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Synthesis and biological evaluation of (phenylpiperazinyl-propyl)arylsulfonamides as selective 5-HT$_{2A}$ receptor antagonists

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ABSTRACT

A novel series of 5-HT$_{2A}$ ligands that contain a (phenylpiperazinyl-propyl)arylsulfonamides skeleton was synthesized. Thirty-seven *N*-(cycloalkylmethyl)-4-methoxy-*N*-(3-(4-arylpiperazin-1-yl)propyl)-arylsulfonamide and *N*-(4-(4-arylpiperazin-1-yl)butan-2-yl)-arylsulfonamide compounds were obtained. The binding of these compounds to the 5-HT$_{2A}$, 5-HT$_{2C}$, and 5-HT$_7$ receptors was evaluated. Most of the compounds showed IC$_{50}$ values of less than 100 nM and exhibited high selectivity for the 5-HT$_{2A}$ receptor. Among the synthesized compounds, **16a** and **16d** showed good affinity at 5-HT$_{2A}$ (IC$_{50}$ = 0.7 nM and 0.5 nM) and good selectivity over 5-HT$_{2C}$ (50–100 times) and 5-HT$_7$ (1500–3000 times).

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has been recognized as an effector in various types of smooth muscle, as an agent that enhances platelet aggregation and a neurotransmitter in the central nervous system (CNS). As a major modulatory transmitter in the brain, 5-HT is involved in the control of numerous behavioral and physiological processes. Perceptive operational studies have revealed that 5-HT elicits these responses through at least 14 subtypes of 5-HT receptors.[1–3]

Today, there is evidence that 5-HT$_2$ receptors might be involved in schizophrenia, depression, anxiety, appetite control, and cardiovascular function. The three 5-HT$_2$ receptor family subtypes, 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$, are G-protein coupled receptors (GPCRs) that couple to the G_q and G_{11} proteins eliciting their second messenger effects through increases in the activity of phospholipase C (diacylglycerol pathway) and/or phospholipase A (arachidonic acid pathway). These subtypes share an overall amino acid homology of approximately 50%. 5-HT$_{2A}$ receptors are broadly distributed in the prefrontal, parietal, and somatosensory cortex, claustrum and platelets. The 5-HT$_{2A}$ receptor has been implicated as a therapeutic target for schizophrenia and depression.[4] 5-HT$_2$ receptors were first identified in 1979 and since the early 1980s, numerous, structurally diverse antagonists of this receptor have been published (Fig. 1).[5]

Classification of 5-HT$_{2A}$ ligands is difficult because they appear to belong to so many different chemical classes. The 2-aryltryptamine **1**, for example, is a new antagonist member of the indolealkylamine class. Eplivanserin (**2**), a phenylalkylamine is a highly selective 5-HT$_{2A}$ antagonist that has been shown to improve sleep maintenance, by reducing wake after sleep onset, decreasing the number of awakenings, increasing the total sleep time, and improving the quality of sleep. MDL-100907 (**3**) which is one of the more highly studied selective 5-HT$_{2A}$ antagonists is an arylpiperidine,[6,7] and fananserin (**4**) is a newer arylpiperazine antagonist.[8] Piperazine amides and sulfonamides, such as EMD-281014 (**5**)[9] and **6**, show high affinity as 5-HT$_{2A}$ antagonists.[10–12]

Several pharmacophore models for 5-HT$_{2A}$ receptors have been proposed based on the structure–activity relationships of known antagonists. Typically, the essential geometric characteristics are described by the distances between two aromatic rings (4.6–7.3 Å) and the distances between each aromatic ring and the basic amine nitrogen (5.2–8.4 Å and 5.7–8.5 Å). The reported pharmacophoric hypothesis suggested the minimal structural requirements for 5-HT$_{2A}$ antagonism consisted of two aryl rings and a basic nitrogen.[13] Based on our previous work,[14] we designed arylsulfonamide derivatives **11**–**24** and **28** to possess the arylpiperazine moieties as well as a three carbon spacer.

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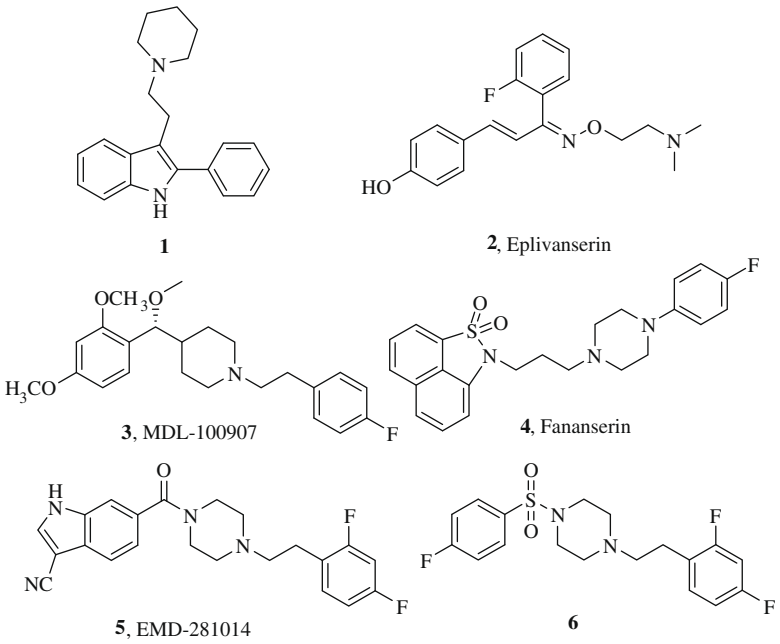


Figure 1. 5-HT_{2A} antagonists.

2. Results

2.1. Chemistry

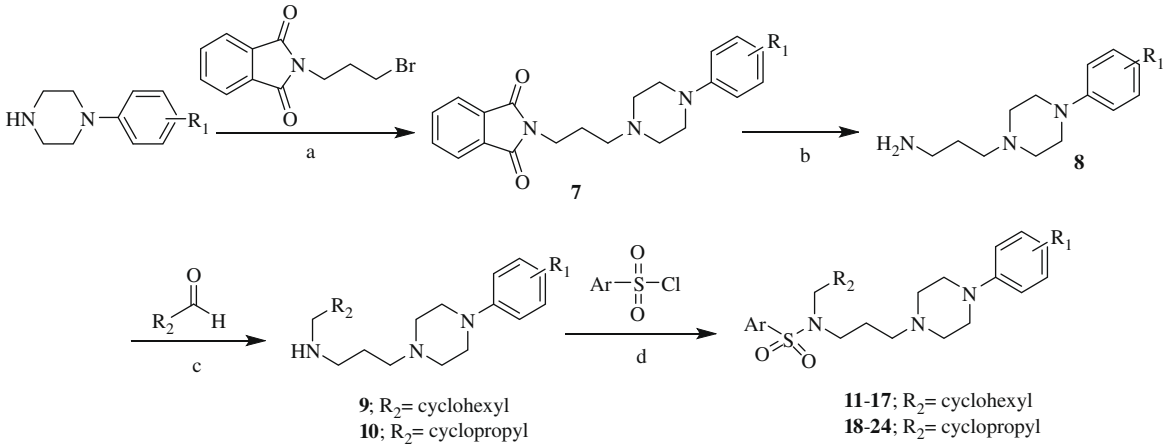
The synthetic procedures used to prepare arylsulfonamides **11**–**24** are illustrated in Scheme 1.

Substituted arylpiperazine was reacted with *N*-(3-bromopropyl)phthalimide and triethylamine to give 2-(3-(4-(R_1-phenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione **7a–d**. Hydrazine monohydrate was used to cleave N-alkylated phthalimide and 3-(4-(R_1-phenyl)piperazin-1-yl)propan-1-amine was produced. Then cyclohexyl/cyclopropylcarboxaldehyde were used to introduce a cycloalkyl group on the nitrogen of sulfonamide. Reductive amination took place between 3-(4-(R_1-phenyl)piperazin-1-yl)propan-1-amine **8a–d** and two kinds of aldehyde in the presence of sodium triacetoxyborohydride as a reducing agent. Lastly, *N*-(R_2-methyl)-3-(4-(R_1-phenyl)piperazin-1-yl)propan-1-amine **9a–d** and **10a–d** were converted to the desired sulfonamide derivatives **11**–**24** by nucleophilic displacement. Thirty-three compounds with different substituents such as 1-naphtyl, 2-naphtyl, 8-quinolinyl, 4-OCH_3 phenyl, 4-CF_3 phenyl, 4-F phenyl, and 4-NO_2 phenyl group were prepared and the structures of the synthesized compounds are given in Tables 1 and 2.

The sulfonamide derivatives which have a methyl group at the C-3 position of the three carbon spacer were synthesized using 1,3-butanediol as a space unit (Scheme 2). Mono-tosylation of 1,3-butanediol to 1-tosyl-3-hydroxy-butane followed by reaction with substituted arylpiperazine gave 4-(4-(*R*-phenyl)piperazin-1-yl)butan-2-ol **26a–d**. Further tosylation of the hydroxyl group of **26a–d** and substitution of the tosyl group with 2-naphthylsulfonamide was achieved to yield the desired compounds **28a–d** (Table 3).

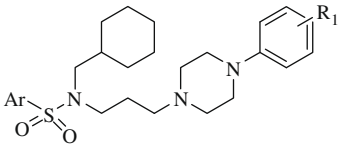
2.2. Biological evaluation

All the synthesized compounds were evaluated in vitro against the human recombinant 5-HT_{2A} serotonin receptor in stable CHO cell line. [^{3}H]Ketanserin binding assay results are shown in Tables 1–3. Most compounds showed good binding affinity to the 5-HT_{2A}



Scheme 1. Reagents and conditions: (a) TEA, CH_3CN, reflux, overnight; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 5 h; (c) $Na(OCOCH_3)_3BH$, CH_2Cl_2, rt, overnight; (d) NaH, DMF, 100 °C, overnight.

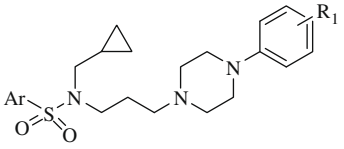
Table 1
Structure and IC_{50} values of the cyclohexylmethyl derivatives **11–17**



11-17

Compound	R_1	Ar	Binding affinity, IC_{50} (nM)		
			5-HT_{2A}	5-HT_{2C}	5-HT_7
11	H	1-Naphtyl	2.6	50.7	195
12	H	4-CF_3 Phenyl	7.1	156.2	456
13	H	4-F Phenyl	13.2	293.6	110
14	H	4-NO_2 Phenyl	4.2	45.7	87
15a	H	4-OCH_3 Phenyl	9.4	79	567
15b	2-OCH_3	4-OCH_3 Phenyl	16.3	200	172
15c	3-CF_3	4-OCH_3 Phenyl	19.5	33	678
15d	4-F	4-OCH_3 Phenyl	3.4	40	980
16a	H	2-Naphtyl	0.7	65	1236
16b	2-OCH_3	2-Naphtyl	11.6	70	500
16c	3-CF_3	2-Naphtyl	13.1	66	888
16d	4-F	2-Naphtyl	0.5	24	1508
17a	H	8-Quinolinyl	34.6	842.7	419
17b	2-OCH_3	8-Quinolinyl	59.9	117.9	24
17c	3-CF_3	8-Quinolinyl	29.1	38.8	160
17d	4-F	8-Quinolinyl	5.1	135.8	442
17e	3,4-Cl_2	8-Quinolinyl	7.7	66.5	2296

Table 2
Structure and IC_{50} values of the cyclopropylmethyl derivatives **18–24**



18-24

Compound	R_1	Ar	Binding affinity, IC_{50} (nM)		
			5-HT_{2A}	5-HT_{2C}	5-HT_7
18	H	1-Naphtyl	171	1459	152
19	H	4-CF_3 Phenyl	70.8	565	334
20	H	4-F Phenyl	142	1981	147
21	H	4-NO_2 Phenyl	180	1943	500
22a	H	4-OCH_3 Phenyl	136	691	121
22b	2-OCH_3	4-OCH_3 Phenyl	2210	1976	316
22c	3-CF_3	4-OCH_3 Phenyl	726	1034	124
22d	4-F	4-OCH_3 Phenyl	72.5	723	93
23a	H	2-Naphtyl	35.9	479	117
23b	2-OCH_3	2-Naphtyl	85.8	549	188
23c	3-CF_3	2-Naphtyl	221	304	342
23d	4-F	2-Naphtyl	51	343	49.6
24a	H	8-Quinolinyl	292	2159	749
24b	2-OCH_3	8-Quinolinyl	561	8312	12.3
24c	3-CF_3	8-Quinolinyl	75	694	6.3
24d	4-F	8-Quinolinyl	8.3	4755	35.3

receptor with IC_{50} values less than 100 nM. The synthesized 5-HT_{2A} antagonists showed different affinities to the 5-HT_{2A} receptor depending on the substitution on the nitrogen of sulfonamide, the piperazine, or the sulfonyl group. The most active compound (**16d**) had an IC_{50} value of 0.5 nM, which has 4-F phenyl substitution on the piperazine and 2-naphtyl substitution on the sulfonyl group of the cyclohexylmethyl containing compound. The synthesized compounds were further evaluated for their selectivity on the 5-HT_{2A} over the 5-HT_{2C} and 5-HT_7 receptor (Tables 1–3).

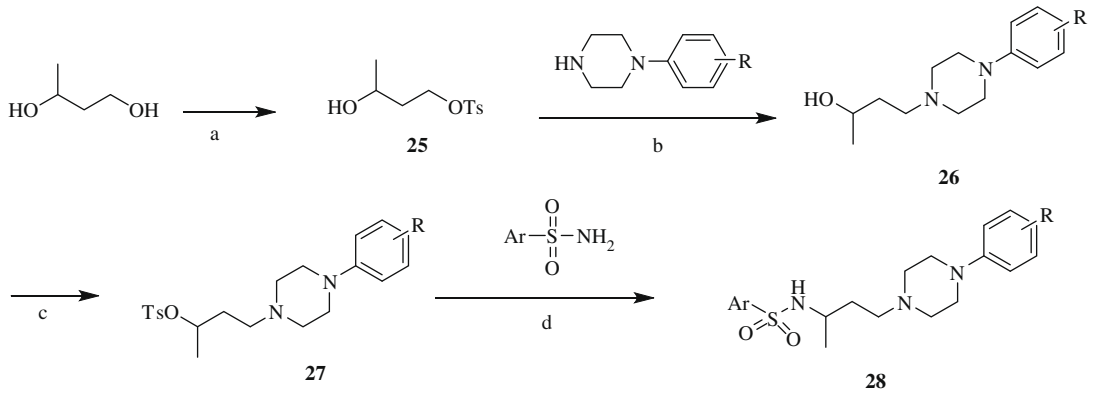
3. Discussion

It is well known that arylpiperazine-containing compounds can bind to at least three populations of neurotransmitter receptors (serotonergic, dopaminergic, and adrenergic). Therefore, the development of compounds that have good affinity and selectivity for the 5-HT_{2A} receptor as therapeutic agents and chemical tools is important. The structural diversity of 5-HT_{2A} ligands presents a challenge in terms of defining a pharmacophore model. However, as mentioned above, the pharmacophore models that have been proposed agree that two aryl rings and a basic nitrogen are required for binding at the receptor.[15] Therefore, on the basis of these pharmacophore models, we synthesized and evaluated (phenylpiperazinyl-propyl)arylsulfonamides. In order to obtain compounds that have good affinity and selectivity for 5-HT_{2A} receptor antagonism, we modified three parts of structure that are the cycloalkyl group, the phenylpiperazine group, and the arylsulfonamide group.

First of all, we explored the influence of different substituents at the first position, cyclohexylmethyl and cyclopropylmethyl group on the nitrogen of sulfonamide for 5-HT_{2A} receptor affinity. As a result, cyclohexylmethyl derivatives **11–17** showed increased affinity on the 5-HT_{2A} receptor with IC_{50} values ranging from 0.5 to 59.9 nM. Compared to our previous work, the introduction of cyclohexylmethyl group on the nitrogen of sulfonamide enhanced the 5-HT_{2A} receptor affinity. Compound **15d** (IC_{50} = 3.4 nM) exhibited better affinity than the previously reported compound 4-methoxy-*N*-{3-[4-(*p*-fluorophenyl)-piperazin-1-yl]-propyl}-benzene sulfonamide on the 5-HT_{2A} receptor (IC_{50} = 74 nM).[14] Also, when compared with cyclopropylmethyl derivatives, cyclohexylmethyl derivatives proved to have increased affinity against 5-HT_{2A} receptor with higher selectivity over 5-HT_7 receptor. Cyclopropylmethyl derivatives showed higher affinity than cyclohexylmethyl derivatives against 5-HT_7 receptor. Therefore, we could say that cyclohexylmethyl derivatives are more selective for the 5-HT_{2A} receptor. In the case of compound **16d**, this compound showed 3000 times higher affinity against 5-HT_{2A} over 5-HT_7 receptor. Among the synthesized compounds, **16a** and **16d** exhibited high 5-HT_{2A} receptor affinity (IC_{50} = 0.7 nM and 0.5 nM, respectively) and good selectivity over 5-HT_{2C} (IC_{50} = 65 nM and 24 nM, respectively) and 5-HT_7 (IC_{50} = 1236 nM and 1508 nM, respectively).

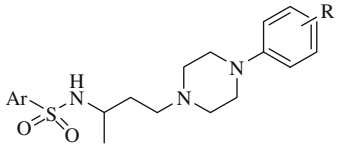
In subsequent experiments, we performed modification of the phenylpiperazine group by introduction of different substituted phenylpiperazines such as 2-OCH_3 phenylpiperazine (**b**), 3-CF_3 phenylpiperazine (**c**), and 4-F phenylpiperazine (**d**) to determine the optimal substituent on the piperazine. Compounds that had 1-phenylpiperazine (**a**) without any substituent demonstrated modest affinity. The introduction of 4-F phenyl group on the piperazine improved binding affinity to the 5-HT_{2A} receptor, with the exception of **23d** (**23a** >**23d**) as shown in compounds **15d** (IC_{50} = 3.4 nM), **16d** (IC_{50} = 0.5 nM), **17d** (IC_{50} = 5.1 nM), **22d** (IC_{50} = 72.5 nM), **24d** (IC_{50} = 3.4 nM), and **28d** (IC_{50} = 8.3 nM). The results led us to conclude that, among the phenylpiperazine derivatives, the compounds with a 4-F substituent were superior to others (R_1 = 2-OCH_3 and 3-CF_3) in terms of 5-HT_{2A} receptor affinity and selectivity over 5-HT_{2C} and 5-HT_7 receptor. In contrast, some 2-OCH_3 phenylpiperazine compounds showed good affinity against 5-HT_7 receptor (**17b**, **22b**, and **24b**). Concerning the substitution on the piperazine, our results are in accordance with the structure of other 5-HT_{2A} active agents as shown in Figure 1.

When seven substituents (1-naphtyl, 2-naphtyl, 8-quinolinyl, 4-OCH_3 phenyl, 4-CF_3 phenyl, 4-F phenyl, and 4-NO_2 phenyl) on the sulfonyl group were compared by keeping the phenylpiperazine unsubstituted (R_1 = H) and by keeping the cycloalkyl group on



Scheme 2. Reagents and conditions: (a) *p*-TsCl, pyridine, −20 °C, 30 min→−25 °C, 1 h; (b) CH_3CN, reflux, 16 h; (c) *p*-TsCl, pyridine, rt, 16 h; (d) NaH, DMF, 100 °C, overnight.

Table 3
Structure and IC_{50} values of the sulfonamide derivatives **28a–d**



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Compound	R	Ar	Binding affinity, IC_{50} (nM)		
			5-HT_{2A}	5-HT_{2C}	5-HT_7
28a	H	2-Naphtyl	12.7	200	657
28b	2-Methoxy	2-Naphtyl	664	539	316
28c	3-Trifluoromethyl	2-Naphtyl	180	942	363
28d	4-Fluoro	2-Naphtyl	6.2	90	526

the nitrogen of sulfonamide fixed (R_2 = cyclohexyl or cyclopropyl), the 2-naphthylsulfonamides generally exhibited increased affinity (**16a**; IC_{50} = 0.7 nM and **23a**; IC_{50} = 35.9 nM) than other derivatives.

A study was conducted regarding the impact of the methyl group at the C-3 position of the three carbon spacer between the arylpiperazine and the arylsulfonamide group on 5-HT_{2A}, 5-HT_{2c}, and 5-HT_7 receptor affinity. Four naphthalene-2-sulfonamide derivatives that had a methyl group at the C-3 position of the three carbon spacer (**28a–d**) were synthesized and showed good affinity to the 5-HT_{2A} receptor (Table 3). Among them, **28d** which have 4-F phenylpiperazine group exhibited the best 5-HT_{2A} receptor binding affinity. These compounds also presented good selectivity. Against the 5-HT_{2A} receptor, **28a** showed 16 and 50 times higher affinity than against the 5-HT_{2c} and the 5-HT_7 receptor, respectively (IC_{50} = 12.7 nM, 200 nM, and 657 nM, respectively), and **28d** showed 15 and 85 times higher affinity than against the 5-HT_{2c} and 5-HT_7 receptor, respectively (IC_{50} = 6.2 nM, 90 nM, and 526 nM, respectively).

4. Conclusion

Thirty-seven arylsulfonamides linked with a spacer to phenylpiperazine were synthesized and evaluated as 5-HT_{2A} antagonists. The synthesized compounds showed different affinity depending on the substitution on the nitrogen of sulfonamide, the piperazine, and the sulfonyl group. Compounds with a cyclohexylmethyl group on the nitrogen of sulfonamide showed better affinity and selectivity against 5-HT_{2A} receptor than compounds with a cyclopropylmethyl group. And compounds with 4-F phenylpiperazine and naphthalene-2-sulfonamide exhibited good affinity with IC_{50} values in the nanomolar range. Among the synthesized compounds, **16a** and **16d** showed good affinity against 5-HT_{2A} (IC_{50} = 0.7 nM and 0.5 nM) and good selectivity over 5-HT_{2C} (50–100 times) and 5-HT_7 (1500–3000 times).

5. Experimental

5.1. Materials and methods

All melting points of the synthesized compounds were taken in Pyrex capillaries using electrothermal digital melting point apparatus (Buchi) and were not corrected. ^1H NMR and ^{13}C NMR spectra were recorded on Varian FT-NMR 400 (or 300) and Bruker Advance 400 spectrometer. Mass spectral data were obtained on a Jeol JMS 700 high resolution mass spectrometer at the Korea Basic Science Institute (Daegu). Most of the reagents were purchased from Aldrich Chemical Company and Merck Company.

5.2. Procedures for the preparation of *N*-(R_2-methyl)-4-methoxy-*N*-(3-(4-(R_1-phenyl) piperazin-1-yl)propyl)-Ar-sulfonamides

5.2.1. General procedure for the preparation of 2-(3-(4-(R_1-phenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (7a–d)

To a solution of *N*-(3-bromopropyl)phthalimide (1.86 mmol, 1 equiv) in dry acetonitrile (30 mL) were added R_1-phenylpiperazine (1.86 mmol, 1 equiv) and triethylamine (3.72 mmol, 2 equiv) and the mixture was refluxed for 16 h. After cooling to room temperature, the mixture was quenched with water and extracted with methylene chloride (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo.

5.2.1.1. 2-(3-(4-Phenylpiperazin-1-yl)propyl)isoindoline-1,3-dione (7a). Light brown solid (83%), mp 126–127 °C: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, *J* = 2.8 Hz, 2H), 7.69 (dd, *J* = 3.2 Hz, 2H), 7.23 (t, *J* = 8.4 Hz, 3H), 6.84 (dd, *J* = 7.6 Hz, 2H), 3.80 (t, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 4.8 Hz, 4H), 2.55 (t, *J* = 4.8 Hz, 4H), 2.84 (t, *J* = 6.8 Hz, 2H), 1.95–1.88 (m, 2H).

5.2.1.2. 2-(3-(4-(2-(Methoxyphenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (7b). White solid (90%), mp 98 °C: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, *J* = 3.2 Hz, 2H), 7.70 (dd, *J* = 3.2 Hz, 2H), 6.97 (t, *J* = 6.8 Hz, 1H), 6.89 (t, *J* = 6.8 Hz, 1H), 6.83 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.92 (s, 4H), 2.58 (s, 4H), 2.49 (t, *J* = 6.8 Hz, 2H), 1.93–1.89 (m, 2H).

5.2.1.3. 2-(3-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (7c). Yellow oil (85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, J = 2.8 Hz, 2H), 7.69 (dd, J = 3.2 Hz, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.06–7.02 (m, 2H), 6.99 (d, J = 8.0 Hz, 1H), 3.80 (t, J = 6.8 Hz, 2H), 3.06 (t, J = 5.2 Hz, 4H), 2.54 (t, J = 5.2 Hz, 4H), 2.48 (t, J = 6.8 Hz, 2H), 1.92–1.89 (m, 2H).

5.2.1.4. 2-(3-(4-(4-Fluorophenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (7d). Pale yellow solid (80%), mp 93–94 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, J = 2.8 Hz, 2H), 7.69 (dd, J = 3.2 Hz, 2H), 6.93 (t, J = 8.0 Hz, 2H), 6.80 (dd, J = 4.4 Hz, 2H), 3.80 (t, J = 6.8 Hz, 2H), 2.96 (s, 4H), 2.55 (s, 4H), 2.49 (t, J = 6.8 Hz, 2H), 1.93–1.90 (m, 2H).

5.2.2. General procedure for the preparation of 3-(4-(R_1-phenyl)-piperazin-1-yl)propan-1-amine (8a–d)

A solution of 2-(3-(4-(R_1-phenyl)piperazin-1-yl)propyl)isoindoline-1,3-dione **7** (2 mmol, 1 equiv) and hydrazine monohydrate (6 mmol, 3 equiv) in EtOH (20 mL) was refluxed for 5 h. After cooling to room temperature, the mixture was alkalinized with 5% NaOH (pH 8), the organic solvents were evaporated under vacuum, and water was extracted with methylene chloride (3 × 20 mL). The organic layer was dried, Na_2SO_4 was filtered off, and the solvent was evaporated to dryness.

5.2.2.1. 3-(4-Phenylpiperazin-1-yl)propan-1-amine (8a). Pale yellow solid (42%), mp 75 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (t, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.85 (t, J = 7.6 Hz, 1H), 3.21 (t, J = 5.2 Hz, 4H), 2.79 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 5.2 Hz, 4H), 2.47 (t, J = 7.2 Hz, 2H), 1.72–1.65 (m, 2H), 1.35 (br s, 2H).

5.2.2.2. 3-(4-(2-Methoxyphenyl)piperazin-1-yl)propan-1-amine (8b). Yellow oil (94%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02–6.96 (m, 1H), 6.94–6.90 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.10 (s, 4H), 2.80 (t, J = 6.8 Hz, 2H), 2.67 (s, 4H), 2.49 (t, J = 7.2 Hz, 2H), 1.75–1.67 (m, 4H).

5.2.2.3. 3-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)propan-1-amine (8c). Yellow oil (59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (t, J = 8.0 Hz, 1H), 7.11 (s, 1H), 7.08–7.04 (m, 2H), 3.25 (t, J = 5.2 Hz, 4H), 2.82 (t, J = 6.8 Hz, 2H), 2.62 (t, J = 5.2 Hz, 4H), 2.49 (t, J = 7.2 Hz, 2H), 1.76–1.67 (m, 4H).

5.2.2.4. 3-(4-(4-Fluorophenyl)piperazin-1-yl)propan-1-amine (8d). Yellow oil (73%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (t, J = 8.4 Hz, 2H), 6.90–6.85 (m, 2H), 3.12 (t, J = 4.8 Hz, 4H), 2.81 (t, J = 6.4 Hz, 2H), 2.62 (t, J = 4.8 Hz, 4H), 2.48 (t, J = 7.2 Hz, 2H), 1.76–1.68 (m, 4H).

5.2.3. General procedure for the preparation of *N*-(R_2-methyl)-3-(4-(R_1-phenyl)piperazin-1-yl)propan-1-amine (9a–d and 10a–d)

3-(4-(R_1-phenylpiperazin-1-yl)propan-1-amine **8** (10 mmol, 1 equiv) and R_2-carboxaldehyde (10 mmol, 1 equiv) were mixed in methylene chloride (15 mL) and then treated with sodium triacetoxyborohydride 3.0 g (14 mmol, 1.4 equiv). The mixture was stirred at rt under a N_2 atmosphere for 16 h. The reaction mixture was quenched by adding aqueous satd $NaHCO_3$, and the mixture was extracted with methylene chloride (CH_2Cl_2). The CH_2Cl_2 extract was dried ($MgSO_4$), and the solvent was evaporated.

5.2.3.1. *N*-(Cyclohexylmethyl)-3-(4-phenylpiperazin-1-yl)propan-1-amine (9a). White solid (22%), mp 171–173 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.28 (br s, 1H), 7.30–7.26 (m, 3H), 6.90 (dd, J = 7.2 Hz, 2H), 3.22 (s, 4H), 3.14 (t, J = 7.6 Hz, 2H), 2.83 (s, 4H), 2.75–2.70 (m, 4H), 2.19–2.14 (m, 2H), 1.85 (d, J = 8.0 Hz, 2H), 1.73–1.64 (m, 4H), 1.31–1.20 (m, 2H), 1.14 (t, J = 12.0 Hz, 1H), 0.99 (q, J = 11.6 Hz, 2H).

5.2.3.2. *N*-(Cyclohexylmethyl)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-amine (9b). White solid (44%), mp 144–146 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.19 (br s, 1H), 7.05–7.00 (m, 1H), 6.93–6.90 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.13 (t, J = 5.2 Hz, 6H), 2.87 (s, 4H), 2.73 (dd, J = 10.0 Hz, 4H), 2.15–2.13 (m, 2H), 1.19 (d, J = 8.8 Hz, 3H), 1.76–1.67 (m, 4H), 1.31–1.24 (m, 2H), 1.03–0.99 (m, 2H).

5.2.3.3. *N*-(Cyclohexylmethyl)-3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-1-amine (9c). White solid (31%), mp 146–147 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.16 (br s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 4.0 Hz, 2H), 7.06 (d, J = 4.0 Hz, 1H), 3.26 (t, J = 4.8 Hz, 4H), 3.14 (t, J = 4.2 Hz, 2H), 2.83 (s, 4H), 2.75 (d, J = 4.2 Hz, 2H), 2.72 (t, J = 5.6 Hz, 2H), 2.21–2.15 (m, 2H), 1.88–1.83 (m, 3H), 1.73–1.64 (m, 3H), 1.30–1.20 (m, 2H), 1.17–1.11 (m, 1H), 1.03–0.97 (m, 2H).

5.2.3.4. *N*-(Cyclohexylmethyl)-3-(4-(4-fluorophenyl)piperazin-1-yl)propan-1-amine (9d). White solid (29%), mp 186–187 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.28 (br s, 1H), 6.97 (t, J = 8.8 Hz, 2H), 6.87 (dd, J = 4.8 Hz, 2H), 3.15–3.13 (m, 6H), 2.83 (s, 4H), 2.75–2.71 (m, 4H), 2.19–2.15 (m, 2H), 1.88–1.84 (m, 3H), 1.73–1.65 (m, 4H), 1.30–1.17 (m, 2H), 0.90 (q, J = 10.4 Hz, 2H).

5.2.3.5. *N*-(Cyclopropylmethyl)-3-(4-phenylpiperazin-1-yl)propan-1-amine (10a). Yellow oil (59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.24 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.90–6.84 (m, 1H), 3.24 (t, J = 4.8 Hz, 2H), 3.09 (s, 2H), 3.20 (t, J = 4.8 Hz, 2H), 2.79 (s, 2H), 2.73 (d, J = 8.0 Hz, 2H), 2.69 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 4.8 Hz, 2H), 2.46 (t, J = 6.8 Hz, 2H), 0.89–0.85 (m, 1H), 0.66 (q, J = 8.0 Hz, 2H), 0.32 (q, J = 4.8 Hz, 2H).

5.2.3.6. *N*-(Cyclopropylmethyl)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-amine (10b). Yellow oil (25%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08–7.03 (m, 1H), 6.93 (d, J = 4.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.34 (s, 4H), 3.20 (t, J = 6.0 Hz, 4H), 3.14 (s, 4H), 2.85 (d, J = 7.6 Hz, 2H), 2.43 (t, J = 5.6 Hz, 2H), 1.37–1.34 (m, 1H), 0.73 (q, J = 4.8 Hz, 2H), 0.46 (q, J = 5.2 Hz, 2H).

5.2.3.7. *N*-(Cyclopropylmethyl)-3-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)propan-1-amine (10c). Yellow oil (86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 4.0 Hz, 2H), 6.85 (d, J = 4.0 Hz, 1H), 3.26 (t, J = 7.4 Hz, 2H), 3.21 (t, J = 5.2 Hz, 4H), 3.02 (d, J = 6.8 Hz, 2H), 2.54 (t, J = 5.0 Hz, 4H), 2.43 (t, J = 7.2 Hz, 2H), 1.83–1.81 (m, 2H), 0.90–0.86 (m, 1H), 0.52 (q, J = 6.0 Hz, 2H), 0.18 (q, J = 5.2 Hz, 2H).

5.2.3.8. *N*-(Cyclopropylmethyl)-3-(4-(4-fluorophenyl)piperazin-1-yl)propan-1-amine (10d). Yellow oil (71%): ^{1}H ($CDCl_3$, 400 MHz) δ 6.99–6.95 (m, 2H), 6.89–6.86 (m, 2H), 3.16 (t, J = 4.8 Hz, 4H), 2.79 (s, 4H), 2.74–2.68 (m, 4H), 2.62 (t, J = 4.8 Hz, 2H), 2.09–2.07 (m, 2H), 0.88 (s, 1H), 0.66 (q, J = 7.2 Hz, 2H), 0.32 (q, J = 5.2 Hz, 2H).

5.2.4. General procedure for the preparation of *N*-(R_2-methyl)-4-methoxy-*N*-(3-(4-(R_1-phenyl)piperazin-1-yl)propyl)-Ar-sulfonamide (11–24)

For the further conversion to sulfonamides, sodium hydride (1 mmol, 2 equiv) was added to a suspension of *N*-(R_2-methyl)-3-(4-(R_1-phenyl)piperazin-1-yl)propan-1-amine **9** and **10** (0.5 mmol, 1 equiv) in DMF (5 mL). After stirring at 60 °C for 30 min under nitrogen, Ar-sulfonylchloride (0.75 mmol, 1.5 equiv) in DMF (5 mL) was added. The reaction mixture was stirred at 100 °C for

16 h. After cooling to rt, the mixture was quenched with satd $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography to give ethyl acetate.

5.2.4.1. *N*-(Cyclohexylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)naphthalene-1-sulfonamide (11). Transparent oil, 13.9 mg (14%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.62 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 17.2 Hz, 1H), 7.58 (t, J = 16.0 Hz, 1H), 7.53 (t, J = 15.9 Hz, 1H), 7.28–7.24 (m, 2H), 6.90 (d, J = 10.0 Hz, 2H), 6.85 (t, J = 14.8 Hz, 1H), 3.30 (t, J = 15.2 Hz, 2H), 3.17 (d, J = 7.6 Hz, 2H), 3.10 (t, J = 10.0 Hz, 4H), 2.36 (t, J = 10.0 Hz, 4H), 2.13 (t, J = 14.4 Hz, 2H), 1.66–1.59 (m, 7H), 1.16–1.06 (m, 4H), 0.83–0.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.46, 135.44, 134.58, 134.19, 130.17, 129.32, 129.06, 128.16, 126.97, 125.37, 124.29, 119.91, 116.21, 55.63, 53.36, 53.24, 49.26, 45.42, 36.01, 30.92, 29.92, 26.55, 25.97, 25.24. HR-FABMS Calcd for $C_{30}H_{40}N_3O_2S$ (M^++H): 506.2841, Found: 506.2846.

5.2.4.2. *N*-(Cyclohexylmethyl)-*N*-[3-(4-phenyl-piperazine)-propyl]-4-trifluoromethylbenzenesulfonamide (12). Yellow oil, 32.6 mg (11%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.29–7.24 (m, 2H), 6.92 (d, J = 10.0 Hz, 2H), 6.86 (t, J = 15.6 Hz, 1H), 3.20–3.16 (m, 6H), 2.98 (d, J = 9.2 Hz, 2H), 2.54 (t, J = 10.0 Hz, 4H), 2.34 (t, J = 12.8 Hz, 2H), 1.80–1.70 (m, 7H), 1.23–1.16 (m, 4H), 0.90–0.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.41, 129.30, 127.82, 127.05, 126.35, 125.90, 119.96, 116.21, 55.62, 55.37, 53.34, 49.27, 47.37, 36.61, 31.02, 29.90, 26.56, 26.51, 26.31. HR-FABMS Calcd for $C_{27}H_{37}F_3N_3O_2S$ (M^++H): 524.2559, Found: 524.2556.

5.2.4.3. *N*-(Cyclohexylmethyl)-*N*-[3-(4-phenyl-piperazine)-propyl]-4-fluorobenzenesulfonamide (13). White solid, 35.2 mg (14%), mp 88–90 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.80 (m, 2H), 7.26 (t, J = 16.0 Hz, 2H), 7.18 (t, J = 17.2 Hz, 2H), 6.93 (d, J = 10.0 Hz, 2H), 6.86 (t, J = 14.4 Hz, 1H), 3.19 (t, J = 10.0 Hz, 4H), 3.14 (d, J = 8.0 Hz, 2H), 2.95 (d, J = 7.6 Hz, 2H), 2.55 (t, J = 10.0 Hz, 4H), 2.35 (t, J = 14.4 Hz, 2H), 1.78–1.68 (m, 7H), 1.28–1.23 (m, 4H), 0.90–0.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.34, 151.46, 136.21, 136.18, 130.03, 129.94, 129.32, 119.93, 116.46, 116.21, 55.53, 53.39, 49.33, 47.34, 36.65, 31.03, 26.60, 26.34, 26.01. HR-FABMS Calcd for $C_{26}H_{37}FN_3O_2S$ (M^++H): 474.2591, Found: 474.2586.

5.2.4.4. *N*-(Cyclohexylmethyl)-*N*-[3-(4-phenylpiperazine)-propyl]-4-nitrobenzenesulfonamide (14). Yellow solid, 59.6 mg (23%), mp 82–87 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, J = 13.6 Hz, 2H), 7.99 (d, J = 13.6 Hz, 2H), 7.29–7.25 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.86 (t, J = 14.8 Hz, 1H), 3.23–3.17 (m, 6H), 3.00 (d, J = 7.2 Hz, 2H), 2.56 (t, J = 10.0 Hz, 4H), 2.36 (t, J = 14.0 Hz, 2H), 1.80–1.69 (m, 7H), 1.27–1.16 (m, 4H), 0.92–0.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.38, 150.03, 145.97, 129.32, 128.49, 124.46, 119.98, 116.20, 55.55, 55.36, 53.38, 49.31, 47.37, 36.57, 30.96, 26.51, 26.37, 25.94. HR-FABMS Calcd for $C_{26}H_{37}N_4O_4S$ (M^++H): 501.2536, Found: 501.2537.

5.2.4.5. *N*-(Cyclohexylmethyl)-4-methoxy-*N*-(3-(4-phenylpiperazin-1-yl)propyl)benzenesulfonamide (15a). Light brown solid, 45 mg (30%), mp 86–88 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 6.8 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 6.98 (d, J = 6.8 Hz, 2H), 6.91–6.87 (m, 3H), 3.86 (s, 3H), 3.46 (s, 4H), 3.14 (t, J = 6.8 Hz, 2H), 2.91–2.88 (m, 4H), 2.72 (d, J = 7.6 Hz, 2H), 2.12 (s, 2H), 1.70 (d, J = 7.6 Hz, 2H), 1.28–1.15 (m, 8H), 0.88–0.84 (m, 3H).. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.02, 150.37, 130.73, 129.59, 129.45, 120.86, 116.82, 114.44, 56.40, 55.82, 55.61, 52.49, 47.62, 36.77, 31.10, 29.90, 26.60, 25.94, 24.62. HR-FABMS Calcd for $C_{27}H_{40}N_3O_3S$ (M^++H): 486.2790, Found: 486.2795.

5.2.4.6. *N*-(Cyclohexylmethyl)-4-methoxy-*N*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)benzenesulfonamide (15b). Brown oil, 158 mg (88%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (dd, J = 7.2 Hz, 2H), 7.01–6.92 (m, 4H), 6.90 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.86 (s, 6H), 3.28 (s, 4H), 3.14 (t, J = 6.8 Hz, 2H), 2.88 (d, J = 4.0 Hz, 2H), 1.73–1.70 (m, 4H), 1.67 (m, 3H), 1.28–1.16 (m, 8H), 0.88–0.84 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.97, 152.27, 140.21, 130.83, 129.56, 123.78, 121.25, 118.80, 114.40, 111.41, 56.19, 55.90, 55.60, 52.95. HR-FABMS Calcd for $C_{28}H_{42}N_3O_4S$ (M^++H): 516.2896, Found: 516.2894.

5.2.4.7. *N*-(Cyclohexylmethyl)-4-methoxy-N-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)benzenesulfonamide (15c). Brown oil, 157 mg (58%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (dd, J = 9.2 Hz, 2H), 7.34 (t, J = 8.2 Hz, 1H), 7.11 (s, 1H), 7.06 (m, 2H), 6.97 (d, J = 4.4 Hz, 2H), 3.86 (s, 3H), 3.22 (t, J = 4.2 Hz, 4H), 3.13 (t, J = 7.6 Hz, 2H), 2.92 (d, J = 7.2 Hz, 2H), 2.56 (t, J = 4.8 Hz, 4H), 2.24 (t, J = 6.8 Hz, 2H), 1.80–1.72 (m, 6H), 1.68–1.55 (m, 5H), 1.226–1.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.83, 151.54, 131.70, 129.75, 129.48, 123.36, 118.84, 115.98, 114.29, 112.30, 112.26, 55.79, 55.74, 55.50, 53.15, 48.84, 47.44, 36.79, 31.10, 26.66, 26.40, 26.06. HR-FABMS Calcd for $C_{28}H_{39}F_3N_3O_3S$ (M^++H): 554.2664, Found: 554.2668.

5.2.4.8. *N*-(Cyclohexylmethyl)-*N*-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-methoxybenzenesulfonamide (15d). Brown solid, 62 mg (31%), mp 81–82 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (dd, J = 6.8 Hz, 2H), 6.98–6.94 (m, 4H), 6.89–6.85 (m, 2H), 3.86 (s, 3H), 3.14–3.09 (m, 4H), 2.96–2.88 (m, 4H), 2.55 (t, J = 4.8 Hz, 4H), 2.36 (t, J = 7.2 Hz, 2H), 1.80–1.72 (m, 4H), 1.28–1.22 (m, 5H), 0.89–0.84 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.82, 156.18, 148.16, 131.74, 129.48, 117.97, 117.90, 115.82, 115.60, 114.28, 55.79, 55.43, 53.39, 50.37, 47.44, 36.76, 31.09, 26.66, 26.40, 26.06. HR-FABMS Calcd for $C_{27}H_{39}FN_3O_3S$ (M^++H): 504.2696, Found: 504.2694.

5.2.4.9. *N*-(Cyclohexylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)naphthalene-2-sulfonamide (16a). White solid, 70 mg (37%), mp 124–126 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 7.96 (t, J = 8.8 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.4 Hz, 1H), 7.65–7.60 (m, 2H), 7.28–7.24 (m, 2H), 6.91–6.87 (m, 3H), 3.46 (t, J = 7.2 Hz, 4H), 3.24 (d, J = 6.8 Hz, 2H), 3.00 (s, 4H), 2.94 (d, J = 7.2 Hz, 2H), 2.17 (s, 2H), 1.70–1.55 (m, 8H), 1.19–1.14 (m, 3H), 0.88–0.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.06, 135.99, 134.96, 132.42, 129.64, 129.48, 128.96, 128.81, 128.07, 127.80, 122.85, 121.05, 116.94, 56.51, 55.50, 52.24, 47.61, 47.15, 36.76, 31.06, 26.564, 25.89, 24.14. HR-FABMS Calcd for $C_{30}H_{40}N_3O_2S$ (M^++H): 506.2841, Found: 506.2846.

5.2.4.10. *N*-(Cyclohexylmethyl)-*N*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (16b). Pale yellow solid, 23 mg (15%), mp 128–129 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 8.01–7.95 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.4 Hz, 1H), 7.67–7.59 (m, 2H), 7.06–7.00 (m, 1H), 6.91–6.81 (m, 3H), 3.87 (s, 3H), 3.49–3.31 (m, 6H), 2.27 (t, J = 6.8 Hz, 2H), 3.13–3.06 (m, 4H), 2.96 (d, J = 8.0 Hz, 2H), 1.71–1.44 (m, 8H), 1.17–1.15 (m, 3H), 0.90–0.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.25, 135.85, 135.01, 132.43, 129.69, 129.53, 129.01, 128.86, 128.09, 127.83, 124.29, 123.50, 122.79, 121.38, 119.05, 111.49, 56.53, 55.68, 52.88, 47.96, 47.48, 36.80,

31.08, 26.55, 25.89. HR-FABMS Calcd for $C_{31}H_{42}N_3O_3S$ (M^++H): 536.2947, Found: 536.2950.

5.2.4.11. *N*-(Cyclohexylmethyl)-*N*-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (16c). Pale yellow solid, 50 mg (24%), mp 74–75 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 7.98–7.94 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.8 Hz, 1H), 7.66–7.59 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.08–7.07 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 3.21 (t, J = 7.6 Hz, 2H), 3.15 (t, J = 5.2 Hz, 4H), 3.05 (d, J = 7.6 Hz, 2H), 2.48 (t, J = 5.2 Hz, 4H), 2.34 (t, J = 7.2 Hz, 2H), 1.77–1.59 (m, 8H), 1.22–1.17 (m, 3H), 0.93–0.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.52, 137.01, 134.87, 132.41, 129.73, 129.45, 129.37, 128.83, 128.66, 128.08, 127.71, 122.85, 118.83, 116.00, 112.27, 112.23, 55.63, 55.29, 53.06, 48.77, 47.19, 36.75, 31.07, 26.63, 26.22, 26.05. HR-FABMS Calcd for $C_{31}H_{39}F_3N_3O_2S$ (M^++H): 574.2715, Found: 574.2717.

5.2.4.12. *N*-(Cyclohexylmethyl)-*N*-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (16d). White solid, 140 mg (45%), mp 116–117 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 7.97 (t, J = 8.8 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.4 Hz, 1H), 7.66–7.59 (m, 2H), 7.00–6.93 (m, 2H), 6.87–6.83 (m, 2H), 3.24–3.18 (m, 6H), 3.00 (d, J = 3.2 Hz, 2H), 2.86–2.46 (m, 6H), 1.74–1.57 (m, 8H), 1.20–1.15 (m, 3H), 0.94–0.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.42, 147.57, 136.55, 134.88, 132.38, 129.51, 129.40, 128.87, 128.68, 128.06, 127.72, 122.81, 118.40, 118.33, 115.89, 115.67, 55.76, 55.61, 52.93, 49.44, 47.36, 36.73, 31.04, 26.58, 25.96, 25.42. HR-FABMS Calcd for $C_{30}H_{39}FN_3O_2S$ (M^++H): 524.2747, Found: 524.2742.

5.2.4.13. *N*-(Cyclohexylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)quinoline-8-sulfonamide (17a). Brown oil, 53.7 mg (10%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.06 (s, 1H), 8.51 (d, J = 9.2 Hz, 1H), 8.22 (d, J = 10.0 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.61 (t, J = 15.6 Hz, 1H), 7.52–7.49 (m, 1H), 7.26 (t, J = 16.0 Hz, 2H), 6.90 (d, J = 9.6 Hz, 2H), 6.85 (t, J = 14.8 Hz, 1H), 3.45 (t, J = 15.2 Hz, 2H), 3.32 (d, J = 7.6 Hz, 2H), 3.12 (t, J = 10.0 Hz, 4H), 2.42 (t, J = 10.0 Hz, 4H), 2.22 (t, J = 14.8 Hz, 2H), 1.69–1.63 (m, 8H), 1.13 (s, 3H), 0.89–0.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.40, 143.45, 137.70, 135.75, 132.32, 128.44, 128.25, 124.77, 121.23, 119.10, 115.37, 54.74, 52.32, 48.18, 46.15, 35.82, 30.09, 25.78, 25.15. HR-FABMS Calcd for $C_{29}H_{39}N_4O_2S$ (M^++H): 507.2794, Found: 507.2798.

5.2.4.14. *N*-(Cyclohexylmethyl)-*N*-[3-(4-(2-methoxyphenyl)-piperazin-1-yl)-propyl]quinoline-8-sulfonamide (17b). Yellow oil, 62 mg (22%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.07 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 10.0 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.60 (t, J = 15.6 Hz, 1H), 7.52–7.48 (m, 1H), 7.01–6.97 (m, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 7.6 Hz, 1H), 3.85 (s, 3H), 3.45 (t, J = 16.0 Hz, 2H), 3.32 (d, J = 7.6 Hz, 2H), 3.11–3.01 (m, 4H), 2.46–2.41 (m, 4H), 2.22 (t, J = 15.2 Hz, 2H), 1.94 (d, J = 14.4 Hz, 2H), 1.70–1.62 (m, 6H), 1.37–1.27 (m, 3H), 0.94–0.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.28, 152.15, 150.89, 144.09, 141.20, 138.36, 132.85, 129.97, 125.35, 122.33, 121.75, 121.45, 118.60, 111.06, 55.44, 53.34, 50.49, 46.58, 36.36, 31.83, 30.68, 27.01, 26.61, 26.12. HR-FABMS Calcd for $C_{30}H_{41}N_4O_3S$ (M^++H): 537.2899, Found: 537.2897.

5.2.4.15. *N*-(Cyclohexylmethyl)-*N*-[3-(4-(3-trifluoromethylphenyl)-piperazin-1-yl)-propyl]quinoline-8-sulfonamide (17c). Yellow oil, 105 mg (34%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.06 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 10.4 Hz, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.61 (t, J = 15.2 Hz, 1H), 7.52–7.49 (m, 1H), 7.08–6.70 (m, 4H), 3.47 (t, J = 15.2 Hz, 2H), 3.30 (d, J = 7.2 Hz, 2H), 3.17 (t, J = 9.6 Hz, 4H), 2.43 (t, J = 10.0 Hz, 4H), 2.25 (t, J = 14.8 Hz, 2H), 1.71–1.62 (m, 8H), 1.15–1.05 (m, 3H), 0.95–0.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.05, 144.02, 138.32, 136.34, 131.21, 129.14, 125.31, 121.80, 118.51, 115.56, 111.86, 55.29, 52.72, 48.40, 46.74, 36.43, 30.68, 26.36, 25.82. HR-FABMS Calcd for $C_{30}H_{38}F_3N_4O_2S$ (M^++H): 575.2668, Found: 575.2665.

5.2.4.16. *N*-(Cyclohexylmethyl)-*N*-[3-(4-(4-fluorophenyl)-piperazin-1-yl)-propyl]quinoline-8-sulfonamide (17d). Yellow oil, 112 mg (56%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.06 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 10.0 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.61 (t, J = 15.6 Hz, 1H), 7.52–7.49 (m, 1H), 6.95 (t, J = 17.6 Hz, 2H), 6.87–6.83 (m, 2H), 3.46 (t, J = 14.8 Hz, 2H), 3.30 (d, J = 7.6 Hz, 2H), 3.05 (t, J = 9.6 Hz, 4H), 2.43 (t, J = 10.0 Hz, 4H), 2.23 (t, J = 14.8 Hz, 2H), 1.71–1.64 (m, 8H), 1.16–1.08 (m, 3H), 0.94–0.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.44, 150.89, 147.85, 144.06, 138.37, 136.30, 132.87, 128.82, 125.33, 121.78, 117.61, 115.39, 55.30, 53.00, 49.97, 46.72, 36.41, 30.68, 29.62, 26.38, 25.88, 25.08. HR-FABMS Calcd for $C_{29}H_{38}FN_4O_2S$ (M^++H): 525.2700, Found: 525.2703.

5.2.4.17. *N*-(Cyclohexylmethyl)-*N*-[3-(4-(3,4-dichlorophenyl)-piperazin-1-yl)-propyl]quinoline-8-sulfonamide (17e). Brown solid, 132 mg (47%), mp 111–115 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.06 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 10.0 Hz, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.61 (t, J = 15.6 Hz, 1H), 7.52–7.49 (m, 1H), 7.26 (t, J = 8.8 Hz, 1H), 6.92 (s, 1H), 6.71 (d, J = 12.0 Hz, 1H), 3.47 (t, J = 15.2 Hz, 2H), 3.29 (d, J = 7.6 Hz, 2H), 3.10 (t, J = 10.0 Hz, 4H), 2.41 (t, J = 10.4 Hz, 4H), 2.25 (t, J = 14.4 Hz, 2H), 1.70–1.65 (m, 8H), 1.14–1.08 (m, 3H), 0.92–0.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.16, 150.83, 144.36, 138.70, 136.56, 133.15, 130.60, 129.12, 125.64, 122.06, 117.29, 115.40, 55.59, 52.93, 48.77, 47.10, 36.75, 30.98, 26.65, 26.23, 26.08. HR-FABMS Calcd for $C_{29}H_{37}Cl_2N_4O_2S$ (M^++H): 575.2014, Found: 575.2009.

5.2.4.18. *N*-(Cyclopropylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)-propyl)naphthalene-1-sulfonamide (18). Yellow oil, 133 mg (27%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.628 (d, J = 8.0 Hz, 1H), 8.22 (dd, J = 7.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 8.0 Hz, 2H), 6.90 (d, J = 4.8 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.45 (t, J = 7.4 Hz, 2H), 3.26 (d, J = 6.8 Hz, 2H), 3.10 (t, J = 5.0 Hz, 4H), 2.39 (t, J = 5.0 Hz, 4H), 2.18 (t, J = 6.8 Hz, 2H), 1.70–1.77 (m, 2H), 0.93–0.89 (m, 1H), 0.49 (q, J = 5.6 Hz, 2H), 0.16 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.59, 134.53, 133.55, 129.04, 128.44, 128.13, 127.31, 126.15, 124.46, 123.42, 119.01, 115.32, 54.76, 52.39, 50.65, 48.34, 44.26, 24.66, 9.11, 3.41. HR-FABMS Calcd for $C_{27}H_{34}N_3O_2S$ (M^++H): 464.2372, Found: 464.2375.

5.2.4.19. *N*-(Cyclopropylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)-propyl)-4-(trifluoromethyl)benzenesulfonamide (19). Yellow oil, 116 mg (31%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 9.2 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 3.34 (t, J = 7.6 Hz, 2H), 3.19 (t, J = 5.0 Hz, 4H), 3.12 (d, J = 6.8 Hz, 2H), 2.59 (t, J = 5.0 Hz, 4H), 2.41 (t, J = 7.2 Hz, 2H), 1.89–1.84 (m, 2H), 0.94–0.86 (m, 1H), 0.53 (q, J = 5.6 Hz, 2H), 0.21 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.57, 133.56, 130.23, 128.46, 128.14, 126.86, 125.45, 120.82, 119.08, 115.34, 54.77, 52.42, 48.42, 45.51, 25.61, 9.21, 3.50. HR-FABMS Calcd for $C_{24}H_{31}F_3N_3O_2S$ (M^++H): 482.2089, Found: 482.2090.

5.2.4.20. *N*-(Cyclopropylmethyl)-4-fluoro-*N*-(3-(4-phenylpiperazin-1-yl)propyl)benzenesulfonamide (20). Yellow oil, 119 mg (47%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85–7.81 (m, 2H), 7.26 (t, J = 8.8 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 6.93 (d, J = 7.6 Hz, 2H), 6.86

(t, J = 7.2 Hz, 1H), 3.31 (t, J = 7.2 Hz, 2H), 3.19 (t, J = 5.2 Hz, 4H), 3.08 (d, J = 6.8 Hz, 2H), 2.58 (t, J = 5.0 Hz, 4H), 2.41 (t, J = 7.2 Hz, 2H), 1.89–1.83 (m, 2H), 0.88–0.86 (m, 1H), 0.52 (q, J = 5.6 Hz, 2H), 0.19 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.87, 150.60, 135.77, 129.08, 128.37, 122.48, 115.68, 115.36, 54.85, 52.38, 48.43, 45.41, 25.59, 9.18, 3.47. HR-FABMS Calcd for $C_{23}H_{31}FN_3O_2S$ (M^++H): 432.2121, Found: 432.2124.

5.2.4.21. *N*-(Cyclopropylmethyl)-4-nitro-*N*-(3-(4-phenylpiperazin-1-yl)propyl)benzenesulfonamide (21). Brown oil, 103 mg (41%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J = 6.8 Hz, 1H), 8.35 (d, J = 6.8 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.86 (t, J = 6.0 Hz, 1H), 3.37 (t, J = 7.4 Hz, 2H), 3.19 (t, J = 5.2 Hz, 4H), 3.14 (d, J = 6.8 Hz, 2H), 2.58 (t, J = 5.0 Hz, 4H), 2.42 (t, J = 7.0 Hz, 2H), 1.89–1.85 (m, 2H), 0.88–0.84 (m, 1H), 0.54 (q, J = 5.6 Hz, 2H), 0.21 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.40, 150.01, 146.51, 129.29, 128.37, 124.49, 119.92, 116.17, 55.53, 53.41, 53.14, 49.30, 46.43, 26.49, 10.01, 4.39. HR-FABMS Calcd for $C_{23}H_{31}N_4O_4S$ (M^++H): 459.2066, Found: 459.2071.

5.2.4.22. *N*-(Cyclopropylmethyl)-4-methoxy-*N*-(3-(4-phenylpiperazin-1-yl)propyl)benzenesulfonamide (22a). Yellow oil, 119 mg (43%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 6.8 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 6.97–6.92 (m, 4H), 6.85 (t, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.29 (t, J = 7.4 Hz, 2H), 3.19 (t, J = 1.0 Hz, 4H), 3.05 (d, J = 6.8 Hz, 2H), 2.58 (t, J = 5.0 Hz, 4H), 2.41 (t, J = 7.2 Hz, 2H), 1.88–1.81 (m, 2H), 0.90–0.86 (m, 1H), 0.51 (q, J = 5.6 Hz, 2H), 0.18 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.93, 150.62, 131.24, 128.50, 128.44, 119.01, 115.32, 113.45, 54.92, 52.54, 52.20, 48.42, 45.36, 25.59, 9.23, 3.44. HR-FABMS Calcd for $C_{24}H_{34}N_3O_3S$ (M^++H): 444.2321, Found: 444.2318.

5.2.4.23. *N*-(Cyclopropylmethyl)-4-methoxy-*N*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)benzenesulfonamide (22b). Pale yellow solid, 138 mg (88%), mp 92–93 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 7.0 Hz, 2H), 7.02–6.91 (m, 5H), 6.86 (d, J = 8.0 Hz, 1H), 3.86 (s, 6H), 3.29 (t, J = 7.4 Hz, 2H), 3.08 (s, 4H), 3.06 (d, J = 6.8 Hz, 2H), 2.62 (s, 4H), 2.42 (t, J = 7.2 Hz, 2H), 1.87–1.80 (m, 2H), 0.91–0.86 (m, 1H), 0.51 (q, J = 5.6 Hz, 2H), 0.19 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.74, 152.44, 141.50, 132.19, 129.33, 123.05, 121.14, 118.31, 114.27, 111.38, 55.88, 55.73, 55.53, 53.60, 52.93, 50.81, 46.21, 26.37, 10.06, 4.26. HR-FABMS Calcd for $C_{25}H_{36}N_3O_4S$ (M^++H): 474.2427, Found: 474.2430.

5.2.4.24. *N*-(Cyclopropylmethyl)-4-methoxy-*N*-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)benzenesulfonamide (22c). Brown oil, 314 mg (48%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 6.8 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.10–7.04 (m, 3H), 6.96 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.29 (t, J = 7.4 Hz, 2H), 3.23 (t, J = 5.2 Hz, 4H), 3.05 (d, J = 6.8 Hz, 2H), 2.58 (t, J = 5.0 Hz, 4H), 2.43 (t, J = 7.2 Hz, 2H), 1.83–1.81 (m, 2H), 0.90–0.86 (m, 1H), 0.52 (q, J = 6.0 Hz, 2H), 0.18 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.76, 151.50, 132.01, 131.62, 131.31, 129.67, 129.28, 118.75, 115.83, 115.79, 114.26, 112.13, 112.09, 55.69, 55.63, 53.10, 53.05, 48.71, 46.17, 26.41, 10.03, 4.24. HR-FABMS Calcd for $C_{25}H_{33}F_3N_3O_3S$ (M^++H): 512.2195, Found: 512.2193.

5.2.4.25. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)-4-methoxybenzenesulfonamide (22d). Yellow oil, 121 mg (31%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 9.6 Hz, 2H), 6.98–6.93 (m, 4H), 6.90–6.85 (m, 2H), 3.86 (s, 3H), 3.29 (t, J = 7 4 Hz, 2H), 3.11 (t, J = 5.0 Hz, 4H), 3.05 (d, J = 6.8 Hz, 2H), 2.58 (t, J = 5.0 Hz, 4H), 2.42 (t, J = 7.2 Hz, 2H), 1.88–1.80 (m, 2H), 0.90–0.85 (m, 1H), 0.51 (q, J = 6.0 Hz, 2H), 0.18 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.66, 158.29, 155.92, 148.06, 131.95, 129.19, 117.75, 117.70, 115.61, 115.39, 114.19, 55.63, 53.24, 52.93, 50.12, 46.11, 26.34, 9.96, 4.17. HR-FABMS Calcd for $C_{24}H_{33}FN_3O_3S$ (M^++H): 462.2227, Found: 462.2223.

5.2.4.26. *N*-(Cyclopropylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)naphthalene-2-sulfonamide (23a). Yellow oil, 165 mg (38%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.395 (s, 1H), 7.97–7.93 (m, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (dd, J = 8.8 Hz, 1H), 7.65–7.58 (m, 2H), 7.26 (t, J = 7.2 Hz, 2H), 6.91 (d, J = 7.6 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.38 (t, J = 7.6 Hz, 2H), 3.16–3.13 (m, 6H), 2.53 (t, J = 5.0 Hz, 4H), 2.40 (t, J = 8.8 Hz, 2H), 1.89–1.81 (m, 2H), 0.94–0.87 (m, 1H), 0.51 (q, J = 5.6 Hz, 2H), 0.20 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.29, 137.21, 134.65, 132.22, 129.11, 128.47, 127.71, 122.57, 119.66, 115.99, 55.56, 53.19, 49.07, 46.07, 26.26, 10.01, 4.17. HR-FABMS Calcd for $C_{27}H_{34}N_3O_2S$ (M^++H): 464.2372, Found: 464.2375.

5.2.4.27. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (23b). Brown solid, 134 mg (29%), mp 90–91 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (s, 1H), 7.98–7.93 (m, 2H), 7.90 (d, J = 7.0 Hz, 1H), 7.79 (dd, J = 8.8 Hz, 1H), 7.65–7.60 (m, 2H), 7.02–6.99 (m, 1H), 6.91 (d, J = 4.6 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.38 (t, J = 7.6 Hz, 2H), 3.15 (d, J = 6.8 Hz, 2H), 3.05 (s, 4H), 2.58 (s, 4H), 2.41 (t, J = 7.2 Hz, 2H), 1.88–1.83 (m, 2H), 0.91 (m, 1H), 0.51 (q, J = 5.6 Hz, 2H), 0.20 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.47, 141.46, 137.43, 134.85, 132.43, 129.49, 129.39, 128.78, 128.53, 128.07, 127.66, 123.12, 122.78, 121.18, 118.39, 111.40, 55.85, 55.56, 53.59, 53.00, 50.74, 46.26, 26.34, 10.17, 4.33. HR-FABMS Calcd for $C_{28}H_{36}N_3O_3S$ (M^++H): 494.2477, Found: 494.2476.

5.2.4.28. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (23c). Brown oil, 302 mg (53%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (s, 1H), 7.97–7.94 (m, 2H), 7.91 (d, J = 8.8 Hz, 1H), 7.79 (dd, J = 8.8 Hz, 1H), 7.66–7.59 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.08–7.06 (m, 2H), 7.04 (d, J = 8.8 Hz, 1H), 3.38 (t, J = 7.4 Hz, 2H), 3.19–3.15 (m, 6H), 2.53 (t, J = 5.0 Hz, 4H), 2.41 (t, J = 7.4 Hz, 2H), 1.89–1.83 (m, 2H), 0.93–0.89 (m, 1H), 0.45 (q, J = 5.6 Hz, 2H), 0.20 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.68, 136.53, 133.95, 131.51, 130.57, 128.66, 127.79, 127.03, 125.57, 121.87, 117.93, 114.88, 111.20, 54.68, 52.19, 47.78, 45.31, 25.52, 9.34, 3.46. HR-FABMS Calcd for $C_{28}H_{33}F_3N_3O_2S$ (M^++H): 532.2246, Found: 532.2247.

5.2.4.29. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)naphthalene-2-sulfonamide (23d). Brown oil, 211 mg (40%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 7.97–7.93 (m, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (dd, J = 8.8 Hz, 1H), 7.66–7.59 (m, 2H), 6.96 (t, J = 7.2 Hz, 2H), 6.87–6.84 (m, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.15 (d, J = 6.8 Hz, 2H), 3.07 (t, J = 4.8 Hz, 4H), 2.54 (t, J = 4.8 Hz, 4H), 2.41 (t, J = 7.4 Hz, 2H), 1.87–1.83 (m, 2H), 0.90–0.88 (m, 1H), 0.51 (q, J =5.2 Hz, 2H), 0.20 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.99, 147.29, 136.51, 133.96, 131.52, 128.57, 127.78, 127.03, 121.87, 117.00, 114.79, 54.79, 52.32, 49.35, 45.37, 25.55, 9.32, 3.48. HR-FABMS Calcd for $C_{27}H_{33}FN_3O_2S$ (M^++H): 482.2278, Found: 482.2280.

5.2.4.30. *N*-(Cyclopropylmethyl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)quinoline-8-sulfonamide (24a). Yellow oil, 106 mg (30%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.4 Hz, 1H), 8.50 (dd, J = 7.2 Hz, 1H), 8.22 (dd, J = 8.4 Hz, 1H), 8.00 (dd, J = 8.0 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.50 (dd, J = 8.4 Hz, 1H), 7.26 (t, J=6.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.62 (t, J = 7.6 Hz, 2H), 3.38 (d, J = 6.8 Hz, 2H), 3.15

(t, J = 5.0 Hz, 4H), 2.50 (t, J = 5.0 Hz, 4H), 2.34 (t, J = 7.4 Hz, 2H), 1.83–1.80 (m, 2H), 0.86 (m, 1H), 0.40 (q, J = 5.2 Hz, 2H), 0.14 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.60, 150.29, 143.47, 137.94, 135.72, 132.21, 130.60, 128.35, 127.14, 123.54, 119.22, 117.35, 56.60, 52.50, 47.66, 43.71, 25.58, 9.62, 3.35. HR-FABMS Calcd for $C_{26}H_{33}N_4O_2S$ (M^++H): 465.2324, Found: 465.2328.

5.2.4.31. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(2-methoxyphenyl)-piperazin-1-yl)propyl)quinoline-8-sulfonamide (24b). Brown oil, 117 mg (27%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.4 Hz, 1H), 8.50 (dd, J = 7.6 Hz, 1H), 8.21 (dd, J = 8.4 Hz, 1H), 8.00 (dd, J = 8.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.50 (q, J = 4.0 Hz, 1H), 7.01–6.97 (m, 1H), 6.93–6.90 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.60 (t, J = 7.6 Hz, 2H), 3.39 (d, J = 7.2 Hz, 2H), 3.04 (s, 4H), 2.53 (s, 4H), 2.33 (t, J = 7.6 Hz, 2H), 1.82–1.78 (m, 2H), 0.87 (m, 1H), 0.41 (q, J = 5.2 Hz, 2H), 0.15 (q, J = 5.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.26, 150.93, 144.08, 141.28, 138.54, 136.41, 132.85, 128.91, 125.38, 122.87, 121.88, 120.94, 118.11, 111.18, 55.77, 55.35, 53.34, 50.57, 46.50, 26.19, 10.31, 4.01. HR-FABMS Calcd for $C_{27}H_{35}N_4O_3S$ (M^++H): 495.2430, Found: 495.2433.

5.2.4.32. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)quinoline-8-sulfonamide (24c). Dark brown oil, 473 mg (32%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.0 Hz, 1H), 8.50 (dd, J = 7.2 Hz, 1H), 8.22 (dd, J = 8.4 Hz, 1H), 8.01 (dd, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.43 (q, J = 4.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.09–7.03 (m, 2H), 3.63 (t, J = 7.6 Hz, 2H), 3.37 (d, J = 6.8 Hz, 2H), 3.19 (t, J = 5.2 Hz, 4H), 2.50 (t, J = 5.2 Hz, 4H), 2.35 (t, J = 7.6 Hz, 2H), 1.86–1.79 (m, 2H), 0.88–0.82 (m, 1H), 0.40 (q, J = 4.8 Hz, 2H), 0.13 (q, J = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.33, 150.93, 144.05, 138.49, 136.44, 132.87, 131.22, 129.54, 128.92, 125.72, 125.36, 123.01, 120.31, 118.57, 115.54, 111.85, 55.59, 52.86, 48.46, 46.51, 26.27, 10.28, 4.00. HR-FABMS Calcd for $C_{27}H_{32}F_3N_4O_2S$ (M^++H): 533.2198, Found: 533.2195.

5.2.4.33. *N*-(Cyclopropylmethyl)-*N*-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)quinoline-8-sulfonamide (24d). Brown oil, 443 mg (41%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.0 Hz, 1H), 8.50 (dd, J = 7.2 Hz, 1H), 8.22 (dd, J = 8.4 Hz, 1H), 8.00 (dd, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.50 (q, J = 4.0 Hz, 1H), 6.97 (m, 2H), 6.87–6.84 (m, 2H), 3.62 (t, J = 7.6 Hz, 2H), 3.38 (d, J = 8.0 Hz, 2H), 3.07 (t, J = 5.2 Hz, 4H), 2.50 (t, J = 5.2 Hz, 4H), 2.34 (t, J = 7.6 Hz, 2H), 1.85–1.80 (m, 2H), 0.87–0.83 (m, 1H), 0.39 (q, J = 4.8 Hz, 2H), 0.13 (q, J = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.83, 154.70, 150.24, 147.27, 147.25, 143.33, 137.76, 135.77, 132.35, 128.22, 124.65, 121.23, 116.93, 114.69, 54.90, 52.48, 52.37, 49.22, 45.79, 25.54, 9.61, 3.32. HR-FABMS Calcd for $C_{26}H_{32}FN_4O_2S$ (M^++H): 483.2230, Found: 483.2227.

5.3. Procedures for the preparation of *N*-(4-(4-(R_1-phenyl)piperazin-1-yl)butan-2-yl)-Ar-sulfonamides

5.3.1. General procedure for the preparation of 2-hydroxy-4-tosyl-butane (25)

p-Toluenesulfonyl chloride (72 mmol, 1.1 equiv) in 30 mL of pyridine was added dropwise to the solution of 1,3-butanediol (0.68 mmol, 1 equiv) in 2 mL pyridine at −20 °C. The mixture was stirred at −25 °C for 1 h. Pyridine was removed. The reaction mixture was extracted with chloroform and water. The organic layer was washed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude oil was purified by column chromatography with ethyl acetate.

5.3.1.1. 2-Hydroxy-4-tosyl-butane (25). Yellow oil (51%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.27–4.09 (m, 2H), 3.96–3.94 (m, 1H), 2.45 (s, 3H), 1.84–1.67 (m, 2H), 1.19 (d, J = 6.4 Hz, 3H).

5.3.2. General procedure for the preparation of 4-(4-(*R*-phenyl)piperazin-1-yl)butan-2-ol (26a–d)

1-Tosyl-3-hydroxybutane **25** (0.5 mmol, 1 equiv) and *R*-phenylpiperazine (0.75 mmol, 1.5 equiv) were refluxed in acetonitrile (25 mL) for 16 h under nitrogen. After cooling to rt, the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and washed with satd $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude oil was purified by column chromatography (ethyl acetate/methanol = 1:1).

5.3.2.1. 4-(4-(1-Phenylpiperazin-1-yl)butan-2-ol (26a). Pale yellow solid (96%), mp 107 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.24 (m, 3H), 6.91 (d, J = 7.0 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 4.02–3.97 (m, 1H), 3.22–3.19 (m, 4H), 2.85–2.62 (m, 4H), 2.61–2.54 (m, 2H), 1.71–1.52 (m, 2H), 1.19 (d, J = 6.0 Hz, 3H).

5.3.2.2. 4-(4-(2-Methoxyphenyl)piperazin-1-yl)butan-2-ol (26b). Yellow oil (88%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03–6.99 (m, 1H), 6.92–6.90 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 4.03–3.99 (m, 1H), 3.86 (s, 3H), 3.13 (s, 4H), 2.92 (s, 2H), 2.73 (s, 4H), 1.26 (t, J = 7.2 Hz, 2H), 1.20 (d, J = 6.4 Hz, 3H).

5.3.2.3. 4-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)butan-2-ol (26c). Yellow oil (73%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (t, J = 8.0 Hz, 1H), 7.10–7.03 (m, 3H), 4.02–3.97 (m, 1H), 3.28–3.21 (m, 4H), 2.85–2.60 (m, 4H), 2.59–2.53 (m, 2H), 1.74–1.52 (m, 2H), 1.19 (d, J = 6.0 Hz, 3H).

5.3.2.4. 4-(4-(4-Fluorophenyl)piperazin-1-yl)butan-2-ol (26d). Pale yellow solid (41%), mp 94–96 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99–6.93 (m, 2H), 6.88–6.84 (m, 2H), 4.02–3.97 (m, 1H), 3.15–3.12 (m, 4H), 2.87–2.62 (m, 4H), 2.61–2.56 (m, 2H), 1.74–1.52 (m, 2H), 1.19 (d, J = 6.0 Hz, 3H).

5.3.3. General procedure for the preparation of 4-(4-(*R*-phenyl)-piperazin-1-yl)butan-2-yl-4-methyl benzenesulfonate (27a–d)

p-Toluenesulfonyl chloride (0.75 mmol, 1.5 equiv) in 10 mL of pyridine was added to a pyridine solution of 4-(4-(*R*-phenyl)piperazin-1-yl)butan-2-ol **26** (0.5 mmol, 1 equiv) at rt. The mixture was stirred at rt for 16 h. The reaction mixture was quenched with water and extracted with chloroform. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel with ethyl acetate to give 4-(4-(*R*-phenyl)piperazin-1-yl)butan-2-yl-4-methylbenzenesulfonate.

5.3.3.1. 4-(4-1-Phenylpiperazin-1-yl)butan-2-yl 4-methylbenzenesulfonate (27a). Yellow oil (31%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 4.77–4.72 (m, 1H), 3.13 (t, J = 4.8 Hz, 4H), 2.51–2.42 (m, 7H), 2.35–2.28 (m, 2H), 1.89–1.70 (m, 2H), 1.30 (d, J = 6.0 Hz, 3H).

5.3.3.2. 4-(4-(2-Methoxyphenyl)piperazin-1-yl)butan-2-yl 4-methylbenzenesulfonate (27b). Yellow oil (52%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.02–6.98 (m, 1H), 6.94–6.90 (m, 2H), 4.76–4.70 (m, 1H), 3.86 (s, 3H), 3.14–3.09 (m, 2H), 3.06–3.02 (m,

4H), 2.54–2.49 (m, 4H), 2.44 (s, 3H), 1.59 (d, J = 6.4 Hz, 2H), 1.32 (d, J = 6.4 Hz, 3H).

5.3.3.3. 4-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)butan-2-yl-4-methylbenzenesulfonate (27c). Yellow oil (34%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 6.4 Hz, 2H), 7.36–7.32 (m, 3H), 7.80–7.03 (m, 3H), 4.76 (q, J = 6.4 Hz, 1H), 3.17 (t, J = 5.2 Hz, 4H), 2.51–2.45 (m, 7H), 2.34 (q, J = 7.2 Hz, 2H), 1.30 (d, J = 6.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 2H).

5.3.3.4. 4-(4-(4-Fluorophenyl)piperazin-1-yl)butan-2-yl-4-methylbenzenesulfonate (27d). Yellow oil (22%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.96 (t, J = 8.4 Hz, 2H), 6.86 (dd, J = 4.8 Hz, 2H), 4.77–4.72 (m, 1H), 3.05 (t, J = 4.8 Hz, 4H), 2.50–2.47 (m, 4H), 2.45 (s, 3H), 2.36–2.29 (m, 2H), 1.56–1.54 (m, 2H), 1.30 (d, J = 6.0 Hz, 3H).

5.3.4. General procedure for the preparation of *N*-(4-(4-(*R*-phenyl)piperazin-1-yl)butan-2-yl)-Ar-sulfonamide (28a–d)

For the further conversion to sulfonamides, NaH (0.5 mmol, 1 equiv) was added to a solution of Ar-sulfonamide (0.5 mmol, 1 equiv) in DMF (15 mL), and the reaction mixture was stirred at 60 °C for 30 min under nitrogen. 4-(4-(*R*-Phenyl)piperazin-1-yl)-butan-2-yl-4-methylbenzenesulfonate **27** (0.5 mmol, 1 equiv) in DMF (10 mL) was added slowly to the reaction mixture. The mixture was stirred at 100 °C overnight under nitrogen. After cooling to rt, the mixture was quenched with satd $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography with ethyl acetate.

5.3.4.1. *N*-(4-(4-Phenylpiperazin-1-yl)butan-2-yl)naphthalene-2-sulfonamide (28a). White solid, 167 mg (47%), mp 88–90 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.81 (dd, J = 8.8 Hz, 1H), 7.66–7.58 (m, 2H), 7.27 (t, J = 7.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.88 (t, J = 7.6 Hz, 1H), 3.29–3.17 (m, 5H), 2.99 (t, J = 10.8 Hz, 1H), 2.81–2.76 (m, 2H), 2.71–2.65 (m, 1H), 2.55–2.49 (m, 2H), 1.80–1.70 (m, 1H), 1.46–1.40 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.23, 137.11, 134.82, 132.32, 129.53, 129.28, 128.76, 128.38, 128.05, 127.66, 122.52, 120.21, 116.50, 60.23, 49.63, 48.08, 43.30, 30.77, 13.39. HR-FABMS Calcd for $C_{24}H_{30}N_3O_2S$ (M^++H): 424.2059, Found: 424.2055.

5.3.4.2. *N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butan-2-yl)-naphthalene-2-sulfonamide (28b). White solid, 372 mg (49%), mp 119–120 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.83 (dd, J = 8.8 Hz, 1H), 7.66–7.58 (m, 2H), 7.03 (t, J = 7.2 Hz, 1H), 6.99–6.92 (m, 2H), 6.87 (d, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.30–3.25 (m, 1H), 3.13 (s, 4H), 3.03–2.95 (m, 1H), 2.87–2.81 (m, 2H), 2.68–2.64 (m, 1H), 2.59–2.54 (m, 2H), 1.76–1.73 (m, 1H), 1.41–1.37 (m, 1H), 0.94 (d, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.39, 141.14, 137.22, 134.86, 132.40, 129.51, 129.36, 128.74, 128.46, 128.10, 127.66, 123.37, 122.63, 121.29, 118.77, 111.29, 60.74, 55.55, 51.17, 43.76, 30.44, 13.60. HR-FABMS Calcd for $C_{25}H_{32}N_3O_3S$ (M^++H): 454.2164, Found: 454.2160.

5.3.4.3. *N*-(4-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)butan-2-yl)naphthalene-2-sulfonamide (28c). Yellow oil, 153 mg (40%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.00–7.94 (m, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 8.4 Hz, 1H), 7.66–7.58 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.11–7.10 (m, 2H), 7.05 (d, J = 6.4 Hz, 1H), 3.28–3.19 (m, 5H), 3.01 (t, J = 11.2 Hz, 1H), 2.81–2.76 (m, 2H), 2.74–2.69 (m, 1H), 2.55–2.50 (m, 2H), 1.78–1.73 (m, 1H), 1.49–1.43 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.31, 137.06, 134.90, 132.37, 129.81, 129.61, 129.34, 128.87, 128.50, 128.10, 127.76, 122.53, 119.07, 116.41, 116.37, 112.67, 112.63, 60.19, 49.08, 47.98, 43.14, 30.96, 13.41. HR-FABMS Calcd for $C_{25}H_{29}F_3N_3O_2S$ (M^++H): 492.1933, Found: 492.1929.

5.3.4.4. *N*-(4-(4-(4-Fluorophenyl)piperazin-1-yl)butan-2-yl)naphthalene-2-sulfonamide (28d). Yellow oil, 294 mg (59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 7.97–7.93 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 8.4 Hz, 1H), 7.66–7.58 (m, 2H), 6.97 (t, J = 9.2 Hz, 2H), 6.90–6.85 (m, 2H), 3.28–3.23 (m, 1H), 3.17–3.088 (m, 4H), 2.99 (t, J = 11.2 Hz, 1H), 2.82–2.77 (m, 2H), 2.72–2.67 (m, 1H), 2.55–2.50 (m, 2H), 1.80–1.70 (m, 1H), 1.46–1.40 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.59, 156.22, 147.78, 136.98, 134.76, 132.24, 129.52, 129.22, 128.74, 128.34, 128.01, 127.63, 122.46, 118.15, 115.72, 115.50, 59.91, 50.41, 47.98, 43.00, 30.75, 13.35. HR-FABMS Calcd for $C_{24}H_{29}FN_3O_2S$ (M^++H): 442.1965, Found: 442.1966.

5.4. Radioligand binding assays[16]

5.4.1. [^{3}H]Ketanserin binding to serotonin 5-HT$_{2a}$ receptor

For serotonin 5-HT$_{2a}$ binding, an aliquot of frozen membrane from avCHO-K1 cell line expressing the human recombinant 5-HT$_{2a}$ receptor and [^{3}H]Ketanserin (1 nM) were used in the presence of mianserin (0.5 AM) as nonspecific. The reaction mixture was incubated for 15 min at 37 °C using 50 mM Tris–HCl (pH 7.4) buffer, and harvested through Whatman GF/C glass fiber filter presoaked in 0.05% Brij.

5.4.2. [^{3}H]Mesulergine binding to serotonin 5-HT$_{2c}$ receptor

Frozen membranes from a stable CHO-K1 cell line expressing the human recombinant 5-HT$_{2c}$ receptor were used. For the binding assay, [^{3}H]Mesulergine (1 nM), receptor membrane and test compounds were added into 50 mM Tris–HCl (pH 7.7) buffer containing 0.1% ascorbic acid and 10 AM pargyline. Nonspecific binding was determined using 0.5 AM mianserin. The incubations were performed for 30 min at 37 °C, and these were terminated by rapid filtration through Whatman GF/C glass fiber filter presoaked in 1% BSA.

5.4.3. [^{3}H]LSD binding to serotonin 5-HT$_7$ receptor

Membranes from stable CHO cell line expressing the human recombinant 5-HT$_7$ serotonin receptor (Perkin Elmer Life and Analytical Sciences, Boston, USA) were used. For 5-HT$_7$ receptor binding assay, cell membrane, 3 nM [^{3}H]LSD and appropriate concentrations of test compounds were added to 0.25 mL of 50 mM Tris–HCl (pH 7.4) buffer containing 10 mM $MgCl_2$ and 0.5 mM EDTA. The mixture was incubated for 90 min at 27 °C, and the reaction was terminated by rapid filtration through Whatman GF/C glass fiber filter presoaked in 0.3% polyethylenimine. The filter was covered with Melti-Lex, sealed in a sample bag followed by drying in the microwave oven, and counted by MicroBeta Plus (Wallac, Finland). Nonspecific binding was determined in the presence of 0.5 l M methiothepin. Competition binding studies were carried out with 7–8 varied concentrations of the test compounds run in duplicate tubes, and isotherms from three assays were calculated by computerized nonlinear regression analysis (GraphPad Prism Program, San Diego, USA) to yield inhibition values (IC_{50}).

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References and notes

1. Nichols, D. E.; Nichols, C. D. *Chem. Rev.* **2008**, *108*, 1614.
2. Mohammad-Zadeh, L. F.; Moses, L.; Gwaltney-Brant, S. M. *J. Vet. Pharmacol. Ther.* **2008**, *31*, 187.
3. Schloss, P.; Williams, D. C. *J. Psychopharmacol.* **1998**, *12*, 115.
4. Awadallah, F. M. *Sci. Pharm.* **2008**, *76*, 415.
5. Ladduwahetty, T.; Boase, A. L.; Mitchinson, A.; Quin, C.; Patel, S.; Chapman, K.; MacLeod, A. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3201.
6. Teegarden, B. R.; Shamma, H. A.; Xiong, Y. *Curr. Top. Med. Chem.* **2008**, *8*, 969.
7. Schmidt, C. J.; Kehne, J. H.; Carr, A. A. *CNS Drug Rev.* **1997**, *3*, 49.
8. Fletcher, S. R.; Burkamp, F.; Blurton, P.; Cheng, S. K. F.; Clarkson, R.; O'Connor, D.; Spinks, D.; Tudge, M.; van Niel, M. B.; Patel, S.; Chapman, K.; Marwood, R.; Shepheard, S.; Bentley, G.; Cook, G. P.; Bristow, L. J.; Castro, J. L.; Hutson, P. H.; MacLeod, A. M. *J. Med. Chem.* **2002**, *45*, 492.
9. Bartoszyk, G. D.; van Amsterdam, C.; Böttcher, H.; Seyfried, C. A. *Eur. J. Pharmacol.* **2003**, *473*, 229.
10. Westkaemper, R. B.; Glennon, R. A. *Curr. Top. Med. Chem.* **2002**, *2*, 575.
11. Shireman, B. T.; Dvorak, C. A.; Rudolph, D. A.; Bonaventure, P.; Nepomuceno, D.; Dvorak, L.; Miller, K. L.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2103.
12. Runyon, S. P.; Mosier, P. D.; Roth, B. L.; Glennon, R. A.; Westkaemper, R. B. *J. Med. Chem.* **2008**, *51*, 6808.
13. Rowley, M.; Bristow, L. J.; Hutson, P. H. *J. Med. Chem.* **2001**, *44*, 477.
14. Yoon, J.; Yoo, E. A.; Kim, J.-Y.; Pae, A. N.; Rhim, H.; Park, W.-K.; Kong, J. Y.; Park Choo, H.-Y. *Bioorg. Med. Chem.* **2008**, *16*, 5405.
15. Bojarski, A. J.; Paluchowska, M. H.; Duszyńska, B.; Kłodzinska, A.; Tatarczynska, E.; Chojnacka-Wojcik, E. *Bioorg. Med. Chem.* **2005**, *13*, 2293.
16. Park, W.-K.; Jeong, D.; Cho, H.; Lee, S. J.; Cha, M. Y.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kong, J. Y. *Pharmacol., Biochem. Behav.* **2005**, *82*, 361.