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Synthesis and Studies on Antidepressant Effect of 5,7-Dihydroxyflavanone Derivatives

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A series of 5,7-dihydroxyflavanone derivatives were synthesized and evaluated their antidepressant activities. The results showed that of nine compounds significantly reduced times during the forced swimming test at a dose of 10 mg/kg, indicative of antidepressant activity. Among the compounds, **4o** (4′-methoxy-5,7,3′-trihydroxyflavanone) was found to be the most potent and it was observed that the compound **4o** at dose of 10, 20 and 40 mg/kg significantly reduced the duration of immobility times in the Forced swimming test in mice 0.5 h after treatment.

Key Words: 5,7-Dihydroxyflavanone derivatives, Synthesis, Antidepressant activity

INTRODUCTION

Major depressive disorder was ranked by the World Health Organization (WHO) as the fourth greatest cause of illness burden in the year 2000 and projection indicate that by the year 2020 it will become the second leading cause of disease worldwide, occupying the first position among psychiatric disorders[1-4]. It is a serious disorder with an estimate of life-time prevalence as high as 20 % and a significant number of patients (30 %) do not respond to current medical treatment[5,6]. Most of these drugs, however, have undesirable side effects. Thus, there is an unmet need for new antidepressants.

In recent years, it was reported that flavonoids possessed antidepressant activities[7-9]. Apigenin (5,7,4′-trihydroxy-flavoniod) (Fig. 1), one type of bioflavonoid widely found in citrus fruit, was found to exert a variety of pharmacological actions on the central nervous system, such as anxiolytic and sedative properties[10,11]. Lorenzo and Han *et al.* reported that apigenin possessed antidepressant-like effect[12,13]. In addition, other reports demonstrated that apigenin exhibited antidepressant activity[14,15]. Flavanones are a group of flavonoids, analyzing the structure of apigenin, 2,3-positions on C-ring was hydrogenated, the flavanone compound **I** (5,7,4′-trihydroxyflavanone) was obtained and examined it antidepressant activity. The results showed that compound **I** significantly reduced the duration of immobility times at 10 mg/kg dose level when compared to the control ($p < 0.01$), indicative of antidepressant activity.

In order to obtain compounds with better antidepressant activity, in this paper, we designed and synthesized a series of 5,7-dihydroxyflavanone derivatives using compound **I** as the lead compound. The antidepressant activities of the synthesized compounds were also determined by using Porsolt's behavioural despair (Forced Swimming Test: FST)[16]. The synthesized compounds were characterized by IR, ^{1}H NMR and MS.

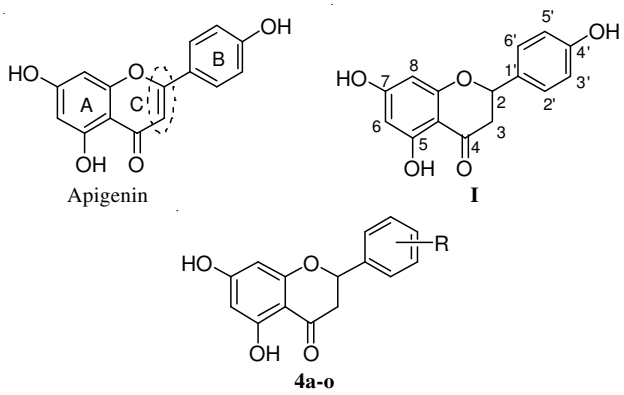


Fig. 1. Structures of compounds apigenin, **I** and **4a-o**

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 tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Alderich Chemical Corporation. All other chemicals were the analytical grade.

Synthesis of 2′-hydroxy-3-fluoro-4′,6′-*bis*(methoxymethoxy)chalcone (2b): To a stirred solution of KOH (2.0 g, 45.6 mmol) in water (2 mL) cooled to 0 ºC in an ice bath was added dropwise a solution of 2-hydroxy-4,6-*bis*methoxymethoxyactetophenone (1.0 mmol) and 3-fluoro-benzaldehyde (2.0 mmol) in ethanol under nitrogen. The reaction mixture was kept at 0 ºC for 3 h and at room for 24 h. The mixture was poured into ice-water, adjusted to pH 2-3 with 1 M HCl and the extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$[17-19]. After removing solvents, products were purified by silica gel column chromatography (petroleum ether:ethyl acetate = 6:1). The yellow solid was obtained. Yield 70 %; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 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, 1636; MS: m/z [M + 1] 363.

Synthesis of 3′-methoxy-4′-hydroxy-5,7-*bis*(methoxymethoxy-flavanone (3o): A stirred solution of **2o** and sodium acetate in 5 mL ethanol containing three drops of water was refluxed for 24 h. The mixture was poured into cold water and extracted with ethyl ether. The organic phase was washed with brine, dried over anhydrous $MgSO_4$. After removing solvents, products were purified by silica gel column chromatography (petroleum ether:ethyl acetate = 4:1)[20,21]. The pale yellow solid was obtained. Yield 73 %; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.66 (1H, dd, *J* = 16.5, 2.3 Hz, 3-H), 2.78 (1H, dd, *J* = 12.1, 16.5 Hz, 3-H), 2.98 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 5.18 (s, 2H, -OCH_2O-), 5.28 (s, 2H, -OCH_2O-), 5.36 (1H, dd, *J* = 12.1, 2.3 Hz, 2-H), 6.41-7.20 (m, 5H, Ar-H), 10.25 (s, H, -OH),; IR (KBr) cm^{-1}: 2963, 1676; MS: m/z [M + 1] 435.

General procedure for the preparation of compounds (4a-o): In a round-bottomed flask, to a stirred solution of chalcones **3a-o** (0.25 mmol) in methanol was added dropwise 5 M HCl, the mixture was refluxed for 0.5 h. 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 are given below.

2′-Fluoro-5,7-dihydroxyflavanone (4a): Yield 37 %; m.p. 182-184 ºC; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.78 (1H, dd, *J* = 17.0, 2.8 Hz, 3-H), 3.37 (1H, dd, *J* = 12.8, 17.0 Hz, 3-H), 5.81 (1H, dd, *J* = 12.8, 2.8 Hz, 2-H), 5.92-7.67 (m, 6H, Ar-H), 10.85 (s, H, -OH), 12.11 (s, H, -OH); IR (KBr) cm^{-1}: 3117, 1637; MS: m/z [M + 1] 275.

3′-Fluoro-5,7-dihydroxyflavanone (4b): Yield 34 %; m.p. 164-166 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.78 (1H, dd, *J* = 16.8, 2.9 Hz, 3-H), 3.37 (1H, dd, *J* = 12.8, 16.8 Hz, 3-H), 5.81 (1H, dd, *J* = 12.8, 2.9 Hz, 2-H), 5.91-7.50 (m, 6H, Ar-H), 10.86 (s, H, -OH), 12.10 (s, H, -OH); IR (KBr) cm^{-1}: 3115, 1638; MS: m/z [M + 1] 275.

4′-Fluoro-5,7-dihydroxyflavanone (4c): Yield 41 %; m.p. 138-140 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.78 (1H, dd, *J* = 17.0, 3.0 Hz, 3-H), 3.28 (1H, dd, *J* = 12.7, 17.0 Hz, 3-H), 5.60 (1H, dd, *J* = 12.7, 3.0 Hz, 2-H), 5.91-7.60 (m, 6H, Ar-H), 10.83 (s, H, -OH), 12.12 (s, H, -OH); IR (KBr) cm^{-1}: 3118, 1639; MS: m/z [M + 1] 275.

2′-Chloro-5,7-dihydroxyflavanone (4d): Yield 40 %; m.p. 232-234 ºC; ^{1}H NMR 300 MHz, DMSO-d_6, TMS): δ 2.78 (1H, dd, *J* = 17.1, 2.9 Hz, 3-H), 3.27 (1H, dd, *J* = 13.1, 17.1 Hz, 3-H), 5.84 (1H, dd, *J* = 13.1, 2.9 Hz, 2-H), 5.93-7.75 (m, 6H, Ar-H), 10.88 (s, H, -OH),12.08 (s, H, -OH); IR (KBr) cm^{-1}: 3115, 1638; MS: m/z [M + 1] 291.

3′-Chloro-5,7-dihydroxyflavanone (4e): Yield 48 %; m.p. 221-222 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.82 (1H, dd, *J* = 17.0, 2.9 Hz, 3-H), 3.30 (1H, dd, *J* = 12.6, 17.0 Hz, 3-H), 5.62 (1H, dd, *J* = 12.6, 2.9 Hz, 2-H), 5.92-7.61 (m, 6H, Ar-H), 10.86 (s, H, -OH), 12.10 (s, H, -OH); IR (KBr) cm^{-1}: 3114, 1639; MS: m/z [M + 1] 291.

4′-Chloro-5,7-dihydroxyflavanone (4f): Yield 50 %; m.p. 231-232 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.83 (1H, dd, *J* = 17.0, 2.9 Hz, 3-H), 3.32 (1H, dd, *J* = 12.6, 17.0 Hz, 3-H), 5.65 (1H, dd, *J* = 12.6, 2.9 Hz, 2-H), 5.93-7.63 (m, 6H, Ar-H), 10.87 (s, H, -OH), 12.09 (s, H, -OH); IR (KBr) cm^{-1}: 3112, 1637; MS: m/z [M + 1] 291.

2′-Bromo-5,7-dihydroxyflavanone (4g): Yield 45 %; m.p. 236-238 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.79 (1H, dd, *J* = 17.1, 2.9 Hz, 3-H), 3.31 (1H, dd, *J* = 13.1, 17.1 Hz, 3-H), 5.75 (1H, dd, *J* = 13.1, 2.9 Hz, 2-H), 5.94-7.74 (m, 6H, Ar-H), 10.88 (s, H, -OH), 12.06 (s, H, -OH); IR (KBr) cm^{-1}: 3116, 1638; MS: m/z [M + 1] 334.

3′-Bromo-5,7-dihydroxyflavanone (4h): Yield 48 %; m.p. 226-228 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.81 (1H, dd, *J* = 17.1, 3.0 Hz, 3-H), 3.25 (1H, dd, *J* = 12.7, 17.1 Hz, 3-H), 5.61 (1H, dd, *J* = 12.7, 3.0 Hz, 2-H), 5.91-7.74 (m, 6H, Ar-H), 10.86 (s, H, -OH), 12.10 (s, H, -OH); IR (KBr) cm^{-1}: 3115, 1637; MS: m/z [M + 1] 334.

4′-Bromo-5,7-dihydroxyflavanone (4i): Yield 51 %; m.p. 210-212 ºC; ^{1}H NMR 300 MHz, DMSO-d_6, TMS): δ 2.80 (1H, dd, *J* = 17.1, 3.0 Hz, 3-H), 3.21 (1H, dd, *J* = 12.7, 17.1 Hz, 3-H), 5.60 (1H, dd, *J* = 12.7, 3.0 Hz, 2-H), 5.90-7.90 (m, 6H, Ar-H), 10.87 (s, H, -OH), 12.11 (s, H, -OH); IR (KBr) cm^{-1}: 3117, 1638; MS: m/z [M + 1] 334.

3′-Trifluoro-5,7-dihydroxyflavanone (4j): Yield 43 %; m.p. 234-236 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.86 (1H, dd, *J* = 17.1, 2.9 Hz, 3-H), 3.24 (1H, dd, *J* = 12.8, 17.1 Hz, 3-H), 5.59 (1H, dd, *J* = 12.8, 2.9 Hz, 2-H), 5.92-7.90 (m, 6H, Ar-H), 10.87 (s, H, -OH), 12.11 (s, H, -OH); IR (KBr) cm^{-1}: 3117, 1638; MS m/z: 325 [M + 1].

2′,4′-Dichloro-5,7-dihydroxyflavanone (4k): Yield 41 %; m.p. 236-237 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 2.86 (1H, dd, *J* = 17.1, 2.9 Hz, 3-H), 3.24 (1H, dd, *J* = 13.1, 17.1 Hz, 3-H), 5.59 (1H, dd, *J* = 13.1, 2.9 Hz, 2-H), 5.93-7.76 (m, 5H, Ar-H), 10.86 (s, H, -OH), 12.12 (s, H, -OH); IR (KBr) cm^{-1}: 3115, 1637; MS: m/z [M + 1] 325.

5,7-Dihydroxyflavanone (4l): Yield 65 %; m.p. 168-170 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): 2.78 (1H, dd, *J* = 17.1, 2.8 Hz, 3-H), 3.24 (1H, dd, *J* = 12.8, 17.1 Hz, 3-H),

5.59 (1H, dd, *J* = 12.8, 2.8 Hz, 2-H), 5.90-7.53 (m, 7H, Ar-H), 10.83 (s, H, -OH), 12.13 (s, H, -OH); IR (KBr) cm^{-1}: 3116, 1639; MS m/z: 257 [M + 1].

4′-Methyl-5,7-dihydroxyflavanone (4m): Yield 75 %; m.p. 196-197 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): 2.34 (s, 3H, CH_3), 2.60 (1H, dd, *J* = 16.5, 2.9 Hz, 3-H), 3.29 (1H, dd, *J* = 12.4, 16.5 Hz, 3-H), 5.46 (1H, dd, *J* = 12.4, 2.9 Hz, 2-H), 5.94-7.36 (m, 6H, Ar-H), 10.81 (s, H, -OH), 12.16 (s, H, -OH); IR (KBr) cm^{-1}: 3116, 1638; MS: m/z [M + 1]271.

4′-Methoxy-5,7-dihydroxyflavanone (4n): Yield 79 %; m.p. 198-200 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): 2.64 (1H, dd, *J* = 16.8, 2.8 Hz, 3-H), 3.31 (1H, dd, *J* = 12.4, 16.8 Hz, 3-H), 3.76 (s, 3H, OCH_3), 5.44 (1H, dd, *J* = 12.4, 2.8 Hz, 2-H), 5.88-7.44 (m, 6H, Ar-H), 10.78 (s, H, -OH), 12.13 (s, H, -OH); IR (KBr) cm^{-1}: 3118, 1641; MS: m/z [M + 1] 287.

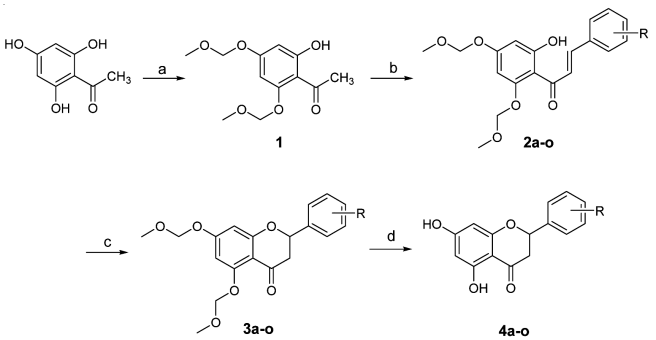
4′-Methoxy-5,7,3′-trihydroxyflavanone (4o): Yield 76 %; m.p. 228-230 ºC; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): 2.67 (1H, dd, *J* = 17.0, 2.9 Hz, 3-H), 3.38 (1H, dd, *J* = 12.4, 17.0 Hz, 3-H), 3.78 (s, 3H, OCH_3), 5.42 (1H, dd, *J* = 12.4, 2.9 Hz, 2-H), 6.77-7.09 (m, 5H, Ar-H), 9.15 (s, H, -OH), 10.79 (s, H, -OH), 12.15 (s, H, -OH); IR (KBr) cm^{-1}: 3196, 1668; MS: m/z [M + 1] 303.

Forced swimming test (FST): The synthesized compounds were screened for their antidepressant activity using Porsolt's behavioural despair (forced swimming) test[16]. 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 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 23-25 ºC[22]. 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, 0.5 h prior to the test. Control animal received 0.5 % aqueous solution of methylcellulose. 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. 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.

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 **4a-o** was synthesized according to **Scheme-I**. Compound **1** was prepared as reported previously[17]. Intermediates **2a-o** was prepared by Claisen-Schmidt condensation of **1** with appropriate aromatic aldehydes or hydroxyaromatic aldehydes, protected as chloromethyl methyl ether[17-19]. Then intermediates **2a-o** was treated with NaOAc in ethanol to give compounds **3a-o**[20,21]. The derivatives **4a-o** was obtained with 5 M HCl in methanol in good yield.



R = **4a** = 2-F, **4b** = 3-F, **4c** = 4-F, **4d** = 2-Cl, **4e** = 3-Cl, **4f** = 4-Cl, **4g** = 2-Br, **4h** = 3-Br, **4i** = 4-Br, **4j** = 3-CF_3, **4k** = 2,4-Cl_2, **4l** = H, **4m** = 4-CH_3, **4n** = 4-OCH_3, **4o** = 3-OCH_3-4-OH

Reagents & conditions: (a) $ClCH_2OCH_3$, K_2CO_3, acetone, 0 ºC to room temperature; (b) aromatic aldehyde, 10 % KOH, EtOH; (c) NaOAc, EtOH, reflux; (d) 5 M HCl, MeOH, reflux

Scheme-I: Synthesis route of target compounds **4a-o**

Pharmacological evaluations: First, the forced swimming test is a behavioural test used to predict the efficacy of antidepressant treatments[16]. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and a typical antidepressants[23]. It has good predictive value for antidepressant potency in humans[24]. The obtained data on the antidepressant activity of the compounds and reference drug are given in Table-1. In present study, all of the compounds except **4a**, **4b**, **4f**, **4g**, **4j**, **4l** and **4n** 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

TABLE-1
ANTIDEPRESSANT ACTIVITIES OF THE COMPOUNDS

Compd.	R	Dose (mg/kg)	Antidepressant activities	
			Duration of immobility (s) (mean±SEM)	Change from control (%)
I	–	10	102.4±15.3**	-27.38
4a	2-F	10	118.1±20.0	-16.24
4b	3-F	10	123.8±18.2	-12.20
4c	4-F	10	104.1±15.4**	-26.17
4d	2-Cl	10	120.3±19.2*	-14.68
4e	3-Cl	10	103.9±18.9**	-26.31
4f	4-Cl	10	120.9±16.4	-14.26
4g	2-Br	10	124.4±10.1	-11.77
4h	3-Br	10	113.9±17.4**	-19.22
4i	4-Br	10	113.3±20.9*	-19.66
4j	3-CF_3	10	129.5±8.7	-8.16
4k	2,4-Cl_2	10	98.1±18.9**	-30.43
4l	4-H	10	121.6±17.1	-13.76
4m	4-CH_3	10	108.0±18**	-23.40
4n	4-OCH_3	10	110.0±15.7	-21.99
4o	3-OCH_3-4-OH	10	92.2±17.3***	-34.61
Fluoxetine		10	70.3±5.8***	-50.14
Control		–	141.0±14.2	–

Values represent the mean ± SEM (n = 10).
*Significantly compared to control (Dunnet's test: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)

the compound **4o** (4′-methoxy-5,7,3′-trihydroxyflavanone) 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 **4a-o**, the following structural activity relation was gained. From compounds **4a-k**, as halogen substituted on B ring of flavanone compounds, alternating variations of activity were observed. The atom Cl gave more contribution to the antidepressant activity than atom F and Br, the rank of activity order of halogen substituted derivatives was Cl > Br > F. Among the compound **4k** (2′,4′-dichloro-5,7-dihydroxyflavanone) showed the most antidepressant activity, which reduced immobility time by 30.43 % at 10 mg/kg. 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 4-F > 2-F > 3-F. The rank of activity order of the Cl-substituted derivatives was 2,4-Cl_2 > 3-Cl > 2-Cl > 4-Cl. The rank of activity order of the Br-substituted derivatives was 3-Br > 4-Br > 2-Br.

Compared the influence of electron-donor group to antidepressant activity (Table-1), their contribution order is 3-OCH_3-4-OH > **I** (4-OH) > 4-CH_3 > 4-OCH_3 > -H. The compound **4o** revealed better antidepressant activity at 10 mg/kg dose level when compared to the control ($P < 0.001$). Comparing with the compound **4l**, compounds **4m**, **4o** and **I** had potent antidepressant effects. It seemed that the increase of hydroxyl group on flavanone B ring could influence activity. The similar result had been reported that the number of hydroxyl group influenced activity[25].

Finally, as shown in Fig. 2, immobility in the Forced swimming test was significantly reduced after treatment with all three doses of compound **4o**, similar to the positive fluoxetine, indicating a significant antidepressant-like effect. 10 mg/kg showed most significant activity among three doses of **4o** in test. The forced swimming is the accepted stress models of depression. Immobility has been shown to reflect a state of 'behavioural despair and variants' or 'failure to adapt to stress'[26,27]. Immobility displayed in the behavioural despair models have been hypothesized to reflect behavioural despair which in turn may reflect depressive disorders in human. There was a significant correlation between clinical potency and the potency of antidepressant in both models. The compound **4o** produced significant antidepressant-like activity in the Forced swimming test in mice, which indicates compound **4o** has some antidepressant effects.

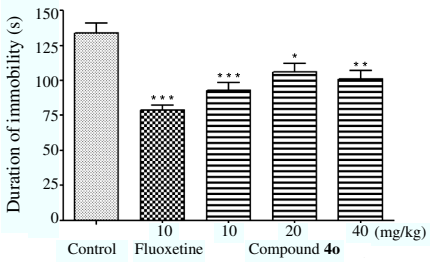


Fig. 2. Immobility time of compound **4o** in mouse FST. Data expressed as mesn ± SEM (n = 8); statistical analysis of data was carried out by one-way analysis of variance followed by the t-test; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ *vs.* control

Conclusion

A series of 5,7-dihydroxyflavanone derivatives were synthesized and evaluated their antidepressant activities. The results showed that compound **4o** (4′-methoxy-5,7,3′-trihydroxyflavanone) 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 Forced swimming test. Further studies should be initiated to reveal the mechanism of the antidepressant-like effect of the compound **4o**.

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