SYNTHESIS OF 2-ARYL-4-(4-β-D-ALLOPYRANOSYLOXYPHENYL)-4,6,7,8-TETRAHYDROQUINOLIN-5(1*H*)-ONE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS AND STUDY OF SEDATIVE ACTIVITY

Congling Yang,[1] Shiming Lv,[2] Ying Li,[2] and Shufan Yin[2]*

UDC 547.74+547.589

*Under solvent-free conditions, syntheses of 2-aryl-4-(4-β-D-allopyranosyloxyphenyl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one derivatives were carried out from chalcone (**2a–2e**), cyclohexane-1,3-dione (**3**), and NH_4OAc in excellent yield without using any catalysts. The structure of the new compounds were characterized by ^1H NMR, IR, and HR-MS spectroscopy. The preliminary bioassay tests of **4a–4j** indicated that compounds **4b**, **4e**, and **4f** exhibited potent sedative and hypnotic activity.*

Keywords: chalcone, 4,6,7,8-tetrahydroquinolin-5(1*H*)-one, solvent-free, sedative-hypnotic activity.

The natural compound helicid (**1**) [4-formylphenyl-β-D-allopyranoside, $C_{13}H_{16}O_7$], extracted from the fruit of *Helicia nilagirica* Beed [1], distributed widely in Yunnan Province of China, is a major active ingredient of Chinese herb medicine. It has been reported that helicid possesses a variety of biological effects on the central nervous system such as sedative, hypnotic, and anticonvulsant activity; moreover no obvious side effect has been reported [2]. However, the drug also shows some disadvantage, including large dose and low bioavailability. Our work focuses on epigenetic modifications at the aldehyde group of helicid in order to improve its pharmacological and therapeutic activity [3–6].

4-Substituted 1, 4-dihydroquinolines are analogues of NADH coenzymes that exhibit a wide range of biological and pharmacological properties such as antihypertensive, anticonvulsant, etc. [7, 8]. Therefore, there has been intense research activity in this area recently, leading to the development of many methods for the synthesis of hydroquinoline derivatives [9, 10]. Nevertheless, these methods often involved harsh conditions, long reaction times, unsatisfactory yields, and amounts of organic solvents, which are usually volatile, flammable, toxic, and thus environmentally hazardous. Keeping in view the biological importance of the hydroquinoline and our ongoing endeavors in the development of environmental benign tactics, we now choose a solid state approach without catalyst [11]. Herein, we reported the solvent-free synthesis of hydroquinoline derivatives **4a–4j** by the reaction of different chalcones **2a–2e** from helicid with cyclohexane-1,3-dione (or 5,5-dimethyl-cyclohexane-1,3-dione) **3** in the presence of ammonium acetate, as shown in Scheme 1. The sedative-hypnotic activities of the target compounds were evaluated, and the result showed that derivatives **4b**, **4e**, **4h**, and **4f** showed good activities.

First, we examined the feasibility of the present procedure using *E*-(4-β-D-allopyranosyloxyphenyl)-1-phenyl-propenone **2a** as a model substrate. Compound **2a**, ammonium acetate, and cyclohexane-1, 3-dione **3** were mixed together and heated at 80°C in the absence of solvent for 3 h. However, subsequent TLC analyses showed that the reaction resulted in a complicated mixture with a mere 27% yield. As an alternative, we first heated the mixture of ammonium acetate and cyclohexane-1, 3-dione **3**. After half an hour, TLC analyses indicated that the reactants were consumed completely and an enamine intermediate was formed. Then, after adding **2a**, the mixture was heated constantly (monitored by TLC). Finally, when the reaction was prolonged for 3 h, a wonderful conversion of the reactans took place, with the desired product **4a** obtained in 84% yield. We did some comparative experiments where the reaction was performed at different temperatures 75°, 80°, and 85° with 70%, 84%, and 73% yields, respectively; we found that 80° was the best choice. Then, we extended the one-pot three-component condensation reaction to the other chalcones **2a–2e** and to 5,5-dimethylcyclohexane-1,3-dione. The results are summarized in Table 1.

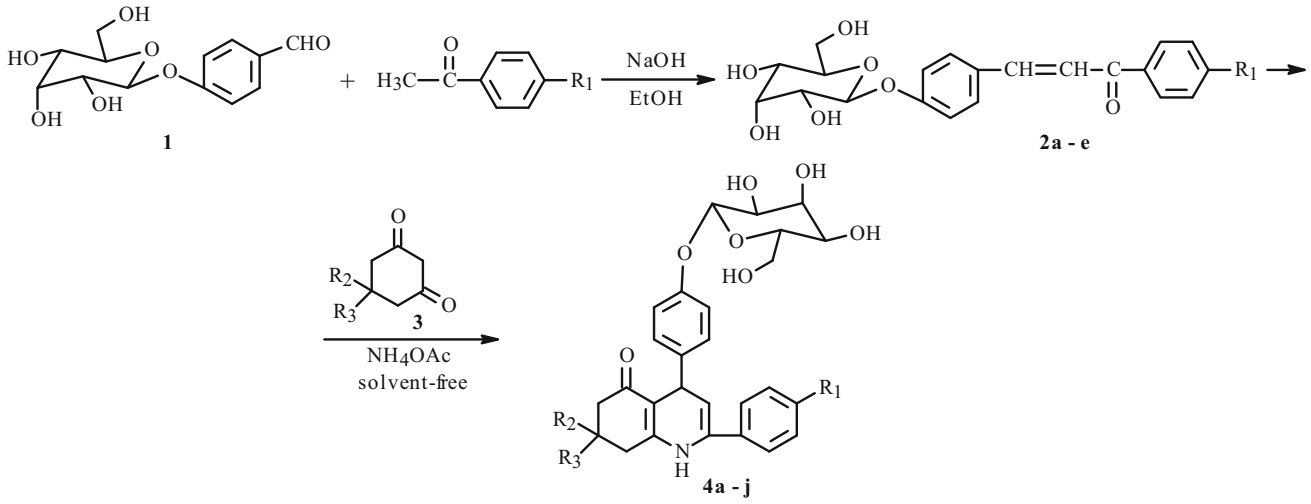
1) College of Chemical and Material Science, Sichuan Normal University, Chengdu 610066; 2) College of Chemistry, Sichuan University, Chengdu 610064, China, e-mail: chuandayouji217@163.com. Published in Khimiya Prirodnykh Soedinenii, No. 6, pp. 775–778, November–December, 2010. Original article submitted June 9, 2009.

 0009-3130/11/4606-0910

TABLE 1. The Sedative-hypnotic Activities of the Target Compounds Evaluated Using the Spontaneous Locomotor Activity Test

Compound	Number of movements per minute (movements/min)			
	initial	after 30 min	after 60 min	after 90 min
A	215.83±32.37	211.83±26.48	223.00±26.09	216.00±28.10
B	228.50±31.63	4.17±3.64***	1.67±2.73**	1.50±2.26***
1	232.33±38.53	199.17±20.80	168.00±24.22	130.21±29.23
4a	227.83±38.37	212.33±81.28	171.00±91.88	152.67±36.63
4b	239.83±10.83	101.00±22.29*	57.67±21.15**	86.67±19.35*
4c	226.83±30.97	192.50±25.95	151.67±41.63	142.67±33.51
4d	229.50±38.35	215.00±53.57	147.67±83.83	106.00±50.01*
4e	230.00±52.28	132.00±52.89	174.50±11.55	91.00±30.02*
4f	232.00±21.51	168.17±39.60	142.00±83.07	83.00±62.18*
4g	207.33±58.88	172.33±94.56	158.83±93.17	140.83±117.64
4h	231.17±21.41	159.17±80.16	107.83±79.51*	90.83±95.04*
4i	231.67±21.15	174.17±45.45	151.50±69.20	118.17±39.43
4j	226.50±29.52	150.83±96.01	109.33±98.52	141.83±95.80

Dose of **1** and **4a–4j**: 200 mg·kg^{-1}. Dose of A: –; dose of B: 20 mg·kg^{-1}.
Values are means ± S.
*P < 0.05, **P < 0.01, ***P < 0.001 compared with A, A: saline, B: diazepam, **1**: helicid.



1 **2a - e** **3** **4a - j**

2a: R_1 = H; **2b:** R_1 = Me; **2c:** R_1 = F; **2d:** R_1 = Cl; **2e:** R_1 = Br; **4a, 4f:** R_1 = H; **4b, 4g:** R_1 = Me
4c, 4h: R_1 = F; **4d, 4i:** R_1 = Cl; **4e, 4j:** R_1 = Br; **4a - 4e:** $R_2 = R_3$ = H; **4f - 4j:** $R_2 = R_3$ = Me

Scheme 1

Herein, ten novel helicid derivatives **4a–4j** have been successfully synthesized under solvent-free conditions with good yields (75–85%). It is remarkable that the electronic property of the aromatic ring of chalcones has some effects on the rate of the condensation reaction. Substrates bearing electron-withdrawing groups on the aromatic ring require shorter reaction times [**4c–4e** (3, 32, 3.5 h), **4h–4j** (3.5, 4.0, 4.4 h)], while substrates bearing electron-donating groups afford the corresponding products with satisfactory yields but requiring longer reaction times to complete the total reaction [**4a**, **4b**, **4f**, **4g** (4, 4.5, 5, 5.6 h)].

In summary, ten novel helicid derivatives were successfully synthesized, characterized, and tested for sedative-hypnotic activity in our study (Table 1). These helicid derivatives can serve as lead compounds for designing new compounds possessing potential sedative-hypnotic activity with high selectivity, low toxicity, and additional pharmaceutical effects. Further study is now in progress.

EXPERIMENTAL

Materials. All reagents were purchased from commercial suppliers. Compounds **2a**, **2b**, **2d**, and **2e** were prepared according to the literature method [3]. Helicid was purchased from Yunnan Chemical Company, China. The solvents used were purified according to the standard methods. Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. ^{1}H NMR spectra were measured with a Bruker AV-400 MHz. IR spectra were measured with a Perkin–Elmer 16PC-FT infrared spectrometer. HR-MS spectra were measured with a Bruker Daltonics ESI-Bio TOF-Q mass spectroscope. Mice (Kunming strain) weighing 18–22 g were obtained from West China School of Pharmacy, Sichuan University (Chengdu, China). All samples were dissolved in 0.05% CMC from different concentrations of solutions for later use.

***E*-(4-β-D-Allopyranosyloxyphenyl)-1-(4-fluorophenyl)-propenone (2c)**. Under ice bath, to a solution of helicid (5 mmol) in 12 mL of 10% sodium hydroxide aqueous solution and 30 mL of anhydrous ethanol, 4-fluoroacetophenone (5.5 mmol) was added dropwise (monitored by TLC). At completion, the reaction mixture was neutralized with diluted hydrochloric acid (3 mol/L) and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave a crude product, which was recrystallized from ethanol (95%) to give a yellow crystal product **2c** in yield 86%, mp 108–110°C.

IR (KBr, ν, cm^{-1}): 3400, 3072, 2900, 1655, 1598, 1509, 1426, 1333, 1180, 1084, 1030, 870, 824. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.45–3.95 (6H, m), 4.51–5.11 (4H, br, 4OH), 5.20 (1H, d, J = 8.0, H-1), 6.87 (2H, d, J = 8.6, ArH), 7.16 (2H, d, J = 8.6, ArH), 7.62 (2H, d, J = 7.2, ArH), 7.73 (1H, d, J = 16.0, CH=CH), 7.83 (1H, d, J = 16.0, CH=CHCO), 8.24 (2H, d, J = 7.2, ArH), HR-MS-ESI *m/z* calcd for $C_{21}H_{22}O_7F$ $[M + H]^+$ 405.1344, found 405.1362.

General Procedure for the Preparation of Compounds 4a–4j. Cyclohexane-1,3-dione (or 5,5-dimethylcyclohexane-1,3-dione) **3** (1 mmol) and ammonium acetate (2.5 mmol) were mixed together and heated at 80°C in a 10 mL open flask for about 0.5 h. Then, **2** (1 mmol) was added and the mixture was exposed to continuous heating for a period of time sufficient to complete the reaction (monitored by TLC). After cooling to room temperature, the solid was transferred to a small amount of ethanol and then filtered. The obtained solid was washed three times with water to leave a crude product, which was purified by chromatography (MeOH–$CHCl_2$, 1:6, v/v) over silica gel to furnish the pure product **4**.

2-Phenyl-4-(4-β-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4a). This compound was prepared from **2a**, cyclohexane-1,3-dione, and ammonium acetate; yield 84%, yellow powder, mp 145–146°C.

IR (KBr, ν, cm^{-1}): 3399, 2951, 2926, 2887, 1666, 1590, 1485, 1389, 1227, 916, 847, 696. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.04–1.07 (2H, m, H-7), 2.09–2.20 (2H, m, H-8), 2.49–2.51 (2H, m, H-6) 3.43–3.90 (6H, m), 4.49–5.11 (4H, br, 4OH), 4.53 (1H, d, J = 5.6, H-4), 5.06 (1H, d, J = 5.6, H-3), 5.20 (1H, d, J = 8.0, H-1), 6.87 (2H, d, J = 8.0, ArH), 7.12 (2H, d, J = 8.0, ArH), 7.37–7.39 (3H, m, ArH), 7.48 (2H, d, J = 8.4, ArH), 8.67 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{27}H_{28}NO_7$ $[M - H]^-$ 478.1866, found 478.1858.

2-(4-Methylphenyl)-4-(4-β-*D*-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4b). This compound was prepared from **2b**, cyclohexane-1,3-dione, and ammonium acetate; yield 85%, yellow powder, mp 139–140°C.

IR (KBr, ν, cm^{-1}): 3387, 2953, 2926, 2887, 1660, 1597, 1485, 1391, 1232, 1036, 835, 696. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.03–1.23 (2H, m, H-7), 2.24 (3H, s, CH_3), 2.31–2.40 (2H, m, H-8), 2.47–2.49 (2H, m, H-6), 3.35–3.91 (6H, m), 4.34–4.52 (4H, br, 4OH), 4.50 (1H, d, J = 5.6, H-4), 5.05 (1H, d, J = 5.6, H-3), 5.17 (1H, d, J = 8.0, H-1), 6.88 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.20 (2H, d, J = 8.4, ArH), 7.38 (2H, d, J = 8.4, ArH), 8.62 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{28}H_{31}NNaO_7$ $[M + Na]^+$ 516.1998, found 516.1970.

2-(4-Fluorophenyl)-4-(4-β-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4c). This compound was prepared from **2c**, cyclohexane-1,3-dione, and ammonium acetate; yield 75%, yellow powder, mp 130–132°C.

IR (KBr, ν, cm^{-1}): 3332, 2958, 2926, 2887, 1660, 1595, 1486, 1391, 1229, 1037, 832, 615. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.03–1.07 (2H, m, H-7), 1.78–2.20 (2H, m, H-8), 2.45–2.50 (2H, m, H-6), 3.32–3.90 (6H, m), 4.63–5.10 (4H, br, 4OH), 4.70 (1H, d, J = 5.6, H-4), 5.06 (1H, d, J = 5.6, H-3), 5.17 (1H, d, J = 8.0, H-1), 6.89 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.30 (2H, d, J = 8.4, ArH), 7.52 (2H, d, J = 8.4, ArH), 8.69 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{27}H_{28}FNNaO_7$ $[M + Na]^+$ 520.1748, found 520.1669.

2-(4-Chlorophenyl)-4-(4-β-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4d). This compound was prepared from **2d**, cyclohexane-1,3-dione, and ammonium acetate; yield 80%, yellow powder, mp 150–151°.

IR (KBr, ν, cm^{-1}): 3375, 2933, 2926, 2871, 1660, 1596, 1485, 1392, 1230, 1037, 835, 762. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.82–1.90 (2H, m, H-7), 2.44–2.50 (2H, m, H-8), 2.59–2.64 (2H, m, H-6), 3.35–3.90 (6H, m), 4.60–5.11

(4H, br, 4OH), 4.62 (1H, d, J = 5.6, H-4), 5.06 (1H, d, J = 5.6, H-3), 5.24 (1H, d, J = 8.0, H-1), 6.89 (2H, d, J = 8.0, ArH), 7.12 (2H, d, J = 8.0, ArH), 7.44 (2H, d, J = 8.4, ArH), 7.53 (2H, d, J = 8.4, ArH), 8.69 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{27}H_{28}ClNNaO_7$ $[M + Na]^+$ 536.1452, found 536.1450.

2-(4-Bromophenyl)-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4e). This compound was prepared from **2e**, cyclohexane-1,3-dione, and ammonium acetate; yield 81%, yellow powder, mp 152–154°C.

IR (KBr, ν, cm^{-1}): 3361, 2953, 2926, 2887, 1654, 1594, 1485, 1444, 1391, 1078, 828, 619. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.03–1.07 (2H, m, H-7), 1.81–1.90 (2H, m, H-8), 2.50–2.65 (2H, m, H-6), 3.36–3.91 (6H, m), 4.52 (1H, d, J = 5.6, H-4), 4.59–5.12 (4H, br, 4OH), 5.04 (1H, d, J = 5.6, H-3), 5.25 (1H, d, J = 8.0, H-1), 6.88 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.45 (2H, d, J = 8.4, ArH), 7.57 (2H, d, J = 8.4, ArH), 8.71 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{27}H_{28}BrNNaO_7$ $[M + Na]^+$ 580.0947, found 580.0963.

7,7-Dimethyl-2-phenyl-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4f). This compound was prepared from **2a**, 5,5-dimethylcylohexane-1,3-dione, and ammonium acetate; yield 83%, yellow powder, mp 172–174°C.

IR (KBr, ν, cm^{-1}): 3416, 2925, 2865, 1744, 1599, 1652, 1485, 1388, 1116, 1094, 835, 618. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.94 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.98 (1H, d, J = 16.0, H-8), 2.16 (1H, d, J = 16.0, H-8), 2.46 (2H, s, H-6), 3.34–3.90 (6H, m), 4.50 (1H, d, J = 5.6, H-4), 4.59–5.10 (4H, br, 4OH), 5.05 (1H, d, J = 5.6, H-3), 5.20 (1H, d, J = 8.0, H-1), 6.89 (2H, d, J = 8.0, ArH), 7.13 (2H, d, J = 8.0, ArH), 7.35–7.40 (3H, m, ArH), 7.49 (2H, d, J = 8.4, ArH), 8.60 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{29}H_{33}NNaO_7$ $[M + Na]^+$ 530.2155, found 530.2021.

7,7-Dimethyl-2-(4-methylphenyl)-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4g). This compound was prepared from **2b**, 5,5-dimethyl-cylohexane-1,3-dione, and ammonium acetate; yield 84%, yellow powder, mp 139–141°C.

IR (KBr, ν, cm^{-1}): 3362, 2925, 2882, 1660, 1592, 1485, 1390, 1227, 1085, 830, 619. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.93 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.99 (1H, d, J = 16.0, H-8), 2.14 (1H, d, J = 16.0, H-8), 2.24 (3H, s, CH_3), 2.48 (2H, s, H-6), 3.42–3.47 (6H, m), 4.51 (1H, d, J = 5.6, H-4), 4.59–5.10 (4H, br, 4OH), 5.06 (1H, d, J = 5.6, H-3), 5.19 (1H, d, J = 8.0, H-1), 6.89 (2H, d, J = 8.0, ArH), 7.12 (2H, d, J = 8.0, ArH), 7.38 (2H, d, J = 8.4, ArH), 7.50 (2H, d, J = 8.4, ArH), 8.61 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{30}H_{35}NNaO_7$ $[M + Na]^+$ 544.2311, found 544.2307.

7,7-Dimethyl-2-(4-fluorophenyl)-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4h). This compound was prepared from **2c**, 5,5-dimethyl-cyclohexane-1,3-dione, and ammonium acetate; yield 76%, yellow powder, mp 163–165°C.

IR (KBr, ν, cm^{-1}): 3352, 2925, 2882, 1661, 1595, 1485, 1390, 1228, 914, 839, 620. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.96 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.92 (1H, d, J = 16.0, H-8), 2.15 (1H, d, J = 16.0, H-8), 2.48 (2H, s, H-6), 3.34–3.90 (6H, m), 4.49 (1H, d, J = 5.6, H-4), 4.58–5.09 (4H, br, 4OH), 5.03 (1H, d, J = 5.6, H-3), 5.16 (1H, d, J = 8.0, H-1), 6.90 (2H, d, J = 8.0, ArH), 7.12 (2H, d, J = 8.0, ArH), 7.22 (2H, d, J = 8.4, ArH), 7.52 (2H, d, J = 8.4, ArH), 8.60 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{29}H_{31}FO_7$ $[M - H]^-$ 524.2085, found 524.2101.

7,7-Dimethyl-2-(4-chlorophenyl)-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4i). This compound was prepared from **2d**, 5,5-dimethyl-cyclohexane-1,3-dione, and ammonium acetate; yield 79%, yellow powder, mp 142–143°C.

IR (KBr, ν, cm^{-1}): 3361, 2953, 2826, 1660, 1597, 1490, 1390, 1230, 1038, 838, 620. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.93 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.00 (1H, d, J = 16.0, H-8), 2.16 (1H, d, J = 16.0, H-8), 2.49 (2H, s, H-6), 3.35–3.90 (6H, m), 4.47–5.02 (4H, br, 4OH), 4.55 (1H, d, J = 5.6, H-4), 5.05 (1H, d, J = 5.6, H-3), 5.23 (1H, d, J = 8.0, H-1), 6.88 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.44 (2H, d, J = 8.4, ArH), 7.52 (2H, d, J = 8.4, ArH), 8.62 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{29}H_{31}ClNO_7$ $[M - H]^-$ 540.1789, found 540.1790.

7,7-Dimethyl-2-(4-bromophenyl)-4-(4-*β*-D-allopyranosyloxyphenyl)-5-oxo-4,6,7,8-tetrahydroquinoline (4j). This compound was prepared from **2e**, 5,5-dimethyl-cyclohexane-1,3-dione, and ammonium acetate; yield 77%, yellow powder, mp 163–165°C.

IR (KBr, ν, cm^{-1}): 3353, 2927, 2871, 1670, 1589, 1485, 1393, 1228, 1035, 825, 618. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.95 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.07 (1H, d, J = 16.0, H-8), 2.16 (1H, d, J = 16.0, H-8), 2.47 (2H, s, H-6), 3.35–3.90 (6H, m), 4.51 (1H, d, J = 5.6, H-4), 4.59–5.10 (4H, br, 4OH), 5.05 (1H, d, J = 5.6, H-3), 5.24 (1H, d, J = 8.0, H-1), 6.89 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.45 (2H, d, J = 8.4, ArH), 7.58 (2H, d, J = 8.4, ArH), 8.63 (1H, s, NH).

HR-MS-ESI *m/z* calcd for $C_{29}H_{32}BrNNaO_7$ $[M + Na]^+$ 608.1260, found 608.1258.

Mice (Kunming strain) weighing 18–22 g were obtained from West China School of Pharmacy, Sichuan University (Chengdu China). Diazepam was purchased from Tianjin Pharmaceutical Co. Ltd. (China). All samples were dissolved in 0.05% CMC to form different concentrations of solutions for later use.

The sedative-hypnotic activities of the compounds were investigated by recording the number of spontaneous locomotion in mice using an actophotometer [12, 13]. Seventy-two mice were randomized into 12 groups of 6 mice each (3 males and 3 females). When testing, the basal activity score was taken and then a solution of the drugs in 0.05% CMC and saline was injected into the mouse stomach with a syringe in a volume of 0.2 mL/10 g body weight. Scores were recorded before the drug and saline injection and at 15, 30, 60, and 90 min after the drug and saline injection. The data were expressed as number of movements per minute, averaged over 7 min.

As shown in Table 2, the parent compound helicid (**1**) exhibited weak activity and compounds **4b**, **4e**, and **4f** demonstrated greater activity than helicid. It is interesting that compound **4b**, which bears a *p*-methyl substituent, showed potent sedative-hypnotic activity. These results confirm that the lipophilic property might play a vital role in determining their activities. So, further modification of helicid to improve its lipophilic property will be worthwhile.

ACKNOWLEDGMENT

The authors thank the Analytical & Testing Center, Sichuan University, P. R. China for assistance in obtaining analytical data, and Mr. Bao (Department of Pharmacy, Sichuan University) who performed the sedative-hypnotic tests.

REFERENCES

1. W. S. Chen, S. D. Lu, and B. Eberhard, *Liebigs Ann. Chem.,* **10**, 1893 (1981).
2. J. Z. Sha and H. K. Mao, *Chin. Pharm. Bull.,* **22** (1), 27 (1987); P. Liu, J. Li, D.Q. Na, J. M. Geng, and S. Li, *Zhongcaoyao,* **33**, 238 (2002).
3. B. Fan, J. L. Li, Y. Li, and S. F. Yin, *Chin. J. Org. Chem*., **27**, 1150 (2007).
4. Q. L. Zhu, Q. Tang, Y. Li, and S. F. Yin, *Chin. J. Org. Chem.*, **26**, 1264 (2006).
5. M. Liu, Y. Li, and S. F. Yin, *Chin. J. Org. Chem*., **28**, 348 (2008).
6. H. J. Yang, C. Hu, Y. Li, and S. F. Yin, *Chin. J. Org. Chem*., **28**, 899 (2008).
7. F. F. Elslager, F. H. Tendick, L. Werbel, and F. D. Worth, *J. Med. Chem.*, **12**, 970 (1969).
8. N. M. Williamson, P. R. March, and A. D. Ward, *Tetrahedron Lett*., **36**, 7721 (1995).
9. S. Margarita, O. Eatael, V. Yamila, P. Beatriz, M. Lourdes, M. Nazario, Q. Margarita, S. Carlos, N. Hector, B. Norbert, and M. P. Oswald, *Tetrahedron*, **55**, 875 (1999).
10. X. S. Wang, D. J. Shi, and S. J. Tu, *Syn. Commun.*, **32**, 3449 (2002); V. K. Ahluwalia, B. Goyal, and U. Das, *J. Chem. Res*., **7**, 1501 (1997).
11. A. Shaabani, A. Bazgir, and F. Teimour, *Tetrahedron Lett*., **44**, 857 (2003).
12. C. O. Kappe, *Eur. J. Med. Chem*., **35**, 1043 (2000).
13. H. Wen, C. Lin, L. Que, H. Ge, L. Ma, R. Cao, Y. Q. Wan, W. L. Peng, Z. H. Wang, and H. C. Song , *Eur. J. Med. Chem.,* **43**, 166 (2008).