Structure−Activity Study on Antiinflammatory Pyrazole Carboxylic Acid Hydrazide Analogs Using Molecular Connectivity Indices

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The relationship between molecular connectivity indices and the antiinflammatory activity of a series of pyrazole carboxylic acid hydrazide analogs has been investigated. The values of molecular connectivity index, valence molecular connectivity index, and a modified index, termed as atomic molecular connectivity index for 76 compounds, were computed and active ranges were identified. Each compound was assigned an activity which was subsequently compared with the reported activity against lipoxygenase enzyme. Predictions with a degree of accuracy above 80% were observed using the valence molecular connectivity index.

INTRODUCTION

Quantitative structure−activity relationships (QSARs) have been shown to be a powerful research tool and are being used in many fields.[1] QSARs are mathematical models which aim at predicting properties of molecules from their structure.[2] The basic assumption underlying this field of research is that the structure of a molecule determines its behavior.[3]

There are two basic kinds of molecular predictors used in QSAR. One of them involves parameters that bear relation to free energy and usually represent some important physicochemical properties of molecules, e.g., hydrophobic, electronic, and steric parameters.[1] The other category of molecular descriptor is the topological index or numerical graph invariant which is produced directly from molecular structure.[4]

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.[5] Thus molecular structures are translated into characteristic numerical descriptors known as topological indices, which may then be used in the development of QSAR studies.[6] The use of numerical graph invariants in QSAR seems to play an important role in situations where the 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 atoms or the nature of chemical bonding) may be the major determinant of biological activity of a molecule.[5]

A large number of numerical graph invariants of diverse nature have been reported which have been extensively reviewed.[6−10] Katritzky and Gordeeva[7] compared the relative performance of 84 graph invariants published during past two decades with regard to physicochemical properties and biological activities and concluded that for the correlation of biological activity, combination of topological indices with geometrical descriptors produced regression models of the best quality. Though many numerical graph invariants have been devised so far, only a handful of them have been employed in SAR studies.

In present investigations the molecular connectivity index, the valence molecular connectivity index, and atomic molecular connectivity index were studied for possible correlation with antiinflammatory activity of pyrazole carboxylic acid hydrazides.

Molecular Connectivity Indices. The molecular connectivity index was introduced by Randic.[11] Numerous modifications have been introduced since its presentation.[12,13] The molecular connectivity index is the most widely used graph invariant which has been found to have a high degree of accuracy in prediction of activity. 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 edges (i,j) in a hydrogen suppressed molecular structure.

In order to take into account the influence of heteroatoms on the biological activity of a molecule, Kier and Hall[12] introduced a modified connectivity index termed as valence molecular connectivity index (χ^V).

A novel numerical graph invariant based on modification of Randić's molecular connectivity index and termed as atomic molecular connectivity index (χ^A) is now proposed. This index takes into consideration the influence of the relative size of heteroatoms in a hydrogen depleted molecular structure. The atomic molecular connectivity index can be defined as the sum over all edges ij

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

where V_i and V_j represent modified valencies of a pair of vertices joined by the edges (i,j).

The computation of atomic molecular connectivity index is conducted in a manner similar to that described by Kier and Hall,[12] except that the modified valency of each vertex involved in a pair is calculated by summing up relative atomic weights of all the adjacent atoms. Relative atomic

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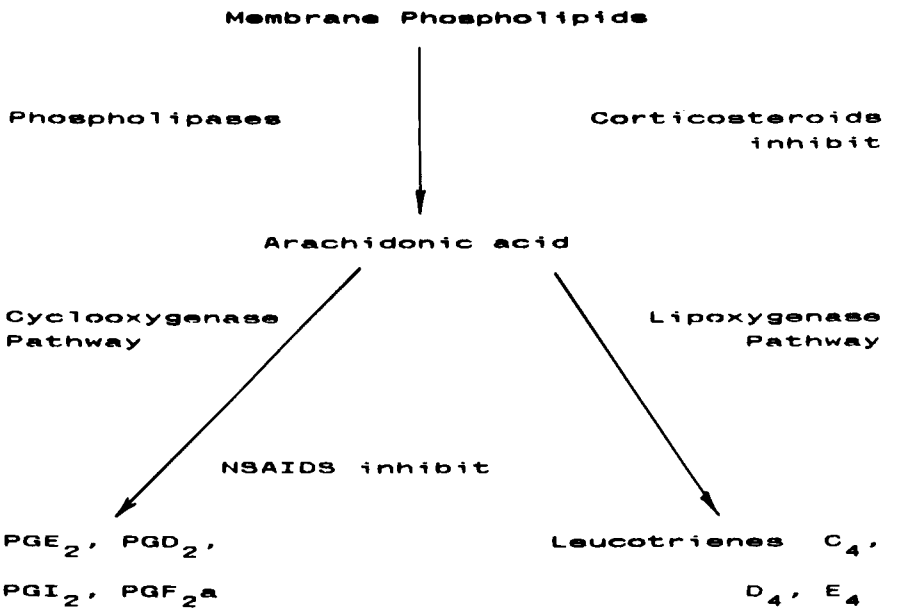

Figure 1. Mediators derived from arachidonic acid.

weights of heteroatoms are calculated with reference to carbon atom. Accordingly carbon, nitrogen, oxygen, chlorine, fluorine, and bromine were assigned the values of 1, 1.16, 1.33, 2.96, 1.58, and 6.66, respectively. In addition a provision of cyclicity has also been made as per the method of Kier and Hall.[12]

Antiinflammatory Agents. Antiinflammatory agents are drugs used to counteract inflammation, a morbid process affecting some part of the body, characterized by excessive heat, swelling, pain, and redness.[14-16]

The two most important classes of pharmacological agents that inhibit the acute or chronic inflammatory response are (1) the nonsteroidal antiinflammatory drugs (NSAIDS, typically carboxylic or enolic organic acids), the prototype of which is aspirin, and (2) the adrenal glucocorticosteroid hormone or steroidal antiinflammatory drugs (SAIDS), the prototype being hydrocortisone (cortisol).[14,17]

Both SAIDs and NSAIDs interfere with the synthesis and release of prostaglandins (PGs) and of a large number of other mediators of inflammation derived from arachidonic acid.[18] According to Trowbridge and Emling[19] arachidonic acid metabolism proceeds along two different pathways as depicted in Figure 1.

As shown in Figure 1, the glucocorticoids act by inhibiting the enzyme phospholipase A_2 which is responsible for the release of arachidonic acid from membrane phospholipids.[20] The therapeutic usefulness of glucocorticoids, however, is limited owing to their inherent toxicity.

The aspirin-like drugs inhibit cyclooxygenase and this results in diversion of the metabolism toward the lipoxygenase pathways to afford large amounts of the unfavorable leucotrienes.[20,21] Furthermore, the inhibition of cyclooxygenase enzyme may cause gastrointestinal side effects by blocking the prostaglandin biosynthesis.[22]

Consequently, the need to design a new category of drugs that have lesser side effects is enormous. To assist in the identification and development of more effective antiinflammatory agents, the SAR of pyrazole carboxylic acid hydrazide analogs has been studied in present investigations.

These compounds have been shown to possess a high lipoxygenase inhibitory activity, but they hardly inhibit cyclooxygenase enzyme.

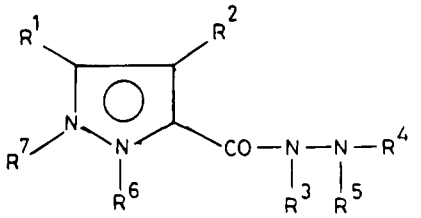

Figure 2. Basic structure of pyrazole carboxylic acid hydrazide analogs.

Methodology. A training set consisting of 76 active and inactive compounds[29] based on pyrazole carboxylic acid hydrazide analogs was selected. The basic structure of these analogs is depicted in Figure 2, and their substituents have been listed in Table 1.

Molecular connectivity index, valence molecular connectivity index, and atomic molecular connectivity index values of each compound were computed and active ranges were identified. Each analog was subsequently assigned a biological activity which was then compared with the reported activity against lipoxygenase enzyme. Results have been compiled in Tables 2 and 3.

RESULTS AND DISCUSSION

Analysis of data pertaining to valence molecular connectivity index values of all the 76 analogs in the training set yielded encouraging results. Once the χ^V 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 the number of compounds predicted correctly to that of the total number of compounds present in the range. The 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

Table 1. Various Substituents of Pyrazole Carboxylic Acid Hydrazide Analogs[a]

no.	R^1	R^2	R^3	R^4	R^5	R^6	R^7 [b]
1	Me	H	H	H	H		H
2	H	Me	H	H	H		H
3	Me	H	Me	H	H		H
4	Me	H	H	H	Me		H
5	H	Me	H	H	Me		H
6	Me	H	Me	H	Me		H
7	Me	H	H	Me	Me		H
8	Me	H	H	H	*i*Pr		H
9	Me	H	H	H	*t*Bu		H
10	Me	H	H	H	cC_5H_9		H
11	Me	H	H	H	cC_6H_{11}		H
12	Me	H	H	H	CH_2Ph		H
13	Me	H	H	H	2,6-di-$ClCH_2Ph$		H
14	Me	H	H	H	Ph		H
15	Me	H	H	H	2-ClPh		H
16	Me	H	H	H	3-ClPh		H
17	Me	H	H	H	4-ClPh		H
18	Me	H	H	H	4-CH_3Ph		H
19	Me	H	H	H	3-CF_3Ph		H
20	Me	H	H	H	2,3-di-ClPh		H
21	Me	H	H	H	2,6-di-ClPh		H
22	Me	H	H	H	2-Cl-6-CH_3Ph		H
23	H	Me	H	H	2-Cl-6-CH_3Ph		H
24	Me	H	H	H	5-Cl-2-CH_3Ph		H
25	Me	H	H	H	2,6-di-CH_3Ph		H
26	Me	H	H	H	2,6-di-C_2H_5Ph		H
27	Me	H	H	H	4-Br-2-Cl-6-CH_3Ph		H
28	Me	Br	H	H	4-Br-2-Cl-6-CH_3Ph		H
29	Me	H	H	H	2,4,6-tri-CH_3Ph		H
30	Ph	H	H	H	Me		H
31	Ph	H	H	H	Ph		H
32	Me	H	H	$=C(CH_3)_2$			H
33	Me	H	H	$=C(CH_3)_2$		Me	
34	Me	H	H	$=C(CH_3)_2$			Me
35	Me	H	H	$=C(CH_2)_4$			H
36	Me	H	H	$=C(CH_2)_5$			H
37	Me	H	H	=CHPh			H
38	Me	H	Me	=CHPh			H
39	Me	H	Ph	=CHPh		$-CH_2Ph$	
40	Me	H	Ph	=CHPh			$-CH_2Ph$
41	Me	H	H	=CH-2,6-di-ClPh			H
42	Me	H	H	=CH-3,4,5,-tri-OCH_3Ph			H
43	Me	H	Me	H	Ac		H
44	Me	H	H	H	CO-3,4,5-tri-OCH_3Ph		H
45	Me	H	Me	H	CO-3,4,5,tri-OCH_3Ph		H
46	Me	H	H	Me	CHO		H
47	H	Me	H	Me	CHO		H
48	Me	H	H	Me	Ac		H
49	Me	H	Me	Me	Ac		H
50	Me	H	H	Me	COEt		H
51	Me	H	H	Me	CO-3,4,5-tri-OCH_3Ph		H
52	Me	H	H	*i*Pr	CHO		H
53	Me	H	H	cC_6H_{11}	CHO		H
54	Me	H	H	CH_2Ph	CHO		H
55	Me	H	H	CH_2-2,6-di-Cl-Ph	CHO		H
56	Me	H	H	Ph	CHO		H
57	Me	H	H	Ph	Ac		H
58	Me	H	H	2,6-di-ClPh	CHO		H
59	Me	H	H	H	H	Me	
60	Me	H	H	H	H		Me
61	Me	H	H	H	Me	Me	
62	Me	H	H	H	Me		Me
63	Me	H	H	H	*i*Pr	Me	
64	Me	H	Ph	H	CH_2Ph		CH_2Ph
65	Me	H	H	H	Ph		Me
66	Me	H	H	H	3-CF_3Ph		Me
67	H	Me	H	H	2-Cl-6-CH_3Ph	2,6-di-Cl-Ph	
68	Me	H	Me	Ac	H		Ac
69	Me	H	H	Ac	Me	Me	
70	Me	H	H	Ac	Me		Ac
71	Me	H	H	COEt	Me		COEt
72	Me	H	H	Ac	*i*Pr	Me	
73	Me	H	H	CHO	*i*Pr		Ac
74	Me	H	H	Ac	Ph		Ac
75	Me	H	H	H	2,6-di-ClPh		Ac
76	Me	H	H	CHO	2,6-di-ClPh		Ac

[a] Me, methyl; Et, ethyl; Ac, acetyl; *i*Pr, isopropyl; Ph, phenyl and/or substituted phenyl group; cC_5H_9, cyclopentyl; cC_6H_{11}, cyclohexyl; $=C(CH_2)_5$, cyclohexylidene; $=C(CH_2)_4$, cyclopentylidene. [b] For compounds numbers 1−31 and 43−58, "H" can be placed either on R^6 or R^7 position with no adverse effect on the index values.

Table 2. Relationship between Antiinflammatory Activity and Molecular Connectivity Indices of Various Pyrazole Carboxylic Acid Hydrazide Analogs[a]

compd no.	χ	χ^V	χ^A	activity predicted			activity reported	compd no.	χ	χ^V	χ^A	activity predicted			activity reported
				χ	χ^V	χ^A						χ	χ^V	χ^A	
1	4.24	2.90	4.02	−	−	−	−	39	12.80	11.39	12.44	−	−	−	−
2	4.25	2.89	3.97	−	−	−	−	40	12.80	11.39	12.44	−	−	−	−
3	4.61	3.29	4.37	−	−	−	−	41	8.08	6.94	7.26	+	±	±	+
4	4.74	3.36	4.48	−	−	−	−	42	10.18	7.38	9.49	−	±	−	+
5	4.75	3.35	4.44	−	−	−	−	43	6.00	4.36	5.66	−	−	−	−
6	5.15	3.75	4.86	−	−	−	−	44	10.59	7.54	9.84	−	±	−	−
7	5.09	3.73	4.82	−	−	−	−	45	10.99	7.93	10.22	−	±	−	+
8	5.59	4.31	5.36	−	−	−	+	46	5.63	3.88	5.28	−	−	−	−
9	5.88	4.61	5.65	−	−	−	−	47	5.65	3.87	5.24	−	−	−	−
10	6.26	4.97	6.02	−	±	±	+	48	6.00	4.35	5.30	−	−	−	−
11	6.76	5.47	6.53	+	±	+	+	49	6.43	4.74	6.06	−	−	±	−
12	7.26	5.94	7.02	+	±	±	−	50	6.54	4.89	6.22	−	−	±	−
13	8.08	6.99	7.26	+	±	±	−	51	10.99	7.93	10.22	−	±	−	−
14	6.76	5.46	6.53	+	±	+	+	52	6.54	4.86	6.20	−	−	±	−
15	7.17	5.99	6.65	+	+	+	+	53	7.70	6.02	7.37	+	+	±	+
16	7.15	5.98	6.61	+	+	+	+	54	8.19	6.48	7.85	+	+	±	+
17	7.15	5.98	6.61	+	+	+	+	55	9.01	7.54	8.09	−	±	±	+
18	7.15	5.86	6.92	+	±	±	+	56	7.70	6.02	7.37	+	+	±	+
19	8.36	5.24	7.84	+	±	±	+	57	8.08	6.48	7.75	+	+	±	+
20	7.58	6.53	6.80	+	+	+	+	58	8.52	7.07	7.62	−	±	±	−
21	7.58	6.53	6.77	+	+	+	+	59	4.74	3.29	4.39	−	−	−	−
22	7.58	6.41	7.06	+	+	±	+	60	4.74	3.29	4.39	−	−	−	−
23	7.59	6.39	7.02	+	+	±	−	61	5.24	3.76	4.86	−	−	−	−
24	7.56	6.39	7.03	+	+	±	−	62	5.24	3.76	4.86	−	−	−	−
25	7.58	6.29	7.36	+	+	±	+	63	6.09	4.69	5.73	−	−	±	−
26	8.65	7.37	8.43	−	±	−	−	64	12.79	11.45	12.44	−	−	−	−
27	8.06	7.46	6.98	+	±	±	+	65	7.26	5.86	6.90	+	±	±	−
28	8.49	8.53	6.92	−	−	±	−	66	8.86	5.63	8.21	−	±	−	−
29	8.06	6.77	7.84	+	+	±	+	67	10.89	10.08	9.73	−	−	−	−
30	6.81	5.44	6.56	+	±	+	−	68	7.42	5.37	6.88	+	±	+	+
31	8.83	7.54	8.61	−	±	−	−	69	6.51	4.75	6.04	−	−	±	−
32	5.59	4.25	5.36	−	−	−	−	70	7.42	5.37	6.88	+	±	+	−
33	6.09	4.64	5.73	−	−	±	+	71	8.49	6.87	7.99	−	±	±	−
34	6.09	4.64	5.73	−	−	±	−	72	7.42	5.71	6.96	+	±	±	−
35	6.26	4.91	6.03	−	±	±	+	73	7.95	5.87	7.43	+	±	±	−
36	6.76	5.41	6.53	+	±	+	−	74	9.49	7.50	8.98	−	±	−	−
37	7.26	5.88	7.02	+	±	±	+	75	8.99	7.54	7.99	−	±	±	+
38	7.67	6.27	7.40	+	+	±	−	76	9.94	8.09	8.84	−	−	−	−

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

range were not taken into consideration while determining overall accuracy of prediction. Data pertaining to molecular connectivity index and atomic molecular connectivity index was similarly analyzed.

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

1. Using "χ" as a descriptor, a total of 58 out of 76 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 76%.

2. Transitional range could not be identified.

3. Sixty−five percent of the compounds in the active range exhibited antiinflammatory activity.

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

1. A total of 41 out of 46 compounds were classified correctly in both active and inactive ranges. Hence, using "χ^V" as a descriptor, it was possible to assign antiinflammatory activity with an accuracy of 89%.

2. Two transitional ranges with index values of 4.9−5.97 and 6.79−8.07 were identified for valence molecular connectivity 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. Eighty percent of the compounds in the active range exhibited antiinflammatory activity.

Retrofit analysis of data presented in Tables 2 and 3 (part c) reveals the following information:

1. On employing atomic molecular connectivity index, 36 out of 42 compounds were classified correctly in both active and inactive ranges. The overall accuracy of prediction was found to be 86%.

2. Two transitional ranges with index values of 5.68−6.52 and 6.9−8.2 were identified for atomic molecular connectivity index.

3. Seventy-three percent of the compounds in the active range exhibited antiinflammatory activity.

The valence molecular connectivity index exhibited the highest correlating ability of the order of 89% which was closely followed by the atomic molecular connectivity index with a value of 86%. Hence these correlations can be exploited for developing a better antiinflammatory agent.

Table 3

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

value of χ	type of range	total no. of compds in the range	no. of compds predicted correctly	accuracy of prediction (%)
6.74 or less	inactive	27	24	89
6.75−8.47	active	31	20	65
8.48 or more	inactive	18	14	78

(b) Relative Distribution of Valence Molecular Connectivity Index Values of Test Compounds in Various Ranges

value of χ^V	type of range	total no. of compds in the range	no. of compds predicted correctly	accuracy of prediction
4.89 or less	inactive	25	23	92
4.9−5.97	transitional	16	na[a]	na
5.98−6.78	active	15	12	80
6.79−8.07	transitional	14	na	na
8.08 or more	inactive	6	6	100

(c) Relative Distribution of Atomic Molecular Connectivity Index Values of Test Compounds in Various Ranges

value of χ^A	type of range	total no. of compds in the range	no. of compds predicted correctly	accuracy of prediction (%)
5.67 or less	inactive	18	17	94
5.68−6.52	transitional	9	na	na
6.53−6.89	active	11	8	73
6.90−8.20	transitional	25	na	na
8.21 or more	inactive	13	11	85

[a] Not applicable is represented by the abbreviation "na".

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