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Selective inhibitory action of Biginelli-type dihydropyrimidines on depolarization-induced arterial smooth muscle contraction

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Keywords
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Abstract

Objectives Dihydropyridine calcium channel blockers have some disadvantages such as light sensitivity and relatively short plasma half-lives. Stability of dihydropyrimidines analogues could be of advantage, yet they remain less well characterized. We aimed to test four newly synthesized Biginelli-type dihydropyrimidines for their calcium channel blocking activity on rat isolated aorta.

Methods Dihydropyrimidines (compounds **A**–**D**) were prepared by the Biginelli-like three-component condensation of benzaldehydes with urea/thiourea and dimethyl or diethyl acetone-1,3-dicarboxylate, and their physicochemical properties and effects on depolarization-induced and noradrenaline-induced contractions of rat isolated aorta were evaluated.

Key findings Dihydropyrimidines **A** and **C** blocked KCl-induced contraction only weakly (–log(IC50) = 5.03 and 3.73, respectively), while dihydropyrimidine **D** (–log(IC50) = 7.03) was almost as potent as nifedipine (–log(IC50) = 8.14). Washout experiments revealed that dihydropyrimidine **D** may bind strongly to the L-type calcium channel or remains bound to membrane. All tested dihydropyrimidines only marginally inhibited noradrenaline-induced contractions of rat isolated aorta (20% reduction of noradrenaline E_{max}), indicating a more selective action on L-type calcium channel than nifedipine with 75% inhibition of noradrenaline E_{max} at 10^{-4} M nifedipine).

Conclusions Compounds **A** and, particularly, **D** are potent calcium channel blockers *in vitro*, with a better selectivity in inhibiting depolarization-induced arterial smooth muscle contraction than nifedipine.

Introduction

Dihydropyridine derivates are the largest group of calcium antagonists used in the treatment of cardiovascular diseases. The high affinity of dihydropyridines for channels responsible for the L-type calcium currents have served for study of channel structure and function.[1–3] However, all compounds of this class are characteristic by their high photosensitivity.[4–6] Generally, the dihydropyridines with an *ortho*-nitro group on the phenyl ring (nifedipine) are light-sensitive because a nitroso radical generated from nitro group by light irradiation removes hydrogen from the 1,4-dihydropyridine moiety causing aromatization of the heterocyclic ring,[7] which leads to subsequent irreversible structural changes[8,9] and loss of potency or therapeutic inactivity.[10] The dihydropyridines with a *meta*-nitrophenyl substituent are far less sensitive to light, although their pharmacological activity is usually less potent than that of the *ortho*-substituted compounds.[4,7] By contrast, dihydropyrimidines with *ortho*-nitro groups are stable against sunlight, because dehydrogenation is more difficult. Sunlight stability and structural similarity of dihydropyrimidines with dihydropyridines of the Hantzsch type[11] has led to the development of a variety of dihydropyrimidines that have been found to exhibit a similar pharmacological profile to dihydropyridine calcium channel modulators of the nifedipine type.[12,13]

Biginelli-type dihydropyrimidines are aza-analogues of dihydropyridines of the Hantzsch type and their antiviral,[14] antimitotic,[15] antibacterial and anti-inflammatory[16] effects have been described. In addition, they also act as

melanin-concentrating hormone receptor (MCH1-R) antagonists,[17] chemical modulators of heat shock protein 70 (Hsp 70),[18] hepatitis B replication inhibitors[19] and inhibitors of fatty acid transporters.[20]

Recently we have explored the Biginelli-like three-component condensation of benzaldehydes with urea/thiourea and dimethyl or diethyl acetone-1,3-dicarboxylate.[21] X-ray diffraction of the dimethyl ester revealed that its molecular conformation possesses, in contrast to the diethyl analogue, a favourable spatial arrangement in terms of Triggle dihydropyridine receptor binding requirements. Thus, these findings stimulated us to extend our series by producing derivatives with a 4-phenyl group bearing nitro and chloro substituents in *ortho*- or *meta*-positions. As seen, the selected functionality pattern is related to known dihydropyridine calcium channel blockers. However, synthesis of the target derivatives could not be carried out according to our solvent-free protocol due to solidifying reaction mixture. Consequently, a time-consuming treatment of reactants in refluxing isopropanol under concentrated HCl catalysis had to be used.

The aim of our study was to describe the characteristics of four newly synthesized previously uncharacterized Biginelli type dihydropyrimidines, whose molecular conformation is in accordance with the Triggle dihydropyridine receptor binding model,[22] and to obtain novel pharmacological data regarding their activity and selectivity of action on depolarization versus noradrenaline-induced vascular smooth muscle contraction in comparison with the reference calcium channel blocker nifedipine. Data we obtained on these novel compounds show that some exhibit a similar efficacy to that of the reference drug, with an even better selectivity for the inhibition of depolarization-induced contraction.

Materials and Methods

General procedure for synthesis of tested substances

4-Aryl-6-methoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (compounds **A**–**D**) were prepared as follows: a solution composed of aldehyde (10 mmol), dimethyl acetone-1,3-dicarboxylate (10 mmol) and urea or thiourea (12 mmol) in isopropanol (30 ml) was refluxed for 48 h. After removal of the solvent, the oily residue was dissolved in ethanol and left to crystallize. The resulting product was then recrystallized from ethanol. All the compounds reported here gave satisfactory CHN microanalyses.

Studies on isolated vessels

Noradrenaline (norepinephrine) and nifedipine were obtained from Sigma Aldrich (Bratislava, Slovakia). We used 12-week-old male Wistar rats. All animal care and experimental procedures were approved by the Ethics Committee of the Faculty of Pharmacy, Comenius University on September 21, 2009 and were approved by The State Veterinary and Food Administration of the Slovak Republic on November 10, 2009 (file number 2485/09221). Rats were killed by asphyxiation by means of CO_2. The thoracic aorta was removed, cleared of connective tissue and fat and cut into rings (approximately 2 mm length). Rings were mounted under a tension of 20 mN in a 15 ml organ bath containing Krebs–Henseleit solution (composition in mM: 122 NaCl, 5.9 KCl, 15 $NaHCO_3$, 11 glucose, 1.25 $CaCl_2$, 1.2 $MgCl_2$), which was kept at 37 C and aerated with O_2. Indometacin (10^{-5} M) and L-NAME 3.10^{-4} M) were added to the solution to exclude a contribution of prostaglandins and endothelial nitric oxide to contractile responses measured. Arteries were equilibrated for 45 min, including washes with fresh buffer every 15 min. After stabilization, aortic rings were incubated either with three different concentrations of four different dihydropyrimidines (at 10^{-6}, 10^{-5} or 10^{-4} M) or dimethyl sulfoxide (DMSO, final concentration 0.05% v/v) for 30 min. Subsequently, aorta contractions induced by a membrane-depolarizing solution containing 101 mM potassium (composition in mM: 27 NaCl, 101 KCl, 15 $NaHCO_3$, 11 glucose, 1.25 $CaCl_2$: 1.2 $MgCl_2$) or noradrenaline (10^{-9} M to 10^{-5} M) were measured. When used, drugs continued to be present in the organ baths along with contractile agents in the same concentrations as during drug pre-incubation.

Data are reported as mean ± SD. Statistical significance was evaluated by analysis of variance (GraphPad Instat; GraphPad Inc., La Jolla, USA). E_{max} (maximal response to noradrenaline), pD2 (negative log of the concentration producing half the maximal effect) and IC50 (concentration inducing half-maximal inhibition of KCl-induced contraction) values were calculated using GraphPad Prism (GraphPad Inc., La Jolla, USA).

Results

Characteristics of synthesized compounds

Obtained analytical and spectral data for the synthesized compounds **A**–**D** are in accordance with presented structures and are given below.

A: Mp 213–215°C (EtOH), yield 40%; IR (KBr) ν_{max} 3380 (NH); 1731 (COO); 1700 (COO + NCON); 1653 (C = C); 1358 (NO_2)/cm; ^{1}H NMR (DMSO-d_6) δ3.37 (s, 3H, CH_3 ester-5); 3.64 (s, 3H, CH_3 ester); 3.68 (d, J = 17.1 Hz, 1H, CH_2); 3.89 (d, J = 17.1 Hz, 1H, CH_2); 5.85 (d, J = 3.0 Hz, 1H, H-4); 7.53 (t, 1H, H-4′); 7.74 (br s, 2H, H-5′ + H-6′); 7.90 (d, 2H, H-3′ + NH-3); 9.54 (s, 1H, NH-1); ^{13}C NMR (DMSO-d_6) $\delta\delta$ 36.7 (CH2); 49.1 (CH_3 ester-5); 51.1 (CH_3 ester); 52.0 (CH-4); 99.8 (C-5); 124.1 (CH-3′); 129.07 (CH-4′/6′); 129.1 (CH-6′/4′); 134.2 (CH-5′); 138.6 (C-1′); 146.0 (C-2′/C-6); 147.4 (C-6/C-2′); 151.2 (NCON); 164.8 (COO-5); 169.2 (COO).

Table 1 Effect of dihydropyrimidines **A**–**D** and nifedipine on KCl-induced contraction of isolated aorta

	KCl-induced contraction (mN)						
		Drug			Washout		
	Control	10^{-6} M	10^{-5} M	10^{-4} M	10^{-6} M	10^{-5} M	10^{-4} M
Drug **A**	8.9 ± 5.18	7.65 ± 4.94	4.12 ± 2.46*	0.93 ± 0.74*	10.75 ± 4.54	13.15 ± 6.56#	7.69 ± 4.49#
Drug **B**	10.74 ± 3.90	9.62 ± 4.48	9.50 ± 4.14	5.70 ± 2.43	11.25 ± 5.03	11.86 ± 4.04	10.78 ± 4.99#
Drug **C**	12.92 ± 5.98	11.44 ± 1.83	8.06 ± 3.63	1.83 ± 1.42*	13.70 ± 2.41	12.32 ± 4.31	9.70 ± 5.43#
Drug **D**	12.40 ± 3.36	3.25 ± 1.80*	1.41 ± 1.95*	0.50 ± 0.55*	15.00 ± 5.50	4.77 ± 3.98*#	0.86 ± 0.37*
Nifedipine	10.07 ± 6.17	1.62 ± 1.46*	0.66 ± 0.38*	0.07 ± 0.14*	1.76 ± 1.76	0.69 ± 0.56	0.19 ± 0.25*

*$P < 0.05$ vs control, #$P < 0.05$ washout vs drug.

B: Mp 196–198°C (EtOH), yield 43%; IR (KBr) ν_{max} 3389 (NH); 1738 (COO); 1710 (COO + NCON); 1646 (C = C); 1355 (NO_2)/cm; ^{1}H NMR (DMSO-d_6) δ: 3.49 (s, 3H, CH_3 ester-5); 3.65 (d, J = 16.8 Hz, 1H, CH_2); 3.66 (s, 3H, CH_3 ester); 3.89 (d, J = 16.8 Hz, 1H, CH_2); 5.38 (d, J = 3.3 Hz, 1H, H-4); 7.66 (t, 1H, H-5′); 7.79 (d, 1H, H-6′); 7.99 (br s, 1H, NH-3); 8.14 (d, 1H, H-4′); 8.20 (br s, 1H, H-2′); 9.49 (s, 1H, NH-1); ^{13}C NMR (DMSO-d_6) δ 36.8 (CH2); 51.1 (Me ester-5); 52.0 (Me ester); 53.5 (CH-4); 99.6 (C-5); 121.3 (CH-2′/CH-4′); 122.6 (CH-4′/CH-2′); 130.3 (CH-5′/CH-6′); 133.2 (CH-6′/CH-5′); 146.0; 146.2; 148.0 (C-1′/C-3′/C-6); 151.5 (NCON); 165.1 (COO-5); 169.1 (COO).

C: Mp 168–171°C (EtOH), yield 32%; IR (KBr) ν_{max} 3380 (NH); 1736 (COO); 1703 (COO + NCON); 1657 (C = C)/cm; ^{1}H NMR (DMSO-d_6) δ: 3.43 (s, 3H, CH_3 ester-5); 3.57 (d, J = 16.5 Hz, 1H, CH_2); 3.66 (s, 3H, CH_3 ester); 3.93 (d, J = 16.5 Hz, 1H, CH_2); 5.66 (d, J = 3.6 Hz, 1H, H-4); 7.31 (m, 2H, H_{Ar}); 7.41 (dt,1H, H_{Ar}); 7.56 (dd, 1H, H_{Ar}); 7.82 (br s, 1H, NH-3); 9.42 (s, 1H, NH-1).

D: Mp 221–223°C (EtOH), yield 28%; IR (KBr) ν_{max} 3333 (NH); 1744 (COO); 1705 (COO + NCON); 1656 (C = C); 1357 (NO_2)/cm; ^{1}H NMR (DMSO-d_6) δ: 3.34 (s, 3H, CH_3 ester-5); 3.64 (s, 3H, CH_3 ester); 3.70 (d, J = 16.8 Hz, 1H, CH_2); 3.95 (d, J = 16.8 Hz, 1H, CH_2); 5.99 (d, J = 3.3 Hz, 1H, H-4); 7.57 (t, 1H, H-4′); 7.69 (d, 1H, H-6′); 7.79 (t, 1H, H- 5′); 7.96 (d, 1H, H-3′); 9.76 (br s, 1H, NH); 10.61(d, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.0 (CH2); 48.9 (CH_3 ester-5); 51.3 (CH_3 ester); 52.0 (CH-4); 101.5 (C-5); 124.3 (CH-3′); 129.4 (CH-4′/CH-6′); 129.5 (CH-6′/CH-4′); 134.2 (CH-5′); 137.5 (C-1′); 142.2 (C-2′/C-6); 147.2 (C-6/C-2′); 164.6 (COO-5); 169.1 (COO); 174.2 (C = S).

Studies on isolated vessels

To test the selective inhibitory effect of distinct dihydropyrimidines on L-type calcium-channel-mediated contraction, we evaluated the effects of dihydropyrimidines on depolarization-induced (101 mM KCl) and noradrenaline-induced contractions of rat isolated aorta. We determined that DMSO, a vehicle of the drugs, had no effect on KCl-induced or noradrenaline-induced contractions at the final concentration of 0.05%. Among the substances tested, derivative **D** was the most effective in inhibiting L-type calcium-channel-mediated contractions, effectively blocking KCl-induced contractions (Table 1) with an estimated IC50 value comparable with that of nifedipine (Table 2). Dihydropyrimidine **A** was less effective in blocking depolarization-induced contraction, being significantly active at concentrations 10^{-5} M and 10^{-4} M. Compound **C** only inihibited KCl-induced contraction at 10^{-4} M. Compound **B** showed only an insignificant inhibitory trend at lower millimolar range (Table 1). The IC50 values for KCl-induced contraction are listed in Table 2. Compared to the reference drug nifedipine, compounds **A**, **B** and **C** had weaker calcium channel antagonist activity. Derivative **D** was the most active compound, causing 50% inhibition of rat aorta contraction at 9.38×10^{-8} M, which was comparable with the reference drug nifedipine (Table 2).

Table 2 Effect of tested dihydropyrimidines (**A**–**D**) and nifedipine on depolarization-induced aorta contraction

Drug	IC50 (mol/l)	–Log(IC50)
A	9.41×10^{-6}	5.03
B	$>1.00 \times 10^{-4}$	<4.00
C	5.81×10^{-5}	4.24
D	9.38×10^{-8}	7.03
Nifedipine	7.28×10^{-9}	8.14

IC50, concentration inducing half-maximal inhibition of KCl-induced contraction.

To determine whether the vasodilatory effect of the substance was reversible, rings incubated with distinct dihydropyrimidines were washed after recording KCl contraction and challenged again with KCl. We observed that with respect to examined heterocycles **A**, **B** and **C**, KCl-induced contraction could be restored after washout even at the highest concentration of drugs used, and only the highest concentration of sample **D** (10^{-4} M) could not be significantly reversed by washout (Table 1). KCl-induced contractions remained partly inhibited after washing rings incubated with the two higher concentrations of derivative **D**. The effect of substance **D** was comparable with that of nifedipine on depolarization-

Table 3 Effect of dihydropyrimidines (**A**–**D**) and nifedipine on noradrenaline-induced contraction

Norepinephrine		
	E_{max}	pD_2
Drug **A**		
Control	17.90 ± 3.30	6.99 ± 0.27
10^{-6} M	17.98 ± 3.35	7.01 ± 0.32
10^{-5} M	16.65 ± 2.11	6.83 ± 0.28
10^{-4} M	14.48 ± 1.87	6.41 ± 0.20*
Drug **B**		
Control	19.16 ± 3.17	7.28 ± 0.51
10^{-6} M	17.06 ± 5.60	7.08 ± 0.36
10^{-5} M	16.65 ± 4.05	6.97 ± 0.49
10^{-4} M	15.33 ± 3.60	6.69 ± 0.24*
Drug **C**		
Control	20.05 ± 2.51	7.25 ± 0.21
10^{-6} M	18.25 ± 4.73	7.12 ± 0.44
10^{-5} M	17.03 ± 2.16	6.93 ± 0.39
10^{-4} M	16.59 ± 3.61	6.47 ± 0.12*
Drug **D**		
Control	19.47 ± 4.39	7.03 ± 0.34
10^{-6} M	17.02 ± 6.64	6.67 ± 0.27
10^{-5} M	14.83 ± 7.02	6.56 ± 0.28*
10^{-4} M	15.42 ± 7.12	6.59 ± 0.26
Nifedipine		
Control	17.61 ± 3.93	6.99 ± 0.33
10^{-6} M	15.62 ± 3.93	6.44 ± 0.10*
10^{-5} M	15.39 ± 4.15	6.45 ± 0.18*
10^{-4} M	6.14 ± 2.85*	6.06 ± 0.37*

E_{max}, maximal response to noradrenaline; pD_2, negative log of the concentration producing half the maximal effect. *$P < 0.05$ vs control.

induced isolated aorta contraction, the main difference being that even the effect of the lowest concentration of nifedipine (10^{-6} M) contraction could not be reversed by washing.

To characterize the effect of synthesized dihydropyrimidines on inhibition of noradrenaline-induced contraction, concentration–response curves of noradrenaline were obtained in the presence or absence of different concentration of each substance (10^{-6} M to 10^{-4} M).

The concentrations of noradrenaline inducing a half-maximal response, with respective pD2 values, are listed in Table 3. Maximal response (E_{max}) to noradrenaline was only slightly and insignificantly decreased by the highest concentrations of derivatives **A** and **B** (by 19.1% and 20,0%, respectively, $P > 0.05$, Table 3) while it was markedly reduced by nifedipine (by 65.1%, $P < 0.05$, Table 3). Concentration–response curves were shifted to the right by the higher concentration of all substances tested (Figure 1 and Table 3). Surprisingly, compared with the newly synthesized dihydropyrimidines, nifedipine was the least selective drug for inhibiting depolarization-induced contraction compared with noradrenaline-induced contraction, producing the largest decrease of E_{max} and a rightward concentration–effect curve shift for noradrenaline (Figure 1 and Table 3).

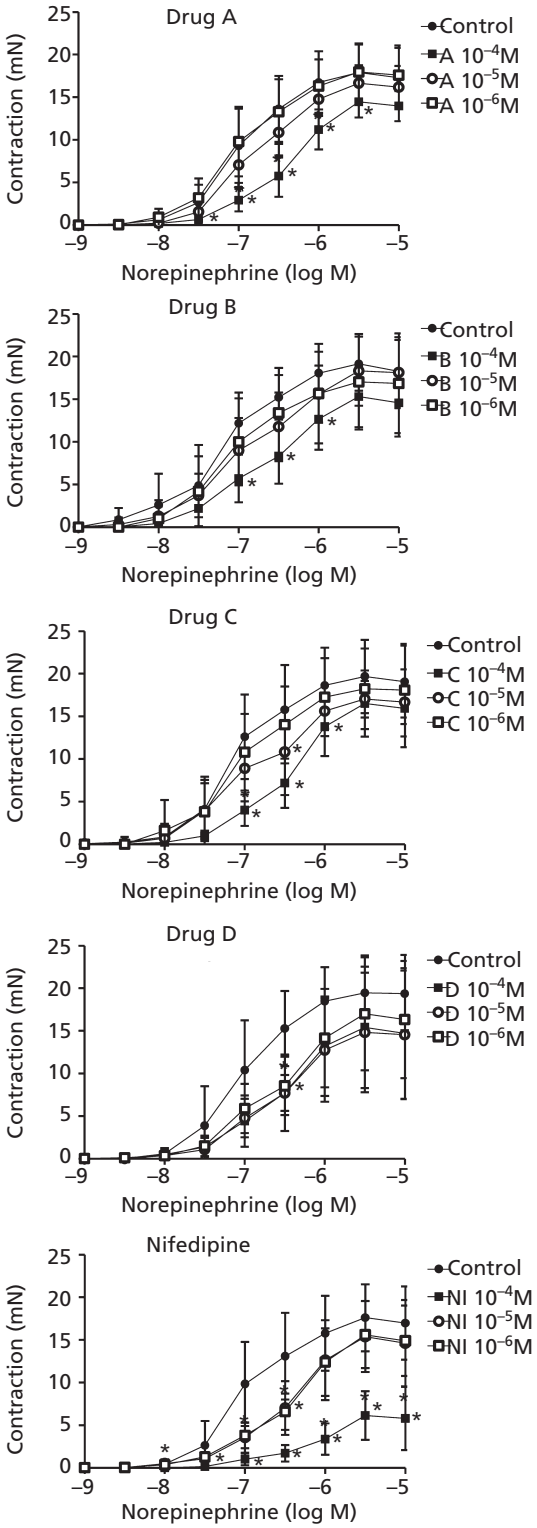

Figure 1 Effect of dihydropyrimidines A–D and nifedipine on noradrenaline-induced contractions of isolated aorta. Aortic rings were contracted by norepinephrine (10-10 . . . 10-5 mol.l-1) in the presence of tested drugs or nifedipine at 10-6, 10-5 and 10-4 mol.l-1 or only in the presence of vehicle (Control). *$P < 0.05$ vs control.

Discussion

The newly prepared compounds[21] were characterized and screened for their calcium channel blocking activity based on their ability to relax a noradrenaline-induced and depolarization-induced contraction of vascular smooth muscle, and were compared with the reference drug nifedipine. Dihydropyrimidines **A** and **C** effectively blocked KCl-induced contraction only at high concentrations, while dihydropyrimidine **D** was as potent as nifedipine. Derivative **D** may bind strongly to the L-type calcium channel or remain bound to membrane similarly to nifedipine. Dihydropyrimidines **A**, **B**, **C** and **D** inhibited KCl-induced contraction selectively and minimally affected noradrenaline-induced contractions of rat isolated aorta, indicating a more selective action on L-type calcium channel than the reference compound nifedipine.

Vasorelaxing potency was determined by comparison of the IC50 values obtained from concentration–effect curves with strips of KCl-depolarized rat thoracic aorta. Relaxation of the KCl-depolarized strips is predictive of calcium channel blocking activity. Our findings showed that dihydropyrimidine **D** was the most effective compound whereas compounds **A**, **B** and **C** were weak calcium antagonists compared with nifedipine; data are present in Table 1. By means of washout experiment, we found out that compound **D** (at concentration 10^{-5} M and 10^{-4} M), as well as nifedipine, caused persistent inhibition of depolarization-induced contraction, while for drugs **A**, **B** and **C**, washout restored depolarization-induced contractions.

The activity of dihydropyrimidines seems to be largely controlled by lipophilicity of the molecule.[23] Movement of the calcium channel blockers through the membrane is a function of their lipid solubility or their lipid–water partition coefficients. The most important determinants for the approach of calcium channel blockers to their receptor sites have been proposed to be their rates of partition into the lipid bilayer and diffusion within it.[24]

The vasodilatory potency of a compound is determined also by the effect of the substituents on the phenyl ring. Among individual substituents at the *ortho* or *meta* position, the nitro functionality is more potent than the chloro; potency is in the following order: *ortho* NO_2, *ortho* Cl, *meta* NO_2.[7,25] This is in accordance with our results, where substance **D** with a nitro substituent on the phenyl ring at the *ortho* position and with sulfur at the C2 position of the dihydropyrimidine ring, antagonized the KCl-induced contraction completely (IC50 = 9.378×10^{-9} M). The other compounds blocked the contraction partially in the following order: compound **A** with oxygen at C2 position and nitro group at the *ortho* position on the phenyl ring (IC50 = 9.411×10^{-6} M), compound **C** with oxygen at C2 position and chlorine at the *ortho* position on the phenyl ring (IC50 = 5.815×10^{-5} M) and compound **B** with similar chemical structure to compound **C** except for replacement of chlorine by the nitro group (IC50 = 1.849×10^{-4} M).

Dihydropyrimidines are inherently asymmetric and the urea moiety embedded in the dihydropyrimidine ring clearly defines the right-hand side of the molecule and thus allows a selective functionalization of this biologically less important side of dihydropyrimidines. Bioavailability, solubility and basicity of dihydropyrimidines may be controlled by such simple right-hand-side functionalizations.[26] In the solid state they adopt a molecular conformation similar to that of dihydropyridines.[23] Dihydropyrimidines may operate as agonists or antagonists. Calcium channel modulation (antagonist vs agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the 4-aryl group acts as a molecular switch between antagonist and agonist activity. In receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting, the boat-like dihydropyrimidine ring, with the 4-aryl substituent preferring the synperiplanar orientation. A *cis*-carbonyl ester orientation was also found mandatory for optimum calcium channel activity.[27]

By stimulation of $\alpha 1$ adrenoceptors, noradrenaline produces a contraction that may be characterized by an initial fast component followed by a sustained tonic component. The tonic-sustained component is partly dependent on a noradrenaline-dependent calcium influx related to the opening of channels allowing calcium to enter the cell according to its electrochemical gradient. Calcium channel blockers prevent this increased calcium entry without affecting resting calcium fluxes or intracellular calcium release.[1] It was observed that they are less potent against calcium entry stimulated by receptors than by high potassium depolarization.[28] There are differences between vessels – mesenteric arteries are more sensitive than rat aorta to the blocking action of calcium antagonists, whereas aorta is resistant.[29]

In the aortic strips, noradrenaline-induced contractions were only partially inhibited by the new compounds (approximately 20% at concentration 10^{-4} M), while nifedipine diminished contractile response markedly (75% at concentration 10^{-4} M). Similar results for the inhibitory action of nifedipine on noradrenaline-induced contraction (EC50 = 50%) have been observed by Godfraind *et al.*[30]

Despite their high potency and widespread use in the treatment of cardiovascular diseases, dihydropyridines have practical disadvantages, such as light-sensitivity, and have relatively short plasma half-lives, consequently require multiple dosing to achieve enough clinical efficacy.[31] To optimize their efficacy and safety they have undergone several changes and numerous improved derivatives have been developed. Besides various optimizations, some groups approached the problems by synthesizing new types of compounds.[24,32–34] The most promising analogues seem

to be dihydropyrimidines because of their structural similarity with dihydropyridines and better light stability.

Conclusions

Our study concerning the first screening test for the pharmacological activity of the compounds clearly show that newly synthesized compound **D** is a potent calcium channel blocking agent *in vitro*, with a vasorelaxing potency comparable with that of the reference calcium channel blocker nifedipine, a better selectivity in inhibiting depolarization-induced arterial smooth muscle contraction and better reversibility of action than nifedipine. Substance **A** also displayed promising potency, although it was slightly less potent than nifedipine. Results warrant a further investigation of these compounds (e.g. with respect to electrophysiological aspects of their action and determination of selectivity of their inhibitory action on L-type channels in different vascular beds arteries and the heart). This could reveal a potential for their possible future pharmacological utilization.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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