Structure−Activity Relationship Studies of Highly Selective Inhibitors of the Dopamine Transporter: *N*-Benzylpiperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine

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A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethyl-1-benzylpiperidines were examined for their ability to bind to the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET). Binding results indicated that the presence of an electron-withdrawing group in the C_4-position of the *N*-benzyl group is beneficial for binding to the DAT. Several analogues have been identified with high affinity for the DAT, up to 500-fold selectivity over the SERT and about 170-fold selectivity over the NET in binding and uptake inhibition assays.

Introduction

Cocaine is known to be one of the most widely abused drugs because of its powerful reinforcing properties. Its abuse has had great effect on public health, exacerbating the spread of HIV-1, hepatitis B and C, and drug-resistant tuberculosis.[1] Cocaine inhibits the reuptake of neurotransmitters such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE). However, the main target for cocaine is the dopamine transporter (DAT). Because the mesolimbic dopaminergic system mediates reinforcement and the dependence-producing properties of drugs of abuse,[2,3] drug-induced changes in this system may be one of the factors that drive the compulsive use of cocaine.[2,4]

A promising approach to developing a potential therapeutic for cocaine abuse is to find a competitive inhibitor of the DAT that would bind tightly and dissociate slowly from the transporter, thus creating an insurmountable blockade of the effects of cocaine mediated via elevation of extracellular DA.[5] To avoid the development of unwanted side effects such as sympathomimetic side effects by binding of these agents at the norepinephrine transporter (NET), we focused on the development of highly selective DAT inhibitors.

Among the first agents to be characterized as high-affinity and selective DA reuptake inhibitors were aryl-1,4-dialk(en)ylpiperazines.[6,7] 1-[2-[Bis(4-fluorophenyl)-methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909, **1a**, Figure 1) binds tightly to the DAT but is less efficient than cocaine in increasing DA-mediated motoric behaviors.[5,8,9] Recently, in a study with a long-chain ester preparation of a hydroxy derivative of **1a**, self-administration of cocaine in rhesus monkeys was largely eliminated without a significant effect on normal behavior as measured by food-maintained responding.[10,11] Given the favorable properties of **1a** and its analogues, these compounds have been identified as promising novel agents for the pharmacotherapy of cocaine abuse in humans.[12,13] Compound **1a** is currently in clinical trials as a cocaine abuse therapeutic.

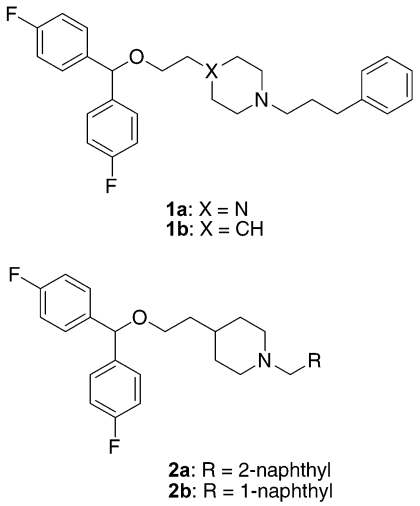

Figure 1. Structures of GBR 12909 (**1a**) and its piperidine analogues.

Studies have shown that one distal nitrogen atom in the GBR series (i.e., **1b**) is sufficient for binding with high affinity and selectivity for the DAT.[14] In our attempt to further elucidate the structure−activity relationships (SAR) in this series, we focused on differently *N*-substituted[2-[bis(4-fluorophenyl)methoxy]ethyl-piperidine analogues as potential cocaine abuse therapeutics. In our most recent research,[15] we found that a 2-naphthylmethyl substituent on the nitrogen produced a high-affinity and selective ligand (**2a**, Scheme 1) for DAT over SERT (300-fold). In the reuptake inhibition assay, **2a** displayed a relatively slight selectivity over 5-HT and NE (40-fold and 10-fold).

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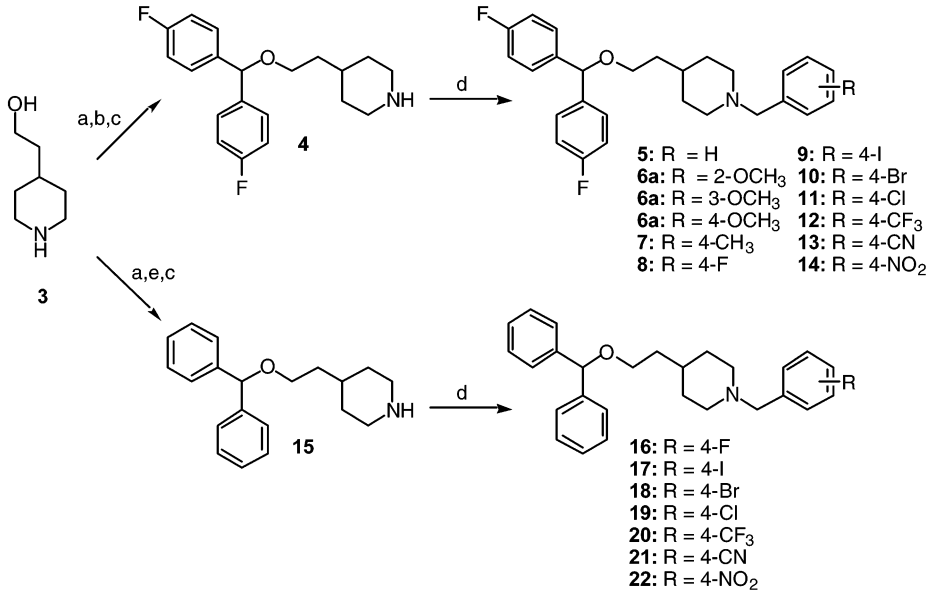
Scheme 1[a]



[a] (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.

Interestingly, the binding affinity of **2a** for the DAT was in the subnanomolar range whereas the 1-naphthylmethyl analogue **2b** showed about a 100-fold decreased binding affinity at the DAT compared to **2a**. It appeared that an extended conformation was preferred in this series and that substitution of the phenyl ring in the benzylic position has a distinct influence on the ability of these compounds to bind to the transporters. Because of the observed difference in the pharmacological properties of **2a** and **2b**, we thought that substitution in the C_2-position might be detrimental for affinity to the transporters. In an effort to study the SAR in this region of the molecule, we synthesized a series of compounds with different substitution patterns on the phenyl ring of the *N*-substituent with the idea that the correct structural modification might lead to analogues with enhanced selectivity for the DAT over the SERT and NE transporters. The affinity of these compounds for the DAT, SERT, and NET was examined and compared to the affinity of their desfluoro analogues and **2a**.[16,17]

Chemistry

The series of [2-[bis(4-fluorophenyl)methoxy]ethylpiperidines was synthesized in several steps from commercially available 4-piperidineethanol **3** (Scheme 1). A three-step sequence of *N*-protection with benzoyl chloride, ether formation using 4,4′-difluorobenzhydrol in toluene under azeotropic distillation conditions, and *N*-deprotection under basic conditions gave the key intermediate 4-[2-[bis(4-fluorophenyl)methoxy]ethylpiperidine **4**.[15] This intermediate was then treated with the appropriate benzyl halides to give targets **5**−**14** in 60−90% yield. Their known desfluoro analogues **15**−**22** were resynthesized in a similar manner (Scheme 1).[17−19]

Results and Discussion

We began the exploration of this series with the introduction of a methoxy group in the C_2-, C_3-, or C_4-position of the phenyl ring of the *N*-substituent (**6a**−**c**) and compared their binding affinities to the 2-naphthylmethyl analogue **2a** and the unsubstituted benzyl analogue **5** that was previously described as being moderately selective for the DAT over the SERT (20-fold).[14] We initially examined the compounds at DAT and SERT. We sought compounds that had high affinity at DAT (preferably, those with K_i < 10 nM) and a high SERT/DAT ratio. Compounds that met those criteria were further evaluated at NET. We initially examined the methoxy compounds to see what ring position was favored and if the presence of an electron-donating group (EDG) would enhance affinity for the transporters and, as well, where a second methoxy derivative could be added to the ring that would cause the least harm to its pharmacological properties. The second methoxy substituent could, in the future, be considered as starting material for a long-chain ester derivative.

Table 1. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 of **1**, **2**, and **5**−**14** (K_i ± SD, nM)

compds[a]	R	σ_p [b]	DAT[c]	SERT[c]	SERT/DAT
1a			3.7 ± 0.4	126 ± 5	34
2a			0.7 ± 0.1	88 ± 10	323
2b			16 ± 1	370 ± 27	23
5	H	0.00	9.9 ± 0.5	171 ± 9	17
6a	2-OCH_3		63 ± 4	248 ± 29	4
6b	3-OCH_3		13.3 ± 0.5	161 ± 14	12
6c	4-OCH_3	−0.27	7.9 ± 0.5	266 ± 25	34
7	4-CH_3	−0.17	5.7 ± 0.3	239 ± 14	42
8	4-F	0.06	2.3 ± 0.2	245 ± 13	107
9	4-I	0.18	2.1 ± 0.2	205 ± 14	98
10	4-Br	0.23	1.1 ± 0.1	199 ± 29	181
11	4-Cl	0.23	1.2 ± 0.1	238 ± 7	198
12	4-CF_3	0.54	1.1 ± 0.1	442 ± 59	402
13	4-CN	0.66	1.2 ± 0.1	606 ± 73	505
14	4-NO_2	0.78	1.2 ± 0.1	387 ± 20	323

[a] Prepared and tested as oxalate salt. [b] Value from ref 21. [c] Values determined as in ref 11.

We found (Table 1) that the C_4-methoxy compound **6c** had similar or higher affinity at DAT and was more selective at SERT than the unsubstituted compound **5**, suggesting that the C_4-position on the aromatic ring might play a role in DAT selectivity. The C_3-methoxy

Table 2. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 of Compounds **16**−**22** (K_i ± SD, nM)

compds[a]	R	σ_p [b]	DAT[c]	SERT[c]	SERT/DAT
16	4-F	0.06	5.1 ± 0.5	902 ± 94	177
17	4-I	0.18	7.2 ± 0.7	457 ± 29	63
18	4-Br	0.23	6.4 ± 0.5	988 ± 120	154
19	4-Cl	0.23	3.8 ± 0.4	531 ± 98	140
20	4-CF_3	0.54	3.5 ± 0.1	2270 ± 265	648
21	4-CN	0.66	5.7 ± 0.4	2230 ± 198	390
22	4-NO_2	0.78	2.5 ± 0.4	2150 ± 264	859

[a] Prepared and tested as oxalate salt. [b] Value from ref 21. [c] Values determined as in ref 11.

compound **6b** had similar or less affinity at DAT than **5** and was, as well, similar to **5** in affinity at SERT. The C_2-methoxy compound **6a** was found to have lower affinity than **5** (or the other methoxy compounds) at both DAT and SERT. Compared to **2a**, all of the methoxy compounds, **6a**−**c**, showed lower affinity and selectivity for the DAT. On the basis of these preliminary results, we decided to explore the effect of different substituents in the C_4-position with respect to their σ_p values (electronic character of the C_4-substituent, Table 1) in an attempt to increase DAT affinity and selectivity over the SERT.

The binding results for **5**−**14** showed that an electron-withdrawing group (EWG) in the *N*-benzyl ring was generally more favorable for DAT affinity than an EDG (Table 1). The C_4-methyl-substituted analogue **7** displayed a binding profile comparable to the C_4-methoxy-substituted compound **6c** (6 nM for the DAT and 240 nM for the SERT), and its affinity was less than that of any of the EWG compounds. Substitution of various halogens, i.e., **8**−**11**, increased affinity and selectivity for the DAT compared to **6c** (Table 1). The nature of the halogen seemed to have only a minor influence on the affinity and selectivity of the compounds for the transporters. Introduction of a trifluoromethyl substituent (**12**) gave a compound with high affinity (1.1 nM) and good selectivity over the SERT (400-fold). The presence of a C_4-cyano group (**13**) gave a compound with high affinity (1.2 nM) for the DAT and the best selectivity in this series over the SERT (500-fold). From these data, it appeared that increasing the σ_p value would increase selectivity for the DAT (Table 1). However, although the C_4-nitro derivative **14**, which has the largest σ_p value (0.78) of the examined substituents, retained high affinity (1.2 nM), it displayed decreased selectivity compared to **13**.

In an effort to further understand the SAR of these compounds, several known desfluoro analogues were resynthesized[17−19] and reevaluated. For this series, effects at DAT were minimal. The desfluoro analogues **16**−**22** (Table 2) had slightly lower affinity for DAT compared to the fluoro analogues **8**−**14**, with values in the low nanomolar range (2.5−7 nM). Their selectivity for the SERT was generally better than that of the corresponding fluorinated derivatives except for the C_4-iodo-, C_4-bromo-, and the C_4-chloro-substituted analogues **17**, **18**, and **19**. The most interesting compound in this series was the C_4-nitro analogue **22** that displayed the greatest selectivity over the SERT (860-fold) of all the compounds examined. In our hands, this compound also had a binding profile better than previously reported,[18] perhaps because of the use of a different radioligand in our assay. The data in Table 1 indicate that enhancement of affinity at the DAT maximizes around a σ_p value of 0.6 and that the maximum enhancement of selectivity over the SERT is at a σ_p value of approximately 0.7 (Tables 1 and 2). It is obvious, though, that the σ_p value does not completely describe affinity or selectivity. The sterically most, as well as the sterically least, demanding halogen substituents (C_4−I and C_4−F) showed similar binding affinities despite their very different σ_p values (0.06 and 0.18). Hence, other factors, perhaps steric effects, are likely to be involved.

Table 3. Uptake Inhibition Studies for Selected Compounds (**8**, **9**, **14**, **17**, **18**, and **22**) (K_i ± SD, nM)

compds[a]	[^{3}H]DA[b]	[^{3}H]5-HT[b]	[^{3}H]NE[b]	5-HT/ DA	NE/qDA
1a	4.3 ± 0.3	73 ± 2	79 ± 5	17	18
2a	7.2 ± 0.4	227 ± 15	93 ± 8	38	13
8	3.8 ± 0.3	601 ± 89	639 ± 89	158	168
9	13.6 ± 1.4	1020 ± 69	546 ± 87	75	40
14	6.9 ± 0.7	1560 ± 105	231 ± 28	226	33
17	5.1 ± 0.4	2570 ± 179	479 ± 68	500	93
18	5.3 ± 0.6	1320 ± 87	534 ± 33	250	101
22	2.7 ± 0.3	3580 ± 440	208 ± 16	1310	76

[a] Prepared and tested as oxalate salt. [b] Values determined as in ref 22.

The most promising compounds in this series were further examined in uptake inhibition assays (Table 3). All of the newly synthesized compounds tested showed higher selectivity in inhibiting DA over NE and 5-HT uptake than **1a** or **2a**. The C_4-fluoro analogue **8** displayed the highest selectivity in inhibiting DA over NE uptake (170-fold). Within the desfluoro series, the C_4−I analogue **17** and the C_4−Br analogue **18** showed the highest selectivity in inhibiting DA over NE uptake (about 100-fold). In addition, all of the compounds in the desfluoro series exhibited much higher selectivity in inhibiting DA over 5-HT uptake than the fluorinated analogues, with compound **22** being the most selective inhibitor (1300-fold).

A direct comparison of the DAT binding affinities (K_i) of six of our desfluorophenyl compounds with literature IC_{50} data[17−19] shows major differences. These differences were also seen when the activity of the compounds relative to the activity of the standard compound (ratio of the affinity of GBR 12909 to that of the ligand) was used. For example, the iodo-substituted compound was formerly reported[17] to have high DAT affinity (using the radioligands [^{3}H]WIN 35,428 and [^{3}H]citalopram for DAT and SERT binding affinities, respectively); we found that it was among those with the least affinity in the desfluoro series (Table 2), using [^{125}I]RTI-55 as the radioligand. We retested our iodo compound and found that its DAT affinity and the literature value[17] were still different by more than an order of magnitude. The major causes for the discrepancies are likely to be the different radioligands used and the difficulty inherent in comparing IC_{50} data[17] and the K_i values in Table 2.

Our use of the radioligand [^{125}I]RTI-55 was supported by previous work[11] that established that [^{125}I]RTI-55 had very low nonspecific binding, much lower than that of [^{3}H]paroxetine, and, further, that the higher specific activity of [^{125}I]RTI-55 allowed the use of less tissue per assay tube.[20] The RTI-55 radioligand gave uptake/binding ratios for three desfluorophenyl compounds (**17**, **18**, **22**) that were less than 1.5 times different, compared with a desfluorophenyl series where a 4-fold difference

was obtained.[17] However, the near-equivalence of uptake and binding that was found may be limited to this small subset of compounds; larger uptake/binding ratios were found in the difluorophenyl series (two compounds, **9** and **14**, were more than 5-fold different). Although the 4-fold difference noted in the literature for desfluorophenyl compounds was assigned to the different radioligands associated with the characterization of uptake and binding of ligands, our uptake/binding ratios suggest that there may be other reasons as well.

Conclusions

A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethyl-1-benzylpiperidines were examined for their ability to bind to the DAT and the SERT. Binding results indicated that in this series of compounds the presence of an EWG in the C_4-position of the *N*-benzyl group is beneficial for binding to the DAT. In addition, the results showed that substitution in the C_3- and C_4-positions are better tolerated than in the C_2-position, in agreement with our observations in the 2-naphthylmethyl case. This work has resulted in the identification of several analogues with high affinity for the DAT and up to 500-fold selectivity over the SERT. Furthermore, the newly synthesized compounds displayed up to 170-fold selectivity over NE uptake. One compound (**22**) displayed 1300-fold selectivity over 5-HT uptake in the uptake inhibition assay.

Experimental Section

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 using DMSO-d_6 as solvent, δ values in ppm (TMS as internal standard), and J (Hz) assignments of ^{1}H resonance coupling. Chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.250 mm Analtech GHLF silica gel plates using *n*-hexane/EtOAc, 7:3, as the solvent system. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(2-methoxybenzyl)piperidine Oxalate (6a). A suspension of **4**·oxalate[15] (1.5 g, 3.6 mmol), K_2CO_3 (1.5 g, 10.8 mmol), a catalytic amount of NaI, and 2-methoxybenzyl chloride (0.6 g, 4.0 mmol) in dry DMF (30 mL) was heated at reflux overnight. H_2O (150 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined EtOAc portion was washed with H_2O (2 × 50 mL) and saturated NaCl (2 × 75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in acetone. Oxalic acid (1.1 equiv) was added and the precipitate was collected, washed with anhydrous Et_2O (100 mL), and dried to afford 1.4 g (72%) of **6a** as colorless crystals, mp 108−112 °C. ^{1}H NMR: δ 7.0−7.5 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (bs, NH, CH_2NH), 3.8 (s, 3H, $-OCH_3$), 3.2−3.5 (m, 3H), 2.5−2.9 (m, 3H), 1.1−2.0 (m, 5H). MS: 452.3 [M + 1]$^+$. Anal. ($C_{28}H_{31}F_2NO_2$·$C_2H_2O_4$·1.25H_2O) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(3-methoxybenzyl)piperidine Oxalate (6b). 6b was synthesized as described for **6a** from **4**·oxalate using 3-methoxybenzyl chloride to afford 1.9 g (97%) of **6b** as colorless crystals, mp 143−146 °C. ^{1}H NMR: δ 6.9−7.4 (m, 12H, aromatic), 6.0 (bs, NH), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.8 (s, 3H, $-OCH_3$), 3.2−3.4 (m, 3H), 2.5−2.9 (m, 3H), 1.1−2.0 (m, 7H). MS: 452.3 [M + 1]$^+$. Anal. ($C_{28}H_{31}F_2NO_2$·$C_2H_2O_4$·0.25H_2O) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-methoxybenzyl)piperidine Oxalate (6c). 6c was synthesized as described for **6a** from **4**·oxalate using 4-methoxybenzyl chloride to afford 1.5 g (78%) of **6c** as colorless crystals, mp 118−122 °C. ^{1}H NMR: δ 6.9−7.4 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 5.0 (bs, NH), 4.1 (s, 2H, CH_2NH), 3.8 (s, 3H, $-OCH_3$), 3.2−3.5 (m, 4H), 2.5−2.9 (m, 3H), 1.1−2.0 (m, 7H). MS: 452.3 [M + 1]$^+$. Anal. ($C_{28}H_{31}F_2NO_2$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-methylbenzyl)piperidine Oxalate (7). 7 was synthesized as described for **6a** from **4**·oxalate using 4-methylbenzyl bromide to afford 1.4 g (72%) of **7** as colorless crystals, mp 148−150 °C. ^{1}H NMR: δ 7.1−7.4 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.9 (m, 6H), 1.2−1.8 (m, 6H). MS: 436.3 [M + 1]$^+$. Anal. ($C_{28}H_{31}F_2NO$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-fluorobenzyl)piperidine Oxalate (8). 8 was synthesized as described for **6a** from **4**·oxalate using 4-fluorobenzylbromide to afford 1.0 g (53%) of **8** as colorless crystals, mp 166−168 °C. ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.9 (m, 3H), 1.2−1.8 (m, 6H). MS: 440.3 [M + 1]$^+$. Anal. ($C_{27}H_{28}F_3NO$·$C_2H_2O_4$·0.25H_2O) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-iodobenzyl)piperidine Oxalate (9). 9 was synthesized as described for **6a** from **4**·oxalate using 4-iodobenzyl bromide to afford 2.0 g (87%) of **9** as colorless crystals, mp 150−152 °C. ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.0 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.7 (m, 3H), 1.2−1.8 (m, 6H). MS: 549.2 [M + 1]$^+$. Anal. ($C_{27}H_{28}F_2NIO$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-bromobenzyl)piperidine Oxalate (10). 10 was synthesized as described for **6a** from **4**·oxalate using 4-bromobenzyl bromide to afford 1.5 g (71%) of **10** as colorless crystals, mp 140−143 °C. ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.9 (m, 3H), 1.2−1.8 (m, 6H). MS: 500.2 [M + 1]$^+$. Anal. ($C_{27}H_{28}F_2NOBr$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-chlorobenzyl)piperidine Oxalate (11). 11 was synthesized as described for **6a** from **4**·oxalate using 4-chlorobenzyl chloride to afford 1.0 g (76%) of **11** as colorless crystals, mp 154−157 °C. ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.7 (m, 3H), 1.2−1.8 (m, 6H). MS: 456.3 [M + 1]$^+$. Anal. ($C_{27}H_{28}ClF_2NO$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-trifluoromethylbenzyl)piperidine Oxalate (12). 12 was synthesized as described for **6a** from **4**·oxalate using 4-trifluoromethylbenzyl bromide to afford 1.2 g (58%) of **12** as colorless crystals, mp 138−140 °C. ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.9 (m, 3H), 1.2−1.8 (m, 6H). MS: 490.3 [M + 1]$^+$. Anal. ($C_{28}H_{28}F_5NO$·$C_2H_2O_4$) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-cyanobenzyl)piperidine Oxalate (13). 13 was synthesized as described for **6a** from **4**·oxalate using α-bromo-*p*-tolunitrile to afford 2.1 g (82%) of **13** as colorless crystals, mp 154−156 °C. ^{1}H NMR: δ 7.1−7.9 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.0−3.5 (m, 4H), 2.5−2.7 (m, 3H), 1.2−1.8 (m, 6H). MS: 447.3 [M + 1]$^+$. Anal. $C_{28}H_{28}F_2N_2O$·$C_2H_2O_4$·0.25H_2O) C, H, N.

4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(4-nitrobenzyl)piperidine Oxalate (14). 14 was synthesized as described for **6a** from **4**·oxalate using 4-nitrobenzyl bromide to afford 1.7 g (85%) of **14** as colorless crystals, mp 108 °C (dec). ^{1}H NMR: δ 7.1−7.6 (m, 12H, aromatic), 5.5 (s, 1H, CH−O), 4.1 (s, 2H, CH_2NH), 3.1−3.4 (m, 4H), 2.5−2.9 (m, 3H), 1.2−1.8 (m, 6H). MS: 467.3 [M + 1]$^+$. Anal. ($C_{27}H_{28}F_2N_2O_3$·$C_2H_2O_4$) C, H, N.

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