Synthesis and Anticonvulsant Activity of New Dibenzo[1,2]thiazepine *S,S*-Dioxides

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A new series of 11-substituted 6,11-dihydro-6-methyl-dibenzo[*c,f*]-[1,2]thiazepine *S,S*-dioxides was synthesized. Some of the components show significant anticonvulsant activity in the MES, pentetrazol and strychnine tests. The more active compounds are devoid of neurotoxic effects.

Synthese und antikonvulsive Wirkung neuer Dibenzo[1,2]thiazepin-*S,S*-Dioxide

Eine neue Reihe 11-substituierter 6,11-Dihydro-6-methyl-dibenzo[*c,f*]-[1,2]thiazepin-*S,S*-dioxide wurde synthetisiert. Einige dieser Verbindungen zeigen beträchtliche antikonvulsive Aktivität in MES-Pentetrazol- und Strychnin-Testen. Die aktivsten Derivate zeigen keine neurotoxische Wirkung.

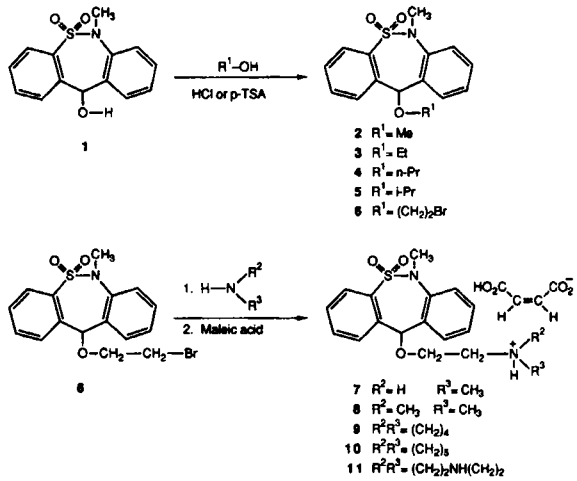
Most antiepileptic drugs in clinical use modify the ability of the brain to respond to various seizure-evoking stimuli, cause several adverse neurophysiological changes and, as a consequence, affect its normal functions leading to undesirable side effects. Thus, many anticonvulsants have sedative activity, and some produce mental disturbances, ataxia, gastrointestinal symptoms, hepatoxicity, etc. For this reason, the last research efforts in this field were directed to the preparation of other compounds with highly selective anticonvulsant action, a broad spectrum of antiepileptic efficacy, and minimal side effects.

Following these guidelines, a group of *Menarini* synthesized etazepine[1,2], an 11-ethoxy-derivative of the 5,6-dihydro-5-methyl-11*H*-dibenzo[*b,e*]azepin-6-one ring system which possesses a long lasting anticonvulsant activity toward electroshock- and pentetrazol-induced convulsions in both mice and rats and is also effective in antagonising other convulsant agents like nicotine, strychnine, cefazoline, and kainic acid.

In an attempt to find new compounds with similar or better anticonvulsant properties we have prepared a series of 11-substituted 6,11-dihydro-6-methyl-dibenzo[*c,f*][1,2]-thiazepine *S,S*-dioxides **1-11** in which the amidic carbonyl group of the etazepine molecule was replaced by an isosteric sulfonyl function[3]. This paper deals with the synthesis of these compounds and the evaluation of their anticonvulsant activities.

Chemistry

The new dibenzo-thiazepine derivatives were synthesized from 6,11-dihydro-6-methyl-5,5,11-trioxo-dibenzo[*c,f*]-[1,2]thiazepine[4] which was chosen as starting material. Thus, reduction of this ketone with $NaBH_4$ by the method of *Weber* and *Frossard*[5] gave the 11-hydroxy derivative **1** in 88% yield.



Scheme 1

The ether compounds **2** and **3** (Scheme 1) were accomplished by direct dehydration between the hydroxy derivative **1** and methanol and ethanol, respectively, in the presence of conc. HCl. The use in this reaction of *n*-propanol and *i*-propanol did not lead, however, to the corresponding *n*-propyl and *i*-propyl ethers **4** and **5** but to white crystals which presented in both cases identical analytical and spectroscopic data. These data permitted the identification of the product as 6,11-dihydro-6-methyl-dibenzo[*c,f*][1,2]thiazepine *S,S*-dioxide (**12**), apparently formed by reduction of the starting 11-hydroxy derivative **1**. In fact, its ^{1}HNMR spectrum in $CDCl_3$ exhibits a singlet at $\delta = 4.45$ ppm, corresponding to the two H of a CH_2-group and the ^{13}C-NMR

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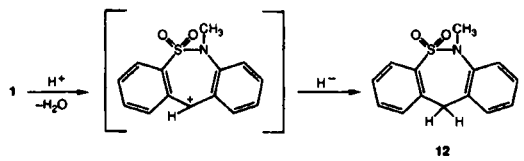
spectrum presented a signal at δ = 41.28 ppm which showed the normal behavior of a methylene C-atom submitted to a 135° pulse sequence in the DEPT spectrum. This transformation (Scheme 2) can be explained in terms of a hydride transfer, presumably from the aliphatic alcohol, to a particularly stable cation of the tropylium type which is formed by loss of water from the protonated alcohol **1**. In this respect, *Bartlett* and *McCollum*[6] have reported a number of examples of triphenylmethanol, as its cation, abstracting hydride from aliphatic alcohols.



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Scheme 2

Alkylethers **4**, **5**, and **6** can be better obtained by reacting alcohol **1** with *n*-propanol, *i*-propanol and 2-bromoethanol, respectively, using *p*-toluenesulfonic acid. Dialkylaminoethylethers **7-11** were readily prepared by displacement of the Br-atom of the haloether **6** by the corresponding amines in tetrahydrofuran.

The IR spectra of all the compounds showed bands at 1360-1310 and 1170-1140 cm^{-1} (SO_2) and their ^{1}H-NMR spectra presented the signals of the sulfonamidic *N*-methyl protons as a singlet at δ = 3.33 - 3.47.

Anticonvulsant activity

Except compound **6** (not tested) all the components were submitted for acute toxicity and preliminary anticonvulsant screening. Antagonism to strychnine, pentetrazol and maximal electroshock seizures (MES.) was studied in male mice. Results and the LD_{50} values: Table 1. Diazepam and diphenylhydantoin were chosen as reference standards.

According to Table 1, several compounds significantly antagonized the deleterious effects induced by strychnine, electroshock and pentetrazol. Especially the alkylethers **2** and **3** (R^1 = Me; Et) and in a lesser extent the alcohol **1** (R^1 = H), showed a clear anticonvulsant activity which was maintained at least up to 4 h after their administration. Compounds **2** and **3** were also the less toxic of the series, with LD_{50} values higher than 750 mg/kg *p.o.* which permits interesting pharmacological margins. Replacement of the methyl and ethyl substituents by bulkier alkyl or dialkylaminoalkyl functions (compounds **4**, **5**, **7-11**) reduced or even abolished the anticonvulsant properties.

With respect to the gross behavioral effects of these compounds, they did not show any important activity in the *Irwin* test and did not modify the body temp., even at the doses of 1/3 LD_{50} or up to 500 mg/kg *p.o.*, when it was possible (cases of **1**, **2**, and **3**). The data of spontaneous motor activity (Table 2) which indicate their possible depressant effects on CNS, showed a very light decrease of the number of movements in clear contrast to those obtained for diazepam. Our products provided scarce miorelaxant and motor

Table 1: Toxicity and anticonvulsant activity of compounds **1-11**

Compound	Toxicity Approx LD_{50} (mg/kg p.o.)	Anticonvulsant activity* Oral ED_{50} values (95 % confidence interval)		
		Strychnine	Pentetrazol	M.E.S.
1	> 750	25.7 (9.5-43.7)	>100	63.0 (46.2-77.7)
		32.4 (15.8-47.1)**	85.6 (79.5-140.2)**	68.3 (47.3-80.1)**
2	> 750	17.9 (8.3-31.4)	61.3 (45.3-80.5)	29.2 (24.5-36.4)
		23.4 (15.0-39.3)**	78.7 (47.5-90.7)**	36.3 (22.7-43.8)**
3	> 750	21.3 (10.0-39.5)	79.1 (47.5-90.7)	39.3 (32.1-48.9)
		28.4 (14.7-43.0)**	78.5 (53.7-97.3)**	47.8 (27.4-66.1)**
4	368	100	> 1/3 LD_{50}	> 1/3 LD_{50}
5	390	100	> 1/3 LD_{50}	> 1/3 LD_{50}
7	321	100	> 1/3 LD_{50}	> 1/3 LD_{50}
8	293	Inactive***	> 1/3 LD_{50}	> 1/3 LD_{50}
9	309	Inactive	Inactive	Inactive
10	233	Inactive	Inactive	Inactive
11	367	63.0 (48.5-78.7)	> 1/3 LD_{50}	100
Diaz	—	< 5	< 5	—
Dph	—	—	—	< 10

* 1 hour.

** 4 hours.

*** Inactive after administration *p.o.* 1/3 LD_{50}

Diaz: Diazepam.

Dph: Diphenylhydantoin.

Table 2: Side effects data of compounds **1-11**

Compound	Dose (mg/kg p.o.)	Motor Activity*		Neurotoxic Effects			
				Traction Test**		Rotarod Test***	
		1 hour	2 hours	1 hour	2 hours	1 hour	2 hours
1	250	—17.28	—18.27	0	25	90	70
2	250	—14.37	—1.27	17	17	75	85
3	250	—13.28	—14.38	8	0	85	95
4	1/3 LD_{50}	—16.42	—17.28	17	17	80	85
5	1/3 LD_{50}	—14.22	—15.64	0	0	70	80
7	1/3 LD_{50}	6.73	—2.49	0	17	70	75
8	1/3 LD_{50}	—4.81	—1.33	17	17	85	80
9	1/3 LD_{50}	7.62	5.28	0	0	100	100
10	1/3 LD_{50}	—10.23	—2.05	0	0	90	100
11	1/3 LD_{50}	—4.86	—15.27	33****	17****	40	80
Diazepam	5	—59.46****	—72.91****	33****	58****	20	10

* % variation of number of movements. Values referred to controls.
** % of failures.
*** % of mice running on rotarod.
**** $p < 0.05$.

incoordination effects in the traction and rotarod tests as compared to those produced by the reference standard and they did not modify the thiopental induced sleeping time.

In summary, some components of this series possess anticonvulsant activity. Compounds **2** and **3** were most effective in antagonizing the convulsant effects elicited in mice by strychnine, M.E.S and pentetrazol, presenting also low toxicities and scarce neurotoxic effects. As regards structure-activity relationships it was concluded that an alcoholic function, or even better a low chain alkoxy group (Me, Et) at C-11 is necessary for a good anticonvulsant activity. An increase of steric hindrance in this position reduced or abolished the anticonvulsant properties as it happened with etazepine analogues[1] and increased toxicity.

These results seem to confirm the isosteric bioequivalence between the sulfonamidic heterocycles studied in this investigation and their amido analogs since compound **3** (R^1 = Et) had approximately the same activity than etazepine[1,2] in the strychnine and MES assays (etazepine oral ED_{50} in mice: strychnine 16 mg/kg 0.5 h, MES 27.2 mg/kg 0.5 h and 34.5 mg/kg 2 h) and was slightly less active in the pentetrazol test (oral ED_{50} in mice: 34.7 mg/kg 0.5 h). Compounds **2** (R^1 = Me) and **1** (R^1 = H) presented also, in this order, activities comparable to those described for their amido analogs. Derivatives **2** and **3** were selected for further pharmacological studies.

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Experimental Part

Chemistry

Melting points: Gallenkamp capillary apparatus, uncorrected.- IR spectra: Shimadzu IR-435 spectrophotometer.- ^{1}H-NMR spectra, TMS as internal standard: Varian XL-300 and Bruker AM-200 spectrometers (Chemical shifts in δ units (ppm)).- Temp. in °C.

6,11-Dihydro-11-hydroxy-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide (**1**)

6,11-dihydro-6-methyl-5,5,11-trioxo-dibenzo[*c,f*][1,2]thiazepine (32 g, 0.12 mole) was suspended in methanol (600 ml) and treated with a solution of sodium borohydride (6 g, 0.16 mole) in water. The reaction mixture was kept at room temp. overnight, heated to dissolve precipitated material, acidified with 10 % acetic acid and allowed to cool. The white crystalline product was collected, washed with water and recrystallized. M.p. 132-133° (isopropanol).- $C_{14}H_{13}NO_3S$ (275.3) Calc. C 61.1 H 4.75 N 5.1 S 11.6 Found C 60.9 H 5.09 N 4.9 S 9.8.- IR (KBr): 3450; 1300; 1140; 1130 cm^{-1}.- ^{1}H-NMR ([D_6]DMSO): δ = 7.90-7.30 (m, 8H, aromat.), 6.57 (br. s, 1H, OH exchange with D_2O), 6.30 (s, 1H, CH), 3.33 (s, 3H, CH_3).

6,11-Dihydro-11-alkoxy-6-methyl-dibenzo[c,f,][1,2]thiazepine S,S-dioxides

Method **A**

A mixture of **1** (0.002 mole), the alkyl alcohol (8 ml) and 35% HCl (1.5 ml) was refluxed for 3 h. The solution was kept at room temp. overnight and the precipitated solid was filtered, dried and recrystallized from the appropriated solvent.

6,11-Dihydro-11-methoxy-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide (**2**)

88% Yield, white solid, m.p. 88-90° (methanol).- $C_{15}H_{15}NO_3S$ (289.3) Calc. C 62.3 H 5.22 N 4.8 S 11.0 Found C 62.4 H 5.25 N 5.1 S 10.9.- IR (KBr): 1330; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.80-7.40 (m, 8H, aromat.), 5.73 (s, 1H, CH), 3.38 (s, 3H, OCH_3), 3.36 (s, 3H, NCH_3).

6,11-Dihydro-11-ethoxy-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide (**3**)

82% Yield, white solid, m.p. 112-115° (ethanol).- $C_{16}H_{17}NO_3S$ (303.4) Calc. C 63.5 H 5.57 N 4.9 S 10.6 Found C 63.3 H 5.64 N 4.6 S 10.6.- IR (KBr): 1320; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.84-7.37 (m, 8H, aromat.), 5.83 (s, 1H, CH), 3.53 (q, J = 7.0 Hz, 2H, CH_2), 3.38 (s, 3H, NCH_3), 1.20 (t, J = 7.0 Hz, 3H, CH_2-$C\underline{H}_3$).

Method **B**

A mixture of the alcohol **1** (0.002 mole), the alkyl alcohol (8 ml) and *p*-toluenesulfonic acid (0.02 g) was refluxed for 2 h. The mixture was concentrated to dryness at reduced pressure and the oily residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave the desired alkylether.

6,11-Dihydro-11-(n-propoxy)-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide (**4**)

61% Yield, white solid, m.p. 76-78° (hexane).- $C_{17}H_{19}NO_3S$ (317.4) Calc. C 64.3 H 6.03 N 4.4 S 10.1 Found C 64.7 H 6.26 N 4.6 S 10.6.- IR (nujol): 1320; 1145 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 7.95-7.26 (m, 8H, aromat.), 5.95 (s, 1H, CH), 3.57 (t, J = 6.5 Hz, 2H, CH_2), 3.47 (s, 3H, CH_3), 1.74 (m, 2H, CH_2), 1.03 (t, J = 7.4 Hz, 3H, CH_2-$C\underline{H}_3$).

6,11-Dihydro-11-(i-propoxy)-6-methyl-dibenzo[c,f][1,2]thiazepine-S,S dioxide (**5**)

37% Yield, white solid, m.p. 66° (isopropanol).- $C_{17}H_{19}NO_3S$ (317.4) Calc. C 64.3 H 6.03 N 4.4 S 10.1 Found C 64.6 H 6.31 N 4.5 S 10.7.- IR (nujol): 1315; 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 7.94-7.26 (m, 8H, aromat.), 6.10 (s, 1H, CH), 3.80 (m, 1H, CH), 3.40 (s, 3H,CH_3), 1.26 (m, 6H, $CH(C\underline{H}_3)_2$).

Method **C**

6,11-Dihydro-11-(2-bromo)ethoxy-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide (**6**)

A solution of alcohol **1** (5.5 g, 0.02 mole), 2-bromoethanol (1.4 ml, 0.02 mole) and *p*-toluenesulfonic acid (0.5 g) in toluene (150 ml) was refluxed for 1 h and the water formed in the reaction was azeotropically eliminated by a Dean Stark apparatus. After cooling, the mixture was washed with water (100 ml), 10% $NaHCO_3$ (50 ml) and water (50 ml). The org. layer was separated, dried ($MgSO_4$) and evaporated *in vacuo*, giving an oil which crystallized from methanol. Yield 6.3 g (82%). The product was irritant to the skin and eyes and for this reason it was employed as such in the following step.- IR (KBr): 1310; 1140 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.97-7.30 (m, 8H, aromat.), 6.07 (s, 1H, CH), 3.80 (m, 4H, $2CH_2$), 3.47 (s, 3H, NCH_3).

6,11-Dihydro-11-(2-alkylamino)ethoxy-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxides

General method

A solution of the bromo derivative **6** (1.91 g, 0.005 mole) in tetrahydrofuran (15 ml) and the desired amine was kept at room temp. for 24 h and then concentrated to dryness *in vacuo*. The residue was dissolved in chloroform (25 ml) and the solution was washed with brine and extracted with 20% acetic acid (3 x 20 ml). The acid extracts were basified with 20% NaOH. The precipitated material was extracted into methylene chloride (3 x 20 ml) and the extracts were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The products so obtained were dissolved in the minimum quantity of ethanol and one molar proportion of maleic acid was added. The maleates were recrystallized from ethanol.

6,11-Dihydro-11[2-(methylamino)ethoxy]-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide, maleate (1:1) (**7**)

44% Yield from a 33% ethanolic methylamine solution (5 ml, 0.04 mole), white solid, m.p. 154-156°.- $C_{21}H_{24}N_2O_7S$ (448.5) Calc. C 56.2 H 5.39 N 6.2 S 7.2 Found C 56.3 H 5.54 N 6.3 S 7.3.- IR (KBr): 1320; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 8.51 (br. s, 2H, NH, exchange with D_2O), 7.85 (m, 2H, aromat.), 7.69-7.41 (m, 6H, aromat.), 6.03 (s, 2H, CH maleic acid), 6.01 (s, 1H, CH), 3.72 (m, 2H, CH_2), 3.41 (s, 3H, NCH_3), 3.24 (t, J = 5.1 Hz, 2H, CH_2), 2.63 (S, 3H, NCH_3).

6,11-Dihydro-11-[2-(dimethylamino)ethoxy]-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide, maleate (1:1) (**8**)

38% Yield from a 33% ethanolic dimethylamine solution (10 ml, 0.055 mole), white solid, m.p. 155-157°.- $C_{22}H_{26}N_2O_7S$ (462.5) Calc. C 57.1 H 5.66 N 6.1 S 6.9 Found C 57.2 H 5.54 N 6.1 S 7.4.- IR (KBr): 1320; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.82 (m, 2H, arom.), 7.73-7.37 (m, 6H, arom.), 6.05 (s, 2H, CH maleic acid), 6.02 (s, 1H, CH), 3.78 (t, J = 4.5 Hz, 2H, CH_2), 3.42 (s, 3H, NCH_3), 3.37 (t, J = 4.5 Hz, 2H, CH_2), 2.83 (s, 6H, $N(CH_3)_2$).

6,11-Dihydro-11-[2-(pyrrolidino)ethoxy]-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide, maleate (1:1) (**9**)

42% Yield from pyrrolidine (1.66 ml, 0.02 mole), white solid, m.p. 142-143°.- $C_{24}H_{28}N_2O_7S$ (488.5) Calc. C 59.0 H 5.77 N 5.7 S 6.6 Found C 58.8 H 5.78 N 5.9 S 6.4.- IR (KBr): 1320; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.79 (m, 2H, arom.), 7.63-7.43 (m, 6H, arom.), 6.00 (s, 2H, CH maleic acid), 5.98 (s, 1H, CH), 3.72 (t, J = 5.3 Hz, 2H, CH_2), 3.50-3.10 (m, 9H, CH_3 and 3 CH_2), 1.89 (m, 4H, 2 CH_2).

6,11-Dihydro-11-[2-(piperidino)ethoxy]-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide, maleate (1:1) (**10**)

40% Yield from piperidine (2 ml, 0.02 mole), white solid, m.p. 112-113°.- $C_{25}H_{30}N_2O_7S$ (502.6) Calc. C 59.7 H 6.01 N 5.6 S 6.4 Found C 59.5 H 5.80 N 5.6 S 6.2.- IR (KBr): 1310; 1140 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.78 (m, 2H, arom.), 7.60-7.44 (m, 6H, arom.), 6.00 (s, 2H, CH maleic acid), 5.97 (s, 1H, CH), 3.74 (t, J = 5.0 Hz, 2H, CH_2), 3.50-3.29 (m, 9H, CH_3 and 3 CH_2), 1.92 (m, 2H, CH_2), 1.66 (m, 4H, 2 CH_2).

6,11-Dihydro-11-[2-(piperazino)ethoxy]-6-methyl-dibenzo[c,f][1,2]thiazepine S,S-dioxide, dimaleate (1:2) (**11**)

58% Yield from piperazine (1.72 g, 0.02 mole), white solid, m.p. 124-125°.- $C_{28}H_{33}N_3O_{11}S$ (619.6) Calc. C 54.3 H 5.36 N 6.8 S 5.2 Found C 54.3 H 5.10 N 6.5 S 5.4.- IR (KBr): 1360; 1150 cm^{-1}.- ^{1}H-NMR ([D$_6$]DMSO): δ = 7.87-7.38 (m, 8H, arom.), 6.15 (s, 4H, CH maleic acid), 5.92 (s, 1H, CH), 3.65 (t, 2H, OCH_2), 3.40 (s, 3H, CH_3), 3.07 (m, 4H, CH_2N), 2.72-2.57 (m, 8H, piperazine).

6,11-dihydro-6-methyl-dibenzo[c,f][1,2]thiazepine-S,S-dioxide (**12**)

12 was formed from alcohol **1** and isopropanol following the conditions of *Method* **A**. Yield 75%. White solid, m.p. 126-128° (isopropanol).- $C_{14}H_{13}NO_2S$ (259.3) Calc. C 64.8 H 5.05 N 5.4 S 12.4 Found C 64.9 H

5.10 N 5.5 S 12.5.- IR (nujol): 1320; 1140 cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 7.94-7.22 (m, 8H, arom.), 4.45 (s, 2H, CH_2), 3.21 (s, 3H, CH_3). When n-propanol was used 60% of **12** were obtained.

Biological tests

Male Swiss albino mice (Interfarma, Barcelona, Spain), 20-25 g were used in groups of 12. All compounds were administered by oral gavage in 1% carboxymethylcellulose suspension.

Gross behavioral effects and toxicity

Irwin's polidimensional test[7] was used. The compounds were administered at various doses and detailed observation was performed 3 and 24 h after treatment; the animals were observed for 7 days to detect any sign of toxicity[8].

Sedative activity and neurotoxicity

The spontaneous motor activity was determined in an actimeter (Digiscan) following *Boissier* and *Simon*[9]. The modification of the barbituric acid induced sleep was evaluated after the administration of a dose of thiopental sodium (30 mg/kg i.p.). Rotarod[10] and traction[11] tests were utilized to fix the neurotoxic effects.

Anticonvulsant activity

Compounds were tested for their ability to protect mice against tonic extension of the hind limbs produced by maximal electroshock seizures (50 Hz, 120 V for 0.5 s delivered auricular electrodes)[12] and chemically induced convulsions [pentylenetetrazol (120 mg/kg i.p.)[13] and strychnine (1.5 mg/kg s.c.)][14].

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