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Synthesis and calcium channel antagonist activity of nifedipine analogues with methylthioimidazole substituent

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Abstract

Various diester analogues of nifedipine, in which the orthonitrophenyl group at position 4 is replaced by 1-methyl-2-methylthio-5-imidazolyl substituent, were synthesized and evaluated as calcium channel antagonists on guinea-pig ileal smooth muscle. Nifedipine was used as standard. Comparison of the activities of symmetrical esters (**3a**–**e**) indicate that increasing the length of alkyl chain in C3 and C5 ester substituents increases the antagonist activity and the *n*-propyl ester being preferred ($IC_{50} = 2.66 \times 10^{-9}$ M). In asymmetrical series (**6a**–**g**), compound **6g** having ethyl and *n*-butyl ester at C3 and C5 positions of basic dihydropyridine structure was found to be the most active ($IC_{50} = 1.32 \times 10^{-9}$ M).

Keywords: Calcium channel blockers; Dihydropyridines

1. Introduction

Calcium channel blockers are used extensively for treating high blood pressure and angina [1]. The increase in the number of available calcium antagonists (as new formulation of pre-existing drugs or new chemical entities) over recent years has contributed to an ever-changing scenario regarding their appropriate use compared with other anti-hypertensive agents [2]. Within this class of cardiovascular agents, the dihydropyridines (e.g. nifedipine) have found widespread use in the clinic and have been the subject of many structure–activity relationship studies [3–5]. Recently, the syntheses and calcium channel antagonist activity of nifedipine analogues with nitroimidazole [6] or methylsulfonylimidazole [7] at C4 position, have been reported. In this paper, we report the syntheses and calcium channel antagonist activities of alkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylates.

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2. Material and methods

2.1. Synthesis of the products

Melting points were determined on an Electrothermal IA 9100 apparatus and are uncorrected. ^{1}H NMR spectra were run on a Brucker FT-80 spectrometer. Tetramethylsilan (TMS) was used as an internal standard. Mass spectra were measured with a Finnigan TSQ-70 spectrometer at 70 eV. The IR spectra were recorded on a Shimadzu 470 spectrophotometer.

Elemental analyses (C, H, N) for compounds **3a**–**e** and **6a**–**g** were within $\pm 0.4\%$ from the theoretical values.

Thin layer chromatography was performed on Merck grade 60 silica gel with 254 and 366 nm fluorescent indicators.

2.1.1. Syntheses of symmetrical esters *3a*–*e*

*2.1.1.1. Dimethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**3a**).* A solution of ammonium hydroxide (25%, 0.4 ml)

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was added to a stirring solution of 1-methyl-2-methylthio-1H-imidazole-5-carbaldehyde (**2**) [8] (390 mg, 2.5 mmol) and methyl 3-oxobutanoate (**1a**, 580 mg, 5 mmol) in absolute methanol (5 ml). The mixture was protected from light and heated overnight under reflux. The reaction was cooled. Methanol was removed and the residue was purified by thin layer chromatography (chloroform–ethanol; 95:5) to give 526 mg (60%) of **3a**, m.p. 200–201 °C (methanol): IR (KBr): 3200 (N–H), 3080 (H–C4 imidazole), 2960 (C–H aliphatic), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 6.77 (brs, 2H, NH, H–C4 imidazole), 4.87(s,1H, H–C4 dihydropyridine), 3.72 (s, 6H, CH_3O), 3.66 (s, 3H, CH_3N), 2.51 (s, 3H, CH_3S) and 2.29 ppm (s, 6H, CH_3).

Other compounds **3b**–**e** (Table 1) were prepared similarly.

*2.1.1.2. Diethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**3b**).* Yield 49%; m.p. = 180–181 °C (ether); IR (KBr): 3200 (N–H), 3080 (H–C4 imidazole), 2944 (C–H aliphatic), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.47 (brs, 1H, NH), 6.77 (s, 1H, H–C4 imidazole), 4.88 (s, 1H, 1H–C4 dihydropyridine), 4.13 (q, 4H, CH_2O), 3.76 (s, 3H, CH_3N), 2.48 (s, 3H, CH_3S), 2.29 (s, 6H, CH_3) and 1.24 ppm (t, 6H, CH_3); Mass: m/z (%) 380 ($M^+ + 1$, 100), 306(43), 252(30), 196(30), 129(10).

*2.1.1.3. Dipropyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**3c**).* Yield 51%; m.p. = 177–178 °C (ether); IR (KBr): 3200 (N–H), 3080 (H–C4 imidazole), 2944 (C–H aliphatic), 1698 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.77 (brs, 1H, NH), 6.77 (s, 1H, H–C4 imidazole), 4.90 (s, 1H, H–C4 dihydropyridine), 4.03 (t, 4H, CH_2O), 3.75 (s, 3H, CH_3N), 2.48 (s, 3H, CH_3S), 2.29 (s, 6H, CH_3), 1.65–1.55 (m, 4H, CH_2), 0.89 ppm (t, 6H, CH_3); Mass: m/z (%) 408 ($M^+ + 1$, 100), 321(19), 270(19), 242(10), 182(19),149(25), 129(30), 71(32).

*2.1.1.4. Di(1-methylethyl) 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)3,5-pyridinedicarboxylate (**3d**).* Yield 53%; m.p. = 181–182 °C (ether); IR (KBr): 3200 (N–H), 3080 (H–C4 imidazole), 2944 (C–H aliphatic), 1699 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.77 (brs, 1H, NH), 6.76 (s, 1H, H–C4 imidazole) 5.09–4.93 (m, 3H, 2CH, H–C4 dihydropyridine), 3.77 (s, 3H, CH_3N), 2.48 (s, 3H, CH_3S), 2.28 (s,6H,CH_3), 1.20 ppm (d, 12H, CH_3); Mass: m/z (%) 408($M^+ + 1$, 88), 380(30), 320(12), 218(10), 196(60), 176(10), 129(14), 43(100).

*2.1.1.5. Dibutyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**3e**).* Yield 50%; m.p. = 127–128 °C (ether); IR (KBr): 3188 (N–H), 3072 (H–C4 imidazole), 2944 (C–H aliphatic), 1696 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.77 (brs, 1H, NH), 6.76 (s, 1H, H–C4 imidazole), 4.98 (s, 1H, H–C4 dihydropyridine), 4.08 (t, 4H, CH_2O), 3.70 (s, 3H, CH_3N), 2.48 (s, 3H, CH_3S), 2.30 (s, 6H, CH_3), 1.89–0.80 ppm (m, 14H, $CH_2CH_2CH_3$).

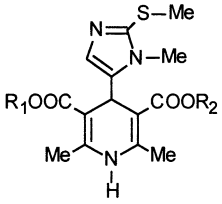
*2.1.2. Syntheses of intermediate compounds **4a**–**e***

*2.1.2.1. Methyl 2-[(1-methyl-2-methylthio-5-imidazolyl) methylene]-3-oxobutanoate (**4a**).* A solution of compound **2** (156 mg, 1 mmol), methyl 3-oxobutanoate (**1a**, 116 mg, 1 mmol), glacial acetic acid (0.1 ml), piperidine (0.04 ml) and dry benzene (20 ml) was refluxed for 2 h, during which the water was removed via a Dean–Stark trap. The benzene was removed under reduced pressure and the residue was purified by thin layer chromatography (chloroform–ethanol; 95:5) to give 147 mg (58%) of **4a**, m.p. = 178–179 °C (ether) IR (KBr): 1700 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$, δ): 7.53 (s, 1H, H–C4 imidazole), 7.41 (s, 1H, =CH), 3.90 (s, 3H, CH_3O), 3.50 (s, 3H, CH_3N), 2.61 (s, 3H, CH_3S), 2.35 ppm (s, 3H, CH_3).

Other compounds **4b**–**e** were prepared similarly.

*2.1.2.2. Ethyl 2-[(1-methyl-2-methylthio-5-imidazolyl) methylene]-3-oxobutanoate (**4b**).* Yield 60%; m.p. = 173–174 °C; IR (KBr): 1700 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$, δ): 7.51 (s, 1H, H–C4 imidazole), 7.39 (s, 1H, =CH), 4.34 (q, 2H, CH_2O), 3.58 (s, 3H, CH_3N), 2.67 (s, 3H, CH_3S), 2.36 ppm (s, 3H, CH_3).

Table 1
Calcium channel antagonist activities of compounds **3a**–**e** and **6a**–**g**



Compound	R_1	R_2	Calcium channel antagonist activity IC_{50} M
3a	CH_3	CH_3	$1.45\ (0.26)\times10^{-5}$
3b	C_2H_5	C_2H_5	$2.06\ (0.50)\times10^{-6}$
3c	n-C_3H_7	n-C_3H_7	$2.66\ (0.99)\times10^{-9}$
3d	i-C_3H_7	i-C_3H_7	$2.35\ (0.71)\times10^{-6}$
3e	n-C_4H_9	n-C_4H_9	$1.36\ (0.27)\times10^{-8}$
6a	CH_3	C_2H_5	$3.42\ (029)\times10^{-6}$
6b	CH_3	n-C_3H_7	$1.03\ (0.12)\times10^{-5}$
6c	CH_3	i-C_3H_7	$2.08\ (0.28)\times10^{-5}$
6d	CH_3	n-C_4H_9	$1.09\ (0.17)\times10^{-6}$
6e	C_2H_5	n-C_3H_7	$3.16\ (0.88)\times10^{-6}$
6f	C_2H_5	i-C_3H_7	$1.09\ (0.12)\times10^{-8}$
6g	C_2H_5	n-C_4H_9	$1.32\ (0.18)\times10^{-9}$
Nifedipine			$1.26(0.36)\times10^{-9}$

$n = 6$, Standard deviations in parentheses.

*2.1.2.3. Propyl 2-[(1-methyl-2-methylthio-5-imidazolyl) methylene]-3-oxobutanoate (**4c**).* Yield 83%; oily compound; IR (neat): 1700 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$, δ): 7.58 (s, 1H, H–C4 imidazole), 7.31 (s, 1H, =CH), 4.18–3.60 (m, 5H, CH_2O, CH_3N), 2.67 (s, 3H, CH_3S), 2.38 (s, 3H, CH_3), 1.69–1.50 (m, 2H, CH_2), 0.89 ppm (t, 3H, CH_3).

*2.1.2.4. 1-Methylethyl 2-[(1-methyl-2-methylthio-5-imidazolyl) methylene]-3-oxobutanoate (**4d**).* Yield 86%; oily compound; IR (neat): 1700 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$, δ): 7.57 (s, 1H, H–C4 imidazole), 7.51 (s, 1H, =CH), 5.12–5.08 (m, 1H, CH), 4.01 (s, 3H, CH_3N), 2.67 (s, 3H, CH_3S), 2.38 (s, 3H, CH_3CO), 1.21 ppm (d, 6H, CH_3).

*2.1.2.5. Butyl 2-[(1-methyl-2-methylthio-5-imidazolyl) methylene]-3-oxobutanoate (**4e**).* Yield 86%; oily compound; IR (neat): 1700 cm^{-1} (C=O ester); ^1H NMR ($CDCl_3$, δ): 7.57 (s, 1H, H–C4 imidazole), 7.51 (s, 1H, =CH), 4.25–3.80 (m, 5H, CH_2O, CH_3N), 2.67 (s, 3H, CH_3S), 2.39 (s,3H, CH_3), 1.70–0.70 ppm (m, 7H, $CH_3CH_2CH_2$).

*2.1.3. Syntheses of asymmetrical ester **6a–g***

*2.1.3.1. 3-Ethyl, 5-methyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6a**).* To a stirring solution of compound **4a** (254 mg, 1 mmol) in absolute methanol (5 ml), ethyl 3-aminocrotonate **5b** ($R_2 = C_2H_5$, 129 mg, 1 mmol) was added, the solution was protected from light and refluxed overnight. After cooling, methanol was removed under reduced pressure and the residue was purified by thin layer chromatography (chloroform–ethanol; 95:5) to give 219 mg (60%) of **6a**, m.p. = 212–213 °C (methanol), IR (KBr): 3190 (N–H), 3080 (H–C4 imidazole), 2944 (C–H aliphatic), 1700 (C=O); ^1H NMR ($CDCl_3$, δ): 6.91 (brs, 1H, NH), 6.81 (s,1H, H–C4 imidazole), 4.87 (s, 1H, H–C4 dihydropyridine), 4.12 (q, 2H, CH_2O), 3.75 (s, 3H, CH_3N), 3.66 (s, 3H, CH_3O), 2.50 (s, 3H, CH_3S), 2.29, 2.32 (2s, 6H, CH_3), 1.24 ppm (t, 3H,CH_3).

Other compounds **6b–g** were prepared similarly.

*2.1.3.2. 3-Methyl, 5-propyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6b**).* Yield 48%; m.p. = 163–164 °C (methanol); IR (KBr): 3200 (NH), 3080 (H–C4 imidazole), 2960 (C–H aliphatic), 1699 cm^{-1} (C=O), ^1H NMR ($CDCl_3$, δ): 6.78 (brs, 2H, NH and H–C4 imidazole), 4.87 (s, 1H, H–C4 dihydropyridine), 3.87 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3N), 3.73 (t, 2H, CH_2O), 2.48 (s, 3H, CH_3S), 2.27, 2.30 (2s, 6H, CH_3), 1.66 (m, 2H, CH_2), 0.88 ppm (t, 3H, CH_3).

*2.1.3.3. 3-Methyl, 5-(1-methylethyl) 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6c**).* Yield 48%; m.p. = 202–203 °C (methanol), IR (KBr): 3200 (N–H), 3088 (H–C4 imidazole), 2960 (C–H aliphatic), 1699 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.40 (brs, 2H, NH), 6.78 (s, 1H, H–C4 imidazole), 5.01–4.79 (m, 2H, CH, H–C4 dihydropyridine), 3.73 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3N), 2.48 (s, 3H, CH_3S), 2.28, 2.31 (2s, 6H, CH_3), 1.22 ppm (d, 6H, CH_3).

*2.1.3.4. 3-Butyl, 5-methyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6d**).* Yield 53%; oily compound; IR (KBr): 3184 (N–H), 3074 (H–C4 imidazole), 1697 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, δ): 7.60 (brs, 1H, NH), 6.76 (s, 1H, H–C4 imidazole), 4.88 (s, 1H, H–C4 dihydropyridine), 3.99–3.79 (m, 5H, CH_2O, CH_3N), 3.68 (s, 3H, CH_3O), 2.72 (s, 3H, CH_3S), 2.29, 2.23 (2s, 6H, CH_3), 1.70–0.75 ppm (m, 7H, $CH_2CH_2CH_3$).

*2.1.3.5. 3-Ethyl, 5-propyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6e**).* Yield 48%; m.p. = 189–190 °C (methanol); IR (KBr): 3190 (N–H), 3072 (H–C4 imidazole), 2976 (C–H aliphatic), 1697 cm^{-1} (C=O), ^1H NMR ($CDCl_3$, δ): 7.03 (brs, 1H, N–H), 6.77 (s, 1H, H–C4 imidazole), 4.88 (s, 1H, H–C4 dihydropyridine), 4.08–4.08 (m, 4H, CH_2O), 3.75 (S, 3H, CH_3N), 2.49 (s, 3H, CH_3S), 2.29, 2.31 (2s, 6H, CH_3), 1.65–1.60 (m, 2H, CH_2), 1.24 (t, 3H, CH_3), 0.88 ppm (t, 3H, CH_3).

*2.1.3.6. 3-Ethyl, 5-(1-methylethyl) 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6f**).* Yield 87%; m.p. = 199–200 °C (methanol); IR (KBr): 3188 (N–H), 3060 (H–C4 imidazole), 2960 (C–H aliphatic), 1696 cm^{-1} (C=O), ^1H NMR ($CDCl_3$, δ): 6.80 (brs, 2H, NH and H–C4 imidazole), 4.94–4.79 (m, 2H, CH, H–C4 dihydropyridine), 4.65–4.11 (m, 5H, CH_3N, CH_2O), 2.48 (s, 3H, CH_3S), 2.28, 2.31 (2s, 6H, CH_3), 1.24–1.20 (m, 9H, CH_3).

*2.1.3.7. 3-Butyl, 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (**6g**).* Yield 87%; m.p. = 193–194 °C(methanol); IR (KBr): 3188 (N–H), 3072 (H–C4 imidazole), 2944 (C–H aliphatic), 1696 cm^{-1} (C=O), ^1H NMR ($CDCl_3$, δ): 7.00 (brs, 1H, NH), 6.58 (s, 1H, H–C4 imidazole), 4.86 (s, 1H, H–C4 dihydropyridine), 4.12–3.99 (m, 5H, CH_2O, CH_3N), 3.68 (s, 3H, CH_3O), 2.50 (s, 3H, CH_3S), 2.27, 2.30 (2s, 6H, CH_3), 1.60–0.61 ppm (m, 7H, $CH_2CH_2CH_3$).

2.2. Biological assay

Male albino guinea-pigs (300–450 g) were killed by a blow on the head and exsanguinated. The intestine was

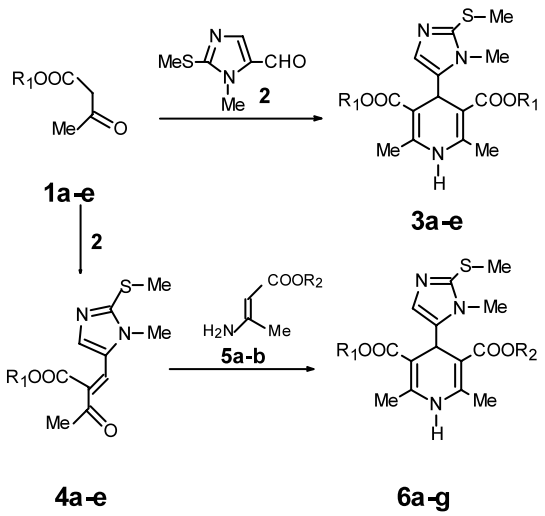


Fig. 1. Syntheses of compounds **3a**–**e** and **6a**–**g**.

removed above the ileocecal junction and longitudinal smooth muscle segments of 2-cm length were mounted under a resting tension of 0.5 g. The segments were maintained at 37 °C in a 20 ml jacketed organ bath containing oxygenated physiological saline solution of the following millimolar composition: NaCl, 137; $CaCl_2$, 1.8; KCl, 2.7; $MgSO_4$, 1.1; NaH_2PO_4, 0.4; $NaHCO_3$, 12 and glucose, 5. The muscles were equilibrated for 1 h with a solution change every 15 min. The contractions were recorded with a force displacement transducer (F-50) on a Beckman physiograph. Test agents were prepared as 10^{-2} M stock solution in DMSO and stored protected from light. Nifedipine was used for comparison. Dilutions were made into double distilled water. To control for solvent effects, control and drug solutions all contained the same amount of DMSO. The contractile response was taken as the 100% value for the tonic (slow) component of the response. The contraction was elicited with 80-millimolar KCl. Test compounds were cumulatively added and compound induced relaxation of contracted muscle was expressed as percent of control. The IC_{50} values (concentration needed to produce 50% relaxation on contracted ileal smooth muscle) were graphically determined from the concentration–response curves [9].

3. Results and discussion

Symmetrical (**3a**–**e**) and asymmetrical (**6a**–**g**) analogues of nifedipine were synthesized according to Fig. 1. The symmetrical analogues (**3a**–**e**) were prepared by classical Hantzsch condensation [10] in which 1-methyl-2-methylthio-1*H*-imidazole-5-carbaldehyde (**2**) [8] was reacted with 3-oxobutanoic acid esters **1a**–**e** [11] and ammonium hydroxide. The asymmetrical analogues **6a**–**g** were prepared by a procedure reported by Meyer et al. [12].

The calcium channel antagonist activities (IC_{50}) of compounds **3a**–**e** and **6a**–**g** were determined as the concentration needed to produce 50% relaxation on contracted guinea-pig ileal longitudinal smooth muscle [9]. The test results are summarized in Table 1. Nifedipine was used as the reference drug. Comparison of the activities of symmetrical esters **3a**–**e** indicate that increasing the length of alkyl chain in C-3, C-5 ester substituents increases the antagonist activity, thus compounds **3c** and **3e** ($R_1 = R_2 = n\text{-}C_3H_7$ and $n\text{-}C_4H_9$) were more potent than **3a** and **3b** ($R_1 = R_2 = CH_3$ and C_2H_5). However, compound **3d** bearing an isopropyl group at C-3 and C-5 positions of the basic structure displayed a weak antagonist activity.

In asymmetrical series of dihydropyridines **6a**–**g**, when R_1 is a methyl group, all derivatives (**6a**–**d**) show a weak calcium channel blocker activity ($IC_{50} = 2.08 \times 10^{-5}$–$1.09 \times 10^{-6}$ M). However, changing methyl to an ethyl group (**6e**–**g**) increased the potency and the activity depends on the size of ester group at C5 position of dihydropyridine. While compound **6e** having *n*-propyl group at C5 position has weak calcium channel blocking activity ($IC_{50} = 3.16 \times 10^{-6}$), compound **6g** with an *n*-butyl group at C5 position shows a comparable activity to reference drug nifedipine ($IC_{50} = 1.32 \times 10^{-9}$ M).

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