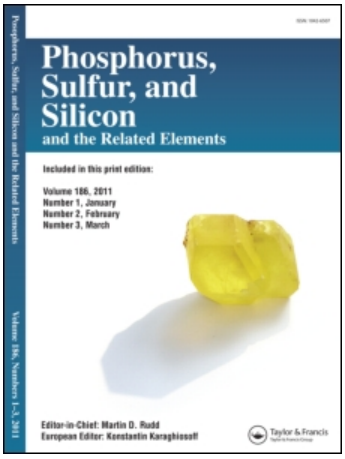

Phosphorus, Sulfur, and Silicon and the Related Elements

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The Synthesis and Characterization of New Asymmetrical Dihydropyridine Derivatives Containing a 2,4-Dichloro-5-Thiazolyl Substituent

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The Synthesis and Characterization of New Asymmetrical Dihydropyridine Derivatives Containing a 2,4-Dichloro-5-Thiazolyl Substituent

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Dihydropyridines (DHP) having a heterocyclic aryl substituent at position-4 are calcium channel antagonists. In this report a new group of DHP derivatives

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*with different esters at the C_3 and C_5 position (asymmetrical diesters) containing 2,4-dichloro-5-thiazolyl at position-4 were synthesized by a condensation reaction of alkyl, cycloalkyl, and aryl acetoacetate in the presence of ammonium acetate in a new shorter pathway. The structure of all compounds was confirmed by IR, ^{1}H NMR, and mass spectrometry. The calcium channel antagonist activity of compounds **6a–6f** demonstrated that the compound **6a** was the most active compound.*

Keywords 1,4-dihydropyridines; Ca^{2+}-channel-antagonist; heterocyclic compounds; thiazole

INTRODUCTION

The discovery that the 1,4-dihydropyridine class of calcium channel antagonists inhibits the Ca^{2+} influx represented a major therapeutic advance in the treatment of cardiovascular diseases, such as hypertension, angina pectoris, and other spastic smooth muscle diseases.[1] Dihydropyridine (DHP) derivatives substituted in position-4 are analogues of nifedipine (CAS 218 29-25-4) and an important class of drugs.[2] For example, amilodepine, nifedipine, and related dihydropyridine are Ca^{2+} channel antagonists.

In the human body, it has been observed that these compounds undergo oxidation to form pyridine derivatives. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds.[3]

Felodipine (Figure 1, having two chlorosubstituents) has high calcium antagonist potency that is comparable to nifedipine.[4] Therefore,

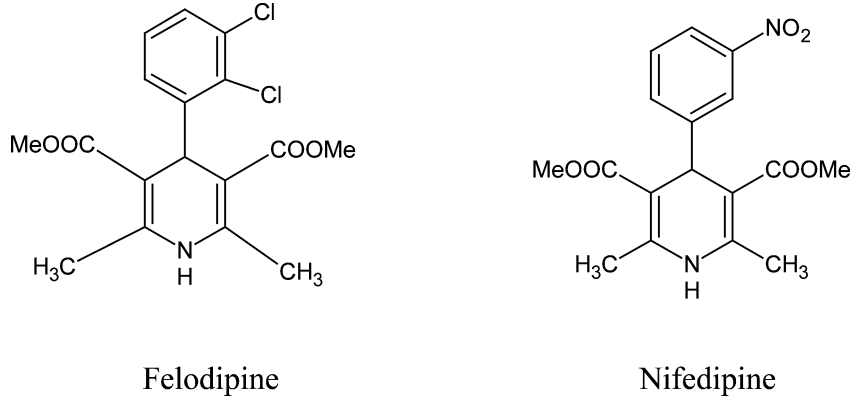


FIGURE 1 Two types of a calcium channel antagonist.

chlorine substitution in the aryl rings on the C_4 position can lead to potent compounds. In addition, several papers illustrated that C_4 heterocycle substituents gave compounds as calcium channel antagonists.[5–7]

The esters structure in the 3 and 5 positions affect the type and amount of DHP activity. DHPs having imidazole and its derivatives as substituents in the 4-position are very active compounds as calcium channels antagonist.[8–10] Symmetrical diesters (with the same esters at the C_3 and C_5-position) were synthesized by Hantzsch condensation,[11] and asymmetrical derivatives with different esters at the C_3 and C_5-position were prepared by the Meyer method.[12]

Memarian et al. illustrated that dihydropyridines having the aromatic ring substituent in position-4 in the presence of oxidizing reagents and also light have been oxidized to related pyridines.[13,14] This observation suggests that these compounds should be prepared in darkness and in the absence of oxidizing materials.

In this report, a modified method for the synthesis of a novel group of asymmetrical dialkyl, alkyl aryl, and alkyl cyclohexyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dichlorothiazol-5-yl)-3,5-pyridinecarboxylates is described.

For the selection of this heterocyclic substituent in position-4, the following reasons were considered.

1. Some heterocyclic rings were effective as 4-aryl in the dihydropyridine structure.[5,6]
2. The substitution of chlorine instead of NO_2 in the 4-aryl ring produced active compounds.[4]
3. A bulky substituent in the aryl group at the 4-position was tolerated by a receptor.[7,8]

MATERIAL AND METHODS

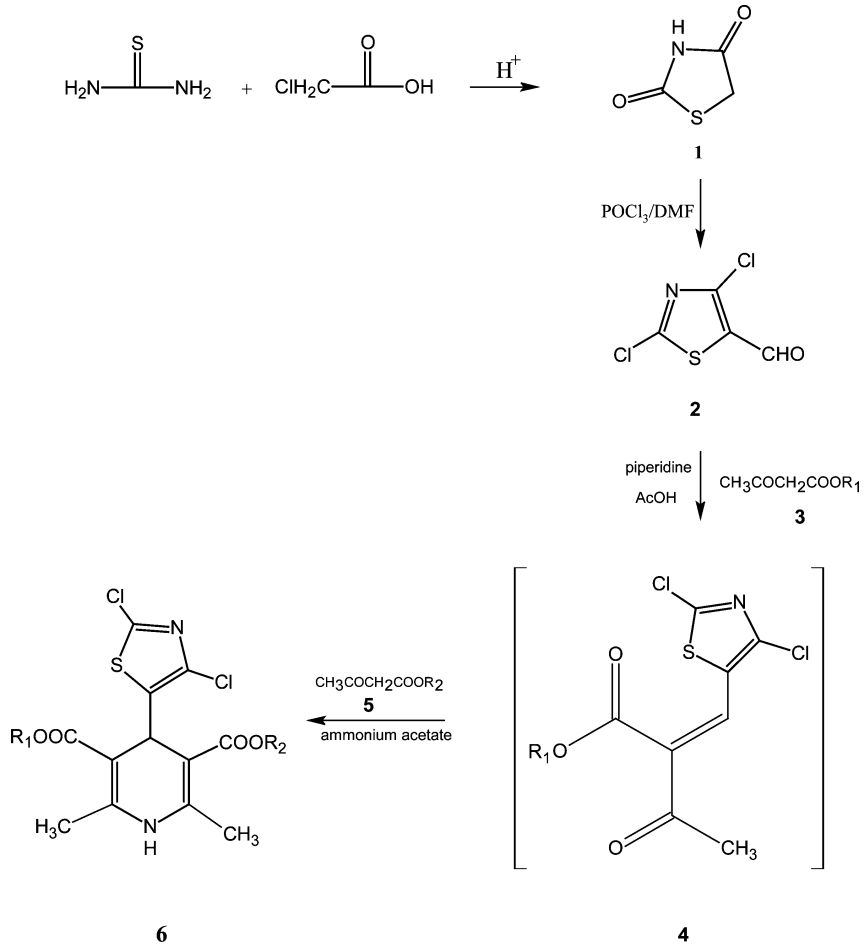
Instrumentation and Chemistry

Melting points were determined using a Thomas-Hoover capillary apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker FT-80 spectrometer (Bruker, Rheinstetten, Germany). TMS was used as an internal standard. Infrared spectra were acquired on a Nicolet 550-FT spectrometer (Madison,WI, USA). Mass spectra were measured with a Finigan TSQ-70 spectrometer (Finnigan MAT, Bremen, Germany) at 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus (Perkin-Elmer, Norwalk, CT, USA). The result of the elemental analyses (C, H, and N,) were within $\pm 0.4\%$ of

the calculated amounts. Some of the alkyl acetoacetates (3-oxobutanoic acid esters) were prepared according to the literature procedure.[15,16]

Synthesis

Asymmetrical diester analogues **6a–f** of nifedipine were synthesized according to Scheme 1. These compounds were synthesized in a shorter modified pathway. Since these compounds undergo oxidation[13,14] during synthesis, the preparation, collection, and purification of the product



SCHEME 1 The synthesis of 1,4-dihydropyridines with different ester groups in the 3- and 5-position.

should be carried out in the absence of oxidizing materials and in darkness. 2,4-dichlorothiazole-5-carboxaldehyde **2** was prepared in two steps. First chloroacetic acid and thiourea were refluxed for a desired time to give 1,3-thiazolidine-2,4-diones **1**.[17] The reaction of **1** with $POCl_3$ and DMF gave the desired aldehyde **2**.[18]

The asymmetrical analogues were prepared by the condensation of **2** with 3-oxobutanoic acid ester **3** and ammonium acetate in a new modified shorter pathway. Alkyl acetoacetates **3** were synthesized by known methods[15,16] in which 2,2,6- trimethyl-4**H**-1,3-dioxine-4-one was used as starting material.

The structure of all compounds was confirmed by elemental analyses, IR, H NMR, and mass spectroscopy.

EXPERIMENTAL

The Preparation of 1,3-Thiazolidine-2,4-dione (1)

To stirring solution of thiourea (10.13 g, 0.133 mol) in 100 mL of water was added chloroacetic acid (12.613 g, 0.133 mol) in the presence of conc. HCl and was refluxed for 7 h.[17] The precipitate was collected and crystallized from water to give 13 g (83%) of **1**, m.p. (123–125)°C; IR (KBr, cm^{-1}): 1736, 1666 (CO); ^{1}H NMR (DMSO-d_6), δ: 1.59 (s, 2H, CH_2), 4.03 (s, 1H, NH); MS, m/z (%): 117 (M^+, 85), 89 (50), 74 (65), 46 (100); Anal. calcd. for $C_3H_3O_2NS$: C, 30.76; H, 2.58; N, 11.96. Found: C, 30.70; H, 2.63; N, 12.05.

The Preparation of 2,4-Dichlorothiazole-5-carbaldehyde (2)

A mixture of compound **1** (10 g, 0.0584 mol) and $POCl_3$ (78.6 g, 0.51 mol) in 6.8 mL of DMF was refluxed for 6 h[18] and cooled to r.t. The product was purified by column chromatography (silica gel) and was crystallized in methanol to give 8.7 g (56%) of **2**, m.p. 45–46°C; IR (KBr, cm^{-1}): 1690 (CO); ^{1}H NMR($CDCl_3$), δ: 9.96 (s, CHO); MS, m/z (%): 185 (M^+, 80), 182 (100), 154 (37), 152 (43), 91 (53), 79 (32), 57 (30). Anal. calcd. for $C_4H_1Cl_2NOS$: C, 26.39; H, 0.55; N, 7.69. Found: C, 26.43; H, 0.54; N, 7.72.

The Preparation of Methyl Benzyl 1,4-Dihydro-2,6-dimethyl-4-(2,4-dichlorothiazole-5-yl)-3,5-pyridinedicarboxylate (6a)

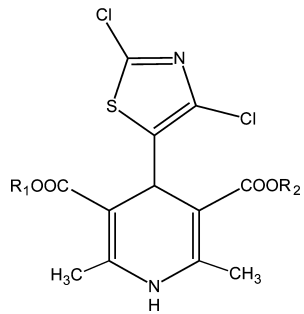
A solution of compound **2** (500 mg, 2.7 mmol) and methyl 3-oxobutanoate **3** (321 mg, 2.77 mmol) in the presence of 0.1 mL of piperidine and 0.25 mL of glacial acetic acid in 50 mL of benzene was refluxed

for 72 h. After removing the solvent, the reaction mixture was added to benzyl 3-oxobutanoate **5** (532 mg, 2.77 mmol) and ammonium acetate (231 mg, 3 mmol) in 30 mL of methanol and then refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was poured into 100 mL of water; the emulsion was extracted with ethyl acetate. The solvent was removed, and the residue was purified by a silica gel column using CH_2Cl_2: ethanol = 98:2 as eluent. The product was crystallized from methanol-water to give 373 mg (30%) of **6a** m.p. 151–152°C; IR (KBr, cm^{-1}): 3324, 3240 (NH), 1696 (CO); ^1H NMR ($CDCl_3$, 80 MHz):δ, 2.32 (s, 6H, C_2, C_6-CH_3), 3.66 (s, 3H, $COOCH_3$), 5.35 (s, 1H, H_4- DHP), 5.15 (s, 2H, $COOCH_2Ph$) 5.90 (bs, 1H, NH-DHP), 7.31 (s, 5H, Phenyl); MS, m/z (%): 452 (M^+, 32), 393 (12), 361 (32), 300 (97), 267 (32), 165 (70), 150 (37), 91 (100), 67 (45). Anal. calcd. for $C_{20}H_{18}Cl_2N_2O_4S$: C, 52.99; H, 4.00; N, 6.18. Found: C, 52.72; H, 4.02; N, 6.16.

Compounds **6b–c** (Table I) were prepared similarly.

6b, m.p. 165–166°C; yield = 47%; IR (KBr, cm^{-1}): 3306, 3240 (NH), 1705 (CO); ^1H NMR ($CDCl_3$): δ, 1.24 (dd, J = 6.4 Hz, 6H, $COOCH(CH_3)_2$), 2.32 (s, 6H, C_2, C_6-CH_3), 3.70 (s, 3H, $COOCH_3$), 4.85–5.2 (m, 1H, $CH(CH_3)_2$), 5.32 (s, 1H, H_4- DHP), 5.92 (bs, 1H, NH- DHP);

TABLE I Physical and Calcium Channel Modulation Data for Compounds 6a–f



Compound No.	R_1	R_2	M.P. (°C)	Yield (%)	Formula	Calcium Channel Antagonist Activity (IC_{50} ± SEM)
6a	CH_3	$CH_2C_6H_5$	151–152	30	$C_{20}H_{18}Cl_2N_2O_4S$	$2.1 \pm 0.84 \times 10^{-7}$
6b	CH_3	$CH(CH_3)_2$	165–166	47	$C_{16}H_{18}Cl_2N_2O_4S$	$1.1 \pm 0.24 \times 10^{-6}$
6c	CH_3	$CH_2C_6H_{11}$	Oil	28	$C_{20}H_{24}Cl_2N_2O_4S$	$5.9 \pm 0.99 \times 10^{-6}$
6d	$CH(CH_3)_2$	C_6H_{11}	119–120	40	$C_{21}H_{26}Cl_2N_2O_4S$	$2.2 \pm 0.3 \times 10^{-6}$
6e	$CH(CH_3)_2$	CH_2CH_3	Oil	39	$C_{17}H_{20}Cl_2N_2O_4S$	$9.5 \pm 3.8 \times 10^{-7}$
6f	$CH(CH_3)_2$	$CH_2CH_2C_6H_5$	107–108	42	$C_{23}H_{24}Cl_2N_2O_4S$	$8.0 \pm 2.9 \times 10^{-7}$
Nifedipine						$1.1 \pm 0.4 \times 10^{-8}$

MS, m/z (%): 404 (M^+, 22), 369 (23), 317 (62), 210 (100), 150 (27), 67 (15). Anal. calcd. for $C_{16}H_{18}Cl_2N_2O_4S$: C, 47.42; H, 4.48; N, 6.91. Found: C, 47.59; H, 4.46; N, 6.97.

6c, oil; yield = 28%; IR (KBr, cm^{-1}): 3411, 3296 (NH), 1701(CO); ^1H NMR ($CDCl_3$): δ, 0.6–2 (m, 13H, Cyclohexyl-CH_2), 2.17 and 2.34 (2s, C_2, C_6-CH_3), 3.70 (s, 3H, COO CH_3), 3.95–4.5 (m, 2H, $COOCH_2$—), 5.16 (s, 1H, H_4- DHP), 5.95(bs, 1H, NH-DHP); MS, m/z (%): 472 (M^+, 472, 63), 437 (97), 317 (100), 279 (40), 269 (18), 210 (87), 167 (25), 149 (32), 93 (12), 59 (10). Anal. calcd. for $C_{20}H_{24}Cl_2N_2O_4S$: C, 52.29; H, 5.23; N, 6.10. Found: C, 52.39; H, 5.45; N, 6.26.

The Preparation of Isopropyl Cyclohexyl 1,4-Dihydro-2,6-dimethyl-4-(2,4-dichlorothiazole-5-yl)-3,5-pyridinedicarboxylate (6d)

A solution of compound **2** (500 mg, 2.7 mmol) and isopropyl 3-oxobutanoate **3** (393 mg, 2.77 mmol) in the presence of 0.1 mL of piperidine and 0.25 mL of glacial acetic acid in 50 mL of benzene was refluxed for 48 h. After removing the solvent, the reaction mixture was added to cyclohexyl 3-oxobutanoate **5** (510 mg, 2.77 mmol) and ammonium acetate (231 mg, 3 mmol) in 30 mL of methanol and then refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was poured into 100 mL of water; the emulsion was extracted with ethyl acetate, and the solvent was removed. The residue was purified by a silica gel column using CH_2Cl_2: ethanol = 99:1 as aneluent. The product was crystallized from methanol-water to give 520 mg (40%) of **6d** m.p. 119–120°C; IR (KBr, cm^{-1}): 3240, 3293 (NH), 1699 (CO); ^1H NMR ($CDCl_3$): δ, 1.2–1.85 (m, 16H, cyclohexyl, $CH(CH_3)_2$), 2.33 (s, 6H, C_2, C_6-CH_3), 5.04 (m, 2H, COOCH—), 5.35 (s, 1H, H_4–DHP), 5.92 (bs, 1H, NH-DHP); MS, m/z (%): 472 (M^+, 22), 437 (40), 347 (42), 303 (59), 267 (22), 196 (100), 150 (15), 83 (21). Anal. calcd. for $C_{21}H_{26}Cl_2N_2O_4S$: C, 53.28; H, 5.54; N, 5.92. Found: C, 53.42; H, 5.53; N, 5.91.

Compounds **6e–f** (Table I) were prepared similarly.

6e, oil; yield = 39%; IR (KBr, cm^{-1}): 3475, 3408 (NH), 1702 (CO); ^1H NMR ($CDCl_3$): δ, 1.17–1.379 (m, 9H, $COOCH_2CH_3$ and $COOCH(CH_3)_2$), 2.34 (s, 6H, C_2, C_6-CH_3), 4.12 (q, J = 6.4 HZ, 2H, $COOCH_2CH_3$), 5.08 (m, 1H, $CH(CH_3)_2$), 5.34 (s, 1H, H_4-DHP), 5.83 (bs, 1H, NH-DHP); MS, m/z (%): 418 (M^+, 57), 331 (100), 266 (95), 224 (98), 196 (96), 150 (52), 106 (18). Anal. calcd. for $C_{17}H_{20}Cl_2N_2O_4S$: C, 48.69; H, 4.81; N, 6.68. Found: C, 48.45; H, 4.84; N, 6.73.

6f, m.p. 107–108°C; yield = 42%; IR (KBr, cm^{-1}): 3417, 3294(NH), 1699(CO); ^1H NMR ($CDCl_3$): δ, 1.24 (dd, J = 6.4 HZ, 6H, $CH(CH_3)_2$),

2.26 and 2.32 (2s, 6H, C_2, C_6-CH_3), 2.98 (t, 2H, $COOCH_2CH_2Ph$), 4.35 (m, 3H, $COOCH_2$—, COOCH), 5.30 (s, 1H, H_4-DHP), 5.85 (bs, 1H, NH-DHP); MS, m/z (%): 494 (M^+, 46), 459 (40), 342 (42), 303 (45), 267 (20), 196 (100), 150 (23), 105 (97), 79 (17). Anal. calcd. for $C_{23}H_{24}Cl_2N_2O_4S$: C, 55.76; H, 4.88; N, 5.65. Found: C, 55.53; H, 4.83; N, 5.66.

PHARMACOLOGY

Male guinea pigs weighing 300–400 g were killed by a blow on the head. The animals were deprived from food 18 h before sacrifice but had free access to water. The non-terminal part of the ileum was removed and cut into segments of 10–15 mm in length. Each ileal segment was suspended in an organ bath and connected to an isometric transducer (K30, Hugo Sachs Electronic, Germany). The organ bath contained 20 mL of physiological solution of the following composition (in mM): NaCl, 119; KCl, 2.7; $CaCl_2$, $MgCl_2$, 0.88; NaH_2PO_4, 0.36; $NaHCO_3$, 12; glucose 5.5. The physiologic salt solution was continuously gassed with a mixture of 95% O_2 and 5% CO_2, and its temperature was held at 37°C. The fluid of the organ bath was changed every 15 min. A resting tension of 0.5 g was applied to the ileal segments, and they were allowed to equilibrate for 1 h. Contractions of the ileal segments were recorded using an amplifier (Plugsys, Hugo Sachs Electronic, Germany) and a recorder (Graphtec, model WR3320).

In order to study the effects of synthesized dihydropyridines on a KCl-induced contraction of ileum, at the first step, several contractions with KCl (40 mM) were made. No significant differences between KCl-induced contractions were considered as the stability of tissue, and thereafter the main experiments were started. At this step, a KCl (40 mM)-induced contraction was recorded again, and the peak of the first phase (phasic contraction) was considered as the control. Then, tissues were pre-incubated with one certain concentration of each compound (for 15 min), and then the effect of KCl (40 mM) was assessed once again. Each segment was treated with only one compound. From concentration-response curves, the pIC_{50}(-log IC_{50}) value of each compound was calculated. Nifedipine was used as a reference compound.

Statistical Methods

Results are expressed as means ± s. e. Comparing pEC130s of compounds on an isolated guinea-pig atrium and pIC_{50}s of them on isolated guinea were performed using one-way ANOVA followed by a Dunnet test. A P value <0.05 was considered to be significant.

RESULTS AND DISCUSSION

Asymmetrical DHPs were often prepared according to the reported procedure[12] in which the compounds were synthesized by three steps. In the first step, aldehyde **2** was reacted with alkyl acetoacetates **3** to give intermediate **4**; the product was synthesized by a reaction of **4** and alkyl aminocrotonate (with different alkyl or aryl). Some aminocrotonates, such as methyl, ethyl, and isopropyl, were commercially available but others had to be prepared. Therefore, an extra synthesis procedure was used to prepare the other alkyl aminocrotonates. In the present method according to Scheme 1, DHP **6** was synthesized in a shorter pathway because alkyl acetoacetate was used instead of alkyl aminocrotonate. In the presence of ammonium acetate, the aminocrotonate was formed in situ. The structure of the synthesized compounds was confirmed by IR, H NMR, and mass spectroscopy. The yields of the product in comparison to asymmetrical DHPs containing imidazole substituents were almost the same.[7,8] A trace amount of symmetrical DHPs was produced during the preparation of our desired compounds. Therefore, this method is applicable to synthesize some asymmetrical DHPs in a shorter procedure.

The Ca^{2+} channel antagonist activities of compounds **6a–f** determined as the concentration needed to produce 50% inhibition of the guinea-pig ileal longitudinal smooth muscle contractility are summarized in Table I. As it can be seen from Table I, the most active compound was compound **6a**, which had comparable activity with nifedipine as a reference drug. The structure activity data indicate that 4-(2,4-dichloro-5-thiazolyl moiety is a bioisoester of the *o*-nitrophenyl group of nifedipine.

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