Brief Articles

Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter

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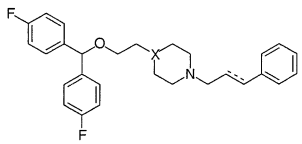
A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethylpiperidines were examined for their ability to bind to the dopamine transporter (DAT), the norepinephrine transporter, and the serotonin transporter (SERT). In particular, the role of the *N*-substituent on affinity and selectivity for the DAT was probed. 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl-1-(2-naphthylmethyl)piperidine was found to possess subnanomolar affinity (K_i = 0.7 nM) and good selectivity for the DAT (SERT/DAT = 323).

Introduction

Cocaine is a widely abused drug, and its abuse has had great effects on public health, through the spread of human immunodeficiency virus (HIV), hepatitis, and tuberculosis.[1−9] Unfortunately, there are no U.S. Food and Drug Administration (FDA)-approved therapeutic agents available for the treatment of cocaine abuse or for the prevention of relapse.[10] Among the various agents tested clinically, the best results appear to have been achieved with dextroamphetamine,[11] supporting the hypothesis that agonist substitution therapy is a reasonable approach to developing pharmacotherapies for cocaine dependence.

On a molecular level, cocaine inhibits the reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE). Evidence suggests, however, that its binding to the dopamine transporter (DAT) and subsequent inhibition of DA reuptake may be responsible for its reinforcing properties and a good target for the design of an agonist substitution type medication for cocaine abuse.[12−16]

Our approach to developing this type of potential therapeutic for cocaine abuse is to find a competitive inhibitor of the DAT that dissociates very slowly.[17] 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)-piperazine (GBR 12909) (**1**, Figure 1) was among the first agents to be characterized as a high-affinity and selective inhibitor of DA reuptake.[18,19] Studies with rhesus monkeys have shown that in cocaine and food self-administration studies, **1** decreases cocaine-maintained responding without affecting food-maintained responding.[20,21] Given the promising properties of **1** and its analogues, these compounds have been identified as novel agents for the potential pharmacotherapy of cocaine abuse in humans.



1: X = N, bond = single
2: X = CH, bond = single
3: X = N, bond = double
4: X = CH, bond = double

Figure 1. Structure of 1-{2-[bis-(4-fluoro-phenyl)methoxy]-ethyl}-4-(3-phenylpropyl)piperazine analogues.

The binding of these agents at the transporter for norepinephrine (NET) is a possible source of sympathomimetic side effects. In our continuing efforts to develop new agents that might reduce cocaine self-administration, we are attempting to find more selective and high-affinity DAT inhibitors.[20−26] Our efforts were focused on analogues, where a piperidine ring was substituted for the piperazine ring in **1**. Several piperidine analogues have been prepared.[27] Compound **2** was reported to have good affinity for the DAT but was not very selective.[27] Previous reports have shown that modification of this compound may lead to analogues with enhanced selectivity for the DAT over the serotonin transporter (SERT).[28,29]

Chemistry

The *N*-substituted piperidines were synthesized from the commercially available 4-piperidineethanol (Scheme 1). The reaction of 4-piperidineethanol with hydrocinnamoyl chloride, followed by reduction of the corresponding amide with LAH, and ether formation using 4,4′-difluorobenzhydrol in toluene under azeotropic distillation conditions gave **2** in good yield.[27] Alternately, a three step sequence of *N*-protection, ether formation, and *N*-deprotection afforded **5**.[27,30] The coupling of piperidine **5** with *trans*-cinnamic acid using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), followed by reduction of the corresponding amide with AlH_3, afforded alkene **4**.[31,32]

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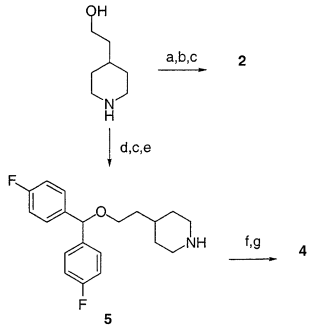
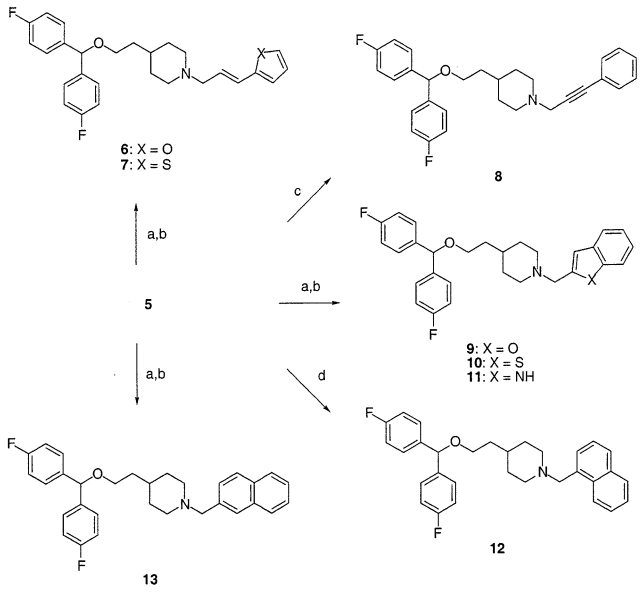
Scheme 1[a]



[a] Reagents: (a) Hydrocinnamoyl chloride, NEt_3, CH_2Cl_2. (b) LAH, THF. (c) 4,4-Difluorobenzhydrol, *p*-TsOH·H_2O, toluene. (d) Benzoyl chloride, NEt_3, CH_2Cl_2. (e) NaOH, EtOH. (f) *trans*-Cinnamic acid, EDCI, CH_2Cl_2. (g) LAH, H_2SO_4, THF.

Scheme 2[a]



[a] Reagents: (a) Appropriate acid, EDCI, CH_2Cl_2. (b) LAH, H_2SO_4, THF. (c) Phenylacetylene, $(CH_2O)_n$, $CuSO_4$, THF. (d) 1-Chloromethylnaphthalene, K_2CO_3, DMF.

Targets **6**, **7**, **9**−**11**, and **13** were prepared from **5** using a procedure similar to the preparation of **4** (Scheme 2). The coupling of **5** with the appropriate acid using EDCI followed by reduction of the corresponding amide with AlH_3 gave **6**, **7**, **9**−**11**, and **13**.[33,34] A modified Mannich reaction using **5**, phenylacetylene, and paraformaldehyde gave **8**. The treatment of **5** with 1-chloromethylnaphthalene under basic conditions afforded **12**.

Results and Discussion

We resynthesized **2** to compare (Table 1) its binding affinities with those of our new analogues. It was hoped that the introduction of different functional groups into the *N*-alkyl group of **2** would give us a compound with high affinity and better selectivity than **1**. These analogues might represent a second generation cocaine abuse treatment agent.

We found that the affinity of **2** in our binding assay (Table 1) was higher than previously reported.[27] It had higher affinity (K_i = 1.1 nM) for the DAT and greater selectivity over the SERT (68-fold) than **1**. This might be due to the use of [^{125}I]RTI-55 to label a site on the DAT rather than the formerly used[27] [^{3}H]WIN 35,428.

Table 1. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 of **2**, **4**, and **6**−**13** (K_i ± SD, nM)

compds[a]	DAT[b]	SERT[b]	SERT/DAT
1	3.7 ± 0.4	126 ± 27	34
2	1.1 ± 0.1	68 ± 8	65
4	0.45 ± 0.03	47 ± 2	104
6	0.99 ± 0.07	41 ± 6	41
7	1.3 ± 0.1	45 ± 5	35
8	5.3 ± 0.4	164 ± 26	31
9	1.01 ± 0.18	85 ± 10	84
10	1.61 ± 0.15	246 ± 33	153
11	0.73 ± 0.07	88 ± 10	121
12	16 ± 1	370 ± 27	23
13	0.71 ± 0.06	229 ± 21	323

[a] Prepared and tested as oxalate salt. [b] Values determined as in ref 23 using [^{125}I]RTI-55 as radioligand for the DAT and SERT.

On the basis of this observation and our previous discovery that 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylallyl)piperazine (GBR 13069, **3**) also had higher affinity for the DAT than **1**,[23] we thought it might be of great interest to prepare **4**. Although it was prepared previously, we thought it possible that **4** might have greater affinity for the DAT in our assay. We found that **4** had higher affinity for the DAT (K_i = 0.45 nM) than **2** (K_i = 1.1 nM). This result, however, was also in contrast to previous findings where the affinity of **4** was reported to be 41.4 nM.[32] In an attempt to better understand these results, we evaluated several additional analogues with *N*-substituents that had been previously investigated in the piperazine series.[22] In particular, we chose to examine *N*-substituents in the piperidine series that displayed high affinity ($K_i \leq$ 10 nM) in the piperazine series, such as a 3-furan-2-ylallyl and a 3-thiophen-2-ylallyl substituent, as well as several others.[22] It was hoped that these specific alterations might provide an explanation for the mode of binding of the two series relative to one another.

The binding results showed that the replacement of the phenyl ring in **4** with a 2-furyl, **6**, or 2-thienyl, **7**, group resulted in a decrease in affinity for the DAT as compared to **4**. These compounds were similar to **4** in their affinity for the SERT.

The role of the trans-alkene in **4** was then tested. The introduction of an alkyne, i.e., **8**, decreased affinity for the DAT (10-fold) as compared to **4**. This seemed to indicate that a trans-alkene was favored over a linear conformation, i.e., **8**. Furthermore, the trans-alkene in **4** was then incorporated into several heterocycles, **9**−**11**. These modifications decreased affinity for the DAT and the SERT as compared to **4**. We noted that the introduction of an indole moiety, **11**, was optimal for affinity (K_i = 0.73 nM) among the heterocycles, **9**−**11**. However, the benzothiophene analogue, **10**, had the best selectivity over the SERT (153-fold).

In an attempt to further investigate the binding region of the *N*-substituent, we synthesized two naphthalene isomers. 1-Naphthylmethyl analogue **12** had the least affinity for the DAT (K_i = 16 nM) and the SERT (K_i = 370 nM) of this series of ligands. Remarkably, 2-naphthylmethyl analogue, **13**, was found to have subnanomolar affinity (K_i = 0.71 nM) for the DAT and the best selectivity over the SERT (323-fold) of the compounds examined.

The functional binding assays (Table 2) were carried out for two of the most interesting ligands, **10** and **13**.

Table 2. Reuptake Inhibition Studies of **1**, **10**, and **13** ($IC_{50} \pm$ SD, nM)

compds[a]	DA[b]	5-HT[b]	NE[b]	5-HT/DA	NE/DA
1	4.3 ± 0.3	73 ± 2	79 ± 5	17	18
10	11.9 ± 1.0	1037 ± 92	260 ± 21	87	22
13	7.2 ± 0.4	277 ± 15	93 ± 8	38	13

[a] Prepared and tested as oxalate salt. [b] Values determined as in ref 23b.

These compounds were chosen because they had the best selectivity over the SERT in this series. The uptake assay showed that both **10** and **13** had slightly lower potency than **1** in inhibiting DA uptake. However, both had increased selectivity over inhibiting 5-HT uptake as compared to **1**, and **10** showed the desired increase in selectivity over NE.

In comparison with the piperazine series, the piperidine analogues generally had higher affinity for both the DAT and the SERT.[22] In agreement with the piperazine series,[22] 2-furyl analogue **6** ($K_i = 0.99$ nM) had slightly higher affinity for the DAT than the 2-thienyl analogue **7** ($K_i = 1.3$ nM). Compounds **9** and **10** had higher affinity and better selectivity than the corresponding piperazine analogues. Compound **11** was nearly identical to its piperazine counterpart. The only difference was a slightly higher affinity for the SERT that was responsible for a lower selectivity. Compounds **12** and **13** showed very different results. In the piperazine series, the 2-naphthylmethyl derivative had lower affinity for the DAT than the 1-naphthylmethyl derivative. It was thought that if the piperidine series was binding in an identical manner to the piperazine series, then compound **12** would have higher affinity than **13** for the DAT. Interestingly, **13** had subnanomolar affinity for the DAT and the best selectivity over the SERT in this series of ligands. Apparently, an extended conformation is preferred in the piperidine series. It also appears that previous piperazine structure−activity relationships (SAR) may not be applicable to the piperidine series, suggesting that these two series are not binding in an identical manner at the DAT.

Conclusions

A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethylpiperidines were synthesized and evaluated. Several ligands were identified with subnanomolar affinity to DAT. The 2-naphthyl derivative (**13**) was more than 300-fold selective for DAT over the SERT, and in reuptake inhibition studies, the benzothiophene compound **10** was found to have somewhat better selectivity for DAT over the NET than **1**. This study indicates that previous SAR seen in the GBR-12909 piperazine series do not hold for the corresponding piperidine series. Further exploration of this is currently underway.

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used without further purification. The instrumentation used has been previously noted.[26]

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperidine Oxalate (5). A solution of benzoyl chloride (16.3 g, 116.1 mmol) in dry CH_2Cl_2 (200 mL) was added in a dropwise manner to a solution of 4-piperidineethanol (15.0 g, 116.1 mmol) and triethylamine (11.7 g, 116.1 mmol) in dry CH_2Cl_2 (400 mL) at 0 °C. The mixture was stirred at room temperature overnight, washed successively with H_2O (3 × 100 mL), 2 N HCl (3 × 100 mL), and saturated NaCl (2 × 200 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was used without further purification. A mixture of crude oil, *p*-toluenesulfonic acid monohydrate (13.8 g, 72.6 mmol), and 4,4-difluorobenzhydrol (26.8 g, 121.9 mmol) in dry toluene (800 mL) was heated at reflux under azeotropic distillation conditions overnight. The solvent was removed under reduced pressure, and EtOAc (600 mL) was added. The EtOAc portion was washed with H_2O (3 × 100 mL) and saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that solidified upon addition of hexane. A solution of the crude solid, NaOH (21.2 g, 529 mmol), H_2O (50 mL), and absolute EtOH (500 mL) was heated at reflux for 36 h. The solvent was removed under reduced pressure, and H_2O (300 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in dry acetone. Oxalic acid (1.1 equiv) was added, and precipitate was collected and dried to afford 36.1 g (74%) of **5** as a white solid; mp 146−148 °C. ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 8H, aromatic); 5.5 (s, 1H, CH−O); 3.9 (bs, NH); 3.1−3.4 (m, 4H); 2.5−2.9 (m, 5H); 1.1−2.0 (m, 5H).

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-(3-phenylallyl)piperidine Oxalate (4). A solution of the free base of **5** (1.5 g, 4.5 mmol), *trans*-cinnamic acid (0.7 g, 4.5 mmol), and EDCI (0.9 g, 5.0 mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the ethyl acetate (125 mL) was added to the residue. The ethyl acetate solution was washed successively with 1 N HCl (2 × 50 mL), 10% K_2CO_3 (2 × 50 mL), and saturated NaCl (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford 2.0 g (96%) of the corresponding amide as an oil that was used without further characterization. A 100% amount of H_2SO_4 ($d = 1.84$) (1.1 g, 11.0 mmol) was added cautiously to a suspension of LAH (0.8 g, 22 mmol) in dry tetrahydrofuran (THF, 100 mmol) at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 1 h. A solution of the crude amide in dry THF (50 mL) was added in a dropwise manner. The resulting mixture was stirred for 2 h, and 10% NaOH (150 mL) was added cautiously. The layers separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic portion was washed with H_2O (100 mL) and saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in dry acetone. Oxalic acid (1.1 equiv) was added, and the solvent was removed under reduced pressure. Anhydrous Et_2O was added, and the precipitate was collected and dried to afford 1.6 g (67%) of **4** as a white solid; mp 158−160 °C (literature[2] 162.7−163.5 °C). Anal. ($C_{29}H_{31}F_2NO{\cdot}C_2H_2O_4{\cdot}0.5H_2O$): C, H, N.

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-(3-phenylprop-2-ynyl)piperidine Oxalate (8). A mixture of the free base of **5** (1.5 g, 4.7 mmol), phenylacetylene (0.7 g, 7.1 mmol), $CuSO_4$ (0.8 g, 4.7 mmol), and paraformaldehyde (0.4 g, 14.1 mmol) in dry THF (45 mL) was heated at reflux for 2 h. Et_2O (100 mL) was added, and the mixture was filtered through a pad of Celite. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 portion was washed with H_2O (5 × 50 mL) and saturated NaCl (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure affording a crude oil that was dissolved in anhydrous Et_2O. Oxalic acid (1.1 equiv) was added, and the precipitate was collected, washed with cold absolute EtOH (20 mL), and dried to afford 2.0 g (80%) of **8** as a white solid; mp 134−136 °C. ^{1}H NMR (DMSO-d_6): δ 7.1−7.6 (m, 13H, aromatic); 5.5 (s, 1H, CH−O); 4.0 (s, 2H, NCH_2); 3.1−3.4 (m, 4H); 2.5−2.9 (m, 5H); 1.0−2.0 (m, 5H). Anal. ($C_{29}H_{29}F_2NO{\cdot}C_2H_2O_4$): C, H, N.

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-naphthalen-1-ylmethylpiperidine Oxalate (12). A suspension of **5** (1.0 g, 2.4 mmol), K_2CO_3 (1.0 g, 7.2 mmol), a catalytic amount of NaI, and 1-chloromethylnaphthalene (0.5 g, 2.6 mmol) in dimethylformamide (DMF, 30 mL) was stirred at 100 °C overnight. The mixture was poured into H_2O (200 mL) and extracted with ethyl acetate (3 × 60 mL). The combined ethyl acetate portion was washed with H_2O (2 × 75 mL) and saturated NaCl (2 × 75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a residue that was dissolved in anhydrous Et_2O. Oxalic acid (1.1 equiv) was added, and the precipitate was collected, recrystallized from absolute EtOH, and dried to afford 0.9 g (67%) of **12** as a white solid; mp 176−178 °C. ^{1}H NMR (DMSO-d_6): δ 7.1−8.4 (m, 15H, aromatic); 5.5 (s, 1H, CH−O); 4.5 (s, 2H, $ArCH_2$-); 3.1−3.4 (m, 4H); 2.5−2.9 (m, 5H); 1.1−2.0 (m, 5H). Anal. ($C_{31}H_{31}F_2NO\cdot C_2H_2O_4$): C, H, N.

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(33) All of the new compounds were found to be within ±0.4 of the theoretical values for C, H, and N. ^{1}H NMR (300 MHz, DMSO-d_6) was in agreement with assigned structures.

(34) Uncorrected melting points of oxalate salts: **4**, mp 158−160 °C; **5**, mp 146−148 °C; **6**, mp 148−149 °C; **7**, mp 150−152 °C; **8**, mp 134−136 °C; **9**, mp 156−159 °C; **10**, mp 155−159 °C; **11**, mp 180−183 °C; **12**, mp 176−178 °C; **13**, mp 161−162 °C.

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