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Short communication

Dihydropyridines bearing an imidazo[2,1-*b*]thiazole system

A Andreani[1], A Leoni[1], M Rambaldi[1], A Locatelli[1],
R Bossa[2], I Galatulas[2], M Chiericozzi[2], M Bissoli[2]

[1]*Dipartimento di Scienze Farmaceutiche, Università di Bologna, Via Belmeloro 6, 40126 Bologna;*
[2]*Dipartimento di Farmacologia, CTM, Università di Milano, Via Vanvitelli 32, 20129 Milan, Italy*

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Summary — This paper reports the synthesis of imidazo[2,1-*b*]thiazoles, bearing a dihydropyridine ring at the 5 or 6 position, which were tested for antiarrhythmic, inotropic and chronotropic activities. Nine of the ten compounds bearing double bond at the 2,3 position and the same dihydropyridine as nifedipine at the 5 position, were antiarrhythmic; moreover one of them (bearing a methyl group at the 2 position) was devoid of negative inotropic activity.

imidazo[2,1-*b*]thiazole / dihydropyridine / nifedipine / verapamil / antiarrhythmic activity / inotropic activity / chronotropic activity

Nifedipine, a powerful drug patented by Bayer for the management of angina pectoris and hypertension [1, 2], is the most well-known dihydropyridine. At the beginning of the 80's several types of cardiovascular activity were detected within this class of compounds [3–5], and now the interest is mainly shifted to the development of selective derivatives including even positive inotropic agents [6–9]. Bay k 8644 [10] is the most well-known dihydropyridine to act as a calcium channel agonist. However, calcium entry into vascular smooth muscle is also increased by this compound and the resulting vasoconstriction precludes its use in the treatment of congestive heart failure. In contrast to nifedipine, Bay k 8644 is chiral and the racemate exhibits calcium channel agonism [11, 12] since the (–)-*S* enantiomer (agonist) is about tenfold more potent than its (+)-*R* antipode (antagonist) [13].

Taking into account that among the numerous analogs of nifedipine even the substitution of the aromatic ring with a bicyclic system has been successfully performed (eg, oxodipine [14], elgodipine [15], isradipine [16] and its *N*-oxide [17]) and considering our experience on the positive inotropic activity of imidazo[2,1-*b*]thiazole derivatives [18–24], we planned the synthesis of some dihydropyridines bearing this bicyclic system, in order to obtain a new class of calcium modulators and a preliminary evaluation of the features which could possibly shift the activity from antagonism to agonism.

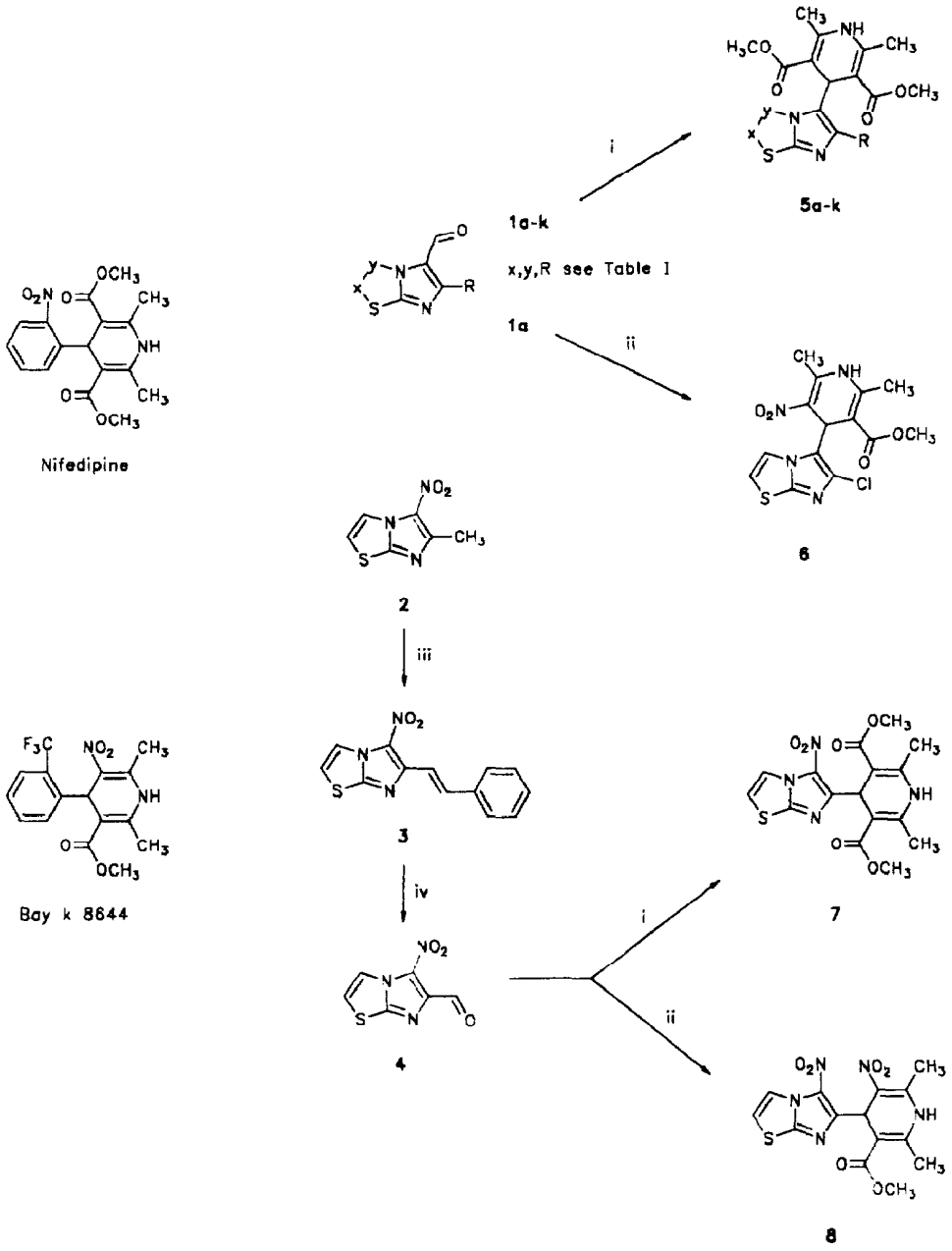
Chemistry

The imidazo[2,1-*b*]thiazoles **5–8** (scheme 1) were prepared by means of the well-known Hantzsch reaction [25]. In compounds **5** and **7**, the dihydropyridine ring bears the same substituents as nifedipine (compound **7** has the closest resemblance due to the nitro group at the 5 position) whereas in compounds **6** and **8** the substitution pattern is the same as in Bay k 8644.

The starting aldehydes **1**, which are necessary for the preparation of compounds **5** and **6**, have been reported in the literature [26–31] (see table I) except 6-(2-nitrophenyl)imidazo[2,1-*b*]thiazole-5-carboxaldehyde (for the synthesis of **5f**), which was prepared by means of the Vilsmeier reaction on 6-(2-nitrophenyl)imidazo[2,1-*b*]thiazole (see *Experimental protocols*). The starting aldehyde for the synthesis of compounds **7** and **8** was 5-nitroimidazo[2,1-*b*]-thiazole-6-carboxaldehyde **4**, which was prepared by oxidation with osmium tetroxide of 5-nitro-6-styryl-imidazo[2,1-*b*]thiazole **3**, obtained in turn from 6-methyl-5-nitroimidazo[2,1-*b*]thiazole **2** [32]. ^{1}H-NMR data for compounds **5–8** are presented in table II.

Pharmacological results

Compounds **5–8** were subjected to a preliminary test on the rat portal vein in order to look for a possible effect on the relaxation of phasic vascular tone,



Scheme 1. Synthesis of compounds **5–8**. i) Methylacetoacetate, NH_4OH; ii) methyl 3-aminocrotonate, nitroacetone; iii) benzaldehyde, piperidine; iv) $NaIO_4$, OsO_4.

which, in turn, could be predictive for a possible vasodilatory action. Under this test, the most potent compounds were 90-fold less active than nifedipine.

The other pharmacological tests performed on compounds **5–8** are reported in tables III and IV. Guinea-pig left atria, stimulated at different frequencies, were used to evaluate the antiarrhythmic activity (table III). Except for **5f,k** and **6–8**, all the compounds were active with a maximum for **5a,c,d,e,h,j**. On spontaneously beating guinea-pig atria (table IV), all the compounds showed negative inotropic activity except the 2-methyl derivatives **5i,j**. Compound **5j** is the most interesting since it showed antiarrhythmic but not cardiodepressant activity.

Table I. Compounds **5–8**.

Compound	*x*	*y*	*R*	*Starting aldehyde reference*	*Formula (mw)*	*Mp (°C)*	ν_{max} *(cm^{-1})*
5a	CH	CH	Cl	26	$C_{16}H_{16}ClN_3O_4S$ (381.8)	213–216	1660, 1495, 1325, 1200, 1110
5b	CH	CH	CH_3	26	$C_{17}H_{19}N_3O_4S$ (361.4)	228–230 dec	1685, 1510, 1270, 1205, 1095
5c	CH	CH	C_6H_5	26	$C_{22}H_{21}N_3O_4S$ (423.5)	211–215	1690, 1270, 1200, 1110, 1090
5d	CH	CH	C_6H_4Cl (4)	27	$C_{22}H_{20}ClN_3O_4S$ (457.9)	227–228 dec	1685, 1490, 1265, 1195, 1090
5e	CH	CH	$C_6H_4CH_3$ (4)	27	$C_{23}H_{23}N_3O_4S$ (437.5)	220–222	1695, 1495, 1265, 1200, 1090
5f	CH	CH	$C_6H_4NO_2$ (2)	–	$C_{22}H_{20}N_4O_6S$ (468.5)	257–259 dec	1670, 1330, 1210, 1120, 1010
5g	CH	CH	$C_6H_4NO_2$ (4)	28	$C_{22}H_{20}N_4O_6S$ (468.5)	232–235 dec	1685, 1335, 1200, 1110, 1010
5h	CH	CH	$C_6H_4OCH_3$ (4)	29	$C_{23}H_{23}N_3O_5S$ (453.5)	200–202	1690, 1495, 1270, 1200, 1090
5i	CCH_3	CH	C_6H_5	30	$C_{23}H_{23}N_3O_4S$ (437.5)	193–195	1690, 1475, 1265, 1195, 1085
5j	CCH_3	CH	C_6H_4Cl (4)	31	$C_{23}H_{22}ClN_3O_4S$ (472.0)	240–242	1680, 1320, 1200, 1110, 1080
5k	CH_2	CH_2	C_6H_5	26	$C_{22}H_{23}N_3O_4S$ (425.5)	255–257 dec	1685, 1625, 1270, 1195, 1090
6				26	$C_{14}H_{13}ClN_4O_4S$ (368.8)	137–140	1680, 1300, 1220, 1150, 1015
7				–	$C_{16}H_{16}N_4O_6S$ (392.4)	305–306 dec	1695, 1320, 1230, 1200, 1150
8				–	$C_{14}H_{13}N_5O_6S$ (379.3)	276–278 dec	1700, 1630, 1470, 1210, 1040

In order to select candidates for the search of a new lead in the field of antiarrhythmic dihydropyridines, some useful considerations are possible observing the results reported in tables III and IV.

First, the 5-nitro derivatives bearing the dihydropyridine ring at the 6 position (**7** and **8**) are not useful candidates.

Second, a comparison between **5a** (bearing the same dihydropyridine as nifedipine) and **6** (bearing the same dihydropyridine as Bay k 8644) shows the expected difference in the inotropic activity but this feature is less important than the methyl group at the 2-position (**5i,j**) in obtaining positive inotropic agents. On the other hand, an evident drop of antiarrhythmic activity excludes compound **6** from the possible candidates.

Finally, the series of compounds bearing the symmetrical dihydropyridine at the 5 position is promising in the search for new leads. A comparison between compounds **5c** and **5k** confirms that the double bond at position 2,3 is necessary for the activity.

Experimental protocols

Chemistry

The melting points are uncorrected. Analyses (C, H, N) were within ±0.4% of the theoretical values. Bakerflex plates (silica gel IB2-F) were used for TLC and Kieselgel 60 (Merck) for column chromatography. The IR spectra were recorded in Nujol on a Perkin-Elmer 683. The ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Varian Gemini (300 MHz) using TMS as the internal standard. Coupling constants (*J*) are reported in Hz.

5-Nitro-6-styrylimidazo[2,1-b]thiazole 3

A mixture of 5-nitro-6-methylimidazo[2,1-*b*]thiazole **2** [32] (22 mmol), benzaldehyde (14 mL) and piperidine (2.4 mL) was heated at 120–130 °C for 6 h. After cooling, the resulting precipitate was collected by filtration and crystallized from ethanol. The yield was 63% of a yellow solid.

$C_{13}H_9N_3O_2S$ (271.3); mp 207–210 °C; ν_{max} (cm^{-1}): 1340, 1240, 1140, 1040, 965. δ (ppm): 7.41 (3H: 2H, t, ar + 1H, d, -CH=, *J* = 7.5); 7.61 (1H, d, th, *J* = 4.5); 7.66 (2H: 1H, t, ar + 1H, d, -CH=, *J* = 7.5); 7.77 (2H, d, ar); 8.31 (1H, d, th, *J* = 4.5).

Table II. ^{1}H-NMR of compounds **5–8**.

Compound	*δ (ppm); J (Hz) in DMSO-d_6*[a]
5a	2.26 (6H, s, CH_3), 3.46 (6H, s, OCH_3), 5.25 (1H, s, py), 7.34 (1H, d, th, J = 4.5), 7.74 (1H, d, th, J = 4.5), 9.13 (1H, s, NH)
5b	2.09 (3H, s, CH_3-im), 2.26 (6H, s, CH_3), 3.48 (6H, s, OCH_3), 5.21 (1H, s, py), 7.15 (1H, d, th, J = 4.5), 7.39 (1H, d, th, J = 4.5), 9.06 (1H, s, NH),
5c	2.18 (6H, s, CH_3), 3.19 (6H, s, OCH_3), 5.68 (1H, s, py), 7.35 (5H, m: 2H, th + 3H, ar), 7.82 (2H, d, ar), 9.00 (1H, s, NH)
5d	2.21 (6H, s, CH_3), 3.24 (6H, s, OCH_3), 5.67 (1H, s, py), 7.29 (1H, d, th, J = 4.5), 7.32 (1H, d, th, J = 4.5), 7.50 (2H, d, ar, J = 8.5), 7.87 (2H, d, ar, J = 8.5), 9.08 (1H, s, NH)
5e	2.19 (6H, s, CH_3), 2.35 (3H, s, CH_3-*p*), 3.21 (6H, s, OCH_3), 5.68 (1H, s, py), 7.22 (2H, d, ar, J = 8.0), 7.27 (2H, s, th), 7.72 (2H, d, ar, J = 8.0), 9.01 (1H, s, NH)
5f	2.06 (6H, s, CH_3), 3.35 (6H, s, OCH_3), 5.38 (1H, s, py), 7.29 (1H, d, th, J = 4.5), 7.61 (2H, m: 1H, th + 1H, ar), 7.73 (2H, m, ar), 7.95 (1H, d, ar, J = 8), 8.66 (1H, s, NH)
5g	2.22 (6H, s, CH_3), 3.22 (6H, s, OCH_3), 5.76 (1H, s, py), 7.31 (1H, d, th, J = 4.5), 7.37 (1H, d, th, J = 4.5), 8.16 (2H, d, ar, J = 9.0), 8.32 (2H, d, ar, J = 9.0), 9.13 (1H, s, NH)
5h	2.17 (6H, s, CH_3), 3.22 (6H, s, OCH_3), 3.80 (3H, s, OCH_3-*p*), 5.63 (1H, s, py), 6.96 (2H, d, ar, J = 9.0), 7.26 (2H, s, th), 7.72 (2H, d, ar, J = 9), 8.99 (1H, s, NH)
5i	2.18 (6H, s, CH_3), 2.41 (3H, s, CH_3-th), 3.20 (6H, s, OCH_3), 5.64 (1H, s, py), 7.04 (1H, s, th), 7.29 (1H, t, ar, J = 7), 7.40 (2H, t, ar, J = 7), 7.79 (2H, d, ar, J = 7), 8.97 (1H, s, NH)
5j	2.19 (6H, s, CH_3), 2.41 (3H, s, CH_3-th), 3.23 (6H, s, OCH_3), 5.61 (1H, s, py), 7.03 (1H, s, th), 7.46 (2H, d, ar, J = 7.2), 7.83 (2H, d, ar, J = 7.2), 9.03 (1H, s, NH)
5k	2.15 (6H, s, CH_3), 3.22 (6H, s, OCH_3), 3.87 (2H, m, thn), 3.95 (2H, m, thn), 5.44 (1H, s, py), 7.22 (1H, t, ar, J = 7), 7.35 (2H, t, ar, J = 7), 7.69 (2H, d, ar, J = 7), 8.87 (1H, s, NH)
6	2.30 (3H, s, CH_3), 2.50 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 5.62 (1H, s, py), 7.38 (1H, d, th, J = 4.5), 8.02 (1H, d, th, J = 4.5), 9.87 (1H, s, NH)
7	2.22 (6H, s, CH_3), 3.41 (6H, s, OCH_3), 5.80 (1H, s, py), 7.59 (1H, d, th, J = 4.5), 8.29 (1H, d, th, J = 4.5), 8.94 (1H, s, NH)
8	2.28 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.50 (3H, s, OCH_3), 6.18 (1H, s, py), 7.64 (1H, d, th, J = 4.4), 8.34 (1H, d, th, J = 4.4), 9.71 (1H, s, NH)

[a]Py = dihydropyridine; th = thiazole; thn = thiazoline; im = imidazole; ar = aromatic.

5-Nitroimidazo[2,1-b]thiazole-6-carboxaldehyde **4**

A solution of sodium periodate (74 mmol) in 30 mL water was added to a stirred solution of compound **3** (34 mmol) in 500 mL THF. After addition of osmium tetroxide (4 mmol), the mixture was stirred at room temperature for 48 h. The resulting precipitate was collected by filtration, washed with diethyl ether, and suspended in 200 mL water. The suspension was stirred for 30 min at room temperature and filtered, yielding 82% of a yellow solid.

$C_6H_3N_3O_3S$ (197.2); mp 216–218 °C; ν_{max} (cm^{-1}): 1675, 1335, 1300, 1245, 1155. δ (ppm): 7.86 (1H, d, th, J = 4.5); 8.44 (1H, d, th, J = 4.5); 10.39 (1H, s, CHO).

6-(2-Nitrophenyl)imidazo[2,1-b]thiazole

A solution of bromine (30 mmol) in $CHCl_3$ (10 mL) was dropped into a solution of 2-nitroacetophenone (30 mmol) dissolved in $CHCl_3$ (25 mL). After 15 min at room temperature, the mixture was evaporated under reduced pressure and the resulting oil, crude 2-bromo-1-(2-nitrophenyl)ethanone, was treated with 2-aminothiazole (30 mmol) dissolved in acetone (80 mL). The reaction mixture was refluxed for 3 h and the resulting precipitate, crude 2-(2-imino-3-thiazolyl)-1-(2-nitrophenyl)ethanone, was collected and refluxed for 1 h with 150 mL of 2 N HCl. The solution, basified with 20% NH_4OH, yielded 68% of 6-(2-nitrophenyl)-imidazo[2,1-*b*]thiazole, which was crystallized from ethanol.

Table III. Antiarrhythmic activity of compounds **5–8** on guinea-pig left atria stimulated at different frequencies (3–10 Hz).

Compound	*Concentration (μg/mL)*	*Effective refractory duration (ms)*		*Difference (%)*	*Significance*[a]
		Controls	*Treated*		
5a	16	122.9 ± 15.7	202.3 ± 44	164.6	*
5b	8	103.7 ± 3.7	150.7 ± 7.9	145.4	*
5b	16	103.7 ± 3.7	152.7 ± 13.9	147.3	*
5c	16	115.7 ± 4.7	205.5 ± 24.2	177.6	*
5d	4	118 ± 7.2	142.8 ± 0	121	*
5d	8	118 ± 7.2	166.6 ± 0	141.1	*
5d	16	118 ± 7.2	200 ± 0	169.5	*
5e	16	112 ± 7.2	188.9 ± 11.1	168.6	*
5f	20	126.3 ± 9.2	120.3 ± 4.7	95.2	ns
5g	16	122.6 ± 12.4	186.5 ± 32.5	152.1	*
5g	20	122.6 ± 12.4	188.9 ± 11.1	154.1	*
5h	8	115.7 ± 4.7	188.9 ± 11.1	163.3	*
5i	4	116.7 ± 8.3	152.7 ± 13.9	130.8	*
5i	8	116.7 ± 8.3	166 ± 0	142.8	*
5i	16	116.7 ± 8.3	177.7 ± 11.1	152.3	*
5j	8	116.7 ± 8.3	169.8 ± 16.6	145.5	*
5j	16	116.7 ± 8.3	188.9 ± 11.1	161.9	*
5k	20	117.5 ± 5.1	150.2 ± 10.1	128.2	ns
6	16	111 ± 0	136.8 ± 5.9	123.2	ns
7	20	118 ± 7	118 ± 7	100	ns
8	20	142.8 ± 0	125 ± 0	87.5	ns
Nifedipine	1.6	126.3 ± 9.2	177 ± 11.1	140.1	ns
Verapamil	1	100 ± 0	166.6 ± 0	166.6	*
Verapamil	2	100 ± 0	200 ± 0	200	*

[a]* $P \leq 0.05$; ns = not significant.

$C_{11}H_7N_3O_2S$ (245.3); mp 163–166 °C; ν_{max} (cm^{-1}): 1520, 1190, 850, 740, 650. δ (ppm): 7.32 (1H, d, th, J = 4.5); 7.52 (1H, t, ar); 7.67 (1H, t, ar); 7.79 (1H, d, ar); 7.84 (1H, d, ar); 7.96 (1H, d, th, J = 4.5); 8.14 (1H, s, im).

6-(2-Nitrophenyl)imidazo[2,1-b]thiazole-5-carboxaldehyde
The Vilsmeier reagent was prepared at 0–5 °C by dropping 32 mmol of $POCl_3$ into a stirred solution of DMF (39 mmol) in $CHCl_3$ (5 mL). 6-(2-Nitrophenyl)imidazo[2,1-*b*]thiazole (12 mmol), dissolved in $CHCl_3$ (60 mL), was added dropwise, under stirring at 0–5 °C, to the Vilsmeier reagent. After 3 h at room temperature, the reaction mixture was refluxed for 14 h and the solvent was evaporated under reduced pressure. The oily residue was poured into ice and the resulting precipitate was collected and crystallized from ethanol with a yield of 87%.

$C_{12}H_7N_3O_3S$ (273.3); mp 225–228 °C dec; ν_{max} (cm^{-1}): 1635, 1530, 1520, 1320, 1280. δ (ppm): 7.65 (1H, d, th, J = 4.4); 7.76 (1H, t, ar); 7.84 (1H, t, ar); 7.91 (1H, d, ar); 8.07 (1H, d, ar); 8.43 (1H, d, th, J = 4.4); 9.71 (1H, s, CHO).

*General procedure for the synthesis of the dihydropyridines **5a–k** and **7***
Methylacetoacetate (2 mmol) and 30% NH_4OH (4 mmol) were added to a stirred solution of the appropriate aldehyde (1 mmol) dissolved in ethanol (50 mL). The reaction mixture was refluxed for 36 h and, after cooling, evaporated to dryness under reduced pressure. Compound **7** (see tables I and II) was obtained by washing with ethanol (yield 28%); all the other derivatives were purified by column chromatography with the following eluents: petroleum ether/acetone 80:20 (**5a,e,g,i,k**), petroleum ether/ethyl acetate 80:20 (**5b–d,f,h,j**). The yield was 10–15%.

Table IV. Effect of compounds **5–8** on contractile force and frequency of spontaneously beating guinea-pig atria.

Compound	*Concentration (μg/mL)*	*Spontaneously beating guinea-pig atria*	
		Contractile force[a]	*Frequency*[b]
5a	10	51.1 ± 3.7	86.8 ± 7.7
	20	0*	0*
		(0.50 ± 0.12)	(185 ± 5)
5b	10	92.8 ± 1.9	71.6 ± 1.8*
	20	57.1 ± 21.9	28.9 ± 3.6*
		(0.63 ± 0.25)	(195 ± 5)
5c	20	62 ± 3.2*	69 ± 4.6*
		(0.57 ± 0.11)	(190 ± 0)
5d	10	54.8 ± 9.3*	68.3 ± 1.6*
	20	38.2 ± 15.5*	41.6 ± 3.4*
		(0.61 ± 0.17)	(190 ± 10)
5e	10	47.6 ± 0.75*	44.2 ± 3.1
	20	35 ± 6.9*	23.7 ± 7.9*
		(0.63 ± 0.01)	(190 ± 0)
5f	20	94.4 ± 0	63.2 ± 10.9
		(0.72 ± 0)	(190 ± 0)
5g	10	59.9 ± 9.9	70.6 ± 0*
	20	43.4 ± 10.1*	58.8 ± 0*
		(0.5 ± 0.03)	(170 ± 0)
5h	10	51 ± 16.6	21.9 ± 4.3*
	20	0*	0*
		(0.79 ± 0.07)	(180 ± 10)
5i	20	143.3 ± 6.7*	55.7 ± 29.3*
		(0.71 ± 0.09)	(195 ± 5)
5j	20	114 ± 7.04	85 ± 0
	40	140.9 ± 3.7*	65 ± 5*
		(0.81 ± 0.05)	(200 ± 0)
5k	20	63.73 ± 11.2	29.2 ± 5.7*
		(0.51 ± 0.07)	(185 ± 15)
6	20	101.7 ± 8.75	59.4 ± 5.4*
		(0.62 ± 0.07)	(190 ± 5.8)
7	20	99.8 ± 3.1	91.9 ± 3
		(0.65 ± 0.05)	(195 ± 5)
8	10	102.1 ± 2.1	91.6 ± 3.4*
	20	96.4 ± 7.8	72.8 ± 2.2*
		(0.59 ± 0.11)	(185 ± 15)
Nifedipine	1	50.5 ± 9.5*	49.4 ± 9.4*
	2	0*	0*
		(0.55 ± 0.13)	(185 ± 15)
Verapamil	1	36.7 ± 3.34*	70.8 ± 4.2*
		(0.49 ± 0.01)	(195 ± 15)

[a]Percentage variations with respect to the controls whose contractile frequency is reported in parentheses (g). [b]Percentage variations with respect to the controls (in parentheses). *($P \leq 0.05$).

*General procedure for the synthesis of the dihydropyridines **6** and **8***

Methyl 3-aminocrotonate (1 mmol) and nitroacetone (1 mmol) were added to a stirred solution of the appropriate aldehyde (1 mmol) in ethanol (50 mL). The mixture was refluxed for 24 h and, after cooling, evaporated under reduced pressure. The crude product was subjected to column chromatography with petroleum ether/ethyl acetate 70:30 as the eluent (see tables I and II). The yield was 8–10%.

Pharmacology

The data reported in tables III–IV are expressed as mean ± SEM and analyzed by ANOVA for repeated treatment. The data significance ($P \leq 0.05$) between groups was analyzed by Bonferroni *t*-test.

Relaxation of phasic vascular tone [33]

Male Outbred rats (250–350 g) were killed, exsanguinated and a 2–3 cm length of mesenteric portal vein was removed. The portal vein was incubated in a 20 mL bath of physiological solution (composition in g/L: NaCl 7.8; KCl 0.42; $CaCl_2$ 0.6; $MgSO_4$ 0.24; $NaHCO_3$ 2.0; Na_2HPO_4 0.16; glucose 2.0) at 35 °C and bubbled with carbogen. An initial tension of 0.5 g, in isometric conditions, was applied to the preparation and the spontaneous contractions were recorded by an isometric strain-gauge transducer, connected to a recording microdynamometer. After 1 h equilibrium period, the compounds (dissolved in DMSO, except verapamil, which was dissolved in water) were added to the bath in increasing concentrations. Contractile force was determined 0 and 10 min after each administration. The values obtained were analyzed by linear regression analysis in order to calculate the 50% of inhibition (IC_{50}).

Antiarrhythmic activity [34]

The experiments were carried out on isolated left atria of guinea pig (400–500 g). Each experiment was repeated three to five times on different atria. The preparation was incubated in a 20 mL bath of Tyrode solution (composition in g/L: NaCl 8.0; $NaHCO_3$ 1.0; KCl 0.2; NaH_2PO_4 0.05; $MgCl_2$ 0.1; $CaCl_2$ 0.2; glucose 1.0) at 37 °C and bubbled with carbogen.

The isolated atrium was stimulated (in isometric conditions and under an initial tension of 1 *g*) by gradually increasing frequency from 3 to 10 Hz, until a point is reached at which the preparation can no longer respond to each stimulus and begins to miss beats. The stimulation frequency at which this occurs is determined by the effective refractory period of the atrium, ie, the interval between any two consecutive stimuli at the maximum frequency that the atrium can follow.

After an equilibrium period of 30–40 min, the compounds (dissolved in DMSO, except verapamil which was dissolved in water) were added to the bath by increasing cumulative doses (2, 4, 8, 16, 20 μg/mL). The doses were 0.2, 0.4, 0.8 and 1.6 μg/mL for nifedipine and 0.25, 0.5, 1, 2 and 4 μg/mL for verapamil.

Inotropic and chronotropic activity

The experiments were carried out on spontaneously beating atria of guinea pigs (350–500 g): each experiment was repeated three to four times on different atria. The preparation was incubated in a bath of Tyrode solution at 37 °C and bubbled with carbogen. An initial tension of 1 *g* was applied to the preparation. Isometric contractions were recorded by a strain gauge transducer connected to a recording microdynamometer. After stabilization for 30–40 min, the test compound was added to the bath by increasing cumulative doses: nifedipine (1 and 2 μg/mL), verapamil (1, 2 and 4 μg/mL), compounds **5–8** (10, 20 and 40 μg/mL). At the concentration employed, DMSO did not produce appreciable effects (verapamil was dissolved in water).

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