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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

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

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Abstract The antihypertensive activity of nitrendipine analogues can be improved by properly lengthening its alkyl chain in 3- or 5-position. Nitrendipine and its seven analogues were synthesized, and their antihypertensive activities in spontaneously hypertensive rats (SHR) were evaluated by *ig* administration. It was found that 5-*n*-heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [(±)-5] exhibited the strongest antihypertensive effect amongst eight compounds. (+)-5-*n*-heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [(+)-5] was also prepared. Antihypertensive activities of (±)-5 and (+)-5 in SHR were compared. The results showed that (±)-5 and (+)-5 had a higher potency than nitrendipine, and (+)-isomer was 1.79-fold the raceme at a dose of 2 mg/kg.

Keywords Antihypertensive activity · 1,4-Dihydropyridines · Nitrendipine analogues · Enantiomer · SHR

Introduction

1,4-Dihydropyridines (DHPs), a class of calcium antagonist, is widely used in clinic for the treatment of cardiovascular diseases, such as hypertension, etc. (Sabitha *et al*., 2003; Zolfigol *et al*., 2006). Amlodipine (Liu *et al*., 2010; Levine *et al*., 2003), lacidipine (Raju *et al*., 2009; Motomura *et al*., 1993), felodipine (Trachtman *et al*., 2003), etc. are long-acting and high active DHPs calcium antagonists. Though effective as antihypertensive drugs, they are relatively complicated in producing and high in manufacturing cost, and some intermediates are harmful to environment. Therefore, it is necessary to develop new DHPs calcium antagonists with simple structure, facile synthesis and effective antihypertensive.

Nitrendipine is a DHPs calcium antagonist with a simple structure, but its effectiveness is not high. Studies indicate that the antihypertensive activity of nitrendipine analogues can be improved by lengthening its alkyl chain in 3- or 5-position (Baindur *et al*., 1993; Peri *et al*., 2000). For this reason, we synthesized nitrendipine and its seven analogues [3-methyl 5-straight alkyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] (Fig. 1). Antihypertensive activity of compounds 1–8 in spontaneously hypertensive rats (SHR) was compared. It was found that 5-*n*-heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (compound **5**) exhibited the strongest antihypertensive effect amongst all synthesized compounds. The substituted groups in 3- and 5-position in compound **5** are different, so there are a couple of enantiomers. Studies showed that calcium antagonistic activity of the *S*-enantiomer and *R*-enantiomer is different. For example, *S*-enantiomer of nilvadipine is about 100 times more potent than the *R*-enantiomer in its antihypertensive action (Fu *et al*., 2003; Tokuma and Noguchi, 1995). In the case of amlodipine, *S/R* is 1000 (Park *et al*., 2006). Meanwhile it was elucidated that (*S*)-(+)-enantiomer is the active isomer in the nitrendipine analogues (Zhang *et al*., 2010). So (+)-5-*n*-heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Fig. 1) was also prepared. The

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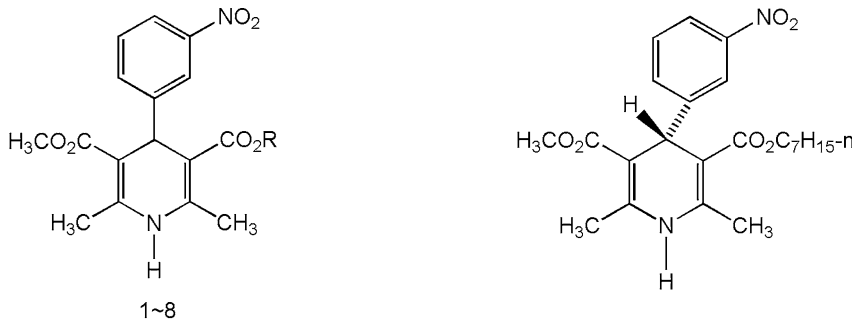
Fig. 1 The structures of synthesized compounds



1: R=CH_3; 2: R=C_2H_5; 3: R=n-C_3H_7; 4: R=n-C_5H_{11};

5:R=n-C_7H_{15}; 6: R=n-C_8H_{17}; 7: R=n-$C_{10}H_{21}$; 8: R=n-$C_{12}H_{25}$

antihypertensive activity of (±)-5 and (+)-5 in SHR was compared. Here, we report the synthesis and antihypertensive activity of nitrendipine and its seven analogues.

Materials and methods

Quinidine was obtained from J&K Chemical Ltd. 3-nitrobenzaldehyde, methyl acetoacetate, glacial acetic acid, piperidine and solvent were purchased from SCRC, China. Straight alkyl 3-aminocrotonate[methyl ester–dodecyl ester] was prepared by ourselves.

All melting points were determined on a Beijing micro melting-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 measurement of e.e was performed in a Shimadzu LC-10AT HPLC instrument. Optical rotation was measured on a full circle manual polarimeter (WXG-4). The blood pressure of SHR was measured by a BP-6 animal non-invasive tail-cuff plethysmography, Chengdu Thai Union Technology Co., Ltd. China. Spontaneously hypertensive rats (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.

Synthesis of dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1,m-nifedipine)

Trichloroacetic acid (16.86 g, 100 mmol) and methyl 3-aminocrotonate (12.08 g, 110 mmol) were added in sequence to a solution of 3-nitrobenzaldehyde (6.02 g, 40 mmol) in ethanol (40 ml) cooled with ice water under stirring. After the addition was completed, the mixture was stirred for 1 h at the same temperature. The precipitated solid was collected by filtration, rinsed with ethanol and then dried to give compound 1. Yield 74.2%; mp 194.0–195.5°C [lit. mp 188.0–191.0°C (Ghorbani-Choghamarani *et al*., 2008)]; MS (*m/z*): 347.1 (M+1); ^{1}H NMR ($CDCl_3$) δ:2.36 (s, 6H, 2×–CH_3), 3.65 (s, 6H, 2×–OCH_3), 5.10 (s, 1H, CH), 5.86 (s, 1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.62 (d, 1H, 6′-Ph-H), 8.00 (d, 1H, 4′-Ph-H), 8.09 (s, 1H, 2′-Ph-H).

Synthesis of straight alkyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2–8**)

Methyl 2-(3-nitrobenzylidene)-3-oxobutanoate was synthesized according to reported procedure (Wu *et al*., 2003), mp 151–154°C [lit. mp 156–158°C].

A mixture of methyl 2-(3-nitrobenzylidene)-3-oxobutanoate (23.42 g, 90 mmol) and a straight alkyl 3-aminocrotonate (ethyl ester–dodecyl ester, 90 mmol) in anhydrous ethanol (120 ml) was heated to reflux for 6 h under stirring. Solvent (about 50 ml) was removed under reduced pressure and the mixture was kept at ambient temperature. When a crystal was formed, the mixture was kept in a refrigerator overnight. The crystals were collected by filtration and recrystallized from ethanol (40 ml) to give the corresponding compounds **2–8**.

5-Ethyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2, nitrendipine): Yield 86.0%; mp 157.0–159.0°C [lit. mp 157.0–158.0°C (Palacios *et al*., 2007)]; MS (*m/z*): 361.1 (M+1); ^{1}H NMR ($CDCl_3$) δ:1.33 (t, 3H, –CH_3), 2.36 (s, 3H, –CH_3), 2.37 (s, 3H, –CH_3), 3.65 (s, 3H, –OCH_3), 4.03 (m, 2H, –OCH_2–), 5.10 (s, 1H, CH), 5.75 (s,1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.63 (d, 1H, 6′-Ph-H), 7.99 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H).

3-Methyl 5-*n*-propyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3): Yield 60.2%; mp 145.0–146.5°C; MS (*m/z*): 375.1 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.86 (t, 3H, –CH_3), 1.61 (m, 2H, –CH_2–), 2.36 (s, 3H, –CH_3), 2.37 (s, 3H, –CH_3), 3.65 (s, 3H, –OCH_3), 4.03 (m, 2H, –OCH_2–), 5.10 (s, 1H, CH), 5.75 (s, 1H,

–NH–), 7.37 (t, 1H, 5′-Ph-H), 7.63 (d, 1H, 6′-Ph-H), 7.99 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H) [Ar–H].

3-Methyl 5-*n*-pentyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4): Yield 64.2%; mp 90.0–91.5°C; MS (*m/z*): 403.2 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.26 (m, 4H, 2×$–CH_2–$), 1.58 (m, 2H, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.37 (s, 3H, $–CH_3$), 3.65 (s, 3H, $–OCH_3$), 4.02 (m, 2H, $–OCH_2–$), 5.09 (s, 1H, CH), 5.74 (s, 1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.63 (d, 1H, 6′-Ph-H), 8.00 (d, 1H, 4′-Ph-H), 8.10 (s, 1H, 2′-Ph-H).

5-*n*-Heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5): Yield 85.0%; mp 112.5–114.0°C; MS (*m/z*): 431.4 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.25 (m, 8H, 4×$–CH_2–$), 1.59 (m, 2H, $–CH_2–$), 2.37 (s, 6H, 2×$–CH_3$), 3.66 (s, 3H, $–OCH_3$), 4.03 (t, 2H, $–OCH_2–$), 5.10 (s, 1H, CH), 5.82 (s, 1H, –NH–), 7.37–8.12 (m, 4H, Ph-H).

3-Methyl 5-*n*-octyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6): Yield 70.2%; mp 99.0–100.5°C [lit. mp 100.0°C (Wehinger *et al*., 1983)]; MS (*m/z*): 445.2 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.23 (s, 10H, 5×$–CH_2–$), 1.57 (m, 2H, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.37 (s, 3H, $–CH_3$), 3.65 (s, 3H, $–OCH_3$), 4.02 (m, 2H, $–OCH_2–$), 5.09 (s, 1H, CH), 5.82 (s, 1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.64 (d, 1H, 6′-Ph-H), 7.99 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H).

5-*n*-Decyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7): Yield 74.2%; mp 88.0–90.0°C [lit. mp 90.0°C (Wehinger *et al*., 1983)]; MS (*m/z*): 473.3 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.23 (s, 14H, 7×$–CH_2–$), 1.57 (m, 2H, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.37 (s, 3H, $–CH_3$), 3.65 (s, 3H, $–OCH_3$), 4.02 (m, 2H, $–OCH_2–$), 5.09 (s, 1H, CH), 5.82 (s, 1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.64 (d, 1H, 6′-Ph-H), 7.99 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H).

5-*n*-Dodecyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate(8): Yield 78.0%; mp 91.0–92.5°C [lit. mp 94.0°C (Wehinger *et al*., 1983)]; MS (*m/z*): 501.3 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.23 (s, 18H, 9×$–CH_2–$), 1.58 (m, 2H, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.37 (s, 3H, $–CH_3$), 3.65 (s, 3H, $–OCH_3$), 4.03 (m, 2H, $–OCH_2–$), 5.09 (s, 1H, CH), 5.77 (s, 1H, –NH–), 7.37 (t, 1H, 5′-Ph-H), 7.64 (d, 1H, 6′-Ph-H), 7.99 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H).

Synthesis of (+)-5-*n*-heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [(+)-5]

(−)-5-(Methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridine- carboxylic acid was prepared by resolution of (±)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic acid according to reported procedure (Ashimori *et al*., 1991). mp 168–172°C, $[\alpha]_D = -16.25^\circ$ (c = 0.04 g/ml, THF). lit. (Shibanuma *et al*., 1980). mp 169–170°C, $[\alpha]_D = -19.6^\circ$ (c = 0.542 g/ml, acetone). A solution of $SOCl_2$ (0.8 ml, 9.61 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a suspension of (−)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic acid (2.66 g, 8.01 mmol) in CH_2Cl_2 (10 ml) and DMF (4.5 ml) at −1°C to 2°C under N_2 atmosphere. After the addition was completed, the mixture was stirred for 2.5 h at the same temperature, added a solution of *n*-heptanol (2.1 ml, 14.42 mmol) in CH_2Cl_2 (6 ml), and stirred for another 3.5 h below 3°C, diluted with CH_2Cl_2 (20 ml), then washed with water, a solution of K_2CO_3 (0.5 M) and brine. The organic phase was dried over sodium sulphate and the volatile was removed under reduced pressure. Flash chromatograph of the residue over silica gel, using petroleum ether–ethyl acetate (8:1), gave (+)-5 as pale yellow solid. The solid was recrystallized in ethanol to produce (+)-5 (2.30 g). Yield 67.6%; mp 103.0–105.0°C; $[\alpha]_D = +16.25^\circ$ (c = 0.04 g/ml, acetone); MS (*m/z*): 431.4 (M+1); ^{1}H NMR ($CDCl_3$) δ:0.88 (t, 3H, $–CH_3$), 1.24 (m, 8H, 4×$–CH_2–$), 1.58 (m, 2H, $–CH_2–$), 2.36 (s, 3H, $–CH_3$), 2.38 (s, 3H, $–CH_3$), 3.65 (s, 3H, $–OCH_3$), 4.03 (t, 2H, $–OCH_2–$), 5.10 (s, 1H, CH), 5.76 (s, 1H, –NH–), 7.34 (t, 1H, 5′-Ph-H), 7.63 (d, 1H, 6′-Ph-H), 8.01 (d, 1H, 4′-Ph-H), 8.11 (s, 1H, 2′-Ph-H).

Determination of enantiomeric excess of (+)-5

The enantiomeric excess of (+)-5 was determined by high performance liquid chromatography (HPLC) analyses using chiral stationary phase columns, Chiral-AGP (150 mm × 4.0 mm, 5 μm) [column temperature, 25°C; maintained by a HT-230Acomlum heater, mobile phase, 2-propanol-ammonium acetate (pH 6.87, 5:95, v/v); flow rate, 0.5 ml/min; sample load volume, 10 μL; detection, ultraviolet (UV) at 240 nm].

Antihypertensive activity

Male SHR weighing 250–300 g was trained for 5 days. The blood pressure was measured via a non-invasive tail-cuff plethysmography method. The rats were 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 minutes 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 averaging value was recorded as the blood pressure of an individual animal. The values of blood pressure were measured before and 1, 2 4 h after *ig* administration of drugs.

Results and discussion

Organic synthesis

3-Methyl 5-straight alkyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate were synthesized following the routes in Scheme 1.

The condensation of 3-nitrobenzaldehyde and methyl 3-aminocrotonate in the presence of trichloroacetic acid yielded dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**1**, Scheme 1). The condensation of 3-nitrobenzaldehyde and methyl acetoacetate in the presence of glacial acetic acid and piperidine at 30°C produced methyl 2-(3-nitrobenzylidene)-3-oxobutanoate. The reaction was carried out under solvent-free condition. The work-up was simple and the yield was satisfied. Refluxing of methyl 2-(3-nitrobenzylidene)-3-oxobutanoate and straight alkyl 3-aminocrotonate in ethanol afforded methyl straight alkyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**2–8**). The synthesis of compound **5** was not found in the literature. The structures of synthesized compounds were characterized by MS and ^{1}H NMR.

(+)-5-*n*-Heptyl 3-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [(+)-5] was synthesized following the routes in Scheme 2.

(−)-5-(Methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3- pyridinecarboxylic acid was prepared by resolution of (±)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic acid using quinidine as resolution agent (Ashimori *et al.*, 1991). The reaction of (−)-acid with thionyl chloride and *n*-heptanol in sequence gave (+)-5. (−)-5 was not prepared because it was elucidated that (+)-enantiomer is the active isomer in the nitrendipine analogues (Zhang *et al.*, 2010). THF was used as solvent to measure optical rotation of (−)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridine- carboxylic acid since the compound was not dissolved in acetone.

Enantiomeric excess of (+)-5

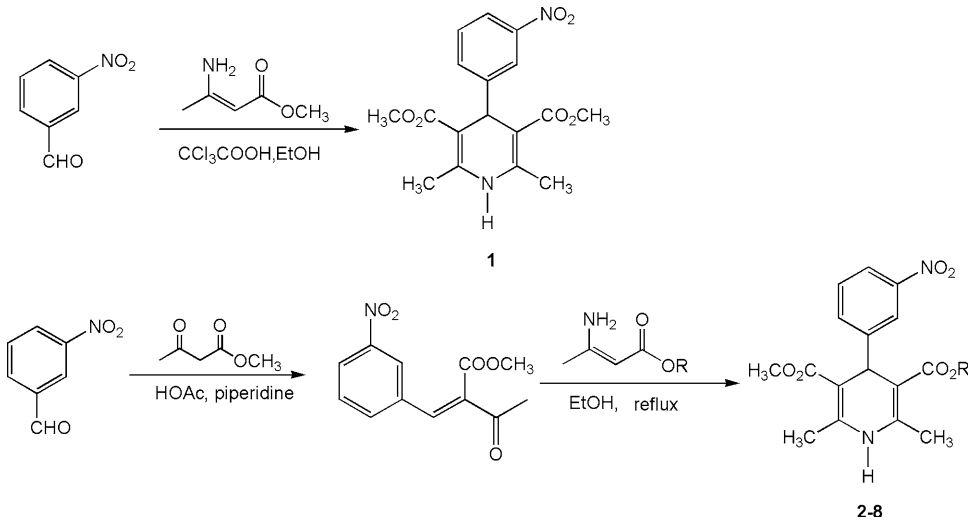
Retention time of (+)-5 was 3.4 min. The (±)-5 was also determined in the same condition. There were two peaks with retention times: (+)-5, 3.4 min; (−)-5, 8.1 min. Since the peak of (−)-5 was not detected in chromatogram of (+)-5, the enantiomeric excess of (+)-5 was concluded to be almost 100%.

Results of antihypertensive activity

The antihypertensive effects of compounds 1–8 in SHR were summarized in Table 1.

The results showed that antihypertensive effects of nitrendipine analogues is closely related to the length of the alkyl chain in 5-position. Short and long alkyl chain in 5-position of DHP reduced their antihypertensive effects. The seven saturated carbon is most suitable length in 5-position of DHP and compound **5** is the most effective drug in the tested compounds.

The antihypertensive effects of nitrendipine, (±)-5 and (+)-5, in SHR were summarized in Table 2. The data showed that antihypertensive effects of (±)-5, (+)-5 had a higher potency than nitrendipine, and (+)-isomer was 1.79-fold the raceme, 2.34-fold nitrendipine at a dose of 2 mg/kg, respectively. The antihypertensive effect of (±)-5 depends mostly on (+)-5, which is consistent with enantiomer activity of nitrendipine analogue. (±)-5 was tested at 1.0, 2.0 and 4.0 mg/kg; the results showed that the antihypertensive activity can maintain 8 h at 4.0 mg/kg, and its activity, as well as lasting time, were dose-dependent.



Scheme 1 Synthesis of compounds **1–8**

Scheme 2 Synthesis of (+)-5

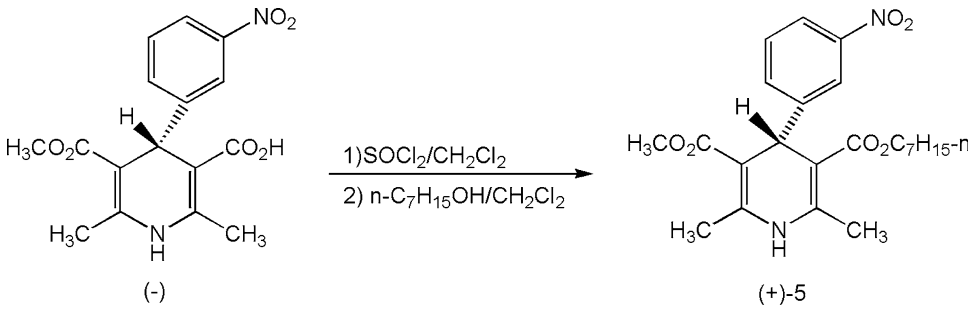


Table 1 Effects of compounds **1–8** on systolic blood pressure (SBP) in SHR at l h ($x \pm s$, $n = 6$)

Drugs	SBP before drugs (mmHg)	SBP after drugs administration (mmHg)[a]	
		Measured value	Reduced value
l(*m*-ninifedipine)	209 ± 8	183 ± 4	26 ± 5
2(nitrendipine)	208 ± 8	170 ± 4	39 ± 6
3	210 ± 8	167 ± 3	43 ± 5
4	211 ± 8	167 ± 3	44 ± 5
5	208 ± 6	156 ± 3	52 ± 5
6	209 ± 6	171 ± 4	38 ± 6
7	210 ± 6	179 ± 3	31 ± 6
8	212 ± 7	195 ± 3	17 ± 4
Solvent[b]	211 ± 6	214 ± 4	−3 ± 3

[a] All compounds were administrated by *ig* at 2 mg/kg

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

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

Drugs	Dose (mg/kg)	SBP before drugs (mmHg)	Reduced SBP after drugs administration (mmHg)				
			1 h	2 h	4 h	6 h	8 h
Nitrendipine	2.0	208 ± 8	39 ± 6	8 ± 7	−2 ± 3		
	1.0	196 ± 9	33 ± 4	0 ± 4			
(±)-5	2.0	208 ± 6	52 ± 5	42 ± 15	−4 ± 3		
	4.0	214 ± 6	119 ± 8	107 ± 9	67 ± 15	45 ± 17	21 ± 8
(+)-5	2.0	212 ± 9	93 ± 10	47 ± 12	−2 ± 1		
Solvent		211 ± 6	−3 ± 3	−6 ± 5	−6 ± 5	−6 ± 5	−6 ± 6

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

Conclusion

Nitrendipine and its seven analogues were synthesized, and their antihypertensive activities in spontaneously hypertensive rats (SHR) were evaluated by *ig* administration. The results suggested that seven saturated carbon (*n*-heptyl) is the most suitable length in 5-position of DHP. Compound **5** is the most effective drug in the tested compounds, and its activity, as well as lasting time, was dose-dependent. The antihypertensive effect of (+)-5 was 1.79-fold the raceme.

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