SYNTHESIS AND SMOOTH MUSCLE CALCIUM CHANNEL ANTAGONIST EFFECT OF ALKYL, AMINOALKYL 1,4-DIHYDRO-2,6-DIMETHYL-4-NITROIMIDAZOLE-3,5 PYRIDINE DICARBOXYLATES

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ABSTRACT

The discovery that 1,4-dihydropyridine (DHP) class of calcium channel antagonist inhibits the Ca^{+2} influx represented a major therapeutic advance in the treatment of cardiovascular diseases such as hypertension, angina pectoris and other spastic smooth muscle disorders. A novel class of calcium channel antagonist of flunarizine containing arylpiperazinyl moiety has recently been reported. It was therefore of interest to determine the effect that selected C-3 substituents contained amino alkyl and arylpiperazine, in conjunction with a C-4 1-methyl-5-nitro-2-imidazolyl substituents on calcium channel antagonist activity. The unsymmetrical analogues were prepared by a procedure reported by Meyer in which 1-methyl-5-nitro-imidazol-2-carboxaldehyde was reacted with acetoacetic esters and alkyl 3-aminocrotonate. *In vitro* calcium channel antagonist activities were determined by the use of high K^+ contraction of guinea pig ileal longitudinal smooth muscle. All compounds exhibited comparable calcium channel antagonist activity (IC_{50} =10^{-9} to 10^{-11} M) against reference drug nifedipine (IC_{50}= 2.75±0.36 x 10^{-10} M).

Key words: Ca^{+2} channel antagonist, Nitroimidazole, DHP, Arylpiperazine

INTRODUCTION

The L-type class of voltage dependent calcium channels provides an important pathway for entry of Ca^{+2} into vascular and cardiac muscles (1-2). The discovery that 1,4-dihydropyridine (DHP) class of calcium channel antagonist inhibits this Ca^{+2} influx represented a major therapeutic advance in the treatment of cardiovascular diseases such as hypertension, angina pectoris and other spastic smooth muscle disorders (3-5).

The dihydropyridine class of compounds in which nifedipine is the prototype, has been the aim of many structure activity relationship studies. The changes in the substitution pattern at C-3, C-4, and C-5 positions of nifedipine alter activity and tissue selectivity (6-8). A novel class of calcium channel antagonist of Flunarizine containing arylpiperazinyl moiety has recently been reported (9). Previously we reported that 1-methyl-5-nitro-2-imidazolyl is bioisoester of nitrophenyl in nifedipine analogues (10). It was therefore of interest to determine the effect of the selected C-3 substituents contained amino-alkyl and aryl-piperazine, in conjunction with a C-4 1-methyl-5-nitro-imidazolyl substituents on calcium channel antagonist activity.

MATERIAL AND METHODS

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H-NMR spectra were run on a Varian Unity Plus 400 MHz spectrometer. Chemical shift are reported in parts per million (δ) relative to TMS as an internal standard. The mass spectra were measured with a Finnigan TSQ-70 spectrometer at 70 ev. The IR spectra were obtained by using a Nicolet 50X-FT spectrophotometer (KBr disks). All spectra were consistent with the assigned structures.

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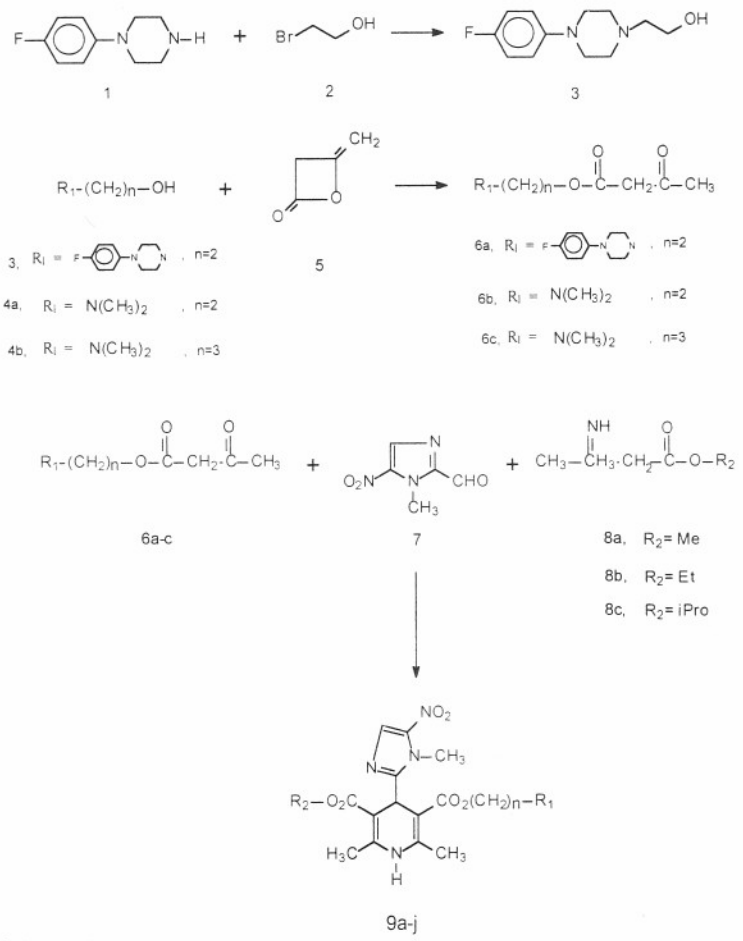


Scheme 1

Chemistry: The 2-[4-(*p*-fluorophenyl)piperazine-1-yl]ethanol **3** were obtained from reaction of 1-(*p*-fluorophenyl) piperazine **1** and 2-bromoethanol **2** in presence of triethyl amine as catalyst. Reaction of alcohols **4a-c** with diketene **5** afforded the corresponding acetoacetic esters **6a-c** (11-12). The unsymmetrical analogues **9a-j** were prepared by modified Hantsch reaction reported by Meyer in which 1-methyl-5-nitro-imidazole-2-carboxaldehyde **7** was reacted with 3-oxobutanoic acid esters **6a-c** and alkyl 3-aminocrotonate **8a-c** (13-15). (Scheme **1**)

2-[4-(p-fluorophenyl) piperazine-1-yl] ethanol (3)
A solution of 1-(*p*-fluorophenyl)piperazine (4.5 g, 25 mmol),2-bromoethanol (3.17 g, 25 mmol) and triethyl amine (7 ml, 50.2 mmol) in acetone (50 ml) were refluxed for 24 hours. The solvent was removed *in vacuo* and the residue obtained was dissolved in CH_2Cl_2 (50 ml) and washed with water (3 x 25 m). The organic phase was dried (Na_2SO_4), the solvent was removed, and the residue obtained was purified by silica gel column chromatography using CH_2Cl_2-MeOH (96:4,V/V) as eluent to give **3** as a white solid (3.08g, 55%). The assignment of piperazinyl protons was based on the fact that the H-3 and H-4 protons are deshielded by the p-flurophenyl substituent resulting in their appearance at lower field (δ =3.15), whereas the H-2 and H-5 piperazinyl protons which are not affected appear at higher field (δ =2.71).
^{1}H-NMR($CDCl_3$): 6.86-7.01 (m, 4H, aryl-H), 3.68(t, J=4.9 Hz, 4H, piperazinyl H-3 and H-5), 2.87(s, 1H, OH, exchanges with D_2O), 2.71 (t, J=4.9 Hz, 4H, piperazinyl H-2 and H-6), 2.64 (t, J=5.4 Hz, 2H, CH_2CH_2N).

General procedure for the synthesis of Acetoacetate derivatives 6a-c (procedure A):
Diketen **5** (0.84g, 10mmol) was added dropwise with stirring to respective alcohol **3**, **4a or 4b** (10mmol) pre-heated to 50-60 °C in presence of a catalytic amount of Et_3N (5 drop). Diketene was

added at such a rate that the temperature of the reaction mixture did not exceed 80°C, and then the reaction was allowed to proceed for 1 h at 80°C. The product was isolated by silica gel column chromatography or distillation *in vacuo*.

2-[4-(p-Fluorophenyl) piperazine-1-yl] ethyl acetoacetate (6a)

The method was used similar to that described in procedure A. Reaction of 2-[4-(*p*-fluorophenyl) piperazine-1-yl] ethanol **3** (2.42 g, 10 mmol) and diketene **5** (0.84 g, 10 mmol) and triethylamine (5 drop) gave a product which was isolated by silica gel column chromatography with CH_2Cl_2-MeOH (96:4, V/V) as eluent. The product **6a** was isolated as a yellow oil (2.62 g, 85%).

H^1 NMR ($CDCl_3$) δ: 6.82-6.97 (m, 4H, aryl-H),4.30(t , J = 5.8 Hz, 2H, $COOCH_2$), 3.47 (s, 2H, $COCH_2COO$) , 3.09 (t,J= 4.9 Hz , 4H, piperazinyl H-3,H-5), 2.63-2.73 (m, 6H, $COOCH_2CH_2$ and piperazinyl H-2 , H-6), 2.27 (s,3H,CH_3CO).

IR (film): 1776 (C=O, ester), 1229 (C-F) cm^{-1}.

2-(N,N-Dimethylamino)ethyl acetoacetate (6b)

The title compound (6b) was prepared according to the procedure A by using N,N-dimethylethanolamine (0.89 g, 10mmol), diketene (0.84g, 10mmol) and triethylamine (5 drop).The reaction mixture was purified by distillation *in vacuo* [bp 98-99°C (3mmHg)] to yield as a colourless liquid (1.46 g, 84.3%).

^{1}HNMR ($CDCl_3$): δ 4.20 (t, J=5.7 Hz, 2H,$COOCH_2$), 3.45 (s, 2H, $COCH_2COO$), 2.53 (t, J=5.7 Hz, 2H, CH_2NMe_2), 2.23 (s, 9H,CH_3CO and NMe_2).

IR (film): 1745 (C=O, ester), 1726(C=O, ketone) cm^{-1}.

3-(N,N-Dimethylamino)propyl acetoacetate (6c)

The title compound (6c) was prepared according to procedure A using 3-(N,N-dimethylamino)propanol (1.03g, 10mmol), diketene(0.84g, 10mmol) and triethylamine (5 drop). The reaction mixture was purified by distillation *in vacuo* [bp 103-104 °C(3mmHg)] to yield as a colourless liquid (1.36g, 73.6%).

H^1 NMR ($CDCl_3$): δ 4.13(t, J=5.7 Hz, 2H, $COOCH_2$), 3.61 (s, 2H, $COCH_2COO$), 2.47(t, J=5.1 Hz, 2H, CH_2NMe_2), 2.11 (s, 9H, CH_3CO and NMe_2) and 1.14(m, 2H, CH_2).

IR (film): 1751(C=O, ester), 1719 (C=O, ketone) cm^{-1}.

General procedure for the synthesis of dihydropyridine derivatives 9a-j (procedure B):

A mixture of the respective acetoacetate ester **6a-c** (5.0 mmol), 1-methyl-5-nitro-imidazol-2-carboxaldehyde (0.78g, 5mmol) and the respective alkyl 3-aminocrotonate (5.0 mmol) **8a-c** in absolute ethanol (25 ml) was refluxed for 10 h with stirring. After cooling, the precipitated product was filtered off, washed with cold ethanol, and then dried *in vacuo*. Recrystallization from methanol gave **9a-j** (38-61%) as yellow or white crystals.

3-[2-(N,N-dimethylamino)ethyl] 5-methyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9a)

H^1 NMR ($CDCl_3$): δ 8.43(br s, 1H, NH), 7.91(s, 1H, imidazole H-4), 5.10(s, 1H, C_4-H), 4.42(t, J=7 Hz, 2H, CO_2CH_2), 4.15(s, 3H, N-CH_3), 4.09(s, 3H, CO_2CH_3), 3.76(t, J=7 Hz, 2H, CH_2NMe_2), 3.69(s, 6H, $N(CH_3)_2$) and 2.39(s, 6H, C_2-CH_3 & C_6-CH_3)

IR(KBr): 3335 (NH),1694(C=O), 1671(C=C), 1526 and 1351 cm^{-1} (NO_2).

MS: m/z(%) 407(M^+,100), 397(93), 318(18), 224(67), 156(12) and 128(9)

3-[2-(N,N-dimethylamino)ethyl] 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9b)

H^1 NMR ($CDCl_3$): δ 8.49(br s, 1H, NH), 7.94(s, 1H, imidazole H-4), 5.16(s, 1H, C_4-H), 4.42(t, J=7.1 Hz, 2H, CO_2CH_2), 4.21(s, 3H, N-CH_3), 4.09(q, J=6.8 Hz, 2H, CO_2CH_2), 3.86(t, J=7.1 Hz, 2H, CH_2NMe_2), 3.67(s, 6H, $N(CH_3)_2$), 2.24(s, 6H, C_2-CH_3 & C_6-CH_3) and 1.23((t, J=6.8 Hz, 3H, CH_3)

IR(KBr): 3415 (NH),1715(C=O), 1661(C=C), 1528 and 1353 cm^{-1} (NO_2).

MS: m/z (%) 421(M^+,18), 393(32), 364(100), 238(93), 156(9) and 128(17)

3-[2-(N,N-dimethylamino)ethyl] 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9c)

H^1 NMR ($CDCl_3$): δ 8.23(br s, 1H, NH), 7.94(s, 1H, imidazole H-4), 5.13(s, 1H, C_4-H), 5.02(m, 1H, $CH(CH_3)_2$), 4.39(t, J=6.4Hz, 2H, CO_2CH_2)4.22(s, 3H, N-CH_3), 3.79(t, J=6.4 Hz, 2H, CH_2NMe_2), 3.66(s, 6H, $N(CH_3)_2$), 2.24(s, 6H, C_2-CH_3 & C_6-CH_3), 1.24 and 1.16((two d, J=6.5 Hz, 3H each, $CH(CH_3)_2$)

IR(KBr): 3375 (NH),1737(C=O), 1626(C=C), 1521 and 1371 cm^{-1} (NO_2).

MS: m/z(%) 435(M^+,8), 407(16), 379(100), 252(93), 156(11) and 128(19)

3-[2-(N,N-dimethylamino)propyl] 5-methyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9d)

H^1 NMR ($CDCl_3$): δ 8.44(br s, 1H, NH), 7.93(s, 1H, imidazole H-4), 5.14(s, 1H, C_4-H), 4.34(t, J=6.8 Hz, 2H, CO_2CH_2), 4.19(s, 3H, N-CH_3), 4.01(s, 1H, CO_2CH_3), 3.71(t, J=6.8 Hz, 2H, CH_2NMe_2), 3.66(s, 6H, $N(CH_3)_2$) and 2.22(s, 6H, C_2-CH_3 & C_6-CH_3) and 1.83(m, 2H, CH_2)

IR(KBr): 3375 (NH),1734(C=O), 1666(C=C), 1521 and 1351 cm^{-1} (NO_2).

MS: m/z(%) 421(M^+,87), 397(25), 351(100), 224(76), 156(10) and 128(14)

3-[2-(N,N-dimethylamino)propyl] 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9e)

H^1 NMR ($CDCl_3$): δ 8.98(br s, 1H, NH), 7.94(s, 1H, imidazole H-4), 5.17(s, 1H, C_4-H), 4.42(t, J=7 Hz, 2H, CO_2CH_2), 4.22(s, 3H, N-CH_3), 4.09(q, 2H, J=7.2 Hz, CO_2CH_2), 3.86(t, J=6.7 Hz, 2H, CH_2NMe_2), 3.67(s, 6H, $N(CH_3)_2$) and 2.24(s, 6H, C_2-CH_3 & C_6-CH_3),1.77(m, 2H, CH_2) and 1.23(t, J=7.2 Hz, 3H,CH_3)

IR(KBr): 3345 (NH),1741(C=O), 1655(C=C), 1513 and 1375 cm^{-1} (NO_2).

MS: m/z(%) 435(M^+,94), 393(28), 364(100), 238(73), 156(9) and 128(12)

3-[2-(N,N-dimethylamino)propyl] 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9f)

H^1 NMR ($CDCl_3$): δ 8.17(br s, 1H, NH), 7.94(s, 1H, imidazole H-4), 5.12(s, 1H, C_4-H), 4.98(m, 1H, $CH(CH_3)_2$), 4.39(t, J=6.6Hz, 2H, CO_2CH_2)4.22(s, 3H, N-CH_3), 3.77(t, J=6.6 Hz, 2H, CH_2NMe_2), 3.66(s, 6H, $N(CH_3)_2$), 2.24(s, 6H, C_2-CH_3 & C_6-CH_3), 1.89(m, 2H, CH_2), 1.25 and 1.17((two d, J=5.2 Hz, 3H each, $CH(CH_3)_2$)

IR(KBr) : 3392 (NH),1740(C=O), 1619(C=C), 1517 and 1379 cm^{-1} (NO_2).

MS: m/z(%) 435(M^+,8), 379(100), 309(9), 252(93), 156(11) and 128(19)

3-[2-[4-(p-Fluorophenyl) piperazine-1-yl] ethyl] 5-methyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate(9g)

H^1 NMR ($CDCl_3$): δ 8.47(br s, 1H, NH), 7.93(s, 1H, imidazole H-4), 6.81(m, 4H, C_6H_4-F), 5.16(s, 1H, C_4-H), 4.23(s, 3H, N-CH_3), 4.20(t, J=7.1 Hz, 2H, CO_2CH_2), 3.66(s, 3H, CO_2CH_3), 2.99(br t, J=4.6 Hz, 4H, piperazenyl H-3 & H-5), 2.62(m, 6H, piperazenyl H-2 & H-6 and CH_2), 2.25 and 2.39(two s, 3H each, C_2-CH_3 & C_6-CH_3)

IR(KBr): 3387 (NH),1736(C=O), 1652(C=C), 1517 and 1379 cm^{-1} (NO_2).

MS: m/z(%) 542(M^+,6), 536(100), 392(41), 265(36), 177(11) and 122(24)

3-[2-[4-(p-Fluorophenyl)piperazine-1-yl]ethyl] 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate(9h)

H^1 NMR ($CDCl_3$): δ 8.67(br s, 1H, NH), 7.93(s, 1H, imidazole H-4), 6.91(m, 4H, C_6H_4-F), 5.16(s, 1H, C_4-H), 4.24(s, 3H, N-CH_3), 4.17(m, 4H, CO_2CH_2), 3.08(br t, J=4.6 Hz, 4H, piperazenyl H-3 & H-5), 2.60(m, 6H, piperazenyl H-2 & H-6 and CH_2), 2.24(s, 6H, C_2-CH_3 & C_6-CH_3) and 1.22((t, J=6.8 Hz, 3H, CH_3)

IR(KBr): 3375 (NH),1716(C=O), 1666(C=C), 1527 and 1371 cm^{-1} (NO_2).

MS: m/z(%) 556(M^+,4), 540(10), 279(79), 206(63), 193(100), 150(46) and 122(30)

3-[2-[4-(p-Fluorophenyl)piperazine-1-yl]ethyl], 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylate (9j)

H^1 NMR ($CDCl_3$): δ 8.49(br s, 1H, NH), 7.94(s, 1H, imidazole H-4), 6.91(m, 4H, C_6H_4-F), 5.14(s, 1H, C_4-H), 4.97(m, 1H, $CH(CH_3)_2$),), 4.26(s, 3H, N-CH_3), 4.20(t, J=6.8 Hz, 2H, CO_2CH_2), 2.99(br t, J=4.3 Hz, 4H, piperazenyl H-3 & H-5), 2.63(m, 6H, piperazenyl H-2 & H-6 and CH_2), 2.23(s, 6H, C_2-CH_3 & C_6-CH_3), 1.22 and 1.14((two d, J=4.6 Hz, 3H each, $CH(CH_3)_2$)

IR(KBr): 3375 (NH),1717(C=O), 1666(C=C), 1527 and 1371 cm^{-1} (NO_2).

MS: m/z(%) 570(M^+,11), 552(16), 291(100), 259(24), 196(47) and 123(27)

Pharmacology:

Male albino guinea pig (body weight 300-450 g) was sacrificed by blow on the head. The intestine was removed above the ileocecal junction longitudinal smooth muscle segments of 2 cm length were mounted under a resting tension of 500 mg. The segments were maintained at 37° C in a 20 ml jacketed organ bath containing oxygenated (100% O_2) physiological saline solution of the following composition (Mm): NaCl: 137, $CaCl_2$ 1.8; KCl: 2.7; $MgSO_4$: 1.1; NaH_2PO_4:.4; $NaHCO_3$:12; Glucose:5. The muscles were equilibrated for 1 hour with a solution changes every 15 min. The contractions were recorded with a force displacement

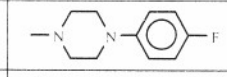
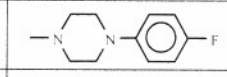
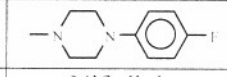
transducer (F-50) on a NARCO physiograph. All compounds were dissolved in DMSO and the same volume of the solvent was used as control. The contractile response was taken as the 100% value for the tonic (slow) component of the response. Test compounds were cumulatively added after the dose response for KCl was determined. Compound-induced relaxation of contracted muscle was expressed as percent of control. The IC_{50} values were graphically determined from the contraction-response curves (16-17).

Statistics: The results obtained were presented as means and evaluated statistically using Student's *t*-test.

RESULTS AND DISCUSSION

Nine unsymmetrical analogues of nifedipine were prepared by a procedure reported by Meyer in which, 1-methyl-5-nitro-imidazol-2-carbox-aldehyde was reacted with 3-oxobutanoic acid esters and 3-aminocrotonate. The *in vitro* calcium channel antagonist activities (IC_{50}) of compound **9a-j** determined as contraction required producing, 50% relaxation of contracted guinea pig ileal lungitudinal smooth muscle (GPILSM). Nifedipine was used as reference drug. The results are summarized in Table 1.

Table 1. Physical properties of compounds 9a-j and their calcium channel antagonist activity in GPILSM

Comp. No.	R_1	R_2	n	Mp (^{0}C)	Yield (%)	Calcium- channel antagonist activity (IC_{50} ± SEM, n=5) M
9a	-N(Me)$_2$	Me	2	303-305	53	$7.15 \pm 1.83 \times 10^{-9}$ *
9b	-N(Me)$_2$	Et	2	242-244	61	$1.09 \pm 0.72 \times 10^{-9}$ *
9c	-N(Me)$_2$	iPro	2	239-240	58	$4.61 \pm 1.60 \times 10^{-10}$
9d	-N(Me)$_2$	Me	3	253-255	55	$3.15 \pm 0.76 \times 10^{-9}$ *
9e	-N(Me)$_2$	Et	3	183-185	40	$4.89 \pm 0.72 \times 10^{-10}$
9f	-N(Me)$_2$	iPro	3	121-123	60	$7.39 \pm 1.12 \times 10^{-11}$ *
9g		Me	2	250-252	38	$2.65 \pm 0.61 \times 10^{-10}$
9h		Et	2	218-220	54	$4.88 \pm 1.34 \times 10^{-11}$ *
9j		iPro	2	186-188	47	$2.12 \pm 0.98 \times 10^{-11}$ *
	Nifedipine					$2.57 \pm 0.36 \times 10^{-10}$

* Single asterisk indicates $P < 0.05$ compared to nifedipine in that experiment using Student's t-test.

The results for asymmetrical esters possessing one R_1 and R_2 substituents indicated that increasing the length of methylene chain in C_3-ester substituent decreases activity .The relative activity profile for the same R_1 and n esters was iPr>Et>Me. Comparison of esters having the same number of methylene (n=2) show that the arylpiperazine compounds were more active than amine derivatives.

Comparison of the activities of compounds **9g-j** with the compounds reported by Shafiee et al. (10) having the same structure without arylpiperazine group reveals that the presence of an arylpiperazine group substituted on C-3 position of the 1,4-dihydropyridine ring increases the smooth muscle relaxant activity. Compound **9j** was the most active compound and its activity was more than the reference drug, nifedipine.

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