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SYNTHESIS AND SEDATIVE-HYPNOTIC ACTIVITY OF HELICID DERIVATIVES CONTAINING A 1,4-DIHYDROPYRIDINE MOIETY

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*Reactions of natural helicid with a number of 1,3-dicarbonyl compounds or β-ketoester in the presence of ammonium acetate or 1-naphthylamine gave a series of helicid derivatives containing a 1,4-dihydropyridine fragment (**2a–2h**). Eight novel helicid derivatives were structurally confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HR-MS spectroscopy and evaluated for their sedative-hypnotic activities on mice. The results demonstrated that two compounds had higher sedative-hypnotic activity compared with helicid.*

Keywords*:* synthesis, helicid, 1,4-dihydropyridine, sedative-hypnotic activity.

Helicid (**1**, 4-formylphenyl-β-D-allopyranoside), is originally isolated from the fruit of *Helicia nilagirica* Beed [1], a plant indigenous to western China. Owing to a rare allopyranoside, it has a variety of biological activities on the central nervous system such as sedative, hypnotic, and anticonvulsant activities [2]. However, its long onset time and low bioavailability prompted us to search for new derivatives of helicid through structure modifications [3–7].

1,4-Dihydropyridines (1,4-DHPs) are among the most widely used drugs for the management of cardiovascular disease [8], which have a broad range of other pharmacological activities, such as antitumor, bronchodilating, antidiabetic, and antiviral [9–12]. 4-Substituted 1,4-dihydropyridines are analogs of NADH coenzymes and an important class of drugs that are potent blockers of calcium (Ca^{2+}) current. A recent computational analysis of the comprehensive medicinal chemistry database found the DHP framework to be among the most prolific chemotypes. From the viewpoint of molecular design, to construct a dual-target drug molecule, a connective molecule can simply be realized by combining two active molecules or their pharmacophores with a linker, while an integrated molecule comes into an entity either by fusing or by merging the common structural or pharmacophoric features of two active molecules, depending on the extent of the common features. This approach facilitates the reduction of molecular size and molecular weight and the optimal overlap between the pharmacodynamic and pharmacokinetic spaces, which will certainly elevate its probability of being a drug. Thus, based on our high throughout work on the structure–activity relationship of helicid, we designed and synthesized eight helicid derivatives containing the DHP framework through the reactions shown in Scheme 1, with the aim to explore new drugs with superior bioactivity and better efficacy [13–15]. Pharmacological test showed that compounds **2a** and **2h** displayed promising sedative-hypnotic activity superior to helicid (Table 1). So, further modification of helicid should be worthwhile.

The most common route for the synthesis of 1,4-dihydropyridines is the Hantzsch reaction. It is the condensation of a β-ketoester or 1,3-dicarbonyl compound with an aldehyde and ammonia or primary amine either in acetic acid or by refluxing in alcohol. However, the reaction times for 6–72 h are too long and the yields are generally low. Therefore, in our preliminary study, a series of helicid derivatives **2a–2e** were synthesized (Scheme 2) through an improved Hantzsch reaction in one pot under solvent-free conditions. This procedure involves a shorter reaction time, good yield, and simple work-up. The initial steps of the reaction involve a Knoevenagel condensation of the 1,3-dicarbonyl compound with 4-(β-D-allopyranosyloxy)-benzaldehyde to give an α,β-unsaturated carbonyl compound and a condensation of ammonia with another equivalent of the 1,3-dicarbonyl compound to give an enamine. The rate-determing step is the Michael addition of the enamine to the α,β-unsaturated carbonyl compound.

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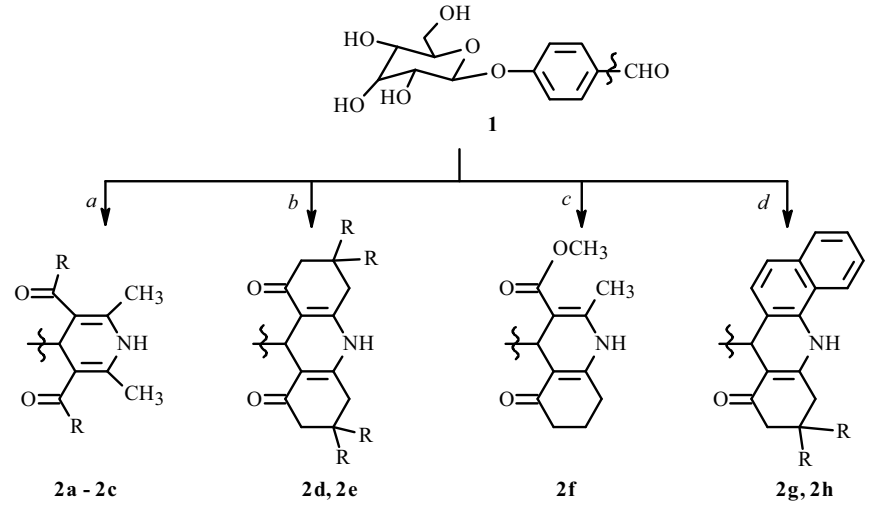
TABLE 1. The Spontaneous Locomotor Activity Test

Compound	Number of movements per minute (movements/min)				
	initial	after 30 min	after 60 min	after 90 min	after 120 min
Saline	186.83 ± 25.86	189.17 ± 48.56	192.67 ± 23.57	183.17 ± 21.55	188.83 ± 45.48
Diazepam	188.00 ± 22.66	7.56 ± 4.17**	1.22 ± 0.50**	5.31 ± 2.17*	5.31 ± 2.17*
Helicid	187.73 ± 26.08	168.55 ± 51.57	162.67 ± 44.47	130.45 ± 49.74	164.35 ± 36.58
2a	182.23 ± 49.57	164.33 ± 30.07	136.83 ± 45.42	105.67 ± 63.52	94.67 ± 59.18*
2b	188.33 ± 44.38	187.83 ± 59.90	160.17 ± 50.45	147.00 ± 38.19	144.17 ± 57.80
2c	185.17 ± 52.57	152.67 ± 47.21	97.50 ± 59.22*	113.00 ± 52.98*	118.50 ± 60.72
2d	181.33 ± 48.61	163.33 ± 45.79	165.33 ± 52.65	133.17 ± 51.81	117.83 ± 64.73
2e	188.33 ± 18.68	141.83 ± 43.13	137.50 ± 30.26	117.00 ± 46.07	145.33 ± 61.71
2f	181.33 ± 40.37	163.83 ± 32.38	175.00 ± 56.20	169.50 ± 43.54	122.33 ± 65.05
2g	187.83 ± 43.59	169.33 ± 39.66	129.17 ± 52.92	86.83 ± 56.68	116.33 ± 49.58
2h	184.67 ± 29.71	141.67 ± 68.24	109.33 ± 49.27	74.83 ± 30.90	55.17 ± 36.64*

Dose of all compounds: 300 mg·kg^{-1} (dose of diazepam: 8 mg·kg^{-1}, saline: –).
Values are means ± S. *P < 0.05, **P < 0.01, compared with saline.



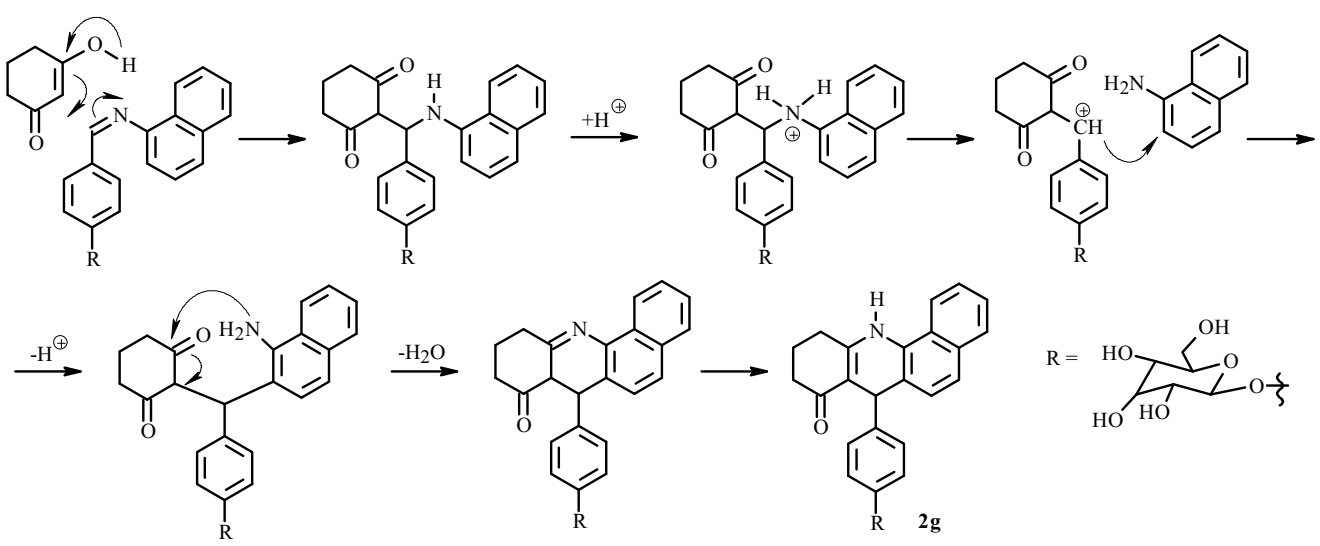
2a: R = OCH_3, **2b:** R = OCH_2CH_3, **2c:** R = CH_3, **2d:** R = H, **2e:** R=CH_3, **2g:** R = H, **2h:** R=CH_3

a. methyl acetoacetate or ethyl acetoacetate or acetylacetone, ammonium acetate, 80°C; *b*. cyclohexane-1,3-dione or 5,5-dimethylcyclohexane-1,3-dione, ammonium acetate, 80°C; *c*. methyl acetoacetate, cyclohexane-1,3-dione, ammonium acetate, 80°C, ultrasonic; *d*. cyclohexane-1,3-dione or 5,5-dimethylcyclohexane-1,3-dione, 1-naphthylamine, anhydrous ethanol, reflux.

Scheme 1. Synthesis routes of compounds **2a**–**2h**.

Subsequently, the addition product undergoes an intramolecular condensation of the amino and carbonyl groups to afford **2a**–**2e**. Compound **2f** was obtained via a one-pot four-component Hantzsch condensation of 4-(*β*-D-allopyranosyloxy)-benzaldehyde, methyl acetoacetate, cyclohexane-1,3-dione, and ammonium acetate under ultrasound irradiation without catalyst. The mechanism of the condensation is similar to **2a**–**2e**.

Compounds **2g** and **2h** were obtained by co-refluxing of 4-(*β*-D-allopyranosyloxy)-benzaldehyde, 1-naphthylamine, cyclohexane-1,3-dione, or 5,5-dimethyl cyclohexane-1,3-dione. At the first stage of the reaction, 4-(*β*-D-allopyranosyloxy)-benzaldehyde (**1**) with 1-naphthylamine should form a Schiff base as an intermediate. The formation of the final compounds involves the process of interaction of the intermediate imine with cyclohexane-1,3-dione, as shown in Scheme 2.



Scheme 2. The reaction mechanism of forming **2g**.

The structure of the new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HR-MS spectroscopy. The molecular weights of the new compounds were confirmed in the form of the ions $[M + H]^+$ and $[M + Na]^+$ in the ESI-HR-MS spectroscopy. Theoretically, in addition to the isotope peaks, the molecular ion peak is present in the spectrum of the highest quality, but when the molecular ion is unstable, it may lead to the disappearance of the molecular ion peak or generate the $[M + H]^+$, $[M – H]^–$, or $[M + Na]^+$ peak in the spectrum. Because of helicid′s high polarity and thermal lability, we adopted the method of electrospray ionization (ESI). The ESI-HR-MS generally showed clear quasi-molecular ion peaks, such as the $[M + H]^+$ peak, and $[M + Na]^+$ and $[M + K]^+$ peaks sometimes occur, while there were few or no fragment ion peaks. In the positive ion mode, the generation of the $[M + Na]^+$ peak is related to the structure of the compounds. Generally, the greater the number of oxygen atoms in compounds such as helicid, the easier it is to form a strong $[M + Na]^+$ peak. The Na^+ may come from the mobile phase, sample solvent, the glassware used for the preparation of sample solution, or the capillary of the high-resolution mass spectrometer.

In conclusion, a concise and effective procedure has been successfully developed for the synthesis of helicid derivatives containing a 1,4-dihydropyridine fragment. The result of the present investigation should be of value in the synthesis of structural analogs.

EXPERIMENTAL

Materials. All common reagents and solvents are procured from standard sources unless otherwise indicated and used without further purification. Helicid was purchased from Yunnan Chemical Company of China.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker AV-400 MHz instrument. IR spectra were measured with a Perkin–Elmer 16PC-FT infrared spectrometer. HR-MS spectra were measured with Bruker Daltonics ESI-Bio TOF-Q mass spectroscopy. Sonication was performed in a Jiangsu KQ-3200DE ultrasonic cleaner with a frequency of 40 kHz and a nominal power 120 W. Column chromatography was performed on silica gel (300–400 mesh, Qingdao, China). Thin-layer chromatography (TLC) was performed on precoated Merck silica gel $60F_{254}$ plates.

General Procedure for the Preparation of Compounds 2a–2e. A mixture of helicid (1 mmol), methyl acetoacetate (2 mmol), and ammonium acetate (2.5 mmol) was thoroughly mixed and heated at 80°C for about 4.5 h. The reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature; ice water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (eluted with methanol–chloroform–petroleum ether, 1:1:4, v/v/v) to furnish the pure product **2a**.

2,6-Dimethyl-3,5-dicarbomethoxy-4-(4-β-D-allopyranosyloxyphenyl)-1,4-dihydropyridine (2a). Yield 81%, yellow powder, mp 122–124°C.

IR (KBr, cm^{-1}): 3349, 2923, 1682, 1503, 1453, 1309, 1219, 1118, 1034, 853, 619.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.26 (6H, s, CH_3-2, CH_3-6), 3.45–3.95 (6H, m), 3.56 (6H, s, $COOCH_3$-3, $COOCH_3$-5), 4.46–4.92 (4H, m, 4OH), 4.81 (1H, s, H-4), 5.05 (1H, d, J = 8.0, OCHO), 6.83 (2H, d, J = 8.8, ArH), 7.01 (2H, d, J = 8.4, ArH), 8.84 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.64, 31.14, 38.15, 51.09, 61.44, 67.55, 70.66, 71.95, 75.01, 98.83, 102.19, 102.24, 116.09, 128.30, 141.73, 145.85, 145.89, 156.39, 167.90.

HR-MS-ESI: calcd for $C_{23}H_{30}NO_{10}$ $[M + H]^+$ 480.1870, found 480.1763; $C_{23}H_{29}NNaO_{10}$ $[M + Na]^+$ 502.1684, found 502.1600.

2,6-Dimethyl-3,5-dicarboethoxy-4-(4-*β*-D-allopyranosyloxyphenyl)-1,4-dihydropyridine (2b). Yield 82%, yellow powder, mp 110–112°C.

IR (KBr, cm^{-1}): 3341, 2979, 2930, 1679, 1503, 1373, 1305, 1217, 1117, 1035, 856, 619.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.12 (6H, t, J = 7.2, 3-$COOCH_2\underline{CH_3}$, 5-$COOCH_2\underline{CH_3}$), 2.24 (6H, s, CH_3-2, CH_3-6), 3.30–3.90 (6H, m), 3.96–4.02 (4H, m, 3-$COO\underline{CH_2}CH_3$, 5-$COO\underline{CH_2}CH_3$), 4.45–4.91 (4H, m, 4OH), 4.79 (1H, s, H-4), 5.05 (1H, d, J = 8.0, OCHO), 6.83 (2H, d, J = 8.0, ArH), 7.03 (2H, d, J = 8.8, ArH), 8.76 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):14.66, 18.66, 31.13, 38.49, 59.42, 61.42, 67.55, 70.68, 71.95, 74.99, 98.82, 102.50, 102.54, 115.90, 128.63, 142.08, 145.50, 156.31, 167.46.

HR-MS-ESI: calcd for $C_{25}H_{34}NO_{10}$ $[M + H]^+$ 508.2183, found 508.1922; $C_{25}H_{33}NNaO_{10}$ $[M + Na]^+$ 530.1997, found 530.2002.

2,6-Dimethyl-3,5-dicarbomethyl-4-(4-*β*-D-allopyranosyloxyphenyl)-1,4-dihydropyridine (2c). Yield 82%, yellow powder, mp 118–120°C.

IR (KBr, cm^{-1}): 3335, 2923, 1606, 1463, 1379, 1224, 1113, 1036, 844, 620.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.17 (6H, s, $COCH_3$-3, $COCH_3$-5), 2.25 (6H, s, CH_3-2, CH_3-6), 3.45–3.89 (6H, m), 4.45–4.99 (4H, m, 4OH), 4.96 (1H, s, H-4), 5.04 (1H, d, J = 8.0, OCHO), 6.84 (2H, d, J = 8.8, ArH), 7.04 (2H, d, J = 8.8, ArH), 8.86 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.48, 30.53, 31.14, 38.43, 61.64, 67.58, 70.68, 71.93, 75.03, 75.25, 79.64, 98.92, 113.21, 116.31, 116.85, 128.43, 132.10, 140.99, 144.61, 144.65, 156.42, 196.94.

HR-MS-ESI: calcd for $C_{23}H_{30}NO_8$ $[M + H]^+$ 448.1971, found 448.1975; $C_{23}H_{29}NNaO_8$ $[M + Na]^+$ 470.1785, found 470.1791.

9-(4-*β*-D-Allopyranosyloxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8 (2*H*,5*H*)-dione (2d). Yield 76%, yellow powder, mp 202–204°C.

IR (KBr, cm^{-1}): 3282, 2062, 2935, 1625, 1477, 1364, 1233, 1178, 1035, 960, 841, 616, 535.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.77–1.92 (4H, m, H-3, 6), 2.18–2.21 (4H, m, H-4, 5), 3.37–3.40 (4H, m, H-2, 7), 3.42–3.90 (6H, m), 4.46–5.01 (4H, m, 4OH), 4.85 (1H, s, H-9), 5.03 (1H, d, J = 8.0, OCHO), 6.79 (2H, d, J = 8.8, ArH), 7.03 (2H, d, J = 8.8, ArH), 9.40 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.27, 26.76, 31.16, 31.75, 37.25, 61.42, 67.54, 70.65, 71.95, 74.98, 79.63, 98.85, 113.11, 115.88, 128.72, 141.28, 151.53, 156.01, 195.30.

HR-MS-ESI: calcd for $C_{25}H_{30}NO_8$ $[M + H]^+$ 472.1965, found 472.1947; $C_{25}H_{29}NNaO_8$ $[M + Na]^+$ 494.1785, found 494.1722.

9-(4-*β*-D-Allopyranosyloxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (2e). Yield 78%, yellow powder, mp 184–186°C.

IR (KBr, cm^{-1}): 3404, 2956, 1625, 1481, 1367, 1224, 1114, 1037, 848, 618, 567.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.88 (6H, s, CH_3-3, CH_3-6), 1.01 (6H, s, CH_3-3, CH_3-6), 1.96–2.18 (4H, m, H-4, H-5), 2.29–2.46 (4H, m, H-2, H-7), 3.42–3.89 (6H, m), 4.46–5.02 (4H, m, 4OH), 4.79 (1H, s, H-9), 5.03 (1H, d, J = 8.0, OCHO), 6.78 (2H, d, J = 8.4, ArH), 7.04 (2H, d, J = 8.4, ArH), 9.25 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 26.97, 27.08, 29.49, 29.58, 31.16, 32.48, 32.60, 32.61, 50.72, 61.35, 67.50, 70.70, 71.93, 74.95, 79.64, 98.82, 112.09, 115.61, 128.86, 141.11, 149.53, 155.98, 194.85.

HR-MS-ESI: calcd for $C_{29}H_{38}NO_8$ $[M + H]^+$ 528.2597, found 528.2520; $C_{29}H_{37}NNaO_8$ $[M + Na]^+$ 550.2411, found 550.2336.

General Procedure for the Preparation of Compound 2f. A mixture of helicid (1 mmol), methyl acetoacetate (1 mmol), cyclohexane-1,3-dione (1 mmol), and ammonium acetate (2.5 mmol) was thoroughly mixed and irradiated in the water bath of an ultrasonic cleaner (frequency 40 kHz and power 120 W) at 80°C for about 4 h. The reaction was followed by

TLC. After completion of the reaction, the mixture was cooled to room temperature; ice water was added, and the mixture was extracted with ethylacetate. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (eluted with methanol–chloroform–petroleum ether, 1:1:8, v/v/v) to give the pure product **2f**.

2-Methyl-3-carbomethoxy-4-(4-β-D-allopyranosyloxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (2f). Yield 81%, yellow powder, mp 232–234°C.

IR (KBr, cm^{-1}): 3276, 3072, 2946, 1680, 1607, 1482, 1381, 1229, 1034, 838, 619, 529.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.51–1.87 (2H, m, H-7), 2.20 (2H, t, J = 6.0, H-8), 2.28 (3H, s, CH_3-2), 2.46–2.48 (2H, m, H-6), 3.33–3.90 (6H, m), 3.52 (3H, s, $COOCH_3$-3), 4.46–5.01 (4H, m, 4OH), 4.85 (1H, s, H-4), 5.03 (1H, d, J = 8.0, OCHO), 6.81 (2H, d, J = 8.0, ArH), 7.02 (2H, d, J = 8.0, ArH), 9.13 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.69, 21.26, 26.55, 31.14, 35.04, 37.18, 51.11, 61.45, 67.58, 70.69, 71.95, 75.01, 98.78, 98.99, 111.83, 115.96, 116.07, 128.50, 141.57, 151.61, 156.24, 167.90, 195.16.

HR-MS-ESI: calcd for $C_{24}H_{30}NO_9$ $[M + H]^+$ 476.1915, found 476.1912; $C_{24}H_{29}NNaO_9$ $[M + Na]^+$ 498.1735, found 498.1631.

General Procedure for the Preparation of Compounds 2g–2h. A mixture of helicid (1 mmol) and 1-naphthylamine (1 mmol) in 15 mL of anhydrous ethanol was refluxed for about 1.5 h. Cyclohexane-1,3-dione (1 mmol) in anhydrous ethanol (15 mL) was added, and the mixture was refluxed for about 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The crude product was filtered and purified by column chromatography (eluted with methanol–chloroform–petroleum ether, 1:1:9, v/v/v) to give the pure compound **2g**.

9-(4-β-D-Allopyranosyloxyphenyl)-5,6,7,8,9,10-hexahydrobenzo[c]acridin-5-one (2g). Yield 76%, brown powder, mp 184–186°C.

IR (KBr, cm^{-1}): 3385, 2922, 1600, 1495, 1388, 1227, 1115, 1037, 757, 619.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.58–1.98 (2H, m, H-7), 2.25 (2H, t, J = 6.0, H-8), 2.52–2.69 (2H, m, H-6), 3.42–3.90 (6H, m), 4.42–5.01 (4H, m, 4OH), 4.90 (1H, m, H-9), 5.18 (1H, d, J = 8.0, OCHO), 6.82 (2H, d, J = 8.0, ArH), 7.11 (2H, d, J = 8.0, ArH), 7.26–7.83 (6H, m, ArH), 9.31 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 33.10, 34.55, 35.91, 37.39, 55.49, 66.05, 66.13, 72.23, 72.26, 75.38, 75.43, 75.53, 76.66, 76.70, 79.70. 79.72. 79.92, 103.34, 103.75, 112.71, 112.74, 120.82, 121.05, 126.33, 126.41, 127.41, 127.84, 127.91, 130.92, 133.41, 134.80, 135.79, 135.83, 137.50, 147.26, 147.30, 156.80, 156.84, 160.86, 160.99, 198.77.

HR-MS-ESI: calcd for $C_{29}H_{30}NO_7$ $[M + H]^+$ 504.2022, found 504.2000; $C_{29}H_{29}NNaO_7$ $[M + Na]^+$ 526.1836, found 526.1711.

7,7-Dimethyl-9-(4-β-D-allopyranosyloxyphenyl)-5,6,7,8,9,10-hexahydrobenzo[c]acridin-5-one (2h). Yield 78%, brown powder, mp 162–164°C.

IR (KBr, cm^{-1}): 3320, 2921, 1598, 1497, 1390, 1229, 1114, 1038, 748, 617.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.99 (3H, s, CH_3-7), 1.08 (3H, s, CH_3-7), 2.21 (2H, s, H-8), 2.67 (2H, s, H-6), 3.42–3.90 (6H, m), 4.42–5.01 (4H, m, 4OH), 4.90 (1H, m, H-9), 5.18 (1H, d, J = 8.0, OCHO), 6.80 (2H, d, J = 8.0, ArH), 7.09 (2H, d, J = 8.0, ArH), 7.24–7.83 (6H, m, ArH), 9.27 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.51, 27.41, 34.53, 37.25, 61.37, 67.50, 70.62, 70.77, 71.91, 74.95, 75.16, 98.72, 98.87, 98.98, 109.15, 115.92, 116.23, 116.29, 116.82, 121.72, 122.61, 123.11, 125.46, 126.11, 128.37, 128.42, 128.64, 130.06, 131.04, 132.72, 146.87, 153.96, 194.46, 198.10.

HR-MS-ESI: calcd for $C_{31}H_{34}NO_7$ $[M + H]^+$ 532.2335, found 532.2303; $C_{31}H_{33}NNaO_7$ $[M + Na]^+$ 554.2149, found 554.2112.

Pharmacological Test. Mice (Kunming strain) weighing 17–22 g were obtained from West China School of Pharmacy of Sichuan University (Chengdu China). All samples were dissolved in 0.05% CMC (sodium carboxymethylcellulose) to form different concentrations of solutions for later use.

The sedative-hypnotic activities of the new compounds were investigated by recording the number of spontaneous locomotions in mice using an actophotometer. Sixty mice were randomized into 10 groups of 6 mice each (3 male and 3 female). When testing, a 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^{-1} body weight. Scores were recorded before the injection of drugs and saline and at 30, 60, 90, and 120 min after the injection of the drugs and saline. The data were expressed as number of movements per minute, averaged over 5 min.

As indicated in Table 1, some of the target compounds had better sedative-hypnotic activities than that of helicid. Moreover, compound **2a** and **2h** exhibited particularly superior sedative-hypnotic activity compared to helicid, especially compound **2h**. Diazepam is a classical clinical sedative-hypnotic drug. So, the pharmacological data of these drugs compared to diazepam were still not ideal for clinical use. This suggested that these kinds of helicid derivatives containing the DHP framework were worthy of further investigation in order to discover new sedative-hypnotic drugs. Currently, further evaluation is still in progress.

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