J. Med. Chem. 2004, 47, 3009−3018 3009

Synthesis, Molecular Modeling, and Biological Studies of Novel Piperidine-Based Analogues of Cocaine: Evidence of Unfavorable Interactions Proximal to the 3α-Position of the Piperidine Ring

Pavel A. Petukhov,*,† Jianrong Zhang,§ Cheng Z. Wang,‡ Yan Ping Ye,‡ Kenneth M. Johnson,‡ and Alan P. Kozikowski†

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy (MC 781), University of Illinois at Chicago, 833 S. Wood Street 539, Chicago, Illinois 60612, Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77555-1031, and Georgetown University Medical Center, 3900 Reservoir Road, N.W., Washington, DC 20007

Received July 7, 2003

A qualitative model for the binding pocket proximal to the 3α-substituent of the piperidine-based monoamine transporter ligands was proposed and tested. Based on this model, a new series of druglike 3α-modified piperidine-based analogues of cocaine were designed, synthesized, and studied for their ability to inhibit reuptake of DA, 5-HT, and NE by the DA, 5-HT, and NE transporters. We found that the insertion of at least one additional methylene group between the piperidine ring and the polar group in the 3α-substituent dramatically improves the activity of the compounds that are generally inactive without this additional linker. Molecular modeling analysis showed that the more flexible 3α-substituents can avoid unfavorable interactions with the binding sites of DAT, SERT, and NET. The present results may have important implications for the elucidation of the structural differences between DA, 5-HT, and NE transporters and for the further design of new leads for development of cocaine abuse medication as well as certain neurological disorders such as ADHD and depression.

Introduction

Multiple studies suggest that alterations in dopamine (DA), serotonin (5-HT), and norepinephrine (NE) neurotransmitter systems play key roles in drug abuse and addiction[1−7] as well as certain neurological disorders.[8−14] Modulation of DA, 5-HT, and NE levels in neurotransmitter systems through blockade of DA, 5-HT, and NE reuptake transporters (DAT, SERT, and NET, respectively) represents one approach to the treatment of CNS disorders[8,15,16] and drug addiction.[17] To uncover details of the 3D-topology of the monoamine transporters and to gain better understanding of structural requirement for desired potency and selectivity, a large number of SAR (reviewed recently in refs 17 and 18) and 2D- and 3D-QSAR[19−32] studies were conducted. Despite the importance of the monoamine transporters, our understanding of the structural features of the DA, 5-HT, and NE transporters is still far from comprehensive. For example, even if the piperdine-based compounds were initially designed as less rigid mimics of cocaine and known tropane-based ligands, it is still unknown whether the piperidine-based compounds bind to the same site as tropane-based ligands or any other monoamine transporters blockers. Thus, a significant number of pieces from the "monoamine transporter puzzle" is missing, and studies providing additional insights into the putative structure and key features of the DA, 5-HT, and NE binding sites in the DAT, SERT, and NET are needed.

Recently, the synthesis and biological properties of several series of piperidine-based analogues of cocaine were published.[33−38] Interestingly, most of the *trans*-(+)-3α-substituted-4-(4-chlorophenyl)piperidine-based ligands[33,37,38] excluding bivalent ligands[35,36] are active at the DAT and NET. It was also found that 3α-amido and bulky 3α-oxadiazolyl *trans*-(+)-piperidine-based ligands, which are biogenenically more stable than esters and thus more attractive as potential therapies, are inactive,[35−37] which led us to hypothesize that the binding site of the DAT and NET in close proximity to the 3α-position of the piperidine ring is compact and cannot accommodate bulky rigid substituents such as 3-substituted 1,2,4-oxadiazolyl groups.[37] On the basis of these data, we reasoned that the insertion of additional flexible lipophillic chain may lead to greater activity at one or more monoamine transporters.

To support the above hypothesis and to gain a better understanding of both key structural features and differences among the monoamine transporters, we have prepared and tested the ability of several new compounds in a series of piperidine-based analogues of cocaine to inhibit biogenic amine transport by the DAT, NET, and SERT.

Chemistry

The synthetic pathways to the majority of the C-0 series (Figure 1) of compounds were published earlier[35−37] and are not shown. The synthesis of compounds **1b**, **1g**, and **1l** was carried out following the procedures de-

* To whom correspondence should be addressed: Phone: +1-312-996-4174. Fax: +1-312-996-7107. E-mail: pap4@uic.edu. Former address: Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3900 Reservoir Road, N. W., Washington, DC 20007.
† University of Illinois at Chicago.
‡ University of Texas Medical Branch.
§ Georgetown University Medical Center.

10.1021/jm0303296 CCC: $27.50 © 2004 American Chemical Society
Published on Web 05/12/2004

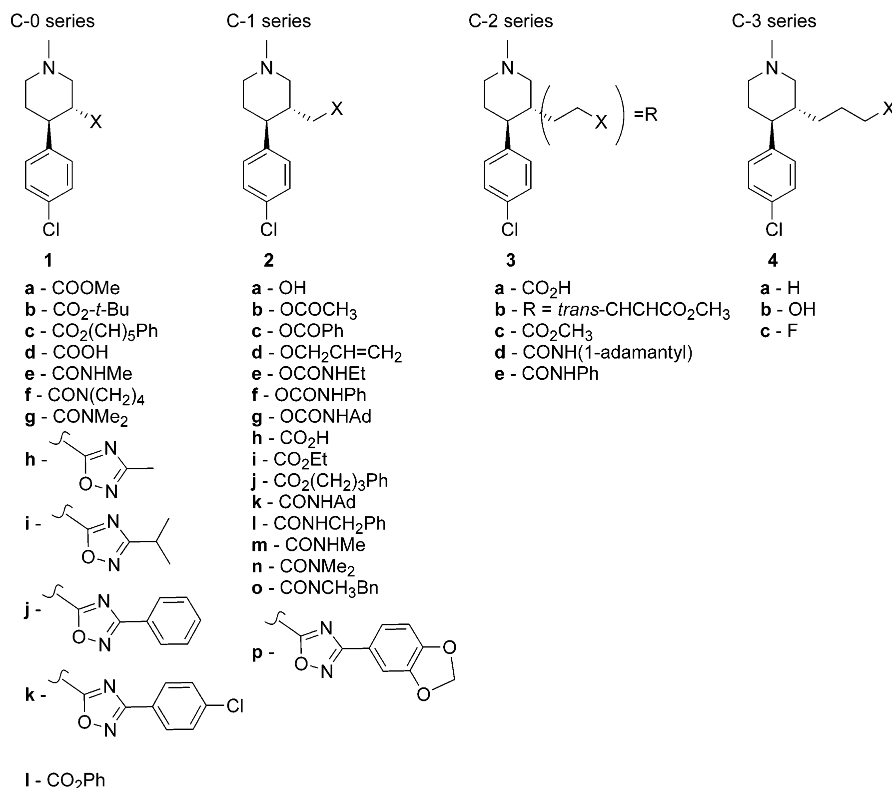
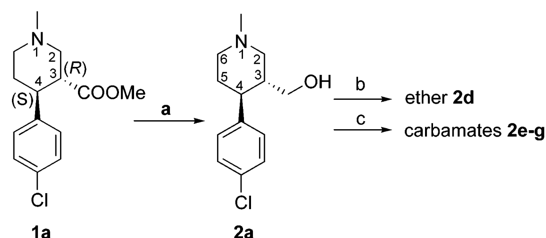


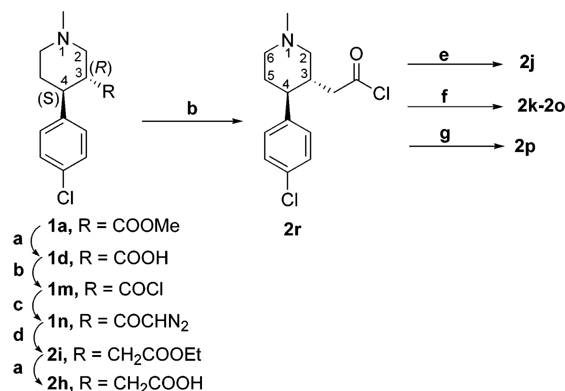
Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF; (b) (i) NaH, (ii) $CH_2{=}CHCH_2Br$; (c) isocyanate, CuCl, pyridine–toluene.

Scheme 2[a]



[a] Reagents and conditions: (a) 6 N HCl, reflux; (b) oxalyl chloride, cat. DMF, CH_2Cl_2; (c) CH_2N_2, NEt_3, Et_2O; (d) $PhCO_2Ag$, Et_3N, EtOH, reflux; (e) pyridine, ROH; (f) NHR^1R^2; (g) (i) 3,4-methylenedioxybenzamidoxime, pyridine, reflux; (ii) AcOH, reflux.

scribed earlier[33−38] for their analogues and is not shown as well. The synthesis of the C-1 series of compounds is outlined in Scheme 1 and Scheme 2. Alkylation of alcohol **2a**[38] with allyl bromide led to ether **2d**. The reaction of alcohol **2a** with the corresponding isocyanates in the presence of CuCl as catalyst afforded carbamates **2e**−**g** (Scheme 1). Ester **2i** was synthesized according to the Arndt−Eistert procedure (Scheme 2). Accordingly, *trans*-(+)-ester **1a** was converted to the acid chloride **1m**, which was then reacted with diazomethane to give the corresponding diazoketone **1n**. The Wolff rearrangement of **1n** in the presence of silver benzoate and triethylamine in ethanol gave ester **2i** as a single diastereoisomer with retention of configuration. Next, ester **2i** was hydrolyzed to the acid **2h**, which was converted to the acid chloride **2r**. The resulting acid chloride **2r** was used as the starting material for the straightforward synthesis of ester **2j**, amides **2k**−**o**, and oxadiazole **2p** as described earlier.[33−38]

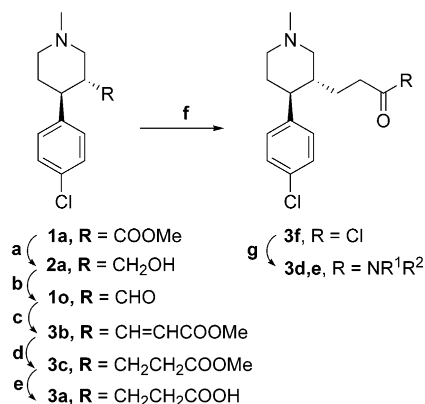
The compounds of series C-2 were synthesized as shown in Scheme 3. Ester **1a** was reduced, and the resulting alcohol **2a** was oxidized to the aldehyde **1o** using Swern conditions. Aldehyde **1o** was then reacted with trimethyl phosphonoacetate to give predominantly *E*-**3b**. The double bond in **3b** was reduced with magnesium in methanol to give the saturated ester **3c**. The synthesis of amides **3d** and **3e** was performed according to the procedure described earlier for amides **1e**−**g**.[36]

The synthesis of the C-3 series of compounds is outlined in Scheme 4. Swern oxidation of **2a** and Wittig olefination of the resultant aldehyde **1o** with ethylidenetriphenylphosphorane afforded compound **4a**. Reduction of **3c** with LAH in THF gave alcohol **4b**, which was then converted to the fluoride **4c** using diethylaminosulfur trifluoride.

Pharmacological and Biological Evaluation

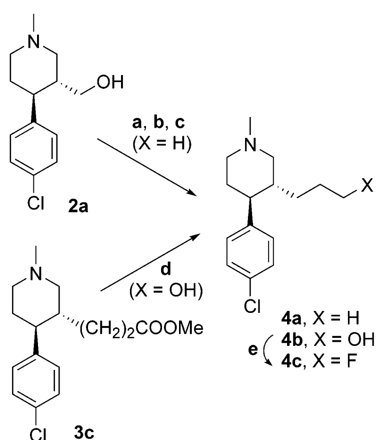
Compounds **1b**−**d**, **1f**, **1g**, **1l**, **2b**−**p**, **3a**−**e**, and **4a**−**c** were tested for their ability to inhibit high affinity uptake of [^{3}H]DA, [^{3}H]5-HT, and [^{3}H]NE using rat nerve endings (synaptosomes) obtained from brain regions

Scheme 3[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF; (b) oxalyl chloride, DMSO; (c) NaH, trimethyl phosphonoacetate, THF; (d) Mg, methanol; (e) 6 N HCl, reflux; (f) oxalyl chloride, cat. DMF, CH_2Cl_2; (g) NHR^1R^2, pyridine.

Scheme 4[a]



[a] Reagents and conditions: (a) oxalyl chloride, DMSO; (b) $Ph_3P{=}CHCH_3$, THF; (c) H_2, 5% Pt/C; (d) $LiAlH_4$, THF; (e) DAST, CH_2Cl_2.

enriched in DAT, SERT, and NET, respectively, according to protocols described earlier.[34] The results of reuptake assays for the monoamine transporters and selectivity ratios derived from the K_i values are shown in Table 1. Compounds **1a**, **1e**, **1h**–**k**, **2a** were tested earlier.[35–37]

Molecular Modeling

All calculations were perfomed using variuos modules availbale in Sybyl.[39] Amide **2l** was manually superimposed on the molecule of WIN35428 using the piperdine ring in a "chair" conformation as a template. The position of the 3α-substituent of **2l** was adjusted to maintain the closest overlap between the ester group of WIN35428 and the amide group of **2l**. All ligands in C0–C3 series were minimized using default settings in MAXIMIN2 minimizer and Tripos force field.[39] AM1 charges were assigned to all minimized ligands using MOPAC module. The ligands making up the C0–C3 series were flexibly superimposed on **2l** using the FlexS[40,41] module. The following parameters were used for the FlexS setup: the piperidine ring was used as a template for flexible alignment; minimum volume overlap was set at 0.6; number of alignments per ligands was 30. Compounds **1b** and **1e** failed to be overlaid and thus were superimposed manually. After that, the ligands in the resulting overlay were additionally aligned using the "align database" feature in Sybyl. The resulting superposition is shown in Figure 2A.

A Connoly surface of the superposition was constructed using MOLCAD module. The resulting surface was mapped by the electrostatic (Figure 2B) and lipophillic (Figure 2C) potentials of the molecules in the superposition. The space occupied by the 3α-substituents in C0–C3 series was split onto four different areas according to the nature of the occupying it groups: (1) electrostatic exclusion area (EEA) occupied by electron-rich groups in 3α-substituents in the C0 series; (2) steric exclusion area (SEA) occupied by bulky 3α-substituents in the C0 series; (3) electrostatic inclusion area (EIA) occupied by electron-rich groups in 3α-substituents in C1–C3 series; (4) steric inclusion area (SIA) occupied by the lipophilic groups in C0–C3 series. The C0 series was separated from C1–C3 series, and additional Connoly surfaces were constructed for the series C0 and C1–C3. To simplify the representation, only most electronegative areas of the resulting surfaces are shown in Figure 3. CLogP of all compounds in Table 1 were calculated using the CLogP module.

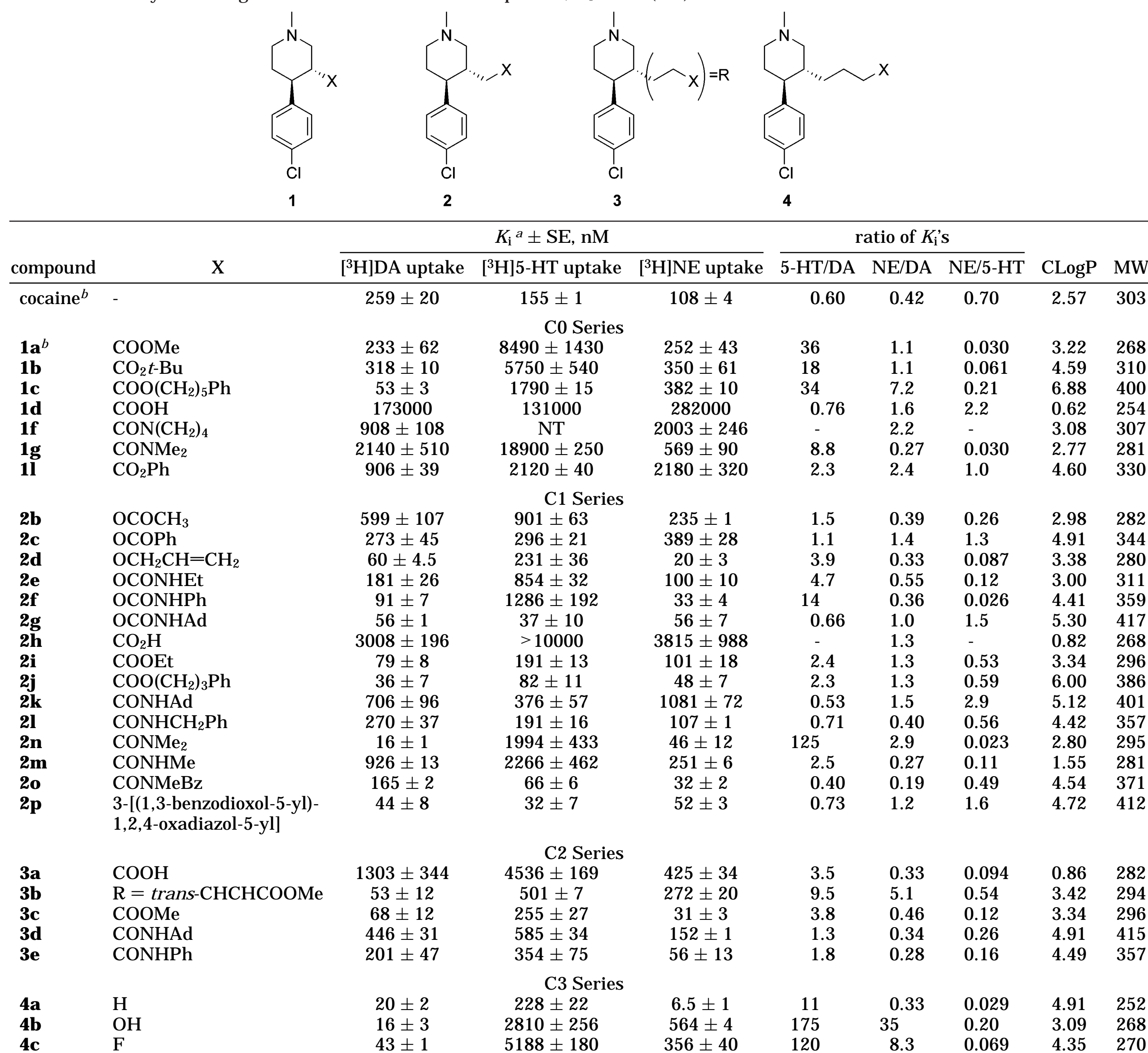
Results and Discussion

A new series of piperidine ligands was designed to garner support for our hypothesis that a region of steric exclusion in the DA, 5-HT, and NE transporters not only exists as suggested earlier[37] but can be avoided by using proper ligand design. Our present results have shown that, in general, the compounds from the C1–C3 series are more active at all transporters than compounds from the C0 series. The data are summarized in Table 1.

tert-Butyl ester **1b** is slightly less active at all monoamine transporters than methyl ester **1a**. The replacement of the ester methyl group in **1a** with 5-phenylpentyl substituent in **1c** led to 4.4- and 4.7-fold improvement of the activity at the DAT and SERT, respectively, whereas the activity at the NET remained almost the same. Unlike them, phenyl ester **1l** is 3.9- and 8.7-fold less active in blocking the DAT and NET, respectively, and 4.0-fold more active at the SERT than **1a**. Esters **2i**, **2j**, and **3c** are 2.9-, 6.5-, and 3.4-fold more active in blocking reuptake at the DAT, 44-, 104-, and 33-fold more active at the SERT, and 2.5-, 5.3-, and 8.1-fold more active at the NET than ester **1a**, respectively. Unlike flexible analogues, the rigid ester **3b** exhibited 4.4- and 17-fold increased activity at the DAT and SERT compared to **1a**, respectively, and only modest changes at the NET.

An additional methylene group between the piperidine ring and the carboxyl group in acid **2h** improved its activity 58- and 74-fold at the DAT and NET, respectively, compared to that of **1d**. Introduction of one additional methylene group in **3a** led to even more dramatic effect, **3a** is 133-, 29-, and 664-fold more active at the DAT, SERT, and NET than **1d**. Similarly, introduction of flexible methylene linkers into the amides resulted in a significant increase in activity of these amides. Amides **1e**–**g** (but not bivalent amides[34,35]) in the C0 series of ligands generally exhibit poor activities in the 0.6 μM–53 mM range at all transporters. Unlike amides from the C0 series, their homologues

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



compound	X	K_i [a] ± SE, nM [³H]DA uptake	[³H]5-HT uptake	[³H]NE uptake	ratio of K_i's 5-HT/DA	NE/DA	NE/5-HT	CLogP	MW
cocaine[b]	-	259 ± 20	155 ± 1	108 ± 4	0.60	0.42	0.70	2.57	303
			C0 Series						
1a[b]	COOMe	233 ± 62	8490 ± 1430	252 ± 43	36	1.1	0.030	3.22	268
1b	CO_2*t*-Bu	318 ± 10	5750 ± 540	350 ± 61	18	1.1	0.061	4.59	310
1c	$COO(CH_2)_5Ph$	53 ± 3	1790 ± 15	382 ± 10	34	7.2	0.21	6.88	400
1d	COOH	173000	131000	282000	0.76	1.6	2.2	0.62	254
1f	$CON(CH_2)_4$	908 ± 108	NT	2003 ± 246	-	2.2	-	3.08	307
1g	$CONMe_2$	2140 ± 510	18900 ± 250	569 ± 90	8.8	0.27	0.030	2.77	281
1l	CO_2Ph	906 ± 39	2120 ± 40	2180 ± 320	2.3	2.4	1.0	4.60	330
			C1 Series						
2b	$OCOCH_3$	599 ± 107	901 ± 63	235 ± 1	1.5	0.39	0.26	2.98	282
2c	OCOPh	273 ± 45	296 ± 21	389 ± 28	1.1	1.4	1.3	4.91	344
2d	$OCH_2CH{=}CH_2$	60 ± 4.5	231 ± 36	20 ± 3	3.9	0.33	0.087	3.38	280
2e	OCONHEt	181 ± 26	854 ± 32	100 ± 10	4.7	0.55	0.12	3.00	311
2f	OCONHPh	91 ± 7	1286 ± 192	33 ± 4	14	0.36	0.026	4.41	359
2g	OCONHAd	56 ± 1	37 ± 10	56 ± 7	0.66	1.0	1.5	5.30	417
2h	CO_2H	3008 ± 196	>10000	3815 ± 988	-	1.3	-	0.82	268
2i	COOEt	79 ± 8	191 ± 13	101 ± 18	2.4	1.3	0.53	3.34	296
2j	$COO(CH_2)_3Ph$	36 ± 7	82 ± 11	48 ± 7	2.3	1.3	0.59	6.00	386
2k	CONHAd	706 ± 96	376 ± 57	1081 ± 72	0.53	1.5	2.9	5.12	401
2l	$CONHCH_2Ph$	270 ± 37	191 ± 16	107 ± 1	0.71	0.40	0.56	4.42	357
2n	$CONMe_2$	16 ± 1	1994 ± 433	46 ± 12	125	2.9	0.023	2.80	295
2m	CONHMe	926 ± 13	2266 ± 462	251 ± 6	2.5	0.27	0.11	1.55	281
2o	CONMeBz	165 ± 2	66 ± 6	32 ± 2	0.40	0.19	0.49	4.54	371
2p	3-[(1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]	44 ± 8	32 ± 7	52 ± 3	0.73	1.2	1.6	4.72	412
			C2 Series						
3a	COOH	1303 ± 344	4536 ± 169	425 ± 34	3.5	0.33	0.094	0.86	282
3b	R = *trans*-CHCHCOOMe	53 ± 12	501 ± 7	272 ± 20	9.5	5.1	0.54	3.42	294
3c	COOMe	68 ± 12	255 ± 27	31 ± 3	3.8	0.46	0.12	3.34	296
3d	CONHAd	446 ± 31	585 ± 34	152 ± 1	1.3	0.34	0.26	4.91	415
3e	CONHPh	201 ± 47	354 ± 75	56 ± 13	1.8	0.28	0.16	4.49	357
			C3 Series						
4a	H	20 ± 2	228 ± 22	6.5 ± 1	11	0.33	0.029	4.91	252
4b	OH	16 ± 3	2810 ± 256	564 ± 4	175	35	0.20	3.09	268
4c	F	43 ± 1	5188 ± 180	356 ± 40	120	8.3	0.069	4.35	270

[a] Data are mean ± standard error of at least three experiments as described in ref 34. [b] Data taken from ref 38.

in the C1 and C2 series exhibit much higher activities that range between 16 nM and 926 nM at the DAT, between 66 nM and 2266 nM at the SERT, and between 32 nM and 1081 nM at the NET. Similar to other compounds in the C1 series, the carbamates **2e**–**g**, ether **2d**, and oxadiazole **2p** also exhibit improved activity at all transporters, compared to that of the ester **1a**. It is of worth to note that the oxadiazole **2p** is one of the most active compounds at the DAT, SERT, and NET among all compounds from the C0–C3 series, whereas its closest homologue without the flexible linker is completely inactive at all transporters.[37] In the C3 series of ligands, only compound **4a** exhibits superior activity at all monoamine transporters in comparison to **1a**, whereas alcohol **4b** and fluoride **4c** show 14.6- and 5.4-fold better inhibitory activity at the DAT than **1a** but only modest changes at the SERT and NET.

One possible explanation for the finding that compounds from the C1–C3 series are more active than compounds from the C0 series is that the polar group present in the more flexible 3α-appendage of the C1–C3 ligands is able to avoid unfavorable interactions with the binding site in close proximity to the piperidine ring. For the same reason the 3α-appendage in C1–C3 series may more closely, but not precisely, mimic the binding mode of the more active *cis*-3*β*-substituted piperidine-based and probably 2*β*-substituted tropane-based ligands.[18,33–38]

To better understand the difference between the C0 and C1–C3 series, the compounds from the C0–C3 series were minimized and flexibly superimposed on WIN35428 using the piperidine ring as a template. Additionally, the conformation of the 3α-substituents was adjusted to maintain the closest possible overlap with the 2*β*-substituent of WIN35428 (Figure 2), which simultaneously allows the bulky substituents in the C1–C3 series to avoid any unfavorable interactions with the steric exclusion area (SEA) discovered earlier.[37]

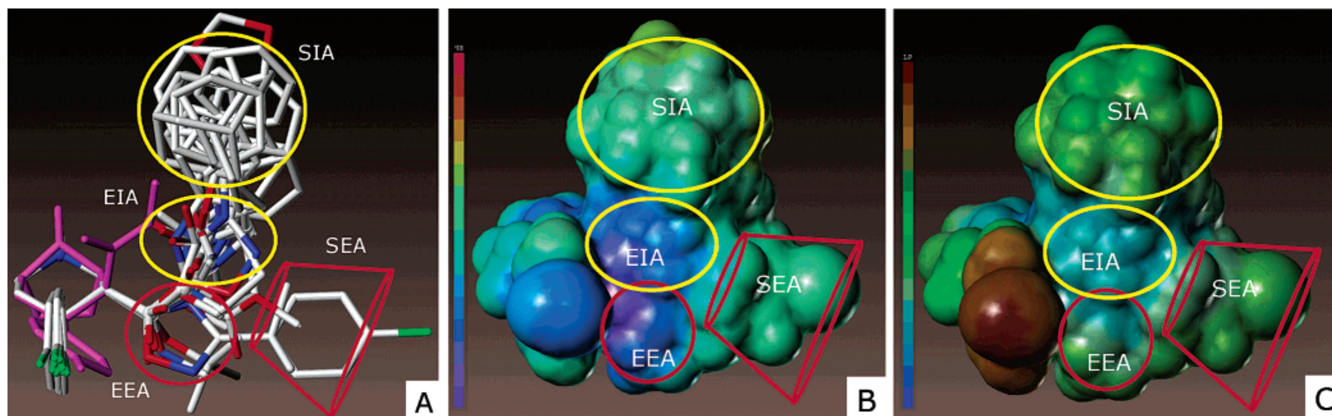


Figure 2. (A) Superposition of the C0−C3 series of ligands. EEA, electrostatic exclusion area (red ellipse); SEA, steric exclusion area (red trapezoid); EIA, electrostatic inclusion area (yellow ellipse); SIA, steric inclusion area (green ellipse); WIN35428, magenta model. (B) Connoly surface constructed around the superposition shown in A. The surface is colored by the electrostatic potential: blue = electronegative, red = electropositive. (C) Same as B. The surface is colored by the lipophilic potential, blue = hydrophobic, brown = lipophilic.

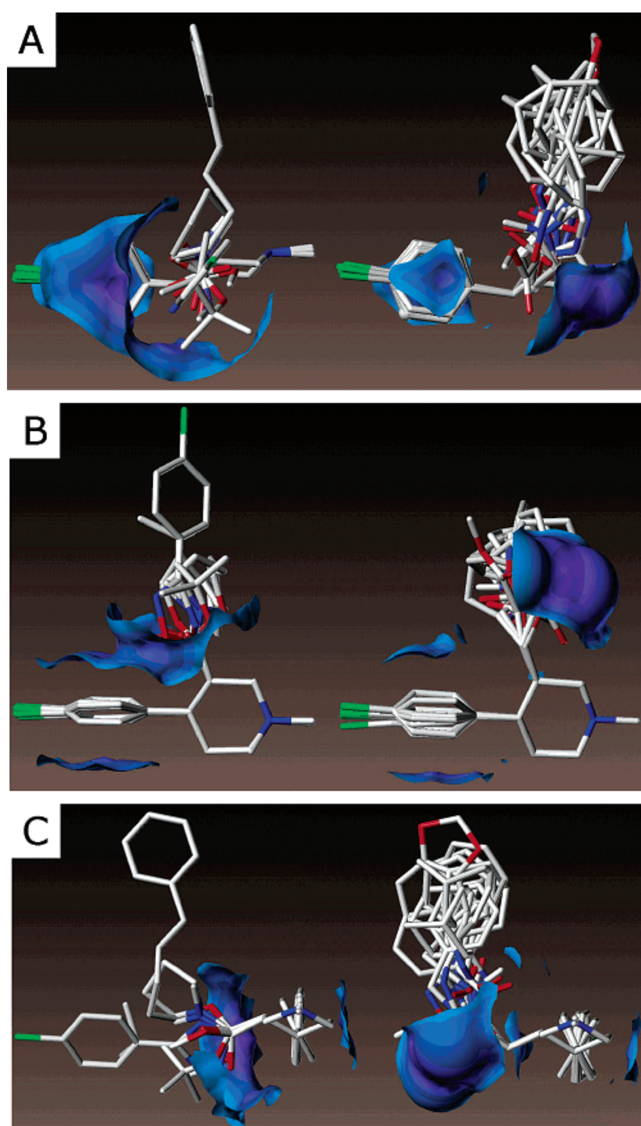


Figure 3. (A) Comparison of the EEA of C0 (left) and C1−C3 (right) series of ligands. Darker blue color corresponds to higher electron density. (B and C) Different projections of A.

The resulting overlay shows that only the C1−C3 ligands are able to adopt a conformation in which the polar group of the 3α-substituent occupies the position proximal to that of the 2β-polar group in WIN35428. This place in Figure 2 is designated as electrostatic inclusion area (EIA). Similar region was found in the CoMFA model published by Davis et al.[24] for the tropane-based compounds. It seems, however, that the presence of a polar group in the 3α-substituent of the piperidine-based series of ligands is not required for good activity since **4a** exhibits excellent activity at all monoamine transporters. This finding is consistent with the SAR of the tropane-based ligands where it was found that the activity of ligands is not affected by the change in proximity of the polar electron-rich 2β-substitutents[42] and, moreover, that the presense of such a group is not required at all.[43] A more extensive SAR work is needed to confirm the generality of this finding for the piperidine-based series of ligands.

Figure 3 shows the difference between the location of the most electron-rich areas in C0 and C1−C3 series on ligands. The most electron-rich (marked by blue) area in the C0 series of ligands is located on the side opposite the 3β-substituent of the piperidine ring, and it is, clearly, much closer to the piperidine ring than that in the C1−C3 series. This suggests that in addition to the SEA there is an electrostatic exclusion area (EEA) in close proximity to the 3α-position of the piperidine ring that makes the C0 ligands less active than the corresponding homologues from the C1−C3 series. The presence of the EEA may also explain why the 3α-substituted ligands are less active in general than the 3β-substituted piperidine-based ligands. It should be noted that unlike the DAT and NET, the SERT is probably much more sensitive to the presence of polar groups in the EEA, which may explain why the ligands in the C0 series are in general DAT/NET selective.

Interestingly, C1 ligands with bulky lipophilic groups at the end of the 3α-substituent such as carbamate **2g**, ester **2j**, amide **2o**, and oxadiazole **2p** are the most SERT-active (K_i < 90 nM) compounds in the C1 series. Thus, the presence of large lipophilic group in steric inclusion area (SIA, Figure 2) improves the activity of ligands at the SERT suggesting that the SERT binding site has a lipophilic binding pocket able to bind relatively large aliphatic and aromatic groups. Unlike the SERT, the DAT and NET do not exhibit any systematic preferences with regard to the size and lipophilicity of

the 3α-substituents. It may indirectly indicate that the functional groups on the far end of the 3α-substituents do not form a contact with the DAT and NET proteins because the region occupied by the 3α-substituent is located either in a cleft much larger than the 3α-substituent or outside the protein. This is consistent with the observation made by Trudell et al.[42] for the tropane-based DAT ligands.

Most of the active compounds in the C0−C3 series meet the "druglike" criteria (MW < 500, CLogP < 5),[44] whereas compounds **1h**, **2a**, **2b**, **2n**, and **2m** satisfy and compounds **2e** and **4b** marginally satisfy (compounds with low activity are not included) the criteria of "leadlikeness" (100 < MW < 350, 1 < CLogP < 3.0).[45] Thus, the latter compounds can be used in a further lead-optimization phase when additional interactions of the ligands with the binding sites of the monoamine transporters are discovered and exploited.

Conclusions

We have shown that the DAT, NET and especially the SERT activity of the poorly active *trans*-(+)-3α-piperidine-based ligands can be dramatically improved by insertion of a flexible linker between the piperidine ring and the polar group of the 3α-substituent. Several novel classes of piperidine-based ligands have been prepared. Moreover, piperidine-based amides and bulky oxadiazoles, which were originally found to be undesirable for animal studies due to low monoamine blocking ability, are now available for such studies. Overall, the results of the biological tests point to the existence of steric and electrostatic exclusion areas and steric and electrostatic inclusion areas, a finding that can be used for further ligand design. To identify the exact position of the exclusion and inclusion areas, we are developing CoMFA and CoMSIA models of the monoamine transporters.

The new series of *trans*-(+)-piperidine-based ligands are druglike and can be used directly in animal tests. Compounds **1h**, **2a**, **2b**, **2e**, **2m, 2n**, and **4b** are also leadlike and can be used in further optimization of their pharmacological, metabolic, and pharmacokinetic profiles.

The present results add to our understanding of the structural differences between the monoamine transporters and can be exploited for the design of new leads in the discovery of medications to treat cocaine addiction as well as certain neurological disorders such as ADHD and depression.

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, ^{13}C NMR spectra 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; ABq, AB quartet; and br, broad. Melting points were determined in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are not corrected. Optical rotation was measured on a 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), particle size 32-63 μm was used for column chromatography (CC). Merck silica gel 60 F_{254} (No. 5715-7), layer thickness 250 μm was used for TLC; the spots were visualized with UV light or ammonium molybdate/H_2SO_4 solution.

General Procedure A: Esterification. To a suspension of acid (1 mmol, HCl salt) in dry CH_2Cl_2 (5 mL) were added at room-temperature oxalyl chloride (2 mmol) and dry DMF (1 μL). The resulting suspension was stirred at room temperature for 1.5 h, the solvent was removed, and the residue was dissolved in chloroform (3 mL). To the resulting solution were added pyridine (2 mmol, 163 μL) and corresponding alcohol (2−5 equiv). The resulting solution was stirred at room temperature for 1.5 h and then mixed with a saturated solution of Na_2CO_3 (10 mL) and extracted with ether (3 × 10 mL). The combined organic solutions were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography.

General Procedure B: Amidation. To a suspension of acid (1 mmol) in dry CH_2Cl_2 (5 mL) were added at room-temperature oxalyl chloride (5 mmol) and dry DMF (1 μL). The resulting suspension was stirred at room temperature for 1.5 h, the solvent was removed, and the residue was dissolved in chloroform (3 mL). To the resulting solution was added an amine (5 mmol). The resulting solution was stirred at room temperature for 24 h and then mixed with a saturated solution of Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solutions were concentrated and re-evaporated with $CHCl_3$. The residue was purified by column chromatography.

General Procedure C: Formation of Carbamates. A solution of alcohol (1.0 mmol), isocyanate (1.1 mmol), and CuCl (100 μmol) in a mixture of toluene (1 mL) and pyridine (1 mL) in a thick-walled tube was heated at 80 °C for 15 h. After being cooled to room temperature, the reaction mixture was mixed with water (10 mL) and extracted with ether (3 × 10 mL). The combined organic solutions were concentrated, and the residue was purified by column chromatography.

(+)-*tert*-Butyl (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-carboxylate (1b). Following the above general procedure A, acid **1e** (566 mg, 1.95 mmol) and *tert*-butyl alcohol (390 mg, 5.26 mmol, 497 μL) gave crude ester **1b**. Column chromatography with EtOAc/hexanes/Et_3N (30:65:5) as eluent afforded pure ester **1b** as colorless glassy solid (420 mg, 69%): $[\alpha]_D$ +41.5 (*c* 0.52, $CHCl_3$); IR (film) ν 2937, 1723, 1493, 1367, 1151, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.72−1.84 (m, 2H), 2.02−2.20 (m, 2H), 2.35 (s, 3H), 2.60−2.82 (m, 2H), 2.88−3.00 (m, 1H), 3.08 (dd, J = 11.4, 2.1 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.0, 33.8, 44.7, 46.4, 50.0, 56.0, 58.4, 80.7, 128.6, 129.2, 132.3, 142.3, 172.5. Anal. ($C_{17}H_{20}ClNO_2$) C, H, N.

(+)-5-Phenylpentyl (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-carboxylate (1c). Following the above general procedure A, acid **1e** (200 mg, 690 μmol) and 5-phenyl-1-pentanol (230 mg, 1.38 mmol, 230 μL) gave crude ester **1c**. Column chromatography with EtOAc/hexanes/Et_3N (20:75:5) as eluent afforded pure ester **1c** as colorless glassy solid (230 mg, 83%): $[\alpha]_D$ +32.3 (*c* 0.33, $CHCl_3$); IR (film) ν 2940, 1747, 1495, 1365, 1145, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06−1.18 (m, 2H), 1.50−1.70 (m, 4H), 1.72−1.86 (m, 2H), 2.02−2.24 (m, 2H), 2.34 (s, 3H), 2.55 (t, J = 7.5 Hz, 2H), 2.58−2.90 (m, 2H), 2.90−3.00 (m, 1H), 3.06 (dd, J = 11.1, 2.1 Hz, 1H), 3.74−3.92 (m, 2H), 7.10−7.30 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 25.4, 29.4, 30.1, 32.5, 33.8, 35.7, 44.3, 46.9, 49.6, 55.8, 66.8, 125.2, 127.9, 128.2, 128.4, 129.8, 131.9, 141.2, 142.1, 171.8. Anal. ($C_{24}H_{30}ClNO_2$) C, H, N.

(3*R*,4*S*)-(+)-4-(4-Chlorophenyl)-1-methylpiperidine-3-carboxylic Acid Dimethylamide (1g). Following the above general procedure B, acid **1e** (100 mg, 350 μmol) and dimethylamine (52 μL, 1.03 mmol) gave crude amide **1g**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure amide **1g** as a white solid (0.085 g, 88%): $[\alpha]_D$ +23.3 (*c*

0.52, $CHCl_3$); IR (film) ν 2936, 1754, 1639, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79–2.03 (m, 2H), 2.14 (td, J = 11.4, 3.3 Hz, 1H), 2.28 (t, J = 11.4 Hz, 1H), 2.35 (s, 3H), 2.72 (s, 3H), 2.74 (s, 3H), 2.85–3.02 (m, 3H), 3.09 (td, J = 11.4, 3.9 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.0, 35.2, 36.8, 43.5, 45.7, 45.9, 55.4, 58.1, 128.2, 128.6, 131.9, 142.0, 172.0. **1g**·HCl: Anal. ($C_{15}H_{21}ClN_2O$·1.1HCl) C, H, N.

(+)-Phenyl (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-carboxylate (1l). Following the above general procedure A, acid **1d** (146 mg, 500 μmol) and phenol (57 mg, 600 μmol) gave crude ester **1k**. Column chromatography with EtOAc/hexanes/Et_3N (30:65:5) as eluent afforded pure ester **1k** as a colorless glassy solid (0.110 g, 67%): $[\alpha]_D$ +72.0 (*c* 1.02, $CHCl_3$); IR (film) ν 2938, 1754, 1493, 1195, 1123, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86–1.96 (m, 2H), 2.14–2.24 (m, 2H), 2.36 (t, J = 11.1 Hz, 1H), 2.43 (s, 1H), 2.81–2.94 (m, 1H), 3.02 (d, J = 11.1 Hz, 1H), 3.13 (dt, J = 11.1, 3.6 Hz, 1H), 3.29 (dd, J = 11.1, 2.1 Hz, 1H), 6.67 (d, J = 7.8 Hz, 2H), 7.18 (t, J = 7.8 Hz, 1H), 7.23–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 33.4, 44.7, 46.4, 49.4, 55.9, 58.1, 121.5, 126.0, 129.2, 129.5, 132.8, 141.8, 150.4, 171.8. Anal. ($C_{19}H_{20}ClNO_2$) C, H, N.

(3*R*,4*S*)-(+)-3-(Benzoyloxymethyl)-4-(4-chlorophenyl)-1-methylpiperidine (2c). Ester **2c** was synthesized from alcohol **2a** (50 mg, 210 μmol) and benzoyl chloride (32 μL, 270 μmol) according to procedure published earlier.[33] Column chromatography with EtOAc/hexanes/Et_3N (3:6:1) as eluent afforded pure ester **2c** as a colorless glass (58 mg, 88%): $[\alpha]_D$ +62.8 (*c* 0.33, $CHCl_3$); IR (film) ν 2945, 1737, 1491 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79–2.04 (m, 3H), 2.06 (dd, J = 11.1, 4.5 Hz, 1H), 2.26–2.46 (m, 2H), 2.35 (s, 3H), 2.97 (d, J = 11.7, 1H), 3.16 (d, J = 12.3 Hz, 1H), 3.92 (dd, J = 11.1, 6.6 Hz, 1H), 4.07 (dd, J = 11.7, 3.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.94 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.4, 41.2, 44.3, 46.4, 56.0, 59.3, 65.6, 128.2, 128.6, 128.7, 129.3, 129.9, 132.1, 132.8, 142.1, 166.1. **2c**·HCl: Anal. ($C_{20}H_{22}ClNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-(+)-3-(Allyloxymethyl)-4-(4-chlorophenyl)-1-methylpiperidine (2d). To a suspension of alcohol **2a** (300 mg, 1.25 mmol) in dry THF (5 mL) was added at room-temperature sodium hydride (33 mg, 1.38 mmol). The resulting suspension was stirred at room temperature for 30 min, and to the resulting solution was added a solution of allyl bromide (140 μL, 1.63 mmol) in THF (1 mL). The resulting solution was stirred at room temperature for 15 h, and then it was mixed with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic solutions were washed with brine, dried over $MgSO_4$, and concentrated. Column chromatography with EtOAc/hexanes/Et_3N (45:45:1) as eluent afforded pure ether **2d** as a yellowish oil (260 mg, 74%): $[\alpha]_D$ +63.2 (*c* 0.45, $CHCl_3$); IR (film) ν 2934, 1492, 1104, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71–2.14 (m, 5H), 2.26–2.40 (m, 1H), 2.34 (s, 3H), 2.88–2.98 (m, 1H), 3.00 (dd, J = 9.6, 6.9 Hz, 1H), 3.08–3.18 (m, 2H), 3.77 (qt, J = 12.9, 1.5 Hz, 2H), 5.08–5.22 (m, 2H), 5.72–5.88 (m, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7, 2H); ^{13}C NMR ($CDCl_3$) δ 34.3, 42.1, 43.7, 46.8, 56.0, 59.7, 70.9, 71.8, 116.5, 128.5, 128.7, 131.8, 134.7, 142.9. **2d**·HCl: Anal. ($C_{16}H_{22}ClNO$·1.1HCl) C, H, N.

(+)-Ethylcarbamic Acid (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-ylmethyl Ester (2e). Following the above general procedure C, alcohol **2a** (200 mg, 830 μmol) and ethyl isocyanate (86 μL, 1.09 mmol) gave crude carbamate **2e**. Column chromatography with EtOAc/NEt_3/MeOH (90:5:5) as eluent afforded pure carbamate **2e** as a colorless glass (240 mg, 93%): $[\alpha]_D$ +55.2 (*c* 0.34, $CHCl_3$); IR (film) ν 3333, 2939, 1718, 1537, 1254, 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2, 3H), 1.72–1.88 (m, 3H), 1.94–2.06 (m, 1H), 2.12–2.30 (m, 2H), 2.32 (s, 3H), 2.84–2.98 (m, 1H), 3.02–3.20 (m, 3H), 3.56–3.72 (m, 1H), 3.80 (d, J = 11.1 Hz, 1H), 5.03 (br s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.0, 34.2, 35.5, 41.0, 44.0, 46.2, 55.8, 59.2, 65.3, 128.5, 128.5, 131.9, 142.1, 156.1. **2e**·HCl: Anal. ($C_{16}H_{23}ClN_2O_2$·1.1HCl) C, H, N.

(+)-Phenylcarbamic Acid (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-ylmethyl Ester (2f). Following the above general procedure C, alcohol **1a** (100 mg, 420 μmol) and phenyl isocyanate (50 μL, 460 μmol) gave crude carbamate **2f**. Column chromatography with EtOAc/NEt_3/MeOH (90:5:5) as eluent afforded pure carbamate **2f** as a colorless glass (0.12 g, 80%): $[\alpha]_D$ +60.2 (*c* 0.84, $CHCl_3$); IR (film) ν 3350, 1705, 1523, 1260, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–1.92 (m, 3H), 1.94–2.08 (m, 1H), 2.18–2.30 (m, 2H), 2.34 (s, 3H), 2.94 (d, J = 11.4 Hz, 1H), 3.13 (d, J = 10.8 Hz, 1H), 3.75 (dd, J = 10.8, 7.5 Hz, 1H), 3.91 (dd, J = 10.8, 2.7 Hz, 1H), 6.92–7.1 (m, 1H), 7.09 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.24–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 34.2, 41.0, 44.1, 46.3, 55.9, 59.1, 65.9, 118.7, 123.3, 128.5, 128.7, 128.8, 132.0, 137.6, 142.0, 153.2. **2f**·HCl: Anal. ($C_{20}H_{23}ClN_2O_2$·1.2HCl) C, H, N.

(+)-1-Adamantylcarbamic Acid (3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-ylmethyl Ester (2g). Following the above general procedure C, alcohol **2a** (100 mg, 420 μmol) and 1-adamantyl isocyanate (89 mg, 500 μmol) gave crude carbamate **2g**. Column chromatography with EtOAc/NEt_3/MeOH (90:5:5) as eluent afforded pure carbamate **2g** as a colorless glass (130 mg, 75%): $[\alpha]_D$ +40.5 (*c* 1.12, $CHCl_3$); IR (film) ν 3335, 2930, 1720, 1532, 1256, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62–1.74 (m, 6H), 1.76–1.88 (m, 1H), 1.88–1.98 (m, 8H), 2.00–2.16 (m, 4H), 2.26–2.36 (m, 1H), 2. 36 (s, 3H), 2.98 (d, J = 12.3 Hz, 1H), 3.11 (d, J = 9.3 Hz, 1H), 3.36–3.64 (m, 1H), 3.64–3.80 (m, 1H), 5.21 (br s, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.8, 33.2, 35.6, 40.4, 40.9, 41.7, 43.3, 45.3, 55.2, 58.4, 64.0, 128.1, 128.1, 131.6, 141.4, 155.6. **2g** HCl: Anal. ($C_{24}H_{33}ClN_2O_2$·1.3HCl) C, H, N.

(3*R*,4*S*)-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-acetic Acid (2h). A solution of ester **2i** (700 mg, 2.37 mmol) in 6 N hydrochloric acid (10 mL) was heated at reflux for 12 h. The solvent was removed, and the resulting crude hydrochloride salt of acid **2h** (650 mg) was dried in vacuo and used for further reactions without purification.

(3*R*,4*S*)-(+)-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]acetic Acid Ethyl Ester (2i). Acid chloride **1m** was prepared from acid **1d** (180 mg, 620 μmol) and oxalyl chloride as described earlier.[38] A suspension of acid chloride **1m** in a solution of NEt_3 (216 μL, 1.60 mmol) and Et_2O (10 mL) was added to a magnetically stirred ice-cold solution of CH_2N_2 (5 mL of 320 μmol/mL solution in Et_2O). The suspension was stirred for 3 h at 0 °C, and NEt_3 hydrochloride was removed by filtration and washed with Et_2O (2 × 10 mL). The filtrate was concentrated, ether (5 mL) was added to the residue, and the resulting suspension was filtered again. The filtrate was concentrated and dried in vacuo. The residue of **1n** was dissolved in ethanol (10 mL), the resulting solution was heated to reflux, and a solution of silver benzoate (100 mg in 500 μL of NEt_3) was added to the reaction mixture portionwise (5 × 100 μL) with 2 min intervals. The resulting suspension was heated at reflux for 3 h. The solvent was removed, the residue was mixed with a saturated solution of $NaHCO_3$ (15 mL), and the product was extracted into ether (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated to dryness. Column chromatography with EtOAc/NEt_3/MeOH (45:45:10) as eluent afforded pure ester **2i** as a colorless oil (160 mg, 87%): $[\alpha]_D$ +21.5 (*c* 0.59, $CHCl_3$); IR (film) ν 2933, 2781, 1731, 1493, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H) 1.72–1.82 (m, 2H), 1.89 (dd, J = 15.6, 9.3 Hz, 2H), 2.00 (dt, J = 11.4, 4.2 Hz, 1H), 2.12 (dd, J = 15.0, 3.6 Hz, 2H), 2.19 (dd, J = 11.1, 5.1 Hz, 1H), 2.28–2.40 (m, 1H), 2.32 (s, 3H), 2.94 (br d, J = 11.1 Hz, 1H) 3.05 (dddd, J = 11.4, 5.4, 3.6, 1.8 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 34.5 (CH_2), 36.9 (CH_2), 38.4 (CH), 46.2 (CH_3), 47.3 (CH), 56.0 (CH_2), 60.1 (CH_2), 61.2 (CH_2), 128.6 (CH), 128.9 (CH), 132.1 (C), 142.3 (C), 172.1 (C). **2i**·HCl: Anal. ($C_{16}H_{22}ClNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-(+)-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]acetic Acid 3-Phenylpropyl Ester (2j). Following the above general procedure A, acid **2h** (75 mg, 260 μmol) and

3-phenylpropanol (87 μL, 650 μmol) gave crude amide **2j**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure ester **2j** as a colorless solid (87 mg, 87%): $[\alpha]_D$ +19.9 (*c* 1.05, $CHCl_3$); IR (film) ν 2935, 2781, 1733, 1494, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72−2.06 (m, 7H), 2.08−2.24 (m, 2H), 2.26−2.42 (m, 1H), 2.32 (s, 3H), 2.63 (t, J = 7.5 Hz, 2H) 2.94 (d, J = 11.4 Hz, 1H) 3.05 (ddd, J = 11.1, 3.6, 1.5 Hz, 1H), 3.96 (t, J = 6.6 Hz, 2H), 7.10−7.32 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 30.0, 32.0, 34.5, 36.8, 38.5, 46.3, 47.3, 56.0, 61.2, 63.6, 125.9, 128.2, 128.3, 128.6, 129.0, 132.1, 141.0, 142.3, 172.2. **2j**·HCl: Anal. ($C_{23}H_{28}ClNO_2$·1.5HCl) C, H, N.

(3*R*,4*S*)-(+)-*N*-(1-Adamantyl)-2-[4-(4-chlorophenyl)-1-methyl-piperidin-3-yl]acetamide (2k). Following the above general procedure B, acid **2h** (66 mg, 227 μmol) and 1-adamantylamine (172 mg, 172 μmol) gave crude amide **2k**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure amide **2k** as a white solid (75 mg, 82%): $[\alpha]_D$ +44.7 (*c* 0.52, $CHCl_3$); IR (film) ν 3307, 2909, 1643, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58−1.70 (m, 7H), 1.72−1.86 (m, 2H), 1.86−1.93 (m, 7H), 1.94−2.08 (m, 5H), 2.15−2.28 (m, 2H), 2.33 (s, 3H), 2.94 (d, J = 11.4 Hz, 1H), 3.09 (d, J = 11.1 Hz, 1H), 4.83 (br s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.2, 34.5, 36.2, 39.0, 40.1, 41.4, 46.2, 47.2, 51.7, 55.9, 61.0, 128.7, 129.0, 132.0, 142.6, 170.2. **2k**·HCl: Anal. ($C_{24}H_{33}ClN_2O$·1.2HCl) C, H, N.

(3*R*,4*S*)-(+)-*N*-Benzyl-2-[4-(4-chlorophenyl)-1-methylpiperidin-3-yl]acetamide (2l). Following the above general procedure B, acid **2h** (75 mg, 247 μmol) and benzylamine (70 μL, 640 μmol) gave crude amide **2l**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure amide **2l** as a white solid (0.079 g, 90%): $[\alpha]_D$ +31.7 (*c* 0.60, $CHCl_3$); mp 148−150 °C ($CHCl_3$); IR (film) ν 3287, 2934, 1643, 1551, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72−1.90 (m, 4H), 1.94−2.06 (m, 2H), 2.12−2.26 (m, 1H), 2.26−2.40 (m, 1H), 2.30 (s, 3H), 2.92 (d, J = 11.4 Hz, 1H), 3.10 (ddd, J = 11.1, 3.3, 1.5 Hz, 1H), 4.30 (qd, J = 14.7, 5.7 Hz, 2H), 5.53 (br s, 1H), 7.10 (d, J = 8.7 Hz, 2H), 7.17−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 34.5, 38.9, 39.0, 43.4, 46.2, 47.4, 55.9, 61.2, 127.4, 127.7, 128.5, 128.7, 128.9, 132.0, 138.0, 142.5, 171.0. **2l**·HCl: Anal. ($C_{21}H_{25}ClN_2O$·1.3HCl) C, H, N.

(3*R*,4*S*)-(+)-2-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-*N*-methylacetamide (2m). Following the above general procedure B, acid **2h** (212 mg, 880 μmol) and dimethylamine (0.3 mL of a 40% aqueous solution, 4 mmol) gave crude amide **2m**. Column chromatography with EtOAc/MeOH/NEt_3 (8:1:1) as eluent afforded pure amide **2m** as a yellow solid (200 mg, 81%): $[\alpha]_D$ +24.2 (*c* 1.55, $CHCl_3$); IR (film) ν 3291, 2936, 2787, 1644, 1556, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68−1.92 (m, 4H), 1.94−2.12 (m, 2H), 2.14−2.38 (m, 2H) 2.32 (s, 3H), 2.68 (d, J = 4.8 Hz, 3H), 2.95 (d, J = 11.1 Hz, 1H), 3.11 (dd, J = 11.1, 1.5 Hz, 1H), 5.26 (br s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.1, 34.5, 38.9, 39.0, 46.2, 47.3, 56.0, 61.2, 128.7, 129.0, 132.1, 142.6, 171.9. **2m**·HCl: Anal. ($C_{15}H_{21}ClN_2O$·1.7HCl) C, H, N.

(3*R*,4*S*)-(+)-2-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-*N*,*N*-dimethylacetamide (2n). Following the above general procedure B, acid **2h** (212 mg, 880 μmol) and dimethylamine (0.5 mL of a 40% aqueous solution, 4 mmol) gave crude amide **2n**. Column chromatography with EtOAc/MeOH/NEt_3 (8:1:1) as eluent afforded pure amide **2n** as a yellow solid (220 mg, 84%): $[\alpha]_D$ +37.5 (*c* 0.88, $CHCl_3$); IR (film) ν 3432, 2934, 2781, 1643, 1493, 1397 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70−1.92 (m, 4H), 1.92−2.06 (m, 1H), 2.06−2.22 (m, 2H), 2.22−2.34 (m, 1H), 2.29 (s, 3H), 2.70 (s, 3H), 2.80 (s, 3H), 2.92 (d, J = 11.1 Hz, 1H), 3.12 (ddd, J = 11.7, 3.6, 1.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.5, 35.2, 35.8, 37.2, 38.4, 46.2, 47.5, 56.0, 61.4, 128.6, 129.0, 132.1, 142.7, 171.3. **2n**·HCl: Anal. ($C_{16}H_{23}ClN_2O$·1.2HCl) C, H, N.

(3*R*,4*S*)-(+)-*N*-Benzyl-2-[4-(4-chlorophenyl)-1-methylpiperidin-3-yl]-*N*-methylacetamide (2o). Following the above general procedure B, acid **2h** (70 mg, 230 μmol) and benzylmethylamine (39 μL, 300 μmol) gave crude amide **2o**. Column chromatography with EtOAc/MeOH/NEt_3 (8:1:1) as eluent afforded pure amide **2o** as a colorless solid (62 mg, 73%, according to NMR a mixture of *Z*- and *E*-amide rotamers): $[\alpha]_D$ +44.55 (*c* 1.06, $CHCl_3$); IR (film) ν 2933, 2778, 1643, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70−2.08 (m, 5H), 2.10−2.32 (m, 2H), 2.32−2.44 (m, 1H) 2.32 and 2.33 (two s, 3H), 2.64 (s, 1.7H), 2.86 (s, 1.3H), 2.88−3.00 (m, 1H), 3.12−3.30 (m, 1H), 4.16, 4.26 (ABq, J = 16.8 Hz, 1H, *Z* or *E* rotamer), 4.45, 4.53 (ABq, J = 14.7 Hz, 1H, *E* or *Z* rotamer), 6.90 (d, J = 7.8 Hz, 1H), 7.02−7.34 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 33.9, 34.4, 34.5, 34.7, 35.3, 36.0, 38.6, 38.8, 46.3, 47.3, 47.7, 50.7, 53.1, 56.0, 61.4, 61.7, 125.9, 127.2, 127.9, 128.5, 128.6, 128.7, 128.7, 129.0, 132.1, 136.3, 137.2, 142.7, 171.3, 171.8. **2o**·HCl: Anal. ($C_{22}H_{27}ClN_2O$·1.3HCl) C, H, N.

(3*R*,4*S*)-(+)-3-[(1,3-Benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-4-(4-chlorophenyl)-1-methylpiperidine (2p). Following the procedure published in ref 37 acid **2h** (70 mg, 230 μmol) and 3,4-methylenedioxybenzamidoxime (46 mg, 250 μmol) gave crude oxadiazole **2p**. Column chromatography with EtOAc/hexanes/NEt_3 (45:45:10) as eluent afforded pure oxadiazole **2p** as a colorless solid (65 mg, 69%): $[\alpha]_D$ +16.5 (*c* 1.98, $CHCl_3$); IR (film) ν 2933, 2778, 1643, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78−1.94 (m, 3H), 1.96−2.10 (m, 1H), 2.26−2.36 (m, 1H), 2.30 (s, 3H), 2.40−2.62 (m, 2H), 2.68−2.78 (m, 1H), 2.95 (d, J = 11.4 Hz, 1H), 2.80−3.06 (m, 1H), 6.03 (s, 2H), 6.89 (dd, J = 8.1, 0.6 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.48 (dd, J = 1.8, 0.6 Hz, 1H), 7.59 (dd, J = 8.1, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.9, 34.6, 40.1, 46.3, 47.3, 56.0, 60.8, 101.5, 107.4, 108.6, 120.6, 122.2, 128.9, 129.0, 132.4, 141.9, 148.0, 150.0, 167.8, 177.8. **2p**·HCl: Anal. ($C_{22}H_{22}ClN_3O_3$·1.1HCl) C, H, N.

(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-carbaldehyde (1o). To a solution of oxalyl chloride (80 μL, 920 μmol) in anhydrous CH_2Cl_2 (6 mL) was added DMSO (127 μL, 1.79 mmol) at −78 °C. After 5 min, a solution of alcohol **2a** (200 mg, 830 μmol) in CH_2Cl_2 (4 mL) was added. The mixture was stirred for 2 h at −78 °C and then quenched with Et_3N (2 mL). The reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 (10 mL), washed with a saturated solution of NH_4Cl (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), concentrated, re-evaporated with $CHCl_3$, and dried in vacuo to afford the aldehyde **1j** (200 mg), which was used for further reactions without purification.

(3*R*,4*S*)-(+)-(*E*)-3-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]acrylic Acid Methyl Ester (3b). A suspension of NaH (30 mg, 1.25 mmol) in dry THF (15 mL) was cooled to 0 °C. Trimethyl phosphonoacetate (217 μL, 1.50 mmol) was added to the stirred suspension over a period of 20 min. The mixture was cooled to −78 °C, and a solution of crude aldehyde **1o** (195 mg, 820 μmol) in THF (10 mL) was added over a period of 10 min. The mixture was stirred for an additional 15 min at −78 °C, and then the temperature was allowed to rise to room temperature within 2 h. The reaction was quenched with a saturated solution of ammonium chloride (20 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated to dryness. Column chromatography with EtOAc/hexanes/NEt_3 (45:45:10) yielded **3b** as a colorless oil (140 mg, 57%): $[\alpha]_D$ +109.7 (*c* 0.68, $CHCl_3$); IR (film) ν 2939, 2784, 1742, 1659, 1493, 1435, 1327, 1282, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75−1.84 (m, 2H), 1.95 (t, J = 11.1, 1H), 1.96−2.10 (m, 1H), 2.35 2.45 (m, 1H), 2.34 (s, 3H), 2.62−2.78 (m, 1H), 2.90−3.02 (m, 2H), 3.63 (s, 3H), 5.61 (dd, J = 15.9, 1.2 Hz, 1H), 6.59 (dd, J = 15.9, 8.1 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 44.8, 46.1, 46.5, 51.2, 55.7, 60.3, 121.8, 128.5, 128.6, 131.9, 141.8, 148.4, 166.3. **3b** HCl: Anal. ($C_{16}H_{20}ClNO_2$ 1.2HCl)·C, H, N.

(3*R*,4*S*)-(+)-3-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]propionic Acid Methyl Ester (3c). To a solution of alkene **3b** (600 mg, 2.04 mmol) in MeOH (3 mL) were added magnesium turnings (199 mg, 8.17 mmol) under nitrogen. The resulting mixture was heated for 5 s at reflux, cooled to room temperature, and stirred for 3 h, and then it was washed with a saturated solution of NH_4Cl (20 mL) followed by a saturated solution of $NaHCO_3$ (20 mL) and extracted with ether (3 × 20

mL). The combined organic extracts were washed with brine (20 mL) and concentrated. Column chromatography with CH_2Cl_2/MeOH (9:1) as eluent afforded ester **3c** as a colorless oil (560 mg, 96%): $[\alpha]_D$ +45.2 (*c* 0.60, $CHCl_3$); IR (film) ν 2935, 2780, 1739, 1493, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.28 (m, 1H) 1.45−1.57 (m, 1H), 1.69 (t, J = 11.1 Hz, 1H), 1.71−1.90 (m, 3H), 1.95−2.12 (m, 4H), 2.33 (s, 3H), 2.93 (br d, J = 11.1 Hz, 1H) 3.06 (ddd, J = 11.1, 3.3, 1.5 Hz, 1H), 3.59 (s, 3H), 7.10 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.6 (CH_2), 31.2 (CH_2), 34.7 (CH_2), 40.4 (CH), 46.3 (CH_3), 47.9 (CH), 51.3 (CH_3), 55.9 (CH_2), 60.9 (CH_2), 128.5 (CH), 128.8 (CH), 131.8 (C), 142.8 (C), 173.5 (C). **3c**·HCl: Anal. ($C_{16}H_{22}ClNO_2$·1.1HCl) C, H, N.

(3*R*,4*S*)-(+)-*N*-(1-Adamantyl)-3-[4-(4-chlorophenyl)-1-methylpiperidin-3-yl]propionamide (3d). Following the above general procedure B, acid **3a** (100 mg, 310 μmol) and 1-adamantylamine (238 mg, 1.57 mmol) gave crude amide **3d**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure amide **3d** as a white solid (120 mg, 92%): mp 168−170 °C ($CHCl_3$); $[\alpha]_D$ +30.9 (*c* 1.57, $CHCl_3$); IR (film) ν 3302, 2909, 1644, 1546, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18−1.36 (m, 1H), 1.36−1.48 (m, 1H), 1.60−1.68 (m, 6H), 1.68−1.88 (m, 5H), 1.92 (d, J = 3.0 Hz, 6H), 1.94−2.18 (m, 6H), 2.34 (s, 3H), 2.95 (d, J = 10.8 Hz, 1H) 3.05 (d, J = 9.6 Hz, 1H), 4.92 (br s, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.4, 29.2, 34.5, 34.9, 36.2, 40.8, 41.5, 46.3, 48.0, 51.6, 55.9, 61.2, 128.6, 128.9, 131.8, 143.0, 171.4. **3d**·HCl: Anal. ($C_{25}H_{35}ClN_2O$·2.1HCl) C, H, N.

(3*R*,4*S*)-(+)-3-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-*N*-phenylpropionamide (3e). Following the above general procedure B, acid **3a** (100 mg, 310 μmol) and aniline (143 μL, 1.57 mmol) gave crude amide **3e**. Column chromatography with $CHCl_3$/MeOH (9:1) as eluent afforded pure amide **3e** as a yellow solid (95 mg, 85%): $[\alpha]_D$ +36.2 (*c* 1.93, $CHCl_3$); IR (film) ν 3288, 2934, 2793, 1663, 1599, 1547, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22−1.44 (m, 1H), 1.46−1.64 (m, 1H), 1.70−2.04 (m, 4H), 2.04−2.34 (m, 4H), 2.40 (s, 3H), 3.04 (d, J = 11.7 Hz, 1H), 3.18 (d, J = 9.9 Hz, 1H) 4.63 (br s, 1H), 7.02−7.14 (m, 3H), 7.18−7.34 (m, 4H), 7.49 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.1, 33.8, 34.6, 40.2, 45.7, 47.4, 55.6, 60.5, 119.6, 123.9, 128.7, 128.7, 128.8, 132.0, 137.9, 142.2, 170.8. **3e**·HCl: Anal. ($C_{21}H_{25}ClN_2O$·1.1HCl) C, H, N.

(3*R*,4*S*)-(+)-3-[4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]propan-1-ol (4b). To a solution of **3c** (100 mg, 34 mmol) in THF (5 mL) was added portionwise $LiAlH_4$ (35 mg, 0.92 mmol). The mixture was stirred at room temperature for 2 h, quenched with a saturated solution of Rochelle salt (3.5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried, and concentrated. Column chromatography with Et_2O/NEt_3 (20:1) as eluent afforded alcohol **4b** as a colorless oil (79 mg, 87%): $[\alpha]_D$ +32.4 (*c* 0.50, $CHCl_3$); IR (film) ν 3387, 2936, 1492, 1058, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90−1.08 (m, 1H), 1.17−1.40 (m, 3H), 1.44−1.62 (m, 1H), 1.74−2.08 (m, 4H), 2.17 (td, J = 11.7, 3.3 Hz, 2H), 2.45 (s, 3H), 3.09 (d, J = 9.9 Hz, 1H), 3.22 (d, J = 11.1 Hz, 1H), 3.38−3.55 (m, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.9, 29.7, 34.2, 40.5, 46.1, 47.9, 56.1, 61.1, 62.8, 128.9, 129.2, 132.3, 142.9. Anal. ($C_{15}H_{22}ClNO$) C, H, N.

(3*R*,4*S*)-(+)-4-(4-Chlorophenyl)-3-(3-fluoropropyl)-1-methylpiperidine (4c). A solution of alcohol **4b** (26 mg, 100 μmol) in CH_2Cl_2 (1 mL) was added to a solution of diethylaminosulfur trifluoride (30 μL, 220 μmol) in CH_2Cl_2 (0.5 mL) at −70 °C. The cooling bath was removed, and the reaction mixture was stirred overnight, quenched with water (2 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried and concentrated. Column chromatography with Et_2O/NEt_3 (20:1) as eluent afforded fluoride **4c** as a yellowish oil (16 mg, 61%): $[\alpha]_D$ +34.5 (*c* 0.15, $CHCl_3$); IR (film) ν 2935, 1493, 1381, 1283, 1143, 1090, 1014, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96−1.10 (m, 1H), 1.14−1.30 (m, 1H), 1.30−1.50 (m, 1H), 1.75−1.95 (m, 5H), 1.95−2.20 (m, 2H), 2.38 (s, 3H), 2.95 (d, J = 11.4 Hz, 1H), 3.07 (d, J = 11.1 Hz, 1H), 4.13−4.27 (m, 1H), 4.28−4.40 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.5 (d, J = 5.5 Hz), 27.8 (d, J = 19.7 Hz), 35.1, 41.1, 46.7, 48.4, 56.4, 61.6, 83.2 (d, J = 165 Hz), 128.9, 129.2, 132.1, 143.5. Anal. ($C_{15}H_{21}ClFN$) C, H, N.

Synaptosomal Uptake of [^{3}H]Dopamine, [^{3}H]5-Hydroxytryptamine, and [^{3}H]Norepinephrine.[46] Compounds were tested as the free base. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined as previously described.[22] Striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of rat DAT, SERT, and NET, respectively. These brain regions 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 consisting of (in mM) NaCl (125), KCl (4.8), $MgSO_4$ (1.2), $CaCl_2$ (1.3), KH_2PO_4 (1.2), glucose (5.6), nialamide (0.01), and HEPES (25) (pH 7.4). An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 4 °C and then for 15 min at 37 °C before uptake was initiated by the addition of [^{3}H]biogenic amine (∼5 nM for [^{3}H]DA and [^{3}H]5-HT, 9 nM for [^{3}H]NE, 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. The bound and free [^{3}H]biogenic amines were separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 mL of cold buffer. Radioactivity on the filters was then extracted by allowing the filters to sit overnight with 5 mL of scintillation fluid. The vials were vortexed and counted. Specific uptake of [^{3}H]DA was defined as that which is sensitive to inhibition by 30 μM cocaine. 10 μM Fluoxetine and 3 μM desipramine, respectively, were used to define the specific uptake of [^{3}H]5-HT and [^{3}H]NE. In each instance, it was virtually identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. IC_{50} values were determined using the computer program LIGAND. The Cheng−Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments. The K_m values used were 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE. Even though uptake is a nonequilibrium process, K_i determinations are thought to be appropriate estimates of affinity between these compounds and the biogenic amine transporters because it is likely that the relatively long (45 min) period of incubation of the drug before addition of the [^{3}H] amine is adequate time for equilibrium between the test compound the biogenic amine transporter to occur.

Acknowledgment. We are indebted to the NIH, National Institute of Drug Abuse (DA11548 and 10458), for their support of this work. We thank Dr. Werner Tückmantel for proofreading the manuscript.

References

(1) Melichar, J. K.; Daglish, M. R.; Nutt, D. J. Addiction and withdrawal−current views. *Curr. Opin. Pharmacol.* **2001**, *1*, 84−90.
(2) Spanagel, R.; Weiss, F. The dopamine hypothesis of reward: past and current status. *Trends Neurosci.* **1999**, *22*, 521−527.
(3) Callahan, P. M.; Cunningham, K. A. Modulation of the discriminative stimulus properties of cocaine by 5-HT1B and 5-HT2C receptors. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 1414−1424.
(4) Callahan, P. M.; Cunningham, K. A. Modulation of the discriminative stimulus properties of cocaine: comparison of the effects of fluoxetine with 5-HT1A and 5-HT1B receptor agonists. *Neuropharmacology* **1997**, *36*, 373−381.
(5) McMahon, L. R.; Cunningham, K. A. Antagonism of 5-hydroxytryptamine(2a) receptors attenuates the behavioral effects of cocaine in rats. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 357−363.
(6) Spealman, R. D. Modification of behavioral effects of cocaine by selective serotonin and dopamine uptake inhibitors in squirrel monkeys. *Psychopharmacology (Berlin)* **1993**, *112*, 93−99.
(7) Schama, K. F.; Howell, L. L.; Byrd, L. D. Serotonergic modulation of the discriminative-stimulus effects of cocaine in squirrel monkeys. *Psychopharmacology (Berlin)* **1997**, *132*, 27−34.

(8) Rowley, M.; Bristow, L. J.; Hutson, P. H. Current and novel approaches to the drug treatment of schizophrenia. *J. Med. Chem.* **2001**, *44*, 477−501.
(9) Davids, E.; Zhang, K.; Kula, N. S.; Tarazi, F. I.; Baldessarini, R. J. Effects of norepinephrine and serotonin transporter inhibitors on hyperactivity induced by neonatal 6-hydroxydopamine lesioning in rats. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 1097−1102.
(10) Nieoullon, A. Dopamine and the regulation of cognition and attention. *Prog. Neurobiol.* **2002**, *67*, 53−83.
(11) Castellanos, F. X.; Tannock, R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat. Rev. Neurosci.* **2002**, *3*, 617−628.
(12) Di Matteo, V.; Cacchio, M.; Di Giulio, C.; Esposito, E. Role of serotonin(2C) receptors in the control of brain dopaminergic function. *Pharmacol. Biochem. Behav.* **2002**, *71*, 727−734.
(13) Brunello, N.; Mendlewicz, J.; Kasper, S.; Leonard, B.; Montgomery, S.; Nelson, J.; Paykel, E.; Versiani, M.; Racagni, G. The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. *Eur. Neuropsychopharmacol.* **2002**, *12*, 461−475.
(14) Young, S. N.; Leyton, M. The role of serotonin in human mood and social interaction. Insight from altered tryptophan levels. *Pharmacol. Biochem. Behav.* **2002**, *71*, 857−865.
(15) Smith, M. P.; Hoepping, A.; Johnson, K. M.; Trzcinska, M.; Kozikowski, A. P. Dopaminergic agents for the treatment of cocaine abuse. *Drug Discovery Today* **1999**, *4*, 322−332.
(16) Trzcinska, M.; Pimentel, P.; Stellar, J. R.; Hanson, R. N.; Choi, S. W.; Elmaleh, D. R.; Zhang, J.; Prakash, K. R. C.; Tamiz, A. P.; Kozikowski, A. P.; Johnson, K. M.; Smith, M. P.; Babich, J. W. Novel monoamine transporter ligands reduce cocaine-induced enhancement of brain stimulation reward. *Pharmacol. Biochem. Behav.* **2001**, *68*, 171−180.
(17) Carroll, F. I. 2002 Medicinal Chemistry Division Award address: monoamine transporters and opioid receptors. Targets for addiction therapy. *J. Med. Chem.* **2003**, *46*, 1775−1794.
(18) Singh, S. Chemistry, design, and structure−activity relationship of cocaine antagonists. *Chem. Rev.* **2000**, *100*, 925−1024.
(19) Srivastava, S.; Crippen, G. M. Analysis of cocaine receptor site ligand binding by three-dimensional Voronoi site modeling approach. *J. Med. Chem.* **1993**, *36*, 3572−3579.
(20) Froimowitz, M. Conformational Analysis of Cocaine, the Potent Analogue 2-Carbomethoxy-3β-(4-fluorophenyl)tropane (CFT), and Other Dopamine Reuptake Blockers. *J. Comput. Chem.* **1993**, *14*, 934−943.
(21) Enyedy, I. J.; Zaman, W. A.; Sakamuri, S.; Kozikowski, A. P.; Johnson, K. M.; Wang, S. M. Pharmacophore-based discovery of 3,4-disubstituted pyrrolidines as a novel glass of monoamine transporter inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1113−1118.
(22) Wang, S. M.; Sakamuri, S.; Enyedy, I. J.; Kozikowski, A. P.; Deschaux, O.; Bandyopadhyay, B. C.; Tella, S. R.; Zaman, W. A.; Johnson, K. M. Discovery of a novel dopamine transporter inhibitor, 4-hydroxy-1-methyl-4-(4-methylphenyl)-3-piperidyl 4-methylphenyl ketone, as a potential cocaine antagonist through 3D-database pharmacophore searching. Molecular modeling, structure−activity relationships, and behavioral pharmacological studies. *J. Med. Chem.* **2000**, *43*, 351−360.
(23) Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergmann, J. S. Chemistry and Biology of the 2-Beta-Alkyl-3-Beta-Phenyl Analogues of Cocaine − Subnanomolar Affinity Ligands That Suggest a New Pharmacophore Model at the C-2 Position. *J. Med. Chem.* **1995**, *38*, 3086−3093.
(24) Davies, H. M.; Gilliatt, V.; Kuhn, L. A.; Saikali, E.; Ren, P.; Hammond, P. S.; Sexton, T.; Childers, S. R. Synthesis of 2β-acyl-3β-(substituted naphthyl)-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites. *J. Med. Chem.* **2001**, *44*, 1509−1515.
(25) Hoffman, B. T.; Kopajtic, T.; Katz, J. L.; Newman, A. H. 2D QSAR modeling and preliminary database searching for dopamine transporter inhibitors using genetic algorithm variable selection of Molconn Z descriptors. *J. Med. Chem.* **2000**, *43*, 4151−4159.
(26) Newman, A. H.; Izenwasser, S.; Robarge, M. J.; Kline, R. H. CoMFA study of novel phenyl ring-substituted 3alpha-(diphenylmethoxy)tropane analogues at the dopamine transporter. *J. Med. Chem.* **1999**, *42*, 3502−3509.
(27) Kotian, P.; Mascarella, S. W.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis, ligand binding, and quantitative structure−activity relationship study of 3 beta-(4′-substituted phenyl)-2 beta-heterocyclic tropanes: evidence for an electrostatic interaction at the 2 beta-position. *J. Med. Chem.* **1996**, *39*, 2753−2763.
(28) Robarge, M. J.; Agoston, G. E.; Izenwasser, S.; Kopajtic, T.; George, C.; Katz, J. L.; Newman, A. H. Highly selective chiral N-substituted 3alpha-[bis(4′-fluorophenyl)methoxy]tropane analogues for the dopamine transporter: synthesis and comparative molecular field analysis. *J. Med. Chem.* **2000**, *43*, 1085−1093.
(29) Carroll, F. I.; Gao, Y. G.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, QSAR, and CoMFA study of 3 beta-(p-substituted phenyl)tropane-2 beta-carboxylic acid methyl esters. *J. Med. Chem.* **1991**, *34*, 2719−2725.
(30) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3 beta-(3′-substituted phenyl)-, 3 beta-(4′-substituted phenyl)-, and 3 beta-(3′,4′-disubstituted phenyl)tropane-2 beta-carboxylic acid methyl esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.
(31) Yang, B.; Wright, J.; Eldefrawi, M. E.; Pou, S.; Mackerell, A. D. Conformational, Aqueous Solvation, and Pk(a), Contributions to the Binding and Activity of Cocaine, Win-32−065−2, and the Win Vinyl Analogue. *J. Am. Chem. Soc.* **1994**, *116*, 8722−8732.
(32) Lieske, S. F.; Yang, B.; Eldefrawi, M. E.; MacKerell, A. D.; Wright, J. (−)-3 beta-substituted ecgonine methyl esters as inhibitors for cocaine binding and dopamine uptake. *J. Med. Chem.* **1998**, *41*, 864−876.
(33) Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E. Chemistry and pharmacology of the piperidine-based analogues of cocaine. Identification of potent DAT inhibitors lacking the tropane skeleton. *J. Med. Chem.* **1998**, *41*, 1962−1969.
(34) Tamiz, A. P.; Zhang, J. R.; Flippen-Anderson, J. L.; Zhang, M.; Johnson, K. M.; Deschaux, O.; Tella, S.; Kozikowski, A. P. Further SAR studies of piperidine-based analogues of cocaine. 2. Potent dopamine and serotonin reuptake inhibitors. *J. Med. Chem.* **2000**, *43*, 1215−1222.
(35) Tamiz, A. P.; Zhang, J. R.; Zhang, M.; Wang, C. Z.; Johnson, K. M.; Kozikowski, A. P. Application of the bivalent ligand approach to the design of novel dimeric serotonin reuptake inhibitors. *J. Am. Chem. Soc.* **2000**, *122*, 5393−5394.
(36) Tamiz, A. P.; Bandyopadhyay, B. C.; Zhang, J. R.; Flippen-Anderson, J. L.; Zhang, M.; Wang, C. Z.; Johnson, K. M.; Tella, S.; Kozikowski, A. P. Pharmacological and behavioral analysis of the effects of some bivalent ligand-based monoamine reuptake inhibitors. *J. Med. Chem.* **2001**, *44*, 1615−1622.
(37) Petukhov, P. A.; Zhang, M.; Johnson, K. J.; Tella, S. R.; Kozikowski, A. P. SAR studies of piperidine-based analogues of cocaine. Part 3: Oxadiazoles. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2079−2083.
(38) Petukhov, P. A.; Zhang, J.; Kozikowski, A. P.; Wang, C. Z.; Ye, Y. P.; Johnson, K. M.; Tella, S. R. SAR Studies of Piperidine-Based Analogues of Cocaine. 4. Effect of N−Modification and Ester Replacement. *J. Med. Chem.* **2002**, *45*, 3161−3170.
(39) Sybyl6.9; Tripos Inc.: 1699 South Hanley Rd., St. Louis, MO 63144.
(40) Lemmen, C.; Lengauer, T. Time-efficient flexible superposition of medium-sized molecules. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 357−368.
(41) Lemmen, C.; Lengauer, T.; Klebe, G. FLEXS: a method for fast flexible ligand superposition. *J. Med. Chem.* **1998**, *41*, 4502−4520.
(42) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. Synthesis, cocaine receptor affinity, and dopamine uptake inhibition of several new 2 beta-substituted 3 beta-phenyltropanes. *J. Med. Chem.* **1994**, *37*, 3875−3877.
(43) Kozikowski, A. P.; Araldi, G. L.; Prakash, K. R.; Zhang, M.; Johnson, K. M. Synthesis and biological properties of new 2β-alkyl- and 2β-aryl-3-(substituted phenyl)tropane derivatives: stereochemical effect of C-3 on affinity and selectivity for neuronal dopamine and serotonin transporters. *J. Med. Chem.* **1998**, *41*, 4973−4982.
(44) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3−25.
(45) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. The Design of Leadlike Combinatorial Libraries. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3743−3748.
(46) Zhou, J.; Zhang, A.; Klass, T.; Johnson, K. M.; Wang, C. Z.; Ye, Y. P.; Kozikowski, A. P. Biaryl analogues of conformationally constrained tricyclic tropanes as potent and selective norepinephrine reuptake inhibitors: synthesis and evaluation of their uptake inhibition at monoamine transporter sites. *J. Med. Chem.* **2003**, *46*, 1997−2007.

JM0303296