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Topological Modeling of Benzodiazepine Receptor Binding

Abhilash Thakur,[a] Mamta Thakur[b] and Padmakar Khadikar[c,*]

[a]*Department of Chemistry, Bhopal institute of Technology & Science, Bhopal, India*
[b]*School of Chemical Sciences, D.A.V.V Indore 452009, India*
[c]*Research Division, Laxmi Fumigation & Pest Control, Pvt. Ltd., 3 Khatipura, Indore 452007, India*

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Abstract—The present study reports the QSAR modeling of benzodiazepine receptor binding affinity (pIC_{50}) for a large set of 70 benzodiazepine receptor ligands. The step-wise regression analysis indicated that out of the large pool of molecular descriptors used only hydration energy (He), hydrophobic parameter ($\pi^{3,5}$), steric parameter ($E_s^{2,6}$) are useful for giving statistically significant models. The results are discussed critically using multivariate regression analysis and cross-validation method.

Introduction

Benzodiazepine-receptor (BZR) ligands have attracted medicinal chemists and pharmacists in developing quantitative structure–activity relationship (QSAR). This is obvious because QSAR is one of the most important tools in drug designing in that potential pharmacological activity of novel chemical entities are modeled by the ligand binding assays.[1] By using this tool (QSAR) quite interesting results emerge out relating to the structural requirement of recognition site of receptor. In this regard, BZR is uniquely complex receptor which is associated with a diverse biological activity profile: anxiolytic, hypnotic, sedative, anticonvulsant, muscles relaxing and so on (Fig. 1).[2]

Consequent to above, many attempts were made in developing QSAR models for BZR ligands using various types of different molecular descriptors. In one such attempt we have used negentropy (N) and first-order valance connectivity index (χ^1).[3] The model gave $Se = 0.1873$ and $R = 0.945$.

In another approach, Singh[4] and coworkers using the Wilson approach[5] and Hansch analysis,[6] concluded that hydrophobic and steric parameters of BZR ligands play dominating role in developing QSAR model. Using step-wise regression analysis they attempted regression with 70 and 69 compounds and finally obtained an excellent QSAR model in that 10 compounds were deleted from regression procedure.

None of the two attempts given above gave predictive power of their proposed models. Also, different results were obtained depending and discussed upon the molecular descriptors used. However, the latter model gave better results.

It should be mentioned that if two different methodologies yield similar answer then they provide further confidence that the QSAR are not artifactual as well as deconstructing the use of the most significant value of molecular descriptors.

In view of the above, in the present communication we have used another large set of molecular descriptors for modeling BZR receptor binding. The molecular descriptors used are:[7,8] Molar Refraction (MR), Molar Volume (MV), Parachor (Pc), Index of refraction (IR), Surface tension (ST), Hydration energy (He), Approximate surface area (ASA), Surface area Grid (SAG), in addition to hydrophobic ($\pi^{3,5}$) and steric ($E_s^{2,6}$) parameters used by Singh and coworkers.[4]

We have followed the Singhs methodology[4] in that we started initially with the entire set of 70 compounds, then deleting one compound (i.e., using 69 compounds) and finally arrived at an excellent model using 60 compounds. However, ten compounds deleted in our case were different than those deleted by Singh.[4] Also, the independent variables involved were also quite different. The results, as discussed below, show that in each case our results are better than those obtained by Singh.[4]

*Corresponding author. Tel.: +91-731-253-1906; e-mail: pvhadikar@rediffmail.com

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Table 1. Structural details of benzodiazepine receptor ligands and their biological activity (pIC_{50})

Compd	X	Y	R	R_1	R_2	I_X	I_Y	I_3	pIC_{50}
1	NH	N	Me	H	3-Me	1	1	1	5.05
2	NH	N	Me	H	3-Cl	1	1	1	5.36
3	NH	N	Me	H	4-Cl	1	1	0	4.66
4	NMe	N	Me	H	H	0	1	0	5.47
5	NMe	N	Me	H	3-Me	0	1	1	6.59
6	NMe	N	Me	H	3-Cl	0	1	1	6.00
7	NMe	N	Me	H	4-Cl	0	1	0	5.57
8	NH	N	Me	H	H	1	1	0	4.64
9	NH	N	Me	H	2-Cl	1	1	0	4.40
10	NH	N	Me	H	2-Me	1	1	0	4.44
11	NH	N	Me	H	4-Me	1	1	0	4.68
12	NH	N	Me	H	2-OMe	1	1	0	4.25
13	NH	N	Me	H	3-OMe	1	1	1	5.12
14	NH	N	Me	H	4-OMe	1	1	0	4.40
15	NH	N	Me	H	2-Br	1	1	0	4.70
16	NH	N	Me	H	3-Br	1	1	1	5.60
17	NH	N	Me	H	3-F	1	1	1	4.85
18	NH	N	Me	H	4-F	1	1	0	5.00
19	NH	N	Me	H	$3,5\text{-Me}_2$	1	1	1	5.52
20	NH	N	Me	H	$2,4\text{-Me}_2$	1	1	0	4.35
21	NH	N	Me	H	$2,3\text{-Me}_2$	1	1	1	4.03
22	NH	N	Me	H	$3,4\text{-Me}_2$	1	1	1	5.43
23	NH	N	Me	H	$2,6\text{-Me}_2$	1	1	0	3.66
24	NH	N	Me	H	$2,5\text{-Me}_2$	1	1	0	4.33
25	NH	N	Ph	H	H	1	1	0	4.68
26	NH	N	Ph	H	3-Cl	1	1	1	5.52
27	NH	N	Ph	H	3-Br	1	1	1	5.82
28	NH	N	Ph	H	3-Me	1	1	1	5.52
29	NH	N	Ph	H	4-Cl	1	1	0	4.52
30	NH	N	Ph	H	4-Me	1	1	0	4.41
31	NMe	N	Ph	H	H	0	1	0	5.51
32	NMe	N	Ph	H	3-Cl	0	1	1	7.16
33	NMe	N	Ph	H	3-Br	0	1	1	7.00
34	NMe	N	Ph	H	3-Me	0	1	1	7.05
35	NMe	N	Ph	H	4-Cl	0	1	0	5.94
36	NMe	N	Ph	H	4-Me	0	1	0	5.96
37	O	N	Me	H	H	0	1	0	6.52
38	O	N	Me	H	4-Me	0	1	0	5.70
39	O	N	Me	H	3-Me	0	1	1	6.55
40	O	N	Me	H	2-Me	0	1	0	4.52
41	O	N	Me	H	4-Cl	0	1	0	6.12
42	O	N	Me	H	3-Cl	0	1	1	7.05
43	O	N	Me	H	2-Cl	0	1	0	4.80
44	O	N	Me	H	3-Br	0	1	1	7.00
45	O	N	Me	H	4-NO_2	0	1	0	6.00
46	O	N	Me	H	3-NO_2	0	1	1	6.49
47	O	N	Me	H	2-NO_2	0	1	0	4.37
48	O	N	Me	H	4-OMe	0	1	0	6.15
49	O	N	Me	H	3-OMe	0	1	1	6.12
50	O	N	Me	H	2-OMe	0	1	0	5.10
51	O	N	Me	H	$3,5\text{-Me}_2$	0	1	1	7.19
52	O	N	Me	H	4-NH_2	0	1	0	5.89
53	O	N	Me	H	3-NH_2	0	1	1	5.74
54	O	N	Me	H	2-NH_2	0	1	0	6.20
55	O	N	Me	Br	H	0	1	0	4.96
56	O	N	Me	Br	3-Br	0	1	1	7.19
57	O	N	Me	Br	3-Me	0	1	1	6.85
58	O	N	Me	Br	$3,5\text{-Me}_2$	0	1	1	7.89
59	O	N	Me	NO_2	H	0	1	0	5.74
60	O	N	Me	NO_2	3-Br	0	1	1	6.80
61	O	N	Me	NO_2	3-Me	0	1	1	6.72
62	O	N	Me	NO_2	$3,5\text{-Me}_2$	0	1	1	7.92
63	O	CH	Ph	H	H	0	0	0	7.19
64	O	CH	Ph	H	3-Me	0	0	1	7.60
65	O	CH	Ph	H	4-Me	0	0	0	6.76
66	O	CH	Ph	H	$3,5\text{-Me}_2$	0	0	1	8.07
67	O	CH	Ph	H	3-Cl	0	0	1	8.00
68	O	CH	Ph	H	4-Cl	0	0	0	7.40
69	O	CH	Ph	H	3-OMe	0	0	1	7.32
70	O	CH	Ph	H	4-OMe	0	0	0	7.21

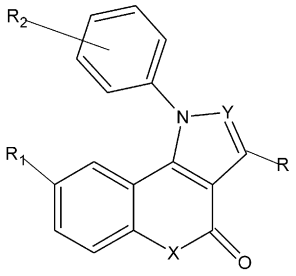

Figure 1. Parent structure of BZR ligands used in present study.

Results and Discussion

The structural details of 70 BZR ligands are given in Table 1. The binding affinity of BZR ligands, as reported by Singh and coworkers[4] is converted into pIC_{50} and used in the present study. Table 1 also records the three indicator parameters used, the two indicator parameters (I_X, I_Y) as used by Singh and coworkers[4] and the third (I_3) introduced by us. Use of these indicator parameters resulted in the improved statistics. These three indicator parameters were chosen for the subscripted position for accounting the presence (indicator parameter = 1) or absence (indicator parameter = 0) of these structural features. Thus, if –NH– is present at X, then $I_X = 1$, otherwise $I_X = 0$. Similarly, I_Y and $I_3 = 1$ when –N– at Y and substituents at the third position are present, respectively.

The initial regression analysis[9] has indicated that out of the large pool of molecular descriptors used, only $d\pi^{3,5}$, $E_s^{2,6}$, ST, Pc and He are useful. In addition, our preliminary regression analysis initiated that the three indicator parameters are needed for obtaining statistically significant models. The use of $\pi^{3,5}$ and $E_s^{2,6}$ in the present case also supports that the hydrophobic and steric factors play dominant roles in the inhibition of receptor binding affinity used in the present study.

It is worth mentioning again that out of the five molecular descriptors mentioned above, only two, namely $\pi^{3,5}$ and $E_s^{2,6}$ were used by Singh and coworkers.[4] The remaining three parameters were introduced by us.

To start with, we first give a comparative chart where our results are compared with those of Singh.[4]

Comparative chart

Comp.	Model					
	R		Se		Q	
	Our	Singh	Our	Singh	Our	Singh
1. (70)	0.954	0.943	0.354	0.395	2.695	2.387
2. (69)	0.959	0.951	0.337	0.366	2.846	2.598
3. (62)	0.976	(NA)	0.250	(NA)	3.904	(NA)
4. (60)	0.980	0.970	0.229	0.348	4.280	2.787

NA, not attempted.

We now discuss the results in detail.
In the present case, none of the lower order regressions gave statistically significant models. However, the following hexaparameteric model was found statistically significant for modeling benzodiazepines receptor binding affinity 'pIC_{50}'.

$$\begin{aligned} pIC_{50} = & -0.0454(\pm 0.0222)He - 1.2406 \\ & \times (\pm 0.0933)I_X - 1.1016(\pm 0.1401)I_Y \\ & + 0.3717(\pm 0.1190)I_3 + 0.8389 \\ & \times (\pm 0.1410)\pi^{3,5} + 0.5629(\pm 0.0851)E_s^{2,6} \\ & + 6.7381 \end{aligned} \quad (1)$$

$n = 70$, Se $= 0.354$, $R = 0.954$, $F = 107.180$, $Q = 2.695$

Here, and there after n is the number of data points, Se, is standard error of estimation, R is correlation coefficient, F is F-statistics and Q is the quality factor.[10]

The aforementioned model indicates that hydration a energy (He) and indicator parameters I_X and I_Y play a negative role in the exhibition of the receptor binding affinity (pIC_{50}). That is, hydration energy and structural arrangement such as –NH– and –N– have retarding effect in the exhibition of pIC_{50}. On the other hand the regression parameters I_3, $d^{3,5}$ and $E_s^{2,6}$ play positive role in the exhibition of pIC_{50}. This means that substitution at the third position, the sum of hydrophobic contribution of the meta substituents of the aryl moiety and steric effect due to substitution at the 2,6-positions are favorable for the exhibition of pIC_{50}. Furthermore, the coefficient of $\pi^{3,5}$ indicates its most dominating effect in the exhibition of pIC_{50}.

The comparison of eq 1 containing 70 compounds with that of Singh[4] (see Comparative chart) indicates that our model has slightly better statistics. The comparison can be made more precise by using the quality factor Q. In the present case, our Q value (2.695) is far better than that of Singh (2.387). Note that both these models used six correlating parameters (though the parameters used are different). Thus, our model containing 70 compounds is not only of better quality but has much improved predictive potential.

We now discuss the models containing 69 compounds in that, from the initial set of 70 compounds, compound **55** is deleted. Our results gave the following model:

$$\begin{aligned} pIC_{50} = & -0.0443\ (\pm 0.0211)\ He \\ & - 1.2656\ (\pm 0.0892)\ I_X \\ & - 1.0735\ (\pm 0.1337)\ I_Y \\ & + 0.3395\ (\pm 0.1138)\ I_3 \\ & + 0.8369\ (\pm 0.1341)\ p^{3,5} \\ & + 0.5792\ (\pm 0.0811)\ E_s^{2,6} + 6.7613 \end{aligned} \quad (2)$$

$n = 69$, Se $= 0.337$, $R = 0.959$, $F = 118.569$, $Q = 2.846$

Now again from the comparative chart given above, we observed that our model based on R, Se, Q values is better than the Singh[4] model.

Unlike Singh[4], our methodology recommended deletion of eight compounds, *6*, *15*, *21*, *37*, *40*, *55*, *58* and *62*, to obtain a model of better statistics than the model discussed above. This resulted in the following model:

$$\begin{aligned} pIC_{50} = & -0.0220(\pm 0.0166)He - 1.2479 \\ & \times (\pm 0.0699)I_X - 1.1289(\pm 0.1009)I_Y \\ & + 0.4683(\pm 0.0879)I_3 + 0.6662 \\ & \times (\pm 0.1055)\pi^{3,5} + 0.4955(\pm 0.0663)E_s^{2,6} \\ & + 6.8806 \end{aligned} \quad (3)$$

$n = 62$, Se $= 0.250$, $R = 0.976$, $F = 183.545$, $Q = 3.904$

The comparative chart shows that our model using 62 compounds is far better even than the Singh's model using 60 compounds. A model containing 62 compounds was not considered by Singh.[4]

Our model containing 62 compounds has two outliers (**38** and **45**). The deletion of these two compounds as outliers resulted into a model containing 60 compounds with excellent statistics:

$$\begin{aligned} pIC_{50} = & -0.0155\ (\pm 0.0153)\ He \\ & - 1.2991\ (\pm 0.0656)\ I_X \\ & - 1.0978\ (\pm 0.0928)\ I_Y \\ & + 0.4492\ (\pm 0.0807)\ I_3 \\ & + 0.6504\ (\pm 0.0967)\ \pi^{3,5} \\ & + 0.451\ (\pm 0.0621)\ E_s^{2,6} + 6.9339 \end{aligned} \quad (4)$$

$n = 60$, Se $= 0.229$, $R = 0.980$, $F = 215.719$, $Q = 4.280$.

Table 2. Cross-validation parameters

Eq	Compds used	Parameters used	PRESS	SSY	PRESS/SSY	r^2_{cv}	SPRESS	PSE
1	70	6	8.1325	80.4392	0.1011	0.8989	0.3593	0.34092
2	69	6	7.0383	80.7602	0.0872	0.9129	0.3369	0.31940
3	62	6	3.4469	69.0173	0.0499	0.9500	0.2481	0.23580
4	60	6	2.7851	68.0154	0.0409	0.9591	0.2271	0.2155

PRESS, predictive residual sum of square; SSY, sum of the squares of response values, r^2_{cv}, cross-validated predictive correlation coefficient; SPRESS, uncertainty of prediction; PSE, prediction square error.

Table 3. Physicochemical descriptors of benzodiazepines receptor ligand used in present study

Compd	$Pi^{3,5}$	$E_s^{2,6}$	He	Pc	ST	logP
1	0.56	0.00	−4.39	594.4	49.5	4.77
2	0.71	0.00	−5.06	592.1	54.3	5.00
3	0.00	0.00	−5.07	592.1	54.3	2.13
4	0.00	0.00	−2.65	608.7	48.9	4.01
5	0.56	0.00	−1.45	639.8	46.2	4.43
6	0.71	0.00	−2.30	637.6	50.2	4.66
7	0.00	0.00	−2.34	637.6	50.2	4.66
8	0.00	0.00	−5.38	563.3	52.9	4.35
9	0.00	−0.97	−4.70	592.1	54.3	5.41
10	0.00	−1.24	−4.08	594.4	49.5	4.77
11	0.00	0.00	−4.22	594.4	49.5	4.77
12	0.00	−0.55	−5.11	613.5	50.1	4.12
13	−0.02	0.00	−6.98	613.5	50.1	4.16
14	0.00	0.00	−7.08	613.5	50.1	4.16
15	0.00	−1.16	−4.64	606.8	56.4	5.65
16	0.86	0.00	−5.01	606.8	56.4	5.26
17	0.14	0.00	−5.08	563.5	50.1	4.60
18	0.00	0.00	−5.11	563.5	50.1	4.60
19	1.12	0.00	−3.27	625.5	46.7	5.19
20	0.00	−1.24	−3.00	625.5	46.7	5.19
21	0.56	−1.24	−3.11	625.5	46.7	5.19
22	0.56	0.00	−3.24	625.5	46.7	5.19
23	0.00	−2.48	−12.98	625.5	46.7	5.19
24	0.56	−1.24	−3.15	625.5	46.7	5.19
25	0.00	0.00	−6.65	709.1	54.0	3.60
26	0.71	0.00	−6.31	737.9	55.1	4.25
27	0.86	0.00	−6.30	752.6	56.8	4.51
28	0.56	0.00	−5.47	740.2	51.1	4.02
29	0.00	0.00	−6.33	737.9	55.1	4.25
30	0.00	0.00	−5.49	740.2	51.1	4.02
31	0.00	0.00	−4.00	754.5	50.6	3.25
32	0.71	0.00	−3.66	783.4	51.7	3.90
33	0.86	0.00	−3.65	798.1	53.3	4.16
34	0.56	0.00	−2.82	785.6	48.2	3.67
35	0.00	0.00	−3.69	783.4	51.7	3.90
36	0.00	0.00	−2.84	785.6	48.2	3.67
37	0.00	0.00	−5.39	562.7	50.9	5.08
38	0.00	0.00	−4.24	593.8	47.8	5.50
39	0.56	0.00	−4.19	593.8	47.8	5.50
40	0.00	−1.24	−4.10	593.8	47.8	5.50
41	0.00	0.00	−5.08	591.5	52.3	5.73
42	0.71	0.00	−5.04	591.5	52.3	5.73
43	0.00	−0.97	−4.72	591.5	52.3	6.14
44	0.86	0.00	−5.03	606.2	54.4	5.99
45	0.00	0.00	−10.37	608.1	62.9	4.81
46	−0.28	0.00	−10.94	608.1	62.9	4.81
47	0.00	−2.57	−7.30	608.1	62.9	5.62
48	0.00	0.00	−7.10	612.9	48.4	4.89
49	−0.02	0.00	−6.98	612.9	48.4	4.89
50	0.00	−0.55	−4.94	612.9	48.4	4.89
51	1.12	0.00	−3.29	624.9	45.1	5.92
52	0.00	0.00	−9.08	569.9	57.0	3.79
53	−1.23	0.00	−8.92	569.9	57.0	3.79
54	0.00	0.00	−6.93	569.9	57.0	4.19
55	0.00	0.00	−5.08	606.2	54.4	5.99
56	0.86	0.00	−4.72	649.8	57.7	6.90
57	0.56	0.00	−3.89	637.3	51.1	6.41
58	1.12	0.00	−3.10	668.4	48.2	6.83
59	0.00	0.00	−8.84	608.1	62.9	4.81
60	0.86	0.00	−8.49	651.7	66.1	5.72
61	0.56	0.00	−7.66	639.2	58.5	5.23
62	1.12	0.00	−5.88	670.3	54.8	5.65
63	0.00	0.00	−6.15	727.3	49.1	5.50
64	0.56	0.00	−5.02	758.4	46.8	5.24
65	0.00	0.00	−5.00	758.4	46.8	5.92
66	1.12	0.00	−4.14	789.5	44.8	6.34
67	0.71	0.00	−5.84	756.2	50.2	6.15
68	0.00	0.00	−5.84	756.2	50.2	6.15
69	−0.02	0.00	−7.89	777.6	47.3	5.31
70	0.00	0.00	−7.91	777.6	47.3	5.31

Table 4. Physicochemical properties of benzodiazepine receptor ligands used in present study

Compd	MR	MV	IR	D	Pol	Sag
1	85.84	224.0	1.692	1.29	34.03	465.09
2	86.02	218.1	1.718	1.41	34.10	464.88
3	86.02	218.1	1.718	1.41	34.10	474.86
4	86.75	230.1	1.677	1.25	34.39	472.51
5	91.17	245.3	1.665	1.23	36.14	499.18
6	91.35	239.4	1.688	1.35	36.21	497.66
7	91.35	239.4	1.688	1.35	36.21	493.89
8	81.42	208.8	1.707	1.31	32.27	449.98
9	86.02	218.1	1.718	1.41	34.10	466.93
10	85.84	224.0	1.692	1.29	34.03	467.21
11	85.84	224.0	1.692	1.29	34.03	477.97
12	87.23	230.5	1.681	1.32	34.58	460.54
13	87.23	230.5	1.681	1.32	34.58	488.02
14	87.23	230.5	1.681	1.32	34.58	486.72
15	88.98	221.4	1.736	1.59	35.27	472.04
16	88.98	221.4	1.736	1.59	35.27	484.96
17	81.29	211.7	1.694	1.38	32.22	455.68
18	81.29	211.7	1.694	1.38	32.22	455.23
19	90.27	239.2	1.678	1.26	35.78	497.71
20	90.27	239.2	1.678	1.26	35.78	492.14
21	90.27	239.2	1.678	1.26	35.78	489.00
22	90.27	239.2	1.678	1.26	35.78	498.04
23	90.27	239.2	1.678	1.26	35.78	469.27
24	90.27	239.2	1.678	1.26	35.78	481.36
25	102.1	261.5	1.709	1.28	40.47	523.43
26	106.7	270.8	1.717	1.37	42.30	549.41
27	109.66	274.0	1.732	1.51	43.47	558.70
28	106.53	276.7	1.696	1.26	42.23	551.95
29	106.7	270.8	1.717	1.37	42.30	549.53
30	106.53	276.7	1.696	1.26	42.23	549.66
31	107.43	282.8	1.684	1.24	42.58	545.53
32	112.03	292.1	1.693	1.32	44.41	568.44
33	114.98	295.3	1.706	1.45	45.58	580.79
34	111.85	298.0	1.674	1.22	44.34	572.97
35	112.03	292.1	1.693	1.32	44.41	571.62
36	111.85	298.0	1.674	1.22	44.34	570.67
37	79.76	210.6	1.681	1.31	31.61	446.44
38	84.18	225.8	1.668	1.28	33.37	471.21
39	84.18	225.8	1.668	1.28	33.37	473.51
40	84.18	225.8	1.668	1.28	33.37	463.67
41	84.36	219.9	1.693	1.41	33.44	471.32
42	84.36	219.9	1.693	1.41	33.44	471.53
43	84.36	219.9	1.693	1.41	33.44	463.42
44	87.31	223.1	1.711	1.59	34.61	481.42
45	85.42	215.9	1.721	1.48	33.86	481.45
46	85.42	215.9	1.721	1.48	33.86	480.58
47	85.42	215.9	1.721	1.48	33.86	466.88
48	85.57	232.3	1.658	1.31	33.92	482.06
49	85.57	232.3	1.658	1.31	33.92	458.74
50	85.57	232.3	1.658	1.31	33.92	458.54
51	88.6	241.0	1.656	1.26	35.12	493.77
52	81.67	207.4	1.717	1.40	32.37	446.58
53	81.67	207.4	1.717	1.40	32.37	464.72
54	81.67	207.4	1.717	1.40	32.37	457.76
55	87.31	223.1	1.711	1.59	34.61	471.35
56	94.87	235.7	1.737	1.84	37.61	504.78
57	91.74	238.3	1.696	1.54	36.36	500.96
58	96.16	253.5	1.683	1.51	38.12	509.78
59	85.42	215.9	1.721	1.48	33.86	469.33
60	92.97	228.4	1.748	1.75	36.85	502.76
61	89.84	231.1	1.705	1.45	35.61	498.94
62	94.26	246.3	1.691	1.41	37.37	508.90
63	101.99	274.7	1.664	1.22	40.43	519.28
64	106.42	289.9	1.655	1.21	42.18	548.12
65	106.42	289.9	1.655	1.21	42.18	546.43
66	110.84	305.0	1.646	1.19	43.94	563.48
67	106.59	284.0	1.674	1.30	42.25	544.97
68	106.59	284.0	1.674	1.30	42.25	545.32
69	107.81	296.3	1.647	1.23	42.73	555.99
70	107.81	296.3	1.647	1.23	42.73	558.31

The comparative chart once again indicates that our model containing 60 compounds is far superior to Singh's[4] model. Note that, though the set of 10 compounds deleted by us and those deleted by Singh[4] are quite different, the results do indicate that the most appropriate model in the both cases is the one containing 60 compounds.

The predictive potential of the models proposed by us are determined using cross-validation method.[9–12] The various cross-validation parameters thus calculated are given in Table 2.

The PRESS (Predictive Residual Sum of Squares) is an important parameter. Its value less than SSY indicates that the proposed model has good predictive power and is better than chance. In our case (Table 2), for all the proposed models PRESS < SSY indicating them to have good predictive power and are better than chance. Furthermore, for a good model PRESS/SSY should be smaller than 0.4, and this ratio < 0.1 indicates an excellent model. The data presented in Table 4 indicate that for all the models proposed by us PRESS/SSY $<< 0.1$ indicating all of them to be excellent models.

Another important cross-validation parameters is the predictive correlation coefficient r^2_{cv}; the highest value of which gave the excellent model. The six parametric model, containing 60 compounds, appears to be the best model.

The cross-validation parameters, namely uncertainty of prediction, S_{PRESS} is of no use in our case as it is found to be the same as that of standard error of estimation, Se, under such a situation we have another cross validation parameter named predictive square error (PSE), the lowest value of PSE proposed a model with highest predictive power.

From all the results of cross-validation methodology (Table 2) we conclude that our six parametric mode containing 60 compounds is not only statistically excellent, but also has excellent predictive power.

Conclusion

The results and discussion made above indicated that better models are obtained using a different set of molecular descriptors and that addition of I_3 and He to the parameters used earlier by Singh and coworkers[4] is beneficial. Furthermore, even for the larger set of 70 compounds, use of I_3 and He resulted in statistically significant model for estimation of pIC_{50}.

Experimental

Molecular descriptors

In the present study molar refractivity (MR), molar volume (MV), parachor (Pc), index of refraction (IR), surface tension (ST), density (D), polarizability (Pol), approximate surface area (Asa), surface area grid (Sag), hydration energy (He) and logarithm of octanol/water partition coefficient (logP) shown in Tables 3 and 4 are tested and calculated from computer software acdlabs[5] and Hyperchem7.[5]

Indicator parameters

Three indicator parameters I_X, I_Y and I_3 were used out of which I_X and I_Y are adapted from work of Singh and coworkers.[4]

Biological activity

The biological activity was adapted from the work of Singh and coworkers.[4]

Regression analysis

In the present study linear mathematical models are developed to study quantitative structure–property activity relationship. Multiple linear regressions are used to developed these models.[9]

The physicochemical properties are used as independent variables to calculate biological activity.

Step-wise regression has been performed to obtain the best model. The presictive power of these models are initially discussed on the basis of quality factor (Q) and finally using cross-validation parameters.

References and Notes

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