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Original article

Synthesis and anticonvulsant activity of *N*-(2-hydroxyethyl) cinnamamide derivatives

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ABSTRACT

A series of novel *N*-(2-hydroxyethyl) cinnamamide derivatives were synthesized and screened for their anticonvulsant activities by the maximal electroshock (MES) test and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). The MES test showed that compounds **I**(*N*-(2-hydroxyethyl) cinnamamide) and **1d** ((*E*)-3-(3-fluorophenyl)-*N*-(2-hydroxyethyl)acrylamide) were found to possess better anticonvulsant activity but also had lower toxicity. In the anti-MES potency test, these compounds exhibited median effective dose (ED_{50}) of 17.7 and 17.0 mg/kg, respectively, and median toxicity dose (TD_{50}) of 154.9 and 211.1, respectively, resulting in a protective index (PI) of 8.8 and 12.4, respectively, which is much greater than the PI of the marked antiepileptic drug carbamazepine. To further investigate the effects of the anticonvulsant activity in several different models, compounds **I** and **1d** were tested against convulsions induced by chemical substances, including pentylenetetrazole (PTZ), isoniazid, 3-mercaptopropionic acid, and thiosemicarbazide.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. The currently available anticonvulsants (AEDs) are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with undesirable side effects ranging from cosmetic (gingival hyperplasia) to life threatening (hepatotoxicity, megaloblastic anemia) [1–3]. Therefore, continued search for safer and more effective AEDs is urgently necessary.

The cinnamamide derivatives exhibit a variety of biological activities, such as central nervous depression, sedative-hypnosis, antidepression, muscle relaxant, local anesthesia, inhibit fungal, and anticonvulsant activities [4–12]. In our search for new compounds with anticonvulsant activity, *N*-(2-hydroxyethyl) cinnamamide (compound **I**) showed a positive anticonvulsant activity with an effective dose of 30 mg/kg in the anti-MES test. In order to obtain compounds with better anticonvulsant activity, we synthesized *N*-(2-hydroxyethyl) cinnamamide derivatives using *N*-(2-hydroxyethyl) cinnamamide (**I**) as the lead compound. The new compounds were evaluated as anticonvulsant agents in experimental epilepsy models, i.e., maximal electroshock test (MES) and neurotoxicity was evaluated by using the rotarod test. The most active compounds (**I** and **1d**) were tested in pentylenetetrazole (sc-PTZ), isoniazid, 3-mercaptopropionic acid, and thiosemicarbazide test, and the possible mechanism of action was conjectured.

2. Results and discussion

2.1. Chemistry

Target compounds were prepared according to Scheme 1. Compounds **1a**–**1p** were obtained in high yield through a one-step reaction using substituted carboxylic acid, methyl chloroformate, triethylamine, and ethanolamine as the starting materials. The reaction mixture was maintained at room temperature for 8–10 h. All the compounds were identified by spectral data. In general, IR spectra showed the C=O peak at 1658–1706, the NH stretching vibrations at 3016–3217 cm^{-1}, and the OH stretching vibrations at 3307–3323 cm^{-1}. In the nuclear magnetic resonance spectra (^1H NMR) the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed the hydrazide (NH) proton as a singlet at 5.56–6.25 ppm and the hydroxyethyl proton (OH) at 2.21–2.83 ppm.

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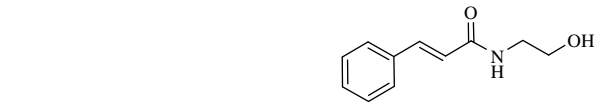

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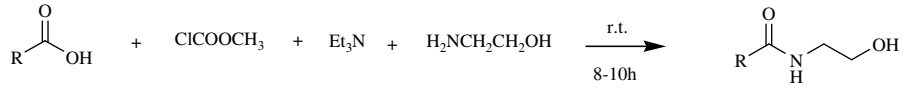

R:

1a: -CH=CHC$_6$H$_4$(*p*-F)	**1b:** -CH=CHC$_6$H$_4$(*p*-Cl)	**1c:** -CH=CHC$_6$H$_4$(*p*-Br)	**1d:** -CH=CHC$_6$H$_4$(*m*-F)
1e: -CH=CHC$_6$H$_4$(*m*-Cl)	**1f:** -CH=CHC$_6$H$_4$(*o*-F)	**1g:** -CH=CHC$_6$H$_4$(*o*-Cl)	**1h:** -CH=CHC$_6$H$_4$(*o*-Br)
1i: -CH=CHC$_6$H$_3$ (2,4-Cl$_2$)	**1j:** -CH=CHC$_6$H$_4$(*p*-CH$_3$O)	**1k:** -CH=CHC$_6$H$_3$(3,4-OCH$_2$O-)	**1l:** -CH=CHC$_6$H$_4$(*p*-CH$_3$)
1m: -CH=CHC$_6$H$_4$(*p*-N(CH$_3$)$_2$)	**1n:** -C$_6$H$_5$	**1o:** -C$_6$H$_5$CH$_2$	**1p:** -C$_6$H$_5$CH$_2$CH$_2$

Scheme 1. Synthesis of compounds **1a**–**1p**.

2.2. Pharmacology

The results of preliminary (phase I) screening of compounds **I** and **1a**–**1p** are summarized in Table 1. All synthesized compounds exhibited anticonvulsant activity, among which five compounds **1d**–**1f**, **1k**, and the lead compound **I** possessed anticonvulsant activity against MES-induced seizure at the dose of 30 mg/kg, and then eight compounds **1a**–**1c**, **1g**–**1h**, **1j**, and **1l**–**1m**, were active at the dose of 100 mg/kg. The remaining four compounds **1n**–**1p**, and **1i** exhibited anti-MES effect only under the high dose of 300 mg/kg. However, none of these compounds exhibited any potency towards anti-MES activity at 4 h after administration.

As a result of preliminary screening, compounds **I**, **1a**–**1h**, **1k**, and **1m** were subjected to phase II trials for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice (Table 2). Among these derivatives, the most potent compound **1d** ((*E*)-3-(3-fluorophenyl)-*N*-(2-hydroxyethyl)acrylamide) exhibited similar activity with ED_{50} value of 17.0 mg/kg to the lead compound **I** with ED_{50} value of 17.7 mg/kg in the MES test, furthermore, it had lower neurotoxicity (TD_{50} = 211.1 mg/kg) than compound **I** (TD_{50} = 154.9 mg/kg), and was weaker than the marked antiepileptic drug carbamazepine (ED_{50} = 8.8 mg/kg). But its neurotoxicity and PI value (PI = 12.4) were superior to that of carbamazepine (TD_{50} = 71.6 mg/kg, PI = 8.1) in the MES test. And the remaining 10 compounds 1, **1a**–**1c**, **1e**–**1k**, and **1m** exhibited comparatively weaker activity than carbamazepine, but these compounds possessed lower neurotoxicity ranging from 98.3 to 304.3 mg/kg.

Analyzing the activities of the synthesized compounds the following structure–activity relationships (SAR) were obtained.

Generally, the anticonvulsant activity of an organic compound might be increased remarkably after the introduction of a halogen atom. So, some halogen substituted derivatives were designed and synthesized in this paper. Comparison of the halogen substituted derivatives indicated that different halogen atoms contributed to the anticonvulsant activity in the order of F > Cl > Br; the introduction of F atom on the benzyl ring led to stronger activity.

Comparing the derivatives with different F-substitution positions on the benzyl ring, their activity order was *m*-F > *o*-F > *p*-F. *m*-F substituted derivative **1d** ((*E*)-3-(3-fluorophenyl)-*N*-(2-hydr oxyethyl)acrylamide) was the strongest in all tested compounds with ED_{50} value of 17.0 mg/kg, and exhibited the lowest neurotoxicity with TD_{50} value of 211.1 mg/kg, a higher protective index (PI = 12.4) was achieved than the reference drug carbamazepine, and activity order of the Cl- and Br atom-substituted derivatives was *m*-Cl > *o*-Cl > *p*-Cl > 2,4-Cl$_2$, and *o*-Br > *p*-Br.

Four electron-donor derivatives were also designed and prepared, containing *p*-OCH$_3$, 3,4-OCH$_2$O–, *p*-CH$_3$, and *p*-N(CH$_3$)$_2$. The pharmacology test revealed that their activities were lower than compound **I** and the activity order was 3,4-OCH$_2$O– > *p*-N(CH$_3$)$_2$ > *p*-OCH$_3$ > *p*-CH$_3$.

Compounds **1n**, **1o**, and **1p** were obtained when the phenylpropylene group of compound **I** was substituted with phenyl group, benzyl group, and phenethyl group, respectively. They exhibited anti-MES effect only under the high dose of 300 mg/kg. This result illustrated that the ethylenic linkage of compound **I** might be an essential structure for the anticonvulsant activity, we reason that the decrease in the anti-MES activity of compounds **1n**, **1o**, and **1p** might be due to lack of conjugation between phenyl ring and amide linkage.

To further investigate the effects of the anticonvulsant activity in several different models, compounds **I** and **1d** were tested against convulsions induced by chemical substances, including PTZ, isoniazid, 3-mercaptopropionic acid, and thiosemicarbazide. Compounds **I** and **1d** were administered into mice i.p. at a dose of 50 mg/kg, which was slightly higher than their 3ED_{50} value and far below their TD_{50} value. The reference drug carbamazepine was also administered i.p. at a dose of 50 mg/kg.

In the sc-PTZ model, compounds **I** and **1d**, and the reference drug carbamazepine did not inhibit the clonic seizures induced by sc-PTZ but they inhibited the tonic seizures and reduced lethality in

Table 1
Phase I evaluation of anticonvulsant activity in mice (i.p.).

Compound	R	Dosage (mg/kg)	MES[a]	
			0.5 h	4 h
I	–CH=CHC$_6$H$_5$	30	4/5	0/5
1a	–CH=CHC$_6$H$_4$ (*p*-F)	100	5/5	0/5
1b	–CH=CHC$_6$H$_4$ (*p*-Cl)	100	4/5	0/5
1c	–CH=CHC$_6$H$_4$ (*p*-Br)	100	2/5	0/5
1d	–CH=CHC$_6$H$_4$ (*m*-F)	30	5/5	0/5
1e	–CH=CHC$_6$H$_4$ (*m*-Cl)	30	4/5	0/5
1f	–CH=CHC$_6$H$_4$ (*o*-F)	30	2/5	0/5
1g	–CH=CHC$_6$H$_4$ (*o*-Cl)	100	5/5	0/5
1h	–CH=CHC$_6$H$_4$ (*o*-Br)	100	3/5	0/5
1i	–CH=CHC$_6$H$_3$ (2,4-Cl$_2$)	300	2/5	0/5
1j	–CH=CHC$_6$H$_4$ (*p*-CH$_3$O)	100	2/5	0/5
1k	–CH=CHC$_6$H$_3$ (3,4-OCH$_2$O–)	30	2/5	0/5
1l	–CH=CHC$_6$H$_4$ (*p*-CH$_3$)	100	1/5	0/5
1m	–CH=CHC$_6$H$_4$ (*p*-N(CH$_3$)$_2$)	100	4/5	0/5
1n	–C$_6$H$_5$	300	2/5	0/5
1o	–C$_6$H$_5$CH$_2$	300	2/5	0/5
1p	–C$_6$H$_5$CH$_2$CH$_2$	300	1/5	0/5

[a] Maximal electroshock test (number of animals protected/number of animals tested), the number of mice is five.