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SYNTHESIS AND CALMING ACTIVITY OF 9-(4-β-D-ALLOPYRANOSYLOXYPHENYL)-DECAHYDROACRIDINE-1,8-DIONE DERIVATIVES

Kuan Zhang, Cong Ling Yang, Shi Ming Lv, Ying Li, and Shu Fan Yin*

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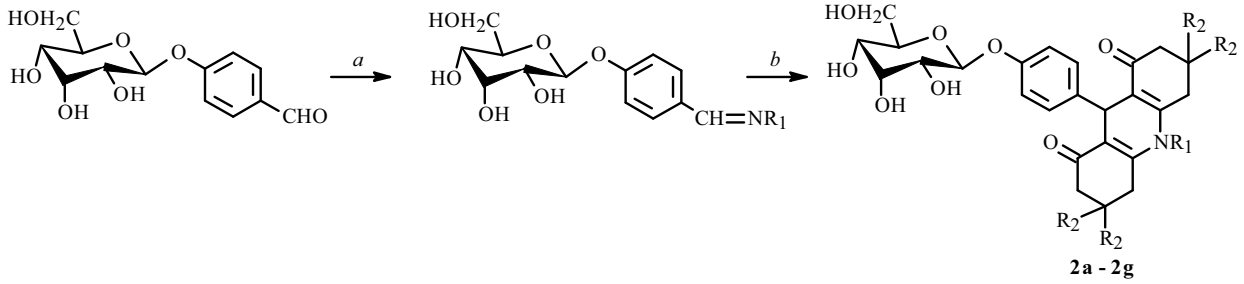
Seven helicid derivatives containing decahydroacridine-1,8-dione were prepared via the reactions between 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione and the corresponding Schiff base. The structures of the helicid derivatives were characterized by IR, ^{1}H NMR, and HR-MS spectrum. The target compounds were evaluated by their hypnotic-sedative activity in vivo*. The preliminary bioassay tests showed that some of the compounds had more potent activity than that of helicid.*

Keywords: helicid, decahydroacridine-1,8-dione, hypnotic-sedative.

Insomnia is a worldwide health problem. Improvements in the treatment of insomnia and its syndrome have already ameliorated sleeping of the insomniac, but the number of new insomniacs continues to rise. Thus, useful drugs with few side effects are required to treat the entire insomnia syndrome.

The natural compound helicid [4-formylphenyl-β-D-allopyranoside, $C_{13}H_{16}O_7$], originally extracted from the fruit of *Helicia nilagirica* Beed [1], has a variety of biological activities on the central nervous system owing to a rare form of allopyranoside. These activities include hypnotic, anti-inflammatory, and anticonvulsant activities [2]. However, its long onset time and low bioavailability limits the scope of clinical application. As part of our efforts to discover new hypnotic-sedative agents, we have synthesized a series of helicid derivatives by introducing the decahydroacridine-1,8-dione framework, which plays an important role in the regulation of different calcium channels [3–6].

The synthesis pathway leading to the title compounds is given in Scheme 1. Treatment of commercially available helicid with appropriate primary amines in the presence of ethanol solvent provided the corresponding Schiff base. By adding 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione to the unpurified Schiff base, we achieved intramolecular cyclization in the target compounds [7–10].



2a: R_1= CH_3, R_2= H, **2b:** R_1= CH_2CH_3, R_2= H, **2c:** R_1= $CH_2CH_2CH_3$, R_2= H, **2d:** R_1= *p*-$CH_3C_6H_4$, R_2= H
2e: R_1= C_6H_5, R_2 = H, **2f:** R_1= CH_3, R_2 = CH_3, **2g:** R_1 = CH_2CH_3, R_2 = CH_3

a. R_1NH_2, CH_3CH_2OH, reflux, 4h, helicid : R_1NH_2 (1:2); *b*. 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione, CH_3CH_2OH, reflux, 10 h.

Scheme 1. Synthesis of compounds **2a**-**2g.**

College of Chemistry, Sichuan University, Chengdu 610064, P. R. China, e-mail: chuandayouji217@163.com.
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TABLE 1. Sedative-Hypnotic Activities of the Target Compounds as Evaluated by the Spontaneous Locomotor Activity Test

Compound	Dose, mg/kg	Number of movements per minute (movements/min)				
		initial	after 30 min	after 60 min	after 90 min	after 120 min
Saline		186.83 ± 72.35	206.66 ± 87.56	164.42 ± 81.18	204.67 ± 21.83	145.67 ± 71.43
Diazepam	20	197.33 ± 55.42	0.00 ± 0.00*	0.16 ± 0.49*	0.00 ± 0.00*	0.00 ± 0.00*
Helicid	100	200.83 ± 63.29	182.30 ± 30.80	151.00 ± 34.22	146.17 ± 74.28	132.33 ± 29.23
2a	100	209.83 ± 20.44	206.83 ± 53.63	206.33 ± 49.89	202.67 ± 58.44	179.67 ± 88.19
2b	100	201.67 ± 24.72	226.50 ± 10.01	209.33 ± 41.92	213.67 ± 37.94	216.83 ± 34.86
2c	100	199.83 ± 44.75	201.33 ± 86.88	218.67 ± 30.72	222.33 ± 27.99	188.83 ± 31.92
2d	100	198.00 ± 64.17	137.17 ± 84.05	184.83 ± 97.31	170.83 ± 90.48	141.00 ± 100.20
2e	100	197.33 ± 88.19	137.17 ± 84.05	143.00 ± 59.55	206.50 ± 66.65	178.50 ± 51.74
2f	100	193.33 ± 47.92	204.17 ± 34.73	194.17 ± 73.53	196.33 ± 71.63	200.50 ± 66.88
2g	100	189.33 ± 34.73	97.17 ± 71.83*	144.67 ± 44.04	147.83 ± 75.41	135.00 ± 87.76

Values are means ± S. *P < 0.05 compared with saline.

In summary, a concise and effective procedure was successfully developed to synthesize helicid derivatives containing decahydroacridine-1,8-dione. The compound **2g** showed better hypnotic-sedative activity than helicid, and its onset time was much shorter (Table 1). Comparison of **2d**, **2e** and **2a**, **2b**, **2c** showed that *N*-aryl substituted compounds were more effective than *N*-alkyl substituted compounds. The present investigation should be continued.

EXPERIMENTAL

Materials. Helicid [4-formylphenyl-β-D-allopyranoside] was purchased from Yunnan Chemical Company of China. The common reagents were provided by standard sources, and the solvents used were purified according to the standard methods.

Mice (Kunming strain) weighing 24–25 g were obtained from West China School of Pharmacy, Sichuan University (Chengdu China). All samples were dissolved in 0.9% NaCl solution to form different concentrations of solutions for the calming test.

Melting points were measured on an Electrothermal Thomas-Hoover melting point apparatus and were uncorrected. Infrared absorption spectra were recorded from a Perkin–Elmer 16PC-FT infrared spectrometer using KBr pellets. ^{1}H NMR spectra were determined on a Bruker AV-400 MHz spectrometer using TMS as an internal standard. HR-MS spectra were measured on a Bruker Daltonics ESI-Bio TOF-Q mass spectroscopy. TLC was performed on silica gel G, and spots were visualized by irradiation with UV light (254 nm).

General Procedure for the Preparation of Compounds 2a–2g. A mixture of helicid (1 mmol, 0.284 g) and corresponding primary amines (2 mmol) was heated under reflux in 10 mL anhydrous ethanol for 4 h. Then, 1,3-cyclohexanedione (1 mmol, 0.080 g) or 5,5-dimethyl-1,3-cyclohexanedione (1 mmol, 0.108 g) was added, and the mixture was heated as before to complete the reaction (monitored by TLC). After completion of the reaction, the mixture was concentrated under reduced pressure in a rotary evaporator. The solid was dissolved in 20 mL ethyl acetate and extracted with water, and the water layer was concentrated *in vacuo*. The crude products was purified by column chromatography (eluted with methanol–chloroform–petroleum ether, 2/1/2, v/v/v) to furnish the pure product **2**.

***N*-Methyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2a)**. Yield 81%, yellow powder, mp 139–141°C. IR (KBr, cm^{-1}): 3409, 2924, 2871, 1624, 1554, 1504, 1465, 1365, 1314, 1233, 1187, 1115, 1037, 945, 839, 619, 544. ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm, J/Hz): 1.82–1.98 (4H, m, 2 × CH_2), 2.16–2.27 (4H, m, 2 × CH_2), 2.46–2.54 (4H, m, 2 × CH_2), 3.27 (3H, s, N-CH_3), 3.40–3.91 (6H, m), 4.47–5.00 (4H, br, 4OH), 5.01 (1H, d, J = 8.0, OCHO), 5.02 (1H, s, CH), 6.78 (2H, d, J = 8.8, ArH), 6.98 (2H, d, J = 8.8, ArH).

HR-MS-ESI *m/z*: calcd for $C_{26}H_{32}NO_8$ $[M + H]^+$ 486.2128, found 486.2130; $C_{26}H_{31}NNaO_8$ $[M + Na]^+$ 508.1947, found 508.1911.

***N*-Ethyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2b)**. Yield 85%, yellow powder, mp 142–144°C. IR (KBr, cm^{-1}): 3395, 2921, 2845, 1623, 1556, 1504, 1453, 1364, 1330, 1231, 1186, 1119, 1082, 1038, 947, 908, 840, 794, 703, 621, 546. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.55–1.69 (4H, m, 2 × CH_2), 1.76–1.88 (4H, m, 2 × CH_2), 1.91–2.01 (4H, m, 2 × CH_2), 2.21 (3H, t, J = 5.6, N-CH_2-CH_3), 2.89 (2H, q, J = 6.0, N-CH_2), 3.40–3.89 (6H, m), 4.46–5.00 (4H, br, 4OH), 5.01 (1H, d, J = 8.0, OCHO), 5.02 (1H, s, CH), 6.79 (2H, d, J = 8.8, ArH), 6.99 (2H, d, J = 8.8, ArH).

HR-MS-ESI *m/z*: calcd for $C_{27}H_{34}NO_8$ $[M + H]^+$ 500.2284, found 500.2283; $C_{27}H_{33}NNaO_8$ $[M + Na]^+$ 522.2014, found 522.2015.

***N*-Propyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2c)**. Yield 80%, yellow powder, mp 144–145°C. IR (KBr, cm^{-1}): 3407, 2925, 2855, 1930, 1623, 1563, 1506, 1459, 1383, 1229, 1185, 1123, 1082, 1041, 950, 836, 619, 547, 470. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.58–1.64 (4H, m, 2 × CH_2), 1.76–1.86 (4H, m, 2 × CH_2), 1.93–2.02 (4H, m, 2 × CH_2), 2.19–2.34 (3H, m, CH_3), 2.26–2.34 (2H, m, CH_2), 2.83–2.89 (2H, m, CH_2), 3.39–3.89 (6H, m), 4.49–5.03 (4H, br, 4OH), 5.03 (1H, d, J = 6.4, OCHO), 5.04 (1H, s, CH), 6.79 (2H, d, J = 8.8, ArH), 6.98 (2H, d, J = 8.8, ArH).

HR-MS-ESI *m/z*: calcd for $C_{28}H_{36}NO_8$ $[M + H]^+$ 514.2441, found 514.2439; $C_{28}H_{35}NNaO_8$ $[M + Na]^+$ 536.2260, found 536.2223.

***N*-(4-Methylphenyl)-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2d)**. Yield 82%, yellow powder, mp 148–150°C. IR (KBr, cm^{-1}): 3414, 2923, 2848, 1724, 1633, 1566, 1507, 1453, 1363, 1286, 1233, 1182, 1113, 1082, 1040, 955, 910, 843, 619, 551. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.58–1.67 (4H, m, 2 × CH_2), 1.89–2.00 (4H, m, 2 × CH_2), 2.17–2.22 (4H, m, 2 × CH_2), 2.39 (3H, s, Ar-CH_3), 3.38–3.93 (6H, m), 4.49–5.04 (4H, br, 4OH), 5.06 (1H, d, J = 8.0, OCHO), 5.08 (1H, s, CH), 6.88 (2H, d, J = 8.8, ArH), 7.18 (3H, d, J = 8.8, ArH), 7.35–7.40 (3H, m, ArH).

HR-MS-ESI *m/z*: calcd for $C_{32}H_{36}NO_8$ $[M + H]^+$ 562.2441, found 563.2437; $C_{32}H_{35}NNaO_8$ $[M + Na]^+$ 584.2260, found 584.2245.

***N*-Phenyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2e)**. Yield 74%, yellow powder, mp 151–152°C. IR (KBr, cm^{-1}): 3413, 2922, 2890, 1631, 1565, 1501, 1453, 1363, 1286, 1233, 1182, 1133, 1081, 1039, 956, 909, 852, 713, 620, 550, 442. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.59–1.84 (4H, m, 2 × CH_2), 1.89–2.20 (4H, m, 2 × CH_2), 2.20–2.24 (4H, m, 2 × CH_2), 3.39–3.90 (6H, m), 4.48–5.03 (4H, br, 4OH), 5.06 (1H, d, J = 8.0, OCHO), 5.09 (1H, s, CH), 6.89 (2H, d, J = 8.8, ArH), 7.19 (3H, d, J = 8.8, ArH), 7.54–7.61 (4H, m, ArH).

HR-MS-ESI *m/z*: calcd for $C_{31}H_{34}NO_8$ $[M + H]^+$ 548.2284, found 548.2271; $C_{31}H_{33}NNaO_8$ $[M + Na]^+$ 570.2014, found 570.2097.

3,3,6,6-Tetramethyl-*N*-methyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2f). Yield 79%, yellow powder, mp 134–136°C. IR (KBr, cm^{-1}): 3409, 2924, 2871, 1625, 1554, 1504, 1465, 1366, 1314, 1234, 1187, 1116, 1037, 945, 839, 619, 544. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.95(6H, s, 2 × CH_3), 0.99 (6H, s, 2 × CH_3), 2.04–2.09 (4H, m, 2 × CH_2), 2.39–2.44 (4H, m, 2 × CH_2) 3.27 (3H, s, N-CH_3), 3.38–3.90 (6H, m), 4.50–4.98 (4H, br, 4OH), 5.00 (1H, d, J = 8.0, OCHO), 5.03 (1H, s, CH), 6.78 (2H, d, J = 8.6, ArH), 6.99 (2H, d, J = 8.6, ArH).

HR-MS-ESI *m/z*: calcd for $C_{30}H_{40}NO_8$ $[M + H]^+$ 542.2754, found 542.2758; $C_{30}H_{39}NNaO_8$ $[M + Na]^+$ 564.2573, found 564.2576.

3,3,6,6-Tetramethyl-*N*-ethyl-9-(4-β-D-allopyranosyloxyphenyl)-decahydroacridine-1,8-dione (2g). Yield 76%, yellow powder, mp 136–138°C. IR (KBr, cm^{-1}): 3425, 2957, 2921, 2852, 1626, 1505, 1465, 1375, 1224, 1113, 1083, 1039, 988, 849, 619, 574. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.89 (6H, s, 2 × CH_3), 1.02 (6H, s, 2 × CH_3), 2 .00–2.10 (4H, m, 2 × CH_2), 2.15 (3H, t, J = 16.01, N-CH_2-CH_3), 2.38–2.46 (4H, m, 2 × CH_2), 2.70 (2H, q, J = 4.52, N-CH_2), 3.42–3.89 (6H, m), 4.46–4.94 (4H, br, 4OH), 4.99 (1H, d, J = 8.0, OCHO), 5.01 (1H, s, CH), 6.78 (2H, d, J = 8.8, ArH), 7.00 (2H, d, J = 8.8, ArH).

HR-MS-ESI *m/z*: calcd for $C_{31}H_{42}NO_8$ $[M + H]^+$ 556.2910, found 556.2915; $C_{31}H_{41}NNaO_8$ $[M + Na]^+$ 578.2730, found 578.2734.

The sedative-hypnotic activities of the compounds were investigated by recording the number of spontaneous locomotion in mice using an actophotometer [11, 12]. Fifty-four mice were randomized into 9 groups of 6 mice each (3 males and 3 females). All the mice were placed in the multi-spontaneous activity recorder before the experiments to adapt to the environment. Group A received saline by injection, group B received diazepam (20 mg/kg, i.p.), group C received helicid (100 mg/kg, i.p.), and groups **2a–2g** received the synthesized compounds (100 mg/kg, i.p.). When testing, the prepared solutions were injected into the mouse stomach with a syringe in a volume of 0.2 mL/10 g body weight, and the spontaneous activity number was recorded for 5 min after 0, 30, 60, 90 and 120 min. The data were recorded as number of movements per minute.

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