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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW 1-[3-(4-PHENYLPIPERAZIN-1-YL)-PROPYL]- AND 1-[3-(4-PHENYLPIPERIDINE)-PROPYL]- 3-ARYL-3-ALKYL-PYRROLIDIN-2-ONE DERIVATIVES WITH ANTIARRHYTHMIC AND ANTIHYPERTENSIVE ACTIVITY

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Abstract: A series of novel phenylpiperazine and phenylpiperidine derivatives bearing a 3,3-disubstituted pyrrolidin-2-one fragment were synthesized and evaluated for their binding affinity for α_1-adrenoceptors (ARs) and for their antiarrhythmic and antihypertensive activities. The highest affinity for α_1-ARs was displayed by 1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)-propyl]-3-phenyl-3-*n*-propyl-pyrrolidin-2-one (**10 a**), which binds with $pK_i = 6.43$. Among the compounds tested, 1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)-propylpyrrolidin-2-one (**5**) was the most active in the prophylactic antiarrhythmic activity in adrenaline induced arrhythmia in anesthetized rats. Its ED_{50} value was 4.9 mg/kg intravenously (*iv*). Some of the compounds tested significantly decreased the systolic and diastolic pressure in normotensive anesthetized rats at a dose of 5.0 mg/ kg *iv* and their hypotensive effects lasted for longer than an hour.

Keywords: a-adrenoceptors blocking activity, antiarrhythmic, hypotensive activity, 3-alkyl-3-phenylpyrrolidin-2-one derivatives

Despite the significant progress made in preventing and treating cardiovascular disease (CVD) is still the leading cause of death in the developed world, and death due to CVD is still increasing in these nations. Approximately 130 million people in the seven major pharmaceutical markets suffer from CVD. Hypertension and atherosclerosis are central to the pathogenesis of coronary artery disease (ischemia, angina, myocardial infarction), heart failure, cerebral (stroke) and peripherial vascular disease (1-4).

There are several cardiac receptor systems that are involved in regulation of contractility and/or hearth rate. Among these, are receptors coupled to the G_s-protein-adenylyl cyclase pathway (β-adrenoceptors (β-ARs), histamine-receptors, serotonin-receptors), receptors coupled to the G_i-protein-adenylyl cyclase pathway (muscarinic-receptors, adenosine-receptors), and receptors that couple to the $G_{q/11}$-protein-phospholipase C-protein kinase C pathway (α_1-ARs, endothelin-receptors, angiotensin II-receptors). A vast body of evidence has accumulated that in heart failure, α_1- and β-ARs changes play an important role. α_1-ARs modulate intercellular biochemical processes in response to changes in extracellular concentration of the neurotransmitter, norepinephrine, and circulating hormone, epinephrine (5-9). Compounds acting as antagonists at various post-junctional α_1-ARs are frequently used in the therapy of high blood pressure, prazosin being the most common drug (6). α_1-ARs antagonists are also used in the treatment of benign prostatic hyperplasia, lower urinary tract symptoms or cardiac arrhythmia (8).

To date, a vast array of structurally unrelated α_1-ARs antagonists have been identified, which makes it difficult to determine the structural requirements that lead to receptor selectivity (10-16). However, some general rules have been postulated by Barbaro et al. (17) and Bremner et al. (18). These

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are: an aromatic region, a basic nitrogen atom with at least one available protonation site and a semipolar region.

This work is part of our rational drug design project. We have previously reported that a series of 1-[3-(4-arylpiperazin-1-yl)-2-hydroxy]- or -propyl-pyrrolidin-2-one derivatives possess affinity for α_1- and α_2-ARs and show marked hypotensive and antiarrhythmic activities. Among the compounds tested, the most active were 1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)-propyl]-pyrrolidin-2-one (**1**) and those which contain the propyl linker (**2**) (19-22). Taking into consideration that the interactions between ligand and receptor may depend on configuration of the asymmetric atom, the enantiomers of compound (**1**) and its analogues were investigated. It was found that their (*S*) enantiomers displayed higher affinity for α_1-ARs than (*R*) ones (23). Additionally, in our last studies, quantitative relationship (QSAR) model explaining the α_1-ARs activity of a series of 1-[3-(4-arylpiperazin-1-yl)-propyl]-pyrrolidin-2-one derivatives was reported (24). This approach was based on the assumption that the variation of the behavior of compounds, as expressed by any measured biological activity, could be correlated with structural features and a physicochemical property (called descriptors) of a set of chemicals compounds (25-30). The molecular descriptors of the α_1-ARs antagonists were obtained by quantum chemical calculations combined with molecular modeling calculations (31, 32). The obtained model was correlated with coefficient equal 0.9, explains more than 88% of the variance and it was successfully validated by appropriate tests such as LOO, LMO and external test. There was also proven that the good statistics obtained for proposed QSAR model is not due to chance correlation or structural dependency of the training set (Y-scrambling test). The 7-parametric equation defines the best model for the data (24). The statistical analysis showed that the α_1-ARs activity of these compounds are mainly determined by PCR, HATS1m, E2m, RDF095p, Qindex, T(O..O), and T(N..F) values (33). On the basis of these results and previous evidence, we could conclude that the interaction of the arylpiperazinyl and arylpiperidinyl moieties with the α_1-adrenoreceptor depends on the structure and geometry of the molecule rather than on its physicochemical properties (24).

According to this, the aim of these studies was to synthesize new derivatives of arylpiperazine propylpyrrolidin-2-one or arylpiperidine propyl-pyrrolidin-2-one derivatives, then measure their biological activity and verified the QSAR model (24). Firstly, the role of piperazine ring in template compounds (**1**) and (**2**) was tested by replacement of this moiety by a piperidine ring. Then, the 2-hydroxypropyl fragment of the obtained compound was changed by a propyl one. The analogues of compound (**1**) and its piperidine equivalent having 3-alkyl-3-phenylpirrolidin-2-one fragment were synthesized. These modifications in the pirrolidin-2-one moiety included an introduction of phenyl- or alkyl-(methyl-, ethyl-, *n*-propyl-, *i*-propyl-) groups. The newly synthesized compounds were tested for α_1-ARs as well as for their antiarrhythmic and hypotensive activity (Fig. 1).

EXPERIMENTAL

Chemistry

Melting points were determined in open glass capillaries on the Büchi 353 melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed on an Elementar Vario EL III (Elementar Analysensysteme, Hanau, Germany) and were within ± 0.4% of the theoretical values. The reaction performed using microwaves were carried out in CEM Discover (CEM Corporation, Matthews, USA) microwave reactor; ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Mercury VX 300 MHz instrument in DMSO-d_6 or $CDCl_3$ at ambient temperature using solvent signal as an internal standard. Thin layer chromatography was carried out on Merck silica gel pre-coated F_{254} plates (0.2 mm) using chloroform/acetone (1:1, v/v), as a developing system. The plates were visualized with the UV light, iodine solution (0.05 M in 10% HCl) or mixture 5% $(NH_4)_xMo_7O_{24}$ and 0,2% $Ce(SO_4)_2$ in 5% H_2SO_4.

1-(2-Hydroxy-3-(4-phenylpiperidin-1-yl)propyl)pyrrolidin-2-one dihydrochloride (**5**)

A solution of 1.4 g (10 mmol) 2,3-epoxypropyl-pyrrolidin-2-one (**4**) and 1.6 g (10 mmol) 4-phenylpiperidine was heated in a closed vessel in microvave reactor 300 W in 150^{o}C for 30 min. The progress of the reaction was monitored by TLC. The obtained oily residue was purified by column chromatography using a mixture chloroform : acetone (1:1, v/v). Then, the obtained oil was dissolved in EtOH and then EtOH saturated with HCl_{gas} was added until the mixture become acidic. The obtained precipitate was crystallized from EtOH.

Yield 2.5 g (68%), m.p. 198-199^{o}C, R_f (acetone : $CHCl_3$ 1:1) 0.47. ^{1}H-NMR (DMSO-d_6, δ ppm): 1.77-1.83 (m, 4H, CH_2CH (piper.)), 1.99 (m, 2H, $CH_2CH_2CH_2$ (pyrrol.)), 2.32 (t, 2H, J = 7.1 Hz,

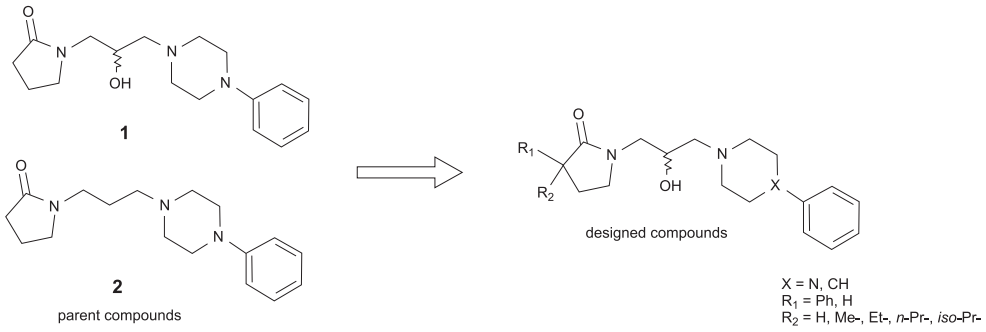


Figure 1. Structure of parent active compounds (**1**) and (**2**) and designed compounds

CH_2CO), 2.41-2.63 (m, 6H, CH(OH)CH_2N, NCH_2), 2.78 (qw., J = 7.0 Hz, 1H, CH), 3.29-3.43 (m, 4H, CH_2CH_2N, NCH_2CH(OH)), 3.58 (s, wide, 1H, OH), 4.08 (m, 1H, CHOH), 7.30-7.37 (m, 5H, arom.); ^{13}C-NMR (DMSO-d_6, δ ppm): 17.7 (CH_2CH_2CO), 31.0 (CH_2CO), 33.2, 42.0, 48.8 (piper.), 51.0 (CH_2N (pirol)), 54.4 (CH_2), 63.8 (CH_2), 66.5 (CHOH), 126.0, 128.1, 128.8, 146.5 (arom), 174.9 (carbonyl). Analysis: calc. for $C_{18}H_{26}N_2O_2 \times 2HCl$, M = 375.33: C 57.60, H 7.52, N 7.46%; found: C 57.78, H 7.76, N 7.54%.

1-(3-(4-Phenylpiperidin-1-yl)propyl)pyrrolidin-2-one dihydrochloride (**7**)

1.6 g (10 mmol) of 1-(3-chloropropyl)pyrrolidin-2-one (**6**) and 1.6 g (10 mmol) 4-phenylpiperidine were heated in a closed vessel in microvave reactor 300 W in 150°C for 40 min. The progress of the reaction was monitored by TLC. The obtained oily residue was purified by column chromatography using a mixture of chloroform : acetone (1:1, v/v) as a solvent. Then, the obtained oil was dissolved in EtOH and HCl gas was bubbled thought the solution until the mixture become acidic. The obtained precipitate was crystallized from EtOH.

Yield: 2.6 g (73%), m.p. 215-216°C, R_f (acetone : $CHCl_3$ 1:1, v/v) 0.53. ^{1}H-NMR (DMSO-d_6, δ ppm): 1.70-1.83 (m, 6H, CH_2CH (piper.), $CH_2CH_2CH_2$), 1.99 (m, 2H, $CH_2CH_2CH_2$ (pyrrol.)), 2.31-2.47 (m, 8H, CH(OH)CH_2N, NCH_2, CH_2CO), 2.78 (q, J = 7.0 Hz, 1H, CH), 3.29-3.43 (m, 4H, CH_2CH_2N, NCH_2CH(OH)), 7.30-7.37 (m, 5H, arom.). ^{13}C-NMR (DMSO-d_6, δ ppm): 17.7 (CH_2CH_2CO), 26.2 ($CH_2CH_2CH_2$), 31.0 (CH_2CO), 33.2, 42.0, 48.5 (piper.), 48.6 (CH_2CH_2), 50.7 (CH_2N), 52.2 (CH_2), 126.0, 128.1, 128.8, 146.5 (arom.), 174.9 (carbonyl). Analysis: calc. for $C_{18}H_{26}N_2O \times 2HCl$, M = 359.33: C 60.16, H 7.85, N 7.80%; found: C 60.43, H 7.94, N 7.92%.

(2*R*)-1-(3-Chloro-2-hydroxypropyl)-3-alkyl-3-phenylpyrrolidin-2-one (**9 a-e**) – *general procedure*

To an ice-cold suspension of 60% NaH (2.6 g, 65 mmol) in 130 mL THF 3-alkyl-3-phenylpyrrolidin-2-one (65 mmol) was added dropwise. The reaction mixture was stirred for 1 h, then (13.5 g, 75 mmol) of (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide was added and the reaction mixture was stirred overnight. The reaction was stoped by addition of 3.6 mL of H_2SO_4 (conc.) and water (1.3 mL). After stirring for 1 h at room temperature, the reaction mixture was neutralized by adding sat. $NaHCO_3$, and extracted with $CHCl_3$ (2 x 20 mL). The organic layers were collected, dried over anh. Na_2SO_4 and evaporated. The obtained oil was purified by column chromatography using a mixture of acetone and chloroform (1:1, v/v).

(2*R*)-1-(3-chloro-2-hydroxypropyl)-3-phenylpyrrolidin-2-one (**9 a**)

Yield 10.3 g (63%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.64. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.17 – 2.29 (m, 2H, CH_2CH), 3.23 – 3.51 (m, 8H, CH_2N, CHCO, OH, NCH_2CH, CH_2Cl), 4.05 – 4.25 (m, 1H, CHOH), 6.84 – 7.03 (m, 5H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 30.5 (CH_2CHCO), 46.6 (CH_2N), 48.0 (CHCO), 48.9 (CH_2Cl), 54.1 (CH_2CHOH), 73.9 (CHOH), 126.0, 128.1, 128.8, 139.2 (arom.), 172.3 (carbonyl). Analysis: calc. for $C_{13}H_{16}NO_2Cl$, M_r = 253.72: C 61.54, H 6.36, N 5.52%; found: C 61.68, H 6.58, N 5.72%.

(2*R*)-1-(3-chloro-2-hydroxypropyl)-3-methyl-3-phenylpyrrolidin-2-one (**9 b**)

Yield 10.8 g (62%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.67. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.82 (s, 3H), 2.17 – 2.29 (m, 2H, CH_2CH), 3.38 – 3.51 (m, 7H, CH_2N, OH, NCH_2CH, CH_2Cl), 4.07 – 4.32 (m, 1H,

C*H*OH), 7.89 – 7.06 (m, 5H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 22.0 (*C*H_3), 25.4 (*C*H_2CCO), 44.1 (*C*H_2N), 48.9 (*C*H_2Cl), 54.4 (*C*H_2CHOH), 55.4 (*C*), 73.9 (*C*HOH), 126.0, 128.1, 128.8, 138.9 (arom.), 183.1 (carbonyl). Analysis: calc. for $C_{14}H_{18}NO_2Cl$, M = 267.10: C 62.80, H 6.78, N 5.23%; found: C 62.98, H 6.95, N 5.56%.

(2*R*)-1-(3-chloro-2-hydroxypropyl)-3-ethyl-3-phenylpyrrolidin-2-one (**9 c**)

Yield 12.4 g (68%), R_f (acetone: $CHCl_3$ 1:1, v/v) 0.68. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, *J* = 8.0 Hz, *C*H_3), 1.86 (q, 2H, *J* = 8.0 Hz, *C*H_2CH$_3$), 2.17 – 2.29 (m, 2H, C*H*$_2$CH), 3.38 – 3.51 (m, 7H, C*H*$_2$N, O*H*, NC*H*$_2$CH, C*H*$_2$Cl), 4.07 – 4.32 (m, 1H, C*H*OH), 6.93 – 7.10 (m, 5H, arom). ^{13}C-NMR ($CDCl_3$, δ ppm): 8.3 (*C*H_3), 22.9 (*C*H_2CCO), 32.8 (*C*H_2CH$_3$), 44.4 (*C*H_2N), 48.9 (*C*H_2Cl), 54.4 (*C*H_2CHOH), 61.3 (*C*), 73.9 (*C*HOH), 126.0, 128.1, 128.8, 138.9 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{15}H_{20}NO_2Cl$, M = 281.78: C 63.94, H 7.15, N 4.97%; found: C 64.07, H 6.99, N 5.05%.

(2*R*)- 1-(3-chloro-2-hydroxypropyl)-3-phenyl-3-*n*-propylpyrrolidin-2-one (**9 d**)

Yield 13.8 g (72%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.71. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, *J* = 8.0 Hz, *C*H_3), 1.26 – 1.34 (m, 2H, C*H*$_2$CH$_3$), 1.82 (q, 2H, *J* = 7.1 Hz, C*H*$_2$CH$_2$), 2.13 – 2.26 (m, 2H, C*H*$_2$CH), 3.38 – 3.51 (m, 7H, C*H*$_2$N, O*H*, NC*H*$_2$CH, C*H*$_2$Cl), 4.07 – 4.32 (m, 1H, C*H*OH), 6.97 – 7.13 (m, 5H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 14.0 (*C*H_3), 16.9 (CH$_3$*C*H$_2$), 23.2 (*C*H_2CCO), 36.9 (*C*H_2CH$_2$), 44.4 (*C*H_2N), 48.9 (*C*H_2Cl), 54.4 (*C*H_2CHOH), 58.8 (*C*), 73.9 (*C*HOH), 126.0, 128.1, 128.8, 139.5 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{16}H_{22}NO_2Cl$, M = 295.80: C 64.97, H 7.50, N 4.74%; found: C 65.17, H 7.75, N 5.12%.

(2*R*)- 1-(3-chloro-2-hydroxypropyl)-3-phenyl-3-*iso*-propylpyrrolidin-2-one (**9 e**)

Yield 13.0 g (68%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.64. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.91 (d, 6H, *J* = 7.5 Hz, *C*H_3), 2.13 – 2.26 (m, 2H, C*H*$_2$CH), 2.40-2.46 (m, 1H, C*H*(CH$_3$)$_2$, 3.38 – 3.51 (m, 7H, C*H*$_2$N, O*H*, NC*H*$_2$CH, C*H*$_2$Cl), 4.07 – 4.32 (m, 1H, C*H*OH), 6.94 – 7.09 (m, 5H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 17.4 (*C*H_3), 20.4 (*C*H_2CH$_2$N), 40.4 ((CH$_3$)$_2$*C*H), 44.4 (*C*H_2N), 48.9 (*C*H_2Cl), 54.4 (*C*H_2CHOH), 58.8 (*C*), 73.9 (*C*HOH), 126.0, 128.1, 128.8, 139.5 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{16}H_{22}NO_2Cl$, M = 295.80: C 64.97, H 7.50, N 4.74%; found: C 65.17, H 7.75, N 5.12%.

(2*S*)-1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propyl]-3-alkyl-3-phenylpyrrolidin-2-ones (**10 a–e**) *general procedure*

5 mmol of (2*R*)-1-(3-chloro-2-hydroxypropyl)-3-alkyl-3-phenylpyrrolidin-2-one (**9 a-e**) and 0.8 g (5 mmol) of 1-phenylpiperazine were dissolved in 5 mL of acetonitrile. Then, 5 mmol of anhydrous K_2CO_3 and 0.05 mmol of TBAI were added. The reaction mixture was stirred at room temperature for 24 h. The inorganic salt was filtered and washed with 5 mL of MeOH. The filtrate was evaporated and the oil obtained was purified by column chromatography using an acetone : chloroform (1:1, v/v) mixture.

(2*S*)-1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)-propyl]-3-phenylpyrrolidin-2-one (**10 a**)

Yield 1.2 g (64%), R_f (acetone: $CHCl_3$ 1:1) 0.53; ^{1}H-NMR ($CDCl_3$, δ ppm:) 2.09-2.21 (m, 2H, C*H*$_2$CH (pyrrol.)), 2.38 (d, 2H, *J* = 7.3 Hz, C*H*$_2$), 2.84 (t, 4 H, *J* = 7.1 Hz, C*H*$_2$ (piper.)), 3.34 – 3.48 (m, 8H, C*H*$_2$ (piper.), C*H*$_2$N, NC*H*$_2$CHOH), 3.51 – 3.58 (m, 2H, C*H*CO, OH), 3.93 – 4.08 (m, 1H, CH$_2$C*H*CH$_2$), 6.94 – 7.40 (10H, m, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 30.5 (*C*H$_2$CHCO), 46.6 (*C*H$_2$N), 48.0 (*C*HCO), 54.7 (*C*H$_2$CH), 56.0, 56.3 (piper.), 63.5 (*C*H$_2$N), 66.5 (*C*HOH), 114.3, 121.9, 126.0, 128.1, 128.8, 129.6, 139.2, 149.6 (arom.), 172.3 (carbonyl). Analysis: calc. for $C_{23}H_{29}N_3O_2$, M = 379.50: C 72.70, H 7.70, N 11.07%; found: C 73.12, H 7.75, N 11.12%.

(2*S*)- 1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propyl]-3-methyl-3-phenylpyrrolidin-2-one (**10 b**)

Yield 1.2 g (62%), R_f (acetone , v/v: $CHCl_3$ 1:1) 0.53. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.82 (s, 3H, C*H*$_3$), 2.20 (t, 2H, *J* = 7.8 Hz, C*H*$_2$CH), 2.63 -2.84 (m, 6H, C*H*$_2$ (piper.), CHC*H*$_2$N), 3.34 – 3.50 (m, 9H, C*H*$_2$ (piper.), C*H*$_2$N, NC*H*$_2$CH, O*H*), 3.37 – 4.12 (m, 1H, C*H*OH), 6.94 – 7.37 (m, 10 H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 22.0 (*C*H$_3$), 25.4 (*C*H$_2$C), 44.1 (CH$_2$*C*H$_2$N), 55.0 (N*C*H$_2$CH), 55.1 (*C*), 56.0, 56.3 (piper.), 63.5 (CH*C*H$_2$N), 66.5 (*C*HOH), 114.3, 121.9, 126.0, 128.1, 128.8, 129.6, 138.9, 149.6 (arom.), 183.1 (carbonyl). Analysis: calc. for $C_{24}H_{31}N_3O_2$, M = 393.52: C 73.25, H 7.94, N 10.68%; found: C 73.12, H 7.69, N 10.47.

(2*S*)- 1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propyl]-3-ethyl-3-phenylpyrrolidin-2-one (**10 c**)

Yield 1.2 g (59%), R_f (acetone: $CHCl_3$ 1:1, v/v) 0.57. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, *J* = 7.1 Hz, C*H*$_3$), 1.86 (q, 2H, *J* = 7.1 Hz, CH$_3$C*H*$_2$), 2.24 (t, 2H, *J* = 7.8 Hz, C*H*$_2$C), 2.67 – 2.80 (m, 6H, C*H*$_2$ (piper.), CHC*H*$_2$N), 3.34 – 3.51 (m, 9H, CH$_2$C*H*$_2$N,

NC*H*$_2$CH, CH$_2$ (piper.), O*H*), 3.92 – 4.02 (m, 1H, C*H*), 6.80 – 7.37 (m, 10H, arom.). ^{13}C-NMR (CDCl$_3$, δ ppm): 8.3 (*C*H$_2$), 22.9 (*C*H$_2$C), 32.8 (*C*), 44.4 (*C*H$_2$N), 55.0 (*C*H$_2$CH), 56.0, 56.3 (piper.), 61.3 (*C*), 63.5 (*C*H$_2$N), 66.5 (*C*HOH), 114.3, 121.9, 126.0, 128.1, 128.8, 129.6, 138.9, 149.6 (arom.), 181.5 (carbonyl). Analysis: calc. for $C_{25}H_{33}N_3O_2$, M = 407.55: C 73.68, H 8.16, N 10.31%; found: C 73.57, H 8.23, N 10.51%.

(2*S*)-1-[2-hydroxy-3-(4-phenylpiperazin-1-yl) propyl]-3-phenyl-3-*n*-propylpyrrolidin-2-one (**10 d**)

Yield 1.3 g (62%), R$_f$ (acetone : CHCl$_3$ 1:1, v/v) 0.53. ^{1}H-NMR (CDCl$_3$, δ ppm): 0.90 (t, 3H, *J* = 7.3 Hz, C*H*$_3$), 1.30 – 1.39 (m, 2H, CH$_3$C*H*$_2$), 1.82 (t, 2H, *J* = 7.4 Hz, CH$_2$C*H*$_2$), 2.13 (t, 2H, *J* = 7.8 Hz, C*H*$_2$C), 2.63 – 2.84 (m, 6H, CHC*H*$_2$N, C*H*$_2$ (piper.)), 3.34 – 3.58 (m, 9H, C*H*$_2$N, NC*H*$_2$CH, C*H*$_2$ (piper.), O*H*), 3.97 – 4.12 (m, 1H, C*H*), 6.94 – 7.37 (m, 10H, arom). ^{13}C-NMR (CDCl$_3$, δ ppm): 14.0 (*C*H$_3$), 16.9 (CH$_3$*C*H$_2$), 23.2 (C*H*$_2$CH$_2$), 36.9 (*C*H$_2$C), 44.4 (*C*H$_2$N), 55.0 (*C*H$_2$N), 56.0, 56.3 (piper), 58.8 (*C*), 63.5 (CH*C*H$_2$N), 66.5 (*C*HOH), 114.3, 121.9, 125.9, 128.1, 128.5, 129.6, 139.5, 149.6 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{26}H_{35}N_3O_2$, M = 421.57: C 74.07, H 8.37, N 9.97%; found: C 73.97, H 8.30, N 9.83.

(2*S*)-1-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propyl]-3-phenyl-3-*iso*-propylpyrrolidin-2-one (**10 e**)

Yield 1.2 g (59%), R$_f$ (acetone : CHCl$_3$ 1:1, v/v) 0.56. ^{1}H-NMR (CDCl$_3$, δ ppm): 0.91 (d, 6H, *J* = 6.4 Hz, C*H*$_3$), 2.23 (t, 2H, *J* = 7.8, C*H*$_2$CH$_2$N), 2.43 (m, 1H, C*H*(CH$_3$)$_2$), 2.72 – 2.84 (m, 6H, C*H*$_2$ (piper.), C*H*$_2$N), 3.34 – 2.58 (m, 9H, C*H*$_2$ (piper.), C*H*$_2$CH, C*H*$_2$N, O*H*), 4.01 – 4.15 (m, 1H, C*H*OH), 6.94 – 7.37 (m, 10H, arom.). ^{13}C-NMR (CDCl$_3$, δ ppm): 17.4 (*C*H$_3$), 20.4 (*C*H$_2$CH$_2$), 40.4 (*C*H(CH$_3$)$_2$), 44.7 (*C*H$_2$N), 55.0 (NC*H*$_2$CH), 56.0, 56.3 (piper.), 63.5 (CH*C*H$_2$N), 66.5 (*C*HOH), 67.7 (*C*), 114.3, 121.9, 125.5, 127.8, 128.5, 129.6, 141.2, 149.6 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{26}H_{35}N_3O_2$, M = 421.57: C 74.07, H 8.37, N 9.97%; found: C 73.91, H 8.43, N 9.94%.

(2*S*)-1-[2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl]-3-alkyl-3-phenylpyrrolidin-2-one (**11 a–e**) *general procedure*

5 mmol of (2*R*)-1-(3-chloro-2-hydroxypropyl)-3-alkyl-3-phenylpyrrolidin-2-one (**9 a-e**) and 0.8g (5 mmol) 1-phenylpiperidine were dissolved in 5 mL of acetonitrile. Then, 5 mmol anhydrous K$_2$CO$_3$ and 0.05 mmol TBAI were added. The reaction mixture was stirred at room temperature for 24 h. The inorganic salt was filtered and washed with 5 mL of MeOH. The filtrate was evaporated and the oil obtained was purified by column chromatography using an acetone: chloroform (1:1) mixture.

(2*S*)-1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl)-3-phenylpyrrolidin-2-one (**11 a**)

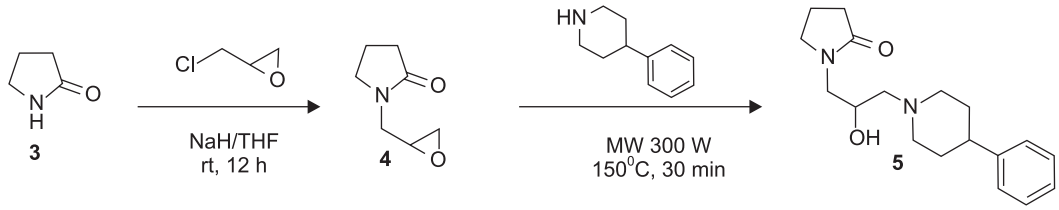
Yield 1.3 g (68%), R$_f$ (acetone : CHCl$_3$ 1:1, v/v) 0.57. ^{1}H-NMR (CDCl$_3$, δ ppm): 1.92 – 2.19 (m, 6H, C*H*$_2$CH$_2$N, C*H*$_2$ (piper.)), 2.51 – 2.78 (m, 7H, C*H* (piper.), C*H*$_2$ (piper.), C*H*$_2$N), 3.34 – 3.58 (m, 6H, C*H*$_2$N, C*H*$_2$CH, O*H*, C*H*), 3.97 – 4.10 (m, 1H, C*H*OH), 7.27 – 7.40 (m, 10H, arom.). ^{13}C-NMR (CDCl$_3$, δ ppm): 30.5 (*C*H$_2$CH$_2$N), 33.2, 42.0, 48.8 (piper.), 46.6 (*C*H$_2$N), 48.0 (*C*H), 54.7 (*C*H$_2$CHOH), 63.8 (*C*H$_2$N), 66.5 (*C*HOH), 126.0, 128.1, 128.8, 139.2, 146.5 (arom.), 172.3 (carbonyl). Analysis: calc. for $C_{24}H_{30}N_2O_2$, M = 378.51: C 76.16, H 7.99, N 7.40%; found: C 76.23, H 8.02, N 7.52.

(2*S*)-1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl)-3-methyl-3-phenylpyrrolidin-2-one (**11 b**)

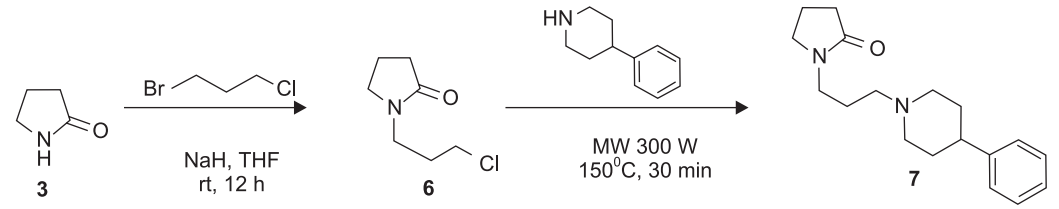
Yield 1.3 g (65%), R$_f$ (acetone : CHCl$_3$ 1:1, v/v) 0.59. ^{1}H-NMR (CDCl$_3$, δ ppm): 1.82 (s, 3H, C*H*$_3$), 1.92 – 2.16 (m, 6H, C*H*$_2$CH$_2$N, C*H*$_2$ (piper.)), 2.51 – 2.70 (m, 7H, C*H*$_2$ (piper.), C*H* (piper.), C*H*$_2$N), 3.34 – 3.58 (m, 5H, CH$_2$C*H*$_2$N, C*H*$_2$CH, O*H*), 3.99 – 4.12 (m, 1H, O*H*), 7.27 – 7.37 (m, 10H, arom.). ^{13}C-NMR (CDCl$_3$, δ ppm): 22.0 (*C*H$_3$), 25.4 (*C*H$_2$CH$_2$N), 33.2, 42.0, 48.8 (piper.), 44.1 (CH$_2$*C*H$_2$N), 55.0 (*C*H$_2$CHOH), 55.4 (*C*), 63.8 (*C*H$_2$N), 66.5 (*C*HOH), 126.0, 128.8, 128.1, 138.9, 146.5 (arom.), 183.1 (carbonyl). Analysis: calc. for $C_{25}H_{32}N_2O_2$, M = 392.53: calc. C 76.49, H 8.22, N 7.14%; found: C 76.54, H 8.20, N 7.12%;

(2*S*)-3-ethyl-1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl)- 3-phenylpyrrolidin-2-one (**11 c**)

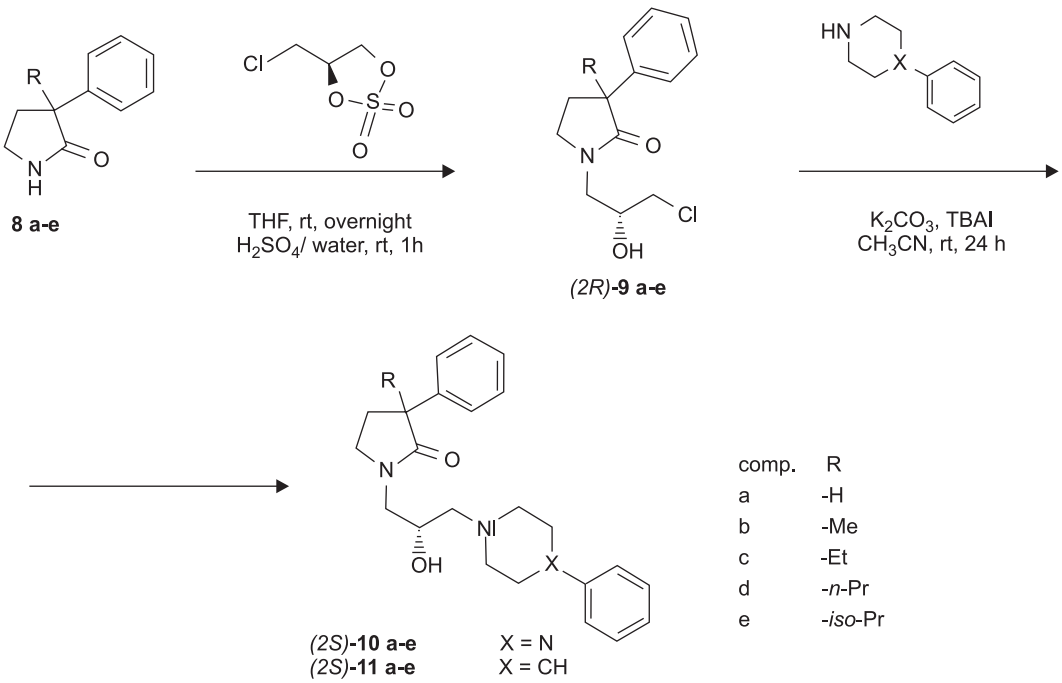
Yield 1.4 g (70%), R$_f$ (acetone : CHCl$_3$ 1:1, v/v) 0.54. ^{1}H-NMR (CDCl$_3$, δ ppm): 0.90 (t, 3H, *J* = 7.1Hz, C*H*$_3$), 1.86 – 2.13 (m, 8H, C*H*$_2$ (piper.), CH$_3$C*H*$_2$, C*H*$_2$CH$_3$), 2.51 – 2.78 (m, 7H, CHC*H*$_2$N,C*H*$_2$ (piper.), C*H* (piper.)), 3.34 – 3.58 (m, 5H, CH$_2$C*H*$_2$, C*H*$_2$CH, O*H*), 4.00 – 4.13 (m, 1H, C*H*OH), 7.27 – 7.37 (m, 10H, arom.). ^{13}C-NMR (CDCl$_3$, δ ppm): 8.3 (*C*H$_3$), 22.9 (*C*H$_2$CH$_2$N), 32.8 (CH$_3$*C*H$_2$), 33.2, 42.0, 48.8 (piper.), 44.4 (CH$_2$*C*H$_2$N), 55.0 (*C*H$_2$CHOH), 61.3 (*C*), 63.8 (*C*H$_2$N), 66.5 (*C*HOH), 126.0, 128.1, 128.8, 138.9, 146.5 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{26}H_{34}N_2O_2$, M = 406.56: C 76.81, H 8.43, N 6.89%; found: C 76.91, H 8.46, N 6.93%.



Scheme 1. Synthesis of 1-[2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl]pirolidin-2-one (**5**)



Scheme 2. Synthesis of 1-[3-(4-phenylpiperidin-1-yl)propyl]-pirolidin-2-one (**7**)



Scheme 3. Synthesis of (2*S*)-1-[3-(4-phenylpiperazin-1-yl)- or (2*S*)-3-[(4-phenylpiperidin-1-yl)-2-hydroxy]- propyl-3-alkyl-3-phenyl-pyrrolidin-2-one derivatives (**10 a – e**) and (**11 a – e**)

Table 1. Affinity of 1-[3-(4-phenylpiperazin-1-yl)- or 3-(4-phenylpiperidin-1-yl)-2-hydroxypropyl]-3-alkyl-3-phenyl-pyrrolidin-2-one derivatives ((S)-**1,** (R)-**1, 5, 7, 10 a, 10 c, 10 d, 10 e, 11 a, 11 b, 11 d**) and model compounds (**1** and **2**) towards α_1-ARs subtypes in rat cerebral cortex.

Compound	pK_i α_1
1 (42)	5.72
(S)-**1**	6.27
(R)-**1**	5.58
2 (22)	6.25
5	5.82
7	5.95
10 a	5.83
10 c	5.79
10 d	6.43
10 e	6.23
11 a	6.36
11 b	5.85
11 d	6.05

The means pK_i values were obtained from three experiments. Inhibition constants (K_i) were calculated according to the equation of Cheng and Prusoff (35)

Table 2. The prophylactic anarrhytmic activity of 1-[3-(4-phenylpiperazin-1-yl)- or 3-(4-phenylpiperidin-1-yl)-2-hydroxypropyl]-3-alkyl-3-phenyl-pyrrolidin-2-one ((*S*)-**1, 5**, **7**, **10 c-e, 11 a** and **11 d**) and model compounds **1** and **2** in adrenaline-induced arrhythmia in anesthetized rats after *i.v.* administration

Compound	ED_{50} (mg/kg)
1 (42)	7.9
(*S*)-**1**	5.1 (4.2 – 6.1)
2	2.8 (2.1 – 3.6)
5	4.9 (3.7-6.4)
7	7.6 (5.4 – 10.6)
10 c	12.9 (10.7 -15.5)
10 d	9.9 (6.7- 14.8)
10 e	10.4 (8.0 – 13.5)
11a	6.2 (4.7 – 8.0)
11d	13.2 (10.6 – 16.5)
tolazoline	3.4 (2.6 – 4.4)

Each value was obtained from three experimental groups. Each group consisted of six animals. The ED_{50} values and their confidence limits were calculated according to the method of Litchfield and Wilcoxon (39)

(2*S*)-1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl)- 3-phenyl-3-*n*-propyl-pyrrolidin-2-one ((2*S*)-**11 d**)

Yield 1.3 g (63%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.52. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, *J* = 7.3 Hz, C*H*$_3$), 1.28 – 1.39 (m, 2H, CH_3CH_2), 1.82 – 2.13 (m, 8H, CH_2CH_2, CH_2CH_2, CH_2 (piper.)), 2.63 – 2.78 (m, 7H, $CHCH_2N$, CH_2 (piper.), C*H* (piper.)), 3.36 – 3.55 (m, 5H, CH_2CH_2N, CH_2CH, O*H*), 4.02 – 4.15 (m, 1H, C*H*OH), 7.27 – 7.37 (m, 10H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 14.1 (*C*H$_3$), 17.8 (CH_3CH_2), 29.1 (CH_2CH_2N), 35.9 (CH_2CH_2), 33.2, 42.0, 48.8 (piper.), 45.3 (CH_2CH_2N), 55.1 (*C*HCHOH), 61.3 (*C*), 63.8 ($CHOHCH_2$), 66.5 (*C*HOH), 109.7, 116.1, 126.0, 128.1, 128.8, 130.4, 135.2, 146.5, 154.2 (arom.), 176.7 (carbonyl). Analysis:. calc. for $C_{27}H_{36}N_2O_2$, M = 420.59: C 77.10, H 8.63, N 6.66%; found: C 77.03, H 8.58, N 6.54%.

(2*S*)-1-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl)- 3-phenyl-3-*iso*-propylpyrrolidin-2-one (**11 e**)

Yield 1.4 g (67%), R_f (acetone : $CHCl_3$ 1:1, v/v) 0.57. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (d, 6H, *J* = 7.2 Hz, C*H*$_3$), 1.92 – 2.13 (m, 6H, CH_2CH_2N, CH_2 (piper.)), 2.43 – 2.68 (m, 8H, $CH(CH_3)_2$, CH_2 (piper.), C*H* (piper.), CH_2N), 3.34 – 3.58 (m, 5H, CH_2CH_2N, CH_2CHOH, O*H*), 4.03 – 4.16 (m, 1H, C*H*OH), 7.30 – 7.37 (m, 10H, arom.). ^{13}C-NMR ($CDCl_3$, δ ppm): 17.4 (*C*H$_3$), 20.4 (CH_2CH_2N), 40.4 ($CH(CH_3)_2$), 44.7 (CH_2CH_2N), 33.2, 42.0, 48.8 (piper.), 55.0 (CH_2CHOH), 63.8 (CH_2N), 66.5 (*C*HOH), 67.7 (CH_2CHCO), 125.5, 126.0, 127.8, 128.1, 128.5, 128.8, 141.2, 146.5 (arom.), 181.7 (carbonyl). Analysis: calc. for $C_{27}H_{36}N_2O_2$, M = 420.59: C 77.10, H 8.63, N 6.66%; found: C 77.17, H 8.76, N 6.76%.

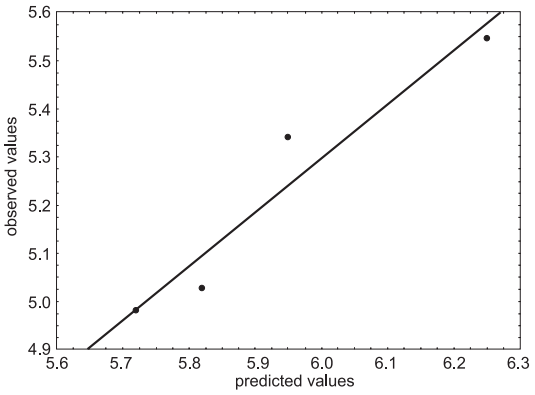


Figure 2. Graphical representation of the observed α_1-ARs activity values *versus* the values predicted by the model [24] for compounds **1**, **2**, **5** and **7**

Table 3. The hypotensive activity of 1-[3-(4-phenylpiperazin-1-yl)- or 3-(4-phenylpiperidin-1-yl)-2-hydroxy]-propyl-3-alkyl-3-phenyl-pyrrolidin-2-one derivatives ((*S*)-**1**, **5**, **7**, **10 c**, **10 d**, **11 a** and **11 d**) in anesthetized normotensive rats after *i.v.* administration

Comp.	Dose	Pressure	Control	5 min	10 min	20 min	30 min	40 min	50 min	60 min
(S)-**1**	5	systolic	138.0 ± 2.6	115.0 ± 3.6***	115.0 ± 6.9**	129.0 ± 2.9*	128.0 ± 3.9*	126.0 ± 3.3*	126.0 ± 5.2*	129.5 ± 9
		diastolic	120.0 ± 4.7	104.0 ± 4.5***	109.5 ± 3.2 **	109.0 ± 2.9**	112.5 ± 5 *	118.0 ±4.5	119.0 ±6.5	116.0 ±6.9
5	5	systolic	121.8 ± 3.0	108.2 ± 4.3	108.7 ± 5.3	104.8 ± 4.2*	104.0 ± 4.7*	98.2 ± 6.4***	95.7 ± 7.2***	97.0 ± 6.6***
		diastolic	101.0 ± 2.7	90.0 ± 5.1	89.5 ± 6.3	85.5 ± 4.5	85.7 ± 5.3	80.8 ±7.9*	78.5 ± 8.4**	80.2 ± 8.2*
	2.5	systolic	111.5 ± 2.5	103.2 ± 3.0	101.5 ± 2.1*	101.5 ± 1.4*	100.0 ± 2.3**	101.2 ± 2.2*	100.5 ± 3.4*	100.0 ± 3.5**
		diastolic	92.0 ± 4.2	82.2 ± 6.1	83.7 ± 2.7	83.2 ± 4.0	82.0 ± 4.2	81.7 ± 4.2	81.5 ± 4.8	81.0 ± 4.6
7	5	systolic	136.2 ± 5.5	124.0 ± 7.7	122.5 ± 6.7	118.5 ± 5.8*	114.5 ± 4.6**	111.7 ± 4.3***	112.7 ± 3.2***	112.5 ± 3.4***
		diastolic	117.7 ± 5.1	105.2 ± 6.2	104.2 ± 6.8	100.7 ± 6.4	95.7 ± 5.6*	93.7 ± 5.4**	93.5 ±4.9**	92.2 ± 4.0***
	2.5	systolic	129.0 ± 4.6	114.2 ± 4.4*	113.5 ± 3.9*	114.2 ± 4.2*	113.0 ± 5.4*	110.0 ± 5.0***	111.2 ±6.9**	111.2 ± 6.6**
		diastolic	107.6 ± 6.4	93.7 ± 7.2	93.7 ± 7.4	95.2 ± 5.9	94.5 ± 6.6	93.0 ± 7.3	94.0 ± 8.8	94.5 ± 7.7
10c	5	systolic	140.9 ± 4.9	133.9 ± 2.2*	138. 0 ± 3.3	135.8 ± 6.3	139.5 ± 8	137.2 ± 8.2	140 ± 9	139.5 ± 5
		diastolic	129.2 ± 6.0 3	127.3 ± 6.2	125 ± 8.4	129 ± 4.9	126 ± 2.9	129 ± 2.5	129 ± 4.8	128 ± 9.4
10d	5	systolic	145.3 ± 4.2	121 ± 4.1****	129.3 ± 3.8***	124 ± 5.5***	129 ± 7**	132 ± 10.3*	133 ± 8.9*	132.9 ± 4.3*
		diastolic	129.5 ± 6.2	111.0 ± 3.9****	118.0 ± 6.1*	114.3 ± 9.4*	119.0 ± 7.1*	122.0 ± 5.5	125.0 ± 4.8	125.0 ± 7
11a	5	systolic	148.0 ± 9.2	119.0 ± 8.1**	119.3 ± 4.9**	125.0 ± 9.5*	131.0 ± 7.1*	138.0 ± 10	135.0 ± 3.9*	139.9 ± 9
		diastolic	124 ± 5.9	115 ± 1.4*	112.7 ± 3.0*	117.0 ± 8.0	119.0 ± 6.6	117.0 ± 9.2	117.9 ± 10.0	118.0 ± 7.0
11d	5	systolic	141.3 ± 4.9	130.9 ± 3.0**	135 ± 1.3*	135.8 ± 3.3*	137.5 ± 4.0	137.9 ± 7.2	138 ± 7.0	139.0 ± 5.9
		diastolic	126 ± 9.3	119 ± 1.1*	119.7 ± 4.2	120.2 ± 7.0	119 ± 9.4	119.7 ± 9.0	122.8 ± 6.4	123 ± 7.9

The data are the means of six experiments ± SEM. Statistical analyses were performed using a one-way ANOVA: * $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$; **** $p < 0.001$

Pharmacology

Materials and Methods

Compounds

[^{3}H] clonidine (Amersham), epinephrine (Adrenalinum hydrochloricum, Polfa), norepinephrine (Levonor, Polfa), methoxamine (Sigma, Aldrich Chemie GmbH), [^{3}H] prazosin (Amersham), tyramine (Sigma, Aldrich Chemie GmbH), sodium heparin (Polfa), thiopental sodium (Biochemie GmbH, Vienna)

Animals

The experiments were carried out on male Wistar rats (180 – 250 g). Animals were housed in constant temperature facilities exposed to 12/12 h light-dark cycle and maintained on a standard pellet diet and tap water was given *ad libitum*. Control and experimental groups consisted of 8 – 10 animals each. All procedures were done according to the Animal Care and Use Committee Guidelines and approved by the Ethical Committee of the Jagiellonian University, Kraków, Poland.

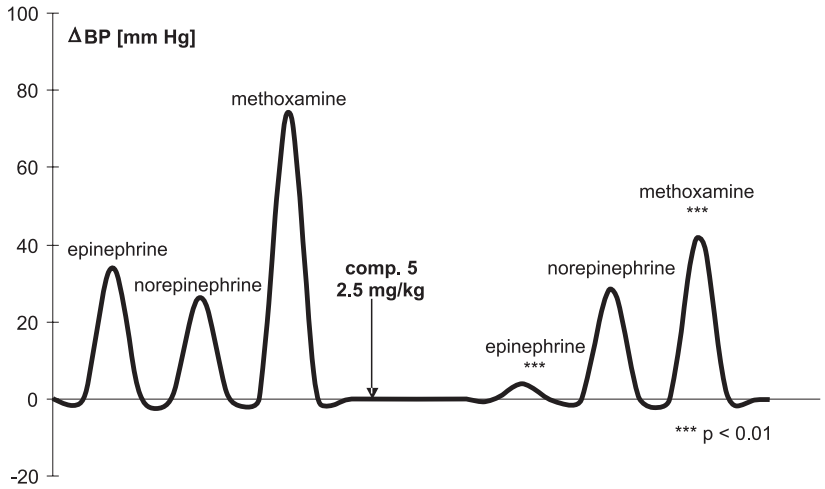


Figure 3. The effect of compound **5** on blood pressure response to epinephrine, norepinephrine and methoxamine

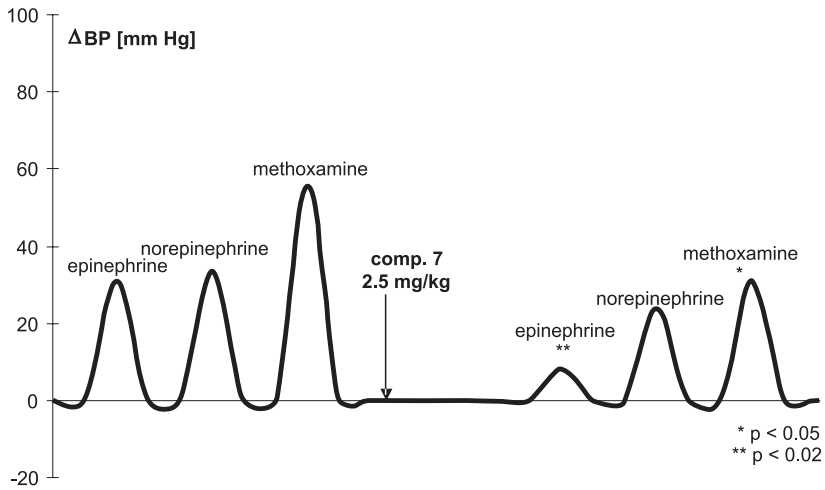


Figure 4. The effect of compound **7** on blood pressure response to epinephrine, norepinephrine and methoxamine

Reference compounds

Compound **1** was used as a reference.

Statistical analysis

The data are expressed as the mean ± SEM. The statistical significance was calculated using a one-way ANOVA. Differences were considered significant when $p < 0.05$.

α_1-Adrenoceptor radioligand binding assay

The experiment was carried out on rat cerebral cortex. [^{3}H]prazosin (19.5 Ci/mmol,) was used. The brains were homogenized in 20 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.6) and were centrifuged at 20 000 × g for 20 min (0 – 4°C). The cell pellet was resuspended in the Tris-HCl buffer and centrifuged again. Radioligand binding assays were performed in plates (MultiScreen/Millipore). The final incubation mixture (final volume 300 mL) consisted of 240 mL of the membrane suspension, 30 mL of [^{3}H]prazosin (0.2 nM) solution and 30 mL of the buffer containing seven to eight concentrations (10^{-11} – 10^{-4}M) of the tested compounds. To measure the unspecific binding, 10 mM phentolamine was applied (34). The incubation was terminated by rapid filtration over glass fiber and placed in scintillation vials with a liquid scintillation cocktail. Radioactivity was measured in a WALLAC 1409 DSA liquid scintillation counter. All assays were made in duplicate. The radioligand binding were analyzed using an iterative curve-fitting routine (GraphPAD/Prism, Version 4.0 – San Diego, CA, USA). K_i values were calculated based on the method described by Cheng and Prusoff (35).

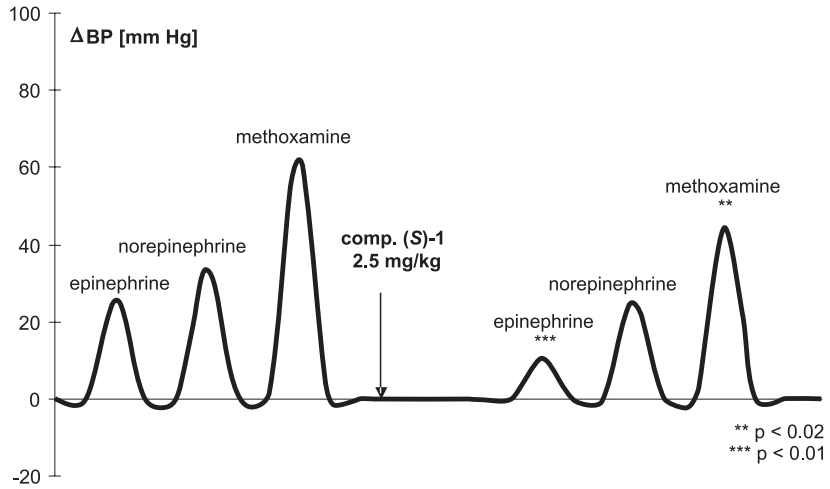


Figure 5. The effect of compound (S)-**1** on blood pressure response to epinephrine, norepinephrine and methoxamine

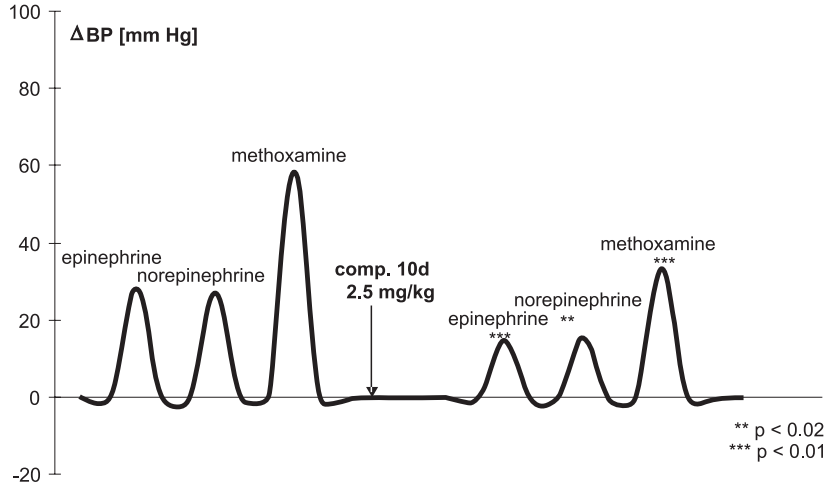


Figure 6. The effect of compound **10d** on blood pressure response to epinephrine, norepinephrine and methoxamine

Prophylactic antiarrhythmic activity in a model of adrenaline-induced arrhythmia according to Szekeres and Papp (36)

Arrhythmia was evoked in thiopental (60 mg/kg, *i.p.*) – anesthetized rats by *i.v.* injection of adrenaline (20 mg/kg). The tested compounds were administered intravenously 15 min before adrenaline. The criterion of antiarrhythmic activity was the lack of premature beats and the inhibition of rhythm disturbances in comparison with the control group (ventricular bradycardia, atrioventricular block, ventricular tachycardia or ventricular fibrillation). The cardiac rhythm disturbances were recorded for 15 min after adrenaline injection. ECGs were analyzed according to the guidelines of the Lambeth Convention (40) on ventricular premature beats (VBs), bigeminy, salvos (less than four successive VBs), ventricular tachycardia (VT, four or more successive VBs) and ventricular fibrillation (VF).

The influence on blood pressure

Male Wistar normotensive rats were anesthetized with thiopental (50 – 75 mg/kg, *i.p.*) The right carotid was cannulated with polyethylene tube filled with heparin in saline to facilitate pressure measurement using the Datamax apparatus (Columbus Instruments). The studied compounds were injected in a single dose of 2.5 or 20 mg/kg

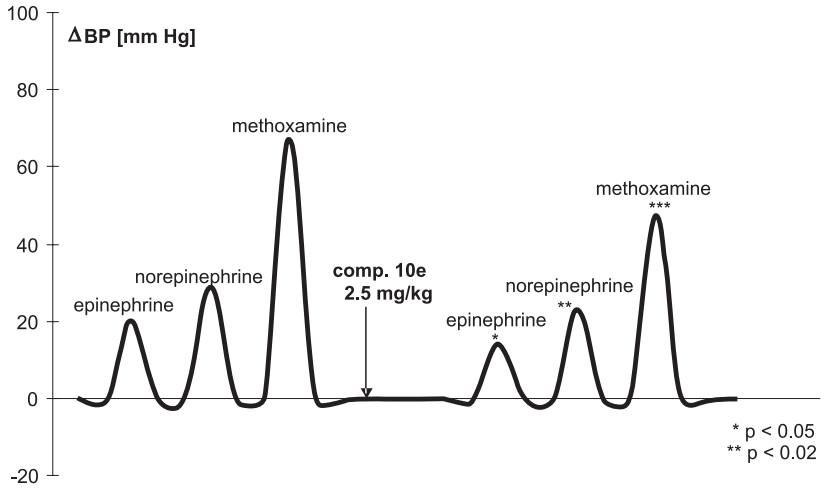


Figure 7. The effect of compound **10 e** on blood pressure response to epinephrine, norepinephrine and methoxamine

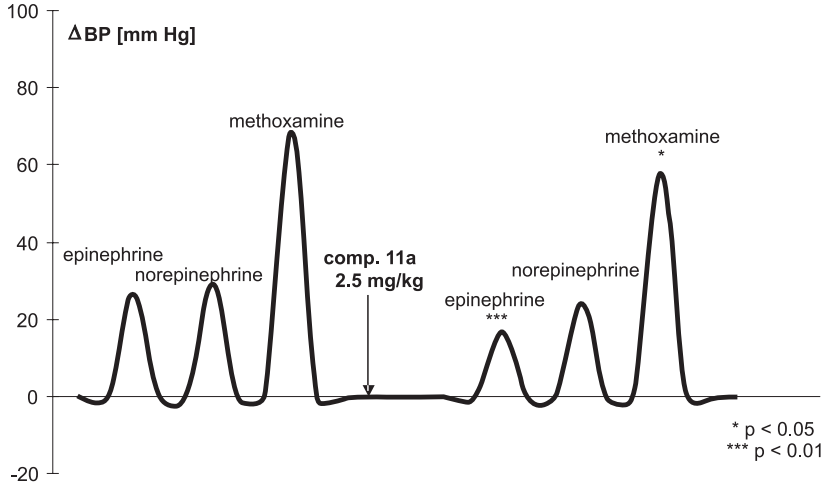


Figure 8. The effect of compound **11 a** on blood pressure response to epinephrine, norepinephrine and methoxamine

into the caudal vein after a 5 min stabilization period at a volume equivalent to 1 mL/kg.

RESULTS

As a staring material for the synthesis of compound **5** earlier described 1-(2,3-epoxypropyl)-pyrrolidin-2-one (**4**), which was synthesized from pyrrolidin-2-one (**3**) and 1-chloro-2,3-epoxypropane, was used (38, 39). Its aminolysis with 4-phenylpiperidine performed in closed vessel in microwave reactor gave racemic mixture of 1-[2-hydroxy-3-(4-phenylpiperidin-1-yl)propyl]-pirolidin-2-one (**5**) with 68% yield (Scheme 1).

The compound 1-[3-(4-phenylpiperidin-1-yl)propyl]-pirolidin-2-one (**7**) was obtained by a simple two stage reaction. Firstly, 1-(3-chloropropyl)pyrrolidin-2-one (**6**) was synthesized. This compound was obtained by alkylation of pyrrolidin-2-one (**3**) with 1-bromo-3-chloro-propane. The reaction was carried out in tetrahydrofuran (THF) using NaH as a base. Then, heating of compound **6** and 4-phenylpiperidine in closed vessel in a microwave reactor, yielded compound **7** in 73% yield.

Taking into consideration that (*S*) enantiomers of compound **1** and its analogues displayed higher affinity for α_1-ARs than the (*R*) ones, 1-[3-(4-phenylpiperazin-1-yl)-2-hydroxy]propyl- or 1-[3-

(4-phenylpiperidin-1-yl)-2-hydroxy]propyl- compounds having 3-alkyl-3-phenylpyrrolidin-2-one fragment were obtained only as derivatives having (*S*) configuration on asymmetric carbon atom of the propyl chain. For this reactions, an earlier elaborated method was applied (23). As a starting material for this synthesis, (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide was used (37, 38). This compound with relevant substituted pyrrolidin-2-one (**8a–e**) gave (2*R*)-2-hydroxy compounds **9a–e**, with yields varied between 62 and 72%. Finally, the alcohols **9a–e** with relevant 4-phenylpiperazine or 4-phenylpiperidine, in the reaction of phase transfer catalysis catalyzed by tetrabutylammonium iodide (TBAI) and carried out in a mixture of acetonitrile/K_2CO_3, gave (2*S*) enantiomers of 1-[3-(4-phenylpiperazin-1-yl)-2-hydroxypropyl]-3-aryl-3-phenylpyrrolidyn-2-one (**10a–e**) and 1-[3-(4-phenylpiperidin-1-yl)-2-hydroxypropyl]-3-aryl-3-phenylpyrrolidyn-2-ones (**11a–e**) with 59-70% yield (Scheme 3).

The structures of the new compounds were confirmed by elemental analysis and spectral data.
In the present study, several pharmacological tests were carried out to assess α_1-AR affinity, antiarrhythmic and hypotensive activity of the novel pyrrolidin-2-ones derivatives (*S*)-**1,** (*R*)-**1**, **5**, **7**, **10a-e** and **11a-e**.

The pharmacological profile of the new compounds was evaluated by radioligand binding assays (the ability to displace [^{3}H] prazosin from α_1-ARs) on rat cerebral cortex (34, 35). All tested compounds displaced [^{3}H]prazosin from cortical binding sites (pK_i α_1-ARs 5.82 - 6.43). The results obtained are presented in Table 1.

The prophylactic antiarrhythmic activity of compounds (*S*)-**1,** (*R*)-**1**, **5**, **7**, **10a-e** and **11a-e** was determined using a model of adrenaline-induced arrhythmia in rats (37). Intravenous (*iv*) injections of adrenaline at a dose of 20 mg/kg caused reflex bradycardia (100%), supraventricular and ventricular extrasystoles (100%), bigeminy and ventricular tachycardia (50%) in rats, which led to the death of ca. 50% of animals within 10 ± 5 min. Compounds (*S*)-**1, 5**, **7**, **10c-e, 11a** and **11d** injected intravenously 15 min before adrenaline, diminished the occurrence of extrasystoles and reduced mortality. The ED_{50} values are presented in Table 2. These data show that compound (S)-**1** was the most active, its ED_{50} value is 4.9 mg/kg.

The hypotensive activity of compounds (*S*)-**1,** (*R*)-**1**, **5**, **7**, **10a-e** and **11a-e** was determined after *iv* administration to normotensive anesthetized rats at doses of 2.5 and 5.0 mg/kg. The results are presented in Table 3. Compounds (*S*)-**1**, **5**, **7**, **10 c**, **10d**, **11a** and **11d** significantly decreased systolic and diastolic pressure. This effect persisted for more than 60 min.

To examine the mechanism of the hypotensive effects of these compounds, their influence on the pressor responses to epinephrine, norepinephrine, methoxamine and tyramine were studied. These compounds given *iv* to rats caused a pressor response at the following doses: epinephrine 2 mg/kg, norepinephrine 2 mg/kg, methoxamine 150 mg/kg, tyramine 200 mg/kg. Compounds **10d** and **10e** given *iv* in doses of 2.5 mg/kg antagonized the pressor response elicited by epinephrine, norepinephrine and methoxamine. Compounds (*S*)-**1**, **5**, **7** and **11a** given in a dose of 2.5 mg/kg decreased pressor response provoked by epinephrine and methoxamine. (Fig. 3 -8) All of these effects were statistically significant. However, compounds *(R)*-**1**, **10a**, **10b**, **10c**, **11b**, **11c**, **11d** and **11e**) had no statistically significant influence on the systolic pressor response generated by epinephrine, norepinephrine, methoxamine and tyramine (data not shown).

RESULTS AND DISCUSSION

All the newly synthesized compounds *(S)*-**1**, *(R)*-**1**, **5**, **7**, **10a**, **10c**, **10d**, **10e**, **11a**, **11b, 11d** were found to possess an affinity toward α_1-ARs, which was comparable to the affinity of the earlier reported compounds. The highest affinity for α_1-ARs (pK_i 6.43) was displayed by compound **10d**, which is a phenylpiperazine derivative with phenyl and *n*-propyl group in the 3rd position of the pirrolidin-2-one ring. Among the isomers of compounds **1** higher affinity for α_1-ARs was displayed by enantiomer (*S*). The replacement of piperazine ring by piperidine one gave compounds **5** and **7**, which affinity to α_1-ARs were comparable to parent compounds **1** and **5**. In case of phenylpiperazine derivatives **1** and **10a-e**, the introduction of phenyl- **10a**, or phenyl- and ethyl-, *n*-propyl- or *iso*-propyl- **10c-e** into 3rd position of pyrrolidin-2-one moiety resulted in the compound having higher than parental compounds affinity for α_1-AR. The increase of α_1-ARs affinity was also observed for compounds having piperidine ring and phenyl- or phenyl and methyl- or *n*-propyl-substituent in the 3rd position of pyrrolidin-2-one moiety.

In order to better understand the mechanism of action displayed by tested compounds, their influence on the pressor response to epinephrine, norepinephrine, methoxamine and tyramine was tested. It is generally accepted that α_1-ARs antagonists invert

pressor response to epinephrine, only partially invert that of norepinephrine, diminish the pressor response of methoxamine and tyramine, and potentiate the hypertensive effect of norepinephrine. The results of these studies are in good agreement with radioligand binding investigations and confirm the α-ARs antagonist activity of the compounds obtained. The compounds obtained diminished or prevented the appearance of epinephrine-induced arrhythmia symptoms. The ED_{50} value obtained for compound **5** was 4.9 mg/kg, comparable to that displayed by tolazoline (the commonly used reference compound in adrenaline-induced model of arrhythmia) and that displayed by compound **1**.

The pyrrolidin-2-one derivatives obtained: (*S*)-**1,** (*R*)-**1**, **5**, **7**, **10a-e** and **11a-e,** were also tested for their hypotensive activity in normotensive anesthetized rats. Compounds: (S)-**1**, **5**, **7**, **10c**, **10d**, **11a** and **11d** significantly decreased the systolic and diastolic pressure. The highest hypotensive activity was displayed by compounds **5** and **7**.

To probe the true predictive power of given QSAR model (24), the comparison of the predictive and observed activities of compounds that were not used in the model development was performed (41).

In this study, the following methodology have been applied. First, four most potent compounds were chosen from early tested derivatives. For these new derivatives the statistical tests showed the correlation coefficient Q^2 of 0.93, which proves a good predictability of earlier proposed model. This is also shown on the plot (Fig. 2.) of the observed α_1-adrenoreceptor binding affinity *vs*. predicted by the model.

In the next step, ten analogues of parent compounds were grouped in two subsets: arylpiperazinyl analogues (compounds **10a–e**) and arylpiperidinyl analogues (compounds **11a–e**). Then, the statistical external test of proposed model in both group of compounds **10** and **11** was performed. In order to identify the effect of the molecular structure on the α_1-ARs activity for two newly selected groups, all calculations were conducted according to the same calculating protocol as it was described in (24). The obtained correlation coefficients were found to be Q^2_{11} 0.30 and Q^2_{10} 0.50, respectively. These results suggest that for the α_1-adrenoreceptor affinity, the most important structural feature is the presence of arylpiperazinyl moiety in the molecular skeleton.

CONCLUSION

The synthesis and preliminary pharmacological data for several new 1-[3-(4-arylpiperazin-1-yl)propyl]-3-alkyl-3-phenylpyrrolidin-2-one and 1-[3-(4-arylpiperidin-1-yl)propyl]-3-alkyl-3-phenylpyrrolidin-2-one derivatives were described. Some of the compounds obtained were found to possess an affinity for α_1-AR comparable to that of the reference compounds **1** and **2**. In case of compound **1,** the absolute configuration of asymmetric carbon atom is important for its antiarrhythmic and hypotensive activities. The introduction of the phenyl- and *iso*-propyl- groups into pyrrolidin-2-one fragment resulted in compounds which in *in vitro* studies displayed antiarrhytmic and hypotensive activity. The replacement of the piperazine ring by a piperidine one led to compounds which have an affinity comparable to their parent compound for both α_1-ARs. The pharmacological results and binding studies suggested that the antiarrhythmic and/or hypotensive effects of these compounds were related to their adrenolytic properties. More extensive structure activity relationship studies are in progress and will be reported in due course. The obtained results are also in good agreement with the earlier descried QSAR model.

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