2β-Substituted Analogues of 4′-Iodococaine: Synthesis and Dopamine Transporter Binding Potencies

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A series of 2β-substituted analogues of 4′-iodococaine (**3**) was synthesized and evaluated in an in vitro dopamine transporter (DAT) binding assay. Selective hydrolysis at the 2β-position of **3** gave the carboxylic acid **15** that served as the intermediate for the synthesis of compounds **4**, **5**, and **6**−**11**. The 2β-alkyl derivatives were obtained from ecgonine methyl ester (**17**) through a series of reactions leading to the aldehyde **20**. Wittig reaction of **20** with methyltriphenylphosphorane followed by hydrogenation and benzoylation gave the products **12** and **13**. The binding affinity of 4′-iodococaine (**3**) was 10-fold less than that of cocaine. The hydroxymethane, acetate, amide, benzyl ester, oxidazole, and ethane derivatives of **3** exhibited decreased binding while the vinyl, phenyl, and ethyl esters showed a moderate increase in binding affinity. Only the isopropyl derivative **8** exhibited a 2-fold increase in binding affinity compared with 4′-iodococaine (**3**). Hydroxylation of **8** at the 2′-position gave **14** which enhanced not only the binding potency at the DAT by another 2-fold but also the selectivity at the DAT over the norepinephrine and serotonin transporters. Compound **14** failed to stimulate locomotor activity in C57BL/6J mice over a wide dose range and blocked cocaine-induced locomotor stimulant action.

Introduction

Cocaine (**1**, Figure 1), a naturally occurring local anesthetic first isolated from the coca leaves (*Erythroxylon coca*) has been recognized to be a potent central nervous stimulant and binds to specific sites in the mammalian brain.[1−5] The behavioral effects of cocaine are characterized by reinforcement of responding and drug seeking,[6,7] drug discrimination ability,[7,8] and locomotor activity stimulation.[9] While cocaine inhibits the neuronal uptake of dopamine,[10] serotonin,[11] and noradrenaline,[12] the rewarding properties of cocaine clearly require activation of the dopaminergic system. Because of the need to curb the current epidemic of cocaine usage, considerable effort has been expended to finding a better understanding of the chemistry and pharmacology of this drug. Improved understanding of the complex neuropharmacological mechanisms underlying the addictive action of cocaine[6−8] and the limited success of current therapies for cocaine addiction[13] have led to the search for direct-acting cocaine antagonists.[8,14,15]

Earlier, we reported that 4′-iodococaine (**3**, Figure 1) possessed reduced locomotor activity in mice and reduced dose-dependent cocaine-induced locomotor stimulation when coadministered with cocaine.[16] Although the binding potency of **3** was 10-fold less than that of cocaine, the in vivo biological profile stimulated our interest in modifying the structure of 4′-iodococaine in such a way as to obtain analogues that might increase the binding potency at the dopamine transporter (DAT) (Figure 2). The choice of different substituents at the 2β-position was based on literature precedence, as these functionalities have led to improved binding affinities and transporter selectivities in the phenyltropanes.[17−20] Compound **14** was synthesized on the basis of our observation that 2′-hydroxylation increased binding affinities of cocaine and 4′-iodococaine to the DAT by 10−11-fold.[21]

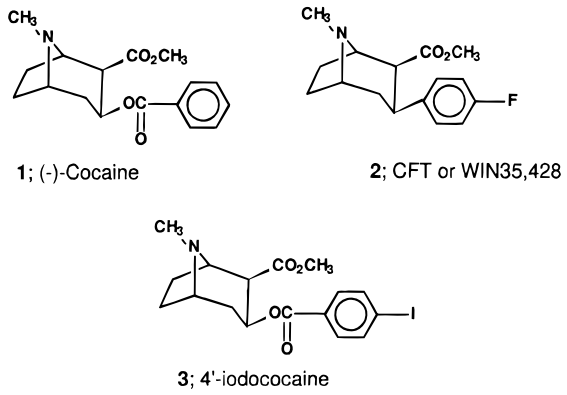

Figure 1.

Chemistry

The synthesis of 4′-iodococaine (**3**) followed the published procedure with some modification.[21] Procedures used for the synthesis of compounds **4**−**11** are summarized in Scheme 1. Hydrolysis of **3** by refluxing in water gave 4′-iodobenzoylecgonine (**15**), which was reduced with diborane to obtain the 2β-methanol **4**. The alcohol **4** was treated with acetic anhydride to give the acetate **5**. Treatment of **15** with *N*,*N*-formyldiimidazole or oxalyl chloride gave the imidazolide **16a** or the acid chloride **16b**, respectively.[17] The *N*-methylamide **6** was prepared by treating **16a** with a mixture of methylamine hydrochloride and sodium carbonate. By treating

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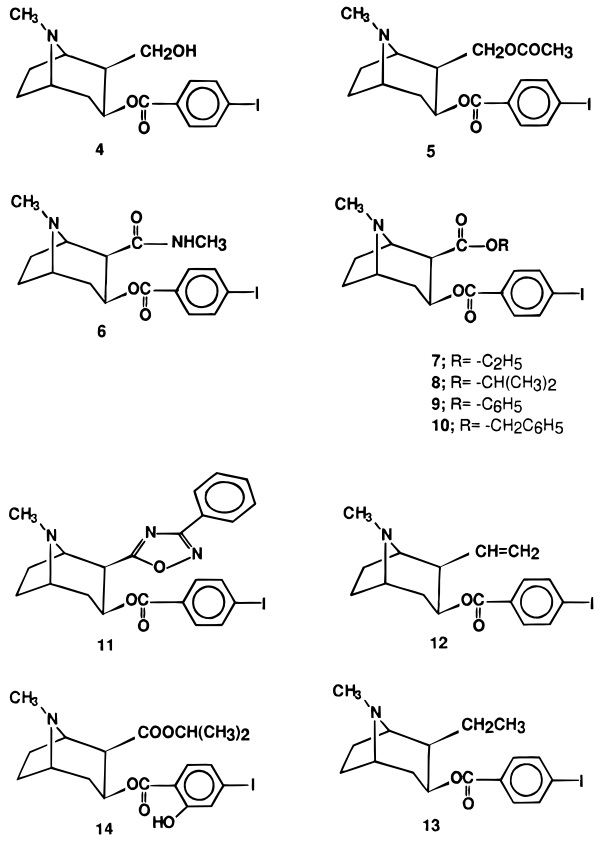


Figure 2.

16a or **16b** with the appropriate alcohols, the esters **7**−**10**[17] were obtained. The 3-aryl-1,2,4-oxadiazole **11** was obtained by treating **16b** with benzamidoxime.[18]

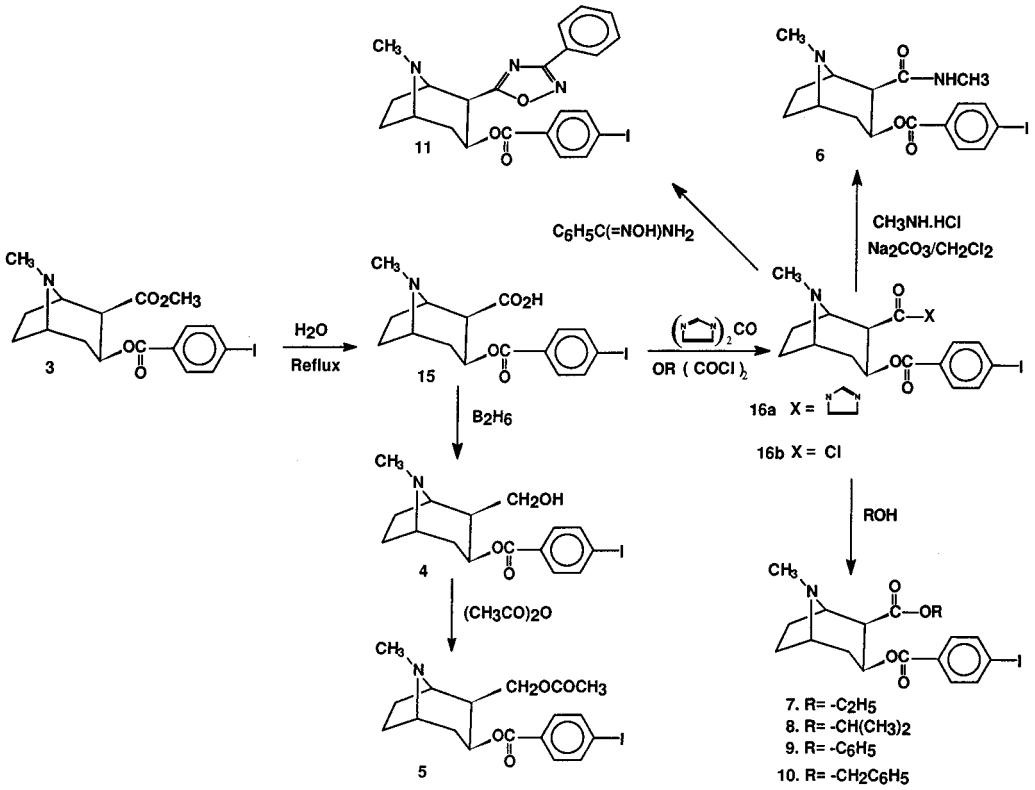
Scheme 2 summarizes the synthesis of compounds **12** and **13**. Ecgonine methyl ester (**17**) was treated with *tert*-butyldimethylsilyl chloride and imidazole by modification of a published procedure[22] to give the protected ester **18**. The ester **18** was reduced with Dibal-H[20] to give the 2β-methanol **19**, which was subjected to Swern oxidation[23] using DMSO and oxalyl chloride in CH_2Cl_2 at −78 °C to obtain the aldehyde **20**. The unstable aldehyde **20** was not purified but converted into the alkene **21**[20] by a Wittig reaction using methyltriphenylphosphorane generated in situ from methyltriphenylphosphonium bromide and butyllithium in THF. The *tert*-butyldimethylsilyl protecting group was removed from the resulting alkene **21** with 75% acetic acid to obtain the 3β-alcohol **22**. Addition of 4-iodobenzoyl chloride to **22** gave the benzoylated alkene **12**. Attempts to reduce **12** to an alkane via catalytic hydrogenation resulted in a hydrodehalogenated product. The deprotected alkene **22** was reduced by catalytic hydrogenation to the 2β-ethane **23** and then treated with 4-iodobenzoyl chloride to obtain the iodobenzoyl alkane **13**.

In Scheme 3, ecgonine (**24**) was reacted with 2-propanol in an acid-catalyzed esterification and then benzoylated with 4-iodosalicyloyl chloride[21] to give the 2′-hydroxylated 2β-isopropyl ester **14**.

Results

The 4′-iodococaine analogues were tested for their ability to displace [^{3}H]WIN 35,428 (**2**, Figure 1), and the IC_{50} values for inhibiting 4 nM of radioligand binding to the DAT are listed in Table 1. As apparent from the table, most of the analogues have low binding affinity compared with the lead compound **3** except esters **7**, **8**, and **9** and the unsaturated analogue **12**. The isopropyl ester **8** showed approximately a 2-fold increase in binding affinity compared to that of **3**, but it was still lower than that of cocaine (249 ± 37 nM). Apparently

Scheme 1



Scheme 2

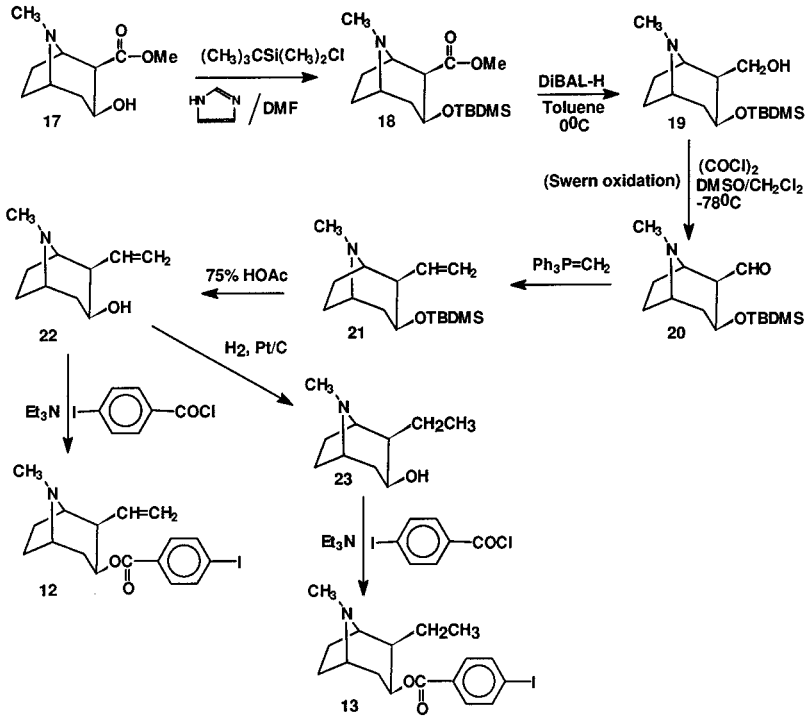
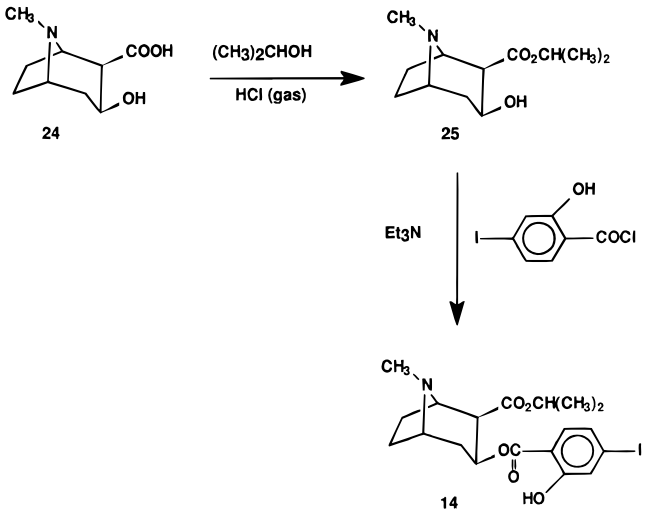


Table 1. Dopamine Transporter Binding Affinities of 4′-Iodococaine Analogues

compound	IC_{50} (nM)[a]	compound	IC_{50} (nM)[a]
cocaine (**1**)	249 ± 37	**8**	1377 ± 10
WIN 35428 (**2**)	24 ± 4	**9**	2019 ± 253
3	2522 ± 4	**10**	4602 ± 325
4	6214 ± 1269	**11**	3459 ± 60
5	2995 ± 223	**12**	2165 ± 253
6	>100000	**13**	2692 ± 486
7	2031 ± 190	**14**	663 ± 70

[a] Data are mean ± standard error of mean (SEM) of two to three experiments performed in triplicate.

Scheme 3



a variety of ester groups at the 2β-position can be accommodated without substantially altering the binding affinity. A further 2-fold enhancement in binding affinity was observed for the 2′-hydroxylated derivative **14**. In contrast to 2′-hydroxycocaine, 4′-iodococaine, and 2′-hydroxy-4′-iodococaine, compound **14** showed decreased binding affinities for the norepinephrine and serotonin transporters with NE/DA and 5-HT/DA ratios of 53 and 7, respectively (Table 2).

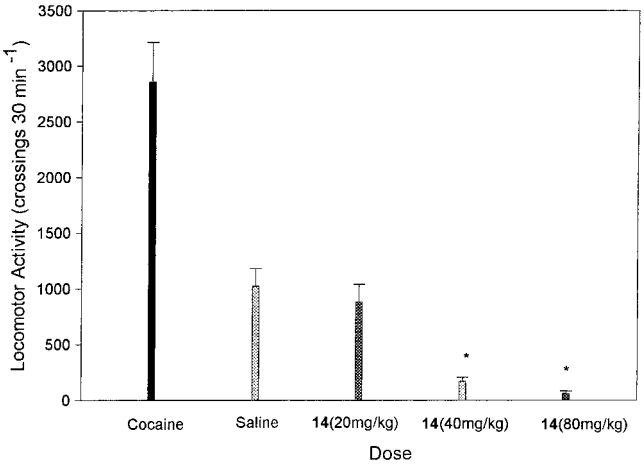


Figure 3. Locomotor activity of compound **14** and of cocaine (20 mg/kg). Values are mean ± sem of six different mice for each drug dosage. *$p < 0.05$ for decreased locomotor activity compared with saline-treated mice (Tukey-Kramer multiple comparisons test).

Compound **14** failed to stimulate locomotor activity at a molar equivalent dose of cocaine from 10 to 110 mg/kg (Figure 3). The effect of coadministration of compound **14** and cocaine on locomotor activity was also investigated to determine how effective this compound is in blocking the stimulant action of cocaine. It antagonized the locomotor stimulant action of cocaine (20 mg/kg) at a low dose of 10 mg/kg with no change in reduction up to 80 mg/kg. A significant reduction in locomotor activity was observed at a dose of 110 mg/kg (Figure 4).

Discussion

The replacement of the carbomethoxy group of **3** with a methylenehydroxy group (**4**) resulted in a 2.5-fold loss

Table 2. Binding Affinity of Analogues at Dopamine, Norepinephrine, and Serotonin Transporters

compound	IC_{50} (nM)[a] dopamine* transporter	norepinephrine** transporter	serotonin*** transporter	NE/DA ratio	5-HT/DA ratio
cocaine (**1**)	249 ± 37	2500 ± 70	615 ± 120	10.0	4.1
WIN 35,428	24 ± 4	258 ± 40	690 ± 16	10.7	28.8
2′-hydroxycocaine	25 ± 4	48 ± 2	143 ± 21	1.9	5.7
4′-iodococaine	2522 ± 4	18458 ± 1073	1052 ± 23	7.3	0.4
2′-hydroxy-4′-iodococaine	215 ± 19	1021 ± 75	195 ± 10	4.7	0.9
14	663 ± 1	34838 ± 796	4507 ± 13	52.5	6.8

[a] IC_{50} values are mean ± standard error of mean (SEM) of two to three experiments performed in triplicates. Radioligand used: *[^{3}H]WIN 35,428, **[^{3}H]nisoxetine, and ***[^{3}H]paroxetine.

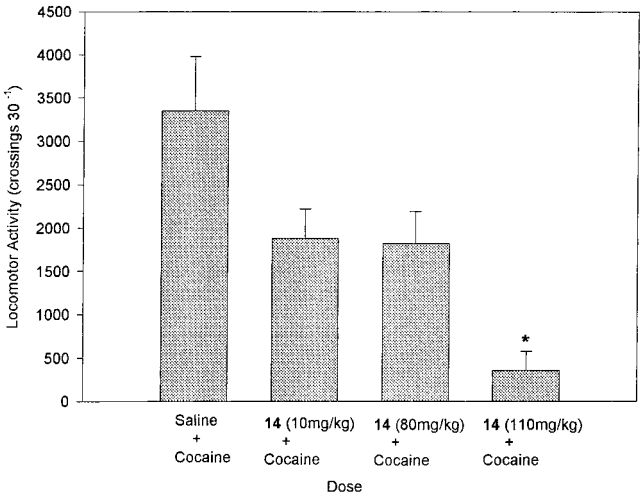


Figure 4. Coadministration of various doses of compound **14** and locomotor stimulating dose of cocaine (20 mg/kg). Values are mean ± sem of six different mice for each drug dosage. *p < 0.05 for decreased locomotor activity compared with cocaine-treated mice (Tukey-Kramer multiple comparisons test).

of binding potency compared with the parent compound **3**. Conversion of the alcohol to the acetate **5** restored the loss in binding affinity; this agrees with the results obtained by Lewin et al.[17] According to these investigators, there are specific hydrogen bond donor groups present within the cocaine recognition site for the binding of the carbomethoxy group. It can be seen that there was a loss of one hydrogen bond accepting oxygen in the alcohol while with the addition of the second oxygen in the acetate restored the binding affinity. The amide derivative **6** showed an IC_{50} greater than 100 μM, a loss in potency far greater than that of the amide derivative of cocaine,[17] while the phenyltropane analogue showed an increase in binding affinity.[19] This cannot be explained in terms of hydrogen bonding; the magnitude of the reduction pointed to other factors, such as the possibility that the amide group may orient itself whereby there was no contribution to binding or may even interfere with binding. The low binding potency of **6** suggested that the hydrogen bonds are highly specific.[17]

With the restoration of the two hydrogen bond acceptors in the esters **7**−**10**, there was little change in binding affinity, and it was no surprise that the ester **8** showed the highest binding potency (2-fold) of all the analogues evaluated in this study. This general trend was also observed with the 2β-substituted cocaine and the phenyltropane analogues.[17] The isopropyl ester of 4′-iodinated phenyltropane showed the highest binding affinity of the 2β-substituted esters. Unlike the alcohol **4**, where there was loss of hydrogen bond acceptors, the oxadiazole **11** did not show dramatic loss in binding potency, therefore supporting the fact that there is an electrostatic interaction between the 2β-substituents and the binding sites on the receptor. The 3-aryl-1,2,4-oxadiazoles of the tropanes also exhibited binding potencies similar to those of the parent esters.[18]

The vinyl analogue **12** that is also a substrate for electrostatic interaction comparable with the ester group showed a binding affinity similar to that of the parent compound **3**. With the hydrogenation of the double bond in **12**, there was a total loss of the electrostatic interaction, and one might have expected a dramatic reduction in binding potency, but the loss in binding potency between **12** and **13** was not significant. This result correlated with what Kozikowski and co-workers[20] had observed in the phenyltropane derivatives. This observation cannot be explained in terms of specific hydrogen bond donor group within the cocaine recognition site as compound **13** lacked a hydrogen bond donor or acceptor group. Kozikowski and co-workers[20] offered an explanation for the existence of a hydrophobic pocket in the vicinity of the C-2 position of cocaine. They concluded that without hydrogen bond acceptors, hydrophobic interactions become important in the region of cocaine recognition site surrounding the C-2 substituents.

Overall, the binding potency of the 2β-substituted cocaine derivatives is higher than that of the 4′-iodococaine analogues while the tropanes exhibited even a much stronger binding affinity. The main difference between these compounds is the N−para substituent distance that may be a critical factor. The shortest length is observed for the 4′-substituted tropanes while the longest is for the 4′-iodo substitution. The tropanes and cocaines seem to fit properly at the binding site on the DAT, while the 4′-IC derivatives are too big to fit into the corresponding site, resulting in poor binding affinity. The high binding potency of the tropanes is also attributed to decreased conformational flexibility, decreased aqueous solvation, and increased pK_as.[24] No correlation between binding affinity and lipophilicity was observed for the 4′-IC derivatives.

Increase in binding affinity of **14** followed the trend observed by Singh et al.[21] with the 2′-hydroxylation of cocaine and 4′-iodococaine. It was postulated that the hydroxyl group may engage in an intermolecular hydrogen bonding with the serine residues at the active site of the dopamine transporter. As can be seen from Table 2, hydroxylation of cocaine at the 2′-position increased the binding affinity to DAT by 10-fold, to the NE by 52-fold, and to the 5-HT by 4-fold, indicating that

Table 3. Calculated Molecular Physical Parameters[a]

molecule	energy (kcal/mol)	distance (N−hydroxy H) (Å)
14[b]	169.095−171.338	7.253−7.467
2′-hydroxy-4′-iodococaine[b]	159.184−161.653	6.819−7.467
2′-hydroxycocaine[b]	171.563−178.900	5.940−7.512
dopamine	74.503−77.689	6.817−6.952 (para) 5.190−7.186 (meta)
norepinephrine	121.178−121.447	6.649−8.204 (para) 5.983−7.693 (meta)
serotonin	−0.056 to 0.145	7.225−8.456

[a] Using Spartan 5.0, Wavefunction Inc., Irvine, CA, running on an SGI Octane workstation. [b] Maintained a 2 Å distance, indicating intramolecular hydrogen bonding between the ester oxygen and the 2′-OH groups on the phenyl ring.

the 2′-hydroxylation enhanced binding potency to different degrees to all the transporters. When 4′-iodococaine and 2′-hydroxy-4′-iodococaine were compared, although there was an increase in binding to all the transporters with the 2′-hydroxylation, there was a preferential enhancement of affinity for the norepinephrine transporter. The increase in binding affinity of 2′-hydroxy-4′-iodococaine is still 10-fold less than that of 2′-hydroxycocaine. The effect of the iodo group in increasing the N−para substituent distance seems to play a role in lowering the binding potency of the hydroxylated 4′-IC analogue. The increase in binding affinity at the DAT is not limited to the 2′-OH group alone. A 2′-NH_2 functionality introduced in cocaine showed a comparable binding potency (IC_{50} 18 ± 2 nM) to the DAT (Singh et al., unpublished results) while the 2′-F exhibited a decreased affinity (IC_{50} 604 ± 67 nM).[25] The results again support our contention that a hydrogen bond donor at the 2′-position will exhibit a high binding potency to the DAT. The fluoro group, a hydrogen bond acceptor, showed reduced binding potency.

With compound **14**, there was enhancement in binding potency to the DAT but not to the norepinephrine and serotonin transporters; this preferential enhancement of potency for the DAT makes this compound unique among the hydroxylated derivatives. The C2-isopropyl group seems to confer selectivity on this compound as observed by Carroll et al.[19]

From the binding studies, we wondered what physical properties could explain the varied binding affinities we observed. Using computer molecular modeling, the distance between the nitrogen and the hydroxy group(s) on the dopamine, norepinephrine, and serotonin molecules were measured in all possible low-energy conformers. This distance was then compared with the distance between the bridgehead nitrogen of the tropane molecule and the 2′-hydroxy group (all possible low-energy conformers) in 2′-hydroxycocaine, 2′-hydroxy-4′-iodococaine, and **14** (Table 3).

With 2′-hydroxycocaine, the distance fits well within the distance of the catecholamines with better compatibility with dopamine. Dopamine binds with high affinity at the DAT and is believed to be due to the ionic interaction between the aliphatic nitrogen and the aspartate residue and the para and meta OH groups hydrogen bonding with the serine 359 and serine 356, respectively.[21] Evidence for dopamine binding domain on the DAT came from the fact that cocaine, methylphenidate, and dopamine have been shown to inhibit [^{3}H]GBR 12935 binding competitively[26] and GBR 12935 binds to only one site on the DAT.[27] These results support the hypothesis that [^{3}H]GBR 12935 labels the dopamine binding site on the transporter. Therefore it can be predicted that any compound with similar physical molecular parameters, i.e., a hydrogen donor at the same distance as the N−OH (para or meta) would exhibit high binding affinity at the DAT. This may be the case with 2′-hydroxycocaine since 2′-hydroxy-4′-iodococaine and **14**, with longer distances than dopamine, exhibited poor binding. Compound **14** with the least compatible distance showed the lowest binding potency to the DAT.

For the NE and 5-HT transporters, 2′-hydrococaine again fits well within the allowed distance observed for NE and 5-HT, leading to the increased binding potency at these transporters. With compound **14**, the distance is out of range, leading to no affinity at these transporter sites. It should be emphasized that the bulky isopropyl and iodo groups have contributed to low-energy conformers with longer distances, therefore preventing better fitting and potential hydrogen bonding with the serine residues at the binding sites of these transporters.

Generally, it has been assumed that an amino function on the monoamines is required for binding on the monoamine transporters. With the synthesis and biological evaluation of aryloxatropanes,[28,29] it was observed that these non-amino compounds bind with high affinity to the DAT, NET, and 5HT. Although this new finding does not rule out the ionic interaction between the receptor and the ligands, it clearly suggests that more than one binding domain for transporter inhibitors and dopamine may exist on the monoamine transporters. Speculating on whether non-amine compounds will offer advantage over conventional nitrogen-based compounds is premature.

In the behavioral assay, compound **14** retained the pharmacological properties of the parent compound 4′-IC despite a 4-fold increase in binding potency at the DAT. The tropane analogues with high binding potency at the DAT are potent in stimulating locomotor activity due to inhibition of dopamine reuptake.[30,31] It would be anticipated, therefore, that with an increase in binding affinity at the DAT, there would be a corresponding increase in locomotor activity. Consistent with this premise, 2′-hydroxycocaine with high binding potency at the DAT was more potent in increasing locomotor activity than cocaine.[32] The lack of locomotor stimulant action coupled with the blockage of a cocaine-induced locomotion by compound **14** is very interesting.

It might be speculated that the lack of locomotor stimulation by compound **14** could be due to a number of reasons, including rapid metabolism and poor brain uptake. There is experimental evidence that the hydroxy group confers stability on the derivatives of cocaine. When 2′-OH cocaine was subjected to *in vitro* esterase hydrolysis using pig liver esterase, no ecgonine methyl ester, a hydrolysis product of the benzoyl group, was observed (Seale et al., unpublished results). It is believed that the 2′-OH is involved in intramolecular hydrogen bonding, resulting in the carbonyl function

being locked in the same plane as the phenyl ring. As a result, the 3β-benzoyl ester group is stable to hydrolysis due to reduction in electrophilicity.[21] HPLC analysis showed 2′-OH cocaine to be more lipophilic than cocaine, therefore with better penetration into the brain. Behavior studies showed 2′-OH cocaine to be a more potent stimulant than cocaine,[32] suggesting brain uptake. Biodistribution studies in mice using ^{125}I-labeled 4′-IC showed 80% of unmetabolized compound in the brain 30 min postdosing. At the end of 120 min, 23% of the parent compound was still present (Basmadjian et al., unpublished results). From these results, we believe that compound **14** which combines the features of 2′-OH cocaine and 4′-IC is entering the brain.

Cocaine also has appreciable binding affinity to the NE and 5HT transporters, complicating the mechanisms responsible for locomotor activity. However, compound **14** has no binding affinity to these transporters; therefore, further studies may offer a less complex explanation. A plausible scenario for the locomotor suppressing properties of compound **14** may be through the inhibition of the sodium channels. Local anesthetic effect by inhibition of the sodium channels has been implicated in the locomotor-depressing properties of cocaine derivatives.[33,34] However, treatment with cocaine can reverse locomotor inhibition induced by norcocaine or the local anesthetic, tetracaine. Administration of cocaine did not reverse the locomotor depressing activity of compound **14**, so this mechanism is not likely. Other likely sites will then be the NE and 5-HT transporters and sigma sites.[35−37] Evidence exists to support the fact that binding to the NE and 5-HT transporters affect behavior.[31] With the low binding potency of compound **14** for these two transporters, a possible mechanism involving these transporters seems unlikely. The pharmacological mechanism(s) which underlies the locomotor antagonizing effect of compound **14** is not well understood, but the possibility of blocking the entry of cocaine into the brain cannot be ruled out.

It can be speculated that the iodo group present in **14** causes an umbrella effect by its size. Thus, despite its low binding potency at the DAT, it prevents cocaine from binding by blocking the binding site. This then explains why compound **14** inhibits the locomotion when coadministered with cocaine, therefore behaving as a cocaine antagonist. Further support for the size effect came from the work of Seale et al., where phenyl[25] and isopropyl groups (Seale et al., unpublished results) at the 4′-position of cocaine not only failed to stimulate locomotor activity in mice but caused locomotor depression when coadministered with cocaine. These compounds, like the iodo derivative, exhibited low binding affinity at the DAT. This clearly shows that the bulkiness of the group at the 4′-position antagonizes cocaine-induced locomotion and is not limited to an iodo group. Stimulant-induced stereotyped behaviors (repetitive biting, sniffing, cage climbing and grooming) in rodents can occupy so much of the behavior repertoire that ambulation is decreased. No obvious decrease in these stereotyped behaviors was observed; therefore, the apparent antagonism of compound **14** cannot be due to development of stereotypy at high doses. No lethality or convulsion was observed at the high doses of the test compound.

Conclusion

A series of 2β-substituted analogues of 4′-iodococaine (**3**) was synthesized to improve upon the binding potency. From the results, compound **8** showed almost a 2-fold increase in binding affinity compared with the parent compound **3**. Since the parent compound had very interesting pharmacological profiles but low binding potency, a 2-fold increase in binding affinity with the isopropyl ester would help us to evaluate the effect of binding potency at the DAT on in vivo biological profile. An initial locomotor activity stimulation screening of **8** showed no stimulation of locomotion, suggesting the possibility of modifying 4′-iodococaine to increase binding affinity and retaining the same behavior pharmacological profile. A correlation plot of binding potencies of tropanes and cocaines showed a poor correlation. This raises the issue of whether the search for a cocaine antagonist is through the high-affinity tropane analogues that are potent inhibitors of dopamine reuptake.

Addition of a hydroxyl group at the 2′-position of cocaine significantly improved the binding potency 10-fold at the DAT, while the same substitution in 4′-iodococaine (**3**) increased the binding affinity to that of cocaine.[21] Introduction of a hydroxyl group at the 2′-position of **8** to give **14** resulted in a 2-fold increase in binding affinity and selectivity for the DAT. The cocaine-induced locomotor blocking effect of **14** clearly warrants further investigation into other low DAT affinity 4′-substituted cocaine derivatives with identical behavior profiles to 4′-IC. Increasing the binding affinity significantly of a low-binding compound is possible and yet retains the biological profile of antagonizing cocaine stimulant effect. A successful design should produce compound(s) that will antagonize cocaine with diminished dopamine uptake inhibition and with high specificity to the DAT versus the NE and 5-HT transporters.

Experimental Section

Melting points were determined on a Thomas Hoover capillary tube apparatus and are uncorrected. Elemental analysis was performed by Midwest Microlab Ltd, Indianapolis, IN. NMR spectra were recorded on a Varian XL-300 spectrometer. FAB-MS was performed with a VG instrument, ZAB-E spectrometer (Manchester, UK). All organic reagents were obtained from Aldrich Chemical Co., except benzamidoxime, which was obtained from TCI America (Portland, OR), and were used without further purification. HPLC grade solvents were obtained from Fisher Scientific (St. Louis, MO). Silica gel (230−400 mesh, 60 Å) used for flash chromatography was obtained from Aldrich and silica gel chromatography sheets with a fluorescent indicator used for TLC were obtained from Eastman Kodak Co., Rochester, NY. [^{3}H]WIN 35,428 was obtained from Dupont-New England Nuclear, Boston, MA.

3-[(4′-Iodobenzoyl))oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-carboxylic Acid (15). To 4′-iodococaine (**3**, 11.6 g, 27 mmol) was added 200 mL of H_2O, and the oily suspension was refluxed for 18 h, changing to a solution as refluxing progressed. The solution was cooled to room temperature and placed in an ice bath. The acid precipitated out as a white fluffy solid that was filtered off and washed with H_2O. The solid was purified by flash chromatography over silica gel (100 g) and eluted with EtOAc/MeOH (70:30) to obtain a white solid (7.50 g, 67%). Mp: 233−234 °C. FAB-MS (3-NBA matrix): *m/e* 416 (MH^+, 100). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8.7 Hz, 2H, C(2′,6′)-H), 7.72 (d, *J* = 8.7 Hz, 2H, C(3′,5′)-H), 5.40−5.32 (m, 1H, C(3)-H), 3.62−

3.57 (m, 1H, C(1)-H), 3.53−3.45 (m, 1H, C(5)-H), 3.06−3.02 (m, 1H, C(2)-H), 2.48 (s, 3H, NCH_3), 2.32−2.17 (m, 4H, C(4,7)-H_2), 1.98−1.96 (m, 2H, C(6)-H_2) ppm.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-hydroxymethane (4). To a stirred suspension of **15** (2.0 g, 5 mmol) in distilled THF (75 mL) at 0 °C (ice bath) was added dropwise a 1.0 M solution of borane−THF complex (18.0 mL, 18 mmol) over a period of 20 min with a clear solution observed after the addition. After the solution was stirred at 0 °C for 2 h and at room temperature for 1 h, excess diborane was carefully destroyed by addition of 20 mL of MeOH. The solution was acidified to pH 1 with 6 N aqueous HCl and concentrated in vacuo, basified with 6 N NH_4OH, and extracted with CH_2Cl_2 (4 × 15 mL). It was dried over $MgSO_4$ and concentrated to an oil, which solidified on standing. The solid was purified by flash chromatography on silica gel (60 g), eluting with 5% MeOH/CH_2Cl_2 to yield a white solid (1.3 g, 65%). Mp: 95−96 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 402 (MH^+, 100), fragment ion at *m/e* 231. ^{1}H NMR ($CDCl_3$): δ 7.79 (s, 4H, C(2′,3′,4′,6′)-H), 5.39−5.30 (m, 1H, C(3)-H), 3.97 (d, J = 2.4 Hz, 2H, CH_2OH), 3.52−3.47 (m, 1H, C(1)-H), 3.35−3.29 (m, 1H, C(5)-H), 3.00−2.27 (m, 1H, C(2)-H), 2.28 (s, 3H, NCH_3), 2.22−2.14 (m, 2H, C(4)-H_2), 2.96−2.05 (m, 2H, C(7)-H_2), 1.80−1.73 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{16}H_{20}NO_3I$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-acetoxymethane (5). To a stirred solution of **4** (0.3 g, 0.7 mmol) and Et_3N (0.25 mL, 1.8 mmol) in 10 mL of CH_2Cl_2 at room temperature was added dropwise acetic anhydride (0.15 mL, 1.5 mmol). After 3 h, TLC in EtOAc showed complete reaction and 10 mL of H_2O was added. The organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with water and dried over Na_2SO_4. Removal of solvent gave an oil (0.3 g, 97%) which was converted to the tartrate salt. Mp: 188−189 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 444 (MH^+, 100). ^{1}H NMR (D_2O): δ 7.75 (d, J = 8.7 Hz, 2H, C(2′,6′)-H), 7.54 (d, J = 8.4 Hz, 2H, C(3′,5′)-H), 5.42−5.34 (m, 1H, C(3)-H), 4.33 (s, 2H, tartaric acid), 4.26 (dd, J = 6.9 Hz, 2H, CH_2O), 3.95−3.86 (m, 2H, C(1,5)-H), 2.88−2.74 (m, 1H, C(2)-H), 2.65 (s, 3H, NCH_3), 2.31−2.12 (m, 4H, C(4,7)-H_2), 2.07−2.04 (m, 2H, C(6)-H_2), 1.68 (s, 3H, $OCOCH_3$) ppm. Anal. ($C_{18}H_{22}NO_4I{\cdot}C_4H_6O_6$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid *N*-Methylamide (6). A solution of **15** (0.20 g, 0.5 mmol) and 1,1′-carbonyldiimidazole (0.40 g, 2 mmol) in 20 mL of dry CH_2Cl_2 was stirred at room temperature for 18 h. To the resulting solution were added methylamine hydrochloride (0.34 g, 5 mmol) and sodium carbonate (1.06 g, 10 mmol), and the flask was stoppered with a rubber septum. The slurry mixture was stirred at room temperature for 18 h; the reaction mixture was then diluted with 25 mL of H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried over $MgSO_4$ and concentated to an oil that was purified by flash chromatography over silica gel (6.0 g) and eluted with EtOAc to obtain an oil (0.18 g, 86%). The oil was converted to the tartrate salt. Mp: 175−176 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 429 (MH^+, 100). ^{1}H NMR ($CDCl_3$): δ 9.42 (br, 1H, NH), 7.77 (d, J = 8.4 Hz, 2H, C(2′,6′)-H), 7.69 (d, J = 8.4 Hz, 2H, C(3′,5′)-H), 5.35−5.26 (m, 1H, C(3)-H), 3.40−3.34 (m, 1H, C(1)-H), 3.34−3.28 (m, 1H, C(5)-H), 2.93−2.90 (m, 1H, C(2)-H), 2.88 (d, J = 8.4 Hz, 3H, $NHCH_3$), 2.29 (s, 3H, NCH_3), 2.22−2.02 (m, 4H, C(4,7)-H_2), 1.82−1.62 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{17}H_{21}N_2O_3I{\cdot}C_4H_6O_6$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Ethyl Ester (7). A solution of **15** (0.80 g, 1.9 mmol) in 25 mL of ethyl alcohol was saturated with HCl gas at 0 °C and stirred at room temperature for 48 h. The residue obtained after the solution was concentrated in vacuo was taken up in 20% NH_4OH and extracted with CH_2Cl_2 (3 × 20 mL). The organic fraction was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (20 g), eluting with EtOAc/petroleum ether (50:50) to obtain an oil (0.60 g, 70%). The oil was converted to the tartrate salt with 0.30 g of tartaric acid. Mp: 180−181 °. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 444 (MH^+, 100). ^{1}H NMR (D_2O): δ 7.77 (d, J = 7.5 Hz, 2H, C(2′,6′)-H), 7.53 (d, J = 6.9 Hz, 2H, C(3′,5′)-H), 5.45−5.34 (m, 1H, C(3)-H), 4.42 (s, 2H, tartaric acid), 4.09−4.02 (m, 1H, C(1)-H), 3.98−3.83 (m, 3H, C(5)-H, OCH_2), 3.50−3.44 (m, 1H, C(2)-H), 2.71 (s, 3H, NCH_3), 2.34−2.20 (m, 4H, C(4,7)-H_2), 2.09−2.00 (m, 2H, C(6)-H_2), 0.68 (t, J = 7.2 Hz, 3H, OCH_2CH_3) ppm. Anal. ($C_{18}H_{22}NO_4I{\cdot}C_4H_6O_6$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Isopropyl Ester (8). A suspension of **15** (0.50 g, 1 mmol) in 30 mL of isopropyl alcohol was saturated with HCl gas, and the mixture was heated to reflux to obtain a solution and cooled to room temperature. The solution was again saturated with HCl gas and stirred at room temperature for 48 h. The mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 and 20% NH_4OH solution. The combined organic extract was washed with H_2O and dried over $MgSO_4$. The residue obtained after removal of solvent was purified by flash chromatography over silica gel (20 g), eluting with EtOAc to obtain a clear oil (0.37 g, 81%). The oil was converted to the tartrate salt with 0.18 g of tartaric acid. Mp: 181−182 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 458 (MH^+, 100). ^{1}H NMR (D_2O): δ 7.76 (d, J = 8.4 Hz, 2H, C(2′,6′)-H), 7.54 (d, J = 8.7 Hz, 2H, C(3′,5′)-H), 5.40−5.30 (m, 1H, C(1)-H), 4.82−4.68 (m, 1H, $CH(CH_3)_2$), 4.34 (s, 2H, tartaric acid), 4.08−4.01 (m, 1H, C(1)-H), 4.96−3.89 (m, 1H, C(5)-H), 3.48−3.41 (m, 1H, C(2)-H), 2.72 (s, 3H, NCH_3), 2.38−2.21 (m, 4H, C(4,7)-H_2), 2.10−2.00 (m, 2H, C(6)-H_2), 0.91 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$), 0.61 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$) ppm. Anal. ($C_{19}H_{24}NO_4I{\cdot}C_4H_6O_6$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Phenyl Ester (9). A mixture of **15** (0.50 g, 1 mmol) and 1,1′-carbonyldiimidazole (0.20 g, 1 mmol) in dried CH_2Cl_2 was stirred at room temperature for 18 h to obtain a solution. The solvent was removed under reduced pressure and the resulting residue taken in 15 mL of acetone and heated under reflux with the phenol (0.09 g, 1 mmol) for 3 h. After removal of solvent in vacuo, the residue obtained was purified by flash chromatography over silica gel (20 g), eluting with EtOAc/petroleum ether (50:50) to obtain a solid (0.45 g, 92%). The free base was converted to the HCl salt. Mp: 119−120 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 492 (MH^+, 100). ^{1}H NMR (D_2O): δ 7.78 (s, 4H, C(2′,3′,5′,6′)-H), 7.41 (d, J = 7.5 Hz, 8.1 Hz, 2H, C(3″,5″)-H), 7.26 (m, 1H, C(4″)-H), 7.13 (dd, J = 2.1 Hz, 5.4 Hz, 2H, C(2″,6″)-H), 5.38−5.30 (m, 1H, C(3)-H), 3.88−3.82 (m, 1H, C(1)-H), 3.40−3.34 (m, 1H, C(5)-H), 3.34−3.25 (m, 1H, C(2)-H), 2.35 (s, 3H, NCH_3), 2.30−2.13 (m, 4H, C(4,7)-H_2), 1.95−1.70 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{22}H_{22}NO_4I{\cdot}HCl{\cdot}3.5H_2O$) C, H, N, I, Cl.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2*β*-carboxylic Acid Benzyl Ester (10). This compound was prepared according to the procedure used for the synthesis of **9** using **15** (0.50 g, 1 mmol), 1,1′-carbonyldiimidazole (1.10 g, 7 mmol), and benzyl alcohol (0.11 g, 1 mmol). The residue obtained after workup was purified by flash chromatography over silica gel (20 g), eluting with EtOAc/petroleum ether (50:50) to furnish a clear oil (0.40 g, 78%). The oil was converted to the tartrate salt with 0.24 g of tartaric acid. Mp: 120−122 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 506 (MH^+, 100). ^{1}H NMR (D_2O): δ 7.47 (d, J = 8.4 Hz, 2H, C(2′,6′)-H), 7.16 (d, J = 8.4 Hz, 2H, C(3′,5′)-H), 7.01-6.97 (m, 1H, C(4″)-H), 6.90 (dd, J = 7.8 Hz, 7.2 Hz, 2H, C(3″,5″)-H), 6.76 (dd, J = 6.9 Hz, 1.5 Hz, 2H, C(2″,6″)-H), 5.30−5.20 (m, 1H, C(3)-H), 4.90, 4.79 (d, J = 12.3 Hz, 1.0 Hz, 12.0 Hz, 1.0 Hz, OCH_2), 4.34 (s, 2H, tartaric acid), 4.09−4.02 (m, 1H, C(1)-H), 3.95−3.88 (m, 1H, C(5)-H), 3.47−3.40 (m, 1H, C(2)-H), 2.38−2.12 (m, 4H, C(4,7)-H_2), 2.00−1.92 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{23}H_{24}NO_4I{\cdot}C_4H_6O_6$) C, H, N, I.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-(3′-phenyl-1′,2′,4′-oxadiazol-5′-yl) (11). To a suspension of **15** (0.6 g, 1 mmol) in 8 mL of CH_2Cl_2 was added dropwise a solution of oxalyl chloride (0.25 mL, 3 mmol) in 3 mL of CH_2Cl_2. After gas evolution ceased, the mixture was stirred for 1.5 h and evaporated to dryness in vacuo. A solution of the benzamidoxime (0.21 g, 2 mmol) in 8 mL of dry pyridine was added to the acid chloride (0.40 g, 1 mmol) in 6 mL of $CHCl_3$ and the mixture heated to reflux for 2 h. The reaction mixture was diluted with 5 mL of H_2O, made basic with 3 N NaOH solution, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was dried over $MgSO_4$, purified by flash chromatography over silica gel (12 g), and eluted with EtOAc/petroleum ether (50:50) to obtain a yellowish oil that solidified on standing (0.20 g, 38%). The solid was converted to the HCl salt. Mp: 221−222 °C. FAB-MS (3-NBA matrix): pseudomolecular ion at *m/e* 516 (MH^+, 100). ^{1}H NMR ($CDCl_3$): δ 8.09 (d, *J* = 8.1 Hz, 2H, C(2′,6′)-H), 7.74 (d, *J* = 8.7 Hz, 2H, C(3′,5′)-H), 7.68 (d, *J* = 8.7 Hz, 2H, C(3″,5″)-H), 7.53−7.46 (m, 3H, C(2″,4″,6″)-H), 5.59−5.49 (m, 1H, C(3)-H), 3.84−3.78 (m, 1H, C(1)-H), 3.74−3.68 (m, 1H, C(5)-H), 3.40−3.33 (m, 1H, C(2)-H), 2.38−2.24 (m, 2H, C(4)-H_2), 2.21 (s, 3H, NCH_3), 2.10−2.00 (m, 2H, C(7)-H_2), 1.94−1.81 (m, 2H, C(6)-H_2) ppm. Anal. ($C_{23}H_{22}N_3O_3I\cdot C_4H_6O_6$) C, H, N, I.

3-[(*tert*-Butyldimethylsilyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-carboxylic Acid Methyl Ester (18). To a solution of *tert*-butyldimethylsilyl chloride (4.50 g, 30 mmol) and imidazole (3.40 g, 50 mmol) in 7 mL of DMF was added ecgonine methyl ester **17** (4.0 g, 20 mmol) in 2 mL of DMF. The solution was heated to 75 °C for 1 h and stirred at room temperature for 18 h. The solution was poured into 15 mL of H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried over $MgSO_4$ and concentrated in vacuo to obtain a liquid that was passed over silica gel and eluted with EtOAc/petroleum ether (50:50) to obtain a clear liquid (5.40 g, 98%). ^{1}H NMR ($CDCl_3$): δ 3.99−3.90 (m, 1H, C(3)-H), 3.70 (s, 3H, OCH_3), 3.43−3.36 (m, 1H, C(1)-H), 3.27−3.20 (m, 1H, C(5)-H), 2.75−2.70 (m, 1H, C(2)-H), 2.21 (s, 3H, NCH_3), 2.18−2.00 (m, 2H, C(4)-H_2), 1.68−1.60 (m, 2H, C(7)-H_2), 1.52−1.45 (m, 2H, C(6)-H_2), 0.86 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, $OSi(CH_3)_2$) ppm.

3-[(*tert*-Butyldimethylsilyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-hydroxymethane (19). To **18** (5.40 g, 17 mmol) in 50 mL of dry toluene and cooled to 0 °C in ice/salt bath was added a 1 M solution of diisobutylaluminum hydride, Dibal-H (34 mL, 34 mmol), in hexanes, and the mixture was stirred for 1 h. The reaction mixture was quenched with 50 mL of saturated Rochelle salt solution and the slurry stirred for 0.5 h, diluted with water, and extracted with $CHCl_3$ (4 × 20 mL). The combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was purified by flash chromatography over silica gel (60 g) using EtOAc as the eluent to obtain a yellowish oil (5.0 g, 100%). ^{1}H NMR ($CDCl_3$): δ 4.08−4.00 (m, 1H, C(3)-H), 3.89 (dd, *J* = 9.0 Hz, 2H, CH_2O), 3.39−3.35 (m, 1H, C(1)-H), 3.20−3.14 (m, 1H, C(5)-H), 2.20 (s, 3H, NCH_3), 2.14−2.05 (m, 1H, C(2)-H), 1.77−1.68 (m, 2H, C(4)-H_2), 1.65−1.49 (m, 4H, C(7,6)-H_2), 0.89 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, $OSi(CH_3)_2$) ppm.

3-[(*tert*-Butyldimethylsilyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-formaldehyde (20). Oxalyl chloride (2.21 g, 17 mmol) was dissolved in 20 mL of CH_2Cl_2 and the solution cooled to −78 °C in dry ice/acetone bath. DMSO (2.66 g, 34 mmol) in 10 mL of CH_2Cl_2 was added, and after 5 min, the alcohol **19** (5.0 g, 17 mmol) in 50 mL of CH_2Cl_2 was added dropwise. Stirring continued for 30 min. The reaction was quenched with Et_3N (8.60 g, 85 mmol) and the resulting solution allowed to warm to room temperature. Water was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo, keeping the temperature under 40 °C. The unstable aldehyde (4.90 g, 99%) was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$): δ 9.99 (d, *J* = 3.3 Hz, 1H, CHO), 4.12−4.05 (m, 1H, C(3)-H), 3.45−3.39 (m, 1H, C(1)-H), 3.30−3.23 (m, 1H, C(5)-H), 2.34−2.219 (m, 1H, C(2)-H), 2.15 (s, 3H, NCH_3), 2.14−1.89 (m, 4H, C(4,7)-H_2), 1.61−1.45 (m, 2H, C(6)-H_2), 0.85 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, $OSi(CH_3)_2$) ppm.

3-[(*tert*-Butyldimethylsilyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-ethene (21). Butyllithium (21.5 mL, 20 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (7.20 g, 20 mmol) in 50 mL of dry THF cooled in ice. After 1 h at room temperature, the solution was recooled in ice, **20** (4.90 g, 17 mmol) dissolved in 30 mL of THF was added dropwise, and the reaction mixture was stirred at room temperature for 16 h. The salts were removed by filtration over Celite, and the resulting solution was diluted with water and extracted with ether (3 × 20 mL). The ethereal extract was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue obtained was purified by flash chromatography over silica gel (80 g) and eluted with EtOAc/petroleum ether (30:70) to obtain an oil (2.68 g, 55%). ^{1}H NMR ($CDCl_3$): δ 6.26−6.12 (m, 1H, C*H*=CH_2), 5.11−4.99 (m, 2H, CH=CH_2), 3.99−3.80 (m, 1H, C(3)-H), 3.18−3.10 (m, 1H, C(1)-H), 3.10−3.03 (m, 1H, C(5)-H), 2.37−2.29 (m, 1H, C(2)-H), 2.19 (s, 3H, NCH_3), 2.12−1.97 (m, 2H, C(4)-H_2), 1.97−1.50 (m, 4H, C(6,7)-H_2), 0.87 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6H, $OSi(CH_3)_2$) ppm.

3-Hydroxy-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]-octane-2β-ethene (22). To **21** (2.0 g, 7 mmol) was added 30 mL of 75% acetic acid in water, and the mixture was stirred for 3 h. The solution was neutralized to pH 7 with concentrated NH_4OH and extracted with CH_3Cl (3 × 20 mL). The organic extracts were dried over Na_2SO_4, and the residue obtained after concentration by rotary evaporation was purified by flash chromatography on silica gel (40 g) using EtOAc/petroleum ether (50:50) as the eluent to furnish an oil (0.59 g, 50%). ^{1}H NMR ($CDCl_3$): δ 6.25−6.12 (m, 1H, C*H*=CH_2), 5.11−4.98 (m, 2H, CH=CH_2), 4.19−4.00 (m, 1H, C(3)-H), 3.18−3.12 (m, 1H, C(1)-H), 3.08−3.02 (m, 1H, C(5)-H), 2.35−2.27 (m, 1H, C(2)-H), 2.00 (s, 3H, NCH_3), 2.10−1.95 (m, 2H, C(4)-H_2), 1.96−1.48 (m, 4H, C(6,7)-H_2) ppm.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-ethene (12). To **22** (0.5 g, 3 mmol) dissolved in 10 mL of dry benzene was added Et_3N (1.36 g, 13 mmol) followed by 4′-iodobenzoyl chloride (1.07 g, 4 mmol) dissolved in 10 mL of benzene dropwise under N_2. The resulting mixture was stirred at 45 °C for 90 min and kept at room temperature overnight. The mixture was transferred to a separatory funnel with 50 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution (4 × 20 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo to obtain a light yellowish oil that was purified by flash chromatography over silica gel (20 g), eluting with EtOAc/petroleum ether (50:50) to obtain a colorless oil (0.58 g, 97%). The oil was converted to the tartrate salt with tartaric acid (0.50 g) to obtain 0.80 g of salt. Mp: 206−207 °C. ^{1}H NMR (D_2O): δ 7.67 (d, *J* = 8.7 Hz, 2H, C(2′,6′)-H), 7.46 (d, *J* = 8.4 Hz, 2H, C(3′,5′)-H), 5.98−5.86 (m, 1H, C*H*=CH_2), 5.29−5.17 (m, 2H, CH=CH_2, C(3)-H), 4.31 (s, 2H, tartaric acid), 3.88−3.81 (m, 2H, C(1,5)-H), 3.15−3.08 (m, 1H, C(2)-H), 2.60 (s, 3H, NCH_3), 2.32−2.16 (m, 2H, C(4)-H_2), 2.16−1.19 (m, 4H, C(7,6)-H_2) ppm. Anal. ($C_{17}H_{20}NO_2I\cdot C_4H_6O_6$) C, H, N, I.

3-Hydroxy-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]-octane-2β-ethane (23). To a solution of **22** (0.20 g, 1 mmol) in 20 mL of cyclohexane was added 20 mg of 5% Pt/C. The flask was evacuated under a vacuum and fitted to a balloon filled with hydrogen gas. The mixture was stirred at room temperature overnight. The reaction mixture was filtered over Celite, and the filtrate was evaporated to dryness to obtain a colorless oil (0.20 g, 100%). ^{1}H NMR ($CDCl_3$): δ 4.00−3.92 (m, 1H, C(3)-H), 3.85−3.70 (m, 2H, C(1,5)-H), 3.35−3.10 (m, 1H, C(2)-H), 2.82 (s, 3H, NCH_3), 2.52−2.30 (m, 4H, C(4,7)-H_2), 2.26−2.15 (m, 2H, C(6)-H_2), 1.88−1.62 (m, 2H, CH_2CH_3), 1.00 (t, *J* = 7.5 Hz, 3H, CH_2CH_3) ppm.

3-[(4′-Iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2β-ethane (13). To **23** (0.2 g, 1 mmol) dissolved in 10 mL of dry benzene was added Et_3N (0.10 g, 1

mmol) followed by a dropwise addition of 4′-iodobenzoyl chloride (0.35 g, 1 mmol) dissolved in 10 mL of benzene under N_2. The resulting mixture was stirred at 45 °C for 90 min and kept at room temperature overnight. The mixture was transferred to a separatory funnel with 20 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution (4 × 5 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo to obtain an oil that was purified by flash chromatography over silica gel (10 g), eluting with EtOAc/petroleum ether (40:60) to obtain a light yellowish oil (0.25 g, 71%). The oil was converted to the tartrate salt with tartaric acid (0.19 g) to obtain 0.34 g of salt. Mp: 207−208 °C. ^{1}H NMR (D_2O): δ 7.91 (d, J = 8.4 Hz, 2H, C(2′,6′)-H), 7.76 (d, J = 8.7 Hz, 2H, C(3′,5′)-H), 5.52−5.45 (m, 1H, C(3)-H), 4.41 (s, 2H, tartaric acid), 4.05−3.96 (m, 2H, C(1,5)-H), 3.34−3.00 (m, 1H, C(2)-H), 2.84 (s, 3H, NCH_3), 2.54−2.32 (m, 4H, C(4,7)-H_2), 2.28−2.18 (m, 2H, C(6)-H_2), 1.88−1.60 (m, 2H, CH_2CH_3), 1.03 (t, J = 7.5 Hz, 3H, CH_2CH_3) ppm. Anal. ($C_{17}H_{22}NO_2I\cdot C_4H_6O_6$) C, H, N, I.

3-[(2′-Hydroxy-4′-iodobenzoyl)oxy]-[1*R*-(*exo,exo*)]-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic Acid Isopropyl Ester (14). To ecgonine HCl (**24**, 0.50 g, 2 mmol) was added 20 mL of 2-propanol, and the mixture was warmed to obtain a solution that was saturated with HCl gas and stirred at room temperature for 12 h. The solution was neutralized with 20% NH_4OH and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extract was concentrated in vacuo and passed through a silica gel plug eluted with petroleum ether/EtOAc (50:50) to obtain an oil (0.50 g, 82%). The oil (0.30 g, 1 mmol) was dissolved in 5 mL of dry benzene, and Et_3N (0.50 mL) was added followed by 4-iodosalicyloyl chloride[21] (0.28 g, 1 mmol) in 1 mL of dry benzene. 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 then washed with 5% aqueous Na_2CO_3 solution (2 × 2 mL) and dried over $MgSO_4$. After solvent removal, the crude product was purified over silica gel (20 g) and eluted with EtOAc/MeOH (50:50) to obtain an oil (0.10 g, 21%) which was converted to the tartrate salt. Mp: 153−155 °C. EIMS (70 eV, DIP): 473 (M^+). ^{1}H NMR (D_2O): δ 7.39 (d, J = 8.4 Hz, 2H, C(3′,5′)-H), 7.25 (d, J = 8.7 Hz, 1H, C(6′)-H), 5.48−5.40 (m, 1H, C(3)-H), 4.83−4.66 (m, 1H, $CH(CH_3)_2$), 4.64 (s, 2H, tartaric acid), 4.10−4.04 (m, 1H, C(1)-H), 4.00−3.90 (m, 1H, C(5)-H), 3.54−3.40 (m, 1H, C(2)-H), 2.74 (s, 3H, NCH_3), 2.36−3.24 (m, 4H, C(4,7)-H_2), 2.09−2.06 (m, 2H, C(6)-H_2), 0.97 9d, J = 6.3 Hz, 3H, $CH(CH_3)_2$), 0.70 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$) ppm. Anal. ($C_{19}H_{24}NO_5I\cdot HCl\cdot 0.5H_2O$) C, H, N, I.

Molecular Modeling. The molecular modeling studies were performed on an SGI Octane workstation (R10000) using Spartan 5.0 (Wavefunction, Inc., Irvine, CA) and InsightII97 (Molecular Simulations, San Diego, CA). All structures were minimized using the built in Semi-Emperical AM1 method in Spartan and the Delphi module in InsightII97. The lowest energy conformers were calculated and used in measuring the distance between the different substituents on the rings and the nitrogen atoms.

Binding Assays. The method of Reith et al.[38] was followed. Whole brains from male Sprague−Dawley rats (Sasco Inc, Wilmington, MA) were rapidly harvested after decapitation with a guillotine. The striata was isolated and homogenized (Polytron, setting 6, 15 s) in ice-cold 0.32 M sucrose solution (1.5 mL/100 mg of tissue). The homogenizer and blade were rinsed with twice the volume of 0.32 M sucrose solution and added to the homogenate. The combined mixture was centrifuged at 3300 rpm for 10 min at 4 °C. The resulting supernatant fraction was subsequently centrifuged at 13800 rpm for 20 min to obtain a pellet, P_2, which was homogenized in ice-cold 35 mM sodium phosphate buffer (obtained by mixing 35 mM NaH_2PO_4 and 17.5 mM Na_2HPO_4 to obtain a pH 7.4 at room temperature). Each assay tube contained 130 μL of buffer or buffer plus 10 μL of unlabeled test compound (1×10^{-10} to 1×10^{-6} M), [^{3}H]WIN 35,428 in the same buffer (20 μL, 4 nM), and 50 μL of membranes (4 mg/mL) to a total volume of 200 μL. Assays performed in triplicates were incubated for 2 h in an ice bath and terminated by rapid filtration through Whatman GF/B glass fiber filters presoaked for 30 min in 0.05% polylysine solution. Membranes were rapidly washed three times with ice-cold buffer. Nonspecific binding of was defined by the presence of 100 μM (−)-cocaine.

Binding potency for the norepinephrine transporter was determined by displacement of [^{3}H]nisoxetine according to the method of Tejani-Butt[39] as modified by Bennett et al.[40] Membranes were freshly prepared after homogenization (Polytron, setting 6, 20 s) of a whole brain minus cerebellum in 30 volumes of ice-cold 50 mM Tris-HCl buffer, pH 7.4, containing 120 mM NaCl and 5 mM KCl and centrifuged. The membranes were resuspended in an ice-cold nisoxetine buffer (50 mM Tris-HCl, pH 7.4, containing 300 mM NaCl and 5 mM KCl). To each assay tube was added 750 μL of membrane solution, 0.7 nM [^{3}H] nisoxetine, and additional buffer containing the test compounds to a final volume of 1 mL. Tubes were incubated at 25 °C for 40 min, and the reaction was terminated by rapid filtration through Whatman GF/B filters presoaked for 1 h in Tris-HCl buffer containing 0.1% bovine serum albumin with three washes of ice-cold buffer. Desipramine (1 μM) was used to define nonspecific binding.

Affinity of analogues at the serotonin transporter was determined by displacement of [^{3}H]paroxetine binding from freshly prepared cortical membranes as assayed by Habert et al.[41] Cortices dissected on ice were homogenized (Polytron, setting 6, 20 s) in 10 volumes (vol:wt) of 50 mM Tris-HCl buffer, pH 7.4, containing 120 mM NaCl and 5 mM KCl and centrifuged twice at 48000*g* for 10 min. Fresh buffer was used to resuspend the membrane pellet from each centrifugation. The incubation mixture contained 50 mg of membranes (original wet weight) in 1500 μL of buffer, 0.4 nM [^{3}H]-paroxetine (100 μL), 300 μL of buffer, and various test compound concentrations (100 μL) in a total volume of 2 mL. The tubes were incubated at 25 °C for 60 min. The reaction was termined by rapid filtration (Brandel) through Whatman GF/B glass filters presoaked in Tris-HCl buffer containing 0.1% bovine serum albumin for at least an hour. Membranes were then rapidly washed three times with an ice-cold buffer. Nonspecific binding was determined in the presence of 10 μM fluoxetine.

Filters containing membrane-bound radioligand were added to vials containing 10 mL of scintillation fluid (EcoLume), stored overnight, and counted on a Beckman LS3801 scintillation counter. IC_{50} values were determined from competition curves of 12 points using the curve-fitting program EBDA (Biosoft Software, Ferguson, MO). Mean values and standard errors were calculated from two to three assays for each test compound.

Locomotor Activity Testing. C57BL/6J mice (Sasco, Omaha, NE), 8-weeks-old, were housed on hardwood litter at constant temperature and humidity with a standard 12 h light/dark cycle. Animals were allowed to acclimatize for 3 days before testing. Locomotor activity was determined in an automated computerized acrylic enclosure, 16 in. × 16 in. × 15 in. (San Diego Instruments, San Diego, CA) with four infrared photobeams on each side. The mice were placed in the testing chamber for 20 min to ensure a steady state level of activity before testing. Locomotor activity was recorded as mean ± sem number of light beam breaks by individual mouse (n = 6/dose) during a 30 min period after ip injection of saline (10 mL/kg), cocaine (20 mg/kg), or test compound (20, 40, and 80 mg/kg) in a 10 mL/kg volume. For inhibition studies, mice were injected ip with saline or test compound; after 10 min, each mouse was challenged with cocaine (20 mg/kg) and locomotor activity was monitored for 30 min.

Data was analyzed utilizing Tukey-Kramer Multiple Comparison Test. In all cases, a p value of 0.05 was considered significant.

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