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ORIGINAL RESEARCH

Synthesis and biological effects of naphthalene-chalcone derivatives

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Abstract

In this paper, 21 naphthalene-chalcone derivatives were synthesized and their biological effects were evaluated. The results showed that compounds **2a–2u** displayed clear antidepressant activity at 30 mg/kg in the forced swimming test. Compounds **2h**, **2o**, **2t**, and **2u** exhibited a good antidepressant effect in the forced swimming test and tail suspension test at 30 mg/kg. Compounds **2h**, **2o**, **2t**, and **2u** but had no effect on locomotor activity in the open-field test in mice. In addition, the most antidepressant activity of compound **2o** is likely mediated by increased serotonin and norepinephrine levels in central nervous system. Compounds **2a–2u** also showed the analgesic and anti-inflammatory effects at 30 mg/kg.

Keywords Chalcone · Forced swimming test · Tail suspension test · Anti-inflammatory · Analgesic

Introduction

Several flavonoids extracted from plants have been reported to possess antidepressant effects in animal studies (Karim et al. 2017; Carradori et al. 2016; Guan and Liu 2016). One of the subclasses of flavonoids are phenolic α,β-unsaturated ketones called "chalcones," which contain a 1,3-diphenyl-2-en-1-one core. They are intermediates and end products in flavonoid biosynthesis, participate in plant–insect interactions, and contribute to the medicinal value of herbs.

Previously, our research team designed and synthesized derivatives of the chalcones 2′,4′,6′- trihydroxychalcone, 2,4-dihydroxychalcone, 2′-hydroxy-4′-isoprenyloxychalcone, and 2′-hydroxy-4′,6′- diisoprenyloxychalcone (Sui et al. 2012; Guan et al. 2013a, b; Xie et al. 2014) and evaluated their antidepressant activity using the forced swimming test and tail suspension test. Among these synthesized compounds, chalcone-1203 (Fig. 1) (Guan et al. 2014), after replacement of the phenyl ring with a naphthalene ring on the chalcone B ring, was employed in two classic tests of animal despair, the forced swimming test and tail suspension test, to evaluate antidepressant activity. The immobility duration was diminished significantly for chalcone-1203 at 1, 5, and 10 mg/kg, suggesting significant antidepressant activity at low doses.

To obtain new compounds with better antidepressant effects and as part of our ongoing research on structure-based design, the naphthalene ring of chalcone-1203 was fixed, and there was no substituent on the phenyl ring. Then, 3-naphthyl-1-phenyl-2-propylene-1-ketone (**I**) was synthesized and its antidepressant effect evaluated. Compound **I** was found to reduce the duration of immobility and showed weaker antidepressant activity. Hence, determination of the structure-activity relationship for the substituent group attached to the phenyl ring could be important. Therefore, introduction of a different group on the phenyl ring was used to prepare a series of novel derivatives of naphthalene-chalcone derivatives (**2a–2u**; Scheme 1) and screening for their antidepressant effects. Antidepressants have been used as analgesic agents for neuropathic and non-neuropathic pain. To explore further the possible mechanism of action, we also evaluated the anti-inflammatory and analgesic effects of compounds **2a–2u** using the xylene-induced ear-edema test and acetic acid-induced abdominal writhing in mice.

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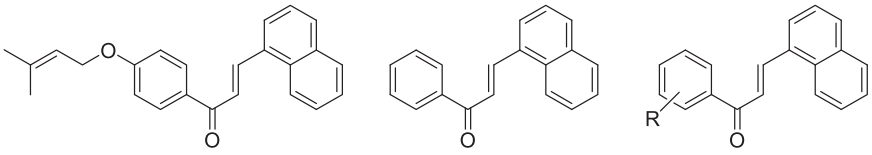
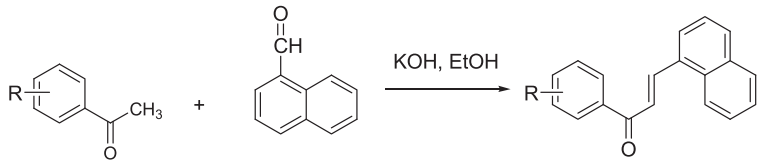


chalcone-1203 **I** **2a-2u**

Fig. 1 Structure of chalcone-1203, compound **I** and **2a–2u**



1 **2a-2u**

Scheme 1 Synthesis routes of target compounds **2a–2u**

R:

2a=2-F	2b=3-F	2c=4-F	2d=2-Cl	2e=3-Cl
2f=4-Cl	2g=2,4-Cl_2	2h=2-Br	2i=3-Br	2j=4-Br
2k=4-CF_3	2l=4-NO_2	2m=4-CH_3	2n=4-OCH_3	2o=4-N$(CH_3)_2$
2p=4-NH_2	2q=4-OH	2r=4-CH_2CH_3	2s=3-OCH_3-4-OH	2t=3,4-$(CH_3)_2$
2u=3.4-$(OCH_3)_2$				

Materials and method

Materials

Fluoxetine-HCl (purity >99%), was purchased from Sigma-Aldrich (Saint Louis, MO, USA). All compounds were synthesized by our research team. Melting points were determined using a digital-display melting point instrument (WRS-1B; Shanghai YiCe Apparatus & Equipment, Shanghai, China). Infrared (IR) spectra were recorded (using KBr disks) on a Fourier transform-infrared (FT-IR) 1730 system (Bruker, Billerica, MA, USA). Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were measured on an AV-300 system (Bruker) and all chemical shifts are given in ppm relative to tetramethylsilane. Mass spectra were measured on a HP1100LC/MS system (Agilent Technologies, Santa Clara, CA, USA). Most chemicals were purchased from Sigma-Aldrich and were of analytical grade.

Chemistry

Synthesis of naphthalene-chalcone derivatives 2a–2u

To a stirred solution of KOH (2.0 g, 46 mmol) in water (5 mL) cooled to 0 °C in an ice bath was added dropwise a solution of substituted acetophenone (1.0 mmol) and 1-naphthalene formaldehyde (2.0 mmol) in ethanol under nitrogen (Guan et al. 2013a; Zhang et al. 2010; Zhao et al. 2005) (Scheme 1). The reaction mixture was maintained at room temperature for 6–12 h. The mixture was poured into ice–water, adjusted to pH 2–3 with 1 M HCl, and extracted with ether. The ether layer was washed with ice–water and saturated brine, and dried over anhydrous Na_2SO_4. After solvent removal, products were purified by silica-gel column chromatography (petroleum ether:ethyl acetate = 20:1). A yellow solid or oil was obtained. The yield, melting point, and spectral data of compounds were elucidated.

1-(2-fluorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2a) Yellow solid; Yield: 67.5%, mp: 82–83 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.32–7.62 (m, 7H, −ArH), 7.54 (*d*, 1H, *J* = 15 Hz, =CH), 7.23–7.79 (m, 4H, $-C_6H_4$), 8.66 (*d*, 1H, *J* = 15 Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 115.24 (*d*, $^2J_{c\text{-}f}$ = 21.50 Hz), 119.78 (*d*, $^2J_{c\text{-}f}$ = 21.74 Hz), 123.25, 123.78 (*d*, $^3J_{c\text{-}f}$ = 12.75 Hz), 124.00, 125.22 (d, $^3J_{c\text{-}f}$ = 12.55 Hz), 125.64, 126.40, 127.10, 128.84, 129.31, 130.41, 131.13, 132.10, 133.76, 140.21, 142.41, 145.23, 154.30, 162.95 (d, $^1J_{c\text{-}f}$ = 245.75 Hz), 188.78(C, C=O). IR (KBr) ν_{max} 1698, 1622, 1231 cm^{-1}. MS *m/z* 277 (MH^+).

1-(3-fluorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2b) Yellow solid; Yield: 36.7%, mp: 92–93 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.33–7.65(m, 7H, −ArH), 7.55 (*d*, 1H, *J* = 15 Hz, =CH), 7.35–7.81 (m, 4H, $-C_6H_4$), 8.73 (*d*, 1H, *J* = 15 Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 115.39 (*d*, $^2J_{c\text{-}f}$ = 22.50 Hz), 119.93 (d, $^2J_{c\text{-}f}$ = 21.75 Hz), 123.34 (d, $^3J_{c\text{-}f}$ = 12.75 Hz), 124.00, 124.26, 125.56 (d,

$^{3}J_{\text{c-f}} = 12.75$ Hz), 125.97, 126.44, 127.12, 128.74, 129.56, 130.31, 131.78, 132.43, 133.56, 140.35, 142.47, 145.33, 156.3, 162.95 (d, $^{1}J_{\text{c-f}} = 246.75$ Hz), 188.88(C, C=O). IR (KBr) $\nu_{\max}$ 1696, 1623, 1230 cm^{-1}. MS *m/z* 277 (MH^{+}).

1-(4-fluorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2c) Yellow solid; Yield: 40.7%, mp: 84–85 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.18$–7.74(m, 7H, −ArH), 7.68 (*d*, 1H, $J = 15$ Hz, =CH), 7.07–8.18 (m, 4H, $-C_6H_4$), 8.58 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 116.02, 118.32, 120.44 (*d*, $^{2}J_{\text{c-f}} = 21.65$ Hz), 124.53, 125.92 (*d*, $^{3}J_{\text{c-f}} = 12.70$ Hz), 126.51, 126.94, 127.14, 128.81, 129.30, 130.11, 131.08, 132.72, 134.41, 135.25, 135.81, 143.80, 140.30, 144.63, 155.3, 158.60 (d, $^{1}J_{\text{c-f}} =$ 244.56 Hz), 191.31(C, C=O). IR (KBr) $\nu_{\max}$ 1696, 1620, 1231 cm^{-1}. MS *m/z* 277 (MH^{+}).

1-(2-chlorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2d) Yellow solid; Yield: 75.4%, mp: 69–70 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.30$–7.60(m, 7H, −ArH), 7.54 (*d*, 1H, $J = 15$ Hz, =CH), 7.25–7.96 (m, 4H, $-C_6H_4$), 8.40 (d, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 123.21, 125.49, 125.52, 126.36, 127.01, 127.10, 128.60, 128.87, 129.58, 130.41, 131.20, 131.43, 131.62, 131.74, 133.73, 139.22, 142.96, 143.56, 154.56, 167.08, 193.63(C, C=O). IR (KBr) $\nu_{\max}$ 1697, 1623, 1230 cm^{-1}. MS *m/z* 293 (MH^{+}), 295 (MH^{+} +2).

1-(3-chlorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2e) Yellow solid; Yield: 55%, mp: 104–105 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.52$–7.63(m, 7H, −ArH), 7.59 (*d*, 1H, $J = 15$ Hz, =CH), 7.49–8.29 (m, 4H, $-C_6H_4$), 8.73 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 123.41, 123.90, 125.25, 125.47, 126.41, 126.65, 127.13, 128.69, 128.85, 130.04, 131.17, 131.78, 132.05, 132.83, 133.76, 135.01, 139.76, 142.55, 188.87(C, C=O). IR (KBr) $\nu_{\max}$ 1698, 1623, 1230 cm^{-1}. MS *m/z* 293 (MH^{+}), 295 (MH^{+} +2).

1-(4-chlorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2f) Yellow solid; Yield: 37.9%, mp: 81–82 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.29$–7.65(m, 7H, −ArH), 7.56 (*d*, 1H, $J = 15$ Hz, =CH), 7.20–8.01 (m, 4H, $-C_6H_4$), 8.70 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 123.31, 125.54, 125.50, 126.42, 127.06, 127.21, 128.46, 128.90, 129.71, 130.45, 131.19, 131.44, 131.68, 131.70, 133.83, 139.52, 142.89, 143.65, 154.76, 167.18, 193.21(C, C=O). IR (KBr) $\nu_{\max}$ 1695, 1621, 1229 cm^{-1}. MS *m/z* 327(MH^{+}), 329(MH^{+} +2).

1-(2,4-dichlorophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2g) Yellow solid; Yield: 65.9%, mp: 113.5–114 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.29$–7.65(m, 7H, −ArH), 7.56 (*d*, 1H, $J = 15$ Hz, =CH), 7.20–8.01 (m, 4H, $-C_6H_4$), 8.70 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 123.31$, 125.54, 125.50, 126.42, 127.06, 127.21, 128.46, 128.90, 129.71, 130.45, 131.19, 131.44, 131.68, 131.70, 133.83, 139.52, 142.89, 143.65, 154.76, 167.18, 193.21(C, C=O). IR (KBr) $\nu_{\max}$: 1695, 1621, 1229 cm^{-1}. MS *m/z* 327(MH^{+}), 329(MH^{+} +2).

1-(2-bromophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2h) Yellow solid; Yield: 61.98%, mp: 71–72 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.73(m, 7H, -ArH), 7.54 (d, 1H, $J = 15$ Hz, =CH), 7.21–8.12 (m, 4H, $-C_6H_4$), 8.36 (d, 1H, $J = 15$ Hz, = CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 119.60$, 123.18, 125.50, 125.53, 126.36, 127.11, 127.51, 128.45, 128.86, 129.38, 131.22, 131.57, 131.72, 133.54, 141.27, 143.33, 194.53(C, C = O). IR (KBr) $\nu_{\max}$ 1698, 1620, 1230 cm^{-1}. MS *m/z* 337(MH^{+}), 339 (MH^{+} +2).

1-(3-bromophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2i) Yellow solid; Yield: 67.9%, mp: 116.5–117 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.61(m, 7H, −ArH), 7.98 (*d*, 1H, $J = 15$ Hz, =CH), 7.43–8.03 (m, 4H, $-C_6H_4$), 8.72 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 123.06$, 123.41, 123.98, 125.25, 125.46, 126.40, 127.09, 127.13, 128.84, 130.28, 131.17, 131.62, 131.78, 132.05, 133.76, 135.73, 139.98, 142.59, 188.78(C, C=O). IR (KBr) $\nu_{\max}$ 1696, 1623, 1230 cm^{-1}. MS *m/z* 337 (MH^{+}), 339 (MH^{+} +2).

1-(4-bromophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2j) Yellow solid; Yield: 64.9%, mp: 110–111 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.54$–7.66(m, 7H, −ArH), 7.75 (*d*, 1H, $J = 15$ Hz, =CH), 7.72–8.20 (m, 4H, $-C_6H_4$), 8.58 (*d*, 1H, $J = 15$ Hz, = CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 123.12$, 123.45, 123.78, 125.24, 125.49, 126.47, 127.12, 127.23, 128.67, 130.30, 131.21, 131.72, 131.80, 132.09, 133.55, 135.82, 139.45, 142.61, 188.90(C, C=O). IR (KBr) $\nu_{\max}$ 1699, 1612, 1221 cm^{-1}. MS *m/z* 337 (MH^{+}), 339 (MH^{+} +2).

1-(4-trifluoromethylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2k) Yellow solid; Yield: 57.7%, mp: 85–86 °C. ^{1}H -NMR ($CDCl_3$, 300 MHz): $\delta = 7.54$–7.66 (m, 7H, −ArH), 7.75 (*d*, 1H, $J = 15$ Hz, =CH), 7.72–8.20 (m, 4H, $-C_6H_4$), 8.58 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 123.12$, 123.45, 123.78, 125.24, 125.49, 126.47, 127.12, 127.23, 128.67, 130.30, 131.21, 131.72, 131.80, 132.09, 133.55, 135.82, 139.45, 142.61, 188.90(C, C=O). IR (KBr) $\nu_{\max}$ 1698, 1622, 1229 cm^{-1}. MS *m/z* 327 (MH^{+}).

1-(4-nitrophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2l) Yellow solid; Yield: 39.5%, mp: 146–147 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.34$–7.67(m, 7H, −ArH), 7.56 (*d*, 1H, $J = 15$ Hz, =CH), 7.32–8.41 (m, 4H, $-C_6H_4$), 8.28 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 115.10, 122.35, 123.23, 124.74, 125.37, 126.27, 127.10, 127.33, 128.57, 130.25, 131.11, 131.62, 131.87, 132.10, 133.35, 135.62, 138.89, 142.73, 188.93(C, C=O). IR (KBr) ν_{max} 1699, 1632, 1222 cm^{-1}. MS *m/z* 304(MH^+).

1-(4-methylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2m) Yellow solid; Yield: 95.4%, mp: 85.7–87 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 2.14$ (s, 3H, $-CH_3$), 7.35–7.63(m, 7H, −ArH), 7.55 (*d*, 1H, $J = 15$ Hz, =CH), 7.33–8.25 (m, 4H, $-C_6H_4$), 8.55 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 23.5$ (C,$-CH_3$), 116.11, 122.34, 123.34, 123.67, 124.23, 125.29, 125.51, 126.58, 127.13, 127.26, 129.17, 130.29, 131.13, 131.58, 131.90, 132.19, 132.98, 135.62, 139.51, 142.70, 188.98 (C, C=O). IR (KBr) ν_{max} 1697, 1622, 1224 cm^{-1}. MS *m/z* 273 (MH^+).

1-(4-methoxylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2n) Yellow solid; Yield: 46%, mp: 96–97 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 3.28$(s, 3H, $-OCH_3$), 7.38–7.68(m, 7H, −ArH), 7.76 (*d*, 1H, $J = 15$ Hz, =CH), 7.50–8.19 (m, 4H, $-C_6H_4$), 8.57 (d, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 55.65$ (C, $-OCH_3$), 98.50, 105.80, 121.81, 123.43, 125.07, 125.68, 126.26, 126.87, 128.79, 129.90, 130.28, 131.63, 132.59, 132.79, 133.69, 138.19, 106.60, 164.48, 189.84 (C, C=O). IR (KBr) ν_{max} 1696, 1622, 1222 cm^{-1}. MS *m/z* 289 (MH^+).

1-(4-dimethylaminephenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2o) Yellow solid; Yield: 39.2%, mp: 133–134 °C. ^{1}H -NMR ($CDCl_3$, 300 MHz): $\delta = 3.11$(s, 3H, $-NCH_3$), 3.16(s, 3H, $-NCH_3$), 7.55–7.72 (m, 7H, −ArH), 7.55 (*d*, 1H, $J = 15$ Hz, =CH), 7.55–8.31 (m, 4H, $-C_6H_4$), 8.66 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta =$ 40.09 (C, $-NCH_3$), 40.14 (C, $-NCH_3$), 110.88, 123.81, 124.83, 125.08, 125.48, 125.91, 126.19, 126.76, 128.66, 130.16, 130.96, 139.53, 153.47, 189.43 (C, C=O). IR (KBr) ν_{max} 1698, 1632, 1221 cm^{-1}. MS *m/z* 302(MH^+).

1-(4-aminophenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2p) Yellow solid; Yield: 41.4%, mp: 199–202 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.49$–7.73(m, 7H, −ArH), 7.64 (*d*, 1H, $J = 15$ Hz, =CH), 7.51–8.20 (m, 4H, $-C_6H_4$), 8.47 (*d*, 1H, $J = 15$ Hz, =CH), 9.30, (s, 1H, −NH), 10.34 (s, 1H, −NH). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 113.48, 123.40, 125.00, 125.70, 126.29, 126.92, 128.80, 130.26, 131.21, 131.63, 132.63, 133.68, 138.73, 153.50, 187.46 (C, C=O). IR (KBr) ν_{max} 3420, 1697, 1622, 1221 cm^{-1}. MS *m/z* 274 (MH^+).

1-(4-hydroxyphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2q) Yellow solid; Yield: 58.6%, mp: 218–219 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 7.50$–7.85 (m, 7H, −ArH), 7.70 (*d*, 1H, $J = 15$ Hz, =CH), 6.88–8.20 (m, 4H, $-C_6H_4$), 8.58 (*d*, 1H, $J = 15$ Hz, =CH), 10.04 (s, 1H, −OH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 115.73$, 123.32, 124.77, 125.74, 126.38, 127.09, 128.89, 130.58, 131.19, 139.58, 162.60, 188.56 (C, C=O). IR (KBr) ν_{max} 3345, 1698, 1624, 1220 cm^{-1}. MS *m/z* 275 (MH^+).

1-(4-ethylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2r) Yellow solid; Yield: 49%, mp: 66-67 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 2.41$ (t, 3H, $-CH_3$), 3.36 (s, 2H, $-CH_2$), 7.35–7.63(m, 7H, −ArH), 7.55 (*d*, 1H, $J = 15$ Hz, = CH), 7.33–8.3(m, 4H, $-C_6H_4$), 8.55 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 19.8$ (C, $-CH_2$), 25.7 (C,$-CH_2$), 118.12, 123.21, 123.66, 123.66, 125.26, 125.50, 126.49, 127.19, 127.33, 128.77, 130.29, 131.22, 131.68, 131.78, 132.10, 133.45, 135.92, 139.33, 142.71, 189.57 (C, C=O). IR (KBr) ν_{max} 1697, 1622, 1223 cm^{-1}. MS *m/z* 287 (MH^+).

1-(3-methoxyl-4-hydroxyphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2s) Yellow oil; Yield: 47.6%. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 3.92$(s, 3H, $-OCH_3$), 7.44–7.65 (m, 7H, −ArH), 7.56 (*d*, 1H, $J = 15$ Hz, =CH), 6.88–8.23 (m, 4H, $-C_6H_3$), 8.60 (*d*, 1H, $J = 15$ Hz, =CH), 10.09 (s, 1H, -OH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 55.95$ (C, $-OCH_3$), 110.15, 110.97, 114.32, 114.45, 117.21, 123.49, 123.75, 124.97, 125.46, 126.24, 126.87, 128.71, 130.53, 140.57, 147.20, 147.56, 151.15, 151.30, 188.34 (C, C=O). IR (KBr) ν_{max} 3350, 1698, 1632, 1221 cm^{-1}. MS *m/z* 305 (MH^+).

1-(3,4-dimethylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2t) Yellow solid; Yield: 54.6%, mp: 92.7–93.5 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 2.36$ (s, 3H, $-CH_3$), 2.45 (s, 3H, $-CH_3$), 7.47–7.69 (m, 7H, −ArH), 7.56 (d, 1H, $J =$ 15 Hz, =CH), 7.16–8.15 (m, 4H, -C_6H_3), 8.35 (*d*, 1H, $J =$ 15 Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 22.81$ (C, $-CH_3$), 23.10 (C, $-CH_3$), 117.12, 123.55, 123.88, 125.20, 125.56, 126.57, 127.11, 127.33, 128.77, 130.33, 131.24, 131.82, 131.85, 132.19, 133.75, 135.77, 139.65, 142.63, 188.94 (C, C=O). IR (KBr) ν_{max} 1697, 1619, 1220 cm^{-1}. MS *m/z* 287 (MH^+).

1-(3,4-dimethoxylphenyl)-3-(naphthalen-1-yl)-2-propen-1-one (2u) Yellow solid; Yield: 41.5%, mp: 77–78 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 3.87$ (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 7.34–7.65 (m, 7H, −ArH), 7.56 (*d*, 1H, $J = 15$ Hz, =CH), 7.32–8.23 (m, 4H, $-C_6H_3$), 8.57 (*d*, 1H, $J = 15$ Hz, =CH). ^{13}C-NMR ($CDCl_3$, 75 MHz): $\delta = 55.65$ (C, $-OCH_3$), 55.90 (C, $-OCH_3$), 115.78, 117.61, 121.81,

123.43, 125.07, 125.68, 126.26, 126.87, 128.79, 129.90, 130.28, 131.63, 132.59, 132.79, 133.69, 138.19, 151.36, 155.62, 189.84 (C,C=O). IR (KBr) ν_{max} 1698, 1622, 1221 cm^{-1}. MS *m/z* 319 (MH^+).

Animals

All animal-handling procedures were conducted in accordance with regulatory guidelines set by the Chinese government. ICR mice (20 ± 2g) were provided by the Laboratory of Animal Research, College of Pharmacy, Zhejiang Academy of Medical Sciences (Zhejiang, China). Animals were allowed to acclimatize for 1 week before experimentation. Before and during experiments, mice were housed under controlled environmental conditions of temperature (23 ± 2 °C) and a 12-h light–dark cycle and maintained (unless stated otherwise) on standard food pellets and tap water *ad libitum*.

The forced swimming test

All compounds were dissolved in polyethylene glycol-400. Fluoxetine was dissolved in isotonic (0.9%) saline solution. The vehicle solvent served as a negative control, and fluoxetine as a positive control. All compounds and fluoxetine were administered intraperitoneal 30 min before the forced swimming test. Male ICR mice were housed in groups of eight. 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 22 ± 3 °C and left in the water for 6 min. After the first 2 min of vigorous struggling, the animals were immobile. The duration of immobility was recorded during the last 4 min of the 6-min test. The immobility duration was regarded to be the time spent by the mouse floating in water without struggling and making only those movements necessary to keep his head above the water (Porsolt et al. 1997; Guan et al. 2013b).

The tail suspension test

Each mouse was suspended by his tail with a clamp (2 cm from the tail tip) in a box (25 × 25 × 30 cm) with his head 5 cm from the bottom of the box. Testing was carried out in a darkened room with minimal background noise. Mice were suspended for 6 min, and the duration of immobility measured during the final 4 min of the tail suspension test. Mice were considered to be immobile only if they hung passively and completely motionless (Steru et al. 1985; Zhen et al. 2016).

The open-field test

The open-field test was carried out in mice according to the method of Archer with slight modifications (Archer 1973; Elliott et al. 1986). Each mouse was placed in the center of the open-field apparatus, and his locomotor activity assessed. The open-field apparatus was a nontransparent plastic container (80 × 60 × 30 cm), with the underside divided into 48 units of size 10 × 10 cm, without walls. Mice were placed gently in the center of the platform and allowed to explore their surroundings. Hand-operated counters were used to score locomotion (ambulation, numbers of line crossed with four paws) and rearing frequencies (number of times the mouse stood on his hind legs) for 5 min. The researchers, who did not know which groups had been treated, scored the behaviors in the open field. Experiments were carried out in a dark room and the apparatus was illuminated by a 60-W bulb giving a yellowish light, positioned 1 m above the center of the apparatus.

The sample preparation

The doses of 30 mg/kg compound **2o** and fluoxetine were employed for testing the effect on monoamine neurotransmitter concentrations in the rat brain. Mice were randomly divided into five groups (eight mice per group were used). Fluoxetine, compound **2o**, normal vehicle and stress vehicle were given orally daily for 7 days. On the last day, the drugs and compound were given 1 h prior to the test. At the end of the experiment, the mice were immediately sacrificed by cervical dislocation, the brain tissue was quickly removed, and rapidly frozen and stored at −80 °C until they were processed for biochemical estimations.

HPLC condition and test

The brain tissues were sonicated in 0.1M NaH_2PO_4 aqueous solution including 0.85 mM OSA, 0.5 mM Na_2·EDTA and centrifuged at 13,000 × *g* for 15 min at 4 °C. Then serotonin and norepinephrine were assayed by HPLC-ECD. Equipment: Shimadzu LC-10ATVP HPLC system, Shimadzu L-ECD-6A electrochemical detector, N2000 HPLC workstation software, Hypersil ODS C18 Column 4.6 × 150 mm 5 μM. The mobile phase consisted of 0.1M NaH_2PO_4 aqueous solution including 0.85 mM OSA, 0.5 mM Na_2·EDTA and 11% methanol adjusted to pH 3.4 with phosphate acid and filtered through 0.45 μM pore size filter. External standard curves were used to quantify the amounts of serotonin and norepinephrine in each sample calculated by area under curve. The volume of injection was 20 μL. The detection limit of the assay was 20 pg/g sample. The filtrate sample was used for quantification of serotonin and norepinephrine by HPLC coupled with electrochemical detection in brain region.

Anti-inflammatory effect

There were ICR eight mice per group. Edema was induced by xylene administered by topical application

(0.05 mL per ear) (Rajahamsa et al. 2013; Gouvea et al. 2016; Abdel-Aziz et al. 2016). Each group of mice was injected intraperitoneally with compounds **2a–2u** and indomethacin, both at 30 mg/kg. Edema was expressed as an increase in ear thickness due to inflammation. Ear thickness was measured before and after inflammation induction. A 6-mm section of ear was obtained and weighed using an analytical balance. The ear swelling induced by xylene was evaluated as the increase in ear weight of the treated group over that of the untreated group, and was called the Edema Index. Percentage anti-inflammatory activity was calculated according to the formula:

$$\text{Percent anti-inflammatory activity} = [(W_c - W_t)/W_c] \times 100$$

where W_c and W_t represent the mean ear weight of control and treated mice, respectively.

Analgesic effect in vivo

The analgesic activity of compounds and drugs was studied by observing the writhing response (i.e., contraction of abdominal muscles and stretching of hind limbs) of mice through intraperitoneal administration of acetic acid (Koster et al. 1959). Test mice were selected randomly and divided into groups ($n = 8$). Compounds **2a–2u** and indomethacin were dissolved in PEG-400 and administered (30 mg/kg, intraperitoneal) to each group of mice 40 min before administration of 0.7% acetic acid (0.1 mL/10 g, intraperitoneal). This 40-min interval was employed to ensure absorption of administered samples. Five minutes after administration of acetic acid, each animal was isolated in an individual observation chamber, and the cumulative number of writhing responses for 10 min recorded. The percent inhibition of writhing in comparison with the control group was taken as an index of analgesia, and was calculated using the formula:

$$\text{Inhibition}\,(\%) = (X_c - Y_t/Y_c) \times 100$$

where X_c is the mean number of writhing reflexes in the control group, and Y_t is the mean number of writhing reflexes in the test group. Then, the reaction time was retested 60 min after injection, and the percent change in the reaction was calculated.

Statistical analyses

Statistical analyses were carried out using Prism v2.0 (GraphPad, San Diego, CA, USA). Results are the mean ± SEM. The Student's t test was used to compare differences between the two groups. $P < 0.05$ was considered significant.

Results and discussion

The structure of target compounds was confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. Molecular ion peaks were observed in accordance with the molecular weight of the respective compound. The IR spectrum of compounds **2q** and **2s** exhibited characteristic absorption bands at 1695–1699 cm^{-1} for −C=O stretching and at 3345 and 3350 cm^{-1} for −OH stretching, respectively. In the ^{1}H-NMR spectra of compounds **2a–2u**, −CH=CH protons of the propylene group were observed at 7.55–7.98 and 8.35–8.73 ppm. In the ^{13}C-NMR spectra of compounds **2a–2u**, −C=O signals were seen at 187.61–194.53 ppm.

The forced swimming test and tail suspension test are validated stress models of depression. These tests induce despair in animals and have good reliability and predictive validity in mice (De Oliveira et al. 2011). In two models, mice are restricted and cannot escape, which induces the characteristic behavior of immobility. The immobility displayed in both of these models has been hypothesized to reflect behavioral despair which, in turn, may reflect depressive disorders in humans. These two models are usually employed to screen/evaluate antidepressant activity (Borsini et al. 1986). In the forced swimming test or tail suspension test, the total duration of immobility is reduced by most antidepressants if administered acutely or subchronically to animals.

The forced swimming test is the most widely used model to screen new antidepressant drugs. A wide variety of antidepressants and compounds with potential antidepressant effects have been shown to reduce the duration of immobility in the forced swimming test (Ma et al. 2016; Jin et al. 2017). In the forced swimming test, the antidepressant effect of target compounds **2a–2u** and fluoxetine is shown in Table 1. All compounds produced a marked reduction in the duration of immobility at 30 mg/kg, indicating important antidepressant effects. Among them, compounds **2h**, **2o**, **2t** and **2u** led to a significant reduction in the duration of immobility compared with the control group ($p < 0.001$) and exhibited an antidepressant effect better than or similar to the positive control fluoxetine ($p < 0.001$). For more detailed understanding of the antidepressant effects of these target compounds, the percent decrease in immobility duration (% DID) was calculated using the formula:

$$\%\,\text{DID} = [(X - Y)/X] \times 100$$

where X is the duration of immobility (s) in the control group and Y is the duration of immobility (s) in the test group (Table 1). Compounds **2h**, **2o**, **2t**, and **2u** reduced the duration of immobility and gave high values of % DID. Among them, the % DID of compounds **2h** (76.7%), **2o**

Table 1 Evaluation of the antidepressant effects of compounds **2a–2u** in the FST

Compounds	R	Antidepressant effects[a]	
		Duration of immobility(s)	DID (%)
I	–	99.3 ± 15.1*	36.8
2a	2-F	88.4 ± 5.2**	43.8
2b	3-F	68.4 ± 3.9**	56.5
2c	4-F	59.0 ± 6.9***	62.5
2d	2-Cl	79.6 ± 9.0**	49.4
2e	3-Cl	74.0 ± 6.3**	52.9
2f	4-Cl	82.8 ± 7.5**	47.3
2g	2,4-Cl_2	76.4 ± 5.8**	51.4
2h	2-Br	36.6 ± 7.6***	76.7
2i	3-Br	57.3 ± 8.1***	63.5
2j	4-Br	78.2 ± 5.7**	50.3
2k	4-CF_3	71.6 ± 4.5**	54.5
2l	4-NO_2	58.2 ± 4.2***	63.0
2m	4-CH_3	70.2 ± 7.3**	55.3
2n	4-OCH_3	95.8 ± 4.4*	39.1
2o	4-$N(CH_3)_2$	27.0 ± 5.0***	82.8
2p	4-NH_2	57.0 ± 9.4***	63.7
2q	4-OH	92.0 ± 4.8*	41.5
2r	4-CH_2CH_3	85.8 ± 7.7**	45.4
2s	3-OCH_3-4-OH	84.0 ± 3.9**	46.6
2t	3,4-$(CH_3)_2$	48.6 ± 6.8***	69.1
2u	3.4-$(OCH_3)_2$	40.6 ± 4.9***	74.2
Fluoxetine		41.8 ± 8.3***	73.4
Control		157.2 ± 4.2	–

Values are the mean ± SEM ($n = 8$)

% DID percentage decrease in immobility duration

*Significantly different compared with control ($p < 0.05$; **$p < 0.01$; ***$p < 0.001$)

[a]Compounds and fluoxetine were administered intraperitoneally at 30 mg/kg

(82.8%), **2t** (69.1%), and **2u** (74.2%) was higher than or similar to that of fluoxetine (73.4%) at 30 mg/kg in the forced swimming test. Compound **2o** led to the greatest reduction in the immobility duration compared with the control group ($p < 0.001$).

Compounds **2h**, **2o**, **2t**, and **2u** had the most potent antidepressant activity in the forced swimming test, and were evaluated further to confirm their antidepressant activity in the tail suspension test (Table 2). In the latter, the decrease in immobility duration of compounds **2h**, **2o**, **2t**, and **2u** was similar to that in the forced swimming test. Compounds **2h**, **2o**, **2t**, and **2u** displayed a significant decrease in immobility duration at 30 mg/kg that was similar to or greater than that of the positive control fluoxetine. The % DID of compounds **2h** (67.6%), **2o** (52.3%), **2t** (47.1%), and **2u** (58.8%) was similar to that of fluoxetine (63.4%) at 30 mg/kg in the tail suspension test, suggesting considerable antidepressant activity.

The structure–activity relationship studies for the antidepressant activity of compounds **2a–2u** shown in Table 1 elicited five main findings. First, all compounds displayed a significant decrease in immobility duration and exhibited good antidepressant activity with electron-withdrawing and electron-donating substituents on the phenyl ring. Second, for nine compounds with an electron-donor substituent such as a $-CH_3$, $-OCH_3$, $-N(CH_3)_2$, $-NH_2$, $-OH$, $-CH_2CH_3$, $-OCH_3-OH_3$, $-(CH_3)_2$, or $-(OCH_3)_2$ group, the antidepressant activity was in the order $4-N(CH_3)_2 > 3.4-(OCH_3)_2 > 3,4-(CH_3)_2 > 4-NH_2 > 4-CH_3 > 3-OCH_3-4-OH > 4-CH_2CH_3 > 4-OH > 4-OCH_3$, respectively. Compound **2o** with a -$N(CH_3)_2$ substituent reduced the immobility duration in the FST significantly, and displayed the greatest antidepressant effect on the phenyl ring. Third, nine compounds with an electron-withdrawing substituent such as an F atom (**2a**, **2b**, and **2c**), Cl atom (**2d**, **2e**, and **2f**), or Br atom (**2g**, **2h**, and **2i**) exhibited an excellent antidepressant effect. The position of the halogen substitution greatly influenced the antidepressant effect. For derivatives with varying halogen-substitution patterns on the phenyl ring, the orders of activity were *p*-F > *m*-F > *o*-F, *m*-Cl > *o*-Cl > *p*-Cl, *o*-Br > *m*-Br > *p*-Br. Fourth, compounds **2k** and **2l** with a trifluoromethyl ($-CF_3$) or nitro group ($-NO_2$) substituent showed an antidepressant effect and decreased the immobility duration in mice by 54.5 and 63.0%, respectively. Also, compound **2j** with a 2,4-dichlolo substituent exhibited antidepressant activity of 51.4%. Finally, absence of a substituent on the phenyl ring of lead compound **I** led to weaker antidepressant activity than that for other compounds. Hence, determination of the structure–activity relationship for the substituent group attached to the phenyl ring may be important.

In the forced swimming test or tail suspension test, some compounds or drugs that change motor activity may give false-positive/false-negative effects. In particular, psychomotor stimulants and drugs can enhance motor activity, which decreases the immobility duration by stimulating the locomotor effect (Elliott et al. 1986). We evaluated the effect of compounds **2h**, **2o**, **2t**, and **2u** on spontaneous locomotor activity in the open-field test. Compounds **2h**, **2o**, **2t**, and **2u** did not change motor activity (crossing, rearing, or grooming) significantly in mice (Table 3). These results suggested that the antidepressant effects induced by compounds **2h**, **2o**, **2t**, and **2u** were not caused by central nervous system-stimulating effects.

Serotonin and norepinephrine have been suggested to play a role in the pathogenesis of depression. In the central nervous system, a metabolic disorder of monoamine neurotransmitters is believed to be the main biochemical cause of depression, and depression can thus be alleviated by increasing the levels of monoamine neurotransmitters in the

Table 2 Evaluation of the antidepressant effects of compounds **2h**, **2o**, **2t** and **2u** in the TST

Compounds	Antidepressant effects[a]	
	Duration of immobility(s)	Change from control (%)[b]
2h	$37.2 \pm 5.5^{***}$	67.6
2o	$54.5 \pm 5.2^{**}$	52.3
2t	$60.4 \pm 9.8^{*}$	47.1
2u	$47.1 \pm 3.5^{**}$	58.8
Fluoxetine	$41.8 \pm 8.3^{***}$	63.4
Control	114.2 ± 4.8	–

Values are the mean ± SEM ($n = 8$)

*Significantly different compared with control ($p < 0.05$; **$p < 0.01$; ***$p < 0.001$)

[a]Compounds and fluoxetine were administered intraperitoneally at 30 mg/kg

[b]% *DID* percentage decrease in immobility duration

Table 3 Compounds **2h**, **2o**, **2t**, and **2u** on exploratory activity in the open-field test

Compounds	Crossing	Rearing	Grooming
2h	87.5 ± 6.7	9.7 ± 5.0	10.5 ± 6.1
2o	86.9 ± 7.2	9.9 ± 9.8	10.2 ± 6.9
2t	88.7 ± 8.8	9.0 ± 5.1	9.8 ± 4.7
2u	87.0 ± 7.5	9.4 ± 6.2	9.6 ± 5.3
Control	88.6 ± 5.8	9.8 ± 3.9	10.1 ± 3.9

Crossing: number of line crossings; rearing: number of times observed standing on hind legs; grooming: number of modifications. Values represent the mean ± SEM ($n = 8$)

central nervous system (Hao et al. 2013; Dhanda and Sandhir 2015). The levels of monoamine neurotransmitters and their metabolites detected in mice brain are summarized in Table 4. In the present study, compound **2o** significantly increased serotonin and norepinephrine levels at the highest doses during the forced swimming test in mice brain, similar to the positive control drug fluoxetine. These findings indicate that the antidepressant effect of compound **2o** is likely mediated by increased serotonin and norepinephrine levels in central nervous system.

We evaluated the anti-inflammatory and analgesic activities of compounds **2a–2u** using the xylene-induced ear-edema test and acetic acid-induced abdominal writhing in mice (Gouvea et al. 2016; Abdel-Sayed et al. 2016). All compounds showed a significant reduction in writhing at 30 mg/kg. The percent inhibition of writhing increased from 52.99 to 99.73% and displayed analgesic activity. Compounds **2a–2u** also displayed a significant anti-inflammatory effect ($p < 0.05$, $p < 0.01$, $p < 0.001$) at 30 mg/kg body compared with the control group (Table 5 and Fig. 2). Inflammation is characterized by pain, swelling, redness and heat, whereas depression is common in people

Table 4 Effect of FST exposure and **2o** on brain monoamine neurotransmitter levels

Groups	Serotonin	Norepinephrine
Normal vehicle	254.7 ± 29.2	287.1 ± 30.2
Stress vehicle	124.1 ± 26.1	115.6 ± 20.4
2o	268.2 ± 31.2***·****	299.4 ± 29.1*·*****
Fluoxetine	283.4 ± 30.0***·*****	302.6 ± 30.4**·******

The doses of **2o** and fluoxetine were 20 mg/kg. Neurotransmitter levels are expressed as ng/g per brain region wet weight. Data are expressed as mean ± SEM ($n = 10$). Statistical analyses of data were conducted using one-way analysis of variance followed by Turkey's test

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. stress vehicle; **** $p < 0.05$; *****$p < 0.01$ vs. normal vehicle

Table 5 Anti-inflammatory activities of the designed compounds **2a–2u**

Compounds	R	Anti-inflammatory activity[a]	
		Ear edema	Inhibition rate (%)
2a	2-F	$1.40 \pm 0.53^{**}$	75.1
2b	3-F	$0.85 \pm 0.06^{***}$	84.7
2c	4-F	$2.12 \pm 1.12^{*}$	62.3
2d	2-Cl	$1.31 \pm 0.93^{**}$	76.7
2e	3-Cl	$2.05 \pm 1.12^{*}$	63.5
2f	4-Cl	$2.33 \pm 1.06^{*}$	58.5
2g	2,4-Cl_2	$0.95 \pm 0.18^{***}$	83.1
2h	2-Br	$2.22 \pm 1.11^{*}$	60.5
2i	3-Br	$1.24 \pm 0.38^{**}$	77.9
2j	4-Br	$1.59 \pm 1.47^{**}$	71.1
2k	4-CF_3	$0.72 \pm 0.32^{***}$	87.2
2l	4-NO_2	$2.82 \pm 1.06^{*}$	50.0
2m	4-CH_3	$0.51 \pm 0.29^{***}$	90.9
2n	4-OCH_3	$2.17 \pm 1.20^{*}$	61.4
2o	4-$N(CH_3)_2$	$1.23 \pm 0.22^{**}$	78.1
2p	4-NH_2	$1.53 \pm 0.52^{**}$	72.8
2q	4-OH	$1.29 \pm 0.46^{**}$	77.0
2r	4-CH_2CH_3	$0.63 \pm 0.37^{***}$	88.8
2s	3-OCH_3-4-OH	$1.83 \pm 0.84^{*}$	67.4
2t	3,4-$(CH_3)_2$	$0.82 \pm 0.33^{***}$	85.4
2u	3.4-$(OCH_3)_2$	$2.26 \pm 1.11^{*}$	59.8
Indomethacin	–	$1.33 \pm .013^{**}$	76.9
Control	–	5.62 ± 2.5	–

*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared with control group

[a]% at 60 min of anti-inflammatory activity

suffering from chronic pain. It has been suggested that pain and depression possess similar neurochemical mechanisms (Boufidou and Nikolaou 2016). Antidepressants have been used as analgesic agents for neuropathic and non-neuropathic pain because they display intrinsic anti-nociceptive effects (Ismail et al. 2017). Monoamine uptake

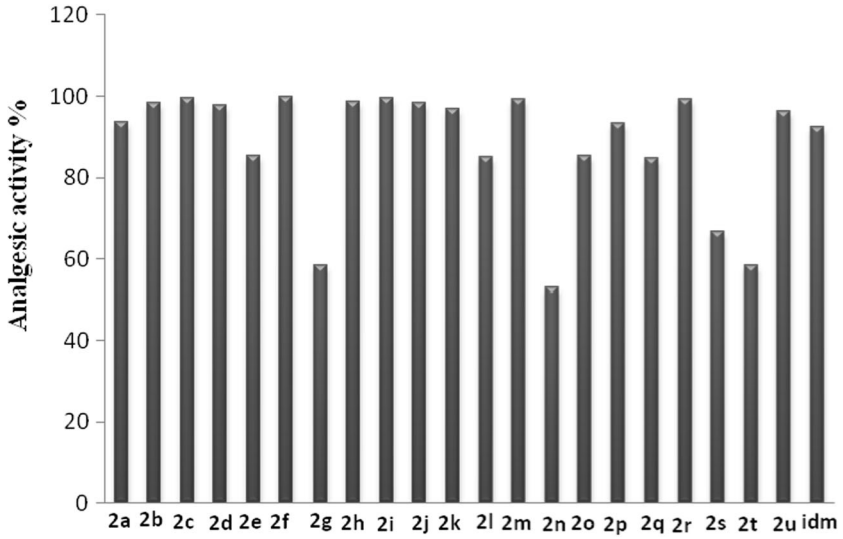


Fig. 2 Analgesic effect of the designed compounds **2a–2u**

is inhibited, which leads to increases in levels of noradrenaline and serotonin, which reinforce pain-inhibitory pathways (Uddin et al. 2018). Several scholars have postulated that the antidepressant drugs displayed the anti-inflammatory and analgesic effects (Ismail et al. 2016), suggesting that they may possess a similar mechanism of action.

Conclusion

In this paper, 21 naphthalene-chalcone derivatives were assessed the antidepressant, anti-inflammatory and analgesic effects. Compounds **2a–2u** showed clear antidepressant activity at 30 mg/kg in the FST. Compounds **2h**, **2o**, **2t**, and **2u** exhibited a good antidepressant effect. And, we found that the antidepressant effect of compound **2o** is likely mediated by increased serotonin and norepinephrine levels in central nervous system. Compounds **2a–2u** also showed analgesic and anti-inflammatory effects. Several scholars have postulated the anti-inflammatory and analgesic effects of antidepressant drugs, suggesting that they may be possess a similar mechanism of action.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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