

SYNTHESIS OF 4-(1-BENZYL-5-IMIDAZOLYL)-1,4-DIHYDROPYRIDINES

F. Hadizadeh^{1,*}, A. Shafiee² and R. Kazemi¹

¹Department of Medicinal Chemistry, Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, P.O. Box 91775-1365, Islamic Republic of Iran

²Department of Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

Abstract

The *o*-nitrophenyl group at position 4 of dihydropyridine of nifedipine analogues was replaced with 2-alkylthio-1-benzyl-5-imidazolyl substituent. Starting from dihydroxyacetone 2-alkylthio-1-benzyl-5-formyl imidazole (**3**) was first synthesized which was subsequently used in synthesizing symmetrical (**5a-f**) and asymmetrical (**6a,b**) dihydropyridines. Primarily pharmacological studies of the title compounds have shown they have good calcium channel antagonist activities.

Keywords: Dihydropyridines; 4-Imidazolyl-Substituted

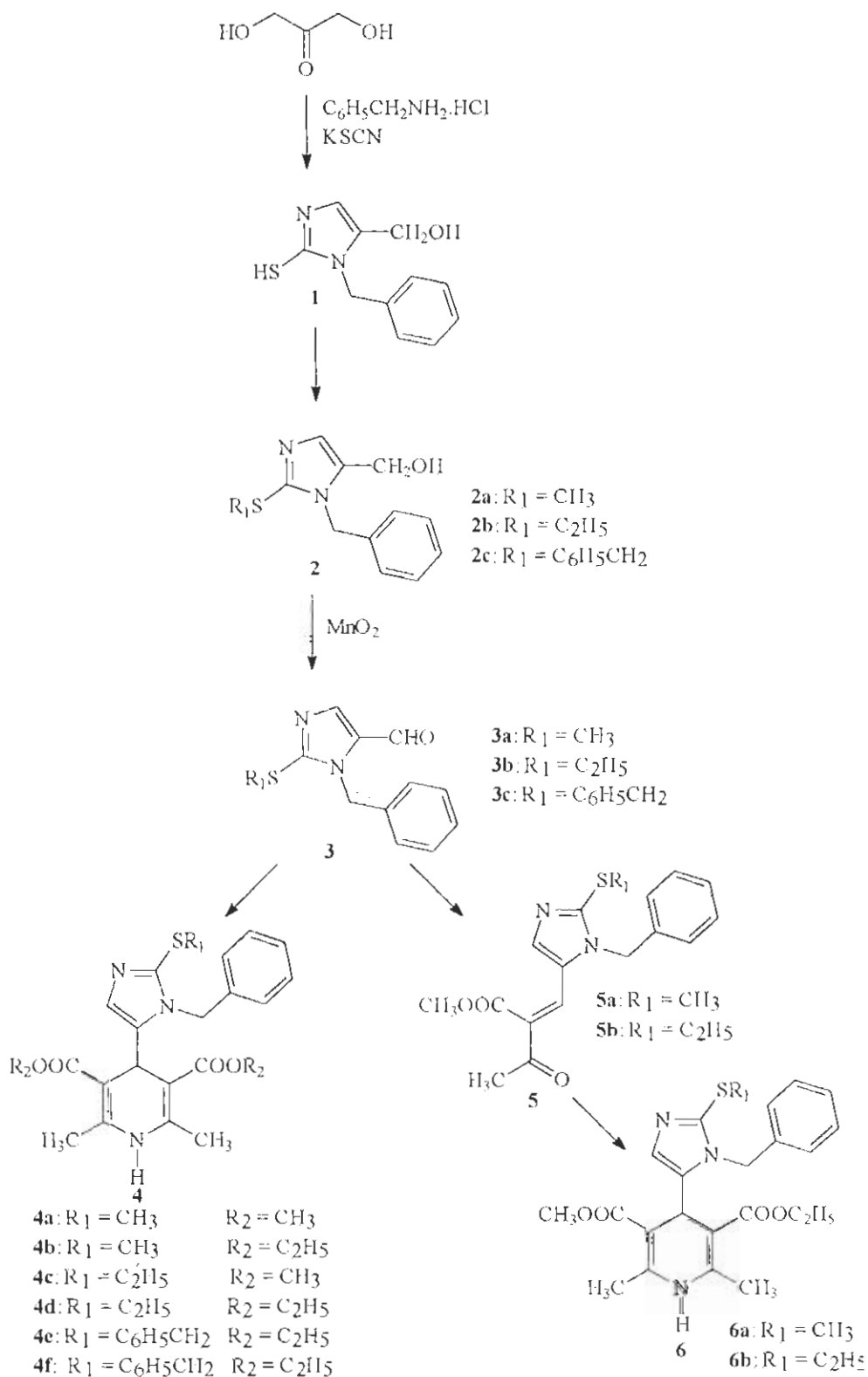
Introduction

The influx of extracellular Ca²⁺ through L-type potential dependent calcium channels is responsible for regulation of many physiological functions, including smooth and cardiac muscle contractions [1]. The discovery that 1,4-dihydropyridine class of calcium channel antagonists inhibits this Ca²⁺ influx represented a major therapeutic advance in the treatment of cardiovascular diseases [2]. The dihydropyridine class of compounds, of which nifedipine is the prototype, has been the subject of many structure activity relation studies [3,4]. Second generation analogues of nifedipine with superior bioavailability, longer duration of action and amenable to once a day dosage regimen are being actively investigated [5,6]. Changes in the substitution pattern at C-3, C-4 and C-5 positions of nifedipine alter activity and tissue selectivity [7-9]. In this paper we wish to report synthesis of nifedipine analogues in

which the 4-position of nifedipine has been substituted by 2-alkylthio-1-benzyl-5-imidazolyl according to Scheme 1.

1-Benzyl-5-hydroxymethyl-2-mercaptoimidazole (**1**) was synthesized from 1,3-dihydroxyacetone [9]. Reaction of **1** with alkyl halides gave corresponding substituted alkylthioimidazoles [10]. Oxidation of **2** with manganese dioxide in chloroform afforded 2-alkylthio-5-formyl-2-phenylmethylimidazoles (**3**) [10]. Symmetrical dihydropyridines (**4a-f**) were synthesized by classical Hantzsch condensation [11] in which the aldehyde **3** was reacted with alkyl acetoacetate and ammonium hydroxide in methanol. The asymmetrical dihydropyridines (**6a-b**) were synthesized in two steps by a modified Meyer procedure [11]. In the first step aldehyde **3** was condensed with methyl acetoacetate to afford the intermediate **5**. In the second step **5** was reacted with ethyl acetoacetate and ammonium hydroxide in methanol to get title compounds (**6a-b**).

*E-mail: fhadizadeh@yahoo.com



Scheme 1

Primarily pharmacological studies of the title compounds on rat and guinea-pig ileum have shown that they have good calcium channel antagonist activities, comparable to that of nifedipine. Details of the pharmacological studies will be reported elsewhere in the literature.

Experimental Section

Melting points were determined on a Gallenkamp capillary apparatus. $^1\text{H-NMR}$ spectra were run on a Bruker AC-80 spectrometer. Infrared spectra were recorded on a FT-IR Perkin-Elmer Paragon 1000 spectrophotometer.

benzyl-5-hydroxymethyl-2-methylthioimidazole (2a)

To a stirring suspension of **1** (5 g, 22.72 mmol) in methanol (372 mL) was added sodium hydroxide (1 N, 23.5 mL) at room temperature. The resulting mixture was stirred for 10 min until a clear pale yellow solution was obtained. Iodomethane (1.5 mL, 23.9 mmol) was added dropwise to the stirring solution and stirring continued overnight. After concentrating the solvent at reduced pressure, water (164 mL) was added to the residue and extracted with chloroform (65 mL \times 3). The chloroform was evaporated to give **2a** (4 g), yield 75%; m.p. 103-105°C (ethyl acetate); IR (KBr): 3200 cm^{-1} (OH); $^1\text{H-NMR}$ δ (CDCl_3): 7.38-6.99 (m, 6H, arom, H-C₄ imidazole), 5.28 (s, 2H, CH₂N), 4.45 (s, 2H, CH₂O), 3.5 (s, 1H, OH), 2.55 ppm (s, 3H, CH₃S).

1-Benzyl-2-ethylthio-5-hydroxymethylimidazole (2b)

2b was prepared similar to **2a**, yield 78%; m.p. 104-105°C (ethyl acetate); IR (KBr): 3200 cm^{-1} (OH); $^1\text{H-NMR}$ δ (CD_3OD): 7.63-7.07 (m, 6H, arom, H-C₄ imidazole), 5.58 (s, 2H, CH₂N), 4.63 (s, 2H, CH₂O), 3.07 (q, 2H, CH₂S, J=8.0 Hz), 1.39 (t, 3H, CH₃, J=8.0 Hz).

1-Benzyl-2-benzylthio-5-hydroxymethylimidazole (2c)

2c was prepared similar to **2a**, yield 83%; m.p. 108-110°C (ethyl acetate); IR (KBr): 3214 cm^{-1} (OH); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.81 (m, 11H, arom, H-C₄ imidazole), 5 (s, 2H, CH₂N), 4.83 (s, 2H, CH₂O), 4.12 ppm (s, 2H, CH₂S).

1-Benzyl-5-formyl-2-methylthioimidazole (3a)

A stirring suspension of **2a** (1 g, 4.27 mmol) and manganese dioxide (2.4 g, 27.6 mmol) in chloroform

(15 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and filtered on diatomaceous earth. The chloroform was evaporated at reduced pressure to give **3a** (0.8 g), yield 80%; m.p. 87-89°C (ethyl acetate); IR (KBr): 1661 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 9.6 (s, 1H, CHO), 7.76 (s, 1H, H-C₄ imidazole), 7.46-7.04 (m, 5H, arom), 5.49 (s, 2H, CH₂N), 2.68 ppm (s, 3H, CH₃S).

1-Benzyl-2-ethylthio-5-formylimidazole (3b)

3b was prepared similar to **3a**, yield 80%; m.p. 44-45°C; IR (KBr): 1661 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 9.6 (s, 1H, CHO), 7.78 (s, 1H, H-C₄ imidazole), 7.46-7.04 (m, 5H, arom), 5.49 (s, 2H, CH₂N), 3.27 (q, 2H, CH₂S, J=8 Hz), 1.39 ppm (t, 3H, CH₃, J=8 Hz).

1-Benzyl-2-benzylthio-5-formylimidazole (3c)

3c was prepared similar to **3a**, yield 86.4%; m.p. 66-68°C; IR (KBr): 1668 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 9.5 (s, 1H, CHO), 7.73 (s, 1H, H-C₄ imidazole), 7.32-6.97 (m, 10H, arom), 5.36 (s, 2H, CH₂N), 4.42 ppm (s, 2H, CH₂S).

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (4a)

A solution of ammonium hydroxide (25%, 0.41 mL) was added to a stirring solution of compound **3a** (0.3 g, 1.26 mmol) and methyl acetoacetate (0.29 g, 2.54 mmol) in methanol (5 mL). The mixture was protected from light and refluxed overnight. The methanol was evaporated at reduced pressure to give **4a** (0.164g), yield 30%; m.p. 205-207°C (ethyl acetate); IR (KBr): 1694 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.91 (m, 6H, arom, H-C₄ imidazole), 6.64 (bs, 1H, NH), 5.35 (s, 2H, CH₂N), 5.0 (s, 1H, H-C₄ dihydropyridine), 3.39 (s, 6H, CH₃O), 2.36 (s, 3H, CH₃S), 2.2 ppm (s, 6H, 2,6-CH₃).

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (4b)

4b was prepared similar to **4a**, yield 34%, m.p. 198-201°C (ethyl acetate); IR (KBr): 1694 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.35 (s, 2H, CH₂N), 5.15 (s, 1H, H-C₄ dihydropyridine), 4.3-3.7 (q, 4H, CH₂O, J=7.2 Hz), 2.33 (s, 3H, CH₃S), 2.17 (s, 6H, 2,6-CH₃), 1.11 ppm (t, 6H, CH₃, J=7.2 Hz).

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (4c)

It was prepared similar to **4a**, yield 56%; m.p. 157-158°C (ethyl acetate); IR (KBr): 1699 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.4 (s, 2H, CH₂N), 5.04 (s, 1H, H-C₄ dihydropyridine), 3.4 (s, 6H, CH₃O), 2.93 (q, 2H, CH₂S, J=7.2 Hz), 2.25 (s, 6H, 2,6-CH₃), 1.22 ppm (t, 3H, CH₃, J=7.2 Hz).

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (4d)

It was prepared similar to **4a**, yield 56%; m.p. 158-160°C (ethyl acetate); IR (KBr): 1695 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.4 (s, 2H, CH₂N), 5.1 (s, 1H, H-C₄ dihydropyridine), 4.15-3.74 (m, 4H, CH₂O), 2.84 (q, 2H, CH₂S, J=8 Hz), 2.21 (s, 6H, 2,6-CH₃), 1.33 ppm (m, 9H, CH₃).

Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-benzylthio-5-imidazolyl)-3,5-pyridine-dicarboxylate (4e)

It was prepared similar to **4a**, yield 78%; m.p. 200-203°C (ethyl acetate); IR (KBr): 1684 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.4 (s, 2H, CH₂N), 5.03 (s, 1H, H-C₄ dihydropyridine), 3.96 (s, 2H, CH₂S), 3.41 (s, 6H, CH₃O), 2.24 (s, 6H, 2,6-CH₃).

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-benzylthio-5-imidazolyl)-3,5-pyridine-dicarboxylate (4f)

It was prepared similar to **4a**, yield 50%; m.p. 178-180°C (ethyl acetate); IR (KBr): 1684 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.5- 6.2 (m, 12H, arom, H-C₄ imidazole, NH), 5.17 (s, 2H, CH₂N), 5.05 (s, 1H, H-C₄ dihydropyridine), 4.25-3.75 (m, 6H, CH₂S, CH₂O), 2.16 (s, 6H, 2,6-CH₃), 1.13 (t, 6H, CH₃, J=7.76 Hz).

Methyl 2-[(1-Benzyl-2-methylthio-5-imidazolyl)methylen]-3-oxobutanoate (5a)

A solution of **3a** (0.23 g, 1 mmol), methyl acetoacetate (0.116 g, 1 mmol), glacial acetic acid (0.1 mL), piperidine (0.04 mL) and dry benzene (20 mL) was refluxed for 2 h, during which the resultant water was removed via a Dean-Stark trap. The benzene was removed to give **5a** (0.2 g) as crude oil, yield 61%. IR

(KBr): 1700 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, =CH), 5.35 (s, 2H, CH₂N), 3.39 (s, 3H, CH₃O), 2.46 (s, 3H, CH₃) 2.36 (s, 3H, CH₃S).

Methyl 2-[(1-Benzyl-2-ethylthio-5-imidazolyl)methylen]-3-oxobutanoate (5b)

It was prepared similar to **5a**, yield 58% IR (KBr): 1700 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, =CH), 5.4 (s, 2H, CH₂N), 3.4 (s, 3H, CH₃O), 2.93 (q, 2H, CH₂S, J=7.2 Hz), 2.46 (s, 3H, CH₃), 1.22 ppm (t, 3H, CH₃, J=7.2 Hz).

5-Ethyl, 3-Methyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-methylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (6a)

To a stirring solution of **5a** (0.23 g, 1 mmol) in methanol (3 mL), ammonium hydroxide (25%, 0.19 mL) and ethyl acetoacetate (0.13 g, 1 mmol) was added. The solution was protected from light and refluxed overnight. After cooling, methanol was removed and the residue was purified by thin layer chromatography (chloroform: ethanol; 97:3) to give **6a** (0.19 g), yield 43%; m.p. 188-189°C (ethyl acetate); IR (KBr): 1693 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.34 (s, 2H, CH₂N), 5.07 (s, 1H, H-C₄ dihydropyridine), 3.95 (q, 2H, CH₂O, J=7.2 Hz), 3.34 (s, 3H, CH₃O), 2.34 (s, 3H, CH₃S), 2.17 (s, 6H, 2,6-CH₃), 1.22-0.85 (t, 3H, CH₃, J=7.2 Hz).

5-Ethyl, 3-Methyl 1,4-Dihydro-2,6-dimethyl-4-(1-benzyl-2-ethylthio-5-imidazolyl)-3,5-pyridinedicarboxylate (6b)

It was prepared from **5b** similar to **6a**, yield 44%; m.p. 188-189°C (ethyl acetate). IR (KBr): 1695 cm^{-1} (C=O); $^1\text{H-NMR}$ δ (CDCl_3): 7.4-6.6 (m, 7H, arom, H-C₄ imidazole, NH), 5.37 (s, 2H, CH₂N), 5.05 (s, 1H, H-C₄ dihydropyridine), 4 (q, 2H, CH₂O, J=7.2 Hz), 3.35 (s, 3H, CH₃O), 2.71 (q, 2H, CH₂S, J=8 Hz), 2.20 (s, 6H, 2,6-CH₃), 1.51-0.84 (m, 6H, CH₃).

Acknowledgements

The authors would like to thank the referees for their helpful comments. This work was partially supported by a grant from the Research Council of the Medical Sciences University of Mashhad.

References

1. Ramesh M, Matowe W.C., Knaus E.E. and Wolowyk M. *Drug Des. Discov.* **8**: 313 (1992).
2. Goldmann S. and Stoltefuss J. *Angew Chem. Int. Ed. Engl.* **30**: 1559 (1991).
3. Langs D.A., Strong P.D. and Triggle D.J. *J. Comput. Aided. Mol. Des.* **4**: 215 (1990).
4. Mager P.P., Coburn R.A., Solo A.J., Triggle D.J. and Rothe H. *Drug Des. Discov.* **8**: 273 (1992).
5. Arrowsmith J.E., Campbell S.F., Cross P.E., Stubbs J.K., Burges R.A., Gardiner D.G. and Blackburn K.J. *J. Med. Chem.* **29**: (1986).
6. Baldwin J.J. and Sweet C.S. *Ann. Rept. Med. Chem.* **23**: 59 (1988).
7. Vo D, Matowe W.C., Ramesh M, Iqbal N, Wolowyk M.W., Howlett S.E. and Knaus E.E. *J. Med. Chem.* **38**: 2851 (1995).
8. Amini M., McEwen C.A. and Knaus E.E. *ARKIVOC*, **Vol. 2**, Part 1, ms 0134 (2001).
9. Derakhshandeh K. and Zarghi A., *British Pharmaceutical Conference Abstract Book* **233** (2001).
10. Denner M.D., Zhang L.H. and Rapport H. *J. Org. Chem.* **58**: 1159 (1993).
11. Shafiee A. and Hadizadeh F. *J. Heterocyclic Chem.* **34**: 549 (1997).
12. Shafiee A., Dehpour A.R., Hadizadeh and Azimi M. *Pharm. Acta Helv.* **73**: 75 (1998).