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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antidepressant-like action of *N*-(2-hydroxyethyl) cinnamamide derivatives in mice

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Abstract This study described the chemical synthesis and pharmacological evaluation of a series of *N*-(2-hydroxyethyl) cinnamamide derivatives. The structures of them were characterized by IR, ^{1}H-NMR, MS and elemental analysis. Their antidepressant activities were evaluated by the forced swimming test (FST) and tail suspension test (TST). Pharmacological results of these compounds showed that some of them, given orally, significantly reduced the immobility time in the FST and TST, indicating the antidepressant-like action. Among them, compounds *N*-(2-hydroxyethyl)cinnamamide (**1g**), (*E*)-3-(4-hydroxy-3-methoxyphenyl)-N-(2-hydroxyethyl)acrylamide (**1i**) and (*E*)-N-(2-hydroxyethyl)-3-(3-hydroxyphenyl)acrylamide (**1n**), active in the two models, were considered as the most promising compounds in this study.

Keywords *N*-(2-hydroxyethyl) cinnamamide · Antidepressant · Forced swimming test · Tail suspension test

Introduction

Depression is one of the most prevalent psychopathologies. It is ranked by the World Health Organization as the fourth greatest cause of global illness burden in the year 2000, and investigations indicate that it will become the second leading cause of disease worldwide by 2020 (Meyer, 2004; Lopez and Murray 1998). Despite the introduction of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) to treat depression and more recent advances in antidepressant treatment, including the discovery of selective serotonin reuptake inhibitors (SSRIs) and specific serotonin–noradrenaline reuptake inhibitors (SNRIs), the therapeutic result is not satisfactory with one third remission rate and the subjects always suffer from the side effects of those clinical antidepressants such as anxiety, sleep disturbance, weight gain and sexual dysfunction (Thase, 2003; Thase *et al.*, 2007; Hirschfeld 1999). Therefore, the discovery of new antidepressant drugs with less side-effects and better efficacy is still necessary.

The cinnamamide derivatives exhibit a variety of biological activities, such as central nervous depression, sedative-hypnosis, anticonvulsant, muscle relaxation, local anesthesia, inhibit fungal, and antidepressant activities (Bruce Moffett, 1964; Van Heyningen *et al.*, 1966; Balsamo *et al.*, 1981, 1975). *N*-(3-hydroxypropyl) cinnamamide was found possessing antidepressant activity in the forced swimming test (FST) in our previous work (Guan *et al.*, 2010). In our further search for new compounds with antidepressant activity, *N*-(2-hydroxyethyl) cinnamamide (Fig. 1, compound **I**) was synthesized and tested its antidepressant activity in the FST, in which *N*-(2-hydroxyethyl) cinnamamide showed a positive antidepressant activity at the dose of 40 mg/kg. In order to obtain compounds with better antidepressant activity, we synthesized *N*-(2-hydroxyethyl) cinnamamide derivatives via modifying the aromatic ring by introducing some substituents to it. Considering that multitude of antidepressant agents are natural produces, methoxyl and hydroxyl substituted compounds are the major in this study. The synthesized compounds were characterized by IR, ^{1}H-NMR, MS and elemental analysis. Their antidepressant activities were evaluated by the FST and tail suspension test (TST), two

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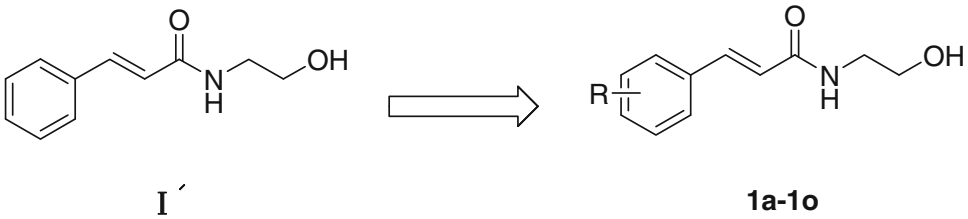


Fig. 1 Structure of *N*-(2-hydroxyethyl) cinnamamide and its derivatives

well-established animal models that have been extensively used as screening models for new antidepressant agents (Porsolt *et al.*, 1977; Steru *et al.*, 1985).

Results and discussion

Synthesis

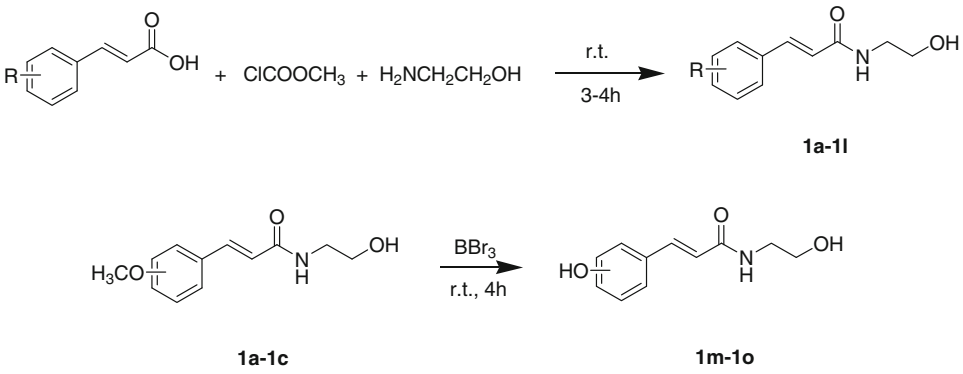
Target compounds were prepared according to Scheme 1. Compounds **1a–1l** were obtained in high yield through a one-step reaction using substituted cinnamic acid, methyl chloroformate, triethylamine, and ethanolamine as the reaction materials. Compounds **1m–1o** were obtained by demethylation of compounds **1a–1c**, respectively. All the compounds were identified by spectral data. In general, IR spectra showed the C=O peak at 1620–1662, the NH stretching vibrations at 3215–3286 cm^{-1}, and the OH stretching vibrations at 3332–3408 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, multiplicities and coupling constants.

Pharmacological evaluations

Compounds prepared were screened for their antidepressant activities in mice using the FST and tail suspension test (TST). The FST was designed by porsolt as a primary screening test for antidepressants, and it remains one of the best models for this purpose for several reasons. It is a low cost, fast, and reliable model to test potential antidepressant treatments with a strong predictive validity. The immobility time observed in the test reflected a state of lowered mood or hopelessness in animal; thus, this animal model is the most widely used tool for preclinical screening of putative antidepressant agents (Cryan *et al.*, 2002; Cryan *et al.*, 2005; Bourin *et al.*, 2005; Petit-Demouliere *et al.*, 2005). The TST is also considered as a mature model for predicting antidepressant activity (Steru *et al.*, 1985).

The results of FST revealed that some of the compounds prepared displayed good antidepressant activity. Acute treatment with the compounds **1g**, **1h**, **1i**, and **1n** promoted a significant decrease in the immobility time in the FST at 40 mg/kg, as depicted in Fig. 2 (control = 183.3 ± 12.67; **1g** = 101.2 ± 17.77; **1h** = 105.5 ± 9.06; **1i** = 55.00 ± 11.12; **1n** = 102.8 ± 28.27; Fluoxetine = 93.50 ± 22.61).

Scheme 1 Synthesis of compounds **1a–1o**



R:

1a: *o* -OCH_3	1e: 3,4-$(OCH_3)_2$	1i: 4-OH, 3-OCH_3	1m: *o* -OH
1b: *m* -OCH_3	1f: 3,4,5-$(OCH_3)_3$	1j: -C_6H_4(*p*-F)	1n: *m* -OH
1c: *p* -OCH_3	1g: -H	1k: -C_6H_4(*p*-Cl)	1o: *p* -OH
1d: 2,4-$(OCH_3)_2$	1h: -$N(CH_3)_2$	1l: -C_6H_4(*p*-Br)	

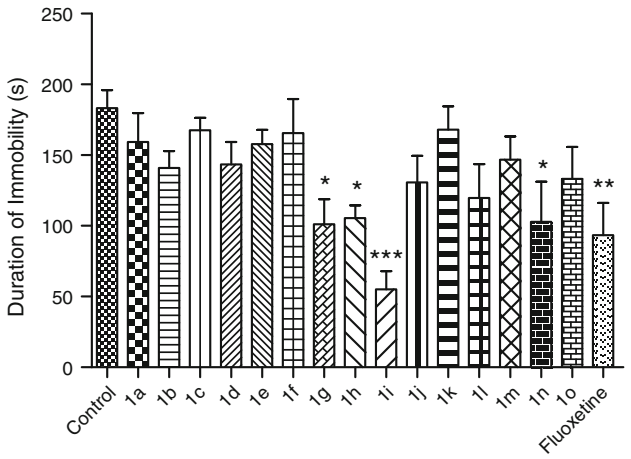


Fig. 2 Effects of the acute treatment with compounds **1a**–**1o**, 40 mg/kg, p.o.) and the standard antidepressant fluoxetine (FLU, 40 mg/kg, p.o.) on the immobility time in the forced swimming test. Each column represents mean ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test)

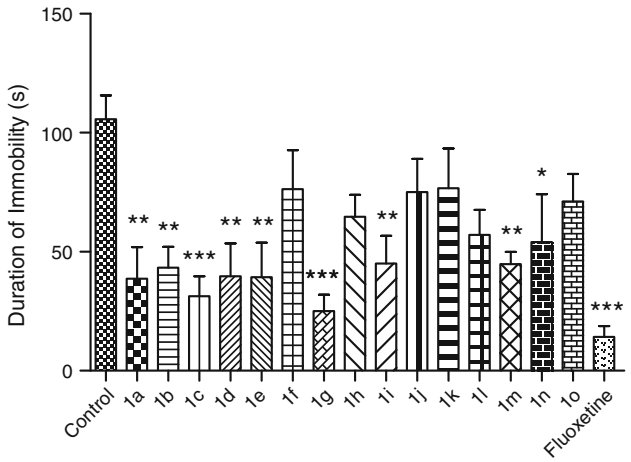


Fig. 3 Effects of the acute treatment with compounds **1a**–**1o**, 40 mg/kg, p.o.) and the standard antidepressant fluoxetine (FLU, 40 mg/kg, p.o.) on the immobility time in tail suspension test. Each column represents mean ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test)

The immobility time of mice treated with the other compounds **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1j**, **1k**, **1l**, **1m**, and **1o** did not statistically differ from control values as shown in Fig. 2 (control = 183.3 ± 12.67; **1a** = 159.1 ± 20.33; **1b** = 141.0 ± 11.77; **1c** = 167.5 ± 8.95; **1d** = 143.5 ± 15.76; **1e** = 157.8 ± 10.06; **1f** = 165.5 ± 24.21; **1j** = 130.8 ± 18.65; **1k** = 168.0 ± 16.47; **1l** = 119.7 ± 24.07; **1m** = 146.7 ± 16.49; **1o** = 133.3 ± 22.37).

The results of TST revealed that most of the compounds prepared displayed antidepressant activity. Acute treatment with the compounds **1a**–**1e**, **1g**, **1i**, and **1m**–**1n** promoted a significant decrease in the immobility time in the TST at 40 mg/kg, as depicted in Fig. 3 (control = 105.7 ± 10.03; **1a** = 38.67 ± 13.24; **1b** = 43.33 ± 8.76; **1c** = 31.33 ± 8.31; **1d** = 39.67 ± 13.89; **1e** = 39.33 ± 14.48; **1g** = 25.00 ± 6.89; **1i** = 45.00 ± 11.74; **1m** = 44.83 ± 5.15; **1n** = 54.00 ± 20.15; Fluoxetine = 14.17 ± 4.70). The immobility time of mice treated with the other compounds **1f**, **1h**, **1j**, **1k**, **1l**, and **1o** did not statistically differ from control values as shown in Fig. 3 (control = 105.7 ± 10.03; **1f** = 76.33 ± 16.30; **1h** = 64.67 ± 9.29; **1j** = 75.00 ± 14.01; **1k** = 76.67 ± 16.78; **1l** = 57.00 ± 10.51; **1o** = 71.00 ± 11.74).

The pharmacology results showed some relationship between structure and antidepressant activity. In the FST, four compounds prepared displayed antidepressant activity. Besides the lead compound **1g**, compounds **1h**, **1i**, and **1n** were also active. The substitutes of compounds **1h**, **1i**, and **1n**, contained dimethyl amine group and hydroxyl group, respectively, are the possible devoter to their antidepressant activity. The dimethyl amine group and hydroxyl group might form hydroxyl bonds with receptors, which lead to activity increase by enhancing the affinity between compounds and receptors. While compounds substituted by methoxyl or halogen groups such as **1a**–**1f**, **1j**–**1l** were all inactive. This might also be the reason of their weak affinity with receptor in vivo. Of the four compounds contained hydroxyl group, **1i** and **1n** were active, and **1m**, **1o** also obviously decrease the immobility time (**1m** = 146.7 ± 16.49; **1o** = 133.3 ± 22.37 versus control = 183.3 ± 12.67) though did not statistically differ from control, indicating that the hydroxyl group in the aromatic ring make a contribution to the antidepressant activity in this series. Comparing the derivatives with different OH-substitution positions on the benzol ring, their activity order was *m*-OH > *p*-OH > *o*-OH.

The results in the TST confirmed previous speculation that molecules contained methoxyl and hydroxyl group might be more active. Compounds **1a**–**1e**, substituted by methoxyl group were all active. Compounds **1m**–**1o**, substituted by hydroxyl group were all active except **1o**. It is cleared that the compounds **1j**, **1k**, and **1l** were inactive in the two models, which indicated that halogen groups in aromatic ring reduced the antidepressant activity in cinnamamide derivatives. Compounds **1g**, **1i**, and **1n**, both active in the two models, were considered as the most promising compounds in this series.

In conclusion, a series of *N*-(2-hydroxyethyl) cinnamamide derivatives were synthesized and their antidepressant activities were investigated using the FST and TST. Most compounds contained methoxyl and hydroxyl group are active in FST or TST. Compounds **1g**, **1i**, and **1n**, active in the two models, were consider as the most promising compounds in this study.

Experimental

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a IRPrestige-21. ^{1}H-NMR spectra were measured on an AV-300(Bruker, Fällanden, Switzerland), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, Santa Clara, CA, USA). Elemental analyses were performed on a 204Q CHN (Perkin Elmer, Fremont, CA, USA). The chemicals were purchased from Aldrich Chemical Corporation (Shanghai, China).

General procedures for the synthesis of the compounds **1a**–**1l**

In a three-necked round-bottomed flask containing substituted cinnamic acid 2 g (0.05 mol), 50 ml dichloromethane and triethylamine (0.1 mol), methyl cholroformate (0.1 mol) was added dropwise slowly under an ice bath with stirring, the mixture was stirred 2 h at room temperature. Then ethanolanmine (0.05 mol) was added dropwise slowly under an ice bath with stirring, the mixture was stirred 3–4 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.

General procedures for the synthesis of the compounds **1m**–**1o**

Compound **1a** (1.10 g, 5 mmol) was dissolved in dichloromethane (50 ml). BBr_3 (25 mmol) was added dropwise to the solution under an ice bath then the mixture was stirred at room temperature. After 4 h, the mixture was added slowly 20 ml ice cold water and allowed to stir for half an hour. The resulting precipitate was filtrated and recrystallized (in water) to afford compound **1m**.

Compounds **1n**, **1o** were obtained similarly from **1b**, **1c**

*(E)-N-(2-hydroxyethyl)-3-(2-methoxyphenyl)acrylamide **1a***

Yield: 65.7%; mp 80–82°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 1H, –OH), 3.32 (q, 2H, $J = 4.3$ Hz, $–CH_2$), 3.77 (t, 2H, $J = 4.7$ Hz, $–CH_2$), 3.81 (s, 3H, OCH_3), 6.56 (d, 1H, $J = 15.8$ Hz, CH=C), 6.71 (s, 1H, –NHCO), 6.82–6.90 (m, 2H, Ar–H), 7.26 (t, 1H, $J = 7.2$ Hz, Ar–H), 7.41 (d, 1H, $J = 6.8$ Hz, Ar–H), 7.88 (d, 1H, $J = 15.8$ Hz, CH=C). IR (KBr) cm^{-1}: 3364 (OH), 3286 (NH), 1626 (C=O). MS (m/z): 222 (M + 1). Anal. Calcd. for C12H15N1O3: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.27; H, 6.91; N, 6.21.

*(E)-N-(2-hydroxyethyl)-3-(3-methoxyphenyl)acrylamide (**1b**)*

Yield: 66.1%; mp 76–78°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.16 (s, 1H, –OH), 3.54 (t, 2H, $J = 5.4$ Hz, $–CH_2$), 3.72–3.84 (m, 5H, $–CH_2$, OCH_3), 6.44 (d, 1H, $J = 15.6$ Hz, CH=C), 6.62 (s, 1H, –NHCO), 6.88 (d, 1H, $J = 8.3$ Hz, Ar–H), 6.99 (s, 1H, Ar–H), 7.06 (d, 1H, $J = 7.5$ Hz, Ar–H), 7.24 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.58 (d, 1H, $J = 15.6$ Hz, CH=C). IR (KBr) cm^{-1}: 3389 (OH), 3266 (NH), 1649 (C=O). MS (m/z): 222 (M + 1). Anal. Calcd. for $C_{12}H_{15}N_1O_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.25; H, 6.87; N, 6.09.

*(E)-N-(2-hydroxyethyl)-3-(4-methoxyphenyl)acrylamide (**1c**)*

Yield: 54.9%; mp 110–112°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.23 (s, 1H, –OH), 3.55 (q, 2H, $J = 5.3$ Hz, $–CH_2$), 3.79 (t, 2H, $J = 4.8$ Hz, $–CH_2$), 3.92 (s, 3H, $–OCH_3$), 6.29 (s, 1H, –NHCO), 6.38 (d, 1H, $J = 15.8$ Hz, CH=C), 7.18 (d, 1H, $J = 8.6$ Hz, Ar–H), 7.50 (d, 1H, $J = 8.6$ Hz, Ar–H), 7.61(d, 1H, $J = 15.8$ Hz, CH=C). IR (KBr) cm^{-1}: 3408 (OH), 3224 (NH), 1651 (C=O). MS (m/z): 222 (M + 1). Anal. Calcd. for $C_{12}H_{15}N_1O_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.93; N, 6.27.

*(E)-3-(2,4-dimethoxyphenyl)-N-(2-hydroxyethyl)acrylamide (**1d**)*

Yield: 71.6%; mp 114–116°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.57 (s, 1H, –OH), 3.55 (t, 2H, $J = 4.9$ Hz, CH_2), 3.70–3.87 (m, 8H, $–CH_2$, $–OCH_3$, $–OCH_3$), 6.33 (s, 1H, –NHCO), 6.41–6.54 (m, 3H, Ar–H), 7.37 (d, 1H, $J = 15.7$ Hz, CH=C), 7.80 (d, 1H, $J = 15.7$ Hz, CH=C). IR (KBr) cm^{-1}: 3374 (OH), 3265 (NH), 1629 (C=O). MS (m/z): 252 (M + 1). Anal. Calcd. for $C_{13}H_{17}N_1O_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 65.26; H, 6.95; N, 5.53.

*(E)-3-(3,4-dimethoxyphenyl)-N-(2-hydroxyethyl)acrylamide (**1e**)*

Yield: 57.8%; mp 116–118°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.61 (s, 1H, –OH), 3.57 (q, 2H, $J = 4.5$ Hz, $–CH_2$), 3.80 (t, 2H, $J = 4.9$ Hz, $–CH_2$), 3.89 (s, 6H, $–OCH_3$, $–OCH_3$), 6.30 (s, 1H, –NHCO), 6.33 (d, 1H, $J = 15.5$ Hz, CH=C), 6.84 (d, 1H, $J = 8.3$ Hz, Ar–H), 7.02 (s, 1H, Ar–H), 7.08 (d, 1H, $J = 8.3$ Hz, Ar–H), 7.58 (d, 1H, $J = 15.5$ Hz, CH=C). IR (KBr) cm^{-1}: 3398 (OH), 3284 (NH), 1624 (C=O). MS (m/z): 252 (M + 1). Anal.

Calcd. for $C_{13}H_{17}N_1O_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 65.24; H, 6.90; N, 5.51.

*(E)-N-(2-hydroxyethyl)-3-(3,4, 5-trimethoxyphenyl)acrylamide (**1f**)*

Yield: 46.3%; mp 120–122°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.55 (s, 1H, -OH), 3.57 (q, 2H, $J = 4.8$ Hz, $–CH_2$), 3.80 (t, 2H, $J = 4.7$ Hz, $–CH_2$), 3.84 (s, 9H, $–OCH_3$, $–OCH_3$, $–OCH_3$), 6.33 (s, 1H, –NHCO), 6.35 (d, 1H, $J = 15.5$ Hz, CH=C), 6.71 (s, 2H, Ar–H), 7.54 (d, 1H, $J = 15.5$ Hz, CH=C). IR (KBr) cm^{-1}: 3405 (OH), 3266 (NH), 1620 (C=O). MS (m/z): 282 (M + 1). Anal. Calcd. for $C_{14}H_{19}N_1O_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.93; H, 6.80; N, 5.06.

*N-(2-hydroxyethyl)cinnamamide (**1g**)*

Yield: 52.7%; mp 100–102°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.61(s, 1H, –OH), 3.56 (q, 2H, $J = 5.0$ Hz, $–CH_2$), 3.80 (t, 2H, $J = 4.8$ Hz, $–CH_2$), 6.42 (s, 1H, –NHCO), 6.44 (d, 1H, $J = 15.7$ Hz, CH=C), 7.36–7.47 (m, 5H, Ar–H), 7.69(d, 1H, $J = 15.7$ Hz, CH=C). IR (KBr) cm^{-1}: 3389 (OH), 3215 (NH), 1661 (C=O). 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, 69.20; H, 6.92; N, 7.39.

*(E)-3-(4-(dimethylamino)phenyl)-N-(2-hydroxyethyl)acrylamide (**1h**)*

Yield: 43.8%; mp 110–112°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.77 (s, 1H, –OH), 3.01 (s, 6H, $–(NH_3)_2$), 3.56 (q, 2H, $J = 5.3$ Hz, $–CH_2$), 3.79 (t, 2H, $J = 4.7$ Hz, $–CH_2$), 5.98 (s, 1H, –NHCO), 6.21 (d, 1H, $J = 15.4$ Hz, CH=C), 6.68 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.40 (d, 2H, $J = 8.4$ Hz, Ar–H), 7.58 (d, 1H, $J = 15.4$ Hz, CH=C). IR (KBr) cm^{-1}: 3356 (OH), 3228 (NH), 1647 (C=O). MS (m/z): 235 (M + 1). Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.77; H, 7.79; N, 11.85.

*(E)-3-(4-hydroxy-3-methoxyphenyl)-N-(2-hydroxyethyl)acrylamide (**1i**)*

Yield: 69.6%; mp 114–116°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 3.23 (q, 2H, $J = 5.8$ Hz, $–CH_2$), 3.44 (t, 2H, $J = 4.5$ Hz, $–CH_2$), 3.79 (s, 3H, $–CH_3$), 4.71 (s, 1H, –OH), 6.49 (d, 1H, $J = 15.7$ Hz, CH=C), 6.78 (d, 1H, $J = 8.1$ Hz, Ar–H), 6.94 (d, 1H, $J = 8.1$ Hz, Ar–H), 7.10 (s, 1H, Ar–H), 7.31 (d, 1H, $J = 15.7$ Hz, CH=C), 7.94 (s, 1H, –NHCO), 9.37 (s, 1H, Ar–OH). IR (KBr) cm^{-1}: 3376 (OH), 3222 (NH), 1632 (C=O). MS (m/z): 238 (M + 1). Anal. Calcd. for $C_{12}H_{15}N_1O_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.44; N, 5.76.

*(E)-3-(4-fluorophenyl)-N-(2-hydroxyethyl)acrylamide (**1j**)*

Yield: 56.1%; mp 90–92°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 1H, –OH), 3.56 (q, 2H, $J = 5.3$ Hz, $–CH_2$), 3.80 (t, 2H, $J = 4.7$ Hz, $–CH_2$), 6.25 (s, 1H, –NHCO), 6.35 (d, 1H, $J = 15.6$ Hz, CH=C), 6.77 (d, 2H, $J = 8.2$ Hz, Ar–H), 7.30 (d, 1H, $J = 15.7$ Hz, CH=C), 7.37 (d, 2H, $J = 8.2$ Hz, Ar–H). IR (KBr) cm^{-1}: 3332 (OH), 3220 (NH), 1640 (C=O). MS (m/z): 210 (M + 1). Anal. Calcd. for $C_{11}H_{13}N_1O_3$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.34; H, 5.85; N, 6.78.

*(E)-3-(4-chlorophenyl)-N-(2-hydroxyethyl)acrylamide (**1k**)*

Yield: 63.6%; mp 130–132°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 1H, –OH), 3.58 (q, 2H, $J = 5.3$ Hz, $–CH_2$), 3.82 (t, 2H, $J = 4.8$ Hz, $–CH_2$), 6.22 (d, 1H, $J = 15.7$ Hz, CH=C), 6.30 (s, 1H, –NHCO), 6.89 (d, 2H, $J = 8.2$ Hz, Ar–H), 7.36 (d, 1H, $J = 15.7$ Hz, CH=C), 7.42 (d, 2H, $J = 8.2$ Hz, Ar–H). IR (KBr) cm^{-1}: 3339 (OH), 3218 (NH), 1644 (C=O). MS (m/z): 226 (M + 1). Anal. Calcd. for $C_{11}H_{13}N_1O_3$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.71; H, 5.44; N, 6.08.

*(E)-3-(4-bromophenyl)-N-(2-hydroxyethyl)acrylamide (**1l**)*

Yield: 59.3%; mp 142–144°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.61 (s, 1H, –OH), 3.57 (s, 1H, $–CH_2$), 3.82 (t, 2H, $J = 4.7$ Hz, $–CH_2$), 6.13 (s, 1H, –NHCO), 6.44 (d, 1H, $J = 16.0$ Hz, CH=C), 7.39 (d, 2H, $J = 8.3$ Hz, Ar–H), 7.53 (d, 2H, $J = 8.3$ Hz, Ar–H), 7.63 (d, 1H, $J = 16.0$ Hz, CH=C). IR (KBr) cm^{-1}: 3342 (OH), 3266 (NH), 1638 (C=O). MS (m/z): 271 (M + 1). Anal. Calcd. for $C_{11}H_{12}N_1O_3Br$: C, 48.91; H, 4.48; N, 5.19. Found: C, 49.09; H, 4.40; N, 5.04.

*(E)-N-(2-hydroxyethyl)-3-(2-hydroxyphenyl)acrylamide (**1m**)*

Yield: 49.7%; mp 152–154°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 3.23 (q, 2H, $J = 5.7$ Hz, $–CH_2$), 3.41 (t, 2H, $J = 5.7$ Hz, $–CH_2$), 4.83 (s, 1H, –OH), 6.65 (d, 1H, $J = 15.9$ Hz, CH=C), 6.80 (t, 1H, $J = 7.4$ Hz, Ar–H), 6.86 (d, 1H, $J = 8.1$ Hz, Ar–H), 7.16 (t, 1H, $J = 6.8$ Hz, Ar–H), 7.41 (d, 1H, $J = 7.2$ Hz, Ar–H), 7.62 (d, 1H, $J = 15.9$ Hz, CH=C), 8.09 (s, 1H, –NHCO), 10.1 (s, 1H, Ar–OH). IR (KBr) cm^{-1}: 3345 (OH), 3229 (NH), 1648 (C=O). MS (m/z): 208 (M + 1). Anal. Calcd. for

$C_{11}H_{13}N_1O_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.92; H, 6.41; N, 6.58.

*(E)-N-(2-hydroxyethyl)-3-(3-hydroxyphenyl)acrylamide (**1n**)*

Yield: 45.5%; mp 70–72°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 3.32 (q, 2H, $J = 5.4$ Hz, –CH_2), 3.55 (t, 2H, $J = 5.7$ Hz, –CH_2), 4.69 (s, 1H, –OH), 6.60 (d, 1H, $J = 15.6$ Hz, CH=C), 6.77 (d, 1H, $J = 7.7$ Hz, Ar–H), 6.92 (s, 1H, Ar–H), 7.08 (d, 1H, $J = 10.6$ Hz, Ar–H), 7.16 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.35 (d, 1H, $J = 15.6$ Hz, CH=C), 8.10 (s, 1H, –NHCO), 9.38 (s, 1H, Ar–OH). IR (KBr) cm^{-1}: 3379 (OH), 3242 (NH), 1662 (C=O). MS (m/z): 208 (M + 1). Anal. Calcd. for $C_{11}H_{13}N_1O_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.97; H, 6.43; N, 6.57.

*(E)-N-(2-hydroxyethyl)-3-(4-hydroxyphenyl)acrylamide (**1o**)*

Yield: 53.1%; mp 138 ~ 140°C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.51 (s, 1H, –OH), 3.22 (t, 2H, $J = 5.7$ Hz, –CH_2), 3.42 (q, 2H, $J = 5.9$ Hz, –CH_2), 6.43 (d, 1H, $J = 15.7$ Hz, CH=C), 6.78 (d, 2H, $J = 8.2$ Hz, Ar–H), 7.30 (d, 1H, $J = 15.7$ Hz, CH=C), 7.38 (d, 2H, $J = 8.2$ Hz, Ar–H), 8.00 (s, 1H, –NHCO) 8.97 (s, 1H, Ar–OH). IR (KBr) cm^{-1}: 3379 (OH), 3219 (NH), 1632 (C=O). MS (m/z): 208 (M + 1). Anal. Calcd. for C11H13N1O3: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.92; H, 6.39; N, 6.67.

Pharmacology

Forced swimming test (FST)

On testing day, totally 102 male KunMing (20–22 g) mice were randomly chosen and divided into 17 groups ($n = 6$ for each group): control group, groups of various compounds (**1a**–**1o**), and positive control group (Fluoxetine), used in the FST (Porsolt *et al.*, 1977). The synthesized compounds and the standard drug Fluoxetine were given as an intraperitoneal injection to mice. Control animals received 3% aqueous solution of Tween 80. Thirty minutes later, the mice were dropped one at a time into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 24–26°C) and left 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 only made slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6 min test.

Tail suspension test (TST)

On testing day, totally 102 male KunMing (20–22 g) mice were randomly chosen and divided into 17 groups ($n = 6$ for each group): control group, groups of various of compounds (**1a**–**1o**), and positive control group (Fluoxetine), used in the tail suspension test (Steru *et al.*, 1985). The synthesized compounds and the standard drug Fluoxetine were given as an intraperitoneal injection to mice. Control animals received 3% aqueous solution of Tween 80. Thirty minutes later, the total duration of immobility induced by tail suspension was measured according to the method described previously. Mice were both acoustically and visually isolated and suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period. The total duration of immobility was recorded during the last 4 min of the 6 min test.

Statistical analysis

Results are expressed as mean ± SEM; 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 statistical significance.

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