Design and syntheses of 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]- and 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]- derivatives of alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-5-pyridinecarboxylates with calcium channel modulating activities

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Dedicated to Rudolph A. Abramovitch on the occasion of his 70th birthday

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Abstract

A group of 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]- derivatives of alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-5-pyridinecarboxylates **8a-e** were synthesized by the regioselective reduction of the corresponding 4-(3-pyridyl)- analogs in the presence of methyl chloroformate using Li(*t*-BuO)3AlH. Alternatively, a related group of 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]- compounds **14-18** were prepared using a modified Hantzsch reaction involving the condensation of 1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl-3-carboxaldehydes **11a-c** with an alkyl 3-aminocrotonate **12** and nitroacetone **13**. In contrast to the 4-(3-pyridyl)-compound **2b**, which exhibits an undesirable calcium channel agonist smooth muscle

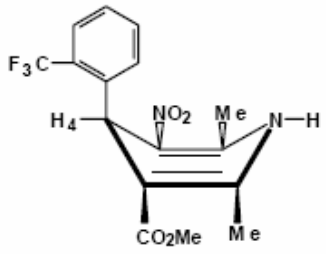
constriction effect, the two classes of compound **8** and **14-18** retain the desired calcium channel agonist cardiac positive inotropic effect elicited by **2b** while simultaneously inducing a calcium channel antagonist smooth muscle relaxant effect. These studies showed that the 4-[3-(1-methylcarbonyl-1,6-dihydropyridyl)]- and 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]- moieties are suitable bioisosteres to a 4-(3-pyridyl)- substituent with respect to calcium channel modulation. Compounds **8**, and **14-18**, could serve as valuable probes to study the structure-function relationships of calcium channel modulation, and provide a new drug design concept applicable to the development of drugs for the treatment of congestive heart failure.

Keywords: Dihydropyridines, regiochemistry, calcium channel modulation, positive inotropic agents, drug design concepts

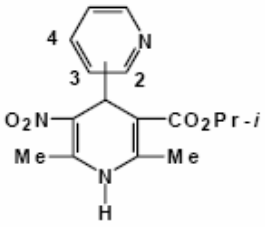
Introduction

The design of cardioselective Hantzsch 1,4-dihydropyridine (DHP) L-type voltage sensitive calcium channel (CC) agonist positive inotropes has presented a significant challenge to medicinal chemistrs.[1-3] Accordingly, the prototype 1,4-DHP CC agonist (S)-(+)-Bay K 8644 **1** simultaneously promotes calcium entry into vascular smooth muscle, inducing vasconstriction, that prevents its clinical use for the treatment of congestive heart failure (CHF).[4-5] Recently, we discovered a novel *third* generation class of isomeric isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(pyridyl)-5-pyridinecarboxylates **2a**-c with different CC modulation activities.[6] The 2-pyridyl isomer (±)-**2a** acted as a *dual cardioselective calcium channel agonist (positive inotrope) / smooth muscle selective calcium channel antagonist (vascular relaxant).* On the other hand, the 3-pyridyl (±)-**2b** and 4-pyridyl (±)-**2c** isomers acted as CC agonists on both cardiac and smooth muscle. The 2-pyridyl enantiomer (+)-**2a** exhibited agonist activity on both cardiac and smooth muscle, but the (-)-2-pyridyl enantiomer (-)-**2a** exhibited clinically desirable cardiac agonist and smooth muscle antagonist effects. Bay K 8644 **1** exists as the synperiplanr rotamer (CF_3 *cis* to the DHP H-4),[7] whereas the agonist Bay K 8643 **3** has the unexpected antiperiplanar rotamer

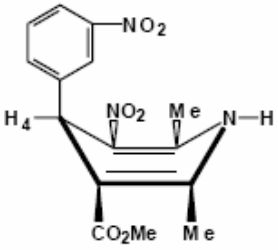
orientation (x-ray structure) which places the *m*-nitro substituent on the phenyl ring directly above the boat-shaped 1,4-DHP ring.[2] Subsequent nuclear Overhauser enhancement (NOE) studies for compounds **4-5** indicated that there is a significant rotamer fraction in solution where the pyridyl nitrogen is oriented above the 1,4-DHP ring, irrespective of whether a substituent (Me, Ph) is located at the 6- (R_1) or 3-position (R_2) of the pyridyl ring. This preferred rotamer orientation was attributed to a potential *H*-bonding interaction between the pyridyl nitrogen free electron pair and the suitably positioned 1,4-DHP N*H* moiety that may stabilize this rotamer orientation.[8] The nature (electronic properties, steric size) and conformation of a heterocyclic ring substituent attached to the C-4 position of the parent 1,4-DHP ring system is expected to be a determinant of electronic charge distribution at the C-4 heterocyclic ring carbons and the global conformation of the molecule due to non-bonded interactions between the parent 1,4-DHP C-3, C-4 and C-5 substituents. These factors may provide an approach to optimize CC binding, CC modulation and/or tissue specificity. It was therefore of interest, as part of our on-going program to acquire structure-activity relationships for CC modulators, to determine the effect which replacement of the 3-pyridyl ring of **2b** by a 3-(1-methoxycarbonyl-1,6-dihydropyridyl)-, or 3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl), ring substituent has upon CC modulation. Accordingly, we now report the synthesis and CC modulation activities for compounds having a quasi-planar C-4 1,6-DHP **8**, and boat-shaped C-4 1,4-DHP **14-18,** ring moiety.



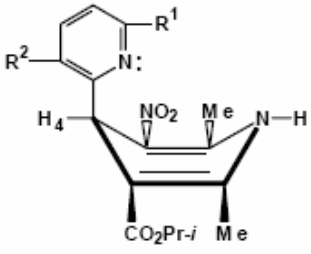
1, (S)-Bay K 8644



2a, 2-pyridyl
2b, 3-pyridyl
2c, 4-pyridyl



3, Bay K 8643

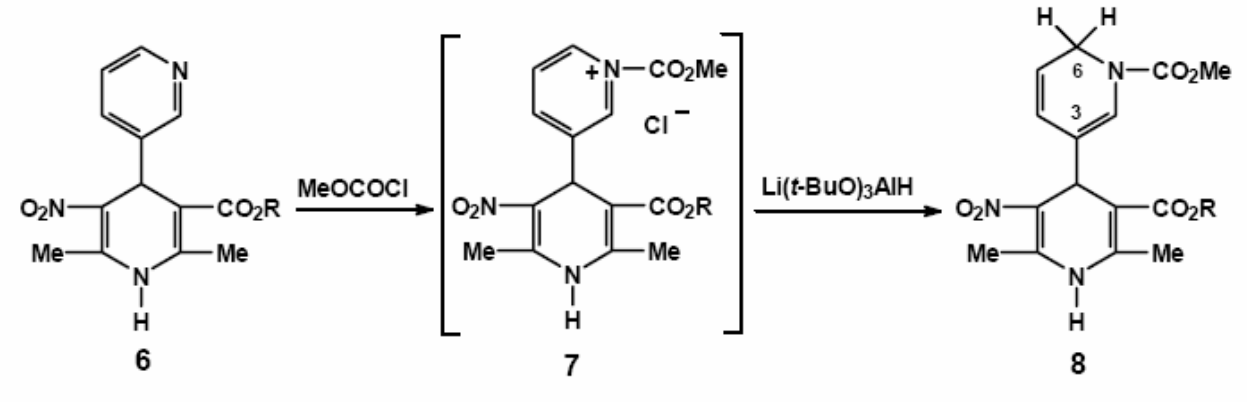


4, R^1 = Me, Ph; R^2 = H
5, R^1 = H; R^2 = Me, Ph

Results and Discussion

Chemistry

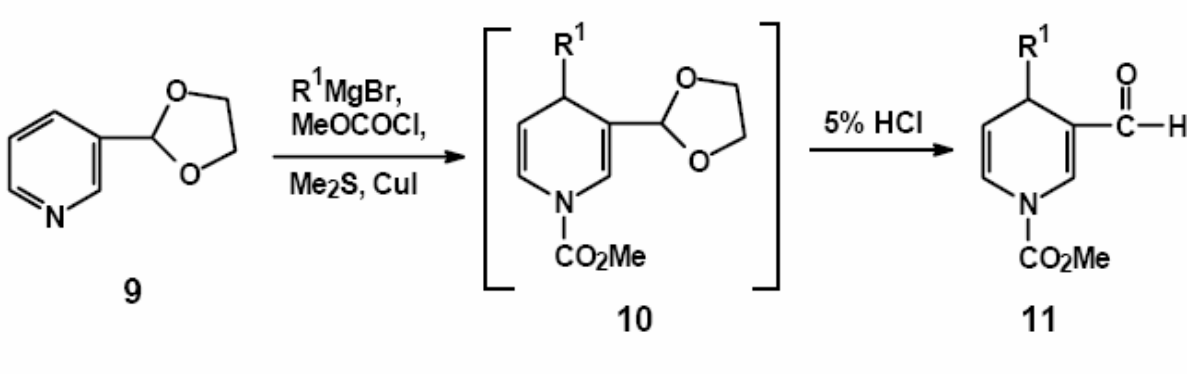
The 3-(1-methoxycarbonyl-1,6-dihydropyridyl) compounds **8a-e** were prepared by reaction of the corresponding pyridines **6a**-e with Li(*t*-BuO_3)AlH and MeOCOCl in THF at –78 °C in 14-22% chemical yield as indicated in Scheme 1. Steric effects due to the 1,4-DHP C-3 and C-5 ring substituents would be expected to be greatest at the C-2 position of the intermediate pyridinium salt **7**. Therefore, this reduction proceeds via regiospecific addition of hydride to the sterically less hindered C-6 position of the pyridinium salt **7**. The ^{1}H NMR spectra for **8a-e** showed dual resonances indicative of the presence of two rotamers that differ in configuration due to restricted rotation about the nitrogen-to-carbonyl bond of the N-CO_2Me moiety.[9] This explanation is in agreement with the observation that acquisition of the ^{1}H NMR spectra for **8a-e** at 78 °C induced coalescence of the dual resonances (rotamers) to give a single set of resonances.



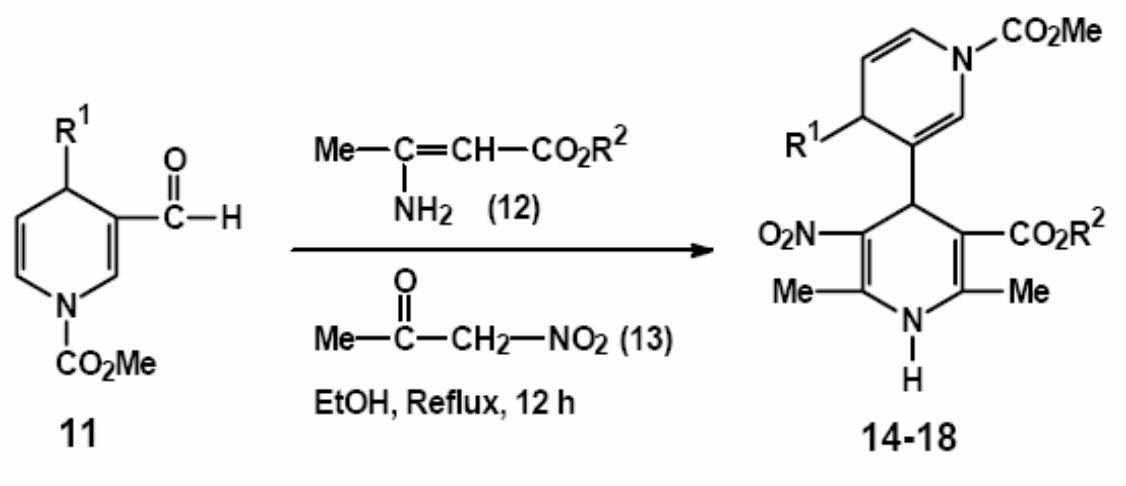
Scheme 1 6-8: **a**, R = Me; **b**, R = Et; *c*, R = *i*-Pr, *d*, R = *i*-Bu; *e*, R = *t*-Bu.

One of the most widely used methods to prepare 1,4-DHPs involves the addition of a nucleophile to activated *N*-alkyl- or *N*-acylpyridinium salts.[10-12] The 1,4- versus 1,2-regioselectivity of this reaction is dependent upon the activating *N*-substituent, the nucleophile, and the nature and position of pyridinium substituents.[10] In the case of *N*-acylpyridinium salts, optimal 1,4-selectivity, using organometallic reagents, was obtained for organocopper reagents.[11] The copper catalyzed reaction of a Grignard reagent with an activated pyridine was first reported by Loev et al.[13] A related reaction for the synthesis of 1,4-DHPs employing an organocuprate reagent was reported later by Piers et al.[14] Subsequently, Comins et al.[15] showed that reaction of an *N*-alkoxycarbonylpyridinium salt with a Grignard reagent in the presence of a catalytic amount of CuI resulted in nearly exclusive formation of the 1,4-DHP product. In this study, attempts to synthesize the novel class of unsymmetrical 1,4-DHP derivatives **14-18a-c** by reaction of the pyridine derivatives **6** with an organocuprate reagent (*n*-BuMgBr + CuI), Grignard reagent (*n*-BuMgBr) or cadmium reagent (*n*-BuMgBr + $CdCl_2$) in the presence of MeOCOCl were not successful. This failure is attributed to an interaction between the 1,4-DHP nitro substituent of compounds **6** and the organometallic reagent since an earlier study showed that similar reactions employing dialkyl 1,4-dihydro-2,6-dimethyl-4-(3-pyridyl)-3,5-pyridinedicarboxylates proceeded as expected to afford the corresponding 4-[3-(1-methoxycarbonyl-1,4-dihydropyridyl)] products in good yield.[16]

An alternate synthetic strategy was therefore employed to by-pass the detrimental effect of the nitro group in compounds **8** starting from the 1-methoxycarbonyl-1,4-dihydropyridyl-3-carboxaldehyde **11**. In this regard, reaction[15,17] of the ketal **9** with MeOCOCl and a Grignard reagent in the presence of Me_2S and CuI afforded the 1,4-DHP ketal derivative **10**, which on deprotection using 5% HCl, yielded the target 1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl-3-carboxaldehydes **11a-c** as illustrated in Scheme 2. The subsequent condensation of an aldehyde **11** with the alkyl 3-aminocrotonate **12** and nitroacetone **13**, using a modified Hantzsch reaction,[6] afforded the respective alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]-5-pyridinecarboxylates **14-18a-c**. The ^{1}H NMR spectra for compounds **14-18** exhibited multiple resonances for a number of protons due to the presence of diasteromeric mixtures (a chiral center is present at the C-4 position of both 1,4-DHP rings) and/or rotamers arising from restricted rotation involving the *N*-CO_2Me moiety.[9]



Scheme 2. 10-11: a, R^1 = Me; **b**, R^1 = *n*-Bu; **c**, R1 = Ph.



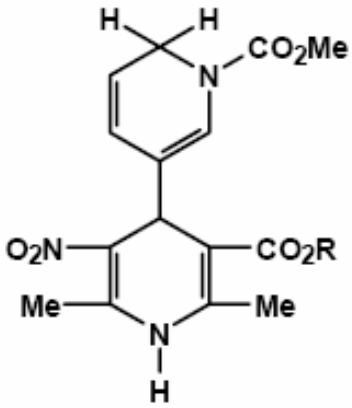
Scheme 3. 14a, R^1 = Me, R^2 = Me; **14b,** R^1 = *n*-Bu, R^2 = Me; **14c**, R^1 = Ph, R^2 = Me; **15a**, R^1 = Me, R^2 = Et; **15b**, R^1 = *n*-Bu, R^2 = Et; **15c**, R^1 = Ph, R^2 = Et; **16a**, R^1 = Me, R^2 = *i*-Pr; **16b**, R^1 = *n*-Bu, R^2 = *i*-Pr; **16c**, R^1 = Ph, R^2 = *i*-Pr; **17a**, R^1 = Me, R^2 = *i*-Bu; **17b**, R^1 = *n*-Bu, R^2 = *i*-Bu; **17c**, R^1 = Ph, R^2 = *i*-Bu; **18a**, R^1 = Me, R^2 = *t*-Bu; **18b**, R^1 = *n*-Bu, R^2 = *t*-Bu; **18c**, R^1 = Ph, R^2 = *t*-Bu.

In vitro calcium channel modulation structure-activity relationships

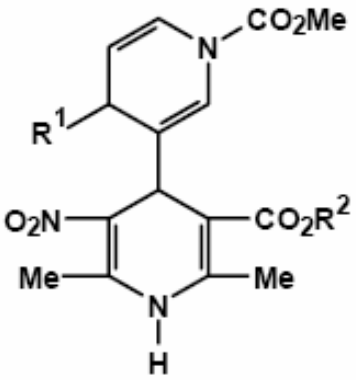
Changes in the substitution pattern at the C-3, C-4, and C-5 positions of modified Hantzsch 3-nitro-1,4-dihydropyridine calcium channel modulators are determinants of the C-4 heteroaryl rotamer orientation, global conformation, potency and tissue selectivity.[6,8] The objective of this study was to determine whether elaboration of the planar 4-(3-pyridyl) substituent of **2b** to a quasi-planar 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]- **8**, or a boat-shaped 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]- **14-18**, ring system would abolish the undesirable calcium channel agonist effect exhibited by **2b** on smooth muscle while still retaining its desirable cardiac agonist positive inotropic effect. It was anticipated that the *N*-CO2Me substituent in the respective 1,6-, or 1,4-dihydropyridyl, ring systems of **8** and **14-18** would mimic a *meta*-substituent on a phenyl ring or the nitrogen-free electron pair on a 3-pyridyl ring substituent like **2b**. These topological differences, present in **8** and **14-18**, could influence interactions with the 1,4-DHP binding site(s), or state (resting, open, inactivated) of the calcium channel receptor.

Elaboration of the 4-(3-pyridyl)- ring system of **2b** to either a 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]- **8,** or a 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]- **14-18**, ring system abolished the adverse calcium channel agonist (vasoconstrictor) effect exhibited by **2b** on guinea pig ileum longitudinal smooth muscle (GPILSM) while simultaneously inducing a modest desirable calcium channel antagonist smooth muscle relaxant effect [$IC_{50} = 10^{-5}$ to 10^{-7} M range relative to the reference calcium channel antagonist drug nifedipine ($IC_{50} = 1.40 \times 10^{-7}$ M) as indicated in Table 1]. Although compounds **8** and **14-18** were less potent calcium channel agonist positive inotropes on heart than the reference drug Bay K 8644, both classes of compounds retained positive cardiac inotropic acitivity (see Table 1). The observation that compounds **14-18** exhibit positive inotropic effects over quite a large range (25-200% increase in cardiac contractile force at a 4.46×10^{-5} M test compound concentration) indicates that the magnitude of the positive cardiac inotropic is dependent upon co-operative and/or interdependent contributions from the parent 1,4-DHP ring C-3, C-4 and C-5 substituents.

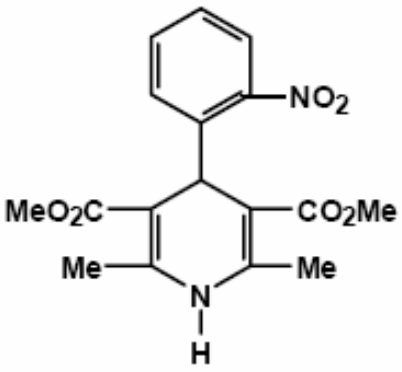
The results of this study show that a 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-, or a 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]-, ring system is a suitable bioisostere for either the 4-(3-pyridyl)- substituent of **2b**, or the 4-(2-trifluoromethylphenyl)- substituent of Bay K 8644, that are devoid of the smooth muscle constrictor effect exhibited by the latter compounds. This group of compounds **8**, and **14-18**, which could serve as valuable probes to study the structure-function relationships of calcium channels, constitute novel types of dihydropyridine cardioselective positive inotropes that provides a new drug design concept relevant to the treatment of congestive heart failure.



8



14-18



Nifedipine

Table 1. In vitro calcium channel antagonist and agonist activities for alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-5-pyridinecarboxylates containing a 4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]- **8a-e**, or 4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]-**14-18a-c** moiety

Compound	R^1	R or R^2	Antagonist activity: IC_{50} (M)[a]	Inotropic effect on GPLA: % Change at concentration (M) stated[b]
8a	¾	Me	Inactive	Inactive
8c	¾	*i*-Pr	$3.38 \pm 0.19 \times 10^{-6}$	$+ 41.3 \pm 30.0\%$ @ 4.46×10^{-5}
8d	¾	*i*-Bu	$1.51 \pm 0.13 \times 10^{-5}$	$+ 35.6 \pm 28.1\%$ @ 4.46×10^{-5}
14a	Me	Me	$> 2.99 \times 10^{-5}$	+ 29.5 ± 25.4% @ 4.46 x 10-5
15a	Me	Et	$> 2.99 \times 10^{-5}$	+ 107.4% @ 4.46×10^{-5} (n = 2)
15b	*n*-Bu	Et	$6.48 \pm 1.43 \times 10^{-6}$	+ 86.1% @ 4.46×10^{-5} (n = 2)
16a	Me	*i*-Pr	$1.00 \pm 0.05 \times 10^{-5}$	$+ 70.9 \pm 49.3\%$ @ 4.46×10^{-5}
16b	*n*-Bu	*i*-Pr	$3.95 \pm 1.55 \times 10^{-5}$	$+ 199.9 \pm 148.0\%$ @ 4.46×10^{-5}
16c	Ph	*i*-Pr	$5.98 \pm 0.07 \times 10^{-6}$	$+ 58.4 \pm 42.0\%$ @ 4.46×10^{-5}
17a	Me	*i*-Bu	$1.73 \pm 0.04 \times 10^{-6}$	$+ 41.1 \pm 31.3\%$ @ 4.46×10^{-5}
17c	Ph	*i*-Bu	$6.88 \pm 0.60 \times 10^{-7}$	Inactive
18a	Me	*t*-Bu	$> 2.99 \times 10^{-5}$	$+ 122.9 \pm 89.4\%$ @ 4.46×10^{-5}
18b	*n*-Bu	*t*-Bu	$1.43 \pm 0.35 \times 10^{-5}$	$+ 57.3 \pm 42.0\%$ @ 4.46×10^{-5}
18c	Ph	*t*-Bu	$2.68 \pm 0.19 \times 10^{-5}$	$+ 25.5 \pm 19.4\%$ @ 4.46×10^{-5}
Nifedipine			$1.40 \pm 0.14 \times 10^{-7}$	□
2b			□	$+ 50.0$ % @ $2.85 \pm 0.20 \times 10^{-5}$ [c]
Bay K 8644			□	$+ 50.0$ % @ $7.70 \pm 5.90 \times 10^{-7}$ [c]

[a] The molar concentration of the test compound causing a 50% decrease in the slow component, or tonic contractile response (IC50 ± SEM, n = 3), in guinea pig ileum smooth longitudinal smooth muscle (GPILSM) by the muscarinic agonist carbachol (1.67×10^{-7} M) was determined graphically from the dose-response curves. [b] 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 (n = 3 unless otherwise stated). [c] Data for the racemate **2b** is taken from a previous study.[6]

Experimental Section

General Procedures.

Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Bruker AM-300 spectrometer, and the assignment of exchangeable protons (N*H*) was confirmed by the addition of D2O. Infrared spectra (IR) were acquired using a Nicolet 550-FT spectrometer. Microanalyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta. Silica gel column chromatography was carried out using Silicyle 7734 (70-230 mesh) silica gel. Preparative silica gel thin layer chromatography was performed with Macherey-Nagel silica gel. Dihydropyridines **6a-e**, [6] acetal **9**[18] and nitroacetone **19**[19] were prepared according to literature procedures. The methyl, ethyl and isopropyl 3-aminocrotonates **12** were purchased from the Aldrich Chemical Co. whereas, isobutyl and *t*-butyl 3-aminocrotonates **12** were prepared by passage of anhydrous ammonia through a solution of the alkyl acetoacetate in absolute EtOH according to the procedure of Joslyn et al. [20]

General procedure for the syntheses of alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridincarboxyates 8a-e

A solution of Li(*t*-BuO)$_3$AlH in THF (1 mL of 1M) was added to a solution of the respective pyridyl compound **6a-e** (1 mmol) in dry THF (15 mL) at –78 °C with stirring. After 10 min, a solution of MeOCOCl (94.5 mg, 1 mmol) in THF (10 mL) was added drop wise via a syringe during 10 min, and the reaction was allowed to proceed at –78 °C for 5 h with stirring. The reaction mixture was allowed to warm to 0 °C, a saturated solution of aqueous NH_4Cl (10 mL) was added to quench the reaction, and the mixture was poured onto water (50 mL). Extraction with CH_2Cl_2 (5 x 25 mL), drying the CH_2Cl_2 extract (Na_2SO_4), and removal of the solvent in vacuo afforded a yellow residue. Purification by silica gel column chromatography using EtOAc-hexane (3:7, v/v) as eluant yielded the respective product **8a-e**. The physical, spectral and microanalytical data for 8a-e are listed below. In the ^{1}H NMR spectral data, the protons of the C-4 1,4-dihydropyridyl ring system are designated by prime numbers.

Methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridinecarboxyate (8a).

Yield: 14%; mp 133-136 °C; IR (KBr): 3330 (NH), 1721 (NCO2Me), 1692 (CO_2Me), 1507, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d6, 78 °C): δ 2.26 (s, 3H, C-6 C*H*$_3$), 2.48 (s, 3H, C-2 C*H*$_3$), 3.69 (s, 3H, CO_2C*H*$_3$), 3.73 (s, 3H, NCO_2C*H*$_3$), 4.12-4.20 (m, 2H, H-6'), 4.73 (s, 1H, H-4), 5.50-5.60 (m, 1H, H-5'), 5.77 (d, *J* = 8.3 Hz, 1H, H-4'), 6.42 (s, 1H, H-2'), 9.6 (s, 1H, N*H*). Anal. calcd. for $C_{16}H_{19}N_3O_6$: C 55.01, H, 5.48, N 12.03. Found: C 54.73, H 5.01, N 12.14.

Ethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridinecarboxyate (8b).

Yield: 16%; mp 122-125 °C; IR (KBr): 3343 (NH), 1718 (NCO_2Me), 1693 (CO_2Et), 1510, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 78 °C): δ 1.24 (t, *J* = 7 Hz, 3H, CH_2C*H*3), 2.30 (s, 3H, C-6 C*H*3), 2.50 (s, 3H, C-2 C*H*3), 3.71 (s, 3H, NCO2C*H*3), 3.98-4.05 (m, 2H, C*H*2CH_3), 4.12-4.20 (m, 2H, H-6'), 4.70 (s, 1H, H-4), 5.50-5.60 (m, 1H, H-5'), 5.70 (d, *J* = 8.0 Hz, 1H, H-4'), 6.47 (s, 1H, H-2'), 9.30 (s, 1H, N*H*). Anal. calcd. for $C_{17}H_{21}N_3O_3$ C 56.14, H, 5.81, N 11.55. Found: C 56.51, H 5.33, N 11.53.

Isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridinecarboxyate (8c).

Yield: 22%; mp 102-104 °C; IR (KBr): 3310 (NH), 1722 (NCO_2Me), 1693 (CO_2Pr-*i*), 1503, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 78 °C): δ 1.25 and 1.29 [two overlapping d, *J* = 7 Hz, 6H, $CH(CH_3)_2$], 2.34 (s, 3H, C-6 C*H*$_3$), 2.50 (s, 3H, C-2 C*H*$_3$), 3.78 (s, 3H, NCO_2C*H*$_3$), 4.22-4.40 (m, 2H, H-6'), 4.83 (s, 1H, H-4), 5.05-5.12 [m, 1H, C*H*$(CH_3)_2$], 5.59-5.76 (m, 1H, H-5'), 5.88 (d, *J*

= 8.2 Hz, 1H, H-4'), 6.55 (s, 1H, H-2'), 9.23 (s, 1H, N*H*). Anal. calcd. for $C_{18}H_{23}N_3O_6$: C 57.29, H, 6.14, N 11.13. Found: C 57.34, H 5.68, N 10.81.

Isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridinecarboxyate (8d).

Yield: 17%; mp 130-132 °C; IR (KBr): 3325 (NH), 1716 (NCO_2Me), 1690 (CO_2Bu-*i*), 1508, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 78 °C): δ 0.95 and 0.97 [two overlapping d, *J* = 7.2 Hz, 6H, $CH(CH_3)_2$], 1.90-2.05 [m, 1H, $CH_2CH(CH_3)_2$], 2.32 (s, 3H, C-6 CH_3), 2.50 (s, 3H, C-2 CH_3), 3.78 (s, 3H, NCO_2CH_3), 3.86-4.00 [m, 2H, $CH_2CH(CH_3)_2$], 4.25-4.32 (m, 2H, H-6'), 4.75 (s, 1H, H-4), 5.50-5.63 (m, 1H, H-5'), 5.78 (d, *J* = 8.2 Hz, 1H, H-4'), 6.49 (s, 1H, H-2'), 9.20 (s, 1H, NH). Anal. calcd. for $C_{19}H_{25}N_3O_6$: C 58.30, H, 6.43, N 10.73. Found: C 58.63, H 6.01, N 11.01.

***t*-Butyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-1,6-dihydropyridyl)]-5-pyridinecarboxyate (8e).**

Yield: 16%; mp 119-122 °C; IR (KBr): 3306 (NH), 1718 (NCO_2Me), 1691 (CO_2Bu-*t*), 1508, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 78 °C): δ 1.39 [s, 9H, $C(CH_3)_3$], 2.30 (s, 3H, C-6 CH_3), 2.49 (s, 3H, C-2 CH_2), 3.78 (s, 3H, NCO_2CH_3), 4.12-4.40 (m, 2H, H-6'), 4.79 (s, 1H, H-4), 5.48-5.68 (m, 1H, H-5'), 5.78 (d, *J* = 8.3 Hz, 1H, H-4'), 6.45 (s, 1H, H-2'), 9.02 (s, 1H, NH). Anal. calcd. for $C_{19}H_{25}N_3O_6$: C 58.30, H, 6.43, N 10.73. Found: C 58.64, H 6.67, N 10.41.

General procedure for the syntheses of 1-methoxycarbonyl-4-substituted-1,4-dihydropyridine-3-carboxaldehydes 11a-c

Me_2S (0.846 g, 13.6 mmol) and CuI (10 mg, 0.05 mmol) were added to a solution of the acetal **9** (0.151 g, 1 mmol) in dry THF (20 mL) under a nitrogen atmosphere, and the mixture was stirred at 25 °C for 15 min. After cooling to –23 °C, a solution of MeOCOCl (94.5 mg, 1 mmol) in dry THF (10 mL) was added, followed by addition of a solution of the respective Grignard reagent (R^1MgBr, R^1 = Me, *n*-Bu, Ph) in THF (1.1 mmol of a 1.4M THF solution) during 10 min, and the reaction was allowed to proceed at –23 °C for 4 h with stirring. The reaction mixture was allowed to warm to 25 °C, a solution of 20% aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with ether (3 x 20 mL). The combined organic extracts were washed with 28% aqueous NH_4OH-20% aqueous NH_4Cl (1:1, v/v) until the aqueous layer was colorless. The organic fraction was washed consecutively with water (2 x 15 mL), 5% HCl (20 mL) and then water (10 mL). The organic fraction was dried (Na_2SO_4) and the solvent was removed *in vacuo* at 25 °C to give a yellow oil that was purified by preparative silica gel thin layer chromatography

using hexane-EtOAc (5:1, v/v) as the development solvent to afford the respective aldehyde **11a-c**. Products **11a-**c were used immediately for the subsequent preparation of compounds **14-18a-c.** The physical, spectral and microanalytical data for **11a-c** are listed below.

1-Methoxycarbonyl-4-methyl-1,4-dihydropyridine-3-carboxaldehyde (11a).

Yield: yellow oil, 55%; ^{1}H NMR ($CDCl_3$, 62 °C): δ 1.12 (d, *J* = 6.7 Hz, 3H, C-4 C*H*$_3$), 3.25-3.40 (m, 1H, H-4), 3.85 (s, 3H, NCO_2C*H*$_3$), 5.10-5.18 (m, 1H, H-5), 6.76 (d, *J* = 7.9 Hz, 1H, H-6), 7.58 (s, 1H, H-2), 9.38 (s, 1H, C*H*O).

4-*n*-Butyl-1-methoxycarbonyl-1,4-dihydropyridine-3-carboxaldehyde (11b).

Yield: yellow oil, 66%; ^{1}H NMR ($CDCl_3$, 25 °C): δ 0.85 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_2C$*H*$_3$), 1.20-1.40 (m, 4H, CH_2C*H*$_2C$*H*$_2CH_3$), 1.50-1.53 (m, 2H, C*H*$_2CH_2CH_2CH_3$), 3.34-3.40 (m, 1H, H-4), 3.85 (s, 3H, NCO_2C*H*$_3$), 5.00-5.15 (m, 1H, H-5), 6.70-6.82 (br m, 1H, H-6), 7.58-7.68 (br s, 1H, H-2), 9.40 (s, 1H, C*H*O).

1-Methoxycarbonyl-4-phenyl-1,4-dihydropyridine-3-carboxaldehyde (11c).

Yield: yellow oil, 47%; ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.97 (s, 3H, NCO_2C*H*$_3$), 4.51 (d, *J* = 4.2 Hz, 1H, H-4), 5.20-5.33 (m, 1H, H-5), 6.90-7.05 (m, 1H, H-6), 7.17-7.78 (m, 6H, H-2, phenyl hydrogens), 9.30 and 9.36 (s, 1H total, C*H*O).

General procedure for the syntheses of alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-substituted-1,4-dihydropyridyl)]-5-pyridinecarboxylates 14-18a-c

A solution of the respective aldehyde **11a-c** (R^1 = Me, *n*-Bu, Ph) (1 mmol), the respective alkyl 3-aminocrotonate **12** (R^2 = Me, Et, *i*-Pr, *i*-Bu, *t*-Bu) (1 mmol) and nitroacetone **13** (1 mmol) in dry EtOH (100 mL) was heated at reflux for 12 h. Removal of the solvent in vacuo, and purification of the residue by preparative silica gel thin layer chromatography using hexane-EtOAc (1:1, v/v) as development solvent afforded the respective product **14-18a-c**, for which the physical, spectral, and microanalytical data are listed below.

Methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (14a).

Yield: 4%; IR (KBr): 3295 (NH), 1720 (NCO_2Me), 1685 (CO_2Me), 1507, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1.8:1) as determined from the integrals for the NCO_2Me resonances: δ 1.02-1.22 (m, 3H, C-4' C*H*$_3$), 2.04 and 2.23 (two s, 3H total, C-6 C*H*$_3$), 2.38 and 2.43 (two s, 3H total, C-2 C*H*$_3$), 2.83-2.90 (m, 1H, H-4'), 3.75 (s, 3H, CO_2CH_3), 3.79 and 3.82 (two s, 3H total, NCO_2CH_3), 5.05-5.07 (m, 2H, H-4, H-5'), 6.48-6.66 (m, 1H, H-6'), 6.72 (br s, 1H, H-2'), 9.65 and 9.78 (two br s, 1H total, N*H*). Anal. calcd. for $C_{17}H_{21}N_3O_6$: C 56.19, H 5.82, N 11.56. Found: C 55.87, H 5.65, N 11.14.

Ethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (15a).

Yield: 5%; IR (KBr): 3300 (NH), 1712 (NCO_2Me), 1689 (CO_2Et), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 2.1:1) as determined from the integrals for the NCO2Me resonances: δ 0.89-1.10 (m, 3H, C-4' C*H*$_3$), 1.18-1.38 (m, 3H, CH_2CH_3), 2.08 and 2.37 (two s, 3H total, C-6 C*H*$_3$), 2.39 and 2.45 (two s, 3H total, C-2 C*H*$_3$), 2.75-2.88 (m, 1H, H-4'), 3.69 and 3.70 (two s, 3H total, NCO_2CH_3), 4.03-4.22 (m, 2H, CH_2CH_3), 4.93-5.12 (m, 2H, H-4, H-5'), 6.46-6.58 (br m, 1H, H-6'), 6.63 (br s, 1H, H-2'), 9.42 and 9.58 (two br s, 1H total, N*H*). Anal. calcd. for $C_{18}H_{23}N_3O_6$: C 57.28, H 6.14, N 11.13. Found: C 56.92, H 6.47, N 11.41.

Isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (16a).

Yield: 7%; IR (KBr): 3315 (NH), 1712 (NCO_2Me), 1690 (CO_2Pr-*i*), 1504, 1312 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1.1:1) as determined from the integrals for the NCO_2Me resonances: δ 0.99-1.06 (m, 3H, C-4' C*H*$_3$), 1.23 [d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$], 1.96 and 2.07 (two s, 3H total, C-6 C*H*$_3$), 2.35 and 2.41 (two s, 3H total, C-2 C*H*$_3$), 2.80-2.90 (m, 1H, H-4'), 3.80 and 3.82 (two s, 3H total, NCO_2CH_3), 4.80-5.19 [m, 3H, H-4, H-5', $CH(CH_3)_2$], 6.38-6.52 (m, 1H, H-6'), 6.61 (br s, 1H, H-2'), 9.32 and 9.55 (two br s, 1H total, N*H*). Anal. calcd. for $C_{19}H_{25}N_3O_6$: C 58.30, H 6.43, N 10.74. Found: C 58.60, H 6.67, N 10.31.

Isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (17a).

Yield: 6%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1685 (CO_2Bu-*i*), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 3.3:1) as determined from the integrals for the NCO_2Me resonances: δ 0.85-1.20 [m, 9H, C-4' C*H*$_3$, CH(C*H*$_3$)$_2$], 1.91-1.98 [m, 1H, CH$_2$C*H*(CH$_3$)$_2$], 2.22 and 2.27 (two s, 3H total, C-6 C*H*$_3$), 2.41 and 2.43 (two s, 3H total, C-2 C*H*$_3$), 2.78-2.89 (m, 1H, H-4'), 3.69 and 3.71 (two s, 3H total, NCO_2CH_3), 3.80-3.87 [m, 2H, C*H*2CH(CH3)2], 4.88-5.05 (m, 2H, H-4, H-5'), 6.36-6.53 (m, 1H, H-6'), 6.62 (br s, 1H, H-2'), 9.51 and 9.62 (two br s, 1H total, N*H*). Anal. calcd. for $C_{20}H_{27}N_3O_6$: C 59.25, H 6.71, N 10.36. Found: C 58.93, H 6.39, N 10.41.

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***t*-Butyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (18a).**

Yield: 6%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1690 (CO_2Bu-*t*), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1.8:1) as determined from the integrals for the NCO_2Me resonances: δ 0.90-1.04 (m, 3H, C-4' C*H*$_3$), 1.35 (s, 9H, C(C*H*$_3$)$_3$], 2.30 and 2.39 (two s, 3H total, C-6 C*H*$_3$), 2.41 and 2.45 (two s, 3H total, C-2 C*H*$_3$), 2.78-2.92 (m, 1H, H-4'), 3.69 and 3.70 (two s, 3H total, NCO_2CH_3), 4.86-5.01 (m, 2H, H-4, H-5'), 6.34-6.52 (m, 1H, H-6'), 6.58 (br s, 1H, H-2'), 9.50 and 9.60 (two br s, 1H total, N*H*). Anal. calcd. for $C_{20}H_{27}N_3O_6$: C 59.25, H 6.71, N 10.36. Found: C 58.61, H 6.02, N 9.91.

Methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-*n*-butyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (14b).

Yield: 6%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1690 (CO_2Me), 1507, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1.2:1) as determined from the integrals for the NCO_2Me resonances: δ 0.78-0.88 (m, 3H, $CH_2CH_2CH_2CH_3$), 1.10-1.70 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.17 and 2.26 (two s, 3H total, C-6 C*H*$_3$), 2.30 and 2.49 (two s, 3H total, C-2 C*H*$_3$), 2.84-2.98 (m, 1H, H-4'), 3.71 (s, 3H, CO_2CH_3), 3.80 and 3.83 (two s, 3H total, NCO_2CH_3), 4.90-4.98 (m, 2H, H-4, H-5'), 6.43-6.61 (m, 1H, H-6'), 6.70 (br s, 1H, H-2'), 9.48 and 9.67 (two br s, 1H total, N*H*). Anal. calcd. for $C_{20}H_{27}N_3O_6$: C 59.25, H 6.71, N 10.36. Found: C 58.96, H 6.94, N 10.02.

Ethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-*n*-butyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (15b).

Yield: 10%; IR (KBr): 3315 (NH), 1712 (NCO_2Me), 1688 (CO_2Et), 1515, 1308 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:2.5) as determined from the integrals for the NCO_2Me resonances: δ 0.78-0.85 (m, 3H, $CH_2CH_2CH_2CH_3$), 1.05-1.65 (m, 9H, $CO_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 2.16 and 2.24 (two s, 3H total, C-6 CH_3), 2.30 and 2.43 (two s, 3H total, C-2 CH_3), 2.77-2.85 (m, 1H, H-4'), 3.78 and 3.81 (two s, 3H total, NCO_2CH_3), 4.02-4.17 (m, 2H, $CO_2CH_2CH_3$), 4.83-5.09 (m, 2H, H-4, H-5'), 6.42-6.63 (m, 1H, H-6'), 6.68 (br s, 1H, H-2'), 9.40 and 9.61 (two br s, 1H total, NH). Anal. calcd. for $C_{21}H_{29}N_3O_6$: C 60.13, H 6.97, N 10.02. Found: C 60.43, H 7.12, N 9.85.

Isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-*n*-butyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (16b).

Yield: 12%; IR (KBr): 3325 (NH), 1710 (NCO_2Me), 1692 (CO_2Pr-*i*), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:2.6) as determined from the integrals for the NCO_2Me resonances: δ 0.85-1.16 (m, 9H, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$), 1.25-1.61 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.26 and 2.32 (two s, 3H total, C-6 CH_3), 2.38 and 2.45 (two s, 3H total, C-2 CH_3), 2.82-2.91 (m, 1H, H-4'), 3.82 and 3.84 (two s, 3H total, NCO_2CH_3), 4.82-5.17 (m, 3H, $CO_2CH(CH_3)_2$, H-4, H-5'), 6.39-6.51 (m, 1H, H-6'), 6.68 (br s, 1H, H-2'), 9.49 and 9.51 (two br s, 1H total, NH). Anal. calcd. for $C_{22}H_{31}N_3O_6$: C 60.95, H 7.20, N 9.69. Found: C 60.89, H 7.01, N 9.92.

Isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-*n*-butyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (17b).

Yield: 8%; IR (KBr): 3310 (NH), 1712 (NCO_2Me), 1690 (CO_2Bu-*i*), 1512, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:2.1) as determined from the integrals for the NCO_2Me resonances: δ 0.73-0.95 (m, 9H, $CH_2CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$), 1.26-1.58 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.84-2.09 [m, 1H, $CH_2CH(CH_3)_2$], 2.20 and 2.35 (two s, 3H total, C-6 CH_3), 2.40 and 2.44 (two s, 3H total, C-2 CH_3), 2.80-2.91 (m, 1H, H-4'), 3.71 and 3.78 (two s, 3H total, NCO_2CH_3), 3.84-3.99 [m, 2H, $CH_2CH(CH_3)_2$], 4.90-5.08 (m, 2H, H-4, H-5'), 6.38-6.52 (m, 1H, H-6'), 6.69 (br s, 1H, H-2'), 9.45 and 9.61 (two br s, 1H total, NH). Anal. calcd. for $C_{23}H_{33}N_3O_6$: C 61.72, H 7.43, N 9.39. Found: C 61.57, H 7.68, N 9.01.

_t_-Butyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-_n_-butyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (18b).

Yield: 5%; IR (KBr): 3300 (NH), 1712 (NCO_2Me), 1691 (CO_2Bu-_t_), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.9) as determined from the integrals for the NCO_2Me resonances: δ 0.78-0.99 (m, 3H, $CH_2CH_2CH_2CH_3$), 1.15-1.57 (m, 15H, $CO_2C(CH_3)_3$, $CH_2CH_2CH_2CH_3$), 2.30 and 2.38 (two s, 3H total, C-6 CH_3), 2.43 and 2.49 (two s, 3H total, C-2 CH_3), 2.72-2.88 (m, 1H, H-4'), 3.76 and 3.80 (two s, 3H total, NCO_2CH_3), 4.86-5.04 (m, 2H, H-4, H-5'), 5.70-5.80 (m, 1H, H-6'), 6.52-6.60 (m, 1H, H-2'), 9.38 and 9.52 (two br s, 1H total, NH). Anal. calcd. for $C_{23}H_{33}N_3O_6$: C 61.72, H 7.43, N 9.39. Found: C 61.54, H 7.23, N 9.44.

Methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (14c).

Yield: 5%; IR (KBr): 3300 (NH), 1715 (NCO_2Me), 1690 (CO_2Me), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.2) as determined from the integrals for the NCO_2Me resonances: δ 2.11 and 2.24 (two s, 3H total, C-6 CH_3), 2.45 and 2.48 (two s, 3H total, C-2 CH_3), 3.59 (s, 3H, CO_2CH_3), 3.78 and 3.80 (two s, 3H total, NCO_2CH_3), 3.89-3.99 (m, 1H, H-4'), 4.86-5.15 (m, 2H, H-4, H-5'), 6.50-6.68 (m, 1H, H-6'), 6.90-7.48 (m, 6H, H-2', phenyl hydrogens), 9.40 and 9.48 (two br s, 1H total, NH). Anal. calcd. for $C_{22}H_{23}N_3O_6$: C 62.11, H 5.45, N 9.87. Found: C 61.92, H 5.12, N 10.13.

Ethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (15c).

Yield: 6%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1692 (CO_2Et), 1513, 1313 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.3) as determined from the integrals for the NCO_2Me resonances: δ 1.10-1.35 (m, 3H, CH_2CH_3), 2.10 and 2.25 (two s, 3H total, C-6 CH_3), 2.42 and 2.47 (two s, 3H total, C-2 CH_3), 3.80 and 3.86 (two s, 3H total, NCO_2CH_3), 3.90-4.20 (m, 3H, $CO_2CH_2CH_3$, H-4'), 4.70-5.09 (m, 2H, H-4, H-5'), 6.50-6.63 (m, 1H, H-6'), 6.92-7.55 (m, 6H, H-2', phenyl hydrogens), 9.40 and 9.51 (two br s, 1H total, NH). Anal. calcd. for $C_{23}H_{25}N_3O_6$: C 62.86, H 5.73, N 9.56. Found: C 62.81, H 5.45, N 9.29.

Isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (16c).

Yield: 7%; IR (KBr): 3300 (NH), 1712 (NCO_2Me), 1690 (CO_2Pr-*i*), 1513, 1313 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.6) as determined from the integrals for the NCO_2Me resonances: δ 1.11-1.21 [m, 6H, $CH(CH_3)_2$], 2.11 and 2.18 (two s, 3H total, C-6 CH_3), 2.43 and 2.45 (two s, 3H total, C-2 CH_3), 3.80 and 3.84 (two s, 3H total, NCO_2CH_3), 3.86-3.92 (m, 1H, H-4'), 4.70-5.11 (m, 3H, $CH(CH_3)_2$, H-4, H-5'), 6.51-6.65 (m, 1H, H-6'), 6.95-7.45 (m, 6H, H-2', phenyl hydrogens), 9.33 and 9.45 (two s, 1H total, NH). Anal. calcd. for $C_{24}H_{27}N_3O_6$: C 63.56, H 6.00, N 9.26. Found: C 63.24, H 5.77, N 9.57.

Isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (17c).

Yield: 6%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1690 (CO_2Bu-*i*), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.5) as determined from the integrals for the NCO_2Me resonances: δ 0.94-1.00 [m, 6H, $CH(CH_3)_2$], 1.96-2.05 [m, 1H, $CH_2CH(CH_3)_2$], 2.12 and 2.18 (two s, 3H total, C-6 CH_3), 2.46 and 2.51 (two s, 3H total, C-2 CH_3), 3.83 and 3.85 (two s, 3H total, NCO_2CH_3), 3.80-3.99 [m, 3H, $CH_2CH(CH_3)_2$, H-4'], 4.72-5.12 (m, 2H, H-4, H-5'), 6.52-6.65 (m, 1H, H-6'), 6.98-7.40 (m, 6H, H-2', phenyl hydrogens), 9.38 and 9.51 (two s, 1H total, NH). Anal. calcd. for $C_{25}H_{29}N_3O_6$: C 64.23, H 6.25, N 8.98. Found: C 63.99, H 6.34, N 8.71.

***t*-Butyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-5-pyridinecarboxylate (18c).**

Yield: 7%; IR (KBr): 3300 (NH), 1710 (NCO_2Me), 1690 (CO_2Bu-*t*), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6, 25 °C), mixture of two rotamers and/or diastereomers (ratio of 1:1.5) as determined from the integrals for the NCO_2Me resonances: δ 1.35 [s, 9H, $C(CH_3)_3$], 2.19 and 2.25 (two s, 3H total, C-6 CH_3), 2.38 and 2.49 (two s, 3H total, C-2 CH_3), 3.75 and 3.78 (two s, 3H total, NCO_2CH_3), 3.88-3.98 (m, 1H, H-4'), 4.78-5.12 (m, 2H, H-4, H-5'), 6.55-6.68 (m, 1H, H-6'), 6.85-7.40 (m, 6H, H-2', phenyl hydrogens), 9.40 and 9.55 (two s, 1H total, NH). Anal. calcd. for $C_{25}H_{29}N_3O_6$: C 64.23, H 6.25, N 8.98. Found: C 64.69, H 6.09, N 9.14.

In vitro calcium channel antagonist and agonist assays

Calcium channel antagonist activity was determined as the molar concentration of the test compound required to produce 50% inhibition of the muscarinic receptor-mediated (carbachol, 1.67 x 10^{-7} M) Ca^{2+}-dependent contraction (tonic response) of guinea pig ileum longitudinal smooth muscle (GPILSM) using the procedure previously reported.[9] The IC_{50} value (± SEM), n = 3) was determined graphically from the dose-response curve.

Calcium channel agonist activity (positive inotropic effect on heart) was determined as the percentage (%) increase in contractile force of isolated guinea pig left atrium (GPLA) induced by a 4.46 x 10^{-5} M (maximum concentration used) test compound concentration relative to its basal contractile force in the absence of test compound.[6]

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References

1. Langs, D. A.; Strong, P. D.; Triggle, D. J. *J. Comput.-Aided Mol. Des.* **1990**, *2*, 215.
2. Langs, D. A.; Kwon, Y. W.; Strong P. D.; Triggle, D. J. *J. Comput.-Aided Mol. Des.* **1991**, *5*, 95.
3. Magner, P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Design Discovery* **1992**, *8*, 273.
4. Gross, R.; Kayser, M.; Schramm, M.; Taniel, R. Thomas, G. *Arch. Int. Pharmacodyn. Ther.* **1985**, *277*, 203.
5. Preuss, K. C.; Brooks, H. L.; Gross G. J.; Warltier, D. C. *Basic Res. Cardiol.* **1985**, *80*, 326.
6. Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **1995**, *38*, 2851.
7. Langs, D. A.; Triggle, D. J. *Mol. Pharmacol.* **1985**, *27,* 544.
8. Iqbal, N.; Akula, M. R.; Vo, D.; Matowe, W. C.; McEwen, C.-A.; Wolowyk, M. W.; Knaus, E. E. *J. Med. Chem.* **1998**, 1*41*, 827.
9. Dagnino, L.; Li-Kwong-Ken, M. C.; Wynn, H.; Wolowyk, M. W.; Triggle, C. R.; Knaus, E. E. *J. Med. Chem.* **1987**, *30*, 640.
10. Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291.
11. Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429.
12. Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.
13. Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 956.
14. Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563.
15. Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47,* 4315.
16. Ramesh, M.; Matowe, W. C.; Knaus, E. E.; Wolowyk, M. W. *Drug Design Discovery* **1992**, *8*, 313.
17. Comins, D. L.; Smith, R. K.; Stroud, E. D. *Heterocycles* **1984**, *22*, 339.
18. Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877.
19. Hurd, C. D.; Nilson, M. E. *J. Org. Chem.* **1955**, *20*, 927.

20. Joslyn, A. F.; Luchowski, E.; Triggle, D. J. *J. Med. Chem.* **1988**, *31*, 1489.