SYNTHESIS AND CALCIUM CHANNEL ANTAGONIST ACTIVITY OF 4-[(HALOBENZYL)IMIDAZOLYL] DIHYDROPYRIDINES

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Seven analogues of nifedipine (in which the ortho nitrophenyl group at position 4) were replaced by 2-alkylthio-1-(halobenzyl-5-imidazolyl substituent) were synthesized and evaluated as calcium antagonists using the high K^+ contraction of rat ileal longitudinal smooth muscle. These analogues of nifedipine decreased the various contractile responses of the longitudinal smooth muscle of the isolated rat ileum in a dose-dependent manner. However, their potencies for inhibition of contraction varied significantly from each other. All tested compounds (except compound **5f**), were stronger than nifedipine with IC_{50} 1.16 x 10^{-13}M. Compound **5a** with IC_{50} 6.73 x 10^{-15}M was the most active compound tested.

Keywords: Halobenzylimidazolyl, dihydropyridine, antihypertension, Ca^{2+} channel blocker.

Introduction

Very soon after the discovery of the cardiovascular properties of 1,4-dihydropyridines, it was found that these substances act by inhibiting the entry of Ca^{2+} into the cells of cardiac and vascular muscle through the voltage-dependent calcium channels (1).

Structurally diverse groups of compounds are known to be effective as calcium antagonists (2). The most potent class of antagonists comprises derivatives of 1,4-dihydropyridine of which the most widely known agent is nifedipine (2,3). This class of compounds have been the subject of many structure-activity relationship studies (4-6). It has been previously proved that bioisosteric replacement of the 4-aryl moiety in nifedipine with a 4-imidazolyl group yields 4-imidazolyl-1,4-dihydropyridines which retain potent calcium-channel antagonist activity (7) and the effects of methyl-sulfonylimidazolyl, nitro-imidazolyl and chloloroimidazoly substituents in conjunction with various C-3, C-5 diesters on calcium channel antagonist activities has been reported (8-11). In a previous paper we described synthesis of 1,4-dihydro-2,6-di-methyl-4-(2-alkylthio-1-benzyl-5-imidazolyl)-3,5-pyridine-dicarboxylic acid esters (12) . All the compounds were tested on rat colon as calcium channel blockers and were found to be less active than nifedipine (13). In this paper we describe synthesis and pharmacological activity of 1,4-dihydro-2,6-dimethyl-4-(2-alkylthio-1-halobenzyl-5-imidazolyl)-3,5-pyridine-dicarboxylic acid esters.

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Materials and Methods

Chemistry

Melting points were determined using the capillary apparatus with a system of Gallenkamp. ^{1}H-NMR spectra were run on a Bruker AC-80 spectrometer. Infrared spectra were recorded on a FT-IR Perkin-Elmer Paragon 1000 spectrophotometer. Compounds **1** to **4** were prepared as reported previously (12).

*Preparation of 5-Hydroxymethyl-2-mercaptoimidazoles (**1a,b**)*

A suspension of dihydroxyacetone (6.4 g, 701 mmol), potassium thiocyanate (10.35 g, 100 mmol) and halobenzylamine hydrochloride (100 mmol) in glacial acetic acid (8 ml) and 1-butanol (50 ml) was stirred for 70 h. After adding water (10 ml), the resulting mixture was filtered. The precipitate was washed with water (30 ml) and diethyl ether (30 ml), respectively to give the corresponding compounds **2a,b.**

*5-Hydroxymethyl-2-mercapto-1-(4-fluorobenzyl)-imidazole (**2a**)*

Yield 65%; mp 186-189^{o}C; IR (KBr): 3112cm^{-1} (OH); ^{1}H NMR (DMSO-d_6): δ 11.8 (bs, 1H, SH), 7.5-7.1 (2d, 4H, H-Ar), 6.59(s, 1H, H-imidazole), 5.06 (s, 2H, CH_2N), 3.91(s, 2H, CH_2O).

*5-Hydroxymethyl-2-mercapto-1-(2-chlorobenzyl)-imidazole (**2b**)*

It was prepared similar to **1a**, yield 74%; mp 171-175 ^{o}C; IR (KBr):3112cm^{-1}(OH); ^{1}H NMR (DMSO-d_6): δ 11.8 (bs, 1H, SH), 7.30-7.06 (m, 4H, H-Ar), 6.68(s, 1H, H-imidazole), 5.35 (s, 2H, CH_2N), 3.91(s, 2H, CH_2O).

*Preparation of 2-alkylthio-5-hydroxymethyl-imidazoles (**3a-d**)*

General Procedures

To a stirred suspension of **2a** (22.72 mmoles) in methanol (350 ml) was added sodium hydroxide (1 N, 24 ml) at room temperature. The resulting mixture was stirred for 10min until a clear pale yellow solution was obtained. Appropriate alkylamine (23.9 mmoles) was then added dropwise while stirring continued overnight. After concentrating the solvent at reduced pressure, water (200ml) was added to the residue and extracted with chloroform (3 x 70 ml). The chloroform was evaporated to give the corresponding compounds **3a-d.**

*5-Hydroxymethyl-2-methylthio-1-(4-fluorobenzyl)-imidazole (**3a**)*

Yield 76%; mp 140-142 ; IR (KBr): 3200 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 7.38-6.99 (m, 5H, Ar-H, H-Imidazole) , 5.28 (s, 2H, CH_2N), 4.45(s, 2H, CH_2O), 3.5 (s, 1H, OH), 2.5 (s, 3H, CH_3S).

*5-Hydroxymethyl-2-ethylthio-1-(4-fluorobenzyl)-imidazole (**3b**)*

Yield 78%; mp 116-119^{o}C; IR (KBr):3200 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 7.60-7.00 (m, 5H, Ar-H, H-imidazole), 5.58 (s, 2H, CH_2N), 4.60 (s, 2H, CH_2O), 3.07(q, 2H, CH_2S, J = 8 Hz), 1.39 (t, 3H, CH_3S, J = 8 Hz).

*5-Hydroxymethyl-2-methylthio-1-(2-chlorobenzyl)-imidazole (**3c**)*

Yield 84%; mp119-121^{o}C; IR (KBr):3200cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 7.38-6.99 (m, 5H, Ar-H, H-Imidazole) , 5.28 (s, 2H, CH_2N), 4.45(s, 2H, CH_2O), 3.5 (s, 1H, OH), 2.5 (s, 3H, CH_3S).

*5-Hydroxymethyl-2-ethylthio-1-(2-chlorobenzyl)-imidazole (3**d**)*

Yield 75%; mp 107-111^{o}C; IR (KBr):3200cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 7.60-7.00 (m, 5H, Ar-H, H-Imidazole), 5.58 (s, 2H, CH_2N), 4.60 (s, 2H, CH_2O), 3.07(q, 2H, CH_2S, J = 8 Hz), 1.39(t, 3H, CH_3S, J = 8 Hz).

*Preparation of formylimidazoles (**4a-d**)*

A stirring suspension of **3a-d** (4.27 mmoles) and manganese dioxide (2.4 g, 27.6 mmoles) in chloroform (50 ml) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered on diatomatceous earth. The chloroform was evaporated at reduced pressure to give the corresponding aldehydes **4a-d.**

*5-Formyl-2-methylthio-1-(4-fluorobenzyl)imidazole (**4a**)*

Yield 80%; mp 84-86^{o}C; IR (KBr): 1660 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 9.6 (s, 1H, CHO), 7.76 (s, 1H, C_4-H imidazole), 7.46-7.04 (m, 4H, Ar-H), 5.49 (s, 2H, CH_2N), 2.68 (s, 3H, CH_3S).

*5-Formyl-2-ethylthio-1-(4-fluorobenzyl)imidazole (**4b**)*

Yield 80%; mp 55.5-57.5^{o}C; IR (KBr):1661 cm^{-1}

(C=O); ^{1}H NMR ($CDCl_3$): δ 9.6 (s, 1H, CHO), 7.78 (s, 1H, C_4-H imidazole), 7.46 -7.04 (m, 5H, Ar-H, H-Imidazole), 5.49 (s, 2H, CH_2N), 3.27(q, 2H, CH_2S, *J* = 8 Hz), 1.39(t, 3H, CH_3S, *J* = 8 Hz).

5-Formyl-2-methylthio-1-(2-chlorobenzyl)imidazole ***(4c)***

Yield 84%; mp 77-82°C; IR (KBr):1661 cm^{-1} (C=O); (^{1}H-NMR ($CDCl_3$): δ 9.6 (s, 1H, CHO), 7.76 (s, 1H, C_4-H imidazole), 7.46-7.04 (m, 4H, Ar-H), 5.49 (s, 2H, CH_2N), 2.68 (s, 3H, CH_3S).

5-Formyl-2-ethylthio-1-(2-chlorobenzyl)imidazole ***(4d)***

Yield 85%; mp 45-48°C; IR (KBr): 1661 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 9.6 (s, 1H, CHO), 7.78 (s, 1H, C_4-H imidazole), 7.46 -7.04 (m, 5H, Ar-H, H-imidazole), 5.49 (s, 2H, CH_2N), 3.27 (q, 2H, CH_2S, *J* = 8 Hz), 1.39 (t, 3H, CH_3S, *J* = 8 Hz).

General procedure for preparation of dialkyl 1,4-dihydro-2,6-dimethyl-4-[1-(4-halobenzyl)-2-alkyl-thio-5-imidazolyl]-3,5-pyridinedicarboxylate (***5a-h***)

Ammonium acetate (0.33g, 1.26 mmol) was added to a stirring solution of compound **4** (1.26 mmol) and alkyl acetoacetate (2.54 mmol) in methanol (5ml). The mixture was protected from light and refluxed for overnight. The solvent was evaporated under reduced pressure to give **5a-h**. Spectral data of compounds (**5a-h**) are given in Table 1.

Pharmacology:

The experiments were performed under the Animals (scientific procedures) Act of 1986 and conform to the National Institutes of Health guidelines for the use of experimental animals. Male Wistar rats (250-300 g) were killed by cervical dislocation. The intestine was removed above the ileocaecal junction and longitudinal smooth muscle segments of 2 cm length were mounted vertically and under a resting tension of 1 g in a 10 ml organ bath containing Tyrode solution of the following composition (mM): NaCl, 136.87; KCl, 2.68; $CaCl_2$, 1.80; $MgSO_4$, 0.81; NaH_2PO_4, 4.16; $NaHCO_3$, 11.9; glucose, 11.1. The bath contents were maintained at 37°C and aerated by 95% O_2 and 5% CO_2.

The muscles were equilibrated for 1 h with a solution which was changed every 15 min. The contractions were recorded with a force displacement transducer (F-50) on a NARCO physiograph. Because of solubility problems, the compounds were dissolved in dimethylsulfoxide (DMSO) and the control responses were taken after the addition of 0.1ml DMSO. Tested compounds were prepared as 10^{-2} M stock solutions in DMSO and stored protected from light. Appropriate dilutions were made into DMSO. The contractile response was taken as the 100% value for the tonic (slow) component of the response. The contraction was elicited with 100 mM KCl . Tested compounds were added cumulatively. Tested compound-induced relaxation of contracted muscle was expressed as percent of control. The IC_{50} values (concentration needed to produce 50% relaxation on contracted ileal smooth muscle) were calculated by use of Prism 3.0 software.

Results and Discussion

Chemistry:

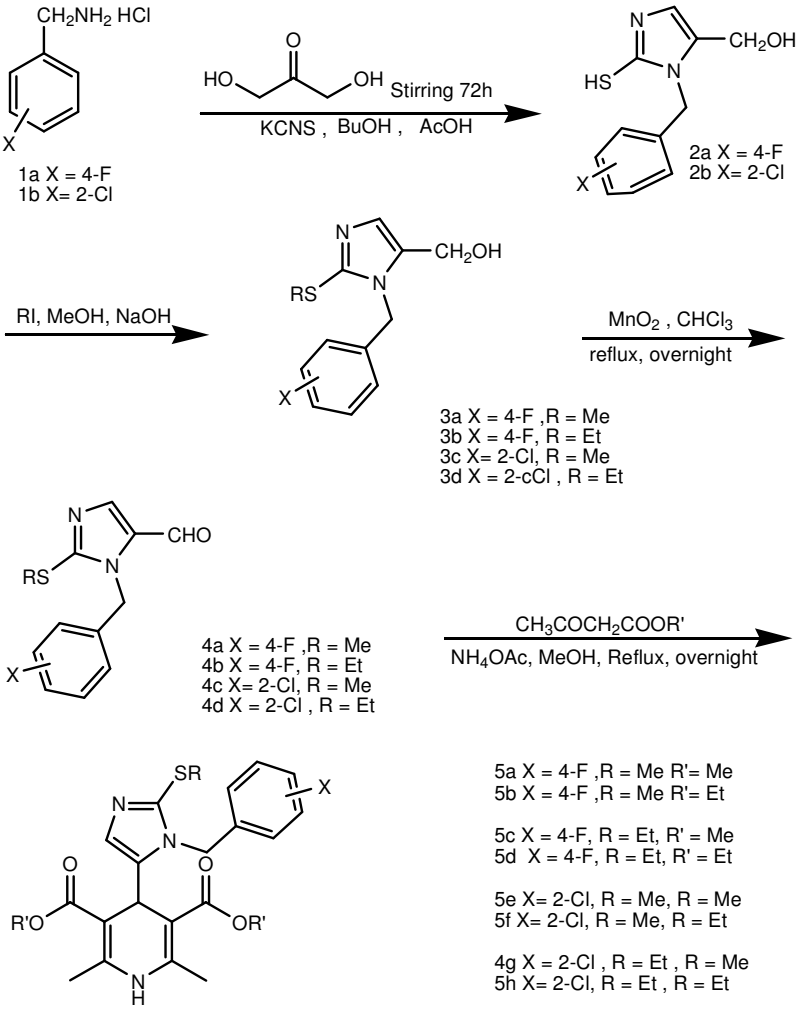
5-Hydroxymethyl -1- (halobenzyl) -2- mercaoto-imidazole (**2a,b)** was prepared from halobenzyl-amine hydrochloride (**1a,b)** and dihydroxyacetone dimmer. Reaction of **2** with alkyl halide afforded corresponding 2-alkylthio-1-halobenzyl-5-hydroxy-methylimidazole (**3a-d)**. Oxidation of **3** with manganese dioxide in chloroform (12) gave corresponding aldehyde (**4a-d)**. The 1,4-dihydropyridines (**5a-h**) were prepared by the classical Hantzsch condensation in which the aldehyde (4**a-d)** were reacted with acetoacetic acid ester and ammonium acetate (Scheme 1). Spectral data of compounds **5a-h** were given in Table 1.

Calcium channel antagonist activity ***5a-e:***

The calcium channel antagonist activities of compounds 5**a-h** were determined as the concentration needed to produces 50% relaxation of contracted rat ileal longitudinal smooth muscle with KCl (IC_{50}) and the results are shown in Table 2.

The results revealed that the synthesized compounds showed a significant inhibitory effect in comparison to reference drug nifedipine. It was worthy to mention that the previously synthesized derivatives of these series, devoid of the halo substituents (12) showed significant lower activity as Ca^{+2} blockers compared to nifedipine (13). These data confirm the necessity of the presence of an electron-withdrawing group for calcium channel blocking activity.

Evaluation of novel compounds effects on potassium chloride induced contraction of the isolated



Scheme 1

rat colon, is a well established assay for screening calcium channel blocking activity (14). Although, the most likely mechanism of action of compounds **5a-h** for decreasing contraction of the isolated rat ileum preparations seems to be calcium channel blockade, we cannot exclude some other effects of these compounds on adrenergic pathway and nonadrenergic-noncholinergic system (NANC). Activation of either β-adrenoreceptors (15) or NANC (16) could have an inhibitory effect on ileal contraction and contractility. Also, further direct investigations on the isolated L-type calcium channel currents recorded from ileal smooth muscle cells employing patch clamp techniques are required for determining affinities of the channels for these drugs under different resting, open and inactivated states.

Acknowledgement

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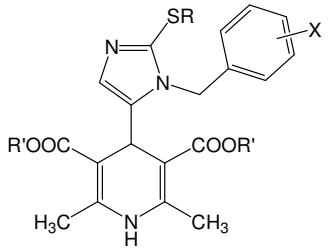
Table 1. Characterization data of dihydropyridines (**5a-e**)

Compd	R	R'	X	Yield (%)	M.P. °C	Mol. Formula* (M.W.)	IR in KBr (C=O) ν, cm^{-1}	^1H NMR($CDCl_3$) δ, ppm
5a	CH_3	CH_3	4-F	76	169.5-173.2	$C_{22}H_{24}FN_3O_4S$ (445.51)	1650	7.21-6.64 (m, 6H, arom, H-C_4 imidazole, NH), 5.35 (s, 2H, CH_2N), 5.0 (s, 1H, H-C_4 dihydropyridine), 3.39 (s, 6H, CH_3O), 2.36 (s, 3H, CH_3S), 2.2 (s, 6H, CH_3-$C_{2,6}$ dihydropyridine)
5b	CH_3	C_2H_5	4-F	89	195-197.2	$C_{24}H_{28}FN_3O_4S$ (473.56)	1650	7.4-6.6 (m, 6H, arom, H-C_4 imidazole, NH), 5.35 (s, 2H, CH_2N), 5.15 (s, 1H, H-C_4 dihydropyridine), 4.3-37 (q, 4H, CH_2O, J = 7.2Hz), 2.33 (s, 3H, CH_3S), 2.17(s, 6H, CH_3-$C_{2,6}$ dihydropyridine), 1.11 (t, 3H, J = 7.2Hz).
5c	C_2H_5	CH_3	4-F	66	170.5-174.7	$C_{23}H_{26}FN_3O_4S$ (459.53)	1650	7.5-6.6 (m, 6H, arom, H-C_4 imidazole, NH), 5.4 (s, 2H, CH_2N), 5.04 (s, 1H, H-C_4 dihydropyridine), 3.4 (s, 6H, CH_3O), 2.93 (q, 2H, CH_2S, J=7.2Hz), 2.25(s, 6H, CH_3-$C_{2,6}$ dihydropyridine), 1.22(t, 3H, CH_3 , J = 7.2Hz).
5d	C_2H_5	C_2H_5	4-F	86	154.4-160.1	$C_{25}H_{30}FN_3O_4S$ (487.59)	1650	7.4 -6.6 (m, 6H, arom, H-C_4 imidazole, NH), 5.94 (s, 2H, CH_2N), 5.1 (s, 1H, H-C_4 dihydropyridine), 4.15-3.74 (m, 4H, CH_2O), 2.84 (q, 2H, CH_2S, J=8.0Hz), 2.21 (s, 6H, CH_3-$C_{2,6}$ dihydropyridine), 1.33-1.00 (m, 9H, CH_3).
5e	CH_3	CH_3	2-Cl	82	207-211	$C_{22}H_{24}ClN_3O_4S$ (461.96)	1650	7.21-6.64(m, 6H, arom, H-C_4 imidazole, NH), 5.35 (s, 2H, CH_2N), 5.0 (s, 1H, H-C_4 dihydropyridine), 3.39 (s, 6H, CH_3O), 2.36 (s, 3H, CH_3S), 2.2 (s, 6H, CH_3-$C_{2,6}$ dihydropyridine)
5f	CH_3	C_2H_5	2-Cl	75	210-215	$C_{24}H_{28}ClN_3O_4S$ (490.01)	1650	7.4-6.6 (m, 6H, arom, H-C_4 imidazole, NH), 5.35 (s, 2H, CH_2N), 5.15 (s, 1H, H-C_4 dihydropyridine), 4.3-37 (q, 4H, CH_2O , J = 7.2Hz), 2.33 (s, 3H, CH_3S), 2.17 (s, 6H, CH_3-$C_{2,6}$ dihydro-pyridine), 1.11 (t, 3H, J = 7.2Hz).
5g	C_2H_5	CH_3	2-Cl	78	187.5-189.5	$C_{23}H_{26}ClN_3O_4S$ (475.99)	1650	7.5-6.6 (m, 6H, , arom, H-C_4 imi-dazole, NH), 5.4 (s, 2H, CH_2N), 5.04 (s, 1H, H-C_4 dihydropyridine),), 3.4 (s, 6H, CH_3O), 2.93 (q, 2H, CH_2S, J=7.2Hz), 2.25(s, 6H, CH_3-$C_{2,6}$ di-hydropyridine), 1.22 (t, 3H, CH_3 , J = 7.2Hz).
5h	C_2H_5	C_2H_5	2-Cl	84	180-182	$C_{25}H_{30}ClN_3O_4S$ (504.04)	1650	7.4-6.6 (m, 6H, arom, H-C_4 imidazole, NH), 5.94 (s, 2H, CH_2N), 5.1 (s, 1H, H-C_4 dihydropyridine), 4.15-3.74 (m, 4H, CH_2O), 2.84 (q, 2H, CH_2S, J=8.0Hz), 2.21 (s, 6H, CH_3-$C_{2,6}$ dihydropyridine), 1.33-1.00 (m, 9H, CH_3).

* C, H, and N analysis were within ±0.4% of the theoretical values for the formula given

Table 2. Calcium channel blocking activities of compounds **5a-e** on contracted rat ileum.



Compd	R	R'	X	EC_{50} (M)* KCl (100 mM)	95% confidence interval
5a	CH_3	CH_3	4-F	6.73×10^{-15}	8.15×10^{-16} to 5.55×10^{-14}
5b	CH_3	C_2H_5	4-F	6.36×10^{-14}	5.99×10^{-15} to 6.74×10^{-13}
5c	C_2H_5	CH_3	4-F	2.94×10^{-14}	3.66×10^{-15} to 2.36×10^{-13}
5d	C_2H_5	C_2H_5	4-F	nd	nd
5e	CH_3	CH_3	2-Cl	8.63×10^{-14}	7.63×10^{-15} to 9.77×10^{-13}
5f	CH_3	C_2H_5	2-Cl	6.89×10^{-14}	5.33×10^{-15} to 8.90×10^{-13}
5g	C_2H_5	CH_3	2-Cl	7.95×10^{-14}	8.13×10^{-15} to 7.76×10^{-13}
5h	C_2H_5	C_2H_5	2-Cl	1.13×10^{-13}	8.03×10^{-15} to 1.56×10^{-12}
Nifedipine				1.16×10^{-13}	2.75×10^{-15} to 4.87×10^{-12}

* n = 7

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تشييد واختبار الفاعلية الصادة لقنوات الكالسيوم لمركبات

فارزن هادي زاده[1,2*] ، محسن إمينشاهدي[3] ، فاطمة محمد بور[1] ، بويا ميهانباراست[3] ، محمود سيفي[2]

ملخص البحث

تم تشييد سبع مشابهات لدواء نفيديبين (والتي تم فيها استبدال مجموعة أورثو نيتروفينيل في الموضع 4 بمستبدلات 2-الكيل ثيو- 1- (هالوبنزيل -5- إيميدازولايل)، وتم تقييمها كصادات كالسيوم باستخدام انقباض العضلة الملساء الطولية اللفائفية للجرذ بالتركيز العالي أيوني بوتاسيوم. وقد عملت هذه المركبات المشابهة لمركب نيفيديبين على خفض الاستجابات الانقباضية المختلفة للعضلة الملساء الطولية للفائفي المعزول بصورة معتمدة على الجرعة. ومع ذلك فإنها اختلفت معنوياً عن بعضها البعض من حيث شدة تثبيط الانقباض. وكانت كل المركبات المختبرة (ماعدا مركب 5f) أقوى من دواء نفيديبين ولها تركيز مثبط نصفي مقداره 10^{-13}x1.16 مولار. أما المركب 5a فكان تركيزه المثبط النصفي 10^{-13}x6.73 مولار وهو أكثر المركبات المختبرة فاعلية.

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