Structure-Activity Study on Antiulcer Agents Using Wiener's Topological Index and Molecular Connectivity Index

Anshu Goel and A. K. Madan*

College of Pharmacy, Pushp Vihar, New Delhi-110 017, India

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The relationship of Wiener's topological index and molecular connectivity index with antiulcer activity of a series of 4-substituted-2-guanidino thiazole analogs has been investigated. The values of Wiener's topological index and molecular connectivity index of 128 compounds were computed and active ranges were identified. The activity assigned to each analog using these topological descriptors was subsequently compared with the reported *in vitro* and *in vivo* activities against gastric hydrogen-potassium stimulated adenosine triphosphatase (H^+K^+-ATPase) enzyme. Predictions with an accuracy of the order of ~89% were observed with regard to *in vivo* activity using these topological indices.

INTRODUCTION

In recent years, there has been some public concern about the use of animals in medicinal research. The finding that the structure of a molecule had an important role to play in its biological activity coupled with the need for safer potent drugs to be developed with minimum expenditure, animal sacrifice, and time loss led to the genesis of structure-activity relationship (SAR) studies.[1] SARs are models which attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties.[2]

The interest in the role and usefulness of molecular topology in investigation of SAR has received substantial attention during past few decades. There are three types of SARs: qualitative structure-activity relationships, structure-activity classifications, and quantitative structure-activity relationships (QSARs). A qualitative SAR relates some structural feature or physicochemical property to the probability of presence or absence of a given biological property. A structure-activity classification relates structural features and physicochemical properties to certain levels of pharmacological activity or to a certain activity profile. Thus a chemical compound may be classified as active, inactive, weakly active, or strongly active depending on its structural features and physicochemical properties.[3] QSARs are mathematical models which aim at predicting properties of molecules from their structure.[4]

The fact that molecular properties and activities are represented by a number but structures are not, poses inherent problems in SAR. Thus molecular topological approach in SAR essentially involves translation of molecular structures into characteristic numerical descriptors known as topological indices for prediction of biological activity.

In recent years, numerical graph invariants or topological indices have emerged as useful molecular descriptors in QSAR studies.[5] The advantage of topological indices is that they may be used directly as simple numerical descriptors in a qualitative or quantitative comparison with physical, chemical, or biological parameters of molecules in structure-activity studies.[6] These topological indices include Randić's molecular connectivity index,[7-11] Hosoya's index,[12,13] Balaban's index,[14-18] Zagreb's group index,[19,20] the comparability index,[21] Platt's number,[22,23] Gordon Scantlebury's index,[24] Smolenskii's additivity index,[25] centric index,[26] Wiener's topological index,[27-30] and its modifications.[31,32] Various topological descriptors have been extensively reviewed.[6,18,33-38]

Although over 120 different topological indices have been proposed, only a handful of them have been employed in SAR studies.[39] In the present investigations the Wiener's topological index and the molecular connectivity index were studied for possible correlation with antiulcer activity of 4-substituted-2-guanidino thiazoles.

WIENER'S TOPOLOGICAL INDEX

A topological index capable of characterizing the "branchedness" of molecule was put forward by Wiener[27-30] in 1947.

The Wiener number of graph "G" is equal to the sum of the elements of the distance matrix $D(G)$

$$W(G) = \frac{1}{2}\sum_{(i,j)} D_{ij}(G)$$

where $D_{ij}(G)$ represents off-diagonal elements of $D(G)$. The smaller the Wiener number, the greater the compactness of the molecule.[6]

Molecular Connectivity Index (χ). This topological index was introduced by Randić.[11] The molecular connectivity index can be defined as the sum over all edges ij

$$\chi = \sum (V_i V_j)^{-0.5}$$

where V_i and V_j are degrees of a pair of vertices joined by the edge (i,j).

Antiulcer Therapy. 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.[40]

Complications such as intractability,[41] obstruction,[42] perforation,[42] and hemorrhage[41] may arise from peptic ulceration of the stomach or duodenum and represent the indication for surgical intervention when medicinal drug treatment has either failed or is contraindicated.[43]

The potential medical strategies for treating peptic ulcer disease are comprised of the following:

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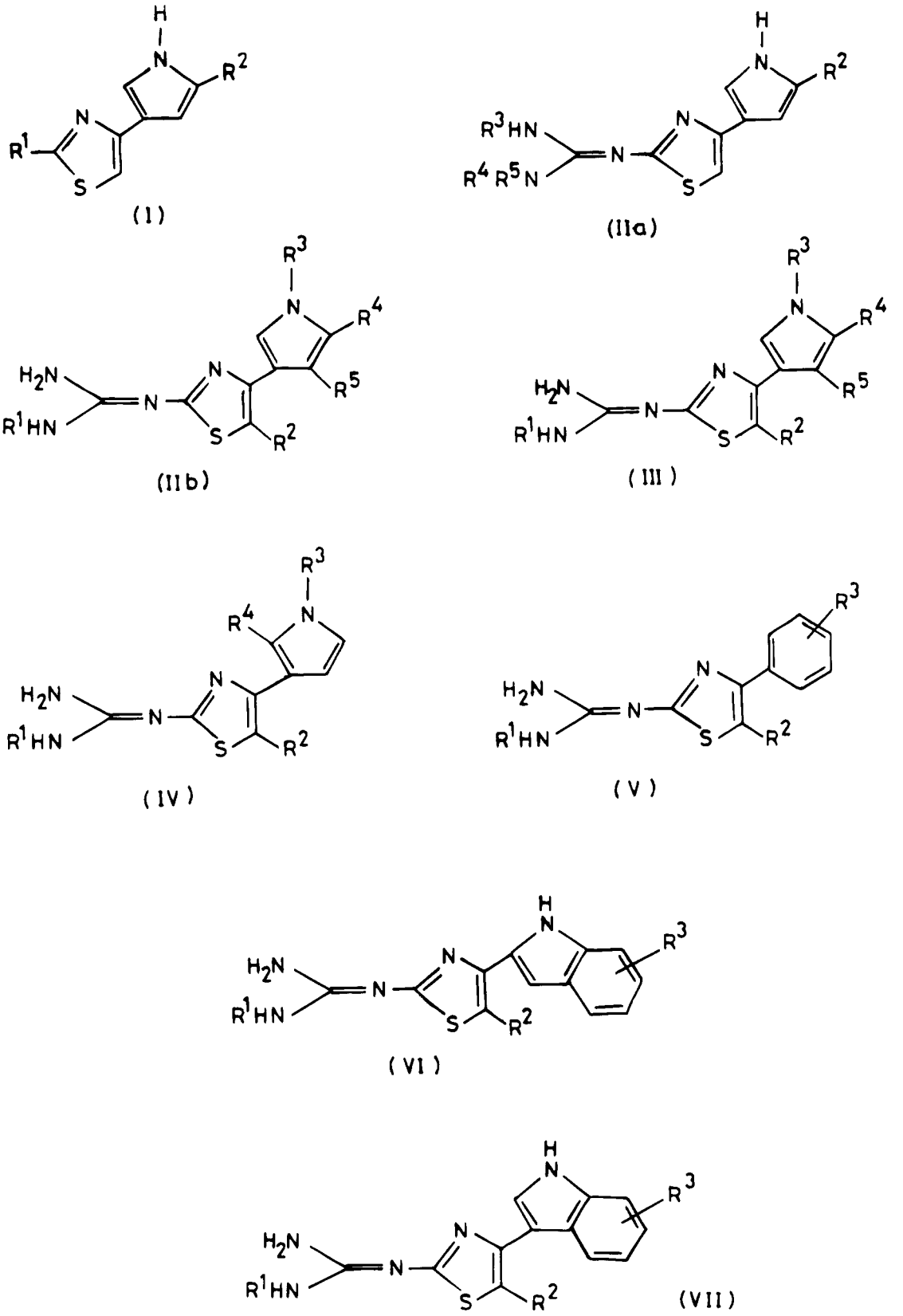

Figure 1. Various base substituents of 4-substituted-2-guanidino thiazoles.

(a) suppression of gastric acid secretion, e.g., H_2-receptor antagonists like ranitidine, famotidine, roxatidine, etc. and H^+,K^+-ATPase inhibitors, e.g., omeprazole

(b) neutralization of gastric acid, e.g., antacids-like mixture of magnesium and aluminum hydroxides

(c) shielding the mucosa and providing cytoprotection, e.g., sucralfate[44,45]

Histamine is one of three key messengers which stimulate acid secretion (the other two being acetylcholine and gastrin).

Recently agents have been identified that completely suppress acid secretion by inhibition of the gastric proton pump H^+,K^+-ATPase an enzyme which catalyzes the terminal step in gastric acid secretion.[46]

Unlike the H_2-receptor which is present in tissues through

Table 1. Various Substituents of 4-Substituted-2-Guanidino Thiazole Analogs[a]

compd no.	base no.	R^1	R^2	R^3	R^4	R^5	compd no.	base no.	R^1	R^2	R^3	R^4	R^5
1	I	$(H_2N)_2C{=}N$	Me				65	V	CH_2Ph	H	3-Me		
2	I	Me	Me				66	V	CH_2Ph	H	4-Me		
3	I	NH_2	Me				67	V	CH_2Ph	H	4-Ph		
4	I	$(H_2N)_2C{=}N$	CHO				68	V	H	H	$3\text{-}NH_2$		
5	I	Me	CHO				69	V	H	H	$3\text{-}NMe_2$		
6	I	NH_2	CHO				70	V	H	H	$4\text{-}NH_2$		
7	IIa		Me	H	$PhCH_2$	H	71	V	H	H	$4\text{-}NMe_2$		
8	IIa		Me	H	*p*-$ClPhCH_2$	H	72	V	CH_2Ph	H	$4\text{-}NH_2$		
9	IIa		Me	H	*n*-hexyl	H	73	V	H	H	2-OMe		
10	IIa		Me	H	*n*-hexyl	Me	74	V	H	H	3-OMe		
11	IIa		Me	Me	*n*-hexyl	H	75	V	H	H	4-OMe		
12	IIa		Me	H	$-(CH_2)_5-$		76	V	CH_2Ph	H	2-OMe		
13	IIa		Me	$-(CH_2)_2-$		H	77	V	CH_2Ph	H	3-OMe		
14	IIa		Me	$-(CH_2)_2-$		Me	78	V	pentyl	H	3-OMe		
15	IIa		Me	$-(CH_2)_3-$		$PhCH_2$	79	V	CH_2Ph	H	4-OMe		
16	IIb	H	H	H	H	H	80	V	H	H	$3,4(OMe)_2$		
17	IIb	H	H	H	CH_2NMe_2	H	81	V	CH_2Ph	H	$3,4\text{-}(OMe)_2$		
18	IIb	H	H	H	$CO(NC_5H_{10})$	H	82	V	H	H	2-OH		
19	IIb	H	H	H	$CH_2(NC_5H_{10})$	H	83	V	H	H	3-OH		
20	IIb	H	H	Me	Me	H	84	V	H	H	4-OH		
21	IIb	H	H	Me	CHO	H	85	V	CH_2Ph	H	2-OH		
22	IIb	H	H	SO_2Ph	Me	H	86	V	CH_2Ph	H	3-OH		
23	IIb	CH_2Ph	H	SO_2Ph	Me	H	87	V	CH_2Ph	H	4-OH		
24	IIb	H	Me	H	Me	H	88	V	H	H	$3,4\text{-}(OH)_2$		
25	IIb	Ph	Me	H	Me	H	89	V	CH_2Ph	H	$3,4\text{-}(OH)_2$		
26	IIb	CH_2Ph	Me	H	Me	H	90	V	H	Me	$3,4\text{-}(OH)_2$		
27	IIb	4-$MePhCH_2$	Me	H	Me	H	91	V	CH_2Ph	Me	$3,4\text{-}(OH)_2$		
28	IIb	CH_2CH_2Ph	Me	H	Me	H	92	VI	H	H	H		
29	IIb	H	Me	H	CHO	H	93	VI	CH_2Ph	H	H		
30	III	H	H	H	H	H	94	VI	CH_2Ph	H	5-Cl		
31	III	CH_2Ph	H	H	H	H	95	VI	H	H	5-F		
32	III	H	H	H	Me	H	96	VI	CH_2Ph	H	5-F		
33	III	CH_2Ph	H	H	Me	H	97	VII	H	H	H		
34	III	H	H	H	Me	CO_2Et	98	VII	CH_2Ph	H	H		
35	III	H	H	H	Me	$CONMe_2$	99	VII	H	Me	H		
36	III	H	H	H	Me	CH_2NMe_2	100	VII	CH_2Ph	Me	H		
37	III	H	H	Me	Me	H	101	VII	H	H	5-OMe		
38	III	H	H	SO_2Ph	Me	H	102	VII	CH_2Ph	H	5-OMe		
39	III	CH_2Ph	H	SO_2Ph	Me	H	103	VII	H	H	$5\text{-}OCH_2Ph$		
40	IV	H	H	H	Me		104	VII	CH_2Ph	H	$5\text{-}OCH_2Ph$		
41	IV	CH_2Ph	H	H	Me		105	VII	H	H	2-Me		
42	IV	H	H	SO_2Ph	Me		106	VII	CH_2Ph	H	2-Me		
43	IV	CH_2Ph	H	SO_2Ph	Me		107	VII	H	Me	2-Me, 5Cl		
44	IV	H	Me	H	Me		108	VII	CH_2Ph	Me	2-Me, 5-Cl		
45	IV	CH_2Ph	Me	H	Me		109	VII	CH_2Ph	H	4-Me		
46	IV	H	Me	SO_2Ph	Me		110	VII	H	H	5-Me		
47	IV	CH_2Ph	Me	SO_2Ph	Me		111	VII	CH_2Ph	H	5-Me		
48	V	H	H	H			112	VII	H	H	6-Me		
49	V	CH_2Ph	H	H			113	VII	CH_2Ph	H	6-Me		
50	V	H	H	2-Cl			114	VII	H	H	7-Me		
51	V	H	H	3-Cl			115	VII	CH_2Ph	H	7-Me		
52	V	H	H	4-Cl			116	VII	H	H	5-Cl		
53	V	H	H	4-F			117	VII	CH_2Ph	H	5-Cl		
54	V	CH_2Ph	H	2-Cl			118	VII	H	Me	5-Cl		
55	V	CH_2Ph	H	3-Cl			119	VII	CH_2Ph	Me	5-Cl		
56	V	CH_2Ph	H	4-Cl			120	VII	H	H	5-Br		
57	V	CH_2Ph	H	4-F			121	VII	CH_2Ph	H	5-Br		
58	V	H	H	2-Me			122	VII	H	H	5-F		
59	V	H	H	$2\text{-}CH_2NMe_2$			123	VII	CH_2Ph	H	5-F		
60	V	H	H	3-Me			124	VII	H	H	$5CO_2Me$		
61	V	H	H	$3\text{-}CH_2NMe_2$			125	VII	CH_2Ph	H	$5CO_2Me$		
62	V	H	H	4-Me			126	VII	H	H	5-CN		
63	V	H	H	4-Ph			127	VII	CH_2Ph	H	5-CN		
64	V	CH_2Ph	H	2-Me			128	VII	CH_2Ph	H	5-NHAc		

[a] Note: Me, methyl; Et, ethyl; Ac, acetyl; Ph, phenyl and/or substituted phenyl.

out the body (e.g., heart), H^+,K^+-ATPase is located predominantly in the parietal cells of the stomach, thus H^+,K^+-ATPase inhibitors should have an intrinsic specificity advantage over H_2-receptor antagonists.[47] The prototypic H^+,K^+-ATPase inhibitor omeprazole (Astra)[48,49] is remarkably effective, but its prolonged inhibition of H^+,K^+-ATPase may lead to potentially serious side effects (e.g., gastric carcinoids) perhaps as a result of elevations in plasma gastrin levels.

If such is the case, then a reversible inhibitor of H^+,K^+-ATPase might be preferable since it could provide more rapid ulcer healing than H_2-receptor antagonists and yet avoid prolonged achlorhydria induced by an irreversible inhibitor.

Table 2. Relationship of Wiener's Topological Index and of the Molecular Connectivity Index with Antiulcer Activity of Various 4-Substituted-2-Guanidino Thiazole Analogs[a]

compd no.	W	χ	activity predicted. W	activity predicted. χ	activity reported in vitro	activity reported in vivo	compd no.	W	χ	activity predicted. W	activity predicted. χ	activity reported in vitro	activity reported in vivo
1	392	6.148	+	+	+	+	65	1421	9.704	−	−	+	NA
2	196	4.754	−	−	−	NA	66	1437	9.704	−	−	−	NA
3	196	4.754	−	−	−	NA	67	2537	11.776	−	−	−	NA
4	477	6.686	+	+	+	+	68	467	6.648	+	+	+	NA
5	252	5.292	−	−	−	NA	69	649	7.558	−	−	+	NA
6	256	5.292	−	−	−	NA	70	476	6.648	+	+	+	+
7	1261	9.203	−	−	+	−	71	676	7.558	−	−	+	−
8	1442	9.597	−	−	+	−	72	1437	9.704	−	−	+	−
9	1168	9.186	−	−	+	−	73	539	7.202	+	+	+	+
10	1281	9.596	−	−	+	NA	74	557	7.186	±	+	+	+
11	1293	9.724	−	−	+	NA	75	575	7.186	±	+	+	+
12	900	8.220	−	−	−	NA	76	1571	10.258	−	−	+	−
13	563	6.810	±	+	−	NA	77	1603	10.242	−	−	+	−
14	654	7.220	−	−	−	NA	78	1282	9.724	−	−	−	NA
15	1644	10.276	−	−	−	NA	79	1261	10.242	−	−	−	NA
16	322	5.754	±	+	+	NA	80	765	8.134	−	−	+	NA
17	681	7.542	−	−	+	−	81	2002	11.190	−	−	−	NA
18	1170	9.130	−	−	+	+	82	458	6.665	+	+	−	NA
19	1088	8.703	−	−	+	NA	83	467	6.648	+	+	+	+
20	465	6.650	+	+	+	+	84	476	6.648	+	+	+	−
21	554	7.188	±	+	+	NA	85	1405	9.720	−	−	+	−
22	1488	10.116	−	−	+	−	86	1421	9.704	−	−	−	NA
23	3283	13.172	−	−	+	NA	87	1437	9.704	−	−	+	NA
24	451	6.650	+	+	+	−	88	553	7.058	±	+	+	−
25	1180	9.206	−	−	+	−	89	1599	10.114	−	−	+	−
26	1384	9.706	−	−	+	−	90	625	7.560	−	−	+	−
27	1577	10.100	−	−	+	−	91	1735	10.616	−	−	+	−
28	1611	10.206	−	−	+	−	92	640	7.312	−	−	+	−
29	543	7.188	±	+	+	+	93	1778	10.368	−	−	+	−
30	322	5.754	±	+	+	+	94	1964	10.778	−	−	+	−
31	1106	8.810	−	−	+	−	95	734	7.722	−	−	+	−
32	392	6.148	+	+	+	+	96	1964	10.778	−	−	+	NA
33	1261	9.204	−	−	+	−	97	622	7.237	−	−	+	−
34	882	8.598	−	−	+	−	98	1746	10.293	−	−	+	−
35	865	8.471	−	−	−	NA	99	699	7.739	−	−	+	−
36	768	8.044	−	−	+	−	100	1887	10.795	−	−	−	NA
37	456	6.575	+	+	−	NA	101	811	8.185	−	−	+	+
38	1407	10.041	−	−	+	−	102	2112	11.241	−	−	+	−
39	3139	13.097	−	−	+	+	103	1766	10.703	−	−	+	−
40	383	6.164	±	+	+	−	104	3392	13.759	−	−	+	−
41	1245	9.220	−	−	+	−	105	701	7.739	−	−	+	−
42	1479	10.041	−	−	+	−	106	1905	10.795	−	−	+	−
43	3267	13.097	−	−	+	NA	107	879	8.651	−	−	+	−
44	441	6.666	+	+	+	−	108	2230	11.707	−	−	+	−
45	1367	9.722	−	−	+	−	109	1897	10.650	−	−	+	−
46	1614	10.543	−	−	+	−	110	707	7.647	−	−	+	−
47	3466	13.599	−	−	−	NA	111	1916	10.703	−	−	+	−
48	393	6.254	+	+	+	+	112	719	7.631	−	−	+	NA
49	1262	9.310	−	−	−	NA	113	1935	10.686	−	−	+	−
50	458	6.665	+	+	+	+	114	728	7.631	−	−	+	−
51	467	6.648	+	+	+	+	115	1951	10.686	−	−	+	−
52	476	6.648	+	+	+	NA	116	707	7.647	−	−	+	−
53	476	6.648	+	+	+	+	117	1916	10.703	−	−	+	−
54	1405	9.720	−	−	+	−	118	790	8.149	−	−	+	−
55	1421	9.704	−	−	+	NA	119	3063	11.205	−	−	+	−
56	1437	9.704	−	−	−	NA	120	707	7.647	−	−	+	−
57	1437	9.704	−	−	−	NA	121	1916	10.703	−	−	+	−
58	458	6.665	+	+	+	+	122	707	7.647	−	−	+	−
59	737	8.058	−	−	−	NA	123	1916	10.703	−	−	+	−
60	467	6.648	+	+	+	+	124	1044	9.095	−	−	+	−
61	773	8.042	−	−	+	+	125	2536	12.151	−	−	+	−
62	476	6.648	+	+	+	NA	126	811	8.185	−	−	+	NA
63	1053	8.720	−	−	−	NA	127	2112	11.241	−	−	+	NA
64	1405	9.720	−	−	+	−	128	2560	12.189	−	−	+	+

[a] +, positive antiulcer activity; −, negative antiulcer activity; ±, transitional range where activity could not be specifically assigned; NA, data not available.

In the present study, relationship of antiulcer activity of reversible gastric H^+,K^+-ATPase inhibitors based on 4-substituted-2-guanidino thiazoles with the Wiener's topological index and molecular connectivity index has been investigated.

METHODOLOGY

A training set comprising of 128 active and inactive compounds[57] based on 4-substituted-2-guanidino thiazoles was selected. Values of Wiener's topological index and

Table 3

(A) Relative Distribution of Wiener's Topological Index Values of Test Compounds in Various Ranges

value of W	type of range	total no. of compds in this range	no. of compds predicted correctly[a]	accuracy of prediction (%)
290 or less	inactive	4	4	100
291−390	lower transitional	3	na[b]	na[b]
391−540	active	16	13	81
541−590	upper transitional	6	na[b]	na[b]
591 or more	inactive	63	57	90

(B) Relative Distribution of the Molecular Connectivity Index Values of Test Compounds in Various Ranges

value of χ	type of range	total no. of compds in this range	no. of compnds predicted correctly[a]	accuracy of prediction (%)
5.74 or less	inactive	4	4	100
5.75−7.20	active	22	17	77
7.21 or more	inactive	63	57	90

[a] Based on *in vivo* activity excepting in compound numbers **2**, **3**, **5**, and **6** which are based on *in vitro* activity in the absence of *in vivo* data. [b] Not applicable is represented by the abbreviation na.

molecular connectivity index of each compound were computed employing hydrogen suppressed molecular structures. Analysis of data after arranging index values in ascending order led to rapid identification of active ranges. After identification of active ranges each compound was assigned a biological activity which was subsequently compared with the *in vitro* and *in vivo* activities as reported by McCarthy et al.[57] Results have been compiled in Tables 2 and 3 (parts a and b). *In vitro* activity was quantitatively reported as percent inhibition of gastric H^+,K^+-ATPase enzyme at 50 μmol. Compounds possessing an activity of $\leq$39% inhibition of enzyme were considered to be inactive as proposed by McCarthy *et al.*[57] *In vivo* activity was similarly quantitatively reported as IC_{50}, i.e., concentration (in μmol) causing 50% inhibition of canine gastric H^+,K^+-ATPase. Compounds possessing an IC_{50} value of $\leq$15 μmol were considered to be inactive, as suggested by McCarthy *et al.*[57] for the purpose of present studies.

RESULTS AND DISCUSSION

Various molecular topological indices have been employed in the past for correlations with biological activities of diverse nature.[58−61] In the present study, Wiener's topological index and molecular connectivity index were employed to investigate possible correlations with antiulcer activity of 4-substituted-2-guanidino thiazoles.

Analysis of data pertaining to Wiener's topological index values of all the analogs in the training set yielded interesting results. Once the Wiener's topological index values of various analogs were arranged in ascending order, the active analogs were observed to be present in a narrow range of the index values, thus facilitating rapid identification of the active range. Subsequent comparison of assigned activities with reported activities yielded excellent correlations as evident from percent degree of prediction. Percent degree of prediction of a particular range was derived from the ratio of number of compounds predicted correctly to that of the total number of compounds present in the range. Overall degree of prediction was derived from the ratio of the total number of compounds predicted correctly to that of the total number of compounds present, in both the active and inactive ranges. Compounds present in the transitional range were not taken into consideration while determining the overall accuracy of prediction. Data pertaining to molecular connectivity index was similarly analyzed.

An excellent correlation between *in vivo* antiulcer activity and both topological indices was observed. In the case of Wiener's topological index the accuracy of prediction was found to be of the order of 89% when compared with *in vivo* activity. Similar results were also obtained with regard to molecular connectivity index. Though the active ranges were found to be identical for both *in vivo* and *in vitro* activities, the correlation was poor in case of the upper inactive range for *in vitro* activity. This was not the case with *in vivo* results in which excellent correlation was observed for all ranges. Undoubtedly, *since the in vivo results are unquestionable*, the significance of excellent relationships of both topological indices with the *in vivo* antiulcer activity cannot be overlooked.

A retrofit study of the data compiled in Tables 2 and 3 (part a) reveals the following information:

(1) On employing Wiener's topological index, a total of 74 out of 83 compounds was classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 89%.

(2) Two transitional ranges with index values of 291−390 and 541−590 were identified for Wiener's topological index. Relative proportions of inactive and active compounds in these transitional ranges were almost the same. The existence of transitional range indicates a gradual change from active range to inactive range and vice-versa.

(3) 81% of the compounds in the active range exhibited antiulcer activity as per *in vivo* results.

A similar distribution of analogs between active and inactive ranges of molecular connectivity index (χ) is shown in Table 3 (part b). Retrofit analysis of data presented in Tables 2 and 3 (part b) reveals the following information:

(1) Using "χ" as descriptor, it was possible to assign antiulcer activity with an accuracy of 88%.

(2) No transitional range could be identified.

(3) 77% of the compounds in the active range exhibited antiulcer activity as per *in vivo* studies.

(4) Excellent correlation was observed for upper inactive range for *in vivo* studies, but *in vitro* results for both topological indices were unsatisfactory.

The possibility of an inactive compound as per *in vitro* studies to be active *in vivo* is remote. Hence, owing to the absence of data regarding *in vivo* activity, the *in vitro* activity has been utilized only for compounds in lower inactive range (compound numbers **2**, **3**, **5**, and **6**).

The 128 compounds which were investigated are bases with diverse structures, but still the active range for each base happens to be the same with both topological indices. Consequently, these topological indices can be exploited for development of an ideal antiulcer agent.

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