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Short communication

Synthesis, antiarrhythmic and hypotensive activity of some novel 1,3-disubstituted ureas and phenyl N-substituted carbamates

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Abstract – Some new 1,3-disubstituted ureas and phenyl N-substituted carbamates were prepared and evaluated in vivo for their antiarrhythmic and hypotensive properties. The compound 1-*tert.*-butyl-1-(3-cyclopentyloxy-2-hydroxypropyl)-3-methylurea **2c** exhibited a strong hypotensive action. The compounds 2-(1-*tert.*-butyl-3-methylureido)-1-(cyclopentyloxymethyl)ethyl N-isopropylcarbamate **3c** and 2-(1-*tert.*-butyl-3-ethylureido)-1-(cyclopentyloxymethyl)ethyl N-isopropylcarbamate **3f** showed an antiarrhythmic activity comparable to that of the reference drug Propranolol. © Elsevier, Paris

1,3-disubstituted ureas / phenyl N-substituted carbamates / antihypertensive activity / antiarrhythmic activity

1. Introduction

Our previous investigations showed that some 1-cycloalkyloxy-3-alkylamino-2-propanols possessed marked β-adrenoreceptor blocking activity together with antiarrhythmic action [1, 2]. Compound 3-*tert.*-butylamino-1-cyclopentyloxy-2-propanol showed an antiarrhythmic activity similar to that of Propranolol.

Structure–activity analysis of several aminopropandiols and their guanidine analogues revealed that the alteration of the electron density of the nitrogen atom by its inclusion in a guanidine structure is favorable to express an antihypertensive and antiarrhythmic effect with long duration [3]. Some piperazine guanidines [4] and N-substituted aminoguanidines [5] have shown antiarrhythmic effect. N,N-Disubstituted ureas have been communicated to own antihypertensive action [6]. Furthermore, several ethyl esters of phenylcarbamic acid [7] have also been reported to possess antiarrhythmic activity.

Following these observations we have designed and synthesized some phenyl N-substituted carbamates and N-alkyl-N′-(3-cyclopentyloxy-2-hydroxypropyl)ureas to study them for antiarrhythmic and hypotensive activities.

2. Chemistry

The synthetic pathway followed for the preparation of the ureas **2a–f**, ethyl carbamates **3a–f** and phenyl carbamates **4a–c** (*table I, II* and experimental protocols) is represented in *figure 1*. The starting 1-cyclopentyloxy-3-alkylamino-2-propanols **1a–c** were obtained according to the method described in a previous communication [1]. The synthesis of 1,3-disubstituted ureas **2a–f** was accomplished through the interaction of equimolar quantities of aminopropanols **1a–c** and alkylisocyanates in anhydrous tetrahydrofuran medium at room temperature.

2-Hydroxypropylureas **2a–f** were refluxed with isopropylisocyanate in anhydrous ethylacetate for 3–4 h (TLC) to afford the requisite 1,2-disubstituted ethyl carbamates **3a–f**. By reaction of the aminopropanols **1a–c** with phenylchloroformate the phenyl N-(3-cyclopentyloxy-2-hydroxypropyl)carbamates **4a–c** were synthesized.

The ^{1}H-NMR (*table III*) and IR-spectra correspond to the structures of all new compounds. The band for OH-group, which is present in the spectra of the starting aminopropanols **1a–c** and of the ureido analogues **2a–f** is missing in the IR-spectra of carbamates **3a–f** in chloro-

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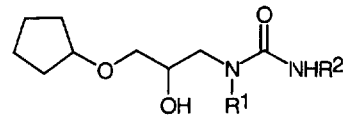
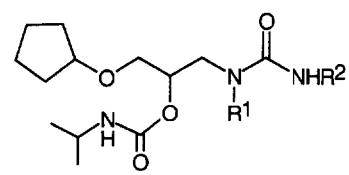
Table I. Physical properties of 3-alkyl-1-(3-cyclopentyloxy-2-hydroxypropyl)ureas **2a–f**.



Compound	R1	R2	M.p. (°C)	Yield (%)	Formula
2a	H	CH_3	81–82	56	$C_{10}H_{20}N_2O_3$
2b	$CH(CH_3)_2$	CH_3	101–103	52	$C_{13}H_{26}N_2O_3$
2c	$C(CH_3)_3$	CH_3	111–114	58	$C_{14}H_{28}N_2O_3$
2d	H	CH_2CH_3	89–91	63	$C_{11}H_{22}N_2O_3$
2e	$CH(CH_3)_2$	CH_2CH_3	109–111	60	$C_{14}H_{28}N_2O_3$
2f	$C(CH_3)_3$	CH_2CH_3	121–123	50	$C_{15}H_{30}N_2O_3$

Table II. Physical properties of 1-(cyclopentyloxymethyl)-2-(substituted ureido)ethyl N-isopropylcarbamates **3a–f**.



Compound	R1	R2	M.p. (°C)	Yield (%)	Formula
3a	H	CH_3	123–124	68	$C_{14}H_{27}N_3O_4$
3b	$CH(CH_3)_2$	CH_3	129–131	53	$C_{17}H_{33}N_3O_4$
3c	$C(CH_3)_3$	CH_3	141–143	52	$C_{18}H_{35}N_3O_4$
3d	H	CH_2CH_3	135–137	70	$C_{15}H_{29}N_3O_4$
3e	$CH(CH_3)_2$	CH_2CH_3	130–131	54	$C_{18}H_{35}N_3O_4$
3f	$C(CH_3)_3$	CH_2CH_3	150–152	56	$C_{19}H_{37}N_3O_4$

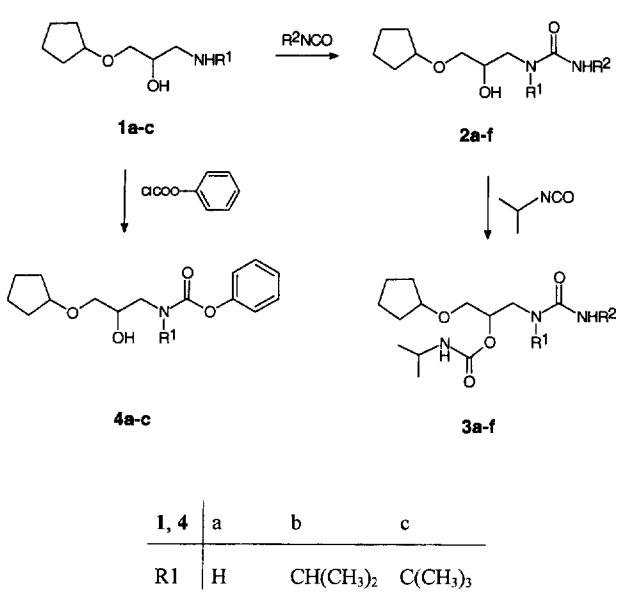


Figure 1.

form. The spectra of **3a–f** and **4a–c** in chloroform show absorption bands for carbonyl group in the 1800 – 1690 cm^{-1} region.

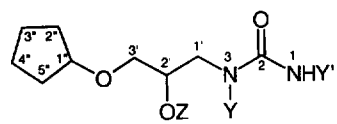
3. Pharmacology

The compounds were examined for acute toxicity on mice by intraperitoneal administration. They were screened with the norepinephrine arrhythmia test in rats, with the control group treated simultaneously with each compound. The effect of the compounds on arterial blood pressure was investigated. These studies were carried out on anesthetised rats. Propranolol was used as reference compound.

4. Results and discussion

The experimental data for the acute toxicity (LD_{50}) of compounds was compared with that of Propranolol.

Table III. ^{1}H-chemical shifts [a,b] (δ-values) of the compounds **2a–f** and **3a–f**.



Compound	H-2″,3″,4″,5″	H-1″, 2H-3′	H-2′	2H-1′	H-Z	H-Y	H-1	H-Y′
2a	1.04–1.80 m	3.32–3.54 m	3.68–3.80 m	3.07–3.18 m	3.78 s	5.04 s	5.20 s	2.76 d
2b	0.98–2.01 m	3.15–3.45 m 3.49 dd, 3.61 dd	3.72–3.94 m ABX	3.23 dd, 3.29 dd ABX	3.75 s	1.46 d, 4.27–4.48 m	5.31 s	2.71 d
2c	1.08–2.10 m	3.35–3.48 m	3.80–3.98 m	3.15–3.31 m	3.59 s	1.43 s	5.18 s	2.71 d
2d	0.99–2.15 m	3.30–3.45 m	3.70–3.84 m	3.02–3.18 m	3.75 s	5.00 s	5.20 s	1.95 t, 3.10 q
2e	1.02–2.05 m	3.15–3.40 m 3.45 dd, 3.56 dd	3.70–3.91 m ABX	3.22 dd, 3.30 dd ABX	3.78 s	1.38 d, 4.30–4.51 m	5.39 s	1.95 t, 3.05 q
2f	1.06–2.09 m	3.30–3.47 m	3.75–3.87 m	3.02–3.15 m	3.57 s	1.45 s	5.20 s	1.97 t, 3.09 q
3a	1.02–1.90 m	3.32–3.52 m	3.67–3.82 m	3.10–3.20 m	2.20 d, 4.30–4.59 m, 6.04 s	5.11 s	5.35 s	2.80 d
3b	1.01–2.05 m	3.18–3.48 m 3.55 dd, 3.65 dd	3.70–3.89 m ABX	3.20 dd, 3.30 dd ABX	1.92 d, 4.35–4.70 m, 6.02 s	1.92 d, 4.35–4.70 m	5.27 s	2.80 d
3c	1.05–2.11 m	3.30–3.50 m	3.79–3.89 m	3.12–3.25 m	2.14 d, 4.32–4.61 m, 6.01 s	1.45 s	5.15 s	2.73 d
3d	1.01–2.11 m	3.31–3.49 m	3.72–3.84 m	3.05–3.18 m	2.15 d, 4.30–4.52 m, 6.00 s	5.01 s	5.29 s	1.98 t, 3.05 q
3e	1.00–2.01 m	3.15–3.38 m 3.45 dd, 3.50 dd	3.70–3.89 m ABX	3.20 dd, 3.28 dd ABX	1.95 d, 4.32–4.71 m 6.02 s	1.95 d, 4.32–4.71 m	5.32 s	2.05 t 3.12 q
3f	1.05–2.08 m	3.30–3.46 m	3.72–3.89 m	3.16–3.31 m	2.12 d, 4.30–4.59 m, 6.10 s	1.48 s	5.18 s	2.10 t, 3.15 q

[a] Examples of coupling constants J (Hz): **2b**: 2H-3′, dd, J = 9.2/7.8, J = 9.2/4.9; 2H-1′, dd, J_{AB} = 17.6, J_{AX} = 3.2, J_{BX} = 8.0; H-Y, d, J = 6.5; H-Y′, d, J = 4.9. [b] Recorded on a Brucker WM 250 (250 MHz) spectrometer.

Analysis of the results showed that the compounds **2c**, **2f**, **3c** and **3f** have significantly lower toxicity than the standard (*table IV*).

The results of the antiarrhythmic activity assays are presented in *table V*. Most of the compounds exhibited antiarrhythmic action. Ureidoethylcarbamates **3c** and **3f** demonstrated the strongest activity. Their antiarrhythmic effect was comparable to that of the reference subctance (Propranolol). Phenyl carbamates **4b** and **4c** manifested an antiarrhythmic action close to the action of Propranolol. Compounds **2a**, **2d** and **4a**, which contain hydrogen as R^1, were inactive.

The compounds decreased the arterial pressure in different degrees (*table VI*), with the exception of compound **4a** which increased it. Compound **2a** has a two-phase effect characterised by an initial increase and a following decrease. The most pronounced hypotensive effect was found for compounds **2c** and **3c**. Their effect is comparable to that of Propranolol in equitoxic doses.

The results of the screening tests showed that the combination of ureido and carbamate structure in a single molecule afforded an agent (compound **3c**) with marked antiarrhythmic and hypotensive effects. Besides these results confirm that the change of the electron density on the nitrogen and oxygen atoms in **1a–c** by their incorporation in an ureido or carbamate structure, respectively, is favourable for displaying distinct hypotensive and antiarrhythmic properties.

5. Conclusion

The pharmacological and toxicological investigations of the compounds indicated that compounds **2c**, **3c** and **3f** have a low toxicity by intraperitoneal administration

Table IV. Acute toxicity (LD_{50}) of the compounds and Propranolol.

Compound	LD_{50} (mg/kg i.p.) and 95% confidence interval
Propranolol	105.5 (94.8–118.3)
2a	100.2 (90.1–115.6)
2b	147.3 [a] (126.2–170.4)
2c	195.8 [a] (180.3–214.4)
2d	185.1 [a] (160.2–216.2)
2e	191.8 [a] (170.6–253.5)
2f	219.5 [a] (201.7–242.8)
3a	130.9 [a] (120.8–156.9)
3b	167.2 [a] (158.2–178.9)
3c	219.1 [a] (202.4–231.3)
3d	156.0 [a] (124.5–210.8)
3e	195.8 [a] (163.6–239.7)
3f	221.2 [a] (192.1–266.3)
4a	103.6 (91.8–125.2)
4b	112.1 (105.9-129.8)
4c	101.8 (93.6–116.9)

[a] $p \leq 0.05$, statistically significant differences compared to Propranolol.

(LD_{50} = 195.8 mg/kg, 219.1 mg/kg and 221.2 mg/kg b.w. respectively). The toxicity of these compounds was significantly lower than the reference compound Propranolol. Moreover, in equitoxic doses, the antiarrhythmic and hypotensive effects of **3c** are comparable to those of Propranolol. Compound **2c** possesses a strong hypotensive effect. Antiarrhythmic activity of **3f** is similar to that of Propranolol. These results illustrate that compounds **2c**, **3c** and **3f** have prospects for further pharmacological and toxicological studies.

6. Experimental protocols

6.1. Chemical synthesis

Melting points were determined using a Boetius hot plate microscope and are uncorrected. IR spectra ($CHCl_3$) were recorded on a UR 20, Karl Zeiss, Jena apparatus. ^{1}H-NMR spectra were recorded on a Brucker 250 WM (250 MHz) or on a Jeol-PS-100 (100 MHz) spectrometers in deuterated dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS D300 double focusing mass spectrometer coupled to a JMA 2000 data system. The compounds were introduced by direct inlet probe, heated from 50 °C to 400 °C at a rate of 100 °C/min. The ionization current was 300 mA, the accelerating voltage 3 kV and the chamber temperature 150 °C. TLC was performed on precoated plates Kieselgel 60 F_{254} Merck with layer thickness 0.25 mm and detection by UV (254 nm). Yields of TLC–homogeneous isolated products are given. Microanalyses were performed by Microanalytical Unit, Chemical and Pharmaceutical Research Institute, Sofia and the results obtained were within ±0.4% of the theoretical values. The mass spectral data (M^+) for all compounds were in good agreement with the proposed molecular masses.

Table V. The effect of the tested compounds on norepinephrine-induced arrhythmia.

Compound	Dose one hundredth of LD_{50} (mg/kg)	Latent time of arrhythmia [a] (s)	Duration of arrhythmia [a] (s)	Full recovery period [a] (s)
Control [b]		8.0 ± 1.1	58.0 ± 2.0	457.0 ± 7.9
Propranolol	1.0	15.5 ± 2.1 [c]	30.0 ± 3.1 [c]	120.5 ± 11.5 [c]
2a	1.0	9.2 ± 2.5	54.5 ± 4.5	439.5 ± 8.7 [c]
2b	1.5	12.7 ± 1.5 [c]	43.7 ± 5.0 [c]	379.6 ± 11.9 [c]
2c	1.9	11.6 ± 1.9	39.5 ± 4.0 [c]	250 ± 18.0 [c]
2d	1.8	8.9 ± 1.4	52.2 ± 5.5	426.8 ± 7.5 [c]
2e	1.9	11.9 ± 1.0 [c]	44.7 ± 5.2 [c]	298.7 ± 15.2 [c]
2f	2.2	11.1 ± 3.5	42.5 ± 4.8 [c]	263.0 ± 21.7 [c]
3a	1.3	11.8 ± 1.2 [c]	45.0 ± 5.3 [c]	291.0 ± 14.5 [c]
3b	1.7	13.5 ± 1.6 [c]	35.6 ± 3.9 [c]	308.7 ± 10.8 [c]
3c	2.2	16.1 ± 2.2 [c]	27.5 ± 3.5 [c]	112.5 ± 16.8 [c]
3d	1.5	10.2 ± 2.8	51.9 ± 4.0 [c]	441.8 ± 14.8
3e	1.9	12.6 ± 1.4 [c]	37.0 ± 3.8 [c]	260.0 ± 12.9 [c]
3f	2.2	15.9 ± 1.9 [c]	28.0 ± 4.0 [c]	130.0 ± 15.6 [c]
4a	1.0	8.5 ± 1.3	50.0 ± 3.5 [c]	452.0 ± 10.8
4b	1.1	13.2 ± 2.2 [c]	32.5 ± 4.0 [c]	150.8 ± 17.4 [c]
4c	1.0	14.2 ± 1.9 [c]	31.7 ± 3.6 [c]	155.2 ± 19.2[c]

[a] n = number of determinations = 6. [b] For control experiments, saline with one or two drops of Tween 80 was used in equivalent volume. [c] $p \leq 0.05$, statistically significant differences compared to the control group.

Table VI. Hypotensive effect of the compounds.

Compound [a]	Dose one hundredth of LD_{50} (mg/kg, i.v.)	X ± SD [b] ($n = 6$)	Duration of the hypotensive effect (min)
Propranolol	1.0	43.0 ± 1.5	20.0 ± 3.4
2b	1.5	31.5 ± 2.1	18.5 ± 1.5
2c	1.9	40.9 ± 1.2	21.4 ± 2.1
2d	1.8	26.6 ± 2.8	33.5 ± 2.5
2e	1.9	23.8 ± 3.0	30.0 ± 3.0
2f	2.2	17.9 ± 4.1	24.5 ± 1.8
3a	1.3	15.3 ± 1.9	24.0 ± 2.0
3b	1.7	34.2 ± 2.3	20.6 ± 1.9
3c	2.2	43.7 ± 1.7	19.8 ± 1.5
3d	1,5	32.3 ± 1.8	18.5 ± 2.1
3e	1.9	16.9 ± 3.5	21.0 ± 1.2
3f	2.2	14.0 ± 2.8	16.5 ± 1.5
4b	1.1	23.0 ± 1.8	25.0 ± 2.1
4c	1.0	21.1 ± 2.2	23.8 ± 1.9

[a] Compound **2a** has a two-phase effect characterised by an initial increase and a following decrease; compound **4a** increases the blood pressure insignificantly. [b] Mean percentage decrease of lowering blood pressure ± SD, compared with the initial value; n = number of determinations.

*6.2. General method for 1-(3-cyclopentyloxy-2-hydroxypropyl)-3-alkylureas **2a–f***

A solution of 20 mmol alkylisocyanate in 10 mL anhydrous THF was added dropwise to a solution of 20 mmol **1a–c** in 10 mL anhydrous THF. The resulting mixture was stirred for 2–4 h (TLC) at temperature 40–50 °C and the solvent was evaporated in vacuo. The residue was dissolved in ethylacetate. The product precipitated at addition of hexane and was recrystallized from an ethylacetate/ethanol mixture.

*6.3. General method for 1,2-disubstituted ethyl N-isopropyl-carbamates **3a–f***

To a solution of 15 mmol **2a–f** in 15 mL anhydrous ethylacetate was added dropwise 15 mmol isopropylisocyanate at room temperature. The mixture was heated under reflux for 3 h. Then the mixture was cooled to room temperature, aceton was added and the resulting solid was recrystallized from ethanol.

*6.4. General method for phenyl carbamates **4a–c***

A solution of 20 mmol phenylchloroformate in 10 mL anhydrous benzene was added dropwise to a solution of 20 mmol **1a–c** in 10 mL anhydrous benzene. The mixture was stirred at room temperature for 2–4 h (TLC) and left overnight at the same temperature. Then it was treated with 5% sodium hydroxyde, washed with water, dried and the benzene was evaporated in vacuo. The residue was dissolved in ethylacetate. The separated product was recrystallized from ethanol/acetone (2:1).

*6.4.1. Phenyl N-(3-cyclopentyloxy-2-hydroxypropyl)carbamate **4a***

Yield 64%, m.p. 117–119 °C. ^{1}H-NMR: 1.02–2.01 (m, 8H, $4(CH_2)$), 3.01–3.29 (m, 2H, NCH_2), 3.32–3.54 (m, 3H, CH of C_5H_9, OCH_2), 3.60 (s, 1H, OH), 3.81 (m, 1H, CH), 5.32 (s, 1H, NH), 6.95 (t, $J = 7.0$, 1H, H-para), 7.23 (dd, $J = 8.2/7.1$, 2H, 2(H-metha)), 7.38 (d, $J = 8.1$, 2H, 2(H-ortho)). Anal. $C_{15}H_{21}NO_4$ (C, H, N).

*6.4.2. Phenyl N-isopropyl-N-(3-cyclopentyloxy-2-hydroxypropyl) carbamate **4b***

Yield 62%, m.p. 127–130 °C. ^{1}H-NMR: 0.99–1.49 (m, 8H, $4(CH_2)$), 1.77 (d, $J = 6.5$, 6H, $2(CH_3)$), 3.18 and 3.25 (2H, AB of ABX, $J_{AB} = 17.4$, $J_{AX} = 3.0$, $J_{BX} = 7.9$, NCH_2), 3.32 (dd, $J = 9.2/7.6$, 1H, OCHH), 3.31–3.42 (m, 1H, CH of C_5H_9), 3.49 and 3.53 (s, 1H and dd, $J = 9.1/4.7$, 1H, OH and OCHH), 3.91 (m, 1H, X of ABX, CH), 4.45 (m, 1H, $CH(CH_3)_2$), 6.96 (t, $J = 7.1$, 1H, H-para), 7.18 (dd, $J = 8.1/7.3$, 2H, 2(H-metha)), 7.33 (d, $J = 8.1$, 2H, 2(H-ortho)). Anal. $C_{18}H_{27}NO_4$ (C, H, N).

*6.4.3. Phenyl N-tert.-butyl-N-(3-cyclopentyloxy-2-hydroxypropyl) carbamate **4c***

Yield 62%, m.p. 130–131 °C. ^{1}H-NMR: 1.01–1.51 (m, 8H, $4(CH_2)$), 1.70 (s, 9H, $3(CH_3)$), 3.10–3.27 (m, 4H, CH of C_5H_9, NCH_2, OCHH), 3.48 (dd, $J = 9.2/4.3$, 1H, OCHH), 3.55 (s, 1H, OH), 3.96 (m, 1H, CH), 6.95 (t, $J = 7.2$, 1H, H-para), 7.16 (dd, $J = 8.0/7.1$, 2H, 2(H-metha)), 7.29 (d, $J = 7.9$, 2H, 2(H-ortho)). Anal. $C_{19}H_{29}NO_4$ (C, H, N).

6.5. Pharmacology

6.5.1. Acute toxicity

The experiments were conducted on white male mice with body weight 18–22 g. Acute toxicity (LD_{50}) of the studied compounds was assessed by dissolving them in saline (0.9% NaCl) with 1–2 drops of Tween 80 and administering them to mice via intraperitoneal (i.p.) route. The percentage mortality within 7 days

was noted. LD_{50} was evaluated for 5 different doses, each on the 6 animals and calculated by the method of Litchfield–Wilcoxon [8].

6.5.2. Antiarrhythmic effect

Cardiac arrhythmia was induced by intravenous (i.v.) administration of norepinephrine (0.01 mg) [9] into anesthetized (Nembutal 30 mg/kg, i.v.) male Wistar rats. The test compounds were imployed i.v. in dose one hundredth of LD_{50} 5 min prior to application of norepinephrine. The ECG-II^{nd} lead was recorded on Transistor-Electrocardiograf-NEK 215 (Germany), starting immediately after norepinephrine injection. The substance-induced delay in the appearance of the arrhythmias was determined and compared to the control group of rats pretreated with physiological saline with 1 or 2 drops of Tween 80. The duration of arrhythmia and the full recovery period were also measured. Each group consisted of 6 animals.

6.5.3. Hypotensive effect

Male Wistar rats (body weight 250–270 g) were anesthetized with Nembutal. The compounds ($n = 6$ for each compound) were administered i.v. in dose one hundredth of LD_{50} and arterial blood pressure was measured indirectly on the tails of rats on 'Indirect Blood Pressure Meter LE 5002' (Hungary). The mean ($X \pm SD$) percentage decrease of blood pressure from the initial value was determined. The duration of lowered blood pressure were also measured.

References

[1] Georgiev A., Dantchev D., Chalina E., Petkov W., Manolov P., Arch. Pharm. (Weinheim) 312 (1979) 881–891.

[2] Dantchev D., Georgiev A., Chalina E., Dobreva D., Staneva D., Arch. Pharm. (Weinheim) 312 (1979) 857–863.

[3] Chalina E., Dantchev D., Georgiev A., Staneva D., Arch. Pharm. (Weinheim) 317 (1984) 63–69.

[4] Pascal J., Pinhas H., Laure F., Eur. J. Med. Chem. 25 (1990) 81–85.

[5] Erczi I., Rabloczky G., Varro A., Somogy G., Kürthy M., Body I., Eur. J. Med. Chem. 28 (1993) 185–193.

[6] Kliose S., Ergott F., Wilker J., Woodward D., J. Med. Chem. 22 (1979) 1497–1504.

[7] Benes L., Scasna M., Czech. CS 27 52 25 CA 119 (1993) 22 57 01 e.

[8] Litchfield J.I., Wilcoxon F., J. Pharmacol. Exp. Ther. 96 (1949) 99–102.

[9] Szekeres L., Papp G., Experimental Cardiac Arrhythmias and Antiarrhythmic Drugs, Akademiai Kiado, Budapest, 1971.