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Topochemical Models for the prediction of 5-HT$_6$ binding affinity of 3-ethyl-1*H*-indoles

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Abstract

Relationship between the topochemical indices and 5-HT$_6$ binding affinity of 3-ethyl-1*H*-indoles has been investigated. *Wiener's topochemical index* - a distance-based topochemical descriptor, *eccentric connectivity topochemical index* and *augmented eccentric connectivity topochemical index* - both adjacency-cum-distance based topochemical descriptors were used for the present investigation. A dataset comprising of 26 analogues of 3-ethyl-1*H*-indoles was selected for the present study. The values of *Wiener's topochemical index, eccentric connectivity topochemical index* and *augmented eccentric connectivity topochemical index* were computed for each of the 26 analogues using an in-house computer program. Resultant data was analyzed and suitable models were developed after identification of the active ranges. Subsequently, a biological activity was assigned to each compound using these models, which was then compared with the reported 5-HT$_6$ binding affinity. Statistical significance of proposed models was investigated using correlation analysis. Accuracy of prediction of proposed models was found to be 81 - 84%.

Keywords: Topochemical indices; Wiener's topochemical index; eccentric connectivity topochemical index; augmented eccentric connectivity topochemical index; 5-HT$_6$ binding affinity; 3-ethyl-1*H*-indoles.

Introduction

During past decade, topological indices (TIs) have emerged as powerful tools for predicting biological activities of molecules, designing combinatorial libraries and lead identification [1]. A topological descriptor is a numerical descriptor of molecular structure based on certain topological features of the molecular graph, offering an effective way of measuring molecular branching, shape, size and molecular similarity [2]. TIs have several obvious advantages when compared with geometrical, electrostatic and quantum descriptors: they are computed only from information contained in molecular graph, they have a unique value for a particular compound and their calculation requires small computational resources [3]. TIs have been successfully employed in developing a suitable correlation between chemical structure and biological activity by translating chemical structures into numerical descriptors [4, 5]. The topostructural and topochemical indices fall into the category normally grouped together as topological indices. Topostructural indices are topological indices which 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 regarding the topology (connectivity of atoms), as well as specific chemical properties of the atoms comprising a molecule [6]. A limited number of topostructural and topochemical indices have shown their successful applications in structure activity relationships. Some of the these topostructural indices include, *Wiener's* index [7], *Hosoya's index* [8], *Randic's molecular connectivity index* [9,10], *Zagreb group parameters* [11], *Balaban's index* [12], *the higher-order connectivity indices*, $^{n}\chi$, for the paths of length *n* defined by Kier and Hall [13], *eccentric connectivity index* [14], *Superpendentic index* [15], and *revised Wiener index* [16]. Topochemical indices, which have been successfully employed in structure activity relationship studies, include m*olecular connectivity topochemical index* [17,18], *eccentric connectivity topochemical index* [19], *Weiner's topochemical index* [20], *Zagreb topochemical indices* [21] *etc.*

The 5-hydroxytryptamine-6 (5-HT$_6$) was one of the additions to the 5-HT receptor family, selective antagonists have recently been developed and potential functional roles are now becoming apparent [22]. The serotonin 5-HT$_6$ receptor, a G-protein-coupled receptor,

displays high affinity for antipsychotic, antidepressant, and psychotropic drugs [23]. Various typical and atypical antipsychotic agents and antidepressants have been demonstrated to bind with high affinity at 5-HT_6 receptors that these receptors be targeted for the development of novel psychotherapeutic agents [24]. The 5-HT_6 receptors appear to regulate cholinergic neurotransmission in the brain, rather than the expected interaction as modulators of dopaminergic transmission. This interaction predicts a possible role for 5-HT_6 receptor antagonists in the treatment of learning and memory disorders [25]. 5-HT_6 receptors are expressed in brain regions associated with learning and memory, and blockade of their function increases central cholinergic and glutamatergic neurotransmission and enhances cognitive processes. This suggests that the 5-HT_6 receptor antagonist-induced enhancement of consolidation involves increased central glutamatergic neurotransmission [26]. The high affinity of a wide range of psychiatric drugs for the 5-HT_6 receptor, together with its almost exclusive expression in the CNS, being abundant in limbic and cortical regions, has stimulated significant research interest.[22] The 5-HT_6 receptor appears to regulate glutamatergic and cholinergic neuronal activity, and increasing evidence suggests that it may be involved in the regulation of cognition, feeding and, possibly, affective state and seizures [27]. Various typical and atypical antipsychotic agents and antidepressants have been demonstrated to bind with high affinity at 5-HT_6 receptors that these receptors be targeted for the development of novel psychotherapeutic agents. Evidence also suggest that 5-HT_6 receptor might modulate cholinergic transmission and GABA function leading to speculation that 5-HT_6 agents could play a role in memory impairment, anxiety, mood-dependent behavior and related disorders [24].

In the present study relationship of *Wiener's topochemical index*, *eccentric connectivity topochemical index* and *augmented eccentric connectivity topochemical index* with 5-HT_6 binding affinity of 3-ethyl-1*H*-indoles has been investigated.

Material and Method

Calculation of topochemical indices

Wiener's topochemical index (W_c): It is a topochemical version of oldest and most widely used distance based topological index – *Wiener's index* [7] and this modified index takes into

consideration the presence as well as relative position of heteroatoms in a hydrogen suppressed molecular structure. *Wiener's topochemical index* is defined as the sum of the chemical distances between all the pairs of vertices in hydrogen suppressed molecular graph [20], i.e.

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

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, n is the maximum possible number of *i* and *j*.

Eccentric connectivity topochemical index (ξ_c^c): Eccentric connectivity topochemical index is a topochemical version of an adjacency-cum-distance based topological index – e*ccentric connectivity index* [14] and this modified index takes into consideration the presence as well as relative position of heteroatom (s) in a hydrogen suppressed molecular structure. *Eccentric connectivity topochemical index* (ξ_c^c) 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 [19], that is

$$\xi_c{}^c = \sum_{i=1}^{n}\left(E_{ic} * V_{ic}\right) \qquad (2)$$

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

Augmented eccentric connectivity topochemical index ($^{Ac}\xi^c$): It is the topochemical version of the adjacency-cum-distance based *augmented eccentric connectivity index*[28] and this refined index takes into consideration the presence as well as relative position of heteroatom (s) in a hydrogen suppressed molecular structure. It is defined as the summation of the quotients of the product of adjacent vertex chemical degrees and chemical eccentricity of the concerned vertex, for all vertices in the hydrogen suppressed molecular graph [29]. It is expressed as

$$^{Ac}\xi^c = \sum_{i-1}^{n} \qquad (3)$$

where, M_{ic} is the product of chemical degrees of all vertices (v_j), adjacent to vertex *i,* E_{ic} is the chemical eccentricity*,* and *n* is the number of vertices in graph G.

Model design and analysis

A dataset comprising of 26 analogues of 3-ethyl-1*H*-indoles was selected for the present investigation [30]. The basic structure of 3-ethyl-1*H*-indoles is shown in Figure 1 and the various substituents enlisted in Table 1.

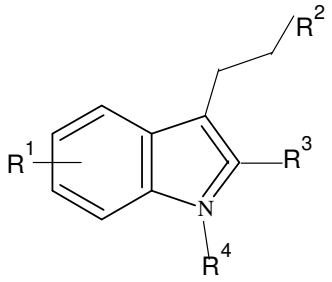

Figure 1. *Basic structure of 3-ethyl-1H-indoles*

Table 1. Relationships between topochemical indices and 5-HT_6 binding affinity

Cpd .No	R^1	R^2	R^3	R^4	W_c	$^{c}\xi_c$	$^{Ac}\xi^{c}$	5-HT_6 binding affinity Predicted Reported			
								W_c	$^{c}\xi_c$	$^{Ac}\xi_c$	
1.	5-OMe	NH_2	H	$PhSO_2$	1387.408	572.816	44.807	–	–	±	–
2.	5-OMe	NMe_2	H	$PhSO_2$	1744.267	626.828	45.704	+	+	+	+
3.	5-OMe	NMe_2	H	2-$ClC_6H_4SO_2$	1946.42	708.592	47.374	+	+	+	+
4.	5-OMe	NMe_2	H	3-$ClC_6H_4SO_2$	1965.42	750.718	44.02	+	+	±	+
5.	5-OMe	NMe_2	H	4-$ClC_6H_4SO_2$	1984.42	792.844	41.88	–	–	–	–
6.	5-OMe	NMe_2	H	4-$MeC_6H_4SO_2$	1959.945	692.33	44.129	+	+	±	–
7.	5-OMe	NMe_2	H	4-$MeOC_6H_4SO_2$	2214.277	782.421	42.586	–	–	–	–
8.	5-OMe	NMe_2	H	2-naphthyl-SO_2	2628.979	841.834	45.166	–	–	±	+
9.	5-OMe	NMe_2	H	2-thienyl-SO_2	1589.76	641.392	54.571	±	+	+	+
10.	5-OMe	NMe_2	H	PhCO	1376.377	468.152	24.908	–	–	–	–
11.	5-OMe	pyrrolidinyl	H	$PhSO_2$	2151.959	731.879	44.589	–	+	±	–
12.	5-OMe	piperidinyl	H	$PhSO_2$	2384.305	793.769	41.701	–	–	–	–
13.	5-OMe	4-methyl-piperazinyl	H	$PhSO_2$	2649	876.189	38.942	–	–	–	–

14.	5-OMe	morpholinyl	H	$PhSO_2$	2407.728	818.596	41.081	–	–	–	–
15.	H	NMe_2	H	$PhSO_2$	1407.599	567.044	44.683	±	–	±	+
16.	H	NMe_2	H	$MeSO_2$	700.047	356.963	36.584	–	–	–	–
17.	5-OBn	NMe_2	H	$PhSO_2$	3240.259	975.012	36.87	–	–	–	–
18.	5-OH	NMe_2	H	$PhSO_2$	1561.935	593.32	45.643	±	–	±	–
19.	5-OH	NMe_2	H	PhCO	1213.052	435.619	24.437	–	–	–	–
20.	5-OH	NMe_2	H	*t*-BuOCO	1111.021	386.266	24.741	–	–	–	–
21.	5-CN	NMe_2	H	$PhSO_2$	1738.457	618.528	46.112	±	–	+	–
22.[A]	5-OMe	NMe_2	H	$PhSO_2$	1744.267	626.828	45.704	+	+	+	–
23.	5-OMe	NMe_2	Me	$PhSO_2$	1871.774	643.496	49.038	+	+	+	+
24.	5-OMe	NMe_2	Me	H	536.176	262.702	20.172	–	–	–	–
25.	H	NMe_2	CO_2Et	H	724.173	296.782	22.95	–	–	–	–
26.	H	NMe_2	[B]	H	2249.414	727.646	22.235	–	+	–	+

+, Active analogue

–, Inactive Analogue

±, Transistional analogue where activity could not be specifically assigned

[A]indoline

[B]3-(3-methoxybenzyl)-1,2,4-oxadiazol-5-yl

The values of the *Wiener's topochemical index* were computed for each analogue using an in-house computer program. Resultant data was analyzed and suitable model was developed after identification of active range by maximization of the moving average with respect to the active analogues (<35% = inactive, 35-65% = transitional, >65% = active) [31]. Subsequently, each analogue was assigned a biological activity using this model, which was then compared with the reported 5-HT$_6$ binding affinity. 5-HT$_6$ binding affinity was reported [30] quantitatively as K_i at different concentrations. The analogues possessing K_i values of $\leq$13 nM were considered to be active and analogues possessing K_i values of >13 nM were considered to be inactive for the purpose of present study. This limit was selected because the drug clozapine, which was use as a control by Russell et al. [30] has a K_i value of 13 nM. Accuracy of prediction of the active and inactive ranges as well as overall degree of prediction of the proposed model was calculated.

A forementioned procedure was similarly adopted for *eccentric connectivity topochemical index,* ξ_c^c and *augmented eccentric connectivity topochemical index,* $^{Ac}\xi^c$.

The intercorrelation between *Wiener's topochemical index, eccentric connectivity topochemical index* and *augmented eccentric connectivity topochemical index* was investigated using the index values of 26 analogues of 3-ethyl-1*H*-indoles. The degree of correlation was appraised by the correlation coefficient r. Pairs of indices with $r \geq 0.97$ are considerably highly intercorrelated, those with $0.90 \leq r < 0.97$ are appreciably correlated, those with $0.50 \leq r \leq 0.89$ are weakly correlated and finally the pairs of indices with low r values (<0.50) are not intercorrelated [32]. The results are summarized in Tables 1-3 and Figures 2-5.

Table 2. Topochemical model for 5-HT_6 binding affinity.

Model Index	Nature of range	Index value	Number of analogues falling in the range / Total Correct	Percent accuracy	Average K_i (nM)*
W_c	Lower Inactive Transitional Active Upper Inactive	<1407.599 1407.599-<1744.267 1744.267-1965.42 >1965.42	07 07 04 N.A. 06 04 09 07	100.00 N.A. 66.67 77.78	174.00 15.80(N.A.) 23.53(8.30) 328.68(421)
ξ_c^c	Lower Inactive Active Upper Inactive	<626.828 626.828-750.718 >750.718	10 09 09 06 07 06	90.00 66.67 85.71	127.29(141.11) 21.64(7.13) 416.11(483.83)
$^{Ac}\xi^c$	Inactive Transitional Active	<44.02 44.02 to <45.704 45.704-54.571	13 12 07 N.A. 06 04	92.31 N.A. 66.67	314.02(340.08) 24.08(N.A.) 21.6 (8.4)

Values in the brackets indicate average K_i values of correctly predicted analogues of the particular range.

Table 3. Intercorrelation matrix

	W_c	ξ_c^c	$^{Ac}\xi^c$
W_c	1	0.974	0.404
ξ_c^c		1	0.537
$^{Ac}\xi^c$			1

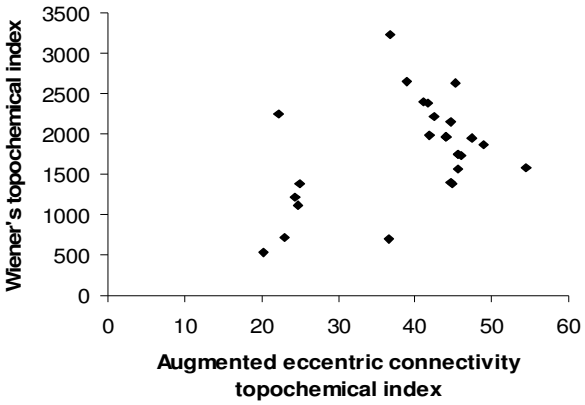

Figure 2. *Intercorrelation between augmented eccentric connectivity topochemical index and Wiener's topochemical index*

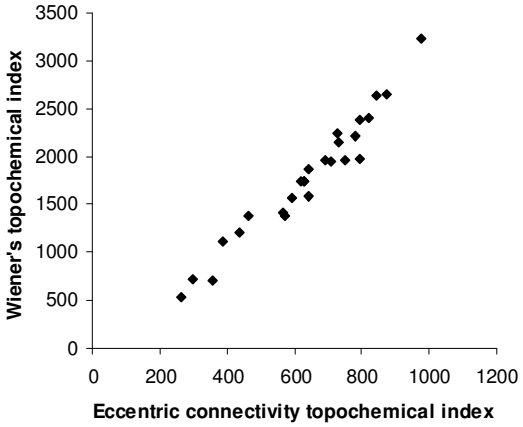

Figure 3. *Intercorrelation between eccentric connectivity topochemical index and Wiener's topochemical index.*

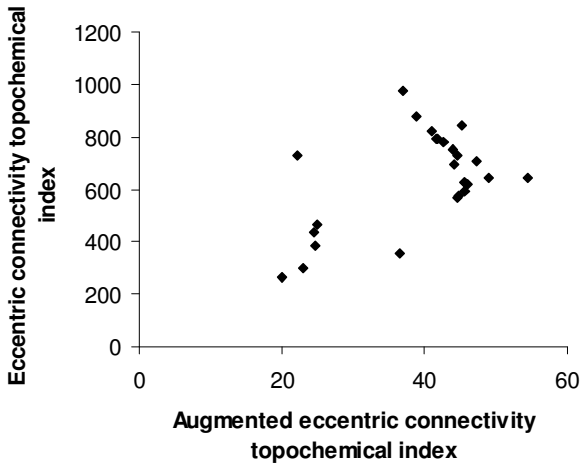

Figure 4. *Intercorrelation between augmented eccentric connectivity topochemical index and eccentric connectivity topochemical index.*

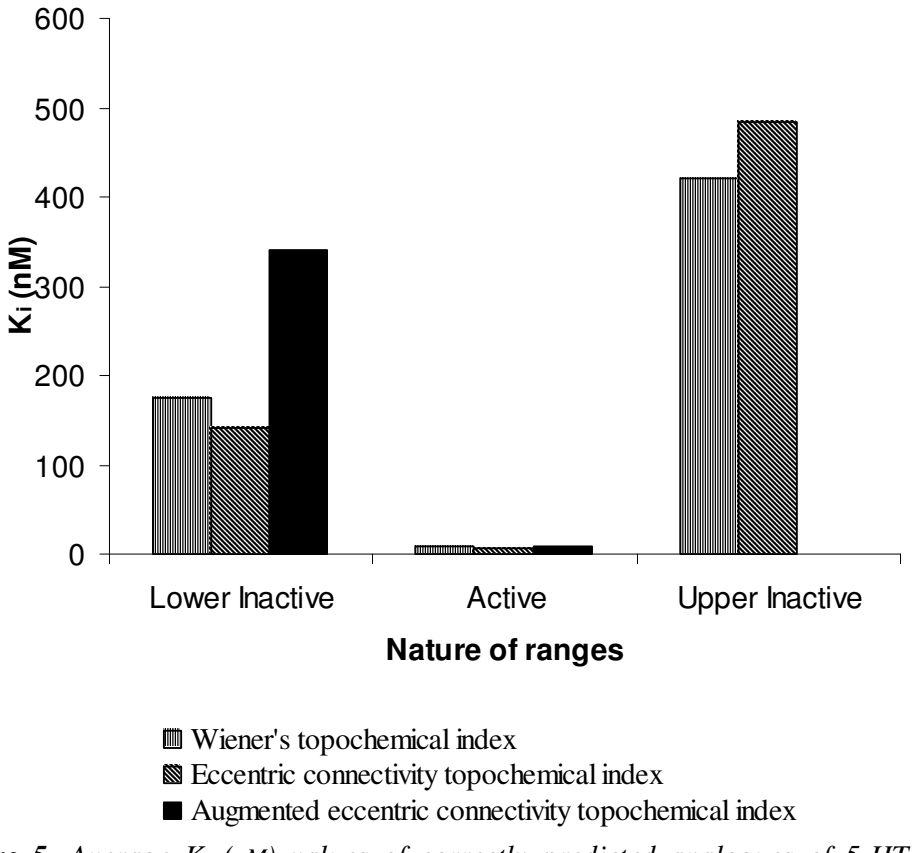

Figure 5. *Average K_i (nM) values of correctly predicted analogues of 5-HT_6 binding affinity in various ranges of proposed topochemical models.*

Results and Discussion

Molecular topology has been demonstrated to be excellent tool for a quick and accurate prediction of physicochemical and biological properties. Matrices from which one can derive a single topological index or a set of them can analytically represent graphs. These indices, whether are well chosen, are a good characterization of molecular structure [33].

Relationship of *Wiener's topochemical index* - a distance-based topochemical descriptor, *eccentric connectivity topochemical index* and *augmented eccentric connectivity topochemical index* – both adjacency-cum-distance based topochemical descriptor of 3-ethyl-1*H*-indoles was studied and suitable models were developed for prediction of 5-HT_6 binding affinity. Though all the analogues in the datasets possess varying degree of biological activity but only those analogues having K_i values of $\leq$13 nM were considered to be active for the

purpose of present study. The methodology used in the present studies aims at the development of suitable models for providing lead molecules through exploitation of the active ranges in the proposed models based on topochemical indices. Proposed models are unique and differ widely from conventional QSAR models. Both systems of modeling have their own advantages and limitations. In the instant case, the modeling system adopted has distinct advantage of identification of narrow active range(s), which may be erroneously skipped during routine regression analysis in conventional QSAR modeling. Since the ultimate goal of modeling is to provide lead structures, therefore, these active ranges can play vital role in lead identification [34].

Retrofit analysis of the data in Tables 1 and 2 reveals following information with regard to *Wiener's topochemical index*:

- Out of 22 analogues, 18 (~82 %) were predicted correctly with respect to 5-HT$_6$ binding affinity.
- The active range had *Wiener's topochemical index* value from 1744.267 to 1965.42. 67 % analogues in the active range were predicted correctly. The average K_i value was found to be 8.3 nM for the correctly predicted compounds. Extremely low K_i value of 8.3 nM clearly indicates high potency of the active range in the proposed model.
- The lower inactive range had *Wiener's topochemical index* values less than 1407.599 and the upper inactive range had *Wiener's topochemical index* values greater than 1965.42. Activity of ~88% analogues in these inactive ranges was predicted correctly.
- A transitional range with index values of 1407.599 to <1744.267 was observed. Existence of a transitional range is ideal because it simply indicates gradual change in biological activity.
- The ratio of average K_i values of active range and lower inactive range was found to be 1:7.4 (1:20.96 for correctly predicted analogues) and ratio of average K_i values of active range and upper inactive range was found to be 1: 13.97 (1: 50.72 for correctly predicted analogues).

Retrofit analysis of the data in Tables 1 and 2 reveals following information with regard to *eccentric connectivity topochemical index*:

- Out of 26 analogues, 21 (~81 %) were predicted correctly with respect to 5-HT$_6$ binding affinity.

- All the compounds in the dataset were classified and there was no transitional range in the proposed model.
- The active range had *eccentric connectivity topochemical index* value from 626.828 to 750.718. 67 % analogues in the active range were predicted correctly. The average K_i value was found to be 7.13 nM for the correctly predicted compounds. *Extremely low K_i value of 7.13 nM simply indicates high potency of the active range in the proposed model.*
- The lower inactive range had *eccentric connectivity topochemical index* values less than 626.828 and the upper inactive range had *eccentric connectivity topochemical index* values greater than 750.718. Activity of 88% analogues in these inactive ranges was predicted correctly.
- The ratio of average K_i values of active range and lower inactive range was found to be 1:5.88 (1:19.79 for correctly predicted analogues) and ratio of average K_i values of active range and upper inactive range was found to be 1: 19.23 (1: 67.86 for correctly predicted analogues).

Retrofit analysis of the data in Tables 1 and 2 reveals following information with regard to *augmented eccentric connectivity topochemical index*:

- Out of 19 analogues, 16 (84%) were predicted correctly with respect to 5-HT_6 binding affinity.
- The active range had *augmented eccentric connectivity topochemical index* value from 45.704 to 54.571. 67 % analogues in the active range were predicted correctly. The average K_i value was found to be 8.4 nM for the correctly predicted compounds. Extremely low K_i value of 8.4 nM indicates high potency of the active range in the proposed model.
- The inactive range had *augmented eccentric connectivity topochemical index* values less than 44.02. Activity of 92% analogues in these inactive ranges was predicted correctly.
- A transitional range with index values of 44.02 to <45.704 was observed. Existence of a transitional range is ideal because it reveals gradual change in biological activity.
- The ratio of average K_i values of active range and inactive range was found to be 1:14.54 (1:40.49 for correctly predicted analogues).

Intercorrelation analysis (Table 3) revealed that *Wiener's topochemical index* is not correlated with *augmented eccentric connectivity topochemical index* (Figure 2). However, *Wiener's topochemical index* was highly correlated with *eccentric connectivity topochemical*

index (Figure 3). The *augmented eccentric connectivity topochemical index* was weakly correlated with *eccentric connectivity topochemical index* (Figure 4).

Conclusions

Investigations reveal significant correlations of all the three-topochemical indices with 5-HT$_6$ binding affinity of 3-ethyl-1*H*-indoles. The overall accuracy of prediction varied from ~81% for model based on *eccentric connectivity topochemical index* to 84% for model based on *augmented eccentric connectivity topochemical index.* These models offer vast potential for providing lead structure for the development of potent therapeutic agents with regard to high binding affinity for 5-HT$_6$ receptors.

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