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Ureylene anticonvulsants and related compounds

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The results from a previous study led to the postulate that a number of aryl semicarbazones displaying anticonvulsant activity in the maximal electroshock (MES) screen interacted at both a hydrophobic and a hydrogen bonding areas on a specific binding site. These two parts of the binding site may be referred to as areas A and B, respectively. In order to circumvent the possible problems of the carbimino group in semicarbazones, such as toxicity and acid lability, some related ureylenes were considered. Initial evidence suggested that a second lipophilic group in the molecule was advantageous; this group may interact at area C on the proposed binding site. Most of the compounds prepared with a view to interacting at areas A, B and C showed protection in mice against MES induced siezures. Of particular interest were the compounds **1d, j** which contained an α-methylbenzyl group attached to the N1 atom of the ureylenes which afforded good protection in the MES screen. The areas A and C at which lipophilic moieties were considered to interact were capable of accommodating groups of different sizes as measured by their solvent accessible surface areas. A number of compounds were active when given orally to rats and devoid of neurotoxicity at the doses utilized. Several compounds including **1d, f, j, 2d** are useful prototypic molecules for subsequent development of further novel anticonvulsants.

1. Introduction

Previous studies from this laboratory have revealed the significant anticonvulsant activity of a variety of aryl semicarbazones [1, 2]. After intraperitoneal injection in mice, many of these compounds displayed activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens. These rodent models are widely used as standard methods for predicting protection against generalized tonic-clonic and generalized absence seizures in humans [3–5]. Neurotoxicity (NT) was often detected after ip injection in mice using the rotorod procedure [6]. In this test, the inability of mice to remain on a rotating rod (6 rpm) for one minute in three separate trials indicated NT. However, after oral administration of the compounds to rats, the MES activity increased while protection in the scPTZ screen as well as evidence of neurotoxicity were virtually abolished at the doses employed. Furthermore NT, determined by observing ataxia and abnormal gait and stance of the rats, was reduced considerably compared to the NT data obtained from ip injection in mice. A binding site hypothesis was proposed to account for the way in which these compounds elicited anti-MES activity whereby the aryl ring and the semicarbazono group ($H_2NCONHN=$) were considered to interact at both an aryl binding site and a hydrogen bonding area, respectively [7]. These locations are designated as A and B in the Fig.

There are two potential problems with the presence of a carbimino group (C=N) in semicarbazones. First, the possibility exists of attack by cellular nucleophiles on the electron-deficient carbimino carbon atom leading to unwanted toxicity. Second, the carbimino group is labile especially under acidic conditions [8]. Thus the preparation of compounds which are structurally related to aryl semicarbazones was considered in which the aryl ring was retained but excision of the carbimino portion of the semicarbazono group was planned leading principally to the related ureylene analogues.

An initial investigation revealed that phenylurea **1a** displayed activity in the murine intraperitoneal (ip) MES screen indicating that alignment at sites A and B is likely taking place. Furthermore the addition of a lipophilic group on the N3 atom led to **1b** which afforded protection in the MES screen after both 0.5 and 4 h in contrast to **1a** which only displayed activity at the end of 0.5 h. This prolongation of activity, which could be a clinically useful attribute, dictated that a lipophilic alkyl or aryl group would be placed on the N3 atom of the compounds prepared in this study. It is conceivable that the N3 group interacts with a second hydrophobic binding site C as indicated in the Fig. The binding site is presumed to be located in the brain since it is in this organ of the body that sudden and excessive electrical activity occurs in epileptics [9].

The design of the ureas **1** was made with a view to evaluating the theory that these compounds would interact at positions A and B of the binding site and possibly at C as well. This hypothesis was examined systematically by varying the nature of the R^1 and R^2 groups in series **1** with particular reference to the size of these substituents. In the first cluster of compounds, in which a n-propyl group was placed on the N3 atom, the spacer groups between the aryl ring and the ureylene group were composed of one (**1c**, **d**), two (**1e**, **g**) or three (**1f**) atoms. Second, compound **1h** is a nor analogue of **1g** and was prepared in order to compare its bioactivity with both **1g** and **1m**. Third, a phenyl substituent was present on the N3 atom in **1i**–**m** and the R^1 group in these compounds was the same as found in **1c**–**g**, respectively. Fourth, compounds **1n**, **o** were designed with a view to discerning

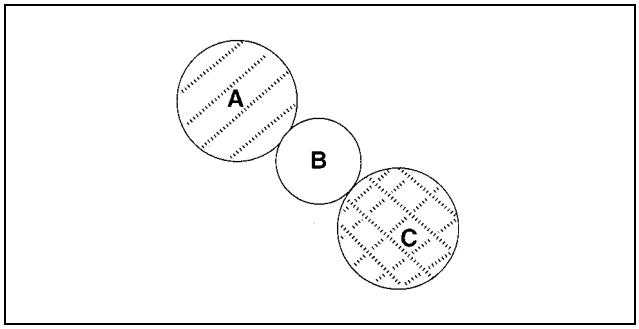
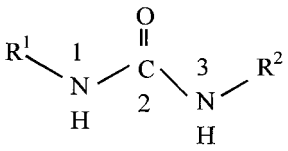
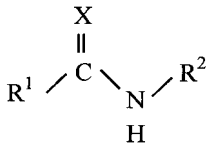


Fig: Proposed binding site of ureylene anticonvulsants. The locations A and C are considered to be hydrophobic binding areas and B is the hydrogen bonding site.



1

1	R^1	R^2
a	C_6H_5	H
b	C_6H_5	$(CH_2)_2CH_3$
c	$C_6H_5CH_2$	$(CH_2)_2CH_3$
d	$C_6H_5CH(CH_3)$	$(CH_2)_2CH_3$
e	$C_6H_5(CH_2)_2$	$(CH_2)_2CH_3$
f	$C_6H_5(CH_2)_3$	$(CH_2)_2CH_3$
g	C_6H_5CONH	$(CH_2)_2CH_3$
h	C_6H_5CONH	C_2H_5
i	$C_6H_5CH_2$	C_6H_5
j	$C_6H_5CH(CH_3)$	C_6H_5
k	$C_6H_5(CH_2)_2$	C_6H_5
l	$C_6H_5(CH_2)_3$	C_6H_5
m	C_6H_5CONH	C_6H_5
n	$CH_3(CH_2)_4$	$(CH_2)_2CH_3$
o	$CH_3(CH_2)_5$	$(CH_2)_2CH_3$



2

2	R^1	R^2	X
a	$C_6H_5(CH_2)_2$ NH	$(CH_2)_2CH_3$	S
b	$C_6H_5(CH_2)_2NH$	C_6H_5	S
c	$C_6H_5(CH_2)_2O$	C_6H_5	O
d	$C_6H_5CH{=}NO$	C_6H_5	O

whether the R^1 groups bereft of an aryl ring could interact at A leading to retention of anticonvulsant activity. Fifth, the preparation of the bioisosteres of various compounds in series **1** was considered. Thus replacement of the oxygen atom of **1e**, **k** by sulphur leading to **2a**, **b**, respectively, was proposed while changing the N1H group of **1k** by oxygen would give rise to **2c**. Finally, substitution of the three-atom spacer between the phenyl ring and the carbonyl carbon atom of **1k** by a more hydrophilic three-atom group leading to **2d** may shed some light on the nature of area B of the binding site.

In summary therefore the objectives of the present investigation were to synthesize the compounds **1a**–**n**, **2a**–**d** for evaluation as candidate anticonvulsants with a view to gaining an insight into the viability of the proposed binding site for these compounds and also to develop structure-activity relationships (SAR).

2. Investigations, results and discussion

The ureas and thioureas were prepared from the appropriate primary amine and *n*-propylisocyanate (**1b**–**g**, **n**, **o**), ethylisocyanate (**1h**), phenylisocyanate (**1i**–**m**), *n*-propylisothiocyanate (**2a**) or phenylisothiocyanate (**2b**). Acylation of 2-phenylethanol and benzaldehyde oxime with phenylisocyanate led to the formation of **2c** and **2d**, respectively.

The compounds in series **1** and **2** were evaluated initially in the mouse intraperitoneal MES, scPTZ and NT screens using doses of 30, 100 and 300 mg/kg; these data are presented in Table 1. The following general observations may

Table 1: Evaluation of compounds 1 and 2 in the mouse intraperitoneal MES, scPTZ and NT screens[a]

Compd.	MES screen			scPTZ screen			NT screen		
	0.5 h	4 h	PS[b]	0.5 h	4 h	PS[b]	0.5 h	4 h	TS[b]
1a	100	–	3	300	–	1	300	–	1
1b	100	100	3	–	–	–	–[c]	–[c]	1
1c	100	–	3	300	–	1	300	–	1
1d	30	–	10	300	–	1	300	–	1
1e	300	–	1	300	–	1	300	–	1
1f	100	300	3	–	–	–	300	–	1
1g	300	–	1	–	–	–	–	–	–
1h	–	300	1	–	–	–	–	300	1
1i	–	–	–	–	–	–	–	–	–
1j	300	30	10	300	300	1	–	–	–
1k	–	–	–	–	–	–	–	–	–
1l	30	–	10	–	–	–	–	–	–
1m	–	300	1	–	–	–	–	–	–
1n	–[d]	–	–	300[e]	–	1	300[f]	–	1
1o	300	–	1	–	–	–	300	–	1
2a	100	300	3	100	300	3	300	300	1
2b	–	300	1	–	300	1	–	300	1
2c	300	–	1	–	–	–	–	–	–
2d	30	–	10	–	–	–	–	–	–
Phenytoin	30	30	10	–	–	–	100	100	3
Carbamazepine	30	100	10	100	300	3	100	300	3
Valproic acid	–	–	–	300	–	1	–	–	–

[a] Doses of 30, 100 and 300 mg/kg of the compounds were administered and the protection and neurotoxicity measured after 0.5 and 4 h. The figures indicate the minimal dose required to cause protection and neurotoxicity in 50% or more of the animals. The symbol – indicates the absence of anticonvulsant activity or neurotoxicity.
[b] The letters PS and TS refer to protection score and toxicity score, respectively; these terms are explained in the text.
[c] Compound evaluated at 30 and 100 mg/kg only since a 300 mg dose proved fatal within 0.5 h.
[d] Of two animals receiving 300 mg/kg of **1n**, one died at the end of 0.5 h while the other mouse was not protected at the end of 4 h.
[e] Of two animals receiving 100 mg/kg of **1n**, one died following continuous seizure activity at the end of 0.5 h while the other mouse was not protected at the end of 4 h.
[f] One of four animals died in the NT screen at a dose of 300 mg/kg after 0.5 h.

be made. First, 84%, of the compounds **1a**–**o**, **2a**–**d** afforded protection in the MES screen in contrast to 37% which were active in the scPTZ test. In order to express the MES-selectivity quantitatively, a protection score (PS) was assigned to each compound based on the allocation of 10, 3 and 1 points for compounds active at 30, 100 and 300 mg/kg, respectively. The average PS values for **1a**–**o**, **2a**–**d** in the MES and scPTZ tests were 3.26 and 0.53, respectively, reflecting a sixfold difference in activity between the two screens. These data re-emphasize the MES-selectivity displayed by the compounds in series **1** and **2**. Subsequent comments will be directed principally to the results in the MES test. Second, neurotoxicity was demonstrated in more than half of the compounds but only at the maximum dose utilized namely 300 mg/kg. The average toxicity score (TS), calculated in the same way as the PS figures, was 0.58 which compared favourably with phenytoin and carbamazepine with a figure of 3.

The assumption was made that the ureas and related compounds would align at the binding site in such a way that the larger hydrophobic group would interact at area A while the smaller group would form van der Waals bonding at the area C. In order to gain some insight into the optimum sizes of the groups interacting at the areas A, B and C on the putative binding site, the shapes of the R^1 and R^2 groups in series **1** and **2** were considered. Various physicochemical constants are available which reflect the topological properties of different substituents and in the present investigation, solvent accessible surface area (SASA) measurements [10] were used since the data generated would provide a measure of the area of the particular group which can interact at a binding site. Statistical analyses between anticonvulsant activity and physicochemical constants used the test for zero correlation [11]. Linear and logarithmic plots were constructed between the PS values and the SASA figures of the R^1 substituents in both the *n*-propyl series (**1b**–**g**) and phenyl analogues (**1i**–**m**). No correlations were noted ($p > 0.1$). One may therefore conclude that area A is capable of accommodating groups of varying sizes. However the branched chain compounds **1d** and **1j** both had PS values of 10 suggesting that an additional hydrophobic area (possible a specific methyl site) may be present on or adjacent to the area A. The average PS figure for the *n*-propyl ureas which contain an aryl ring in the R^1 group namely **1b**–**g** was 3.5 which compared favourably with the average PS value of 0.5 for **1n, o**. The average SASA figures for **1b**–**g** and **1n, o** were 236.2 and 235.7, respectively, which is further evidence that the sizes of the R^1 groups do not influence anticonvulsant activity. However π bonding is possible only with **1b**–**g** which may contribute to their greater bioactivity than **1n**, **o**.

A further question posed was whether differences in the anti-MES activity were explicable in terms of variation in the rate and extent of transportation to a binding site. Thus linear and semilogarithmic plots were made between the PS values of both **1b**–**g** and also **1i**–**m** with the fragment constants (f) of the R^1 substituents in these compounds. No correlations were observed ($p > 0.1$) and hence differences in bioactivity are likely due to the extent of interactions at a binding site.

Several of the compounds were prepared in order to glean some idea of the structural requirements for interaction at the hydrogen bonding area B. Insertion of an amidic group (CONH) between the aryl ring and N1H group of **1b** led to **1g** which was accompanied by a reduction in anticonvulsant activity suggesting that this molecular modification was disadvantageous. The analogues of **1g** namely **1h**, **m** had the same potency as **1g**. On the other hand replacement of the N1H group of **1k** and **1i** by oxygen and iminooxy functions (=NO) producing **2c** and **2d**, respectively, led to increases in activity. It is therefore conceivable that a linear group of up to four atoms capable of hydrogen bond formation is accommodated at area B of the binding site. However when five atoms compose the linker group between the two hydrophobic groups of the molecule (as in **1g**, **h**, **m**), the spacer portion of the molecules may overlap with part of the hydrophobic areas A and C adversely affecting alignment of the molecule at the binding site. In addition, **2a**, **b** were more active than the isosteres **1e**, **k** suggesting that future development of these compounds should include formation of thioureas. The significant potency of **2d** is noteworthy suggesting that arylcarbamoyl esters of oximes may be a fruitful avenue to pursue in the quest for novel anticonvulsants.

The effects of varying the R^2 group in series **1** was considered i.e. comparisons of anticonvulsant potencies were made when the R^1-ureylene group was constant. First, changing the R^2 group from ethyl (**1h**) to *n*-propyl (**1g**) or phenyl (**1m**) did not lead to changes in the PS score suggesting that area C was capable of accommodating groups of different surface areas. Second, the average PS value in the MES screen of the *n*-propyl ureas **1c**–**g** was 3.6 which was similar to the figure of 4.2 obtained for the phenyl analogues **1i**–**m**. These data support the contention that there is significant tolerance for the size of the groups at area C.

Various compounds with differing PS values in the murine intraperitoneal MES screen were administered orally to rats and evaluated for protection in the MES test. These data are summarized in Table 2. At the dosage employed, namely 30 mg/kg, no neurotoxicity was displayed by these compounds. In general, the data obtained were similar to the results noted in the murine intraperitoneal MES screen. First, linear and semilogarithmic plots of both the SASA and f values of the R^1 substituents of **1b**, **c**, **d**, **f**, **o** with the maximum number of animals protected did not reveal any correlations ($p > 0.1$). This observation reinforced the hypothesis that there is tolerance of both the size of the groups interacting at area A on the binding site as well as the hydrophobicity of the R^1 substituents. Second, branching of the R^1 groups of **1d**, **j** led to compounds with good activity thus providing further evidence for a specific methyl site near area A. Third, complete

Table 2: Protection afforded by various ureylenes and related compounds in the MES screen after oral administration to rats[a]

Compd.	Number of rats protected out of four (time in hours)
1a	–
1b	1 (0.25)
1c	1 (0.25, 0.5)
1d	3 (0.5, 1), 2 (0.25)
1f	4 (4), 1 (0.5, 1, 2)
1h	2 (4), 1 (0.25, 0.5, 2)
1j	3 (1, 4), 2 (2)
1l	–
1o	1 (4)
2a	2 (0.25), 1 (0.5)
2d	3 (0.25)
Phenytoin	4 (0.5), 3 (1, 2, 4), 1 (0.25)

[a] A dose of 30 mg/kg was employed and the animals were observed at the end of 0.25,0.5, 1, 2 and 4 h. The symbol – indicates the absence of anticonvulsant activity at all time periods.

protection was provided by **1f** which, coupled to its lack of NT, revealed it to be a useful lead molecule. Fourth, replacement of one of the protons attached to the N3 atom of the orally inactive urea **1a** by a n-propyl group leading to **1b** produced a compound which afforded protection in 25% of the animals. This observation is suggestive of the need for hydrophobic group attached to the N3 atom which interacts at area C. Fifth, the excellent protection of **2d** in the murine ip MES screen was also noted in the rat oral MES test thus affording further evidence that it is indeed a useful prototypic molecule. On the other hand, two observations differed from the results obtained from the murine ip MES screen. Compound **1h** contains a linear chain of five atoms capable of interaction at site B and its oral activity is therefore somewhat greater than expected. In addition **1l**, with a PS value of 10 in the mouse test and structurally related to **1f** (4/4 animals protected in the rat oral MES screen), was inactive at the dose employed when given orally to rats.

Finally if the compounds prepared in this study exerted their activity by a similar mechanism as the established antiepileptic drug phenytoin, the extent of its possible interaction at the putative binding site was considered to be of interest. A comparison was made therefore between the shapes of phenytoin and **1d** since the data in Tables 1 and 2 revealed that both compounds had similar bioactivity. Molecular modeling revealed that when one of the phenyl rings of phenytoin and the aryl ring of **1d** were overlapped, both compounds would interact at sites A and B while only **1d** aligned at area C. This observation suggested the greater importance for anticonvulsants to interact at the binding site at areas A and B than C.

In conclusion this study has evaluated the theory that the anti-MES activity of a series of ureylene derivatives was mediated by interaction at a binding side consisting of two or possibly three contiguous areas. This theory appears to be valid insofar as the majority of the compounds prepared afforded protection in the MES screen. Of considerable interest are the ureylenes with an α-methylbenzyl group on the N1 atom **1d**, **j** which displayed noteworthy activity in both the murine ip and rat oral MES screens. In addition, **1f** gave complete protection when given orally to rats. Hence these three compounds in particular serve as prototypic molecules for subsequent molecular modification in the search for novel anticonvulsants.

3. Experimental

3.1. General procedures for synthesis and spectroscopy

M.p.'s are uncorrected. Compounds **1b**, **h**–**m**, **o**, **2b**, **d** had m.p.'s in accord with literature values. Elemental analyses (C, H, N) were undertaken by Mr. K. Thoms, Department of Chemistry, University of Saskatchewan on **1b**–**o**, **2a**–**d** and were within 0.4% of the calculated values. TLC revealed one spot using silica gel sheets and a solvent system of $CHCl_3$:CH_3OH (7:3). ^{1}H NMR spectra were recorded using a Bruker AMX 500 FT (500 MHz) spectrometer.

*3.1.1. Synthesis of series **1***

Phenylurea **1a** was obtained from a commercial source and recrystallized from C_2H_5OH (95%). The synthesis of a representative compound **1b** was as follows. A solution of *n*-propylisocyanate (0.01 mol) in $(C_2H_5)_2O$ (25 ml) was added dropwise over a period of 0.5 h to a solution of aniline (0.01 mol) in $(C_2H_5)_2O$ (25 ml) at 0 °C. The mixture was then stirred at room temperature for 5 h and the precipitate was collected, washed thoroughly with $(C_2H_5)_2O$ and dried. Compounds **1c**–**f**, n, **o** were prepared in a similar manner from the appropriate amine and n-propylisocyanate while **1i**–**l** were synthesized from various amines and phenylisocyanate. The benzoylaminoureas **1g**, **h**, **m** were prepared by a similar procedure from benzoylhydrazine (dissolved in 25 ml of tetrahydrofuram not $(C_2H_5)_2O$) and *n*-propylisocyanate (**1g**), ethylisocyanate (**1h**) and phenylisocyanate (**1m**). The compounds obtained from the reaction mixture were pure except for **1h** and **1m** which were recrystallized from $CH_3CH(OH)CH_3$ and CH_3OH, respectively. The m.p.'s and percentage yields of the compounds in series **1** were as follows: **1b**: 110–112 °C, 74; **1c**: 84–85 °C, 95; **1d**: 67–69 °C, 70; **1e**: 75–77 °C, 85; **1f**: 33–35 °C, 90; **1g**: 165–167 °C, 93; **1h**: 173–174 °C, 81; **1i**: 167–168 °C, 93; **1j**: 146–148° °C 90; **1k**: 146–148 °C, 92; **1l**: 86–88 °C, 78; **1m**: 210–212 °C, 95; **1n**: 54–56 °C, 95; **1o**: 50–52 °C, 97. The ^{1}H NMR spectrum of a representative compound **1d** was as follows: δ ($CDCl_3$): 0.78 (t, $CH_2\underline{CH_3}$), 1.38 (m, $C\underline{H_2}CH_3$), 1.42 (d, $C\underline{H_3}CH$), 3.04 (m, $NHC\underline{H_2}$), 4.74 (q, $CH_3C\underline{H}$), 7.27 (m, aryl H).

*3.1.2. Synthesis of series **2***

A solution of *n*-propylisothiocyanate (0.01 mol) in $(C_2H_5)_2O$ (25 ml) was added dropwise to a solution of 2-phenylethylamine (0.01 mol) in $(C_2H_5)_2O$ (25 ml) over a period of 0.5 h at 0 °C. The mixture was stirred at room temperature for 5 h and the precipitate was collected, washed thoroughly with $(C_2H_5)_2O$ and dried to give **2a**.

Compound **2b** was prepared in a similar manner from the same amine and phenylisothiocyanate. This procedure was also employed in the synthesis of **2c** using 2-phenylethanol and phenylisocyanate. The acyloxime **2d** was prepared as follows. A solution of hydroxylamine hydrochloride (0.011 mol) and sodium acetate (0.015 mol) in H_2O (10 ml) was added to a solution of benzaldehyde (0.01 mol) in C_2H_5OH (95%, 25ml). The mixture was heated under reflux for 4 h and on cooling, the solvent was removed and the residue recrystallized from ethanol (50%) to give benzaldehyde oxime, m.p. 32–34 °C (lit: [12] m.p. 35 °C dec.) in 81% yield. Acylation of this oxime with phenylisocyanate using the procedure for preparing **2a** led to the formation of **2d**. The compounds obtained from the reaction mixture were pure except that **2d** was recrystallized from C_2H_5OH (50%). The m.p.'s and percentage yields of the compounds in series **2** were as follows: **2a**: 77–78 °C, 88; **2b**: 103–105 °C, 74; **2c**: 73–75 °C, 75; **2d**: 130–132 °C, 41. The ^{1}H NMR spectrum of a representative compound **2b** was as follows: δ($CDCl_3$): 2.90 (t, $C\underline{H_2}NH$), 3.88 (t, $C_6H_5C\underline{H_2}$), 5.96 (s, NH), 7.14 (m, aryl H), 7.68 (s, NH).

3.2. Determination of solvent accessible surface areas and fragment constants

The SASA values were obtained using a MacroModel Version 4.5 programme [10, 13]. The fragment constants for most of the substituents were taken from the literature [14]. The *f* values for the α-methylbenzyl, 2-phenylethyl and 3-phenylethyl groups were calculated using f_H, f_C and $f_{C_6H_5}$ figures of 0.23, 0.20 and 1.90, respectively, and a bond factor (F_b) of −0.12 applied n − 1 times where n is the number of bonds. The fragment constant for the n-hexyl group was calculated in the same way. In addition a chain branch factor (F_{cBr}) of −0.13 was applied once in the case of the α-methylbenzyl group [15]. The respective solvent accessible surface areas (Å^2) and fragment constants used in the correlation analyses are as follows: H: 23.5, 0.23; C_6H_5: 190.4, 1.90; $C_6H_5CH_2$: 222.2, 2.44; $C_6H_5CH(CH_3)$: 236.5, 2.85; $C_6H_5(CH_2)_2$: 249.8, 2.98; $C_6H_5(CH_2)_3$: 281.1, 3.52; C_6H_5CONH: 236.9, −0.03; CH_3CH_2: 1.27, 1.43; $CH_3(CH_2)_2$: 158.6, 1.97; $CH_3(CH_2)_4$: 220.8, 3.10 and $CH_3(CH_2)_5$: 250.6, 3.59.

3.3. Molecular modeling

The structures of **1d** and phenytoin were built and optimised using the MM^+ molecular mechanics module with the Polak-Ribiere algorithm (conjugate gradient) of the HyperChem molecular modeling programme [16]. Molecules were considered to be minimized when there was a difference of energy of 0.01 kcal/mol between two cycles. The optimised structures were then superimposed.

3.4. Anticonvulsant evaluations

The anticonvulsant evaluations were undertaken by the National Institute of Neurological Disorders and Stroke, NIH, USA according to their protocols [17] using male albino CF No. 1 mice (18–25 g) and male albino Sprague-Dawley rats (100–150 g).There was free access to food and water except during the actual testing procedure. All tests were performed using either male Carworth No. 1 mice via ip injection and/or Sprague Dawley rats per os. Dosing, routes of administration and screening times were the same for each compound evaluated. In the murine screen, doses of 30, 100 and 300 mg/kg of each compounds were injected intraperitoneally and the animals were examined at the end of 0.5 and 4 h. A dose of 300 mg/kg of **2a** evoked severe tremors after 4h in the scPTZ test. Oral administration of various compounds to rats was undertaken using a dose of 30 mg/kg and the animals were examined in the MES and NT screens after 0.25, 0.5, 1, 2 and 4 h.

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