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Original Article

Synthesis and Biological Evaluation of New 1, 4-Dihydropyridines as Antihypertensives Agents in Rats

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Abstract

New analogues of nifedipine, as a known calcium channel blocker, were synthesized by replacing the orthonitrophenyl group on position 4 with 1-(4-Nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-Nitrobenzyl)-5-imidazolyl substituent. Effects of the new synthesized compounds on blood pressure were studied at 15, 30 and 60 min after administration by indirect tail-cuff method and compared with nifedipine in male rat.

The results indicate that all compounds reduce mean systolic blood pressure but their effectiveness is less than nifedipine. The onset of action of compounds 6c ,6d ,6e and 6g is also slower than the parent drug.

Keywords: 1,4-Dihydropyridines; Antihypertensive Activity; Rat.

Introduction

The haemodynamic, antianginal and antihypertensive effects of 1,4- di-hydro-pyridine calcium channel blockers have been established and reviewed by several investigators (1, 2).

The prototype of 1,4-dihydropyridines, nifedipine, is an effective drug which is used clinically, but it has some undesirable clinical features (3, 4).

Several attempts have been made to introduce other drugs in this class with improved pharmacokinetic and pharmaco-dynamic properties (5, 6, 7).

Due to selectivity for vessels, some of these drugs affect on vascular beds (8, 9) and decrease the blood pressure efficiently.Changes in the substitution pattern at C-3, C-4 and C-5 positions of nifedipine alter activity and tissue selectivity (10, 7). Therefore, it is interesting to determine the effect of selected C-3 and C-5 substituents, in conjugation with a C-4 1–(4-nitrobenzyl)-5-imidazolyl or 2- methylthio-1-(4-nitrobenzyl)-5-imidazolyl substituents,on blood pressure.

In this study, we have described the synthesis of new alkyl 1,4-dihydro-2,6-dimethyl-4-(1-(4-nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-nitrobenzyl)-5-imidazolyl)-3,5-pyridinedicarboxylates and their activities on blood pressure.

Experimental

Materials

Nifedipine was purchased from Tolidarou Pharmaceuticals (Tehran, Iran). All compounds were dissolved in dimethyl sulphoxide (DMSO). Other analytical grade reagents were obtained from Merck Company (Darmstadt, Germany).

Nifedipine and all new synthesized compounds were dissolved in dimethyl sulphoxide.

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Methods

Chemical procedures

The synthesis of the 1,4-dihydropyridine derivatives 6a-h (Table 1) was achieved following the steps outlined in Figure 1. 5-Hydroxymethyl-1-(4-nitrobenzyl)-2-thio imidazole(2) was prepared according to the procedure described by Denner et al (1993). Reaction of 2 with methyl iodide or dilute nitric acid solution afforded corresponding substituted methylthioimidazole 3 or desulfurated imidazole 4 respectively.

Oxidation of 3 or 4 with manganese dioxide in chloroform gave the corresponding aldehyde 5a or 5b .The symmetrical 1,4-dihydropyridine derivatives 6a-h were prepared (25-56% yield, Table 1) by the classical Hantzsch condensation (11) in which the aldehyde 5a or 5b were reacted with the acetoacetic ester and ammonium hydroxide. The compounds were characterized by ^{1}H nuclear magnetic resonance, infra red and mass spectrometry. The purity of all products was determined by thin layer chromatography using several solvent systems of different polarity.

Nuclear magnetic resonance (NMR)

A 90 MHz FT NMR instrument (Jeol) was used to acquire NMR spectra; chloroform-D was used as solvent.

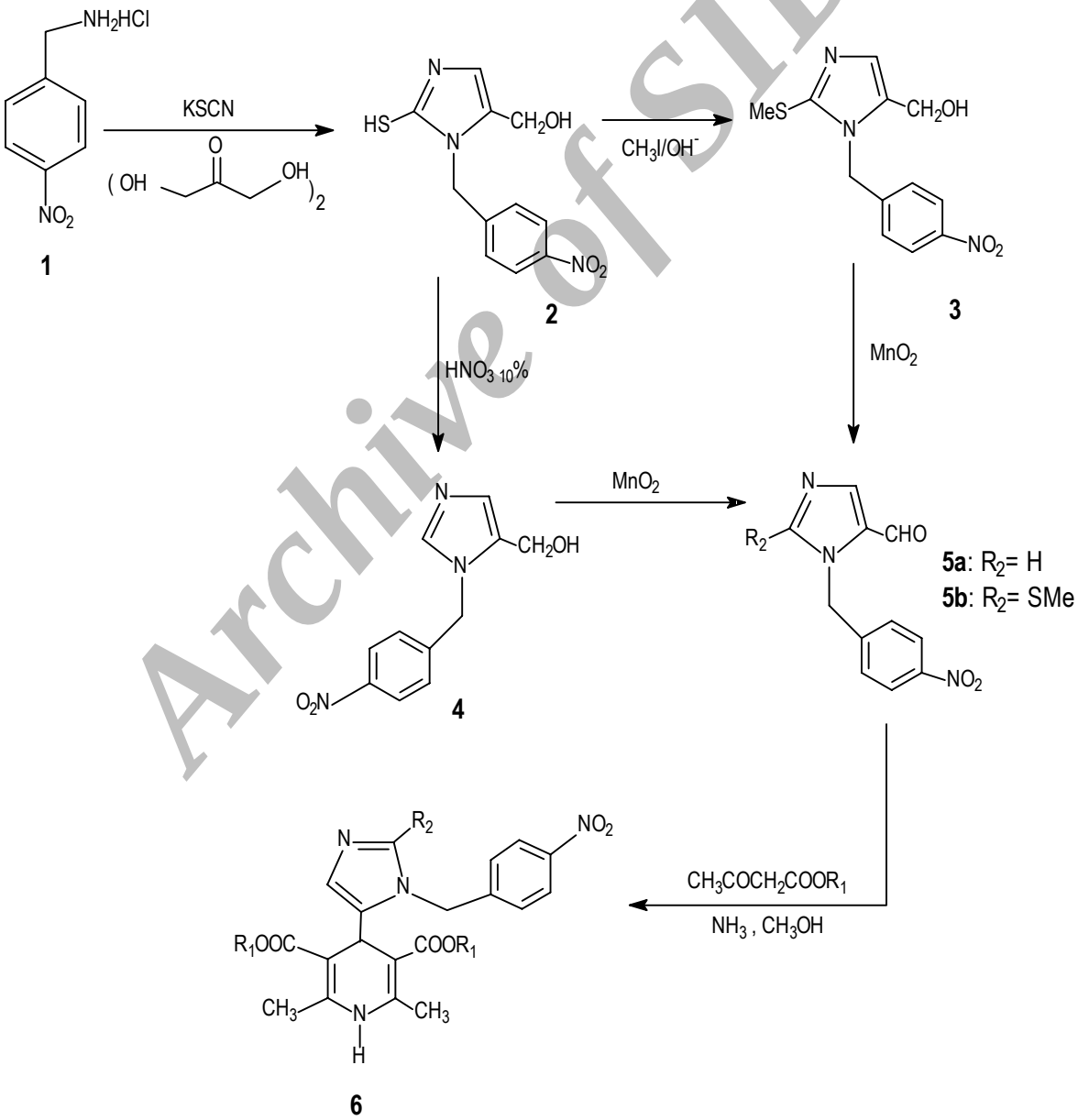

Figure 1. Chemical procedures for the synthesis of 1,4-dihydropyridine derivatives 6a-h. For further details see figure 2.

Table 1. Physical properties of synthesized symmetrical esters 6a-h. For further details see figure 1.

Compound	R1	R2	Mp (º c)	Yield (%)
6a	Me	H	200-201	27
6b	Et	H	203-204	25
6c	Bz	H	198-199	25
6d	TBu	H	193-194	30
6e	Me	SMe	200	43
6f	Et	SMe	212-213	36
6g	Bz	SMe	248	56
6h	TBu	SMe	213-214	31
	Nifedipine		174	

Mass spectrometry

Low-resolution mass spectra were acquired with an MAT CH5/DF (Finnigan) mass spectrometer; high-resolution mass spectra and accurate mass measurements were obtained with an A.E.I. Kratos MS30 spectrometer. Both spectrometers were coupled on line with a Data General DS 50 data system. Electron-impact ionization was performed at an ionizing energy of 70 eV; the source temprature was 250ºC.

Biological Assays

Adult male sprauge–Dawlley rats weighting 250-300 g were used. Animals were housed 4-5 per cage in a temperature controlled room (23±1ºC) and exposed to a 12 h light-dark cycle With Free accces to food and water. Six rats were used for each dose and compound. The control group received DMSO (1 ml/kg, i.p.) only. To reduce spontaneous variations in blood pressure, animals were adjusted to the experimental cage 3-4 times before the start of the experiment for a period of 30-60 min. Changes of blood pressure were measured by using indirect tail-cuff method (12, 13). Automatic measurement of systolic blood pressure was provided by a pressure transducer (International Biomedical Inc. U.S.A.) on a 8 channel polygraph apparatus (Narcotrace 80, Narco Bio-System USA). All test compounds were dissolved in DMSO (Sigma Chem. Co.) and administered intraperitoneally (10 mg/kg) in rats. Blood pressure was measured before and 15, 30 and 60 min after drug administration. Nifedipine was administered as standard compound. Mean values in systolic blood pressure before and 15, 30, 60 min after drug administration were determine.

Table 2. Reduced mean systolic blood pressure after administration of the test compounds.

	Time After Adminstration (min)		
Compound	15	30	60
DMSO	6.66±0.56	6.33±0.76	3.66±0.56
Nifedipine	29±1.02***	33.95±0.88***	27.55±0.90***
6a	16.93±0.75***	22.48±1.22***	10.46±1.32***
6b	11.05±0.66**	14.1±0.98***	8.34±0.53***
6c	4.99±0.26	10.56±0.82**	6.73±0.74*
6d	6.67±0.5	11.18±0.5***	4.36±0.51*
6e	5.88±0.93	11.79±0.44***	3.67±0.79*
6f	11.29±1.23**	14.74±1.46***	6.84±1.21
6g	7.76±2.66	15.75±1.09***	5.75±1.03***
6h	16.29±0.82***	17.91±0.75 ***	111.78±0.37***

* P<0.05, ** P<0.01, *** P<0.001 compared to DMSO.

Statistical methods

Statistical significance of differences was estimated by analysis of variance (ANOVA) followed by Dunnett's test (14). $p< 0.05$ was considered as significant value.

Results and Discussion

Our results showed that all final products were pure and stable compounds. Similar to other analogues of nifedipine, they were lipophilic compounds with very slight solubility in water. All compounds were yellow to orange crystalline powders. They were stable when exposed to daylight and to artificial light. There were no significant differences between the mean blood pressures before and after DMSO administration.

Comparison of the activities of compounds 6a-6h (10 mg/kg, i.p.) with nifedipine (10 mg/kg, i.p.) showed that all compounds reduced the mean systolic blood pressure but all compounds were less potent than nifedipine to decrease the blood pressure (Table 2, Figures 2 and 3).

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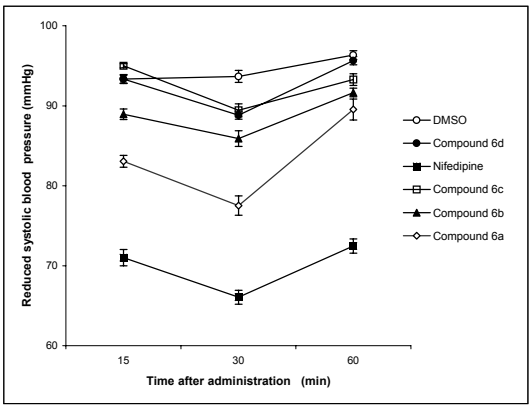

Figure 2. Effects of Nifedipine (■), DMSO(o), 6a(◇), 6b(▲), 6c(□), 6d(•) on the mean systolic blood pressure of rats. Each point represents mean ± sem, n=6 in each experimental groups. Baseline of systolic blood pressure was considered 100 mmHg .

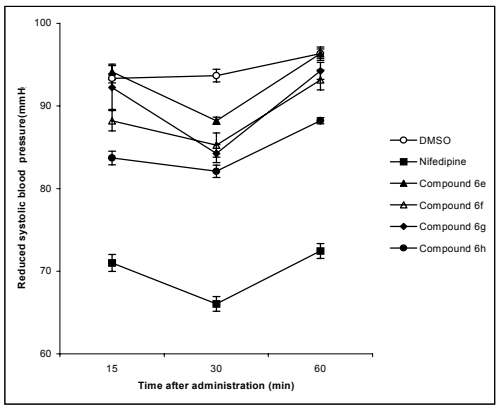

Figure 3. Effects of Nifedipine(■), DMSO(○), 6e(▲), 6f(△), 6g(♦), 6h(•) on the mean systolic blood pressure of rats. Each point represents mean ± sem, n=6 in each experimental groups. Baseline of systolic blood pressure was considered 100 mmHg.

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