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Synthesis and anticonvulsant activity of ethyl 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives

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ABSTRACT

In the present study on the development of new anticonvulsants, twenty three 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives were synthesized and tested for anticonvulsant activity using the maximal electroshock (MES), subcutaneous pentylenetetrazole (*sc*PTZ) screens, which are the most widely employed seizure models for early identification of candidate anticonvulsants. Their neurotoxicity was determined applying the rotorod test. Three compounds **6g**, **6m** and **6w** showed promising anticonvulsant activities in both models employed for anticonvulsant evaluation. The most active compound **6m** showed the MES-induced seizures with ED_{50} value of 9.8 mg/kg and TD_{50} value of 332.2 mg/kg after intraperitoneally injection to mice, which provided compound **6m** with a protective index (TD_{50}/ED_{50}) of 33.9 in the MES test.

1. Introduction

Epilepsy is a chronic neurological disorder affects about 1% of the world's population [1]. It often has devastating effects on patient's quality of life, many of them suffer from epilepsy over their lifetime [2,3]. Despite several new antiepileptic drugs (AEDs) have been marked during the last two decades, there is still a substantial need for the development of more effective and safer AEDs, since about 30% of epileptic patients are not seizure-free with the existing AEDs [4]. Besides, patients often suffer side effects during therapy process, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism [5–7].

The SAR studies of clinically available AEDs and other anticonvulsant active compounds showed that most of these compounds included a general model consist of three essential fragments for anticonvulsant activity in their molecules: (i) amides group as hydrogen binding domain; (ii) an electron donor group; (iii) an aryl group (Fig. 1). Take into consideration of the above our laboratory have demonstrated the potent anticonvulsant activity among the N-3-substituted 5,5-cyclopropanespirohydantoin derivatives, 6-methyl-1-substituted-4,6-diazaspiro [2.4]heptane-5,7-diones derivatives and 1-(8-(benzyloxy)quinolin-2-yl-6-substituted –4,6-diazaspiro [2,4]heptane-5,7-diones derivatives, from which compound **I** with ED_{50} value of 12.5 mg/kg, compound **II** with ED_{50} value of 9.2 mg/kg and a protective index (TD_{50}/ED_{50}) of 45.8, compound **III** with ED_{50} value of 8.6 mg/kg and a protective index (TD_{50}/ED_{50}) of 26.8 in the MES test in mice [8–10] (Fig. 2).

Following these findings, the urea pharmacophore has been attached to aryl hydrazide group and to cyclopropane group in order to develop new potent and safe AEDs (Fig. 3). We synthesized and comparatively evaluated the anticonvulsant activity and neurotoxicity of a number of ethyl 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives (**6a**–**w**). Compounds **6g**, **6m** and **6w** which displayed the remarkable anticonvulsant activity, were chosen for quantification of the pharmacological parameters (ED_{50} and TD_{50}).

2. Chemistry

The synthesis of the compounds **6a**–**w** was accomplished according to the reaction sequence illustrated in Scheme 1. Diethyl 2-(2-methylpropylidene)malonate **1** was obtained by reacting isobutyraldehyde with diethyl malonate in the presence of piperidine and acetic acid. Then bromination of compound **1** with NBS and AIBN in CCl_4 afforded the desired bromo compound **2**. Diethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate **3** was synthesized by

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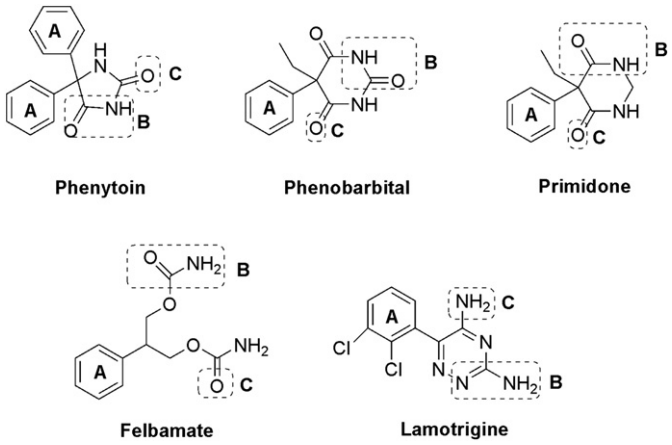


Fig. 1. Structure of anticonvulsant drugs with their vital structural fragments. (A) aryl group, (B) amides group as hydrogen binding domain, (C) electron donor group.

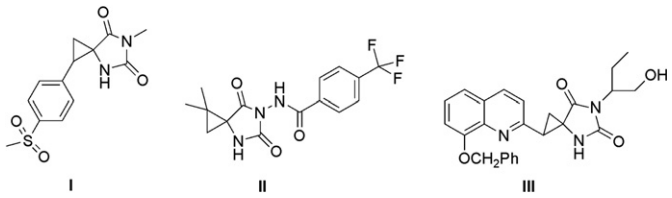


Fig. 2. Structure of compounds **I**, **II** and **III**.

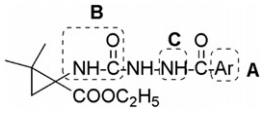


Fig. 3. Pharmacophoric structural fragments of title compounds. (A) aryl group, (B) amides group as hydrogen binding domain, (C) electron donor group.

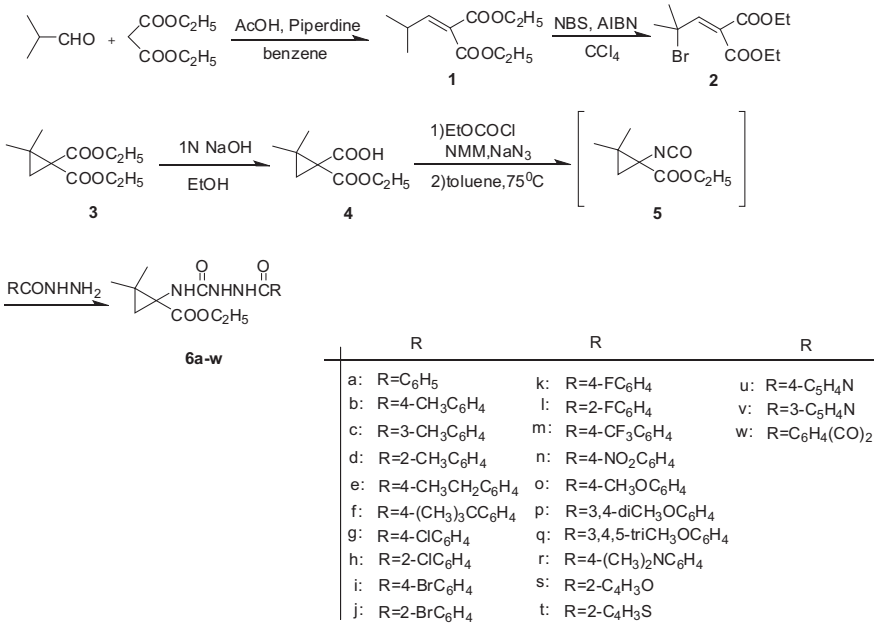
a Michael initiated ring closure (MIRC) reaction according to our previous studies [11,12]. Then monoester **4** was obtained after monosaponification in a 1 N NaOH/ethanol (1.1 equiv) solution at room temperature for 12 h [12,13]. This was then converted to corresponding acyl azide by using ethyl chloroformate in the presence of *N*-methyl morpholine (NMM) followed by reaction with sodium azide in a one-pot synthesis. α-Carboethoxy isocyanate **5** was successfully generated by a Curtius reaction *in situ* on heating the acyl azide in toluene solution at 75 °C. The desired semicarbazides **6a**–**w** were readily obtained by reacting Isocyanate **5** with various aryl hydrazide. Their chemical structures were characterized using ^{1}H-NMR, MS and elemental analysis techniques. The detailed physical and analytical data are listed in Section 5.

3. Pharmacology results and discussion

The anticonvulsant activity and neurotoxicity of the synthesized compounds were evaluated following the standard procedures proposed by the NIH anticonvulsant drug development (ADD) program, via the anticonvulsant screening project (ASP). The initial evaluation (Phase I) included the maximal electroshock seizure (MES), the subcutaneous pentylenetetrazole (*sc*PTZ) and neurotoxicity.

The compounds **6a**–**w** were administrated intraperitoneally (ip) into the mice using dose of 30, 100 and 300 mg/kg and the observations were taken at two different time intervals (0.5 h and 4.0 h). Neurotoxicity was measured by the rotorod test. The calculated LogP (Clogp) values were calculated using the software in ACD Labs 8.0 version. The results are shown in Table 1.

The initial anticonvulsant evaluation indicated that all the compounds were effective in ip MES and/or *sc*PTZ screens. In the MES test, all of the compounds showed protection in half or more of the tested mice after 0.5 h except **6s**, **6t**, **6u** and **6v**, indicative of their ability to prevent seizure spread. Compounds which were active at 100 mg/kg after 0.5 h in MES test included **6b**, **6c**, **6d**, **6f**, **6h**, **6k** and **6n** indicative of their good ability to protect from seizure spread at a higher dose. Among these compounds, **6d** was also active at the same dose after 4.0 h. This showed that this compound



Scheme 1. General method for the synthesis of compounds **6a**–**w**.

Table 1
Anticonvulsant activity and neurotoxicity of compounds **6a**–**w** administered intraperitoneally to mice.

Compounds	Intraperitoneal injection in mice[a]						Clog P[b]
	MES[c]		*sc*PTZ[d]		Neurotoxocity[e]		
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
6a	300	–	300	–	300	–	1.79 ± 0.61
6b	100	–	–	300	–	300	2.25 ± 0.61
6c	100	–	–	–	–	–	2.25 ± 0.61
6d	100	100	100	–	–	–	2.25 ± 0.61
6e	300	300	300	–	–	–	2.78 ± 0.61
6f	100	–	300	–	–	300	3.48 ± 0.62
6g	30	300	–	300	–	300	2.55 ± 0.62
6h	100	300	300	–	–	300	1.96 ± 0.62
6i	100	–	–	–	–	300	2.73 ± 0.64
6j	300	30	300	300	–	–	2.14 ± 0.64
6k	100	300	300	–	–	–	2.01 ± 0.64
6l	300	–	–	–	–	300	1.42 ± 0.64
6m	30	30	300	100	–	–	2.76 ± 0.63
6n	100	–	–	–	–	300	1.75 ± 0.62
6o	300	300	100	–	–	–	1.96 ± 0.62
6p	300	300	–	–	–	300	2.03 ± 0.63
6q	300	300	–	–	300	–	1.98 ± 0.63
6r	300	300	–	–	–	300	2.21 ± 0.62
6s	–	300	–	–	100	300	0.58 ± 0.62
6t	–	100	300	300	100	300	1.39 ± 0.62
6u	–	300	–	–	100	300	−0.05 ± 0.64
6v	–	–	–	300	100	300	0.32 ± 0.88
6w	30	100	100	300	–	–	1.32 ± 0.69
Phenytoin[f]	30	30	–	–	100	100	2.52 ± 0.38
Ethosuximide[g]	–	–	100	300	–	–	0.38 ± 0.46

[a] 30, 100, and 300 mg/kg of doses were administered ip. The figures in the table indicate the minimal dose where by bioactivity was demonstrated in half or more of the mice. The animals were examined at 0.5 h and 4.0 h after injection were administered. A dash indicates an absence of activity at maximum dose administered (300 mg/kg).
[b] Clog P was calculated using software ACD Labs 8.0 version.
[c] Maximal electroshock test.
[d] Subcutaneous pentylenetetrazole test.
[e] Neurotoxocity screening (rotorod test).
[f] Data from Ref. [27].
[g] Data from Ref. [28].

has quick onset and long duration of action at relatively higher dose. From these series **6g**, **6m** and **6w** showed anti-MES activity at the dose of 30 mg/kg at time periods 0.5 h, the most active compound **6m** was active in the MES test both at 0.5 h and 4.0 h in same dose, which was equivalent to phenytoin used as reference anticonvulsant drug.

In *sc*PTZ screen, compounds **6b**, **6g**, **6j**, **6m**, **6t**, **6v** and **6w** were active after 4.0 h at the dose of 300 mg/kg, the other compounds showed no activity.

In the neurotoxicity screen, Compounds **6c**, **6d**, **6e**, **6j**, **6k**, **6m** and **6w** did not show any neurotoxicity in the maximum dose administered (300 mg/kg). Compounds **6s**, **6t**, **6u** and **6w** revealed neurotoxicity at a dose of 100 mg/kg. The majority of these compounds exhibited less neurotoxic than phenytoin.

Compounds **6g**, **6m** and **6w** were selected for quantification of the pharmacological parameters (ED_{50} and TD_{50}). Results of the quantitative test for these compounds, along with the data on the standard drugs (phenytoin, carbamazepine, phenobarbital, and valproate), are reported in Table 2. In the mice MES screen, the tested compounds showed a higher protective index (PI) than all the standard drugs. In the mice ip *sc*PTZ screen, compound **6m** gave an ED_{50} of 58.4 mg/kg and a TD_{50} of 332.2 mg/kg, resulting in a high protective index (PI), that is, TD_{50}/ED_{50}, of 5.9 when compared to phenobarbital and valproate.

The results of the preliminary anticonvulsant screening revealed that 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives exhibit a remarkable anticonvulsant activity. The structure of this series fulfilled the pharmacophoric structural requirements, i.e., the hydrazinecarboxamide fragment and phenyl ring provided the basic structural requirement for anticonvulsant activity [14].

In the present studies, we synthesized a library of compounds with hydrazinecarboxamide as a core fragment. Compounds **6g**, **6m** and **6w** showed apparent activity in MES and *sc*PTZ screen, and the ClogP of these compounds were near from 2.0, which is considered to be the optimum lipophilicity for the congeners that act on the central nervous system [15]. ClogP values may be indicated the importance of lipophilicity as well as electronic properties of the substituents on the activity of these compounds. It was previously shown that there is a correlation between anticonvulsant activity and ClogP values, where an increase in ClogP is correlated with increased anticonvulsant properties [16,17]. Relatively favorable anticonvulsant activity was indicated in one study for compounds displaying ClogP values between 1.84 and 2.64 [18]. The 1-(2-arylhydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate derivatives could be regarded chemically as bioisosteres of the cyclic acylurea moiety of phenytoin. So the inhibition of electrically induced seizures that is characteristic for sulfonylureas and thioureas may indicate the influence of compounds on Na+ 2 HCI-K+ cotransporter as the most plausible mechanism of anticonvulsant action [19,20]. The anticonvulsant properties of 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives could perhaps be mediated by a similar pathway. Further experiments in binding and electrophysiology are clearly necessary to elucidate the mechanism of action of these novel anticonvulsants.

Table 2
Phase-II quantitative anticonvulsant evaluation in mice (test drug administered i.p.).

Compound	ED_{50}[a]		TD_{50}[b]	PI[c]	
	MES	*sc*PTZ		MES	*sc*PTZ
6g	20.1(17.5–24.5)[d]	334.6(311.6–356.8)	382.3(363.9–417.3)	19.0	1.1
6m	9.8(6.4–13.6)	58.4(36.4–81.5)	332.2(311.7–355.6)	33.9	5.9
6w	23.6(14.3–27.9)	212.6(193.7–234.3)	351.6(326.1–376.7)	14.9	1.7
Phenytoin[e]	9.5(8.1–10.4)	>300	65.5(52.5–72.9)	6.9	<0.22
Carbamazepine[e]	8.8(5.5–14.1)	>100	71.6(45.9–135)	8.1	<0.22
Phenobarbital[e]	21.8(21.8–25.5)	13.2(5.8–15.9)	69(62.8–72.9)	3.2	5.2
Valproate[e]	272(247–338)	149(123–177)	426(369–450)	1.6	2.9

Number of animals used: 10; solvent used: polyethylene glycol (0.1 mL, i.p.).
[a] Dose in milligrams per kilogram body mass.
[b] Minimal toxicity which was determined by rotorod test 30 min after the test drug was administered.
[c] Protective index (TD_{50}/ED_{50}).
[d] Date in parentheses are the 95% confidence limits.
[e] Date from reference [29].

4. Conclusions

In summary, the present studies revealed that number of 1-(2-arylhydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate derivatives were effective in the MES and/or *sc*PTZ screens. The anticonvulsant activity depended on the kind and position of substituents at the phenyl moiety. In the neurotoxicity studies some of the active compounds were devoid of toxicity. The most active was *N*-(1,1-dimethyl-5,7-dioxo-4,6-diazaspiro[2.4]heptan-6-yl)-4- fluorobenzamide (**6m**) which showed ED_{50} value of 9.2 mg/kg and a protective index (TD_{50}/ED_{50}) of 45.8 in the MES test in mice. This compound showed good Clog *p* value (2.76 ± 0.63) for the congeners that act on the CNS and greater ED_{50} and lower TD_{50} to standard drugs.

5. Experimental protocols

5.1. Chemistry

All the chemicals and solvent were purchased from commercial sources. Solvents and reagents were dried and purified according to the literature methods. Melting points were uncorrected and measured on an XT-4 apparatus. ^{1}H NMR spectra were obtained on a Varian Mercury VX400 apparatus in DMSO-d_6 and $CDCl_3$ with TMS as internal standard. The elemental analysis (C, H, N) data were obtained from a VarioEL III (German) elemental analyzer. The mass spectra (MS) were recorded on AMD-604 Mass Spectrometer operating at 70 eV.

5.1.1. Synthesis of 1-(ethoxycarbonyl)-2,2-dimethylcyclopropanecarboxylic acid **4**

To a solution of diethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate **3** (4.8 g, 22 mmol) in EtOH (25 mL) was added 1 N sodium hydroxide (25 mL, 1.1 equiv, 25 mmol), and the resulting mixture was stirred at room temperature for 12 h. EtOH was removed under reduced pressure, water was added to the residue, and the mixture was acidified by means of a saturated $KHSO_4$ solution and extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give product **4** (3.75 g, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.33 (t, 3H, J = 7.20 Hz, CH_3), 1.38 (s, 3H, CH_3), 1.78 (s, 1H, Cpr-H), 1.85 (s, 1H, Cpr-H), 4.29 (q, 2H, J = 7.20 Hz, CH_2), 11.28 (br s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.92, 20.75, 21.66, 26.94, 33.50, 38.54, 62.08, 171.30, 181.29.

5.1.2. General procedure for the synthesis of compounds **6a–t**

Compound **4** (10 mmol) was dissolved in dry THF (30 mL) and cooled to −15 °C. After the addition of EtOCOCl (11 mmol) and NMM (12 mmol), the mixture was stirred for 20 min. A solution of NaN_3 (25 mmol) in H_2O was added and stirred for 1 h at −10 °C. The solution was then diluted with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude acyl azide. This crude acyl azide could be further purified by a flash column chromatography (PE-EtOAc, 4:1, R_f = 0.7). Purified acyl azide was dissolved in toluene (30 mL) and the resulting solution was heated to 75 °C under stirring. After gas evolution had stopped toluene was removed under reduced pressure to afford a-carboethoxy isocyanate **5** as clear oil. This alfa-carboethoxy isocyanate **5** was directly used in the next step without further purification. Arylhydrazide (10 mmol) was added to a stirred suspension of isocyanate **5** in appropriate solvent (40 mL) at r.t. (when highly reactive arylhydrazides were used, such as 4-methoxybenzhydrazide, 3,4-dimethoxybenzhydrazide and 3,4,5-tri methoxybenzhydrazide, they should be dissolved in solvent and added dropwise). The solvent was removed under reduced pressure when the reaction was completed (detected by TLC) and the products **6** were purified by a column chromatography.

*5.1.2.1. Ethyl 1-(2-benzoylhydrazinecarboxamido)-2,2-dimethylcyclopropane carboxylate (**6a**).* Yield: 85%. White solid. Mp: 173–174 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.80 (d, 1H, J = 4.92 Hz, Cpr-CH), 1.13(s, 6H, $2CH_3$), 1.17(t, 3H, J = 7.08 Hz, CH_3), 1.51 (d, 1H, J = 4.92 Hz, Cpr-CH), 4.06 (q, 2H, J = 7.08 Hz, CH_2), 7.10 (br, 1H, NH), 7.47–7.54 (m, 2H, $C_{2,6}$-ArH), 7.55–7.57 (m, 1H, C_4-ArH), 7.88–7.90 (m, 2H, $C_{3,5}$-ArH), 7.98 (br, 1H, NH), 10.17 (br, 1H, NH). ESI-MS: 320.2 ($[M + H]^+$). Anal. calc. for $C_{16}H_{21}N_3O_4$: C 60.17, H 6.63, N 13.61; found : C 60.32, H 6.48, N 13.44.

*5.1.2.2. Ethyl 2,2-dimethyl-1-(2-(4-methylbenzoyl)hydrazinecarboxamido) cyclopropanecarboxylate (**6b**).* Yield: 88%. White solid. Mp: 150–151 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, J = 4.00 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.04 Hz, CH_3), 1.51 (d, 1H, J = 4.00 Hz, Cpr-CH), 2.36 (s, 3H, CH_3), 4.05 (q, 2H, J = 7.04 Hz, CH_2), 7.08 (brs, 1H, NH), 7.28 (d, 2H, J = 8.00 Hz, $C_{3,5}$-ArH), 7.79 (d, 2H, J = 8.00 Hz, $C_{2,6}$-ArH), 7.94 (brs, 1H, NH), 10.09 (brs, 1H, NH). ESI-MS: 334.2 ($[M + H]^+$). Anal. calc. for $C_{17}H_{23}N_3O_4$:C 61.25, H 6.95, N 12.60; found: C 61.17, H 6.76, N 12.83.

*5.1.2.3. Ethyl 2,2-dimethyl-1-(2-(3-methylbenzoyl)hydrazinecarboxamido)cyclopropanecarboxylate (**6c**).* Yield: 80%. White solid. Mp: 87–88 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.80 Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.04 Hz, CH_3), 1.50 (d, 1H, J = 4.80 Hz, Cpr-H), 2.35 (s, 3H, CH_3), 4.05 (q, 2H, J = 7.04 Hz, CH_2), 7.07 (brs, 1H, NH), 7.32–7.36 (m, 2H, $C_{4,5}$-ArH), 7.66–7.67 (m, 1H, C_6-ArH), 7.70 (s, 1H, C_2-ArH), 7.96 (brs, 1H, NH), 10.10 (brs, 1H, NH). ESI-MS: 334.2 ($[M + H]^+$). Anal. calc. for $C_{17}H_{23}N_3O_4$:C 61.25, H 6.95, N 12.60; found: C 61.12, H 6.77, N 12.85.

*5.1.2.4. Ethyl 2,2-dimethyl-1-(2-(2-methylbenzoyl)hydrazinecarboxamido)cyclopropanecarboxylate (**6d**).* Yield: 82%. White solid. Mp: 77–79 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.77 (d, 1H, J = 4.12 Hz, Cpr-CH), 1.13(s, 6H, $2CH_3$), 1.18(t, 3H, J = 7.08 Hz, CH_3), 1.51(d, 1H, J = 4.12 Hz, Cpr-H), 2.35(s, 3H, CH_3), 4.04(q, 2H, J = 7.08 Hz, CH_2), 7.13(brs, 1H, NH), 7.29–7.36(m, 2H), 7.38–7.56(m, 2H), 7.94(brs, 1H, NH), 10.22(brs, 1H, NH). ESI-MS: 334.2 ($[M + H]^+$). Anal. calc. for $C_{17}H_{23}N_3O_4$:C 61.25, H 6.95, N 12.60; found: C 61.17, H 6.87, N 12.83.

*5.1.2.5. Ethyl 2,2-dimethyl-1-(2-(4-ethylbenzoyl)hydrazinecarboxamido)cyclopropanecarboxylate (**6e**).* Yield: 90%. White solid. Mp: 78–80 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.62 Hz, Cpr-CH), 1.12(s, 6H, $2CH_3$), 1.18(t, 3H, J = 7.14 Hz, CH_3), 1.25 (t, 3H, J = 7.16 Hz, CH_3), 1.52(d, 1H, J = 4.62 Hz, Cpr-H), 2.60(q, 2H, J = 7.16 Hz, CH_2), 4.04(q, 2H, J = 7.14 Hz, CH_2), 7.21(brs, 1H, NH), 7.28(d, 2H, J = 8.82 Hz), 7.38(d, 2H, J = 8.82 Hz), 8.01(brs, 1H, NH), 10.22(brs, 1H, NH). ESI-MS: 347.2 ($[M + H]^+$). Anal. calc. for $C_{18}H_{25}N_3O_4$:C 62.23, H 7.25, N 12.10; found: C 62.42, H 7.17, N 12.33.

*5.1.2.6. Ethyl 1-(2-(4-tert-butylbenzoyl)hydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate (**6f**).* Yield: 80%. White solid. Mp: 115–116 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 3H, J = 4.88 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.04 Hz, CH_3), 1.30 (s, 9H, $3CH_3$), 1.51 (d, 1H, J = 4.88 Hz, Cpr-CH), 4.06 (q, 2H, J = 7.04 Hz, CH_2), 7.08 (brs, 1H, NH), 7.48 (d, 2H, J = 8.52 Hz, $C_{3,5}$-ArH), 7.82 (d, 2H, J = 8.44 Hz, $C_{2,6}$-ArH), 7.96 (brs, 1H, NH), 10.10 (brs, 1H, NH). ESI-MS: 376.4 ($[M + H]^+$). Anal. calc. for $C_{20}H_{29}N_3O_4$: C 63.98, H 7.79, N 11.19; found: C 63.81, H 7.87, N 11.43.

*5.1.2.7. Ethyl 1-(2-(4-chlorobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6g**).* Yield: 80%. White solid. Mp: 95–96 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H,

J = 4.88 Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.17 (t, 3H, J = 7.08 Hz, CH_3), 1.49 (d, 1H, J = 4.88 Hz, Cpr-CH), 4.05 (q, 2H, J = 7.08 Hz, CH_2), 7.15 (brs, 1H, NH), 7.56 (d, 2H, J = 8.48 Hz, $C_{3,5}$-ArH), 7.89 (d, 2H, J = 8.48 Hz, $C_{2,6}$-ArH), 8.00 (brs, 1H, NH), 10.25 (brs, 1H, NH). ^{13}C-NMR (100 Hz, DMSO-d_6): 13.7, 18.5, 22.6, 27.4, 28.2, 48.4, 60.2, 126.4, 128.2, 129.2, 132.1, 165.3, 170.6, 174.4. ESI-MS: 354.2 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}ClN_3O_4$: C 54.32, H 5.70, N 11.88; found: C 54.53, H 5.61, N 11.95.

*5.1.2.8. Ethyl 1-(2-(2-chlorobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6h**).* Yield: 85%. White solid. Mp: 113–114 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.80 (d, 1H, J = 4.92 Hz, Cpr-CH), 1.13 (s, 3H, $2CH_3$), 1.17 (t, 3H, J = 7.04 Hz, CH_3), 1.52 (d, 1H, J = 4.92 Hz, Cpr-CH), 4.06 (q, 2H, J = 7.04 Hz), 6.95 (brs, 1H, NH), 7.39–7.47 (m, 5H, ArH), 8.13 (brs, 1H, NH), 10.07 (brs, 1H, NH). ESI-MS: 354.2 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}ClN_3O_4$: C 54.32, H 5.70, N 11.88; found: C 54.42, H 5.51, N 11.93.

*5.1.2.9. Ethyl 1-(2-(4-bromobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6i**).* Yield: 82%. White solid. Mp: 101–102 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.77 (d, 1H, J = 4.84 Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.17 (t, 3H, J = 7.12 Hz, CH_3), 1.49 (d, 1H, J = 4.84 Hz, Cpr-CH), 4.05 (q, 2H, J = 7.12 Hz, CH_2), 7.15 (brs, 1H, NH), 7.69 (d, 2H, J = 8.44 Hz, $C_{3,5}$-ArH), 7.82 (d, 2H, J = 8.44 Hz, $C_{2,6}$-ArH), 8.00 (brs, 1H, NH), 10.25 (brs, 1H, NH). ESI-MS: 398.1 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}BrN_3O_4$: C 48.25, H 5.06, N 10.55; found: C 48.32, H 5.23, N 10.32.

*5.1.2.10. Ethyl 1-(2-(2-bromobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6j**).* Yield: 88%. White solid. M.p. 94–96 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, J = 4.64 Hz, Cpr-CH), 1.14(s, 6H, $2CH_3$), 1.19(t, 3H, J = 7.14 Hz, CH_3), 1.51(d, 1H, J = 4.64 Hz, Cpr-CH), 4.07(q, 2H, J = 7.14 Hz, CH_2), 7.15(brs, 1H, NH), 7.31–7.35 (m, 2H), 7.36–7.54 (m, 2H), 8.25 (brs, 1H, NH), 10.15(brs, 1H, NH). ESI-MS: 398.1 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}BrN_3O_4$: C 48.25, H 5.06, N 10.55; found: C 48.34, H 5.30, N 10.44.

*5.1.2.11. Ethyl 1-(2-(4-fluorobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6k**).* Yield: 83%. White solid. Mp: 169–170 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.68 Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.17 (t, 3H, J = 7.08 Hz, CH_3), 1.50 (d, 1H, J = 4.68 Hz, Cpr-CH), 4.05 (q, 2H, J = 7.08 Hz), 7.13 (brs, 1H, NH), 7.29–7.33 (m, 2H, $C_{3,5}$-ArH), 7.93–7.97 (m, 2H, $C_{2,6}$-ArH), 7.99 (brs, 1H, NH), 10.18 (brs, 1H, NH). ESI-MS: 338.3 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}FN_3O_4$: C 56.97, H 5.98, N 12.46; found: C 57.02, H 6.13, N 12.38.

*5.1.2.12. Ethyl 1-(2-(2-fluorobenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6l**).* Yield: 88%. White solid. Mp: 117–118 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, J = 4.88 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.19 (t, 3H, J = 7.04 Hz, CH_3), 1.51 (d, 1H, J = 4.88 Hz, Cpr-CH), 4.06 (q, 2H, J = 7.04 Hz, CH_2), 7.01 (brs, 1H, NH), 7.27–7.32 (m, 2H, ArH), 7.53–7.54 (m, 1H, ArH), 7.65–7.66 (m, 1H, ArH), 8.10 (brs, 1H, NH), 9.99 (brs, 1H, NH). ESI-MS: 338.2 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}FN_3O_4$: C 56.97, H 5.98, N 12.46; found: C 57.12, H 6.11, N 12.23.

*5.1.2.13. Ethyl 2,2-dimethyl-1-(2-(4-(trifluoromethyl)benzoyl)hydrazinecarboxamido) cyclopropanecarboxylate (**6m**).* Yield: 80%. White solid. Mp: 138–139 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.86 (d, 1H, J = 4.84 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.20 Hz, CH_3), 1.51 (d, 1H, J = 4.84 Hz, Cpr-CH), 4.05 (q, 2H, J = 7.20 Hz, CH_2), 7.21 (brs, 1H, NH), 7.87 (d, 2H, J = 8.28 Hz, $C_{3,5}$-ArH), 8.07 (d, 2H, J = 8.28 Hz, $C_{2,6}$-ArH), 8.10 (brs, 1H, NH), 10.41 (brs, 1H, NH). ^{13}C-NMR (100 Hz, DMSO-d_6): 13.2, 18.4, 22.3, 27.2, 28.8, 48.8, 61.2, 126.2, 128.0, 128.3, 164.7, 167.1, 171.2, 175.6. ESI-MS: 388.2 ($[M + H]^+$). Anal. calc. for $C_{17}H_{20}F_3N_3O_4$: C 52.71, H 5.20, N 10.85; found : C 52.72, H 5.31, N 10.81.

*5.1.2.14. Ethyl 2,2-dimethyl-1-(2-(4-nitrobenzoyl)hydrazinecarboxamido) cyclopropanecarboxylate (**6n**).* Yield: 75%. Yellow solid. Mp: 155–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, J = 4.88 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.19 (t, 3H, J = 7.04 Hz, CH_3), 1.51 (d, 1H, J = 4.88 Hz, Cpr-CH), 4.06 (q, 2H, J = 7.04 Hz, CH_2), 7.23 (brs, 1H, NH), 8.10 (brs, 1H, NH), 8.12 (d, 2H, J = 8.72 Hz, $C_{2,6}$-ArH), 8.33 (d, 2H, J = 8.72 Hz, $C_{3,5}$-ArH), 10.51 (brs, 1H, NH). ESI-MS: 365.3 ($[M + H]^+$). Anal. calc. for $C_{16}H_{20}N_4O_6$: C 52.74, H 5.53, N 15.38; found: C 52.66, H 5.37, N 15.46.

*5.1.2.15. Ethyl 1-(2-(4-methoxybenzoyl)hydrazinecarboxamido)-2,2-dimethyl cyclopropanecarboxylate (**6o**).* Yield: 85%. White solid. Mp: 153–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 0.79(d, 1H, J = 4.92 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.19 (t, 3H, J = 7.06 Hz, CH_3), 1.49 (d, 1H, J = 4.92 Hz, Cpr-CH), 3.81 (s, 3H, OCH_3), 4.02 (q, 2H, J = 7.06 Hz, CH_2), 5.37 (brs, 1H, NH), 7.00 (d, 2H, J = 8.88 Hz, $C_{3,5}$-ArH), 7.86 (d, 2H, J = 8.88 Hz, $C_{2,6}$-ArH), 10.03 (brs, 1H, NH), 11.72 (brs, 1H, NH). ESI-MS: 350.1 ($[M + H]^+$). Anal. calc. for $C_{17}H_{23}N_3O_5$: C 58.44, H 6.64, N 12.03; found: C 58.62, H 6.52, N 12.22.

*5.1.2.16. Ethyl 1-(2-(3,4-dimethoxybenzoyl)hydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate (**6p**).* Yield: 85%. White solid. Mp: 134–135 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.80 Hz, Cpr-CH), 1.16 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.00 Hz, CH_3), 1.50 (d, 1H, J = 4.80 Hz, Cpr-CH), 3.80 (s, 6H, 2OMe), 4.05 (q, 2H, J = 7.00 Hz, CH_2), 7.01–7.07 (m, 2H, $C_{4,5}$-ArH), 7.47 (brs, 1H, NH), 7.49–7.51 (m, 1H, C_2-ArH), 7.92 (brs, 1H, NH), 10.04 (brs, 1H, NH). ESI-MS: 380.1 ($[M + H]^+$). Anal. calc. for $C_{18}H_{25}N_3O_6$: C 56.98, H 6.64, N 11.08; found : C 56.82, H 6.42, N 11.12.

*5.1.2.17. Ethyl 1-(2-(3,4,5-trimethoxybenzoyl)hydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate (**6q**).* Yield: 85%. White solid. Mp: 187–188 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.96 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.19 (t, 3H, J = 7.08 Hz, CH_3), 1.51 (d, 1H, J = 4.96 Hz, Cpr-CH), 3.71 (s, 3H, C_4-ArOCH$_3$), 3.82 (s, 6H, $C_{3,5}$-ArOCH3), 4.06 (q, 2H, J = 7.08 Hz, CH_2), 7.11 (brs, 1H, NH), 7.22 (s, 2H, $C_{2,6}$-ArH), 7.97 (brs, 1H, NH), 10.12 (brs, 1H, NH). ESI-MS: 410.1 ($[M + H]^+$). Anal. calc. for $C_{19}H_{27}N_3O_7$: C 55.74, H 6.65, N 10.26; found: C 55.43, H 6.43, N 10.37.

*5.1.2.18. Ethyl 1-(2-(4-(dimethylamino)benzoyl)hydrazinecarboxamido)-2,2-dimethylcyclopropanecarboxylate (**6r**).* Yield: 77%. White solid. Mp: 186–187 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 1H, J = 4.92 Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.18 (t, 3H, J = 7.04 Hz, CH_3), 1.50 (d, J = 4.92 Hz, Cpr-CH), 2.97 (s, 6H, $2CH_3$), 6.70 (d, 2H, J = 8.92 Hz, $C_{3,5}$-2H), 6.99 (brs, 1H, NH), 7.75 (d, 2H, J = 8.80 Hz, $C_{2,6}$-2H), 7.82 (brs, 1H, NH), 9.81 (brs, 1H, NH). ESI-MS: 363.4 ($[M + H]^+$). Anal. calc. for $C_{18}H_{26}N_4O_4$: C 59.65, H 7.23, N 15.46; found: C 59.42, H 7.12, N 15.29.

*5.1.2.19. Ethyl 1-(2-(furan-2-carbonyl)hydrazinecarboxamido)-2,2-dimethylcyclopropane carboxylate (**6s**).* Yield: 80%. White solid. Mp: 120–121 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, J = 4.96 Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.17 (q, 3H, J = 7.08 Hz, CH_3), 1.49 (d, 1H, J = 4.96 Hz, Cpr-CH), 4.05 (q, 2H, J = 7.08 Hz, CH_2), 6.64 (m, 1H, C_4-ArH), 7.04 (brs, 1H, NH), 7.21 (brs, 1H, NH), 7.87–7.88 (m, 1H, C_3-ArH), 7.89–7.90 (m, 1H, C_5-ArH), 10.03 (brs, 1H, NH). ESI-MS: 310.2 ($[M + H]^+$). Anal. calc. for $C_{14}H_{19}N_3O_5$: C 54.36, H 6.19, N 13.58; found: C 54.61, H 6.27, N 13.69.

*5.1.2.20. Ethyl 2,2-dimethyl-1-(2-(thiophene-2-carbonyl)hydrazinecarboxamido)-cyclopropanecarboxylate (**6t**).* Yield: 77%. White solid. Mp: 180–181 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79(d, 1H,

$J = 4.96$ Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.18 (t, 3H, $J = 7.04$ Hz, CH_3), 1.50 (d, 1H, $J = 4.96$ Hz, Cpr-CH), 4.03 (q, 2H, $J = 7.04$ Hz, CH_2), 7.08 (brs, 1H, NH), 7.17–7.19 (m, 1H, C_4-ArH), 7.81–7.82 (m, 2H, $C_{2,5}$-ArH), 8.00 (brs, 1H, NH), 10.19 (brs, 1H, NH). ESI-MS: 326.2 ($[M + H]^+$). Anal. calc. for $C_{14}H_{19}N_3O_4$ S: C 51.68, H 5.89, N 12.91; found: C 51.43, H 6.07, N 13.14.

*5.1.2.21. Ethyl 1-(2-isonicotinoylhydrazinecarboxamido)-2,2-dimethylcyclopropane carboxylate (**6u**).* Yield: 81%. White solid. Mp: 188–189 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 1H, $J = 4.96$ Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.17 (t, 3H, $J = 7.04$ Hz, CH_3), 1.50 (d, 1H, $J = 4.96$ Hz, Cpr-CH), 4.06 (q, 2H, $J = 7.04$ Hz, CH_2), 7.22 (brs, 1H, NH), 7.78(d, 2H, $J = 6.04$ Hz, $C_{3,5}$-ArH), 8.10 (brs, 1H, NH), 8.74 (d, 2H, $J = 6.04$ Hz, $C_{2,6}$-ArH), 10.47 (brs, 1H, NH). ESI-MS: 321.3 ($[M + H]^+$). Anal. calc. for $C_{15}H_{20}N_4O_4$: C 56.24, H 6.29, N 17.49; found: C 56.47, H 6.37, N 17.42.

*5.1.2.22. Ethyl 2,2-dimethyl-1-(2-nicotinoylhydrazinecarboxamido) cyclopropane carboxylate (**6v**).* Yield: 79%. White solid. Mp: 178–179 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.79(d, 1H, $J = 4.84$ Hz, Cpr-CH), 1.13 (s, 6H, $2CH_3$), 1.18 (t, 3H, $J = 7.04$ Hz, CH_3), 1.51(d, 1H, $J = 4.84$ Hz, Cpr-CH), 4.06 (q, 2H, $J = 7.04$ Hz, CH_2), 7.22 (brs, 1H, NH), 7.51–7.56 (m, 1H, ArH), 8.06 (s, 1H, ArH), 8.21–8.23 (m, 1H, ArH), 8.72–8.73 (m, 1H, ArH), 9.03 (brs, 1H, NH), 10.36 (brs, 1H, NH). ESI-MS: 321.3 ($[M + H]^+$). Anal. calc. for $C_{15}H_{20}N_4O_4$: C 56.24, H 6.29, N 17.49; found: C 56.44, H 6.34, N 17.62.

*5.1.2.23. Ethyl 1-(3-(1,3-dioxoisoindolin-2-yl)ureido)-2,2-dimethylcyclopropane carboxylate (**6w**).* Yield: 82%. White solid. Mp: 188–189 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): 0.81 (d, $J = 4.72$ Hz, Cpr-CH), 1.12 (s, 6H, $2CH_3$), 1.21 (t, 3H, $J = 7.06$ Hz, CH_3), 1.48 (d, 1H, $J = 4.72$ Hz, Cpr-CH), 4.06 (q, 2H, $J = 7.06$ Hz, CH_2), 7.62 (brs, 1H, NH), 7.81–7.91 (m, 4H, ArH), 8.58 (brs, 1H, NH). ^{13}C-NMR (100 Hz, DMSO-d_6): 12.1, 19.5, 21.6, 28.1, 28.8, 49.2, 61.3, 124.3, 131.7, 133.6, 164.9, 167.6, 172.3. ESI-MS: 346.3 ($[M + H]^+$). Anal. calc. for $C_{17}H_{19}N_3O_5$: C 59.12, H 5.55, N 12.17; found: C 59.34, H 5.77, N 12.08.

5.2. Anticonvulsant screening

Anticonvulsant activity assays were carried out by the Antiepileptic Drug Development Program, Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health in Bethesda, USA [21]. Male Kunming mice (20 ± 2.0 g) and male Kunming rats (250 ± 5.0 g) were used as experimental animals in this study. Animals of the same age and weight have been selected in order to minimize biological. The animals were approved by the Animal Care Committee of Wuhan University. All the animals were purchased from Wuhan University Laboratory Animal Center (Wuhan, China). The tested compounds were injected intraperitoneally to mice as a suspension in 0.5% methylcellulose at dose of 30, 100, and 300 mg/kg to one to four mice. The anticonvulsant activity of the tested compounds were evaluated by two models namely, MES and scPTZ models. Phenytoin and ethosuximide were used as the standard drugs for the comparison. The neurological toxicity was determined in the rotorod test. Procedures employed for evaluation of anticonvulsant activity and neurotoxicity were described elsewhere [22].

5.2.1. MES-maximal electroshock seizure pattern test

This activity was tested according to the method of Swinyard et al. [23]. In experiments with mice, a 60-Hz current of 50-mA intensity was applied through corneal electrodes for a 0.25 s duration; The procedures caused immediate hindlimb tonic extension. After 0.5 h and 4.0 h of drug administration, electroshocks were via corneal electrodes. Absence of tonic extension suggests that the tested compound was considered as positive criteria.

5.2.2. Pentylenetetrazole (PTZ) induced seizure test

For the chemically induced convulsant test according to the method of Vamecq et al. [24], pentylenetetrazole was dissolved in sufficient 0.9% saline to allow subcutaneous injections to mice or rat. Standard drug in this model was ethosuximide. After 0.5 h and 4.0 h of drug administration the failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5s duration) is defined as protection.

5.2.3. Neurotoxicity screening

Minimal motor impairment was measured in mice or rats by using standardized rotorod test [25]. The mouse was placed on a 1 in. diameter knurled plastic rod rotating at 6 rpm. Trained animals were given an ip injection of the test compounds in doses of 30, 100, and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the four trials.

5.2.4. Quantification studies

Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}), that is, the dose of drug required to produce the biological responses in 50% of animals, neurotoxicity was expressed as the median toxic dose (TD_{50}). For determination of the ED_{50} and TD_{50}, groups of 10 mice were given a range of ip doses of the test drug until at least three points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity [26]. From the plot of these data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slope of the regression line, and standard error of the slope were calculated by means of a computer program written at NINDS, NIH.

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