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Antiarrhythmic properties of some aroxyethylamine derivatives with adrenolytic activity

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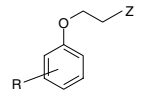
A series of aroxyethylamines (**1**–**10**) have been previously evaluated for antihypertensive and adrenolytic properties. Of the derivatives tested, four (compounds **4**, **7**, **8** and **10**) displayed significant antihypertensive activity and binding affinities for α- and β-adrenergic receptors. As a continuation of our study, we present here the *in vivo* and *in vitro* antiarrhythmic activity of compounds **1**–**10**, as well as their electrocardiographic properties. Only compounds **4**, **7**, **8** and **10** demonstrated strong antiarrhythmic activity in adrenaline induced arrhythmia after intravenous and oral administration. In addition, compounds **4** and **7** significantly decreased heart rhythm disturbances in arrhythmia induced by coronary artery occlusion and reperfusion. The pharmacological results and receptor binding studies suggest that the antiarrhythmic activity of the compounds tested may be related to their adrenolytic properties. Moreover, the presence of a methoxyphenylpiperazine moiety seems to be required for their pharmacological activity.

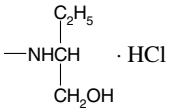
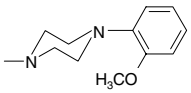
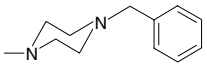
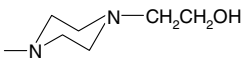
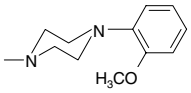
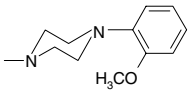
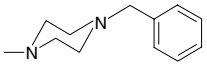
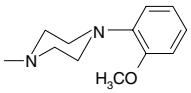
1. Introduction

β-Adrenoceptor (β-AR) blocking agents (β-blockers), the history of which began with the initial discovery of propranolol (Black and Stephenson 1962; Black and Prichard 1973), are normally used to treat cardiovascular diseases such as hypertension, angina pectoris, myocardial infarction, chronic heart failure, cardiac arrhythmias and some other conditions e.g. glaucoma. With respect to their clinical utility, β-blockers are typically differentiated by their selectivity for β-ARs. The non-selective β-blockers, including propranolol, oxprenolol, pindolol, nadolol and timolol, each antagonize both β_1- and β_2-ARs. However, some adverse side effects related to their β_2-blocking activity, for example, peripheral circulatory and respiratory disturbances or hypoglycemia during therapy of diabetics, have limited their clinical use. Some of these problems have been solved by concerted and targeted efforts to develop cardioselective β_1-AR blockers. Selective β_1-blockers, such as metoprolol, atenolol, esmolol and acebutolol, with much greater binding affinity to β_1-ARs, are mostly prescribed for patients in whom β_2-AR antagonism might be associated with an increased risk of adverse effects (e.g. asthma, diabetes, peripheral vascular disease, Raynaud's disease). In order to further improve the pharmacological profiles of β-blockers, a new generation of these drugs (labetalol, celiprolol, carvedilol, bucindolol) also possessing vasodilator activity has been introduced into clinical use. Their beneficial effect on regional circulation in contrast to the classical β-blockers such as propranolol or pindolol is based on their α_1-antagonistic or β_2-agonistic properties (Mann et al. 1986; Von Mollendorff et al. 1986; Marwood and Stokes 1986).

During the past few years, we have been conducting extensive studies aimed at identifying new structures with antihypertensive and/or antiarrhythmic activities (Marona et al. 2001; Maciag et al. 2003). Among the compounds we have investigated there are derivatives which contain some structural elements (aminoisopropanoloxy, aminoalkanol or piperazine moieties) of known circulatory agents such as propranolol, naftopidil or 5-methylurapidil. In our previous study (Marona and Antkiewicz-Michaluk 1998) we reported the anticonvulsant properties of some aminoalkanol derivatives including compounds **1**–**3** (Table 1). One of them, *S*-(+)-2-[(2,6-dimethyl)phenoxyethyl]amino-1-butanol (**2**) potently prevented maximal electroshock (MES) seizures in mice, with an ED_{50} of 7.57 mg/kg and neurotoxicity (TD_{50}) of 34.45 mg/kg, and with a protective index ($PI = TD_{50}/ED_{50}$) of 4.55. It is important to note that these compounds (**1**–**3**) have some structural similarities to propranolol (aminoalkanolic group), and that a high anticonvulsant activity in rodents has also been described for propranolol and its two enantiomers (Fischer 2002). This was why compounds **1**–**3** were also tested for their effect on the circulatory system. Recently, we have reported on the chemical and hypotensive, as well as the α-, β-adrenolytic, properties of compounds **1**–**10**. The most active compounds (**4**, **7**, **8** and **10**), significantly decreased systolic and diastolic blood pressure in normotensive rats following both intravenous and oral administration and displayed affinity for α_1-, α_2- and β-adrenoceptors (Maciag et al. 2003).

Table 1: Chemical structures of compounds tested (1–10)



Compd.	R	Z	
1–3	2,6-CH_3		(R, S), (S) and (R)
4	2,6-CH_3		· 2 HCl
5	2,6-CH_3		· 2 HCl
6	2,6-CH_3		· 2 HCl
7	4-CH_3		· 2 HCl
8	4-OCH_3		· 2 HCl
9	4-OCH_3		· 2 HCl
10	3-CH_3, 4-Cl		· 2 HCl

As a continuation of our previous study, we report here the *in vivo* and *in vitro* antiarrhythmic activity of the above mentioned aroxyethylamine derivatives, as well as their influence on rat electrocardiograms.

2. Investigations and results

2.1. Antiarrhythmic activity

2.1.1. Adrenaline-induced arrhythmia according to Szekeres

All the compounds listed in Table 1 were tested for their antiarrhythmic properties in adrenaline induced arrhythmia

Table 2: Antiarrhythmic activity in adrenaline induced arrhythmia in anaesthetised rats

Compd.	Route of administration	ED_{50} (mg/kg)[a]	Therapeutic index (LD_{50}/ED_{50})[b]
4	i.v.	0.55 (0.33–0.81)	118.2
	p.o.	30.0 (23.1–39.0)	15.6
7	i.v.	1.55 (1.03–2.30)	29.0
	p.o.	25.4 (16.6–38.8)	33.5
8	i.v.	1.08 (0.54–2.16)	42.1
	p.o.	17.4 (7.9–38.6)	64.9
10	i.v.	0.86 (0.49–1.51)	66.0
	p.o.	60.7 (43.4–85.0)	13.9
Propranolol	i.v.	1.05 (0.64–1.73)	37.0
	p.o.	19.5 (14.5–26.1)	24.0
Quinidine	i.v.	8.70 (8.0–9.4)	6.0
	p.o.	38.0 (33.6–42.9)	15.6

[a] ED_{50} values and their confidence were calculated according to the method of Litchfield and Wilcoxon (Litchfield et al. 1949); [b] LD_{50} values for these compounds were published previously (Maciag et al. 2003)

following intravenous administration. Among the aryloxyethylamine derivatives studied, four, compounds **4**, **7**, **8** and **10**, inhibited adrenaline induced heart rhythm disturbances and decreased mortality in this test. In the control group, adrenaline induced extrasystoles were observed in 89% of the animals tested and arrhythmia related mortality was 50%. The most marked antiarrhythmic activity and the highest relative safety (TI = 118) were observed after i.v. administration of compounds **4** (ED_{50} = 0.55 mg/kg, TI = 118) and **10** (ED_{50} = 0.86 mg/kg, TI = 66). The antiarrhythmic potency of these compounds was even higher than that of quinidine and propranolol (Table 2). Compounds **4**, **7**, **8** and **10** also displayed antiarrhythmic activity after oral administration with the following order of potency: **8** > propranolol > **7** > **4** > quinidine > **10** (Table 2).

2.1.2. Ventricular arrhythmias associated with coronary artery occlusion and reperfusion in the non-working isolated perfused rat heart

Compounds with antiarrhythmic activity in adrenaline induced arrhythmia were also tested in arrhythmia induced by occlusion and reperfusion of coronary artery *in vitro*. Only compounds **4** and **7** displayed significant antiarrhythmic activity in this test. Compounds **4** and **7** completely prevented ventricular fibrillation at concentrations of 10^{-6} M and 10^{-7} M, respectively (Fig.). Calculated arrhythmia severity indexes were significantly lower than that of control (Table 3).

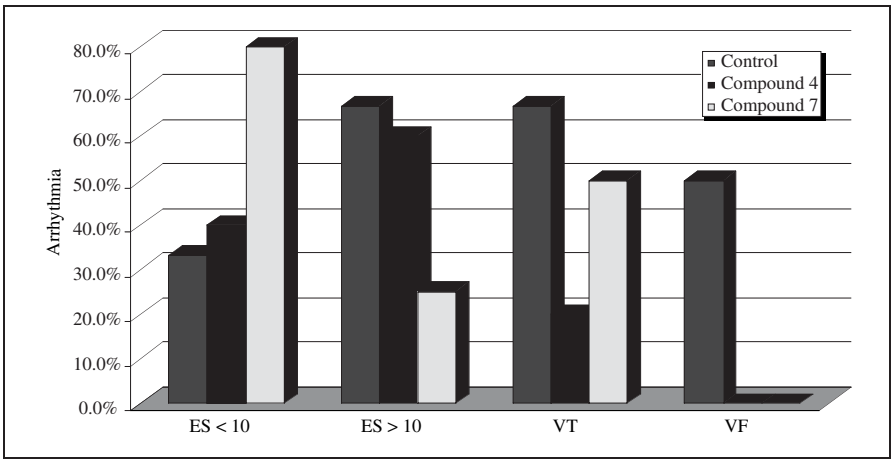


Fig.:
Antiarrhythmic activity of compounds **4** and **7** in oclusion/reperfusion induced arrhythmia *in vitro*. Statistically significant activity of compound **4** and **7** was observed at concentrations of 10^{-6} M and 10^{-7} M, respectively

Table 3: Activity of tested compounds in oclusion/reperfusion induced arrhythmia *in vitro*

Compd.	Concentration (M)	Arrhythmia severity index
Control		5.7 ± 0.7
4	10^{-5}	4.0 ± 0.7
	10^{-6}	$2.2 \pm 0.5^{**}$
	10^{-7}	4.3 ± 0.8
7	10^{-5}	5.5 ± 0.9
	10^{-6}	4.8 ± 1.7
	10^{-7}	$2.8 \pm 1.0^{*}$
8	10^{-5}	5.0 ± 1.6
	10^{-6}	5.3 ± 1.5
	10^{-7}	5.0 ± 0.6
10	10^{-5}	4.3 ± 1.8
	10^{-6}	5.0 ± 1.7
	10^{-7}	4.4 ± 1.4

Each value was obtained from 6–8 isolated hearts. Data represent means ± SEM, Student t-test (* $p < 0.05$, ** $p < 0.01$ vs control)

2.2. Influence on normal electrocardiogram in vivo

The influence of compounds **4**, **7**, **8** and **10** on normal rat electrocardiograms was evaluated following intravenous administration at the highest doses tested (1/5 LD_{50}). Compounds **4** and **10** did not significantly affect heart rate, P-Q, Q-T intervals or QRS complex, whereas compounds **7** and **8** significantly decreased heart rate, 15 minutes and 1 minute after administration, respectively. Compound **8** also significantly prolonged P-Q interval in the 15th and Q-T interval in the 10th and 15th minute of the observation period (Table 4).

3. Discussion

We have previously reported that among the aryloxyethylamines tested (**1**–**10**), compounds **4**, **7**, **8** and **10**, which contain a (2-methoxy)-phenylpiperazine moiety, displayed significant hypotensive activity in normotensive rats. Here, we show that the same compounds were active in adrenaline-induced arrhythmia following both intravenous and oral administration. In general, β-adrenoceptor antagonists are active in this model of arrhythmia (Szekeres et al. 1975), suggesting that the compounds examined may exert their antiarrhythmic effect by blocking β-adrenergic receptors. In fact, our radioligand biding study demonstrated that these compounds display modest affinity for β-ARs (Ki = 3.1–9.8 μM) together with much higher affinity for α_1-(Ki = 26–244.5 nM) and α_2-ARs (Ki = 197–410.8 nM), (Maciag et al. 2003). On the other hand, compounds **4**, **7**, **8** and **10** did not display antiarrhythmic activity in arrhythmia produced by barium chloride (data not shown), indicating that they are not likely to be class I antiarrhythmics. Although the mechanism by which barium chloride exerts its arrhythmogenic activity is not fully understood, it has been postulated that barium ions increase the sodium inward current in Purkinje fibers (Shibata 1973) and this, in turn, leads to heart rhythm disturbances. It is also known that antiarrhythmic drugs with sodium channel blocking properties are typically active in this model of arrhythmia. In an attempt to investigate the mechanism by which the tested compounds might exert their antiarrhythmic activity, their influence on an electrocardiogram following intravenous administration was analyzed. Compounds **4** and **10** did not affect heart rate, P-Q, Q-T intervals or QRS complex, while compounds **7** and **8** significantly decreased heart rate. In addition, significant and non significant prolongation of P-Q and Q-T intervals was observed after administration of compounds **8** and **7**, respectively. The effect of the tested compounds on ECG parameters resembles that of β-adrenolytics at low doses (compounds **4** and **10**) and also that of class III and IV antiarrhythmic drugs (compounds **7** and **8**). It is worth noting that ECG changes produced by the tested compounds differ from those characteristic of class I antiarrhythmics, excluding their having sodium channel blocking properties. Compounds **4** and **7** also displayed significant antiarrhythmic activity in arrhythmia induced by occlusion and reperfusion of coronary artery *in vitro*. This could suggest that these compounds may possess important activity in arrhythmia induced by ischemia, which is often associated with coronary artery disease. This model of arrhythmia has been recommended by Curtis et al. for screening for antiarrhythmic drugs (Curtis et al. 1987), being useful for identifying new antiarrhythmic agents from any of Vaughan Williams' classes. Moreover, according to the literature, α-adrenoceptor blockers, such as prazosin or phentolamine decrease and/or prevent occlusion/reperfusion induced heart rhythm disturbances *in vivo* and *in vitro* (Lamontagne et al. 1986; Bralet et al. 1985). Thus, the antiarrhythmic properties in this model of the

Table 4: Effect of investigated compounds on ECG intervals and heart rate in anaesthetised rats following i.v. administration

Compd.	Dose (mg/kg)	Parameter	Observation period (min)			
			0 (control)	1	5	15
4	13.0	P-Q (ms)	52.5 ± 2.5	52.5 ± 2.5	55.0 ± 2.8	55.0 ± 2.8
		QRS (ms)	22.5 ± 2.5	22.5 ± 2.5	22.5 ± 2.5	22.5 ± 2.5
		Q-T (ms)	75.0 ± 2.8	77.5 ± 2.5	77.5 ± 2.5	77.5 ± 2.5
		Beats/min	401.5 ± 15.3	367.4 ± 22.5	388.2 ± 13.2	388.2 ± 13.2
7	9.0	P-Q (ms)	52.0 ± 2.5	55.0 ± 2.8	55.0 ± 2.8	57.5 ± 2.5
		QRS (ms)	22.5 ± 2.5	22.5 ± 2.5	22.5 ± 2.5	22.5 ± 2.5
		Q-T (ms)	75.0 ± 2.8	75.0 ± 2.8	77.5 ± 4.7	85.0 ± 5.0
		Beats/min	414.7 ± 13.2	388.2 ± 13.2	388.2 ± 13.2	$364.5 \pm 0.4^{**}$
8	9.1	P-Q (ms)	49.7 ± 2.3	55.0 ± 2.2	54.3 ± 2.0	$57.7 \pm 1.9^{*}$
		QRS (ms)	19.9 ± 0.2	19.7 ± 0.2	19.5 ± 0.2	19.8 ± 0.1
		Q-T (ms)	72.3 ± 2.8	80.0 ± 3.1	$82.8 \pm 3.0^{**}$	$82.3 \pm 1.7^{**}$
		Beats/min	365.3 ± 10.1	$316.6 \pm 15.2^{*}$	347.7 ± 19.1	337.0 ± 14.2
10	11.4	P-Q (ms)	49.0 ± 2.7	50.6 ± 2.9	54.3 ± 4.0	54.6 ± 4.2
		QRS (ms)	18.5 ± 0.2	18.8 ± 0.4	19.0 ± 0.4	19.5 ± 0.2
		Q-T (ms)	75.3 ± 2.5	79.0 ± 3.4	76.0 ± 2.7	76.6 ± 3.3
		Beats/min	403.3 ± 23.5	386.0 ± 21.8	387.3 ± 26.9	389.8 ± 27.3

Data represent means ± SEM; one-way analysis of variance (ANOVA) followed by LSD test (* $p < 0.05$, ** $p < 0.02$ vs control)

compounds examined may also be related to their α-blocking activity.

As mentioned before, compounds **4**, **7**, **8** and **10** displaying significant antiarrhythmic and hypotensive properties contain a methoxyphenylpiperazine moiety in their structure. Thus, the presence of this moiety seems to be required for their pharmacological activity. It should be noted that the methoxyphenylpiperazine moiety is present in some other agents with nonselective α-adrenolytic properties, for example, urapidil or naftopidil (Muramatsu et al. 1991; Schoetensack et al. 1983). Furthermore, molecules based on an arylpiperazine core have also been described as ligands of serotonin or dopamine receptors, suggesting that the compounds we tested may possess an affinity to some other receptors (López-Rodríguez et al. 2002; Paluchowska et al. 2003; Jurczyk et al. 2004). In conclusion, on the basis of results presented here and previously reported, we identify 4 novel aryloxyethylamine derivatives (compounds **4**, **7**, **8** and **10)** as potential antiarrhythmic and/or antihypertensive agents with a mechanism of action most likely to be related to their adrenolytic properties. However, further testing *in vitro* and *in vivo* with this group of compounds is required to fully describe their pharmacological profile and pharmacodynamic properties.

4. Experimental

4.1. Materials

Compounds: Epinephrine (Adrenalinum hydrochloricum, Polfa), propranolol (Propranololum hydrochloricum, Polfa), quinidine (Chinidinum sulfuricum, Polfa), heparin (Heparinum sulfuricum, Polfa), thiopental sodium (Thiopentone sodium, Biochemie GmbH), sodium chloride (Natrium chloratum, POCH). Animals: The experiments were carried out on male Wistar rats (180–250 g). Animals were housed under standard laboratory conditions with *ad libitium* access to food and water in a 12 h: 12 h light-dark cycle. Control and experimental groups consisted of 6–8 animals each. Reference compounds: quinidine and propranolol were used as reference compounds. Statistical analysis: Statistical significance of the results was determined with one-way analysis of variance (ANOVA, followed by LSD test) or Student's t-test. Differences were considered significant when $p < 0.05$.

4.2. Antiarrhythmic activity

4.2.1. Adrenaline-induced arrhythmia according to Szekeres (Szekeres et al. 1975)

Arrhythmia was evoked in rats anaesthetised with thiopental (60 mg/kg, i.p.) by i.v. injection of adrenaline (20 μg/kg in a volume of 1 ml/kg). The test compounds were dissolved in saline and administered intravenously 15 min or orally 1 h prior to adrenaline. The criterion of antiarrhythmic activity was the lack of premature beats, inhibition of cardiac arrhythmia and decrease in arrhythmia related mortality in comparison with the control group.

4.2.2. Ventricular arrhythmias associated with coronary artery occlusion and reperfusion in the non-working isolated perfused rat heart

Hearts from thiopental-anaesthetised (45–60 mg/kg, i.p.) rats were perfused according to the Langendorff technique (Langendorff 1985) at a constant pressure of 70 cm H_2O (6.87 kPa) with Chenoweth-Koelle solution continuously gassed with 95% O_2 plus 5% CO_2 of the following composition (M): NaCl (120.0), KCl (5.6), $MgCl_2$ (2.2), $NaHCO_3$ (19.0), $CaCl_2$ (2.4), and glucose (10.0). For electrocardiogram recording two stainless steel electrodes were used (one inserted into the muscle of the ventricular wall and another attached to the metal aortic cannula).

After a 15 min stabilisation period, acute regional myocardial ischemia was evoked for 15 min by installing a clip on the left coronary artery close to its origin (ischemic period). The clip was then reopened, and changes during reperfusion were monitored for 30 min (reperfusion period). Occlusion and reperfusion were verified by measuring coronary flow before occlusion, after occlusion and after reperfusion. Ligation of the coronary artery resulted in a 25–35% reduction in coronary flow. Reperfusion was followed by a return of the coronary flow. Reperfusion induced arrhythmia was manifested by ventricular premature beats (VBs), ventricular tachycardia (VT) and ventricular fibrillation (VF).

Electrocardiograms were analysed according to the guidelines of the Lambeth Conventions (Walker et al. 1988) for ventricular premature beats (VBs), bigeminy, salvos (less than 4 successive VBs), ventricular tachycardia (VT, 4 or more successive VBs) and ventricular fibrillation (VF).

In order to obtain a measure for intensity of the arrhythmia, an arrhythmia severity index was calculated for each heart according to Bernauer Ernenputsch (1988): the occurrence of up to 10 VBs during the first 30 min of reperfusion-value 1, more than 10 VBs – value 2, VT – value 3, and VF – value 4. Bigeminy and salvos were not quantified separately but were included with VBs.

Tested compounds (in concentrations: 10^{-9}–10^{-4} M) were added to the perfusion fluid 15 min before coronary artery ligation and the given concentration was maintained for the rest of the perfusion period.

4.3. Influence on normal electrocardiogram in vivo

Electrocardiographic investigations were carried out on anesthetised rats (thiopental; 60 mg/kg, i.p.) using a Multicard E-30 apparatus. The ECG was recorded from the second standard lead, with a paper speed of 50 mm/s. Test compounds were administered intravenously at doses corresponding to 1/5 LD_{50} i.v. ECG was recorded just before and 1, 5, and 15 min after compound administration.

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