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Predicting anticonvulsant activity of benzamides/benzylamines: computational approach using topological descriptors

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Summary

The relationship of Wiener's index (a distance-based topological descriptor), Zagreb group parameter (an adjacency-based topological descriptor) and eccentric connectivity index (an adjacency-cum-distance-based topological descriptor) with the anticonvulsant activity of a series of substituted benazamides/benzylamines has been investigated. A training set comprising 41 analogues of substituted benazamides/benzylamines was selected for the present investigations. The values of the Wiener's index, Zagreb group parameter and eccentric connectivity index and of each of 41 analogues comprising the data set were computed and active ranges were identified. Subsequently, a biological activity was assigned to each analogue involved in the data set which was then compared with the reported anticonvulsant activity. An exceptionally high accuracy of predictions ranging from a minimum of ∼88% for the Zagreb group parameter to a maximum of ∼97% for Wiener's index were obtained.

Introduction

It has always been the aim of medicinal chemists to predict the biological activity of not yet synthesized or tested compounds. Such predictions can be of a qualitative or a quantitative nature and are dependent on the availability of structure-activity relationships [1]. Rational molecular design includes molecular modeling, quantitative structure-activity relationships (QSAR) and quantum mechanical approaches. In general, rational drug design assumes the existence of known active compounds with well defined structures. The above methods are then used as a basis for designing new compounds with enhanced biological activity [2]. Structure-activity relationships (SARs) are models that relate structural aspects of a molecule to its physicochemical or biological properties, and are used as a tool to develop safer and potent drugs. The inherent problem in SAR to quantify chemical structures can be overcome by molecular topology, by translation of chemical structures into characteristic numerical descriptors [3–8]. Molecular topology, as represented by the connectivity of the atoms can relate biological activity with the analogues. Topological indices developed for predicting physicochemical properties and biological activities of chemical substances can be used for drug design [9–13].

The term epilepsies is a collective designation for a group of central nervous system (CNS) disorders having in common the repeated occurrence of sudden and transitory episodes (seizures) of abnormal phenomena of motor (convulsion), sensory, autonomic, or psychic origin [14]. Studies have shown that 1% of the population suffers from some kind of epilepsy and that 25% of them have seizures that are resistant to available medical therapies [15]. Recurrent seizures, if frequent, interfere with a patient's ability to carry out day-to-day activities. However, judicious use of antiepileptic medications allows about 75% of epileptic patients to remain seizure-free. Major antiepileptic drugs are carbamazepine, phenytoin, valproate, etho-

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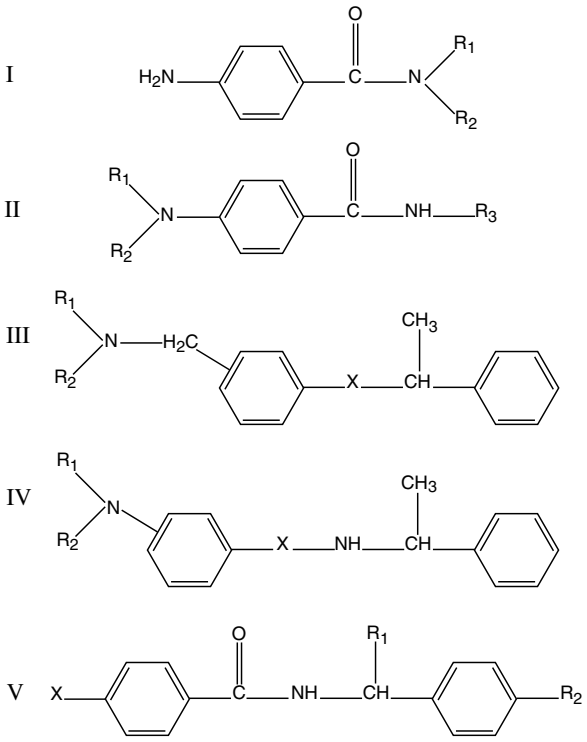

Figure 1. Basic structure of analogues.

succimide, Phenobarbital, primidone and clonazepam [16]. However, the anticonvulsant drugs presently used in clinical practice show a broad range of adverse effects. Consequently there is a strong need for development of potent anti-epileptic agents having greater specificity and fewer side effects.

In the present study, the relationship of *Wiener's index*- a distance based topological descriptor, Zagreb group parameter (an adjacency-based topological descriptor) and eccentric connectivity index (an adjacency-cum-distance-based topological descriptor) with the anticonvulsant activity of a series of substituted benazamides/ benzylamines has been investigated.

Methodology

Calculation of topological indices

The Wiener's index [17–20], a well-known distance-based topological index is defined as the sum of the distances between all the pairs of vertices in a hydrogen-suppressed molecular graph, that is

$$W = 1/2\left(\sum_{i=1}^{n} Pi\right) \tag{1}$$

where *Pi* is the length of the path that contains the least number of edges between vertex *i* and vertex *j* in graph G and *n* is the maximum possible number of *i* and *j*.

The Zagreb group parameter M_1 proposed by Gutman et al. [21–22] is defined as the sum of squares of degrees over all vertices and is represented by following equation:

$$M_1 = \sum_{i=1}^{n}\left(V_i^2\right) \tag{2}$$

where V_i is the degree of vertex i in a hydrogen-suppressed molecular structure. The vertex degree V_i for a vertex i is given as the sum of the entries in a row i of adjacency matrix.

The eccentric connectivity index [23] denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen-suppressed molecular graph having n vertices

$$\xi^c = \sum_{i=1}^{n}(E_i * V_i) \tag{3}$$

where V_i is the degree of the vertex i, E_i is the eccentricity of the vertex i and n is the number of vertices in graph G. The eccentricity E_i of a vertex i in a graph G is the path length from vertex i to vertex j that is farthest from i (E_i = max d*(ij)*; $j\varepsilon$G); The eccentric connectivity index takes into consideration the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

Model development analysis

A data set [24–25] comprising 41 benzamide and benzylamine analogues was selected for the present investigations. The basic structures for these analogues are depicted in Figure 1 and the various substituents are listed in Table 1. The data set comprised of 13 active and 28 inactive compounds. The values of Wiener's index, Zagreb group parameter and eccentric connectivity index were computed for each analogue using an in-house computer program and an active range was identified for each index. For the selection and evaluation of range-specific features, exclusive activity ranges were discovered from the information derived from the moving average of response level [26]. Subsequently, each analogue was assigned a biological

Table 1. Relationship of Wiener's index, Zagreb group parameter and eccentric connectivity index with anticonvulsant activity of substituted benzamides/benzylamines.

Comp. No.	Basic Structure	R_1	R_2	R_3	R_4	W	M_1	ξ^c	Activity Predicted			Activity Reported
									W	M_1	ξ^c	
1	I	H	H	–	–	120	46	88	–	–	–	–
2	I	CH_3	H	–	–	160	50	113	–	–	–	–
3	I	CH_2CH_3	H	–	–	211	54	140	+	+	+	+
4	I	$CH_2CH_2CH_3$	H	–	–	274	58	172	+	+	+	+
5	I	$CH_2CH_2CH_2CH_3$	H	–	–	350	62	206	+	+	+	+
6	I	$CH_2CH_2CH_2CH_2CH_3$	H	–	–	440	66	246	+	+	+	+
7	I	$CH_2CH_2CH_2CH_2CH_2CH_3$	H	–	–	545	70	288	+	+	±	+
8	I	Cyclohexyl	H	–	–	477	78	257	+	+	+	+
9	I	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	–	–	464	72	217	+	+	+	+
10	I	C_6H_5	H	–	–	477	78	257	+	+	+	+
11	I	$CH_2C_6H_5$	H	–	–	592	82	303	±	–	±	+
12	I	$CH(CH_3)$-C_6H_5	H	–	–	664	88	318	±	–	±	+
13	I	CH_2CH_2-C_6H_5	H	–	–	713	86	345	–	–	–	–
14	I	$CH(CH_3)CH_2$-C_6H_5	H	–	–	804	92	366	–	–	–	–
15	I	$CH_2CH(CH_3)$-C_6H_5	H	–	–	808	92	368	–	–	–	–
16	I	CH_2-C_6H_5	CH_3	–	–	661	88	316	±	–	±	+
17	I	CH(C6H5)2	H	–	–	1204	116	432	–	–	–	–
18	II	H	H	$CH(CH_3)$-C_6H_5	–	670	88	345	±	–	–	+
19	II	CH_3	H	$CH(CH_3)$-C_6H_5	–	786	92	360	–	–	–	–
20	II	CH_3	H	CH_2-C_6H_5	–	705	86	343	–	–	–	–
21	II	CH_3	CH_3	$CH(CH_3)$-C_6H_5	–	910	98	383	–	–	–	–
22	II	CH_3	CH_3	CH2-C_6H_5	–	820	92	366	–	–	–	–
23	II	CH_3	CH_3	C_6H_5	–	677	88	318	–	–	±	–
24	II	CH_3	CH_3	CH_2CH_2-C6H5	–	982	96	420	–	–	–	–
25	II	CH_3CO	H	$CH(CH_3)$-C_6H_5	–	1070	102	433	–	–	–	–
26	II	C_2H_5OCO	H	$CH(CH_3)$-C_6H_5	–	1368	110	521	–	–	–	–
27	II	$C_2H_5O_2CCO$	H	$CH(CH_3)$-C_6H_5	–	1070	102	433	–	–	–	–
28	III	CH_3	CH_3	–	CO	897	98	379	–	–	–	–
29	III	H	CH_3	–	CO	787	92	356	–	–	–	–
30	IV	H	H	–	CH_2	574	82	282	±	–	±	–
31	IV	H	H	–	CH_2	584	82	284	±	–	±	–
32	IV	H	H	–	CH_2	594	82	305	±	–	±	–
33	V	CH_3	H	–	H	560	82	278	±	–	±	–
34	V	CH_3	NH_2	–	H	664	88	318	±	–	±	–
35	V	C_2H_5	H	–	NH_2	761	87	325	–	–	–	–
36	V	C_3H_7	H	–	NH_2	870	91	344	–	–	–	–
37	V	C_4H_9	H	–	NH_2	992	100	375	–	–	–	–
38	V	CH_3	CH_3	–	NH_2	780	94	360	–	–	–	–
39	V	CH_3	OCH_3	–	NH_2	915	98	406	–	–	–	+
40	V	CH_3	Cl	–	NH_2	780	94	360	–	–	–	–
41	V	CH_3	F	–	NH_2	780	94	360	–	–	–	–

+, Positive anticonvulsant activity.
–, Negative anticonvulsant activity.
±, Transitional range where activity could not be specifically assigned.

Table 2. The relationship between anticonvulsant activity of substituted benzamides/benzylamines and Wiener's index.

Nature of range	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Lower inactive	<211	02	02	100
Active	211–545	08	08	100
Transitional	546–670	09	N.A.	N.A.
Upper inactive	>670	22	21	95.4

Table 3. The relationship between anticonvulsant activity of substituted benzamides/benzylamines and the Zagreb group parameter.

Nature of range	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Lower inactive	<54	02	02	100
Active	54–78	08	08	100
Upper inactive	>78	31	26	83.8

Table 4. The relationship between anticonvulsant activity of substituted benzamides/benzylamines and the eccentric connectivity index.

Nature of range	Index value	Number of analogues in the range	Number of analogues predicted correctly	Percent accuracy
Lower inactive	<140	02	02	100
Active	140–257	07	07	100
Transitional	258–318	10	N.A.	N.A.
Upper inactive	>318	22	20	90.9

activity which was then compared with the reported [24–25] anticonvulsant activity against MES seizures. Compounds with an activity denoted by ++++ or 4 and +++ or 3 were assumed to be active and those with an activity of ++ or 2 and + or 1 were assumed to be inactive for the purpose of the present study. Percent degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to that of total number of compounds present in the particular 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 active and inactive ranges. The results are summarized in Tables 1 to 4.

Results and discussion

Structure-activity studies have received considerable attention during the past two decades. There is one inherent problem with SAR that is not easily resolved. Most biological and physicochemical properties are quantitatively represented by a number but chemical structures cannot be similarly represented. However,

this problem can be easily overcome by resorting to graph-theoretical techniques for quantification of chemical structures. Suitable correlations can be subsequently developed between quantitative biological activity and quantified chemical structure.

Epileptic siezures vary widely intraindividually and interindividually with respect to magnitude, duration, and frequency of occurrence [24]. The anticonvulsant drugs presently used in clinical practice show a broad range of adverse effects. Consequently there is a strong need for development of potent antiepileptic agents having greater specificity but minimal side effects.

In the present studies, the relationship of Wiener's index, Zagreb group parameter and eccentric connectivity index with the anticonvulsant activity of a series of substituted benazamides/benzylamines has been investigated.

Retrofit analysis of the data in Tables 1 and 2 reveals the following information with regard to Wiener's index:

- A total of 31 out of 32 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 96.8% with regard to anticonvulsant activity.
- A transitional range with a range of 546–670 of Wiener's index values was observed indicating a gradual transition from active to inactive ranges and vice-versa. There were 4 active and 5 inactive compounds in the transitional range. Out of 4 active compounds in the transitional range, 2 compounds possessed ++++ activity.
- The active range had Wiener's index values of 211–545. 100% of the analogues in the active range exhibited anticonvulsant activity.
- In a data set comprising of 41 analogues only 13 analogues were active and out of these 08 were localized in the active range.

Retrofit analysis of the data in tables I and III reveals the following information with regard to the Zagreb group parameter:

- A total of 36 out of 41 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 87.8% with regard to anticonvulsant activity.
- The active range had Zagreb group parameter values of 54–78. 100% of the analogues in the active range exhibited anticonvulsant activity.
- In a data set comprising of 41 analogues only 13 analogues were active and out of these 8 were localized in the active range.
- The relatively low accuracy of prediction was due to the fact that no transitional range was observed and all the compounds were classified.

Retrofit analysis of the data in Tables 1 and 4 reveals the following information with regard to eccentric connectivity index:

- A total of 29 out of 31 compounds were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 93.5% with regard to anticonvulsant activity.
- A transitional range with a range of 258–318 of eccentric connectivity index values was observed indicating a gradual transition from active to inactive ranges and vice versa. There were 4 active and 6 inactive compounds in the transitional range. Out of 4 active compounds in the transitional range, 2 compounds possessed ++++ activity.
- The active range had eccentric connectivity index values of 140–257. 100% of the analogues in the active range exhibited anti-mycobacterial activity.
- In a data set comprising of 41 analogues only 13 analogues were active and out of these 7 were localized in the active range.

Further the active analogues were found to be present in a narrow range of Wiener's index, Zagreb group parameter and eccentric connectivity index values.

Investigations reveal excellent correlations of Wiener's index, Zagreb group parameter and eccentric connectivity index with anticonvulsant activity of substituted benzylamines/benzamides. The overall accuracy of prediction was found to be ∼97% in the case of Wiener's index, ∼88% in the case of Zagreb group parameter and ∼94% in the case of eccentric connectivity index. These correlations can easily provide a valuable lead for the development of an ideal anticonvulsant.

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