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Models For Prediction of Anti-neoplastic Activity of 1,2-Bis(sulfonyl)-1-methylhydrazines: Computational Approach Using Wiener's Indices

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Abstract

Relationship between Wiener's indices and antineoplastic activity of 1,2-bis(sulfonyl)-1-methylhydrazines has been investigated. A dataset comprising of 61 1,2-bis(sulfonyl)-1-methylhydrazines having reported activity against L1210 leukemia and/or B16 melanoma was selected. Values of the Wiener's index and the Wiener's topochemical index of each analogue involved in the dataset were calculated using an in-house computer program. The resulting data was analyzed and suitable models were developed after identification of the active ranges. Subsequently, biological activity was assigned to each analogue involved in the dataset which was then compared with the reported activity against B16 melanoma. High accuracy of prediction was observed using these models.

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Mathematical-topological methods occupy an eminent place in the field of prediction of properties and activities of chemical compounds, and even materials [1]. Developing structure-activity relationships for drug compounds using computational or theoretical methods relies on appropriate representation of molecular structure [2]. Over the past decades graph-based molecular structure descriptors have developed into a quite active field. In these applications a molecular structure is identified to a graph, with vertices representing non-H atoms and edges representing chemical bonds [3]. Chemical graphs are the basic tool used in applying the techniques of mathematical graph theory to the specific problems of chemistry [4, 5, 6]. Graph theory is largely applied to the characterization of chemical structures, as well as to qualitative and quantitative structure-property (QSPR) and structure-activity (QSAR) relations by means of certain numerical characteristics, the so-called topological indices [7]. The first generation topological indices are the integers based on integer graph properties, such as topological distances [8]. The most representative indices of this class are Wiener's index, *W* [9], Hosoya index *Z* [10], Zagreb indices [11] and centric indices of Balaban *B* and *C* [12]. The only one that has been used in drug discovery research is the Wiener's index. The second generation topological indices are real numbers based on integer graph properties. Most of the topological indices used in drug discovery today are of this class, examples include Molecular connectivity indices [13, 14], Balaban *J* index [15], Charge indices [16], Kappa indices of molecular shape and flexibility [17, 18] and electrotopological state (E-state)indices [19, 20]. The third generation topological indices are real numbers based upon real-number local properties of the molecular graph. These indices have few applications in drug discovery research [2].

One of the limitations of the first generation topological indices is their degeneracy and inability to consider the presence and position of heteroatom in a molecule. In order to overcome this problem the theoretical chemists have attempted to modify these indices. One such modification introduced by this group is "Wiener's topochemical index" [21]. This index is the modification of the Wiener's index, has lower degeneracy and is sensitive to the presence as well as relative position of heteroatom. In the present study, the Wiener's topochemical index has been applied for the prediction of antineoplastic activity of 1, 2-bis(sulfonyl)-1-methylhydrazines. Alkylating agents are widely used for the treatment of cancer and work by damaging the cell's DNA, preventing replication of the tumor cells and causing their death. The chemotherapeutic alkylating agents have in common the property of becoming strong electrophiles through the formation of carbonium ion intermediates or of transition complexes with the target molecules. These reactions result in the formation of covalent linkages by alkylation of various nucleophilic moieties such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl and imidazole groups. The chemotherapeutic and cytotoxic effects are directly related to the alkylation of DNA [22]. In addition to the development of model, the ability of Wiener's topochemical index to differentiate between the presence and relative position of heteroatom was also investigated (Table 1).

Calculation of Topological Indices

Wiener's Index: Wiener's number or Wiener's 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 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. Wiener's index is defined as the sum of the distances between all the pairs of vertices in hydrogen suppressed molecular graph, that is

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

where P_{ij} is the length of the path that contains the least number of edges between vertex *i* and vertex *j* in the graph G; *n* is the maximum possible number of *i* and *j*[9, 23-25].

Wiener's topochemical index: It is defined as the sum of the chemical distances between all the pairs of vertices in a hydrogen supressed molecular graph, that is

$$W_c = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij}^{c}$$

where P^{c}_{ij} is the chemical length of the path that contains the least number of edges between vertex *i* and vertex *j* in the graph G; *n* is the maximum possible number of i and j. Wiener's topochemical index (W_c) can be easily calculated from the chemical distance matrix of a hydrogen suppressed molecular structure. When non-zero row elements of a distance matrix represent chemical-distance between the corresponding vertices in a molecular graph, the matrix may be termed as chemical distance matrix. This matrix is obtained by substituting, row elements corresponding to heteroatom, with relative atomic weight with respect to carbon atom. [21].

Model Design and Analysis

A dataset comprising of 61 1,2-bis(sulfonyl)-1-methylhydrazines (Figure 1) having reported activity against L1210 leukemia and/or B16 melanoma was selected [26]. In the dataset, the tumor-inhibitory properties of the compounds were determined by measuring their effect on the survival time of mice bearing either the L1210 leukemia or the B16 melanoma. The results were reported as max % T/C (%T/C = average survival time of treated / control animals x 100). While all of the 1,2-bis(sulfonyl)-1-methylhydrazines had significant activity against B16 melanoma and most were active against L1210 leukemia, a few compounds were inactive against L1210 leukemia. Hence, for model development, activity against only B16 melanoma was considered. For each of the compounds present in the dataset, the values of Wiener's index and Wiener's topochemical index were calculated using an in-house computer program. The resultant data was analyzed and suitable models were developed after identification of the active ranges based on maximization of moving average with respect to active compounds (<35% = inactive, 35-65% = transitional, 65% = active) [27-30]. Subsequently, each compound in the dataset was assigned a biological activity using each of these models, which was then compared with the reported activity against B16 melanoma. The compounds reportedly having % T/C equal to or greater than 200 were considered as

active and those having less than 200 were considered to be potentially inactive for the purpose of this study. The percent degree of prediction was calculated from the ratio of number of compounds with correctly predicted activity to that of total number of compounds present in the respective active of inactive ranges of the proposed models. The overall degree of prediction was obtained from the ratio of total number of compounds with correctly predicted activity to that of total number of compounds in the active and inactive ranges.

Results

The ability of Wiener's topochemical index to assign different numerical values to chemical structures taking into consideration the presence and relative position of heteroatom was investigated and compared with the respective values of Wiener's index (Table 1). Whereas there are just three Wiener's index values for all the structures studied, the Wiener's topochemical index values are mostly variable except for structures 4 and 7.

Table1: Values of Wiener's topochemical index and Wiener's index for five member acyclic structures containing different heteroatom.

No.	Structure	W_c values with different hetroatoms at R							W
		N	O	S	F	Cl	Br	I	
		20.334	20.666	23.334	21.166	23.916	31.334	39.166	20
		20.501	21.665	28.335	-	-	-	-	20
		21.002	21.998	30.002	-	-	-	-	20
		18.334	18.666	21.334	19.166	21.916	29.334	37.166	18
		19.169	-	29.669	-	-	-	-	18
		18.335	19.665	26.335	-	-	-	-	18
		18.334	18.666	21.334	19.166	21.916	29.334	37.166	18
		16.334	16.666	19.334	17.166	19.916	27.334	35.166	16
		-	-	29.336	-	-	-	-	16

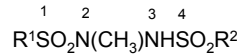

Figure1: Basic structure of 1,2-bis(sulfonyl)-1-methylhydrazines

Retrofit analysis of the data in Table 2 and 3 reveal the following information with regard to the model based upon the Wiener's index

- Out of the total 61 compounds, 86.88% were predicted correctly with respect to antineoplastic activity against B16 melanoma.
- The active range had Wiener's index values 540 or less. 7 out of 9 (77.8%) compounds in the active range were predicted correctly. The %T/C of the correctly predicted compounds was 231.85.
- The inactive range had Wiener's index values greater than 540. 46 out of 52 compounds (88.5%) in the inactive range were predicted correctly. The average % T/C of the correctly predicted compounds was176.30.
- For the estimation of %T/C, the following model was developed

$$\%T/C^{Cal} = 58.282 \times LN(W) + 572.78$$

Retrofit analysis of the data in Table 2 and 3 reveal the following information with regard to the model based upon the Wiener's topochemical index

- Out of the total 61 compounds, 88.52% were predicted correctly with respect to antineoplastic activity against B16 melanoma.
- The active range had Wiener's topochemical index values 923.412 or less. 9 out of 12 (75%) compounds in the active range were predicted correctly. The %T/C of the correctly predicted compounds was 228.89.
- The inactive range had Wiener's topochemical index values greater than 923.412. 45 out of 49 compounds (91.8%) in the inactive range were predicted correctly. The average % T/C of the correctly predicted compounds was 168.51.
- For the estimation of %T/C, the following model was developed

$$\%T/C^{Cal} = 67.007 \times LN(W_c) + 658$$

Table 2: Relationship between Wiener's indices and antineoplastic activity of 1,2-bis(sulfonyl)-1-methylhydrazines.

Comp. No.	Substituents		W	W_c	Antineoplastic activity			
					Assigned			Reported
	R^1	R^2			W	W_c		%TC
1	phenyl	phenyl	930	1378.142	-	-	-	175
2	phenyl	4-tolyl	1072	1562.823	-	-	-	178
3	phenyl	4-chlorophenyl	1072	1583.382	-	-	-	148
4	phenyl	4-bromophenyl	1072	1622.326	-	-	-	187
5	phenyl	4-methoxyphenyl	1236	1780.160	-	-	-	191
6	phenyl	2-naphthyl	1520	2138.866	-	-	-	181
7	phenyl	benzyl	1102	1592.823	-	-	-	186
8	4-tolyl	phenyl	1071	1561.656	-	-	-	168
9	4-tolyl	4-tolyl	1226	1763.005	-	-	-	165
10	4-tolyl	4-methoxyphenyl	1404	1998.509	-	-	+	200
11	4-tolyl	4-chlorophenyl	1226	1784.543	-	-	-	171
12	4-tolyl	4-bromophenyl	1226	1825.343	-	-	-	161
13	4-tolyl	4-nitrophenyl	1584	2231.215	-	-	-	192
14	4-tolyl	benzyl	1258	1795.005	-	-	-	172
15	4-tolyl	methyl	520	778.911	+	+	+	207
16	4-tolyl	ethyl	613	918.260	-	+	-	174
17	4-methoxyphenyl	phenyl	1234	1777.826	-	-	-	151
18	4-methoxyphenyl	4-tolyl	1403	1997.343	-	-	-	151
19	4-methoxyphenyl	4-methoxyphenyl	1596	2252.514	-	-	-	191
20	4-methoxyphenyl	4-bromophenyl	1403	2062.513	-	-	+	205
21	4-methoxyphenyl	2-nitrophenyl	1791	2504.637	-	-	-	158
22	4-methoxyphenyl	2-naphthyl	1932	2677.893	-	-	-	163
23	4-methoxyphenyl	benzyl	1437	2031.343	-	-	-	160
24	4-methoxyphenyl	methyl	624	915.343	-	+	+	204
25	4-chlorophenyl	phenyl	1071	1582.215	-	-	-	146
26	4-chlorophenyl	4-tolyl	1226	1773.521	-	-	-	162
27	4-chlorophenyl	4-methoxyphenyl	1404	2021.026	-	-	-	189
28	4-chlorophenyl	4-chlorophenyl	1226	1806.081	-	-	-	163

29	4-chlorophenyl	2-naphthyl	1713	2413.528	-	-	-	153
30	4-chlorophenyl	methyl	520	781.239	+	+	-	194
31	4-chlorophenyl	ethyl	613	934.903	-	-	-	164
32	4-chlorophenyl	styryl	1468	2073.872	-	-	-	143
33	2-naphthyl	phenyl	1516	2134.198	-	-	-	163
34	2-naphthyl	2-naphthyl	2314	3161.610	-	-	-	164
35	2-naphthyl	methyl	803	1134.433	-	-	-	193
36	4-bromophenyl	phenyl	1071	1621.160	-	-	-	160
37	4-bromophenyl	4-methoxyphenyl	1404	2063.680	-	-	-	167
38	4-bromophenyl	4-chlorophenyl	1226	1846.880	-	-	-	145
39	4-bromophenyl	4-bromophenyl	1226	1887.679	-	-	-	160
40	4-bromophenyl	2-naphthyl	1713	2459.890	-	-	-	146
41	4-bromophenyl	methyl	520	824.247	-	+	+	225
42	4-bromophenyl	ethyl	613	966.430	-	-	-	190
43	4-bromophenyl	styryl	1468	2116.525	-	-	-	178
44	4-acetamidoophenyl	4-bromophenyl	1807	2570.661	-	-	-	164
45	4-iodophenyl	4-tolyl	1226	1868.418	-	-	-	176
46	4-iodophenyl	methyl	520	855.575	+	+	-	195
47	4-iodophenyl	ethyl	613	999.716	-	-	-	177
48	benzyl	phenyl	1101	1591.656	-	-	+	208
49	benzyl	4-tolyl	1258	1795.005	-	-	+	206
50	benzyl	4-methoxyphenyl	1438	2032.509	-	-	-	182
51	benzyl	4-chlorophenyl	1258	1816.543	-	-	-	184
52	benzyl	4-bromophenyl	1258	1857.343	-	-	-	163
53	benzyl	2-naphthyl	1751	2427.052	-	-	-	179
54	benzyl	methyl	540	798.511	+	+	+	203
55	benzyl	benzyl	1290	1827.005	-	-	-	152
56	styryl	styryl	1732	2365.204	-	-	-	171
57	methyl	4-tolyl	526	785.913	+	+	+	256
58	methyl	4-methoxyphenyl	631	923.412	-	+	+	233
59	methyl	4-chlorophenyl	526	801.577	+	+	+	219
60	methyl	4-bromophenyl	526	831.249	+	+	+	235
61	methyl	methyl	156	269.867	+	+	+	278

+ active compounds (compounds having %T/C ≥ 200), - inactive compounds

Table 3: Models for prediction of antineoplastic activity of 1,2-bis(sulfonyl)-1-methylhydrazines.

Model Index	Nature of Range in Proposed Model	Index Value	Number of Compounds falling in the range		Percent Accuracy	Average %T/C		Accuracy of Prediction	Average %T/C	
			Total	Correct		Total	Correct		Total	Correct
W	Active	≤ 540	9	7	77.8	223.56	231.85	86.88	223.56	231.85
	Inactive	> 540	52	46	88.5	173.33	176.30		173.33	176.30
W_c	Active	≤ 923.412	12	9	75.0	228.89	218.58	88.52	218.58	228.89
	Inactive	> 923.412	49	45	91.8	171.47	168.51		171.47	168.51

Discussion and Conclusions

Alkylating agents are important components of several standard treatment regimens for cancer. The individual properties of an alkylating agent determine its pattern of activity and toxicity and therefore its clinical application. Most of the cytotoxic anticancer alkylating agents are bifunctional, i.e. they have two alkylating groups. The 7 nitrogen (N7) of guanine, being strongly nucleophilic, is probably the main molecular target for alkylation of DNA, although N1 and N3 of adenine and N3 of cytosine may also be affected. A bifunctional agent, being able to react with two groups, can cause intra- or interchain cross linking. This can interfere not only with transcription but with replication, which is probably the critical effect of anticancer alkylating agents [31]. This series of compounds appear to be bifunctional agents with *N*-methyl (position 1, Figure 1) group acting as one alkylating group and the second one being either of the substituents R^1 or R^2 (Figure 1). Although all the 1,2-bis(sulfonyl)-1-methylhydrazines reported in this dataset are active against B16 melanoma, but for the purpose for this study the compounds having %T/C of 200 or more were considered as active. Analysis of structures of the compounds in the active ranges reveal that all the active compounds have at one methyl group as substituent R^1 or R^2 (position 1 or 4 in Figure 1). This methyl group is probably the second alkylating group, which makes these compounds bifunctional alkylating agents. This also makes the terminal portion of these compounds similar to busulphan, a drug used in chronic granulocytic leukemia. Another series of sulfonylhydrazines, having structures similar to this class of compounds, has demonstrated broad antitumor activity against a variety of experimental tumor models including some with resistance to conventional chemotherapeutic agents. The lead compound in this class is VNP40101M, reported as 101M in literature, which demonstrated broad antitumor activity against leukemia, melanoma, lung and colon carcinomas in animal models, as well as activity against tumor cells resistant to the standard alkylating agents cyclophosphamide, BCNU and melphalan [32]. These compounds have also been reported to have better safety margin than nitrosoureas [33]. Therefore the series of compounds used in the present study have the potential to be developed further.

The critical step in drug discovery remains the identification and optimization of lead compounds in a rapid and cost effective way. Computational techniques have advanced rapidly over the past decade and accordingly have played a major role in the development of a number of drugs now on the market or going through clinical trials [2]. Amongst the computational tools useful in drug discovery, topological indices have a special status. Topological indices are fundamental in nature and easily computable using simple mathematical tools owing to their conceptual simplicity [34]. One of descriptors used in this study is Wiener's index, is the index that pioneered this concept and which is the most widely used and referred index. The second descriptor, Wiener's topochemical index, is the modification of the Wiener's index and has been recently introduced. Like Wiener's index, Wiener's topochemical index also has application in the field of prediction of properties and activities of chemical compounds. In addition this index has been reported to have less degeneracy and is sensitive to the presence and relative position of heteroatom. The sensitivity of this index towards the presence and relative position of heteroatom was

investigated by calculating and later analyzing the index values of five member acyclic structures containing either of the N, O, S, F, Cl, Br and I as heteroatom at all possible positions. The results show that Wiener's topochemical index successfully discriminates between the presence and by and large the relative position of a heteroatom in the molecule.

In the present study these two indices have been used for the development of model for prediction of antineoplastic activity against B16 melanoma for 1,2-bis(sulfonyl)-1-methylhydrazines. The developed models comprise of only two ranges an active and an inactive range and have 100% classification with all the compounds having been classified into either active or inactive ranges. Both the models have shown good accuracy of prediction. Since the dataset comprised of 61 compounds only, it was not divided into training and test sets for validation of predictive ability of the models. Although there has been a marginal difference in accuracy of prediction between the two models but sill the model based upon the Wiener's topochemical index may be considered better because of relatively wider active range containing 12 compounds when compared to 9 in case of model based upon the Wiener's index. These models can be exploited for further development of this series of antineoplastic agents and may be helpful in predicting the activity of compounds before having been synthesized.

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