

Synthesis and Calcium-channel Antagonist Activity of 4-Imidazolyl-1,4-dihydropyridines

F. POURMORAD, F. HADIZADEH AND A. SHAFIEE

Department of Medicinal Chemistry, Faculty of Pharmacy, The Medical Sciences University of Tehran, Tehran, Iran

Abstract

The *o*-nitrophenyl group at position 4 of dihydropyridine of nifedipine analogues was replaced by 1-methylimidazole. These compounds were evaluated as calcium-channel antagonists using the high K⁺ contraction of guinea-pig ileal longitudinal smooth muscle.

The results for the symmetrical esters showed that increasing the length of methylene chain of ester more than 3 units decreases activity. For cyclic esters, cyclopropylmethyl ester was more active than cyclohexylmethyl ester.

Our results revealed two compounds with activities similar to the reference drug nifedipine; the symmetrical cyclopropylmethyl ester, and the asymmetrical phenethyl ethyl derivatives were the most potent antagonists tested.

The influx of extracellular Ca²⁺ through the L-type potential-dependent calcium channel is responsible for the regulation of many physiological functions, including smooth and cardiac muscle contraction (Ramesh et al 1992). The discovery that the 1,4-dihydropyridine class of calcium-channel antagonists inhibits this Ca²⁺ influx represented a major therapeutic advance in the treatment of cardiovascular diseases such as hypertension, angina pectoris, and other spastic smooth muscle disorders (Triggle 1992). The dihydropyridine class of compounds, of which nifedipine is the prototype, has been the subject of many structure-activity relationship studies (Langs et al 1990; Mager et al 1992). Second-generation analogues of nifedipine with superior bioavailability, slower onset and longer duration of action, and amenable to a once-a-day dosage regimen are being actively investigated (Arrowsmith et al 1986; Baldwin & Sweet 1988). Changes in the substitution pattern at the C-3, C-4 and C-5 positions of nifedipine alter activity and tissue selectivity (Janis & Triggle 1983; Spedding et al 1990; Vo et al 1995). It was therefore of interest to determine the effect that selected C-3 or C-5 substituents, in conjunction with C-4 1-methyl-5-imidazolyl substituents, had on calcium-channel antagonist activity. We previously reported the synthesis and calcium-channel antagonist

activity of nifedipine analogues containing nitroimidazolyl substituents (Shafiee et al 1996); we now report the synthesis and calcium-channel antagonist activities of alkyl, cycloalkyl and arylalkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-imidazolyl)-3,5-pyridinedicarboxylates.

Material and Methods

Chemical procedures

Reaction of the alcohol **1** with 2,2,6-trimethyl-4H-1,3-dioxine-4-one (**2**) afforded acetoacetic esters (**3**) in 76-92% yield (Clemens & Hyatt 1985). The symmetrical analogues **5a-r** were prepared in 43-95% yield by the classical Hantzsch condensation (Hantzsch 1882) in which 1-methylimidazole-5-carboxaldehyde **4** (Denner et al 1993) was reacted with the acetoacetic ester **3** and ammonium hydroxide (Figure 1). The asymmetrical analogues **8a-j** were synthesized by a procedure reported by Meyer et al (1981, Figure 1).

The compounds were characterized by ¹H nuclear magnetic resonance, infra-red spectroscopy and microanalysis. The purity of all products was determined by thin-layer chromatography using several solvent systems of different polarity.

Evaluation of pharmacological activity

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 and segments of 2-cm length were

Correspondence: A. Shafiee, Department of Medicinal Chemistry, Faculty of Pharmacy, The Medical Sciences University of Tehran, Tehran, Iran.

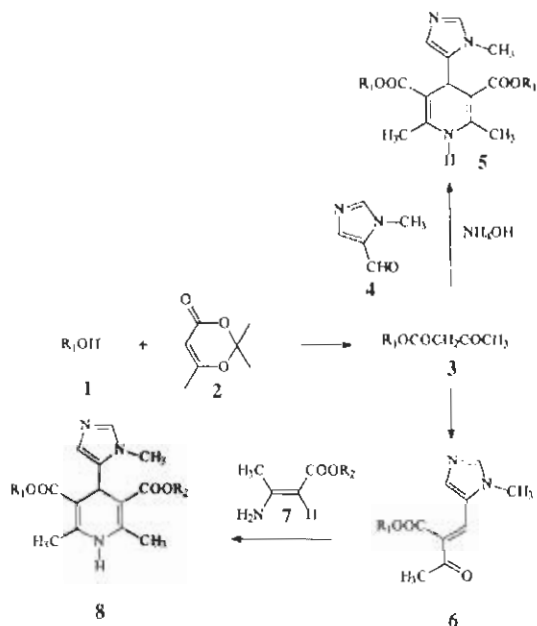


Figure 1. Synthesis of 4-imidazolyl-1,4-dihydropyridines.

mounted under a resting tension of 400–500 mg. The segments were maintained at 37°C in a 20-mL jacketed organ bath containing oxygenated (100% O₂) physiological saline of the following (mM)

composition: NaCl 137, CaCl₂ 1.8, KCl 2.7, MgSO₄ 1.1, NaH₂PO₄ 0.4, NaHCO₃ 12 and glucose 5. The muscles were equilibrated for 1 h with a solution change every 15 min. The contractions were recorded with a force displacement transducer (F-50) on a Narco physiograph. All compounds were dissolved in dimethylsulphoxide and the same volume of the solvent was used as a control in the absence of the test compound. The contractile response was taken as the 100% value for the tonic (slow) component of the response. Test compounds were cumulatively added after the dose–response for KCl was determined. Test compound-induced relaxation of contracted muscle was expressed as percent of control. The IC₅₀ values were graphically determined from the concentration–response curves (Triggle et al 1979; Rovnyak et al 1992).

Results and Discussion

The calcium-channel antagonist activity (IC₅₀) of **5a–r** and **8a–j** was determined as the concentration needed to produce 50% relaxation of contracted guinea-pig ileal longitudinal smooth muscle. The test results are presented in Tables 1 and 2. Comparison of the activities of symmetrical aliphatic

Table 1. Physical properties and calcium-channel antagonist activities of symmetrical esters.

Compound	R ₁	mp (°C)	Yield (%)	IC ₅₀ ^a (M)
5a	methyl	241–242	67	2.22 ± 0.65 × 10 ⁻⁶
5b	ethyl	220–221	60	0.50 ± 0.71 × 10 ⁻⁶
5c	propyl	196–197	43	3.35 ± 0.90 × 10 ⁻⁷
5d	isopropyl	252–253	54	5.33 ± 0.65 × 10 ⁻⁷
5e	<i>n</i> -butyl	156–157	46	5.36 ± 0.81 × 10 ⁻⁶
5f	iso-butyl	239–240	43	4.51 ± 0.21 × 10 ⁻⁶
5g	<i>t</i> -butyl	272–273	71	4.44 ± 0.51 × 10 ⁻⁶
5h	<i>n</i> -pentyl	146–147	95	2.59 ± 0.42 × 10 ⁻⁶
5i	cyclopropylmethyl	190–191	67	8.69 ± 0.80 × 10 ⁻⁸
5j	cyclopentylpropyl	201–202	95	2.38 ± 1.01 × 10 ⁻⁷
5k	cyclohexyl	194–195	95	2.95 ± 1.00 × 10 ⁻⁶
5l	cyclohexylmethyl	190–191	80	1.86 ± 1.08 × 10 ⁻⁵
5m	cyclohexylethyl	194–195	88	1.63 ± 0.22 × 10 ⁻⁵
5n	cyclohexylpropyl	212–213	67	1.03 ± 0.23 × 10 ⁻⁷
5o	cyclohexylbutyl	206–207	95	4.53 ± 0.13 × 10 ⁻⁵
5p	phenylethyl	215–216	82	2.69 ± 0.80 × 10 ⁻⁶
5q	phenylpropyl	163–164	90	1.51 ± 0.62 × 10 ⁻⁶
5r	phenylbutyl	154–155	80	4.44 ± 0.82 × 10 ⁻⁶
	Nifedipine			1.40 ± 0.20 × 10 ⁻⁸

^aMean ± s.d., n = 6.

Table 2. Physical properties and calcium-channel antagonist activity of asymmetrical esters.

Compound	R ₁	R ₂	mp (°C)	Yield (%)	IC ₅₀ ^a (M)
8a	ethyl	methyl	236–237	33	2.88 ± 0.22 × 10 ⁻⁶
8b	<i>n</i> -butyl	methyl	183–184	88	4.11 ± 0.81 × 10 ⁻⁶
8c	<i>n</i> -pentyl	methyl	195–196	87	5.75 ± 0.93 × 10 ⁻⁷
8d	<i>n</i> -pentyl	ethyl	193–194	89	7.54 ± 1.08 × 10 ⁻⁷
8e	cyclohexylmethyl	ethyl	204–205	75	2.64 ± 0.88 × 10 ⁻⁶
8f	benzyl	methyl	160–161	67	3.63 ± 0.82 × 10 ⁻⁵
8g	benzyl	ethyl	173–174	50	1.36 ± 0.62 × 10 ⁻⁶
8h	phenylethyl	ethyl	191–192	50	4.45 ± 0.66 × 10 ⁻⁸
8i	phenylpropyl	methyl	130–131	28	2.46 ± 0.41 × 10 ⁻⁶
8j	phenylpropyl Nifedipine	ethyl	144–145	89	2.91 ± 0.91 × 10 ⁻⁶ 1.40 ± 0.20 × 10 ⁻⁸

^aMean ± s.d., n = 6.

esters indicates that increasing the length of the ester chain in C-3, C-5 more than one methylene unit increases activity. However, increasing the length of the chain more than three units decreases activity, that is, the potency sequence observed for these compounds was in the order propyl = isopropyl > ethyl > methyl > butyl. Comparison of the activities of esters **5i**, **5l** indicates the effect of cycloalkyl ring size on potency, that is, cyclopropyl **5i** > cyclohexyl **5l**. Finally, the results show that two compounds (**5i**, **8h**) had activities similar to nifedipine. In addition, these compounds were the most active.

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References

- Arrowsmith, J. E., Campbell S. F., Cross P. E., Stubbs, J. K., Burges, R. A., Gardiner, D. G., Blackburn, K. J. (1986) Long-acting dihydropyridine calcium antagonists. 1,2-Alkoxyethyl derivatives incorporating basic substituents. *J. Med. Chem.* 29: 1696–1702
- Baldwin, J. J., Sweet, C. S. (1988) Antihypertensive agents. *Ann. Rept. Med. Chem.* 23: 59–68
- Clemens, R. J., Hyatt, H. A. (1985) Acetoacetylation with 2,2,6-trimethyl-4H-1,3-dioxin-4-one: a convenient alternative to diketene. *J. Org. Chem.* 50: 2431–2435
- Denner, J. M., Zhang, L. H., Rapoport, H. (1993) An effective chiroselective synthesis of (+)-pilocarpine from L-aspartic acid. *J. Org. Chem.* 58: 1159–1166
- Hantzsch, A. (1882) Ueber die Synthese pyridinartiger Verbindungen aus Acetessigsäure und Aldehydammoniak. *Justus Liebigs Ann. Chem.* 215: 1–82
- Janis, R. A., Triggle, D. J. (1983) New developments in Ca²⁺ channel antagonists. *J. Med. Chem.* 26: 775–785
- Langs, D. A., Strong, P. D., Triggle, D. J. (1990) Receptor model for the molecular basis of tissue selectivity of 1,4-dihydropyridine calcium channel drugs. *J. Comput. Aided Mol. Des.* 4: 215–230
- Mager, P. P., Coburn, R. A., Solo, A. J., Triggle, D. J., Rothe, H. (1992) QSAR, diagnostic statistics and molecular modeling of 1,4-dihydropyridine calcium channel antagonists: a difficult road ahead. *Drug Des. Discov.* 8: 273–289
- Meyer, H., Bossert, F., Wehinger, E., Stoepel, K., Vater, W. (1981) Synthese und vergleichende pharmakologische Untersuchungen von 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarbonsäureestern mit nicht-identischen Esterfunktionen. *Arzneim. Forsch.* 31: 407–409
- Ramesh, M., Matowe, W. C., Knaus, E. E., Wolowyk, M. W. (1992) Synthesis and calcium channel antagonist activity of dialkyl 1,4-dihydro-2,6-dimethyl-4-[3-(1-methoxy-carbonyl-1,4-substituted-1,4-dihydro-pyridyl)]-3,5-pyridinedicarboxylates. *Drug Des. Discov.* 8: 313–323
- Rovnyak, G. C., Atwal, K. S., Hedberg, A., Kimball, S. D., Moreland, S., Gougoutas, J. Z., O'Reilly, B. C., Schwartz, J., Malley, M. F. (1992) Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. *J. Med. Chem.* 35: 3254–3263
- Shafiee, A., Miri, R., Dehpour, A. R., Soleymani, F. (1996) Synthesis and calcium-channel antagonist activity of nifedipine analogues containing nitroimidazolyl substituent in guinea-pig ileal smooth muscle. *Pharm. Sci.* 2: 541–543

- Spedding, M., Fraser, S., Clark, B., Patmore, L. (1990) Factors modifying the tissue calcium selectivity of calcium antagonists. In: Glossmann, H. (ed.) *New Therapeutic Uses of Calcium Channel Blockers*. *J. Neural Transm.* 31 (Suppl.): 5-16
- Triggle, D. G. (1992) Biochemical and pharmacologic differences among calcium channel antagonists: clinical implication. In: Epstein, M. (ed.) *Calcium Antagonists in Clinical Medicine*. Hanley & Belfus, Philadelphia, pp 1-29
- Triggle, C. R., Swamy, V., Triggle, D. J. (1979) Calcium antagonists and contractile responses in vas deferens and guinea pig ileal smooth muscle. *Can. J. Physiol. Pharmacol.* 57: 804-818
- Vo, D., Matowe, W. C., Ramesh, M., Iqbal, N., Wolowyk, M. W., Howlett, S. E., Knaus, E. E. (1995) Syntheses, calcium channel agonist-antagonist modulation activities and voltage-clamp studies of isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridylpyridine-5-carboxylate racemates and enantiomers. *J. Med. Chem.* 38: 2851-2859