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Predicting Dopamine D_3 Receptor Binding Affinity of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides: Computational Approach using Topological Descriptors.

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ABSTRACT

Relationship between the topological indices and Dopamine D_3 receptor binding affinity of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides has been investigated. Three topological indices – the *Wiener's Index*– a distance-based topological descriptor, *Zagreb group parameter*– an adjacency based topological descriptor and *eccentric connectivity index*– an adjacency-cum-distance based topological descriptor were used for the present investigations. A data set comprising of 73 differently substituted N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides was selected for the present studies. The values of the *Wiener's index, Zagreb group parameter and eccentric connectivity index* for each of the 73 analogues

comprising the data set were computed using an in house computer program. Resultant data was subsequently analyzed and suitable models were developed after identification of active ranges. Subsequently, a biological activity was assigned to each analogue using these models, which was then compared with the reported Dopamine D_3 receptor binding affinity. The degree of predictability of these models was found to vary from a minimum of 82% to a maximum of 86%.

Keywords: Topological indices, Wiener's index, Eccentric connectivity index, Zagreb group parameter, D_3 binding affinity, Parkinson's disease: PD.

INTRODUCTION

Numerous attempts have been made in theoretical chemistry to express in numerical form the chemical structure with structural descriptors from various classes, such as constitutional, graph-theoretical, topological, geometrical, electrostatic and quantum descriptors.[1] Such structural descriptors, usually used in quantitative structure-property relationship (QSPR) and quantitative structure-activity relationship (QSAR) models to compute physical, chemical, or biological properties, can be interpreted as measures of the molecular size, shape, branching, cyclicity, or electron distribution.

With the substantial increase in the available databases of chemical structures and properties, attempts have been made to develop structure-activity relationships (SARs) whereby existing molecules can be compared with other molecules (real or hypothetical) on the basis of the various structural descriptors. The properties of the molecules of interest can then be predicted based on the molecular structure without the need for the experimental data.[2] The main problem in this area, however, was the development of easily calculable parameters which encode sufficient structural information useful in the prediction of properties. Molecular topology has

been demonstrated to be an excellent tool for a quick and accurate prediction of physicochemical and biological properties.[3-9] Through a relatively simple formalism such as molecular connectivity, a good molecular characterization with the topological indices or descriptors (TIs) can be obtained.

Topological indices are numerical graph invariants that quantify certain aspects of molecular structure. TIs are sensitive to such structural features as size, shape, bond order, branching, and neighborhood patterns of atoms in the molecules. They can be derived from simple linear graphs, multigraphs, weighted graphs, and weighted pseudographs.[10] Each molecule is assimilated to a graph, where atoms are represented by points (called vertices) and bonds represented by segments (called edges) between vertices. Graphs can be analytically represented by matrices from which a single or a set of TIs can be derived. These indices, whether are well chosen, are a good characterization of the molecular structure and they can be used for the selection and design of new classes of compounds such as new antivirals[11], bronchodilators[12], sedatives[13], analgesics[14] etc, many of which can be considered as lead drugs. Although a number of topological indices have been reported, only a handful of them have been successfully employed in SAR studies. *Hosoya's index*[15-16], *Randic's molecular connectivity index*, χ[17-18], *the higher-order connectivity indices*, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall[3], *Balaban's index*, J[19-22], *Wiener's index*[23-24], *Zagreb group parameters*, M_1 and M_2 [25-26], *Eccentric connectivity index*[27-29] are some of the topological indices used in the SARs studies.

The neurotransmitter dopamine is implicated in various physiological and pathophysiological processes. The dopaminergic system regulates brain functions such as motion, emotion and cognition. Its effects are mediated by dopaminergic receptors, which belong

to the family of G protein-coupled receptors. Dopamine receptors can be classified into five different receptor subtypes and are further classified into two families, the D_1-like (D_1 and D_5) and the D_2-like (D_2, D_3 and D_4), with related pharmacological, structural and genetic properties, respectively.[30-31] An imbalance within the dopaminergic system is related to several psychiatric and neurological disorders, e.g., Parkinson's disease, Huntington's syndrome and schizophrenia. Medical treatment of dopamine related disorders is often limited by side effects as a consequence of binding to various dopamine subreceptors or other related monoamine receptors. Therefore, effective therapy calls for selective dopamine subreceptor ligands.[32] Dopamine D_3 receptors are relatively few in number but display a discrete localization in special limbic areas of the central nervous system, which are thought to control emotional and cognitive but not locomotor functions.[33-34] For a long time dopamine D_2-like receptors antagonists have been used to treat schizophrenia and related psychiatric disorders.[35] D_3 receptor is highly expressed in limbic regions of the brain, but exhibited low expression in motor divisions.[36] A suitable selective dopamine D_3 receptor antagonist may provide antipsychotic properties in the relative absence of limiting extrapyramidal side effects.[37] Another therapeutic use of D_3 agents is for the treatment of Parkinson's disease (PD) because dopamine agonists used in PD therapy have, in many cases, as high or higher affinity for the D_3 receptors.[38] Recently the D_3 preferring agonists pramipexole and ropinirole have been introduced in therapy for the effective treatment of PD.[39] The D_3 receptor subtype would also be involved in the pharmacological effects of psychostimulant drugs.[40] An early study on the D_3-selective agonist 7-OH-DPAT suggested that D_3 receptors played a modulatory role in the self-administration of cocaine.[41] A recent study suggested that the dopamine D_3 receptor antagonistic properties have potential in the treatment of addiction and

withdrawal.[42] However the *in vivo* function of dopamine D_3 receptors and their role in different CNS disorders remains debatable because of the lack of receptor selectivity of the different pharmacological agents.

In the present study relationship of *Wiener's Index* – a distance-based topological descriptor, *Zagreb group parameter* – an adjacency-based topological descriptor and *eccentric connectivity index* – an adjacency-cum-distance based topological descriptor with dopamine D_3 receptor binding affinity of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides has been investigated.

METHODOLOGY

Calculation of topological indices

The *Wiener's index*[43-48], a well-known distance-based topological index is defined as the sum of the distances between all the pairs of vertices in a hydrogen-suppressed molecular graph, that is

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

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

The *Zagreb group parameter* M_1 proposed by Gutman et al.[49-50], an adjacency based topological index, is defined as the sum of squares of degree over all vertices and is represented by following equation:

$$M_1 = \sum_{i=1}^{n} (V_i^2) \qquad (2)$$

Where V_i is the degree of vertex i in a hydrogen-suppressed molecular structure. The vertex degree V_i for a vertex i is given as the sum of the entries in a row i of adjacency matrix.

The *eccentric connectivity index*[51], an adjacency-cum-distance based topological index denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen suppressed molecular graph having n vertices

$$\xi^c = \sum_{i=1}^{n} (E_i * V_i) \qquad (3)$$

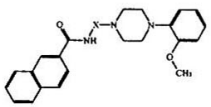
Where V_i is the degree of vertex i, E_i is the eccentricity of the vertex i and n is the number of the vertices in graph G. The eccentricity E_i of a vertex i in a graph G is the path length from vertex i to vertex j that is farthest from i (E_i=max d(ij); $j\varepsilon$G); the eccentric connectivity index takes into consideration the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

MODEL DEVELOPMENT

A data set comprising of 73 analogues of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides was selected for the present investigations.[52] The basic structures for the analogues are depicted in Fig. 1 and various substituents enlisted in Table 1. The data set comprised of both active and inactive compounds.

The values of the *Wiener's 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. Resultant data was analyzed and a suitable model was developed after identification of active ranges by maximization of the moving average with respect to the active compounds.[53] Subsequently, each analogue was assigned a biological activity which was then compared with the reported Dopamine D_3 receptor binding affinity. Dopamine receptor binding affinity was reported quantitatively as K_i values at different concentrations. The analogues possessing K_i values of ≤ 1 nM were considered to be active and analogues possessing K_i values of >1 nM were considered to be inactive for the purpose of present study. 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. The overall degree of prediction was derived from the ratio of the total number of compounds predicted correctly to that of the total number of compounds present in both the active and inactive ranges.

Aforementioned procedure was similarly adopted for *Zagreb group parameter*, M_1 and *Eccentric connectivity index*, ξ^c. The results are summarized in Table 1 to 4.



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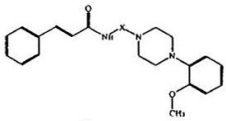

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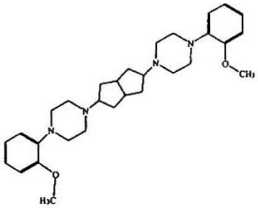

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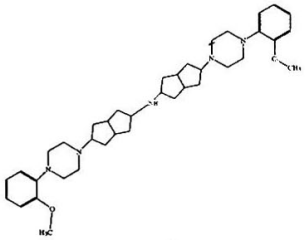

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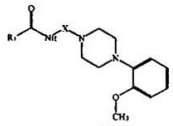

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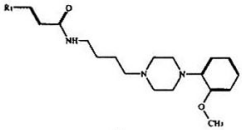

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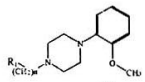

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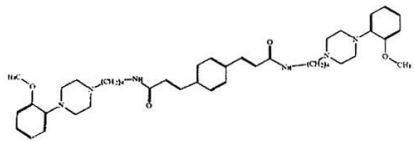

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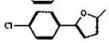
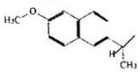
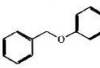
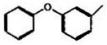
Figure 1.

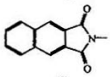
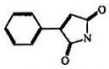
Table 1. Relationship of *Wiener's index, Zagreb group parameter* and *eccentric connectivity index* with Dopamine D_3 receptor binding affinity.

Comp. No.	R_1	X	n	W	M_1	ξ_c	D_3 binding affinity: Predicted W	Predicted M_1	Predicted ξ_c	Reported
A_1	-		-	4416	184	1137	–	–	–	–
A_2	-		-	4626	184	1205	–	–	–	–
A_3	-		-	4836	184	1273	–	–	–	–
A_4	-		-	4539	194	1221	–	–	–	–
5.*	-		-	3896	166	1044	–	–	–	–
6.*	-	-	-	4913	198	1256	–	–	–	–
7.*	-	-	-	9750	254	2075	–	–	–	–
B_1		$(CH_2)_4$	-	3522	158	1025	–	–	–	+
B_2		$(CH_2)_4$	-	2675	138	848	–	±	+	+
B_3		$(CH_2)_4$	-	2675	138	848	–	±	+	–
B_4		$(CH_2)_3$	-	2348	134	772	–	–	–	–
B_5		$(CH_2)_4$	-	3283	148	957	+	+	+	+
B_6		$(CH_2)_4$	-	3590	156	994	–	–	±	–
B_7		$(CH_2)_4$	-	4320	166	1189	–	–	–	–
B_8		$(CH_2)_4$	-	5096	176	1312	–	–	–	–
B_9		$(CH_2)_4$	-	2654	138	813	–	±	–	–

B_{10}		$(CH_2)_3$	-	2328	134	737	–	–	–	–
B_{11}		$(CH_2)_4$	-	2633	138	811	–	±	–	–
B_{12}		$(CH_2)_3$	-	2308	134	735	–	–	–	–
B_{13}		$(CH_2)_4$	-	3522	158	1025	–	–	–	–
B_{14}		$(CH_2)_4$	-	3522	158	1025	–	–	–	–
B_{15}		$(CH_2)_4$	-	3438	158	980	–	–	±	–
B_{16}		$(CH_2)_4$	-	3771	164	1056	–	–	–	–
B_{17}		$(CH_2)_4$	-	3775	164	1056	–	–	–	–
B_{18}		$(CH_2)_4$	-	3507	160	1052	–	–	–	–
B_{19}		$(CH_2)_4$	-	4279	168	1182	–	–	–	–
B_{20}		$(CH_2)_4$	-	4631	186	1191	–	–	–	–
B_{21}		$(CH_2)_4$	-	3942	162	1111	–	–	–	–
B_{22}		$(CH_2)_3$	-	3514	158	1023	–	–	–	–
B_{23}		$(CH_2)_3$	-	3430	158	978	–	–	±	–
B_{24}		$(CH_2)_3$	-	4461	174	1202	–	–	–	–
B_{25}		$(CH_2)_4$	-	3985	170	1078	–	–	–	–
B_{26}		$(CH_2)_4$	-	3282	154	991	+	–	±	–

B_{27}		$(CH_2)_4$	-	3062	140	932	+	+	+	–
C_1		-	-	3062	140	932	+	+	+	+
C_2		-	-	3390	146	1006	+	+	±	+
C_3		-	-	3390	146	1006	+	+	±	+
C_4		-	-	3390	146	1006	+	+	±	+
C_5		-	-	3390	146	1006	+	+	±	+
C_6		-	-	4470	164	1166	–	–	–	–
C_7		-	-	3748	150	1084	–	+	–	+
C_8		-	-	4108	156	1125	–	–	–	+
C_9		-	-	3748	150	1084	–	+	–	+
C_{10}		-	-	3748	150	1084	–	+	–	+
C_{11}		-	-	4470	164	1166	–	–	–	–
C_{12}		-	-	8151	218	1590	–	–	–	–
C_{13}		-	-	5318	174	1377	–	–	–	–
C_{14}		-	-	5835	178	1469	–	–	–	–
C_{15}		-	-	6388	182	1565	–	–	–	–
49.*		-	-	17850	256	3066	–	–	–	–
C_{17}		-	-	3367	146	969	+	+	+	+

C_{18}		-	-	3367	146	969	+	+	+	–
C_{19}		-	-	4378	164	1121	–	–	–	–
C_{20}		-	-	5674	178	1414	–	–	–	–
C_{21}		-	-	3344	146	967	+	+	+	+
C_{22}		-	-	3344	146	967	+	+	+	+
C_{23}		-	-	3656	150	1004	–	+	±	+
C_{24}		-	-	3698	152	1043	–	–	–	–
C_{25}		-	-	3676	152	1041	–	–	–	–
C_{26}		-	-	4030	162	1122	–	–	–	+
C_{27}		-	-	3961	162	1079	–	–	–	+
C_{28}		-	-	4725	166	1197	–	–	–	–
C_{29}		-	-	2760	136	859	+	±	+	+
C_{30}		-	-	2760	136	859	+	±	+	+
C_{31}		-	-	2760	136	859	+	±	+	+
C_{32}		-	-	3062	140	932	+	+	+	+
C_{33}		-	-	4396	166	1201	–	–	–	+
C_{34}		-	-	3840	148	1096	–	+	–	–
D_1		-	4	2719	152	820	–	–	–	–

D_2		-	3	2380	148	742	–	+	–	–
D_3		-	4	3847	178	1058	–	–	–	–
D_4		-	4	3736	178	1014	–	–	–	–
D_5		-	4	3408	160	981	–	–	±	–

–, Inactive compound, +, Active compound

±, Compound in the transitional range where activity could not be specifically assigned.

*, Structures shown in Fig. 1.

RESULTS AND DISCUSSION

Structure-activity-relationship (SAR) studies play a vital role to develop efficient and cost-effective drug development process. The problem in the development of a suitable correlation between chemical structures and properties can be attributed to the non-quantitative nature of chemical structures. Graph theory when applied to SAR essentially involves the translation of chemical structures into numerical values in the form of a characteristic polynomial, a matrix, a sequence or graph invariant.[54] Topological descriptors are such numerical graph invariants which quantify the chemical structures so as to facilitate the development of suitable correlations with quantified biological activities.

The endogenous catecholamine dopamine produces a variety of biological effects by interaction with specific dopamine receptors. The cloning of the gene for dopamine D_3 receptor and subsequent identification of its distribution in the brain and pharmacology allowed for serious consideration of the possibility that might be a target for antipsychotic and antiparkinsonian drugs.[39] However the lack of selective agents for the D_3 receptors as well as the D_4 receptors makes the role of these receptors in CNS disorders unclear.

Relationship of topological indices i.e. *Wiener's Index* – a distance-based topological descriptor, *Zagreb group parameter* – an adjacency-based topological descriptor and *eccentric connectivity index* – an adjacency-cum-distance based topological descriptor with dopamine D_3 receptor binding affinity has been investigated in the present study.

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

- A total of 60 out of 73 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 82.2 % with regard to D_3 receptor binding affinity.
- The active range had *Wiener's index* values of 2760-3390. 13 out of 16 analogues in the active range exhibited D_3 receptor binding affinity.
- The average K_i value was found to be 0.57 nM for correctly predicted active compounds, indicating the presence of highly active compounds in the active range.

Retrofit analysis of the data in Tables 1 and 3 reveals the following information with regard to *Zagreb group parameter*:

- A total of 57 out of 66 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 86.4 % with regard to D_3 receptor binding affinity.
- The active range had *Zagreb group parameter* values of 140-150. 14 out of 18 analogues in the active range exhibited D_3 receptor binding affinity.
- The average K_i value was found to be 0.55 nM for correctly predicted active compounds, indicating the presence of highly active compounds in the active range.

Retrofit analysis of the data in Tables 1 and 4 reveals the following information with regard to *eccentric connectivity index*:

- A total of 52 out of 63 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 82.5 % with regard to D_3 receptor binding affinity.
- The active range had *eccentric connectivity index* values of 848-969. 10 out of 13 analogues in the active range exhibited D_3 receptor binding affinity.
- The average K_i value was found to be 0.58 nM for correctly predicted active compounds, indicating the presence of highly active compounds in the active range.

The intercorrelation between Wiener's index, Zagreb group parameter and eccentric connectivity index was investigated (Table 5). The degree of correlation was appraised by the correlation coefficient r. Pairs of indices with $r \geq 0.97$ are considered highly intercorrelated, those with $0.90 \leq r \leq 0.97$ 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.[55] The results reveal that *Zagreb group parameter* is very weakly correlated with the *Wiener's index* as well as the *eccentric connectivity index*, however *Wiener's index* and *eccentric connectivity index* are appreciably correlated.

Models based upon all the three topological descriptors i.e. *Wiener's index*- a distance-based topological descriptor, *Zagreb group parameter* – an adjacency-based topological descriptor and *eccentric connectivity index* – an adjacency-cum-distance based topological descriptor exhibited high degree of predictability ranging from 82.2% to 86.4% with regard to dopamine D_3 receptor binding affinity. These models offer a vast potential for providing lead

structures for the development of therapeutic agents particularly with regard to dopamine D_3 receptor binding affinity.

Table 2. The relationship between the Dopamine D_3 receptor binding affinity and *Wiener's 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)
Lower Inactive	<2760	09	08	88.88	169.8(190.9)
Active	2760-3390	16	13	81.25	1.8(0.57)
Upper Inactive	>3390	48	39	81.25	73.34(90.12)

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

Table 3. The relationship between the Dopamine D_3 receptor binding affinity and *Zagreb group parameter*

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)
Lower Inactive	<136	03	03	100	159.3
Transitional	136-138	07	NA	NA	3.3(NA)
Active	140-150	18	14	77.8	31.9(0.55)
Upper Inactive	>150	45	40	88.9	79.34(89.16)

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

Table 4. The relationship between the Dopamine D_3 receptor binding affinity and *eccentric connectivity 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)
Lower Inactive	<848	07	07	100	217.7
Active	848-969	13	10	76.9	1.21(0.58)
Transitional	978-1006	10	NA	NA	46.37(NA)
Upper Inactive	>1006	43	35	81.4	71.50(87.68)

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

Table 5. The Intercorrelation Matrix

	W	M_1	ξ^c
W	1	0.86	0.987
M_1		1	0.88
ξ^c			1

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