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Predicting Anti cancer activity of Marine Pyridoacridine alkaloids – Computation approach using Topological indices

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ABSTRACT

A topological index is a numeric quantity that is mathematically derived in a direct and unambiguous manner from the structural graph of a molecule. Topological indices contain valuable structural information as evidenced by the success of their widespread application in QSAR and QSPR studies. In this paper we study the relationship of Wiener Index, First and second Zagreb indices for the anti cancer activity of some marine pyridoacridine alkaloids. The values of all the three indices for each of the 60 analogs comprising the dataset were computed, and it is compared with the biological activity of the reported anticancer activity. Accuracy of prediction is found to be approximately 95% based upon Wiener, First and Second Zagreb topological indices.

Keywords: Graph, vertices, wiener index, degree, atom, distance, pyridoacridine alkaloids

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INTRODUCTION

Drugs and other chemical compounds are often modeled as various polygonal shapes, paths, trees, graphs etc. Each vertex in the polygonal path or tree represents an atom of the molecule, and covalent bonds between atoms are represented by edges between the corresponding vertices. This polygonal shape derived from a chemical compound is often called its molecular graph. As the geometry of proteins play an important role in determining the function of the protein[2], topological properties of the molecular graphs of chemical compounds are to be correlated to their chemical properties. In recent years a large number of topological indices have been reported and utilized for chemical documentation, isomer discrimination, study of molecular complexity, chirality, similarity/dissimilarity, QSAR/QSPR, drug design and database selection, lead optimization, rational combinatorial library design and for deriving multilinear regression models [21]. These include Wiener index [1], Balaban index [5], Hosoya index [3], molecular connectivity indices [4] and eccentric connectivity index [12,15]. Use of topological indices in structure-activity relationship studies seems to play an important role in situations where biological activity is determined predominantly by topological architecture of molecular structure, i.e., where simple connectivity among neighboring atoms, without considering the chemical nature of atom or nature of chemical bonding, may be the major determinant of biological activity of a molecule [10]. Wiener number or Wiener index, W, is the first reported and used topological index in chemistry. It was invented in 1940s. Wiener index is a useful topological index in the structure-property relationship because it is a measure of the compactness of a molecule in terms of its structural characteristics, such as branching and cyclicity [11]. It is defined as the sum of the distances between all the pairs of vertices of a molecular graph. The Wiener index [14] is also one of the oldest molecular graph based structure descriptors. The Wiener number W(G) originated from the work of H.Wiener as a topological index to study the relation between molecular structure and physical and chemical properties of certain hydrocarbon compounds.

In natural sources, plants, animals and microorganisms have been the main source of biologically important molecules. Ocean has been considered as the main source of medicines and during the past two decades thousands of compounds and their metabolites with several different type of biological activity such as antimicrobial, anti-inflammatory, antimalarial, antioxidant, anti HIV[19,20,26] and anticancer activity have been isolated from marine microorganisms

[16,21,24]. But till date only few anticancer drugs such as citarabine vidarabine etc have been commercially developed from marine compounds while several others are currently in different stages of clinical trials. Over 18000 compounds have been isolated from marine source and approximately 150 compounds are cytotoxic against the different tumor cells [13,22]. Some of the prominent anticancer compounds which are in different stages of clinical trials include aplidine, ecteinascidin-734 (Yondelis), bryostatin-1, squalamine, dolastatin- 10, ILX651, and KRN7000 (*α*-galactosylceramide). Pyridoacridines are highly coloured marine natural products having polycyclic planar heteroaromatic 11*H*- pyrido acridine system (**1**) [2]. They are probably the largest class among marine alkaloids and are almost universally isolated from sponges, ascidians as well as from a mollusc and a coelenterate [17]. Pyridoacridine alkaloids show significant biological activityprimarily cytotoxicity and certain specific biological properties *viz*. fungicidaland bactericidal properties, inhibition of topoisomerase II, anti HIV[23], intercalationof DNA property, Ca^{+2} releasing activity, production of reactive oxygen species[6-9]. These activities depends upon the substitution pattern of the basic structure of pyridoacridine, therefore many synthetic analogues have also beensynthesized keeping the basic skeleton of pyridoacridine in mind. The synthesis of these analogues and their biological activity evaluation revealed that in most of the cases cytotoxicity of the analogues has improved compared to the parent molecule. Pyridoacridines[25] can be divided into tetracyclic, pentacyclic, hexacyclic, heptacyclic and octacyclic alkaloids. In this paper we study the relationship of Wiener Index, First and second Zagreb indices with the anti cancer activity of some marine pyridoacridine alkaloids and anti-cancer activity of the molecules are predicted.

MATERIALS AND METHODS

The Wiener index is a distance-based graph invariant used as one of the structure descriptors for predicting physicochemical properties of organic compounds. *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.* $W(G)=\frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n}d\left(v_i,v_j\right)$

where d (v_i,v_j) is the number of edges in a shortest path connecting the vertices v_i and v_j.

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

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

$$M_2(G)=\sum_{(i,j)}D_iD_j \qquad (2)$$

where D_j stands for the degree of a vertex j. The sum in (1) is over all vertices of *G*, while the sum in (2) is over all edges of *G*.

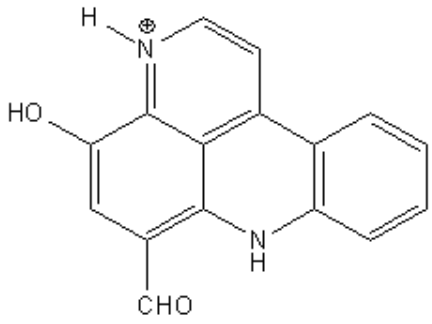


Figure 1: Molecular structure of Tetracyclic alkaloids

Figure 1 above displays the molecular structure of Tetracyclic alkaloids and Figure 2 represents the molecular graph of Tetra cyclic alkaloids as a chemical compound.
In this graph, total number of vertices is isomorphic to the graph G. We calculate the Wiener index of the graph in Figure 2 as

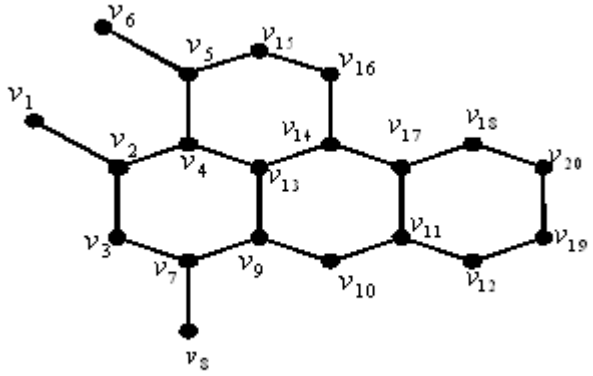


Figure 2: Molecular graph representing the chemical compound Tetracyclic alkaloids

The Wiener Index $W(G) = 701$.

The First Zagreb Index $\mathrm{M}_1(G) = \sum_{j=1}^{N} D_j^2 = 116$

The Second Zagreb Index $\mathrm{M}_2(G) = \sum_{ij \in E(\mathrm{G})} D_i D_j = 145$

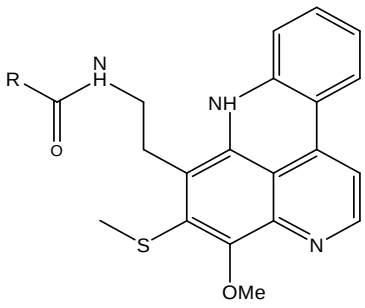
3. Model development

A data set comprising 60 compounds containing pyridoacridine alkaloids was used for the investigation of structure-activity relationship. From the above Table 1, The degeneracy of the compounds can be calculated by number of compounds having same value divided by total number of compounds with same number of vertices.

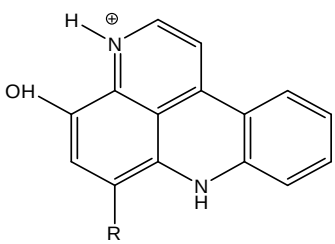
Table 1: Comparison of degeneracy of Wiener Index, First and second Zagreb indices for all possible structures with three and four vertices containing only one nitrogen as heteroatom

	W	M_1	M_2
For three vertices			
Minimum value	3	6	4
Maximum value	4	12	12
Ratio	1:1.333	2	3
Degeneracy	1/3	1/3	1/3
For four vertices			
Minimum value	6	10	8
Maximum value	10	36	54
Ratio	1:1.67	3.6	6.75
Degeneracy	6/11	6/11	6/11

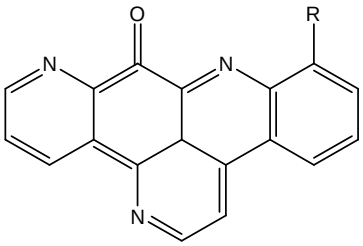
Table 2 Basic structures of pyridoacridine alkaloids



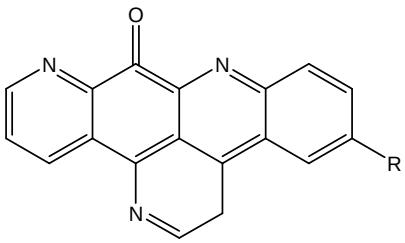
I (Compounds 1-9)



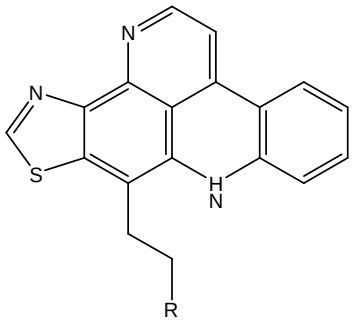
II (Compounds 10-18)



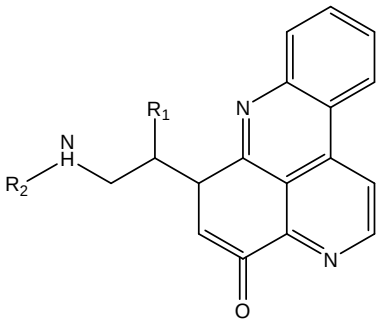
III (Compounds 19-23)



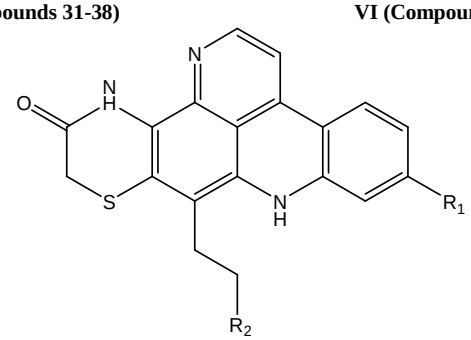
IV (Compounds 24-30)



V (Compounds 31-38)



VI (Compounds 39-50)



VII (Compounds 51-60)

The basic structure of the compounds has been presented in Table 2 and various substituent described in Table 3. The data set comprising of both active and inactive analogs. The values of Wiener Index, First and Second Zagreb indices were calculated and suitable model developed after identification of active range by maximization of moving average with respect to active analogs. Subsequently, each analog was assigned a biological activity using the proposed model, which was then compared with the reported anti-cancer activity.

RESULTS AND DISCUSSION

By using graph theoretic invariants as descriptors, we utilize a set of well-understood mathematical properties to describe more complex physico-chemical and biological behavior of molecules. Such an approach is different from the traditional QSAR methodology, where one employs selected simpler physico-chemical properties to predict biological activities of molecules.

Table 3 Relationship of anti-cancer activity of Marine Pyridoacridine alkaloids with Wiener Index (W), and First (M_1) and Second (M_2) Zagreb Indices

No	Compound Basic Structure	Functional group (R)	Index values			Anti-Cancer activity			
						Assigned			Reported
			W	M_1	M_2	W	M_1	M_2	
		R							
1	I	CH_2CH_3	1694	150	166	+	+	+	+
2	I	CH_2- CH_2. CH_2. CH_3	2397	154	170	-	+	+	-
3	I	Cyclopentane	2901	170	190	-	-	+	-
4	I	CH_3	1513	146	162	+	+	+	+
5	I	Nitrobenzene	3441	180	201	-	-	-	-
6	I	Methoxyphenyl	3441	180	201	-	-	-	-
7	I	Benzaldehyde	3387	180	201	-	-	-	-
8	I	H	1513	146	162	+	+	+	+
9	I	Cl	1513	146	162	+	+	+	+
10	II	CHO	701	116	145	+	+	+	+
11	II	$C_6H_5CH_3$	1253	148	182	+	+	+	+
12	II	H_3C-CH_2-CH_2-C_6 H_5	1589	156	190	+	+	+	-
		OH							
		l							
13	II	H_3C-CH-CH_2-NH_3	1382	134	165	+	+	+	+
14	II	NO_2	807	116	145	+	+	+	+
15	II	NMe_2	815	126	157	+	+	+	+
16	II	$H_2C(CH_3)$-CH_2-$CH(CH_3)$(PhOH)	2802	181	213	-	-	-	-
17	II	Butane	1236	128	158	+	+	+	+
18	II	OHC-CH_2-CH(COOH)(Ph(OCH_3)(OH))	2555	174	208	-	-	-	-
19	III	H	973	136	175	+	+	+	+
20	III	NO_2	973	136	175	+	+	+	+
21	III	NH_2	973	136	175	+	+	+	+
22	III	Benzaldehyde	2255	174	179	-	-	+	-
23	III	CH_2- CH_2. CH_2. CH_3	1448	148	145	+	+	+	-
24	IV	Br	987	136	172	+	+	+	+
25	IV	Cyclopentane	1594	155	202	+	+	-	-
26	IV	Nitrobenzene	2257	174	214	-	-	-	-
27	IV	Methoxyphenyl	2257	174	214	-	-	-	-
28	IV	Benzoic acid	2257	174	214	-	-	-	-
29	IV	NH_x	987	136	172	+	+	+	+
30	IV	NMe_2	987	136	172	+	+	+	+
31	V	NH_3	996	131	169	+	+	+	+
32	V	Nitrobenzene	2359	169	212	-	-	-	-
33	V	NHCOCH	1145	135	173	+	+	+	+
34	V	$NHCOCH_3$	1145	135	173	+	+	+	+
35	V	Methoxyphenyl	2359	169	212	-	-	-	-
36	V	Benzoic acid	2359	169	212	-	-	-	-
37	V	$NHCOCH_2CH_3$	1295	139	177	+	+	+	+
38	V	$NHCOCH_2CH(CH_3)_2$	1740	147	186	+	+	+	+
		R_1 R2							
39	VI	$NHCOCH_3$ ethyl	2328	136	165	-	+	+	-
40	VI	H $CH_3COC(CH_3)CH$ CH_3 $CH_3COCHC(CH_3)_2$	2218	156	191	+	+	-	+
41	VI	$NHCOCH_3$	3106	168	201	-	-	-	-
42	VI	Fluorophenyl H_2C-CH_2-CH_3	2871	174	211	-	-	-	-
43	VI	Methoxyphenyl HC=CH-CH=CH_3	2871	178	215	-	-	-	-
44	VI	Eyhoxyphenyl OCH_3	2382	170	219	-	-	-	-
45	VI	Nitrophenyl O_2H_5	2620	170	204	-	-	+	-
46	VI	OH $CH_3COCHC(CH_3)_2$	2218	156	187	+	+	-	+
47	VI	2,6 dimethyl phenyl NO_2	2485	171	214	-	-	-	-
48	VI	3-Bromo,6-methoxyphenyl COOH	2670	172	207	-	-	-	-
49	VI	2-pyridyl CHO	2379	160	195	-	-	+	-
50	VI	OMe $CH_3COC(CH_3)CH$ CH_3	2218	156	191	+	+	+	+
51	VII	Br NHCOMe	1370	150	190	+	+	+	+
52	VII	H NHCOMe	1370	150	190	+	+	+	+
53	VII	H NHCOCH	1514	154	194	+	+	-	+
54	VII	Fluorophenyl H_2C-CH_2-CH_3	3639	196	243	-	-	-	-
55	VII	Methoxyphenyl HC=CH-CH=CH_3	3951	200	249	-	-	-	-
56	VII	Eyhoxyphenyl OCH_3	3045	188	235	-	-	+	-
57	VII	H NMe_2	1370	150	190	+	+	-	+
58	VII	Nitrophenyl O_2H_5	3768	192	239	-	-	+	-
59	VII	H $N(O)NMe_2$	1370	150	190	+	+	-	+
60	VII	3-Bromo,6-methoxyphenyl COOH	3400	194	243	-	-		-

In the present study, the relationship of Wiener Index, First and Zagreb Indices with the anti-cancer activity of marine pyridoacridine alkaloids has been investigated.

Analysis of the data in Table 3 reveals the following information:

- With respect to the Wiener index, out of the total 60 compounds, 32 compounds are active and 28 compounds are inactive. The active range had Wiener index value of 700-2218. As many as 29 out of 32 compounds in the active range were active with regard to anti-cancer activity of reported value. The overall accuracy of prediction was found to be 90.625% with regard to the anti-cancer activity.
- With respect to the First Zagreb index, out of the total 60 compounds, 34 compounds are active and 26 compounds are inactive. The active range had First Zagreb index value between 116-156. As many as 29 out of 34 compounds in the active range were active with regard to anti-cancer activity. The overall accuracy of prediction was found to be 85% with regard to the anti-cancer activity.
- With respect of the Second Zagreb index, out of the total 60 compounds, 35 compounds are active and 25 compounds are inactive. The active range had First Zagreb index value between 156-194. As many as 29 out of 35 compounds in the active range were active with regard to anti-cancer activity. The overall accuracy of prediction was found to be 82% with regard to the anti-cancer activity.
- High predictability of the models derived from Wiener index as well as First and second Zagreb indices can provide valuable leads for development of Marine pyridoacridine alkaloids of anti-cancer agents. Moreover, high discriminating power amalgamated with low degeneracy of Wiener index offers a vast potential for its use in the structure activity/property studies.

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