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Predicting anti-HIV activity of TIBO derivatives: a computational approach using a novel topological descriptor

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Abstract A novel highly discriminating adjacency-cum-distance-based topological descriptor, termed the *adjacent eccentric distance sum index*, has been conceptualized and its discriminating power investigated with regard to the anti-HIV activity of 4,5,6,7-tetrahydro-imidazo-[4,5,1-*jk*] [1,4] benzodiazepin-2 (1*H*)-one (TIBO) derivatives. The discriminating power of the adjacent eccentric distance sum index was compared with that of the *eccentric connectivity index* – another adjacency-cum-distance-based topological descriptor. The values of the eccentric connectivity index and the adjacent eccentric distance sum index of each of 121 analogues comprising the data set were computed and active ranges were identified. Subsequently, a biological activity was assigned to each analogue involved in the data set and this was then compared with the reported anti-HIV activity. Excellent correlations were observed between anti-HIV activity and both the topological descriptors. Although the overall accuracy of prediction was found to be ~84% in case of the eccentric connectivity index and ~86% in case of adjacent eccentric distance sum index, the predictability using the adjacent eccentric distance sum index in the active range itself was >92%. The proposed index offers a vast potential for structure–activity/property studies.

Keywords Adjacent eccentric distance sum index · Anti-HIV activity · Eccentric connectivity index · Structure–activity relationship · TIBO derivatives and topological descriptors

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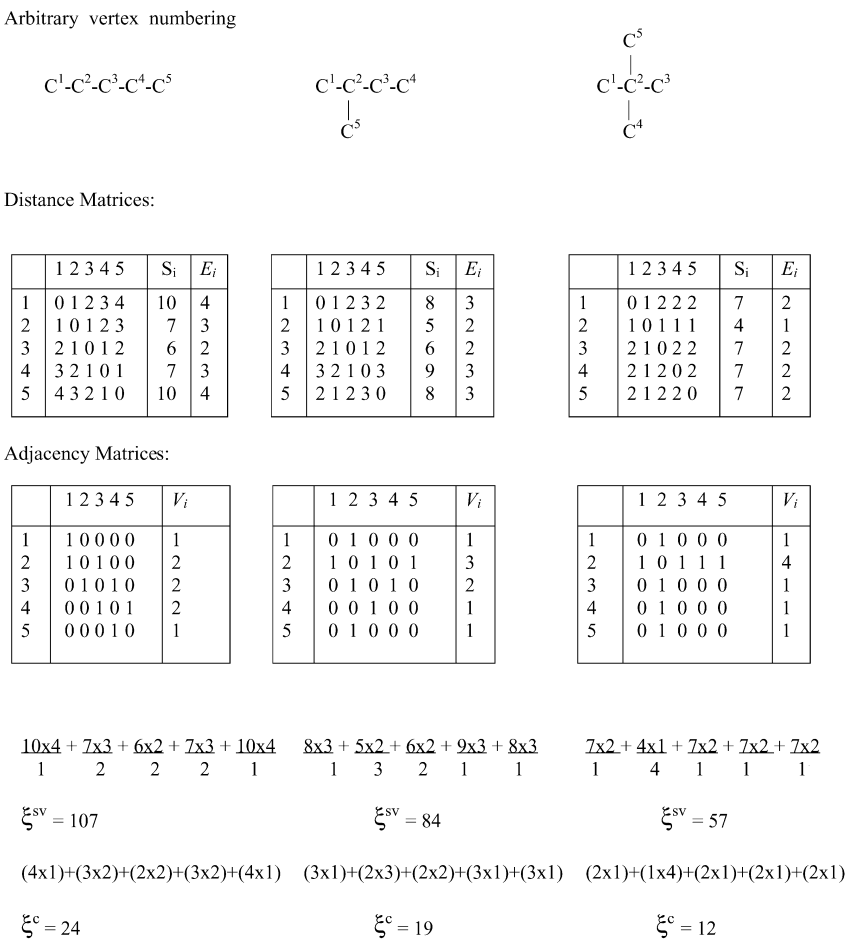
Introduction

A contemporary trend in pharmaceutical drug design is the quantitative prediction of properties of biologically active molecules using theoretical parameters. [1, 2, 3, 4, 5] The important step in the mathematical characterization of structures, which can be accomplished by a matrix, a set of numbers, a polynomial or a single numerical index, has been the introduction of the so-called topological indices. These are numerical quantities or molecular descriptors that one can derive from a known molecular skeletal form. In recent years topological indices have been found to be useful in chemical documentation, isomer discrimination, structure–property relationships, structure–activity (SAR) relationships and pharmaceutical drug design. [6, 7] Although a number of topological indices have been reported, only a handful of them have been employed successfully in SAR studies. These include Wiener's index, [8, 9, 10, 11, 12, 13] Balaban's index, [14, 15, 16, 17, 18] Hosoya's index, [19, 20] Randic's molecular connectivity index, [21] and the eccentric connectivity index. [22, 23] A number of indices have been derived from eccentricity. Some of the eccentricity-based indices include eccentric connectivity index, [22, 23] graph shape index, [24] and connective eccentricity index. [25]

Acquired immune deficiency syndrome (AIDS) may be considered a secondary immunodeficiency disease induced by the human immunodeficiency viruses HIV-1 and 2. The immunologic profile exhibited in AIDS from early infection to terminal stage illness shows effects of the gradual devastation of the immune system. [26]

Therapeutic intervention for the treatment of human immunodeficiency virus type I (HIV-1), which eventually results in AIDS, is limited to AZT (zidovudine) and a few other drugs approved for this disease. Unfortunately, these suffer from a number of limitations including limiting side effects and the revelation of the possible emergence of drug-resistant mutants of the virus. [27] Since retroviruses such as HIV-1 possess a unique replication cycle, a variety of molecular targets are now available

Fig. 1 Calculation of the values of the adjacent eccentric distance sum index and the eccentric connectivity index for three isomers of pentane



for chemotherapeutic intervention. [28] One such target of considerable interest is the virally encoded reverse transcriptase (RT), which mediates conversion of the viral RNA genome to proviral DNA. Use of nucleoside analogues such as AZT, [29, 30] which inhibits the operation of RT, is limited by significant toxicities. [31, 32, 33] Potent non-nucleoside, HIV-1 specific RT inhibitors have now been described in several chemically diverse series. [34, 35]

In the present investigations, a novel adjacency-cum-distance-based topological descriptor, termed the *adjacent eccentric distance sum index*, has been conceptualized and its discriminating power investigated with regard to the anti-HIV activity of 4,5,6,7-tetrahydroimidazo-[4,5,1-*jk*] [1,4] benzodiazepin-2 (1*H*)-one (TIBO) derivatives. The discriminating power of the proposed index was subsequently compared with that of another adjacency-cum-distance-based topological descriptor – the *eccentric connectivity index*. QSAR modeling of TIBO derivatives with the electrotopological state based on chemical graph theory has been reported by Huuskonen. [36] The models developed in the present study are of an entirely different kind and are much more useful in drug design. Moreover, the size of the data set of TIBO derivatives used by the authors in the present study is much larger than the one used by Huuskonen.

Methodology

Calculation of topological indices

The eccentric connectivity index [22] 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.

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

where V_i is the degree of the vertex i, E_i is the eccentricity of vertex i and n is the number of 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 is an integer number and takes into consideration the eccentricity as well as the valency of the vertices in a hydrogen-suppressed graph.

A novel adjacency-cum-distance-based topological descriptor has been conceptualized. This index is termed the adjacent eccentric distance sum index (ξ^{sv}) and is defined as the summation of the values of the product of distance sum and eccentricity and divided by the degree of the corresponding vertex for all the vertices in the hydrogen-suppressed molecular graph.

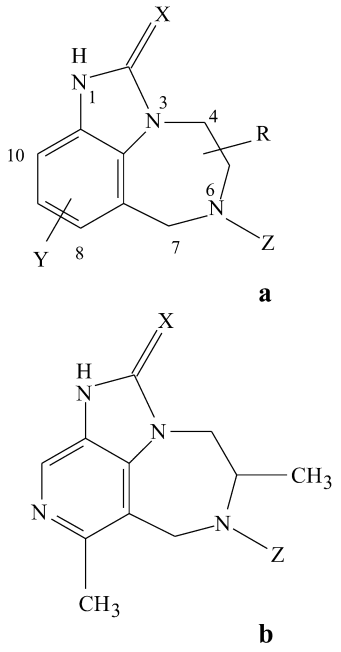


Fig. 2 Basic structures of TIBO derivatives

$$\xi^{sv} = \sum_{i=1}^{n} S_i E_i / V_i$$

where S_i is the distance sum of vertex i, E_i is the eccentricity of vertex i and V is the degree over all vertices. The degree is the valency of a vertex, which can be obtained easily by summation of all the elements in the corresponding row of the adjacency matrix of the hydrogen-suppressed molecular structure.

The adjacent eccentric distance sum index is a real number and can be calculated easily from distance and adjacency matrices of the hydrogen-suppressed molecular structure of a compound. Calculation of the adjacent eccentric distance sum index and the eccentric connectivity index of three isomers of pentane is exemplified in Fig. 1.

Model development analysis

A data set [37, 38] comprising 121 TIBO derivatives was selected for the present investigations. The basic structures for these analogues are depicted in Fig. 2 and various substituents listed in Table 1. The data set comprised both the active and inactive compounds. Anti-HIV activity was reported quantitatively as IC_{50} at different concentrations. The analogues possessing IC_{50} values of less than 1 μM were considered to be active and analogues possessing an IC_{50} value of 1 μM or more were considered to be inactive for the purpose of present study. The values of the eccentric connectivity index were computed for each analogue using an in-house computer program. The resultant data were analyzed and an active range was identified based on the maximization of moving average with respect to active compounds (<35%= inactive, 35–65%=transitional, ^65%=active). [39] Subsequently, each analogue was assigned a biological activity that was then compared with the reported anti-HIV activity. 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.

The aforementioned procedure was adopted similarly in the case of the adjacent eccentric distance sum index.

The results are summarized in Tables 1, 2 and 3. Since the values of the adjacent eccentric distance sum index were relatively very large, they were reduced to the nearest whole numbers for the sake of simplicity.

Results and discussion

Today SAR is a vital tool for developing safer and potent drugs. The emphasis is on conservation of time and minimization of animal sacrifice and expenditure. An inherent problem in SAR is the quantification of chemical structures. It is difficult to obtain a correlation between quantitative biological activity and qualitative chemical structures. However, the said problem can be solved easily by resorting to graph theory, which provides a large number of topological descriptors of a diverse nature for the quantification of chemical structures so as to facilitate the development of suitable correlations with quantified biological activities. Accordingly, a novel adjacency-cum-distance-based topological descriptor, termed the adjacent eccentric distance sum index has been conceptualized in the present investigations. As observed from Fig. 1, the index exhibits high discriminating power with regard to three isomers of pentane, for which the index value decreases steeply from 107 to just 57 with an increase in branching.

AIDS is caused by a virus, HIV, first isolated in 1983. It has been identified in over 200 countries and territories worldwide and is spreading rapidly in many affected populations, particularly in developing countries. Currently approved drugs for AIDS suffer from a number of limitations including limiting side effects and the emergence of drug-resistant mutants of the virus. Therefore, there is a strong need for the development of newer potent anti-HIV agents with fewer side effects. Accordingly, the relationship of the eccentric connective index and the proposed adjacent eccentric distance sum index with anti-HIV activity of TIBO derivatives has been investigated in the present study. Excellent correlations between these indices and the anti-HIV activity of TIBO derivatives were observed.

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

Table 1 Relationship of the eccentric connectivity index and the adjacent eccentric distance sum index with anti-HIV activity of TIBO derivatives

Comp No	Basic structure	R	X	Y	Z[a]	ξ^c	ξ^{sv}	Anti HIV activity[b]		
								Predicted		Reported
								ξ^c	ξ^{sv}	
1	a	H	S	8-Cl	DMA	313	6897	–	±	+
2	a	H	S	9-Cl	DMA	317	7093	–	±	+
3	a	5-Et	O	–	H	197	2395	–	–	–
4	a	5-Et	O	–	2-MA	277	5770	–	–	–
5	a	5-i-Pr	O	–	H	210	3050	–	–	–
6	a	5-i-Pr	O	–	2-MA	290	6704	–	±	–
7	a	5-i-Pr(S)	O	–	H	210	3050	–	–	–
8	a	5-i-Pr(S)	O	–	DMA	335	8605	±	±	–
9	a	5-i-Pr(S)	S	–	DMA	335	8605	±	±	–
10	a	5-i-Pr(S)	O	9-Cl	H	238	4118	–	–	–
11	a	5-i-Pr(S)	O	9-Cl	DMA	360	10347	–	–	–
12	a	5-i-Pr(S)	S	9-Cl	DMA	360	10347	–	–	–
13	a	5-n-Pr	O	–	H	236	3331	–	–	–
14	a	5-n-Pr	O	–	2-MA	299	6854	–	±	–
15	a	5-Ph	O	–	H	324	5272	+	–	–
16	a	5-Ph	O	–	2-MA	378	9339	–	–	–
17	a	5,5-di-Me	O	–	H	174	2159	–	–	–
18	a	5,5-di-Me	O	–	2-MA	275	5716	–	–	–
19	a	5-keto	O	–	n-Pr	249	4018	–	–	–
20	a	4-Me	O	–	H	155	1608	–	–	–
21	a	4-Me	O	–	2-MA	264	5001	–	–	–
22	a	4-Me(S)	S	9-Cl	2-MA	285	6151	–	±	+
23	a	4-Me(R)	S	9-Cl	CH_2-c-Pr	301	5319	–	–	–
24	a	4-i-Pr	O	–	H	219	3112	–	–	–
25	a	4-i-Pr	O	–	n-Pr	275	5520	–	–	–
26	a	4-i-Pr	O	–	2-MA	290	6691	–	±	–
27	a	4-n-Pr	O	–	H	221	3065	–	–	–
28	a	4-n-Pr	O	–	n-Pr	286	5691	–	–	–
29	a	4-n-Pr	O	–	2-MA	301	6876	–	±	–
30	a	4-Ph	O	–	H	311	4887	–	–	–
31	a	4-Ph	O	–	n-Pr	365	8090	–	±	–
32	a	4-Ph	O	–	2-MA	382	9631	–	–	–
33	a	7-Me	O	–	H	157	1660	–	–	–
34	a	7-Me	O	–	n-Pr	249	3990	–	–	–
35	a	7-Me	O	–	DMA	309	6632	–	±	–
36	a	7-Me	O	8-Cl	DMA	324	7677	+	+	+
37	a	7-Me	O	9-Cl	DMA	328	7903	+	+	+
38	a	7-Me	S	–	n-Pr	249	3990	–	–	–
39	a	7-Me	S	–	DMA	309	6632	–	±	+
40	a	7-Me	S	8-Cl	DMA	324	7677	+	+	+
41	a	7-Me	S	9-Cl	DMA	328	7903	+	+	+
42	a	7-(2-Me-propyl)	O	9-Cl	DMA	371	11466	–	–	–
43	a	7-(2-Me-propyl)	S	9-Cl	DMA	369	11171	–	–	–
44	a	7-Ph	S	–	DMA	403	11127	–	–	–
45	a	4,5-di-Me(cis)	O	–	DMA	322	7540	–	±	–
46	a	4,5-di-Me(cis)	S	–	DMA	322	7540	–	±	–
47	a	4,5-di-Me(trans)	S	–	CH_2-c-Pr	291	4890	–	–	–
48	a	4,5-di-Me(trans)	S	–	DMA	322	7537	–	–	
49	a	4-keto-5-Me	S	9-Cl	n-Pr	283	5823	–	–	–
50	a	7-oxo-4,5-benzo	S	–	H	346	3448	–	–	–
51	a	4,5-benzo	S	–	CH_2-c-Pr	331	5688	±	–	–
52	a	5,7-di-Me(trans)	S	–	DMA	320	7447	–	±	+
53	a	5,7-di-Me(cis)	S	–	DMA	320	7447	–	±	–
54	a	5,7-di-Me(R,R;trans)	O	9-Cl	DMA	341	8888	±	±	+
55	a	5,7-di-Me(R,R;trans)	S	9-Cl	DMA	341	8888	±	±	+
56	a	5,7-di-Me(S,S;trans)	O	9-Cl	DMA	341	8888	±	±	–
57	a	5,7-di-Me(S,S;trans)	S	9-Cl	DMA	341	8888	±	±	–
58	a	5-Me-7-keto	O	–	n-Pr	260	4636	–	–	–
59	a	4,7-di-Me(trans)	S	–	DMA	322	7533	–	±	–
60	a	4,7-di-Me(cis)	S	–	DMA	322	7533	–	±	–
61	a	5,6-$(CH_2)_4$	O	–	–	244	3064	–	–	–
62	a	5,6-$(CH_2)_3$	O	–	–	214	2355	–	–	–
63	a	5,6-$CH_2C(=CH_2)CH_2$(S)	S	9-Cl	–	275	4385	–	–	–

Table 1 (continued)

Comp No	Basic structure	R	X	Y	Z[a]	ξ^c	ξ^{sv}	Anti HIV activity[b]		
								Predicted		Reported
								ξ^c	ξ^{sv}	
64	a	5,6-$CH_2C(=CHCH_3)CH_2$(S)	S	9-Cl	–	318	5789	–	–	–
65	a	6,7-$(CH_2)_3$	S	9-Cl	–	226	2986	–	–	–
66	a	6,7-$(COCH_2CH_2)$	S	9-Cl	–	253	3946	–	–	–
67	a	6,7-$(CH_2)_4$	S	9-Cl	–	254	3739	–	–	–
68	a	7,8-$(CH_2)_2$	S	9-Cl	DMA	317	7093	–	±	–
69	a	5-Me(S)	S	8-Cl	DMA	324	7730	+	+	+
70	a	5-Me(S)	O	9-Cl	H	189	2436	–	–	–
71	a	5-Me(S)	O	9-Cl	DMA	330	8032	+	±	+
72	a	5-Me(S)	S	9-Cl	DMA	330	8032	+	±	+
73	a	5-Me(S)	S	9-Cl	CH_2-c-Pr	301	5332	–	–	+
74	a	5-Me(S)	S	–	CH_2-c-Pr	280	4246	–	–	+
75	a	5-Me	O	–	H	163	1689	–	–	–
76	a	5-Me	O	–	n-Pr	249	4018	–	–	–
77	a	5-Me	S	–	n-Pr	249	4018	–	–	–
78	a	5-Me	O	–	2-MA	264	5006	–	–	–
79	a	5-Me	S	–	DMA	309	6662	–	±	+
80	a	5-Me(S)	O	–	DMA	309	6662	–	±	–
81	a	5-Me(S)	S	–	2-MA	264	5006	–	–	+
82	a	5-Me	S	–	DMA	309	6661	–	±	+
83	a	5-Me	S	9-Cl	DMA	309	6662	–	±	+
84	a	5-Me	S	8-Cl	DMA	264	5006	–	–	+
85	a	5-Me	S	8-F	DMA	324	7730	+	+	+
86	a	5-Me	S	8-SCH_3	DMA	345	8895	±	±	+
87	a	5-Me	S	8-OCH_3	DMA	345	8895	±	±	+
88	a	5-Me	S	8-OEt	DMA	382	11034	–	–	+
89	a	5-Me	O	8-CN	DMA	345	8895	±	±	–
90	a	5-Me	S	8-CN	DMA	345	8895	±	±	+
91	a	5-Me	S	8-CHO	DMA	362	10430	–	–	+
92	a	5-Me	O	8-$CONH_2$	DMA	362	10430	–	–	–
93	a	5-Me	O	8-Br	DMA	324	7730	+	+	+
94	a	5-Me	S	8-Br	DMA	324	7730	+	+	+
95	a	5-Me	O	8-I	DMA	324	7730	+	+	+
96	a	5-Me	S	8-I	DMA	324	7730	+	+	+
97	a	5-Me	O	8-C=CH	DMA	345	8895	±	±	+
98	a	5-Me	S	8-C=CH	DMA	345	8895	±	±	+
99	a	5-Me	O	8-CH_2CH_3	DMA	345	8895	±	±	–
100	a	5-Me	O	8-CH_3	DMA	324	7730	+	+	+
101	a	5-Me	S	8-CH_3	DMA	324	7730	+	+	+
102	a	5-Me	O	9-NO_2	CPM	353	8031	–	±	–
103	a	5-Me	O	8-NH_2	CPM	293	5046	–	–	–
104	a	5-Me	O	8-$N(CH_3)_2$	CPM	329	7181	+	±	–
105	a	5-Me	O	8-$NHCOCH_3$	CPM	366	9034	–	–	–
106	a	5-Me	O	9-NH_2	CPM	301	5332	–	–	–
107	a	5-Me	O	9-$N(CH_3)_2$	CPM	353	8031	–	±	–
108	a	5-Me	O	9-$NHCOCH_3$	CPM	397	10176	–	–	–
109	a	5-Me	S	9-NO_2	CPM	353	8031	–	±	–
110	a	5-Me	S	9-F	DMA	330	8032	+	±	+
111	a	5-Me	O	9-CF_3	DMA	405	13444	–	–	–
112	a	5-Me	S	9-CF_3	DMA	405	13444	–	–	+
113	a	5-Me	O	9-CH_3	DEA	398	11649	–	–	+
114	a	5-Me	O	10-OCH_3	DMA	383	10546	–	–	–
115	a	5-Me	S	10-OCH_3	DMA	383	10546	–	–	–
116	a	5-Me	S	9,10-diCl	DMA	361	9879	–	–	+
117	a	5-Me	S	10-Br	DMA	344	8528	±	±	–
118	b	–	O	–	DMA	324	7730	+	+	–
119	b	–	O	–	DEA	396	11402	–	–	–
120	b	–	S	–	DEA	396	11402	–	–	–
121	b	–	O	–	CPM	293	5046	–	–	–

[a] Me, methyl; Et, ethyl; n-pr, *n*-propyl; i-pr, isopropyl; n-bu, *n*-butyl, ph, phenyl; CPM, cyclopropylmethyl; DMA, 3,3-dimethylallyl; DEA, 3,3-diethylallyl

[b] +, positive anti-HIV activity, –, negative anti-HIV activity, ±, transitional range where activity could not be specifically assigned

Table 2 The relationship between anti-HIV activity of TIBO derivatives and the eccentric connectivity index

Nature of range	Index value	Total number of analogues in the range	Number of analogues predicted correctly	Percent accuracy	Average IC_{50} of correctly predicted analogues in the range (μM)
Lower inactive	<301	46	41	89.13	157.7
Lower transitional	301–322	18	NA[a]	NA[a]	21.2
Active	323–330	18	15	83.33	0.12
Upper transitional	331–345	15	NA[a]	NA[a]	3.6
Upper inactive	>345	24	18	75	86.8

[a] Not applicable

Table 3 The relationship between anti-HIV activity of TIBO derivatives and the adjacent eccentric distance sum index

Nature of range	Index value	Total number of analogues in the range	Number of analogues predicted correctly	Percent accuracy	Average IC_{50} of correctly predicted analogues in the range (μM)
Lower inactive	<6151	45	41	91.11	168.3
Lower transitional	6151–7540	22	NA[a]	NA[a]	9.8
Active	7540–7903	13	12	92.30	0.13
Upper transitional	7904–8895	21	NA[a]	NA[a]	16.1
Upper inactive	>8895	20	14	70	90.5

[a] Not applicable

- Biological activity was assigned to a total number of 88 analogues in both the active and inactive ranges, out of which the activity of 74 analogues was predicted correctly, resulting in ~84% accuracy with regard to anti-HIV activity.
- The active range had eccentric connectivity index values of 323–330. As many as ~83% of the analogues in the active range exhibited anti-HIV activity.
- The active range was bracketed by two transitional ranges, indicating a gradual change in anti-HIV activity. A total of 33 analogues were present in the transitional range.
- The average IC_{50} value was found to be 0.12 μM for correctly predicted compounds, indicating the presence of highly active compounds in the active range. However, the overall average IC_{50} value was 62.8 μM due to the presence of three inactive compounds with high IC_{50} values in the active range.

Retrofit analysis of the data in Tables 1 and 3 reveals the following information with regard to the adjacent eccentric distance sum index:

- Biological activity was assigned to a total of 78 analogues in both the active and inactive ranges out of which the activity of 67 analogues was predicted correctly, resulting in ~86% accuracy with regard to anti-HIV activity.
- The active range had adjacent eccentric distance sum index values of 7540–7903. As many as ~92% of the analogues in the active range exhibited anti-HIV activity.
- The active range was bracketed by two transitional ranges indicating a gradual change in anti-HIV activity. A total of 43 analogues were present in the transitional range.
- The average IC_{50} value was found to be 0.13 μM for correctly predicted compounds, indicating the presence of highly active compounds in the active range. However, the overall average IC_{50} value was 67.2 μM due to presence of only one inactive compound but with a very high IC_{50} value in the active range.

Further the active analogues were found to be present in a narrow range of eccentric connectivity index and adjacent eccentric distance sum index values. The above results clearly indicate excellent correlations of both the adjacent eccentric distance sum index and the eccentric connectivity index with regard to anti-HIV activity of TIBO derivatives.

The adjacent eccentric distance sum index is superior to the eccentric connectivity index, not just because of marginally higher predictability (86% compared to 84% on the average and 92% against 83% in the active range) but mainly because of its high discriminating power and extremely low degeneracy. The adjacent eccentric distance sum index did not exhibit any degeneracy for all possible structures up to four vertices and exhibited degeneracy in only one case for all possible structures up to five vertices. For comparison, the eccentric connectivity index showed degeneracy even in the case of structures up to three vertices. All possible structures up to five vertices along with values for the adjacent eccentric distance sum index and the eccentric connectivity index are shown in Fig. 3. As observed from Fig. 3 and Table 4, the discriminating power of the adjacent eccentric distance sum index is much superior to that of the eccentric connectivity index, if one just compares the ratio of the maximum index and minimum index values for three, four and five vertices.

Table 4 Minimum and maximum values of the eccentric connectivity index and the adjacent eccentric distance sum index for all possible structures up to five vertices

Index	Up to three vertices			Up to four vertices			Up to five vertices		
	Minimum value	Maximum value	Ratio	Minimum value	Maximum value	Ratio	Minimum value	Maximum value	Ratio
ξ^c	6	6	1:1	9	16	1:1.77	12	28	1:2.33
ξ^{sv}	3	13	1:4.33	4	44	1:11	5	107	1:21.4

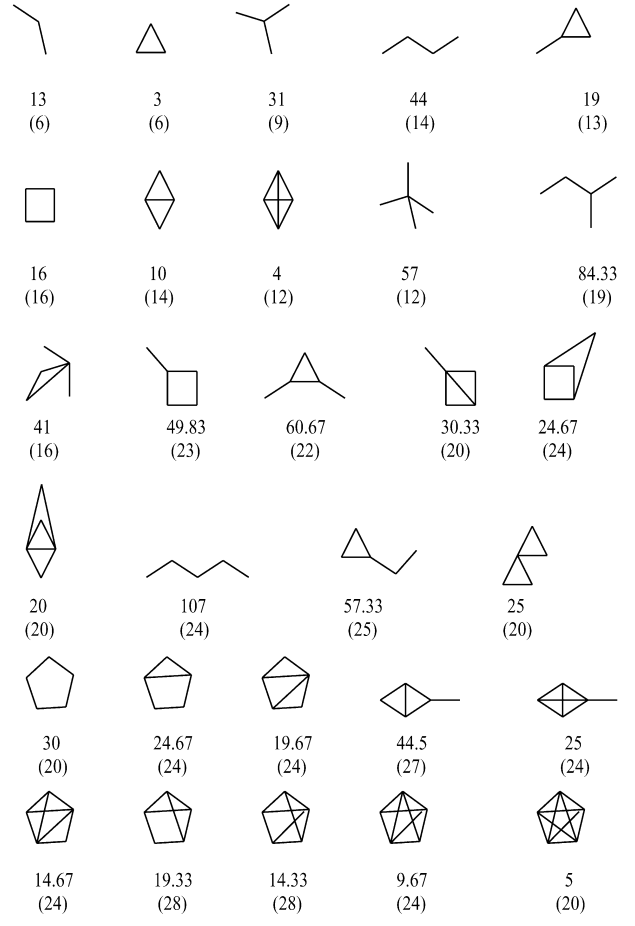


Fig. 3 Values of the adjacent eccentric distance sum index and the eccentric connectivity index (in brackets) for all possible isomers up to five vertices

The simplicity and high discriminating power of the proposed adjacent eccentric distance sum index can be exploited easily for structure–activity/property studies. Such studies can easily provide valuable leads for developing a wide range of potent therapeutic agents of a diverse nature. Topological descriptors used for the present study do not discriminate among various heteroatoms. Further work with regard to the development of topological descriptors capable of differentiating heteroatoms as well is in progress.

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