Predicting Anti HIV Activity of Quinolone Carboxylic Acids – Computation Approach Using Topological Indices

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Abstract

Background: Quantitative structure–activity relationships (QSAR) are a major factor in contemporary drug designing. Thus, it is quite clear that a large number of users of QSAR are located in industrial research units.
Objectives: A Topological Index is a numeric quantity that is mathematically derived in a direct and uambiguous manner from the structural graph of a molecule. In structure-activity relationship studies, molecular topology quantifies chemical structure into characteristic numerical descriptors. All structural formulas of chemical compounds are molecular graphs where vertices represent the set of atoms and edges represent chemical bonds. The construction and investigation of topological indices that could be used to describe molecular structures is one of the important directions of mathematical chemistry Topological descriptors developed for predicting physicochemical properties and biological activities of chemical substances can be used for drug design.
Matherials and Methods: A number of successful QSAR studies were made based on the Wiener index, Terminal Wiener Index and Platt Number. These indices are derived from matrices, like distance matrix and adjacency matrix which represents a molecular graph. Zagreb Index is based on degree connectivity indices.
Results and Conclusion: In this paper we analyze, Quantitative structure activity relationship studies were performed on anti- HIV activity of Quinolone carboxylic acid for Wiener Index, Terminal Wiener Index, Platt Number and Zagreb Index.

Keywords

Graph, vertices, wiener index, degree, atom, quinolone carboxylic acid

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1 Introduction

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS has led to enormous efforts to unravel the basic action of the virus at a molecular level. From this effort, a variety of targets for potential intervention of HIV multiplication have been identified. Anti-HIV therapy, today, is in need of new drugs, which are less toxic, active against the drug resistant mutants selected by current therapies in the viral replicative cycle.

In the last decade, synthetic chemists have done tremendous research efforts for the development of newer anti-HIV agents [3]. Structure-based design, spurred by the significant pitfalls of the traditional method and the rapid advances in molecular-structure determination and computational resources, has now been accepted as a rational approach for the generation of new pharmaceuticals. The successful implementation of quantitative structure–property/activity relationship (QSPR/QSAR) certainly decreases the number of compounds synthesized, by making it possible to select most promising compounds. Non empirical parameters of chemical structure derived from graph theoretic formalism are being used more frequently by many researchers in QSAR studies pertaining to molecular design, pharmaceutical drug-design, and environmental hazard assessment of chemicals. In chemistry, a graph represents the topology of a molecule in the sense that it depicts the pattern of connectedness of atoms in the molecule, being at the same time, independent of such metric aspects of molecular structure as equilibrium distance between nuclei, bond angles, etc. When a single number represents a graph invariant, it is known as topological index or topological descriptor. These indices are derived from matrices, like distance matrix and adjacency matrix, which represent a molecular graph. Though numerous topological descriptors have been reported in the literature but only handful of them has been successfully

employed for structure–activity relationship studies. Notable amongst these are Wiener index, Terminal Wiener Index, Zagreb index and Platt Number.

In the present investigation, relationship of Wiener index, Terminal Wiener Index, Zagreb index and Platt Number for anti-HIV activity of Quinolone Carboxylic Acid has been investigated and suitable models have been developed for prediction of anti-HIV activity.

1.1 Definition

The Wiener index [2] is a distance-based graph invariant used as one of the structure descriptors for predicting physicochemical properties of organic compounds. The Wiener index was introduced by the chemist H. Wiener about 60 years ago to demonstrate correlations between physicochemical properties of organic compounds and the topological structure of their molecular graphs. This concept has been one of the most widely used descriptors in relating a chemical compound's property to its molecular graph.

The Wiener index $W(G)$ of a graph G is defined as the sum of the half of the distances between every pair of vertices of G.

$$W(G) = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} d(v_i, v_j) \tag{1}$$

Where $d(v_i, v_j)$ is the number of edges in a shortest path connecting the vertices v_i, and v_j. Wiener index of a complete graph K_n is

$$W(K_n) = \frac{n^2 - n}{2} \tag{2}$$

and path graph P_n,

$$W(P_n) = \frac{n^3 - n}{6}. \tag{3}$$

Among all the trees on n vertices, the star $K_{1,n-1}$ has the lowest Wiener number and the path P_n has the largest Wiener number and hence

$$W(K_{1,n-1}) \leq W(T) \leq W(P_n). \tag{4}$$

1.2 Definition

The Terminal distance matrix [4] or reduced distance matrix of trees was introduced by Gutman, B. Furtula, and M. Petrovic. If an n-vertex graph G has k pendent vertices (vertices of degree one), labeled $v_1, v_2, v_3, \ldots, v_k$, then its terminal distance matrix is the square matrix of order k whose (i, j) – entry is $d(v_i, v_j \mid G)$. The Terminal Wiener index $TW(G)$ of a graph G is the sum of the distances between all pairs of pendent vertices.

$$TW(G) = \sum_{1 \leq i \leq j \leq k} d(v_i, v_j \mid G) \tag{5}$$

where $d(v_i, v_j \mid G)$ is the distance between pair of pendent vertices in a graph G. Consider a graph G, vertices having degree one is called pendent vertices or terminal vertices and vertices having more than one degree are called interior vertices.

1.3 Definition

The Zagreb group indexes of a graph G denoted by $M_1(G)$ (first Zagreb index) [1] and $M_2(G)$ (second Zagreb index) are defined as

$$M_1(G) = \sum_{j=1}^{N} D_j^2 \tag{6}$$

$$M_2(G) = \sum_{i,j} D_i D_j \tag{7}$$

where D_j stands for the degree of a vertex j. The sum in (6) is over all vertices of G, while the sum in (7) is over all edges of G.

1.4 Definition

Platt was also interested in devising a scheme for predicting the physical parameters (molar refractions, molar volumes, boiling points, heats of formation, heats of vaporization) of alkanes. He introduced an index $F(G)$, which is equal to the total sum of degrees of edges in a graph. The degree of an edge e, $D(e)$ is the number of the adjacency edges.

$$F(G) = \sum_{i=1}^{M} D(e_i) \tag{8}$$

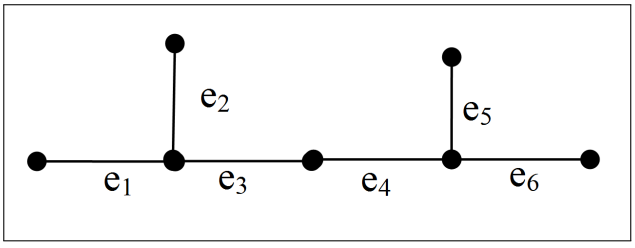

Figure 1: The Graph G.

$$\begin{aligned} F(G) &= D(e_1) + D(e_2) + D(e_3) + D(e_4) + D(e_5) + D(e_6) \\ F(G) &= 2 + 2 + 3 + 3 + 2 + 2 \\ F(G) &= 14 \end{aligned} \tag{9}$$

The calculation of Wiener index, Terminal Wiener Index for three isomers of eight-membered molecule (heptylamine) has been exemplified in Figure 2.

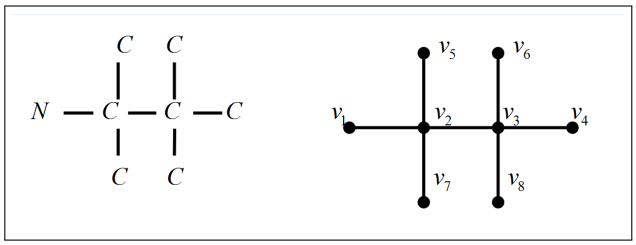

Figure 2: The chemical compound heptylamine is isomorphic to 1,4 biregular-caterpillar graph.

1.5 Chemical Distance Matrices

In the above Figure 2, the chemical compound heptylamine is isomorphic to the coresponding graph 1,4 biregular-caterpillar. In the graph, total number of vertices is eight and number of pendent vertices is six. We calculate the Wiener Index and Terminal Wiener Index of 1,4 biregular graph and tabulated below.

Table 1: Calculation of Wiener Index of 1, 4 bi regular caterpillar graph.

	1	2	3	4	5	6	7	8	$W(G)$
1	0	1	2	3	2	3	2	3	16
2	1	0	1	2	1	2	1	2	10
3	2	1	0	1	2	1	2	1	10
4	3	2	1	0	3	2	3	2	16
5	2	1	2	3	0	3	2	3	16
6	3	2	1	2	3	2	3	0	16
7	2	1	2	3	2	3	0	3	16
8	3	2	1	2	3	2	3	0	16

Table 2: Calculation of Wiener Index and Terminal Wiener Index of 1,4 bi regular caterpillar graph.

	1	2	3	4	5	6	$TW(G)$
1	0	3	2	3	2	3	13
2	3	0	3	2	3	2	13
3	2	3	0	3	2	3	13
4	3	2	3	0	3	2	13
5	2	3	2	3	0	3	13
6	3	2	3	2	3	0	13

Using the Table 1, The Wiener Index for 1,4 bi regular-caterpillar graph is

$$W(G) = \frac{16+10+10+16+16+16+16+16}{2} = = \frac{116}{2} = 58. \quad (10)$$

Using the Table 2, The Terminal Wiener Index for 1,4 bi regular-caterpillar graph is

$$TW(G) = \frac{13+13+13+13+13+13}{2} = = \frac{78}{2} = 39. \quad (11)$$

2 Results

In this paper we analyse Wiener index, Terminal Wiener Index, Zagreb index and Platt number for anti-HIV activity of Quinolone Carboxylic Acid [5].

We attach the functional group in the basic structures of quinolone carboxylic acid and calculate the values of Wiener Index, Terminal Wiener Index, Zagreb Index and Platt Number.

3 Discussion and Conclusion

We have fixed the active and inactive range values for the compounds as per the reference [3] where eccentric conductivity topochemcal index,molecular conductivity topochemical index and Balaban's mean square distance topochemmmmical index are discussed. In our paper we have anlized Wiener index $W(G)$, Terminal wiener index $TW(G)$, Zagreb Index $Z(G)$ and Platt Number $F(G)$. Models based on Wiener Index, above the range 2049, quinolone carboxylic acid is active. Out of 46 compounds 38 compounds are inactive. But for the Terminal Wiener Index, the value depends on the pendent vertices hence quinolone carboxylic acid is in transitional range. In the case of Zagreb Index, below the range of 152 the quinolone carboxylic acid is inactive. In case of Platt Number above the range 96 the quinolone carboxylic acid is active.

From the Figure 4, high predictability of the models derived from Wiener Index can provide valuable leads for development of anti HIV agents. Moreover high discriminating amalgamated of Wiener Index with low degeneracy of Platt Number and Zagreb Index offers a vast potential for its use in structure-activity / property studies.

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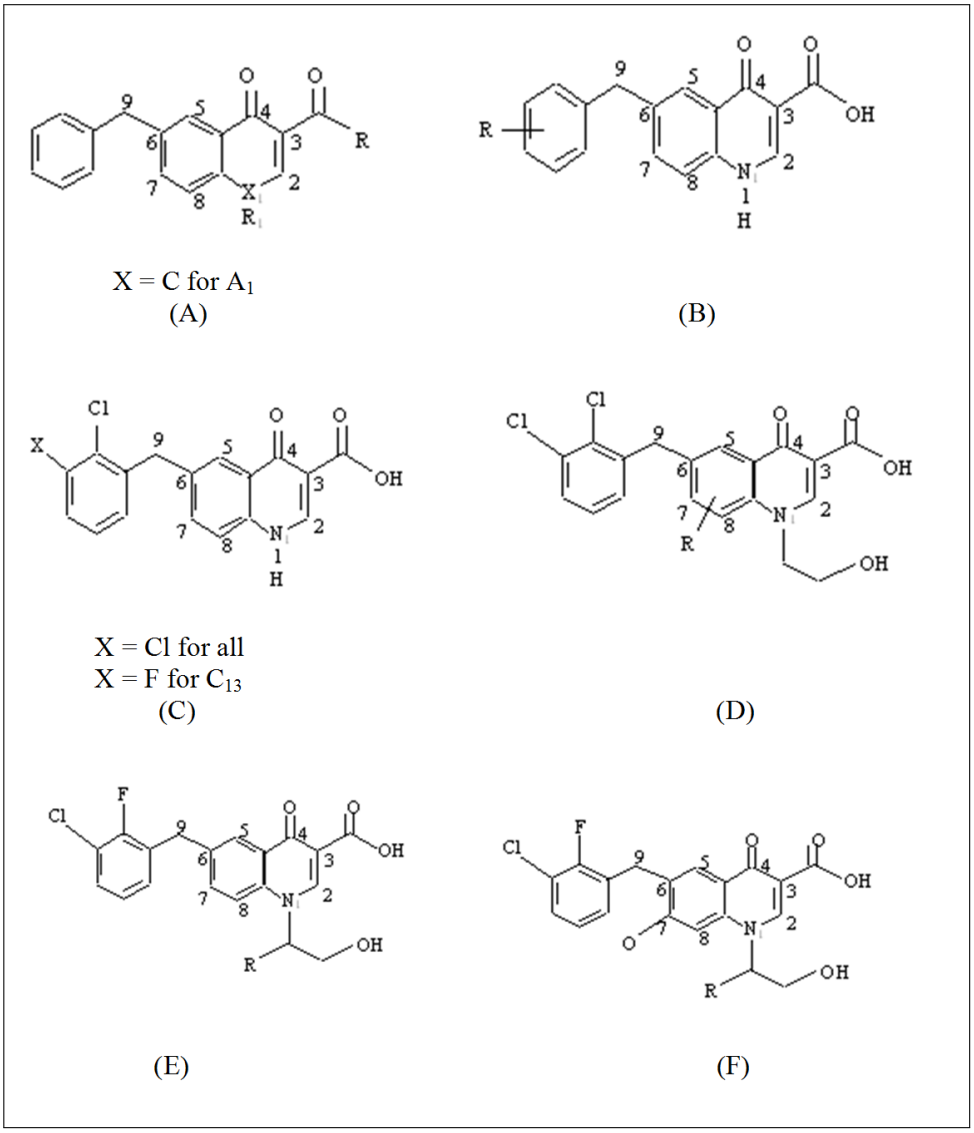

Figure 3: Basic structures and arbitrary atom numbering scheme for the quinolone carboxylic acid.

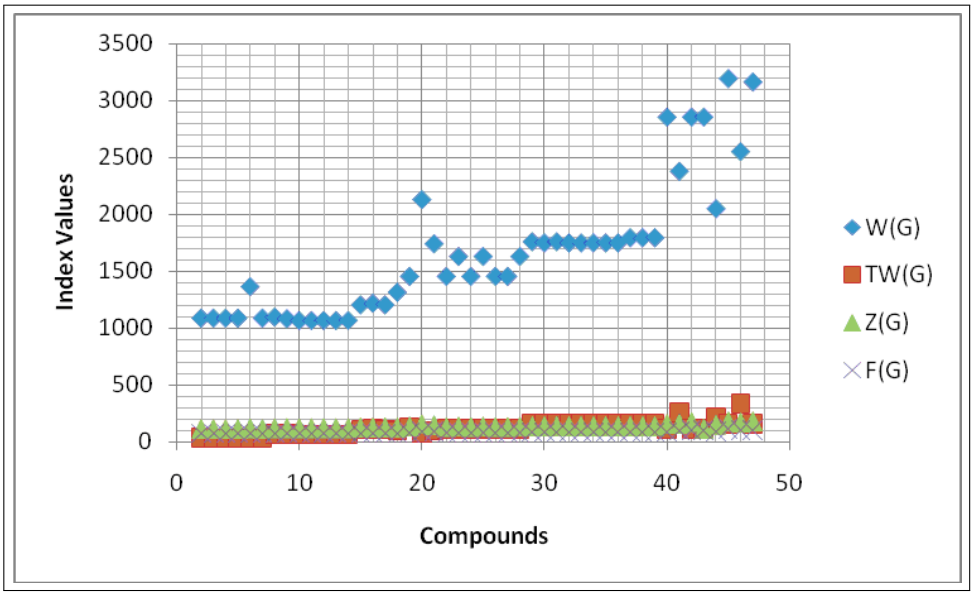

Figure 4: Graphically significant values of $W(G)$, $TW(G)$, $F(G)$ and $Z(G)$.

Table 3: Calculation of Wiener Index, Terminal Wiener Index, Zagreb Index and Platt Number for HIV integrase inhibitory activity.

Compound Number	R/R_1 (Functional group)	$W(G)$	$TW(G)$	$M_1(G)$	$F(G)$	HIV integrase inhibitory activity		
						$W(G)$	$M_1(G)$	$F(G)$
A_1	–COCOOH	1088	34	115	72	–	–	–
A_2	–COCOOH /–CH_3	1088	31	115	74	–	–	–
A_3	–OH	1088	31	115	72	–	–	–
A_4	–OH / –CH_3	1088	31	115	72	–	–	–
A_5	–OE_t	1364	31	120	76	–	–	–
A_6	NH_2	1088	31	115	72	–	–	–
B_1	3 –Cl	1097	70	122	72	–	–	–
B_2	2 –Cl	1082	66	122	72	–	–	–
B_3	1 –Cl	1067	62	122	72	–	–	–
B_4	1 –F	1067	62	122	72	–	–	–
B_5	1 –Me	1067	62	122	72	–	–	–
B_6	1 –OMe	1067	62	122	72	–	–	–
B_7	1 –CF_3	1067	62	122	72	–	–	–
B_8	1,4 –Cl_2	1205	108	128	76	–	–	–
B_9	2,4 –Cl_2	1219	112	128	76	–	–	–
B_{10}	1,2 –Cl_2	1205	106	128	76	–	–	–
C_1	–Me	1315	94	128	76	–	–	–
C_2	–Et	1455	129	138	78	–	–	–
C_3	–Pr	2129	72	156	91	–	+	–
C_4	–Bu	1741	94	146	88	–	–	–
C_5	CH_2CO_2H	1455	111	132	78	–	–	–
C_6	$CH_2CH_2CO_2H$	1630	116	136	80	–	–	–
C_7	CH_2CONH_2	1455	111	132	78	–	–	–
C_8	$(CH_2)_2CONH_2$	1630	116	136	80	–	–	–
C_9	$(CH_2)_2NH_2$	1455	111	132	78	–	–	–
C_{10}	$(CH_2)_2OH$	1455	111	132	78	–	–	–
C_{11}	$(CH_2)_3OH$	1630	116	136	80	–	–	–
D_1	8 –F	1759	160	142	84	–	–	–
D_2	5 –F	1749	155	142	84	–	–	–
D_3	9 –F	1759	160	142	84	–	–	–
D_4	5 –OMe	1749	160	142	84	–	–	–
D_5	5 –Cl	1749	160	142	84	–	–	–
D_6	5 –Me	1749	160	142	84	–	–	–
D_7	5 –CF_3	1749	160	142	84	–	–	–
D_8	5 –CN	1749	160	142	84	–	–	–
E_1	–H	1794	156	142	86	–	–	–
E_2	–Me	1794	156	142	86	–	–	–
E_3	–Et	1794	156	142	86	–	–	–
E_4	–Pr	2854	115	160	86	+	+	–
E_5	iBu	2378	259	160	96	+	+	+
E_6	Cyclohexyl	2854	115	174	100	+	+	+
E_7	Ph	2854	115	116	100	+	–	+
F_1	5 –OMe	2049	211	152	90	+	+	–
F_2	–Pr	3192	160	180	116	+	+	+
F_3	iBu	2551	338	170	100	+	+	+
F_4	Cyclohexyl	3162	160	180	104	+	+	+

+, active compound; – inactive compound