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Synthesis and Dopamine Transporter Affinity of Chiral 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-hydroxypropyl)piperazines as Potential Cocaine Abuse Therapeutic Agents

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Abstract—A series of optically pure phenyl-and non-phenyl-substituted 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(2-hydroxypropyl)piperazines was synthesized and their binding affinity for dopamine transporter (DAT) was investigated. The analogues with a hydroxyl group in the *S* configuration were more selective for the DAT over the serotonin transporter (SERT) than the corresponding *R* enantiomers. Compound (+)-**11** showed high affinity and selectivity for DAT over the SERT and, therefore, is a potential candidate for the development of a long-acting cocaine abuse therapeutic agent.

Cocaine is one of the most widely abused drugs in the world. Its abuse continues to result in serious public health and societal problems.[1,2] Numerous studies have indicated that the reinforcing and locomotor stimulating properties of cocaine are mainly mediated by the binding of cocaine to the dopamine transporter (DAT) and subsequent blockade of dopamine (DA) reuptake into presynaptic terminals resulting in increased neurotransmission in the mesolimbic dopaminergic system.[3–5] High affinity and selective DAT ligands, have been sought that may reduce the effects of cocaine and therefore, could be potential treatment agents for cocaine abuse.[6,7]

Our research has focused on the development of novel analogues of the disubstituted piperazine GBR12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)-piperazine, **1**) and GBR12935 (1-[2-(diphenylmethoxy)-ethyl]-4-(3-phenylpropyl)piperazine, **2**)[8] (Fig. 1). Previous work in this laboratory has shown that acute doses of **1** or **2** could decrease cocaine-maintained responding in rhesus monkeys at lower doses than those affecting food-maintained responding.[9] Recently, in an effort to develop long-acting cocaine abuse therapeutic agents, we prepared benzylic hydroxyl analogues (±)-**3**, (*S*)-**3**, and (*R*)-**3**.[10,11] Their pharmacological profiles were similar to that of **1**.[10] In a test of this concept, the decanoate ester of (±)-**3** was synthesized and shown to successful in suppressing cocaine-maintained responding in rhesus monkeys without affecting food intake for almost thirty days.[10]

Our continued studies on the structure–activity relationships (SARs) of the hydroxyl-containing analogues of **1** and **2** have shown that the *S* and *R* enantiomers of the 2-hydroxylated derivatives possessed quite different pharmacological profiles[12,13] whereas the enantiomers of benzylic alcohols [i.e., (*S*)-**3** and (*R*)-**3**] displayed very similar biological activities.[11] In the 2-hydroxyl substituted series, the *S* isomers showed much higher affinity for the DAT and as DA reuptake inhibitors than the corresponding *R* isomers, whereas the *R* isomers showed higher affinity for the serotonin transporter (SERT) and at inhibiting the reuptake of serotonin than the *S* isomers.[12,13] The alcohols (*S*)-**4** and (*S*)-**5** are among those with highest affinity and selectivity DAT ligands yet known (Table 1).[13] Furthermore, (*S*)-**4** effectively elevated extracellular dopamine (ECDA) levels in

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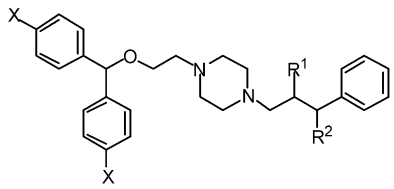


1: X = F, $R^1 = R^2 = H$
2: X = $R^1 = R^2 = H$
3: X = F, $R^1 = H$, $R^2 = OH$
(*S*)-**3**: X = F, $R^1 = H$, $R^2 = (S)$-OH
(*R*)-**3**: X = F, $R^1 = H$, $R^2 = (R)$-OH
(*S*)-**4**: X = F, $R^1 = (S)$-OH, $R^2 = H$
(*R*)-**4**: X = F, $R^1 = (R)$-OH, $R^2 = H$
(*S*)-**5**: X = H, $R^1 = (S)$-OH, $R^2 = H$
(*R*)-**5**: X = H, $R^1 = (R)$-OH, $R^2 = H$

Figure 1. Structures of GBR 12909 (**1**) and GBR 12935 (**2**) analogues.

Table 1. Binding affinities and selectivities of compounds **1**, **2**, **4**, **5**, **8**–**12**

Compds[a]	DAT K_i (nM)[b]	SERT K_i (nM)[b]	SERT/DAT
1	3.7 (±0.4)	126 (±5)	34
2	3.7 (±0.3)	623 (±13)	168
(±)-**3**	2.1 (±0.1)	117 (±7)	56
(*S*)-(+)-**3**	3.0 (±0.3)	85 (±3)	28
(*R*)-(−)-**3**	4.4 (±0.5)	135 (±5)	31
(±)-**4**	2.3 (±0.1)	124 (±4)	54
(*S*)-(+)-**4**	0.75 (±0.03)	230 (±7)	307
(*R*)-(−)-**4**	12.0 (±0.3)	162 (±4)	14
(*S*)-(+)-**5**	2.3 (±0.1)	2160 (±79)	939
(*R*)-(−)-**5**	25 (±1)	1830 (±86)	73
8a	34 (±6)	2090 (±143)	61
8b	40 (±4)	888 (±44)	22
8c	65 (±5)	1650 (±160)	25
(*S*)-(+)-**9**	23 (±1)	981 (±71)	43
(*R*)-(−)-**9**	76 (±10)	588 (±30)	8
(*S*)-(+)-**10**	44 (±1)	12,900 (±500)	293
(*R*)-(−)-**10**	48 (±2)	10,400 (±275)	217
(±)-**11**	20 (±1)	298 (±17)	15
(*S*)-(+)-**11**	5.6 (±0.6)	281 (±19)	50
(*R*)-(−)-**11**	140 (±5)	520 (±31)	4
(1*S*,2*R*)-(+)-**12**	13 (±1)	565 (±34)	43
(1*R*,2*S*)-(−)-**12**	36 (±3)	583 (±55)	16

[a]Prepared and tested as dimaleate salt.
[b]Value determined as in ref 14.

vivo, and was more potent than **1** and (*R*)-4 in decreasing cocaine self-administration without affecting similar responding maintained by food in rhesus monkeys.

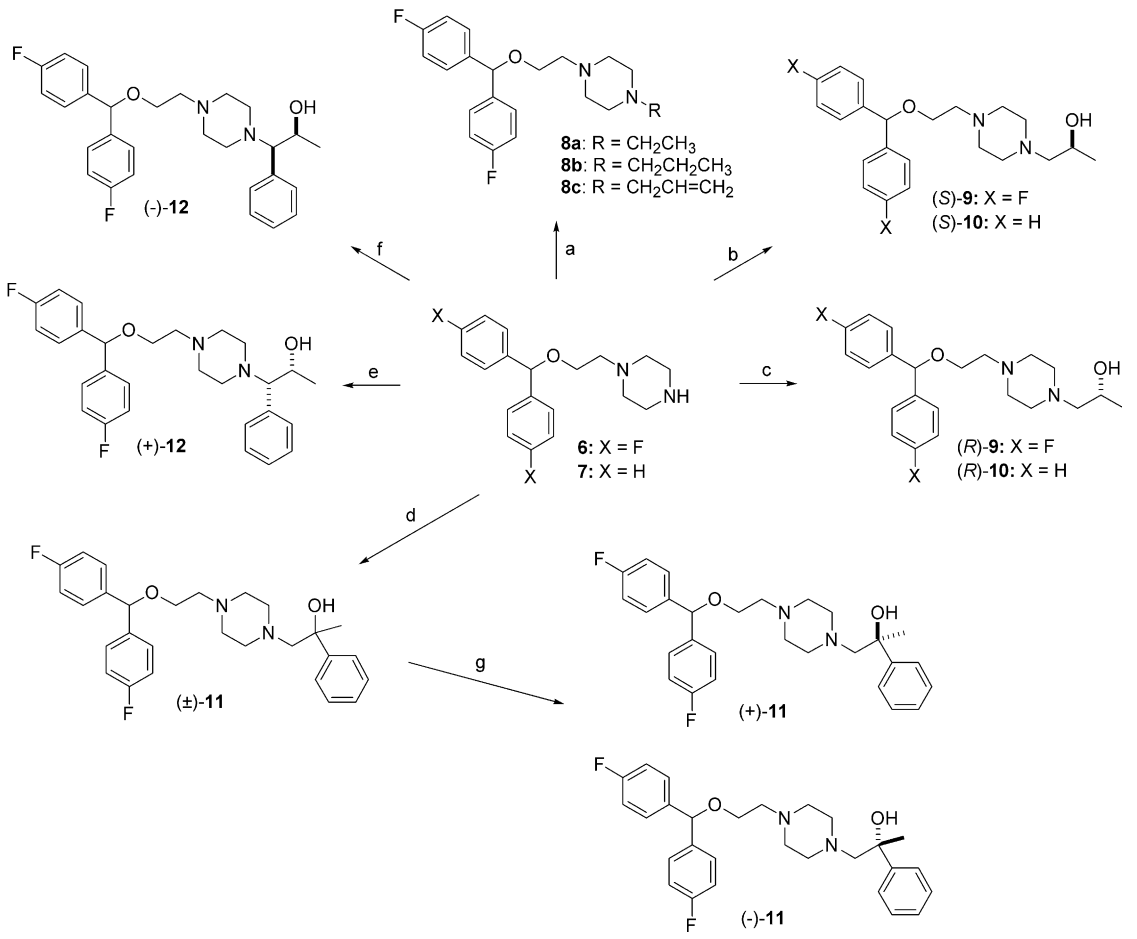
Based on these observations, further SAR studies to determine the effects (including DAT binding affinity, transporter selectivity, enantioselectivity, etc.) of the phenyl and hydroxyl substituents in these chiral hydroxyl-containing analogues are essential for the discovery and development of high affinity, selective, and long-acting DAT inhibitors as potential treatment agents for cocaine abuse. Thus, we have designed a novel series of optically pure 2-hydroxylated derivatives of **1** and **2** with phenyl groups omitted (**8**–**10**) or located at different positions (**11**–**12**), to evaluate their DAT and SERT binding affinities, DAT selectivity versus SERT, and their enantioselectivity.

The monosubstituted piperazines, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine (**6**) and 1-[2-(diphenylmethoxy)ethyl]piperazine (**7**) were synthesized in two steps according to the literature method[8] with modification.[11,13] *N*-Alkylation of **6** with the appropriate halide in the presence of K_2CO_3 in *N,N*-dimethylformamide (DMF) afforded **8a**–**8c** (Scheme 1).[17–21] The chiral hydroxyl substituted analogues, (*S*)-**9**, (*R*)-**9**, (*S*)-**10**, and (*R*)-**10**, were prepared by heating piperazines **6** and **7** with (*S*)-(−)-propylene oxide or (*R*)-(+)-propylene oxide, respectively, at 60 °C in DMF for 48 h under argon.[18] Regioselective epoxide ring-opening of 2-phenylpropylene oxide, (1*R*,2*R*)-(+)-1-phenylpropylene oxide, and (1*S*,2*S*)-(−)-1-phenylpropylene oxide by piperazine **6** afforded the racemic 2-phenyl substituted analogue (±)-**11** and the chiral 1-phenyl substituted analogues (+)-**12** and (−)-**12**, respectively. The chiral 2-phenyl substituted analogues (+)-**11** and (−)-**11** were prepared from (±)-**11** using semi-preparative chiral HPLC[21] followed by recrystallization of their maleate salts. The enantiomeric excess (ee) values of these novel chiral hydroxyl-containing compounds were determined by chiral HPLC,[21] and all were higher than 98%.

Ligands **8a** and **8b** were synthesized as reference compounds to evaluate the effect of the phenyl group of **1** on its pharmacological profile (Table 1). Compared with **1**, they showed a significant decrease in both DAT and SERT binding affinities. Interestingly, the *N*-ethyl analogue (**8a**) had a modest increase in selectivity for the DAT. Based on our previous finding that the introduction of an alkene to the phenylpropyl side enhances both affinity and selectivity for the DAT,[14] **8c** was synthesized. However, the introduction of an alkene did not enhance affinity of **8b** for the DAT. Thus, the phenyl substituent seems to be crucial to high affinity and selectivity for DAT.

The 2-hydroxylated enantiomers (*S*)-**9** and (*R*)-**9** showed some enantioselectivity in binding to the DAT and SERT, and DAT selectivity versus SERT. (*S*)-**9** is more selective than **8b,** and its enantiomer (*R*)-**9,** and had, as well as, higher affinity to the DAT, whereas (*R*)-**9** showed higher affinity to the SERT than **8b** and enantiomer (*S*)-**9**. As we previously observed, the bis-fluoro analogues (e.g., **1** and **4**) generally displayed greater affinity to the DAT, while the des-fluoro analogues (e.g., **2**, **5**) were usually more selective for DAT relative to SERT.[11–13] Therefore, we prepared the des-fluoro 2-hydroxyl analogues (*S*)-**10** and (*R*)-**10**, and they did show much higher selectivity in binding to the DAT versus binding to the SERT than the corresponding bis-fluoro analogues (*S*)-**9** and (*R*)-**9**. Furthermore, (*S*)-**10** and (*R*)-**10** possessed similar enantioselectivity to that of (*S*)-**9** and (*R*)-**9**. (*S*)-**10** displayed higher affinity for the DAT than the *R* isomer (*R*)-**10**, while (*R*)-**10** showed greater affinity for the SERT than (*S*)-**10**. (*S*)-**10** is the most selective DAT ligand (293-fold) in this series of hydroxylated derivatives.

Relocation of the 3-phenyl substituent in compound **4** to the 2-position afforded (±)-**11**, which showed reduced DAT binding affinity and lower DAT selectivity than (±)-**4**. In contrast to previous SAR studies in which the phenylethyl analogues had higher affinity



Scheme 1. (a) Appropriate halide, K_2CO_3, DMF; (b) (*S*)-(−)-propylene oxide; (c) (*R*)-(+)-propylene oxide; (d) 2-phenylpropylene oxide; (e) (1*R*,2*R*)-(+)-1-phenylpropylene oxide; (f) (1*S*,2*S*)-(−)-1-phenylpropylene oxide; (g) semi-preparative chiral HPLC.

than the corresponding phenylpropyl analogues in binding to the SERT,[12] (±)-**11** showed less SERT affinity than (±)-**4**. However, the differences in enantioselectivity demonstrated in previous studies[11,13] and in the analogues **9** and **10** imply that conducting pharmacological studies on racemic compounds may be very misleading for SAR studies. Thus, enantiomers (+)-**11** and (−)-**11** were separated from (±)-**11** and investigated pharmacologically. The absolute configurations of (+)-**11** and (−)-**11** were assigned as *S* and *R* respectively, based on signs of optical rotation[20] and the relative retention times, 10.2 and 11.1 respectively, in chiral HPLC analysis. This finding was confirmed by the synthesis of (−)-**11** from (*R*)-atrolactic acid.[15,16] (+)-**11** and (−)-**11** had lower binding affinities for the DAT and SERT and less DAT selectivity relative to the SERT, compared to (*S*)-**4** and (*R*)-**4**, respectively. (+)-**11** had much higher affinity and selectivity in DAT binding than (−)-**11** (25- and 14-fold, respectively) and showed the highest DAT binding affinity ($K_i = 5.6$ nM) in this series.

The 1-phenyl substituted analogue **12** possessed two chiral centers and therefore, the evaluation of SARs was more complex. Previous SARs for the 2-hydroxylated analogues demonstrated that the (*S*)-(+) isomer usually displayed higher DAT binding affinity and selectivity than the corresponding (*R*)-(−) isomer (e.g., **9**–**11**). The (1*S*,2*R*)-(+)-**12** had higher affinity and selectivity than (1*R*,2*S*)-(−)-**12** for the DAT. The 1*S* and dextrorotatory characters of (1*S*,2*R*)-(+)-**12** were consistent with the SARs for a high affinity and selective DAT ligand, whereas compounds with the 2*R* configuration for the hydroxyl substituent had, as expected from these and previous[12] SAR studies, less selectivity and lower affinity.

In summary, a novel series of optically pure hydroxyl-containing disubstituted piperazines was synthesized and its SAR was examined. It was found that the enantiomers of these 2-hydroxyl substituted ligands displayed substantial enantioselectivity in binding affinity and selectivity for DAT. The *S* isomers had higher affinity and selectivity for the DAT than the corresponding *R* isomers. In addition, the phenyl ring in this series is essential for high affinity and selectivity for the DAT but not necessary for enantioselectivity. In the series, the enantiomers of the 2-phenyl substituted analogue **11** displayed the highest enantioselectivity for binding to the DAT and (*S*)-(+)-**11** had the highest affinity for the DAT. Moreover, (*S*)-(+)-**10** demonstrated the highest selectivity for the DAT and is among the most selective DAT ligands that have been found. The hydroxyl substituent in (*S*)-(+)-**11** would allow conversion to an oil-soluble prodrug; the high affinity and selectivity for DAT make (*S*)-(+)-**11** the best candidate among the new compounds reported herein for the development of

another potential long-acting therapeutic agent for the treatment of cocaine dependence. Further pharmacological and SAR studies are in progress and will be published in due course.

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17. Satisfactory ^{1}H NMR, mass spectral data were obtained for all final products. Elemental analyses were within $\pm 0.4\%$ for C, H, and N.
18. General procedure: A stirred solution of **6** (0.3 g, 1 mmol) and (*R*)-(+)-propylene oxide (0.2 g, 3 mmol) in DMF (3 mL) was heated at 60 °C under argon for 48 h. The reaction was cooled, quenched with water, and then the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (silica gel, 8% MeOH in CH_2Cl_2) to afford (*R*)-**9** as a pale-yellow oil. The oil was dissolved in MeOH and maleic acid (2.2 equiv) was added. The precipitate was collected by filtration, recrystallized from MeOH to give 0.4 g (60%) of (*R*)-**9**-dimaleate as a white crystalline solid.
19. Uncorrected melting points: **8a**: 182–184 °C; **8b**: 183–185 °C; **8c**: 180–182 °C; (*S*)-(+)-**9**: 167–168 °C; (*R*)-(−)-**9**: 169–170 °C; (*S*)-(+)-**10**: 163–164 °C; (*R*)-(−)-**10**: 164–165 °C; (±)-**11**: 182–183 °C; (*S*)-(+)-**11**: 181–182 °C; (*R*)-(−)-**11**: 182–183 °C; (1*S*,2*R*)-(+)-**12**: 169–170 °C; (1*R*,2*S*)-(−)-**12**: 168–169 °C.
20. The enantiomers were separated by HPLC using a semi-preparative chiral column (Daicel chiralcel OD, 2 cm × 25 cm); UV detection at 254 nm; flow rate 6 mL/min; 2% 2-propanol in *n*-hexane in the presence of 0.2% diethylamine.
21. The ee values were determined by HPLC using a chiral column (Daicel chiralcel OD, 0.46 cm × 25 cm); UV detection at 254 nm; flow rate 1 mL/min; 1∼5% 2-propanol in *n*-hexane with 0.2% diethylamine. Optical rotations were obtained using DMF as solvent: (*S*)-(+)-**9**, $[\alpha]_D^{20} = +7.0°$; (*R*)-(−)-**9**, $[\alpha]_D^{20} = -7.2°$; (*S*)-(+)-**10**, $[\alpha]_D^{20} = +7.3°$; (*R*)-(−)-**10**, $[\alpha]_D^{20} = -8.2°$; (*S*)-(+)-**11**, $[\alpha]_D^{20} = +0.3°$; (*R*)-(−)-**11**, $[\alpha]_D^{20} = -0.3°$; (1*S*,2*R*)-(+)-**12**, $[\alpha]_D^{20} = +12.4°$; (1*R*,2*S*)-(−)-**12**, $[\alpha]_D^{20} = -12.6°$.