Synthesis and Calciun Channel Antagonist Activity of 2-Dimethylamino / 4-Benzylimidazolyl Substituted Dihydropyridines

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ABSTRACT

Four analogues of nifedipine in which the ortho nitrophenyl group at position 4 were replaced by 2-alkylthio-1-benzyl-5-imidazolyl substituent, were synthesized and evaluated as calcium antagonists on guinea-pig ileal smooth muscle. These analogues of nifedipine decreased the various contractile responses of the longitudinal smooth muscle of the isolated guinea pig ileum in a dose-dependent manner. However, their potencies for inhibition of contraction varied significantly from each other.

Key words: Calcium channel blockers; Dihydropyridine, Nifedipine analogues.

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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[3]. This class of compounds have been the subject of many structure-activity relation-ship studies[4-6]. Previously the effect of methylsulfonylimidazolyl , nitoimidazolyl and indolyl substituents in conjunction with various C-3, C-5 diesters on calcium channel antagonist activities has been reported [7-9]. In a recent 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 [10] . In this work pharmacological activities of these compounds (**5a-c**) and a newly synthesized 2-dimethylamino-substituted dihydroptyridine(**6a**) is described.

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 **5a-c** were synthesized as described previously[10]. The developed procedure is exemplified with the obtaining of 1,4-dihydro-2-methyl-6-[2-(dimethylamino)ethyl]-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate dimethyl ester (**6a**).

1,4-dihydro-2-methyl-6-[2-(dimethylamino)ethyl]-4-(1-benzyl-2-methylthio-5-
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A *solution of* **5a** (1.2g, 2.72mmoles), dimethylamine hydrochloride (0.33g, 4mmoles), paraformaldehyde (0.12g, 4mmoles) and 0.05ml of concentrated hydrochloric acid in ethanol (5ml) while protected from light was heated at reflux for 10h. The solvent was then evaporated and the residue was partitioned between hydrochloric acid (2M, 30ml) and ethyl acetate (15ml). The aqueous phase separated , basified with aqueous ammonia , and extracted into diethyl ether (3 x 30ml). The extract was dried and evaporated and the residue was chromatographed to give 0.4g (40%) of 1,4-dihydro-2-methyl-6-[2-(dimethylamino)ethyl]-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate dimethyl ester (**6a**) as brown oil. IR (KBr) : 1704, 1690cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): 7.4-6.7 (m, 7H, arom, H-C_4 imidazole, NH), 5.4(s, 2H, CH_2N), 5.1 (s, 1H, H-C_4 dihydropyridine), 3.4(s, 6H, CH_3O), 3.0-2.8(m, 4, CH_2), 2.5 (s, 6H, NCH_3), 2.3 (s, 3H, CH_3), 2.2(s., 3H, CH_3).

Pharmacology:

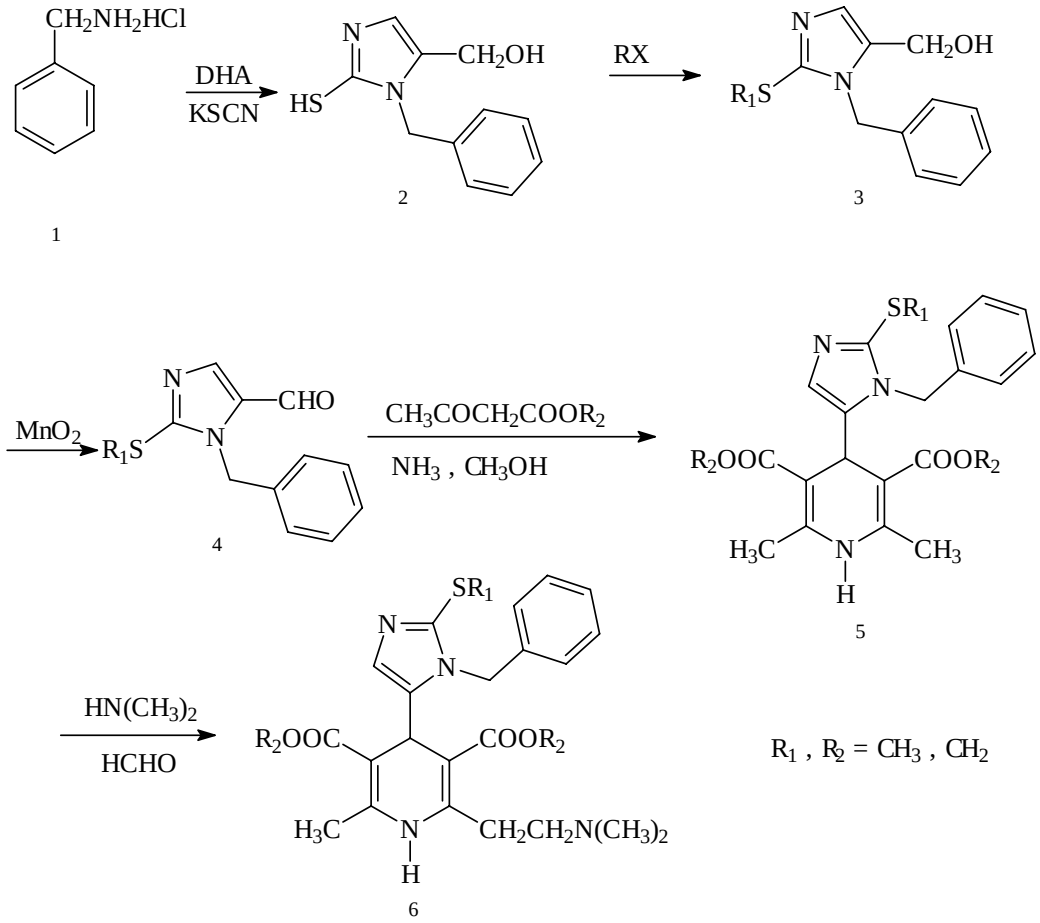
Male albino guinea-pigs (300-450 g) were killed by a blow on the head. The intestine was removed above the ileocaecal junction and longitudinal smooth muscle segments of 2 cm length were mounted under a resting tension of 0.5 g. The segments were maintained at

37°C in a 20-ml jacketed organ bath containing oxygenated physiological saline solution of the following millimolar composition: NaCl, 137; $CaCl_2$, 1.8; KCl, 2.7; $MgSO_4$, 1.1; NaH_2PO_4, 0.4; $NaHCO_3$, 12 and glucose, 5. The muscles were equilibrated for 1 h with a solution which change was every 15 min. The contractions were recorded with a force displacement transducer (F-50) on a NARCO physiograph. Test agents were prepared as 10^{-2} M stock solutions in ethanol and stored protected from light. Dilutions were made into double distilled water. 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 ,0.1mM acetylcholine (Ach). Test compounds were added cumulatively. Test 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: The desired compounds **5a-c** were synthesized by the reported method [10] according to the procedure depicted in Scheme 1. 5-Hydroxymethyl-1-benzyl-2-mercaotoimidazole (**2a,b)** was prepared from benzylamine hydrochloride (**1)** and dihydroxyacetone dimmer. Reaction of **2** with alkyl halide afforded corresponding 2-alkylthio-1-benzyl-5-hydroxymethylimidazole (**3a-b)**. Oxidation of **3** with manganese dioxide in chloroform gave corresponding aldehyde (**4a-b)**. The symmetrical 1,4-dihydropyridines (**5a-c**) were prepared by the classical Hantzsch condensation in which the aldehyde (4**a-b)** were reacted with acetoacetic acid ester and ammonium hydroxide. Finally

reaction of **5a** with formaldehyde and dimethylamine according to procedure reported previously [11]gave 1,4-dihydro-2-methyl-6-[2-(dimethylamino)ethyl]-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate dimethyl ester (**6a**).



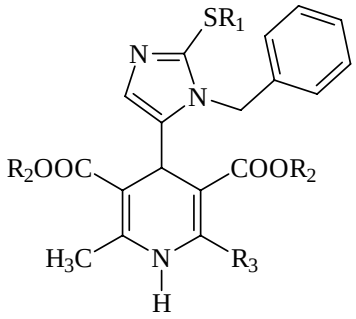
Scheme 1

Pharmacology: The calcium channel antagonist activities (IC_{50}) of compounds 5**a-c** and **6a** were determined as the concentration needed to produces 50% relaxation of contracted guinea-pig ileal longitudinal smooth muscle with KCl or acetylcholine[12] and the results are summarized in tables 1.

The inhibitory effect of these compounds are more likely due to blockade of L-type calcium channels. These analogues of nifedipine decreased the various contractile

responses of the longitudinal smooth muscle of the isolated guinea pig ileum in a dose-dependent manner. However, their potencies for inhibition of contraction varied significantly from each other. A comparison of the activities of dihydropyridines **5a** and **6a** indicate that replacement of dimethylamino substituent at 2 position (R_3) does not alter activity significantly. Compound **5b** was found to be more active than **5c**, this may indicate that ethythio substituent is better tolerated than methylthio one. Compound **5a** with dimethyl ester substituent ($R_1 = CH_3$) was 10 times less active than **5b** with diethyl ester substituent ($R_1 = C_2H_5$). We previously reported [13]in a similar work IC_{50} for nifedipine to be 1.40×10^{-8}M against KCl.

Table 1: Calcium channel blocking activities of compound **5a-c** and **6a** on contracted guinea-pig ileum



Comp	R_1	R_2	R_3	IC_{50} [a](M) x 10^{-4} KCl(100mM)	IC_{50} [a](M) x 10^{-5} Ach (0.1mM)
5a	CH_3	CH_3	CH_3	2.37(1.50-3.75)	23.9(9.5-60.42)
6a	CH_3	CH_3	$C_2H_5N(CH_3)_2$	2.96(1.35-6.49)	27.6(11.68-65.31)
5b	C_2H_5	CH_3	CH_3	0.84(0.57-1.25)	3.76(2.47-5.80)
5c	C_2H_5	C_2H_5	CH_3	5.66(4.36–7.35)	6.28 (3.75-10.54)
nifedipine[b]				1.40(1.20-1.60)x 10^{-8}	-

[a] n=5, 95%confidence intervals are shown in paranthesis [b] previously reported[9]

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