

Hao Sun, Chengxiang Shang, Longfei Jin and Jian Zhang*

Synthesis and antioxidant activity of a series of novel 3-chalcone-substituted 1,4-dihydropyridine derivatives

Abstract: New 3-chalcone-substituted 1,4-dihydropyridine (DHP) derivatives have been synthesized based on dimethyl or diethyl 2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate. Their structures were confirmed by IR, ¹H NMR, ¹³C NMR, and elemental analyses. The synthesized compounds were also screened for antioxidant properties.

Keywords: antioxidant; chalcone; 1,4-dihydropyridine; synthesis.

*Corresponding author: Jian Zhang, College of Chemistry and Materials, South-Central University for Nationalities, Wuhan 430074, PR China, e-mail: jianzhangye@gmail.com

Hao Sun, Chengxiang Shang and Longfei Jin: College of Chemistry and Materials, South-Central University for Nationalities, Wuhan 430074, PR China

substituents in the 3- and 5-positions. The structure-activity relationships of DHPs have indicated that the groups in the 3- and 5-positions are very important for pharmacological effects (Donkor et al., 1998; Foroumadi et al., 2002; Roh et al., 2008). It has been reported that DHPs substituted by flavone in the 4-position show a good bradycardic activity (Budriesi et al., 2005), but the DHPs substituted by flavone in the 3- or 5-position have not been described.

In view of these observations, we decided to introduce a chalcone moiety to the 3- or 5-position of the DHP ring, in the hope of changing the biological activities of these compounds. New 3-chalcone-substituted 1,4-DHP derivatives were synthesized, and their radical-scavenging effects investigated.

Results and discussion

Synthesis of compounds 4a–g

Introduction

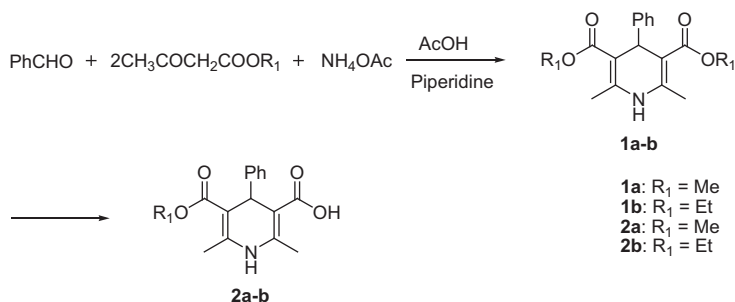
1,4-Dihydropyridine (DHP) and its derivatives have been studied because of their biological activities (Fernandes et al., 2003; Matsubara et al., 2004; Ryabokon et al., 2005) such as antitubercular (Fassihi et al., 2009), anti-inflammatory (Klegeris et al., 2002), and antitumor properties (Abbsa et al., 2010). Some of these compounds have been used for the treatment of cardiovascular diseases (nifedipine and amlodipine). Their antioxidant properties (Diaz-Araya et al., 1998; Cominacini et al., 2003; Berkels et al., 2005; Borovic et al., 2006; Plotniece et al., 2009; Vijesh et al., 2011) have received more attention in recent years. Studies on cardiac and liver membranes point to an antioxidant protective effect of these compounds that may contribute to their pharmacological activity (Hassan et al., 2009).

Chalcone and its derivatives have been reported to possess various pharmacological activities, including anti-inflammatory, anticancer, and antioxidant properties (Anto et al., 1995; Liu et al., 2007). Both 1,4-DHP and chalcone have antioxidant properties. For a long time, we have been interested in the study of 1,4-DHPs bearing different

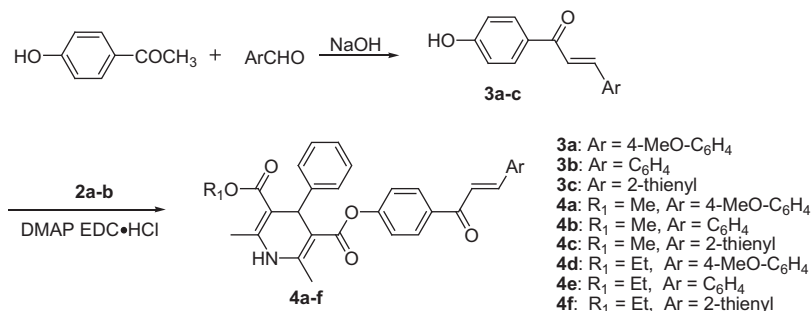
The synthetic route to compounds 4a–g is outlined in Schemes 1–3. The DHPs 1a,b (Scheme 1) were prepared using Hantzsch reaction (Hadizadeh et al., 2002). The monoester derivatives 2a,b were prepared by partial hydrolysis of 1a,b. The chalcones 3a–d (Schemes 2 and 3) were synthesized in high yields by using a general procedure reported in literature (Luo et al., 2012).

A subsequent condensation of 1,4-dihydropyridine acids (DHPAs) 2a,b with chalcones 3a–d furnished the desired 1,4-DHP derivatives 4a–g in 42–72% yields (Schemes 2 and 3).

Most of 1,4-DHP derivatives were prepared using a three-compound condensation reaction of β -keto ester, aromatic aldehyde, and ammonium hydroxide. At the beginning, we wanted to introduce the chalcone moiety directly to the 1,4-DHP ring by one-step synthesis. A chalcone containing a β -diketone group was allowed to react with aromatic aldehyde and ammonium hydroxide instead of β -keto ester. This approach was not successful. The target compounds 4a–g were synthesized via



Scheme 1

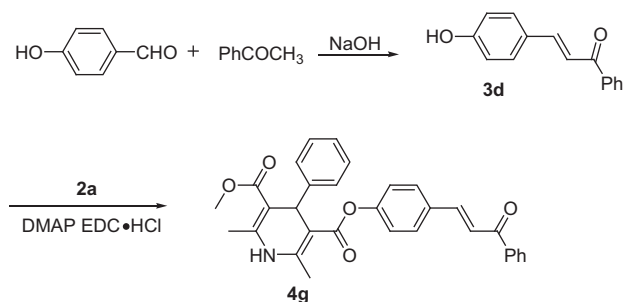


Scheme 2

4-dimethylaminopyridine (DMAP)/1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl)-catalyzed two-component condensation reaction of 1,4-DHP **2** and hydroxy-substituted chalcone. At first, we attempted to use dicyclohexylcarbodiimide (DCC) as a dehydrating agent, but the workup proved to be difficult. The preparation of **4a–g** was successful with EDC•HCl as the dehydrating agent. The structures of these products were fully consistent with their IR, ¹H NMR, and ¹³C NMR spectral data. The elemental analysis results were also satisfactory.

Antioxidant studies: DPPH radical-scavenging assay

This assay is based on the measurement of the scavenging ability of compounds toward the stable radical DPPH.



Scheme 3

Data for the decolorization of DPPH solution by the test samples are shown in Table 1, which express the free radical-scavenging capability. All compounds **4a–g** exhibit free radical-scavenging activities. Thienyl derivatives **4c** and **4f** show better scavenging activities than the remaining compounds **4**. Compared with compound **1a** and **1b**, compounds **4a–g** showed downward trend of radical-scavenging activity.

Conclusions

Compounds **4** are good scavengers of radicals.

Experimental section

IR spectra were taken in KBr pellets. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker 400 spectrometer at 400 and 100 MHz, respectively.

Compound	4a	4b	4c	4d	4e
IC ₅₀ (μM)	313±24	281±12	172±8	320±31	254±12
	4f	4g	1a	1b	
IC ₅₀ (μM)	184±10	621±43	132±7	156±11	

Table 1 DPPH radical-scavenging activity of compounds **1a,b** and **4a–g**.

General procedure for the synthesis of DHPs 1a,b

A solution of benzaldehyde (2.5 mL, 0.025 mol), a keto ester (4.4 mL, 0.05 mol), ammonium acetate (3.80 g, 0.05 mol), two drops of acetic acid, and two drops of piperidine in ethanol (50 mL) was stirred at the reflux temperature. After the completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The yellow residue of **1a,b** was crystallized from ethanol.

Dimethyl 2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (1a) Yellow crystals; yield 82%; mp 158–160°C; IR: 3340, 3060, 1712, 1690, 1650, 1631, 1370, 1123, 1090, 1020, 768, 703, 679 cm⁻¹; ¹H NMR: δ 7.14–7.42 (m, 5H), 5.70 (s, 1H), 4.92 (s, 1H), 3.57 (s, 6H), 2.32 (s, 6H).

Diethyl 2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (1b) Yellow crystals; yield 84%; mp 159–160°C; IR: 3290, 2996, 1711, 1674, 1332, 1209, 1123, 1090, 1020, 767, 691, 679 cm⁻¹; ¹H NMR: δ 7.12–7.31 (m, 5H), 5.55 (s, 1H), 4.11 (m, 4H), 4.02 (s, 1H), 2.37 (s, 6H), 1.25 (t, 6H).

General procedure for the synthesis of compounds 2a,b

DHP **1a,b** (0.01 mol) was suspended in methanol (30 mL) and treated with a solution of NaOH (1.60 g, 0.04 mol) in water at room temperature with stirring. The mixture was stirred under reflux for 5 h, cooled, quenched with water (200 mL), and filtered. The filtrate was treated with activated carbon (0.20 g), and the mixture was stirred at 55°C for 30 min. After cooling, the carbon was filtered off, the filtrate was acidified with 1 N HCl to pH 2.5, and the resultant precipitate of **2a,b** was filtered and crystallized from methanol.

5-(Methoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-DHP-3-carboxylic acid (2a) White crystals; yield 72%; mp 202–204°C; ¹H NMR: δ 11.66 (s, 1H), 8.75 (s, 1H), 7.20–7.09 (m, 5H), 4.88 (s, 1H), 3.54 (s, 3H), 2.25 (s, 6H).

5-(Ethoxycarbonyl)-2,6-dimethyl-4-phenyl-1,4-DHP-3-carboxylic acid (2b) White crystals; yield 75%; mp 191–192°C; ¹H NMR: δ 11.64 (s, 1H), 8.72 (s, 1H), 7.20–7.10 (m, 5H), 4.88 (s, 1H), 3.99–3.55 (m, 2H), 2.26 (s, 6H), 1.19–1.15 (t, 3H).

General procedure for the synthesis of chalcones 3a–d

A mixture of a solution of KOH (5.60 g) in 40 mL methanol, 4-hydroxyacetophenone (0.02 mol), or 4-hydroxybenzaldehyde (0.02 mol) was stirred under nitrogen atmosphere for 24 h and then acidified with 1 N HCl to pH 1. The resultant yellow solid of **3a–d** was filtered under reduced pressure and crystallized from methanol. The structures of compounds **3a–d** were confirmed by comparison of their melting points with those reported in the literature; **3a**: mp 181.2–182.3°C, lit. mp 180–182°C (Dimmock et al., 1998); **3b**: mp 172.4–173.2°C, lit. mp 172–173°C (Dimmock et al., 1998); **3c**: mp 172.6–173.8°C, lit. mp 172°C (Gul et al., 2008); **3d**: mp 180.6–181.7°C, lit. mp 180–181°C (Dimmock et al., 1998).

General procedure for the synthesis of compounds 4a–g

A mixture of compound **2a,b** (0.01 mol), compound **3a,d** (0.01 mol), 4-dimethylaminopyridine (0.20 g), and a solution of EDC•HCl (1.00 g) in dichloromethane (50 mL) was stirred under a nitrogen atmosphere at room temperature for 24 h and then concentrated on a rotary evaporator (water bath at 38°C). The yellow residue of **4a–g** was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:4).

4-[3-(E)-(4-Methoxyphenyl)acryloyl]phenyl-5-methyl-2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (4a) Yellow crystals; yield 72%; mp 101.1–102.3°C; IR: 3318, 3029, 2951, 1702, 1596 cm⁻¹; ¹H NMR: δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.30–7.27 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.90 (s, 1H), 5.19 (s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 1.28 (s, 6H); ¹³C NMR: δ 189.7, 168.1, 165.1, 161.8, 156.3, 154.7, 147.6, 145.0, 144.1, 135.5, 130.3, 129.9, 128.2, 127.9, 127.5, 126.5, 122.2, 119.6, 114.5, 104.7, 102.3, 55.4, 51.1, 39.7, 19.6, 19.2. Anal. Calcd for C₃₂H₂₉NO₆: C, 73.41; H, 5.58; N, 2.68. Found: C, 73.27; H, 5.56; N, 2.64.

Methyl 4-[3-(E)-phenylacryloyl]phenyl-2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (4b) Yellow crystals; yield 62%; mp 92.3–94.1°C; IR: 3338, 3032, 2952, 1700, 1604 cm⁻¹; ¹H NMR: δ 8.03 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 16.0 Hz, 1H, -CH-), 7.66 (d, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.45–7.44 (m, 3H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.31–7.27 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 1H), 5.19 (s, 1H), 3.68 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H); ¹³C NMR: δ 189.7, 168.0, 165.8, 156.4, 154.9, 147.5, 145.1, 143.9, 135.2, 134.8, 130.6, 130.0, 129.3, 129.0, 128.5, 128.2, 127.9, 122.3, 122.0, 104.8, 102.3, 51.1, 39.7, 19.7, 19.3. Anal. Calcd for C₃₁H₂₇NO₅: C, 75.44; H, 5.51; N, 2.84. Found: C, 75.27; H, 5.44; N, 2.82.

Methyl 4-[3-(E)-(2-thienyl)acryloyl]phenyl-2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (4c) Yellow crystals; yield 55%; mp 80.7–81.8°C; IR: 3336, 3026, 2946, 1698 cm⁻¹; ¹H NMR: δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.44 (br s, 1H), 7.37 (m, 3H), 7.31 (d, *J* = 15.6 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.10 (m, 3H), 6.49 (s, 1H), 5.19 (s, 1H), 3.67 (s, 3H), 2.38, 2.36 (2s, 6H); ¹³C NMR: δ 190.0, 168.0, 165.7, 154.8, 147.5, 143.9, 140.2, 137.3, 135.1, 132.1, 130.0, 129.9, 129.0, 128.6, 128.4, 128.2, 127.9, 126.5, 122.3, 104.8, 102.4, 51.1, 39.7, 19.7, 19.3. Anal. Calcd for C₂₉H₂₅NO₅S: C, 69.72; H, 5.04; N, 2.80; S, 6.42. Found: C, 69.58; H, 4.97; N, 2.75; S, 6.32.

Ethyl 4-[3-(E)-(4-methoxyphenyl)acryloyl]phenyl 2,6-dimethyl-4-phenyl-1,4-DHP-3,5-dicarboxylate (4d) Yellow crystals; yield 68%; mp 98.8–100.4°C; IR: 3337, 3026, 2951, 1698, 1597 cm⁻¹; ¹H NMR: δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 16.0 Hz, 1H), 7.61 (d, 2H, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 16.0 Hz, 1H), 7.37–7.28 (m, 3H), 7.21 (d, *J* = 6.8 Hz, 2H), 7.076 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.12 (s, 1H), 5.18 (s, 1H), 4.33–3.68 (m, 2H), 3.87 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 1.47–1.00 (m, 3H); ¹³C NMR: δ 189.7, 168.1, 165.9, 161.8, 156.4, 154.7, 147.6, 145.0, 144.2, 135.5, 130.4, 129.9, 128.2, 127.9, 127.5, 126.5, 122.2, 119.5, 114.5, 104.6, 102.2, 55.4, 51.1, 39.6, 19.7, 19.3, 14.3. Anal. Calcd for C₃₃H₃₁NO₆: C, 73.73; H, 5.81; N, 2.61. Found: C, 73.58; H, 5.73; N, 2.56.

Ethyl 4-[3-(E)-phenylacryloylphenyl-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4e) Yellow crystals; yield 67%; mp 87.2–88.5°C; IR: 3334, 3029, 2951, 1704, 1606 cm^{-1} ; ^1H NMR: δ 8.05 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 15.6 Hz), 7.65 (d, J = 6.6 Hz, 2H), 7.54 (d, J = 15.6 Hz, 1H), 7.46–7.40 (m, 3H), 7.40 (d, J = 8.4 Hz), 7.32–7.26 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), δ 5.22, (s, 1H), δ 5.18 (s, 1H), δ 3.60–3.51 (m, 2H), δ 2.37 (s, 3H), 2.34 (s, 3H), δ 1.31–1.26 (m, 3H); ^{13}C NMR: δ 189.7, 168.3, 166.0, 155.4, 155.0, 147.7, 145.2, 144.6, 135.2, 134.7, 130.8, 130.1, 129.1, 128.6, 128.4, 128.0, 126.6, 122.4, 121.9, 104.5, 101.9, 60.0, 39.7, 19.6, 19.1, 14.3. Anal. Calcd for $\text{C}_{32}\text{H}_{29}\text{NO}_5$: C, 75.72; H, 5.76; N, 2.76. Found: C, 75.56; H, 5.69; N, 2.74.

Ethyl 4-[3-(E)-(2-thienyl)acryloylphenyl-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4f) Yellow crystals; yield 42%; mp 78.2–79.6°C; IR: 3334, 3026, 2928, 1698, 1594 cm^{-1} ; ^1H NMR: δ 8.01 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 15.6 Hz, 1H), 7.38 (br s, 3H), 7.30 (d, J = 15.6, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.21 (br s, 2H), 7.11–7.07 (m, 3H), 5.97 (s, 1H), 5.18 (s, 1H), 3.68 (m, 2H), 2.42 (s, 3H), 2.40 (s, 1H), 1.28–1.23 (m, 3H); ^{13}C NMR: δ 189.1, 168.3, 165.9, 155.0, 147.8, 144.6, 140.1, 137.3, 135.0, 132.4, 129.9, 129.3, 128.5, 128.2, 128.1, 127.9, 126.5, 122.4, 120.5, 104.4, 101.9, 60.0, 39.7, 19.5, 19.1, 14.32. Anal. Calcd for $\text{C}_{30}\text{H}_{27}\text{NO}_5\text{S}$: C, 70.16; H, 5.30; N, 2.73. Found: C, 69.95; H, 5.27; N, 2.68.

Methyl 4-[3-oxo-3-phenylprop-1(E)-enyl]phenyl-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4g) Yellow crystals; yield 62%; mp 103.2–105.1°C; IR: 3339, 3026, 2948, 1698, 1603

cm^{-1} ; ^1H NMR: δ 8.03 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 16.0 Hz, 1H), 7.65 (d, J = 6.8 Hz, 2H), 7.51 (d, J = 16.0 Hz, 1H), 7.44 (br s, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.31–7.19 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 5.91 (s, 1H), 5.19 (s, 1H), 3.68 (s, 3H), 2.43 (s, 3H), δ 2.40 (s, 3H); ^{13}C NMR: δ 189.7, 168.2, 165.9, 154.9, 148.1, 147.7, 145.2, 144.3, 135.2, 134.7, 130.8, 130.1, 129.1, 128.6, 128.2, 127.9, 126.5, 122.4, 121.9, 104.6, 102.1, 51.2, 39.7, 19.6, 19.2. Anal. Calcd for $\text{C}_{31}\text{H}_{27}\text{NO}_5$: C, 75.44; H, 5.51; N, 2.84. Found: C, 74.34; H, 5.42; N, 2.80.

Evaluation of the antioxidative activity

The free radical-scavenging activity of test samples **4a–g** was determined using DPPH. Briefly, a methanol solution (3 mL) of 100 μM DPPH was mixed with 1 mL of different concentrations (from 10^{-5} to 10^{-3} mol) of compound (1 mL), and the mixture was incubated at 40°C. A decrease in absorbance was measured at 517 nm (Hitachi 557 UV-VIS spectrophotometer). The inhibition of colorization was expressed as percentage and IC_{50} (obtained from the inhibition curve).

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