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Synthesis of dopamine transporter selective 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives

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Abstract—A series of diarylmethoxymethyltropane-GBR hybrid analogues with all three possible stereochemical orientations at C3 were synthesized and evaluated at dopamine and serotonin transporters. The 3α derivatives were found to be the most potent compounds with the 3α-di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane **15b** (K_i = 5 nM) being the most potent compound of the series. The corresponding 3-di(4-fluorophenyl)-methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]oct-2-ene **12b** (K_i = 12 nM) was slightly less potent than the 3α-analogue, while the 3β-di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane **23b** (K_i = 78 nM) exhibited only modest affinity for the dopamine transporter. Only the 3α-analogue **15b** (SERT/DAT = 48) exhibited higher SERT/DAT selectivity than GBR 12909. These results indicate that the dopamine transporter can tolerate some variability in proximity of the benzhydryl ether to the basic nitrogen atom of the tropane without loss in potency. In addition, the structure–activity data for these tropane-GBR 12909 hybrid analogues support previous findings that the stereochemical and conformational effects imparted by unsaturation at C3 are important for dopamine transporter selectivity over the serotonin transporter.

1. Introduction

The abuse of cocaine still remains a serious social and economic problem in the United States. However, despite an increasing population of users and abusers there is no effective medication available for the treatment of cocaine addiction.[1] Efforts to develop a cocaine therapeutic have been primarily focused upon the identification of a selective dopamine transporter uptake inhibitor to be used in a cocaine substitution therapy.[2,3] Although a wide variety of structurally diverse compounds have been prepared and studied,[2–4] the disubstituted piperazine GBR 12909 (**1**)[5–7] and related derivatives have shown some of the greatest potential for development of a dopamine uptake inhibitor therapeutic agent for cocaine addiction.[8–10] While GBR 12909 has yet to be established as a clinically useful therapeutic for the treatment of cocaine addiction, numerous laboratories have employed GBR 12909 as a template to investigate the structural requirements for high-affinity and selective binding to the dopamine transporter (DAT) as well as to identify new lead compounds for medications development.[11–22]

Recent studies in our laboratories have identified 3-diarylmethoxyethylidenyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octanes (**2**) as potent and selective ligands for the DAT.[23] The 3-ethylidenyltropanes **2** were slightly more potent than GBR 12909 but were more selective for the DAT over the serotonin transporter (SERT). The unsaturated analogues **2** exhibited similar potency to that of the corresponding 3α-tropane congeners **3** but were significantly more selective for the DAT than **3**.[23] Based upon the structure–activity relationships of **2** and related tropane analogues **3**, the high DAT selectivity of **2** appeared to be derived from either the conformationally rigid 3-ethylidenyltropane ring system or the stereochemical effects imparted by unsaturation at C3. To investigate further the effects of unsaturation and stereochemistry at C3 of these tropane-GBR 12909 hybrid analogues on DAT and SERT binding affinities, a series of 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]oct-2-enes (**4**) have been designed and synthesized. It is envisaged that if unsaturation at C3 is

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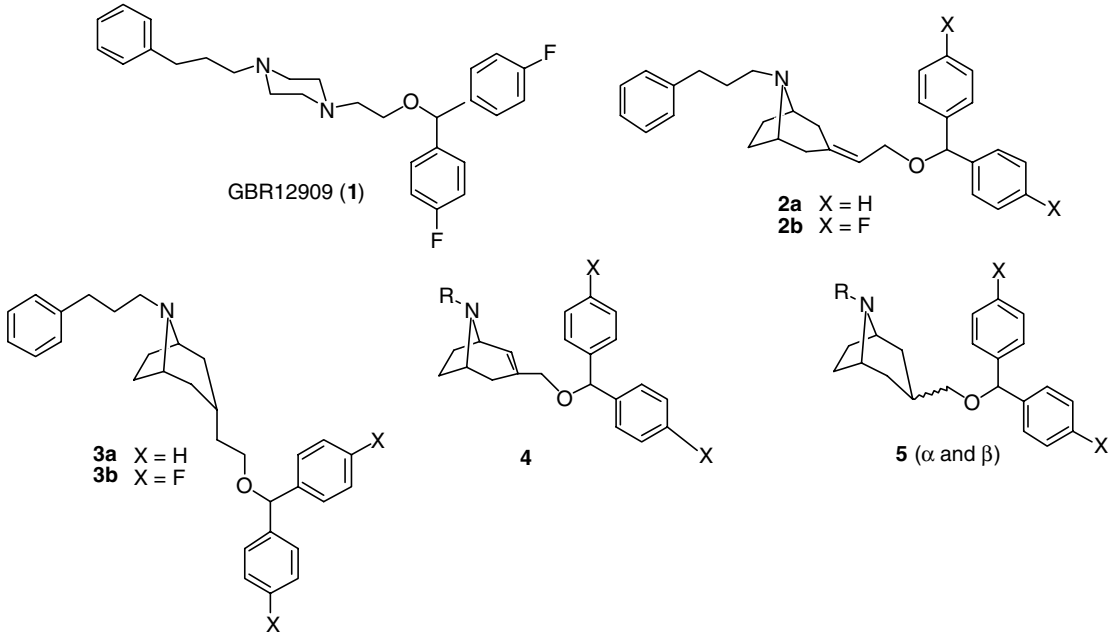


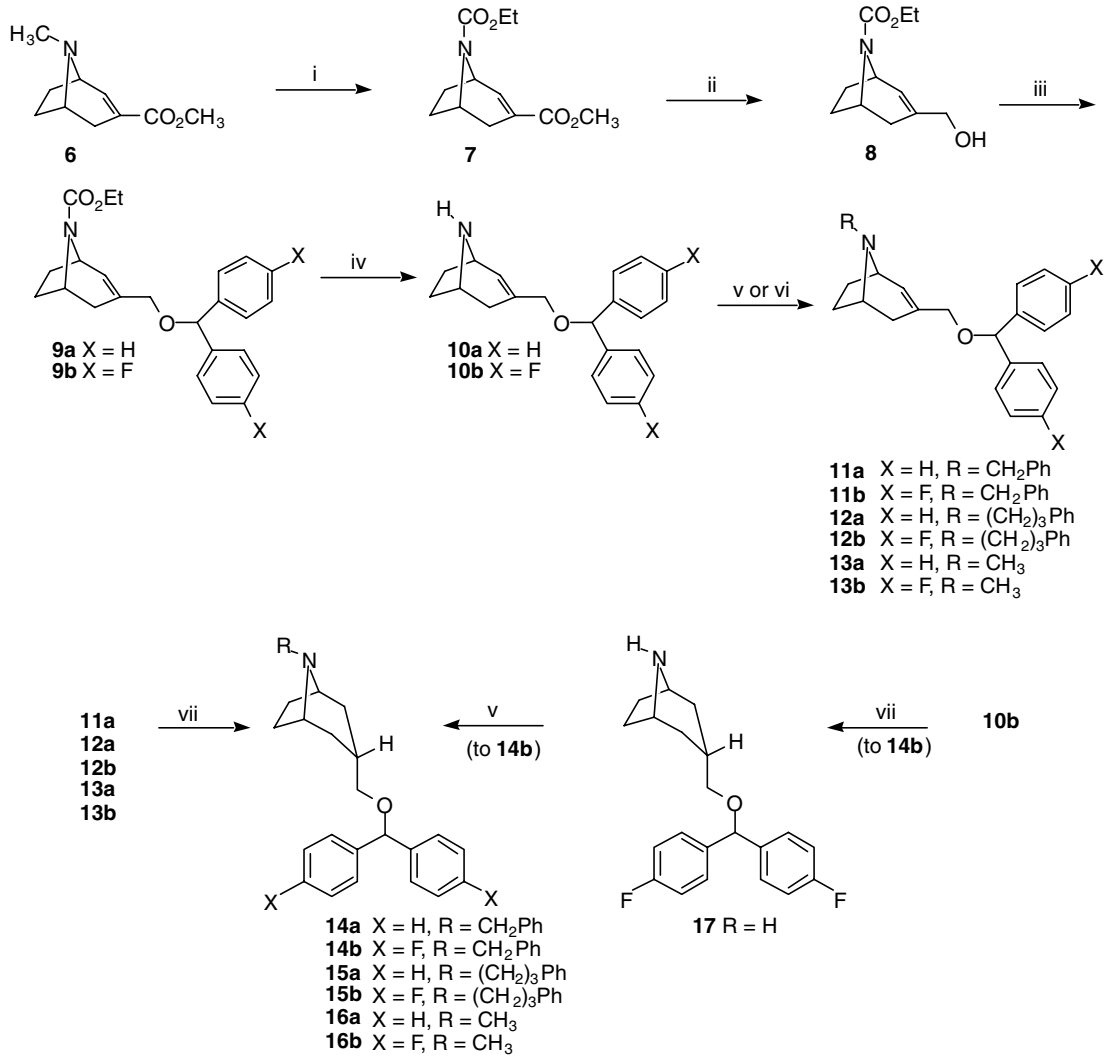
Figure 1.

important in these tropane systems for high DAT selectivity, then the tropene congeners **4** would be expected to exhibit similar DAT selectivity to that observed for the 3-ethylidinyltropanes **2**. However, if unsaturation and conformational rigidity at C3 is not as important as the relative proximity and conformation of the ethylidenyl benzhydryl ether moiety to the tropane ring system, then tropene analogues **4** may exhibit DAT selectivity more similar to GBR 12909 and the 3α-tropane derivatives **3**. In addition, to address further the question of stereochemical proximity of the benzhydryl ether moiety relative to DAT affinity, the 3α- and 3β-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives **5** have been designed and synthesized to evaluate the stereochemical/proximity effects of the benzhydryl ether moiety relative to the tropane ring system. Herein, we describe the synthetic details and in vitro pharmacological profile at the DAT and SERT of a series of 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]oct-2-ene and 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives (Fig. 1).

2. Chemistry

The syntheses of the 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]oct-2-ene and 3α-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives were envisaged to proceed from 3-carbomethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (**6**), which is readily available from tropinone.[24] As illustrated in Scheme 1, demethylation of **6** with ethyl chloroformate in toluene at reflux afforded the carbamate **7** in 95% yield. The removal of the methyl group and introduction of the carbamate served to reduce the basicity of the bridging nitrogen atom of **7**, which greatly facilitated the isolation and purification of subsequent intermediates. Selective reduction of the ester moiety of **7** with lithium aluminum hydride was achieved in THF at 0 °C to furnish the alcohol **8** in 60% yield. The diaryl ethers **9a** and **9b** were obtained in 80% and 87% yields, respectively, by simply heating the alcohol **8** neat at 160 °C with the corresponding diaryl methylchloride. This procedure originally developed for the synthesis of benztropine analogues was found to work exceptionally well in these homologous tropane systems.[25] Removal of the carbamate moiety with hydrazine hydrate in ethylene glycol then furnished the secondary amines **10a** (71%) and **10b** (77%) in good yield. Treatment of **10a** and **10b** with either benzyl bromide or 1-bromo-3-phenylpropane in DMF afforded the corresponding derivatives **11a**, **11b** and **12a**, **12b** in 81–88% yield. Alternatively, N-methylation of **10a** and **10b** was achieved by reductive amination with aqueous formaldehyde and sodium cyanoborohydride in acetonitrile at room temperature to furnish **13a** and **13b**, both in 81% yield.

The synthesis of the 3α-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives was achieved by hydrogenation of the C2–C3 double bond of the corresponding 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]oct-2-ene under ambient conditions over 10% palladium on carbon in methanol (Scheme 1). The 3α-tropane derivatives **14a**, and **15a**, **15b**, **16a**, **16b** were obtained stereoselectively as single diastereoisomers in greater than 90% yield. It was interesting that attempts to convert **11b** into **14b** under similar conditions gave only saturated and debenzylated material. Therefore, to overcome this anomalous reactivity the 3α-tropane derivative **14b** was prepared by an alternative route illustrated at the bottom of Scheme 1. Hydrogenation of the secondary amine **10b** gave the 3α-nortropane **17** as single diastereoisomer and N-alkylation with benzyl bromide furnished **14b** in 78% overall yield.



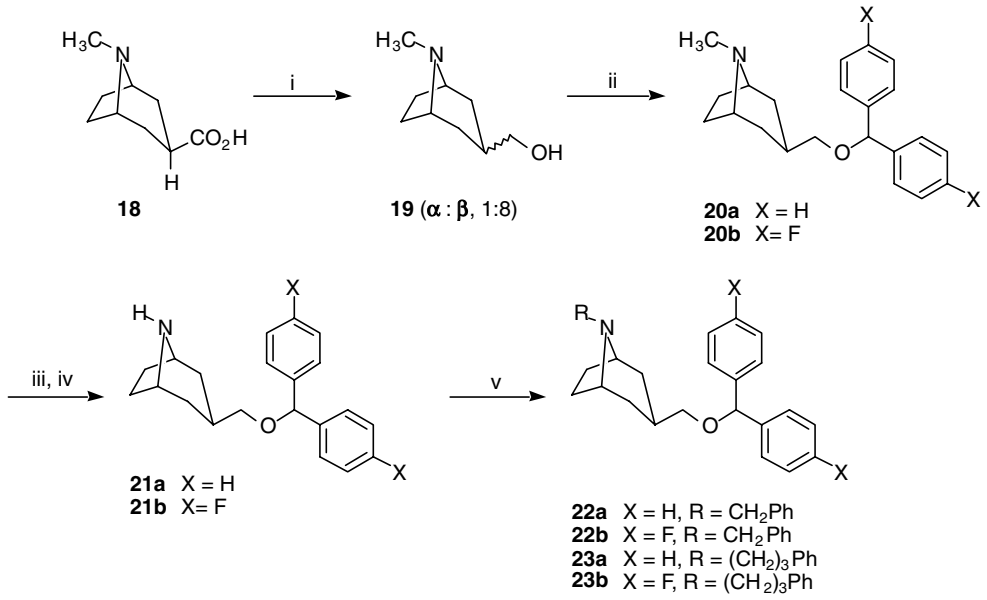
Scheme 1. Reagents and conditions: (i) $ClCO_2Et$, K_2CO_3, toluene, reflux; (ii) $LiAlH_4$, THF, 0 °C; (iii) $ClCH(4\text{-}X\text{–}C_6H_5)_2$, 160 °C; (iv) KOH, $NH_2NH_2H_2O$, $HOCH_2CH_2OH$, reflux; (v) RBr, K_2CO_3, DMF, 80–85 °C; (vi) 37% HCHO, CH_3CN, $NaCNBH_3$; (vii) H_2, 10% Pd/C, CH_3OH.

The 3β-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives were synthesized from the readily available 3β-tropane carboxylic acid (**18**) (Scheme 2). Reduction of the carboxyl group of **18** with lithium aluminum hydride in THF at −78 °C to room temperature gave alcohol **19** as a mixture of C3-isomers (α:β, 1:8). Without separation of the isomers, the alcohol **19** was heated at 150 °C neat with the corresponding diaryl methylchloride. This afforded a mixture of 3α- and 3β-tropane ethers that were easily separated by column chromatography to furnish the 3β-diarylmethoxymethyl-8-methyl-8-azabicyclo[3.2.1]octane derivatives **20a** and **20b** in 60% and 67% overall yield, respectively. The 3α-isomers **16a** and **16b** were each also obtained in 8% yield.

The *N*-phenylpropyl and ***N***-benzyl substituted 3β-isomers were prepared by treatment of methyl congeners **20a** and **20b** with ethyl chloroformate with concomitant decarbonylation using hydrazine hydrate to give the secondary amines **21a** (67%) and **21b** (74%) in good overall yields (Scheme 2). Attempts to directly prepare **21** from **20** by using α-chloroethyl chloroformate (ACE-Cl), even under vigorous conditions, were unsuccessful. Treatment of **21a** and **21b** with either benzyl bromide or 1-bromo-3-phenylpropane afforded the corresponding derivatives **22a**, **22b**, and **23a**, **23b** in 76–78% yield.

3. Results and discussion

The DAT and SERT binding affinities were determined for the tropene and tropane analogues by their ability to displace bound radiolabeled ligands from rat caudate-putamen tissue.[26] The K_i values that are reported in Table 1 are inhibition constants derived for the unlabeled ligands. The binding affinities of the tropene and tropane analogues were determined at DAT by inhibition of [^{3}H]WIN 35,428 binding.[26] For compounds that exhibited potent DAT affinity with K_i values less than 100 nM, the inhibition of [^{3}H]dopamine uptake (DUI)[26] and the SERT affinity (inhibition of [^{3}H]citalopram binding) were determined.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C; (ii) $ClCH(4\text{-}X\text{–}C_6H_5)_2$, 150 °C; (iii) $ClCO_2Et$, K_2CO_3, toluene, reflux; (iv) KOH, $NH_2NH_2{\cdot}H_2O$, $HOCH_2CH_2OH$, reflux; (v) RBr, K_2CO_3, DMF, 80–85 °C.

Table 1. In vitro binding data at the DAT, the SERT and dopamine uptake inhibition

Compound[a]	[^{3}H]WIN 35,428 (DAT) K_i[b] (nM)	[^{3}H]DA (DUI) IC_{50}[b] (nM)	[^{3}H]Citalopram (SERT) K_i[b] (nM)	DAT/SERT
1	12 ± 2			34[c]
2a	4.1 ± 0.6	3.3 ± 0.6	1340 ± 240	327
2b	3.7 ± 0.4	2.1 ± 0.2	563 ± 200	152
3a	18 ± 2	15 ± 4	750 ± 41	42
3b	7.4 ± 3.0	5.4 ± 1.1	175 ± 23	24
11a	732 ± 22			
11b	441 ± 73			
12a	219 ± 56			
12b	12 ± 3	9.1 ± 2.0	553 ± 89	48
13a	1678 ± 25			
13b	208 ± 18			
14a	167 ± 35			
14b	151 ± 8			
15a	67 ± 9	21 ± 6	595 ± 9	9
15b	5.1 ± 1.3	5.2 ± 1.7	101 ± 10	20
16a	280 ± 23			
16b	46 ± 5	37 ± 6	998 ± 137	22
20a	1612 ± 65			
20b	327 ± 65			
22a	2255 ± 192			
22b	684 ± 37			
23a	359 ± 37			
23b	78 ± 5	39 ± 8	310 ± 68	5

[a] All compounds were tested as the oxalate salt.
[b] All values are means ± SEM of three experiments each performed in triplicate.
[c] Value reproduced from Ref. 22.

As summarized in Table 1, the 3α-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives **14**, **15**, and **16** were found to be the most potent compounds of the class at dopamine transporters. The 3α-di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane **15b** (K_i = 5 nM) was the most potent compound of the series and was equipotent with the tropane-GBR hybrid analogues **2b** and **3b** that have been reported previously.[16,23] The corresponding 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]oct-2-ene analogues **11**, **12**, and **13** were generally less potent than the 3α-analogues; however, 3-di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]oct-2-ene **12b** (K_i = 12 nM) exhibited only slightly diminished DAT affinity relative to **15b** and was equipotent with GBR 12909 (**1**). The 3β-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo[3.2.1]octane derivatives **22** and **23** were significantly less potent at DAT than the

unsaturated and 3α-isomers. Only the 3β-di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane **23b** (K_i = 78 nM) exhibited modest affinity for the dopamine transporter (e.g., DAT binding affinity **15b** > **12b** > **23b**). The trend in DAT affinity for the unsaturated and 3α isomers was expected, given that **2b** was slightly more potent than the 3α analogue **3b**. However, the 3β-isomers **22** and **23** are the first reported ligands within the tropane-GBR 12909 hybrid series that possess β-stereochemistry at the 3-position. As such, the 16-fold reduction in potency of the 3β-isomer **23b** was not anticipated based on the stereochemical SAR of cocaine and the 3β-aryltropanes at the DAT. Within these two ligand classes, the 3β-isomers generally exhibited significantly higher affinities than the 3α-congeners.[2–4,27,28] Based upon these results, the tropane-GBR12909 hybrid stereoselectivity at dopamine transporters appears to be more similar to that observed for derivatives of benztropine than that observed for derivatives of cocaine.[29]

In general, *N*-(3-phenylpropyl) derivatives **12**, **15**, and **23** were more potent than *N*-methyl derivatives **13**, **16**, and **20**, which in turn were more potent than the *N*-benzyl derivatives **11**, **14**, and **22**. This trend is consistent with GBR analogues but differs for benztropines, which favor *N*-methyl substitution,[29] and piperidine-based GBR hybrids, which favor *N*-benzyl substitution.[3] Likewise ligands **12b**, **15b**, and **23b** with fluorine substitution on the benzhydryl ether moiety exhibited greater DAT affinity than the desfluoro-congeners **12a**, **15a**, and **23a**. This trend was consistent with the established SAR for the tropane-GBR 12909 hybrids. However, there was greater difference in DAT affinity between the diarylmethoxymethyl analogues (**12a**:**12b**, **15a**:**15b**, **16a**:**16b**, and **23a**:**23b**) than previously observed for the diarylmethoxyethylidinyl-tropanes (**2a**:**2b**) and 3α-diarylmethoxyethyltropane analogues (**3a**:**3b**). These results are also similar to those reported for the benztropines,[29] while a similar effect of fluorine substitution is not observed for the SAR of piperidine-based GBR analogues.[3,30]

Those compounds (**12b**, **15a**, **15b**, **16b**, and **23b**) that exhibited potent DAT affinities were evaluated for inhibition of dopamine uptake. The IC_{50} values determined for [^{3}H]dopamine uptake inhibition were generally of similar potency to the K_i values for inhibition of DAT binding of [^{3}H]WIN 35,428. This select group of compounds was also evaluated at serotonin transporters for inhibition of [^{3}H]citalopram binding. All of the compounds exhibited poor SERT binding affinity (K_i > 100 nM). The proximity of the benzhydryl ether to the tropane ring due to the shortened ether tether of **15b** did not affect the DAT binding affinity when compared to ethyl homologue **3b**. The analogues **3b** and **15** were found to be equipotent in both DAT and SERT binding affinity as well as for inhibition of dopamine uptake. Generally, all of the compounds tested in this group exhibited modest selectivity for the DAT over the SERT with a SERT/DAT K_i ratio similar to or less than that previously reported for GBR 12909. This is consistent with the SAR of the tropane-GBR hybrids that generally exhibit modest to high selectivity for DAT over SERT or norepinephrine transporters.[16–23] However, it has been reported recently that DAT selectivity among piperidine-based GBR hybrids can be attenuated by substitution of the *N*-phenylpropyl side chain.[22] The unsaturated analogue **12b** (SERT/DAT = 48) exhibited the greatest selectivity for the DAT of this series, while the 3β-isomer **23b** (SERT/DAT = 5) had the lowest selectivity. Although the potency of **23b** was low, the transporter selectivity of the 3β-isomer **23b** is noteworthy and suggests that the 3β-tropane-GBR 12909 hybrids may be viable targets for the development of dual or multi-site monoamine transporter inhibitors that could have therapeutic applications not only for drug abuse but also for the treatment of depression and anxiety.[31] The SERT/DAT selectivity observed for the analogue **12b** is in agreement with previous findings in the diarylmethoxyethylidenyltropane series (**2**) that indicated unsaturation at C3 reduced SERT affinity thus increasing DAT selectivity, albeit **12b** was significantly less selective than **2b** (SERT/DAT = 152). Based upon the SERT/DAT selectivities, it appears that for these tropane-GBR hybrids the exo-cyclic carbon–carbon double bond of **2b** is less well tolerated by the SERT than the endo-cyclic double bond of **12b**. This may be in part due to greater conformational freedom of the diaryl ether moiety imparted by the endo-cyclic double bond. As such the more flexible benzhydryl ether moiety can readily adopt a favorable conformation for binding at the SERT. For this reason, the 3α-congeners **3b** and **15b** exhibit greater affinity for the SERT than **12b** and are less selective for the DAT than **12b**.

In summary, we have prepared a series of diarylmethoxymethyltropane-GBR hybrid analogues with all three possible stereochemical orientations at C3. In general, the diarylmethoxymethyltropane-GBR hybrid analogues exhibited similar DAT structure–activity to that previously reported 3α-diarylmethoxyethyl- and 3-diarylmethoxyethylidinyltropane analogues.[16,23] These results support our hypothesis that the stereochemical and conformational effects imparted by unsaturation at C3 are important for selectivity at the dopamine transporter over the serotonin transporter. This is supported further by the SAR of 3α-isomers in this series, which despite the reduced tether length between the benzhydryl ether moiety and the tropane ring system exhibited similar DAT binding affinity to the 3-diarylmethoxyethylidinyltropanes but were less selective for DAT over SERT. This suggests that the dopamine transporter can tolerate some variability in proximity of the benzhydryl ether to the basic nitrogen atom of the tropane without loss in potency. Only compounds that possessed 3β-stereochemistry were less well accommodated by transporter constraints for potent molecular recognition. Overall this investigation suggests subtle changes in molecular topology can lead to dramatic changes in monoamine transporter selectivity. The degree to which these changes are manifested in cocaine behavioral paradigms is currently under investigation and will be reported in due course.

4. Experimental

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous solvents acetonitrile (J. T. Baker), diethyl ether (VWR), methanol (J. T. Baker), tetrahydrofuran (J. T. Baker), and toluene (VWR) were used under argon without further purification. Chromatography refers to column chromatography on silica gel (Silica Gel 60, 230–400 mesh). Petroleum ether (VWR) refers to pentanes with a boiling point range of 30–60 °C. Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 400 MHz spectrometer. Chemical shifts are reported as δ values with tetramethylsilane (TMS), employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

4.1. General method A. Preparation of oxalate salts

All of the final compounds were converted into the oxalate salts for biological testing as well as for storage and handling purposes. The base (50–100 mg) was dissolved in the minimum amount of Et_2O (1–2 mL) and a saturated ethereal solution (10 mL) of oxalic acid (1.1 equiv) was added. The oxalate salts crystallized and were washed with Et_2O (3× 2 mL) and purified by trituration with Et_2O. Fractional moles of water could not be prevented despite vigorous overnight drying (110 °C) under vacuum (0.01 mmHg). All compounds were homogeneous by TLC ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1).

4.2. General procedure B. Decarbonylation

To a stirred solution of the corresponding carbamate (2.7 mmol) and potassium hydroxide (3.9 g, 70 mmol) in ethylene glycol (40 mL) was added hydrazine hydrate (1.3 mL, 27 mmol). The mixture was heated to reflux for 3 h. The reaction mixture was poured into water and extracted with ether (3× 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography ($EtOAc/CH_3OH/NEt_3$, 80:8:4).

4.3. General procedure C. *N*-Arylalkylation of secondary amines

To a stirred solution of potassium carbonate (230 mg, 1.6 mmol) and secondary amine (0.60 mmol) in DMF (5 mL) was added either benzyl bromide or 1-bromo-3-phenylpropane (0.80 mmol) and the mixture was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). The organic solution was washed with water (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography (EtOAc).

4.4. General procedure D. Hydrogenation

A solution of the tropene (0.2 mmol), 10% Pd/C (14 mg) in CH_3OH (10 mL) was hydrogenated at 55 psi for 24 h on Parr hydrogenation apparatus. The solids were then removed by filtration through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by chromatography using a short column of silica gel (EtOAc).

4.4.1. 8-Ethoxycarbonyl-8-azabicyclo[3.2.1]oct-2ene-3-carboxylic acid methyl ester (7). To a solution of **6** (4.0 g, 22 mmol) and potassium carbonate (150 mg, 1.1 mmol) in toluene (40 mL) was added ethyl chloroformate (11 mL, 110 mmol). The solution was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in water (50 mL). The aqueous mixture was extracted with CH_2Cl_2(3× 50 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane, 2:8) to yield **7** as a colorless oil (5.0 g, 95%). ^{1}H NMR ($CDCl_3$) δ 7.16 (br s, 1H), 4.56–4.47 (m, 2H), 4.17–4.10 (m, 2H), 3.72 (s, 3H), 2.90–2.87 (br s, 2H), 2.21–2.12 (m, 1H), 2.06–1.93 (m, 2H), 1.67–1.58 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.1, 142.5, 95.5, 75.6, 75.5, 61.1, 52.8, 51.7, 51.6, 33.7, 28.0, 14.7. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.97; H, 7.15; N, 5.81.

4.4.2. 8-Ethoxycarbonyl-3-hydroxymethyl-8-azabicyclo[3.2.1]oct-2-ene (8). To a stirred solution of lithium aluminum hydride (711 mg, 18.7 mmol) in THF (60 mL) was added a solution of **7** (4.3 g, 18 mmol) in THF (10 mL) dropwise at 0 °C. After the reaction was complete (TLC), an aqueous solution of potassium hydroxide (5 mL, 10% wt/wt) was added to quench the reaction. The mixture was stirred for 30 min at room temperature. The white precipitate that formed was filtered and rinsed with ethyl acetate. The combined organic solutions were washed with phosphate buffer (pH 7, 1 M, 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography (EtOAc/hexane, 1:1) to yield **8** as a colorless oil (2.4 g, 60%). ^{1}H NMR ($CDCl_3$) δ 5.99 (d, J = 5.2 Hz, 1H), 4.43 (t, J = 5.6, 2H), 3.99–3.91 (m, 2H), 2.71 (d, J = 15.2 Hz, 1H), 2.22–2.14 (m, 2H), 2.06–1.81 (m, 5H), 1.67–1.49 (m, 2H), 1.28–1.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 154.3, 135.2, 126.8, 67.6, 60.8, 52.3, 34.8, 31.9, 29.6, 14.6, 14.1. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 61.34; H, 8.08; N, 6.47.

4.4.3. 8-Ethoxycarbonyl-3-diphenylmethoxymethyl-8-azabicyclo[3.2.1]oct-2-ene (9a). Benzhydryl chloride (970 mg, 4.8 mmol) was added to **8** (710 mg, 3.2 mmol) and heated under nitrogen at 160 °C neat for 2 h. The reaction mixture was allowed to cool to room temperature and the residue was purified by chromatography (EtOAc/hexane, 2:8) to yield **9a** as a colorless oil (1.5 g, 87%). ^{1}H NMR ($CDCl_3$) δ 7.26–7.19 (m, 8H), 7.18–7.16 (m, 2H), 5.14 (d, J = 2.4 Hz, 1H), 5.26 (s, 1H), 4.36 (br s, 2H), 4.06 (q, J = 6.4 Hz, 2H), 3.75 (s, 2H), 2.66 (br s, 1H), 2.11–2.08 (m, 1H), 1.92–1.81 (m, 4H), 1.17 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 154.3, 142.2, 142.1, 128.5, 128.4, 128.3, 127.7, 127.4, 127.0, 126.9, 126.5, 83.5, 82.0, 71.4, 61.0, 60.9, 52.4,

35.1, 29.0, 14.6. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 75.99; H, 7.28; N, 3.74.

4.4.4. 8-Ethoxycarbonyl-3-di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2. 1]oct-2-ene (9b). Bis(4-fluorophenyl)chloromethane (1.1 g, 4.8 mmol) was added to **8** (710 mg, 3.2 mmol) and heated under nitrogen at 160 °C neat for 2 h. The reaction mixture was allowed to cool to room temperature and the residue was purified by chromatography (EtOAc/hexane, 2:8) to yield **9b** as a colorless oil (1.6 g, 80%). ^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (m, 4H), 7.05–6.98 (m, 4H), 5.96 (d, J = 3.6 Hz, 1H), 5.27 (s, 1H), 4.42 (br s, 2H), 4.15–4.08 (m, 2H), 3.77 (s, 2H), 2.66 (br s, 1H), 2.18–2.10 (m, 1H), 2.05–1.83 (m, 2H), 1.68–1.58 (m, 2H), 1.28–1.21 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 163.5, 163.4, 161.0, 154.4, 137.7, 128.6, 128.5, 128.2, 128.1, 115.5, 115.4, 115.3, 115.2, 74.9, 71.5, 61.0, 60.9, 52.8, 51.9, 35.1, 29.4, 14.7. Anal. Calcd for $C_{24}H_{25}F_2NO_3{\cdot}H_2O$: C, 66.81; H, 6.31; N, 3.25. Found: C, 66.23; H, 5.70; N, 3.22.

4.4.5. 3-Diphenylmethoxymethyl-8-azabicyclo[3.2.1]oct-2ene (10a). *General procedure B.* The compound was obtained as a light yellow oil (580 mg, 71%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.23 (m, 8H), 7.20–7.16 (m, 2H), 5.90 (d, J = 5.2 Hz, 1H), 5.28 (s, 1H), 3.83–3.82 (m, 1H), 3.59 (s, 2H), 3.03 (br s, 2H), 2.48 (m, 1H), 1.98–1.77 (m, 4H), 1.52–1.49 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.2, 142.1, 131.5, 130.7, 128.3, 127.4, 127.3, 126.9, 126.8, 82.2, 71.8, 63.4, 53.1, 52.5, 36.8, 35.2, 29.8. Anal. Calcd for $C_{21}H_{23}NO{\cdot}1/2H_2O$: C, 80.22; H, 7.69; N, 4.45. Found: C, 80.01; H, 7.63; N, 4.49.

4.4.6. 3-Di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]oct-2-ene (10b). *General procedure B.* The compound was obtained as a light yellow oil (650 mg, 70%). ^{1}H NMR ($CDCl_3$) δ 7.29–7.25 (m, 4H), 7.03–6.98 (m, 4H), 5.45 (d, J = 5.2 Hz, 1H), 5.31 (s, 1H), 3.78–3.74 (m, 2H), 3.70 (s, 2H), 2.50 (br s, 2H), 1.96–1.83 (m, 4H), 1.60–1.26 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 161.0, 160.9, 138.0, 137.9, 137.8, 137.7, 131.4, 130.9, 128.7, 128.6, 128.5, 115.5, 115.2, 80.8, 71.8, 63.6, 53.2, 36.9, 30.0, 14.2. Anal. Calcd for $C_{21}H_{21}F_2NO$: C, 73.88; H, 6.20; N, 4.10. Found: C, 73.93; H, 6.50; N, 4.23.

4.4.7. 8-Benzyl-3-diphenylmethoxymethyl-8-azabicyclo[3.2.1]oct-2-ene (11a). *General procedure C.* The compound was obtained as a light yellow oil (208 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.39–7.23 (m, 15H), 5.78 (d, J = 5.2 Hz, 1H), 5.40 (s, 1H), 3.89 (ABq, J_{AB} = 12.4 Hz, $\Delta\nu$ = 18.0 Hz, 2H), 3.74–3.70 (m, 2H), 3.39 (br s, 1H), 3.33–3.30 (m, 1H), 2.56 (d, J = 17.2 Hz, 1H), 2.20–2.16 (m, 1H), 2.04–2.00 (m, 1H), 1.83 (t, J = 10.8 Hz, 1H), 1.72 (m, 1H), 1.59–1.52 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.4, 142.2, 141.1, 139.2, 128.9, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.4, 127.3, 127.0, 126.9, 82.0, 71.7, 56.3, 55.5, 33.8, 32.3, 29.7. Anal. Calcd for $C_{28}H_{29}NO{\cdot}C_2H_2O_4{\cdot}1/2H_2O$: C, 72.21; H, 6.52; N, 2.83. Found: C, 72.13; H, 6.47; N, 2.76.

4.4.8. 8-Benzyl-3-di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]oct-2-ene (11b). *General procedure C.* The compound was obtained as a light yellow oil (210 mg, 80%). ^{1}H NMR ($CDCl_3$) δ 7.36–7.22 (m, 10H), 7.04–6.99 (m, 3H), 5.77 (d, J = 5.6 Hz, 1H), 5.36 (s, 1H), 3.84 (ABq, J_{AB} = 12.4 Hz, $\Delta\nu$ = 18.2 Hz, 2H), 3.70–3.66 (m, 2H), 3.37–3.34 (m, 1H), 3.31–3.28 (m, 1H), 2.55–2.51 (m, 1H), 2.20–2.12 (m, 1H), 2.07–1.98 (m, 1H), 1.86–1.83 (m, 1H), 1.71–1.67(m, 1H), 1.56–1.49 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 163.3, 160.9, 139.5, 138.0, 137.8, 131.6, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 126.9, 126.8, 115.4, 115.3, 115.3, 115.2, 115.1, 80.6, 71.8, 56.4, 55.4, 53.1, 33.8, 32.5, 29.7. Anal. Calcd for $C_{28}H_{27}F_2NO{\cdot}C_2H_2O_4{\cdot}1/2H_2O$: C, 67.95; H, 5.69; N, 2.68. Found: C, 67.58; H, 5.65; N, 2.64.

4.4.9. 3-(Diphenylmethoxymethyl)-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]oct-2-ene (12a). *General procedure C.* The compound was obtained as a light yellow oil (220 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 7.33–7.14 (m, 15H), 5.76 (d, J = 4.8 Hz, 1H), 5.35 (s, 1H), 3.82 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu$ = 17.2 Hz, 2H), 3.40–3.39 (m, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 2.46–2.42 (m, 1H), 2.15–2.10 (m, 1H), 2.04–2.00 (m, 1H), 1.91–1.81 (m, 4H), 1.72–1.68 (m, 1H), 1.55–1.48 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.4, 142.2, 131.9, 128.3, 128.2, 127.4, 127.0, 126.9, 125.7, 82.0, 71.6, 56.8, 55.6, 48.4, 33.9, 33.7, 62.2, 30.3, 29.5. Anal. Calcd for $C_{30}H_{33}NO{\cdot}C_2H_2O_4$: C, 74.83; H, 6.87; N, 2.73. Found: C, 74.19; H, 6.82; N, 2.73.

4.4.10. 3-Di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]oct-2-ene (12b). *General procedure C.* The compound was obtained as a light yellow oil (223 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.18 (m, 4H), 7.16–7.14 (m, 5H), 7.03–6.98 (m, 4H), 5.75 (d, J = 4.8 Hz, 1H), 5.30 (s, 1H), 3.78 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu$ = 17.2 Hz, 2H), 3.41 (br s, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 15.2 Hz, 2H), 2.46–2.42 (m, 1H), 2.16–2.14 (m, 1H), 2.05–2.02 (m, 2H), 1.90–1.81 (m, 2H), 1.70–1.66 (m, 1H), 1.55–1.48 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 161.0, 155.2, 138.0, 131.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 125.8, 115.5, 115.4, 115.3, 115.2, 80.7, 75.6, 75.5, 71.6, 60.4, 56.9, 55.7, 48.5, 33.9, 33.6, 32.4, 30.2, 29.5, 14.2. Anal. Calcd for $C_{30}H_{31}F_2NO{\cdot}C_2H_2O_4$: C, 69.93; H, 6.05; N, 2.55. Found: C, 69.65; H, 6.08; N, 2.48.

4.4.11. 8-Methyl-3-diphenylmethoxymethyl-8-azabicyclo[3.2.1]oct-2-ene (13a). To a stirred solution of **10a** (150 mg, 0.5 mmol) and 37% aqueous formaldehyde (0.2 mL, 2.5 mmol) in acetonitrile (10 mL) under nitrogen was added sodium cyanoborohydride (49 mg, 0.7 mmol). The reaction mixture was stirred for 10 min, and then glacial acetic acid was added dropwise until the solution was neutral (pH 7). Stirring was then continued for an additional 45 min, then saturated sodium bicarbonate solution was added until the solution was of pH 9. The acetonitrile was evaporated and the resulting solution was extracted with $CHCl_3$ (3× 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography ($EtOAc/CH_3OH/Et_3N$, 40:2:1) to yield **13a** as a light yellow oil (127 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.19 (m, 10H), 5.72 (d, J = 8.0 Hz, 1H), 5.29 (s, 1H), 3.77

(ABq, J_{AB} = 8.0 Hz, $\Delta\nu$ = 16.0 Hz, 2H), 3.19 (m, 2H), 2.42 (d, J = 8.0 Hz, 1H), 2.29 (s, 3H), 2.14–1.95 (m, 2H), 1.79–1.77 (m, 1H), 1.62–1.60 (m, 1H), 1.51–1.48 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.4, 142.2, 131.4, 128.3, 127.7, 127.4, 127.3, 127.0, 126.9, 82.0, 71.7, 58.8, 57.6, 33.7, 29.7. Anal. Calcd for $C_{22}H_{25}NO\cdot C_2H_2O_4$: C, 70.40; H, 6.65; N, 3.42. Found: C, 69.54; H, 6.65; N, 3.47.

4.4.12. 3-Di(4-fluorophenyl)methoxymethyl-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (13b). To a stirred solution of **10b** (260 mg, 0.8 mmol) and 37% aqueous formaldehyde (0.3 mL, 3.8 mmol) in acetonitrile (10 mL) under nitrogen was added sodium cyanoborohydride (76 mg, 1.1 mmol). The reaction mixture was stirred for 10 min, and then glacial acetic acid was added dropwise until the solution was neutral (pH 7). Stirring was then continued for an additional 45 min, then saturated sodium bicarbonate solution was added until the solution was of pH 9. The acetonitrile was evaporated and the resulting solution was extracted with $CHCl_3$ (3× 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography ($EtOAc/CH_3OH/Et_3N$, 40:2:1) to yield **13b** as a light yellow oil (218 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.25 (m, 4H), 7.02–6.98 (m, 4H), 5.79 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 3.82 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu$ = 17.4 Hz, 2H), 3.28–3.26 (m, 2H), 2.58–2.56 (m, 1H), 2.35 (s, 3H), 2.23–2.17 (m, 2H), 1.97–1.90 (m, 1H), 1.80–1.76 (m, 1H), 1.58 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 160.9, 138.0, 137.8, 131.2, 128.7, 128.6, 128.5, 128.4, 128.0, 115.4, 115.2, 80.6, 71.6, 58.9, 57.6, 33.6, 29.5. Anal. Calcd for $C_{22}H_{23}F_2NO\cdot C_2H_2O_4$: C, 64.71; H, 5.66; N, 3.14. Found: C, 62.39; H, 5.67; N, 3.19.

4.4.13. 8-Benzyl-3α-(diphenylmethoxy)methyl-8-azabicyclo[3.2.1]octane (14a). *General procedure D.* The compound was obtained as a light yellow oil (81 mg, 91%). ^{1}H NMR ($CDCl_3$) δ 7.38–7.21 (m, 15H), 5.23 (s, 1H), 3.54 (s, 2H), 3.41 (d, J = 8.0 Hz, 2H), 3.12 (br s, 2H), 2.18 (t, J = 8.4 Hz, 1H), 2.11–2.05 (m, 2H), 1.97–1.94 (m, 2H), 1.47–1.36 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 142.6, 142.4, 140.0, 132.4, 130.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 127.4, 127.3, 127.0, 126.9, 126.6, 126.5, 83.4, 74.5, 58.9, 58.1, 56.3, 32.5, 29.7, 29.4, 29.3, 28.6, 27.0, 26.7. Anal. Calcd for $C_{28}H_{31}NO\cdot C_2H_2O_4\cdot 2H_2O$: C, 68.89; H, 7.50; N, 2.67. Found: C, 68.00; H, 6.80; N, 2.47.

4.4.14. 8-Benzyl-3α-di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]octane (14b). From **17** general procedure C. The compound was obtained as a colorless oil (226 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 7.40–7.38 (m, 2H), 7.33–7.24 (m, 7H), 7.03–6.98 (m, 4H), 5.28 (s, 1H), 3.55 (s, 2H), 3.38 (d, J = 7.2 Hz, 2H), 3.16 (br s, 2H), 2.20–2.13 (m, 3H), 2.00–1.98 (m, 2H), 1.45–1.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 163.4, 160.9, 138.1, 128.6, 128.5, 128.2, 115.4, 115.1, 82.1, 75.6, 74.3, 58.1, 56.1, 32.3, 28.4, 26.9. Anal. Calcd for $C_{28}H_{29}F_2NO\cdot C_2H_2O_4\cdot 3/2H_2O$: C, 65.68; H, 6.25; N, 2.55. Found: C, 65.67; H, 6.07; N, 2.55.

4.4.15. 3α-Diphenylmethoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (15a). *General procedure D.* The compound was obtained as a colorless oil (78 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (m, 15H), 5.32 (s, 1H), 3.40 (d, J = 8.0 Hz, 2H), 3.20 (br s, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.41 (br s, 2H), 2.08–2.14 (m, 3H), 1.86 (br s, 4H), 1.50–1.47 (m, 2H), 1.37 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 142.3, 142.0, 128.1, 128.0, 127.4, 127.9, 127.1, 126.7, 125.4, 83.1, 74.2, 60.0, 57.9, 50.9, 33.6, 31.4, 30.3, 28.2, 26.6, 20.7, 14.0. Anal. Calcd for $C_{30}H_{35}NO\cdot C_2H_2O_4$: C, 74.54; H, 7.23; N, 2.72. Found: C, 74.03; H, 7.28; N, 2.67.

4.4.16. 3α-Di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (15b). *General procedure D.* The compound was obtained as a colorless oil (83 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.24 (m, 6H), 7.18–7.17 (m, 3H), 7.01–6.97 (m, 4H), 5.27 (s, 1H), 3.59 (d, J = 8.0 Hz, 2H), 3.16 (d, J = 8.0 Hz, 2H), 2.91–2.85 (m, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 2.14–2.12 (m, 4H), 1.87–1.79 (m, 4H), 1.44–1.41 (m, 1H), 1.32 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 163.2, 160.7, 142.1, 138.0,137.9, 128.5, 128.4, 128.2, 128.1, 126.9, 125.5, 115.2, 115.0, 81.9, 74.3, 60.2, 58.0, 51.1, 36.3, 33.6, 31.5, 30.3, 28.3, 26.7, 20.9, 14.0. Anal. Calcd for $C_{30}H_{33}F_2NO\cdot C_2H_2O_4$: C, 69.68; H, 6.40; N, 2.54. Found: C, 69.20; H, 6.45; N, 2.57.

4.4.17. 8-Methyl-3α-diphenylmethoxymethyl-8-azabicyclo[3.2.1]octane (16a). *General procedure D.* The compound was obtained as a colorless oil (64 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.24 (m, 10H), 5.33 (s, 1H), 3.41 (d, J = 7.2 Hz, 2H), 3.15 (br s, 2H), 2.32 (s, 3H), 2.19–2.17 (m, 3H), 2.00–1.97 (m, 2H), 1.57–1.54 (m, 2H), 1.44–1.41 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 142.5, 128.2, 127.3, 127.0, 83.3, 74.3, 60.2, 40.0, 32.1, 28.0, 26.3. Anal. Calcd for $C_{22}H_{27}NO\cdot C_2H_2O_4$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.58; H, 7.07; N, 3.34.

4.4.18. 8-Methyl-3β-di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]octane (16b). *General procedure D.* The compound was obtained as a colorless oil (64 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.25 (m, 4H), 7.02–6.98 (m, 4H), 5.28 (s, 1H), 3.37 (d, J = 8.4 Hz, 2H), 3.20 (br s, 2H), 2.35 (s, 3H), 2.28–2.22 (m, 3H), 2.04–1.97 (m, 2H), 1.55–1.52 (m, 2H), 1.42 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 163.3, 160.9, 138.0, 137.9, 115.4, 115.2, 82.0, 73.8, 60.6, 40.0, 31.5, 27.6, 26.0. Anal. Calcd for $C_{22}H_{25}F_2NO\cdot C_2H_2O_4$: C, 64.42; H, 6.08; N, 3.13. Found: C, 63.86; H, 6.12; N, 3.07.

4.4.19. 3α-Di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]octane (17). *General procedure D.* The compound was obtained as a colorless oil (62 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 7.29–7.25 (m, 4H), 7.03–6.98 (m, 4H), 5.29 (S, 1H), 3.59 (br s, 1H), 3.47 (s, 1H), 3.39 (d, J = 8.0 Hz, 2H), 2.22–2.08 (m, 1H), 1.97–1.86 (m, 4H), 1.58–1.47 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 163.4, 160.9, 137.9, 128.6, 128.5, 115.4, 115.2, 82.1, 73.5, 53.5, 32.4, 29.6, 28.4. Anal. Calcd for $C_{21}H_{23}F_2NO$: C, 73.45; H, 6.75; N, 4.08. Found: C, 73.21; H, 6.56; N, 4.18.

4.4.20. 3β-Hydroxymethyl-8-methyl-8-azabicyclo[3.2.1]octane (19). To a mixture of powdered lithium aluminum hydride (1.9 g, 49 mmol) and solid **18** (2.1 g, 12 mmol) at −78 °C, THF (80 mL) was added dropwise. The mixture was stirred at −78 °C for 8 h then allowed to slowly warm to room temperature overnight. An aqueous solution of potassium hydroxide (10 mL, 10% wt/wt) was added to quench the reaction. The mixture was stirred for 30 min at room temperature. The white precipitate was filtered and rinsed with EtOAc. The combined organic solutions were dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield **19** as a colorless oil that was used in subsequent reactions without purification.

4.4.21. 8-Methyl-3β-diphenylmethoxymethyl-8-azabicyclo[3.2.1]octane (20a). Benzhydryl chloride (2.0 g, 9.9 mmol) was added to **19** (1.0 g, 6.4 mmol) and heated under nitrogen at 150 °C neat for 2 h. The reaction mixture was allowed to cool to room temperature and the residue was purified by chromatography (EtOAc/CH_3OH/NEt_3, 80:8:4) to yield **20a** as a colorless oil (1.2 g, 60%). ^{1}H NMR ($CDCl_3$) δ 7.33–7.22 (m, 10H), 5.28 (s, 1H), 3.25 (d, J = 6.8 Hz, 2H), 3.16 (br s, 2H), 2.26 (s, 3H), 2.02–1.99 (m, 4H), 1.62–1.57 (m, 4H), 1.57–1.54 (m, 2H), 1.49–1.45 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.5, 128.3, 127.3, 126.9, 83.7, 74.5, 61.0, 40.1, 34.9, 28.5, 26.1. Anal. Calcd for $C_{22}H_{27}NO\cdot C_2H_2O_4$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.97; H, 7.23; N, 3.52.

4.4.22. 3β-Di(4-fluorophenyl)methoxymethyl-8-methyl-8-azabicyclo[3.2.1]octane (20b). Chloro-bis(4-fluorophenyl)methane (2.3 g, 9.5 mmol) was added to **19** (1.0 g, 6.4 mmol) and heated under nitrogen at 150 °C neat for 2 h. The reaction mixture was allowed to cool to room temperature and the residue was purified by chromatography (EtOAc/CH_3OH/NEt_3, 80:8:4) to yield **20b** as a colorless oil (1.5 g, 67%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.25 (m, 4H), 7.02–6.98 (m, 4H), 5.25 (s, 1H), 3.26 (d, J = 6.8 Hz, 2H), 3.15 (br s, 2H), 2.26 (s, 3H), 2.02–1.99 (m, 4H), 1.59–1.56 (m, 4H), 1.43–1.39 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 163.2, 160.8, 138.0, 128.4, 128.3, 115.2, 115.0, 82.3, 74.5, 60.9, 40.3, 35.1, 28.5, 26.0. Anal. Calcd for $C_{22}H_{25}F_2NO\cdot HCl\cdot 1/2H_2O$: C, 65.70; H, 6.75; N, 3.48. Found: C, 65.44; H, 6.70; N, 3.38.

4.4.23. 3β-Diphenylmethoxymethyl-8-azabicyclo[3.2.1]octane (21a). *General procedure B.* The compound was obtained as a light yellow oil (630 mg, 77%). ^{1}H NMR ($CDCl_3$) δ 7.33–7.27 (m, 8H), 7.25–7.20 (m, 2H), 5.27 (s, 1H), 3.62 (s, 1H), 3.24 (d, J = 6.4 Hz, 2H), 3.08 (br s, 2H), 2.12–2.03 (m, 1H), 1.82–1.79 (m, 2H), 1.35–1.32 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 142.4, 128.2, 127.2, 126.8, 83.7, 74.5, 63.2, 54.2, 36.5, 29.5, 29.0. Anal. Calcd for $C_{21}H_{23}NO\cdot 1/2H_2O$: C, 79.71; H, 8.28; N, 4.43. Found: C, 79.90; H, 8.08; N, 4.49.

4.4.24. 3β-Di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]octane (21b). *General procedure B.* The compound was obtained as a light yellow oil (710 mg, 77%). ^{1}H NMR ($CDCl_3$) δ 7.29–7.25 (m, 4H), 7.03–6.98 (m, 4H), 5.29 (s, 1H), 3.59 (br s, 1H), 3.47 (s, 1H), 3.39 (d, J = 8.0 Hz, 2H), 2.22–2.08 (m, 1H), 1.97–1.86 (m, 4H), 1.58–1.47 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 163.1, 160.7, 138.0, 137.9, 128.3, 128.2, 115.1, 115.0, 82.1, 74.4, 63.0, 54.1, 36.4, 29.4, 29.0. Anal. Calcd for $C_{21}H_{23}F_2NO$: C, 73.45; H, 6.75; N, 4.08. Found: C, 73.21; H, 6.56; N, 4.18.

4.4.25. 8-Benzyl-3β-diphenylmethoxymethyl-8-azabicyclo[3.2.1]octane (22a). *General procedure D.* The compound was obtained as a colorless oil (60 mg, 76%). ^{1}H NMR ($CDCl_3$) δ 7.38–7.20 (m, 15H), 5.28 (s, 1H), 3.54 (s, 2H), 3.27 (d, J = 6.8 Hz, 2H), 3.20 (br s, 2H), 2.04–1.99 (m, 4H), 1.63–1.53 (m, 4H), 1.50–1.47 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142.5, 128.3, 128.1, 127.3, 126.9, 126.7, 83.7, 74.7, 58.8, 56.3, 34.9, 29.2, 26.6. Anal. Calcd for $C_{28}H_{31}NO\cdot C_2H_2O_4\cdot H_2O$: C, 71.26; H, 6.97; N, 2.77. Found: C, 70.77; H, 6.74; N, 2.76.

4.4.26. 8-Benzyl-3β-di(4-fluorophenyl)methoxymethyl-8-azabicyclo[3.2.1]octane (22b). *General procedure D.* The compound was obtained as a colorless oil (66 mg, 76%). ^{1}H NMR ($CDCl_3$) δ 7.37–7.34 (m, 3H), 7.31–7.22 (m, 7H), 7.01–6.97 (m, 3H), 5.24 (s, 1H), 3.53 (s, 2H), 3.28 (d, J = 6.4 Hz, 2H), 3.20 (br s, 2H), 2.05–1.99 (m, 4H), 11.62–1.51 (m, 4H), 1.46–1.25 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 163.3, 160.9, 138.2, 138.1, 128.6, 128.5, 128.4, 128.1, 126.9, 115.3, 115.1, 82.4, 74.7, 58.8, 56.4, 35.1, 29.2, 26.6. Anal. Calcd for $C_{28}H_{29}F_2NO\cdot C_2H_2O_4$: C, 68.82; H, 5.97; N, 2.68. Found: C, 68.27; H, 6.10; N, 2.57.

4.4.27. 3β-Diphenylmethoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (23a). *General procedure D.* The compound was obtained as a colorless oil (65 mg, 77%). ^{1}H NMR ($CDCl_3$) δ 7.32–7.16 (m, 15H), 5.28 (s, 1H), 3.33 (d, J = 8.0 Hz, 2H), 3.25 (d, J = 6.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.05–2.03 (m, 2H), 1.95–1.85 (m, 4H), 1.62–1.54 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 142.4, 141.8, 128.3, 128.2, 127.3, 126.8, 125.7, 83.7, 75.5, 74.2, 60.3, 58.9, 50.8, 33.6, 29.5, 28.8, 26.3. Anal. Calcd for $C_{30}H_{35}NO\cdot C_2H_2O_4$: C, 74.54; H, 7.23; N, 2.72. Found: C, 73.21; H, 7.14; N, 2.65.

4.4.28. 3β-Di(4-fluorophenyl)methoxymethyl-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (23b). *General procedure D.* The compound was obtained as a colorless oil (72 mg, 78%). ^{1}H NMR ($CDCl_3$) δ 7.28–7.23 (m, 6H), 7.18–7.14 (m, 3H), 7.01–6.97 (m, 4H), 5.23 (s, 1H), 3.24 (br s, 2H), 3.21 (d, J = 6.4 Hz, 2H), 2.63 (t, J = 11.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 1H), 2.03–1.96 (m, 2H), 1.91–1.89 (m, 2H), 1.84–1.77 (m, 2H), 1.56–1.52 (m, 4H), 1.43–1.37 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 163.3, 160.9, 142.2, 138.1, 138.0, 128.5, 128.4, 128.3, 128.2, 125.7, 115.3, 115.1, 82.4, 74.5, 58.9, 51.4, 34.4, 33.7, 30.1, 29.0, 26.4. Anal. Calcd for $C_{30}H_{33}F_2NO\cdot C_2H_2O_4$: C, 69.68; H, 6.40; N, 2.54. Found: C, 69.40; H, 6.32; N, 2.48.

4.5. [^{3}H]Citalopram binding assay

Brains from male Sprague–Dawley rats weighing 200–225 g (Taconic Labs) were removed, midbrain dissected and rapidly frozen. Membranes were prepared by

homogenizing tissues in 25 vol (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C) using a Brinkman Polytron (setting 6 for 20 s) and centrifuged at 20,000*g* for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged, and resuspended in buffer to a concentration of 7.5 mg/mL. Ligand binding experiments were conducted in assay tubes containing 4.0 mL buffer for 60 min at room temperature. Each tube contained 1.4 nM [^{3}H]citalopram (GE Healthcare) and 1.5 mg midbrain tissue (original wet weight). Nonspecific binding was determined using 1 μM citalopram. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.3% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments Gaithersburg, Maryland). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, California). Data were analyzed by using GraphPad Prism software (San Diego, California).

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