Synthesis and Biological Evaluation of Arylsulfonylpiperazine Derivatives as 5-HT$_6$ Receptor Ligands

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The 5-HT$_6$ antagonists are mainly related to the treatment of cognitive dysfunction or impairment associated with Alzheimer's disease and schizophrenia. There have been lots of efforts to develop 5-HT$_6$ antagonists. As in our efforts, arylsulfonylpiperazine derivatives **1-3** were designed, synthesized and biologically evaluated against the human recombinant 5-HT$_6$ serotonin receptor. Total 36 compounds were synthesized and the most active compound among the synthesized compounds is compound **2h** with an IC$_{50}$ value of 1.5 μM. The compound **2h** is novel as 5-HT$_6$ receptor ligand and could act as lead for the novel 5-HT$_6$ receptor ligands.

Key Words : Serotonin, 5-HT$_6$ Receptor, Antagonists

Introduction

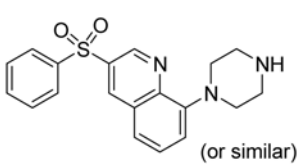
Serotonin (5-hydroxytryptamine, 5-HT) is a major neurotransmitter which interacts with 5-HT receptors to produce a lot of its effects. There are 15 different human serotonin receptors that have been cloned and divided into 7 subclasses (5-HT$_{1\text{-}7}$).[1] The 5-HT$_6$ receptor is one of the latest subtypes to have been identified and belongs to the G-protein coupled receptor (GPCR) superfamily, which is positively coupled to adenylate cyclase.[2] 5-HT$_6$ receptors are present in brain regions such as the cerebral cortex, nucleous accumbens, caudate-putamen and hipocampurs with high densities and thalamus and substantia nigra with low densities, which are associated with learning and memory.[1] Acutually, compromised serotonergic function may have an important contribution to cognitive decline related to aging, Alzheimer's disease (AD) and schizophrenia.[3] Thus serotonergic system became a potential target for the treatment of memory dysfuction.[4] It is also suggested that the 5-HT$_6$ receptor has a major role in obesity, based on the knockout mice study that 5-HT$_6$ receptor-knockout mice are resistant to weight gain when exposed to a high-fat diet.[5]

Up to date, there have been various 5-HT$_6$ receptor antagonists developed, among which three compounds have entered clinical trials (Fig. 1).[6] SB-742457 developed by GlaxoSmithKline is in the phase II clinical trial for the treatment of cognitive dysfunction associated with Alzheimer's disease. The Lilly compound LY-483518 is also in the phase II clinical trial for the treatment of cognitive impairment associated with schizophrenia.[6] SB-271046 is in the phase I clinical trial, developed by GlaxoSmithKline and also for the treatment of Alzheimer's disease and schizophrenia.

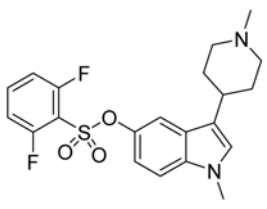
Most of 5-HT$_6$ receptor antagonists have a sulfone moiety and/or a piperazine moiety (Figure 1).[6] As a part of our ongoing project to develop 5-HT$_6$ receptor antagonists, we designed, synthesized and biologically evaluated arylsulfonylpiperazine derivatives **1-3** as novel 5-HT$_6$ receptor ligands (Fig. 2).

Results and Discussion

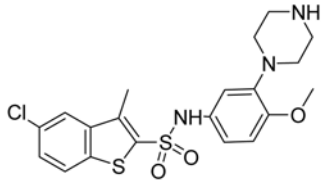
Design. The arylsulfonylpiperazine derivatives **1-3** were designed to possess a sulfone moiety and a piperazine moiety as well as a hydrophobic aromatic group through the structural analysis of the 5-HT$_6$ antagonists reported (Fig. 2). As shown in Figure 1, all the three 5-HT$_6$ antagonists in clinical trial have the three moieties in common. Particularly, the designed compounds have a characteristic arylsulfonyl-



SB-742457 K_i = 0.23 nM

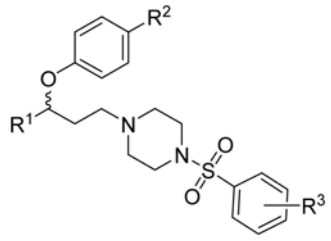


LY-483518 K_i = 1.3 nM



SB-271046 K_i = 1.3 nM

Figure 1. 5-HT$_6$ antagonists under clinical trials.



1 R^1 = phenyl, R^2 = CF_3
2 R^1 = ethyl, R^2 = CF_3
3 R^1 = ethyl, R^2 = CN
R^3 = H, F, Cl, CH_3, OMe or dimethyl

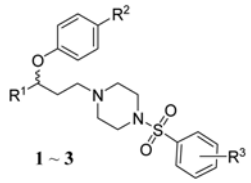
Figure 2. Structures of arylsulfonylpiperazine derivatives.

piperazine which is linked to the hydrophobic group such as a trifluoromethylphenoxy and a cyanophenoxy group.

Chemistry. The arylsulfonylpiperazine derivatives **1-3** were synthesized from β-chloroketones **4** and **5** in three steps, respectively, as racemic mixtures (Scheme 1). The β-chloroketones **4** and **5** were treated with $NaBH_4$ in a solution of aq. THF at room temperature to give secondary alcohols **6** and **7** in 85% and 89% yields, respectively. The secondary alcohols **6** and **7** underwent Mitsunobu reactions with *p*-trifluoromethylphenol **8** (R^2 = CF_3) and *p*-cyanophenol **8** (R^2 = CN) by treating with DIAD and PPh_3 in THF at room temperature to afford compounds **9**, **10** and **11** in 49%, 66% and 28% yields, respectively. The compounds **9**, **10** and **11** were coupled with various arylsulfonylpiperazines **12** which have twelve different R^3 substitutents such as H, *o*-Cl, *m*-Cl, *p*-Cl, *o*-F, *m*-F, *p*-F, *o*-Me, *m*-Me, *p*-Me, *m*-OMe and 3,4-Me_2. Thus, the compounds **9**, **10** and **11** underwent S_N2 type reactions with twelve arylsulfonylpiperazines **12** by treatment with K_2CO_3 in acetonitrile under reflux conditions to give the target compounds **1-3** in 24-96% yields. Total 36 of the title compounds **1-3** were synthesized.

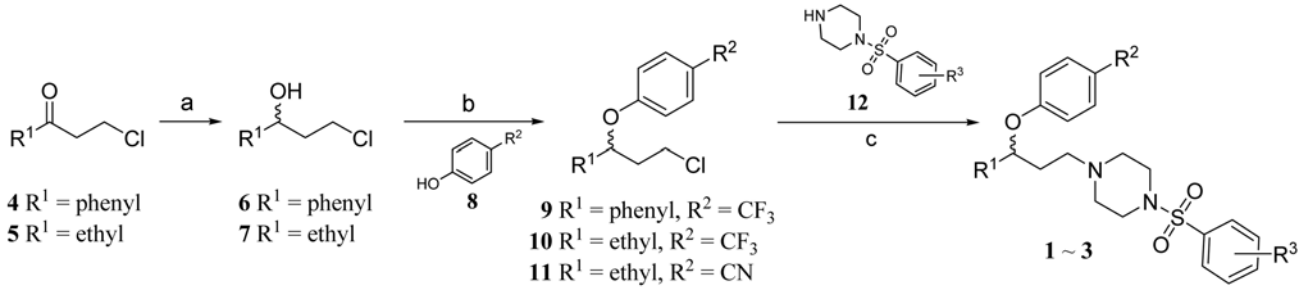
Biological Evaluation. All the synthesized compounds were biologically evaluated against the human recombinant 5-HT_6 serotonin receptor stably expressed by HEK293 cell line through [^{3}H]-lysergic acid diethylamide (LSD) binding assay.[7] The results are summarized in Table 1. The compounds **1** with a phenyl group as R^1 are not active against the human recombinant 5-HT_6 serotonin receptor up to 10 μM, except for the compound **1e** (Table 1) with an *o*-fluoro-

Table 1. IC_{50} values of the arylsulfonylpiperazine derivatives **1** against 5-HT_6 receptor



1 ~ 3

compd	R^1	R^2	R^3	%inhibition at 10 μM	IC_{50} (μM)
1a	phenyl	CF_3	H	24	>10
1b	phenyl	CF_3	*o*-Cl	32	>10
1c	phenyl	CF_3	*m*-Cl	30	>10
1d	phenyl	CF_3	*p*-Cl	23	>10
1e	phenyl	CF_3	*o*-F	52	6.0
1f	phenyl	CF_3	*m*-F	32	>10
1g	phenyl	CF_3	*p*-F	41	>10
1h	phenyl	CF_3	*o*-Me	41	>10
1i	phenyl	CF_3	*m*-Me	34	>10
1j	phenyl	CF_3	*p*-Me	33	>10
1k	phenyl	CF_3	*m*-OMe	30	>10
1l	phenyl	CF_3	3,4-Me_2	20	>10
2a	ethyl	CF_3	H	58	4.2
2b	ethyl	CF_3	*o*-Cl	32	>10
2c	ethyl	CF_3	*m*-Cl	59	4.3
2d	ethyl	CF_3	*p*-Cl	54	7.8
2e	ethyl	CF_3	*o*-F	43	>10
2f	ethyl	CF_3	*m*-F	55	4.7
2g	ethyl	CF_3	*p*-F	44	>10
2h	ethyl	CF_3	*o*-Me	60	1.5
2i	ethyl	CF_3	*m*-Me	50	7.1
2j	ethyl	CF_3	*p*-Me	58	6.2
2k	ethyl	CF_3	*m*-OMe	50	9.6
2l	ethyl	CF_3	3,4-Me_2	47	>10
3a	ethyl	CN	H	29	>10
3b	ethyl	CN	*o*-Cl	37	>10
3c	ethyl	CN	*m*-Cl	43	>10
3d	ethyl	CN	*p*-Cl	37	>10
3e	ethyl	CN	*o*-F	60	3.6
3f	ethyl	CN	*m*-F	67	2.4
3g	ethyl	CN	*p*-F	48	>10
3h	ethyl	CN	*o*-Me	55	3.7
3i	ethyl	CN	*m*-Me	68	2.4
3j	ethyl	CN	*p*-Me	52	7.0
3k	ethyl	CN	*m*-OMe	58	6.7
3l	ethyl	CN	3,4-Me_2	57	5.8
methiothepin					0.0016



Scheme 1. *Reagents and conditions*: (a) $NaBH_4$, aq. THF, rt, 85-89% yields; (b) DIAD, PPh_3, THF, rt 28-66% yields; (c) K_2CO_3, CH_3CN, reflux, 24-96% yield.

phenylsulfonylpiperazine group which has an IC_{50} value of 6.0 μM. The compounds **2** and **3** with an ethyl group as R^1 are relatively more active than the compounds **1**. Among the compounds **2** and **3**, all the compounds **2h-2j** and **3h-3j** with a methyl group as R^3 showed inhibitory activity against the human recombinant 5-HT_6 serotonin receptor with IC_{50} values of 1.5 to 7.1 μM, while only some of the compounds with a fluoro or chloro group showed inhibitory activity with IC_{50} values of 2.4 to 4.7 μM. The compounds **2k** and **3k** with a *m*-methoxy group also show marginal inhibitory activity with IC_{50} values of 9.6 and 6.7 μM, respectively. Among the compounds **1l**, **2l** and **3l** with a 3,4-dimethyl group at R^3, only the compound **3l** show inhibitory activity with an IC_{50} value of 5.8 μM. The most active compound among the series of the synthesized compounds is compound **2h** with an IC_{50} value of 1.5 μM.

Discussion. According to the clinical trials, the 5-HT_6 antagonists are mainly related to the treatment of cognitive dysfunction or impairment associated with Alzheimer's disease and schizophrenia.[6] Until now, there is no marketed drug as 5-HT_6 antagonist. In this study, arylsulfonylpiperazine derivatives were designed, synthesized and biologically evaluated against the human recombinant 5-HT_6 serotonin receptor. The synthesized compounds **1-3** were designed to have three characteristic moieties such as R^1, R^2 and R^3, R^1 is a phenyl group or an ethyl group which consititutes the main skeleton. The hydrophobic phenoxy group with R^2 substituents was expected to be one of the important factors for the inhibitory activity against 5-HT_6 receptor. R^3 substituents gave variety to the arylsulfonylpiperazine moiety.

According to the biological results shown in Table 1, R^1 group prefers a simple alkyl (ethyl) group to the aromatic (phenyl) group. The compounds with a phenyl group as R^1 show no inhibitory activity against 5-HT_6 receptor except the compound **1e**, while most of the compounds with an ethyl group as R^1 are active. There are two substituents as R^2: a trifluoromethyl group and a cyano group. The two electron-withdrawing groups were tested as substituents at the R^2 position. There shows a little activity difference in the position and kind of the subsituents at the R^3 position. The compound **2a** with hydrogen as R^3 shows inhibitory activity with an IC_{50} value of 4.2 μM, while the compound **3a** has no activity up to 10 μM. Among the compounds **2b-2d** and **3b-3d** with a chloro substituent as R^3, only the compound **2c** with a m-chloro substituent shows inhibitory activity with an IC_{50} value of 4.3 μM. In the case of fluoro substituents (compounds **2e-2g** and **3e-3g**), the compounds **2f**, **3e** and **3f** show activity with IC_{50} values of 4.7, 3.6 and 2.4 μM, respectively. On the other hand, all the compounds with a methyl substituent show inhibitory activity with IC_{50} values of 1.5 to 7.1 μM. A methyl substituent may be preferred to electronwithdrawing substituents such as fluoro and chloro for the 5-HT_6 antagonist effect. The compounds **2k** and **3k** with an electrondonating group, a *m*-methoxy group, are only marginally active against 5-HT_6 receptor with IC_{50} values of 9.6 and 6.7 μM, respectively. The compounds **1l** and **2l** with a 3,4-dimethyl group are not active but the compound **3l** is active against 5-HT_6 receptor with an IC_{50} value of 5.8 μM. The compound **2h** with an *o*-methyl group shows the best inhibitory activity against 5-HT_6 receptor among the synthesized compounds **1-3**. The activity of the compound **2h** is not so good compared to that of methiothepin, but the structure of the compound **2h** is novel as a 5-HT_6 ligand. Therefore, the compound **2h** could act as lead for the novel 5-HT_6 receptor ligands.

Based on the results of the limited structure activity relationship study on new 5-HT_6 receptor ligands, more extensive structure-activity relationship studies are under the due. A small molecule library with more various substituents for R^1, R^2 and R^3 positions will be designed, synthesized and biologically evaluated against 5-HT_6 receptor.

Experimental

All the commercially available reagents were obtained from Aldrich and Fluka, and generally used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker Advance 400 (or 300) spectrometer. Nuclear magnetic resonance spectra were acquired at 400 (or 300) MHz for ^{1}H, and 100 MHz for ^{13}C NMR. Infrared spectra were obtained on a Perkin Elmer 16FPC FT-IR spectrometer using KBr pellet, $CHCl_3$ or neat. GC/MSD was obtained on a Hewlett Packard 5890. HRMS spectra were obtained on a JMS-700 mass spectrometer (Jeol). Analytical thin layer chromatographies (TLC) were carried out on precoated silica gel plates (Merck Kieselgel 60F254, layer thickness 0.25 mm). Flash column chromatographies were conducted with silica gel grade 230-400 mesh (Merck Kiesegel 60 Art 9385).

3-Chloro-1-phenylpropan-1-ol (6). To the solution of 3-chloro-1-phenyl-1-propanone **4** (4.0 g, 24 mmol) in 100 mL of THF was added $NaBH_4$ (1.8 g, 48 mmol) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 40 mim and quenched with water. The resulting mixture was extracted with EtOAc (100 mL × 2) and the organic layer was washed with water and brine, dried with $MgSO_4$, filtered and concentrated to afford the product **6** (3.6 g, 21 mmol) in 85 % yield as oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 4H), 7.35-7.32 (m, 1H), 4.98 (dd. J = 8.5, 4.7 Hz, 1H), 3.79-3.74 (m, 1H), 3.62-3.58 (m, 1H), 2.30-2.24 (m, 1H), 2.15-.211 (m, 1H).

1-Chloropentan-3-ol (7). The procedure was same as the preparation of the compound **6**. 1-Chloropentan-3-one **5** was converted to the product **7** in 30 mmol-scale in 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.67 (m, 3H), 1.87-1.85 (m, 2H), 1.54-1.48 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene (9). A solution of 3-chloro-1-phenyl-1-propano1 **6** (1.0 g, 5.9 mmol), 4-(trifluoromethyl)phenol (1.0 g, 5.9 mmol) and triphenylphosphine (1.5 g, 5.9 mmol) in 15 mL of THF was treated with DIAD (1.2 mL, 5.9 mmol) at 0 °C under N_2 atmosphere. After 2 h, the reaction mixture was concentrated and purified by column chromatography with a 60 : 1 mixture of hexanes and EtOAc to give the product **9** (0.90 g,

2.9 mmol) in 49% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.6 Hz, 2H), 7.41-7.32 (m, 5H), 6.93 (d, J = 8.7 Hz, 2H), 5.45 (dd, J = 11.3, 6.2 Hz, 1H), 3.83-3.77 (m, 1H), 3.65-3.58 (m, 1H), 2.51-2.47 (m, 1H), 2.28-2.24 (m, 1H).

1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene (10). The procedure was same as the preparation of the compound **9**. 1-chloropentan-3-ol **7** was converted to the product **10** in 5.3 mmol-scale in 66% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.55 (m, 1H), 3.68-3.65 (m, 2H), 2.19-2.17 (m, 1H), 2.07-2.06 (m, 1H), 1.74-1.69 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

4-(1-Chloropentan-3-yloxy)bezonitrile (11). The procedure was same as the preparation of the compound **9**. 1-chloropentan-3-ol **7** was converted to the product **11** in 2.3 mmol-scale in 28% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.00-6.96 (m, 2H), 4.58-4.55 (m, 1H), 3.67-3.63 (m, 2H), 2.20-2.17 (m, 1H), 2.09-2.06 (m, 1H), 1.77-1.70 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H).

1-(3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-4-(phenylsulfonyl)piperazine (1a). A mixture of 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** (48 mg, 0.15 mmol), 1-(phenyl sulfonyl)piperazine (38 mg, 0.17 mmol) and K_2CO_3 (25 mg, 0.18 mmol) in 2 mL of CH_3CN was refluxed for 48 h at 110 °C. The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified by column chromatography with a 5 : 1 mixture of hexanes and EtOAc to give the product **1a** (31 mg, 0.06 mmol) in 40% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2H), 7.54-7.52 (m, 1H), 7.49-7.47 (m, 2H), 7.32-7.30 (m, 2H), 7.23-7.16 (m, 5H), 6.77 (d, J = 8.6 Hz, 2H), 5.10 (dd, J = 8.0, 5.0 Hz, 1H), 2.94 (br s, 4H), 2.44-2.39 (m, 6H), 2.07-2.04 (m, 1H), 1.89-1.85 (m, 1H). M/S – ESI *m/z* 528.8 $[(M + Na)]^+$.

1-(2-Chlorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1b). The procedure was same as the preparation of the compound **1a**. 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1b** in 0.13 mmol-scale in 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 2H), 7.54-7.47 (m, 2H), 7.42-7.40 (m, 3H), 7.38-7.27 (m, 4H), 7.26-7.24 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 5.24 (dd, J = 7.8, 5.1 Hz, 1H), 3.32-3.29 (m, 4H), 2.50-2.49 (m, 6H), 2.20-2.15 (m, 1H), 2.01-1.95 (m, 1H). M/S – ESI *m/z* 562.9 $[(M + Na)]^+$.

1-(3-Chlorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1c). The procedure was same as the preparation of the compound **1a**. 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1c** in 0.05 mmol-scale in 55% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51-7.47 (m, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.34-7.23 (m, 5H), 6.86 (d, J = 8.5 Hz, 2H), 5.21-5.18 (m, 1H), 3.05 (br s, 4H), 2.53-2.20 (m, 6H), 2.20-2.11 (m, 1H), 1.98-1.93 (m, 1H). M/S – ESI *m/z* 562.9 $[(M + Na)]^+$.

1-(4-Chlorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1d). The procedure was same as the preparation of the compound **1a**. 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1d** in 0.12 mmol-scale in 75% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.68-7.52 (m, 2H), 7.41-7.37 (m, 2H), 7.32-7.25 (m, 5H), 6.85 (d, J = 8.7 Hz, 2H), 4.15-4.07 (m, 1H), 3.02 (br s, 4H), 2.50 (br s, 6H), 2.15-2.10 (m, 1H), 2.00-1.96 (m, 1H). M/S – ESI *m/z* 562.9 $[(M + Na)]^+$.

1-(2-Fluorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1e). The procedure was same as the preparation of the compound **1a**. 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1e** in 0.13 mmol-scale in 85% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.82 (m, 1H), 7.60-7.58 (m, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.30-7.20 (m, 7H), 6.87 (d, J = 8.5 Hz, 2H), 5.23 (dd, J = 7.8, 5.1 Hz, 1H), 3.22 (br s, 4H), 2.52-2.50 (m, 6H), 2.22-2.15 (m, 1H), 1.99-1.95 (m, 1H). M/S – ESI *m/z* 546.9 $[(M + Na)]^+$.

1-(3-Fluorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1f). The procedure was same as the preparation of the compound **1a**. 1-(3-chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1f** in 0.12 mmol-scale in 75% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.47-7.45 (m, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.31-7.22 (m, 6H), 6.84 (d, J = 8.7 Hz, 2H), 5.18 (dd, J = 7.7, 5.0 Hz, 1H), 3.03 (br s, 4H), 2.51-2.46 (m, 6H), 2.15-2.11 (m, 1H), 1.98-1.95 (m, 1H). M/S – ESI *m/z* 546.8 $[(M + Na)]^+$.

1-(4-Fluorophenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1g). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1g** in 0.04 mmol-scale in 24% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H), 7.41-7.32 (m, 2H), 7.31-7.20 (m, 7H), 6.85 (d, J = 8.7 Hz, 2H), 5.21-5.18 (m, 1H), 3.05 (br s, 4H), 2.54 (br s, 6H), 2.19-2.14 (m, 1H), 2.01-1.99 (m, 1H). M/S – ESI *m/z* 546.9 $[(M + Na)]^+$.

1-(3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-4-(*o*-tolysulfonyl)piperazine (1h). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1h** in 0.11 mmol-scale in 59% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 1H), 7.50-7.43 (m, 3H), 7.40-7.24 (m, 7H), 6.88 (d, J = 8.6 Hz, 2H), 5.25 (dd, J = 7.7, 5.1 Hz, 1H), 3.20 (br s, 4H), 2.64 (s, 3H), 2.52 (br s, 6H), 2.22-2.13 (m, 1H), 2.02-1.95 (m, 1H). M/S – ESI *m/z* 542.9 $[(M + Na)]^+$.

1-(3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-4-(*m*-tolysulfonyl)piperazine (1i). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1i** in 0.10 mmol-scale in 66% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 4.9 Hz, 2H), 7.43-7.38 (m, 4H), 7.31-7.25 (m, 6H), 6.85 (d, J = 8.7 Hz, 2H),

5.18 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.02 (br s, 4H), 2.53-2.47 (m, 6H), 2.44 (s, 3H), 2.15-2.12 (m, 1H), 1.97-1.95 (m, 1H). M/S – ESI *m/z* 542.9 $[(M + Na)]^+$.

1-(3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-4-tosylpiperazine (1j). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1j** in 0.08 mmol-scale in 49% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.31-7.14 (m, 10H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.13 (br s, 1H), 2.99 (br s, 4H), 2.50 (br s, 6H), 2.37 (s, 3H), 7.97 (br s, 1H), 1.92 (br s, 1H). M/S – ESI *m/z* 542.9 $[(M + Na)]^+$.

1-(3-Methoxyphenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1k). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1k** in 0.08 mmol-scale in 47% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (m, 3H), 7.34-7.26 (m, 8H), 7.25-7.25 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.19 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.86 (s, 3H), 3.03 (br s, 4H), 2.51-2.47 (m, 6H), 2.17-2.12 (m, 1H), 1.96-1.93 (m, 1H). M/S – ESI *m/z* 558.9 $[(M + Na)]^+$.

1-(3,4-Dimethylphenylsulfonyl)-4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl) piperazine (1l). The procedure was same as the preparation of the compound **1a**. 1-(3-Chloro-1-phenylpropoxy)-4-(trifluoromethyl)benzene **9** was converted to the product **1b** in 0.08 mmol-scale in 51% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.33-7.23 (m, 7H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.18 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.00 (br s, 4H), 2.53-2.16 (m, 6H), 2.29 (s, 6H), 2.17-2.11 (m, 1H), 1.96-1.91 (m, 1H). M/S – ESI *m/z* 556.9 $[(M + Na)]^+$.

1-(Phenylsulfonyl)-4-(3-(4-(trifluoromethyl)phenoxy)-pentyl)piperazine (2a). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2a** in 0.07 mmol-scale in 36% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.63-7.60 (m, 1H), 7.56-7.53 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.28 (br s, 1H), 3.01 (br s, 4H), 2.44-2.31 (m, 6H), 1.77 (br s, 2H), 1.67-1.62 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 480.8 $[(M + Na)]^+$.

1-(2-Chlorophenylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2b). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2b** in 0.11 mmol-scale in 58% yield: ^{1}H NMR (400 MHz, MeOD) δ 8.04-7.01 (m, 1H), 7.63-7.61 (m, 2H), 7.53-7.05 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 4.46-4.45 (m, 1H), 3.27-3.25 (m, 4H), 2.51-2.44 (m, 6H), 1.86-1.82 (m, 2H), 1.71-1.68 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 514.7 $[(M + Na)]^+$.

1-(3-Chlorophenylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2c). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2c** in 0.05 mmol-scale in 29% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.98-7.76 (m, 2H), 7.58-7.53 (m, 2H), 7.48-7.43 (m, 3H), 7.00-6.98 (m, 2H), 4.42-4.39 (m, 2H), 3.29-3.19 (m, 4H), 2.45-2.38 (m, 6H), 1.79-1.77 (m, 2H), 1.64-1.62 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 514.7 $[(M + Na)]^+$.

1-(4-Chlorophenylsulfonyl)-4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2d). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2d** in 0.10 mmol-scale in 52% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.77-7.75 (m, 2H), 7.67-7.64 (m, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 4.46-4.40 (m, 1H), 3.00 (br s, 4H), 2.58-2.55 (m, 2H), 2.51-2.47 (m, 4H), 1.84-1.80 (m, 2H), 1.70-1.65 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 514.7 $[(M + Na)]^+$.

1-(2-Fluorophenylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2e). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2e** in 0.10 mmol-scale in 52% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.84-7.80 (m, 1H), 7.73-7.68 (m, 1H), 7.50-7.48 (m, 2H), 7.40-7.33 (m, 2H), 7.03-7.01 (m, 2H), 4.46-4.40 (m, 1H), 3.13-3.12 (m, 4H), 2.55-2.50 (m, 2H), 2.46-2.44 (m, 4H), 1.87-1.77 (m, 2H), 1.71-1.64 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 498.8 $[(M + Na)]^+$.

1-(3-Fluorophenylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2f). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2f** in 0.06 mmol-scale in 29% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.68-7.64 (m, 1H), 7.61-7.59 (m, 1H), 7.54-7.45 (m, 4H), 7.03-7.00 (m, 2H), 4.44-4.41 (m, 1H), 3.00 (br s, 4H), 2.57-2.53 (m, 2H), 2.51-2.44 (m, 4H), 1.84-1.78 (m, 2H), 1.71-1.64 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 497 $[(M + Na)]^+$.

1-(4-Fluorophenylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2g). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2g** in 0.09 mmol-scale in 46% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.19-7.13 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.23 (br s, 1H), 2.93 (br s, 4H), 2.40 (br s, 4H), 1.98 (br s, 2H), 1.71-7.52 (m, 4H), 0.85 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 498.8 $[(M + Na)]^+$.

1-(*o*-Tolylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)pentyl)piperazine (2h). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2h** in 0.13 mmol-scale in 71% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.88-7.45 (m, 1H), 7.65-7.31 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 5H), 4.34-4.32 (m, 1H), 3.18-3.15 (m, 4H), 2.64 (s, 3H), 2.49-2.42 (m, 6H), 1.81-1.79 (m, 2H), 1.70-1.66 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). M/S – ESI *m/z* 494.8 $[(M + Na)]^+$.

1-(*m*-Tolylsulfonyl)4-(3-(4-trifluoromethyl)phenoxy)-pentyl)piperazine (2i). The procedure was same as the

preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2i** in 0.09 mmol-scale in 48% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.47 (m, 2H), 7.40-7.34 (m, 4H), 6.84 (d, J = 8.7 Hz, 2H), 4.22 (t, J = 5.7 Hz, 1H), 2.96 (br s, 4H), 2.47-2.38 (m, 4H), 1.73 (br s, 2H), 1.63-1.55 (m, 2H), 1.25-1.18 (m, 2H), 0.58 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 493 $[(M + Na)]^+$.

1-Tosyl-4-(3-(4-(trifluoromethyl)phenoxy)pentyl)piperazine (2j). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2j** in 0.12 mmol-scale in 65% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.23-4.19 (m, 1H), 2.94 (br s, 4H), 2.14-2.40 (m, 4H), 1.73 (br s, 2H), 1.60-1.55 (m, 2H), 1.25-1.18 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 494.8 $[(M + Na)]^+$.

1-(3-Methoxyphenylsulfonyl)4-(3-(4-trifluoromethyl)-phenoxy)pentyl)piperazine (2k). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2k** in 0.11 mmol-scale in 59% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.54-7.48 (m, 2H), 7.34-7.31 (m, 1H), 7.26-7.24 (m, 2H), 7.02-7.00 (m, 2H), 4.45-4.39 (m, 1H), 3.88 (s, 3H), 3.06-2.99 (m, 4H), 2.55-2.43 (m, 6H), 1.84-1.76 (m, 2H), 1.71-7.64 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 507 $[(M + Na)]^+$.

1-(3,4-Dimehylphenylsulfonyl)4-(3-(4-trifluoromethyl)-phenoxy)pentyl)piperazine (2l). The procedure was same as the preparation of the compound **1a**. 1-(1-Chloropentan-3-yloxy)-4-(trifluoromethyl)benzene **10** was converted to the product **2l** in 0.06 mmol-scale in 31% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.46 (m, 3H), 7.31-7.26 (m, 2H), 6.91 (d, J = 8.6 Hz, 2H), 4.28 (br s, 1H), 2.99 (br s, 4H), 2.66 (br s, 6H), 2.33 (s, 6H), 1.77-1.64 (m, 2H), 1.58 (br s, 2H), 0.97-0.89 (m, 3H). M/S – ESI *m/z* 507 $[(M + Na)]^+$.

4-(1-(4-(Phenylsulfonayl)piperzine-1yl)pentan-3-yloxy)-benzonitrile (3a). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)-bezonitrile **11**was converted to the product **3a** in 0.15 mmol-scale in 66% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.78-7.76 (m, 2H), 7.72-7.66 (m, 1H), 7.65-7.64 (m, 2H), 7.54-7.51 (m, 2H), 7.02-6.99 (m, 2H), 4.50-4.40 (m, 1H), 2.95 (br s, 4H), 2.51-2.47 (m, 2H), 2.46-2.42 (m, 4H), 1.80 (m, 2H), 1.69-1.67 (m, 2H), 0.92 (t, J = 6.1 Hz, 3H). M/S – ESI *m/z* 436 $[(M + Na)]^+$.

4-(1-(4-(2-Chlorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3b). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11**was converted to the product **3b** in 0.16 mmol-scale in 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-8.02 (m, 1H), 7.55-7.51 (m, 4H), 7.43-7.41 (m, 1H), 6.94-6.91 (m, 2H), 4.37 (t, J = 5.7 Hz, 1H), 3.37-3.31 (m, 4H), 2.47 (br s, 4H), 1.88-1.84 (m, 2H), 1.26 (t, J = 7.1 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H). M/S – ESI *m/z* 470 $[(M + Na)]^+$.

4-(1-(4-(3-Chlorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3c). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11**was converted to the product **3c** in 0.13 mmol-scale in 61% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.69-7.63 (m, 4H), 7.62-7.56 (m, 1H), 7.49-7.47 (m, 2H), 6.95-6.93 (m, 2H), 4.40-4.37 (m, 1H), 2.90 (br s, 4H), 2.47-2.43 (m, 2H), 2.40-2.35 (m, 4H), 1.75-1.72 (m, 2H), 1.62-1.58 (m, 2H), 0.86-0.83 (m, 3H). M/S – ESI *m/z* 470 $[(M + Na)]^+$.

4-(1-(4-(4-Chlorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3d). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11**was converted to the product **3d** in 0.15 mmol-scale in 67% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.76-7.73 (m, 2H), 7.66-7.63 (m, 2H), 7.55-7.52 (m, 2H), 7.02-6.98 (m, 2H), 4.47-4.42 (m, 1H), 2.95 (br s, 4H), 2.52-2.49 (m, 2H), 2.46-2.41 (m, 4H), 1.83-1.76 (m, 2H), 1.68-1.63 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 470 $[(M + Na)]^+$.

4-(1-(4-(2-Fluorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3e). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3e** in 0.21 mmol-scale in 96% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.83-7.82 (m, 1H), 7.75-7.65 (m, 1H), 7.56 (dd, J = 6.9, 2.1 Hz, 2H), 7.42-7.35 (m, 2H), 7.03 (dd, J = 6.9, 2.1 Hz, 2H), 4.51-4.41 (m, 1H), 3.11 (br s, 4H), 2.52-2.51 (m, 2H), 2.47-2.44 (m, 4H), 1.85-1.81 (m, 2H), 1.70-1.67 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 455.1 $[(M + Na)]^+$.

4-(1-(4-(3-Fluorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3f). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3f** in 0.17 mmol-scale in 77% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.69-7.68 (m, 1H), 7.61-7.59 (m, 1H), 7.56-7.48 (m, 4H), 7.02 (dd, J = 6.9, 2.0 Hz, 2H), 4.50-4.39 (m, 1H), 2.99 (br s, 4H), 2.52-2.43 (m, 6H), 1.82-1.80 (m, 2H), 1.69-1.66 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 454 $[(M + Na)]^+$.

4-(1-(4-(4-Fluorophenylsulfonayl)piperzine-1yl)pentan-3-yloxy)benzonitrile (3g). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3g** in 0.21 mmol-scale in 94% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.85-7.82 (m, 2H), 7.56 (dd, J = 6.9, 2.0 Hz, 2H), 7.38 (t, J = 8.7 Hz, 2H), 7.02 (dd, J = 6.9, 2.0 Hz, 2H), 4.50-4.40 (m, 1H), 2.96 (br s, 4H), 2.52-2.42 (m, 6H), 1.81-1.79 (m, 2H), 1.69-1.67 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 454 $[(M + Na)]^+$.

4-(1-(4-(*o*-Tolylsulfonayl)piperzine-1yl)pentan-3-yloxy)-benzonitrile (3h). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)-bezonitrile **11** was converted to the product **3h** in 0.17 mmol-scale in 76% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.87-7.86 (m, 1H), 7.59-7.53 (m, 3H), 7.43-7.40 (m, 2H), 7.04 (dd, J = 6.9, 1.9 Hz, 2H), 4.50-4.40 (m, 1H), 3.12-3.10 (m, 4H), 2.61 (s, 3H), 2.50-2.43 (m, 6H), 1.85-1.83 (m, 2H),

1.70-1.67 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 451.0 $[(M + Na)]^+$.

4-(1-(4-(*m*-Tolylsulfonayl)piperzine-1yl)pentan-3-yloxy)-benzonitrile (3i). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)-bezonitrile **11** was converted to the product **3i** in 0.15 mmol-scale in 68% yield: ^{1}H NMR (300 MHz, MeOD) δ 7.60-7.59 (m, 1H), 7.57-7.51 (m, 5H), 7.03-7.00 (m, 2H), 4.45-4.43 (m, 1H), 2.95-2.94 (m, 4H), 2.51-2.42 (m, 9H), 1.81-1.79 (m, 2H), 1.70-1.66 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 450 $[(M + Na)]^+$.

4-(1-(4-(Tosylpiperzine-1yl)pentan-3-yloxy)benzonitrile (3j). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3j** in 0.18 mmol-scale in 83% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.65-7.63 (m, 2H), 7.53-7.50 (m, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.00 (dd, J = 6.9, 2.0 Hz, 2H), 4.46-4.44 (m, 1H), 2.92 (br s, 4H), 2.51-2.41 (m, 9H), 1.81-1.80 (m, 2H), 1.69-1.65 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 450 $[(M + Na)]^+$.

4-(1-(4-(3-Methoxysulfonylpiperzine-1yl)pentan-3-yloxy)benzonitrile (3k). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3k** in 0.21 mmol-scale in 94% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.54 (dd, J = 6.9, 2.1 Hz, 3H), 7.34-7.31 (m, 1H), 7.28-7.25 (m, 2H), 7.01 (dd, J = 6.9, 2.1 Hz, 2H), 4.50-4.40 (m, 1H), 3.89 (s, 3H), 2.97 (br s, 4H), 2.52-2.51 (m, 2H), 2.48-2.42 (m, 4H), 1.82-1.69 (m, 2H), 1.67-1.66 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 466 $[(M + Na)]^+$.

4-(1-(4-(3,4-Dimethylsulfonylpiperzine-1yl)pentan-3-yloxy)benzonitrile (3l). The procedure was same as the preparation of the compound **1a**. 4-(1-Chloropentan-3-yloxy)bezonitrile **11** was converted to the product **3a** in 0.16 mmol-scale in 74% yield: ^{1}H NMR (400 MHz, MeOD) δ 7.53-7.51 (m, 3H), 7.48-7.46 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 6.9, 2.1 Hz, 2H), 4.50-4.40 (m, 1H), 2.93 (br s, 4H), 2.59-2.50 (m, 2H), 2.50-2.38 (m, 9H), 2.01 (s, 3H), 1.80-1.78 (m, 2H), 1.69-1.65 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). M/S – ESI *m/z* 464 $[(M + Na)]^+$.

[^{3}H]-LSD Binding assay to serotonin 5-HT$_6$ receptor. Membranes from stable HEK-293 cell line expressing the human recombinant 5-HT$_6$ serotonin receptor (Perkinelmer Life and Analytical Sciences, Boston, USA) were used. For the binding assay, aliquots of receptor membranes, 1.6 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. Incubations were carried out for 60 min at 37 °C, and these were terminated by rapid filtration using an Innotech cell harvester (Innotech Biosystems, Switzerland) through Whatman GF/C glass fiber filter presoaked in 0.3% polyethylenimine. The filter was covered with MeltiLex, 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 μM 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

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