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Research Article

DFT Based QSAR Studies of Derivatives of Benzene Sulphonamide Using Quantum Chemical Descriptors

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ABSTRACT

Heat of formation (ΔH_f), molecular weight (MW), total energy (TE), HOMO energy (εHOMO), LUMO Energy (εLUMO), absolute hardness (η) and electronegativity (χ) have been used as descriptors for QSAR studies of derivatives of benzene sulphonamides. Best QSAR model PA1 has been developed using the descriptors viz. heat of formation, molecular weight, total energy and electronegativity which has regression coefficient above 0.91 and cross-validation coefficient above 0.88. These values indicate that the binding constant log K of the derivatives can be best predicted by the QSAR model PA1.

Keywords: QSAR, Multilinear Regression Analysis, HOMO energy, LUMO energy, Absolute Hardness, Electronegativity

1. INTRODUCTION

The chemical, physiological and pathological processes in which binding constant log K are involved were thoroughly investigated due to the chemical and pharmacological applications of benzene sulfonamides [1-3]. It has also been shown [2] that some benzene sulfonamide is important clinical agent. Benzene sulfonamide is mainly used in the treatment of gastro-intestinal–duodenal ulcers, neurological disorders, glaucoma, altitude sickness and tumor [4-8].

Accordingly, a large number of sulfonamides were synthesized and tested for their biological, physiological and pharmacological potential [9]. In the middle of them benzene derivatives of sulfonamides have attracted much consideration [9-10]. Recently, QSAR studies the benzene-sulfonamide have been done which mostly based on the Hansch's [11] approach. 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 carbon dioxide out of tissues. Carbonic anhydrases (CA) are a family of structurally related zinc containing enzyme. Excess production of CA may disturb the normal physiological function of the body. In such an event synthetic inhibitors are required to prevent the over functioning of enzyme. Derivatives of benzene sulfonamides (Fig.-1) which are the most important carbonic anhydrase inhibitors (CAI) [12-17] bind in a tetrahedral geometry of the Zinc ion in deprotonated state, with the nitrogen atom of the benzene sulfonamide moiety and is coordinated to Zinc. Quantitative structure activity relationship (QSAR) studies are tools for predicting endpoints of interest in organic molecules acting as drugs [16]. Many physiological activities of a molecule can be related to their composition and structure. Quantum chemical descriptors, which are numerical representations of the molecular structures, are used for performing QSAR analysis [17].

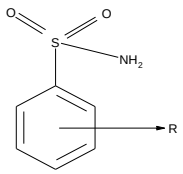


Fig.-1: Derivatives of Benzene Sulphonamide

2. MATERIAL AND METHOD

The study materials of this research work are 29 derivatives of benzene sulphonamides listed in Table-1 whose binding constant (log K) is known. The structures of all the derivatives of benzene sulphonamide have been drawn and their geometries have been optimized with the help of Cache software by DFT method using the basis DZVP. We have used quantum chemical descriptors for QSAR studies of derivatives of benzene sulphonamides as the literature shows that no QSAR studies using quantum chemical descriptors have been reported.

The method of evaluation has been developed within the framework of density functional theory [18-23] and is based on hard and soft acids and bases principle of Pearson.

Table-1: Derivatives of benzene sulphonamides along with the values of binding constant log K

Compound	Substituents (R)	Log K
C1	H	6.69
C2	4-CH_3	7.09
C3	4-C_2H_5	7.53
C4	4-C_3H_7	7.77
C5	4-C_4H_9	8.30
C6	4-C_5H_{11}	8.86
C7	4-CO_2CH_3	7.99
C8	4-$CO_2C_2H_5$	8.50
C9	4-$CO_2C_3H_7$	8.77
C10	4-$CO_2C_4H_9$	9.11
C11	4-$CO_2C_5H_{11}$	9.39
C12	4-$CO_2C_6H_{13}$	9.39
C13	4-$CONHCH_3$	7.08
C14	4-$CONHC_2H_5$	7.53
C15	4-$CONHC_3H_7$	8.08
C16	4-$CONHC_4H_9$	8.49
C17	4-$CONHC_5H_{11}$	8.75
C18	4-$CONHC_6H_{13}$	8.88
C19	4-$CONHC_7H_{15}$	8.93
C20	3-CO_2CH_3	5.87
C21	3-$CO_2C_2H_5$	6.21
C22	3-$CO_2C_3H_7$	6.44
C23	3-$CO_2C_4H_9$	6.95
C24	3-$CO_2C_5H_{11}$	6.86
C25	2-CO_2CH_3	4.41
C26	2-$CO_2C_2H_5$	4.80
C27	2-$CO_2C_3H_7$	5.28
C28	2-$CO_2C_4H_9$	5.76
C29	2-$CO_2C_5H_{11}$	6.18

The basis for the focus on electronegativity [24-25] and hardness [26-27] is provided by density functional theory (DFT), which guarantees that the ground state energy of many electron systems is a unique function of its density. For the change from one ground state to another of an electronic system, the change of electronic energy $E(\rho)$ is given by the formula [28].

$$dE(\rho) = \mu\, dN + \int \rho(r)\, dv(r)\, dr \qquad \text{Eqn-1}$$

where v(r) is the external electronic potential an electron at "r" experiences due to the nuclei, N is the number of electrons, and μ the chemical potential is defined as [29]

$$\mu = (\delta E / \delta N)_{v(r)} \qquad \text{Eqn-2}$$

and the electron density $\rho_{(r)}$ is defined as [30]

$$\rho_{(r)} = [(\delta E / \delta v(r)]_N \qquad \text{Eqn-3}$$

Parr et al [30] have shown that the electronegativity of any chemical species is equal to the negative value of chemical potential indeed it follows rigorously [31] that

$$\chi = -\mu = (I + A)/2 \qquad \text{Eqn-4}$$

where I and A are ionization potential and electron affinity of atomic or molecular system. Eqn- 4 may be written as:

$$A = 2\chi - I \qquad \text{Eqn-5}$$

Density functional theory provides a quantum mechanical justification for electronegativity. A concept use intuitively for a long time and validates Sanderson's postulates [31] that when two and more atoms combine to form a molecule, their electronegativity gets equalized and unique electronegativity exists everywhere in a molecule [32-33].

According to Koopman's theorem the I and A are simply the eigen value of HOMO and LUMO respectively with change in sign [34]. Therefore, from equation-9 we get,

$$A = -(\varepsilon HOMO + \varepsilon LUMO) - I \qquad \text{Eqn-6}$$

The chemical potential itself depend on N and v i.e. $\mu=\mu(N,v)$. Parr and Pearson [34] have defined hardness with respect to N as

$$\eta = \tfrac{1}{2}.\,(\delta\mu/\delta N)_{v(r)} = \tfrac{1}{2}.\,(\delta^2 E/\delta N^2)_{v(r)} = (I - A)/2 \qquad \text{Eqn-7}$$

Heat of formation (ΔH_f), molecular weight (MW), total energy (TE), HOMO energy (εHOMO), LUMO Energy (εLUMO), absolute hardness (η) and electronegativity (χ) have been used as descriptors for QSAR studies of derivatives of benzene sulphonamides.

3. RESULTS AND DISCUSSION

Values of quantum chemical descriptors of derivatives of benzene sulphonamide have been calculated by DFT B88LYP method using DZVP basis with the help of CAChe software and included in Table-2.

Table-2: Values of quantum chemical descriptors of derivatives of benzene sulphonamide

Compound	Heat of Formation (kcal/mole)	Molecular Weight	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness	Electronegativity	Observed Binding Constant
C1	97.891	153.242	-70.505	-8.185	-0.414	3.886	4.300	6.69
C2	88.245	167.268	-77.694	-8.144	-0.416	3.864	4.280	7.09
C3	83.668	181.295	-84.855	-8.149	-0.416	3.866	4.282	7.53
C4	78.571	195.322	-92.011	-8.152	-0.395	3.878	4.273	7.77
C5	73.151	209.349	-99.171	-8.152	-0.395	3.878	4.274	8.30
C6	67.721	223.376	-106.331	-8.153	-0.397	3.878	4.275	8.86
C7	122.000	211.278	-107.210	-8.543	-1.503	3.520	5.023	7.99
C8	117.434	225.305	-114.373	-8.526	-1.495	3.515	5.011	8.50
C9	112.463	239.332	-121.536	-8.539	-1.648	3.446	5.093	8.77
C10	106.505	253.359	-128.694	-8.523	-1.490	3.516	5.006	9.11
C11	101.084	267.385	-135.854	-8.523	-1.490	3.516	5.007	9.39
C12	95.655	281.412	-143.014	-8.524	-1.492	3.516	5.008	9.39
C13	58.979	210.293	-104.561	-8.367	-0.964	3.702	4.666	7.08
C14	52.810	224.320	-111.712	-8.357	-0.950	3.704	4.654	7.53
C15	47.566	238.347	-118.873	-8.359	-0.951	3.704	4.655	8.08
C16	42.139	252.374	-126.033	-8.359	-0.951	3.704	4.655	8.49
C17	36.721	266.401	-133.192	-8.359	-0.952	3.704	4.655	8.75
C18	31.290	280.427	-140.352	-8.359	-0.952	3.704	4.655	8.88
C19	25.548	294.454	-147.522	-8.351	-0.792	3.780	4.571	8.93
C20	121.809	211.278	-107.209	-8.516	-1.336	3.590	4.926	5.87
C21	117.207	225.305	-114.372	-8.505	-1.324	3.590	4.915	6.21
C22	111.802	239.332	-121.531	-8.504	-1.325	3.590	4.914	6.44
C23	106.381	253.359	-128.692	-8.503	-1.325	3.589	4.914	6.95
C24	101.005	267.385	-135.852	-8.501	-1.323	3.589	4.912	6.86
C25	126.099	211.278	-107.200	-8.560	-0.961	3.799	4.760	4.41
C26	121.933	225.305	-114.355	-8.555	-0.911	3.822	4.733	4.80
C27	118.806	239.332	-121.507	-8.488	-0.968	3.760	4.728	5.28
C28	111.497	253.359	-128.667	-8.498	-0.901	3.799	4.700	5.76
C29	105.678	267.385	-135.836	-8.552	-0.915	3.818	4.733	6.18

Table-3: Values of predicted binding constants PA1 to PA10 of derivatives of benzene sulphonamide

Comp.	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8	PA9	PA10
C1	6.811	6.703	6.598	6.660	6.660	6.660	6.660	6.660	6.660	6.610
C2	7.075	7.155	7.233	7.218	7.218	7.218	7.218	7.218	7.218	7.249
C3	7.518	7.561	7.601	7.662	7.662	7.662	7.662	7.662	7.662	7.664
C4	7.853	7.866	7.878	8.007	8.007	8.007	8.007	8.007	8.007	7.984
C5	8.285	8.282	8.279	8.465	8.465	8.465	8.465	8.465	8.465	8.425
C6	8.731	8.706	8.681	8.928	8.928	8.928	8.928	8.928	8.928	8.867
C7	7.391	7.300	7.195	7.200	7.200	7.200	7.200	7.200	7.200	7.168
C8	7.677	7.663	7.631	7.663	7.663	7.663	7.663	7.663	7.663	7.651
C9	8.963	8.862	8.735	8.862	8.862	8.862	8.862	8.862	8.862	8.801
C10	8.491	8.464	8.420	8.558	8.558	8.558	8.558	8.558	8.558	8.519
C11	8.927	8.882	8.821	9.017	9.017	9.017	9.017	9.017	9.017	8.960
C12	9.371	9.304	9.221	9.478	9.478	9.478	9.478	9.478	9.478	9.401
C13	7.147	7.153	7.160	6.696	6.696	6.696	6.696	6.696	6.696	6.796
C14	7.476	7.513	7.550	7.116	7.116	7.116	7.116	7.116	7.116	7.220
C15	7.915	7.929	7.943	7.572	7.572	7.572	7.572	7.572	7.572	7.655
C16	8.345	8.344	8.344	8.029	8.029	8.029	8.029	8.029	8.029	8.095
C17	8.783	8.764	8.745	8.490	8.490	8.490	8.490	8.490	8.490	8.537
C18	9.215	9.179	9.144	8.947	8.947	8.947	8.947	8.947	8.947	8.976
C19	8.760	8.756	8.764	8.597	8.597	8.597	8.597	8.597	8.597	8.631
C20	6.382	6.435	6.483	6.420	6.420	6.420	6.420	6.420	6.420	6.452
C21	6.671	6.776	6.874	6.848	6.848	6.848	6.848	6.848	6.848	6.890
C22	7.103	7.194	7.278	7.309	7.309	7.309	7.309	7.309	7.309	7.334
C23	7.523	7.607	7.683	7.769	7.769	7.769	7.769	7.769	7.769	7.780
C24	7.937	8.015	8.085	8.224	8.224	8.224	8.224	8.224	8.224	8.222
C25	4.575	4.433	4.321	4.381	4.381	4.381	4.381	4.381	4.381	4.319
C26	4.701	4.575	4.482	4.598	4.598	4.598	4.598	4.598	4.598	4.530
C27	5.052	5.268	5.502	5.546	5.546	5.546	5.546	5.546	5.546	5.612
C28	5.215	5.355	5.520	5.628	5.628	5.628	5.628	5.628	5.628	5.653
C29	5.999	5.843	5.720	6.002	6.002	6.002	6.002	6.002	6.002	5.888

Various QSAR models have been developed with the help of multilinear regression (MLR) analysis using four descriptors in maximum. Best ten QSAR models in decreasing order of predictive power are discussed here whose MLR equations are as under-

1. PA1=0.0176679*ΔH_f+0.598498*MW+1.12568*TE+10.4932*χ-48.925 rCV^2=0.884342 r^2=0.914904

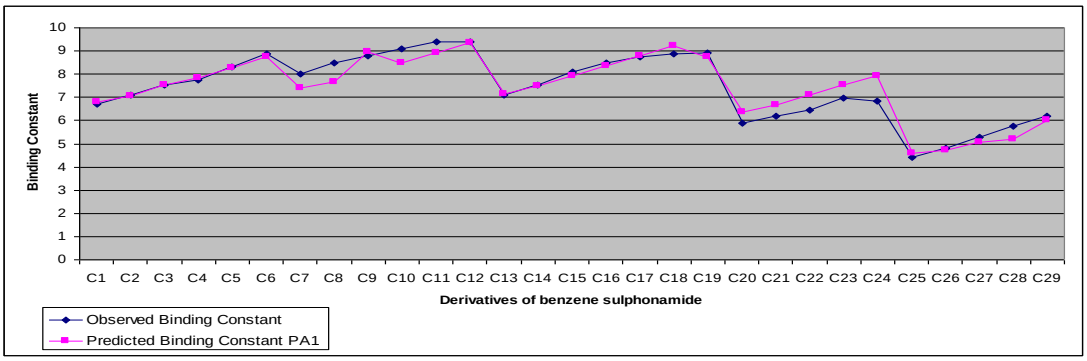
2. PA2=-0.0127974*ΔH_f+0.471287*MW+0.875004*TE-5.20856*εLUMO-4.72977 rCV^2=0.873449 r^2=0.903261
3. PA3=-0.00801033*ΔH_f+0.342941*MW+0.622164*TE-10.1866*η+38.275 rCV^2=0.855413 r^2=0.884457
4. PA4=0.460114*MW+0.837559*TE+2.80742*εHOMO-5.12798*εLUMO+16.0593 rCV^2=0.811631 r^2=0.873373
5. PA5=0.460114*MW+0.837559*TE-2.32055*εHOMO-10.256*η+16.0593 rCV^2=0.811631 r^2=0.873373
6. PA6=0.460114*MW+0.837559*TE+7.9354*εHOMO+10.256*χ+16.0593 rCV^2=0.811631 r^2=0.873373
7. PA7=0.460114*MW+0.837559*TE-2.32055*εLUMO-5.61485*η+16.0593 rCV^2=0.811631 r^2=0.873373
8. PA8=0.460114*MW+0.837559*TE-7.9354*εLUMO-5.61485*χ+16.0593 rCV^2=0.811631 r^2=0.873373
9. PA9=0.460114*MW+0.837559*TE-7.9354*η+2.32055*χ+16.0593 rCV^2=0.811631 r^2=0.873373
10. PA10=0.391357*MW+0.705335*TE-10.2162*η+36.0626 rCV^2=0.833116 r^2=0.871733

QSAR model is said to have good predictive power in the value of regression coefficient (r^2), also called correlation coefficient, is greater than 0.5 and the value of cross-validation coefficient (rCV^2) is greater than 0.2. As the value of regression coefficient increases, the predictive power of QSAR model increases. Hundred percent predictive power is achieved when regression coefficient becomes unity. Values of predicted binding constants of derivatives of benzene sulphonamides have been calculated by substituting the values of descriptors in MLR equations and included in Table-3.

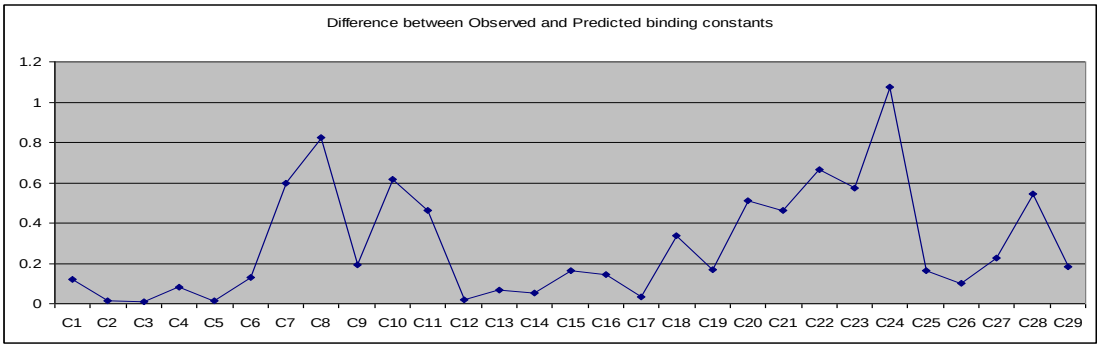
QSAR Model PA1

This is the best QSAR model and has been developed using the descriptors viz. heat of formation, molecular weight, total energy and electronegativity. Value of regression coefficient is 0.914904 and cross-validation coefficient is 0.884342. QSAR model PA1 is very reliable and can be used for the prediction of binding constant of any derivative of benzene sulphonamide. Graph between observed and predicted values of binding constant log K by QSAR model PA1 is shown in Graph-1. Difference between observed and predicted binding constants of derivatives of benzene sulphonamide is shown in Graph-2.

Graph-1: Graph between observed and predicted values of binding constant log K by QSAR model PA1



Graph-2: Difference between observed and predicted binding constants of derivatives of benzene sulphonamide



4. CONCLUSION

Best QSAR model has been developed using heat of formation, molecular weight, total energy and electronegativity as descriptors of binding constant of derivatives of benzene sulphonamide.

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