Synthesis and Ligand Binding Studies of 4′-Iodobenzoyl Esters of Tropanes and Piperidines at the Dopamine Transporter

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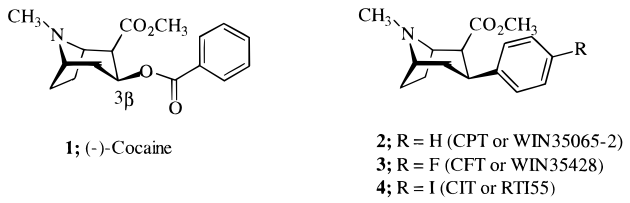
Four analogs and two homologs of cocaine, designed as potent cocaine antagonists, were synthesized. The S_N2 reaction between ecgonine methyl ester (**13**) or appropriately substituted piperidinol (**19**, **21**) and appropriately substituted 4-iodobenzoyl chloride gave 4-iodobenzoyl esters of tropanes and piperidines (**5**−**8**). 2′-Hydroxycocaine (**9**) was obtained from 2′-acetoxycocaine (**12**) by selective transesterification with MeOH saturated with dry HCl gas. 2′-Acetoxycocaine (**12**) was synthesized from acetylsalicyloyl chloride (**23**) and ecgonine methyl ester (**13**). The binding affinities of these compounds were determined at the dopamine transporter for the displacement of [^{3}H]WIN-35428. An iodo group substitution at the 4′-position of cocaine decreased dopamine transporter binding potency, while a hydroxy or acetoxy group at the 2′-position exhibited increased binding potency for the dopamine transporter compared to cocaine (10- and 3.58-fold, respectively). 2′-Hydroxylation also enhanced the binding potency of 4′-iodococaine (**5**) by 10-fold. Replacement of the tropane ring with piperidine led to poor binding affinities.

Introduction

Cocaine (**1**) is a widely abused psychostimulant drug that has powerful reinforcing and europhorigenic properties.[1,2] Drug-seeking behaviors, induction of stereotypies, and stimulation of locomotor activity by cocaine are ascribed to its inhibition of the dopamine uptake at the dopamine transporter (DAT).[3−5] Furthermore, in a recent study involving knockout mice genetically lacking DAT, cocaine had no stimulating effect. This finding directly confirms the crucial role of the DAT in cocaine action.[6] Despite improved knowledge of the neuropharmacological mechanisms underlying the addictive action of cocaine,[3,7] the success of the current therapies for cocaine addiction has been limited.[1,8] This has led to the search for direct-acting, competitive cocaine antagonists. While no antagonists of this type have yet been identified, some very potent cocaine derivatives have been produced.[9−13] The synthetic cocaine congeners such as 2β-carbomethoxy-3β-phenyltropane (**2**, β-CPT, or WIN-35065-2),[14] 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (**3**, β-CFT, or WIN-35428),[14,15] and 2β-carbomethoxy-3β-(4-iodophenyl)tropane (**4**, β-ClT, or RTI-55)[16] are lead compounds for a growing number of relatively stable, long-acting ligands for the DAT. In these phenyltropanes (**2**−**4**; Figure 1), the aromatic ring is attached directly to the tropane ring system, thus avoiding hydrolysis of the 3β-benzoyl ester that produces rapid metabolic inactivation of cocaine.[17] Molecular modeling studies demonstrated that, in the phenyltropanes (**2**−**4**), the distance between the bridge nitrogen atom of the tropane ring system and the centroid of the aromatic ring was shorter (5.6 Å) than cocaine (7.7 Å).[5,10] As predicted from molecular modeling studies, the aromatic ring in the phenyltropanes was located in the more favorable binding regions.[18] These compounds indeed showed higher binding affinity for the cocaine-binding site. However, they also possessed enhanced biological activity and, particularly, increased behavioral stimulation.[19,20]



1; (-)-Cocaine

2; R = H (CPT or WIN35065-2)
3; R = F (CFT or WIN35428)
4; R = I (CIT or RTI55)

Figure 1.

So many substituted phenyltropanes have been synthesized and evaluated yet no compound exhibiting high affinity in the WIN-35428 assay, but low affinity in inhibiting dopamine reuptake has been identified. Perhaps some aspect of how phenyltropanes fit into the cocaine binding site and alter the transporter function reduces the likelihood of finding a derivative of such phenyltropanes which retains binding but has reduced ability to alter DAT.[20] Another approach is to begin with cocaine derivatives. High-affinity (compared to phenyltropanes) cocaine structure-based analogs may be identified, but perhaps the qualitative/functional properties of such cocaine congeners may differ from those of phenyltropanes. Such potential differences await empirical validation. For example 6- and 7-methoxy-substituted analogs of cocaine acted as partial antagonists (or weak agonists).[13] We have recently reported some of the cocaine structure-based analogs, 4′-phenylcocaine[21] and 4′-nitrococaine,[22] which were devoid of locomotor stimulant activity, and also suppressed the locomotor stimulation activity of cocaine when coadministered with cocaine. These analogs contained the ester functionality present at C-3 in cocaine, but more importantly, the distance between the bridge nitrogen atom of the tropane ring and the para substituent on the benzene ring (N−P) was longer than that in cocaine.[21,22] In this publication we report the synthesis of six of the designed cocaine analogs (**5**−**9**, **12**, Figure 2). The reason to synthesize 4′-iodococaine (**5**) was 3-fold: (1) addition of an iodine substituent at

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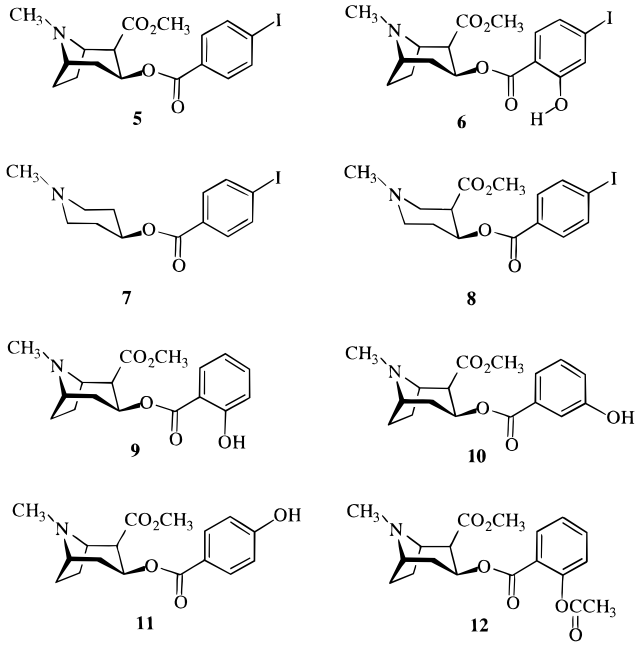
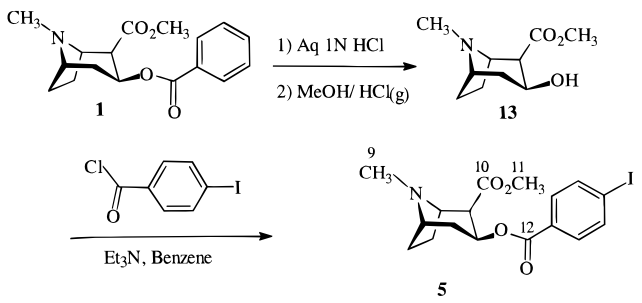


Figure 2.

the C-4′ position of cocaine (**1**) would increase lipophilicity, and subsequently increase brain uptake and possibly binding affinity at the cocaine binding site, (2) iodo-containing phenyltropane (**4**; β-CIT) was more potent than **2** or **3**,[17] and (3) the N−P distance was 10.80 Å, 0.92 and 2.04 Å greater than cocaine (9.88 Å) and β-CIT (8.76 Å), respectively (Figure 3). Compounds **6** and **9** were synthesized because these were less prone to hydrolysis than **5** due to intramolecular hydrogen

Scheme 1



bonding, and consequently were expected to be more stable at the 3β-benzoyl ester. Compounds **7** and **8** were modeled after **5**. In these compounds the N−P distances were essentially the same as in **5**. Compound **12** was an intermediate to compound **9**.

Synthesis

The synthesis of compound **5** was carried out according to the published procedure with modification.[23] Ecgonine methyl ester (**13**) was prepared from crude cocaine hydrochloride by acid-catalyzed hydrolysis followed by esterification with MeOH in the presence of dry HCl gas in quantitative yield. The S_N2 reaction of **13** with 4-iodobenzoyl chloride in the presence of triethylamine to neutralize released acid resulted in the formation of **5** in high yield as shown in Scheme 1. The hydrochloride salt of **5** was very hygroscopic; therefore it was converted into tartaric acid salt by treatment with tartaric acid in absolute EtOH.

The synthesis of 2′-hydroxy-4′-iodococaine (**6**) proceeded from **13** and 2-hydroxy-4-iodobenzoyl chloride

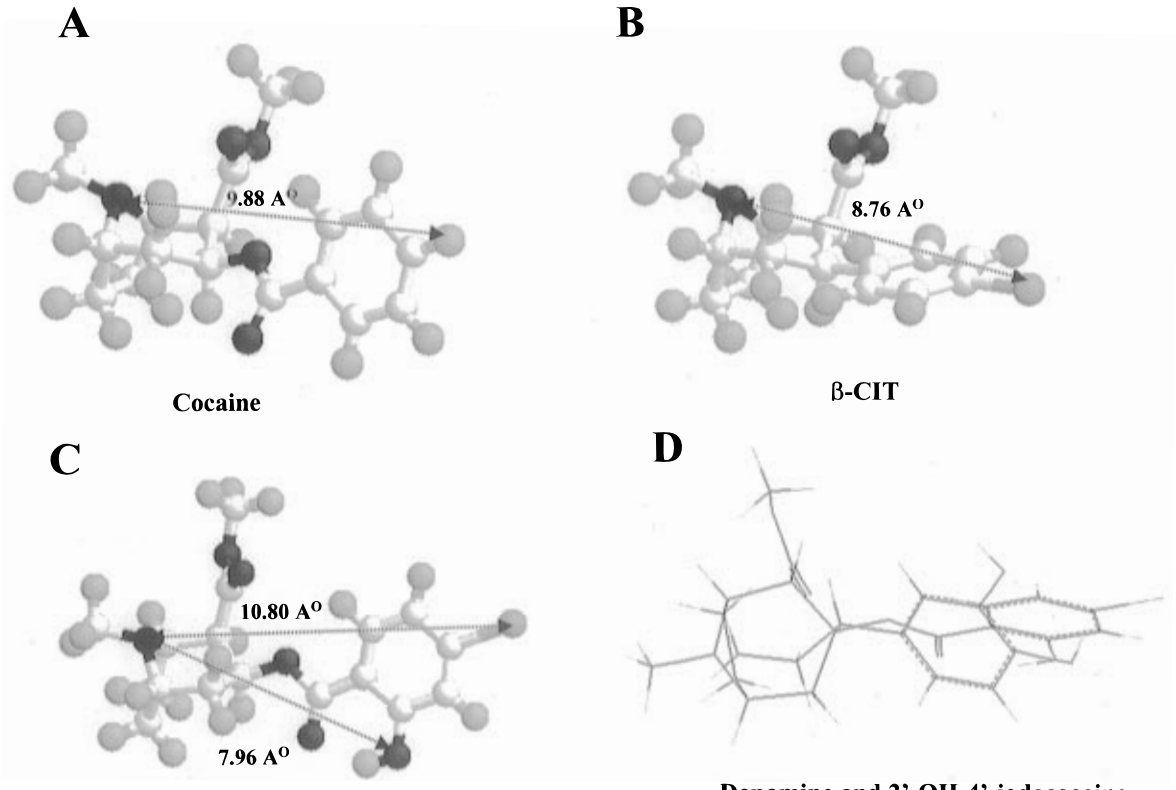
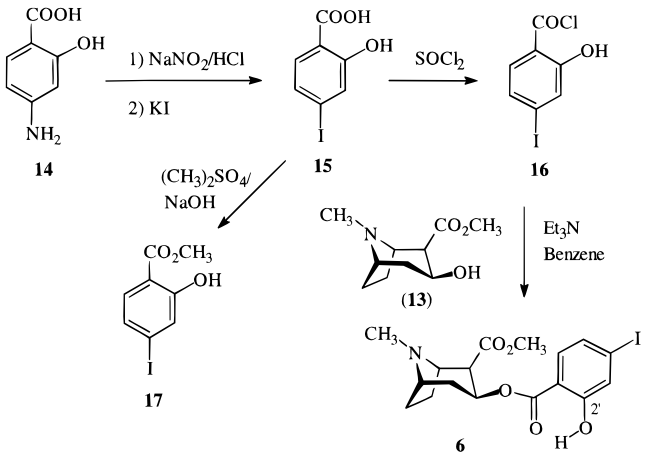
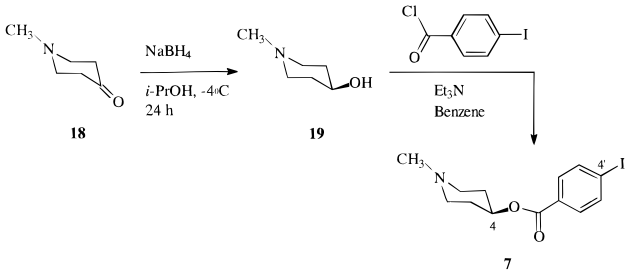


Figure 3. Interatomic distances and relative distribution of atoms in space: (A) bridgehead N to *p*-H of phenyl ring in cocaine (**1**); (B) bridgehead N to *p*-I of phenyl ring in β-CIT (**4**); (C) bridgehead N to *p*-I and *o*-OH of phenyl ring in 2′-hydroxy-4′-iodococaine (**6**); and (D) superimposition of **6** on dopamine.

Scheme 2



Scheme 3

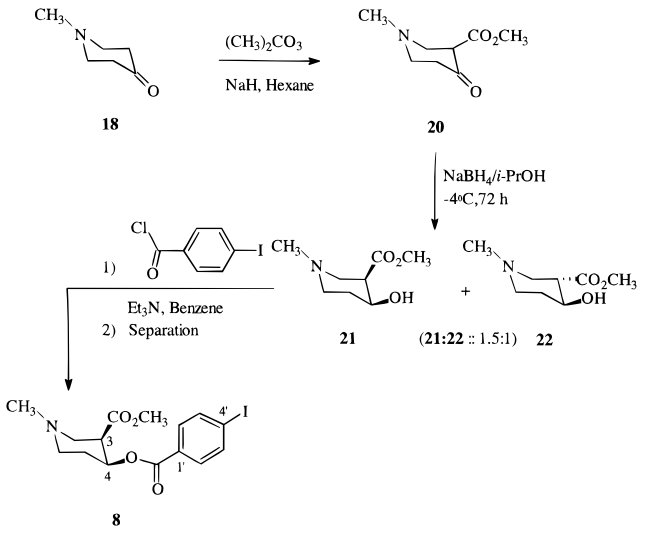


(**16**) as shown in Scheme 2. The commercially available 4-aminosalicylic acid (**14**) was subjected to diazotization followed by aromatic nucleophilic substitution with iodide ion (I^- or I_3^-) generated from KI and concentrated sulfuric acid to give 4-iodosalicylic acid (**15**) in 25% yield.[24] The efforts to alkylate the OH group in **15** with dimethyl sulfate/NaOH were not successful perhaps due to reduced reactivity of the hydroxyl group as a nucleophile due to the presence of an electron-withdrawing group (COOH) in the ortho position and intramolecular hydrogen bonding. The reaction of dimethyl sulfate with **15**, however, gave **17**, in which the only carboxylic acid group was methylated. Therefore, **15** was reacted with thionyl chloride to give acid chloride **16**, which upon reaction with **13** afforded **6** in 22% overall yield. The ^{1}H NMR of **6** and **15** indicated that the OH group in these compounds was indeed hydrogen-bonded as it appeared at 10.75 and 10.39 ppm, respectively (cf. 4.0−7.5 ppm chemical shift for the free phenolic OH group).

Compound **7** was prepared from commercially available 1-methyl-4-piperidone (**18**) in two steps (Scheme 3). Reduction of **18** with $NaBH_4$ in *i*-PrOH at −4 °C gave 1-methyl-4β-piperidinol (**19**) exclusively. This was confirmed by ^{1}H NMR as the proton at C-4 appeared as a broad multiplet at 3.72−3.60 ppm (J = 9.0 Hz), indicating axial−axial coupling with protons at adjacent carbons, C-3 and C-5. Since **18** was relatively unhindered ketone, the approach of the nucleophile (hydride) was expected from the less hindered axial side of the carbonyl group to give an equatorial alcohol (**19**). The alcohol **19** was then reacted with 4-iodobenzoyl chloride to afford **7** without any change in stereochemistry at C-4.

The synthesis of compound **8** proceeded as depicted in Scheme 4. 3-Carbomethoxy-1-methyl-4-piperidone (**20**) was obtained in 60% yield from sodium hydride catalyzed carbomethoxylation of **18**.[25] Since ketone **20**

Scheme 4



was a β-keto ester, it was expected that the $COOCH_3$ group at C-3 in **20** would preferentially remain in an axial position rather than in an equatorial position at equilibrium. Two factors could contribute to the greater stability of the axial $COOCH_3$ group over its equatorial isomer: the dipole−dipole repulsion between the carbonyl function at C-4 and the $COOCH_3$ group at C-3 (or 2-alkyl ketone effect), and reduced synaxial 1,3-interactions due to the presence of a lone pair at N-1.[26] No enol form of **20** was detected in the ^{1}H NMR as there was no resonance in the 8−12 ppm region of the spectrum. The ketone **20** upon reduction with sodium borohydride gave a mixture of two isomers (**21** and **22**). As predicted above, a slight excess of axial $COOCH_3$ group containing alcohol **21** was obtained compared to equatorial $COOCH_3$ group containing alcohol **22** (ratio **21**:**22** = 1.5:1). Attempts to separate the two isomers (**21** and **22**) after converting them into their tartaric acid salts were unsuccessful. Therefore, the mixture of **21** and **22** was acylated with 4-iodobenzoyl chloride, which was accomplished in good yield. The separation of the required isomer (**8**) from its 3β-epimer by column chromatography followed by recrystallization of the tartarate salt from a mixture of methanol/acetone/petroleum ether solvents afforded **8** in 23.1% overall yield.

A convenient synthetic method was developed to prepare 2′-hydroxycocaine (**9**) and 2′-acetoxycocaine (**12**).[27] 2′-Acetoxycocaine (**12**) was synthesized from the reaction of acetylsalicyloyl chloride (**23**) and ecgonine methyl ester, which was then converted into 2′-hydroxycocaine (**9**). The key step in the synthesis of **9** from **12** was selective transesterification of the 2′-acetoxy group, which was accomplished by refluxing **12** in methanol saturated with HCl gas (Scheme 5). No transesterification of the benzoyloxy group was observed under these reaction conditions. 3′-Hydroxycocaine[28] and 4′-hydroxycocaine[22] were synthesized according to previously reported procedures.

Transporter Binding

The effects of cocaine (**1**), 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (**3**, WIN-35428) and eight cocaine analogs on radioligand binding of [^{3}H]-2β-carbomethoxy-3β-(4-fluorophenyl)tropane at the striatal dopamine

Scheme 5

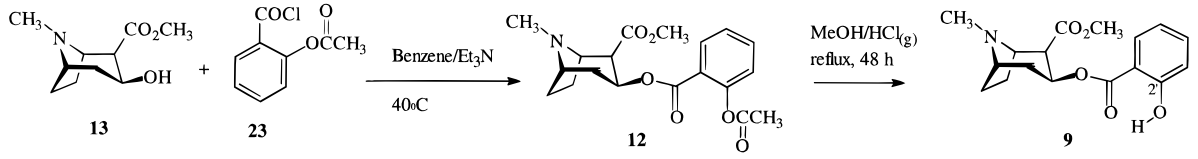


Table 1. Relative Potency of 4′-Iodinated and Hydroxylated Analogs of Cocaine for Displacement of [^{3}H]WIN-35428 from Rat Striatal Membranes

compound	IC_{50} (nM)[a]
WIN-35428	23.6 ± 4
cocaine	249 ± 37
5	2522 ± 4
6	215 ± 19
7	11589 ± 4
8	8064 ± 4
9	25.2 ± 4
10	1183 ± 115
11	153 ± 8
12	69.5 ± 1

[a] IC_{50} values are mean ± SD of two to four replicate determinations.

transporter are shown in Table 1. The potency of cocaine was 10−32 times greater than that of 4′-iodococaine (**5**) and its piperidine homologs (**7**, **8**). 2′-Hydroxy-4′-iodococaine (**6**) was equipotent to cocaine. 2′-Hydoxycocaine (**9**) was 10-fold more potent than cocaine and equipotent to WIN-35428. 3′-Hydoxycocaine (**10**) was 4.75 times less potent than cocaine, and 4′-hydroxycocaine (**11**) was 1.5-fold more potent than cocaine. 2′-Acetoxycocaine (**12**) was 3.58-fold more potent than cocaine.

Molecular Modeling

The molecular modeling studies utilized the Alchemy 2000 (Tripos) and InsightII (Biosym Technologies) software package. Geometry optimizations were performed with the semiemperical quantum mechanics method using PM3 available in the MOPAC program in Alchemy 2000 on a pentium PC. The interatomic distances were measured after an initial full energy minimization. Two hundred steps of energy minimizations were performed on each structure before performing conformational analysis. Following minimum energy conformational analysis, the root-mean-square (RMS) deviation was determined by superimposing lowest energy conformations. For superimposition three atom pairs were picked: three atoms of the cocaine analog (**6**) (bridgehead nitrogen atom, 3β-carbonyl carbon atom attached to the phenyl ring, and oxygen atom of the ortho OH group) and three atoms of dopamine (nitrogen atom, carbon atom of the phenyl ring attached to the side chain, and oxygen atom of the para OH group).

Discussion

The psychostimulant drug cocaine has been shown to inhibit the transport of dopamine. The synthesized compounds were tested for their ability to inhibit [^{3}H]-WIN-35428 binding at the dopamine transporter according to the reported procedure[29] and are shown in Table 1. The binding potency of 4′-iodococaine (**5**) at the dopamine transporter for the displacement of [^{3}H]-WIN-35428 was 10-fold less than that of cocaine. The reduced potency of **5** was unexpected because an iodo group at the para position in phenyltropanes has been shown to increase the potency by a factor of 18.[30] A similar finding was observed in methylphenidate analogs where an iodo group in the aromatic ring increased the potency by a factor of 6.[31] Furthermore, in earlier studies 4′-iodococaine has shown binding potency at par with cocaine (100 vs 70 nM, respectively) for the displacement of [^{3}H]cocaine from rat striatal membranes.[23] It is, however, interesting to note that while an iodo group in phenyltropanes (e.g. **4**) caused dose-related increases in the locomotor activity in mice, with an estimated relative potency at least 10-fold greater than that of cocaine,[20] an iodo group in cocaine (e.g. **5**) caused reduced locomotor activity in mice and on coadministration with cocaine antagonized the motor-stimulating action of cocaine in a dose-dependent manner.[32] Other functional groups, e.g. phenyl and nitro, when added in aromatic ring of cocaine at the para position have also led to reduced locomotor activity stimulation compared to cocaine.[21,22]

The more potent of the analogs was 2′-hydroxy-4′-iodococaine (**6**, Table 1). The binding potency of compound **6** was 11-fold greater than that of 4′-iodococaine (**5**) and the same as that of cocaine. The reason for this difference is unclear. It could be proposed that an OH group at the ortho position would be able to participate in an intramolecular H-bonding, and as a consequence would lock the carbonyl function in the same plane as that of the phenyl ring and also impart stability to the 3β-benzoyl ester functionality toward hydrolysis due to reduced electrophilicity. Further evidence will be required to prove whether an intramolecular H-bonding alone is responsible for such an increase in the binding potency of **6** or some other factors contribute to its high affinity to the dopamine transporter. One of the other factors which can be speculated is the intermolecular H-bonding between **6** and the dopamine transporter. It is known from the site-directed mutagenesis studies that aspartate and serine residues lying within the first and seventh hydrophobic putative transmembrane regions of DAT are crucial for cocaine and dopamine binding.[33] These findings have suggested that aspartic acid residue 79 may engage in an ionic interaction either with dopamine's protonated amino group or with the protonated nitrogen of cocaine in binding to the transporter. Furthermore, serine residues 356 and 359 are involved in H-bonding with the two OH groups of the dopamine molecule, with possibly serine 356 interacting with the meta OH group and serine 359 with the para OH group of the catecholic part of dopamine. Molecular modeling studies with the structures of dopamine and 2′-hydroxy-4′-iodococaine (**6**) showed the interatomic distances between the nitrogen atom and the oxygen atom of the para OH of dopamine and bridgehead nitrogen atom and oxygen atom of the ortho OH group of **6** were 7.83 and 7.96 Å, respectively. The interatomic distance between the nitrogen atom and the oxygen atom of the meta OH group in dopamine is 6.38 Å.

Furthermore, superimposition of **6** on dopamine after minimum-energy conformational analysis indicated a good fit. The RMS was 0.143 (Figure 3). This suggests that the ortho OH group of compound **6** may be involved in an intermolecular H-bonding with serine residue 359 at the dopamine transporter.

To further investigate if the high binding potency of **6** resulted from an intermolecular H-bonding with the serine residues at the dopamine transporter, we studied the dopamine transporter binding affinities of hydroxy-substituted analogs of cocaine. The dopamine transporter binding characteristics of such analogs have not been studied before. As shown in Table 1, 2′-hydroxycocaine (**9**) exhibited a 10-fold greater potency for the dopamine transporter binding compared to that of cocaine (IC_{50} comparable to that of WIN-35428). To find out whether the high binding potency of 2′-hydroxycocaine was structure-specific to its hydroxyl group at C-2′ position or whether the hydroxyl group could be present at any other position in the phenyl ring of cocaine, we studied the binding affinities of 3′- and 4′-hydroxycocaines (**10** and **11**, respectively). 3′-Hydroxylation of cocaine (**10**) reduced the potency by 4.7-fold. 4′-Hydroxycocaine (**11**)[22] and 2′-acetoxycocaine (**12**), on the other hand, were 1.5- and 3.58-fold more potent than cocaine at the dopamine transporter, respectively. Thus 2′-hydroxylation only is capable of increasing potency for the dopamine transporter binding. One of the structural requirements for cocaine binding to dopamine transporter includes the presence of an aryl group connected either directly or indirectly to C-3 and in β-orientation. No 2′-Substituted cocaine analogs have been reported to compare; therefore, it is opening a unique investigation of the role of this position (C-2′) in binding and function of cocaine-like compounds to the dopamine transporter. Further studies directed toward exploring the importance of this new binding site will evaluate this novel finding.

The binding potencies of the piperidine analogs (**7**, **8**) were much weaker than those of cocaine and 4′-iodococaine (**5**). The reason for this decreased binding potency is not apparent because molecular modeling studies showed an N−P distance (interatomic distance between nitrogen atom of piperidine and iodine atom at the para position of the phenyl ring) of 10.80 Å, same as that of 4′-iodococaine and **6**. It could be speculated that the piperidine ring, although containing all the required interactive functionalities as in cocaine, is conformationally less rigid unlike tropane. Its other chair conformation could also exist with functional groups in different configurations, making the entire molecule loosely fit at the active site of the receptor, and leading to poor binding affinity to the dopamine transporter.

Conclusion

In conclusion, syntheses of 4′-iodobenzoyl esters of tropanes and 1-methylpiperidines were accomplished in good yield. The stereochemistry of each step was determined. In contrast to phenyltropanes, an iodo substituent at the 4′-position in cocaine structure reduced the potency for the dopamine transporter. Replacement of the rigid tropane ring with the flexible piperidine ring substantially reduced binding potency. 2′-Hydroxylation increased the potency by 10−11-fold not only of cocaine but also of 4′-iodococaine. Therefore, addition of a hydroxyl group at the C-2′ position of other cocaine congeners, especially those with potential as cocaine antagonists, may lead to high-affinity ligands for the dopamine transporter.

Experimental Section

Benzene and cyclohexane were dried over 5A and 4A types of molecular sieves, respectively. Triethylamine was distilled from CaH_2. Confiscated cocaine hydrochloride was obtained from the National Institute on Drug Abuse. Unless otherwise stated all starting materials were obtained from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. 4-Aminosalicylic acid was obtained from Acros Organics (Pittsburgh, PA). Polylysine was obtained from Sigma Chemical Co. (St. Louis, MO). The HPLC grade solvents were obtained from Fisher Scientific (St. Louis, MO). Silica gel used for the purification of samples refers to 230−400 mesh, 60 Å. Thin layer chromatography (TLC) utilized silica gel plates with fluorescent indicator (Eastman Kodak Co., Rochester, NY).

The melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analysis was performed by Midwest Micro Lab Ltd., Indianapolis, IN. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. Low- and high-resolution FAB-MS was carried out with a VG instruments, ZAB-E spectrometer (Manchester, UK). EIMS was carried out on a Hewlett-Packard GCMS, Model 5895 (Palo Alto, CA).

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo*,*exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Methyl Ester (5): Method 1. To (1*R*)-ecgonine methyl ester (**13**; 0.2 g, 1.0 mmol) free base prepared and purified from acid hydrolysis of (1*R*)-cocaine hydrochloride followed by esterification with methanol in the presence of HCl gas were added benzene (5.0 mL), 4-iodobenzoyl chloride (1.6 g, 6.0 mmol) in 20 mL of benzene, and 2 g of anhydrous Na_2CO_3. The mixture was stirred and heated at reflux for 18 h and cooled to room temperature, and water (20 mL) was added to dissolve the Na_2CO_3. The benzene layer was collected, and the basic aqueous layer was extracted with benzene (3 × 10 mL). The combined benzene layers were extracted with 0.5 N H_2SO_4 (4 × 10 mL). The acid aqueous layers were made basic with 10% aqueous $(NH_4)_2CO_3$ and extracted with diethyl ether (4 × 30 mL). The ether layers were dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo* to yield a clear oil. The hydrochloride salt (1.01 g, 72%) was recrystallized from ethanol and dried under vacuum, mp 141 °C (hygroscopic).

Method 2. (1*R*)-Ecgonine methyl ester free base (**13**; 3.1 g, 15.5 mmol) was dissolved in dry benzene (50 mL), 30 mL of which was distilled off. Dry Et_3N (2.78 mL, 20 mmol) was then added, which was followed by addition of 4-iodobenzoyl chloride (5.0 g; 18 mmol in 15 mL of dry benzene). The reaction mixture was stirred at 40 ± 2 °C for 90 min. It was then cooled, and the contents were transferred to a separatory funnel with $CHCl_3$ (100 mL). The combined organic was washed with cold 5% aqueous Na_2CO_3 solution (4 × 25 mL) and dried over anhydrous Na_2CO_3 and solvent removed under reduced pressure. It was then purified over a SiO_2 column (60 g; EtOAc). A clear viscous oil (5.62 g, 87.4%) was obtained after removal of the solvent. It was then converted into its tartarate salt. The tartaric acid (2.0 g) was dissolved in absolute EtOH (7.0 mL) by heating and added to **5**. A white suspension resulted. The EtOH was removed, and the compound was dissolved in MeOH and precipitated out with ether. A white solid (7.09 g) was obtained, mp 165 °C. The FAB-MS (3-NBA matrix) gave a pseudomolecular ion at *m/e* 430 (MH^+, 99.9%) and a fragment ion at *m/e* 182. Accurate mass measurements on MH^+ gave 430.0500 ($C_{17}H_{21}NO_4I$; calcd 430.0515). ^1H NMR (D_2O): δ 7.73 (d, J = 8.4 Hz, 2H, C(2′,6′)-H), 7.45 (d, J = 8.1 Hz, 2H, C(3′,5′)-H), 5.44−5.35 (m, 1H, C(3)-H), 4.34 (s, 2H, tartaric acid), 4.08−4.05 (m, 1H, C(1)-H), 3.93−3.91 (br m, 1H, C(5)-H), 3.48−3.45 (m, 1H, C(2)-H), 3.45 (s, 3H, OCH_3), 2.72 (s, 3H, NCH_3), 2.36−2.23 (m, 4H, C(4,7)-H_2), 2.09−2.02 (m, 2H, C(6)-H_2) ppm. ^{13}C NMR (D_2O): δ 178.97

(C═O, tartaric acid), 175.78 (C(10)═O), 161.16 (C(12)═O), 140.83 (C-2′,6′), 133.40 (C-3′,5′), 130.54 (C-1′), 104.61 (C-4′), 75.50 (CH, tartaric acid), 67.19 (C-3), 66.48 (C-1), 65.69 (C-5), 55.95 (OCH_3), 48.67 (C-2), 41.46 (NCH_3), 35.21 (C-4), 26.29 (C-7), 25.20 (C-6) ppm. Anal. ($C_{17}H_{21}NO_4I \cdot C_4H_6O_6$) C, H, N, I.

4-Iodosalicylic Acid (15). A suspension of 4-aminosalicylic acid (**14**; 15.3 g, 0.1 mol) in sulfuric acid (100 mL, 14% v/v) was cooled to 5 °C and diazotized by gradual addition of a cold aqueous solution (25 mL) of sodium nitrite (7.0 g, 0.101 mol) at the same temperature. To this suspension was added a cold 1 M sulfuric acid solution (50 mL) of potassium iodide (26 g, 0.156 mol) slowly with stirring so as to control the evolution of N_2. The resultant slurry was heated at 75−95 °C for 20 min and cooled to room temperature when evolution of N_2 completely ceased. The reaction mixture was filtered, and the filtrate was extracted with ether (7 × 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and stripped off under reduced pressure to give 23.0 g of crude product. The dark colored crude product was partially purified over silica gel (100 g, EtOAc). The partially purified compound was dissolved in 10% aqueous NaOH (150 mL) and extracted with ethyl acetate (7 × 50 mL). A dark yellow solid was obtained after removal of the solvent, which was recrystallized from ethyl acetate to give a light yellow solid (6.6 g, 25%). Mp >290 °C dec. EIMS (70 eV, DIP): 263.8 (M^+, $C_7H_5O_3I$). ^{1}H NMR ($CDCl_3$): δ 10.75 (s, 1H, OH), 7.55 (d, J = 8.1 Hz, 1H, C(6)-H), 7.20 (d, J = 1.8 Hz, 1H, C(3)-H), 7.12 (dd, J = 1.8, 8.1 Hz, 1H, C(5)-H) ppm. Anal. ($C_7H_5O_3I$) C, H, I.

4-Iodosalicyloyl Chloride (16). The acid **15** (0.5 g, 1.9 mmol) was dissolved in thionyl chloride (10 mL) and heated to reflux. After 2 h, the reaction mixture was cooled and an excess of thionyl chloride was removed under vacuum to obtain a light yellow oil (0.45 g, 84%) of **16**, which was used without further purification in the next step.

3-[(2′-Hydroxy-4′-iodobenzoyl)oxy]-[1*R*-(*exo*,*exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Methyl Ester (6). Ecgonine methyl ester free base (**13**; 0.3 g, 1.5 mmol) was dissolved in dry benzene (5.0 mL), and dry triethylamine (0.6 mL, 4 molar excess) was added. To this clear solution was added a solution of **16** (0.45 g in 1 mL benzene), and the reaction mixture was stirred at room temperature under dry N_2. After 24 h, the reaction mixture was transferred to a separatory funnel, water (2.0 mL) was added, and the organic layer was separated. The organic layer was further washed with 5% aqueous Na_2CO_3 solution (3 × 2 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent and purification of the crude product over silica gel afforded 0.26 g of a clear oil (39%). The oil was converted into its tartarate salt. Mp: 153 °C. EIMS (70 eV, DIP): 444.9 (M^+; $C_{17}H_{20}NO_5I$). ^{1}H NMR (D_2O): δ 10.39 (s, C(2′)-OH), 7.53 (d, J = 8.1 Hz, C(6′)-H), 7.38 (d, J = 1.8 Hz, 1H, C(3′)-H), 7.23 (dd, J = 1.5, 8.4 Hz, 1H, C(5′)-H) 5.29 (dd, J = 6.0, 14.0 Hz, 1H, C(3)-H), 3.74 (s, 3H, OCH_3), 3.65−3.60 (m, 1H, C(1)-H), 3.34−3.28 (m, 1H, C(5)-H), 3.03−2.98 (m, 1H, C(2)-H), 2.23 (s, 3H, NCH_3), 2.20−1.90 (m, 4H, C(4,7)-H_2), 1.72−1.69 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{17}H_{20}NO_5I \cdot C_4H_6O_6$) C, H, N, I.

1-Methyl-4β-piperidinol (19). 1-Methyl-4-piperidone (**18**; 1.0 g, 7.6 mmol) was dissolved in *i*-PrOH (10 mL), the mixture was cooled, and sodium borohydride (1.0 g, 26.4 mmol) was added. The reaction mixture was kept in the refrigerator (−4 °C) for 24 h with occasional stirring. A part of sodium borohydride remained as solid. The reaction mixture was cooled, concentrated HCl (8 mL) was added slowly, and the *i*-PrOH/HCl mixture was removed under vacuum. The solid residue was dissolved in water (10 mL), basified with solid NaOH (pH 12.0), saturated with NaCl, and extracted with dichloromethane (8 × 10 mL) to afford an oil (0.7 g, 69.3%). ^{1}H NMR ($CDCl_3$): δ 3.72−3.60 (ddd, J = 15.0, 9.0, 3.6 Hz, 1H, C(4)-H), 2.76−2.64 (m, 2H, C(2,6)-H_{eq}), 2.61 (s, 3H, NCH_3), 2.48−2.34 (br, 1H, OH), 2.18−2.04 (m, 2H, C(2,6)-H_{ax}), 1.93−1.80 (m, 2H, C(3,5)-H_{eq}), 1.68−1.52 (m, 2H, C(3,5)-H_{ax}) ppm.

1-Methyl-4β-[(4′-iodobenzoyl)oxy]piperidine (7). 1-Methyl-4β-piperidinol (**19**, 1.9 g, 14.28 mmol) and triethylamine (2.78 mL, 20 mmol) were dissolved in 40 mL of dry benzene, and 4-iodobenzoyl chloride (4.26 g, 16 mmol) was added in one lot. The resulting reaction was stirred under dry N_2 at room temperature. After 48 h, the reaction mixture was washed with water (10 mL), 5% aqueous Na_2CO_3 (3 × 10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain a solid, which was recrystallized from $CHCl_3$/benzene in 68.1% yield (3.53 g), mp 130 °C: FAB-MS (3-NBA matrix) showed a pseudomolecular ion $(M + H)^+$ at m/e = 346.0 (100%). The high-resolution mass measurements on MH^+ gave m/e = 346.0272 ($C_{13}H_{17}NO_2I$; calcd m/e = 346.0305). ^{1}H NMR ($CDCl_3$): δ 7.81 (d, J = 8.4 Hz, 2H C(2′,6′)-H), 7.75 (d, J = 8.4 Hz, 2H, C(3′,5′)-H), 5.10−5.00 (m, 1H, C(4)-H), 2.75−2.65 (m, 2H, C(2,6)-H_{eq}), 2.40−2.30 (m, 2H, C(2,6)-H_{ax}), 2.33 (s, 3H, NCH_3), 2.08−1.98 (m, 2H, C(3,5)-H_{eq}), 1.93−1.80 (m, 2H, C(3,5)-H_{ax}) ppm. Anal. ($C_{13}H_{16}NO_2I$) C, H, N, I.

1-Methyl-3-carbomethoxy-4-piperidone (20). To a suspension of NaH (60% dispersion, 11.83 g, 0.296 mol) in dry hexane (60 mL) and dimethyl carbonate (27.4 mL, 0.325 mol) was added 1-methyl-4-piperidone (**18**; 16.7 g, 0.148 mol) in dry cyclohexane (140 mL) dropwise while maintaining gentle reflux. After ∼30 mL of addition, a vigorous reaction ensued with evolution of H_2. Heat was removed, and the rest of **18** was added (total addition time 3.5 h). MeOH (0.5 mL) was added at the end of addition. The reaction mixture was heated at reflux until effervescence ceased (2 h). Water (150 mL) was added after the reaction mixture was cooled to room temperature. The layers were separated, and the cyclohexane layer was washed with additional water (2 × 100 mL). The combined aqueous layers were saturated with NH_4Cl (64.0 g) and extracted with CH_2Cl_2 (8 × 100 mL). All of the organic layers (including cyclohexane) were dried over Na_2CO_3 and concentrated in vacuo to yield 22.1 g (90%) of an oil. The crude product was purified over a silica gel column (200 g, CH_2Cl_2/EtOAc, 100:1 to 1:100) to afford 13.0 g of a clear oil of **20** (59.6%). ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, OCH_3), 3.12 (t, J = 1.7 Hz, 1H, C(3)-H), 2.85−2.63 (m, 3H, C(2)-H_2, C(6)-H_{eq}), 2.50−2.42 (m, 3H, C(5)-H_2, C(6)-H_{ax}), 2.41 (s, 3H, NCH_3) ppm. Anal. ($C_8H_{12}NO_3$) C, H, N.

1-Methyl-3β-carbomethoxy-4β-piperidinol (21) and 1-Methyl-3α-carbomethoxy-4β-piperidinol (22). The ketone **20** (12.0 g, 70.1 mmol) was dissolved in 150 mL of *i*-PrOH and cooled, and solid sodium borohydride (4.25 g, 115 mmol) was added. The resulting reaction mixture was left in the refrigerator for 3 days. Cold concentrated HCl (30 mL) was added slowly, and the *i*-PrOH/HCl mixture was removed under vacuum. The solid residue was dissolved in water (50 mL), neutralized with NH_4OH, and repeatedly extracted with $CHCl_3$ (25 × 50 mL). The combined organic layers were dried over anhydrous Na_2CO_3 and stripped off at reduced pressure to obtain 6.1 g (50%) of a light yellow oil. The ^{1}H NMR spectrum showed two sets of resonances with the integral ratio of 1.5:1. The resonances were then assigned based on literature precedence[25] and selective decoupling experiments. The following resonances were assigned to **21** ($CDCl_3$): δ 4.18−4.15 (m, 1H, C(4)-H), 3.74 (s, 3H, OCH_3), 3.13−3.08 (m, 1H, C(3)-H), 2.96−2.92, 2.92−2.88 (m, 2H, C(2,6)-H_{eq}), 2.68−2.55 (m, 2H, C(2,6)-H_{ax}), 2.50−2.40 (m, 2H, C(5)-H_2), 2.30 (s, 3H, NCH_3) ppm.

The resonances for **22** appeared at δ 4.25−4.20 (m, 1H, C(4)-H), 3.74 (s, 3H, OCH_3), 3.10−3.05 (m, 1H, C(3)-H), 2.85−2.82, 2.80−2.76 (m, 2H, C(2,6)-H_{eq}), 2.68−2.55 (m, 2H, C(2,6)-H_{ax}), 2.50−2.40 (m, 2H, C(5)-H_2), 2.31 (s, 3H, NCH_3) ppm. Anal. ($C_8H_{14}NO_3$) C, H, N. Attempts to separate the mixture of **21** and **22** by fractional crystallization after converting them into their tartaric acid salts were not successful.

1-Methyl-3β-carbomethoxy-4β-[(4′-iodobenzoyl)oxy]piperidine (8). A mixture of **21** and **22** (ratio 1.5:1) (6.1 g, 35.2 mmol) in 50 mL of dry benzene was added to a stirred solution of 4-iodobenzoyl chloride (9.939 g, 39.0 mmol) and triethylamine (7.0 mL, 50 mmol) in 20 mL of dry benzene. The reaction mixture was stirred at room temperature under dry N_2. After 48 h, 5% aqueous Na_2CO_3 solution (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was repeatedly extracted with $CHCl_3$ (10 × 50 mL). The combined organic layers were dried over anhydrous Na_2CO_3 and concentrated *in vacuo* to give 12.0 g (84.5%) of dark brown oil. The ^{1}H NMR of the crude product

showed it to be a mixture of **8** and its C-3 epimer. The purification and separation of the mixture of two isomers over silica gel (200 g, $CHCl_3$/EtOAc, 100:1 to 70:30) afforded 1.98 g (23.1% based on the percent of **21**) of an oil of **8**. FAB-MS (3-NBA matrix) showed a pseudomolecular ion $(M + H)^+$ at $m/e = 404.0$ (100%). The exact mass measurements on MH^+ gave $m/e = 404.0361$ ($C_{15}H_{19}NO_4I$; calcd $m/e = 404.0359$). ^1H NMR ($CDCl_3$): δ 7.81 (dd, $J = 1.8$, 8.7 Hz, 2H C(2′,6′)-H), 7.74 (dd, $J = 1.8$, 8.7 Hz, 2H, C(3′,5′)-H), 5.31−5.21 (m, 1H, C(4)-H), 3.66 (s, 3H, OCH_3), 3.00−2.91 (m, 2H, C(2,6)H_{eq}), 2.82−2.77 (m, 1H, C(3)-H), 2.48−2.38 (m, 1H, C(2)-H_{ax}), 2.34 (s, 3H, NCH_3), 2.28−2.22 (m, 1H, C(6)-H_{ax}), 2.22−2.15 (m, 1H, C(5)-H_{eq}), 1.82−1.72 (m, 1H, C(5)-H_{ax}) ppm. The oil was converted into the tartarate salt in quantitative yield, mp 158 °C. Anal. ($C_{15}H_{18}NO_4I \cdot C_4H_6O_6$) C, H, N, I.

3-[(2′-Acetoxybenzoyl)oxy]-[1*R*-(*exo*,*exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Methyl Ester (12). Ecgonine methyl ester free base (**13**; 0.9 g, 4.5 mmol) was dissolved in dry benzene (15 mL), and triethylamine (1 mL, 10 mmol) was added. To this stirred solution was added commercially available acetylsalicyloyl chloride (**23**; 1.4 g, 7.0 mmol) under dry N_2. The resulting reaction mixture was stirred at 40 °C overnight. The reaction was stopped, and the product was washed with water (5.0 mL) and 5% aqueous Na_2CO_3 solution (3 × 5.0 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum to give an oil. The oily product was dissolved in ether and dry HCl gas passed to obtain hydrochloride salt of **12** (1.24 g, 76%). Mp: 78−80 °C. FAB/MS (3-NBA matrix): 362.1 (MH^+; $C_{19}H_{24}NO_6$). ^1H NMR (D_2O): δ 7.78 (dd, $J = 8.4$, 1.2 Hz, 1H, C(6′)-H), 7.58−7.48 (m, 1H, C(4′)-H), 7.26 (d, $J = 8.7$ Hz, 1H, C(5′)-H), 7.05 (d, $J = 8.7$ Hz, 1H, C(3′)-H), 5.38−5.28 (m, 1H, C(3)-H), 4.07−4.01 (m, 1H, C(1)-H), 3.93−3.87 (m, 1H, C(5)-H), 3.46−3.40 (m, 1H, C(2)-H), 3.45 (s, 3H, OCH_3), 2.69 (s, 3H, NCH_3), 2.18 (s, 3H, C(2′)-$COCH_3$), 2.35−2.25 (m, 4H, C(4,7)-H_2), 2.05−1.95 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{19}H_{23}NO_6 \cdot HCl \cdot 2H_2O$) C, H, N.

3-[(2′-Hydroxybenzoyl)oxy]-[1*R*-(*exo*,*exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Methyl Ester (9). 2′-Acetoxycocaine hydrochloride (**12**; 0.9 g, 2.5 mmol) was dissolved in 40 mL of MeOH, and dry HCl gas was passed. The resulting solution was refluxed with stirring for 48 h. It was then cooled, and solvent was removed under vacuum to obtain a white solid of **9** (0.75 g, 94%). Mp: 104 °C. FAB/MS (3-NBA matrix): 320.1 (MH^+; $C_{17}H_{22}NO_5$). ^1H NMR (D_2O): δ 7.58 (dd, $J = 7.8$, 1.5 Hz, 1H, C(6′)-H), 7.44−7.34 (m, 1H, C(4′)-H), 6.88−6.80 (m, 2H, C(3′,5′)-H), 5.52−5.42 (m, 1H, C(3)-H), 4.10−4.05 (m, 1H, C(1)-H), 3.95−3.90 (m, 1H, C(5)-H), 3.52−3.47 (m, 1H, C(2)-H), 3.46 (s, 3H, OCH_3), 2.70 (s, 3H, NCH_3), 2.35−2.20 (m, 4H, C(4,7)-H_2), 2.10−2.02 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{17}H_{21}NO_5 \cdot HCl \cdot 1/2H_2O$) C, H, N.

Transporter Potency. Binding of analogs to the dopamine transporter was determined by displacement of [^{3}H]WIN-35428 binding to rat striatal membranes according to published procedure.[29] Briefly, whole brain was rapidly harvested from rats (300 g male Sprague-Dawley, Sasco Inc.) following decapitation with a guillotine. The striatum was isolated on ice, and P2 striatal membranes were prepared from fresh tissue and used immediately. Each assay tube contained buffer (35 mmol of sodium phosphate, pH 7.4, 120 μL) or buffer plus 10 μL of unlabeled test compound (drug concentrations ranging from 1×10^{-10} to 1×10^{-4} mol), [^{3}H]WIN-35428 in the same buffer (20 μL, 4 nmol), and membranes (50 μL, final concentration 4 mg mL^{-1}) to a total volume of 200 μL. Assay points were conducted in triplicate. Incubation was carried out for 2 h in an ice−water bath. The binding reaction was terminated by rapid filtration through Whatman GF/B glass fiber filters presoaked for 30 min in 0.05% polylysine followed by rapid washing of the filters three times with ice-cold buffer. Cocaine (100 μmol) was used to determine nonspecific binding.

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References

(1) Withers, N. W.; Pulvirenti, L.; Koob, G. F.; Gillin, J. C. Cocaine abuse and dependence J. *Clin. Psychopharmacol.* **1995**, *15*, 63−78.
(2) Johnson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. *Pharmacol. Rev.* **1989**, *41*, 3−52.
(3) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991**, *14*, 299−302.
(4) Robinson, T.; Barridge, K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Rev.* **1993**, *18*, 249−291.
(5) Ritz, M. C.; Lamb, R. J.; Goldberg, R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223.
(6) Giros, B.; Jaber, M.; Jones, S. R.; Wightman, R. M.; Caron, M. G. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* **1996**, *379*, 606−612.
(7) Witkin, J. M. Pharmacotherapy of cocaine abuse: preclinical development. *Neurosci. Behav. Rev.* **1994**, *18*, 121−142.
(8) Tutton, C. S.; Crayton, J. W. Current pharmacotherapies for cocaine abuse: a review. *J. Addict. Dis.* **1993**, *12*, 109−127.
(9) Kotian, P.; Mascarella, S. W.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis, ligand binding, and quantitative structure−activity relationship study of 3β-(4′-substituted phenyl)-2β-heterocyclic tropanes: evidence for an electrostatic interaction at the 2β position. *J. Med. Chem.* **1996**, *39*, 2753−2763.
(10) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; KuharM. J. Synthesis, ligand binding, QSAR, and CoMFA study of 3β-(p-substituted phenyl)-tropane-20-carboxylic acid methyl esters. *J. Med. Chem.* **1991**, *34*, 2719−2725.
(11) Meltzer, P. C.; Lian, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras B. K. Substituted 3β-phenyltropane analogs of cocaine: synthesis, inhibition of binding at cocaine recognition sites, and positron emission tomography imaging. *J. Med. Chem.* **1993**, *36*, 855−862.
(12) 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 3β-(4-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogs. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, *38*, 379−388.
(13) Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergman, J. S.; Ball, R. G. Methoxylation of cocaine reduces binding affinity and produces compounds of differential binding and dopamine uptake inhibitory activity: discovery of a weak cocaine antagonist. *J. Med. Chem.* **1993**, *36*, 3975−3977.
(14) Scheffel, U.; Boja, J. W.; Kuhar, M. J. Cocaine receptors: in viva labeling with [^{3}H]-(−)-cocaine, [^{3}H] WIN 35,065-2 and [^{3}H]WIN 35,428. *Synapse* **1989**, *4*, 390−392.
(15) Madras, B. K.; Spealman, R. D.; Fahey, M. A. Cocaine receptors labeled by [^{3}H]-2-carbomethoxy-3-(4-fluorophenyl)tropane. *Mol. Pharmacol.* **1989**, *36*, 518−124.
(16) Boja, J. W.; Patel, A.; Carroll, F. I.; Rahman, M. A.; Philip, A.; Lewin, A. H.; Kopajtic, T. A.; Kuhar, M. J. [^{125}I]RTI-55: a potent ligand for dopamine transporters. *Eur. J. Pharmacol.* **1991**, *194*, 133−134.
(17) Neumeyer, J. L.; Wang, S.; Milius, R. A.; Balwin, R. M.; Zeaponce, Y.; Hoffer, P. B.; Symbirska, E.; Al-Tikriti, M.; Charney, D. S.; Malison, R. T.; Laruelle, M.; Innis, R. B. [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane: high affinity SPECT radiotracer of monoamine reuptake sites in brain. *J. Med. Chem.* **1991**, *34*, 3144−3146.
(18) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: biochemical characterization and structure−activity relationships of cocaine analogues at the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969−981.
(19) Tolliver, B. K.; Carney, J. M. Locomotor stimulant effects of cocaine and novel cocaine analogs in DBA/2J and C57BL/6J inbred mice. *Pharmacol. Biochem. Behav.* **1995**, *50*, 163−169.
(20) Fleckenstein, A. E.; Kopajtic, T. A.; Boja, J. W.; Carroll, F. I.; Kuhar, M. J. Highly potent cocaine analogs cause long-lasting increases in locomotor activity. *Eur. J. Pharmacol.* **1996**, *311*, 109−114.
(21) Seale, T. W.; Niekrasz, I.; Chang, F.; Singh, S.; Basmadjian, G. P. Selective behavioral alterations on addition of a 4′-phenyl group to cocaine. *NeuroReport* **1996**, *7*, 617−621.
(22) Seale T. W.; Sastrodjojo, B.; Niekrasz, I.; Singh, S.; Avor, K.; Basmadjian, G. P. 4′-NO_2- and OH-substituted cocaine differ behaviorally and neurochemically. *NeuroReport*, in press.
(23) Yu, D.-W.; Galley, S. J.; Wolf, A. P.; Macgregor, R. R.; Dewey, S. L.; Fowler, J. S.; Schlyer, D. J. Synthesis of carbon-11 labeled iodinated cocaine derivatives and their distribution in baboon brain measured using positron emission tomography. *J. Med. Chem.* **1992**, *35*, 2178−2183.

(24) Carey, J. G.; Millar, I. T. Formation and stability of aryldiazonium iodides and triiodides. *Chem. Ind. (London)* **1960**, 97.
(25) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. The discovery of an unusually selective and novel cocaine analog: difluoropine. Synthesis and inhibition of binding at cocaine recognition sites. *J. Med. Chem.* **1994**, *37*, 2001−2010.
(26) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 665−834.
(27) Smith, R. M. Arylhydroxymetabolites of cocaine in the urine of cocaine users. *J. Anal. Toxicol.* **1984**, *8*, 35−37.
(28) Tamagnan, G.; Gao, Y.; Bakthavachalam, V.; White, W. L.; Neumeyer, J. L. An efficient synthesis of m-hydroxycocaine and m-hydroxybenzoylecgonine, two metabolites of cocaine. *Tetrahedron Lett.* **1995**, *36*, 5861−5864.
(29) Reith, M. E. A.; Coffey, L. L. Cationic and anionic requirements for the binding of 2β-carbomethoxy-3β-(4-fluorophenyl)[^{3}H]-tropane to the dopamine uptake carrier. *J. Neurochem.* **1993**, *61*, 167−177.
(30) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3β-(3′-substituted phenyl)-, 3β-(4′-substituted phenyl)-, and 3β-(3′,4′-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.
(31) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. Synthesis and pharmacology of potential cocaine antagonists. 2. Structure−activity relationship studies of aromatic ring-substituted methylphenidate analogs. *J. Med. Chem.* **1996**, *39*, 1201−1209.
(32) Basmadjian, G. P.; Seale, T. W.; Chang, F.; Zhang, Y.; Sastrodjojo, B.; Singh, S.; Avor, K. S.; Mills, S. L. A novel cocaine analog, 4′-iodococaine (4-IC), selectively blocks cocaine's action and binding at the dopamine transporter. ACS National Meeting, Anaheim, CA; Div. of Med. Chem. Poster No. 208, 1995.
(33) Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D. M.; Uhl, G. R. Dopamine transporter site-directed mutations differentially alter substrate transport and cocaine binding. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7782−7785.

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