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Articles

SAR Studies of Piperidine-Based Analogues of Cocaine. 4. Effect of N-Modification and Ester Replacement

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A series of novel N- and 3α-modified piperidine-based analogues of cocaine were synthesized and tested for their ability to inhibit reuptake of DA, 5-HT, and NE by the DA, 5-HT, and NE transporters. N-Demethylation of *trans*-(+)-3α-piperidine-based ligands leads to improved activity at the SERT and NET and modest changes at the DAT. Replacement of the *N*-methyl group in *trans*-(+)-ester **1a** with phenylalkyl groups leads to a modest 2.3-fold improvement in activity at the SERT ($K_i \leq 3.27$ μM), insignificant changes at the NET, and a 3.5-fold loss in activity at the DAT ($K_i \geq 810$ nM); however, such replacement in *cis*-(−)-ester **4**, the more potent isomer of **1a**, leads, in general, to a significant decrease in activity at all monoamine transporters ($K_i > 1$ μM). Other N-modified ligands, including the ligands with polar groups incorporated in the *N*-alkyl substituent (**3e**−**g**) and ligands lacking the basic nitrogen (**3i** and **6d**), show decreased activity at all monoamine transporters, though ligands **3e**−**g** are similar in potency at the NET to **1a**. *N*-Norester **2a**, a possible metabolite of the lead compound **1a**, and alcohol **1c**, a compound with a 3α-substituent that is more stable to metabolism than **1a**, were selected for further behavioral tests in animals. Alcohol **1c** and ester **2a** are similar in potency at the DAT to cocaine, ester **1a**, and oxadiazole **1b**, and both fully substitute for cocaine and have potency similar to that of cocaine in drug discrimination tests. Like cocaine, **1c** increased locomotor activity (LMA) monotonically with time, whereas **2a** produces biphasic effects consisting of initial locomotor depression followed by delayed locomotor stimulation. An interesting difference between cocaine, ester **1a**, alcohol **1c**, and *N*-norester **2a** is that **1c** and **2a** are significantly longer acting in LMA tests. Although this result was anticipated for alcohol **1c**, it is rather surprising for **2a** which has an ester function susceptible to hydrolysis, a pathway of in vivo deactivation of cocaine and its ester analogues. The present results may have important implications for our understanding of the pharmacological mechanisms underlying the behavioral actions of cocaine and of the structural features needed for the design of the new leads in the discovery of a cocaine abuse medication.

Introduction

Cocaine is a widely abused drug. The development of pharmacotherapies that could assist the patient in initiating and maintaining abstinence and in preventing relapse is urgently needed. The complexity of the mechanisms mediating the addictive properties of co-

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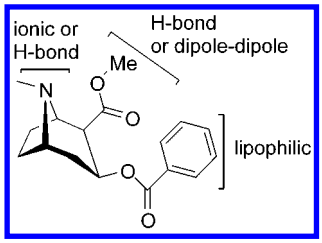


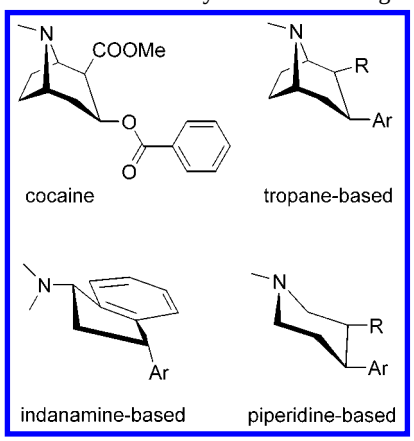
Figure 1. Schematic representation of the key interactions between monoamine reuptake inhibitors and the binding site of the monoamine transporters.

caine is such that it is difficult to define appropriate targets for medication development. Nevertheless, the predominant model for the origin of the reinforcing and rewarding properties of cocaine is the blockade of the dopamine transporter (DAT); most of the drugs generated to date have targeted either the DA receptors or DA transporters.[1−3] Although the importance of the interaction of cocaine with the dopaminergic system ("DA hypothesis") is strongly supported by experimental data, cocaine's effect on the serotonergic system has also been implicated in the cocaine-seeking behavior observed in rats[4−6] and monkeys.[7,8] Recent studies of DAT+SERT knockout mice have shown that the SERT plays an important role in mediating the behavioral actions of cocaine,[9] although interaction with $mGlu_5$ receptor may be involved as well.[10] The DAT, SERT, and NET are also targets for PCP, amphetamines, and other drugs of abuse. Thus, investigation of compounds with various combinations of DAT, SERT, and NET activity might lead to the development of medications or strategies for the treatment of drug abuse and addiction.

The rational design of ligands with a predetermined potency at and selectivity for the DA, 5-HT, and NE transporters is hindered by the lack of knowledge about their 3D structure.[11,12] Most of the potent tropane-based DAT, SERT, and NET inhibitors, including cocaine, are believed to have at least three major interactions with the transporter binding site: one ionic or H-bonding interaction of the basic nitrogen, one dipole−dipole or H-bonding interaction of the ester group of the ligand, and an interaction of the aryl group of the ligand with a lipophilic binding pocket (Figure 1).[13−15] This model has been successfully used for the design of new ligands,[15,16] though for each particular class of ligands certain additional requirements may be present.[17] Although this pharmacophore model was widely recognized, it was shown later for the case of tropane-based compounds that neither the basic nitrogen[18−20] nor the ester group, or indeed any polar group,[21] is needed for high-affinity binding and inhibition of reuptake of monoamines. Therefore, further studies are needed to clarify and rationalize the differences and similarities in the properties and structure of monoamine transporters and their inhibitors.

It is widely recognized that the pharmacodynamics of a drug of abuse and the abuse potential of a drug are closely related.[22] The development of LAAM, a slow onset-of-action drug for treating heroin addiction which is metabolized in vivo to a more active N-demethylated compound, is an excellent example of how N-demethylation could be used for drug development.[23,24] A similar approach has been used for the development of cocaine analogues possessing a slow onset of action[25] as potential medications for cocaine abuse. As previously reported, N-demethylation leads to increased activity of tropane-based[14,26−28] and indanamine-based[25] ligands at the SERT and NET (Chart 1). In the case of tropane-based[29] and indanamine-based ligands,[25] large *N*-alkyl groups were found to cause reduced activity at the DAT, SERT, and NET, although, interestingly, *N*-bromopropyl-, chloropropyl-, fluoropropyl-, and *N*-fluoroethyltropane-based ligands have been found to have a greater affinity for the SERT and a lower affinity for the DAT and NET than the corresponding N-methylated ligands. Therefore, manipulation of the nature of the N-substituent seems to be a reasonable approach for the design of new monoamine blockers.

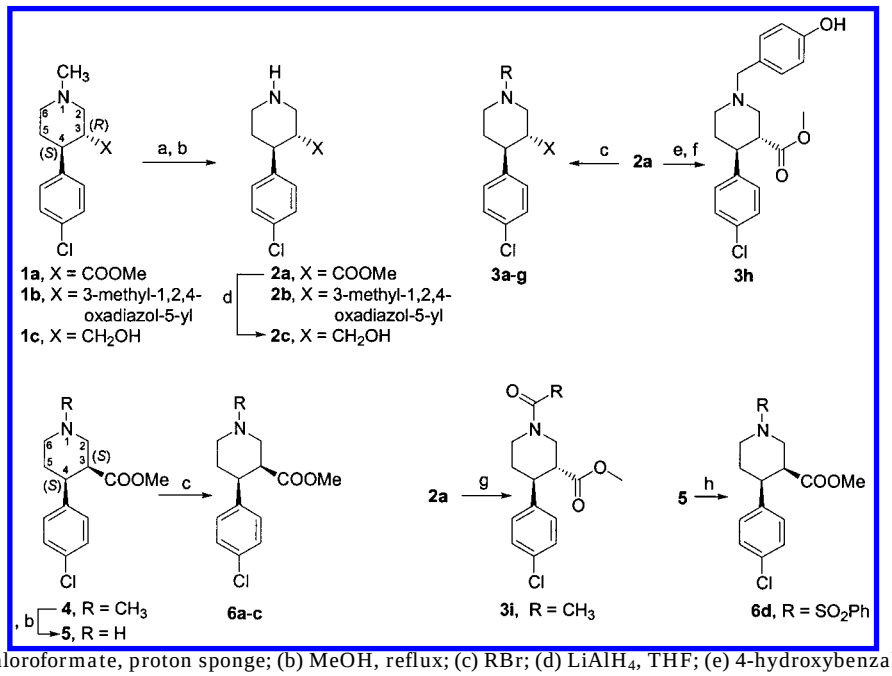
Chart 1. Cocaine and Its Synethetic Analogues



The above considerations led us to the design and synthesis of novel piperidine-based analogues of cocaine that, while remaining potent DAT and NET inhibitors, also exhibit increased activity at the SERT. Recently, the synthesis, pharmacology, and LMA studies of some 3,4-disubstituted piperidine-based ligands and novel bivalent compounds based on these ligands have been reported from our laboratory.[30−32] Most of these compounds represent a series of potent DA and NE reuptake inhibitors with K_i values in the nanomolar range that are less potent inhibitors of the SERT. The results of different animal behavioral tests strongly suggest that ester **1a**, a modestly DAT/NET selective compound, could be used during the treatment of cocaine addiction to prevent relapse.[33] Other piperidine-based ligands have also been found to attenuate the behavioral effects of cocaine.[32] Therefore, ester **1a** was used as the lead compound.

Although the in vivo metabolism of lead compound **1a** is also likely to involve N-demethylation, metabolism of **1a** to the corresponding acid, a compound that is inactive at all monoamine transporters, through esterase action probably will be the dominant pathway in vivo.[34] We reasoned that metabolism via esterase action could be avoided by replacement of the ester group with a bioisosteric group that is more stable to metabolic degradation. In fact, in our previous studies we found that oxadiazole **1b**, although completely cocaine-like, exhibits a significantly longer duration of action,[17b] probably because of its slower rate of metabolism. Therefore, exploration of the effect of N-alkylation and ester replacement on biogenic amine transport in vitro and, for certain selected compounds, on in vivo behavior appears to be a reasonable approach to improving our lead compound.

Scheme 1[a]



[a] (a) α-chloroethyl chloroformate, proton sponge; (b) MeOH, reflux; (c) RBr; (d) $LiAlH_4$, THF; (e) 4-hydroxybenzaldehyde; (f) $NaBH_3CN$, KOH, MeOH; (g) CH_3COCl, NEt_3, CH_2Cl_2; (h) $PhSO_2Cl$, NEt_3, CH_2Cl_2.

Herein, we describe the synthesis of novel N- and 3α-modified piperidine-based analogues of cocaine, and we also report the results of preliminary behavioral studies of **1c** and **2a**.

Chemistry

The synthesis of N- and 3α-modified compounds is outlined in Scheme 1. *Trans*-(+)-ester **1a** and *cis*-(−)-ester **4** were used as the starting materials. The reaction of ester **1a** with α-chloroethyl chloroformate in the presence of 1,8-bis(dimethylamino)naphthalene and reflux of the resulting intermediate in methanol gave the N-demethylated ester **2a**.[35] This N-demethylation procedure was found to be compatible with the oxadiazole moiety, and oxadiazole **2b** was synthesized from oxadiazole **1b** using the same procedure as described for ester **1a**. Alcohols **1c** and **2c** were synthesized by reduction of esters **1a** and **2a** with lithium aluminum hydride. *N*-Norester **2a** was further alkylated by various alkyl bromides in the presence of potassium carbonate using DMF as a solvent to give the corresponding N-substituted esters **3a**−**g** (Scheme 1 and Table 1). The same conditions as above were used to synthesize *cis*-3,4-disubstituted ligands **6a**−**c** from ester **4**. Amides **3i** and **6d** were obtained from *N*-noresters **2a** and **5**, respectively, and the corresponding acid chlorides. Because of the insufficient solubility of the *N*-benzyl compound **3b** for pharmacological tests, we decided to synthesize the more soluble analogue **3h**. Reductive alkylation of the *N*-norester **2a** with 4-hydroxybenzaldehyde and sodium cyanoborohydride gave the *N*-(4-hydroxybenzyl)piperidine ester **3h** in good yield.

Pharmacological and Biological Evaluation

Compounds **2a**−**c**, **3a**, **3c**−**i**, and **6a**−**d** were tested for their ability to inhibit high-affinity uptake of [^{3}H]-DA, [^{3}H]5-HT, and [^{3}H]NE using rat nerve endings (synaptosomes) obtained from brain regions enriched in DAT, SERT, and NET, respectively, according to protocols described earlier.[16,31] The results of reuptake assays for the monoamine transporters and selectivity ratios derived from the K_i values are shown in Table 1.

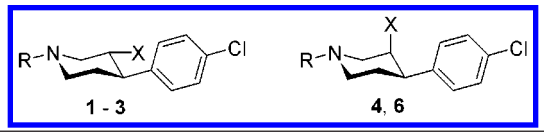
To explore the behavioral consequences of functionalization of lead compound **1a**, we examined compounds **1c** and **2a** in the LMA test in mice and in a drug discrimination paradigm in rats. Locomotor activity of male Swiss-Webster mice was recorded using a Truscan activity monitor (Coulbourn Instruments, Allentown, PA) and a computer, according to a procedure described elsewhere.[16] Following 1 h of habituation to test arenas, several groups of mice were injected intraperitoneally (ip) with different doses of cocaine, test drugs, or appropriate vehicles in a volume of 10 mL/kg. Locomotor activity was measured in 10 min bins for 2 h. The raw data were converted to 30 min totals, which are presented as a function of dose and time in Figure 3.

The drug discrimination study was conducted using Sprague-Dawley rats according to the procedure described earlier.[16] Rats were trained to discriminate cocaine (10 mg/kg, ip) from saline. All drugs were administered intraperitoneally. Cocaine and **2a** were administered 10 min prior to the testing. The LMA tests revealed delayed peak locomotor responses to **1c** occurring about 90 min after its injection. Therefore, **1c** was given 90 min prior to the drug discrimination testing so as to coincide with the time of its peak effect. The response rate on both keys and the percent of cocaine lever-appropriate responding were calculated for each rat. The response rates following the test drug injections were presented as the percent of its corresponding vehicle control response rates. The results are provided in Figure 4.

Results and Discussion

In general, relative to the corresponding *N*-methyl compounds (**1a**−**c**), the *N*-norpiperidines **2a**−**c** exhibited an increased activity at the SERT and NET and only modest changes at the DAT. *N*-Norester **2a** is 20-

Table 1. K_i's for the Inhibition of Reuptake of Monoamines, and Ratios of K_i's for N-modified Piperidine-based Ligands **1a**−**c**, **2a**−**c**, **3a**,**c**−**i**, **4**, **6a**−**d**, and Cocaine



			K_i [a] ± SE, nM			ratio of K_i's		
compd	R	X	[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake	5-HT/DA	NE/DA	NE/5-HT
cocaine[b]	−	−	259 ± 20	155 ± 1	108 ± 4	0.60	0.42	0.70
(+)-**1a**[b]	CH_3	$COOCH_3$	233 ± 62	8490 ± 1430	252 ± 43	36.4	1.08	0.03
(+)-**1b**[b]	CH_3	3-methyl-1,2,4-oxadiazol-5-yl	187 ± 3	5960 ± 80	256 ± 17	31.8	1.37	0.04
(+)-**1c**	CH_3	CH_2OH	497 ± 58	1550 ± 360	198 ± 53	3.12	0.40	0.13
(+)-**2a**	H	$COOCH_3$	279 ± 98	434 ± 50	7.9 ± 3.0	1.56	0.03	0.02
(+)-**2b**	H	3-methyl-1,2,4-oxadiazol-5-yl	189 ± 24	373 ± 4	34 ± 6	1.97	0.18	0.09
(+)-**2c**	H	CH_2OH	836 ± 35	239 ± 28	69 ± 6	0.29	0.08	0.29
(+)-**3a**	isopropyl	$COOCH_3$	6980 ± 130	3740 ± 600	1840 ± 260	0.54	0.26	0.49
(+)-**3b**[c]	$PhCH_2$	$COOCH_3$	−	−	−	−	−	−
(+)-**3c**	$PhCH_2CH_2$	$COOCH_3$	1080 ± 30	2890 ± 80	142 ± 22	2.68	0.13	0.05
(+)-**3d**	$PhCH_2CH_2CH_2$	$COOCH_3$	810 ± 78	3270 ± 160	488 ± 30	4.04	0.60	0.15
(+)-**3e**	$CH_2CH_2CH_2F$	$COOCH_3$	4280 ± 220	>10000	335 ± 74	>2.3	0.08	<0.03
(+)-**3f**	$CH_2CH_2CH_2Cl$	$COOCH_3$	3150 ± 420	>10000	441 ± 86	>3.17	0.14	<0.04
(+)-**3g**	$CH_2CH_2COOCH_2CH_3$	$COOCH_3$	>10000	>10000	2100 ± 650	−	<0.21	<0.21
(+)-**3h**	*p*-$HOPhCH_2$	$COOCH_3$	1620 ± 30	2650 ± 150	1080 ± 60	1.64	0.67	0.41
(+)-**3i**	CH_3CO	$COOCH_3$	>10000	>10000	>10000	−	−	−
(−)-**4**[d]	CH_3	$COOCH_3$	69 ± 8	391 ± 27	88 ± 3	5.67	1.28	0.23
(−)-**6a**	$PhCH_2$	$COOCH_3$	3280 ± 50	2190 ± 50	2980 ± 120	0.67	0.91	1.36
(−)-**6b**	$PhCH_2CH_2$	$COOCH_3$	1020 ± 150	1880 ± 160	233 ± 30	1.84	0.23	0.12
(−)-**6c**	$Ph_2CHCH_2CH_2$	$COOCH_3$	4290 ± 120	2690 ± 40	4340 ± 230	0.63	1.01	1.61
(−)-**6d**	$PhSO_2$	$COOCH_3$	19500	36100	16100	1.85	0.83	0.45

[a] Data are mean ± standard error of at least three experiments as described in ref 31. [b] Data taken from ref 17b. [c] Insoluble, not tested. [d] Data taken from ref 31.

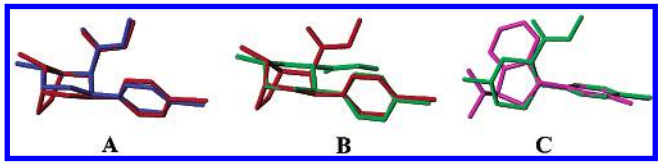


Figure 2. (A) Overlay of *cis*-(−)-piperidine **4** in blue on tropane-based compound RTI-55 in red; (B) overlay of *trans*-(+)-piperidine **1a** in green on tropane-based compound RTI-55 in red; (C) overlay of *trans*-(+)-piperidine **1a** in green on *trans*-*N*,*N*-dimethyl[3-(3′,4′-dichlorophenyl)indan-1-yl]amine in magenta. The lowest-energy conformations of the ligands were minimized using the "Tripos" force field and were overlaid on each other using the "Fit atoms" menu in SYBYL (Tripos, Inc).

and 32-fold more active, oxadiazole **2b** is 16.0- and 7.5-fold more active, and alcohol **2c** is 6.5- and 2.9-fold more active in blocking the reuptake at the SERT and NET, respectively, than the corresponding *N*-methyl ligands **1a**−**c**. The activity at the DAT of *N*-norester **2a** is not different from the activity of the *N*-methyl ester **1a**. The DAT activity of oxadiazole **2b** is almost unchanged, whereas the activity of alcohol **2c** is 1.7-fold lower than the activity of **1c**. The increase of activity at the SERT and NET is in agreement with the previously reported increase of activity at the SERT and NET of N-demethylated tropane-based[26,27] and indanamine-based ligands.[25] Therefore, these results suggest that N-demethylation could provide a rather universal tool for increasing the blocking ability at the SERT and NET, irrespective of the other functional groups of the ligands.

In general, the monoamine-blocking ability of most of the *N*-alkyl compounds in the *trans*-series of piperidine-based ligands without a polar group incorporated into the N-substituent is lower at the DAT and higher at the SERT, with insignificant changes at the NET, compared to that of the lead compound **1a**. The *N*-isopropyl ligand **3a** and the *N*-phenylalkyl ligands **3c**,**d**,**h** are 2.3−3.2-fold more active at the SERT than the parent *N*-methyl compound **1a**, while they are 3.5−29.9-fold less potent at the DAT than **1a**. A loss of activity at the DAT and the SERT was observed for the N-modified esters **3e**,**f** with polar groups incorporated into the N-substituents, which gave rise to especially high activity at the SERT and low activity at the DAT and NET in the case of the corresponding tropane-based ligands. To explore the importance of equatorial (*trans*-series) versus axial (*cis*-series) orientation of the ester group, the *cis*-(−)-piperidine-based ligands **6a**−**d** were also synthesized. Even though ligands from the *cis*-piperidine series mimic the structure of cocaine more precisely and are usually more potent than ligands from the *trans*-piperidine series,[31] compounds **6a**−**c** show lower activity at all monoamine transporters than the *N*-methyl ester **4**. Moreover, phenylalkyl-substituted ligands **6a**−**c** from the *cis*-(−)-series are almost equally inactive at the DAT and SERT as the phenylalkyl-substituted ligands **3c**,**d** from the *trans*-(+)-series. Interestingly, *N*-phenylpropyl and *N*-phenylpentyltropane-based compounds were significantly more potent for the DAT and the SERT compared to the corresponding *N*-methyl ligand WIN35428, whereas *N*-benzyltropane-based ligands were less potent at these transporters.[14]

The difference between the NET-blocking activity of ligands *trans*-(+)-**3c**−**f** and *cis*-(−)-**6b** and the corresponding *N*-methyl ligands *trans*-(+)-**1a** and *cis*-(−)-**4** is insignificant. Interestingly, *trans*-(+)-ligands **3a**, **3g**, and **3h** were 7.3-, 8.3-, and 4.3-fold less active than *N*-methyl ligand **1a**, respectively, whereas *cis*-(−)-

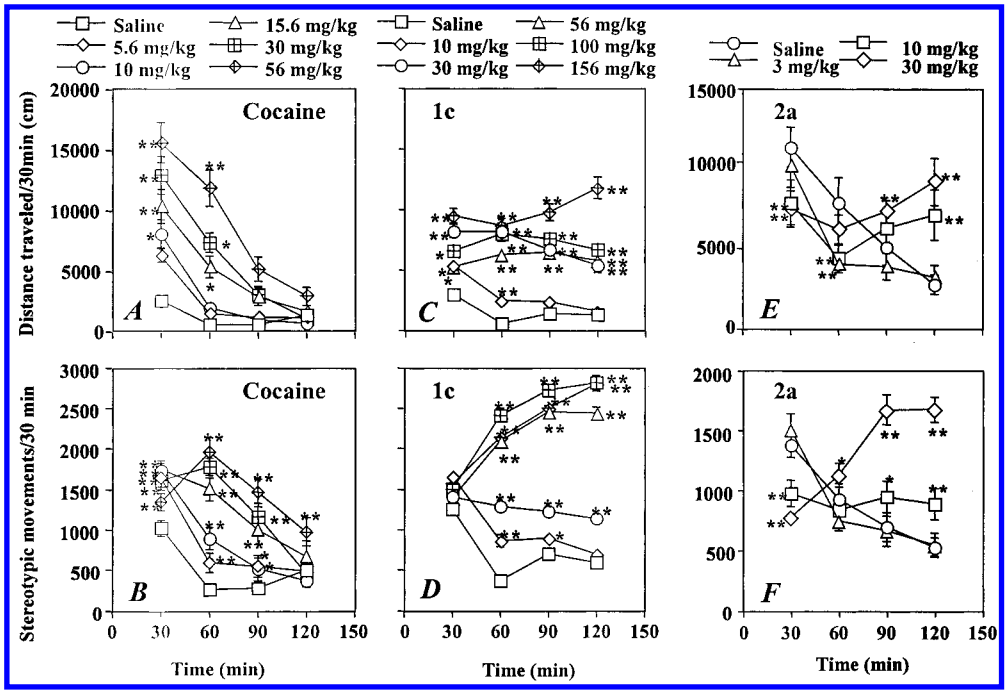


Figure 3. Locomotor effect of cocaine (A, B), **1c** (C, D), and **2a** (E, F) as a function of dose and time during 120-min sessions in male Swiss-Webster mice. *P < 0.05 and **P < 0.01 as compared to the corresponding saline control responses.

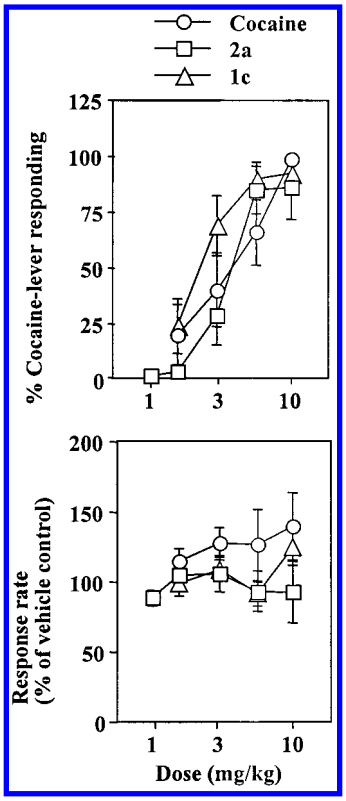


Figure 4. Discriminative stimulus effects of cocaine, **1c**, and **2a** in Sprague-Dawley rats trained to discriminate cocaine (10 mg/kg) from saline.

ligands **6a** and **6c** were 33.9- and 49.3-fold less active than *N*-methyl ligand **4**, respectively. Thus, the NET is much less tolerant to N-substitution in the *cis*-(−)-series than in the *trans*-(+)-series of ligands. Moreover, it appears that the NET is more tolerant to the overall size of the N-substituent, especially if it contains an aryl or polar group, although it might be more sensitive to the bulk of the N-substituent in close proximity to the piperidine ring, because **3a**, **3h**, and **6a** show K_i values greater than 1.0 μM at the NET. In contrast, the activity at the NET of tropane-based and indanamine-based ligands is very sensitive to the overall size of the N-substituent.[14,25,26,28,29]

Ligands **3i** and **6d**, with an amido nitrogen instead of a basic amino nitrogen, were found to be very weak blockers with K_i values greater than 10 μM at all monoamine transporters. This suggests that for piperidine-based ligands protonation of the basic nitrogen may be required for the effective blockade of the monoamines at the DAT, SERT, and NET, although for tropane-based ligands the presence of the basic nitrogen is not essential for high activity.[18−20]

On the basis of the models shown in Figure 2, the dissimilarity in the SAR pattern of the N-modified piperidine-based and indanamine-based compounds could be a result of their different, poorly superimposing scaffolds (Figure 2C). It is, however, quite surprising that the perfectly superimposing N-modified *cis*-(−)-piperidine-based and tropane-based compounds (Figure 2A) also display a nonmatching SAR pattern. The *trans* orientation of the ester group (Figure 2B) may be responsible for a different SAR pattern in the case of the N-modified *trans*-(+)-piperidine-based compounds. An increased flexibility of the piperidine-based ligands compared to the flexibility of the indanamine-based and tropane-based ligands may also be a reason the SAR patterns of these compounds are different.

Despite the fact that alcohol **1c** has only one electron donor atom in its 3α-substituent, it exhibits reuptake-blocking properties comparable to those of ester **1a** and oxadiazole **1b**, compounds with two and three electron donor atoms, respectively. Moreover, alcohol **1c** shows even 5.5-fold higher activity at the SERT (K_i = 1550 nM) than the lead compound **1a**, while alcohol **1c** is 2.1-fold less active at the DAT and 1.3-fold more active at the NET. The fact that *N*-noralcohol **2c** also exhibits a

Table 2. Effect of the Presence of Functional Groups on the Pharmacological Profiles and Behavioral Effects of **1a**−**c** and **2a** in LMA and Drug Discrimination Tests

compd	functional groups N−R[a]	functional groups X[a]	pharm. profile selectivity	locomotor test, cocaine-like	drug discrimination test, cocaine-like	prolonged action[b]
1a[c]	N−CH_3	$COOCH_3$	DAT+NET	reduced	yes	no[d]
1b[e]	N−CH_3	oxadiazolyl	DAT+NET	yes	yes	yes
1c	N−CH_3	CH_2OH	DAT+NET	yes	yes	yes
2a	N−H	$COOCH_3$	NET	yes[f,g]	yes	yes[f]

[a] For definition of N−R and X see general structure **3**. [b] Prolonged action when compared to ester **1a**. [c] Data taken from ref 33. [d] When compared to cocaine. [e] Data taken from ref 17b. [f] At 10 and 30 mg/kg. [g] Significant depressant action at 30 and 60 min.

3-fold decrease in DAT activity, a 1.8-fold increase in SERT activity, and an 8.7-fold decrease in NET activity compared to *N*-norester **2a** indicates that the presence of an ester or oxadiazole group as the 3α-substituent is important for blocking reuptake at the DAT, whereas the presence of an alcohol group favors inhibition of reuptake at the SERT.

To determine how the behavioral pharmacology of **1c** and **2a** differs from that of cocaine, lead compound **1a**, and oxadiazole **1b**, we have used LMA tests in mice and drug discrimination tests in rats. The small structural modifications in the lead molecule, ester **1a**, resulted in intriguing behavioral properties that are summarized in Table 2. The behavioral effects of lead compound **1a** and oxadiazole **1b** were studied earlier,[17b,33] and it has been shown that ester **1a** and oxadiazole **1b** are completely cocaine-like in LMA and drug discrimination tests when tested alone, though **1a** has lower efficacy than cocaine in increasing LMA.

Cocaine (5.6−30 mg/kg) produced rapid and dose-dependent enhancements in the distance traveled ($F_{4,58} = 20.44$, $P < 0.001$) and stereotypic movements ($F_{4,58} = 5.1$, $P = 0.001$) in mice (panels A and B of Figure 3). The duration of locomotor effects of cocaine lasted about 2 h at the maximal dose (30 mg/kg) tested. A two-way analysis revealed significant effects for cocaine-induced changes in the distance traveled ($F(\text{dose})_{1,61} = 55.4$, $P < 0.001$; $F(\text{time})_{3,183} = 0.5$, $P = 0.68$; $F(\text{dose} \times \text{time})_{3,183} = 34.2$, $P < 0.001$) and in the stereotypic movements ($F(\text{dose})_{1,61} = 28.3$, $P < 0.001$; $F(\text{time})_{3,183} = 17.1$, $P < 0.001$; $F(\text{dose} \times \text{time})_{3,183} = 4.6$, $P < 0.01$). Although **1c** is almost 2-fold less potent at the DAT than cocaine, the parent compound **1a**, and oxadiazole **1b**, it produced significant and dose-dependent enhancements in the distance traveled ($F_{5,72} = 7.7$, $P < 0.001$) and stereotypic movements ($F_{5,72} = 31.6$, $P < 0.001$) (panels C and D of Figure 3). A two-way analysis revealed significant effects for **1c**-induced changes in distance traveled ($F(\text{dose})_{5,72} = 9.98$, $P < 0.001$; $F(\text{time})_{3,216} = 3.64$, $P = 0.014$; $F(\text{dose} \times \text{time})_{15,216} = 5.89$, $P < 0.001$) and stereotypic movements ($F(\text{dose})_{5,72} = 52.1$, $P < 0.001$; $F(\text{time})_{3,216} = 12.76$, $P < 0.001$; $F(\text{dose} \times \text{time})_{15,216} = 20.84$, $P = 0.001$). However, the locomotor effects of **1c** were relatively prolonged compared to cocaine and lasted at least 2 h following 30−56 mg/kg doses of **1c**. This may be due to its slower metabolism relative to cocaine, as **1c** lacks an ester group and, thus, will not be subjected to rapid hydrolysis in vivo. The onset of action for **1c** was relatively slower as compared to cocaine, especially on stereotypic movements, which peaked about 90 min after the injection.

In contrast to cocaine and alcohol **1c**, *N*-norester **2a** produced biphasic effects on LMA (panels E and F of Figure 3). A two-way analysis revealed significant changes in the distance traveled ($F(\text{dose})_{1,45} = 0.441$, $P < 0.51$; $F(\text{time})_{3,135} = 37.32$, $P < 0.001$; $F(\text{dose} \times \text{time})_{3,135} = 23.18$, $P < 0.001$) and in the stereotypic movements ($F(\text{dose})_{1,45} = 9.3$, $P < 0.01$; $F(\text{time})_{3,135} = 60.8$, $P < 0.001$; $F(\text{dose} \times \text{time})_{3,135} = 54.4$, $P < 0.001$). There were initial and significant reductions in both distance traveled and stereotypic movements compared to the vehicle control responses 30 and 60 min following 10 and 30 mg/kg doses. Following these initial reductions, there were significant delayed enhancements in the distance traveled and stereotypic movements 90 and 120 min after the administration of 10 and 30 mg/kg doses of **2a**. Doses of **2a** greater than 30 mg/kg produced convulsions (locomotor data are not shown for high doses).

Cocaine produced dose-dependent (1.56−10 mg/kg) and full substitution for cocaine in cocaine-trained animals in a drug discrimination test (Figure 4). Despite some differences in the locomotor effects of **2a** and **1c**, these compounds completely substituted for cocaine in the drug discrimination test. The doses (95% confidence limits) of cocaine, **2a**, and **1c** that produced 50% (ED_{50}) cocaine-appropriate lever responding were 3.48 (2.47−4.65), 3.55 (2.85−4.77), and 2.42 (1.65−3.11) mg/kg, respectively. There were no significant differences in the rates of responding following cocaine injection ($F_{5,60} = 0.46$, $P = 0.83$) and **2a** ($F_{5,30} = 0.45$, $P = 0.8$). However, both **2a** (10 mg/kg) and **1c** (30 mg/kg) at high doses produced either partial (failure to complete all 20 trials of the session) or complete suppression of the responding in 3 out of 10 and 4 out of 12 animals, respectively. Analysis of the data after the exclusion of the above missing data points confirmed that neither **2a** ($F_{5,30} = 0.45$, $P = 0.8$) nor **1c** ($F_{5,35} = 1.5$, $P = 0.2$) had any significant effects on the rates of responding.

An interesting difference between cocaine, ester **1a**, alcohol **1c**, and *N*-norester **2a** is that the latter two compounds are substantially longer acting than cocaine in LMA tests (Figure 3). Although prolonged action is anticipated from compounds lacking the 3α-ester group, such as alcohol **1c** and oxadiazole **1b**, this is a surprising and intriguing fact for *N*-norester **2a**, because the 3α-ester group **2a** should be equally susceptible to hydrolysis as the ester group of cocaine and **1a**. Another interesting result of N-demethylation is the initial depressant action of **2a** followed by delayed locomotor stimulation (panels E and F of Figure 3). We hypothesize that **2a** may initially act on an unidentified pharmacological target that counteracts the LMA produced by **2a**. The initial depression may be a result of the different population of DA, 5-HT, and NE receptors by corresponding monoamines due to the decreased ratio

of K_i values of 5-HT to DA (36.4, 31.8, 3.12, and 1.56 for **1a**, **1b**, **1c**, and **2a**, respectively) and/or the decreased ratio of K_i values of NE to DA (1.08, 1.37, 0.4, and 0.03, respectively), though in that case it is not clear what causes the delayed locomotor stimulation. This hypothesis is supported by the fact that norcocaine, which is, like **2a**, more active at the SERT and NET than cocaine, produced locomotor inhibition when injected intraperitoneally.[36] However, we cannot exclude a direct action of **2a** on other pharmacological systems, such as sodium channels[36] or GABA[37−40] receptors, that have been reported to selectively reduce LMA while leaving intact discriminative stimulus effects. Thus, further investigation of the pharmacological activity of these compounds is clearly warranted.

Conclusions

We have demonstrated that N-demethylation can be successfully used to improve SERT and NET activity of the *trans*-(+)-piperidine-based ligands, and the effect of N-demethylation is independent of the nature of the 3α-substituent. Although N-alkylation can also be used for improving SERT activity in the case of the *trans*-(+) ligands, there appear to be restrictions for the size of the N-substituent and the presence of functional groups in it. The results of the preliminary behavioral tests of **1c** and **2a** are consistent with the DA hypothesis. The prolonged duration of action for oxadiazole **1b** and alcohol **1c** suggests that cleavage of the ester group in **1a** could be one of the pathways of metabolic deactivation of **1a** in vivo. We hypothesize that **2a** has an additional pharmacological action that may be responsible for its initial depressant effects, while its metabolites may be responsible for the delayed locomotor stimulation, although thorough and systematic studies of the neurotransmitter activity of these compounds have yet to be performed. The present results may have important implications for our understanding of the pharmacological mechanisms underlying the behavioral actions of cocaine and of the structural features needed for the design of new leads in the discovery of a cocaine abuse medication.

Experimental Procedures

General Methods. Reagent-grade solvents were used without further purification. All reagents were purchased from commercial sources and were used as received. All reactions were conducted under an atmosphere of nitrogen. ^{1}H and ^{13}C NMR spectra were acquired at nominal frequencies of 300 and 75 MHz, respectively, on a Varian Unity Inova 300 spectrometer. ^{1}H NMR spectra are referenced to internal TMS, and ^{13}C NMR spectra are referenced to the signal of $CDCl_3$ (δ 77.00 ppm). ^{1}H NMR splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). NMR assignments were made with the help of COSY and DEPT experiments. Melting points were determined in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are not corrected. Mass spectra were recorded via direct inlet in the EI mode at an ionization potential of 70 eV on a Shimadzu QP-5000 mass spectrometer. Optical rotation was measured on an Rudolph AUTOPOL III polarimeter. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. Combustion analyses were performed by Micro-Analysis, Inc. (Wilmington, DE). Merck silica gel 60 Geduran (No. 110832-1) with a particle size of 32−63 μm was used for column chromatography. Merck silica gel 60 F_{254} (No. 5715-7) with a layer thickness of 250 μm was used for TLC; the spots were visualized with UV light or an ammonium molybdate/H_2SO_4 solution. Ester **3h** was synthesized according to a procedure published in ref 41. The synthesis of esters **1a** and **4** is described in ref 30.

General Procedure A: N-Demethylation. To a solution of N-methylated compound (3.73 mmol) in CH_2Cl_2 (50 mL) were added 1,8-bisdimethylaminonaphthalene (0.44 g, 2.1 mmol, 0.55 equiv) and α-chloroethyl chloroformate (4.16 g, 29.1 mmol, 3.14 mL, 7.8 eq). The resulting solution was heated at reflux for 1.5 h. After the mixture had cooled to room temperature, 1 M anhydrous hydrogen chloride solution in ether (200 mL) was added; the suspension was filtered though a silica gel plug, and the residue was rinsed with CH_2Cl_2 (2 × 25 mL). The filtrate was concentrated under a flow of argon and mixed with methanol (50 mL). The resulting mixture was stirred at reflux for 1 h, concentrated, mixed with a 0.5 M solution of KOH (30 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (10 mL), concentrated, and purified by column chromatography.

General Procedure B: N-Alkylation. To a solution of *N*-norester **2a** (0.39 mmol) in dry DMF (2 mL) were added alkyl bromide (0.49 mmol, 1.25 equiv) and K_2CO_3 (1.22 mmol, 3.1 equiv) at room temperature. The resulting suspension was stirred in a sealed tube at 90 °C for the amount of time indicated for each compound. The reaction mixture was cooled to room temperature, mixed with water (10 mL), and extracted with ether (3 × 10 mL). The combined organic solutions were washed with brine, concentrated, and purified by column chromatography.

General Procedure C: N-Alkylation. To a solution of ester **4** (0.15 mmol) in acetone (9 mL) were added alkyl bromide (0.5 mmol), NEt_3 (0.11 mL, 0.77 mmol), and KI (0.043 g, 0.26 mmol) at room temperature. The resulting suspension was heated under reflux for 2 h. The reaction mixture was cooled to room temperature, concentrated, diluted with CH_2Cl_2 (30 mL), washed with brine, dried, and again concentrated. The residue was purified by column chromatography.

(3*R*,4*S*)-4-(4-Chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (2a). Following general procedure A, ester **1a** (1.00 g, 3.73 mmol), 1,8-bisdimethylaminonaphthalene (0.44 g, 2.1 mmol), and α-chloroethyl chloroformate (4.16 g, 29.1 mmol, 3.14 mL) gave crude *N*-norester **2a**. Column chromatography with EtOAc/NEt_3/MeOH (8:1:1) as eluent afforded pure *N*-norester **2a** as a colorless glass (0.63 g, 67%): $[\alpha]_D$ +54.0 (*c* 1.33, $CHCl_3$); IR (film) 3331, 2946, 1731, 1493, 1432, 1197, 1171, 1143, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (H_{5ax}, qd, J = 12.0, 4.2 Hz, 1H), 1.81 (H_{5eq}, ddt, J = 13.2, 3.9, 2.7 Hz, 1H), 2.68 (H_3, td, J = 11.1, 3.6 Hz, 1H), 2.76 (H_{6ax}, td, J = 12.6, 3.0 Hz, 1H), 2.83 (H_{2ax}, dd, J = 12.0, 11.1 Hz, 1H), 2.91 (H_4, td, J = 11.4, 3.9 Hz, 1H), 3.18 (H_{6eq}, brd, J = 12.9 Hz, 1H), 3.34 (H_{2eq}, ddd, J = 12.0, 3.6, 0.9 Hz, 1H), 3.45 (s, 3H), 7.14 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 33.86 (CH_2), 44.51 (CH), 46.34 (CH_2), 49.36 (CH_2), 50.04 (CH), 51.26 (CH_3), 128.40 (CH_2), 128.40 (CH_2), 132.00 (C), 142.07 (C), 173.30 (C); MS *m*/*z* (%) 57 (100), 87 (31), 115 (63), 128 (12), 165 (10), 180 (10), 194 (55), 222 (7), 253 (M^+, 32). **2a**·HCl: anal. ($C_{13}H_{16}ClNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-3-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine (2b). Following general procedure A, oxadiazole **1b** (90 mg, 309 μmol), 1,8-bisdimethylaminonaphthalene (364 mg, 170 μmol), and α-chloroethyl chloroformate (2.4 mmol, 260 μL) gave crude oxadiazole **2b**. Column chromatography with EtOAc/NEt_3/MeOH (8:1:1) as eluent afforded pure oxadiazole **2b** as a colorless glass (82 mg, 95%): IR (film) 3319, 2932, 1578, 1493, 1437, 1394, 1364, 1088, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (qd, J = 12.3, 3.9 Hz, 1H), 1.91 (brd, J = 11.7 Hz, 1H), 2.27 (s, 3H), 2.84 (td, J = 12.0, 2.1 Hz, 1H), 2.91−3.14 (m, 2H), 3.20−3.46 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.28, 34.24, 42.43, 45.97, 46.22, 50.51, 128.28, 128.58, 132.36, 140.91, 166.55, 178.93; MS *m*/*z* (%) 59 (100), 82 (19), 98 (11), 111 (28), 138 (15), 165 (9), 190 (24), 221 (8), 235 (4). **2b**·HCl: $[\alpha]_D$ +71.1 (*c* 0.76, $CHCl_3$); anal. ($C_{14}H_{16}ClN_3O$·1.2HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-3-(hydroxymethyl)piperidine (2c). To a solution of *N*-norester **2a** (0.45 g, 1.8 mmol) in anhydrous THF (10 mL) that was cooled to 0 °C was added $LiAlH_4$ (0.07 g, 1.8 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h, mixed with a saturated solution of NH_4Cl (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was concentrated and purified by column chromatography on SiO_2 with EtOAc/NEt_3/MeOH (6:2:2) as eluent to yield pure alcohol **2c** as a colorless glass (0.36 g, 89%): $[\alpha]_D$ +34.6 (*c* 1.36, $CHCl_3$); IR (film) 3290, 2914, 1492, 1090, 1014, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (qd, J = 12.3, 3.9 Hz, 1H), 1.68−1.86 (m, 2H), 3.02−3.16 (m, 2H), 3.20−3.36 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.73 (CH_2), 44.32 (CH), 44.44 (CH), 46.43 (CH_2), 49.66 (CH_2), 62.52 (CH_2), 128.43 (CH), 128.54 (CH), 131.66 (C), 142.79 (C); MS *m*/*z* (%) 56 (72), 69 (18), 86 (45), 103 (8), 115 (15), 125 (14), 138 (7), 152 (14), 194 (37), 225 (M^+, 30). **2c**·HCl: anal. ($C_{12}H_{17}ClNO$·HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-isopropylpiperidine-3-carboxylic Acid Methyl Ester (3a). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and 2-bromopropane (46 μL, 490 μmol) gave crude ester **3a** after 60 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:15:1) as eluent afforded pure ester **3a** as a colorless oil (130 mg, 92%): IR (film) 2964, 1735, 1493, 1173, 1157, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (dd, J = 6.6, 2.7 Hz, 6H), 1.76−1.90 (m, 2H), 2.24−2.40 (m, 1H), 2.38 (t, J = 10.8 Hz, 1H), 2.68−2.90 (m, 3H), 2.95 (bd, J = 11.1 Hz, 1H), 3.11 (ddd, J = 10.8, 3.0, 1.8 Hz, 1H), 3.45 (s, 3H), 7.14 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.87, 18.15, 33.09, 44.75, 48.73, 49.10, 51.38, 51.43, 54.67, 128.45, 128.57, 132.10, 141.87, 173.60; MS *m*/*z* (%) 56 (42), 72 (6), 110 (5), 115 (8), 280 (100), 236 (38), 295 (M^+, 9). **3a**·HCl: $[\alpha]_D$ +43.7 (*c* 0.49, $CHCl_3$); anal. ($C_{16}H_{22}ClNO_2$·HCl) C, H, N.

(3*R*,4*S*)-1-Benzyl-4-(4-chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (3b). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and benzyl bromide (58 μL, 490 μmol) gave crude ester **3b** after 30 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **3b** as a colorless oil (110 mg, 81%): $[\alpha]_D$ +16.4 (*c* 1.07, $CHCl_3$); IR (film) 2946, 2804, 1735, 1493, 1156, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72−1.88 (m, 2H), 2.08−2.20 (m, 1H), 2.21 (t, J = 10.8 Hz, 1H), 2.70−2.84 (m, 1H), 2.86 (td, J = 11.7, 3.6 Hz, 1H), 2.97 (brd, J = 11.4 Hz, 1H), 3.13 (ddd, J = 11.1, 3.6, 1.8 Hz, 1H), 3.40 (s, 3H), 3.50−3.62 (m, 2H), 7.13 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.24−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.92 (CH_2), 44.43 (CH), 48.95 (CH), 51.28 (CH_3), 53.41 (CH_2), 55.82 (CH_2), 62.74 (CH_2), 127.00 (CH), 128.13 (CH), 128.40 (CH), 128.51 (CH), 128.91 (CH), 132.04 (C), 137.76 (C), 141.88 (C), 173.35 (C); MS *m*/*z* (%) 91 (100), 120 (20), 132 (13), 146 (12), 190 (6), 252 (28), 284 (10), 343 (M^+, 11). **3b**·HCl: anal. ($C_{20}H_{22}ClNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(2-phenylethyl)piperidine-3-carboxylic Acid Methyl Ester (3c). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and (2-bromoethyl)benzene (67 μL, 490 μmol) gave crude ester **3c** after 30 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **3c** as a colorless solid (130 mg, 92%): $[\alpha]_D$ +26.8 (*c* 0.605, $CHCl_3$); IR (film) 2947, 1735, 1493, 1193, 1157, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76−1.84 (m, 1H), 1.84 (dd, J = 7.8, 3.3 Hz, 1H), 2.12−2.24 (m, 1H), 2.28 (t, J = 11.1 Hz, 1H), 2.62−2.72 (m, 2H), 2.75−2.96 (m, 4H), 3.10 (brd, J = 11.1 Hz, 1H), 3.26 (ddd, J = 11.1, 3.3, 1.8 Hz, 1H), 3.46 (s, 3H), 7.15 (d, J = 8.4 Hz, 2H), 7.18−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 32.96, 33.49, 44.43, 48.93, 51.42, 53.52, 55.98, 60.23, 125.99, 128.30, 128.48, 128.54, 128.55, 132.15, 139.97, 141.82, 173.36; MS *m*/*z* (%) 91 (6), 105 (100), 163 (6), 223 (19), 266 (100), 326 (3). **3c**·HCl: anal. ($C_{21}H_{24}ClNO_2$·0.9HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(3-phenylpropyl)piperidine-3-carboxylic Acid Methyl Ester (3d). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and 1-bromo-3-phenylpropane (75 μL, 490 μmol) gave crude ester **3d** after 30 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **3d** as a colorless solid (140 mg, 96%): $[\alpha]_D$ +20.9 (*c* 0.575, $CHCl_3$); IR (film) 2946, 1735, 1494, 1157, 1123, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72−1.92 (m, 4H), 2.10−2.12 (m, 1H), 2.16 (t, J = 10.8 Hz, 1H), 2.43 (dd, J = 6.6, 1.1 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.70−2.81 (m, 1H), 2.86 (td, J = 11.4, 3.6 Hz, 1H), 3.00 (brd, J = 11.4 Hz, 1H), 3.16 (ddd, J = 11.1, 3.6, 1.5 Hz, 1H), 3.44 (s, 3H), 7.13 (brd, J = 8.7 Hz, 2H), 7.16−7.31 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 28.51, 32.96, 33.48, 44.41, 48.89, 51.32, 53.50, 56.02, 57.60, 125.63, 128.16, 128.22, 128.41, 128.50, 132.04, 141.85, 141.89, 173.34; MS *m*/*z* (%) 55 (11), 70 (9), 91 (27), 115 (10), 128 (7), 163 (7), 223 (20), 252 (11), 266 (100), 236 (38), 371 (M^+, 11). **3d**·HCl: anal. ($C_{22}H_{26}ClNO_2$·1.2HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(3-fluoropropyl)piperidine-3-carboxylic Acid Methyl Ester (3e). Following general procedure B, *N*-norester **2a** (120 mg, 470 μmol) and 1-bromo-3-fluoropropane (54 μL, 590 μmol) gave crude ester **3e** after 20 h. Column chromatography with EtOAc/hexanes (4:6) as eluent afforded pure ester **3e** as a colorless oil (130 mg, 88%): $[\alpha]_D$ +31.9 (*c* 1.04, $CHCl_3$) IR (film): 2952, 2815, 1731, 1494, 1157, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68−2.00 (m, 4H), 2.08−2.18 (m, 1H), 2.20 (t, J = 10.8 Hz, 1H), 2.54 (brt, J = 7.8 Hz, 2H), 2.72−2.84 (m, 1H), 2.87 (td, J = 11.4, 3.6 Hz, 1H), 3.00 (brd, J = 11.4 Hz, 1H), 3.15 (ddd, J = 10.8, 3.6, 1.8 Hz, 1H), 3.45 (s, 3H), 4.40 (dt, J = 47.4, 6.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.92 (CH_2, d, J_{C-C-F} = 19.6 Hz), 32.99 (CH_2), 44.43 (CH), 48.95 (CH), 51.44 (CH_3), 53.58 (CH_2), 53.98 (CH_2, d, $J_{C-C-C-F}$ = 5.0 Hz), 56.12 (CH_2), 82.26 (CH_2, d, J_{C-F} = 164.0 Hz), 128.51 (CH_2), 128.58 (CH_2), 132.16 (C), 141.89 (C), 173.34 (C); MS *m*/*z* (%) 70 (10), 90 (25), 102 (13), 115 (12), 128 (8), 163 (8), 223 (25), 266 (100), 268 (34), 313 (M^+, 9). **3e**·HCl: anal. ($C_{16}H_{21}ClFNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(3-chloropropyl)piperidine-3-carboxylic Acid Methyl Ester (3f). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and 1-bromo-3-chloropropane (53 μL, 490 μmol) gave crude ester **3f** after 20 h. Column chromatography with EtOAc/hexanes (4:6) as eluent afforded pure ester **3f** as a colorless oil (105 mg, 81%): $[\alpha]_D$ +20.9 (*c* 0.555, $CHCl_3$); IR (film) 2950, 1734, 1494, 1158, 1130, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70−1.86 (m, 2H), 1.97 (brt, J = 7.2 Hz, 2H), 2.13 (td, J = 10.8, 3.6 Hz, 1H), 2.21 (t, J = 10.8 Hz, 1H), 2.55 (t, J = 6.9 Hz, 2H), 2.77 (td, J = 11.1, 5.1 Hz, 1H), 2.85 (td, J = 11.7, 3.6 Hz, 1H), 2.99 (brd, J = 10.8 Hz, 1H), 3.14 (brd, J = 10.8 Hz, 1H), 3.46 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.92 (CH_2), 33.08 (CH_2), 43.10 (CH_2), 44.50 (CH), 49.05 (CH), 51.54 (CH_3), 53.71 (CH_2), 55.14 (CH_2), 56.24 (CH_2), 128.60 (CH), 128.65 (CH), 132.28 (C), 141.93 (C), 173.32 (C); MS *m*/*z* (%) 70 (14), 98 (6), 106 (8), 115 (9), 128 (5), 223 (17), 266 (71), 268 (24), 329 (M^+, 3). **3f**·HCl: anal. ($C_{16}H_{21}Cl_2NO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(2-ethoxycarbonylethyl)-piperidine-3-carboxylic Acid Methyl Ester (3g). Following general procedure B, *N*-norester **2a** (100 mg, 390 μmol) and ethyl 3-bromopropionate (63 μL, 490 μmol) gave crude ester **3g** after 20 h. Column chromatography with EtOAc/hexanes (4:6) as eluent afforded pure ester **3g** as a colorless oil (103 mg, 74%): $[\alpha]_D$ +22.0 (*c* 1.29, $CHCl_3$); IR (film) 2950, 1733, 1494, 1190, 1158, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.66−1.84 (m, 2H), 2.17 (td, J = 10.8, 3.9 Hz, 1H), 2.25 (t, J = 10.8 Hz, 1H), 2.51 (t, J = 7.5 Hz, 2H), 2.70−2.90 (m, 4H), 3.00 (brd, J = 11.1 Hz, 1H), 3.14 (ddd, J = 10.8, 3.3, 1.8 Hz, 1H), 3.45 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.15 (CH_3), 32.32 (CH_2), 32.92 (CH_2), 44.33 (CH), 48.88 (CH), 51.43 (CH_3), 53.24 (CH_2), 53.32 (CH_2), 55.83 (CH_2), 60.36 (CH_2), 128.51 (CH), 128.57 (CH), 132.18 (C), 141.83 (C), 172.28 (C), 173.28 (C); MS *m*/*z* (%) 115 (12), 130 (14), 163 (7), 222 (21), 266 (100), 294 (9), 353 (M^+, 8). **3g**·HCl: anal. ($C_{18}H_{24}ClNO_4$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-(4-hydroxybenzyl)piperidine-3-carboxylic Acid Methyl Ester (3h). To a solution of the hydrochloride of *N*-norester **2a** (100 mg, 340 μmol) in methanol (3 mL) was added 4-hydroxybenzaldehyde (46 mg, 379 μmol). The resulting suspension was stirred at room temperature for 15 min before a solution of sodium cyanoborohydride (3.9 mg, 103 μmol) and potassium hydroxide (6 mg, 103 μM) in methanol (0.5 mL) was added dropwise, and the stirring was continued for 2 h. The solvent was removed, and the residue was mixed with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extract was concentrated and purified by column chromatography (EtOAc/hexanes/NEt_3, 4.5:4.5:1) to give pure ester **3h** as a colorless oil (85 mg, 69%): IR (film) 3409, 2949, 1732, 1515, 1493, 1203, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74−1.88 (m, 2H), 2.10−2.22 (m, 1H), 2.22 (dd, J = 10.8, 10.8 Hz, 1H), 2.70−2.84 (m, 1H), 2.91 (td, J = 11.1, 3.6 Hz, 1H), 3.06 (brd, J = 12.3 Hz, 1H), 3.17 (m, 1H), 3.43 (s, 3H), 3.46−3.60 (m, 2H), 6.68 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.53 (CH_2), 44.38 (CH), 48.61 (CH), 51.55 (CH_3), 53.21 (CH_2), 55.46 (CH_2), 62.24 (CH_2), 115.37 (CH), 128.48 (CH), 128.54 (CH), 130.82 (CH), 132.19 (C), 141.60 (CH), 155.44 (C), 173.72 (C); MS *m*/*z* (%) 42 (23), 56 (18), 77 (18), 107 (100), 148 (9), 162 (5), 194 (9), 252 (30), 300 (6), 328 (3), 359 (M^+, 10). **3h**·HCl: $[\alpha]_D$ +29.2 (*c* 0.39, $CHCl_3$); anal. ($C_{20}H_{22}ClNO_3$·1.2HCl) C, H, N.

(3*R*,4*S*)-1-Acetyl-4-(4-chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (3i). To a solution of *N*-norester **2a** (200 mg, 790 μmol) in dry CH_2Cl_2 (3 mL) were added acetyl chloride (73 μL, 1.02 mmol) and NEt_3 (142 μL, 1.02 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. A saturated solution of NH_4Cl (10 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The combined organic solutions were washed with brine, concentrated, and purified by column chromatography with EtOAc as eluent. Evaporation of the solvent gave pure compound **3i** as a colorless glass (mixture of *Z* and *E* isomers, 220 mg, 94%): $[\alpha]_D$ +12.9 (*c* 0.84, $CHCl_3$); IR (film) 2950, 1733, 1494, 1190, 1158, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54−1.74 (m, 2H), 1.80−1.96 (m, 2H), 2.15 (s, 3H, $NCOCH_3$, *Z* or *E* isomer), 2.16 (s, 3H, $NCOCH_3$, *E* or *Z* isomer), 2.58−2.78 (m, 4H), 2.94−3.08 (m, 2H), 3.14−3.34 (m, 2H), 3.94 (brd, J = 13.8 Hz, 1H), 4.04 (bd, J = 11.7 Hz, 1H), 4.77 (brd, J = 13.8 Hz, 1H), 4.88−5.20 (m, 1H), 7.11 (brd, J = 8.1 Hz, 4H), 7.27 (brd, J = 8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.27, 21.30, 31.95, 33.04, 41.61, 43.67, 44.58, 44.81, 46.43, 47.92, 48.55, 49.20, 51.50, 51.65, 128.36, 128.39, 128.59, 132.54, 140.57, 168.74, 172.35; MS *m*/*z* (%) 82 (11), 114 (11), 151 (3), 194 (6), 236 (21), 252 (15), 295 (M^+, 12). **3i**·HCl: anal. ($C_{15}H_{18}ClNO_3$) C, H, N.

(3*S*,4*S*)-4-(4-Chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (5). Following general procedure A, ester **4** (300 mg, 1.18 mmol), 1,8-bisdimethylaminonaphthalene (140 mg, 660 μmol), and α-chloroethyl chloroformate (9.26 mmol, 1.0 mL) gave crude *N*-norester **5**. Column chromatography with EtOAc/NEt_3/MeOH (8:1:1) as eluent afforded pure *N*-norester **5** as a colorless glass (210 mg, 74%): $[\alpha]_D$ −143.0 (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.62−1.73 (m, 1H), 2.34 (qd, J = 12.6, 3.9 Hz, 1H), 2.68−2.84 (m, 2H), 2.93−3.16 (m, 3H), 3.34 (t, J = 13.5 Hz, 2H), 3.45 (s, 3H), 7.12 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.7, 42.9, 45.7, 46.4, 48.9, 51.3, 128.6, 128.7, 132.5, 141.8, 174.0; MS *m*/*z* (%) 57 (100), 194 (41), 253 (M^+, 20).

(3*S*,4*S*)-1-Benzyl-4-(4-chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (6a). Following general procedure C, amine **4** (37 mg, 150 μmol) and benzyl bromide (60 μL, 500 μmol) gave crude ester **6a** after 2 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **6a** as a white solid (42 mg, 83%): mp 119−120 °C; $[\alpha]_D$ −23.0 (*c* 0.56, $CHCl_3$); IR (film) 2801, 1734, 1492, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76−1.86 (m, 1H), 2.24 (td, J = 11.4, 3.0 Hz, 1H), 2.34 (dd, J = 11.4, 3.0 Hz, 1H), 2.70 (qd, J = 11.7, 3.9 Hz, 1H), 2.78−2.85 (m, 1H), 2.90−2.96 (m, 1H), 3.06 (d, J = 11.1 Hz, 1H), 3.22 (d, J = 11.4 Hz, 1H), 3.42 (d, J = 13.5 Hz, 1H), 3.49 (s, 3H), 3.67 (d, J = 13.2 Hz, 1H), 7.30 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 26.7, 42.1, 46.5, 51.3, 54.3, 56.2, 62.7, 127.2, 128.3, 128.9, 129.3, 132.0, 138.7, 142.0, 172.6; MS *m*/*z* (%) 91 (100), 252 (26), 343 (M^+, 7). Anal. ($C_{20}H_{22}ClNO_2$) C, H, N.

(3*S*,4*S*)-4-(4-Chlorophenyl)-1-(2-phenylethyl)piperidine-3-carboxylic Acid Methyl Ester (6b). Following general procedure B, ester **4** (52 mg, 210 μmol) and (2-bromoethyl)-benzene (34 μL, 250 μmol) gave crude ester **6b** after 12 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **6b** as a colorless oil (54 mg, 73%): $[\alpha]_D$ −15.3 (*c* 0.43, $CHCl_3$); IR (film) 2950, 1744, 1493, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (dd, J = 12.6, 3.0 Hz, 1H), 2.23 (dt, J = 11.1, 2.7 Hz, 1H), 2.44 (dd, J = 11.4, 3.3 Hz, 1H), 2.50−2.90 (m, 6H), 2.96−3.03 (m, 1H), 3.07 (d, J = 10.8 Hz, 1H), 3.38 (dd, J = 11.1, 1.5 Hz, 1H), 3.50 (s, 3H), 7.15−7.31 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 26.9, 33.7, 42.0, 46.4, 51.5, 54.3, 56.3, 60.4, 126.2, 128.3, 128.5, 129.0, 129.2, 132.0, 140.7, 141.9, 172.7; MS *m*/*z* (%) 223 (43), 266 (M^+, 100). Anal. ($C_{21}H_{24}ClNO_2$) C, H, N.

(3*S*,4*S*)-4-(4-Chlorophenyl)-1-(3,3-diphenylpropyl)piperidine-3-carboxylic Acid Methyl Ester (6c). Following general procedure B, amine **4** (32 mg, 130 μmol) and Ph_2CHCH_2I (50 mg, 150 μmol) gave crude ester **6c** after 12 h. Column chromatography with EtOAc/hexanes/NEt_3 (4:6:1) as eluent afforded pure ester **6c** as a colorless oil (0.045 g, 80%): $[\alpha]_D$ −35.1 (*c* 0.57, $CHCl_3$); IR (film) 2948, 1742, 1493, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (dd, J = 12.3, 3.3 Hz, 1H), 2.04−2.38 (m, 6H), 2.64 (dq, J = 11.4, 3.9 Hz, 1H), 2.78 (dt, J = 12.0, 4.2 Hz, 1H), 2.86−3.00 (m, 2H), 3.27 (dd, J = 11.4, 1.5 Hz, 1H), 3.52 (s, 3H), 4.06 (t, J = 7.5 Hz, 1H), 7.12−7.32 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 26.8, 32.9, 42.1, 46.5, 48.4, 51.4, 54.3, 56.3, 126.2, 126.3, 128.1, 128.2, 128.3, 128.5, 128.6, 129.2, 132.0, 142.0, 145.0, 145.2, 172.7; MS *m*/*z* (%) 266 (100), 447 (M^+, 15). Anal. ($C_{28}H_{30}ClNO_2$) C, H, N.

(3*S*,4*S*)-1-Benzenesulfonyl-4-(4-chlorophenyl)piperidine-3-carboxylic Acid Methyl Ester (6d). Following the procedure described for **3i**, amine **4** (42 mg, 170 μmol) and $PhSO_2Cl$ (25 μL, 200 μmol) gave crude amide **6d** after 2 h. Column chromatography with EtOAc/hexanes (4:6) as eluent afforded pure amide **6d** as a white solid (51 mg, 82%): mp 76−78 °C; $[\alpha]_D$ −9.8 (*c* 0.44, $CHCl_3$); IR (film) 2853, 1740, 1493, 1236, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82−1.92 (m, 1H), 2.58 (td, 1H, J = 11.1, 2.7 Hz, 1H), 2.72 (qd, J = 12.0, 3.6 Hz, 1H), 2.56−2.87 (m, 2H), 2.97−3.04 (m, 1H), 3.55 (s, 3H), 3.86 (dd, J = 11.7, 1.8 Hz, 1H), 4.09 (qd, J = 12.0, 1.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.52−7.66 (m, 3H), 7.77−7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.1, 41.5, 45.3, 46.3, 48.7, 51.9, 127.8, 128.6, 129.1, 129.3, 132.6, 133.1, 136.7, 140.4, 171.0; MS *m*/*z* (%) 220 (15), 252 (M^+, 100). Anal. ($C_{19}H_{20}ClNO_4S$) C, H, N.

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