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SYNTHESIS AND CALMING ACTIVITY OF HELICID DERIVATIVES CONTAINING THE 3,4-DIHYDROPYRIMIDIN-2(*H*)-ONE AND 3,4-DIHYDROPYRIMIDINE-2(*H*)-THIONE MOIETY

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*A series of novel helicid derivatives containing 3,4-dihydropyrimidin-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione moiety (**3a–3f** and **4a–4f**) were synthesized starting from helicid. The structure of the new compounds were characterized by ^{1}H NMR, IR and HR-MS spectra. The sedative-hypnotic activities of the target compounds were evaluated using the test of spontaneous locomotor activity in mice. All of the derivatives produced moderate to high activities; in particular, compound **4a** presented the most potent sedative-hypnotic effect in comparison to the other derivatives, and derivatives **3a**, **3c**, **3d**, **3e** and **3f** also showed potent activities.*

Keywords: helicid, 3,4-dihydropyrimidine, Biginelli reaction, sedative-hypnotic activity.

Helicid (**1**), a pure compound extracted from the fruit of *Helicia nilagirica* Beed [1], is distributed widely in Yunnan Province of China. It is a major active ingredient of Chinese herbal medicine that has been reported to possess a variety of biological effects on the central nervous system, including sedative, hypnotic, and anticonvulsant activities; moreover, no obvious side effect has been reported [2]. However, the drug also has some disadvantages, such as the large dose required and low bioavailability. Recently it has been demonstrated that epigenetic modifications at the aldehyde group of helicid play a key role in improving its pharmacological and therapeutic activities [3–6].

3,4-Dihydropyrimidines (DHPMs) and their derivatives are very important compounds in the realm of synthetic organic chemistry because they exhibit a wide range of biological and pharmacological properties, including antitumor and anti-inflammatory actions [7–11]. It has been observed that in compounds containing the DHPM moiety, the absolute configuration of the stereogenic center influences the biological effects [12]. In order to obtain novel helicid derivatives possessing better biological effects, we synthesized a series of novel helicid derivatives containing the 3,4-dihydropyrimidin-2(1*H*)-one and thioxo-3,4-dihydropyrimidine-2(1*H*)-thione moiety (**3a–3f**, **4a–4f**) by modifying helicid at the aldehyde group and hydroxyl groups (described in Scheme 1). The sedative-hypnotic activities of the target compounds were evaluated, and the result showed that derivatives **3a**, **3c**, **3d**, **3e**, **3f**, and **4a** possess good activities.

In the present study, six novel helicid derivatives **3a–3f** have been successfully synthesized by the one-pot Biginelli reaction using easily and cheaply available sulfamic acid as a catalyst. This synthesis was carried out by ultrasonic radiation at a power of 120 W for 40–60 min for a variety of compounds, and this approach was used to prepare a series of helicid derivatives with good purities and good yields (85–95%). In this study, we did some comparative experiments using different catalysts, and we found that sulfamic acid was the best catalyst. Six novel helicid derivatives **4a–4f** have been synthesized by reacting compounds **3a–3f** with sodium methoxide in methanol at room temperature to give good yields (89–95%).

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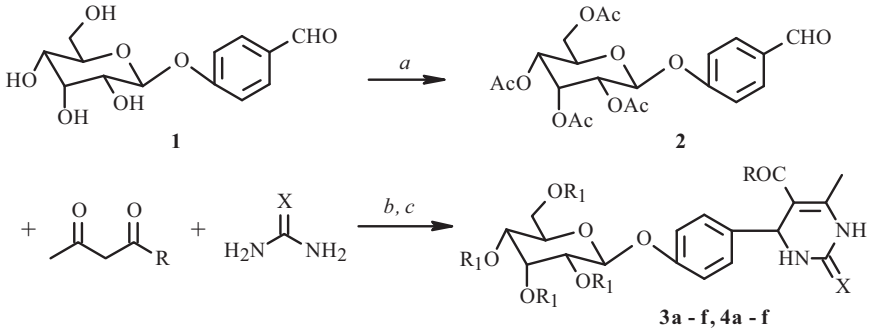
TABLE 1 Sedative-Hypnotic Activities of the Target Compounds Evaluated Using the Spontaneous Locomotor Activity Test

Compound	Dose, mg·kg^{-1}	Number of movements per minute (movements/min)			
		0 min	after 30 min	after 60 min	after 90 min
A	–	204.33±35.76	168.50±50.75	153.33±57.67	157.83±57.96
B	20	200.17±24.44	0.00±0.00***	14.00±31.45**	0.00±0.00***
1	200	192.33±38.53	159.17±20.80	171.00±24.22	172.33±29.23
2	200	193.17±45.96	128.30±62.82	148.50±64.11	153.50±57.51
3a	200	197.67±46.80	53.00±54.86*	61.67±62.84	32.33±15.33**
3b	200	193.67±12.52	113.00±69.84	123.00±61.41	87.33±83.85
3c	200	197.33±36.31	82.17±48.46*	117.33±50.57	111.50±55.71
3d	200	190.33±20.72	87.50±49.29*	147.67±51.02	96.00±50.04
3e	200	188.83±42.36	72.83±42.30**	96.00±66.48*	95.50±31.89
3f	200	205.00±32.01	88.50±40.40*	91.33±58.91*	114.17±47.74
4a	200	197.67±9.07	32.83±52.34**	58.67±74.19	18.50±27.52***
4b	200	197.50±22.90	108.50±63.98	109.17±73.55	131.17±73.96
4c	200	192.67±26.16	92.00±73.65	85.50±84.80	91.83±69.01
4d	200	200.33±24.94	136.67±49.82	123.00±54.60	85.83±31.38
4e	200	198.17±44.48	130.17±87.17	110.50±67.15	132.50±58.63
4f	200	200.67±40.48	145.67±82.15	163.17±51.97	164.33±46.41

Values are means ±S. *P<0.05, **P<0.01, ***P<0.001 compared with A, A: saline, B: diazepam, **1**: helicid, **2**: 4-formylphenyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-allopyranoside.



3a, 4a: R = Me, X = O; **3b,4b:** R = Me; X = S; **3c, 4c:** R = OMe, X = O; **3d, 4d:** R = OMe, X = S
3e, 4e: R = OEt, X = O; **3f, 4f:** R = OEt, X = S; **3a - f:** R_1 = Ac; **4a - f:** R_1 = H

a. Ac_2O, DMF, triethylamine; *b*. sulfamic acid, ultrasonic radiation, 60°C, EtOH; *c*. NaOMe, MeOH, room temperature

Scheme 1

In summary, twelve novel helicid derivatives were successfully synthesized, characterized, and tested for sedative-hypnotic activity in our study, which suggested that these helicid derivatives might 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

4-Formylphenyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-allopyranoside (2). Acetic anhydride (2.5 g, 25 mmol) was added dropwise to a solution of helicid (**1**) (1.0 g, 3.5 mmol) in 2 mL of DMF and 3 mL of triethylamine in an ice bath. The mixture was stirred vigorously at room temperature for 5 h and then poured into 20 mL of ice water. The precipitate was filtered, washed with ice water, and recrystallized to get a white powder (**2**); yield 94%, mp 140–142°C (lit.[13], 135–136°C).

General Procedure for the Preparation of Compounds 3a–3f. A mixture of compound **2** (2 mmol), the 1,3-dicarbonyl compound (3 mmol), urea or thiourea (3 mmol), and sulfamic acid (0.6 g) was exposed to ultrasonic radiation at a power of 120 W for 40–60 min; the temperature at the end of the reaction was 60°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and poured into ice water and stirred for 5 to 10 min. The solid was filtered, washed with ice water, and then recrystallized from ethanol to afford pure products **3a–3f**.

5-Acetyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidin-2(1*H*)-one (3a). This compound was prepared from **2**, acetylacetone, and urea; yield 93%, white powder, mp 182–184°C. IR (KBr, ν, cm^{-1}): 3434, 3291, 2991, 1618, 1508, 1215, 1084, 1010, 847, 804. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.99 (3H, s, CH_3), 2.03–2.50 (15H, m, $5CH_3CO$), 4.15–4.36 (3H, m), 4.95–5.00 (2H, m, OCHO, CH), 5.22–5.61 (3H, m), 7.03–7.53 (4H, m, ArH), 7.79 (1H, s, NH), 9.15(1H, s, NH). HR-MS(ESI) calcd for $C_{27}H_{32}N_2Na_1O_{12}$ $[M + Na]^+$ 599.1847, found 599.1819.

5-Acetyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidine-2(1*H*)-thione (3b). This compound was prepared from **2**, acetylacetone, and thiourea; yield 85%, white powder, mp 160–161°C. IR (KBr, ν, cm^{-1}): 3288, 3181, 2994, 1754, 1614, 1453, 1223, 1089, 1044, 852, 777. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.98 (3H, s, CH_3), 1.99–2.32 (15H, m, $5CH_3CO$), 4.23–4.39 (3H, m), 4.78–5.00 (2H, m, OCHO, CH), 5.25–5.79 (3H, m), 7.03–7.51 (4H, m, ArH), 9.73 (1H, s, NH), 10.28 (1H, s, NH). HR-MS (ESI) calcd for $C_{27}H_{32}N_2Na_1O_{11}S_1$ $[M + Na]^+$ 615.1619, found 615.1616.

5-Methoxycarbonyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidin-2(1*H*)-one (3c). This compound was prepared from **2**, methyl acetoacetate, and urea; yield 95%, white powder, mp 140–142°C. IR (KBr, ν, cm^{-1}): 3321, 3231, 3115, 2953, 1750, 1667, 1508, 1222, 1091, 1038, 754, 717. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.00 (3H, s, CH_3), 1.98–2.24 (12H, m, $4CH_3CO$), 3.53 (3H, s, OCH_3), 4.18–4.36 (3H, m), 4.95–5.00 (2H, m, OCHO, CH), 5.11–5.61 (3H, m), 7.01–7.19 (4H, m, ArH), 7.73 (1H, s, NH), 9.21 (1H, s, NH). HR-MS(ESI) calcd for $C_{27}H_{32}N_2Na_1O_{13}$ $[M + Na]^+$ 615.1797, found 615.1810.

5-Methoxycarbonyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidine-2(1*H*)-thione (3d). This compound was prepared from **2**, methyl acetoacetate, and thiourea; yield 90%, white powder, mp 118–120°C. IR (KBr, ν, cm^{-1}): 3323, 2954, 1754, 1608, 1564, 1434, 1223, 1095, 1045, 854, 719. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.97 (3H, s, CH_3), 1.98–2.27 (12H, m, $4CH_3CO$), 3.54 (3H, s, OCH_3), 4.16–4.35 (3H, m), 4.93–5.00 (2H, m, OCHO, CH), 5.12–5.60 (3H, m), 7.01–7.19 (4H, m, ArH), 9.64 (1H, s, NH), 10.35 (1H, s, NH). HR-MS(ESI) calcd for $C_{27}H_{32}N_2Na_1O_{12}S_1$ $[M + Na]^+$ 631.1568, found 631.1589.

5-Ethoxycarbonyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidin-2(1*H*)-one (3e). This compound was prepared from **2**, ethyl acetoacetate, and urea; yield 94%, white powder, mp 104–106°C. IR (KBr, ν, cm^{-1}): 3340, 3244, 3119, 2979, 1755, 1698, 1508, 1444, 1091, 1044, 758, 711. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.17 (3H, t, J = 7.2, OCH_2CH_3), 2.00 (3H, s, CH_3), 1.98–2.24 (12H, m, $4CH_3CO$), 4.01 (2H, q, J = 7.2, OCH_2CH_3), 4.15–4.36 (3H, m), 4.95–4.98 (2H, m, OCHO, CH), 5.11–5.61 (3H, m), 7.07–7.20 (4H, m, ArH), 7.71 (1H, s, NH), 9.19 (1H, s, NH). HR-MS(ESI) calcd for $C_{28}H_{34}N_2Na_1O_{13}$ $[M + Na]^+$ 629.1953, found 629.1930.

5-Ethoxycarbonyl-6-methyl-4-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-allopyranosyloxy)benzylidene]-3,4-dihydropyrimidine-2(1*H*)-thione (3f). This compound was prepared from **2**, ethyl acetoacetate, and thiourea; yield 88%, white powder, mp 100–102°C. IR (KBr, ν, cm^{-1}): 3321, 3202, 2982, 1756, 1710, 1652, 1608, 1451, 1219, 1094, 854, 712. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.13 (3H, t, J = 4.8, OCH_2CH_3), 2.00 (3H, s, CH_3), 2.01–2.31 (12H, m, $4CH_3CO$), 4.02 (2H, q, J = 7.2, OCH_2CH_3), 4.15–4.36 (3H, m), 4.95–4.98 (2H, m, OCHO, CH), 5.11–5.61 (3H, m, CH), 7.07–7.20 (4H, m, ArH), 9.65 (1H, s, NH), 10.36 (1H, s, NH). HR-MS(ESI) calcd for $C_{28}H_{34}N_2Na_1O_{12}S_1$ $[M + Na]^+$ 645.1725, found 645.1738.

General Procedure for the Synthesis of Compounds 4a–4f. To a solution of compounds **3a–3f** (2 mmol) in 20 mL of methanol, 20 mL of methanol solution of 0.2 mol/L sodium methoxide was added. The mixture was stirred for 5 h at room temperature. The solution was concentrated by evaporation in vacuo in methanol, and the residue was purified by chromatography (MeOH–CH_2Cl_2, 1:10, v/v) to give pure compounds **4a–4f**.

5-Acetyl-6-methyl-4-(4-β-D-allopyranosyloxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4a). This compound was prepared from **3a**; yield 95%, white powder, mp 178–179°C. IR (KBr, ν, cm^{-1}): 3306, 2923, 2344, 1688, 1508, 1451, 1081, 1037, 763, 720. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.09 (3H, s, CH_3), 2.26 (3H, s, CH_3CO), 3.42–3.93 (6H, m), 4.48–5.20 (4H, br, 4-OH), 5.05–5.09 (2H, m, OCHO, CH), 6.95–7.16 (4H, m, ArH), 7.77 (1H, s, NH), 9.15 (1H, s, NH). HR-MS(ESI) calcd for $C_{19}H_{24}N_2Na_1O_8$ $[M + Na]^+$ 431.1425, found 431.1412.

5-Acetyl-6-methyl-4-(4-β-D-allopyranosyloxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione (4b). This compound was prepared from **3b**; yield 93%, white powder, mp 199–200°C.

IR (KBr, ν, cm^{-1}): 3288, 2925, 2847, 1692, 1574, 1508, 1463, 1085, 1033, 841, 769. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.09 (3H, s, CH_3), 2.26 (1H, s, CH_3CO), 3.42–3.93 (6H, m), 4.47–5.10 (4H, br, 4-OH), 5.05–5.09 (2H, m, OCHO, CH), 6.96–7.15 (4H, m, ArH), 9.70 (1H, s, NH), 10.24 (1H, s, NH). HR-MS(ESI) calcd for $C_{19}H_{24}N_2Na_1O_7S_1$ $[M + Na]^+$ 447.1196, found 447.1175.

5-Methoxycarbonyl-6-methyl-4-(4-β-D-allopyranosyloxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c). This compound was prepared from **3c**; yield 89%, white powder, mp 200–202°C. IR (KBr, ν, cm^{-1}): 3348, 2903, 2877, 1671, 1433, 1273, 1086, 937 810, 759. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.24 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 3.32–3.92 (6H, m), 4.45–5.09 (4H, br, 4-OH), 5.04–5.09 (2H, m, OCHO, CH), 6.94–7.15 (4H, m, ArH), 7.69 (1H, s, NH), 9.18 (1H, s, NH). HR-MS(ESI) calcd for $C_{19}H_{24}N_2Na_1O_9$ $[M + Na]^+$ 447.1374, found 447.1361.

5-Methoxycarbonyl-6-methyl-4-(4-β-D-allopyranosyloxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione (4d). This compound was prepared from **3d**; yield 92%, white powder, mp 174–176°C. IR (KBr, ν, cm^{-1}): 3390, 2927, 2340, 1696, 1434, 1320, 1230, 1180, 1103, 1078, 1036, 847, 605. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.29 (3H, s, CH_3), 3.45 (3H, s, OCH_3), 3.33–4.03 (6H, m), 4.51–5.13 (4H, br, 4-OH), 5.05–5.09 (2H, m, OCHO, CH), 6.96–7.13 (4H, m, ArH), 9.61 (1H, s, NH), 10.29 (1H, s, NH). HR-MS(ESI) calcd for $C_{19}H_{24}N_2Na_1O_8S_1$ $[M + Na]^+$ 463.1146, found 463.1136.

5-Ethoxycarbonyl-4-(4-β-D-allopyranosyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4e). This compound was prepared from **3e**; yield 91%, white powder, mp 180–182°C. IR (KBr, ν, cm^{-1}): 3361, 2978, 2931, 1694, 1508, 1226, 1089, 1038, 844, 759. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.09 (3H, t, J = 7.2, OCH_2CH_3), 2.24 (3H, s, CH_3), 3.98 (2H, q, J = 7.2, OCH_2CH_3), 3.33–3.91 (6H, m), 4.62–5.10 (4H, br, 4-OH), 5.04–5.09 (2H, m, OCHO, CH), 6.94–7.15 (4H, m, ArH), 7.67 (1H, s, NH), 9.14 (1H, s, NH). HR-MS(ESI) calcd for $C_{20}H_{26}N_2Na_1O_9$ $[M + Na]^+$ 461.1531, found 461.1508.

5-Ethoxycarbonyl-4-(4-β-D-allopyranosyloxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (4f). This compound was prepared from **3f**; yield 93%, white powder, mp 182–184°C. IR (KBr, ν, cm^{-1}): 3307, 2971, 2925, 1692, 1608, 1508, 1086, 1035, 841, 768. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.10 (3H, t, J = 7.2, OCH_2CH_3), 2.29 (3H, s, CH_3), 4.02 (2H, q, J = 7.2, OCH_2CH_3), 3.42–3.91 (6H, m), 4.45–5.10 (4H, br, 4-OH), 5.04–5.12 (2H, m, OCHO, CH), 6.94–7.13 (4H, m, ArH), 9.61 (1H, s, NH), 10.29 (1H, s, NH). HR-MS(ESI) calcd for $C_{20}H_{26}N_2Na_1O_8S_1$ $[M + Na]^+$ 477.1302, found 477.1288.

Mice (Kunming strain) weighting 18–22 g were obtained from West China School of Pharmacy, Sichuan University (Chengdu, China). Diazepam was purchased from Huayin Jinqiancheng 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 locomotions in mice using an actophotometer [14, 15]. Ninety-six mice were randomized into 16 groups of 6 mice each (3 male and 3 female). When testing, 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 at 0, 30, 60, and 90 min after the drugs and saline injection, respectively. The data were expressed as number of movements per minute, averaged over 5 min.

The results of the spontaneous locomotor activity test are shown in Table 1. According to the data, helicid (**1**) and 4-formylphenyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-allopyranoside (**2**) exhibited mild sedative-hypnotic activities. The sedative-hypnotic activities of compounds **3a**, **3c**, **3d**, **3e**, **3f**, and **4a** were better than that of helicid (**1**). Except for compound **3b**, the higher sedative-hypnotic activities of derivatives **3a**, **3c**, **3d**, **3e,** and **3f** suggested that the introduction of the acetyl group in the sugar moiety led to an increase in the sedative-hypnotic effect. So, further modification of helicid should be worthwhile.

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