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Arylsulfonamide derivatives of (aryloxy)ethyl pyrrolidines and piperidines as α_1-adrenergic receptor antagonist with uro-selective activity

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ABSTRACT

A series of arylsulfonamide derivatives of (aryloxy)ethyl pyrrolidines and piperidines was synthesized to develop new α_1-adrenoceptor antagonists with uroselective profile. Biological evaluation for α_1- and α_2-adrenorecepor showed that tested compounds **13**–**37** displayed high-to-moderate affinity for the α_1-adrenoceptor (K_i = 34–348 nM) and moderate selectivity over α_2-receptor subtype. Compounds with highest affinity and selectivity for α_1-adrenoceptor were evaluated in vitro for their intrinsic activity toward α_{1A}- and α_{1B}-adrenoceptor subtypes. All compounds behaved as antagonists at both α_1-adrenoceptor subtypes, displaying 2- to 6-fold functional preference to α_{1A}-subtype. Among them, *N*-{1-[2-(2-methoxyphenoxy)ethyl]piperidin-4-yl}isoquinoline-4-sulfonamide (**25**) and 3-chloro-2-fluoro-*N*-{[1-(2-(2-isopropoxyphenoxy)ethyl)piperidin-4-yl]methyl}benzene sulfonamide (**34**) displayed the highest preference to α_{1A}-adrenoceptor. Finally, compounds **25** and **34** (2–5 mg/kg, iv), in contrast to tamsulosin (1–2 mg/kg, iv), did not significantly decrease systolic and diastolic blood pressure in normotensive anesthetized rats to determine their influence on blood pressure.

1. Introduction

Benign prostatic hyperplasia (BPH) is highly prevalent neoplasm in aging men, affecting up to 70% of patients over the age of 80.[1] Enlargement and elevated muscle tone of the prostate gland lead to obstruction of the bladder outlet and manifests clinically with lower urinary tract symptoms (LUTS).[2,3] Although BPH is rarely a life-threatening condition, the symptoms tend to be bothersome and result in significant impairment of quality of life. Moreover BPH can be a progressive disease, especially if left untreated. Therefore the aim of pharmacological therapy is to relieve urinary symptoms, prevent progression and the development of long term complications.[4–6]

There are several classes of medications available for the treatment of BPH, but despite the different mechanisms of action, their beneficial effects are not observed in all patients.[7–10] According to the current European Association of Urology guidelines, alpha$_1$-adrenoceptor blockers have an advantage over other groups as they improve LUTS in a short period of time. In consequence, they are considered the first-line drug treatment for BPH.[11] Various α_1-adrenoceptor blockers are currently available for the treatment of BPH with different selectivity for adrenoceptor subtypes, efficacy and side-effect profile.

To date, four subtypes of α_1-adrenoceptor have been identified in human organs: α_{1A}-, α_{1B}-, α_{1D}-, and α_{1L}-adrenoceptors.[12] Distribution studies have shown that α_{1A}- and α_{1D}-adrenoceptor subtypes are three to nine fold greater expressed in the prostatic gland in BPH comparing to healthy tissue.[13] On the contrary, α_{1B}-adrenoceptors seem to be important for systematic blood pressure control, as they are highly prevalent in vascular smooth muscle.[14] It has been demonstrated that blockade of α_{1A}-adrenoceptors relaxes prostate smooth muscle thus relieving obstructive outflow symptoms, whereas α_{1D}-adrenoceptor antagonists decrease

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bladder over activity through direct influence on the bladder detrusor muscle.[12] The blockade of α_{1B}-adrenoceptor may promote blood pressure-related side-effects, particularly orthostatic hypotension, as it mediates vasodilation in blood vessels.[15] The most commonly used α_1-adrenolitic drugs, derived from quinazoline moiety, i.e. doxazosin, terazosin and alfuzosin, nonspecifically interact with all α_1-adrenoceptor subtypes.[16] On the contrary, tamsulosin and the most recently introduced silodosin and naftopidil, show specific affinity for α_{1A}-adrenoceptor and α_{1D}-adrenoceptor subtypes.[15–18] These new selective α_1-adrenoceptor blockers decrease risk for cardiovascular side effects comparing to the non-selective representatives, due to the lower interaction with α_{1B}-adrenoceptor subtype.[19]

In this context the search for α_1-adrenoreceptor antagonists with stronger uroselective profile is still considered an important approach in search for effective treatment of BPH. Among several classes of α_1-adrenoceptors ligands, long-chain arylpiperazines (LCAPs) represent one of the most privileged structure for developing derivatives with high affinity for α_{1A} and α_{1D}-receptors and high selectivity over the α_{1B} subtypes[20–22] (Fig. 1). Moreover, it was found that a kind of substituent at the arylpiperazine moiety as well as a kind of terminal fragment highly influenced interaction with α_1-adrenoreceptors.[23–28]

Recently, Zajdel et al.[29,30] have proposed a concept of biomimetics of long-chain arylpiperazine derivatives. The idea was based on the premise that arylpiperazine moiety might be replaced with aryloxyalkyl alicyclic amines, e.g. piperidines and pyrrolidines. Extended structure–activity relationship studies in a group of arylsulfonamide derivatives of (aryloxy)ethyl piperidines revealed that receptor affinity and selectivity, especially for serotonin 5-HT_7 and 5-HT_{1A}, dopamine D_2 and also α_1-adrenergic receptors, was highly depended upon a kind of substituent in the aryloxy moiety. It was found that, an introduction of small and electron donating substituents e.g. methoxy in a *ortho*-position at the (aryloxy)ethyl fragment decreased the affinity for 5-HT_7Rs (K_i >300 nM) when compared with close analogs containing steric hindered substituents (i.e. isopropyl, *t*-butyl, phenyl, K_i <50 nM).[30,31] At the same time, this modification was favorable for interaction with α_1-adrenoreceptors.

Inspired by these finding, we designed and synthesized a new library of arylsulfonamide derivatives of (aryloxy)ethyl pyrrolidines and piperidines as a novel group of α_{1A}-/α_{1D}-receptor antagonists (Fig. 2).

Structural modifications comprised an introduction of small or sterically encumbered electron donor substituent in position-2 of aryloxy fragment (methoxy and isopropoxy), different amine cores

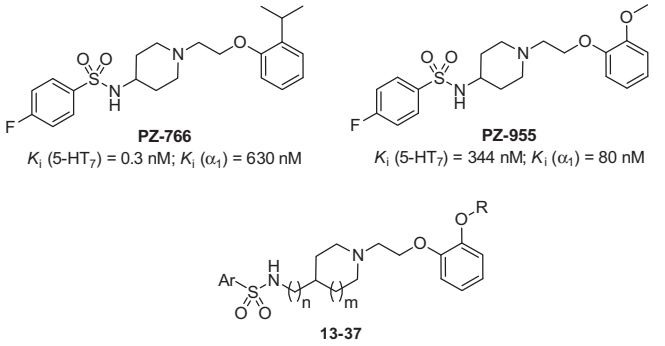


Figure 2. General structure of compounds PZ-766, PZ-955 and designed compounds **13**–**37**.

(*R* and *S* 3-aminopyrrolidine, 4-aminopiperidine and 4-aminomethylpiperidine) as well as diversification at the arylsulfonamide moiety. Pharmacological tests were carried out to assess the affinity for α_1- and α_2-adrenoceptors, to determine their intrinsic activity using in vitro functional assay, and finally to evaluate an influence of selected compounds on blood pressure in animal models.

2. Chemistry

The synthesis of designed compounds **13**–**37** was performed according to a multistep procedure reported in Scheme 1. In the first step, commercially available phenols **1**–**2** were treated with 1,2-dibromoethane, in presence of potassium carbonate, in refluxing acetone. Subsequently, the obtained alkylating agents **3**–**4** reacted with selected Boc-protected secondary amine (*R* and *S*-3-amino-pyrrolidine, 4-amino-piperidine and 4-aminomethyl-piperidine) yielding intermediates **5**–**12**. After removal of Boc group, final arylsulfonamides **13**–**37** were obtained upon treatment of primary amines with the selected arylsulfonyl chlorides.

3. Pharmacology

3.1. In vitro radioligand binding and functional evaluation

The pharmacological profile of the new compounds was evaluated by radioligand binding assays (the ability to displace [^{3}H]-Prazosin or [^{3}H]-Clonidine from α_1- and α_2-adrenoceptor, respectively) using a tissue from the rat cerebral cortex.[32]

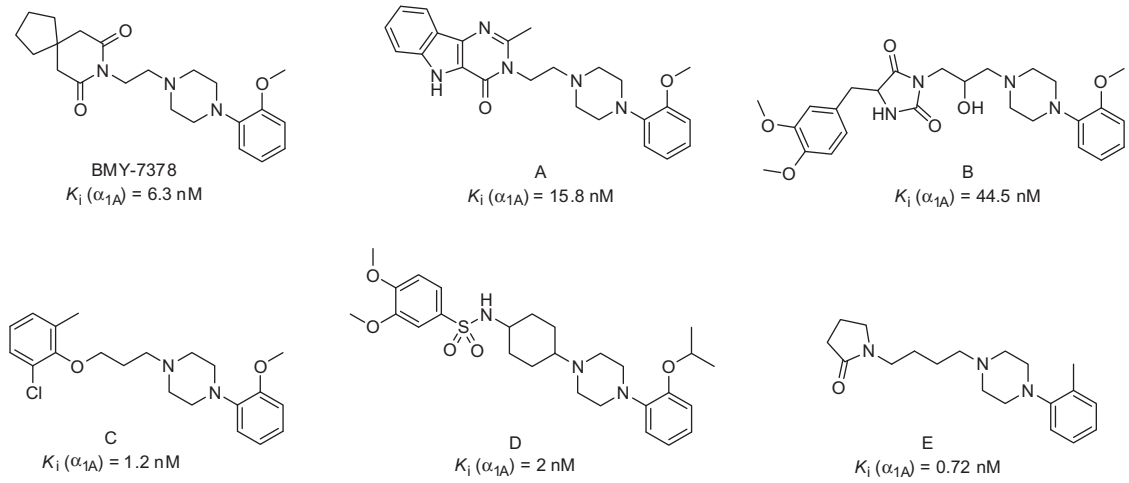
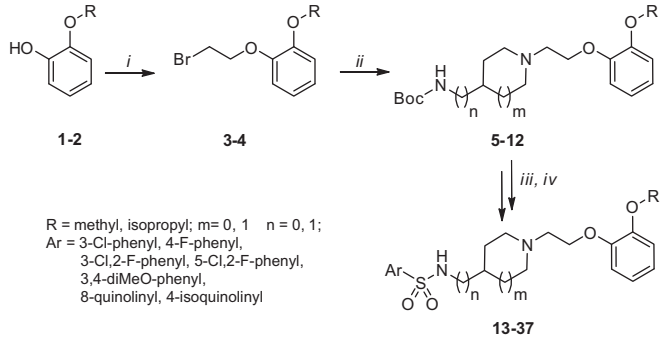


Figure 1. General structure of differently functionalized LCAPs as α_1-adrenoreceptor antagonists.



Scheme 1. Synthesis of compounds **13**–**37**. Reagents and conditions: (i) 1,2-dibromoethane, K_2CO_3, KI, $(CH_3)_2CO$, 60 °C, 48–72 h; (ii) alicyclic amine, K_2CO_3, KI, $(CH_3)_2CO$, 60 °C, 48 h; (iii) TFA/CH_2Cl_2 (80:20; v/v), 2 h; (iv) $ArSO_2Cl$, TEA·CH_2Cl_2, 0 °C, 2–6 h.

The inhibition constants (K_i) were calculated from the Cheng–Prusoff equation.[33]

Selected compounds which showed high affinity for α_1-adrenoceptor K_i <100 nM, and displayed α_1/α_2 selectivity above 5 were subsequently evaluated for their intrinsic activity at α_{1A}- and α_{1B}-adrenoceptor test.

The intrinsic activity at α_{1A}-adrenoceptor was assessed by fluorescence detection of β-lactamase reporter gene using a FRET-enabled substrate. The intrinsic activity at α_{1B}-adrenoceptor was assessed by luminescence detection of calcium mobilization using the recombinant expressed jellyfish photoprotein, aequorin.

Finally, selected compounds with the highest functional selectivity were further tested to determine their affinity for 5-HT_{1A} and 5-HT_7Rs in screening radioligand binding studies using [^{3}H]-8-Hydroxy-2-(dipropylamino)tetralin ([^{3}H]-8-OH-DPAT) and [^{3}H]-Lysergic acid diethylamide ([^{3}H]-LSD), respectively. Experiments were performed using membranes from CHO-K1 cells stably transfected with the human 5-HT_{1A} and 5-HT_7Rs according to the methods previously described.[34]

3.2. In vivo pharmacology

Knowing that blockade of α_{1A}-adrenoceptors reduce the prostate smooth muscle tone whereas α_{1B} adrenoceptor antagonists promote blood pressure related side effects, compounds **25** and **34**, with the highest α_{1A}/α_{1B} selectivity ratio were chosen for further in vivo evaluation. The hypotensive activity was determined after one time iv administration to normotensive anaesthetized rats at single doses of 2 and 5 mg/kg.

4. Results and discussion

We have previously reported on the synthesis, in vitro and in vivo pharmacological evaluation of a series of arylsulfonamide derivatives of aryloxyalkyl piperidines and pyrrolidines.[29–31] The study confirmed, that the receptor binding profile, especially for 5-HT_{1A}, 5-HT_7, and α_1 receptors, was highly dependent upon a kind of a substituent in position-2 at the aryloxy fragment. It was found that an introduction of small methoxy group with strong electron donating properties (**PZ-955**, Fig. 2) was preferred for an interaction with adrenergic α_1Rs (K_i = 80 nM).[31] These findings opened the possibility towards exploration of the structural determinants which enable the development of a novel group of α_{1A}-/α_{1D}-receptor antagonists.

All newly synthesized compounds were tested in radioligand binding assays to assess their affinity for α_1- and α_2-adrenoceptors. The study showed that evaluated compounds displayed high-to-moderate affinity for α_1-adrenoceptors (K_i = 34–348 nM), and low-to-moderate selectivity over α_2-adrenoceptor subtypes (Table 1).

Structure–affinity relationship studies revealed that replacement of the small methoxy substituent) in position-2 at the (aryloxy)ethyl fragment with the symmetric and sterically encumbered isopropoxy one maintained high affinity for α_1-adrenoceptors (**25** vs **28** and **32** vs **37**). Although it was difficult to precisely determine the most favorable amine core, it was found that 4-amino and 4-aminomethyl piperidine scaffolds were more preferable for interaction with α_1-adrenoceptor than the 3-aminopyrrolidine (**15** vs **22** and **30**, and **18** vs **27** and **35**). Interestingly, compounds with 3-aminopyrrolidine core showed the highest selectivity over α_2-adrenoceptors (**16** vs **22** and **29**, and **18** vs **26** and **34**). It was also found, that within this sub-series, enantiomers *S* displayed a slight preference for α_1R over their *R* counterparts (**13** vs **14** and **17** vs **18**).

To extend the structural modifications around this class of derivatives, different substituents with electron-donating or electron-withdrawing properties at the arylsulfonamide fragments were introduced. The selection was partially inspired by the work of Chiu et al.[25] who reported on a series of (phenylpiperidinyl)cyclohexylsulfonamides as potent α_1R antagonists. In line with those data, it seems that the type, the position as well as the number of substituents at the sulfonamide did not influenced the affinity for α_1Rs. Yet, an introduction of di-halogenated substituents generally increased the selectivity over the α_2R subtypes (**29** and **30** vs **31**, **34** and **36** vs **33**). Further structural modifications were based on our previous findings demonstrating that localization of the nitrogen atom in the azine moiety significantly impacted the interaction of azinesulfonamides of LCAPs and 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles with serotonin 5-HT_{1A}, 5-HT_6, 5-HT_7Rs and dopaminergic D_2Rs.[35–37] It was found that, among tested azinesulfonamides (with sulfonyl group in α-position at azine fragment), compounds with the sulfonamide localized at the pyridine ring (4-isoquinolinyl) displayed higher affinity for α_1Rs than their 8-quinolinyl analogs with sulfonamide at the phenyl moiety (**24** vs **25** and **36** vs **37**).

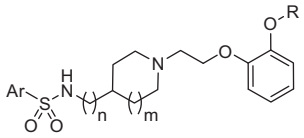
In the next step, selected compounds with the highest affinity for α_1-adrenoceptors (K_i < 100 nM) and selectivity over α_2-adrenoceptor subtypes (>5-fold) were in vitro tested for their intrinsic activity behaving as potent antagonists at α_{1A}- and α_{1B}-adrenoceptors (Table 2).

It was found, that compounds containing benzene ring with electron donating substituent as well as azine moieties at the sulfonamide displayed moderate selectivity for α_{1A}Rs over the α_{1B}Rs (**31**, **32** and **36**). On the contrary, compounds **21**, **29** and **30** with halogen substituent at the sulfonamide revealed no preference amongst tested receptors.

In the next step, selected compounds with the highest functional selectivity were evaluated for their affinity for serotonin 5-HT_{1A}, and 5-HT_7 receptors, displaying moderate affinity for the evaluated receptors (Table 3).

Compounds with the highest α_{1A}/α_{1B} selectivity ratio in in vitro intrinsic activity studies—**25** and **34** were chosen for further in vivo evaluation to assess their influence on blood pressure parameters. The hypotensive activity was determined after one time i.v. administration to normotensive anaesthetized rats at single doses 2.0 and 5.0 mg/kg. It was found that both compounds **25** and **34** did not significantly decrease systolic (SBP) and diastolic blood pressure (DBP) at dose range of 2–5 mg/kg i.v. in the whole period of observation (60 min). Compound **25** at dose of 5 mg/kg reduced SBP from mean 124 to 110–116 mmHg (6–11%) and DBP from 92 to 85–90 mmHg (2–8%). At lower dose (2 mg/kg), the compound **25** reduced SBP from 133 to 120–127 mmHg (4–10%) and DBP from 97 to 89–93 mmHg (4–8%). Compound **34** at dose of 5 mg/kg reduced the SBP from 126 to 120–124 mmHg (2–5%) and caused

Table 1
The binding data of the synthesized compounds **13–37** for α_1 and α_2Rs



13-37

Compound	Ar	Enant	*n*	*m*	R	K_i[a] (nM) ± SEM		
						α_1	α_2	[b]$S_{\alpha2/\alpha1}$
13	3-Cl,2-F-phenyl	*R*	0	0	Methyl	241 ± 14	1944 ± 10	8
14	3-Cl,2-F-phenyl	*S*	0	0	Methyl	348 ± 36	>10,000	>29
15	5-Cl,2-F-phenyl	*R*	0	0	Methyl	289 ± 6	2354 ± 63	8
16	5-Cl,2-F-phenyl	*S*	0	0	Methyl	214 ± 22	>10,000	>35
17	3-Cl,2-F-phenyl	*R*	0	0	Isopropyl	176 ± 13	378 ± 12	2
18	3-Cl,2-F-phenyl	*S*	0	0	Isopropyl	92 ± 8	>10,000	>109
19	5-Cl,2-F-phenyl	*R*	0	0	Isopropyl	106 ± 9	398 ± 40	4
20	5-Cl,2-F-phenyl	*S*	0	0	Isopropyl	242 ± 16	>10,000	>41
21	3-Cl-phenyl	—	0	1	Methyl	46 ± 12	439 ± 18	10
22	5-Cl,2-F-phenyl	—	0	1	Methyl	34 ± 7	129 ± 15	4
23	3,4-DiOMe-phenyl	—	0	1	Methyl	99 ± 2	2140 ± 35	22
24	8-Quinolinyl	—	0	1	Methyl	93 ± 5	131 ± 21	1
25	4-Isoquinolinyl	—	0	1	Methyl	52 ± 3	297 ± 20	6
26	3-Cl,2-F-phenyl	—	0	1	Isopropyl	131 ± 1	188 ± 23	1
27	5-Cl,2-F-phenyl	—	0	1	Isopropyl	118 ± 22	293 ± 35	3
28	4-Isoquinolinyl	—	0	1	Isopropyl	73 ± 2	194 ± 15	3
29	3-Cl,2-F-phenyl	—	1	1	Methyl	48 ± 5	678 ± 39	14
30	5-Cl,2-F-phenyl	—	1	1	Methyl	56 ± 4	1345 ± 55	24
31	3,4-DiOMe-phenyl	—	1	1	Methyl	81 ± 6	644 ± 70	8
32	4-Isoquinolinyl	—	1	1	Methyl	90 ± 9	695 ± 53	8
33	4-F-phenyl	—	1	1	Isopropyl	77 ± 4	416 ± 51	5
34	3-Cl,2-F-phenyl	—	1	1	Isopropyl	71 ± 4	1212 ± 99	17
35	5-Cl,2-F-phenyl	—	1	1	Isopropyl	133 ± 10	870 ± 28	7
36	8-Quinolinyl	—	1	1	Isopropyl	95 ± 8	947 ± 25	10
37	4-Isoquinolinyl	—	1	1	Isopropyl	67 ± 2	578 ± 51	9

[a] K_i values based on two independent binding experiments.
[b] Ratio of affinity for α_2 and α_1 adrenoreceptors.

Table 2
The intrinsic activity of selected compounds and references for α_{1A}- and α_{1B}-adrenoceptors

Compound	α_{1A}		α_{1B}		$S_{1B/1A}$
	EC_{50} (nM)	Profile	EC_{50} (nM)	Profile	
21	120.6	ANT[a]	15.5	ANT	0.13
23	191.6	ANT	461.1	ANT	2.40
25	99.7	ANT	608.4	ANT	6.10
29	84.2	ANT	14.15	ANT	0.17
30	148.2	ANT	12.65	ANT	0.08
31	160.7	ANT	598.6	ANT	3.73
32	140.1	ANT	514.8	ANT	3.68
34	11.1	ANT	42.1	ANT	3.80
36	34.1	ANT	104.8	ANT	3.07
Tamsulosin	0.07	ANT	0.13	ANT	1.93
Terazosin	51.89	ANT	1.73	ANT	0.03
Phenylephrine	55.99	AGO[a]	0.86	AGO	0.01

[a] AGO—agonist, ANT—antagonist. The means EC_{50} values were obtained from three experiments.

Table 3
The binding data of selective compounds for α_1, 5-HT_{1A} and 5-HT_7 receptors

Compound	α_1 K_i[a] (nM)	5-HT_{1A} %inh @ 10^{-6}	5-HT_7 %inh @ $10^{-6}/10^{-7}$
25	52 ± 3	69	87:41
31	81 ± 6	72	52:16
32	90 ± 9	78	89:54
34	71 ± 4	59	90:45
36	95 ± 8	61	91:51

[a] K_i values based on two independent binding experiments.

no DBP reduction. At lower dose (2 mg/kg), compound **34** reduced SBP from 132 to 123 mmHg (7%) whereas reduction in DBP has not been observed as well. In comparison, the highly α1A – selective compound **tamsulosin** decreased SBP from 124 to 103–110 mmHg (11–17%) and DBP from 94 to 77–84 mmHg (11–18%) already at a dose of 2 mg/kg after i.v. administration (Fig. 3). Based on these results we hypothesized that **25** and **34** reveal uroselective profile, which may be slightly more potent than that of tamsulosin. In order to confirm this expectances further pharmacological studies will be undertaken.

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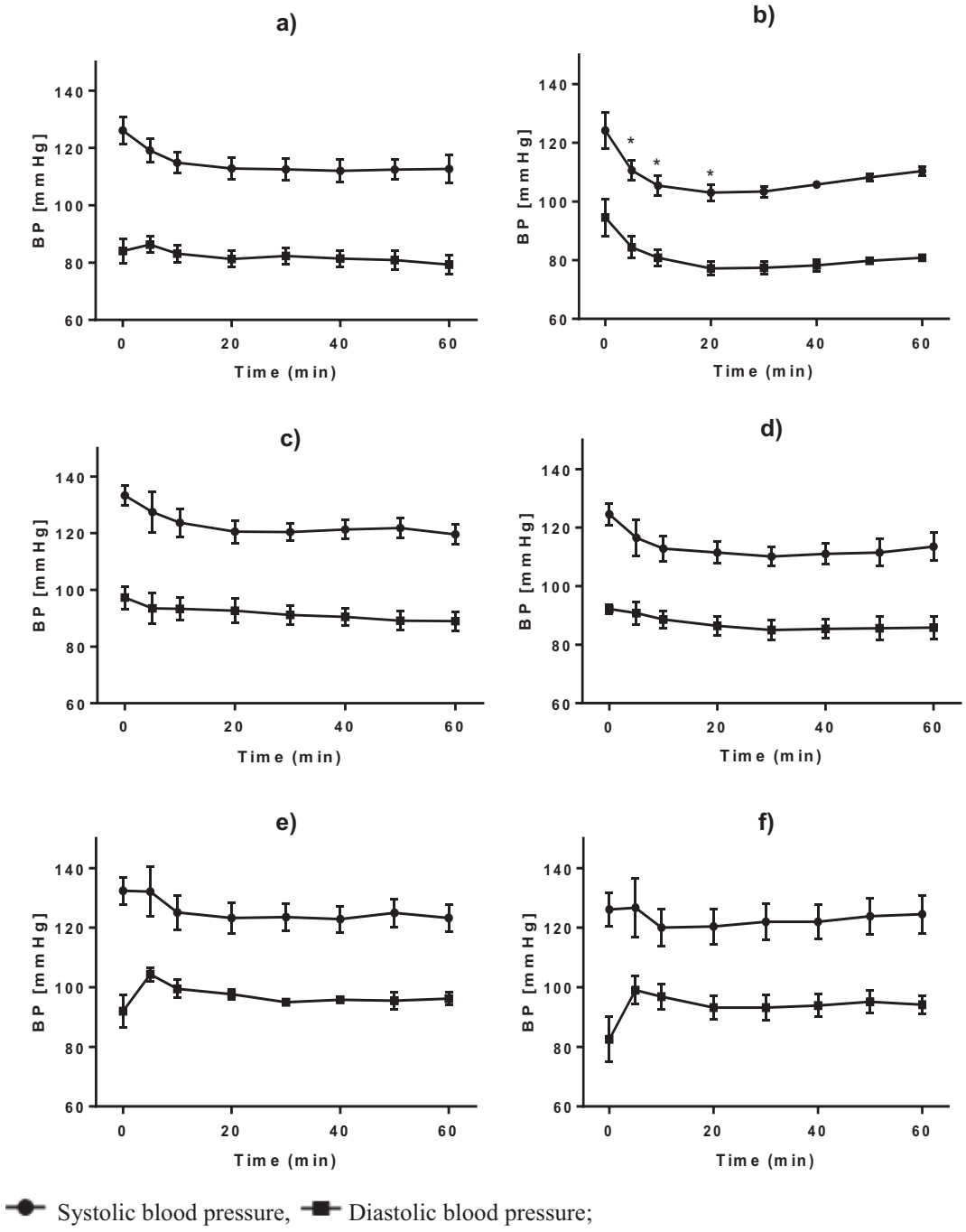

Figure 3. The hypotensive activity of compounds tamsulosin, **25** and **34** in anaesthetised rats after iv administration. (A) tamsulosin at the dose 1 mg/kg b.w., iv; (B) tamsulosin at the dose 2 mg/kg b.w., iv; (C) compound **25** at the dose 2 mg/kg b.w., iv; (D) compound **25** at the dose 5 mg/kg b.w., iv; (E) compound **34** at the dose 2 mg/kg b.w., iv; (F) compound **34** at the dose 5 mg/kg b.w., iv. Values are presented as the mean ± SEM of $N = 6–8$ experiments. The statistical significance was calculated using a one-way ANOVA post-hoc Dunnett's Multiple Comparison Test., Significant to time before compound administration (0 min): $^{*}p < 0.05$.

5. Conclusion

In summary, the design, synthesis and pharmacological evaluation of a series of new arylsulfonamide derivatives of (aryloxy) ethyl pyrrolidines and piperidines was described. Study directed on identification of potent α_1-adrenoceptor antagonists with selectivity for α_{1A}-adrenoceptor over α_{1B}-subtype allowed identification of compounds **25** and **34**. Selected derivatives displayed no significant changes in the blood pressure parameters at doses 2 and 5 mg/kg (iv) in rats. Considering that tamsulosin, used as a reference drug, significantly decreased blood pressure parameters after one time iv administration at a dose of 2 mg/kg, compounds **25** and **34** appear promising for further development as new uroselective α_1-adrenoceptor antagonists.

6. Experimental

6.1. Chemistry

6.1.1. General chemical methods

Organic transformations were carried out at ambient temperature, unless indicated otherwise. Organic solvents used in

this study (Sigma–Aldrich, Chempur) were of reagent grade and were used without purification. All other commercially available reagents were of the highest purity (from Sigma–Aldrich, Fluorochem). All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

Mass spectra were recorded on a UPLC-MS/MS system consisted of a Waters ACQUITY® UPLC® (Waters Corporation, Milford, MA, USA) coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole). Chromatographic separations were carried out using the Acquity UPLC BEH (bridged ethyl hybrid) C18 column; 2.1 × 100 mm, and 1.7 μm particle size, equipped with Acquity UPLC BEH C18 VanGuard pre-column; 2.1 × 5 mm, and 1.7 μm particle size. The column was maintained at 40 °C, and eluted under gradient conditions from 95% to 0% of eluent A over 10 min, at a flow rate of 0.3 mL min^{-1}. Eluent A: water/formic acid (0.1%, v/v); eluent B: acetonitrile/formic acid (0.1%, v/v). Chromatograms were made using Waters eλ PDA detector. Spectra were analyzed in 200–700 nm range with 1.2 nm resolution and sampling rate 20 points/s. MS detection settings of Waters TQD mass spectrometer were as follows: source temperature 150 °C, desolvation temperature 350 °C, desolvation gas flow rate 600 L h^{-1}, cone gas flow 100 L h^{-1}, capillary potential 3.00 kV, cone potential 40 V. Nitrogen was used for both nebulizing and drying gas. The data were obtained in a scan mode ranging from 50 to 1000 *m*/*z* in time 0.5 s intervals. Data acquisition software was MassLynx V 4.1 (Waters). The UPLC/MS purity of all the final compounds was confirmed to be 95% or higher.

^{1}H NMR and ^{13}C NMR spectra were obtained in Varian BB 200 spectrometer using TMS (0.00 ppm) as an internal standard in d_6-DMSO, and were recorded at 300 and 75 MHz, respectively. The *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet).

Elemental analyses for C, H, N and S were carried out using the elemental Vario EL III Elemental Analyser (Hanau, Germany). All values are given as percentages, and were within ± 0.4% of the calculated values.

Melting points (mp) were determined with a Büchi apparatus and are uncorrected.

6.1.2. General procedure for the alkylation of phenols (3–4)

Commercial phenols **1**–**2** (0.05 mol) was dissolved in acetone (30 ml). Then K_2CO_3 (0.15 mol) and catalytic amount of KI were added followed by dropwise addition of 1,2-dibromoethane (0.2 mol). The reaction was refluxed for 48–72 h. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel with AcOEt/hexane (1:9 v/v) as an eluting system.

6.1.3. General procedure for the alkylation with the ((aryloxy) ethyl)bromides of Boc-protected-amines (5–12)

Commercial Boc-protected amines (0.015 mol) was dissolved in acetone (15 ml). Then K_2CO_3 (0.045 mol) and catalytic amount of KI were added followed by dropwise addition of (aryloxy)ethylbromide (0.018 mol). The reaction was refluxed for 48 h. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel with CH_2Cl_2/MeOH (9:0.7 v/v) as an eluting system.

6.1.4. Boc-deprotection protocol

TFA (4 ml) was added to the solution of Boc-protected intermediates (**5**–**12**) in CH_2Cl_2 (2 ml) and stirred for 2 h at room temperature. The excess of reagent and solvent were removed under reduced pressure and left under vacuum overnight.

6.1.5. General procedure for preparation of final compounds (13–37)

A mixture of the appropriate deprotected amine (0.38 mmol) in CH_2Cl_2 (3 mL), and TEA (1.14 mmol) was cooled down (ice bath), and arylsulfonyl chloride (1.37 mmol) was added at 0 °C in one portion. The reaction mixture was stirred for 2–6 h under cooling. Then, the solvent was evaporated and the sulfonamides were purified using silica gel column with CH_2Cl_2/MeOH (9:0.7 v/v) as an eluting system. Compound **24**, which evaluated in in vivo testes was further converted into the hydrochloride salts by treatment of their solution in anhydrous ethanol with 1.25 M HCl in MeOH.

6.1.6. Characterization of final compounds

6.1.6.1. (*R*)-3-Chloro-2-fluoro-*N*-{1-[2-(2-methoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (13). Yellow oil, 110 mg (78% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 99%, t_R = 4.31, $C_{19}H_{22}ClFN_2O_4S$, MW 428.90, Monoisotopic Mass 428.10, $[M+H]^+$ 429.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61–1.73 (m, 2H), 2.29–2.39 (m, 2H), 2.71 (dd, *J* = 9.9, 2.2 Hz, 2H), 2.79–3.03 (m, 3H), 3.84 (s, 3H), 3.98 (br s, 1H), 4.07 (t, *J* = 5.7 Hz, 2H), 6.84–6.97 (m, 4H), 7.19 (td, *J* = 8.0, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.6, 1.7 Hz, 1H), 7.79 (ddd, *J* = 7.9, 6.3, 1.6 Hz, 1H).

6.1.6.2. (*S*)-3-Chloro-2-fluoro-*N*-{1-[2-(2-methoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (14). Yellow oil, 120 mg (80% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 96%, t_R = 4.26, $C_{19}H_{22}ClFN_2O_4S$, MW 428.90, Monoisotopic Mass 428.10, $[M+H]^+$ 429.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61–1.73 (m, 2H), 2.29–2.39 (m, 2H), 2.74 (dd, *J* = 10.0, 2.7 Hz, 2H), 2.81–3.03 (m, 3H), 3.85 (s, 3H), 4.01 (br s, 1H), 4.08 (t, *J* = 5.8 Hz, 2H), 6.84–6.95 (m, 4H), 7.19 (td, *J* = 7.9, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.6, 1.7 Hz, 1H), 7.79 (ddd, *J* = 7.9, 6.3, 1.7 Hz, 1H).

6.1.6.3. (*R*)-5-Chloro-2-fluoro-*N*-{1-[2-(2-methoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (15). Yellow oil, 90 mg (72% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 95%, t_R = 4.55, $C_{19}H_{22}ClFN_2O_4S$, MW 428.90, Monoisotopic Mass 428.10, $[M+H]^+$ 429.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61–1.73 (m, 2H), 2.29–2.39 (m, 2H), 2.71 (dd, *J* = 9.9, 2.2 Hz, 2H), 2.79–3.03 (m, 3H), 3.84 (s, 3H), 3.98 (br s, 1H), 4.07 (t, *J* = 5.7 Hz, 2H), 6.84–6.96 (m, 4H), 7.02 (t, *J* = 9.0 Hz, 1H), 7.43 (ddd, *J* = 8.7, 4.2, 2.7 Hz, 1H), 7.87 (dd, *J* = 6.1, 2.6 Hz, 1H).

6.1.6.4. (*S*)-5-Chloro-2-fluoro-*N*-{1-[2-(2-methoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (16). Yellow oil, 100 mg (75% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 95%, t_R = 4.63, $C_{19}H_{22}ClFN_2O_4S$, MW 428.90, Monoisotopic Mass 428.10, $[M+H]^+$ 429.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61–1.73 (m, 2H), 2.29–2.39 (m, 2H), 2.71 (dd, *J* = 9.9, 2.2 Hz, 2H), 2.79–3.03 (m, 3H), 3.84 (s, 3H), 3.98 (br s, 1H), 4.07–4.12 (m, 2H), 6.84–6.96 (m, 4H), 7.03 (t, *J* = 9.0 Hz, 1H), 7.43 (ddd, *J* = 8.7, 4.2, 2.7 Hz, 1H), 7.86 (dd, *J* = 6.1, 2.6 Hz, 1H).

6.1.6.5. (*R*)-3-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (17). Yellow oil, 90 mg (71% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 4.82, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.0 Hz, 6H), 1.65–1.71 (m 2H), 2.19–2.29 (m, 1H), 2.30–2.39 (m, 1H), 2.63 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.71–2.76 (m, 1H), 2.78–3.01 (m, 3H), 3.93 (br s, 1H), 4.06 (t, *J* = 5.6 Hz, 2H), 4.46 (spt, *J* = 6.1 Hz, 1H),

6.83–6.91 (m, 4H) 7.17 (td, *J* = 8.0, 1.1 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.6, 1.6 Hz, 1H), 7.78 (ddd, *J* = 7.9, 6.3, 1.7 Hz, 1H).

6.1.6.6. (*S*)-3-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (18). Yellow oil, 100 mg (75% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 4.84, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.0 Hz, 6H), 1.61–1.73 (m, 2H), 2.19–2.29 (m, 1H), 2.30–2.39 (m, 1H), 2.68–2.72 (m, 1H), 2.75–2.77 (m, 1H), 2.80–3.02 (m, 3H), 3.98 (br s, 1H), 4.05 (t, *J* = 5.6 Hz, 2H), 4.46 (spt, *J* = 6.0 Hz, 1H), 6.84–6.92 (m, 4H), 7.18 (td, *J* = 8.0, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.6, 1.6 Hz, 1H), 7.79 (ddd, *J* = 7.9, 6.2, 1.6 Hz, 1H).

6.1.6.7. (*R*)-5-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (19). Yellow oil, 100 mg (74% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 5.01, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.4.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.0 Hz, 6H), 1.67–1.81 (m, 2H), 2.19–2.27 (m, 1H), 2.39–2.51 (m, 1H), 2.64 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.82–2.89 (m, 1H), 2.91–3.04 (m, 2H), 3.12 (t, *J* = 9.0, 4.2 Hz, 1H), 4.04 (br s, 1H), 4.05 (t, *J* = 5.5 Hz, 2H), 4.45 (spt, *J* = 6.0 Hz, 1H), 6.83–6.91 (m, 4H), 7.03 (t, *J* = 9.0 Hz, 1H), 7.44 (ddd, *J* = 8.7, 4.2, 2.7 Hz, 1H), 7.86 (dd, *J* = 6.1, 2.6 Hz, 1H).

6.1.6.8. (*S*)-5-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]pyrrolidin-3-yl}benzenesulfonamide (20). Yellow oil, 110 mg (76% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 5.01, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.0 Hz, 6H), 1.67–1.81 (m, 2H), 2.19 (dtd, *J* = 13.3,, 8.8, 4.3 Hz, 1H), 2.39–2.51 (m, 1H), 2.64 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.82–2.89 (m, 1H), 2.91–3.04 (m, 2H), 3.12 (t, *J* = 9.0, 4.2 Hz, 1H), 4.04 (br s, 1H), 4.05 (t, *J* = 5.4 Hz, 2H), 4.46 (spt, *J* = 6.0 Hz, 1H), 6.82–6.93 (m, 4H), 7.03 (t, *J* = 9.0 Hz, 1H), 7.44 (ddd, *J* = 8.7, 4.2, 2.6 Hz, 1H), 7.86 (dd, *J* = 6.1, 2.6 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 21.80, 52.43, 64.53, 115.40, 118.35, 118.66, 122.88, 129.78, 129.79, 134.69, 134.80, 147.51, 147.58, 147.60, 155.33, 158.70.

6.1.6.9. 3-Chloro-*N*-{[1-(2-(2-methoxyphenoxy)ethyl)piperidin-4-yl]methyl}benzenesulfonamide (21). Yellow oil, 120 mg (82% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 4.50, $C_{21}H_{27}ClN_2O_4S$, MW 438.97, Monoisotopic Mass 438.14, $[M+H]^+$ 439.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.39 (m, 2H), 1.49–1.54 (m, 1H), 1.67–1.72 (m, 2H), 2.12–2.19 (m, 2H), 2.86–2.91 (m, 4H), 3.05–3.09 (m, 2H), 3.83 (s, 3H), 4.12–4.16 (m, 2H), 6.86–6.94 (m, 4H), 7.41–7.46 (m, 1H), 7.51–7.54 (m, 1H), 7.72–7.75 (m, 1H), 7.83–7.84 (m, 1H).

6.1.6.10. 5-Chloro-2-fluoro-*N*-{1-[2-(2-methoxyphenoxy)ethyl] piperidin-4-yl}benzenesulfonamide (22). Yellow oil, 100 mg (76% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 100%, t_R = 4.57, $C_{20}H_{24}ClFN_2O_4S$, MW 442.93, Monoisotopic Mass 442.11, $[M+H]^+$ 443.2.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53–1.62 (m, 2H), 1.80–1.83 (m, 2H), 2.20–2.27 (m, 2H), 2.81–2.92 (m, 4H), 3.28–3.31 (m, 1H), 3.84 (s, 3H), 4.07–4.11 (m, 2H), 6.86–6.94 (m, 4H), 7.12–7.18 (m, 1H), 7.48–7.54 (m, 1H), 7.87–7.9 (m, 1H).

6.1.6.11. 3,4-Dimethoxy-*N*-{1-[2-(2-methoxyphenoxy)ethyl] piperidin-4-yl}benzenesulfonamide (23). Yellow oil, 130 mg (79% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 100%, t_R = 3.89, $C_{22}H_{30}N_2O_6S$, MW 450.55, Monoisotopic Mass 450.18, $[M+H]^+$ 451.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.61 (m, 2H), 1.76–1.80 (m, 2H), 2.16–2.22 (m, 2H), 2.80 (t, *J* = 6.1 Hz, 2H), 2.83–2.93 (m, 2H), 3.11–3.20 (m, 1H), 3.83 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.05–4.12 (m, 2H), 4.92 (br s, 1H), 6.83–6.94 (m, 5H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.84, 50.52, 52.33, 55.85, 56.13, 56.26, 56.86, 66.68, 109.44, 110.48, 111.87, 113.55, 120.79, 120.85, 121.40, 132.88, 148.11, 149.12, 149.46, 152.39.

6.1.6.12. *N*-(1-(2-(2-Methoxyphenoxy)ethyl)piperidin-4-yl) quinoline-8-sulfonamide (24). Yellow oil, 120 mg (85% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 100%, t_R = 3.96, $C_{23}H_{27}N_3O_4S$, MW 441.54, Monoisotopic Mass 441.17, $[M+H]^+$ 442.2.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.47 (m, 3H), 1.65–1.71 (m, 2H), 2.08–2.16 (m, 2H), 2.71–2.77 (m, 4H), 3.80 (s, 3H), 4.01–4.05 (m, 2H), 6.36–6.39 (m, 1H), 6.80–7.25 (m, 4H), 7.53–7.57 (m, 1H), 7.62–7.67 (m, 1H), 8.04 (dd, *J* = 7.1, 1.3 Hz, 1H), 8.27 (dd, *J* = 7.1, 1.7 Hz, 1H), 8.42 (dd, *J* = 7.1, 1.5 Hz, 1H), 8.99–9.02 (m, 1H).

6.1.6.13. *N*-{1-[2-(2-Methoxyphenoxy)ethyl]piperidin-4-yl}isoquinoline-4-sulfonamide (25). Yellow oil, 90 (74% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 100%, t_R = 3.76, $C_{23}H_{27}N_3O_4S$, MW 441.54, Monoisotopic Mass 441.17, $[M+H]^+$ 442.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.55 (m, 2H), 1.69–1.72 (m, 2H), 2.08–2.16 (m, 2H), 2.73–2.77 (m, 4H), 2.79–2.84 (m, 1H), 3.84 (s, 3H), 4.01–4.03 (m, 2H), 6.85–6.97 (m, 4H), 7.71–7.76 (m, 1H), 7.83–7.89 (m, 1H), 8.08–8.11 (m, 1H), 8.57–8.59 (m, 1H), 9.15 (s, 1H), 9.41 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 29.85, 52.21, 55.57, 55.85, 63.93, 66.90, 111.91, 115.02, 115.20, 120.96, 123.06, 124.98, 128.06, 131.45, 131.85, 133.30, 133.69, 135.67, 138.53, 146.43, 149.48, 151.49.

Anal. calcd for $C_{23}H_{27}N_3O_4S{\cdot}2HCl$: C: 53.70, H: 5.68, N: 8.17, S: 6.23; Found C: 53.47, H: 5.99, N: 8.78, S: 6.45. Mp for $C_{23}H_{27}N_3O_4S{\cdot}2HCl$ 140.5–141.2 °C.

6.1.6.14. 3-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]piperidin-4-yl}benzenesulfonamide (26). Yellow oil, 120 mg (77% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 5.07, $C_{22}H_{28}ClFN_2O_4S$, MW 470.99, Monoisotopic Mass 470.14, $[M+H]^+$ 471.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.0 Hz, 6H), 1.49–1.67 (m, 2H), 1.76–1.85 (m, 2H), 2.26 (t, *J* = 10.5 Hz, 2H), 2.81 (t, *J* = 5.5 Hz, 2H), 2.96 (d, *J* = 12.0 Hz, 2H), 3.30–3.33 (m, 1H), 4.07 (t, *J* = 5.5 Hz, 2H), 4.46 (spt, *J* = 6.0 Hz, 1H), 6.85–6.90 (m, 4H), 7.21 (td, *J* = 8.0, 1.0 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.7, 1.6 Hz, 1H), 7.80 (ddd, *J* = 7.9, 6.3, 1.6 Hz, 1H).

6.1.6.15. 5-Chloro-2-fluoro-*N*-{1-[2-(2-isopropoxyphenoxy) ethyl]piperidin-4-yl}benzenesulfonamide (27). Yellow oil, 110 mg (78% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 97%, t_R = 5.11, $C_{22}H_{28}ClFN_2O_4S$, MW 470.99, Monoisotopic Mass 470.14, $[M+H]^+$ 471.2.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.0 Hz, 6H), 1.47–1.61 (m, 2H), 1.80 (dd, *J* = 12.7, 3.6 Hz, 2H), 2.18–2.29 (m, 2H), 2.79 (t, *J* = 5.6 Hz, 2H), 2.91 (d, *J* = 12.2 Hz, 2H), 3.11–3.25 (m, 1H), 4.06 (t, *J* = 5.6 Hz, 2H), 4.46 (spt, *J* = 6.0 Hz, 1H), 6.85–6.91 (m, 4H), 7.15 (t, *J* = 9.0 Hz, 1H), 7.51 (ddd, *J* = 8.7, 4.2, 2.7 Hz, 1H), 7.89 (dd, *J* = 6.1, 2.6 Hz, 1H).

6.1.6.16. *N*-{1-[2-(2-Isopropoxyphenoxy)ethyl]piperidin-4-yl} quinoline-8-sulfonamide (28). Yellow oil, 100 mg (75%

yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 100%, t_R = 4.54, $C_{25}H_{31}N_3O_4S$, MW 469.60, Monoisotopic Mass 469.20, $[M+H]^+$ 470.4.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 1.0 Hz, 6H), 1.31–1.45 (m, 2H), 1.65 (dd, J = 12.8, 3.8 Hz, 2H), 2.11 (t, J = 10.3 Hz, 2H), 2.70 (t, J = 5.7 Hz, 2H), 2.75–2.80 (m, 1H), 3.28 (d, J = 7.2 Hz, 2H), 3.99 (t, J = 5.7 Hz, 2H), 4.41 (spt, J = 6.1 Hz, 1H), 6.38 (d, J = 7.3 Hz, 1H), 6.81–6.84 (m, 1H), 6.84–6.87 (m, 2H), 7.54 (dd, J = 8.3, 4.3 Hz, 1H), 7.64 (dd, J = 8.1, 7.3 Hz, 1H), 8.04 (dd, J = 8.2, 1.3 Hz, 1H), 8.27 (dd, J = 8.3, 1.7 Hz, 1H), 8.42 (dd, J = 7.2, 1.4 Hz, 1H), 9.00 (dd, J = 4.2, 1.7 Hz, 1H).

6.1.6.17. 3-Chloro-2-fluoro-*N*-{[1-(2-(2-methoxyphenoxy)ethyl) piperidin-4-yl]methyl}benzenesulfonamide (29). Yellow oil, 80 mg (65% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 96%, t_R = 4.50, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.36 (m, 2H), 1.48–1.53 (m, 1H), 1.71–1.74 (m, 2H), 2.12–2.17 (m, 2H), 2.84–2.91 (m, 4H), 3.03–3.07 (m, 2H), 3.86 (s, 3H), 4.12–4.17 (m, 2H), 6.86–6.94 (m, 4H), 7.19–7.25 (m, 1H), 7.59–7.64 (m, 1H), 7.76–7.81 (m, 1H).

6.1.6.18. 5-Chloro-2-fluoro-*N*-{[1-(2-(2-methoxyphenoxy)ethyl) piperidin-4-yl]methyl}benzenesulfonamide (30). Yellow oil, 90 mg (72% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 95%, t_R = 4.73, $C_{21}H_{26}ClFN_2O_4S$, MW 456.96, Monoisotopic Mass 456.13, $[M+H]^+$ 457.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.37 (m, 2H), 1.38–1.53 (m, 1H), 1.71–1.74 (m, 2H), 2.12–2.21 (m, 2H), 2.86–2.91 (m, 4H), 3.05–3.09 (m, 2H), 3.84 (s, 3H), 4.13–4.17 (m, 2H), 6.86–6.94 (m, 4H), 7.12–7.18 (m, 1H), 7.48–7.53 (m, 1H), 7.84–7.87 (m, 1H).

6.1.6.19. 3,4-Dimethoxy-*N*-{[1-(2-(2-methoxyphenoxy)ethyl) piperidin-4-yl]methyl}benzenesulfonamide (31). Yellow oil, 100 mg (74% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 99%, t_R = 3.96, $C_{23}H_{32}N_2O_6S$, MW 464.57, Monoisotopic Mass 464.2, $[M+H]^+$ 465.3.^{1}H NMR ($CDCl_3$) δ 1.24–1.32 (m, 2H), 1.37–1.51 (m, 2H), 1.68–1.72 (m, 2H), 2.13–2.21 (m, 2H), 2.78–2.91 (m, 4H), 3.05–3.09 (m, 2H), 3.83 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.13–4.17 (m, 2H), 6.86–6.94 (m, 4H), 7.32–7.33 (m, 1H), 7.44–7.48 (m, 1H).

6.1.6.20. *N*-{[1-(2-(2-Methoxyphenoxy)ethyl)piperidin-4-yl] methyl}isoquinoline-4-sulfonamide (32). Yellow oil, 90 mg (70% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 96%, t_R = 3.99, $C_{24}H_{29}N_3O_4S$, MW 455.77, Monoisotopic Mass 455.19, $[M+H]^+$ 456.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.34 (m, 2H), 1.35–1.49 (m, 2H), 1.89–1.93 (m, 4H), 2.87–3.01 (m, 2H), 3.43–3.45 (m, 4H), 3.84 (s, 3H), 4.32–4.34 (m, 2H), 6.84–6.88 (m, 4H), 7.69–7.74 (m, 1H), 7.82–7.87 (m, 1H), 8.06–8.08 (m, 1H), 8.60–8.63 (m, 1H), 9.07 (s, 1H), 9.38 (s, 1H).

6.1.6.21. 4-Fluoro-*N*-{[1-(2-(2-isopropoxyphenoxy)ethyl)piperidin-4-yl]methyl}benzenesulfonamide (33). Yellow oil, 100 mg (76% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 95%, t_R = 4.85, $C_{23}H_{31}FN_2O_4S$, MW 450.57, Monoisotopic Mass 450.20, $[M+H]^+$ 451.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.28 (m, 2H), 1.30 (d, J = 5.9 Hz, 6H), 1.84–2.00 (m, 4H), 2.73–2.82 (m, 1H), 3.10–3.24 (m, 2H), 3.55–3.64 (m, 2H), 3.91 (d, J = 9.7 Hz, 2H), 4.38–4.49 (m, 3H), 6.74–6.92 (m, 4H), 7.12 (t, J = 8.1 Hz, 2H), 7.89–8.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.21, 27.30, 33.85, 47.44, 53.06, 56.43, 64.90, 70.95, 76.68, 115.48, 115.65, 116.17, 116.47, 121.13, 122.62, 129.89, 130.01, 135.54, 135.58, 147.88, 148.08, 163.27, 166.64.

6.1.6.22. 3-Chloro-2-fluoro-*N*-{[1-(2-(2-isopropoxyphenoxy) ethyl)piperidin-4-yl]methyl}benzenesulfonamide (34). Yellow oil, 120 mg (79% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 98%, t_R = 5.16, $C_{23}H_{30}ClFN_2O_4S$, MW 485.01, Monoisotopic Mass 484.16, $[M+H]^+$ 485.8.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.26 (m, 2H), 1.31 (d, J = 1.0 Hz, 6H), 1.41–1.56 (m, 2H), 1.70 (d, J = 12.8 Hz, 2H), 2.11 (td, J = 11.7, 1.9 Hz, 2H), 2.83 (t, J = 5.7 Hz, 2H), 2.88–2.90 (m, 1H), 3.06 (d, J = 11.8 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 4.47 (spt, J = 6.0 Hz, 1H), 6.86–6.92 (m, 4H), 7.22 (td, J = 8.0, 1.1 Hz, 1H), 7.62 (ddd, J = 8.1, 6.7, 1.7 Hz, 1H), 7.79 (ddd, J = 7.9, 6.3, 1.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.21, 29.52, 35.95, 48.75, 53.56, 57.31, 67.04, 71.81, 114.58, 117.32, 121.40, 121.62, 124.72, 124.79, 128.61, 129.60, 135.19, 147.82, 149.86, 152.67, 156.05.

Anal. calcd for $C_{23}H_{30}ClFN_2O_4S$·HCl: C: 52.97, H: 5.99, N: 5.37, S: 6.15; Found C: 52.72, H: 6.35, N: 5.18, S: 6.39. Mp for $C_{23}H_{30}ClFN_2O_4S$·HCl: 133.5–134.2 °C.

6.1.6.23. 5-Chloro-2-fluoro-*N*-{[1-(2-(2-isopropoxyphenoxy) ethyl)piperidin-4-yl]methyl}benzenesulfonamide (35). Yellow oil, 110 mg (78% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 95%, t_R = 5.24, $C_{23}H_{30}ClFN_2O_4S$, MW 485.01, Monoisotopic Mass 484.16, $[M+H]^+$ 485.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.28 (m, 2H), 1.30 (d, J = 5.90 Hz, 6H), 1.84–2.00 (m, 4H), 2.73–2.82 (m, 1H), 3.10–3.24 (m, 2H), 3.55–3.64 (m, 2H), 3.91 (d, J = 9.75 Hz, 4H), 4.38–4.49 (m, 1H), 6.74–6.92 (m, 4H), 7.15 (t, J = 9.09 Hz, 2H), 7.89–8.02 (m, 1H).

6.1.6.24. *N*-{[1-(2-(2-Isopropoxyphenoxy)ethyl)piperidin-4-yl] methyl}quinoline-8-sulfonamide (36). Yellow oil, 100 mg (73% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 94%, t_R = 4.82, $C_{26}H_{33}N_3O_4S$, MW 483.62, Monoisotopic Mass 483.22, $[M+H]^+$ 484.3.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.29 (m, 2H), 1.31 (d, J = 1.0 Hz, 6H), 1.61–1.73 (m, 2H), 2.28–2.35 (m, 2H), 2.69 (t, J = 6.7 Hz, 2H), 2.79–2.85 (m, 1H), 3.00 (d, J = 11.2 Hz, 2H), 3.98 (dd, J = 5.8, 1.4 Hz, 2H), 4.08 (t, J = 5.8 Hz, 2H), 4.39–4.53 (m, 1H), 6.36–6.43 (m, 1H), 6.85–6.91 (m, 3H), 7.57 (dd, J = 8.3, 4.3 Hz, 1H), 7.67 (dd, J = 8.1, 7.3 Hz, 1H), 8.06 (dd, J = 8.2, 1.4 Hz, 1H), 8.29 (dd, J = 8.3, 1.7 Hz, 1H), 8.44 (dd, J = 7.2, 1.4 Hz, 1H), 9.02 (dd, J = 4.3, 1.7 Hz, 1H).

6.1.6.25. *N*-{1-[2-(2-Isopropoxyphenoxy)ethyl]pyrrolidin-3-yl} isoquinoline-4-sulfonamide (37). Yellow oil, 90 mg (70% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9:0.7), UPLC/MS purity 99%, t_R = 4.46, $C_{25}H_{31}N_3O_4S$, MW 469.59, Monoisotopic Mass 469.20, $[M+H]^+$ 470.2.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 1.0 Hz, 6H), 1.41–1.56 (m, 2H), 1.71–1.81 (m, 2H), 2.16–2.28 (m, 2H), 2.78 (t, J = 5.6 Hz, 2H), 2.90 (d, J = 12.3 Hz, 2H) 3.11–3.25 (m, 1H), 4.18 (t, J = 5.6 Hz, 2H), 4.44 (spt, J = 6.0 Hz, 1H), 6.80–6.93 (m, 4H), 7.67–7.75 (m, 1H), 7.90 (t, J = 7.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 8.6 Hz, 1H), 9.15 (s, 1H), 9.39 (s, 1H).

6.2. In vitro pharmacology

6.2.1. Determination of the affinity of the tested compounds at the α_1-adrenoreceptors and α_2-adrenoreceptors

The affinity of the obtained compounds was evaluated by radioligand binding assays (the ability to displace [^{3}H]-Prazosin and [^{3}H]-Clonidine from α_1- and α_2-adrenoceptor, respectively) on rat

cerebral cortex. The brains is homogenized in 20 volumes of an ice-cold 50 mM Tris–HCl buffer (pH 7.6) and is centrifuged at 20,000 g for 20 min (0–4 °C). The cell pellet is resuspended in the Tris–HCl buffer and centrifuged again. Radioligand binding assays are performed in plates (MultiScreen/Millipore).The final incubation mixture (final volume 300 μl) consisted of 240 μl of the membrane suspension, 30 μl of [^{3}H]-Prazosin (0.2 nM) or [^{3}H]-Clonidine (2 nM) solution and 30 μl of the buffer containing seven to eight concentrations (10^{-11} to 10^{-4} M) of the tested compounds. For measuring the unspecific binding, phentolamine, 10 μM (in the case of [^{3}H]-Prazosin) and clonidine, 10 μM (in the case of [^{3}H]-Clonidine) are applied. The incubation is terminated by rapid filtration over glass fiber filters (Whatman GF/C)using a vacuum manifold (Millipore). The filters are then washed twice with the assay buffer and placed in scintillation vials with a liquid scintillation cocktail. Radioactivity was measured in a WALLAC 1409 DSA liquid scintillation counter. All the assays were made in duplicate.

6.2.2. Determination of the affinity of the tested compounds at the 5-HT$_{1A}$ and 5-HT$_7$ receptors

Binding experiments were conducted in 96-well microplates in a total volume of 250 μl of appropriate buffers. The composition of the assay buffers was as follows: 50 mM Tris–HCl, 0.1 mM EDTA, 10 mM $MgCl_2$. Reaction mix included 50 μl solution of test compound, 50 μl of radioligand and 150 μl of diluted membranes. All assays were incubated for 1 h (5-HT$_{1A}$Rs) or 2 h (5-HT$_7$Rs) at 37 °C. Radioactivity was counted in MicroBeta2 scintillation counter (PerkinElmer). Non-specific binding is defined with 10 μM of 5-HT and 10 μM of methiothepine in 5-HT$_{1A}$R and 5-HT$_7$R binding experiments, respectively. Each compound was tested in screening assay at two final concentrations of 10 μM and 1 μM. Results were expressed as percent inhibition of specific binding.

6.2.3. Determination of the intrinsic activity of the α_{1A}-adrenoreceptors

Intrinsic activity assay was performed according to the manufacturer of the assay kit (Invitrogen, Life Technologies). The cells were harvested and suspended in Assay Medium to a density of 312,500 cells/ml. 32 μl per well of the cell suspension was added to the Test Compound wells, the Unstimulated Control wells, and Stimulated Control wells and incubated per 16–24 h. To perform an agonist assay 8 concentrations of 8 μl of the tested compound (10^{-4}–10^{-11} M), e.g. in 5 fold higher concentration in comparison to the final tested concentration in the well, was added to the cells. To perform an antagonist assay 8 concentrations of 4 μl of the tested compound (10^{-4}–10^{-11} M), e.g. in 10 fold higher concentration in comparison to the final tested concentration in the well, was added to the cells. Then, after 30 min 4 μl of standard agonist in EC_{80} (10 fold higher concentration in comparison to the EC_{80} in the well), in Assay Medium, was added to the cells. Then both the agonist and the antagonist plate were incubated in a humidified 37 °C/5% CO_2 incubator for 5 h. After the incubation 8 μl of LiveBLAzer™-FRET B/G Substrate Mixture (CCF4-AM) was loaded cells in the absence of direct strong lighting, covered and incubated at room temperature for 2 h.

6.2.4. Determination of the intrinsic activity of the α_{1B}-adrenoreceptors

Intrinsic activity assay was performed according to the manufacturer of the ready to use cells with stable expression of the α_{1B}-adrenoreceptors (Perkin Elmer). For measurement cells (frozen, ready to use) were thawed and re-suspended in 10-ml of assay buffer containing 5 μM coelenterazine h. This cells suspension was put in a 10-ml Falcon tube, fixed onto a rotating heel and incubated for overnight at rt in the dark (8 rpm; 45°angle). Cells were diluted with Assay Buffer to 5000 cells/20 μL. Agonistic ligands 2 × (50 μL/well), diluted in Assay Buffer, were prepared in ½ white polystyrene area plates, and the cell suspension was dispensed in 50 μl volume on the ligands using the injector. The light emitted was record for 20 s. Cells with antagonist were incubate for 15 min at room temperature. Therefore 50 μl of agonist (3 × EC_{80} final concentration) was injected onto the mix of cells and antagonist and record the light emitted for 20 s.

6.3. In vivo pharmacology

6.3.1. Determination of the effect of the test compounds on blood pressure after a single administration in rats

The normotensive rats were anesthetized with thiopental (70 mg/kg) by ip injection. The left carotid artery was cannulated with polyethylene tubing filled with heparin solution in saline to facilitate pressure measurements using PowerLab Apparatus (ADInstruments). Blood pressure was measured: before administration of the compounds—time 0 min (control pressure) and 60 min thereafter. For each compound, studies were performed in three doses: 2 mg/kg, 5 mg/kg and 10 mg/kg b.w. Compounds were dissolved in water and administered intravenously.

6.3.2. Animals

The experiments were carried out on male Wistar rats (body weight 200–250 g). The animals were housed in pairs in plastic cages in constant temperature facilities exposed to 12:12 h light/-dark cycle, water and food were available ad libitum. Experimental groups consisted of six animals each. All experiments were conducted according to the guidelines of the Animal Use and Care Committee of the Jagiellonian University (2012, Poland).

6.3.3. Statistical analysis

Statistical calculations were carried out with the GraphPadPrism 6 program. Results are given as the arithmetic means with standard error of the mean (SEM). The statistical significance was calculated using a one-way ANOVA post-hoc Dunnett's Multiple Comparison Test. Differences were considered statistically significant at: $^{*}p \leqslant 0.05$, $^{**}p \leqslant 0.01$, $^{***}p \leqslant 0.001$. Differences were considered statistically significant at: $^{*}p$ 0.05, $^{**}p$ 0.01, $^{***}p$ 0.001.

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A. Supplementary data

MS, ^{1}H NMR and ^{13}C NMR spectra for representative final compounds. This material is available free of charge via the Internet. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.09.017.

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