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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

N-palmitoylethanolamide derivatives: synthesis and studies on anticonvulsant and antidepressant activities

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Abstract A series novel of *N*-palmitoylethanolamide derivatives was synthesized and screened for their anticonvulsant and antidepressant activities. Anticonvulsant activities and neurotoxicities of compounds when injected intraperitoneally (i.p.) were determined by maximal electroshock seizure (MES) test and a rotarod test, respectively, in mice. Only four of the synthesized compounds (**3a**, **3b**, **3c**, and **3d**) showed anticonvulsant activity at a dose of 100 mg/kg. Six compounds showed reduced immobility durations during the forced swimming test at a dose of 10 mg/kg, indicative of antidepressant activity. Among the compounds, *N*-(3-hydroxypropyl)cinnamamide (**3a**) was the most promising compound and significantly reduced the duration of immobility duration by 23.36% at a dose of 10 mg/kg compared with the control ($P < 0.01$).

Keywords *N*-palmitoylethanolamide derivatives · Anticonvulsant activity · Antidepressant activity

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Introduction

N-Palmitoylethanolamide (PEA) belongs to a family of endogenous lipid amides, of which anandamide is a well-known member (Bachur *et al.*, 1965; Schmid *et al.*, 1990). Lambert *et al.* (2001) reported the effects of PEA on electroshock-induced convulsion in mice and found dose-dependent protection against maximal electroshock seizure (MES) at nontoxic doses.

In our previous studies, we synthesized a series of *N*-(2-hydroxyethyl) amide derivatives and tested them for their anticonvulsant activities (Guan *et al.*, 2009a, b). Among this series, the compounds *N*-(2-hydroxyethyl) palmitamide (**I**), *N*-(2-hydroxyethyl) stearamdie (**II**), and *N*-(2-hydroxyethyl)cinnamamide (**III**) (Fig. 1) were found to show a better anticonvulsant activity and also had lower toxicity. In the anti-MES potency test, these compounds exhibited median effective doses (ED_{50}) of 23.3, 20.5, and 17.7 mg/kg, respectively (Guan *et al.*, 2009a, b).

As part of our continuous efforts in this area, a series of new PEA derivatives have been synthesized according to Scheme 1 and evaluated for their anticonvulsant activities by using the MES test. Seizure assays and neurotoxicity were evaluated by the rotarod toxicity test according to the phase-I tests of Antiepileptic Drug Development (ADD) program which were developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Schäfer 1985; Krall *et al.*, 1978).

In addition, it is reported that the cinnamamide derivatives exhibit a variety of biological activities, such as central nervous depression, anticonvulsant, and antidepressant activities (Moffet, 1964; Balsamo *et al.*, 1975; Van Heyningen *et al.*, 1966). Therefore, antidepressant activities of the synthesized compounds were also determined using Porsolt's behavioral despair (forced swimming) test

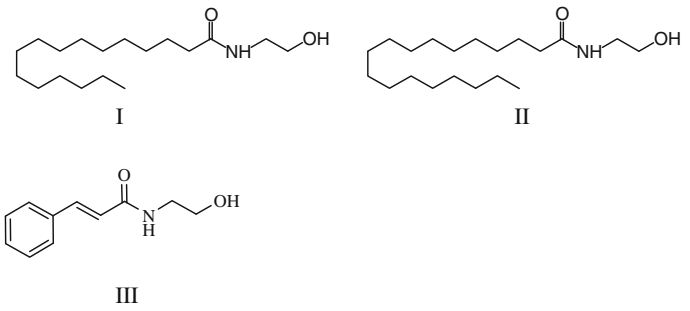
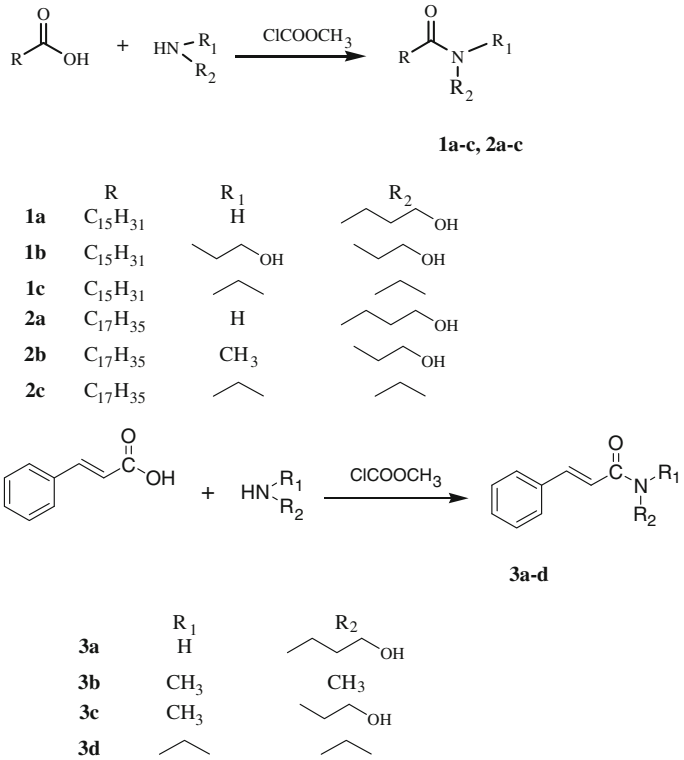


Fig. 1 Structure of **I**, **II**, and **III**

Scheme 1 Synthesis of compounds **1a–c**, **2a–c**, and **3a–d**



(Raiendra Prasad *et al.*, 2005). The synthesized compounds were characterized by IR, ^{1}H-NMR, and MS.

Experimental

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR1730 (Bruker, Switzerland), ^{1}H-NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all the chemical shifts were given in ppm relative to tetramethysilane. 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.

General procedure for the preparation of (**1a–c**, **2a–c**, **3a–d**)

In a three-necked round-bottomed flask containing substituted carboxylic acid (0.05 mol), 50 ml dichlorme-thane and triethylamine (0.1 mol), methyl chloroformate (0.1 mol) was added dropwise slowly under an ice bath with stirring; the mixture was stirred for 2 h at room temperature. Then, ethanolamine (0.1 mol) was added dropwise slowly under an ice bath with stirring; the mixture was stirred 8–10 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 precipitate thus obtained after filtration was recrystallized in hot water to afford a white color solid (Guan *et al.*, 2009a, b).

*N-(3-hydroxypropyl)palmitamide (**1a**)*

Yield = 82%, mp: 96–98°C. IR (KBr) cm^{-1}: 1712 (C=O), 3090 (NH), 3320 (OH). ^{1}H-NMR ($CDCl_3$): 0.87 (t, 3H, J = 6.9 Hz, CH_3), 1.26–1.69 (m, 26H, $(CH_2)_{13}$), 1.85 (m, 2H, CH_2), 2.19 (t, 2H, J = 7.5 Hz, CH_2CO), 3.40 (m, 2H, CH_2), 3.48 (s, 1H, OH), 3.63 (m, 2H, CH_2), 5.95 (s, 1H, NH). $C_{19}H_{39}NO_2$. MS: m/z 314 (M + 1).

*N,N-bis(2-hydroxyethyl)palmitamide (**1b**)*

Yield = 67%, mp: 89–91°C. IR (KBr) cm^{-1}: 1705 (C = O), 1123 (C–N), 3317 (OH). ^{1}H-NMR ($CDCl_3$): 0.88 (t, 3H, J = 6.4 Hz, CH_3), 1.25-1.63 (m, 26H, $(CH_2)_{13}$), 2.39 (t, 2H, J = 7.6 Hz, CH_2CO), 3.50 (t, 2H, J = 6.0 Hz, CH_2), 3.56 (t, 2H, J = 6.0 Hz, CH_2), 3.61 (s, H, OH), 3.65 (s, H, OH), 3.79 (t, 2H, J = 6.0 Hz, CH_2), 3.85 (t, 2H, J = 6.0 Hz, CH_2). $C_{20}H_{41}NO_3$. MS: m/z 344 (M + 1).

*N,N-diethylpalmitamide (**1c**)*

Yield = 75%, oil. ^{1}H-NMR ($CDCl_3$): 0.87 (t, 3H, J = 6.5 Hz, CH_3), 1.08–1.19 (m, 6H, $(CH_3)_2$), 1.25–1.65 (m, 26H, $(CH_2)_{14}$), 2.28 (t, 2H, J = 7.7 Hz, CH_2CO), 3.26–3.40 (m, 4H, $(CH_2)_2$). $C_{20}H_{41}NO$. MS: m/z 312 (M + 1).

*N-(3-hydroxypropyl)stearamide (**2a**)*

Yield = 79%, mp: 90–92°C. IR (KBr) cm^{-1}: 1709 (C=O), 3209 (NH), 3324 (OH). ^{1}H-NMR ($CDCl_3$): 0.87 (t, 3H, J = 6.9 Hz, CH_3), 1.64 (m, 2H, CH_2), 1.24–1.68 (m, 30H, $(CH_2)_{15}$), 2.18 (t, 2H, J = 7.5 Hz, CH_2CO), 3.37 (m, 2H, CH_2), 3.41 (s, 1H, OH), 3.63 (m, 2H, CH_2), 5.99 (s, 1H, NH). $C_{21}H_{43}NO_2$. MS: m/z 342 (M + 1).

*N-(2-hydroxyethyl)-N-methylstearamide (**2b**)*

Yield = 63%, mp: 96–97°C. IR (KBr) cm^{-1}: 1684 (C=O), 1176 (C–N), 3326 (OH). ^{1}H-NMR ($CDCl_3$): 0.87 (t, 3H, J = 6.3 Hz, CH_3), 1.25–1.63 (m, 30H, $(CH_2)_{15}$), 2.33 (t, 2H, J = 7.6 Hz, CH_2CO), 3.06 (s, 1H, OH), 3.46 (m, 3H, CH_3), 3.55 (m, 2H, CH_2), 3.77 (m, 2H, CH_2). $C_{21}H_{43}NO_2$. MS: m/z 342 (M + 1).

*N,N-diethylstearamide (**2c**)*

Yield = 71%, oil. ^{1}H-NMR ($CDCl_3$): 0.86 (t, 3H, J = 6.7 Hz,CH_3), 1.06–1.18 (m, 6H, $(CH_3)_2$), 1.24–1.64 (m, 30H, $(CH_2)_{15}$), 2.27 (t, 2H, J = 7.3 Hz, CH_2CO), 3.25–3.39 (m, 4H, $(CH_2)_2$). $C_{22}H_{45}NO$. MS : m/z 340 (M + 1).

*N-(3-hydroxypropyl)cinnamamide (**3a**)*

Yield = 57%, mp: 91–92°C. IR (KBr) cm^{-1}: 1709 (C=O), 3127 (NH), 3315 (OH). ^{1}H-NMR ($CDCl_3$): 1.74 (m, 2H, CH_2), 3,49 (s, 1H, OH), 3.58 (t, 2H, $–CH_2NHCO$), 3.68 (t, 2H, $–CH_2OH$), 6.40 (d, 1H, J = 15.6 Hz, =CHCO), 7.65 (d, 1H, J = 15.6 Hz, CH=C), 7.36–7.51 (m, 5H, $–C_6H_5$). $C_{12}H_{15}NO_2$. MS: m/z 206 (M + 1).

*N,N-dimethylcinnamamide (**3b**)*

Yield = 52%, mp: 101–103°C. IR (KBr) cm^{-1}: 1705 (C=O), 1172 (C–N). ^{1}H-NMR ($CDCl_3$): 3.08 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 6.90 (d, 1H, J = 15.5 Hz, =CHCO), 7.68 (d, 1H, J = 15.5 Hz, CH=C), 7.36–7.55 (m, 5H, $–C_6H_5$). $C_{11}H_{13}NO$. MS : m/z 176 (M + 1).

*N-(2-hydroxyethyl)-N-methylcinnamamide (**3c**)*

Yield = 56%, mp: 96–97°C. IR (KBr) cm^{-1}: 1698 (C=O), 1120 (C–N), 3309 (OH). ^{1}H-NMR ($CDCl_3$): 3.25 (s, 3H, CH_3), 3.41 (s, 1H, OH), 3.68 (m, 2H, $–CH_2NCO$), 3.85 (m, 2H, $–CH_2OH$), 6.88 (d, 1H, J = 15.4 Hz, =CHCO), 7.71 (d, 1H, J = 15.4 Hz, CH=C), 7.38–7.52 (m, 5H, $–C_6H_5$). $C_{12}H_{15}NO_2$. MS: m/z 206 (M + 1).

*N,N-diethylcinnamamide (**3d**)*

Yield = 47%, mp: 86–87°C. IR (KBr) cm^{-1}: 1706 (C=O), 1124 (C–N); ^{1}H-NMR ($CDCl_3$): 1.23 (m, 6H, $(CH_3)_2$), 3.49 (m, 4H, $(CH_2)_2$), 6.82 (d, 1H, J = 15.4 Hz, =CHCO), 7.72 (d, 1H, J = 15.4 Hz, CH=C), 7.36–7.54 (m, 5H, $–C_6H_5$). $C_{13}H_{17}NO$. MS: m/z 204 (M + 1).

Anticonvulsant activity

The MES test and the rotarod test were carried out according to the standard protocols described in the ADD Program of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Schäfer, 1985; Krall *et al.*, 1978). All the compounds were tested for anticonvulsant activities with Kunming mice in the 18–25 g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. Mice were housed collectively in groups of 10 in polycarbonate cages. They were maintained on a 12-h light/dark cycle in a temperature-controlled (23 ± 2°C) laboratory. Food and water were available ad libitum. The tested compounds were prepared as a suspension in a 0.5% aqueous solution of methylcellulose and injected i.p. in a standard volume of 0.05 ml/20 g body weight.

In Phase-I screening (Table 1), each compound was administered at the dose levels of 30, 100, and 300 mg/kg

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

Compounds	MES[a]						Toxicity[b]					
	1/2 h			4 h			1/2 h			4 h		
	mg kg^{-1}			mg kg^{-1}			mg kg^{-1}			mg kg^{-1}		
	30	100	300	30	100	300	30	100	300	30	100	300
I	2/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
II	3/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
III	3/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3
1a	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
1b	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
1c	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
2a	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
2b	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
2c	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
3a	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3
3b	0/3	1/3	3/3	0/3	1/3	1/3	0/3	0/3	3/3	0/3	0/3	0/3
3c	0/3	1/3	3/3	0/3	0/3	1/3	0/3	0/3	3/3	0/3	0/3	0/3
3d	0/3	2/3	3/3	0/3	1/3	1/3	0/3	0/3	3/3	0/3	0/3	0/3

[a] Maximal electroshock test (number of animals protected/number of animals tested)

[b] Rotarod toxicity test (number of animals exhibiting toxicity/number of animals tested)

for evaluating the anticonvulsant activity, and its neurotoxicity was measured at 30-min and 4-h intervals after administration. Anticonvulsant efficacy was measured in the MES test. In the MES test, 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. The 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. Anticonvulsant drug-induced neurologic deficit was detected in mice by using the rotorod ataxia test on a 1-inch diameter knurled wooden rod, rotating at 6 rpm.

Antidepressant activity

The synthesized compounds were screened for their antidepressant activities using Porsolt's behavioral despair (forced swimming) test (Raiendra Prasad *et al.*, 2005) Local breed, male Kunming mice (20–24 g) were used in the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On the test day, mice were dropped one at a time into a plexiglass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 23–25°C (Porsolt *et al.*, 1977). On this day, mice were assigned into different groups (n = 8–10 for each group). The synthesized compounds (10 mg/kg) and fluoxetine as a reference antidepressant drug (10 mg/kg) were suspended in a 0.5% aqueous solution of methylcellulose injected i.p. in a standard volume of 0.05 ml/20 g body weight, 30 min prior to the test. Control animal received 0.5% aqueous solution of methylcellulose. Then, the mice were dropped individually into the pelxiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements to prevent sinking. The duration of immobility was recorded during the last 4 min of the 6 min test.

Statistical analysis

Results are expressed as mean ± S.E.M.; n represents the number of animals. Data obtained from pharmacological experiments were analyzed with one-way analysis of variance (ANOVA) followed by Dunnet's post hoc test, using Pharmacologic Calculation System Version 4.1. (Microcomputer Specialists). A P-value of less than 0.05 was considered statistically significant.

Results and discussion

Target compounds were prepared according to Scheme 1. Compounds **1a–c**, **2a–c**, and **3a–d** were obtained in good yield through a one-step reaction using substituted

carboxylic acid, methyl chloroformate, triethyl amine, and ethanolamine as the starting material. Reaction mixture was maintained at room temperature for 8–10 h. All the compounds were identified by the spectral data (Guan *et al*., 2009a, b). In general, IR spectra showed the C=O peak at 1684–1712 cm^{-1}, the NH stretching vibrations at 3090–3209 cm^{-1}, the C–N stretching vibrations at 1098–1176 cm^{-1}, and the OH stretching vibrations at 3309–3326 cm^{-1}. In the nuclear magnetic resonance spectra (^{1}H-NMR), the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, mutiplicities, and coupling constants. The spectra showed the amide (NH) proton as a singlet at 5.30–5.99 ppm, and the hydroxyl proton (OH) at 3.06–3.65 ppm.

Pharmacological tests of the PEA derivatives **1a–c**, **2a-c**, and **3a–d** were conducted at the Epilepsy Branch of the National institute of Neurological Disorders and Stroke (NINDS) following the protocol adopted by the ADD program (Schäfer, 1985; Krall *et al*., 1978).

The anticonvulsant activities of the synthesized compounds were investigated by MES, and results from these experiments are shown in Table 1. According to the results of the experiments, it is clear that anticonvulsant activities of all compounds were weak. Only *N*,*N*-dimethylcinnamamide (**3b**), *N*-(2-hydroxyethyl)-*N*-methylcinnamamide (**3c**), and *N*,*N*-diethylcinnamamide (**3d**) exhibited activity against MES-induced seizures at 100 mg/kg dose level. Only compounds **3b**, **3c**, and **3d** showed neurotoxicity at a dose of 300 mg/kg, while with the remaining synthesized compounds' neurotoxicity was not observed at a dose of 300 mg/kg (Table 1).

Analyzing the anticonvulsant activities of the synthesized compounds **1a–c**, **2a–c**, and **3a–d**, the following SAR was gained (Table 1). Compounds **I** (*N*-(2-hydroxyethyl) palmitamide) and **II** (*N*-(2-hydroxyethyl) stearamdie) showed activity against MES-induced seizures at 30 mg/kg dose level, however, compounds **1a–c** and **2a–c** had not shown anticonvulsant active at a dose of 300 mg/kg. These results indicated that the N atom of compounds **I** and **II** with a substituted *N*-(3-hydroxypropyl)-, *N*,*N*-bis(2-hydroxyethyl)-, *N*,*N*-diethyl-, and *N*-(2-hydroxyethyl)-*N*-methyl- had not shown anticonvulsant activity. However, compounds **3a–d** showed significant anticonvulsant activity, in which the N atom of compound **III** was substituted with a *N*-(3-hydroxypropyl)-, *N*,*N*-dimethyl-, *N*,*N*-diethyl-, and *N*-(2-hydroxyet-hyl)-*N*-methyl-.

The forced swimming test is a behavioral test used to predict the efficacy of antidepressant treatments. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants (Porsolt, 1981). It has good predictive value for antidepressant potency in humans (Willner, 1991). The obtained data on the antidepressant activity of the compounds (**1a–c**, **2a–c**, and **3a–d**) and reference drug (Fluoxetine) are given in Table 2. The results showed that *N*-(2-hydroxyethyl)cinnamamide (**III**), *N*,*N*-bis(2-hydroxyethyl)palmitamide (**1b**), *N*-(2-hydroxyethyl)-*N*-methylstearamide (**2b**), *N*,*N*-dimethylcinnamamide (**3b**), and

Table 2 Antidepressant activities of the compounds

Compounds	Dose (mg/kg)	Antidepressant activities	
		Duration of immobility(s) (mean ± S.E.M.)	Change from control (%)
I	10	126.0 ± 9.0	−6.25
II	10	126.8 ± 5.3	−5.65
III	10	99.6 ± 14.7*	−25.89
1a	10	104.6 ± 19.9	−22.17
1b	10	99.0 ± 18.5*	−26.34
1c	10	111.1 ± 17.7	−17.34
2a	10	115.5 ± 18.5	−14.06
2b	10	104.8 ± 13.7*	−22.02
2c	10	109.6 ± 18.5	−18.45
3a	10	103.0 ± 11.8**	−23.36
3b	10	107.8 ± 15.1*	−19.97
3c	10	123.1 ± 15.7	−8.41
3d	10	109.9 ± 9.7*	−18.23
Fluoxetine	10	81.5 ± 12.8***	−39.36
Control	–	134.4 ± 24.4	–

Values represent the mean ± S.E.M. ($n = 8$)

Significantly compared to control (Dunnet's test: * $P < 0.05$, ** $P < 0.01$, *** $P \leq 0.001$)

N,*N*-diethylcinnamamide (**3d**) significantly reduced the duration of immobility at 10 mg/kg dose level when compared to control ($P < 0.05$, Table 2). Among all the compounds, *N*-(3-hydroxypropyl)cinnamamide (**3a**) was the most promising compound and significantly reduced the duration of immobility by 23.36% at a dose of 10 mg/kg compared with the control ($P < 0.01$); it is similar to reference drug fluoxetine.

Conclusion

In conclusion, the results of this study demonstrated that four of the synthesized compounds (**3a–d**) have anticonvulsant activities. However, the synthesized compounds have also possessed remarkable antidepressant activities. Therefore, they may be really promising compounds for the treatment of depression. In fact, *N*-(3-hydroxypropyl)cinnamamide (**3a**) was the most promising compound and significantly reduced the duration of immobility by 23.36% at a dose of 10 mg/kg compared with the control ($P < 0.01$); it is similarly to reference drug fluoxetine.

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