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Application of graph theory: Models for prediction of carbonic anhydrase inhibitory activity of sulfonamides

Vipin Kumar and A.K. Madan*

Faculty of Pharmaceutical Sciences, M.D. University, Rohtak-124 001, India
E-mail: madan_ak@yahoo.com

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The relationship of *Wiener's index*–a distance-based topological descriptor, *Zagreb group parameter* – M_1, an adjacency-based topological descriptor and *eccentric connectivity index*–an adjacency-cum-distance based topological descriptor with the carbonic anhydrase (CA) isozyme-II inhibitory activity of sulfonamides has been investigated. A training set comprising of 34 analogues of substituted sulfonamides was selected for the present investigations. The values of the *Wiener's index*, *Zagreb group parameter*, and *eccentric connectivity index* for each of 34 analogues comprising the data set were computed. Resulting data was analyzed and suitable models were developed after identification of active ranges. Subsequently, a biological activity was assigned to each analogue involved in the data set using these models, which was then compared with the reported CA isozyme-II inhibitory activity. Accuracy of prediction was found to vary from a minimum of 82% for model based on *Wiener's index* to a maximum of 88% for the model based on *Zagreb group parameter.* Moreover, highly active range of the proposed models also exhibited appreciable inhibitory activity against CA isozyme-I and CA isozyme-IV.

KEY WORDS: Wiener's index, eccentric connectivity index, zagreb group parameter, sulfonamides, carbonic anhydrase inhibitory activity

1. Introduction

Molecular graph theory is a powerful tool to encode into numbers the constitutional features of the molecular structure, and many useful molecular graph descriptors have been proposed [1,2]. Topological indices are used with success to model various properties and they are valuable descriptors of chemical structure [3,4]. The interest of developing new graph descriptors for organic compounds revived in recent years following new applications of topological indices in similarity and diversity assessment, database mining, and in the virtual screening of combinatorial libraries [5,6].

*Corresponding author.

In the molecular graph theory [7], an organic compound containing heteroatoms and multiple bonds can be represented as a vertex- and edge-weighted molecular graph in which the atom i is represented by the vertex v_i and the covalent bond between atoms i and j corresponds to the edge e_{ij} from the molecular graph. A molecular graph G consists of a vertex set $V = V(G)$, an edge set $E = E(G)$. The number of vertices in the graph G is $V(G)$ [8,9].

Recently, several molecular descriptors based on the two-dimensional topological structure of molecules have been defined and tested in structure activity/property models [10,11]. Topological indices are the required vehicle for capturing all structural information into one single numerical value. Although a number of topological indices of diverse nature have been reported in literature but only a handful of them have been successfully employed in SAR studies. These include *Hosoya's in*dex [12,13], *Randic's molecular connectivity index*, χ [14], *the higher-order connectivity indices*, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall [15], *Balaban's index*, J [16,17], *Wiener's* index [18,19], *Zagreb group parameters*, M_1 and M_2 [20,21], *eccentric connectivity index* [22–25], *superpendentic index* [26,27], and *eccentric adjacency index* [28].

The carbonic anhydrases (CAs) are ubiquitous zinc enzymes, being encoded by three distinct, evolutionarily unrelated gene families: the α-CAs, the β-CAs, and the γ-CAs. In higher vertebrates, including humans, 14 different CA isozymes or CA-related proteins were described with very different subcellular localization and tissue distribution [29]. Basically, there are several cytosolic forms, four membrane-bound isozymes, one mitochondrial form as well as a secreted CA isozyme [30].

Carbonic anhydrases are enzymes that catalyze the hydration of carbon dioxide and the dehydration of bicarbonate. These CA-driven reactions are of great importance in a number of tissues [31]. Many of these isozymes are important targets for the design of inhibitors with clinical applications [32]. Pharmacologic effects of the CA inhibitors include decreased formation of aqueous humor, thereby reducing intraocular pressure; increased renal tubular secretion of sodium and potassium and, to a greater extent, bicarbonate, leading to increased urine alkalinity and volume, anticonvulsant activity, which is independent of its diuretic effects [33].

These are used for their effects on aqueous humor production in the treatment of glaucoma, used for diuretic action, in the treatment of metabolic alkalosis, used as adjunctive therapy for epilepsy and for acute high-altitude sickness. The CA is a common enzyme, and it is contained in key regulatory organs [34]. In the kidney, CA is involved in regulating acid-base equilibrium [35]. Its action on the renal tubules produces a mild metabolic acidosis by increasing bicarbonate excretion, which increases pulmonary ventilation. The inhibition of this enzyme by acetazolamide is used as a prophylactic treatment for acute mountain sickness [36–38]. In the lungs, red cell CA is responsible for the dehydration of

H_2CO_3 and its hydration in the tissues. Without a catalyst, the interconversion between CO_2 and H_2CO_3 requires more than 1 minute for completion, while the capillary transit of red cells takes 1 second. The acceleration of these reactions between 13,000 and 25,000-fold is achieved by red cell CA [39].

Carbonic-anhydrase inhibitors are used in the treatment of hypokalaemic periodic paralysis and related channelopathies [40]. The CA is thought to be involved in the process of calcium carbonate deposition in calcified tissues of many organisms. Barnacles form hard-calcified shells for protection against predation, and represent a class of marine-fouling animals. These findings strongly support the idea that CA is involved in calcification [41]. The CA inhibitor used for a variety of purposes, including adjunctively in the management of various types of epilepsy. A previous study on its psychotropic effects suggested the possibility of efficacy in atypical psychotic states, especially those characterized by cyclicity [42], and some has limited usefulness in the treatment of essential voice tremor [43]. During rapid eye movement sleep, the arterial pressure undergoes large fluctuations in the rat, cat, and other mammals, including humans, and it has been suggested that this effect originates in the forebrain. In addition, acetazolamide, a CA inhibitor, is known to be effective in the treatment of central sleep apnea or epilepsy. Acetazolamide may act as a stabilizing factor preventing arterial pressure fluctuations during rapid eye movement sleep [44].

In the present study relationship of *Wiener's Index* – a distance-based topological descriptor, *Zagreb group parameter* – an adjacency-based topological descriptor and *eccentric connectivity index* – an adjacency-cum-distance based topological descriptor with carbonic anhydrase isozyme-II (CA II) inhibitory activity of sulfonamides has been investigated.

2. Methodology

2.1. Calculations of topological indices

The *Wiener's index* [18,19], a well-known distance-based topological index is defined as the sum of the distances between all the pairs of vertices in a hydrogen-suppressed molecular graph, that is

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

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

The *Zagreb group parameter* M_1 proposed by Gutman and Randic [20] and Gutman et al. [21] is defined as the sum of squares of degree over all vertices and is represented by following equation:

$$M_1 = \sum_{i=1}^{n} \left(V_i^2 \right), \tag{2}$$

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

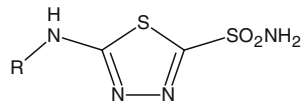
The *eccentric connectivity index* [22–25] denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen-suppressed molecular graph having n vertices, that is

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

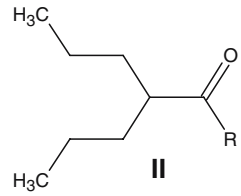
where V_i is the degree of vertex i, E_i the eccentricity of the vertex i, and n is the number of the vertices in graph G. The eccentricity E_i of a vertex i in a graph G is the path length from vertex i to vertex j that is farthest from i ($E_i = \max d(ij)$; $j \varepsilon G$); the eccentricity connectivity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

2.2. Model development analysis

A data set [45] comprising of 34 analogues of sulfonamides was selected for the present investigations. The structures for these analogues are depicted in table 1 and these include the analogues of the following series:



I



II

The values of the *Wiener's index* were computed for each analog using an in-house computer program and a suitable model was developed after identification of active range by moving average analysis, which is based on the maximization of moving average with respect to active compounds ($< 35\%$ = inactive, 35–65% = transitional, $\geqslant 65\%$ = active) [28]. Subsequently, each analog was assigned a biological activity, which was then compared with the reported [45] CA II inhibitory activity of sulfonamides. The CA inhibitory activity of sulfonamides was reported quantitatively as K_i (nM) at different concentrations for human cloned carbonic anhydrase isozyme- I (hCA I), human cloned carbonic anhydrase isozyme- II (hCA II) and bovine lung microsome carbonic anhydrase isozyme- IV (bCA IV). The analogues possessing K_i (nM) values of < 15 nM for

Table 1
Relationship of Wiener's index, Zagreb group parameter and eccentric connectivity index with hCA II inhibitory activity.

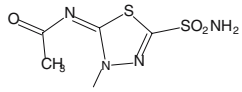
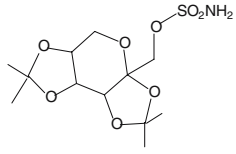
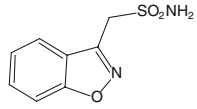
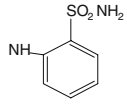
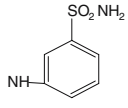
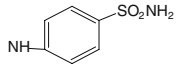
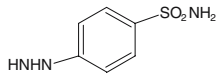
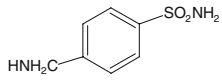
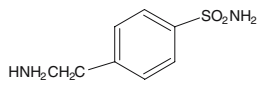
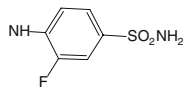
Comp. No.	R	Series	W	M_1	ξ^c	Predicted activity			Reported activity
						W	M_1	ξ^c	
1	-CO(CH$_3$)	I	257	64	140	+	+	+	+
2		–	304	70	149	+	+	+	+
3		–	799	126	279	+	+	+	+
4		–	293	74	160	+	+	+	–
5	-CO(OC(CH$_3$)$_3$)	I	569	86	241	+	+	+	+
6		II	835	94	289	+	–	+	–
7		II	875	94	314	+	–	–	–
8		II	915	94	341	–	–	–	–
9		II	1092	98	393	–	–	–	–
10		II	1092	98	393	–	–	–	–
11		II	1290	102	449	–	–	±	–
12		II	1008	100	356	–	–	–	–

Table 1 *(Continued)*

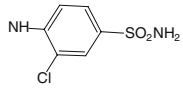
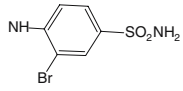
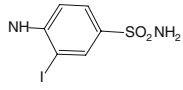
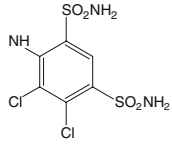
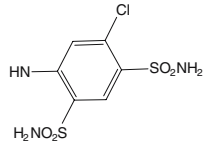
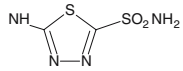
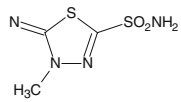
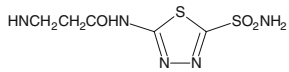
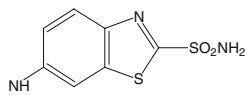
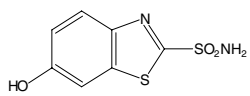
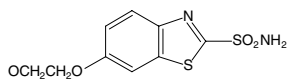
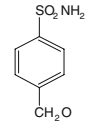
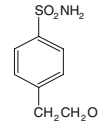
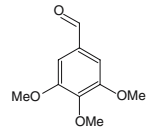
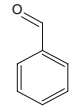
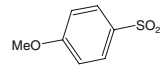
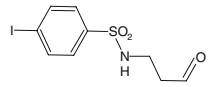
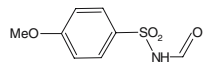
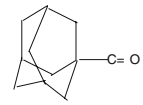
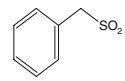
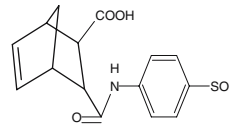
Comp. No.	R	Series	W	M_1	ξ^c	Predicted activity			Reported activity
						W	M_1	ξ^c	
13		II	1008	100	356	–	–	–	–
14		II	1008	100	356	–	–	–	–
15		II	1008	100	356	–	–	–	–
16		II	1593	130	439	+	+	–	–
17		II	1478	124	424	+	+	–	–
18		II	775	90	296	+	+	+	+
19		II	864	96	311	+	–	+	+
20		II	1660	112	529	+	+	+	+
21		II	1299	116	443	+	+	±	+
22		II	1299	116	443	+	+	±	+
23		II	2047	128	637	+	+	+	+

Table 1 *(Continued)*

Comp. No.	R	Series	W	M_1	ξ^c	Predicted activity			Reported activity
						W	M_1	ξ^c	
24		II	1092	98	393	–	–	–	–
25		II	1290	102	449	–	–	±	–
26		I	1414	122	462	+	+	+	+
27		I	657	92	296	+	+	+	+
28		I	853	106	351	+	+	–	+
29		I	1803	128	606	+	+	+	+
30		I	1323	120	478	+	+	+	+
31		I	1046	130	404	–	+	–	+
32	-CO(C(CH$_3$)$_3$)	I	525	90	214	+	+	+	+
33		I	879	104	357	+	+	–	+
34		I	3334	178	883	+	+	+	+

+ Active compound; – Inactive compound; ± Compound in the transitional range where activity could not be specifically assigned.

Table 2
Topological models for hCA II inhibitory activity of sulfonamides.

Model index	Proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy	Average K_i(nM)* for hCA II	Average K_i(nM) for hCA I	Average K_i(nM) for HCA IV
W	Active	< 915	13	10	76.92	7.6	3722.5	206.41
	Inactive	$915 - < 1299$	11	10	90.90	185.3	6550	279.09
	Highly active	$\geqslant 1299$	10	08	80	5.83	346.05	59.5
M_1	Active	94	07	06	85.71	8.66	389.66	113.66
	Inactive	$94 - < 104$	13	12	92.30	194.08	8713.07	364.38
	Highly active	$\geqslant 104$	14	12	85.71	5.89	326.6	51.64
ξ^c	Active	< 314	10	08	80	8.37	2850.88	192
	Inactive	$314 - < 443$	14	11	78.57	112.9	6288	256.71
	Transitional	$443 - < 462$	04	N.A.	N.A.	235.5	1228	136
	Highly active	$\geqslant 462$	06	06	100	5.45	263.08	46

N.A., not applicable.
*for correctly predicted analogues.

hCA II were considered to be active and analogues possessing a K_i (nM) values of $\geqslant$ 15 nM for hCA II were considered to be inactive for the purpose of present study.

The percentage degree of prediction of a particular range and overall degree of predictions were calculated. The average K_i (nM) values for all the analogues as well as correctly predicted analogues in various ranges of the proposed model were calculated for hCA II inhibitory activity. Similarly, the average K_i (nM)

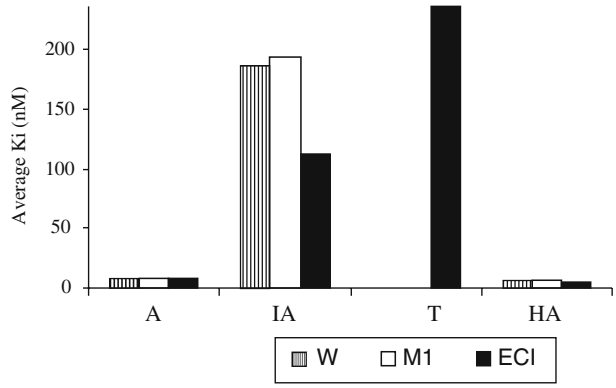


Figure 1. Average k_i (nM) values for hCa II inhibitory activity and characterization of various ranges using Wiener's index (W), Zagreb group parameter (M_1), and eccentric connectivity index (ECI) (I = inactive, A = active, T = transitional, HA = highly active).

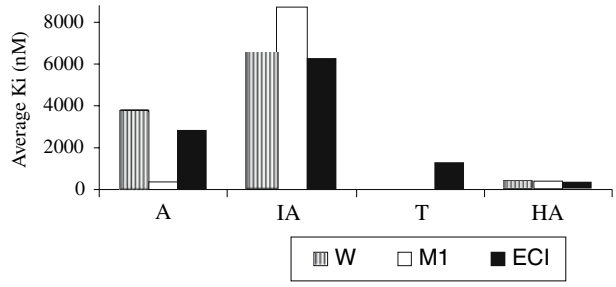


Figure 2. Average k_i (nM) values for hCA I inhibitory activity using Wiener's index (W), Zagreb group parameter (M_1), and eccentric connectivity index (ECI) (I = inactive, A = active, T = transitional, HA = highly active).

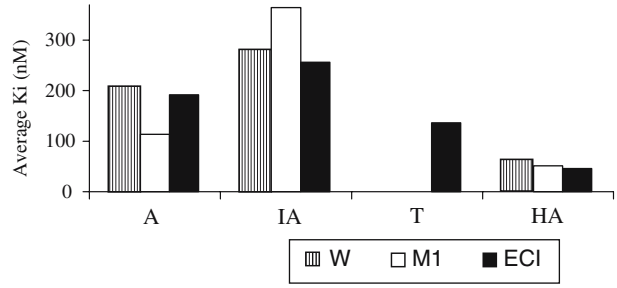


Figure 3. Average k_i (nM) values for hCA IV inhibitory activity using Wiener's index (W), Zagreb group parameter (M_1), and eccentric connectivity index (ECI) (I = inactive, A = active, T = transitional, HA = highly active).

values of the analogues for hCA I inhibitory activity and bCA IV inhibitory activity of various ranges of the proposed model for hCA II were also calculated.

Aforementioned procedure was similarly followed for *eccentric connectivity index*, ξ^c and *Zagreb group parameter*, M_1. The results are summarized in tables 1, 2 and figures 1–3.

3. Results and discussion

The use of global graph invariants in structure activity/property relationships studies has become of major interest in recent years, and especially the structure activity/property relationship models have become a powerful tool for predicting numerous physicochemical properties and biological activities of hypothetical compounds as well as for molecular design [46]. The topological indices are used to characterize features of chemical structures in numerical form. Since topological indices can translate molecular structure into characteristic numerical descriptors, therefore, these are being widely employed in SAR/SPR stud-

ies. The ability to predict with a high-confidence level the physical, chemical, or biological properties for new chemicals significantly reduces the cost and time involved in the design of compounds with desired properties. Many structure activity/property relationship models were developed for the prediction of a wide range of properties [47]. In the present study relationship of three topological descriptors of diverse nature with CA II inhibitory activity of sulfonamides derivatives has been investigated.

The CAs are wide spread enzymes, present in mammals in at least 14 different isoforms. Several important physiological and physio-pathological functions are played by many CA isozymes, which are strongly inhibited by aromatic and heterocyclic sulfonamides [48].

The CA is also quite abundant in the brain, being present in the glia but not neurons. The inhibition of the brain CA causes a selective increase of the cerebral blood flow, with the concomitant raising of the carbon dioxide partial pressure [49,50]. As a consequence these, CA inhibitors are useful in the treatment of conditions associated with increased intracranial pressure [51], as well as different neurological/ neuromuscular pathologies such as epilepsy [52], genetic hemiplegic migrain and ataxia [53], tardive dyskinesia [54], hypokalemic periodic paralysis [55,56], essential tremor and parkinson's disease [57], and mountain sickness [58,59], among others.

Although all the analogues in the dataset reportedly possess some degree of biological activity against hCA II, but only those analogues possessing K_i value of < 15 nM have been considered to be active in the present study so as to facilitate development of various models. Utility of this approach is evident from the fact that the average K_i (nM) value of the highly active range is just a fraction of the average K_i (nM) value of the inactive range in the proposed model. The proposed models are unique in a way in that existence of active ranges is specifically and precisely defined so as to facilitate ease in providing lead structures for development of potent therapeutic agents. These models differ widely from conventional QSAR models. Both types of models have got their own advantages and limitations. Narrow active ranges, which can be easily skipped as possible errors during regression analysis in conventional QSAR modeling, are easily identified with pinpoint accuracy in present system of modeling. These active ranges are extremely beneficial in providing lead structures [60].

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

- Biological activity was assigned to a total of 34 analogues in both the active and inactive ranges, out of which activity of 28 analogues was correctly predicted resulting in 82.35% accuracy with regard to hCA II inhibitory activity of sulfonamides.

- The active range had *Wiener's index* values of < 915. Ten out of 13 analogues in the active range were correctly predicted. The average K_i for the correctly predicted analogues in active range was found to be only 7.6 nM for hCA II inhibitory activity.
- The inactive range had *Wiener's index* values of 915 to < 1299. Biological activity of ten out of 11 analogues in the inactive range was correctly predicted resulting in 90.9% accuracy. The average K_i (nM) for the correctly predicted analogues in inactive range were found to be 185.3 nM for hCA II inhibitory activity.
- The highly active range had *Wiener's index* values of $\geqslant 1299$. Eight out of 10 analogues in the highly active range exhibited hCA II inhibitory activity resulting in 80% accuracy with regard to highly active range of hCA II inhibitory activity. The average K_i (nM) for the correctly predicted analogues in highly active range was found to be only 5.83 nM for hCA II inhibitory activity. The ratio of average K_i (nM) values for correctly predicted analogues of inactive range and highly active range was found to be 32:1.
- Surprisingly, the pattern of biological activity of various ranges in model developed for hCA II inhibitory activity was similar as well with regard to hCA I inhibitory activity and bCA IV inhibitory activity. As observed from table 2, the average K_i value of various analogues in the highly active range was 346.05 nM (with regard to hCA I) and 59.5 nM (with regard to bCA IV) compared to 6550 nM (with regard to hCA I) and 279.09 nM (with regard to bCA IV) in the inactive range.

Retrofit analysis of data in tables 1 and 2 reveals the following information with regard to model based upon *Zagreb group parameter*:

- Biological activity was assigned to a total of 34 analogues in both the active and inactive ranges, out of which activity of 30 analogues was correctly predicted resulting in 88.23% accuracy with regard to hCA II inhibitory activity of sulfonamides.
- The active range had *Zagreb group parameter* values of less than 94. Six out of seven analogues in the active range were correctly predicted. The average K_i (nM) for the correctly predicted analogues in active range was found to be only 8.66 nM for hCA II inhibitory activity.
- The inactive range had *Zagreb group parameter* values of 94 to < 104. Biological activity of 12 out of 13 analogues in the inactive range was correctly predicted resulting in 92.3% accuracy. The average K_i (nM) for the correctly predicted analogues in the inactive range were found to be 194.08 nM for hCA II inhibitory activity.

- The highly active range had *Zagreb group parameter* values of $\geqslant$ 104. Twelve out of 14 analogues in the highly active range exhibited hCA II inhibitory activity resulting in 85.71% accuracy with regard to highly active range of hCA II inhibitory activity. The average K_i (nM) for the correctly predicted analogues in highly active range was found to be only 5.89 nM for hCA II inhibitory activity. The ratio of average K_i (nM) values for correctly predicted analogues of inactive range and highly active range was found to be 33:1.
- Surprisingly, the pattern of biological activity of various ranges in model developed for hCA II inhibitory activity was similar as well with regard to both hCA I inhibitory activity and bCA IV inhibitory activity. As observed from table 2, the average K_i value of various analogues in the highly active range was 326.6 nM (with regard to hCA I) and 51.64 nM (with regard to bCA IV) compared to 8713.07 nM (with regard to hCA I) and 364.38 nM (with regard to bCA IV) in the inactive range.

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

- Biological activity was assigned to a total of 30 analogues in both the active and inactive ranges, out of which activity of 26 analogues was correctly predicted resulting in 86.67% accuracy with regard to hCA II inhibitory activity of sulfonamides.
- The active range had *eccentric connectivity index* values of $<$ 314. Activity of eight out of 10 analogues, in the active range was correctly predicted. The average K_i (nM) for correctly predicted analogues in the active range was found to be only 8.37 nM for hCA II inhibitory activity.
- The inactive range had *eccentric connectivity index* values of 314 to $<$ 443. Activity of 11 out of 14 analogues in the inactive range was correctly predicted. The average K_i (nM) for the correctly predicted analogues in inactive range was found to be 112.9 nM for hCA II inhibitory activity.
- A transitional range between inactive range and highly active range was also observed indicating a gradual change in hCA II inhibitory activity.
- The highly active range had *eccentric connectivity index* values of $\geqslant$ 462. All the analogues in the highly active range exhibited hCA II inhibitory activity resulting in 100% accuracy of prediction. The average K_i (nM) for the analogues in highly active range was found to be only 5.45 nM for hCA II inhibitory activity. The ratio of average K_i (nM) values for correctly predicted analogues of inactive range and highly active range was found to be 21:1.

- Surprisingly, the pattern of biological activity of various ranges in model developed for hCA II inhibitory activity was similar as well with regard to both hCA I inhibitory activity and bCA IV inhibitory activity. As observed from table 2, the average K_i value of various analogues in the highly active range was 263.08 nM (with regard to hCA I) and 46 nM (with regard to bCA IV) compared to 6288 nM (with regard to hCA I) and 256.71 nM (with regard to bCA IV) in the inactive range.

The intercorrelation between *Wiener's index*, *Zagreb group parameter* and *eccentric connectivity index* for all of 34 sulfonamide derivatives was also investigated (figures 4–6). The degree of correlation was appraised by the correlation coefficient r. Pairs of indices with $r > 0.97$ are considered highly correlated, those with $0.90 < r < 0.97$ are appreciably correlated, those with $0.50 < r < 0.89$ are weakly correlated and finally the pairs of indices with low r-values (< 0.50) are not intercorrelated [61]. The results reveal that the pairs, Wiener's index – Zagreb group parameter ($r = 0.89$) and Zagreb group parameter – eccentric connectivity index ($r = 0.88$), are weakly correlated and the pair, Wiener's index – eccen-

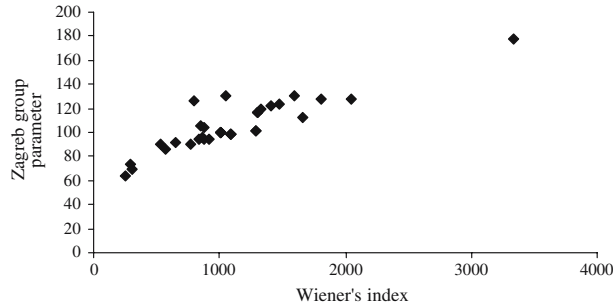


Figure 4. Intercorrelation between Wiener's index and Zagreb group parameter for all of 34 sulfonamides.

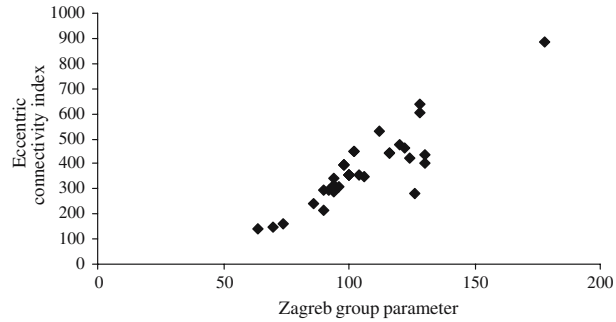


Figure 5. Intercorrelation between Zagreb group parameter and eccentric connectivity index for all of 34 sulfonamides.

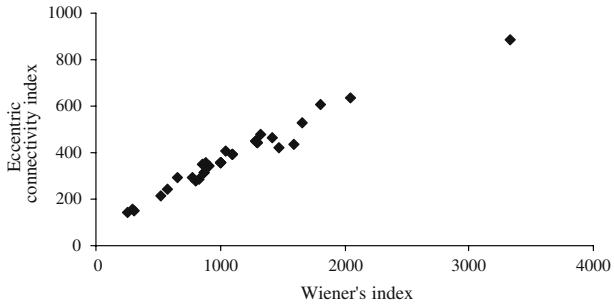


Figure 6. Intercorrelation between Wiener's index and eccentric connectivity index for all of 34 sulfonamides.

tric connectivity index ($r = 0.98$), is highly correlated for all of 34 sulfonamide derivatives.

Investigations reveal significant correlations f all the three topological indices with CA II inhibitory activity of sulfonamide analogues. The overall accuracy of prediction varied from a minimum of 82% for model based on *Wiener's index* to a maximum of 88% for the model based on Zagreb *group parameter*. These models possess vast potential for providing vital lead structures for development of potent CA II inhibitors.

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