Interaction of *cis*-(6-Benzhydrylpiperidin-3-yl)benzylamine Analogues with Monoamine Transporters: Structure−Activity Relationship Study of Structurally Constrained 3,6-Disubstituted Piperidine Analogues of (2,2-Diphenylethyl)-[1-(4-fluorobenzyl)piperidin-4-ylmethyl]amine

Rohit B. Kolhatkar,[†] Sujit K. Ghorai,[†] Clifford George,[‡] Maarten E. A. Reith,[§] and Aloke K. Dutta*[,†]

Wayne State University, Department of Pharmaceutical Sciences, Detroit, Michigan 48202, Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, D. C. 20735, and University of Illinois, College of Medicine, Department of Biomedical and Therapeutic Sciences, Peoria, Illinois 61656

Received December 20, 2002

To explore structure−activity relationships (SAR) of a novel conformationally constrained lead cis-3,6-disubstituted piperidine derivative derived from (2,2-diphenylethyl)-[1-(4-fluorobenzyl)-piperidine-4-ylmethyl]amine (**I**), a series of compounds was synthesized by derivatizing the exocyclic N-atom at the 3-position of the lead. This study led to the formation of substituted phenyl and heterocyclic derivatives. All novel compounds were tested for their affinity at the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) in the brain by measuring their potency in competing for the binding of [^{3}H]WIN 35 428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively. Selected compounds were also evaluated for their activity in inhibiting the uptake of [^{3}H]DA. The SAR results demonstrated that the nature of substitutions on the phenyl ring is important in activity at the DAT with the presence of an electron-withdrawing group having the maximum effect on potency. Replacement of the phenyl ring in the benzyl group by heterocyclic moieties resulted in the development of compounds with moderate activity for the DAT. Two most potent racemic compounds were separated by a diastereoisomeric separation procedure, and differential affinities were observed for the enantiomers. Absolute configuration of the enantiomers was obtained unambiguously by X-ray crystal structural study. One of the enantiomers, compound *S,S*-(−)-**19a,** exhibited the highest potency for the DAT (IC_{50} = 11.3 nM) among all the compounds tested and was as potent as GBR 12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine). However, the compound (−)-**19a** was more selective than GBR 12909 in binding to the DAT compared with binding to the SERT and NET. The present results establish the newly developed 3,6-disubstituted piperidine derivatives as a novel template for high-affinity inhibitors of DAT. Structurally these molecules are more constrained compared to our earlier flexible piperidine molecules and, thus, should provide more insights about their bioactive conformations.

Introduction

(−)-Cocaine is a naturally occurring alkaloid isolated from Erythroxylon coca and has been around in our society for over a century.[1,2] Harmful addictive effect of cocaine was first recognized by Sigmund Freud almost a century ago. Early medicinal application of cocaine was mainly restricted in its use as a local anesthetic for minor surgery. Cocaine has continued to be abused through out the world due to its powerful reinforcing effect and has impacted the public health system to a significant extent.[3] The results of many biochemical and pharmacological experiments demonstrated cocaine's interaction with the three monoamine neurotransporter systems in the brain while the generation of cocaine's powerful reinforcing effect is thought to be mediated by binding to the dopamine transporter (DAT) system in the CNS.[4−7] However, recent results from knock out mice and behavioral intervention experiments indicated that the serotonergic system might also play a role in the reinforcing effect of cocaine.[8,9]

DAT has been a target for the development of medications for cocaine addiction for some time.[10] DAT was cloned a decade ago and was shown to contain a putative 12-transmembrane (TM) domain protein.[11] DAT is a presynaptically located protein which translocates extracellular DA into nerve endings of DA neurons. Molecular biological studies on DAT with the help of site-directed mutagenesis demonstrated the potential of developing a cocaine antagonist.[12,13] A large number of studies have been carried out with various DAT mutants and cocaine analogues. These studies indicated that DAT portions of TM domains involved in binding DA and cocaine analogues are not exactly identical raising the possibility of developing a cocaine antagonist.[12−14] However, no single amino acid residue has yet been shown to be differentially involved in cocaine and dopamine binding. So far no such studies have been carried out systematically with other classes of nontropane DAT blockers which might shed more light into this aspect. Finally, there is yet a compound

* Correspondence address: Aloke K. Dutta, Ph.D., Department of Pharmaceutical Sciences, Applebaum College of Pharmacy & Health Sciences, Rm# 3128, Detroit, MI 48202, Tel: 1-313-577-1064, Fax: 1-313-577-2033, e-mail: adutta@ea.cphs.wayne.edu.
[†] Wayne State University.
[‡] Naval Research Laboratory.
[§] University of Illinois.

10.1021/jm020561w CCC: $25.00 © 2003 American Chemical Society
Published on Web 04/19/2003

to be found which exhibits the property of interfering with cocaine binding while sparing the interaction between DA and DAT. A potential application of an antagonist against cocaine binding is the treatment of cocaine overdose toxicity. On the other hand, a partial agonist with slower onset and longer duration of action than cocaine might find application in a substitution maintenance treatment program for cocaine dependence. Currently both cocaine antagonists and partial agonists are being pursued as probable pharmacotherapeutic treatment agents.

Various molecules belonging to diverse chemical structures have been developed for the DAT. They can be classified as tropane, benztropine, mazindol, or methylphenidate derivatives, and as either piperazine or piperidine derivatives of GBR 12935.[15−26] This wide variety of molecular classes might indicate the presence of flexible binding pockets in the receptor which can accommodate the different molecular templates. This should increase the likelihood of developing a cocaine antagonist.

In our effort to develop potent and selective blockers for the DAT, a large number of potent piperidine analogues of GBR 12935 was synthesized and biologically characterized.[27−31] Most of these molecules have a high degree of structural flexibility, and consequently, it is rather difficult to elucidate their biologically active conformational structure(s) which might interact with the target receptor. It is quite possible that these flexible piperidine analogues might interact with the transporter molecule via an induced-fit conformational change conforming them to a right orientation for their interaction with the DAT.[32] Previous studies in conformationally constrained molecular structures indicated that rigidification of ligand molecules can potentially influence their biological activity either by decreasing or increasing their potencies and selectivities for the target receptors. From the thermodynamic point of view, a conformationally constrained molecule with correct bioactive conformation should exhibit enhanced affinity as the reduction in flexibilities reduces loss of entropy upon binding normally occurring when a rotationally free compound becomes more restricted upon alignment with the binding site.[33] In addition, such transformation is also a powerful tool to illustrate possible bioactive conformation of a flexible parent molecule. In the opioid area, conformational constrained versions of opioid peptides led to high degree of receptor selectivity and potency.[34] GBR 12935 and related molecules are known for the flexibility in their molecular structures. Structurally constrained versions of these molecules might produce interesting properties as they might display altered pharmacological and pharmacokinetic properties. As a result of such transformations, it might improve their overall pharmacological properties which may include their blood−brain barrier crossing ability.

In our effort to design structurally constrained piperidine analogues of GBR 12935, we embarked on a molecular design which transformed one of our flexible analogues into a more structurally constrained novel 3,6-piperidine derivative (Figure 2). Thus, in our earlier reported study, the synthesis of two isomeric 3,6-disubstituted cis and trans piperidine derivatives was reported, from which cis-3,6-disubstituted compound

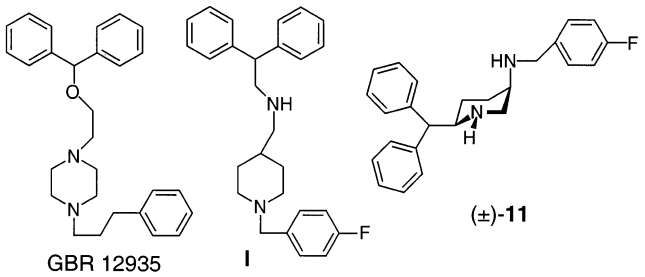


Figure 1. Molecular structure of dopamine transporter blockers.

exhibited more activity and selectivity for the DAT.[35] The active cis version represents a considerable structural rigidity compared to our original piperidine analogue I, Figure 1. Moreover, this molecule also represents a novel molecular template as a 3,6-disubstituted piperidine derivative for the first time was shown to have affinity for DAT.

In our current study, further structural variations of our initial lead compound (±)-**11** (Figure 1) were undertaken to develop a biological receptor binding profile of this novel 3,6-disubstituted piperidine template. In particular, experiments were aimed at exploring the effect of different substitutions with the variations of steric and electronic effects on the exocyclic N-atom of the cis compound.

Chemistry

The synthesis of our target molecules is shown in Schemes 1−4 which describe mostly a linear step synthesis process. In Scheme 1, the starting 2-chloro-5-nitropyridine was reacted with diphenylacetonitrile under phase-transfer conditions consisting of toluene, tetrabutylammonium fluoride, and 50% NaOH to furnish (5-nitro-pyridin-2-yl)diphenylacetonitrile **2** in very good yield.[35] Acidic hydrolysis of nitrile **2** by brief treatment with aqueous sulfuric acid produced amide intermediate **3** in good yield.[36] The nitro group of **3** was first reduced by hydrogenation in the presence of 10% Pd−C as a catalyst producing amino-amide **4** in almost quantitative yield. Then **4** was hydrolyzed and decarboxylated to **5** by refluxing with 37% HCl in excellent yield. Compound **5** was next transformed into acetyl derivative by reacting with acetyl chloride in excellent yield, and the acetyl derivative **6** was next hydrogenated in the presence of platinum oxide catalyst into cis and trans derivatives of 3,6-disubstituted piperidine molecules **7a** and **7b** which were separated by column chromatography. As described in Supporting Information, ^{1}H NMR spectra of **7a** and **7b** clearly indicate cis and trans orientation of these two compounds.

Racemic *cis*-**7a** was next used as a starting precursor for the synthesis of various other analogues by derivatizing the exocyclic N-atom in **7a** as shown in Scheme 3. Compounds **13a**−**i** were produced by initial hydrolysis of *cis*-**7a** to liberate *cis*-diamine **12** which on reductive amination with appropriate aldehyde produced the targets **13a**−**i**. The precursor for **13f**, 2-substituted indole aldehyde **17**, was synthesized from the starting material **15** via Weinreb amide intermediate **16** by following a published procedure.[38] Synthesis of **13j** was carried out by first acylation of **12** followed by reduction of the intermediate **14** with borane−THF complex.

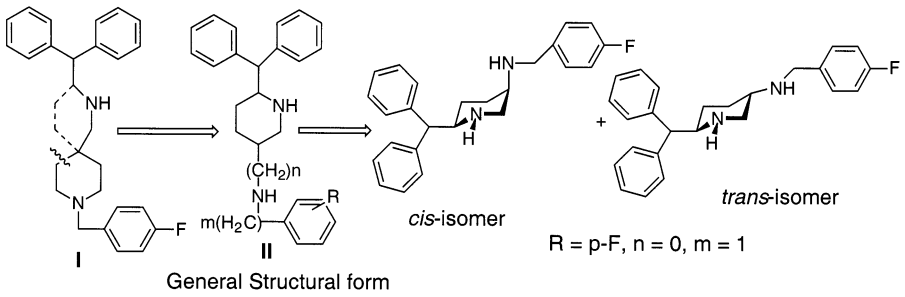
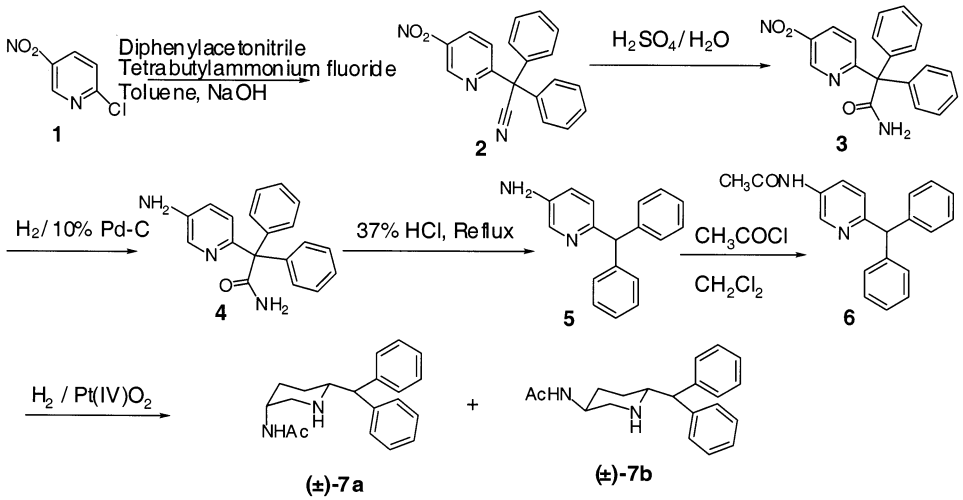
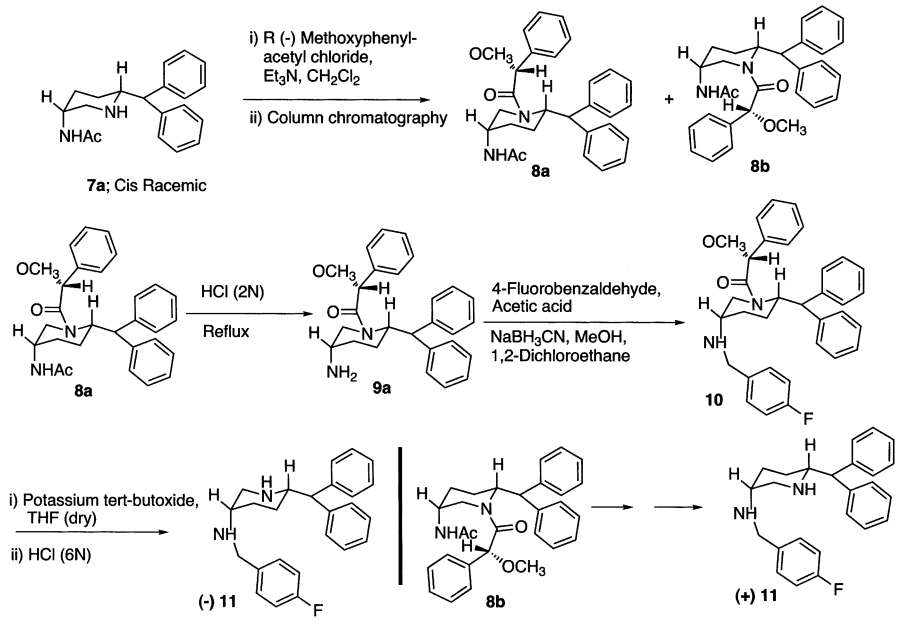


Figure 2. Rationale for structural transformation of flexible piperidine analogue I to relatively more constrained cis- and trans-derivatives.

Scheme 1

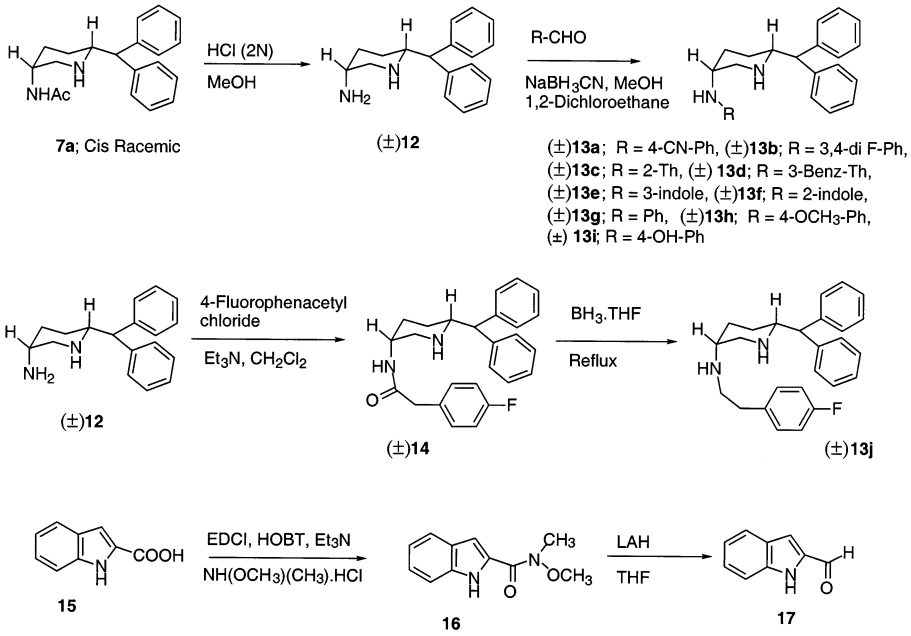


Scheme 2



Subsequently, resolution of one of the lead compounds (±)-**11** was carried out which is shown in Scheme 2**.** The resolution was complicated due to the presence of the two basic N-atoms in the molecule. In our initial attempt of reaction of **(**±)-**11** with an optically active acid a complex diastereomeric reaction mixture resulted which was difficult to separate. On the other hand, treatment with optically active tartaric acid did not yield any good results either. At that point, it was decided to go ahead with the racemic compound *cis*-(±)-**7a** for enantiomeric separation. Reaction of (±)-**7a** with **R**-(−)-methoxyphenylacetyl chloride produced two diastereomeric compounds **8a** and **8b** which were separated by column chromatography. Next each one of these two diastereomers was treated separately to produce the optically active target compounds. Thus, treatment of **8a** with HCl (2 N) liberated amine **9a** which on reductive amination with *p*-fluorobenzaldehyde under standard

Scheme 3



condition produced N-benzylated **10**. Final hydrolysis of the mandalate moiety was carried out in two steps which involved first basic hydrolysis with potassium *tert*-butoxide followed by acidic hydrolysis of the intermediate aldehyde to produce the final optically active amine (−)-**11**.[39a,b] Similarly the other diastereomer **8b** was subjected to the same sequence of reactions to produce (+)-**11**. Separation of racemic (±)-**13a**, however, was carried out in a slightly modified way and is shown in Scheme 4. In this modified procedure optically active diamine **18a** was first produced from **9a** by hydrolysis of the mandalate moiety as described above. The compound **18a** was then subjected to reductive amination with *p*-cyanobenzaldehyde to produce optically pure target (−)-**19a**. The other enantiomer (+)-**19b** was produced in the similar fashion. This modified procedure was adopted to avoid any unwanted hydrolysis of the cyano group during the hydrolysis of the mandalate group.

The absolute configurations of the enantiomers of the compounds **11** and **13a** was evaluated by X-ray crystallography. For this purpose, one of the diastereomeric intermediates formed in the separation of (±)-**11** and (±)-**13a** was crystallized for X-ray study. Thus, the more polar diastereomer **8b** was first hydrolyzed with HCl (2 N) to hydrolyze selectively the exocyclic *N*-acetyl moiety to liberate amine **9b** which was then crystallized from methanol/water (2:1) mixture for X-ray structure evaluation. The absolute configuration assignment from this X-ray structure determination corresponded to a designation of *R*,*R* at the 3 and 6 carbon centers in the piperidine ring of the compound **9b**, Figure 3. Consequently, (+)-**11** and (+)-**19b** which are derived directly from the functionalization of the exocyclic amine of **9b**, have also the *R*,*R*-configuration at the 3 and 6 carbon centers. The corresponding enantiomers (−)-**11** and (−)-**19a** must then have *S*,*S*-configurations at their asymmetric 3,6-centers.

Result and Discussion

Our attempt to derive conformationally constrained versions of piperidine analogues of GBR 12935 led us

Scheme 4

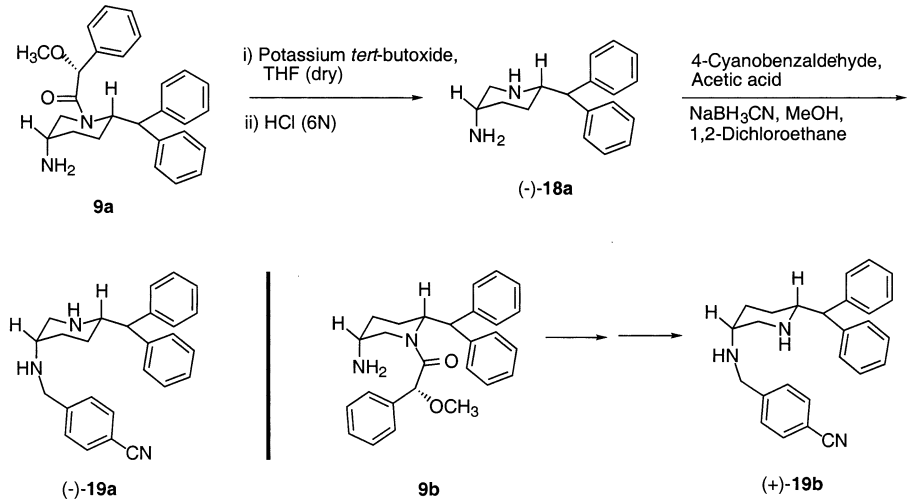


Table 1. Affinity of Drugs at the Dopamine, Serotonin, and Norepinephrine Transporters in Rat Striatum and in Inhibition of DA Reuptake

compd	DAT binding, IC_{50}, nM, [^{3}H]WIN 35, 428[a]	SERT binding, IC_{50}, nM, [^{3}H]citalopram[a]	NET binding, IC_{50}, nM, [^{3}H]nisoxetine[a]	DAT uptake, IC_{50}, nM, [^{3}H]DA [a]
cocaine	266 ± 37[b]	737 ± 160	3530 ± 550	
GBR 12909	10.6 ± 1.9[b]	132 ± 0	496 ± 22	6.63 ± 0.43
I	19.7 ± 1.4[b]	137 ± 46	1110 ± 120	49.6 ± 7.2
(±)-**11**	32.5 ± 12.6	2220 ± 590	1020 ± 70	45.7 ± 5.1
(−)*S*,*S*-**11**	33.8 ± 5	1330 ± 120	1420 ± 560	53.8 ± 7.4
(+)*R*,*R*-**11**	229 ± 17	3540 ± 640	2290 ± 230	142 ± 25
13a	31.5 ± 5.3	1130 ± 250	3200 ± 940	30.2 ± 5.2
13b	63.5 ± 3.2	2250 ± 490	1590 ± 140	77.0 ± 9.7
13c	267 ± 91	3650 ± 1110	4730 ± 1080	
13d	515 ± 130	2770 ± 680	1050 ± 460	
13e	834 ± 70	3010 ± 950	3790 ± 1170	
13f	95.4 ± 20.2	1800 ± 280	1010 ± 490	51.0 ± 21.9
13g	114 ± 10.6	2130 ± 110	612 ± 130	
13h	47.5 ± 6.2	1040 ± 110	1110 ± 60	40.5 ± 21.8
13i	65.9 ± 8.2	862 ± 57	201 ± 13	
13j	173 ± 4	2190 ± 80	1740 ± 100	
(−)*S*,*S*-**19a**	11.3 ± 0.9	434 ± 27	1670 ± 90	9.10 ± 1.86
(+)*R*,*R*-**19b**	109.0 ± 16.7	1550 ± 420	16600 ± 410	152 ± 41

[a] For binding, the DAT was labeled with [^{3}H]WIN 35, 428, the SERT with [^{3}H]citalopram and the NET with [^{3}H]nisoxetine. For uptake by DAT, [^{3}H]DA accumulation was measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate. [b] See reference 30.

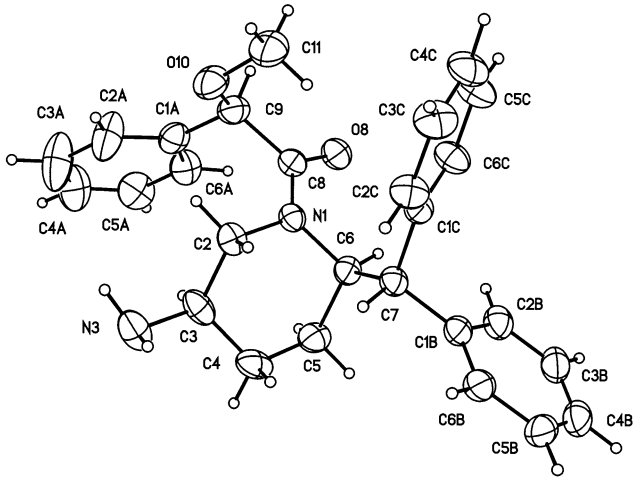


Figure 3. The molecular structure and numbering scheme for compound **9b** with displacement ellipsoids drawn at the 30% probability level.

to design and synthesize two preliminary molecules as reported earlier.[35] Further SAR exploration on our initial lead structure was taken up to better understand its structural and functional properties in interacting with monoamine transporter systems. In this report, results of an SAR study conducted through derivatization of the exocyclic N-atom at the 3-position of the cis-isomer is presented. Differently substituted benzyl derivatives along with bioisosteric heterocyclic replacement were introduced on the N-atom. The effect of these different substitutions on biological activity will enable us to understand the roles of steric and electronic factors and the role of bioisosteric heterocyclic moieties at this molecular center in interacting with the DAT. Also comparison of these results with our previously developed more flexible piperidine analogues will enable us to better understand the mode of binding interactions.

Replacement of the 4-fluorophenyl ring by 4-cyanophenyl, 3,4-difluorophenyl, 4-methoxyphenyl, and unsubstituted phenyl groups resulted in the production of potently active to moderately active compounds in interacting with DAT. In our earlier study with flexible piperidine analogues, similar 4-cyanophenyl and 3,4-difluorophenyl substitutions resulted in generation of potent compounds for the DAT.[28,30] In fact, a cyano-substituted derivative, thus produced from our earlier study, was turned out to be one of the most potent and selective compounds for the DAT.[30] In the present study, racemic cyano **13a** exhibited the highest activity (IC_{50} = 31.5 nM, Table 1), and thus, indicated a similar SAR result. As cyano is a strong electron-withdrawing group, the effect of this group on the aromatic ring might have positively influenced the interaction with DAT. On the other hand, the presence of an electron-donating methoxy group in compound **13h** also produced a potent compound for the DAT (IC_{50} = 47.5 nM). The same relative decrease in potency for the DAT from changing an electron-withdrawing to an electron-donating groups was also maintained in our flexible analogues. However, as opposed to our earlier results, the present data indicate that the presence of either electron-withdrawing or electron-donating groups improve activity for DAT in these molecules compared to the unsubstituted phenyl ring **13g**. An interesting observation was made when the methoxy group in compound **13h** was converted into a hydroxyl functionality in **13i**. This transformation resulted in 5.5-fold increase in NET activity for **13i** compared to **13h** (IC50 of 201 vs 1110 nM), indicating the possible involvement of an H-bond interaction emanating from the hydroxyl functionality in **13i** with the NET. Overall rank order of DAT activity of the substituted benzyl derivatives is as follows: 4-Ph-CN (**13a**) > 4-Ph-F (**11**) > 4-Ph-OCH_3 (**13h**) > 3,4-bis-Ph-F (**13b**) > 4-Ph-OH (**13i**) > Ph (**13g**).

Replacement of the phenyl group by bioisosteric heterocyclic moieties resulted in **13c**−**f**. In our previous study with the flexible piperidine analogues, thiophene and benzothiophene moieties were introduced as the bioisosteric replacement for the phenyl ring. In that study, the thiophene ring turned out to be the most potent bioisostere. In the current study, in addition to thiophene and benzothiophene rings, an indole moiety was also included for such bioisosteric replacement. Such replacement mostly produced weakly active to

Table 2. Selectivity of Various Ligands for Their Activity at Monoamine Transporters

compound	SERT binding/ DAT binding	NET binding/ DAT binding	[^{3}H]DA uptake/ DAT binding
GBR 12909	12	47	0.62
I	7	56	2.5
11	68	31	1.4
(−)-**11**	39	42	1.6
(+)-**11**	15	10	0.62
13a	36	100	0.95
13b	35	25	1.2
13c	14	18	
13d	5.4	2	
13e	3.6	4.5	
13f	19	11	0.53
13g	19	5.4	
13h	22	23	0.85
13i	13	3	
13j	13	10	
(−)-*S*,*S*-**19a**	38	148	0.8
(+)-*R*,*R*-**19b**	14	15	1.4

moderately active compounds for the DAT. Unlike our earlier thiophene derivative, in the current series the thiophene version was much less potent. Interestingly, compounds **13f** and **13e** which are the positional isomers of 2- and 3-substituted indole derivatives, exhibited differential activities. Thus, the compound **13f** exhibited approximately 9-fold more activity for the DAT compared to **13e** (95.4 nM vs 834 nM, Table 1). This differential activity can probably be attributed to the generation of different electronic effects arising from substitutions at the two different positions in the indole ring since molecular orbital calculation demonstrated that the C-3 of the indole ring carries a greater π-electron density than the C-2 position.[40] Altenatively, it may be due to steric or positional effects which produced unfavorable interactions with the DAT in the case of the 3-substituted derivative **13e**. All heterocyclic analogues showed moderate to appreciable selectivity for the DAT when their binding was compared with that to SERT and NET (Table 2).

A drop in DAT activity was observed in compound **13j** compared to **11** when 4-fluorobenzyl was replaced by 4-fluorophenylethyl moiety (32.5 nM vs 173 nM). This result was somewhat surprising and contrasted to earlier results found in our flexible piperidine analogues where no such drop in activity was observed.[27] In fact, replacement of the methylene linker in the *N*-benzyl moiety by either ethyl or propyl linker produced some of the most potent DAT blockers in structurally flexible piperidine derivatives.[29] As it was eluded earlier, this might be an indication of the role of an induced-fit mechanism in the binding interaction, resulting in production of receptor bound conformation for our flexible analogues which might be more restricted in our current molecules due to structural rigidity. Another possibility is that with the current structural modifications, these new molecules might bind to different sites on the DAT. This is a possibility our future experiments will address.

Our previous report describes the activity of the racemic version of compound **11**.[35] Here, enantiomeric separation of the racemic **11** and the most potent cyano derivative **13a** was carried out. Higher activity at DAT was found in the (−)-*S*,*S*-isomer of both **11** and **13a** (33.8 nM for (−)-*S*,*S*-**11** and 11.3 nM for (−)-*S*,*S*-**19a** vs. 229 nM and 109 nM, respectively, for the (+)-isomers). Thus, appreciable separation of DAT activity was observed between the two enantiomers which might be indicative of structural rigidity resulting in a better fit selectively for one of the enantiomers. The enantiomer (−)-*S*,*S*-**19a** turned out to be the most potent compound developed in the current series.

Selected compounds showing relatively higher potency for the DAT were tested in the DA uptake inhibition assay. For the most part, binding and uptake activity correlated very well with compound (−)-**19a** exhibiting the highest DA uptake inhibitory activity (IC_{50} = 9.10 nM). No significant differential uptake and binding activity was observed for any one of these compounds, providing no indication for potential cocaine antagonist activity.

Conclusion

In this SAR study, 3,6-disubstituted piperidine derivatives were further established as a novel template for DAT. Exploration of various substituents on the exocyclic N-atom produced potent and selective compounds for the DAT. The optically active (−)-*S*,*S*-**19a** with an electron-withdrawing cyano substituent turned out to be the most potent DAT compound with a potency comparable to that of GBR 12909. However, it was more selective than GBR 12909 for binding to the DAT when compared with SERT and NET (Table 2). These novel molecules are structurally constrained versions of our earlier flexible compounds and, thus, reflect more closely to their bioactive conformers. Our ongoing studies to probe and identify further active molecular determinants will shed more light on their mode of interactions with the DAT in comparison to that of the flexible piperidine analogues. In this regard, our photoaffinity ligand binding study with a flexible piperidine derivative demonstrated dual incorporation into two regions that are distal in the primary sequence of DAT.[41] Similar experiments will be carried out with a suitable photoaffinity ligand derived from the current structurally constrained series allowing comparison of sites of incorporation.

Experimental Section

Analytical silica gel-coated TLC plates (Si 250F) were purchased from Baker, Inc and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 mM. ^{1}H NMR spectra were routinely obtained at GE-300 and 400 MHz FT NMR. The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc and were within ±0.4% of the theoretical value.

[^{3}H]WIN 35,428 (86.0 Ci/mmol), [^{3}H]nisoxetine (80.0 Ci/mmol), and [^{3}H]dopamine (48.2 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA). [^{3}H]Citalopram (85.0 Ci/mmol) was from Amersham Pharmacia Biotech Inc. (Piscataway, NJ). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO). WIN 35,428 naphthalene sulfonate was purchased from Research Biochemicals, Inc. (Natick, MA). (−)-Cocaine HCl was obtained from the National Institute on Drug Abuse. GBR 12909 dihydrochloride (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine) was purchased from SIGMA-Aldrich (#D-052; St. Louis, MO).

Synthesis of (5-Nitropyridin-2-yl)diphenylacetonitrile (2). To a mixture of 2-chloro-5-nitropyridine (1.0 g, 6.3 mmol), diphenylacetonitrile (1.33 g, 6.9 mmol, 1.1 equiv), and tetrabutylammonium fluoride (0.70 g, 3.15 mmol, 0.5 equiv) in 10 mL of toluene was added dropwise 1.5 mL 50% aqueous NaOH. After 30 min the mixture was filtered through a short plug of silica to remove tars, and solvent was evaporated to get a slightly yellow oil. The crude oil was purified by flash chromatography over a silica gel column using hexane:EtOAc (3:1), to get the title compound (1.7 g, 86%) as colorless plates. mp 94−9 °C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.20−7.29 (5H, m, ArH), 7.35−7.42 (5H, m, ArH), 7.54 (1H, d, J = 8.7 Hz, H-3), 8.49 (1H, dd, J = 3 and 9 Hz, H-4), 9.48 (1H, d, J = 2.4 Hz, H-6). Anal. ($C_{19}H_{13}N_3O_2$): C, H, N.

Synthesis of 2-(5-Nitropyridin-2-yl)2,2-diphenylacetamide(3). A mixture of (5-nitropyridin-2-yl)diphenylacetonitrile (5.0 g, 15.8 mmol) was added to a magnetically stirred, room-temperature solution of 40 mL of concentrated H_2SO_4 diluted with 10 mL of H_2O. The mixture was then stirred for 24 h at 90 °C. The dark solution was then poured onto crushed ice and water and stirred for 1 h. The mixture was extracted thrice with EtOAc. All organic extracts were pooled, washed with brine, and dried over $MgSO_4$, and solvent was evaporated. The crude product was purified by flash chromatography over a silica gel column using hexane:EtOAc (2:1) to furnish the title compound (4.74 g, 90%) as an amorphous tan solid. mp 160−4 °C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 5.9 (1H, bs, NH), 7.05−7.1 (4H, m, ArH), 7.26 (1H, d, J = 8.4 Hz, H-3), 7.3−7.4 (6H, m, ArH), 8.19 (1H, bs, NH), 8.36 (1H, dd, J = 2.4 and 6.3 Hz, H-4), 9.43 (1H, d, J = 1.8 Hz, H-6). Anal. ($C_{19}H_{15}N_3O_3$) C, H, N.

Synthesis of 2-(5-Aminopyridin-2-yl)-2,2-diphenylacetamide (4). A mixture of 2-(5-nitropyridin-2-yl)-2,2-diphenylacetamide (8.86 g, 26.5 mmol) in 50% EtOH/glacial AcOH with Pd/C (10%) was stirred for 24 h. The mixture was then filtered through a bed of Celite, and ethanol was evaporated under reduced pressure. The aquous portion was then basified with K_2CO_3 and extracted with EtOAc (4×). All organic portions were pooled, washed with brine, dried over $MgSO_4$, and the solvent was evaporated. Obtained crude product was purified by flash chromatography over a silica gel column using hexane:EtOAc (2:1) to furnish the title compound (7.9 g, 98%) as a tan crystal. mp 215−20 °C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.85 (2H, broad singlet, NH_2), 5.88 (1H, broad singlet, CONH), 6.54 (1H, d, J = 8.4 Hz, H-3), 6.84 (1H, dd, J = 3 and 8.7 Hz, H-4), 7.01−7.06 (4H, m, ArH), 7.24−7.32 (6H, m, ArH), 8.11 (1H, d, J = 2.4 Hz, H-6), 9.57 (1H, bs, CONH). Anal. ($C_{19}H_{17}N_3O\cdot 0.25\ H_2O$) C, H, N.

Synthesis of 6-Benzhydrylpyridin-3-ylamine (5). A mixture of 2-(5-aminopyridin-2-yl)-2,2-diphenylacetamide (5.28 g, 17.4 mmol) and 150 mL of 37% HCl under a N_2 atmosphere was refluxed for 24 h. The mixture was then cooled and poured over/onto 300 g of ice and H_2O and basified with K_2CO_3. The mixture was then extracted thrice with EtOAc (150 mL). All organic portions were pooled, washed with brine, and dried over $MgSO_4$, and the solvent was evaporated to yield a green oil that solidified. This crude oil was purified by flash chromatography over a silica gel column using hexane:EtOAc (1:1), to furnish the title compound (4.09 g, 90%) as a tan crystalline solid. mp 130−4 °C. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.52 (2H, broad singlet, NH), 5.61 (1H, s, $CH(Ph)_2$), 6.83−6.91 (2H, m, ArH), 7.15−7.32 (10H, m, ArH), 8.08 (1H, d, J = 2.4 Hz, H-2). Anal. ($C_{18}H_{16}N_2$) C, H, N.

Synthesis of *N*-(6-Benzhydrylpyridin-3-yl)acetamide (6). To a solution of 6-benzhydrylpyridin-3-ylamine (0.100 g, 0.38 mmol) in dry CH_2Cl_2 (20 mL) were added acetyl chloride (0.033 g, 0.42 mmol) and Et_3N (0.76 g, 0.76 mmol). The solution was stirred for 3 h after which the solution was diluted with CH_2Cl_2 and the organic layer was washed three times with water and finally with brine. It was then dried over Na_2SO_4, and the solvent was evaporated in vacuo to give **6** (0.1053 g, 90.77%). ^{1}H NMR ($CDCl_3$ 300 MHz): δ 2.10 (3H, s, $COCH_3$), 5.64 (1H, s, $(Ph)_2CH$), 7.01−7.30 (11H, m, ArH), 7.91 (1H, broad singlet, NH), 8.05 (1H, dd, J = 2.4 Hz J = 8.7 Hz, ArH), 8.45 (1H, d, J = 2.4 Hz, ArH).

Synthesis of *cis*- and *trans*-*N*-(6-Benzhydrylpiperidin-3-yl)acetamide (7a and 7b). To a solution of *N*-(6-benzhydrylpyridin-3-yl)acetamide dihydrochloride salt (1.11 g, 3.28 mmol) in 20 mL of methanol was added platinum(IV) oxide (0.11 g, 10%), and the mixture was shaken on Parr hydrogenator at room temperature under H_2 atmosphere (60 psi) for 12 h. The reaction mixture was then filtered through Celite, and the methanol was evaporated. The residue was basified with saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (5×). The extracts were pooled, washed with brine, and dried over Na_2SO_4, and the solvent was evaporated in vacuo to give crude product which was purified by flash chromatography over a silica gel column using hexane/EtOAc/MeOH/Et_3N (52:40:4:4). **7a** *cis*-*N*-(6-Benzhydrylpiperidin-3-yl)acetamide was eluted first (0.4865 g, 48%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.17−1.27 (1H, m, H-5), 1.38−1.53 (2H, m, H-5,H-4_{ax}), 1.81−1.88 (1H, m, H-4_{eq}), 2.0 (3H, s, $COCH_3$), 2.81−2.84 (2H, m, H-2), 3.24 (1H, dt, J = 2.4 Hz J = 10.4 Hz, H-6), 3.71 (1H, d, J = 10.8 Hz, Ph_2CH), 4.03−4.09 (1H, m, H-3_{eq}), 6.42−6.53 (1H, broad doublet, CONH), 7.15−7.39 (10H, m, ArH). Eluting second was **7b** *trans*-*N*-(6-Benzhydrylpiperidin-3-yl)-acetamide (0.27 g, 27%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11−1.31 (3H, m, H-5, H-4), 1.56−1.63 (1H, m, H-4), 1.92 (3H, s, $COCH_3$), 2.30 (1H, t, J = 10.4 Hz, H-2_{ax}), 3.17−3.24 (2H, m, H-6, H-2_{eq}), 3.76 (1H, d, J = 10.4 Hz,Ph_2CH), 3.80−3.90 (1H, m, H-3_{ax}), 5.25−5.42 (1H, broad doublet, NHCO), 7.15−7.39 (10 H, m, ArH).

Procedure A. Synthesis of *N*-[6-Benzhydryl-1-(methoxyphenylacetyl)piperidin-3-yl]acetamide (8a and 8b). Racemic *cis*-*N*-(6-benzhydrylpiperidin-3-yl)acetamide **7a** (1 g, 3.2 mmol) was dissolved in dry CH_2Cl_2 and into it was added Et_3N (1.63 g, 16.23 mmol). The solution was stirred for few minutes (5 min) and into it was added (−)-*R*-mandelic acid chloride freshly prepared from (−)-*R*-mandelic acid (1.07 g, 6.49 mmol) and oxalyl chloride (3.29 g, 25.9 mmol). The mixture was stirred overnight under N_2 atmosphere. After 12 h the solution was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was then separated and dried over Na_2SO_4 . The solvent was evaporated in vacuo to give a crude mixture of two diastereomers which was separated by flash chromatography over a silica gel column using hexane/EtOAc/MeOH/Et_3N (52:40:4:4).

Eluting first **8a** (0.5393 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52−1.84 (4H, m, H-5, H-4), 1.92 (3H, s, $COCH_3$), 2.62−2.74 (1H, m,H-2_{ax}), 3.32 (3H, s, OCH_3), 3.42−3.61(1H, m, H-3), 3.95(1H, dd, J = 13.5 Hz J = 3.6 Hz, H-2_{eq}), 4.32 (1H, d, J = 12.3 Hz, Ph_2CH), 4.86 (1H, s, Ar−CH), 5.38 (1H, broad doublet, NH), 5.75 (1H, d, J = 12.3 Hz, H-6), 6.99 (2H, d, J = 6.9 Hz, ArH), 7.12−7.48 (13H, m, ArH). Eluting second **8b** (0.640 g, 43%) ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.55−1.76 (4H, m, H-5,H-4), 1.92 (3H, s, $COCH_3$), 2.54−2.66 (1H, m,H-2_{ax}), 3.13 (3H, s, OCH_3), 3.30−3.47 (1H, m, H-3), 3.90 (1H, dd, J = 14.1 Hz, J = 3.6 Hz, H-2_{eq}), 4.25 (1H, d, J = 12.3, Ph_2-CH), 4.95 (1H, s, Ar−CH), 5.54 (1H, broad doublet, NH), 5.75 (1H, d, J = 11.1 Hz, H-6), 6.96 (2H, d, J = 7.2 Hz, ArH), 7.1−7.44 (13H, m, ArH).

Procedure B. Synthesis of 1-(5-Amino-2-benzhydrylpiperidin-1-yl)-2-methoxy-2-phenylethanone (9a). *N*-[6-Benzhydryl-1-(methoxyphenylacetyl)piperidin-3-yl]acetamide **8a** (0.200 g, 0.43 mmol) was dissolved in 2 N HCl in MeOH (10 mL), and the solution was refluxed for 24 h. Methanol was then evaporated, and the residue was neutralized using soild $NaHCO_3$. It was then extracted with EtOAc (3×). The extracts were pooled, washed with brine, and dried over Na_2SO_4. Removing the solvent in vacuo gave a crude mixture, which was purified by flash chromatography over a silica gel column with hexane/EtOAc/MeOH/Et_3N (52:40:4:4) to yield **9a** (0.131 g, yield 72%). ^{1}H NMR ($CDCl_3$ 300 MHz): δ 1.32−1.68 (6H, m, H-5, H-4, NH_2), 2.22−2.32 (1H, m, H-3), 2.49 (1H, t, J = 13.2 Hz, H-2), 3.38 (3H, s, OCH_3), 3.52 (1H, dd, J = 13.6 Hz, J = 3 Hz, H-2), 4.31 (1H, d, J = 12.4 Hz,

Ph_2CH), 4.75 (1H, s, Ar−CH), 5.68−5.74 (1H, m, H-6), 6.91 (2H, d, J = 10 Hz, ArH), 7.12−7.5 (13H, m, ArH).

Procedure C. Synthesis of 1-[2-Benzhydryl-5-(4-fluorobenzylamino)piperidin-1-yl]-2-methoxy-2-phenylethanone (10). 1-(5-Amino-2-benzhydrylpiperidin-1-yl)-2-methoxy-2-phenylethanone **9a** (0.2908 g, 0.7024 mmol) was dissolved in 1,2 dichloroethane (10 mL), and into it was added *p*-fluorobenzaldehyde (0.1741 g, 1.404 mmol) followed by acetic acid (0.08424 g, 1.4 mmol). After 15−20 min of stirring under N_2 sodium cyanoborohydride (0.1323 g, 2.107 mmol) was added followed by 1 mL of methanol. The mixture was stirred for 3−4 h. Into the solution was then added 3−4 mL of water followed by few drops of HCl. Excess HCl was then neutralized with $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3x). All extracts were pooled, washed with brine, and dried over Na_2SO_4, and the solvent was evaporated in vacuo to give crude product which was purified by flash chromatography over a silica gel column using hexane:EtOAc:MeOH (50:40:10) to yield **10** (0.3212 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50−1.70 (4H, m, H-5, H-4), 2.15−2.22 (1H, m, H-3), 2.47−2.55(1H, m, H-2), 3.33(3H, s, OCH_3), 3.38−3.54 (2H, m, $ArCH_2$), 3.71(1H, dd, J = 14 Hz, J = 4 Hz, H-2), 4.33 (1H, d, J = 12 Hz, Ph_2CH), 4.75 (1H, s, (CO)CH), 5.74 (1H, m, H-6), 6.90−7.01 (4H, m, ArH), 7.13−7.29 (11H, m, ArH), 7.39−7.47 (4H, m, ArH).

Procedure D. Synthesis of (−)-*cis*-(6-Benzhydrylpiperidin-3-yl)(4-fluorobenzyl)amine (11). 1-[2-Benzhydryl-5-(4-fluorobenzylamino)piperidin-1-yl]-2-methoxy-2-phenylethanone **10** (0.100 g, 0.195 mmol) was dissolved in dry THF, into it was added potassium *tert*-butoxide (0.171 g, 1.56 mmol), and the mixture was stirred overnight under N_2 atmosphere. Stirring was stopped after 24 h, and into the solution was added water. THF was evaporated, and the mixture was extracted with CH_2Cl_2 (3×). All organic extracts were pooled, washed with brine, and dried over Na_2SO_4. Solvent was then evaporated in vacuo to obtain a crude mixture which was used without any further purification in the next step.

The crude mixture was dissolved in HCl (6 N, 5 mL) and 1 mL of methanol. The solution was refluxed for 3−4 h. Methanol was then evaporated in vacuo, and the solution was neutralized with saturated solution of $NaHCO_3$. The mixture was then extracted with EtOAc (3×). All organic extracts were pooled, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo gave a crude mixture which was purified by flash chromatography over a silica gel column using hexane: EtOAc:MeOH (50:40:10) to give (−)-**11** (0.036 g, 51%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.30−1.42 (2H, m, H-5), 1.49 (1H, tt, J = 4 Hz, J = 12.8 Hz, H-4_{ax}), 1.80−1.89 (2H, m, H-4_{eq}, NH), 2.67−2.74 (2H, m, H-3_{eq}, H-2_{ax}), 2.96−3.02 (1H, m, H-2_{eq}), 3.28 (1H, dt, J = 3.2 Hz, J = 9.6 Hz, H-6_{ax}), 3.72 (2H, s, $ArCH_2$), 3.81-(1H, d, (J = 10.4 Hz), Ph_2CH), 6.96−7.02 (2H, m, ArH), 7.15−7.38 (12H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = -27$ ° (*c* 1, MeOH). The free base was converted into a hydrochloride salt. mp 246−265 °C. Anal. ($C_{25}H_{27}FN_2 \cdot 2HCl \cdot H_2O$) C, H, N.

Synthesis of (+)-*cis*-(6-Benzhydrylpiperidin-3-yl)(4-fluorobenzyl)amine (11). Compound **8b** was refluxed with 2 N HCl in methanol (Procedure B) to produce 1-(5-amino-2-benzhydrylpiperidin-1-yl)-2-methoxy-2-phenylethanone) (70%) which was then reacted with 4-fluorobenzaldehyde (Procedure C) to yield 1-[2-benzhydryl-5-(4-fluorobenzylamino)piperidin-1-yl]-2-methoxy-2-phenylethanone (89%). This compound was then hydrolyzed using potassium *tert*-butoxide followed by treatment with (6 N) HCl (Procedure D) to give (+)*cis*-(6-benzhydrylpiperidin-3-yl)(4-fluorobenzyl)amine, (+)-**11** (54%) (overall yield 33%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.30−1.42 (2H, m, H-5), 1.49 (1H, tt, J = 4 Hz, J = 12.8 Hz, H-4_{ax}), 1.80−1.90 (2H, m, H-4_{eq}, NH), 2.68−2.74 (2H, m, H-3_{eq}, H-2_{ax}), 2.96−3.02 (1H, m, H-2_{eq}), 3.28 (1H, dt, J = 3.2 Hz, J = 9.6 Hz, H-6_{ax}), 3.72 (2H, s, $ArCH_2$), 3.81(1H, d, (J = 9.6 Hz), Ph_2CH), 6.96−7.02 (2H, m, ArH), 7.13−7.33 (10H, m, ArH), 7.35−7.40 (2H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = +28$ ° (*c* 1, MeOH). The free amine was converted into hydrochloride salt. mp 244−257 °C. Anal. ($C_{25}H_{27}FN_2 \cdot 2HCl \cdot 0.9\ H_2O$) C, H, N.

Synthesis of Racemic *cis*-6-Benzhydrylpiperidin-3-ylamine (12). A solution of racemic *cis*-*N*-(6-benzhydrylpiperidin-3-yl)acetamide **7a** (0.4 g, 1.29 mmol) in 2 N HCl/methanol (25 mL) was refluxed for 48 h. Methanol was then evaporated under vacuum, and the aqueous solution was neutralized by using saturated $NaHCO_3$ solution. The mixture was then extracted using EtOAc (3×). All organic extracts were combined, washed with brine and dried over Na_2SO_4. The solvent was then evaporated in vacuo to give **12** (0.324 g, 94%). This was used without further purification in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36−1.42 (2H, m, H-5), 1.59−1.62 (2H, m, H-4), 2.08 (2H, broad singlet, NH), 2.79−2.80 (2H, m, H-2), 2.97−3.02 (1H, m, H-3), 3.25 (1H, dt, J = 4 Hz, J = 10 Hz, H-6), 3.80 (1H, d, J = 10.4, $(Ph)_2CH$), 7.13−7.40 (10H, m, ArH).

Procedure E. Synthesis of Racemic *cis*-4-[(6-Benzhydrylpiperidin-3-ylamino)methyl]benzonitrile (13a). A mixture of racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.080 g, 0.31 mmol), 4-cyanobenzaldehyde (0.032 g, 0.25 mmol), and acetic acid (0.018 g, 0.31 mmol) in 1,2 dichloroethane (5 mL) was stirred at room temperature under N_2 atmosphere for 15−20 min. Sodium cyanoborohydride (0.029 g, 0.46 mmol) and methanol (1 mL) were added next, and the mixture was stirred for 3−4 h. Water (5 mL) was added followed by few drops of HCl. Excess HCl was then neutralized with saturated $NaHCO_3$ solution. The mixture was then extracted with CH_2Cl_2 (3×). All organic extracts were combined and washed with brine and dried over Na_2SO_4. The solvent was then evaporated in vacuo to give crude product which was purified by flash chromatography over a silica gel column using hexane/EtOAc/MeOH (50:40:10) to furnish the title compound **13a** (0.058 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29−1.44 (2H, m, H-5), 1.50 (1H, tt, J = 13.2 Hz, J = 3.6 Hz, H-4_{ax}), 1.81−1.88 (3H, m, 2NH, H-4_{eq}), 2.65−2.76 (2H, m, H-3, H-2), 2.99 (1H, td, J = 2.4 Hz, J = 11.2 Hz, H-2_{eq}), 3.28 (1H, dt, J = 3.2 Hz, J = 9.6 Hz, H-6_{ax}), 3.77−3.84 (3H, m, $ArCH_2$, $(Ph)_2CH$),7.14−7.35(8H, m, ArH), 7.36−7.42(2H, m, ArH), 7.44−7.50(2H, m, ArH), 7.56−7.62-(2H, m, ArH). The free base was converted into oxalate salt mp 226−228 °C. Anal. ($C_{26}H_{27}N_3 \cdot (COOH)_2 \cdot 0.7H_2O$) C, H, N.

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)(3,4-difluorobenzyl)amine (13b). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.040 g, 0.15 mmol) was reacted with 3,4-diflurobenzaldehyde (0.017 g, 0.11 mmol) (Procedure E) to yield **13b** (0.019 g, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.29−1.43 (2H, m, H-5), 1.49 (1H, tt, J = 12.8 Hz, J = 4.0 Hz, H-4_{ax}), 1.79−1.87 (1H, m, H-4_{eq}), 2.65−2.75 (2H, m, H-2_{ax}, H-3_{eq}), 2.99 (1H, td, J = 2.4 Hz, J = 11.2 Hz, H-2_{eq}), 3.28 (1H, dt, J = 2.8 Hz, J = 10.0 Hz, H-6_{ax}), 3.71 (2H, s, $ArCH_2$), 3.80 (1H, d, J = 10.4 Hz, $(Ph)_2CH$), 7.00−7.42 (13H, m, ArH). The free base was converted into oxalate salt. mp 114−130 °C. Anal. ($C_{25}H_{36}N_2F_2 \cdot 2(COOH)_2 \cdot 1.1H_2O$) C, H, N.

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)thiophen-2-ylmethylamine (13c). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.080 g, 0.30 mmol) was reacted with thiophene-2-carbaldehyde (0.028 g, 0.25 mmol) (Procedure E) to give **13c** (0.037 g, 41.11%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31−1.42 (2H, m, H-5), 1.50 (1H, tt, J = 12 Hz, J = 4.0 Hz, H-4_{ax}), 1.78−1.88 (2H, m, NH, H-4), 2.71 (1H, dd, J = 2.4 Hz, J = 12.4 Hz, H-2_{ax}), 2.74−2.80(1H, m, H-3_{eq}), 2.99 (1H, td, J = 2.4 Hz, J = 11.2 Hz, H-2_{eq}), 3.27 (1H, dt, J = 3.6 Hz, J = 10.0 Hz, H-6_{ax}), 3.80 (1H, d, J = 9.6 Hz, $(Ph)_2CH$), 3.97 (2H, s, (2-thiophene)CH_2(NH)), 6.90−6.97 (2H, m, ArH), 7.13−7.42 (11H, m, ArH). The free base was converted into hydrochloride salt. mp 247−255 °C. Anal. ($C_{23}H_{26}N_2S \cdot 2HCl \cdot 1.1H_2O$) C, H, N.

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)benzo[*b*]thiophen-3-ylmethylamine (13d). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.080 g, 0.30 mmol) was reacted with benzo[*b*]thiophene-3-carbaldehyde (0.040 g, 0.25 mmol) (Procedure E) to give **13d** (0.067 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34−1.44 (2H, m, H-5), 1.55 (1H, tt, J = 11.2 Hz, J = 4.0 Hz, H-4_{ax}), 1.87−1.95 (1H, m, H-4_{eq}), 2.76

(1H, dd, J = 2.4 Hz, J = 11.2 Hz, H-2_{ax}), 2.80−2.85 (1H, m, H-3_{eq}), 3.04−3.11 (1H, m, H-2_{eq}), 3.31 (1H, dt, J = 4 Hz, J = 9.6 Hz, H-6_{ax}), 3.83 (1H, d, J = 10.4 Hz, $(Ph)_2CH$), 4.02 (2H, s, (2-benzthiophene) CH_2), 7.14−7.42 (13H, m, ArH) 7.83−7.88 (2H, m, ArH). The free base was converted into hydrochloride salt. mp 227−240 °C. Anal. ($C_{27}H_{28}N_2S\cdot 2HCl\cdot 1.1H_2O$) C, H, N.

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)(1*H*-indol-3-ylmethyl)amine (13e). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.080 g, 0.30 mmol) was reacted with 1*H*-indole-3-carbaldehyde (0.036 g, 0.25 mmol) (Procedure E) to give **13e** (0.045 g, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.39−1.46 (2H, m, H-5), 1.51−1.62 (1H, m, H-4_{ax}), 1.87−1.96 (1H, m, H-4_{eq}), 2.77 (1H, dd, J = 2.4 Hz, J = 11.2 Hz, H-2_{ax}), 2.84−2.89 (1H, m, H-3_{eq}), 3.06−3.12 (1H, m, H-2_{eq}), 3.31−3.38 (1H, m, H-6_{ax}), 3.86 (1H, d, J = 10.8 Hz, $(Ph)_2CH$), 3.98 (2H, s, (3-indole)CH_2), 7.04−7.42 (14H, m, ArH) 7.68 (1H, d, J = 8 Hz, ArH), 8.69 (1H, broad singlet, indole-NH). The free base was converted into oxalate salt. mp 100−113 °C. Anal. ($C_{27}H_{39}N_3\cdot(COOH)_2\cdot 1.9H_2O$) C, H, N.

Synthesis of racemic *cis*-(6-Benzhydrylpiperidin-3-yl)-benzylamine (13g). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.023 g, 0.089 mmol) was reacted with benzaldehyde (0.0076 g, 0.07 mmol) (Procedure E) to give **13g** (0.012 g, yield 48%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30−1.39 (2H, m, H-5), 1.44−1.56 (1H, m, H-4_{ax}), 1.68 (2H, broad singlet, NH), 1.80−1.91(1H, m, H-4_{eq}), 2.70−2.76 (2H, m, H-3_{eq}, H-2_{ax}), 3.00 (1H, bd, J = 10.5 Hz, H-2_{eq}) 3.21−3.39 (1H, m, H-6_{ax}), 3.76(2H, s, CH_2Ph), 3.82 (1H, d, J = 10.2 Hz, $CH(Ph)_2$), 7.13−7.38 (15H, m, ArH). Free base was converted into its hydrochloride salt, mp 267−268 °C. Anal. ($C_{25}H_{30}Cl_2N_2\cdot 1.3H_2O$) C, H, N.

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)(4-methoxybenzyl)amine (13h). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12 (**0.100 g, 0.39 mmol) was reacted with 4-methoxybenzaldehyde (0.042 g, 0.31 mmol) (Procedure E) to give **13h** (0.039 g, 32%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 1.30−1.42 (2H, m, H-5), 1.44−1.54 (1H, m, H-4_{ax}), 1.78−1.92 (2H, m, H-4_{eq}, NH), 2.68−2.74 (2H, m, H-3_{eq}, H-2_{ax}), 2.96−3.02 (1H, m, H-2_{eq}), 3.25−3.32 (1H, m, H-6_{ax}), 3.69 (2H, s, $ArCH_2$), 3.79 (3H, s, OCH_3), 3.82 (1H, d, J = 9.6 Hz, Ph_2CH), 6.84−6.88 (2H, m, ArH), 7.13−7.34 (10H, m, ArH), 7.35−7.40 (2H, m, ArH). Anal. ($C_{26}H_{30}N_2O\cdot(COOH)_2\cdot 1.1H_2O$) C, H, N.

Synthesis of Racemic *cis*-4-[(6-Benzhydrylpiperidin-3-ylamino)methyl]phenol (13i). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12** (0.075 g, 0.28 mmol) was reacted with 4-hydroxybenzaldehyde (0.027 g, 0.22 mmol) (Procedure E) to furnish the title compound **13i** (0.035 g, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34−1.84 (5H, m, H-5, H-4_{ax}, 2NH), 1.86−1.98 (1H, m, H-4_{eq}), 2.68−2.76 (1H, m, H-2_{ax}), 2.78−2.84 (1H, m, H-3), 3.00−3.08 (1H, m, H-2_{eq}), 3.35 (1H, dt, J = 2.0 Hz, J = 8.8 Hz, H-6_{ax}), 3.58−3.68 (2H, m, $ArCH_2$), 3.90 (1H, d, J = 10.4 Hz, $(Ph)_2CH$), 6.49−6.54 (2H, m, ArH), 7.01−7.05 (2H, m, ArH), 7.11−7.33 (8H, m, ArH), 7.35−7.38 (2H, m, ArH). Anal. ($C_{27}H_{30}N_2O\cdot 2.1H_2O$) C, H, N.

Synthesis of Racemic cis-*N*-(6-Benzhydrylpiperidin-3-yl)-2-(4-fluorophenyl)acetamide (14). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine,**12** (0.085 g, 0.332 mmol) was reacted with (4-fluorophenyl)acetyl chloride (0.0515 g, 0.29 mmol) in the presence of excess Et_3N in CH_2Cl_2 to give a crude product, which was purified using flash chromatography (hexane:EtOAc:MeOH 70:30:2) to yield **14** (0.040 g, 48%). mp: 105−106 °C.^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90−1.08 (1H, m, H-5_{ax}), 1.30−1.42 (1H, m, H-5_{eq}), 1.46 (1H, td, J = 3.6 Hz, J = 13 Hz, H-4_{ax}), 1.74−1.86 (2H, m, H-4_{eq}, NH), 2.75 (2H, m, H-2), 3.14−3.25 (1H, m, H-6_{ax}), 3.48−3.56 (3H, m, $ArCH_2$, $(Ph)_2CH$), 3.87−4.05 (1H, m, H-3_{eq}), 6.50−6.58 (1H, m, CONH), 7.07 (2H, t, J = 8.7 Hz, ArH), 7.14−7.34 (12H, m, ArH).

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)-[2-(4-fluorophenyl)ethyl]amine (13j). Into the solution of **14** (0.035 g, 0.087 mmol) in 5 mL of dry THF was added 1 M BH_3/THF (0.5 mL, 5 mmol). The reaction mixture was refluxed for 6 h. After the solution was cooled to room temperature, methanol (2 mL) was added slowly. The solvent was removed under reduced pressure, 10% HCl/MeOH (5 mL) was added into the residue, and the solution was refluxed for 1 h. Solid $NaHCO_3$ was added, and the methanol was removed in vacuo. The mixture was extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated to give the crude product which was purified by flash chromatography over a silica gel column using hexane:acetone:Et_3N (7:2:0.2) to give a colorless oil **13j** (0.025 g, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03−1.13 (1H, m, H-5_{ax}), 1.28−1.38 (1H, m, H-5_{eq}), 1.48 (1H, tt, J = 4 Hz, J = 13.2 Hz, H-4_{ax}), 1.87 (1H, td, J = 2.8 Hz, J = 14 Hz, H-4_{eq}), 2.69 (1H, dd, J = 12 Hz, J = 2.4 Hz, H-2_{ax}), 2.82−2.88 (5H, m, $CH_2CH_2C_6H_4F$, H-3_{eq}), 2.98 (1H, td, J = 2.4 Hz, J = 12 Hz, H-2_{eq}), 3.24 (1H, dt, J = 9.6 Hz, J = 2.4 Hz, H-6_{ax}), 3.63 (1H, d, J = 10.8 Hz, $CH(Ph)_2$), 4.02 (1H, broad singlet, NH), 7.00 (2H, t, J = 8.8 Hz, ArH), 7.12−7.33 (12H, m, ArH).

Free base was converted into its hydrochloride salt, mp 228−230°C. Anal. ($C_{26}H_{31}Cl_2FN_2\cdot 1.9H_2O$) C, H, N.

Synthesis of *N*-Methoxy-*N*-methyl-1*H*-indole-2-carboxamide (16). A solution of indole-2-carboxylic acid **15** (0.500 g, 3.1 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidehydrochloride (EDCI) (1.19 g, 6.2 mmol) in Et_3N(1.5 mL), and dry CH_2Cl_2 (20 mL) was stirred at room temperature for 1 h. *N*,*O*-Dimethylhydroxylamine hydrochloride (0.331 g, 3.4 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added to the above reaction mixture. The solution was stirred at room temperature for overnight. The solution was then diluted with CH_2Cl_2, and the organic phase was washed with water and brine and finally dried over Na_2SO_4. The solvent was removed in vacuo to give a crude product which was purified by flash chromatography over a silica gel column using EtOAc:hexane (1:1) to collect **16** (0.510 g, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.45 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 7.12 (1H, t, J = 7.9 Hz, ArH), 7.23−7.33 (2H, m, ArH), 7.45 (1H, d, J = 8.4 Hz, ArH), 7.69 (1H, d, J = 8.7 Hz, ArH), 9.89 (1H, broad singlet, NH).

Synthesis of 1*H*-Indole-2-carbaldehyde (17). Into a solution of *N*-methoxy-*N*-methyl-1*H*-indole-2-carboxamide **16** (0.200 g, 0.98 mmol) in anhydrous THF (10 mL) at −30 °C was added dropwise 5 mL suspension of LAH in THF (2 g in 100 mL refluxed overnight) under nitrogen atmosphere. The reaction mixture was stirred for 2 h, and ice−water was then added to destroy excess hydride. The reaction mixture was then evaporated in vacuo until most of the THF was removed, and the aqueous residue was extracted with CH_2Cl_2 (3×). All organic fractions were combined, washed with brine, and dried over Na_2SO_4. The solvent removed in vacuo leaving to obtain **17** (0.091 g, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (1H, t, J = 7.8 Hz, ArH), 7.29 (1H, s, ArH), 7.40 (1H, t, J = 8.1 Hz, ArH), 7.50 (1H, d, J = 8.1 Hz, ArH), 7.76 (1H, d, J = 8.7 Hz, ArH), 9.60 (1H, broad singlet, NH), 9.87 (1H, s, CHO).

Synthesis of Racemic *cis*-(6-Benzhydrylpiperidin-3-yl)(1*H*-indol-2-ylmethyl)amine (13f). Racemic *cis*-6-benzhydrylpiperidin-3-ylamine **12 (**0.145 g, 0.54 mmol) was reacted with 1*H*-indole-2-carbaldehyde **17** (0.055 g, 0.38 mmol) (Procedure E) to give **13f** (0.093 g, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29−1.60 (3H, m, H-5, H-4_{ax}), 1.82−1.92 (1H, m, H-4_{eq}), 2.72 (1H, dd, J = 2.4 Hz, J = 11.7 Hz, H-2_{ax}), 2.75−2.82 (1H, m, H-3_{eq}), 3.03 (1H, td, J = 2.4 Hz, J = 11.7 Hz, H-2_{eq}), 3.27−3.38 (1H, m, H-6_{ax}), 3.81 (1H, d, J = 10.2 Hz, $(Ph)_2CH$), 3.88−4.10 (2H, m, (2-indole)CH_2), 6.32 (1H, s, ArH), 7.02−7.42 (13H, m, ArH) 7.57 (1H, d, J = 7.5 Hz, ArH), 9.36 (1H, broad singlet, indole-NH). The free base was converted into oxalate salt, mp 215−217 °C. Anal. ($C_{27}H_{29}N_3\cdot(COOH)_2\cdot 1.9H_2O$) C, H, N.

Synthesis of (−)-*cis*-6-Benzhydrylpiperidin-3-ylamine (18a). Compound **8a** was refluxed with 2 N HCl in methanol (procedure B) to produce **9a** (70%). Compound **9a** (0.336 g, 0.811 mmol) was dissolved in dry THF, into it was added potassium *tert*-butoxide (0.728 g, 6.48 mmol), and the mixture was stirred overnight under N_2 atmosphere. After 24 h, stirring was stopped, and into the solution water was added. THF was evaporated in vacuo, and the mixture was extracted with CH_2Cl_2 (3×). All extracts were pooled, washed with brine

and dried over Na_2SO_4. The solvent was removed in vacuo to give a crude mixture which was used without any purification in the next step. The crude mixture was dissolved in HCl (6 N, 10 mL), 2 mL of methanol was added to dissolve the mixture completely, and the solution was refluxed for 3−4 h. Methanol was then evaporated in vacuo, and the solution was neutralized with $NaHCO_3$. The mixture was then extracted with CH_2CL_2 (3×). All extracts were pooled, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give a crude mixture, which was purified using flash chromatography over a silica gel column using EtOAc:MeOH:Et_3N (60:35:5) to furnish the title compound **18a** (0.109 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35−1.43 (2H, m, H-5), 1.59−1.64 (2H, m, H-4), 2.18 (2H, broad singlet, NH), 2.79−2.81 (2H, m, H-2), 2.98−3.04 (1H, m, H-3), 3.25 (1H, dt, J = 4 Hz, J = 10 Hz, H-6_{ax}), 3.80 (1H, d, (J = 10.2), $(Ph)_2CH$), 7.12−7.40 (10H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = -43°$ (c 1, MeOH).

Synthesis of (−)-*cis*-4-[(6-Benzhydrylpiperidin-3-ylamino)methyl]benzonitrile (19a). (−)-*cis*-6-benzhydrylpiperidin-3-ylamine **18a** (0.075 g, 0.28 mmol) was reacted with 4-cyanobenzaldehyde (0.029 g, 0.22 mmol) (Procedure E) to yield **19a** (0.057 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24−1.42 (2H, m, H-5), 1.50 (1H, tt, J = 4 Hz, J = 12.8 Hz, H-4_{ax}), 1.80−1.96 (3H, m, H-4_{eq}, 2NH), 2.66−2.76 (2H, m, H-3_{eq}, H-2_{ax}), 3.00 (1H, td, J = 2.4 Hz, J = 11.2 Hz, H-2_{eq}), 3.28 (1H, dt, J = 3.2 Hz, J = 9.6 Hz, H-6_{ax}), 3.77−3.83 (3H, m, $ArCH_2$, $(Ph)_2CH$), 7.14−7.34 (8H, m, ArH), 7.36−7.40 (2H, m, ArH), 7.44−7.49 (2H, m, ArH), 7.57−7.62 (2H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = -32°$ (c 1, MeOH). The free base was converted into oxalate salt, mp 226−228 °C. Anal. ($C_{26}H_{27}N_3$,$(COOH)_2$·0.5H_2O) C, H, N.

Synthesis of (+)-*cis*-6-Benzhydrylpiperidin-3-ylamine (18b). 1-(5-Amino-2-benzhydrylpiperidin-1-yl)-2-methoxy-2-phenylethanone **9b** (0.172 g, 0.415 mmol) was dissolved in dry THF, into it was added potassium *tert*-butoxide (0.372 g, 3.32 mmol), and the mixture was stirred overnight under N_2 atmosphere. Stirring was stopped after 24 h, and into the solution was added water. THF was evaporated in vacuo, and the mixture was extracted with CH_2Cl_2 (3×). All extracts were pooled, washed with brine, and dried over Na_2SO_4. The solvent was then evaporated in vacuo to obtain a crude mixture which was used without any further purification in the next step. The crude mixture was dissolved in HCl (6 N, 10 mL), 2 mL of methanol was added to dissolve the mixture completely, and the solution was refluxed for 3−4 h. Methanol was then evaporated under vacuum, and the solution was neutralized with saturated solution of $NaHCO_3$. The mixture was then extracted with CH_2CL_2 (3×). All extracts were pooled, washed with brine, and dried over Na_2SO_4. The solvent was evaporated in vacuo to give a crude mixture which was purified by flash chromatography using EtOAc:MeOH:Et_3N (60:35:5) to give **18b** (0.082 g, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36−1.42 (2H, m, H-5), 1.59−1.62 (2H, m, H-4), 2.08 (2H, broad singlet, NH), 2.79−2.80 (2H, m, H-2), 2.97−3.02 (1H, m, H-3), 3.25 (1H, dt, J = 4 Hz, J = 10 Hz, H-6), 3.80 (1H, d, (J = 10.4), $(Ph)_2CH$), 7.13−7.40 (10H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = +39°$ (c 1, MeOH).

Synthesis of (+)-*cis*-4-[(6-Benzhydrylpiperidin-3-ylamino)methyl]benzonitrile (19b). (+)-*cis*-6-Benzhydrylpiperidin-3-ylamine **18** (0.053 g, 0.28 mmol) was reacted with 4-cynobenzaldehyde (0.020 g, 0.22 mmol) (Procedure E) to yield 0.025 g (yield 43%) of **19b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30−1.44 (2H, m, H-5), 1.50(1H, tt, J = 12.8 Hz, J = 3.2 Hz, H-4_{ax}) 1.70−1.90 (3H, m, H-4_{eq}, 2NH), 2.66−2.76 (2H, m, H-3_{eq}, H-2_{ax}), 2.97−3.04 (1H, m, H-2_{eq}), 3.27 (1H, dt, J = 3.6 Hz, J = 9.6 Hz, H-6_{ax}), 3.76−3.84 (3H, m, $ArCH_2$, $(Ph)_2CH$), 7.14−7.34 (8H, m, ArH), 7.35−7.41 (2H, m, ArH), 7.44−7.50 (2H, m, ArH), 7.57−7.62 (2H, m, ArH). The optical rotation was measured in Perkin-Elmer 241 polarimeter, $[\alpha]^{25}_D = +32°$ (c 1, MeOH). The free base was converted into oxalate salt mp 226−228 °C. Anal. ($C_{26}H_{27}N_3$·$(COOH)_2$·0.4H_2O) C, H, N.

Biology. The affinity of test compounds in binding to rat DAT, SERT, and NET was assessed by measuring inhibition of binding of [^{3}H]WIN 35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively, exactly as described by us previously.[31] Briefly, rat striatum was the source for DAT, and cerebral cortex for SERT and NET. Final [Na^+] was 30 mM for DAT and SERT assays, and 225 mM for NET assays. All binding assays were conducted at 0−4°C, for a period of 2 h for [^{3}H]-WIN 35,428 and [^{3}H]citalopram binding, and 3 h for [^{3}H]-nisoxetine binding. Nonspecific binding of [^{3}H]WIN 35,428 and [^{3}H]citalopram binding was defined with 100 μM cocaine, and that of [^{3}H]nisoxetine binding with 1 μM desipramine. Test compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted out in 10% (v/v) DMSO. Additions from the latter stocks resulted in a final concentration of DMSO of 0.5%, which by itself did not interfere with radioligand binding. At least five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value. For DAT uptake assays, uptake of [^{3}H]DA into rat striatal synaptosomes was measured exactly as described by us previously.[31] Briefly, rat striatal P_2 membrane fractions were incubated with test drug for 8 min followed by the additional presence of [^{3}H]DA for 4 min at 25°C. Nonspecific uptake was defined with 100 μM cocaine. Construction of inhibition curves and dissolvement of test compounds were as described above.

Single-crystal X-ray Diffraction Analysis of 9b. $C_{27}H_{30}N_2O_2$·0.187(H_2O), FW = 417.91, orthorhombic space group $P2_12_12_1$, a = 12.0787(5), b = 13.6177(5), c = 14.6543(5) Å, V = 2410.40(16) Å^3, Z = 4, ρ_{calc} = 1.152 mg mm^{-3}, μ(Cu Kα) = 1.54178 Å, μ = 0.574 mm^{-1}, F(000) = 896, T = 293 K.

A clear colorless 0.63 × 0.08 × 0.08 mm crystal was used for data collection with a Bruker SMART[1] 6K CCD detector on a Platform goniometer. The Rigaku rotating Cu anode source was equipped with an incident beam Gobel mirrors. Lattice parameters were determined using SAINT[42] from 5759 reflections within 7.3< 2σ < 125.6. Data were collected to 2θ = 135.5°. A set of 11938 reflections was collected in the ω scan mode. There were 4119 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL[43] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 used three restraints and varied 297 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms except the lower occupancy solvate atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96 to 0.93 Å, Hθangles idealized, U_{iso}-(H) were set to 1.2 to 1.5 U_{eq}(C). Final residuals were $R1$ = 0.050 for the 3069 observed data with $F_o > 4\sigma(F_o)$ and 0.067 for all data. Final difference Fourier excursions of 0.15 and −0.13 eÅ^{-3}. The asymmetric unit contains a molecule of the title compound and water at the partial occupancy of 0.187.

Tables of coordinates, bond distances and bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge, CB2, and 1EW, England.

Acknowledgment. This work was supported by the National Institute on Drug Abuse, Grant No. DA 12449 (A.K.D.). We thank Janet Berfield and Li Juan Wang for conducting the binding and uptake assays.

Supporting Information Available: Crystal Structure data and additional ^{1}H NMR data interpretation are available free of charge via the Internet at http://pubs.acs.org.

References

(1) Musto, D. F. *Opium, Cocaine and Marijuana in American History. Sci. Am.* **1991**, *256*, 40−47.
(2) Johanson, C. E.; Fischman, M. W. *The Pharmacology of Cocaine Related to its Abuse. Pharmacol. Rev.* **1989**, *41* (1), 3−52.
(3) Swan, N. Drug Abuse cost to society set at $9.7 billion, continued steady increase since 1975. *NIDA Notes* **1998**, 13.
(4) Ritz, M. C.; Cone, E. J.; Kuhar, M. J. Cocaine inhibition of ligand binding at dopamine, norpinephrine and serotonin transporters: A structure−activity study. *Life Sci.* **1990**, *46*, 635−645.

(5) Ritz, M. C.; Lamb, R. J.; Goldberg, R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223.
(6) Robinson, T.; Barridge, K. C. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain. Res. Rev.* **1993**, *18*, 249−291.
(7) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends. Neurosci.* **1991**, *14*, 299−302.
(8) Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S.; Ator, R.; Giros, B.; Miller G. W.; Caron, M. Cocaine self-administration in dopamine transporter knockout mice. *Nature Neurosci.* **1998**, *1*, 132−137.
(9) Walsh, S. L.; Cunningham, K. A. Serotonergic mechanisms involved in the discrimination stimulus, reinforcing and subjective effects of cocaine. *Psychopharmacology* **1997**, *130*, 41−58.
(10) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for Treatment of Cocaine Abuse: Preclinical Aspects. *J. Med. Chem.* **1999**, *42*, 2721−2736.
(11) Shimada, S.; Kitayama, S.; Lin, C. L.; Patel, A.; Nanthakumar, E.; Gregor, P.; Kuhar, M.; Uhl, G. Cloning and expression of a cocaine-sensitive dopamine transporter complementary DNA. *Science* **1991**, *254*, 576−578.
(12) Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D.; Uhl, G. Dopamine transporter site-directed mutations differentially alter substrate transport and cocaine binding. *Proc. Natl. Acad. Sci.* **1992**, *89*, 7782−7785.
(13) Giros, B.; Wang, Y.-M.; Suter, S.; McLeskey, S. B.; Pifl, C.; Caron, M. G. Delineation of discrete domains for substrate, cocaine and tricyclic antidepressant interactions using chimeric dopamine-norepinephrine transporters. *J. Biol. Chem.* **1994**, *269*, 15985−15988.
(14) Lin, Z.; Uhl, G. R. Dopamine transporter mutants with cocaine resistance and normal dopamine uptake provide targets for cocaine antagonism. *Mol. Pharmacol.* **2002**, *61*, 885−891.
(15) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogues. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, 38, 379−388.
(16) Bennett, B. A.; Wichems, C. H.; Hollingsworth, C. K.; Davies, H. M.; Thornley, C.; Sexton, T.; Childers, S. R. Novel 2-substituted cocaine analogues: Uptake and ligand binding studies at dopamine, serotonin and norepinephrine transport sites in the rat brain. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 1176−1186.
(17) Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George, C.; Madras, B. K. 2-Carbomethoxy-3-aryl-8-oxabicyclo-[3.2.1]octanes: Potent non-nitrogen inhibitors of monoamine transporters. *J. Med. Chem.* **1997**, *40*, 2661−2673.
(18) Zhang, C.; Izenwasser, S.; Katz, J. L.; Terry, P. D.; Trudell, M. L. Synthesis and dopamine transporter affinity of the four stereoisomers of (±)-2-(methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo[2.2.1]heptane. **1998**, *41*, 2430−2435.
(19) 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.
(20) Agoston, G. E.; Wu, J. H.; Izenwasser, S.; George, C.; Katz, J.; Kline, R. H.; Newman, A.-H. Novel N-substituted 3a-[bis(4′-fluorophenyl)methoxy]tropane analogues: selective ligands for the dopamine transporter. *J. Med. Chem.* **1997**, *40*, 4329−4339.
(21) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. Synthesis and Pharmacology of Potential Cocaine antagonists. 2. Structure−Activity Relationship Studies of Aromatic Ring-Substituted Methylphenidate Analogues. *J. Med. Chem.* **1996**, *39*, 1201−1209.
(22) Aeberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. 5-Aryl-2,3-dihydro-5H-imidazole[2,1-a]isoindol-5-ols. A novel class of anorectic agents. *J. Med. Chem.* **1975**, *18*, 177−182.
(23) Van der Zee. P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-dialk(en)ylpiperazines as selective and very potent inhibitors of dopamine uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363−370.
(24) Matecka, D.; Lewis, D.; Rothman, R. B.; Dersch, C. M.; Wojnicki, F. H. E.; Glowa, J. R.; DeVries, C.; Pert, A.; Rice, K. C. Heteroaromatic analogues of 1-[2-(diphenylmethoxy)ethyl]- and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as high-affinity dopamine reuptake inhibitors. *J. Med. Chem.* **1997**, *40*, 705−716.
(25) Carrol, F. I.; Lewin, A. H.; Mascarella, S. W. Dopamine transporter uptake blockers: Structure activity relationships. In *Neurotransmitter Transporters: Structure and Function*, 2nd ed.; Reith, M. E. A., Eds.; Human Press: Totowa, NJ, 2002; pp 381−432.
(26) Singh, S. Chemistry, design, and structure−activity relationship of cocaine antagonists. *Chem. Rev.* **2000**, *100*, 925−1024.
(27) Dutta, A. K.; Xu, C.; Reith, M. E. A. Structure−Activity Relationship Studies of Novel 4-[2-[Bis(4-fluorophenyl)methoxy]-ethyl]-1-(3-phenylpropyl)piperidine Analogues: Synthesis and Biological Evaluation at the Dopamine and Serotonin Transporter Sites. *J. Med. Chem.* **1996**, *39*, 749−756.
(28) Dutta, A. K.; Coffey, L. L.; Reith, M. E. A. Highly selective, novel analogues of 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine for the dopamine transporter: Effect of different aromatic substitutions on their affinity and selectivity. *J. Med. Chem.* **1997**, *40*, 35−43.
(29) Dutta, A. K.; Coffey, L. L.; Reith, M. E. A. Potent and selective ligands for the dopamine transporter (DAT): Structure−activity relationship studies of novel 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine analogues. *J. Med. Chem.* **1998**, *41*, 699−705.
(30) Dutta, A. K.; Fei, X.-S.; Beardsley, P.; Newman, J.; Reith, M. E. A. Structure−Activity Relationship Studies of 4-[2-(Diphenylmethoxy)-ethyl]-1-benzylpiperidine Derivatives and their N-analogues: Evaluation of Behavioral Activity of O-and N-Analogues and their Binding to Monoamine transporters. *J. Med. Chem.* **2001**, *44*, 937−948.
(31) Dutta, A. K.; Davis, M.; Fei X−S.; Beardsley, P. M.; Cook, C. D.; Reith M. E. A. Expansion of Structure−Activity Studies in piperidine analogues of 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12935) compounds by altering substitutions in the N-benzyl moiety and behavioral pharmacology of selected molecules. *J. Med. Chem.* **2002**, *45*, 654−662.
(32) Koshland, D. E. Biological specificity in protein small molecule interactions. *Biochem. Pharmacol.* **1961**, *8*, 57.
(33) (a) Hruby, V. J. Conformational restrictions of biologically active peptides via amino acid side chain groups. *Life Sci.* **1982**, *31*, 189−199. (b) Avbelj, F.; Hadzi, D. Potential energy functions and the role of the conformational entropy of clonidine-like imidazolidines in determining their affinity for a-adrenergic receptors. *Mol. Pharmacol.* **1985**, *27*, 466−470.
(34) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.; Wilkes, B. C.; Chung, N. N.; Lemieux, C. Conformationally restricted deltorphin analogues. *J. Med. Chem.* **1992**, *35*, 3956−3961.
(35) Dutta, A. K.; Davis, M. C.; Reith, M. E. A. Rational Design and synthesis of novel conformationally constrained 2,5-disubstituted cis- and trans-piperidine derivatives exhibiting differential activity for the dopamine transporter. *Bioorg. Med. Lett.* **2001**, *11*, 2337−2340.
(36) Makosza, M.; Wojciechowski, K.; Jawdosiuk M. Reactions of organic anions. Part LXXIX. Aromatic nucleophilic substitution in chloronitrobenzenes by carbinols derived from N-substituted oxindoles. *Pol. J. Chem.* **1978**, *52*, 1173−1178.
(37) Sury, E.; Hoffmann, K. *Helv. Chem. Acta* **1954**, *247−248*, 2133-214.
(38) Basha.; Lipton, M.; Weinreb, M. A mild general method for conversion of esters to amides. *Tetrahedron Lett.* **1977**, *48*, 4171−4174.
(39) (a) Wikstrom, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. Resolved 3-(3-hydroxyphenyl)-N−*n*-propylpiperidine and its analogues: Central dopamine receptor activity. *J. Med. Chem.* **1984**, *27*, 1030−1036. (b) Brozda, D.; Koroniak, L.; Rozwadowska, M. Stereoselective synthesis of 3-mono- and 1,3-disubstituted 4-phenyl-1, 2, 3, 4-tetrahydroisoquinolines. *Tetrahedron: Asymmetry* **2000**, *11*, 3017−3025.
(40) *Handbook of Heterocyclic Chemistry*, 2nd ed.; Katritzky, A. R., Pozharskii, A. F., Eds.; Pergamon Press: New York, 2000.
(41) Vaughan, R. A.; Gaffaney, J. D.; Lever, J. R.; Reith, M. E. A.; Dutta. Dual Incorporation of Photoaffinity Ligands on Dopamine Transporters Implicates Proximity of Labeled Domains. *Mol. Pharmacol.* **2001**, *59*, 1157−1164.
(42) Bruker 1995 SMART and SAINT Data *Collection and Reduction Software for the SMART system*. Bruker-AXS, Madison, WI.
(43) Sheldrick, G. M. *SHELXTL* Version 5.1 Bruker Analytical X-ray Instruments, Madison, WI, 1997.

JM020561W