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QSAR studies on psychotomimetic phenylalkylamines

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Abstract—Quantitative Structure–Activity Relationship (QSAR) studies on a series of psychotomimetic phenylalkylamines have been made using a combination of Minimum Topological Difference (MTD) method and topological methodology. The topological indices used being a pool of distance-based topological indices. The regression analyses have shown that excellent results are obtained in multiparametric model containing MTD parameters, topological indices in that quantum chemical parameters has to be introduced. The predictive power of the proposed model is discussed on the basis of cross-validation parameters.
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1. Introduction

The phenylalkylamines have been tested on human beings.[1–3] Their psychotomimetic activity is generally expressed in mescaline units (MU), defined as the ratio of the effective dose of mescaline to the effective dose of tested compound. The potency is usually expressed as logMU, where MU is taken as mole mascaline/mole of the tested phenylalkylamine. In addition, some phenylalkylamines acts as unselective on seroternergic[4–7] or adrenergic receptors.[8–10]

The quantitative structure–activity relationship (QSAR) is made on this class of compounds.[11–13] Earlier, Mracec and coworkers[13] have reported QSARs with orthogonal descriptors. In their multiple linear regressions the best model has been obtained with Minimum Topological Difference (MTD) and electrotopological state indices, showing the importance of steric, electronic and lipophilicity parameters. Most of their regression expressions implied that the 4-position of the phenyl ring is responsible for both steric and electronic effects. However, to date, no topological approach is used in QSAR studies on psychotomimetic phenylalkylamines. This was, therefore, the primary objective of the present study in that we have used the same set of 49 psychotomimetic phenylalkylamines used by Mracec and coworker,[13] and adopted their psychotomimetic activity (logMU). The activity (logMU) is then modeled using distance- based topological indices: Wiener (W),[14] Szged (Sz),[15,16] and Balaban (J)[17] indices.

2. Results and discussion

The phenylalkylamines, their adopted psychotomimetic activity (logMU) and MTD parameters are reported in Table 1. The distance-based topological indices calculated for the set of 49 phenylalkylamines are presented in Table 2. The intercorrelation of the used descriptors and their correlation with logMU is shown in Table 3. The cross-validation parameters[18,19] used for investigating predictive power of the proposed models are recorded in Table 4. Finally, Table 5 records the comparison of observed and estimated logMU from some of the better regression models.

At this stage, it is worth summarizing the results of Mracec and coworkers.[13] As stated earlier, they obtained statistically significant models with steric, electronic and lipophilic descriptors. Their results are summarized as below:

Number of compounds	Parameters used	R^2	R
49	MTD_1, S_3, q_4	0.887	0.941
49	sMTD, S_3, q_4	0.848	0.920
49	Ω_1, Ω_2, Ω_3	0.885	0.940
45	sMTD, F_4, q_4	0.880	0.938
45	Ω_1, Ω_2, Ω_3	0.880	0.938

Keywords: QSAR; Regression analysis; Phenylalkylamine; Topological indices; MTD parameters.
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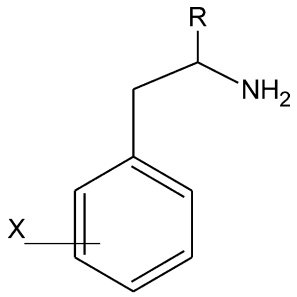
Table 1. Substituents, biological activity of phenylalkylamines used in the present investigation



Compd	X	R	LogMU (Obsd)
1	2,5-OMe,4-I	Me	2.78
2	2,5-OMe,4-Br	Me	2.72
3	2,5-OMe,4-SEt	Me	1.96
4	2,5-OMe,4-Et	Me	2.02
5	2,5-OMe,4-Pr	Me	1.95
6	3,5-OMe,4-Br	Me	1.91
7	2,5-OMe,4-Me	Me	1.90
8	2,5-OMe,4-S-iPr	Me	1.71
9	2,5-OMe,4-Br	H	1.69
10	2,5-Ome,4-Bu	Me	1.68
11	2,5-Ome,4-SMe	Me	1.66
12	3,5-Ome,4-SEt	H	1.36
13	2,4,5-Ome	Me	1.33
14	2,5-Ome,4-Et	H	1.25
15	3,5-Ome,4-SPr	H	1.29
16	2,5-Ome,4-Me	H	1.27
17	2,5-Ome,3-OCH_2O-4	Me	1.14
18	2,5-Ome,4-Oet	Me	1.36
19	3,5-Ome,4-SMe*	H	1.11
20	2-Ome,3-OCH_2O-4	Me	1.00
21	2,5-Ome,4-*n*-Pentyl	Me	1.10
22	3,5-Ome,4-Oet	Me	1.05
23	2-Ome,4-OCH_2O-5	Me	1.00
24	2,5-Ome,4-Opr	Me	1.38
25	3,5-Ome,4-Oet	H	0.87
26	2,3,4,5-Ome	Me	0.86
27	3,5-Ome,4-Opr	H	0.83
28	3,4-Ome,5-Set	H	0.84
29	3-OMe,4-OEt,5-Sme	H	0.84
30	3,4-Ome,5-Sme	H	0.81
31	2,3-Ome,4-OCH_2O-5	Me	0.76
32	3-OEt,4-SMe,5-Ome	H	0.66
33	3-OEt,4-SEt,5-Ome	H	0.68
34	2,4-Ome	Me	0.67
35	4-Me	Me	0.59
36	3,5-Ome,4-Sbu	H	0.58
37	3,5-Ome,4-$OCH_2C_6H_5$	Me	0.46
38	3-OMe,4-OCH_2O-5	Me	0.43
39	3-OCH_2O-4	Me	0.41
40	3,5-Ome,4-Obu	H	0.38
41	3-SEt,4-OEt,5-Ome	H	0.38
42	3,4-Oet,5-Sme	H	0.38
43	3,4,5-Ome	Me	0.33
44	3,4-Oet,5-Ome	H	0.23
45	3-OEt,4,5-Ome	H	0.03
46	3,4,5-Ome	H	0.00
47	2,3,4-Ome	H	−0.03
48	3,4-Ome	Me	−0.06
49	3,4-OMe	H	−0.67

It is needless to state that they have not used topological indices in their work. Under such situation, the present work in which along with topological indices two of the parameters of Mracec et al.[13] are also used is a new attempt for QSAR modeling of psychotomimetic activity (logMU) of the phenylalkylamines used.

Under the situation when earlier work is repeated using entirely a new set of parameters or using some of the earlier parameters along with some new, then the new results should be either of better statistics or of equivalent quality. If the latter is the case then it establishes that the QSARs are not antifactual as well as demonstrating the use of more general of the molecular parameters used. This is so in the present study also and is in favour of Hansch's[20] findings, who stated: "the fact that the two quite different methodologies yield similar answers providing further confidence that the QSAR is not artifactual". Similar results were obtained in our earlier publication also.[21]

Table 2 shows the presence of degeneracy in all the distance-based topological indices. This is so as they belong to first- and second-generation topological indices.[22,23] According to Balaban,[22] such indices inspite of the observed degeneracy can be used successfully in QSAR studies.

A perusal of Table 3 shows that the distance-based topological indices are highly correlated but none correlated with the activity (logMU). They are, therefore, incapable of yielding any monoparameteric model. Both the MTD parameters, namely single MTD and optimized MTD (MTD_1 and sMTD) correlate significantly with the activity (logMU).

The aforementioned results show that MTD_1 and sMTD are dominating parameters for modeling psychotomimetic activity (logMU). Their significant correlation with logMU indicates steric interactions. Such were the results obtained by Mracec and coworkers also.[13] Another parameter found useful is the logP. That is, in addition to steric effect, lipophilicity is responsible for the better exhibition of logMU. This is so because, a tri-parametric model containing MTD_1, sMTD and logP was found statistically significant:

$$\begin{aligned}\log\mathrm{MU} = {} & -0.2880(\pm 0.0554)\mathrm{MTD}_1 - 0.1976 \\ & \times (\pm 0.0672)\mathrm{sMTD} + 0.2035 \\ & \times (\pm 0.0620)\log\mathrm{P} + 2.3644 \qquad (1)\end{aligned}$$

$$n = 49,\ \ \mathrm{Se} = 0.3088,\ \ R = 0.9070,\ \ F = 69.732,\ \ Q = 2.9378$$

Here, and hereafter, n is the number of compounds, Se is the standard error of estimation, R is the correlation coefficient, F is the F-static[18,24,25] and Q is the quality factor. The quality factor Q is defined[26,27] as the ratio of correlation coefficient to the standard error of estimation, that is $Q = R/\mathrm{Se}$. This is the parameter used to account for the predictive power of the model. The negative coefficient of MTD_1 and sMTD in the above model (eq 1) indicates their retarding effect on the exhibition of logMU, while the positive coefficient of logP indicates favourable effects of lipophilicity in the exhibition of the activity.

Table 2. Molecular descriptors (W, J, Sz, MTD_1, sMTD, E, MR, logP)[a] for substituted phenylalkyl amine used in the present investigation

Compd	W	J	Sz	MTD_1	sMTD	E	MR	LogP
1	522	2.6008	720	1	2	33.263	70.19	2.66
2	522	2.6008	720	1	2	33.263	64.97	2.34
3	718	2.6522	982	2	3	35.515	74.23	2.46
4	611	2.6443	842	2	3	34.013	74.23	2.34
5	718	2.6522	982	2	3	35.106	66.83	2.87
6	528	2.5644	732	3	2	33.263	71.46	3.48
7	522	2.6008	720	1	2	32.513	64.97	1.82
8	827	2.6844	1124	2	4	36.393	62.11	3.16
9	453	2.5035	633	2	3	31.430	78.84	2.05
10	844	2.6349	1141	2	3	35.180	60.38	3.41
11	611	2.6443	842	2	3	34.346	76.10	1.92
12	632	2.5678	872	4	4	34.037	69.60	2.19
13	611	2.6443	842	2	3	36.013	74.23	1.43
14	534	2.5550	744	3	4	32.180	63.96	2.04
15	746	2.5627	1014	4	4	35.513	62.24	2.73
16	453	2.5035	633	2	3	30.680	74.26	1.52
17	669	2.0781	950	2	1	38.683	57.51	0.24
18	718	2.6522	982	2	3	37.565	63.44	1.92
19	536	2.5432	748	5	4	32.513	68.59	1.65
20	507	1.9685	722	4	3	33.513	65.00	0.77
21	990	2.6010	1320	3	4	38.513	65.00	3.95
22	720	2.6419	986	4	3	37.513	80.73	1.58
23	513	1.9417	734	3	4	33.513	68.59	1.11
24	844	2.6349	1141	2	3	39.013	56.76	2.45
25	632	2.5678	872	4	4	35.680	73.23	1.28
26	776	2.8727	1065	3	2	41.183	64.00	0.56
27	746	2.5627	1014	4	4	37.180	70.64	1.82
28	629	2.5777	866	4	3	34.013	68.63	2.28
29	632	2.5678	872	4	4	34.013	69.63	2.22
30	536	2.5432	748	5	4	32.513	69.63	1.74
31	667	2.0816	946	4	3	38.683	65.00	0.24
32	629	2.5777	866	5	5	34.013	63.44	2.13
33	732	2.6112	998	4	5	35.513	69.63	2.67
34	458	2.4644	631	4	5	30.843	74.26	1.40
35	337	2.2157	472	5	6	25.673	57.28	1.59
36	879	2.5373	1175	4	5	37.013	50.60	3.26
37	434	1.8958	2044	5	4	47.183	78.89	2.70
38	519	1.9189	746	5	4	33.513	93.08	0.77
39	381	1.7972	554	5	4	28.343	61.40	1.49
40	879	2.5373	1175	4	5	38.680	50.09	2.36
41	732	2.6112	998	4	5	35.513	73.27	2.77
42	732	2.6112	998	4	5	35.513	74.26	2.71
43	615	2.6224	850	4	3	36.013	74.26	1.09
44	732	2.6112	998	4	5	37.180	63.96	1.77
45	629	2.5777	866	5	5	35.680	68.63	1.28
46	536	2.5432	748	5	4	34.180	64.00	0.80
47	526	2.5996	728	6	5	34.180	59.37	0.80
48	466	2.4125	647	6	5	30.843	59.37	1.63
49	400	2.3204	562	7	6	29.010	57.28	1.33

[a] W, Wiener index; J, Balaban index; Sz, Szeged index; MTD_1, single minimum topological difference; sMTD, optimized minimum topological difference; E, elecrotopological index; MR, molar refractivity; logP, octanol/water partition coefficient.

Table 3. Correlation matrix of parameters used in the present study

	LogMU	W	J	Sz	MTD_1	sMTD	E	LogP	MR
LogMU	1.0000								
W	0.1159	1.0000							
J	0.2912	0.5009	1.0000						
Sz	−0.0053	0.5905	0.0615	1.0000					
MTD_1	−0.8776	−0.2796	−0.3335	−0.0873	1.0000				
sMTD	−0.7199	−0.0627	−0.0932	−0.0337	0.7423	1.0000			
E	0.0064	0.6122	0.1148	0.8995	−0.1588	−0.2431	1.0000		
LogP	0.3978	0.4534	0.3936	0.4259	−0.3050	0.0660	0.1298	1.0000	
MR	0.1647	−0.2473	−0.0612	−0.0043	−0.0962	−0.1961	0.0423	−0.0790	1.0000

Table 4. Cross-validation parameters analyses in the present study

Model/(eq)	Parameters	PRESS	SSY	PRESS/SSY	r^2_{cv}	S_{PRESS}	PSE
1 (1)	MTD_1, sMTD logP	4.2910	19.9481	0.2151	0.7849	0.3088	0.2959
2 (2)	MTD_1, sMTD, Sz, *E*	3.9341	20.3050	0.1938	0.8062	0.2990	0.2834
3 (3)	MTD_1, sMTD, Sz, *E*, J	3.7519	20.4872	0.1831	0.8169	0.2954	0.2767
4 (4)	MTD_1, sMTD, logP, Sz	3.4090	20.8301	0.1637	0.8363	0.2784	0.2638
5 (6)	MTD_1, sMTD, logP, *E*, MR	3.1889	21.0502	0.1515	0.8485	0.2723	0.2551
6 (7)	MTD_1, sMTD, logP, *E*, MR	2.8901	21.3362	0.1353	0.8645	0.2623	0.2454

Table 5. Observed and calculated biological activity (logMU) of phenylalkylamines

Compd	logMU (obsd)	logMU (calcd)[a]	Residual	logMU (calcd)[b]	Residual
1	2.78	2.36	0.41	2.36	0.42
2	2.72	2.25	0.47	2.25	0.47
3	1.96	1.73	0.22	1.73	0.23
4	2.02	1.77	0.25	1.76	0.26
5	1.95	1.80	0.14	1.80	0.15
6	1.91	2.04	−0.13	1.99	−0.08
7	1.90	2.16	−0.26	2.16	−0.26
8	1.71	1.55	0.16	1.56	0.15
9	1.69	1.84	−0.15	1.83	−0.14
10	1.68	1.89	−0.21	1.88	−0.20
11	1.66	1.66	−0.00	1.66	−0.00
12	1.36	0.92	0.43	0.90	0.46
13	1.33	1.46	−0.13	1.47	−0.14
14	1.25	1.20	0.05	1.19	0.06
15	1.29	0.95	0.34	0.92	0.37
16	1.27	1.71	−0.44	1.71	−0.44
17	1.14	1.43	−0.29	1.42	−0.28
18	1.36	1.44	−0.08	1.45	−0.09
19	1.11	0.58	0.52	0.54[c]	0.57
20	1.00	0.81	0.19	0.78	0.22
21	1.10	1.40	−0.30	1.39	−0.29
22	1.05	0.94	0.11	0.91	0.14
23	1.00	0.94	0.06	0.95	0.05
24	1.38	1.47	−0.09	1.48	−0.10
25	0.87	0.65	0.22	0.64	0.23
26	0.86	0.93	−0.07	0.92	−0.06
27	0.83	0.70	0.13	0.69	0.14
28	0.84	1.19	−0.35	1.14	−0.30
29	0.84	0.93	−0.09	0.91	−0.07
30	0.81	0.61	0.20	0.57	0.24
31	0.76	0.46	0.30	0.44	0.32
32	0.66	0.36	0.30	0.34	0.32
33	0.68	0.74	−0.06	0.73	−0.05
34	0.67	0.66	0.01	0.65	0.02
35	0.59	0.31	0.28	0.29	0.30
36	0.58	0.69	−0.11	0.69	−0.11
37	0.46	0.27	0.19	0.25	0.21
38	0.43	0.48	−0.05	0.44	−0.01
39	0.41	0.68	−0.27	0.63	−0.22
40	0.38	0.39	−0.01	0.40	−0.02
41	0.38	0.78	−0.40	0.77	−0.39
42	0.38	0.77	−0.39	0.77	−0.39
43	0.33	0.84	−0.51	0.81	−0.48
44	0.23	0.40	−0.17	0.41	−0.18
45	0.03	0.11	−0.08	0.10	−0.07
46	0.00	0.27	−0.27	0.24	−0.24
47	−0.03	−0.27	0.24	−0.30	0.27
48	−0.06	0.08	−0.14	0.04	−0.10
49	−0.67	−0.43	−0.24	−0.48	−0.19

[a] Calculated biological activity (logMU) from eq 6.
[b] Calculated biological activity (logMU) from eq 7.
[c] Data point not included in calculation in eq 7.

A tetra-parametric model containing MTD_1, sMTD, Sz, and E gave better results than the above model (eq 1):

$$\begin{aligned}\log MU = {} & -0.3355(\pm 0.048)MTD_1 - 0.2287 \\ & \times (\pm 0.0684)sMTD + 0.0014 \\ & \times \left(\pm 4.66^{*}10^{-4}\right)Sz - 0.1285(\pm 0.0345)E \\ & + 6.2857 \end{aligned} \quad (2)$$

$n = 49$, Se = 0.299, $R = 0.9153$, $F = 56.774$, $Q = 3.0612$

Introduction of Balaban index J, in the above model (eq 2) slightly improved the statistics:

$$\begin{aligned}\log MU = {} & -0.3011(\pm 0.053)MTD_1 - 0.2639 \\ & \times (\pm 0.0713)MTD_S + 0.0015 \\ & \times \left(\pm 4.7269^{*}10^{-4}\right)Sz - 0.1416 \\ & \times (\pm 0.0353)E + 0.2893(\pm 0.2002)J \\ & + 5.8911 \end{aligned} \quad (3)$$

$n = 49$, Se = 0.2954, $R = 0.9194$, $F = 46.901$, $Q = 3.1124$

The added parameter J is the most discriminating index and represents extended connectivity. It is a good descriptor for the shape of the molecule. Furthermore, values of J do not substantially increase with the molecular size and the number of rings present. All these factors are taken care of by the positive coefficient of J in that above model (eq 3).

Addition of Szeged index Sz, to eq 1 resulted into tetra-parametric model with still better statistics:

$$\begin{aligned}\log MU = {} & -0.258(\pm 0.0507)MTD_1 - 0.2353 \\ & \times (\pm 0.0616)sMTD + 0.298 \\ & \times (\pm 0.0626)\log P - 6.1359^{*}10^{-4} \\ & \times \left(\pm 1.8185^{*}10^{-4}\right)Sz + 2.7603 \end{aligned} \quad (4)$$

$n = 49$, Se = 0.2783, $R = 0.9270$, $F = 67.214$, $Q = 3.3309$

When electrotopological state parameter (E) is introduced in the above tetra-parametric model (eq 4) we obtained a penta-parametric model with slightly better statistics:

$$\begin{aligned}\log MU = {} & -0.2649(\pm 0.509)MTD_1 - 0.2575 \\ & \times (\pm 0.0642)sMTD + 0.2357\ (\pm 0.0823) \\ & + 8.6844^{*}10^{-5}(\pm 6.2559)Sz - 0.0494 \\ & \times (\pm 0.0423)E + 4.0875 \end{aligned} \quad (5)$$

$n = 49$, Se = 0.2772, $R = 0.9294$, $F = 54.495$, $Q = 3.3528$

However, this model is to be discarded on the ground that the coefficient of Sz is significantly smaller than its standard deviation. Such models are not allowed statistically. It is worthy to mention that no other model containing topological index rather than Sz gave statistically significant model better than (eq 5).

The aforementioned results and the results obtained by Mracec et al.[13] promoted us that the use of polarizability parameters in place of Sz and J may perhaps yield a model with better quality. We have, therefore, used Molar Refraction (MR) to account for the polorizability effect. The parameter MR is a thermodynamic parameter and is a combined effect of size and polarizability of the substituents. It characterizes deformation of molecular electrons distribution.

Using MR as one of the correlating parameters, we obtained a penta-parametric model containing MTD_1, sMTD, logP, E-state and MR giving better statistics than the model discussed above:

$$\begin{aligned}\log MU = {} & -0.2666(\pm 0.0494)MTD_1 - 0.244 \\ & \times (\pm 0.062)sMTD + 0.2462 \\ & \times (\pm 0.0558)\log P - 0.0438(\pm 0.012)E \\ & + 0.0064(\pm 0.0051)MR + 3.4735 \end{aligned} \quad (6)$$

$n = 49$, 0.5Se = 0.2723, $R = 0.9319$, $F = 56.770$, $Q = 3.4223$

The positive coefficient of MR in the above model (eq 6) indicates that polarizability has enough say in the exhibition of activity (logMU).

The deletion of compound **19** from the regression procedure yielded a model with considerable improvement in the statistics:

$$\begin{aligned}\log MU = {} & -0.2866(\pm 0.0485)MTD_1 - 0.2253 \\ & \times (\pm 0.0604)sMTD + 0.2376 \\ & \times (\pm 0.0539)\log P - 0.0411(\pm 0.0117)E \\ & + 0.0062(\pm 0.0049)MR + 3.3954 \end{aligned} \quad (7)$$

$n = 48$, Se = 0.2653, $R = 0.9385$, $F = 62.052$, $Q = 3.5375$

From the above results and discussion, we conclude that the methodology used by us is similar to Mracec and coworker[13] indicating thereby that QSARs are not antifactual.

We now discuss the predictive power of the models proposed by us. Such attempt was not made earlier. As

stated earlier we will do so firstly on the basis of Q values.[26,27] The above mentioned regression (eqs 1–7) show that there is consistent increase in Q value as we pass from tri- to penta-parametric models, and that the model expressed by (eq 7) has the highest Q value. This means that as we pass from tri- to penta-parametric models the predictive power of the resulting model likewise go on increasing and that model expressed by (eq 7) has the highest predictive power.

Though the use of Q-factor is found useful in the present case, its use is criticized by Todeschini.[28] In view of this, we have attempted cross-validation method and cross-validation parameters are recorded in Table 4.

As apposed to traditional regression methods, method of cross-validation evaluates the validity of a model by how well it predicts data rather than how well it fits data. For acquiring this the method uses cross-validated parameters: PRESS (predicted residual sum squares), SSY (sum of the squares of response value), r^2_{cv} (overall predictive ability), S_{PRESS} (uncertainty of prediction), PSE (predictive square of error).

PRESS is an important cross-validation parameter as it is a good estimate of the real predictive error of the models. Its value less than SSY indicate that the model predicts better than chance and can be considered statistically significant. In the present case all the proposed models have PRESS $<<$ SSY indicating them to be better than chance and statistically significant.

Furthermore, the ratio PRESS/SSY is used to estimate the confidence interval of the psychotomimetic activity. To have a reliable QSAR model, PRESS/SSY should be smaller than 0.4 and the value of the ratio smaller than 0.1 is indicative of a reasonably good model. In our case the ratio PRESS/SSY ranges between 0.1355 and 0.2151 indicating that all the proposed models are reasonable QSAR models.

The indication of the performance of the model is obtained from r^2_{cv} (the overall predictive ability). In our case highest r^2_{cv} is found for the model expressed by eq 7, indicating that it has an excellent predictive power.

Another useful cross-validated parameter is S_{PRESS}, which is used in deciding uncertainty of prediction. However, this parameter in the present case is of no value as it is equivalent to the standard error of estimation (Se). Under such situation the parameter PSE is used. The lowest value of PSE, the better is the predictive power which indicates that the model has excellent correlation ability. Based on PSE values (Table 4) once again we observed that the model 6 (eq 7) has the excellent correlation ability and predictability.

3. Conclusion

From our results, we conclude that the new models based on MTD_1 and sMTD in combination with Sz, J, or MR have statistical quality equivalent to those reported earlier by Mracec and coworkers.[13]

4. Experimental

4.1. Psychotomimetic activity

The psychotomimetic activity expressed as logMU was adopted from the literature.[13]

4.2. Topological indices

All the topological indices were calculated from the hydrogen suppressed graph in that all the hydrogens from the molecular structure are deleted.[24,25]

4.2.1. Wiener index (W). Wiener index W = W(G) of a graph G is defined[14] as the half sum of the elements of the distance matrix (D):

$$W = W(G) = \sum_{i=1}\sum_{j=1} (D)_{ij}$$

where, $(D)_{ij}$ is the ijth element of the distance matrix (D) which denotes the shortest graph — theoretical distance between sites i and j of G.

4.2.2. Szeged index (Sz). The Szeged index, Sz = Sz(G), is calculated[15,16] according to the following expression:

$$Sz = Sz(G) = \sum_{\text{edges}} n_u.n_v$$

where n_u is the number of vertices lying closer to one end of the edge e = uv, the meaning of n_v is analogous. Edges equidistance from both the ends of an edge, e = uv are not taken into account.

4.2.3. Balaban index (J). The Balaban index J = J(G) of G is defined[17,18] as

$$J = M/ + 1\Sigma\left(d_i.d_j\right)^{-0.5}_{\text{bonds}}$$

where M is the number of bonds in G, μ is the cyclomatic number of G, and d_i (i = 1,2,3,....N), N is the number of vertices in G and d_i, d_j are the distance sum J.

The cyclomatic number μ = μ(G) of a cyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related acyclic graph. In case of monocyclic graph μ = 1 otherwise μ is calculated by means of the following expression:

$$\mu = M - N + 1$$

4.3. Regression analysis

All the regressions are carried out using maximum r^2 method.[18,19] Step-wise regression has been performed for

obtaining the best model. The predictive potential of these models are initially discussed on the basis of quality factor (Q) and finally using cross-validation parameters.

4.4. Software

The calculation of topological indices and regression analysis were performed using software developed by Professor Istvan Lukovits, Hungarian Academy of Sciences, Budapest, Hungary.

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