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COMMUNICATIONS

A pattern recognition study of acyclic ureide anticonvulsants

MAGED KHALIL, DONALD F. WEAVER*, *Department of Chemistry, and Division of Neurology,* Department of Medicine, Queen's University, Kingston, Canada*

Abstract—A pattern recognition structure-activity study employing topological, geometric and physicochemical descriptors was performed on 27 acyclic ureide anticonvulsants. Twelve numerical descriptors were used as variables in a discriminant function analysis which categorized the ureide analogues with respect to their bioactivity. The results from the discriminant function analysis were interpreted to support a model for antiepileptic activity.

The establishment of structure-activity relations (SAR) for anticonvulsant drugs has been complicated by the chemical diversity of the molecules and by the complexity of the physiological and biochemical processes that initiate and propagate seizure activity.

We have analysed a single class of compounds with known antiepileptic activity, the acyclic ureas (Table 1).

To investigate antiepileptic structure-activity relationships and to identify a simple molecular fragment fundamental for anticonvulsant activity, a pattern recognition SAR technique (Blankley 1983) has been used to evaluate these compounds.

Methods

General approach of the pattern recognition SAR technique. The data set consisted of ureides of known biological properties. A set of molecular descriptors was generated to describe each compound in the set and a statistical method was applied to the set to differentiate active from inactive cogeners. In this method, each analogue is represented by a point in the n-dimensional space defined by the n independent descriptor variables. The compounds of similar activity are assumed to cluster in the same general region of space and, if two clusters result, then these two clusters can be separated from each other by a linear surface. The discriminant function analysis was performed using the SPSSX package (SPSSX Inc. 1983).

Descriptor set. The set of descriptors used for the chosen class of compounds is listed in Table 1 and may be sub-classified as geometric, topological, physicochemical and ad hoc.

Geometric descriptors. These represent three-dimensional structural properties, reflecting aspects of molecular size. This study used a molecular volume geometric descriptor calculated using the volume fragment technique of Motoc & Marshall (1985).

Topological descriptors. Topological descriptors encode aspects of molecular connectivity. The topology of a molecule may be expressed as a function of the number of heavy atoms and their adjacency relationships or bonding. A 'graph' is used to represent this pattern of atoms and bonds (Kier & Hall 1976).

Correspondence to: D. F. Weaver, Department of Chemistry, Frost Wing. Queen's University, Kingston, Ontario, Canada K7L 3N6.

The notion that graphs may be analysed to yield information-rich indices was introduced by Wiener (1947). Subsequent contributions from Randic (1975), Balaban (1979) and Gutmann & Trinajstic (1972) have diversified such graph techniques. In this study, topological descriptors were derived from the Zagreb group indices, M1 and M2, and the molecular connectivity indices, ^0X, ^1X, ^2X, as described by Kier & Hall (1976).

Table 1. List of descriptors.

a	^0X	zero order connectivity index
b	^1X	first order connectivity index
c	3X	second order connectivity index
d	M1	first Zagreb index
e	M2	second Zagreb index
f	log P	
g	R/R2	ratio of substituent volumes
h		total of number of atoms
i		number of carbon atoms
j		total number of bonds
k		number of single bonds
l		number of double bonds

Physicochemical descriptors. Hansch & Fujita (1964) have illustrated the importance of physicochemical parameters in SAR studies. In particular, the partition coefficient, log P, which describes molecular lipophilicity is central in assessing drug transport and in interpreting the pharmacological mode of action at the molecular level. The physicochemical descriptors in this study were determined by the Medchem CLOGP computerized calculation (supplied by a referee).

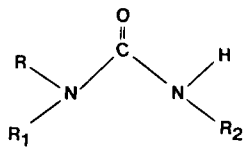
Ad hoc descriptors. These are simply atom and bond descriptors (Seybold et al 1987). The most direct descriptor is the total number of atoms in the structure. This parameter is a measure of gross molecular bulk. Another similar parameter is the total number of bonds in the structure. Hence, ad hoc descriptors may be regarded as simplified topological indices.

Data set. A literature review provided data on biological activity against electro-shock induced seizures for 27 uniformly tested analogues. These 27 analogues constituted the data set (see Table 2).

Results

The discriminant function analysis results are presented in Table 3. The coefficients define the linear surface separating the cluster of active from the cluster of inactive anticonvulsant ureides. The most important coefficients are those of the topological indices (^0X and ^2X: a and c), the ad hoc index (number of single bonds: k), and the physicochemical value (log P:f). The coefficient of variable 'l', (the number of double bonds) does not appear in this

Table 2. Data set.



Compound	R	R1	R2
1	$(C_2H_5)_2CHCH_2$	H	H
2	C_6H_5	CH_3CH_2	H
3	$C_6H_5CH_2$	H	H
4	$C_6H_5CH_2CH_2$	H	H
5	C_6H_5	H	H
6	t-C_5H_{11}	H	H
7	$(C_6H_5)_2CH$	H	H
8	t-C_4H_9	H	H
9	sec-C_4H_9	H	H
10	n-C_3H_7	H	n-C_3H_7
11	i-C_4H_9	H	H
12	cyclo-C_6H_{11}	H	H
13	C_2H_5	C_2H_5	H
14	$C_6H_5CH_2$	$C_6H_5CH_2$	H
15	$C_6H_5CH(CH_3)$	H	H
16	$C_6H_5C(CH_3)_2$	H	H
17	n-$C_3H_7CH(CH_3)$	H	H
18	$(CH_3)_2CHCH_2CH(CH_3)$	H	H
19	n-C_7H_{15}	CH_3	H
20	n-C_4H_9	n-C_4H_9	H
21	i-C_4H_9	i-C_4H_9	H
22	C_6H_5	C_6H_5	H
23	$(C_6H_5)_2CH$	H	$(C_6H_5)_2CH$
24	$C_6H_5CH_2(CH_3)$	H	H
25	$C_6H_5C(CH_3)_2CH_2$	H	H
26	fluorenyl	H	H
27	$(C_6H_5)_2CHCH_2$	H	H

Table 3. Some statistics of the analysis.

Coefficients:		Correlations within groups:	
a	2·523366	g	0·33607
b	0·008365	l	−0·23062
c	−2·114711	c	−0·22776
d	−0·058349	h	−0·22661
e	−0·067579	a	−0·18492
f	1·448243	j	−0·12199
g	0·203062	f	−0·11688
h	−0·083018	k	0·09434
i	−1·196210	d	−0·05500
j	−0·062175	i	−0·04629
k	2·722517	b	−0·03699
		e	−0·01377
Prior probabilities:		Discriminant functions evaluated at group centriods:	
group prior active:	0·48148	active	1·13013
inactive	0·51852	inactive	−1·04941

table since it failed the default tolerance level of 0·001. More importantly, the variables are ordered in Table 3 according to their correlation within the cluster. The most highly correlated descriptor is the R/R2 volume ratio (g), which is an indication of the steric influence of the ureide substituents.

The acceptability of the derived discriminant function was tested on the original data. Twelve of the 13 active analogues and 12 of the 14 inactive analogues were classified correctly. These results indicate an 89% rate of correct classification.

Discussion

The acyclic ureides were the first group of anticonvulsant substances to depart from the heterocyclic structures (imidazolidinediones, oxazolidinediones) which dominated antiepileptic therapy before 1945. After extensive studies, phenylacetylurea, 2-phenylbutyrylurea, and 1-acetyl-3-(2-phenylbutyryl) urea were used in the clinical management of epileptic patients. However, early enthusiasm for their effectiveness was marred by reports of hepatotoxicity, nephrotoxicity, aplastic anaemia and death (Forster & Frankel 1949; Levy et al 1950; Tyler & King 1951). Those toxicological problems limited their clinical use. Nevertheless, the antiepileptic ureas exhibit a broad spectrum of anticonvulsant activity in experimental animal models and, because of their unique, yet simple, acyclic structure, they are of interest in understanding anticonvulsant structure-activity relations.

The pattern recognition SAR evaluation reported in this study has revealed the ability of geometric, topological and physicochemical descriptors to predict linear ureide activity against electroshock induced seizures, with a success rate of 89%.

As a corollary to this discriminant function analysis, it is also possible to propose a bioactive molecular fragment involved in anticonvulsant activity. The high correlation of the R/R2 volume ratios in each cluster indicates a shape restriction for ureide antiepileptic bioactivity. One end of the ureide analogue must bear a bulky substituent; the high correlation of the second order topological index and the importance of the physicochemical log P value to the discriminant function indicate that this bulky substituent should be both branched and lipophilic. The other end of the ureide analogue must be sterically unencumbered. Thus the antiepileptic bioactive fragment consists of an amide moiety, with both hydrogens sterically unrestricted, bonded via the carbonyl carbon through the remaining ureide nitrogen atom to a large, preferably aromatic, lipophilic group(s). This bioactive fragment is similar to that described for imidazolidinedione (phenytoin) and iminostilbene (carbamazepine) anticonvulsants as described by Jones et al (1981) and Codding et al (1984).

Invoking complementarity, it is possible to formulate a simple, putative model of the ureide anticonvulsant receptor site—a macromolecular structure with the capacity to bind the antiepileptic bioactive molecular fragment stereospecifically. Although the analogues evaluated in this study possessed lipophilic *R*-substituents, compounds devoid of such substituents are biologically inactive (Spielman et al 1961). Accordingly, the model of the putative receptor site consists of a large lipophilic pocket capable of interacting with hydrophobic substituents and a nearby hydrogen bonding surface capable of anchoring the terminal amide portion of the ureide anticonvulsant (Fig. 1). An unhindered interaction between the hydrogen bonding surface and the unencumbered amide portion appears to be crucial for biological efficacy.

Pharmacological investigations have revealed that both acyclic ureide anticonvulsants and cyclic ureide anticonvulsants abolish the tonic component of electroshock seizures, inhibit the violent phase of maximal electroshock seizures, obtund the seizures induced by intracerebral ouabain administration, display local anaesthetic properties and fail to prevent seizures induced by netrazol infusion (Orloff et al 1951; Everett & Richards 1952; Peters & Vonderahe 1953; Davidson et al 1978). These similarities suggest that antiepileptic acyclic ureas may function in a process analogous to the antiepileptic mechanism of cyclic ureides, such as phenytoin. Thus it is interesting that the SAR results of this study are in agreement with SAR studies for cyclic ureides by Jones et al (1981) and Codding et al (1984).

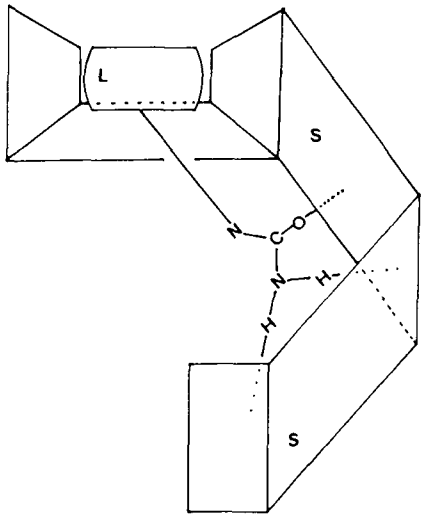


Fig. 1. Schematic representation of receptor site. (L = lipophilic substituent, S = hydrogen bonding surface).

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