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Synthesis and biological evaluation of XB-1 analogues as novel histamine H_3 receptor antagonists and neuroprotective agents†

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A novel class of H_3 receptor antagonists, **XB-1** analogues based on benzophenone or oxydibenzene scaffolds were synthesized, and their biological activities were evaluated to determine their *in vitro* neuroprotective effects against $A\beta_{25-35}$-induced damage in primary cortical neurons and against glutamate-induced neuronal injury in primary cerebellar granule neurons. The results indicated that all of the tested analogues displayed neuroprotective activity at 0.1 μM or 1 μM. These findings may provide new insights into the development of novel promising H_3 receptor antagonists with potential neuroprotective activity.

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by the accumulation of β-amyloid peptide (Aβ) in brain areas associated with learning and memory functions.[1,2] Aβ is the major component of senile plaques, and extensive Aβ deposition in AD brain plays a critical role in the development and pathogenesis of AD.[3] The neurotoxicity of Aβ appears to depend on its ability to aggregate, and the active portion of the Aβ molecule appears to be the fragment of amino acids 25 to 35.[4,5] Many lines of evidence have confirmed that Aβ exhibits neurotoxicity and induces apoptosis.[6,7] Glutamate-induced excitotoxicity has also been implicated in Alzheimer's disease.[8–10] H_3 receptor antagonists are currently being evaluated for their potential use in a number of central nervous system disorders, including AD.[11–15] Histamine subtype 3 (H_3) receptor, one of the four G-protein coupled receptors of the histamine receptor family, is mainly located presynaptically on histaminergic neurons in the central nervous system (CNS), where it regulates histamine biosynthesis and the release of histaminergic neurons.[16] The knowledge of histamine H_3 receptors suggests the potential therapeutic applications of histamine H_3 receptor antagonists for several CNS diseases, such as Alzheimer's disease.[17] Several studies using genetic mouse models of AD have shown that treatment with an H_3 receptor antagonist attenuates learning and memory deficits.[12,14,18] Therefore, the H_3 receptor is expected to be a promising therapeutic target for the treatment of AD. Several H_3 receptor antagonists have been demonstrated to have promising neuroprotective activity. For example, the H_3 antagonist clobenpropit was shown to have significant neuroprotective activity against Aβ-induced neurotoxicity in PC12 cells,[19] and the H_3 antagonist thioperamide was indicated to exert a neuroprotective effect.[20]

Interest in the development of H_3 antagonists as drugs for the treatment of a variety of CNS disorders has recently grown dramatically. Several H_3 receptor antagonists, such as thioperamide,[21] ciproxifan,[22] GT-2331,[23] FUB-181,[24] iodoproxyfan,[25] and SCH-79876,[26] have been reported (Fig. 1), but almost all of these compounds contain an imidazole ring in their structures and have been found to exhibit some disadvantages, such as significantly binding discrepancies across species[27] and undesired affinity for cytochrome P450.[28] To avoid these drawbacks, scientists are now focusing on exploring new classes of non-imidazole H_3 receptor antagonists. Several new classes of non-imidazole H_3 receptor antagonists, such as BF-2.649,[29] ABT-239,[30] A-349821 (ref. 32) and JNJ-5207852 (ref. 34) (Fig. 2), have

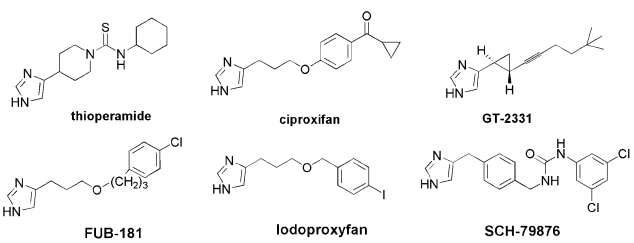

Fig. 1 Imidazole-based H_3 receptor antagonists.

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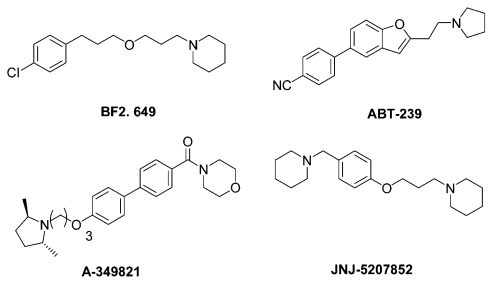


Fig. 2 Non-imidazole-based H_3 receptor antagonists.

been reported to show promising results in animal experiments. To date, however, few molecules are successfully progressing through to advanced stage trials because of poor drug-like properties, such as poor selectivity and poor brain permeability.[32,34,39]

Recently, several new non-imidazole-based compounds, such as **CEP-26401** and its analogues,[33] have been described in the literature as excellent H_3R antagonists with high affinity for both hH_3Rs (K_i = 2.0 nM) and rH_3Rs (K_i = 7.2 nM) (Fig. 3). Reports showed that substitution of *N*-pyridazin-3-one nitrogen with methyl, ethyl, isopropyl, benzyl, and phenyl group could not affect its binding affinity and had essentially equivalent binding affinity for both hH_3R and rH_3R compared to **CEP-26401**.[33] On the other hand, incorporating an alcohol on the (*R*)-2-methyl pyrrolidine or substituting it with piperidine side chain significantly reduced its binding affinity in 7-fold and 15-fold respectively.[33] GlaxoSmithKline has also reported a compound (**GSK189254**,[31] Fig. 3) as a novel H_3R antagonist with high binding affinity for human H_3R (K_i = 0.26 nM). We previously reported the successful preparation of two new non-imidazole H_3 receptor antagonists:[35,36] **XB-1** and its nitro analogue **2** (Fig. 3). Both **XB-1** and **2** were found to have high affinity and selectivity to the human H_3 receptor (K_i = 1.9 nM and 0.4 nM respectively), and **2** was further developed as a PET radioligand, denoted [^{18}F]**XB-1**, for the imaging of brain H_3 receptors. Inspired by these encouraging results, in this study, we aimed to synthesize a novel class of H_3 receptor antagonists, **XB-1** analogues, based on benzophenone or oxydibenzene scaffolds. We hypothesize that these analogues of **XB-1** might also behave as promising H_3 receptor antagonists with potential neuroprotective activity.

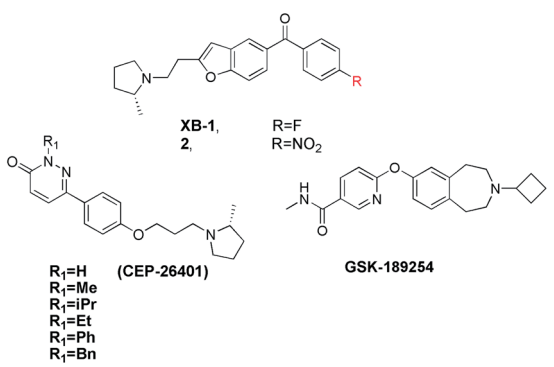


Fig. 3 Chemical structures of H_3R antagonists.

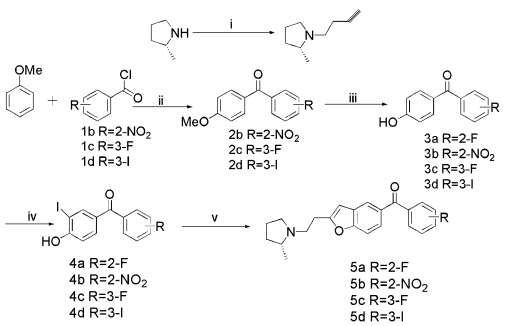
Results and discussion

Synthesis of cyclized benzophenone XB-1 analogues 5a–d

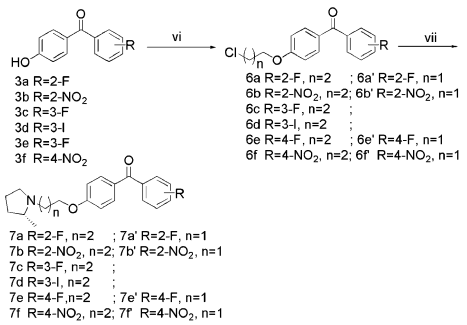
The preparation of the targeted cyclized benzophenone H_3 receptor antagonists required several distinct synthetic routes, which are depicted in Scheme 1. (*R*)-2-Methylpyrrolidine was alkylated with 3-butynnyl *p*-toluenesulfonate to yield (*R*)-1-(3-butynyl)-2-methylpyrrolidine. For the preparation of the target analogues **5a–d**, compounds **1b–d** were converted to **2b–d** through Friedel–Crafts acylation with anisole at yields of 33%, 81%, and 95%, respectively. The selective demethylation of **2b–d** to **3b–d** was readily achieved with the use of the non-nucleophilic Brønsted acid HBr in AcOH; these compounds were obtained at yields of 51%, 92%, and 80%, respectively. The treatment of **3a–d** with 0.5 eq. of iodine and potassium iodine selectively produced **4a–d**, which contain iodine in the *ortho* position to the hydroxyl group, at yields of 94%, 35%, 70%, and 49%, respectively. The use of a substoichiometric amount of iodine reduced the unwanted diiodination that we observed with the use of a stoichiometric amount of iodine. The Pd-catalyzed reaction of **4a–d** with (*R*)-1-(3-butynyl)-2-methyl pyrrolidine solution in CH_3CN (0.1 M) gave the target products **5a–d** at isolated yields of 19%, 16%, 21%, and 18%, respectively.

Synthesis of noncyclized benzophenone XB-1 analogues 7a–f and 7a′–f′

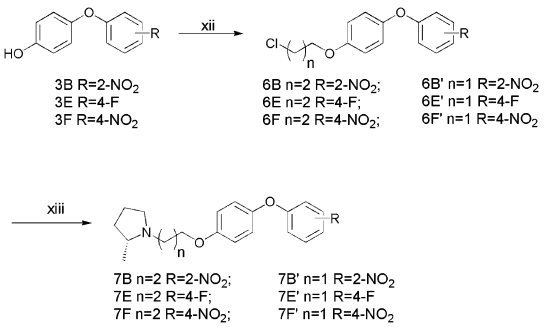
A different synthetic route was used to produce the targeted noncyclized benzophenone **XB-1** analogues **7a–f** and **7a′–f′**, as shown in Scheme 2. Compounds **6a–f** and **6a′–f′** were obtained at high yield through the alkylation of **3a–f** with 1-bromo-3-chloropropane or 1-bromo-2-chloromethane in the presence of K_2CO_3 in CH_3CN. Lower yields of **6a,b** and **6a′,b′** were achieved through the alkylation of **3a,b** with 1,3-dibromopropane or 1,2-dibromopropane. The coupling of **6a–f** and **6a′–f′** with (*R*)-2-methyl pyrrolidine in the presence of KI and K_2CO_3 in CH_3CN yielded the targeted compounds **7a–f** and **7a′–f′**, respectively. The detailed experimental procedures and the characterization of the new compounds are described in the experimental section.



Scheme 1 Synthesis of **5a–d**. *Reagents and conditions*: (i) 3-butynyl *p*-toluenesulfonate, K_2CO_3, CH_3CN, 50 °C, 24 h; (ii) $AlCl_3$, CH_2Cl_2, rt, 4 h; (iii) HBr, AcOH, reflux, 24 h; (iv) NH_4OH, I_2, KI, rt, 18 h; (v) (a): $Pd(OAc)_2$, (*p*-tol)$_3$P, CuI, CH_3CN, (*R*)-1-(3-butyny1)-2-methyl-pyrrolidine, rt, 10 min; (b): iPr_2NH, 60 °C, 20 h. **3a** was purchased from Sigma Aldrich (China).



Scheme 2 Synthesis of **7a–f**, **7a′–f**. *Reagents and conditions*: (vi) 1-bromo-3-chloropropane/1-bromo-2-chloroethane, K_2CO_3, CH_3CN, reflux, 24 h; (vii) (*R*)-2-methyl pyrrolidine, KI, K_2CO_3, CH_3CN, reflux, 24 h.



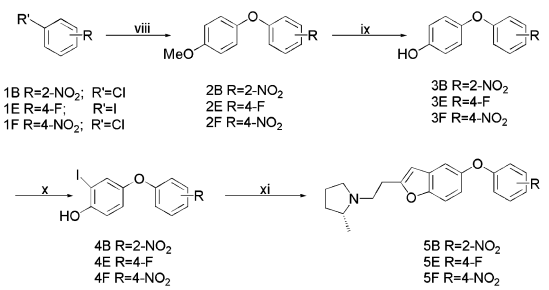
Scheme 4 Synthesis of **7B**, **7E**, **7F**, **7B′**, **7E′** and **7F′**. *Reagents and conditions*: (xii) 1-bromo-3-chloropropane/1-bromo-2-chloroethane, K_2CO_3, CH_3CN; (xiii) (*R*)-2-methylpyrrolidine, KI, K_2CO_3, CH_3CN.

Synthesis of cyclized oxydibenzene XB-1 analogues 5B–5F

The preparation of the targeted cyclized oxydibenzene **XB-1** analogues **5B–5F** required different synthetic routes from **5a–d**, which are depicted in Scheme 3. Compounds **1B–F** were converted to **2B–F** through their coupling with 4-methoxyphenol in the presence of KOH, CuI, *n*-Bu_4NBr, and K_3PO_3 in DMF at yields of 84.9%, 31.6%, and 77.8%, respectively, followed by procedures analogous to those used to prepare **5a–d**. The detailed experimental procedures and characterization of the new compounds are described in the ESI.†

Synthesis of noncyclized oxydibenzene XB-1 analogues 7B–F and 7B′–F′

The syntheses of the targeted noncyclized oxydibenzene **XB-1** analogues **7B**, **7E**, **7F**, **7B′**, **7E′**, and **7F′** are shown in Scheme 4. The synthetic procedures are analogues to those used to prepare **7a–f**. Compounds **6B–F**, **6B′** and, **6E′–F′** were obtained at high yield through the alkylation of **3B–F** with 1-bromo-3-chloropropane or 1-bromo-2-chloromethane in the presence of K_2CO_3 in CH_3CN. The coupling of **6B–F** and **6B′–F′** with (*R*)-2-methyl pyrrolidine in the presence of KI and K_2CO_3 in CH_3CN formed the target compounds **7B–F** and **7B′–F′** at high yields. Details of the reaction procedures and the characterization of the new compounds are described in the ESI.†



Scheme 3 Synthesis of **5B**, **5E**,and **5F**. *Reagents and conditions*: (viii) 4-methoxyphenol, KOH/CuI, *n*-Bu_4NBr, K_3PO_4, DMF; (ix) HBr, CH_3CCOOH; (x) $MeNH_2$, I_2, KI; (xi) $Pb(OAC)_2$, (*p*-to1)$_3$P, CuI, iPr_2NH, (*R*)-1-(but-3-yn-1-yl)-2-methylpyrrolidine, CH_3CN.

Preliminary evaluation of biological activity

Primary cortical neurons cultures were obtained from fetal Sprague Dawley rats at embryonic day 18 (E18).[37] Cerebellar granule neuronal cells (CGCs) were isolated from 8-day-old Sprague Dawley rat pups, as described previously.[38] The cortical neurons and CGCs were cultured in complete Neurobasal culture medium supplemented with 2% B27 and 0.5 mM GlutaMax, and the cultures were incubated in a humidified atmosphere of 5% CO_2 and 95% air at 37 °C. The cortical neurons cultured at DIV4 were pretreated with the compounds for 24 h and then incubated with 5 μM $A\beta_{25-35}$ for an additional 24 h. The CGCs cultured at DIV6 were pretreated with the compounds for 24 h and then incubated with 100 μM glutamate for an additional 24 h. The cell viability was evaluated by incubating with 0.5 mg mL^{-1} 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) for 4 h under 5% CO_2/95% air at 37 °C. The media were replaced with 100 μL of DMSO, and the absorbance was read at 570 nM. The data are expressed as the means ± SD.

H_3 antagonists have been shown to exhibit neuroprotective roles in Alzheimer's disease. To determine their biological activities, all of the compounds were evaluated for their *in vitro* neuroprotective effects against $A\beta_{25-35}$ (the toxic fragment of Aβ)-induced damage in primary cortical neurons and glutamate-induced neuronal injury in primary cerebellar granule neurons. The results are shown in Table 1 and 2. Compared with the parent compound **2**, all of the compounds displayed neuroprotective activity at 0.1 μM or 1 μM. Notably, compound **7B** at 0.1 μM exhibited a somewhat better protective effect compared to parent compound **2** against glutamate-induced neuronal injury. The SAR trend showed that the oxydibenzene moiety series exhibited a little better protective effects compared to benzophenone moiety series at 0.1 μM against glutamate-induced neuronal injury. Decreasing the rigidity by substitution of noncyclized oxydibenzene moiety with cyclized oxydibenzene moiety had no significant affect on the neuroprotective activity against glutamate-induced neuronal injury at 0.1 μM or 1 μM. Pallas software was also used to predict the lipophilicity for these compounds and their computed cLogP values are calculated to be between 3.0 and 5.0. Particularly,

Table 1 Neuroprotective effects of all of the compounds against $A\beta_{25-35}$-induced neurotoxicity in primary rat cortical neurons

		Cell viability[a] (%)	
No.	Compound	0.1 μM	1 μM
1	**2**	57.7 ± 3.6	80.8 ± 7.2
2	**7a′**	73.0 ± 4.1	62.2 ± 3.6
3	**7b**	58.2 ± 4.0	77.7 ± 6.4
4	**7b′**	66.6 ± 5.1	69.3 ± 1.8
5	**7c**	74.7 ± 7.2	73.0 ± 2.4
6	**7d**	69.5 ± 6.8	72.7 ± 3.8
7	**7e**	62.1 ± 2.1	80.6 ± 2.0
8	**7e′**	66.9 ± 4.9	78.1 ± 4.1
9	**7f**	68.1 ± 5.1	76.4 ± 3.5
10	**7f′**	70.3 ± 6.1	72.5 ± 3.4
11	**5B**	60.3 ± 1.5	73.6 ± 1.3
12	**5E**	62.4 ± 4.2	76.8 ± 1.0
13	**5F**	59.7 ± 2.8	75.0 ± 1.0
14	**7B**	59.5 ± 2.8	76.2 ± 1.7
15	**7B′**	57.7 ± 1.0	76.1 ± 1.1
16	**7E**	58.9 ± 1.8	75.1 ± 1.6
17	**7F**	57.9 ± 2.5	76.9 ± 2.9
18	**7F′**	60.8 ± 1.5	74.1 ± 1.6
19	Thioperamide	N.T.[b]	67.3 ± 3.0

[a] The neuroprotective effects of these compounds against $A\beta_{25-35}$-induced neurotoxicity in cortical neurons. The cell viability obtained with the control was considered 100%, and the average cell viability after $A\beta_{25-35}$ exposure was 54.6% ± 4.0. The positive control is thioperamide. [b] N.T. means not tested.

Table 2 Neuroprotective effects of all of the compounds against glutamate-induced neurotoxicity in primary rat cerebellar granule neuronal cells (CGCs)

		Cell viability[a] (%)	
No.	Compound	0.1 μM	1 μM
1	**2**	76.7 ± 4.3	86.6 ± 4.5
2	**7a′**	75.5 ± 5.2	84.9 ± 4.7
3	**7b**	76.6 ± 4.7	75.9 ± 2.9
4	**7b′**	73.4 ± 4.0	79.1 ± 4.4
5	**7c**	75.2 ± 4.3	75.3 ± 7.9
6	**7d**	74.8 ± 9.3	75.6 ± 7.6
7	**7e**	72.2 ± 4.8	75.9 ± 5.2
8	**7e′**	77.3 ± 6.5	71.5 ± 7.1
9	**7f**	73.5 ± 2.2	82.7 ± 7.7
10	**7f′**	76.1 ± 1.5	85.9 ± 9.5
11	**5B**	79.2 ± 7.4	77.7 ± 4.4
12	**5E**	83.8 ± 7.2	79.7 ± 7.4
13	**5F**	79.5 ± 2.2	71.7 ± 3.4
14	**7B**	92.7 ± 3.5	79.9 ± 4.6
15	**7B′**	78.0 ± 2.8	75.7 ± 3.4
16	**7E**	79.0 ± 4.7	75.0 ± 2.4
17	**7F**	82.2 ± 2.2	72.9 ± 3.8
18	**7F′**	75.0 ± 5.5	69.4 ± 6.0
19	Thioperamide	N.T.[b]	92.8 ± 5.7

[a] The neuroprotective effects of these compounds against glutamate-induced neurotoxicity in cerebellar granule neurons. The cell viability obtained with the control was considered 100%, and the average cell viability after glutamate exposure was 63.3%. The positive control is thioperamide. [b] N.T. means not tested.

compound **7B** has low computed cLogP value of 3.16 ± 0.44. It has been reported that the cLogP value for parent compound **2** is 4.34 ± 0.34 and it can penetrate into the brain to show good PET imaging in the specific brain area.[36] So these analogues may have the penetration ability of blood–brain barrier to show biological activity. These data indicate that these compounds may have the potential as H_3 receptor antagonists for the treatment of Alzheimer's disease.

Experimental section

All of the reagents and organic solvents were ACS grade or higher and used without further purification. Unless otherwise noted, all of the chemicals were purchased from J&K Scientific (China) and Sigma Aldrich (China). The reactions were performed under an argon atmosphere with standard Schlenk techniques. Thin-layer chromatography was performed on a HAIYANG silica gel F254 plate, and the compounds were visualized under UV light (λ = 254 nm). Column chromatography was conducted using HAIYANG silica gel (type: 200–300 mesh ZCX-2). The ^{1}H (500 MHz), ^{13}C NMR (126 MHz), and ^{19}F NMR (470 MHz) spectra were recorded on an Avance 500 spectrometer (Bruker; Billerica, MA, USA). The chemical shifts are reported in δ units (ppm) downfield relative to the chemical shift for tetramethylsilane. The GC-MS spectra were obtained on a Trace DSQ GC-MS instrument (Thermo Fisher Scientific Corp., Waltham, MA, USA), and the ESI-MS were obtained on a TSQ Quantum ESI-MS (Thermo Fisher Scientific Corp., Waltham, MA, USA).

(2-Fluorophenyl)(4-hydroxy-3-iodophenyl)methanone (4a)

A solution of 1.0 g (4.6 mmol) of **3a** in 60 mL of NH_4OH (25–28%) was stirred at 25 °C for 15 min and then treated with a solution of KI (3.74 g, 22.5 mmol) and I_2 (1.17 g, 4.62 mmol) in 10 mL of H_2O. After stirring at 25 °C for 18 h, the reaction mixture was adjusted to pH 7, extracted with EtOAc, washed with H_2O and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give **4a** (1.5 g, 94.3%). ^{1}H NMR (DMSO-d_6): δ 11.56 (s, 1H), 8.06 (d, 1H, J = 3.6 Hz), 7.63 (m, 2H), 7.52 (m, 1H), 7.35 (m, 2H), 7.01 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 189.30, 161.32, 159.32, 157.35, 140.19, 132.66, 131.53, 129.53, 126.03, 124.25, 115.71, 114.18, 84.38.

(R)-(2-Fluorophenyl)(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-benzofuran-5-yl)methanone (5a)

(*R*)-1-(3-Butynyl)-2-methylpyrrolidine (52 mL of 0.1 M solution in CH_3CN, 5.2 mmol) and compound **4a** (1.5 g, 4.38 mmol) were mixed in a 100 mL round bottom flask. $Pd(OAc)_2$ (30 mg, 0.12 mmol), tri(4-methylpenyl)phosphine (80 mg, 0.25 mmol), and CuI (125.3 mg, 0.66 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (6.3 mL, 44.25 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was

concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to yield 5a (290 mg, 19%). ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.75 (m, 1H), 7.59 (m, 1H), 7.51 (m, 2H), 7.32 (td, 1H, $J_1 = 0.8$ Hz, $J_2 = 7.5$ Hz), 7.24 (m, 1H), 6.63 (s, 1H), 3.23 (m, 2H), 3.02 (m, 2H), 2.46 (m, 2H), 2.25 (m, 1H), 1.98 (m, 1H), 1.76 (m, 2H), 1.43 (m, 1H), 1.13 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 194.81, 160.85, 160.28, 159.16, 134.29, 133.92, 131.59, 130.61, 126.86, 125.64, 124.72, 117.40, 117.22, 112.04, 104.47, 61.64, 54.73, 52.91, 33.64, 28.49, 22.48, 18.71; ^{19}F NMR ($CDCl_3$): δ −114.13. ESI-MS (M^+ + 1): found 352.95; calculated for $C_{21}H_{24}FNO_2$, 352.17.

(4-Methoxyphenyl)(2-nitrophenyl)methanone (2b)

2-Nitrobenzoyl chloride (4 g, 21.56 mmol) and 3.45 g of anhydrous aluminum chloride were suspended in 160 mL of toluene. Anisole (2.331 g, 21.56 mmol) was gradually added to the mixture. The reaction mixture was slowly heated to 40 °C, stirred for 24 h, cooled to room temperature, and extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After the removal of the organic solvent under vacuum, the residue was purified through column chromatography and eluted with 20% EtOAc/hexane to provide **2b** (1.885 g, 33%) as a yellow powder. ^{1}H NMR ($CDCl_3$): δ 8.23 (dd, 1H, $J_1 = 0.80$ Hz, $J_2 = 8.2$ Hz), 7.76 (td, 1H, $J_1 = 1.1$ Hz, $J_2 = 7.5$ Hz), 7.73 (d, 2H, $J = 8.8$ Hz), 7.66 (m, 1H), 7.48 (dd, 1H, $J_1 = 1.3$ Hz, $J_2 = 7.5$ Hz), 6.93 (d, 2H, $J = 8.9$ Hz), 3.87 (s, 3H).

(4-Hydroxyphenyl)(2-nitrophenyl)methanone (3b)

(4-Methoxyphenyl) (2-nitrophenyl)methanone (1.885 g, 7.33 mmol) was suspended in hydrobromic acid (75 mL, 40%) and acetic acid (63 mL, 99.7%). The reaction mixture was refluxed for 24 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% hexane/20% EtOAc to yield **3b** (909 mg, 51%) as a grey solid; mp: 122 °C. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, 2H, $J = 8.2$ Hz), 7.77 (m, 2H), 7.68 (m, 3H), 7.48 (dd, 2H, $J_1 = 1.1$ Hz, $J_2 = 7.5$ Hz), 6.87 (d, 2H, $J = 8.8$ Hz).

(4-Hydroxy-3-iodophenyl)(2-nitrophenyl)methanone (4b)

A solution of 3.0 g (12 mmol) of **3b** in 180 mL of NH_4OH (25–28%) was stirred at 25 °C for 15 min and then treated with a solution of KI (10.1 g) and I_2 (1.4 g) in 10 mL of H_2O. After stirring at 25 °C for 48 h, the reaction mixture was adjusted to pH 7, extracted with EtOAc, washed with H_2O and brine, dried, and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give **4b** (1.6 g, 35.2%). ^{1}H NMR (DMSO-d_6): δ 8.25 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 0.8$ Hz), 8.16 (d, 1H, $J = 2.0$ Hz), 7.79 (t, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.1$ Hz), 7.70 (m, 1H), 7.59 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 2.0$ Hz), 7.46 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.3$ Hz), 7.01 (d, 1H, $J = 8.5$ Hz), 5.88 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 189.82, 161.46, 145.79, 139.67, 134.49, 134.24, 131.23, 130.67, 128.36, 128.27, 124.21, 114.30, 84.78. ESI-MS (M^- + 1): found 367.79; calculated for $C_{21}H_{24}FNO_2$, 367.94.

(R)-(2-(2-(2-Methylpyrrolidin-1-yl)ethyl)benzofuran-5-yl)(2-nitrophenyl)methanone (5b)

(*R*)-1-(3-Butynyl)-2-methylpyrrolidine (51 mL of 0.1 M solution in CH_3CN, 5.1 mmol) and compound **4b** (1.5 g, 4.08 mmol) were mixed in a 100 mL round bottom flask. $Pd(OAc)_2$ (27 mg, 0.12 mmol), tri(4-methylpenyl) phosphine (73 mg, 0.24 mmol), and CuI (231 mg, 1.6 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (5.7 mL, 80.3 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to provide **5b** (246 mg, 16%). ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, $J = 8.0$ Hz), 7.87 (d, 1H, $J = 1.2$ Hz), 7.78 (m, 1H), 7.70 (m, 2H), 7.52 (m, 1H), 7.46 (d, 1H, $J = 8.4$ Hz), 6.48 (s, 1H), 3.20 (m, 2H), 3.0 (m, 2H), 2.50 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.72 (m, 2H), 1.44 (m, 1H), 1.14 (d, 1H, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 194.55, 158.99, 156.63, 148.03, 144.36, 137.70, 135.87, 133.34, 130.96, 130.31, 127.10, 126.02, 124.83, 112.89, 106.68, 66.24, 54.74, 51.65, 32.80, 26.52, 22.81, 17.12. ESI-MS (M^+ + 1): found 379.02; calculated for $C_{22}H_{22}N_2O_4$, 379.16.

(3-Fluorophenyl)(4-methoxyphenyl)methanone (2c)

3-Fluorobenzoyl chloride (5 g, 31.5 mmol) and 5.04 g of anhydrous aluminum chloride were suspended in 25 mL of dichloromethane. Anisole (3.41 g, 31.5 mmol) was gradually added to the mixture. The mixture was then slowly heated to 40 °C, stirred for 24 h, cooled to room temperature, and extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with column chromatography and eluted with 80% hexane/20% EtOAc to provide **2c** (5.6 g, 81%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.84 (m, 2H), 7.52 (m, 1H), 7.46 (m, 2H), 7.28 (m, 1H), 6.99 (m, 2H), 3.90 (s, 3H).

(3-Fluorophenyl)(4-hydroxyphenyl)methanone (3c)

(3-Fluorophenyl)(4-methyloxyphenyl)methanone (4.84 g, 21 mmol) was suspended in hydrobromic acid (160 mL, 40%) and acetic acid (133 mL, 99.7%). The reaction mixture was refluxed for 24 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% hexane/20% EtOAc to yield **3c** (4.18 g, 92%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.93 (m, 2H), 7.68 (m, 1H), 7.62 (m, 1H), 7.60 (m, 1H), 7.44 (m, 1H), 7.11 (m, 2H).

(3-Fluorophenyl)(4-hydroxy-3-iodophenyl)methanone (4c)

A solution of 1.0 g (2.31 mmol) of **3c** in 39 mL of NH_4OH (25–28%) was stirred at 25 °C for 15 min and then treated with a solution of KI (3.74 g, 22.5 mmol) and I_2 (1.17 g, 4.62 mmol) in 10 mL of H_2O. The reaction mixture was stirred at 25 °C for 18 h. The reaction mixture was adjusted to pH 7, extracted with EtOAc, washed with H_2O and brine, dried, and filtered, and the

filtrate was concentrated under vacuum. The residue was purified by flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give **4c** (1.1 g, 70%). ^{1}H NMR (CD_3OD): δ 8.17 (d, 1H, J = 2.1 Hz), 7.67 (dd, 1H, J_1 = 2.2 Hz, J_2 = 6.4 Hz), 7.54 (m, 1H), 7.49 (m, 1H), 7.41 (m, 1H), 7.36 (m, 1H), 6.92 (d, 2H, J = 8.5 Hz).

(R)-(3-Fluorophenyl)(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-benzofuran-5-yl)methanone (5c)

(*R*)-1-(3-butynyl)-2-methylpyrrolidine (30 mL of 0.1 M solution in CH_3CN, 3 mmol) and compound **4c** (1 g, 3.08 mmol) were mixed in a 100 mL round bottom flask. $Pd(OAc)_2$ (21 mg, 0.09 mmol), tri(4-methylpenyl)phosphine (56 mg, 0.19 mmol), and CuI (88 mg, 0.5 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (4.6 mL, 32.3 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to yield **5c** (224 mg, 21%). ^{1}H NMR ($CDCl_3$): δ 7.95 (s, 1H), 7.74 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.6 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7.49 (m, 2H), 7.45 (m, 1H), 7.28 (m, 1H), 6.53 (s, 1H), 3.22 (m, 2H), 3.02 (m, 2H), 2.49 (m, 1H), 2.38 (m, 1H), 2.22 (m, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.45 (m, 1H), 1.14 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 195.21, 163.49, 161.52, 159.94, 157.23, 140. 57, 133.99, 132.01, 129.96, 129.01, 125.99, 123.54, 119.13, 118.96, 116.85, 116.67, 110.84, 103.02, 60.04, 53.91, 51.85, 32.81, 28.25, 21.81, 19.09; ^{19}F NMR ($CDCl_3$): δ −112.11. ESI-MS (M^+ + 1): found 352.10; calculated for $C_{22}H_{22}FNO_2$, 352.17.

(3-Iodophenyl)(4-methoxyphenyl)methanone (2d)

Dichloromethane (178 mL) was cooled in an ice bath and treated portionwise with $AlCl_3$ (2.52 g, 18.9 mmol). 3-Iodobenzoyl chloride **1d** (4.7 g, 17.64 mmol) in dichloromethane was then added to the mixture while ensuring that the temperature did not exceed 10 °C. The reaction mixture was stirred at 0 °C for 10 min, and anisole (1.78 g, 16.48 mmol) was added dropwise such that the temperature did not exceed 10 °C. The solution was allowed to warm to room temperature overnight. The mixture was concentrated under vacuum and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with column chromatography and eluted with 90% hexane/10% EtOAc to obtain **2d** (5.66 g, 95%) as a white powder. ^{1}H NMR (CDCl3): δ 8.08 (s, 1H), 7.9 (d, 1H, J = 7.8 Hz), 7.81 (d, 2H, J = 8.2 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.21 (t, 1H, J = 7.7 Hz), 6.98 (d, 2H, J = 5 Hz), 3.90 (s, 3H).

(4-Hydroxyphenyl)(3-iodophenyl)methanone (3d)

Compound **2d** (5.95 g, 17.61 mmol) was suspended in hydrobromic acid (164 mL, 40%) and acetic acid (136 mL, 99.7%). The reaction mixture was refluxed for 24 h. The reaction mixture was allowed to cool and then extracted with EtOAc/brine, EtOAc/aqueous $NaHCO_3$, and EtOAc/H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% hexane/20% EtOAc to yield **3d** (4.57 g, 80%) as a white power. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 10.36 (s, 1H), 7.92 (m, 2H), 7.62 (m, 3H), 7.29 (m, 1H), 6.88 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 192.10, 161.77, 139.68, 139.52, 136.70, 131.89, 129.66, 127.78, 126.78, 114.73, 93.87. ESI-MS (M^- + 1): found 322.85; calculated for $C_{22}H_{22}FNO_2$, 322.96.

(4-Hydroxy-3-iodophenyl)(3-iodophenyl)methanone (4d)

A solution of 3.68 g (11.36 mmol) of **3d** in 137 mL of NH_4OH (25–28%) was stirred at 25 °C for 15 min and then treated with a solution of KI (9.42 g, 56.8 mmol) and I_2 (1.447 g, 5.7 mmol) in 15 mL of H_2O. The reaction mixture was stirred at 25 °C for 14 h. The reaction mixture was adjusted to pH 7, extracted with EtOAc, washed with H_2O and brine, dried, and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give **4d** (2.15 g, 49%) as a yellow solid; mp: 210–212 °C. ^{1}H NMR (DMSO-d_6): δ 11.45 (s, 1H), 8.07 (d, 1H, J = 2.1 Hz), 7.99 (m, 1H), 7.96 (m, 1H), 7.63 (m, 2H), 7.34 (m, 1H), 7.01 (d, 1H, J = 8.5 Hz); ^{13}C-NMR (DMSO-d_6): δ 191.12, 160.76, 140.52, 139.97, 139.06, 136.71, 131.87, 129.98, 128.70, 127.94, 113.95, 94.36, 84.41; ESI-MS (M^- + 1): found 448.68; calculated for $C_{22}H_{22}N_2O_4$, 448.85.

(R)-(3-Iodophenyl)(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-benzofuran-5-yl)methanone (5d)

(*R*)-1-(but-3-yn-1-yl)-2-methylpyrrolidine (20 mL of 0.1 M solution in CH_3CN, 2 mmol) and compound **4d** (612 mg, 1.36 mmol) were mixed in a 100 mL round bottom flask. $Pd(OAc)_2$ (9 mg, 0.04 mmol), tri(4-methylpenyl)phosphine (24 mg, 0.08 mmol), and CuI (77 mg, 0.4 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (1.9 mL, 13.55 mmol) and then heated at 60 °C under N_2 for 20 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to provide **5d** (112 mg, 18%). ^{1}H NMR ($CDCl_3$): δ 8.12 (t, 1H, J = 1.5 Hz), 7.94 (d, 1H, J = 1.6 Hz), 7.91 (m, 1H), 7.73 (m, 2H), 7.50 (d, 1H, J = 8.6 Hz), 7.23 (t, 1H, J = 7.8 Hz), 6.55 (s, 1H), 3.27 (m, 2H), 3.06 (t, 2H, J = 7.8 Hz), 2.55 (m, 1H), 2.47 (m, 1H), 2.28 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.50 (m, 1H), 1.19 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$): 196.45, 160.90, 158.70, 142.28, 141.84, 140.00, 133.41, 131.36, 130.50, 130.40, 127.50, 125.02, 112.32, 104.69, 95.45, 61.87, 55.22, 53.16, 34.08, 31.18, 23.19, 20.11. ESI-MS (M^+ + 1): found 459.92; calculated for $C_{12}H_{22}INO_2$, 460.08.

(4-(3-Chloropropoxy)phenyl)(2-fluorophenyl)methanone (6a)

(2-Fluorophenyl)(4-hydroxyphenyl)methanone (865 mg, 4 mmol) and 1-bromo-3-chloropropane (1.26 g, 8 mmol) were suspended in 10 mL of acetonitrile. Anhydrous potassium carbonate (1.66 g, 12 mmol) was then added to the reaction mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal

of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% hexane/20% EtOAc to provide compound **6a** (1.02 g, 87.1%) as a white wax; mp: 61–63 °C. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 2H, J = 8.0 Hz), 7.51 (m, 2H), 7.25 (m, 1H), 7.15 (m, 1H), 6.96 (d, 2H, J = 8.8 Hz), 4.19 (t, 2H, J = 5.8 Hz), 3.75 (d, 2H, J = 6.2 Hz), 2.26 (q, 2H, J_1 = 6.0 Hz, J_2 = 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 192.02, 163.20, 160.87, 158.87, 132.77, 132.45, 130.58, 127.63, 124.41, 116.38, 114.34, 64.68, 41.41, 32.14 ppm. GC-MS (M^+): found 292.01; calculated for $C_{16}H_{14}ClFO_2$, 292.07.

(R)-(2-Fluorophenyl)(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)methanone (7a)

Compound **6a** (522 mg, 1.78 mmol), (*R*)-2-methylprrodine (303.13 mg, 3.56 mmol), potassium iodide (295.48 mg, 1.78 mmol), anhydrous potassium carbonate (738 mg, 5.34 mmol), and acetonitrile (99.0%, 15 mL) were added to a round-bottom flask. The mixture was heated at reflux for 24 h. The mixture was then cooled to room temperature and concentrated, and the product was purified by column chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give **7a** (505 mg, 83.2%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 2H, J = 7.7 Hz), 7.45 (m, 2H), 7.20 (t, 1H, J = 7.5), 7.09 (t, 1H, J = 8.6 Hz), 6.88 (d, 2H, J = 7.6 Hz), 4.12 (t, 2H, J = 5.4 Hz), 3.79 (m, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 3.23 (m, 1H), 3.13 (m, 1H), 2.58 (m, 1H), 2.29 (m, 2H), 2.17 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.02, 162.65, 160.79, 158.79, 132.90, 132.85, 132.37, 130.65, 130.47, 127.37, 127.25, 124.44, 116.38, 116.38, 114.41, 114.15, 65.34, 53.36, 50.41, 31.57, 29.73, 25.38, 21.39, 15.61 ppm. ESI-MS (M^+ + 1): found 342.04; calculated for $C_{21}H_{24}FNO_2$, 342.19.

(4-(2-Chloroethoxy)phenyl)(2-fluorophenyl)methanone (6a′)

(2-Fluorophenyl)(4-hydroxyphenyl)methanone (1.000 g, 4.6 mmol) and 1-bromo-2-chloroethane (0.766 mL, 9.2 mmol) were suspended in 20 mL of acetonitrile. Anhydrous potassium carbonate (1.908 g, 13.8 mmol) was then added to the mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to provide compound **6a′** (660 mg, 51.5%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.81 (d, 2H, J = 7.9 Hz), 7.47 (m, 2H), 7.23 (t, 1H, J = 7.5 Hz), 7.12 (t, 1H, J = 9.0 Hz), 6.94 (d, 2H, J = 9.0 Hz), 4.26 (t, 2H, J = 5.7 Hz), 3.81 (t, 2H, J = 5.8 Hz); ^{13}CNMR ($CDCl_3$): δ 191.93, 162.59, 160.83, 158.84, 132.85, 132.40, 130.79, 127.45, 124.41, 116.35, 114.43, 68.22, 41.87 ppm. GC-MS (M^+): found 277.93; calculated for $C_{15}H_{12}ClFO_2$, 278.05.

(R)-(2-Fluorophenyl)(4-(2-(2-methylpyrrolidin-1-yl)ethoxy)-phenyl)methanone (7a′)

A mixture of compound **6a′** (560 mg, 2 mmol), K_2CO_3 (829 mg, 6 mmol), KI (332 mg, 2 mmol), and (*R*)-2-methylpyrrolidine (242 μL, 2.4 mmol) in acetonitrile (25 mL) was heated at 85 °C for 24 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with 99% MeOH/1% CH_2Cl_2 to give compound **7a′** (452 mg, 69.0%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 2H, J = 7.80 Hz), 7.50 (m, 2H), 7.25 (t, 1H, J = 7.50 Hz), 7.15 (t, 1H, J = 8.90 Hz), 6.96 (d, 2H, J = 8.90 Hz), 4.19 (m, 2H), 3.25 (m, 2H), 2.60 (m, 1H, J_1 = 6.05 Hz, J_2 = 6.55 Hz), 2.50 (m, 1H), 2.33 (m, 1H), 1.95 (m, 1H), 1.83 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.16 (d, 3H, J = 6.10 Hz). ^{13}CNMR ($CDCl_3$): δ 193.43, 164.69, 163.97, 162.24, 160.24, 148.58, 133.79, 132.39, 132.32, 131.93, 128.79, 125.70, 117.89, 117.72, 117.55, 116.17, 115.78, 115.38, 68.92, 61.97, 56.31, 54.05, 33.89, 23.40, 20.46 ppm. ^{19}F NMR ($CDCl_3$): δ −111.99 ppm. ESI-MS (M^+ + 1): 328.02; calculated for $C_{20}H_{23}FNO_2$, 328.16.

(4-(3-Chloropropoxy)phenyl)(2-nitrophenyl)methanone (6b)

(4-Hydroxy phenyl)(2-nitrophenyl)methanone (848 mg, 3.48 mmol) and 1-bromo-3-chloro propane (1.096 g, 6.96 mmol) were suspended in 10 mL of acetonitrile (99.0%). Anhydrous potassium carbonate (1.443 g, 10.44 mmol) was then added in the reaction mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% hexane/20% EtOAc to provide **7b** (1.369 g, 78.3%) as a pale yellow solid; mp: 99–102 °C. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H, J = 8.20 Hz), 7.73 (t, 1H, J = 7.5 Hz), 7.70 (d, 2H, J = 8.85 Hz), 7.62 (m, 1H, J_1 = 1.2 Hz, J_2 = 7.25 Hz), 7.44 (m, 1H, J_1 = 1.05 Hz, J_2 = 7.5 Hz), 6.91 (d, 2H, 8.85 Hz), 4.14 (t, 2H, J = 5.85 Hz), 3.70 (d, 2H, J= 6.30 Hz), 2.21 (m, 2H, J_1 = 6.00 Hz, J_2 = 6.10 Hz); ^{13}C NMR (CDCl3): δ 192.24, 163.40, 146.78, 136.47, 134.29, 131.85, 130.55, 129.20, 128.97, 124.61, 114.66, 64.76, 41.44, 32.06. GC-MS (M^+): found 318.99; calculated for $C_{16}H_{14}ClNO_4$, 319.06.

(R)-(4-(3-(2-Methylpyrrolidin-1-yl)propoxy)phenyl)(2-nitrophenyl)methanone (7b)

(4-(3-Chloropropoxy)phenyl)(2-nitrophenyl)methanone (639 mg, 2 mmol), (*R*)-2-methylprrodine (340.6 mg, 4 mmol), potassium iodide (332 mg, 2 mmol), potassium carbonate anhydrous (829 mg, 3 mmol), and acetonitrile (99.0%, 20 mL) were added to a round-bottom flask. The mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated, and the product was purified by column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **7b** (634 mg, 86.1%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.23 (d, 1H, J = 8.25 Hz), 7.83 (m, 1H), 7.73 (m, 1H), 7.69 (d, 2H, J = 8.75 Hz), 7.50 (m, 1H), 6.99 (d, 2H, J = 8.80 Hz), 4.10 (t, 2H, J = 5.75 Hz), 3.18 (m, 1H, J_1 = 3.80 Hz, J_2 = 6.60 Hz), 3.05 (m, 1H), 2.40 (dd, 1H, J_1 = 6.95 Hz, J_2 = 7.70 Hz), 2.23 (m, 2H), 2.01 (m, 3H), 1.75 (m, 2H), 1.42 (m, 1H), 1.12 (d, 3H, J = 6.15 Hz); ^{13}C NMR ($CDCl_3$): δ 192.83, 163.91, 146.97, 136.15, 134.11, 131.65, 130.62, 128.92, 128.80, 124.33, 114.40, 66.53, 60.67, 53.54, 50.60, 32.14, 27.68, 21.03, 17.22. ESI-MS (M^+ + 1): found 368.99; calculated for $C_{11}H_{24}N_2O_4$ 369.18.

(4-(2-Chloroethoxy)phenyl)(2-nitrophenyl)methanone (6b′)

(4-Hydroxyphen yl)(2-nitrophenyl)methanone (500 mg, 2.06 mmol) and 1-bromo-2-chloroethane (341 μL, 4.12 mmol) were suspended in 30 mL of acetonitrile. Anhydrous potassium carbonate (854 mg, 6.18 mmol) was then added to the mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to yield compound **6b′** (460 mg, 72.8%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 8.23 (d, 1H, $J = 7.30$ Hz), 7.77 (t, 1H, $J = 6.40$ Hz), 7.73 (d, 2H, $J = 8.90$ Hz), 7.67 (t, 1H, $J = 6.95$ Hz), 7.48 (d, 1H, $J = 6.15$ Hz), 6.95 (d, 2H, $J = 8.95$ Hz), 4.30 (t, 2H, $J = 5.75$ Hz), 3.83 (t, 2H, $J = 4.70$ Hz); ^{13}CNMR ($CDCl_3$): δ 192.28, 162.80, 146.75, 136.36, 134.27, 131.84, 130.55, 129.56, 128.94, 124.60, 114.72, 68.25, 41.77 ppm. GC-MS (M^+): found 305.03; calculated for $C_{15}H_{12}ClNO_4$, 305.04.

(R)-(4-(2-(2-Methylpyrrolidin-1-yl)ethoxy)phenyl)(2-nitrophenyl)methanone (7b′)

A mixture of compound **6b′** (450 mg, 1.5 mmol), K_2CO_3 (622 mg, 4.5 mmol), KI (249 mg, 1.5 mmol), and (*R*)-2-methylpyrrolidine (182 μL, 1.8 mmol) in acetonitrile (25 mL) was heated at 85 °C for 48 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give compound **7b′** (438 mg, 82.6%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 1H, $J = 8.25$ Hz), 7.74 (t, 1H, $J = 7.45$ Hz), 7.70 (d, 2H, $J = 8.75$ Hz), 7.64 (t, 1H, $J = 7.60$ Hz), 7.46 (d, 1H, $J = 7.30$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 4.19 (t, 2H, $J = 6.00$ Hz), 3.25 (m, 2H), 2.63 (m, 1H, $J_1 = 5.95$ Hz, $J_2 = 6.50$ Hz), 2.54 (m, 1H), 2.36 (q, 1H, $J = 8.90$ Hz), 1.95 (m, 1H), 1.83 (m, 1H), 1.75 (m, 1H), 1.48 (m, 1H), 1.17 (d, 3H, $J = 6.10$ Hz); ^{13}C NMR ($CDCl_3$): δ 192.21, 163.42, 146.88, 136.62, 134.18, 131.83, 130.44, 129.19, 129.04, 124.61, 114.76, 67.30, 60.96, 54.90, 52.57, 32.45, 22.02, 18.86 ppm. ESI-MS (M^+ + 1): found 355.01, calculated for $C_{20}H_{23}N_2O_4$, 355.16.

(4-(3-Chloropropoxy)phenyl)(3-fluorophenyl)methanone (6c)

(3-Fluorophenyl) (4-hydroxyphenyl)methanone **3c** (500 mg, 2.3 mmol) and 1-bromo-3-chloropropane (455 μL, 4.6 mmol) were suspended in 25 mL of acetonitrile. Anhydrous potassium carbonate (954 mg, 6.9 mmol) was then added to the reaction mixture. The reaction mixture was refluxed for 19 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to yield compound **6c** (663 mg, 98.5%) as a chromatic transparent oil. ^{1}H NMR ($CDCl_3$): δ 7.81 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.25 (m, 1H), 6.97 (dd, 2H, $J_1 = 6.8$ Hz, $J_2 = 2.0$ Hz), 4.20 (t, 2H, J= 5.85 Hz), 3.76 (t, 2H, $J = 6.3$ Hz), 2.27 (q, 2H, $J_1 = 6.0$ Hz, $J_2 = 12.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.91, 163.48, 162.70, 161.51, 140.43, 132.60, 130.02, 125.53, 119.01, 116.58, 114.27, 64.68, 41.37, 32.10.

(R)-(3-Fluorophenyl)(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)methanone (7c)

(4-(3-Chloropropoxy)phenyl)(3-fluorophenyl)methanone **6c** (250 mg, 0.85 mmol), (*R*)-2-methylprrodine (103 μL, 1.02 mmol), KI (141 mg, 0.85 mmol), anhydrous potassium carbonate (235 mg, 1.7 mmol), and acetonitrile (25 mL) were added to a round-bottom flask. The mixture was heated at reflux for 30 h, cooled to room temperature, and concentrated, and the product was purified by column chromatography and eluted with 98% CH_2Cl_2/2% MeOH to yield compound **7c** (229 mg, 78.9%) as a primrose yellow transparent oil. ^{1}H NMR ($CDCl_3$): δ 7.80 (m, 2H), 7.51 (d, 1H, $J = 7.7$ Hz), 7.43 (m, 2H), 7.24 (m, 1H), 6.96 (d, 2H, $J = 8.8$ Hz), 4.11 (m, 2H), 3.19 (m, 1H), 3.00 (m, 1H), 2.35 (m, 1H), 2.24 (m, 1H), 2.16 (m, 1H), 2.03 (m, 2H), 1.93 (m, 1H), 1.78 (m, 1H), 1.69 (m, 1H), 1.44 (m, 1H), 1.11 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 194.04, 163.47, 163.08, 161.50, 140.52, 132.58, 129.95, 129.90, 129.50, 125.48, 118.94, 118.77, 116.60, 116.42, 114.27, 66.72, 60.57, 53.99, 50.64, 32.69, 28.26, 21.73, 18.80; ^{19}F NMR ($CDCl_3$): δ −112.17. ESI-MS (M^+ + 1): found 342.3, calculated for $C_{20}H_{23}N_2O_4$, 342.19.

(4-(3-Chloropropoxy)phenyl)(3-iodophenyl)methanone (6d)

(4-Hydroxyphenyl)(3-iodophenyl)methanone **3d** (450 mg, 1.4 mmol) and 1-bromo-3-chloropropane (277 μL, 2.8 mmol) were suspended in 25 mL of acetonitrile. Anhydrous potassium carbonate (580 mg, 4.2 mmol) was then added to the reaction mixture. The reaction mixture was refluxed for 15 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to provide compound **6d** (538 mg, 95.9%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.08 (m, 1H), 7.89 (d, 1H, $J = 7.9$ Hz), 7.79 (m, 1H), 7.69 (m, 1H), 7.21 (t, 1H, $J = 7.8$ Hz), 6.98 (d, $J = 8.8$ Hz, 2H), 4.22 (t, 2H, $J = 5.8$ Hz), 3.77 (t, 2H, $J = 6.3$ Hz), 2.29 (q, 2H, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.77, 162.73, 140.75, 140.28, 138.40, 132.66, 130.01, 129.73, 128.88 (s), 114.33, 94.14, 64.69, 41.40, 32.14.

(R)-(3-Iodophenyl)(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)methanone (7d)

Compound **6d** (350 mg, 0.87 mmol), (*R*)-2-methylprrodine (106 μL, 1.04 mmol), KI (144 mg, 0.87 mmol), anhydrous potassium carbonate (361 mg, 2.61 mmol), and acetonitrile (30 mL) were added to a round-bottom flask. The mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated, and the product was purified by column chromatography and eluted with 98% CH_2Cl_2/2% MeOH to provide compound **7d** (244 mg, 62.1%) as a primrose yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 1H), 7.88 (d, 1H, $J = 7.9$ Hz), 7.78 (d, 2H, $J = 8.8$ Hz), 7.68 (d, 1H, $J = 7.7$ Hz), 7.20 (t, 1H, $J = 7.8$ Hz), 6.96 (d, 2H, $J = 8.8$ Hz), 4.12 (m, 2H), 3.28 (m, 1H), 3.06 (m, 1H), 2.49 (m, 1H), 2.36 (m, 1H), 2.28 (m, 1H), 2.09 (m, 2H), 1.99 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.52 (m, 1H), 1.17 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.85, 163.02, 140.69, 140.34, 138.36,

132.63, 129.97, 129.49, 128.83, 114.31, 94.06, 66.61, 61.00, 53.90, 50.66, 32.56, 27.97, 21.70, 18.44. ESI-MS ($M^+ + 1$): found 450.2, calculated for $C_{20}H_{24}INO_2$, 450.09.

(4-(3-Chloropropoxy)phenyl)(4-fluorophenyl)methanone (6e)

(4-Fluorophenyl)(4-hydroxyphenyl)methanone (1.08 g, 5 mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol) were suspended in 10 mL of acetonitrile (99.0%). Anhydrous potassium carbonate (2.07 g, 15 mmol) was then added to the reaction mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 20% EtOAc/hexane to provide 1 (789 mg, 54.6%) as a white wax; mp: 47–48 °C. ^{1}H NMR (CDCl3): δ 7.82 (m, 4H), 7.17 (t, 2H, $J = 8.6$ Hz), 7.00 (d, 2H, $J = 8.8$ Hz), 4.22 (t, 2H, $J = 5.8$ Hz), 3.79 (t, 2H, $J = 6.2$ Hz), 2.30 (q, 2H, $J_1 = 6.0$ Hz, $J_2 = 12$ Hz); ^{13}C NMR ($CDCl_3$): δ 194.02, 166.06, 164.05, 162.34, 134.38, 132.23, 130.20, 115.22, 114.08, 64.49, 41.24, 32.02. GC-MS (M^+): found 291.93; calculated for $C_{16}H_{14}ClFO_2$, 292.07.

(R)-(4-Fluorophenyl)(4-(3-(2-methylpyrrolidin-1-yl)propoxy)-phenyl)methanone (7e)

Compound **6e** (292 mg, 1 mmol), (*R*)-2-methylprrodine (170.3 mg, 2 mmol), potassium iodide (166 mg, 1 mmol), anhydrous potassium carbonate (415 mg, 3 mmol), and acetonitrile (99.0%, 10 mL) were added to a round-bottom flask. The mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated, and the product was purified by column chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give 7e (212 mg, 62%) as a light brown solid; mp: 127–129 °C. ^{1}H NMR ($CDCl_3$): δ 7.79 (m, 4H), 7.15 (t, 2H, $J = 8.2$ Hz), 6.97 (d, 2H, $J = 8.2$ Hz), 4.19 (m, 2H), 3.74 (s, 1H), 3.43 (m, 2H), 3.07 (m, 2H), 2.5 (m, 1H), 2.28 (m, 2H), 2.16 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.57 (d, 3H, $J = 6.1$ Hz); ^{13}CNMR ($CDCl_3$): δ 193.95, 166.12, 164.11, 161.72, 134.19, 132.39, 132.31, 133.24, 130.62, 115.46, 115.29, 114.05, 65.22, 53.17, 50.55, 31.48, 29.65, 25.39, 21.25, 15.51. ESI-MS ($M^+ + 1$): found 342.04; calculated for $C_{14}H_{24}FNO_2$, 342.19.

(4-(2-Chloroethoxy)phenyl)(4-fluorophenyl)methanone (6e′)

(4-Fluorophenyl)(4-hydroxyphenyl)methanone (1.000 g, 4.6 mmol) and 1-bromo-2-chloroethane (0.766 mL, 9.2 mmol) were suspended in 20 mL of acetonitrile. Anhydrous potassium carbonate (1.908 g, 13.8 mmol) was then added to the mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to provide compound **6e′** (700 mg, 54.6%) as a white wax. ^{1}H NMR (CDCl3): δ 7.80 (m, 4H), 7.15 (t, 2H, $J = 8.6$ Hz), 6.99 (d, 2H, $J = 8.7$ Hz), 4.31 (t, 2H, $J = 5.8$ Hz), 3.85 (t, 2H, $J = 5.8$ Hz); ^{13}C NMR (CDCl3): δ 193.01, 165.13, 163.12, 160.79, 133.28, 131.43, 129.64, 114.48, 113.24, 67.11, 40.67. GC-MS (M^+): found 278.03; calculated for $C_{15}H_{12}ClFO_2$, 278.05.

(R)-(4-Fluorophenyl)(4-(2-(2-methylpyrrolidin-1-yl)ethoxy)-phenyl)methanone (7e′)

A mixture of compound **6e′** (279 mg, 1 mmol), K_2CO_3 (484 mg, 3.5 mmol), KI (100 mg, 0.6 mmol), and (*R*)-2-methylpyrrolidine (200 μL, 2 mmol) in acetonitrile (15 mL) was heated at 85 °C for 24 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to give compound **7e′** (173 mg, 53.0%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.79 (m, 4H), 7.15 (t, 2H, $J = 8.6$ Hs), 6.98 (d, 2H, $J = 8.8$ Hs), 4.19 (m, 2H), 3.25 (m, 2H), 2.58 (m, 1H, $J_1 = 6.0$ Hz, $J_2 = 6.4$ Hz), 2.44 (m, 1H), 2.30 (q, 1H, $J = 8.8$ Hz), 1.94 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.45 (m, 1H), 1.15 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 194.20, 166.16, 164.14, 162.66, 134.56, 132.42, 132.36, 130.08, 115.51, 115.34, 114.30, 67.58, 60.58, 55.01, 52.75, 32.52, 22.03, 19.17; ^{19}FNMR ($CDCl_3$): δ −106.95. ESI-MS ($M^+ + 1$): 328.01; calculated for $C_{20}H_{23}FNO_2$, 328.16.

(4-(3-Chloropropoxy)phenyl)(4-nitrophenyl)methanone (6f)

(4-Hydroxyphenyl)(4-nitrophenyl)methanone (1.332 g, 5.48 mmol) and 1-bromo-3-chloropropane (3.451 g, 10.96 mmol) were suspended in 20 mL of acetonitrile (99.0%). Anhydrous potassium carbonate (2.272 g, 16.44 mmol) was then added to the reaction mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and then extracted with EtOAc and H_2O. The organic layer was collected and dried with $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 80% EtOAc/20% hexane to provide 1 (1.369 g, 78.3%) as a pale yellow solid; mp: 110–112 °C. ^{1}H NMR ($CDCl_3$): δ 8.36 (d, 2H, $J = 8.6$ Hz), 7.91 (d, 2H, $J = 8.6$ Hz), 7.83 (d, 2H, $J = 8.8$ Hz), 7.02 (d, 2H, $J = 8.8$ Hz), 4.24 (t, 2H, $J = 5.8$ Hz), 3.79 (t, 2H, $J = 6.2$ Hz), 2.31 (q, 2H, $J_1 = 6.0$ Hz, $J_2 = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.42, 163.14, 149.57, 143.76, 132.67, 130.34, 129.14, 123.50, 114.45, 64.66, 41.20, 32.00. GC-MS (M^+): found 319.01; calculated for $C_{16}H_{14}ClNO_4$, 319.06.

(R)-(4-(3-(2-Methylpyrrolidin-1-yl)propoxy)phenyl)(4-nitrophenyl)methanone (7f)

Compound **6f** (319 mg, 1 mmol), (*R*)-2-methylprrodine (170.3 mg, 2 mmol), potassium iodide (166 mg, 1 mmol), anhydrous potassium carbonate (415 mg, 3 mmol), and acetonitrile (99.0%, 10 mL) were added to a round-bottom flask. The mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated, and the product was purified by column chromatography and eluted with 95% CH_2Cl_2/5% MeOH to give 6 (288 mg, 78.2%) as a yellow oil; mp: 167–169 °C. ^{1}H NMR (CDCl3): δ 8.33 (d, 2H, $J = 8.4$ Hz), 7.88 (d, 2H, $J = 8.4$ Hz), 7.80 (d, 2H, $J = 8.6$ Hz), 7.00 (d, 2H, $J = 8.6$ Hz), 4.23 (t, 2H, $J = 5.4$ Hz), 3.88 (m, 1H), 3.57 (m, 2H), 3.24 (m, 2H), 2.67 (m, 1H), 2.38 (m, 2H), 2.26 (m, 1H), 2.16 (m, 1H), 2.05 (m, 1H), 1.66 (s, 3H); ^{13}C NMR (CDCl3): δ 192.35, 161.54, 148.52, 142.55,

131.64, 129.35, 128.40, 122.50, 113.47, 64.35, 52.21, 49.34, 30.44, 28.65, 24.30, 20.32, 14.47. ESI-MS ($M^+ + 1$): found 369.02; calculated for $C_{21}H_{24}N_2O_4$, 369.18.

(4-(2-Chloroethoxy)phenyl)(4-nitrophenyl)methanone (6f′)

(4-Hydroxylphenyl)(4-nitrophenyl)methanone (1.483 g, 6.1 mmol) and 1-bromo-2-chloroethane (1.015 mL, 12.2 mmol) were suspended in 50 mL of acetonitrile. Anhydrous potassium carbonate (2.529 g, 12.2 mmol) was then added to the mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with 90% hexane/10% EtOAc to obtain compound **6f′** (1.120 g, 60.7%) as a white wax. ^{1}H NMR ($CDCl_3$): δ 8.35 (d, 2H, $J = 8.7$ Hz), 7.90 (d, 2H, $J = 8.8$ Hz), 7.83 (d, 2H, $J = 8.8$ Hz), 7.02 (d, 2H, $J = 8.8$ Hz), 4.34 (t, 2H, $J = 5.8$ Hz), 3.87 (t, 2H, $J = 5.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.51, 162.65, 149.67, 143.70, 132.80, 130.48, 129.62, 123.63, 114.66, 68.33, 41.77 ppm. GC-MS (M^+): found 305.02; calculated for $C_{15}H_{12}ClNO_4$, 305.04.

(R)-(4-(2-(2-Methylpyrrolidin-1-yl)ethoxy)phenyl)(4-nitrophenyl)methanone (7f′)

A mixture of compound **6f′** (611 mg, 2 mmol), K_2CO_3 (829 mg, 6 mmol), KI (332 mg, 2 mmol), and (*R*)-2-methylpyrrolidine (240 μL, 2.4 mmol) in acetonitrile (25 mL) was heated at 85 °C for 24 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified through flash chromatography and eluted with 98% CH_2Cl_2/2% MeOH to yield compound **7f′** (590 mg, 83.0%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.34 (d, 2H, $J = 8.8$ Hz), 7.89 (d, 2H, $J = 8.8$ Hz), 7.81 (d, 2H, $J = 8.8$ Hz), 7.00 (d, 2H, $J = 9.0$ Hz), 4.20 (m, 2H), 3.26 (m, 2H), 2.59 (m, 1H, $J_1 = 6.1$ Hz, $J_2 = 6.4$ Hz), 2.47 (m, 1H), 2.31 (q, 1H, $J = 8.8$ Hz), 1.95 (m, 1H), 1.83 (m, 1H), 1.74 (m, 1H), 1.45 (m, 1H), 1.15 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 193.45, 163.39, 149.52, 143.88, 132.71, 130.40, 128.90, 123.53, 114.59, 67.78, 60.49, 55.01, 52.69, 32.52, 22.02, 19.22 ppm. ESI-MS ($M^+ + 1$): found 355.04, calculated for $C_{20}H_{23}N_2O_4$, 355.16.

1-(4-Methoxyphenoxy)-2-nitrobenzene (2B)

A mixture of 4-methoxyphenol (4.0 g, 32.2 mmol) and anhydrous potassium hydroxide (2.0 g, 35.6 mmol) was heated at 150 °C and stirred for 10 min. After the mixture melted, 1-chloro-2-nitrobenzene (4.0 g, 25.4 mmol) was added, and the mixture was stirred at 170 °C for 2 h (TLC monitor). The reaction mixture was poured into 80 mL of 3% potassium hydroxide aqueous solution, stirred at room temperature for approximately 2 h, and then cooled to 4 °C. The solid was filtered with suction and washed with water. The crude product was then dissolved in CH_2Cl_2, introduced onto a silica gel column, and eluted with 10% EtOAc/90% hexane to obtain compound **2B** (5.29 g, 84.9%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.02 (dd, 1H, $J_1 = 1.65$ Hz, $J_2 = 8.15$ Hz), 7.62 (m, 1H), 7.27 (m, 1H), 7.08 (m, 2H), 6.99 (m, 3H), 3.76 (s, 3H) ppm.

4-(2-Nitrophenoxy)phenol (3B)

Compound **2B** (3.724 g, 15.2 mmol) was suspended in hydrobromic acid (155 mL, 40%) and acetic acid (125 mL, 99.7%). The reaction mixture was refluxed for 16 h and extracted with CH_2Cl_2 and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (20 : 80, v/v) to provide compound **3B** (3.299 g, 93.9%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 7.98 (dd, 1H, $J_1 = 1.55$ Hz, $J_2 = 8.10$ Hz), 7.58 (m, 1H), 7.22 (m, 1H), 6.93 (m, 3H), 6.80 (m, 2H) ppm.

2-Iodo-4-(2-nitrophenoxy)phenol (4B)

At 0 °C, 40% aqueous $MeNH_2$ (14.8 mL) and then a solution of KI (5.93 g, 35.7 mmol) and I_2 (2.40 g, 9.45 mmol) in H_2O (18.5 mL) were added to a solution of 4-(4-nitrophenoxy)phenol (1.46 g, 6.30 mmol) in EtOH (148 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with CH_2Cl_2 to give **4B** (1.086 g, 48.3%). ^{1}H NMR (DMSO-d_6): δ 10.38 (s, 1H), 8.00 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.1$ Hz), 7.61 (m, 1H), 7.43 (d, 1H, $J = 2.9$ Hz), 7.26 (m, 1H), 7.00 (m, 2H), 6.91 (d, 1H, $J = 8.8$ Hz); ^{13}C NMR (DMSO-d_6): δ 154.73, 151.05, 147.97, 140.88, 135.44, 130.11, 126.07, 123.79, 121.44, 119.72, 115.94, 85.18 ppm.

(R)-2-Methyl-1-(2-(5-(2-nitrophenoxy)benzofuran-2-yl)ethyl)-pyrrolidine (5B)

(*R*)-1-(But-3-yn-1-yl)-2-methylpyrrolidine (20 mL of 0.1 M solution in CH_3CN, 2.0 mmol) and compound **4B** (500 mg, 1.40 mmol) were mixed in a 100 mL round-bottom flask. $Pd(OAc)_2$ (9 mg, 0.041 mmol), tri(4-methylpenyl)phosphine (25 mg, 0.082 mmol), and CuI (78 mg, 0.41 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (1.96 mL, 13.94 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to provide **5B** (145 mg, 28.2%). ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 8.2$ Hz), 7.48 (m, 1H), 7.40 (d, 1H, $J = 8.8$ Hz), 7.18 (m, 2H), 6.97 (m, 2H), 6.62 (s, 1H), 3.80 (m, 1H), 3.65 (m, 3H), 3.48 (m, 1H), 3.35 (m, 1H), 3.04 (m, 1H), 2.31 (m, 1H), 2.22 (m, 1H), 2.09 (m, 1H), 2.00 (m, 1H), 1.66 (d, 3H, $J = 5.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.50, 151.84, 141.00, 134.32, 129.55, 125.79, 122.86, 119.77, 116.65, 112.14, 111.51, 105.25, 65.04, 53.27, 50.76, 31.40, 25.18, 21.41, 15.55. ESI-MS: found $[M + H]^+$ 367.12; calculated for $C_{21}H_{22}N_2O_4$, $[M^+ + H]$, 367.16.

1-Fluoro-4-(4-methoxyphenoxy)benzene (2E)

1-Fluoro-4-iodobenzene (444 mg, 2 mmol), CuI (38 mg, 0.2 mmol), *n*-Bu_4NBr (64 mg, 0.2 mmol), and K_3PO_4 (849 mg, 4 mmol) were added to a round-bottom flask containing 4-methoxyphenol (248 mg, 2 mmol) under a N_2 atmosphere; DMF

(2 mL) was then added to the mixture. The reaction mixture was vigorously refluxed for 22 h. After cooling to room temperature, saturated NH_4Cl (20 mL) was added, and the organic layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was then washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The reside was purified using a silica gel column with EtOAc/hexane (5 : 95, v/v) to obtain compound **2E** (138 mg, 31.6%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.98 (t, 2H, J = 9.05 Hz), 6.95 (d, 2H, J = 9.1 Hz), 6.90 (m, 2H), 6.88 (d, 2H, J = 9.05 Hz), 3.79 (s, 3H) ppm; ^{19}FNMR ($CDCl_3$): δ 121.34 ppm.

4-(4-Fluorophenoxy)phenol (3E)

Compound **2E** (1.472 g, 6.75 mmol) was suspended in hydrobromic acid (70 mL, 40%) and acetic acid (58 mL, 99.7%). The reaction mixture was refluxed for 16 h and extracted with CH_2Cl_2 and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with CH_2Cl_2 (100%) to yield compound **3E** (1.005 g, 72.9%) as a milky white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.00 (t, 2H, J = 8.75 Hz), 6.91 (m, 4H), 6.82 (d, 2H, J = 8.85 Hz), 4.92 (s, 1H).

2-Iodo-4-(4-fluorophenoxy)phenol (4E)

At 0 °C, 40% aqueous $MeNH_2$ (11.4 mL) and then a solution of KI (4.55 g, 27.4 mmol) and I_2 (1.65 g, 6.52 mmol) in H_2O (15 mL) were added to a solution of compound **3E** (987 mg, 4.83 mmol) in EtOH (114 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with CH_2Cl_2 to give **4E** (1.157 g, 72.6%). ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 1H, J = 2.6 Hz), 7.00 (t, 2H, J = 9.1 Hz), 6.94 (d, 1H, J = 8.8 Hz), 6.91 (m, 3H), 5.18 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 159.70, 157.78, 153.63, 151.34, 128.32, 121.06, 119.67, 116.52, 115.43, 85.22 ppm.

(R)-2-Methyl-1-(2-(5-(4-fluorophenoxy)benzofuran-2-yl)ethyl)-pyrrolidine (5E)

(*R*)-1-(But-3-yn-1-yl)-2-methylpyrrolidine (20 mL of 0.1 M solution in CH_3CN, 2.0 mmol) and compound **4E** (510 mg, 1.54 mmol) were mixed in a 100 mL round-bottom flask. $Pd(OAc)_2$ (10 mg, 0.0454 mmol), tri(4-methylpenyl)phosphine (28 mg, 0.0909 mmol), and CuI (86 mg, 0.454 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (2.17 mL, 15.4 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to provide **5E** (155 mg, 29.6%). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H, J = 8.85 Hz), 7.08 (d, 1H, J = 2.45 Hz), 7.01 (t, 2H, J = 8.65 Hz), 6.94 (m, 3H), 6.60 (s, 1H), 4.16–3.92 (m, 1H), 3.82–3.63 (m, 2H), 3.61–3.45 (m, 2H), 3.41–3.30 (m, 1H), 3.04–2.80 (m, 1H), 2.39–2.21 (m, 2H), 2.17–1.97 (m, 2H), 1.82–1.59 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 159.49, 157.57, 154.12, 153.30, 151.19, 129.29, 119.65, 119.59, 116.37, 116.28, 116.19, 111.82, 110.56, 105.22, 65.12, 53.28, 50.65, 31.37, 25.13, 21.41, 15.50 ppm; ^{19}F NMR ($CDCl_3$): δ 121.34 ppm. ESI-MS: found $[M + H]^+$ 340.03; calculated for $C_{21}H_{22}FNO_2$, $[M^+ + H]$, 340.16.

1-(4-Methoxyphenoxy)-4-nitrobenzene (2F)

A mixture of 4-methoxyphenol (2.0 g, 16.1 mmol) and anhydrous potassium hydroxide (1.0 g, 17.8 mmol) were heated at 150 °C and stirred for 10 min. After the mixture melted, 1-chloro-4-nitrobenzene (2.0 g, 12.7 mmol) was added, and the mixture was stirred at 170 °C for 2 h (TLC monitor). The reaction mixture was poured into 50 mL of 3% potassium hydroxide aqueous solution, stirred at room temperature for approximately 2 h, and then cooled to 4 °C. The solid was filtered with suction and washed with water. The crude product was dissolved in CH_2Cl_2, introduced onto a silica gel column, and eluted with 10% EtOAc/90% hexane to provide compound **2F** (2.432 g, 77.8%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.24 (d, 2H, J = 9.25 Hz), 7.16 (d, 2H, J = 9.05 Hz), 7.05 (m, 4H), 3.79 (s, 3H).

4-(4-Nitrophenoxy)phenol (3F)

Compound **2F** (1.80 g, 7.34 mmol) was suspended in hydrobromic acid (77 mL, 40%) and acetic acid (63 mL, 99.7%). The reaction mixture was refluxed for 16 h and extracted with CH_2Cl_2 and H_2O. The organic layer was collected and dried over Na_2SO_4. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (20 : 80, v/v) to provide compound **3F** (1.65 g, 96.8%) as a yellow powder. ^{1}H NMR (DMSO-d_6): δ 9.57 (s, 1H), 8.21 (d, 2H, J = 9.35 Hz), 7.02 (m, 4H), 6.85 (d, 2H, J = 8.95 Hz).

2-Iodo-4-(4-nitrophenoxy)phenol (4F)

At 0 °C, 40% aqueous $MeNH_2$ (18 mL) and then a solution of KI (7.32 g, 44.1 mmol) and I_2 (2.66 g, 10.5 mmol) in H_2O (10 mL) were added to a solution of 4-(4-nitrophenoxy)phenol (1.80 g, 7.78 mmol) in EtOH (183 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with CH_2Cl_2 to give **4F** (1.013 g, 36.5%). ^{1}H NMR (DMSO-d_6): δ 10.46 (s, 1H), 8.22 (d, 1H, J = 9.2 Hz), 7.52 (d, 1H, J = 2.8 Hz), 7.07 (m, 3H), 6.97 (d, 1H, J = 8.7 Hz); ^{13}C NMR (DMSO-d_6): δ 164.19, 155.22, 146.97, 142.48, 131.30, 126.70, 122.57, 117.16, 116.04.

(R)-2-Methyl-1-(2-(5-(4-nitrophenoxy)benzofuran-2-yl)ethyl)-pyrrolidine (5F)

(*R*)-1-(But-3-yn-1-yl)-2-methylpyrrolidine (20 mL of 0.1 M solution in CH_3CN, 2.0 mmol) and compound **4F** (500 mg, 1.40 mmol) were mixed in a 100 mL round bottom flask. $Pd(OAc)_2$ (9 mg, 0.041 mmol), tri(4-methylpenyl)phosphine (25 mg, 0.082 mmol), and CuI (78 mg, 0.41 mmol) were then added to the reaction mixture. After stirring at 25 °C for 10 min, the reaction mixture was treated with i-Pr_2NH (1.96 mL, 13.94 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction

mixture was allowed to cool and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel and eluted with 98% CH_2Cl_2/2% MeOH to provide **5F** (145 mg, 28.2%). ^{1}H NMR (DMSO-d_6): δ 8.19 (d, 2H, $J = 9.2$ Hz), 7.45 (d, 1H, $J = 8.8$ Hz), 7.24 (d, 1H, $J = 2.4$ Hz), 6.99 (m, 3H), 6.66 (s, 1H), 3.79 (m, 1H), 3.65 (m, 2H), 3.48 (m, 2H), 3.26 (m, 1H), 2.94 (m, 1H), 2.26 (m, 2H), 2.04 (m, 2H), 1.64 (d, 3H, $J = 5.7$ Hz) ppm; ^{13}C NMR (DMSO-d_6): δ 164.19, 154.79, 152.21, 150.46, 142.53, 129.78, 126.03, 117.47, 116.69, 112.84, 112.33, 105.25, 65.03, 53.25, 50.87, 31.45, 25.29, 21.42, 15.60. ESI-MS: found $[M + H]^+$, 367.06; calculated for $C_{21}H_{22}N_2O_4$, $[M^+ + H]$, 367.16.

1-(4-(3-Chloropropoxy)phenoxy)-2-nitrobenzene (6B)

Compound **3B** (500 mg, 2.16 mmol) and 1-bromo-3-chloropropane (427 μL, 4.32 mmol) were suspended in 25 mL acetonitrile. Anhydrous potassium carbonate (896 mg, 6.48 mmol) was then added to the mixture. The reaction mixture was refluxed for 38 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (10 : 90, v/v) to provide compound **6B** (573 mg, 86.1%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.94 (dd, 1H, $J_1 = 1.50$ Hz, $J_2 = 8.15$ Hz), 7.46 (m, 1H), 7.14 (m, 1H), 7.03 (m, 2H), 6.93 (d, 3H, $J = 8.85$ Hz), 4.12 (t, 2H, $J = 5.80$ Hz), 3.77 (t, 2H, $J = 6.30$ Hz), 2.26 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 156.01, 151.91, 148.87, 140.75, 134.24, 125.74, 122.48, 121.18, 119.13, 115.90, 64.87, 41.64, 32.30 ppm.

(R)-2-Methyl-1-(3-(4-(2-nitrophenoxy)phenoxy)propyl) pyrrolidine (7B)

A mixture of compound **6B** (450 mg, 1.46 mmol), K_2CO_3 (605 mg, 4.38 mmol), KI (242 mg, 1.46 mmol), and (*R*)-2-methylpyrrolidine (177 μL, 1.75 mmol) in acetonitrile (25 mL) was heated at 85 °C for 48 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (3 : 97, v/v) to obtain compound **7B** (237 mg, 45.5%) as a buff oil. ^{1}H NMR ($CDCl_3$): δ 7.92 (dd, 1H, $J_1 = 1.30$ Hz, $J_1 = 8.15$ Hz), 7.44 (m, 1H), 7.12 (m, 1H), 7.01 (m, 2H), 6.92 (m, 3H), 4.03 (m, 2H), 3.20 (m, 1H), 3.01 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.16 (m, 1H), 2.04 (m, 2H), 1.92 (m, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.45 (m, 1H), 1.12 (d, 3H, $J = 6.00$ Hz); ^{13}C NMR ($CDCl_3$): δ 156.35, 152.06, 148.50, 140.66, 134.12, 125.71, 122.27, 121.18, 118.94, 115.85 67.00, 60.43, 54.06, 50.85, 32.76, 28.59, 21.73, 19.00 ppm. ESI-MS: found $[M + H]^+$, 357.17; calculated for $C_{19}H_{22}N_2O_4$, $[M^+ + H]$, 357.19.

1-(4-(2-Chloroethoxy)phenoxy)-2-nitrobenzene (6B′)

Compound **3B** (1 g, 4.32 mmol) and 1-bromo-2-chloroethane (716 μL, 8.64 mmol) were suspended in 30 mL of acetonitrile. Anhydrous potassium carbonate (1.792 g, 12.96 mmol) was then added to the mixture. The reaction mixture was refluxed for 33 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (10 : 90, v/v) to provide compound **6B′** (555 mg, 43.8%) as a jasmine solid. ^{1}H NMR ($CDCl_3$): δ 7.92 (dd, 1H, $J_1 = 1.60$ Hz, $J_2 = 8.15$ Hz), 7.45 (m, 1H), 7.13 (m, 1H), 7.02 (m, 2H), 6.92 (m, 3H), 4.22 (t, 2H, $J = 5.80$ Hz), 3.82 (2H, t, $J = 5.85$ Hz); ^{13}C NMR ($CDCl_3$): δ 155.44, 151.75, 149.31, 140.78, 134.29, 125.78, 122.62, 121.17, 119.25, 116.21, 68.67, 42.18 ppm.

(R)-2-Methyl-1-(2-(4-(2-nitrophenoxy)phenoxy)ethyl) pyrrolidine (7B′)

A mixture of compound **6B′** (300 mg, 1.02 mmol), K_2CO_3 (846 mg, 6.12 mmol), KI (338 mg, 2.04 mmol), and (*R*)-2-methylpyrrolidine (206 μL, 2.04 mmol) in acetonitrile (20 mL) was heated at 85 °C for 48 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (3 : 97, v/v) to give compound **7B′** (253 mg, 72.5%) as a deep yellow wax. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, $J = 8.10$ Hz), 7.45 (m, 1H), 7.12 (t, 1H, $J = 7.90$ Hz), 6.99 (m, 2H), 6.92 (t, 3H, $J = 7.95$ Hz), 4.17 (t, 2H, $J = 4.95$ Hz), 3.34 (m, 1H), 3.28 (m, 1H), 2.67 (m, 1H), 2.60 (m, 1H), 2.44 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.53 (m, 1H), 1.23 (d, 3H, $J = 6.10$ Hz); ^{13}C NMR ($CDCl_3$): δ 155.89, 151.97, 148.80, 140.71, 134.17, 125.75, 122.37, 121.19, 119.05, 115.93, 67.10, 61.17, 54.82, 52.71, 32.29, 21.89, 18.62 ppm. ESI-MS: found $[M + H]^+$, 343.08; calculated for $C_{19}H_{22}N_2O_4$, $[M^+ + H]$, 343.16.

1-(4-(3-Chloropropoxy)phenoxy)-4-fluorobenzene (6E)

Compound **3E** (408 mg, 2.0 mmol) and 1-bromo-3-chloropropane (396 μL, 4.0 mmol) were suspended in 10 mL of acetonitrile. Adding anhydrous potassium carbonate (829 mg, 6.0 mmol) was then added to the mixture. The reaction mixture was refluxed for 43 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (5 : 95, v/v) to provide compound **6E** (547 mg, 97.5%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.03–6.99 (m, 2H), 6.98–6.89 (m, 6H), 4.11 (t, 2H, $J = 5.90$ Hz), 3.78 (t, 2H, $J = 6.35$ Hz), 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 159.41, 157.50, 155.05, 150.96, 120.38, 119.34, 116.37, 115.70, 64.84, 41.66, 32.40 ppm; ^{19}F NMR ($CDCl_3$): δ −121.20 ppm.

(R)-1-(3-(4-(4-Fluorophenoxy)phenoxy)propyl)-2-methylpyrrolidine (7E)

A mixture of compound **6E** (500 mg, 1.785 mmol), K_2CO_3 (740 mg, 5.355 mmol), KI (296 mg, 1.785 mmol), and (*R*)-2-methylpyrrolidine (244 μL, 2.412 mmol) in acetonitrile (20 mL) was heated at 85 °C for 48 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (3 : 97, v/v) to give compound **7E** (443 mg, 75.4%) as a

pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.00–6.93 (m, 2H), 6.92–6.86 (m, 6H), 4.01 (m, 2H), 3.22 (m, 1H), 3.01 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.17 (m, 1H), 2.02 (m, 2H), 1.92 (m, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.46 (m, 1H), 1.13 (d, 3H, J = 6.1 5 Hz); ^{13}C NMR ($CDCl_3$): δ 159.32, 157.41, 155.34, 154.34, 150.62, 120.32, 119.19, 119.13, 116.26, 116.07, 115.65, 66.99, 60.55, 54.07, 50.94, 32.74, 28.60, 21.72, 18.93 ppm; ^{19}F NMR ($CDCl_3$): δ −121.41 ppm. ESI-MS: found $[M + H]^+$, 330.07; calculated for $C_{20}H_{24}FNO_2$, $[M^+ + H]$, 330.18.

1-(4-(2-Chloroethoxy)phenoxy)-4-fluorobenzene (6E′)

Compound **3E** (530 mg, 2.6 mmol) and 1-bromo-2-chloroethane (433 μL, 5.2 mmol) were suspended in 10 mL of acetonitrile. Anhydrous potassium carbonate (1.078 g, 7.8 mmol) was then added to the mixture. The reaction mixture was refluxed for 45 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (5 : 95, v/v) to provide compound **6E′** (330 mg, 47.7%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.04–6.99 (m, 2H), 6.97–6.90 (m, 6H), 4.22 (t, 2H, J = 5.85 Hz), 3.82 (t, 2H, J = 5.85 Hz); ^{13}C NMR ($CDCl_3$): δ 159.48, 157.56, 154.45, 151.44, 120.31, 119.49, 116.38, 116.06, 68.72, 42.12 ppm; ^{19}F NMR ($CDCl_3$): δ −120.89 ppm.

(R)-1-(2-(4-(4-Fluorophenoxy)phenoxy)ethyl)-2-methylpyrrolidine (7E′)

A mixture of compound **6E′** (320 mg, 1.2 mmol), K_2CO_3 (498 mg, 3.6 mmol), KI (199 mg, 1.2 mmol), and (*R*)-2-methylpyrrolidine (146 μL, 1.44 mmol) in acetonitrile (20 mL) was heated at 85 °C for 48 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (3 : 97, v/v) to give compound **7E′** (263 mg, 69.2%) as a pale orange oil. ^{1}H NMR ($CDCl_3$): δ 7.01–6.96 (m, 2H), 6.93–6.87 (m, 6H), 4.09 (m, 2H), 3.24 (m, 2H), 2.53 (m, 1H), 2.43 (m, 1H), 2.29 (m, 1H), 1.92 (m, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.15 (d, 3H, J = 6.10 Hz); ^{13}C NMR ($CDCl_3$): δ 159.32, 157.44, 155.14, 154.29, 150.73, 120.27, 119.26, 119.20, 116.27, 116.08, 115.67, 67.69, 60.56, 54.07, 52.97, 32.51, 21.99, 19.18 ppm; ^{19}F NMR ($CDCl_3$): δ −121.33 ppm. ESI-MS: found $[M + H]^+$, 316.06; calculated for $C_{19}H_{22}N_2O_4$, $[M^+ + H]$, 316.16.

1-(4-(3-Chloropropoxy)phenoxy)-4-nitrobenzene (6F)

Compound **3F** (500 mg, 2.16 mmol) and 1-bromo-3-chloropropane (0.427 mL, 4.32 mmol) were suspended in 25 mL of acetonitrile. Anhydrous potassium carbonate (896 g, 6.48 mmol) was then added to the mixture. The reaction mixture was refluxed for 24 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (10 : 90, v/v) to provide compound **6F** (563 mg, 84.7%) as a light brown solid. ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, J = 9.25 Hz), 7.05 (d, 2H, J = 9.05 Hz), 6.98 (m, 4H), 4.15 (t, 2H, J = 5.80 Hz), 3.79 (t, 2H, J = 6.30 Hz), 2.28 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 164.22, 156.40, 148.02, 142.35, 126.00, 122.00, 116.47, 116.00, 64.83, 41.62, 32.29 ppm.

(R)-2-Methyl-1-(3-(4-(4-nitrophenoxy)phenoxy)propyl) pyrrolidine (7F)

A mixture of compound **6F** (450 mg, 1.46 mmol), K_2CO_3 (605 mg, 4.38 mmol), KI (242 mg, 1.46 mmol), and (*R*)-2-methylpyrrolidine (177 μL, 1.75 mmol) in acetonitrile (25 mL) was heated at 85 °C for 34 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (3 : 97, v/v) to give compound **7F** (182 mg, 34.9%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, J = 9.20 Hz), 7.00 (d, 2H, J = 9.05 Hz), 6.94 (m, 4H), 4.03 (m, 2H), 3.21 (m, 1H), 3.01 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.16 (m, 1H), 2.02 (m, 2H), 1.93 (m, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.45 (m, 1H), 1.12 (d, 3H, J = 6.10 Hz); ^{13}C NMR ($CDCl_3$): δ 164.28, 156.71, 147.70, 142.27, 125.95, 121.88, 116.38, 115.96, 66.99, 60.40, 54.07, 50.85, 32.77, 28.62, 21.73, 19.03 ppm. ESI-MS: found $[M + H]^+$, 357.17; calculated for $C_{19}H_{22}N_2O_4$, $[M^+ + H]$, 357.03.

1-(4-(2-Chloroethoxy)phenoxy)-4-nitrobenzene (6F′)

Compound **3F′** (500 mg, 2.16 mmol) and 1-bromo-2-chloroethane (0.358 mL, 4.32 mmol) were suspended in 25 mL of acetonitrile. Anhydrous potassium carbonate (896 mg, 6.48 mmol) was then added to the mixture. The reaction mixture was refluxed for 36 h, concentrated under vacuum, and extracted with EtOAc and H_2O. The organic layer was collected and dried over $MgSO_4$. After removal of the organic solvent under vacuum, the residue was purified with flash chromatography and eluted with EtOAc/hexane (10 : 90, v/v) to provide compound **6F′** (377 mg, 59.3%) as a jasmine solid. ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, J = 9.25 Hz), 7.06 (d, 2H, J = 9.05 Hz), 6.98 (m, 4H), 4.26 (t, 2H, J = 5.80 Hz), 3.85 (t, 2H, J = 5.80 Hz); ^{13}C NMR ($CDCl_3$): δ 164.07, 155.85, 148.51, 142.46, 126.01, 122.03, 116.55, 116.34, 68.67, 42.03 ppm.

(R)-2-Methyl-1-(2-(4-(4-nitrophenoxy)phenoxy)ethyl) pyrrolidine (7F′)

A mixture of compound **6F′** (300 mg, 1.02 mmol), K_2CO_3 (423 mg, 3.06 mmol), KI (169 mg, 1.02 mmol), and (*R*)-2-methylpyrrolidine (123 μL, 1.22 mmol) in acetonitrile (20 mL) was heated at 85 °C for 37 h. The reaction mixture was cooled to room temperature and filtered through diatomite, and the filtrate was concentrated under reduced pressure. The residue was purified with flash chromatography and eluted with MeOH/CH_2Cl_2 (2 : 98, v/v) to give compound **7F′** (271 mg, 77.5%) as a brown wax. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2H, J = 9.30 Hz), 7.02 (d, 2H, J = 9.1 Hz), 6.96 (m, 4H), 4.23 (m, 2H), 3.35 (m, 2H), 2.75 (m, 2H), 2.52 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.60 (m, 1H), 1.29 (d, 3H, J = 6.00 Hz); ^{13}C NMR ($CDCl_3$): δ 164.17, 156.03, 148.15, 142.36, 125.99, 121.96, 116.49, 116.12, 66.51, 61.85, 54.72, 52.56, 32.09, 21.83, 18.11 ppm. ESI-MS: found $[M + H]^+$, 343.05; calculated for $C_{19}H_{22}N_2O_4$, $[M^+ + H]$, 343.16.

Conclusions

In summary, a series of **XB-1** analogues were synthesized and evaluated at two low concentrations (0.1 μM and 1 μM) to determine their neuroprotective effects in an *in vitro* neuronal injury model in primary neurons. The biological results indicated that all of the synthesized compounds displayed neuroprotective effects against $A\beta_{25-35}$- and glutamate-induced neurotoxicity. Of the tested compounds, **7B** exhibited a marked protective effect at a very low concentration of 0.1 μM. Further studies to improve the neuroprotective activity and clarify the neuroprotective mechanism of these compounds are currently in progress and will pave the way for the exploitation of these compounds as novel potential PET radioligands.

Conflict of interests

The authors declare no competing financial interest.

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Notes and references

1 C. Sturchler-Pierrat, D. Abramowski, M. Duke, K. H. Wiederhold, C. Mistl, S. Rothacher, B. Ledermann, K. Bürki, P. Frey, P. A. Paganetti, C. Waridel, M. E. Calhoun, M. Jucker, A. Probst, M. Staufenbiel and B. Sommer, *Proc. Natl. Acad. Sci. U. S. A.*, 1997, **94**, 13287.
2 D. J. Selkoe, *Nature*, 1999, **399**, A23.
3 B. A. Yankner, *Neuron*, 1996, **16**, 921.
4 C. Velez-Pardo, G. G. Ospina and del Rio M. Jimenez, *NeuroToxicology*, 2002, **23**, 351.
5 F. Misiti, B. Sampaolese, M. Pezzotti, S. Marini, M. Coletta, L. Ceccarelli, B. Giardina and M. E. Clementi, *Neurochem. Int.*, 2005, **46**, 575.
6 T. Harkany, I. Abrahám, C. Kónya, C. Nyakas, M. Zarándi, B. Penke and P. G. Luiten, *Rev. Neurosci.*, 2000, **11**, 329.
7 D. Watson, E. Castaño, T. A. Kokjohn, Y. M. Kuo, Y. Lyubchenko, D. Pinsky, E. S. Connolly, C. Esh, D. C. Luehrs, W. B. Stine, L. M. Rowse, M. R. Emmerling and A. E. Roher, *Neurol. Res.*, 2005, **27**, 869.
8 N. W. Hu, T. Ondrejcak and M. J. Rowan, *Pharmacol., Biochem. Behav.*, 2012, **100**, 855.
9 W. Danysz and C. G. Parsons, *Br. J. Pharmacol.*, 2012, **167**, 324.
10 T. J. Revett, G. B. Baker, J. Jhamandas and S. Kar, *J. Psychiatry Neurosci.*, 2013, **38**, 6.
11 G. B. Fox, T. A. Esbenshade, J. B. Pan, R. J. Radek, K. M. Krueger, B. B. Yao, K. E. Browman, M. J. Buckley, M. E. Ballard, V. A. Komater, H. Miner, M. Zhang, R. Faghih, L. E. Rueter, R. S. Bitner, K. U. Drescher, J. Wetter, K. Marsh, M. Lemaire, R. D. Porsolt, Y. L. Bennani, J. P. Sullivan, M. D. Cowart, M. W. Decker and A. A. Hancock, *J. Pharmacol. Exp. Ther.*, 2005, **313**, 176.
12 A. D. Medhurst, A. R. Atkins, I. J. Beresford, K. Brackenborough, M. A. Briggs, A. R. Calver, J. Cilia, J. E. Cluderay, B. Crook, J. B. Davis, R. K. Davis, R. P. Davis, L. A. Dawson, A. G. Foley, J. Gartlon, M. I. Gonzalez, T. Heslop, W. D. Hirst, C. Jennings, D. N. Jones, L. P. Lacroix, A. Martyn, S. Ociepka, A. Ray, C. M. Regan, J. C. Roberts, J. Schogger, E. Southam, T. O. Stean, B. K. Trail, N. Upton, G. Wadsworth, J. A. Wald, T. White, J. Witherington, M. L. Woolley, A. Worby and D. M. Wilson, *J. Pharmacol. Exp. Ther.*, 2007, **321**, 1032.
13 T. A. Esbenshade, K. E. Browman, R. S. Bitner, M. Strakhova, M. D. Cowart and J. D. Brioni, *Br. J. Pharmacol.*, 2008, **154**, 1166.
14 M. E. Bardgett, N. N. Davis, P. J. Schultheis and M. S. Griffith, *Neurobiol. Learn Mem.*, 2011, **95**, 64.
15 P. J. Nathan, R. Boardley, N. Scott, A. Berges, P. Maruff, T. Sivananthan, N. Upton, M. T. Lowy, P. J. Nestor and R. Lai, *Curr. Alzheimer Res.*, 2013, **10**, 240.
16 J. M. Arrang, M. Garbarg and J. C. Schwartz, *Nature*, 1983, **302**, 832.
17 D. Vohora and M. Bhowmik, *Front. Syst. Neurosci.*, 2012, **6**, 72.
18 R. S. Bitner, S. Markosyan, A. L. Nikkel and J. D. Brioni, *Neuropharmacology*, 2011, **60**, 460.
19 Q. Fu, H. Dai, P. He, W. Hu, Y. Fan, W. Zhang and Z. Chen, *Pharmazie*, 2010, **65**, 257.
20 D. Vohora, S. N. Pal and K. K. Pillai, *Eur. Neuropsychopharmacol.*, 2007, **17**, 375.
21 J. M. Arrang, M. Garbarg, J. C. Lancelot, J. M. Lecomte, H. Pollard, M. Robba, W. Schunack and J. C. Schwartz, *Nature*, 1987, **327**, 117.
22 X. Ligneau, J. Lin, G. Vanni-Mercier, M. Jouvet, J. L. Muir, C. R. Ganellin, H. Stark, S. Elz, W. Schunack and J. C. Schwartz, *J. Pharmacol. Exp. Ther.*, 1998, **287**, 658.
23 C. E. Tedford, M. Hoffmann, N. Seyedi, R. Maruyama, R. Levi, S. L. Yates, S. M. Ali and J. G. Phillips, *Eur. J. Pharmacol.*, 1998, **351**, 307.
24 G. Meier, J. Apelt, U. Reichert, S. Grassmann, X. Ligneau, S. Elz, F. Leurquin, C. R. Ganellin, J. C. Schwartz, W. Schunack and H. Stark, *Eur. J. Pharm. Sci.*, 2001, **13**, 249.
25 E. Schlicker, M. Kathmann, H. Bitschnau, I. Marr, S. Reidemeister, H. Stark and W. Schunack, *Naunyn Schmiedeberg's Arch. Pharmacol.*, 1996, **353**, 482.
26 R. Aslanian, M. W. Mutahi, N. Y. Shih, K. D. McCormick, J. J. Piwinski, P. C. Ting, M. M. Albanese, M. Y. Berlin, X. Zhu, S. C. Wong, S. B. Rosenblum, Y. Jiang, R. West, S. She, S. M. Williams, M. Bryant and J. A. Hey, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 937.

27 H. Stark, W. Sippl, X. Ligneau, J. M. Arrang, C. R. Ganellin, J. C. Schwartz and W. Schunack, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 951.
28 R. Yang, J. A. Hey, R. Aslanian and C. A. Rizzo, *Pharmacology*, 2002, **66**, 128.
29 X. Ligneau, D. Perrin, L. Landais, J. C. Camelin, T. P. Calmels, I. Berrebi-Bertrand, J. M. Lecomte, R. Parmentier, C. Anaclet, J. S. Lin, V. Bertaina-Anglade, C. D. la Rochelle, F. d'Aniello, A. Rouleau, F. Gbahou, J. M. Arrang, C. R. Ganellin, H. Stark, W. Schunack and J. C. Schwartz, *J. Pharmacol. Exp. Ther.*, 2007, **320**, 365.
30 M. Cowart, R. Faghih, M. P. Curtis, G. A. Gfesser, Y. L. Bennani, L. A. Black, L. Pan, K. C. Marsh, J. P. Sullivan, T. A. Esbenshade, G. B. Fox and A. A. Hancock, *J. Med. Chem.*, 2005, **48**, 38.
31 A. D. Medhurst, A. R. Atkins, I. J. Beresford, K. Brackenborough, M. A. Briggs, A. R. Calver, J. Cilia, J. E. Cluderay, B. Crook, J. B. Davis, R. K. Davis, R. P. Davis, L. A. Dawson, A. G. Foley, J. Gartlon, M. I. Gonzalez, T. Heslop, W. D. Hirst, C. Jennings, D. N. Jones, L. P. Lacroix, A. Martyn, S. Ociepka, A. Ray, C. M. Regan, J. C. Roberts, J. Schogger, E. Southam, T. O. Stean, B. K. Trail, N. Upton, G. Wadsworth, J. A. Wald, T. White, J. Witherington, M. L. Woolley, A. Worby and D. M. Wilson, *J. Pharmacol. Exp. Ther.*, 2007, **321**, 1032.
32 T. A. Esbenshade, G. B. Fox, K. M. Krueger, J. L. Baranowski, T. R. Miller, C. H. Kang, L. I. Denny, D. G. Witte, B. B. Yao, J. B. Pan, R. Faghih, Y. L. Bennani, M. Williams and A. A. Hancock, *Biochem. Pharmacol.*, 2004, **68**, 933.
33 R. L. Hudkins, R. Raddatz, M. Tao, J. R. Mathiasen, L. D. Aimone, N. C. Becknell, C. P. Prouty, L. J. Knutsen, M. Yazdanian, G. Moachon, M. A. Ator, J. P. Mallamo, M. J. Marino, E. R. Bacon and M. Williams, *J. Med. Chem.*, 2011, **54**, 4781.
34 A. J. Barbier, C. Berridge, C. Dugovic, A. D. Laposky, S. J. Wilson, J. Boggs, L. Aluisio, B. Lord, C. Mazur, C. M. Pudiak, X. Langlois, W. Xiao, R. Apodaca, N. I. Carruthers and T. W. Lovenberg, *Br. J. Pharmacol.*, 2004, **143**, 649.
35 X. Bao, S. Lu, J. S. Liow, S. S. Zoghbi, K. J. Jenko, D. T. Clark, C. L. Morse, R. L. Gladding, R. B. Innis and V. W. Pike, *J. Labelled Compd. Radiopharm.*, 2011, **54**, S83.
36 X. Bao, S. Lu, J. S. Liow, S. S. Zoghbi, K. J. Jenko, D. T. Clark, R. L. Gladding, R. B. Innis and V. W. Pike, *J. Med. Chem.*, 2012, **55**, 2406.
37 J. Benicky, E. Sanchez-Lemus, M. Honda, T. Pang, M. Orecna, J. Wang, Y. Leng, D. M. Chuang and J. M. Saavedra, *Neuropsychopharmacology*, 2011, **36**, 857.
38 T. Pang, J. Wang, J. Benicky, E. Sanchez-Lemus and J. M. Saavedra, *J. Neuroinflammation*, 2012, **9**, 102.
39 (*a*) T. A. Esbenshade, K. E. Browman, R. S. Bitner, M. Strakhova, M. D. Cowart and J. D. Brioni, *Br. J. Pharmacol.*, 2008, **154**, 1166; (*b*) A. A. Hancock, *Biochem. Pharmacol.*, 2006, **71**, 1103.