Substituted 3-Phenyltropane Analogs of Cocaine: Synthesis, Inhibition of Binding at Cocaine Recognition Sites, and Positron Emission Tomography Imaging

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It is now accepted that (-)-cocaine binds to specific recognition sites associated with monoamine transporters in the mammalian brain. In this study, several analogs of 3β-phenyltropane-2β-carboxylic acid methyl ester were prepared and their potency for inhibiting the binding of [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester to primate caudate–putamen was evaluated. The synthesis and binding affinity of 3β-(3,4-dichlorophenyl)tropane-2β-carboxylic acid methyl ester, one of the most potent cocaine congeners yet reported, is presented. The feasibility of synthesizing high-affinity ligands for cocaine recognition sites and their suitability as PET imaging ligands for cocaine receptors in vivo is demonstrated.

Introduction

In recent years cocaine has become one of the most prevalent and problematic drugs of abuse and considerable effort has been expended in the study of its mechanisms of action. It is now widely accepted that (-)-cocaine, a stimulant and powerful reinforcer, binds to specific recognition sites associated with monoamine transporters[1,2] in the mammalian brain. Its primary mechanism of action has been ascribed to its ability to inhibit the dopamine transporter.[2-5] Detailed structure–activity studies of these sites have only begun to emerge and these have been aided considerably by the study of a series of 3β-(aryltropanyl)-2β-(carboxymethyl) analogs of cocaine reported by Clarke et al. in 1973.[6] An excellent perspective on the cocaine receptor has recently been published.[7] One of the most potent congeners at [^{3}H]cocaine binding sites in striatum is 3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester, 4a, also known as WIN 35,428 or CFT.[2,4] This compound was recently radiolabeled[8] and has proved to be extremely useful for the study of behaviorally relevant cocaine binding sites.[8,9] It has served as a lead compound for many of the research programs now under way.[10,11] To date, the advantages of [^{3}H]-4a, a compound with moderately high affinity and selectivity for the dopamine transporter,[8,9] have not been improved by novel probes.

Niznik et al.[12] have recently reported that the dopamine transporter labeled by a photoaffinity derivative of GBR12935 is absent in solubilized and purified membranes of Parkinson's diseased putamen. A similar observation has been reported in organized tissue sections using [^{3}H]-4a, and the potential of this compound as a tool for detection of Parkinson's disease has been reported.[13] There is, however, a considerable need for the design and synthesis of compounds with even higher affinity and selectivity for the dopamine transporter. We have therefore embarked on a program to prepare and evaluate congeners of 4a which have different substitutions on the aromatic ring at C_3 of the parent molecule. We now report the synthesis of several of these tropane analogs, including a 3,4-dichlorotropane analog, which displays very high affinity for [^{3}H]-4a binding sites.

Chemistry

The structures of the compounds selected for synthesis are shown in Scheme I. The synthetic approach which we adopted was based upon the early work of Clarke et al.[6] The essential feature of this approach was the reaction of a suitable aromatic Grignard reagent with the critical intermediate anhydroecgonine methyl ester, 3. The resultant mixture of epimers at C_2 was separated to obtain the pure 2β-carbomethoxy products. We have now utilized this pathway in the synthesis of a number of tropane analogs and have developed an experimental procedure which improves considerably on the earlier published procedures of Clarke et al.[6] and offers some advantage over the more recent procedures of Milius et al.[14] and Carroll et al.[15] We routinely obtain total yields of about 80% (4a: β, 54%; α, 29%). Specifically, the Grignard reaction with 3 is carried out at low temperature and quenched with ethereal hydrogen chloride followed by ice water. The α- and β-isomers (e.g. 7 and 4) are then separated by flash chromatography.

Thus, (-)-cocaine, 1, was refluxed with dilute hydrochloric acid followed by dehydration with phosphorus oxychloride and subsequent Fisher esterification with methanol, to provide (*R*)-(-)-anhydroecgonine[6] as the methyl ester, 3, in 82% yield from 1. This compound was then used in all the subsequent Grignard reactions. The Grignard reagents were prepared from the commercially available bromo compounds. We have found that the Grignard reaction is best carried out at -20 °C in ether. The method of quenching this reaction determines the relative distribution of α- and β-carbomethoxy isomers. We have examined the reported procedures[6,14,15] and have noted that considerable amounts of the unwanted α-isomer result. Since the α-isomer is biologically inactive,[4,8] it was desirable to optimize the yield of the 2β-carbomethoxy compound. The removal of the α-isomer, when present, has been cumbersome and, in some instances, incomplete. We have developed a quenching procedure in which ethereal hydrogen chloride is added to the reaction mixture at -20 °C followed by addition of ice. This procedure leads to substantially more of the desired β-isomers than the reported aqueous quenching procedures. The α- and β-epimers are then readily separated by flash column

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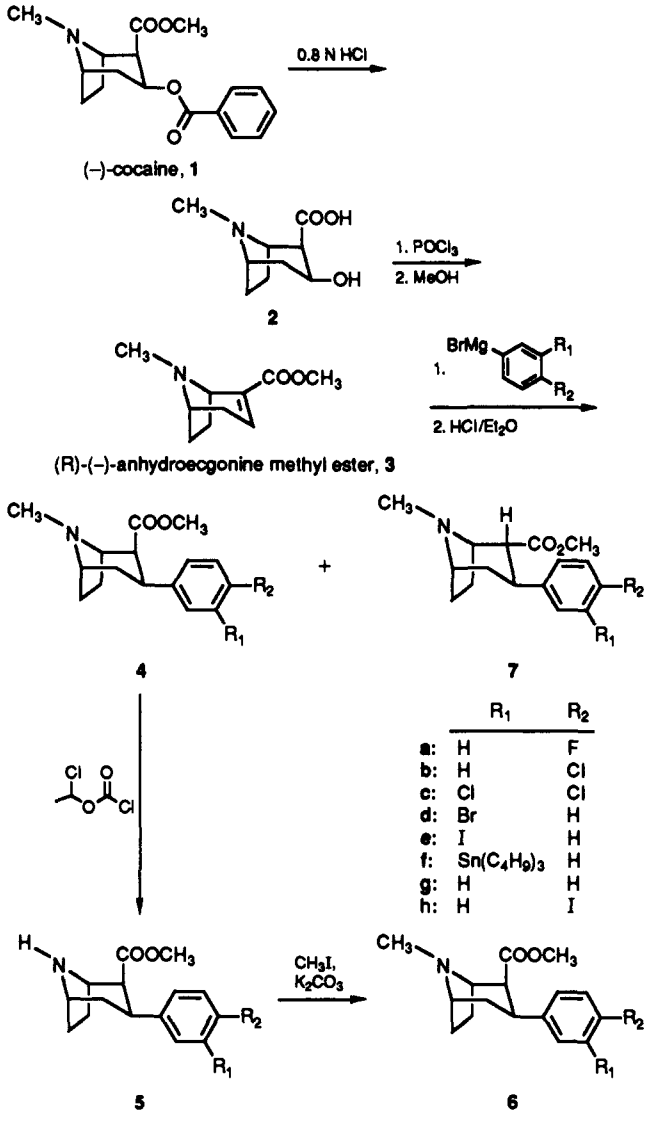
Scheme I



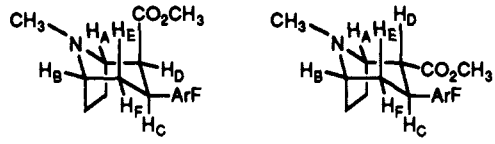
chromatography. In this simple manner, a total yield of the β-isomer of about 60% can routinely be obtained.

The presence of the α-isomer is clearly evidenced by the ^{1}H NMR spectrum. The diagnostic *N*-methyl resonance generally appears at δ 2.40 for the α-isomer and at δ 2.23 for the β-isomer. In addition, the coupling constants for the protons at C_2, C_3, and C_4 are diagnostic for the stereochemistry at C_2. Energy minimization of **4a** and **7a** was carried out using Chem3D Plus,[31] and dihedral angles were obtained from the minimized structures. The expected coupling constants were then calculated from the Karplus equation.[32] The results are presented in Table I.

An examination of the energy-minimized epimers **4a** and **7a** shows that in both cases the phenyl ring lies perpendicular to the plane of the tropane and thus bisects the angle described by C_2–C_3–C_4. The result is that in the case of **4a** (β-epimer) there is restricted rotation about the C_2–CO bond and the carbonyl of the 2β-carbomethoxy group is thus forced to point toward the H_E proton. Consequently, H_D lies in the shielding cone of the phenyl ring while H_E is deshielded by both the phenyl and the carbonyl moieties.

In epimer **7a** (α-epimer), H_D and H_E are in the deshielding cone of the phenyl ring, but H_E is no longer

Table I. Resonance Positions and Coupling Constants for Protons at C_2, C_3, and C_4 in Epimers **4a** and **7a**[a]



4a **7a**

	H_C	H_D	H_E	J_{AD}	J_{CD}
Compound **4a** (2β-CO_2CH_3)					
chemical shift, δ	2.95	2.84	2.54		
measured, Hz				3.9	3.9
calculated, Hz				2.2	4.7
dihedral angle				H_A–C_1–C_2–H_D	H_C–C_3–C_2–H_D
angle, deg				62	44
Compound **7a** (2α-CO_2CH_3)					
chemical shift, δ	δ3.11	δ3.05	δ2.09		
measured, Hz				ca. 0.0	11.9
calculated, Hz				0.6	8.7
dihedral angle				H_A–C_1–C_2–H_D	H_C–C_3–C_2–H_D
angle, deg				79	175

[a] Measured coupling constants were obtained from the 400-MHz ^{1}H-NMR spectra. Calculated coupling constants were calculated using the Karplus equation[32] from dihedral angles obtained upon energy minimization of **4a** and **7a** using Chem3D Plus.[31]

effected by the carbonyl group. The observed resonance positions for H_C, H_D, and H_E conform to this interpretation.

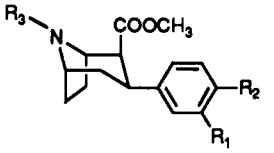
More importantly, the dihedral angle described by H_C–C_3–C_2–H_D changes from 44° in the 2β-carbomethoxy epimer to 175° in the 2α-carbomethoxy epimer. The associated coupling constants are consequently expected to be small in **4a** and large in **7a**. From Table I it can be seen that measured and calculated constants are in reasonable relative agreement. The coupling constants J_{CF} and J_{CE} are similar in both epimers (see Experimental Section), thus demonstrating that there is no epimerization at C_3. Values for J_{AD} and J_{CD} are different for each epimer. In particular, J_{CD} is small, as expected, for **4a** while a larger constant is observed for **7a**. These coupling data and resonance positions are consistent with those reported by Carroll et al.[33] for (–)-cocaine.

Since we wished to obtain the 3-bromo (**4d**) as well as the 3-iodo (**4e**) compound, we prepared these compounds by reaction of **3** with the mono-Grignard formed from 1,3-dibromobenzene.[16] Standard stannylation conditions then provided the 3-tributyltin analog **4f**, which was iodinated with iodine in methylene chloride to provide the 3-iodo compound **4e**. This route to the 3-iodo analog is in contrast to those used by Carroll[15] (via diazotization of the *p*-amino analog) and Neumeyer[17] (by treatment of **4g** with I_2, HNO_3–H_2SO_4) in their syntheses of the 4-iodo compound **4h**.

The desired 3-bromo analog **4d** was initially obtained contaminated with a small amount (<5%) of unsubstituted **4g**. The latter arose from the presence of some di-Grignard and subsequent quenching with a protic source. Since **4d** and **4g** were not readily separated chromatographically, it was most expeditious to convert the stannyl derivative **4f** to the 4-bromo compound **4d**, by treatment with *N*-bromosuccinimide in tetrahydrofuran in order to obtain a pure sample for pharmacological evaluation.

Demethylation of the *N*-methyltropane analogs has most usually been carried out by hydrolysis of an intermediate carbamate.[15,17] We have found α-chloroethyl chloroformate (ACE-Cl)[18] to be particularly useful. The conditions required for hydrolysis of the intermediate carbamate are suitable for use in the presence of sensitive functionality.

Table II. Inhibition of [^{3}H]-3β-(4-Fluorophenyl)tropane-2β-carboxylic Acid Methyl Ester, [^{3}H]-**4a**, Binding to the Dopamine Transporter (DA) and [^{3}H]Citalopram Binding to the Serotonin Transporter (5HT) by Cocaine Analogs, **4**, in Cynomolgus Monkey Caudate–Putamen



4

				IC_{50},[b] nM		
compd[a]	R_1	R_2	R_3	DA	5HT	DA/5HT selectivity
4a	H	F	CH_3	11.0 ± 1.0	160 ± 20	15
4b	H	Cl	CH_3	1.40 ± 0.04	5.87 ± 2.8	4
4c	Cl	Cl	CH_3	1.09 ± 0.02	2.47 ± 0.14	2
4d	Br	H	CH_3	7.93 ± 0.08	20.4 ± 1.1	3
4e	I	H	CH_3	27.8 ± 3.1	9.88 ± 1.1	0.4
4f	$Sn(C_4H_9)_3$	H	CH_3	1100 ± 170		
4g[e]	H	H	CH_3	65 ± 12[c]		
4h[f]	H	I	CH_3	1.08 ± 0.06	2.53 ± 0.02	2
(−)-cocaine			CH_3	95.6 ± 14.4	270 ± 120	3
5a	H	F	H	33.7 ± 6.6		
5b	H	Cl	H	1.48 ± 0.04	1.63 ± 0.7	1
5c	Cl	Cl	H	0.66 ± 0.24	1.4[d]	2

[a] Each radioligand was incubated with tissue (4 mg/mL original wet tissue weight) and 7–14 concentrations of a cocaine congener as described in the methods. Nonspecific binding of [^{3}H]-**4a** was measured with 30 μM (−)-cocaine and that of [^{3}H]citalopram with 1 μM fluoxetine.[b] IC_{50} values were computed by the EBDA computer program and are the means (±SD) of two to seven independent experiments, each conducted in triplicate. Data from Madras et al., in preparation. [c] Data from Madras et al.[8] [d] n = 1. [e] Compound **4g** was donated by Sterling Winthrop and NIDA. [f] Compound **4h** was donated by F. I. Carroll.

Thus, the *N*-methyl compounds **4** were reacted with neat α-chloroethyl chloroformate to provide the α-chloroethyl carbamate. Hydrolysis was then effected with methanol at reflux over 30 min to provide the nor compounds **5**. Purification of the nor compounds was accomplished either by preparative TLC or by flash chromatography.

The [^{11}C]methyl analogs **6** were prepared by reaction of the nor compounds **5** with [^{11}C]methyl iodide in acetonitrile/dimethylformamide (10:1) in the presence of potassium carbonate. It is noteworthy that use of a stronger base leads to epimerization at C_2 to provide the thermodynamically more stable, but biologically inactive, 2α-carbomethoxy compound.

Results and Discussion

Biology: Receptor Binding. The affinities of **4a**, other analogs, and (-)-cocaine for the dopamine and serotonin transporters were determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester, [^{3}H]-**4a** ([^{3}H]WIN 35,428 or [^{3}H]CFT), to label elements of the dopamine transporter and [^{3}H]citalopram to label the serotonin transporter (Table II). The studies were conducted in cynomolgus monkey striatum for two reasons. First, cynomolgus monkeys were used as subjects for the PET imaging studies. Second, as these compounds may be suitable for monitoring Parkinson's disease, it is necessary to determine the DA/5HT transporter selectivities in the brain region, the striatum, that undergoes the most severe depletion of dopamine nerve terminals.

Competition studies were conducted with nonsaturating concentrations of the radioligand and a range of concentrations of the test drug. All drugs inhibited [^{3}H]-**4a** binding in a concentration-dependent manner and fully inhibited [^{3}H]-**4a** binding. Comparison of the IC_{50} values (Table II) revealed that, with the exception of the stannyl derivative **4f**, each drug was more potent than (−)-cocaine itself (IC_{50} value of 95.6 ± 14.4 nM). These data are consistent with previous reports that removal of the ester link in the C_3 position increases the potency of cocaine-like drugs at these sites.[2,4] A further enhancement of potency was observed with compounds containing halogen substituents either on the 3 and/or 4 position of the aromatic ring. Of compounds with halogens in the 4 position, the most potent drug was the 3,4-dichloro analog **4c**, which is among the most potent compounds at [^{3}H]-**4a** binding sites yet identified and is almost 100 times more potent than cocaine. The affinity of **4c** was higher than that of the 4-monochloro analog **4b**[15] and indicated that the presence of a 3-chloro group clearly enhanced the affinity of the compound. The potency of **4c** was similar to that of **4h**, the 4-iodo analog (RTI55 or CIT).[17,19]

Compounds with halogens at the 3-position also were more potent than the unsubstituted phenyltropane. The affinities of the 3-bromo analog **4d** (IC_{50} = 7.93 ± 0.08 nM) and the 3-iodo analog **4e** (IC_{50} = 27.8 ± 3.1 nM) were higher than that of **4g** (IC_{50} = 65 ± 12 nM). However, for the iodo derivatives, substitution on the 3 position was less favorable than on the 4 position. In this regard, the potency of the 3-iodo derivative **4e** was 27.8 ± 3.1 nM and that of the 4-iodo analog **4h**, 1.08 ± 0.06 nM. The potency of the stannyl derivative **4f**, used as a precursor for the 3-iodo and 3-bromo compounds, was very weak at these sites. The resulting rank order of potency of these drugs was 3,4-Cl_2, 4-I > 4-Cl > 3-Br > 4-F > 3-I > H > (−)-cocaine > 4-$Sn(C_4H_9)_3$.

Desmethyl derivatives of **4a**, **4b**, and **4c** were prepared as precursors for methylation either with a radiolabeled positron-emitting group ($^{11}CH_3$) for PET imaging or with a tritiated group (C^3H_3) for in vitro assays. The potency of **5a** was reduced compared with that of the parent compound, **4a**. In contrast, the potency of the 4-chloro analog **5b** was unchanged whereas the desmethyl 3,4-dichloro analog **5c** was increased relative to their respective parent compounds. As N-demethylation is a possible route of metabolism for these compounds, it is apparent that

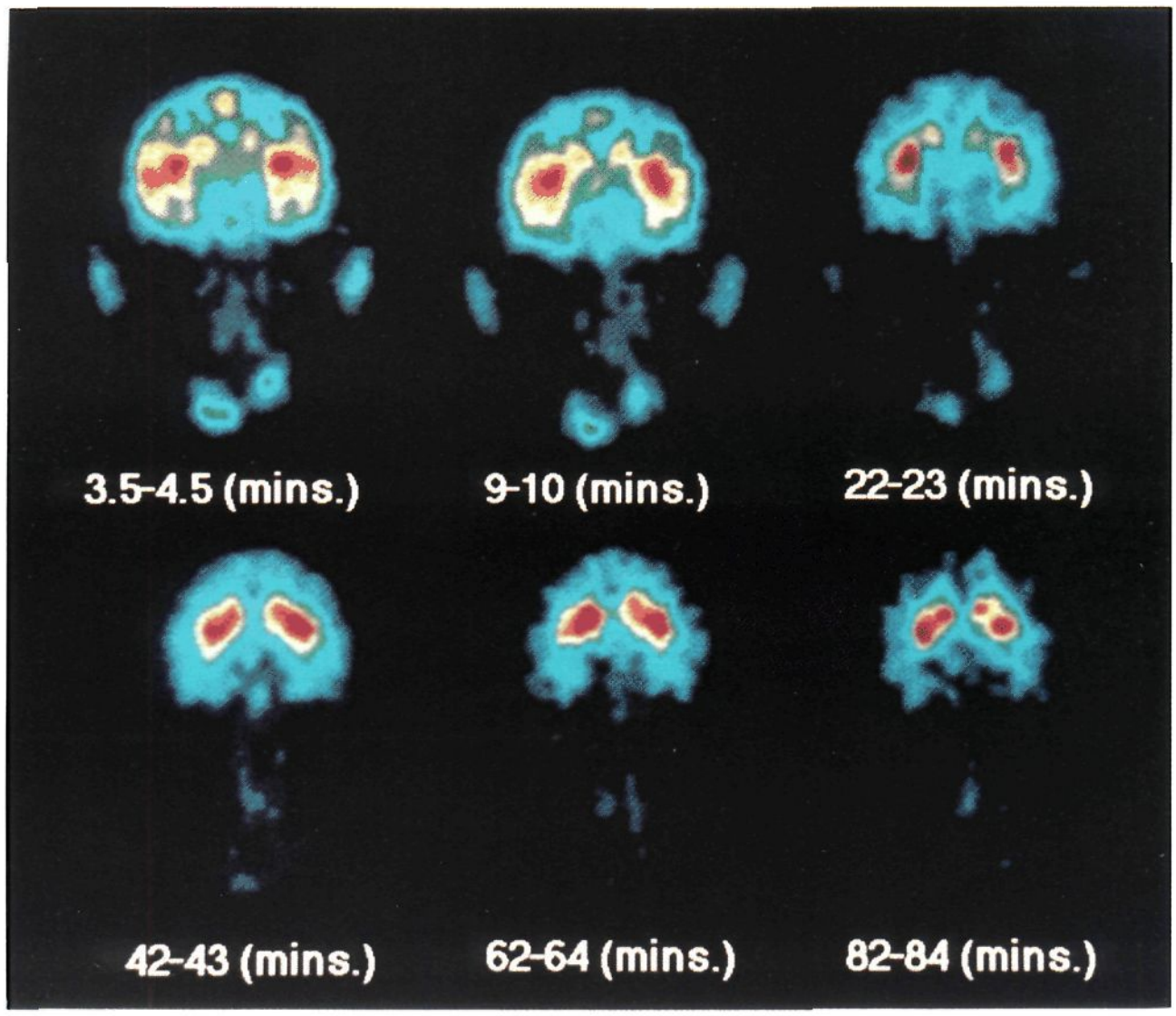


Figure 1. Sequential images of the caudate–putamen level of a cynomolgus monkey injected with [^{11}C]-**4a**.

the affinities of the nonradioactive desmethyl metabolites are sufficiently high to occupy monoamine transporters.

The relative affinities of this series of compounds for the dopamine and serotonin transporters varied considerably. Of the halogenated derivatives, the 4-fluoro derivative **4a** was 15 times more selective for the dopamine over the serotonin transporter, thereby corroborating the highly selective distribution of [^{3}H]-**4a** to dopamine-rich brain regions.[9,21,25] Like (−)-cocaine, none of the other derivatives were more than 3–4-fold selective for the dopamine transporter. Interestingly, the 3-iodo derivative was 3-fold selective for the serotonin transporter over the dopamine transporter, in contrast to the 4-iodo analog, which was marginally selective for the dopamine transporter.

PET Imaging. Positron emission tomography (PET) imaging can provide a sensitive and powerful means for probing cocaine recognition sites on the dopamine transporter. Probing the dopamine transporter by [^{11}C]ligands has two potential applications. First, imaging of these sites in vivo may be useful for monitoring behaviorally relevant cocaine recognition sites in brain. Second, imaging dopamine nerve terminals in neurodegenerative disorders such as Parkinson's disease may have substantial clinical implications. Clearly, a selective, high-affinity probe may be useful for dual purposes, as cocaine recognition sites are localized primarily on dopamine terminals. The feasibility of synthesizing the new analogs of **4a** and **4b** combined with the selectivity and distribution of **4a** were sufficiently encouraging[8,9,13] to initiate evaluation of [^{11}C]-**4a** and [^{11}C]-**4b** as PET imaging ligands. Preliminary results from these studies have been presented elsewhere.[20–22] In Figure 1, images of a squirrel monkey injected with [^{11}C]-**4a** show that the accumulation of [^{11}C]-**4a** in brain was evident within 2.5 min and initially was observed in cortex, striatum, and additional brain regions. At 40 min and thereafter, dynamic images showed high uptake of [^{11}C]-**4a** in the caudate and putamen, which increased as a function of time for at least 100 min.

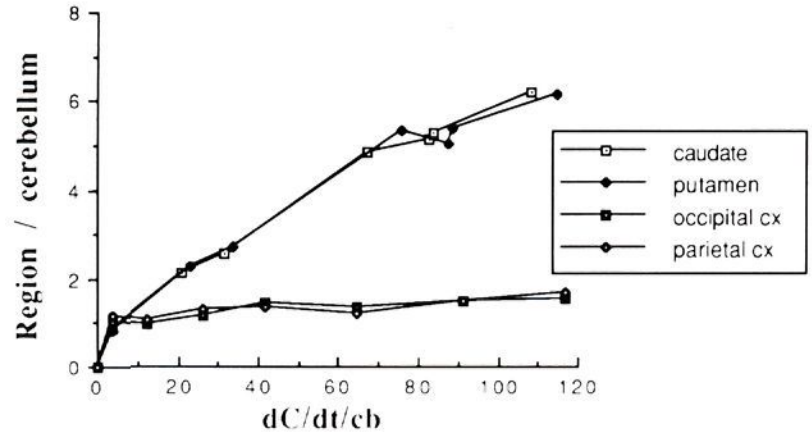


Figure 2. Time-activity curve expressed as tissue to cerebellum ratio of [^{11}C]-**4a** in the caudate–putamen and cerebellum. The *X*-axis is normalized time in seconds.

Figure 2 is a typical time–activity curve of [^{11}C]-**4a** in the caudate putamen and cerebellum areas. The *X*-axis is normalized time in seconds. This normalization takes into account the changes in blood activity with time. The time–activity curve shows that the caudate to putamen to cerebellum ratios increase with time and that activity is persistent in the area of the caudate putamen while it washes out of the cerebellum area. Cortex activity also washes out to the levels of the cerebellum area. At 90 min most of the activity observed in the brain is localized in the caudate and putamen.

The ratio of specific to nonspecific binding was determined by comparing uptake in the caudate nucleus and putamen with cerebellum (in the cynomolgus monkey) and was equivalent to ≥5 at 90 min.

The higher affinity probe [^{11}C]-**4b** was evaluated using methods similar to the ones described above for [^{11}C]-**4a**. As with [^{11}C]-**4a**, [^{11}C]-**4b** accumulated in the striatum and achieved a caudate:cerebellar ratio which was ≥4 in the cynomolgus monkey.

This study indicates the feasibility of synthesizing N-demethylated precursors for the synthesis of *N*-[^{11}C]-methyl PET imaging ligands. These results clearly indicate that [^{11}C]-**4a** and [^{11}C]-**4b** are promising ligands for monitoring cocaine recognition sites in the striatum. The striatal:cerebellar ratio for [^{11}C]-**4a** (≥5) and for [^{11}C]-**4b** (≥4) are higher than corresponding values for other PET ligands used to monitor the dopamine transporter or dopamine nerve terminals.[23,24] The brain distribution is appropriate,[9,25] the level of nonspecific binding is very low,[8] and the pharmacokinetic properties are suitable for imaging. Furthermore, the metabolism of **4a** in squirrel monkeys appears to be minimal within 30 min of iv administration of trace doses of [^{3}H]-**4a**. In this regard, radioactivity in the supernatants of brain striatum, liver, and lung migrated as a single peak on thin-layer chromatography in two solvent systems. For each tissue preparation, the peaks corresponded to standard [^{3}H]-**4a**.[25] Although the data should be considered preliminary in nature and require further confirmation by HPLC, the results support the suitability of **4a** or higher affinity congeners as imaging agents. These PET imaging ligands may be useful for monitoring behaviorally relevant cocaine recognition sites in brain with a number of clinical and basic research applications.[21]

Conclusions

In this report, we have described improved procedures for the preparation of **4a** as well as its ring-substituted analogs. An improved method of N-demethylation and introduction of a ^{11}C label is also described. The results presented demonstrate the feasibility of synthesizing high-affinity ligands for cocaine recognition sites. Furthermore, their suitability as PET imaging ligands for cocaine receptors in vivo is also demonstrated. Previous studies have shown that the affinity of (−)-cocaine for the dopamine transporter is relatively weak but is increased by removal of the C_3 ester link. In this regard, the phenyltropane analog of (−)-cocaine (**4g**) is more potent than (−)-cocaine at cocaine binding sites labeled either by [^{3}H]cocaine or by [^{3}H]-**4a**.[2,4,8] The affinity of **4g** is further enhanced by 4-fluoro substitution on the aromatic ring. The relatively high affinity of **4a** prompted its development as a probe for cocaine recognition sites[4,8] and as a marker for dopamine terminals in Parkinson's disease[13] and led to the synthesis of other analogs of **4a**.[7,10,11] In the present study, we report the synthesis of other halogenated analogs of **4a** and highlight the 3,4-dichloro analog **4c**, which is among the most potent cocaine congeners yet described. The affinities of **4c** and other halogenated derivatives indicate that halogen substituents in the 4 position of the aromatic ring confer high affinity on phenyltropane derivatives, although substitution on the 3 position may increase or decrease the apparent affinity and/or selectivity of a compound for the dopamine or serotonin transporter.

Experimental Section

NMR spectra were recorded on either a Varian T-60, a Varian XL 400, or a Bruker 300 NMR spectrometer. TMS was used as an internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Optical rotations were measured at the sodium D line at 21 °C using a JASCO DIP 320 polarimeter (1-dm cell). Thin-layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with either iodine vapor, UV exposure, or treatment with phosphomolybdic acid (PMA). Preparative TLC was carried out on Analtech uniplates silica gel GF (2000 μm). Flash chromatography was carried out on Baker silica gel (40 μM). Elemental Analyses were performed by Atlantic Microlab, Atlanta, GA. A Beckman 1801 scintillation counter was used for scintillation spectrometry. Bovine serum albumin (0.1%) and (−)-cocaine were purchased from Sigma Chemicals.

[^{3}H]CFT ([^{3}H]WIN 35,428, 2β-carbomethoxy-3β-(4-fluorophenyl)tropane-*N-methyl-t*, 79.4–87.0 Ci/mmol) and [^{3}H]-citalopram (86.8 Ci/mmol) were purchased from Du Pont–New England Nuclear (Boston, MA). Compound **4g**-tartrate and (−)-cocaine hydrochloride for the pharmacological studies were donated by the National Institute on Drug Abuse [NIDA] and compound **4g** was also donated by Sterling Winthrop. Compound **4h** was donated by F. I. Carroll. Fluoxetine was donated by E. Lilly & Co.

(R)-(−)-Anhydroecgonine Methyl Ester (3). (−)-Cocaine (15.0 g, 0.049 mol) and 0.8 N HCl (200 mL) were combined and heated at reflux overnight. The reaction mixture was cooled to room temperature and extracted with ether (200 mL). The aqueous layer was concentrated to dryness. $POCl_3$ (60 mL) was added to the residue and the mixture heated at reflux for 1 h. Excess $POCl_3$ was removed under reduced pressure. After chilling of the residue (dry ice–acetone bath), MeOH (60 mL) was added. The mixture was warmed slowly to room temperature with swirling and the MeOH was removed under reduced pressure. The residue was dissolved in water (100 mL), basified with NH_4OH, saturated with NaCl, and extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were dried over K_2CO_3, filtered, and concentrated to dryness. The residue was purified by flash chromatography with 5% MeOH in EtOAc as eluent to afford 7.4 g (82%) of **3** as a clear oil: R_f 0.45 (10% MeOH in EtOAc + NH_4OH); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.4–2.2 (m, 6 H), 2.35 (s, 3 H, NC*H*$_3$), 2.4–3.4 (m, 2 H), 3.58 (s, 3 H, OC*H*$_3$), 6.83 (m, 1 H).

2β-Carbomethoxy-3β-(4-fluorophenyl)tropane (4a). A mixture of (4-fluorophenyl)magnesium bromide (2 M, 27 mL, 54 mmol) and anhydrous ether (200 mL) was cooled to −20 °C. Anhydroecgonine methyl ester (**3**; 5.0 g, 28 mmol) in anhydrous ether (100 mL) was added dropwise. The reaction mixture was stirred at −20 °C for 1 h. Ethereal HCl (1.7 M, 80 mL) was added, the mixture was stirred for 5 min, and then ice (ca. 400 g) was added. The reaction mixture was allowed to warm to room temperature. The aqueous layer was basified with NH_4OH, saturated with NaCl, and extracted with CH_2Cl_2 (2 × 200 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (5% Et_3N/Et_2O to 10% Et_3N/Et_2O) to afford 4.13 g (54%) of the β-epimer [2.24 g (29%) of the α-epimer was also obtained; see below]: mp 93–94 °C (lit.[6] mp 94–96 °C); R_f 0.42 (*i*-$PrNH_2/Et_2O$/pentane 5:30:65); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.75 (m, 3 H), 2.0–2.2 (m, 2 H), 2.23 (s, 3 H, NC*H*$_3$), 2.54 (ddd, 1 H, *H*-4), 2.84 (t, 1 H, *H*-2), 2.95 (ddd, 1 H, *H*-3, *J* = 5.3, 12.7 Hz), 3.36 (m, 1 H, *H*-5), 3.50 (s, 3 H, OCH_3), 3.55 (m, 1 H, *H*-1), 6.9–7.25 (m, 4 H, Ar*H*); $[\alpha]^{21}_D$ −45.6° (*c* = 1, CH_3OH). Anal. ($C_{16}H_{20}NO_2F$) C, H, N. α-Epimer **7a**: mp 66–67 °C; R_f 0.35 (*i*-$PrNH_2/Et_2O$/pentane 5:30:65) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.72 (m, 2 H, *H*-6,7), 1.8–1.95 (m, 3 H), 2.09 (ddd, 1 H, *H*-4), 2.40 (s, 3 H, NC*H*$_3$), 3.05 (brd, 1 H, *H*-2), 3.11 (ddd, 1 H, *H*-3, *J* = 5.5, 11.9 Hz), 3.24 (m, 1 H, *H*-5), 3.40 (m, 1 H, *H*-1), 3.50 (s, 3 H, OCH_3), 6.9–7.25 (m, 4 H, Ar*H*).

2β-Carbomethoxy-3β-(4-chlorophenyl)tropane (4b). This compound was prepared as described above for **4a**, quenched as described by Clarke et al.,[6] and worked up as was **4a** to yield 15%: mp 118–119 °C (white solid); R_f 0.49 (*i*-$PrNH_2/Et_2O$/pentane 3:30:67); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.4–2.1 (m, 6 H), 2.25 (s, 3 H, NC*H*$_3$), 2.25–3.1 (m, 2 H), 3.50 (s, 3 H, OCH_3), 7.26 (s, 4 H); $[\alpha]^{21}_D$ = 44.0° (*c* = 1, CH_3OH). Anal. ($C_{16}H_{20}NO_2Cl$) C, H, N, Cl.

2β-Carbomethoxy-3β-(3,4-dichlorophenyl)tropane (4c). This compound was prepared as described above for **4a**, quenched as described by Clarke et al.,[6] and worked up as was **4a** to yield 14%: mp 82.5–83.5 °C (white solid); R_f 0.43 (*i*-PrNH$_2$/Et$_2$O/pentane 3:30:67); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.6–1.7 (m, 3 H), 2.0–2.1 (m, 2 H), 2.21 (s, 3 H, NC*H*$_3$), 2.50 (ddd, 1 H, *H*-4), 2.86 (m, 1 H, *H*-2), 2.92 (m, 1 H, *H*-3), 3.33 (m, 1 H, *H*-5), 3.52 (s, 3 H, OC*H*$_3$), 3.55 (m, 1 H, *H*-1), 7.07–7.32 (m, 4 H, Ar*H*); $[\alpha]^{21}_D$ −27.0° (*c* = 1, CH$_3$OH). Anal. (C$_{16}$H$_{19}$NO$_2$Cl$_2$) C, H, N, Cl.

2β-Carbomethoxy-3β-(3-bromophenyl)tropane (4d). This compound was prepared as described above for **4a**, quenched as described by Clarke et al.,[6] and worked up as was **4a** to yield 27%: R_f 0.56 (*i*-PrNH$_2$/Et$_2$O/pentane 5:30:65); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.56–1.71 (m, 3 H), 2.07–2.2 (m, 2 H, *H*-6,7), 2.20 (s, 3 H, NC*H*$_3$), 2.52 (ddd, 1 H, *H*-4), 2.87 (m, 1 H, *H*-2), 2.94 (m, 1 H, *H*-3), 3.33 (m, 1 H, *H*-5), 3.49 (s, 3 H, OC*H*$_3$), 3.55 (m, 1 H, *H*-1), 7.1–7.4 (m, 4 H, Ar*H*).

A pure sample of **4d** was obtained from **4f** by the following procedure.

2β-Carbomethoxy-3β-[3-(tributylstannyl)phenyl]tropane (**4f**; 153.5 mg, 0.28 mmol) in THF (7 mL) was degassed by bubbling nitrogen through the solution for 5 min. *N*-Bromosuccinimide (55 mg, 0.31 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. The volatiles were removed at a rotary evaporator, and the residue was purified by flash chromatography (10% Et$_3$N/hexane) to afford 81.4 mg (85%) of **4d**. The 1,5-naphthalenedisulfonate salt was then obtained as the dihydrate: mp 158–160 °C; $[\alpha]^{21}_D$ −54.1° (*c* = 1, CH$_3$OH). Anal. (C$_{26}$H$_{32}$NS$_2$O$_{10}$Br) C, H, N, S, Br.

2β-Carbomethoxy-3β-[3-(tributylstannyl)phenyl]tropane (4f). 2β-Carbomethoxy-3β-(3-bromophenyl)tropane (**4d**; 0.9 g, 2.7 mmol) in toluene (16 mL) was degassed by bubbling nitrogen into the mixture. Bis(tributyltin) (3.32 g, 6.25 mmol) was added, followed by tetrakis(triphenylphosphine)palladium (48.8 mg, 0.042 mmol). Degassing was continued for another 15 min.

The reaction mixture was heated at reflux for 2.5 h, filtered through Celite, and washed with CH$_2$Cl$_2$. The filtrate was concentrated to dryness. The residue was purified by flash chromatography with (2% *i*-PrNH$_2$ in hexane as eluent) to afford 690 mg (47%) of a light brown oil: R_f 0.73 (*i*-PrNH$_2$/Et$_2$O/hexane 3:30:67); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.8–1.5 (m, 27 H), 1.5–1.76 (m, 3 H), 2.1–2.2 (m, 2 H), 2.21 (s, 3 H, NC*H*$_3$), 2.56 (ddd, 1 H, *H*-4), 2.89 (m, 1 H, *H*-2), 2.95 (m, 1 H, *H*-3), 3.35 (m, 1 H, *H*-5), 3.45 (s, 3 H, OC*H*$_3$), 3.52 (m, 1 H, *H*-1), 7.15–7.24 (m, 4 H, Ar*H*). Anal. (C$_{28}$H$_{47}$NO$_2$Sn) C, H, N.

2β-Carbomethoxy-3β-(3-iodophenyl)tropane (4e). Compound **4f** (155 mg, 0.28 mmol) in CH$_2$Cl$_2$ (20 mL, dried over molecular sieves) was degassed by bubbling with nitrogen for 10 min. Iodine (427 mg, 1.7 mmol) was added and the reaction mixture was stirred overnight at room temperature under nitrogen. The reaction mixture was quenched with 10 mL of 1% Na$_2$S$_2$O$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined CH$_2$Cl$_2$ layers were dried over K$_2$CO$_3$, filtered, and concentrated to dryness. The residue was triturated with small amount of CH$_2$Cl$_2$ and the white insoluble material was filtered and stirred with CH$_2$Cl$_2$ and dilute NH$_4$OH until all had dissolved. The CH$_2$Cl$_2$ layer was dried over K$_2$CO$_3$, filtered, and concentrated to afford 61 mg (56%) of **4e**: (60 MHz, CDCl$_3$) δ 1.22–2.11 (m, 4 H), 2.22 (s, 3 H, NC*H*$_3$), 2.45–3.5 (m, 2 H), 3.53 (s, 3 H, OC*H*$_3$), 6.85–7.65 (m, 4 H, Ar*H*).

The 1,5-naphthalenedisulfonate salt was prepared by adding 1,5-naphthalenedisulfonic acid tetrahydrate (60 mg, 1.01 equiv) in reagent alcohol to **4e**. The salt was recrystallized from reagent alcohol and ether to afford 94 mg (82%): R_f 0.52 (*i*-PrNH$_2$/Et$_2$O/hexane 3:30:67); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.75–1.79 (m, 1 H), 1.98–2.25 (m, 4 H), 2.48 (ddd, 1 H, *H*-4), 2.67 (s, 3 H, NHC*H*$_3$), 2.95 (dd, 1 H, *H*-2), 3.25 (s, 3 H, OC*H*$_3$), 3.37 (m, 1 H, *H*-3), 3.80 (m, 1 H, *H*-5), 3.93 (m, 1 H, *H*-1), 6.97 (t, 1 H, Ar*H*), 7.09 (m, 1 H, Ar*H*), 7.45 (m, 3 H, Ar*H*), 8.09 (d, 2 H, Ar*H*), 8.90 (d, 2 H, Ar*H*); $[\alpha]^{21}_D$ −65.9° (*c* = 1, CH$_3$OH). Anal. (C$_{26}$H$_{34}$NO$_{11}$IS$_2$) C, H, N, S, I.

2β-Carbomethoxy-3β-(4-fluorophenyl)nortropane(5a). 2β-Carbomethoxy-3β-(4-fluorophenyl)tropane (**4a**; 2.6 g, 9.38 mmol) and α-chloroethyl chloroformate (ACE-Cl) (7 mL, 68 mmol) were combined and heated at 100 °C (oil-bath temperature) for 1 h. Excess ACE-Cl was then removed under reduced pressure, and methanol (50 mL) was added to the residue. The mixture was then heated at reflux for 30 min and then concentrated to dryness. The residue obtained was dissolved in CH$_2$Cl$_2$ (75 mL), washed with saturated NaHCO$_3$ solution, dried over sodium sulfate, filtered, and concentrated to afford the crude demethylated product (2.58 g). Purification by flash chromatography (10% Et$_3$N/Et$_2$O) gave **5a** as a tan solid (1.82 g, 74%): mp 115–116.5 °C; R_f 0.18 (*i*-PrNH$_2$/EtOAc/hexane 3:47:50); ^{1}H NMR (CDCl$_3$) δ 0.75–3.23 (m, 8 H), 3.42 (s, 3 H, OC*H*$_3$), 3.75 (m, 3 H), 6.78–7.38 (m, 4 H, Ar*H*); $[\alpha]^{21}_D$ −102.1° (*c* = 1, CH$_3$OH). Anal. (C$_{15}$H$_{18}$NO$_2$F) C, H, N.

2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (5b). This compound was prepared as described above for **5a** and purified by preparative TLC (*i*-PrNH$_2$/EtOAc/hexane 3:47:50); yield 46%; mp 97–98 °C (beige solid); R_f 0.18 (*i*-PrNH$_2$/EtOAc/hexane 3:47:50); ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.7–3.3 (m, 8 H), 3.43 (s, 3 H, OC*H*$_3$), 3.6 (m, 3 H), 7.1–7.4 (m, 4 H, Ar*H*). Anal. (C$_{15}$H$_{18}$NO$_2$Cl·0.25H$_2$O) C, H, N, Cl.

2β-Carbomethoxy-3β-(3,4-dichlorophenyl)nortropane (5c). This compound was prepared as described above for **5a** (eluent for preparative TLC: 10% Et$_3$N in ether): yield 65%; mp 102–103 °C (beige solid); R_f 0.19 (10% Et$_3$N in ether); ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.87–3.4 (m, 8 H), 3.48 (s, 3 H, OC*H*$_3$), 3.8 (m, 3 H), 7.0–7.53 (m, 4 H, Ar*H*); $[\alpha]^{21}_D$ −108.1° (*c* = 1, CH$_3$OH). Anal. (C$_{15}$H$_{17}$NO$_2$Cl$_2$) C, H, N, Cl.

[*N*-^{11}C]-2β-Carbomethoxy-3β-(4-fluorophenyl)tropane ([^{11}CH$_3$]-4a). [^{11}C]methyl iodide was produced by a modification of the published methods.[30] Thus, ^{11}CO$_2$ produced by the nuclear reaction ^{13}N(p,α)^{11}C in a Scandatronix 17MeV cyclotron was collected in a stainless steel coil that was cooled in liquid nitrogen. It was transferred by means of a stream of nitrogen into a solution of 0.5 M lithium aluminum hydride in anhydrous tetrahydrofuran (5 mL). The THF was removed and a 57% HI (0.5 mL) solution was added dropwise to the organometallic complex. Subsequent heating at 130 °C generated [^{11}C]methyl iodide, which was distilled through a tube into a reaction vial containing 0.05–0.1 mg of **5a** in acetonitrile (0.1 mL which contained 10 μL of DMF). The reaction mixture was then heated at 110 °C for 4 min. The solvent was evaporated and the residue was dissolved in Ringer's lactate (2 mL). The solution was filtered over a 0.22-μm millipore filter and was ready for injection. Typical yields were 35–65 mCi/run with effective specific activities of over 400 mCi/μmol. The effective specific activity was calculated to end of synthesis (EOS) from the activity measured per micromole of [^{11}CH$_3$]-**4a**, taking into account the difference in affinity of **5a** to **4a** (ratio, 3:1) and assuming that all **5a** was in solution at time of injection. No cold **4a** was observed by HPLC analysis of the final product.

Biology. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and of the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication No. (NIH)85-23, revised 1985.

Tissue Preparation. Radioreceptor assays are essentially those described by Madras et al.[8] Brain tissue was harvested within 30 min of death from adult male and female cynomolgus monkeys (*Macaca fascicularis*) euthanized in the course of other studies. Tissue was stored in the brain bank at the New England Regional Primate Research Center at −85 °C. The caudate–putamen was dissected from coronal sections of brains and each caudate–putamen was homogenized and used separately. Membranes were prepared as described previously.[4] Briefly, the tissue was homogenized in 10 volumes (w/v) of ice-cold Tris HCl buffer (50 mM, pH 7.4 at 0–4 °C) and centrifuged at 38700*g* for 20 min in the cold. The resulting pellet was resuspended in 40 volumes of buffer, and the entire wash procedure was repeated twice. The membrane suspension (25 mg original wet weight of tissue/mL) was diluted to 12 mg/mL in buffer just prior to assay and dispersed with a Brinkmann polytron (setting #5) for 15 s. All experiments were conducted in triplicate, and each experiment was repeated in each of two to seven individual tissue preparations.

Competition Assays. The potency of novel drugs was determined at the dopamine and serotonin transporter in monkey caudate–putamen by incubating tissue with a fixed concentration

of [^{3}H]-**4a** (dopamine transporter) or [^{3}H]citalopram (serotonin transporter) and a range of concentrations of the test compound. Stock solutions of water-soluble drugs were dissolved in water or buffer, and stock solutions of other drugs were made in a range of ethanol/HCl solutions. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium. The assay tubes received, in Tris HCl buffer (50 mM, pH 7.4, at 0–4 °C; 100 mM NaCl), these constituents at a final assay concentration: 0.2 mL of drug (approximate range: 1 pM–100 μM), [^{3}H]-**4a** (0.3 nM, 0.2 mL) or [^{3}H]citalopram (1 nM, 0.2 mL), and 0.2 mL of membrane preparation (4 mg original wet weight of tissue/mL). The 2-h incubation (0–4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass-fiber filters presoaked for at least 40 min in 0.1% bovine serum albumin ([^{3}H]-**4a**) or 0.1% polyethylenimine ([^{3}H]citalopram). The filters were washed twice with 5 mL of Tris HCl buffer (50 mM), incubated overnight at 0–4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry. Cpm values were converted to dpm following determination of counting efficiency (49–53%) of each vial by external standardization. For the dopamine transporter, total binding was defined as [^{3}H]-**4a** bound in the presence of ineffective concentrations of drug (1 or 10 pM). Nonspecific binding was defined as [^{3}H]-**4a** bound in the presence of an excess (30 μM) of (−)-cocaine. Specific binding was the difference between the two values. For the serotonin transporter, total binding was defined as [^{3}H]citalopram bound in the presence of ineffective concentrations of drug (1 or 10 pM) and nonspecific binding was defined as [^{3}H]citalopram bound in the presence of an excess (1 μM) of fluoxetine.

Data Analysis. Data were analyzed by the EBDA computer software programs (Elsevier-Biosoft, U.K.). Final estimates of IC_{50} values were computed by the EBDA program. Baseline values for the individual drugs were established from the competition curves and these generally were similar to baseline values established by 30 μM (−)-cocaine or 1 μM fluoxetine.

Positron Emission Tomography. Adult cynomolgus monkeys were used as subjects. PET imaging studies were conducted with a high-resolution positron emission tomograph, PCR-I.[26] Each monkey was anesthetized by an initial iv injection of ketamine–xylazine (15 and 1.5 mg/kg) which was repeated, as needed. The animal was positioned ventrally and, to secure a stable head position, the head was placed in a Plexiglas head holder fitted with ear and eyebars. [^{11}C]-**4a** (>300 Ci/mmol, <1 μg, 0.5–2 mL, approximately) or [^{11}C]-**4b** (>300 Ci/mmol) was injected iv at doses that were generally below the threshold dose for producing stimulation. Sequential dynamic imaging for 90 min was carried out and data were corrected for sensitivity[27] and attenuation using a mathematical correction. For image reconstruction, a Hanning windowed filtered convolution backprojection was used.[28] Regions of interest (ROI) were drawn over the caudate, putamen, and cerebellum, the striatal:cerebellar ratio was calculated, and the corresponding time activity ratio curves were determined according to the model of Patlak.[29]

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