Superpendentic Index: A Novel Topological Descriptor for Predicting Biological Activity

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A simple highly degenerating, pendenticity based, topological descriptor termed as *superpendentic index* has been conceptualized and its discriminating power investigated with regard to antiulcer activity. A data set consisting of 128 analogues of 4-substituted-2-guanidino thiazoles was selected for the present study. These analogues are reversible, competitive, and selective inhibitors of gastric H^+,K^+-ATPase enzyme. The value of *superpendentic index* of each analogue in the data set was computed and active range was identified. The biological activity assigned to each analogue using *superpendentic index* was subsequently compared with the reported in vitro and in vivo inhibitory activities. The accuracy of classification of analogues based on in vivo activity was found to be 82% in the active range using superpendentic index.

INTRODUCTION

Genesis of structure−activity relationship (SAR) studies dates back to the finding that structure of a molecule plays an important role in determining its biological activity. Today SAR is a tool to develop safer and potent drugs. The emphasis is on minimum expenditure, conservation of time, and a growing concern against sacrifice of animals.[1] SARs are models that relate structural aspects of a molecule to its physicochemical or biological properties.

The inherent problem in SAR is that it is difficult to quantify chemical structures. Molecular topology when applied to SAR essentially involves translation of chemical structures into characteristic numerical descriptors.[2−7] These descriptors known as topological indices are derived from information based on connectivity of a molecule. Although over 120 topological indices are reported, only a handful of them have been widely employed—Randić's molecular connectivity index,[8,9] Hosaya's index,[10,11] Balaban's index,[12−15] Wiener index, and its modifications.[16,17] Topological indices developed for predicting physicochemical properties and biological activities, of chemical substances, can be used for drug design.[18−24]

In the present study, a pendenticity based, new topological descriptor termed as *superpendentic index* has been proposed. *Superpendentic index* is computed from *pendent matrix*. Pendent matrix, D_p, of a graph G is a submatrix of distance matrix obtained by retaining the columns corresponding to pendent vertexes. *Superpendentic index*, denoted by $\int^p$, of a hydrogen suppressed molecular graph can be defined as the square root of the sum of products of nonzero row elements in the pendent matrix

$$\int^p = \{\sum_{i=1,j=1}^{n}\sum^{n} P_{(i,j)}\}^{0.5}$$

where $P_{(i,j)}$ is length of the path that contains the least number of edges between vertex i and vertex j in graph G; m and n are maximum possible numbers of i and j, respectively. Calculation of *superpendentic index* for three isomers of pentane is shown in Figure 1.

The Wiener index of a hydrogen suppressed molecular graph is defined as the sum of the elements in a distance matrix

$$W = {}^1/_2\{\sum_{i=1,j=1}^{n} P_{(ij)}\}$$

where $P_{(i,j)}$ is length of the path that contains the least number of edges between vertex i and vertex j in graph G; n is the maximum possible number of i and j.

In the present study the utility of a novel topological descriptor, *superpendentic index*, has been investigated with regard to antiulcer activity of 4-substituted-2-guanidino thiazoles, and the results have been compared with the distance based Wiener's index. Ulcers are believed to result from an imbalance between offensive factors (acid, bile reflux, and antiinflammatory drugs) and defensive factors (bicarbonate, carbonic anhydrase inhibitors, and mucus) in gastroduodenal mucosa.[25] The potential strategies[26] for treating peptic ulcers are

- shielding the mucosa using cytoprotective agents e.g., sucralfate;
- neutralization of gastric acid using antacids i.e., magnesium and aluminum hydroxides;
- suppression of gastric acid secretion using H_2-receptor antagonists e.g., ranitidine, famotidine, roxatidine, or H^+K^+-ATPase inhibitors such as omeprazole.

Gastric acid secretion is suppressed by blocking histamine (H_2) receptors. Histamine is one of the three key messengers that stimulate acid secretion (other two being acetylcholine and gastrin). Acid secretion is also suppressed by inhibition of the enzyme, H^+K^+-ATPase, that catalyzes the terminal

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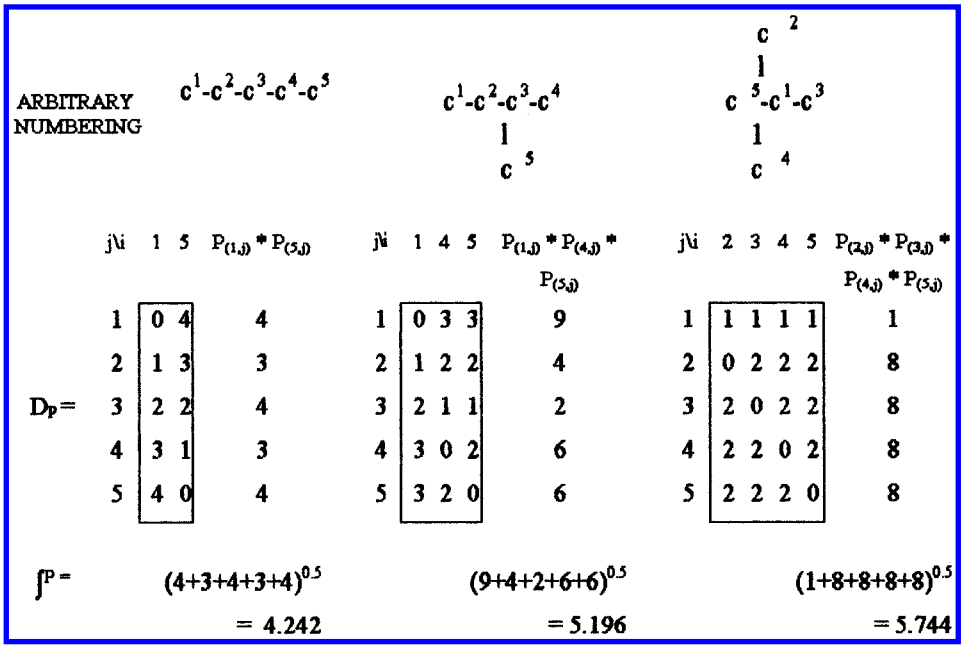

Figure 1. Calculation of superpendentic index values for three isomers of pentane.

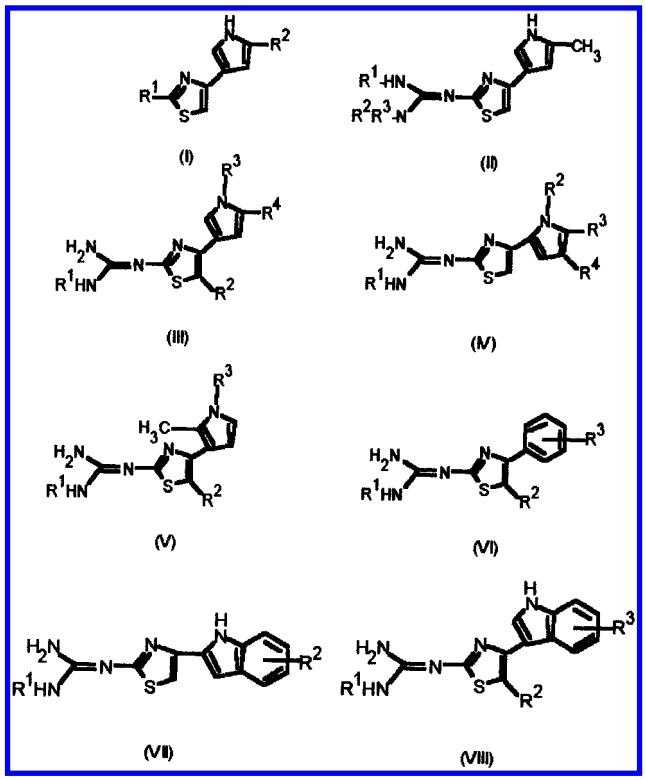

Figure 2. Basic structures of 4-substituted-2-guanidino thiazoles.

step in gastric acid secretion. H_2-receptors are present through out the body, whereas H^+K^+-ATPase is located predominantly in parietal cells of the stomach. Thus, H^+K^+-ATPase inhibitors (omeprazole) exhibit site specific action but their prolonged duration of action can lead to serious side effects as a result of elevation in plasma gastrin levels (gastric carcinoids).[27] In such circumstances reversible inhibitors (4-substituted-2-guanidino thiazoles) of H^+K^+-ATPase are useful. The present study has been carried out using a data set consisting of 128 analogues of 4-substituted-2- guanidino thiazoles.[28]

METHODOLOGY

All 128 4-substituted-2-guanidino thiazoles reported by LaMattina et al. were selected as a data set for testing the utility of superpendentic index. This data set comprised of both active and inactive compounds. The basic structures of 4-substitited-2-guanidino thiazoles have been depicted in Figure 2.

The values of superpendentic index were computed for each analogue using hydrogen suppressed structure. The index values were arranged according to ascending order, and the resulting data were analyzed to identify active range. Subsequently, each analogue was assigned a biological activity which was then compared with the reported[28] in vitro antiulcer activities of 128 compounds and in vivo antiulcer activities of 85 compounds. In vitro activity was quantitatively reported as percent inhibition of gastric H^+K^+-ATPase enzyme at 50 μmol. Compounds exhibiting more than or equal to 89% inhibition of enzyme were considered to be active. In vivo activity was reported as IC_{50} (concentration in μmol causing 50% inhibition of canine gastric H^+K^+-ATPase). Compounds possessing IC_{50} less than or equal to 5 μmol were considered to be active. The percent degree of classification for each range was computed from the ratio of number of compounds with correctly classified activity to that of the number of compounds present in the range. The overall degree of classification was obtained from the ratio of total number of compounds with correctly predicted activity to that of total number of compounds present in both the active and inactive ranges.

The values of Wiener's index were computed for each analogue using hydrogen suppressed structure, and the aforementioned procedure was used to assign antiulcer activities. The results are summarized in Tables 1−3.

RESULTS AND DISCUSSION

The use of topological descriptors in predicting the physicochemical properties and biological properties is well

Table 1. Relationship of Superpendentic Index and Wiener's Index with Antiulcer Activity of 4-Substituted-2-guanidino Thiazoles

compd no.	basic structure	R^1	R^2	R^3	R^4	W	J^p	antiulcer activity: assigned W	antiulcer activity: assigned J^p	antiulcer activity: reported in vitro	antiulcer activity: reported in vivo[b]
1	I	$(H_2N)_2C{=}N$	Me			392	33.955	−	−	−	−
2	I	Me	Me			196	11.135	−	−	−	NA
3	I	NH_2	Me			196	11.135	−	−	−	NA
4	I	$(H_2N)_2C{=}N$	CHO			477	40.187	−	−	−	−
5	I	Me	CHO			252	13.038	−	−	−	NA
6	I	NH_2	CHO			252	13.038	−	−	−	NA
7	II	H	$PhCH_2$	H		1261	26.267	−	−	+	−
8	II	H	*p*-$ClPhCH_2$	H		1442	61.668	−	−	+	−
9	II	H	*n*-hexyl	H		1168	58.881	−	−	+	−
10	II	H	*n*-hexyl	Me		1281	141.711	−	−	−	NA
11	II	Me	*n*-hexyl	H		1293	65.795	−	−	−	NA
12	II	H	$-(CH_2)_5-$			900	21.213	−	−	−	NA
13	II	$-(CH_2)_2-$		H		563	9.486	−	−	−	NA
14	II	$-(CH_2)_2-$		Me		654	19.078	−	−	−	NA
15	II	$-(CH_2)_3-$		$PhCH_2$		1644	13.638	+	−	−	NA
16	III	H	H	H	H	322	19.026	−	−	−	NA
17	III	H	H	H	CH_2NMe_2	681	104.086	−	−	+	−
18	III	H	H	H	$CO(NC_5H_{10})$	1170	67.364	−	−	−	−
19	III	H	H	H	$CH_2(NC_5H_{10})$	1064	35.242	−	−	−	NA
20	III	H	H	Me	Me	465	67.549	−	−	−	−
21	III	H	H	Me	CHO	554	78.204	−	−	−	NA
22	III	H	H	$PhSO_2$	Me	1392	319.106	−	−	+	+
23	III	$PhCH_2$	H	$PhSO_2$	Me	3145	313.354	−[a]	−	−	NA
24	III	H	Me	H	Me	451	65.215	−	−	+	+
25	III	Ph	Me	H	Me	1180	60.522	−	−	−	−
26	III	$PhCH_2$	Me	H	Me	1384	71.895	−	−	−	−
27	III	4-$MePhCH_2$	Me	H	Me	1577	144.274	+	−	+	+
28	III	$PhCH_2CH_2$	Me	H	Me	1611	84.539	+	−	−	−
29	III	H	Me	H	CHO	543	79.724	−	−	−	−
30	IV	H	H	H	H	322	19.026	−	−	−	−
31	IV	$PhCH_2$	H	H	H	1106	9.899	−	−	−	−
32	IV	H	H	Me	H	392	33.955	−	−	−	−
33	IV	$PhCH_2$	H	Me	H	1261	26.267	−	−	−	−
34	IV	H	H	Me	CO_2Et	882	224.541	−	−	+	−
35	IV	H	H	Me	$CONMe_2$	865	517.820	−	−	−	NA
36	IV	H	H	Me	CH_2NMe_2	768	214.858	−	−	−	−
37	IV	H	Me	Me	H	456	63.906	−	−	−	NA
38	IV	H	$PhSO_2$	Me	H	1311	289.815	−	−	+	−
39	IV	$PhCH_2$	$PhSO_2$	Me	H	3001	289.772	−[a]	−	−	−
40	V	H	H	H		383	32.848	−	−	+	−
41	V	$PhCH_2$	H	H		1245	25.079	−	−	+	−
42	V	H	H	$PhSO_2$		1383	313.004	−	−	+	+
43	V	$PhCH_2$	H	$PhSO_2$		3129	300.586	−[a]	−	−	NA
44	V	H	Me	H		441	64.498	−	−	+	+
45	V	$PhCH_2$	Me	H		1367	69.397	−	−	−	−
46	V	H	Me	$PhSO_2$		1512	867.308	+	−	+	+
47	V	$PhCH_2$	Me	$PhSO_2$		3322	911.528	−[a]	−	−	NA
48	VI	H	H	H		393	21.047	−	−	−	−
49	VI	$PhCH_2$	H	H		1262	10.344	−	−	−	NA
50	VI	H	H	2-Cl		458	37.229	−	−	−	−
51	VI	H	H	3-Cl		467	37.788	−	−	−	−
52	VI	H	H	4-Cl		476	38.755	−	−	−	NA
53	VI	H	H	4-F		476	38.755	−	−	−	−
54	VI	$PhCH_2$	H	2-Cl		1405	25.768	−	−	+	−
55	VI	$PhCH_2$	H	3-Cl		1421	26.888	−	−	−	NA
56	VI	$PhCH_2$	H	4-Cl		1437	28.000	−	−	−	NA
57	VI	$PhCH_2$	H	4-F		1437	28.000	−	−	−	NA
58	VI	H	H	2-Me		458	37.229	−	−	−	−
59	VI	H	H	2-CH_2NMe_2		737	111.332	−	−	−	NA
60	VI	H	H	3-Me		467	37.788	−	−	−	−
61	VI	H	H	3-CH_2NMe_2		773	115.086	−	−	−	−
62	VI	H	H	4-Me		476	38.755	−	−	−	NA
63	VI	H	H	4-Ph		1053	35.242	−	−	−	NA
64	VI	$PhCH_2$	H	2-Me		1405	25.768	−	−	+	−
65	VI	$PhCH_2$	H	3-Me		1421	26.888	−	−	−	NA
66	VI	$PhCH_2$	H	4-Me		1437	28.000	−	−	−	NA
67	VI	$PhCH_2$	H	4-Ph		2537	13.304	−[a]	−	−	NA
68	VI	H	H	3-NH_2		467	37.788	−	−	−	NA
69	VI	H	H	3-NMe_2		649	93.781	−	−	−	NA

Table 1 Continued

compd no.	basic structure	R^1	R^2	R^3	R^4	W	J^p	antiulcer activity: assigned W	antiulcer activity: assigned J^p	antiulcer activity: reported in vitro	antiulcer activity: reported in vivo[b]
70	VI	H	H	4-NH_2		476	38.755	−	−	−	−
71	VI	H	H	4-NMe_2		676	99.724	−	−	−	−
72	VI	$PhCH_2$	H	4-NH_2		1437	28.000	−	−	−	−
73	VI	H	H	2-OMe		539	43.703	−	−	−	−
74	VI	H	H	3-OMe		557	44.395	−	−	−	−
75	VI	H	H	4-OMe		575	45.453	−	−	−	−
76	VI	$PhCH_2$	H	2-OMe		1571	27.946	+	−	+	+
77	VI	$PhCH_2$	H	3-OMe		1603	29.000	+	+	−	−
78	VI	*n*-pentyl	H	3-OMe		1282	65.810	−	−	−	NA
79	VI	$PhCH_2$	H	4-OMe		1635	30.049	+	+	−	NA
80	VI	H	H	3,4-$(OMe)_2$		755	102.200	−	−	−	NA
81	VI	$PhCH_2$	H	3,4-$(OMe)_2$		1992	96.161	−[a]	−	−	NA
82	VI	H	H	2-OH		458	37.229	−	−	−	NA
83	VI	H	H	3-OH		467	37.788	−	−	−	−
84	VI	H	H	4-OH		476	38.755	−	−	−	−
85	VI	$PhCH_2$	H	2-OH		1405	25.768	−	−	−	−
86	VI	$PhCH_2$	H	3-OH		1421	26.888	−	−	−	NA
87	VI	$PhCH_2$	H	4-OH		1437	28.000	−	−	−	NA
88	VI	H	H	3,4-$(OH)_2$		553	77.246	−	−	+	+
89	VI	$PhCH_2$	H	3,4-$(OH)_2$		1599	86.758	+	−	+	+
90	VI	H	Me	3,4-$(OH)_2$		625	150.033	−	−	+	+
91	VI	$PhCH_2$	Me	3,4-$(OH)_2$		1735	253.392	+	−	+	+
92	VII	H	H			640	26.907	−	−	−	−
93	VII	$PhCH_2$	H			1178	11.661	−	−	−	−
94	VII	$PhCH_2$	5-Cl			1983	31.064	−[a]	+	+	−
95	VII	H	5-F			746	51.205	−	−	−	+
96	VII	$PhCH_2$	5-F			1983	31.064	−[a]	+	−	NA
97	VIII	H	H	H		622	26.229	−	−	+	−
98	VIII	$PhCH_2$	H	H		1745	11.575	+	−	+	+
99	VIII	H	Me	H		699	58.266	−	−	+	−
100	VIII	$PhCH_2$	Me	H		1887	28.160	+	+	−	NA
101	VIII	H	H	5-OMe		835	57.445	−	−	−	−
102	VIII	$PhCH_2$	H	5-OMe		2150	32.357	−[a]	+	+	+
103	VIII	H	H	5-OCH_2Ph		1858	44.810	+	−	−	+
104	VIII	$PhCH_2$	H	5-OCH_2Ph		3872	15.362	−[a]	−	+	+
105	VIII	H	H	2-Me		701	50.635	−	−	−	−
106	VIII	$PhCH_2$	H	2-Me		1903	28.142	+	+	+	+
107	VIII	H	Me	2-Me,5-Cl		893	208.374	−	−	+	+
108	VIII	$PhCH_2$	Me	2-Me,5-Cl		2251	247.951	−[a]	−	+	+
109	VIII	$PhCH_2$	H	4-Me		1916	28.653	+	+	+	+
110	VIII	H	H	5-Me		719	49.909	−	−	−	+
111	VIII	$PhCH_2$	H	5-Me		1935	30.016	+	+	+	+
112	VIII	H	H	6-Me		728	50.328	−	−	−	NA
113	VIII	$PhCH_2$	H	6-Me		1951	30.983	+	+	+	+
114	VIII	H	H	7-Me		716	48.104	−	−	−	−
115	VIII	$PhCH_2$	H	7-Me		1932	29.631	+	+	+	+
116	VIII	H	H	5-Cl		719	49.909	−	−	+	+
117	VIII	$PhCH_2$	H	5-Cl		1935	30.016	+	+	+	+
118	VIII	H	Me	5-Cl		803	106.442	−	−	+	+
119	VIII	$PhCH_2$	Me	5-Cl		2083	79.899	−[a]	−	+	+
120	VIII	H	H	5-Br		719	49.909	−	−	+	+
121	VIII	$PhCH_2$	H	5-Br		1935	30.016	+	+	+	+
122	VIII	H	H	5-F		719	49.909	−	−	+	−
123	VIII	$PhCH_2$	H	5-F		1935	30.016	+	+	+	+
124	VIII	H	H	5-CO_2Me		1092	142.059	−	−	−	−
125	VIII	$PhCH_2$	H	5-CO_2Me		2612	108.328	−[a]	−	+	+
126	VIII	H	H	5-CN		835	57.445	−	−	−	NA
127	VIII	$PhCH_2$	H	5-CN		2152	32.357	−[a]	+	−	NA
128	VIII	$PhCH_2$	H	5-NHAc		2934	124.257	−[a]	−	−	

[a] Active in vivo. [b] NA = not available.

established. A novel pendenticity based index termed as *superpendentic index* has been conceptualized in the present investigation. This index can be easily calculated from *pendent matrix*, a submatrix of distance matrix. Superpendentic index takes into consideration all pendent vertexes. The index value changes significantly with a small change in the branching of a molecule. The disproportionate increase in the index value with minor change in the structure of a molecule had to be rationalized by taking square root of the summation. Superpendentic index is based on the simple fact that a necessary condition for drug-receptor interaction is proper fit like lock and key.

Table 2. Relative Distribution of Compounds with Respect to in Vitro Antiulcer Activity

	value		total no. of compds		correctly classified compds		accuracy (%)	
range	W	J^p	W	J^p	W	J^p	W	J^p
lower inactive	≤1450	≤28.0	93	34	70	26	75.27	76.47
active	1450−1975	28.1−32.5	20	15	14	10	70.00	66.67
upper inactive	≥1975	≥32.5	15	79	9	54	60.00	68.35

Table 3. Relative Distribution of Compounds with Respect to in Vivo Antiulcer Activity

	value		total no. of compds		correctly classified compds		accuracy (%)	
range	W	J^p	W	J^p	W	J^p	W	J^p
lower inactive	≤1450	≤28.0	60	16	48	13	80.00	81.25
active	≥1450	28.1−32.5	25	11	20	9	80.00	81.81
upper inactive		≥32.5		58		38		65.51

The utility of superpendentic with regard to antiulcer activity is reported in a data set consisting of 128 analogues of 4-substituted-2-guanidino thiazoles. These analogues are reversible, competitive, and selective inhibitors of gastric H^+,K^+-ATPase enzyme. Both active and inactive compounds were included in the set by random selection. Superpendentic index value was computed for each analogue. The active analogues were found to be present in the narrow range of index values, thus, facilitating rapid identification of the active range.

Using superpendentic index the active range was the same for both in vitro and in vivo activity, but the correlation of the index was relatively better with in vivo activity. The study revealed the following information

•The percentage accuracy of lower inactive, active, and upper inactive ranges of in vivo activity was either comparable or better than the corresponding individual ranges of in vitro activity.

•A total of 60 out of 85 compounds were classified correctly in both active and inactive ranges.

•An active range was observed having the superpendentic index value of 28.1−32.5. As many as 82% of compounds exhibited antiulcer activity. Surprisingly, the active range was narrow irrespective of numerous basic structures.

The accuracy of classification for active and inactive ranges are compiled in Tables 2 and 3. Similarly, the study using Wiener's index revealed following information

•Upper inactive range was not observed for in vivo activity. Ideally, an active range should be bracketed by inactive ranges i.e., lower inactive range and upper inactive range.

•A total of 66 out of 85 compounds were classified correctly in both active and inactive ranges.

•An active range with index value of more than 1450 was observed. The accuracy of classification in the active range was 80%.

The possibility of a compound proved inactive in vitro to be active in vivo is remote; therefore, only those compounds were considered which exhibited antiulcer activity in vitro. Using a superpendentic index the percentage accuracy of classification with respect to in vivo activity in the active range was found to be better than that using Wiener's index. The superpendentic index has proved the degenerating power with regard to antiulcer activity in a data set consisting of relatively large number of analogues. The simplicity in calculation of this index can also be exploited in other QSPR/QSAR studies. Such studies can ultimately provide valuable leads for the development of potent therapeutic agents.

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