Synthesis of Dialkyl 1,4-Dihydro-2,6-dimethylpyridine-3,5-dicarboxylates and Alkyl 1,4-Dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylates Possessing a C-4 2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (uracil) Substituent to Determine Calcium Channel Modulation Structure-Activity Relationships

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The Hantzsch condensation of 5-formyluracil (**1**) with methyl, isopropyl or isobutyl acetoacetate (**2a-c**) in the presence of ammonium hydroxide afforded the respective dialkyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3a-c**). A group of alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylates (**6a-c**) were also prepared using a modified Hantzsch reaction that involved the condensation of 5-formyluracil with nitroacetone and either methyl, isopropyl or isobutyl 3-aminocrotonate (**5a-c**). A C-4 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl substituent is not a suitable bioisostere for the traditional C-4 aryl or heteroaryl substituents present in 1,4-dihydropyridine calcium channel modulators since diisopropyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3b**) and isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6c**) did not exhibit any *in vitro* calcium channel antagonist activity using a guinea pig smooth muscle calcium channel antagonist assay, or a guinea pig left atrium calcium channel agonist (positive inotropic) assay.

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Introduction.

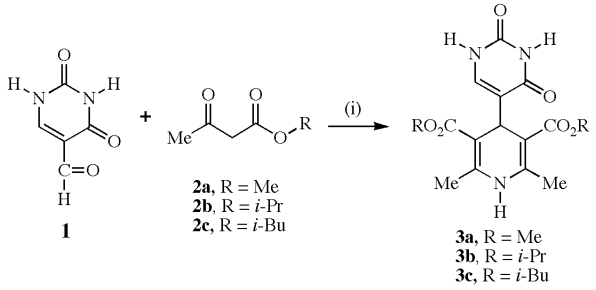
The calcium ion channel is an important drug design target since it has specific binding sites for both antagonist and agonist ligands that are controlled by the respective closed and open conformational state of the calcium channel. The closed and open states of the channel have different affinities 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 [2], tissue selectivity [3,4] and the conformation of the boat-shaped 1,4-dihydropyridine ring [5,6]. Hantzsch 1,4-dihydropyridines 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 [7], 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 [8]. Structure-activity relationships have shown that tissue selective 1,4-dihydropyridine calcium channel antagonists may exhibit a variety of pharmacological actions. For example, calcium channel antagonists that induce vascular smooth muscle relaxation are useful for the treatment of angina pectoris and hypertension [9], some lipophilic calcium channel antagonists undergo selective uptake in brain to exhibit anticonvulsant activity [10,11], calcium channel antagonists that act as calmodulin antagonists suppress tumor cell proliferation [12], and calcium channel antagonists that bind to P-glycoprotein that is responsible for the efflux of anticancer drugs from multidrug resistant tumor cells exhibit anticancer activity [13,14]. As part of our ongoing program to develop structure-activity relationships for C-4 heterocyclic derivatives of 1,4-dihydropyridines with calcium channel modulating effects, 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 C-4 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (uracil) derivatives of dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (**3a-c**) and alkyl 1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylates (**6a-c**).

Chemistry.

Reaction of uracil with paraformaldehyde according to the method reported by Chu [15] afforded 5-hydroxymethyluracil which on subsequent oxidation using ceric ammonium nitrate following the method reported by Ressner *et al* [16] gave 5-formyluracil (**1**). The dialkyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylates (**3a-c**) were synthesized using a three-component Hantzsch reaction [17]. Accordingly, condensation of 5-formyluracil (**1**) with an alkyl acetoacetate (**2a**, **2b** or **2c**) in the presence of ammonium hydroxide in methanol at reflux afforded the respective 1,4-dihydropyridine product **3a-c** in 55-67% yield (Scheme 1).

A group of structurally related alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrim-

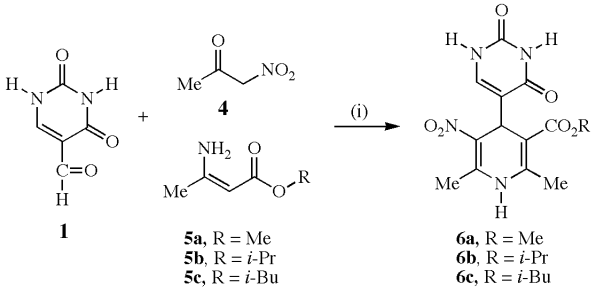
Scheme 1[a]



[a] Reagents and conditions: (i) NH_4OH, MeOH, reflux, 18 hours.

idin-5-yl)pyridine-5-carboxylates (**6a-c**) possessing a 3-nitro substituent were prepared using a modified Hantzsch reaction as illustrated in Scheme 2. Thus, condensation of 5-formyluracil (**1**) with nitroacetone (**4**) and an alkyl 3-aminocrotonate (**5a**, **5b** or **5c**) in ethanol at 45-50 °C afforded the respective alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6a-c**) in 10-18% yield.

Scheme 2[a]



[a] Reagents and conditions: (i) EtOH, 45-50 °C, 36 hours.

Biological Results.

Hantzsch 1,4-dihydropyridines having C-3 and C-5 alkyl ester substituents in conjunction with a C-4 heterocyclic ring system such as 3-pyridyl (**7a**) [18], 1-methoxycarbonyl-1,2-dihydropyrid-3-yl and 1-methoxycarbonyl-1,6-dihydropyrid-3-yl (**7b**) [19], and 1-methoxycarbonyl-4-methyl-1,4-dihydropyrid-3-yl (**7c**) [20] exhibit calcium channel antagonist activity on smooth muscle resulting in vascular relaxation (vasodilation) that would reduce blood pressure (see structures **7a-c** in Figure 1). Alternatively, modified Hantzsch 1,4-dihyropyridines having a C-3 nitro substituent and C-5 alkyl ester substituent in conjunction with a C-4 heterocyclic ring system such as 3-pyridyl (**8a**) [21], 1-methoxycarbonyl-1,2-dihydropyrid-3-yl and 1-methoxycarbonyl-1,6-dihydropyrid-3-yl (**8b**) [22,23], and 1-methoxycarbonyl-4-methyl-1,4-dihydropyrid-3-yl (**8c**) [23] exhibit a calcium channel agonist effect that enhances the force of heart contractions (positive inotropic effect on heart) (see structures **8a-c** in Figure 1). Drugs that simultaneously relax vascular smooth muscle by a calcium channel antagonist action and exhibit a calcium channel agonist positive inotropic effect on heart would have desirable properties for the treatment of congestive heart failure [21-23]. The objective of this study was to determine whether the planar 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (uracil ring system) was a suitable bioisosteric replacement for the planar 4-(3-pyridyl) ring present in the smooth muscle calcium channel antagonist compound **7a** and the cardiac calcium channel agonist compound (**8a**). Unfortunately, diisopropyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3b**) and isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6c**) were both inactive since they did not relax guinea pig ileum longitudinal smooth muscle (GPILSM) at a very high concentration of 1.0 x 10^{-3} *M* in an *in vitro* calcium channel antagonist assay [24]. Similarly, isobutyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxy-

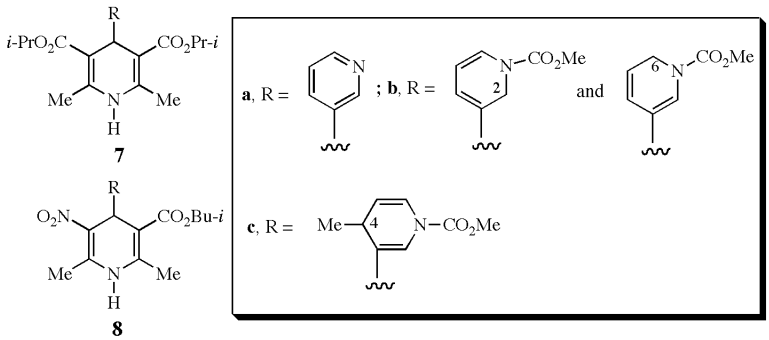


Figure 1. Structures of 1,4-dihydropyridine smooth muscle calcium channel antagonist (**7a-c**) [18-20], non-selective smooth and cardiac muscle calcium channel agonist (**8a**) [21], and dual smooth muscle selective calcium channel antagonist/cardioselective calcium channel agonist (**8b**) [22,23] and (**8c**) [23] compounds.

late (**6c**) was also an inactive cardiac calcium channel agonist (positive inotrope) since it did not increase the contractile force of guinea pig left atrium (GPLA) at a very high concentration of 1 x 10^{-2} *M* in an *in vitro* cardiac calcium channel agonist assay [24]. These calcium channel modulation assay data indicate that a 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl ring substituent is not a suitable bioisostere for the traditional C-4 aryl or heteroaryl substituents present in 1,4-dihydropyridine calcium channel modulators.

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. Infrared (IR) spectra were acquired using a Nic-Plan IR Microscope attached to a Nicolet Magna 750 FT-IR spectrometer. Silica gel column chromatography was carried out using Merck 7734 (60-200 mesh) silica gel. Methyl acetoacetate (**2a**), isobutyl acetoacetate (**2c**), methyl 3-aminocrotonate (**5a**) and isopropyl 3-aminocrotonate (**5b**) were purchased from the Aldrich Chemical Co. Isopropyl acetoacetate (**2b**) was purchased from the Lancaster Chemical Co. 5-Formyluracil (**1**) [15,16], nitroacetone (**4**) [25], and isobutyl 3-aminocrotonate (**5c**) [26] were prepared according to the literature procedures. Elemental analyses were performed for C, H and N (Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta).

Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylates (**3a-c**).

General Procedure.

A mixture of 5-formyluracil (**1**, 0.14 g, 1 mmol), an alkyl acetoacetate (**2a**, **2b** or **2c**, 2 mmol), and ammonium hydroxide (30% w/v, 1.5 mmol) in methanol (15 mL) was heated at reflux for 18 hours. Removal of the solvent *in vacuo*, purification of the residue obtained by silica gel column chromatography using chloroform-methanol (75:25, v/v) as eluent, and then recrystallization of the product from methanol yielded the respective dialkyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3a-c**). The percentage yield, mp, ir and ^{1}H nmr spectral data for **3a-c** are reported below.

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3a**).

Compound **3a** was obtained as a white solid in 67% yield; mp 285 °C dec; ir (solid state): 3203 (NH), 1687 (CO_2) cm^{-1}; ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.16 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me*'s), 3.54 (s, 6H, CO_2CH_3), 4.65 (s, 1H, 1,4-dihydropyridine H-4), 6.73 (s, 1H, 1,4-dihydropyridine N*H*), 8.83 (s, 1H, 2,4-pyrimidinedione H-6), 10.47 (br s, 1H, 2,4-pyrimidinedione N*H*), 10.81 (br s, 1H, 2,4- pyrimidinedione N*H*).

Anal. Calcd. for $C_{15}H_{17}N_3O_6$: C, 53.73; H, 5.11. Found: C, 53.79; H, 5.14.

Diisopropyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3b**).

Compound **3b** was obtained as a white solid in 61% yield; mp 280 °C dec; ir (solid state): 3216 (NH), 1695 (CO_2) cm^{-1}; ^{1}H nmr (deuteriodimethylsulfoxide): δ 1.10 and 1.15 (two d, $J_{CH,Me}$ = 6.0 Hz, 6H each, CHMe_2), 2.14 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me*'s), 4.55 (s, 1H, 1,4-dihydropyridine H-4), 4.85 (septet, $J_{CH,Me}$ = 6.0 Hz, 2H, C*H*Me_2), 6.80 (s, 1H, 1,4-dihydropyridine N*H*), 8.66 (s, 1H, 2,4-pyrimidinedione H-6), 10.50 (br s , 1H, 2,4-pyrimidinedione N*H*), 10.80 (s, 1H, 2,4-pyrimidinedione N*H*).

Anal. Calcd. for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.22; H, 6.45; N, 10.50.

Diisobutyl 1,4-Dihydro-2,6-dimethyl-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-3,5-dicarboxylate (**3c**).

This compound was obtained as a white solid in 55% yield; mp 260 °C dec; ir (solid state): 3234 (NH), 1715 (CO_2) cm^{-1}; ^{1}H nmr (deuteriodimethylsulfoxide): δ 0.81-0.99 (m, 12H, CHMe_2), 1.81-1.91 (m, 2H, C*H*Me_2), 2.15 (s, 6H, 1,4-dihydropyridine C-2 and C-6 *Me*'s), 3.69-3.82 (m, 4H, CH_2CHMe_2), 4.75 (s, 1H, 1,4-dihydropyridine H-4), 6.75 (s, 1H, 1,4-dihydropyridine N*H*), 8.82 (s, 1H, 2,4-pyrimidinedione H-6), 10.48 (br s, 1H, 2,4-pyrimidinedione N*H*), 10.80 (s, 1H, 2,4-pyrimidinedione N*H*).

Anal. Calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.13; H, 7.08; N, 9.78.

Alkyl 1,4-Dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) pyridine-5-carboxylates (**6a-c**).

General Procedure.

A mixture of 5-formyluracil (**1**, 0.154 g, 1.1 mmol), nitroacetone (**4**, 0.124 g, 1.2 mmol), and an alkyl 3-aminocrotonate (**5a**, **5b** or **5c**, 1.0 mmol) in ethanol (15 mL) was heated at 45-50 °C for 36 hours. Removal of the solvent *in vacuo*, purification of the residue obtained by silica gel column chromatography using chloroform-glacial acetic acid (95:5, v/v for **6a** and 92:8, v/v for **6b** and **6c**) as eluent, and then recrystallization of the product from ethanol yielded the respective alkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6a-c**). The percentage yield, mp, ir and ^{1}H nmr spectral data for **6a-c** are listed below.

Methyl 1,4-Dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6a**).

Compound **6a** was obtained as a pale yellow solid in 16% yield; mp 285 °C dec; ir (solid state): 3196 (NH), 1702 (CO_2), 1492, 1304 (NO_2) cm^{-1}; ^{1}H nmr (deuteriodimethylsulfoxide): δ 2.25 (s, 3H, 1,4-dihydropyridine C-6 *Me*), 2.45 (s, 3H, 1,4-dihydropyridine C-2 *Me*), 3.54 (s, 3H, CO_2CH_3), 4.94 (s, 1H, 1,4-dihydropyridine H-4), 7.11 (s, 1H, 1,4-dihydropyridine N*H*), 9.57 (s, 1H, 2,4-pyrimidinedione H-6), 10.75 (br s, 1H, 2,4-pyrimidinedione N*H*), 10.90 (s, 1H, 2,4-pyrimidinedione N*H*).

Anal. Calcd. for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38. Found: C, 47.97; H, 4.52.

Isopropyl 1,4-Dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6b**).

Product **6b** was obtained as a pale yellow solid in 18% yield; mp 280 °C dec; ir (solid state): 3193 (NH), 1701 (CO_2), 1503, 1314 (NO_2) cm^{-1}; ^{1}H nmr (deuteriodimethylsulfoxide): δ 1.12 and 1.19, (two d, $J_{CH,Me}$ = 6.0 Hz, 3H each, CHMe_2), 2.18 (s, 3H, 1,4-dihydropyridine C-6 *Me*), 2.40 (s, 3H, 1,4-dihydropyridine C-2 *Me*), 4.88 (septet, $J_{CH,Me}$ = 6.0 Hz, 1H, C*H*Me_2), 4.90 (s, 1H, 1,4-dihydropyridine H-4), 7.11 (s, 1H, 1,4-dihydropyridine N*H*), 9.54 (s, 1H, 2,4-pyrimidinedione H-6), 10.75 (br s, 1H,

2,4-pyrimidinedione N*H*), 10.90 (s, 1H, 2,4-pyrimidinedione N*H*).

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18. Found: C, 51.09; H, 5.00.

Isobutyl 1,4-Dihydro-2,6-dimethyl-3-nitro-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyridine-5-carboxylate (**6c**).

Compound **6c** was obtained as a pale yellow solid in 10% yield; mp 220 ˚C dec; ir (solid state): 3215 (NH), 1707 (CO_2), 1484, 1308 (NO_2) cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 0.83-1.00 (m, 6H, CH*Me*$_2$), 1.82-1.90 (m, 1H, C*H*Me$_2$), 2.18 (s, 3H, 1,4-dihydropyridine C-6 *Me*), 2.48 (s, 3H, 1,4-dihydropyridine C-2 *Me*), 3.72-3.90 (m, 2H, C*H*$_2$CHMe$_2$), 4.93 (s, 1H, 1,4-dihydropyridine H-4), 7.07 (s, 1H, 1,4-dihydropyridine N*H*), 9.60 (s, 1H, 2,4-pyrimidinedione H-6), 10.75 (br s, 1H, 2,4-pyrimidinedione N*H*), 10.90 (s, 1H, 2,4-pyrimidinedione N*H*).

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53. Found: C, 52.38; H, 5.54.

In vitro Smooth Muscle Calcium Channel Antagonist (relaxation) and Cardiac Calcium Channel Agonist (positive inotropic) 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 [24]. The IC_{50} (± SEM, n=3) is 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) is determined graphically from the dose-response curve [24].

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