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Antiarrhythmic and hypotensive activities of 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl]-pyrrolidin-2-one (MG-1(R,S)) and its enantiomers

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Abstract:
The compound MG-1(R,S), (1-[2-hydroxy-3(4-phenyl-1-piperazinyl)propyl]-pyrrolidin-2-one, and its enantiomers were tested for electrocardiographic, antiarrhythmic and hypotensive activities. The racemic mixture (MG-1(R,S)) and its S-enantiomer significantly decreased systolic and diastolic blood pressure and possessed antiarrhythmic activity. The S-enantiomer displayed the greatest effect. The R-enantiomer did not show antiarrhythmic or hypotensive activity. The results suggest that the antiarrhythmic and hypotensive effects of these compounds are related to their adrenolytic properties.

Key words:
phenylpiperazine-pyrrolidine-2-one, antiarrhythmic, α-adrenoceptor blocking activity, enantiomer

Introduction

The most frequently diagnosed arrhythmias with major clinical implications include heart chamber fibrillations, such as atrial fibrillation (AF, atrial arrhythmias) and/or ventricular fibrillation (VF, ventricular arrhythmias) [25]. Cardiac arrhythmias remain a major cause of morbidity and mortality in developed countries. AF is the most common arrhythmia in the population (and the single most common factor in stroke of the elderly) [28, 29], whereas VF is the most common cause of sudden cardiac death [10]. Ventricular fibrillation is a major cause of death in acute myocardial infarction in both the pre-hospital and in-hospital phases. The effective prevention of VF is therefore a most important aspect of the management of patients with acute myocardial infarction. At present, completely effective and safe antiarrhythmic agents have not yet been identified to treat these arrhythmias [9, 12, 24, 26, 31, 37].

The myocardial α_1-adrenergic receptors are functionally active in human hearts. *In vitro* and *in vivo* studies in animals have shown that stimulation of myocardial α_1-adrenergic receptors can play a role in mediating myocyte hypertrophy [17, 23] and modulating the degree of contractile dysfunction after brief periods of myocardial ischemia [30, 32]. The α_1-adrenergic receptors in the heart can be of importance in the genesis of ischemia- and reperfusion-related ventricular arrhythmias [6, 13]. α_1-Blocking drugs, such as prazosin and phentolamine, have been shown to be effective against ischemia-induced arrhythmias in a variety of animal models [1, 2, 5, 18, 36].

This paper reports the results of preliminary pharmacological testing of enantiomers (S and R) of the compound MG-1(R,S), (1-[2-hydroxy-3(4-phenyl-1-piperazinyl)propyl]-pyrrolidin-2-one. Our earlier research has shown that MG-1(R,S) has marked significant antiarrhythmic (adrenaline- and barium chloride-induced) and hypotensive activities. This compound has affinity for α_1- and α_2-adrenoceptors and antagonizes the pressor response elicited by epinephrine and methoxamine. MG-1(R,S) statistically diminishes arrhythmias associated with coronary artery occlusion and reperfusion in isolated rat hearts. In addition, this compound demonstrates weaker potent local anesthetic properties and depresses the depolarization phase of the action potential of cardiac cells [3, 11, 14, 21, 22,]. According to the Vaughan-Williams classification, MG-1 could be considered to be a class Ia antiarrhythmic drug [38–41]. As a continuation of our previous study, we tested the S and R enantiomers of MG-1 (Scheme 1).

Materials and Methods

Animals

The experiments were carried out using male Wistar rats (180–250 g). The animals were housed in constant temperature facilities exposed to 12:12 h light/dark cycles and were maintained on a standard pellet diet with tap water given *ad libitum*. All procedures were conducted according to the Animal Care and Use Committee Guidelines and approved by the Ethical Committee of Jagiellonian University, Kraków. Control and experimental groups consisted of 6–8 animals each.

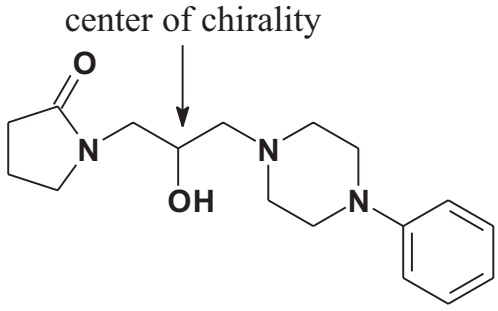
Tested and reference compounds

All tested compounds (Scheme 1) were synthesized by Dr. Katarzyna Kulig in the Department of Physicochemical Drug Analysis, Faculty of Pharmacy, Jagiellonian University [14–16].

The materials used included diphenylhydantoin sodium salt (Epanutin, Parke-Davis, USA), quinidine (Chinidinum sulfuricum-Polfa, Poland), barium chloride (POCh, Poland), sodium heparin (Polfa, Poland), thiopental sodium (Biochemie GmbH, Austria), and adrenaline (Polfa, Poland).

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

Hearts from thiopental-anesthetized (45–60 mg/kg, intraperitoneally – *ip*) rats were perfused according to the modified Langendorff technique [19, 20] 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 (mmol/l): NaCl (120.0), KCl (5.6), $MgCl_2$ (2.2), $NaHCO_3$ (19.0), $CaCl_2$ (2.4), and glucose (10.0). The effect of the tested compounds, at concentrations of 10^{-6} to 10^{-4} M, on coronary flow (cardiac effluent), electrocardiogram (obtained by two stainless steel electrodes, one inserted into the muscle of the ventricular wall and another attached to the metal aortic cannula) were assessed after 15–20 min of initial stabilization. Non-working isolated hearts were mounted as described above for recording coronary flow and electrocardiogram (ECG). After a 15 min stabilization period, acute regional myocardial ischemia was produced 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 24–28% reduction in coronary flow. Reperfusion was followed by a return of the coronary flow. Reperfusion induced arrhythmias, manifested by ventricular premature beats (VBs), ventricular tachycardia (VT) and ventricular fibrillation (VF). Electrocardiograms were analyzed according to the guidelines of the Lambeth Conventions for ventricu-



Scheme 1. Structural formula of the tested compound MG-1 – 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl]-pyrrolidin-2-one

lar premature beats (VBs), bigeminy, salvos (less than 4 successive VBs), ventricular tachycardia (VT, 4 or more successive VBs) and ventricular fibrillation (VF) [43]. To obtain a measure for the intensity of the arrhythmias, an Arrhythmia Severity Index was calculated for each heart according to Bernauer [1]: the occurrence of up to 10 ventricular extrasystoles during the first 30 min of reperfusion was given a value of 1, more than 10 given a value of 2, ventricular tachycardia or ventricular flutter given a value of 3 and ventricular fibrillation given a value of 4. Bigeminy and salvos were not quantified separately, but were included with VBs. Agents were added to the perfusion medium 15 min before coronary artery ligation, and the concentration was maintained for the rest of the perfusion period.

Therapeutic and prophylactic antiarrhythmic activity in adrenaline-induced arrhythmia

The arrhythmia was evoked in rats anesthetized with thiopental (60 mg/kg, *ip*) by intravenously (*iv*) injection of adrenaline into the caudal vein (20 μg/kg, in a volume of 1 ml/kg). The tested compounds were administered *iv* at the peak of arrhythmia, immediately after administration of adrenaline therapeutic activity or orally (*po*) 1 h before the arrhythmogen. The criterion for antiarrhythmic activity was the lack of premature beats and inhibition of cardiac arrhythmia in comparison to the control group [34, 35].

Therapeutic and prophylactic antiarrhythmic activity in barium chloride-induced arrhythmia

Barium chloride solution was injected into the caudal vein of rats (32 mg/kg, in a volume of 1 ml/kg). The tested compounds were administered *iv* at the peak of arrhythmia, immediately after administration of barium chloride therapeutic activity or *po* 1 h before the arrhythmogen. The criterion for antiarrhythmic activity was a gradual disappearance of the arrhythmia and restoration of the sinus rhythm [34, 35].

Influence on the blood pressure

Arterial blood pressure in the common carotic artery of normotensive anesthetized rats was measured using a Datamax apparatus (Columbus Instruments). The studied compounds were administered *po* at a dose of 10 mg/kg.

Statistical analysis

The data are expressed as the means ± SEM. The data were evaluated by one-way analysis of variance (ANOVA) followed by the Duncan test. Values of $p < 0.05$ were considered to be significant.

Results

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

Compared to the control hearts, the S-enantiomer (similar to MG-1 (R,S)) significantly diminished the incidence of ventricular tachycardia and ventricular fibrillation. The concentration of 10^{-6}–10^{-5} M significantly reduced the incidence of VBs (approximately 50–20%), VT (approximately 90–80%) and VF (15%). The arrhythmia index was lower (2.1–2.9) than in the control hearts (5.3) (Tab. 1). The R-enantiomer, used at concentrations of 10^{-6} – 10^{-4} M, did not show antiarrhythmic activity in this test. The reference drugs in this model, phenytoin and quinidine (class I Vaughan Williams classification) [40, 42], showed significant effects at concentrations of 10^{-5} (phenytoin) and 10^{-6} – 5×10^{-6} M (quinidine) (Tab. 1).

Effect of electrocardiogram *in vitro* (non-working heart perfusion)

MG-1(R,S) and its S- and R-enantiomers decreased the number of cardiac beats per minute and prolonged the P-Q and Q-T intervals and QRS complex (Figs. 1–4). The QT_c was calculated according to the formula of Bazzett: QT_c = Q-T/ RR (Fig. 5) [4]. The compound MG-1(R,S), used at concentrations of 10^{-8}–10^{-4} M, decreased the number of cardiac beats per minute (by 6–22%) and prolonged the P-Q (by 7–33%) and Q-T (by 4.7–23%) intervals and QRS complex (by 6.7–34%). The S-enantiomer, given at doses of 10^{-8}–10^{-4} M, decreased the number of cardiac beats per minute (by 7–29%) and prolonged the P-Q (by 6–35%) and Q-T (by 6.7–32%) intervals and QRS complex (by 7.9–38%). Similarly, the R-enantiomer, given at analogous concentrations, decreased the number of cardiac beats per minute (by 5.1–24%) and prolonged the P-Q (by 6–29%) and Q-T (by 4–26%) intervals and QRS

complex (by 6.9–32%). The MG-1(R,S) and its S- and R-enantiomers similarly prolonged QT_c (by 11–13.4%) at a concentration of 10^{-4} M) (Fig. 5). The influence of the tested compounds on the ECG parameters was similar. The electrocardiographic changes observed after administration of the tested compounds were similar to those observed for quinidine, whereas phenytoin prolonged the P-Q and Q-T intervals, but did not change the QRS complex (Figs. 1–4) [38].

Tab. 1. Effect of tested compounds, phenytoin and quinidine, on reperfusion-induced arrhythmias

Compound	Concentration (M)	VBs incidence (%)	Bigeminy incidence (%)	Salvos incidence (%)	VT incidence (%)	VF incidence (%)	Arrhythmias severity index
Control	–	100	37.5	12.5	100	25	5.3 ± 0.4
MG-1(R,S)	10^{-6}	100	60	60	20	0	2.4 ± 0.7***
	5 10^{-6}	100	62.5	50	34.5	12.5	3.5 ± 1*
	10^{-5}	100	57.1	28.6	14.3	14.3	2.6 ± 1**
Control	–	100	50	30	60	50	5.4 ± 0.6
MG-1(S)	10^{-6}	50	25	0	10	10	2.1 ± 0.4***
	10^{-5}	80	20	0	20	10	2.9 ± 0.8*
	10^{-4}	100	50	17	33	33	4.0 ± 0.9
MG-1(R)	10^{-6}	100	70	60	75	25	5.2 ± 0.2
	10^{-5}	100	50	33	50	25	4.5 ± 0.8
	10^{-4}	100	60	33	50	25	4.5 ± 0.8
Phenytoin	10^{-6}	100	0	0	75	0	4.3 ± 0.3
	10^{-5}	100	0	0	25	0	2.6 ± 0.4**
	10^{-4}	100	25	0	40	20	4.1 ± 0.7
Quinidine	10^{-6}	83.3	16.7	0	50	0	2.3 ± 0.8**
	5 10^{-6}	16.7	0	0	33.3	0	1.2 ± 0.6****

Each value was obtained from 6–8 hearts. Significantly different from the control: * $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.001$

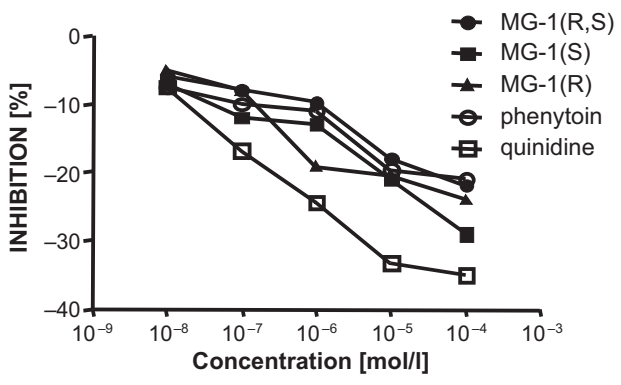


Fig. 1. Influence of tested compounds on the heart rate

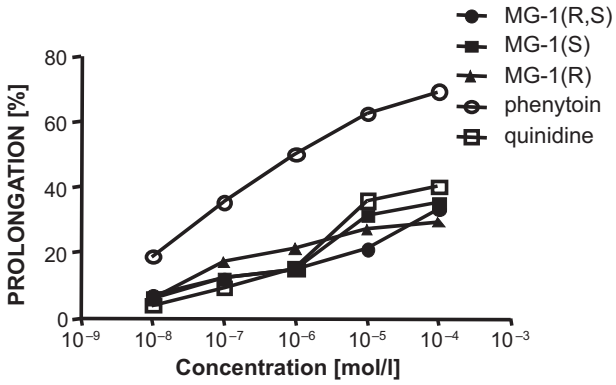


Fig. 2. Influence of tested compounds on the P-Q intervals

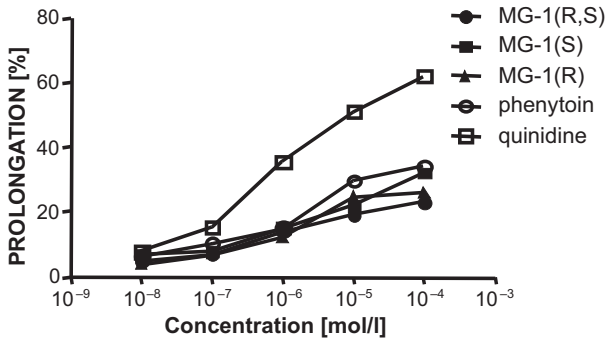


Fig. 3. Influence of tested compounds on the Q-T intervals

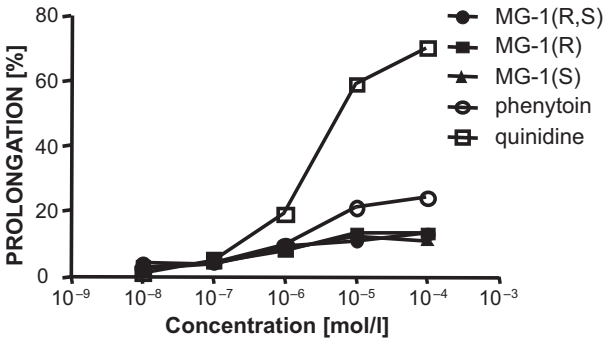


Fig. 5. Influence of tested compounds on the QT_c intervals

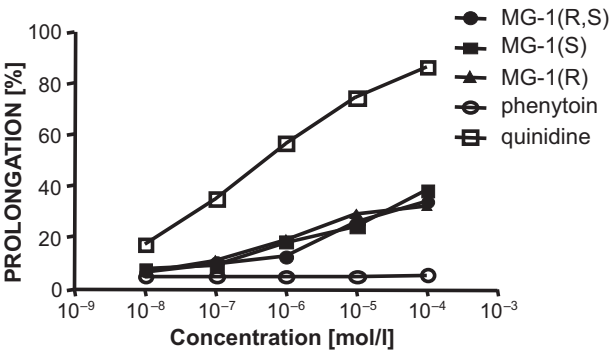


Fig. 4. Influence of tested compounds on the QRS complex

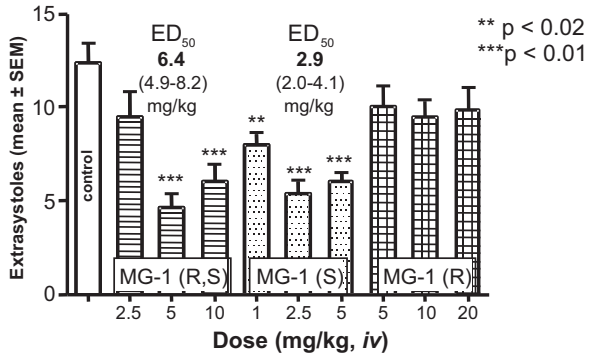


Fig. 6. Therapeutic antiarrhythmic activity of MG-1(R,S), MG-1(S) and MG-1(R) in adrenaline-induced arrhythmia

Antiarrhythmic activity in adrenaline-induced arrhythmia

In anesthetized rats, *iv* injections of adrenaline (20 μg/kg) caused atrioventricular disturbances and ventricular and supraventricular extrasystoles (in 100% of the animals, with a mean of 13–15 extrasystoles during the 15 min of observation), which led to the death of approximately 60% of the animals.

To assess therapeutic antiarrhythmic activity, the tested compounds or drugs were administered after an arrhythmogenic substance (adrenaline or barium chloride). To measure prophylactic antiarrhythmic activity, the tested compounds or drugs were administered before (15, 30 or 60 min) an arrhythmogenic substance.

Therapeutic antiarrhythmic activity

The compounds MG-1(R,S) and MG-1(S) administered intravenously at the peak of arrhythmia prevented and/or reduced the number of premature ventricular beats in a statistically significant manner. The ED_{50} value of the S-enantiomer was approximately 2 times lower than that of MG-1(R,S). The R-enantiomer, given at doses of 5–20 mg/kg, did not show therapeutic antiarrhythmic activity in this model (Fig. 6). Quinidine given at doses of 2.5–10 mg/kg reduced the number of premature ventricular beats (ED_{50} = 3.2 mg/kg) in a statistically significant manner.

Prophylactic antiarrhythmic activity

The most active compound after oral administration was the S-enantiomer. The ED_{50} value of the S-enantiomer was approximately 3 times lower than that of MG-1(R,S). The R-enantiomer, given at doses of 10–30 mg/kg, did not show antiarrhythmic activity after *po* administration (Fig. 7). Quinidine given at doses of 10–30 mg/kg reduced the number of premature ventricular beats (ED_{50} = 28 mg/kg) in a statistically significant manner.

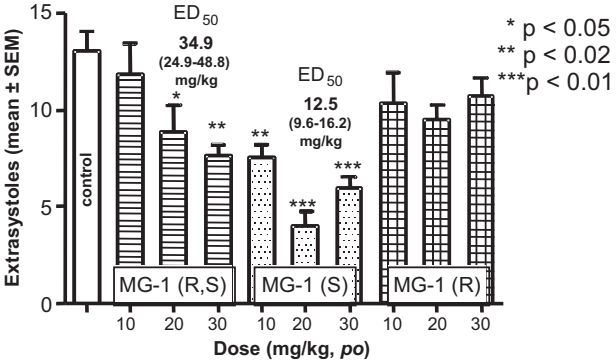


Fig. 7. Prophylactic antiarrhythmic activity of MG-1(R,S), MG-1(S) and MG-1(R) in adrenaline-induced arrhythmia

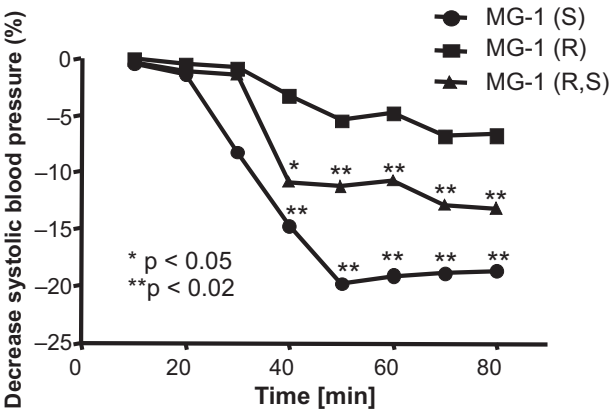


Fig. 8. Hypotensive activity of tested compounds in rats – systolic blood pressure

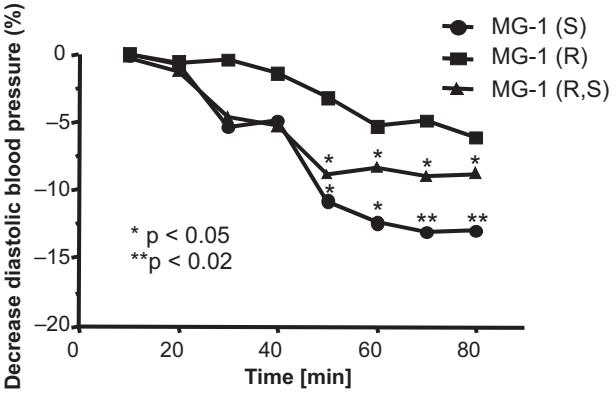


Fig. 9. Hypotensive activity of tested compounds in rats – diastolic blood pressure

Antiarrhythmic activity in barium chloride-induced arrhythmia

Intravenous injections of a high dose of barium chloride (32 mg/kg) caused rapid ventricular extrasystoles and ventricular fibrillation in all animals (100%), which led to death within 3–8 min.

Therapeutic antiarrhythmic activity

The MG-1(R,S) and its S- and R-enantiomers administered intravenously at doses of 10–30 mg/kg at the peak of arrhythmia did not show therapeutic antiarrhythmic activity in this model.

Prophylactic antiarrhythmic activity

The ED_{50} values of MG-1(R,S) and MG-1(S) after oral administration in barium chloride-induced arrhythmia were similar: ED_{50} = 22.0–38.1 for 29 mg/kg MG-1(R,S) and ED_{50} = 19.3–37.8 for 27 mg/kg MG-1(S). The R-enantiomer given at doses of 10–30 mg/kg did not show significant antiarrhythmic activity after oral administration.

Influence on the blood pressure

The hypotensive activity of the MG-1(R,S) compound and both enantiomers was determined after oral administration in normotensive anesthetized rats (Figs. 8, 9). The highest hypotensive activity was observed with the S-enantiomer, which significantly decreased the systolic (15–18%) and diastolic (11–13%) blood pressure throughout the whole observation period in the dose range of 10 mg/kg. The compound MG-1(R,S) significantly decreased the systolic (11–13%) and diastolic (8–9%) blood pressure. The significant hypotensive effect was observed within 40–50 min after oral administration of the compound. The R-enantiomer did not show hypotensive activity after oral administration (Figs. 8, 9).

Discussion

In previous studies, we have demonstrated that the compound MG-1(R,S) significantly reduces the blood pressure in normotensive rats and reverses the pressor

response to adrenaline and methoxamine [11, 14, 21, 22]. The pharmacological properties of the S-enantiomer and R-enantiomer were investigated in comparison with the racemic mixture compound MG-1(R,S). The preliminary results suggest that MG-1(R,S) possesses α-adrenolytic properties. Binding studies that were presented in a previous paper [15] have shown that the S-enantiomer has the strongest affinity for the α_1-adrenoceptor (K_i = 528 nM). The compound MG-1(R,S) and the R-enantiomer have weak affinity for α_1-adrenoceptors (MG-1(R,S) K_i = 1900 nM; R-enantiomer K_i = 1500 nM). The S-enantiomer did not show affinity for the α_2-adrenoceptor (K_i > 100 μM), but MG-1(R,S) and the R-enantiomer had weak affinity for α_2-adrenoceptors (MG-1(R,S) K_i = 29 μM; R-enantiomer K_i = 6.9 μM). These results correlate with the antiarrhythmic and hypotensive properties of the S-enantiomer, which had the strongest activity in *in vivo* tests. The antiarrhythmic effects of the compounds were examined in rats using a model of adrenaline-induced arrhythmia and a model of ventricular arrhythmias associated with coronary artery occlusion and reperfusion in the non-working isolated perfused rat heart. In the ventricular model of arrhythmias associated with coronary artery occlusion and reperfusion, the compounds MG-1(R,S) and MG-1(S) significantly diminished the incidence of ventricular tachycardia and ventricular fibrillation. This effect was similar to quinidine. Curtis et al. [8] have concluded that inhibitors of the fast inward current (class I agents) and inhibitors of the inward current (class IV agents) appear to be particularly effective antiarrhythmics in rats against both ischemia- and reperfusion-induced arrhythmias. On the other hand, relatively high doses of α-blocking agents (phentolamine, prazosin, corynanthine, rauwolscine and yohimbine) are well known to diminish or prevent reperfusion arrhythmias [1, 2, 5, 18, 27, 33, 36]. The data presented here suggest that the antiarrhythmic effect of the compounds MG-1(R,S) and MG-1(S) may be related to their α-adrenolytic activity. Furthermore, these compounds may also possess affinity for cardiac Na^+ and K^+ channels (similar to class I antiarrhythmic agents), but further assessment of this affinity is required [38, 40, 41].

Preliminary pharmacological experiments *in vitro* showed that the compound MG-1 and its S- and R-enantiomers slightly decreased the heart rate and prolonged the P-Q and Q-T intervals and QRS complex. The changes in ECG were similar, but weaker than the effects of quinidine. In addition, these compounds did not significantly prolong the calculated QT_c interval (Bazzett formula), as opposed to quinidine. This lack of an effect on the QT_c interval is essential because compounds which significantly prolong the calculated QT_c interval can have proarrhythmic properties [4, 6, 7]. These data show that the S-enantiomer was the most active in adrenaline-induced arrhythmia after intravenous administration at the peak of arrhythmia and after oral administration. The ED_{50} values for the S-enantiomer were approximately 2–3 times lower than for MG-1(R,S) (Figs. 6, 7). This effect was similar to the therapeutic activity of quinidine (ED_{50} = 3.2 mg/kg for quinidine, ED_{50} = 2.9 mg/kg for S-enantiomer). The antiarrhythmic effect of the S-enantiomer was higher than the antiarrhythmic effect of quinidine after oral administration in testing the prophylactic activity in the adrenaline model of arrhythmia; ED_{50} was 28 mg/kg for quinidine and 12.5 mg/kg for the S-enantiomer). The R-enantiomer did not show antiarrhythmic activity in this test.

Similar to the racemic mixture, the S-enantiomer (but not the R-enantiomer) was active in barium chloride-induced arrhythmia after oral administration. The greatest hypotensive effect was shown by the S-enantiomer, which significantly diminished blood pressure after oral administration (Figs. 8, 9).

These data suggest that the S-enantiomer had high affinity to α-adrenergic receptors and had the greatest antiarrhythmic and hypotensive activities. The antiarrhythmic and hypotensive effects of the S-enantiomer are related to its adrenolytic properties. Our results indicate that the S-enantiomer plays a crucial role in the antiarrhythmic and hypotensive properties of the compound MG-1(R,S). Further pharmacological utility of the MG-1(S) compound should be investigated.

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