QUANTUM MECHANICAL PARAMETERS BASED 2D QSAR STUDY OF ARYL SULPHONAMIDES AS 5-HT$_6$ SEROTONIN LIGAND USING DFT METHODS

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Abstract. In the present work, quantum mechanical descriptors have been used for the development of quantitative structure activity relationship (QSAR) models for the thirty-two derivatives of aryl sulphonamide and sulfone based 5-HT$_6$ antagonists. Among several classes of serotonin 5-HT$_6$ receptor ligands, aryl sulphonamides reported better affinity towards the receptor. Drugs acting as serotonin ligands are useful in the treatment of a variety of mental disorders. The descriptors that have been used in our study are total energy, log *P*, molecular weight, dipole moment, heat of formation, LUMO energy, HOMO energy and electrophilicity index. The geometry optimization and evaluation of descriptors of all the compounds has been done with the help of CAChe Pro software using DFT-B88-LYP method with double-zeta valence polarized (DZVP) basis set. The best QSAR model for this set of derivatives has been obtained by combination of descriptors molecular weight, dipole moment and heat of formation. The descriptor molecular weight gives a mono-parametric QSAR model with remarkable predictive ability with positive contribution. The descriptor molecular weight is present in all best bi-parametric and tri-parametric QSAR models. Statistical parameters such as correlation coefficient, cross validation coefficient, standard error etc. were used to validate the predictability of QSAR models.

Key words: Aryl sulphonamide, serotonin ligands, density functional theory (DFT), quantum mechanical descriptors.

INTRODUCTION

Serotonin is a neurotransmitter [2] which plays an important role in various cognitive and behavioral functions. Improper serotonergic signaling leads to mental disorders such as depression, anxiety, aggression, mood swing, cognitive dysfunction, schizophrenia, suicidal behavior, infantile autism, obsessive compulsive disorder, etc. [4, 5, 15]. Serotonin is found in the central nervous system,

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where it has proven to have a number of varied and extremely important functions. In mammalian species, serotonin in the brain arises from specialized groups of cell bodies known as the raphe nuclei located in the brainstem reticular formation.
Binding of serotonin to certain receptors on the cell surface mediates the serotonin signaling [24, 28, 31]. Drugs acting as serotonin ligands are useful in the treatment of a variety of disorders. The drug development involving serotonin receptors is an important area of research [1, 10, 21].

5-HT_6 serotonin receptor is present in various regions of the brain. It belongs to the family of G-protein coupled receptors [11, 16]. The 5-HT_6 receptor is expressed almost exclusively within the mammalian central nervous system (CNS). The highest levels of expression are found in the striatum, nucleus accumbens, cortex, and olfactory tubercle. Expression also is seen in the thalamus, amygdala, hypothalamus, and cerebellum [8, 34]. Serotonin 5-HT_6 receptor turned out to be promising biological targets for the modulation of CNS mediated disorders. Blocking of the function of 5-HT_6 receptor enhances the cognitive process. 5-HT_6 receptor antagonists can increase glutamate release in cortex [6]. It also has been demonstrated that drugs acting at 5-HT_6 receptors can alter dopamine levels as well as GABA and norepinepherine levels [23]. These effects on neurotransmission and behavior have made the receptor an attractive target for potential cognitive enhancement and in the treatment of various cognitive deficits. Therefore, serotonin 5-HT_6 receptor ligands are useful in various disorders involving central nervous system dysfunctions. [13, 20].

Among several classes of serotonin 5-HT_6 receptor ligands, aryl sulphonamides reported better affinity towards the receptor [14]. Various highly active aryl sulphonamides based 5-HT_6 antagonists have been synthesized and studied [19, 30, 33].

In our previous work, topological descriptors were successfully applied for the development of QSAR models for the derivatives of aryl sulphonamide and sulfone based serotonin ligands [17]. In the present work, quantum mechanical descriptors have been used for the development of QSAR models for the thirty-two derivatives of aryl sulphonamide and sulfone based 5-HT_6 antagonists. In QSAR studies, quantum mechanical descriptors gained much importance. In recent years QSAR studies of different set of compounds have been made using quantum mechanical parameters [7, 9, 18, 22, 32]. The descriptors that have been used in our study are total energy, log *P*, molecular weight, dipole moment, heat of formation, LUMO energy, HOMO energy and electrophilicity index. The predicted activities obtained from developed QSAR models, using these quantum mechanical parameters, were found close to reported observed activities.

MATERIAL AND METHODS

The quantitative structure activity relationship (QSAR) is a mathematical representation of biological activity in terms of structural properties (called descriptors) of a series of homologue molecules [12]. The main objective of QSAR is to look for new molecules with required properties using chemical intuition and experience transformed into a mathematically quantified and computerized form. Once a correlation is established, the structure of any number of compounds with desired properties can be predicted. Thus, QSAR methodology saves resources and expedites the process of development of new molecules and drugs.

Thirty-two derivatives of aryl sulphonamide and sulfone based 5-HT_6 antagonists, listed in Table 1, were used as study material. These derivatives have been taken from literature [33]. The observed biological activities of these compounds are in terms of pKi. The geometry optimization of all the compounds has been done with the help of Workspace program associated with CAChe Pro software developed by Fujitsu Corporation of Japan, using density functional theory (DFT) method [25]. Evaluation of values of descriptors has been done with the help of same software using DFT-B88-LYP method with DZVP basis set. The QSAR models have been developed by multi linear regression (MLR) analysis with the help of Project Leader program associated with CAChe Pro. The descriptors that have been used are described below: The molecular weight It is the sum of atomic weights of all the atoms of the compound. The water/octanol partition coefficient (log *P*) is the ratio of concentrations of un-ionized compound between the two solutions. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is noted log *P* [29].

$$\log P = \log\left(\frac{[solute]_{octanol}}{[solute]_{water}}\right) \quad (1)$$

The total energy (*TE* in hartree) of a molecular system is the sum of the total electronic energy (*E*ee in hartree) and the energy of internuclear repulsion (*E*nr in hartree) [26].

$$TE = Eee + Enr \quad (2)$$

The total electronic energy of the system is given by

$$Eee = 1/2\ [\mathbf{P}]\ (\mathbf{H} + \mathbf{F}) \quad (3)$$

where **[P]** is the density matrix, **H** is the one-electron matrix, and **F** is the Fock matrix.

HOMO energy is the energy required to remove an electron from the highest occupied molecular orbital (HOMO). LUMO energy is the energy gained when an electron is added to the lowest unoccupied molecular orbital (LUMO).

The heat of formation is defined as:

$$\Delta H_f = E_{elect} + E_{nuc} - E_{isol} + E_{atom} \quad (4)$$

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 [3]; all are in in kcal/mol.

Parr *et al.* introduced the electrophilicity index (ω in eV), in terms of the chemical potential (μ in eV) and hardness (η in eV) [27]. The operational definition of the electrophilicity index may be written as:

$$\omega = \mu^2/2\eta \quad (5)$$

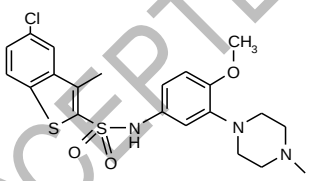
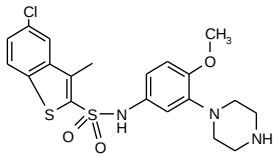
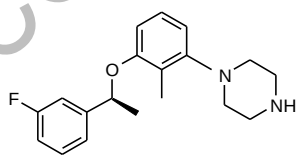
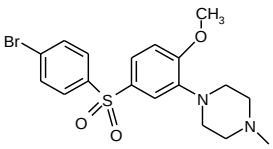
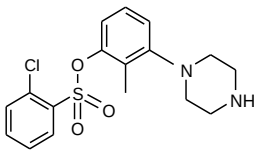
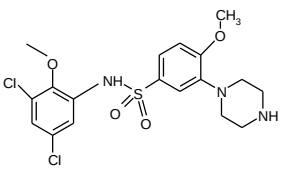
A molecule consists of several atoms. Each pair of atoms will have a bond dipole moment due to chemical bonding, represented by magnitude and direction. However, the overall dipole moment of a molecule will depend upon the magnitude and direction of the individual bond dipole moments. Therefore, the net dipole moment is the vector addition of the individual moments,

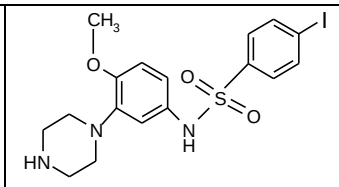
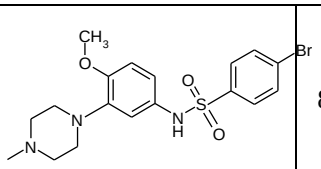
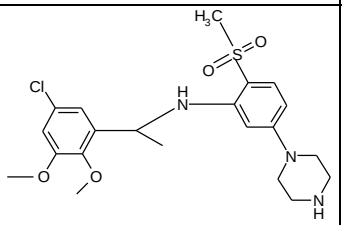
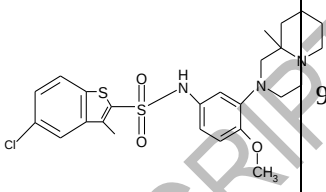
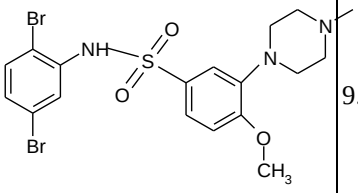
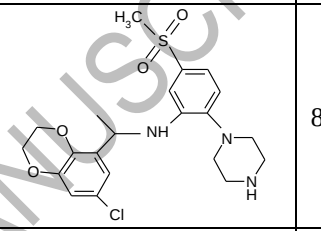
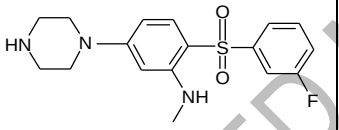
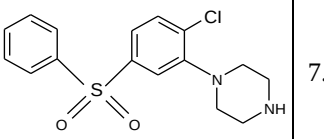
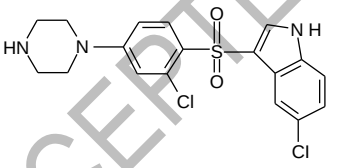
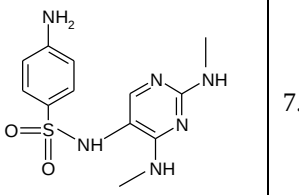
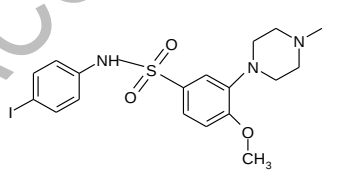
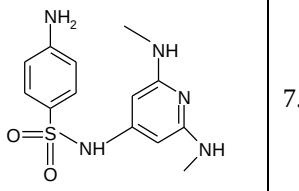
$$D = \Sigma\, q_i\, r_i \quad (6)$$

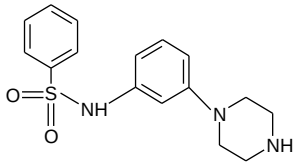
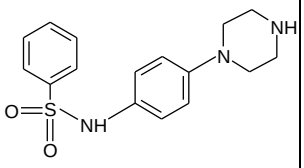
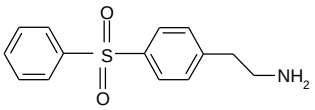
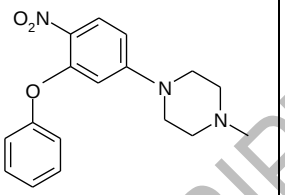
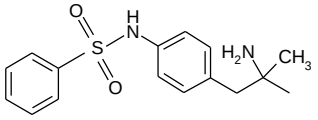
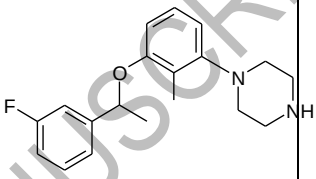
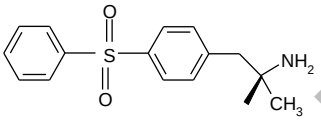
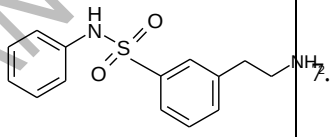
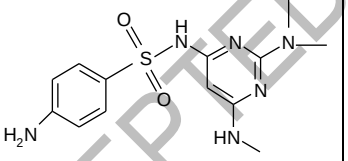
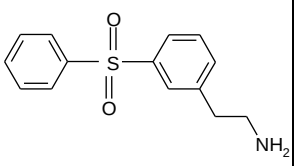
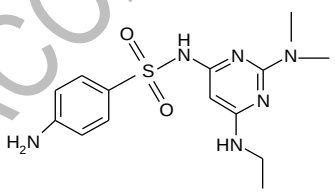
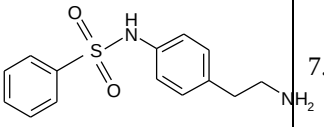
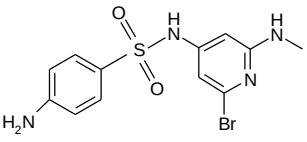
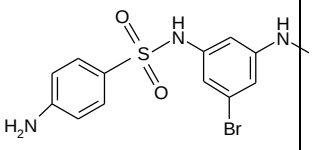
where D (Cm) is the dipole moment of the molecule, q_i (C) is the charge on i^{th} atom, and r_i (m) is the distance vector representing the position of the i^{th} atom.

Table 1

Aryl sulphonamides as 5-HT$_6$ serotonin ligand with their experimental pKi

S. No	Structure	pKi	S. No	Structure	pKi
1		9.22	**2**		8.88
3		8.16	**4**		8.55
5		8.22	**6**		9.09

7		8.74	**8**		8.3
9		8.39	**10**		9.09
11		9.00	**12**		8.88
13		8.05	**14**		7.49
15		8.01	**16**		7.32
17		8.69	**18**		7.92

19		7.20	**20**		7.07
21		7.43	**22**		7.56
23		7.46	**24**		7.4
25		7.13	**26**		7.15
27		7.3	**28**		7.3
29		7.39	**30**		7.42
31		7.3	**32**		7.69

RESULTS AND DISCUSSION

Thirty-two derivatives of aryl sulphonamides are given in Table 1 alongwith their biological activity in terms of pKi. The values of calculated eight descriptors are given in Table 2. To determine the effect of structural features of aryl sulphonamides on their 5-HT_6 antagonist activity, QSAR models were generated. Different combinations of descriptors have been used in the multi linear regression (MLR) analysis for the development of QSAR models. In the development of QSAR models eight descriptors were taken as independent variables and pKi as the dependent variable. Statistical parameters such as correlation coefficient, cross validation coefficient, standard error etc. were used to validate the predictability of QSAR model.

Table 2

Values of descriptors and experimental pKi of aryl sulphonamides

C. No.	E_T	log *P*	*MW*	*D*	ΔH_f	ε_{LUMO}	ε_{HOMO}	ω	Obs. Act.
1	–2460.64	3.942	466.012	11.299×10^{-30}	-38.252	-2.680	-3.714	9.885	9.22
2	-2421.34	3.581	451.985	7.216×10^{-30}	-33.109	-2.642	-3.575	10.349	8.88
3	-1022.15	4.295	314.402	6.325×10^{-30}	-36.500	-1.116	-3.936	2.263	8.16
4	-4005.25	3.478	425.340	19.526×10^{-30}	-32.833	-2.138	-4.337	4.767	8.55
5	-1852.39	3.462	366.862	16.246×10^{-30}	-58.847	-2.891	-4.003	10.685	8.22
6	-2481.78	2.729	446.348	23.032×10^{-30}	-91.860	-1.808	-4.672	3.665	9.09
7	-8367.42	3.204	473.327	15.085×10^{-30}	-23.212	-2.472	-3.504	8.651	8.74
8	-4060.55	3.099	440.354	16.370×10^{-30}	-38.255	-2.422	-3.519	8.054	8.30
9	-2140.13	2.672	453.983	9.848×10^{-30}	-95.873	-0.788	-4.019	1.789	8.39
10	-2616.61	4.813	520.103	10.095×10^{-30}	-47.936	-2.679	-3.547	11.164	9.09
11	-6633.65	3.891	519.250	19.913×10^{-30}	-30.105	-1.749	-4.555	3.541	9.00
12	-2138.94	2.494	451.967	14.598×10^{-30}	-93.214	-1.249	-3.910	2.501	8.88
13	-1471.55	0.129	349.422	18.401×10^{-30}	-35.902	-2.119	-4.184	4.809	8.05
14	-1737.89	3.096	336.836	17.341×10^{-30}	-5.662	-2.109	-4.765	4.448	7.49
15	-2329.00	2.922	410.317	9.714×10^{-30}	1.108	-1.534	-5.031	3.081	8.01
16	-1343.70	0.105	308.357	32.406×10^{-30}	-5.772	-1.466	-3.459	3.040	7.32

17	-8406.72	3.565	487.354	27.205×10^{-30}	-25.760	-1.780	-4.655	3.601	8.69
18	-1327.67	0.944	307.370	21.593×10^{-30}	-17.718	-1.549	-3.509	3.263	7.92
19	-1333.65	2.199	317.405	20.309×10^{-30}	-10.682	-2.210	-3.807	5.669	7.20
20	-1333.64	2.199	317.405	15.956×10^{-30}	-11.554	-2.135	-3.457	5.913	7.07
21	-1145.64	2.242	261.338	21.263×10^{-30}	-12.966	-2.170	-5.469	4.422	7.43
22	-1048.82	3.495	313.355	37.216×10^{-30}	-27.513	2.626	2.536	74.017	7.56
23	-1279.53	2.355	304.406	18.865×10^{-30}	-30.303	-2.343	-4.633	5.313	7.46
24	-1022.14	4.295	314.402	32.572×10^{-30}	-35.926	-1.066	-3.992	2.186	7.40
25	-1224.22	2.733	289.392	21.354×10^{-30}	-24.884	-2.267	-5.404	4.687	7.13
26	-1200.94	1.863	276.353	14.388×10^{-30}	-21.007	-2.225	-4.790	4.796	7.15
27	-1383.03	1.494	322.384	21.817×10^{-30}	-14.837	-1.492	-3.935	3.012	7.30
28	-1145.64	2.242	261.338	22.311×10^{-30}	-12.211	-2.306	-5.431	4.789	7.30
29	-1422.33	1.836	336.411	22.438×10^{-30}	-20.498	-1.488	-3.920	3.006	7.39
30	-1200.94	1.863	276.353	15.219×10^{-30}	-19.383	-2.320	-4.638	5.222	7.42
31	-3806.16	1.861	357.224	26.581×10^{-30}	-6.198	-1.743	-4.327	3.565	7.30
32	-3790.10	2.077	356.237	21.424×10^{-30}	-10.927	-1.655	-4.096	3.390	7.69

where, E_T = total energy in hartree, *MW* = molecular weight in g/mol, *D* = dipole moment in C·m, ΔH_f = heat of formation in kcal/mol, ε_{LUMO} = energy of LUMO in eV, ε_{HOMO} = energy of HOMO in eV, ω = electrophilicity index in eV, Obs. Act. in terms of pKi.

MONO-PARAMETRIC QSAR MODELS

From MLR analysis, a QSAR model with good predictive power was obtained by using only one descriptor. It means that the activity of 5-HT_6 serotonin ligand can be predicted by a mono-parametric regression equation using descriptor molecular weight. This QSAR model is given by the following regression equation:

$$^{MONO-}PA1 = 0.00795819 \times MW + 5.01956 \quad (7)$$

$r^2 = 0.811169$, $rCV^2 = 0.776267$, *Std. Error* = 0.0881, *SEE* = 0.3090, *N* = 32, *VC* = 1.

In the above regression equation, r^2 is the correlation coefficient, rCV^2 is the cross-validation coefficient, *Std. Error* is standard error, *SEE* is standard error of estimate, *N* is the number of compounds and *VC* is variable count. In the above regression equation, the value of r^2 is sufficiently higher than 0.5, which is the essential condition for the validity of a QSAR model. From the higher values of the correlation coefficient (r^2) and cross-validation coefficient (rCV^2) for the above QSAR model, it is clear that the model has high predictive power. Also, the low value of standard error and standard error of estimate for this regression supports the predictive capacity of this QSAR model. The predicted activities ($^{MONO-}$PA1)

obtained from above MLR equation are given in Table 3 also the trend of observed activity verses predicted activity ($^{MONO-}$PA1) is illustrated in Figure 1.

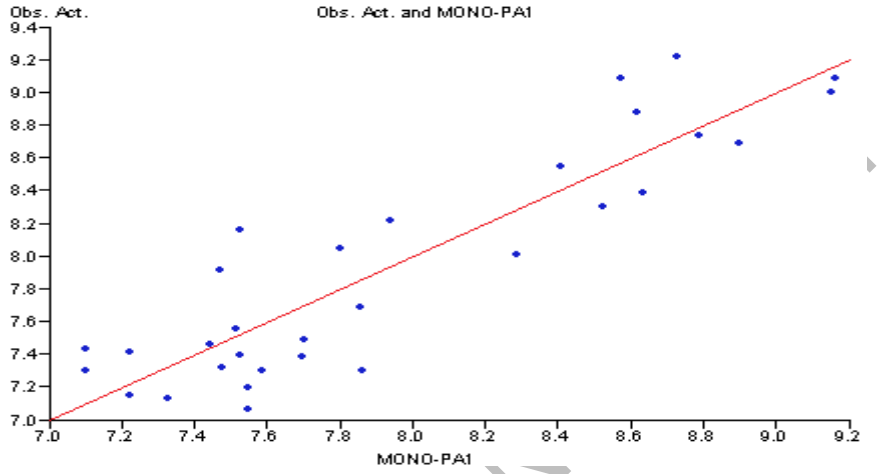


Fig. 1. Trend of observed activity and predicted activity $^{MONO-}$PA1 in terms of pKi.

BI-PARAMETRIC QSAR MODELS

By the combination of two descriptors, QSAR models with improved predictive power were obtained. These bi-parametric QSAR models are given by following regression equation.

$$^{BI-}PA1 = 0.00776983 \times MW - 0.0435301 \times D + 5.33046 \quad (8)$$

$r^2 = 0.826575$, $rCV^2 = 0.748439$, *Std. Error* = 0.0836, *SEE* = 0.2961, $N = 32$, $VC = 2$.

The above QSAR model is the best bi-parametric model which involves molecular weight as first descriptor and dipole moment as second descriptor.
Another bi-parametric model with improved predictive power is given by the following regression equation.

$$^{BI-}PA2 = 0.0504168 \times log\ P + 0.00758912 \times MW + 5.02185 \quad (9)$$

$r^2 = 0.815898$, $rCV^2 = 0.763495$, *Std. Error* = 0.0867, *SEE* = 0.3052, $N = 32$, $VC = 2$

The above QSAR model involves log *P* as first descriptor and molecular weight as second descriptor.

From the higher values of correlation coefficient (r^2) and cross-validation coefficient (rCV^2) and lower value of standard error and standard error of estimate for both the above QSAR models, it is clear that the model has higher predictive power. The predicted activities (^{BI}-PA1 and ^{BI}-PA2) obtained from above MLR equations are given in Table 3

TRI-PARAMETRIC QSAR MODELS

By the combination of three descriptors, QSAR models with much improved predictive power were obtained. The best tri-parametric QSAR model is given by following regression equation.

$$^{TRI}\text{-PA1} = 0.00700475\times MW - 0.0245181\times D - 0.00560176\times \Delta H_f + 5.33846 \quad (10)$$

$r^2 = 0.853198$, $rCV^2 = 0.752930$, *Std. Error* = 0.0757, *SEE* = 0.2725, $N = 32$, $VC = 3$.

The above QSAR model is obtained by using molecular weight as first descriptor, dipole moment as second descriptor and heat of formation as third descriptor. This QSAR model is the best among all the developed models and has the excellent predictive power as it has the highest value of correlation coefficient. Values of other statistical parameters also supports that this QSAR model is best in predictability. The predicted activities (^{TRI}-PA1) obtained from above MLR equation are given in Table 3 also the trend of observed activity verses predicted activity (^{TRI}-PA1) is illustrated in Figure 2.

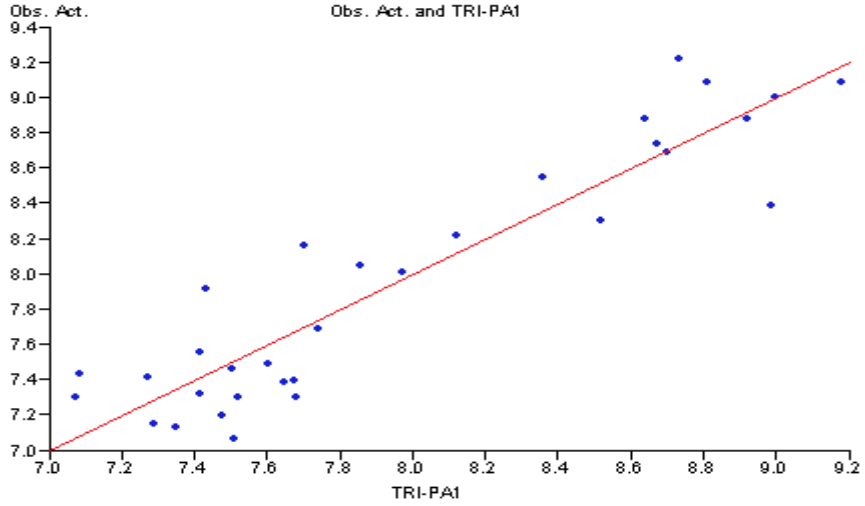


Fig. 2. Trend of observed activity and predicted activity ^{TRI}-PA1 in terms of pKi.

Other developed tri-parametric QSAR models with remarkably improved predictive power are given below,

^{TRI}PA2 = 0.0452347 × *log P* + 0.0066823 × *MW* - 0.0062458 × ΔH_f + 5.18194 (11)

r^2 = 0.852598, rCV^2 = 0.786307, *Std. Error* = 0.0759, *SEE* = 0.2731, *N* = 32, *VC* = 3.

The above QSAR model is obtained by using log *P* as first descriptor, molecular weight as second descriptor and heat of formation as third descriptor.

^{TRI}PA3 = 0.00687317 × *MW* - 0.00665369 × ΔH_f - 0.0442986 × ε_{LUMO} + 5.13913 (12)

r^2 = 0.852314, rCV^2 = 0.792921, *Std. Error* = 0.0760, *SEE* = 0.2733, *N* = 32, *VC* = 3.

The above QSAR model involves molecular weight as first descriptor, heat of formation as second descriptor and energy of LUMO as third descriptor. From the values of correlation coefficient (r^2) and other statistical parameters, for both the above QSAR models, it is clear that these models have excellent predictive power. The predicted activities (^{TRI}PA2 and ^{TRI}PA3) obtained from above MLR equations are given in Table 3. The correlation summary of developed QSAR models is given in Table 4.

Table 3

Experimental and predicted activities (pKi) of thirty-two aryl sulphonamides.

C. No.	Obs. Act.	^{MONO}PA1	^{BI}PA1	^{BI}PA2	^{TRI}PA1	^{TRI}PA2	^{TRI}PA3
1	9.22	8.728	8.804	8.757	8.734	8.713	8.715
2	8.88	8.617	8.748	8.633	8.637	8.571	8.583
3	8.16	7.522	7.691	7.624	7.699	7.705	7.592
4	8.55	8.404	8.380	8.425	8.358	8.387	8.376
5	8.22	7.939	7.969	7.981	8.118	8.158	8.180
6	9.09	8.572	8.498	8.547	8.810	8.862	8.898
7	8.74	8.786	8.811	8.776	8.673	8.635	8.656
8	8.30	8.524	8.538	8.520	8.517	8.504	8.528
9	8.39	8.632	8.729	8.602	8.983	8.935	8.932
10	9.09	9.159	9.240	9.212	9.176	9.175	9.152
11	9.00	9.152	9.105	9.159	8.998	9.016	8.986
12	8.88	8.616	8.652	8.578	8.919	8.897	8.921
13	8.05	7.800	7.805	7.680	7.852	7.747	7.874
14	7.49	7.700	7.721	7.734	7.602	7.608	7.585

15	8.01	8.285	8.096	8.283	7.968	8.049	8.020
16	7.32	7.474	7.515	7.367	7.412	7.283	7.362
17	8.69	8.898	8.762	8.900	8.697	8.761	8.739
18	7.92	7.466	7.437	7.402	7.432	7.389	7.438
19	7.20	7.546	7.532	7.542	7.472	7.469	7.490
20	7.07	7.546	7.588	7.542	7.509	7.475	7.492
21	7.43	7.099	7.084	7.118	7.085	7.111	7.118
22	7.56	7.513	7.280	7.576	7.414	7.606	7.360
23	7.46	7.442	7.449	7.451	7.502	7.512	7.537
24	7.40	7.522	7.646	7.624	7.670	7.702	7.586
25	7.13	7.323	7.300	7.356	7.348	7.395	7.394
26	7.15	7.219	7.290	7.213	7.286	7.244	7.277
27	7.30	7.585	7.551	7.544	7.519	7.496	7.520
28	7.30	7.099	7.070	7.118	7.073	7.106	7.119
29	7.39	7.697	7.652	7.667	7.645	7.641	7.654
30	7.42	7.219	7.279	7.213	7.271	7.234	7.270
31	7.30	7.862	7.759	7.827	7.680	7.692	7.713
32	7.69	7.855	7.819	7.830	7.738	7.725	7.734

Table 4

Correlation summery of QSAR models in decreasing order of predictive power

QSAR model	r^2	rCV^2	***Std. Error***	***SEE***	**Descriptor used**	***VC***
^{TRI}-PA1	0.853198	0.752930	0.0757	0.2725	Molecular weight, Dipole moment, Heat of formation	3
^{TRI}-PA2	0.852598	0.786307	0.0759	0.2731	log *P*, Molecular weight, Heat of formation	3
^{TRI}-PA3	0.852314	0.792921	0.0760	0.2733	Molecular weight, Heat of formation, LUMO energy	3
^{BI}-PA1	0.826575	0.748439	0.0836	0.2961	Molecular weight, Dipole moment	2
^{BI}-PA2	0.815898	0.763495	0.0867	0.3052	log *P*, Molecular weight	2
^{MONO}-PA1	0.811169	0.776267	0.0881	0.3090	Molecular weight	1

CONCLUSION

From Table 4, it is clear that molecular weight appears an important descriptor for the QSAR study of aryl sulphonamides. The descriptor molecular weight gives a mono-parametric QSAR model with remarkable predictive ability with positive contribution. It implies that an increase in the values of molecular weight increases the value of pKi. The descriptor molecular weight is present in all best bi-parametric and tri-parametric QSAR models. The best bi-parametric QSAR model (^{BI}-PA1) is obtained by combination of descriptors molecular weight and dipole moment with positive and negative contribution respectively. The best tri-parametric QSAR model (^{TRI}-PA1), which is the overall best model of our study, is obtained by combination of descriptors molecular weight, dipole moment and heat of formation. The best QSAR model obtained indicates the positive contribution of molecular weight whereas negative contribution of dipole moment and heat of formation. The QSAR models developed in our study have excellent predictive power and can be used to find the activity of any new derivative of aryl sulphonamides.

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