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Synthesis and calcium antagonist activity of 1,4-dihydropyridines containing phenylaminoimidazolyl substituents

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Abstract

Alkyl ester analogues of nifedipine, in which the ortho-nitrophenyl group at position 4 is replaced by 2-methylthio-1-phenylamino-5-imidazolyl substituent, were synthesized and evaluated as calcium-channel antagonists using the high K^+ contraction of guinea-pig ileal longitudinal smooth muscle. The results for the symmetrical esters showed that in the series of alkyl esters increasing the length of methylene chain in C-3 and C-5 ester substituents for more than two methylene units decreases activity. In the phenylalkyl ester series increasing the length of methylene chain also decreases activity. The results demonstrate that most of the compounds had similar activity to the reference drug nifedipine. In addition, two compounds, **5b** and **5f** were more active than the nifedipine.

Keywords: Dihyropyridines; Phenylaminoimidazoles; Nifedipine analogues; Calcium channel anatagonists

1. Introduction

1,4-Dihydropyridine calcium channel antagonists are an important class of drugs which induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiac muscle [1]. They exert these effects by binding to a high affinity binding site in L-type voltage-dependent Ca^{2+} channels [2]. In therapy, this class of drugs is effective in the treatment of hypertension, angina pectoris and other cardiovascular disorders [3]. Because the prototype of 1,4-dihydropyridines, nifedipine, does not have the optimum pharmacokinetic and pharmacodynamic characteristics, several attempts have been made to introduce other drugs in this class with improved properties. The results of these efforts are new drugs with a slower onset, longer duration of action and fewer side effects [4,5]. Some of these drugs have selectivity for the vessels and even for the vascular bed upon which they act. Changes in the substitution pattern at the C_3, C_4, C_5 positions of nifedipine alter activity and tissue selectivity [4–10]. Several papers illustrated that C_4 heterocycle substituents of dihydropyridine were potent antagonists [11–13]. In previous studies, we reported that a C_4 imidazole substituent gave very active compounds as calcium channel antagonist [13–16]. It was therefore of interest to determine the effect of selected C_3 and C_5 substituents, in conjugation with 2-methylthio-1-phenylamino-5-imidazolyl as C_4 substituent on calcium channel antagonist activity. We now report the synthesis and calcium antagonist activities of new alkyl 1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylates.

2. Chemistry

The synthesis of the 1,4-dihydropyridine derivatives **5a**–**h** (Table 1) was achieved following the steps outlined in Fig. 1. 5-Hydroxymethyl-2-mercapto-1-phenylami-

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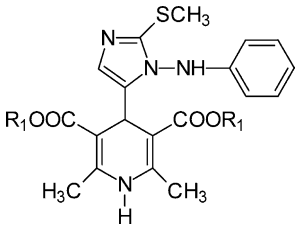
Table 1
Physical and calcium channel modulation data for compounds **5a**–**h**



Comp.	R_1	Mp (°C)	Yield (%)	Formula [a]	Calcium channel antagonist activity [b]
5a	Me	197–198	50	$C_{21}H_{24}N_4O_4S$	$3.54 \pm 0.85 \times 10^{-9}$
5b	Et	142–143	35	$C_{23}H_{28}N_4O_4S$	$1.69 \pm 0.43 \times 10^{-9}$
5c	Pr	141–142	56	$C_{25}H_{32}N_4O_4S$	$2.29 \pm 0.79 \times 10^{-9}$
5d	*i*-Pr	186–188	35	$C_{25}H_{32}N_4O_4S$	$2.16 \pm 0.76 \times 10^{-9}$
5e	*t*-Bu	227–228	23	$C_{27}H_{36}N_4O_4S$	$1.21 \pm 0.27 \times 10^{-7}$
5f	Benzyl	176–177	52	$C_{33}H_{32}N_4O_4S$	$1.49 \pm 0.39 \times 10^{-9}$
5g	Phenylethyl	133–134	23	$C_{35}H_{36}N_4O_4S$	$2.79 \pm 0.69 \times 10^{-9}$
5h	Phenylpropyl	132–133	44	$C_{37}H_{40}N_4O_4S$	$3.15 \pm 0.71 \times 10^{-9}$
Nifedipine					$2.55 \pm 0.21 \times 10^{-9}$

[a] Microanalyses were within ±0.4% of theoretical values.
[b] The molar concentration of antagonist test compound causing a 50% in the tonic contractile response ($IC_{50} \pm SEM$) in guinea-pig ileal longitudinal smooth muscle by KCl (80 mmol/l) was determined graphically from dose-response curve ($n = 6$).

noimidazole (**2**) was prepared according to the procedure described by Dener et al. [17]. Reaction of **2** with methyl iodide afforded corresponding substituted methylthio imidazole **3**. Oxidation of **3** with manganese dioxide in chloroform gave the corresponding aldehyde **4**. The symmetrical 1,4-dihydropyridine derivatives **5a**–**h** were prepared (23–56% yield) by the classical Hantzch condensation [18,19] in which the aldehyde **4** was reacted with the acetoacetate ester and ammonium acetate. The compounds were characterized by ^1H nuclear magnetic resonance, infrared and mass spectroscopy. The purity of all products was determined by thin layer chromatography using several solvent systems of different polarity. The physical properties of final compounds are summarized in Table 1. All final products were pure and stable compounds. Similar to other analogues of nifedipine, they are lipophilic compounds with very slight solubility in water.

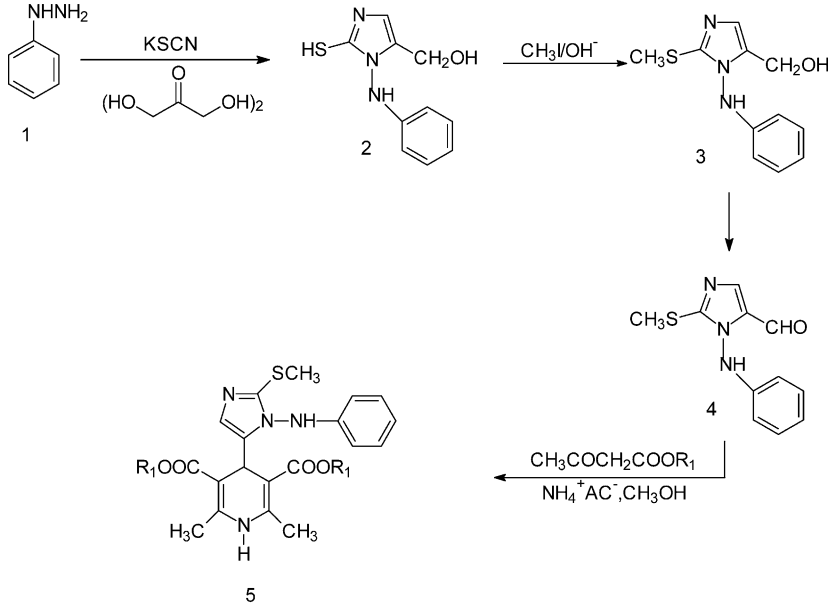


Fig. 1. Synthesis of nifedipine analogues.

3. Experimental

3.1. Chemistry

Melting points were determined using a Mettler FP61 capillary apparatus. Infrared spectra acquired on a Perkin–Elmer 1420 recording spectrometer. A Bruker FT-80 instrument was used to acquire ^{1}H NMR spectra; with tetramethylsilane as the internal standard. Mass spectra were acquired with a Finnigan TSQ-70 mass spectrometer. Electron-impact ionization was performed at an ionizing energy of 70 eV. Elemental analyses were carried out with a Perkin–Elmer Model 240-C apparatus. Elemental microanalyses were within $\pm$0.4% of the theoretical values for C, H and N.

3.1.1. 5-Hydroxymethyl-2-mercapto-1-phenylaminoimidazole (**2**)

To a mixture of dihydroxyacetone (4.26 g, 46 mmol), potassium thiocyanate (6.9 g, 70 mmol) and phenylhydrazine (8.66 g, 60 mmol) in 30 ml of butanol, 5.4 ml of glacial acetic acid was added. The reaction mixture was stirred at room temperature for 72 h and the precipitate was collected. After washing with ether, the precipitate was dried under reduce pressure to give 12.7 g (65%) of **2**. Mp 133–134 °C; ^{1}H NMR ($CDCl_3$): δ 8.2 (s, 1H, H_4-imidazole), 7.9–8.1 (m, 2H, phenyl), 7.1–7.5 (m, 3H, phenyl), 6.0 (s, 1H, SH), 4.6 (s, 2H, CH_2O), 3.7 (s, 1H, OH).

3.1.2. 5-Hydroxymethyl-2-methylthio-1-phenylaminoimidazole (**3**)

To a stirring solution of compound **2** (2.81 g, 10 mmol) and potassium hydroxide (1.4 g, 25 mmol) in 5 ml of methanol a solution of methyl iodide (2.13 g, 15 mmol) in 2.5 ml of methanol was added drop-wise. After 2 h the mixture was poured into water and the precipitate was collected, washed with water, and dried. The residue was recrystallized from acetone–petroleum ether to give 1.58 g (67%) of **3**, mp: 92–93 °C.

^{1}H NMR ($CDCl_3$): δ 7.3–7.7 (m, 6H, H_4-imidazole and phenyl), 4.8 (s, 2H, CH_2O), 3.2 (bs, 1H, OH), 2.7 (s, 3H, SCH_3).

3.1.3. 2-Methylthio-1-phenylaminoimidazole-5-carboxaldehyde (**4**)

A mixture of compound **3** (5 g, 21.3 mmol) and activated magnesium dioxide (7.4 g, 85.2 mmol) in 35 ml of acetonitrile was refluxed for 9 h. After cooling, the mixture was filtered on diatomaceous earth and the solvent removed under reduced pressure. The residue was crystallized in a mixture of acetone and petroleum ether to yield 4.2 g (85%) white needle crystals of compound **4**; mp: 84–85 °C; IR (KBr): ν (cm^{-1}) 3300 (NH), 1710 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 10.0 (s, 1H, CHO), 7.8–7.2 (m, 6H, H_4-imidazole and phenyl), 2.8 (s, 3H, SCH_3).

3.1.4. General procedure for the synthesis of dihydropyridine derivatives (**5a–h**)

A mixture of compound **4** (100 mg, 0.429 mmol), appropriate acetoacetate ester (0.858 mmol) and ammonium acetate (33 mg, 0.429 mmol) in 3 ml of methanol was refluxed for 24 h. The solvent was evaporated and the residue was purified by preparative thin-layer chromatography. Silica gel GF254 was used as adsorbent and chloroform was used as mobile phase.

3.1.5. 3,5-Dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyyridinedicarboxylate (**5a**)

Mp: 197–198 °C; IR (KBr): ν (cm^{-1}) 3348 (NH), 1704 (CO); ^{1}H NMR ($CDCl_3$): δ 7.60–7.20 (m, 5H, phenyl), 6.90 (s, 1H, H-C_4 imidazole), 6.55 (bs, 1H, NH), 5.40 (s, 1H, H-C_4 dihydropyridine), 3.70 (s, 6H, OCH_3), 2.65 (s, 3H, SCH_3), 2.30 (s, 6H, CH_3–C_2 and CH_3–C_6). Mass; *m*/*z* (%): 428 (M^+,10), 414 (86), 400 (21), 383 (19), 382 (40), 355 (100), 335 (31), 325 (13), 323 (74), 224 (35).

3.1.6. 3,5-Diethyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5b**)

Mp: 142–143 °C; IR (KBr): ν (cm^{-1}) 3343 (NH), 1692 (CO); ^{1}H NMR ($CDCl_3$): 7.60–7.20 (m, 5H, phenyl), 6.90 (s, 1H, H-C_4 imidazole), 6.55 (bs, 1H, NH), 5.40 (s, 1H, H-C_4 dihydropyridine), 4.20 (q, 4H, OCH_2), 2.65 (s, 3H, SCH_3), 2.25 (s, 6H, CH_3–C_2 and CH_3–C_6), 1.30 (t, 6H, CH_3). MS; *m*/*z* (%): 456 (M^+,8), 442 (37), 396 (20), 369 (100), 349.0 (26), 323 (64), 252 (37).

3.1.7. 3,5-Dipropyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5c**)

Mp: 141–142 °C; IR (KBr): ν (cm^{-1}) 3206, 3270 (NH), 1694 (CO). ^{1}H NMR ($CDCl_3$): δ 7.60–7.20 (m, 5H, phenyl), 6.90 (s, 1H, H-C_4 imidazole), 6.50 (bs, 1H, NH), 5.40 (s, 1H, H-C_4 dihydropyridine), 4.05 (t, 4H, OCH_2), 2.50 (s, 3H, SCH_3), 2.10 (s, 6H, CH_3–C_2 and CH_3–C_6), 1.65 (m, 4H, CH_2), 0.90 (t, 6H, CH_3). MS; *m*/*z* (%): 484 (M^+,5), 470 (34), 410 (18), 385 (18), 383 (100), 363 (30), 323 (68), 280 (54), 196 (24).

3.1.8. 3,5-Diisopropyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5d**)

Mp: 186–188 °C; IR (KBr): ν (cm^{-1}) 3252 (NH), 1688 (CO); ^{1}H NMR ($CDCl_3$): δ 7.55–7.20 (m, 5H, phenyl), 6.85 (s, 1H, H–C_4 imidazole), 6.50 (bs, 1H, NH), 5.40 (s, 1H, H–C_4 dihydropyridine), 5.05 (m, 2H,

OCH), 2.60 (s, 3H, SCH_3), 2.10 (s, 6H, CH_3–C_2 and CH_3–C_6), 1.30 (d, 12H, CH_3). MS; *m/z* (%): 484 (M^+,5), 473 (26), 470 (57), 411 (31), 410 (19), 383 (100), 364 (23), 341 (66), 297 (62), 280 (29), 196 (19).

*3.1.9. 3,5-Ditertiarybutyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5e**)*

Mp: 227–228 °C; IR (KBr): *v* (cm^{-1}) 3270 (NH), 1690 (CO); ^{1}H NMR ($CDCl_3$): δ 7.55–7.20 (m, 5H, phenyl), 6.85 (s, 1H, H–C_4 imidazole), 6.40 (bs, 1H, NH), 5.40 (s, 1H, H–C_4 dihydropyridine), 2.65 (s, 3H, SCH_3), 2.25 (s, 6H, CH_3–C_2 and CH_3–C_6), 1.50 (s, 18H, CH_3). MS; *m/z* (%): 512 (M^+), 502 (34), 499 (100), 441 (20), 429 (30), 425 (86).

*3.1.10. 3,5-Dibenzyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5f**)*

Mp: 176–177 °C; IR (KBr): *v* (cm^{-1}) 3210, 3280 (NH), 1698 (CO); ^{1}H NMR ($CDCl_3$): δ 7.65–7.05 (m, 15H, phenyl), 6.85 (s, 1H, H–C_4 imidazole), 6.40 (bs, 1H, NH), 5.45 (s, 1H, H–C_4 dihydropyridine), 5.20 (s, 4H, $CH_2C_6H_5$), 2.50 (s, 3H, SCH_3), 2.25 (s, 6H, CH_3–C_2 and CH_3–C_6). MS; *m/z* (%): 580 (M^+,8), 566 (25), 433 (22), 431 (100), 376 (42), 323 (23).

*3.1.11. 3,5-Diphenethyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5g**)*

Mp: 133–134 °C; IR (KBr): *v* (cm^{-1}) 3200, 3270 (NH), 1693 (CO); ^{1}H NMR ($CDCl_3$): δ 7.65–7.00 (m, 15H, phenyl), 6.85 (s, 1H, H–C_4 imidazole), 6.30 (bs, 1H, NH), 5.45 (s, 1H, H–C_4 dihydropyridine), 4.40 (t, 4H, OCH_2), 2.95 (t, 4H, $CH_2C_6H_5$), 2.55 (s, 3H, SCH_3), 2.20 (s, 6H, CH_3–C_2 and CH_3–C_6). MS, *m/z* (%): 608 (M^+,10), 594 (18), 447 (19), 445 (100), 426 (28), 404 (48), 323 (37).

*3.1.12. 3,5-Diphenpropyl-1,4-dihydro-2,6-dimethyl-4-(2-methylthio-1-phenylamino-5-imidazolyl)-3,5-pyridinedicarboxylate (**5h**)*

Mp: 132–133 °C; IR (KBr): *v* (cm^{-1}) 3219, 3272 (NH), 1692 (CO); ^{1}H NMR ($CDCl_3$): δ 7.65 − 7.00 (m, 15H, phenyl), 6.85 (s, 1H, H–C_4 imidazole), 6.30 (bs, 1H, NH), 5.50 (s, 1H, H–C_4 dihydropyridine), 4.20 (t, 4H, OCH_2), 2.70 (t, 4H, $CH_2C_6H_5$), 2.50 (s, 3H, SCH_3), 2.20 (s, 6H, CH_3–C_2 and CH_3–C_6), 1.95 (m, 4H, CH_2CH_2). MS, *m/z* (%): 636.0 (M^+,8), 612 (28), 486 (26), 459 (100), 438 (36), 432 (40), 328 (19), 323 (76), 196 (13), 117 (21), 91 (53).

3.2. Pharmacology

Male albino guinea pigs (300–450 g) were killed by a blow to the head. The intestine was removed above the ileocaecal junction and longitudinal smooth muscle segments of 2 cm length were mounted under a resting tension of 400–500 mg. The segments were maintained at 37 °C in a 20 ml jacketed organ bath containing oxygenated (100% O_2) physiological saline solution at 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 concentrations were recorded with a force displacement transducer (F-50) on a NARCO physiograph. Test agents were dissolved in dimethylsulfoxide and the same volume of the solvent was used as a control in the absence of the test compounds. The contractile response was taken as the 100% value for the tonic (slow) component of the response. The contraction was elicited with 80 mmol/l KCl. Test compounds were cumulatively added and compound-induced relaxation of contracted muscle was expressed as percent of control. The IC_{50} of each compound was graphically determined from the concentration-response curves [20,21]. Results are expressed as mean ± s.e. Differences between the IC_{50} and response percentage ratio values of compounds in each preparation were compared by use of two-tailed Students' *t*-test. A P value < 0.05 was considered to be indicative of significance. The research protocol and experimental animals have been approved by ethics committee of Shaheed Beheshti University of Medical Sciences.

4. Results and discussion

The calcium-channel antagonist activities (IC_{50}) of **5a**–**h**, determined as the contraction needed to produce 50% relaxation of contracted guinea pig ileal longitudinal smooth muscle, are presented in Table 1.

The results of biological study showed that these new dihydropyridines caused dose-dependent inhibition of the contractile responses induced by high K^+ concentration, guinea-pig ileum. These effects were similar to those obtained with nifedipine, and may be explained as being caused by inhibition of entry of Ca^{2+} through voltage-dependent calcium channels in the muscle membrane. However, it should be taken into account that a complex network of neuronal and muscular tissues exists in the intestine and we could not rule out the possibility of different action of the synthesized compounds at several neuronal and muscular sites on which they might act. Comparison of the activities of synthesized symmetrical esters **5a**–**h** indicated that in aliphatic alkyl esters series, increasing the length of methylene chain in C-3 and C-5 ester substituents for more than two methylene units decreases activity especially when increasing of the length is accompanied with increasing the hindrance. Therefore, *t*-butyl ester

5e is the weakest compound in this series. In phenyl alkyl ester series **5f**–**h** increasing the length of methylene chain also decreases activity. These results are in agreement with our previous works, which carried out on 1,4-dihydropyridines containing nitroimidazolyl or nitrobenzylimidazolyl [13,14] substituents. Finally, the results show that most compounds have activity similar to nifedipine and two compounds **5b** and **5f** are more active than the reference drug nifedipine. Therefore, they have potential for use in disorders normally treated with calcium-channel blockers.

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