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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antihypertensive activity evaluation in spontaneously hypertensive rats of lacidipine analogues

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Abstract Six analogues of lacidipine, (*E*)-diethyl 4-(2-(3-amino)-3-oxoprop-1-enyl)phenyl-2, 6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (compounds **1**–**6**), were synthesized and their antihypertensive effects in spontaneously hypertensive rats were evaluated by *ig* administration. Amongst the tested compounds, compound **5** exhibited the highest antihypertensive effect. The lasting time and potency of compound **5** showed a dose-dependent manner. The results suggested that *N-tert*-butyl acrylamide moiety at 2′-position of 4-phenyl in the structure of analogues of lacidipine is necessary to keep antihypertensive effects.

Keywords Antihypertensive effect · 1,4-Dihydropyridines · Lacidipine analogues · Spontaneously hypertensive rats (SHR)

Introduction

1,4-Dihydropyridines (1,4-DHPs), a class of calcium channel blockers (CCB), has been used extensively in clinic for the treatment of cardiovascular diseases, such as hypertension (Sabitha *et al*., 2003; Zolfigol *et al*., 2006). Interestingly, 1,4-DHP has emerged as one of the most important drug scaffold in the field of medicinal chemistry. 1,4-DHP derivatives have been found to exhibit anticancer (Sirisha *et al*., 2010), antitubercular (Kharkar *et al*., 2002), antibacterial (Dasgupta *et al*., 2010), anticoagulant (Kumar *et al*., 2011) and antiviral (Hilgeroth and Lilie, 2003) activities besides antihypertensive activity. 1,4-DHPs are also known to act as chemosensitizers in MDR tumour therapy (Edraki *et al*., 2009; Viale *et al*., 2011) and BACE-1 inhibitors (Choi *et al*., 2010). Therefore, synthesis and evaluation of novel 1, 4-DHPs derivatives are necessary to develop new drugs.

Lacidipine, a third generation CCB, exhibits the characteristic of long-acting, high potency as an antihypertension medication (McCormack and Wagstaff, 2003; Motomura *et al*., 1993). A dose of 2–8 mg of lacidipine a day can lower blood pressure for 24 h (Zanchetti *et al*., 2007). In addition to reduce blood pressure, lacidipine also possesses anti-atherosclerosis (Yetik-Anacak *et al*., 2010) by protecting endothelial function (Ferri *et al*., 1999), inhibiting adhesion molecules expression (Park *et al*., 2002), adjusting matrix metalloproteinases (Bellosta *et al*., 2001) and beneficial effect on bone metabolism (Halici *et al*., 2008).

The structure–activity relationship of 1,4-DHPs indicates that ester structures at 3- and 5-position are necessary to keep their antihypertensive activity (Zhou *et al*., 2005). There is a *tert*-butyl acrylate moiety at 2′-position of 4-phenyl in the structure of lacidipine. The synthesis and activity of *N-tert*-butyl acrylamide moiety at 2′-position of 4-phenyl of 1,4-DHP have not been studied yet. The aim of this study is to synthesize and evaluate new analogues of lacidipine. Therefore (*E*)-diethyl 4-(2-(3-substitutedamino)-3-oxoprop-1-enyl)phenyl-2, 6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (compounds **1**–**6**, Fig. 1) were synthesized and their antihypertensive effects in spontaneously hypertensive rats (SHR) were evaluated. Here, we report the synthesis and antihypertensive effect of six lacidipine analogues.

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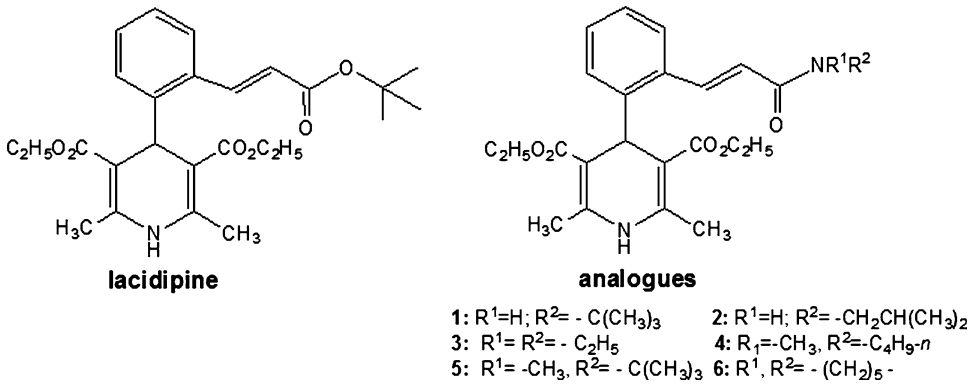


Fig. 1 The structures of lacidipine and its analogues

Materials and methods

Trichloroacetic acid, *tert*-butylamine, diethylamine, *iso*-butylamine, piperidine and solvent were purchased from SCRC, China. *N*-methyl-*tert*-butylamine and *N*-methyl-*n*-butylamine were purchased from Alfa Aesar. Ethyl 3-aminocrotonate, lacidipine and chloroacetamides were prepared in our laboratory.

All melting points were determined on a Beijing micromelting-point apparatus and thermometer was uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 300 MHz with an internal reference tetramethylsilane (TMS), Bruker NMR spectrometer. All chemical shifts are reported in parts per million (ppm). Mass spectra were performed on a Shimadzu GC–MS-QP2010 instrument. The blood pressure of SHR was measured by a BP-6 animal non-invasive tail-cuff plethysmography, Chengdu Thai Union Technology Co., Ltd., China. SHR were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd., China. The experimental protocol was approved by Ethic's Committee of Xi'an Jiaotong University.

General procedure for synthesis of phosphonium chloride

2-*N*-substituted amino-2-oxoethyl phosphonium chloride can easily be prepared by refluxing of equal mole of triphenylphosphine and corresponding *N*-substituted chloroacetamide in toluene for 8–12 h.

2-*N*-*tert*-butyl-2-oxoethyl phosphonium chloride: yield 84.5%, m.p: 227–230°C.

2-*N*-*iso*-butyl-2-oxoethyl phosphonium chloride: yield 98.0%, m.p: 188–190°C.

2-*N*,*N*-diethyl-2-oxoethyl phosphonium chloride: yield 78.0%, m.p: 185–187°C.

2-*N*-methyl-*N*-*n*-butyl-2-oxoethyl phosphonium chloride: yield 78.2%, m.p: 165–168°C.

2-*N*-methyl-*N*-*tert*-butyl-2-oxoethyl phosphonium chloride: yield 81.5%, m.p: 172–175°C.

2-(1-Piperidyl)-2-oxoethyl phosphonium chloride: yield 75.1%, m.p: 159–163°C.

General procedure for synthesis of compounds **1–6**

To a mixture containing phthalaldehyde (2.0 g, 14.9 mmol), phosphonium chloride (14.9 mmol) and dichloromethane (50 ml) cooled to 0°C was added dropwise a solution of diisopropylethylamine (3 ml, 17.2 mmol) in dichloromethane (10 ml) under nitrogen atmosphere. After addition, the resulting mixture was stirred for 6 h at room temperature, washed with water (50 ml), diluted hydrochloric acid (1 M, 50 ml×2) and brine (50 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a brown residue, which was suspended in isopropanol (60 ml). Ethyl 3-aminocrotonate (3.87 g, 30 mmol) and trichloroacetic acid (5.72 g, 35 mmol) were added to above suspension cooled to 0°C. After addition, the mixture was stirred for 3 h below 3°C and for 3 h at room temperature, concentrated in vacuo to give a residue, which was dissolved in ethyl acetate (100 ml). The organic phase was washed with water (100 ml), saturated $NaHCO_3$ solution (100×2 ml), diluted hydrochloric acid (1 M, 50 ml) and brine (50 ml×2), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether–ethyl acetate/8:1–3:1) to afford the target compound as pale yellow solid. The solid was recrystallized in ethyl acetate to produce pure compounds **1–6**.

*(E)-diethyl 4-(2-(3-(tert-butylamino)-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**)*

Yield 49.1%; m.p 213.0–215.5°C; MS (*m/z*): 455 (M + 1), 477 (M + Na); IR, ν(cm^{-1}): 3446, 3353, 1691, 1654; ^{1}H NMR ($CDCl_3$), δ: 1.16 (t, J = 5.40 Hz, 6H, 2×–CH_3), 1.43 (s, 9H, 3×–CH_3), 2.31 (s, 6H, 2×–CH_3), 4.00–4.04 (m, 4H, 2×–OCH_2–), 5.33 (s, 1H, CH), 5.57 (s, 1H, –NH–), 5.82 (s, 1H, –NH–CO), 6.13 (d, J = 15.38 Hz, 1H, CH), 7.11 (t, J = 5.51 Hz 1H, Ar–H), 7.22 (t, J = 4.73 Hz, 1H,

Ar–H), 7.37(d, $J = 6.34$ Hz, 2H, Ar–H), 8.26 (d, $J = 15.49$ Hz, 1H, CH).

*(E)-Diethyl 4-(2-(3-(iso-butylamino)-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2**)*

Yield 43.3%; m.p 197–200°C; MS (*m/z*): 455 (M + 1); IR, *v* (cm^{-1}): 3450, 3352, 1695, 1660; ^1H NMR ($CDCl_3$) δ:0.97 (d, $J = 6.61$ Hz, 6H, 2×–CH_3), 1.16 (t, $J = 5.54$ Hz 6H, 2×–CH_3), 1.85 (m, 1H, CH), 2.32 (s, 6H, 2×–CH_3), 3.23 (m, 2H, –CH_2–), 3.98–4.03 (m, 4H, 2× –OCH_2–), 5.34 (s, 1H, CH), 5.82 (s, 2H, 2×–NH–), 6.23(d, 1H, CH, $J = 15.31$ Hz), 7.12–7.43 (m, 4H, Ar–H), 8.33 (d, 1H, CH, $J = 15.36$ Hz).

*(E)-Diethyl 4-(2-(3-(N,N-diethylamino)-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3**)*

Yield 26.1%; m.p 215–218°C; MS (*m/z*): 455 (M + 1), 477 (M + Na); IR, *v* (cm^{-1}): 3350, 1697, 1658; ^1H NMR ($CDCl_3$) δ:1.16 (t, $J = 5.63$ Hz, 6H, 2×–CH_3), 1.26 (t, $J = 5.57$ Hz, 6H, 2×–CH_3), 2.30 (s, 6H, 2×–CH_3), 3.48 (m, 4H, 2×–NCH_2–), 3.94–4.01 (m, 4H, 2×–OCH_2–), 5.33 (s, 1H, CH), 6.06 (s, 1H, –NH–), 6.63(d, $J = 15.16$ Hz, 1H, CH), 7.15 (t, $J = 5.65$ Hz, 1H, Ar–H), 7.25 (t, $J = 5.58$ Hz, 1H, Ar–H), 7.41(d, $J = 7.30$ Hz, 2H, Ar–H), 8.41 (d, $J = 15.13$ Hz, 1H, CH).

*(E)-Diethyl 4-(2-(3-(N-methyl-N-n-butyl)amino-3-oxoprop-1-enyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4**)*

Yield 36.6%; m.p 181–183°C; MS (*m/z*): 468 (M); IR, *v* (cm^{-1}): 3355, 1695, 1663; ^1H NMR ($CDCl_3$) δ: 0.96 (t, $J = 5.60$ Hz, 3H, –CH_3), 1.13 (t, $J = 5.68$ Hz, 6H, 2× –CH_3), 1.25 (m, 2H, –CH_2–), 1.36 (m, 2H, –CH_2–), 2.30 (s, 6H, 2×–CH_3), 3.10 (s, 3H, N–CH_3), 3.44 (t, $J = 6.16$ Hz, 2H, N–CH_2–), 3.98–4.11 (m, 4H, 2×–OCH_2–), 5.32 (s, 1H, CH), 5.77 (s, 1H, –NH–), 6.67(d, $J = 15.24$ Hz, 1H, CH), 7.13 (t, $J = 5.83$ Hz, 1H, Ar–H), 7.22 (t, $J = 5.04$ Hz, 1H, Ar–H), 7.40 (d, $J = 6.63$ Hz, 2H, Ar–H), 8.38 (d, $J = 14.31$ Hz, 1H, CH).

*(E)-Diethyl 4-(2-(3-(N-methyl-N-tert-butyl)amino-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5**)*

Yield 20.5%; m.p 164–167°C; MS (*m/z*): 468 (M), 491 (M + Na); IR, *v* (cm^{-1}): 3350, 1697, 1661; ^1H NMR ($CDCl_3$), δ: 1.14 (t, $J = 4.51$ Hz, 6H, 2×–CH_3), 1.47 (s, 9H, 3×–CH_3), 2.30 (s, 6H, 2×–CH_3), 3.05 (s, 3H, N–CH_3), 4.00–4.04 (m, 4H, 2×–OCH_2–), 5.32 (s, 1H, CH), 5.68 (s, 1H, –NH–), 6.65 (d, $J = 15.30$ Hz, 1H, CH), 7.12 (t, $J = 5.72$ Hz, 1H, Ar–H), 7.26 (t, $J = 4.7$ Hz, 1H, Ar–H), 7.46 (d, $J = 6.6$ Hz, 2H, Ar–H), 8.36 (d, $J = 15.38$ Hz, 1H, CH).

*(E)-Diethyl 4-(2-(3-(piperidin-1-yl)-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**6**)*

Yield 43.5%; m.p 213.5–216.0°C; MS (*m/z*): 466 (M), 489 (M + Na); IR, *v* (cm^{-1}): 3355, 1698, 1667; ^1H NMR ($CDCl_3$) δ:1.14 (t, $J = 5.70$ Hz, 6H, 2×–CH_3), 1.60–1.67 [m, 6H, –$(CH_2)_3$–)], 2.31 (s, 6H, 2×–CH_3), 3.63 (m, 4H, –CH_2–N–CH_2–), 4.02 (m, 4H, 2×–OCH_2–), 5.31 (s, 1H, CH), 5.90 (s, 1H, –NH–), 6.71(d, $J = 15.21$ Hz, 1H, CH), 7.12-7.43 (m, 4H, Ar–H), 8.34 (d, $J = 15.30$ Hz, 1H, CH).

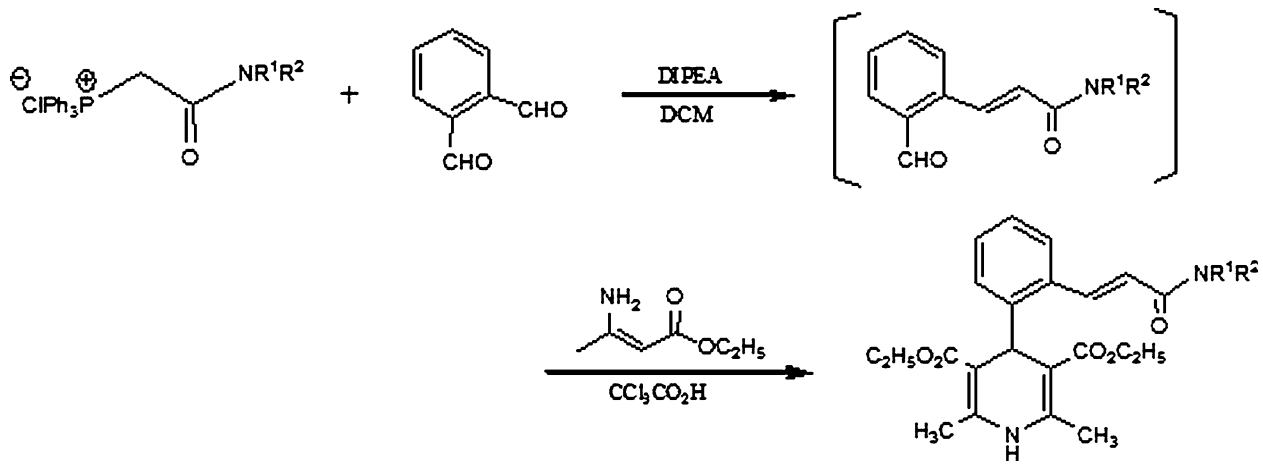
Antihypertensive activity

The blood pressure was measured via a non-invasive tail-cuff plethysmography method. Male SHR weighing 240–280 g was trained for 5 days, loaded in a cage and set into test box in which the temperature was 37°C. The tail was passed through the pulse detector and a cuff balloon and stabilized for 10 to 15 min so that the tail artery was fully expanded. When the test signal was stable, the blood pressure was measured and systolic blood pressure was read. The measurement was repeated two times, and an average was recorded as the blood pressure of an individual animal. The values of blood pressure were measured before and at various hours after *ig* administration of drugs.

Result and discussion

Organic synthesis

In the synthesis of compounds **1**–**6**, phosphonium chloride was converted to the corresponding Wittig reagent in situ by reaction with DIPEA (Raju *et al*., 2009). The reaction of Wittig intermediate with equal mole of phthalaldehyde gave (*E*)-*N*-substituted-3-(2-formylphenyl) acrylamide. With simple work-up, treatment of the acrylamide with 2 equivalent of ethyl β-aminocrotonate in isopropanol in the presence of trichloroacetic acid afforded the corresponding compounds **1**–**6** in 20.5–49.5% yields (Scheme 1). The yields were not optimized. The structures of compounds **1**–**6** were characterized by ^1H NMR, MS and IR.



Scheme 1 Synthesis of compounds **1–6**

Results of antihypertensive activity

The antihypertensive activities of compounds **1–6** in SHR were evaluated by *ig* administration. The results are summarized in Table 1.

The data indicated that antihypertensive effects of compound **1** and **5** were near to lacidipine and antihypertensive effects of compound **2–4** and **6** were weaker than lacidipine. Furthermore, the results demonstrated that antihypertensive effects of compound **1–6** were closely related to the structure of the *N*-substituted group in acrylamide moiety at 2′-position of 4-phenyl. The antihypertensive potency of compounds **1** and **5** was higher than that of compounds **2–4** and **6** because there is a *N-tert*-butyl moiety in both the compounds **1** and **5**. So *N-tert*-butyl is a favourable group to keep the antihypertensive effect. The liposolubility (log *P* in Table 1) of compounds **1–6** does not connect with their antihypertensive effects. Compound **5** is the most effective drug in the tested compounds.

Table 1 Effects of compound **1–6** on systolic blood pressure (SBP) in SHR at 1 h ($\bar{x} \pm s, n = 6$

Drugs	Log P[b]	SBP before drugs (mmHg)	SBP after drugs administration (mmHg)[c]	
			Measured value	Reduced value
1	1.82	164 ± 4	120 ± 10	44 ± 11
2	2.17	167 ± 6	152 ± 6	15 ± 3
3	1.85	166 ± 5	133 ± 11	33 ± 10
4	2.45	156 ± 11	129 ± 3	27 ± 11
5	2.05	163 ± 7	121 ± 12	46 ± 13
6	1.91	162 ± 10	140 ± 7	22 ± 10
Lacidipine	2.50	164 ± 3	114 ± 11	50 ± 12
Solvent[a]		156 ± 3	155 ± 7	1 ± 3

[a] 30% Tween-80, 20% EtOH, 50% distilled water

[b] Predicted by ChemDraw

[c] All compounds were administrated by *ig* 1.0 mg/kg

The antihypertensive effects of compound **5** in SHR in different dose and lasting time are summarized in Table 2.

Compound **5** was administrated by *ig* at 0.5, 1.0 and 2.0 mg/kg. The data in Table 2 showed that the antihypertensive effect, as well as lasting time, was dose dependent. The antihypertensive effect of compound **5** can last for 4 h at a dose of 1.0 mg/kg and for 20 h at 2.0 mg/kg, respectively.

Conclusions

Six analogues of lacidipine were synthesized and their antihypertensive activities in SHR were evaluated by *ig*

Table 2 Effects of compound 5 on systolic blood pressure in SHR ($\bar{x} \pm s, n = 6$)

Dose (mg/kg)	SBP before drugs (mmHg)	Reduced SBP after drugs administration (mmHg)					
		1 h	2 h	4 h	6 h	8 h	20 h
0.5	162 ± 5	11 ± 5					
1.0	162 ± 3	46 ± 8	34 ± 5	20 ± 6	3 ± 3		
2–0	153 ± 3	44 ± 9	53 ± 4	47 ± 3	45 ± 5	43 ± 6	25 ± 2
0[a]	156 ± 3	1 ± 3	−1 ± 2	−1 ± 3	−2 ± 3	−3 ± 3	−2 ± 4

[a] 30% Tween-80, 20% EtOH, 50% distilled water

administration. The data demonstrated that antihypertensive effects of compound **1** and **5** are near to lacidipine and antihypertensive effects of compound **2**, **3**, **4** and **6** are weaker than that of lacidipine. The results suggested that *N-tert*-butyl acrylamide moiety at 2′-position of 4-phenyl in the structure of analogues of lacidipine is a favourable group to keep their antihypertensive activity, and the lasting time and activity of compound **5** are dose dependent.

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