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Design, synthesis, and biological evaluation of arylpiperazine–benzylpiperidines with dual serotonin and norepinephrine reuptake inhibitory activities

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Abstract

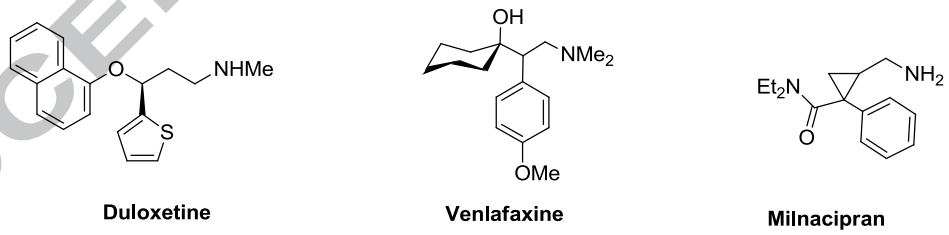
The limitations of established serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) reuptake inhibitors necessitate the development of safer and more effective therapeutic agents. Based on the structures of 4-benzylpiperidine carboxamides and trazodone, arylpiperazine–benzylpiperidines with chemical scaffolds different from those of marketed drugs were designed, synthesized, and evaluated for their neurotransmitter reuptake inhibitory activities. The majority of the synthesized compounds showed greater NE than 5-HT reuptake inhibition. The activities were even greater than those of the standard drug, venlafaxine hydrochloride were. The derivatives with a three-carbon linker showed better activities than the derivatives with a two-carbon linker. Among the newly synthesized compounds, **2d** exhibited the strongest reuptake inhibition of the neurotransmitters (IC_{50} = 0.38 μM for NE and 1.18 μM for 5-HT). The biological activity data demonstrate that arylpiperazine–benzylpiperidines have the potential to be developed as a new class of therapeutic agents to treat neuropsychiatric and neurodegenerative disorders.

Keywords: Arylpiperazine–benzylpiperidine, dual serotonin and norepinephrine reuptake inhibitor, neuropsychiatric disorder, neurodegenerative disorder

1. Introduction

Serotonin and norepinephrine transporters regulate synaptic cleft concentrations of the corresponding neurotransmitters, serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE), via a reuptake mechanism.[1–5] 5-HT and NE are involved in the control of human behaviors such as mood, sleep, pain, appetite, aggression, and sexual activity.[6,7] Reduction in the synaptic levels of 5-HT and NE is associated with various neuropsychiatric and neurodegenerative disorders, such as attention deficit hyperactivity disorder, anxiety, and depression.[8–15] One of the attractive approaches to the treatment of these disorders is inhibition of reuptake of the neurotransmitters to increase their concentrations in the synaptic cleft.[16–21]

Dual 5-HT and NE reuptake inhibitors such as duloxetine, venlafaxine, and milnacipran (Fig. 1) have been used for the treatment of disorders, including depression, anxiety, and painful peripheral neuropathy.[22–27] However, these drugs have several limitations and cause side effects. Suicidal risk is high in patients prescribed duloxetine and venlafaxine. Duloxetine can cause hepatotoxicity and severe cutaneous hypersensitivity reactions. Treatment with venlafaxine can exacerbate or trigger migraines, and the patients may develop potentially life-threatening serotonin syndrome. Moreover, all of these dual reuptake inhibitors may cause cardiac disorders such as arterial hypertension, tachycardia, and arrhythmias.[28–32]



Duloxetine Venlafaxine Milnacipran

Figure 1. Some of the marketed dual serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) reuptake inhibitors.

A common strategy to avoid drug-related side effects is to design molecules with a different chemical scaffold. With this fact in mind, we successfully developed 4-benzylpiperidine

carboxamides as dual reuptake inhibitors.[33] Inspired by the initial success of the 4-benzylpiperidine carboxamides and the quest to identify safe and effective dual reuptake inhibitors, we designed a series of arylpiperazine–benzylpiperidines (Fig. 2). An arylpiperazine–benzylpiperidine derivative is a hybrid structure of 4-benzylpiperidine carboxamide and trazodone. Trazodone, a 5-HT reuptake inhibitor, was considered for the design of new dual reuptake inhibitors since it has structural similarity with 4-benzylpiperidine carboxamides (Ar1–linker–Ar2) and exhibits a reduced onset of action with no side effects commonly displayed by conventional selective 5-HT reuptake inhibitors.[34–41] The details of the synthetic pathways employed, biological evaluation, and structure–activity relationship of these compounds are discussed in the following sections.

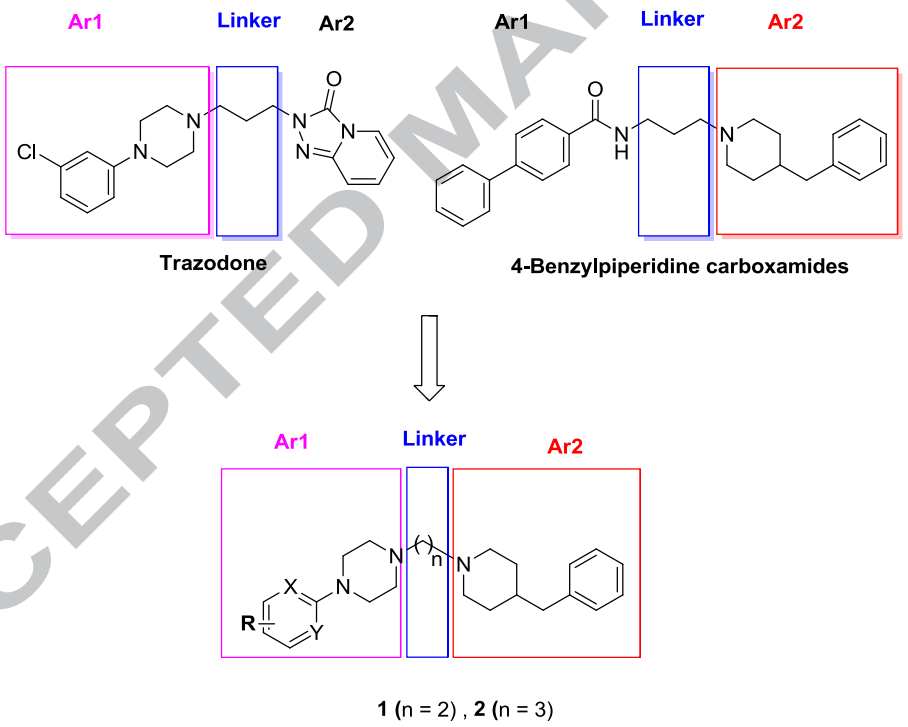
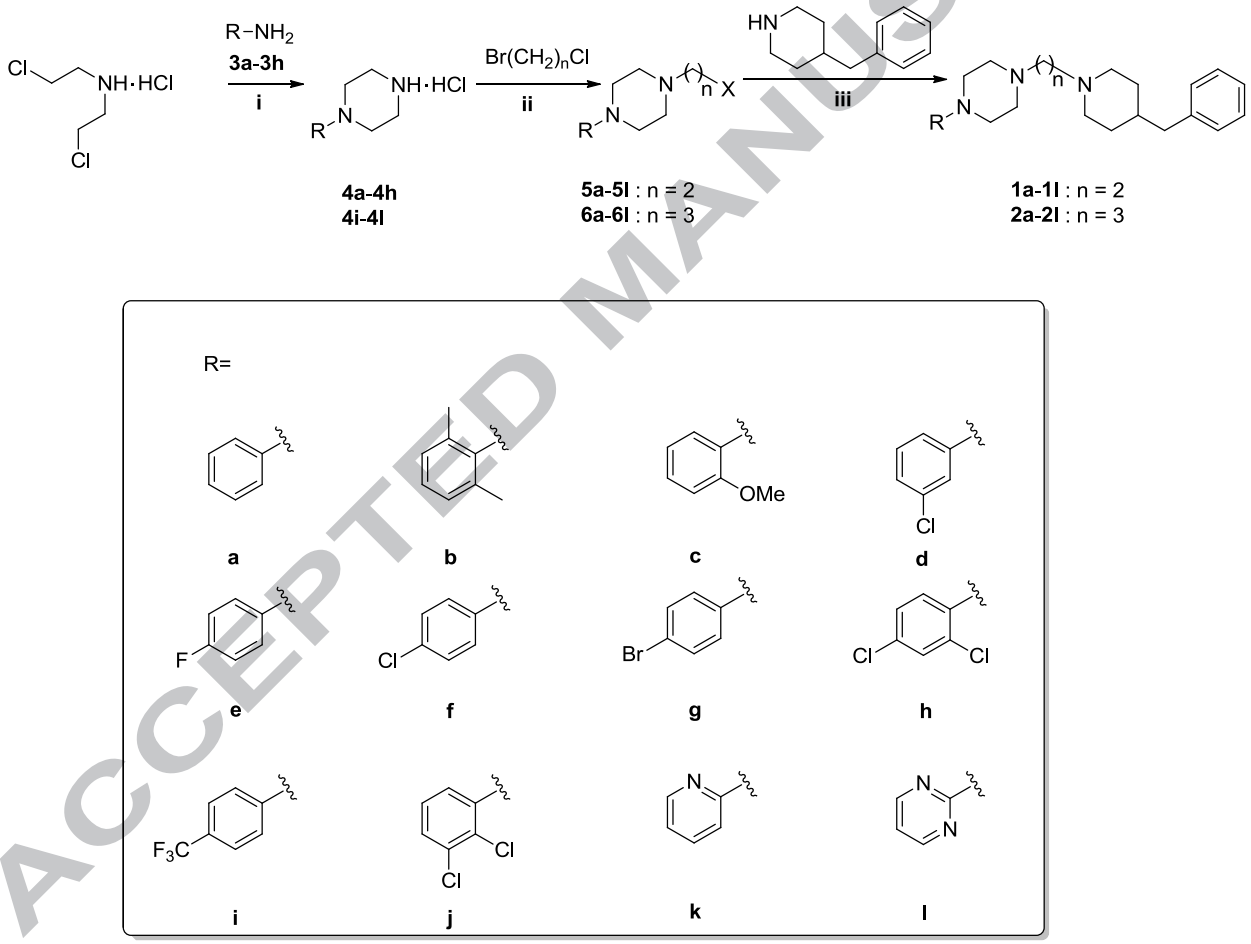


Figure 2. Design of arylpiperazine–benzylpiperidines **1** and **2**.

2. Chemistry

The detailed synthetic procedures for obtaining arylpiperazine–benzylpiperidines are shown in Scheme 1. Various aromatic amines, **3a**–**3h,** were reacted with bis(2-chloroethyl)amine hydrochloride to obtain 4-phenylpiperazine hydrochloride salts **4a**–**4h** (**4i**–**4l** were commercially available**)**. Substitution reactions between 4-phenylpiperazines **4a–4l** and 1-bromo-2-chloroethane or 1-bromo-3-chloropropane gave various haloalkyl-4-phenylpiperazines, **5a**–**5l** (n = 2) and **6a**–**6l** (n = 3). Finally, arylpiperazine–benzylpiperidines **1a**–**1l** and **2a**–**2l** were obtained by substitution reactions of **5a**–**5l** and **6a**–**6l** with 4-benzylpiperidine, respectively.



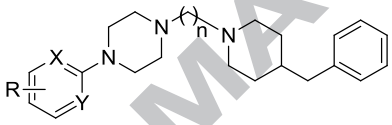
Scheme 1. Synthesis of arylpiperazine–benzylpiperidines **1** and **2**. Reagents and conditions: (i) diethylene glycol monomethyl ether, 150 °C; (ii) K_2CO_3, acetone, room temperature (r.t.); (iii) dimethyl sulfoxide (DMSO), triethylamine (TEA), 100 °C.

3. Results and discussion

3.1. Biological assay

Inhibition of 5-HT and NE reuptake was assessed using a neurotransmitter uptake assay. Human embryonic kidney 293 (HEK-293) cells stably transfected with human serotonin transporter (hSERT) and human norepinephrine transporter (hNET) were used in this assay. The 5-HT and NE reuptake-inhibiting activities of the arylpiperazine–benzylpiperidines are presented in Table 1.

Table 1. Relative serotonin (5-HT) and norepinephrine (NE) reuptake inhibition by arylpiperazine–benzylpiperidines **1a**–**1l** (n = 2) and **2a**–**2l** (n = 3**)**.



Compound	R	X	Y	5-HT[a]	NE[b]	Compd	R	X	Y	5-HT[a]	NE[b]
1a	-H	C	C	0.89	1.0	**2a**	-H	C	C	0.58	1.51
1b	2,6-Me_2	C	C	0.93	1.26	**2b**	2,6-Me_2	C	C	2.83	1.37
1c	2-OMe	C	C	0.27	0.20[c]	**2c**	2-OMe	C	C	2.40	1.36
1d	3-Cl	C	C	0.41	1.29	**2d**	3-Cl	C	C	0.69	1.41
1e	4-F	C	C	0.41	1.16	**2e**	4-F	C	C	0.27	1.40
1f	4-Cl	C	C	0.56	1.18	**2f**	4-Cl	C	C	0.44	1.46
1g	4-Br	C	C	1.01	1.31	**2g**	4-Br	C	C	0.87	1.60
1h	2,4-$(Cl)_2$	C	C	0.85	1.29	**2h**	2,4-$(Cl)_2$	C	C	1.06	1.45
1i	4-CF_3	C	C	0.69	1.26	**2i**	4-CF_3	C	C	0.76	1.34
1j	2,3-$(Cl)_2$	C	C	0.64	0.41[c]	**2j**	2,3-$(Cl)_2$	C	C	0.79	1.63
1k	-H	N	C	0.31	0.08[c]	**2k**	-H	N	C	0.32	1.23
1l	-H	N	N	0.33	-0.05[c]	**2l**	-H	N	N	0.08	1.01

[a]5-HT reuptake inhibition by the test compounds at 1 μM relative to that by venlafaxine·HCl.

[b]NE reuptake inhibition by the test compounds at 10 μM relative to that by venlafaxine HCl.

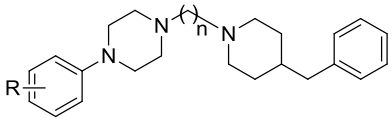
[c]NE reuptake inhibition by the test compounds at 1 μM relative to that by GBR-12909.

The 5-HT reuptake-inhibiting activities of the arylpiperazine–benzylpiperidine derivatives, measured relative to that of venlafaxine·HCl, were 0.08–2.83. Consistent with our previous results,[33] most of the arylpiperazine–benzylpiperidines with three carbon units in the linker displayed better 5-HT reuptake inhibition than the derivatives with two carbon units. Interestingly, the activity of 2-Me compound **1c** increased significantly (9-fold) when the length of the linker was extended from two to three carbons. However, compounds **1a**, **1f**, and **1l** with shorter linkers were more effective than their longer-linker analogs **2a**, **2f**, and **2l**. The 5-HT reuptake inhibitory activities of the derivatives with mono-halogen substitution were in the following order: 3-Cl (**1d**) = 4-F (**1e**) < 4-Cl (**1f**) < 4-Br (**1g**) for the compounds with two-carbon-unit linkers and 4-Br (**2g**) > 3-Cl (**2d**) > 4-Cl (**2f**) > 4-F (**2e**) for the compounds with three-carbon-unit linkers. The derivatives with 2,4-$(Cl)_2$ substitutions (**1h** and **2h**) had greater activities than the derivatives with 2,3-$(Cl)_2$ substitutions (**1j** and **2j**), irrespective of the linker size. Moreover, the longer-linker derivatives with two halogen substitutions showed better activities than the derivatives having a mono-halogen substitution (except 4-Br-substituted compound **2g**). Overall, derivative **1l** with a 2-pyrimidyl ring exhibited the lowest relative inhibition (RI) of 5-HT reuptake (RI = 0.08), while 2,6-Me_2 substituted analog **2b** showed the highest relative inhibitory activity (RI = 2.83).

The relative inhibition of NE reuptake by all the synthesized compounds was equal to or greater than that shown by the standard drugs, venlafaxine·HCl and GBR-12909, except the compounds with heteroaromatic rings, 2-pyridyl (**1k)**, 2-pyrimidyl (**1l**), 2-OMe (**1c**), and 2,3-$(Cl)_2$ (**1j**). The inhibitory activities of the derivatives correlated with the length of the linker. All three-carbon linker compounds were more active than the two-carbon linker ones, which is in agreement with our previous results.[33] The activity increased significantly, 10-fold for 2-pyrimidyl (**1l**) and 4-fold for 2-Me (**1c**) and 2,3-$(Cl)_2$ (**1j**) compounds, when the linker size was increased from two to three carbon units. The lowest reuptake inhibitory activities (RI = −0.05–0.08) were observed for the derivatives with the heteroaromatic ring (**1k** and **1l**), whereas moderate activities (RI = 0.20–0.41) were shown by the derivatives with 2-OMe (**1c**) and 2,3-$(Cl)_2$ (**1j**) substitutions. Furthermore, the remaining compounds displayed equal or more potent activities (RI = 1–1.63) than the standard drug, venlafaxine hydrochloride.

Derivatives **1g**, **1h**, **2a**–**2d**, and **2f**–**2j**, with the relative reuptake inhibitory activities for 5-HT ≥ 0.44 and for NE ≥ 1.29, were selected for the determination of IC_{50}. The IC_{50} values of the compounds for 5-HT and NE reuptake inhibition are presented in Table 2.

Table 2. Serotonin (5-HT) and norepinephrine (NE) reuptake inhibition (IC_{50}) by arylpiperazine–benzylpiperidines.



Compound	R	n	5-HT (μM)	NE (μM)
1g	4-Br	2	4.92	2.10
1h	2,4-$(Cl)_2$	2	4.32	2.50
2a	-H	3	1.36	0.60
2b	2,6-Me_2	3	2.00	1.07
2c	2-OMe	3	1.76	0.89
2d	3-Cl	3	1.18	0.38
2f	4-Cl	3	2.03	0.53
2g	4-Br	3	2.25	0.61
2h	2,4-$(Cl)_2$	3	1.46	0.76
2i	4-CF_3	3	2.61	1.17
2j	2,3-$(Cl)_2$	3	2.51	0.56
VenlafaxineHCl	-	-	0.20	2.55

The levels of inhibition of the 5-HT reuptake shown by compounds **2g** and **2h** confirmed that arylpiperazine–benzylpiperidines having three carbon units in the linker were better inhibitors than those with two carbon units (Fig. 3). Unsubstituted phenyl derivative **2a** was more potent than the 2-OMe-, 2,6-Me_2-, and 4-CF_3-substituted phenyl compounds (**2c**, **2b**, and **2i**, respectively). The inhibitory activities of the compounds with mono-halogen substitution were in the following order: 3-Cl > 4-Cl > 4-Br. However, compound **2h** with 2,4-$(Cl)_2$ was more potent than the 2,3-$(Cl)_2$ derivative (**2j**).

The NE reuptake-inhibiting activities of all the arylpiperazine-benzylpiperidines were greater than that of the standard drug, venlafaxine hydrochloride. The data obtained for derivatives **2g** and **2h** confirmed that derivatives with three carbon units were more active than those with a two-carbon-unit linker were.

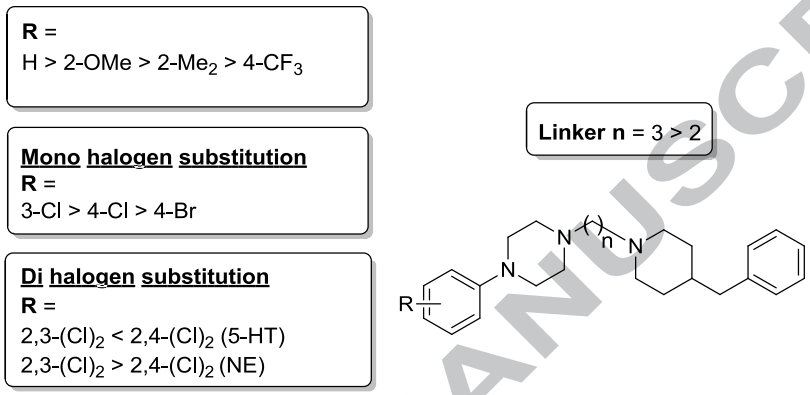


Figure 3. Structure–activity relationship (SAR) of arylpiperazine–benzylpiperidines.

4. Conclusions

A series of arylpiperazine–benzylpiperidines with chemical scaffolds different from those of marketed drugs were designed and synthesized to explore their effects on inhibition of neurotransmitter reuptake. These derivatives differed in the length of the linker and in the substituents on the aromatic ring. As expected, the compounds that contained a longer linker were more active than those with a shorter linker. The majority of the compounds displayed better NE than 5-HT reuptake inhibitory activities (IC_{50} = 0.38–2.50 µM for NE and 1.18–4.92 µM for 5-HT). We believe that the synthetic pathway, structure–activity relationship, and biological results obtained for the arylpiperazine–benzylpiperidines will provide a framework for further design and development of safe and effective therapeutic agents against neuropsychiatric and neurodegenerative disorders.

5. Experimental Section

5.1. Chemistry

A Thomas Hoover melting point apparatus was used for the determination of the melting point (mp) by the capillary method, and the values were uncorrected. Varian Unity Plus 300 MHz and Bruker BioSpin GmbH spectrometers were used to obtain ^{1}H and ^{13}C NMR data, which are reported in ppm downfield from the peak of the internal standard, tetramethylsilane. The data are reported as chemical shift, number of protons, and multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet, dd: doublet of doublets). Merck silica gel 60 (70–230 mesh) was used for column chromatography. Plates coated with silica gel 60 F254 (Merck) were used for thin-layer chromatography. Reagents were purchased from Sigma–Aldrich and Alfa Aesar and used without further purification.

5.1.1. 1-Phenylpiperazine hydrochloride (4a)

A mixture of compound **3a** (279.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) was heated at 150 °C for about 12 h. The reaction mixture was cooled to room temperature and dissolved in methanol (4 mL), followed by the addition of diethyl ether (150 mL). The precipitate formed was recovered by filtration and washed with diethyl ether to provide **4a** as an HCl salt (530 mg, 89%). The HCl salt was used for the next reaction without further purification.

5.1.2. 1-(2,6-Dimethylphenyl)piperazine hydrochloride (4b)

The procedure described for the preparation of **4a** was used with compound **3b** (363.5 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol), and diethylene glycol monomethyl ether (0.75 mL) to obtain **4b** as an HCl salt (540 mg, 79%). The HCl salt was used for the next reaction without further purification.

5.1.3. 1-(2-Methoxyphenyl)piperazine hydrochloride (4c)

The procedure described for the preparation of **4a** was used with compound **3c** (369.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol

monomethyl ether (0.75 mL) to obtain **4c** as an HCl salt (510 mg, 74%). The HCl salt was used for next reaction without further purification.

5.1.4. 1-(3-Chlorophenyl)piperazine hydrochloride (4d)

The procedure described for the preparation of **4a** was used with compound **3d** (321.5 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **4d** as an HCl salt (490 mg, 70%). The HCl salt was used for next reaction without further purification.

5.1.5. 1-(4-Fluorophenyl)piperazine hydrochloride (4e)

The procedure described for the preparation of **4a** was used with compound **3e** (333.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **4e** as an HCl salt (550 mg, 85%). The HCl salt was used for next reaction without further purification.

5.1.6. 1-(4-Chlorophenyl)piperazine hydrochloride (4f)

The procedure described for the preparation of **4a** was used with compound **3f** (321.4 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **4f** as an HCl salt (630 mg, 90%). The HCl salt was used for next reaction without purification.

5.1.7. 1-(4-Bromophenyl)piperazine hydrochloride (4g)

The procedure described for the preparation of **4a** was used with compound **3g** (516.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol monomethyl ether (0.75 mL) to obtain **4g** as an HCl salt (540 mg, 65%). The HCl salt was used for next reaction without purification.

5.1.8. 1-(2,4-Dichlorophenyl)piperazine hydrochloride (4h)

The procedure described for the preparation of **4a** was used with compound **3h** (486.1 mg, 3 mmol), bis(2-chloroethyl)amine hydrochloride (535.5 mg, 3 mmol) and diethylene glycol

monomethyl ether (0.75 mL) to obtain **4h** as an HCl salt (640 mg, 80%). The HCl salt was used for next reaction without purification.

5.1.9. 1-(2-Chloroethyl)-4-phenylpiperazine (5a)

Compound **4a** (200 mg, 1.0 mmol) was dissolved in acetone (10 mL), potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) was added and followed by dropwise addition of 1-bromo-2-chloroethane (0.17 mL, 2.01 mmol) The reaction mixture was stirred at room temperature (r.t.) The reaction mixture was filtered after the completion of reaction and was concentrated. The obtained product was purified by column chromatography with *n*-hexane: ethyl acetate (EtOAc) = 6:1 to obtain **5a** (133 mg, 58%) as clear liquid. Retention factor R_f = 0.66 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.23 (m, 2H), 6.94–6.83 (m, 3H), 3.65–3.60 (m, 2H), 3.21 (t, *J* = 5.1 Hz, 4H), 2.81–2.77 (m, 2H), 2.68 (t, *J* = 5.1 Hz, 4H).

5.1.10 1-(2-Chloroethyl)-4-(2,6-dimethylphenyl)piperazine (5b)

The procedure described for the preparation of **5a** was used with compound **4b** (220 mg, 0.97 mmol), potassium carbonate (K_2CO_3, 268 mg, 1.94 mmol) and 1-bromo-2-chloroethane (0.16 mL, 1.94 mmol) to obtain **5b** (120 mg, 49%) as clear liquid. R_f = 0.73 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00–6.91 (m, 3H), 3.66–3.61 (m, 2H), 3.12 (t, *J* = 4.8 Hz, 4H), 2.82–2.77 (m, 4H), 2.61 (t, *J* = 4.8 Hz, 4H), 2.31 (s, 6H).

5.1.11 1-(2-Chloroethyl)-4-(2-methoxyphenyl)piperazine (5c)

The procedure described for the preparation of **5a** was used with compound **4c** (230 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2.00 mmol) and 1-bromo-2-chloroethane (0.16 mL, 2.0 mmol) to obtain **5C** (130 mg, 51%) as clear liquid. R_f = 0.43 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08–6.84 (m, 4H), 3.86 (s, -OCH_3), 3.65–3.61 (m, 2H), 3.10–3.09 (m, 4H), 2.83–2.78 (m, 2H), 2.74–2.71 (m, 4H).

5.1.12 1-(2-Chloroethyl)-4-(3-chlorophenyl)piperazine (5d)

The procedure described for the preparation of **5a** was used with compound **4d** (230 mg, 0.98 mmol), potassium carbonate (K_2CO_3, 271 mg, 1.96 mmol) and 1-bromo-2-chloroethane (0.16 mL, 1.96 mmol.) to obtain **5d** (140 mg, 55%) as light yellow liquid. R_f = 0.66 (*n*-hexane: EtOAc

= 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (t, *J* = 8.1 Hz, 1H), 6.86–6.74 (m, 3H), 3.63–3.58 (m, 2H), 3.21–3.17 (m, 4H), 2.77–2.74 (m, 2H), 2.64 (t, *J* = 5.1 Hz, 4H).

5.1.13 1-(2-Chloroethyl)-4-(4-fluorophenyl)piperazine (5e)

The procedure described for the preparation of **5a** was used with compound **4e** (220, 1 mmol) potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) and 1-bromo-2-chloroethane (0.16 mL, 2.0 mmol) to obtain **5e** (110 mg, 45%) as solid. R_f = 0.69 (*n*-hexane: EtOAc = 1:1). Mp ; 346–348 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99–6.81 (m, 4H), 3.65–3.60 (m, 2H), 3.14–3.11 (m, 4H), 2.82–2.77 (m, 2H), 2.70–2.67 (m, 4H).

5.1.14 1-(2-Chloroethyl)-4-(4-chlorophenyl)piperazine (5f)

The procedure described for the preparation of **5a** was used with compound **4f** (222 mg, 0.95 mmol), potassium carbonate (K_2CO_3, 262 mg, 1.9 mmol) and 1-bromo-2-chloroethane (0.16 mL, 1.9 mmol) to obtain **5f** (123 mg, 50%) as clear liquid. R_f = 0.60 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.17 (m, 2H), 6.86–6.80 (m, 2H), 3.62–3.60 (t, *J* = 6.9 Hz, 2H), 3.19–3.16 (m, 4H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 5.1 Hz, 4H).

5.1.15 1-(4-Bromophenyl)-4-(2-chloroethyl)piperazine (5g)

The procedure described for the preparation of **5a** was used with compound **4g** (280 mg, 1.16 mmol), potassium carbonate (K_2CO_3, 320 mg, 2.32 mmol) and 1-bromo-2-chloroethane (0.19 mL, 2.32 mmol) to obtain **5g** (186 mg, 53%) as brown solid. R_f = 0.70 (*n*-hexane: EtOAc = 2:1). Mp; 348–350 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.23 (m, 2H, overlapped with $CDCl_3$), 6.95–6.84 (m, 3H), 3.65–3.60 (m, 2H), 3.21 (t, *J* = 5.1 Hz, 4H), 2.82–2.77 (m, 2H), 2.69 (t, *J* = 5.1 Hz, 4H).

5.1.16 1-(2-Chloroethyl)-4-(2,4-dichlorophenyl)piperazine (5h)

The procedure described for the preparation of **5a** was used with compound **4h** (270 mg, 1 mmol) potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) and 1-bromo-2-chloroethane (0.16 mL, 2.0 mmol) to obtain **5h** (180 mg, 61%) as clear liquid. R_f = 0.54 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.4 Hz 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.07–3.04 (m, 4H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.72–2.69 (m, 4H).

5.1.17 1-(2-Chloroethyl)-4-(4-(trifluoromethyl)phenyl)piperazine (5i)

The procedure described for the preparation of **5a** was used with compound **4i** (230 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) and 1-bromo-2-chloroethane (0.16 mL, 2 mmol) to obtain **5i** (150 mg, 51%) as solid. R_f = 0.75 (*n*-hexane: EtOAc = 1:1). Mp; 73–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 9.3, 0.6 Hz, 2H), 6.91 (d, *J* = 8.4 Hz 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.29 (t, *J* = 5.1 Hz, 4H), 2.81–2.77 (m, 2H), 2.69–2.66 (m, 4H).

5.1.18 1-(2-Chloroethyl)-4-(2,3-dichlorophenyl)piperazine (5j)

The procedure described for the preparation of **5a** was used with compound **4j** (200 mg, 0.74 mmol), potassium carbonate (K_2CO_3, 204 mg, 1.48 mmol) and 1-bromo-2-chloroethane (0.12 mL, 1.48 mmol) to obtain **5j** (120 mg, 55%) as clear liquid. R_f = 0.70 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.11 (m, 2H), 6.97–6.93 (m, 1H), 3.65–3.61 (m, 2H), 3.09–3.06 (m, 4H), 2.82 (t, *J* = 6.9 Hz, 2H), 2.73–2.70 (m, 4H).

5.1.19 1-(2-Chloroethyl)-4-(pyridin-2-yl)piperazine (5k)

The procedure described for the preparation of **5a** was used with compound **4k** (200 mg, 1.22 mmol), potassium carbonate (K_2CO_3, 337 mg, 2.44 mmol) and 1-bromo-2-chloroethane (0.2 mL, 2.44 mmol) to obtain **5k** (151 mg, 55%) as clear liquid. R_f = 0.48 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.17 (m, 1H), 7.50–7.49 (m, 1H), 6.65–6.60 (m, 2H), 3.65–3.61 (m, 2H), 3.58–3.54 (m, 4H), 2.81–2.76 (m, 2H), 2.63 (t, *J* = 5.1 Hz, 4H).

5.1.20 2-(4-(2-Chloroethyl)piperazin-1-yl)pyrimidine (5l)

The procedure described for the preparation of **5a** was used with compound **4l** (200 mg, 1.21 mmol), potassium carbonate (K_2CO_3, 334 mg, 2.42 mmol) and 1-bromo-2-chloroethane (0.2 mL, 2.42 mmol) to obtain **5l** (140 mg, 51%) as clear liquid. R_f = 0.45 (*n*-hexane: EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 4.8 Hz, 2H), 6.48 (m, 1H), 3.84 (d, *J* = 5.1 Hz, 4H), 3.63 (t, *J* = 6.9 Hz, 2H), 2.80–2.75 (m, 4H), 2.58 (t, *J* = 5.1 Hz, 4H).

5.1.21. 1-(3-Chloropropyl)-4-phenylpiperazine (6a)

Compound **4a** (200 mg, 1.0 mmol) was dissolved in acetone (10 mL), potassium carbonate (K_2CO_3, 276 mg, 2.00 mmol) was added and followed by dropwise addition of 1-bromo-3-chloropropane (0.19 mL, 2.0 mmol). The reaction mixture was stirred at r.t. The reaction mixture was filtered after the completion of reaction and was concentrated. The obtained product was purified by column chromatography with *n*-hexane: ethyl acetate (EtOAc) = 3:1 to obtain **6a** (150 mg, 62%) as clear liquid. R_f = 0.75 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.21 (m, 2H), 6.92– 6.81(m, 3H), 3.62–3.57 (m, 2H), 3.17 (t, *J* = 5.1 Hz, 4H), 2.60–2.49 (m, 6H), 1.96 (quin, *J* = 6.75 Hz, 2H).

5.1.22 1-(3-Chloropropyl)-4-(2,6-dimethylphenyl)piperazine (6b)

The procedure described for the preparation of **6a** was used with compound **4b** (222 mg, 0.98 mmol), potassium carbonate (K_2CO_3, 271 mg, 1.96 mmol) and 1-bromo-3-chloropropane (0.19 mL, 1.96 mmol) to obtain **6b** (130 mg, 50%) as clear liquid. R_f = 0.75 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06–6.97 (m, 3H), 3.71–3.66 (m, 2H), 3.19–3.16 (m, 4H), 2.63–2.59 (m, 6H), 2.39 (s, 6H), 2.06 (quin, *J* = 6.9 Hz, 2H).

5.1.23 1-(3-Chloropropyl)-4-(2-methoxyphenyl)piperazine (6c)

The procedure described for the preparation of **6a** was used with compound **4b** (238 mg, 1.04 mmol), potassium carbonate (K_2CO_3, 287 mg, 2.08 mmol) and 1-bromo-3-chloropropane (0.20 mL, 2.08 mmol) to obtain **6c** (140 mg, 50%) as clear liquid. R_f = 0.68 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02–6.84 (m, 4H), 3.86 (s, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.09 (s, 4H), 2.67–2.65 (m, 4H), 2.58–2.53 (m, 2H), 1.99 (quin, *J* = 6.9 Hz, 2H).

5.1.24 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine (6d)

The procedure described for the preparation of **6a** was used with compound **4d** (230 mg, 0.98 mmol), potassium carbonate (K_2CO_3, 271 mg, 1.96 mmol) and 1-bromo-3-chloropropane (0.19 mL, 1.96 mmol) to obtain **6d** (155 mg, 58%) as clear liquid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (t, *J* = 8.1 Hz, 1H), 6.87–6.75 (m, 3H), 3.64–3.61 (m, 2H), 3.20–3.17 (m, 4H), 2.60–2.51 (m, 6H), 2.04–1.93 (m, 2H).

5.1.25 1-(3-Chloropropyl)-4-(4-fluorophenyl)piperazine (6e)

The procedure described for the preparation of **6a** was used with compound **4e** (220 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2 mmol) and 1-bromo-3-chloropropane (0.19 mL, 2 mmol) to obtain **6e** as **(**126 mg, 49%) as clear liquid. R_f = 0.63 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99–6.83 (m, 4H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.13–3.10 (m, 4H), 2.62–2.52 (m, 6H), 1.98 (quin, *J* = 6.7 Hz, 2H).

5.1.26 1-(4-Chlorophenyl)-4-(3-chloropropyl)piperazine (6f)

The procedure described for the preparation of **6a** was used with compound **4f** (230 mg, 0.98 mmol), potassium carbonate (K_2CO_3, 271 mg, 1.96 mmol) and 1-bromo-3-chloropropane (0.19 mL, 1.96 mmol) to obtain **6f** (155 mg, 58%) as clear liquid. R_f = 0.71 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.16 (m, 2H), 6.85–6.80 (m, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.16–3.13 (m, 4H), 2.61–2.51 (m, 6H), 1.97 (quin, *J* = 6.7 Hz, 2H).

5.1.27 1-(4-Bromophenyl)-4-(3-chloropropyl)piperazine (6g)

The procedure described for the preparation of **6a** was used with compound **4g** (216 mg, 0.78 mmol), potassium carbonate (K_2CO_3, 215 mg, 1.56 mmol) and 1-bromo-3-chloropropane (0.15 mL, 1.56 mmol) to obtain **6g** (112 mg, 45%) as clear liquid. R_f = 0.68 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.21 (m, 2H, overlapped with $CDCl_3$), 6.94–6.82 (m, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.20 (t, *J* = 5.1 Hz, 4H), 2.63–2.53 (m, 6H), 1.99 (quin, *J* = 6.8 Hz, 2H).

5.1.28 1-(3-Chloropropyl)-4-(2,4-dichlorophenyl)piperazines (6h)

The procedure described for the preparation of **6a** was used with compound **4h** (270 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2 mmol) and 1-bromo-3-chloropropane (0.19 mL, 2 mmol) to obtain **6h** as clear liquid (185 mg, 60%) as clear liquid. R_f = 0.59 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 2.4 Hz, 1H), 7.20–7.16 (m, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 3.64–3.60 (m, 2H), 3.03 (s, 4H), 2.63–2.54 (m, 6H), 1.98 (quin, *J* = 6.8 Hz, 2H).

5.1.29 1-(3-Chloropropyl)-4-(4-(trifluoromethyl)phenyl)piperazine (6i)

The procedure described for the preparation of **6a** was used with compound **4i** (230 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2 mmol) and 1-bromo-3-chloropropane (0.19 mL, 2 mmol) to obtain **6i** (165 mg, 54%) as clear liquid. R_f = 0.65 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300

MHz, $CDCl_3$): δ 7.47 (dd, *J* = 9, 0.6 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 5.1 Hz, 4H), 2.60–2.51 (m, 6H), 1.98 (quin, *J* = 6.75 Hz, 2H).

5.1.30 1-(3-Chloropropyl)-4-(2,3-dichlorophenyl)piperazine (6j)

The procedure described for the preparation of **6a** was used with compound **4j** (270 mg, 1 mmol), potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) and 1-bromo-3-chloropropane (0.19 mL, 2.0 mmol) to obtain **6j** (149 mg, 48%) as clear liquid. R_f = 0.60 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.10 (m, 2H), 6.98–6.93 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.06 (s, 4H), 2.64–2.55 (m, 6H), 1.99 (quin, *J* = 6.8 Hz, 2H).

5.1.31 1-(3-Chloropropyl)-4-(pyridin-2-yl)piperazine (6k)

The procedure described for the preparation of **6a** was used with compound **4k** (200 mg, 1.22 mmol), potassium carbonate (K_2CO_3, 337 mg, 2.44 mmol) and 1-bromo-3-chloropropane (0.24 mL, 2.44 mmol) to obtain **6k** (146 mg, 50%) as clear liquid. R_f = 0.60 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.17 (m, 1H), 7.50–7.44 (m, 1H), 6.65–6.59 (m, 2H), 3.65–3.60 (m, 2H), 3.54 (t, *J* = 5.1 Hz, 4H), 2.57–2.51 (m, 6H), 1.99 (quin, *J* = 6.8 Hz, 2H).

5.1.32 2-(4-(3-Chloropropyl)piperazin-1-yl)pyrimidine (6l)

The procedure described for the preparation of **6a** was used with compound **4l** (231 mg, 1.40 mmol), potassium carbonate (K_2CO_3, 387 mg, 2.8 mmol) and 1-bromo-3-chloropropane (0.27 mL, 2.8 mmol) to obtain **6l** (176 mg, 52%) as clear liquid. R_f = 0.74 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 4.8 Hz, 2H), 6.47 (t, *J* = 4.8 Hz, 1H), 3 .84–3.80 (m, 4H), 3.65–3.61 (m, 2H), 2.54–2.48 (m, 6H), 2.04–1.94 (m, 2H).

5.1.33 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-phenylpiperazine (1a)

A mixture of compound **5a** (130 mg, 0.57 mmol), 4-benzylpiperidine (0.12 mL, 0.68 mmol), triethylamine (TEA) (0.24 mL, 1.71 mmol) and dimethyl sulfoxide (DMSO) (1.5 mL) was stirred at 100 ^{o}C. After the reaction was completed, the water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated. The obtained product was purified by column chromatography on silica gel with *n*-hexane: EtOAc: MeOH (10:1.5:0.5) to obtain **1a** (93 mg, 45%) as light brown liquid. R_f = 0.45

(*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.17 (m, ≈ 8H, overlapped with $CHCl_3$ peaks) 6.92–6.81 (m, 3H), 3.18 (t, *J* = 5.1 Hz, 4H), 2.91 (d, *J* = 11.7 Hz, 2H), 2.64–2.61 (m, 4H), 1.97–1.88 (m, 2H), 1.65–1.45 (m, 3H), 1.37–1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 140.6, 129.1, 129.0, 128.1, 125.7, 119.6, 115.9, 56.2, 56.1, 54.4, 53.6, 49.0, 43.2, 37.8, 32.1.

5.1.34 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(2,6-dimethylphenyl)piperazine (1b)

The procedure described for the preparation of **1a** was used with compound **5b** (115 mg, 0.45 mmol), 4-benzylpiperidine (0.10 mL, 0.54 mmol), TEA (0.19 mL, 1.35 mmol) and DMSO (1.5 mL) to obtain **1b** (70 mg, 40%) as light brown liquid. R_f = 0.75 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.98–6.89 (m, 3H), 3.11–3.08 (m, 4H), 2.93 (d, *J* = 11.4 Hz, 2H), 2.58–2.51 (m, 10H), 2.31 (s, 6H), 1.94 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.65–1.45 (m, 3H), 1.38–1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 140.7, 137.0, 129.1, 128.9, 128.1, 125.8, 125.0, 56.6, 55.0, 54.5, 49.6, 43.2, 37.9, 32.2, 19.7.

5.1.35 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(2-methoxyphenyl)piperazine (1c)

The procedure described for the preparation of **1a** was used with compound **5c** (130 mg, 0.51 mmol), 4-benzylpiperidine (0.11 mL, 0.61 mmol), TEA (0.21 mL, 1.53 mmol) and DMSO (1.5 mL) to obtain **1c** (80 mg, 40%) as light brown liquid. R_f = 0.33 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 7.01–6.83 (m, 4H), 3.85 (s, 3H), 3.08 (s, 4H), 2.93 (d, *J* = 11.7 Hz, 2H), 2.68–2.51 (m, 10H), 1.98–1.90 (m, 2H), 1.65–1.45 (m, 3H), 1.38–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.1, 140.8, 139.4, 139.1, 129.0, 128.99, 128.4, 128.38, 128.3, 123.1, 120.9, 118.1, 111.2, 55.3, 53.5, 53.3, 50.2, 43.9, 42.0, 40.9, 36.4, 36.2, 29.4, 28.4.

5.1.36 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(3-chlorophenyl)piperazine (1d)

The procedure described for the preparation of **1a** was used with compound **5d** (130 mg, 0.5 mmol), 4-benzylpiperidine (0.1 mL, 0.6 mmol), TEA (0.20 mL, 1.5 mmol) and DMSO (1.5 mL) to obtain **1d** (98 mg, 49%) as light brown liquid. R_f = 0.32 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.09 (m, ≈ 7H, overlapped with $CHCl_3$ peaks),

6.85–6.72 (m, 3H), 3.17–3.13 (m, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.60–2.50 (m, 10H), 1.95–1.87 (m, 2H), 1.63–1.44 (m, 3H), 1.36–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 152.2, 140.5, 134.8, 129.0, 128.3, 128.1, 125.8, 119.0,115.5, 113.7, 56.1, 56.0, 54.4, 53.4, 48.5, 43.1, 37.7, 32.0.

5.1.37 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(4-fluorophenyl)piperazine (1e)

The procedure described for the preparation of **1a** was used with compound **5e** (110 mg, 0.43 mmol), 4-benzylpiperidine (0.09 mL, 0.51 mmol), TEA (0.18 mL, 1.2 mmol) and DMSO (1.5 mL) to obtain **1e** (80 mg, 47%) as light brown liquid. R_f = 0.22 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks) 6.97–6.83 (m, 4H), 3.12–3.09 (m, 4H), 2.92 (d, *J* = 11.7 Hz, 2H), 2.63–2.46 (m, 10H), 1.97–1.89 (m, 2H), 1.65–1.45 (m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 155.9, 148.0, 147.9, 140.6, 129.1, 128.1, 125.8, 117.8, 117.7, 115.6, 115.3, 56.2, 56.1, 54.4, 53.7, 50.1, 43.2, 37.8, 32.1.

5.1.38 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(4-chlorophenyl)piperazine (1f)

The procedure described for the preparation of **1a** was used with compound **5f** (120 mg, 0.46 mmol), 4-benzylpiperidine (0.1 mL, 0.55 mmol), TEA (0.19 mL, 1.38 mmol) and DMSO (1.5 mL) to obtain **1f** (70 mg, 38%) as light brown liquid. R_f = 0.51 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.11 (m, ≈ 8H, overlapped with $CHCl_3$ peaks) 6.83–6.78 (m, 2H), 3.15–3.11 (m, 4H), 2.91 (d, *J* = 11.7 Hz, 2H), 2.63–2.47 (m, 10H), 1.97–1.88 (m, 2H), 1.64–1.44 (m, 3H), 1.37–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 140.5, 129.0, 128.8, 128.0, 125.7, 124.3, 117.0, 56.11, 56.0, 54.3, 53.4, 49.0, 43.1, 37.7, 32.0.

5.1.39 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(4-bromophenyl)piperazine (1g)

The procedure described for the preparation of **1a** was used with compound **5g** (150 mg, 0.49 mmol), 4-benzylpiperidine (0.1 mL, 0.59 mmol), TEA (0.20 mL, 1.48 mmol) and DMSO (2 mL) to obtain **1g** (76 mg, 35%) as light brown liquid. R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.11 (m, ≈ 8H, overlapped with $CHCl_3$ peaks) 6.93–6.73 (m, 2H), 3.20–3.12 (m, 4H), 2.91 (d, *J* = 11.7 Hz, 2H), 2.65–2.47 (m, 10H), 1.93 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.65–1.45 (m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

151.3, 150.3, 140.6, 131.8, 129.0, 128.1, 125.8, 119.6, 117.5, 116.0, 111.7, 56.2, 56.0, 54.4, 53.6, 53.4, 49.0, 48.9, 43.2, 37.8, 32.1.

5.1.40 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(2,4-dichlorophenyl)piperazine (1h)

The procedure described for the preparation of **1a** was used with compound **5h** (120 mg, 0.40 mmol), 4-benzylpiperidine (0.09 mL, 0.48 mmol), TEA (0.20 mL, 1.44 mmol) and DMSO (1.5 mL) to obtain **1h** (95 mg, 55%) as light brown liquid. R_f = 0.31 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.12 (m, ≈ 8H, overlapped with $CHCl_3$ peaks) 6.93 (d, *J* = 11.7 Hz , 1H), 3.04–3.01 (m, 4H), 2.92 (d, *J* = 11.7 Hz, 2H), 2.65–2.48 (m, 10H), 1.93 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.65–1.45 (m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 140.6, 130.2, 129.3, 129.0, 128.3, 128.1, 128.0, 127.5, 125.7, 121.0, 56.2, 56.0, 53.7, 51.1, 43.1, 37.8, 32.1.

5.1.41 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)piperazine (1i)

The procedure described for the preparation of **1a** was used with compound **5i** (140 mg, 0.48 mmol), 4-benzylpiperidine (0.1 mL, 0.57 mmol), TEA (0.20 mL, 1.44 mmol) and DMSO (1.5 mL) to obtain **1i** (99 mg, 48%) as light brown liquid. R_f = 0.61 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$)): δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.90 (d, *J* = 8.7 Hz , 2H), 3.28–3.25 (m, 4H), 2.92 (d, *J* = 11.7 Hz, 2H), 2.64–2.51 (m, 10H), 1.93 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.65–1.48 (m, 3H), 1.37–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 139.5, 128.1, 127.1, 125.4, 125.34, 125.3,125.27,124.8, 113.4, 55.1, 54.9, 53.4, 52.3, 46.9, 42.1, 36.7, 31.0.

5.1.42 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(2,3-dichlorophenyl)piperazine (1j)

The procedure described for the preparation of **1a** was used with compound **5j** (120 mg, 0.40 mmol), 4-benzylpiperidine (0.09 mL, 0.48 mmol), TEA (0.17 mL, 1.2 mmol) and DMSO (1 mL) to obtain **1j** (75 mg, 44%) as light brown liquid. R_f = 0.47 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 8H, overlapped with $CHCl_3$ peaks), 6.95–6.92 (m, 1H), 3.05 (s, 4H), 2.92 (d, *J* = 11.4 Hz, 2H), 2.67–2.49 (m, 10H), 1.93 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.65–1.45 (m, 3H), 1.38–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 140.6, 134.0, 129.1, 128.2, 127.4, 125.8, 124.5, 118.6, 56.2, 56.0, 54.4, 53.7, 51.3, 43.2, 37.8, 32.0.

5.1.43 1-(2-(4-Benzylpiperidin-1-yl)ethyl)-4-(pyridin-2-yl)piperazine (1k)

The procedure described for the preparation of **1a** was used with compound **5k** (150 mg, 0.66 mmol), 4-benzylpiperidine (0.14 mL, 0.8 mmol), TEA (0.27 mL, 1.98 mmol) and DMSO (2 mL) to obtain **1k** (96 mg, 40%) as light brown liquid. R_f = 0.35 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 4.8, 1.5 Hz, 2H), 7.49–7.43 (m, 1H), 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.64–6.58 (m, 2H), 3.53 (t, *J* = 5.1 Hz, 4H), 2.92 (d, *J* = 11.7 Hz, 2H), 2.60–2.51 (m, 10H), 1.98–1.89 (m, 2H), 1.65–1.45 (m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 147.8, 138.3, 137.6, 129.1, 129., 128.6, 128.5, 126.6, 126.3, 113.7, 107.3, 57.8, 53.1, 52.9, 51.1, 45.1, 34.0, 25.7.

5.1.44 2-(4-(2-(4-Benzylpiperidin-1-yl)ethyl)piperazin-1-yl)pyrimidine (1l)

The procedure described for the preparation of **1a** was used with compound **5l** (140 mg, 0.61 mmol), 4-benzylpiperidine (0.13 mL, 0.73 mmol), TEA (0.25 mL, 1.83 mmol) and DMSO (2 mL) to obtain **1l** (90 mg, 40%) as light brown liquid. R_f = 0.32 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, *J* = 4.8, 2H), 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.46 (t, *J* = 4.8, 1H), 3.81 ((t, *J* = 5.1 Hz, 4H), 2.91 (d, *J* = 11.7 Hz, 2H), 2.54–2.51 (m, 10H), 1.97–1.88 (m, 2H), 1.65–1.46 (m, 3H), 1.36–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 157.7, 140.6, 129.1, 128.1, 125.7, 109.8, 56.3, 56.2, 54.5, 53.5, 43.6, 43.2, 37.8, 32.1.

5.1.45 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-phenylpiperazine (2a)

The procedure described for the preparation of **1a** was used with compound **6a** (140 mg, 0.58 mmol), 4-benzylpiperidine (0.12 mL, 0.70 mmol) and TEA (0.24 mL, 1.74 mmol) in DMSO (1.5 mL) to obtain **2a** (121 mg, 55%) as light brown liquid. R_f = 0.50 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 8H, overlapped with $CHCl_3$ peaks), 6.93–6.81 (m, 3H), 3.19 (t, *J* = 5.1 Hz, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.61–2.51 (m, 6H), 2.39–2.31 (m, 4H), 1.89–1.45 (m, 7H), 1.37–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 150.0, 149.8, 140.6, 129.1, 129.06, 129.0, 128.2, 125.8, 117.9, 117.1, 57.0, 56.7, 55.5, 54.0, 53.1, 49.4, 49.1, 43.2, 37.8, 32.2, 32.0.

5.1.46 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(2,6-dimethylphenyl)piperazine (2b)

The procedure described for the preparation of **1a** was used with compound **6b** (130 mg, 0.48 mmol), 4-benzylpiperidine (0.1 mL, 0.57 mmol), TEA (0.20 mL, 1.44 mmol) and DMSO (1.5 mL) to obtain **2b** (98 mg, 59%) as light brown liquid. R_f = 0.66 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.99–6.90 (m, 3H), 3.12–3.09 (m, 4H), 2.91 (d, *J* = 11.7 Hz, 2H), 2.54–2.51 (m, 6H), 2.42–2.30 (m, 10H), 1.89–1.47 (m, 7H), 1.37–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 139.6, 135.8, 128.0, 127.8, 127.1, 124.7, 123.9, 56.2, 56.0, 53.5, 52.9, 48.5, 42.1, 36.9, 31.0, 23.3, 18.6.

5.1.47 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(2-methoxyphenyl)piperazine (2c)

The procedure described for the preparation of **1a** was used with compound **6c** (135 mg, 0.50 mmol), 4-benzylpiperidine (0.1 mL, 0.6 mmol), TEA (0.20 mL, 1.5 mmol) and DMSO (1.5 mL) to obtain **2c** (90 mg, 44%) as light brown liquid. R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.18 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 7.01–6.82 (m, 4H), 3.84 (s, 3H), 3.09 (s, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.64–2.51 (m, 10H), 1.89–1.81 (m, 2H), 1.77–1.70 (m, 2H), 1.65–1.45 (m, 3H), 1.36–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 141.2, 140.5, 129.0, 128.0, 122.7, 120.9, 118.0, 111.0, 56.9, 56.8, 53.8, 53.4, 50.5, 43.1, 37.8, 32.0, 24.4.

5.1.48 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(3-chlorophenyl)piperazine (2d)

The procedure described for the preparation of **1a** was used with compound **6d** (150 mg, 0.55 mmol), 4-benzylpiperidine (0.12 mL, 0.66 mmol), TEA (0.23 mL, 1.65 mmol) and DMSO (2 mL) to obtain **2d** (95 mg, 42%) as light brown liquid. R_f = 0.31 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 7H, overlapped with $CHCl_3$ peaks), 6.93–6.81 (m, 3H), 3.18 (t, *J* = 5.1 Hz, 4H), 2.90 (d, *J* = 11.7 Hz, 2H, 2.58–2.51 (m, 6H), 2.41–2.31 (m, 4H), 1.89–1.46 (m, 7H), 1.37–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.30, 139.7, 133.9, 128.9, 128.1, 127.1, 124.7, 118.1, 114.6, 112.7, 56.0, 55.7, 52.9, 52.0, 47.6, 42.2, 36.9, 31.0, 28.7, 23.5.

5.1.49 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(4-fluorophenyl)piperazine (2e)

The procedure described for the preparation of **1a** was used with compound **6e** (120 mg, 0.49 mmol), 4-benzylpiperidine (0.1 mL, 0.59 mmol), TEA (0.20 mL, 1.47 mmol) and DMSO (1.5

mL) to obtain **2e** (86 mg, 46%) as light brown liquid. R_f = 0.21 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.11 (m, 5H), 6.97–6.82 (m, 4H), 3.12–3.08 (m, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.60–2.51 (m, 6H), 2.41–2.30 (m, 4H), 1.89–1.41 (m, 7H), 1.37–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.28, 155.9, 148.0, 147.9, 140.5, 129.1, 128.2, 125.8, 117.7, 117.6, 115.6, 115.3, 56.9, 56.6, 53.9, 53.2, 50.1, 43.0, 37.8, 31.8, 24.2.

5.1.50 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(4-chlorophenyl)piperazine (2f)

The procedure described for the preparation of **1a** was used with compound **6f** (150 mg, 0.54 mmol), 4-benzylpiperidine (0.11 mL, 0.65 mmol), TEA (0.22 mL, 1.62 mmol) and DMSO (2 mL) to obtain **2f** (100 mg, 45%) as light brown liquid. R_f = 0.53 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.11 (m, ≈ 8H, overlapped with $CHCl_3$ peaks), 6.84–6.80 (m, 4H), 3.16–3.06 (m, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.59–2.28 (m, 10H), 1.89–1.28 (m, 9H).

5.1.51 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(4-bromophenyl)piperazine (2g)

The procedure described for the preparation of **1a** was used with compound **6g** (100 mg, 0.31 mmol), 4-benzylpiperidine (0.07 mL, 0.37 mmol), TEA (0.13 mL, 0.93 mmol) and DMSO (1 mL) to obtain **2g** (61 mg, 43%) as light brown liquid. R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.22 (m, ≈ 4H, overlapped with $CHCl_3$ peaks), 7.20–7.12 (m, 3H), 6.94–6.82 (m, 3H), 3.21–3.18 (m, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.61–2.52 (m, 6H), 2.42–2.31 (m, 4H), 1.89–1.47 (m, 7H), 1.37–1.27 (m, 2H);.^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 140.7, 129.1, 129.08, 128.1, 125.8, 119.6, 116.0, 57.0, 56.8, 54.0, 53.2, 49.1, 43.2, 37.9, 32.1, 24.5.

5.1.52 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(2,4-dichlorophenyl)piperazine (2h)

The procedure described for the preparation of **1a** was used with compound **6h** (140 mg, 0.45 mmol), 4-benzylpiperidine (0.1 mL, 0.54 mmol), TEA (0.19 mL, 1.35 mmol) and DMSO (1.5 mL) to obtain **2h** (121 mg, 60%) as light brown liquid. R_f = 0.30 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.14 (m, ≈ 8H overlapped with $CHCl_3$ peaks), 6.95 (d, *J* = 8.7 Hz, 1H), 3.03 (s, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.61–2.30 (m, 10H), 1.89–1.46

(m, 7H), 1.36–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 140.6, 130.1, 129.3, 129.0, 128.0, 127.9, 127.5, 125.7, 121.0, 57.0, 56.7, 53.9, 53.2, 53.1, 43.2, 37.9, 32.1, 24.5.

5.1.53 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(4-(trifluoromethyl)phenyl)piperazine (2i)

The procedure described for the preparation of **1a** was used with compound **6i** (150 mg, 0.49 mmol), 4-benzylpiperidine (0.10 mL, 0.59 mmol), TEA (0.20 mL, 1.47 mmol) and DMSO (2 mL) to obtain **2i** (111 mg, 51%) as white solid. R_f = 0.62 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp; 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.90 (d, *J* = 8.7 Hz, 2H), 3.29–3.25 (m, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.59–2.52 (m, 6H), 2.42–2.31 (m, 4H), 1.90–1.81 (m, 2H), 1.77–1.45 (m, 5H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 139.6, 128.1, 127.1, 124.7, 122.4, 113.3, 55.96, 55.7, 53.0, 51.9, 46.8, 42.2, 36.9, 31.1, 23.6.

5.1.54 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(2,3-dichlorophenyl)piperazine (2j)

The procedure described for the preparation of **1a** was used with compound **6j** (140 mg, 0.45 mmol), 4-benzylpiperidine (0.1 mL, 0.54 mmol), TEA (0.18 mL, 1.35 mmol) and DMSO (1.5 mL) to obtain **2j** (80 mg, 40%) as light brown liquid. R_f = 0.47 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.12 (m, ≈ 8H, overlapped with $CHCl_3$ peaks), 6.96–6.93 (m, 1H), 3.06 (s, 4H), 2.91 (d, *J* = 11.7 Hz, 2H,), 2.62–2.51 (m, 6H), 2.44–2.31 (m, 4H), 1.89–1.82 (m, 2H), 1.75–1.44 (m, 5H), 1.37–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 140.7, 133.9, 129.1, 127.45, 127.40, 125.7, 124.5, 118.5, 57.0, 56.7, 53.3, 51.3, 43.2, 37.9, 32.1, 24.5.

5.1.55 1-(3-(4-Benzylpiperidin-1-yl)propyl)-4-(pyridin-2-yl)piperazine (2k)

The procedure described for the preparation of **1a** was used with compound **6k** (140 mg, 0.58 mmol), 4-benzylpiperidine (0.13 mL, 0.69 mmol), TEA (0.24 mL, 1.74 mmol) and DMSO (1.5 mL) to obtain **2k** (140 mg, 64%) as light brown liquid. R_f = 0.41 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19–8.16 (m, 1H), 7.48–7.42 (m, 1H), 7.29–7.12 (m, ≈ 6H, overlapped with $CHCl_3$ peaks), 6.64–6.58 (m, 2H), 3.53 (t, *J* = 5.1 Hz, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.54–2.51 (m, 6H), 2.41–2.31 (m, 4H), 1.85(dd, *J* =11.7, 2.1 Hz, 2H), 1.77–1.70

(m, 2H), 1.67–1.44 (m, 3H), 1.38–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 147.9, 140.6, 137.3, 129.1, 128.1, 125.7, 113.1, 106.9, 56.9, 56.8, 53.9, 53.0, 45.1, 43.2, 37.9, 32.1, 24.5.

5.1.56 2-(4-(3-(4-Benzylpiperidin-1-yl)propyl)piperazin-1-yl)pyrimidine (2l)

The procedure described for the preparation of **1a** was used with compound **6l** (170 mg, 0.70 mmol), 4-benzylpiperidine (0.15 mL, 0.84 125), TEA (0.29 mL, 2.1 mmol) and DMSO (2 mL) to obtain **2l** (160 mg, 60%) as light brown liquid. R_f = 0.41 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 4.5Hz, 2H), 7.29–7.12 (m, 5H), 6.48–6.43 (m, 1H,), 3.82 (t, *J* = 5.1 Hz, 4H), 2.90 (d, *J* = 11.7 Hz, 2H), 2.53–2.27 (m, 10H), 1.89–1.44 (m, 7H), 1.36–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 157.7, 140.6, 129.1, 128.1, 125.8, 109.8, 57.0, 56.9, 54.0, 53.1, 43.6, 43.2, 37.9, 32.1, 24.5.

6. Neurotransmitter uptake assay

The assay was performed following the method described in the literature.[33] HEK-293 cells were cultured in a medium with fetal bovine serum and transfected with hSERT and hNET. Radiolabeled [^{3}H]-5-HT (PerkinElmer, Waltham, MA, USA) and [^{3}H]-NE (PerkinElmer) were used at a concentration of 20 nM in the assay. Radioactivity was measured using a Wallac 1450 MicroBeta® TriLux liquid scintillation counter (PerkinElmer). Venlafaxine hydrochloride and GBR-12909 were used as standard neurotransmitter reuptake inhibitors.

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Graphical Abstract

Design, synthesis and biological evaluation of arylpiperazine–benzylpiperidines with dual serotonin and norepinephrine reuptake inhibitory actvities

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