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Development of 3-Phenyltropane Analogs with High Affinity for the Dopamine and Serotonin Transporters and Low Affinity for the Norepinephrine Transporter

Chunyang Jin, **Hernán A. Navarro**, and **F. Ivy Carroll***
[†]Center for Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina 27709-2194

Abstract

Previous studies showed that the mixed monoamine transporter inhibitor (**6**, RTI-112) reduced cocaine self-administration at a high level of serotonin transporter (5-HTT) occupancy with no detectable dopamine transporter (DAT) occupancy. In this study, a series of 3β-(substituted phenyl) tropane-2β-carboxylic acid methyl esters **7a-g**, 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid esters **8a-j**, and 3β-(4-methoxyphenyl)-2β-[3-(4′-methylphenyl)isoxazol-5-yl]tropane (**9**) were synthesized and evaluated for their monoamine transporter binding affinities to identify potent and selective compounds for both the DAT and 5-HTT relative to the norepinephrine transporter (NET). A number of compounds showed high binding affinities for both the DAT and 5-HTT and low affinity for the NET. 3β-(4-Methoxyphenyl)tropane-2β-carboxylic acid 2-(3-iodo-4-aminophenyl)ethyl ester (**8i**) with an IC_{50} value of 2.5 nM for the DAT and K_i values of 3.5 nM and 2040 nM for the 5-HTT and NET, respectively, is the most potent and selective compound for the DAT and 5-HTT relative to the NET in this study.

Introduction

Studies in the low-to-mid 1980s established that cocaine (**1**) blocks the uptake of dopamine (DA),[1] serotonin (5-HT), and norepinephrine (NE).[1,2] However, the behavioral stimulant and reinforcing effects of cocaine associated with its abuse liability have been linked more closely to inhibition of dopamine uptake.[3–5] The results from these studies led to the so-called "dopamine hypothesis" which proposed that the reinforcing properties of cocaine were due to the inhibition of dopamine uptake resulting in a buildup of dopamine in the synaptic cleft, leading to significant potentiation of dopaminergic transmission.[4,6] Numerous cocaine-discrimination and self-administration studies in laboratory animals support this dopamine hypothesis.[7] Importantly, neuroimaging studies in humans showed a significant correlation between the level of dopamine transporter (DAT) occupancy in the brain and the magnitude of the subjective high reported following administration of cocaine[8] and methylphenidate (**2**).[9] Collectively, the results obtained in behavioral and neuroimaging studies provide compelling evidence that dopamine plays a major role in the neuropharmacology and addictive properties of cocaine. Based on the importance of the DAT in the addictive properties of cocaine,

*Corresponding author: Dr. F. Ivy Carroll, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709-2194, Telephone: 919 541-6679, Fax: 919 541-8868, fic@rti.org.

Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pub.acs.org.

[1]Abbreviations: DA, dopamine; 5-HT, serotonin; NE, norepinephrine; DAT, dopamine transporter; 5-HTT, serotonin transporter; NET, norepinephrine transporter; SAR, structure activity relationship; TFA, trifluoroacetic acid; NBS, *N*-bromosuccinimide; DMF, dimethylformamide; THF, tetrahydrofuran; APCI, atmospheric pressure chemical ionization; ESI, turbospray ionization; EI, electron impact.

compounds that target the DAT and share some, but not all of the pharmacological properties of cocaine, are of interest as indirect dopamine agonist pharmacotherapies to treat cocaine addiction and dependence.[10–13]

Over the last several years, the DAT selective 3β-(4-chlorophenyl)-2β-[3-(4′-methylphenyl) isoxazol-5-yl]tropane (**3**, RTI-336) has been developed as an indirect dopamine agonist (DAT inhibitor) as a potential pharmacotherapy for treating patients addicted to cocaine.[14–18] Pretreatment of rhesus monkeys with 3 produced a dose-dependent reduction in cocaine maintained responding in all subjects trained to self-administer cocaine under a multiple second-order schedule.[19] Co-administration of the dose of **3** that reduced cocaine-maintained behavior by 50% (ED_{50}) with the selective serotonin transporter (5-HTT) inhibitor fluoxetine (**4**) or citalopram (**5**) produced a more robust reduction in cocaine self-administration compared with **3** alone.

Other preclinical studies have also suggested that inhibition of the 5-HTT can modulate the behavioral effects of psychomotor stimulants. For example, the early studies that reported a positive correlation between compounds binding to the DAT and their reinforcing effects in animals reported a negative relationship between the potencies of several cocaine-like compounds in self-administration studies and their binding potencies to the 5-HTT.[6,20]

3β-(4-Chloro-3-methylphenyl)tropane-2β-carboxylic acid methyl ester (**6**, RTI-112) is a 3-phenyltropane analog that shows subnanomolar affinity for inhibition of both the DAT and 5-HTT.[21] In a study to characterize the effects of **6** in pretreatment in rhesus monkeys trained to self-administer cocaine under a second-order schedule of i.v. drug delivery, **6** possessed an ED_{50} of 0.03 mg/kg.[22] Even though **6** showed greater than 70% DAT occupancy at the highest dose tested, DAT occupancy was below the limits of detection at the ED_{50} for reduction of cocaine self-administration.[22] Compound **6**, which has about equal affinity for DAT and 5-HTT inhibition, showed 84% occupancy of the 5-HTT at the ED_{50} dose.[22] Importantly, **6** failed to maintain robust drug self-administration in any of the three rhesus monkeys studied.[22] In addition, **6** did not exhibit any reinforcement effects in squirrel monkeys.[23] Overall, these results suggest that mixed action inhibitors of DAT and 5-HTT warrant consideration as potential pharmacotherapies for treating cocaine abuse.

The present study was undertaken to characterize the SAR of 3β-phenyltropanes to develop novel compounds with high affinities for both the DAT and 5-HTT while having low affinity for the NET. In this paper, we describe the design, synthesis, and monoamine transporter binding properties of several new 3β-(substituted phenyl)tropane analogs **7a-g**, **8a-j**, and **9**. We report that 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid 2-(3-iodo-4-aminophenyl) ethyl ester (**8i**) has high-binding affinity at the DAT with an IC_{50} value of 2.5 nM and the 5-HTT with a K_i value of 3.5 nM, respectively, and good selectivity for the DAT and 5-HTT relative to the NET (K_i = 2040 nM).

Chemistry

All the compounds described in this study were prepared starting from natural (−)-cocaine, and therefore, they are optically active and possess the same absolute configuration as (−)-cocaine. The synthesis of 3β-(substituted phenyl)tropane-2β-carboxylic acid methyl esters **7a-g** starting from anhydroecgonine methyl ester (**10**) is outlined in Scheme 1. Conjugate addition of **10** with the appropriate Grignard reagent at −45 °C in ethyl ether followed by trifluroacetic acid (TFA) afforded **7a-c** in the range of 20–73% yield. Bromination of 3β-(4-methoxyphenyl) tropane-2β-carboxylic acid methyl ester (7**a**) with 1.1 equivalents of bromine in the presence of tin(IV) chloride gave the 3β-(3-bromo-4-methoxyphenyl)tropane **7d** in 86% yield. Treatment of **7a** with 2.2 equivalents of bromine provided a 67% yield of 3β-(3,5-dibromo-4-methoxyphenyl)tropane **7e**. Iodination of **7a** with iodine chloride in acetic acid yielded the

3β-(3-iodo-4-methoxyphenyl)tropane **7f** in 23% yield. The 3β-(3,5-diiodo-4-methoxyphenyl) analog **7g** was synthesized in 94% yield by treatment of **7a** with bis(pyridine)iodonium (I) tetrafluoroborate and TFA in dioxane.

Scheme 2 and Scheme 3 outline the synthesis of 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid esters **8a-j**. Hydrolysis of **7a** in aqueous dioxane gave the carboxylic acid **11** (Scheme 2). Treatment of **11** with oxalyl chloride afforded the corresponding acid chloride, which was converted to the esters **8a-d** in the range of 46–92% yield, by treatment with the appropriate alcohol. Selective reduction of the *p*-nitrophenethyl ester **8d** by hydrogenation with catalytic platinum oxide in methanol provided the amine **8e** in 97% yield (Scheme 3). Treatment of **8e** with acetyl chloride and triethylamine gave the amide **8f** in 93% yield. Bromination of amine **8e** with 1 equivalent of *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) provided a 64% yield of 3-bromo-4-amino analog **8g** as the only isolated product. The dibrominated product was not detected under this reaction condition. Alternately, treatment of **8e** with 2 equivalents of bromine in acetic acid gave the 3,5-dibromo-4-amino compound **8h** in 79% yield. Iodination of **8e** with 1.1 equivalents of iodine chloride in acetic acid yielded the 3-iodo-4-amino compound **8i** in 31% yield as well as the 3,5-diiodo-4-amino analog **8j** in 17% yield. The 3β-(4-methoxyphenyl)-2β-[3-(4′-methylphenyl)isoxazol-5-yl]tropane (**9**) was synthesized using the procedure, outlined in Scheme 4. Treatment of 4-methylacetophenone oxime with a solution of n-butyl lithium in hexanes, followed by the addition of **7a** yielded the ketoxime, which was cyclized with 3N hydrochloric acid in tetrahydrofuran (THF) to give **9** in 68% yield.[14] The ^{1}H NMR spectra of the target compounds are in agreement with the assigned structures. The chemical shift and coupling pattern of the C(**2**)-H and C(**3**)-H are consistent with previously reported compounds that possess the 2β,3β-stereochemistry.[24–26]

Biology

The binding affinities for the target compounds at the DAT, 5-HTT, and NET were determined via competitive binding assays using the previously reported procedures.[27,28] The final concentration of radioligands in the assays were 0.5 nM [^{3}H]-(−)-2β-carbomethoxy-3β-(4-fluorophenyl)tropane (**12**, [^{3}H]WIN 35,428)[27,28] for the DAT, 0.5 nM [^{3}H]-3-(2-methoxyphenoxy)-*N*-methyl-3-phenylpropan-1-amine ([^{3}H]nisoxetine) for the NET, and 0.2 nM [^{3}H]-(3*S*)-*trans*-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ([^{3}H] paroxetine) for the 5-HTT. The results of the binding studies, along with binding data of cocaine and **6**[29] for comparison are listed in Tables 1 and 2. Since the DAT has two binding sites, IC_{50} values are reported. Since the 5-HTT and NET have only one binding site, K_i values were calculated for inhibition of binding at these two transporters.

Results and Discussion

Despite extensive efforts directed toward the development of a pharmacotherapy for cocaine abuse, at present no clinically approved drugs are available. Since the DAT is the critical recognition site for cocaine and contributes to its abuse liability, DAT inhibitors represent a promising approach in drug development.[17] Cocaine also inhibits 5-HT uptake. Animal behaviour studies have demonstrated that selective 5-HT uptake inhibitors as well as dopamine uptake inhibitors can attenuate cocaine-induced stimulant and reinforce effects.[6] Thus, the synthesis and pharmacological study of compounds having high affinities for both the DAT and 5-HTT but with low affinity for the NET should further understanding of the mechanism of cocaine abuse and lead to new pharmacotherapies for treatment.

Studies directed toward the 3-phenyltropane class of DAT uptake inhibitors have provided valuable information about the pharmacophore for the DAT as well as the 5-HTT and NET.[18,30] SAR studies from our laboratory as well as others have shown that the binding affinity

for the monoamine transporters is highly dependent on the nature and position of the substituents on the 3β-phenyl ring.[18,30] In our original studies of 3β-phenyltropane analogs, we reported that 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid methyl ester (**7a**) possessed an IC_{50} value of 6.5 nM at the DAT.[24] Later, we found that **7a** also exhibited high affinity at the 5-HTT (K_i = 4.3 nM), while having much less affinity at the NET (K_i = 1110 nM). In the present study, we further explored the effect of adding additional substituents to the 3β-(4-methoxyphenyl) ring of **7a** (**7b–g**) or replacing the 2β-carbomethoxy of **7a** with other ester groups (**8a–j**) or an isoxazole heterocyclic group (**9**) on DAT, 5-HTT, and NET binding affinity. The ratio of K_i/IC_{50} values of NET/DAT and the ratio of K_i values of NET/5-HTT were calculated as a measure of the in vitro selectivity of the compounds for the DAT relative to the NET and the 5-HTT relative to the NET, respectively. The binding properties of **7a** and the 3β-phenyltropane analogs **7b–g** with modifications on the 3β-phenyl ring are presented in Table 1. Compound **7a** with an IC_{50} value of 6.5 nM at the DAT and a K_i value of 4.3 nM at the 5-HTT is highly potent at both transporters. Importantly, it has a K_i value of 1110 nM at the NET, and thus, is also highly selective for the DAT and 5-HTT relative to the NET. Replacement of the 4-methoxy group of **7a** with the larger ethoxy substitution afforded **7b** with slightly increased affinity at the 5-HTT (4.3 nM vs. 1.7 nM) but having 14-fold less affinity at the DAT (6.5 nM vs. 92 nM). The addition of one halogen atom (F, Br or I) *ortho* to the 4-methoxy group of **7a** had a little effect on the binding affinity at the 5-HTT with K_i values ranging from 3.1 to 4.8 nM (**7c**, **7d**, and **7e**). However, these compounds showed 4- to 7-fold increase of potency at the NET (160–270 nM vs. 1100 nM of **7a**) while having decreased affinity at the DAT (16–170 nM vs. 6.5 nM of **7a**). It is interesting to note that the addition of dibromo or diiodo substitutions *ortho* to the 4-methoxy group, which led to **7f** and **7g** resulted in approximately 4- to 5-fold loss of binding affinity at the NET. Thus, **7f** with NET/5-HTT ratio of 1413 is the most selective compound for the 5-HTT relative to the NET in the series **7a-g**. It appears that the 5-HTT is more tolerant to steric substituents on the 3β-(4-methoxyphenyl) ring than the NET. However, none of the 3β-(substituted phenyl)-2β-carboxylic methyl ester analogs **7b-g** are as potent and selective for both the DAT and 5-HTT as the parent compound **7a**.

A variety of functional groups and substituents are well tolerated at 2-position of 3β-phenyltropanes without loss of high affinity for the DAT, yet the nature of the substituents at 2-position has a profound effect on the monoamine transporter selectivity.[17,31–34] We previously reported that the methyl group of the 2β-carbomethoxy substituent of cocaine can be replaced with large groups (e.g. isopropyl, cyclopropyl, phenyl, phenylethyl, etc.) without significant loss in binding affinity at the DAT.[35] Later determination of these ligands on binding at the 5-HTT and NET revealed that the isopropyl and phenyl esters of cocaine analogs were reasonably selective for the DAT relative to the 5-HTT and NET.[21] Surprisingly, the phenylethyl ester analog showed increased potency at the 5-HTT compared to cocaine. Accordingly, modification of the 2β-cabomethoxy substituents of **7a** was examined and the binding results are presented in Table 2. Changing the methyl ester of **7a** to the larger isopropyl, cyclopropyl or cyclobutyl groups to give the esters **8a-c** resulted in slightly decreased affinity for the DAT (IC_{50} = 6.0–14 nM) while having much larger loss of affinities for both the 5-HTT and NET. Somewhat surprisingly, the 4-nitrophenethyl ester **8d** led to increase of affinities for both the 5-HTT and NET, with K_i values of 2.9 nM and 330 nM, respectively, but exhibited 6-fold decreased affinity for the DAT (IC_{50} = 42 nM) as compared to **7a**. In contrast, reduction of the 4-nitro group of **8d** to give the 4-amino analog **8e** regained the high-binding affinity for the DAT (IC_{50} = 7.0 nM) while having much less affinity for the NET (K_i = 2200 nM). Thus, **8e** is a potent and selective DAT/5-HTT ligand relative to the NET. Acylation of the 4-amino group to give the 4-acetylamino analog **8f** had little effect on the binding affinities for all three transporters. Further modifications on the 4-aminophenyl ring of **8e** by addition of bromo or iodo groups to the *ortho* position to give **8g** and **8i**, respectively, slightly increased the binding affinities for both the DAT and 5-HTT making **8i** more potent

and selective DAT/5-HTT ligand relative to the NET. The addition of dibromo or diiodo groups to the *ortho* position led to **8h** and **8j**, respectively, resulting in even better binding potency for the 5-HTT. Unfortunately, **8h** and **8j** had decreased affinity for the DAT with IC_{50} values of 15 nM and 100 nM, respectively. All the 4-aminophenethyl ester analogs **8e-j** possessed low-binding affinities at the NET, with K_i values ranging from 1460–2600 nM. Thus, 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid 2-(3,5-diiodo-4-aminophenyl)ethyl ester (**8j**) with K_i values of 1.0 nM at the 5-HTT and 2600 nM at the NET, respectively, is the most potent and selective compound for the 5-HTT relative to the NET in this study. The most potent and selective compound for both the DAT and 5-HTT is 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid 2-(3-iodo-4-aminophenyl)ethyl ester (**8i**) with IC_{50} value of 2.5 nM for the DAT and K_i values of 3.5 nM and 2040 nM for the 5-HTT and NET, respectively. Finally, the 3β-(4-methoxyphenyl)-2β-[3-(4′-methylphenyl)isoxazol-5-yl]tropane (**9**) is a selective compound for the DAT relative to the 5-HTT and NET, which is analogous to the previously reported 2β-isoxazoltropanes.[14]

In summary, a series of 3β-(substituted phenyl)tropane-2β-carboxylic acid methyl esters **7a-g**, 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid esters **8a-j**, and 2β-isoxazoltropane analog **9** were synthesized and evaluated for their monoamine transporter binding affinities. A number of compounds (**7a** and **8e-i**) exhibited high-binding affinities for both the DAT and 5-HTT and low affinity for the NET. In this study, the most potent and selective compound for both the DAT and 5-HTT relative to the NET is 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid 2-(3-iodo-4-aminophenyl)ethyl ester (**8i**). Since the mixed action inhibitors of DAT and 5-HTT may provide new pharmacotherapies for treating cocaine abuse, **7a**, **8f**, and **8i** are promising candidates for further investigation.

Experimental Section

Melting points were determined using a MEL-TEMP II capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a Bruker Avance DPX-300 MHz NMR spectrometer or a Varian Unity Inova 500 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were run on a Perkin-Elmer Sciex API 150 EX mass spectrometer equipped with APCI (atmospheric pressure chemical ionization) or ESI (turbospray) sources or on a Hewlett Packard 5989A instrument by electron impact. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Analytical thin-layer chromatography (TLC) TLC plates. TLC visualization was achieved with a UV lamp or was carried out using EMD silica gel 60 F_{254} in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using Isco prepacked silica gel columns or using EM Science silica gel 60Å (230–400 mesh). Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7a)

Magnesium (1.44 g, 60.0 mmol) was weighed into a 500 mL round bottom flask. A single crystal of iodine was added and the flask was flushed with nitrogen and flame dried. After cooling to room temperature, anhydrous Et_2O (4 mL) was added. A solution of 4-bromoanisole (6.26 mL, 50.0 mmol) in anhydrous Et_2O (40 mL) was prepared and 5 mL was added. After addition of a catalytic amount of 1,2-dibromoethane, the orange iodine color disappeared which indicated the initiation was successful. The rest of the 4-bromoanisole solution was added slowly over 30 min while the solution was kept refluxing. After addition, the reaction mixture was refluxed for 1 h. The fleshly prepared Grignard solution was then diluted with anhydrous

Et_2O (152 mL) and cooled to −45 °C. A solution of anhydroecgonine methyl ester (**10**) (3.68 g, 20.0 mmol) in 1:1 mixture of CH_2Cl_2–Et_2O (24 mL) was added slowly and the reaction mixture was stirred at −45 °C for another 2 h. After cooling to −78 °C, the reaction was quenched by slow addition of a solution of TFA (9.24 mL, 120 mmol) in Et_2O (24 mL). The mixture was warmed to room temperature and 6 N HCl (80 mL) was added. The aqueous layer was separated, made basic to pH 11 using NH_4OH and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 20% Et_2O in hexanes with the addition of 5% Et_3N afforded **7a** (4.10 g, 71%) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.25–7.12 (m, 2H), 6.87–6.77 (m, 2H), 3.76 (s, 3H), 3.60–3.46 (m, 4H), 3.40–3.33 (m, 1H), 2.96 (ddd, *J* = 12.6, 5.1, 5.1 Hz, 1H), 2.90–2.82 (m, 1H), 2.57 (ddd, *J* = 12.6, 12.6, 3.0 Hz, 1H), 2.28–2.00 (m, 5H), 1.78–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.4, 157.2, 134.4, 127.8, 112.8, 64.8, 61.9, 54.5, 52.4, 50.4, 41.5, 33.8, 32.6, 25.4, 24.7; MS (APCI) *m/z* 290.2 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 158–160 °C; $[\alpha]^{20}_D$ −123.1° (*c* 0.29, CH_3OH); Anal. ($C_{17}H_{24}ClNO_3 \cdot H_2O$) C, H, N.

3β-(4-Ethoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7b)

The procedure for **7a** was followed using 0.90 g (5.00 mmol) of **10** to give 1.10 g (73%) of **7b** as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.20–7.11 (m, 2H), 6.83–6.75 (m, 2H), 3.99 (q, *J* = 6.5 Hz, 2H), 3.56–3.50 (m, 1H), 3.49 (s, 3H), 3.40–3.33 (m, 1H), 2.95 (ddd, *J* = 12.5, 5.4, 5.4 Hz, 1H), 2.87–2.80 (m, 1H), 2.56 (ddd, *J* = 12.3, 12.5, 2.7 Hz, 1H), 2.30–2.00 (m, 5H), 1.78–1.54 (m, 3H), 1.38 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.0, 157.0, 134.7, 128.2, 113.9, 65.3, 63.1, 62.3, 52.9, 50.9, 41.9, 34.3, 33.1, 25.9, 25.1, 14.8; MS (EI) *m/z* 303 (M^+). The free base was converted to the hydrochloride salt: mp 164–165 °C; $[\alpha]^{20}_D$ −114.0° (*c* 0.34, CH_3OH); Anal. ($C_{18}H_{26}ClNO_3 \cdot 1.75H_2O$) C, H, N.

3β-(3-Fluoro-4-methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7c)

The procedure for **7a** was followed using 1.80 g (10.0 mmol) of **10** to give 0.68 g (20%) of **7c** as a solid: mp 74–76 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.04–6.81 (m, 3H), 3.85 (s, 3H), 3.60–3.48 (m, 4H), 3.42–3.33 (m, 1H), 2.93 (ddd, *J* = 12.6, 5.1, 5.1 Hz, 1H), 2.90–2.82 (m, 1H), 2.51 (ddd, *J* = 12.6, 12.6, 2.7 Hz, 1H), 2.30–2.02 (m, 5H), 1.79–1.55 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.2, 152.2 (d, *J* = 243 Hz), 145.7 (d, *J* = 11 Hz), 136.5 (d, *J* = 5.8 Hz), 122.9 (d, *J* = 3.5 Hz), 115.4 (d, *J* = 18 Hz), 113.2 (d, *J* = 2.0 Hz), 65.5, 62.4, 56.4, 52.9, 51.4, 42.1, 34.4, 33.2, 26.1, 25.4; MS (EI) *m/z* 308 (M^+). The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −103.3° (*c* 0.24, CH_3OH); Anal ($C_{17}H_{23}ClFNO_3 \cdot 1.25H_2O$) C, H, N.

3β-(3-Bromo-4-methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7d)

To a stirred solution of **7a** (289 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added $SnCl_4$ (0.23 mL, 2.00 mmol) followed by Br_2 (0.06 mL, 1.10 mmol). After stirring at 0 °C for 30 min, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 5% Et_2O in hexanes with the addition of 5% Et_3N afforded **7d** (315 mg, 86%) as a solid: mp 72–74 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.39 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.60–3.50 (m, 4H), 3.42–3.33 (m, 1H), 2.93 (ddd, *J* = 12.5, 5.1, 5.1 Hz, 1H), 2.88–2.81 (m, 1H), 2.51 (ddd, *J* = 12.6, 12.5, 1.8 Hz, 1H), 2.32–2.02 (m, 5H), 1.77–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.0, 154.0, 136.9, 132.4, 127.4, 111.6, 111.1, 65.4, 62.3, 56.2, 52.8, 51.2, 42.0, 34.3, 33.0, 25.9,

25.3; MS (ESI) *m/z* 368.5 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 145–148 °C; $[\alpha]^{20}_D$ −89.6° (*c* 0.27, CH_3OH); Anal. ($C_{17}H_{23}BrClNO_3 \cdot 0.75H_2O$) C, H, N.

3β-(3,5-Dibromo-4-methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7e)

To a stirred solution of **7a** (145 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added $SnCl_4$ (0.23 mL, 2.00 mmol) followed by Br_2 (0.056 mL, 1.10 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et_3N in hexanes afforded **7e** (150 mg, 67%) as a solid: mp 145–147 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.37 (s, 2H), 3.84 (s, 3H), 3.63–3.52 (m, 4H), 3.42–3.31 (m, 1H), 3.00–2.83 (m, 2H), 2.46 (ddd, *J* = 12.3, 12.3, 2.5 Hz, 1H), 2.30–2.02 (m, 5H), 1.78–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.9, 152.1, 142.3, 131.7, 117.7, 65.4, 62.2, 60.7, 52.5, 51.5, 42.0, 34.2, 33.2, 25.9, 25.4; MS (ESI) *m/z* 448.8 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 183–185 °C; $[\alpha]^{20}_D$ −78.6° (*c* 0.29, CH_3OH); Anal. ($C_{17}H_{22}Br_2ClNO_3$) C, H, N.

3β-(3-Iodo-4-methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7f)

To a stirred solution of **7a** (289 mg, 1.00 mmol) in 1:1 mixture of AcOH–CH_2Cl_2 (10 mL) at room temperature under nitrogen was added ICl (0.10 mL, 2.00 mmol). After stirring at room temperature for 24 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et_3N in hexanes afforded **7f** (95.0 mg, 23%) as an oil: ^1H NMR (300 MHz; $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 3H), 3.52–3.42 (m, 4H), 3.35–3.28 (m, 1H), 2.85 (ddd, *J* = 12.3, 5.4, 5.4 Hz, 1H), 3.38–3.26 (m, 1H), 2.46 (ddd, *J* = 12.6, 12.3, 2.4 Hz, 1H), 2.22–1.94 (m, 5H), 1.71–1.48 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.0, 155.2, 137.5, 136.3, 127.4, 109.5, 84.5, 64.3, 61.2, 55.3, 51.7, 50.2, 40.9, 33.2, 31.9, 24.9, 24.2; MS (APCI) *m/z* 416.5 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 151–153 °C; $[\alpha]^{20}_D$ −82.3° (*c* 0.22, CH_3OH); Anal. ($C_{17}H_{23}ClINO_3 \cdot H_2O$) C, H, N.

3β-(3,5-Diiodo-4-methoxyphenyl)tropane-2β-carboxylic Acid Methyl Ester (7g)

To a stirred solution of $I(Py)_2BF_4$ (558 mg, 1.50 mmol) in dioxane (5 mL) at room temperature under nitrogen was added CF_3SO_3H (0.18 mL, 2.00 mmol). After stirring for 10 min, a solution of **7a** (145 mg, 0.50 mmol) in dioxane (1 mL) was added and the stirring was continued for another 3 h. The mixture was diluted with EtOAc (50 mL), washed with NH_4OH (10 mL), brine (3 × 10 mL) and dried (Na_2SO_4). The solvent was concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et_3N in hexanes afforded **7g** (255 mg, 94%) as a solid: mp 181–183 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.62 (s, 2H), 3.81 (s, 3H), 3.62–3.52 (m, 4H), 3.39–3.30 (m, 1H), 2.93–2.79 (m, 2H), 2.44 (ddd, *J* = 12.0, 12.0, 2.7 Hz, 1H), 2.30–2.02 (m, 5H), 1.76–1.48 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.9, 156.9, 143.4, 139.0, 90.1, 65.4, 62.2, 60.8, 52.6, 51.5, 42.0, 34.3, 32.8, 25.9, 25.4. MS (ESI) *m/z* 542.2 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 167–169 °C; $[\alpha]^{20}_D$ −62.1° (*c* 0.24, CH_3OH); Anal. ($C_{17}H_{22}ClI_2NO_3 \cdot 0.5H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid (11)

A mixture of **7a** (1.90 g, 6.57 mmol) in 50% dioxane–H_2O was refluxed for 3 d. The solvent was removed under reduced pressure. Recrystallization of the crude product from acetone-hexanes afforded **11** (1.65 g, 92%) as a solid: mp 132–134 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.22–7.12 (m, 2H), 7.90–7.80 (m, 2H), 3.76 (s, 3H), 3.61–3.46 (m, 2H), 3.21–3.08 (m, 1H),

2.70–2.51 (m, 2H), 2.48 (s, 3H), 2.38–2.21 (m, 2H), 2.03–1.90 (m, 2H), 1.82–1.70 (m, 1H), MS (ESI) *m/z* 306.5 $(M + 1)^+$.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid Isopropyl Ester (8a)

To a stirred solution of **11** (138 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added a 2 M solution of oxalyl chloride in CH_2Cl_2 (0.5 mL, 1.00 mmol). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure followed by vacuum drying to remove the residual oxalyl chloride. The resultant acid chloride was dissolved in anhydrous CH_2Cl_2 (5 mL) at room temperature under nitrogen and isopropanol (0.12 mL, 1.50 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and quenched by addition of $NaHCO_3$. The CH_2Cl_2 phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 5% Et_2O in hexanes with the addition of 5% Et_3N afforded **8a** (145 mg, 92%) as a solid: mp 71–72 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.24–7.15 (m, 2H), 6.88–6.78 (m, 2H), 4.97–4.80 (m, 1H), 3.77 (s, 3H), 3.60–3.50 (m, 1H), 3.41–3.33 (m, 1H), 2.94 (ddd, *J* = 12.3, 5.1, 5.1 Hz, 1H), 2.86–2.78 (m, 1H), 2.57 (ddd, *J* = 12.3, 12.3, 2.1 Hz, 1H), 2.28–2.02 (m, 5H), 1.80–1.54 (m, 3H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.2, 157.7, 135.3, 128.4, 113.4, 66.5, 65.4, 62.4, 55.2, 52.9, 42.0, 34.3, 33.1, 26.0, 25.3, 21.8, 21.7; MS (APCI) *m/z* 318.1 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 226–227 °C; $[\alpha]^{20}_D$ −93.7° (*c* 0.41, CH_3OH); Anal. ($C_{19}H_{28}ClNO_3$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid Cyclopropyl Ester (8b)

The procedure for **8a** was followed using 275 mg (1.00 mmol) of **11** and 0.20 mL (3.00 mmol) of cyclopropanol to give 145 mg (46%) of **8b** as a solid: mp 101–102 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.24–7.13 (m, 2H), 6.89–6.78 (m, 2H), 4.01–3.92 (m, 1H), 3.77 (s, 3H), 3.54–3.45 (m, 1H), 3.42–3.32 (m, 1H), 2.94 (ddd, *J* = 12.8, 5.7, 5.7 Hz, 1H), 2.86–2.78 (m, 1H), 2.54 (ddd, *J* = 12.8, 12.6, 2.7 Hz, 1H), 2.30–2.02 (m, 5H), 1.80–1.54 (m, 3H), 0.67–0.42 (m, 3H), 0.41–0.28 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 172.9, 157.8, 135.1, 128.3, 113.5, 65.4, 62.5, 55.3, 52.8, 48.2, 42.1, 34.3, 33.0, 26.0, 25.3, 5.5, 4.9; MS (ESI) *m/z* 316.4 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 190–192 °C; $[\alpha]^{20}_D$ −60.9° (*c* 0.32, CH_3OH); Anal. ($C_{19}H_{26}ClNO_3 \cdot 1.25H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid Cyclobutyl Ester (8c)

The procedure for **8a** was followed using 275 mg (1.00 mmol) of **11** and 0.24 mL (3.00 mmol) of cyclobutanol to give 270 mg (82%) of **8c** as a solid: mp 90–91 °C; ^1H NMR (300 MHz; $CDCl_3$) δ 7.24–7.14 (m, 2H), 6.88–6.78 (m, 2H), 4.90–4.78 (m, 1H), 3.77 (s, 3H), 3.62–3.52 (m, 1H), 3.42–3.32 (m, 1H), 2.94 (ddd, *J* = 12.6, 5.1, 5.1 Hz, 1H), 2.86–2.77 (m, 1H), 2.56 (ddd, *J* = 12.6, 12.6, 2.4 Hz, 1H), 2.35–2.01 (m, 7H), 1.98–1.42 (m, 7H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.1, 157.7, 135.2, 128.4, 113.4, 68.2, 65.4, 62.4, 55.3, 52.8, 42.1, 34.3, 33.1, 30.7, 29.8, 26.0, 25.3, 13.7; MS (ESI) *m/z* 330.1 $(M + 1)^+$. The free base was converted to the hydrochloride salt: mp 245–246 °C; $[\alpha]^{20}_D$ −75.9° (*c* 0.29, CH_3OH); Anal. ($C_{20}H_{28}ClNO_3$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(4-Nitrophenyl)ethyl Ester (8d)

To a stirred solution of **11** (1.00 g, 3.64 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under nitrogen was added a 2 M solution of oxalyl chloride in CH_2Cl_2 (3.64 mL, 7.28 mmol). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure followed by vacuum drying to remove the residual oxalyl chloride. The resultant acid chloride was dissolved in anhydrous CH_2Cl_2 (20 mL) at room temperature under nitrogen, and 4-

nitrophenylethyl alcohol (1.22 g, 7.28 mmol) and Et_3N (2.05 mL, 14.6 mmol) were then added. The reaction mixture was stirred at room temperature for 16 h, poured into H_2O and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was partitioned between 6 N HCl (20 mL) and Et_2O (20 mL). The aqueous phase was separated, washed with ether (3 × 20 mL), made basic using NH_4OH and extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the crude product from CH_3OH afforded **8d** (1.30 g, 84%) as a solid: mp 122–124 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.28–4.10 (m, 2H), 3.76 (s, 3H), 3.45–3.30 (m, 2H), 3.01–2.75 (m, 4H), 2.51 (ddd, *J* = 12.6, 12.6, 2.7 Hz, 1H), 2.23–2.00 (m, 5H), 1.78–1.52 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.6, 157.8, 146.7, 146.2, 134.9, 129.7, 128.3, 123.6, 113.4, 65.3, 63.0, 62.4, 55.2, 52.9, 42.0, 34.8, 34.3, 33.1, 26.0, 25.2; MS (APCI) *m/z* 425.5 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −40.0° (*c* 0.27, CH_3OH); Anal. ($C_{24}H_{29}ClN_2O_5 \cdot 0.75H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(4-Aminophenyl)ethyl Ester (8e)

A mixture of **8d** (150 mg, 0.35 mmol) and PtO_2 (15.0 mg) in MeOH was hydrogenated at 1 atmospheric pressure for 3 h. Afterwards, the mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 2% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8e** (135 mg, 97%) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 4.21–4.10 (m, 1H), 4.04–3.91 (m, 1H), 3.75 (s, 3H), 3.52 (br s, 2H), 3.50–3.41 (m, 1H), 3.39–3.30 (m, 1H), 2.93 (ddd, *J* = 12.6, 5.7, 5.7 Hz, 1H), 2.88–2.80 (m, 1H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.56 (ddd, *J* = 12.8, 12.6, 2.7 Hz, 1H), 2.26–1.99 (m, 5H), 1.78–1.52 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.8, 157.8, 144.9, 135.2, 129.8, 128.5, 128.1, 115.3, 113.5, 65.4, 64.6, 62.5, 55.3, 53.0, 42.1, 34.4, 34.3, 33.2, 26.1, 25.4; MS (APCI) *m/z* 395.6 $(M + 1)^+$. The free base was converted to the dihydrochloride salt: $[\alpha]^{20}_D$ −58.3° (*c* 0.24, CH_3OH); Anal. ($C_{24}H_{32}Cl_2N_2O_3 \cdot H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(4-Acetylaminophenyl)ethyl Ester (8f)

To a stirred solution of **8e** (65.0 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under nitrogen was added Et_3N (0.07 mL, 0.48 mmol) followed by acetyl chloride (0.02 mL, 0.32 mmol). After stirring at 0 °C for 1 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 2% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8f** (65.0 mg, 93%) as an oil: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.24–4.11 (m, 1H), 4.10–3.98 (m, 1H), 3.76 (s, 3H), 3.50–3.40 (m, 1H), 3.39–3.31 (m, 1H), 2.94 (ddd, *J* = 12.3, 5.1, 5.1 Hz, 1H), 2.86–2.79 (m, 1H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.54 (ddd, *J* = 12.5, 12.3, 2.1 Hz, 1H), 2.22–2.00 (m, 8H), 1.75–1.56 (m, 4H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 171.8, 168.4, 157.9, 136.4, 135.2, 134.4, 129.5, 128.6, 120.1, 113.6, 65.5, 64.2, 62.5, 55.4, 53.1, 42.1, 34.6, 34.4, 33.3, 26.1, 25.4, 24.8; MS (ESI) *m/z* 437.7 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −62.7° (*c* 0.26, CH_3OH); Anal. ($C_{26}H_{33}ClN_2O_4 \cdot 1.5H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(3-Bromo-4-aminophenyl)ethyl Ester (8g)

To a stirred solution of **8e** (150 mg, 0.38 mmol) in DMF (2.5 mL) at room temperature under nitrogen was added NBS (67.6 mg, 0.38 mmol). After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with EtOAc (3 × 30 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 3% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8g** (115 mg, 64%) as an oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.21 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.14–4.08 (m, 1H), 4.02–3.96 (m, 3H), 3.76 (s, 3H), 3.48–3.44 (m, 1H), 3.36–3.32 (m, 1H), 2.93 (ddd, *J* = 12.6, 5.5, 5.5 Hz, 1H), 2.84–2.80 (m, 1H), 2.63 (dt, *J* = 2.5, 7.0 Hz, 2H), 2.54 (ddd, *J* = 12.8, 12.6, 3.0 Hz, 1H), 2.24–2.02 (m, 5H), 1.74–1.56 (m, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 171.5, 157.5, 142.3, 134.9, 132.7, 129.3, 128.7, 128.2, 115.6, 113.3, 109.1, 65.2, 64.1, 62.2, 55.1, 52.7, 41.8, 34.1, 33.6, 32.9, 25.8, 25.1; MS (APCI) *m/z* 475.8 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −53.3° (*c* 0.26, CH_3OH); Anal. ($C_{24}H_{30}BrClN_2O_3 \cdot 1.25H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(3,5-Dibromo-4-aminophenyl)ethyl Ester (8h)

To a stirred solution of **8e** (150 mg, 0.38 mmol) in 1:1 mixture of AcOH–CH_2Cl_2 (10 mL) at room temperature under nitrogen was added Br_2 (0.039 mL, 0.76 mmol). After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 10% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8h** (165 mg, 79%) as an oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.18 (s, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.44 (s, 2H), 4.10–3.93 (m, 2H), 3.76 (s, 3H), 3.48–3.44 (m, 1H), 3.38–3.32 (m, 1H), 2.94 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H), 2.86–2.82 (m, 1H), 2.64–2.58 (m, 2H), 2.52 (ddd, *J* = 11.0, 11.5, 3.0 Hz, 1H), 2.22–2.02 (m, 5H), 1.74–1.56 (m, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 171.5, 157.5, 140.3, 134.8, 132.0, 129.7, 128.2, 113.3, 108.5, 65.2, 63.8, 62.2, 55.1, 52.8, 41.8, 34.1, 33.4, 32.9, 25.9, 25.1; MS (APCI) *m/z* 553.5 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −37.4° (*c* 0.27, CH_3OH); Anal. ($C_{24}H_{29}Br_2ClN_2O_3 \cdot H_2O$) C, H, N.

3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(3-Iodo-4-aminophenyl)ethyl Ester (8i) and 3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid 2-(3,5-Diiodo-4-aminophenyl)ethyl Ester (8j)

To a stirred solution of **8e** (158 mg, 0.40 mmol) in 1:1 mixture of AcOH–CH_2Cl_2 (10 mL) at room temperature under nitrogen was added ICl (0.02 mL, 0.44 mmol). After stirring at room temperature for 1 h, the reaction mixture was poured into a mixture of $NaHCO_3$–ice and extracted with EtOAc (3 × 30 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 5% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8i** (65.0 mg, 31%) and **8j** (45.0 mg, 17%) as oil.

8i—^{1}H NMR (300 MHz; $CDCl_3$) δ 7.45 (d, *J* = 1.5 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 2H), 6.90 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 4.17–4.06 (m, 1H), 4.05–3.92 (m, 3H), 3.77 (s, 3H), 3.50–3.43 (m, 1H), 3.40–3.32 (m, 1H), 2.92 (ddd, *J* = 12.6, 5.5, 5.5 Hz, 1H), 2.86–2.80 (m, 1H), 2.66–2.46 (m, 3H), 2.30–2.00 (m, 5H), 1.78–1.51 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.8, 157.8, 145.4, 139.3, 135.2, 130.1, 130.0, 128.5,

114.8, 113.6, 84.3, 65.5, 64.3, 62.5, 55.4, 53.0, 42.1, 34.4, 33.7, 33.2, 26.1, 25.4; MS (ESI) *m/z* 521.7 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −53.1° (*c* 0.26, CH_3OH); Anal. ($C_{24}H_{30}ClIN_2O_3 \cdot 1.5H_2O$) C, H, N.

8j—^{1}H NMR (300 MHz; $CDCl_3$) δ 7.44 (s, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 4.50 (s, 2H), 4.10–3.92 (m, 2H), 3.76 (s, 3H), 3.50–3.41 (m, 1H), 3.40–3.31 (m, 1H), 2.93 (ddd, *J* = 12.8, 5.0, 5.0 Hz, 1H), 2.88–2.80 (m, 1H), 2.65–2.45 (m, 3H), 2.28–2.00 (m, 5H), 1.79–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 171.8, 157.8, 144.8, 139.9, 135.1, 131.6, 128.4, 113.6, 81.5, 65.5, 64.1, 62.6, 55.4, 53.1, 42.1, 34.4, 33.2, 33.1, 26.1, 25.4; MS (ESI) *m/z* 647.3 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −34.2° (*c* 0.26, CH_3OH); Anal. ($C_{24}H_{29}ClI_2N_2O_3 \cdot H_2O$) C, H, N.

3β-(4-Methoxyphenyl)-2β-[3-(4′-methylphenyl)isoxazol-5-yl]tropane (9)

To a stirred solution of 4-methylacetophenone oxime (0.45 g, 3.00 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen was added BuLi (1.6 M, 3.75 mL, 6.00 mmol). After stirring at room temperature for 1 h, a solution of **7a** (0.29 g, 1.00 mmol) in anhydrous THF (2 mL) was then added and the stirring was continued for another 16 h. Afterwards, the reaction was quenched by addition of 20% NH_4Cl aqueous solution (2 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was partitioned between Et_2O (20 mL) and 2 N HCl (20 mL). The aqueous phase was separated, made basic using $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were then washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was dissolved in 1:1 mixture of 3 N HCl–THF (20 mL) and refluxed for 5 h. After cooling to room temperature, the mixture was made basic using $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 10% Et_2O in hexanes with the addition of 5% Et_3N afforded **9** (0.27 g, 68%) as a solid: mp 154–156 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 3.71 (s, 3H), 3.40–3.17 (m, 4H), 2.38 (s, 3H), 3.32–2.06 (m, 6H), 1.88–1.55 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 3 δ 173.9, 161.6, 158.2, 139.5, 133.8, 129.5, 128.4, 127.2, 126.8, 113.7, 101.5, 65.6, 61.9, 55.1, 46.6, 42.1, 35.3, 35.2, 26.5, 25.2, 21.5; MS (ESI) *m/z* 389.8 $(M + 1)^+$. The free base was converted to the hydrochloride salt: $[\alpha]^{20}_D$ −107.0° (*c* 0.32, CH_3OH); Anal. ($C_{25}H_{29}ClN_2O_2 \cdot 0.25H_2O$) C, H, N.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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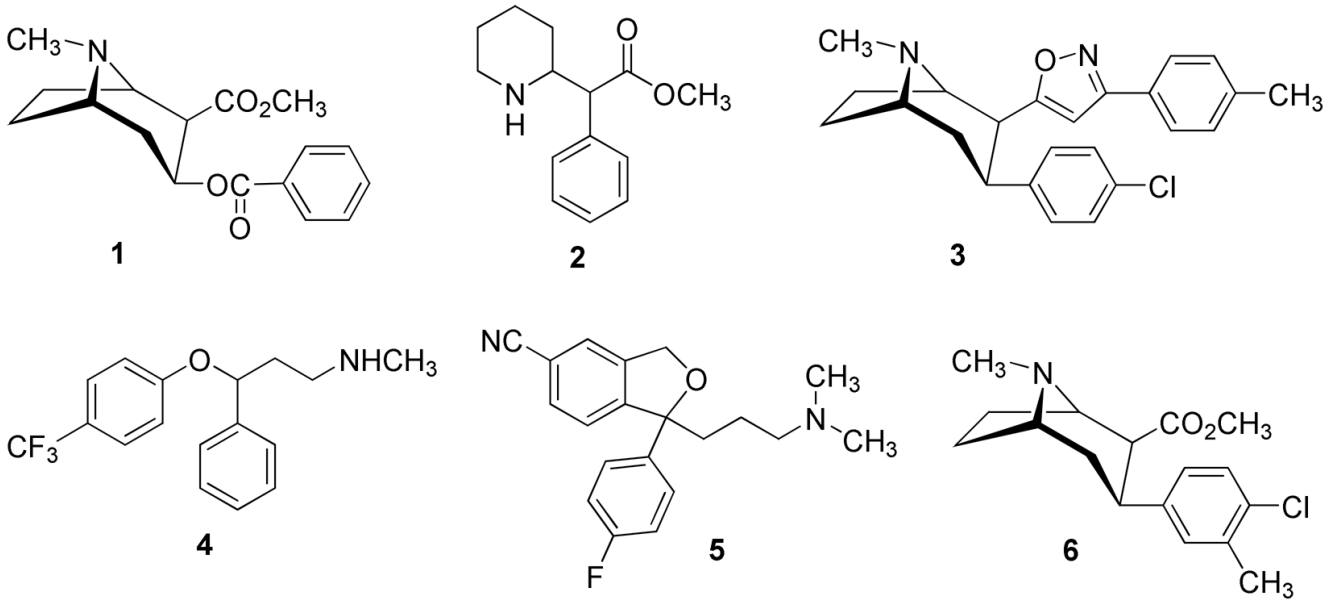
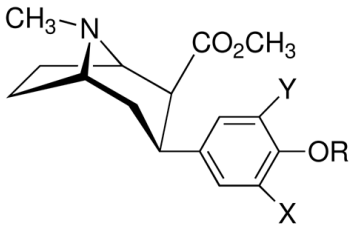
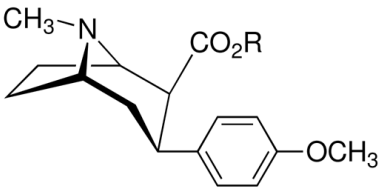


Figure 1.
Structures of ligands



7a, R = CH_3, X = Y = H
7b, R = C_2H_5, X = Y = H
7c, R = CH_3, X = F, Y = H
7d, R = CH_3, X = Br, Y = H
7e, R = CH_3, X = Y = Br
7f, R = CH_3, X = I, Y = H
7g, R = CH_3, X = Y = I



8a, R = $(CH_3)_2CH$
8b, R = cyclopropyl
8c, R = cyclobutyl
8d, R = (4-nitro)$C_6H_4(CH_2)_2$
8e, R = (4-amino)$C_6H_4(CH_2)_2$
8f, R = (4-acetylamino)$C_6H_4(CH_2)_2$
8g, R = (4-amino-3-bromo)$C_6H_4(CH_2)_2$
8h, R = (4-amino-3,5-dibromo)$C_6H_4(CH_2)_2$
8i, R = (4-amino-3-iodo)$C_6H_4(CH_2)_2$
8j, R = (4-amino-3,5-diiodo)$C_6H_4(CH_2)_2$

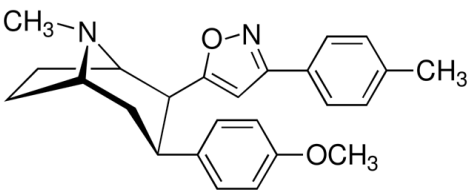


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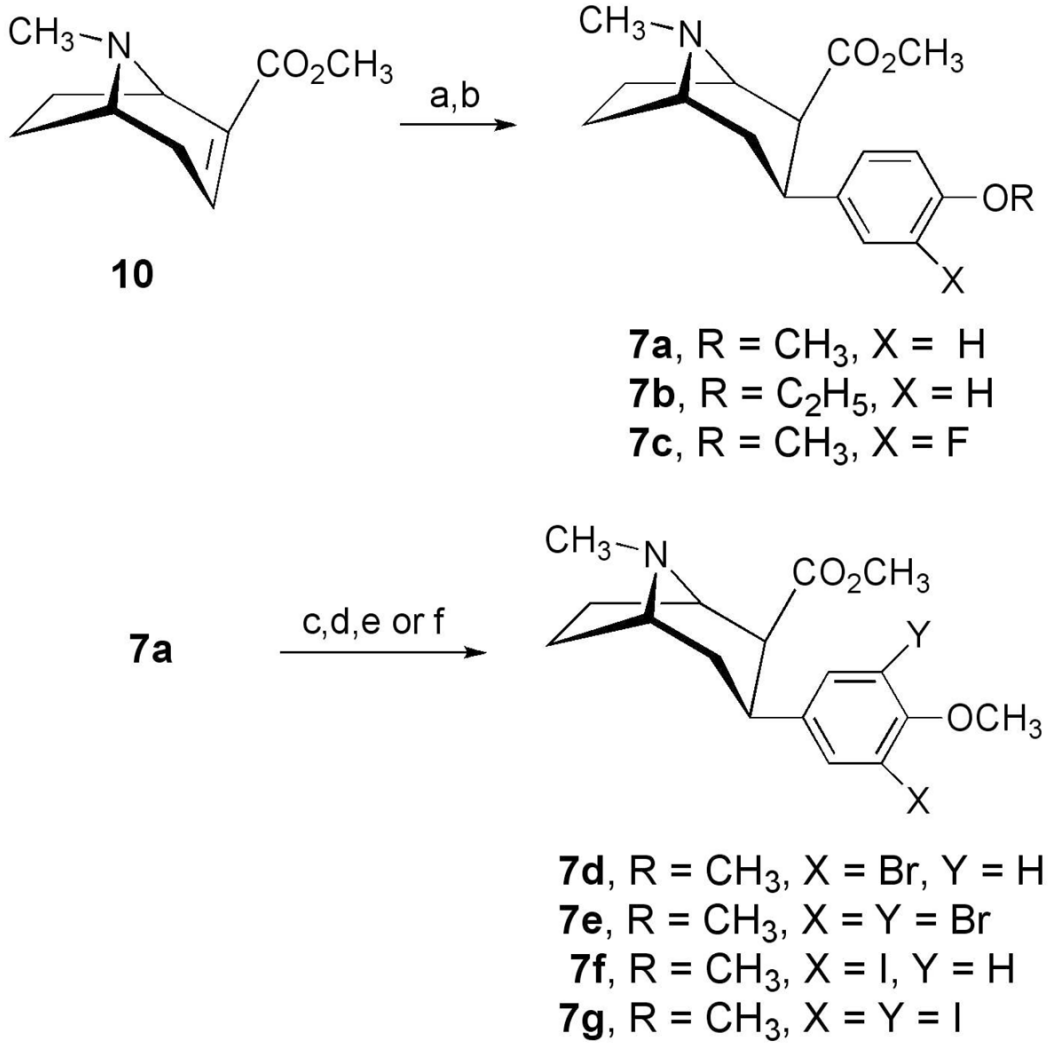
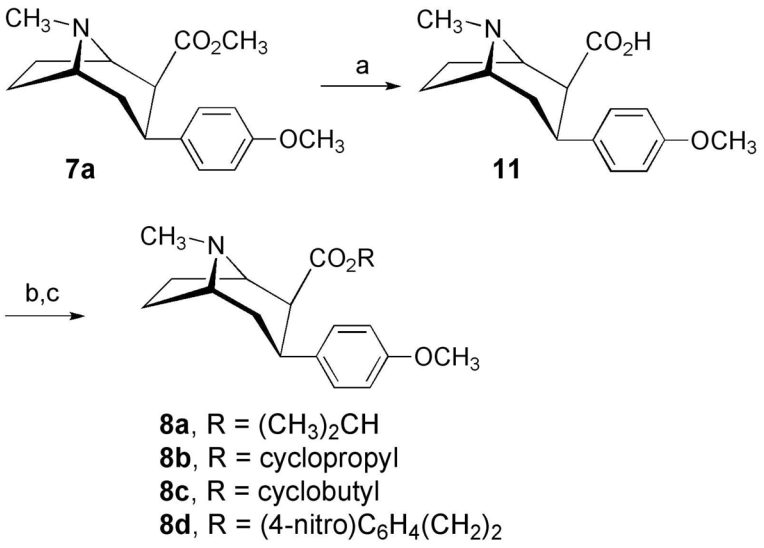
Figure 2.
3β-Phenyltropanes



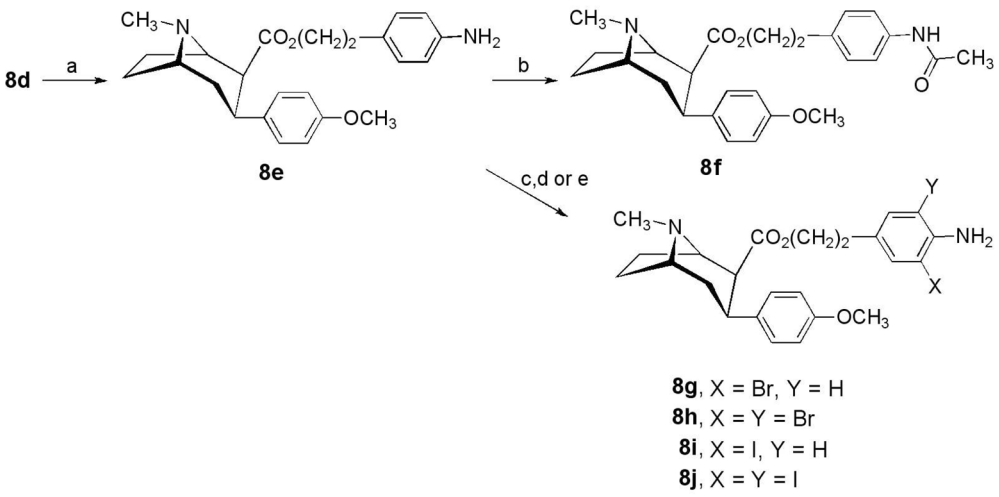
Scheme 1a.

[a] Reagents: (a) ArMgBr, Et_2O, −45 °C, 2 h, then −78 °C; (b) TFA; (c) 1.1 eq. Br_2, 2.0 eq. $SnCl_4$, 0 °C, 30 min for **7d**; (d) 2.2 eq. Br_2, 4.0 eq. $SnCl_4$, room temperature, 3 h for **7e**; (e) ICl, AcOH, room temperature, 24 h for **7f**; (f) $I(Py)_2BF_4$, CF_3SO_3H, dioxane, room temperature, 3 h for **7g**.



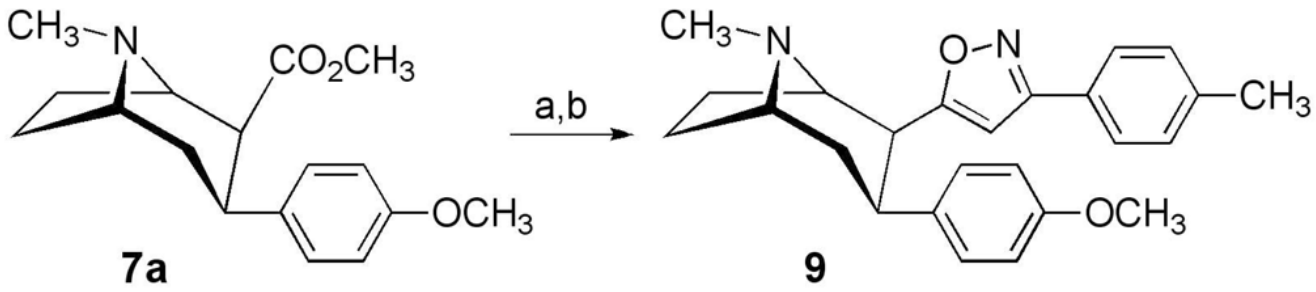
Scheme 2a.

[a] Reagents: (a) 50% dioxane/H_2O, reflux, 3 d; (b) $(COCl)_2$, CH_2Cl_2, room temperature, 1 h; (c) ROH, room temperature.



Scheme 3a.

[a] Reagents: (a) PtO_2, H_2, MeOH, 3 h; (b) acetyl chloride, Et_3N, CH_2Cl_2, 0 °C, 1 h; (c) 1 eq. NBS, DMF, room temperature, 1 h for **8g**; (d) 2 eq. Br_2, AcOH, CH_2Cl_2, room temperature, 1 h for **8h**; (e) 1.1 eq. ICl, AcOH, CH_2Cl_2, room temperature, 1 h for **8i** and **8j**.

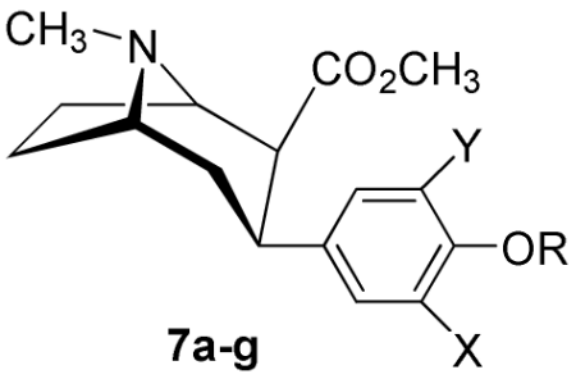


Scheme 4a.

[a] Reagents: (a) 4-methylacetophenone oxime/BuLi, room temperature, 16 h; (b) 3 N HCl, THF, 70 °C, 5 h.

Table 1

Monoamine Transporter Binding Properties of 3β-(Substituted phenyl)tropane-2β-carboxylic Acid Methyl Esters



Compd[a]	X	Y	R	DAT, IC_{50}[b] (nM) [^{3}H]12	5-HTT, K_i[b] (nM) [^{3}H]paroxetine	NET, K_i[b] (nM) [^{3}H]nisoxetine	NET/DAT Ratio[c]	NET/5-HTT Ratio[d]
Cocaine				89.1	95	1990	22	21
6				0.82 ± 0.05	0.95 ± 0.04	21.8 ± 0.6	27	23
7a	H	H	CH_3	6.5 ± 1.3	4.3 ± 0.5	1110 ± 64	171	258
7b	H	H	C_2H_5	92 ± 8	1.7 ± 0.4	1690 ± 50	18	994
7c	F	H	CH_3	16 ± 1	4.8 ± 0.5	270 ± 50	17	56
7d	Br	H	CH_3	47 ± 15	3.1 ± 0.1	160 ± 20	3	52
7f	Br	Br	CH_3	92 ± 22	2.9 ± 0.1	4100 ± 400[e]	45	1413
7e	I	H	CH_3	170 ± 60	3.5 ± 0.4	180 ± 20	1	51
7g	I	I	CH_3	1300 ± 200	7.5 ± 0.8	>5000	4	667

[a] All compounds were tested as the HCl salt.

[b] All values are means ± standard error of three or four experiments performed in triplicate.

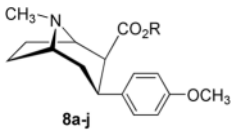
[c] NET/DA are ratios of K_i/IC_{50} values.

[d] NET/5-HTT are ratios of K_i values.

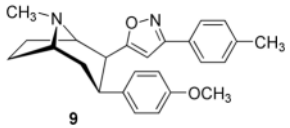
[e] N=2.

Table 2

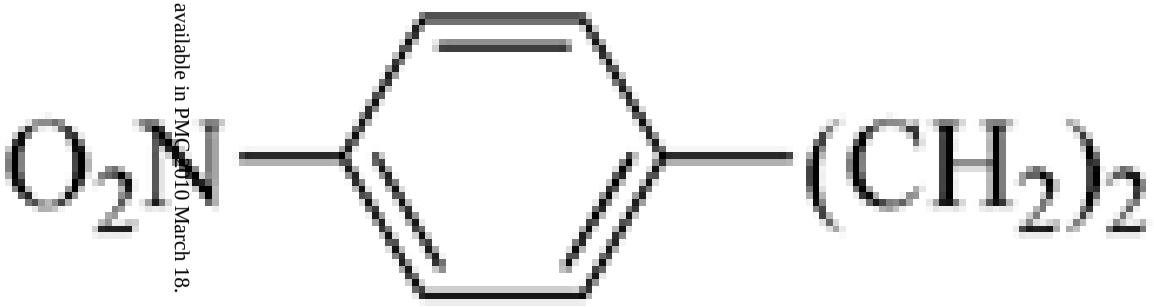
ne Transporter Binding Properties of 3β-(4-Methoxyphenyl)tropane-2β-carboxylic Acid Ester Analogs

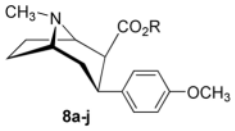


8a-j

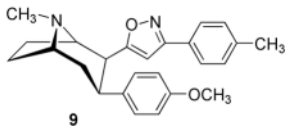


9

R	DAT, IC_{50}[b] (nM) [^{3}H]12	5-HTT, K_i[b] (nM) [^{3}H]paroxetine	NET, K_i[b] (nM) [^{3}H]nisoxetine	NET/DAT Ratio[c]	NET/5-HTT Ratio[d]
CH_3	6.5 ± 1.3	4.3 ± 0.5	1110 ± 64	171	258
$(CH_3)_2CH$	14 ± 3	135 ± 35	2010 ± 200	144	15
	6.0 ± 2	29 ± 3	1230 ± 140	205	42
	13 ± 3	100 ± 8	>3000	231	30
	42 ± 8	2.9 ± 0.2	330 ± 20	8	114



8a-j



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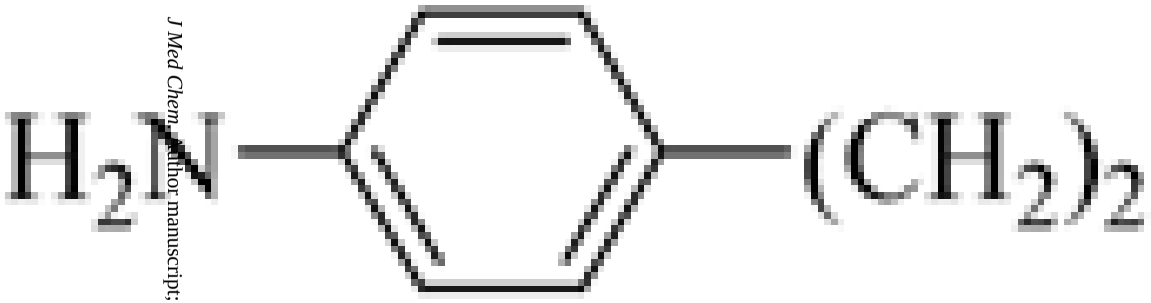
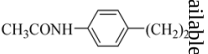
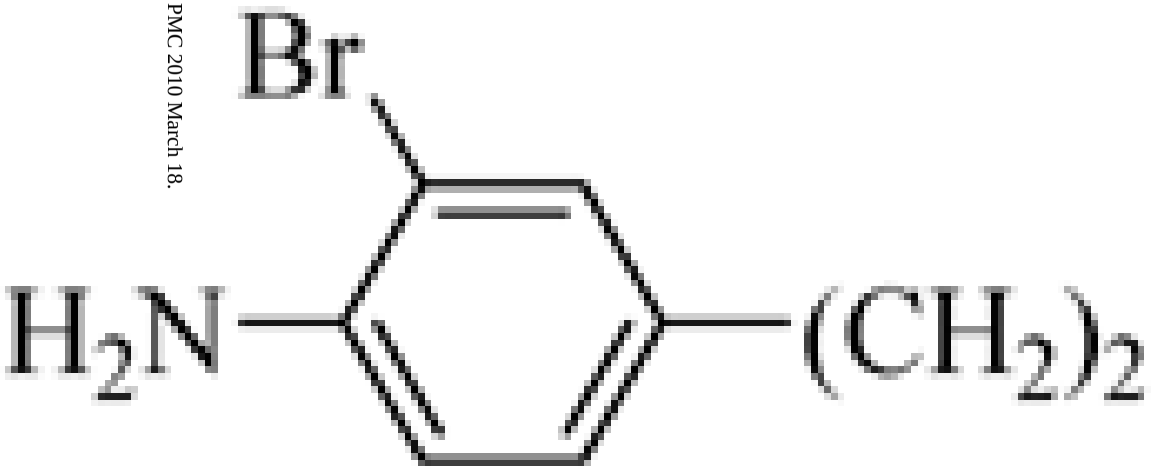
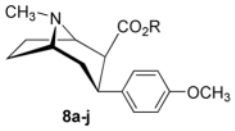
R	DAT, IC_{50}[b] (nM) [^{3}H]12	5-HTT, K_i[b] (nM) [^{3}H]paroxetine	NET, K_i[b] (nM) [^{3}H]nisoxetine	NET/DAT Ratio[c]	NET/5-HTT Ratio[d]
	7.0 ± 2	8.3 ± 0.4	2200 ± 300[e]	314	265
	6.0 ± 1	5.5 ± 0.5	1460 ± 30	243	265
	3.3 ± 1.4	4.1 ± 0.6	1850 ± 90	561	451

J Med Chem. Author manuscript; available in PMC 2010 March 18.



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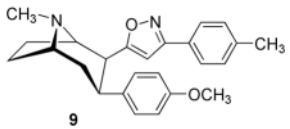
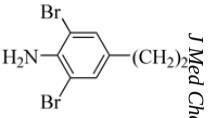
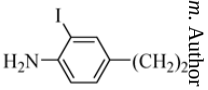
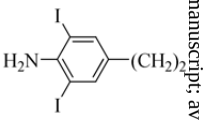


9

R	DAT, IC_{50}[b] (nM) [^{3}H]12	5-HTT, K_i[b] (nM) [^{3}H]paroxetine	NET, K_i[b] (nM) [^{3}H]nisoxetine	NET/DAT Ratio[c]	NET/5-HTT Ratio[d]
	15 ± 6	2.0 ± 0.4	2710 ± 250[e]	181	1360
	2.5 ± 0.7	3.5 ± 1	2040 ± 300[e]	816	583
	102 ± 15	1.0 ± 0.1	2600 ± 200[e]	25	2600
	18 ± 6	860 ± 170	>3000	167	3

ls were tested as the HCl salt.

means ± standard error of three or four experiments performed in triplicate.

ratios of K_i/IC_{50} values.

re ratios of K_i values.

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