Further SAR Studies of Piperidine-Based Analogues of Cocaine. 2. Potent Dopamine and Serotonin Reuptake Inhibitors

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The synthesis and monoamine transporter activity of additional members of a series of 3,4-disubstituted piperidines (truncated analogues of the WIN series) are described. All members of this series were prepared from arecoline hydrobromide in optically pure form and were evaluated for their ability to inhibit high affinity uptake of dopamine (DA), serotonin (5-HT) and norepinephrine (NE) into rat brain nerve endings (synaptosomes). Most of the compounds prepared in this series are reasonably potent DAT inhibitors (K_i values of 4−400 nM) and have selectivity for the 5-HT transporter relative to both the NE transporter (3−9-fold) and to the DAT (≈25-fold). In the present series, (−)-methyl 1-methyl-4β-(2-naphthyl)piperidine-3β-carboxylate **(6)** was found to be the most potent piperidine-based ligand, exhibiting K_i's of 21 nM and 7.6 nM at the DAT and 5-HTT, respectively. While the 5-HTT activity of compound **6** is comparable to that of the antidepressant medication fluoxetine, it is less selective. As is apparent from the data presented, the naphthyl substituted piperidines **6**−**9,** which differ in their stereochemistry, show different degrees of selectivity for the three transporters. Consistent with results reported in the literature for the tropane analogues, removal of the methyl group from the nitrogen atom of **9** leads to a further enhancement in 5-HTT activity. To examine the in vivo effects of these piperidines, preliminary behavioral screening was carried out on piperidine **14**. Despite its 2.5-fold greater DAT activity compared to cocaine, piperidine **14** was found to be about 2.5-fold less potent in increasing distance traveled in mice. However, consistent with its DAT activity, piperidine **14** was found to be about 2.5-fold more potent than cocaine in enhancing stereotypic movements. Further studies of these piperidine-based ligands may provide valuable insights into the pharmacological mechanisms underlying the enhancement in distance traveled versus stereotypic movements. The present results have important implications for better understanding the structural motifs required in the design of agents with specific potency and selectivity at monoamine transporters.

Introduction

Selective monoamine reuptake inhibitors of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) have been developed to treat a variety of neurological disorders. For example, selective norepinephrine transporter (NET) inhibitors such as desipramine[1] and serotonin transporter (5-HTT) inhibitors such as paroxetine[2] and fluoxetine[3] are currently being used for the treatment of depression (Chart 1).[4] Selective dopamine transporter (DAT) antagonists are clinically used for the treatment of Parkinson's disease and attention deficit disorders.[5] There has also been considerable interest in recent years in the development of DA reuptake inhibitors as substitute medications for the treatment of cocaine abuse. Various studies have shown that the ability of cocaine to bind to the DAT and inhibit the reuptake of DA is likely responsible for the reinforcing properties of this drug.[6] Cocaine also inhibits serotonin reuptake, and serotonergic systems have been implicated in compulsive cocaine seeking behavior (craving). Accordingly, 5-HT-based agents are being investigated as possible medications for the treatment of cocaine abuse as well.[7] Interestingly, serotonin inhibitors lacking dopaminergic activity do not produce reward or euphoria in primates.[8]

Serotonin selective reuptake inhibitors (SSRIs) are widely used not only in major depression but also in severe anxiety disorders, including panic-agoraphobia syndrome, and obsessive compulsive disorder (OCD).[9] There is an implied correlation between craving and OCD. However, clinical trials would suggest that the use of SSRI alone would not likely result in significant efficacy for the treatment of cocaine withdrawal.[10] Yet, there has been some reported success in polytherapy (combination of DA reuptake inhibitor and 5-HT releaser) in recent studies for cocaine withdrawal therapy.[11] The pilot studies conducted using such a polytherapeutic approach report little to no side effects associated with the combination of DA reuptake inhibitor and 5-HT releaser regimen. Therefore, it is possible that the combination of 5-HT and DAT reuptake inhibitory properties into a single molecule may offer a more

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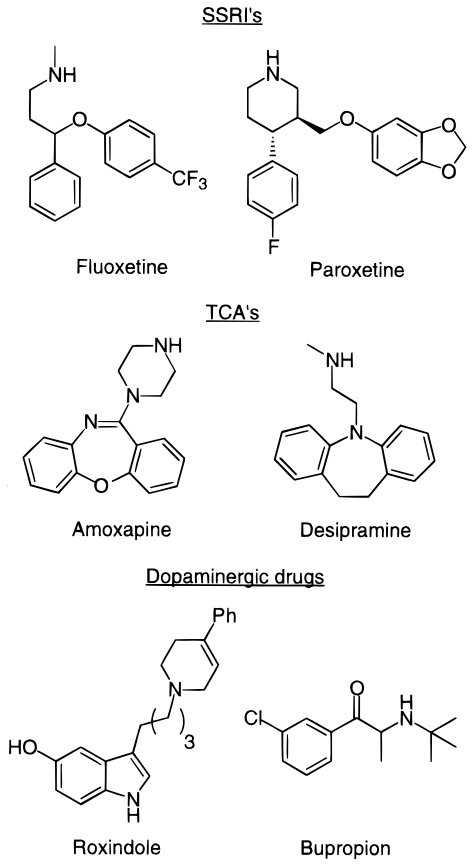
Chart 1

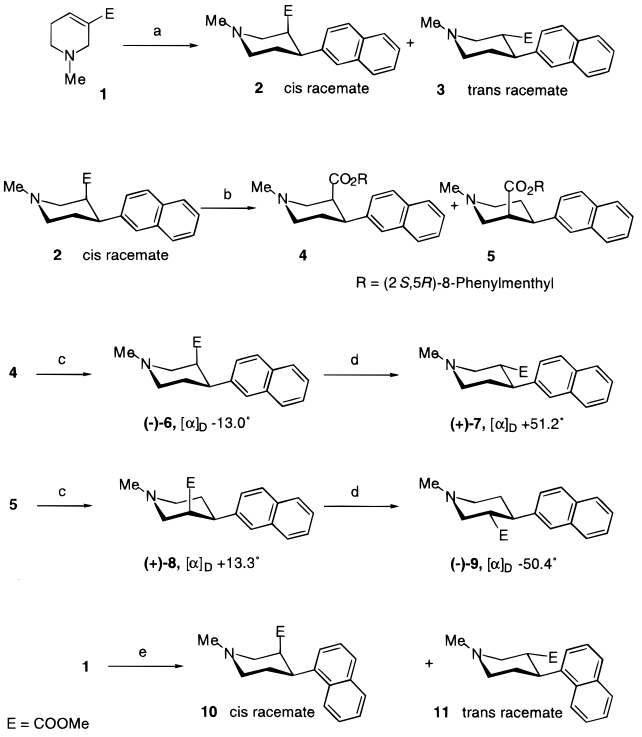


effective approach to OCD management than conventional monotherapies targeting the DAT or 5-HTT alone.

Recently mild DA reuptake inhibitors, such as bupropion, have proven beneficial in treatment of depression.[12] The mesolimbic DA system is believed to underlie the common mechanism of current antidepressant treatment by a mechanism which enhances the endogenous reward system. Therefore, compounds with a strong 5-HT inhibitory activity combined with a moderate DA reuptake inhibiting property have been argued to be most beneficial as antidepressants with a rapid onset of action. Clinical studies with roxindole (a DA receptor agonist with 5-HT reuptake activity) have shown potent antidepressant properties with a rapid onset of action.[13] Recent clinical studies suggest that fluoxetine can be safely and usefully combined with bupropion (DAT $IC_{50} = 2\ \mu M$) in partial responders to monotherapy of depression.[14] In a related study, Labbate and co-workers have shown that the SSRIs associated sexual dysfunction in patients can be diminished using an adjunctive bupropion treatment.[15] It has become apparent that the combination of a SSRI and a DAT reuptake inhibitor may offer a safer and possibly more effective treatment than conventional monotherapy.[16]

Less is known about the neurochemical and physiological actions of compounds that exhibit dual DA and 5-HT transporter potency, especially as cocaine treatment medications, possibly due to the limited number of studies of such agents. We recently reported on a series of piperidine-based analogues of cocaine that bind to the cocaine recognition site and inhibit DA reuptake with potencies comparable to that of cocaine.[17] In particular, based upon results reported in the tropane series, we wished to examine related structural modifications to the piperidines which might lead to improved 5-HTT activity while maintaining the DAT potency.[18] The present structure−activity relationship (SAR) studies in this series of piperidines have led us to the identification of a series of cis disubstituted piperidines that exhibit high potency at 5-HTT and DAT. Synthesis and monoamine uptake activity of these novel compounds are described.

Scheme 1[a]



[a] Reagents and conditions: (a) 2-naphthylMgBr, ether, −10 °C; (b) HCl (6 N); $(COCl)_2$, CH_2Cl_2; 8-phenylmenthol, *n*-BuLi, ether; (c) HCl (6 N); HCl/MeOH (1 M); (d) NaOMe (cat.), MeOH; (e) 1-naphthylMgBr, ether, −10 °C.

Chemistry

The route of chemical synthesis of the 2-naphthylpiperidines **6**−**9** shown in Table 1 is outlined in Scheme 1. Reaction of arecoline as its free base with 2-naphthylmagnesium bromide[19] resulted in a mixture of cis and trans disubstituted piperidines **2** and **3**, which was separated by flash chromatography on silica gel. The (±)-cis isomer **2** was converted to its acid chloride (structure not shown) in two steps and reacted with 8-phenylmenthol to give diastereomers **4** and **5** that were readily separated by flash chromatography. The absolute stereochemistry of **4** was established by crystallographic methods (Figure 1). Hydrolysis of the diastereomeric phenyl menthyl esters **4** and **5** followed by their treatment with HCl (catalyst) in methanol yielded the cis enantiomers (−)-**6** and (+)-**8**, respectively. The optically pure enantiomers (−)-**6** and (+)-**8** were converted to their respective trans enantiomers (+)-**7** and (−)-**9** using a catalytic amount of NaOMe in MeOH. The 4-(1-naphthyl)piperidine analogues **10** and **11** were also prepared using the Grignard method. We were unable to separate the individual enantiomers of the cis

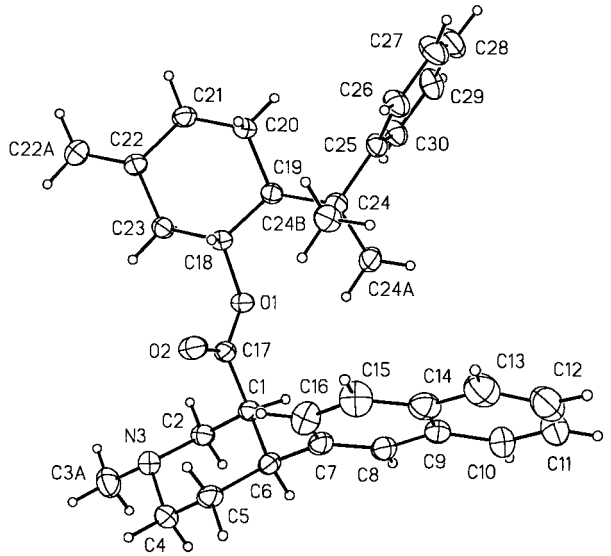


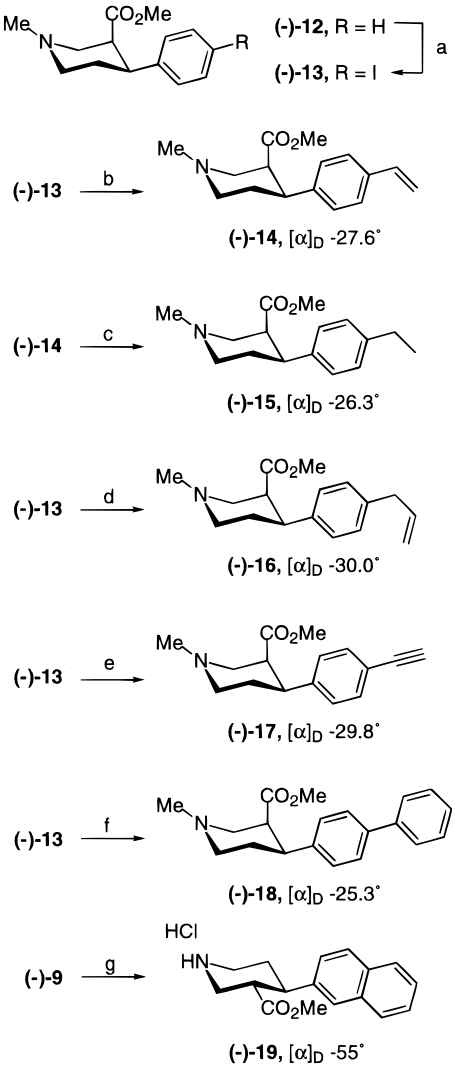
Figure 1. ORTEP drawing of piperidine (−)-**4** which establishes its absolute stereochemistry.

piperidine **10** using classical methods of chemical resolution. The *p*-phenyl substituted piperidines **14**−**18** were prepared as shown in Scheme 2. Here, 4-(4-iodophenyl)piperidine **13** prepared in one step from piperidine **12** was used as a key intermediate for the synthesis of piperidines **14**−**18**. Stille's palladium coupling methodology originally described for the WIN series by Carroll and co-workers was used to prepare piperidines **14** and **16**−**18**.[20] *N*-Demethylation of piperidine **9** using α-chloroethyl chloroformate followed by subsequent heating of the carbamate intermediate (structure not shown) in MeOH gave piperidine **19** which was isolated as its HCl salt.

Structure−Activity Relationships

All compounds were tested for their ability to inhibit high affinity uptake of DA, 5-HT, and NE into nerve endings (synaptosomes).[21] The uptake data and selectivity profiles (based on the K_i values) of these compounds are listed in Table 1. All data are mean values ± range or SEM of two to five separate experiments, each conducted with six drug concentrations in triplicate. Using piperidine **20** as a starting point for this work, we examined the effect of structural modifications to this compound that are similar to those reported by Carroll in the WIN series (Chart 2) and, specifically, modifications known to improve the 5-HTT inhibitory potency. Replacement of the 4-chloro group in **20** with a vinyl group gave piperidine **14** which showed a 3-fold increase in potency at the 5-HTT. Replacement of the 4-chloro group in **20** with a ethynyl group gave piperidine **17** that exhibited a 2-fold increase in its 5-HTT potency. Piperidine **17** has a lower potency at the NET than does piperidine **14**. Catalytic hydrogenation of piperidine **14** gave the ethyl bearing ligand **15** which showed a reduced affinity for all three transporters. The allyl bearing piperidine **17**, on the other hand, has a 5-HTT potency similar to that of the parent piperidine **20**, while its DAT potency is diminished by more than 13-fold. Replacement of the 4-chloro group in **20** with a 4-phenyl group gave piperidine **18**. This compound showed a 6-fold improvement in potency at the 5-HTT compared to **20**. Piperidine **18** is approximately 3-fold more selective for the 5-HTT versus the DAT and the NET. Introduction of a 2-naphthyl group gave piperidine (−)-**6**; this analogue showed improved potency for all three transporters, with the highest potency (7.6 nM) being displayed at the 5-HTT. As is apparent from the data (Table 1), the 4-(2-naphthyl)piperidines **6**−**9** interact stereoselectively with the respective transporters, with analogue **8** showing the highest NET activity, while analogue **7** exhibits the best selectivity for the 5-HTT versus the DAT and NET. *N*-Demethylation of piperidine **9** gave **19** and resulted in a 3-fold increase in potency at the 5-HTT. This result is consistent with related work in the WIN series.[22] In the present series, piperidine (−)-**6** exhibits a 5-HTT potency that is comparable to that of fluoxetine (K_i = 7 nM); however, fluoxetine has lower affinity for the DAT and the NET.

Scheme 2[a]

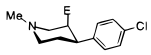
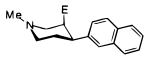
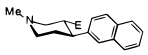
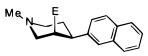
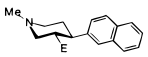
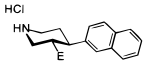
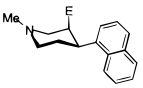
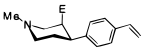
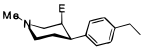
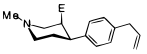
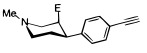
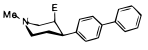


[a] Reagents and conditions: (a) $HClO_4$, HgO, AcOH, I_2; (b) $Bu_3SnCH{=}CH_2$, $(Ph_3P)_4Pd$, dioxane; (c) Pd/C (10%), H_2 (1 atm), MeOH; (d) $Bu_3SnCH_2CH{=}CH_2$, $(Ph_3P)_4Pd$, dioxane; (e) trimethylsilylacetylene, CuI, $(Ph_3P)_2PdCl_2$, $[(CH_3)_2CH]_2NH$; TBAF, THF; (f) $PhSnMe_3$, $(Ph_3P)_4Pd$, PPh_3, dioxane; (g) $CH_3CH(Cl)OCOCl$, 1,2-dichloroethane; MeOH, reflux; HCl/ether (1 M).

Behavioral Studies

Piperidine **14** was selected as a representative member of this series for preliminary behavioral screening for its effect on locomotor activity in mice. The primary

Table 1. Activity at Monoamine Transporters, $K_i \pm$ SE (nM)

Comd. #	Structure	[^{3}H]DA uptake (nM)[a]		[^{3}H]NE uptake (nM)[a]		[^{3}H]5-HTT uptake (nM)[a]		Uptake ratio (K_i's)	
		IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	DA/5-HT	NE/5-HT
	Cocaine	459 ± 159	423 ± 147	127 ± 4.1	108 ± 3.5	168 ± 0.4	155 ± 0.4	2.7	0.69
	Fluoxetine	>4500	>2500	193 ± 4.1	176 ± 3.5	8.1 ± 0.7	7.3 ± 0.7	624	24
20[b,c]		75 ± 9.1	69 ± 8.1	101 ± 3.3	88 ± 2.9	440 ± 30	391 ± 27	0.18	0.23
6		23 ± 1.0	21 ± 0.9	-	34 ± 0.8	8.2 ± 0.3	7.6 ± 0.2	2.8	4.5
7		>1000	947 ± 135	-	241 ± 1.7	46 ± 4.4	42 ± 4.0	22.6	5.7
8		94 ± 9.6	87 ± 8.9	-	27 ± 1.6	209 ± 17	192 ± 16	0.45	0.14
9		293 ± 6.4	271 ± 5.9	-	38 ± 4.0	13 ± 0.7	12 ± 0.7	23	3.2
19		97 ± 8.6	90 ± 8.0	34 ± 2.5	30 ± 2.3	3.9 ± 0.5	3.5 ± 0.5	26	8.6
10		326 ± 1.2	304 ± 1.1	337 ± 37	281 ± 30	113 ± 4.3	101 ± 3.8	3.0	2.8
14		144 ± 20	131 ± 18	204 ± 5.6	175 ± 4.8	155 ± 3.9	138 ± 3.5	0.95	1.3
15		>1800	>1700	>1300	>1100	275 ± 39	255 ± 37	>6	>4
16		>1000	964 ± 100	>1200	>1000	334 ± 48	309 ± 44	3.1	3.5
17		213 ± 30	187 ± 26	399 ± 12	364 ± 9.2	189 ± 37	175 ± 34	1.1	2.1
18		184 ± 30	173 ± 26	239 ± 42	203 ± 36	67 ± 4.5	62 ± 4.1	2.8	3.3

[a] Data are mean ± standard error of at least three experiments performed in triplicate. [b] See ref 5. [c] E = COOMe.

mechanism underlying cocaine's behavioral effects including locomotor stimulation is thought to be due to its ability to bind to dopamine transporters and thereby inhibit dopamine reuptake. In agreement with the dopamine hypothesis, both cocaine and piperidine **14** inhibited dopamine reuptake and increased motor effects. Employing the standard locomotor assay, both cocaine (3−56 mg/kg) and piperidine **14** (10−56 mg/kg) produced dose-dependent enhancements in the distance traveled and stereotypic movements (Figure 2). However, cocaine is about 2.5-fold (95% confidence limits: 1.56−4.6) more potent (by parallel lines bioassay test) than piperidine **14** in increasing the distance traveled. In contrast, piperidine **14** is about 2.4-fold (95% confidence limits: 1.46−4.37) more potent than cocaine in enhancing stereotypic movements. Cocaine is also significantly ($P < 0.01$) more efficacious than piperidine **14** in increasing distance at the maximal dose (56 mg/kg) tested. Both cocaine and piperidine **14** had a similar time-course of locomotor effects (data not shown). For example, the stimulant effects on horizontal distance of both cocaine and piperidine **14** at 56 mg/kg dose lasted about 2 h.

Piperidine **14** is about 2.5-fold more potent than cocaine in enhancing stereotypic movements (Figure 2). This is consistent with the 3-fold higher potency of piperidine **14** in inhibiting dopamine uptake. Unlike its effects on stereotypic movements, piperidine **14** is about 2.5 times less potent than cocaine in increasing the distance traveled. This suggests that besides the inhibition of dopamine uptake, other mechanisms might also play a modulatory role in enhancing the distance traveled. The inhibition of norepinephrine and serotonin uptake are unlikely to be involved, since both compounds had similar potencies at these transporters. Thus, the piperidine **14** may serve as a useful biological tool to understand the differences in the pharmacological mechanisms underlying the cocaine-induced enhancements in the distance traveled versus stereotypic movements.

Conclusions

The chemical synthesis and monoamine transporter activity of a series of piperidine-based monoamine reuptake inhibitors are presented. While these molecules lack the tropane nucleus which is characteristic of the WIN series of cocaine analogues, some members of the present series are potent inhibitors of the monoamine transporters. The naphthyl bearing ligand **6** represents the most potent ligand at the DAT and the 5-HTT. As in the WIN series, *N*-demethylation of the piperidine in the case of **9** leads to a compound **19** of

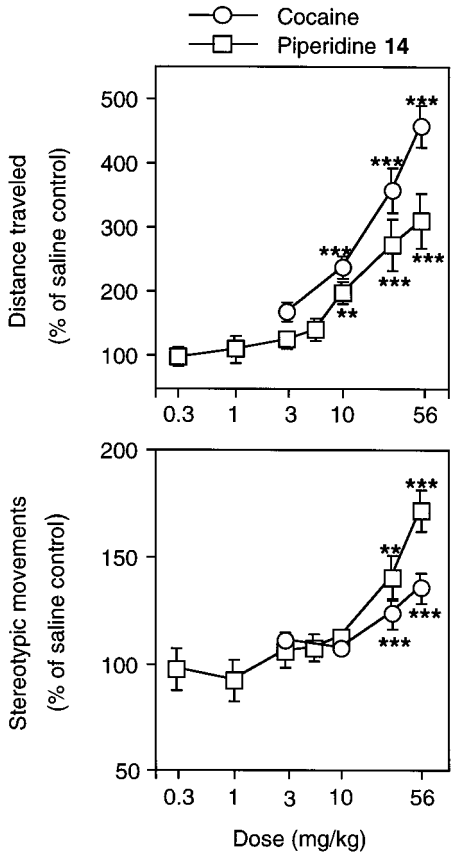


Figure 2. The dose−effect curves for the effect of cocaine and piperidine **14** on horizontal distance traveled (top panel) and the stereotypic movements (bottom panel) in male Swiss−Webster mice. The maximal 30 min total from the original 2 h data for each dose of a given drug was identified and used for statistical analysis. These 30 min maximal responses were expressed as the percent of mean of the corresponding saline control group. The data points in the figure represent the mean ± SEM of these percent changes for different doses of cocaine and piperidine **14**. Both piperidine **14** ($F_{7,110} = 18.58$, $P < 0.001$) and cocaine ($F_{4,115} = 61.67$, $P < 0.001$) produced significant and dose-dependent increases in horizontal distance traveled. Similarly, piperidine **14** ($F_{7,110} = 18.57$, $P < 0.001$) and cocaine ($F_{4,115} = 7.89$, $P < 0.001$) significantly increased stereotypic movements. The horizontal activity and stereotypic movement responses in the saline control group were 3775 ± 216 cm and 1833 ± 70, respectively. $^{**}P < 0.01$; $^{***}P < 0.001$ as compared to the corresponding responses in the saline control group by Tukey's post hoc test.

improved 5-HTT activity (3.5 nM). Piperidine **7**, on the other hand, shows the best overall selectivity for the 5-HTT. Locomotor studies with the 4-(4-vinylphenyl)-piperidine **14** reveals differential effects on distance traveled versus stereotypic movements, which contrasts with the effects found for cocaine in the same study. As a consequence of the potency of some of these piperidines as multitransporter inhibitors combined with the unexpected results from the locomotor studies, further in vivo studies of these piperidines as possible cocaine medications and as antidepressants[23] are now being conducted.

Experimental Procedures

General. Reagents and solvents were obtained from commercial suppliers and used as received. All starting materials were commercially available unless otherwise indicated. Solvent removal was routinely performed on a rotory evaporator at 30−40 °C. All reactions were performed under inert atmosphere (Ar or N_2) unless otherwise noted. Diethyl ether was freshly distilled under nitrogen from sodium benzophenone. IR spectra were collected on an ATI Mattson Genesis spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Unity Inova instrument at 300 and 75.46 MHz, respectively. ^{1}H chemical shifts (δ) are reported in ppm downfield from internal TMS. ^{13}C chemical shifts are referred to $CDCl_3$ (central peak, $\delta = 77.0$ ppm). Melting points were taken in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are not corrected. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. TLC was performed on Merck silica gel 60 F_{254} glass plates; column chromatography was performed using Merck silica gel (60−200 mesh). Yields are of purified product and are not optimized.

(±)-Methyl 1-Methyl-4-(2-naphthyl)piperidine-3-carboxylate (2, 3). To a stirred suspension of Mg (240 mg, 10.0 mmol) in ether (10 mL) were added 2-bromonaphthalene (2.07 g, 10.0 mmol) in ether (3.0 mL) followed by 1,2-dibromoethane (140 mg, 0.750 mmol), and the mixture was heated at reflux until all of the Mg had disappeared. Arecoline (630 mg, 4.10 mmol) in ether (15 mL) was added dropwise to the 2-naphthyl Grignard solution with stirring at −20 °C, and the resulting suspension was stirred at −15 °C for 0.5 h. The mixture was cooled to −40 °C and treated with HCl (10% aqueous, 30 mL). The aqueous layer was separated, washed with ether (20 mL), and neutralized with saturated sodium bicarbonate solution while being cooled in an ice bath. The aqueous phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give an oil. Flash chromatography (ether/Et_3N, 99:1) gave the faster moving cis isomer **2** (259 mg, 20%) then the trans isomer **3** (120 mg, 9%).

Compound **2**: mp 100−101 °C; IR (KBr) 758, 1019, 1165, 1743, 2783, 2941 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92 (dd, 1H, J = 3.0, 12.6 Hz), 2.11 (dt, 1H, J = 2.7, 11.1 Hz), 2.30 (s, 3H), 2.41 (dd, 1H, J = 3.6, 11.4 Hz), 2.81 (dq, 1H, J = 3.6, 11.7 Hz), 2.96−3.08 (m, 2H), 3.12 (d, 1H, J = 3.3 Hz), 3.23 (dd, 1H, J = 1.8, 11.4 Hz), 3.45 (s, 3H), 7.38−7.48 (m, 3H), 7.70−7.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.3, 37.4, 41.7, 42.1, 46.8, 51.4, 53.9, 120.9, 121.3, 121.6, 121.9, 123.0, 123.1, 123.4, 127.6, 128.8, 136.0, 168.2; MS m/z% 44 (63), 70 (100), 252 (2), 283 (M^+, 16). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

Compound **3**: IR (film) 746, 819, 1194, 1733, 2789, 2939 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85−2.10 (m, 2H), 2.18 (dt, 1H, J = 3.3, 11.1 Hz), 2.26 (t, 1H, J = 10.5 Hz), 2.40 (s, 3H), 2.90−3.20 (m, 4H), 3.38 (s, 3H), 7.36−7.48 (m, 3H), 7.65 (s, 1H), 7.74−7.82 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 33.4, 44.9, 46.4, 49.2, 51.7, 56.1, 58.4, 125.6, 125.9, 126.1, 127.8, 127.9, 128.3, 132.7, 133.7, 141.1, 173.8; MS m/z% 44 (33), 70 (100), 224 (8), 283 (M^+, 12).

(2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (3*R*,4*S*)-1-Methyl-4-(2-naphthyl)piperidine-3-carboxylate (4) and (2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (3*S*,4*R*)-1-Methyl-4-(2-naphthyl)piperidine-3-carboxylate (5). A solution of piperidine **2** (1.0 g, 3.5 mmol) in HCl (6 N, 20 mL) was stirred at reflux for 5 h and concentrated in vacuo to give the acid intermediate as a white solid. The acid was suspended in CH_2Cl_2 (10 mL) and treated with oxalyl chloride (1.0 mL, 12 mmol) with stirring for 2 h at room temperature. The solvent was removed in vacuo to give the acid chloride intermediate as a solid. To a solution of (−)-8-phenylmenthol (2.38 g, 10.2 mmol) in ether (40 mL) was added *n*-butyllithium (2.5 M in hexane, 4.0 mL, 10 mmol) at 0 °C. The solution was warmed to room temperature and added dropwise to a suspension of the acid chloride intermediate in ether (40 mL), and the resulting mixture was stirred overnight. The solution was diluted with ether (30 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated to give an oil. Flash chromatography (ether/Et_3N 99:1) gave the faster moving isomer **4** (610 mg, 36%) followed by the isomer **5** (620 mg, 36%).

Compound **4**: IR (film) 700, 1734, 2783, 2952 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66−1.00 (m, 12H), 1.22−1.56 (m, 3H), 1.70−1.94 (m, 3H), 2.00−2.18 (m, 2H), 2.24 (s, 3H), 2.50−2.58 (m, 1H), 2.76−3.02 (m, 4H), 4.55 (dt, 1H, J = 4.2, 10.8 Hz), 6.94−7.16 (m, 5H), 7.36−7.48 (m, 3H), 7.70−7.84 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.9, 26.0, 26.5, 26.9, 27.2, 31.4, 34.8, 39.7, 41.5, 42.2, 46.5, 46.8, 50.5, 56.1, 58.4, 74.2, 125.0, 125.5, 125.6, 125.9, 126.7, 127.1, 127.6, 127.7, 127.9, 128.0, 132.4, 133.5, 140.9, 151.8, 171.7; MS m/z% 44 (100), 483 (M^+, 5).

Compound **5**: IR (KBr) 700, 1729, 2783, 2934 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.31 (d, 3H, J = 6.3 Hz), 0.38−0.56 (m, 1H), 0.76−1.18 (m, 10H), 1.28−1.42 (m, 2H), 1.62 (dt, 1H, J = 3.0, 10.2 Hz), 1.82−1.98 (m, 1H), 2.12−2.60 (m, 7H), 2.63−2.96 (m, 3H), 4.57 (dt, 1H, J = 4.2, 10.8 Hz), 7.10−7.20 (m, 3H), 7.20−7.35 (m, 3H), 7.35−7.48 (m, 2H), 7.56 (s, 1H), 7.64−7.82 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.0, 26.6, 27.1, 28.6, 30.9, 34.5, 39.9, 40.8, 41.0, 45.5, 46.9, 50.1, 54.4, 56.2, 74.1, 125.1, 125.5, 125.6, 126.0, 126.3, 127.4, 127.5, 127.6, 128.0, 128.1, 132.2, 133.4, 140.6, 152.0, 171.9; MS m/z% 49 (100), 483 (M^+, 2).

(−)-Methyl 1-Methyl-4*β*-(2-naphthyl)piperidine-3*β*-carboxylate (6). A solution of piperidine **4** (257 mg, 0.53 mmol) in HCl (6 N, 25 mL) was stirred at reflux for 24 h. The solvent was removed in vacuo to give a white solid. This solid was dissolved in a saturated methanolic solution of HCl (g) (3 mL), and the resulting solution was stirred at room temperature overnight. The solvent was removed in vacuo to give a white solid which was dissolved in saturated $NaHCO_3$ (20 mL), and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated to give an oil. Flash chromatography (ether/Et_3N, 99:1) gave the title compound **6** (80 mg, 53%) as a white solid: mp 77−78 °C; $[\alpha]_D$ −13.0° (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.94 (dd, 1H, J = 2.7, 12.6 Hz), 2.14 (dt, 1H, J = 2.7, 11.1 Hz), 2.32 (s, 3H), 2.43 (dd, 1H, J = 3.3, 11.4 Hz), 2.81 (dq, 1H, J = 3.6, 12.0 Hz), 2.94−3.08 (m, 2H), 3.08−3.16 (m, 1H), 3.23 (d, 1H, J = 11.1 Hz), 3.46 (s, 3H), 7.38−7.48 (m, 3H), 7.70−7.83 (m, 4H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(+)-Methyl 1-Methyl-4*β*-(2-naphthyl)piperidine-3*β*-carboxylate (8) was prepared similarly to naphthylpiperidine (−)-**6**. From naphthylpiperidine **5** (285 mg, 0.59 mmol) was obtained piperidine (+)-**8** (100 mg, 60%) as a white solid: mp 77−79 °C; $[\alpha]_D$ +13.3° (c 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.89−2.00 (m, 1H), 2.15 (dt, 1H, J = 2.7, 11.1 Hz), 2.32 (s, 3H), 2.44 (dd, 1H, J = 3.3, 11.4 Hz), 2.81 (dq, 1H, J = 3.6, 11.4 Hz), 2.96−3.08 (m, 2H), 3.09−3.17 (m, 1H), 3.23 (dd, 1H, J = 2.1, 11.7 Hz), 3.46 (s, 3H), 7.38−7.48 (m, 3H), 7.69−7.83 (m, 4H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(+)-Methyl 1-Methyl-4*β*-(2-naphthyl)piperidine-3α-carboxylate (7). A solution of (−)-**6** (0.12 g, 0.42 mmol) and sodium methoxide (30% in MeOH, 5 drops) in MeOH (5 mL) was stirred at reflux for 24 h. The solvent was removed in vacuo to give an oil. Flash chromatography gave the title compound (110 mg, 93%) as an oil which solidified upon standing: mp 71−72 °C; $[\alpha]_D$ +50.4° (c 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.85−2.10 (m, 2H), 2.18 (dt, 1H, J = 3.3, 11.1 Hz), 2.26 (t, 1H, J = 10.8 Hz), 2.38 (s, 3H), 2.90−3.20 (m, 4H), 3.38 (s, 3H), 7.36−7.48 (m, 3H), 7.65 (s, 1H), 7.74−7.82 (m, 3H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(−)-Methyl 1-Methyl-4*β*-(2-naphthyl)piperidine-3α-carboxylate (9) was prepared similarly to piperidine (+)-**7**. From piperidine (+)-**8** (0.15 g, 0.53 mmol) was obtained piperidine (−)-**9** (140 mg, 93%) as an oil which solidified upon standing: mp 71−72 °C; $[\alpha]_D$ −51.2° (c 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.85−2.10 (m, 2H), 2.18 (dt, 1H, J = 3.3, 11.4 Hz), 2.26 (t, 1H, J = 10.5 Hz), 2.38 (s, 3H), 2.90−3.20 (m, 4H), 3.38 (s, 3H), 7.36−7.48 (m, 3H), 7.65 (s, 1H), 7.74−7.82 (m, 3H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(±)-Methyl 1-Methyl-4*β*-(1-naphthyl)piperidine-3*β*-carboxylate (10). To a stirred suspension of Mg (480 mg, 20.0 mmol) in ether (20 mL) were added I_2 (2−3 crystals) and α-bromonaphthalene (0.5 mL, 3.6 mmol), and the mixture was heated until the color of I_2 disappeared. To this mixture was added α-bromonaphthalene (2.30 mL, 16.4 mmol) in ether (20 mL) at such a rate that the reaction proceeded vigorously. The resulting solution was further refluxed until all of the Mg had disappeared. The solution was diluted with ether (30 mL) and cooled to −15 °C at which time a solution of arecoline (1.5 g, 9.7 mmol) in ether (20 mL) was added dropwise. The resulting mixture was stirred at −15 °C for 1 h, poured onto cracked ice, and treated with HCl (10%, 22 mL). The aqueous layer was separated, washed with ether (20 mL), and neutralized with saturated sodium bicarbonate solution while being cooled in an ice bath. The aqueous phase was extracted with ether (3 × 40 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated to give an oil. Flash chromatography (ether/Et_3N, 99:1) gave the cis isomer **10** (700 mg, 26%) as a white solid: mp 108−109 °C; IR (KBr) 776, 1157, 1379, 1747, 2792, 2931 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78−1.87 (m, 1H), 2.21 (dt, 1H, J = 2.7, 11.1 Hz), 2.35 (s, 3H), 2.54 (dd, 1H, J = 3.3, 11.1 Hz), 2.92−3.18 (m, 2H), 3.18−3.32 (m, 2H), 3.41 (s, 3H), 3.51−3.63 (m, 1H), 7.40−7.56 (m, 3H), 7.61 (d, 1H, J = 6.9 Hz), 7.72 (d, 1H, J = 8.1 Hz), 7.86 (dd, 1H, J = 1.5, 7.2 Hz), 7.97 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 33.7, 40.6, 42.2, 46.6, 52.2, 54.3, 118.0, 120.6, 120.9, 121.0, 121.4, 122.5, 124.8, 126.8, 129.3, 133.5, 168.1; MS m/z% 44 (83), 70 (100), 283 (M^+, 44). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

(−)-Methyl 4*β*-(4-Iodophenyl)-1-methylpiperidine-3*β*-carboxylate (13). Perchloric acid (70%, 5.25 mL) was added to a stirred slurry of mercuric oxide (975 mg, 4.49 mmol) in glacial acetic acid (10 mL), and the slurry was stirred until all of the orange solid had dissolved. To this solution was added piperidine **12** (1.05 g, 4.51 mmol) followed by acetic acid (5 mL). After 15 min, a solution of iodine (2.85 g, 11.2 mmol) in acetic acid (21 mL) and CH_2Cl_2 (41 mL) was added, and the resulting slurry was stirred at room temperature for 5 h. The orange solid was removed through a plug of Celite, and the filtrate was neutralized with concentrated ammonium hydroxide. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated to give an oil. Flash chromatography gave the title compound (800 mg, 50%) as a white solid: $[\alpha]_D$ −27.1° (c 0.55, $CHCl_3$); IR (film) 772, 842, 1168, 1739, 2784, 2942 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73−1.85 (m, 1H), 2.07 (dt, 1H, J = 2.7, 11.4 Hz), 2.28 (s, 3H), 2.35 (dd, 1H, J = 3.3, 11.4 Hz), 2.64 (dq, 1H, J = 3.3, 11.7 Hz), 2.72−2.82 (m, 1H), 2.92−3.04 (m, 2H), 3.18 (d, 1H, J = 11.4 Hz), 3.55 (s, 3H), 7.05 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 26.6, 41.7, 46.3, 46.8, 51.6, 56.1, 58.6, 91.7, 130.0, 137.3, 143.0, 172.7; MS m/z% 44 (100), 300 (17), 359 (M^+, 13). Anal. ($C_{14}H_{18}INO_2$) C, H, N.

(−)-Methyl 1-Methyl-4*β*-(4-vinylphenyl)piperidine-3*β*-carboxylate (14). A solution of piperidine (−)-**13** (223 mg, 0.720 mmol), a catalytic amount of 4-*tert*-butylcatechol, triphenylphosphine (18 mg, 0.069 μmol), vinyltributyltin (240 μL, 800 μmol), and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) in dioxane (7 mL) was stirred at reflux for 6 h. The mixture was cooled to room temperature and then diluted with pyridine-HF (1 M in THF, 2.0 mL). The resulting solution was stirred at room temperature for 16 h, diluted with ether (30 mL), and filtered through a small pad of Celite. The filtrate was washed with aqueous NH_4Cl (20 mL), water (20 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated to give an oil. Flash chromatography (ether/Et_3N, 99:1) gave the title compound (100 mg, 54%) as a crystalline solid: mp 68−69 °C; $[\alpha]_D$ −27.6° (c 0.46, $CHCl_3$); IR (KBr) 850, 1016, 1165, 1241, 1629, 1745, 2783, 2942 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78−1.88 (m, 1H), 2.09 (dt, 1H, J = 2.7, 11.1 Hz), 2.29 (s, 3H), 2.37 (dd, 1H, J = 3.3, 11.4 Hz), 2.68 (dq, 1H, J = 3.6, 12.0 Hz), 2.78−2.87 (m, 1H), 2.93−3.02 (m, 2H), 3.18 (dd, 1H, J = 1.5, 11.1 Hz), 3.52 (s, 3H), 5.20 (d, 1H, J = 10.8 Hz), 5.71 (d, 1H, J = 17.4 Hz), 6.68 (dd, 1H, J = 10.8, 17.4 Hz), 7.25 (d, 2H, J = 8.1 Hz), 7.34 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 26.9, 41.8, 46.4, 46.9, 51.5, 56.2, 58.6, 113.4, 126.2, 128.0, 135.7, 136.8, 143.0, 172.9; MS m/z% 44 (100), 200 (16), 259 (M^+, 14). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

(−)-Methyl 4*β*-(4-Ethylphenyl)-1-methylpiperidine-3*β*-carboxylate (15). A suspension of piperidine (−)-**14** (200 mg,

0.772 mmol) and Pd/C (10%, 20 mg) in MeOH (10 mL) was stirred at room temperature under H_2 (1 atm) for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated to afford the title compound (195 mg, 97%) as an oil which solidified upon standing: $[\alpha]_D = -26.3°$ (*c* 0.48, $CHCl_3$); IR (film) 778, 843, 1017, 1164, 1241, 1379, 1515, 1746, 2782, 2963 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, $J = 7.5$ Hz), 1.76−1.87 (m, 1H), 2.08 (dt, 1H, $J = 2.7$, 11.1 Hz), 2.28 (s, 3H), 2.37 (dd, 1H, $J = 3.6$, 11.7 Hz), 2.61 (q, 2H, $J = 7.5$ Hz), 2.64−2.75 (m, 1H), 2.76−2.86 (m, 1H), 2.92−3.04 (m, 2H), 3.16 (dd, 1H, $J = 2.1$, 11.4 Hz), 3.52 (s, 3H), 7.11 (d, 2H, $J = 8.1$ Hz), 7.21 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 15.6, 27.0, 28.5, 41.6, 46.4, 46.8, 51.3, 56.2, 58.5, 127.7, 140.4, 142.1, 173.0; MS *m*/*z*% 44 (75), 70 (100), 202 (25), 261 (M^+, 22). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

(−)-Methyl 1-Methyl-4*β*-[4-(2-propenyl)phenyl]-piperidine-3*β*-carboxylate (16). A solution of piperidine (−)-**13** (90 mg, 0.24 mmol), 4-*tert*-butylcatechol (catalytic), triphenylphosphine (37 mg, 0.14 mmol), allyltributyltin (0.11 mL, 0.35 mmol), and $Pd(PPh_3)_4$ (40 mg, 0.034 mmol) in dioxane (5 mL) was stirred at reflux for 1.5 h. The solvent was removed in vacuo to give an yellow oil which was dissolved in ether (30 mL) and extracted with hydrochloric acid (1 M, 3 × 10 mL). The combined aqueous layers were neutralized with saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was dried over Na_2SO_4 and concentrated to give a solid. Flash chromatography (ether/Et_3N, 99:1) gave the title compound (51 mg, 75%) as an oil that solidified upon standing: $[\alpha]_D$ −30.0° (*c* 0.45, $CHCl_3$); IR (film) 913, 1017, 1164, 1638, 1746, 2782, 2941 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (dd, 1H, $J = 2.7$, 12.3 Hz), 2.11 (dt, 1H, $J = 2.4$, 10.8 Hz), 2.29 (s, 3H), 2.38 (dd, 1H, $J = 3.3$, 11.4 Hz), 2.67 (dq, 1H, $J = 3.3$, 12.0 Hz), 2.76−2.88 (m, 1H), 2.92−3.04 (m, 2H), 3.16 (dd, 1H, $J = 2.1$, 11.4 Hz), 3.34 (d, 2H, $J = 6.6$ Hz), 3.55 (s, 3H), 5.00−5.12 (m, 2H), 5.88−6.02 (m, 1H), 7.11 (d, 2H, $J = 7.8$ Hz), 7.22 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 27.0, 40.0, 41.7, 46.4, 46.8, 51.5, 56.2, 58.5, 115.8, 127.9, 128.5, 137.7, 138.0, 141.0, 173.0; MS *m*/*z*% 44 (100), 214 (8), 258 (1), 273 (M^+, 7). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

(−)-Methyl 4*β*-(4-Ethynylphenyl)-1-methylpiperidine-3*β*-carboxylate (17). To a solution of piperidine **13** (223 mg, 0.620 mmol) in diisopropylamine (7.0 mL) in a pressure tube were added CuI (7.0 mg, 0.037 mmol), and bis(triphenylphosphine)palladium(II) chloride (44 mg, 0.062 mmol) followed by trimethylsilylacetylene (0.11 mL, 0.77 mmol), and the mixture was stirred for 3 h at 100 °C. The residue was diluted with EtOAc (20 mL), filtered through a plug of silica gel, and concentrated under reduced pressure to give an oil. The oil was dissolved in THF (6 mL) and added to tetrabutylammonium fluoride (1.0 M in THF, 0.8 mL) dropwise at 0 °C. The solution was stirred for 5 min and diluted with saturated aqueous sodium bicarbonate (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated to give an oil. Column chromatography (ether/Et_3N, 99:1) gave the title compound (126 mg, 79%) as a white solid: mp 48−50 °C; $[\alpha]_D = -29.8°$ (*c* 0.57, $CHCl_3$); IR (film) 849, 1017, 1168, 1741, 2785, 2943, 3289 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (dd, 1H, $J = 3.3$, 12.9 Hz), 2.11 (dt, 1H, $J = 2.7$, 11.1 Hz), 2.28 (s, 3H), 2.38 (dd, 1H, $J = 3.6$, 11.7 Hz), 2.66 (dq, 1H, $J = 3.9$, 11.7 Hz), 2.82 (dt, 1H, $J = 3.9$, 12.0 Hz), 2.92−3.00 (m, 2H), 3.03 (s, 1H), 3.16 (dd, 1H, $J = 1.8$, 11.4 Hz), 3.55 (s, 3H), 7.25 (d, 2H, $J = 8.1$ Hz), 7.42 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 26.6, 41.9, 46.2, 46.8, 51.5, 56.0, 58.5, 77.0, 83.9, 120.0, 127.8, 132.1, 144.3, 172.7; MS *m*/*z*% 44 (100), 198 (9), 257 (M^+, 6). Anal. ($C_{16}H_{19}NO_2$) C, H, N.

(−)-Methyl 1-Methyl-4*β*-(4-phenylphenyl)-piperidine-3*β*-carboxylate (18). A suspension of piperidine (−)-**13** (78 mg, 0.25 mmol), a few crystals of 4-*tert*-butylcatechol, triphenylphosphine (approximately 5 mg), trimethylphenyltin (72 mg, 0.30 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in dioxane (4.0 mL) was heated at reflux for 12 h. The solution was cooled to room temperature and diluted with pyridine-HF (1 M, 0.5 mL). The resulting solution was stirred at room temperature for 16 h, diluted with ether (30 mL), and filtered through a small pad of Celite. The filtrate was washed with NH_4Cl (20 mL), dried over Na_2SO_4, and concentrated to give a solid. Flash chromatography (ether/Et_3N, 99:1) gave the title compound (32 mg, 41%) as a white solid: mp 120−121 °C; $[\alpha]_D$ −25.3° (*c* 0.47, $CHCl_3$); IR (film) 764, 1170, 1738, 2782, 2954 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (dd, 1H, $J = 3.0$, 12.3 Hz), 2.11 (dt, 1H, $J = 2.7$, 11.1 Hz), 2.30 (s, 3H), 2.40 (dd, 1H, $J = 3.6$, 11.7 Hz), 2.73 (dq, 1H, $J = 3.3$, 12.0 Hz), 2.82−2.94 (m, 1H), 2.94−3.09 (m, 2H), 3.18 (dd, 1H, $J = 1.8$, 11.4 Hz), 3.55 (s, 3H), 7.28−7.47 (m, 5H), 7.48−7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 26.9, 41.8, 46.4, 46.9, 51.5, 56.2, 58.7, 127.0, 127.2, 127.3, 128.3, 128.9, 139.2, 141.1, 142.4, 173.0; MS *m*/*z* (%) 44 (100), 250 (5), 309 (M^+, 6). Anal. ($C_{20}H_{23}NO_2$) C, H, N.

(−)-Methyl 4*β*-(2-Naphthyl)piperidine-3α-carboxylate Hydrochloride (−)-19. A suspension of piperidine (−)-**9** (30 mg, 0.11 mmol), 1,8-bis-(dimethylamino)naphthalene (50 mg, 0.23 mmol), and α-chloroethyl chloroformate (0.10 mL) in 1,2-dichloroethane (6 mL) was stirred at reflux for 3 h. The mixture was cooled to room temperature, diluted with HCl/ether (1.0 M, 20 mL), and the resulting suspension was passed through a short path of silica gel. The silica gel was washed with CH_2Cl_2, and the combined fractions were evaporated in vacuo to give an oil. The oil was dissolved in MeOH (14 mL), and the solution was stirred at reflux for 3 h. The solvent was removed in vacuo to give an oil. This oil was dissolved in ether (3 mL) and treated with HCl/ether (1.0 M, 1 mL), and the resulting suspension was stirred at room temperature for 1 h. The solid was removed by filtration and washed with ether (2 × 5 mL) to give the title compound (24 mg, 71%) as a white solid: mp 78−80 °C; $[\alpha]_D$ −55° (*c* 0.25, $CHCl_3$); ^1H NMR (CD_3OD) δ 2.18 (m, 2H), 3.2−3.4 (m, 3H), 3.40 (s, 3H), 3.56 (d, 1H, $J = 12.6$ Hz), 3.70 (d, 1H, $J = 12.2$ Hz), 3.29 (dd, 1H, $J = 3.6$, 12.0 Hz), 7.30−7.40 (m, 3H), 7.73 (s, 1H), 7.89 (m, 3H). Anal. ($C_{17}H_{19}NO \cdot 1.1HCl$) C, H, N.

Biological Methods. Synaptosomal Uptake of [^{3}H]-Dopamine. The effect of candidate compounds in antagonizing dopamine high affinity uptake was determined using a method previously employed. For [^{3}H]DA uptake, dissected rat striata were homogenized with a Teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at 1000*g*. The supernatant was centrifuged at 17500*g* for 20 min. This P_2 synaptosomal pellet was resuspended in 30 volumes of ice-cold modified KRH buffer. An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 37 °C, and uptake was initiated by the addition of [^{3}H]-dopamine (3−5 nM, final concentration). After 5 min, uptake was terminated by adding 5 mL of cold buffer containing glucosamine as a substitute for NaCl and then finally by rapid vacuum filtration over GF-C glass fiber filters, followed by washing with two 5 mL volumes of ice-cold, sodium-free buffer. Radioactivity retained on the filters was determined by liquid scintillation spectrometry. Specific uptake was defined as that which is sensitive to inhibition by 30 μM cocaine. It is identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. The K_m for [^{3}H]DA uptake in this assay is 50 nM.

Synaptosomal Uptake of [^{3}H]5-Hydroxytryptamine and [^{3}H]Norepinephrine. [^{3}H]5-HT and [^{3}H]NE uptake were measured in an entirely analogous fashion using synaptosomes prepared from rat midbrain or parietal and occipital cortices, respectively. The same buffer was used in all uptake and binding assays. The specific uptake of [^{3}H]5-HT and [^{3}H]NE was defined with 10 μM fluoxetine or 3 μM desipramine, respectively. The K_m values and substrate concentrations used for calculating K_i from IC_{50} values in uptake experiments were 53 nM and 4−5 nM for [^{3}H]5-HT and 54 nM and 8−10 nM for [^{3}H]NE.

Locomotor Studies. Locomotor activity of male Swiss−Webster mice was recorded using Truscan activity monitors (Coulbourn Instruments, Allentown, PA) and a computer. The activity monitors consist of acrylic chambers which are placed inside the sensor ring. The sensor ring is equipped with light-sensitive detectors and infrared light beams. The *X*−*Y* coor-

dinates of the body center of the subject are sampled by scanning the beams, and then the successive locations of coordinates are compared. The sum of distances between successive coordinates is measured as the distance traveled, while the total number of coordinate changes are recorded as the stereotypic movements. Following 1 h of habituation to test arenas, several groups of mice were injected intraperitoneally with different doses of cocaine, piperidine **14**, or saline in a volume of 10 mL/kg. Locomotor activity was recorded in 10 min bins for the next 2 h. The raw data were converted to 30 min totals. The maximal 30 min activity, occurring within the 2 h session following test drug injection, was determined for each dose level and used for plotting dose−response curves.

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Supporting Information Available: Analytical data for compounds listed in Table 1 and tables of crystal data, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters for (−)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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