

Development of 3-Phenyltropane Analogues 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

Received September 16, 2008

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 3 β -(substituted phenyl)tropane-2 β -carboxylic acid methyl esters (**7a–g**), 3 β -(4-methoxyphenyl)tropane-2 β -carboxylic acid esters (**8a–j**), and 3 β -(4-methoxyphenyl)-2 β -[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. 3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic acid 2-(3-iodo-4-aminophenyl)ethyl ester (**8i**) with an IC₅₀ value of 2.5 nM for the DAT and K_i values of 3.5 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^a), 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 cocaine⁸ 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. On the basis of the importance of the DAT in the addictive properties of cocaine, 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 3 β -(4-chlorophenyl)-2 β -[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 Coadministration of the dose of **3** that reduced cocaine-maintained behavior by 50% (ED₅₀) 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 (Figure 1).

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}

3 β -(4-Chloro-3-methylphenyl)tropane-2 β -carboxylic acid methyl ester (**6**, RTI-112) is a 3-phenyltropane analogue 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 iv drug delivery, **6** possessed an ED₅₀ 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 ED₅₀ 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 ED₅₀ 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 3 β -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

* To whom correspondence should be addressed. Phone: 919 541-6679. Fax: 919 541-8868. E-mail: fic@rti.org. Address: Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709-2194.

^a 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, electrospray ionization; EI, electron impact.

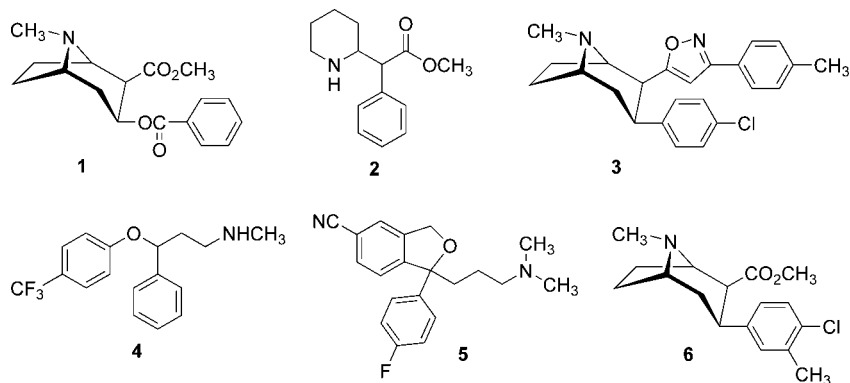


Figure 1. Structures of ligands.

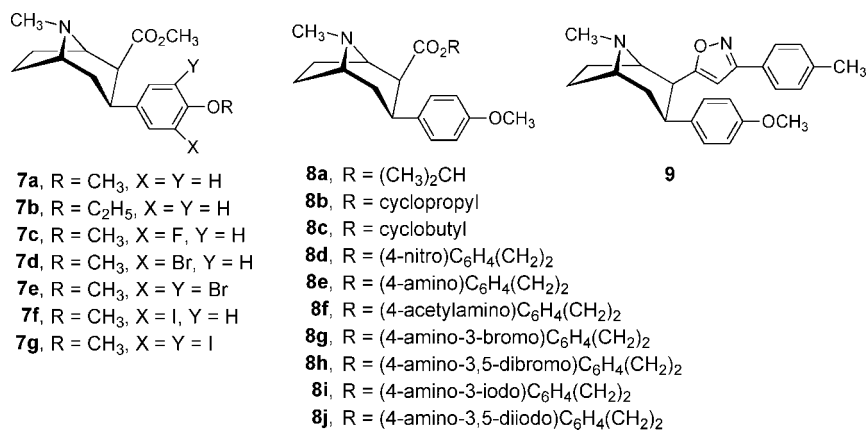
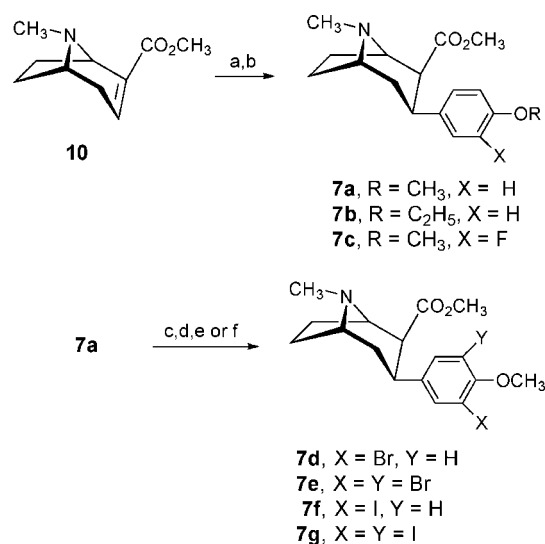


Figure 2. 3β-Phenyltropanes.

3β-(substituted phenyl)tropane analogues **7a–g**, **8a–j**, and **9** (Figure 2). 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 IC₅₀ 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).

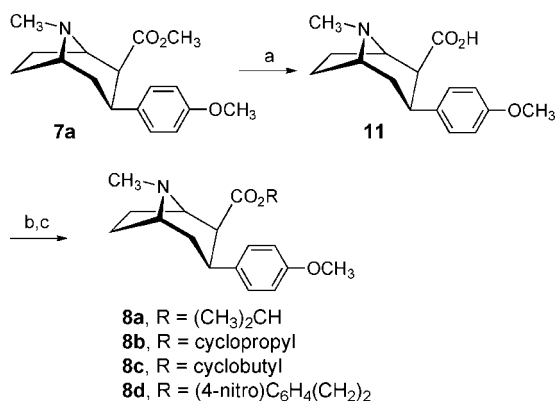
Chemistry. All the compounds described in this study were prepared starting from natural (–)-cocaine, and therefore, they are optically active and possess the same absolute configuration as (–)-cocaine. The synthesis of 3β-(substituted phenyl)tropane-2β-carboxylic acid methyl esters **7a–g** starting 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 trifluoroacetic acid (TFA) afforded **7a–c** in the range of 20–73% yield. Bromination of 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid methyl ester (**7a**) with 1.1 equiv 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 equiv 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) analogue **7g** was synthesized in 94% yield by treatment of **7a** with bis(pyridine)iodonium (I) tetrafluoroborate and trifluoromethanesulfonic acid 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

Scheme 1^a

^a Reagents: (a) ArMgBr, Et₂O, –45 °C, 2 h, then –78 °C; (b) TFA; (c) 1.1 equiv Br₂, 2.0 equiv SnCl₄, 0 °C, 30 min for **7d**; (d) 2.2 equiv Br₂, 4.0 equiv SnCl₄, room temperature, 3 h for **7e**; (e) ICl, AcOH, room temperature, 24 h for **7f**; (f) I(Py)₂BF₄, CF₃SO₃H, dioxane, room temperature, 3 h for **7g**.

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 equiv of *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) provided a 64% yield of 3-bromo-4-amino analogue **8g**

Scheme 2^a

^a Reagents: (a) 50% dioxane/H₂O, reflux, 3 d; (b) (COCl)₂, CH₂Cl₂, room temperature, 1 h; (c) ROH, room temperature.

as the only isolated product. The dibrominated product was not detected under this reaction condition. Alternately, treatment of **8e** with 2 equiv of bromine in acetic acid gave the 3,5-dibromo-4-amino compound **8h** in 79% yield. Iodination of **8e** with 1.1 equiv 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 analogue **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 ¹H 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 [³H](–)-2β-carbomethoxy-3β-(4-fluorophenyl)tropane (**12**, [³H]WIN 35,428)^{27,28} for the DAT, 0.5 nM [³H]-3-(2-methoxyphenoxy)-*N*-methyl-3-phenylpropan-1-amine ([³H]nisoxetine) for the NET, and 0.2 nM [³H]-(3*S*)-*trans*-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ([³H]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. The DAT has two binding sites; thus, IC₅₀ values are reported. Because the 5-HTT and NET have only one binding site, K_i values were calculated for inhibition of binding at these two transporters.

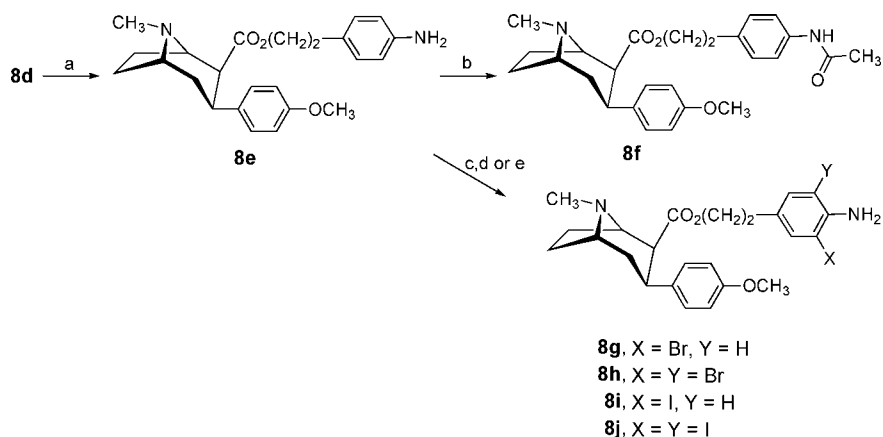
Results and Discussion

Despite extensive efforts directed toward the development of a pharmacotherapy for cocaine abuse, at present no clinically approved drugs are available. Because 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 behavior 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

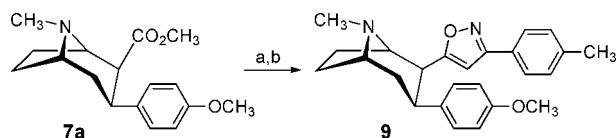
should further understanding of the mechanism of cocaine abuse and lead to new pharmacotherapies for treatment.

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 analogues, we reported that 3β-(4-methoxyphenyl)tropane-2β-carboxylic acid methyl ester (**7a**) possessed an IC₅₀ 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/IC₅₀ 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 analogues **7b–g** with modifications on the 3β-phenyl ring are presented in Table 1. Compound **7a** with an IC₅₀ 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 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 analogues **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 analogues were reasonably selective for the DAT relative to the 5-HTT and NET.²¹ Surprisingly, the phenylethyl ester analogue showed increased potency at the 5-HTT compared to cocaine. Accordingly, modification of the 2β-carbomethoxy substituents of **7a** was examined and the binding

Scheme 3^a

^a Reagents: (a) PtO₂, H₂, MeOH, 3 h; (b) acetyl chloride, Et₃N, CH₂Cl₂, 0 °C, 1 h; (c) 1 equiv NBS, DMF, room temperature, 1 h for **8g**; (d) 2 equiv Br₂, AcOH, CH₂Cl₂, room temperature, 1 h for **8h**; (e) 1.1 equiv ICl, AcOH, CH₂Cl₂, room temperature, 1 h for **8i** and **8j**.

Scheme 4^a

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

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 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 analogue **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 analogue **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 and 100 nM, respectively. All the 4-aminophenethyl ester analogues **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 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

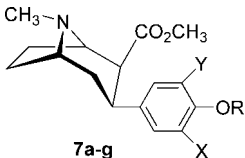
selective compound for the DAT relative to the 5-HTT and NET, which is analogous to the previously reported 2β-isoxazoltropanes.¹⁴

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 analogue **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**). Because 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 (¹H NMR and ¹³C 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) was carried out using EMD silica gel 60 F₂₅₄ TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using Isco prepac silica gel columns or using EM Science silica gel 60A (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 Et₂O (4 mL) was added. A solution of 4-bromoanisole (6.26 mL, 50.0 mmol) in anhydrous Et₂O (40 mL) was prepared and 5 mL was added. After addition of a catalytic amount of 1,2-dibromoethane, the orange iodine color

Table 1. Monoamine Transporter Binding Properties of 3 β -(Substituted phenyl)tropane-2 β -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 ₂ H 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/IC₅₀ values. ^d NET/5-HTT are ratios of K_i values. ^e N = 2.

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 freshly prepared Grignard solution was then diluted with anhydrous Et₂O (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 CH₂Cl₂-Et₂O (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 Et₂O (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 NH₄OH and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with brine (3 × 50 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 20% Et₂O in hexanes with the addition of 5% Et₃N afforded **7a** (4.10 g, 71%) as an oil. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ -123.1° (c 0.29, CH₃OH). Anal. (C₁₇H₂₄ClNO₃·H₂O) C, H, N.

3 β -(4-Ethoxyphenyl)tropane-2 β -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. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ -114.0° (c 0.34, CH₃OH). Anal. (C₁₈H₂₆ClNO₃·1.75H₂O) C, H, N.

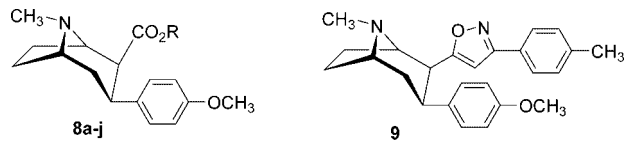
3 β -(3-Fluoro-4-methoxyphenyl)tropane-2 β -carboxylic Acid Methyl Ester (7c). The procedure for **7a** was followed using 1.80 g (10.0 mmol) of **10** to give 0.68 g (20%) of **7c** as a solid: mp 74–76 °C. ¹H NMR (300 MHz; CDCl₃) δ 7.04–6.81 (m, 3H), 3.85 (s, 3H), 3.60–3.48 (m, 4H), 3.42–3.33 (m, 1H), 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). ¹³C NMR



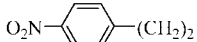
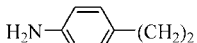
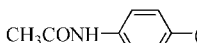
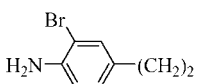
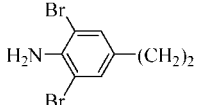
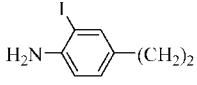
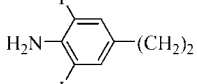
(75 MHz; CDCl₃) δ 172.2, 152.2 (d, J = 243 Hz), 145.7 (d, J = 11 Hz), 136.5 (d, J = 5.8 Hz), 122.9 (d, J = 3.5 Hz), 115.4 (d, J = 18 Hz), 113.2 (d, J = 2.0 Hz), 65.5, 62.4, 56.4, 52.9, 51.4, 42.1, 34.4, 33.2, 26.1, 25.4. MS (EI) *m/z* 308 (M⁺). The free base was converted to the hydrochloride salt: [α]_D²⁰ -103.3° (c 0.24, CH₃OH). Anal. (C₁₇H₂₃ClFNO₃·1.25H₂O) C, H, N.

3 β -(3-Bromo-4-methoxyphenyl)tropane-2 β -carboxylic Acid Methyl Ester (7d). To a stirred solution of **7a** (289 mg, 1.00 mmol) in CH₂Cl₂ (5 mL) at 0 °C under nitrogen was added SnCl₄ (0.23 mL, 2.00 mmol) followed by Br₂ (0.06 mL, 1.10 mmol). After stirring at 0 °C for 30 min, the reaction mixture was poured into a mixture of NaHCO₃-ice and extracted with CH₂Cl₂ (3 × 50 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 → 5% Et₂O in hexanes with the addition of 5% Et₃N afforded **7d** (315 mg, 86%) as a solid: mp 72–74 °C. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ -89.6° (c 0.27, CH₃OH). Anal. (C₁₇H₂₃BrClNO₃·0.75H₂O) C, H, N.

3 β -(3,5-Dibromo-4-methoxyphenyl)tropane-2 β -carboxylic Acid Methyl Ester (7e). To a stirred solution of **7a** (145 mg, 0.50 mmol) in CH₂Cl₂ (5 mL) at 0 °C under nitrogen was added SnCl₄ (0.23 mL, 2.00 mmol) followed by Br₂ (0.056 mL, 1.10 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured into a mixture of NaHCO₃-ice and extracted with CH₂Cl₂ (3 × 30 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et₃N in hexanes afforded **7e** (150 mg, 67%) as a solid: mp 145–147 °C. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ -78.6° (c 0.29, CH₃OH). Anal. (C₁₇H₂₂Br₂ClNO₃) C, H, N.

3 β -(3-Iodo-4-methoxyphenyl)tropane-2 β -carboxylic Acid Methyl Ester (7f). To a stirred solution of **7a** (289 mg, 1.00 mmol) in 1:1 mixture of AcOH-CH₂Cl₂ (10 mL) at room temperature under

Table 2. Monoamine Transporter Binding Properties of 3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid Ester Analogues


Compd ^a	R	DAT, IC ₅₀ ^b (nM)	5-HTT, K _i ^b (nM)	NET, K _i ^b (nM)	NET/DAT	NET/5-HTT
		[³ H] 12	[³ H]paroxetine	[³ H]nisoxetine	Ratio ^c	Ratio ^d
7a	CH ₃	6.5 ± 1.3	4.3 ± 0.5	1110 ± 64	171	258
8a	(CH ₃) ₂ CH	14 ± 3	135 ± 35	2010 ± 200	144	15
8b		6.0 ± 2	29 ± 3	1230 ± 140	205	42
8c		13 ± 3	100 ± 8	>3000	231	30
8d	 -(CH ₂) ₂	42 ± 8	2.9 ± 0.2	330 ± 20	8	114
8e	 -(CH ₂) ₂	7.0 ± 2	8.3 ± 0.4	2200 ± 300 ^e	314	265
8f	CH ₃ CONH-  -(CH ₂) ₂	6.0 ± 1	5.5 ± 0.5	1460 ± 30	243	265
8g	 -(CH ₂) ₂	3.3 ± 1.4	4.1 ± 0.6	1850 ± 90	561	451
8h	 -(CH ₂) ₂	15 ± 6	2.0 ± 0.4	2710 ± 250 ^e	181	1360
8i	 -(CH ₂) ₂	2.5 ± 0.7	3.5 ± 1	2040 ± 300 ^e	816	583
8j	 -(CH ₂) ₂	102 ± 15	1.0 ± 0.1	2600 ± 200 ^e	25	2600
9		18 ± 6	860 ± 170	>3000	167	3

^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/DAT are ratios of K_i/IC₅₀ values. ^d NET/5-HTT are ratios of K_i values. ^e N = 2.

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 NaHCO₃-ice and extracted with CH₂Cl₂ (3 × 50 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et₃N in hexanes afforded **7f** (95.0 mg, 23%) as an oil. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ –82.3° (c 0.22, CH₃OH). Anal. (C₁₇H₂₃ClINO₃·H₂O) C, H, N.

3 β -(3,5-Diiodo-4-methoxyphenyl)tropane-2 β -carboxylic Acid Methyl Ester (7g). To a stirred solution of I(Py)₂BF₄ (558 mg, 1.50 mmol) in dioxane (5 mL) at room temperature under nitrogen was added CF₃SO₃H (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 NH₄OH (10 mL), brine (3 × 10 mL), and dried (Na₂SO₄). The solvent was concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 5% Et₃N in hexanes afforded **7g** (255 mg, 94%) as a solid: mp 181–183 °C. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ –62.1° (c 0.24, CH₃OH). Anal. (C₁₇H₂₂ClI₂NO₃·0.5H₂O) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid (11). A mixture of **7a** (1.90 g, 6.57 mmol) in 50% dioxane-H₂O 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; CDCl₃) 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 ($M + 1$)⁺.

3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid Isopropyl Ester (8a). To a stirred solution of **11** (138 mg, 0.50 mmol) in anhydrous CH₂Cl₂ (5 mL) at 0 °C under nitrogen was added a 2 M solution of oxalyl chloride in CH₂Cl₂ (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 CH₂Cl₂ (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 NaHCO₃. The CH₂Cl₂ phase was separated and the aqueous phase was extracted with CH₂Cl₂ (3 \times 30 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 \rightarrow 5% Et₂O in hexanes with the addition of 5% Et₃N afforded **8a** (145 mg, 92%) as a solid: mp 71–72 °C. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ –93.7° (c 0.41, CH₃OH). Anal. (C₁₉H₂₈ClNO₃) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -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; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ –60.9° (c 0.32, CH₃OH). Anal. (C₁₉H₂₆ClNO₃·1.25H₂O) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -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; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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; [α]_D²⁰ –75.9° (c 0.29, CH₃OH). Anal. (C₂₀H₂₈ClNO₃) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid 2-(4-Nitrophenyl)ethyl Ester (8d). To a stirred solution of **11** (1.00 g, 3.64 mmol) in anhydrous CH₂Cl₂ (10 mL) at 0 °C under nitrogen was added a 2 M solution of oxalyl chloride in CH₂Cl₂ (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 CH₂Cl₂ (20 mL) at room temperature under nitrogen, and 4-nitrophenylethyl alcohol (1.22 g, 7.28 mmol) and Et₃N (2.05 mL, 14.6 mmol) were then added. The reaction mixture was stirred at room temperature for 16 h, poured into H₂O, and extracted with CH₂Cl₂ (3 \times 50 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was partitioned between 6 N HCl (20 mL) and Et₂O (20 mL). The aqueous phase was separated,

washed with ether (3 \times 20 mL), made basic using NH₄OH and extracted with EtOAc (3 \times 50 mL). The combined EtOAc extracts were washed with brine (3 \times 30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Recrystallization of the crude product from CH₃OH afforded **8d** (1.30 g, 84%) as a solid: mp 122–124 °C. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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: [α]_D²⁰ –40.0° (c 0.27, CH₃OH). Anal. (C₂₄H₂₉ClN₂O₅·0.75H₂O) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid 2-(4-Aminophenyl)ethyl Ester (8e). A mixture of **8d** (150 mg, 0.35 mmol) and PtO₂ (15.0 mg) in MeOH was hydrogenated at 1 atmospheric pressure for 3 h. Afterward, 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 \rightarrow 2% MeOH in CH₂Cl₂ with the addition of 1% NH₄OH afforded **8e** (135 mg, 97%) as an oil. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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: [α]_D²⁰ –58.3° (c 0.24, CH₃OH). Anal. (C₂₄H₃₂Cl₂N₂O₃·H₂O) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -carboxylic Acid 2-(4-Acetylaminophenyl)ethyl Ester (8f). To a stirred solution of **8e** (65.0 mg, 0.16 mmol) in anhydrous CH₂Cl₂ (5 mL) at 0 °C under nitrogen was added Et₃N (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 NaHCO₃-ice and extracted with CH₂Cl₂ (3 \times 30 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 \rightarrow 2% MeOH in CH₂Cl₂ with the addition of 1% NH₄OH afforded **8f** (65.0 mg, 93%) as an oil. ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (125 MHz; CDCl₃) 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: [α]_D²⁰ –62.7° (c 0.26, CH₃OH). Anal. (C₂₆H₃₃ClN₂O₄·1.5H₂O) C, H, N.

3 β -(4-Methoxyphenyl)tropane-2 β -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 NaHCO₃-ice and extracted with EtOAc (3 \times 30 mL). The combined EtOAc extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography of the crude product on silica gel using 0 \rightarrow 3% MeOH in CH₂Cl₂ with the addition of 1% NH₄OH afforded **8g** (115 mg, 64%) as an oil. ¹H NMR (500 MHz; CDCl₃) 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: $[\alpha]_D^{20} -53.3^\circ$ (c 0.26, CH_3OH). Anal. ($\text{C}_{24}\text{H}_{30}\text{BrClIN}_2\text{O}_3 \cdot 1.25\text{H}_2\text{O}$) 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 $\text{AcOH}-\text{CH}_2\text{Cl}_2$ (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 \rightarrow 10% MeOH in CH_2Cl_2 with the addition of 1% NH_4OH afforded **8h** (165 mg, 79%) as an oil. ^1H 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: $[\alpha]_D^{20} -37.4^\circ$ (c 0.27, CH_3OH). Anal. ($\text{C}_{24}\text{H}_{29}\text{Br}_2\text{ClIN}_2\text{O}_3 \cdot \text{H}_2\text{O}$) 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 $\text{AcOH}-\text{CH}_2\text{Cl}_2$ (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 \rightarrow 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: ^1H 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: $[\alpha]_D^{20} -53.1^\circ$ (c 0.26, CH_3OH). Anal. ($\text{C}_{24}\text{H}_{30}\text{ClIN}_2\text{O}_3 \cdot 1.5\text{H}_2\text{O}$) C, H, N.

8j: ^1H 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: $[\alpha]_D^{20} -34.2^\circ$ (c 0.26, CH_3OH). Anal. ($\text{C}_{24}\text{H}_{29}\text{ClI}_2\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$) 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 $^\circ\text{C}$ 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. Afterward, 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 \rightarrow 10% Et_2O in hexanes with the addition of 5% Et_3N afforded **9** (0.27 g, 68%) as a solid: mp 154–156 $^\circ\text{C}$. ^1H 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) 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: $[\alpha]_D^{20} -107.0^\circ$ (c 0.32, CH_3OH). Anal. ($\text{C}_{25}\text{H}_{29}\text{ClIN}_2\text{O}_2 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

Acknowledgment. This research was supported by the National Institute on Drug Abuse, grant no. DA05477.

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

References

- Reith, M. E. A.; Meisler, B. E.; Serhsen, H.; Lajtha, A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. *Biochem. Pharmacol.* **1986**, *35*, 1123–1129.
- Heikkila, R. E.; Manzino, L. Behavioral properties of GBR 12909, GBR 13069, and GBR 13098: Specific inhibitors of dopamine uptake. *Eur. J. Pharmacol.* **1984**, *103*, 241–248.
- Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150–155.
- Kuhar, M. J. Neurotransmitter transporters as drug targets: Recent research with a focus on the dopamine transporter. *Pharmacologist* **1993**, *35*, 28–33.
- Wise, R. A. Neural mechanisms of the reinforcing action of cocaine. *NIDA Res. Monogr.* **1984**, *50*, 15–33.
- Ritz, M. C.; Kuhar, M. J. Relationship between self-administration of amphetamine and monoamine receptors in brain: Comparison with cocaine. *J. Pharmacol. Exp. Ther.* **1989**, *248*, 1010–1017.
- Pierce, R. C.; Kumaresan, V. The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse. *Neurosci. Biobehav. Rev.* **2006**, *30*, 215–238.
- Volkow, N. D.; Wang, G.-J.; Fischman, M. W.; Foltin, R. W.; Fowler, J. S.; Abumrad, N. N.; Vitkun, S.; Logan, J.; Gatley, S. J.; Pappas, N.; Hitzemann, R.; Shea, C. E. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* **1997**, *386*, 827–833.
- Volkow, N. D.; Wang, G. J.; Fowler, J. S.; Gatley, S. J.; Logan, J.; Ding, Y. S.; Dewey, S. L.; Hitzemann, R.; Gifford, A. N.; Pappas, N. R. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of “High”. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 14–20.
- Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for treatment of cocaine abuse: Preclinical aspects. *J. Med. Chem.* **1999**, *42*, 2721–2736.
- Grabowski, J.; Shearer, J.; Merrill, J.; Negus, S. S. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. *Addict. Behav.* **2004**, *29*, 1439–1464.
- Howell, L. L.; Wilcox, K. M. The dopamine transporter and cocaine medication development: Drug self-administration in nonhuman primates. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 1–6.

- (13) Mello, N. K.; Negus, S. S. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* **1996**, *14*, 375–424.
- (14) Carroll, F. I.; Pawlusch, N.; Kuhar, M. J.; Pollard, G. T.; Howard, J. L. Synthesis, monoamine transporter binding properties, and behavioral pharmacology of a series of 3 β -(substituted phenyl)-2 β -(3'-substituted isoxazol-5-yl)tropanes. *J. Med. Chem.* **2004**, *47*, 296–302.
- (15) Carroll, F. I.; Howard, J. L.; Howell, L. L.; Fox, B. S.; Kuhar, M. J. Development of the dopamine transporter selective RTI-336 as a pharmacotherapy for cocaine abuse. *AAPS J.* **2006**, *8*, E196–E203.
- (16) Carroll, F. I.; Fox, B. S.; Kuhar, M. J.; Howard, J. L.; Pollard, G. T.; Schenk, S. Effects of dopamine transporter selective 3-phenyltropane analogs on locomotor activity, drug discrimination, and cocaine self-administration after oral administration. *Eur. J. Pharmacol.* **2006**, *553*, 149–156.
- (17) Runyon, S. P.; Carroll, F. I. Dopamine transporter ligands: Recent developments and therapeutic potential. *Curr. Top. Med. Chem.* **2006**, *6*, 1825–1843.
- (18) Runyon, S. P.; Carroll, F. I. Tropane-based dopamine transporter uptake inhibitors. In *Dopamine Transporters, Chemistry, Biology and Pharmacology*; Trudell, M. L.; Izenwasser, S., Eds. Wiley: New York, 2007.
- (19) Howell, L. L.; Carroll, F. I.; Votaw, J. R.; Goodman, M. M.; Kimmel, H. L. Effects of combined dopamine and serotonin transporter inhibitors on cocaine self-administration in rhesus monkeys. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 757–765.
- (20) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219–1223.
- (21) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3 β -(4'-substituted phenyl)tropane-2 β -carboxylic acid ester and amide analogues. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, *38*, 379–388.
- (22) Lindsey, K. P.; Wilcox, K. M.; Votaw, J. R.; Goodman, M. M.; Plisson, C.; Carroll, F. I.; Rice, K. C.; Howell, L. L. Effects of dopamine transporter inhibitors on cocaine self-administration in rhesus monkeys: Relationship to transporter occupancy determined by positron emission tomography neuroimaging. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 959–969.
- (23) Kimmel, H. L.; O'Connor, J. A.; Carroll, F. I.; Howell, L. L. Faster onset and dopamine transporter selectivity predict stimulant and reinforcing effects of cocaine analogs in squirrel monkeys. *Pharmacol., Biochem. Behav.* **2007**, *86*, 45–54.
- (24) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, QSAR, and COMFA study of 3 β -(p-substituted phenyl)tropane-2 β -carboxylic acid methylesters. *J. Med. Chem.* **1991**, *34*, 2719–2925.
- (25) Carroll, F. I.; Gao, Y.; Abraham, P.; Lewin, A. H.; Lew, R.; Patel, A.; Boja, J. W.; Kuhar, M. J. Probes for the cocaine receptor. Potentially irreversible ligands for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 1813–1817.
- (26) Carroll, F. I.; Abraham, P.; Lewin, A. H.; Parham, K. A.; Boja, J. W.; Kuhar, M. J. Isopropyl and phenyl esters of 3 β -(4-substituted phenyl)tropane-2 β -carboxylic acids. Potent and selective compounds for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 2497–2500.
- (27) Boja, J. W.; Rahman, M. A.; Philip, A.; Lewin, A. H.; Carroll, F. I.; Kuhar, M. J. Isothiocyanate derivatives of cocaine: Irreversible inhibition of ligand binding at the dopamine transporter. *Mol. Pharmacol.* **1991**, *39*, 339–345.
- (28) Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. 3-Aryl-2-(3'-substituted-1',2',4'-oxadiazol-5'-yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.* **1993**, *36*, 2886–2890.
- (29) Carroll, F. I.; Blough, B. E.; Nie, Z.; Kuhar, M. J.; Howell, L. L.; Navarro, H. A. Synthesis and monoamine transporter binding properties of 3 β -(3',4'-disubstituted phenyl)tropane-2 β -carboxylic acid methyl esters. *J. Med. Chem.* **2005**, *48*, 2767–2771.
- (30) Carroll, F. I. 2002 Medicinal Chemistry Division Award Address: Monoamine transporters and opioid receptors. Targets for addiction therapy. *J. Med. Chem.* **2003**, *46*, 1775–1794.
- (31) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliat, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 2 β -acyl-3 β -aryl-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites in rat striatum and frontal cortex. *J. Med. Chem.* **1994**, *37*, 1262–1268.
- (32) Xu, L.; Kelkar, S. V.; Lomenzo, S. A.; Izenwasser, S.; Katz, J. L.; Kline, R. H.; Trudell, M. L. Synthesis, dopamine transporter affinity, dopamine uptake inhibition, and locomotor stimulant activity of 2-substituted 3 β -phenyltropane derivatives. *J. Med. Chem.* **1997**, *40*, 858–863.
- (33) Kozikowski, A. P.; Araldi, G. L.; Prakash, K. R.; Zhang, M.; Johnson, K. M. Synthesis and biological properties of new 2 β -alkyl- and 2 β -aryl-3-(substituted phenyl)tropane derivatives: Stereochemical effect of C-3 on affinity and selectivity for neuronal dopamine and serotonin transporters. *J. Med. Chem.* **1998**, *41*, 4973–4982.
- (34) Jin, C.; Navarro, H. A.; Carroll, F. I. Synthesis and receptor binding properties of 2 β -alkynyl and 2 β -(1,2,3-triazol)substituted 3 β -(substituted phenyl)tropane derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 5529–5535.
- (35) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: Biochemical characterization and structure–activity relationships for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969–981.

JM801162Z