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Application of Graph Theory: Relationship of Molecular Connectivity Index, Wiener's Index and Eccentric Connectivity Index with Diuretic Activity

S. Sardana, Hindu College of Pharmacy, Sonipat-131001, India

A.K. Madan*, Faculty of Pharmaceutical Sciences, M.D. Univ., Rohtak-124001, India

* For correspondence, E-mail : madan_ak@yahoo.com

ABSTRACT

Relationship between topological indices and diuretic activity of sulfamoylbenzoic acid derivatives has been investigated. Three topological indices – the *molecular connectivity index*, an adjacency based topological index, *Wiener's index*, a distance based topological index and the *eccentric connectivity index*, an adjacency cum distance based topological index were used for present investigation. The values of the *molecular connectivity index, Wiener's index*, and the *eccentric connectivity index* of each of 68 analogues comprising the data set were computed and active ranges were identified. Subsequently, a biological activity was assigned to each analogue involved in the data set which was then compared with the reported diuretic activity in terms of volume of water excreted per hour. Accuracy of prediction was found to vary from a minimum of ~82% in case of *molecular connectivity index* to a maximum of ~90% in case of the *eccentric connectivity index.*

Keywords : *diuretic activity, eccentric connectivity index, molecular connectivity index, structure activity relationship, sulfamoylbenzoic acid, topological indices and Wiener's index.*

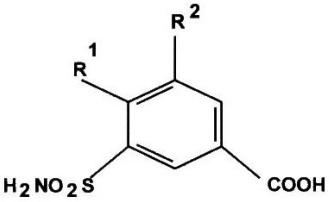
INTRODUCTION

A recent trend in structure-activity relationship (SAR) and pharmaceutical drug design is the quantitative prediction of physicochemical, biochemical and toxicological properties of biologically active molecules using topological indices [1-5]. The objective of all such studies is to explore the role of connectedness of atoms in the expression of biological activities of molecules [6]. Thus, the molecular structures are translated into characteristic numerical descriptors known as topological indices, which may then be used in the development of SAR studies. Although a number of topological indices have been reported, only a handful of them have been successfully employed in SAR studies. These include Wiener's index [7-12], Balaban's index [13-17], Hosoya's index [18-19], the Randic's molecular connectivity index [20] and the eccentric connectivity index[21].

Diuretics are the drugs which increase the output of urine resulting in an increased excretion of water and sodium. Diuretics are normally required to remove oedema fluid which is composed of water and solutes, of which sodium is most important. These drugs are used in *hypertension, congestive heart failure* and *oedemas* associated with other conditions. Diuretics mainly act at one of the four main sites i.e. the proximal tubule, ascending limb of Henele's loop, cortical diluting segment and the distal tubule. Sulfamoylbenzoic acid derivatives like bumetanide (compound no.67) are loop diuretics These are the most powerful of all diuretics, capable of causing 15-25% of the sodium in the filtrate to be excreted; thus they are termed *high ceiling* diuretics. These drugs act primarily at thick segment of the ascending loop of Henele, inhibiting the transport of sodium chloride out of the tubule into the interstitial tissue by inhibiting the $Na^+/K^+/2Cl^-$

carrier in the luminal membrane. Bumetanide, a therapeutically used diuretic in the treatment of oedemas of cardiac, hepatic or renal origin, is a 3- aminobenzoic acid derivative and has a direct inhibiting effect on the chloride binding site[22-24].

Figure-1: Basic Structure of Sulfamoylbenzoic acid derivatives



In the present study the relationship of *molecular connectivity index, Wiener's index* and the *eccentric connectivity index* with diuretic activity of sulfamoylbenzoic acid derivatives has been investigated.

METHODOLOGY

Calculation of topological indices :

The *molecular connectivity index* [20] proposed by Randic, is denoted by χ and is defined as the sum over all the edges (*ij*) as per following :

$$\chi=\sum_{j=1}^{n}(V_iV_j)^{-1/2}$$

Where V_i and V_j are the degrees of adjacent vertices i and j and n is the number of vertices in a hydrogen suppressed molecular structure.

The *Wiener's index* [7-12], a well known distance based topological index is defined as the sum of the distances between all the pairs of vertices in a hydrogen suppressed molecular graph, that is

$$W = \tfrac{1}{2} \left(\sum_{i=1}^{n} Pi \right)$$

where Pi is the length of the path that contains the least number of edges between vertex i and vertex j in graph G and n is the maximum possible number of i and j.

Eccentric connectivity index [21] denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen suppressed molecular graph having n vertices.

$$\xi^c = \sum_{i=1}^{n} (E_i * V_i)$$

Where V_i is the degree of the vertex i, E_i is the eccentricity of vertex i and n is the number of vertices in graph G. *Eccentric connectivity index* takes into consideration the eccentricity as well as valency of the vertices in a hydrogen suppressed graph.

Model development analysis:

68 out of 72 sulfamoylbenzoic acid analogues reported by Peter W. Feit *et al* [25] were selected as data set for present investigations. Four analogues which were employed as

control by Peter W. Feit *et al* [25] were omitted for obvious reasons. This data set comprised of both the active and inactive compounds. Diuretic activity was quantitatively reported as ml/kg per 3 hr water excretion. Compounds which caused water excretion of 8 ml/kg per 3 hr or more in a dose of 0.1 mg/kg body weight and the compounds which caused water excretion of 20 ml/kg per 3 hr or more in a dose of 1 mg/kg body weight were considered to be active for the purpose of present study. The values of the *molecular connectivity index* were computed for each analogue using an in-house computer program and an active range was identified. Subsequently, each analogue was assigned a biological activity which was then compared with the reported diuretic activity. Percent degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to that of total number of compounds present in that range. The overall degree of prediction was derived from the ratio of the total number of compounds predicted correctly to that of the total number of compounds present in both the active and inactive ranges.

Aforementioned procedure was similarly adopted in case of *Wiener's index* and the *eccentric connectivity index.*

The results are summarized in tables I to IV.

RESULTS AND DISCUSSION

For generations, a cherished goal of chemists has been to create molecules with specific properties. However, because of combination of serendipity and empiricism as the basis of new drug discovery, finding new drugs has been an extremely challenging process [26]. The finding that the structure of a molecule had an important role to play in its biological

activity coupled with need for safer potent drug to be developed with minimum expenditure, animal sacrifice and time loss led to the genesis of SAR studies [27]. Numerous mathematical tools of diverse nature are being presently employed in SAR and structure – property relationship (SPR) studies. Topological indices represent one class of mathematical tools. Since topological indices can translate molecular structures into characteristic numerical descriptors, therefore, these are being widely employed in SAR/SPR studies. In present investigations, the *molecular connectivity index* – a widely used adjacency based topological index, the *Wiener's index* – a well known distance based topological index and the *eccentric connectivity index* – an adjacency cum distance based topological index have been employed to study relationship with diuretic activity of sulfamoylbenzoic acid derivatives. These compounds possess high diuretic activity leading to increased excretion of water, sodium, potassium and chloride. The selected data set comprising of 68 analogues included both the active and inactive compounds. Retrofit analysis of the data in tables I and II reveals the following information with regard to *molecular connectivity index*:

- Biological activity was assigned to a total number of 56 analogues in both the active and inactive ranges, out of which activity of 46 analogues was correctly predicted resulting in ~82% accuracy with regard to diuretic activity.
- A transitional range was observed indicating a gradual change in diuretic activity. A total of 12 analogues were present in the transitional range.
- The active range had *molecular connectivity index* values of more than 11.99. As many as ~79% of the analogues in the active range exhibited diuretic activity.

Retrofit analysis of the data in tables I and III reveals the following information with regard to *Wiener's index*:

- Biological activity was assigned to a total number of 52 analogues in both the active and inactive ranges out of which activity of 44 analogues was correctly predicted resulting in ~85% accuracy with regard to diuretic activity.
- A transitional range was observed indicating a gradual change in diuretic activity. A total of 16 analogues were present in the transitional range.
- The active range had *Wiener's index* values of more than 1468. As many as ~81% of the analogues in the active range exhibited diuretic activity.

Retrofit analysis of the data in tables I and IV reveals the following information with regard to *eccentric connectivity index*:

- A total of 39 analogues were classified into active and inactive ranges, out of which 35 analogues were correctly predicted resulting in ~90% accuracy with regard to diuretic activity.
- Lower and upper transitional ranges were observed, indicating a gradual change in diuretic activity from the inactive to the active range and vice-versa. A total of 29 analogues were present in these transitional ranges.
- The active range had *eccentric connectivity index* values of 434-573. As many as 26 out of 30 analogues in this range exhibited diuretic activity resulting in ~87% accuracy. Further the active analogues were found to be present in narrow range of eccentric connectivity index values thus providing useful lead for a potent diuretic.

Investigations reveal significant correlations of all the three topological indices with diuretic activity of sulfamoylbenzoic acid derivatives. The overall accuracy of prediction

varied from a minimum of ~82% in case of *molecular connectivity index* to a maximum of ~90% in case of *eccentric connectivity index*. High accuracy of prediction in case of *eccentric connectivity index* may be attributable to the combined use of the adjacency and distance parameters in the same topological index rather than using these parameters separately as in case of *molecular connectivity index* and *Wiener's index* respectively. These studies can be exploited to provide a useful lead for development of a potent diuretic. Topological indices in combination with other mathematical tools provide a vast potential for development of various therapeutic agents of diverse nature.

REFERENCES

1. Kier, L.B. and Hall, L.H., in *Molecular Connectivity in Structure Activity Analysis*, Research Studies Press Ltd., Letchworth, England, (1986) pp 1 –257.
2. Trinajstic,N., In *Chemical Graph Theory*, CRC Press, Boca Raton, Florida, (1983) Vol I&II.
3. Balaban,A.T., Motoc.I., Bonchev,D. and Mekennyan,O., Topological indices for structure activity correlations. *Top. Curr. Chem.* (1983), 114,21-55.
4. Basak, S.C., Burtlsen, S. and Grunwold, G.D., Application of graph theoretical parameters in quantifying molecular similarity and structure activity relationships. *J. Chem. Inf. Comput. Sci.* (1994),34,270-276.
5. Sablic,A. and Trinajstic,N., Quantitative structure activity relationships; The role of topological indices. *Acta Pharm. Jugsol.*,(1981),31,189-214.
6. Klopman,G. and Raychoudhary, C., A novel approach to graph theory in structure activity relationship studies. Application to the qualitative of mutagenicity in a series of nonfused ring aromatic compounds. *J.Comput.Chem.*, (1988),9,232-253.

7. Wiener.H., Correlation of heat of isomerization and difference in heat of vaporization of isomers among paraffin hydrocarbons. *J.Am.Chem.Soc.*(1947),69,2636-2638.
8. Wiener,H., Influence of interatomic forces on paraffin properties. *J.Chem.Phys.* (1947),15,766.
9. Wiener,H.,Vapour-pressure-temperature relations among the branched paraffin hydrocarbons. *J.Chem.Phys.*(1948),15,425-430.
10. Wiener,H., Relationship of physical properties of isomeric alkanes to molecular structure, surface tension, specific dispersion and critical solution temperature in aniline. *J.Phys.Colloid.Chem.*(1948),52,1082-1089.
11. Randic,M.,Guo,X.,Oxely,T.and Krishnapriyan,H., Wiener Matrix; Source of novel graph invariants. *J.Chem.Inf.Comput.Sci.*(1993),33,709-716.
12. Randic,M., Guo,X., Oxely,T., Krishnapriyan,H. and Naylor,L., Wiener Matrix Invariants. *J.Chem.Inf.Comput.Sci.*(1994),34,361-367.
13. Balaban,A.T., Chiriac,A.,Motoc.I.and Simon,Z., Steric fit in QSAR. *Lect.Notes Chem.*(1980),15,22-27.
14. Balaban,A.T., Highly discriminating distance based topological index. *Chem. Phys. Lett.* (1982),89,399-404.
15. Balaban,A.T., Applications of graph theory in chemistry. *J. Chem. Inf. Comput. Sci.* (1985),25,334-343.
16. Balaban,A.T.and Filip,P., Computer Programme for topological index J (average distance sum connectivity) *J. Math. Chem.* (1984),16,163-190.
17. Balaban, A.T. and Quintar, L.B., The smallest graphs, trees and 4-trees with degenerate topological index *J. Math. Chem.*, (1983),14,213-233.

18. Hosoya,H., Topological index; Newly proposed quantity characterizing the topological nature of structure of isomers of saturated hydrocarbons. *Bull. Chem. Soc. Jpn.* (1971),44,2332-2337.

19. Hosoya,H., Topological index as strong sorting device for coding chemical structure *J.Chem.Doc.*(1972),12,181-183.

20. Randic,M., On characterization of molecular branching. *J.Am.Chem.Soc.* (1975),97,6609-6615.

21. Sharma,V.,Goswami,R.and Madan,A.K., Eccentric connectivity index; A novel highly discriminating topological descriptor for structure property and structure activity studies. *J.Chem.Inf.Comput.Sci.*(1997),37,273-282.

22. Laurence, D.R., Bennet, P. N. and Brown, M.J., *Clinical Pharmacology*,8th Edition, Churchil Livingstone, pp 484 –485.

23. Rang, H.P., Dale, M.M. and Ritter, J.M., *Pharmacology*, 3rd Edition, pp 376 –377.

24. Irwin, M. Weiner, Diuretics and other agents employed in the mobilization of oedema fluid, In Goodman and Gilman's *The Pharmacological Basis of Therapeutics*,8th Edition, 1990, pp 713 –731.

25. Ole, B. Tvaermose Niellsen, Herta Bruun, Clause Bretting and Peter W. Feit, Amino benzoic acid diuretics,7,3-substiuted 4-Phenyl-,4-Arylcarbonyl-, and 4-Arylmethyl-5-sulfamoylbenzoic acids and related compounds. *J.Med.Chem.*, (1975) 18 No.1,41-50.

26. Grover,M, Singh,B., Bakshi,M. and Singh S., Quantitative structure property relationship in pharmaceutical research-Part I. *Reviews/ Research focus*, (2000), 3 No.1, 28-35.

27. Martin Y.C., *Quantitative drug design*, Dekker Press, N.Y. 1978.

Table I: Relationship of the molecular connectivity index, Wiener's index and the eccentric connectivity index with diuretic activity of sulfamoylbenzoic acid analogues.

S. No.	R^1	R^2	ξ^c	χ	W	Diuretic Activity			
						Assigned			Reported
						ξ^c	χ	W	
1.	C_6H_5	NH-n-Bu	385	11.579	1294	±	±	±	-
2.	C_6H_5	$NHCH_2C_6H_5$	504	13.097	1772	+	+	+	+
3.	C_6H_5	$NHCH_2CCHCHCH0$	515	12.662	1562	+	+	+	-
4.	C_6H_5	$NHCH_2CH_2CCHCHNCHCH$	574	13.597	1857	±	+	+	-
5.	COC_6H_5	OEt	377	11.490	1240	±	-	±	-
6.	COC_6H_5	O-n-Pr	396	11.990	1398	±	±	±	+
7.	COC_6H_5	$OCH_2CH{=}CH_2$	396	11.990	1398	±	±	±	-
8.	COC_6H_5	$OCH_2C{=}CH$	396	11.990	1398	±	±	±	-
9.	COC_6H_5	O-n-Bu	448	12.490	1581	+	+	+	+
10.	COC_6H_4-4-Me	O-n-Bu	494	12.883	1770	+	+	+	+
11.	COC_6H_4-4-Cl	O-n-Bu	494	12.883	1770	+	+	+	+
12.	COC_6H_5	O-n-Am	517	13.112	1790	+	+	+	+
13.	COC_6H_5	$O(CH_2)_3CH_3$	574	13.490	2026	±	+	+	-
14.	COC_6H_5	$OCH_2C_6H_5$	504	13.097	2144	+	+	+	+
15.	COC_6H_4-4-Me	$OCH_2C_6H_5$	622	14.401	2369	±	+	+	+
16.	COC_6H_4-4-Cl	$OCH_2C_6H_5$	622	14.401	2369	±	+	+	+
17.	COC_6H_5	$OCH_2C_6H_4$-4-Cl	637	14.401	2385	±	+	+	+
18.	COC_6H_5	$OCH_2CH_2C_6H_5$	643	14.507	2431	±	+	+	+
19.	COC_6H_5	$O(CH_2)_3C_6H_5$	721	14.970	2748	±	+	+	-
20.	COC_6H_5	$OCH_2CCHCHSCH$	503	13.595	1929	+	+	+	+
21.	COC_6H_5	$OCH_2CCHCHCHCHN$	504	13.097	2144	+	+	+	+
22.	C_6H_5	O-n-Bu	385	11.579	1272	±	±	±	-
23.	C_6H_5	O-n-Am	447	12.079	1458	+	+	±	-
24.	C_6H_5	$OCH_2C_6H_5$	504	13.097	1999	+	+	+	+
25.	C_6H_5	$OCH_2CH_2C_6H_5$	574	13.597	2079	±	+	+	-
26.	C_6H_5	$OCH_2CCHCHSCH$	441	12.597	1580	+	+	+	+
27.	CH_3	O-n-Pr	240	8.506	598	-	-	-	-
28.	CH_3	O-n-Bu	283	9.006	718	-	-	-	-
29.	CH_3	$OCH_2C_6H_5CH_3$	390	10.524	724	±	-	-	-
30.	CH_3	$OCH_2CCHCHSCH$	339	10.024	943	-	-	-	-
31.	COC_6H_5	Sme	360	10.990	1101	-	-	-	-
32.	COC_6H_5	S-n-Pr	396	11.990	1398	±	±	±	+
33.	COC_6H_5	$SCH_2CH{=}CH_2$	396	11.990	1398	±	±	±	-
34.	COC_6H_5	S-n-Bu	449	12.490	1563	+	+	+	+
35.	COC_6H_5	S-i-Am	470	12.845	1766	+	+	+	+
36.	COC_6H_5	$SCH_2C_6H_5$	567	14.007	2319	+	+	+	+
37.	C_6H_5	S-n-Pr	338	11.079	1110	-	-	-	-
38.	C_6H_5	S-n-Bu	385	11.579	1272	±	±	±	-
39.	C_6H_5	$SCH_2C_6H_5$	504	13.097	1772	+	+	+	-
40.	COC_6H_5	$CH_2CH_2C_6H_5$	567	14.007	2319	+	+	+	+
41.	$CH_2C_6H_5$	Oet	364	11.082	1142	±	-	±	-
42.	$CH_2C_6H_5$	O-n-Pr	383	11.562	1293	±	±	±	+
43.	$CH_2C_6H_5$	$OCH_2CH{=}CH_2$	383	11.562	1203	±	±	±	+
44.	$CH_2C_6H_5$	O-n-Bu	434	12.062	1468	+	+	+	+
45.	$CH_2C_6H_4$-4-Cl	O-n-Bu	479	12.456	1651	+	+	+	+
46.	$CH_2C_6H_5$	O-n-Am	487	12.562	1668	+	+	+	-
47.	$CH_2C_6H_5$	$O(CH_2)_3CH_3$	555	13.062	1894	+	+	+	-
48.	$CH_2C_6H_4$-4-Me	$OCH_2C_6H_5$	605	13.974	2121	±	+	+	+

49.	$CH_2C_6H_4$-4-Cl	$OCH_2C_6H_5$	605	13.974	2121	±	+	+	+
50.	$CH_2C_6H_5$	$CH_2CH_2C_6H_5$	550	13.580	2007	+	+	+	+
51.	$CH_2C_6H_5$	SMe	347	10.562	1014	-	-	-	-
52.	$CH_2C_6H_5$	SEt	364	11.062	1142	±	-	±	+
53.	$CH_2C_6H_5$	S-n-Pr	383	11.562	1293	±	±	±	+
54.	$CH_2C_6H_5$	$SCH_2CH{=}CH_2$	383	11.562	1293	±	±	±	+
55.	$CH_2C_6H_5$	S-n-Bu	434	12.062	1468	+	+	+	+
56.	$CH_2C_6H_5$	S-n-Am	487	12.562	1668	+	+	+	+
57.	$CH_2C_6H_5$	$SCH_2C_6H_5$	550	13.580	2007	+	+	+	+
58.	$CH_2C_6H_5$	$SCH_2C_6H_4$-3-OMe	641	14.512	2454	+	+	+	-
59.	$CH_2C_6H_5$	$SCH_2CCHCHCHO$	496	13.080	1801	+	+	+	+
60.	$CH_2C_6H_5$	$SCH_2CCHCHSCH$	496	13.080	1801	+	+	+	+
61.	$CH_2C_6H_5$	$SCH_2CCHCHNCHCH$	550	13.580	2007	+	+	+	+
62.	$CH_2C_6H_5$	$SCH_2CH_2CCHCHNCHCH$	624	14.080	2282	±	+	+	+
63.	CH_3	S-n-Pr	240	8.506	600	-	-	-	-
64.	CH_3	S-n-Bu	283	9.006	718	-	-	-	-
65.	CH_3	$SCH_2C_6H_5$	390	10.524	1086	±	-	-	-
66.	CH_3	$SCH_2CCHCHSCH$	339	10.024	943	-	-	-	-
67.	3-n-Butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide)		434	12.062	1468	+	+	+	+
68.	4-Benzyl-3-n-butylamino-5-sulfamoylbenzoic acid (besunide)		434	12.062	1468	+	+	+	+

+ , Active compound
- , Inactive compound
± , Compound in the transitional range

Table II : The relationship between diuretic activity of sulfamoylbenzoic acid derivatives and the *molecular connectivity index.*

Nature of Range	Index value	Number of analogues in the range		Accuracy (%)
		Total	Correctly Predicted	
Inactive	< 11.562	14	13	92.85
Transitional	11.562 –11.990	12	N.A.	N.A.
Active	> 11.990	42	33	78.57

N.A. , not applicable

Table III : The relationship between diuretic activity of sulfamoylbenzoic acid derivatives and the *Wiener's index.*

Nature of range	Index value	Predicted analogues		Accuracy (%)
		Total	Correct	
Inactive	< 1142	11	11	100
Transitional	1142 –1467	16	N.A.	N.A.
Active	> 1468	41	33	80.48

N.A. , not applicable

Table IV : The relationship between diuretic activity of sulfamoylbenzoic acid derivatives and the *eccentric connectivity index.*

Nature of range	Index value	Predicted analogues		Accuracy (%)
		Total	Correct	
Lower Inactive	<364	09	09	100
Lower Transitional	364-433	17	N.A.	N.A.
Active	434-573	30	26	86.66
Upper Transitional	574-721	12	N.A.	N.A.

N.A. , not applicable