Structure-Activity Study on Anticonvulsant (Thio) Hydantoins Using Molecular Connectivity Indices

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The relationship between molecular connectivity indices and anticonvulsant activity of a series of hydantoin/thiohydantoin analogs has been investigated. The values of molecular connectivity index and valence molecular connectivity index of 82 compounds were computed and active ranges were identified. The activity assigned to each analog using these topological descriptors was subsequently compared with the reported activity against maximal electroshock convulsions. Predictions with high degree of accuracy were observed using these indices.

INTRODUCTION

The finding that 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] SAR studies have been given due recognition in medicinal chemistry and the pharmaceutical industry and is one of the sacred tool of the drug design.[2,3] Structure-activity relationships refer simultaneously to two types of properties of chemical compounds: biological activity and either structural features or physicochemical properties. There are three types of structure-activity relationships: qualitative structure-activity relationships, structure-activity classifications, and quantitative structure-activity relationships (QSAR). A qualitative structure-activity relationship 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. QSAR is a mathematical equation which on the basis of numerically expressible structural or physicochemical properties, allows a more or less precise calculation of the potency of chemical compounds.[73]

Numerous mathematical and quantum chemical approaches have been propounded and the pioneering contributions in the field of SAR studies have been of Free-Wilson,[4] Hansch,[4-6] Camerman and Camerman.[7] The basic requirement in SAR is the selection of an ideal property as a descriptor which correlates well with the physical and biological properties of the group of compounds being analyzed.[8-10] The descriptor chosen as the mathematical tool constitutes the basis for SAR studies, may either be a physical or geometrical characteristic or determined by quantum mechanical computations. For implementation of SAR descriptors as predictive tools in preliminary research work it is necessary that the descriptor be highly specific and accurate.[11] The need for simple and highly specific descriptors paved the way for translation of molecular structures into numerical descriptors[12,13] which are derived by assuming atoms to be vertices and connecting bonds as edges, thereby representing molecular structures as molecular graphs.[10,17,18] One of the main advantages of using molecular graphs is that it allows for representation of a molecule by means of a single numerical index.[19,20] The topological indices have been recently used in SAR studies because of the ease and accuracy in their use and their wide range of applicability.[21-23] Use of topological indices in SAR 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 atoms or nature of chemical bonding, may be the major detriminant of the biological activity of a molecule.

TOPOLOGICAL INDICES

Topological indices, i.e., numerical descriptors of chemical graph theory, are based either on atom-atom connectivity or topological distances in a chemical graph G. The topological indices are derived either by using adjacency matrix (**A**),[24,25] Wiener matrix,[74,75] or distance matrix (**D**)[24,25] of a molecular graph. Most commonly used topological indices based on atom-atom connectivity are Zagreb index,[25] Z index,[29] the comparability index,[30] and the connectivity index,[31,37] while those based on topological distances are Wiener's number,[38,39] Platt's number,[21] Gordon Scantlebury's index,[40] the centric index,[41] Altenburg's polynomial,[44] and the information content.[26]

In present investigations the molecular connectivity index and the valence molecular connectivity index were studied for possible correlation with anticonvulsant activity of hydantoins.

MOLECULAR CONNECTIVITY INDEX

This topological index was introduced by Randic.[31] Numerous modifications have been affected since its presentation.[37,51] The molecular connectivity index is the most widely used topological index which has been found to have a high degree of accuracy in prediction of activity.[45-48] The molecular connectivity index (χ) can be defined as the sum over all edges ij

$$\chi = \sum (\nu_i \nu_j)^{-0.5}$$

where ν_i and ν_j are degrees of a pair of vertices joined by the edges (i,j).

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Table 1. Various Substituents of Hydantoin Analogs

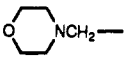
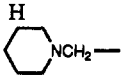
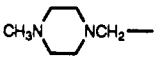
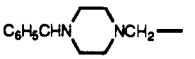
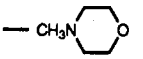
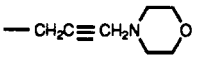
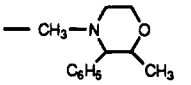
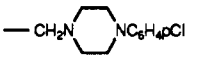
compd no.	R	R^1	R^2	R^3
1	CH_3	$(CH_3)_3C$	H	H
2	CH_3	C_6H_5	H	H
3	c-C_3H_5	c-C_3H_5	H	H
4	C_2H_5	C_6H_5	H	H
5	n-C_3H_7	C_6H_5	H	H
6	c-C_3H_5	C_6H_5	H	H
7	$(CH_3)_2CH$	C_6H_5	H	H
8	n-C_4H_9	C_6H_5	H	H
9	$CH_3CH_2(CH)CH_3$	C_6H_5	H	H
10	$(CH_3)_2CHCH_2$	C_6H_5	H	H
11	$(CH_3)_3C$	C_6H_5	H	H
12	C_6H_5	C_6H_5	H	H
13	C_6H_5	$C_6H_5CH_2$	H	H
14	C_2H_5	C_6H_5	H	H
15	C_2H_5	C_6H_5	H	CH_3
16	C_2H_5	C_6H_5	H	C_2H_5
17	C_2H_5	C_6H_5	H	$CH{\equiv}CCH_2^-$
18	C_2H_5	C_6H_5	CH_3	CH_3
19	C_2H_5	C_6H_5	$CH{\equiv}CCH_2^-$	CH_3
20	c-C_3H_5	C_6H_5	H	CH_3
21	C_6H_5	C_6H_5	H	CH_3
22	C_6H_5	C_6H_5	H	$CH{\equiv}CCH_2^-$
23	C_6H_5	C_6H_5	H	$C_6H_5CH_2^-$
24	C_6H_5	C_6H_5	$CH{\equiv}CCH_2^-$	$CH{\equiv}CCH_2^-$
25	2-C_4H_3S	CH_3	H	$HO_2CCH_2CH_2$
26	CH_3	CH_3	H	
27	2-C_4H_3S	c-C_3H_5	H	H
28	C_6H_5	C_6H_5	H	
29	C_6H_5	C_6H_5	H	
30	C_6H_5	C_6H_5	H	
31	C_6H_5	C_6H_5	H	
32	C_6H_5	C_6H_5	H	
33	C_6H_5	C_6H_5	H	
34	C_6H_5	C_6H_5	H	
35	H	C_6H_5	H	$-CH_2CH_2OH$
36	CH_3	C_6H_5	H	$-CH_2CH_2OH$
37	CH_3	C_6H_5	H	$-CH_2OH$
38	CH_3	$pBrC_6H_4$	H	$-CH_2CH_2OH$
39	C_2H_5	C_6H_5	H	$-CH_2OH$
40	C_2H_5	C_6H_5	H	$-CH_2CH_2OH$
41	C_2H_5	p-BrC_6H_4	H	$-CH_2CH_2OH$
42	C_2H_5	p-ClC_6H_4	H	$-CH_2CH_2OH$
43	C_2H_5	p-FC_6H_4	H	$-CH_2CH_2OH$
44	CH_3	p-ClC_6H_4	H	$-CH_2CH_2OH$
45	CH_3	p-FC_6H_4	H	$-CH_2CH_2OH$
46	C_6H_5	C_6H_5	H	$-CH_2CH_2OH$
47	$C_6H_5CH_2$	o-OHC_6H_4	H	H
48	$C_6H_5CH_2$	o-OH, $pCH_3OC_6H_3H$	H	H
49	o-OHC_6H_4	p-$CH_3OC_6H_4CH_2$	H	H
50	o-OH; p-$CH_3OC_6H_3$	p-$CH_3OC_6H_4CH_2$	H	H
51	H	C_6H_5	H	$(C_2H_5)_2NCH_2CH_2^-$
52	CH_3	C_6H_5	H	$(C_2H_5)_2NCH_2CH_2^-$
53	CH_3	C_6H_5	H	$(CH_3)_2NCH_2CH_2^-$
54	C_6H_5	C_6H_5	H	$(CH_3)_2NCH_2CH_2^-$
55	C_2H_5	C_6H_5	H	$(CH_3)_2NCH_2CH_2^-$
56	C_6H_5	C_6H_5	H	$(C_2H_5)_2NCH_2^-$
57	C_6H_5	C_6H_5	H	$(C_2H_5)_2NCH_2CH2^-$
58	C_6H_5	C_6H_5	H	$(CH_3)_2NCH_2C{\equiv}CCH_2^-$
59	C36H_5	C_6H_5	H	$(C_2H_5)_2NCH_2C{\equiv}CCH_2^-$
60	C_6H_5	C_6H_5	H	H
61	C_6H_5CO	C_6H_5	H	H
62	C_6H_5CO	C_6H_5	CH_3	H

Table 1 (Continued)

compd no.	R	R^1	R^2	R^3
63	C_6H_5CO	C_6H_5	CH_3	CH_3
64	C_6H_5CO	C_6H_5	C_6H_5	H
65	C_6H_5CO	C_6H_5	CH_3	CH_3
66	C_6H_5CHOH	C_6H_5	H	H
67	C_6H_5CHOH	C_6H_5	CH_3	H
68	C_6H_5CHOH	C_6H_5	CH_3	CH_3
69	C_6H_5CHOH	C_6H_5	C_6H_5	H

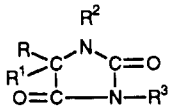


Figure 1.

In order to overcome the influence of heteroatoms on the biological activity on a molecule, Kier and Hall[37] introduced a modified connectivity index termed as *valence molecular connectivity index* (χ^v), in which heteroatoms have been allowed for by assigning for non-halogen heteroatoms values according to the following formula

$$\delta = Z - N_H$$

δ = difference between the number of valence electrons in heteroatom and the number of hydrogen atoms to which it is attached, Z = number of valence electrons, and N_H = number of attached hydrogen atoms.

ANTICONVULSANT HYDANTOINS

Hydantoins are the most widely used group of anticonvulsants. Diphenylhydantoin, the first anticonvulsant hydantoin was introduced in 1938 by Meritt and Putnam. Though introduced as the miracle drug to cure epilepsy, its limitation against petit mal seizures was soon realized. An ideal anticonvulsant should possess the following characteristics: (1) capability to limit the spread of seizure discharge and to increase seizure threshold of excitable neurons to be effective in all types of seizures (grand mal, petit mal, and jacksonian), (2) selectivity of action, particularly on neurohumoral mechanisms involving biogenic amines and other endogenous substances, and (3) nontoxicity largely on an empirical basis; a number of excellent drugs have been made available for treatment of epilepsy. Their therapeutic usefulness, however, is limited owing to their inherent toxicity. SARs of anticonvulsants have been extensively investigated during past few years.[32-35] Most of the studies have been confined to barbiturates,[36] 1,4-benzodiazepines[34] using topological indices. Hydantoins, however, have not been investigated using these indices. SAR of hydantoins using molecular connectivity index and valence molecular connectivity index has been investigated in the present study.

METHODOLOGY

A training set consisting of 82 active and inactive compounds was chosen at random. It comprised 69 hydantoin analogs whose basic structure is depicted by Figure 1 and whose substituents are listed in Table 1, and 13 thiohydantoins analogs whose basic structure is depicted by Figure 2 and whose substituents are listed in Table 2. Molecular connectivity index and valence molecular connectivity index values were computed and active, transitional, and inactive ranges identified for assigning anticonvulsant activity to compounds having molecular connectivity index values in ranges shown

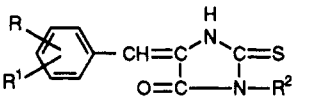


Figure 2.

Table 2. Various Substituents of Thiohydantoin Analogs

compd no.	R	R^1	R^2
70	H	H	C_6H_5
71	H	*o*-CH_3	*p*-BrC_6H_4
72	*o*-CH_3	*p*-CH_3	C_6H_5
73	*o*-CH_3	*p*-CH_3	*p*-$CH_3C_6H_4$
74	*m*-CH_3	*p*-CH_3	*p*-$CH_3C_6H_4$
75	*o*-CH_3	*p*-CH_3	*p*-BrC_6H_4
76	*m*-CH_3	*p*-CH_3	*p*-BrC_6H_4
77	H	*o*-CH_3O	*p*-Brc_6H_4
78	H	*m*-CH_3O	*p*-BrC_6H_4
79	H	*p*-CH_3O	*p*-BrC_6H_4
80	*o*-CH_3O	*p*-CH_3O	*p*-BrC_6H_4
81	*o*-CH_3O	*m*-CH_3O	*p*-BrC_6H_4
82	*m*-CH_3O	*p*-CH_3O	*p*-BrC_6H_4

in Table 4 (parts A and B), against maximal electroshock (MES).

RESULTS AND DISCUSSIONS

Various molecular topological indices have been employed in the past for correlations with biological activities of diverse nature. In the present study, molecular connectivity index and valence molecular connectivity index were employed to investigate possible correlation with anticonvulsant activity of hydantoins and thiohydantoins. Though hydantoin/thiohydantoin analogs contained a broad spectrum of substituents, interesting results were obtained with regard to the relationship between the values of molecular connectivity indices and anticonvulsant activity. Analysis of data pertaining to the values of molecular connectivity indices facilitated rapid categorization into active, inactive, and transitional ranges. Rapid identification of active range allowed prediction of biological activity of each analog involved in the training set. Data pertaining to predicted and reported activities of each analog have been compiled in Table 3. A retrofit analysis of data presented in tables led to the following conclusions: (1) The valence molecular connectivity index had a lower number of degenerate sets as compared to the molecular connectivity index. The predictive powers of χ^v and χ were found to be 85.5 and 85.10%, respectively. (2) Anticonvulsant activity changed gradually from active range to inactive range leading to transitional ranges of 6.21–7.25 and 9.61–10.60 for χ^v and χ, respectively. Relative proportions of inactive and active compounds in these transitional ranges were almost the same. This can be compared with the fact that ~94% of the compounds in the active range exhibited anticonvulsant activity for both indices. (3) Though the ranges with values lower than 4.0 and 6.5 for χ^v and χ, respectively, have been categorized as inactive ranges, their possibility of being transitional ranges cannot be ruled out owing to the fact that there are only two compounds (both being inactive) in the

Table 3. Relationship between Anticonvulsant Activities and Molecular Connectivity Indices of Various Hydantoin/Thiohydantoin Analogs[a]

			activity predicted							activity predicted			
compd no.	χ	χ^v	χ	χ^v	activity reported	ref	compd no.	χ	χ^v	χ	χ^v	activity reported	ref
1	5.26	3.91	–	–	–	54	**42**	9.05	6.86	+	+	+	70
2	6.62	4.32	+	+	+	55	**43**	9.05	6.14	+	+	+	70
3	6.23	4.87	–	+	–	53	**44**	8.49	5.31	+	+	+	70
4	7.19	4.88	+	+	+	56	**45**	8.49	4.59	+	+	+	70
5	7.69	5.38	+	+	+	53	**46**	10.7	7.07	+	±	+	70
6	7.73	5.43	+	+	+	54	**47**	9.13	6.92	+	±	–	57
7	7.57	5.26	+	+	+	54	**48**	10.23	6.71	±	±	–	57
8	8.19	5.88	+	+	+	54	**49**	10.51	7.27	±	–	–	57
9	8.11	6.1	+	+	+	54	**50**	11.04	7.51	–	–	–	57
10	8.05	5.73	+	+	+	54	**51**	9.66	7.04	±	±	+	69
11	7.87	5.57	+	+	+	54	**52**	10.02	6.29	±	±	+	69
12	8.88	5.99	+	+	+	56	**53**	8.95	7.44	+	–	+	69
13	9.71	6.45	±	±	–	57	**54**	11.56	7.55	–	–	+	70
14	7.27	5.28	+	+	–	71	**56**	10.59	6.59	±	±	+	66
15	7.62	5.28	+	+	+	72	**56**	12.12	8.3	–	–	–	66
16	6.52	5.86	+	+	+	71	**57**	12.92	8.48	–	–	+	69
17	8.65	6.5	+	±	+	63	**58**	13.62	9.07	–	–	–	63
18	8.05	5.66	+	+	+	71	**59**	12.56	7.48	–	–	–	63
19	9.08	6.17	+	+	+	63	**60**	16.56	7.82	–	–	–	64
20	8.18	5.83	+	+	+	53	**61**	10.14	6.43	±	±	–	61
21	9.66	6.38	±	±	+	56	**62**	10.58	6.83	±	±	+	61
22	10.40	6.89	±	±	+	63	**63**	11.0	7.23	–	±	+	61
23	12.71	8.51	–	–	–	64	**64**	13.15	8.51	–	–	–	61
24	12.16	7.38	–	–	–	64	**65**	13.24	8.91	–	–	–	61
25	8.04	5.36	+	+	+	65	**66**	10.14	6.57	±	±	–	61
26	7.96	5.45	+	+	–	66	**67**	10.58	6.97	±	±	+	61
27	7.23	4.92	+	+	+	53	**68**	11.0	7.37	–	–	–	61
28	12.71	9.2	–	–	–	66	**69**	13.15	8.65	–	–	–	61
29	13.11	9.29	–	–	+	67	**70**	9.75	6.23	±	±	–	61
30	16.16	10.4	–	–	+	68	**71**	10.56	7.33	±	–	–	61
31	12.71	8.77	–	–	+	66	**72**	10.58	7.06	±	±	–	58
32	14.21	6.54	–	±	–	63	**73**	10.96	7.5	–	–	–	59
33	16.11	10.09	–	–	–	67	**74**	10.96	7.47	–	–	–	60
34	15.07	11.9	–	–	–	68	**75**	10.96	7.96	–	–	–	60
35	7.59	5.01	+	+	+	69	**76**	10.96	7.96	–	–	–	59
36	80.9	5.40	+	+	+	69	**77**	11.08	7.65	–	–	–	59
37	7.59	4.90	+	+	+	69	**78**	11.08	7.95	–	–	–	59
38	8.49	5.7	+	+	+	70	**79**	11.08	7.65	–	–	–	59
39	8.15	5.46	+	+	+	70	**80**	12.03	8.19	–	–	–	59
40	8.65	5.96	+	±	+	70	**81**	12.03	8.19	–	–	–	62
41	9.05	7.25	+	●	+	70	**82**	12.03	8.19	–	–	–	62

[a] +, compounds possessing anticonvulsant activity against MES; –, compounds devoid of activity against MES; ±, transitional range where activity could not be specifically assigned.

Table 4.

Relative Distribution of 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 compds predicted correctly	accuracy of prediction (%)
6.5 or less	inactive	2	2	100
6.51–9.60	active	33	31	94
9.61–10.60	transitional	15	na[a]	na[a]
10.61 or more	inactive	32	24	75

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 this range	no. of compds predicted correctly	accuracy of prediction (%)
4 or less	inactive	1	1	100
4–6.20	active	30	28	93.33
6.21–7.25	transitional	20	na[a]	na[a]
7.26 or more	inactive	31	24	77.77

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

entire training set which fall in this range. (4) The active range was identical for analogs based upon hydantoin as well as thiohydantoin core rings. Moreover, this active range is also not influenced by substituents of diverse nature in a training set comprising of 82 analogs. Excellent correlation has been obtained between molecular connectivity indices and anticonvulsant activity of hydantoin/thiohydantoin analogs; this relationship can be exploited for designing a suitable anticonvulsant.

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