Med Chem Res (2013) 22:4615–4621
DOI 10.1007/s00044-012-0415-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A simple synthesis of *trans*-3,4,5-trimethoxycinnamamides and evaluation of their biologic activity

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Received: 6 March 2012 / Accepted: 11 December 2012 / Published online: 17 January 2013

Abstract A simple synthesis and biologic evaluation of *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** as novel antinarcotic agents is described. The synthetic key strategies involve condensation reaction and coupling reaction to generate *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11**. They were evaluated for free radical scavenging, inhibitory action for neurotoxicity in cultured neurons, and antinarcotic activity in mice. It was found that compounds **10a**, **10d**, and **10e** displayed significant inhibitory action of the glutamate-induced neurotoxicity and **10a–e** and **11** showed high antinarcotic activity in mice.

Keywords *Trans*-3,4,5-trimethoxycinnamamides · Condensation reaction · Coupling reaction · Antineurotoxicity · Free radical scavenging · Antinarcotic activity

Introduction

Many methoxycinnamic acids and their derivatives have been of interest for their antibacterial (Srivastava *et al.*, 2007), antiviral (King *et al.*, 2009; Lee *et al.*, 2007), anti-inflammatory (Chen *et al.*, 2007), antitumor (Fong *et al.*, 2008), antioxidant (Carlotti *et al.*, 2008), and antipyretic effect (Sultana *et al.*, 2005; Kurokawa *et al.*, 1998). In particular, *trans*-cinnamic acids and its derivatives are very effective to modulate central nervous system (CNS) including attention deficit hyperactivity disorder (ADHD), narcolepsy effects (Nardi *et al.*, 2008), and antidepressant-like effects were related to sedative activity by suppressing norepinephrine content in locus coeruleus (Kawashima *et al.*, 2004) (Fig. 1).

3,4,5-Trimethoxycinnamic acid (TMCA) is a component of the root of *Polygala tenuifolia* WILLLDENOW (polygalaceae) and its extract was used as a sedative in Japanese traditional Kampo medicine (Kawashima *et al.*, 2004). The Kawashima group studied the effect of TMCA on stress-induced corticotrophin-releasing hormone (CRH) release and found that TMCA exhibits sedative effects by suppressing norepinephrine (NE) content in the locus coeruleus (LC) (Kawashima *et al.*, 2004). Hyperactivity of LC neurons is an important component of opiate withdrawal. Opiate withdrawal syndrome is mediated by an excitatory amino acid (glutamate) input to the LC and causes hyperactivity in the LC region (Akaoka and Aston-Jones, 1993). To determine the development of morphine dependence in mice or rats, naloxone (opioid receptor antagonist) was injected and jumping behavior was measured (Jung *et al.*, 2011). During naloxone-induced jumping behavior, there was a further significant increase in the extracellular levels of NE (Fuentealba *et al.*, 2000). These studies suggest that TMCA may be working at opioid withdrawal by suppressing NE or blocking excitatory amino acid input to the LC. Recently, Keung group (Tao *et al.*, 2005) demonstrated that aromatic-substituted cinnamic acid and its structural analogs inhibit monoamine oxidase A and exhibit antidepressant-like activity in mice.

The Geraci group (Consoli *et al.*, 2006) described the synthesis of hydroxycinnamic acid clustered by a calixarene

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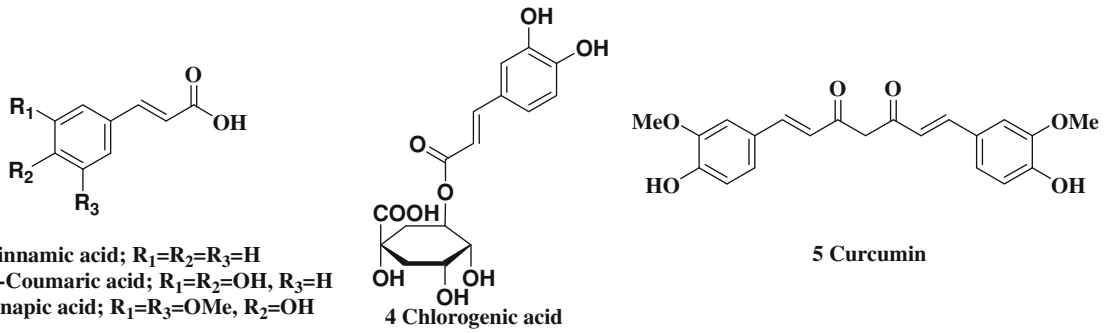


Fig. 1 Chemical structures of cinnamic acid (**1**), *p*-coumaric acid (**2**), sinapic acid (**3**), chlorogenic acid (**4**), and curcumin (**5**)

and evaluated its radical scavenging and antioxidant activity using 1,1-diphenyl-2-picryl hydrazyl (DPPH)-induced radicals and the 2,2′-azobis(isobutyronitrile) (AIBN)-induced linoleic acid peroxidation test. Priorities of current research for the *trans*-3,4,5-methoxycinnamamides are focused on antioxidant effect, inhibitory action for the glutamate-induced neurotoxicity in neuronal cells, and antinarcotic activity in mice. Previously, we reported that *trans*-3,4,5-methoxyphenylacrylamides showed antinarcotic activity in mice (Jung *et al.*, 2010). Recent reports described a simple synthesis and structural modification of *trans*-3,4,5-trimethoxycinnamamides by Pathan group (Pathan and Patil, 2008) and Nudelman group (Hedvati *et al.*, 2002), respectively. The Zhang group (Yang *et al.*, 2010) has developed to a new protocol for the synthesis of *trans*-3,4,5-trimethoxycinnamamide analogs through silica gel-mediated amide bond formation.

In the context of our pharmacological research program dealing with the synthesis of more biologically active *trans*-3,4,5-methoxycinnamamides, we wish to report simple synthesis of *trans*-3,4,5-methoxycinnamamides and its derivatives derived from condensation reaction and coupling reaction. In addition, biologic activities of *trans*-3,4,5-methoxycinnamamides and its structural analogs for antinarcotic activity in mice could suggest us some possible antinarcotic lead compounds.

Materials and methods

Chemistry

General

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl before use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates from Analtech and visualized with 254 nm UV light. Flash chromatography was carried out on silica gel 60 [Scientific Adsorbents Incorporated (SAI), particle size 32–63 μM, pore size 60 Å]. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 500 at 500 and 125 MHz, respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J* values are in Hz. Infrared (IR) spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded using a Waters Micromass ZQ LC-Mass system and high resolution mass spectra (HRMS) were measured with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). When necessary, chemicals were purified according to the reported procedures (Armarego and Perrin, 1997).

*General procedure for the preparation of trans-3,4,5-trimethoxycinnamamides **10a–e** and **11***

To a stirred solution of amide (**9**, 1.0 g, 4.2 mmol) in dry dichloromethane (30 mL) 1-ethyl(dimethylaminopropyl) carbodiimide (EDCI, 0.97 g, 5.0 mmol), 1-hydroxybenzotriazole (HOBt, 0.68 g, 5.0 mmol), and triethylamine (TEA, 0.70 mL, 5.0 mmol) were added and then the reaction mixture was stirred at room temperature for 30 min. The amines were then added into the reaction mixture and the resulting mixture stirred at room temperature for 24 h. The reaction mixture was washed with brine (20 mL) and water (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate/hexanes = 2:1, v/v).

*(E)-N-2-hydroxyethyl 3,4,5-trimethoxycinnamamide (**10a–e and 11**)* White solid. mp 135–136 °C. Yield: 60 %; $R_f = 0.6$ (dichloromethane/MeOH = 9:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3367 (O–H), 2939 (C–C), 1659 (C=O), 1620 (C=C), 1585, 1551, 1506, 1455, 1420, 1384, 1324, 1281, 1243 (C–O), 1218, 1153, 1125, 998, 827, 784 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500.14 MHz) δ 7.53 (d, 1H, $J = 15.4$ Hz),

6.70 (s, 2H), 6.59 (s, 1H), 6.39 (d, 1H, $J = 15.4$ Hz), 3.86 (s, 3H), 3.84 (s, 6H), 3.73–3.79 (m, 2H), 3.50–3.56 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125.76 MHz) δ 167.2, 153.5, 141.4, 139.7, 130.4, 119.9, 105.3, 62.3, 61.0, 56.3, 42.8; LC–MS (ESI) m/z 304 $[M + Na]^+$; HRMS: $m/z = 282.1334$ (calcd. 282.1341 for $C_{14}H_{20}NO_5$: $[M+H]^+$).

*(E)-N-(3-(2-oxopyrrolidin-1-yl)propyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (**10b**)* Pale yellow solid. mp 114–115 °C. Yield: 80 %; $R_f = 0.6$ (MC/MeOH = 10:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3417 (N–H), 3063, 2938 (C–C), 2837, 1666 (C=O), 1621 (C=C), 1583, 1505, 1452, 1421, 1323, 1279, 1216 (C–O), 1185, 1154, 1124, 1001, 827 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500.14 MHz) δ 7.52 (d, 1H, $J = 15.6$ Hz), 7.14 (t, 1H, $J = 6.1$ Hz), 6.75 (s, 2H), 6.41 (d, 1H, $J = 15.6$ Hz), 3.88 (s, 6H), 3.87 (s, 3H), 3.38–3.44 (m, 4H), 3.29–3.37 (m, 2H), 2.45 (t, 2H, $J = 7.9$ Hz), 2.08 (m, 2H), 1.75 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125.76 MHz) δ 176.2, 165.9, 153.4, 140.4, 139.4, 130.6, 120.7, 104.9, 60.9, 56.2, 47.4, 39.5, 35.5, 31.0, 26.4, 18.0; LC–MS (ESI) m/z 385 $[M+Na]^+$; HRMS: $m/z = 363.1931$ (calcd. 363.1920 for $C_{19}H_{27}N_2O_5$: $[M+H]^+$).

*(E)-1-morpholin-4-yl(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**10c**)* White solid. mp 134–135 °C. Yield: 78 %; $R_f = 0.3$ (ethyl acetate/hexanes = 2:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3448, 2852 (C–C), 1645 (C=O), 1587, 1505, 1459, 1341, 1273, 1228 (C–O), 1152, 1127, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.14 MHz) δ 7.62 (d, 1H, $J = 15.3$ Hz), 6.74 (d, 1H, $J = 15.3$ Hz), 6.75 (s, 2H) 3.90 (s, 6H), 3.88 (s, 3H), 3.73 (s, 8H); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 165.5, 153.4, 143.3, 139.6, 130.7, 115.7, 105.0, 100.0, 66.9, 61.0, 56.2; LC–MS (ESI) m/z 330.17 $[M+Na]^+$; HRMS: $m/z = 308.1485$ (calcd. 308.1498 for $C_{16}H_{22}NO_5$: $[M+H]^+$).

*(E)-1-(4-benzoylpiperazin-1-yl)-3-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (**10d**)* White solid. mp 179–180 °C. Yield: 85 %; $R_f = 0.7$ (MC/MeOH = 10:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3423, 2998 (C–C), 2937 (C–C), 2838, 1721(C=O), 1631 (C=C), 1603, 1582, 1505, 1455, 1421, 1339, 1266, 1219 (C–O), 1153, 1124, 1031, 1007, 923, 824 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500.14 MHz) δ 7.63 (d, 1H, $J = 15.3$ Hz), 7.44 (s, 5H), 7.39 (d, 1H, $J = 12.8$ Hz), 6.75 (s, 2H), 3.90 (s, 6H), 3.88 (s, 3H), 3.74 (s, 8H); ^{13}C-NMR ($CDCl_3$, 125.76 MHz) δ 170.8, 165.8, 153.6, 143.9, 140.0, 135.3, 130.6, 130.2, 128.8, 127.2, 115.8, 105.3, 61.1, 56.4, 53.5; LC–MS (ESI) m/z 433 $[M+Na]^+$; HRMS: $m/z = 411.1912$ (calcd. 411.1920 for $C_{23}H_{27}N_2O_5$: $[M+H]^+$).

*(E)-1-thiomorpholino-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**10e**)* White solid. mp 128–130 °C. Yield: 72 %; $R_f = 0.3$ (ethyl acetate/*n*-hexane = 2:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3424, 2923 (C–C), 2837, 1693 (C=O), 1644 (C=C), 1603, 1583, 1505, 1453, 1417, 1341, 1295, 1263, 1212 (C–O), 1187, 1151, 1124, 1047, 1004, 959, 824 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500.14 MHz) δ 7.59 (d, 1H, $J = 15.2$ Hz), 6.74 (s, 2H), 6.72 (d, 1H, $J = 15.2$ Hz), 3.97 (s, 4H), 3.90 (s, 6H), 3.88 (q, 3H, $J = 4.5$ Hz), 2.69 (dd, 4H, $J = 5.2$, 4.8 Hz); ^{13}C-NMR ($CDCl_3$, 125.76 MHz) δ 165.8, 153.6, 143.5, 140.0, 130.4, 116.3, 105.2, 61.1, 56.4, 45.1, 28.4, 27.5; LC–MS (ESI) m/z 346.34 $[M+Na]^+$; HRMS: $m/z = 324.1270$ (calcd. 324.1258 for $C_{16}H_{22}NO_4S$: $[M+H]^+$).

*(2E,2′E)-1,1′-(piperazine-1,4-diyl)bis(3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one) (**11**)* White solid. mp 262–264 °C. Yield: 80 %; $R_f = 0.1$ (ethyl acetate/*n*-hexane = 2:1, v/v); IR ν_{max} ($CHCl_3$, KBr) ν 3417, 3001, 2939 (C–C), 2838, 1710 (C=O), 1644 (C=C), 1601, 1583, 1505, 1454, 1418, 1337, 1265, 1213 (C–O), 1154, 1124, 1034, 988, 822 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500.14 MHz) δ 7.66 (d, 2H, $J = 15.1$ Hz), 6.77 (d, 2H $J = 15.1$ Hz), 6.76 (s, 4H), 3.92 (s, 12H), 3.87 (s, 6H), 3.84–3.77 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125.76 MHz) δ 165.8, 153.6, 144.0, 140.1, 130.7, 115.7, 105.3, 61.1, 56.4; LC–MS (ESI) m/z 549.54 $[M+Na]^+$; HRMS: $m/z = 527.2379$ (calcd. 527.2393 for $C_{28}H_{35}N_2O_8$: $[M+H]^+$).

Biologic testing

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging effects

We used DPPH to test free radical scavenging activity. DPPH is one of a few stable and commercially available organic nitrogen radicals and has a UV-via absorption maximum at 515 nm. Upon reduction, the solution color fades; the reaction progress is conveniently monitored using a spectrophotometer. To test the free radical scavenging effects using DPPH, compounds **10a–e** and **11** were adjusted with methanol solution to final concentration of 10, 50, 1000 μM. Tris–base buffer (0.1 mM) was added and DPPH radical ethanol solution (1 mL, 0.5 mM) was added after 5 min. The mixture was warmed in the water bath for 25 min at 37 °C. After 20 min, absorbance was measured using a spectrophotometer (515 nm). The DPPH radical scavenging rate of each sample and the 50 % scavenging concentration based on the DPPH radical scavenging rate were calculated using the following rate (%).

$$\text{DPPH radical-scavenging rate (\%)} = \left\{1 - \frac{A - C}{B}\right\} \times 100$$

where A is the absorbance of the sample (DPPH + compounds) when a blank was substituted for tris–base buffer,

B is the absorbance of the DPPH radical–ethanol solution when a blank was substituted for tris–base buffer, and *C* is the absorbance of the sample (compounds) alone.

Cortical neuron culture

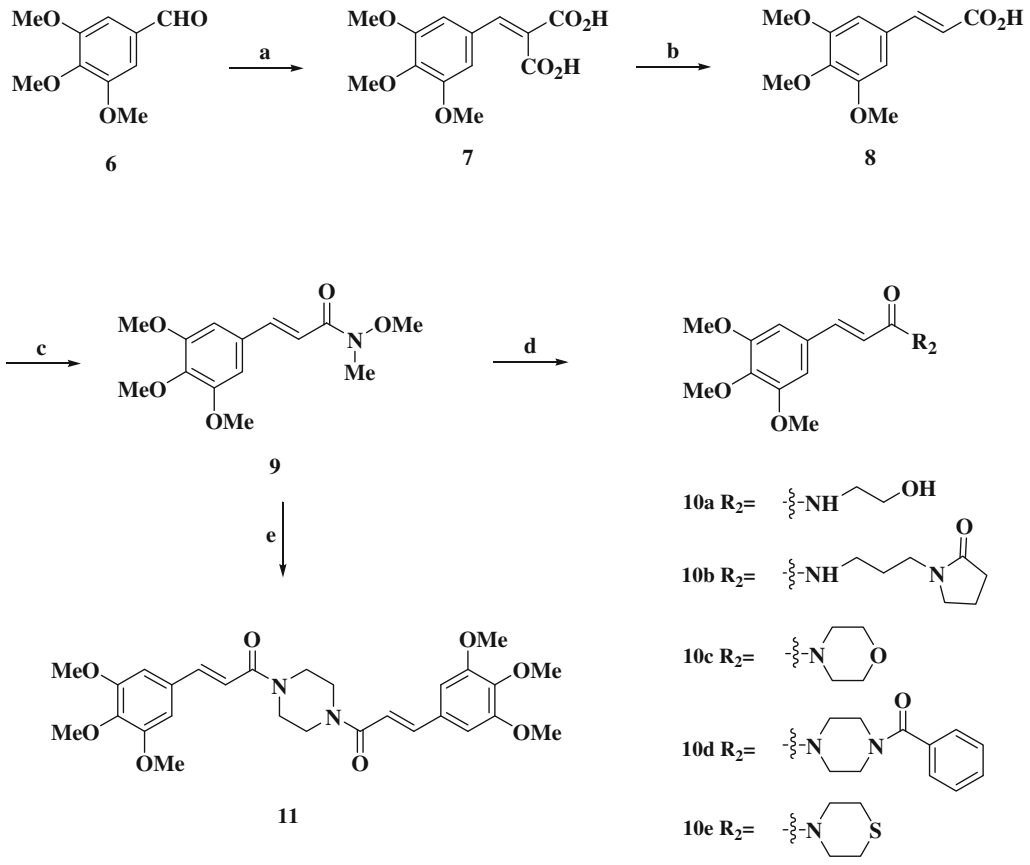
Cortical cell cultures were prepared from embryo of the ICR mice (Daehan Biolink, Eumsung, Korea), gestational age of 15 days. The cortex was dissected and kept in an ice-cold solution. The cortical tissues were dissociated to single cells by a gentle suspension. The cell suspension was centrifuged at 1,000 rpm for 5 min and then the resulting pellets were resuspended in the minimal essential media (MEM), which was supplemented with 5 % heat-inactivated fetal calf serum, mouse serum, glutamine, and glucose. The cells were transferred onto plates coated with poly-D-lysine and laminin at the density of 4.8×10^5 cells/well in 24-well cultured plates. The cells were cultured in a CO_2 incubator (5 % [v/v], 37 °C). Seven days after plating, the cells were treated with 10 μM cytosine arabinofuranoside (Ara C) to reduce the growth of contaminating non-neuronal cells. After treatment for 48 h, cells were fed with fresh media (without fetal calf serum).

Lactate dehydrogenase (LDH) assay

Lactate dehydrogenases are of great value as in vitro markers for cellular toxicity. Lactate dehydrogenases released into the culture medium were measured by monitoring the production of NAD^+ from NADH during the conversion of pyruvate to lactate. The cell supernatant (30 μL) was incubated in the 120 μL of NADPH buffer (0.45 mg/mL), after 2 min, followed by addition of pyruvate (22 mM). The rate of NAD^+ formation was monitored for 5 min at 11-s intervals at 340 nm by spectrophotometer.

Animals and drug administration

C57BL/6 mice were obtained from Daehan Biolink (Eumsung, Korea). They were housed in a 12-h light–dark cycle and maintained at 24 ± 3 °C. All animal procedures were in accordance with the Institutional Animal Care and



Scheme 1 Reagents and conditions *a* $CH(CO_2H)_2$, β-alanine, pyridine, reflux, 1.5 h, and conc-HCl, r. t., 1 h (70 %); *b* 1 N NaOH/MeOH, r. t., 16 h (73 %); *c* *N*,*O*-dimethylhydroxyamine·HCl, Me_3Al, CH_2Cl_2, 0 °C to r. t., 4 h (85 % from methyl ester) or *N*,*O*-dimethylhydroxyamine·HCl, HATU, CH_2Cl_2, r. t., 2 h (81 % from acid); *d* amines, HOBt, EDCI, CH_2Cl_2, r. t., 2 h (60–85 %); *e* piperazine, HATU, CH_2Cl_2, r. t., 2 h (80 %)

Use Committee of Ewha Womans University. The mice (male, 20 ± 2 g) were randomly divided into groups and given saline, morphine, or both morphine and *trans*-3,4,5-trimethoxycinnamamides. The morphine chloride (10 mg/kg/day, Myungmun Pharm., Seoul) was dissolved in saline and *trans*-3,4,5-trimethoxycinnamamides (20 mg/kg/day) were dissolved in 10 % cremophor solution containing 2 % dimethyl sulfoxide. Morphine and *trans*-3,4,5-trimethoxycinnamamides were administered daily for 7 days intraperitoneally. *Trans*-3,4,5-trimethoxycinnamamides were administered 30 min before injection of morphine. Naloxone hydrochloride (5 mg/kg, i.p.) was injected 6 h after the final morphine injection for induction of morphine withdrawal syndrome in mice.

Measurement of antinarcotic behavior on morphine

Morphine withdrawal syndrome was induced by the injection of naloxone (5 mg/kg), which is a competitive antagonist with high opioid receptor affinity. Immediately after the naloxone injection, mice were placed into the individual observation cylinders (24 cm in diameter and 50 cm in high) and the frequency of jumps of each mouse was observed for 30 min.

Results and discussion

Chemistry

The preparation of *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** was initiated from commercially available 3,4,5-trimethoxyaldehyde (**6**) as a starting material, treated with malonic acid and β-alanine in pyridine to give diacid **7**, and readily decarboxylated in the presence of acidic media to generate acid **8** in 70 % yield in two steps (Stabile and Dicks, 2004). Compound **7** was also treated with basic media as 1 N sodium hydroxide in methanol to yield acid **8** in 73 % yield. Compound **8** was treated with *N*,*O*-dimethylhydroxyamine-mono hydrochloride salt in the presence of Me_3Al in dichloromethane to give amide **9** in 85 % yield. Acid **8** also was directly transferred to give amide **9** under coupling condition [(2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU), diisopropylamine (DIPEA) in dichloromethane) in 81 % yield. Amide **9** was treated with various amines through coupling condition [ethyl(dimethylaminopropyl)carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), and triethylamine (TEA) in dichloromethane to generate *trans*-3,4,5-trimethoxycinnamamides **10a–e** in 60–85 % yields (Scheme 1).

Interestingly, the coupling of amide **9** with HATU/CH_2Cl_2 to produce dimmer (2*E*, 2′*E*)-1,1′-(piperazine-1,4-diyl)-bis-[3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one] (**11**) in 80 % yield.

Biology

Radical scavenging activity

DPPH radicals are a useful method for the preliminary screening of compounds capable of scavenging activated oxygen species since these nitrogen radicals are much more stable and easier to handle than oxygen free radicals. The radical scavenging activities of the *trans*-3,4,5-trimethoxycinnamamides were evaluated by an established test method (Lawinski *et al.*, 2005) over the concentration range of 10, 50, and 1000 μM (Fig. 2). Scavenging effects were found for almost all the compounds **10a–e** over 20 % at the higher concentration although 1 mM actions were less effective than the reference material, resveratrol. We have found that the piperazine based *trans*-3,4,5-trimethoxycinnamamides possessed relatively higher antioxidant activity than morpholin-based *trans*-3,4,5-trimethoxycinnamamides in vitro.

Cell viability assay

Lactate dehydrogenases are valuable in vitro markers for cellular toxicity. In these studies, LDH activity was used as a measure of the neuroprotective effects of *trans*-3,4,5-trimethoxycinnamamide compounds. The *trans*-3,4,5-trimethoxycinnamamide derivatives **10a**, **10d**, and **10e** showed the most potent neuroprotective activity in glutamate-induced primary cortical neuronal cells at the relatively low doses (5–20 μM; Fig. 3).

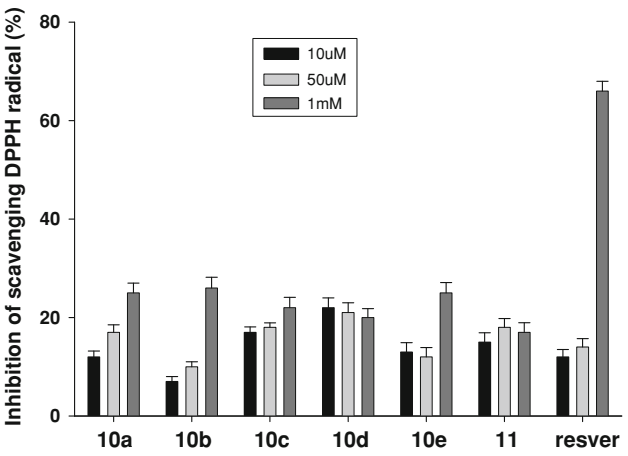


Fig. 2 Inhibitory actions of *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** on scavenging of DPPH radical with different concentrations (10, 50, and 1000 μM). Data represent the mean ± standard error of three observations

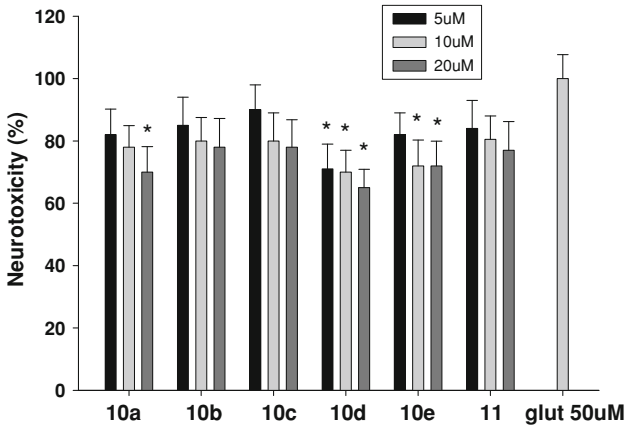


Fig. 3 Protective actions of *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** on glutamate-induced neurotoxicity in cultured cortical neurons with different concentrations (5, 10, and 20 μM). Compounds were co-treated with excitatory amino acid, glutamate (50 μM) for 24 h at 37 °C. Data represent the mean ± standard error of three observations. $*p < 0.05$ in comparison with glutamate only group

Antinarcotic properties

The mice received morphine (10 mg/kg/day, i.p.) for 7 days to develop dependence on morphine and examined the effects of *trans*-3,4,5-trimethoxycinnamamides (20 mg/kg/day, i.p.) on naloxone-induced jumping behavior in morphine-dependent mice. As shown in Fig. 4, jumping frequencies as indicator of morphine withdrawal symptom were strongly decreased by treatment with TMCA **8** and

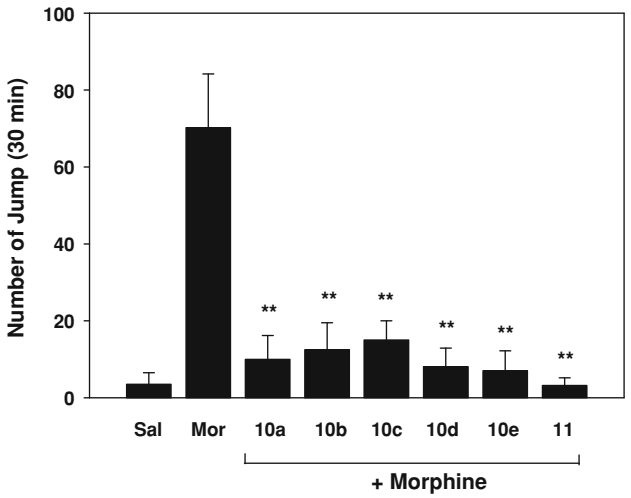


Fig. 4 Effects of *trans*-3,4,5-trimethoxycinnamamides on naloxone-induced jumping behavior in morphine-dependent mice. *Trans*-3,4,5-trimethoxycinnamamides (20 mg/kg, i.p.) were injected 30 min before the morphine injection (10 mg/kg, i.p.) for 7 days. On 7th day, naloxone (5 mg/kg, i.p.) was injected 6 h after final drug administration. Jumping frequencies were observed for 30 min after naloxone injection. $*p < 0.05$, $**p < 0.01$ in comparison with morphine only group

trans-3,4,5-trimethoxycinnamamides. All of *trans*-3,4,5-trimethoxycinnamamides significantly inhibited the jumping frequencies in morphine-dependent mice. We found that *trans*-3,4,5-trimethoxycinnamamides attenuated jumping frequency effectively about 80–90 % after naloxone injection. Interestingly, compound **11** which contains two trimethoxyphenyl groups showed a very strong antinarcotic effect. There is an interesting report that sinapic acid which contains two methoxyl groups and one hydroxyl group instead of three hydroxyl groups on the aromatic ring showed anxiolytic-like effect in mice (Yoon *et al.*, 2007). This result suggests that sinapic acid may have an antinarcotic effect.

Conclusions

We have prepared *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** from inexpensive and readily available materials and evaluated their biologic activities. We have found that the piperazine-based *trans*-3,4,5-trimethoxycinnamamides showed inhibitory activity on neurotoxicity in vitro. Interestingly, *trans*-3,4,5-trimethoxycinnamamides **10a–e** and **11** showed very strong inhibitory activity on the morphine withdrawal syndrome in mice. We conclude that simple synthesis of *trans*-3,4,5-trimethoxycinnamamides and key fragments are useful for the development of antinarcotic agents for the treatment of morphine withdrawal syndrome.

Acknowledgments This research was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korea Government (MEST) (MRC, 2010-0029355).

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