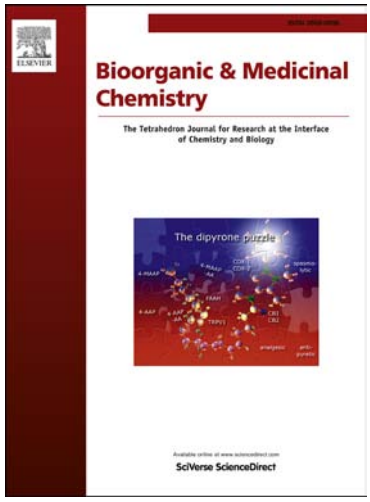

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Design and synthesis of 4-benzylpiperidine carboxamides as dual serotonin and norepinephrine reuptake inhibitors

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Abstract:

A series of 4-benzylpiperidine carboxamides were designed and synthesized, and tested for their dual (serotonin and norepinephrine) reuptake inhibition. The synthesis of 4-benzylpiperidine carboxamides involved two main steps: amidation and substitution. Derivatives with 3 carbon linker displayed better activity than with 2 carbon linker. 4-Biphenyl- and 2-naphthyl-substituted derivatives **7e** and **7j** showed greater dual reuptake inhibition than standard drug venlafaxine HCl.

Keywords: 4-Benzylpiperidine carboxamide, serotonin reuptake inhibitor, norepinephrine reuptake inhibitor

1. Introduction:

Depression is a common and severe illness.[1, 2] Chronic sadness, loss of interest, disruption in sleep patterns, fatigue and sometimes suicidal intension are common features observed in depressed individuals.[3-5] The primary cause of depression is deficiency of monoamine neurotransmitters, serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain. Monoamine reuptake inhibitors maintain the concentration of neurotransmitters in the brain through inhibition of presynaptic monoamine reuptake transporter.[6-10] Drugs that inhibit dual (5-HT and NE) neurotransmitters reuptake are prescribed for the treatment of several central nervous system (CNS) illnesses including depression.[11-16]

Drawbacks of the selective 5-HT reuptake inhibitors fluoxetine (**1**), paroxetine (**2**) and sertraline (**3**) include delayed onset of action and side effects of insomnia and sexual dysfunction (Fig. 1).[17] Trazodone (**4**), which has a different chemical scaffold than the other antidepressant drugs, works as a 5-HT reuptake inhibitor and is devoid of these limitations and side effects.[18, 19] The drug essentially consists of heterocyclic amine (A), linker (B) and aromatic region (C) (Fig. 2). Arylpiperazine-containing pyrimidine 4-carboxamide derivatives **5** that have three fundamental components also display good binding affinity for 5-HT transporter and may work as serotonin reuptake inhibitors.[20] Furthermore, arylalkanol-piperidine derivatives **6** with similar structural moieties also possess serotonin and norepinephrine reuptake inhibition.[21] Thus, considering the structure of trazodone, **5** and **6**, we designed 4-benzylpiperidine carboxamides **7, 8** as possible dual reuptake inhibitors (Fig. 2). 4-Benzylpiperidine carboxamides **7** and **8** which differ in the length of linker were considered to explore their impact on inhibition of neurotransmitters reuptake. The synthesis, biological evaluation and detailed structure-activity relationship (SAR) of the 4-benzylpiperidine carboxamides are detailed below.

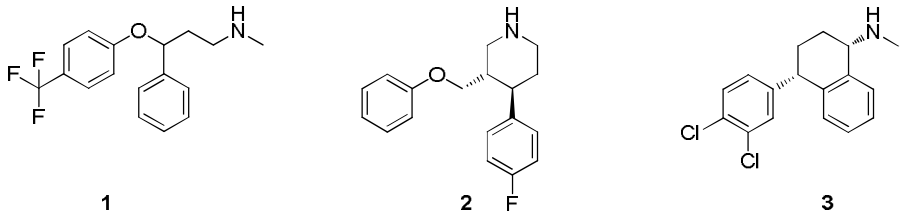


Figure 1. Some marketed antidepressants (selective 5-HT reuptake inhibitors) - Fluoxetine (**1**), paroxetine (**2**) and sertraline (**3**)

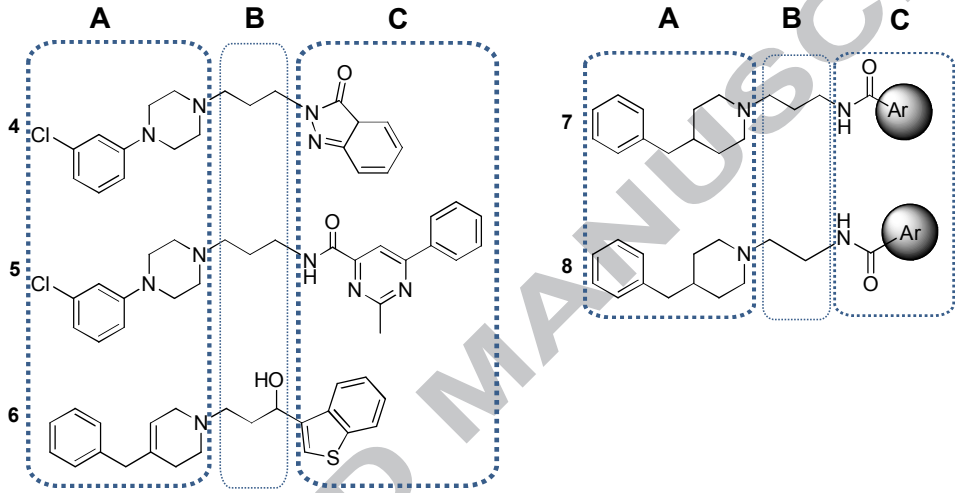
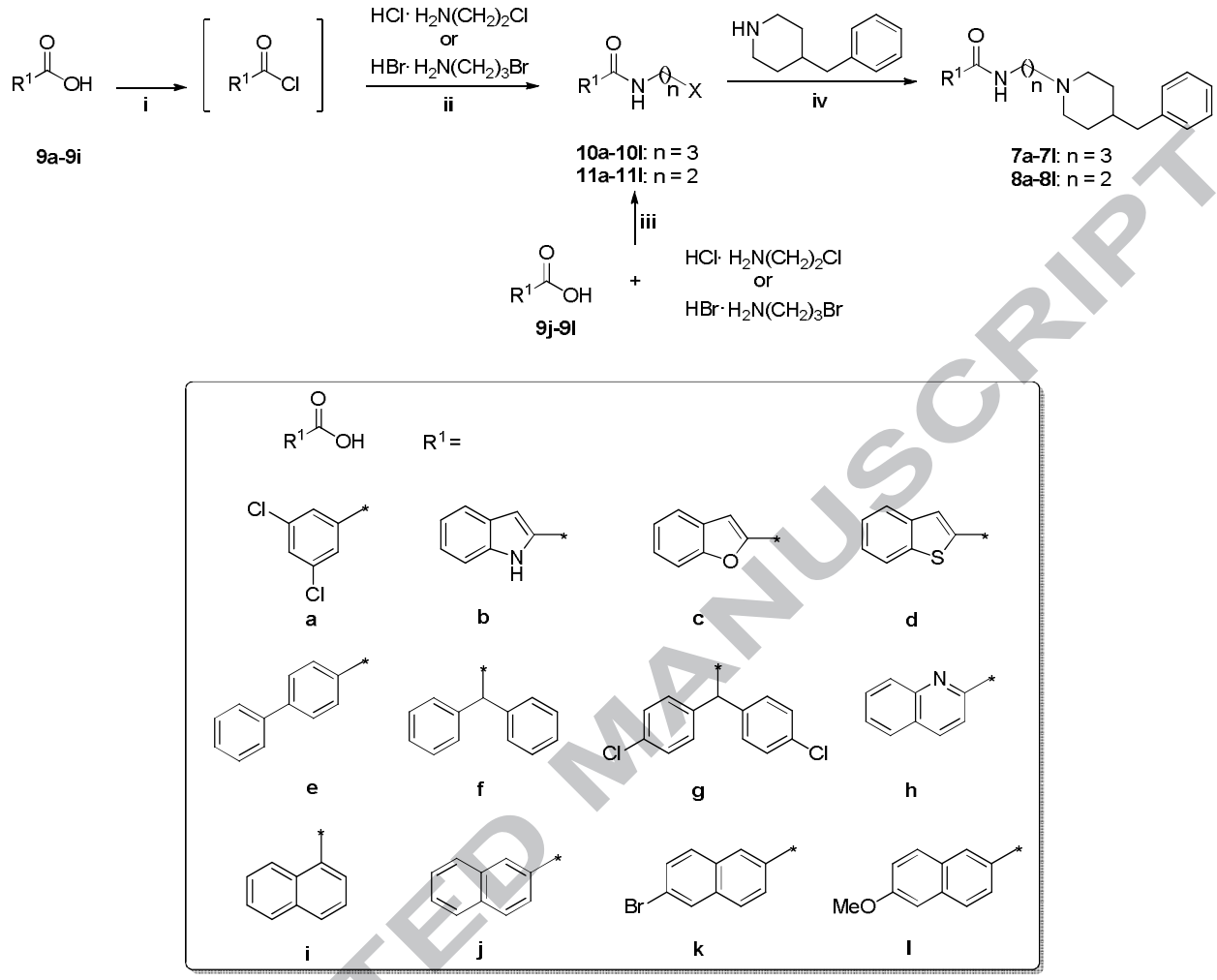


Figure 2. Design of 4-benzylpiperidine carboxamides

2. Chemistry

Various aromatic carboxylic acids **9a–9i** were refluxed overnight with excess thionyl chloride and the residue obtained by evaporating the solvent was further reacted with 3-bromopropylamine hydrobromide or 2-chloroethylamine hydrochloride in the presence of triethylamine (TEA) to give different amides **10a–10i** and **11a–11i** (Scheme 1). Alternatively, amidation reaction between aromatic carboxylic acid **9j–9l** and 3-bromopropylamine hydrobromide or 2-chloroethylamine hydrochloride using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI·HCl) as a coupling reagent gave corresponding amides **10j–10l** and **11j–11l.** The substitution reaction of **10a–10l** and **11a–11l** with 4-benzylpiperidine gave carboxamides derivatives **7a–7l** and **8a–8l**.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, benzene/toluene/tetrahydrofuran, reflux (ii) CH_2Cl_2, TEA, 0 °C–r.t. (iii) EDCI·HCl, DMAP, TEA, r.t. (iv) DMSO, TEA, 100 °C.

3. Result and discussion

3.1 Biological Screening

Serotonin and norepinephrine reuptake activities were measured by a neurotransmitter uptake assay. In the assay, human embryonic kidney 293 (HEK-293) cells were stably transfected with human serotonin transporter (hSERT) and human norepinephrine transporter (hNET). The serotonin and norepinephrine inhibitory activities of the synthesized compounds are presented in Table 1.

Table 1: Serotonin and norepinephrine reuptake inhibition by 4-benzylpiperidine carboxamides **7a–l** and **8a–l.**

Compd	R^1	RI[a]	RI[b]	Compd	R^1	RI[a]	RI[b]
7a	3,5-dichlorophenyl	0.83	1.12	**8a**	3,5-dichlorophenyl	0.64	1.00
7b	2-indolyl	0.84	1.72[c]	**8b**	2-indolyl	0.58	1.49[c]
7c	benzo(*b*)furanyl	0.84	1.54[c]	**8c**	benzo(*b*)furanyl	0.78	1.09[c]
7d	benzo(*b*)thiophenyl	1.10	1.80[c]	**8d**	benzo(*b*)thiophenyl	0.77	1.92[c]
7e	4-biphenyl	1.01	1.59[c]	**8e**	4-biphenyl	0.98	1.49[c]
7f	diphenylacetyl	0.26	1.19[c]	**8f**	diphenylacetyl	0.29	1.04[c]
7g	bis(4-chlorophenyl)acetyl	0.19	1.37[c]	**8g**	bis(4-chlorophenyl)acetyl	0.40	1.54[c]
7h	2-quinolyl	0.85	0.62[c]	**8h**	2-quinolyl	1.03	0.53
7i	1-naphthyl	0.6	1.32	**8i**	1-naphthyl	0.91	0.10
7j	2-naphthyl	0.95	1.03	**8j**	2-naphthyl	0.8	1.27
7k	6-bromo-2-naphthyl	1.11	0.94	**8k**	6-bromo-2-naphthyl	0.51	0.83
7l	6-methoxy-2-naphthyl	0.98	1.00	**8l**	6-methoxy-2-naphthyl	0.63	1.97[c]

[a] Relative inhibition (serotonin reuptake inhibition at 1 μM by compound under test/venlafaxine HCl)

[b] Relative inhibition (norepinephrine reuptake inhibition at 1 μM by compound under test/GBR-12909)

[c] Relative inhibition (norepinephrine reuptake inhibition at 3 μM by compound under test/venlafaxine HCl)

Generally, 4-benzylpiperidine carboxamide derivatives with three carbon units in the linker showed better serotonin reuptake inhibitory activities than the compounds with two carbon units. However, compounds **7h** and **7i** with longer linkers were less active than analogs **8h** and **8i** with shorter linkers. The serotonin reuptake inhibition of derivatives **7f–7g** and **8f–8g** with bulky diphenyl acetyl groups was very low irrespective of the length of the linker. The remaining derivatives possessed moderate to potent serotonin reuptake inhibitory activity compared to venlafaxine (RI: 0.5–1.11).

Inhibition of reuptake of norepinephrine by 4-benzylpiperidine carboxamides also varied mainly on the length of linker. The compounds with a three-carbon linker showed better activity than compounds with a two-carbon linker. Interestingly, the activity of 1-naphthyl compound **7i** was increased significantly by 13-fold when the length of linker was extended from two to three carbons. Majority of 4-benzylpiperidine carboxamides displayed equipotent or more potent inhibition of norepinephrine reuptake than venlafaxine and GBR-12909.

4-Benzylpiperidine carboxamides **7a**, **7b**, **7c**, **7d**, **7e**, **7j**, **7k**, **7l**, **8e**, and **8h** with potent relative serotonin/norepinephrine reuptake inhibitory activities (RI > 0.8) were further analyzed to determine IC_{50} values. The IC_{50} values of serotonin and norepinephrine reuptake inhibitory activity of the selected compounds are presented in Table 2.

Table 2: IC_{50} value for serotonin and norepinephrine reuptake inhibition of the compounds

Compd	n	R^1	hSERT (μM)	hNET (μM)
7a	3	3,5-dichlorophenyl	0.422	0.267
7b	3	2-indolyl	0.546	0.268
7c	3	benzo(*b*)furanyl	0.500	0.621
7d	3	benzo(*b*)thiophenyl	0.449	4.75
7e	3	4-biphenyl	0.056	0.153
7j	3	2-naphthyl	0.108	0.342
7k	3	6-bromo-2-naphthyl	1.914	0.885
7l	3	6-methoxy-2-naphthyl	0.323	0.238
8e	2	4-biphenyl	0.986	0.472
8h	2	2-quinolyl	0.786	0.275
Venlafaxine HCl	-	-	0.204	2.553

The fact that serotonin reuptake inhibition by 4-benzylpiperidine carboxamides with a three-carbon linker is better than the compounds with a two-carbon linker was reinforced by the IC_{50} values of 4-biphenyl derivatives **7e** and **8e**. The activity of **7e** was 17-times better than of **8e**. The serotonin reuptake inhibitory activities of compounds containing fused heterocyclic ring were in the following increasing order: 2-indolyl (**7b**) < benzo(*b*)furanyl (**7c**) < benzo(*b*)thiophenyl (**7d**). Furthermore, the activity of unsubstituted naphthyl derivative **7j** was greater than 6-bromo- **7k** and 6-methoxy-substituted **7l** naphthyl compounds. Among 10, 4-benzylpiperidine carboxamides, compounds **7e** and **7j** showed 3.5- and 2-times better serotonin reuptake inhibitory activity than the standard drug, venlafaxine HCl.

Norepinephrine reuptake inhibition by all 4-benzylpiperidine carboxamides, except **7d** (IC_{50}: 4.75 μM), was greater than the standard drug, venlafaxine HCl. The norepinephrine reuptake inhibitory activity of 4-biphenyl derivative **7e** is additional evidence of the greater activity achieved with a three-carbon linker than with a two-carbon linker.

4. Conclusion

In summary, we developed 4-benzylpiperidine carboxamide-based dual reuptake inhibitors. Compounds with various linker lengths and aromatic rings were synthesized by amidation and substitution reactions. Primary screening at a single concentration and IC_{50} values showed that the compounds having a three-carbon linker were more active than the ones with a two-carbon linker. 4-Biphenyl- and 2-naphthyl-substituted derivatives **7e** and **7j** showed better dual reuptake inhibition than the standard drug, venlafaxine HCl. Thus, based on the presented results, 4-benzylpiperidine carboxamide can be the basis for the further development of promising antidepressant drugs.

5. Experimental Section

5.1. Chemistry

Melting points were determined by the capillary method on Thomas Hoover melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a JASCO-FT IR spectrometer using KBr pellets. ^{1}H and ^{13}C NMR data were collected on a Varian 75, 125 and 300 MHz spectrometer and are reported in ppm, downfield from the peak of the internal standard, tetramethylsilane. Data are reported as chemical shift, number of protons, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet). Mass spectra were obtained on a Shimadzu UFLC-MS liquid chromatograph mass spectrometer using the electron spray ionization (ESI) method. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). Thin-layer chromatography was performed using plates coated with silica gel 60 F254 (Merck). Chemical reagents were purchased from Sigma-Aldrich and Alfa Aesar, and were used without further purification.

5.1.1. *N*-(3-Bromopropyl)-3,5-dichlorobenzamide (10a). Compound **9a** (191 mg, 1 mmol) was refluxed in excess of thionyl chloride (3 mL) overnight. Excess of thionyl chloride was evaporated and the residue was dissolved in CH_2Cl_2, 3-bromopropylamine hydrobromide (328 mg, 1.5 mmol was added followed by triethylamine (TEA; 0.42 mL, 3 mmol). The reaction mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was diluted with CH_2Cl_2 and sequentially washed with water, 1N HCl and saturated $NaHCO_3$.

The organic layer was dried over $MgSO_4$, filtered and concentrated. The obtained product was purified by column chromatography with *n*-hexane: Ethyl acetate (EtOAc) = 4:1 to obtain **10a,** (236 mg, 76%) as white solid. Retention factor R_f = 0.85 (*n*-hexane: EtOAc = 1:1). Mp = 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 1.8 Hz, 2H, Ar-H), 7.49 (s, *J* = 1.8 Hz, 1H, Ar-H), 6.38 (s, 1H, -CONH), 3.62 (q, *J* = 6.4 Hz, -CONH-C$\underline{H}_2$), 3.49 (t, *J* = 6.3 Hz, 2H, -C$\underline{H}_2$Br), 2.21 (quin, *J* = 6.5 Hz, 2H, -C$\underline{H}_2$CH_2Br).

5.1.2 *N*-(3-Bromopropyl)-1*H*-indole-2-carboxamide (10b). The procedure described for the preparation of **10a** was used with compound **9b** (400 mg, 2.48 mmol), thionyl chloride (8 mL) in presence of THF (10 mL), 3-bromopropylamine hydrobromide (814 mg, 3.71 mmol) and TEA (1 mL, 7.44 mmol) to obtain **10b** (314 mg, 45%) as light yellow solid. R_f = 0.75 (*n*-hexane: EtOAc = 1:1). Mp = 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (s, 1H, -NH), 7.65 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar-H), 7.44 (dd, *J* = 8.4, 0.9 Hz, 1H, Ar-H), 7.32–7.26 (m, ≈ 3H, Ar-H, overlapped with $CHCl_3$ peak), 7.17–7.12 (m, 1H, Ar-H), 6.84 (dd, *J* = 2.1, 0.9 Hz, 1H, Ar-H), 6.37 (s, 1H, -CONH), 3.66 (q, *J* = 6.5 Hz, 2H, -CONH-C$\underline{H}_2$), 3.51 (t, *J* = 6.45 Hz, 2H, -C$\underline{H}_2$Br), 2.33 (quin, *J* = 6.45 Hz, 2H, -C$\underline{H}_2$CH_2Br).

5.1.3 *N*-(3-Bromopropyl)benzo(*b*)furan-2-carboxamide (10c). The procedure described for the preparation of **10a** was used with compound **9c** (300 mg, 1.85 mmol), thionyl chloride (5 mL) in presence of benzene (10 mL), 3-bromopropylamine hydrobromide (607mg, 2.77 mmol), TEA (0.77 mL, 5.55 mmol) to obtain **10c** (480 mg, 92%) as white solid. R_f = 0.72 (*n*-hexane: EtOAc = 1:1). Mp = 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H, Ar-H), 7.48–7.45 (m, 2H, Ar-H), 7.39 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H, Ar-H), 7.29–7.24 (m, 1H, Ar-H), 7.04 (s, 1H, -CONH), 3.64 (q, *J* = 6.5 Hz, 2H, -CONH-C$\underline{H}_2$), 3.49 (t, *J* = 6.6 Hz, 2H, -CH_2Br), 2.21 (quin, *J* = 6.5 Hz, 2H, - C$\underline{H}_2$CH_2Br).

5.1.4 *N*-(3-Bromopropyl)benzo[*b*]thiophene-2-carboxamide (10d). The procedure described for the preparation of **10a** was used with compound **9d** (220 mg, 1.23 mmol), thionyl chloride (3 mL) in presence of toluene (5 mL), 3-bromopropylamine hydrobromide (402mg, 1.84 mmol) and TEA (0.51 mL, 3.69 mmol to obtain **10d** (325 mg, 89%) as white solid. R_f = 0.74 (*n*-hexane: EtOAc = 1:1). Mp = 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.79 (m, 3H, Ar-H), 7.43–

7.38 (m, 2H, Ar-H), 6.47 (s, 1H,-CONH), 3.64 (q, *J* = 6.4 Hz, 2H, -CONH-C<u>H</u>$_2$), 3.51 (t, *J* = 6.3 Hz, 2H, -CH_2Br), 2.23 (quin, *J* = 6.4 Hz, 2H, - C<u>H</u>$_2$$CH_2$Br).

5.1.5 *N*-(3-Bromopropyl)-1,2-dihydro-[1,1′-biphenyl]-4-carboxamide (10e). The procedure described for the preparation of **10a** was used with compound **9e** (1000mg, 4.99 mmol), thionyl chloride (20 mL) in presence of benzene (20 mL), 3-bromopropylamine hydrobromide (1637 mg, 7.48 mmol and TEA (2 mL, 14.97 mmol) to obtain **10e (**952 mg, 60%) as white solid**.** R_f = 0.62 (*n*-hexane: EtOAc = 1:1). Mp = 135 °C. IR (cm^{-1}): 3324 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.82 (m, 2H, Ar-H), 7.67–7.58 (m, 4H, Ar-H), 7.50–7.36 (m, 3H, Ar-H), 6.42 (s, 1H, -CONH), 3.69–3.61 (m, 2H), 3.51 (t, *J* = 6.4 Hz, 2H, -CH_2Br), 2.20 (quin, *J* = 6.5, 2H, - C<u>H</u>$_2$$CH_2$Br).

5.1.6 *N*-(3-Bromopropyl)-2,2-diphenylacetamide (10f). The procedure described for the preparation of **10a** was used with compound **9f** (600 mg, 2.82 mmol), thionyl chloride (10 mL) in presence of benzene (10 mL), 3-bromopropylamine hydrobromide (926mg, 4.23mmol and TEA (1.17 (10 mL), 8.46 mmol) to obtain **10f** (563 mg, 63%) as light brown liquid. R_f = 0.82 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.32 (m, ≈ 11H, Ar-H, overlapped with $CHCl_3$), 7.16 (s, 1H, -CONH), 3.51 (q, *J* = 6.4 Hz, 2H, -CONH-C<u>H</u>$_2$), 3.38 (t, *J* = 6.4 Hz, 2H, -CH_2Br), 2.17–2.10 (m, 2H, -C<u>H</u>$_2$$CH_2$Br).

5.1.7 *N*-(3-Bromopropyl)-2,2-bis(4-chlorophenyl)acetamide (10g). The procedure described for the preparation of **10a** was used with compound **9g** (300mg, 1.06 mmol), thionyl chloride (5 mL), 3-bromopropylamine hydrobromide (348 mg, 1.59 mmol and TEA (0.44 mL, 3.18 mmol) to obtain **10g** (175 mg, 43%) as white solid R_f = 0.83 (*n*-hexane: EtOAc = 1:1). Mp = 109 °C. IR (cm^{-1}): 3448 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (m, ≈ 11H, overlapped with $CHCl_3$ peak), 3.56–3.43 (m, 2H, -CONH-C<u>H</u>$_2$), 3.37 (t, *J* = 6.45, 2H, -C<u>H</u>$_2$Br), 2.11 (q, *J* = 6.5, 2H, - C<u>H</u>$_2$$CH_2$Br).

5.1.8 *N*-(3-Bromopropyl)quinoline-2-carboxamide (10h). The procedure described for the preparation of **10a** was used with compound **9h** (550 mg, 3.17 mmol), thionyl chloride (8 mL), 3-bromopropylamine hydrobromide (1040 mg, 4.75mmol and TEA (1.32 mL, 9.51 mmol) to obtain 10h (697 mg, 75%) as white solid R_f = 0.87 (*n*-hexane: EtOAc = 1:1). Mp = 94 °C. IR (cm^{-1}): 3526 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H, -CONH), 8.30 (s, 2H, Ar-H),

7.88 (ddd, *J* = 8.1, 1.5, 0.6 Hz, 1H, Ar-H), 7.77 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, Ar-H), 7.62 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, Ar-H), 7.59 (d, *J* = 6.9 Hz, 1H, Ar-H), 3.74–3.66 (m, 2H, -CONH-C$\underline{H}_2$), 3.53 (t, *J* = 6.6 Hz, 2H, -CH_2Br), 2.27 (quin, *J* = 6.6, 2H, -C$\underline{H}_2CH_2$Br).

5.1.9 *N*-(3-Bromopropyl)-1-naphthamide (10i). The procedure described for the preparation of **10a** was used with compound **9i** (500 mg, 2.90 mmol), thionyl chloride (10 mL) in presence of toluene (10 mL), 3-bromopropylamine hydrobromide (952mg, 4.35) and TEA (1.21 mL, 8.7 mmol) to obtain **10i (**626 mg 74%) as white solid. R_f = 0.74 (*n*-hexane: EtOAc = 1:1). Mp = 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24–8.21 (m, 1H, Ar-H), 7.88–7.82 (m, 2H, Ar-H), 7.52–7.49 (m, 3H, Ar-H),7.40–7.35 (m, 1H, Ar-H), 6.41 (s, 1H, -CONH), 3.59 (q, *J* = 6.4 Hz, 2H, -CONHC$\underline{H}_2$), 3.46 (t, *J* = 6.4 Hz, 2H, -C$\underline{H}_2$Br), 2.18 (quin, *J* = 6.4 Hz, 2H, -C$\underline{H}_2CH_2$Br).

5.1.10 *N*-(3-Bromopropyl)-2-naphthamide (10j). The **9j** (250 mg, 1.45 mmol) was dissolved in CH_2Cl_2 (5 mL). EDCI·HCl (333 mg, 1.74 mmol) was added to reaction mixture followed by DMAP (8.9 mg, 0.07mmol). To the reaction solution 3-bromopropylamine hydrobromide (317 mg, 1.45 mmol) was added and stirred for 30 minutes. TEA (0.66 mL, 4.78 mmol) was poured slowly drop wise and stirred reaction at room temperature. After the reaction was completed, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The obtained product was purified by column chromatography with Hexane: EtOAc (4:1) to obtain **10j** (266 mg, 63%) as white solid. R_f = 0.79 (*n*-hexane: EtOAc = 1:1). Mp = 124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, 1-H), 7.92–7.80 (m, 4H, Ar-H), 7.60–7.51 (m, 2H, Ar-H), 6.54 (s, 1H, -CONH), 3.68 (q, *J* = 6.4 Hz, 2 Hz, -CONH-C$\underline{H}_2$), 3.53 (t, *J* = 6.3, 2H, -C$\underline{H}_2$Br), 2.25 (quin, *J* = 6.6 Hz, 2H, -C$\underline{H}_2CH_2$Br).

5.1.11 6-Bromo-*N*-(3-chloropropyl)-2-naphthamide (10k). The procedure described for the preparation of **10j** was used with compound **9k** (300 mg, 1.19 mmol), EDCI·HCl (272 mg, 1.42 mmol), DMAP (11.31mg, 0.06 mmol), 3-bromopropylamine hydrobromide (260 mg, 1.19 mmol) and TEA (0.54 mL, 3.92 mmol) to obtain **10k (**242 mg, 55%) as white solid. R_f = 0.71 (*n*-hexane: EtOAc = 1:1). Mp = 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H, Ar-H), 8.04 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.86–7.77 (m, 3H, Ar-H), 7.61 (dd, *J* = 8.7, 1.8 Hz, 1H, 7-H), 6.5 (s, 1H, -CONH), 3.68 (q, *J* = 6.4, 2H, -CONH-C$\underline{H}_2$), 3.53 (t, *J* = 6.45, 2H, -C$\underline{H}_2$Br), 2.26 (quin, *J* = 6.45, 2H, -C$\underline{H}_2CH_2$Br).

5.1.12 *N*-(3-Bromopropyl)-6-methoxy-2-naphthamide (10l). The procedure described for the preparation of **10j** was used with compound **9l** (500 mg, 2.47 mmol), EDCI·HCl (567 mg, 2.96 mmol), DMAP (14.6 mg, 0.12 mmol), 3-bromopropylamine hydrobromide (540 mg, 2.47 mmol) and TEA (1.1 mL, 8.15 mmol) to obtain **10l** (493 mg, 62 %) as white solid. R_f = 0.54 (*n*-hexane: EtOAc = 1:1). Mp = 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$)): δ 8.20 (s, 1H, Ar-H), 7.81–7.74 (m, 3H, Ar-H), 7.20–7.13 (m, 2H, Ar-H), 6.54 (s, 1H, -CONH), 3.93 (s, 1H, -OCH_3), 3.66 (q, *J* = 6.4 Hz, 2H, -CONHC$\underline{H}_2$), 3.52 (t, *J* = 6.4 Hz, 2H, -C$\underline{H}_2$Br), 2.24 (quin, *J* = 6.4 Hz, 2H, -C$\underline{H}_2$CH_2Br).

5.1.13. 3, 5-Dichloro-*N*-(2-chloroethyl)benzamide (11a). The procedure described for the preparation of **10a** was used with compound **9a** (400 mg, 2.09 mmol), thionyl chloride (5 mL), 2-chloroethylamine hydrochloride (365 mg, 3.14 mmol) and triethylamine (TEA; 0.87 mL, 6.27 mmol) to obtain **11a** (422 mg, 80%) as white solid. R_f = 0.85 (*n*-hexane: EtOAc = 1:1). Mp = 135 °C. IR (cm^{-1}): 1634 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (s, 1H, -CONH), 7.87 (d, *J* = 1.8 Hz, 2H, Ar-H), 7.83 (t, *J* = 1.95 Hz, 1H, Ar-H), 3.73 (t, *J* = 11.7 Hz, -CONH-C$\underline{H}_2$).

5.1.14 *N*-(2-Chloroethyl)-1*H*-indole-2-carboxamide (11b). The procedure described for the preparation of **10a** was used with compound **9b** (500mg, 3.10 mmol), thionyl chloride (10 mL) in presence of THF (10 mL), 2-chloroethylamine hydrochloride (835 mg, 4.65 mmol) and TEA (1.3 mL, 9.3 mmol) to obtain **11b** (345 mg, 50%) as light yellow solid. R_f = 0.74 (*n*-hexane: EtOAc = 1:1). Mp = 158 °C. IR (cm^{-1}): 3444 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.43 (s, 1H, -NH), 7.65 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar-H), 7.57 (t, *J* = 5.4 Hz, 1H, -CONH), 7.41 (m, 1H, Ar-H), 7.31 (m, 1H, Ar-H), 7.24 s, 1H, Ar-H), 7.20 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, Ar-H), 3.94 (q, *J* = 5.7 Hz, 2H, -CONH-C$\underline{H}_2$), 3.78 (t, *J* = 5.8 Hz, 2H, -C$\underline{H}_2$Cl).

5.1.15 *N*-(2-Chloroethyl)benzo(*b*)furan-2-carboxamide (11c). The procedure described for the preparation of **10a** was used with compound **9c** (324 mg, 2 mmol), thionyl chloride (5 mL) in presence of benzene (10 mL), 2-chloroethylamine hydrochloride (348 mg, 3 mmol) and TEA (0.83 mL, 6 mmol) to obtain **11c** (402 mg, 90%) as white solid**.** R_f = 0.72 (*n*-hexane: EtOAc = 1:1). Mp = 115 °C. IR (cm^{-1}): 3691 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.66 (m, 1H, Ar-H), 7.54–7.49 (m, 2H, Ar-H), 7.46–7.4 (m, 1H, Ar-H), 7.33–7.27 (m, 1H, Ar-H), 7.04 (s, 1H, -CONH), 3.88–3.82 (m, 2H), 3.78–3.73 (m, 2H).

5.1.16 *N*-(2-Chloroethyl)benzo[*b*]thiophene-2-carboxamide (11d). The procedure described for the preparation of **10a** was used with compound **9d** (200 mg, 1.12 mmol), thionyl chloride (3 mL) in presence of toluene (5 mL), 2-chloroethylamine hydrochloride (195mg, 1.68 mmol) and TEA (0.46 mL, 3.36 mmol) to obtain **11d** (228 mg, 85%) as white solid. R_f = 0.73 (*n*-hexane: EtOAc = 1:1). Mp = 144 °C. IR (cm^{-1}): 3316 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.80 (m, 3H, Ar-H), 7.46–7.37 (m, 2H, Ar-H), 6.62 (s, 1H,-CONH), 3.86–3.80 (m, 2H), 3.77–3.73 (m, 2H).

5.1.17 *N*-(2-Chloroethyl)-1,2-dihydro-[1,1′-biphenyl]-4-carboxamide (11e). The procedure described for the preparation of **10a** was used with compound **9e** (1000 mg, 4.99 mmol), thionyl chloride (20 mL) in presence of benzene (20 mL), 2-chloroethylamine hydrochloride (867mg, 7.48 mmol and TEA (2 mL, 14.97 mmol) to obtain **11e** (718 mg, 55%) as white solid. R_f = 0.61 (*n*-hexane: EtOAc = 1:1). Mp = 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.84 (m, 2H, Ar-H), 7.70–7.60 (m, 4H, Ar-H), 7.50–7.36 (m, 3H, Ar-H), 6.58 (s, 1H,-CONH), 3.87–3.75 (m, 4H).

5.1.18 *N*-(2-Chloroethyl)-2,2-diphenylacetamide (11f). The procedure described for the preparation of **10a** was used with compound **9f** (530 mg, 2.49 mmol), thionyl chloride (10 mL) in presence of benzene, 2-chloroethylamine hydrochloride (432mg, 3.73 mmol and TEA (1 mL, 7.47 mmol) to obtain **11f** (386 mg, 60%) as light yellow liquid. R_f = 0.82 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.33 (m, 11H), 3.73–3.65 (m, 4H).

5.1.19 *N*-(2-Chloroethyl)-2,2-bis(4-chlorophenyl)acetamide (11g). The procedure described for the preparation of **10a** was used with compound **9g** (300 mg, 1.06 mmol), thionyl chloride (5 mL), 2-chloroethylamine hydrochloride (184 mg, 1.59 mmol and TEA (0.44 mL), 3.18 mmol) to obtain **11g** (138 mg, 40%) as white solid. R_f = 0.85 (*n*-hexane: EtOAc = 1:1). Mp = 129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.42 (m, 1H, -CONH), 7.37–7.30 (m, ≈ 9H, Ar-H, overlapped with $CHCl_3$ peak), 3.73–3.64 (m, 4H).

5.1.20 *N*-(2-Chloroethyl)quinoline-2-carboxamide (11h). The procedure described for the preparation of **10a** was used with compound **9h** (200 mg, 1.15 mmol), thionyl chloride (3 mL), 2-chloroethylamine hydrochloride (200 mg, 1.72 mmol and TEA (0.48 mL, 3.45 mmol) to obtain **11h** (200 mg, 74%) as white solid. R_f = 0.68 (*n*-hexane: EtOAc = 1:1). Mp = 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H, -CONH), 8.30 (d, *J* = 2.1 Hz, 2H, Ar-H), 8.14–8.11 (m, 1H,

Ar-H), 7.8 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar-H), 7.75 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, Ar-H), 7.62 (ddd, *J* = 8.1, 6.9, 1.5 Hz, 1H, Ar-H), 3.93–3.86 (m, 2H), 3.80–3.76 (m, 2H).

5.1.21 *N*-(2-Chloroethyl)-1-naphthamide (11i). The procedure described for the preparation of **10a** was used with compound **9i** (600 mg, 3.48 mmol), thionyl chloride (10 mL) in presence of toluene (10 mL), 2-chloroethylamine hydrochloride (605 mg, 5.22 mmol) and TEA (1.45 ml, 8.7 mmol) to obtain **11i** (528 mg (65%) as white solid. R_f = 0.60 (*n*-hexane: EtOAc = 1:1). Mp = 104 °C. IR (cm^{-1}): 3310(NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21–8.18 (m, 1H, 1-H), 7.82–7.77 (m, 2H, Ar-H), 7.48–7.44 (m, 3H, Ar-H), 7.32–7.27 (m, 1H, Ar-H), 6.80 (s, 1H,-CONH), 3.68–3.58 (m, 4H).

5.1.22 *N*-(2-Chloroethyl)-2-naphthamide (11j). The procedure described for the preparation of **10j** was used with compound **9j** (320 mg, 1.85 mmol), EDCI·HCl (425 mg, 2.22 mmol), DMAP (11 mg, 0.01mmol), 2-chloroethylamine hydrochloride (214 mg, 1.85 mmol) and TEA (0.85 mL, 6.10 mmol) to obtain **11j** (259 mg, 60%) as white solid. R_f = 0.60 (*n*-hexane: EtOAc = 1:1). Mp = 138 °C. IR (cm^{-1}): 3058 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H, Ar-H), 7.95–7.82 (m, 4H, Ar-H), 7.61–7.52 (m, 2H, Ar-H), 6.71 (s, 1H, -CONH), 3.91–3.77 (m, 4H).

5.1.23 6-Bromo-*N*-(2-chloroethyl)-2-naphthamide (11k). The procedure described for the preparation of **10j** was used with compound **9k** (251 mg, 0.99 mmol), EDCI·HCl (226 mg, 1.18 mmol), DMAP (6 mg, 0.05 mmol), 2-chloroethylamine hydrochloride (115 mg, 0.99 mmol) and TEA (0.45 mL, 3.26 mmol) to obtain **11k** (161 mg, 52%) as white solid. R_f = 0.77 (*n*-hexane: EtOAc = 1:1). Mp = 150 °C. IR (cm^{-1}): 307 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 7.88–7.77 (m, 3H, Ar-H), 7.63–7.59 (m, 1H, Ar-H), 6.75 (s, 1H, -CONH), 3.90–3.76 (m, 4H).

5.1.24 *N*-(2-Chloroethyl)-6-methoxy-2-naphthamide (11l). The procedure described for the preparation of **10j** was used with compound **9l** (500 mg, 2.47 mmol), EDCI·HCl (567 mg, 2.96 mmol), DMAP (14.6 mg, 0.12 mmol), 2-chloroethylamine hydrochloride (286 mg, 2.47 mmol) and TEA (1.1 mL, 8.15 mmol) to obtain **11l** (390 mg, 60%) as white solid .R_f = 0.57 (*n*-hexane: EtOAc = 1:1). Mp = 133 °C. IR (cm^{-1}): 3657 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, Ar-H), 7.83–7.76 (m, 3H, Ar-H), 7.22–7.15 (m, 2H, Ar-H), 6.69 (s, 1H, -CONH), 3.94 (s, 1H, -OCH_3), 3.89–3.83 (m, 2H), 3.80–3.76 (m, 2H).

5.1.25 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-3, 5-dichlorobenzamide (7a). The mixture of compound **10a** (130 mg, 0.41 mmol), 4-benzylpiperidine (0.15 mL, 0.83 mmol), TEA (0.23 mL, 1.67 mmol) and DMSO (1 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 **7a** (101 mg, 60%) as white solid. R_f = 0.51 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 105 °C. IR (cm^{-1}): 3311 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 1H, -CONH), 7.73 (d, *J* = 2.1Hz, 2-H), 7.51 (t, *J* = 1.8 Hz, 1H, 4-H), 7.30–7.17 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 3.55 (q, *J* = 5.2 Hz, 2H, -CONH-C$\underline{H}_2$), 3.00 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.58–2.52 (m, 4H), 1.85 (t, *J* = 10.95, 2H, -CH_2N), 1.78–1.49 (m, 5H), 1.31–1.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 140.6, 138.0, 135.2, 131.0, 129.0, 128.2, 125.9, 125.8, 59.5, 54.3, 42.8, 42.0, 38.1, 32.5, 23.5. HRMS (ESI): *m/z* 405.1443 $(M+H)^+$ (calcd for $C_{22}H_{27}Cl_2N_2O$, 405.1500).

5.1.26 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-1*H*-indole-2-carboxamide (7b). The procedure described for the preparation of **7a** was used with compound **10b** (400 mg, 1.42 mmol), 4-benzylpiperidine (0.50 mL, 2.84 mmol), TEA (0.79 mL, 5.68 mmol) and DMSO (3 mL) to obtain **7b** (239 mg, 45%) as light yellow solid. R_f = 0.42 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 113 °C. IR (cm^{-1}): 3344 (NH). ^{1}H NMR (300 MHz, $CDCl_3$)): δ 7.65 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.57 (t, *J* = 5.6 Hz, 1H, -CONH), 7.46 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.35–7.08 (m, 9H), 3.65 (q, *J* = 6.3 Hz, 2H, -CONH-C$\underline{H}_2$), 2.91 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.51–2.43 (m, 4H), 1.89–1.81 (m, 4H), 1.62–1.45 (m, 3H), 1.36–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.9, 140.6, 134.6, 129.1, 128.2, 125.8, 125.7, 125.3, 125.9, 121.0, 119.2, 112.7, 105.1, 56.6, 54.1, 43.2, 38.2, 37.9, 31.9, 29.8, 26.3.

5.1.27 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)benzo(*b*)furan-2-carboxamide (7c). The procedure described for the preparation of **7a** was used with compound **10c** (300 mg, 1.06 mmol), 4-benzylpiperidine (0.37 mL, 2.12 mmol), TEA (0.59 mL, 4.24 mmol) and DMSO (2.5 mL) to obtain **7c** (183 mg, 46%) as white solid. R_f = 0.40 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 104 °C. IR (cm^{-1}): 3203 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H, -CONH), 7.68–7.65 (m, 1H, Ar-H), 7.55 (dd, *J* = 8.4, 0.9 Hz, 1H, Ar-H), 7.45–7.38 (m, 2H, Ar-H), 7.31–7.11 (m, ≈ 7H, Ar-H, overlapped with $CHCl_3$), 3.58 (q, *J* = 5.6 Hz, 2H, -CONH-C$\underline{H}_2$), 2.98 (d, *J* = 11.7 Hz,

2H, -C<u>H</u>$_2$Ph), 2.60 (d, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 5.8 Hz, 2H, -C<u>H</u>$_2$N), 1.92–1.38 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 154.8, 149.6, 140.6, 129.0, 128.3, 127.8, 126.5, 125.9, 123.6, 122.7, 111.5, 109.9, 58.6, 54.2, 43.3, 40.2, 38.2, 32.3, 24.7. HRMS (ESI): *m/z* 377.2162 $(M+H)^+$ (calcd for $C_{24}H_{29}N_2O_2$, 377.2229).

5.1.28 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)benzo[*b*]thiophene-2-carboxamide (7d). The procedure described for the preparation of **7a** was used with compound **10d** (310 mg, 1.04 mmol), 4-benzylpiperidine (0.37 mL, 2.08 mmol), TEA (0.58 mL, 4.16 mmol) and DMSO (2.5 mL) to obtain **7d** (221 mg, 54%) as white solid. R_f = 0.31 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 111 °C. IR (cm^{-1}): 3225 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (s,1H, -CONH), 7.90–7.81 (m, 3H, Ar-H), 7.46–7.38 (m, 2H, Ar-H), 7.29–7.07 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 3.57 (q, *J* = 5.4 Hz, 2H, -CONH-C<u>H</u>$_2$), 3.00 (d, *J* = 12 Hz, 2H, -C<u>H</u>$_2$Ph), 2.52–2.50 (m, 4H), 1.91–1.83 (m, 2H), 1.79–1.72 (m, 2H), 1.69–1.51 (m, 3H), 1.43–1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 140.8, 140.4, 139.6, 139.2, 129.0, 128.3, 126.1, 125.9, 124.9, 124.8, 122.7, 58.8, 54.2, 43.5, 41.3, 37.8, 32.4, 24.4. HRMS (ESI): *m/z* 393.1943 $(M+H)^+$ (calcd for $C_{24}H_{29}N_2OS$, 393.2000).

5.1.29 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-[1,1′-biphenyl]-4-carboxamide (7e). The procedure described for the preparation of **7a** was used with compound **10e** (300 mg, 0.94 mmol), 4-benzylpiperidine (0.33 mL, 1.88 mmol), TEA (0.52 mL, 3.76 mmol) and DMSO (3 mL) to obtain **7e** (213 mg, 55%) as white solid. R_f = 0.28 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 108 °C. IR (cm^{-1}): 3103 (NH). ^{1}H NMR (300 MHz, $CDCl_3$)): δ 8.62 (s, 1H, -CONH), 7.92–7.88 (m, 2H, Ar-H), 7.67–7.61 (m, 4H, Ar-H), 7.50–7.30 (m, 3H, Ar-H), 7.27–7.08 (m, ≈ 7H, Ar-H, overlapped with $CHCl_3$), 3.58 (q, *J* = 5.4 Hz, 2H, -CONH-C<u>H</u>$_2$), 2.99 (d, *J* = 11.7 Hz, 2H, -C<u>H</u>$_2$Ph), 2.55–2.52 (m, 4H), 1.92–1.73 (m, 4H), 1.66–1.52 (m, 3H), 1.31–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 143.9, 140.4, 140.2, 133.9, 129.1, 129.0, 128.3, 128.0, 127.8, 127.2, 127.0, 125.9, 58.7, 54.1, 43.5, 41.0, 37.8, 32.4, 24.6. HRMS (ESI): *m/z* 413.2527 $(M+H)^+$ (calcd for $C_{28}H_{33}N_2O$, 413.2593).

5.1.30 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-2,2-diphenylacetamide (7f). The procedure described for the preparation of **7a** was used with compound **10f** (350 mg, 1.05 mmol), 4-benzylpiperidine (0.37 mL, 2.1 mmol), TEA (0.58 mL, 4.2 mmol) and DMSO (3 mL) to obtain **7f** (237 mg, 53%) as white solid. R_f = 0.40 (*n*-hexane: EtOAc = 1:1). Mp = 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.01 (m, ≈ 17H, overlapped with $CHCl_3$), 4.79 (s, 1H, -CH), 3.29 (q, *J* = 5.7 Hz, 2H, -CONH-C<u>H</u>$_2$), 2.75 (d, *J* = 10.8 Hz, 2H, -C<u>H</u>$_2$Ph), 2.49 (d, *J* = 6.6 Hz, 2H), 2.29 (t, *J* = 6.3 Hz, 2H, -CH_2N), 1.74 (t, *J* = 11.1, Hz),1.59–1.43 (m, 5H), 1.14–1.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 140.9, 139.6, 128.9, 128.7, 128.4, 128.0, 126.9, 125.7, 59.0, 57.2, 53.7, 42.9, 39.4, 37.6, 31.9, 25.1.

5.1.31 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-2,2-bis(4-chlorophenyl) acetamide (7g). The procedure described for the preparation of **7a** was used with compound **10g** (200 mg, 0.49 mmol), 4-benzylpiperidine (0.17 mL, 0.98 mmol), TEA (0.27 mL, 2.96 mmol) and DMSO (2 mL) to obtain **7g** (84 mg, 35%) as light brown liquid. R_f = 0.30, (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (t, *J* = 4.0 Hz, 1H, -CONH), 7.36–7.25 (m, ≈ 7H, Ar-H, overlapped with $CHCl_3$), 7.20–7.16 (m, 2H, Ar-H), 3.35 (q, *J* = 5.7Hz, 2H, -CONH-C<u>H</u>$_2$), 2.80 (d, *J* = 11.7 Hz, 2H, -C<u>H</u>$_2$Ph), 2.51 (d, *J* = 6.9 Hz, 2H), 2.36 (t, *J* = 6.1, 2H, -CH_2N), 1.83–1.75 (m, 2H), 1.66–1.45 (m, 5H), 1.11–1.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ170.7, 140.2, 137.9, 133.2, 130.0, 129.1, 128.8, 128.2, 125.9, 57.70, 57.66, 53.8, 43.0, 40.0, 37.7, 32.0, 24.6.

5.1.32 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)quinoline-2-carboxamide (7h). The procedure described for the preparation of **7a** was used with compound **10h** (100 mg, 0.34 mmol), 4-benzylpiperidine (0.12 mL, 0.68 mmol), TEA (0.19 mL, 1.36 mmol) and DMSO (2 mL) to obtain **7h** (70 mg, 53%) as white solid. R_f = 0.34 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 130 °C. IR (cm^{-1}): 3280 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H, -CONH), 8.30 (t, *J* = 9 Hz, 1H, Ar-H), 8.18 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.88 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.80–7.75 (m, 1H, Ar-H), 7.61 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.27–7.08 (m, 5H, Ar-H), 3.62 (q, *J* = 9.3 Hz, 2H, -CONH-C<u>H</u>$_2$), 2.97 (d, *J* = 11.4 Hz, 2H, -C<u>H</u>$_2$Ph), 2.53–2.47 (m, 4H), 1.91–1.64 (M, 4H), 1.60–1.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 150.0, 146.5, 140.2, 137.2, 130.0, 129.8,

129.3, 129.0, 128.2, 127.85, 127.75, 125.9, 118.9, 56.8, 53.8, 42.7, 41.0, 38.5, 37.6, 31.1, 29.7, 25.8.

5.1.33 *N*-[3-(4-Benzylpiperidin-1-yl)propyl]-1-naphthamide (7i). The procedure described for the preparation of **7a** was used with compound **10i** (100 mg, 0.34 mmol), 4-benzylpiperidine (0.12 mL, 0.68 mmol), TEA (0.19 mL, 1.36 mmol) and DMSO (1 mL) to obtain **7i** (59 mg, 45%) as white solid. R_f = 0.66 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 125°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H, -CONH), 8.38–8.35 (m, 1H, Ar-H), 7.94–7.86 (m, 2H, Ar-H), 7.64–7.49 (m, 4H, Ar-H), 7.25–7.12 (m, 3H, Ar-H), 6.97–6.95 (m, 2H, Ar-H), 3.63 (q, *J* = 5.5 Hz, 2H, -CONH-C$\underline{H}_2$), 2.81 (d, *J* = 11.4 Hz, 2H, -C$\underline{H}_2$Ph), 2.47 (t, *J* = 5.8, 2H), 2.15 (d, *J* = 5.8 Hz, 2H), 1.79–1.69 (m, 4H), 1.36–1.25 (m, 3H), 0.66–0.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 140.5, 135.4, 133.7, 130.3, 130.2, 129.0, 128.3, 128.1, 126.9, 126.3, 125.8, 125.7, 125.0, 124.7, 58.3, 53.7, 43.0, 40.8, 37.5,32.0, 29.7, 24.6.

5.1.34 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-2-naphthamide (7j). The procedure described for the preparation of **7a** was used with compound **10j** (100 mg, 0.52 mmol), 4-benzylpiperidine (0.19 mL, 1.04 mmol), TEA (0.29 mL, 2.08 mmol) and DMSO (1 mL) to obtain **7j** (100 mg, 50%) as white solid. R_f = 0.36 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 118 °C. IR (cm^{-1}): 3226 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H, -CONH), 8.34 (s, 1H, 1-H), 7.99–7.87 (m, 4H, Ar-H), 7.59–7.53 (m, 2H, Ar-H), 7.26–7.11 (m, 2H, Ar-H, overlapped with $CHCl_3$), 7.03–7.01(m, 2H, Ar-H), 3.62 (q, *J* = 5.3 Hz, 2H, -CONHC$\underline{H}_2$), 3.00 (d, *J* = 11.7 Hz, 2H,-C$\underline{H}_2$Ph), 2.55 (t, *J* = 5.7 Hz, 2H, -CH_2N), 2.43 (d, *J* = 6.9 Hz, 2H), 1.91–1.75 (m, 4H), 1.64–1.49 (m, 3H), 1.29–1.17 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.5, 140.4, 134.7, 132.7, 132.6, 129.0, 128.9, 128.23, 128.15, 127.8, 127.4, 127.3, 126.6, 125.9, 124.2, 58.9, 54.1, 43.2, 41.3, 37.8, 32.4, 24.4. HRMS (ESI): *m/z* 387.2329 $(M+H)^+$ (calcd for $C_{26}H_{31}N_2O$, 387.2436).

5.1.35 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-6-bromo-2-naphthamide (7k). The procedure described for the preparation of **7a** was used with compound **10k** (120 mg, 0.32 mmol), 4-benzylpiperidine (0.11 mL, 0.64 mmol), TEA (0.18 mL, 1.28 mmol) and DMSO (1 mL) to obtain **7k** (65 mg, 44%) as white solid. R_f = 0.38 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 100 °C. IR (cm^{-1}): 3286 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (t, *J* = 4.3 Hz, 1H, -CONH),

8.08 (d, *J* = 1.8Hz, 1H, Ar-H), 7.94 (d, *J* = 1.5Hz, 1H, Ar-H), 7.85–7.77 (m, 2H, Ar-H), 7.63 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H, Ar-H), 7.29–7.14 (m, ≈ 4H, Ar-H, overlapped with $CHCl_3$), 7.05–7.02 (m, 2H, Ar-H), 3.61 (q, *J* = 5.4 Hz, 2H, -CONH-CH_2), 2.30 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.55 (t, *J* = 5.5 Hz, 2H), 2.45 (d, *J* = 6.9, 2H), 1.91–1.70 (m, 4H), 1.66–1.50 (m, 3H), 1.25–1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ167.1, 140.1, 135.6, 132.7, 131.0, 130.4, 130.0, 129.9, 128.9, 128.2, 127.3, 127.2, 125.9, 125.1, 121.6, 58.5, 53.9, 43.0, 40.9, 37.6, 32.0, 24.1. HRMS (ESI): *m/z* 465.1505 $(M+H)^+$ (calcd for $C_{26}H_{30}{}^{79}BrN_2O$, 465.1542), 467.1478 $(M+H)^+$ (calcd for $C_{26}H_{30}{}^{81}BrN_2O$, 467.1521).

5.1.36 *N*-(3-(4-Benzylpiperidin-1-yl)propyl)-6-methoxy-2-naphthamide (7l). The procedure described for the preparation of **7a** was used with compound **10l** (200 mg, 0.62 mmol), 4-benzylpiperidine (0.22 mL, 1.24 mmol), TEA (0.34 mL, 2.48 mmol) and DMSO (2 mL) to obtain **7l** (129 mg, 50%) as brown solid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 118 °C. IR (cm^{-1}): 3277 (NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H, CONH), 8.38 (d, *J* = 1.2Hz, 1H, Ar-H), 8.28 (d, *J* = 8.7 Hz, 1H, Ar-H),7.98 (dd, *J* = 9.1, 8.1 Hz, 1H, Ar-H), 7.91 (d, *J* = 9.3Hz, 1H, Ar-H), 7.38 (d, *J* = 9 Hz, 1H, Ar-H), 7.28–7.15 (m, ≈ 5H, Ar-H, overlapped with $CHCl_3$), 7.07–7.04 (m, 2H, Ar-H), 4.06 (s, 3H, -OCH_3), 3.62 (q, *J* = 5.3 Hz, 2H, -CONH-C$\underline{H}_2$), 3.01 (d, *J* = 11.1 Hz, 2H, -C$\underline{H}_2$Ph), 2.56 (t, *J* = 5.5 Hz, 2H), 2.47 (d, *J* = 6.9 Hz, 2H), 1.92–1.75 (m, 4H), 1.66–1.48 (m, 3H), 1.30–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 158.9, 140.4, 136.1, 130.33, 130.28, 129.0, 128.2, 128.0, 127.2, 126.8, 125.9, 124.8, 119.5, 105.7, 58.7, 55.3, 54.0, 43.2, 41.0, 37.8, 32.3, 24.6. HRMS (ESI): *m/z* 417.2480 $(M+H)^+$ (calcd for $C_{27}H_{33}N_2O_2$, 417.2542).

5.1.37 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-3,5-dichlorobenzamide (8a). The procedure described for the preparation of **7a** was used with compound **11a** (100 mg, 0.40 mmol), 4-benzylpiperidine (0.14 mL, 0.80 mmol) and TEA (0.22 mL, 1.6 mmol) in DMSO (1 mL) to obtain **8a** (101 mg, 60%) as white solid. R_f = 0.61 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 1.8 Hz, 2H, Ar-H), 7.48 (t, *J* = 1.8 Hz, 1H, Ar-H), 7.30–7.25 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 6.84 (s, 1H, -CONH), 3.49 (q, *J* = 5.6 Hz, 2H, -CONH-C$\underline{H}_2$), 2.88 (d, *J* = 11.7 Hz, 2H,- C$\underline{H}_2$Ph), 2.56–2.52 (m, 4H),1.97 (ddd, *J* = 11.7, 2.1 Hz, 2H, -CH_2N), 1.69–1.48 (m, 3H), 1.35–1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 140.5, 137.7, 135.3, 131.1, 129.1, 128.2, 125.9, 125.7, 56.6, 53.7, 43.1, 37.9, 36.9, 32.2.

5.1.38 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-1*H*-indole-2-carboxamide (8b). The procedure described for the preparation of **7a** was used with compound **11b** (300 mg, 1.34 mmol), 4-benzylpiperidine (0.47 mL, 2.68 mmol), TEA (0.74 mL, 5.36 mmol) and DMSO (2 mL) to obtain **8b** (208 mg, 43%) as light yellow solid. R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.2, 1H, Ar-H), 7.46–7.43 (m, 1H, Ar-H). 7.30–7.10 (m, ≈ 10H, Ar-H, overlapped with $CHCl_3$), 7.03 (s, *J* = 4.5 Hz, 1H, -CONH), 6.84 (d, *J* = 1.2Hz, 1H, Ar-H), 3.5 (q, *J* = 5.7 Hz, 2H, -CONH-C$\underline{H}_2$), 2.92 (d, *J* = 11.7, 2H, -C$\underline{H}_2$Ph), 2.62–2.48 (m, 4H), 2.02–1.94 (m, 2H), 1.69–1.51 (m, 3H), 1.38–1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 140.4, 136.3, 130.9, 129.0, 128.2, 127.6, 125.9, 124.2, 121.8, 120.4, 112.0, 102.3, 56.8, 53.6, 43.0, 37.8, 36.1, 31.9.

5.1.39 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)benzo(*b*)furan-2-carboxamide (8c). The procedure described for the preparation of **7a** was used with compound **11c** (400 mg, 1.78 mmol), 4-benzylpiperidine (0.63 mL, 3.56 mmol), TEA (1.0 mL, 7.12 mmol) and DMSO (3 mL) to obtain **8c** (342 mg, 53%) as white solid .R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (ddd, 7.8, 1.2, 0.6 Hz, 1H), 7.54–7.51 (m, 1H), 7.44-7.38 (m, 2H), 7.31–7.14 (m, ≈ 8H, overlapped with $CHCl_3$), 3.55 (q, *J* = 5.8 Hz, 2H, -CONH-C$\underline{H}_2$), 2.91 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.58–2.55 (m, 4H), 2.02–1.93 (m, 2H), 1.68–1.48 (m, 3H), 1.39–1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 154.8, 149.1, 140.6, 129.1, 128.2, 127.7, 126.7, 125.8, 123.6, 122.6, 111.8, 110.1, 56.8, 53.8, 43.2, 37.9, 36.3, 32.3.

5.1.40 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)benzo[*b*]thiophene-2-carboxamide (8d). The procedure described for the preparation of **7a** was used with compound **11d** (250 mg, 1.04 mmol), 4-benzylpiperidine (0.37 mL, 2.08 mmol), TEA (0.58 mL, 4.16 mmol) and DMSO (2 mL) to obtain **8d** (204 mg, 52%) as white solid. R_f = 0.45 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.77 (m, 3H, Ar-H), 7.42–7.11 (m, ≈ 8H, Ar-H, overlapped with $CHCl_3$), 7.08 (s, 1H, -CONH), 3.51 (q, *J* = 5.7 Hz, 2H, -CONH-C$\underline{H}_2$), 2.88 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.52–2.51 (m, 4H), 1.99–1.91 (m, 2H), 1.67–1.48 (m, 3H), 1.35–1.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 140.8, 140.5, 139.2, 138.8, 129.1, 128.2, 126.2, 125.9, 125.1, 125.0, 124.8, 122.7, 56.8, 53.6, 43.1, 37.9, 36.7, 32.3.

5.1.41 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-[1,1′-biphenyl]-4-carboxamide (8e). The procedure described for the preparation of **7a** was used with compound **11e** (250 mg, 0.96 mmol), 4-benzylpiperidine (0.34 mL, 1.92 mmol), TEA (0.53 mL, 3.84 mmol) and DMSO (2 mL) to obtain **8e** (191 mg, 50%) as white solid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 148 °C. IR (cm^{-1}): 3027(NH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.84 (m, 2H, Ar-H), 7.68–7.39 (m, 4H, Ar-H), 7.49–7.35(m, 3H, Ar-H), 7.31–7.16 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 7.02 (s, 1H, -CONH), 3.54 (q, *J* = 5.6 Hz, 2H, -CONH-C$\underline{H}_2$), 2.90 (d, *J* = 11.7, 2H, -C$\underline{H}_2$Ph), 2.59–2.51 (m, 6H), 2.10–1.93 (m, 2H), 1.68–1.51 (m, 3H), 1.35–1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 144.0, 140.6, 140.1, 133.5, 129.2, 129.0, 128.3, 128.0, 127.7, 127.20, 127.15, 125.9, 56.9, 53.7, 43.2, 37.9, 36.9, 32.4. HRMS (ESI): *m/z* 399.2386 $(M+H)^+$ (calcd for $C_{27}H_{31}N_2O$, 399.2436).

5.1.42 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-2,2-diphenylacetamide (8f). The procedure described for the preparation of **7a** was used with compound **11f** (150 mg, 0.54 mmol), 4-benzylpiperidine (0.19 mL, 1.08 mmol), TEA (0.30 mL, 2.16 mmol) and DMSO (2 mL) to obtain **8f** (111 mg, 50%) as light brown liquid. R_f = 0.31 (*n*-hexane: EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.42 (m, 1H, Ar-H), 7.29–7.20 (m, 12H, Ar-H overlapped with $CHCl_3$), 7.10–7.08 (m, 3H, Ar-H), 6.51 (s, 1H, -CONH), 3.30–3.23 (m, 2H), 2.62 (d, *J* = 11.1 Hz, 2H, -C$\underline{H}_2$Ph), 2.46 (d, *J* = 6.9 Hz, 2H), 2.29 (t, *J* = 6.15, 2H), 1.78 (t, *J* = 10.8 Hz, 2H), 1.51–1.38 (m, 3H), 1.10–0.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 140.5, 139.7, 129.1, 129.0, 128.7, 128.4, 128.2, 127.9, 127.6, 127.1, 125.9, 59.2, 56.2, 53.4, 43.2, 37.7, 36.4, 32.0.

5.1.43 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-2,2-bis(4-chlorophenyl)acetamide (8g). The procedure described for the preparation of **7a** was used with compound **11g** (180 mg, 0.52 mmol), 4-benzylpiperidine (0.18 mL, 1.04 mmol), TEA (0.29 mL, 2.08 mmol) and DMSO (2 mL) to obtain **8g** (82 mg, 33%) as white solid. R_f = 0.35 (*n*-hexane: EtOAc = 1:1). Mp = 107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.24 (m, 6H, Ar-H), 7.18–7.12 (m, 7H, Ar-H), 6.50 (s, 1H, -CONH), 4.83 (s, 1H, -CH), 3.28 (q, *J* = 5.5 Hz, 2H, CONH-C$\underline{H}_2$), 2.64 (d, J = 11.4 Hz, 2H, -C$\underline{H}_2$Ph), 2.50 (d, *J* = 6.9 Hz, 2H), 2.33 (t, *J* = 5.8 Hz, 2H, -CH_2N), 1.81 (t, *J* = 10.8 Hz, 2H),

1.55–1.37 (m, 3H), 1.04–0.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 160.8, 140.6, 137.9, 133.3, 130.3, 129.1, 128.9, 128.2, 125.9, 57.1, 56.1, 53.4, 43.2, 37.8, 36.4, 32.2.

5.1.44 ***N*-(2-(4-Benzylpiperidin-1-yl)ethyl)quinoline-2-carboxamide (8h).** The procedure described for the preparation of **7a** was used with compound **11h** (100 mg, 0.43 mmol), 4-benzylpiperidine (0.15 mL, 0.86 mmol), TEA (0.24 mL, 1.72 mmol) and DMSO (2 mL) to obtain **8h** (112 mg, 55%) as white solid. R_f = 0.78 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (t, *J* = 4.8 Hz, 1H, -CONH), 8.23–8.26 (m, 2H, Ar-H), 8.10 (d, *J* = 8.7 Hz, 1H, 5-H), 7.85 (d, *J* = 8.1 Hz, 1H, 3-H), 7.79–7.73 (m, 1H, Ar-H), 7.63–7.57 (m, 1H, Ar-H), 7.30–7.14 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 3.62 (q, *J* = 6.20 Hz, 2H, CONH-C$\underline{H}_2$), 2.96 (d, *J* = 11.4 Hz, 2H, -C$\underline{H}_2$Ph), 2.62 (t, *J* = 6.4Hz, 2H), 2.56 (d, *J* = 6.9Hz, 2H), 2.04–1.96 (m, 2H), 1.68–1.49 (m, 3H), 1.41–1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 149.9, 146.4, 140.6, 137.3, 129.9, 129.7, 129.2, 129.0, 128.1, 127.7, 127.6, 125.7, 118.8, 57.1, 53.8, 43.1, 37.9, 36.6, 32.2. HRMS (ESI): m/z 374.2221 $(M+H)^+$ (calcd for $C_{24}H_{28}N_3O$, 374.2232).

5.1.45 ***N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-1-naphthamide (8i).** The procedure described for the preparation of **7a** was used with compound **11i** (100 mg, 0.43 mmol), 4-benzylpiperidine (0.15 mL, 0.86 mmol), TEA (0.24 mL, 1.72 mmol) and DMSO (1 mL) to obtain **8i** (69 mg, 43%) as brown solid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37–8.32 (m, 1H, Ar-H), 7.93–7.85 (m, 2H, Ar-H), 7.61 (dd, *J* = 7.2, 1.2 Hz, 1H, Ar-H), 7.56–7.4 (m, 3H, Ar-H), 7.29–7.10 (m, ≈ 6H, Ar-H, overlapped with $CHCl_3$), 6.60 (s, 1H,-CONH), 3.61 (q, *J* = 5.7 Hz, 2H, -CONH-C$\underline{H}_2$), 2.89 (d, *J* = 11.4 Hz, 2H, -C$\underline{H}_2$Ph), 2.57 (t, *J* = 6 Hz, 2H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.00–1.91 (m, 2H), 1.65–1.49 (m, 3H), 1.29–1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 140.5, 134.7, 133.7, 130.4, 130.2, 129.1, 128.3, 128.2, 127.0, 126.3, 125.9, 125.5, 125.1, 124.8, 56.8, 53.7, 43.1, 37.9, 36.8, 32.1, 29.7.

5.1.46 ***N*-(2-(4-Benzylpiperidin-1-yl) ethyl)-2-naphthamide (8j).** The procedure described for the preparation of **7a** was used with compound **11j** (100 mg, 0.43 mmol), 4-benzylpiperidine (0.15 mL, 0.86 mmol), TEA (0.24 mL, 1.72 mmol) and DMSO (1 mL) to obtain **8j** (77 mg, 48%) as white solid. R_f = 0.72 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 110 °C. ^{1}H NMR (300

MHz, $CDCl_3$): δ 8.30 (s, 1H, Ar-H), 7.95–7.81 (m, 4H, Ar-H), 7.59–7.52 (m, 2H, Ar-H), 7.30–7.25 (m, ≈ 3H, Ar-H, overlapped with $CHCl_3$), 7.21–7.13 (m, 3H, Ar-H), 3.58 (q, *J* = 5.6 Hz, 2H, -CONH-C$\underline{H}_2$), 2.93 (d, *J* = 11.7, 2H, -C$\underline{H}_2$Ph), 2.62–2.54 (m, 4H), 2.04–1.96 (m, 2H,-CH_2N), 1.70–1.50 ((m, 3H), 1.37–1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 140.6, 134.7, 132.7, 132.0, 129.1, 129.0, 128.4, 128.2, 127.7, 127.5, 126.7, 125.9, 123.7, 56.8, 53.7, 43.2, 37.9, 36.9, 32.3.

5.1.47 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-6-bromo-2-naphthamide (8k). The procedure described for the preparation of **7a** was used with compound **11k** (100 mg, 0.32 mmol), 4-benzylpiperidine (0.11 mL, 0.64 mmol), TEA (0.18 mL, 1.28 mmol) and DMSO (1 mL) to obtain **8k** (60 mg, 42%) as white solid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, Ar-H), 8.04 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.87–7.78 (m, 3H, Ar-H), 7.30–7.13 (m, ≈ 7H, overlapped with $CHCl_3$), 3.58 (q, *J* = 5.5 Hz, 2H, -CONH-C$\underline{H}_2$), 2.94 (d, *J* = 11.7 Hz, 2H, -C$\underline{H}_2$Ph), 2.62–2.54 (m, 4H), 2.05–1.96 (m, 2H), 1.70–1.51 (m, 3H), 1.38–1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 139.9, 135.6, 131.8, 131.0, 130.7, 130.0, 129.7, 129.0, 128.3, 127.8, 127.3, 126.1, 124.9, 121.8, 57.0, 53.6, 42.7, 37.2, 36.2, 31.0.

5.1.48 *N*-(2-(4-Benzylpiperidin-1-yl)ethyl)-6-methoxy-2-naphthamide (8l). The procedure described for the preparation of **7a** was used with compound **11l** (350 mg, 1.33 mmol), 4-benzylpiperidine (0.47 mL, 2.66 mmol), TEA (0.74 mL, 5.32 mmol) and DMSO (3 mL) to obtain **8l** (256 mg, 48%) as white solid. R_f = 0.29 (*n*-hexane: EtOAc: MeOH = 2.5:1.5:1). Mp = 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, 1-H), 7.83–7.74 (m, 3H, Ar-H), 7.30–7.12 (m, ≈ 8H, Ar-H, overlapped with $CHCl_3$), 7.06 (t, *J* = 4.2 Hz, 1H, -CONH), 3.92 (s, 1H, -OCH_3), 3.56 (q, *J* = 5.6 Hz, 2H, -CONH-C$\underline{H}_2$), 2.91 (d, *J* = 11.4 Hz, 2H, -C$\underline{H}_2$Ph), 2.59–2.53 (m, 4H), 2.01–1.92 (m, 2H), 1.68–1.48 (m, 3H), 1.36–1.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.0, 140.5, 136.2, 130.5, 129.7, 129.1, 128.2, 128.1, 127.3, 127.0, 125.9, 124.2, 119.6, 105.6, 56.8, 55.4, 53.7, 43.1, 37.9, 36.6, 32.2.

6. Neurotransmitter uptake assay

Human embryonic kidney 293 (HEK-293) cells were subcultured in fetal bovine serum (FBS) in a 100 mm x 20 mm polystyrene dish (Corning, Corning, NY, USA) and incubated in a

humidified 5% CO_2 incubator at 37 °C (Sanyo Electric Biomedical, Osaka, Japan) for 48 hr. When the confluency was 60–70%, the cells were transfected with human serotonin transporter (hSERT) and human norepinephrine transporter (hNET) (cDNA: 3 μg/100 mm dish, PEI: 10 μL) and maintained in a humidified 5% CO_2 incubator at 37 °C for 24 hr. The prepared HEK293 cells were subseeded in 24-well plates (poly-L-lysine coated, clear flat-bottomed, round well shaped, volume 3.4 mL; Corning) and incubated for 24 hr. The medium was removed and cells were washed once with 200 μL of uptake buffer/well prior to the addition of 180 μL of uptake buffer (5 mM Tris base, 7.5 mM HEPES, 120 mM NaCl, 5.4 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1 mM ascorbic acid and 5 mM glucose; pH 7.1) to every wells followed by addition of drugs/compound under test dissolved in 20 μL uptake buffer. The 24-well plates were incubated at 37 °C in a slide warmer for 15–20 min. After 15 min, 100 μL of the radiolabeled 60 nM ^{3}H-SERT (PerkinElmer, Waltham, MA, USA) or 60 nM ^{3}H-NET (PerkinElmer) per well was added (final concentration/well, 20 nM) and incubated for about 5 min at 37 °C using a slide warmer (Fisher, Pittsburgh, PA, USA). Prepared cells were washed three times with ice cold uptake buffer (200 μL/ well). Cell lysis was done by 0.3 mL of 1% sodium dodecyl sulfate per well with shaking in a KMC-1205S shaker (Vision Scientific, Daejeon, South Korea) for about 2 hr. Radioactivity was measured using a Wallac 1450 MicroBeta® TriLux liquid scintillation counter (PerkinElmer). Venlafaxine hydrochloride was used as a standard dual (5-HT and NA) reuptake inhibitor and GBR 12909 was used as the standard NA reuptake inhibitor.

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Graphical Abstract

Design and synthesis of 4-benzylpiperidine carboxamides as dual serotonin and norepinephrine reuptake inhibitors

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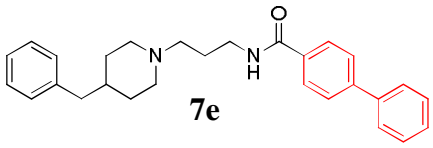

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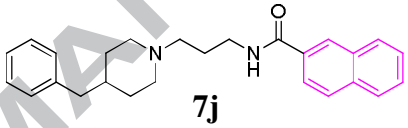

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IC_{50} (nM):
56 (5-HT), 153 (NE)

IC_{50} (nM):
108 (5-HT), 342 (NE)