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QSAR study of sulfonamides as inhibitors of carbonic anhydrase

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ABSTRACT

Quantum chemical reactivity descriptors based QSAR study of 48 sulfonamide derivatives as inhibitors of carbonic anhydrase has been studied in three different sets. The best QSAR model has correlation coefficient above 0.84 in one set the other two sets have the corresponding values above 0.79 and 0.81. The most important descriptor is heat of formation followed by molecular weight and total energy. The combination of descriptors providing the best model are heat of formation, molecular weight,total energy and LUMO energy.The CA enzyme-sulfonamide reaction appears to be favoured by energy change.

KEYWORDS

QSAR;
LUMO;
CAIs.

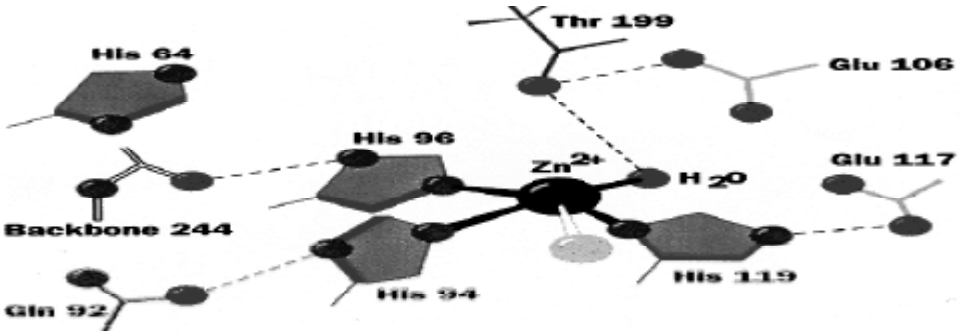
INTRODUCTION

The primary function of the enzyme carbonic anhydrase is to inter convert carbon dioxide and bicarbonate to maintain acid-base balance in blood and other tissues and to help transport carbondioxide out of tissues.The structure of enzyme is given in figure 1.

The mode of action of the enzyme is demonstrated by the following diagram figure 2, which shows stepwise action.

Mode of action of inhibitor

Two main classes of carbonic-anhydrase inhibitors (CAIs) are known; the metal complexing anions and the unsubstituted sulfonamides, which bind to the zinc ion of the enzyme either by substituting the non-protein zinc ligand or add to the metal coordination sphere generating trigonal bipyramidal species.



His -Histidine, Thr-Threonine, Gln-glutamine, Glu-glutamic acid
Figure 1: Structure of carbonic-anhydrase

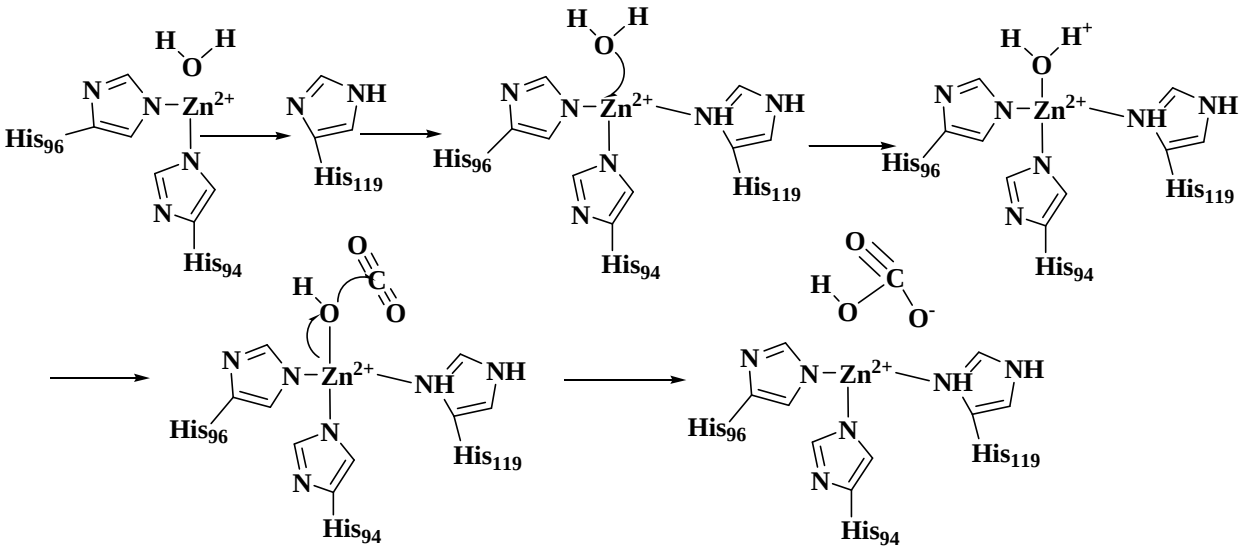


Figure 2 : Mechanism of action of carbonic-anhydrase

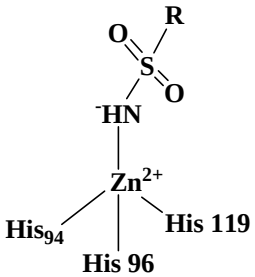
Sulfonamides,which are the most important CAIs[1,2] bind in a tetrahedral geometry of the Zinc ion in deprotonated state, with the nitrogen atom of the sulfonamide moiety and is coordinated to Zinc. In all these adducts the deprotonated sulfonamide is coordinated to the Zinc ion of the enzyme, and its NH moiety donates a hydrogen bond to the Oxygen of Thr 199, which in turn donates a hydrogen bond to the carboxylate group of Glu 106.

One of the oxygen atoms of the SO_2NH moiety also participates in a hydrogen bond with the back bone NH moiety of Thr 199 in figure 3.

Extensive hydrophobic and heterocyclic /aromatic part of the inhibitor molecule and active site of the aminoacid residues assure a strong affinity of sulfonamides to the CA active site.

Prediction of the biological activity of a molecule

$$E\text{-}Zn^{2+}\text{-}OH_2 + I \Leftrightarrow E\text{-}Zn^{2+}\text{-}I + H_2O \text{(substitution)}$$



Tetrahedral adduct (sulfonamide)

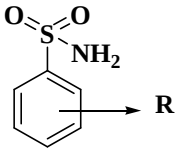
Figure 3: CA inhibition mechanism by sulfonamide and anionic inhibitors.

from a set of structure-based descriptors is very useful for drug discovery[3]. Quantitative structure-activity relation ship (QSAR) can be captured in statistical models relating structure to activity relationship in a particular reaction. The QSAR procedure begins with the identification of set of molecules and measured activities by chemical methods.

In this chapter we present the QSAR prediction of forty eight derivatives of sulfonamide which are inhibitors of CA. The set of descriptors used for QSAR are given under materials and method. Descriptors in different combinations have been used for statistical model by making MLR analysis.

MATERIAL AND METHOD

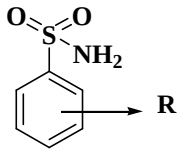
The study materials of this chapter are 48 derivatives of benzene sulfonamides



as carbonic anhydrase inhibitors,whose biological activity has been measured by two different methods. On the basis of the measurement of their biological activity, they have been presented in two different sets (TABLES 1 and 2)[4].

The activity of compounds of TABLE A are given

TABLE 1: Bovine carbonic anhydrase inhibition activities of sulfonamides



Benzene sulfonamide

Compound	R	pK^a_i (0.2°C)	pK^a_i (15°C)
1	H	0.215	0.124
2	p-NH_2	-0.363	-0.398
3	p-Cl	0.721	0.959
4	p-CH_3	0.420	0.496
5	p-CN	0.959	1.187
6	p-Br	0.921	0.959
7	p-NO_2	1.046	1.26
8	p-CH_3O	0.347	0.301
9	p-CH_3NH	-0.176	-0.046
10	p-CH_3CO	0.959	0.886
11	m,p-$(Cl)_2$	1.400	1.552
12	M-NO_2-p-Cl	1.769	1.602
13	m-CF_3-p-NO_2	1.854	1.658
14	m-Cl	0.638	0.921
15	m-CH_3	0.301	0.223
16	M-NO_2	0.886	1.125
17	o-CH_3	-0.204	-0.008
18	o-Cl	0.496	0.62
19	o-NO_2	0.331	0.455

PK^a_i is measured in units of 10^{-5} M, Bovine means ox\ cow family

in terms of PK^a_i at two different temperatures and of TABLE B are given in terms of log K values.

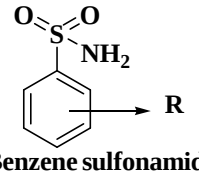
The study has accordingly been made under three sets. First set includes the sulfonamide derivatives whose biological activity is given in terms of PK^a_i at temperature 0.2^0C, the second set includes whose acivity is reported in terms of

PK^a_i but at temperature 15^0C. The third set includes derivatives whose activity is reported in terms of log K.

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 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: -

a. Heat of Formation (ΔH_f)
b. Molecular Weight (MW)
c. Total Energy (TE)
d. HOMO Energy ($\in$HOMO)
e. LUMO Energy ($\in$LUMO)
f. Electronegativity (χ)

TABLE 2: Human carbonic anhydrase inhibition activities of sulfonamides



Benzene sulfonamide

Compound	R	Log K
20	H	6.69
21	4-CH_3	7.09
22	4-C_2H_5	7.53
23	4-C_3H_7	7.77
24	4-C_4H_9	8.3
25	4-C_5H_{11}	8.86
26	4-CO_2CH_3	7.99
27	4-$CO_2C_2H_5$	8.5
28	4-$CO_2C_3H_7$	8.77
29	4-$CO_2C_4H_9$	9.11
30	4-$CO_2C_5H_{11}$	9.39
31	4-$CO_2C_6H_{13}$	9.39
32	4-$CONHCH_3$	7.08
33	4-$CONHC_2H_5$	7.53
34	4-$CONHC_3H_7$	8.08
35	4-$CONHC_4H_9$	8.49
36	4-$CONHC_5H_{11}$	8.75
37	4-$CONHC_6H_{13}$	8.88
38	4-$CONHC_7H_{15}$	8.93
39	3-CO_2CH_3	5.87
40	3-$CO_2C_2H_5$	6.21
41	3-$CO_2C_3H_7$	6.44
42	3-$CO_2C_4H_9$	6.95
43	3-$CO_2C_5H_{11}$	6.86
44	2-CO_2CH_3	4.41
45	2-$CO_2C_2H_5$	4.8
46	2-$CO_2C_3H_7$	5.28
47	2-$CO_2C_4H_9$	5.76
48	2-$CO_2C_5H_{11}$	6.18

g. Absolute Hardness (η)

The values of these descriptors have been calculated with the help of following equation given under theory using the Win MOPAC 7.21 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 with a constant external potential $\nu(\gamma)$[5].

$$\mu = -\chi = -(E / N)\nu(\gamma) \quad (1)$$

In accordance with the earlier work of Iczkowski and Margrave[6], 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[7]. 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[8-10]. The absolute hardness η is defined as[11].

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

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

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

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 A is the eigenvalue of the LUMO with change of sign[12]; 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[13].

$$E = 1/2\,R(HF) \quad (7)$$

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

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

RESULTS AND DISCUSSION

Inhibition of CA is influenced by energy, entropy, polarity and reactivity indices of sulfonamide compounds[14]. The sulfonamides bind as anions to the zinc ion of the CA active site[15,16]. The inhibition properties of these compounds can be accounted by several factors.These include the stability of CA enzyme-sulfonamide complex which is stabilized by a large favorable enthalpy change. Another factor that influences inhibition properties of the, inhibitors is a weak coordination bond between the active site zinc ion and sulfonamide nitrogen which is enormously supplemented by the cooperative interaction of the organic moieties of the inhibitor with the amino acid side chains of the active site. It was found that there is no involvement of a positive hydrophobic term (log P) in the inhibition process, suggesting that the binding of the sulfonamides to the active centre does not depend on hydrophobic interactions[17].

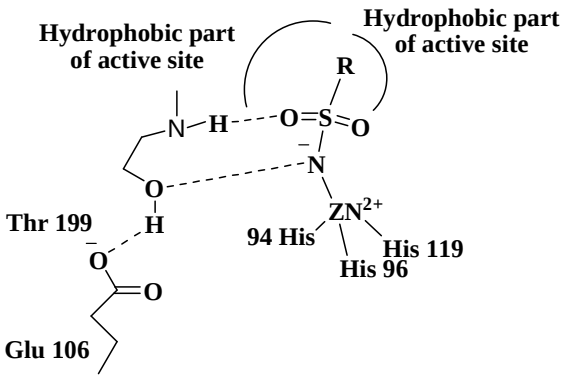


Figure 4: Interaction of sulfonamides with the active centre of carbonic anhydrase

Shinagawa[18] assumed that the NH_2 group of sulfonamide is probably involved in hydrogen bonding with the OH^- ion on one side and the imidazole ring on the other side.

In the enzyme an oxygen atom of the SO_2 of sulfonamide is supposed to bind with the zinc ion of the enzyme. The model is presented below in figure 4.

Since inhibition of CA is influenced by enthalpy change, and also by energy, entropy,polarity and reactivity indices of sulfonamide, we have chosen such descriptors for QSAR study which meet these requirements. The QSAR mainly is based on two sets of descriptors one is quantum chemical parameters such as ε HOMO, ε LUMO,absolute hardness (η), electronegativity (x), and another energy parameters such as heat of formation ▲ Hf°, total Energy TE. The two sets of descriptors were used in deriving regression models.

The values of descriptors have been evaluated by solving the relevant equations given in theory with the help of Win MOPAC 7.21 software using the semiempirical PM3 Hamiltonian.

First set

This set includes those sulfonamide derivatives

TABLE 3: Values of descriptors and activity in terms of PKi at 0.2^{0}C and at 15^{0}C

Comp.	R	Heat of formation (kcal/mole)	Molecular Weight	Total energy (Hartree)	HOMO energy (eV)	LUMO energy (eV)	Absolute hardness	Electroneg ativity	Activity PKi 0.2°C	Activity PKi 15°C
1	H	106.162	157.187	-79.969	-9.552	-1.883	3.835	-5.717	0.215	0.124
2	p-NH_2	102.803	172.201	-89.425	-8.966	-1.763	3.602	-5.364	-0.363	-0.398
3	p-Cl	99.745	191.632	-91.737	-9.531	-1.981	3.775	-5.756	0.721	0.959
4	p-CH_3	96.482	171.214	-87.159	-9.492	-1.843	3.824	-5.667	0.420	0.496
5	p-CN	142.516	182.197	-92.757	-9.737	-2.219	3.759	-5.978	0.959	1.187
6	p-Br	114.494	236.083	-89.856	-9.655	-2.026	3.815	-5.840	0.921	0.959
7	p-NO_2	187.215	202.184	-111.647	-9.610	-2.520	3.545	-6.065	1.046	1.260
8	p-CH_3O	67.190	187.213	-99.351	-9.374	-1.801	3.787	-5.588	0.347	0.301
9	p-CH_3NH	102.146	186.228	-96.553	-8.875	-1.750	3.563	-5.313	-0.176	-0.046
10	p-CH_3CO	65.203	199.224	-104.625	-9.656	-2.023	3.817	-5.839	0.959	0.886
11	m,p-$(Cl)_2$	94.707	226.077	-103.503	-9.512	-2.056	3.728	-5.784	1.400	1.552
12	M-NO_2-p-Cl	181.872	236.630	-123.415	-9.731	-2.358	3.686	-6.044	1.769	1.602
13	m-CF_3-p-NO_2	35.070	270.183	-166.547	-9.949	-2.839	3.555	-6.394	1.854	1.658
14	m-Cl	100.047	191.632	-91.734	-9.608	-1.986	3.811	-5.797	0.638	0.921
15	m-CH_3	96.787	171.214	-87.157	-9.510	-1.859	3.825	-5.685	0.301	0.223
16	M-NO_2	186.938	202.184	-111.642	-9.942	-2.302	3.820	-6.122	0.886	1.125
17	o-CH_3	99.041	171.214	-87.153	-9.411	-1.877	3.767	-5.644	-0.204	-0.080
18	o-Cl	102.185	191.632	-91.734	-9.479	-1.959	3.760	-5.719	0.496	0.620
19	o-NO_2	191.133	202.184	-111.636	-9.737	-2.303	3.717	-6.020	0.331	0.455

whose inhibition activity is reported at 0.2^{0}C. The values of various quantum chemical descriptors of the derivatives, have been evaluated by techniques described earlier and results are presented above in TABLE 3.

Using the values of descriptors given in TABLE 1, several QSAR models using different combinations of descriptors have been tried and MLR equations have been solved but only 18 combinations have been chosen which have correlation coefficient value above 0.81. Such MLR equations are presented below:-

APA1=0.0132407*Mw-0.968732*HOMO-11.1984
rCV^2=0.6811
r^2=0.81108
APA2=0.0138332*Mw+0.00112645*TE-0.978615*HOMO-11.2959
rCV^2=0.421382
r^2=0.81148
APA3=0.0140986*Mw+0.00732505*TE-1.29366*AH-8.89576
rCV^2=0.455042
r^2=0.811188
APA4=0.0127658*Mw-0.918336*HOMO-0.0954868*LUMO-10.8215
rCV^2=0.555849
r^2=0.811617
APA5=0.0127658*Mw-1.01382*HOMO-0.190974*En-10.8215
rCV^2=0.555849
r^2=0.811617
APA6=0.0127658*Mw-0.82285*HOMO-0.190974*AH-10.8215
rCV^2=0.555849
r^2=0.811617
APA7=0.0127658*Mw-1.01382*LUMO+1.83667*En-10.8215
rCV^2=0.555849 r^2=0.811617
APA8=0.0127658*Mw+0.82285*LUMO-1.83667*AH-10.8215
rCV^2=0.555849
r^2=0.811617
APA9=0.0127658*Mw+0.82285*En-1.01382*AH-10.8215
rCV^2=0.555849
r^2=0.811617
APA10=-0.000196709*Hf+0.0137977*Mw+0.00117945*TE-0.990936*HOMO-11.3787
rCV^2=0.413362
r^2=0.811659
APA11=-0.00188959*Hf+0.0149091*Mw+0.0160461*TE-1.611*LUMO-3.78303
rCV^2=0.119792
r^2=0.77626
APA12=-0.00125417*Hf+0.0137966*Mw+0.00855005*TE-1.44832*AH-9.46736
rCV^2=0.47182
r^2=0.817438
APA13=0.0139012*Mw+0.00431402*TE-0.835874*HOMO-0.323446*LUMO-10.2952
rCV^2=0.406946
r^2=0.814434
APA14=0.0139012*Mw+0.00431402*TE-1.15932*HOMO-0.646892*En-10.2952
rCV^2=0.406946
r^2=0.814434
APA15=0.0139012*Mw+0.00431402*TE-0.512428*HOMO-0.646892*AH-10.2952
rCV^2=0.406946
r^2=0.814434

APA16=0.0139012*Mw+0.00431402*TE-1.15932*LUMO +1.67175*En-10.2952
rCV^2=0.406946
r^2=0.814434
APA17=0.0139012*Mw+0.00431402*TE+0.512428*LUMO-1.67175*AH-10.2952
rCV^2=0.406946
r^2=0.814434
APA18=0.0139012*Mw+0.00431402*TE+0.512428*En-1.15932*AH-10.2952
rCV^2=0.406946
r^2=0.814434

All the above 18 models have very high predictive power as their correlation coefficients are above 0.81, and cross validation coefficients above 0.40. The best models are APA 12 and APA 13. Their coefficient values, and combination of descriptors are given below :-

Predicted activity	rCV^2	r^2	Descriptors used in regression analysis
APA12	0.47	0.81	Heat of Formation, Molecular Weight, Total Energy, Absolute Hardness
APA13	0.40	0.81	Molecular Weight, Total Energy, HOMO Energy, LUMO Energy

The predicted activities along with their observed activity of these models are given below TABLE 4, which clearly indicates the closeness between the two values.The closeness in the values is also demonstrated by the graph figure 5.

TABLE 4: Predicted and observed activity

Comp.	Predicted activity APA12	Predicted activity APA13	Observed activity
1	0.165	0.138	0.215
2	-0.216	-0.223	-0.363
3	0.604	0.580	0.721
4	0.237	0.239	0.420
5	0.732	0.694	0.959
6	1.337	1.325	0.921
7	0.917	0.882	1.046
8	0.275	0.297	0.347
9	-0.157	-0.138	-0.176
10	0.762	0.749	0.959
11	1.025	1.017	1.400
12	1.268	1.358	1.769
13	2.053	1.977	1.854
14	0.663	0.647	0.638
15	0.261	0.259	0.301
16	1.000	1.089	0.886
17	0.200	0.183	-0.204
18	0.547	0.530	0.496
19	0.847	0.918	0.331

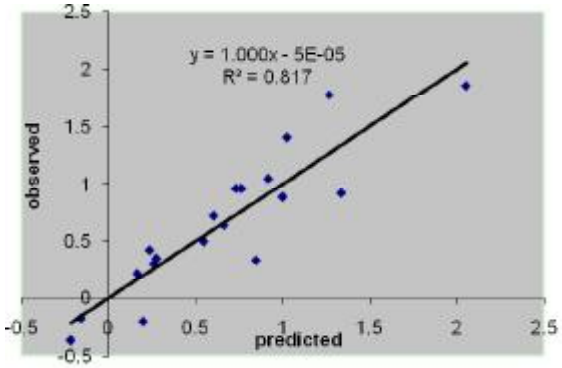


Figure 5 : Plot of APA 12 showing observed activity versus predicted activity for the 19 compounds

Second set

The values of descriptors for the compounds whose activity has been measured in terms of PKi, but at temperature 15^0C have been evaluated and are presented in TABLE 3, along with the activity measured in terms of PKi at temperature 15^0C.

Several QSAR models using the values of TABLE 3 in different combinations of descriptors have been tried and MLR equations have been developed, but only 14 combinations have been chosen which have correlation coefficient values above 0.74.

The MLR equations of these combinations are given below :-

PA1=0.0114642*Mw-1.05477*HOMO-11.6015
rCV^2=0.512319
r^2=0.757454
PA2=0.00901599*Mw-1.2237*AH-8.15849
rCV^2=0.438204
r^2=0.745429
PA3=0.0140942*Mw+0.00500001*TE-1.09864*HOMO-12.0344
rCV^2=0.462112
r^2=0.765559
PA4=0.0154489*Mw+0.0201582*TE-1.6764*LUMO-3.75833
rCV^2=0.477954
r^2=0.754417
PA5=0.0142036*Mw+0.0127161*TE-1.55112*AH-9.79995
rCV^2=0.50891
r^2=0.788957
PA6=0.0106105*Mw-0.964172*HOMO-0.171663*LUMO-10.9239
rCV^2=0.479968
r^2=0.759236
PA7=0.0106105*Mw-1.13584*HOMO-0.343327*En-10.9239
rCV^2=0.479968
r^2=0.759236
PA8=0.0106105*Mw-0.792509*HOMO-0.343327*AH-10.9239
rCV^2=0.479968

r^2=0.759236
PA9=0.0106105*Mw-1.13584*LUMO+1.92834*En-10.9239
rCV^2=0.479968
r^2=0.759236
PA10=0.0106105*Mw+0.792509*LUMO-1.92834*AH-10.9239
rCV^2=0.479968
r^2=0.759236
PA11=0.0106105*Mw+0.792509*En-1.13584*AH-10.9239
rCV^2=0.479968
r^2=0.759236
PA12=0.000986033*Hf+0.0142721*Mw+0.00473432*TE-1.03688*HOMO-11.6196
rCV^2=0.333619
r^2=0.770173
PA13=-0.000242821*Hf+0.0141451*Mw+0.0129533*TE-1.58107*AH-9.91062
rCV^2=0.497159
r^2=0.789198
PA14=0.0142854*Mw+0.0139631*TE-0.697268*HOMO-0.909495*LUMO-9.22037
rCV^2=0.512993
r^2=0.789529

The best models are PA 13 and PA14 whose coefficient values and combination of descriptors are presented below :-

Predicted activity	rCV^2	r^2	Descriptors used in regression analysis
APA12	0.512993	0.789529	Molecular Weight, Total Energy, HOMO Energy, LUMO Energy
APA13	0.497159	0.789198	Heat of Formation, Molecular Weight, Total Energy, Absolute Hardness

The predicted activities and the observed activity of these models are given below TABLE 5, and are demonstrated in graph figure 6 which clearly shows closeness between the observed and predicted activity.

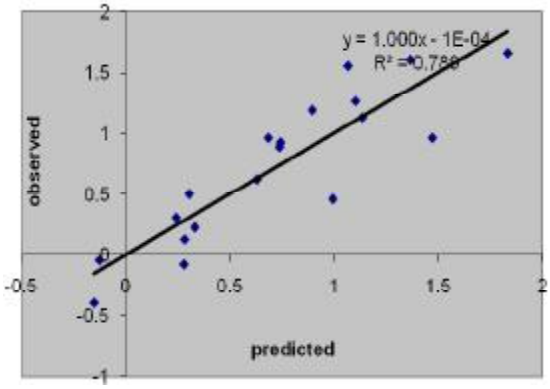


Figure 6 : Plot of PA 13 showing observed activity versus predicted activity for the 19 compounds

TABLE 5: Predicted and observed activity

Comp.	Predicted activity PA 13	Predicted activity PA 14	Observed activity
1	0.281	0.291	0.124
2	-0.154	-0.177	-0.398
3	0.684	0.688	0.959
4	0.303	0.319	0.496
5	0.894	0.882	1.187
6	1.472	1.471	0.959
7	1.102	1.047	1.260
8	0.241	0.269	0.301
9	-0.128	-0.152	-0.046
10	0.737	0.769	0.886
11	1.066	1.069	1.552
12	1.366	1.350	1.602
13	1.833	1.855	1.658
14	0.742	0.753	0.921
15	0.330	0.347	0.223
16	1.135	1.137	1.125
17	0.278	0.282	-0.080
18	0.628	0.629	0.620
19	0.993	0.975	0.455

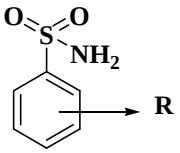
Third set

The inhibition activity of derivatives of benzene sulfonamides are reported in terms of log K.The values of various quantum chemical descriptors of the derivatives, have been evaluated by techniques described in material and method and the results are presented below in TABLE 6 along with the observed activity in terms of log K.

Seven QSAR models which have correlation coefficient values above 0.81 have been chosen, which are presented below: -

SPA 1=-0.0193872*Hf+0.871599*Mw+1.66239*TE-27.8945*LUMO-47.0456
rCV^2=0.682865
r^2=0.848966
SPA2=-0.0170746*Hf+0.278119*Mw+0.498118*TE-20.3694*En+82.5278
rCV^2=0.56173
r^2=0.840678
SPA3=0.677959*Mw+1.25548*TE-13.4802*HOMO-37.9962*En+17.7615
rCV^2=0.584151
r^2=0.816355
SPA4=0.677959*Mw+1.25548*TE+24.516*HOMO-37.9962*AH+17.7615
rCV^2=0.584151
r^2=0.816355
SPA5=0.677959*Mw+1.25548*TE-13.4802*LUMO-11.0357*

TABLE 6: Values of descriptors and activity in terms of log K



Benzene sulfonamide

Comp.	R	Heat of Formation (kcal/mole)	Molecular weight	Total energy (Hartree)	HOMO energy (eV)	LUMO energy (eV)	Absolute hardness	Electroneg ativity	Activity
20	H	106.162	157.187	-79.969	-9.552	-1.883	3.834	-5.717	6.690
21	4-CH_3	96.482	171.214	-87.159	-9.493	-1.843	3.825	-5.668	7.090
22	4-C_2H_5	92.863	185.240	-94.316	-9.488	-1.837	3.826	-5.662	7.530
23	4-C_3H_7	86.654	199.267	-101.480	-9.504	-1.849	3.827	-5.676	7.770
24	4-C_4H_9	81.232	213.294	-108.640	-9.512	-1.848	3.832	-5.680	8.300
25	4-C_5H_{11}	75.801	227.321	-115.799	-9.510	-1.849	3.830	-5.680	8.860
26	4-CO_2CH_3	130.385	215.223	-116.676	-9.596	-2.289	3.654	-5.942	7.980
27	4-$CO_2C_2H_5$	126.307	229.250	-123.836	-9.491	-2.330	3.581	-5.910	8.500
28	4-$CO_2C_3H_7$	120.832	243.277	-131.001	-9.647	-2.261	3.693	-5.954	8.770
29	4-$CO_2C_4H_9$	115.431	257.304	-138.162	-9.648	-2.260	3.694	-5.954	9.110
30	4-$CO_2C_5H_{11}$	110.005	271.331	-145.322	-9.648	-2.261	3.694	-5.955	9.390
31	4-$CO_2C_6H_{13}$	104.579	285.357	-152.482	-9.650	-2.260	3.695	-5.955	9.390
32	4-$CONHCH_3$	67.316	214.239	-114.025	-9.663	-2.097	3.783	-5.880	7.080
33	4-$CONHC_2H_5$	61.140	228.265	-121.177	-9.657	-2.088	3.785	-5.872	7.530
34	4-$CONHC_3H_7$	55.895	242.292	-128.337	-9.657	-2.089	3.784	-5.873	9.080
35	4-$CONHC_4H_9$	50.468	256.319	-135.497	-9.655	-2.089	3.783	-5.872	8.490
36	4-$CONHC_5H_{11}$	45.049	270.346	-142.657	-9.654	-2.089	3.782	-5.872	8.750
37	4-$CONHC_6H_{13}$	39.618	284.373	-149.817	-9.653	-2.089	3.782	-5.871	8.880
38	4-$CONHC_7H_{15}$	34.189	298.399	-156.977	-9.656	-2.089	3.783	-5.873	8.930
39	3-CO_2CH_3	130.284	215.223	-116.674	-9.656	-2.189	3.733	-5.922	5.870
40	3-$CO_2C_2H_5$	125.830	229.250	-123.837	-9.691	-2.201	3.745	-5.946	6.210
41	3-$CO_2C_3H_7$	120.767	243.277	-130.993	-9.555	-2.186	3.684	-5.870	6.440
42	3-$CO_2C_4H_9$	114.893	257.304	-138.158	-9.688	-2.198	3.745	-5.943	6.950
43	3-$CO_2C_5H_{11}$	109.471	271.331	-145.318	-9.689	-2.198	3.745	-5.944	6.860
44	2-CO_2CH_3	134.094	215.223	-116.669	-9.775	-2.200	3.787	-5.988	4.410
45	2-$CO_2C_2H_5$	130.199	229.250	-123.834	-9.792	-2.189	3.802	-5.990	4.800
46	2-CO_2C_3H7	124.769	243.277	-130.994	-9.788	-2.186	3.801	-5.987	5.280
47	2-$CO_2C_4H_9$	119.353	257.304	-138.155	-9.788	-2.187	3.801	-5.987	5.760
48	2-$CO_2C_5H_{11}$	113.933	271.331	-145.315	-9.789	-2.187	3.801	-5.988	6.180

En+17.7615
rCV^2=0.584151
r^2=0.816355
SPA6=0.677959*Mw+1.25548*TE-24.516*LUMO+11.0357*AH+17.7615
rCV^2=0.584151
r^2=0.816355
SPA7=0.677959*Mw+1.25548*TE-24.516*En-13.4802*AH+17.7615
rCV^2=0.584151
r^2=0.816355

Best QSAR models are obtained by MLR equations are SPA-1 and SPA-2 the combination of descriptors of these models are given below along with coefficient values.

Predicted activity	rCV^2	r^2	Descriptors used in regression analysis
SPA1	0.682865	0.848966	Heat of Formation, Molecular Weight, Total Energy, LUMO Energy
SPA2	0.561730	0.840678	Heat of Formation, Molecular Weight, Total Energy, Electronegativity

Predicted activity of compounds along with the observed activity of the best models are given below in TABLE 7.

Full Paper

TABLE 7: Predicted and observed activity

Comp.	Predicted activity SPA1	Predicted activity SPA2	Observed activity
20	7.480	6.494	6.690
21	6.829	7.170	7.090
22	7.054	7.557	7.530
23	7.831	7.959	7.770
24	8.246	8.293	8.300
25	8.702	8.754	8.860
26	7.893	7.620	7.980
27	9.446	9.512	8.500
28	7.959	7.647	8.770
29	8.352	8.055	9.110
30	8.791	8.482	9.390
31	9.215	8.889	9.390
32	7.333	7.111	7.080
33	7.520	7.516	7.530
34	7.970	7.948	9.080
35	8.396	8.400	8.490
36	8.841	8.842	8.750
37	9.277	9.282	8.880
38	9.703	9.676	8.930
39	5.116	5.996	5.870
40	5.871	6.171	6.210
41	5.867	7.825	6.440
42	6.633	7.025	6.950
43	7.066	7.442	6.860
44	5.367	4.836	4.410
45	5.432	4.937	4.800
46	5.791	5.388	5.280
47	6.232	5.819	5.760
48	6.665	6.235	6.180

QSAR models SPA-1,SPA-2 provide predicted values which are close to observed values (log K). For better representation the closeness in values is also demonstrated by graphs figure 7.

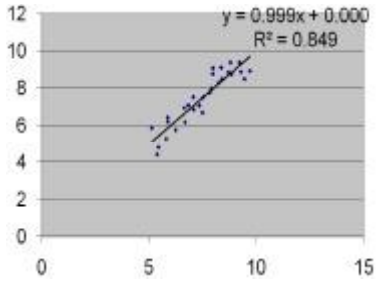


Figure 7 : Plot of SPA 1 showing observed activity versus predicted activity for the 29 compounds

CONCLUSIONS

1. The correlation coefficient values of the best QSAR model of the inhibitors of the first set is 0.81, of the second set is 0.789 and of the third set is 0.84. The values clearly indicate that the models have reliable predictive power.
2. The first descriptor in almost all the above models is heat of formation. This indicates that CA enzyme-sulfonamide complex is stabilized by favorable enthalpy change.
3. The second important descriptor is molecular weight,which is a parameter of steric factor.This factor also be considered as influencing factor.
4. Total energy is the third important descriptor, The CA enzyme -sulfonamide reaction appears to be favoured by energy change.

REFERENCES

[1] L.Tarko, S.Calafeteanu, Rev.Chim., Bucureşti, **58**, 191 **(2007)**.
[2] Lorentz Jantschi, Sorana Daniela Bolboaca; Electron J.Biomed., **2**, 22-33 **(2006)**.
[3] S.P.Gupta; Chem.Rev., **87**, 1183 **(1987)**.
[4] N.Kakeya, N.Yata, A.Kamada, M.Aoki; Chem. Pharm. Bull., **17**, 1010 **(1969)**.
[5] R.G.Parr, W.Yang; 'Density Functional Theory of Atoms and Molecules', Oxford University Press, New York, **(1989)**.
[6] R.P.Iczkowski, J.L.Margrave; J.Am.Chem.Soc., **83**, 3547 **(1961)**.
[7] R.S.Mulliken; J.Chem.Phys., **2**, 782 **(1934)**.
[8] R.T.Sanderson; Science, **121**, 207 **(1955)**.
[9] R.T.Sanderson; 'Chemical Bonds and Bond Energy', Academic: New York, **(1976)**.
[10] R.T.Sanderson; 'Polar Covalence', Academic Press: New York, **(1983)**.
[11] R.G.Parr, R.G.Pearson; J.Am.Chem.Soc., **105**, 7512 **(1983)**.
[12] R.G.Parr, R.A.Donnelly, M.Levy, W.E.Palke; J.Chem.Phys., **68**, 3801 **(1978)**.
[13] R.G.Parr, L.V.Szentpaly, S.Liu; J.Am.Chem.Soc., **121**, 1922 **(1999)**.
[14] Erol Eroglu, Hasan Türkmen, Semra Guler, Selami Palaz, Oral Oltulu; Int.J.Mol.Sci., **8**, 145-155 **(2007)**.
[15] F.Abbate, A.Casini, T.Owa, A.Scozzafava, C.T. Supuran; Bioorg.Med.Chem.Lett., **14**, 217 **(2004)**.
[16] B.W.Clare, C.T.Supuran; European Journal of Medicinal Chemistry, **32(4)**, 311-319 **(1997)**.
[17] Abhilash Thakur, Mamta Thakur, Padmakar V.Khadikar; 'General Papers', ARKIVOC, **14**, 87-102 **(2006)**.
[18] Y.Shinagawa, Y.Shinagawa; Int.J.Quantum Chem.Quantum Boil.Symp., **1**, 169 **(1974)**.