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# Synthesis and antihypertensive activity of new 1,4-dihydropyridines

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A series of 1,4-dihydropyridines bearing dimethylamino **2a-f** or 1*H*-imidazol-1-yl **3a-f** side chain in the 2 position have been synthesized from unsubstituted ones **1a-f** and tested for antihypertensive activity in desoxycorticosterone acetate (DOCA)-induced hypertensive rats. All the compounds have been found to be less active than nifedipine.

**Keywords**: antihypertensive activity, 1,4-dihydropyridines, imidazole, desoxycorticosterone acetate

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Nifedipine, 2,6-dimethyl-3,5-dicarbomethoxy-4-[2-nitrophenyl]-1,4-dihydropyridine is a first generation calcium channel blocker that interacts with a specific class of voltage-gated calcium channel – the L-type channel – to produce its cardiovascular effects, including the relief of hypertension and angina. Nifedipine has now been joined in the clinical market place by several second and third generation 1,4-dihydropyridines including amlodipine, felodipine, isradipine, nicardipine, nimodipine, nitrendipine, lacidipine and lercanidipine. These agents differ in their overall pharmacological and pharmacokinetic characteristics, although they do share a fundamental similarity in their mode of action[1] . This class of compounds has been the subject of many structure-activity relationship studies[2-5] and recent developments in the chemistry of DHPs has been reviewed[6]. In a recent paper, we described the synthesis of 1,4-dihydro-2,6-dimethyl-4-(2-alkylthio-1-benzyl-5-imidazolyl)-3,5–pyridinedicarboxylic acid esters[7] .

The present study was designed to assess the antihypertensive effects of some novel 1,4-dihydro-2-methyl-6-[2-(dimethyamino)ethyl]-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylates **2a-f** and 1,4-dihydro-2-methyl-6-[2-(1-imidazolyl)ethyl]-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylates **3a-f** from the dihydropyridine class in DOCA induced hypertension in rats.

## Results and Discussion

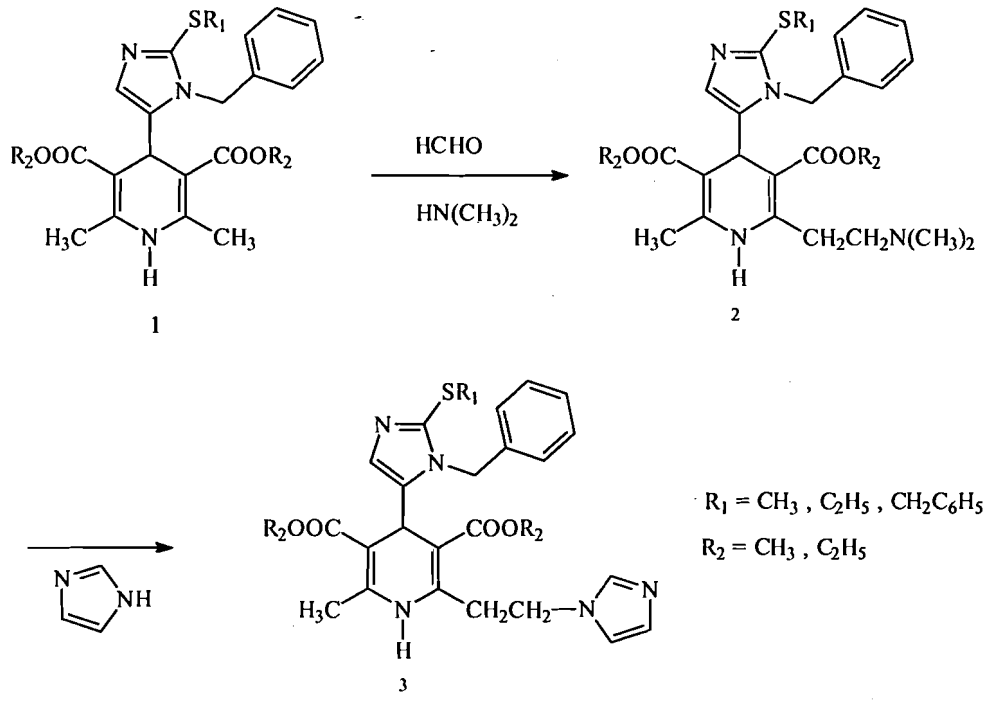
### Chemistry

Symmetrical dihydropyridines **1** were synthesized by classical Hantzch condensation as described previously[7]. Mannich condensation of the latter with paraformaldehyde and dimethylamine hydrochloride[8] gave (±) dialkyl 1,4-dihydro-2-[2-(dimethylamino)-ethyl]-6-methyl-4-(1-benzyl-2-alkylthio-5-imidazolyl)-3,5-pyrdinedicarboxylates **2** as a racemate. Base-catalyzed displacement of dimethylamino group of compound **2** with imidazole[8] gave dialkyl 1,4-dihydro-2-methyl-6-[2-(1-imidazolyl)ethyl]-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridine dicarboxylate **3** (**Scheme I**).

The compounds were characterized by $^1$H NMR and IR spectroscopy (**Table I**). The purity of all compounds was determined by thin layer chromatography.

### Pharmacology

**Effects of test agents on normotensive rats.** Intravenous administration of compounds **2** and **3** (0.3, 3, and 30mg/kg b.w.) produced blood pressure lowering effects in thiopental-anesthetized normotensive male Sprague Dawley rats. After 20 min (for stabilization), mean arterial blood pressure fall was measured (**Table II**).




**Scheme I**

**Table I** — Characterization data of new dihydropyridines

| Compd | $R_1$ | $R_2$ | Y | Yield (%) | Mol. formula* (Mol. wt.) | $^1$H NMR($CDCl_3$) δ, ppm |
|---|---|---|---|---|---|---|
| **2a** | $CH_3$ | $CH_3$ | $N(CH_3)_2$ | 40 | $C_{25}H_{32}N_4O_4S$ (484.61) | 7.4 -6.7 (m, 7H, arom, H-C4 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, 4H, $CH_2$), 2.5 [s, 6H, $N(CH_3)_2$], 2.36 (s, 3H, $CH_3S$), 2.19 (s, 3H,$CH_3$-$C_6$ dihydropyridine). |
| **2b** | $CH_3$ | $C_2H_5$ | $N(CH_3)_2$ | 38 | $C_{27}H_{36}N_4O_4S$ (512.66) | 7.4 -6.7 (m, 7H, arom, H-C4 imidazole, NH), 5.4 (s, 2H, $CH_2N$), 5.1 (s, 1H, H-$C_4$ dihydropyridine), 4.1(q, 4H, $CH_2O$), 3.0 -2. 8 (m, 4H, $CH_2$), 2.5 [s, 6H, $N(CH_3)_2$], 2.36 (s, 3H, $CH_3S$), 2.19(s, 3H,$CH_3$-$C_6$ dihydropyridine), 1.2(t, 6H, $CH_3$). |
| **2c** | $C_2H_5$ | $CH_3$ | $N(CH_3)_2$ | 29 | $C_{26}H_{34}N_4O_4S$ (498.64) | 7.65-6.92 (m, 7H, arom, H-C4 imidazole, NH), 5.59(s, 2H, $CH_2N$), 5.3 (s, 1H, H-$C_4$ dihydropyridine), 3.6 (s, 6H, $CH_3O$), 3.15-2.68 (m, 6H, $CH_2$), 2.55 [s, 6H, $N(CH_3)_2$], 2.34 (s, 3H, $CH_3$-$C_6$ dihydropyridine), 1.34(t, 3H, $CH_3$). |
| **2d** | $C_2H_5$ | $C_2H_5$ | $N(CH_3)_2$ | 35 | $C_{28}H_{38}N_4O_4S$ (526.69) | 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), 4.1(q, 4H, $CH_2O$), 3.2 -2. 8 (m, 6H, $CH_2$), 2.5 [s, 6H, $N(CH_3)_2$], 2.36 (s, 3H, $CH_3S$), 2.19 (s, 3H,$CH_3$-$C_6$ dihydropyridine), 1.3(m, 6H, $CH_3$). |
| **2e** | $CH_2$ $C_6H_5$ | $CH_3$ | $N(CH_3)_2$ | 20 | $C_{31}H_{36}N_4O_4S$ (560.71) | 7.3 -6.5 (m, 12H, arom, H-C4 imidazole, NH), 5.09(s, 2H, $CH_2N$), 4.89(s, 1H, H-$C_4$ dihydropyridine), 3.9(s, 2H, $CH_2S$), 3.45 (s, 6H, $CH_3O$), 2.9-2.5(m, 4H, $CH_2$), 2.3 [s, 6H, $N(CH_3)_2$], 2.1 (s, 3H, $CH_3$-$C_6$ dihydropyridine). |
| **2f** | $CH_2$ $C_6H_5$ | $C_2H_5$ | $N(CH_3)_2$ | 42 | $C_{33}H_{40}N_4O_4S$ (588.76) | $^1$H NMR ($CDCl_3$): 7.3-6.5 (m, 12H, arom, H-C4 imidazole, NH), 5.09(s, 2H, $CH_2N$), 4.89(s, 1H, H-$C_4$ dihydropyridine), 3.9(s, 2H, $CH_2S$), 2.9-2.5 (m, 4H, (-COO-*$CH_2$*-$CH_3$)], 2.3 [s, 6H, $N(CH_3)_2$], 2.1 (s, 3H, $CH_3$-$C_6$ dihydropyridine), 1.3[t, 6H, (-$CH_2$-*$CH_3$*)]. |

*— Contd*

**Table I** — Characterization data of new dihydropyridines — *Contd*

| Compd | $R_1$ | $R_2$ | Y | Yield (%) | Mol. formula* (Mol. wt.) | $^1$H NMR($CDCl_3$) δ, ppm |
|---|---|---|---|---|---|---|
| **3a** | $CH_3$ | $CH_3$ | imidazolyl | 58 | $C_{26}H_{29}N_5O_4S$ (507.6) | 7.65(s, 1H, H-$C_2$ imidazole), 7.36 -6.83 (m, 9H, arom, H-C imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (t, 2H, $CH_2$), 3.84(s, 6H, $OCH_3$), 2.4 (s, 3H, $CH_3S$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$–$C_6$ dihydropyridine). |
| **3b** | $CH_3$ | $C_2H_5$ | imidazolyl | 63 | $C_{28}H_{33}N_5O_4S$ (535.66) | 7.65(s, 1H, H-$C_2$ imidazole), 7.36 -6.83 (m, 9H, arom, H-C imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (m, 6H, $CH_2$), 2.4 (s, 3H, $CH_3S$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$–$C_6$ dihydropyridine),1.2(t, 6H, $CH_3$). |
| **3c** | $C_2H_5$ | $CH_3$ | imidazolyl | 50 | $C_{27}H_{31}N_5O_4S$ (521.63) | 7.65(s, 1H, H-$C_2$ imidazole), 7.36 -6.83 (m, 9H, arom, H-$C_4$ imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (t, 2H, $CH_2$), 3.84(s, 6H, $OCH_3$), 2.82 (q, 2H, $CH_2S$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$–$C_6$ dihydropyridine), 1.25 (t, 3H, $CH_3$). |
| **3d** | $C_2H_5$ | $C_2H_5$ | imidazolyl | 57 | $C_{29}H_{35}N_5O_4S$ (549.68) | 7.65(s, 1H, H-$C_2$ imidazole), 7.36 -6.83 (m, 9H, arom, H-C imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (m, 6H, $CH_2$), 2.82 (q, 2H, $CH_2S$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$–$C_6$ dihydropyridine), 1.23 (m, 9H, $CH_3$) |
| **3e** | $CH_2$ $C_6H_5$ | $CH_3$ | imidazolyl | 35 | $C_{32}H_{33}N_5O_4S$ (583.70) | 7.8-6.83 (m, 15H, arom, H-C imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (m, 4H, $CH_2$), 3.7 (s, 6H, $CH_3O$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$ dihydropyridine) |
| **3f** | $CH_2$ $C_6H_5$ | $C_2H_5$ | imidazolyl | 40 | $C_{34}H_{37}N_5O_4S$ (611.75) | 7.8-6.83 (m, 15H, arom, H-C imidazole, NH), 5.5(s, 2H, $CH_2N$), 5.08 (s, 1H, H-$C_4$ dihydropyridine), 4.15 (m, 8H, $CH_2$), 2.6 (t, 2H, $CH_2$), 2.21 (s, 3H, $CH_3$ dihydropyridine), 1.3(t, 6H, $CH_3$) |

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

**Table II** — Fall in blood pressure after administration of new 1,4-DHPs in normotensive and hypertensive rats

| Compd | MABP fall (SEM)[a] in rats in doses C, in mg/kg b.w., i.v. | | | | | |
|---|---|---|---|---|---|---|
| | Normotensive | | | Hypertensive | | |
| | 0.3 | 3 | 30 | 0.3 | 3 | 30 |
| **2a** | 26.00(2.00) | 42.00(3.00) | 47.20(3.03) | 38.40(5.37) | 46.40(2.19) | 50.00(2.00) |
| **2b** | nd | nd | nd | nd | nd | nd |
| **2c** | 22.00(2.00) | 42.00(2.00) | 57.2(2.16) | 29.60(4.56) | 54.40(7.79) | 58.00(2.73) |
| **2d** | 18.00(2.00) | 42.00(2.00) | 47.00(1.67) | 22.40(3.58) | 48.00(1.78) | 49.20(1.78) |
| **2e** | nd | nd | nd | nd | nd | nd |
| **2f** | nd | nd | nd | nd | nd | nd |
| **3a** | 17.20(2.68) | 41.60(20.60) | 53.20(2.28) | 28.00(6.20) | 52.80(11.79) | 55.20(2.28) |
| **3b** | 26.40(5.80) | 37.20(1.55) | 38.60(3.83) | 29.00(2.9) | 45.75(8.87) | 50.80(6.60) |
| **3c** | 23.20(7.69) | 44.80(3.34) | 56.80(3.34) | 35.20(3.35) | 56.00(4.00) | 56.80(3.34) |
| **3d** | 27.60(1.82) | 37.40(1.15) | 36.60(3.63) | 29.00(5.10) | 42.00(7.30) | 44.5(7.60) |
| **3e** | 15.40(0.27) | 28.60(1.09) | 33.00(1.41) | 28.00(4.70) | 36.80(1.60) | 51.00(8.70) |
| **3f** | 17.40(1.03) | 26.60(3.19) | 36.80(5.30) | 24.80(4.56) | 42.00(5.40) | 48.00(7.40) |
| Nifedipine | 27.20(2.68) | 59.60(3.84) | nd | 42.40(5.36) | 61.20(14.46) | nd |
| DMSO | 12.00(5.65) | 12.00(5.65) | 12.00(5.65) | 14.80(6.72) | 14.80(6.72) | 14.80(6.72) |

[a] Mean arterial blood pressure fall: standard errors the mean (SEM) are indicated in parenthesis. All results were analyzed for statistically significant differences from control DMSO (0.3mL/kg b.w., i.v.) by analysis of variance and all showed significant difference
($p<0.05$), nd: not determined

**Effects of test agents on hypertensive rats.** Intravenous administration of compounds **2** and **3** (0.3, 3, and 30mg/kg b.w.) produced blood pressure lowering effects in thiopental-anesthetized hypertensive male Sprague Dawley rats. After 20 min (for stabilization), mean arterial blood pressure fall was measured (**Table II**).

The outcome of this study was, that although all new dihydropyridines were less active than nifedipine, they significantly reduced the systemic arterial blood pressure in hypertensive as well as normotensive rats in comparison with the solvent DMSO. However, further experiments are needed to investigate the effects of these test compounds on vascular tonicity in different vasculatures such as aorta and mesenteric beds.

## Experimental

**General procedures**. Melting points were determined on a Capillary Gallenkamp apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker AC-80 spectrometer and IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer.

The various drugs used, *viz.* desoxycorticosterone acetate (Iran-Hormone), acetylcholine chloride, heparin sodium and nifedipine were obtained from Sigma Chemical Co. (St. Loius, MO, USA) whereas sodium thiopental was obtained from Biochemie GmbH Vienna, Austria. Other analytical grade reagents were obtained from Merck Company. Nifedipine and all newly synthesized dihydropyridines were dissolved in DMSO. The stock solutions were kept at -20°C and this study was carried out (Razi Institutes, Mashhad, Iran) using male Sprague Dawley rats, weighing between 250 to 300 g.

## Synthesis

Symmetrical dihydropyridines **1a-f** were synthesized by classical Hantzch condensation as described previously.

**General procedure for preparation of dialkyl 1,4-dihydro-2-methyl-6-[2-(dimethylamino)ethyl]-4-(1-benzyl-2-alkylthio-5-imidazolyl)-3,5-pyridine-dicarboxylate 2a-f.** A solution of **1** (3.91mmoles), dimethylamine hydrochloride (0.47g, 5.87mmoles), paraformaldehyde (0.17g, 5.87mmoles) and concentrated hydrochloric acid (0.7mL) in ethanol (7mL) while protected from light, was heated under reflux overnight. The solvent was then evaporated, and the residue was partitioned between hydrochloric acid (2 M, 30 mL) and ethyl acetate (15 mL). The aqueous phase was separated, basified with aqueous ammonia while cooling, and extracted with diethyl ether (3×30mL). The extracts were dried over anhydrous sodium sulfate and evaporated. The resultant residue was chromatographed (ethanol : chloroform 9:10) to give **2a-f** as brown oils. Spectral data of compounds are given in **Table I**.

**General procedure for preparation of dialkyl 1,4-dihydro-2-methyl-6-[2-(1-imidazolyl)ethyl]-4-(1-benzyl-2-alkylthio-5-imidazolyl)-3,5-pyridine dicarboxylate 3a-f.** A solution of **2** (0.743 mmole), 1.8-diazabicylo[5.4.0]undec-7-ene (0.1mL), and imidazole (0.2g, 2.97 mmoles) in chlorobenzene (7.5mL) while protected from light was heated at reflux for 24 hr. The solution was diluted with chloroform (7.5 mL), washed with water (15 mL), dried over anhydrous sodium sulfate, and evaporated to give **3a-f** as oil. Spectral data of compounds are given in **Table I**.

## Pharmacology

**Induction of experimental hypertension**. The experiments were performed in accordance with the Animals (scientific procedures) Act of 1986 (Britain) and conform to the National Institutes of Health guidelines for the use of experimental animals, in Britain. Rats were housed in temperature and humidity controlled, light-cycled quarters. Animals were randomly divided into two groups including normotensive and hypertensive. Normotensive rats received saline injection (0.5 mL/kg, twice weekly, for 5 weeks, s.c., n=20) whereas hypertension was induced by DOCA-salt injection (20 mg/kg b.w. twice weekly, for 5 weeks, s.c., n=20) and NaCl (1%) was added to their drinking water[9].

**Studies on anaesthetized rats**. Five weeks after saline or DOCA injection, animals were anaesthetized with sodium thiopental (30 mg/kg b.w. by i.p. injection). The right common carotid artery was catheterized for the measurement of blood pressure, right and left jugular veins were cannulated for the administration, throughout the experiment, of anesthetic (sodium thiopental, 10 mg/kg b.w.) and different agents such as acetylcholine, sodium nitroprusside and phenylephrine, respectively. The trachea was cannulated and the animals were allowed to breathe spontaneously. Body temperature was recorded using a rectal thermostat probe and was maintained at 37 ± 0.5 °C using an incandescent lamp

placed over the abdomen. After 20 min (for stabilization), arterial blood pressure (systolic, diastolic and mean) and heart rate were measured.

**Measurement of hypotensive effects.** All test agents were administered in a dose of 0.3, 3 and 30g/kg b.w. to the normotensive rats through cannula in a volume of 0.3 mL/kg b.w. Equivolumetric injections of vehicle were administered to the control animals. Nifedipine was used as standard with the same doses.

**Measurement of antihypertensive effects.** All test agents were also administered with the same doses as mentioned above to the hypertensive rats in a volume of 0.3 mL/kg b.w. Equivolumetric injections of vehicle were administered to the control animals. Nifedipine was used as standard with the same doses.

**Statistical analysis of data.** Results are expressed throughout as means ± S.E.M. and were analyzed by one way analysis of variance (ANOVA) followed by a Tukey-Kramer multiple comparison test (for comparison of responses to dihydropyridine in hypertensive rats). A P value of less than 0.05 was considered to be significant.

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