Synthesis of Alkyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylates Possessing a N-3 Nitro Substituent to Determine Calcium Channel Modulation Structure-Activity Relationships

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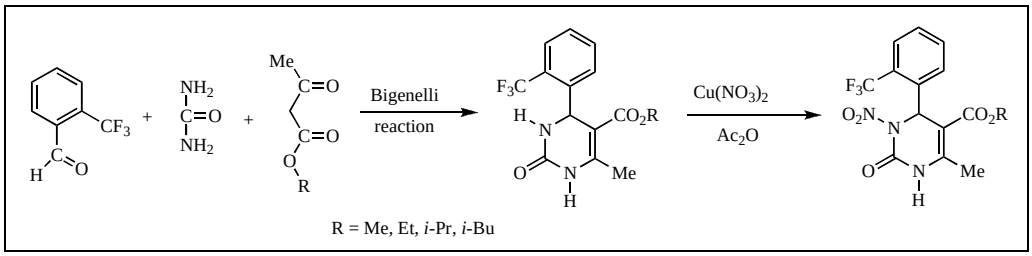

The Bigenelli acid catalyzed condensation of 2-trifluoromethylbenzaldehyde (**1**), urea (**2**) and an alkyl acetoacetate (**3**) afforded the respective alkyl (Me, Et, *i*-Pr, *i*-Bu) 6-methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylate (**4-7**). Subsequent N^3-nitration of the alkyl esters (**4-7**) using $Cu(NO_3)_2 \bullet 3H_2O$ and Ac_2O furnished the target alkyl 6-methyl-3-nitro-4-(2-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylates (**8-11**). The N^3-nitro compounds (**8-11**) were less potent calcium channel antagonists (IC_{50} values in the 1.9 x 10^{-7} to 3.9 x 10^{-6} M range) on guinea pig ileal longitudinal smooth muscle than the reference drug nifedipine (Adalat®, IC_{50} = 1.4 x 10^{-8} M). *In vitro* calcium channel modulation studies on guinea pig left atrium (GPLA) showed that the methyl and ethyl esters (**8-9**) induced a weak-to-modest positive inotropic (agonist) effect, and that the inactive isopropyl (**10**) and isobutyl (**11**) esters did not alter the cardiac contractile force of GPLA.

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INTRODUCTION

The calcium ion channel is an important drug design receptor target which has specific binding sites for both antagonist and agonist ligands that control the respective closed and open conformational state of the calcium channel. The closed and open states of the channel have different affinities and/or access for drugs which may result in quantitative and qualitative differences in calcium channel modulation structure-activity relationships [1]. Changes in the substituent pattern at the C-3, C-4, and C-5 positions of the 1,4-dihydropyridine ring alters potency, tissue selectivity and the conformation of the boat-shaped 1,4-dihydropyridine ring [2]. Hantzsch 1,4-dihydropyridines (see structures in Figure 1) such as dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl) pyridine-3,5-dicarboxylate (nifedipine) possessing C-3 and C-5 alkyl ester substitutents exhibit calcium channel antagonist activity [3], whereas modified Hantzsch 1,4-dihydropyridines having a C-3 nitro substituent such as methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate (Bay K8644) exhibit calcium channel agonist activity [4]. It has been proposed, based on MOPAC calculations, that the important conformational feature which differentiates agonist and antagonist activity is the orientation of the ester (*synperiplanar* for antagonists) and nitro (*antiperiplanar* for agonists). In antagonists both ester groups are thought to be preferentially oriented in a plane which intersects the plane of the dihydropyridine (DHP) ring with an angle of between 30 and 60°. In the agonist BAY K8644, the 3-nitro group is oriented in the plane of the DHP ring [5].

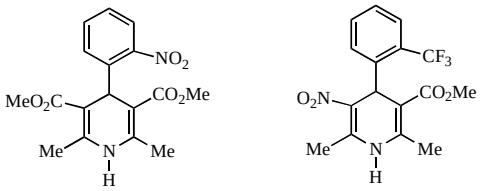


Figure 1.

A number of N^3-substituted-3,4-DHPMs (DHPMs = dihydrodpyrimidines) with vasodilative and antihypertensive activity [6], 2-hetero-substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters (active *in vitro* but inactive *in vivo*) [7], 3-substituted (alkyl esters)-4-aryl-1,4-dihydro-6-methyl-5-pyrimidine-carboxylic acid esters (inactive *in vivo* due to metabolism to the 3-NH metabolite) [8], 3-carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters (orally active and metabolically stable) [9], and structurally related pyrimidine analogs [10-11] have been reported. These 1,4-DHPMs, designed as mimics of

DHPs, can adopt a conformation similar to DHPs [7], they bind to the DHP CC receptor but with lower affinity [7], the DHPM ring is more stable to oxidation than the DHP ring [8], a N^3-amido substituent on a 2-pyrimidinone ring is metabolically stable, and the N^3-H compounds are very weak calcium channel antagonists [9].

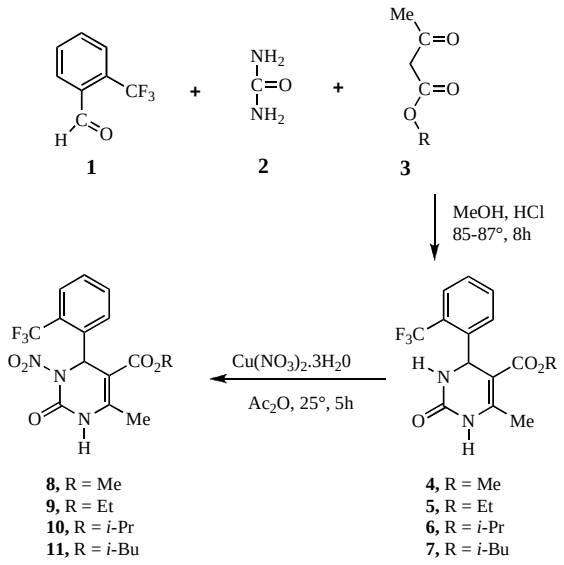
As part of our ongoing program to develop structure-activity relationships for heterocyclic mimics of 1,4-dihydropyridines with calcium channel modulating effects, and for use as probes to study the structure-function relationships of calcium channels, we now describe the synthesis and calcium channel modulating effects for a group of hitherto unknown N^3-nitro derivatives of alkyl 6-methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylates (**8-11**).

RESULTS AND DISCUSSION

A group of alkyl (Me, Et, *i*-Pr, *i*-Bu) 6-methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylates (**4-7**) were prepared using a classical Biginelli reaction as illustrated in Scheme 1. Thus, the acid catalyzed condensation of 2-trifluoromethyl-benzaldehyde (**1**), urea (**2**) and an alkyl acetoacetate (3) in MeOH at 85-87° for 8 hours afforded the respective product (**4-7**) in 27-50% yield. Nitration of the alkyl esters (**4-7**) using $Cu(NO_3)_2 \cdot 3H_2O$ and Ac_2O [12], following a procedure similar to that used for the preparation of 1-methyl-3-nitrouracil [13], furnished the respective alkyl 6-methyl-3-nitro-4-(2-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylate (**8-11**) in 35-51% yield. ^{1}H nmr spectral data indicates that nitration occurs at the N-3, rather than the N-1, position since the H-4 proton in the 3-nitro compounds **8-11** was deshielded relative to the corresponding H-4 proton in compounds **4-7**, and the C-6 Me resonances in the two groups of compounds **4-7** and **8-11** were nearly identical. One plausible explanation for N-3 nitration is that the N-1 nitrogen is deactivated due to its enamine character.

The objective of this study was to determine whether the alkyl 6-methyl-3-nitro-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylate moiety present in the target compounds (**8-11**) was a bioisostere of the methyl 1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate moiety present in the calcium channel agonist Bay K8644. *In vitro* calcium channel modulation studies (see data in Table 1) showed that compounds **8-11**, unlike Bay K8644, which induces a calcium channel agonist effect, exhibited a calcium channel antagonist effect (IC_{50} values in the 1.9 x 10^{-7} to 3.9 x 10^{-6} M range) on guinea pig ileal longitudinal smooth muscle (GPILSM). Compounds **8-11** are less potent calcium channel antagonists than the reference drug nifedipine (Adalat®, IC_{50} = 1.4 x 10^{-8} M). *In vitro* calcium channel modulation studies on guinea pig left atrium (GPLA) showed that the methyl ester (**8**) induced a modest positive inotropic calcium channel agonist effect where cardiac contractile force was increased by about 20% at a drug concentration of 1.61 x 10^{-6} M (see data in Table 1). In similar studies, the ethyl ester (**8**) produced a weaker positive inotropic effect than the methyl ester (**9**), and the inactive isopropyl (**10**) and isobutyl (**11**) esters that did not change the contractile force of GPLA. These structure-activity studies on GPLA show that the alkyl 6-methyl-3-nitro-1,2,3,4-tetrahydro-2*H*-pyrimidine-2-one-5-carboxylate moiety present in compounds **8** (R = Me) and **9** (R = Et) is a partial bioisostere of the methyl 1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylate moiety present in the calcium channel agonist Bay K8644 with respect to a positive inotropic effect on GPLA.

Scheme I



8, R = Me
9, R = Et
10, R = *i*-Pr
11, R = *i*-Bu

4, R = Me
5, R = Et
6, R = *i*-Pr
7, R = *i*-Bu

Table 1

In Vitro Calcium Channel Modulation Effects

Compound	Calcium Channel Antagonist Effect On GPILSM (IC_{50})[a]	Calcium Channel Agonist Effect On GPLA[b]	
		% Inotropic Effect	Drug Concentration (M)
8	3.9 ± 0.61 x 10^{-6}	20.4 ± 6.0	1.61 x 10^{-6}
9	2.1 ± 0.12 x 10^{-6}	10.6 ± 6.4	1.61 x 10^{-6}
10	1.9 ± 0.22 x 10^{-7}	Inactive	1.61 x 10^{-6}
11	3.1 ± 1.20 x 10^{-6}	Inactive	1.61 x 10^{-6}
Nifedipine[c]	1.4 ± 0.19 x 10^{-8}	—	—

[a] The molar concentration of the test compound causing a 50% decrease in the slow component or tonic contractile response (IC_{50} ± SEM, n = 3) in guinea pig ileal longitudinal muscle induced by the muscarinic agonist carbachol (1.6 x 10^{-7} M) was determined graphically from the dose-response curve. [b] The % increase in cardiac contractile force (agonist effect, positive inotropic effect) exhibited by the test compound on guinea pig left atrium was determined from the dose-response curve at the highest molar concentration used (1.61 x 10^{-6}.M). [c] Nifedipine chemical name is dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Bruker AM-300 spectrometer. The assignment of exchangeable protons (NH) was confirmed by the addition of D_2O. Silica gel column chromatography was carried out using Silicyle (70-230 mesh) silica gel. Isopropyl acetoacetate was purchased from the Lancaster Chemical Co. All other reagents were purchased from the Aldrich Chemical Co. Elemental analyses were performed for C, H and N (Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta). *In vitro* calcium channel antagonist and agonist activities were determined using protocols approved by the Health Sciences Animal Welfare Committee at the University of Alberta.

General Procedure for the Synthesis of Alkyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-ones (4-7). Urea (**2**) (2.1 g, 40 mmoles) was added to a solution of 2-trifluoromethylbenzaldehyde (**1**) (6.97 g, 40 mmoles) and an alkyl acetoacetate (**3**) (40 mmoles) with strirring. Concentrated hydrochloric acid (4 drops of 37%, w/v) was added, the reaction was allowed to proceed at 85-87° for 8 hours with stirring, the reaction mixture was cooled to 25° and stirring was continued at 25° for 1 hour. Removal of volatile components in vacuo gave an off-white residue that was washed with cold water to remove urea and other water soluble impurities. Recrystallization of this material from EtOH (98%, v/v) afforded the respective product (**4,** R = Me; **5**, R = Et; **6**, R = *i*-Pr; **7**, R = *i*-Bu). The physical and spectral data for compounds **4-7** are listed below.

Methyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (4). Compound **4** was obtained as a white solid in 27% yield, mp 210-212°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.33 (s, 3H, C-6 C*H*$_3$), 3.38 (s, 3H, CO_2CH_3), 5.54 (s, 1H, H-4), 7.40 (s, 1H, N^3-*H*), 7.42-7.51 (m, 2H, phenyl H-4, H-6), 7.61-7.70 (m, 2H, phenyl H-3, H-5), 9.37 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.53; H, 4.28; N, 8.67.

Ethyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (5). Compound **5** was obtained as a white solid in 50% yield, mp 200-202° (lit[14] mp 198-200°); ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.87 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 2.34 (s, 3H, C-6 C*H*$_3$), 3.85 (q, *J* = 7.0 Hz, 2H, CH_2CH_3), 5.56 (s, 1H, H-4), 7.30 (s, 1H, N^3-*H*), 7.45-7.52 (m, 2H, phenyl H-4, H-6), 7.62-7.70 (m, 2H, phenyl H-3, H-5), 9.35 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{15}H_{15}F_3N_2O_3$: C, 54.22; H, 4.69; N, 8.43. Found: C, 54.15; H, 4.52; N, 8.52.

Isopropyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (6). Compound **6** was obtained as a white solid in 40% yield, mp 193-195°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.64 and 1.03 [two d, *J* = 6.0 Hz, 3H each, $CH(CH_3)_2$], 2.33 (s, 3H, C-6 C*H*$_3$), 4.73 [heptet, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$], 5.55 (s, 1H, H-4), 7.21 (s, 1H, N^3-*H*), 7.42-7.51 (m, 2H, phenyl H-4, H-6), 7.63-7.70 (m, 2H, phenyl H-3, H-5), 9.32 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{16}H_{16}F_3N_2O_3$•1/9 H_2O: C, 55.84; H, 5.04; N, 8.14. Found: C, 55.84; H, 5.02; N, 8.35.

Isobutyl 6-Methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (7). Compound **7** was obtained as a white solid in 37% yield, mp 173-175°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.51 and 0.68 [two d, *J* = 6.0 Hz, 3H each, $CH_2CH(CH_3)_2$], 1.56-1.65 [m, 1H, $CH_2CH(CH_3)_2$], 2.36 (s, 3H, C-6 C*H*$_3$), 3.54 [d, *J*gem = 10.6 of d, *J*vic = 6.4 Hz, 1H, C*H*H'$CH(CH_3)_2$], 3.72 [d, *J*gem = 10.6 of d, *J*vic = 7.1 Hz, 1H, CH*H*'$CH(CH_3)_2$], 5.56 (s, 1H, H-4), 7.25 (s, 1H, N^3-*H*), 7.42-7.51 (m, 2H, phenyl H-4, H-6), 7.62-7.70 (m, 2H, phenyl H-3, H-5), 9.39 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{17}H_{19}F_3N_2O_3$: C, 57.30; H, 5.37; N, 7.86. Found: C, 57.28; H, 5.11; N, 8.00.

General Procedure for the Synthesis of Alkyl 6-Methyl-3-nitro-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-ones (8-11). A mixture of $Cu(NO_3)_2$•$3H_2O$ (1.21 g, 5.0 mmoles) and acetic anhydride (9.0 ml, 12.1 mmoles) was stirred at 25° for 1.5 hours, one of the alkyl 6-methyl-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-ones (either **4**, **5**, **6** or **7**) (5.0 mmoles) was added, and the reaction was allowed to continue at 25° for 5 hours with stirring. Methanol (50 ml) was added to quench the reaction, and the mixture was stirred for a futher 30 minutes at 25°. The volatile components were removed *in vacuo*, the residue was partitioned between water (100 ml) and chloroform (100 ml), the aqueous fraction was extracted with chloroform (4 x 100 ml), the combined organic fractions were washed with water, and the organic fraction was dried ($MgSO_4$). Removal of the solvent from the organic fraction *in vacuo* gave a residue that was partially purified by silica gel column chromatography using ethyl acetate:hexane (1:2, v/v) as eluant. Removal of the solvent in vacuo gave a residue that was recrystallized from EtOH (98%, v/v) to furnish the respective product **8**, **9**, **10** or **11**. The physical and spectral data for products **8-11** are listed below.

Methyl 6-Methyl-3-nitro-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (8). Compound **8** was obtained as a white solid in 35% yield, mp 182-185°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.34 (s, 3H, C-6 C*H*$_3$), 3.54 (s, 3H, CO_2CH_3), 7.02 (s, 1H, H-4), 7.50 (d, *J* = 8.0 Hz, 1H, phenyl H-6), 7.60 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-4), 7.72 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-5), 7.78 (d, *J* = 8.0 Hz, 1H, phenyl H-3), 10.89 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{14}H_{12}F_3N_3O_5$•2/9H_2O: C, 46.29; H, 3.45; N, 11.57. Found: C, 46.21; H, 3.63; N, 11.87.

Ethyl 6-Methyl-3-nitro-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (9). Compound **9** was obtained as a white solid in 36% yield, mp 164-166°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 1.06 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 2.35 (s, 3H, C-6 C*H*$_3$), 3.95-4.10 (m, 2H, CH_2CH_3), 7.06 (s, 1H, H-4), 7.51 (d, *J* = 8.0 Hz, 1H, phenyl H-6), 7.60 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-4), 7.70 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-5), 7.78 (d, *J* = 8.0 Hz, 1H, phenyl H-3), 10.89 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{15}H_{14}F_3N_3O_5$: C, 48.27; H, 3.78; N, 11.26. Found: C, 48.11; H, 3.71; N, 11.26.

Isopropyl 6-Methyl-3-nitro-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (10). Compound **10** was obtained as a white solid in 46% yield, mp 145-146°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.92 and 1.15 [two d, *J* = 7.0 Hz, 3H each, $CH(CH_3)_2$], 1.78 (heptet, *J* = 7 Hz, 1H, C*H*$(CH_3)_2$], 2.36 (s, 3H, C-6 C*H*$_3$), 7.06 (s, 1H, H-4), 7.50 (d, *J* = 8.0 Hz, 1H, phenyl H-6), 7.61 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-4), 7.71 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-5), 7.78 (d, *J* = 8.0 Hz, 1H, phenyl H-3), 10.98 (s, 1H, N^1-*H*). *Anal.* Calcd. for $C_{16}H_{16}F_3N_3O_5$: C, 49.62; H, 4.16; N, 10.85. Found: C, 49.75; H, 4.16; N, 10.78.

Isobutyl 6-Methyl-3-nitro-4-(2-trifluoromethylphenyl)-1,2,3,4-tetrahydro-(2*H*)-pyrimidine-2-one (11). Compound **11** was obtained as a white solid in 51% yield, mp 124-126°; ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.68 and 0.71 [two d, *J* = 6.0 Hz, 3H each, $CH_2CH(CH_3)_2$], 1.71-1.80 [m, 1H, $CH_2CH(CH_3)_2$],

2.39 (s, 3H, C-6 CH_3), 3.78 [d, *J*gem = 10.6 Hz, 2H, CH_2CH(CH_3)$_2$], 7.14 (s, 1H, H-4), 7.48 (d, *J* = 8.0 Hz, 1H, phenyl H-6), 7.60 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-4), 7.71 (dd, *J* = 8.0, 7.6 Hz, 1H, phenyl H-5), 7.78 (d, *J* = 8.0 Hz, 1H, phenyl H-3), 10.98 (s, 1H, N^1-*H*). *Anal*. Calcd. for $C_{17}H_{18}F_3N_3O_5$: C, 50.88; H, 4.52; N, 10.47. Found: C, 50.64; H, 4.37; N, 10.22.

In Vitro Calcium Channel Antagonist and Agonist Assays. Smooth muscle calcium channel antagonist activity was determined as the micromolar (μM) concentration of the test compound required to produce 50% inhibition of the muscarinic receptor-mediated (carbachol, 0.167 μM) Ca^{+2}-dependent contraction (tonic response) of guinea pig ileum longitudinal smooth muscle (GPILSM) using the procedure previously reported[15]. The IC_{50} value (± SEM, n=3) was determined graphically from the dose-response curve.

The cardiac calcium channel agonist effect was calculated as the percentage increase (positive inotropic effect) in contractile force of isolated guinea pig left atrium (GPLA) relative to its basal contractile force in the absence of test compound. The positive inotropic EC_{50} value (± SEM, n=3) was determined graphically from the dose-response curve.

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