Eccentric Connectivity Index: A Novel Highly Discriminating Topological Descriptor for Structure−Property and Structure−Activity Studies

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A novel, distance-cum-adjacency topological descriptor, termed as *eccentric connectivity index*, has been conceptualized, and its discriminating power has been investigated with regard to physical/biological properties of molecules. Correlation coefficients ranging from 95% to 99% were obtained using eccentric connectivity index in various datasets with regard to physical properties of diverse nature. These correlations were far superior to those correspondingly derived from the Wiener index. For structure−activity studies, a dataset, comprised of 94 substituted piperidinyl methyl ester and methylene methyl ester analogs as analgesic agents, was selected. Values of the eccentric connectivity index, the Wiener index, and Randić's molecular connectivity index were calculated, and active ranges were identified. Good correlations between topological descriptors and analgesic activity of these analogs were obtained. Eccentric connectivity index exhibited highest predictibility of the order of 86%. High discriminating power as revealed by excellent correlations obtained from structure−property and structure−activity studies offers an eccentric connectivity index of vast potential in QSPR/QSAR.

INTRODUCTION

During the past two decades, there has been considerable progress in the application of algebraic graph theory in chemistry.[1−4] Graph theory is concerned with manipulations of structures and structural information. This involves classification of structures, that is, their grouping into smaller lots, characterization of structures, which can be accomplished by enumeration of selected structural invariants, and ordering of structures, which implies a decision of which among two or more structures should be taken first in a sequence.[5]

One of the ways in which chemical information is derived is through graph theoretical invariants, which have been found useful in chemical documentation, isomer discrimination, structural-property correlations, and chemical structural-biological activity relationships.[6]

A graph invariant is a graph-theoretic property which is preserved by isomorphism.[7] For several years attention was mainly on the so called topological indices which are molecular descriptors derived from information on connectivity and composition of molecule and thus used for the mathematical characterization of molecules.[8] Chemical structures, using apt topological indices, can be represented by a number, a sequence, a matrix, or a polynomial. All such representations aim to be unique for a given molecular graph.[9]

Topological indices developed for the purpose of obtaining correlations with physicochemical properties and biological activity of chemical substances have been applied for a very extensive range. The current major applications include bibliographical species classification, physicochemical parameter evaluation, and pharmaceutical drug design.[10−16]

In the present investigations, a new distance-cum-adjacency based index, termed as *eccentric connectivity index*, has been conceptualized. This index takes into consideration the eccentricity and valency of each vertex involved in a molecular graph.

The eccentricity $E(i)$, also referrred to as *associated number* or *separation*,[17] of a vertex i in a graph G is the distance from i to the vertex farthest from i in G, that is

$$E(i) = \max_{j \in G} d(i,j)$$

By the distance $d(i,j)$ between vertices $i,j \in V(G)$, we mean the length of a simple path which joins the vertices i and j in the graph G and contains the minimal number of edges. A more generalized defination of eccentricity is given by Petitjean.[18]

The *eccentric connectivity index*, denoted by ξ^c, can be defined as the sum total of the product of eccentricity and degree of each vertex in a hydrogen-suppressed molecular graph having n total vertices, that is

$$\xi^c = \sum_{i=1}^{n} E(i)V(i)$$

where, $E(i)$ is the eccentricity and $V(i)$ is the degree of vertex i.

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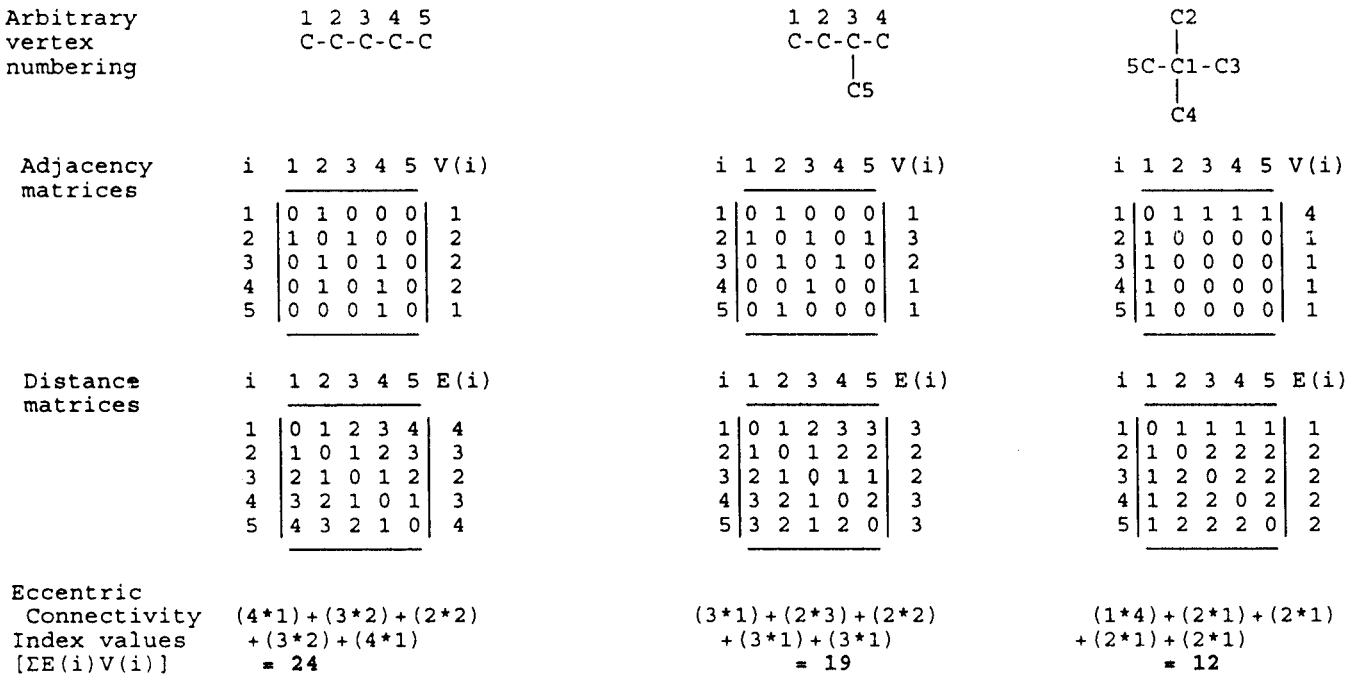

Figure 1. Calculation of eccentric connectivity index values for pentanes.

Eccentric connectivity index can be easily calculated from the distance matrix of a hydrogen-suppressed molecular graph after the vertices have been numbered arbitrarily. Calculation of eccentric connectivity index for three isomers of pentanes has been exemplified in Figure 1.

Correlating ability of eccentric connectivity index, for various physical properties, has been compared with the classical Wiener toplogical index.

The potential of eccentric connectivity index in structure−activity relationships has also been explored in the present studies. Investigations have been carried out on correlating ability of the eccentric connectivity index, the Wiener index, and Randić's molecular connectivity index in predicting analgesic activity of substituted piperidinyl methyl ester and methylene methyl ester analogs.

The Wiener index,[10] a well-known distance based toplogical index, is defined as the sum of distances between all pair of vertices in a molecular graph, that is

$$W(G) = 1/2\sum_{(i,j)} Di,j$$

where, Di,j (G) represents off-diagonal elements of the distance matrix $D(G)$.

Randić,[19] in 1975, proposed an index for characterization of branching. This index, termed as *molecular connectivity index* and later as *first-order molecular connectivity index* by Kier and Hall,[20] is denoted by "$^1\chi$" and is defined as the sum over all the edges (i,j) as

$$^1\chi = \sum_{i=1}^{n} (v_i v_j)^{-1/2}$$

where v_i and v_j are the degrees of adjacent vertices i and j, and n is the number of vertices in a hydrogen-suppressed structure.

METHODOLOGY

Various datasets, for properties ranging from physical to biological, were selected in order to test the validity of the proposed *eccentric connectivity index*. These comprise the following:

(1) A group of 62 straight chain, branched, and cyclic alcohols along with their boiling points and cross sectional areas[21,22] (Tables 1 and 2).

(2) A group of 21 primary and 13 secondary amines along with their boiling points[23] (Table 1).

(3) A group of 48 heterogenous chemical compounds comprising of ethers, amines, and alcohols along with their molar refraction values[23] (Table 3).

(4) A dataset comprising of 91 substituted piperidinyl methyl ester and methylene methyl ester analogs[24] (Figure 2, Table 4).

In case of physical properties (datasets 1−3), values for the eccentric connectivity index and the Wiener index were calculated for all the compounds, and the resultant data were subjected to both linear as well as nonlinear regression analysis. Appropriate equations along with correlation coefficients, average errors (calculated from percentage error of each compound in a dataset), and root mean square (RMS) errors were determined. Results have been compiled in Tables 1−3 and Figures 3−14.

For dataset comprising of substituted piperidinyl methyl ester and methylene methyl ester analogs as analgesic agents, values of the eccentric connectivity index, the Wiener index, and Randić's molecular connectivity index were computed for all the compounds using hydrogen suppressed structures, and active, inactive, and transitional ranges were identified. Using each topological index every analog was then assigned an activity which was subsequently compared with the reported[19] analgesic activity. Compounds possesing an ED_{50} value of less than 0.1 mg/kg were arbitrarily assigned a positive activity and those possesing an ED_{50} value of 0.1 mg/kg or more were poorly active and considered to be negative for present studies. Results have been compiled in Tables 4 and 5.

Table 1. Relationship of Eccentric Connectivity Index (ξ^c) and Wiener Index (W) with Boiling Points of Primary Amines, Secondary Amines, and Alcohols

			boiling points, °C						boiling points, °C		
				predicted[a]						predicted[a]	
compound	ξ^c	W	exptl	ξ^c	W	compound	ξ^c	W	exptl	ξ^c	W
Primary Amines											
n-propylamine	18	10	49	58.68	33.65	4-methylpentylamine	45	52	125	123.09	135.21
				53.31	31.53					113.27	126.40
2-aminopropane	9	9	33	31.11	30.47	*n*-hexylamine	54	56	130	139.31	142.08
				28.14	28.56					128.75	132.78
2-amino-2-methylproprane	12	16	46	40.68	51.89	3-methylpentylamine	45	50	114	123.09	131.61
				36.85	48.61					113.27	123.05
2-aminobutane	19	18	63	61.54	57.67	4-aminoheptane	61	75	139	150.37	169.33
				55.93	54.02					139.44	185.52
2-methylpropylamine	19	18	69	61.54	57.67	2-aminoheptane	65	79	142	156.11	174.04
				55.93	54.02					145.05	162.43
n-butylamine	24	20	77	75.25	63.29	*n*-heptylamine	74	84	155	167.63	179.46
				68.56	59.28					156.42	167.44
2-amino-2-methylbutane	24	28	78	75.25	84.36	*n*-octylamine	96	120	180	188.47	205.53
				68.56	78.98					177.74	191.36
2-aminopentane	31	32	92	92.88	94.08	*n*-nonylamine	122	165	201	202.26	214.38
				84.90	88.05					193.14	199.08
3-methylbutylamine	31	31	96	92.88	91.70	2-aminoundecane	168	277	237	206.52	180.95
				84.90	85.83					201.60	166.92
2-methylbutylamine	29	32	96	88.02	94.08	3-aminopentane	29	31	91	88.02	91.7
				80.38	88.05					80.38	85.83
n-pentylamine	38	35	104	108.78	101.02						
				99.77	94.53						
Secondary Amines											
N-(methyl)ethylamine	18	10	36	44.08	27.78	*N*-methyl-1-methylbutylamine	45	50	105	97.44	109.58
				53.31	31.54					113.27	123.05
N-methyl-1-methylethylamine	19	18	50	46.32	47.69	dipropylamine	54	56	109.5	112.24	118.45
				55.93	54.02					128.75	132.79
diethylamine	24	20	56	57.19	52.36	bis(2-methylpropyl)amine	76	108	139	142.90	167.85
				68.56	49.28					158.72	185.52
N-methyl-1-methylpropylamine	29	31	78.5	67.54	76.04	dibutylamine	56	120	159	164.79	173.70
				80.38	85.83					177.74	191.36
N-(ethyl)propylamine	38	35	80.5	84.95	83.84	bis(3-methylbutyl)amine	126	202	187.5	188.67	179.87
				99.77	94.53					194.72	193.77
bis(1-methylethyl)amine	38	48	84	84.95	106.45	dipentylamine	150	220	205	201.75	176.08
				99.77	119.60					200.61	188.75
N-(methyl)butylamine	38	35	90.5	84.95	83.84						
				99.77	94.53						
Alcohols											
ethanol	6	4	78.5	88.67	92.39	2,3-dimethyl-2-pentanol	43	63	139.7	144.71	152.2
2-propanol	9	9	82.4	98.08	107.0	2,3-dimethyl-3-pentanol	41	62	139.0	143.00	151.75
1-propanol	18	10	97.4	116.53	109.06	2,4-dimethyl-2-pentanol	45	66	133.0	146.35	153.48
1-butanol	24	20	117.7	125.17	123.65	2,4-dimethyl-3-pentanol	43	65	138.8	144.71	153.06
2-methylpropanol	19	18	107.9	118.11	121.31	2,2-dimethyl-3-pentanol	43	65	136.0	144.71	153.06
2-butanol	19	18	99.5	118.11	121.31	3-heptanol	63	76	156.8	159.13	157.45
1-pentanol	38	35	137.8	140.33	136.83	4-heptanol	61	75	155.0	157.86	157.08
3-methylbutanol	31	32	131.2	133.40	134.63	1-octanol	96	120	195.2	176.70	171.03
2-methylbutanol	29	31	128.7	131.20	133.86	2,2,3-trimethyl-3-pentanol	48	82	152.5	148.72	159.64
2-pentanol	31	32	119.0	133.40	134.63	2-octanol	87	114	179.8	172.43	168.45
3-pentanol	29	31	115.3	131.20	133.86	2-ethylhexanol	77	104	184.6	167.27	166.65
3-methyl-2-butanol	24	29	111.5	125.17	132.25	1-nonanol	122	165	213.1	187.54	181.17
2-methyl-2-butanol	24	28	102.0	125.17	132.25	2-nonanol	111	158	198.5	183.20	179.76
1-hexanol	54	56	157.0	153.14	148.98	3-nonanol	109	153	194.7	182.37	178.72
2-hexanol	47	52	139.9	147.94	147.0	4-nonanol	107	150	193.0	181.53	178.08
3-hexanol	45	50	135.4	146.35	145.96	5-nonanol	105	149	195.1	180.68	177.87
3-methyl-3-pentanol	34	44	122.4	136.50	142.62	2,6-dimethyl-3-heptanol	85	136	178.0	171.43	174.95
2-methyl-2-pentanol	38	46	121.4	140.33	143.77	3,5-diethyl-4-heptanol	79	125	187.0	168.34	172.29
2-methyl-3-pentanol	36	46	126.5	138.45	143.77	1,1-dimethylpentanol	83	129	192.0	170.42	173.28
3-methyl-2-pentanol	36	46	134.2	138.45	143.77	7-methyloctanol	111	158	206.0	183.20	179.76
2,3-dimethyl-2-butanol	29	42	118.6	131.20	141.42	3,5,5-trimethylhexanol	83	131	193.0	170.42	173.76
3,3-dimethylbutanol	38	46	143.0	140.33	143.77	1-dodecanol	240	364	230.2	221.93	209.08
3,3-dimethyl-2-butanol	29	42	120.2	131.20	141.42	cyclopentanol	29	26	140.85	131.20	129.66
4-methylpentanol	45	52	151.8	146.35	147.0	cycloheptanol	53	61	185.0	152.43	151.31
4-methyl-2-pentanol	38	48	131.7	140.33	144.88	1-ethylcyclohexanol	67	84	166.0	161.58	160.33
2-ethylbutanol	36	48	146.5	138.45	144.88	2-ethylcyclohexanol	67	86	181.0	161.58	161.02
cyclohexanol	45	42	161.0	146.35	141.41	1-methylcyclohexanol	52	59	155.0	151.71	150.4
1-heptanol	74	84	176.3	165.62	160.33	2-methylcyclohexanol	54	60	165.0	153.14	150.86
2-methyl-2-hexanol	56	71	142.5	154.53	155.52	3-methylcyclohexanol	54	61	174.5	153.14	151.31
3-methyl-3-hexanol	52	48	142.4	151.71	144.88	4-methylcyclohexanol	58	62	173.5	155.89	151.75
3-ethyl-3-pentanol	41	64	142.5	143.00	152.63	1,3,5-trimethylcyclohexanol	70	109	181.0	163.35	168.08

[a] The upper predicted values for each compound are for primary and secondary amines as different datasets and the lower predicted values are for the combined dataset. [b] ξ^c and W represent the eccentric connectivity index and the Wiener index, respectively.

Table 2. Relationship of Eccentric Connectivity Index (ξ^c) and Wiener Index (W) with Cross Sectional Areas of Alcohols

			cross sectional area		
				predicted[a]	
compound	ξ^c	W	exptl	ξ^c	W
1-butanol	24	20	272.1	284.08	287.33
2-methylpropanol	19	18	263.8	268.69	283.01
2-butanol	19	18	264.1	268.69	283.01
1-pentanol	38	35	303.9	316.95	313.45
3-methylbutanol	31	32	291.4	301.94	307.45
2-methylbutanol	29	31	289.4	297.18	306.45
2-pentanol	31	32	295.9	301.94	307.45
3-pentanol	29	31	293.5	297.18	306.05
3-methyl-2-butanol	24	29	284.3	284.08	303.13
2-methyl-2-butanol	24	28	282.5	284.08	301.60
1-hexanol	54	56	335.7	344.64	333.26
2-hexanol	47	52	327.7	333.42	329.72
3-hexanol	45	50	325.3	329.98	327.86
3-methyl-3-pentanol	34	44	305.8	308.66	321.88
2-methyl-2-pentanol	38	46	314.3	316.95	323.95
2-methyl-3-pentanol	36	46	314.3	312.89	323.95
3-methyl-2-pentanol	36	46	311.3	312.89	323.95
2,3-dimethyl-2-butanol	29	42	301.2	297.18	319.73
3,3-dimethylbutanol	38	46	307.5	316.95	323.95
3,3-dimethyl-2-butanol	29	42	296.7	297.18	319.73
4-methylpentanol	45	52	323.0	329.98	329.72
4-methyl-2-pentanol	38	48	314.9	316.95	325.94
2-ethylbutanol	36	48	308.6	312.89	325.94
1-heptanol	74	84	367.5	371.51	353.30
2-methyl-2-hexanol	56	71	346.1	347.64	344.84
3-methyl-3-hexanol	52	48	337.7	341.55	325.94
3-ethyl-3-pentanol	41	64	324.4	322.74	339.73
2,3-dimethyl-2-pentanol	43	63	323.8	326.43	338.96
2,3-dimethyl-3-pentanol	41	62	321.8	322.74	338.18
2,4-dimethyl-2-pentanol	45	66	328.6	329.98	341.24
2,4-dimethyl-3-pentanol	43	65	331.7	326.43	340.49
2,2-dimethyl-3-pentanol	43	65	326.1	326.43	340.49
3-heptanol	63	76	357.1	357.53	348.24
4-heptanol	61	75	357.1	354.79	347.58
1-octanol	96	120	399.4	395.28	371.92
2,2,3-trimethyl-3-pentanol	48	82	335.2	335.10	352.07
2-octanol	87	114	391.0	386.12	369.18
2-ethylhexanol	77	104	371.3	375.04	364.33
1-nonanol	122	165	431.2	418.52	389.37
2-nonanol	111	158	423.2	409.20	386.95
3-nonanol	109	153	420.8	407.43	385.16
4-nonanol	107	150	420.8	405.63	384.06
5-nonanol	105	149	420.8	403.81	383.69
2,6-dimethyl-4-heptanol	83	135	394.0	381.81	378.28
3,5-dimethyl-4-heptanol	79	125	379.3	377.34	374.11
2,2-dimethylpentanol	70	121	372.5	370.31	372.36
7-methyloctanol	111	158	418.7	409.20	386.95
3,5,5-trimethylhexanol	83	131	376.6	381.81	376.64
1-decanol	150	220	463.0	439.64	405.84
1-dedecanol	240	364	527.0	491.74	436.36

Table 3. Relationship of Eccentric Connectivity Index (ξ^c) and Wiener Index (W) with Molar Refractions of Mixed Compounds

			molar refraction		
				predicted[a]	
compound	ξ^c	W	exptl	ξ^c	W
butyl methyl ether	38	35	27.020	30.169	26.292
dibutyl ether	96	120	40.987	49.785	61.321
dipropyl ether	54	56	32.226	36.479	36.317
ethyl 1-methylethyl ether	31	32	27.678	27.025	24.721
ethyl pentyl ether	74	84	36.363	43.251	47.989
1-methylpropyl ethyl ether	45	50	31.560	33.056	33.596
butyl 1-methylethyl ether	65	79	36.027	40.324	46.007
1-methylpropyl methyl ether	29	31	31.337	26.068	24.188
butyldimethylamine	47	52	33.816	33.842	34.514
methyl-2-methylpropylamine	31	32	33.852	27.025	24.721
dimethylpentylamine	65	79	38.281	40.324	46.007
triethylamine	36	48	33.793	29.300	32.666
trimethylamine	9	9	19.594	13.850	10.338
tripropylamine	81	128	47.780	45.417	64.103
1-aminopropane	18	10	19.400	20.145	11.114
1-aminobutane	24	20	24.079	23.534	17.897
1-amino-3-methylbutane	31	32	28.672	27.025	24.721
1-aminopentane	38	35	28.727	30.169	26.292
3-aminopentane	29	31	28.617	26.068	24.188
1-aminohexane	54	56	33.290	35.479	36.317
1-aminoheptane	74	84	38.003	43.251	47.989
2-aminoheptane	65	79	38.037	40.324	46.007
1-aminononane	122	165	47.277	56.670	76.325
2-propanol	9	9	17.705	13.850	10.338
2-pentanol	31	32	26.680	27.025	24.721
3-pentanol	29	31	26.639	26.068	24.188
1-hexanol	54	56	31.428	36.479	36.317
1-heptanol	74	84	36.093	43.251	47.989
3-methyl-1-butanol	31	32	26.904	27.025	24.721
2-methyl-1-butanol	29	31	26.697	26.068	24.188
2-methyl-2-butanol	24	28	26.721	23.534	22.553
4-methyl-1-pentanol	45	52	31.489	33.056	34.514
2-methyl-1-pentanol	45	50	31.164	33.056	33.596
2-ethyl-1-butanol	36	48	31.180	29.300	32.666
2-methyl-2-pentanol	38	46	31.210	30.169	31.725
2-methyl-3-pentanol	36	46	31.138	29.300	31.725
4-methyl-2-pentanol	38	48	31.355	30.169	32.666
2,2-dimethyl-1-butanol	34	44	31.268	28.409	30.770
3-methyl-3-pentanol	34	44	31.182	28.409	30.770
2-methyl-1-hexanol	63	76	35.930	39.648	44.799
3-ethyl-3-pentanol	54	64	35.821	36.479	39.808
2-ethyl-1-hexanol	74	104	40.625	43.251	55.577
2-methyl-1-propanol	19	18	22.103	20.742	16.647
4-ethyl-4-heptanol	77	126	44.919	44.190	63.412
6-methyl-1-heptanol	87	114	40.736	47.205	59.197
3-methyl-3-heptanol	66	98	40.446	40.658	53.353
4-methyl-4-heptanol	68	96	40.439	41.319	52.602
1-octanol	96	120	40.637	49.785	61.321

RESULTS AND DISCUSSION

In contemporary biomedicinal chemistry, quantum chemical, physicochemical, and topological parameters have been extensively utilized in the prediction of biological activity of molecules. Since graph-theoretical indices are sensitive to different structural characteristics, QSPR/QSAR studies using a particular topological descriptor might lead to a simple structural interpretation of biological action and physicochemical properties of molecules.[25]

The present study is an attempt to explore correlating ability of a newly proposed topological index, *eccentric connectivity index*, in predicting physical properties and biological activities.

With regard to various physical properties, linear as well as nonlinear regression analysis was performed on all the datasets, using eccentric connectivity index and Wiener index. It was found that nonlinear regression analysis could give better correlation coefficients with less RMS errors as compared to linear regression analysis. Hence results obtained from nonlinear regression analysis only are discussed.

The various nonlinear regression equations along with statistical analysis for various datasets and physical properties involved have been compiled in Table 6.

As evident from Table 6, excellent correlations were obtained using the eccentric connectivity index in all six datasets employed in present investigations. These correlations were far superior to those correspondingly obtained by using Wiener's topological index. Correlation coefficients ranging from 95% to as high as 99%, using the eccentric connectivity index, in at least five datasets, clearly indicate the high predicting ability of this index over Wiener index, where lower correlation coefficients were obtained in the respective datasets. The average errors and the RMS errors

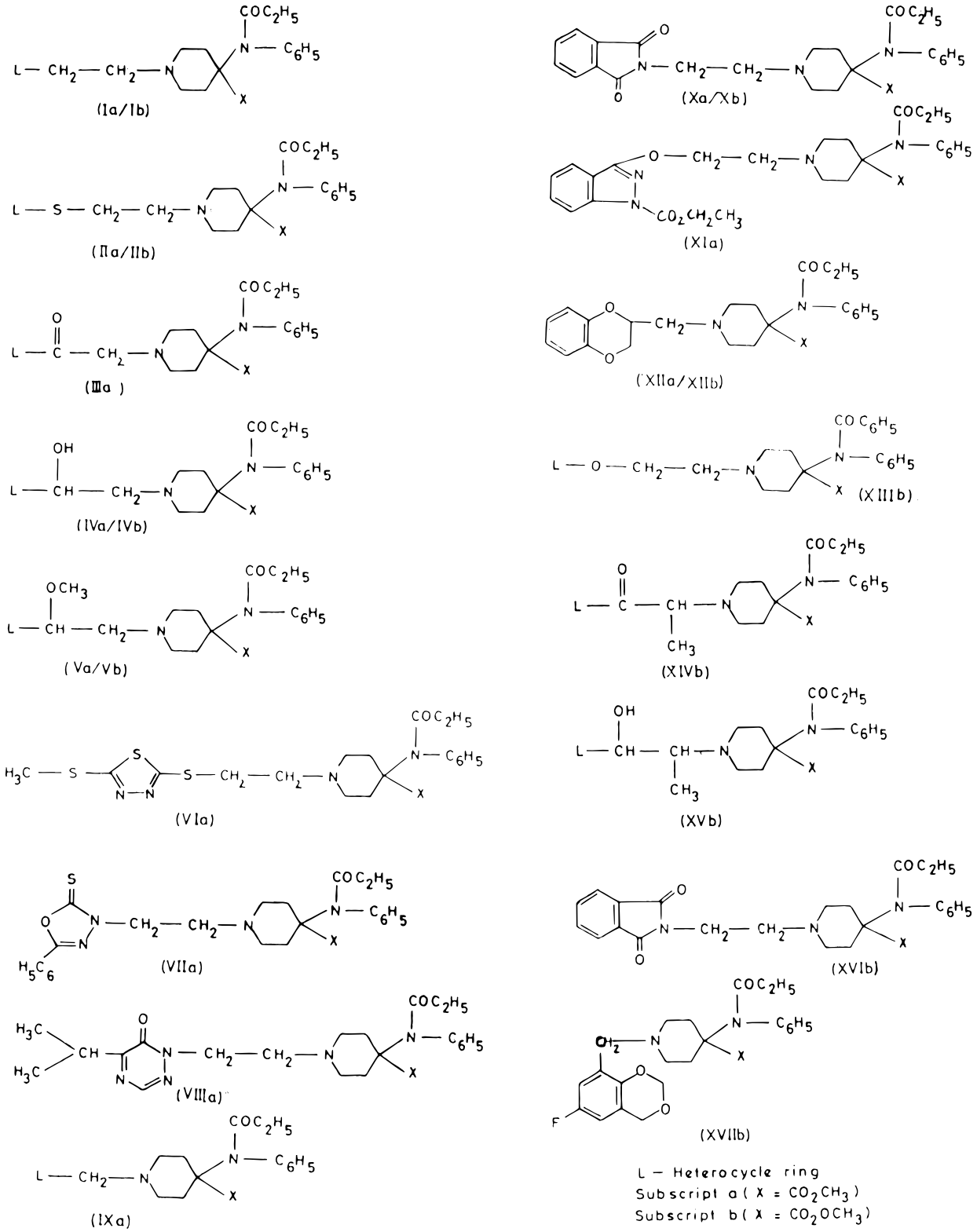

Figure 2. Basic structures of substituted piperidinyl methyl ester/methylene methyl ether analogs.

were also on the much lower side for eccentric connectivity index thus establishing its higher correlating abilities.

With regard to molar refraction of heterogenous organic compounds, though the Wiener index has shown better correlation coefficients (96%) as compared to eccentric connectivity index (93%), however, the average and RMS errors were on a much higher side for the Wiener index, with individual percentage error as high as above 50% (Figure 13, Figure 14) indicating its less correlating abilities.

Histograms of percentage errors (calculated as observed value − predicted value/observed value * 100) obtained for all the datasets using the eccentric connectivity index and the Wiener index are shown in Figures 3−14. Data from these figures clearly reveal that, for all the datasets used, a significantly higher number of compounds fall within an acceptable range as compared to the Wiener index. Evidently, eccentric connectivity index exhibited its superior correaling ability over Wiener index in all the six datasets involved.

Table 4. Relationship between Analgesic Activity of Substituted Piperidinyl Methyl Ester/Methylene Methyl Ester Analogs and Various Topological Indices

						activity predicted			
compd no.	basic structure	L	$^1\chi$	W	ξ^c	χ	W	ξ^c	activity reported[24]
1.	I_a	1-pyrrolyl	12.12	1899	607	+	+[a]	+	+
2.	I_a	2-aldehydo-1-pyrrolyl	13.25	2502	691	+	+	+	+
3.	I_a	1-pyrazolyl	12.12	1899	607	+	+	+	+
4.	I_a	3-methyl-1-pyrazolyl	12.79	2126	666	+	+	+	+
5.	I_a	3,5-dimethyl-1-pyrazolyl	13.61	2356	693	+	+	+	+
6.	I_a	4-iodo-1-pyrazolyl	12.79	2126	666	+	+	+	+
7.	I_a	3,5-di[ethyl ester]-1-pyrazolyl	17.10	4656	1056	−	−[b]	−	−
8.	I_a	5-nitro-1-imidazolyl	13.12	2571	718	+	±[c]	±	−
9.	I_a	2-methyl-5-nitro-1-imidazolyl	14.13	2789	743	±	±	±	−
10.	I_a	4,5-di-[ethyl-ester]-1-imidazolyl	17.11	4631	1060	−	−	−	−
11.	II_a	1-methyl-2-imidazolyl	13.21	2402	699	+	+	±	−
12.	I_a	1-tetrazolyl	13.12	1899	607	+	+	+	−
13.	I_a	2-phenyl-1-tetrazolyl	14.86	3540	989	±	±	−	−
14.	II_a	1-methyl-5-tetrazolyl	13.21	2402	699	+	+	±	−
15.	III_a	2-thiophenyl	12.71	2062	622	+	+	+	+
16.	IV_a	2-thiophenyl	12.71	2062	622	+	+	+	+
17.	I_a	3-thiophenyl	12.12	1899	607	+	+	+	+
18.	I_a	5-methyl-4-thiazolyl	12.71	2103	626	+	+	+	+
19.	V_a	5-methyl-4-thiazolyl	13.66	2648	670	±	±	+	+
20.	I_a	2-oxo-3-oxazolyl	12.71	2103	626	+	+	+	−
21.	I_a	5-oxo-2-phenyl-1-pyrazolyl	15.29	3641	966	−	−	−	−
22.	I_a	4-methyl-2,5-dioxo-4-phenyl-1-imidazolyl	16.13	4538	1029	−	−	−	−
23.	VI_a		13.83	1177	816	±	+	±	−
24.	VII_a		15.27	4018	1006	−	−	−	−
25.	I_a	2-pyridyl	12.80	2278	667	+	+	+	+
26.	I_a	3-pyridyl	12.80	2278	667	+	+	+	+
27.	I_a	4-pyridyl	12.80	2278	667	+	+	+	+
28.	I_a	3,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyridyl	15.58	3858	875	−	−	−	−
29.	I_a	3-ethyl-2,6-dioxo-3-phenyl-1-piperidinyl	17.19	5146	1115	−	−	−	−
30.	I_a	5-methyl-6-oxo-2-thiomethyl-1,6-dihydro-1-pyrimidyl	14.74	3246	771	±	±	±	+
31.	I_a	3-ethyl-2,4-dioxo-1-pyrimidyl	14.41	3310	809	±	±	±	−
32.	I_a	3-methyl-6-oxo-1,6-dihydro-1-pyridazinyl	13.70	1522	740	+	+	±	+
33.	$VIII_a$		14.37	3312	817	±	±	±	−
34.	IX_a	3-indolyl	13.38	2659	751	+	±	±	−
35.	I_a	1-oxindolyl	14.36	3260	774	±	±	±	+
36.	I_a	3,3-dimethyl-1-oxindolyl	15.12	3543	901	±	±	−	+
37.	I_a	3-spiropropan-1-oxindolyl	15.12	3543	901	±	±	−	+
38.	X_a		14.79	3543	873	±	−	−	−
39.	I_a	1-benzimidazolyl	13.88	3023	798	±	±	±	−
40.	VI_a	2-benzimidazolyl	13.38	2659	751	+	±	±	−
41.	XI_a		15.81	5095	1156	−	−	−	−
42.	I_a	3-ethyl-2-oxo-1-benzimidazolyl	15.33	3521	898	−	±	−	−
43.	I_a	2-oxo-1-benzoxazolyl	14.37	3260	817	±	±	±	+
44.	I_a	6-chloro-2-oxo-1-benzoxazolyl	14.94	3663	878	±	−	−	−
45.	III_a	2-oxo-5-benzoxazolyl	14.76	3590	918	±	−	−	−
46.	IX_a	7-methoxy-4-(α-benzopyronyl)	14.89	3748	930	±	−	−	−
47.	XII_a		13.86	3048	813	±	±	±	+
48.	I_a	2-oxo-1-phenothiazinyl	14.86	3695	813	±	−	±	+
49.	I_a	2-methyl-4-oxo-3-quinazolinyl	15.27	3862	948	−	−	−	−
50.	I_a	2,4-dioxo-3-quinazolinyl	15.27	3862	948	−	−	−	−
51.	I_a	1-ethyl-2,4-dioxo-3-quinazolinyl	16.24	4131	1004	−	−	−	−
52.	I_a	4,6-dimethyl-5, 7-dioxo-1-xanthinyl	15.28	4049	929	−	−	−	−
53.	I_a	1,4 dimethyl-5,7-dioxo-6-xanthinyl	15.70	3858	930	−	−	−	−
54.	I_a	*N*-(naphthylamine sulfonic acid)	15.70	4105	1073	−	−	−	−
55.	I_a	*N*-(naphthalimidinyl)	16.27	5146	1066	−	−	−	−
56.	I_b	1-pyrrolyl	12.62	2084	630	+	+	+	+
57.	I_b	2-aldehydo-1-pyrrolyl	13.75	2544	716	+	+	+	+
58.	I_b	1-pyrazolyl	12.62	2084	630	+	+	+	+
59.	I_b	3,5-methyl-1-pyrazolyl	14.11	2565	718	±	+	±	+
60.	I_b	4-iodo-1-pyrazolyl	13.29	2130	691	+	+	+	+
61.	I_b	2-methyl-5-nitro-1-imidazolyl	12.63	3020	768	+	±	±	−
62.	II_b	1-methyl-2-imidazolyl	13.71	2613	724	±	±	±	−
63.	II_b	5-(flouromethyl)-1-methyl-2-triazolyl	14.22	2883	797	±	±	±	−
64.	I_b	1-tetrazolyl	12.62	2084	630	+	+	+	−
65.	I_b	4-morpholinyl-1-tetrazolyl	15.36	3806	1022	−	−	−	−
66.	XIV_b	2-thiophenyl	13.64	2591	664	+	±	+	−
67.	IV_b	2-thiophenyl	13.21	2256	645	+	+	+	+
68.	XV_b	2-thiophenyl	13.64	2414	636	+	+	+	+
69.	IV_b	3-thiophenyl	12.62	2084	630	+	+	+	+
70.	IV_b	2-furyl	13.64	2256	645	+	+	+	+
71.	IV_b	5-methyl-2-furyl	13.70	2677	702	+	±	±	+
72.	I_b	5-methyl-4-thiazolyl	13.21	2460	649	+	+	+	+
73.	V_b	5-methyl-4-thiazolyl	14.16	2682	693	±	±	+	+
74.	I_b	3-ethyl-2-oxo-1−1-imidazolyl	14.25	2814	792	±	±	±	+

Table 4 (Continued)

compd no.	basic structure	L	$^1\chi$	W	ξ^c	activity predicted χ	activity predicted W	activity predicted ξ^c	activity reported[24]
75.	I_b	5-oxo-2-phenyl-1-pyrazolyl	15.79	4167	989	−	−	−	−
76.	I_b	4-amino-3-methyl-5-oxo-1-triazolyl	14.20	2980	743	±	±	±	−
77.	I_b	2-pyridyl	13.30	2485	692	+	+	+	+
78.	I_b	3-pyridyl	13.30	2485	692	+	+	+	+
79.	I_b	3,3-diethyl-2,4-dioxo-1,2,3,4 tetrahydro-1-pyridyl	16.08	4145	902	±	−	−	−
80.	I_b	4-methyl-5-oxo-2-thiomethyl-1,6dihydro-1-pyrimidinyl	15.24	3503	794	±	±	±	+
81.	I_b	3-ethyl-2,1-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl	14.91	3570	836	±	−	−	−
82.	I_b	3-oxindolyl	14.86	3518	801	±	±	±	+
83.	I_b	3,3-dimethyl-1-oxindolyl	15.62	4068	928	−	−	−	+
84.	I_b	3-spiropropan-1-oxindolyl	15.62	4068	928	−	−	−	+
85.	XVI_b		14.86	3518	801	±	±	±	−
86.	X_b		15.29	3815	900	−	−	−	−
87.	I_b	3-ethyl-2-oxo-1-benzimidazolyl	15.83	3730	925	−	−	−	+
88.	I_b	2-oxo-3-benzoxazolyl	14.87	3518	844	±	±	−	−
89	$XIII_b$	7-(α-benzopyrozyl)	15.85	4673	1048	−	+	−	−
90.	XII_b		14.36	3226	840	±	±	−	−
91.	$XVII_b$		14.77	3550	812	±	−	±	−
92.	I_b	2-methyl-4-oxo-3-quinazolinyl	15.77	4149	977	−	−	−	−
93.	I_b	1-ethyl-2,4-dioxo-3-quinozolinyl	16.74	4752	1033	−	−	−	−
94.	I_b	*N*-(naphthalimidinyl)	15.86	3696	1048	−	−	−	−

[a] +, positive analgesic activity. [b] −, negative analgesic activity. [c] ±, transitional range where activity could not be specifically assigned. [d] $ED_{50} < 0.1$ mg/kg assumed to be active and denoted by + in the table. [e] $ED_{50} \geq 0.1$ mg/kg assumed to be inactive and denoted by − in the table. [f] $^1\chi$, W, and ξ^c represent Randić's molecular connectivity index, the Wiener index, and the eccentric connectivity index, respectively.

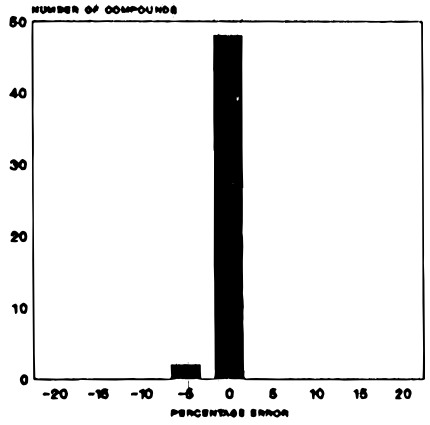

Figure 3. Percentage error between experimental and predictied CSA of alcohols using the eccentric connectivity index.

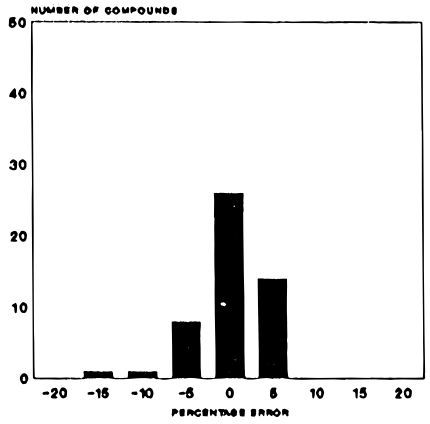

Figure 4. Percentage error between experimental and predicted CSA of alcohols using the Wiener index.

Eccentric connectivity index also exhibited high correlating ability with regard to biological properties of molecules. Analysis of the data pertaining to the values of the eccentric connectivity index, the Wiener index, and Randić's molecular connectivity index and analgesic activity of substituted

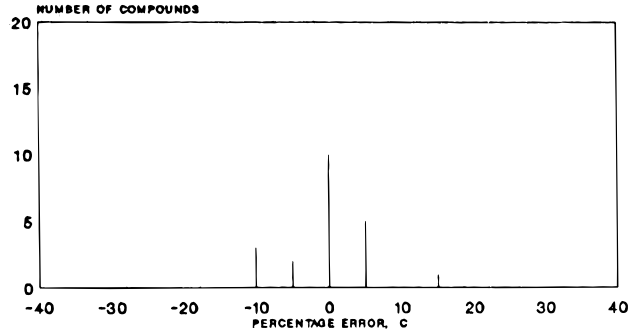

Figure 5. Percentage error between experimental and predicted boiling points of primary amines using the eccentric connectivity index.

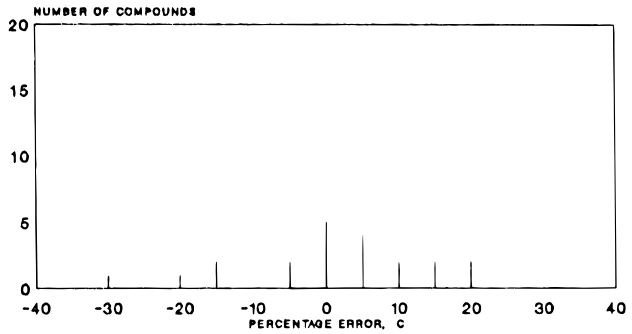

Figure 6. Percentage error between experimental and predicted boiling points of primary amines using the Wiener index.

piperidinyl methyl ester and methylene methyl ester analogs facilitated rapid categorization of compounds into active, inactive, and transitional ranges.

Retrofit analysis of the data compiled in Tables 4 and 5 (part A) reveals the following information:

1. A total of 50 out of 63 compounds were classified correctly in both active and inactive ranges using Randić's molecular connectivity index resulting in 79% overall accuracy of prediction.

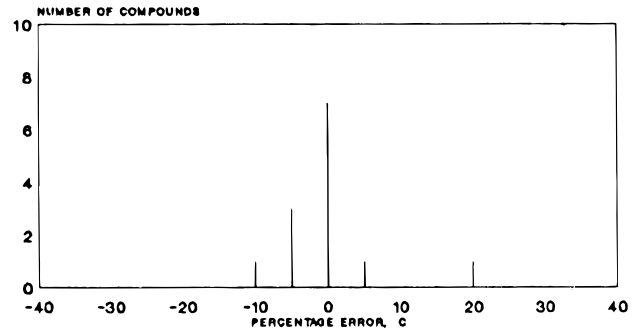

Figure 7. Percentage error between experimental and predicted boiling points of secondary amines using the eccentric connectivity index.

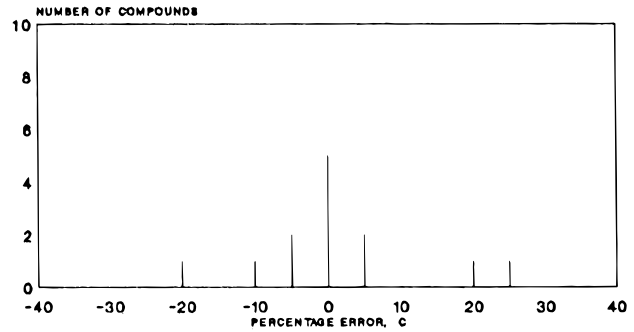

Figure 8. Percentage error between experimental and predicted boiling points of secondary amines using the Wiener index.

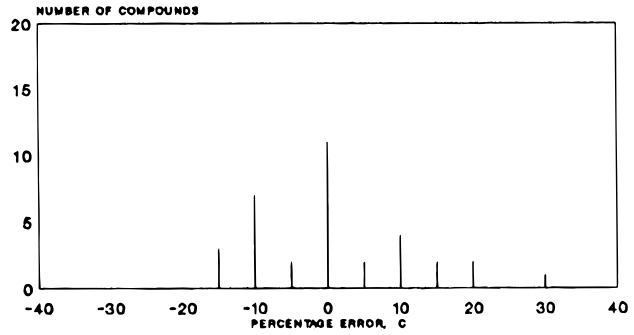

Figure 9. Percentage error between experimental and predicted boiling points of primary and secondary amines using the eccentric connectivity index.

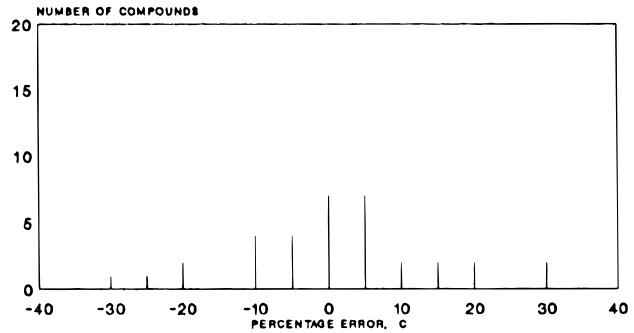

Figure 10. Percentage error between experimental and predicted boiling points of both primary and secondary amines using the Wiener index.

2. A transitional range was observed indicating a gradual change in biological activity from inactive to active range.

3. 72% of the compounds in the active range exhibited analgesic activity.

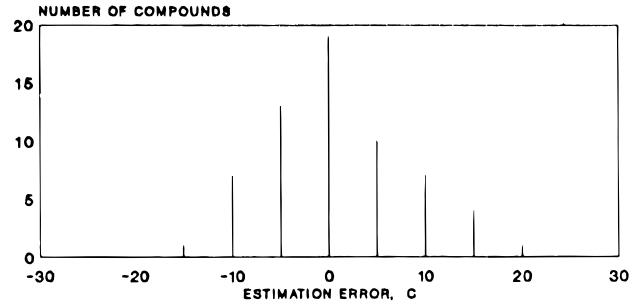

Figure 11. Percentage error between experimental and predicted boiling points of alcohols using the eccentric connectivity index.

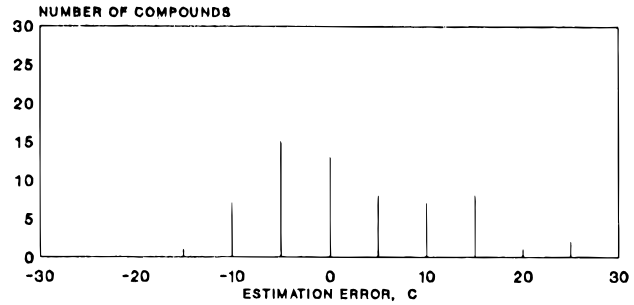

Figure 12. Percentage error between experimental and predicted boiling points of alcohols using the Wiener index.

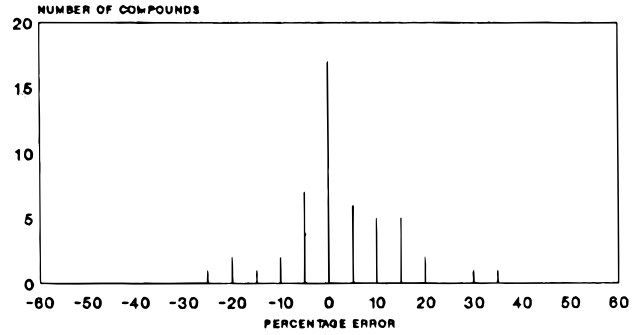

Figure 13. Percentage error between experimental and predicted molar refractions of compounds in Table 3 using the eccentric connectivity index.

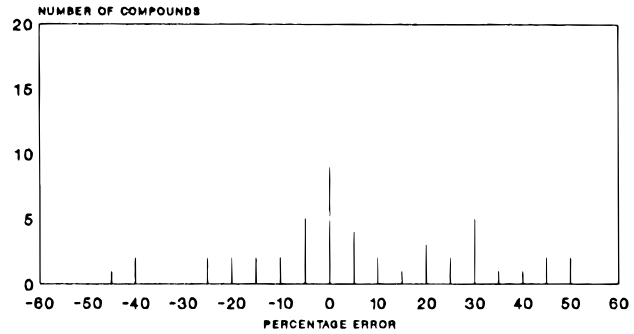

Figure 14. Percentage error between experimental and predicted molar refractions of compounds in Table 3 using the Wiener index.

Retrofit analysis of the data compiled in Tables 4 and 5 (part B) reveals the following information:

1. Using the Wiener index, a total of 53 out of 64 compounds were classified correctly in both active and inactive ranges. The overall accuracy of prediction was found to be 83%.

2. A transitional range was observed indicating gradual change in analgesic activity from inactive to active range.

Table 5. Relative Distribution of Test Compounds in Various Ranges of the Molecular Connectivity Index, Wiener's Index, and the Eccentric Connectivity Index

a. Molecular Connectivity Index

s. no.	ranges of $^1\chi$	nature of range	total no. of compds in this range	compds predicted correctly	% accuracy of prediction	av ED_{50} value (mg/kg)
1.	less than 13.71	active	36	26	72	0.4
2.	13.71−15.26	transitional	31	NA[a]	NA	0.67
3.	more than 15.26	inactive	27	24	89	1.49

b. Wiener's Index

s. no.	ranges of W	nature of range	total no. of compds in this range	compds predicted correctly	% accuracy of prediction	av ED_{50} value (mg/kg)
1.	less than 2571	active	32	25	78	0.08
2.	2571−3545	transitional	30	NA	NA	0.85
3.	more than 3545	inactive	32	28	87.5	1.78

c. Eccentric Connectivity Index

s. no.	ranges of ξ^c	nature of range	total no. of compds in this range	compds predicted correctly	% accuracy of prediction	av ED_{50} value (mg/kg)
1.	less than 695	active	29	25	86	0.07
2.	695−825	transitional	28	NA	NA	0.64
3.	more than 825	inactive	37	32	86	1.63

[a] This abbreviation NA stands for not applicable.

Table 6. Relationship of the Eccentric Connectivity Index (ξ^c) and the Wiener Index (W) with Various Physical Properties

s. no.	property	index	n	equations	correlation coefficients (%)	av errors (%)	RMS errors (%)
1.	cross sectional area of alcohols	ξ^c	50	$\log_e \text{CSA} = 4.8927 + 0.238 \log_e \xi^c$	99	1.74	2.28
		W		$\log_e \text{CSA} = 5.2298 + 0.144 \log_e W$	97	4.96	5.95
2.	boiling points of primary amines	ξ^c	21	$\log_e \text{bp} = 1.2291 + \log_e \xi^c - 0.00650\ \xi^c$	98	6.55	8.01
		W		$\log_e \text{bp} = 1.2751 + \log_e W - 0.00614\ W$	93	12.03	14.47
3.	boiling points of secondary amines	ξ^c	13	$\log_e \text{bp} = 0.9776 + \log_e \xi^c - 0.00455\ \xi^c$	99	5.94	8.36
		W		$\log_e \text{bp} = 1.0808 + \log_e W - 0.00593\ W$	95	10.47	13.05
4.	boiling points of primary and secondary amines as combined dataset	ξ^c	34	$\log_e \text{bp} = 1.1943 + \log_e \xi^c - 0.00602\ \xi^c$	97	11.10	14.46
		W		$\log_e \text{bp} = 1.2104 + \log_e W - 0.00620\ W$	92	12.96	16.51
5.	boiling points of alcohols	ξ^c	62	$\log_e \text{bp} = 4.0401 + 0.249 \log_e \xi^c$	95	8.10	9.52
		W		$\log_e \text{bp} = 4.2799 + 0.181 \log_e W$	92	10.07	11.89
6.	molar refractions of heterogenous compds	ξ^c	48	$\log_e \text{mr} = 1.4409 + 0.54 \log_e \xi^c$	93	9.18	11.64
		W		$\log_e \text{mr} = 0.8256 + 0.69 \log_e W$	96	20.66	25.97

3. 78% of the compounds in the active range exhibited analgesic activity.

Retrofit analysis of the data compiled in Tables 4 and 5 (part C) reveals the following information:

1. *A total of 57 out of 66 compounds were classified correctly in both active and inactive ranges using eccentric connectivity index resulting in an overall accuracy of prediction of 86%.*

2. A transitional range was observed indicating a gradual change of biological activity from inactive to active range.

3. *86%* of the compounds in the active range exhibited analgesic activity.

Aforementioned results clearly indicate that eccentric connectivity index has shown excellent correlations with regard to analgesic activity of piperidinyl methyl ester and methylene methyl ester analogs. It is also noteworthy that even though the average ED_{50} of the active range was found to be 0.07 mg/kg, using eccentric connectivity index, it was, however, only 0.014 mg/kg if the only four inactives in this range are excluded while determining the average.

Physical properties to a much extent are responsible for the biological activity of a chemical compound. The above results are highly encouraging in view of the fact that the proposed eccentric connectivity index provides excellent correlations with regard to both physical and biological properties. The simplicity amalgamated with high correlating ability of this index can be easily exploited in QSPR/QSAR studies. Such studies can easily provide valuable leads for the development of numerous potent therapeutic agents.

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