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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and studies on antidepressant activity of 2′,4′,6′-trihydroxychalcone derivatives

Xin Sui · Ying-Chun Quan · Yue Chang · Rui-Peng Zhang · Yin-Feng Xu · Li-Ping Guan

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Abstract In this study, we synthesized a series of 2′,4′,6′-trihydroxychalcone derivatives and evaluated their antidepressant activities. The results of the nine compounds showed significantly reduced times during the forced swimming test at a dose of 10 mg/kg, indicative of antidepressant activity. Among the compounds, 2-bromo-2′,4′,6′-trihydroxychalcone (**3h**) was found to be the most potent, and it was observed that compound **3h** at dose of 10, 20, and 40 mg/kg significantly reduced the duration of immobility times in the FST and TST in mice 30 min after treatment.

Keywords 2′,4′,6′-Trihydroxychalcone derivatives · Synthesis · Antidepressant activity

X. Sui · Y.-F. Xu · L.-P. Guan (✉)
Food and Pharmacy College, Zhejiang Ocean University, Zhoushan City, Zhejiang Province 316004, People's Republic of China
e-mail: glp730@yahoo.com.cn

X. Sui
e-mail: suixin_iam@163.com

Y.-F. Xu
e-mail: YFxu@zjou.edu.cn

X. Sui · Y.-C. Quan · Y. Chang · R.-P. Zhang
College of Pharmacy, Yanbian University, Yanji, Jilin 133000, People's Republic of China
e-mail: ycquan@yahoo.com.cn

Y. Chang
e-mail: chyba207@yahoo.com.cn

R.-P. Zhang
e-mail: rui-pengazhang@126.com

Introduction

Depression is one of the major mental disorders. Symptoms of depression include lowered mood and reduced interest and pleasure. According to latest available data from the World Health Organization (WHO), depression is expected to become the second leading cause of disease-related disability by the year 2020 (Murray and Lopez, 1996; Rybnikova *et al*., 2007). It is a serious disorder with an estimate of lifetime prevalence as high as 20% and a significant number of patients (30%) do not respond to current medical treatment (Charney *et al*., 2002; Cryan *et al*., 2002). Most of these drugs, however, have undesirable side effects. Thus, there is an unmet need for new antidepressants.

Chalcones are a group of flavonoids that exhibit a wide variety of pharmacological effects, including antibacterial, antifungal, antiviral, and analgesic properties (Bekhit *et al*., 2001; Lopez *et al*., 2001; Viana *et al*., 2003; Wu *et al*., 2003) et al. In recent years, it is reported that flavonoids possess antidepressant activity (Butterweck *et al*., 2000; Nakazawa *et al*., 2003). Wang *et al.* (2007) also reported that ten natural flavonoid compounds exhibited antidepressant activity. Apigenin (5,7,4′-trihydroxyflavonoid) (Fig. 1), one type of bioflavonoid widely found in citrus fruit, was reported to possess antidepressant effect (Yi *et al*., 2008). Analyzing the structure of apigenin, if C-ring of apigenin is opened, the chalcone compound **I** (4,2′,4′,6′-tetrahydroxychalcone) was obtained and its antidepressant activity was examined. The pharmacological results showed that the compound **I** reduced significantly the duration of immobility times at 10 mg/kg dose level when compared to the control ($P < 0.05$), indicative of antidepressant activity. In order to obtain compounds with better antidepressant activity, in this article, we designed and

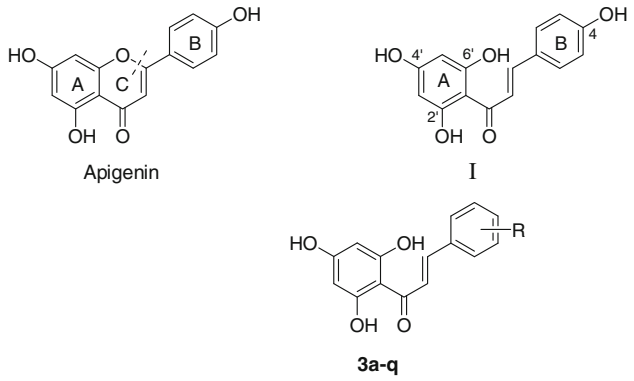


Fig. 1 **Apigenin**: 5,7,4′-trihydroxyflavonoid; **I**: 4,2′,4′,6′-tetrahydroxychalcone; **3a–q**: 2′,4′,6′-trihydroxychalcone derivatives

synthesized a series of 2′,4′,6′-trihydroxychalcone derivatives with ring C opened using compound **I** as the lead compound. The antidepressant activities of the synthesized compounds were also determined by using Porsolt's behavioral despair (Forced Swimming Test: FST) (Porsolt *et al*., 1977) and Steru's behavioral despair (Tail Suspension Test: TST) (Steru *et al*., 1985).The synthesized compounds were characterized by IR, ^{1}H-NMR, and MS.

Experimental

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR1730 (Bruker, Switzerland), ^{1}H-NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to tetramethylsilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Alderich Chemical Corporation. All other chemicals were of the analytical grade.

Synthesis of 2′-hydroxy-3-fluoro-4′,6′-bis(methoxymethoxy)chalcone (**2c**)

To a stirred solution of KOH (2.0 g, 45.6 mmol) in water (2 ml) cooled to 0°C in an ice bath was added dropwise a solution of 2-hydroxy-4,6-bis (methoxymethoxy) acetophenone (1.0 mmol), and 3-fluorobenzaldehyde (2.0 mmol) in ethanol under nitrogen (Nishida and Kawabata, 2006). The reaction mixture was kept at room for 24 h. The mixture was poured into ice-water, adjusted to pH 2–3 with 1 M HCl, and then extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$. After removing solvents, products were purified by silica gel column chromatography (petroleum ether:ethyl acetate = 6:1). The yellow solid was obtained.

MP 70–72°C; yield = 71%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.49 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 6.25–7.37 (m, 6H, Ar–H). 7.73 (d, 1H, J = 15.6 Hz, H_α), 7.91 (d, 1H, J = 15.6 Hz, H_β), 13.76 (s, H, –OH); IR (KBr) cm^{-1}: 3312 (OH), 1636 (C=O); MS m/z 363 (M + 1).

General procedure for the preparation of compounds (**3a–q**)

In a round-bottomed flask, to a stirred solution of chalcones **2a–q** (0.25 mmol) in methanol was added dropwise 3 M HCl, the mixture was refluxed for 30 min. The solvents were removed under reduced pressure and diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the resultant was recrystallized from ethanol. The yield, melting point, and spectral data of part compounds are given below.

2′,4′,6-Trihydroxychalcone (**3a**)

MP 124–126°C; yield = 81%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.86–7.46 (m, 7H, Ar–H), 7.69 (d, 1H, J = 15.9 Hz, H_α), 8.13 (d, 1H, J = 15.7 Hz, H_β), 10.48 (s, H, –OH), 12.48 (s, H, –OH); IR (KBr) cm^{-1}: 3328(OH), 1646 (C=O); MS m/z 257 (M + 1).

2-Fluoro-2′,4′,6′-trihydroxychalcone (**3b**)

MP 172–174°C; yield = 62%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.87–7.79 (m, 6H, Ar–H), 7.73 (d, 1H, J = 15.9 Hz, H_α), 8.24 (d, 1H, J = 15.9 Hz, H_β), 10.54 (s, H, –OH), 12.47 (s, H, –OH); IR (KBr) cm^{-1}: 3334 (OH), 1646 (C=O); MS m/z 275 (M + 1).

3-Fluoro-2′,4′,6′-trihydroxychalcone (**3c**)

MP 178–180°C; yield = 66%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.86–7.53 (m, 6H, Ar–H), 7.66 (d, 1H, J = 15.7 Hz, H_α), 8.12 (d, 1H, J = 15.7 Hz, H_β), 10.52 (s, H, –OH), 12.44 (s, H, –OH); IR (KBr) cm^{-1}: 3328 (OH), 1642 (C=O); MS m/z 275 (M + 1).

4-Fluoro-2′,4′,6′-trihydroxychalcone (**3d**)

MP 168–170°C; yield = 70%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.85–7.53 (m, 6H, Ar–H), 7.68 (d, 1H, J = 16.2 Hz, H_α), 8.12 (d, 1H, J = 16.2 Hz, H_β), 10.48 (s, H, –OH), 12.47 (s, H, –OH); IR (KBr) cm^{-1}: 3330 (OH), 1644 (C=O); MS m/z 275 (M + 1).

2-Chloro-2′,4′,6′-trihydroxychalcone (**3e**)

MP 160–162°C; yield = 63%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.88–7.84 (m, 6H, Ar–H), 7.94 (d, 1H, J = 15.6 Hz, H_α), 8.16 (d, 1H, J = 15.6 Hz, H_β), 10.57 (s, H, –OH), 12.45 (s, H, –OH); IR (KBr) cm^{-1}: 3322 (OH), 1644 (C=O); MS m/z 291 (M + 1).

3-Chloro-2′,4′,6′-trihydroxychalcone (**3f**)

MP 178–180°C; yield = 72%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.92–7.74 (m, 6H, Ar–H), 7.63 (d, 1H, J = 15.7 Hz, H_α), 8.13 (d, 1H, J = 15.7 Hz, H_β), 10.53 (s, H, –OH), 12.45 (s, H, –OH); IR (KBr) cm^{-1}: 3327 (OH), 1647 (C=O); MS m/z 291 (M + 1).

4-Chloro-2′,4′,6′-trihydroxychalcone (**3g**)

MP 175–177°C; yield = 78%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.86–7.71 (m, 6H, Ar–H), 7.67 (d, 1H, J = 15.1 Hz, H_α), 8.11 (d, 1H, J = 15.7 Hz, H_β), 10.51 (s, H, –OH), 12.46 (s, H, –OH); IR (KBr) cm^{-1}: 3328 (OH), 1649 (C=O); MS m/z 291 (M + 1).

2-Bromo-2′,4′,6′-trihydroxychalcone (**3h**)

MP 186–188°C; yield = 53%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.87–7.82 (m, 6H, Ar–H), 7.90 (d, 1H, J = 15.5 Hz, H_α), 8.10 (d, 1H, J = 15.5 Hz, H_β), 10.55 (s, H, –OH), 12.43 (s, H, –OH); IR (KBr) cm^{-1}: 3328 (OH), 1640 (C=O); MS m/z 334 (M + 1).

3-Bromo-2′,4′,6′-trihydroxychalcone (**3i**)

MP 182–184°C; yield = 65%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.86–7.88 (m, 6H, Ar–H), 7.63 (d, 1H, J = 15.7 Hz, H_α), 8.12 (d, 1H, J = 15.7 Hz, H_β), 10.52 (s, H, –OH), 12.45 (s, H, –OH); IR (KBr) cm^{-1}: 3335 (OH), 1651 (C=O); MS m/z 334 (M + 1).

4-Bromo-2′,4′,6′-trihydroxychalcone (**3j**)

MP 192–194°C; yield = 69%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.86–7.65 (m, 6H, Ar–H), 7.65 (d, 1H, J = 15.7 Hz, H_α), 8.12 (d, 1H, J = 15.7 Hz, H_β), 10.51 (s, H, –OH), 12.46 (s, H, –OH); IR (KBr) cm^{-1}: 3322 (OH), 1647 (C=O); MS m/z 334 (M + 1).

2,4-Dichloro-2′,4′,6′-trihydroxychalcone (**3k**)

MP 179–181°C; yield = 71%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.88–7.76 (m, 5H, Ar–H), 7.86 (d, 1H, J = 15.7 Hz, H_α), 8.14 (d, 1H, J = 15.6 Hz, H_β), 10.57 (s, H, –OH), 12.41 (s, H, –OH); IR (KBr) cm^{-1}: 3328 (OH), 1649 (C=O); MS m/z 325 (M + 1).

4-Methyl-2′,4′,6′-trihydroxychalcone (**3l**)

MP 117–119°C; yield = 60%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.35 (s, 3H, CH_3), 5.90–7.44 (m, 6H, Ar–H), 7.67 (d, 1H, J = 15.7 Hz, H_α), 8.09 (d, 1H, J = 15.7 Hz, H_β), 10.46 (s, H, –OH), 12.50 (s, H, –OH); IR (KBr) cm^{-1}: 3330 (OH), 1646 (C=O); MS m/z 271 (M + 1).

3,4-Dimethyl-2′,4′,6′-trihydroxychalcone (**3m**)

MP 156–158°C; yield = 68%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.23 (s, 6H, $(CH_3)_2$), 5.85–7.44 (m, 5H, Ar–H), 7.64 (d, 1H, J = 15.7 Hz, H_α), 8.09 (d, 1H, J = 15.7 Hz, H_β), 10.44 (s, H, –OH), 12.50 (s, H, –OH); IR (KBr) cm^{-1}: 3329 (OH), 1645 (C=O); MS m/z 285 (M + 1).

4-Methoxyl-2′,4′,6′-trihydroxychalcone (**3n**)

MP 107–109°C; yield = 68%; ^{1}H-NMR (DMSO-d_6, 300 MHz):δ 3.82 (s, 3H, OCH_3), 5.85–7.65 (m, 6H, Ar–H), 7.69 (d, 1H, J = 15.8 Hz, H_α), 8.03 (d, 1H, J = 15.6 Hz, H_β), 10.42 (s, H, –OH), 12.52 (s, H, –OH); IR (KBr) cm^{-1}: 3327 (OH), 1646 (C=O); MS m/z 287 (M + 1).

3,4-Dimethoxy-2′,4′,6′-trihydroxychalcone (**3o**)

MP 112–114°C; yield = 68%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 3.77, 3.82 (each s, 3H, OCH_3-3,4), 5.90–7.65 (m, 5H, Ar–H), 7.64 (d, 1H, J = 15.7 Hz, H_α), 8.09 (d, 1H, J = 15.7 Hz, H_β), 10.41 (s, H, –OH), 12.53 (s, H, –OH); IR (KBr) cm^{-1}: 3327 (OH), 1646 (C=O); MS m/z 317 (M + 1).

3,4,2′,4′,6′-Pentahydroxychalcone (**3p**)

MP 202–204°C; yield = 68%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 5.89–7.41 (m, 5H, Ar–H), 7.65 (d, 1H, J = 15.6 Hz, H_α), 8.06 (d, 1H, J = 15.7 Hz, H_β), 9.67 (s, H, –OH), 10.37 (s, H, –OH), 12.12 (s, H, –OH), 12.51 (s, H, –OH); IR (KBr) cm^{-1}: 3328 (OH), 1647 (C=O); MS m/z 289 (M + 1).

3-Methoxy-4,2′,4′,6′-tetrahydroxychalcone (**3q**)

MP 188–190°C; yield = 68%; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 3.83 (s, 3H, OCH_3), 5.89–7.27 (m, 5H, Ar–H), 7.65 (d, 1H, J = 15.5 Hz, H_α), 7.99 (d, 1H, J = 15.7 Hz, H_β), 10.38 (s, H, –OH), 10.78 (s, H, –OH);

12.16 (s, H, –OH), 12.54 (s, H, –OH); IR (KBr) cm^{-1}: 3329 (OH), 1645 (C=O); MS *m/z* 303 (*M* + 1).

Pharmacology

Forced swimming test (FST)

The synthesized compounds were screened for their antidepressant activity using Porsolt's behavioral despair (forced swimming) test (Porsolt *et al*., 1977). Local breed, male Kunming mice (20–24 g) were used in the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On the test day, mice were dropped one at a time into a plexiglass cylinder (height 25 cm, diameter 10 cm^3) containing 10 cm of water at 23–25°C. On this day, mice were assigned into different groups (n = 10 for each group). The synthesized compounds (10 mg/kg) and Fluoxetine as a reference antidepressant drug (10 mg/kg) were suspended in a 0.5% aqueous solution of methylcellulose injected intraperitoneally (*ip*) in a standard volume of 0.05 ml/20 g body weight, 30 min prior to the test. Control animal received 0.5% aqueous solution of methylcellulose. Then, the mice were dropped individually into the plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements in order to prevent sinking. The duration of immobility was recorded during the last 4 min of the 6 min test.

Tail suspension test (TST)

The tail suspension test was based on the method of Steru *et al*. (1985). Briefly, each mouse was individually suspended by its tail using a clamp (2 cm from the end) for 6 min in a box (25 × 25 × 30 cm) with the head 5 cm from the bottom. Testing was carried out in a darkened room with minimal background noise. On this day, mice were assigned into different groups (*n* = 10 for each group). The synthesized compounds (10 mg/kg) and Fluoxetine as a reference antidepressant drug (10 mg/kg) were suspended in a 0.5% aqueous solution of methylcellulose injected intraperitoneally (*ip*) in a standard volume of 0.05 ml/20 g body weight, 30 min prior to the test. Control animal received 0.5% aqueous solution of methylcellulose. 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.

Statistical analysis

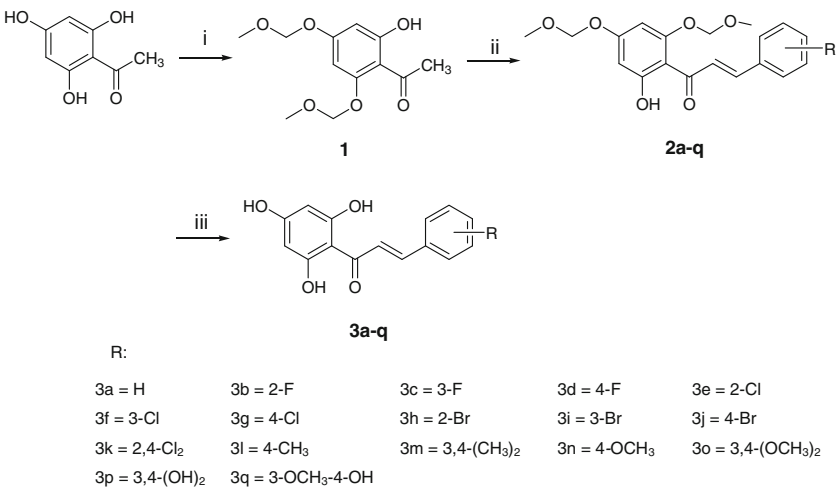
Results are expressed as mean ± SEM; *n* represents the number of animals. Data obtained from pharmacological experiments were analyzed with one-way analysis of variance (ANOVA) followed by Dunnet's post hoc test, using Pharmacologic Calculation System Version 4.1. (Microcomputer Specialists). A *P*-value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

Results and discussion

The target compounds **3a–q** was synthesized according to Scheme 1. Compound **1** (1-(2-hydroxy-4,6-bismethoxymethoxy-phenyl)-ethanone was prepared as reported previously (Raiendra Prasad *et al*., 2005). Intermediates **2a–q** was prepared by Claisen–Schmidt condensation of **1** with appropriate aromatic aldehydes or hydroxyaromatic aldehydes, protected as chloromethyl methyl ether (Raiendra Prasad *et al*., 2005; Zhao *et al*., 2005; Nishida *et al*., 2007). Then intermediates **2a–q** were treated with 3 M HCl in methanol to yield the hydroxychalcones **3a–q** in good yield.

First, the forced swimming test is a behavioral test used to predict the efficacy of antidepressant treatments (Porsolt *et al*., 1977). It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants (Porsolt, 1981). It has good predictive value for antidepressant potency in humans (Willner and Mitchell, 2002). The obtained data on the antidepressant activity of the compounds and reference drug are given in Table 1. In our study, all of the compounds except **3a**, **3c**, **3d**, **3e**, **3j**, **3l**, **3m**, **3n**, and **3o** significantly reduced the duration of immobility time at 10 mg/kg compared to control ($P < 0.05$, $P < 0.01$, or $P < 0.001$, Table 1). Among the compounds, **3h** (2-bromo-2′,4′,6′-trihydroxychalcone) was the most antidepressant activity and significantly reduced the duration of immobility times at 10 mg/kg dose level when compared to the control ($P < 0.001$).

Analyzing the antidepressant activities of synthesized compounds **3a–q**, the following SAR was gained. From compounds **3b–j**, as halogen substituted on B ring of chalcone compounds, alternating variations of activity were observed. The atom Br gave more contribution to the antidepressant activity than atoms F and Cl, the rank of activity order of halogen substituted derivatives was Br > Cl > F. Among the compounds, **3h** (2-bromo-2′,4′,6′-trihydroxychalcone) showed the most antidepressant activity, which reduced immobility time by 50.04% at 10 mg/kg compared with the same dose of Fluoxetine (58.68%), and compared with the leading compound



Scheme 1 The synthesis route of target compounds **3a–q**. Reagents and conditions:(i) $ClCH_2OCH_3$, K_2CO_3, acetone; (ii) aromatic aldehyde, KOH, EtOH; (iii) 3 M HCl, MeOH

Table 1 Antidepressant activities of the compounds

Compounds	R	Dose (mg/kg)	Antidepressant activities	
			Duration of immobility (s) (mean ± SEM)	Change from control (%)
I	–	10	99.3 ± 15.1*	−28.51
3a	H	10	121.6 ± 17.4	−14.23
3b	2-F	10	92.3 ± 12.9**	−33.55
3c	3-F	10	115.0 ± 14.0	−17.21
3d	4-F	10	132.8 ± 15.8	−4.39
3e	2-Cl	10	112.9 ± 11.6	−18.72
3f	3-Cl	10	100.6 ± 13.0**	−27.57
3g	4-Cl	10	101.3 ± 14.4*	−27.07
3h	2-Br	10	69.4 ± 9.1***	−50.04
3i	3-Br	10	101.9 ± 12.0**	−26.64
3j	4-Br	10	112.1 ± 15.1	−19.29
3k	$2,4\text{-}Cl_2$	10	100.8 ± 14.5*	−27.43
3l	$4\text{-}CH_3$	10	114.8 ± 12.8	−17.35
3m	$3,4\text{-}(CH_3)_2$	10	120.4 ± 13.5	−13.31
3n	$4\text{-}OCH_3$	10	123.5 ± 14.7	−11.09
3o	$3,4\text{-}(OCH_3)_2$	10	114.3 ± 15.2	−17.57
3p	$3,4\text{-}(OH)_2$	10	98.5 ± 11.0**	−29.09
3q	$3\text{-}OCH_3\text{-}4\text{-}OH$	10	107.1 ± 11.6**	−22.89
Fluoxetine		10	57.4 ± 8.9***	−58.68
Control		–	138.9 ± 25.3	–

Values represent the mean ± SEM ($n = 10$)

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

I exhibited enhanced antidepressant activity. In addition, the position of halogen substituted on the phenyl ring greatly influenced the antidepressant activity, compared with the derivatives with different F-substituted positions on phenyl ring, their rank of activity order was 2-F > 3-F > 4-F. The rank of activity order of the Cl-substituted derivatives was 3-Cl > $2,4\text{-}Cl_2$ > 4-Cl > 2-Cl. The rank of activity order of the Br-substituted derivatives was 2-Br > 3-Br > 4-Br.

Next, the influence of the electron-donor group with antidepressant activity was compared (Table 1). Their contribution order was $3,4\text{-}(OH)_2$ > 4-OH (**I**) > $3\text{-}OCH_3$-4-OH > $3,4\text{-}(OCH_3)_2$ > $4\text{-}CH_3$ > H > $3,4\text{-}(CH_3)_2$ > $4\text{-}OCH_3$. Comparing with the compound **3a**, compounds **3p**,

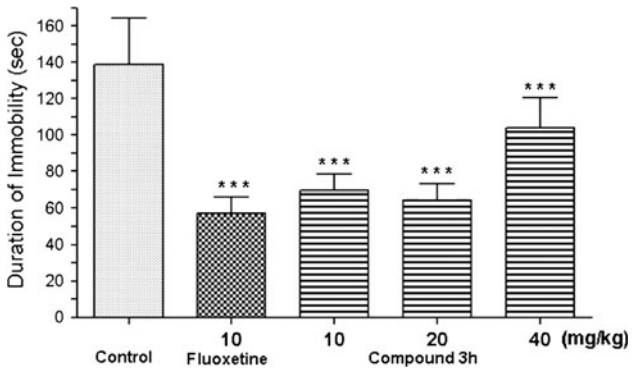


Fig. 2 Immobility time of compound **3h** in mouse FST. Data expressed as mean ± SEM ($n = 10$). Statistical analysis of data was carried out by one-way analysis of variance followed by the *t*-test. ***$P < 0.001$ versus control

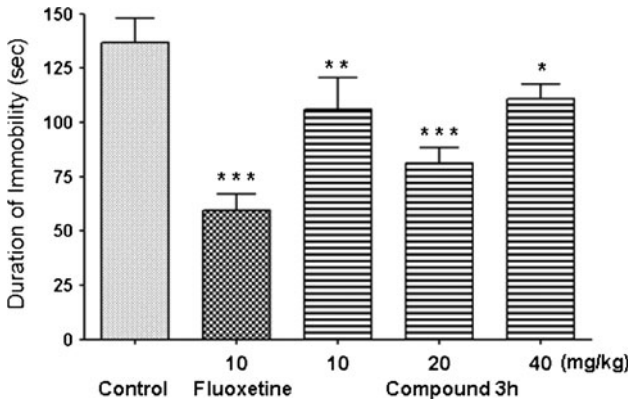


Fig. 3 Immobility time of compound **3h** in mouse TST. Data expressed as mean ± SEM ($n = 10$). Statistical analysis of data was carried out by one-way analysis of variance followed by the *t*-test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus control

3q, and **I** had potent antidepressant effects, and it seemed that the increase of hydroxyl group on chalcone B ring could influence activity. The similar result had been reported that the number of hydroxyl group influenced activity (Husan *et al*., 1987).

Finally, as shown in Fig. 2, immobility in the FST was significantly reduced after treatment with all three doses of compound **3h**, similar to the positive Fluoxetine, indicating a significant antidepressant-like effect. The decrease in immobility time in the TST showed similarity to that seen in the FST, See Fig. 3. 20 mg/kg showed most significant activity among three doses of **3h** in both tests. Both forced swimming and tail suspension tests are the accepted stress models of depression. Immobility has been shown to reflect a state of 'behavioral despair and variants' or 'failure to adapt to stress' (Borsini *et al*., 1986; Willner, 1991). Immobility displayed in both of these behavioral despair models has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. There was a significant correlation between clinical potency and the potency of antidepressant in both models. The compound **3h** produced significant antidepressant-like activity in both the FST and TST in mice, which indicates that compound **3h** has some antidepressant effects.

Conclusion

In conclusion, a series 2′,4′,6′-trihydroxychalcone derivatives were synthesized and their antidepressant activities was evaluated. The results showed that compound **3h** (2-bromo-2′,4′,6′-trihydroxy-chalcone) was the most promising compound and significantly reduced the duration of immobility times at 10 mg/kg dose level when compared to the control ($P < 0.001$) in the FST and the TST. Further studies should be initiated to reveal the mechanism of the antidepressant-like effect of the compound **3h**.

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