5.164	5.164	5.164	5.164	5.164	5.164	5.164	5.097
62	6.380	5.157	5.157	5.157	5.157	5.157	5.157	5.157	4.967
63	7.060	6.611	6.611	6.611	6.611	6.611	6.611	6.611	6.671
64	6.660	6.701	6.701	6.701	6.701	6.701	6.701	6.701	6.758
65	5.890	6.324	6.324	6.324	6.324	6.324	6.324	6.324	6.048
66	6.300	7.390	7.390	7.390	7.390	7.390	7.390	7.390	7.498
67	4.760	5.681	5.681	5.681	5.681	5.681	5.681	5.681	5.572
68	6.570	5.315	5.315	5.315	5.315	5.315	5.315	5.315	5.312
69	5.520	5.744	5.744	5.744	5.744	5.744	5.744	5.744	5.659
70	5.660	5.273	5.273	5.273	5.273	5.273	5.273	5.273	5.053
71	2.190	2.923	2.923	2.923	2.923	2.923	2.923	2.923	2.608
72	5.340	4.406	4.406	4.406	4.406	4.406	4.406	4.406	4.232
73	6.630	6.632	6.632	6.632	6.632	6.632	6.632	6.632	6.867
74	6.580	6.260	6.260	6.260	6.260	6.260	6.260	6.260	5.841
75	6.750	5.609	5.609	5.609	5.609	5.609	5.609	5.609	5.507
76	7.000	6.818	6.818	6.818	6.818	6.818	6.818	6.818	6.823
77	4.580	6.986	6.986	6.986	6.986	6.986	6.986	6.986	7.126
78	6.820	6.756	6.756	6.756	6.756	6.756	6.756	6.756	6.823
79	6.860	5.991	5.991	5.991	5.991	5.991	5.991	5.991	5.862
80	6.570	6.316	6.316	6.316	6.316	6.316	6.316	6.316	6.587
81	6.180	6.981	6.981	6.981	6.981	6.981	6.981	6.981	7.126
82	7.070	6.530	6.530	6.530	6.530	6.530	6.530	6.530	6.607
83	6.770	6.529	6.529	6.529	6.529	6.529	6.529	6.529	6.607
84	7.110	6.589	6.589	6.589	6.589	6.589	6.589	6.589	6.607
85	6.920	6.193	6.193	6.193	6.193	6.193	6.193	6.193	6.166
86	6.920	5.770	5.770	5.770	5.770	5.770	5.770	5.770	5.724
87	6.770	6.979	6.979	6.979	6.979	6.979	6.979	6.979	7.256
88	6.480	5.362	5.362	5.362	5.362	5.362	5.362	5.362	5.139
89	6.160	5.354	5.354	5.354	5.354	5.354	5.354	5.354	5.139
90	6.260	5.837	5.837	5.837	5.837	5.837	5.837	5.837	5.746

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TABLE 11: Correlation and cross validation coefficients in decreasing order of predictive power

Sr.	Pred. Activity	r^2	rCV^2	Sum of r^2 and rCV^2	Descriptors used
1	PA9	0.826017	0.805440	1.631457	Heat of formation, molecular weight, electronegativity
2	PA13	0.826017	0.805440	1.631457	Molecular weight, total energy, electronegativity
3	PA8	0.827389	0.800160	1.627549	Heat of formation, molecular weight, total energy
4	PA12	0.827389	0.800160	1.627549	Molecular weight, total energy, LUMO energy
5	PA21	0.827717	0.799647	1.627364	Heat of formation, molecular weight, HOMO energy, LUMO energy
6	PA22	0.827717	0.799647	1.627364	Heat of formation, molecular weight, HOMO energy, electronegativity
7	PA23	0.827717	0.799647	1.627364	Heat of formation, molecular weight, HOMO energy, absolute hardness
8	PA24	0.827717	0.799647	1.627364	Heat of formation, molecular weight, LUMO energy, electronegativity
9	PA25	0.827717	0.799647	1.627364	Heat of formation, molecular weight, LUMO energy, absolute hardness
10	PA26	0.827717	0.799647	1.627364	Heat of formation, molecular weight, electronegativity, absolute hardness
11	PA27	0.827717	0.799647	1.627364	Molecular weight, total energy, HOMO energy, LUMO energy
12	PA28	0.827717	0.799647	1.627364	Molecular weight, total energy, HOMO energy, electronegativity
13	PA29	0.827717	0.799647	1.627364	Molecular weight, total energy, HOMO energy, absolute hardness
14	PA30	0.827717	0.799647	1.627364	Molecular weight, total energy, LUMO energy, electronegativity
15	PA31	0.827717	0.799647	1.627364	Molecular weight, total energy, LUMO energy, absolute hardness
16	PA1	0.820990	0.803299	1.624289	Heat of formation, molecular weight
17	PA7	0.820990	0.803299	1.624289	Molecular weight, total energy
18	PA7	0.820991	0.800451	1.621442	Heat of formation, molecular weight, HOMO energy
19	PA11	0.820991	0.800451	1.621442	Molecular weight, total energy, HOMO energy
20	PA5	0.821889	0.798292	1.620181	Molecular weight, electronegativity
21	PA15	0.825027	0.795112	1.620139	Molecular weight, HOMO energy, LUMO energy
22	PA16	0.825027	0.795112	1.620139	Molecular weight, HOMO energy, electronegativity
23	PA17	0.825027	0.795112	1.620139	Molecular weight, HOMO energy, absolute hardness
24	PA18	0.825027	0.795112	1.620139	Molecular weight, LUMO energy, electronegativity
25	PA19	0.825027	0.795112	1.620139	Molecular weight, LUMO energy, absolute hardness
26	PA20	0.825027	0.795112	1.620139	Molecular weight, electronegativity, absolute hardness
27	PA10	0.824284	0.795433	1.619717	Heat of formation, molecular weight, absolute hardness
28	PA14	0.824284	0.795433	1.619717	Molecular weight, total energy, absolute hardness
29	PA4	0.824334	0.795021	1.619355	Molecular weight, LUMO energy
30	PA6	0.817263	0.783835	1.601098	Molecular weight, absolute hardness
31	PA32	0.807431	0.783708	1.591139	Molecular weight
32	PA3	0.807438	0.781199	1.588637	Molecular weight, HOMO energy

The predicted values of all the models PA1-PA32 are included in TABLES 7-10. Each table includes the predicted values of eight models, because the placement of PA values of thirty-two models in one table is difficult. The values of cross validation and correlation coefficient and their sum are included in TABLE 11 alongwith the combinations of descriptors. A reference to this table indicates that correlation coefficients and cross validation coefficients are above 0.80 and 0.79 respectively, which shows that these model have a high predictive power. The three best models are described as below.

Best QSAR models are obtained by MLR equations- PA9 and PA13. The combinations of descriptors in the former are heat of formation, molecular weight and electronegativity and in the latter molecular weight, total energy and electronenegativity. The next best combinations are (a) heat of formation, molecular weight and total energy. (b) Molecular weight total energy and LUMO energy. The corresponding MLR equations are PA8 and PA12 respectively. At position third there are eleven combinations, and the representative MLR equations are PA21- PA31.

CONCLUSION

(1) Five different groups of compounds have been used as inhibitor against GAO, but the QSAR study of the compounds of all the groups has been collectively made irrespective of their structural difference. The correlation and cross validation coefficient in 32 models are close to 0.80, showing high degree of predictive power. This is

perhaps for the first time when inhibitory potency has been related to quantum mechanical parameters without any significance to structure of the compounds.

(2) The combinations of descriptors providing best predictivity are (a) heat of formation, molecular weight and electronenegativity (b) molecular weight, total energy and electronegativity.

(3) The second best combinations are (a) heat of formation, molecular weight and total energy (b) molecular weight, total energy and LUMO energy. There are eleven combinations at third rank.

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