European Journal of Medicinal Chemistry 44 (2009) 3654–3657

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

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

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ARTICLE INFO

Article history:
Received 23 July 2008
Received in revised form
1 February 2009
Accepted 12 February 2009
Available online 21 February 2009

Keywords:
Cinnamamide derivatives
Maximal electroshock (MES)
Chemical induced models
Neurotoxicity

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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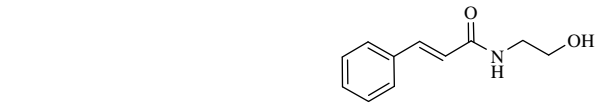
doi:10.1016/j.ejmech.2009.02.015



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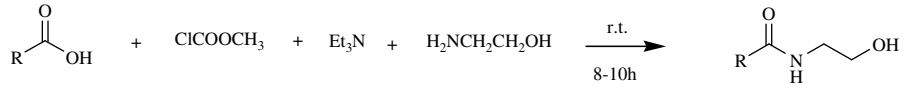

R:

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.

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

Compound	Rotarod toxicity		
	MES, ED_{50}[a]	TD_{50}[b]	PI[c] (TD_{50}/ED_{50})
I	17.7 (14.8–21.2)[d]	154.9 (137.6–174.4)	8.8
1a	45.6 (37.9–54.8)	98.3 (84.2–114.7)	2.2
1b	73.4 (61.0–88.1)	98.4 (64.6–148.7)	1.3
1c	76.0 (63.2–91.4)	98.3 (84.2–114.7)	1.3
1d	17.0 (14.1–20.4)	211.1 (175.6–253.8)	12.4
1e	25.0 (20.8–30.0)	126.8 (105.5–152.4)	5.1
1f	35.3 (29.4–42.3)	219.1 (182.2–263.4)	6.2
1g	59.0 (49.0–70.8)	152.1 (126.5–182.9)	2.6
1h	68.2 (56.9–81.8)	228.2 (203.4–256.0)	3.3
1k	32.4 (27.0–38.8)	105.4 (87.7–126.7)	3.3
1m	66.1 (55.1–79.3)	304.3 (271.2–341.4)	4.6
Carbamazepine	8.8 (5.5–14.1)	71.6 (45.9–135)	8.1

[a] ED_{50} – median effective dose required to assure anticonvulsant protection in 50% animals, the number of mice is ten.
[b] TD_{50} – median toxic dose eliciting minimal neurological toxicity in 50% animals.
[c] PI – protective index (TD_{50}/ED_{50}).
[d] 95% Confidence limits given in parentheses.

significant degrees (Table 3). In the isoniazid model, carbamazepine inhibited the clonic seizures, tonic seizures and death induced by isoniazid at the rate of 50%, 100% and 100%, respectively; and compounds **I** and **1d** did not affect the clonic seizures and showed partial inhibition of the tonic seizures and death induced by isoniazid (Table 4). PTZ and isoniazid have been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission [13,14]. GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Inhibition of GABAergic neurotransmission or activity has been shown to promote and facilitate seizures [15], while enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures. The findings of the present study suggest that the newly synthesized compounds **I** and **1d** might have not inhibited or attenuated PTZ-induced and isoniazid-induced seizures in mice by enhancing GABAergic neurotransmission.

In the 3-mercaptopropionic acid-induced seizure model, carbamazepine inhibited the clonic seizures, tonic seizures and death at the rate of 0%, 100%, and 100%, respectively. In comparison, compounds **I** and **1d** showed the effect pattern similar to that of carbamazepine in inhibiting the clonic seizures, and showed partial inhibition of the tonic seizures and death induced by 3-mercaptopropionic acid. Compound **I** showed inhibition at the rate of 0%, 90% and 90%, respectively, and compound **1d** showed inhibition of at the rate of 0%, 70% and 50%, respectively (Table 5). In the thiosemicarbazide-induced convulsion, the effect pattern is similar to that of the 3-mercaptopropionic acid-induced seizure model where, compared to the reference drug, compound **I** showed inhibition at the rate of 0%, 60% and 70%, respectively of the clonic seizures, tonic seizures and death. And compound **1d** showed inhibition at the rate of 0%, 50% and 60%, respectively (Table 6). 3-Mercaptopropionic acid and thiosemicarbazide were competitive inhibitors of GABA synthesis enzyme glutamate decarboxylase (GAD), and they inhibit the synthesis of GABA resulting in decreased GABA level in the brain [16]. Compounds **I** and **1d** showed moderate antagonism to 3-mercaptopropionic acid-induced seizures and thiosemicarbazide-induced seizures, suggesting that they might activate GAD or inhibit aminotransferase (GABA-T) in the brain.

In conclusion, the results of this study demonstrated that *N*-(2-hydroxyethyl) cinnamamide derivatives have potent anticonvulsant activity. Especially, compounds **I** and **1d** showed better anticonvulsant activity but also much lower toxicity than a benchmark marketed drug. In addition, compounds **I** and **1d** demonstrated antagonistic activity against seizures induced by 3-mercaptopropionic acid and thiosemicarbazide, but failed to control those induced by PTZ and isoniazid. These experiments suggested that compounds **I** and **1d** might activate glutamate decarboxylase (GAD) or inhibit GABA alpha-oxogluturate aminotransferase (GABA-T).

Table 3
Effect of compounds on PTZ-induced convulsion in mice.

Compound	Doses (mg/kg)	Test time (h)	Clonic seizures (%)	Tonic seizures (%)	Lethality (%)
DMSO: CMC-Na	–	0.5	100	100	0
Carbamazepine	50	0.5	100	0	10
I	50	0.5	100	20	10
1d	50	0.5	100	40	20

Table 4
Effect of compounds on isoniazid-induced convulsion in mice.

Compound	Doses (mg/kg)	Test time (h)	Clonic seizures (%)	Tonic seizures (%)	Lethality (%)
DMSO: CMC-Na		0.5	100	100	0
Carbamazepine	50	0.5	50	0	0
I	50	0.5	100	70	20
1e	50	0.5	100	80	20

3. Experimental section

3.1. Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on an FT-IR1730 (Bruker, Switzerland), ^{1}H NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to tetramethylsilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Aldrich Chemical Corporation. All other chemicals were of analytical grade.

3.2. General procedure for the preparation of *I*, *1a*–*1p*

In a three-necked round-bottomed flask containing substituted carboxylic acid 2 g (0.05 mol), 50 ml dichloromethane and triethylamine (0.1 mol), methyl chloroformate (0.1 mol) was added dropwise slowly under an ice bath with stirring, the mixture was stirred 2 h at room temperature. Then ethanolamine (0.1 mol) was added dropwise slowly under an ice bath with stirring, the mixture was stirred 6–8 h at room temperature. The solvents were removed under reduced pressure. The residue was poured into 100 ml ice water and stirred for 10 min. The solid obtained after filtration was recrystallized in water to afford a white solid.

Table 5
Effect of compounds on 3-mercaptopropionic acid-induced convulsion in mice.

Compound	Doses (mg/kg)	Test time (h)	Clonic seizures (%)	Tonic seizures (%)	Lethality (%)
DMSO: CMC-Na		0.5	100	100	80
Carbamazepine	50	0.5	100	0	0
I	50	0.5	100	10	10
1d	50	0.5	100	30	50

Table 6
Effect of compounds on thiosemicarbazide-induced convulsion in mice.

Compound	Doses (mg/kg)	Test time (h)	Clonic seizures (%)	Tonic seizures (%)	Lethality (%)
DMSO: CMC-Na		2.5	100	100	100
Carbamazepine	50	2.5	100	0	20
I	50	2.5	100	40	30
1d	50	2.5	100	50	40

3.3. Analytical data for compounds ***I***, ***1d***, and ***1k***

3.3.1. N-(2-Hydroxyethyl) cinnamamide (***I***)

Yield: 82%; m.p.:100–102 °C. ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 1H, –OH), 3.54 (t, 2H, $-CH_2OH$), 3.80 (t, 2H, $-CH_2NHCO$), 6.19 (s, 1H, –NH), 6.47 (dd, 1H, $J = 15$ Hz, =CHCO), 7.66 (dd, 1H, $J = 15$ Hz, CH=C), 7.34–7.47 (m, 5H, $-C_6H_5$). MS *m*/*z*: 192 (M + 1). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.91; H, 6.72; N, 7.20.

3.3.2. (E)-3-(3-Fluorophenyl)-N-(2-hydroxyethyl)acrylamide (***1d***)

Yield: 78%; m.p.:98–100 °C. ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 1H, –OH), 3.57 (t, 2H, $-CH_2OH$), 3.81 (t, 2H, $-CH_2NHCO$), 6.25 (s, 1H, –NH), 6.45 (dd, 1H, $J = 15$ Hz, =CHCO), 7.63 (dd, 1H, $J = 15$ Hz, CH=C), 7.05–7.37 (m, 5H, $-C_6H_5$). MS *m*/*z*: 210 (M + 1). Anal. Calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.02; H, 5.65; N, 6.58.

3.3.3. (E)-3-(Benzo[d][1,3]dioxol-5-yl)-N-(2-hydroxyethyl)acrylamide (***1k***)

Yield: 85%; m.p.: 96–99 °C. ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 2H, $-OCH_2O-$), 2.57 (s, 1H, –OH), 3.57 (t, 2H, $-CH_2OH$), 3.83 (t, 2H, $-CH_2NHCO$), 6.21 (s, 1H, –NH), 6.33 (dd, 1H, $J = 15$ Hz, =CHCO), 7.63 (dd, 1H, $J = 15$ Hz, CH=C), 6.89–7.46 (m, 5H, $-C_6H_5$). MS *m*/*z*: 236 (M + 1). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.15; H, 5.49; N, 5.87.

3.4. Pharmacology

All compounds were tested for anticonvulsant activity with Kunming mice in the 18–25 g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. The tested compounds were prepared as a suspension in a mixture of 1:19 (vol/vol) dimethylsulfoxide/saline (0.9% NaCl) containing 0.5% methylcellulose. All compounds were tested by the MES test; otherwise, compounds **I** and **1d** were tested by sc-PTZ, isoniazid, 3-mercaptopropionic acid, and thiosemicarbazide tests.

3.4.1. Anticonvulsant effects in the maximal electroshock seizure (MES) test [17,18]

Seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. The current was applied via corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. At 30 min after the administration of the compounds, the activities were evaluated in MES test.

3.4.2. sc-PTZ-induced seizures [19,20]

At 30 min after the administration of the test compounds, 85 mg/kg PTZ dissolved in saline was administered sc. The animals placed in individual cages and observed for 30 min. The number of clonic and tonic seizures as well as the number of deaths was noted.

3.4.3. Isoniazid-induced seizures test [21]

At 30 min after the administration of the compounds at various doses, the animals were given an i.p. dose of isoniazid (250 mg/kg), a dose at which 100% of the animals showed convulsive reactions. The mice were placed in individual cages and observed for 1 h. The dose which prevented 50% of the treated animals from tonic convulsions (ED_{50}) was calculated.

3.4.4. 3-Mercaptopropionic acid-induced seizures test [22]

At 30 min after the administration of the compounds, 60 mg/kg of 3-mercaptopropionic acid in saline solution was injected sc. Latency and duration of convulsions as well as latency and percentage of lethality were recorded during the 1 h following 3-mercaptopropionic acid administration. The dose which prevented 50% of the treated animals from tonic convulsions (ED_{50}) was calculated.

3.4.5. Thiosemicarbazide-induced seizures test [23]

At 30 min after the administration of compounds, the animals were given an i.p. dose of thiosemicarbazide (50 mg/kg). The mice were placed in individual cages and observed for 2.5 h. The time of onset of the seizure, the number of clonic seizures, tonic seizures and the lethality were recorded.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (No. 30460151 and No. 30760290) and Important Item Foundation of Ministry of Education, PR China (No. 20070422029).

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