Bioorganic & Medicinal Chemistry xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and anticonvulsant activity of bioisosteres of trimethadione, N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides from α-hydroxyamides

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ARTICLE INFO

Article history:
Received 11 October 2012
Revised 13 December 2012
Accepted 22 December 2012
Available online xxxx

Keywords:
N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides
α-Hydroxyamides
Microwave synthesis
Anticonvulsant screening

ABSTRACT

The synthesis and anticonvulsant activity of novel heterocycles N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides, bioisosteres of trimethadione (TMD, oxazolidine-2,4-dione) and phenytoin (PHE), are described. TMD is an anticonvulsant drug widely used against absences seizures in the early 80's and PHE is an antiepileptic drug with a wide spectrum activity. The intermediates of synthesis of N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides, α-hydroxyamides, were obtained using microwave assisted synthesis. Anticonvulsant screening was performed in mice after intraperitoneal administration in the maximal electroshock seizure test (MES) and subcutaneous pentylenetetrazole seizures test (scPTZ). These new compounds showed a wide spectrum activity and were no neurotoxic in the RotoRod test. α-Hydroxyamides and N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides were 3–4700 times more potent than valproic acid in the MES test. Quantification of anticonvulsant protection was calculated (ED_{50}) for the most active candidates; α-hydroxyamides **3a–c** and **3e**, and N-derivative-oxathiazolidine-4-one-2,2-dioxides **5a–c** with ED_{50} values of 9.1, 53.9, 44.6, 25.2, 15.1, 91.1 and 0.06 mg/kg, respectively, in the MES test.

1. 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. New antiepileptics drugs (AEDs) currently in used provide adequate seizure control in a significant number of the patients.[1–4] Between 1990 and 2011 fifteen new antiepileptic drugs (AEDs) were approved: eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, retigabine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide. Many AEDs enlarge serious side effects that are increased when a lifelong medication is required.[5] Pharmacoresistance and therapeutic failure in 20–25% of the patients remain the main reasons to continue the search for safer and more efficacious drugs for this devastating disease.[6,7] As a result, intensive efforts are being devoted to find new antiepileptic compounds with more selective activity and lower toxicity.[8]

Treatment of seizures with bromides in 1850 is considered the first attempt for AED therapy.[9–11] Phenobarbital (PB) and phenytoin (PHE) were introduced as anticonvulsant agents in 1912 and 1940, respectively.[12,13] These two compounds were the best choices for patients with epilepsy for many years. Even today PHE is one of the major drugs used in epilepsy treatment. Although both drugs have a broad anti-epileptic spectrum they have no effect on absence seizures. In 1945, trimethadione (TMD) was developed as the first drug specific for absence seizures.[14,15] For the next fifteen years many new antiepileptic drugs were developed by modification of these molecules that were effective against different types of seizures.[16]

TMD is the most important of several antiepileptic oxazolidinediones.[17] Its selective efficacy against absence seizure in man and its profile of efficacy in experimental animal models were quickly recognized and were the contrary for those of PHE. Although it was the drug of choice, as it was the only truly effective drug for treatment of absence seizures, interest in TMD has declined since the introduction of ethosuximide and valproic acid. Moreover, TMD caused '*fetal trimethadione syndrome*' so this led to withdrawal from the marketplace.[18]

Clinically the oxazolidinediones are effective in the control of absence and related seizure types but not of partial or generalized tonic–clonic seizures.[19] N-Substituted oxazolidinediones, TMD derivatives, were synthesized by the pyrolysis of carbonate esters of the corresponding α-hydroxyamides[20] and anticonvulsant activity for some α-hydroxyamides have been already described.[21]

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http://dx.doi.org/10.1016/j.bmc.2012.12.033

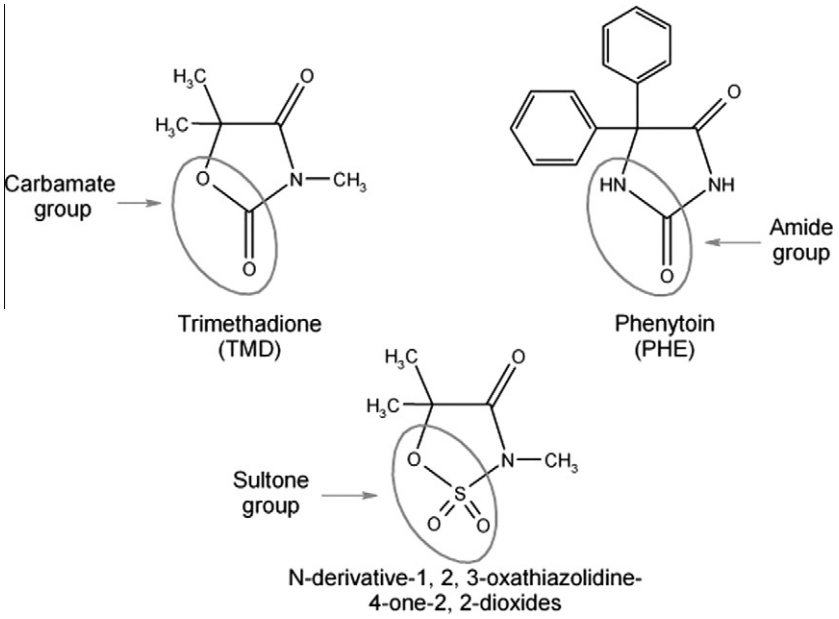


Figure 1. Molecular structures of trimethadione, phenytoin and N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides.

In the present investigation we show some bioisosteres of TMD and PHE, called N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides and 5,5-diphenyl-N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides, respectively (Fig. 1). α-Hydroxyamides were used to obtain the desired N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxide. Many different methods have been proved to get an α-hydroxyamide function.[22–24] Biological methods were also described via *Pseudomonas cepacia*[25] and biocatalytic methods using *Candida antarctica* lipase.[26] We found that microwave (MW) radiation has simplified and improved the synthesis of α-hydroxyamides, with better yields, shortened reaction times compared to traditional synthesis and reactions carried out without solvents or catalysts.

Here we report the synthesis of TMD and PHE bioisosteres: N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides, the traditional and MW assisted synthesis of α-hydroxyamides, intermediates of synthesis, and the evaluation of their anticonvulsant activities.

2. Results and discussion

2.1. Chemistry

Ammonolysis of 2-hidroxyisobutyl methyl ester, 2-hydroxyisobutyric acid and methyl benzylate with primary amines to obtained α-hydroxyamides (**3a–f**) were tested in (a) reflux system in a proper solvent where reaction time varies from 2 to 7 days[27] and (b) solvent free microwave reactor (Discover CEM) where reaction time varies from 15 to 25 min (Scheme 1). When necessary, boric acid was used as catalyst. Time and temperature conditions were previously determined. This is the first report of the MW synthesis of these types of α-hydroxyamides.

Cyclization with thionyl chloride (compounds **4a–d**) and oxidation with sodium periodate catalyzed by ruthenium trichloride (compounds **5a–d**) (Scheme 1) were conducted accordingly to previously reported procedures with slight modifications.[28–30]

The conditions used in the MW reactor for compund **3a–g** are shown in Table 1. Melting points were recorded on Electrothermal IA6034 apparatus and are uncorrected.

The MW reaction conditions for the synthesis of α-hydroxyamides were selected in order to define the best possible procedures. All the compounds were characterized by IR, ^{1}H and ^{13}C NMR. The purity of the compounds was confirmed by elemental analysis and the data were found in accordance with ±0.3%.

N-derivative-oxathiazolidine-4-one-2,2-dioxides were obtained with very good yields (75–95%) using ruthenium trichloride to oxidize and sodium periodate as catalyst (Scheme 1). Previous studies reported that the cyclization of flexible 1,2 dioles and α-hydroxyamides give very good yields comparing to those that used sulfuryl chloride.

2.2. Anticonvulsant screening

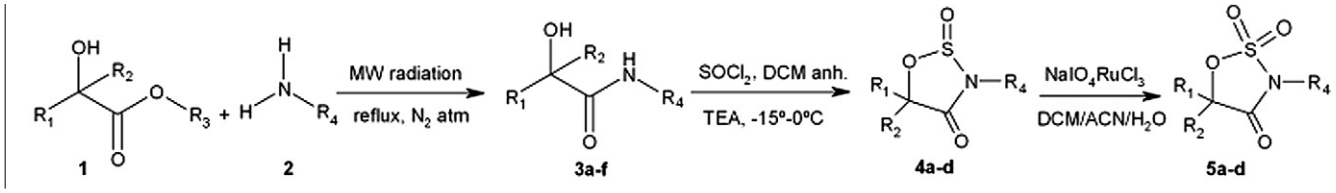
The biological evaluation of α-hydroxyamides **3a–e**, **3f** and N-derivative-oxathiazolidine-4-one-2,2-dioxides **5a–c**, was performed in acute models, using the procedures proposed by the National Institute of Health (NIH) via the Anticonvulsant Screening Project (ASP).[31] The primary evaluation (phase 1) includes the use of two anticonvulsant tests: Maximal Electroshock Seizure test (MES) and subcutaneous Pentylenetetrazole Seizure test (scPTZ). Toxicity is primary detected using the standardized RotoRod test, which is also include in this phase.[32]

It is well accepted that the MES test, which uses an electrical stimulus, is related to the generalized tonic–clonic seizures. It is used to identify those compounds that prevent seizures spread. The scPTZ test involves a chemical induction to generate the convulsion and is related to myoclonic seizures. It helps to identify those compounds that may act raising seizure threshold.[33–36]

The compounds were administrated intraperitoneally (ip) to adult male Swiss Albino mice (18–23 g) at the doses of 30 and 100 mg/kg and the assays were performed 0.5 and 4 h later.

Phase 2 of ASP was also performed, where the Maximal Time Effect (MTE) and the Median Effective Dose (ED_{50}) in MES test was evaluated for α-hydroxyamides **3a–c** and **3e** and N-derivative-oxathiazolidine-4-one-2,2-dioxides **5a–c**.

The tested compounds can be classified into four classes according to their activity,[36] (1) anticonvulsant activity at 100 mg/kg or less; (2) anticonvulsant activity at doses higher than 100 mg/kg;



1a: R_1=R_2= R_3= methyl
1b: R_1=R_2= methy, R_3= H
1c: R_1=R_2= phenyl, R_3= methyl

2a: R_4= benzyl
2b: R_4= phenethyl
2c, 2f: R_4= *n*-butyl
2d: R_4= *n*-propyl
2e: R_4= cyclohexyl

3a, 4a, 5a: R_1=R_2= methyl, R_4= benzyl
3b, 4b, 5b: R_1=R_2= methyl, R_4= phenethyl
3c, 4c, 5c: R_1=R_2= methyl, R_4= *n*-butyl
3d, 4d, 5d: R_1=R_2= methyl, R_4= *n*-propyl
3e: R_1=R_2= methyl, R_4= cyclohexyl
3f: R_1=R_2= phenyl, R_4= *n*-butyl

Scheme 1. Synthesis of the compounds.

Table 1
MW reaction conditions for the synthesis of α-hydroxyamides

Compound	Reaction time (min)	Reaction temperature (°C)	Mp[a] (°C)
3a	15	150	67–68.5
3b	15	150	103–105
3c	15	150	58–59
3d	25	150	54–55
3e[b]	15	150	81–82.5
3f	10	150	66–67

[a] Melting point of the α-hydroxyamides synthesized.
[b] Boric acid as catalyst.

(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.

2.2.1. PTZ test

The PTZ test, induced seizure entailed the subcutaneous (sc) administration of 85 mg/kg of PTZ as a 0.5% solution in 0.9% saline in the posterior midline of the mice. The animals were observed for 30 min. Protection was defined as the failure to observe even a threshold seizure (single episode of clonic spasms of at least 5 s duration) (Table 2). Compounds **3d** and **3f** and **5d** did not evidence any anticonvulsant activity in the PTZ test.

Neither of the compounds tested showed any failure to maintain balance on the rotating rod of the RotoRod assay evidencing that the compounds did not produce neurological deficits.

2.2.2. MES test

The absence of tonic extension of the hind legs after an electroshock by ear clips means that the compounds administrated protect against this test. All the evaluated compounds showed this protection. Therefore, they could be classified in class 1, as they protected against the MES test at doses lower than 100 mg/kg.

Compounds **3a–c**, **3e–f** were active at 0.5 h with a 100% of protection at 100 mg/kg, while compounds **3d, 3e–3f** and **5a** showed 100% of protection at 30 mg/kg after 4 h of its ip administration (Table 2).

MTE and ED_{50} in MES test were evaluated only for those N-derivative-oxathiazolidine-4-one-2,2-dioxides whose α-hydroxyamide precursors showed activity in both MES and PTZ tests.

Table 2
Pharmacological profile, MTE and ED_{50} (mg/kg) of α-hydroxyamides and N-derivatives-1,2,3-oxathiazolidine-4-one-2,2-dioxides and their *M*log*P* values

Compound	*M*log*P*[a]	Dose (mg/kg)	MES[b]		PTZ[c]		Neurotoxicity screen[d]		MTE[e] (h)	ED_{50}[f] (mg/kg)
			0.5 h	4 h	0.5 h	4 h	0.5 h	4 h		
3a	1.44	30	3/3	1/3	2/2	0/2	0/5	0/5	0.25	9.1
		100	3/3	0/3	2/2	2/2	0/5	0/5		
3b	1.72	30	1/3	1/3	0/2	0/2	0/5	0/5	1	53.9
		100	3/3	1/3	2/2	2/2	0/5	0/5		
3c	0.82	30	0/3	2/3	1/2	2/2	0/5	0/5	6	44.6
		100	3/3	2/3	0/2	2/2	0/5	0/5		
3d	0.46	30	1/3	3/3	0/2	0/2	0/5	0/5	nd	nd
		100	1/3	0/3	0/2	0/2	0/5	0/5		
3e	1.44	30	1/3	3/3	0/2	0/2	0/5	0/5	0.5	25.2
		100	3/3	2/3	0/2	0/2	0/5	0/5		
3f	2.99	30	1/3	3/3	0/2	0/2	0/5	0/5	nd	nd
		100	3/3	2/3	0/2	0/2	0/5	0/5		
5a	1.72	30	1/3	2/3	0/2	0/2	0/5	0/5	4	15.1
		100	2/3	3/3	1/2	0/2	0/5	0/5		
5b	1.99	30	2/3	1/2	2/2	0/2	0/5	0/5	2	91.1
		100	2/3	2/3	1/2	1/2	0/5	0/5		
5c	1.06	30	1/3	2/3	1/2	1/2	0/5	0/5	2	0.06
		100	0/3	2/3	0/2	1/2	0/5	0/5		
5d	0.73	30	1/3	0/3	0/2	0/2	0/5	0/5	nd	nd
		100	1/3	1/3	0/2	0/2	0/5	0/5		

Values represent number of mice protected from seizures or with neurotoxic effects divided by the number of mice tested.
[a] *M*log*P*: coefficient of partition octane–water calculated with Moriguchi method.[37]
[b] Maximal electroshock seizure.
[c] Pentylenetetrazol test.
[d] Toxicity evaluated in RotoRod test.[28]
[e] MTE: maximal time effect.
[f] ED_{50}: median effective dose. nd: not determined. MTE and ED_{50} values for phenytoin and trimethadione are 1 h and 5.54 mg/kg,[41] 0.5 h and 627 mg/kg,[34] respectively.

Valproic acid, a typical antiepileptic drug of broad spectrum in clinical practice, showed an ED_{50} of 283 mg/kg in the MES test. The α-hydroxyamides and the N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides studied here are more active than this classical anticonvulsant actually in use. For example, compound **3a** is 30 times more active than valproic acid. On the other hand, TMD and PHE showed ED_{50} values of 627 and 5.5 mg/kg, respectively, in the MES test.[34] Compound **5a**, a bioisostere of TMD, is almost 19 times more active than valproic acid and 40 times more active than TMD. Outstandingly, compound **5c** demonstrated a striking effect in the MES test, as it showed the most anticonvulsant effect, being almost 90 times more active than PHE, 4700 times more active than valproic acid and 10,000 times more active than TMD.

It is also important to stress here that none of the mice treated with the α-hydroxyamides or the N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides studied died during the assays.

It is known that the CNS action of a drug, including its anticonvulsant activity, depends on its lipophilicity, which enables the compound to cross the blood brain barrier (BBB) and to reach the cellular site of action. The calculated lipophilicities, *M*Log*P*, of the present series of compounds are shown in Table 2 and were estimated using the HyperChem QSAR Properties, version 7.01, Hypercube, Inc.[37,38] It has been determined that a log*P* = 2 is the best value for a compound to have passive diffusion through the BBB. Compounds **3a–f** and **5a–d**, with broad structural variations, showed a wide range of *M*Log*P* values (2.99 to 0.46). Although no relation between *M*log*P* values and anticonvulsant activity could be established, it could be assume that these values are high enough to allow the delivery of the compounds to the active site. We also observe that a difference of one methylene group in compounds **3a** and **3b**; and in compounds **5a** and **5b**; benzyl or phenethyl group, respectively; decrease in 6 times the activity of the compounds (ED_{50} **3a**: 9.1 mg/kg; ED_{50} **3b**: 53.9 mg/kg and ED_{50} **5a**: 15.1 mg/kg; ED_{50} **5b**: 91.1 mg/kg).

3. Conclusion

In this study a series of novel N-derivative-1,2,3-oxathiazolidines-4-one-2,2-dioxides bioisostere of TMD and PHE, were synthesized with good yields. α-Hydroxyamides, intermediates of these syntheses, were obtained with good yields by a MW reactor with a non contaminated, reproducible, versatile and fast method. These intermediates also showed anticonvulsant activities in both MES and PTZ tests, were not neurotoxic and showed better biological activities compared to antiepileptic drugs use in clinical nowadays.

α-Hydroxyamides **3a–c**, **3e**, and compounds **5a–5c** show an astounding anticonvulsant effect in the MES test. Moreover, compound **5c** the most active drug obtained, with an ED_{50} of 60 μg/kg, was 10,000 more active than TMD the reference compound in this work and 90 times more active than valproic acid, an anticonvulsant drug presently in use in clinic.

The obtained results showed that α-hydroxyamides and N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides could be useful as a template for future design, modification and investigation to produce more active analogs.

4. Experimental protocols

4.1. Chemistry

All the required chemicals were purchased from Sigma–Aldrich and Acros Company. Precoated aluminium sheets (silica gel 60 F_{254}, Merck, ref 1.05554) were use for thin layer chromatography (TLC) and spots were visualized under UV light and revealed by sulfomolibdic acid solution. Elemental analysis was carried out on CHNS Carlo Erba EA 1108 and the results were within ±0.3% of the theoretical values. IR spectra were recorded in Bruker IFS 66 FT/IR spectrophotometer as KBr disc. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 MHz and Bruker AC-50 MHz spectrometer respectively using $CDCl_3$ as a solvent and trimethylsilane (TMS) as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet, m, multiplet. Chemical shift are given in ppm. ESI-MS spectra of the α-hydroxyamides were recorded on a LCQ Duo (ESI-Trap) Thermo and in an Agilent 1100 LC system (Agilent Technologies, USA) coupled with a MSD VL quadrupole (Agilent Technologies, USA) for the N-derivatives 1,2,3-oxathiazolidin-4-one-2-oxide and N-derivatives 1,2,3-oxathiazolidin-4-one-2,2-dioxides.

4.2. Synthesis of α-hydroxyamides using microwave reactor (3a–f)

MW-assisted free solvent synthesis was performed by means of the following procedure: α-hydroxyacid, α-hydroxyisobutyl methyl ester or methyl benzilate were put into a dry vessel with the corresponding primary amine and a Teflon-coated magnetic stirring bar. The reactor was set at 300 W and 250 psi. Reaction time for compounds **3a–c** and **3e** was 15 min; **3d** 25 min, and for compound **3f** 10 min; all at 150 °C. The reaction mixture was monitored by TLC. The compounds were purified on column chromatography silica gel 60 (70–230 mesh, Merck). A white solid was obtained in all cases except for compounds **5c** and **5d** that were obtained as oil. Crystallization was carried out using the appropriate solvent where necessary. As cyclohexylamine is little reactive, boric acid was used as catalyst for the synthesis of the α-hydroxyamide **3e**.

4.2.1. *N*-Benzyl-2-hydroxyisobutylamide (3a)

Yield 60% (hexane); mp: 67–68.5; Anal. Calcd for $C_{11}H_{15}NO_2$: C 66.6, H 7.8, O 17.8, N 7.8. Found: C 66.9, H 8.1, O 17.5, N 7.5%; IR (cm^{-1}): 3408 (NH), 3306–3327 (OH), 2947–3076 (Ar), 1660 (C=O), 1541 (band II NH). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.40–7.20 (m, Ar), 7.08 (s, OH), 4.45 (d, J = 7.1 Hz –NH–CH_2–Ar), 2.55 (s, NH), 1.50 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 176.5 (CO), 138.4–128.9–127.9–127.7 (Ar), 73.9 ((CH_3)$_2$–*C*–OH), 43.5 (–NH–CH_2–Bz), 28.2 (CH_3). MS (ESI): *m/z* 194.1 $[M+1]^+$.

4.2.2. *N*-Phenethyl-2-hydroxyisobutylamide (3b)

Yield 40% (acetonitrinile); mp: 103–105 °C; Anal. Calcd for $C_{12}H_{17}NO_2$: C 69.5, H 8.3, O 15.4, N 6.7. Found: C 69.5, H 8.1, O 15.6, N 6.8.%; IR (cm^{-1}): 3357 (NH), 3228 (OH), 3037.6 (Ar), 2970 (alcane), 1650 (C=O), 1547.7 (NH band II); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.40–7.20 (m, 5H, Ar), 6.85 (s, 1H, OH), 3.20 (s, 1H, –NH), 3.54–3.15 (m, 2H, –NH–CH_2–CH_2–), 2.80 (t, 2H, J = 7.1 Hz, –CH_2–CH_2–Bz), 1.40 (s, 6H, (CH_3)$_2$); ^{13}CNMR ($CDCl_3$) δ (ppm): 176.9 (CO), 129.8–128.9–128.8–127.3 (Ar), 74.5 ((CH_3)$_2$–*C* –OH), 42.1 (–NH–CH_2–CH_2–Bz), 35.9 (–NH–CH_2–CH_2–Bz), 28.1 (CH_3). MS (ESI): *m/z* 208.1 $[M+1]^+$.

4.2.3. *N*-Butyl-2-hydroxyisobutylamide (3c)

Yield 40% (dichloromethane); mp: 58–59 °C; Anal. Calcd for $C_8H_{17}NO_2$: C 60.3, H 10.8, O 20.2, N 8.7. Found: C 60.3, H 10.6, O 20.7, N 8.4%; IR (cm^{-1}): 3346.7 (NH), 3254.5 (OH), 2937–2973 (alcane), 2876 (CH_3), 1647.7 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.86 (s, 1H, OH), 3.57 (s, 1H, –NH–), 3.29–3.19 (dd, 2H, J_1 = 6.79 Hz, J_2 = 12.83 Hz –NH–CH_2–), 1.46–1.33 (m, 2H, –CH_2–), 1.46–1.39 (m, 2H, –CH_2–CH_3), 1.41 (s, 6H, (CH_3)$_2$), 0.96–0.89

(t, 3H, J = 7.1 Hz, –CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm):176.9 (CO), 73.5 (–*C*–OH), 39.2 (–NH–*C*H_2–), 31.8 (–NH–CH_2–*C*H_2–), 28.0 ((CH_3)$_2$), 20.2 (–CH_2–CH_3), 13.9 (–CH_2–*C*H_3). MS (ESI): m/z 160.1 [M+1]$^+$.

4.2.4. *N*-Propyl-2-hydroxyisobutylamide (3d)

Yield 30% (hexane); mp: 54–55 °C; Anal. Calcd for $C_7H_{15}NO_2$: C 57.9, H 10.4, O 22.1, N 9.6. Found: C 57.7, H 10.3, O 22.4, N 9.6%; IR (cm^{-1}): 3400.7 (NH), 3300.5 (OH), 2950–2975–2875 (CH_3), 1650 (C=O), 1550.7 (NH band II); ^{1}H NMR ($CDCl_3$) δ (ppm): 6.95 (s, 1H, OH), 3.66 (s, 1H, NH), 3.21–3.11 (dd, 2H, J_1 = 6.91 Hz, J_2 = 13.13 Hz –NH–C*H*$_2$–), 1.55–1.44 (m, 2H, –CH_2–), 1.40 (s, 6H, (CH_3)$_2$), 0.92–0.85 (t, 3H, J = 7.34 Hz CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 176.9 (CO), 73.5 (–C–OH), 41.1 (–NH–CH_2–), 28.1 (CH_3)$_2$), 22.9 (–*C*H_2–CH_3), 11.4 (CH_3). MS (ESI): m/z 146.1 [M+1]$^+$.

4.2.5. *N*-Cyclohexyl-2-hydroxyisobutylamide (3e)

Yield 5% (acetonitrile); mp: 81–82.5 °C; Anal. Calcd for $C_{10}H_{19}NO_2$: C 64.8, H 10.3, O 17.2, N 7.6. Found: C 64.9, H 10.4, O 17.3, N 7.4%; IR (cm^{-1}): 3400(NH), 3100 (OH), 2850–2950 (alcane), 1600 (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm): 6.76 (s, 1H, OH), 3.75–3.61 (m, 1H, –CH– cyclohexyl), 2.92–1.31(m, 10 H, cyclohexyl), 3.16 (s, 1H, NH), 1.40 (s, 6H, (CH_3)$_2$), ^{13}C NMR ($CDCl_3$) δ (ppm):184.1 (CO), 72.5 (–C–OH), 50.5 (–NH–*C* H–), 31.4–28.1–25.0 (C, cyclohexyl), 24.6 ((CH_3)$_2$). MS (ESI): m/z 186.1 [M+1]$^+$.

4.2.6. *N*-Butyl-2,2-diphenyl-2-hydroxyacetamide (3f)

Yield 20% (dichloromethane/hexane); mp: 66–67 °C; Anal. Calcd for $C_{18}H_{21}NO_2$; C 76.3, H 7.5, O 11.3, N 4.9. Found: C 76.2, H 7.6, O 11.5, N 4.7%; IR (cm^{-1}): 3360-(NH), 3275 (OH), 3095–3050 (Ar), 2875–2950 (alcane), 1625 (C=O), 1550 (band II NH); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.40–7.34 (m, 6H, Ar), 6.30 (s, 1H, OH), 4.00 (s, 1H, NH), 3.35–3.25 (dd, 2H, J_1 = 6.95 Hz, J_2 = 12.97 Hz –NH–C*H*$_2$–), 1.55–1.41 (m, 2H, –CH_2–), 1.36–1.29 (m, 2H, –CH_2–), 0.92–0.89 (t, 3H, J = 7.13 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.4 (CO), 143.2–128.6–127.7 (Ar), 81.6 (–C–OH), 40.0 (–CH_2–), 31.7 (–CH_2–), 20.2 (–CH_2–), 13.9 (CH_3). MS (ESI): m/z 284.1 [M+1]$^+$.

4.3. Synthesis of N-derivative-1,2,3-oxathiazolidine-4-one-2-oxide (4a–d)

The monoxides were synthesized as previously described for cyclic sulfamates.[26] The product was extracted twice with dichloromethane and concentrated to dryness under reduce pressure. Silica gel 60 (70–230 mesh, Merck, ref 1.07734.1000) column chromatography yields yellow oil products. The monoxide isomers obtained in the synthesis were not separated.[39,40]

To a mixture of *N*-benzyl-2-hydroxyisobutylamide (3 mmol) and triethylamine (6.5 mmol) in CH_2Cl_2 anhydrous (8 ml) at −15 °C thionyl chloride (4 mmol) in CH_2Cl_2 anhydrous (2 ml)was added dropwise, followed by triethylamine (6.5 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred under N_2 overnight, concentrated to dryness under reduce pressure and the residue was chromatographed on a silica-gel silica gel 60 (70–230 mesh, Merck) column to give N-derivative-1,2,3oxatiazolidine-4-one-2-oxides as yellow oils.

N-butyl-1,2,3-oxathiazolidine-4-one-2-oxide (**4c**), with R_f (1) of 0.86 and R_f (2) of 0.66 (dichloromethane); and *N*-propyl-1,2,3-oxathiazolidine-4-one-2-oxide (**4d**), with R_f (1) of 0.85 and R_f (2) of 0.76 (dichloromethane); were directly cyclized.

4.3.1. *N*-benzyl-1,2,3-oxathiazolidine-4-one-2-oxide (4a)

Yield: 70% R_f (1): 0.76 and R_f (2): 0.67 (dichloromethane). IR (cm^{-1}): 2910–3050 (Ar), 1721 (CO), 1330 (SO), 1451.4, (C–N). ^{1}H NMR ($CDCl_3$) δ (ppm): 7. 41–7. 25 (m, 5H Ar), 4.45–4.42 (d, 2H, J = 5.88 Hz, –N–CH_2–Ar), 1.48 (s, 6H, CH_3).^{13}CNMR ($CDCl_3$): 174.2 (CO), 134.8–129.2–128.6–128.5 (Ar), 86.9 (CH_3)$_2$–C–O–), 44.3 (–N–CH_2–Ar), 28.0 (CH_3). MS (ESI): m/z 240.1 [M+1]$^+$.

4.3.2. *N*-phenethyl-1,2,3-oxathiazolidine-4-one-2-oxide (4b)

Yield: 25%. R_f (1): 0.79 and R_f (2): 0.70 (dichloromethane). IR (cm^{-1}): 2925–3025 (CH Ar), 2880 (CH alcane), 1775 (CO), 1340 (SO). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.36–7.17 (m, 5H Ar), 4.03–3.89 (q, 1H, J_1 = 6.76 Hz, J_2 = 7.17 Hz –N–CH_2–), 3.69–3.58 (q, J_1 = 6.45 Hz, J_2 = 7.46 Hz, –N–CH_2–), 3.02–2.95 (t, 2H, J = 7.05 Hz, –CH_2–), 1.67 (s, 3H, CH_3), 1.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 174.2 (CO), 137.5–129.0–128.9–127.2 (Ar), 86.5 ((CH_3)$_2$–C–O–), 42.0 (–N–CH_2–CH_2–Ar), 34.9 (–N–CH_2–CH_2–Ar), 27.9 (CH_3), 25.6 (CH_3). MS (ESI): m/z 254.1 [M+1]$^+$.

4.4. Synthesis of N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxides (5a–d)

The dioxides were obtained after oxidation with $NaIO_4$-R-uCl_3·6H_2O. Column chromatography on silica gel 60 (70–230 mesh, Merck) afforded the N-derivative-1,2,3-oxathiazolidine-4-one-2,2-dioxide as white solids.

To a solution of N-derivative-1,2,3-oxathiazolidine-4-one-2-oxides (4.5 mmol) in acetonitrile (6 ml) and dichloromethane (6 ml) at 0 °C an aqueous solution of $NaIO_4$ (7 mmol) and ruthenium chloride ca was added dropwise. The mixture was warm to room temperature and an hour later extracted twice with dichloromethane. The organic phases were combined, washed with water and brine, dried (Na_2SO_4) and concentrated to dryness. The residue obtained was flash chromatographed on silica-gel 60 (70–230 mesh, Merck) to give a white solid which was recristallized from hexane.

4.4.1. 3-Benzyl-5,5-dimethyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide (5a)

Yield: 80%. R_f: 0.84 (dichloromethane). mp: 71–72.5 °C. Anal. Calcd for $C_{11}H_{13}NO_4S$. C: 51.8, H: 5.1, O: 25.0, N: 5.5, S: 12.6. Found: C: 51.8, H: 5.1, N: 5.3, O: 25.4, S: 12.4. IR cm^{-1}: 2996–3094 (CH Ar), 1754 (CO), 1357 (SO_2). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.44–7.24 (m, 5H, Ar), 4.78 (s, 2H, –N–CH_2–Bz), 1.66 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 168.7 (C=O), 133.4–129.8–129.1–128.9 (Ar), 93.6 ((CH_3)$_2$–C–O–), 45.7 (–N–CH_2–Bz), 27.9 (CH_3), 24.5 (CH_3). MS (ESI): m/z 254.1 [M−1]$^+$.

4.4.2. 3-Phenethyl-5,5-dimethyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide (5b)

Yield: 25%. R_f: 0.75 (dichloromethane), mp: 57–58 °C. Anal. Calcd for $C_{12}H_{15}NO_4S$ C: 53.6, H: 5.6, N: 5.2, O: 25.5, S: 10.1. Found: C: 53.8, H: 5.8, N: 5.0, O: 25.7, S: 9.7%. IR cm^{-1}: 3032 (CH Ar), 2939.6 (CH alcane), 1743 (CO), 1356 (SO_2). ^{1}H NMR ($CDCl_3$), δ ppm: 7.32–7.23 (m, 5H, Ar), 3.92–3.84 (t, 2H, J = 6.43 Hz, –N–CH_2–CH_2–Bz), 3.10–3.03 (t, 2H, J = 6.39 Hz, –N–CH_2–CH_2–Bz), 1.66 (CH_3). ^{13}C NMR ($CDCl_3$): 168.4 (CO), 138.8–129.2–128.8–127.3 (Ar), 93.8 ((CH_3)$_2$–C–O–), 42.9 (–N–CH_2–CH_2–Bz), 34.0 (–N–CH_2–CH_2–Bz), 24.5 (CH_3). MS (ESI): m/z 268.0 [M-1]$^+$.

4.4.3. 3-Butyl-5,5-dimethyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide (5c)

Yield: 75%. R_f: 0.46 (dichloromethane), oil. Anal. Calcd for $C_8H_{15}NO_4S$ C: 43.4, H: 6.8, O: 28.9, N: 6.3, S: 14.5. Found: C: 43.4, H: 6.8, O: 28.8, N: 6.5, S: 14.5% IR cm^{-1}:2990–2940 (CH alcane), 2883 (CH_3), 1756 (CO), 1357 (SO_2). ^{1}H NMR ($CDCl_3$), δ ppm: 3.68–3.62 (t, 2H, J = 7.32 Hz, –N–CH_2–), 1.85–1.68 (m, 2H, (–CH_2–), 1.48–1.41 (m, 2H, –CH_2–), 0.99–0.92 (t, 3H, J = 7.32 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.8 (CO), 93.5 ((CH_3)$_2$–C–O–), 42.0 (–N–CH_2–CH_2–), 29.8 (–N–CH_2–CH_2–), 24.5 (CH_3), 19.9 (–CH_2–CH_3), 13.6 (–CH_2–CH_3). MS (ESI): m/z 220.1 [M−1]$^+$.

4.4.4. 3-Propyl-5,5-dimethyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide (5d)

Yield: 29% R_f: 0.68 (dichloromethane), oil. Anal. Calcd for $C_7H_{13}NO_4S$ C: 40.6, H: 6.3, O: 30.9, N: 6.7, S: 15.5% found C: 40.8, H: 6.8, O: 30.6, N: 6.9, S: 15.4%.IR cm^{-1}: 2939.6–2960.3 (CH alcane), 2883 (CH_3), 1743.5 (CO), 1367–1346 (SO_2). ^1H NMR ($CDCl_3$), δ, ppm: 3.65–3.58 (t, 2H, J = 6.6 Hz, –N–CH_2–), 1.83–1.75 (m, 2H, –CH_2–), 1.73 (s, 6H, $(CH_3)_2$), 1.01–0.97 (t, 3H, J = 7.34 Hz, CH_3). ^{13}C NMR ($CDCl_3$): 168.8 (CO), 93.5 ($(CH_3)_2$–C–O–), 43.7 (–N–CH_2–CH_2–CH_3), 24.6 (–N–CH_2–CH_2–CH_3), 21.3 ($(CH_3)_2$–C–O–), 11.2 (CH_3). MS (ESI): m/z 206.1 $[M-1]^+$.

4.5. Biological data

The evaluation of the anticonvulsant activity followed the Anticonvulsant Drug Development (ADD) Program of the National Institute of Health. Adult male Swiss 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 substances were 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.

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

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

4.5.2. Neurotoxicity tests

The RotoRod test is used exclusively in mice to assess minimal neurotoxicity. A normal mouse can maintain its equilibrium on a rotating rod (6 rpm) for long periods of time. Neurological deficit is indicated by failure to maintain balance on a rotating rod in each of three trials of 1 min each.

Acknowledgments

Dr. L.E. Bruno-Blanch is a member of the Faculty of Exact Science, National University of La Plata; Dr. V. Pastore is fellowship holders of Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina (CONICET). This research was supported in part through grants from Agencia de Promoción Científica y Tecnológica, CONICET, University of Buenos Aires and National University of La Plata, Argentina.

Dr. M. Marder is a member of the Faculty of Pharmacy and Biochemistry of National University of Buenos Aires and researcher of CONICET. Authors are in debt to LANAIS-PRO EM, IQUIFIB-CONICET, and Dr. Damián J. Marino from Faculty of Exact Science, National University of La Plata for performing MS spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.12.033. These data include MOL files and InChiKeys of the most important compounds described in this article.

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