Eur. J. Med. Chem. 34 (1999) 859–865

Short communication

Vasodilating and antiarrhythmic activity of heteryl lactones

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(Received 27 October 1998; revised 22 March 1999; accepted 23 March 1999)

Abstract – A new series of unsaturated γ- and δ-lactones with pyridyl, quinolyl and nitrophenyl substituents (**9**, **10**) have been synthesized by the condensation of unsaturated methyl lactones with heteryl aldehyde or nitrobenzaldehyde in the base-catalysed aldol reaction. The antiarrhythmic, vasodilating and cardiotonic activities of the synthesized compounds have been studied in vivo and ex vivo. 3-Cyano-5,5-dimethyl-4-[4'-(4-pyridyl)-1',3'-butadienyl)]-2(5H)-furanone (**9e**) displayed a significant vasodilating activity. The antiarrhythmic activity of this compound was higher, but its toxicity lower than that of the procainamide reference drug. Five-membered lactones, particularly 3-cyano-4-(4-pyridylvinyl)-5,5-dimethyl-2(5H)-furanone (**9c**), exhibited a remarkable cardiotonic activity. The replacement of a pyridyl substituent by a nitrophenyl group in the pyranone derivative did not change the cardiovascular activity and toxicity. © 1999 Éditions scientifiques et médicales Elsevier SAS

heteryl lactones / antiarrythmic activity / vasodilating activity / cardiotonic activity

1. Introduction

Some of the synthetic and natural compounds containing an unsaturated five-membered lactone moiety exhibit a cardiotonic activity [1]. For example, the heart glycosides contain a γ-lactone unit. On the other hand, it should be noted that the majority of cardiotonic substances of a novel generation is derived from N-heterocyclic compounds [2]. To determine the role of lactone units and heteryl substituents as pharmacophores responsible for antiarrhythmic and cardiotonic activity, pyridyl, quinolyl and nitrophenyl derivatives of unsaturated γ- and δ-lactones have been prepared and tested in vivo and ex vivo.

2. Chemistry

Pyridyl, quinolyl and nitrophenyl derivatives of unsaturated γ- and δ-lactones were synthesized according to the procedure elaborated for the pyridyl derivatives of furanone and pyranone [3]. Methyl lactones **7** and **8** were condensed with aldehydes (**1–6**) in the presence of NaOH as a catalyst *(figure 1)*. The unusual reactivity of 2-, 3- and 4-pyridinecarboxaldehyde with γ- and δ-lactones in a base-catalysed aldol reaction was shown earlier [3]. It was found that the synthesis of heteryl lactones **9a–c** and **10a–c** was accompanied by the formation of the [bis(2-oxo-3-cyano-5,5-dimethyl-2(5H)-furanyl-4-methyl)-methyl]-pyridines and [bis(2-oxo-3-cyano-6,6-dimethyl-5,6-dihydropyranyl-4-methyl)-methyl]pyridines. To avoid this addition we used a 2-fold excess of pyridine carboxaldehyde. The aldol condensation reaction of aldehydes **4–6** with lactones occurred traditionally and yielded the corresponding unsaturated derivatives of lactones only. Lactone **9d** was synthesized by the reaction of the ethoxycarbonyl derivative of methyl furanone **7b** with aldehyde **2**. The ester was converted into the sodium salt by the additional amount of sodium hydroxide. The reaction of aldehyde **4** with furanone **7a** was carried out in the presence of a catalytic amount of NaOH at room temperature to give furanone **9e** in 21% yield. This was significantly lower than in the case of aldehyde **3** condensation reaction (yield 54%). Raising the temperature did not increase the yield. In all cases the values of

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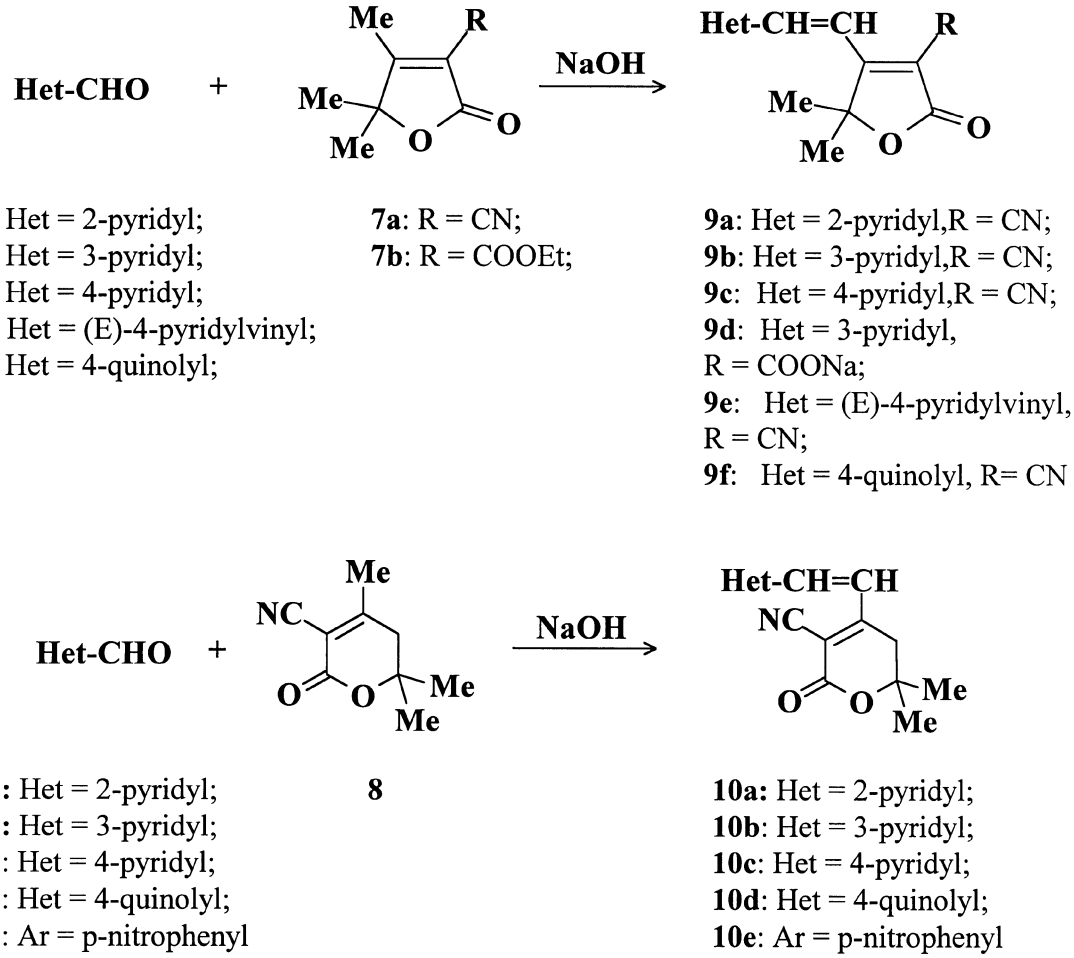

Figure 1. Synthesis of heteroaryl lactones.

spin-spin coupling constants of the double bond CH=CH protons (16–17 Hz) indicated that only *E*- or *E,E*-isomers were isolated. The coupling constant of α,β-protons in chain $CH{=}CH_{\alpha}{-}CH_{\beta}{=}CH$ (compound **9e)** equalled 10.7 Hz. A similar value of coupling constant (10.4 Hz) is in agreement with the *E*-isomer of butadiene [4]. To obtain an additional proof for the configuration of the unsaturated synthesized compounds, *E-Z* photoisomerization caused by UV irradiation of the condensation products **9a** and **10b**, **d** and **e** was studied. The isomerization process was controlled by electron absorption spectroscopy. When the solution in ethanol was irradiated with UV light the intensity of the *E*-isomer absorption band at 332–344 nm decreased and a band at 220–285 nm appeared. According to NMR data the formation of the *E*- and *Z*-isomer mixture caused such changes in spectra. The spin-spin coupling constants of the double bond CH=CH protons in isomers appeared during irradiation and were 11–13 Hz. This means that the compounds described in the present article really have *E*-configuration. The characteristics of the compounds are listed in *tables I* and *II*.

3. Results and discussion

The proposed cardiovascular activity of newly synthesized compounds was tested in ex vivo experiments on the isolated rabbit ear artery and in vitro on anaesthetized laboratory animals. These models were chosen in order not to miss the compounds with antiarrhythmic, vasodilating and/or cardiotonic activities. *Table III* summarizes the data of the antiarrhythmic screening test and acute

Table I. Reaction conditions and characteristics of compounds **9 d–f** and **10 d** and **e**.

Compound	Reaction temperature (°C)	Reaction time (h)	Yield (%)	M.p. (°C)	Formula[a]
9d	80	4	52	275-280	$C_{14}H_{12}NO_4Na$
9e	80	2	21	161-163	$C_{16}H_{14}N_2O_2$
9f	20	1.5	41	229-230	$C_{18}H_{14}N_2O_2$
10d	20	3	44	222-224 (dec)	$C_{19}H_{16}N_2O_2$
10e	80	1.2	61	224-226	$C_{16}H_{14}N_2O_4$

[a] all compounds were analysed for C, H and N.

toxicity obtained for heteryl lactones. The acute toxicity of the studied compounds was low (LD_{50} was over 400 mg/kg). Only the acute toxicity of compound **9c** (LD_{50} 180 mg/kg) and **9d** (200 mg/kg) was comparable with that of lidocaine (LD_{50} 238 mg/kg). The five-membered pyridyl lactones **9 a–e** had a toxicity similar to its six-membered analogues except 3- and 4-pyridylfuranones, the toxicity of which was about 2-fold higher than that of the substituted pyranones. The replacement of pyridyl substituents for a quinolyl group appeared slightly less toxic (see **9c** and **f**, **10c** and **d**).

Heteryl derivatives **9c**, **e** and **10d** injected i.p. in doses of 15 and 30 mg/kg caused the statistically significant protection against $CaCl_2$-induced arrhythmia. Their activity was higher but toxicity lower than that of the reference drug procainamide. The antiarrhythmic activity was more marked for heteryl lactones with 4-pyridyl substituent within the furanone series.

Compounds **9b** and **c** were also investigated on anaesthetized rats. It was shown *(table IV)* that these pyridyl furanones decreased the number of animals with lethal arrhythmia induced by calcium chloride, but to a lower extent than lidocaine. Compound **9c** (dose = 1 mg/kg, i.v.) also protected against ventricular ectopic beats. So, we established that the 4-isomer of pyridyl furanone, **9c**, revealed the most pronounced antiarrhythmic activity and the highest toxicity among all compounds studied *(table III)*.

Almost all of the studied heteryl derivatives of unsaturated γ-and δ-lactones caused a more or less marked relaxation of the previously contracted vessels of the rabbit ear *(table V)*. Compound **9e** exhibited a pronounced vasodilating activity. At the same time, pyridyl lactone **9a** demonstrated two phases of vasodilation/vasoconstriction but **9b** showed a trend towards vasoconstriction. In this test, six-membered lactones (**10a**, **b** and **c**) possessed more pronounced vasodilation than five-membered ones (**9a**, **b** and **c**) and **10a** (2-pyridyl) was more active than **10b** and **c** (3- and 4-isomers). In the series of pyridyl lactones, we found a tendency of 2-pyridyl substituents to induce a more selective vasodilation in comparison with 3- and 4-pyridyl substituents, as already stated with calcium channel modulators [5]. Compounds **9e**, **9f** and **10d** induced a significant vasodilation at a concentration of 50 μM (**9e** being the most active). This means that these compounds may show a

Table II. ^1H NMR chemical shifts (δ, ppm) and spin-spin coupling constants of compounds **9d–f** and **10d** and **e**.

Compound	CH=CH (J_{HH} Hz)	Pyrone CH_2	Pyrone or furanone CH_3	Phenyl, pyridyl or quinolyl CH (J_{HH} Hz)
9d*	7.52, d (16.6); 7.31, d (16.6)	-	1.54, s	8.74, d, H-2, (1.4); 8.49, dd (4.2, 1.4); 8.00, dt, H-4, (8.2, 1.4); 7.40, dd, H-5 (8.2, 4.2)
9e**	6.54, d (15.7); 7.01, d (15.7); 7.14, dd (10.7, 15.7); 7.55, dd (10.7, 15.7)	-	1.65, s	7.34, m, H-3, 5 (6.5); 8.66, m, H-2, 6 (6.1)
9f**	7.06, d (16.4); 8.60, d (16.4)	-	1.75, s	7.65, d, H-3, (4.4); 7.70, m, H-6 (1.4; 6.9; 8.5); 7.82, m, H-7 (1.4; 6.9; 8.5); 8.10, d, H-5 (8.5); 8.20, d, H-8 (8.5); 9.01, d, H-2 (4.4)
10d*	7.54, d (15.7); 8.42, d (15.7)	3.35, s	1.50, s	7.74, m, H-6, (1.2, 7.8, 7.9); 7.86, m, H-7 (1.2, 7.8, 7.9); 7.93, d, H-3 (4.6); 8.11, d, H-5 (7.8); 8.50, d, H-8 (8.0); 9.00, d, H-8 (8.0); 9.00, d, H-2 (4.6)
10e**	7.24, d (16.0); 7.59, d (16.0)	2.86, s	1.55, s	7.70-8.35, m, H-4

DMSO-d_6, ** $CDCl_3$

Table III. Antiarrhythmic activity and acute toxicity of pyridyl lactones in mice.

Compound	Dose (mg/kg, i.p.)	Antiarrhythmic activity (Y/N)[a]	Acute toxicity LD_{50} (mg/kg, i.p.)
9a	30	1/5	> 400
	90	2/5	
9b	30	1/5	> 400
	90	1/5	
9c	15	3/5*	180 (138.5-234)
	30	3/5*	
9d	15	1/5	200 (153.8-260)
	30	2/5	
9e	15	3/5*	480 (347.8-662.4)
	30	2/5	
	90	2/5	
9f	30	1/5	> 600
	90	2/5	
10a	30	1/5	> 400
	90	2/5	
10b	30	1/5	> 400
	90	1/5	
10c	30	1/5	> 400
	90	1/5	
10d	15	1/5	> 600
	30	3/5*	
	90	2/5	
10e	30	1/5	≥ 600
	90	1/5	
Procainamide	30	1/5	360 (257-504)
	90	3/5*	
Lidocaine	15	2/5	238 (180.3-314)
	30	4/5*	
Control		0/10	

[a] Y, the number of mice protected against $CaCl_2$-induced arrhythmia; N, total number of experimental animals; *$P < 0.05$ vs. control group.

strong TXA_2 receptor antagonist activity in the rabbit blood vessels. The replacement of a 4-pyridyl substituent of furanone and pyranone (**9c**, **10c**) for a 4-quinolyl group (**9f**, **10d**) patently increased vasodilating properties in both cases. Unlike pyridyl derivatives of furanone and pyranone a nitrophenyl pyranone **10e** did not possess the vasodilating activity.

Cardiotonic and vasodilating properties of heteryl lactones were also studied on anaesthetized cats. Maximum variations in the haemodynamic parameters were registered about 1–5 min after i.v. administration. The results obtained are shown in *table VI*. The compounds **9b** and **c** possess a significant cardiotonic activity. Compound **9c** (dose = 0.5 mg/kg) increased the systolic pressure of the left ventricle by 30%, but dP/dt by 32%, and the mean arterial blood pressure by 18%. At the same time, the heart rate remained unchanged. The positive inotropic effect was observed with **9b** and **9c** at doses of 0.1–2.0 mg/kg (duration of action was slightly shorter for

Table IV. Effect of compounds **9b** and **c** on $CaCl_2$-induced arrhythmia and lethality in rats.

Compound	Dose (mg/kg, i.v.)	Arrhythmia-scores (M ± SD)	Survival (%)
9b	0.3	3.3 ± 0.4	20
	1.0	3.0 ± 0.5	40
	3.0	2.8 ± 0.5	60*
9c	0.3	2.9 ± 0.5	40
	1.0	2.3 ± 0.3*	60*
	3.0	2.6 ± 0.5	60*
Lidocaine	0.3	3.0 ± 0.4	20
	1.0	2.1 ± 0.3*	60*
	3.0	1.8 ± 0.4*	80*
	-	3.8 ± 0.5	0

*$P < 0.05$ vs. control.

Table V. Vasodilating activity of the investigated compounds in rabbit ear artery.

Compound	Concentration (μM)	Relaxation[a] (%)
9a	10	5÷(-3)
	50	10÷(-5)
9b	10	-2
	50	-8
9c	10	-3
	50	-5
9e	10	30*
	50	50*
9f	10	20
	50	30*
10a	10	12
	50	27*
10b	10	15
	50	20
10c	10	2
	50	15
10d	10	19
	50	32*
10e	10	5
	50	15
Papaverine	1	8
	10	35*
	50	76*
Control	-	0
Solvent	-	8

[a] positive value means relaxation; negative one, vasoconstriction; *$P < 0.05$ vs. control.

Table VI. Haemodynamic effects. Results are in % (in reference to the control initial value).

Compound	Dose (mg/kg, i.v.)	MABP[a]	HR[a]	LVSP	dP/dt	FBF[a]	CBF[a]
9a	1.0	5	0	-	-	-	12
	3.0	-20÷5	-5	-	-	-	-5÷12
9b	0.1	0	-5	6	8	0	0
	0.5	12	3÷(-10)	23	26	10	12
	2.0	29	5	45	33	12	22
9c	0.1	3	-2	10	15	-5	3
	0.5	18	0	30	32	12	16
	2.0	30	6	50	38	15	20
10b	0.1	0	0	0	0	0	0
	0.5	0	0	0	5	0	3
	2.0	6	-3	5	8	5	5
10c	0.1	-3	0	0	0	0	0
	0.5	5	0	5	7	0	6
	2.0	10÷(-5)	5÷(-5)	7	10	5÷(-5)	3
Verapamil (hydrohloride)	0.02	-8	-5	-3	-3	18	15
	0.1	-35	-12	-9	-16	45	80

MABP, mean arterial blood pressure; HR, heart rate; LVSP, left ventricular systolic pressure; dP/dt, left ventricular contractility; FBF, femoral artery blood flow; CBF, carotid artery blood flow.
[a]Haemodynamic parameters are expressed as % change: predrug/postdrug; increase/decrease; positive value means increase; negative one, decrease.

9b). However, **9b** caused a more marked change in heart rate (within +5 to –10%), compared with **9c**. Both pyridyl furanones **9b** and **c** similarly increased the blood flow in the femoral and carotid arteries, but this increase was less than the change in the blood pressure.

The vasodilating effect of a nitrophenyl substituent was similar to that of a pyridyl one. The vasodilating activity of pyranone with a nitrophenyl substituent is similar to that of pyridyl derivatives of furanone and pyranone.

4. Conclusions

New derivatives of γ- and δ-lactones with pyridyl, quinolyl and phenyl substituents with *E*-configuration were synthesized, their antiarrhythmic, vasodilating and cardiotonic activities investigated. The acute toxicity of the compounds studied was low. On the whole, the five-membered pyridyl lactones had a toxicity similar to their six-membered analogues (except 3- and 4-pyridylfuranones). The pyridyl substituents of pyridyl lactones may be responsible for a higher toxicity in comparison with quinolyl lactones.

Pyridyl and quinolyl lactones caused a significant protection against $CaCl_2$-induced arrhythmia. The activity depended on the position of a substituent in the heterocycle. The most active were 4-isomers – 3-cyano-4-(4-pyridylvinyl)-5,5-dimethyl-2(5H)-furanone **9c** and 3-cyano-4-(4-quinolylvinyl)-6,6-dimethyl-(5,6-dihydro)-2-pyranone **10d**. The replacement of a 4-pyridyl substituent of furanone for a 4-quinolyl group decreased the antiarrhythmic activity. The similar replacement in the case of 4-pyridylpyranone caused the activity increase.

The vasodilating activity depended on the ring size of the lactone, on the type of heteryl substituent, and on the position of the substituent in the ring. Six-membered lactones revealed more pronounced vasodilation than five-membered ones. 2-Pyridylfuranone and 2-pyridylpyranone demonstrated more marked vasodilation than 3- and 4-isomers. Besides, this 2-pyridylfuranone also possessed a vasoconstricting action. The insertion of the second vinyl group in the aliphatic chain between the pyridine and lactone rings increased the activity of pyridyl furanone. Thus 3-cyano-5,5-dimethyl-4-[4'-(4-pyridyl)-1',3'-butadienyl)]-2(5H)-furanone **9e** was the most active among the compounds studied.

The vasodilating effect of a nitrophenyl substituent is similar to that of a pyridyl substituent. Cardiotonic activity is more pronounced for 3- and 4-isomers of pyridyl furanones. Cardiotonic activity of the corresponding 6-membered lactones is lower.

5. Experimental protocols

5.1. Chemistry

5.1.1. Methods

The ^{1}H NMR spectra were recorded on a Bruker WH-90/DS and on an AM-360 (360 MHz) spectrometers in $CDCl_3$ or DMSO-d_6, TMS internal standard. The mass spectra were obtained on a Kratos MS-25 chromatograph-mass-spectrometer with an ionizing energy of 70 eV. Elemental analysis was performed on an Elemental Analyzer Carlo Erba 1108. Silufol UV-254 plates were used for TLC analysis, eluents – benzene-acetone 3:1. The melting points were determined on a Boetius stage and reported without corrections. *E-Z* photoisomerization has been studied in ethanol solution of compounds **9a**, **10b**, **d** and **e** by irradiation with UV light at 336, 332, 340 and 344 nm respectively for 45 min. Electronic absorption spectra were recorded on a Specord UV-VIS spectrometer. Starting furanones **7** and pyrone **8** were synthesized according to [6] and [7], respectively. Pyridine aldehydes **1–3** were synthesized by vapour phase oxidation of methyl pyridines over V_2O_5-MoO_3 catalyst [8]. Starting 1'-(4-pyridyl)acroleine **4** and 4-quinolinealdehyde **5** were synthesized according to the methods described in [9] and [10]. All solvents were of an analytical grade and used without further purification.

5.1.2. General procedure for the synthesis of compounds **9d–f**, **10d** *and* **e**

A mixture of methyl lactone **7** or **8** (20 mmol), the aldehyde **4–6** (20 mmol) and NaOH (1.25 mmol) in MeOH (20 mL) was stirred at room temperature or refluxed for 1.2–4 h. The condensation products precipitated, and were filtered off after cooling to room temperature. The precipitates of compounds **9e**, **f**, **10d** and **e** were recrystallyzed from EtOH.

Compound **9d** was synthesized as described above but when the condensation was completed NaOH (21 mmol) was added to the cooled mixture. The resulting precipitate was filtered off, washed with EtOH and air-dried. The reaction conditions, yields and NMR data are shown in *tables I* and *II*. Procedures for the synthesis of compounds **9a–c** and **10a–c** and their chemical and physical data are given in [3].

5.2. Pharmacological methods

5.2.1. Experiments ex vivo

The modified method for the experiments on the isolated perfused rabbit ear blood vessels was used [11, 12]. Male and female rabbits (2.6–3.3 kg) were euthanazed by i.v. injection of Na pentabarbital (80 mg/kg). The central ear artery was dissected free at the ear base and cannulated with polyethylene tube and perfused at a constant flow from a 4-channel peristaltic pump, Geminy (Italy). The perfusion fluid was (mmol): NaCl 136.9; KCl 2.68; $CaCl_2$ 1.8; $MgCl_2$ 1.05; $NaHCO_3$ 11.9; NaH_2PO_4 0.42; glucose 5.6 (pH 7.35). Intraluminal inflow perfusion pressure was measured with a Statham P23I transducer and recorded on a physiograph DMP-4B (Narco Bio-System, Huston, USA). As flow remained constant, the alterations in perfusion pressure reflected changes in the blood vessel resistance, i.e., the degree of vasoconstriction or relaxation. Vasoconstriction was caused by intraluminal infusion of U-46619 (thromboxane A_2 receptor agonist). The relaxant responses to the investigated compounds used in different concentrations were tested. The responses were expressed as a per cent relaxation (% changes in perfusion pressure) without and with the investigated compounds or solvent.

5.2.2. Experiments in vivo

5.2.2.1. Antiarrhythmic activity

5.2.2.1.1. Antiarrhythmic screening test

Antiarrhythmic activity was tested in the experimental antiarrhythmic screening model on male ICR:JCL mice (19–23 g) as was described earlier [13]. The tested compounds or solvents were administered i.p. 15 min before i.v. infusion of 2% $CaCl_2$ solution at a constant rate (0.02 mL/sec) in a dose of 180 mg/kg. The number of animals protected from $CaCl_2$-induced lethal arrhythmia was defined. The investigated compounds were dissolved in NaCl 0.9% solution or in dimethyl acetamide and then diluted with the NaCl 0.9% solution.

5.2.2.1.2. Calcium chloride-induced arrhythmia.

The experiments were performed according to the classical method [14]. In brief, Wistar male rats (180–220 g) were anaesthesized with urethan (1.20 mg/kg, i.p.). ECG was registered in II standard lead on a physiograph DMP-4B (Narco Bio-Systems, Huston, USA). The 5% $CaCl_2$ solution was i.v. injected at a dose of 180 mg/kg. Heart rhythm disturbances in scores [15] and lethality of animals were estimated. Solutions of the compounds to be tested were administrated into the femoral vein 3 min prior to $CaCl_2$. Every dose was tested on five rats.

5.2.2.2. Cardiotonic action and hypotensive activity

The method used was described already in [16]. Adult mongrel male and female cats (3.0–4.2 kg) were anaesthesized with α-glucochloralose and urethan (80 and 200 mg/kg, i.p.). The trachea was catheterized and con-

nected to an intermittent positive-pressure respirator (DP-8, SU). Arterial blood pressure from the right femoral artery, left ventricular pressure (electromanometer P 23 ID) and the first derivative (dP/dt) were registered on a physiograph DMP-4B (Narco Bio-Systems, Houston, USA). The blood flow from the left femoral and left common carotid arteries was measured with an electromagnetic flowmeter MFV-1200 (Nihon Kohden, Tokyo, Japan). The heart rate was calculated using the blood pressure wave. The solutions of the compounds investigated were injected through a catheter placed in the femoral vein.

5.2.2.3. Toxicological examination

Acute toxicity of the unsaturated five- and six-membered lactones was studied in albino male and female ICR:JCL mice (18–22 g). Solutions or suspensions of the compounds (prepared with 0.6% Tween-80) were injected i.p. The experimental animals were observed for 10 days. Common state, mobility of animals, toxic symptoms and survival were estimated. To reduce the number of used animals, the maximal dose was 400 mg/kg. If possible, LD_{50} was calculated when 50% of the animals died.

All references drugs (Procainamide, Lidocaine, Verapamil, Papaverine) were from commercial sources.

Acknowledgements

We are grateful to the Latvian Science Council for the financial support of the programme ‘The Development of Modern Directions in the Organic Chemistry for the Production of New Medical Agents’. The authors acknowledge with gratitude and affection the financial help they have also received from the Taiho Latvian Foundation.

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