Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 296–302
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis and potential anticonvulsant activity of new *N*-3-substituted 5,5-cyclopropanespirohydantoins

Qifeng Zhu, Yuanhu Pan, Zaixu Xu, Ruimin Li, Guofu Qiu, Wenjin Xu, Xianbing Ke, Lamei Wu, Xianming Hu*

State Key Laboratory of Virology, College of Pharmacy, Wuhan University, Wuhan 430072, China

Received 12 November 2007; received in revised form 2 January 2008; accepted 25 February 2008
Available online 7 March 2008

Abstract

Thirteen new 5-cyclopropanespirohydantoins with various *N*-3 substituents were synthesized and their pharmacological activity was determined with the objective to better understand their structure–activity relationship (SAR) for anticonvulsant activity. The anticonvulsant effects of these compounds were evaluated by maximal electroshock seizure (MES) test and subcutaneous pentylenetetrazole (scPTZ) test models in mice. All compounds substituted with cyclopropyl group at fifth position of hydantoin ring showed better protection against MES test. Compounds **5b**, **5d**, **5e**, **5g** and **5j** were found to be the most potent compounds of this series and compared with the reference drug phenytoin sodium in MES test. Compound **5j** also showed equipotent activity with the standard drug sodium valproate at the doses of 20 and 40 mg kg^{-1} in scPTZ test.

Keywords: Cyclopropanespirohydantoin; Anticonvulsant activity; Maximal electroshock seizure test; Pentylenetetrazole test

1. Introduction

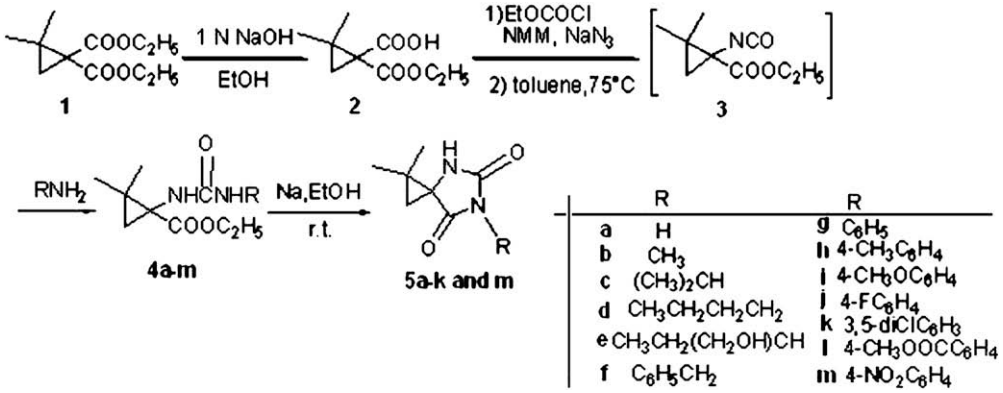
Epilepsy is a major neurological disorder affecting a large section of people both male and female throughout the world. Currently available drugs for the treatment of epilepsy are symptomatically effective in only 60–70% of patients [1]. In recent times several new drugs such as topiramate [2], tiagabine [3], felbamate [4], zonisamide [5], and vigabatrin [6] have emerged to treat epilepsy. Although these drugs have been shown to be effective in controlling the seizures, their efficacy does not appear to be superior to that of the established antiepileptic drugs (e.g. diphenylhydantoin, carbamazepine, valproate) [1]. Therefore, it is essential to search for new chemical entities for the treatment of epilepsy with greater efficacy and fewer side effects. Most of the compounds with anticonvulsant activity contain a cyclic ureide ring system [7]. Then many hydantoin [8] and spirohydantoin [9–11] analogs, such as 5,5-cyclopentanespirohydantoins [12], 5,5-cyclohexanespirohydantoins [13], 5,5-cycloheptanespirohydantoins [14], and 5,5-cyclooctanespirohydantoins [14], have been synthesized and shown to have anticonvulsant activity. In this paper, we set out to modify hydantoin by introducing a three-membered ring to obtain spirocyclopropanated hydantoin analogs and examine their anticonvulsant activities by electroshock (MES test) and PTZ (scPTZ test). It was especially of great interest to see, whether the introduction of a spiroannelated cyclopropane ring, which is known for its alkene-like properties [15,16], causes any effect upon biological activities. The pharmacological activity of various *N*-3 substituted 5,5-cyclopropanespirohydantoins can help better understand their structure–activity relationship (SAR).

2. Chemistry

The synthetic routes of compounds are outlined in Scheme 1. Diethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate **1** was synthesized by a Michael initiated ring closure (MIRC) reaction

* Corresponding author.
E-mail address: xmhu@whu.edu.cn (X. Hu).

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.02.024



Scheme 1.

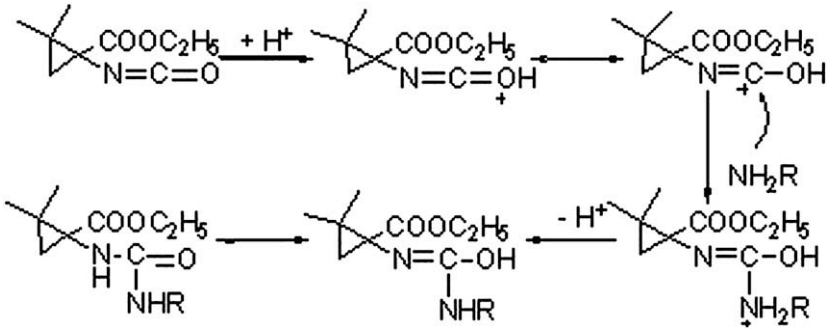
according to our previous studies [17,18]. Then monoester **2** was obtained after monosaponification in a 1 N NaOH/ethanol (1.1 equiv) solution at room temperature for 12 h [18,19]. This was then converted to corresponding acyl azide by using ethyl chloroformate in the presence of *N*-methyl morpholine (NMM) followed by reaction with sodium azide in a one-pot synthesis. α-Carboethoxy isocyanate **3** was successfully generated by a Curtius reaction in situ on heating the acyl azide in toluene solution at 75 °C. Isocyanate **3** was allowed to react directly with various amines without isolation. The desired α-carboethoxy ureas **4** were readily obtained. However, no obvious reaction was observed between the aromatic amines with strongly electron-withdrawing groups like *nitro* and methoxylcarbonyl and isocyanate **3** under the same condition. Attempts to promote the reaction by prolonging the reaction time (24 h) failed, presumably due to the weak nucleophilic attack of aromatic amines with strongly electron-withdrawing groups. Nevertheless, the reactions would be carried out fast when the catalytic amount of 4-methylbenzenesulfonic acid was added. The proposed reaction mechanism is shown in Scheme 2. The carbonyl of isocyanate can be activated by the form of the active carbon cation in the presence of acid, which can also react with the aromatic amines with strongly electron-withdrawing groups by the nucleophilic attack.

Finally, those *N*,*N*′-asymmetric ureas (**4a**–**k** and **4m**) cyclized on treatment with Na (1 equiv) in EtOH and provided 3′-substituted spirohydantoins **5** with a cyclopropane ring in good yields (yield ≥ 92%). The reaction of urea **4l** under the same condition did not give the desired compound, but instead, afforded the hydrolysis of methyl ester. Although excessive amounts of Na (2 or 5 or 10 equiv) were attempted, similar results were obtained.

All of these compounds were prepared as racemic mixtures and no attempt was made to resolve the enantiomers.

3. Pharmacological results and discussion

The anticonvulsant activities of the synthesized compounds were determined by in vivo test. The pharmacological data of all the compounds of this series have been reported in Table 1. These compounds when screened for their anticonvulsant activity against maximal electroshock induced seizures tested at 30 mg kg^{-1} p.o., exhibited substantive anticonvulsant activity. The characteristic feature of this series is the presence of the substituted cyclopropyl group at fifth position and the different substituted group at third position of hydantoin ring. While evaluating the anticonvulsant activity, it was observed that all compounds **5a**–**m**, substituted with different alkyl and aryl at third position of hydantoin ring, have shown varying degrees (50–90% protection) of anticonvulsant activity. Compounds **5b**, **5d**, **5e**, **5g** and **5j** have shown most potent response against MES test i.e. 90 and 80% protection. Among the *N*-3-alkyl-substituted hydantoins, methyl substituent (**5b**), hydroxy alkyl substituent (**5e**) and the straight chain butyl substituent (**5d**) have shown more potent response in comparison to other substituted derivatives. When the alkyl group



Scheme 2.

Table 1
Pharmacological data of compounds **5a–k** and **5m**

Compounds	Dose (mg kg^{-1} p.o.)		Anticonvulsant activity (% inhibition)	
	For MES model	For PTZ model	For MES model	For PTZ model
5a	30	–	50*	–
5b	30	80	90***	60**
	15	40	50*	30
	7.5	20	40	20
5c	30	–	70**	–
5d	30	80	90***	60**
	15	40	50*	40
	7.5	20	20	30
5e	30	80	90***	70**
	15	40	50*	40
	7.5	20	30	20
5f	30	–	70**	–
5g	30	80	80***	60**
	15	40	40	40
	7.5	20	20	20
5h	30	–	50*	–
5i	30	–	60**	–
5j	30	80	80***	70**
	15	40	50*	50*
	7.5	20	30	30
5k	30	–	50*	–
5m	30	–	60**	–
C.C.[a]	0.2 mL	0.2 mL	0	0
Phenytoin sodium[b]	30	–	90***	–
	15	–	50*	–
	7.5	–	20	–
Sodium valproate[c]	–	80	–	80***
	–	40	–	50*
	–	20	–	30

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] 0.5% Carboxymethyl cellulose–0.9% saline standard for control group.
[b] Standard drug for MES pattern test.
[c] Standard drug for PTZ seizure pattern test.

at the *N*-3 position was replaced by a phenyl ring, substitution of a small lipophilic group like fluorine (**5j**) at the *para* position of the *N*-3-phenyl ring of **5g** resulted in increased activity, which is in agreement with the reported SAR for spirohydantoins [11]. However, substitution with dichloro group (**5k**) at the 3′- and 5′-position of the *N*-3-phenyl ring of **5g** resulted in decreased activity. Electron-donating group like methoxy (**5i**) and strongly electron-withdrawing group like *nitro* (**5m**) at the 4-position of the phenyl ring cause a decrease in activity compared to **5g** in MES test. From the above results, it is obvious that among the *N*-3-phenyl-substituted derivatives, compounds **5j** and **5g** have shown more potent response in comparison to other compounds.

In the MES model, compounds **5b**, **5d**, **5e**, **5g** and **5j** were also tested at three graded doses i.e. 7.5, 15 and 30 mg kg^{-1} p.o. Compounds **5b**, **5d** and **5e** showed equipotent anticonvulsant activity as compared to standard drug phenytoin sodium at the doses of 30 and 15 mg kg^{-1} p.o. whereas compounds **5b** and **5e** showed more potent activity but compound **5d** showed equipotent activity at the dose of 7.5 mg kg^{-1} p.o. Compound **5j** showed more potent anticonvulsant activity at the dose of 7.5 mg kg^{-1}, equipotent at the dose of 15 mg kg^{-1} while less potent activity at 30 mg kg^{-1} p.o. than the standard drug phenytoin sodium. Compound **5g** showed equipotent anticonvulsant activity at the dose of 7.5 mg kg^{-1} with the standard drug phenytoin sodium while less potent activity at the doses of 30 and 15 mg kg^{-1} p.o.

Therefore, considering the results of these compounds, it may be concluded that compounds **5b**, **5d** and **5e** have shown more potent and equipotent activity as the standard drug phenytoin sodium while compounds **5g** and **5j** have shown equipotent and less activity than the standard drug phenytoin sodium in MES test.

Being the most potent compounds of this series, compounds **5b**, **5d**, **5e**, **5g** and **5j** were also tested for PTZ model and compared with reference drug sodium valproate. Compounds **5b**, **5e**, and **5g** have shown less activity at all three doses (20, 40 and 80 mg kg^{-1}) than the standard drug sodium valproate. However, compound **5j** has shown equipotent response at the doses of 20 and 40 mg kg^{-1} (i.e. 30 and 50% inhibition) and lower degree of protection (i.e. 70% inhibition) at the dose of 80 mg kg^{-1} than the reference drug sodium valproate. Compound **5d** has been found to exhibit less potent response at the doses of 40 and 80 mg kg^{-1} (i.e. 40 and 60% inhibition, respectively) and equipotent effect (i.e. 30% inhibition) at the dose of 20 mg kg^{-1} (Table 1) in the PTZ model.

4. Conclusion

Considering the results of all the synthesized compounds, the following may be concluded.

- All of the compounds substituted with cyclopropyl group at fifth position of hydantoin ring showed better protection against MES test but less response toward scPTZ test.
- Unbranched (i.e. **5b** and **5d**) and hydroxy (i.e. **5e**) alkyl substituents showed promising anticonvulsant activity in MES test.
- *p*-Fluorophenyl compound (i.e. **5j**) substituted at the third position of hydantoin ring showed more promising results than the other phenyl-substituted ones in both MES and scPTZ tests.

5. Experimental

5.1. Chemistry

Reagents 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. IR spectra were recorded from KBr pellets at a range of 400–4000 cm^{-1} on a Perkin–Elmer (Spectrum One) spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury VX300 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.

*5.1.1. The synthesis of 1-(ethoxycarbonyl)-2,2-dimethylcyclopropanecarboxylic acid **2***

To a solution of diethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate **1** (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 **2** (3.75 g, 90%) as a colorless oil: IR (KBr, cm^{-1}): 2983 (O–H), 1732 (C=O), 1698 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H, $-CH_3$), 1.33 (t, 3H, $J = 7.2$ 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, $J = 7.2$ 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 N,N′-asymmetric ureas **4a–m***

Compound **2** (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 α-carboethoxy isocyanate **3** as clear oil. This α-carboethoxy isocyanate **3** was directly used in the next step without further purification. Amine (10 mmol) was added to a stirred suspension of isocyanate **3** in appropriate solvent (40 mL) at r.t. (when highly reactive amines were used, 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 **4** were purified by a column chromatography.

*5.1.2.1. Ethyl 2,2-dimethyl-1-ureidocyclopropanecarboxylate (**4a**).* White solid (52%); Mp: 127–129 °C. IR (KBr, cm^{-1}): 3355 (N–H), 1704 (C=O), 1658 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 1H, $J = 4.6$ Hz, Cpr–H), 1.20 (s, 3H, $-CH_3$), 1.27 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.29 (s, 3H, $-CH_3$), 1.72 (d, 1H, $J = 4.6$ Hz, Cpr–H), 4.19 (q, 2H, $J = 7.2$ Hz, CH_2), 4.97–5.01 (m, 2H, NH), 5.62 (br s, 1H, NH). MS (*m/z*): 223 [M + Na]. Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.05; N, 13.99; Found: C, 54.05; H, 7.83; N, 14.18%.

*5.1.2.2. Ethyl 2,2-dimethyl-1-(3-methylureido) cyclopropanecarboxylate (**4b**).* White solid (58%); Mp: 133–135 °C. IR (KBr, cm^{-1}): 3350 (N–H), 1724 (C=O), 1651 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, 1H, $J = 2.4$ Hz, Cpr–H), 1.15 (s, 3H, $-CH_3$), 1.23 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.67 (d, 1H, $J = 2.4$ Hz, Cpr–H), 2.77 (d, 3H, $J = 2.4$ Hz, CH_3), 4.16 (q, 2H, $J = 7.2$ Hz, CH_2), 4.87 (br s, 1H, NH), 5.21 (s, 1H, NH). MS (*m/z*): 237 [M + Na]. Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.07; Found: C, 55.98; H, 8.52; N, 12.96%.

*5.1.2.3. Ethyl 2,2-dimethyl-1-(3-isopropylureido) cyclopropanecarboxylate (**4c**).* White solid (63%); Mp: 137–139 °C. IR (KBr, cm^{-1}): 3370 (N–H), 1723 (C=O), 1646 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, 1H, $J = 2.7$ Hz, Cpr–H), 1.12 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.16–1.22 (m, 6H, 2-CH_3), 1.24 (t, 3H, $J = 5.1$ Hz, $-CH_3$), 1.66 (d, 1H, $J = 2.7$ Hz, Cpr–H), 3.90–3.95 (m, 1H, CH), 4.14–4.17 (m, 2H, CH_2), 4.61 (br s, 1H, NH), 4.99 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.54, 20.08, 21.81, 23.52, 23.58, 28.20, 42.26, 43.45, 61.62, 158.11, 171.98. MS (*m/z*): 265 [M + Na]. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56; Found: C, 59.25; H, 9.33; N, 11.64%.

*5.1.2.4. Ethyl 2,2-dimethyl-1-(3-butylureido) cyclopropanecarboxylate (**4d**).* White solid (80%); Mp: 70–72 °C. IR (KBr, cm^{-1}): 3364 (N–H), 1724 (C=O), 1640 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91–0.94 (m, 3H, CH_3), 0.95 (d, 1H, $J = 4.5$ Hz, Cpr–H), 1.20 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.26–1.30 (m, 3H, $-CH_3$), 1.33–1.41 (m, 2H, $-CH_2$), 1.44–1.52 (m, 2H, $-CH_2$), 1.71 (d, 1H, $J = 4.5$ Hz, Cpr–H), 3.18–3.27 (m, 2H, CH_2), 4.19 (q, 2H, $J = 7.2$ Hz, CH_2), 4.86 (br s, 1H, NH), 5.09 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.99, 14.49, 20.10, 20.16, 21.84, 28.21, 32.54, 40.15, 43.45, 61.51, 158.95, 172.16. MS (*m/z*): 279 [M + Na]. Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93; Found: C, 61.15; H, 9.35; N, 10.64%.

*5.1.2.5. Ethyl 2,2-dimethyl-1-[3-(1-hydroxybutan-2-yl) ureido] cyclopropanecarboxylate (**4e**).* White solid (63%); Mp: 75–77 °C. IR (KBr, cm^{-1}): 3373 (N–H), 1708 (C=O), 1668 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, 1H, $J = 7.2$ Hz, Cpr–H), 0.95 (t, 3H, $J = 4.8$ Hz, $-CH_3$), 1.12 (s, 6H, 2-CH_3), 1.26 (t, 3H, $-CH_3$), 1.40–1.58 (m, 2H, CH_2), 1.70 (d, 1H, $J = 7.2$ Hz, Cpr–H), 3.51–3.54 (m, 3H, $-CH_2$, $-CH$), 3.63 (br s, 1H, OH), 4.16 (q, 2H, $J = 7.2$ Hz, CH_2), 5.39 (br s, 1H, NH), 5.86 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.80, 14.49, 20.13, 22.00, 24.76, 28.35, 28.45, 43.48, 54.58, 61.70, 66.52, 160.02, 172.51. MS (*m/z*): 295 [M + Na]. Anal. Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29; Found: C, 57.21; H, 9.03; N, 10.44%.

*5.1.2.6. Ethyl 2,2-dimethyl-1-(3-benzylureido) cyclopropanecarboxylate (**4f**).* White solid (54%); Mp: 110–112 °C. IR (KBr, cm^{-1}): 3348 (N–H), 1721 (C=O), 1638 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (d, 1H, $J = 4.5$ Hz, Cpr–H), 1.11 (s, 3H, $-CH_3$), 1.17 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.49 (d, 1H, $J = 4.5$ Hz, Cpr–H), 4.06 (q, 2H, $J = 7.2$ Hz, CH_2), 4.14 (dd, 1H, $J = 15.3$ Hz,

$J = 5.1$ Hz, CH_2), 4.28 (dd, 1H, $J = 15.3$ Hz, $J = 6.6$ Hz, CH_2), 6.41 (s, 1H, NH), 6.62 (s, 1H, NH), 7.19–7.33 (m, 5H, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.49, 20.04, 21.89, 28.39, 43.40, 44.33, 61.68, 127.42, 127.49, 128.76, 139.50, 158.83, 172.05. MS (*m/z*): 313 [M + Na]. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65; Found: C, 66.02; H, 7.73; N, 9.92%.

*5.1.2.7. Ethyl 2,2-dimethyl-1-(3-phenylureido) cyclopropanecarboxylate (**4g**).* White solid (55%); Mp: 153–155 °C. IR (KBr, cm^{-1}): 3375 (N–H), 1725 (C=O), 1651 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.21 (s, 3H, $-CH_3$), 1.25 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.29 (s, 3H, $-CH_3$), 1.72 (d, 1H, $J = 5.1$ Hz, Cpr–H), 4.14 (q, 2H, $J = 7.2$ Hz, CH_2), 6.55 (s, 1H, NH), 6.89–6.94 (m, 1H, Ar–H), 7.18–7.23 (m, 2H, Ar–H), 7.39–7.42 (m, 2H, Ar–H), 8.27 (s, 1H, NH). MS (*m/z*): 299 [M + Na]. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14; Found: C, 65.31; H, 7.46; N, 9.88%.

*5.1.2.8. Ethyl 2,2-dimethyl-1-[3-(4-methylphenyl) ureido] cyclopropanecarboxylate (**4h**).* White solid (57%); Mp: 120–122 °C. IR (KBr, cm^{-1}): 3342 (N–H), 1728 (C=O), 1654 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.14 (s, 3H, $-CH_3$), 1.14 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.54 (d, 1H, $J = 5.1$ Hz, Cpr–H), 2.21 (s, 3H, CH_3), 4.01–4.12 (m, 2H, CH_2), 6.71 (s, 1H, NH), 7.03 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.26 (d, 2H, $J = 8.4$ Hz, Ar–H), 8.41 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.52, 20.12, 21.01, 22.12, 28.22, 28.66, 43.45, 61.70, 120.97, 129.81, 133.40, 136.06, 156.90, 172.42. MS (*m/z*): 313 [M + Na]. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65; Found: C, 66.36; H, 7.42; N, 9.49%.

*5.1.2.9. Ethyl 2,2-dimethyl-1-[3-(4-methoxyphenyl) ureido] cyclopropanecarboxylate (**4i**).* White solid (60%); Mp: 123–125 °C. IR (KBr, cm^{-1}): 3374 (N–H), 1725 (C=O), 1653 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, 1H, $J = 2.4$ Hz, Cpr–H), 1.20 (s, 3H, $-CH_3$), 1.26 (t, 3H, $J = 3.6$ Hz, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.79 (d, 1H, $J = 2.4$ Hz, Cpr–H), 3.76 (s, 3H, CH_3), 4.18 (q, 2H, $J = 3.6$ Hz, CH_2), 5.69 (s, 1H, NH), 6.81 (d, 2H, $J = 3.9$ Hz, Ar–H), 7.03 (s, 1H, NH), 7.22 (d, 2H, $J = 3.9$ Hz, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 9.76, 15.34, 17.36, 23.33, 23.93, 38.65, 50.92, 56.86, 109.76, 118.52, 126.80, 151.77, 152.40, 167.68. MS (*m/z*): 329 [M + Na]. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14; Found: C, 62.55; H, 7.36; N, 9.32%.

*5.1.2.10. Ethyl 2,2-dimethyl-1-[3-(4-fluorophenyl) ureido] cyclopropanecarboxylate (**4j**).* White solid (30%); Mp: 125–127 °C. IR (KBr, cm^{-1}): 3352 (N–H), 1711 (C=O), 1670 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, 1H, $J = 5.4$ Hz, Cpr–H), 1.22 (s, 3H, $-CH_3$), 1.26 (t, 3H, $J = 3.6$ Hz, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.80 (d, 1H, $J = 5.4$ Hz, Cpr–H), 4.20 (q, 2H, $J = 6.6$ Hz, CH_2), 5.65 (s, 1H, NH), 6.91–6.97 (m, 2H, Ar–H), 7.08 (s, 1H, NH), 7.26–7.29 (m, 2H, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.51, 20.20, 22.06, 28.28, 28.56, 43.50, 61.88, 115.95, 122.35, 134.61, 156.58, 160.92, 172.59. MS (*m/z*): 317 [M + Na]. Anal. Calcd for $C_{15}H_{19}FN_2O_3$: C, 61.21; H, 6.51; N, 9.52; Found: C, 61.05; H, 6.33; N, 9.64%.

*5.1.2.11. Ethyl 2,2-dimethyl-1-[3-(3,5-dichlorophenyl) ureido] cyclopropanecarboxylate (**4k**).* White solid (53%); Mp: 163–165 °C. IR (KBr, cm^{-1}): 3364 (N–H), 1723 (C=O), 1653 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.26 (s, 3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.30 (t, 3H, $J = 6.9$ Hz, $-CH_3$), 1.87 (d, 1H, $J = 5.4$ Hz, Cpr–H), 4.26 (q, 2H, $J = 6.2$ Hz, CH_2), 6.21 (s, 1H, NH), 6.90–7.22 (m, 3H, Ar–H), 7.38 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.46, 20.39, 22.30, 28.28, 28.88, 43.43, 62.43, 117.17, 122.80, 135.13, 140.73, 155.80, 164.59. MS (*m/z*): 368 [M + Na]. Anal. Calcd for $C_{15}H_{18}Cl_2N_2O_3$: C, 52.19; H, 5.26; N, 8.11; Found: C, 52.22; H, 5.18; N, 8.02%.

*5.1.2.12. Ethyl 2,2-dimethyl-1-[3-(4-methoxycarbonylphenyl) ureido] cyclopropanecarboxylate (**4l**).* White solid (45%); Mp: 159–161 °C. IR (KBr, cm^{-1}): 3391 (N–H), 1712 (C=O), 1687 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.23 (s, 3H, $-CH_3$), 1.27 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.83 (d, 1H, $J = 5.1$ Hz, Cpr–H), 3.86 (s, 3H, CH_3), 4.18–4.25 (m, 2H, CH_2), 7.36 (d, 2H, Ar–H), 7.85 (d, 2H, Ar–H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.94, 20.27, 22.67, 27.28, 29.11, 42.86, 52.43, 61.13, 117.46, 122.61, 131.09, 145.46, 155.78, 166.64, 172.11. MS (*m/z*): 357 [M + Na]. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38; Found: C, 59.86; H, 6.83; N, 8.21%.

*5.1.2.13. Ethyl 2,2-dimethyl-1-[3-(4-nitrylphenyl) ureido] cyclopropanecarboxylate (**4m**).* Pale yellow solid (43%); Mp: 166–168 °C. IR (KBr, cm^{-1}): 3385 (N–H), 1693 (C=O), 1605 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.13 (t, 3H, $J = 7.2$ Hz, $-CH_3$), 1.14 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.54 (d, 1H, $J = 5.1$ Hz, Cpr–H), 4.60 (q, 2H, $J = 5.1$ Hz, CH_2), 7.07 (s, 1H, NH), 7.60 (d, 2H, Ar–H), 8.12 (d, 2H, Ar–H), 9.32 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.92, 20.21, 22.67, 27.40, 29.10, 42.88, 61.14, 117.62, 125.83, 141.30, 147.42, 155.56, 171.96. MS (*m/z*): 344 [M + Na]. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08; Found: C, 55.89; H, 6.08; N, 12.84%.

*5.1.3. General procedure for the synthesis of 3′-substituted cyclopropanespirohydantoins **5a–k** and **5m***

To a solution of compound **4** (1 mmol) and EtOH (10 mL) was added sodium (1.2 mmol), and the reaction mixture was stirred at room temperature for 2 h. EtOH was removed under reduced pressure. Ethyl acetate and water were added to the residue. The ethyl acetate layer was

dried over anhydrous Na_2SO_4, concentrated, and recrystallized to give compound **5**.

*5.1.3.1. 1,1-Dimethyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5a**).* White solid (94%); Mp: 196–198 °C. IR (KBr, cm^{-1}): 3441 (N–H), 1767 (C=O), 1722 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 1H, Cpr–H), 1.03 (s, 1H, Cpr–H), 1.18 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 8.15 (s, 1H, NH), 10.65 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.83, 22.28, 26.12, 26.36, 49.32, 157.66, 175.44. MS (*m/z*): 177 [M + Na]. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.45; H, 6.54; N, 18.17; Found: C, 54.18; H, 6.66; N, 17.94%.

*5.1.3.2. 1,1-Dimethyl-6-methyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5b**).* Needle-shaped crystals (95%); Mp: 155–157 °C. IR (KBr, cm^{-1}): 3431 (N–H), 1755 (C=O), 1703 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, 1H, $J = 3.0$ Hz, Cpr–H), 1.29 (s, 3H, $-CH_3$), 1.38 (s, 3H, $-CH_3$), 1.48 (d, 1H, $J = 3.0$ Hz, Cpr–H), 3.04 (s, 3H, $-CH_3$), 7.52 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.53, 22.55, 24.83, 26.99, 27.65, 48.78, 158.78, 173.80. MS (*m/z*): 191 [M + Na]. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66; Found: C, 57.25; H, 7.25; N, 16.30%.

*5.1.3.3. 1,1-Dimethyl-6-isopropyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5c**).* Needle-shaped crystals (92%); Mp: 122–124 °C. IR (KBr, cm^{-1}): 3427 (N–H), 1768 (C=O), 1708 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.28 (s, 6H, 2-CH_3), 1.36 (d, 6H, 2-CH_3), 1.42 (d, 1H, $J = 5.1$ Hz, Cpr–H), 4.30–4.39 (m, 1H, CH), 7.54 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.41, 19.96, 22.53, 26.79, 27.74, 43.72, 48.13, 158.64, 173.52. MS (*m/z*): 219 [M + Na]. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27; Found: C, 61.08; H, 8.11; N, 14.14%.

*5.1.3.4. 1,1-Dimethyl-6-butyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5d**).* Needle-shaped crystals (95%); Mp: 104–106 °C. IR (KBr, cm^{-1}): 3426 (N–H), 1755 (C=O), 1709 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, $J = 3.6$ Hz, CH_3), 1.16 (d, 1H, $J = 2.7$ Hz, Cpr–H), 1.28 (s, 3H, $-CH_3$), 1.31–1.36 (m, 2H, CH_2), 1.37 (s, 3H, $-CH_3$), 1.47 (d, 1H, $J = 2.7$ Hz, Cpr–H), 1.60–1.63 (m, 2H, CH_2), 3.52 (t, 2H, $J = 3.6$ Hz, $-CH_2-$), 7.57 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.09, 15.74, 17.43, 19.75, 24.14, 24.89, 27.73, 35.90, 45.81, 156.03, 173.93. MS (*m/z*): 233 [M + Na]. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32; Found: C, 62.76; H, 8.70; N, 13.45%.

*5.1.3.5. 1,1-Dimethyl-6-(1-hydroxybutan-2-yl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5e**).* White solid (93%); Mp: 94–95 °C. IR (KBr, cm^{-1}): 3519 (N–H), 1760 (C=O), 1692 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (m, 3H, $-CH_3$), 1.18 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.26 (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 1.47 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.83–1.96 (m, 2H, $-CH_2$), 3.73–3.91 (m, 3H, $-CH_2$, $-CH$), 4.07 (br s, 1H, OH), 7.60 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.92, 18.39, 21.69, 22.50, 27.55, 28.19, 48.59, 56.03, 63.29, 159.31, 174.36. MS (*m/z*): 249 [M + Na]. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38; Found: C, 58.06; H, 8.26; N, 12.09%.

*5.1.3.6. 1,1-Dimethyl-6-benzyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5f**).* White solid (95%); Mp: 142–144 °C. IR (KBr, cm^{-1}): 3218 (N–H), 1755 (C=O), 1712 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.21 (s, 3H, $-CH_3$), 1.27 (s, 3H, $-CH_3$), 1.28 (d, 1H, $J = 5.1$ Hz, Cpr–H), 4.57 (s, 2H, $-CH_2$), 7.25–7.37 (m, 5H, Ar–H), 8.57 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.53, 22.52, 26.99, 27.92, 42.50, 48.71, 127.98, 128.82, 136.57, 158.14, 173.23. MS (*m/z*): 267 [M + Na]. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; Found: C, 68.96; H, 6.32; N, 11.64%.

*5.1.3.7. 1,1-Dimethyl-6-phenyl-4,6-diazaspiro [2.4] heptane-5,7-dione (**5g**).* White solid (93%); Mp: 155–157 °C. IR (KBr, cm^{-1}): 3447 (N–H), 1767 (C=O), 1709 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, 1H, $J = 3.0$ Hz, Cpr–H), 1.43 (s, 3H, $-CH_3$), 1.31 (s, 3H, $-CH_3$), 1.59 (d, 1H, $J = 3.0$ Hz, Cpr–H), 6.74 (s, 1H, NH), 7.36–7.47 (m, 5H, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.46, 22.59, 27.42, 28.15, 48.41, 126.43, 128.23, 129.20, 132.11, 156.95, 172.24. MS (*m/z*): 253 [M + Na]. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17; Found: C, 68.06; H, 5.91; N, 11.84%.

*5.1.3.8. 1,1-Dimethyl-6-(4-methylphenyl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5h**).* White solid (93%); Mp: 178–180 °C. IR (KBr, cm^{-1}): 3445 (N–H), 1762 (C=O), 1713 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.29 (s, 3H, $-CH_3$), 1.41 (s, 3H, $-CH_3$), 1.54 (d, 1H, $J = 5.1$ Hz, Cpr–H), 2.38 (s, 3H, $-CH_3$), 7.36 (s, 1H, NH), 7.26 (d, 2H, $J = 12$ Hz, Ar–H), 7.29 (d, 2H, $J = 12$ Hz, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.53, 21.41, 22.57, 27.51, 28.06, 48.51, 126.35, 129.47, 129.86, 138.23, 157.52, 172.52. MS (*m/z*): 267 [M + Na]. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; Found: C, 69.06; H, 6.52; N, 11.64%.

*5.1.3.9. 1,1-Dimethyl-6-(4-methoxyphenyl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5i**).* Needle-shaped crystals (94%); Mp: 143–145 °C. IR (KBr, cm^{-1}): 3446 (N–H), 1759 (C=O), 1717 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, 1H, $J = 5.1$ Hz, Cpr–H), 1.29 (s, 3H, $-CH_3$), 1.40 (s, 3H, $-CH_3$), 1.55 (d, 1H, $J = 5.1$ Hz, Cpr–H), 3.82 (s, 3H, $-OCH_3$), 7.00 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.05 (br s, 1H, NH), 7.32 (d, 2H, $J = 8.4$ Hz, Ar–H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.54, 22.57, 27.51, 28.06, 48.51, 55.72, 114.56, 124.82, 127.87, 157.64, 159.36, 172.67. MS (*m/z*): 283 [M + Na]. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; Found: C, 64.79; H, 6.05; N, 10.43%.

*5.1.3.10. 1,1-Dimethyl-6-(4-fluorophenyl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5j**).* Needle-shaped crystals (93%); Mp:

150–151 °C. IR (KBr, cm^{-1}): 3447 (N–H), 1769 (C=O), 1709 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 1H, $J = 5.7$ Hz, Cpr–H), 1.29 (s, 3H, $-CH_3$), 1.41 (s, 3H, $-CH_3$), 1.56 (d, 1H, $J = 5.7$ Hz, Cpr–H), 7.12–7.43 (m, 4H, Ar–H), 7.73 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.52, 22.51, 27.81, 28.23, 48.55, 116.18, 128.04, 128.28, 157.32, 161.55, 172.40 ppm. MS (*m/z*): 271 [M + Na]. Anal. Calcd for $C_{13}H_{13}FN_2O_2$: C, 62.90; H, 5.28; N, 11.28; Found: C, 62.68; H, 5.15; N, 11.04%.

*5.1.3.11. 1,1-Dimethyl-6-(3,5-dichlorophenyl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5k**).* Needle-shaped crystals (92%); Mp: 194–196 °C. IR (KBr, cm^{-1}): 3446 (N–H), 1770 (C=O), 1721 (C=O). ^1H NMR (300 MHz, DMSO-d_6): δ 1.17 (d, 1H, $J = 2.7$ Hz, Cpr–H), 1.22 (s, 3H, $-CH_3$), 1.27 (s, 3H, $-CH_3$), 1.33 (d, 1H, $J = 2.7$ Hz, Cpr–H), 7.54 (s, 2H, Ar–H), 7.63 (s, 1H, Ar–H), 8.90 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 23.73, 26.96, 32.08, 32.27, 53.11, 130.66, 132.54, 139.13, 140.06, 159.89, 177.02. MS (*m/z*): 322 [M + Na]. Anal. Calcd for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36; Found: C, 52.26; H, 3.87; N, 9.23%.

*5.1.3.12. 1,1-Dimethyl-6-(4-nitrylphenyl)-4,6-diazaspiro [2.4] heptane-5,7-dione (**5m**).* Pale yellow needle-shaped crystals (92%); Mp: 162–164 °C. IR (KBr, cm^{-1}): 3217 (N–H), 1771 (C=O), 1716 (C=O). ^1H NMR (300 MHz, DMSO-d_6): δ 1.21 (d, 1H, $J = 5.4$ Hz, Cpr–H), 1.25 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.37 (d, 1H, $J = 5.4$ Hz, Cpr–H), 7.76 (d, 2H, $J = 9.3$ Hz, Ar–H), 8.32 (d, 2H, $J = 9.3$ Hz, Ar–H), 8.97 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 18.95, 22.20, 27.43, 27.70, 48.39, 124.66, 127.38, 138.95, 146.33, 155.10, 172.30. MS (*m/z*): 298 [M + Na]. Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27; Found: C, 56.64; H, 4.65; N, 15.09%.

5.2. Pharmacology

The anticonvulsant activity was evaluated by maximal electroshock seizure (MES) test and subcutaneous pentylenetetrazole (scPTZ) test models. The tested compounds were suspended in 0.5% carboxymethyl cellulose–0.9% saline mixture. The animals used in this study were approved by the Animal Care Committee of Wuhan University. Male Kunming mice (20 ± 2.0 g) were purchased from Wuhan University Laboratory Animal Center (Wuhan, China).

5.2.1. MES – maximal electroshock seizure pattern test

This activity was tested according to the method of Tomon et al. [20]. Male mice were divided into the groups of 10 animals each. The mice were treated with the different doses of test drugs or phenytoin sodium 30 mg kg^{-1} p.o. After 1 h they were subjected to the shock of 25 mA by convulsiometer through ear electrodes for 0.25 s. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animals protected/number of animals tested.

5.2.2. Pentylenetetrazole (PTZ) induced seizure test

For the chemically induced convulsant test according to the method of Vamecq et al. [21], pentylenetetrazole was dissolved in sufficient 0.9% saline to allow subcutaneous injections to mice. The animals given subcutaneous pentylenetetrazole (scPTZ) in a dose of 70 mg kg^{-1} in the scruff of neck were observed for at least 30 min for the presence or absence of a seizure [22,23]. Standard drug in this model was sodium valproate (80 mg kg^{-1} p.o.) and was injected 60 min prior to PTZ challenge. The failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) is defined as protection.

References

[1] E. Perucca, Br. J. Clin. Pharmacol. 42 (1996) 531–543.
[2] R.P. Shank, J.F. Gardocki, A.J. Streeter, B.E. Maryanoff, Epilepsia 41 (2000) 3–9.
[3] E.B. Nielsen, P.D. Suzdak, K.E. Andersen, L.J. Knutsen, U. Sonnewald, C. Braestrup, Eur. J. Pharmacol. 196 (1991) 257–266.
[4] R.H. Fuerst, N.M. Graves, I.E. Leppik, R.C. Brundage, G.B. Holmes, R.P. Remmel, Epilepsia 29 (1988) 488–491.
[5] M. Kubota, M. Nishi-Nagase, Y. Sakakihara, S. Noma, M. Nakamoto, H. Kawaguchi, M. Yanagisawa, Brain Dev. 22 (2000) 230–233.
[6] J.A. French, Epilepsia 40 (1999) 11–16.
[7] M.J. Brodie, Epilepsy Res. 45 (2001) 3–6.
[8] C.-H. Kung, J.N. Wurpel, C.-H. Kwon, Drug Dev. Res. 47 (1999) 17–26.
[9] W. Oldfield, C.H. Cashin, J. Med. Chem. 8 (1965) 239–249.
[10] E. Naydenova, N. Pencheva, J. Popova, N. Stoyanov, M. Lazarova, B. Aleksiev, Il Farmaco 57 (2002) 189–194.
[11] H.J. Patel, J. Sarra, F. Caruso, M. Rossi, U. Doshia, R.A. Stephania, Bioorg. Med. Chem. Lett. 16 (2006) 4644–4647.
[12] B. Ho, A. Michael Crider, J.P. Stables, Eur. J. Med. Chem. 36 (2001) 265–286.
[13] S.D. Upham, O.C. Dermer, J. Org. Chem. 22 (1957) 799–802.
[14] H.C. Brimelow, C.H. Vasey, GB 807,678. Chem. Abstr. 53 (1959) 67757.
[15] A. de Meijere, Angew. Chem. 91 (1979) 867–884.
[16] A. de Meijere, Angew. Chem., Int. Ed. Engl. 18 (1979) 809–826.
[17] J. Su, G. Qiu, S. Liang, X. Hu, Synth. Commun. 35 (2005) 1427–1433.
[18] J. Su, J. Xiong, S. Liang, G. Qiu, X. Feng, H. Teng, L. Wu, X. Hu, Synth. Commun. 36 (2006) 693–699.
[19] N.D. Kimpe, M. Boeykens, J. Org. Chem. 59 (1994) 8215–8219.
[20] J.E.P. Tomon, E.A. Swinyard, L.S. Goodman, J. Neurophysiol. 9 (1946) 231–240.
[21] J. Vamecq, D. Lambert, J.H. Poupaert, B. Masereel, J.P. Stables, J. Med. Chem. 41 (1998) 3307–3313.
[22] H.-J. Lankau, K. Unverferth, C. Grunwald, H. Hartenhauer, K. Heinecke, K. Bernoster, R. Dost, U. Egerland, C. Rundfeldt, Eur. J. Med. Chem. 42 (2007) 873–879.
[23] A. Agarwal, S. Lata, K.K. Saxena, V.K. Srivastava, A. Kumar, Eur. J. Med. Chem. 41 (2006) 1223–1229.