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Original research paper

Validation of topochemical models for the prediction of permeability through the blood-brain barrier

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Recently published topochemical models for permeability through the blood-brain barrier were validated and cross-validated in the present study. Five models based on 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, for permeability of structurally and chemically diverse molecules through blood-brain barrier were used in the present investigation. A data set comprising 62 structurally and chemically diverse compounds was selected. This data set was divided into two sets of 31 compounds each – one to serve as the validation set and other as the cross-validation set. The values of all the three-topochemical indices in the original as well as in the normalized form for each of the 31 compounds of the validation set were computed using an in-house computer program. Resultant data was analyzed and each compound was assigned a permeability characteristic using topochemical models, which was then compared with the reported permeability through the blood-brain barrier. Accuracy of prediction of these models was calculated. The same procedure was similarly followed for the cross-validation set. Studies revealed accuracy of prediction of the order of 70–80% during validation. Surprisingly, very high predictability of the order of 77–91% was observed during cross-validation. High predictability observed during validation as well as cross-validation authenticates topochemical models for prediction of permeability through the blood-brain barrier.

Keywords: topochemical indices, Wiener's topochemical index, molecular connectivity topochemical index, eccentric connectivity topochemical index, permeability, blood--brain barrier

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An important aspect of drug design is the consideration of the potential for penetration of the blood-brain barrier by a new candidate drug molecule (1). There has been a surge in computational efforts to compute absorption, distribution, metabolism, excretion, and toxicity properties, including blood-brain barrier (BBB) partitioning, of structurally diverse compounds, including drugs (2–5). A good example of the great utility of a predictive computational model in drug discovery is the model for predicting BBB penetration (6). Prediction of passage across the BBB is of importance for centrally acting drugs or peripherally acting drugs, which should be devoid of CNS side effects (7). The BBB is a selective barrier formed by the endothelial cells that line cerebral microvessels. It acts as a physical barrier because complex tight junctions between adjacent endothelial cells force most molecular traffic to take a transcellular route across the BBB, rather than moving paracellularly through the junctions, like in most endothelia (8). Modeling blood-brain portioning is a challenging problem both because of the paucity of data and the task of establishing a useful relation between the molecular structure and measured blood-brain partitioning (1). Experimental determination of brain-blood partitioning is time-consuming, difficult and expensive (9). A broadly applicable method for predicting the BBB permeation of candidates at an early stage of discovery would have a great impact on drug research and development (10).

Physicochemical properties and biological activities of organic compounds change in a very systematic way with changes in chemical structure (11). Topological indices have been successfully employed in developing a suitable correlation between chemical structure and biological activity by translating chemical structures into numerical descriptors (12). Topostructural and topochemical indices fall into the category normally grouped together as topological indices. Topostructural indices are topological indices that encode information about the adjacency and distance of atoms in molecular structures, 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 about the topology (connectivity of atoms), as well as specific chemical properties of the atoms making a molecule (13).

The objective of the present study is to validate the recently published topochemical models (14) for the prediction of permeability through the blood-brain barrier using external validation and cross-validation sets. Validation and cross-validation of the topochemical models based on Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index in the original and their normalized forms for permeability through the blood-brain barrier have been investigated.

EXPERIMENTAL

Calculations of topochemical indices

Wiener's topochemical index (W_c) (15) is a modified form of the oldest and most widely used distance based topological index – Wiener's index (16) and this modified

index takes into consideration the presence as well as relative position of heteroatoms in a molecular structure. It is defined as the sum of chemical distances between all the pairs of vertices in a hydrogen suppressed molecular graph, *i.e.*:

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

where $P_{i_c j_c}$ is the chemical length of the path containing the smallest number of edges between vertex i and j in graph G, n is the maximum possible number of i and j.

The normalized Wiener topochemical index (nW_c) values were calculated as the ratio of Wiener's topochemical index value to the total number of vertices in a hydrogen suppressed molecular graph.

Molecular connectivity topochemical index (χ^A) (17, 18) is defined as the summation of the modified bond values of adjacent vertices for all the edges in the hydrogen suppressed molecular graph according to the following equation:

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

where n is the number of vertices, V_i^c and V_j^c are modified degrees of adjacent vertices i and j forming the edge $\{i, j\}$ in a graph G. This is a modified form of one of the most widely used adjacency based topological indices – molecular connectivity index (19) and it takes into consideration the presence as well as relative position of heteroatom(s) in a molecular structure.

The normalized molecular connectivity topochemical index ($n\chi^A$) was calculated as the ratio of the molecular connectivity topochemical index value to that of the total number of vertices in a hydrogen suppressed molecular graph.

The eccentric connectivity topochemical index (ξ_c^c) (20) is a modified form of an adjacency-cum-distance based topological index – eccentric connectivity index (21) and this modified index takes into consideration the presence as well as relative position of the heteroatom(s) in a molecular structure. The eccentric connectivity topochemical index 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:

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

where V_{ic} is the chemical degree of vertex i, E_{ic} is the chemical eccentricity of vertex i and n is the number of vertices in graph G.

The normalized eccentric connectivity topochemical index ($n\xi_c^c$) was calculated as the ratio of the eccentric connectivity topochemical index value to that of the total number of vertices in a hydrogen suppressed molecular graph.

The authors made an attempt at a simpler approach to predict the permeability through BBB of diverse series of compounds using topochemical models. These reported

Table I. Topochemical models derived from a training set of 28 chemically and structurally diverse compounds (14)

Index	Range in the model	Index value	Overall accuracy of prediction (%)
Wiener's topochemical index (W_c)	Permeable Transitional Impermeable	≤ 910.056 > 910.056 – < 3004.191 ≥ 3004.191	93.8
Normalized Wiener's topochemical index (nW_c)	Permeable Transitional Impermeable	≤ 49.04 > 49.04 – < 92.27 ≥ 92.27	94.7
Molecular connectivity topochemical index (χ^A)	Permeable Transitional Impermeable	≤ 12.086 > 12.086 – < 13.744 ≥ 13.744	83.3
Eccentric connectivity topochemical index (ξ_c^c)	Permeable Transitional Impermeable	≤ 404.227 > 404.227 – < 1032.901 ≥ 1032.901	94.1
Normalized eccentric connectivity topochemical index ($n\xi_c^c$)	Permeable Transitional Impermeable	≤ 19.249 > 19.249 – < 31.949 ≥ 31.949	88.9

topochemical models (Table I) were developed using a training set of 28 structurally and chemically different compounds with established CNS permeation tendency, having the predictability from 83 to 95% (14). The aforementioned topochemical models were validated by an external test set of 31 compounds and cross-validated using another external test set of 31 chemically and structurally diverse compounds.

A reliable and predictive model should be statistically significant and robust, provide accurate prediction for an external dataset not used during model development and have its application boundaries defined. Iyer *et al.* (22) have reported a BBB study on a training set of 56 structurally and chemically diverse molecules and 7 molecules for the test set. The authors have omitted one molecule (methane) from this data set for lack of sufficient computed properties and used the remaining 55 compounds of training set and 7 compounds of the test set. These 62 compounds were divided into two sets. Compounds having an odd serial number were designated as the test or validation set and those having an even number were separated as the cross-validation set. The 31 compounds for validation set are listed in Table II and 31 compounds for the cross-validation set are listed in Table III.

The values of Wiener's topochemical index/normalized Wiener's topochemical index were computed for each compound using an in-house computer program. Subsequently, characteristic permeability was assigned to each compound using the reported models (14), which was then compared with the reported permeability (22). Permeability was reported quantitatively as log BB value. The compounds possessing log BB values of ≤ –0.3 were considered to be permeable and compounds possessing log BB values of > –0.3 were considered to be impermeable for the purpose of the present study. Vari-

Table II. Relationships between topochemical indices and permeability through blood-brain barrier for validation set comprising of 31 compounds

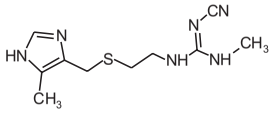
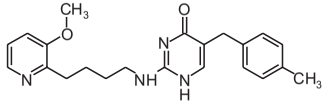
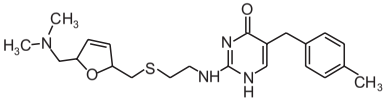
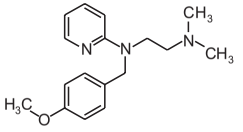
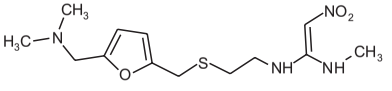
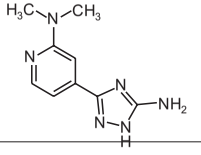
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted				Reported	
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
1		698.904	43.682	6.958	390.311	24.394	+	+	+	+	±	−
3		2739.88	97.853	13.092	899.333	32.119	±	−	±	±	−	−
5		3478.19	119.938	12.923	1173.39	40.462	−	−	±	−	−	−
7		1049.06	49.955	9.741	415.918	19.806	±	±	+	±	±	+
9		1479.41	70.448	8.865	633.454	30.164	±	±	+	±	±	−
11		386.201	25.747	6.749	218.52	14.568	+	+	+	+	+	−

Table II. continued

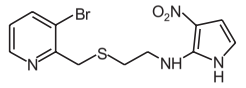
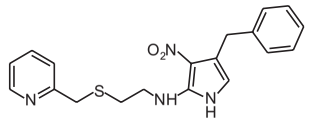
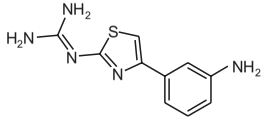
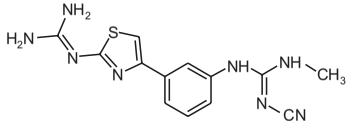
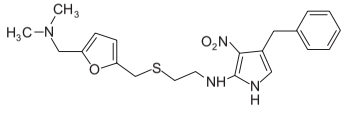
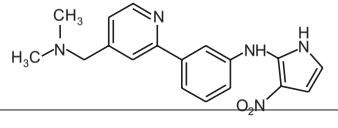
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted			Reported		
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
13		1250.09	62.505	8.197	743.368	37.168	±	±	+	±	−	−
15		2295.96	88.306	11.795	848.217	32.624	±	±	+	±	−	+
17		504.292	31.518	6.953	280.972	17.561	+	+	+	+	+	−
19		1268.79	57.672	9.694	530.286	24.104	±	±	+	±	±	−
21		3255.47	112.258	12.915	1075.72	37.094	−	−	±	−	−	−
23		1684.1	67.364	11.459	595.538	23.822	±	±	+	±	±	+

Table II. continued

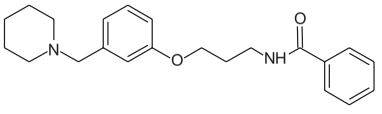
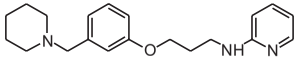
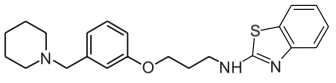
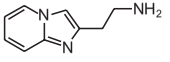
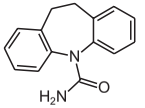
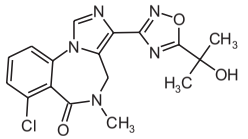
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted			Reported		
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
25		2264.03	87.078	12.432	795.744	30.606	±	±	±	±	±	+
27		1809.29	75.387	11.517	695.952	28.998	±	±	+	±	±	+
29		2593.08	96.04	12.553	960.121	35.56	±	−	±	±	−	+
31	Butanone	18.666	3.733	2.19	20.665	4.133	+	+	+	+	+	+
33	3-methylpentane	31	5.167	2.808	29	4.833	+	+	+	+	+	+
35	2-propanol	9.5	2.375	1.643	11.109	2.777	+	+	+	+	+	+
37	2-methylpentane	32	5.333	2.77	31	5.167	+	+	+	+	+	+
39	1,1,1-trifluoro-2-chloroethane	37.268	6.211	1.963	52.919	8.82	+	+	+	+	+	+
41	Diethylether	21.998	4.4	2.235	28.218	5.644	+	+	+	+	+	+
43	Ethanol	4.333	1.444	1.309	7.443	2.481	+	+	+	+	+	+
45	Halothane	98.809	12.351	2.377	177.248	22.156	+	+	+	+	±	+

Table II. continued

No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted				Reported	
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
47	Hexane	35	5.833	2.914	38	6.333	+	+	+	+	+	+
49	Methylcyclopentane	26	4.333	2.894	29	4.833	+	+	+	+	+	+
51	Propanol	10.5	2.625	1.825	15.665	3.916	+	+	+	+	+	+
53	Teflurane	93.997	11.75	2.436	168.081	21.01	+	+	+	+	±	+
55	Trichloroehtane	29.748	5.95	1.454	57.913	11.583	+	+	+	+	+	+
57		204.264	17.022	5.692	150.44	12.537	+	+	+	+	+	–
59		538.192	29.9	8.571	235.683	13.094	+	+	+	+	+	+
61		1628.326	62.628	11.417	603.393	23.207	±	±	+	±	±	–

(+) – Permeable compound, (–) – impermeable compound, (±) – compounds in the transitional range where permeability could not be specifically assigned.

Table III. Relationships between topochemical indices and permeability through blood-brain barrier for a cross-validation set comprising of another 31 compounds

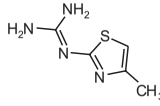
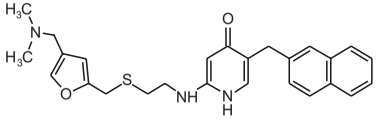
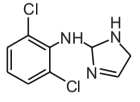
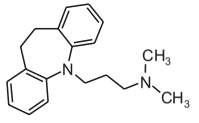
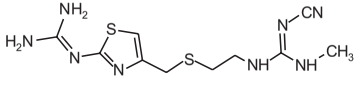
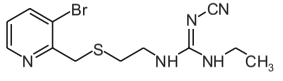
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted			Reported		
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
2		146.019	14.602	4.017	121.447	12.145	+	+	+	+	+	+
4		4445.05	138.908	14.569	1376.22	43.007	–	–	–	–	–	–
6		339.73	24.266	5.991	215.087	15.363	+	+	+	+	+	+
8		910.056	43.336	10.039	351.653	16.745	+	+	+	+	+	+
10		1315.98	65.799	8.228	626.207	31.31	±	±	+	±	±	–
12		1130.6	59.505	7.907	658.446	34.655	±	±	+	±	-	–

Table III. continued

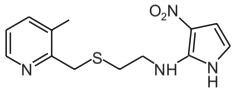
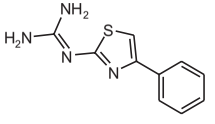
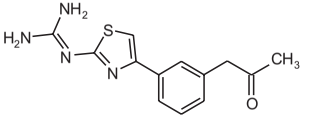
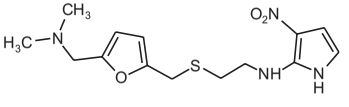
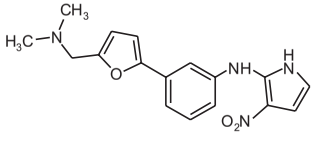
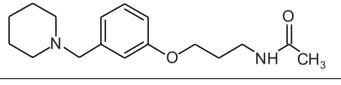
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted			Reported		
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
14		1056.58	55.61	8.323	520.118	27.375	±	±	+	±	±	−
16		426.536	28.436	6.596	258.794	17.253	+	+	+	+	+	+
18		828.565	43.609	8.235	396.473	20.867	+	+	+	+	±	−
20		1631.59	74.163	9.443	693.957	31.544	±	±	+	±	±	−
22		1556.05	64.835	10.908	588.595	24.525	±	±	+	±	±	+
24		1219.51	58.072	9.842	520.173	24.77	±	±	+	±	±	−

Table III. continued

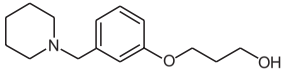
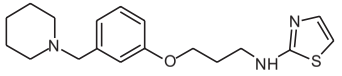
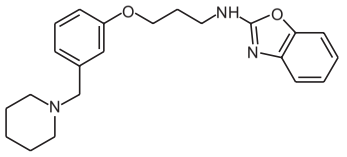
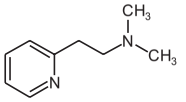
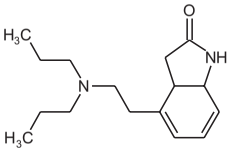
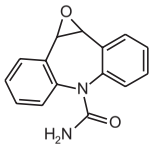
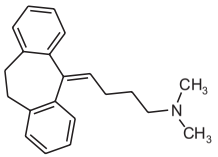
No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted				Reported	
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
26		738.583	41.032	8.551	375.768	20.876	+	+	+	+	±	+
28		1637.38	71.19	10.547	721.113	31.353	±	±	+	±	±	+
30		2528.2	93.637	12.879	886.768	32.843	±	−	±	±	−	+
32	Benzene	27	4.5	3	36	6	+	+	+	+	+	+
34	3-methylhexane	50	7.143	3.308	45	6.249	+	+	+	+	+	+
36	3-methylpropanol	18.666	3.733	2.187	21.331	4.266	+	+	+	+	+	+
38	2,2-dimethylbutane	28	4.667	2.561	24	4	+	+	+	+	+	+
40	1,1,1-trichloroethane	27.748	5.55	1.273	45.039	9.008	+	+	+	+	+	+
42	Enflurane	149.421	14.942	3.462	123.554	12.355	+	+	+	+	+	+
44	Fluroxene	81.617	10.202	3.105	73.236	9.155	+	+	+	+	+	+
46	Heptane	56	8	3.414	54	7.714	+	+	+	+	+	+
48	Isoflurane	152.421	15.242	3.451	115.948	11.595	+	+	+	+	+	+

Table III. continued

No.	Compound	W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	Permeability through blood-brain barrier					
							Predicted					Reported
							W_c	nW_c	χ^A	ξ_c^c	$n\xi_c^c$	
50	Pentane	20	4	2.414	24	4.8	+	+	+	+	+	+
52	Propanone	9.5	2.375	1.643	11.109	2.777	+	+	+	+	+	+
54	Toluene	42	6	3.394	45	6.249	+	+	+	+	+	+
56		179.511	16.319	5.094	127.821	11.62	+	+	+	+	+	+
58		779.532	41.028	8.999	334.016	17.58	+	+	+	+	+	+
60		607.024	31.949	8.962	266.232	14.012	+	+	+	+	+	–
62		889.849	42.374	10.133	341.41	16.258	+	+	+	+	+	+

(+) – Permeable compound, (–) – impermeable compound, (±) – compounds in the transitional range where permeability could not be specifically assigned.

ous researchers including Iyer *et al.* (22) and Abraham *et al.* (23) had reported that compounds with log BB values of > 0.3 are readily permeated into the brain whereas compounds with values <–1 are poorly permeated into the brain. The cut-off value consi- dered for the present study was the average value of the ranges reported by earlier researchers (22, 23). Accuracy of prediction of permeable and impermeable ranges as well as the overall degree of prediction of the validated model were also calculated. A similar procedure was followed for the molecular connectivity topochemical index and the eccentric connectivity topochemical index/normalized eccentric connectivity topochemical index.

The aforementioned procedure was similarly followed during cross-validation of the second set of 31 compounds. The results are summarized in Tables II and III.

RESULTS AND DISCUSSION

Among the pharmacokinetics issues in the design of new drugs, prediction of the BBB permeability is a crucial factor (24). The relationship of topochemical models based on Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index with permeability through BBB was evaluated for prediction of permeability through the blood-brain barrier.

All the 62 compounds reported by Iyer *et al.* (22) were employed for validation study of topochemical models. These compounds were divided equally into two different groups to constitute validation and cross-validation sets. Compounds having odd serial numbers were designated as validation set while those having even numbers were categorized as cross-validation set.

The accuracy of prediction for the test set and for the cross-validation set are shown in Table IV. The methodology used in the present study relates to validation of topochemical models. These models have high potential for providing permeable compounds through exploitation of permeable ranges in the models derived from topochemical indices. These models are unique and differ widely from conventional QSAR models. Both systems of modeling have their advantages and limitations. In the present case, the modeling system adopted has the 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, these permeability ranges can play a vital role in providing permeable compounds (14).

Retrofit analyses of the data (Tables I to IV) for validation and cross-validation sets reveal that the compounds were classified either as permeable or impermeable using the aforementioned models. A transitional range between permeable and impermeable ranges is ideal because it simply reveals the gradual change in permeability from the permeable range to an impermeable range. The overall accuracy of prediction during validation was found to vary from 70 to 80% (Table IV). However, the overall accuracy of prediction during cross-validation was found to be from 77 to 91% (Table IV). Four out of five models revealed overall accuracy of prediction > 87% during cross-validation.

Investigations on the use of topochemical indices on a test set comprising structurally and chemically diverse molecules have led to successful validation of topochemical

Table IV. Evaluation of topochemical models using validation set and cross-validation set

Index	Nature of range in the model	Number of compounds in the range		Number of compounds predicted correctly		Percent accuracy (%)		Overall accuracy of prediction (%)	
		Validation set	Cross-vali-dation set	Validation set	Cross-vali-dation set	Validation set	Cross-vali-dation set	Validation set	Cross-vali-dation set
W_c	Permeable	18	22	14	20	77.8	90.9	80.0	91.3
	Transitional	11	8	NA	NA	NA	NA		
	Impermeable	2	1	2	1	100.0	100.0		
$n W_c$	Permeable	18	22	14	20	77.8	90.9	77.3	87.5
	Transitional	9	7	NA	NA	NA	NA		
	Impermeable	4	2	3	1	75.0	50.0		
χ^A	Permeable	26	29	18	22	69.2	75.9	69.2	76.7
	Transitional	5	1	NA	NA	NA	NA		
	Impermeable	0	1	NA	1	NA	100.0		
ξ_c^c	Permeable	18	22	14	20	77.8	90.9	80.0	91.3
	Transitional	11	8	NA	NA	NA	NA		
	Impermeable	2	1	2	1	100.0	100.0		
$n\xi_c^c$	Permeable	15	20	12	19	80.0	95.0	76.2	91.3
	Transitional	10	8	NA	NA	NA	NA		
	Impermeable	6	3	4	2	66.7	66.7		

NA – Not applicable

models, which are highly beneficial for prediction of permeability through the blood--brain barrier. The overall accuracy of prediction of models for the validation set varied from a minimum of 70% for a model based on the molecular connectivity topochemical index to a maximum of 80% in case of models based upon Wiener's topochemical index and eccentric connectivity topochemical index. Surprisingly, these topochemical models also confirm the high prediction potential during cross-validation from a minimum of 77% for a model based on molecular connectivity topochemical index to a maximum of 91% in case of models based upon Wiener's topochemical index, eccentric connectivity topochemical index and normalized eccentric connectivity topochemical index. The results clearly reveal that the aforementioned topochemical models bear high predictability and can be utilized for permeability prediction of drugs and drug-like molecules.

CONCLUSIONS

Models derived from the topochemical indices can be used for fast screening of virtual libraries having millions of molecules and providing potent therapeutic agents with high permeability through the blood-brain barrier.

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SAŽETAK

Validacija topokemijskih modela za predviđanje permeabilnosti kroz krvno-moždanu barijeru

HARISH DUREJA i ANIL KUMAR MADAN

U ovom su radu validirani i unakrsno validirani nedavno objavljeni topokemijski modeli za permeabilnost kroz krvno-moždanu barijeru. Predviđanje prolaska kroz krvno-moždanu barijeru strukturno i kemijski različitih molekula provedeno je na pet modela koji se temelje na tri topološka indeksa, Wienerovom topološkom indeksu, topološkom indeksu molekularne povezanosti i topološkom indeksu ekscentrične povezanosti. Ukupno 62 spoja podijeljena su u dva seta koji su sadržavali 31 spoj. Jedan set upotrebljen je za validaciju, a drugi za unakrsnu validaciju. Vrijednosti svih triju topoloških indeksa u početnom setu i u normaliziranom setu su računate pomoću kompjutorskog programa. Rezultati su analizirani i svakom spoju je pridružena teorijska vrijednost permeabilnosti, koja je zatim uspoređivana s objavljenim eksperimentalnim podacima za permeabilnost kroz krvno-moždanu barijeru. Točnost predviđanja bila je između 70 i 80%. Isti postupak je proveden za unakrsno validacijski set, a točnost je bila iznenađujuće velika (77–91%), što ukazuje da se upotrebljeni topokemijski modeli mogu upotrijebiti za predviđanje permeabilnost kroz krvno-moždanu barijeru.

Ključne riječi: topokemijski indeksi, Wienerov topološki indeks, topološki indeks molekularne povezanosti, topološki indeks ekscentrične povezanosti, permeabilnost, krvno-moždana barijera

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