

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

Vikas Sharma

Ranbaxy Research Laboratories, Plot-20, Sector-18, Udyog Vihar, Gurgaon - 122001, India

Reena Goswami

College of Pharmacy, Pushp Vihar, Sector-III, New Delhi - 110017, India

A. K. Madan*

Department of Pharmaceutical Sciences, M. D. University, Rohtak - 124001, India

Received May 27, 1996[⊗]

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 predictability 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 referred 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 definition 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 .

[⊗] Abstract published in *Advance ACS Abstracts*, February 1, 1997.

| | | | |
|--|---|---|---|
| Arbitrary vertex numbering | $ \begin{array}{c} 1 \ 2 \ 3 \ 4 \ 5 \\ \text{C}-\text{C}-\text{C}-\text{C}-\text{C} \end{array} $ | $ \begin{array}{c} 1 \ 2 \ 3 \ 4 \\ \text{C}-\text{C}-\text{C}-\text{C} \\ \\ \text{C5} \end{array} $ | $ \begin{array}{c} \text{C2} \\ \\ 5\text{C}-\text{C1}-\text{C3} \\ \\ \text{C4} \end{array} $ |
| Adjacency matrices | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & V(i) \\ \hline 1 & 0 & 1 & 0 & 0 & 0 & 1 \\ 2 & 1 & 0 & 1 & 0 & 0 & 2 \\ 3 & 0 & 1 & 0 & 1 & 0 & 2 \\ 4 & 0 & 1 & 0 & 1 & 0 & 2 \\ 5 & 0 & 0 & 0 & 1 & 0 & 1 \end{array} $ | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & V(i) \\ \hline 1 & 0 & 1 & 0 & 0 & 0 & 1 \\ 2 & 1 & 0 & 1 & 0 & 1 & 3 \\ 3 & 0 & 1 & 0 & 1 & 0 & 2 \\ 4 & 0 & 0 & 1 & 0 & 0 & 1 \\ 5 & 0 & 1 & 0 & 0 & 0 & 1 \end{array} $ | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & V(i) \\ \hline 1 & 0 & 1 & 1 & 1 & 1 & 4 \\ 2 & 1 & 0 & 0 & 0 & 0 & 1 \\ 3 & 1 & 0 & 0 & 0 & 0 & 1 \\ 4 & 1 & 0 & 0 & 0 & 0 & 1 \\ 5 & 1 & 0 & 0 & 0 & 0 & 1 \end{array} $ |
| Distance matrices | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & E(i) \\ \hline 1 & 0 & 1 & 2 & 3 & 4 & 4 \\ 2 & 1 & 0 & 1 & 2 & 3 & 3 \\ 3 & 2 & 1 & 0 & 1 & 2 & 2 \\ 4 & 3 & 2 & 1 & 0 & 1 & 3 \\ 5 & 4 & 3 & 2 & 1 & 0 & 4 \end{array} $ | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & E(i) \\ \hline 1 & 0 & 1 & 2 & 3 & 3 & 3 \\ 2 & 1 & 0 & 1 & 2 & 2 & 2 \\ 3 & 2 & 1 & 0 & 1 & 1 & 2 \\ 4 & 3 & 2 & 1 & 0 & 2 & 3 \\ 5 & 3 & 2 & 1 & 2 & 0 & 3 \end{array} $ | $ \begin{array}{c ccccc c} i & 1 & 2 & 3 & 4 & 5 & E(i) \\ \hline 1 & 0 & 1 & 1 & 1 & 1 & 1 \\ 2 & 1 & 0 & 2 & 2 & 2 & 2 \\ 3 & 1 & 2 & 0 & 2 & 2 & 2 \\ 4 & 1 & 2 & 2 & 0 & 2 & 2 \\ 5 & 1 & 2 & 2 & 2 & 0 & 2 \end{array} $ |
| Eccentric Connectivity Index values [$\sum E(i)V(i)$] | $ \begin{aligned} &(4*1) + (3*2) + (2*2) \\ &+ (3*2) + (4*1) \\ &= 24 \end{aligned} $ | $ \begin{aligned} &(3*1) + (2*3) + (2*2) \\ &+ (3*1) + (3*1) \\ &= 19 \end{aligned} $ | $ \begin{aligned} &(1*4) + (2*1) + (2*1) \\ &+ (2*1) + (2*1) \\ &= 12 \end{aligned} $ |

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 topological 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 topological index, is defined as the sum of distances between all pair of vertices in a molecular graph, that is

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

where, $D_{i,j}$ (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 points²³ (Table 1).

(3) A group of 48 heterogenous chemical compounds comprising of ethers, amines, and alcohols along with their molar refraction values²³ (Table 3).

(4) A dataset comprising of 91 substituted piperidinyl methyl ester and methylene methyl ester analogs²⁴ (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 reported¹⁹ analgesic activity. Compounds possessing an ED_{50} value of less than 0.1 mg/kg were arbitrarily assigned a positive activity and those possessing 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

| compound | ξ^c | W | exptl | boiling points, °C | | compound | ξ^c | W | exptl | boiling points, °C | |
|--------------------------------------|---------|----|-------|------------------------|--------|-------------------------------------|---------|-----|--------|------------------------|--------|
| | | | | predicted ^a | | | | | | predicted ^a | |
| | | | | ξ^c | W | | | | | ξ^c | W |
| Primary Amines | | | | | | | | | | | |
| <i>n</i> -propylamine | 18 | 10 | 49 | 58.68 | 33.65 | 4-methylpentylamine | 45 | 52 | 125 | 123.09 | 135.21 |
| 2-aminopropane | 9 | 9 | 33 | 53.31 | 31.53 | <i>n</i> -hexylamine | 54 | 56 | 130 | 113.27 | 126.40 |
| | | | | 31.11 | 30.47 | | | | | 139.31 | 142.08 |
| | | | | 28.14 | 28.56 | | | | | 128.75 | 132.78 |
| 2-amino-2-methylpropane | 12 | 16 | 46 | 40.68 | 51.89 | 3-methylpentylamine | 45 | 50 | 114 | 123.09 | 131.61 |
| 2-aminobutane | 19 | 18 | 63 | 36.85 | 48.61 | 4-aminoheptane | 61 | 75 | 139 | 113.27 | 123.05 |
| | | | | 61.54 | 57.67 | | | | | 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 |
| <i>n</i> -butylamine | 24 | 20 | 77 | 55.93 | 54.02 | <i>n</i> -heptylamine | 74 | 84 | 155 | 145.05 | 162.43 |
| | | | | 75.25 | 63.29 | | | | | 167.63 | 179.46 |
| | | | | 68.56 | 59.28 | | | | | 156.42 | 167.44 |
| 2-amino-2-methylbutane | 24 | 28 | 78 | 75.25 | 84.36 | <i>n</i> -octylamine | 96 | 120 | 180 | 188.47 | 205.53 |
| 2-aminopentane | 31 | 32 | 92 | 68.56 | 78.98 | <i>n</i> -nonylamine | 122 | 165 | 201 | 177.74 | 191.36 |
| | | | | 92.88 | 94.08 | | | | | 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 |
| 2-methylbutylamine | 29 | 32 | 96 | 84.90 | 85.83 | 3-aminopentane | 29 | 31 | 91 | 201.60 | 166.92 |
| | | | | 88.02 | 94.08 | | | | | 88.02 | 91.7 |
| | | | | 80.38 | 88.05 | | | | | 80.38 | 85.83 |
| <i>n</i> -pentylamine | 38 | 35 | 104 | 108.78 | 101.02 | | | | | | |
| | | | | 99.77 | 94.53 | | | | | | |
| Secondary Amines | | | | | | | | | | | |
| <i>N</i> -(methyl)ethylamine | 18 | 10 | 36 | 44.08 | 27.78 | <i>N</i> -methyl-1-methylbutylamine | 45 | 50 | 105 | 97.44 | 109.58 |
| <i>N</i> -methyl-1-methylethylamine | 19 | 18 | 50 | 53.31 | 31.54 | dipropylamine | 54 | 56 | 109.5 | 113.27 | 123.05 |
| | | | | 46.32 | 47.69 | | | | | 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 |
| <i>N</i> -methyl-1-methylpropylamine | 29 | 31 | 78.5 | 68.56 | 49.28 | dibutylamine | 56 | 120 | 159 | 158.72 | 185.52 |
| | | | | 67.54 | 76.04 | | | | | 164.79 | 173.70 |
| | | | | 80.38 | 85.83 | | | | | 177.74 | 191.36 |
| <i>N</i> -(ethyl)propylamine | 38 | 35 | 80.5 | 84.95 | 83.84 | bis(3-methylbutyl)amine | 126 | 202 | 187.5 | 188.67 | 179.87 |
| bis(1-methylethyl)amine | 38 | 48 | 84 | 99.77 | 94.53 | dipentylamine | 150 | 220 | 205 | 194.72 | 193.77 |
| | | | | 84.95 | 106.45 | | | | | 201.75 | 176.08 |
| | | | | 99.77 | 119.60 | | | | | 200.61 | 188.75 |
| <i>N</i> -(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

| compound | ξ^c | W | cross sectional area | | |
|----------------------------|---------|-----|----------------------|------------------------|--------|
| | | | exptl | predicted ^a | |
| | | | | 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-1-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 |

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

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

| compound | ξ^c | W | molar refraction | | |
|-----------------------------|---------|-----|------------------|------------------------|--------|
| | | | exptl | predicted ^a | |
| | | | | 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-aminohexane | 74 | 84 | 38.003 | 43.251 | 47.989 |
| 2-aminohexane | 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 |

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

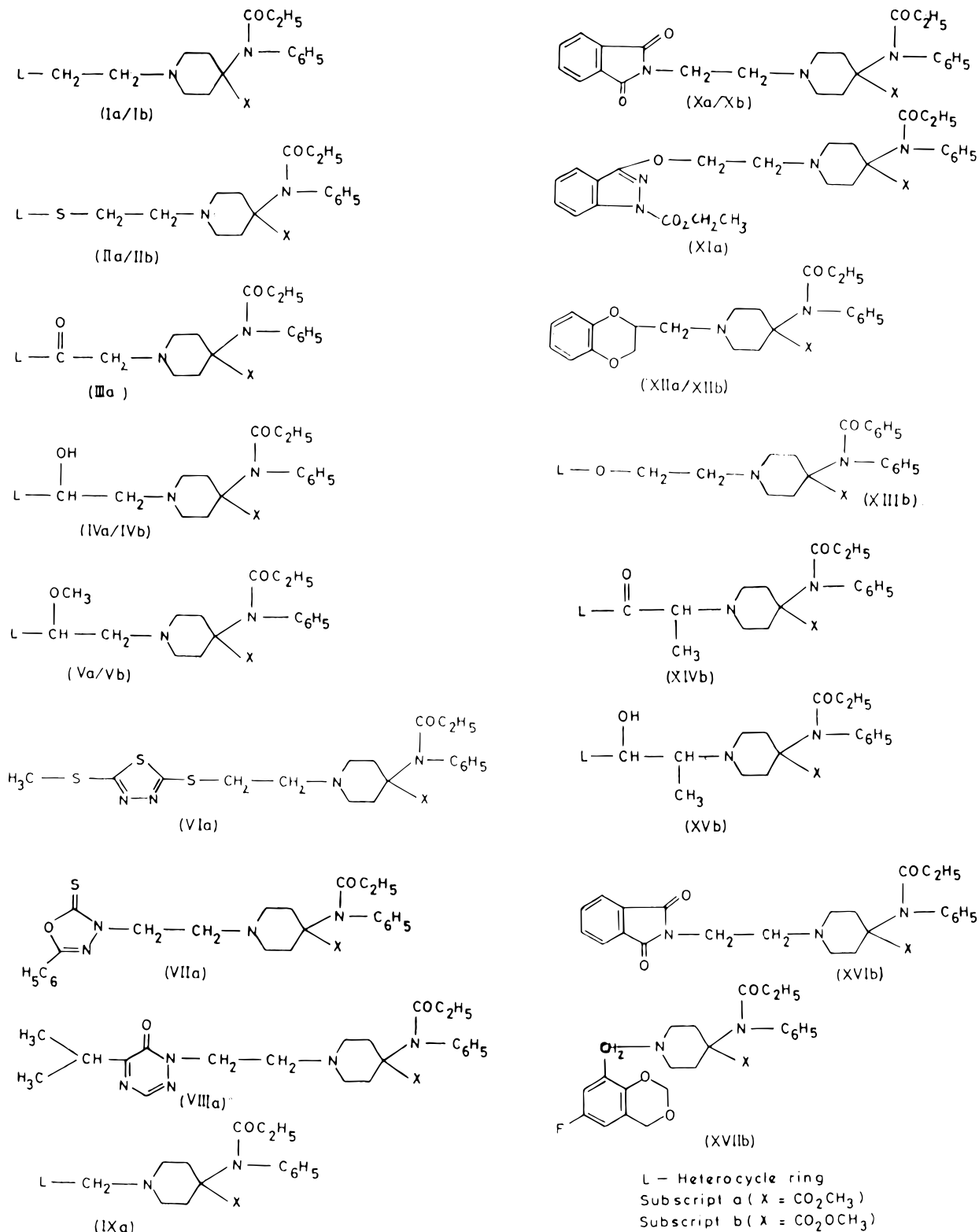


Figure 2. Basic structures of substituted piperidiny methyl ester/methylene methyl ether analogs.

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 correlating 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

| compd no. | basic structure | L | $^1\chi$ | W | ξ^c | activity predicted | | | activity reported ²⁴ |
|-----------|-------------------|---|----------|------|---------|--------------------|----------------|---------|---------------------------------|
| | | | | | | χ | W | ξ^c | |
| 1. | I _a | 1-pyrrolyl | 12.12 | 1899 | 607 | + | + | + | + |
| 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-imidazolyl | 14.25 | 2814 | 792 | ± | ± | ± | + |

Table 4 (Continued)

| compd no. | basic structure | L | $^1\chi$ | W | ξ^c | activity predicted | | | activity reported ²⁴ |
|-----------|-------------------|--|----------|------|---------|--------------------|---|---------|---------------------------------|
| | | | | | | χ | W | ξ^c | |
| 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 -benzopyrozylyl) | 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-quinazolinyl | 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 ED₅₀ < 0.1 mg/kg assumed to be active and denoted by + in the table. ^e ED₅₀ ≥ 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.

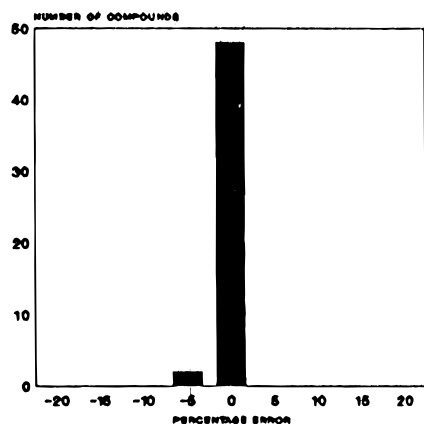


Figure 3. Percentage error between experimental and predicted CSA of alcohols using the eccentric connectivity index.

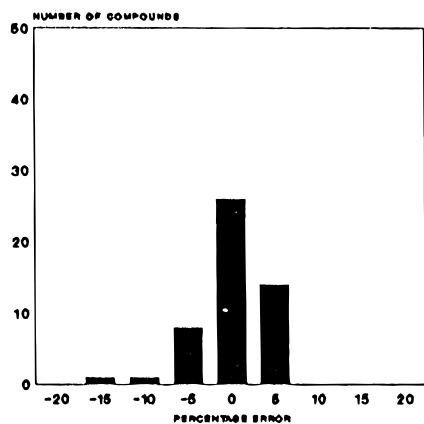


Figure 4. Percentage error between experimental and predicted CSA of alcohols using the Wiener index.

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

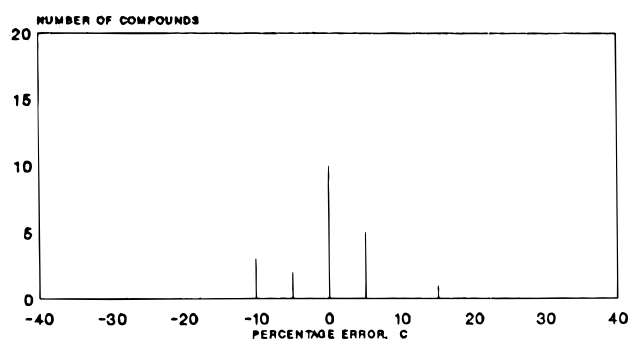


Figure 5. Percentage error between experimental and predicted boiling points of primary amines using the eccentric connectivity index.

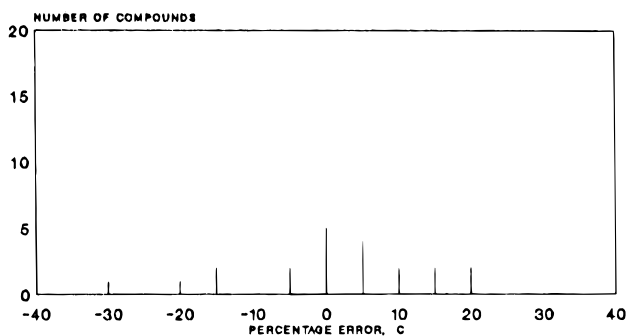


Figure 6. Percentage error between experimental and predicted boiling points of primary amines using the Wiener index.

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.

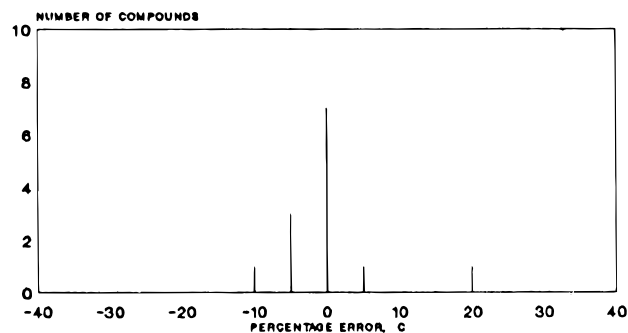


Figure 7. Percentage error between experimental and predicted boiling points of secondary amines using the eccentric connectivity index.

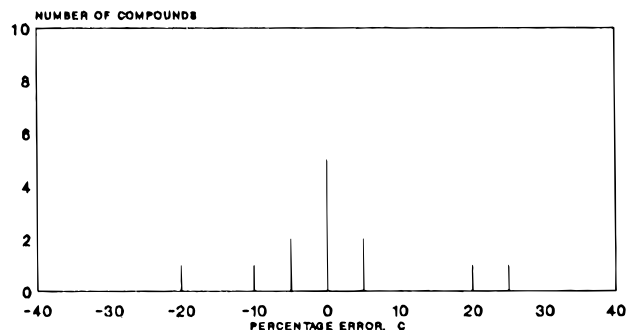


Figure 8. Percentage error between experimental and predicted boiling points of secondary amines using the Wiener index.

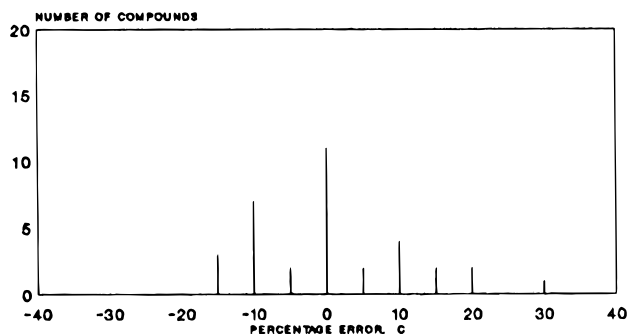


Figure 9. Percentage error between experimental and predicted boiling points of primary and secondary amines using the eccentric connectivity index.

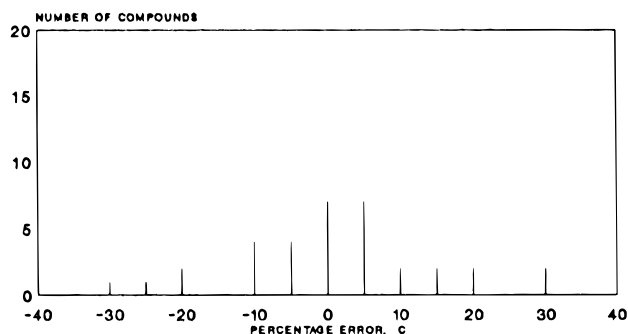


Figure 10. Percentage error between experimental and predicted boiling points of both primary and secondary amines using the Wiener index.

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.

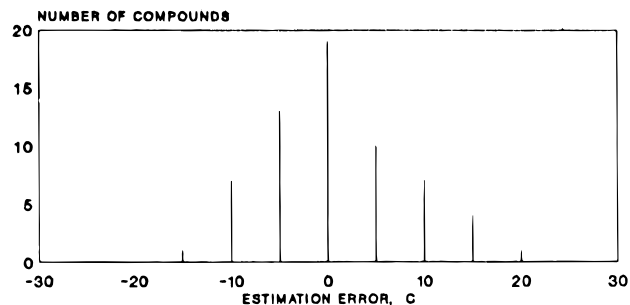


Figure 11. Percentage error between experimental and predicted boiling points of alcohols using the eccentric connectivity index.

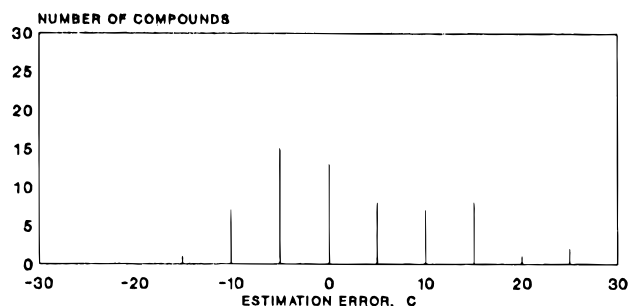


Figure 12. Percentage error between experimental and predicted boiling points of alcohols using the Wiener index.

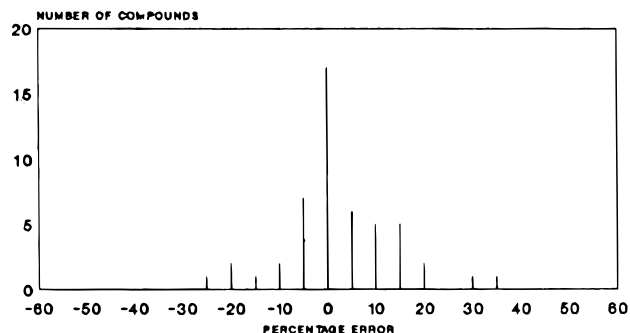


Figure 13. Percentage error between experimental and predicted molar refractions of compounds in Table 3 using the eccentric connectivity index.

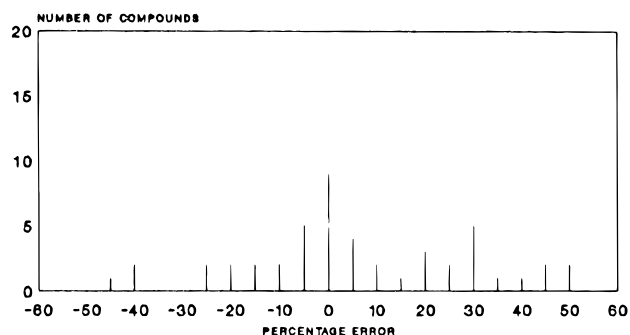


Figure 14. Percentage error between experimental and predicted molar refractions of compounds in Table 3 using the Wiener index.

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 comps in this range | comps 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 comps in this range | comps 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 comps in this range | comps 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 piperidiny methyl ester and methylene methyl ester analogs. It is also noteworthy that even though the average ED₅₀ 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.

REFERENCES AND NOTES

- Trinajstić, N. In *Chemical Graph Theory*; CRC Press: Boca Raton, FL, 1983; Vols. I and II.
- Kier, L. B.; Hall, L. H. In *Molecular Connectivity in Structure-Activity Analysis*; Research Studies Press Ltd.: Letchworth, England, 1986.
- Basak, S. C.; Bertelsen, S.; Grunwald, G. D. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 270.
- Balaban, A. T.; Motoc, J.; Bonchev, D.; Mekenyan, O. *Top. Curr. Chem.* **1983**, *114*, 23.
- Randić, M. *Int. J. Quant. Chem. Biol. Symp.* **1978**, *5*, 245.
- Basak, S. C.; Magnuson, V. R.; Niemi, G. J.; Regal, R. R.; Veith, G. D. *Math. Modelling* **1987**, *8*, 300.
- Basak, S. C.; Niemi, G. J.; Veith, G. D. *J. Math. Chem.* **1991**, *7*, 243.
- Katritzky, A. K.; Gordeeva, E. V. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 835.
- Randić, M.; Wodoworth, W. L.; Graovac, A. *Int. J. Quant. Chem.* **1983**, *24*, 435.
- Wiener, H. *J. Chem. Phys.* **1947**, *25*, 766.
- Galvez, J.; Garcia-Domenec, R.; Julian-Ortiz, J. V.; Soler, R. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 272.
- Sablic, A.; Trinajstić, N. *Acta. Pharm. Jugosl.* **1981**, *31*, 189.
- Kier, L. B.; Hall, H. In *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976.
- Rouvray, D. H. *J. Mol. Struct. (THEOCHEM)* **1989**, *185*, 187.
- Balaban, A. T.; Rouvray, D. H. In *Applications of Graph Theory*; Wilson, R. J., Beinelke, L. W., Eds.; Academic Press: London, 1976.
- Muller, W. R.; Szymanski, K.; Knop, J. V.; Trinajstić, N. *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 160.

- (17) Rao, N. In *Graph Theory*; Forsythe, G., Ed.; Prentice Hall: New Delhi, 1994.
- (18) Petitjean, M. *J. Chem. Inf. Comput. Sci.* **1992**, 32, 331.
- (19) Randić, M. *J. Am. Chem. Soc.* **1975**, 97, 6609.
- (20) Kier, L. B.; Hall, L. H. *J. Med. Chem.* **1977**, 20, 1631.
- (21) Hall, L. H.; Kier, L. B.; Murray, W. J. *J. Pharm. Sci.* **1975**, 64, 1974.
- (22) Kier, L. B.; Hall, L. H.; Murray, W. J.; Randić, M. *J. Pharm. Sci.* **1975**, 64, 1971.
- (23) Kier, L. B.; Hall, L. H. *J. Pharm. Sci.* **1976**, 65, 1806.
- (24) Baghey, J. R.; Thomas, S. A.; Rudo, F. G.; Spencer, H. K.; Doorley, B. M.; Oeshrev, M. H.; Jetossi, T. P.; Benvenga, M. J.; Spaulding, T. *J. Med. Chem.* **1991**, 34(2), 827.
- (25) Randić, M.; Razinger, M. *J. Chem. Inf. Comput. Sci.* **1995**, 35, 140.
- (26) Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1995**, 35, 339.

CI960049H