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Prediction of h5-HT_{2A} receptor antagonistic activity of arylindoles: Computational approach using topochemical descriptors

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Abstract

Relationship between the topochemical indices and h5-HT_{2A} receptor antagonistic activity of arylindoles 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 31 differently substituted arylindoles was selected for the present study. The values of the Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index were computed for all the analogues involved in the data set 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 analogue using these models, which was then compared with the reported h5-HT_{2A} receptor antagonistic activity. Accuracy of prediction was found to vary from a minimum of ~81% to a maximum of ~84%.

Keywords: Topochemical indices; Wiener's topochemical index; Molecular connectivity topochemical index; Eccentric connectivity topochemical index; h5-HT_{2A} receptor antagonistic activity; Schizophrenia

1. Introduction

An important goal in the field of pharmaceutical drug design is the prediction of physicochemical, pharmacological and toxicological properties of molecules directly from their structure [1]. Structure–activity relationships (SARs) are models, which attempt to relate certain structural aspect of molecules to their physicochemical/biological/toxicological properties [2]. The inherent problem in structure–activity relationship (SAR) in quantifying chemical structures can be easily overcome, by molecular topology, by translation of chemical structures into characteristic numerical descriptors [3]. Molecular structure can be represented by planar graphs, $G = (V, E)$, where the vertex set V represents the atoms and edge set E represents the bonds [4]. The topological indices are 2D molecular descriptors whose values are associated with the structural constitution of a chemical compound [5]. Topological indices have several obvious advantages when compared with geometrical, electrostatic, and quantum descriptors: they are computed only from the information contained in the molecular graph; they have a unique value for a particular chemical compound and their calculations require small computational resources [6]. These topological indices facilitate characterization of the molecular structure [7] and can be used for the selection and design of new lead drug molecule [8–12]. The topostructural and topochemical descriptors are collectively referred to as topological descriptors [13]. Topostructural descriptors encode information strictly on the adjacency and connectedness of atoms within a molecule whereas topochemical descriptors encode information relating to both molecular topology and the chemical nature of atoms and bonds within a molecule [14].

Though number of topostructural and topochemical indices has been reported in literature but only few of them have been successfully employed in SARs. Some of the topostructural and topochemical indices, which have been successfully employed in SAR studies include *Hosoya's index* [15], *Randic's molecular connectivity index*, [16,17], *Molecular connectivity topochemical index*, [18,19], *Balaban's index* [20,21], *Wiener's index* [22,23], *Weiner's topochemical index* [24], *Zagreb group parameters* [25–27], *Zagreb topochemical index* [28], *eccentric*

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connectivity index [29–33], *eccentric connectivity topochemical index*, [34] *and eccentric adjacency topochemical index* [35] and s*uperadjacency topochemical index* [36].

Schizophrenia is a severe psychiatric illness, which is characterized by positive symptoms, including delusions, hallucinations and irrational fears, negative symptoms such as social withdrawal and the inability to experience pleasure and cognitive symptoms [37]. The pathophysiology of schizophrenia has involved the dopamine hypothesis and serotonin hypothesis. The dopamine hypothesis arises from the apparent effectiveness of typical antipsychotics in treating the core symptoms of the disease. Typical antipsychotics drugs are brought to act mainly by D_2 receptor blockade, which is believed to be associated with extrapyramidal side effects, such as tardive dyskinesia. The introduction of atypical antipsychotics, which has greater affinity for h5-HT_2 receptor than for hD_2 receptor and shows a much lower incidence of extrapyramidal side effects [38,39]. It has been suggested that drugs may demonstrate atypical features if they have atleast ten times higher affinity for h5-HT_2 receptor than hD_2 receptor [40,41]. Many typical and atypical antipsychotics agents bind with high affinity to 5-HT_2 (particularly 5-HT_{2A}) receptors. Alterations in serotonergic systems have been correlated with specific symptoms of schizophrenia, and novel antipsychotic agents, which function as 5-HT_{2A} antagonists appear to be superior to neuroleptics for treating negative symptoms and treatment-resistant schizophrenia [42,43]. The 5-HT_{2A} receptors are important for many physiologic processes including platelet aggregation, smooth muscle contraction, and the modulation of mood and perception. A large number of pharmaceutical agents mediate their actions, at least in part, by modulating the number and/or activity of 5-HT_{2A} receptors. Drugs with action at 5-HT_{2A} receptors are used in the treatment of many disorders, including schizophrenia, depression, and anxiety disorders [44].

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 with h5-HT_{2A} receptor antagonistic activity of arylindoles has been investigated.

2. Methodology

2.1. Calculation of topochemical indices

Wiener's topochemical index (W_c) is a modified form of oldest and widely used distance based topological index—*Wiener's index* [22,23] and this modified index takes into consideration the presence as well as relative position of heteroatoms in a molecular structure. *Wiener's topochemical index* [24] is defined as the sum of the chemical distances between all 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, n is the maximum possible number of i and j.

Molecular connectivity topochemical index or *atomic molecular connectivity index* (χ^A) is a modified form of a popular and widely used adjacency based topological index—*molecular connectivity index* [16,17] and it takes into consideration the presence as well as relative position of heteroatom(s) in a molecular structure. The *molecular connectivity topochemical index* [18,19] is expressed as

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

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.

Eccentric connectivity topochemical index (ξ_c^c) [34] 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

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

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. *Eccentric connectivity topochemical index* is a modified form of an adjacency-cum-distance based topological index—*eccentric connectivity index* [29–33] and this modified index takes into consideration the presence as well as relative position of heteroatom(s) in a molecular structure.

2.2. Model development

A data set [45] comprising 31 analogues of arylindole was selected for the present investigation. The basic structure for these analogues is depicted in Fig. 1 and various substituents are enlisted in Table 1.

The values of the *Wiener's topochemical index* were computed for each analogue using an in-house computer program. For the selection and evaluation of range specific features, exclusive activity ranges were discovered from the frequency distribution of response level and subsequently identifying the active range by analyzing the resultant data by maximization of the moving average with respect to the active compounds ($<$35% = inactive, 35–65% = transitional, $\geq$65% = active) [46]. Subsequently, each analogue was assigned a biological activity, which was then compared with the reported [45] h5-HT_{2A} receptor antagonistic activity. The h5-HT_{2A} receptor antagonistic activity was reported quantitatively as K_i values in different concentrations. The analogues possessing K_i values of $\leq$0.5 nM were considered to be active and analogues possessing K_i values of $>$0.5 nM were considered to be inactive for the purpose of present study. The percentage degree of

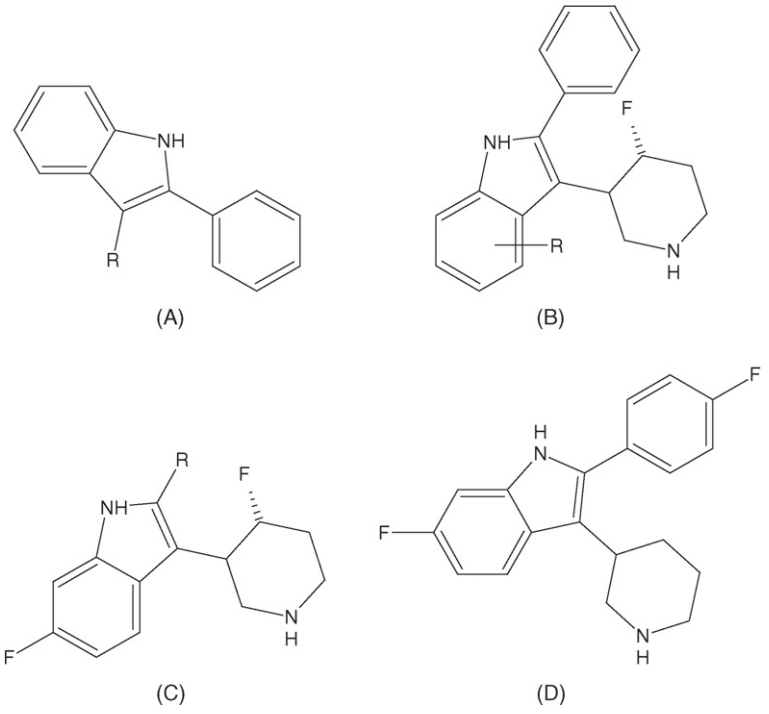


Fig. 1. Basic structures of arylindole analogues.

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. 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. Average value of K_i for each range of the proposed model was also calculated.

Aforementioned procedure was similarly followed for *molecular connectivity topochemical index*, χ^A and *eccentric connectivity topochemical index*, ξ_c^c. The results are summarized in Tables 1 and 2.

Table 1
Relationship of Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index with h5-HT_{2A} receptor antagonistic activity

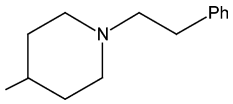
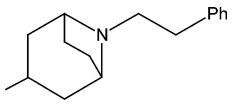
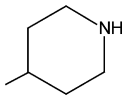
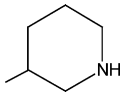
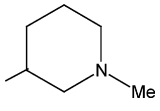
Compound no.	R	W_c	χ^A	ξ_c^c	h5-HT_{2A} receptor antagonistic activity			
					Predicted			Reported
					W_c	χ^A	ξ_c^c	
A_1		2440.069	14.216	786.12	–	–	–	+
A_2		2760.075	15.209	838.12	–	–	–	–
A_3		854.014	10.295	338.74	–	–	–	–
A_4		854.014	10.298	335.706	–	–	–	–
A_5		971.521	10.656	357.438	–	–	–	–

Table 1 (*Continued*)

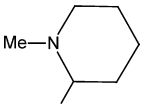
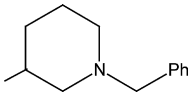
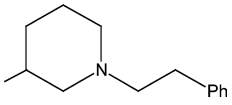
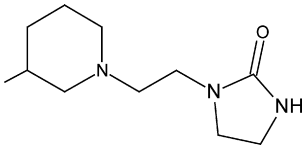
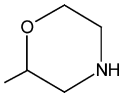
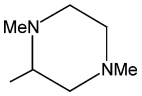
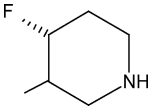
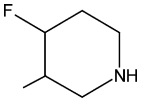
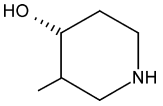
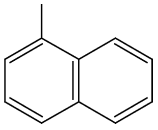
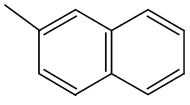
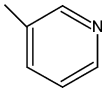
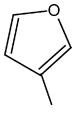
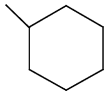
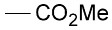
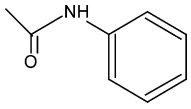
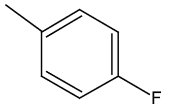
Compound no.	R	W_c	χ^A	ξ_c^c	h5-HT$_{2A}$ receptor antagonistic activity			
					Predicted			Reported
					W_c	χ^A	ξ_c^c	
A_6		959.026	10.677	352.265	–	–	–	–
A_7		2033.563	13.723	655.617	–	–	–	–
A_8		2320.069	14.219	729.98	–	–	–	–
A_9		2325.281	13.895	721.999	–	–	–	–
A_{10}		865.511	10.167	344.541	–	–	–	–
A_{11}		1086.71	10.961	377.03	–	–	–	–
A_{12}		959.302	10.597	354.787	–	–	–	+
A_{13}		959.302	10.597	354.787	–	–	–	–
A_{14}		956.677	10.641	353.037	–	–	–	–
B_1	5-F	1086.174	10.872	385.876	–	+	–	–
B_2	5-Cl	1101.299	10.681	439.144	+	–	+	–
B_3	6-F	1094.343	10.872	400.036	+	+	+	+
B_4	6-Cl	1109.468	10.681	459.506	+	–	+	–
B_5	7-F	1078.343	10.898	374.299	–	+	–	+
B_6	7-Cl	1093.468	10.719	420.464	–	–	+	–
C_1	H	503.835	7.882	279.908	–	–	–	–
C_2		1654.015	12.855	519.175	+	+	+	+
C_3		1722.015	12.839	567.633	+	+	+	+
C_4		1096.347	10.797	402.959	+	+	+	+
C_5		966.754	10.231	379.733	–	–	–	–

Table 1 (*Continued*)

Compound no.	R	W_c	χ^A	ξ_c^c	h5-HT_{2A} receptor antagonistic activity			
					Predicted			Reported
					W_c	χ^A	ξ_c^c	
C_6		981.428	9.873	420.803	–	–	+	+
C_7		1094.343	10.872	400.036	+	+	+	+
C_8		868.494	9.529	348.092	–	–	–	–
C_9		1629.885	12.136	546.488	+	+	+	+
C_{10}		1252.465	11.148	472.819	+	+	+	+
D[a]	–	1129.011	10.849	449.649	+	+	+	+

–, inactive compoun; +, active compound.
[a] Structure shown in Fig. 1.

Table 2
Proposed models for the prediction of h5-HT_{2A} receptor antagonistic activity

Index	Nature of range in the proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy	Average K_i (nM) for correctly predicted analogues
W_c	Lower inactive	<1094.343	16	13	81.25	52.20
	Active	1094.343–1722.015	10	8	80.00	0.19
	Upper inactive	>1722.015	5	4	80.00	26.55
χ^A	Lower inactive	<10.797	15	13	86.67	28.24
	Active	10.797–12.855	11	9	81.81	0.22
	Upper inactive	>12.855	5	4	80.00	26.55
ξ_c^c	Lower inactive	<400.036	14	12	85.71	56.49
	Active	400.036–567.633	12	9	75.00	0.18
	Upper inactive	>567.633	5	4	80.00	26.55

3. Results and discussion

In recent years, graph theoretic topological indices have received considerable attention because they can be derived directly from molecular structure without any experimental efforts [4]. These indices are numerical graph invariants that quantitatively characterize molecular structure and are sensitive to such key constitutive features as size, symmetry and heterogeneity of atomic environment in the molecule [2]. These numerical graph invariants quantify the chemical structures so as to facilitate the development of suitable correlations with quantitative biological activities.

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 with h5-HT_{2A} receptor antagonistic activity of arylindoles was studied and suitable models were developed for prediction of h5-HT_{2A} receptor antagonistic activity. Though all the analogues in the datasets possess varying degree of biological activity but only those analogues having K_i values of $\leq$0.5 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 system of modeling have their advantages and limitations. In the instant modeling, the system adopted has distinct advantage of identification of narrow active ranges, which may be erroneously skipped during regression analysis in conventional QSAR. Since the ultimate goal of modeling is to provide lead structures, therefore, active ranges of the proposed models can play vital role in providing lead structures.

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

- A total of 25 out of 31 compounds were classified correctly in both the active and inactive ranges using the model based upon *Wiener's topochemical index*. The overall accuracy of prediction was found to be ∼81% with regard to h5-HT_{2A} receptor antagonistic activity.
- The active range had *Wiener's topochemical index* values of 1094.343–1722.015. Eighty percent of the analogues in the active range exhibited h5-HT_{2A} receptor antagonistic activity. The average K_i value of correctly predicted compounds in the active range was found to be only 0.19 nM. This clearly indicates exceptionally high potency of the active range.
- Two inactive ranges—a lower inactive range with index values of <1094.343 and an upper inactive range with index values of >1722.015 were observed. Activity of 17 out of 21 compounds in these inactive ranges was predicted correctly.
- The ratio of average K_i values of active range and lower inactive range for correctly predicted analogues was found to be 1:274.74 and ratio of average K_i values of active range and upper inactive range for correctly predicted analogues was found to be 1:139.74.

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

- A total of 26 out of 31 compounds were classified correctly in both the active and inactive ranges using model based upon *molecular connectivity topochemical index*. The overall accuracy of prediction was found to be ∼84% with regard to h5-HT_{2A} receptor antagonistic activity.
- The active range had *molecular connectivity topochemical index* values of 10.797–12.855. Eighty-two percent of the analogues in the active range exhibited h5-HT_{2A} receptor antagonistic activity. The average K_i value was found to be 0.22 nM for correctly predicted compounds in the active range. This clearly indicates high potency of the active range.
- Two inactive ranges—a lower inactive range with index values of <10.797 and an upper inactive range with index values of >12.855 were observed. Activity of 17 out of 20 compounds in these inactive ranges was predicted correctly.
- The ratio of average K_i values of active range and lower inactive range for correctly predicted analogues was found to be 1:128.36 and ratio of average K_i values of active range and upper inactive range for correctly predicted analogues was found to be 1:120.68.

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

- A total of 25 out of 31 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be ∼81% with regard to h5-HT_{2A} receptor antagonistic activity.
- The active range had *eccentric connectivity topochemical index* values of 400.036–567.633. Seventy-five percent of the analogues in the active range exhibited h5-HT_{2A} receptor antagonistic activity. The average K_i value was found to be 0.18 nM for correctly predicted compounds in the active range. This clearly indicates high potency of the active range.
- Two inactive ranges bracketed the active range. Lower inactive range and upper inactive range had index values of <400.036 and >567.633, respectively. Activity of 16 out of 19 compounds in these inactive ranges was predicted correctly.
- The ratio of average K_i values of active range and lower inactive range for correctly predicted analogues was found to be 1:313.83 and ratio of average K_i values of active range and upper inactive range for correctly predicted analogues was found to be 1:147.50.

4. Conclusion

Investigations reveal significant correlations of all the three-topochemical indices with h5-HT_{2A} receptor antagonistic activity of arylindoles. The overall accuracy of prediction varied from minimum of ∼81% for models based on *Wiener's topochemical index* and *eccentric connectivity topochemical index* to a maximum of ∼84% in case of *molecular connectivity topochemical index*.

High predictability of the proposed models based upon the topochemical indices offer a vast potential for providing lead structures for the development of potent therapeutic agents with regard to h5-HT_{2A} receptor antagonistic activity.

References

[1] R. Todeschini, V. Consonni, Handbook of Molecular Descriptors, Wiley-VCH, Weuinheim, 2000.
[2] S.C. Basak, Use of molecular complexity indices in predictive pharmacology and toxicology: a QSAR approach, Med. Sci. Res. 15 (1987) 605–609.
[3] V. Lather, A.K. Madan, Topological models for the prediction of HIV-protease inhibitory activity of tetrahydropyrimidin-2-ones, J. Mol. Graphics Modell. 23 (2005) 339–345.
[4] N. Trinajstic, Chemical Graph Theory, 2nd ed., CRC Press, Boca Raton, 1983.
[5] S.L. Taraviras, O. Ivanciuc, D. Cabrol-Bass, Identification of groupings of graph theoretical molecular descriptors using a hybrid cluster analysis approach, J. Chem. Inf. Comput. Sci. 40 (2000) 1128–1146.
[6] O. Ivanciuc, S.L. Taraviras, D. Cabrol-Bass, Quasi-orthogonal basis sets of molecular graph descriptors as a chemical diversity measure, J. Chem. Inf. Comput. Sci. 40 (2000) 126–134.
[7] M. Randic, On characterization of chemical structure, J. Chem. Inf. Comput. Sci. 37 (1997) 672–686.
[8] J. Galvez, R. Garcia-Domenech, J.V. de Julian-Ortiz, R. Soler, Topological approach to drug design, J. Chem. Inf. Comput. Sci. 35 (1995) 272–284.
[9] R. Garcia-Domenech, F.J. Gracia-March, R. Soler, J. Galvez, G.M. Anton-Fos, J.V. de Julian-Ortiz, New analgesics designed by molecular topology, Quant. Struct.-Act. Relat. 15 (1996) 201–207.
[10] E. Estrada, P. Pena, R. Garcia-Domenech, Designing sedative hypnotic compounds from a novel substructural graph-theoretical approach, J. Comput. Aid. Mol. Des. 12 (1998) 583–595.

[11] I. Rios-Santamarina, R. Garcia-Domenech, J. Galvez, J. Cortijo, P. Santamaria, E. Morcillo, New bronchodilators selected by molecular topology, Bioorg. Med. Chem. Lett. 8 (1998) 477–482.
[12] G. Grassy, B. Calas, A. Yasri, R. Lahana, J. Woo, S. Iyer, M. Kaczorek, R. Floc'h, R. Buelow, Computer-assisted rational design of immunosuppressive compounds, Nat. Biotechnol. 16 (1998) 748–752.
[13] S.C. Basak, B.D. Gute, G.D. Grunwald, Use of topostructural, topochemical, and geometric parameters in the prediction of vapor pressure: a hierarchical QSAR approach, J. Chem. Inf. Comput. Sci. 37 (1997) 651–655.
[14] S.C. Basak, D. Mills, D.M. Hawkins, H.A. EL-Masri, Prediction of tissue-air partition coefficients: a comparison of structure-based and property-based methods, SAR QSAR Environ. Res. 13 (2002) 649–665.
[15] H. Hosoya, Topological index; newly proposed quantity characterizing the topological nature of structure of isomers of saturated hydrocarbons, Bull. Chem. Soc. Jpn. 44 (1971) 2332–2337.
[16] M. Randic, On characterization of molecular branching, J. Am. Chem. Soc. 97 (1975) 6609–6615.
[17] M. Randic, The connectivity index 25 years after, J. Mol. Graph. Modell. 20 (2001) 19–35.
[18] S. Gupta, M. Singh, A.K. Madan, Application of graph theory: relationship of molecular connectivity index and atomic molecular connectivity index with anti-HSV activity, J. Mol. Struct. (THEOCHEM) 571 (2001) 147–152.
[19] H. Dureja, A.K. Madan, Topochemical models for prediction of cyclin-dependent kinase 2 inhibitory activity of indole-2-ones, J. Mol. Modell. 11 (2005) 525–531.
[20] A.T. Balaban, Highly discriminating distance based topological index, Chem. Phys. Lett. 89 (1982) 399–404.
[21] A.T. Balaban, Applications of graph theory in chemistry, J. Chem. Inf. Comput. Sci. 25 (1985) 334–343.
[22] H. Wiener, Correlation of heat of isomerization and difference in heat of vaporization of isomers among paraffin hydrocarbons, J. Am. Chem. Soc. 69 (1947) 2636–2638.
[23] H. Wiener, Influence of interatomic forces on paraffin properties, J. Chem. Phys 15 (1947) 766.
[24] S. Bajaj, S.S. Sambi, A.K. Madan, Predicting anti-HIV activity of phenethylthiazolethiourea (PETT) analogs: computational approach using Wiener's topochemical index, J. Mol. Struct. (THEOCHEM) 684 (2004) 197–203.
[25] I. Gutman, N. Trinajstic, Graph theory and molecular orbitals. Total π-electron energy of alternant hydrocarbons, Chem. Phys. Lett. 17 (1972) 535–538.
[26] I. Gutman, B. Ruscic, N. Trinajstic, C.F. Wicox, Graph theory and molecular orbitals. XII. Acyclic polyenes, J. Chem. Phys. 62 (1975) 3399–3405.
[27] S. Nikolic, G. Kovacevic, A. Milicevic, N. Trinajstic, The Zegrab indices 30 years after, Croat. Chem. Acta 76 (2003) 113–124.
[28] S. Bajaj, S.S. Sambi, A.K. Madan, Prediction of anti-inflammatory activity of *N*-arylanthranilic acids: computational approach using refined Zagreb indices, Croat. Chem. Actas 78 (2005) 165–174.
[29] V. Sharma, R. Goswami, A.K. Madan, Eccentric connectivity index: a novel highly discriminating topological descriptor for structure property and structure activity studies, J. Chem. Inf. Comput. Sci. 37 (1997) 273–282.
[30] S. Gupta, M. Singh, A.K. Madan, Application of graph theory: relationship of eccentric connectivity index and Wiener's index with anti-inflammatory activity, J. Math. Anal. Appl. 266 (2002) 259–268.
[31] S. Sardana, A.K. Madan, Topological models for prediction of antihypertensive activity of substituted benzylimidazoles, J. Mol. Struct. (THEOCHEM) 638 (2003) 41–49.
[32] V. Lather, A.K. Madan, Models for the prediction of adenosine receptors binding activity of 4-amino[1,2,4]triazolo[4,3-a]quinoxalines, J. Mol. Struct. (THEOCHEM) 678 (2004) 1–9.
[33] V. Kumar, A.K. Madan, Topological models for the prediction of alpha-1 adrenoceptor antagonistic activity of arylpiperazines, J. Theo. Comput. Chem. 3 (2004) 245–255.
[34] V. Kumar, S. Sardana, A.K. Madan, Predicting anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones: computational approach using reformed eccentric connectivity index, J. Mol. Modell. 10 (2004) 399–407.
[35] S. Gupta, M. Singh, A.K. Madan, Novel topochemical descriptors for predicting anti-HIV activity, Indian J. Chem. 42A (2003) 1414–1425.
[36] S. Bajaj, S.S. Sambi, A.K. Madan, Prediction of carbonic anhydrase activation by tri-/tetrasubstituted-pyridinium-azole compounds: a computational approach using novel topochemical descriptor, QSAR Combinatorial Sci. 23 (2004) 506–514.
[37] J.M. Kane, in: N.C. Andreason (Ed.), Schizophrenia, from mind to molecule, American Psychiatric Press, Washington, DC, 1994 , pp. 173–187.
[38] P. Seeman, T. Lee, Antipsychotic drugs, direct correlation between clinical potency and presynaptic action on dopamine neurons, Science 188 (1975) 1217–1219.
[39] P. Seeman, Dopamine receptors and the dopamine hypothesis of schizophrenia, Synapse (N.Y.) 1 (1987) 133–152.
[40] H.Y. Meltzer, S. Masubara, J.C. Lee, The ratios of serotonin-2 and dopamine-2 affinities differentiate atypical and typical antipsychotics drugs, Psychopharmacol. Bull. 25 (1989) 390–392.
[41] H.Y. Meltzer, S. Masubara, J.C. Lee, Classification of typical and atypical antipsychotics drugs on the basis of dopamine D_1, D_2 and serotonin-2 pK_1 values, J. Pharmacol. Exp. Ther. 251 (1989) 238–246.
[42] S. Kapur, G. Remington, Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia, Annu. Rev. Med. 52 (2001) 503–517.
[43] C.A. Tamminga, The science of antipsychotics: mechanistic insight, CNS Spectro. 11 (Suppl. 2) (2003) 5–9.
[44] J.A. Gray, B.L. Roth, Paradoxical trafficking and regulation of 5-HT_{2A} receptors by agonists and antagonists, Brain Res. Bull. 56 (2001) 441–451.
[45] M. Rowley, D.J. Hallett, S. Goodacre, C. Moyes, J. Crawforth, T.J. Sparey, S. Patel, R. Marwood, S. Patel, S. Thomas, L. Hitzel, D.O. Connor, N. Szeto, J.L. Castro, P.H. Hutson, A.M. Macleod, 3-(4-Flouoropiperidin-3-yl)-2-phenylindoles as high affinity, selective, and orally bioavailable h5-HT_{2A} receptor antagonists, J. Med. Chem. 44 (2001) 1603–1614.
[46] S. Gupta, M. Singh, A.K. Madan, Predicting anti-HIV activity: computational approach using novel topological descriptor, J. Comput. Aid. Mol. Des. 15 (2000) 671–678.