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Topochemical models for the prediction of permeability through blood–brain barrier

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Abstract

Relationship between the topochemical indices and permeability of diverse series of compounds through blood–brain barrier has been investigated. Three-topochemical indices, Wiener's topochemical index—a distance-based topochemical descriptor, molecular connectivity topochemical index—an adjacency based topochemical descriptor and eccentric connectivity topochemical index—an adjacency-cum-distance based topochemical descriptor, were used for the present investigation. A data set comprising of 28 compounds with established CNS permeation tendency was selected for present study. The values of all the three-topochemical indices in the original as well as in the normalized form for each of the 28 compounds comprising the data set were computed using an in-house computer program. Resultant data was analyzed and suitable models were developed after identification of the permeable ranges. Subsequently, permeability characteristic was assigned to each compound involved in the data set using these models, which was then compared with the reported permeability through blood–brain barrier. Accuracy of prediction was found to vary from a minimum of 83% to a maximum of ∼95% using these models.

Keywords: Topochemical indices; Wiener's topochemical index; Molecular connectivity topochemical index; Eccentric connectivity topochemical index; Permeability; Blood–brain barrier

1. Introduction

For central nervous system (CNS) acting drugs, a major rate-limiting step for uptake into the brain is passage through the blood–brain barrier (BBB) (Rubin and Staddon, 1999). BBB is the biological barrier that protects the brain by regulating the flow of numerous substances into the brain (Hanin, 1996). BBB is comprised of brain microvascular endothelial cells, which are connected by a tight junction that circumferentially surround the endothelial cell margin (Ballabh et al., 2004). The tight junctions between the endothelial cells seal off the vascular lumen from the abluminal side (Ulrich, 2005) and are responsible for preventing and/or restricting the passage of most compounds in blood into CNS (Rubin and Staddon, 1999; Ballabh et al., 2004). The delivery of drugs to human brain by microvascular route is so efficient that the drugs could be distributed to all parts of the brain once the vascular barrier is traversed. However, the transvascular route to the brain is virtually impenetrable by the majority of drugs (Jong and Huang, 2005). The chemistry-based approaches are straightforward and rely on lipid-mediated BBB drug transport as substances that readily permeate the BBB usually include small lipophilic or hydrophobic molecules with a molecular weight of less than 500 Da (Lipinski, 2000). The physiological integrity of the BBB is undoubtedly important to maintaining a homeostatic microenvironment for the cerebral tissue (Pardridge, 2003). Valid information about permeability of drug candidates at BBB is needed to decrease the attrition rate in drug discovery/development, as poor pharmacokinetics has been recognized as one of the leading causes of failure (Kennedy, 1997; Van de Waterbeemd and Gifford, 2003).

The characterization of structure in studying relationship between molecular structure and properties has attracted considerable attention in recent years (Randic, 1984; Rouvray, 1988; Basak et al., 1988). For the purpose of studying the relationship between chemical structure and property, the bonding topology of a molecule is converted into an expression, which may be

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a matrix, a polynomial, a sequence of numbers or a numerical index. Such a numerical index characterizing chemical structure is called a topological index (Basak, 1999). Topological indices have proved useful in the prediction of diverse physical, chemical and biological properties (Kier and Hall, 1986). Topostructural and topochemical indices are numerical indices, which are usually derived from molecular graphs. The topostructural indices only encode information about the adjacency and distance of atoms (vertices) in molecular structure (graph), irrespective of the chemical nature of the atoms involved in bonding or factors such as hybridization states and the number of core/valence electrons in individual atoms. Topochemical indices are parameters that quantify information regarding the topology (connectivity of atoms), as well as specific chemical properties of the atoms comprising a molecule (Gute and Basak, 1997). However, a limited number of topostructural and topochemical indices have been successfully employed in structure activity relationship (SAR) studies. These topostructural indices include, Wiener's index, W (Wiener, 1947a,b), Hosoya's index (Hosoya, 1971, 1972), Randic's molecular connectivity index, χ (Randic, 1975; Gupta et al., 2001a), Zagreb group parameters, M_1 and M_2 (Gutman et al., 1975; Gutman and Randic, 1977), Balaban's index, J (Balaban et al., 1980; Balaban, 1985), the higher-order connectivity indices, ${}^n\chi$, for the paths of length n defined by Kier and Hall (1986), eccentric connectivity index (Sharma et al., 1997; Gupta et al., 2002a; Lather and Madan, 2003; Kumar and Madan, 2004) and superpendentic index (Gupta et al., 1999). Topochemical indices which have been successfully employed in SARs include molecular connectivity topochemical index (Goel and Madan, 1995; Dureja and Madan, 2005), eccentric adjacency topochemical index (Gupta et al., 2003), eccentric connectivity topochemical index (Kumar et al., 2004), Weiner's topochemical index (Bajaj et al., 2004a), superadjacency topochemical index (Bajaj et al., 2004b) and Zagreb topochemical index, M_1 (Bajaj et al., 2005), etc.

In the present study, relationship of Wiener's topochemical index—a distance-based topochemical descriptor, molecular connectivity topochemical index—an adjacency-based topochemical descriptor and eccentric connectivity topochemical index—an adjacency-cum-distance based topochemical descriptor in the original and their normalized forms with permeability through blood–brain barrier has been investigated.

2. Methodology

2.1. Calculations of topochemical indices

2.1.1. Wiener's topochemical index (W_c)

Wiener's topochemical index (Bajaj et al., 2004a) is defined as the sum of the chemical distances between all the pairs of vertices in hydrogen suppressed molecular graph, i.e.

$$W_c = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{i_c j_c} \quad (1)$$

where $P_{i_c j_c}$ is the chemical length of the path that contains the least number of edges between vertex i and j in the graph G and n is the maximum possible number of i and j. It is a modified form of oldest and most widely used distance-based topological index—Wiener's index (Wiener, 1947a,b) and this modified index takes into consideration the presence as well as relative position of hetero-atoms in a molecular structure.

The normalized Wiener's topochemical index (nW_c) values were calculated as the ratio of Wiener's topochemical index value and total number of vertices present in the compound.

2.1.2. Molecular connectivity topochemical index (χ^A)

It is a modified form of one of the most widely used adjacency based topological index—molecular connectivity index (Randic, 1975; Gupta et al., 2001a) and it takes into consideration the presence as well as relative position of heteroatoms in a molecular structure. The molecular connectivity topochemical index (Goel and Madan, 1995; Dureja and Madan, 2005) is defined as the summation of the modified bond values of adjacent vertices for all the edges in the hydrogen suppressed molecular graph as per the following equation:

$$\chi^A = \sum_{i=1}^{n} (V_i^c V_j^c)^{-1/2} \quad (2)$$

where n is the number of vertices, V_i^c and V_j^c are the modified degrees of adjacent vertices i and j forming the edge $\{i, j\}$ in a graph G. The modified degree of a vertex can be obtained from the adjacency matrix by substituting row element corresponding to heteroatom, with relative atomic weight with respect to carbon atom.

The normalized molecular connectivity topochemical index (nχ^A) values were calculated as the ratio of Molecular connectivity topochemical index value to that of total number of vertices present in the compound.

Eccentric connectivity topochemical index (ξ_c^c): Eccentric connectivity topochemical index (Kumar et al., 2004) is defined as the summation of the product of chemical eccentricity and the chemical degree of each vertex in the hydrogen suppressed molecular graph having n vertices, that is,

$$\xi_c^c = \sum_{i=1}^{n} (E_{i_c} V_{i_c}) \quad (3)$$

where V_{i_c} is the chemical degree of vertex i, E_{i_c} the chemical eccentricity of the vertex i and n is the number of the vertices in graph G. Eccentric connectivity topochemical index is a modified form of an adjacency-cum-distance based topological index—eccentric connectivity index (Sharma et al., 1997; Gupta et al., 2002a,b; Lather and Madan, 2003; Kumar and Madan, 2004) and this modified index takes into consideration the presence as well as relative position of heteroatoms in a molecular structure.

The normalized eccentric connectivity topochemical index nξ_c^c values were calculated as the ratio of eccentric connectivity topochemical index value to that of total number of vertices present in the compound.

2.2. Model development

A data set comprising of 28 compounds of diverse series but with established CNS permeation tendency on the basis of broad clinical experience or unambiguous experimental data (Seelig et al., 1994) was selected for the present investigation. The compounds are enlisted in Tables 1 and 2.

The values of the Wiener's topochemical index/normalized Wiener's topochemical index were computed for each compound using an in-house computer program. Resultant data was analyzed and a suitable model was developed after identification of the permeability range by moving average analysis (Gupta et al., 2001b). The permeability of the compounds were reported as CNS^+, which permeate easily into the central nervous system, and the compounds, which did not permeate or permeate only weakly were reported as CNS^- (Seelig et al., 1994). Subsequently, characteristic permeability was assigned to each compound which was then compared with the reported permeability. The percentage degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to the total number of compounds present in that range (Gupta et al., 2001b). 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 permeable and impermeable ranges.

Aforementioned procedure was similarly followed for molecular connectivity topochemical index/normalized molecular connectivity topochemical index and eccentric connectivity topochemical index/normalized eccentric connectivity topochemical index. The results are summarized in Tables 1–3.

3. Results and discussion

An important aspect of drug design is the consideration of the potential for penetration of the blood–brain barrier by any new candidate drug molecule (Rose and Hall, 2002). In drug design, topological index based methods have resulted in the discovery of new lead from the analysis of databases (Lajiness, 1990). The topological indices are numerical graph invariants that quantify certain aspects of molecular structure and are sensitive to such structural features as size, shape, bond order, branching, and neighborhood patternsf of atoms in the molecules. They can be derived from simple linear graphs, multigraphs, weighted graphs, and weighted pseudographs (Gute and Basak, 1997). Molecular topology as represented by the connectivity of the

Table 1
Relationship of Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index with permeability through blood–brain barrier

Compound no.	Compound	W_c	χ^A	ξ_c^c	Permeability through blood–brain barrier			Reported
					Predicted			
					W_c	χ^A	ξ_c^c	
1	(R)-Apomorphine HCl	691.754	9.427	297.637	+	+	+	+
2	Chlorpromazine HCl	941.131	9.624	404.227	±	+	+	+
3	Clonidine HCl	339.73	5.991	215.087	+	+	+	+
4	Desipramine HCl	781.378	9.713	332.593	+	+	+	+
5	Doxylamine succinate	842.996	9.308	326.036	+	+	+	+
6	*cis*-Flupentixol 2HCl	2733.956	13.4	911.889	±	±	±	+
7	Haloperidol HCl	2103.394	11.799	855.76	±	+	±	+
8	Imipramine HCl	910.056	10.039	351.653	+	+	+	+
9	Naltrxone HCl	1226.01	11.652	464.36	±	+	±	+
10	Perphenazine 2HCl	2142.776	12.086	845.895	±	+	±	+
11	Promazine HCl	846.392	9.087	367.219	+	+	+	+
12	Promethazine HCl	801.392	9.002	325.55	+	+	+	+
13	Roxindole methane sulfonate	2110.723	12.548	765.022	±	±	±	±
14	Tamitinol 2HCl	505.519	6.969	281.14	+	+	+	+
15	Thiopental sodium	422.01	6.981	231.353	+	+	+	+
16	Thioridazine HCl	1577.432	11.087	605.511	±	+	±	+
17	Astemizole 2HCl	4262.229	16.082	1260.957	−	−	−	−
18	Carebastine	5670.657	17.411	1357.001	−	−	−	−
19	Domperidone HCl	3004.191	13.744	1061.392	−	−	−	−
20	Ebastine methane sulfonate	4828.832	16.605	1202.696	−	−	−	−
21	Loperamide HCl	3560.914	15.699	1032.901	−	−	−	−
22	Terfenadine	4485.921	16.553	1118.221	−	−	−	−
23	Atenolol	936.152	8.577	414.767	±	+	±	−
24	Mequitazine	1147.563	10.737	446.046	±	+	±	−
25	Salbutamol hemisulfate	577.344	7.541	257.029	+	+	+	−
26	Carmoxirol HCl	2583.559	13.388	866.908	±	±	±	−
27	Furosemide	1104.947	8.274	510.696	±	+	±	−
28	Pirenzepine HCl	1609.864	12.093	562.432	±	±	±	−

+, Permeable compound; −, impermeable compound; ±, compounds in the transitional range, where permeability could not be specifically assigned.

Table 2
Relationship of normalized Wiener's topochemical index and normalized eccentric connectivity topochemical index with permeability through blood–brain barrier

Compound no.	Compound	nW_c	$n\xi_c^c$	Permeability through blood–brain barrier		Reported
				Predicted		
				nW_c	$n\xi_c^c$	
1	(*R*)-Apomorphine HCl	34.588	14.882	+	+	+
2	Chlorpromazine HCl	43.387	19.249	+	+	+
3	Clonidine HCl	24.266	15.363	+	+	+
4	Desipramine HCl	39.069	16.63	+	+	+
5	Doxylamine succinate	42.15	16.302	+	+	+
6	*cis*-Flupentixol 2HCl	91.132	30.396	±	±	+
7	Haloperidol HCl	80.9	32.914	±	−	+
8	Imipramine HCl	43.336	16.745	+	+	+
9	Naltrxone HCl	49.04	18.574	+	+	+
10	Perphenazine 2HCl	79.362	31.294	±	±	+
11	Promazine HCl	42.32	18.361	+	+	+
12	Promethazine HCl	40.07	16.278	+	+	+
13	Roxindole methane sulfonate	81.182	29.424	±	±	+
14	Tamitinol 2HCl	31.595	17.571	+	+	+
15	Thiopental sodium	26.376	14.46	+	+	+
16	Thioridazine HCl	63.097	24.22	±	±	+
17	Astemizole 2HCl	125.36	37.087	−	−	−
18	Carebastine	153.261	36.675	−	−	−
19	Domperidone HCl	100.14	35.38	−	−	−
20	Ebastine methane sulfonate	137.967	34.363	−	−	−
21	Loperamide HCl	104.733	30.379	−	±	−
22	Terfenadine	128.169	31.949	−	−	−
23	Atenolol	49.271	21.83	±	±	−
24	Mequitazine	49.894	19.393	±	±	−
25	Salbutamol hemisulfate	33.961	15.119	+	+	−
26	Carmoxirol HCl	92.27	30.961	−	±	−
27	Furosemide	52.617	24.319	±	±	−
28	Pirenzepine HCl	61.918	21.632	±	±	−

+, Permeable compound; −, impermeable compound; ±, compounds in the transitional range, where permeability could not be specifically assigned.

atoms can relate physical properties and biological activity with the analogue (Gupta et al., 2002b).

Relationship of Wiener's topochemical index—a distance-based topochemical descriptor, molecular connectivity topochemical index—an adjacency-based topochemical descriptor and eccentric connectivity topochemical index—an adjacency-cum-distance based topochemical descriptor in the original and their normalized form with permeability through

Table 3
Proposed models for the prediction of permeability through blood–brain barrier

Index	Nature of range in the proposed model	Index value	Number of compounds in the range	Number of compounds predicted correctly	Percent accuracy	Overall accuracy of prediction
W_c	Permeable	≤910.056	10	09	90.00	93.75
	Transitional	>910.056 to <3004.191	12	NA[a]	NA	
	Impermeable	≥3004.191	06	06	100.00	
nW_c	Permeable	≤49.04	12	11	91.67	94.74
	Transitional	>49.04 to <92.27	09	09	NA	
	Impermeable	≥92.27	07	07	100.00	
χ^A	Permeable	≤12.086	18	14	77.78	83.33
	Transitional	>12.086 to <13.744	04	NA	NA	
	Impermeable	≥13.744	06	06	100.00	
ξ_c^c	Permeable	≤404.227	11	10	90.91	94.12
	Transitional	>404.227 to <1032.901	11	NA	NA	
	Impermeable	≥1032.901	06	06	100.00	
nξ_c^c	Permeable	≤19.249	12	11	91.67	88.89
	Transitional	>19.249 to <31.949	10	10	NA	
	Impermeable	≥31.949	06	05	83.33	

[a] Not applicable.

blood–brain barrier was studied and suitable models were developed for prediction of permeability through blood–brain barrier. Ability to predict the permeability through blood–brain barrier of the compounds is unquestionably of utmost significance. Methods have been developed for the estimation of permeability through blood–brain barrier with varying success and applicability (Basak et al., 1996; Ma et al., 2005). Authors have made an attempt for a simpler approach to predict the permeability through blood–brain barrier of diverse series of compounds. The methodology used in the present studies aims at the development of suitable models for providing permeable compounds through exploitation of the permeable ranges in the proposed models derived from topochemical indices. Proposed models are unique and differ widely from conventional QSAR models. Both system of modeling have their advantages and limitations. In the instant case, the modeling system adopted has distinct advantage of identification of narrow permeable ranges, which may be erroneously skipped during routine regression analysis in conventional QSAR modeling. Since the ultimate goal is to provide permeable compounds, therefore, these permeability ranges can play vital role in providing permeable compounds.

Retrofit analysis of the data in Tables 1–3 reveals the following information with regard to models based upon Wiener's topochemical index:

- A total of 16 compounds out of 28 compounds were classified as permeable or impermeable compounds using the model based upon Wiener's topochemical index.
- Out of 16 compounds, 15 compounds were classified correctly in both the permeable and impermeable ranges using the model based upon Wiener's topochemical index. The overall accuracy of prediction was found to be 93.75%.
- The permeable range had Wiener's topochemical index values of $\leq$910.056. About 90% of the compounds in the permeable range were predicted correctly.
- An impermeable range with Wiener's topochemical index value of $\geq$3004.191 was observed. About 100% of the compounds in the impermeable range were predicted correctly.
- A transitional range between permeable and impermeable range with Wiener's topochemical index value >910.056 to <3004.191 was observed. A total of 12 compounds were present in the transitional range.

Retrofit analysis of the data in Tables 2 and 3 reveals the following information with regard to models based upon normalized Wiener's topochemical index:

- A total of 19 compounds out of 28 compounds were classified as permeable or impermeable compounds using the model based upon normalized Wiener's topochemical index.
- Out of 19 compounds, 18 compounds were classified correctly in both the permeable and impermeable ranges using the model based upon normalized Wiener's topochemical index. The overall accuracy of prediction was found to be 94.74%.
- The permeable range had normalized Wiener's topochemical index values of $\leq$49.04. Approximately 92% of the compounds in the permeable range were predicted correctly.
- An impermeable range with normalized Wiener's topochemical index value of $\geq$92.27 was observed. About 100% of the compounds in the impermeable range were predicted correctly.
- A transitional range between permeable and impermeable range with normalized Wiener's topochemical index value >49.04 to <92.27 was observed. A total of 09 compounds were present in the transitional range.

Retrofit analysis of the data in Tables 1 and 3 reveals the following information with regard to model based upon molecular connectivity topochemical index:

- A total of 24 compounds out of a 28 compounds were classified as permeable or impermeable compounds using the model based upon molecular connectivity topochemical index.
- Out of 24 compounds, 20 compounds were classified correctly in both the permeable and impermeable ranges using the model based upon molecular connectivity topochemical index. The overall accuracy of prediction was found to be 83.33%.
- The permeable range had molecular connectivity topochemical index values of $\leq$12.086. About 77.78% of the compounds in the permeable range were predicted correctly.
- An impermeable range with molecular connectivity topochemical index values of $\geq$13.744 were observed. About 100% of the compounds in the impermeable range were predicted correctly.
- A transitional range between permeable and impermeable range with molecular connectivity topochemical index value $\geq$12.086 to <13.744 was observed. A total of 04 compounds were present in the transitional range.

Retrofit data analysis in respect of normalized molecular connectivity topochemical index revealed that a suitable model could not be developed.

Retrofit analysis of the data in Tables 1 and 3 reveals the following information with regard to eccentric connectivity topochemical index:

- A total of 17 compounds out of a 28 compounds were classified as permeable or impermeable compounds using the model based upon eccentric connectivity topochemical index.
- Out of 17 compounds, 16 compounds were classified correctly in both the permeable and impermeable ranges using the model based upon eccentric connectivity topochemical index. The overall accuracy of prediction was found to be 94.12%.
- The permeable range had eccentric connectivity topochemical index values of $\leq$404.227. About 90.91% of the compounds in the permeable range were predicted correctly.
- An impermeable range with eccentric connectivity topochemical index value of $\geq$1032.901was observed. About 100% of the compounds in the impermeable range were predicted correctly.
- A transitional range between permeable and impermeable range with eccentric connectivity index value >404.227 to

<1032.901 was observed. A total of 11 compounds were present in the transitional range.

Retrofit analysis of the data in Tables 2 and 3 reveals the following information with regard to normalized eccentric connectivity topochemical index:

- A total of 18 compounds out of a 28 compounds were classified as permeable or impermeable compounds using the model based upon normalized eccentric connectivity topochemical index.
- Out of 18 compounds, 16 compounds were classified correctly in both the permeable and impermeable ranges using the model based upon normalized eccentric connectivity topochemical index. The overall accuracy of prediction was found to be ∼89%.
- The permeable range had normalized eccentric connectivity topochemical index values of ≤19.249. Approximately 92% of the compounds in the permeable range were predicted correctly.
- An impermeable range with normalized eccentric connectivity topochemical index values of ≥31.949 were observed. About 83% of the compounds in the impermeable range were predicted correctly.
- A transitional range between permeable and impermeable range with normalized eccentric connectivity index value >19.249 to <31.949 was observed. A total of 10 compounds were present in the transitional range.

4. Conclusion

Investigations on use of various topochemical indices on a data set comprising of 28 diverse series of compounds but with established CNS permeation tendency has led to successful development of models which are highly beneficial for prediction of permeability through blood–brain barrier. The overall accuracy of prediction of models varied from minimum of ∼83% for a model based on molecular connectivity topochemical index to a maximum of 95% in case of a model based upon normalized Wiener's topochemical index. High predictability of the proposed models derived from the topochemical indices offer a vast potential for providing compounds for the development of potent therapeutic agents with high permeability through blood–brain barrier.

References

Bajaj, S., Sambi, S.S., Madan, A.K., 2005. Prediction of anti-inflammatory activity of *N*-arylanthranilic acids: computational approach using refined Zagreb indices. Croat. Chem. Acta 78, 165–174.

Bajaj, S., Sambi, S.S., Madan, A.K., 2004a. Predicting anti-HIV activity of phenethylthiazolethiourea (PETT) analogs: computational approach using Wiener's topochemical index. J. Mol. Struct. Theochem. 684, 197–203.

Bajaj, S., Sambi, S.S., Madan, A.K., 2004b. Prediction of carbonic anhydrase activation by tri-/tetrasubstituted-pyridinium-azole compounds: a computational approach using novel topochemical descriptor. Quant. Struct. Act. Rel. Comb. Sci. 23, 506–514.

Balaban, A.T., 1985. Applications of graph theory in chemistry. J. Chem. Inf. Comput. Sci. 25, 334–343.

Balaban, A.T., Chiriac, A., Motoc, I., Simon, Z., 1980. Steric Fit in QSAR. Lecture Notes in Chemistry, vol. 15, 22–27.

Ballabh, P., Braun, A., Nedergaard, M., 2004. The blood–brain barrier: an overview: structure, regulation, and clinical implications. Neurol. Dis. 16, 1–13.

Basak, S.C., 1999. Information theoretic indices of neighborhood complexity and their applications. In: Devillers, J., Balaban, A.T. (Eds.), Topological Indices and Related Descriptors in QSAR and QSPR. Gordon and Breach Science Publishers, Amsterdam, The Netherlands, pp. 563–593.

Basak, S.C., Gute, B.D., Drewes, L.R., 1996. Predicting blood–brain transport of drugs: a computational approach. Pharm. Res. 13, 775–778.

Basak, S.C., Magnuson, V.R., Niemi, G.J., Regal, R.R., 1988. Determining structural similarity of chemicals using graph-theoretic indices. Discrete Appl. Math. 19, 17–44.

Dureja, H., Madan, A.K., 2005. Topochemical models for prediction of cyclin-dependent kinase 2 inhibitory activity of indole-2-ones. J. Mol. Model 11, 525–531.

Goel, A., Madan, A.K., 1995. Structure–activity study on anti-inflammatory pyrazole carboxylic acid hydrazide analogs using molecular connectivity indices. J. Chem. Inf. Comput. Sci. 35, 510–514.

Gupta, S., Singh, M., Madan, A.K., 1999. Superpendentic index: a novel topological descriptor for prediction of biological activity. J. Chem. Inf. Comput. Sci. 39, 272–277.

Gupta, S., Singh, M., Madan, A.K., 2001a. Application of graph theory: relationship of molecular connectivity index and atomic molecular connectivity index with anti-HSV activity. J. Mol. Struct. Theochem. 571, 147–152.

Gupta, S., Singh, M., Madan, A.K., 2001b. Predicting anti-HIV activity: computational approach using a novel topological descriptor. J. Comput. Aid. Mol. Des. 15, 671–678.

Gupta, S., Singh, M., Madan, A.K., 2002a. Application of graph theory: relationship of eccentric connectivity index and Wiener's index with anti-inflammatory activity. J. Math. Anal. Appl. 266, 259–268.

Gupta, S., Singh, M., Madan, A.K., 2002b. Eccentric distance sum: a novel graph invariant for predicting biological and physical properties. J. Math. Anal. Appl. 275, 386–401.

Gupta, S., Singh, M., Madan, A.K., 2003. Novel topochemical descriptors for predicting anti-HIV activity. Indian J. Chem. 42A, 1414–1425.

Gute, B.D., Basak, S.C., 1997. Predicting acute toxicity (LC_{50}) of benzene derivatives using theoretical molecular descriptors: a hierarchical QSAR approach. SAR QSAR Environ. Res. 7, 117–131.

Gutman, I., Randic, M., 1977. Algebric characterization of skeletal branching. Chem. Phys. Lett. 47, 15–19.

Gutman, I., Ruscic, B., Trinajstic, N., Wicox, C.F., 1975. Graph theory and molecular orbitals. XII. Acyclic polyenes. J. Chem. Phys. 62, 3399–3405.

Hanin, I., 1996. The Gulf War, stress and a leaky blood–brain barrier. Nat. Med. 2, 1307–1308.

Hosoya, H., 1971. Topological index; newly proposed quantity characterizing the topological nature of structure of isomers of saturated hydrocarbons. Bull. Chem. Soc. Jpn. 44, 2332–2337.

Hosoya, H., 1972. Topological index as strong sorting device for coding chemical structure. J. Chem. Doc. 12, 181–183.

Jong, A., Huang, S.-H., 2005. Blood–brain barrier drug discovery for central nervous system infections. Curr. Drug Tar. Infect. Dis. 5, 65–72.

Kennedy, T., 1997. Managing the drug discovery/development interface. Drug Discov. Today 2, 436–444.

Kier, L.B., Hall, L.H., 1986. Published studies using molecular connectivity. In: Molecular Connectivity in Structure–Activity Analysis. Letchworth Research Studies Press, UK, pp. 436–444.

Kumar, V., Madan, A.K., 2004. Topological models for the prediction of cyclin-dependent kinase 2 inhibitory activity of aminothiazoles. Math. Commun. Math. Comput. Chem. 51, 59–78.

Kumar, V., Sardana, S., Madan, A.K., 2004. Predicting anti-HIV activity of 2,3-diaryl-1, 3-thiazolidin-4-ones: computational approach using reformed eccentric connectivity index. J. Mol. Model 10, 399–407.

Lajiness, M.S., 1990. Molecular similarity-based methods for selecting compounds for screening. In: Rouvray, R.H. (Ed.), Computational Chemical Graph Theory. Nova, New York, pp. 299–316.

Lather, V., Madan, A.K., 2003. Predicting acyl-coenzyme A: cholesterol o-acyltransferase inhibitory activity: computational approach using topological descriptors. Drug Des. Disc. 18, 117–122.

Lipinski, C.A., 2000. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Meth. 44, 235–249.

Ma, X.-L., Chen, C., Yang, J., 2005. Predictive model of blood–brain barrier penetration of organic compounds. Acta Pharmacol. Sinica 26, 500–512.

Pardridge, W.M., 2003. Blood–brain barrier drug targeting: the future of brain drug development. Mole. Interv. 3, 90–105.

Randic, M., 1975. On characterization of molecular branching. J. Am. Chem. Soc. 97, 6609–6615.

Randic, M., 1984. On molecular identification numbers. J. Chem. Inf. Comput. Sci. 24, 164–175.

Rose, K., Hall, L.H., 2002. Modeling blood–brain barrier partitioning using the electrotopological state. J. Chem. Inf. Comput. Sci. 42, 651–666.

Rouvray, D.H., 1988. The challenge of characterizing branching molecular species. Discrete Appl. Math. 19, 317–338.

Rubin, L.L., Staddon, J.M., 1999. The cell biology of the blood–brain barrier. Annu. Rev. Neurosci. 22, 11–28.

Seelig, A., Gottschlich, R., Devant, R.M., 1994. A method to determine the ability to diffuse through the blood–brain barrier. Proc. Natl. Acad. Sci. USA 91, 68–72.

Sharma, V., Goswami, R., Madan, A.K., 1997. Eccentric connectivity index: a novel highly discriminating topological descriptor for structure property and structure activity studies. J. Chem. Inf. Comput. Sci. 37, 273–282.

Ulrich, B., 2005. How to measure drug transport across the blood–brain barrier. Neurorx. 2, 15–26.

Van de Waterbeemd, H., Gifford, E., 2003. ADMET in silico modelling: towards prediction paradise? Nat. Rev. Drug Discov. 2, 192–204.

Wiener, H., 1947a. Correlation of heat of isomerization and difference in heat of vaporization of isomers among paraffin hydrocarbons. J. Am. Chem. Soc. 69, 2636–2638.

Wiener, H., 1947b. Influence of interatomic forces on paraffin properties. J. Chem. Phys. 15, 766.