International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
October - November, 2015, Vol. 4, No.6, pp 1838-1845
ISSN (P): 2393-932X, ISSN (E): 2278-0238

Research Article

LIGAND BASED DRUG DESIGN STRATEGY FOR THE MODELING OF PHENYLALKYLAMINES AS A PSYCHOTOMIMETIC AGENT

Abhilash Thakur[1], Mamta Thakur[*2], Jaya V Gade[3]

1. National Institute of Teachers Training and Research, Department of Applied Sciences, Bhopal, (M.P.), INDIA.
2. Department of Chemistry, Softvision College, Indore (M.P.), INDIA.
3. Department of Analytical Chemistry, S.H.P.T College, SNDT women's University Mumbai, INDIA

***Corresponding Author: Email** mamtaathakur@yahoo.co.in

(Received: July 28, 2015; **Accepted:** September 03, 2015**)**

ABSTRACT

Quantitative Structure Activity Relationship (QSAR) studies of 49 Phenyl alkyl amines derivatives have been performed using various structural descriptors, volumetric parameters and hydrophobic properties of the compounds. These derivatives are used as psychotomimetic agent. In present work, QSAR were determined by using multiple linear regression method (MLR). Five molecular descriptors accounting for the substitution at 2nd and 5th position, hydrophobicity, Surface area, branching and molar refractivity of the compounds were selected by stepwise regression method to built QSAR models. The study was further narrowed down by using modeling parameter on the selected set of compounds; results illustrate the importance of dipole moment and total energy on the psychotomimetic activity of the compounds.

Keywords: Ligand based drug design,Phenylalkylamines, QSAR, Psychotomimetic agents.

1. INTRODUCTION

Phenylalkyamines form a class of hallucinogenic agents which are pharmacologically diverse and a heterogeneous group of agents.[1] Different properties of phenylalkylamine derivatives, (which were known to display hallucinogenic, central stimulant, empathogenic activity, or a combination of activities) have been studied for a long time using different approaches.[1,2] Phenylalkylamines are one of the few types of psychotomimetic compounds whose structure–activity relationships (SAR) have been investigated.[3] Snyder and Merril first reported a correlation of hallucinogenic activity with a quantum index that was calculated using the Hückel molecular orbital theory.[4] They found that high activity is associated with the highest occupied molecular orbital (HOMO) energy in a small number of phenylalkylamines. Moreover, in our previous work quantitative structure–activity relationship (QSAR) studies were reported recently on this class of compounds [5–7] by combining the minimum topological difference and topological descriptors.[6]

The phenylalkylamines have been tested on human beings.[8-10] Their psychotomimetic activity is generally expressed in mescaline units (MU), In addition, some phenylalkylamines acts as unselective on seroternergic[11-14] or adrenergic receptors.[15-17]

The purpose of present study is to investigate the role of those factors which are still hidden but actively regulating the psychotomimetic activity of phenyl alkyl amines derivatives.

In order to achieve this objective, a large pool of descriptors has been calculated and the selection of relevant parameters has been done by stepwise multiple linear regression method.

The parent structure of Phenylalkylamine used in present study is shown in Figure 1.

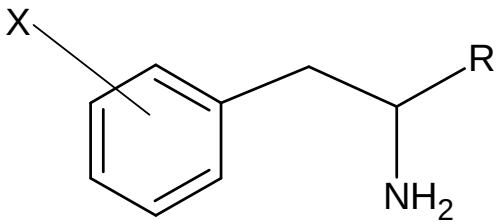

Fig 1: Parent Structure of Phenylalkylamine investigated in present study.

2. MATERIAL AND METHOD

2.1 Experimental dataset: In present study a data set of 49 phenylalkylamines has been taken from the literature for QSAR study. The psychometric activity of drugs are generally expressed in mescaline units (*MU*), defined as the ratio of the effective dose of mescaline to the effective dose of the tested compound. The potency is usually expressed as log *MU*, where *MU* is taken as mole of mescaline/mole of the tested phenylalkylamine. The data set in this work consisted of the log *MU* values of 48 phenylalkylamine derivatives, which were taken from the literature.[6] The structural features of these compounds and their experimental log *MU* values are presented in **Table 1.**

2.2 Topological Descriptors: It includes Wiener Index(W)[18], different types of Balaban branching index(JhetZ, Jhetm, Jhetv, Jhete, Jhetp)[19], Szeged Index[20], Molecular topological index[21] and Electrotopological index[22] and zero to 5^{th} order connectivity index[23].

2.3 Physicochemical Descriptor: Physicochemical properties tested in present study are, Molar refractivity (MR), Molar volume (MV), Parachor (Pc), Index of refraction (IR), Surface tension (ST), Density (D), Polarizability (Pol) and Octanol water partition coefficient (logP).

2.4 Volumetric Parameter: Parameters such as Approximate Surface area (ASA), Surface Area Grid (SAG), Hydration energy (HE) and Heat of Formation (HF) were tested in this category.

In order to indicate the significance of substitutent at particular site, dummy parameters called indicator parameters are used, The indicator parameters are the user defined variables and indicated by unity i.e. 1 (for the presence) and zero i.e. 0 (for the absence) for substituents.

2.5 Regression Analysis: Dataset of 49 molecules was subjected to regression analysis using MLR as model building method. QSAR models were generated using logMU values as the dependent variable and various descriptors values as independent variables. Statistical measures were used for the evaluation of QSAR models were the number of compounds in regression n, regression coefficient r^2, standard error of estimation Se and Fischer Ratio F

The model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of dependant variable (logMU) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable.

Regression equation takes the form

$Y = b1 * x1 \pm b2 * x2 \pm b3 * x3 \pm c$

where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c'is a regression constant or intercept [24,25].

2.6 Selection of compounds for molecular modeling: Biological activity in the form of log MU has been calculated using QSAR model obtained as a result of MLR analysis shown in **Table 1**. Set of 10 compounds were chosen for molecular modeling study, the selection is based on minimum residue values. Residual values are the difference between experimental logMU and estimated logMU. The molecular modeling parameters tested for this study are Dipole moment, Total energy, Root mean square gradient of these 10 compounds.

3. RESULT AND DISCUSSION:

As mentioned above, the numbers of descriptors and properties were calculated for the QSAR study of 49 phenylalkylamines derivatives with logMU as psychotomimetic activity of phenylalkylamines. The topological descriptors has been calculated using Dragon software, physicochemical properties of the compounds were calculated using hyperchem 7.1 ver and volumetric parameters are obtained from ChemSw software. Out of the

large set of descriptors obtained from mentioned software, the descriptors showing relevant or significant correlation with logMU were selected by Multiple linear regression analysis and QSAR models has been developed. The selected descriptors for 49 phenylalkylamines are presented in **Table 2.**

In stepwise multiple linear regression analysis the model obtained ranges from univariate to multivariate model. From the assessment of possible univariate model, it has been observed that none of the topological, physicochemical or volumetric descriptors are having the statistically significant results.

3.1 Model construction: The stepwise regression analysis leads to several model, however the best out of all univariate models is obtained with indicator parameter $I_{2,5}$ The models obtained from $I_{2,5}$ parameters is as below :

$$\log MU = 0.9643(\pm 0.1523)\ I_{2,5} + 0.5843 \qquad \text{Eq.(1)}$$

n = 49; Se = 0.5276; r = 0.6785; F = 40.091; Q = 1.286

In order to obtain more efficient model bi, tri tetra and penta variate models has been developed. Only the best model obtained in each step is present below. The statistical parameter on the basis of which these models are selected for QSAR study is also mentioned with each model.

The model obtained from bivariate combination is as below

$$\log MU = 0.9472(\pm 0.1323)\ I_{2,5} + 0.3149(\pm 0.0778)\ \log P - 0.0178 \qquad \text{Eq.(2)}$$

n = 49; Se = 0.4580; r = 0.7759; F = 34.783; Q = 1.694

For the detailed structural analysis the tri and tetra-variate combinations are tested and the models obtained from the calculations are as below:

$$\log MU = 0.8293(\pm 0.1219)\ I_{2,5} + 0.4645(\pm 0.0804)\ \log P - 0.0055(\pm 0.0015)\ SAG + 2.1827 \qquad \text{Eq.(3)}$$

n = 49; Se = 0.4069; r = 0.8322; F = 33.792; Q = 2.045

$$\log MU = 0.8597(\pm 0.1144)\ I_{2,5} + 0.4287(\pm 0.0762)\ \log P - 0.0065(\pm 0.0015)\ SAG + 0.4289(\pm 0.1553)\ J_{het_M} + 1.2670 \qquad \text{Eq.(4)}$$

n = 49; Se = 0.3799; r = 0.8591; F = 30.981; Q = 2.261

For the further improvement of the predictive potential of the model penta-variate combinations are tested and the models obtained is presented as below

$$\log MU = 0.8233(\pm 0.1097)\ I_{2,5} + 0.4040(\pm 0.0731)\ \log P - 0.0062(\pm 0.0014)\ SAG + 0.4109(\pm 0.1478)\ J_{het_M} + 1.29175 \times 10^{-4}(5.39061 \times 10^{-5})\ MR + 1.2076 \qquad \text{Eq. (5)}$$

n = 49; Se = 0.3610; r = 0.8768; F = 28.604; Q = 2.430

As we pass from the Eq. 1 to 5 there is continues increase in the value of r from 0.67 to 0.8768 along with the decrease in the value of Se., increase in the value of r is obvious with the addition of parameter but simultaneous decrease in the value of Se justify the addition of parameters in the models. Continues increase from eq. 1 to 5, in the statistically generated parameter (quality factor) Q also justify the equations and their predictive potential.

3.2 Interpretation of QSAR Model: The best QSAR model obtained in present study presented above as Eq (5). The presence of indicator parameter $I_{2,5}$ with positive correlation coefficient of 0.8233 suggests that ; 2,5 substitution on the molecule influencing the psychotomimetic activity or the substitution on position 2 and 5 favor the psychotomimetic activity logMU.

The presence of hydrophobic parameter logP with positive correlation coefficient of 0.404 suggestive of positive impact of hydrophobicity on logMU. Therefore, any substitutent which increases hydrophobicity will be favorable for the biological activity of the compounds.

The Eq (5) shows negative correlation coefficient of SAG, which shows lower surface area grid is favorable for the psychotomimetic activity.

On the other hand positive coefficient of J_{het_M} and MR supports higher values of both the descriptor to enhance biological impact of the compounds. These parameters revels branching and refractivity in the compounds.

As the model obtained from pentavariate combinations the Eq.5 having the 2 outlier, compound no 2 and 48. After the deletion of both compounds from calculation, model obtained is as below:

Table 1: Data set and corresponding observed and calculated values of log MU using Eq 7 (MU is taken as the moles of mescaline/moles of the tested phenylalkylamine)

Comp.No	X	R	Obs logMU	Calc logMU	Residue
1.	2,5-OMe,4-I	Me	2.78	1.83	0.94
2.	2,5-OMe,4-Br	Me	2.72a	1.78	0.94
3.	2,5-OMe,4-SEt	Me	1.96	1.59	0.37
4.	2,5-OMe,4-Et	Me	2.02	1.63	0.39
5.	2,5-OMe,4-Pr	Me	1.95	1.66	0.29
6.	3,5-OMe,4-Br	Me	1.91	1.51	0.40
7.	2,5-OMe,4-Me	Me	1.90	1.60	0.30
8.	2,5-OMe,4-S-iPr	Me	1.71	1.79	-0.08
9.	2,5-OMe,4-Br	H	1.69	1.81	-0.12
10.	2,5-OMe,4-Bu	Me	1.68	1.63	0.05
11.	2,5-OMe,4-SMe	Me	1.66	1.61	0.05
12.	3,5-OMe,4-SEt	H	1.36	0.87	0.48
13.	2,4,5-OMe	Me	1.33	1.46	-0.13
14.	2,5-OMe,4-Et	H	1.25	1.63	-0.38
15.	3,5-OMe,4-SPr	H	1.29	0.87	0.42
16.	2,5-OMe,4-Me	H	1.27	1.61	-0.34
17.	2,5-OMe,3-OCH2O-4	Me	1.14	0.73	0.41
18.	2,5-OMe,4-OEt	Me	1.36	1.41	-0.05
19.	3,5-OMe,4-SMe	H	1.11	0.84	0.27
20.	2-OMe,3-OCH2O-4	Me	1.00	1.02	-0.02
21.	2,5-OMe,4-n-Pentyl	Me	1.10	1.57	-0.47
22.	3,5-OMe,4-OEt	Me	1.05	0.55	0.50
23.	2-OMe,4-OCH2O-5	Me	1.00	1.27	-0.27
24.	2,5-OMe,4-OPr	Me	1.38	1.45	-0.07
25.	3,5-OMe,4-OEt	H	0.87	0.50	0.37
26.	2,3,4,5-OMe	Me	0.86	1.11	-0.25
27.	3,5-OMe,4-OPr	H	0.83	0.50	0.33
28.	3,4-OMe,5-SEt	H	0.84	0.88	-0.04
29.	3-OMe,4-OEt,5-SMe	H	0.84	0.85	-0.01
30.	3,4-OMe,5-SMe	H	0.81	0.66	0.15
31.	2,3-OMe,4-OCH2O-5	Me	0.76	0.70	0.06
32.	3-OEt,4-SMe,5-OMe	H	0.66	0.86	-0.20
33.	3-OEt,4-SEt,5-OMe	H	0.68	0.83	-0.15
34.	2,4-OMe	Me	0.67	0.78	-0.11
35.	4-Me	Me	0.59	0.85	-0.26
36.	3,5-OMe,4-SBu	H	0.58	0.84	-0.26
37.	3,5-OMe,4-OCH2C6H5	Me	0.46	0.33	0.13
38.	3-OMe,4-OCH2O-5	Me	0.43	0.21	0.22
39.	3- OCH2O-4	Me	0.41	0.65	-0.24
40.	3,5-OMe,4-OBu	H	0.38	0.46	-0.08
41.	3-SEt,4-OEt,5-OMe	H	0.38	0.86	-0.48
42.	3,4-OEt,5-SMe	H	0.38	0.81	-0.43
43.	3,4,5-OMe	Me	0.33	0.58	-0.25
44.	3,4-OEt,5-OMe	H	0.23	0.47	-0.2
45.	3-OEt,4,5-OMe	H	0.03	0.45	-0.42
46.	3,4,5-OMe	H	0.00	0.50	-0.50
47.	2,3,4-OMe	H	-0.03a	0.67	-0.70
48.	3,4-OMe	Me	-0.06a	0.76	-0.82
49.	3,4-OMe	H	-0.67	-0.64	-0.03

*a = Data point not incorporated in calculation from Eq. 7

Table 2 : Descriptors Selected by multiple linear regression analysis for the QSAR study of Phenylalkylamines.

Comp.	$I_{2,5}$	logP	SAG	Jhetm	MR
1	1	2.659	-7.11	2.572	70.19
2	1	2.34	-7.15	2.56	64.97
3	1	2.464	-1.06	2.676	74.23
4	1	2.338	-5.69	2.62	74.23
5	1	2.874	-2.53	2.648	66.83
6	0	3.476	-4.38	2.548	71.46
7	1	1.819	-6.39	2.537	64.97
8	1	3.164	-2.34	2.503	62.11
9	1	2.046	-7.91	2.503	78.84
10	1	3.41	-2.11	2.638	60.38
11	1	1.918	-4	2.638	76.1
12	0	2.192	-6.63	2.639	69.6
13	1	1.434	-7.96	2.427	74.23
14	1	2.044	-6.43	2.565	63.96
15	0	2.728	-6.12	2.638	62.24
16	1	1.525	-7.15	2.478	74.26
17	1	0.241	-7.49	1.895	57.51
18	1	1.919	-6.89	2.366	63.44
19	0	1.646	-7.29	2.594	68.59
20	1	0.774	-9.32	1.869	65
21	1	3.946	-4.31	2.604	65
22	0	1.578	-5.64	2.368	80.73
23	1	1.115	-4.82	1.892	68.59
24	1	2.455	-3.68	2.3	56.76
25	0	1.284	-6.76	2.301	73.23
26	1	0.56	-4.18	2.548	64
27	0	1.82	-6.25	2.236	70.64
28	0	2.283	-6.51	2.644	68.63
29	0	2.222	-6.38	2.499	69.63
30	0	1.737	-6.38	2.499	69.63
31	1	0.241	-6.79	1.898	65
32	0	2.131	-6.25	2.615	63.44
33	0	2.677	-5.72	2.561	69.63
34	0	1.4	-5.69	2.36	74.26
35	0	1.592	-3.65	2.6	57.28
36	0	3.264	-5.67	2.607	50.6
37	0	2.703	-3.41	1.667	78.89
38	0	0.774	-8.84	1.843	93.08
39	0	1.487	-6.69	2.025	61.4
40	0	2.356	-5.78	2.171	50.09
41	0	2.768	-4.87	2.563	73.27
42	0	2.707	5.44	2.44	74.26
43	0	1.093	-3.46	2.424	74.26
44	0	1.769	-5.81	2.268	63.96
45	0	1.284	-6.47	2.304	68.63
46	0	0.799	-7.49	2.362	64
47	0	0.799	-7.28	2.387	59.37
48	0	1.626	-6.22	2.337	59.37
49	0	1.332	-7.41	2.282	57.28

$I_{2,5}$ = Indiacator parameter for substituent on 2nd and 5th position ; logP = Octanol water partition coefficient
SAG = Surface Area Grid J_{hetM} = Mass weighted Balaban branching index MR = Molar Refractivity

Table 3 : Modeling parameters calculated for selected compounds with minimum residue.

Comp. No	TE	DpM	RMSg
09	8.895122	2.4630	0.09995
11	10.16977	1.8890	0.19300
18	11.71051	1.9590	0.09943
19	10.31566	0.0000	0.09092
21	10.99653	0.9497	0.09986
25	12.80846	1.2020	0.23080
29	8.869143	1.1630	0.14440
30	8.897106	1.1700	0.18790
32	15.92621	1.7730	0.09788
42	12.15490	0.0000	0.08572

TE = Total Energy
DpM = Dipole Moment
RMSg = Root Mean Square gradient

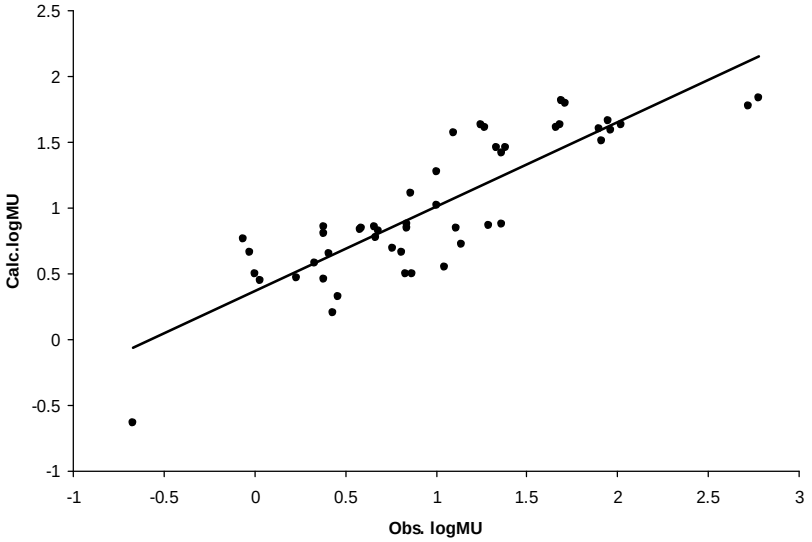

Figure 2 : Graphical representation of correlation between observed and calculated logMU

$logMU = 0.7426(\pm0.1097)\ I_{2,5} + 0.3924(\pm0.0651)\ logP - 0.0062(\pm0.0013)\ SAG + 0.3658(\pm0.1311)\ Jhet_M + 1.38329 \times 10^{-4}\ (4.77681 \times 10^{-5})\ MR + 1.4045$

Eq. (6)

n = 47; Se = 0.3190; r = 0.8904; F = 31.387; Q = 2.791

This eq. 6 also has compound no.47 as outlier and deletion of the same from calculation produce the following model:

$logMU = 0.7155(\pm0.0963)\ I_{2,5} + 0.3738(\pm0.0631)\ logP - 0.0065(\pm0.0012)\ SAG + 0.4098(\pm0.1276)\ Jhet_M + 1.38683 \times 10^{-4}\ (\pm4.58898 \times 10^{-5})\ MR + 1.488$ Eq.(7)

n = 46; Se = 0.3065; r = 0.8962; F = 32.660; Q = 2.924

Calculated values of logMU from Eq. 7 are presented in **Table 1** and graphically presented in **Figure 2.**

The QSAR features obtained in the above findings were further extended by applying some modeling parameters on selective compounds. The selection of these compounds is made on the basis of their minimum residual values. The residual values are the difference between observed and calculated logMU. Ten compounds selected for this study has been presented in **Table 3** along with their modeling parameters.

The model obtained for logMU with modeling parameters includes dipole moment and total energy, and relationship can be expressed as Eq (8)

$logMU = 0.3310\ (\pm0.1261)\ DpM - 0.0828\ (\pm0.0462)\ TE + 1.5489$ Eq. (8)

N = 10; Se = 0.3060; R = 0.7715; F = 5.147; Q = 2.521

It is observed from Eq (8) that the logMU having the dependence over the dipole moment and total Energy. Eq (8) also suggests the lower energy requirement for the significant logMU.

4. CONCLUSION:

Ligand based drug design strategies have been widely employed to quantitatively explore common chemical characteristics among a considerable number of biologically active systems with great diversity. Results of QSAR modeling clearly suggest the importance of Substitution at 2nd and 5th position on phenyl moiety, hydrophobic nature of the ligands, Branching in the ligands and molar refractivity of the compounds and also suggests that increase in these features will be favorable for the psychotomimetic activity (logMU) of phenylalkylamines. Also, it is worthy to note that the lower value of surface area grid is favorable for the biological activity.

Molecular modeling study of phenylalkylamines favors higher dipole moment and lower total energy of the system for efficient biological response.

Successful application of these QSAR models as a query for searching chemical databases and identification of new chemical entities supports their possible use in the assessment of biological responses.

REFERENCES

1. Glennon R.A, (1999), Pharmacol. Biochem. Behav. 64, 251
2. Taurian O. E,Contreras R. H, (2000), J. Mol. Struct. (Theochem) 504, 119
3. Nieforth K. A, (1971),J. Pharm. Sci. 60, 655
4. Synder S. H, Merril C. R, (1965), Natl. Acad. Sci. U.S.A. 54, 258
5. MracecM, Mracec M, Kurunczi L., Nussar T., Simon Z., Naray-Szabo G., (1996), J. Mol. Str. (Theochem) 367, 139.
6. Thakur M., Thakur A., Khadikar P. V., (2004), Bioorg. Med. Chem. 12, 825
7. Altun A., Golcuk K., Kumru M., Jalbout A. F., (2003), Bioorg. Med. Chem. 11,3861
8. Braun, U.,Braun, G., Jacob, P., III;Nichols, D. E.; Shulgin, A.T. In QSAR Research Monograph;Branett, G., Trsic, M., Rillette, R., Eds.;NIDA: Rockville, 1978;Vol. 22, p 27.
9. Hopman, G.,Macina, O. T.(1985) J. Theor. Biol. 113, 637.
10. Clare, B. W. (1990), Med. Chem., 33, 687.
11. Nichols, D. E.,Oberlendor, R.,McKenna, D. J(1991). Biochemistry and Physiology of Substance Abuse;Watson, R. R., Ed.;RC: Boca Raton, Boston, Vol. III, p 5.
12. Glennon, R. A.,Dukat, M. (1991)Pharmacol. Biochem. Bolav. 40, 1009.
13. Glennon, R. A.,Raghupati, R., Bartyzel, P.,Titler, M., Leonhadt, S. J.(1992) Med. Chem. 35, 734.
14. Westakaemper, R. B.;Glennon, R. A.(1993), Med. Chem. Res.3, 317.
15. Ruffolo, R. R.(1993) Drug Design Discov. 9, 351.
16. Tarciso, V.,Meroni, R.,Dagani, R.,Baldi, G.,Paghi, M., Bevilaquen, M.,Norriato, G. J. (1985) Pharm. Pharmacol., 37, 593.
17. Srlurojer, T.,Hodsiek, M.,Hadzi, D.,Lukovits, I.(1984), QSAR Pharmacol. Chem. Bio. 3, 51.
18. Wiener, H. J.(1947), Am.Chem. Soc. 69, 17.
19. Balaban, A. T.(1982) Chem. Phys. Lett., 89, 399.

20. Khadikar, P. V.,Deshpande, N. N.,Kali, P. A.,Dohirnin, A.,Gutman, I.,Donewfor, G. J.(1995) Chem. Inf. Compt. Sci., 35, 547.
21. Shultz, H. P. (1989),J. Chem. Inf. Comp Sci., 29, 227.
22. Kier, L.B.; Hall, L.H. (1997), J. Chem. Inf. Comp. Sci., 37, 548.
23. Randic, M. (1975),J. Am.Chem. Soc., 97, 6609.
24. Croux C, Joossens K (2005). J Multivar Anal 96:348.
25. Devillers J (1996) Academic Press, London

