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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Study on synthesis and biological effects of a series of 3,4-dihydroisoquinoline-2(1*H*)-carboxamide derivatives

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Abstract

In this paper, we have reported the synthesis and biological evaluation of nineteen (*S*)-*N*-substituted-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide derivatives as novel candidate antidepressant and anticonvulsant agents. Compounds **2h**, **2k**, **2r**, and **2s** exhibited better potent antidepressant activity and displayed the antidepressant effects in a dose-dependent manner from 10 to 30 mg/kg in the FST and TST. And, we found that the best antidepressant effect of compounds **2r** and **2s** are likely mediated by an increase in central nervous system 5-HT and NE. In addition, compounds **2r** and **2s** also exhibited the anticonvulsant activity against MES-induced seizures. Thus, compounds **2r** and **2s** may be a useful antidepressant adjunct therapy for treating depression in patients with epilepsy. In addition, compounds **2r** and **2s** showed the anti-inflammatory activity and the excellent analgesic activity. Several scholars have postulated the anti-inflammatory and analgesic effects of antidepressant drugs, suggesting that they may be possess a similar mechanism of action.

Keywords Isoquinoline-2(1*H*)-carboxamide · Synthesis · Antidepressant · Anticonvulsant · Neurotransmitter

Introduction

Depression and epilepsy are the commonly encountered neurological disorders (McNamara 2011; Meyer 2004). Depression is a common comorbidity associated with epilepsy and an important factor that affects quality of life in the individuals and contributing considerably to the global burden of the disease. The search for a novel and increasingly effective drugs with antidepressant and anticonvulsant effects represents an important and challenging in the area of the medicinal chemistry.

Quinolinone compounds are generally used in medicine and in the literature due to their broad biological effects, including anti-cancer (Brajša et al. 2016; Fang et al. 2015; Franci et al. 2015), antibacterial (Naeem et al. 2016; Gaidukevich et al. 2016), anticonvulsant (Deng et al. 2014; Jin et al. 2017; Sun et al. 2009), anti-inflammatory, and antifungal (D'Angelo et al. 2016; Liu et al. 2016) and antidepressant effects (Kumar et al. 2011; Obaid et al. 2013; Sun et al. 2012). In addition, Oshiro et al. (2000) reported 3,4-dihydro-2-(1*H*)-quinolinones derivatives (I) possessed the antidepressant activity. Bauman et al. (2008) described the antidepressant properties of aripiprazole with 3,4-dihydro-2(1*H*)-quinolinone-containing compound, which was initially marketed as an antipsychotic agent. Deng et al. (2014) have recently confirmed that 19 new triazole-containing 3,4-dihydroquinolinones (II) exhibited the antidepressant and anticonvulsant in this area (Fig. 1).

Our research group has been studying with the chemical structure and biological properties of the antidepressant and anticonvulsant effect of heterocyclic. We found drug solifenacin including isoquinoline showed antidepressant activity at a dose of 100 mg/kg. In addition, the antidepressant drug moclobemide possess formamide (–CONH–) (Fig. 2), so, research attempt to find the new antidepressant and anticonvulsant compounds with improved safety profile and therapeutic potency, in this work, the electronic isostere principle

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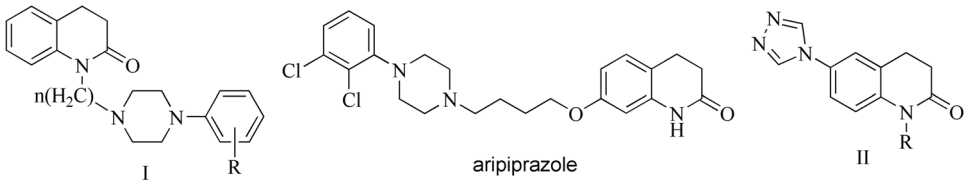


Fig. 1 Chemical structures of quinolinone derivatives possess antidepressant effects

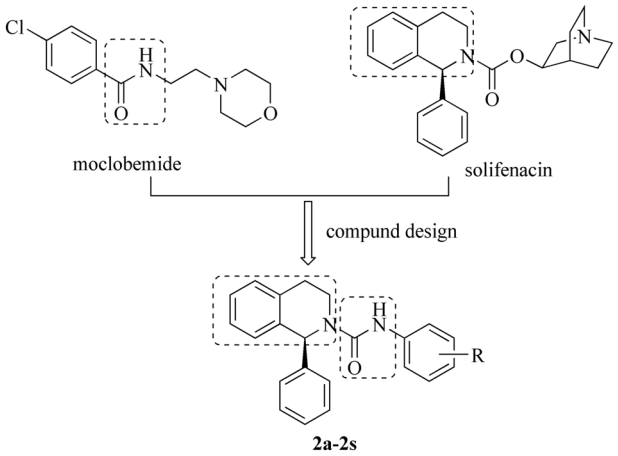


Fig. 2 Chemical structures of solifenacin and antidepressant drug moclobemide and the designed derivatives **2a**–**2s**

was developed by introducing –NH– to replace –O– for solifenacin, which obtained isoquinoline, meanwhile, a series of (*S*)-*N*-substituted-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide derivatives was designed, synthesized and evaluated their antidepressant and anticonvulsant activities.

Methods and materials

Chemistry

A positive control, fluoxetine-HCl and valproate (purity > 99%), was purchased from Sigma-Aldrich (Saint Louis, MO, USA). 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. High resolution mass spectra were measured on an MALDI-TOF/TOF mass spectrometer (Bruker, Germany). Most chemicals were purchased from Sigma-Aldrich and were of analytical grade.

The synthesis of (*S*)-ethyl-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (1)

A mixture of *(S)*-1-phenyl-1,2,3,4-tetrahydroisoquinoline (1 mmol, 0.6 g) and K_2CO_3 (0.52 mmol, 0.4 g) in 30 mL toluene and water (3:2, v/v) was stirred at room temperature for 5 min, then was slowly added ethyl chlorocarbonate (0.52 mmol, 2.8 mL) at ice-water. The reaction mixture was stirred at room temperature for 20 min. The organic layer was successively washed with 30 mL water, 1 mol/mL 5 mL HCl, 10 mL water, and 15 mL saturated solution of NaCl, dried with $MgSO_4$ and concentrated to give the oil products. The crude products were washed with hexane to furnish the pure compound.

The synthesis of (*S*)-substitued-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (2a–2s)

To a flask containing toluene (30 mL) and compound **1** (1 mmol, 0.75 g) was heated at 110 °C under reflux for 2 h. Then, substituted aniline (5 mmol) and NaH (1.6 mmol, 0.1 g) was added, the reaction mixture was heated at 110–120 °C. The reaction was monitored by TLC until the reaction was over. Then the products was added sodium chloride and extracted with acetic ether (30 mL × 2), acetic ether layer was washed with 5 mL 20 % HCl, then adjusted pH 10 with 2 mol/L NaOH, the crude product was purified using 95 % EtOH. The yield, melting point and spectral data of each compound are given as below.

(*S*)-*N*,1-diphenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (2a)

Yield 64.7%, m.p. 132–133 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.93–2.95 (2H, t, $-CH_2$), 3.70–3.75 (2H, t, $-CH_2$), 6.44 (1H, s, –CH), 6.54 (1H, s, –NH), 6.96–7.00 (4H, m, $-C_6H_4$), 7.01–7.27 (5H, m, $-C_6H_5$), 7.29–7.35 (5H, m, $-C_6H_5$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.50, 40.43, 58.04, 120.02, 123.10, 126.52, 127.27, 127.50, 128.21, 128.44, 128.66, 128.84, 134.90, 136.21, 139.03, 142.54, 155.08; IR (KBr) cm^{-1}: 3281, 1719, 1610, 1249; ESI-HRMS calcd for $C_{22}H_{20}N_2O^+$([M+H]$^+$): 328.4070; found: 328.4062.

(*S*)-1-phenyl-*N*-o-tolyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (2b)

Yield 59.5%, m.p. 149–152 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.02 (3H, s, $-CH_3$), 2.91–3.03 (2H, t, $-CH_2$), 3.81–3.85 (2H, t, $-CH_2$), 6.40 (1H, s, –CH), 6.47 (1H, s, –NH), 7.00–7.15 (4H, m, $-C_6H_4$), 7.01–7.43 (4H, m, $-C_6H_4$), 7.13–7.37 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 17.52, 28.68, 40.86, 58.67, 122.70, 123.84, 126.58, 126.73, 127.34, 127.69, 128.06, 128.37, 128.46, 128.80, 130.23, 135.04, 136.34, 137.10, 142.68, 155.44; IR (KBr) cm^{-1}: 3287, 1721, 1611, 1247; ESI-HRMS calcd for $C_{23}H_{22}N_2O^+$([M+H]$^+$): 342.4336; found: 342.4330.

***(S)*-1-phenyl-*N*-*m*-tolyl-3,4-dihydroisoquinoline-2(*1H*)-carboxamide (2c)**

Yield 70%, m.p. 116–117 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.30 (3H, s, $-CH_3$), 2.92–2.98 (2H, t, $-CH_2$), 3.80–3.84 (2H, t, $-CH_2$), 6.47 (1H, s, –CH), 6.48 (1H, s, –NH), 6.86–7.12 (4H, m, $-C_6H_4$), 7.05–7.30 (4H, m, $-C_6H_4$), 7.10–7.33 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.51, 28.52, 40.46, 58.01, 117.03, 120.71, 123.92, 126.50, 127.27, 127.50, 128.23, 128.45, 128.67, 134.90, 136.28, 138.79, 138.91, 142.53, 155.10; IR (KBr) cm^{-1}: 3284, 1721, 1610, 1251; ESI-HRMS calcd for $C_{23}H_{22}N_2O^+$([M+H]$^+$): 342.4336; found: 342.4342.

***(S)*-1-phenyl-*N*-*p*-tolyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2d)**

Yield 53%, m.p. 128–130 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.32 (3H, s, $-CH_3$), 2.90–2.97 (2H, t, $-CH_2$), 3.72–3.73 (2H, t, $-CH_2$), 6.46 (1H, s, –CH), 6.52 (1H, s, –NH), 7.10–7.24 (4H, m, $-C_6H_4$), 7.21–7.33 (4H, m, $-C_6H_4$), 7.25–7.34 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.73, 28.51, 40.40, 57.96, 120.30, 126.43, 127.29, 127.48, 127.55, 128.26, 128.65, 129.38, 142.55, 155.28; IR (KBr) cm^{-1}: 3227, 1718, 1621, 1249; ESI-HRMS calcd for $C_{23}H_{22}N_2O^+$([M+H]$^+$): 342.4336; found: 342.4326.

***(S)*-*N*-(*o*-methoxyphenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2e)**

Yield 68%, m.p. 78–80 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.80–2.97 (2H, t, $-CH_2$), 3.71 (3H, s, $-OCH_3$), 3.47–4.09 (2H, t, $-CH_2$), 6.47 (1H, s, –CH), 6.82 (1H, s, –NH), 6.91–7.24 (4H, m, $-C_6H_4$), 7.21–7.34 (4H, m, $-C_6H_4$), 7.21–7.35 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.45, 40.41, 55.52, 57.86, 114.06, 122.33, 126.51, 127.27, 127.45, 127.54, 128.25, 128.47, 128.62, 134.80, 136.32, 142.64, 155.53; IR (KBr) cm^{-1}: 3235, 1719, 1612, 1246; ESI-HRMS calcd for $C_{23}H_{22}N_2O_2^+$([M+H]$^+$): 358.4330; found: 358.4340.

***(S)*-*N*-(*m*-methoxyphenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2f)**

Yield 63.5%, m.p. 117–119 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.83–3.12 (2H, t, $-CH_2$), 3.74 (3H, s, $-OCH_3$), 4.10–4.17 (2H, t, $-CH_2$), 6.46 (1H, s, –CH), 6.80 (1H, s, –NH), 6.90–7.29 (4H, m, $-C_6H_4$), 7.20–7.35 (4H, m, $-C_6H_4$), 7.22–7.35 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.70, 40.42, 55.51, 57.92, 114.12, 122.33, 126.52, 127.27, 127.42, 127.57, 128.25, 128.46, 128.62, 134.90, 136.34, 142.65, 155.46; IR (KBr) cm^{-1}: 3287, 1721, 1621, 1248; ESI-HRMS calcd for $C_{23}H_{22}N_2O_2^+$([M+H]$^+$): 358.4330; found: 358.4321.

***(S)*-*N*-(*p*-methoxyphenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2g)**

Yield 77%, m.p. 148–150 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.85–3.07 (2H, t, $-CH_2$), 3.74 (3H, s, $-OCH_3$), 4.10–4.17 (2H, t, $-CH_2$), 6.46 (1H, s, –CH), 6.83 (1H, s, –NH), 6.88–7.24 (4H, m, $-C_6H_4$), 7.20–7.34 (4H, m, $-C_6H_4$), 7.20–7.31 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.70, 40.42, 55.51, 57.94, 114.12, 122.35, 126.46, 127.24, 127.46, 127.55, 128.22, 128.45, 128.62, 134.90, 136.33, 142.61, 155.87; IR (KBr) cm^{-1}: 3239, 1719, 1617, 1248; ESI-HRMS calcd for $C_{23}H_{22}N_2O_2^+$([M+H]$^+$): 358.4330; found: 358.4342.

***(S)*-*N*-(*o*-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2h)**

Yield: 63%, m.p. 107–108 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.92–3.03 (2H, t, $-CH_2-$), 3.74–3.82 (2H, t, $-CH_2-$), 6.46 (1H, s, –CH), 6.93 (1H, s, –NH), 7.12–7.26 (4H, m, $-C_6H_4$), 7.22–7.35 (5H, m, $-C_6H_5$), 7.25–7.33 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.43, 40.44, 58.10, 114.37, 126.56, 127.48, 127.55, 128.23, 128.48, 128.70, 134.82, 136.12, 142.25, 154.42; IR (KBr) cm^{-1}: 3285, 1721, 1620, 1250; ESI-HRMS calcd for $C_{22}H_{19}FN_2O^+$([M+H]$^+$): 346.3975; found: 346.3961.

***(S)*-*N*-(*m*-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2i)**

Yield 65.7%, m.p. 149–150 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.82–2.89 (2H, t, $-CH_2-$), 3.73–3.84 (2H, t, $-CH_2-$), 6.45 (1H, s, –CH), 6.70 (1H, s, –NH), 6.71–6.98 (4H, m, $-C_6H_4$), 6.78–7.32 (5H, m, $-C_6H_5$), 7.19–7.33 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.47, 40.50, 58.12, 109.54, 109.79, 114.93, 126.59, 127.36, 127.45, 127.66, 128.20, 128.46, 128.73, 134.70, 136.08, 142.30, 154.61; IR (KBr) cm^{-1}: 3228, 1720, 1621, 1248; ESI-

HRMS calcd for $C_{22}H_{19}FN_2O^+([M+H]^+)$: 346.3975; found: 346.3967.

(S)-N-(p-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2j)

Yield 78.3%, m.p. 115–116 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.89–2.98 (2H, t, $-CH_2-$), 3.70–3.81 (2H, t, $-CH_2-$), 6.45 (1H, s, –CH), 6.65 (1H, s, –NH), 6.90–7.76 (4H, m, $-C_6H_4$), 6.93–7.32 (5H, m, $-C_6H_5$), 7.21–7.35 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.51, 40.43, 58.12, 115.45, 115.62, 127.43, 127.53, 128.25, 128.66, 128.87, 134.83, 136.26, 142.46, 155.28; IR (KBr) cm^{-1}: 3283, 1721, 1619, 1249; ESI-HRMS calcd for $C_{22}H_{19}FN_2O^+([M+H]^+)$: 346.3975; found: 346.3980.

(S)-N-(o-chlorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2k)

Yield 69.6%, m.p. 123–124 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.93–3.01 (2H, t, $-CH_2-$), 3.83–3.85 (2H, t, $-CH_2-$), 6.48 (1H, s, –CH), 6.68 (1H, s, –NH), 6.90–7.11 (4H, m, $-C_6H_4$), 6.87–7.32 (5H, m, $-C_6H_5$), 7.21–7.81 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.33, 40.69, 58.13, 115.20, 121.15, 122.36, 123.15, 126.66, 127.42, 127.50, 127.59, 127.67, 128.20, 128.45, 128.69, 128.73, 134.87, 135.80, 136.19, 142.12, 154.38. IR (KBr) cm^{-1}: 3281, 1722, 1619, 1252; ESI-HRMS calcd for $C_{22}H_{19}ClN_2O^+([M+H]^+)$: 362.8521; found: 362.8530.

(S)-N-(m-chlorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2l)

Yield 66%, m.p. 172–173 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.91–2.97 (2H, t, $-CH_2-$), 3.71–3.73 (2H, t, $-CH_2-$), 6.46 (1H, s, –CH), 6.59 (1H, s, –NH), 6.93–7.14 (4H, m, $-C_6H_4$), 6.96–7.33 (5H, m, $-C_6H_5$), 7.17–7.50 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.44, 40.51, 58.15, 117.84, 119.97, 123.12, 126.63, 127.38, 127.47, 127.63, 128.20, 128.47, 128.73, 129.78, 134.49, 134.76, 136.05, 140.30, 142.26, 154.59; IR (KBr) cm^{-1}: 3286, 1720, 1619, 1248; ESI-HRMS calcd for $C_{22}H_{19}ClN_2O^+([M+H]^+)$: 362.8521; found: 362.8534.

(S)-N-(p-chlorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2m)

Yield 81%, m.p. 183–184C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.91–2.93 (2H, t, $-CH_2-$), 3.71–3.78 (2H, t, $-CH_2-$), 6.45 (1H, s, –CH), 6.66 (1H, s, –NH), 7.11–7.21 (4H, m, $-C_6H_4$), 7.15–7.32 (5H, m, $-C_6H_5$), 7.21–7.33 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.43, 40.44, 58.07, 114.68, 120.18, 121.29, 126.37, 127.37, 127.44, 128.17, 128.73, 128.78, 134.14, 134.87, 136.07, 137.58, 142.32, 154.82; IR (KBr) cm^{-1}: 3256, 1720, 1620, 1248; ESI-HRMS calcd for $C_{14}H_{10}N_2O^+([M+H]^+)$: $C_{22}H_{19}ClN_2O^+([M+H]^+)$: 362.8521; found: 362.8531.

(S)-N-(2,6-dichlorophenyl)-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2n)

Yield 77.5%, m.p. 185–187 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.11–3.18 (2H, t, $-CH_2-$), 3.73–3.80 (2H, t, $-CH_2-$), 6.54 (1H, s, –CH), 6.65 (1H, s, –NH), 6.87–7.18 (4H, m, $-C_6H_4$), 7.00–7.31 (5H, m, $-C_6H_5$), 7.21–7.33 (3H, m, $-C_6H_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.70, 39.08, 68.49, 118.43, 121.45, 125.59, 125.84, 127.57, 127.69, 127.93, 128.22, 128.35, 128.49, 128.61, 128.79, 130.03, 132.85, 135.55, 137.46, 145.22, 153.57; IR (KBr) cm^{-1}: 3285, 1718, 1615, 1252; ESI-HRMS calcd for $C_{22}H_{18}Cl_2N_2O^+([M+H]^+)$: 397.2971; found: 397.2960.

(S)-N-(o-bromophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2o)

Yield 74.5%, m.p. 118.4–119.4 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.93–3.02 (2H, t, $-CH_2-$), 3.70–3.72 (2H, t, $-CH_2-$), 6.44 (1H, s, –CH), 6.65 (1H, s, –NH), 6.91–7.19 (4H, m, $-C_6H_4$), 7.21–7.34 (5H, m, $-C_6H_5$), 7.23–7.41 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.43, 40.42, 58.04, 115.22, 115.50, 127.31, 127.50, 128.22, 128.46, 128.64, 134.86, 136.18, 142.41, 155.24; IR (KBr) cm^{-1}: 3286, 1721, 1621, 1247; ESI-HRMS calcd for $C_{22}H_{19}BrN_2O^+([M+H]^+)$: 407.3031; found: 407.3020.

(S)-N-(m-bromophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2p)

Yield 77.5%, m.p. 181–183 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.93–3.04 (2H, t, $-CH_2-$), 3.71–3.76 (2H, t, $-CH_2-$), 6.46 (1H, s, –CH), 6.65 (1H, s, –NH), 7.09–7.19 (4H, m, $-C_6H_4$), 7.11–7.34 (5H, m, $-C_6H_5$), 7.21–7.54 (4H, m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.40, 40.54, 58.12, 118.41, 122.47, 122.80, 125.96, 126.63, 127.40, 127.46, 127.64, 128.21, 128.49, 128.72, 130.04, 134.71, 136.04, 140.40, 142.22, 154.62. IR (KBr) cm^{-1}: 3278, 1721, 1619, 1251; ESI-HRMS calcd for $C_{22}H_{19}BrN_2O^+([M+H]^+)$: 407.3031; found: 407.3044.

(S)-N-(p-bromophenyl)-1-phenyl-3,4-dihydroisoquinoline-2 *(1H)*-carboxamide (2q)

Yield 61.6%, m.p. 120–121 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.91–2.93 (2H, t, $-CH_2-$), 3.71–3.85 (2H, t, $-CH_2-$), 6.45 (1H, s, –CH), 6.58 (1H, s, –NH), 7.10–7.25 (4H, m, $-C_6H_4$), 7.20–7.32 (5H, m, $-C_6H_5$), 7.20–7.38 (4H,

m, $-C_6H_4$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.41, 40.49, 58.10, 115.66, 121.89, 126.56, 127.36, 127.47, 127.63, 128.20, 128.49, 128.71, 131.74, 134.78, 136.08, 138.21, 142.27, 154.81; IR (KBr) cm^{-1}: 3249, 1722, 1617, 1248; ESI-HRMS calcd for $C_{22}H_{19}BrN_2O^+$([M+H]$^+$): 407.3031; found: 407.3043.

(S)-N,N,1-triphenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2r)

Yield 84%, m.p. 189–190 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.88–2.94 (2H, t, $-CH_2-$), 3.82–4.06 (2H, t, $-CH_2-$), 6.40 (1H, s, –CH), 6.92–7.05 (4H, m, $-C_6H_4$), 7.02–7.26 (5H, m, $-C_6H_5$), 7.30–7.41 (5H, m, $-C_6H_5$), 7.34–7.40 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.70, 43.64, 72.18, 116.21, 119.33, 119.95, 122.68, 125.81, 126.95, 127.52, 127.93, 128.54, 128.61, 129.19, 129.72, 136.66, 138.63, 143.05, 143.46, 155.90; IR (KBr) cm^{-1}: 1721, 1617, 1249; ESI-HRMS calcd for $C_{28}H_{24}N_2O^+$([M+H]$^+$): 404.5030; found: 404.5039.

(S)-N-benzyl-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide (2s)

Yield 73%, m.p. 116–118 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.86–2.98 (2H, t, $-CH_2-$), 3.73–3.87 (2H, t, $-CH_2-$), 4.48 (2H, s, $-CH_2$), 6.45 (1H, s, –CH), 6.67 (1H, s, –NH), 6.90–7.10 (4H, m, $-C_6H_4$), 6.95–7.31 (5H, m, $-C_6H_5$), 7.25–7.40 (5H, m, $-C_6H_5$); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.32, 40.15, 45.11, 57.80, 126.41, 127.19, 127.25, 127.52, 127.67, 128.31, 128.46, 128.49, 128.62, 135.06, 136.54, 139.49, 142.82, 157.48; IR (KBr) cm^{-1}: 3280, 1718, 1619, 1247; ESI-HRMS calcd for $C_{23}H_{22}N_2O^+$([M+H]$^+$): 342.4336; found: 342.4342.

Pharmacology

The forced swimming test

Male ICR mice (20 ± 2 g) were used in the forced swimming test (FST) 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 22 ± 3 °C. Mice were assigned into different groups ($n = 8$ for each group). 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. The duration of immobility was recorded during the last 4 min of the 6-min test. Immobility period was regarded as the time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above the water (Porsolt et al. 1997).

The tail suspension test (TST)

Male ICR mice were individually suspended by tail with clamp (2 cm from the tip of the end) in a box (25 × 25 × 30 cm) with the head 5 cm to the bottom. Testing was carried out in a darkened room with minimal background noise. All animals were suspended for total 6 min, and the duration of immobility was observed and measured during the final 4-min interval of the test. Mice were considered to be immobile only when they hung passively and completely motionless (Steru et al. 1985).

The sample preparation

The doses of 20 mg/kg **2r**, **2s** and fluoxetine were employed for testing the effect on monoamine neurotransmitter concentrations in the rat brain. Mice were randomly divided into five groups (10 mice per group were used). Normal vehicle, stress vehicle, **2r**, **2s** and fluoxetine were given orally daily for 7 days. On the last day, the drugs 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 0.1 M NaH_2PO_4 aqueous solution including 0.85 mM OSA, 0.5 mM Na_2·EDTA (ethylenediamine tetraacetic acid disodium) and centrifuged at 13,000×*g* for 15 min at 4 °C. Then 5-HT, NE, and 5-HIAA 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 0.1 M 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 5-HT, NE and 5-HIAA 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 5-HT, NE and 5-HIAA by HPLC coupled with electrochemical detection in brain region.

Anticonvulsant effects in the maximal electroshock seizure (MES) test

Half male and female ICR mice (20 ± 2 g) was used the maximal electroshock seizure 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. Protection against the spread of the maximal electroshock seizure-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. At 30 min after the administration of compounds, the effects were evaluated in the maximal electroshock seizure test (Porter et al. 1984).

Neurotoxicity screening

The neurotoxicity of the compounds was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 circles per minutes. Trained animals were given an intraperitoneal injection of the tested compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials (Guan et al. 2013).

Statistical analysis

Results are expressed as mean ± SEM. *n* represents the number of animals. Data obtained from pharmacological experiments were analyzed with the Turkey's comparison tests, using GRAPHPAD PRISM program (GraphPad Software, Inc., San Diego, CA, USA). A *p*-value of < 0.05 was considered statistically significant.

Results and discussion

Chemistry

The synthetic routes of the target derivatives are illustrated in Scheme 1. Compound **1** was synthesized to underwent a nucleophile substitution reaction with commercial compound (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline at room temperature in a good yield (95%). (*S*)-*N*-substituted-1-phenyl-3,4-dihydro-isoquinoline-2*(1H)*-carboxamide derivatives (**2a**–**2s**) were obtained by stirring compound **1** with the appropriate substituted aniline in methylbenzene containing sodium hydride at 110–120 °C in 53–84% yield. The structures of compounds **2a**–**2s** were confirmed by spectral data and high resolution mass spectra. The IR spectra of the synthesized target derivatives **2a**–**2s** showed absorption bands at 3221–3287, 1718–1722, 1610–1621 cm^{-1} corresponding to (NH), C=O stretching and (C=N) group, respectively. ^{1}H-NMR showed disappearance of the –NH group as singlet signals at 6.46–6.71 ppm and the –CH group as singlet signals at 6.38–6.58 ppm. ^{13}C-NMR spectra displayed the appearance of the new peak at 153.38–157.49 ppm for the O=C group.

Biological evaluation

The antidepressant effects of the synthesized compounds were evaluated applying the FST and TST in mice in vivo. Both the FST and TST, which is the behavioral test, used to predict the efficacy of antidepressant treatments (Zhen et al. 2016). In the two models, mice are restricted and cannot escape, inducing a characteristic behavior of immobility. It also has a good predictive value for the antidepressant potency in humans (Xu et al. 2015).

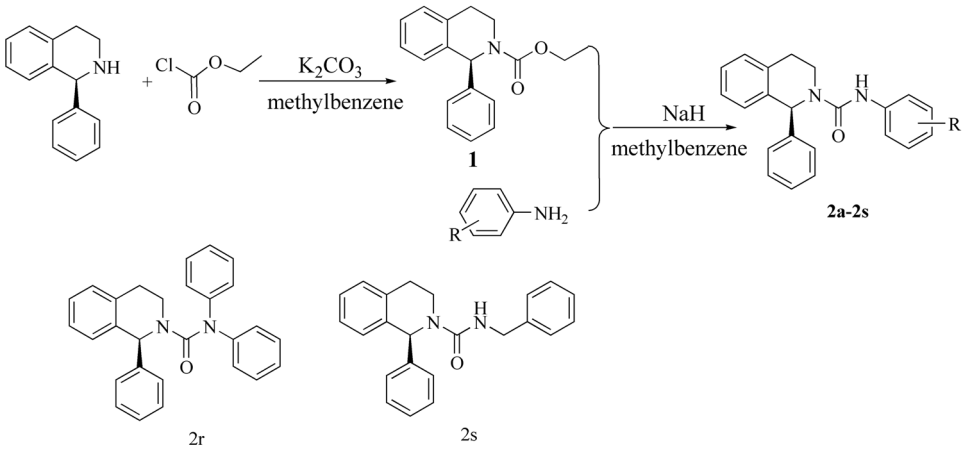
The obtained data on the antidepressant activity of the synthesized compounds was comparable to fluoxetine as reference drugs (Table 1). Except compounds **2i**, **2n**, and **2q**, other compounds showed the antidepressant activity at a dose of 50 mg/kg administered intraperitoneally with percentage decrease in immobility duration values range of 39.1–87.7% (Duration of immobility(s): 11.0 ± 7.1–54.6 ± 10.2). Among the synthesized compounds **2h** and **2k**, both with electron-withdrawing substituent *o*-fluoro and *o*-chloro for the phenly ring, and compounds **2r** (*N,N*-diphenyl) and **2s** (*N*-benzyl) with electron-donor groups, showed the best antidepressant activity in the FST (DID: 82.4, 81.3, 85.5, and 87.7%, respectively), which was greater than that or nearly equivalent to that of fluoxetine (79.1%).

Next, compounds **2h**, **2k**, **2r**, and **2s** exhibited the most potent antidepressant activity and were further evaluated antidepressant effects after treatment with three low doses (10, 20, and 30 mg/kg) (Table 2). It should be noted that compounds **2h**, **2k**, **2r**, and **2s** displayed to reduce the duration of immobility in the FST in mice, and also exhibited the antidepressant effects in a dose-dependent manner from 10 to 30 mg/kg. Compound **2s** showed antidepressant activity with DID value 74.2% which was better than that of fluoxetine (70.4%) at a dose of 20 mg/kg.

In addition, compounds **2h**, **2k**, **2r**, and **2s** were further evaluated antidepressant effects after treatment with three low doses (10, 20, and 30 mg/kg) in the TST (Table 3). Compounds **2h**, **2k**, **2r**, and **2s** also showed to reduce the duration of immobility in the TST in mice and displayed the antidepressant effects in a dose-dependent manner from 10 to 30 mg/kg. Compound **2s** showed the antidepressant activity with DID value 39.1% which was nearly equivalent to that of fluoxetine (39.5%) with a dose of 20 mg/kg.

Structure–activity relationship (SAR) studies for the antidepressant activity of derivatives **2a**–**2s** mentioned above in the FST (Table 1) displayed that: (1) all compounds except compounds **2i**, **2n**, and **2q** reduce the

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



R:

2a=H	2b=*o*-CH_3	2c=*m*-CH_3	2d=*p*-CH_3	2e=*o*-OCH_3	2f=*m*-OCH_3	2g=*p*-OCH_3
2h= *o*-F	2i= *m*-F	2j= *p*-F	2k= *o*-Cl	2l= *m*-Cl	2m= *p*-Cl	2n=2,6-Cl_2
2o= *o*-Br	2p= *m*-Br	2q= *p*-Br				

duration of immobility not only with electron-donating substituent, but also with electron-withdrawing substituent groups. (2) For six electron-donor groups on the phenyl ring with the introduction of $–CH_3$ and $–OCH_3$, it was obvious to afford the excellent antidepressant activity at the *meta*-positions of the phenyl ring as compounds **2c** and **2f**. In addition, the position of the substituted greatly influenced antidepressant effects, the obtained data clearly revealed that the six compounds with $–CH_3$ and $–OCH_3$ substituent are active in the order of: **2c > 2d > 2b** and **2f > 2g > 2e**, respectively. (3) For nine with electron-withdrawing substituent with the introduction of F atoms (**2h**, **2i**, and **2j**), Cl atoms (**2k**, **2l**, and **2m**), or Br atoms (**2o**, **2p**, and **2q**), which also exhibited the excellent antidepressant activity at the *orth*-positions of the phenyl ring as compounds 2h, **2k**, and **2o**. The position of the halogen atom substituted greatly influenced the antidepressant effects. Compared with compounds with different F-substituted positions on the phenyl ring, the order of activity was *o*-F > *p*-F > *m*-F, and the order of activity observed for Cl-substituted positions was *o*-Cl > *m*-Cl > *p*-Cl. The order of activity for with different Br-substituted positions was *o*-Br > *m*-Br > *p*-Br. But compound **2n** with 2,6-dichlolo substituent did not show the antidepressant activity. (4) Compounds **2r** and **2s** with *N,N*-diphenyl and *N*-benzyl substituent marked reduced the duration of immobility and displayed the excellent antidepressant activity in mice, by 85.5 and 87.7%, respectively. For this reason, it was difficult to determine a structure–activity relationship for the different substituent group attached to phenyl ring. (5) It is worth mentioning that the presence of no substituent on the phenyl ring compound **2a** showed the antidepressant effect (63.4%), which was similar to the lead compound solifenacin (64.8%).

A dysregulation of the central nervous system including the neurotransmitters 5-HT and NE has been suggested to play a role in the pathogenesis of depression and the mainstream of research has principally focused on 5-HT and NE systems in 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 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, compounds **2r** and **2s** significantly increased 5-HT and NE levels at the highest doses during the FST in mice brain, similar to the positive control drug fluoxetine. In addition, compounds **2r** and **2s** significantly increased 5-HIAA levels, indicating a reduced 5-HT metabolism. These findings indicate that the antidepressant effect of EECS is likely mediated through an increase 5-HT and NE in central nervous system.

The anticonvulsant activities of the synthesized compounds were also investigated by maximal electroshock and results from these experiments are shown in Table 5. Seizure assays and neurotoxicity were determined by rotarod toxicity test. Eight compounds **2a**, **2b**, **2e**, **2h**, **2n**, **2p**, **2r**, and **2s** exhibited better anticonvulsant activity against MES at a dose of 100 mg/kg. Eight compounds **2c**, **2f**, **2j–2m**, **2o**, and **2q** showed the anticonvulsant effect against MES at a dose of 300 mg/kg. Three compounds **2d**, **2g**, and **2i** did not display the anticonvulsant activity against MES at a dose of 300 mg/kg. But the lead compound solifenacin and reference drug valproate exhibited the excellent anticonvulsant activity against MES at a dose of 100 mg/kg. The rotarod toxicity test results displayed that all compounds did not

Table 1 Evaluation of antidepressant activity of compounds **2a–2s** in the FST

Compounds	Antidepressant activity[a]	
	Duration of immobility(s)	DID (%)[b]
Solifenacin	31.5 ± 7.8**	64.8
2a	32.8 ± 9.5**	63.4
2b	43.4 ± 9.5*	51.6
2c	24.6 ± 12.1**	72.5
2d	34.6 ± 7.4*	61.4
2e	50.2 ± 7.2*	44.0
2f	24.4 ± 10.0**	72.8
2g	42.8 ± 6.8*	52.2
2h	15.8 ± 9.4***	82.4
2i	82.3 ± 9.5	8.1
2j	35.2 ± 8.4**	60.7
2k	16.8 ± 11.4***	81.3
2l	19.4 ± 11.8***	78.3
2m	24.6 ± 9.4***	72.5
2n	63.2 ± 10.6	29.5
2o	28.2 ± 11.9***	68.5
2p	54.6 ± 10.2*	39.1
2q	83.1 ± 7.9	7.3
2r	13.0 ± 8.4***	85.5
2s	11.0 ± 7.1***	87.7
Fluoxetine	18.7 ± 9.1***	79.1
Control	89.6 ± 16.1	–

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

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

[a]Compounds and fluoxetine were administered intraperitoneally at 50 mg/kg

[b]% DID: percentage decrease in immobility duration. %DID = $[(Y-X)/Y] \times 100$, where Y is the duration of immobility (s) in the control group and X is the duration of immobility (s) in the test group.

show the neurotoxic effects for doses up to and including 300 mg/kg.

Depression and epilepsy are common neurological disorders (Schröder et al. 2014). Patients with epilepsy are at high risk of developing depressive symptoms, Anticonvulsant drugs may improve depressive symptoms though clinical research. Treatment of depression may independently improve outcome for epilepsy and for quality of life (Drinovac et al. 2015). The present study demonstrated that compounds **2r** and **2s** induced significant antidepressant effects in the FST and TST. And, we found that the antidepressant effect of compounds **2r** and **2s** are likely mediated by an increase in central nervous system 5-HT and NE. In addition, compounds **2r** and **2s** also exhibited the anticonvulsant activity against MES-induced seizures. Thus, compounds **2r** and **2s** may be a useful antidepressant

Table 2 Evaluation of antidepressant activity of compounds **2h**, **2k**, **2r**, and **2s** in the FST

Compounds	Dose (mg/kg)	Antidepressant activity[a]	
		Duration of immobility (s)	DID (%)[b]
2h	10	70.2 ± 7.5*	28.8
	20	66.8 ± 9.5*	32.3
	30	52.4 ± 10.5**	46.9
2k	10	69.7 ± 7.1*	29.3
	20	54.8 ± 9.5**	44.4
	30	42.4 ± 10.5**	57.0
2r	10	64.0 ± 5.7*	35.1
	20	51.0 ± 9.0**	48.3
	30	41.4 ± 11.0**	58.0
2s	10	40.0 ± 6.9**	59.4
	20	25.4 ± 7.1***	74.2
	30	15.4 ± 3.1***	84.4
Fluoxetine	20	29.2 ± 8.5***	70.4
Control	–	98.6 ± 9.7	–

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

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

[a]Compounds and fluoxetine were administered intraperitoneally

[b]% DID: percentage decrease in immobility duration

Table 3 Evaluation of antidepressant activity of compounds **2h**, **2k**, **2r**, and **2s** in the TST

Compounds	Dose (mg/kg)	Antidepressant activity[a]	
		Duration of immobility(s)	DID (%)[b]
2h	10	124.1 ± 11.5*	17.0
	20	110.4 ± 12.4*	26.2
	30	72.5 ± 10.5***	51.5
2k	10	124.3 ± 5.5*	16.9
	20	120.2 ± 7.8*	19.6
	30	88.5 ± 6.5***	40.8
2r	10	107.7 ± 8.5*	28.0
	20	99.3 ± 13.1**	33.6
	30	86.7 ± 7.8***	42.0
2s	10	89.7 ± 7.3**	40.0
	20	91.2 ± 8.0**	39.0
	30	85.0 ± 9.4***	43.1
Fluoxetine	20	90.4 ± 9.6**	39.5
Control	–	149.5 ± 13.8	–

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

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

[a]Compounds and Fluoxetine were administered intraperitoneally

[b]% DID: percentage decrease in immobility duration

Table 4 Effect of FST exposure and **2r**, **2s** on brain monoamine neurotransmitter levels

Groups	5-HT	5-HIAA	NE
Normal vehicle	326.3 ± 30.6	237.1 ± 29.2	313.0 ± 26.5
Stress vehicle	202.6 ± 31.0	157.8 ± 19.5	205.4 ± 24.7
2r	378.3 ± 31.7[a,e]	243.8 ± 21.4[a]	346.6 ± 30.4 [a,d]
2s	398.2 ± 32.7[c,d]	250.1 ± 28.2[a,e]	337.1 ± 30.0[a,e]
fluoxetine	391.6 ± 33.1[c,e]	248.5 ± 30.3[a,e]	325.4 ± 28.3[b,e]

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

[a]$P < 0.05$

[b]$P < 0.01$

[c]$P < 0.001$ vs. stress vehicle

[d]$P < 0.05$

[e]$P < 0.01$ vs. normal vehicle

Table 5 Anticonvulsant effects and neurotoxocity of compounds **2a**–**2s**

Compounds	Dosage (mg/kg)	MES[a]		Neurotoxocity[b]	
		0.5 h	4 h	0.5 h	4 h
Solifenacin	100	3/3	0/3	0/3	0/3[c]
2a	100	2/3	0/3	0/3	0/3
2b	100	1/3	0/3	0/3	0/3
2c	300	1/3	0/3	0/3	0/3
2d	300	0/3	0/3	0/3	0/3
2e	100	1/3	0/3	0/3	0/3
2f	300	1/3	0/3	0/3	0/3
2g	300	0/3	0/3	0/3	0/3
2h	100	1/3	0/3	0/3	0/3
2i	300	0/3	0/3	0/3	0/3
2j	300	1/3	0/3	0/3	0/3
2k	300	1/3	0/3	0/3	0/3
2l	300	1/3	0/3	0/3	0/3
2m	300	1/3	0/3	0/3	0/3
2n	100	1/3	0/3	0/3	0/3
2o	300	2/3	0/3	0/3	0/3
2p	100	1/3	0/3	0/3	0/3
2q	300	1/3	0/3	0/3	0/3
2r	100	1/3	0/3	0/3	0/3
2s	100	1/3	0/3	0/3	0/3
Valproate	100	3/3	0/3	0/3	0/3

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

[b]Toxicity: rotarod test (number of animals exhibiting toxicity/number of animals tested). The animals were examined at 0.5 h and 4.0 h after injection

[c]Compounds are metabolized/excreted at 4 h

adjunct therapy for treating depression in patients with epilepsy.

In addition, inflammation is characterized by pain, swelling, redness and heat, whereas depression is common in people 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 is inhibited, which leads to increases in levels of noradrenaline and serotonin, which reinforce pain-inhibitory pathways (Uddin et al. 2018). In our previous studies (Guan et al. 2017), we found that compounds **2r** and **2s** displayed to be able to decrease the ear edema in mice, by 86.3 and 77.4%, respectively showed the anti-inflammatory activity. Compounds **2r** and **2s** also exhibited the excellent analgesic activity (inhibition rate: 73.3 and 96.3%, respectively). Several scholars have postulated the anti-inflammatory and analgesic effects of antidepressant drugs, suggesting that they may be possess a similar mechanism of action.

Conclusion

In summary, we have reported the synthesis and biological evaluation of nineteen (*S*)-*N*-substituted-1-phenyl-3,4-dihydroisoquinoline-2*(1H)*-carboxamide derivatives as novel candidate antidepressant and anticonvulsant agents. Compounds **2h**, **2k**, **2r**, and **2s** exhibited the most potent antidepressant activity, which was greater than that or nearly equivalent to that of fluoxetine in the FST, and displayed the antidepressant effects in a dose-dependent manner from 10 mg/kg to 30 mg/kg in the FST and TST. And, we found that the antidepressant effect of compounds **2r** and **2s** are likely mediated by an increase in central nervous system 5-HT and NE. In addition, compounds **2r** and **2s** also exhibited the anticonvulsant activity against MES-induced seizures. Thus, compounds **2r** and **2s** may be a useful antidepressant adjunct therapy for treating depression in patients with epilepsy. In addition, compounds **2r** and **2s** showed the anti-inflammatory activity and the excellent analgesic activity. 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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