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Application of graph theory: Prediction of cytosolic phospholipase A_2 inhibitory activity of propan-2-ones

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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 cytosolic phospholipase A_2 inhibitory activity of propan-2-ones has been investigated. A training set comprising 44 analogues of substituted propan-2-ones was selected for the present investigations. The values of the *Wiener's index*, *Zagreb group parameter* and *eccentric connectivity index* for each of 44 analogues comprising the data set were computed. Resultant data was analyzed and suitable models were developed after identification of active ranges. Subsequently, biological activity was predicted for each analogue involved in the data set using these models, which was then compared with the reported cytosolic phospholipase A_2 inhibitory activity. Accuracy of prediction was found to vary from a minimum of ~84% for model based on *Zagreb group parameter* to a maximum of 88% for model based on *eccentric connectivity index*.

KEY WORDS: cytosolic phospholipase A_2 inhibitory activity, eccentric connectivity index, propan-2-ones, Wiener's index, Zagreb group parameter

1. Introduction

Structure activity/property relationships are the models that attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties [1]. With the help of graph theory structure property/activity relationship becomes a property–property relationship in which one parallels mathematical properties of a structure to physicochemical and biological properties of a chemical compound. A large number of structure activity/property relationship studies have been reported in recent literature using theoretical molecular descriptors in predicting physicochemical, pharmacological and toxicological properties of molecules [2]. Graph theoretical parameters have been widely used in the characterization of molecular structure and

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quantification of chemical similarity [3,4]. This has been accomplished by using graph invariants. The path numbers, and connectivity type as well as information theoretic graph invariants have been used in predicting molecular properties and in quantifying chemical similarity of diverse sets of molecules [5–7]. A graph can represent structural formulae for a large number of organic compounds. Since more than 90% of chemical compounds described so far are either organic or contain organic ligands, such a graph has been found to be useful in chemistry [8]. Graph theoretical invariants have been found useful in chemical documentation, isomer discrimination, structure-property correlations, and chemical structural–biological activity relationships [9]. Topological indices have been successfully employed in developing a suitable correlation between chemical structures and biological activity by translating chemical structures in to numerical descriptors [10–12]. Although a number of topological indices have been reported but only a handful of them have been successfully employed in SAR studies. These include *Hosoya's index* [13,14], *Randic's molecular connectivity index*, χ [15], *the higher-order connectivity indices*, ${}^{n}\chi$, for the paths of length n defined by Kier and Hall [7], *Superpendentic index* [16,17], *Balaban's index*, J [18,19], *Wiener's* index [20–22], *Zagreb group parameters*, M_1 and M_2 [23,24], *eccentric connectivity index* [25–29] and eccentric adjacency index [30]. Topological indices developed for predicting physicochemical properties and biological activities, of chemical substances, can be exploited for drug design [31–33].

Phospholipases A_2 (PLA_2) is a class of estrases that cleave the sn-2 ester bond of membrane phospholipids [34]. These enzymes liberate arachidonic acid from cellular phospholipids for the biosynthesis of eicosanoids and thus are of interest for understanding inflammation. Cytosolic phospholipases A_2 are phosphorylated as part of its activation process [35]. Prostaglandins, synthesized from arachidonic acid, are involved in the facilitation of nociceptive processing in the spinal cord. This indicates an essential role of spinal PLA_2 in the central facilitation of nociceptive processing due to acute peripheral inflammation [36].

Cytosolic phospholipases A_2 is involved in the pathogenesis of a variety of disease processes that are characterized by substantial inflammatory and oxidative stress components. These diseases include septic shock, acute pancreatitis, Crohn's disease, ischemic stroke, myocardial infarction and rheumatic disorders [37]. Cytosolic phospholipases A_2 inhibitors can be used as neuroprotective and anti-inflammatory agents in neurodegenerative diseases. Phospholipase A_2 inhibitors are potent inhibitor of inflammation and cartilage catabolism, and phospholipase A_2 is involved in the pathophysiology of human recombinant interleukin-1 alph**a** -induced arthritis in rabbits [38].

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 cytosolic phospholipase A_2 inhibitory activity of propan-2-ones has been investigated.

2. Methodology

2.1. Calculations of topological indices

The *Wiener's index* [20–22], 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

$$W = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}, \tag{1}$$

where P_i 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 et al. [23,24] is defined as the sum of squares of degree over all vertices and is represented by following equation:

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

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 e*ccentric connectivity index* [25–29] 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

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

where V_i is the degree of vertex i, E_i is 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 $i (E_i = \max \mathrm{d}(ij);\ j\varepsilon \mathrm{G})$; the eccentricity connectivity index takes into consideration the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

3. Model development analysis

A data set [39] comprising of 44 analogues of propan-2-ones was selected for the present investigations. The basic structure for these analogues is depicted in figure 1 and various substituents enlisted in table 1. The values of the *Wiener's index* were computed for each analogue using an in-house computer

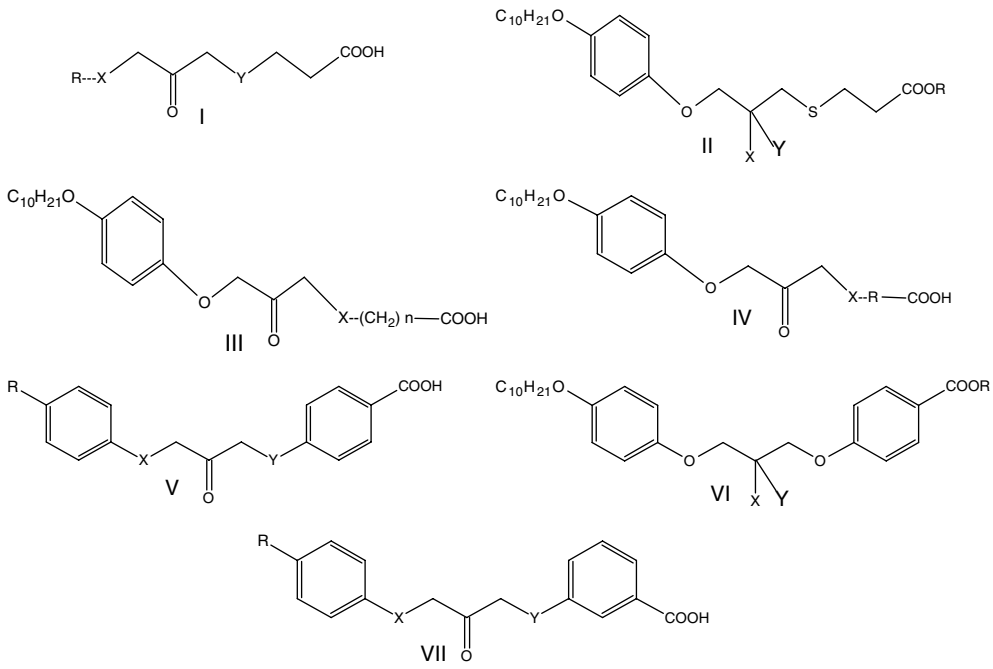


Figure 1. Basic structures of propane-2-one series.

program and a suitable model was developed after identification of active range by maximization of moving average with respect to active compounds [30]. Subsequently, each analogue was assigned a biological activity using the said model, which was then compared with the reported cytosolic phospholipase A_2 inhibitory activity. Inhibitors were reportedly [39] tested against the action of cytosolic phospholipase A_2 in a bilayer-based assay in which the substrate is comprised of an aggregated form of phospholipid and the cytosolic phospholipase A_2 inhibitory activity was reported quantitatively as IC_{50} (μM) at different concentrations [39]. The analogues possessing IC_{50} values of $< 0.1\,\mu$M were considered to be active and analogues possessing an IC_{50} values of $> 0.1\,\mu$M were considered to be inactive for the purpose of present study.

The percentage degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to the total number of compounds present in that range. The overall degree of prediction was derived from the ratio of the total number of compounds correctly to that of the total number of compounds present in both the active and inactive ranges.

Aforementioned procedure was similarly followed for e*ccentric connectivity index*, ξ^c and *Zagreb group parameter,* M_1. The results are summarized in tables 1 & 2.

Table 1
Relationsip of Wiener's index Zagreb group parameter and eccentric connctivity index with cytosolic phosholipase A_2 inhibitory activity.

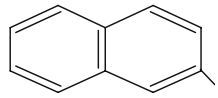
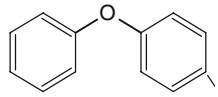
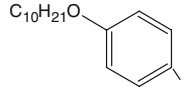
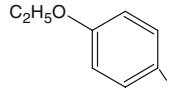
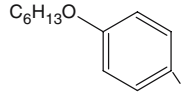
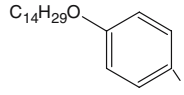
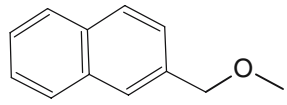
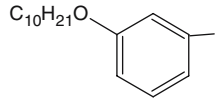
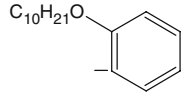
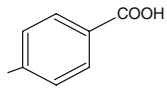
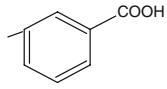
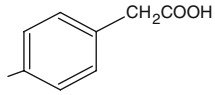
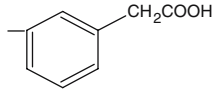
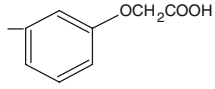
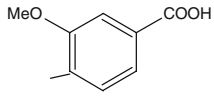
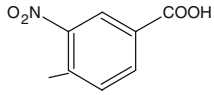
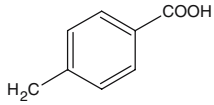
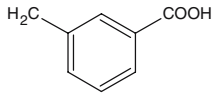
Comp No.	Series	R	X	Y	*n*	W	M_1	ξ^c	Predicted activity *W*	Predicted activity M_1	Predicted activity ξ^c	Reported activity
1	I		O	S	–	1162	100	476	–	–	–	–
2	I		O	S	–	1788	112	646	–	–	–	–
3	I		O	S	–	3114	120	950	–	–	–	–
4	I		O	S	–	1078	88	449	–	–	–	–
5	I		O	S	–	1904	104	670	–	–	–	–
6	I		O	S	–	4772	136	1289	+	±	+	–
7	I		O	S	–	3048	142	943	–	±	–	–
8	I		O	S	–	2993	120	904	–	–	–	–
9	I		O	S	–	2872	120	861	–	–	–	–
10	II	Me	=O	–	–	3448	124	1021	–	–	–	–
11	II	H	H	OH	–	3114	120	950	–	–	–	–
12	II	H	H	H	–	2898	114	915	–	–	–	–
13	III	–	S	–	1	2784	116	879	–	–	–	–
14	III	–	S	–	3	3472	124	1023	–	–	–	–
15	III	–	S	–	4	3859	128	1102	±	±	±	+
16	III	–	SO	–	2	3362	126	989	–	–	–	–
17	III	–	SO_2	–	2	3612	134	1028	±	±	–	–
18	III	–	O	–	2	3114	120	950	–	–	–	–
19	III	–	O	–	3	3472	124	1023	–	–	–	–
20	III	–	O	–	4	3859	128	1102	±	±	±	+

Table 1 (*Continued*)

21	IV		O	–	–	4422	146	1231	±	±	±	+
22	IV		O	–	–	4353	146	1197	±	±	±	+
23	IV		O	–	–	4850	150	1312	+	+	+	+
24	IV		O	–	–	4758	150	1276	+	+	+	+
25	IV		O	–	–	5196	154	1357	+	+	+	+
26	IV		O	–	–	5063	156	1319	+	+	+	+
27	IV		O	–	–	5402	162	1364	+	+	+	+
28	IV		O	–	–	4890	150	1318	+	+	+	+
29	IV		O	–	–	4818	150	1284	+	+	+	+
30	V	$C_8H_{17}O$	O	O	–	3581	138	1063	±	±	±	+
31	V	$C_6H_{13}O$	O	O	–	2860	130	910	–	±	–	–
32	V	C_4H_9O	O	O	–	2251	122	770	–	–	–	–
33	V	C_2H_5O	O	O	–	1746	114	642	–	–	–	–
34	V	$Ph(CH_2)_5O$	O	O	–	4720	158	1279	+	+	+	+
35	V	$PhCH_2O$	O	O	–	3060	142	949	–	±	–	–
36	V	$4\text{-}MeOPhCH_2O$	O	O	–	3736	152	1095	±	+	±	–
37	V	$4\text{-}NO_2PhCH_2O$	O	O	–	4091	158	1138	±	+	±	–
38	VI	allyl	=O	–	–	5722	158	1482	+	+	+	–
39	VI	H	H	OH	–	4422	146	1231	±	±	±	–
40	VI	H	H	H	–	4176	140	1196	±	±	±	–
41	V	$Ph(CH_2)_5S$	O	O	–	4720	158	1279	+	+	+	+
42	V	$Ph(CH_2)_5S$	O	CH_2	–	4720	158	1279	+	+	+	–
43	VII	$C_{10}H_{21}O$	CH_2	O	–	4353	146	1197	±	±	±	–
44	VII	$C_{10}H_{21}O$	CH_2O	O	–	4826	150	1286	+	+	+	–

+ Active compound; – Inactive compound; ± Compound in the transitional range.

4. Results and discussion

An important area of research in computational and mathematical chemistry is the characterization of molecular structure using structural invariants [40–42]. Researchers in chemical documentation have searched for a set of invariants that will be more convenient than the adjacency matrix (or connection tables) for the storage and comparison of chemical structures [43]. Invariants have been used to order sets of molecules [44–46]. Numerical graph invariants or topological indices are the molecular descriptors, which are produced directly from molecular structure [47]. The interest in the influence of molecular topology on molecular properties has grown remarkably during the past few years. The objective of all such studies is to explore the role of connectedness of atoms in the expression of biological activities of molecules [48]. In the present study relationship of three topological descriptors of diverse nature with cytosolic phospholipase A_2 inhibitory activity of propan-2-one derivatives has been investigated.

The action of cytosolic phospholipases A_2 on phospholipid containing arachidonic acid at the *sn*-2 position releases arachidonic acid and lysophospholipids, precursors for various proinflammatory lipid mediators including prostaglandins, leukotrienes, thromboxanes, and platelet activating factor [49]. Cytosolic phospholipase A_2 is a particularly attractive target for drug development because it is the rate-limiting provider of proinflammatory mediators. Such inhibitors are able to block the production of arachidonic acid and prostaglandin E_2 in cells, and demonstrate potent *in vivo* anti-inflammatory and analgesic activity [50]. The selected data set comprising of 44 analogues included both the active and inactive compounds. Though all the analogues in the dataset reportedly possess varying degree of cytosolic phospholipase A_2 inhibitory activity, but only those analogues possessing IC_{50} values of $< 0.1\,\mu M$ have been considered to be active for the purpose of present study.

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 33 analogues in both the active and inactive ranges, out of which activity of 29 analogues was correctly predicted resulting in 87.8% accuracy with regard to cytosolic phospholipase A_2 inhibitory activity of propan-2-ones.
- The active range had *Wiener's index* values of $\geqslant$ 4720. 09 out of 13 analogues in the active range exhibited cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the all the analogues in the active range was found to be $0.97\,\mu M$ and average IC_{50} value for correctly predicted analogues in the active range was found to be $0.039\,\mu M$.
- The inactive range had *Wiener's index* values of $<$ 3581. All the analogues in the inactive range were correctly predicted resulting in 100%

Table 2
Topological models for cytosolic phosholipase A_2 inhibitory activity of propan-2-ones.

Model Index	Nature of range in proposed model	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy	Average IC_{50} (μM)
Wiener's index	Inactive	< 3581	20	20	100	56.697
	Transitional	3581 to < 4720	11	N.A.	N.A.	3.335
	Active	$\geqslant 4720$	13	09	69.23	0.97 (0.039)
Zagreb group parameter	Inactive	< 128	17	17	100	66.421
	Transitional	128 to < 150	13	N.A.	N.A.	2.913
	Active	$\geqslant 150$	14	09	64.28	1.158 (0.039)
Eccentric connectivity index	Inactive	< 1063	21	21	100	54.02
	Transitional	1063 to < 1276	10	N.A.	N.A.	3.619
	Active	$\geqslant 1276$	13	09	69.23	0.97 (0.039)

Note: N.A., not applicable; Values in brackets indicate average IC_{50} (μM) of correctly predicted analogues.

accuracy with regard to inactive range of cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the analogues in the inactive range was found to be 56.697 μM.

- A transitional range between active and inactive ranges was observed. Existence of such a range is ideal because simply signifies a gradual change in cytosolic phospholipase A_2 inhibitory activity. A total of 11 analogues were present in the transitional range. The average IC_{50} value for all analogues in the transitional range was found to be 3.335 μM.
- The ratio of average IC_{50} values of inactive range and active range (for correctly predicted analogues) was found to be 1453:1.

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

- Biological activity was assigned to a total of 31 analogues in both the active and inactive ranges, out of which activity of 26 analogues was correctly predicted resulting in 83.8% accuracy with regard to cytosolic phospholipase A_2 inhibitory activity of propan-2-ones.
- The active range had *Zagreb group parameter* values of $\geqslant$ 150. 09 out of 14 analogues in the active range exhibited cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the all the analogues in the

active range was found to be 1.158 μM and average IC_{50} value for correctly predicted analogues in the active range was found to be 0.039 μM.

- The inactive range had *Zagreb group parameter* values of < 128. All the analogues in the inactive range were correctly predicted resulting in 100% accuracy with regard to inactive range of cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the analogues in the inactive range was found to be 66.421 μM.
- A transitional range was observed indicating a gradual change in cytosolic phospholipase A_2 inhibitory activity. A total of 13 analogues were present in the transitional range. The average IC_{50} value for all analogues in the transitional range was found to be 2.913 μM.
- The ratio of average IC_{50} values of inactive range and active range (for correctly predicted analogues) was found to be 1703:1.

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 34 analogues in both the active and inactive ranges, out of which activity of 30 analogues was correctly predicted resulting in 88.2% accuracy with regard to cytosolic phospholipase A_2 inhibitory activity of propan-2-ones.
- The active range had *eccentric connectivity index* values of $\geqslant 1276.09$ out of 13 analogues in the active range exhibited cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the all the analogues in the active range was found to be 0.97 μM and average IC_{50} value for correctly predicted analogues in the active range was found to be 0.039 μM.
- The inactive range had *eccentric connectivity index* values of < 1063. All of the analogues in the inactive range were correctly predicted resulting in 100% accuracy with regard to inactive range of cytosolic phospholipase A_2 inhibitory activity. The average IC_{50} value for the analogues in the inactive range was found to be 54.02 μM.
- A transitional range was observed indicating a gradual change in cytosolic phospholipase A_2 inhibitory activity. A total of 10 analogues were present in the transitional range. The average IC_{50} value for all analogues in the transitional range was found to be 3.619 μM.
- The ratio of average IC_{50} values of inactive range and active range (for correctly predicted analogues) was found to be 1385:1.

Investigations reveal significant correlations of all the three topological indices with cytosolic phospholipase A_2 inhibitory activity of propan-2-one ana-

logues. The overall accuracy of prediction varied from a minimum of ~84% for model based on *Zagreb group parameter* to a maximum of 88% for model based on *eccentric connectivity index*. These models possess vast potential for providing vital lead structures for development of potent cytosolic phospholipase A_2 inhibitors.

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