Journal of Medicinal Chemistry

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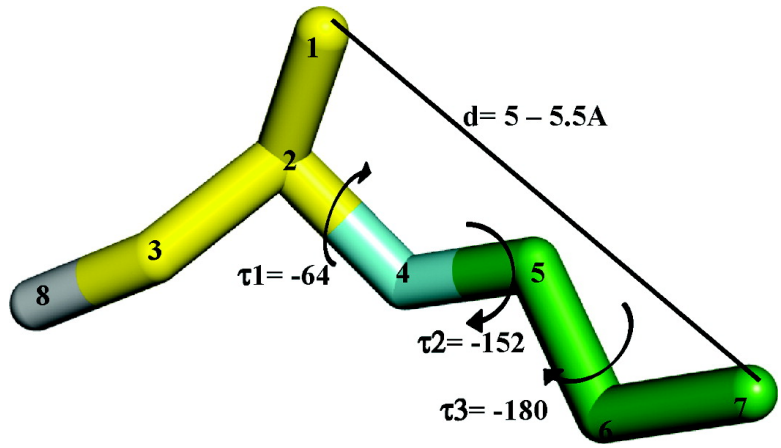
J. Med. Chem., **2009**, 52 (6), 1592-1601• DOI: 10.1021/jm800764p • Publication Date (Web): 27 February 2009



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Synthesis and Anticonvulsant Activity of Amino Acid-Derived Sulfamides

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Received June 23, 2008

Sulfamides are promising functions for the design of new antiepileptic drugs (*Bioorg. Med. Chem.* **2007**, *15*, 1556−1567; 5604−5614). Following previous research in this line, a set of amino acid-derived sulfamides has been designed, synthesized, and tested as new anticonvulsant compounds. The experimental data confirmed the ability of some of the structures to suppress the convulsions originated by the electrical seizure (MES test) at low doses (100 mg/kg).

Introduction

The past decades have witnessed many advances in the development of new strategies for the treatment of epilepsy, mainly focused in the prevention of seizures. The new antiepileptic drugs (AEDs[a]) presently used provide adequate seizure control in a significant number of the patients.[1−4] Unfortunately, it is estimated that up to 30% of the affected people are still resistant to the available medication.[5,6] Furthermore, many AEDs have serious side effects, increasing their toxic actions when a lifelong medication is required.[7] As a result, intensive research efforts are being devoted to find new antiepileptic compounds with more selective activity and lower toxicity.[8]

The incomplete information about the cellular basis of human epilepsy makes it difficult to find a common way to design new drugs. Current AEDs can be broadly classified into four categories on the basis of the main molecular mechanisms through which they act. Their actions include: (i) modulation of voltage-dependent Na^+ or Ca^{2+} channels, (ii) enhancement of GABA-mediated inhibition or other effect on the GABA system, (iii) inhibition of synaptic excitation mediated by ionotropic glutamate receptors, (iv) modulation of synaptic release.[9] However, the use of rational methodologies of design that need the knowledge of the mechanism of action of the active compounds is limited because most of the AEDs interact with more than one receptor. The alternative rational design of new AEDs based on pharmacophoric patterns overcome this difficulty as it works on the optimization of the potency of a particular mode of action and is therefore broadly used in the discovery of new chemical entities.[10−15]

Recent research in our group has analyzed aryl and alkyl sulfamides as new targets of antiepileptic drugs.[16,17] The structures were chosen as potentially active as they comply with the requirements imposed by a pharmacophore for the activity in the maximal electroshock (MES) test,[18] one of the most popular seizure models, usually used together with the subcutaneous pentylenetetrazol (PTZ) test.[18] The pharmacophore previously defined consists of a polar group with a well determined charge distribution, attached to a hydrophobic chain containing at least three carbon atoms (Figure 1), in a well defined spatial orientation.[17] When sulfamide defines the polar function and aryl or alkyl chains are used to satisfy the lipophilic requirements, the activity of the resulting structures in the MES test has been confirmed.[16,17] With a particular aim in improving the physiological characteristics of the drugs, we decided to increase the diversity of our set including amino acids as one of the substituents.

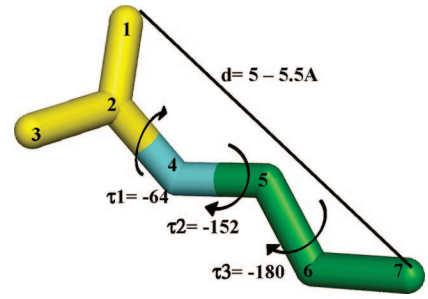

Figure 1. Structure of the pharmacophore proposed.[17] The 3D requirements for the structures to manifest the anti-MES activity can be summarized in: (1) a polar moiety (atoms 1−3, in yellow), (2) a hydrophobic chain (atoms 5−7 in green), placed in a conformation defined by $\tau 1$, $\tau 2$, $\tau 3$, and d and connected through a link atom (atom 4, in cyan).

Amino acids and their derivatives have been investigated for their anticonvulsant action, and some of them were found to be potent AEDs. Several second-generation drugs, as well as drugs in development, have this functionality in their structures (Figure 2).[8]

Amino acids, the fundamental units of peptides, play a significant role in medicinal chemistry. Small peptides represent excellent targets for the design of new drugs due to their potential ability to minimize the difficulties related to the pharmacokinetic of larger peptides without losing the characteristics involved in molecular recognition.[19−21] Unfortunately, even small peptides undergo limitations related to their poor stability toward proteolysis, limited transport properties, rapid metabolism/excretion through the liver and kidneys, and their

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[a] Abbreviations: MES, maximal electroshock seizure; AEDs, antiepileptic drugs; GABA, γ-amino butyric acid; VPA, valproic acid; PTZ, pentylenetetrazol seizure; CSI, chlorosulfonyl isocyanate; NIH, National Institutes of Health; ADD, anticonvulsant drug development; ASP, anticonvulsant screening project; DIAD, diisopropylazodicarboxylate, PEG, polyethylene glycol; VRL, valrocemide; TPE, time of peak effect.

10.1021/jm800764p CCC: $40.75
Published on Web 02/27/2009

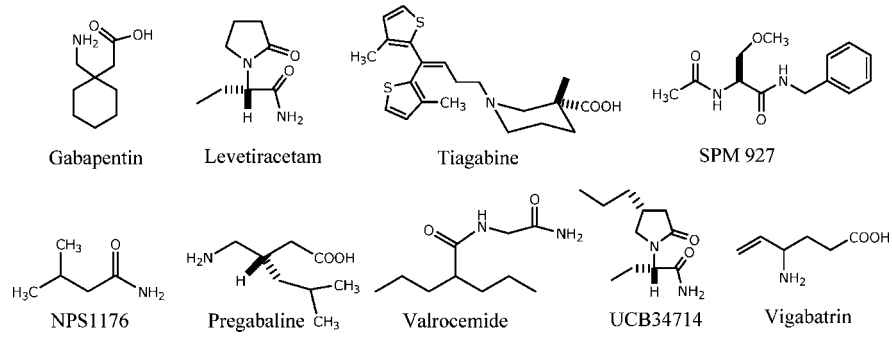


Figure 2. Amino acids and their derivatives acknowledged as antiepileptic drugs.

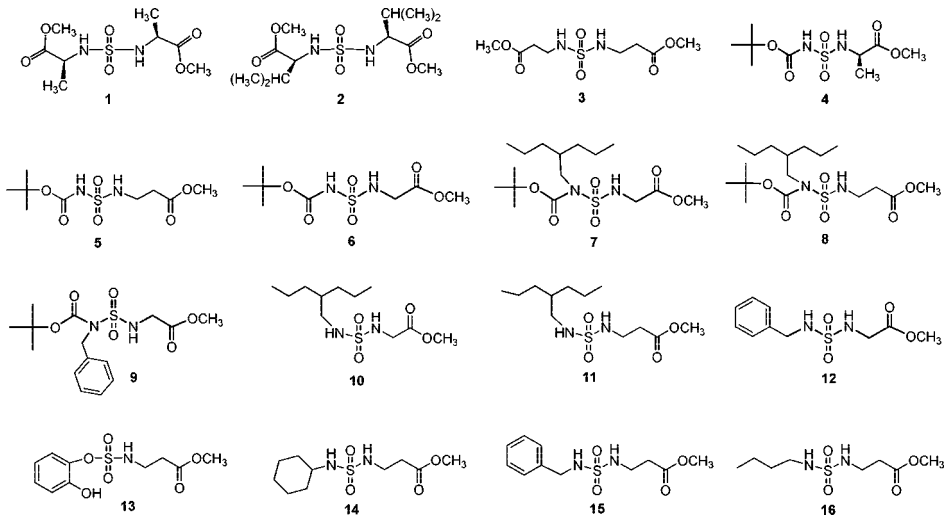


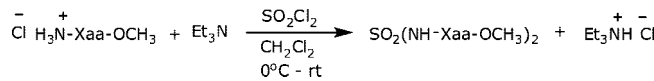
Figure 3. Chemical structures of the compounds synthesized.

inherent flexibility that enables interaction with multiple receptors besides the target (with undesired side-effects). The diminution of the peptide characteristics by means of structural modifications defines a good strategy for the design of new compounds with more desirable physiological and physicochemical characteristics (peptide mimics). In relation to this approach, the urea moiety has been demonstrated to be a useful nonhydrolyzable linker and/or hydrogen bond acceptor.[22−25] Similarly, the sulfamide functionality has been studied as a nonhydrolyzable component of peptide mimetics, showing selectivity and inhibitory activity against proteases.[26−30]

We report herein the synthesis and anticonvulsant activity of a set of amino acid-derived sulfamides. In some compounds, the sulfamide is a nonhydrolyzable linker of two amino ester groups (compounds **1**−**3**, Figure 3), whereas in other structures it connects a lipophilic (alkyl/aryl) group with amino esters (**10**−**12** and **14**−**16**, Figure 3). Figure 3 also include some intermediates whose anticonvulsant activity has been determined (compounds **4**−**9** and the sulfamate **13**). Butyl, benzyl, or cyclohexyl groups have been chosen for the lipophilic chains on the basis of previous data[16] that showed a higher anti-MES potency for sulfamides bearing these substituents.

We have also chosen a 2-propylpentyl substituent to build the lipophilic chain, which is homologous to the hydrophobic backbone in 2-propylpentanoic acid (valproic acid, VPA), one of the first-line AEDs used in the long-term treatment of epilepsy. This decision is further justified by the need of designing VPA related compounds that conserve its anticonvulsant action avoiding its dangerous side effects (mainly related with teratogenicity and hepatotoxicity).[31,32] Amino acid derivatives of VPA have been tested with promising results.[33−35] In particular, *N*-valproyl glycinamide (named valrocemide: VRL, Figure 2) has a broad spectrum of action and is currently undergoing phase II clinical trials in patients with drug-refractory epilepsy.[35]

Scheme 1. Synthetic Route for Symmetric Sulfamides[a]



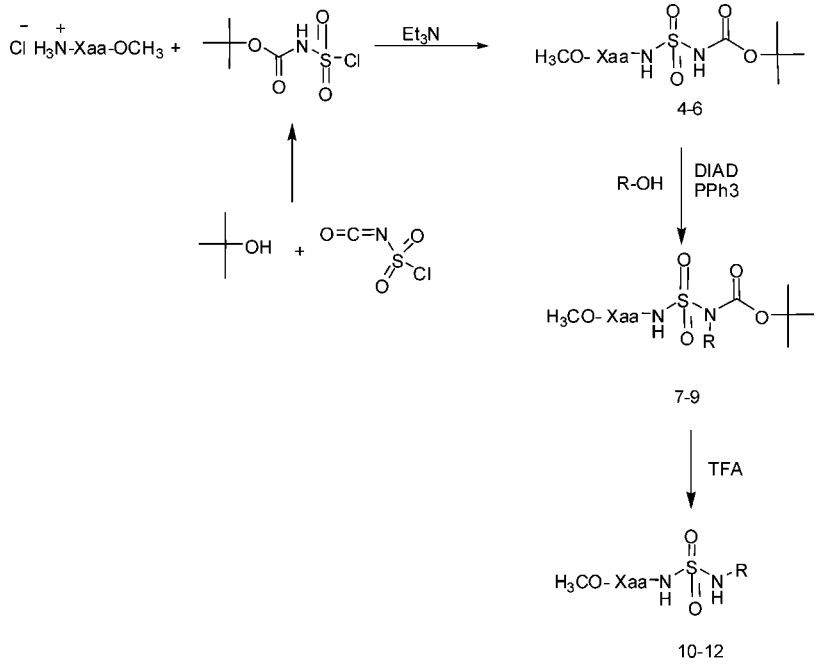
[a] **1**: N-Xaa-O = L-alanine; **2**: N- Xaa-O = L-valine; **3**: N-Xaa-O = β-alanine.

Chemistry. The synthetic processes have been selected according to the sulfamide substituents. The route used for the amino acid-derived symmetric sulfamides is outlined in Scheme 1. Condensation of the corresponding salts of amino esters with sulfuryl chloride in presence of triethylamine produces the sulfamides **1**−**3**.[36]

N-alkyl/aryl, *N*′-sulfamoylaminoesters (compounds **10**−**12** Scheme 2) were prepared by means of the usual procedure:[37,38] one pot synthesis of *N*-terbutoxycarbonyl sulfamides from chlorosulfonyl isocyanate (CSI), *tert*-butanol and the corresponding amino ester in presence of triethylamine; followed by alkylation under Mitsunobu conditions[39] and then acidic hydrolysis (Scheme 2). The greater nucleophilicity of the nitrogen atom of the *N*-acyl group in *N*-terbutoxycarbonyl sulfamides (compounds **4**−**6**, Scheme 2) allows the selective alkylation by means of the Mitsunobu tandem triphenylphosphine (PPh_3) and diisopropylazodicarboxylate (DIAD).

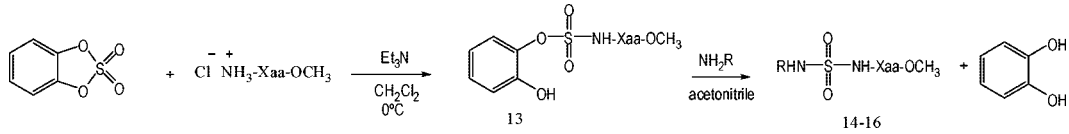
To promote a higher efficiency in the synthetic procedure, an alternative route has been considered: The reaction between

Scheme 2[a]



[a] Synthetic route for *N*-alkyl amino acid derived sulfamides. **4**: N-Xaa-O = L-alanine; **5**: N-Xaa-O = β-alanine; **6**: N-Xaa-O = glycine; 7: N-Xaa-O = glycine, R = 2-propylpentyl; **8**: N-Xaa-O = β-alanine, R = 2-propylpentyl; **9**: N-Xaa-O = glycine, R = benzyl; **10**: N-Xaa-O = glycine, R = 2-propylpentyl; **11**: N-Xaa-O = β-alanine, R = 2-propylpentyl; **12**: N-Xaa-O = glycine, R = benzyl.

Scheme 3. Alternative Synthetic Route for *N*-Alkyl Amino Acid Derived Sulfamides[a]



[a] **13**: HN-Xaa-O = β-alanine; **14**: HN-Xaa-O = β-alanine, cyclohexyl; **15**: HN-Xaa-O = β-alanine, benzyl; 16: HN-Xaa-O = β-alanine, butyl.

catechol sulfate (prepared with catechol and sulfuryl chloride)[40] and the corresponding amino ester under controlled reaction conditions (Scheme 3) to yield a sulfamate ester derivative (compound **13** Scheme 3). The resulting sulfamate compound reacts with the alkyl/aryl amine to yield nonsymmetric sulfamides (structures **14**−**16**, Scheme 3). This method reduces the number of the steps of the reaction relative to the synthetic route previously considered and was successfully applied to the synthesis of aliphatic *N*,*N*′-disubstituted sulfamides.[41]

According to the synthetic procedures selected, the preparation of nonsymmetric sulfamides involves the formation of intermediate products (**4**−**9**, Scheme 2 and **13**, Scheme 3), which were included in the biological analysis. Compounds **4**−**9** were considered as sulfamide derivatives. Compound **13** presents a sulfamate function that is related to the sulfamide moiety as a bioisosteric partner according to Grimm's hydride displacement law.[42,43]

Pharmacology. The biological evaluation of the synthesized compounds was performed following the standard procedures proposed by The NIH anticonvulsant drug development (ADD) program, via the anticonvulsant screening project (ASP).[18] The initial evaluation (phase 1) includes the use of two convulsant tests: maximal electroshock seizure test (MES) and pentylenetetrazole test (PTZ).

The MES test is associated with the electrical induction of the seizure, whereas PTZ test involves a chemical induction to generate the convulsion. Toxicity is primary detected using the standardized RotoRod test, which is also included in the primary phase.

The compounds were administrated to animals (mice) intraperitoneally at three doses (30, 100, and 300 mg/Kg), and all the assays were performed at 0.5 and 4 h.

Quantitative biological studies (phase II) were performed for the most promising compounds from phase I (in MES test). At this stage, the anticonvulsant activity was expressed as median effective dose, ED_{50}, which determines the drug concentration that is effective in the 50% of the tested animals. The evaluations were performed at the time of peak effect (TPE) previously determined.

Details of the evaluation of anticonvulsant activity are given in the Experimental Section.

Results

The results of the biological evaluations are summarized in Tables 1 and 2. The experimental data obtained from the initial evaluation (phase 1, Table 1) allowed us to select the most promising compounds to be promoted to the next stage of the program: quantitative in vivo anticonvulsant evaluations (phase II).

The results presented in Table 1 pointed out that several compounds of the set with positive response in the MES test show a phenytoin-like profile: they exhibit activity in the MES test but they did not show protection in PTZ-induced convulsions, at the same doses and times evaluated. Molecules **11**, **13**, and **15** showed protection against both MES and PTZ test, with responses at doses of 30 mg/kg in the last assay.

No toxicity was observed for the molecules of the set at the evaluated doses. The lack of sedative effects at this early stage

Table 1. Pharmacological Profile (Phase I) of the Synthesized Compounds

compd	class[a]	dose (mg/kg)	activity MES[b] time (h)		TOX[c] time (h)		activity PTZ[d] time (h)	
	1, 2, 3, 4		0.5	4	0.5	4	0.5	4
1	3	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/4	0/4	0/8	0/7	0/4	0/3
		300	0/3	0/3	0/5	0/5	0/2	0/2
2	1	30	0/3	0/3	0/6	0/6	0/3	0/3
		100	1/4	0/3	0/7	0/6	0/3	0/3
		300	1/3	0/3	0/5	0/5	0/2	0/2
3	1	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	1/4	0/4	0/6	0/6	0/2	0/2
		300	1/3	0/3	0/5	0/5	0/2	0/2
4	3	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/3	0/3	0/5	0/5	0/2	0/2
		300	0/3	0/3	0/5	0/5	0/2	0/2
5	2	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/3	0/3	0/5	0/5	0/2	0/2
		300	1/3	0/3	0/5	0/5	0/2	0/2
6	3	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/3	0/3	0/5	0/5	0/2	0/2
		300	0/3	0/3	0/5	0/5	0/2	0/2
7	2	30	0/4	0/3	0/4	0/3	0/2	0/2
		100	0/3	0/3	0/3	0/3	0/2	0/2
		300	0/3	1/3	0/3	0/3	0/2	0/2
8	**3**	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
9	3	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/3	0/3	0/5	0/5	0/2	0/2
		300	0/3	0/3	0/5	0/5	0/2	0/2
10	1	30	0/3	0/3	0/5	0/5	0/3	0/3
		100	1/3	1/3	0/5	0/5	0/3	0/3
		300	1/2	2/3	0/5	0/5	0/3	0/3
11	1	30	1/3	3/3	0/5	0/5	1/2	0/2
		100	0/3	0/3	0/5	0/5	2/2	0/2
		300	1/3	1/3	0/3	0/3	NT	NT
12	3	30	0/3	0/3	0/5	0/5	0/2	0/2
		100	0/3	0/3	0/5	0/5	0/2	0/2
		300	0/2	0/2	0/4	0/4	0/2	0/2
13	1	30	0/3	0/3	0/6	0/6	1/3	0/3
		100	1/3	1/3	0/6	0/6	0/3	0/3
		300	0/3	0/3	0/6	0/6	1/2	0/3
14	1	30	0/3	0/3	0/3	0/3	NT	NT
		100	1/3	2/3	0/3	0/3	NT	NT
		300	0/3	0/3	0/3	0/3	NT	NT
15	1	30	0/3	0/3	0/6	0/6	0/3	1/3
		100	1/3	0/3	0/6	0/6	0/3	0/3
		300	1/3	0/3	0/6	0/5	0/2	0/3
16	1	30	1/3	1/3	0/6	0/6	0/3	0/3
		100	1/3	1/3	0/3	0/6	0/3	0/3
		300	2/3	1/3	0/3	0/6	0/3	0/3

[a] The tested compounds can be classified into four classes according to their activity:[44] (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. We have found eight molecules that belong to class 1 anticonvulsants, the most potent class of antiepileptic drugs. [b] Maximal electroshock seizure. [c] Toxicity evaluated in rotorod test. [d] Pentylentetrazol test. NT: not tested.

of the evaluation process supports the use of amino acids as suitable functionalities for the design of anticonvulsant compounds.

The most promising compounds are **10**, **11**, and **16**, and for them the ED_{50} values for the anticonvulsant activity in the MES test, were determined. As mentioned before, ED_{50} measures the

Table 2. Activity Values against MES Test (ED_{50}, μmol/kg) and Time of Peak Effect (TPE) Determined in Mice for the Sulfamide Derivatives Designed[a]

	MES test		
compd	TPE (h)	ED_{50} (μmol/kg)	RP[b]
10	2	139	7.3
11	2	79	12.8
16	2	71	14.2
13	4	374	2.7
VRL	0.5	755	1.3
VPA	0.25	1008	1

[a] Experimental data for VPA, and VRL were taken from literature.[12,35] [b] RP (relative potency) = $ED_{50VPA}/ED_{50compound}$.

dose that is effective in 50% of the tested animals; details of its determination are given in Experimental Section. Compounds **11** and **16** show positive response at the doses assayed in phase 1 (see Table 1). Compound **10** is similar to **11** in having the same hydrocarbon chain, which is similar also to the hydrophobic backbone in VPA. Finally, ED_{50} was also determined for compound **13** because it is the only structure of the set having a sulfamate function. The results are listed in Table 2, together with the experimental data previously reported for known anticonvulsant drugs structurally related.[12,35]

In spite of the results found in phase I for compounds **11** and **13**, where the number of protected animals remained constant or decreased at the higher dosage, typical dose−response curves were found in phase II for all the four selected compounds and ED_{50} values were calculated based on six animals per dose. These results are not surprising considering that biological data obtained from phase I are not enough to claim a compound active. Accordingly, the SAR analyses have been mainly based on the more reliable phase II derived data.

The pharmacological profile of the new compounds shown in Table 2 is attractive, as they at least duplicate the protection of VPA or VRL at this stage of anticonvulsant biological evaluation. Particularly, the active compounds **10** and **11** contain the 2-propylpentyl hydrocarbon chain as the lipophilic group, linked through the sulfamide function to the amino esters (Figure 3). These structures exhibit some similarities with VRL, a valproic acid derivative with a glycinamide moiety linked to the valpromide function (Figure 2), but significantly improve the antiepileptic activity, which, for compound **11**, is almost 10 times higher than for VRL.

The structures in Table 2 have at least one substituent composed by no less than three carbon atoms attached to the sulfamide/sulfamate function (Figure 4). A superposition analysis (Figure 5) shows that they are able to comply with the requirements defined by the pharmacophore for the anti-MES activity,[2] which further demonstrates the capacity of the model for the design of new active compounds. It is worth mentioning that previous investigations demonstrated that VPA, VRL, and other valproic acid derivatives also complain with the pharmacophore requirements.[12,16]

No positive response was detected for the sulfamides **1**, **4**, **6**, **8**, **9**, and **12** in the initial evaluations of anticonvulsant activity (Table 1). The biological data obtained for these compounds should be considered as preliminary because only phase 1 of the anticonvulsant program has been yet performed. Nevertheless, the proposed pharmacophore allows us to justify the lack of activity of compounds **1**, **4**, and **6**, as they do not comply with the requirements of lipophilicity. This is not the case of compounds **5**, **7**, **8**, and **9**, whose superposition is shown in Figure 6. The compounds in Figure 6 show, as a common feature, a Boc substituent of a sulfamide nitrogen. The inhibition

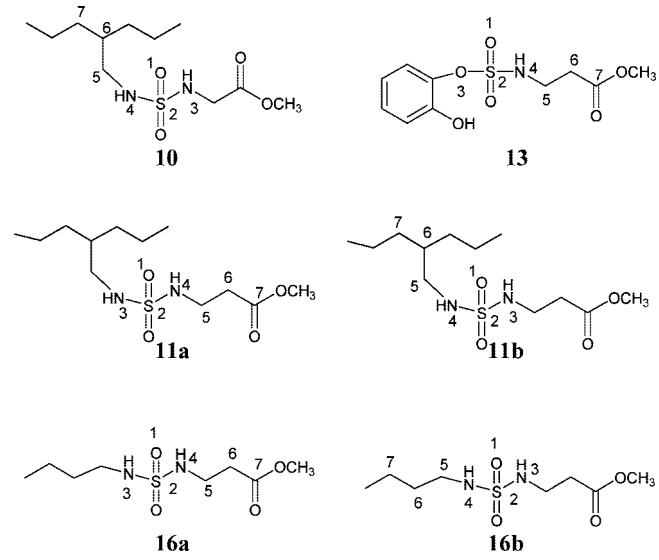


Figure 4. Structures selected for ED50 determination (Table 2). Atoms are numbered for the centers that define the pharmacophoric pattern. In the case of compounds **11** and **16**, the pattern can be satisfied in two different ways.

of the activity by this substitution can be originated in either steric or electronic constrains. We are at this time more prompt to associate it with an electronic effect for the reasons that will be further discussed when analyzing the lower activity of compounds **10** and **13** vs compounds **11** and **16**.

Compounds **11** and **16** can satisfy the pharmacophoric requirements in two different manners. Conversely, compound **10** can only match the requirements if the valproyl moiety is overlapped with the lipophilic portion (Figure 4). The comparison of **10** and **11** shows that, overlapping the 2-propylpentyl chains, a Gly substituent in the first, rather than β-Ala in the second, is attached to the sulfamide nitrogen numbered as 3 in the pharmacophoric pattern (compound **11b**, Figure 4). The attachment of a polar, electron attractor substituent closer to nitrogen 3 has a negative effect, decreasing the activity of compound **10** relative to compound **11**. This fact can also help to understand the lack of protection of compound **12** in phase I. Compound **13** can be brought to the similarity analysis to demonstrate that it places an oxygen atom in the same region as compound **10** (Figure 7), a characteristic not found for the most active compounds **11** and **16**. Compounds **2**, **3**, **14**, and **15** show some activity in phase I, and they comply with the requirements of the previously proposed pharmacophore. Any further SAR analysis was considered tentative as the ED_{50} values have not been determined.

The previous SAR analysis shows that a polar, electron attractor substituent attached near the nitrogen atom 3 of the pharmacophore (oxygen atom 3 in sulfamate) severely hampers the activity (compounds **10** and **13** vs compounds **11** and **16**). Moreover, the lack of antiepileptic activity of compounds **5**, **7**, **8**, and **9** can be originated in a similar effect, leading us to infer that this effect may be distance dependent, and can also explain the diminished activity of compound **3** relative to compound **16**. The best activity has been determined for compounds **11** and **16**, which combine lipophilic and polar moieties. A polar, electron attractor substituent close to atom 7 of the pharmacophore increase the potency relative to *N*,*N*-dibutyl-sulfamide (ED_{50} = 295 μmol/kg), but similar substitutions on the second sulfamide nitrogen have a negative effect. The dependence of this effect on the distance has to be analyzed in more detail.

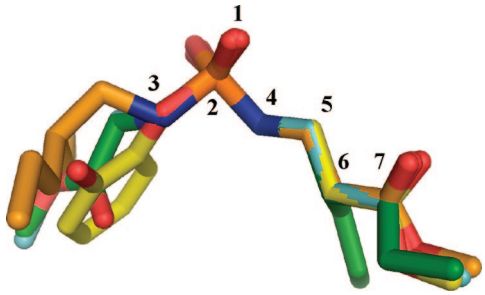


Figure 5. Superposition of the compounds whose ED_{50} was determined, aligned in the conformation defined by the pharmacophore. For molecules **11** and **16**, the amino ester hydrocarbon chains were used as the nonpolar requirement (structures **11a** and **16a** in Figure 4). Color code as follow: compound **10**, green; compound **11**, orange; compound **13**, yellow; compound **16**, cyan. Atoms are numbered for the centers that define the pharmacophoric pattern. Hydrogen atoms were omitted for clarity.

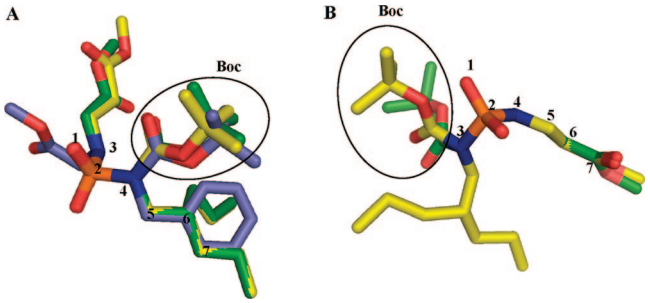


Figure 6. (A) Structures of the compounds **7** (green), **8** (yellow), and **9** (blue). Compound **8** was fitted using the hydrocarbon chain as nonpolar requirement. (B) Structures of the compounds **5** (green) and **8** (yellow). Compound **8** was fitted using the amino ester hydrocarbon chain as nonpolar requirement. Atoms are numbered for the centers that define the pharmacophoric pattern. Hydrogen atoms were omitted.

On the basis of the previous analysis, a new requirement can be proposed, associated with the nature a substituent attached to N 3. This requirement is sketched in Figure 8.

Conclusions

Sulfamides have proven to be attractive targets for the design of new antiepileptic drugs. Compounds containing this functionality have been designed, synthesized, and evaluated in our research group, with promising results.[16,17] Along this research, a pharmacophore has been proposed that has guided our further efforts toward the optimization of the pharmacological profile of new structures.[16,17]

With the aim of improving the physiological and physicochemical characteristics of the drugs, we have synthesized amino acid-substituted sulfamides and tested them in their ability to suppress the epileptic seizure. The results are encouraging, as compounds as active as valpromide (ED_{50} = 353 μmol/kg), zonizamide (ED_{50} = 92 μmol/kg), or phenobarbital (ED_{50} = 94 μmol/kg) have been attained.[16] A SAR analysis has allowed us to extrapolate new requirements for the activity, mainly related to the characteristics of a second substituent in the sulfamide function. The comparison of *N*,*N*-dibutyl-sulfamide (ED_{50} = 295 μmol/kg) and compound **16** (ED_{50} = 71 μmol/kg), shows that a carboxymethy substituent in the position 7 of the pharmacophore has a positive effect in the activity. Nevertheless, substitutions with polar, electron attractor substituents on both nitrogen atoms invert the trend, with a negative effect in the activity.

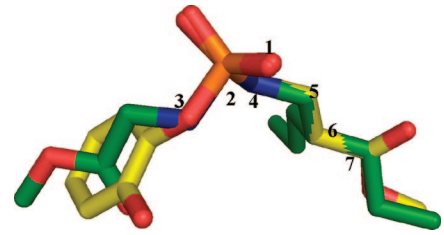


Figure 7. Compounds **10** (green) and **13** (yelllow) aligned according to the pharmacophore requirements. Hydrogen atoms were ommited.

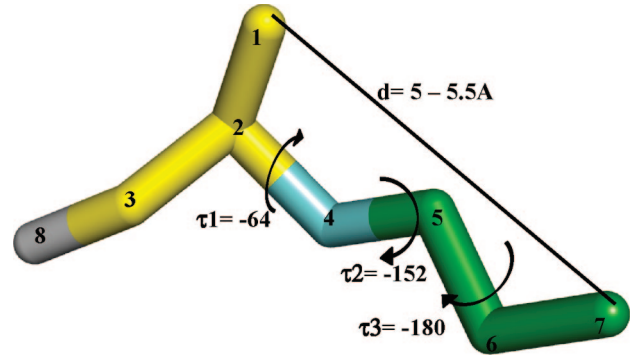


Figure 8. New pharmacophoric pattern proposed, which establish conditions for the group attached to the polar end, represented by atom 8. The anti-MES requirements can be summarized as: (1) a polar moiety (atoms 1−3, in yellow), (2) a hydrophobic chain (atoms 5−7 in green), placed in a conformation defined by t1, t2, t3 and d and connected to the polar moiety through a link atom (atom 4, in cyan), (3) any group attached to atom 3 should be nonpolar or H.

It seems early in this research to establish uniquely new pharmacophore requirements for anti-MES activity. This will require a systematic analysis of a series of compounds bearing polar substitutions at different distances of the sulfamide moiety. Nevertheless, from this study, we can better tune the characteristics of a possible substitution on N3, which are described by the new pharmacophore shown in Figure 8.

We hope that the research presented here will guide rational modifications that lead to new compounds of better potency, achieved by a balanced combination of polar and nonpolar groups in *N*,*N*′-disubstituted sulfamides.

Experimental Section

Chemistry: General Information. Melting points were determined using capillary tubes with an electrothermal melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed with aluminum backed sheets with silica gel 60 F254 (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). Then 200 MHz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer. The chemical shifts were reported in ppm (δ scale) relative to internal TMS, and coupling constants were reported in Hertz (Hz). IR spectra were run on a FT/IR Perkin-Elmer spectrophotometer. Absorption values were expressed as wave numbers (cm^{-1}); only significant absorption bands are given. ES-MS spectra were recorded for some compounds with an Agilent 1100 series spectrometer; only molecular ions (M + H, M − H, and M + Na) are given. Analytical grade solvents were used for crystallization, while pure for synthesis solvents were used in the reactions, extractions, and column chromatography. Commercial amines were distilled prior to their use. All reagents used in the present study were of analytical grade (Sigma-Aldrich, Fluka). Elemental analyses were carried out at the Mycroanalysis Service

of INQUIMAE (Argentina) and results were within ±0.3% of the theoretical values.

Methyl Esters of Amino Acid Symmetric Sulfamides. The synthesis of these compounds, starting from the corresponding salt of the amino acid esters, triethylamine and sulfuryl chloride was carried out according to the general procedures previously described.[36]

***N,N′*-Sulfonyl Bis-L-alanine Dimethyl Ester (1).**[36] Melting point 125−126 °C. IR (KBr) ν 3271, 1738, 1348, 1132 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.26 (d broad, $J \approx 7.0$ Hz, 2H, NH), 4.10 (m, 2H, CH), 3.77 (s, 6H, O-CH_3), 1.45 (d, $J = 7.1$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 173.66 (C═O), 52.69 (CH), 51.81 (O-CH_3), 19.24 (CH_3). Anal. calcd for $C_8H_{16}N_2O_6S$: C 35.8, H 6.0, N 10.4, S 12.0; found: C 35.7, H 6.1, N 10.3, S 12.0.

***N,N′*-Sulfonyl Bis-L-valine Dimethyl Ester (2).**[36] Melting point 78−79 °C. IR (KBr) ν 3321, 3268, 1738, 1327, 1138 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.10 (d, $J = 9.5$ Hz, 2H, NH), 3.88 (dd, $J = 9.5$, 4.5 Hz, 2H, CH-N), 3.77 (s, 6H, O-CH_3), 2.13 (m, 2H, CH isopropyl), 1.01 (d, $J = 6.8$ Hz, 6H, CH_3 isopropyl), 0.90 (d, $J = 6.8$ Hz, 6H, CH_3 isopropyl). ^{13}C NMR ($CDCl_3$) δ 172.85 (C═O), 61.13 (C−N), 52.39 (O-CH_3), 31.47 (CH isopropyl), 18.78 (CH_3 isopropyl), 17.43 (CH_3 isopropyl). Anal. calcd for $C_{12}H_{24}N_2O_6S$: C 44.4, H 7.5, N 8.6, S 9.9; found: C 44.7, H 7.4, N 8.3, S 9.7.

***N,N′*-Sulfonyl Bis-*β*-alanine Dimethyl Ester (3).** A solution of H-*β*-Ala-OMe·HCl (2.08 g, 14.6 mmol) and CH_2Cl_2 (50 mL) was cooled to 0 °C. Et_3N (6.12 mL, 43.8 mmol) was added slowly, and the resulting solution was stirred for 20 min. A solution of SO_2Cl_2 (0.6 mL, 7.31 mmol) in dichloromethane (5.0 mL) was added dropwise in dark conditions over 40 min. The reaction mixture was warmed to room temperature, stirred for 4 h, and monitored by TLC (SiO2). The medium was diluted with 50.0 mL of CH_2Cl_2 and washed with aqueous $NaHSO_4$ and brine (3×). The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Crystallization with diethyl ether afforded the product as a white solid (0.41 g, 21%). Melting point 40.5−41 °C. IR (KBr) ν 3301, 1736, 1323, 1153 cm^{-1}. ^1H NMR ($CDCl_3$), δ 5.01 (t, $J = 6.4$ Hz, 2H, NH), 3.72 (s, 6H, O-CH3), 3.31 (system AM2 × 2, $J = 6.4$, 6.1 Hz, 4H, N-CH_2), 2.03 (t, $J = 6.1$ Hz, 4H, CH_2−CO). ^{13}C NMR ($CDCl_3$) δ 172.55 (C═O), 51.94 (O-CH3), 38.72 (C−N), 33.76 (C-CO). Anal. calcd for $C_8H_{16}N_2O_6S$: C 35.8, H 6.0, N 10.4, S 12.0; found: C 35.6, H 5.7, N 10.5, S 12.2.

MethylEstersof[*N*-(*N′*-*tert*-Butoxycarbonyl)-sulfamoyl]Amino Acids. Typically the synthesis was carried out according to literature procedures. The reaction involved the use of chlorosulfonyl isocianate (CSI), tert-butanol and the corresponding salt of the amino acid esters.[37]

(*S*)(−)-Methyl [*N*-(*N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-alaninate (4).[37] Melting point 126−127 °C. IR (KBr) ν 3296, 3267, 1745, 1720, 1371, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.56 (s, 1H, NH-Boc), 5.91 (d, $J = 8.1$ Hz 1H, NH Ala), 4.26 (m, 1H, CH), 3.77 (s, 3H, O-CH_3), 1.50 (s, 9H, CH_3 *tert*-butyl), 1.47 (d, $J = 7.3$ Hz, 3H, CH_3 Ala). ^{13}C NMR ($CDCl_3$) δ 172.44 (C═O ester), 149.95 (C═O Boc), 83.92 ($C(CH_3)_3$), 52.73 (CH), 52.39 (O-CH_3), 27.91 (CH_3 *tert*-butyl), 19.31 (CH_3 Ala). Anal. calcd for $C_9H_{18}N_2O_6S$: C 38.3, H 6.4, N 9.9, S 11.4; found: C 38.2, H 6.4, N 9.8, S 11.5.

Methyl [*N*-(*N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-*β*-alaninate (5). A solution of CSI (2.5 mL, 28.7 mmol) and *tert*-butanol (4.8 mL, 71.8 mmol) in CH_2Cl_2 (40.0 mL) was added to a cold solution (0 °C) of H-*β*-Ala-OMe·HCl (3.80 g, 27.8 mmol) and Et_3N (8.0 mL, 56.9 mmol) in CH_2Cl_2 (60.0 mL). The reaction mixture was warmed to room temperature, stirred for 18 h, and monitored by TLC (SiO_2). The medium was diluted with 50 mL CH_2Cl_2 and washed with 1% acetic acid (2×) and brine (2×). The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Crystallization with hexane/CH_2Cl_2 afforded the product as a white solid (4.83 g, 62%). Melting point 103−105 °C. IR (KBr) ν 3279, 3208, 1736, 1701, 1370, 1147 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39 (s, 1H, NH-Boc), 5.74 (t, $J = 6.1$ Hz, 1H, NH *β*-Ala), 3.72 (s, 3H, O-CH_3), 3.38 (system AM_2X_2, $J = 6.1$, 6.1 Hz, 2H, N-CH_2), 2.64 (t, $J = 6.1$ Hz 2H, CH_2−CO), 1.51 (s, 9H, CH_3 *tert*-butyl). ^{13}C NMR ($CDCl_3$) δ 172.05 (C═O ester), 150.07 (C═O Boc), 84.02 ($C(CH_3)_3$), 51.98 (O-CH_3), 39.34 (N−C *β*-Ala), 33.46 (C-CO), 27.94 (CH_3 *tert*-butyl). Anal. calcd for $C_9H_{18}N_2O_6S$: C 38.3, H 6.4, N 9.9, S 11.4; found: C 38.5, H 6.3, N 9.7, S 11.5.

Methyl [*N*-(*N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-glycinate (6).[37] Melting point 106−108 °C. IR (KBr) ν 3264, 1748, 1720, 1364, 1148. ^1H NMR ($CDCl_3$) δ 7.52 (s broad, 1H, NH-Boc), 5.79 (s broad, 1H, NH-Gly), 3.99 (d, $J = 5.4$ Hz, 2H, CH_2), 3.78 (s, 3H, O-CH_3), 1.50 (s, 9H, CH_3 *tert*-butyl). ^{13}C NMR ($CDCl_3$) δ 169.25 (C═O ester), 149.97 (C═O Boc), 84.06 ($C(CH_3)_3$), 52.61 (O-CH_3), 44.91 (N−C), 27.96 (CH_3 *tert*-butyl). Anal. calcd for $C_8H_{16}N_2O_6S$: C 35.8, H 6.0, N 10.4, S 12.0; found: C 35.8, H 6.1, N 10.2, S 12.0.

General Procedure of Mitsunobu Reaction. The reactions were performed following the experimental data achieved from literature,[37,38] using equimolar quantities of the tandem PPh_3/DIAD.[39]

Methyl [*N*-(*N′*-2-Propylpentyl, *N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-glycinate (7). To a cold solution (0 °C) of PPh_3 (0.97 g, 3.7 mmol) and 2-propyl-1-pentanol (0.6 mL, 3.7 mmol) in THF (4.0 mL) was added a solution of the [Boc-sulfamide] amino ester **6** (1.00 g, 3.7 mmol) and DIAD (0.8 mL, 3.7 mmol) in THF (4 mL). The reaction medium was stirred at 0 °C for 1 h under argon atmosphere. The solvent was removed under reduced pressure, and the crude residue was purified by chromatography (CH_2Cl_2) followed by crystallization (hexane), affording the product as a white solid (1.34 g, 74%). Melting point 57.5−58 °C. IR (KBr) ν 3368, 2960, 2932, 2870, 1733, 1706, 1358, 1142 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.88 (t, $J = 5.4$ Hz, 1H, NH-Gly), 3.87 (d, $J = 5.4$ Hz, 2H, CH_2 Gly), 3.78 (s, 3H, O-CH_3), 3.54 (d, $J = 7.3$ Hz, 2H, N-CH_2 2-propylpentyl), 1.79 (m, 1H, CH 2-propylpentyl), 1.54 (s, 9H, CH_3 *tert*-butyl), 1.39−1.19 (m, 8H, CH_2−CH_2 2-propylpentyl), 0.89 (t, $J = 6.7$ Hz, 6H, CH_3 2-propylpentyl). ^{13}C NMR ($CDCl_3$), δ: 168.90 (C═O ester), 152.09 (C═O Boc), 84.19 ($C(CH_3)_3$), 52.62 (O-CH_3), 52.00 (N−C 2-propylpentyl), 44.82 (N−C Gly), 37.56 (*β*-C 2-propylpentyl), 33.23 (*γ*-C 2-propylpentyl), 27.93 (CH_3 *tert*-butyl), 19.34 (*δ*-C 2-propylpentyl), 14.38 (CH_3 2-propylpentyl). Anal. calcd for $C_{16}H_{32}N_2O_6S$: C 50.5, H 8.5, N 7.4, S 8.4; found: C 50.5, H 8.6, N 7.1, S 8.3.

Methyl [*N*-(*N′*-2-Propylpentyl, *N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-*β*-alaninate (8). To a cold solution (0 °C) of PPh_3 (4.52 g, 17.2 mmol) and 2-propyl-1-pentanol (2.7 mL, 17.2 mmol) in THF (19.0 mL) was added a solution of the [Boc-sulfamide] amino ester **5** (4.86 g, 17.2 mmol) and DIAD (3.39 mL, 17.2 mmol) in THF (19.0 mL). The reaction medium was stirred at 0 °C for 2 h under argon atmosphere. The solvent was removed under reduced pressure and the crude residue was purified by chromatography (CH_2Cl_2) followed by crystallization (hexane), affording the product as a white solid (3.97 g, 59%). Melting point 36−37 °C. IR (KBr) ν 3368, 2960, 2933, 2872, 1762, 1704, 1358, 1141 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.89 (t, $J = 6.6$ Hz, 1H, NH-*β*-Ala), 3.71 (s, 3H, O-CH_3), 3.57 (d, $J = 7.3$ Hz, 2H, N-CH_2 2-propylpentyl), 3.25 (system AM_2X_2, $J = 6.6$, 6.1 Hz, 2H, N-CH_2 *β*-Ala), 2.60 (t, $J = 6.1$ Hz, 2H, CH_2−CO), 1.81 (m, 1H, CH 2-propylpentyl), 1.54 (s, 9H, CH_3 *tert*-butyl), 1.39−1.22 (m, 8H, CH_2−CH_2 2-propylpentyl), 0.89 (t, $J = 6.6$ hz, 6H, CH_3 2-propylpentyl). ^{13}C NMR ($CDCl_3$) δ 172.19 (C═O ester), 153.31 (C═O Boc), 84.33 ($C(CH_3)_3$), 52.20 (O-CH_3), 52.10 (N−C 2-propylpentyl), 39.4 (N−C *β*-Ala), 37.81 (*β*-C 2-propylpentyl), 34.13, (C-CO), 33.67 (*γ*-C 2-propylpentyl), 28.20 (CH_3 *tert*-butyl), 19.62 (*δ*-C 2-propylpentyl), 14.63 (CH_3 2-propylpentyl). Anal. calcd for $C_{17}H_{34}N_2O_6S$: C 51.8, H 8.7, N 7.2, S 8.1; found: C 51.5, H 8.9, N 7.5, S 8.2.

Methyl [*N*-(*N′*-Benzyl, *N′*-*tert*-Butoxycarbonyl)-sulfamoyl]-glycinate (9).[37] Melting point 114−115 °C. IR (KBr) ν 3331, 3091, 3035, 1734, 1369, 1154. ^1H NMR ($CDCl_3$), δ 7.38−7.24 (m, 5H, Ar−H), 5.74 (t, $J = 5.4$ Hz, 1H, NH Gly), 4.83 (s, 2H, CH_2 benzyl), 3.69 (s, 3H, O-CH_3), 3.62 (d, $J = 5.4$ Hz, 2H, CH_2 Gly), 1.52 (s, 9H, CH_3 *tert*-butyl). ^{13}C NMR ($CDCl_3$) δ 168.81 (C═O ester), 151.67 (C═O Boc), 137.48 (C^1−Ar), 128.49, 128.11, 127.75 ($C^{2,3,4}$-Ar), 84.71 ($C(CH_3)_3$), 52.50 (O-CH_3), 50.59 (CH_2 benzyl), 44.43 (N−C Gly), 27.95 (CH_3 *tert*-butyl). Anal. calcd for $C_{15}H_{22}N_2O_6S$: C 50.3, H 6.2, N 7.8, S 8.9; found: C 50.5, H 6.5, N 7.5, S 9.0.

General Procedure for Acidic Decarbamylation. The N-Boc (alkyl/aryl) sulfamides derivatives (7−9) were treated with a solution of trifluoroacetic acid in CH_2Cl_2 as described in literature.[37]

Methyl [*N*-(*N*′-2-Propylpentyl)-sulfamoyl]-glycinate (10). A solution of 50% v/v of trifluoroacetic acid (1.5 mL, 18.9 mmol) in CH_2Cl_2 was added dropwise to the N-Boc alkyl sulfamide 7 (0.79 g, 2.1 mmol), which was previously dissolved in 22.0 mL of CH_2Cl_2 and cooled to 0 °C. The reaction medium was warmed to room temperature and stirred for 21 h, concentrated under reduced pressure, and coevaporated with diethyl ether. The crude residue was purified by chromatography (CH_2Cl_2), affording the product as a white solid (0.24 g, 41%). Melting point 41−42 °C. IR (KBr) γ 3350, 3285, 2971, 2928, 1734, 1328, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.06 (s broad, 1H, NH-Gly), 4.40 (s broad, 1H, NH 2-propylpentyl), 3.83 (s, 3H, O-CH_3), 3.80 (s broad, 2H, CH2 Gly), 2.97 (d, J = 5.9 2H, N-CH_2 2-propylpentyl), 1.55 (m, 1H, CH 2-propylpentyl), 1.37−1.20 (m, 8H, CH_2−CH_2 2-propylpentyl), 0.88 (t, J = 6.7, CH_3 2-propylpentyl). ^{13}C NMR ($CDCl_3$) δ 170.56 (C═O ester), 52.83 (O-CH3), 46.49 (N−C 2-propylpentyl), 44.51 (N−C Gly), 37.44 (β-C 2-propylpentyl), 34.01 (γ-C 2-propylpentyl), 19.86 (δ-C 2-propylpentyl), 14.38 (CH_3 2-propylpentyl). Anal. calcd for $C_{11}H_{24}N_2O_4S$: C 47.1, H 8.6, N 10.0, S 11.4; found: C 47.0, H 8.7, N 10.2, S 11.5.

Methyl [*N*-(*N*′-2-Propylpentyl)-sulfamoyl]-β-alaninate (11). A solution of 50% v/v of trifluoroacetic acid (2.5 mL, 33.9 mmol) in CH_2Cl_2 was added dropwise to the N-Boc alkyl sulfamide **8** (3.97 g, 10.1 mmol), which was previously dissolved in 25.0 mL of CH_2Cl_2 and cooled to 0 °C. The reaction medium was warmed to room temperature and stirred for 44 h, concentrated under reduced pressure. The crude residue was purified by chromatography (CH_2Cl_2) followed by crystallization (hexane), affording the product as a white solid (1.03, 36%). Melting point 48−49.5 °C. IR (KBr), γ 3357, 3286, 2971, 2942, 1757, 1329, 1157. ^1H NMR ($CDCl_3$) δ 4.94 (s broad, 1H, NH-β-Ala), 4.32 (s broad, 1H, NH 2-propylpentyl), 3.72 (s, 3H, O-CH_3), 3.31 (t broad, J = 6.1 Hz, 2H, N-CH_2 β-Ala), 2.95 (d broad, J = 5.8 Hz, 2H, N-CH_2 2-propylpentyl), 2.64 (t, J = 6.1 Hz, 2H, CH_2−CO), 1.55 (m, 1H, CH 2-propylpentyl), 1.49−1.20 (m, 8H, CH_2−CH_2 2-propylpentyl), 0.87 (t, J = 6.6 Hz, 6H, CH_3 2-propylpentyl). ^{13}C NMR ($CDCl_3$) δ 172.84 (C═O), 52.18 (O-CH_3), 46.44 (N−C 2-propylpentyl), 38.95 (N−C-β-Ala), 37.45 (β-C 2-propylpentyl), 34.13, (C-CO), 34.05 (γ-C 2-propylpentyl), 19.90 (δ-C 2-propylpentyl), 14.53 (CH_3 2-propylpentyl). Anal. calcd for $C_{12}H_{26}N_2O_4S$: C 49.0, H 8.8, N 9.5, S 10.9; found: C 49.0, H 8.9, N 9.4, S 10.9.

Methyl [*N*-(*N*′-Benzyl)-sulfamoyl]-glycinate (12).[37] Melting point 72−72.5 °C. IR (KBr) ν 3297, 3280, 3064, 3034, 1741, 1359, 1154. ^1H NMR (CDCl3) δ 7.65−7.26 (m, 5H: Ar−H), 5.02 (t, $J \approx$ 5.5 Hz, 1H, NH Gly), 4.81 (t, $J \approx$ 6.0 Hz, 1H, NH-benzyl), 4.17 (d, J = 6.0 Hz, 2H, CH2 benzyl), 3.73 (d, J = 5.5 Hz, 2H, CH2 Gly), 3.67 (s, 3H, O-CH3). ^{13}C NMR (CDCl3) δ 170.44 (C═O ester), 136.86 (C^1−Ar), 128.99, 128.27, 128.18 ($C^{2,3,4}$-Ar), 52.83 (O-CH_3), 47.50 (CH_2 benzyl), 44.46 (N−C Gly). Anal. calcd for $C_{10}H_{14}N_2O_4S$: C 46.5, H 5.5, N 10.8, S 12.4; found: C 46.4, H 5.6, N 11.1, S 12.4.

General Procedure for the Synthesis via Catechol Sulfate. The reaction starts with the preparation of the sulfamate intermediate **13**, using procedures reported in literature.[40] The product reacts with the corresponding amine to give the expected sulfamide.

2-Hydroxyphenyl-*N*-β-alanine-methyl Ester Sulfamate (13). A solution of catechol sulfate (5.68 g., 33.0 mmol) in 10.0 mL of CH_2Cl_2 was added dropwise to a solution of H-β-Ala-OMe.HCl (4.17 g, 30.0 mmol) and triethylamine (9.2 mL, 66.0 mmol) in 50.0 mL of CH_2Cl_2 with vigorous stirring at 0 °C under dry argon. After 6 h, the reaction mixture was washed with 15 mL of 5% hydrochloric acid (3×), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization with CH_2Cl_2 afforded the product as a white solid (6.60 g, 80.0%). Melting point 102−104 °C. IR (KBr) ν 3484, 3208, 1712, 1374, 1151. ^1H NMR ($CDCl_3$) δ 7.26−6.87 (m, 4H, Ar−H), 6.45 (s broad, 1H, OH), 5.74 (s broad, 1H, NH-β-Ala), 3.78 (s, 3H, O-CH_3), 3.52 (system AM_2X_2, J = 5.8, 5.8 Hz 2H, N-CH_2 β-Ala), 2.65 (t, J = 5.8, 2H, CH_2−CO). ^{13}C NMR ($CDCl_3$) δ 171.24 (C═O), 149.81 (C-OH), 137.69 (C^1 Ar), 127.47, 123.58, 119.13, 117.38 ($C^{2,3,4,5}$ Ar), 51.55 (O-CH_3), 38.68 (N−C-β-Ala), 33.78 (C-CO). Anal. calcd for $C_{10}H_{13}NO_6S$: C 43.6, H 4.7, N 5.1, S 11.7; found: C 43.6, H 4.7, N 5.1, S 11.7. MS (ES): m/z 274.0 (M − H).

Methyl [*N*-(*N*′Cyclohexyl)-sulfamoyl]-β-alaninate (14). A solution of cyclohexylamine (0.44 g, 4.4 mmol) and acetonitrile (5.0 mL) was added dropwise to a solution of the sulfamate **13** (1.1 g., 4 mmol) in 15.0 mL of acetonitrile at 0 °C under dry argon. The reaction medium was stirred, warmed, and refluxed during 6 h. The crude product was concentrated under reduced pressure and purified by chromatography (CH_2Cl_2) to give white solid that was crystallized with CH_2Cl_2 (0.61 g, 58%). Melting point 49−50 °C. IR (KBr) ν 3300, 3264, 1740, 1325, 1140 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.00 (t, J = 6.3 Hz, 1H, NH-β-Ala), 4.57 (d broad, 1H, NH-cyclohexyl), 3.68 (s, 3H, O-CH_3), 3.27 (system AM_2X_2, J = 6.3, 6.2 Hz 2H, N-CH_2 β-Ala), 2.60 (t, J = 6.2, 2H: CH_2−CO), 1.98−1.16 (m, 10H, CH_2-cyclohexyl).^{13}C NMR ($CDCl_3$) δ 172.79 (C═O), 52.92 (O-CH_3), 52.13 (N−C-cyclohexyl), 38.96 (N−C-β-Ala), 34.13 (C-CO), 34.13 (β-C cyclohexyl), 25.48 (γ-C cyclohexyl), 25.00 (δ-C cyclohexyl). Anal. calcd for $C_{10}H_{20}N_2O_4S$: C 45.5, H 7.6, N 10.6, S 12.1; found: C 45.4, H 7.6, N 10.7, S 12.2. MS (ES): m/z 265.0 (M + H), 287.0 (M + Na).

Methyl [*N*-(*N*′Benzyl)-sulfamoyl]-β-alaninate (15). A solution of benzylamine (1.41 g, 13.2 mmol) and acetonitrile (5.0 mL) was added dropwise to a solution of the sulfamate **13** (3.3 g., 12 mmol) in 15.0 mL of acetonitrile at 0 °C under dry argon. The reaction medium was stirred, warmed, and refluxed during 16 h. Workup required washed with 1 N NaOH (2×), brine (1×), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by chromatography (CH_2Cl_2) to give white solid, which was crystallized with CH_2Cl_2 (1.63 g, 50%). Melting point: 59−60 °C. IR (KBr) γ 3264, 3250, 3030, 1744, 1319, 1154 cm^{-1}. ^1H NMR ($CDCl_3$), δ 7.35−7.25 (m, 5H, Ar−H), 5.03 (t, J = 6.3, 1H, NH β-Ala), 4.96 (t, J = 6.3, 1H, NH-benzyl), 4.17 (d, J = 6.3, 2H, CH_2-benzyl), 3.66 (s, 3H, O-CH_3), 3.23 (system AM_2X_2, J = 6.25, 6.25 N-CH_2 β-Ala), 2.52 (t, J = 6.3 2H, CH_2−CO). ^{13}C NMR ($CDCl_3$) δ 172.78 (C═O), 137.08 (C^1 Ar), 128.97, 128.29, 128.13 ($C^{2,3,4}$ Ar), 52.17 (O-CH_3), 47.40 (CH_2 benzyl), 38.90 (N−C β-Ala), 34.06 (C-CO). Anal. calcd for $C_{11}H_{16}N_2O_4S$: C 48.5, H 5.9, N 10.3, S 11.8; found: C 48.6, H 5.8, N 10.3, S 11.7. MS (ES): m/z: 273.0 (M + H), 295.0 (M + Na).

Methyl [*N*-(*N*′Butyl)-sulfamoyl]-β-alaninate (16). A solution of butylamine (0.64 g, 8.8 mmol) and acetonitrile (5.0 mL) was added dropwise to a solution of the sulfamate **13** (2.2 g., 8 mmol) in 15.0 mL of acetonitrile. The reaction medium was stirred, warmed, and refluxed during 6 h. Workup required washed with 1 N NaOH (2×) and brine (1×), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by chromatography (CH_2Cl_2) to give white solid, which was crystallized with CH_2Cl_2 (0.94 g, 50%). Melting point: 47−48 °C. IR (KBr) ν 3281, 3261, 1737, 1142. ^1H NMR ($CDCl_3$) δ 5.03 (t, J = 6.4, 1H, NH β-Ala), 4.60 (t, J = 5.9 1H, NH-butyl), 3.68 (s, 3H, O-CH_3), 3.27 (system AM_2X_2, J = 6.4, 6.4 N-CH_2 β-Ala), 2.99 (m, 2H, N-CH_2 butyl), 2.6 (t, J = 6.4 2H, CH_2−CO β-Ala), 1.55−1.28 (m, 4H, CH_2−CH_2 butyl), 0.89 (t, J = 6.9 3H, CH_3 butyl). ^{13}C NMR ($CDCl_3$) δ 172.78 (C═O ester), 52.12 (O-CH_3), 43.12 (α-C butyl), 38.92 (N−C β-Ala), 34.16 (C-CO β-Ala), 31.74 (β-C butyl), 20.07 (γ-C butyl), 13.82 (CH_3-butyl). Anal. calcd for $C_8H_{18}N_2O_4S$: C 40.3, H 7.6, N 11.8, S 13.4; found: C 40.2, H 7.7, N 11.8, S 13.4. MS (ES): m/z: 239.0 (M + H), 261.0 (M + Na).

Biological Data. The evaluation of the anticonvulsant activity was performed by following the anticonvulsant drug development (ADD) program of the National Institutes of Health.[45] Adult male albino mice (18−23 g) were used as experimental animals. Animals of the same age and weight have been 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 structures tested were dissolved properly in

the vehicle in all the cases, without solubility problems. The drugs were administrated intraperitoneally (ip) in mice in a volume of 0.01 mL/g body weight.

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 was used to compute the ED_{50} values.[46]

Acknowledgment. L. E. Bruno-Blanch is a member of the Facultad de Ciencias Exactas, Universidad Nacional de La Plata; L. Gavernet, G. A. Samaja, and V. Pastore are fellowship holders of Consejo Nacional de Investigaciones Científicas y Técnicas de la República Argentina (CONICET); J. E. Elvira is a fellowship holder of Agencia Nacional de Promoción Científica y Tecnológica. We also thank the reviewers, who have helped with the improvement of the quality of our work with their valuable comments and suggestions. This research was supported in part through grants from Agencia de Promoción Científica y Tecnológica (PICT 06-11985/2004), CONICET, and Universidad Nacional de La Plata, Argentina.

Supporting Information Available: Data from microanalysis for all compounds and ES-MS spectra for structures **13** to **16** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM800764P