IN SILICO DRUG-RECEPTOR INTERACTION STUDY OF ARYL SULPHONAMIDE DERIVATIVES AS 5-HT$_6$ SEROTONIN LIGAND USING INTERACTION ENERGY PARAMETER

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Abstract. Aryl sulphonamide derivatives were reported to have better affinity towards 5-HT$_6$ receptor among the several classes of serotonin 5-HT$_6$ receptor ligands. In the present work, the interaction energy parameter has been used in the drug-receptor interaction study for a series of aryl sulphonamide and sulfone based derivatives acting as 5-HT$_6$ serotonin ligands. Serotonin ligand based drugs were found useful in the treatment of various mental disorders. Recent studies suggested that serotonin interacts with aspartic acid, tyrosine, phenylalanine, asparagine, arginine and proline residues of 5-HT$_6$ receptor. The interaction energy has been calculated between thirty two derivatives of aryl sulphonamide and these amino acid residues of 5-HT$_6$ receptor. The calculated values of interaction energy for different amino acids have been used as descriptors for the QSAR (quantitative structure activity relationship) study of this set of aryl sulphonamide compounds. The best QSAR model, for the set of compounds under study, has been obtained by interaction energy with Aspartic acid as first descriptor and interaction energy with proline as second descriptor. This QSAR model has high predictive power and can be used to find the activity of any new derivative of this class of serotonin ligands.

Key words: Drug-receptor interaction, aryl sulphonamide, 5-HT$_6$ receptor, interaction energy.

INTRODUCTION

The concept of interaction energy was successfully applied in drug-receptor interaction by Singh and Khan [17].

In this article, the interaction energy parameter has been used in the drug-receptor interaction study for a set of thirty-two compounds of aryl sulphonamide and sulfone-based derivatives acting as 5-HT$_6$ serotonin ligands. Aryl sulphonamide derivatives were reported to have better affinity towards 5-HT$_6$ receptor among the

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several classes of serotonin 5-HT_6 receptor ligands. [5]. In our previous work, topological and quantum mechanical parameters were successfully used for the same series of compounds [8, 9].

5-HT_6 serotonin receptor is present in different regions of the brain and very important biological target for controlling the central nervous system (CNS) mediated disorders [13]. The importance of serotonin 5-HT_6 receptor ligands are in various disorders which involve central nervous system dysfunctions such as anxiety, depression, bipolar disorder, mania, mood swing, cognitive dysfunction, schizophrenia, obsessive compulsive disorder, suicidal behavior, dementia, etc. [2, 6, 10, 11].

The structural basis of 5-HT_6 receptor activity is not very clear. However, in a recent study, Sheng Wang *et al*. [18] reported the structural features involved in the constitutive activity of 5-HT_6 serotonin receptor. Their study observed that serotonin forms a salt bridge with aspartic acid residue. In addition, the interaction with tyrosine, phenylalanine, asparagine, arginine and proline residues has been observed. In another recent study the interaction of aryl sulphonamides with aspartic acid and arginine residue of 5-HT_6 receptor has been established by Adam Bucki *et al*. [1].

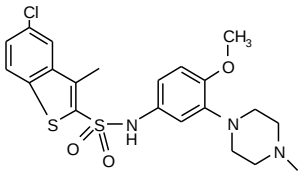
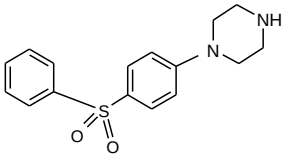
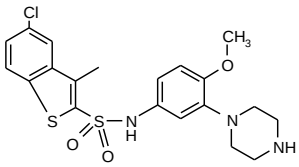
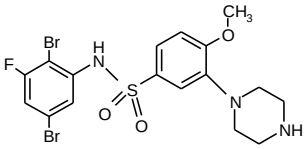
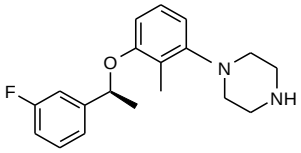
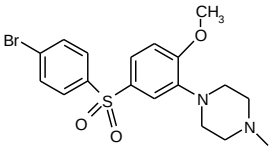
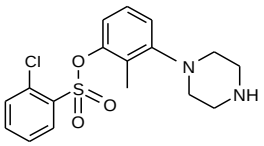
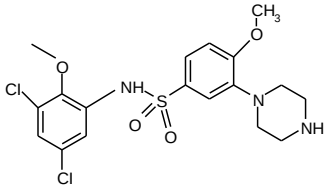
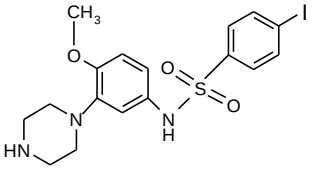
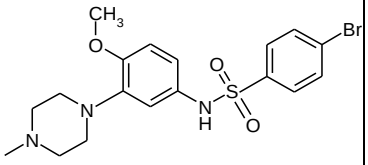
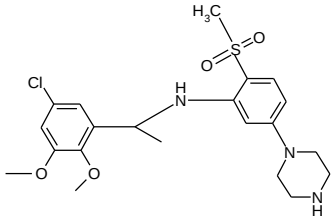
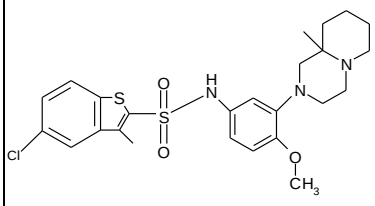
Our aim was to calculate the interaction energy between thirty-two derivatives of aryl sulphonamide and these amino acid residues of 5-HT_6 receptor. The calculated values of interaction energy for different amino acids have been used as descriptors for the QSAR (quantitative structure activity relationship) study of this set of compounds.

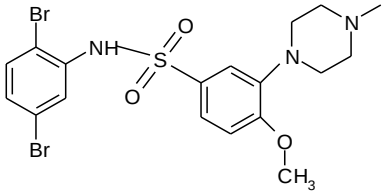
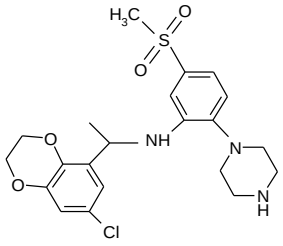
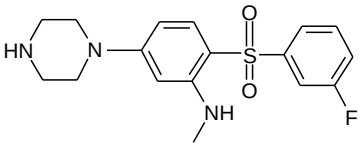
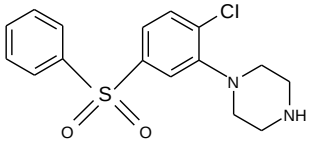
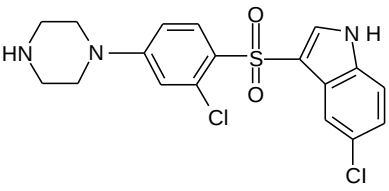
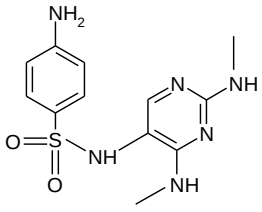
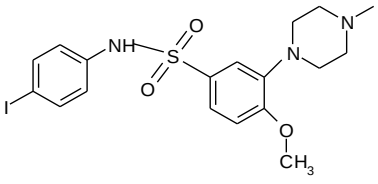
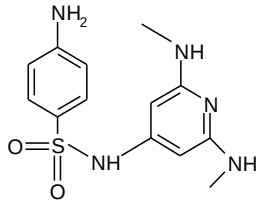
MATERIALS AND METHODS

Thirty-two compounds of aryl sulphonamide and sulfone derivatives as 5-HT_6 serotonin ligands were used as study material. The structure and observed biological activity of these compounds are given in Table 1. The structures of amino acids with which the interaction energy of these compounds were calculated are given in Table 2. CAChe Pro software developed by Fujitsu Corporation of Japan has been used for the geometry optimization process of all the compounds. The calculation of values of various descriptors has been done by the same software with the help of DFT-B88-LYP method having DZVP basis set [7, 14]. Multi linear regression (MLR) analysis method has been used for the development of QSAR models with the help of Project Leader program of CAChe Pro software. The parameters that have been calculated are discussed below.

Table 1

Structure of aryl sulphonamide derivatives with their experimental biological activity

S. No.	Structure	pKi	S. No.	Structure	pKi
1		9.22	**2**		8.16
3		8.88	**4**		8.58
5		8.16	**6**		8.55
7		8.22	**8**		9.09
9		8.74	**10**		8.30
11		8.39	**12**		9.09

13		9.00	**14**		8.88
15		8.05	**16**		7.49
17		8.01	**18**		7.32
19		8.69	**20**		7.92

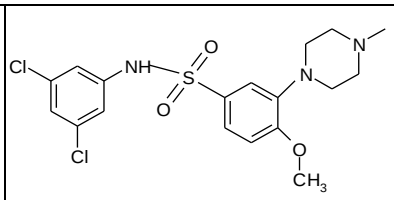
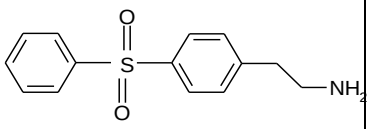
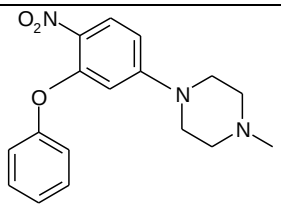
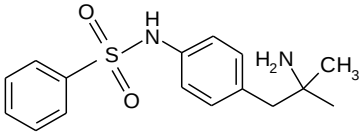
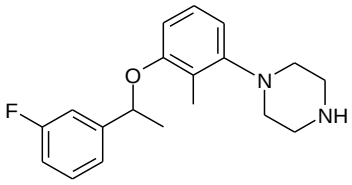
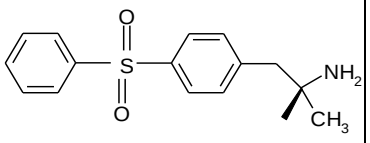
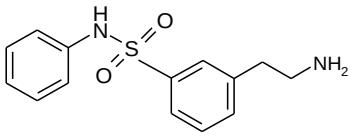
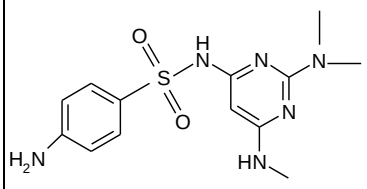
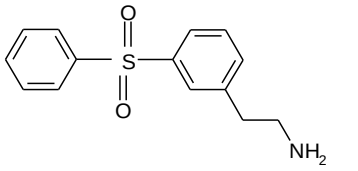
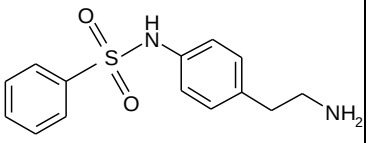
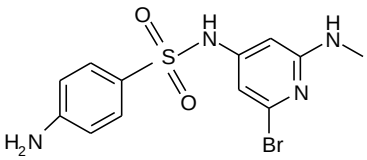
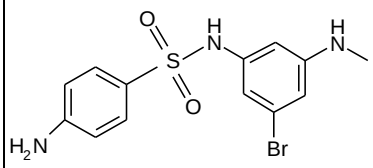
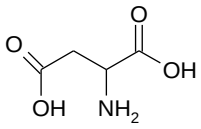
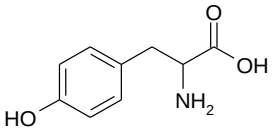
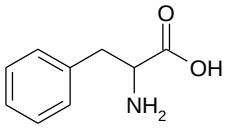
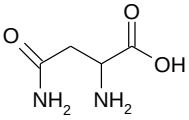
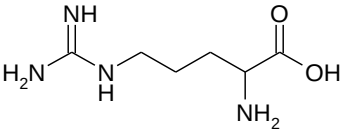
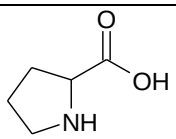
21		9.20	**22**		7.43
23		7.56	**24**		7.46
25		7.40	**26**		7.13
27		7.15	**28**		7.30
29		7.30	**30**		7.42
31		7.30	**32**		7.69

Table 2

The structures of amino acids with which the interaction energy of aryl sulphonamide derivatives were calculated

 ASPARTIC ACID	 TYROSINE	 PHENYLALANINE
 ASPARAGINE	 ARGININE	 PROLINE

The density functional theory (DFT) suggests the term interaction energy as:

$$\Delta E_{\text{int}} = E[\rho AB] - E[\rho A] - E[\rho B] \quad (1)$$

This gives the measure of interaction between a stable molecule A and a stable molecule B, having a total number of valence electrons N_A and N_B respectively [12]. In the above equation, $E[\rho]$ is the ground state energy in electronic density $\rho_{(r)}$ terms.

By applying the properties of hardness and softness functions the interaction energy can be divided into two steps and then above equation can be written as follows [3, 4]:

$$\Delta E_{\text{int}} = \Delta E_{\text{V}} + \Delta E_{\mu} \quad (2)$$

ΔE_V and ΔE_μ are defined as:

$$\Delta E_{\text{V}} \approx -\tfrac{1}{2} \times (\mu_{\text{A}} - \mu_{\text{B}})^2 \times S_{\text{A}} S_{\text{B}} / (S_{\text{A}} + S_{\text{B}}) \quad (3)$$

$$\Delta E_{\mu} \approx -\tfrac{1}{2} \times \lambda / (S_{\text{A}} + S_{\text{B}}) \quad (4)$$

where μ_A and μ_B are the chemical potential, and S_A and S_B are the global softness of molecule A and molecule B respectively. λ is a constant, which is equal to $(N_A + N_B)^2 / 2000$. The value of λ manifests the effective number of valence electrons involving in the interaction between molecule A and molecule B [15].

The first term, ΔE_V manifests the charge transfer process between molecule A and molecule B which comes from the chemical potential equalization principle at fixed external potential value. Whereas the term ΔE_μ manifests the reshuffling process of charge distribution.

In the above equations the global softness (*S*) and chemical potential (μ) are calculated using the following equations [16]:

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

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

where, ε_{HOMO} and ε_{LUMO} are the HOMO energy and the LUMO energy, respectively.

RESULTS AND DISCUSSION

Thirty-two compounds of aryl sulphonamide derivatives are given in Table 1, along with their pKi values. The structures of amino acids with which the interaction energy of these compounds was calculated are given in Table 2. The quantum mechanical parameters of aryl sulphonamide derivatives and that of amino acids used in calculation of interaction energy are given in Table 3 and Table 4 respectively. The value of interaction energies between aryl sulphonamide derivatives and amino acids are given in Table 5. QSAR models were developed to study the effect of interaction energy parameter on the 5-HT_6 antagonist activity of aryl sulphonamides. Different combinations of six descriptors were used to develop QSAR models with the help of MLR (multi linear regression) analysis. In the development of QSAR models the biological activities (pKi) were taken as the dependent variable whereas the six descriptors (interaction energy) were taken as independent variables. The reliability of QSAR models were judged by statistical parameters like correlation coefficient and cross validation coefficient. Combinations of maximum two descriptors were used in the development of MLR equations. In the QSAR analysis, many models with reliable predictive power were obtained. We present below our best four models, each with a correlation coefficient higher than 0.7.

Table 3

The quantum mechanical parameters of aryl sulphonamide derivatives used in calculation of interaction energy

C. No.	ε_{HOMO}	ε_{LUMO}	μ_A	S_A	N_A
1	–3.714	–2.680	3.197	1.934	160
2	–4.948	–1.705	3.327	0.617	110
3	–3.575	–2.642	3.109	2.144	154
4	–4.604	–1.924	3.264	0.746	146
5	–3.936	–1.116	2.526	0.709	122

6	–4.337	–2.138	3.238	0.910	134
7	–4.003	–2.891	3.447	1.799	128
8	–4.672	–1.808	3.240	0.698	152
9	–3.504	–2.472	2.988	1.938	134
10	–3.519	–2.422	2.971	1.823	140
11	–4.019	–0.788	2.404	0.619	164
12	–3.547	–2.679	3.113	2.304	182
13	–4.555	–1.749	3.152	0.713	146
14	–3.91	–1.249	2.580	0.752	162
15	–4.184	–2.119	3.152	0.969	128
16	–4.765	–2.109	3.437	0.753	116
17	–5.031	–1.534	3.283	0.572	136
18	–3.459	–1.466	2.463	1.004	112
19	–4.655	–1.78	3.218	0.696	140
20	–3.509	–1.549	2.529	1.020	112
21	–4.697	–1.843	3.270	0.701	146
22	–5.469	–2.17	3.820	0.606	94
23	2.536	2.626	–2.581	22.222	121
24	–4.633	–2.343	3.488	0.873	112
25	–3.992	–1.066	2.529	0.684	122
26	–5.404	–2.267	3.836	0.638	106
27	–4.79	–2.225	3.508	0.780	100
28	–3.935	–1.492	2.714	0.819	118
29	–5.431	–2.306	3.869	0.640	94
30	–4.638	–2.32	3.479	0.863	100
31	–4.327	–1.743	3.035	0.774	106
32	–4.096	–1.655	2.876	0.819	106

ε_{HOMO} = the HOMO energy (in eV), ε_{LUMO} = the LUMO energy (in eV), μ_A = the chemical potential of aryl sulphonamide derivatives, S_A = the global softness of aryl sulphonamide derivatives, N_A = the total number of valence electrons in the aryl sulphonamide molecule.

Table 4

The quantum mechanical parameters of amino acids used in calculation of interaction energy

Amino acid	ε_{HOMO}	ε_{LUMO}	μ_B	S_B	N_B
Aspartic acid (D)	–5.669	–1.308	3.489	0.459	52
Tyrosine (Y)	–5.236	–1.197	3.217	0.495	70
Phenylalanine (F)	–5.501	–1.142	3.322	0.459	64
Asparagine (N)	–5.477	–1.288	3.383	0.477	52
Arginine (R)	–5.235	–0.759	2.997	0.447	70
Proline (P)	–4.922	–0.800	2.861	0.485	46

ε_{HOMO} = HOMO energy (in eV), ε_{LUMO} = LUMO energy (in eV), μ_B = the chemical potential of the amino acid, S_B = the global softness of the amino acid, N_B = the total number of valence electrons in the amino acid molecule.

Table 5

Interaction energy between aryl sulphonamide derivatives and amino acids along with the observed biological activities (Obs. act.) as pKi values

C. No.	$^{D}E_{int}$	$^{Y}E_{int}$	$^{F}E_{int}$	$^{N}E_{int}$	$^{R}E_{int}$	$^{P}E_{int}$	Obs. act.
1	–93.929	–108.874	–104.839	–93.187	–111.092	–87.720	9.22
2	–122.032	–145.700	–140.749	–119.929	–152.335	–110.455	8.16
3	–81.565	–95.076	–91.315	–80.967	–96.850	–76.092	8.88
4	–162.696	–187.911	–182.974	–160.187	–195.535	–149.699	8.58
5	–129.754	–153.109	–148.182	–127.673	–159.470	–118.165	8.16
6	–126.446	–148.134	–143.257	–124.723	–153.422	–116.176	8.55
7	–71.772	–85.469	–81.655	–71.178	–87.335	–66.351	8.22
8	–179.863	–206.469	–201.601	–176.977	–215.194	–165.644	9.09
9	–72.224	–85.529	–81.804	–71.645	–87.252	–66.857	8.74
10	–80.829	–95.124	–91.207	–80.151	–97.137	–74.939	8.30
11	–216.633	–245.815	–241.264	–212.890	–256.916	–199.720	8.39
12	–99.124	–113.430	–109.521	–98.440	–115.423	–93.196	9.09
13	–167.358	–193.124	–188.212	–164.703	–201.179	–153.874	9.00
14	–189.325	–215.914	–211.063	–186.402	–224.586	–174.915	8.88

15	–113.532	–133.922	–129.139	–112.045	–138.499	–104.146	8.05
16	–116.472	–138.593	–133.684	–114.690	–144.196	–106.024	7.49
17	–171.490	–198.840	–194.036	–168.409	–208.286	–156.694	8.01
18	–92.142	–110.605	–106.029	–90.943	–114.238	–83.870	7.32
19	–159.697	–185.166	–180.240	–157.127	–193.008	–146.505	8.69
20	–91.071	–109.357	–104.803	–89.901	–112.913	–82.921	7.92
21	–169.080	–195.060	–190.154	–166.373	–203.287	–155.441	9.20
22	–100.103	–122.147	–117.227	–98.375	–127.790	–89.913	7.43
23	–14.874	–16.170	–15.376	–14.904	–14.861	–13.172	7.56
24	–100.963	–121.032	–116.264	–99.557	–125.487	–91.938	7.46
25	–132.667	–156.444	–151.511	–130.494	–163.093	–120.762	7.40
26	–113.886	–136.786	–131.834	–111.975	–142.921	–103.021	7.13
27	–93.286	–113.355	–108.584	–91.891	–117.847	–84.320	7.15
28	–113.220	–134.546	–129.700	–111.555	–139.657	–103.143	7.30
29	–97.033	–118.526	–113.634	–95.411	–123.836	–87.236	7.30
30	–87.421	–106.419	–101.757	–86.194	–110.370	–79.124	7.42
31	–101.295	–122.038	–117.223	–99.759	–126.866	–91.746	7.30
32	–97.728	–117.841	–113.083	–96.293	–122.324	–88.552	7.69

$^{D}E_{int}$ = Interaction energy between aspartic acid and aryl sulphonamide derivatives, $^{Y}E_{int}$ = interaction energy between tyrosine and aryl sulphonamide derivatives, $^{F}E_{int}$ = interaction energy between phenylalanine and aryl sulphonamide derivatives, $^{N}E_{int}$ = interaction energy between asparagine and aryl sulphonamide derivatives, $^{R}E_{int}$ = interaction energy between arginine and aryl sulphonamide derivatives, $^{P}E_{int}$ = interaction energy between proline and aryl sulphonamide derivatives. All the energies are in eV.

FIRST BEST QSAR MODEL

The best QSAR model is given by MLR equation using interaction energy with aspartic acid as first descriptor and interaction energy with proline as second descriptor. The regression equation for this QSAR model is given below:

$$PA1 = 0.478003 \times {}^{D}E_{int} - 0.525268 \times {}^{P}E_{int} + 7.74966$$

$$r^2 = 0.759614,\ r^2_{CV} = 0.63260,\ N = 32,\ VC = 2 \quad (7)$$

In the above regression equations, r^2 represents the correlation coefficient, r^2_{CV} represents the cross-validation coefficient, N is the total number of compounds under

study and *VC* is the number of descriptors used in MLR analysis (variable count). The essential condition for the validity of a QSAR model is that the value of r^2 should be higher than 0.5. The higher values of correlation coefficient (r^2) and cross-validation coefficient (r^2_{CV}), for the above QSAR model, exhibit that the model has high predictive power. The predicted activities presented as pKi values (*PA*1–*PA*4) obtained from the MLR equations (7)–(10) are given in Table 6.

SECOND BEST QSAR MODEL

The second best QSAR model is given by following regression equation:

$$PA2 = 0.60945 \times {}^{N}E_{int} - 0.654447 \times {}^{P}E_{int} + 8.25746$$

$$r^2 = 0.751993,\ r^2_{CV} = 0.615342,\ N = 32,\ VC = 2 \quad (8)$$

The above MLR equation is obtained by using interaction energy with asparagine as first descriptor and interaction energy with proline as second descriptor. Values of r^2 and r^2_{CV} for this QSAR model are high which exhibit that this QSAR model has good predictive power. The values of predicted activities (*PA*2) obtained from above MLR equation are given in Table 6.

THIRD BEST QSAR MODEL

The third best QSAR model is given by following regression equation,

$$PA3 = 0.167354 \times {}^{F}E_{int} - 0.208597 \times {}^{P}E_{int} + 7.99813$$

$$r^2 = 0.711151,\ r^2_{CV} = 0.540321,\ N = 32,\ VC = 2 \quad (9)$$

The above MLR equation is obtained by using interaction energy with phenylalanine as first descriptor and interaction energy with proline as second descriptor. Values of r^2 and r^2_{CV} for this QSAR model are high which exhibit that this regression model has good predictive power. The values of predicted activities (*PA*3) obtained from above MLR equation are given in Table 6.

FOURTH BEST QSAR MODEL

The fourth best QSAR model is given by using interaction energy with arginine as first descriptor and interaction energy with tyrosine as second descriptor. This QSAR model is obtained by following regression equation,

$$PA4 = 0.713158 \times {}^{R}E_{int} - 0.758527 \times {}^{Y}E_{int} + 5.54929$$

$$r^2 = 0.700379,\ r^2_{CV} = 0.591797,\ N = 32,\ VC = 2 \quad (10)$$

Values of correlation coefficient and cross validation coefficient exhibit that this model has good predictive power. The predicted activities (*PA*4) obtained from above MLR equation are given in Table 6.

Table 6

Observed (Obs. act.) and predicted activities of compounds under study

C. No.	Obs. act.	Predicted activity							
		***PA*1**	**Residual**	***PA*2**	**Residual**	***PA*3**	**Residual**	***PA*4**	**Residual**
1	9.22	8.928	0.292	8.873	0.347	8.751	0.469	8.907	0.313
2	8.16	7.437	0.723	7.454	0.706	7.484	0.676	7.428	0.732
3	8.88	8.730	0.150	8.710	0.170	8.589	0.291	8.598	0.282
4	8.58	8.613	0.033	8.601	0.021	8.604	0.024	8.637	0.057
5	8.16	7.795	0.365	7.780	0.380	7.848	0.312	7.959	0.201
6	8.55	8.332	0.218	8.276	0.274	8.258	0.292	8.499	0.051
7	8.22	8.295	0.075	8.301	0.081	8.174	0.046	8.096	0.124
8	9.09	8.782	0.308	8.804	0.286	8.812	0.278	8.694	0.396
9	8.74	8.344	0.396	8.348	0.392	8.254	0.486	8.201	0.539
10	8.30	8.476	0.176	8.453	0.153	8.366	0.066	8.429	0.129
11	8.39	9.105	0.715	9.218	0.828	9.283	0.893	8.785	0.395
12	9.09	9.321	0.231	9.255	0.165	9.110	0.020	9.274	0.184
13	9.00	8.577	0.423	8.582	0.418	8.598	0.402	8.567	0.433
14	8.88	9.129	0.249	9.127	0.247	9.163	0.283	9.161	0.281
15	8.05	8.186	0.136	8.130	0.080	8.111	0.061	8.361	0.311
16	7.49	7.767	0.277	7.747	0.257	7.742	0.252	7.841	0.351
17	8.01	8.083	0.073	8.168	0.158	8.211	0.201	7.834	0.176
18	7.32	7.760	0.440	7.721	0.401	7.749	0.429	7.976	0.656
19	8.69	8.368	0.322	8.376	0.314	8.395	0.295	8.357	0.333

20	7.92	7.773	0.147	7.735	0.185	7.756	0.164	7.975	0.055
21	9.20	8.577	0.623	8.589	0.611	8.600	0.600	8.532	0.668
22	7.43	7.129	0.301	7.146	0.284	7.135	0.295	7.067	0.363
23	7.56	7.559	0.001	7.795	0.235	8.173	0.613	7.216	0.344
24	7.46	7.781	0.321	7.751	0.291	7.719	0.259	7.863	0.403
25	7.40	7.767	0.367	7.760	0.360	7.833	0.433	7.905	0.505
26	7.13	7.425	0.295	7.436	0.306	7.425	0.295	7.380	0.250
27	7.15	7.449	0.299	7.437	0.287	7.415	0.265	7.489	0.339
28	7.30	7.808	0.508	7.772	0.472	7.808	0.508	8.009	0.709
29	7.30	7.190	0.110	7.201	0.099	7.178	0.122	7.140	0.160
30	7.42	7.524	0.104	7.509	0.089	7.474	0.054	7.560	0.140
31	7.30	7.522	0.222	7.502	0.202	7.518	0.218	7.643	0.343
32	7.69	7.549	0.141	7.524	0.166	7.545	0.145	7.698	0.008

CONCLUSION

From the above study, it is clear that the best combination of descriptors is interaction energy with aspartic acid as first descriptor and interaction energy with proline as second descriptor for the QSAR study of aryl sulphonamide derivatives as 5-HT_6 serotonin ligands. This model has a high predictive power and can be used to accurately predict the activity of any new derivative of this class of compounds. Also, in all of the top three QSAR models, the descriptor interaction energy with proline is present with a negative contribution, which implies that an increase in the value of the descriptor decreases the value of biological activity.

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