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Structure–activity relationships of substituted *N*-benzyl piperidines in the GBR series: Synthesis of 4-(2-(bis(4-fluorophenyl)methoxy)ethyl)-1-(2-trifluoromethylbenzyl) piperidine, an allosteric modulator of the serotonin transporter

Terrence L. Boos,[a] Elisabeth Greiner,[a] W. Jason Calhoun,[a] Thomas E. Prisinzano,[a,†] Barbara Nightingale,[b] Christina M. Dersch,[b] Richard B. Rothman,[b] Arthur E. Jacobson[a] and Kenner C. Rice[a,*]

[a]*Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892, USA*
[b]*Clinical Psychopharmacology Section, National Institute on Drug Abuse, Addiction Research Center, Department of Health and Human Services, Baltimore, MD 21224, USA*

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Abstract—A series of 4-(2-(bis(4-fluorophenyl)methoxy)ethyl)-(substituted benzyl) piperidines with substituents at the *ortho* and *meta* positions in the aromatic ring of the *N*-benzyl side chain were synthesized and their affinities and selectivities for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) were determined. One analogue, 4-(2-(bis(4-fluorophenyl)methoxy)ethyl)-1-(2-trifluoromethylbenzyl)piperidine (the C_2-trifluoromethyl substituted compound), has been found to act as an allosteric modulator of hSERT binding and function. It had little affinity for any of the transporters. Several compounds showed affinity for the DAT in the low nanomolar range and displayed a broad range of SERT/DAT selectivity ratios and very little affinity for the NET. The pharmacological tools provided by the availability of compounds with varying transporter affinity and selectivity could be used to obtain additional information about the properties a compound should have to act as a useful pharmacotherapeutic agent for cocaine addiction and help unravel the pharmacological mechanisms relevant to stimulant abuse.
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1. Introduction

The abuse of cocaine (**1**, Fig. 1) is recognized as a significant global health issue. The misuse of this potent CNS stimulant is linked to numerous health risks, ranging from cardiovascular complications to chronic inflammation; it also indirectly exacerbates the spread of HIV-1, hepatitis B and C, and drug-resistant tuberculosis.[1,2] In the United States, there are large numbers of individuals reporting cocaine use and dependence. The 2003 National Survey on Drug Use and Health report[3] indicates that more than 34 million Americans over the age of 12 have used it at least once in their lifetime, and a considerable number of people routinely abuse the drug.

Currently, there are no FDA approved pharmacotherapeutic agents for the treatment of cocaine addiction and relapse. Over the past decade, cocaine addiction has been the focus of many multidisciplinary research efforts from which details on molecular mechanisms of action have been obtained. The euphoric and reinforcing properties of cocaine are believed to be primarily associated with perturbation of the dopaminergic system,[4–6] although other data strongly suggests that stimulant-induced increases in norepinephrine contribute to the stimulant 'high.'[7,8] Cocaine is also a potent reuptake inhibitor of serotonin (5-HT).[9] Knockout studies in

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* Corresponding author. Tel.: +1 301 496 1856; fax: +1 301 402 0589; e-mail: kr21f@nih.gov
† Present address: S327 PHAR, MNPC, College of Pharmacy, The University of Iowa, 115 So. Grand Avenue, Iowa City, IA 52242-1112, USA.

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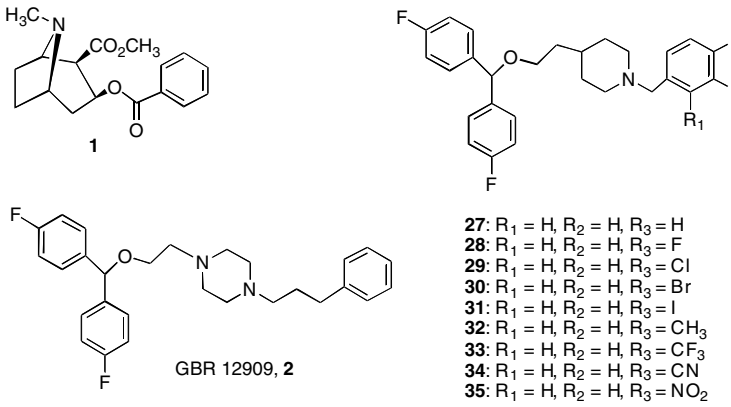
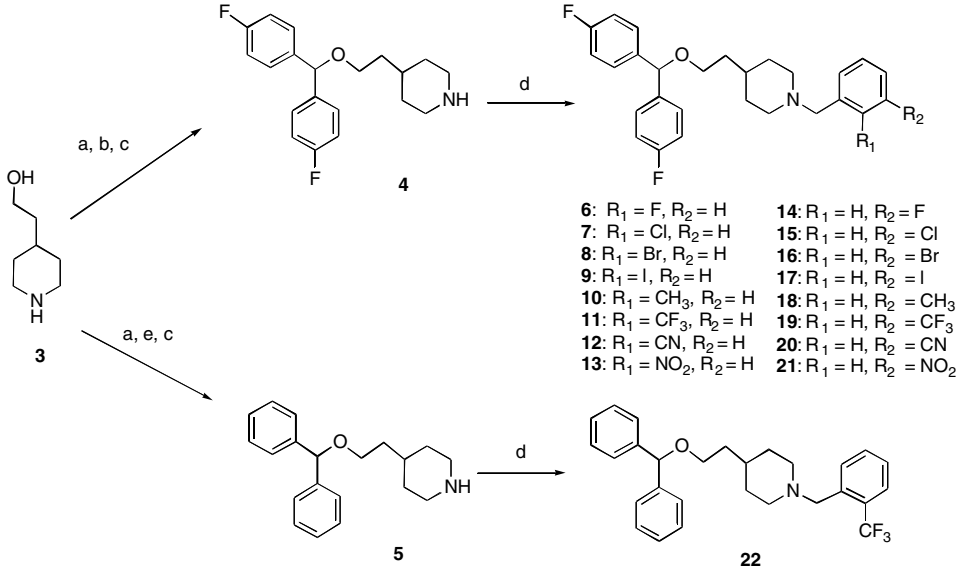


Figure 1. Structures of cocaine (**1**), GBR 12909 (**2**), the unsubstituted *N*-benzyl analogue **27**, and the R_3-substituted compounds **28**–**35**.

the mouse have shown that removal of dopamine transporters (DAT) and serotonin (SERT) transporters eliminates cocaine reward.[9] Perinatal cocaine exposure in the rat produced impaired myocardial function;[10] the norepinephrine transporter (NET) is integral to the regulation of cardiac function. These findings suggest that a drug bearing a customized binding profile for the bioamine transporters might produce an effective treatment agent that minimizes the effects that might be caused by interaction with the norepinephrine transporter.

This study has concentrated on the development of novel analogues of 1-(2-(bis(4-fluorophenyl)methoxy)ethyl)-4-(3-phenylpropyl)piperazine (GBR 12909, **2**, Fig. 1); compound **2** has been found[11] to be a high affinity, selective, long-lasting inhibitor of DA reuptake and a noncompetitive blocker of the DA transporter in rats.[12] This new series of analogues structurally resemble **2**. These compounds, with substituents in the *ortho* (**7**–**13**) and *meta* (**14**–**21**) positions of the *N*-benzyl group, were pharmacologically evaluated to identify ligands with varying transporter affinity and selectivity (Fig. 1 and Scheme 1) in our continuing search to determine the appropriate binding profile at the three transporters for an effective treatment agent that would have little or no effect on normal CNS functions (i.e., a useful pharmacotherapeutic agent for cocaine abuse with few side effects).

It has been found that the distal nitrogen in the piperazine ring in the GBR compound **2** is essential for its binding to DAT and that piperidine-based compounds appeared to have increased DAT affinity and selectivity compared to analogous piperazine compounds.[13–15] Additionally, the piperidine-containing compounds may have a reduced affinity for a 'piperazine acceptor site,' possibly minimizing sympathomimetic side effects that could be caused by piperazine-containing ligands.[15] We have recently reported[16] that the *N*-benzyl piperidine GBR 12909-like compounds (**27**–**35**, Fig. 1), especially those substituted at R_3 on the *N*-benzyl moiety with an electron-withdrawing group, had very high



Scheme 1. Reagents: (a) benzoyl chloride, NEt_3, CH_2Cl_2; (b) 4,4′-difluorobenzhydrol, *p*-TsOH·H_2O, toluene; (c) NaOH, EtOH; (d) appropriate benzyl halide, NaI, K_2CO_3, DMF; (e) benzhydrol, *p*-TsOH·H_2O, toluene.

affinity and were very DAT selective (e.g., compound **34**, in Table 1, with a CN-substituent at R_3 and **35** with a NO_2-substituent at R_3, $K_i = 1.2$ nM, SERT/DAT > 500, NET/DAT > 660 and 1.2 nM, SERT/DAT > 300, NET/DAT > 850, respectively). Since the NET affinities of the R_3-substituted analogues were not examined in the previous study, these data have been included in Table 1, with redetermined activities for those compounds at the DAT and the SERT.

The preparation of compounds with substituents in the *ortho* (**6**–**13**) and *meta* (**14**–**21**) position of the *N*-benzyl group now allows us to examine the electronic and steric effects of these substituents and compare them with those of the formerly prepared *para*-series of compounds (**28**–**35**, Fig. 1) and with the unsubstituted *N*-benzyl compound **27** (Fig. 1).[16] Due to the increased affinity observed with the bis-4-fluorophenyl analogues, we chose to restrict the investigation to the fluorinated compounds, with the exception of **22**. Both **22** and the piperazine compound **26** were prepared because they structurally resembled **11**, since **11** was found to act unusually as an allosteric modulator of hSERT binding and function.

2. Chemistry

Commercially available 4-piperideneethanol **3** was used to prepare 4-(2-(bis(4-fluorophenyl)methoxy)ethyl)piperidine **4** and 4-(2-(benzhydryloxy)ethyl)piperidine **5** in three steps (Scheme 1).[16] The procedure was initiated with N-protection of 4-piperidineethanol **3** with benzoyl chloride, ether formation using the appropriate benzhydrol, and an N-deprotection under basic conditions to give the key intermediates **4** and **5**. These intermediates were treated with the appropriate benzyl-substituted halide under basic conditions, as previously described,[11] to afford target compounds **6**–**22** in 44–83% yield (not optimized). In a two-step conversion, 4,4′-difluorobenzhydrol **23** was used to obtain the diarylmethoxyethyl chloride **24**, and subsequent coupling afforded the monosubstituted piperazine intermediate 1-(2-(bis(4-fluorophenyl)methoxy)ethyl)piperazine **25**, in ca. 70% yield (Scheme 2).[11] Piperazine **25** was treated with 1-bromomethyl-2-trifluoromethylbenzene under basic conditions to give target compound **26** in 67% yield.

Table 1. Binding affinities ($K_i \pm$ SD, nM)[a] of *ortho* R_1- (**6**–**13**), *meta* R_2-substituted compounds (**14**–**21**), and the *para* R_3-substituted series (**28**–**35**)

Compound[b]	R_1	R_2	R_3	DAT	SERT	NET	SERT/DAT	NET/DAT
2				3.7 ± 0.4	126 ± 5	426 ± 33	34	18
6	F	H	H	52 ± 3	336 ± 12	5820 ± 340	6	112
7	Cl	H	H	67 ± 3	308 ± 15	>10,000	5	>149
8	Br	H	H	105 ± 7	354 ± 12	>10,000	3	>95
9	I	H	H	193 ± 9	552 ± 32	>10,000	3	>52
10	CH_3	H	H	48 ± 1	276 ± 8	6850 ± 667	6	>143
11[c]	CF_3	H	H	439 ± 9	1075 ± 285[e]	>10,000	11	>23
12	CN	H	H	134 ± 8	345 ± 15	8140 ± 1261	3	61
13	NO_2	H	H	135 ± 7	544 ± 23	>10,000	4	>74
14	H	F	H	9.8 ± 0.67	212 ± 7	4980 ± 345	22	508
15	H	Cl	H	2.6 ± 0.21	146 ± 7	2835 ± 178	56	1090
16	H	Br	H	2.2 ± 0.11	92 ± 3	2160 ± 140	42	982
17	H	I	H	2.9 ± 0.26	79 ± 4	1036 ± 135	27	357
18	H	CH_3	H	4.4 ± 0.36	134 ± 6	1964 ± 209	30	446
19	H	CF_3	H	4.9 ± 0.22	79 ± 2	1906 ± 164	16	389
20	H	CN	H	21 ± 1	209 ± 8	1214 ± 99	10	58
21	H	NO_2	H	11 ± 0.44	133 ± 5	3120 ± 305	12	284
22	CF_3	H	H	2570 ± 202	>10,000	>10,000	>4	>4
26[f]	CF_3	H	H	128 ± 7	996 ± 65	1392 ± 112	8	11
27[d]	H	H	H	9.9 ± 0.5	171 ± 9	2310 ± 46	17	233
28[d,e]	H	H	F	1.8 ± 0.15	251 ± 10	4600 ± 350	139	2556
29[d,e]	H	H	Cl	0.98 ± 0.08	210 ± 11	4030 ± 411	210	4112
30[d,e]	H	H	Br	0.96 ± 0.06	184 ± 19	3800 ± 250	184	3958
31[d,e]	H	H	I	1.9 ± 0.15	205 ± 12	4110 ± 286	108	2163
32[d,e]	H	H	CH_3	5.1 ± 0.79	194 ± 17	2900 ± 153	38	569
33[d,e]	H	H	CF_3	1.4 ± 0.16	389 ± 40	4120 ± 373	278	2943
34[d,e]	H	H	CN	1.2 ± 0.1	606 ± 73	801 ± 42	505	668
35[d,e]	H	H	NO_2	1.2 ± 0.1	387 ± 20	1027 ± 28	323	856

[a] Experimental methodology previously reported.[17] Binding affinities at the DAT and SERT labeled with [^{125}I]RTI-55 and at the NET with [^{3}H]nisoxetine.

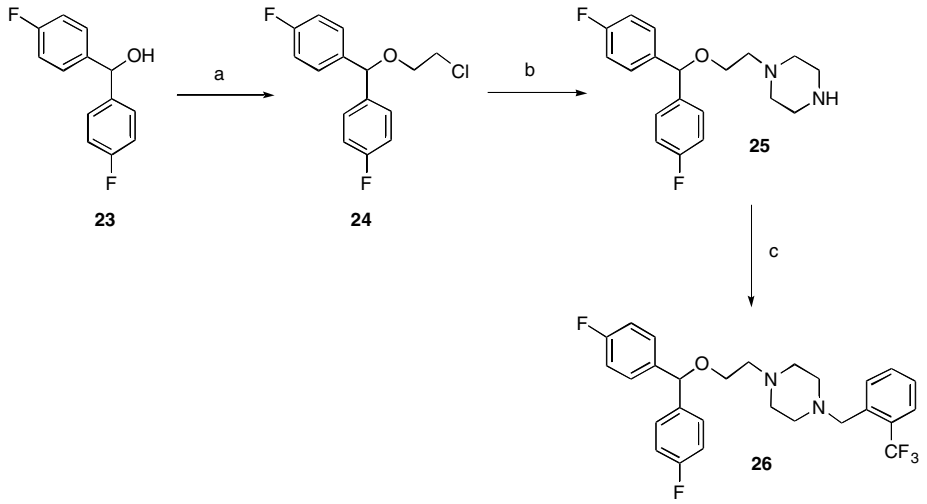
[b] Prepared and tested as oxalate salt.

[c] Compound **11**, formerly identified as TB-1-099,[18] partially inhibits hSERT binding. The apparent IC_{50} is 1075 ± 285 and the curve plateaus at 21 ± 4%.

[d] Previously reported.[16]

[e] DAT and SERT were redetermined (data similar to those previously reported).[16] NET data not previously reported.

[f] Piperazine series.



Scheme 2. Reagents: (a) $HOCH_2CH_2Cl$, H_2SO_4, toluene; (b) (i) piperazine, K_2CO_3, toluene, (ii) aqueous citric acid–$CHCl_3$, (iii) aqueous NH_3–$CHCl_3$; (c) 1-bromomethyl-2-trifluoromethylbenzene, NaI, K_2CO_3, DMF.

3. Results and discussion

The *N*-benzyl analogue (**27**) without a substituent at R_1, R_2, or R_3 (Fig. 1) has been found to have lower affinity than GBR 12909 (**2**) at all of the transporters (Table 1),[14,16] but displayed a higher selectivity for DAT over NET than that of **2**. As mentioned, compounds with an electron-withdrawing group at R_3 were generally found to have high affinity and selectivity (Table 1, **28**–**35**).[16] Compounds **27**–**35** were reevaluated at DAT, SERT, and NET and the newly synthesized **6**–**22** and **26** were evaluated using the same procedures.[16] Some of the latter compounds also have relatively high affinity and selectivity, as can be seen in Table 1.

With the exception of the R_2-methyl analog **18**, the R_1 (*ortho*)- and R_2 (*meta*)-substituted compounds **6**–**21** displayed weaker DAT affinity than the analogous, previously investigated, R_3 (*para*)-substituted compounds.[16] In the R_1-substituted series, none of the compounds had good affinity for DAT. However, the pharmacology of compound **11**, where R_1 = trifluoromethyl, was interesting; it had little affinity for DAT, SERT or NET, and it was found to be an allosteric modulator of the SERT.[18] As previously noted,[18] compound **11** noncompetitively inhibited both [^{125}I]RTI-55 binding to SERT and [^{3}H]5-HT uptake by rat brain synaptosomes and also affected the kinetics of [^{125}I]RTI-55 binding to SERT in an uncompetitive manner. These data collectively suggested that compound **11** modulates the availability of SERT-binding sites and the functional capacity of the transporter via an allosteric binding site on SERT. However, higher affinity ligands will be needed to obtain more definitive evidence. We therefore prepared close analogues of **11**, the defluorinated analogue in the piperazine series (**22**) (Scheme 1) and its piperazine analogue in the bis(4-fluorophenyl) series (**26**, Scheme 2), and these were examined to see whether compounds that were structurally similar to **11** would also act as allosteric modulators. Neither **22** nor **26** partially inhibited hSERT binding, suggesting that allosteric modulation was unique to **11** among the compounds in Table 1.

In the R_2-substituted series, the bromo derivative **16** displayed the highest affinity (2.2 nM) and the cyano derivative **20** displayed the weakest affinity (21 nM) at the DAT. The fluoro-substituted analogue **14** displayed the same DAT affinity as the unsubstituted compound **27**; it showed a 2-fold decrease in NET binding affinity, and binding affinity at SERT remained about the same as in **27**. Halogen substitution in **6**–**9** in the R_1-series gave compounds with binding affinities ranging from 52 nM to 193 nM at the DAT (K_i of **6** (F) > **7** (Cl) > **8** (Br) > **9** (I)); the bulkier substituents had less affinity for DAT. Trends associated with positional substitution were less pronounced at the SERT (K_i = 310–350 nM for **6**–**8** and ca. 550 nM for **9**, the iodo-substituted compound). At R_2, however, the comparable halogen-substituted compounds **14**–**17** had quite different effects. All but the fluoro-substituted compound **14** had very high affinity for DAT. Compound **14** had about one-third the affinity (K_i = 9 nM) of **15**–**17**. At SERT and NET, affinity related to the size of the substituent. The analogue with the largest halogen at R_2 (iodo, **17**) had the highest affinity, the smallest (fluoro, **14**) the least affinity for SERT and NET. Compounds **15**–**17** were found to have the highest DAT affinity and were among those with the best selectivity of all of the newly synthesized R_1 and R_2 compounds. The noted relationships found between size and affinity are in contrast to that seen with compounds bearing halogen-substituents at R_3. As seen in Table 1, all of those (**28**–**31**) were found[16] to have ca. 1 or 2 nM affinity at DAT, ca. 200 nM affinity at SERT, and ca. 2000–4000 nM affinity at NET.

The DAT affinities of the trifluoromethyl compounds **11**, **19**, and **33** were different. The R_1-trifluoromethyl-substituted compound **11** has little affinity. The R_2-trifluoromethyl-substituted compound **19** was one of the most potent in the R_2 series (K_i = 4.9 nM). When the trifluoromethyl substituent was at R_3, the affinity of

compound **33** was found to be 1.4 nM.[16] These data suggest that the electron-withdrawing effect of the trifluoromethyl substituent was not related to DAT affinity. Its bulk, or steric effect, could relate to those differences in affinity, however. This might occur through interference with a necessary part of the receptor, minimizing ligand–transporter interactions; a bulky R_1 substituent apparently forced into a spatial area that cannot accomodate it and disabling interaction between the ligand and its binding site. This was also found with the R_1-methyl (**10**), cyano (**12**), and nitro (**13**) substituents, had the lowest DAT affinity when compared with those of the analogous R_2- and R_3-substituted compounds.

All of the newly synthesized compounds had little affinity for NET, unlike the GBR compound **2**. Among the R_1- and R_2-substituted compounds that had relatively high affinity for DAT, the R_2-chloro (**15**) and R_2-bromo (**16**) analogues had the highest selectivities (NET/DAT = ca. 1000, compared with NET/DAT = 18 for the GBR compound **2**). The SERT/DAT ratios for compounds **15** and **16** were also among the highest observed among the R_1- and R_2-substituted compounds (56 and 42, respectively) and were comparable to, or better than that of the SERT/DAT ratio for the GBR compound **2** (SERT/DAT = 34).

4. Conclusion

We have found that substitutents in the *N*-benzyl group of 1-benzyl-4-(2-(bis(4-fluorophenyl)methoxy)ethyl)piperidine **27** can increase or decrease bioamine transporter affinity, and compounds with higher affinity at the DAT than GBR 12909 (**2**) have been found among the R_1- and R_2-substituted compounds. Some of these compounds also show greater selectivity for DAT over the SERT and NET than has been noted for GBR 12909 (**2**), and this may be relevant to their potential use as pharmacotherapeutic agents (e.g., a significantly lower NET affinity may minimize sympathomimetic side effects; a prerequisite for their use as drug abuse treatment agents). On-going studies will further identify the utility of these compounds and the significance of their binding profiles. Because of their varying binding profiles, these new ligands may serve as pharmacological tools to help elucidate the role of the bioamine transporters in stimulant abuse.

5. Experimental

5.1. Materials and methods

All melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument with DMSO-d_6 as solvent, δ values in ppm (TMS as internal standard), J (Hz) assignments of ^{1}H resonance coupling. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Thin-layer chromatography (TLC) was performed on 250 mm Analtech GHLF silica gel plates using *n*-hexane/EtOAc, 7:3, as the solvent system. Visualization was accomplished under UV or by staining in an iodine chamber. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. All benzyl bromide derivates were purchased from Aldrich Chemical Co., Milwaukee, WI.

5.2. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-fluorobenzyl)piperidine oxalate (6)

A mixture of **4** (1.8 g, 0.0047 mol, free base), 1-bromomethyl-2-fluorobenzene (0.8 g, 0.005 mol), and K_2CO_3 (1.9 g, 0.0141 mol) in MeOH (30 mL) was heated to reflux for 12 h. The mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with saturated NaCl solution (2× 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a crude oil that was purified by column chromatography (silica gel, CH_2CH_2/MeOH, 9:1). The resulting oil was dissolved in ether (50 mL) and oxalic acid (1.1 equiv) was added. The mixture was cooled in an ice bath to induce crystallization. The precipitate was collected and dried to afford 1.2 g (44%) of **6** as a white solid: mp 139–140.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.6 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH), 3.1–3.4 (m, 4H); 2.6–2.7 (m, 2H); 1.3–1.7 (m, 7H). HRMS (EI) calcd for $C_{27}H_{29}F_3NO$ *m*/*z*, 440.2201; found 440.2205. Anal. Calcd for $C_{27}H_{28}F_3NO{\cdot}C_2H_2O_4{\cdot}0.5$ H_2O: C, 64.67; H, 5.80; N, 2.60.

5.3. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-chlorobenzyl)piperidine oxalate (7)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-bromobenzene, **7** was obtained as a white solid (66%): mp 166–168 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.6 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.6–2.7 (m, 2H); 1.3–1.7 (m, 7H). MS (FAB): 456 $[M+1]^+$. Anal. Calcd for $C_{27}H_{28}ClF_2NO{\cdot}C_2H_2O_4$: C, 63.79; H, 5.54; N, 2.57. Found: C, 63.91; H, 5.61; N, 2.65.

5.4. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-bromobenzyl)piperidine oxalate (8)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-chlorobenzene, **8** was obtained as a white solid (82%): mp 166–167 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.7 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.2–3.4 (m, 4H); 3.1 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{27}H_{29}BrF_2NO$ *m*/*z*, 500.1401; found 500.1387. Anal. Calcd for $C_{27}H_{28}BrF_2NO{\cdot}C_2H_2O_4$: C, 58.97; H, 5.12; N, 2.37. Found: C, 58.66; H, 5.19; N, 2.39.

5.5. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-iodobenzyl)piperidine oxalate (9)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-iodobenzene, **9** was obtained as a white solid (48%): mp 161–162 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.9 (m, 12H,

ar); 5.5 (s, 1H, CH–O); 3.9 (s, 2H, CH_2NH); 3.0–3.4 (m, 4H); 2.5 (m, 2H); 1.2–1.7 (m, 7H). MS (FAB): 548 $[M+1]^+$. Anal. Calcd for $C_{27}H_{28}F_2INO{\cdot}C_2H_2O_4$: C, 54.64; H, 4.74; N, 2.20. Found: C, 54.57; H, 4.72; N, 2.31.

5.6. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-methylbenzyl)piperidine oxalate (10)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-methylbenzene, **10** was obtained as a white solid (74%): mp 186 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.4 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.2–3.4 (m, 4H); 2.7 (m, 2H); 2.4 (s, 3H, CH_3); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{28}H_{32}F_2NO$ *m/z*, 436.2452; found 436.2460. Anal. Calcd for $C_{28}H_{31}F_2NO{\cdot}C_2H_2O_4$: C, 68.56; H, 6.33; N, 2.66. Found: C, 68.39; H, 6.30; N, 2.66.

5.7. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-trifluoromethylbenzyl)piperidine oxalate (11)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-trifluoromethylbenzene, **11** was obtained as a white solid (82%): mp 151–152 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.8 (m, 12H, ar); 5.5 (s, 1H, CH–O); 3.9 (s, 2H, CH_2NH); 2.9–3.4 (m, 4H), 2.3–2.4 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{28}H_{29}F_5NO$ *m/z*, 490.2169; found 490.2175. Anal. Calcd for $C_{28}H_{28}F_5NO{\cdot}C_2H_2O_4$: C, 62.17; H, 5.22; N, 2.42. Found: C, 61.86; H, 5.17; N, 2.37.

5.8. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-cyanobenzyl)piperidine oxalate (12)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-cyanobenzene, **12** was obtained as a white solid (47%): mp 126–127 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.9 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.0–3.4 (m, 4H); 2.4–2.5 (m, 2H); 1.2–1.7 (m, 7H). MS (FAB): 447 $[M+1]^+$. Anal. Calcd for $C_{28}H_{28}F_2N_2O{\cdot}C_2H_2O_4{\cdot}0.25\ H_2O$: C, 66.59; H, 5.68; N, 5.18. Found: C, 66.32; H, 5.63; N, 5.34.

5.9. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(2-nitrobenzyl)piperidine oxalate (13)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-2-nitrobenzene, **13** was obtained as a white solid (62%): mp 128 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–8.0 (m, 12H, ar); 5.4 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH), 2.9–3.4 (m, 4H); 2.4–2.5 (m, 2H); 1.1–1.6 (m, 7H). HRMS (EI) calcd for $C_{27}H_{29}F_2N_2O_3$ *m/z*, 467.2146; found 467.2127. Anal. Calcd for $C_{27}H_{28}F_2N_2O_3{\cdot}C_2H_2O_4{\cdot}0.25\ H_2O$: C, 62.08; H, 5.48; N, 4.99. Found: C, 62.10; H, 5.48; N, 5.02.

5.10. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-fluorobenzyl)piperidine oxalate (14)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-fluorobenzene, **14** was obtained as a white solid (51%): mp 151–152 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.5 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.7 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{27}H_{29}F_3NO$ *m/z*, 440.2201; found 440.2206. Anal. Calcd for $C_{27}H_{28}F_3NO{\cdot}C_2H_2O_4$: C, 65.78; H, 5.71; N, 2.65. Found: C, 66.02; H, 5.81; N, 2.67.

5.11. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-chlorobenzyl)piperidine oxalate (15)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-chlorobenzene, **15** was obtained as a white solid (59%): mp 168–169 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.5 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.7 (d, 2H, $J = 6$); 1.1–1.7 (m, 7H) MS (FAB): 456 $[M+1]^+$. Anal. Calcd for $C_{27}H_{28}ClF_2NO{\cdot}C_2H_2O_4{\cdot}$: C, 63.79; H, 5.54; N, 2.57. Found: C, 63.71; H, 5.59; N, 2.53.

5.12. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-bromobenzyl)piperidine oxalate (16)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-bromobenzene, **16** was obtained as a white solid (62%): mp 155–156 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.2–7.7 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.2–3.4 (m, 4H); 2.7–2.8 (m, 2H); 1.3–1.8 (m, 7H). MS (FAB): 500, 502 $[M+1]^+$. Anal. Calcd for $C_{27}H_{28}BrF_2NO{\cdot}C_2H_2O_4{\cdot}0.25\ H_2O$: C, 58.63; H, 5.16; N, 2.36. Found: C, 58.66; H, 5.19; N, 2.39.

5.13. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-iodobenzyl)piperidine oxalate (17)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-iodobenzene, **17** was obtained as a white solid (47%): mp 149–150 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.8 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.5 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{27}H_{28}F_2INO$ *m/z*, 548.1262; found 548.1251. Anal. Calcd for $C_{27}H_{28}F_2INO{\cdot}C_2H_2O_4{\cdot}3\ H_2O$: C, 50.37; H, 5.24; N, 2.03. Found: C, 50.35; H, 5.04; N, 2.14.

5.14. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-methylbenzyl)piperidine oxalate (18)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-methylbenzene, **18** was obtained as a white solid (83%): mp 153–155 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.4 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.2–3.4 (m, 4H); 2.7–2.8 (m, 2H); 2.3 (s, 3H, CH_3) l.1–1.8 (m, 7H). MS (FAB): 436 $[M+1]^+$. Anal. Calcd for $C_{28}H_{31}F_2NO{\cdot}C_2H_2O_4$: C, 68.39; H, 6.33; N, 2.66. Found: C, 68.02; H, 6.29; N, 2.66.

5.15. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-trifluoromethylbenzyl)piperidine oxalate (19)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-trifluorobenzene,

19 was obtained as a white solid (83%): mp 170–171 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.8 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.6 (m, 2H); 1.3–1.7 (m, 7H). HRMS (EI) calcd for $C_{28}H_{29}F_5NO$ *m*/*z*, 490.2169; found 490.2175. Anal. Calcd for $C_{28}H_{28}F_5NO{\cdot}C_2H_2O_4{\cdot}0.25\ H_2O$: C, 61.69; H, 5.26; N, 2.39. Found: C, 61.82; H, 5.17; N, 2.38.

5.16. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-cyanobenzyl)piperidine oxalate (20)

Using a similar procedure as that used to prepare **14** with the substitution of 1-bromomethyl-3-cyanobenzene, **20** was obtained as a white solid (67%): mp 175–176 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.9 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.7 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{28}H_{29}F_2N_2O$ *m*/*z*, 447.2248; found 447.2240. Anal. Calcd for $C_{28}H_{28}F_2N_2O{\cdot}C_2H_2O_4{\cdot}0.25\ H_2O$: C, 66.59; H, 5.68; N, 5.18. Found: C, 66.66; H, 5.66; N, 5.19.

5.17. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(3-nitrobenzyl)piperidine oxalate (21)

Using a similar procedure as that used to prepare **6** with the substitution of 1-bromomethyl-3-nitrobenzene, **21** was obtained as a white solid (73%): mp 182–183 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–8.3 (m, 12H, ar); 5.5 (s, 1H, CH–O); 4.1 (s, 2H, CH_2NH); 3.1–3.4 (m, 4H); 2.7 (m, 2H); 1.2–1.7 (m, 7H). HRMS (EI) calcd for $C_{27}H_{29}F_2N_2O_3$ *m*/*z*, 467.2146; found 467.2168. Anal. Calcd for $C_{27}H_{28}F_2N_2O_3{\cdot}C_2H_2O_4$: C, 62.58; H, 5.43; N, 5.03. Found: C, 62.34; H, 5.45; N, 5.01.

5.18. 4-(2-(Benzhydryloxy)ethyl)-1-(2-(trifluoromethyl)benzyl)piperidine oxalate (22)

4-(2-Benzhydryloxyethyl)-piperidine **5** was prepared as previously noted.[16] 1-Bromomethyl-2-trifluoromethylbenzene was coupled to **5** by a similar procedure to the preparation of **6**. **22** was obtained as a white solid (59%): mp 153–154 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.2–7.8 (m, 14H, ar); 5.4 (s, 1H, CH–O); 3.8 (s, 2H, CH_2NH); 3.0–3.4 (m, 4H). MS (FAB) 454 $[M+1]^+$. Anal. Calcd for $C_{28}H_{30}F_3NO{\cdot}C_2H_2O_4$: C, 66.28; H, 5.93; N, 2.58. Found: C, 66.18; H, 6.01; N, 2.70.

5.19. 1-(2-[Bis(4-fluorophenyl)methoxy)ethyl)-4-(2-trifluoromethylbenzyl)piperazine oxalate (26)

1-(2-(Bis(4-fluorophenyl)methoxy)ethyl)piperazine **25** was prepared as noted.[11] 1-Bromomethyl-2-trifluoromethylbenzene was coupled to **25** by a similar procedure to the preparation of **6**, to obtain **26** as a white solid (67%): mp 201–202 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.1–7.8 (m, 12H, ar); 5.5 (s, 1H, CH–O); 3.6 (s, 2H); 3.5 (t, 2H, J = 6 Hz); 3.3 (m, 3H); 2.6 (t, 2H, J = 5.7 Hz); 2.4 (s, 5 Hz). MS (FAB) 491 $[M+1]^+$. Anal. calcd for $C_{27}H_{27}F_5N_2O{\cdot}2C_2H_2O_4$: C, 55.52; H, 4.66; N, 4.18. Found: C, 55.63; H, 4.75; N, 4.18.

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