Pharmaceutical Research, Vol. 7, No. 9, 1990

Report

Synthesis and Calcium Channel Antagonist Activity of 3-Arylmethyl 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates

Murthy R. Akula,[1] Wandikayi C. Matowe,[1] Michael W. Wolowyk,[1] and Edward E. Knaus[1,2]

Received December 12, 1989; accepted March 13, 1990

Unsymmetrical aryl(heteroaryl)methyl isopropyl ester analogues of nifedipine, in which the 2-nitrophenyl group at C-4 is replaced by a 2- or 3-pyridyl substituent, were synthesized and evaluated as calcium-channel antagonists using guinea pig ileal longitudinal smooth muscle. The point of attachment of the C-4 pyridyl substituent was a determinant of activity where the relative potency order was 2-pyridyl > 3-pyridyl. Within the C-4 2-pyridyl series of compounds, an electronegative substituent such as a trifluoromethyl or bromo at the 4 position of the benzyl ester substituent or a nitrogen atom at the 1 position of a 4-pyridylmethyl ester substituent, enhanced activity relative to the unsubstituted benzyl ester analogue. In contrast, in the C-4 3-pyridyl class of compounds, a variety of aryl(heteroaryl)methyl ester substituents did not alter potency to any significant extent. A number of compounds in the C-4 2-pyridyl series possessing 4-pyridylmethyl, 4-trifluoromethylbenzyl, 4-bromobenzyl, and 3-pyridylmethyl ester substituents were approximately equipotent to nifedipine. The aryl(heteroaryl)methyl ester and C-4 2-pyridyl substituents therefore appear to provide important interdependent contributions to calcium-channel antagonist activity.

KEY WORDS: calcium-channel antagonists; pyridine; 1,4-dihydropyridine; nifedipine analogues.

INTRODUCTION

The discovery that 1,4-dihydropyridine (DHP) calcium-channel antagonists inhibit the influx of extracellular Ca^{2+} via L-type potential-dependent calcium channels (1,2) provided an important chemotherapeutic alternative for the treatment of cardiovascular diseases including hypertension, angina pectoris, and some spastic smooth muscle disorders (3,4). The clinical success of nifedipine (**1a**) (Fig. 1) has stimulated the search for second-generation analogues with superior bioavailability, a slower onset, and a longer duration of action that are amenable to a once-a-day dosage regimen (5,6). The duration of action (5,6), conformation (7), and potency (5,8–11) of analogues of the first-generation antagonist nifedipine (**1a**) are altered by changes in the substitution pattern at the C-3, C-4, and C-5 positions. Strain due to nonbonded interactions between the C-3, C-4, and C-5 substituents is relieved predominately by an increase in planarity of the boat-shaped DHP ring and distortion of the bond angle about C-4, which results in enhanced calcium antagonist activity (7,11). Conformational calculations, using the molecular orbital program MOPAC, suggest that both carbonyl groups in 1,4-DHP calcium-channel antagonists are preferentially orientated in a plane which intersects the DHP ring at an angle between 30 and 60° (12).

Previously, we reported (13) that a 4-(pyridyl) substituent is isosteric with a 4-(nitrophenyl) substituent on a 1,4-DHP ring where 2-, 3-, and 4-nitrophenyl are isosteric with 2-, 3-, and 4-pyridyl, respectively. It was proposed that the pyridyl nitrogen lone electron pair for compounds **1b** can be viewed as a substituent even though the steric effect which an orbital with a free electron pair can induce is obviously much smaller than that of a substituent attached to a phenyl ring. This postulate was supported by calcium antagonist test results, which showed that the relative potency profile for isomeric C-4 pyridyl substituents was 2-pyridyl > 3-pyridyl > 4-pyridyl. Increasing the size of the ester substituents increased activity where the relative potency profile was i-Bu > i-Pr > Et > Me. In contrast, when the C-3(5) ester substituents for **1b** were larger in size, *viz.*, $R^1 = R^2$ = cyclohexyl, the relative potency order for C-4 pyridyl isomers was 3-pyridyl ~ 4-pyridyl > 2-pyridyl. These results suggest that 1,4-DHP calcium antagonists possessing smaller C-3(5) ester substituents with C-4 2-pyridyl or 2-substituted-phenyl substituents should be considered, whereas with antagonists possessing larger C-3(5) ester substituents, C-4 3-pyridyl or 3-substituted-phenyl substituents should be considered (14). Conformational and steric factors play an important role in the binding of these molecules to the 1,4-DHP receptor(s). Structural differences, including the H-bonding strength of the DHP amine, the ester group orientation, and the hydrophobic fit of the ester groups, may control the calcium channel in the closed state favored by calcium antagonists (15). These results prompted us to in-

[1] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8.

[2] To whom correspondence should be addressed.

0724-8741/90/0900-0919$06.00/0

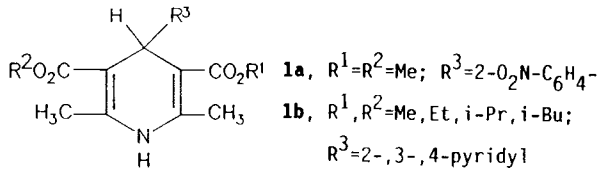


Fig. 1. Structures of nifedipine (**1a**) and C-4 pyridyl analogues (**1b**) thereof.

vestigate the effect that 3-aryl(heteroaryl)methyl R^1 substituents, which are capable of different hydrophobic (H-bonding) and/or electronic interactions with the 1,4-DHP receptor(s), in conjunction with C-4 2-pyridyl or 3-pyridyl R^2 substituents (**5**), have on calcium-channel antagonist activity. 3-Aryl(heteroaryl)methyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates (**5**) have now been synthesized for evaluation as calcium-channel antagonists. This study represents an extension of previous investigations to establish structure–activity correlations by elaboration of the C-3 and C-4 substituents of Hantzsch 1,4-dihydropyridines related to nifedipine (**1a**).

MATERIALS AND METHODS

Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Proton magnetic resonance (NMR) spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ using Me_4Si as internal standard. Infrared (IR) spectra were acquired on a Nicolet 5DX-FT spectrometer. All spectral data were in agreement with the assigned structures. Microanalyses were within ±0.4% of theoretical values for C, H, and N. Column chromatography was performed using Merck 7734 (100- to 200-mesh) silica gel. Isopropyl 3-aminocrotonate (**2**) was prepared by passage of anhydrous ammonia gas through a solution of isopropyl acetoacetate in absolute ethanol according to the procedure of Joslyn *et al.* (16). The aryl(heteroaryl)acetoacetates (**3**) were synthesized by using the procedure of Lawesson *et al.* (17).

SYNTHESIS

General Procedure for the Preparation of 3-Aryl(heteroaryl)methyl 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates (5)

The appropriate aryl(heteroaryl)acetoacetate (**3**; 3 mmol) followed by isopropyl 3-aminocrotonate (**2**; 3 mmol) was added to a solution of the pyridinecarboxaldehyde (**4**; 3 mmol) in absolute ethanol (25 ml). The resulting mixture was heated under reflux for 16 hr, cooled to 25°C, and then poured onto crushed ice (50 g). The crude product (**5a–n**) was separated either by filtration or by extraction with chloroform (3 × 50 ml). When the product was extracted, the combined chloroform extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Each product was purified by elution from a silica gel column (2.5 × 20 cm) using EtOAc–hexane (3:1, v/v) as eluent followed by recrystallization from EtOAc.

Representative spectral data for selected compounds are summarized below.

3-Benzyl 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(2-pyridyl)-3,5-pyridinedicarboxylate (5a)

IR (KBr): 3197 (NH) and 1687 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.05 and 1.19 (two d, J = 7 Hz, 3H each, $CHMe_2$), 2.24 and 2.25 (two s, 3H each, =CMe), 4.93 (m, 1H, $CHMe_2$), 5.03 and 5.11 (two d, J = 12 Hz, 2H, CH_2Ph), 5.21 (s, 1H, H-4), 7.13 (m, 1H, pyridyl H-5), 7.22–7.38 (m, 6H, pyridyl H-3, phenyl hydrogens), 7.48 (m, 1H, pyridyl H-4), 8.49 (d, 1H, $J_{5,6}$ = 5 Hz, pyridyl H-6), 8.94 (s, 1H, NH, exchanges with deuterium oxide).

Anal. ($C_{24}H_{26}N_2O_4$). Calculated: C, 70.94; H, 6.40; N, 6.90. Found: C, 70.62; H, 6.47; N, 6.86.

3-(3-Pyridinylmethyl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-pyridyl)-3,5-pyridinedicarboxylate (5d)

IR (KBr): 3172 (NH) and 1687 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.10 and 1.25 (two d, J = 6 Hz, 3H each, $CHMe_2$), 2.34 and 2.35 (two s, 3H each, =CMe), 4.95 (m, 1H, $CHMe_2$), 4.98 (s, 1H, H-4), 5.06 and 5.16 (two d, J = 12 Hz, 2H, CO_2CH_2), 7.0 (br s, 1H, NH, exchanges with deuterium oxide), 7.14 (m, 1H, pyridyl H-5), 7.26 (m, 1H, pyridinyl H-5), 7.56 (m, 2H, pyridyl H-4, pyridinyl H-4), 8.35 (m, 1H, pyridyl H-6), 8.52 (m, 2H, pyridyl H-2, pyridinyl H-2), 8.56 (m, 1H, pyridinyl H-6).

Anal. ($C_{23}H_{25}N_3O_4$). Calculated: C, 67.81; H, 6.14; N, 10.32. Found: C, 68.20; H, 6.18; N, 10.13.

3-(4-Pyridinylmethyl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(2-pyridyl)-3,5-pyridinedicarboxylate (5e)

IR (KBr): 3172 (NH) and 1696 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.13 and 1.24 (two d, J = 7 Hz, 3H each, $CHMe_2$), 2.27 and 2.31 (two s, 3H each, =CMe), 4.98 (m, 1H, $CHMe_2$), 5.08 and 5.20 (two d, J = 15 Hz, 2H, CO_2CH_2), 5.29 (s, 1H, H-4), 7.1 (d, J = 6 Hz, 2H, pyridinyl H-3, H-5), 7.22 (m, 1H, pyridyl H-5), 7.38 (d, $J_{3,4}$ = 8 Hz, 1H, pyridyl H-3), 7.56 (m, 1H, pyridyl H-4), 8.55 (m, 3H, pyridyl H-6, pyridinyl H-2, H-6), 9.26 (br s, 1H, NH, exchanges with deuterium oxide).

Anal. ($C_{23}H_{25}N_3O_4$). Calculated: C, 67.81; H, 6.14; N, 10.32. Found: C, 67.42; H, 6.28; N, 10.12.

3-(2-Furanylmethyl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-pyridyl)-3,5-pyridinedicarboxylate (5h)

IR (KBr): 3180 (NH) and 1687 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.06 and 1.21 (two d, J = 7 Hz, 3H each, $CHMe_2$), 2.31 and 2.32 (two s, 3H each, =CMe), 4.94 (m, 1H, $CHMe_2$), 4.95 (s, 1H, H-4), 4.98 and 5.06 (two d, J = 12 Hz, 2H, CO_2CH_2), 6.12 (br s, 1H, NH, exchanges with deuterium oxide), 6.32 (m, 2H, furanyl H-3, H-4), 7.09 (m, 1H, pyridyl H-5), 7.40 (d, $J_{4,5}$ = 1.5 Hz, 1H, furanyl H-5), 7.52 (m, 1H, pyridyl H-4), 8.34 (m, 1H, pyridyl H-6), 8.47 (d, J = 1.5 Hz, 1H, pyridyl H-2).

Anal. ($C_{22}H_{24}N_2O_5$). Calculated: C, 66.66; H, 6.06; N, 7.07. Found: C, 66.87; H, 6.01; N, 7.17.

3-(4-Bromobenzyl) 5-Isopropyl 1,4-Dihydro-2, 6-dimethyl-4-(2-pyridyl)-3,5-pyridinedicarboxylate (5i)

IR (KBr): 3182 (NH) and 1696 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.09 and 1.20 (two d, J = 6 Hz, 3H each, $CHMe_2$), 2.24 and 2.25 (two s, 3H each, =CMe), 4.94 (m, 1H, $CHMe_2$), 4.98 and 5.08 (two d, J = 12 Hz, 2H, CO_2CH_2), 5.18 (s, 1H, H-4), 7.08 (d, J = 9 Hz, 2H, phenyl H-2, H-6), 7.10 (m, 1H, pyridyl H-5), 7.25 (d, J = 6 Hz, 1H, pyridyl H-3), 7.42 (d, J = 9 Hz, 2H, phenyl H-3, H-5), 7.48 (m, 1H, pyridyl H-4), 8.42 (br s, 1H, NH, exchanges with deuterium oxide), 8.48 (m, 1H, pyridyl H-6).

Anal. ($C_{24}H_{25}BrN_2O_4$). Calculated: C, 59.38; H, 5.15; N, 5.77. Found: C, 58.98; H, 5.05; N, 5.63.

3-(4-Methylbenzyl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-pyridyl)-3,5-pyridinedicarboxylate (5l)

IR (KBr): 3386 (NH) and 1687 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.08 and 1.22 (two d, J = 6 Hz, 3H each, $CHMe_2$), 2.33 (s, 6H, phenyl C-4 Me, =CMe), 2.34 (s, 3H, =CMe), 4.94 (m, 1H, $CHMe_2$), 5.0 (s, 1H, H-4), 5.04 (s, 2H, CO_2CH_2), 6.0 (br s, 1H, NH, exchanges with deuterium oxide), 7.13 (m, 4H, phenyl hydrogens), 7.52 (m, 1H, pyridyl H-5), 8.35 (d, J = 6 Hz of d, J = 2 Hz, 1H, pyridyl H-6), 8.49 (d, J = 2 Hz, 1H, pyridyl H-2).

Anal. ($C_{25}H_{28}N_2O_4$). C, 71.42; H, 6.66; N, 6.66. Found: C, 71.51; H, 6.76; N, 6.50.

3-(4-Trifluoromethylbenzyl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(2-pyridyl)-3,5-pyridinedicarboxylate (5m)

IR (KBr): 3181 (NH) and 1687 (CO_2) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.10 and 1.21 (two d, J = 6 Hz, 3H each, $CHMe_2$), 2.26 and 2.28 (two s, 3H each, =CMe), 4.94 (m, 1H, $CHMe_2$), 5.07 and 5.17 (two d, J = 12 Hz, 2H, CO_2CH_2), 5.18 (s, 1H, H-4), 7.10 (m, 1H, pyridyl H-5), 7.24 (d, J = 6 Hz, 1H, pyridyl H-3), 7.27 (d, J = 9 Hz, 2H, phenyl H-2, H-6), 7.46 (m, 1H, pyridyl H-4), 7.53 (d, J = 9 Hz, 2H, phenyl H-3, H-5), 8.08 (br s, 1H, NH, exchanges with deuterium oxide), 8.47 (m, 1H, pyridyl H-6).

Anal. ($C_{25}H_{25}F_3N_2O_4$). Calculated: C, 63.28; H, 5.31; N, 5.90. Found: C, 63.09; H, 5.38; N, 5.86.

Calcium-Channel Antagonist Assay

The calcium-channel antagonist activities for **5a–n**, determined as the concentration to produce 50% inhibition of the muscarinic receptor-mediated (carbachol, 1.6×10^{-7} *M*) Ca^{2+}-dependent contraction of guinea pig ileal longitudinal smooth muscle, were measured using the procedure previously reported (8). In each case the inhibition of L-channel activity was confirmed on the high-KCl depolarized tissue response.

RESULTS AND DISCUSSION

Chemistry

The unsymmetrical 3-aryl(heteroaryl)methyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates (**5a–n**) were synthesized by a modified Hantzsch reaction (18), using a procedure reported by Iwanami *et al.* (19). Thus, condensation of isopropyl 3-aminocrotonate (**2**), the appropriate aryl(heteroaryl)acetoacetate (**3**), and a pyridylcarboxaldehyde (**4**) afforded the target products (**5a–n**) in 28–77% yields as illustrated in Scheme I (see Table I for R^1 and R^2 substituents).

Structure–Activity Correlations

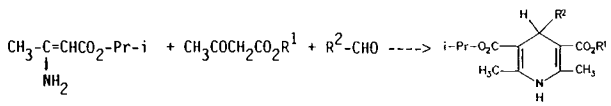
The calcium-channel antagonist activities for **5a–n**, determined as the concentration required to produce 50% inhibition of the guinea pig ileal longitudinal smooth muscle contractility (8), are summarized in Table I.

The point of attachment of the R^2 pyridyl substituent was a determinant of activity since the 2-pyridyl isomers were generally more active than the corresponding 3-pyridyl isomers. The relative potencies were **5a** > **5b** (R^1 = $PhCH_2$-, P = 0.2),[3] **5c** > **5d** (R^1 = 3-pyridyl-CH_2-, P = 0.001), **5e** > **5f** (R^1 = 4-pyridyl-CH_2, P = 0.001), **5i** > **5j** (R^1 = 4-Br-C_6H_4-CH_2-, P = 0.001), **5k** > **5l** (R^1 = 4-Me-C_6H_4-CH_2-, P = 0.60), and **5m** > **5n** (R^1 = 4-CF_3-C_6H_4-CH_2-, P = 0.001). The activity of the 3-pyridyl compound **5h** was not significantly different from that of the 2-pyridyl isomer **5g** (R^1 = 2-furanyl-CH_2-, P = 0.60). These results are consistent with those of a previous investigation which indicated that the potencies exhibited by C-4 2-pyridyl unsymmetrical diesters were greater than that of the corresponding 3-pyridyl isomers (13).

Within the R^2 2-pyridyl series of compounds, the relative potency order was **5e** (4-pyridyl-CH_2-) > **5m** (4-CF_3-C_6H_4-CH_2-) > **5i** (4-Br-C_6H_4-CH_2-) > **5c** (3-pyridyl-CH_2-) > **5k** (4-Me-C_6H_4-CH_2-) > **5a** ($PhCH_2$-) > **5g** (2-furanyl-CH_2-), although the differences in activity were usually small (P = 0.01–0.8). However, the differences in potency between a number of compounds relative to the R^1 benzyl analogue (**5a**) were significant (P = 0.001) where the relative activities were **5c** > **5a**, **5e** > **5a**, **5i** > **5a**, and **5m** > **5a**. In addition, the R^1 4-pyridylmethyl compound **5e** was marginally more active than the analogous 3-pyridylmethyl isomer **5c** (P = 0.3). These structure–activity correlations indicate that an electronegative subsituent such as CF_3 (**5m**) or Br (**5i**) at the C-4 position of the R^1 aryl ring subsituent, or a nitrogen atom at the 1 position of a pyridyl ring (**5e**), enhances activity relative to the R^1 benzyl analogue (**5a**). In contrast, in the R^2 3-pyridyl series of compounds the differences in potencies between compounds **5b**, **5d**, **5f**, **5h**, **5j**, **5l**, and **5n** were generally less than 1 log unit, and the differences in potency were not significant.

A number of compounds within the R^2 2-pyridyl series of compounds (**5e**; R^1 = 4-pyridyl-CH_2-; **5m**, R^1 = 4-CF_3-C_6H_4-CH_2-; **5i**, 4-Br-C_6H_4-CH_2-; **5c**, 3-pyridyl-CH_2-)

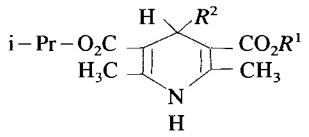
[3] The level of significance was calculated using Student's *t* test.



2 3 4 5

Scheme I. Synthesis of 3-aryl(heteroaryl)methyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates (**5**).

Table I. Some Physical and Calcium-Channel Antagonist Data for 3-Aryl(heteroaryl)methyl 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(pyridyl)-3,5-pyridinedicarboxylates



5

No.	R^1	R^2	mp (°C)	Yield (%)	Formula[a]	Calcium-channel antagonist activity,[b] ID_{50} (M)[c]
5a	$PhCH_2$-	2-pyr	166–168	46	$C_{24}H_{26}N_2O_4$	$3.26 \pm 0.36 \times 10^{-7}$ (3)
5b	$PhCH_2$-	3-pyr	118–120	63	$C_{24}H_{26}N_2O_4$	$6.21 \pm 1.78 \times 10^{-7}$ (4)
5c	3-pyr-CH_2-	2-pyr	173–175	61	$C_{23}H_{25}N_3O_4$	$7.80 \pm 4.36 \times 10^{-8}$ (3)
5d	3-pyr-CH_2-	3-pyr	150–152	77	$C_{23}H_{25}N_3O_4$	$1.79 \pm 0.27 \times 10^{-6}$ (6)
5e	4-pyr-CH_2-	2-pyr	170–172	28	$C_{23}H_{25}N_3O_4$	$2.11 \pm 0.68 \times 10^{-8}$ (3)
5f	4-pyr-CH_2-	3-pyr	180–181	34	$C_{23}H_{25}N_3O_4$	$3.49 \pm 0.76 \times 10^{-7}$ (3)
5g	2-furanyl-CH_2-	2-pyr	150–152	44	$C_{22}H_{24}N_2O_5$	$3.85 \pm 0.49 \times 10^{-7}$ (3)
5h	2-furanyl-CH_2-	3-pyr	172–174	54	$C_{22}H_{24}N_2O_5$	$2.70 \pm 1.75 \times 10^{-7}$ (3)
5i	4-Br-benzyl-	2-pyr	192–194	66	$C_{24}H_{25}N_2O_4Br$	$6.00 \pm 1.92 \times 10^{-8}$ (3)
5j	4-Br-benzyl-	3-pyr	184–186	73	$C_{24}H_{25}N_2O_4Br$	$1.91 \pm 0.69 \times 10^{-7}$ (3)
5k	4-Me-benzyl-	2-pyr	179–181	68	$C_{25}H_{28}N_2O_4$	$1.34 \pm 0.21 \times 10^{-7}$ (3)
5l	4-Me-benzyl-	3-pyr	141–142	64	$C_{25}H_{28}N_2O_4$	$1.81 \pm 0.61 \times 10^{-7}$ (3)
5m	4-CF_3-benzyl-	2-pyr	194–196	48	$C_{25}H_{25}N_2O_4F_3$	$4.78 \pm 2.44 \times 10^{-8}$ (3)
5n	4-CF_3-benzyl-	3-pyr	171–172	72	$C_{25}H_{25}N_2O_4F_3$	$5.13 \pm 2.02 \times 10^{-7}$ (3)
Nifedipine						$1.40 \pm 0.19 \times 10^{-8}$ (18)

[a] Microanalytical analyses were within ±0.4% of theoretical values for C, H, and N, unless otherwise specified.
[b] Inhibitory activity on contractile response to carbachol.
[c] The concentration of antagonist causing a 50% decrease in the slow component or tonic response ($ID_{50} \pm SE$) in the guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist (carbachol) was determined graphically from the dose–response curves. The number of experiments is shown in parentheses.

were approximately equiactive with the reference drug nifedipine since the differences in activity were not significant ($P = 0.10$–0.40). Hence, for 1,4-DHP calcium antagonists with unsymmetrical C-3(5) ester substituents, a C-4 2-pyridyl or 2-substituted-phenyl substituent should be combined with an aryl(heteroaryl)methyl ester substituent possessing an electronegative group at its C-4 position (aryl) or 1 position (pyridyl).

The 1,4-DHP compounds (5) all possess a chiral center at C-4. It is not known if the enantiomers possess different potencies since the racemates were not resolved.

ACKNOWLEDGMENT

We are grateful to the Medical Research Council of Canada (Grant MA-8892) for financial support of this research.

REFERENCES

1. T. Godfraind. *Acta Pharmacol. Toxicol. Suppl. II* 58:5–50 (1986).
2. D. J. Triggle and R. A. Janis. In A. K. Grover and E. E. Daniel (eds.), *Calcium and Contractility,* Humana Press, Clifton, N.J., 1985, p. 37.
3. A. Fleckenstein. In A. Fleckenstein (ed.), *Calcium Antagonism in Heart and Smooth Muscle,* John Wiley and Sons, New York, 1983, p. 286.
4. A. Fleckenstein. *Annu. Rev. Pharmacol. Toxicol.* 17:149–166 (1977).
5. J. J. Baldwin and C. S. Sweet. *Annu. Rep. Med. Chem.* 23:59–68 (1988).
6. J. E. Arrowsmith, S. F. Campbell, P. E. Cross, J. K. Stubbs, R. A. Burges, D. G. Gardiner, and K. J. Blackburn. *J. Med. Chem.* 29:1696–1702 (1986).
7. R. Fossheim. *J. Med. Chem.* 29:305–307 (1986).
8. L. Dagnino, M. C. Li-Kwong-Ken, H. Wynn, M. W. Wolowyk, C. R. Triggle, and E. E. Knaus. *J. Med. Chem.* 30:640–646 (1987).
9. L. Dagnino, M. C. Li-Kwong-Ken, M. W. Wolowyk, C. R. Triggle, and E. E. Knaus. *Eur. J. Med. Chem.* 22:499–503 (1987).
10. M. Ramesh, W. C. Matowe, M. W. Wolowyk, and E. E. Knaus. *Drug Design Deliv.* 3:337–341 (1988).
11. R. A. Janis and D. J. Triggle. *J. Med. Chem.* 26:775–785 (1983).
12. M. Mahmoudian and W. G. Richards. *J. Chem. Soc. Chem. Commun.* 739–741 (1986).
13. L. Dagnino, M. C. Li-Kwong-Ken, M. W. Wolowyk, H. Wynn, C. R. Triggle, and E. E. Knaus. *J. Med. Chem.* 29:2524–2529 (1986).
14. M. R. Akula, W. C. Matowe, M. W. Wolowyk, and E. E. Knaus. *Drug Design Deliv.* 5:117–123 (1989).
15. P. Hess, J. B. Lansman, and R. Tsien. *Nature* 311:538–544 (1984).
16. A. Joslyn, E. Luchowski, and D. J. Triggle. *J. Med. Chem.* 31:1489–1492 (1988).
17. S. Lawesson, S. Gronwell, and R. Sandberg. *Org. Synth.* 42:28–29 (1962).
18. A. Hantzsch. *Justus Liebigs Ann. Chem.* 215:1–82 (1882).
19. M. Iwanami, T. Shibanuma, M. Fujimoto, R. Kawai, K. Tamazawa, T. Takenaka, K. Takahashi, and M. Murakami. *Chem. Pharm. Bull.* 27:1426–1440 (1979).