Synthesis and Pharmacological Evaluation of Novel Silodosin-Based Arylsulfonamide Derivatives as $\alpha_{1A}/\alpha_{1D}$-Adrenergic Receptor Antagonist with Potential Uroselective Profile

Vittorio Canale 1, Aleksandra Rak 2, Magdalena Kotańska 2, Joanna Knutelska 2, Agata Siwek 3, Marek Bednarski 2, Leszek Nowiński 2, Małgorzata Zygmunt 2, Paulina Koczurkiewicz 4, Elżbieta Pekala 4, Jacek Sapa 2,* and Paweł Zajdel 1

1 Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Krakow, Poland; vittorio.canale@uj.edu.pl (V.C.); pawel.zajdel@uj.edu.pl (P.Z.)
2 Department of Pharmacological Screening, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Krakow, Poland; arakus1987@gmail.com (A.R.); magda.dudek@uj.edu.pl (M.K.); joanna.1.knutelska@uj.edu.pl (J.K.); marek.bednarski@uj.edu.pl (M.B.); leszek.nowinski@uj.edu.pl (L.N.); malgorzata.zygmunt@uj.edu.pl (M.Z.)
3 Department of Pharmacobiology, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Krakow, Poland; agat.siwek@uj.edu.pl
4 Department of Pharmaceutical Biochemistry, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Krakow, Poland; paulina.koczurkiewicz@uj.edu.pl (P.K.); elzbieta.pekala@uj.edu.pl (E.P.)

* Correspondence: jacek.sapa@uj.edu.pl

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Abstract: Benign prostatic hyperplasia (BPH) is the most common male clinical problem impacting the quality of life of older men. Clinical studies have indicated that the inhibition of $\alpha_{1A}$-$/\alpha_{1D}$ adrenoceptors might offer effective therapy in lower urinary tract symptoms. Herein, a limited series of arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines was designed, synthesized, and biologically evaluated as potent $\alpha_1$-adrenoceptor antagonists with uroselective profile. Among them, compound 9 (3-chloro-2-fluoro-N-[1-(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)piperidin-4-yl)methyl]benzenesulfonamide) behaved as an $\alpha_{1A}$/-$\alpha_{1D}$-adrenoceptor antagonist ($K_i(\alpha_{1A}) = 50 \text{nM}$, $EC_{50}(\alpha_{1A}) = 0.8 \text{nM}$, $EC_{50}(\alpha_{1D}) = 1.1 \text{nM}$), displayed selectivity over $\alpha_2$-adrenoceptors ($K_i(\alpha_{2}) = 858 \text{nM}$), and a 5-fold functional preference over the $\alpha_{1B}$ subtype. Compound 9 showed adequate metabolic stability in rat-liver microsome assay similar to the reference drug tamsulosin (Clint = 67 and 41 $\mu$L/min/mg, respectively). Compound 9 did not decrease systolic and diastolic blood pressure in normotensive anesthetized rats in the dose of 2 mg/kg, i.v. These data support development of uroselective agents in the group of arylsulfonamides of alicyclic amines with potential efficacy in the treatment of lower urinary tract symptoms associated to benign prostatic hyperplasia.

Keywords: arylsulfonamides of alicyclic amines; $\alpha_1$-adrenoceptor antagonists; $\alpha_{1A/B/D}$ receptor selectivity; silodosin; tamsulosin; uroselective activity; benign prostatic hyperplasia

1. Introduction

$\alpha_1$-Adrenergic receptors ($\alpha_1$-ARs) belong to the G-protein-coupled receptor superfamily. They generally mediate their actions through $G_{q/11}$ proteins, which stimulate the activation of phospholipase C, via generation of the inositol triphosphate and diacylglycerol, liberation of calcium from the endoplasmic reticulum, and/or activation of genes. To date, three subtypes of $\alpha_1$-AR, i.e., $\alpha_{1A}$,
\(\alpha_{1B}\) and \(\alpha_{1D}\) have been identified in human tissues [1]. Although these subtypes display high structural homology, they differ in biological structure, tissue distributions, and pharmacological actions [2]. Several studies revealed that \(\alpha_1\)-AR subtypes are highly expressed in blood vessels—mainly \(\alpha_{1B}\)-ARs, in the urogenital area (prostate, urethra, bladder, ureter)—mainly \(\alpha_{1A}\) and \(\alpha_{1D}\)-ARs, and central nervous system [3]. \(\alpha_1\)-ARs play an important role in the pathogenesis of hypertension and benign prostatic hyperplasia (BPH) [4,5].

An increased \(\alpha_1\)-adrenergic prostate smooth muscle tone together with enhanced prostate volume are recognized causes of the disease [6]. BPH clinically manifests with lower urinary tract symptoms (LUTS) as storage (irritative) symptoms (nocturia, urgency, incontinence, altered bladder sensations, increased frequency) or obstructive (voiding) symptoms (hesitancy, slow stream, intermittency, splitting, straining, terminal dribble) [7]. Some of them commonly occur secondary to obstructive symptoms, and result from exaggerated, spontaneous detrusor contractions (known as bladder overactivity) [7,8]. BPH affects the majority of men with increasing frequency as they get older [9]. LUTS, if left untreated, result in significant impairment of quality of life and lead to long-term complications, such as recurrent urinary tract infections or renal insufficiency [10].

Despite several classes of BPH medications available, studies have shown that \(\alpha_1\)-adrenolitics are considered as the first-line drug treatment [11]. It has been suggested that enhanced, three-to-nine-fold greater expression of \(\alpha_{1A}\)- and \(\alpha_{1D}\)-ARs in an enlarged prostate and bladder neck, comparing to healthy tissue, remains in strong contribution with LUTS occurrence [12]. Consequently, an \(\alpha_{1A}\)- and \(\alpha_{1D}\)-AR blockade relieves obstructive and voiding symptoms by relaxation of the smooth muscle in the prostate and bladder detrusor, respectively [13].

In contrast, a blockade of \(\alpha_{1B}\)-ARs, which are predominantly expressed in vascular smooth muscle [14], results in vasodilation of blood vessels leading to cardiovascular side effects, especially orthostatic hypotension [15]. The old \(\alpha_1\)-adrenolitics, bearing quinazoline scaffold, i.e., doxazosin or terazosin, display nonspecific interaction with all \(\alpha_1\)-AR subtypes [5]. On the other hand, naftopidil, tamsulosin, and silodosin (Figure 1), displaying relatively high \(\alpha_{1A}\)- and \(\alpha_{1D}\)-AR subtype selectivity, effectively relieve symptoms related to BPH/LUTS disease without undesirable side effects on blood pressure [16–18].

Integrating a concept of arylpiperazine biomimetics recently adapted for development of selective and potent 5-HT\(_7\)-R antagonists [19], we explored the common chemical space with tamsulosin to propose modifications leading to increased \(\alpha_{1A}\)-AR properties. Associating arylsulfonamide and aryloxyalkyl fragments identified compound 1, which behaved as an \(\alpha_{1A}\)-AR antagonist and displayed a moderate selectivity receptor profile over \(\alpha_{1B}\)-AR subtype [20]. In an attempt to further increase the uroselective profile, a limited series of compounds integrating silodosin-derived chemical scaffold was designed (Figure 2). Selection of the central amine core (4-aminomethyl-piperidine and 3-amino-pyrrolidine), as well as a kind of substituent at the arylsulfonamide moiety, was based on our previously reported data presenting their preference for \(\alpha_{1A}\)-AR over 5-HT\(_1A\), and 5-HT\(_7\)-R [20–22].

All the synthesized derivatives were in vitro evaluated to assess their affinity for \(\alpha_2\)-AR and selectivity over \(\alpha_{2}\)-AR subtypes. Then, antagonist properties of selected derivatives against \(\alpha_{1A}\)-, \(\alpha_{1B}\)-, and \(\alpha_{1D}\)-AR subtypes were determined in cellular functional assays. The most representative compounds with uroselective functional profile were submitted under extended in vitro screening towards off-targets responsible for potential side effects, and were evaluated in metabolic stability.
in in vitro assay to assess their susceptibility to biotransformation. Finally, selected compounds were administered to normotensive anesthetized rats to evaluate their effects on blood pressure as a measure of their potential in vivo uroselectivity and to exclude hypotensive effects unfavorable to the treatment of lower urinary tract symptoms associated to benign prostatic hyperplasia.

![Diagram](image)

**Figure 2.** Design strategy for arylosulfonamide derivatives of alicyclic amines as silodosin analogs.

2. Chemistry

The multistep protocol for synthesis of compounds 8–18 in outlined in Schemes 1 and 2. Initially, (2,2,2-trifluoroethoxy)phenol (3) was synthesized by alkylation of commercially available guaiacol 1, followed by demethylation of intermediate 2 in the presence of boron tribromide (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Synthesis of phenol 3. Reagents and conditions: (i) 2-ido-1,1,1-trifluoroethane, K₂CO₃, KI, DMF, 90 °C, 24 h; (ii) BBr₃, CH₂Cl₂ anh, 0 °C → r.t., 2 h.

Next, the alkylation of phenol 3 under biphasic conditions yielded the corresponding (aryloxy)ethyl bromide 4. Subsequently, this alkylating agent reacted with selected Boc-protected alicyclic amines (4-aminomethyl-piperidine, R-3-amino-pyrrolidine, and S-3-amino-pyrrolidine), giving intermediates 5–7. Removal of the protecting group, followed by the treatment with selected arylosulfonyl chloride, yielded final arylosulfonamide derivatives 8–18.

![Scheme 2](image)

**Scheme 2.** Synthesis of silodosin analogs 8–18. Reagents and conditions: (i) 1,2-dibromoethane, K₂CO₃, KI, (CH₃)₂CO, 60 °C, 48 h; (ii) alicyclic amine, K₂CO₃, KI, (CH₃)₂CO, 60 °C, 24 h; (iii) TFA/CH₂Cl₂ (80/20; v/v), r.t., 2 h; (iv) arylosulfonyl chloride, TEA, CH₂Cl₂, 0 °C, 2–6 h.
3. In Vitro Experiments

3.1. Radioligand Binding and Functional Evaluation

The pharmacological profile of the new compounds was assessed in radioligand-binding assays as the ability to displace \(^{3}H\)-Prazosin or \(^{3}H\)-Clonidine from \(\alpha_1\) and \(\alpha_2\)-ARs, respectively, on rat cerebral cortex [23]. The inhibition constants (\(K_i\)) were calculated from the Cheng-Prusoff equation [24].

The intrinsic activity at \(\alpha_{1A}\)-ARs of the selected compounds was assessed by fluorescence detection (Invitrogen, Thermo Fisher Scientific, Carlsbad, CA, USA) of \(\beta\)-lactamase reporter genes using a FRET-enabled substrate. The intrinsic activity at \(\alpha_{1B}\)-ARs and \(\alpha_{1D}\)-ARs was determined by luminescence detection (PerkinElmer, Zaventem, Belgium) of calcium mobilization using the recombinant-expressed jellyfish photoprotein (Aequorin).

The most representative compounds, 9 and 10, with the highest functional selectivity were further tested to determine the affinity for 5-HT\(_{1A}\) and 5-HT\(_{7}\)Rs 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\(_{7}\)Rs according to the methods previously described [25].

Finally, the percentage of inhibition for selected compounds 9 and 10 for off-target histaminic H\(_1\)R, muscarinic M\(_1\)R, adrenergic \(\beta_1\)-AR and potassium ion channel hERG were assessed at Eurofins (Celle-Lévescault, France) according to the procedure online at www.eurofins.com [26].

3.2. Metabolic Stability

\(\text{In vitro}\) biotransformation assays of selected compounds 9 and 10 were performed using rat-liver microsomes (RLM), potassium-phosphate buffer, NADPH-regenerating system (NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase), and levallorphan as internal standard, according to the previously published procedure [27]. Compound I and the drug tamsulosin were used as reference standard. UPLC/MS analysis (Waters Corporation, Milford, MA, USA) was performed to determine the quantity of the starting material left in solution. The \(\text{in vitro}\) half-time (\(t_{1/2}\)) for test compounds was determined from the slope of the linear regression of ln % parent compound remaining versus incubation time. The calculated \(t_{1/2}\) was incorporated into the following equation to obtain intrinsic clearance: \((\text{Cl}_{\text{int}}) = \text{(volume of incubation [\(\mu\text{L}\])/protein in the incubation [mg])} \times 0.693/t_{1/2}\).

4. In Vivo Pharmacology

Compounds 9 and 10, which displayed the highest \(\alpha_{1B}/\alpha_{1A}\) selectivity profile, were selected for \(\text{in vivo}\) evaluation to determine their influence on blood pressure of normotensive anaesthetized rats after acute administration at single dose of 2 mg/kg \((i.v.)\). The experiments were performed to our previously reported method.

5. Results and Discussion

All synthesized compounds were \(\text{in vitro}\) evaluated in binding assays for their affinity for \(\alpha_1\)-AR and selectivity over \(\alpha_2\)-AR subtype. Compounds showed high-to-moderate affinity for \(\alpha_1\)-ARs (\(K_i = 19–171 \text{ nM}\)), and low-to-moderate selectivity over \(\alpha_2\)-AR subtype (Table 1). Analysis of the influence of substituent in position-2 at the aryloxy fragment showed that an increase of its volume by replacing the isopropoxy group present in compound I and II with the 2,2,2-trifluoroethoxy one (present in a new series) only slightly increased the affinity for \(\alpha_1\)-ARs (I vs. 9, II vs. 16).

In line with our previous results [20], the 4-aminomethylpiperidine core was more favorable for the binding at \(\alpha_1\)-AR than 3-aminopyrrolidine one (8 vs. 13 and 14, 12 vs. 17 and 18). Although among compounds with 3-aminopyrrolidine no stereochemical preference towards \(\alpha_1\)-AR was observed, the S enantiomers showed higher selectivity over \(\alpha_2\)-AR than their \(R\) counterparts (13 vs. 14, 15 vs. 16, 17 vs. 18).
Further modifications involved the introduction of different electron-withdrawing or electron-donating substituents at the phenyl ring of sulfonamide moiety. A fluorine atom in 4-position was sufficient for obtaining a potent α1-AR ligand 8 (Kᵢ = 20 nM) among the 4-aminomethyl-piperidine subset, but did not significantly improve the affinity of pyrrolidine derivatives 13 and 14 for α1-AR (Kᵢ = 188 and 134 nM, respectively). Interestingly, the presence of the 4-F substituent in both series led to derivatives with the highest selectivity over the α2-AR subtype (S₂α₂/α₁ ≥ 46). An introduction of two halogen substituents did not affect the affinity for α1-AR while decreasing the selectivity over the α2-AR subtype (8 vs. 9 and 10, 13 vs. 15, and 14 vs. 16). Replacing one of the halogen substituents (e.g., 2-F) in compound 10, with an electron-donating substituent as the 2-methoxy, up to 4-fold reduced both affinity for α1-AR and selectivity over α2-AR (10 vs. 11). Finally, compounds 12, 17, and 18, with two methoxy groups in 3,4-position at the phenyl ring of sulfonamide moiety, showed higher affinity for α1-AR than the 4-F direct analogs (8 vs. 12, 13 vs. 17, and 14 vs. 18); however, this modification decreased the selectivity over α2-AR subtype. Selected compounds with the highest affinity for α1-ARs (Kᵢ ≤ 50 nM) and selectivity ratio, which equals >15-fold over α2-AR subtype, behaved as potent antagonists at α₁A-, α₁B-, and α₁D-ARs in in-vitro functional tests (Table 2). Compounds 8, 9, and 10 were classified as more potent antagonists than previously reported compound 1 at all tested α₁A-, α₁B-, and α₁D-ARs. Compounds 9 and 10, bearing two halogen atoms in ortho and meta position (i.e., 3-Cl,2-F and 5-Cl,2-F) at the phenyl ring of sulfonamide moiety displayed the highest α₁B/α₁A selectivity ratio. An introduction of the strong electron-donating substituent in meta and para position (e.g., 3,4-diOMe), switched the functional-selectivity profile of compound 12, which behaved as a selective α₁B-AR antagonist (IC₅₀ = 0.022 nM).

It is well known that a blockade of α₁A- and α₁D-ARs relaxes the enhanced prostate and bladder detrusor smooth muscle tone, whereas α₁B-AR antagonism is involved in blood-pressure regulation. Normal detrusor, obtained from surgical patients, expresses predominantly α₁D-ARs. Some pharmacological experiments revealed that highly selective α₁A-AR antagonists are effective in relaxing prostate smooth muscle and therefore improving urine flow in men in this area. However, relaxation of smooth muscle of the prostate alone does not alter reported LUTS scores in men with BPH. Reduction of these symptoms is reported only when pharmacotherapy includes drugs with both α₁A- and α₁D-AR antagonistic activity. Such activity improves bladder-based symptoms in humans and is used in LUTS pharmacotherapy [13].

### Table 1. The biological data of compounds 8-18 for adrenergic α₁- and α₂-receptors.

| Compd. | R₁   | Enant | n  | m  | R     | Kᵢ [nM] ± SEM |
|--------|------|-------|----|----|-------|---------------|
|        |      |       |    |    |       | α₁   | α₂   | S₂α₂/α₁ |
| I ¹    | 3-Cl | -     | 1  | 1  | Isopropyl | 71 ± 4 | 1212 ± 99 | 17 |
| 8      | 4-F  | -     | 1  | 1  | TFE   | 20 ± 2 | 919 ± 25 | 46 |
| 9      | 3-Cl | -     | 1  | 1  | TFE   | 50 ± 2 | 858 ± 69 | 17 |
| 10     | 5-Cl | -     | 1  | 1  | TFE   | 26 ± 1 | 579 ± 20 | 23 |
| 11     | 5-Cl | OMe  | -  | 1  | TFE   | 95 ± 3 | 1092 ± 62 | 12 |
| 12     | 3,4-diOMe | -  | 1  | 1  | TFE   | 19 ± 3 | 524 ± 31 | 27 |
| II ²   | 5-Cl | S     | 0  | 0  | Isopropyl | 242 ± 16 | >10,000 | >41 |
| 13     | 4-F  | R     | 0  | 0  | TFE   | 188 ± 3 | 1697 ± 85 | 9 |
| 14     | 2-F  | S     | 0  | 0  | TFE   | 134 ± 16 | >10,000 | >70 |
| 15     | 5-Cl | F    | 0  | 0  | TFE   | 171 ± 4 | 1188 ± 74 | 7 |
| 16     | 5-Cl | F    | 0  | 0  | TFE   | 117 ± 10 | 1466 ± 80 | 13 |
| 17     | 3,4-diOMe | R  | 0  | 0  | TFE   | 105 ± 7 | 435 ± 21 | 4 |
| 18     | 3,4-diOMe | S  | 0  | 0  | TFE   | 70 ± 1 | 1141 ± 42 | 16 |

¹ Kᵢ values based on two independent binding experiments; ² Ratio of affinity for α₂- and α₁-ARs; ³ data taken from Reference [20]; ⁴ TFE = 2,2,2-trifluoroethyl.

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showed strong antagonistic properties against the α1D-AR subtype with EC\textsubscript{50} in the range of 1.1 to 2.7 nM. However, among the tested compounds, only 9 and 10 showed a similar inhibitory effect on intrinsic signal transduction in cells with stable expression of human α1A- and α1D-ARs.

Table 2. The functional activity of selected derivatives and reference drugs for α1A-, α1B-, and α1D-ARs.

| Compd. | α\textsubscript{1A} | α\textsubscript{1B} | α\textsubscript{1D} |
|--------|------------------|------------------|------------------|
|        | IC\textsubscript{50} [nM] | Profile | IC\textsubscript{50} [nM] | Profile | IC\textsubscript{50} [nM] | Profile |
| 1 c    | 11.1 ANT\textsuperscript{b} | 42.1 ANT     | 15.1 ANT     |
| 8      | 3.8 ANT          | 8.3 ANT      | 1.1 ANT      |
| 9      | 0.8 ANT          | 3.9 ANT      | 1.1 ANT      |
| 10     | 2.1 ANT          | 10.1 ANT     | 2.7 ANT      |
| 12     | 15.0 ANT         | 0.02 ANT     | 2.6 ANT      |
| tamsulosin | 0.07 ANT | 1.3 ANT | 0.005 ANT |
| terazosin    | 51.9 ANT     | 1.7 ANT     | 0.2 ANT      |
| phenylephrine | 56.0 (EC\textsubscript{50}) AGO\textsuperscript{b} | 0.9 (EC\textsubscript{50}) AGO | 12.1 (EC\textsubscript{50}) AGO |

\textsuperscript{a} The EC\textsubscript{50}/IC\textsubscript{50} values were based on three independent experiments;\textsuperscript{b} ANT—antagonist, AGO—agonist.

Some pieces of evidence suggest an involvement of serotonin 5-HT\textsubscript{1A} and 5-HT\textsubscript{7}Rs in regulation of rodent bladder and urethral-sphincter contractions in both in vitro and in vivo models [28,29]. Thus, 5-HT\textsubscript{1A} and 5-HT\textsubscript{7}R ligands may be regarded as adjunctive agents in alleviating LUTS associated to BPH. Compounds 9 and 10 displayed high-to-moderate affinity for 5-HT\textsubscript{1A} and 5-HT\textsubscript{7}Rs (Table 3).

Table 3. The binding data of selective compounds for 5-HT\textsubscript{1A} and 5-HT\textsubscript{7}Rs.

| Compd. | 5-HT\textsubscript{1A} | 5-HT\textsubscript{7} |
|--------|------------------|------------------|
|        | \(K_i\) [nM] \± SEM | %inh @ 10\textsuperscript{-6}/10\textsuperscript{-7} M |
| 9      | 70 \± 3.5        | 93/57            |
| 10     | 46 \± 0.6        | 94/61            |

\textsuperscript{a} \(K_i\) values based on two independent binding experiments.

The same compounds were further evaluated for their affinity for “off-target” receptor panels at Eurofins Cerep, and displayed weak affinity for histamine H\textsubscript{1}, muscarinic M\textsubscript{1}, adrenergic β\textsubscript{1}, and hERG channels (<50% @ 1 µM) [26]. These may suggest a low risk of compounds to evoke undesirable cardiovascular or CNS side effects. An initial assessment of the metabolic fate in liver was subsequently performed in an in-vitro RLM model. Compounds 9 and 10 showed relatively low clearances (Cl\textsubscript{int} = 67 and 91.7 µL/min/mg, respectively, Table 4), with values similar to those of reference compound I and the drug tamsulosin (Cl\textsubscript{int} = 87 and 41 µL/min/mg, respectively). The values of internal clearance calculated for the tested compounds are in line with the value of clearance of reference drugs (i.e., propranolol, verapamil) reported in the literature [30,31].

Table 4. Metabolic stability of compounds I, 9, 10 and reference drug tamsulosin.

| Compd. | \(t_\frac{1}{2}\) [min] | Cl\textsubscript{int} [µL/min/mg] | Major Metabolic Pathway |
|--------|------------------|------------------|------------------|
| 1      | 40               | 87               | N-dealkylation   |
| 9      | 51.5             | 67               | N-dealkylation   |
| 10     | 37.8             | 91.7             | N-dealkylation   |
| Tamsulosin | 83              | 41               | N-dealkylation   |

Identified compounds 9 and 10 with favorable α\textsubscript{1B}/α\textsubscript{1D} profile and acceptable metabolic stability were selected for in vivo tests to evaluate their influence on blood pressure. Hypotensive activity was determined after one time i.v. administration to normotensive anaesthetized rats at single doses of 2 mg/kg according to our previously reported method [32].
Compound 9 given at the dose of 2 mg/kg decreased SBP about 5.9–10.9 mmHg (5.1–9.4%), and DBP about 2–5.3 mmHg (2.4–6.5%) insignificantly.

Compound 10 in a dose of 2 mg/kg reduced both, SBP about 7–18 mmHg (5.8–15.1%), and DBP about 7–16.4 mmHg (7.8–18.3%). A statistically significant drop in systolic blood pressure was observed from 30 min after administration (Figures 3 and 4).

![Figure 3](image.png)

**Figure 3.** An influence of tamsulosin and compounds 9 and 10, given in a dose of 2 mg/kg (i.v.), on systolic pressure in anaesthetized rats. Significant to control group (0.9% NaCl): *p < 0.05, **p < 0.02, ***p < 0.01.

![Figure 4](image.png)

**Figure 4.** An influence of tamsulosin and compounds 9 and 10, given in a dose of 2 mg/kg (i.v.), on diastolic pressure in anaesthetized rats. Significant to control group (0.9% NaCl): *p < 0.05.

In contrast, the highly α1A-AR-selective drug tamsulosin administered intravenously at a dose of 2 mg/kg decreased SBP 16.2–23.7 mmHg (12.9–18.9%) and the DBP about 13.3–16.6 mmHg (14.4–17.9%) significantly through whole period of observation (Figures 3 and 4).

It thus seems that compound 9 revealed a potential uroselective profile, comparable to tamsulosin, without evoking hypotension as a side effect. These data warrant further investigation of compound 9 in *ex vivo* preclinical models of BPH disease.

6. Conclusions

By combining the 2-(2,2,2-trifluoroethoxy)phenoxy fragment of silodosin with an alicyclic amine core functionalized with arylsulfonamide moiety, derived from previously reported compound I, we designed and synthesized a new series of arylsulfonamides of (aryloxy)ethyl pyrrolidines and piperidines as α1-AR antagonists. Structure–activity relationship studies revealed
that the 4-aminomethylpiperidine core was preferential for binding with the \( \alpha_1 \)-AR over the 3-aminopyrrolidine analog. Additionally, a kind of substituent at the phenyl ring of sulfonamide significantly impacted the selectivity of evaluated compounds over \( \alpha_{1B} \) and \( \alpha_2 \)-AR subtypes. The study allowed the identification of compound 9 as a potent and metabolically stable \( \alpha_1A \)-AR antagonist with improved \( \alpha_{1B}/\alpha_1A \) selectivity ratio, comparing with previously reported series. Moreover, compound 9 showed \( \alpha_{1D} \)-AR antagonistic activity that may be beneficial in terms of LUTS therapy. In contrast to the reference drug tamsulosin, the tested compound did not decrease blood-pressure parameters after acute administration at the dose of 2 mg/kg (i.v.) in rats. Preliminary data for compound 9 are promising enough to warrant its further detailed mechanistic studies as a potential uroselective \( \alpha_1A \) and \( \alpha_{1D} \)-AR antagonist in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia.

7. Experimental

7.1. Chemistry

7.1.1. General Chemical Methods

Organic transformations were carried out at ambient temperature unless indicated otherwise. Organic solvents (Sigma-Aldrich, Merck Group, Darmstadt, Germany) used in this study were of reagent grade and were used without purification. All other commercially available reagents were of the highest purity (Sigma-Aldrich). 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 precolumn (Waters Corporation, Milford, MA, USA); 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 the 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 Corporation, Milford, MA, USA). 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 300 spectrometer (Varian, Palo Alto, CA, USA) in CDCl\(_3\) or \(d_6\)-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), dt (doublet of triplets), td (triplet of doublets), ddd (doublet of doublet of doublets), m (multiplet).

Elemental analyses for C, H, N and S were carried out using the elemental Vario EL III Elemental Analyser (Elementar Analyensysteme GmbH, 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 (Flawil, Switzerland) and are uncorrected.

The general procedures used for the synthesis of intermediate and final compounds were in accordance with previously reported methodology [20].

Spectroscopic data (MS, \(^1\)H-NMR and \(^{13}\)C-NMR spectra) for representative final compounds are presented in Supplementary Materials.
7.1.2. Preparation of 1-Methoxy-2-(2,2,2-trifluoroethoxy)benzene (2)

2-Methoxy-phenol 1 (5.19 g, 0.04 mol) was dissolved in DMF (25 mL), after addition of K$_2$CO$_3$, (16.6 g, 0.12 mol) a mixture that was heated to 90 °C. Then 2-iodo-1,1,1-trifluoroethane (4.2 mL, 0.05 mol) was added dropwise in 30 min. The reaction mixture was then heated under reflux for 24 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 (isolated yield 65%). Yellow oil (5.6 g); UPLC/MS purity 99%, $t_R$ = 6.52. C$_8$H$_7$F$_3$O$_2$, MW 206.16. Monoisotopic Mass 206.06, [M + H]$^+$ 207.1. $^1$H-NMR (300 MHz, CDCl$_3$) δ 5.91 (s, 3H, O–CH$_3$), 4.36 (q, $J$ = 8.4 Hz, 2H, O–CH$_2$–CF$_3$), 6.81–7.11 (m, 4H, Ar–H). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 56.4, 68.3, 119.0, 121.5, 122.3, 123.8, 126.1, 127.2, 138.9.

7.1.3. Preparation of 2-(2,2,2-Trifluoroethoxy)phenol (3)

A 1 M solution of boron tribromide (30 mL, 0.03 mol) in CH$_2$Cl$_2$ was added to a solution of intermediate 2 (4.3 g, 0.02 mol) in anhydrous CH$_2$Cl$_2$ (50 mL) at −20 °C. The reaction mixture was warmed to room temperature and, after, quenched by addition of excess saturated aqueous sodium bicarbonate solution (40 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude material was sufficiently pure to be used directly in the next step (yield 98%). Yellow oil (3.8 g); UPLC/MS purity 99%, $t_R$ = 5.37. C$_8$H$_7$F$_3$O$_2$, MW 192.14. Monoisotopic Mass 191.0. $^1$H-NMR (300 MHz, CDCl$_3$) δ 4.36 (q, $J$ = 8.4 Hz, 2H, O–CH$_2$–CF$_3$), 6.81–7.11 (m, 4H, Ar–H), 9.72 (br.s., 1H, O–H). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 56.2, 64.1, 65.8, 68.1, 119.3. Yellow oil (5.6 g); UPLC/MS purity 99%, $t_R$ = 75%. Yellow oil (5.6 g); UPLC/MS purity 99%, $t_R$ = 6.52. C$_8$H$_7$F$_3$O$_2$, MW 206.16. Monoisotopic Mass 206.06, [M + H]$^+$ 207.1. $^1$H-NMR (300 MHz, CDCl$_3$) δ 5.91 (s, 3H, O–CH$_3$), 4.36 (q, $J$ = 8.4 Hz, 2H, O–CH$_2$–CF$_3$), 6.81–7.11 (m, 4H, Ar–H), 9.72 (br.s., 1H, O–H). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 56.2, 68.1, 119.2, 121.5, 122.4, 123.7, 126.4, 127.3, 136.4.

7.1.4. Preparation of 1-(2-Bromoethoxy)-2-(2,2,2-trifluoroethoxy)benzene (4)

Phenol 3 (4.8 g, 0.025 mol) was dissolved in acetone (30 mL). Then K$_2$CO$_3$ (10.4 g, 0.075 mol) and catalytic amount of KI (0.08 g, 0.0005 mol) were added, followed by dropwise addition of 1,2-dibromoethane (12.9 mL, 0.15 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 AcOEt/Hexane (1/9, v/v) as an eluting system (isolated yield 75%). Yellow oil (5.61 g); UPLC/MS purity 99%, $t_R$ = 6.5 Hz, 2H, N–CH$_2$–CF$_3$), 6.82 (dd, $J$ = 5.2, 1.0 Hz, 1H, Ar–H), 6.99 (td, $J$ = 7.6, 1.1 Hz, 1H, Ar–H), 7.14 (td, $J$ = 8.0, 1.8 Hz, 1H, Ar–H), 7.24–7.28 (m, 1H, Ar–H). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ 56.2, 64.1, 65.8, 68.1, 119.3, 121.5, 122.4, 123.7, 126.4, 127.3, 136.4.

7.1.5. General Procedure for the Alkylation of Boc-Protected Amines (5-7)

Commercial Boc-protected amines (1 eq) were dissolved in acetone (15 mL). Then K$_2$CO$_3$ (3 eq) and a catalytic amount of KI (0.02 eq) were added, followed by dropwise addition of (aryloxy)ethyl bromide 4 (1.2 eq) in 30 min. The reaction was heated under reflux for 48 h. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude products were purified according to the methods described below (isolated yields 68–75%).

tert-Butyl ((1-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)piperidin-4-yl)methyl)carbamate (5)

Compound 5 was prepared using 4-Boc-aminomethyl-piperidine (1.1 g, 5.8 mmol), K$_2$CO$_3$ (2.4 g, 17.4 mmol), KI (0.02 g, 0.12 mmol) and (aryloxy)ethyl bromide 4 (2.1 g, 6.96 mmol). Yellow oil 2.06 g, (isolated yield 68%), following chromatographic purification over silica gel with CH$_2$Cl$_2$/MeOH (9/0.7, v/v); UPLC/MS purity 97%, $t_R$ = 4.57. C$_{21}$H$_{31}$F$_3$N$_2$O$_4$, MW 432.48, Monoisotopic Mass 432.22, [M + H]$^+$ 433.5. $^1$H-NMR (300 MHz, CDCl$_3$) δ 1.08–1.20 (m, 2H), 1.34–1.42 (m, 1H, piperidine), 1.45 (s, 9H, (CH$_3$)$_3$–C), 1.56–1.60 (m, 2H, piperidine), 1.92–1.99 (m, 2H, piperidine), 2.79–2.88 (m, 4H, piperidine), 3.45 (t, $J$ = 6.5 Hz, 2H, N–CH$_2$–CH$_2$), 4.29 (t, $J$ = 6.5 Hz, 2H, O–CH$_2$–CH$_2$), 4.36 (q, $J$ = 7.6 Hz, 2H, O–CH$_2$–CH$_2$), 4.94 (t, $J$ = 7.6 Hz, 2H, N–CH$_2$–CH$_2$), 5.61 (s, 1H, O–H)
J = 8.4 Hz, 2H, O–CH₂–CF₃), 4.52 (br.s, 1H, SO₂–NH–CH₂), 6.82 (dd, J = 5.2, 1.0 Hz, 1H, Ar–H), 6.99 (td, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.14 (td, J = 8.0, 1.8 Hz, 1H, Ar–H), 7.24–7.28 (m, 1H, Ar–H). ¹³C-NMR (75 MHz, CDCl₃) δ 27.0, 28.3, 34.0, 47.6, 52.6, 55.4, 64.1, 65.8, 66.3, 79.2, 120.7, 122.1, 122.7, 123.4, 126.3, 128.9, 135.6, 155.5.

**tert-Butyl (R)-(1-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)pyrrolidin-3-yl)carbamate (6)**

Compound 6 was prepared using (R)-3-Boc-amino-pyrrolidine (0.75 g, 4.03 mmol), K₂CO₃ (1.67 g, 12.09 mmol), KI (0.01 g, 0.08 mmol), and (aryloxy)ethyl bromide (1.5 g, 4.84 mmol). Yellow oil 1.17 g, (isolated yield 72%), following chromatographic purification over silica gel with CH₂Cl₂/MeOH (9/0.7 v/v); UPLC/MS purity 98%, tᵣ = 4.72. C₁₉H₂₂F₃N₂O₄S, MW 404.43, Monoisotopic Mass 404.19, [M + H]+ 405.1. ¹H-NMR (300 MHz, CDCl₃) δ 1.43 (2, 9H, (CH₃)₃–C), 1.51–1.64 (m, 1H, pyrrolidine), 2.04–2.18 (m, 1H, piperidine), 2.33 (td, J = 8.91, 7.16 Hz, 1H, piperidine), 2.71–2.92 (m, 4H, piperidine), 3.45 (t, J = 6.5 Hz, 2H, N–CH₂–CH₂), 3.79 (br.s, 1H, SO₂–NH–CH), 4.29 (t, J = 6.5 Hz, 2H, O–CH₂–CH₂), 4.36 (q, J = 8.4 Hz, 2H, O–CH₂–CF₃), 6.82 (dd, J = 5.2, 1.0 Hz, 1H, Ar–H), 6.99 (td, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.14 (td, J = 8.0, 1.8 Hz, 1H, Ar–H), 7.24–7.28 (m, 1H, Ar–H). ¹³C-NMR (75 MHz, CDCl₃) δ 28.3, 29.0, 32.5, 52.7, 54.0, 60.8, 64.1, 65.8, 66.3, 79.2, 120.7, 122.1, 122.7, 123.4, 126.3, 128.9, 135.6, 156.1.

**tert-Butyl (S)-(1-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)pyrrolidin-3-yl)carbamate (7)**

Compound 7 was prepared using (S)-3-Boc-amino-pyrrolidine (0.75 g, 4.03 mmol), K₂CO₃ (1.67 g, 12.09 mmol), KI (0.01 g, 0.08 mmol), and (aryloxy)ethyl bromide (1.5 g, 4.84 mmol). Yellow oil 1.22 g, (isolated yield 75%), following chromatographic purification over silica gel with CH₂Cl₂/MeOH (9/0.7 v/v); UPLC/MS purity 98%, tᵣ = 4.84. C₁₉H₂₄F₃N₂O₄S, MW 404.43, Monoisotopic Mass 404.19, [M + H]+ 405.3. ¹H-NMR (300 MHz, CDCl₃) δ 1.43 (2, 9H, (CH₃)₃–C), 1.51–1.64 (m, 1H, pyrrolidine), 2.04–2.18 (m, 1H, pyrrolidine), 2.33 (td, J = 8.91, 7.16 Hz, 1H, pyrrolidine), 2.71–2.92 (m, 4H, pyrrolidine), 3.45 (t, J = 6.5 Hz, 2H, N–CH₂–CH₂), 3.79 (br.s, 1H, SO₂–NH–CH), 4.29 (t, J = 6.5 Hz, 2H, O–CH₂–CH₂), 4.36 (q, J = 8.4 Hz, 2H, O–CH₂–CF₃), 6.82 (dd, J = 5.2, 1.0 Hz, 1H, Ar–H), 6.99 (td, J = 7.6, 1.1 Hz, 1H, Ar–H), 7.14 (td, J = 8.0, 1.8 Hz, 1H, Ar–H), 7.24–7.28 (m, 1H, Ar–H). ¹³C-NMR (75 MHz, CDCl₃) δ 28.2, 29.0, 32.4, 52.7, 54.0, 60.7, 64.1, 65.8, 66.1, 79.2, 120.7, 122.0, 122.7, 123.5, 126.3, 128.9, 135.3, 156.5.

7.1.6. General Procedure for Preparation of Final Compounds (8-18)

Intermediates 5-7 were converted into their TFA salts by treatment with a mixture of TFA/CH₂Cl₂ (4 mL/1 mL). The excess reagent and solvent were removed under reduced pressure and maintained overnight under vacuum. A mixture of the appropriate (aryloxy)ethyl acyclic amine (1 eq) in CH₂Cl₂ (3 mL) and TEA (3 eq) was then cooled in an ice bath, and the proper arylsulfonyl chloride (1.2 eq) was added at 0 °C (the entire amount was added at the same time). The reaction mixture was stirred for 2-6 h under cooling. The solvent was evaporated, and the sulfonamides were a purified silica-gel column with CH₂Cl₂/MeOH (9/0.7, v/v) as an eluting system (isolated yields 55–87%). Compounds 9 and 10, selected for in vivo pharmacological evaluation, were further converted into the hydrochloride salts by treatment of their solution in anhydrous ethanol with 1.25 M HCl in MeOH.

4-Fluoro-N-[(1-{2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)piperidin-4-yl)methyl]benzenesulfonamide (8)

Compound 8 was prepared using intermediate 5 (150 mg, 0.45 mmol), TEA (0.19 mL, 1.35 mmol), and 4-fluorobenzenesulfonyl chloride (110 mg, 0.54 mmol). Yellow oil 200 mg (isolated yield 87%); UPLC/MS purity 100%, tᵣ = 4.92. C₂₂H₂₆F₁₄N₂O₅S, MW 491.49, Monoisotopic Mass 491.49, [M + H]+ 491.4. ¹H-NMR (300 MHz, CDCl₃) δ 1.25–1.37 (m, 2H, piperidine), 1.51–1.64 (m, 1H, pyrrolidine), 1.70 (d, J = 13.5 Hz, 2H, piperidine), 2.22 (t, J = 11.5 Hz, 2H, piperidine), 2.83 (t, J = 6.5 Hz, 2H, piperidine), 2.91 (t, J = 5.4 Hz, 2H, N–CH₂–CH₂), 3.12 (d, J = 11.3 Hz, 2H, NH–CH₂–CH₂), 4.17 (t, J = 5.5 Hz, 2H, O–CH₂–CF₃), 4.38 (q, J = 8.4 Hz, 2H, O–CH₂–CF₃), 6.88–6.95 (m, 3H, 1H, Ar–H), 6.96–7.06 (m, 1H, Ar–H), 7.14–7.22 (m, 2H, Ar–H), 7.83–7.91 (m, 2H, Ar–H). Anal. calc'd for C₂₂H₂₆F₁₄N₂O₅S...
3-Chloro-2-fluoro-N-[(1-[2-[2,2,2-trifluoroethoxy]phenoxy)ethyl]piperidin-4-yl]methyl benzensulfonylamide (9)

Compound 9 was prepared using intermediate 5 (150 mg, 0.45 mmol), TEA (0.19 mL, 1.35 mmol), and 3-chloro-2-fluorobenzenesulfonyl chloride (0.08 mL, 0.54 mmol). Yellow oil, 190 mg (isolated yield 82%); UPLC/MS purity 100%, t_R = 5.35. C_{22}H_{25}ClF_{4}N_{2}O_{4}S, MW 524.96, Monoisotopic Mass 524.12, [M + H]^+ 525.3. 1H-NMR (300 MHz, CDCl_3) δ 1.15–1.30 (m, 2H, piperidine), 1.48–1.55 (m, 1H, piperidine), 1.70 (d, J = 13.1 Hz, 2H, piperidine), 2.11 (td, J = 11.7, 2.0 Hz, 2H, piperidine), 2.82 (t, J = 5.7 Hz, 2H, piperidine), 2.88 (t, J = 6.2 Hz, 2H, N–CH2–CH2), 3.02 (d, J = 11.7 Hz, 2H, NH–CH2–CH), 4.12 (t, J = 5.7 Hz, 2H, O–CH2–CH2), 4.39 (q, J = 8.5 Hz, 2H, O–CH2–CF3), 6.89–6.93 (m, 2H, Ar–H), 6.96–7.06 (m, 1H, Ar–H), 7.19–7.25 (m, 1H, Ar–H), 7.62 (dd, J = 8.2, 6.7, 1.7 Hz, 1H, Ar–H), 7.79 (ddd, J = 7.9, 6.3, 1.7 Hz, 1H, Ar–H). 13C-NMR (75 MHz, DMSO-d_6) δ 27.0, 34.0, 47.6, 52.6, 55.4, 64.1, 65.8, 66.3, 115.0 (d, J = 80.6 Hz), 121.7, 122.1 (d, J = 10.4 Hz), 122.7, 123.4, 126.2 (d, J = 4.6 Hz), 126.3, 128.9, 130.5 (d, J = 13.8 Hz), 135.6, 147.1 (d, J = 58.7 Hz), 154.0 (d, J = 255.7 Hz). Anal. calcd for C_{22}H_{25}ClF_{4}N_{2}O_{4}S HCl: C: 47.07, H: 4.67, N: 4.99, S: 5.71; Found C: 47.09, H: 4.48, N: 4.74, S: 5.32. Mp for C_{22}H_{25}ClF_{4}N_{2}O_{4}S HCl: 163.1–164.9 °C.

5-Chloro-2-fluoro-N-[(1-[2-[2,2,2-trifluoroethoxy]phenoxy)ethyl]piperidin-4-yl]methyl benzensulfonylamide (10)

Compound 10 was prepared using intermediate 5 (150 mg, 0.45 mmol), TEA (0.19 mL, 1.35 mmol), and 5-chloro-2-fluorobenzenesulfonyl chloride (120 mg, 0.54 mmol). Yellow oil, 190 mg (isolated yield 81%); UPLC/MS purity 100%, t_R = 5.41. C_{22}H_{25}ClF_{4}N_{2}O_{4}S, MW 524.96, Monoisotopic Mass 524.12, [M + H]^+ 525.3. 1H-NMR (300 MHz, CDCl_3) δ 1.15–1.32 (m, 2H, piperidine), 1.43–1.57 (m, 1H, piperidine), 1.70 (d, J = 13.3 Hz, 2H, piperidine), 2.08–2.18 (m, 2H, piperidine), 2.83 (t, J = 5.7 Hz, 2H, piperidine), 2.87 (t, J = 6.2 Hz, 2H, N–CH2–CH2), 3.04 (d, J = 11.8 Hz, 2H, NH–CH2–CH), 4.13 (t, J = 5.6 Hz, 2H, O–CH2–CH2), 4.41 (q, J = 8.5 Hz, 2H, O–CH2–CF3), 4.90 (br.s., 1H, SO2–NH–CH2), 6.89–6.93 (m, 2H, Ar–H), 6.96–7.06 (m, 2H, Ar–H), 7.12–7.19 (m, 1H, Ar–H), 7.52 (ddd, J = 8.8, 4.3, 2.7 Hz, 1H, Ar–H), 7.87 (dd, J = 6.1, 2.7 Hz, 1H, Ar–H). 13C-NMR (75 MHz, DMSO-d_6) δ 27.0, 34.0, 47.5, 52.6, 55.4, 64.1, 65.6, 66.2, 115.0 (d, J = 74.9 Hz), 119.9 (d, J = 21.9 Hz), 122.1, 123.4, 129.1 (d, J = 3.5 Hz), 130.4 (d, J = 16.1 Hz), 135.3 (d, J = 9.2 Hz), 147.4 (d, J = 57.6 Hz), 157.3 (d, J = 249.9 Hz). Anal. calcd for C_{22}H_{25}ClF_{4}N_{2}O_{4}S HCl: C: 47.07, H: 4.67, N: 4.99, S: 5.71; Found C: 47.17, H: 4.32, N: 4.74, S: 5.39. Mp for C_{22}H_{25}ClF_{4}N_{2}O_{4}S HCl: 165.0–166.6 °C.

5-Chloro-2-methoxy-N-[(1-[2-[2,2,2-trifluoroethoxy]phenoxy)ethyl]piperidin-4-yl]methyl benzensulfonylamide (11)

Compound 11 was prepared using intermediate 5 (150 mg, 0.45 mmol), TEA (0.19 mL, 1.35 mmol), and 5-chloro-2-methoxybenzenesulfonyl chloride (130 mg, 0.54 mmol). Yellow oil, 140 mg (isolated yield 58%); UPLC/MS purity 98%, t_R = 5.35. C_{23}H_{28}ClF_{4}N_{2}O_{4}S, MW 536.14, Monoisotopic Mass 536.99, [M + H]^+ 537.2. 1H-NMR (300 MHz, CDCl_3) δ 1.14–1.29 (m, 2H, piperidine), 1.50–1.58 (m, 1H, piperidine), 1.70 (d, J = 12.5 Hz, 2H, piperidine), 2.17 (t, J = 11.0 Hz, 2H, piperidine), 2.73 (t, J = 6.6 Hz, 2H, piperidine), 2.86 (t, J = 5.5 Hz, 2H, N–CH2–CH2), 3.04–3.11 (m, 2H, NH–CH2–CH), 3.95 (s, 3H, O–CH3), 4.15 (t, J = 5.5 Hz, 2H, O–CH2–CH2), 4.38 (q, J = 8.4 Hz, 2H, O–CH2–CF3), 5.04 (br.s., 1H, SO2–NH–CH2), 6.94 (dd, J = 16.5, 8.1 Hz, 4H, Ar–H), 6.99–7.05 (m, 1H, Ar–H), 7.48 (dd, J = 8.9, 2.7 Hz, 1H, Ar–H), 7.87 (d, J = 2.7 Hz, 1H, Ar–H). Anal. calcd for C_{23}H_{29}ClF_{4}N_{2}O_{4}S: C: 51.44, H: 5.26, N: 5.22, S: 5.97; Found C: 51.13, H: 5.06, N: 5.07, S: 5.65.
3,4-Dimethoxy-N-[(1-[2-[(2,2,2-trifluoroethoxy)phenoxy]ethyl]piperidin-4-yl)methyl]benzenesulfonamide (12)

Compound 12 was prepared using intermediate 5 (150 mg, 0.45 mmol), TEA (0.19 mL, 1.35 mmol), and 3,4-dimethoxybenzenesulfonyl chloride (130 mg, 0.54 mmol). Yellow oil, 180 mg (isolated yield 77%); UPLC/MS purity 98%, t_R = 4.71. C_{24}H_{31}F_{3}N_{2}O_{6}S, MW 532.57, Monoisotopic Mass 532.19, [M + H]^+ 533.4. 1H-NMR (300 MHz, CDCl_3) δ 1.14–1.29 (m, 2H, piperidine), 1.46–1.54 (m, 1H, piperidine), 1.67 (d, J = 12.8 Hz, 2H, pyrrolidine), 2.11 (t, J = 11.0 Hz, 2H, piperidine), 2.77–2.80 (m, 2H), 2.82–2.86 (m, 2H, N–CH₂–CH₂), 3.02 (d, J = 11.5 Hz, 2H, NH–CH₂–CH₂), 3.91 (s, 3H, O–CH₃), 3.93 (s, 3H, O–CH₃), 4.12 (t, J = 5.6 Hz, 2H, O–CH₂–CH₂), 4.39 (q, J = 8.5 Hz, 2H, O–CH₂–CF₃), 4.68 (br.s., 1H, SO₂–NH–CH₂), 6.86–6.97 (m, 4H, Ar–H), 6.98–7.05 (m, 1H, Ar–H), 7.33 (d, J = 2.1 Hz, 1H, Ar–H), 7.46 (dd, J = 8.5, 2.2 Hz, 1H, Ar–H). Anal. calcd for C_{24}H_{31}F_{3}N_{2}O_{6}S: C: 54.13, H: 5.87, N: 5.26, S: 6.02; Found C: 54.33, H: 6.01, N: 5.45, S: 6.34.

(R)-4-Fluoro-N-[(1-[2-[(2,2,2-trifluoroethoxy)phenoxy]ethyl]pyrrolidin-3-yl)benzenesulfonamide (13)

Compound 13 was prepared using intermediate 6 (150 mg, 0.5 mmol), TEA (0.21 mL, 1.5 mmol), and 4-fluorobenzenesulfonyl chloride (120 mg, 0.6 mmol). Yellow oil, 150 mg (isolated yield 65%); UPLC/MS purity 95%, t_R = 5.07. C_{20}H_{22}F_{2}N_{2}O_{4}S, MW 462.46, Monoisotopic Mass 462.12, [M + H]^+ 463.3. 1H-NMR (300 MHz, CDCl_3) δ 1.52–1.64 (m, 2H, pyrrolidine), 2.09–2.11 (m 1H, pyrrolidine), 2.31–2.41 (m, 1H, pyrrolidine), 2.58–2.64 (m, 1H, pyrrolidine), 2.82–2.86 (m, 2H, pyrrolidine), 2.93 (td, J = 9.0, 4.3 Hz, 2H, NH–CH₂–CH₂), 4.06 (t, J = 1.0 Hz, 2H, O–CH₂–CH₂), 4.36 (q, J = 8.4 Hz, 2H, O–CH₂–CF₃), 5.11 (br.s., 1H, SO₂–NH–CH₂), 6.87–6.96 (m, 3H, Ar–H), 6.97–7.07 (m, 1H, Ar–H), 7.09–7.17 (m, 2H, Ar–H), 7.81–7.89 (m, 2H, Ar–H). 13C-NMR (75 MHz, CDCl_3) δ 29.1, 32.5, 52.7, 54.0, 60.8, 67.7, 115.3 (d, J = 131.3 Hz), 116.8 (d, J = 59.9 Hz), 121.6, 121.7, 124.1, 129.7 (d, J = 9.2 Hz), 148.3 (d, J = 155.5 Hz), 165.0 (d, J = 252.2 Hz). Anal. calcd for C_{20}H_{22}F_{2}N_{2}O_{4}S: C: 51.94, H: 4.80, N: 6.06, S: 6.93; Found C: 51.75, H: 4.64, N: 6.35, S: 6.97.

(S)-4-Fluoro-N-[(1-[2-[(2,2,2-trifluoroethoxy)phenoxy]ethyl]pyrrolidin-3-yl)benzenesulfonamide (14)

Compound 14 was prepared using intermediate 7 (150 mg, 0.5 mmol), TEA (0.21 mL, 1.5 mmol), and 4-fluorobenzenesulfonyl chloride (120 mg, 0.6 mmol). Yellow oil, 140 mg (isolated yield 61%); UPLC/MS purity 95%, t_R = 4.80. C_{20}H_{22}F_{2}N_{2}O_{4}S, MW 462.46, Monoisotopic Mass 462.12, [M + H]^+ 463.2. 1H-NMR (300 MHz, CDCl_3) δ 1.52–1.64 (m, 2H, pyrrolidine), 2.09–2.11 (m 1H, pyrrolidine), 2.31–2.41 (m, 1H, pyrrolidine), 2.58–2.64 (m, 1H, pyrrolidine), 2.82–2.86 (m, 2H, pyrrolidine), 2.93 (td, J = 9.0, 4.3 Hz, 2H, NH–CH₂–CH₂), 4.06 (t, J = 1.0 Hz, 2H, O–CH₂–CH₂), 4.36 (q, J = 8.4 Hz, 2H, O–CH₂–CF₃), 5.11 (br.s., 1H, SO₂–NH–CH₂), 6.87–6.96 (m, 3H, Ar–H), 6.97–7.07 (m, 1H, Ar–H), 7.09–7.17 (m, 2H, Ar–H), 7.81–7.89 (m, 2H, Ar–H). Anal. calcd for C_{20}H_{22}F_{2}N_{2}O_{4}S: C: 51.94, H: 4.80, N: 6.06, S: 6.93; Found C: 51.73, H: 4.62, N: 6.33, S: 6.95.

(R)-5-Chloro-2-fluoro-N-[(1-[2-[(2,2,2-trifluoroethoxy)phenoxy]ethyl]pyrrolidin-3-yl)benzenesulfonamide (15)

Compound 15 was prepared using intermediate 6 (150 mg, 0.5 mmol), TEA (0.21 mL, 1.5 mmol), and 5-chloro-2-fluorobenzenesulfonyl chloride (140 mg, 0.6 mmol). Yellow oil, 170 mg (isolated yield 68%); UPLC/MS purity 95%, t_R = 5.19. C_{20}H_{21}ClF_{4}N_{2}O_{4}S, MW 496.90, Monoisotopic Mass 496.08, [M + H]^+ 497.3. 1H-NMR (300 MHz, CDCl_3) δ 1.60–1.72 (m, 2H, pyrrolidine), 2.11–2.16 (m, 1H, pyrrolidine), 2.32–2.42 (m, 1H, pyrrolidine), 2.50–2.57 (m, 1H, pyrrolidine), 2.67–2.73 (m, 1H, pyrrolidine), 2.88 (dt, J = 8.0, 5.4 Hz, 2H, NH–CH₂–CH₂), 2.94–3.02 (m, 1H, pyrrolidine), 4.08 (t, J = 5.4 Hz, 2H, O–CH₂–CH₂), 4.34 (q, J = 8.3 Hz, 2H, O–CH₂–CF₃), 6.88–6.98 (m, 3H, Ar–H), 7.00–7.07 (m, 2H, Ar–H), 7.43 (ddd, J = 8.8, 4.3, 2.7 Hz, 1H, Ar–H), 7.87 (dd, J = 6.1, 2.7 Hz, 1H, Ar–H). Anal. calcd for C_{20}H_{21}ClF_{4}N_{2}O_{4}S: C: 48.34, H: 4.26, N: 5.64, S: 6.45; Found C: 48.47, H: 4.55, N: 5.99, S: 6.75.
(S)-5-Chloro-2-fluoro-N-(1-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)pyrrolidin-3-yl benzenesulfonamide (16)

Compound 16 was prepared using intermediate 7 (150 mg, 0.5 mmol), TEA (0.21 mL, 1.5 mmol), and 5-chloro-2-fluorobenzensulfonamide chloride (140 mg, 0.6 mmol). Yellow oil, 130 mg (isolated yield 55%); UPLC/MS purity 98%, \( t_R = 5.20 \). \( \text{C}_{29} \text{H}_{21} \text{ClF}_4 \text{N}_2 \text{O}_6 \text{S}, MW = 496.90, \) Monoisotopic Mass 496.08, \([\text{M + H}]^+ = 497.2. \) \(^{1} \text{H}-\text{NMR} (300 MHz, CDCl}_3 \) \( \delta = 1.60–1.72 \) (m, 2H, pyrrolidine), 2.07–2.20 (m, 1H, pyrrolidine), 2.31–2.41 (m, 1H, pyrrolidine), 2.51–2.57 (m, 1H, pyrrolidine), 2.65–2.70 (m, 1H, pyrrolidine), 2.79–2.90 (m, 2H, NH–CH), 2.92–3.00 (m, 1H, pyrrolidine), 3.95 (br. s., 1H, SO\(_2\)-NH–CH), 4.07 (t, \( J = 5.2 \) Hz, 2H, O–CH\(_2\)-CF\(_3\)), 4.34 (q, \( J = 8.2 \) Hz, 2H, O–CH\(_2\)-CF\(_3\)), 6.87–6.97 (m, 3H, Ar–H), 7.03 (t, \( J = 8.7 \) Hz, 2H, Ar–H), 7.40–7.46 (m, 1H, Ar–H), 7.86 (dd, \( J = 5.7, 2.2 \) Hz, 1H, Ar–H). Anal. calcd for \( \text{C}_{29} \text{H}_{21} \text{ClF}_4 \text{N}_2 \text{O}_6 \text{S}: \) C: 56.2, 60.8, 67.5, 67.7, 67.9, 109.5, 110.5, 114.4, 117.4, 120.9, 121.5, 124.0, 132.4, 147.3, 149.0, 152.4. Anal. calcd for \( \text{C}_{29} \text{H}_{21} \text{ClF}_4 \text{N}_2 \text{O}_6 \text{S}: \) C: 52.37, H: 5.39, N: 5.55, S: 6.35; Found C: 52.19, H: 5.18, N: 5.29, S: 6.09.

7.2. In Vitro Pharmacology

7.2.1. Determination of the Affinity of the Tested Compounds at the \( \alpha_1 \)- and \( \alpha_2 \)-ARs

The affinity of the obtained compounds was evaluated by radioligand-binding assays (the ability to displace \(^{3} \text{H}\)-Prazosin and \(^{3} \text{H}\)-Clonidine from \( \alpha_1 \)- and \( \alpha_2 \)-ARs, respectively) on rat cerebral cortex. The brains are homogenized in 20 volumes of an ice-cold 50 mM Tris-HCl buffer (pH 7.6) and is centrifuged (MPW Med. Instruments, Warsaw, Poland) at 20,000 \( g \) for 20 min (0–4 \( ^\circ \)C). The cell pellet is resuspended in the Tris-HCl buffer and centrifuged again. Radioligand-binding assays are performed in plates (MultiScreen/Millipore, Burlington, MA, USA). The final incubation mixture (final volume 300 \( \mu \)L) consisted of 240 \( \mu \)L of the membrane suspension, 30 \( \mu \)L of \(^{3} \text{H}\)-Prazosin (0.2 nM)
or [3H]-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 [3H]-Prazosin) and clonidine, and 10 µM (in the case of [3H]-Clonidine), were applied. The incubation was terminated by rapid filtration over glass fiber filters (Whatman GF/C, Sigma-Aldrich) using a vacuum manifold (Millipore). The filters were 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 (BioSurplus, San Diego, CA, USA). All the assays were made in duplicate.

7.2.2. Determination of the Affinity of the Tested Compounds at the 5-HT₁A and 5-HT₇Rs

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 MgCl₂. The 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-HT₁ARs) or 2 h (5-HT₇Rs) at 37 °C. Radioactivity was counted in MicroBeta2 scintillation counter (PerkinElmer, Waltham, MA, USA). Nonspecific binding is defined with 10 µM of 5-HT and 10 µM of methiothepine in 5-HT₁AR and 5-HT₇R binding experiments, respectively. Each compound was tested in screening assay at two final concentrations of 10 µM and 1 µM.

7.2.3. Determination of the Intrinsic Activity of the α₁A-ARs

Intrinsic activity assay was performed according to the manufacturer of the assay kit (Invitrogen, Thermo Fisher Scientific corporation, Carlsbad, CA, USA). The cells were harvested and suspended in Assay Medium to a density of 312,500 cells/mL. Of the cell suspension, 32 µL per well 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, were added to the cells. To perform an antagonist assay, 8 concentrations of 4 µL of the tested compound (10⁻⁴–10⁻¹¹M), e.g., in 10-fold higher concentration in comparison to the final tested concentration in the well, were added to the cells. Then, after 30 min, 4 µL of standard agonist in EC₈₀ (10-fold higher concentration in comparison to the EC₈₀ 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% CO₂ incubator for 5 h. After the incubation 8 µL of LiveBLAzer™-FRET B/G Substrate Mixture (CCF4-AM, Thermo Fisher Scientific corporation) was loaded cells in the absence of direct strong lighting, covered, and incubated at room temperature for 2 h.

7.2.4. Determination of the Intrinsic Activity of the α₁B- and α₁D-ARs

Intrinsic activity assay to α₁B- and α₁D-ARs was performed according to the manufacturer of the ready-to-use cells with stable expression of the α₁B-adrenoreceptors and α₁D-adrenoreceptors, respectively (PerkinElmer, Zaventem, Belgium). For measurement, cells (frozen, ready to use) were thawed and resuspended 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 ¼ white polystyrene area plates, and the cell suspension was dispensed in 50 µL volume on the ligands using the injector. The light emitted was recorded for 20 s. Cells with antagonist were incubated for 15 min at room temperature. Thereafter, 50 µL of agonist (3 × EC₈₀ final concentration) was injected into the mix of cells and antagonist and the light emitted was recorded for 20 s.
7.2.5. Determination of In Vitro Metabolic Stability

Metabolic stability of tested compound was analyzed using incubation systems, composed of: tested compounds (10 μM), RLMs (microsomes from rat male liver, pooled; 0.2 mg/mL; Sigma Aldrich), NADPH-regenerating system (NADP+, glucose-6-phosphate and glucose-6-phosphate dehydrogenase in 100 mM potassium buffer, pH 7.4; all from Sigma Aldrich), and potassium buffer, pH 7.4. Stock solution of tested compounds was prepared in methanol (the final methanol concentration in incubation mixture does not exceed 0.2%). Firstly, all samples contained incubation mixture (without NADPH-regenerating system) were preincubated in a thermoblock at 37 °C for 10 min. Then reaction was initiated by the addition of NADPH-regenerating system. In control samples NADPH-regenerating system was replaced with potassium buffer. Probes were incubated in thermoblock for 15 and 30 min at 37 °C. After addition of internal standard (levallorphan, 10 μM), the biotransformation process was stopped by addition of perchloric acid (69–72%, by volume). Next, samples were centrifuged (Centrifuge 5427 R, Eppendorf, Hamburg, Germany) and supernatants were analyzed using UPLC/MS (Waters Corporation). All experiments were run in duplicates. Half-life time was evaluated using a nonlinear regression model using Graph Pad Prism software (Graph Pad Software, La Jolla, San Diego, CA, USA) and intrinsic clearance was calculated from the equation Cl\text{int} = (volume of incubation [µL]/protein in the incubation [mg]) × 0.693/t\text{1/2} [33].

7.3. In Vivo Pharmacology

7.3.1. 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 a 12:12 h light/dark cycle; water and food were available ad libitum. Experimental groups consisted of 6 animals each. All experiments were conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals and were approved by the Animal Use and Care Committee of the Jagiellonian University (2012, Kraków, Poland).

7.3.2. Determination of the Effect of the Tested Compounds on Blood Pressure after a Single Administration in Rats

The normotensive rats were anesthetized with thiopental (70 mg/kg) by i.p. injection. The left carotid artery was cannulated with polyethylene tubing filled with heparin solution in saline to facilitate pressure measurements using PowerLab Apparatus (ADInstruments, Sydney, Australia). 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 the dose of 2 mg/kg b.w. Compounds were dissolved in water and administered intravenously. Initial blood pressure before administration of the tested compounds in all groups was similar.

7.3.3. Statistical Analysis

Statistical calculations were carried out with the GraphPad Prism 6 program (GraphPad Software). Results are given as the arithmetic means with standard deviation (SD). The statistical significance was calculated using a one-way ANOVA and posthoc Bonferroni Test in comparison to 0.9% NaCl. Differences were considered statistically significant at: *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

Supplementary Materials: Supporting Information Available: MS, 1H-NMR and 13C-NMR spectra for representative final compounds.

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Sample Availability: Samples of the compounds 2–18 are available from the authors.