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Design, synthesis, and anticonvulsant activity of some sulfamides

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Abstract—As part of our search for potential anticonvulsant agents, a set of compounds were designed, synthesized, and evaluated against MES and PTZ tests. Bioisosteric functional group information was used to design a new functionality, sulfamides, that complies with the requirements of the pharmacophore previously defined. Some of the molecules showed a promising anticonvulsant profile as selective anti-MES drugs, being active at low concentrations (30 mg/kg). The biological data were confirmed in Phase II of the Anticonvulsant Drug Development Program of the National Institute of Health.

1. Introduction

Epilepsy is not a specific disease, but a syndrome originated by different cerebral disorders of the central nervous system.[1] It is characterized by excessive discharges of large number of neurons, that alter the brain's normal electrochemical balance.[2]

Epileptic episodes are called seizures and have different manifestations, ranging from brief lapses of lack of attention to limited motor, sensory, or psychological changes. In severe cases they include prolonged losses of consciousness with convulsive motor activity.[3]

Researchers have concentrated their actions in developing therapies to control and prevent these seizures, mainly with the use of medications. However, several epileptic episodes cannot be controlled by currently available antiepileptic drugs (AED), since 25% of patients continue to have epileptic episodes despite optimal therapy. Moreover, AED treatment is usually necessary for several years and side effects may appear. Some of them are detected immediately after drug exposure[4] and others are reversible by means of reduction of the dose. However, chronic side effects appear only after extended periods of treatment, and most of them are not dose-related.[5,6]

The necessity for novel compounds with high potency and specificity, as well as low toxicity, is also evidenced by inspection of the marketed AED. Classical AED are not ideal, and they present significant side effects in some cases.[7–9] Recently, second generation AED were introduced, but their efficacy is similar to classical AED and they also have considerable adverse effects in several cases.[8,9]

The mechanism of action of AED is not always related with a specific binding site, and most of the drugs interact with more than one receptor. For that reason, it is difficult to define a rigorous classification of AED according to their mode of action. However, some of the cellular mechanisms involved are: potentiation of GABA-ergic transmission,[10] blockade of voltage gated sodium channel (VGSC),[11] attenuation of excitatory neurotransmission,[11–13] and/or modulation of voltage-sensitive calcium channels.[14]

Two main strategies have been employed to design new AED: the search of new compounds that cause a modification of a certain stage of the cellular mechanism (mechanism-based design) and the optimization of pre-existing compounds (structure-based design). Some of the new generation AED have been developed following these approaches.[15–17] Additionally, the use of new animal models of epilepsy (genetic or kindled models) has demonstrated the efficacy and safety of a new compound, levetiracetam, which presents a new mechanism of action.[15]

However, among the experimental models developed to evaluate the anticonvulsant activity, conventional acute

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seizure models are the most widely used. The maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (PTZ) test are the most popular.[18] Related to the biological target, AED that have a good response to VGSC are active in MES test. Additionally, it is accepted that active drugs against the MES test and inactive against PTZ test present a pharmacological profile analogous to phenytoin (PHE), and are named phenytoin-like compounds.[19,20]

Over the years we and other authors have advanced in the knowledge of the molecular requirements of AED associated with ligands that act through interactions that cause this in-vivo profile. Since the knowledge of the mechanism of action of this kind of ligands is not straightforward, research on the origin of the activity is centered on the analysis of the active compounds. Accordingly, several pharmacophoric models have been developed from different methodologies mainly associated with the comparison of structures and QSAR analysis.[21–27]

One of them has recognized a common pattern based on the examination of 12 dissimilar compounds with anti-MES activity, and the crucial electronic and structural features were identified.[23] This previous discussion allowed the authors to define the 3D requirements for the structures to manifest the anti-MES activity. They can be summarized in: (1) a hydrophobic chain (atoms 5–7, Fig. 1), (2) a polar moiety (atoms 1–3, Fig. 1); placed in a well defined conformation.[27]

From this study, new active compounds derived from valpromides have been designed, synthesized, and evaluated.[23] The training set of AED used to define these requirements included models for structurally different classes of compounds with similar action in the experimental anticonvulsant model, MES test (Fig. 2). It comprised classical drugs, new generation ones, and compounds that have overcome the development stage. Most of them showed a PHE-like profile being active against the MES test and inactive against PTZ. Drugs like felbamate (FLB), remacemide (RMC), ethosuximide (ETH), and vinpocentine (VIN) are also active in the PTZ test. ETH, one of the major antiepileptics used in absence of seizures, has been included as an inactive analog; because it is inactive against MES test.[23]

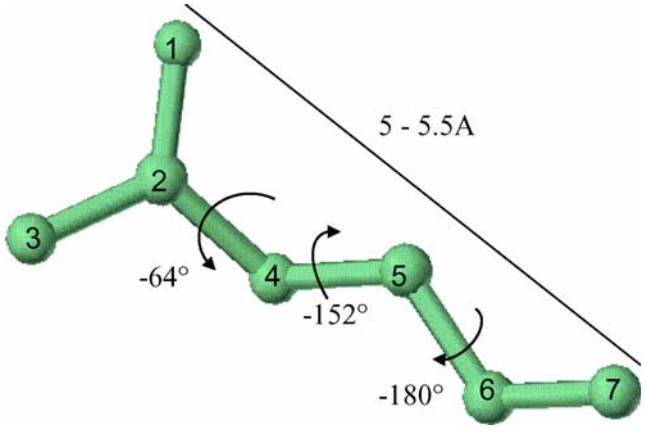


Figure 1. Structure of the pharmacophore previously proposed.

We have used the knowledge acquired in the preceding research about the active conformation determined by the pharmacophore (Fig. 1). We have focused on the design of sulfamides as novel ligands with anti-MES activity, as part of our search for potential anticonvulsant agents.[27]

It may be interesting to examine whether different compounds bearing this functionality reflect the conditions derived from the previous pharmacophore model. The results demonstrated the high quality of the pharmacophore pattern proposed, and their ability to predict the activity of the designed compounds.

Considered an attractive target for medicinal chemists, sulfamides have been studied as HIV protease inhibitors,[28,29] agonists of the 5-HTID receptor,[30] active components in epinephrine analogs,[31] non-hydrolyzable components of peptide-mimetics,[32] and carbonic anhydrase inhibitors.[33–35] Recently we have considered this functionality as the result of the bioisosteric replacement for the polar portion of the pharmacophore.[27] For a quantitative verification of the presence of the pharmacophore polar end, the electronic characteristics of one set of sulfamides were compared with the pharmacophore corresponding atoms in AED. The set includes sulfamides and sulfamide derivatives containing different hydrocarbon chains. The compounds were synthesized and anticonvulsant evaluations were performed.

2. Results and discussion

2.1. Pharmacophore polar end

We have based the criterion of considering different chemical functions for the pharmacophore polar end in the ability of their atoms to fulfill the requirements defined for this portion.

First, we have considered some of the compounds included in the training set used to define the pharmacophore (Fig. 2). The compounds were selected so their functionalities were varied. Charges among the atomic centers of the polar end have been calculated by means of density functional calculation GAUSSIAN 98 (G98),[36] using B3LYP functional and 6-31 G** basis. The electronic distribution was derived from calculated potentials (Chelp G). The results are given in Table 1. The organic functions considered were detailed. As expected, the results correlated with the charge distribution defined in the pharmacophore: a negative end distributed among two atomic centers defined by N or O, and a positive end centered in a C or S atom.

Then, we have incorporated the sulfamide function to the set. By inspection of the atoms that defined the polar moiety of the pharmacophore (numbered 1–3 in Fig. 1), we can assign a bioisosteric equivalence between the functions involved. In other words, bioisosteres

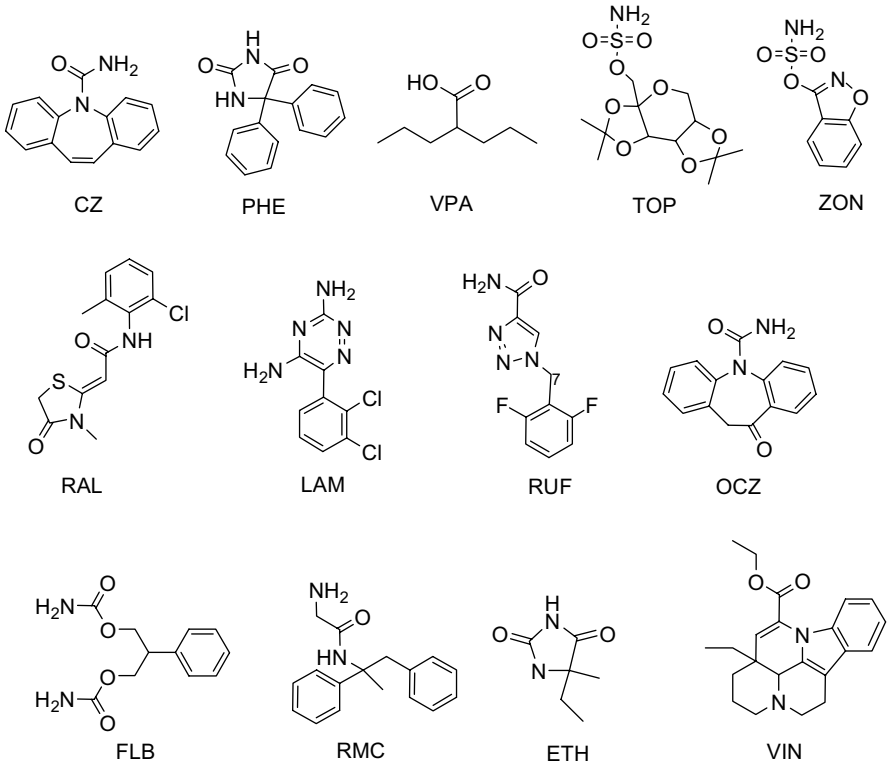


Figure 2. Structures of the antiepileptic drugs that are active in the MES test and used to define the training set.

Table 1. Electronic distribution among the pharmacophore polar end

Compound	Function	Q_1	Q_2	Q_3	Compound	Function	Q_1	Q_2	Q_3
CZ	Urea	−0.563	0.905	−0.928	**5a**	Sulfamide	−0.475	0.927	−0.285
PHE	Amide	−0.488	0.568	−0.652	**6a**	Sulfamide	−0.464	0.897	−0.437
VPA	Acid	−0.559	0.633	−0.535	**7a**	Sulfamide	−0.464	0.895	−0.433
FLB	Carbamate	−0.583	0.911	−0.937	**8a**	Sulfamide	−0.466	1.021	−0.729
TOP	Sulfamate	−0.551	1.433	−1.043	**9a**	Sulfamide	−0.496	0.931	−0.724
ZON	Sulfonamide	−0.481	0.957	−0.870	**10b**	Sulfamide	−0.460	0.925	−0.575
VIN	Ester	−0.518	0.742	−0.468	**11b**	Sulfamide	−0.459	0.923	−0.859
OCZ	Urea	−0.542	0.850	−0.940	**12b**	Sulfamide	−0.454	0.942	−0.639
1a	Sulfamide	−0.487	1.120	−0.721	**13b**	Sulfamide	−0.460	0.977	−0.648
2a	Sulfamide	−0.470	1.018	−0.850	**14c**	Sulfamide	−0.489	1.014	−0.868
3a	Sulfamide	−0.468	0.981	−0.615	**15c**	Sulfamide	−0.491	0.949	−0.764
4a	Sulfamide	−0.492	0.991	−0.722	**16c**	Sulfamide	−0.486	0.947	−0.805
					17c	Sulfamide	−0.474	0.965	−0.807

comprise the polar end in the pharmacophore definition for anti-MES activity.

Groups CH, O, and NH are isosteres according to Grimm's hydride displacement law.[37–39] Sulfoxides and sulfones are recognized as nonclassical bioisosteres suitable to replace a carbonyl group.[39] The replacement of the carbonyl group by a sulfoxide, and the substitution of the groups CH and O by NH generate the sulfamide functionality as a result of the bioisosteric replacement (Fig. 3).

Another function related may be sulfate (Fig. 3). This functionality is included in active molecules like topiramate derivatives, which present anticonvulsant properties in MES test.[27,40] Their ability to comply with the requirements of the pharmacophore pattern has been demonstrated before, using the sulfate function as the polar end.[27,41]

After defining this new functionality, seventeen sulfamide derivatives have been selected and their atomic charges have been calculated at the same level of theory. The set includes mono-substituted sulfamides, di-substituted sulfamides, tetra-substituted sulfamides, and sulfonyl carbamates (Fig. 4).

The analysis reveals that the charge distribution around the atoms that define the pharmacophore polar end remains constant in all sulfamides: the negative charges

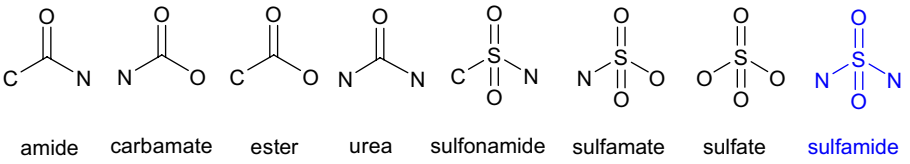


Figure 3. Chemical functions involved in the pharmacophore polar end of the antiepileptic drugs used in the training set. Sulfamide and sulfate functions were included.

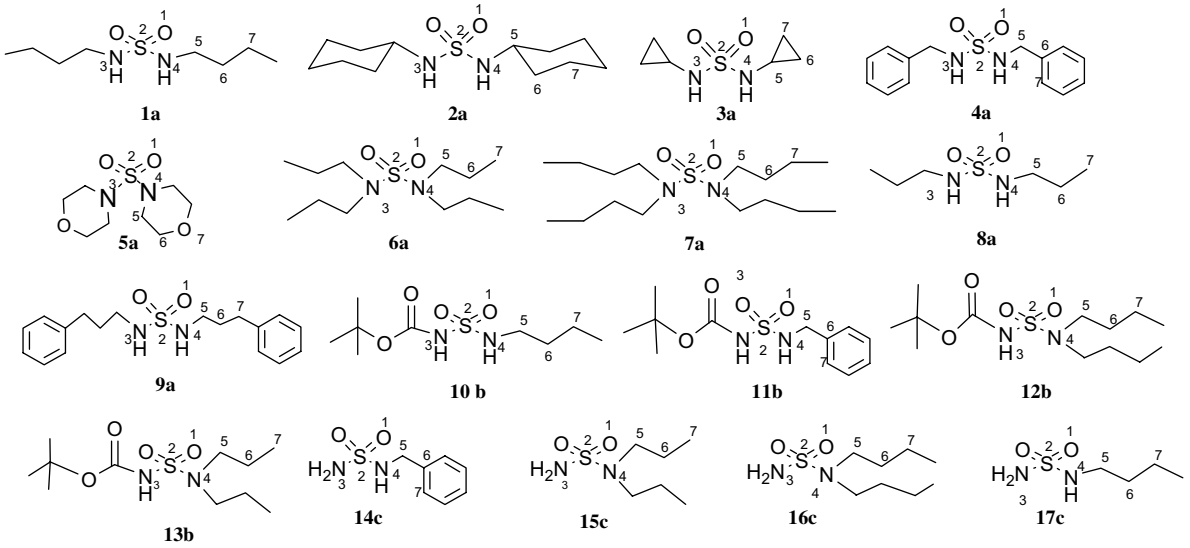


Figure 4. Structures of the sulfamides synthesized and evaluated. Atoms are numbered for the centers that are implicated in the pharmacophoric pattern.

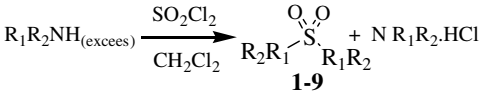
are distributed among one N and O atoms, whereas the positive center is focused on the S atom.

In the model, the anti-MES biological response is contingent on the presence of the polar fragment. The compounds should also contain a hydrophobic region consistent with the non-polar portion of the pharmacophore. For verification of the entire pattern, and to understand the influence of the hydrophilic portion, the sulfamide derivatives were synthesized and evaluated. Seventeen compounds were included in the set, with aromatic or aliphatic chains chosen so that their size was varied.

2.2. Synthesis

The synthetic route has been selected according to the position of the subtituents. Symmetric *N*,*N*′-disubstituted sulfamides and tetrasubstituted sulfamides were prepared in concordance with typical procedures by condensation of an excess of amine with sulfuryl chloride (Scheme 1 compounds **1a** to **9a**).[42–47] We have found a non-favorable effect of pyridine in the reaction,[48,49] and it has not been used as a reactant.

Mono-substituted sulfamides and *N*,*N*-disubstituted sulfamides were also synthesized following standard procedures (Scheme 2 compounds **14c** to **17c**).[50–54]



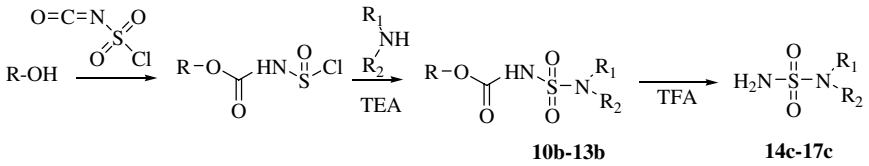
Scheme 1. Synthetic route for symmetric *N*,*N*′-disubstituted sulfamides and tetrasubstituted sulfamides. Method A: 1—R1 = *n*Bu, R2 = H; 2—R1 = cyclohexyl, R2 = H; 3—R1 = cyclopropyl, R2 = H; 4—R1 = Benzyl R2=H; 5—R1R2 = Morpholin; 6—R1R2 = nPropyl ; 7—R1R2 = n Butyl; 8—R1 = *n*Propyl, R2 = H; 9—R1 = Phenethyl, R2 = H.

Initially *N*-alkoxycarbonyl sulfamides were prepared in one-pot synthesis from chlorosulfonyl isocyanate, *tert*-butanol, and the corresponding amine in presence of triethylamine. The *tert*-butoxy carbonyl group was then removed via acidic hydrolysis.

The *N*-acyl-substituted products (Scheme 2, compounds **10b** to **13b**) were also included in the biological analysis, as sulfamide derivatives.

2.3. Pharmacology

Preliminary anticonvulsant evaluation (phase 1) of the synthesized compounds was performed following the standard procedure provided by the antiepileptic drug development program.[55] It includes qualitative assays using MES test and PTZ test. The first assay is related



Scheme 2. Synthetic route for sulfamides type B and C: 10 and 17, R1 = *n*Bu, R2 = H; 11 and 14, R1 = Benzyl R2 = H; 12 and 16, R1 = R2 = *n*Bu, 13 and 15, R1R2 = *n*Propyl.

to electrical induction of the seizure and the second test generates the convulsion by chemical induction. The RotoRod test was used to determine the possible neurotoxic effects. The compounds were administered to animals intraperitoneally at three doses (30, 100, and 300 mg/kg), and all the assays were performed at 0.5 and 4 h. Details of the evaluation of anticonvulsant activity are given in the Section 4. The results are summarized in Table 2.

Due to the low solubility of five sulfamides at high doses (**1a**, **2a**, **4a**, **5a**, and **9a**), intraperitoneal testing was difficult and, in these cases, we reported only reliable results. Taking into account that physicochemical properties like lipophlicity may have influence on the pharmacological properties of the compounds, it has been expressed as partition coefficients (log *P* parameters) for each sulfamide of the set (Table 2). The calculated values were estimated using the HyperChem QSAR Properties, version 7.01, Hypercube, Inc.[56]

As anticipated, the results of the pharmacological investigation reveal that the biological activity is related to the presence and disposition of the lateral chains in sulfamides.

The most active sulfamides against MES test were **1a**, **2a**, **4a**, **10b**, **12b**, **14c**, and **17c**. They were active at doses of 30 mg/kg: 1/3 animals protected in all cases 0.5 h after administration (with exception of **12b** and **17c**); and 1/3 animals protected 4 h after administration for **12b**, **14c**, and **17c**. For these molecules, toxicity was only observed in case of **17c** at the tested doses.

Compound **9a** showed significant protection against the MES test at 100 mg/kg (3/3 animals protected) 0.5 h after administration. Compound **16 c** also showed anti-MES activity at 100 mg/kg at the same time, in conjunction with neurological toxicity at higher doses. Compounds **8a** and**13b** demonstrated a activity against MES test at doses of 300 mg/kg at 0.5 h. Compound **8a** also showed a weak neurotoxicity at the same time (1/3 animals).

Most of the active compounds present a PHE-like profile, being active in the MES test and inactive in PTZ-induced convulsions, at the doses and times evaluated. However, sulfamides **8a** and **16c** showed protection against both test. In PTZ test, both compounds were active at 100 mg/kg (2/3 and 1/3 animals protected, respectively).

All the compounds mentioned above are able to adopt the active conformation defined by the pharmacophore for anti-MES activity, supporting the application of the model.

Neither anti-MES activity nor neurological toxicity was detected in **3a**, **5a**, **6a**, **7a**, and **11b**. This behavior can be explained for compounds **3a** and **5a**, which are not able to adopt the pharmacopore conformation due to their rigidity.

No explanation can be given for the lack of activity presented in **11b** and **7a**, and ideas for future molecular modification to improve the pharmacophore pattern may be derived from these data.

As mentioned before, compounds **15c**, **16c**, and **17c** showed neurological toxicity in the RotoRod test. According to the high toxicity found for **15c** (3/3 animals affected at doses of 30 mg/kg) the MES and PTZ test were performed only at low doses. We considered this compound too toxic to continue the experimental procedures at higher doses. The same criteria was applied for **16c** and **17c**. Related to their structures, all of these compounds present a free NH_2 group in the sulfamide function. Although the number of evaluated compounds is not significantly high, we could infer that the presence of unsubstituted nitrogen in the sulfamide function increases the neurological toxicity. Moreover, the presence of the NH group could be important to the activity as well as in the modulation of the toxicity. This relation between the number and the position of the substituents and the neurotoxic effect may indicate key features to be considered in the further design of new ligands.

According to the results in MES test, the molecules were grouped into four classes (Table 2)[22]: (1) anticonvulsant activity at 100 mg/kg or less; (2) anticonvulsant activity at doses higher than 100 mg/kg; (3) compound inactive at any doses up to 300 mg/kg; (4) compound inactive at 300 mg/kg and toxic at 30 mg/kg or less.

Biological data were derived to phase II testing for some of the most active compounds in MES test: **1a**, **2a**, **4a**, **9a**, and **14c**. The assays were performed following the standard procedures provided by the antiepileptic drug development program.[55] The results obtained are listed in Table 3. The anticonvulsant activity was expressed as ED50, which measures the dose that is effective in 50% of the tested animals. The ED_{50} values obtained for **1a**, **2a**, and **4a** have been reported by us in a previous investigation.[27] Additionally, the neurotoxicity was

Table 2. Pharmacological profile (phase I) of the sulfamides and their log *P* values

Compound	Class	log *P*	Dose (mg/kg)	Activity MES[A] time (h)		TOX[B] time (h)		Activity PTZ[C] time (h)	
	1, **2**, **3**, **4**			0.5	4	0.5	4	0.5	4
1a	**1**	1.23	30	1/3	0/3	0/3	0/3	0/2	0/2
			100	2/3	0/3	0/3	0/3	0/2	0/2
			300	Nt	Nt	Nt	Nt	Nt	Nt
2a	**1**	2.59	30	1/3	0/3	0/3	0/3	0/2	0/2
			100	3/4	0/4	0/3	0/3	0/2	0/2
			300	Nt	Nt	Nt	Nt	Nt	Nt
3a	**3**	0.21	30	0/3	0/3	0/3	0/3	0/2	0/2
			100	0/3	0/3	0/3	0/3	0/4	0/2
			300	0/3	0/3	0/3	0/3	0/2	0/2
4a	**1**	1.45	30	1/3	0/3	0/3	0/3	0/3	0/3
			100	3/3	0/3	0/3	0/3	0/3	0/3
			300	Nt	Nt	Nt	Nt	Nt	Nt
5a	—	−1.44	30	0/4	0/4	0/4	0/4	0/4	0/4
			100	0/4	0/4	0/4	0/4	0/4	0/4
			300	Nt	Nt	Nt	Nt	Nt	Nt
6a	**3**	2.49	30	0/3	0/3	0/3	0/3	0/2	0/2
			100	0/3	0/3	0/3	0/3	0/2	0/2
			300	0/3	0/3	0/3	0/3	0/2	0/2
7a	**3**	4.69	30	0/3	0/3	0/3	0/3	0/3	1/3
			100	0/3	0/3	0/3	0/3	0/3	0/3
			300	0/3	0/3	0/3	0/3	0/3	0/3
8a	**2**	1.04	30	0/3	0/3	0/3	0/3	0/3	1/3
			100	0/3	0/3	0/3	0/3	1/3	0/3
			300	3/3	0/3	1/3	0/3	3/3	0/3
9a	**1**	1.95	30	0/3	0/3	0/3	0/3	0/2	0/2
			100	3/3	0/3	0/3	0/3	0/2	0/2
			300	Nt	Nt	Nt	Nt	Nt	Nt
10b	**1**	0.67	30	1/3	0/3	0/3	0/3	0/2	0/2
			100	3/3	1/3	0/3	0/3	0/2	0/2
			300	3/3	1/3	0/3	0/3	0/2	0/1
11b	**3**	0.48	30	0/3	0/3	0/3	0/3	0/2	0/2
			100	0/3	0/3	0/3	0/3	0/2	0/2
			300	0/3	0/3	0/3	0/3	0/2	0/2
12b	**1**	1.79	30	0/3	1/3	0/3	0/3	0/2	0/2
			100	2/3	0/3	0/3	0/3	0/2	0/2
			300	2/3	2/3	0/3	0/3	0/2	0/2
13b	**2**	1.39	30	0/3	0/3	0/3	0/3	0/2	0/2
			100	0/3	0/3	0/3	0/3	0/2	0/2
			300	1/3	0/3	0/3	0/3	0/2	0/2
14c	**1**	0.41	30	1/3	1/3	0/3	0/3	0/2	0/2
			100	3/3	1/2	0/3	0/3	0/2	0/2
			300	3/3	3/3	0/3	0/3	0/2	0/2
15c	—	0.22	30	0/3	0/3	3/3	3/3	0/2	0/2
			100	Nt[a]	Nt[a]	3/3	3/3	Nt[a]	Nt[a]
			300	Nt[a]	Nt[a]	Nt[a]	Nt[a]	Nt[a]	Nt[a]
16c	**1**	1.53	30	0/3	0/3	0/3	0/3	0/3	0/3
			100	2/3	0/3	0/3	0/3	2/3	0/3
			300	Nt[a]	Nt[a]	3/3	3/3	Nt[a]	Nt[a]
17c	**1**	1.14	30	0/3	1/3	0/3	0/3	0/2	0/2
			100	0/3	1/3	2/3	0/3	0/2	0/2
			300	Nt[a]	Nt[a]	3/3	2/3	Nt[a]	Nt[a]

Nt, not tested due to the low solubility of the drug. Nt[a], not tested due to the high neurotoxicity of the drug.
[A] Maximal electroshock seizure.
[B] Toxicity evaluated in RotoRod test.
[C] Pentylenetetrazol test.

quantified as TD_{50}, which measures the doses that present neurotoxicity in 50% of the tested animals.

We were not able to determine the values of TD_{50} for compounds **1a**, **2a**, **4a**, and **9a** due to solubility problems at high doses, and maximal concentrations evaluated were reported in Table 3.

The time of peak effect (TPE) was determined previously to calculate the ED_{50} and TD_{50} values for the compounds,

Table 3. Time of peak effect (TPE), activity values (ED_{50}, μmol/kg), and toxicity values (TD_{50}, μmol/kg) determined (mice) for some of the most active sulfamide derivatives designed in this research

Compound	MES test		RotoRod test		PI[a]	PTZ test	
	TPE (h)	ED_{50} (μmol/kg)	TPEN (h)	TD_{50} (μmol/kg)		TPE (h)	ED_{50} (μmol/kg)
1a	2	295	—	0% (481)	>1.6	—	Inactive (481)
2a	0.5	151	—	0% (385)	>2.5	—	Inactive (385)
4a	2	238	—	0% (362)	>1.5	—	Inactive (362)
9a	0.5	263	—	0% (329)	>1.3	—	Inactive (329)
14c	0.5	239	0.5	1422	5.9	—	Inactive (1613)

Compounds are defined as Inactive when they are not effective at the maximal doses evaluated, expressed between brackets.
TPE, time of peak effect; TPEN, Neurotoxic time of peak effect.
[a] PI (protective index) = TD_{50}/ED_{50}, calculated for the MES test.

and are expressed in Table 3. Details for determination of TPE ED_{50} and TD_{50} are given in Section 4.

3. Conclusions

Based on the results of molecular modeling, a set of sulfamides were designed, synthesized, and evaluated.

The selection of this functionality was supported by the bioisosteric equivalence of this kind of molecules with the groups that previously defined the polar portion of the pharmacophore (Table 1). Compounds bearing this functionality were synthesized and evaluated according to the standard procedures. From this investigation we have found nine compounds classified as class **1** anticonvulsants (anticonvulsant activity at 100 mg/kg or less), the most potent class of antiepileptic drugs. Additionally, most of the sulfamides that are able to adopt the active conformation show the anti-MES profile and some of them display the characteristic of phenytoin-like compounds.

The ED_{50} values determined for the most active sulfamides are comparable with classical and new generation drugs.[27]

No relation between log *P* and anticonvulsant activity can be established. Lipophilicity can be related with the capability of the drugs to be transported through the biological membranes. In spite of the lack of a more detailed conclusion, we can assume that the log *P* values are high enough to allow the delivery of the compounds to the active site.

More sulfamide derivatives would be investigated in order to offer a better understanding of the structural and electronic characteristics that are responsible for the activity.

4. Experimental

4.1. Chemistry

Melting points were determined using capillary tubes with a Electrothermal melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed with aluminum backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and the spots were visualized with UV light and 5% aqueous solution of Ammonium molybdate (VI) tetrahydrate. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck, ref 1.07734.1000).

Two hundred megahertz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer.

The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in Hertz (Hz). IR spectra were run on a FT/IR Perkin–Elmer spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only significant absorption bands are given. Analytical grade solvents were used for crystallization, while pure for synthesis solvents were used in the reactions, extractions, and column chromatography. All reactions were carried out in flame-dried glassware, under positive pressure of Argon. Commercial amines were distilled prior to their use. Sulfuryl chloride was distilled and stored under nitrogen at 5 °C.

Elemental analyses were carried out at the Mycroanalysis Service of INQUIMAE (Argentine) and results were within ±0.4% of the theoretical values.

4.2. General procedure A for the preparation of *N,N′*-disubstituted symmetric sulfamides (1a–9a)

Compounds **1**–**9** were prepared as described in the literature.[47] The reaction was carried out by dropwise addition of a solution of sulfuryl chloride (16.5 mmol, 1 equiv) in dichloromethane (5 mL) to a solution of the corresponding amine (4–6 equiv) in dichloromethane (6-8 mL) at 0 °C in dark condition. Gas evolution was observed during the addition.

The reaction mixture was warmed to room temperature, stirred for 5–30 h, and monitored by TLC (SiO_2). The crude was washed with acidic and basic aqueous solutions and if it was necessary a column chromatography was carried out. Purification was performed as indicated in each example. The synthetic procedure for compounds *1a* to *5a* was detailed in a previous paper.[27]

4.2.1. *N,N,N′,N′*-Tetrapropylsulfamide (6a).[58] This compound was prepared according to the general procedure A, using a solution of *N,N*-dipropylamine (9.0 mL, 66.0 mmol, 4 equiv) in CH_2Cl_2 (5 mL) and SO_2Cl_2 (1.3 mL, 16.5 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After 24 h of reaction the resulting yellow solution was concentrated under reduced pressure to leave a yellow solid crude. Dichloromethane (20 mL) was added, the solution was washed with 5% acetic acid (2×), brine (2×) and dried (SO_4Na_2). The solution was filtered, concentrated under reduced pressure to leave a crude oil. Column chromatography (CH_2Cl_2) afforded (1.8 g, 41% yield) of sulfamide **6a**, as a colorless oil. R_f: 0.65 (SiO_2, CH_2Cl_2). IR (ClAg): 1372 (S–O), 1146 (S–O). ^{1}H NMR ($CDCl_3$): 0.88 (t, J = 7.7 Hz, 12H: CH_3), 1.58 [ddd, $J \approx 7.7$ Hz, $J' \approx 5.5$ Hz, 8H: β-CH_2], 3.05 [dd, $J \approx 5.5$ Hz, 8H: α-CH_2]. ^{13}C NMR ($CDCl_3$): 11.5 (CH_3), 21.7 (β-C), 49.8 (α-C).Anal. Calcd for $C_{12}H_{28}N_2O_2S$: C: 54.5%, H: 10.7, N: 10.6, S: 12.1. Found: C: 54.0, H: 11.0, N: 10.7, S: 12.2.

4.2.2. *N,N,N′,N′*-Tetrabutylsulfamide (7a). This compound was prepared according to the general procedure A, using a solution of *N,N*-dibutylamine (6.1 mL, 66.0 mmol, 4 equiv) in CH_2Cl_2 (5 mL) and SO_2Cl_2 (1.3 mL, 16.5 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After 11 h of reaction the resulting yellow solution was concentrated under reduced pressure to leave a yellow syrup crude. Dichloromethane (20 mL) was added, the solution was washed with 5% acetic acid (2×), brine (2×) and dried (SO_4Na_2). The solution was filtered, concentrated under reduced pressure to leave a crude oil. Column chromatography (CH_2Cl_2) afforded (2.5 g, 47% yield) sulfamide **7a**, as a colorless oil, bp 126–128 °C/1 mmHg. R_f: 0.65 [SiO_2, CH_2Cl_2/hexane (1:1)]. IR (ClAg): 1387 (S–O), 1101 (S–O). ^{1}H NMR ($CDCl_3$): 0.95 (t, J = 7.3 Hz, 12H: CH_3), 1.39 (m, 8H)], 1.67 (m, 8H), 3.05 [t, $J \approx 7.7$ Hz, 8H: α-CH_2]. ^{13}C NMR ($CDCl_3$): 13.8 (CH_3), 20.1 (α-C), 51.1 (β-C). Anal. Calcd for $C_{16}H_{36}N_2O_2S$: C: 60.0.%, H: 11.3, N: 8.7, S: 10.0. Found: C: 59.8, H: 11.4, N: 8.6, S: 10.4.

4.2.3. *N,N′*-Dipropylsulfamide (8a).[57] This compound was prepared according to the general procedure A, using a solution of *N*-propylamine (11 mL, 133.2 mmol, 6 equiv) in CH_2Cl_2 (5 mL) and SO_2Cl_2 (1.8 mL, 22.5 mmol, 1 equiv) in CH_2Cl_2 (4 mL). After 24 h of reaction the resulting orange solution was concentrated under reduced pressure to leave a yellow solid crude. Dichloromethane (15 mL) was added, the solution was washed with 5% acetic acid (2×), brine (2×) and dried (SO_4Na_2). The solution was filtered, concentrated under reduced pressure to leave a yellow solid crude. Column chromatography (CH_2Cl_2) afforded (2.6 g, 65% yield) of sulfamide **8a**, as a white solid, mp 118–119 °C (described 119 °C)[46] R_f: 0.49 [SiO_2, CH_2Cl_2/MeOH (20:1)]. IR (KBr): 3280 (*N*–H), 1314 (S–O), 1147 (S–O). ^{1}H NMR ($CDCl_3$): 0.98 (t, J = 7.3 Hz, 6H: CH_3), 1.53 (sext, $J \approx J' \approx 7.2$ Hz, 4H: β-CH_2), 2.97 (m, 4H: α-CH_2), 4.54 (t broad, $J'' \approx 5.8$ Hz, 2H: NH).

^{13}C NMR ($CDCl_3$): 11.5 (γ-C), 23.1 (β-C), 45.1 (α-C).

4.2.4. *N,N′*-Diphenethylsulfamide (9a).[58] This compound was prepared according to the general procedure A, using a solution of *N*-phenethylamine (8.3 mL, 65.8 mmol, 5 equiv) in CH_2Cl_2 (5 mL) and SO_2Cl_2 (1.05 mL, 13.2 mmol, 1 equiv) in CH_2Cl_2 (4 mL). After 24 h of reaction solution was concentrated under reduced pressure to leave a solid crude, (10.1 g). Column chromatography (CH_2Cl_2) afforded (2.4 g, 70% yield) sulfamide **9a**, as a white solid, mp 100–101 °C (CH_2Cl_2) (described: 100–101 °C).[59] R_f: 0.48 [(SiO_2, CH_2Cl_2/MeOH (20:1)], IR (KBr) : 3280 (NH), 1300 (S–O), 1137 (S–O). ^{1}H NMR ($CDCl_3$): 2.80 (dd, $J \cong J' = 6.8$ Hz, 4H:β-CH_2), 3.20 (dd, $J \cong J' = 6.8$ Hz, 4H: γ-CH_2), 4.31 [t broad, 2H, $J \cong 6.2$ Hz, NH), 7.17-7.20 (m complex signal, 10 H, Ar (Ar′)-H). ^{13}C NMR ($CDCl_3$): 35.9 (α-C), 44.4 (β-C), 127.0 (C^4-Ar), 129.0 ($C^{2,6}$-Ar), 129.05 ($C^{3,5}$-Ar), 138.3 (C^1-Ar). Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C: 63.2, H: 6.6, N: 9.2, S: 10.5. Found: C: 63.1, H: 6.8, N: 9.3, S: 10.4.

4.3. General procedure B for the preparation of *N*-Boc-sulfamides (10b–13b)

The synthesis of *N*-Boc-sulfamides **10–13b** is performed in dried dichloromethane with successive additions of *t*-BuOH and RR′NH/triethylamine (TEA) into chlorosulfonyl isocyanate (CSI). *N*-chlorosulfonyl (*tert*-butyl) carbamate was prepared by addition of *tert*-butanol (1.4 equiv, in 6 mL of dried dichloromethane) into a solution of CSI (1 equiv, in the same solvent). This reagent was slowly added at 0 °C into a solution containing a primary (or secondary) amine (1 equiv in dried dichloromethane) and 1.1 equiv of triethylamine. The reaction was achieved in 45–60 min at 0 °C and 2–3 h at rt. The medium was diluted with dichloromethane, washed with two fractions of HC1 0.1 N, dried (SO_4Na_2), and concentrated under reduced pressure. The crude residue was then purified by column chromatography and crystallization (yield 50–80%).

4.3.1. *N*-(*tert*-Butoxycarbonyl)-*N′*-(butyl)sulfamide (10b).[53] This compound was prepared according to the general procedure B, using a solution of CSI (1.2 mL, 14 mmol, 1 equiv) in CH_2Cl_2 (7 mL), *tert*-butanol (1.3 mL, 19 mmol, 1.4 equiv), *n*-butylamine (1.4 mL, 14 mmol, 1 equiv), and TEA (2,2 mL, 15,4 mmol, 1.1 equiv) in a solution of dried CH_2Cl_2 (28 mL).

The solid obtained by evaporation of the reaction mixture (6.0 g) was purified using column chromatography (SiO_2, CH_2Cl_2/MeOH mixtures) affording the sulfamide **10b** as a white solid, (2,02 g, 58% yield), mp 144–145 °C [CH_2Cl_2/Hexano (1:3)], (described: 154–155 °C).[60] R_f: 0.73 [SiO_2, CH_2Cl_2/MeOH (20:1)]. IR (KBr): 3366 y 3222 (CONH and NH), 1701(C=O), 1347(S–O), 1140 (S–O). ^{1}H NMR ($CDCl_3$): 0.93 (t, J = 7.2 Hz, 3H: CH_3), 1.29–1.62 [m, 13H: 4H: β and γ-CH_2 and 9H: CH_3 *tert*-But, 3.06 (*c*, J = 6.8 Hz, 2H: α-CH_2), 5.07 (t, $J \approx 6.0$ Hz, 1H: NH), 7.25 (s broad signal, 1H: NH_2). ^{13}C NMR ($CDCl_3$): 13.7 (CH_3), 19.9 (γ-CH_2), 28.2 (CH_3, *tert*-Bu), 31.2 (β-CH_2), 43.8 (α-CH_2), 83.9 [$C(CH_3)_3$], 150.6 (C, C=O). Anal. Calcd for

$C_9H_{20}N_2O_4S$: C: 42.8, H: 8.0, N: 11.1, S: 12.7. Found: C: 43.1, H: 8.1, N: 11.2, S: 12.3.

4.3.2. *N*-(benzyl)-*N*′-(*tert*-butoxycarbonyl)sulfamide (11b).[51,54] This compound was prepared according to the general procedure B, using a solution of CSI (2.13 mL, 24.0 mmol; 1 equiv) in CH_2Cl_2 (25 mL), *tert*-butanol (2.4 mL, 33.6 mmol, 1.4 equiv), benzylamine (2.62 mL, 24 mmol 1.1 equiv), and TEA (3.78 mL, 26.9 mmol, 1.1 equiv) in a solution of dried CH_2Cl_2 (50 mL). The white solid (10.2 g) obtained by evaporation of the reaction mixture was purified using column chromatography (SiO_2, CH_2Cl_2) affording the sulfamide **11b**, as a white solid, (4.7 g, 68% yield), mp 129.5–130 °C, (described: 137–139 °C and 111–113 °C).[51,54] R_f: 0.52 [SiO_2, CH_2Cl_2/MeOH (60:1)]. IR (KBr): 3300, 3273 (NH), 3068, 3033 (CH aromático), 1713 (C=O), 1358, 1148 (SO_2). ^{1}H NMR ($CDCl_3$): 7.35–7.26 (m, 6H: Ar-H and NH-Boc), 5.61 (t, broad signal, $J \approx 6.1$ 1H: NH- Bz), 4.25 (d, $J = 6.1$, 2H: CH_2), 1.44 (s, 9H: CH_3 *tert*-Bu) ^{13}C NMR ($CDCl_3$): 150.37 (C=O), 135.88 (C^1-Ar), 129.09, 128.36, 128.33 ($C^{2,3,4}$-Ar), 84.09 ($C(CH_3)_3$), 45.81 (CH_2), 28.20 (CH_3, *tert*-Bu). Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C: 50.3, H: 6.3, N: 9.8, S: 11.2. Found: C: 50.4, H: 6.1, N: 9.5, S: 11.2.

4.3.3. *N*,*N*-(Dibutyl)-*N*′-(*tert*-butoxycarbonyl)sulfamide (12b). This compound was prepared according to the general procedure B, using a solution of CSI (1.2 mL, 14 mmol, 1 equiv) in CH_2Cl_2 (8 mL), *tert*-butanol (1.4 mL, 19 mmol, 1.4 equiv), *N*,*N*-di-butylamine (1.3 mL, 14 mmol, 1 equiv), and (TEA) (2.2 mL, 15.4 mmol, 1.1 equiv) in a solution of dried CH_2Cl_2 (25 mL). The oil (6.8 g) obtained by evaporation of the reaction mixture was purified using column chromatography (SiO_2, CH_2Cl_2/Hexane) affording the sulfamide **12b**, as colorless oil (2.04 g, 48% yield). R_f: 0.49 (SiO_2, CH_2Cl_2). IR (ClAg): 3273 (CON–H), 1701 (C=O), 1366, (S–O), 1140 (S–O). ^{1}H NMR ($CDCl_3$): 0.93 (t, $J \approx 7.3$ Hz, 6H, CH_3), 1.29–1.62 [m, 17H: 8H: β-CH_2 and γ-CH_2; 9H: CH_3 *tert*-But, 3.31 (t, $J \approx 7.6$ Hz, 4H, α-CH_2),7.16 (s, broad signal, 1H: NH). ^{13}C NMR ($CDCl_3$): 14.0 (CH_3), 20.1 (γ-C), 28.3 (CH_3, *t*-CH_3), 30.6 (β-C), 48.9 (α-C), 83.4 [$C(CH_3)_3$], 150.2 (C=O).

4.3.4. *N*,*N*-(Dipropyl)-*N*′-(*tert*-butoxycarbonyl)sulfamide (13b). This compound was prepared according to the general procedure B, using a solution of CSI (2.21 mL, 25 mmol, 1 equiv) in CH_2Cl_2 (25 mL), *tert*-butanol (2.4 mL, 33.6 mmol, 1.4 equiv), *N*,*N*-di-propylamine (3.5 mL, 25 mmol, 1 equiv), and (TEA) (3.86 mL, 27.5 mmol, 1.1 equiv) in a solution of dried CH_2Cl_2 (50 mL). The white solid (10.3 g) obtained by evaporation of the reaction mixture was purified using column chromatography (SiO_2, hexane) affording the sulfamide **13 b**, as a white solid, (4.5 g, 66% yield), mp 52–53 °C, (described: 62–63 °C).[59] R_f: 0,57 [SiO_2, CH_2Cl_2]. IR (KBr), cm^{-1}: 3272 (NH), 1736 (C=O), 1350, 1130 (SO_2). ^{1}H NMR ($CDCl_3$): 0.91 (t, $J = 7.4$ Hz, 6H: CH_3), 1.47 (s, 9H: CH_3 *tert*-Bu), 1.62 (m, 4H: β-CH_2), 3.27 (t, $J = 7.6$ Hz, 4H: α-CH_2), 7.26 (s, 1H: NH-Boc). ^{13}C NMR ($CDCl_3$): 11.32 (CH_3), 21.75 (β-CH_2), 28.26 (CH_3, *tert*-Bu), 50.97 (α-CH_2), 83.38 [$C(CH_3)_3$],150.20 (C=O). Anal. Calcd for $C_{11}H_{24}N_2O_4S$: C: 47.1, H: 8.6, N: 10.0, S: 11.4. Found: C: 47.5, H: 8.6, N: 9.7, S: 11.0.

4.4. General procedure C for the preparation of *N*- and *N*,*N*-substituted sulfamides (14c–17c)

A solution of trifluoroacetic acid (50% in dried dichloromethane; 3–6 equiv) was added dropwise into a stirred solution of substituted *N*-Boc-sulfamides (1 equiv), in dried dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred during 2 h at 0 °C, and 6–24 h at rt. Concentrated under reduced pressure and coevaporated with diethyl ether. Purification was performed as indicated in each example.

4.4.1. *N*-Benzylsulfamide (14c).[58] This compound was prepared according to the general procedure C, using a solution of **11b** (1.48 g, 5.2 mmol, 1 equiv) in CH_2Cl_2 (10 mL), and a solution of TFA 50% (1.16 mL, 15.6 mmol, 3 equiv). After 14 h of reaction the solution was concentrated under reduced pressure to leave a crude solid (1.3 g). Column chromatography [SiO_2, CH_2Cl_2/MeOH (25:1)] afforded (912 mg, 62% yield) sulfamide **14 c** mp 104–105 °C (CH_2Cl_2) (described: 106–107 °C).[59] R_f: 0.50 [SiO_2, CH_2Cl_2/MeOH (30:1)]. IR (KBr): 3325, 3273 (NH, NH_2), 3039 (CH, Ar), 1334, 1153 (SO_2). ^{1}H NMR (DMSO-d_6): 4.05 (d, $J = 6.6$, 2H: CH_2), 6.59 (s, 2H: NH_2), 7.00 (t, $J = 6.6$ Hz, 1H: NH-benzyl), 7.41–7.19 (m, 5H: Ar-H). ^{13}C NMR (DMSO-d_6): 46.79 (CH_2), 127.61, 128.35, 128.85 ($C^{2,3,4}$-Ar),139.361 (C^1-Ar). Anal. Calcd for $C_7H_{10}N_2O_2S$: C: 45.2, H: 5.4, N: 15.0, S: 17.2. Found: C: 45.3, H: 5.6, N: 15.0, O: 16.8, S: 17.3.

4.4.2. *N*,*N*-Dipropylsulfamide (15c).[57] This compound was prepared according to the general procedure C, using a solution of **13b** (1.41 g, 5.0 mmol, 1 equiv) in CH_2Cl_2 (10 mL) and TFA 50% (1.1 mL, 15.0 mmol, 3 equiv). After 6 h of reaction the solution was concentrated under reduced pressure to leave a solid crude (824 mg). Crystallization with CH_2Cl_2 afforded (442 mg, 49% yield) sulfamide **15c** as a white solid, mp 67–68 °C (described: 62–63 °C).[57] R_f: 0.67 (SiO_2, CH_2Cl_2/MeOH 30:1). IR (KBr): 3358, 3270 (NH, NH_2), 1335, 1152 (SO_2). ^{1}H NMR ($CDCl_3$): 0.92 (t, $J = 7.3$ Hz, 6H: CH_3), 1.62 (m, 4H: β-CH_2), 3.12 (t, $J = 7.6$ Hz, 4H: α-CH_2), 4.65 (s, 2H: NH_2). ^{13}C NMR ($CDCl_3$): 11.44 (CH_3),21.70 (β-CH_2), 50.38 (α-CH_2). Anal. Calcd for $C_6H_{16}N_2O_2S$: C: 40.0, H: 8.9, N: 15.5, S: 17.8. Found: C: 40.1, H: 9.0, N: 15.5, S: 17.9.

4.4.3. *N*,*N*-Dibutylsulfamide (16c).[57] This compound was prepared according to the general procedure C using a solution of **12b** (741 mg, 2.4 mmol, 1 equiv) in CH_2Cl_2 (3.5 mL) and TFA 50% (0.53 mL, 7.2 mL, 3 equiv). After 23 h of reaction the solution was concentrated under reduced pressure to leave a solid crude (432 mg). Column chromatography (SiO_2, CH_2Cl_2) afforded sulfamide **16c** (329 mg, 66% yield) as a white solid, mp 65–65.5 °C (CH_2Cl_2). R_f: 0.33 (SiO_2, CH_2Cl_2). IR (KBr): 3383 and 3260 (NH_2), 1353 (S=O), 1147 (S=O). ^{1}H NMR ($CDCl_3$): 0.95 (t, $J \approx 7.3$ Hz, 6H: CH_3), 1.35 (m, 4 H: β-CH_2), 1.60 (m, 4 H: γ-CH_2),

3.14 (t, $J \approx 7.4$ Hz, 4H:α-CH_2), 4.58 (s, broad signal, 1H:NH). ^{13}C NMR ($CDCl_3$): 14.0 (CH_3), 20.2 (CH_2, γ-C), 30.5 (β-C), 48.3 (α-C). Anal. Calcd for $C_8H_{20}N_2O_2S$: C: 46.1, H: 9.7, N: 13.4, S: 15.4. Found: C: 46.3, H: 9.5, N: 13.4, S: 15.1.

4.4.4. *N*-Butylsulfamide (17c).[57] This compound was prepared according to the general procedure C using a solution of **10b** (1.00 g, 3.96 mmol, 1 equiv) in CH_2Cl_2 (10 mL) and TFA 50% (0.9 mL, 12.0 mmol, 3 equiv). After 23 h of reaction the solution was concentrated under reduced pressure to leave a solid crude (700 mg). Column chromatography (SiO_2, CH_2Cl_2) afforded sulfamide **17c** (543 mg, 82% yield) as a white solid, mp 47–48 °C [CH_2Cl_2/Hexane (1:2)] (described: 52 °C)[57] R_f: 0.29 (SiO_2), CH_2Cl_2/MeOH (20:1). IR (KBr): 3325, 3318 and 3273 (NH, NH_2), 1340 (S–O), 1160 (S–O) cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (t, $J \approx 7.3$ Hz, 3H: CH_3), 1.23–1.61 (m, 4H: β and γ -CH_2), 3.08 (*c*, $J \approx 6.8$ Hz, 2H: α-CH_2), 4.74 (t broad, 1H: NH), 4.93 (s broad, 2H: NH_2). ^{13}C NMR ($CDCl_3$) δ: 13.8 (CH_3), 20.0 (γ-CH_2), 31.6 (β-CH_2), 43.6 (α-CH_2).

4.5. Biological data

The evaluation of the anticonvulsant activity followed the Anticonvulsant Drug Development (ADD) Program of the National Institute of Health.[55] Adult male and female albino mice (18–25 g) were used as experimental animals. Animals of the same age and weight were selected, in order to minimize biological variability. The animals were maintained on a 12 h. light/dark cycle and allowed free access to food and water, except during the time they were removed from their cages for testing. The test substance was administered in 30% polyethylene glycol 400 (PEG) and 10% water. The drugs were administered intraperitoneally (ip) in mice in a volume of 0.01 mL/g body weight.

4.6. Determination of median effective dose (ED_{50})

All quantitative studies were conducted at the previously determined time of peak effect (TPE). The ED_{50} was determined by treating groups of six albino mice. Different doses were used for each drug at TPE. The method of Litchfield and Wilcoxon[60] was used to compute the ED_{50} and 95% confidence intervals.

4.7. Determination of median neurotoxic dose (TD_{50})

Groups of six animals per dose were injected and tested with the RotoRod test. The percentages of animals showing minimal neurotoxicity were recorded and the higher dose producing neurotoxic effects is reported. TD_{50} estimations could not be completed due to solubility problems with high doses.

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