

Basic pharmacological evaluation of modified phenyl carbamic acid derivatives on cardiovascular functions under *in vitro* conditions in rats

Eva Kralova¹ and Ivan Malik²

¹ Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia

² Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia

Abstract. The study aimed to evaluate the basic pharmacological effects of modified phenyl carbamic acid derivatives with a basic part made of *N*-phenylpiperazine (compounds 6a, 6b, 6c, 6d) in Wistar rats. The compounds were evaluated for their ability to decrease the phenylephrine-induced contraction of the aortic strips of rats after repeated administration of the compounds and their ability to inhibit the positive chronotropic effect of isoproterenol on spontaneously beating rat atria. The ability to inhibit the vasoconstriction effect of phenylephrine was confirmed in all compounds in the range from 10.39 % to 13.65 %. The most significant vasoconstriction was achieved in compound 6d (86.35%, $p < 0.001$). None of the compounds reached the effect of carvedilol. All compounds proved an antagonistic ability to the positive chronotropic effect of isoproterenol. The highest value of the anti-isoproterenol effect was identified for the compound 6c ($pA_2 = 8.21 \pm 0.56$; $p < 0.05$). Only compound 6a decreased heart rate significantly (by 3.17%, $p < 0.05$), so we can indicate its potential negative chronotropic effect. The obtained results showed that the evaluated compounds confirmed the basic characteristics of beta-blockers with additional α -adrenolytic properties.

Key words: Beta-blockers — Phenyl carbamic acid derivatives — Isolated aorta — Isolated atrium — Rat

Highlights

- Modified phenyl carbamic acid derivatives showed the basic characteristics of beta-blockers with additional α -lytic properties.
- The greatest ability to inhibit the vasoconstriction effect of phenylephrine was confirmed in a compound with methyl substituents in the basic part of the molecule.
- The compound containing a dichloro-substituent proved the greatest antagonistic ability to the positive chronotropic effect of isoproterenol.
- Only compound with unsubstituted *N*-phenylpiperazine group decreased heart rate significantly.

Introduction

β -blockers are an essential class of cardiovascular medications for reducing morbidity and mortality in various cardiac conditions (Fumagalli et al. 2020). Moreover,

more than 50 years after their discovery, new evidence is emerging, suggesting their protective effect beyond the cardiovascular system such as prophylactic treatment of migraine attacks (Jackson et al. 2015; Silberstein 2015) or in cancer therapy (Na et al. 2018; Yap et al. 2018). The pharmacological class of β -blockers includes a lot of molecules with largely different pharmacokinetic and pharmacodynamic characteristics, whose clinical indications stemmed from large randomized clinical trials (Fumagalli et al. 2020).

Correspondence to: Eva Kralova, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University, Kalinčiaková 8, 832 32 Bratislava, Slovakia
E-mail: kralova5@uniba.sk

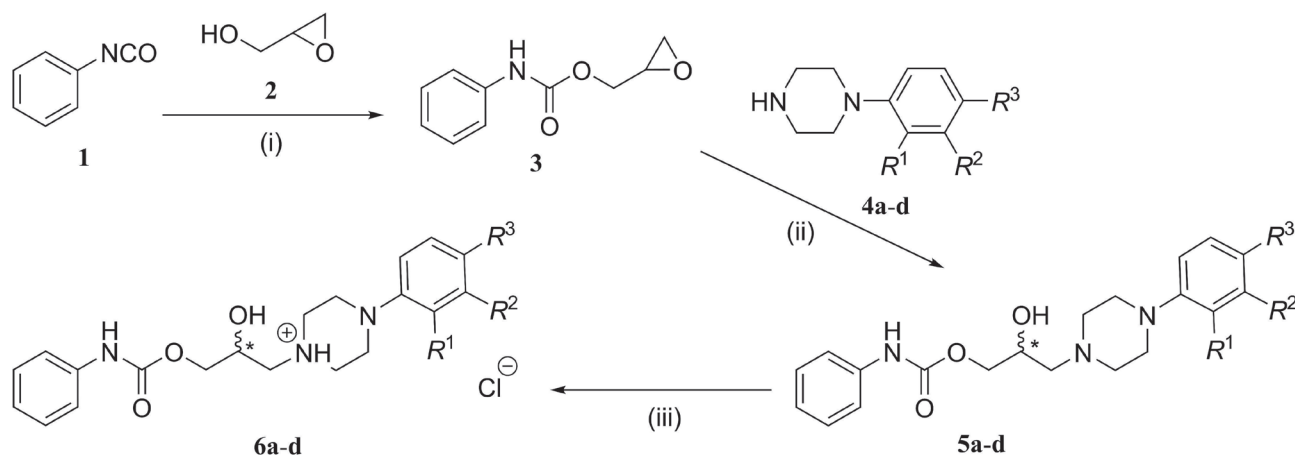


Figure 1. Scheme of synthesis of *in vitro* tested phenylcarbamic acid esters (series 6a–d) containing a so-called privileged *N*-(substituted phenyl) piperazine scaffold. The substituents R^1 , R^2 and R^3 in the structure of the commercially available amines (derivatives 4a–d), basic intermediates (5a–d) and final compounds (6a–d) were as follows – 4a, 5a, 6a: $R^1 = R^2 = R^3 = \text{H}$; 4b, 5b, 6b: $R^1 = R^3 = \text{H}$, $R^2 = \text{CF}_3$; 4c, 5c, 6c: $R^1 = \text{H}$, $R^2 = R^3 = \text{Cl}$; 4d, 5d, 6d: $R^1 = R^2 = \text{CH}_3$, $R^3 = \text{H}$. Reagents and conditions – (i) anhydrous toluene ($V = 50.00 \text{ ml}$), continuous stirring at 70°C for 24 hours, (ii) anhydrous propane-2-ol ($V = 50.00 \text{ ml}$), continuous stirring at reflux for 20 hours, (iii) saturated solution of hydrogen chloride in diethyl ether, continuous stirring for 5 hours.

In the efforts to develop a proper β -blocking effect, the aryloxyaminopropanol skeleton must be preserved, as well as activity in a wider spectrum of substituted and also unsubstituted aromatic nuclei. The substituents on the basic nitrogen are also important. Experimental studies with phenoxyaminopropanols confirmed increased cardioselectivity for *para*-substituted derivatives (Polakovicova and Cizmarikova 2012). Modification in the connecting chain and the salt-forming fragment of *N*-methyl piperazine derivatives also led to a change in the quality of the biological activity (Malik et al. 2014). Compounds that contain a substituted *N*-phenylpiperazine group significantly antagonize α -adrenergic receptors, which makes it possible to design therapeutically active molecules capable of blocking both types of adrenoceptors. Substitution of the phenyl nucleus in the lipophilic part of the molecule in the *para*-position causes a decrease in activity, while substitution in the *ortho*- or *meta*-position enhances the β -blocking effect. Cardioselectivity or other α -blocking properties can be achieved by modifying the salt-forming part of the molecule when the nitrogen-bonded substituent becomes part of the amino-

propanol linking chain (Bruchata and Cizmarikova 2010). The rationale of the tested compounds design was the assumed affinity for both β and particularly α_1 -adrenoceptors because of therapeutically effective phenylpiperazine part (Cecchetti et al. 2000). In an attempt to confirm and/or influence the β -blocking efficiency of the compounds, the primary aryloxyaminopropanol structure of beta-blockers was modified by incorporating a carbamoyl (-NH-CO-) group on the bridge connecting the phenyl nucleus to the *N*-phenylpiperazine group. Although basic β -adrenolytic effects were also observed in the modified structures, they were approximately 10 times weaker than the original aryloxyaminopropanols (Račanská et al. 2005).

This work investigated the pharmacological assessment of basic cardiovascular functions of rats *in vitro* after administration of modified phenyl carbamic acid derivatives. For the biological evaluation, isolated aorta and atria from normotensive Wistar rats were used.

Material and Methods

Tested compounds

A set of original phenylcarbamic acid esters (compounds 6a, 6b, 6c, 6d) containing a so-called privileged *N*-(substituted phenyl) piperazine scaffold (Fig. 1, Table 1) were synthesised and *in vitro* screened focusing on their impact on the contraction of isolated aorta caused by phenylephrine and possible inhibition of a positive chronotropic effect of isoproterenol on isolated atria of rats. Carvedilol, a drug currently

Table 1. Summary formula and molecular weight (M.w.) of *in vitro* tested compounds

Compound	Summary formula	M.w. (g/mol)
6a	$\text{C}_{20}\text{H}_{26}\text{O}_3\text{ClN}_3$	391.90
6b	$\text{C}_{21}\text{H}_{25}\text{O}_3\text{ClF}_3\text{N}_3$	459.89
6c	$\text{C}_{20}\text{H}_{24}\text{O}_3\text{Cl}_3\text{N}_3$	460.78
6d	$\text{C}_{22}\text{H}_{30}\text{O}_3\text{ClN}_3$	419.95

used in clinical practice, was used as a reference drug. The compounds were dissolved in methanol and prepared at a concentration of 10^{-6} mol/l before application.

Synthesis of phenylcarbamic acid esters (6a–d) containing an N-(substituted phenyl) piperazine moiety

Procedure for the preparation of (\pm)-(oxiran-2-yl)methyl phenylcarbamate (3)

Briefly, starting N-phenyl isocyanate (1; CAS Registry Number 103-71-9, n = 60.00 mmol) was dissolved in dried toluene (V = 50.00 ml) and (\pm)-(oxiran-2-yl)methanol (2; CAS Registry Number 556-52-5) was continuously added in 10% excess (n = 66.00 mmol) to this solution (Farrissey and Nashu 1970; Pospisilova et al. 2020; Ćurillová et al. 2022) leading to crude (\pm)-(oxiran-2-yl)methyl phenylcarbamate (3). The solution was concentrated *in vacuo* and the compound 3 was dissolved in chloroform. The solution was properly washed with 3×50 ml distilled water, the organic fraction was collected, properly dried over anhydrous MgSO₄ and filtered. The solution was concentrated *in vacuo* and an oily oxiran-2-yl moiety-containing intermediate 3 (Fig. 1) was isolated.

General procedure for the preparation of 2-hydroxy-3-[4-(substituted phenyl)piperazin-1-yl]propyl phenylcarbamates (5a–c)

The reaction of the compound (3) with commercially available basic amines (Pospisilova et al. 2020; Ćurillová et al. 2022), i.e., 1-phenylpiperazine (4a; CAS Registry Number 92-54-6, n = 12.00 mmol), 1-[3-(trifluoromethyl)phenyl]piperazine (4b; CAS Registry Number 15532-75-9, n = 12.00 mmol), 1-(3,4-dichloro)phenylpiperazine (4c; CAS Registry Number 57260-67-0, n = 12.00 mmol) and 1-(2,3-dimethylphenyl)piperazine (4d; CAS Registry Number 1013-22-5, n = 12.00 mmol), respectively, in anhydrous propan-2-ol (V = 50.00 ml) provided oily 2-hydroxy-3-[4-(substituted phenyl)piperazin-1-yl]propyl phenylcarbamates (5a–d; Fig. 1). The particular solutions were concentrated *in vacuo*, and crude bases (5a–d) were dissolved in chloroform and properly washed with 3×50 ml distilled water. The organic fraction was collected, dried over anhydrous MgSO₄ and filtered. The required oily intermediates (5a–d) were isolated *in vacuo* and used in a final synthetic step.

General procedure for the preparation of 1-[2-hydroxy-3-(phenylcarbamoyloxy)propyl]-4-([substituted] phenyl) piperazin-1-ium chlorides (6a–c)

A saturated solution of hydrogen chloride in diethyl ether was added to particular chloroform solutions of

the bases (5a–d) leading to crude 1-[2-hydroxypropyl-3-(phenylcarbamoyloxy)]-4-phenylpiperazin-1-ium chloride (6a), 1-[2-hydroxypropyl-3-(phenylcarbamoyloxy)]-4-(3-trifluoromethylphenyl)piperazin-1-ium chloride (6b), 1-[2-hydroxypropyl-3-(phenylcarbamoyloxy)]-4-(3,4-dichlorophenyl) piperazine-1-ium chloride (6c) and 1-[2-hydroxypropyl-3-(phenylcarbamoyloxy)]-4-(2,3-dimethylphenyl)piperazin-1-ium chloride (6d), respectively.

The desired racemic solid compounds (6a–d; Fig. 1) screened *in vitro* were crystallised twice from a cyclohexane-ethyl acetate-propane-2-ol mixture (6a) or propane-2-ol (6d). Thus, the yield of the given final synthetic procedure for the derivatives 6a–d was as follows: 41.05% (6a), 39.20% (6b), 42.15% (6c) and 29.80% (6d). The summary formula and molecular weight (in g/mol unit) of prepared salts are listed in Table 1.

Pharmacological evaluation

Animals

All three-month-old male Wistar rats used in the experiments were obtained from the breeding station Dobra Voda (Slovak Republic). Animals were allowed to acclimatize to the housing conditions with free access to food and tap water for at least seven days. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published in the Collection of Laws of the Slovak Republic and was approved by the Ethics Committee of the Faculty of Pharmacy, Comenius University, and by the State Veterinary and Food Administration of the Slovak Republic.

Measurement of vascular contractility in vitro

After male rats were sacrificed (2.5% thiopental, 80 mg/kg bm, *i.p.*, Biochemie GmbH, Austria), the thoracic aorta was excised from the diaphragm to the arch and placed into an isolated tissue bath containing Krebs-Henseleit solution at 37°C (composition in mol/l 118.0; KCl 5.6; NaHCO₃ 25; MgSO₄ 1.2; NaH₂PO₄ 0.18; CaCl₂ 2.5, glucose 11.0, Centralchem, Bratislava) and aerated with a pneumoxide (5% CO₂). Three-millimetre-long segments were cut from the aorta and placed between two stainless steel hooks inserted into the lumen and placed into the apparatus for isolated organs (TSZ-04 Multichamber Tissue Bath, Experimetria, Hungary) for isometric tension recordings. The tonus was set to 2.0 g and stabilized. After 1 hour of equilibration, phenylephrine (Merck Life Science) at concentration 10^{-8} to 10^{-5} was added cumulatively. When the preparations reached a stable level of tension, the acetylcholine (Merck Life Science) at 10^{-5} mol/l was added. After another 15 min

stabilization, the evaluated compounds (6a–d) or carvedilol (kind gift from Zentiva, Slovak Republic) were administered in a concentration of 10^{-6} mol/l and 30 min later phenylephrine was given cumulatively again. The responses were transferred as digital signals (FSG-01 Force/displacement transducer, Experimetria) and recorded with the S.P.E.L. Advanced ISOSYS software (Experimetria). The presented data are expressed as average values of the animals in the group; three recordings were taken from each animal. The effect of the compounds was evaluated according to their ability to inhibit the maximum contraction of the isolated aorta induced by phenylephrine. Concentrations for the vasoconstrictive effect of phenylephrine were constructed from the measured values of contraction increments. We used the β -adrenoceptor antagonist carvedilol as a standard. Carvedilol is a non-selective β -blocker with intrinsic vasodilatory activity due to its anti- α -adrenergic activity and its capacity to enhance nitric oxide release (Villanueva et al. 2022)

Antiisoproterenol activity on isolated atria

The rat right atria from the same animals were connected to an isometric transducer in Krebs-Henseleit solution at 30°C under a resting tension of 1 g and saturated with pneumoxide (O_2 and 5% CO_2). The preparation was allowed to stabilize for at least 30 min. First, the initial heart rate (HR) of the stabilized atrium was recorded. After that, isoproterenol chloride (ISO, dissolved in ascorbic acid 0.05%, Merck Life Science) was added cumulatively in increased concentrations (10^{-12} – 10^{-5} mol/l), at the end of the first minute after the application of ISO, the HR was measured. After repeated washing out of the preparation and HR stabilization, the tested compounds (6a–d) or standard carvedilol were added in a concentration of 10^{-6} mol/l and the 5th, 10th, 15th, 20th minute, HR changes were recorded and the concentration-response curve (CRC) was plotted. After the atria were washed and allowed to re-equilibrate, test compounds or standards were added to the bath 20 min

before the second CRC was obtained and changes in the heart rate were registered. The affinity for isoproterenol was expressed as EC_{50} (agonist concentration producing 50% of maximum response). The antagonist potency of the compounds was calculated from the shift in CRC of isoproterenol and expressed as dissociation constants (pA_2 values), *i.e.*, the negative logarithm of the antagonist molar concentration that caused twofold inhibition in isoproterenol response curves.

Statistical analysis

Results are expressed as mean \pm standard error of the mean (SEM). Means were compared using the Student's unpaired *t*-test. Values were considered statistically significant when $p < 0.05$.

Results

Isolated aorta

To demonstrate the effects of the compounds on endothelial function, we measured the contractile responses of the thoracic aorta. We assessed the ability of the compounds at concentration 10^{-6} mol/l to inhibit the constriction of aortal rings induced by cumulatively giving the α_1 -adrenergic agonist phenylephrine on isolated aortic rings. As is shown in Table 2, the application of all tested compounds to aortal rings decreased significantly ($p \leq 0.01$, $p \leq 0.001$) maximal contractibility of the tissue in a range from 10.39 ± 2.18 (6a) to 13.65 ± 1.33 (6d) without marked differences among them. The tested compounds 6c and 6d inhibited aortic contraction the most compared to the other compounds but did not achieve the effect of carvedilol. Carvedilol used at the same concentration as the evaluated compounds inhibited the phenylephrine-induced aortal contraction to 16.46% of the initial values (Fig. 2).

Table 2. Effect of the tested compounds (10^{-6} mol/l) and carvedilol on the phenylephrine-induced contraction of the isolated aorta from rats

Compound	Contraction of aorta (mN)		Inhibition of contraction	
	before	after	mN	%
Control	3.18 ± 0.04	3.08 ± 0.01	0.10 ± 0.07	1.34 ± 1.01
6a	3.08 ± 0.05	$2.75 \pm 0.07^{**}$	0.33 ± 0.07	10.39 ± 2.18
6b	3.28 ± 0.08	$2.90 \pm 0.05^{***}$	0.38 ± 0.04	11.92 ± 1.36
6c	2.51 ± 0.05	$2.77 \pm 0.04^{***}$	0.44 ± 0.04	12.96 ± 1.00
6d	3.24 ± 0.04	$2.80 \pm 0.04^{***}$	0.44 ± 0.04	13.65 ± 1.33
Carvedilol	3.52 ± 0.03	$1.22 \pm 0.08^{***}$	2.30 ± 0.08	83.54 ± 4.56

Each value represents the mean \pm SEM from 6 experiments. ** $p < 0.01$; *** $p < 0.001$ vs. control values. Contraction of aorta was measured before and after the administration of the compound.

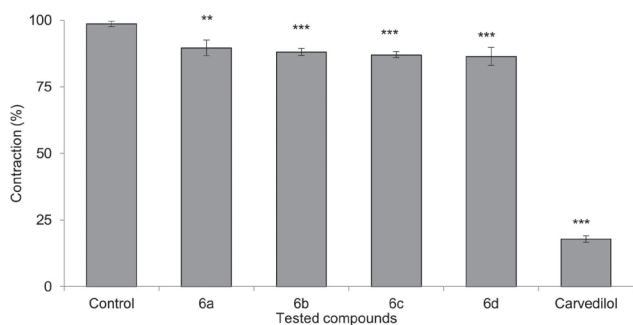


Figure 2. Inhibitory effect of the compounds (6a, 6b, 6c, 6d) and carvedilol at concentration 10^{-6} mol/l on phenylephrine-induced contractility of the isolated aorta. Each value represents the mean \pm SEM from 6 experiments. ** $p < 0.01$; *** $p < 0.001$ vs. control values.

Isolated atria

Antiisoproterenol activity of the compounds on the heart rate was examined *in vitro* in spontaneously beating right atria of rats and expressed as EC_{50} values, from which pA_2 values were calculated. All the evaluated compounds confirmed the effect when their calculated pA_2 values varied from 6.92–8.20 (Table 3). Compared to the used beta-blocker, the carvedilol, compound 6c showed a moderate effect ($p < 0.05$) and only a slight effect was detected for other tested compounds.

After application of the evaluation compound in a concentration of 10^{-6} mol/l, heart frequency (HF) was measured in the 5th, 10th, 15th and 20th minutes (Fig. 3). Changes in HF were compared to the initial HF values of the atria after stabilization (ISO control) due to washing with diluted Krebs-Henseleit solution for 1 hour. However, the resulting values show that the tested compounds did not significantly change the HF of the isolated atria immediately after application, except for compound 6a, which increased it by 5.35%. In the remaining minutes, the expected negative chronotropic effect was manifested only in compound 6a. This reduction reached the value of carvedilol. The other compounds proved to be ineffective in terms of a negative chronotropic effect, as there was a slight increase in HF after administration of the compounds.

Discussion

In the presented study, we evaluated the pharmacological effects of newly synthesized phenyl carbamoyloxyaminopropanol derivatives with the basic part formed by substituted *N*-phenylpiperazine under *in vitro* conditions. Compounds with working labels 6a, 6b, 6c, and 6d represented phenylcarbamoyloxyaminopropanol as the basic skeleton, where the basic part was *N*-phenylpiperazine with various substituents.

Based on the structure of the tested compounds, we expected their beneficial effect on cardiovascular functions. These *N*-arylpiperazine compounds are thought to exhibit dual α - and β -adrenolytic effects. The basic component contains an *N*-phenylpiperazine fragment that binds to α_1 -receptors, causing vasodilation. By interfering with and modifying the basic skeleton of β -blockers of the aryloxyaminopropanol type, it is possible to design new compounds with additive properties for cardiovascular functions.

The experiment aimed to evaluate their effect on the isolated aorta pre-contracted with the α_1 -sympathomimetic phenylephrine and the effect on the isolated atria of normotensive rats, with the determination of their antiisoproterenol efficacy and the ability to influence their heart rate. In practice, this entails evaluating the ability to block enhanced aortic contractility (α_1 -sympatholytic effect) and antagonise positive chronotropy on isolated atria (β_1 -sympatholytic effect). Some studies have shown that the administration of β -blockers is associated with a higher incidence of adverse effects compared to other cardiovascular drugs (Mugoša et al. 2016). As part of a comprehensive study of the relationships between the chemical structure, physicochemical properties and biological (antiarrhythmic, antihypertensive) activity of the compounds, new potential β -blockers are being prepared (Malik et al. 2011). The wide possibility of aromatic ring substitution in β -blockers and substituents on nitrogen leads to the preparation of compounds with combined pharmacological properties. These compounds show affinity not only for the β -adrenergic receptor but also for the α -adrenergic receptor. The backbone of all compounds is the oxypropane-2-ol chain,

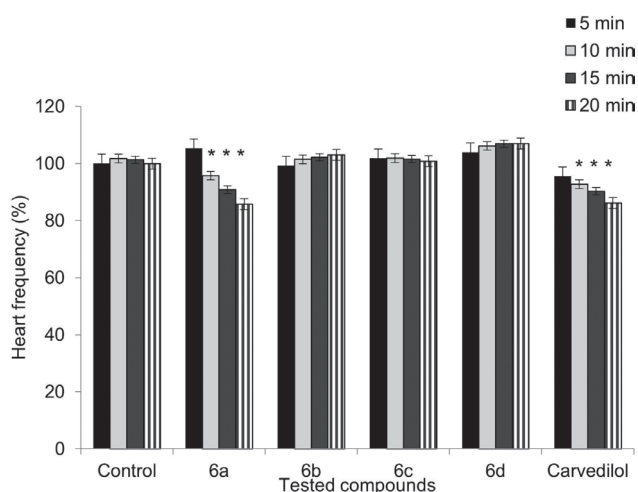


Figure 3. Relative changes in heart rate were evaluated for compounds 6a, 6b, 6c, 6d, and carvedilol at 5, 10, 15, and 20 minutes following compound administration. Each value represents the mean \pm SEM from 6 experiments. * $p < 0.05$ vs. control values.

Table 3. Effective concentrations (EC_{50}) of isoproterenol for the atria heart rate before and after incubation with the evaluated compounds and their pA_2 values

	EC_{50} (isoproterenol, 10^{-9} mol/l)	pA_2
Control	0.630 ± 0.278	6.92 ± 0.12
6a	4.74 ± 1.64	
Control	0.381 ± 0.198	6.54 ± 0.49
6b	5.91 ± 5.29	
Control	0.00483 ± 0.00436	8.20 ± 0.56
6c	$2.33 \pm 1.68^*$	
Control	0.00234 ± 0.00141	7.75 ± 0.61
6d	2.20 ± 1.48	
Control	0.735 ± 0.112	9.20 ± 0.56
Carvedilol	$26.6 \pm 7.8)^*$	

Each value represents the mean \pm SEM from 6 experiments. * $p < 0.05$ vs. control values.

which occurs in classic β -sympatholytics as well as in those with cardioselective, antiarrhythmic and antihypertensive properties (Bruchata and Cizmarikova 2010). The effort to find compounds with a combined antihypertensive effect resulted in the preparation of a series of compounds from the group of aryloxyaminopropanols, containing in their structure substituted phenylpiperazines (urapidil, naftopidil) significantly antagonizing α -adrenergic receptors. Labetalol, carvedilol and celiprolol are currently clinically used compounds with a combined effect on both α and β -adrenergic receptors (Gonec et al. 2008).

The study confirmed that all compounds were able to inhibit the vasoconstrictive effect of α_1 -sympathomimetics, showing a contraction range of 86.35% to 89.61%. With statistical significance ($p < 0.001$), all compounds were effective, with compound 6d demonstrating the greatest inhibition. This effect is attributed to the presence of methyl substituents at the 2nd and 3rd positions of the benzene nucleus in the molecule's basic part. However, none of the compounds were as effective as carvedilol. The inhibitory effect of the compounds on the vasoconstrictor-acting phenylephrine provides information about the potential antihypertensive effect of the tested structures.

In an experiment on isolated beating atria of rats, we observed the antagonistic effect of the tested compounds on the positive chronotropic effect of the β -sympathomimetic – isoproterenol. Based on the results, we calculated the pA_2 value, which indicates the ability to antagonize the effects of the agonist specifically competitively. The highest values of the anti-isoproterenol effect were found for compound 6c, with a pA_2 value closest to that of the positive control, carvedilol. This result can be attributed to the halogen substituents in the basic region of the molecule of this compound which contains a dichloro substituent. A slightly lower pA_2 value

was found for compound 6d, the other two compounds 6a and 6b had close pA_2 values.

We can conclude that the tested compounds show the basic properties of β -blockers, they inhibit the contraction of the isolated aorta caused by phenylephrine and the positive chronotropic effect of isoproterenol on the isolated atria of rats. Compound 6d with methyl substituents showed the strongest inhibition on isolated aortas precontracted with phenylephrine. Compound 6c demonstrated the highest anti-isoproterenol effect values, which can be attributed to the presence of halogen substituents in the basic part of its molecules. On the other hand, only compound 6a, which is formed on the aromatic nucleus by an unsubstituted *N*-phenylpiperazine group, reduced the spontaneous heart rate of isolated rat atria. The results obtained suggest that the structures being investigated have the potential to be used as antihypertensive drugs. However, because these structures have not been previously described and the results obtained are not sufficient for further evaluation, additional research is needed to better characterize the properties of these compounds.

Conflict of interest. The authors declare there are no competing interests.

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Author contribution. EK: conceptualization, methodology, validation, investigation, writing – review & editing, supervision, project administration, funding acquisition. IM: chemical synthesis, validation, writing – review & editing. Both authors read and approved the final manuscript.

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