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

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Received July 24, 2000

In our effort to develop a pharmacotherapy for the treatment of cocaine addiction, we embarked on synthesizing novel molecules targeting the dopamine transporter (DAT) molecule in the brain as DAT has been implicated strongly in the reinforcing effect of cocaine. Our previously developed DAT-selective piperidine analogue, 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine, was the basis for our current structure−activity relationship (SAR) studies exploring the significance of the contribution of the benzhydryl O- and N-atoms in these molecules in interacting with the DAT. Thus, we replaced the benzhydryl O-atom with an N-atom, altered the location of the benzhydryl N-atom to an adjacent position, and in one other occasion converted the benzhydryl O-ether linkage into an oxime-type derivative. Furthermore, we also evaluated the important contribution of the piperidine N-atom to binding by altering its pK_a value chemically. Novel analogues were tested for potency in inhibiting [^{3}H]WIN 35,428, [^{3}H]-citalopram, and [^{3}H]nisoxetine binding at the DAT, serotonin transporter (SERT), and norepinepherine transporter (NET). [^{3}H]DA was used to measure DA reuptake inhibition. The results indicated that the benzhydryl O- and N-atoms are exchangeable for the most part. On the other hand, an enhanced interaction with the SERT was observed when the benzhydryl N-atom moved to an adjacent position (**21a**; DAT (IC_{50}) = 19.7, SERT (IC_{50}) = 137 nM, NET (IC_{50}) = 1111 nM). In either cases, further alkylation of the N-atom reduced the activity for the transporter. The presence of a powerful electron-withdrawing cyano group in compound **5d** expectedly produced the most potent and selective ligand for the DAT (DAT (IC_{50}) = 3.7 nM, DAT/SERT = 615). Selected compounds were further analyzed in the dopamine reuptake inhibition assay. Preliminary behavioral assessment of some of the selected compounds in mice indicated that these compounds are much less stimulating when compared with cocaine at comparable doses. In drug-discrimination studies these selected compounds incompletely generalized from the cocaine stimulus in mice trained to discriminate 10 mg/kg cocaine from vehicle.

Introduction

Cocaine is a powerful reinforcer, and its strong addiction liability leads to widespread drug abuse which is causing a national crisis.[1−5] Currently there is no medication available for the treatment of cocaine addiction, and the development of a medication for cocaine abuse is urgently required. Extensive studies in elucidating the mechanism of action of cocaine revealed its binding to the dopamine transporter (DAT), serotonin transporter (SERT), and norepinepherine transporter (NET) systems in the brain.[6−8] The role of DAT is implicated strongly in the powerful reinforcing effect of cocaine by various experimental evidences.[9−12] Thus, DAT blockers are known to be self-administered readily in animal studies with a significant correlation between their behavioral and DA uptake blocking potencies.[11,12] Direct-acting DA receptor agonists are also found to modulate cocaine self-administration.[13] Similarly DA receptor antagonists also change cocaine self-administration in a fashion expected from antagonists acting on these receptors.[14] The DA hypothesis for cocaine addiction was further strengthened by the demonstration that the destruction of dopaminergic system in the nucleus accumbens in rats selectively attenuated cocaine self-administration.[15] In a recent DAT knock-out (KO) mice experiment, it was demonstrated that the mice without DAT are hyperactive and indifferent to cocaine.[16] Also in another recent PET experiment involving human subjects, the production of a 'high' caused by administration of a psychostimulant correlated very well with the increased level of DA in the limbic region of the brain.[17] Recently the roles of the SERT and the serotonergic systems have also been implicated in modulating some of the effects of cocaine.[18−20] However, the correlation of the effect of SERT blockers and serotonergic receptor agonists in behavior modulation is not very strong.[19] In other behavioral experi-

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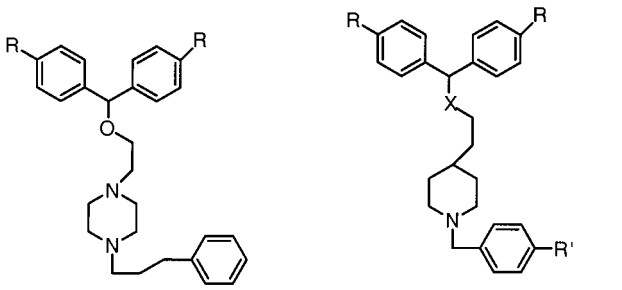
10.1021/jm000311k CCC: $20.00
Published on Web 02/06/2001

Chart 1



ments the modulation in serotonergic activity was shown to have an effect in dopaminergic behavior thus indicating cross-talk between these two systems.[21] In addition, DAT KO mice self-administered cocaine which might indicate the involvement of a more complex mechanism in cocaine's reinforcing effect.[22]

A great number of structurally diversed compounds have been developed for DAT with an aim to develop effective pharmacotherapies for cocaine addiction. Among some of these compounds developed are tropane, GBR, and methylphenidate analogues as some of the most widely studied compounds.[23−31] Recently, piperidine-based nonrigid analogues of cocaine were shown to have good potency and selectivity for the DAT.[32] Our interest in GBR compounds started with the modification of the central piperazine ring of GBR 12909 (Chart 1) into a piperidine moiety which upon extensive structure−activity relationship (SAR) studies led to the development of a series of potent and selective ligands for the DAT.[33−36] In our SAR studies, we established optimal structural requirements in these molecules required for their highest selectivity and potency for the DAT. Thus, the presence of different *N*-benzyl groups in these molecules, unlike in conventional GBR molecules, was best-tolerated for activity at the DAT, while it was not favored by the SERT as reflected in low affinity binding for the SERT.[35] Interestingly, these SAR results turned out to be somewhat different from the SAR results found in conventional GBR molecules.[24,35,36] This led us to speculate the possible involvement of different binding domains of these piperidine analogues in comparison with conventional piperazine GBR molecules.

In one of our latest SAR studies, we have demonstrated that the benzhydryl O-atom could be replaced by an N-atom in the piperidine analogues while maintaining the activity and selectivity for the DAT (1b, Chart 1).[37] We also found that the compound containing the benzhydrylamine N-atom connected to a carbonyl group is rather very weak for the DAT. This might indicate either the need of a basic benzhydryl N-atom for binding interaction or the production of an unfavorable steric or electronic interactions with the DAT due to the presence of an amide moiety.

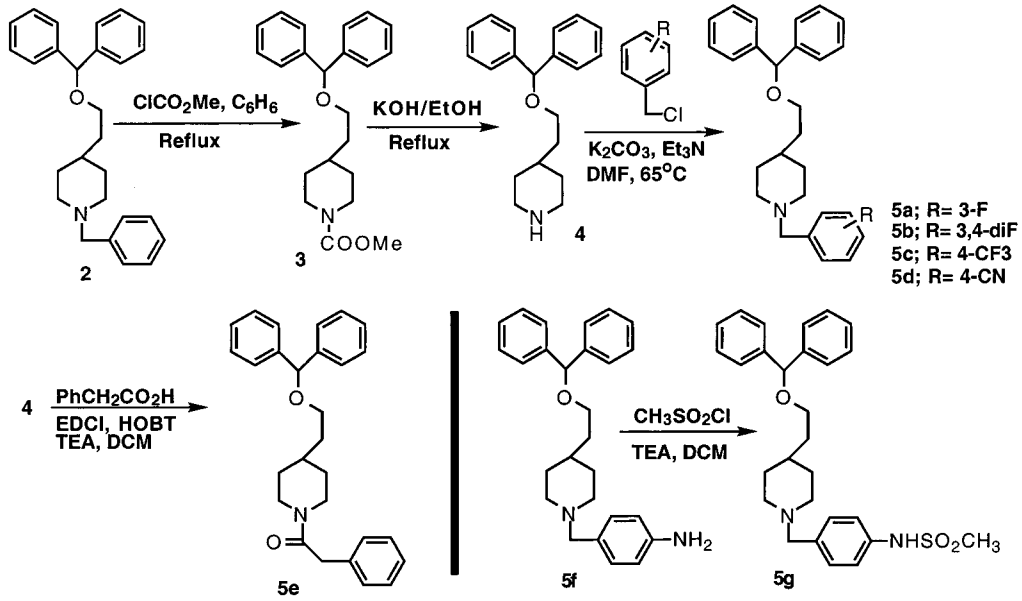
The current hypothesis of our work is based on our previous SAR results in this series of compounds. As a part of extension of our previous results, our current study is focused on: (a) evaluating the importance of the contribution of the benzhydryl O- and N-atoms in interacting with the DAT by altering their steric and electronic environments; (b) examining the impact of replacing the O-atom by an N-atom on activity and selectivity of several analogues; (c) exploring the effect of positional isomers created by relocating the benzhydryl N-atom to an adjacent position in the ethylene chain; and (d) evaluating some selected compounds in behavioral experiments.

Chemistry

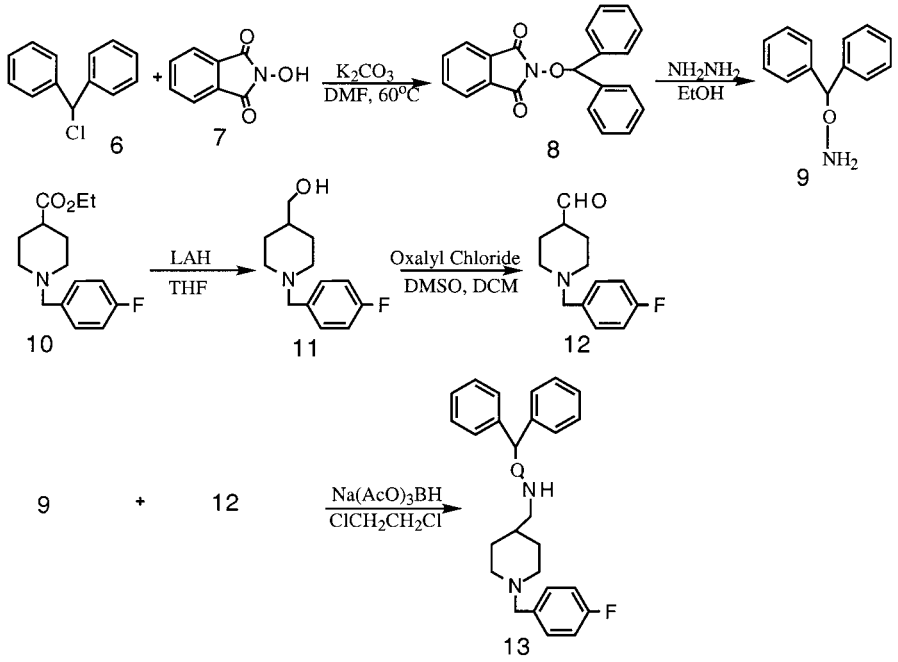
Synthesis of the intermediate **4** in Scheme 1 was accomplished in two steps from the known starting material **2** by converting it to the intermediate carbonate **3** by a reaction with methyl chloroformate. This intermediate carbonate on hydrolysis with KOH produced amine **4**.[38,39] Amine **4** was then alkylated with various benzyl halides in the presence of a base to produce different benzyl-substituted compounds **5a**−**d** in good yield. Compound **5e** was synthesized by following a procedure described by us earlier.[37]

A convergent synthetic approach was adopted in our synthesis of *O*-aralkylhydroxylamine derivative **13**.

Scheme 1



Scheme 2



Thus, as shown in Scheme 2, intermediates **9** and **12** were synthesized separately. Synthesis of **9** was accomplished by following a published procedure which involved a reaction between diphenylbenzhydryl chloride and *N*-hydroxyphthalimide to produce intermediate pthalimide **8**, which on hydrolysis with hydrazine in ethanol furnished *O*-aralkylhydroxylamine **9**.[40] The other intermediate **12** was made from the known ester **10** by reducing it to alcohol **11**, which was followed by oxidation under Swern oxidation condition to aldehyde **12**.[41] Finally, the target compound **13** was made by reacting amine **9** and aldehyde **12** under a modified reductive amination condition in good yield.[42]

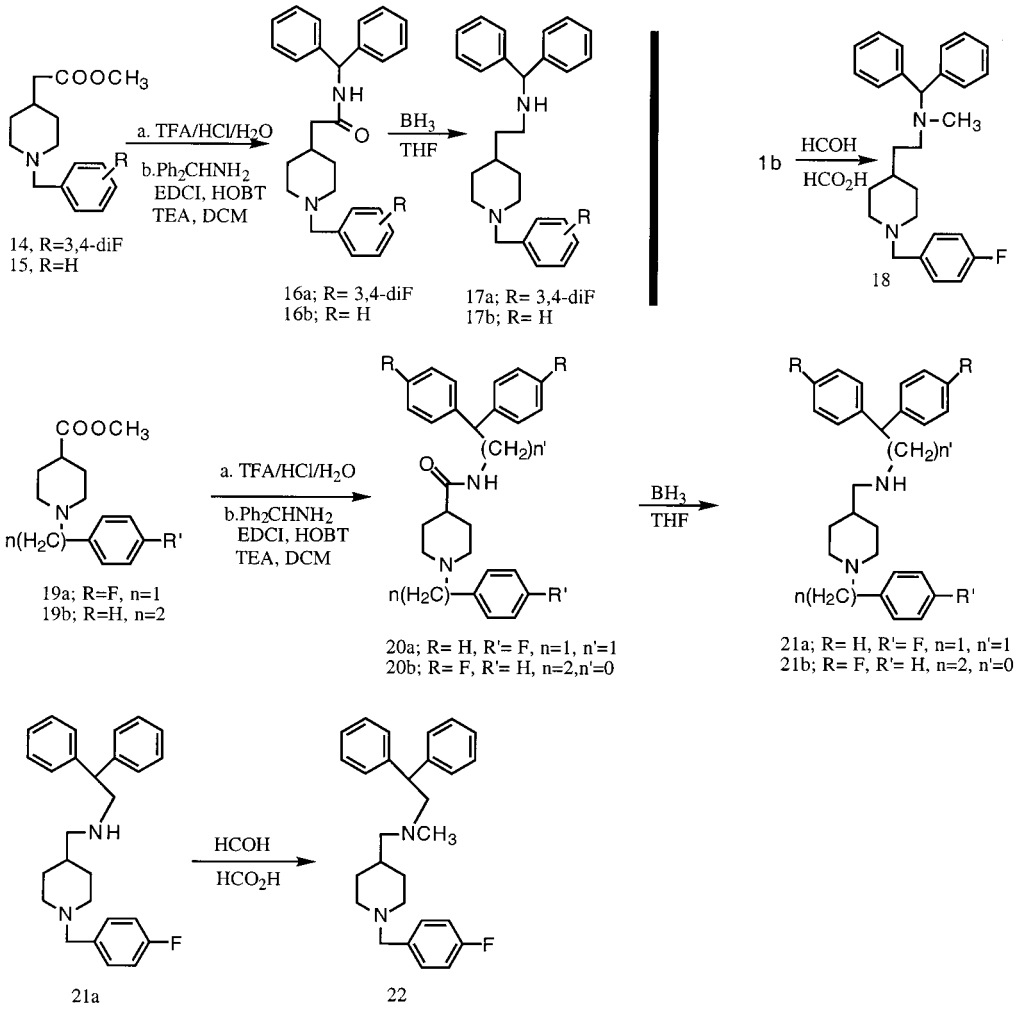
Target compounds **17a,b**, **21a,b**, and **25** were synthesized in good yield by following our previous procedure and are shown in Schemes 3 and 4.[37] Thus the respective starting materials were converted into intermediate acids by treatment with a mixture of trifluoroacetic acid, HCl, and water. The acid was then converted into amides **16a,b**, **20a,b**, and **24** by treatment with water-soluble coupling agent 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide followed by treatment with the appropriate amine. Reduction of the amides with borane/THF complex provided the final compounds.

N-Methyl analogues **18** and **22** were synthesized by following a published procedure.[43] Compound **27** was synthesized in good yield by following Willamson ether synthesis procedure using a phase-transfer catalyst.[44] Thus the known alcohol **26** was treated with (1-bromoethyl)benzene in the presence of sodium hydride and tetrabutylammonium iodide, a phase-transfer catalyst, to produce **27** in good yield.

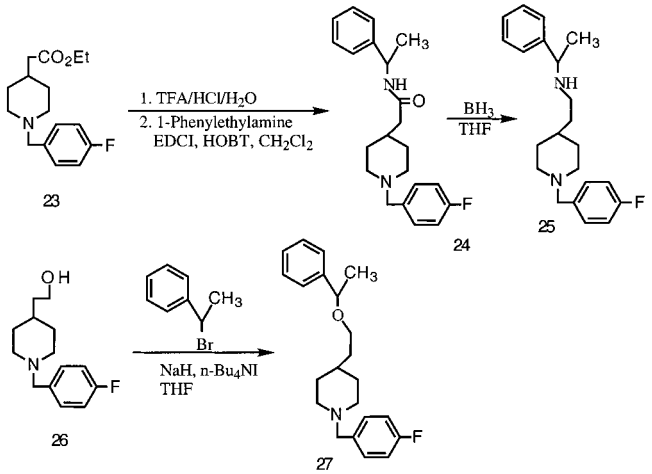
Result and Discussions

Our previous SAR results have demonstrated that the nature of the aromatic−alkyl substitution on the piperidine N-atom of these molecules plays a crucial role in selectivity for the DAT when their binding was compared to the SERT. As we have demonstrated, a longer *N*-alkyl chain connecting the aromatic ring to the piperidine N-atom in these derivatives produced less selective compounds for the DAT even though they maintained strong potencies for the DAT. On the other hand, the selectivity was enhanced significantly when the propyl chain length was reduced to a methylene link connecting the aromatic and the piperidine rings. Additionally, we also found that the presence of an electron-withdrawing group in the aromatic ring of the benzyl substitution further increased the activity and selectivity for the DAT indicating the positive influence of electronic interaction with the transporter. In our effort to extend our previous findings, and to explore the effect of electronegative F-atoms and the strong electron-withdrawing group cyano-substituted in the aromatic ring, compounds **5a**−**d** were designed and synthesized. Conforming to our previous results, we found that these novel compounds exhibited profound selectivity and potency for the DAT (Table 1). Thus, compound **5d**, with a strongly electron-withdrawing cyano group located in the phenyl ring, exhibited remarkable potency and selectivity (IC_{50} = 3.7 nM, DAT/SERT = 615) for the DAT. On the contrary, we have previously found an electron-donating $-NH_2$ group located in the para position of the aromatic ring decreased activity and selectivity.[35] In our current study, we converted this $-NH_2$ group in compound **5f** into methansulfonamide **5g**, which in turn changed it into an electron-withdrawing-type substituent thus altering the electronic character in the original **5f** molecule. As expected, we found potent activity in this compound **5g** compared to its parent amino compound (IC_{50} = 26 nM vs 101 nM, Table 1). Compounds **5a**−**c** containing eletronegative F-atoms at various positions in the phenyl ring, as expected, showed good activity and selectivity for the DAT, where the difluoro compound **5b** was the most active. The rationale behind synthesizing **5e** lied in evaluation of the importance of the basic piperidine N-atom in interaction with the DAT. The weak activity of **5e** for the DAT indicated the

Scheme 3



Scheme 4



requirement of the presence of a basic N-atom in interaction with the DAT.

In our recent study, we have shown that the benzhydryl O-atom can be replaced by an N-atom in these piperidine analogues while maintaining the activity and selectivity for the DAT.[37] In our current investigation, we have extended our initial results by incorporating more analogues for the comparison of the activity of N-analogues and the corresponding O-analogues. Thus compounds **17a,b** and **21b** were designed and synthesized when their corresponding O-analogue versions were also synthesized and characterized. Overall the activities on interchanging the O- and N-atoms in these

Table 1. Affinity and Selectivity of Drugs at the DAT, SERT, and NET in Rat Striatum

	IC_{50}, nM[a]			
compd	DAT [^{3}H]WIN 35,428	SERT [^{3}H]citalopram	NET [^{3}H]nisoxetine	SERT/ DAT
cocaine	266 ± 37	737 ± 160	3530 ± 550	2.7
GBR 12909	10.6 ± 1.9	132 ± 0	496 ± 22	12
1a	17.2 ± 4.7[b]	1920 ± 233		113
1b	9.37 ± 2.62[c]	585 ± 101	945 ± 20	62
5a	23.4 ± 3.8	1150 ± 40		49
5b	10.1 ± 0.93	1220 ± 140	921 ± 110	122
5c	32.1 ± 2.1	2260 ± 140		71
5d	3.67 ± 0.58	2280 ± 470	342 ± 66	615
5e	2156 ± 54	13200 ± 800		6.1
5g	26.6 ± 1.4	586 ± 29		22
13	34.4 ± 4.2	626 ± 33	691 ± 68	19
17a	7.00 ± 1.7	1590 ± 160	1027 ± 94	227
17b	4.50 ± 0.64	1560 ± 210	2620 ± 170	347
18	213 ± 3	1660 ± 470		7.8
21a	19.7 ± 1.4	137 ± 46	1110 ± 120	7.0
21b	65.3 ± 3.2	1100 ± 250		17
22	94.0 ± 12.5	2520 ± 230		27
25	295 ± 41	963 ± 38		3.2
27	751 ± 62	5860 ± 600		7.8

[a] The DAT was labeled with [^{3}H]WIN 35, 428, the SERT with [^{3}H]citalopram, and the NET with [^{3}H]nisoxetine. Results are the average ± SEM of 3 independent experiments assayed in triplicate. [b] See ref 35. [c] See ref 37.

analogues correlated pretty well. Compound **17b** was found to be more potent and selective compared to its previously characterized O-analogue (IC_{50} = 4.5 nM vs 15.2 nM, DAT/SERT = 347 vs 49, Table 1).[34] On the other hand, **21b** was found to be less potent than the corresponding O-analogue characterized earlier,[34] which may reflect more sensitivity toward the alteration of the alkyl chain length between the bisphenyl moiety and the piperidine ring in the case of N-analogues compared to the corresponding O-versions. Future studies will be done to further investigate this.

In our next effort to explore steric and electronic effects on the benzhydryl O- and N-atoms, compounds **13** and **18** (Schemes 2 and 3) were designed and synthesized. In compound **13**, we altered the electronic nature of the benzhydryl O-atom by converting it into a hydroxylamine-type derivative. The binding results indicate that compound **13** is still quite potent for the DAT and has good selectivity, which indicated that the presence of an adjacent N-atom was not detrimental to its activity (Table 1). However, the potency of compound **13** when compared with our previous closely related lead compound **1a** (Chart 1)[35] was a little less, and was much less selective for the DAT, reflecting a somewhat negative impact on selectivity due to the presence of an adjacent N-atom. This result also corresponds somewhat with **21a**, as explained next, where the N-atom is in the same location as in **13** and which also demonstrated much less selectivity. Compound **18**, on the other hand, was weak.

In our next design of compound **21a** we wanted to observe the effect of relocation of the benzhydryl N-atom to an adjacent location which resulted in the formation of a structural isomer of **1b** (Chart 1), our previous N-analogue lead compound.[37] Binding results indicated that such an alteration resulted in the maintenance of activity but a decrease in the selectivity for the DAT; in this regard, it is quite different from **1b** (Table 1). This is quite contrasting in the light of the fact that most of the active piperidine analogues with *N*-benzyl substitutions have exhibited substantial selectivity for the DAT by exhibiting poor affinity for the SERT. Shifting the location of the benzhydryl N-atom to an adjacent position caused a dramatic departure from such selectivity. This might reflect altered molecular interaction resulting from such modification which enhanced its affinity for the SERT. This enhanced interaction with the SERT was lost to a great extent when the N-atom was methylated, as in compound **22**, which may be due to an unfavorable steric interaction.

In our final series of compounds, we wanted to evaluate the contribution of the phenyl ring in the benzhydryl moiety of these molecules in interaction with the transporters. Thus, the N-analogue **25** and the O-analogue **27**, where one of the phenyl rings is replaced by a methyl group, were synthesized and biologically characterized. Compound **27** turned out to be far more weaker than its corresponding bisphenyl counterpart, and the N-analogue compound **25** showed modest activity (Table 1). This illustrated the importance of the presence of a bisphenyl moiety in interaction with the monoamine transporters more so in the case of O-analogues than N-analogues. It is interesting to note that in this instance the activity between the O- and N-analogue versions did not correlate very well. Nevertheless, in both cases the importance of the presence of a bisphenyl moiety in their interaction with the DAT was demonstrated.

Table 2. Inhibition of Dopamine Reuptake in Rat Cytosol

	IC_{50}, nM	
compd	[^{3}H]DA uptake inhib[a]	[^{3}H]DA uptake/ [^{3}H]WIN 35,428 binding
GBR 12909	6.63 ± 0.43	0.62
1a	2.48 ± 0.59	0.14
1b	12.0 ± 1.6	1.33
5d	4.58 ± 0.80	1.23
13	16.6 ± 2.8	0.48
5g	9.73 ± 1.2	0.36
21a	49.6 ± 7.2	2.5
17b	20.6 ± 2.5	4.5
17a	10.7 ± 1.8	1.5

[a] Results are the average ± SEM of 3−4 independent experiments assayed in triplicate.

Some of the selected compounds were tested in a NET assay. In some instances these analogues were more active at the NET than at the SERT. Compound **5d** in this regard was the most active compound (IC_{50} = 342 nM).

The selected compounds were subsequently tested in the dopamine reuptake inhibition assay and compared with the value of the standard compound GBR 12909. For the most part, compounds which showed appreciable potency in binding were also active in the uptake inhibition assay (Table 2). Compounds **21a** and **17b** showed relatively weaker uptake inhibition activity and thus exhibited the highest uptake-to-binding ratios in this current series of compounds. In this regard, compound **17b** was 7-fold less potent than GBR 12909 in the relative activity measure (4.5 vs 0.62). On the other hand, compound **1a** was found to have a low discrimination ratio (0.14). These compounds were chosen for further in vivo testing along with compounds **1a**,**b** and GBR 12909.

The selected compounds were tested in mice for their locomotor activity effects and in mice trained to discriminate 10 mg/kg cocaine from vehicle (Figure 1). The reference compounds cocaine ($F_{3,27}$ = 24.77, $P < 0.0001$) and GBR 12909 ($F_{3,28}$ = 31.11, $P < 0.0001$) significantly altered locomotor activity with 10 and 30 mg/kg, increasing distanced traveled relative to control (Dunnett's, $P < 0.05$). Compound **1a** ($F_{3,28}$ = 13.85, $P < 0.0001$) also significantly altered locomotor activity with 30 mg/kg, increasing distance traveled relative to control (Dunnett's, $P < 0.05$). Compared to the reference compounds, compound **1a** was approximately 3 times less potent than either cocaine or GBR 12909 in increasing locomotor activity. On the other hand, the N-analogue compound **1b** did not affect locomotor activity up to 56 mg/kg, the highest dose tested. The other N-analogue compounds, **17b** ($F_{3,27}$ = 10.72, $P < 0.0001$) and **21a** ($F_{3,28}$ = 8.01, $P < 0.0005$), did affect locomotor activity but decreased it (Dunnett's, $P < 0.05$) at 100 and 30 mg/kg, the highest doses tested, respectively. These results indicate that a molecule containing a benzhydryl O-atom, as in compound **1a**, can produce stimulation of locomotor activity, whereas compounds with either benzhydryl N-atoms, as in **17b** and **1b**, or the N-atom relocated to an adjacent position, as in **21a**, are not stimulatory but inhibitory in this regard. Bind-

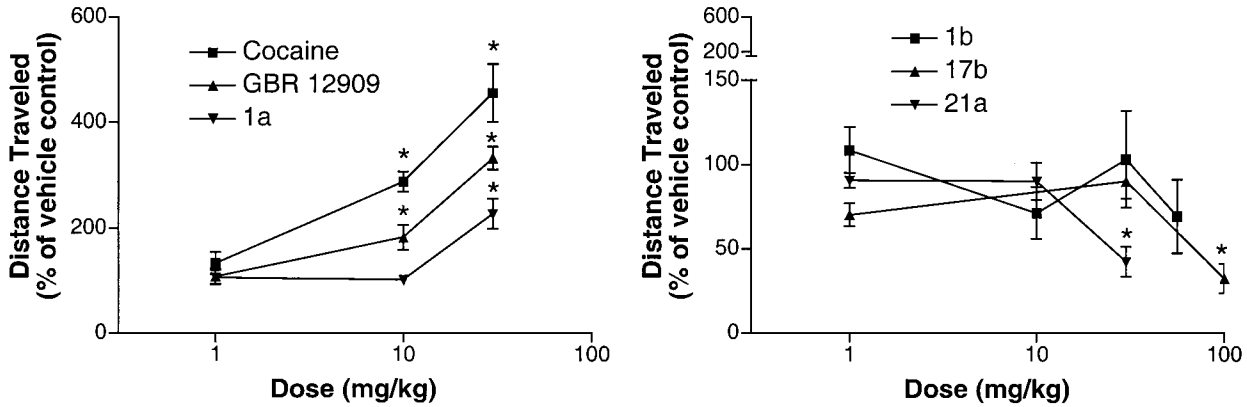


Figure 1. Distance traveled during locomotor activity tests. Each symbol represents the average distance traveled (cm) for each dosage group ($N = 8$; except $N = 7$ for the saline group during cocaine tests and for 30 mg/kg **17b**) during the entire 60-min test session expressed as a percentage of each individual drug's vehicle control. Brackets indicate SEM. ANOVA results with cocaine ($F_{3,27} = 24.77$, $P < 0.0001$), GBR 12909 ($F_{3,28} = 31.11$, $P < 0.0001$), **1a** ($F_{3,28} = 13.85$, $P < 0.0001$), **17b** ($F_{3,27} = 10.72$, $P < 0.0001$), and **21a** ($F_{3,28} = 8.01$, $P < 0.0005$) indicated significant alterations in distance traveled were produced during tests with these compounds. Asterisks indicate that post-hoc Dunnett's tests resulted in a dose producing a significantly different ($P < 0.05$) distance traveled, relative to vehicle control.

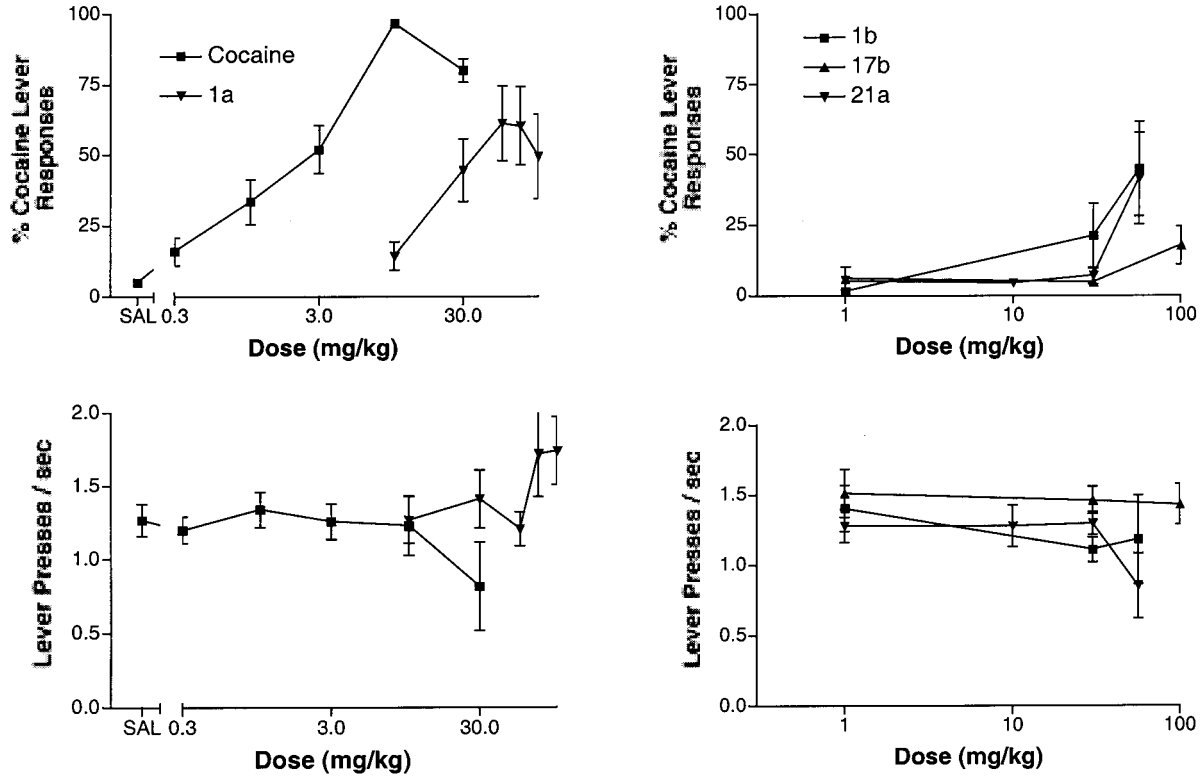


Figure 2. Top: Percentage of lever presses emitted upon cocaine-designated lever. Each symbol represents the mean number of lever presses emitted upon the cocaine-designated lever expressed as a percentage of total lever presses emitted during the test. Brackets indicate SEM. If a mouse failed to lever-press sufficiently to obtain at least one pellet delivery during a test, its data were excluded for calculations of mean drug lever responding for that test (see text): **1b** and **17b** ($N = 6$); **21a** ($N = 7$); **1a** ($N = 8$); cocaine ($N = 21$; except at 3 mg/kg, $N = 20$; and at 30 mg/kg, $N = 19$). Bottom: Response rate expressed as mean lever presses/s. Each symbol represents the mean number of lever presses emitted during the 15-min test session. Brackets indicate SEM: **1b** and **17b** ($N = 6$); **21a** ($N = 7$); **1a** ($N = 8$); cocaine ($N = 21$; except at 3 and 30 mg/kg, $N = 20$).

ing affinities at the three transporters did not predict these differences in locomotor activity effects, for all four compounds, **1a**,**b**, **17b**, and **21a**, had nanomolar affinity at the DAT and poor (between 137 and 1920 nM) affinity at the SERT (Table 1). Compound **1a**'s affinity at the NET was not evaluated, but compounds **1b**, **17b**, and **21a** had micromolar affinity at this transporter suggesting poor activity as well. Interestingly, compound **1a** exhibited a relatively lower discrimination ratio compared to compounds **17b** and **21a**.

Similar to the locomotor activity results, tests in cocaine-discriminating mice showed that the benzhydryl O-atom-containing compound **1a** produced differences relative to compounds **1b**, **17b**, and **21a** (Figure 2). Compound **1a** produced over 60% cocaine lever selection at 56 and 75 mg/kg and increased overall rates of lever pressing relative to vehicle control at 75 and 100 mg/kg. Compounds **1b**, **17b**, and **21a**, however, produced less than 50% cocaine lever selection throughout the dose ranges tested and either had little effect on overall

response rates (**1b** and **17b**) or modestly decreased them (**21a**). These results indicate that none of the tested compounds completely generalized from the cocaine-discriminative stimulus and their effects on overall rates of responding differed in ways similar to their relative differences observed during locomotor activity tests.

Conclusion

In this report, we have demonstrated the development of some very potent and selective compounds for the DAT which includes compound **5d** as among one of the highest selective and potent compounds for DAT known to date. In general, structurally similar N- and O-analogues correlated very well in activity. Relocation of the benzhydryl N-atom to an adjacent position resulted in an enhancement of potency for the SERT without altering DAT activity.

Selected compounds were tested in a dopamine reuptake assay. On the basis of the binding results, some compounds were chosen for in vivo locomotor activity and drug-discrimination studies. In the locomotor assessments, compound **1a** was less stimulating than cocaine and GBR 12909 and did not generalize completely with the cocaine stimulus in drug-discrimination tests. On the other hand, the N-analogues **1b**, **17b**, and **21a** did not exhibit any stimulant action despite their strong potency for the DAT. In drug-discrimination tests they also incompletely generalized with the cocaine-discriminative stimulus. Our continuing and future studies will probe more into differences of in vivo results between O- and N-analogues of these novel piperidine compounds.

Experimental Details

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 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 values.

[^{3}H]WIN 35,428 (86 Ci/mmol), [^{3}H]citalopram (82 Ci/mmol), [^{3}H]nisoxetine (80 Ci/mmol) and [^{3}H]dopamine (60.0 Ci/mmol) were obtained from DuPont-New England Nuclear (Boston, MA). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO). WIN 35,428 naphthalenesulfonate 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).

1-(Methoxycarbonyl)-4-[2-(diphenylmethoxy)ethyl]-piperidine (3). A solution of 4-[2-(diphenylmethoxy)ethyl]-1-(phenylmethyl)piperidine (**2**[34]) (4.62 g, 11.82 mmol) and methyl chloroformate (2.60 g, 23.64 mmol) in benzene (60 mL) was refluxed for 6 h. After TLC showed the completion of reaction, the solvent was removed in vacuo to give a viscous liquid **3**: 4.17 g (99% yield); ^{1}H NMR ($CDCl_3$) δ 7.34−7.18 (10H, m, Ar-H), 5.30 (1H, s, Ph_2CHO), 3.67 (3H, s, OCH_3), 3.50−3.46 (2H, t, J = 6.0 Hz, OCH_2), 2.77−2.68 (2H, t, J = 12.3 Hz, NCH_2), 2.62−2.54 (2H, t, J = 12.0 Hz, NCH_2), 1.67−1.57 (5H, m), 1.26−1.07 (2H, m).

4-[2-(Diphenylmethoxy)ethyl]piperidine (4). Compound **3** (4.17 g, 11.81 mmol) was dissolved in ethanol (100 mL) and KOH (2.5 g) was added into the solution. The reaction mixture was refluxed for 3 days. The solvent was evaporated and EtOAc was added. The EtOAc solution was washed with brine, dried over Na_2SO_4, and evaporated to give crude product which was purified by flash chromatography (EtOAc/MeOH/Et_3N = 100/5/2) to give a white solid **4**: 2.80 g (80% yield); ^{1}H NMR ($CDCl_3$) δ 7.35−7.19 (10H, m, Ar-H), 5.31 (1H, s, Ph_2CHO), 3.50−3.46 (2H, t, J = 6.0 Hz, OCH_2), 3.08−3.04 (2H, bd, J = 2.3 Hz, NCH_2), 2.77−2.68 (2H, t, J = 12.6 Hz), 2.62−2.54 (2H, t, J = 12.3 Hz, NCH_2), 1.82−1.57 (5H, m), 1.14−1.02 (2H, m). Anal. ($C_{20}H_{25}NO\cdot 2.0H_2O$) C, H, N.

Procedure A: 4-[2-(Diphenylmethoxy)ethyl]-1-[(3-fluorophenyl)methyl]piperidine (5a). A mixture of 4-[2-(diphenylmethoxy)ethyl]piperidine (**4**) (58 mg, 0.19 mmol), 3-fluorobenzyl chloride (51 mg, 0.35 mmol), Et_3N (0.5 mL), and anhydrous K_2CO_3 (0.3 g) in DMF (10 mL) was stirred at 65 °C overnight. The reaction mixture was diluted with 30 mL water and extracted with Et_2O. The combined organic phase was dried over Na_2SO_4 and evaporated to give crude product, which was purified by flash chromatography (EtOAc/hexane = 1/3) to give **5a**, a viscous liquid: 62 mg (79% yield); ^{1}H NMR ($CDCl_3$) δ 7.34−7.20 (10H, m, 2Ph), 7.11−7.03 (3H, m, *m*-FPh), 6.95 (1H, m, *m*-FPh), 5.31 (1H, s, Ph_2CH), 3.45−3.44 (2H, t, J = 6.6 Hz, OCH_2), 3.44 (2H, s, *m*-FPhCH_2), 2.84−2.80 (2H, bd, J = 11.1 Hz, NCH_2), 1.97−1.89 (2H, t, J = 11.4 Hz, NCH_2), 1.63−1.51 (4H, m), 1.49−1.44 (1H, m), 1.29−1.21 (2H, m). Free base was converted into its oxalate salt: mp 150−151 °C. Anal. [$C_{27}H_{30}NOF\cdot(COOH)_2\cdot 0.3H_2O$] C, H, N.

4-[2-(Diphenylmethoxy)ethyl]-1-[(3,4-difluorophenyl)-methyl]piperidine (5b). 4-[2-(Diphenylmethoxy)ethyl]piperidine **(4)** (0.12 g, 0.42 mmol) was reacted with 3,4-difluorobenzyl bromide (0.17 g, 0.82 mmol), Et_3N (0.5 mL), and K_2CO_3 (0.6 g) in dry DMF (10 mL) to give **5b**, 0.15 g (86% yield), as a viscous liquid (procedure A): ^{1}H NMR ($CDCl_3$) δ 7.34−6.99 (13H, m, Ar-H), 5.31 (1H, s, Ph_2CH), 3.49−3.45 (2H, t, J = 6.3 Hz, OCH_2), 3.85 (s, 2H, NCH_2Ph), 2.80−2.77 (2H, d, J = 11.4 Hz, NCH_2), 1.95−1.87 (2H, t, J = 11.4 Hz, NCH_2), 1.63−1.55 (4H, m), 1.50−1.42 (1H, m), 1.28−1.15 (2H, m). Free base was converted into its oxalate salt: mp 158−159 °C. Anal. [$C_{27}H_{29}NOF_2\cdot(COOH)_2$] C, H, N.

4-[2-(Diphenylmethoxy)ethyl]-1-[(4-(trifluoromethyl)-phenyl)methyl]piperidine (5c). 4-[2-(Diphenylmethoxy)-ethyl]piperidine **(4)** (0.11 g, 0.37 mmol) was reacted with 4-trifluoromethylbenzyl chloride (0.14 g, 0.72 mmol), Et_3N (0.5 mL) and K_2CO_3 (0.5 g) in DMF (10 mL) to give **5c**, 0.15 g (92% yield), as a viscous liquid (procedure A): ^{1}H NMR ($CDCl_3$) δ 7.64−7.47 (4H, m, CF_3Ph), 7.34−7.23 (10H, m, 2Ph), 5.31 (s, Ph_2CH), 3.52 (2H, s, *p*-FPhCH_2), 3.49−3.45 (2H, t, J = 6.3 Hz, OCH_2), 2.84−2.80 (2H, d, J = 11.1 Hz, NCH_2), 2.00−1.92 (2H, t, J = 11.1 Hz, NCH_2), 1.63−1.55 (4H, m), 1.49−1.42 (1H, m), 1.27−1.15 (2H, m). Free base was converted into its oxalate salt: mp 149−150 °C. Anal. [$C_{28}H_{30}NOF_3\cdot(COOH)_2\cdot 0.70H_2O$] C, H, N.

4-[2-(Diphenylmethoxy)ethyl]-1-[(4-cyanophenyl)-methyl]piperidine (5d). 4-[2-(Diphenylmethoxy)ethyl]piperidine **(4)** (0.15 g, 0.52 mmol) was reacted with 4-cyanobenzyl bromide (0.18 g, 0.92 mmol), Et_3N (0.5 mL) and K_2CO_3 (0.7 g) in 10 mL DMF to give **5d**, 0.17 g (84% yield), as a white solid (procedure A): ^{1}H NMR ($CDCl_3$) δ 7.61−7.58 (2H, d, J = 7.5 Hz, Ar-H), 7.45−7.42 (2H, d, J = 7.5 Hz, Ar-H), 7.33−7.22 (10H, m, Ar-H), 5.31 (1H, s, Ph_2CHO), 3.51 (2H, s, *p*-CNPhCH_2), 3.50−3.46 (2H, t, J = 6.0 Hz, OCH_2CH_2), 2.81−2.77 (2H, bd, J = 10.8 Hz, NCH_2), 2.00−1.93 (2H, t, J = 11.1 Hz, NCH_2), 1.65−1.56 (4H, m), 1.52−1.46 (1H, m, OCH_2-CH_2CH), 1.30−1.18 (2H, m). Free base was converted into its oxalate salt: mp 120−121 °C. Anal. [$C_{28}H_{30}N_2O\cdot(CO_2H)_2\cdot 0.26H_2O$] C, H, N.

Procedure B: 4-[2-(Diphenylmethoxyl)ethyl]-1-[(phenylmethyl)carbonyl]piperidine (5e). A solution of phenylacetic acid (0.11 g, 0.82 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidehydrochloride (EDCI) (0.17 g, 0.88 mmol) and 1-hydroxybenzotriazole (HOBT) (0.11 g, 0.88 mmol) in Et_3N (1 mL) and dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h. 4-[2-(Diphenylmethoxy)ethyl]piperidine **(4)** (0.12 g, 0.41 mmol) dissolved in CH_2Cl_2 (5 mL) was added into the above reaction mixture. The solution was stirred at

room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in EtOAc. The organic phase was washed with 5% citric acid aqueous solution, followed by saturated $NaHCO_3$ solution and finally dried over Na_2SO_4. The organic extract was evaporated to give a crude product which was purified by flash chromatography (EtOAc/hexane = 1/3) to collect a viscous liquid **5e**: 0.27 g (96% yield); ^{1}H NMR ($CDCl_3$) δ 7.32−7.25 (15H, m, Ar-H), 5.29 (1H, s, Ph_2-CHO), 4.62−4.58 (1H, d, J = 12.6 Hz, NCH), 3.84−3.79 (1H, d, J = 13.2 Hz, NCH), 3.72 (2H, s, $PhCH_2$), 3.47−3.43 (2H, t, J = 6.2 Hz, OCH_2), 2.96−2.88 (1H, t, J = 12.6 Hz, NCH), 2.58−2.50 (1H, t, J = 12.3 Hz, NCH), 1.68−1.52 (3H, m), 1.27−1.19 (2H, m), 1.10−1.03 (1H, m), 0.89−0.81 (1H, m). Anal. ($C_{28}H_{31}O_2N\cdot 0.12H_2O$) C, H, N.

4-[2-(Diphenylmethoxy)ethyl]-1-[(4-(methylsulfonylamino)phenyl)methyl]piperidine (5g). 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-aminophenyl)methyl]piperidine **(5f)** (0.11 g, 0.29 mmol) was dissolved in CH_2Cl_2 (5 mL). Methanesulfonyl chloride (0.04 g, 0.35 mmol) and Et_3N (0.1 mL) were added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and EtOAc (50 mL) was added. The organic phase was washed by saturated $NaHCO_3$/H_2O and brine, and dried over Na_2SO_4. After evaporation, the crude product was purified by flash chromatography (EtOAc/MeOH = 100/1) to give pure compound: 26 mg (20% yield); ^{1}H NMR ($CDCl_3$) δ 7.41−7.14 (14H, m, Ar-H), 5.31 (1H, s, Ph_2-CHO), 3.49−3.45 (4H, m, O*CH*$_2$CH$_2$, N*CH*$_2$Ph), 3.40 (1H, s, NH), 2.98(3H, s, CH_3SO_2), 2.85−2.81 (2H, bd, J = 10.8 Hz, NCH_2), 1.97−1.90 (2H, t, J = 10.8 Hz, NCH_2), 1.64−1.51 (4H, m), 1.50−1.45 (1H, m, O(CH$_2$)$_2$*CH*), 1.28−1.17 (2H, m). Free base was converted into its oxalate salt: mp 122−124 °C. Anal. ($C_{28}H_{34}N_2O_3S\cdot COOH\cdot 1.15H_2O$) C, H, N.

***N*-Benzhydryloxyphthalimide (8).** A solution of chlorodiphenylmethane **(6)** (3.42 g, 16.93 mmol), *N*-hydroxyphthalimide **(7)** (2.30 g, 14.11 mmol) and Et_3N (3.0 mL) in DMF (50 mL) was stirred at 60 °C under N_2 for 8 h. After the reaction mixture was cooled to room temperature, water (100 mL) was added. The mixture was extracted with Et_2O. The combined organic phase was dried over Na_2SO_4. After the evaporation of the solvent, the crude product was purified by flash chromatography (hexane/benzene/EtOAc = 20/10/3) to give a white solid: 3.95 g (85% yield); ^{1}H NMR ($CDCl_3$) δ 7.72−7.63 (1H, m), 7.56−7.53 (1H, m), 7.40−7.24 (12H, m), 5.85 (1H, s, Ph_2CH).

***O*-Benzhydrylhydroxylamine (9).** *N*-Benzhydryloxyphthalimide **(8)** (1.03 g, 3.14 mmol) was dissolved in EtOH (20 mL). Hydrazine (0.3 mL, 9.37 mmol) was added into EtOH solution. After the reaction mixture was stirred at room temperature for 0.5 h, EtOH was removed in vacuo and EtOAc (60 mL) was added into the mixture. The mixture was filtered. The solution was collected and dried over Na_2SO_4. After the evaporation of solvent, the crude product was purified by flash chromatography (hexane/EtOAc = 5/1) to give a viscous oil: 0.31 g (50% yield); ^{1}H NMR ($CDCl_3$) δ 7.34−7.26 (10H, m, Ar-H), 5.65 (1H, s, Ph_2CH).

1-[(4-Fluorophenyl)methyl]-4-(hydroxymethyl)piperidine (11). Dry THF (50 mL) was added dropwise into lithium aluminum hydride (0.7 g, 19 mmol) under N_2 in an ice bath. 1-[(4-Fluorophenyl)methyl]-4-(ethoxylcarbonyl)piperidine **(10)** (1.21 g, 4.57 mmol) dissolved in dry THF (10 mL) was added dropwise into the cooled LAH suspension solution. The reaction mixture was refluxed for 2 h and was brought to room temperature followed by cooling in an ice water bath. Saturated NaOH/H_2O (3 mL) was added dropwise into the cold solution. The mixture was filtered. The solution was dried over Na_2SO_4 and evaporated to produce **11**: 0.98 g (98% yield); ^{1}H NMR ($CDCl_3$) δ 7.36−7.26 (2H, m, Ar-H), 7.07−6.96 (2H, m, Ar-H), 4.66 (1H, s, OH), 3.50−3.48 (2H, d, J = 6.0 Hz, CH_2-OH), 3.46 (2H, s, F−$PhCH_2$), 2.90−2.87 (2H, bd, J = 11.1 Hz, NCH_2), 1.99−1.91 (2H, dt, J = 1.8, 11.8 Hz, NCH_2), 1.73−1.68 (3H, m), 1.34−1.22 (2H, m).

1-[(4-Fluorophenyl)methyl]piperidine-4-carboxaldehyde (12). A solution of oxalyl chloride (0.59 mL, 3.95 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C. DMSO (0.95 mL, 13.38 mmol) was added dropwise into oxalyl chrolide solution. The reaction mixture was stirred for 5 min. The alcohol **11** (0.99 g, 4.46 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise into the reaction solution. Stirring was continued for an additional 20 min. Triethylamine (8.0 mL) was added and the reaction mixture was stirred for 10 min and then allowed to warm to room temperature. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was dried over Na_2SO_4. The evaporation of solvent gave an oil: 0.77 g (79% yield); ^{1}H NMR ($CDCl_3$) δ 9.65 (1H, s, CHO), 7.30−7.24 (2H, m, Ar-H), 7.00−6.97 (2H, m, Ar-H), 3.46 (2H, s, *p*-$FPhCH_2$), 2.81−2.76 (2H, m, NCH_2), 2.30−2.20 (1H, m, *CH*CHO), 2.14−2.06 (2H, dt, J = 2.1, 11.3 Hz, NCH_2), 1.92−1.86 (2H, dd, J = 3.5, 13.5 Hz), 1.74−1.62 (2H, m).

Procedure C: 4-[((Diphenylmethoxy)amino)methyl]-1-[(4-fluorophenyl)methyl]piperidine (13). Into the solution of *O*-benzyhydrylhydroxylamine **(9)** (0.25 g, 1.27 mmol) and aldehyde **12** (0.28 g, 1.27 mmol) in $ClCH_2CH_2Cl$ (20 mL) was added $Na(OAc)_3BH$ (0.54 g, 2.55 mmol). The reaction mixture was stirred at room temperature overnight. EtOAc (80 mL) was added and the solution was washed by saturated $NaHCO_3$/H_2O and brine. The organic phase was dried over Na_2SO_4 and evaporated to give crude product, which was purified by chromatography (EtOAc/hexane = 1/2) to give a colorless oil: 0.43 g (84% yield); ^{1}H NMR ($CDCl_3$) δ 7.36−7.23 (12H, m, Ar-H), 7.01−6.95 (2H, t, J = 7.4 Hz, Ar-H), 3.41 (2H, s, *p*-$FPhCH_2$), 2.82−2.78 (2H, bd, J = 11.1 Hz, NCH_2), 2.25−2.21 (1H, m, NH), 2.00−1.93 (2H, t, J = 10.8 Hz, NCH_2), 1.71−1.47 (7H, m). Free base was converted into its oxalate salt: mp 154−155 °C. Anal. ($C_{26}H_{29}FN_2O\cdot COOH\cdot 0.10H_2O$) C, H, N.

Procedure D: 4-[[(Diphenylmethyl)aminocarbonyl]-methyl]-1-[(3,4-difluorophenyl)methyl]piperidine (16a). 1-[(3,4-Difluorophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine **(14)** (0.94 g, 3.16 mmol) was dissolved in 10 mL of a CF_3CO_2H/HCl/H_2O (1:1:1) mixture. The solution was refluxed for 2 h, and the solvent was removed in vacuo to give a solid which was dissolved in 10 mL of CH_2Cl_2 containing excess of Et_3N to liberate the free amine. Into this solution were added EDCI (0.73 g, 3.80 mmol) and HOBT (0.55 g, 4.07 mmol). The solution was stirred for 1 h, and into it was added diphenylaminomethane (0.75 g, 4.10 mmol). The solution was stirred at room temperature overnight. After workup and purification (procedure B) a white solid, 1.03 g (75% yield), was produced: ^{1}H NMR ($CDCl_3$) δ 7.34−6.99 (13H, m, Ar-H), 6.27−6.25 (1H, d, J = 7.8 Hz, Ph_2CH), 6.04−6.02 (1H, d, J = 7.8 Hz, NH), 3.40 (2H, s, F_2PhCH_2), 2.82−2.78 (2H, d, J = 11.4 Hz, NCH_2), 2.18−2.15 (2H, d, J = 7.2 Hz, $COCH_2$), 2.04−1.96 (2H, t, J = 12.0 Hz, NCH_2), 1.92−1.83 (1H, m, $COCH_2CH$), 1.72−1.67 (2H, bd, J = 11.8 Hz), 1.35−1.23 (2H, m).

Procedure E: 4-[2-((Diphenylmethyl)amino)ethyl]-1-[(3,4-difluorophenyl)methyl]piperidine (17a). Into the solution of **16a** (0.12 g, 0.28 mmol) in 20 mL dry THF was added 1 M BH_3/THF (1.0 mL, 1 mmol). The reaction mixture was refluxed for 6 h. After the solution was cooled to room temperature, methanol (5 mL) was added slowly. The solvent was removed under reduced pressure and 10% HCl/MeOH (10 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 dried over Na_2SO_4 and evaporated to give the crude product which was purified by flash chromatography (hexane/EtOAc/Et_3N, 1/2/1%) to give a white solid: 0.11 g (90% yield); ^{1}H NMR ($CDCl_3$) δ 7.39−6.99 (13H, m, Ar-H), 4.79 (1H, s, Ph_2CH), 3.39 (2H, s, F_2PhCH_2), 2.80−2.76 (2H, d, J = 11.1 Hz, NCH_2), 2.60−2.55 (2H, t, J = 7.0 Hz, NCH_2), 1.93−1.86 (2H, t, J = 11.1 Hz, NCH_2), 1.62−1.58 (2H, d, J = 12 Hz), 1,49−1.42 (2H, q, J = 6.3 Hz, NCH_2CH_2), 1.35−1.31 (1H, m, $NCH_2CH_2CH(CH_2)_2$), 1.26−1.19 (2H, t, J = 12.0 Hz). Free base was converted into its HCl salt: mp 280−281 °C. Anal. ($C_{27}H_{30}N_2F_2\cdot 2HCl\cdot 0.25H_2O$) C, H, N.

4-[[(Diphenylmethyl)aminocarbonyl]methyl]-1-(phenylmethyl)piperidine (16b). 1-(Phenylmethyl)-4-[(ethoxycarbonyl)methyl]piperidine (**15**) (0.65 g, 2.51 mmol) was refluxed in a CF_3COOH/HCl/H_2O (1:1:1) mixture to give the intermedi-

ate acid, which reacted with aminodiphenylmethane (0.18 g, 3.10 mmol), EDCI (0.58 g, 2.97 mmol), and HOBT (0.41 g, 3.04 mmol) to produce **16b**: 0.74 g (72% yield) (procedure D); ^{1}H NMR ($CDCl_3$) δ 7.35−7.19 (15H, m, Ar-H), 6.27−6.24 (1H, d, J = 7.8 Hz, 2PhCH), 6.01−5.98 (1H, d, J = 7.1 Hz, NHCO), 3.48 (2H, s, $PhCH_2$), 2.87−2.83 (2H, d, J = 11.4 Hz, $N(CH)_2$), 2.17−2.15 (2H, d, J = 7.2 Hz, $NCOCH_2$), 2.00−1.93 (2H, t, J = 11.4 Hz, NCH_2), 1.90−1.83 (1H, m, $NCOCH_2CH$), 1.71−1.67 (2H, d, J = 10.8 Hz), 1.36−1.23 (2H, m).

4-[2-((Diphenylmethyl)amino)ethyl]-1-(phenylmethyl)-piperidine (17b). Compound **16b** (0.54 g, 1.31 mmol) was reacted with 1 M BH_3/THF (5.0 mL, 5 mmol) in THF (10 mL) to produce **17b**: 0.44 g (84% yield) (procedure E); ^{1}H NMR ($CDCl_3$) δ 7.39−7.19 (15H, m, Ar-H), 4.79 (1H, s, Ph CH), 3.47 (2H, s, $PhCH_2$), 2.86−2.82 (2H, d, J = 11.1 Hz, NCH_2), 2.59−2.55 (2H, t, J = 7.2 Hz, NCH_2), 1.94−1.87 (2H, t, J = 11.1 Hz, NCH_2), 1.61−1.58 (2H, m), 1.48−1.42 (2H, m), 1.34−1.20 (3H, m). Free base was converted into its HCl salt: mp 172−174 °C. Anal. ($C_{27}H_{32}N_2$·2HCl·1.06H_2O) C, H, N.

Procedure F: 4-[2-((Diphenylmethyl)-*N*-methylamino)ethyl]-1-(4-phenylmethyl)piperidine (18). A solution of 4-[(2-diphenylethyl)aminomethyl]-1-[(4-fluorophenyl)methyl]-piperidine **(1b)** (0.23 g, 0.59 mmol), formaldehyde (1.0 g, 37%/H_2O) and formic acid (2.0 g, 88%/H_2O) was refluxed for 3 h. After the reaction solution was cooled to room temperature, the solvent was removed in vacuo. The crude product was purified by flash chromatography (EtOAc/hexane = 1/2) to give a white solid: 0.17 g (71% yield); ^{1}H NMR ($CDCl_3$) δ 7.40−7.16 (12H, m, Ar-H), 7.05−6.95 (2H, t, J = 7.4 Hz, Ar-H), 4.31 (1H, s, Ph_2CHN), 3.41 (2H, s, p-$FPhCH_2N$), 2.80−2.76 (2H, d, J = 11.8 Hz, NCH_2), 2.36−2.30 (2H, t, J = 7.5 Hz, NCH_2), 2.11 (3H, s, NCH_3), 1.91−1.83 (2H, t, J = 11.4 Hz, NCH_2), 1.54−1.50 (2H, d, J = 11.4 Hz), 1.47−1.40 (3H, m, NCH_2CH_2CH), 1.32−1.10 (2H, m). Free base was converted into its HCl salt: mp 260−261 °C. Anal. ($C_{28}H_{33}N_2F$·2HCl·0.50H_2O) C, H, N.

4-[(2-Diphenylethyl)aminocarbonyl]-1-[(4-fluorophenyl)methyl]piperidine (20a). 1-[(4-Fluorophenyl)methyl]-4-(ethoxycarbonyl)piperidine **(19a)** (0.68 g, 2.72 mmol) was converted into carboxylic acid and was reacted with 2,2-diphenylethylamine (0.67 g, 3.40 mmol), EDCI (0.76 g, 3.95 mmol), and HOBT (0.62 g, 4.59 mmol) to produce **20a**: 0.84 g (75% yield) (procedure D); ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (12H, m, Ar-H), 7.01−6.95 (2H, m, Ar-H), 5.39 (1H, bs, NH), 4.21−4.15 (1H, t, J = 7.8 Hz, Ph_2CH), 3.91−3.86 (2H, t, J = 7.5 Hz, CH_2NH), 3.41 (2H, s, p-$FPhCH_2$), 2.84−2.80 (2H, d, J = 11.4 Hz, NCH_2), 1.96−1.87 (3H, m, $NHCOCH$, $NHCH_2$), 1.65−1.58 (4H, m).

4-[(2-Diphenylethyl)aminomethyl]-1-[(4-fluorophenyl-)methyl]piperidine (21a). Compound **20a** (0.32 g, 1.3 mmol) was reacted with 1 M BH_3/THF (4.0 mL, 4 mmol) in THF (20 mL) to produce **21a**: 0.25 g (81% yield) (procedure E); ^{1}H NMR ($CDCl_3$) δ 7.32−7.19 (12H, m, Ar-H), 7.00−6.95 (2H, m, Ar-H), 4.21−4.17 (1H, t, J = 7.7 Hz, $(Ph)_2CH$), 3.67 (1H, s, NH), 3.41 (2H, s, p-$FPhCH_2$), 3.22−3.19 (2H, d, J = 7.8 Hz, $NHCH_2$-$CH(Ph)_2$), 2.83−2.79 (2H, bd, J = 11.1 Hz, NCH_2), 2.52−2.50 (2H, d, J = 6.6 Hz, $NHCH_2CH$), 1.91−1.84 (2H, t, J = 11.1 Hz), 1.58−1.54 (2H, d, J = 12 Hz), 1.45−1.39 (1H, m, $NHCH_2CH$), 1.21−1.14 (2H, t, J = 12 Hz). Free base was converted into its HCl salt: mp 126−127 °C. Anal. ($C_{27}H_{31}$-FN_2O·2HCl) C, H, N.

4-[(Bis(4-fluorophenyl)ethylamino)carbonyl]-1-(phenylethyl)piperidine (20b). 1-(Phenylethyl)-4-(ethoxycarbonyl)piperidine **(19b)** (0.25 g, 0.95 mmol) was converted into carboxylic acid which was then reacted with bis(4-fluorophenyl)methylamine (0.25 g, 1.14 mmol), EDCI (0.25 g, 1.28 mmol), HOBT (0.20 g, 1.48 mmol) in Et_3N (1.5 mL) in CH_2Cl_2 (20 mL) to produce **20b**: 0.32 g (74% yield) (procedure E); ^{1}H NMR ($CDCl_3$) δ 7.29−7.03 (10H, m, Ar-H), 7.05−6.99 (3H, m, Ar-H), 6.22−6.20 (1H, d, J = 7.8 Hz, p-FPh_2CH), 6.00−5.97 (1H, d, J = 7.5 Hz, NH), 3.08−3.04 (2H, bd, J = 11.4 Hz, NCH_2), 2.83−2.78 (2H, d), 2.62−2.57 (2H, m), 2.25−2.15 (1H, m, NCOCH), 2.10−2.03 (2H, t, J = 11.4 Hz, NCH_2), 1.96−1.81 (4H, m).

4-[(Bis(4-fluorophenyl)methylamino)methyl]-1-(2-phenylethyl)piperidine (21b). Compound **20b** (0.30 g, 0.71 mmol) was reacted with 1 M BH_3/THF (4 mL, 4 mmol) in THF (25 mL) to produce a white solid **21b**: 0.28 g (96% yield) (procedure E); ^{1}H NMR ($CDCl_3$) δ 7.35−7.18 (10H, m, Ar-H), 7.00−6.95 (3H, m, Ar-H), 4.74 (1H, s, $(p$-$FPh)_2CH$), 3.02−2.99 (2H, d, J = 10.8 Hz, NCH_2), 2.83−2.78 (2H, m), 2.60−2.55 (2H, m), 2.45−2.43 (2H, d, J = 6.2 Hz, $NHCH_2CH$), 2.04−1.96 (2H, t, J = 11.4 Hz, NCH_2), 1.78−1.26 (5H, m). Free base was converted into its HCl salt: mp 214−215 °C. Anal. ($C_{27}H_{30}F_2N_2$·2HCl·0.50H_2O) Calcd: C, 64.58; H, 6.61; N, 5.57. Found: C, 64.61; H, 6.65; N, 5.43.

4-[(2-Diphenylethyl)-*N*-methylaminomethyl]-1-[(4-fluorophenyl)methyl]piperidine (22). 4-[(2-Diphenylethyl)-aminomethyl]-1-[(4-fluorophenyl)methyl]piperidine **(21a)** (45 mg, 0.11 mmol) was refluxed in formaldehyde (1.0 g) and formic acid (2.0 g, 37%/H_2O) to produce **22**: 44 mg (88% yield) (procedure F); ^{1}H NMR ($CDCl_3$) δ 7.28−7.13 (12H, m, Ar-H), 7.02−6.96 (2H, t, J = 8.4 Hz, Ar-H), 4.15−4.10 (1H, t, J = 7.5 Hz, Ph_2CH), 3.46 (2H, s, F-$PhCH_2$), 2.91−2.88 (2H, d, J = 7.5 Hz, Ph_2CHCH_2N), 2.81−2.77 (2H, d, J = 11.1 Hz, NCH_2), 2.20 (3H, s, CH_3), 2.20−2.17 (2H, d, J = 7.5 Hz, NCH_2CH), 1.90−1.83 (2H, t, J = 11.4 Hz, NCH_2), 1.52−1.47 (2H, d, J = 12.9 Hz), 1.54−1.28 (1H, m, NCH_2CH), 1.14−1.06 (2H, t, J = 12.4 Hz). Free base was converted into its oxalate salt: mp 144−145 °C. Anal. [$C_{28}H_{33}N_2F$·2$(COOH)_2$·1.47H_2O]] C, H, N.

4-[[(1-Phenylethyl)aminocarbonyl]methyl]-1-[(4-fluorophenyl)methyl]piperidine (24). 1-[(4-Fluorophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine **(23)** (0.55 g, 1.97 mmol) was refluxed in 10 mL of CF_3CO_2H/HCl/H_2O (1:1:1) to give acid which reacted with 1-phenylethylamine (0.29 g, 2.40 mmol), EDCI (0.56 g, 2.97 mmol) and HOBT (0.40 g, 2.96 mmol) in CH_2Cl_2 (10 mL) to produce **24** as a solid: 0.33 g (50% yield) (procedure D); ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (7H, m, Ar-H), 7.00−6.94 (2H, t, J = 8.4 Hz, Ar-H), 5.83−5.80 (1H, bd, J = 7.5 Hz, NH), 5.15−5.10 (m, 1H, PhCHMe), 3.42 (s, 2H, p-$PhCH_2N$), 2.83−2.78 (m, 2H, $N(CH)_2$), 2.07−2.05 (2H, d, J = 7.2 Hz, CH_2CO), 1.99−1.89 (2H, m), 1.86−1.78 (1H, m), 1.71−1.61 (2H, t, J = 15 Hz), 1.48−1.45 (3H, d, J = 6.9 Hz, Me), 1.33−1.21 (2H, m).

4-[2-[(1-Phenylethyl)amino]ethyl]-1-[(4-fluorophenyl)-methyl]piperidine (25). Compound **24** (0.33 g, 0.93 mmol) was reacted with 1 M BH_3/THF (5.0 mL, 5 mmol) to produce **25** as a viscous oil: 0.23 g (95% yield) (procedure E); ^{1}H NMR ($CDCl_3$) δ 7.34−7.21 (5H, m, Ar-H), 7.01−6.95 (2H, t, J = 8.4 Hz, Ar-H), 4.09−4.07 (1H, d, J = 6.0 Hz, NH), 3.77−3.71 (1H, q, J = 6.3 Hz, PhCHMe), 3.42 (2H, s, p-$FPhCH_2$), 2.82−2.78 (2H, d, J = 10.8 Hz, NCH_2), 2.55−2.37 (2H, m, NCH_2), 1.91−1.83 (2H, t, J = 11.4 Hz, NCH_2), 1.59−1.53 (4H, m), 1.44−1.38 (1H, m), 1.36−1.34 (3H, d, J = 6.0 Hz, CH_3), 1.25−1.14 (2H, m). Free base was converted into its oxalate salt: mp 172−173 °C. Anal. [$C_{22}H_{29}FN_2$·2$(COOH)_2$] C, H, N.

4-[2-(1-Phenylethoxy)ethyl]-1-[(4-fluorophenyl)methyl]piperidine (27). Alcohol **26** (0.21 g, 0.82 mmol) was dissolved in dry THF (10 mL). *n*-Bu_4NI (0.33 g, 0.89 mmol) and 60% NaH (0.20 g) were added. After the reaction mixture was stirred for 3 h, 1-bromoethylbenzene (0.50 g, 2.70 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and water (5 mL) was added. The mixture was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and evaporated to give crude product, which was purified by chromatography (EtOAc/hexane = 1/3) to give **27** as a viscous oil: 0.15 g (54% yield); ^{1}H NMR ($CDCl_3$) δ 7.35−7.23 (7H, m, Ar-H), 7.01−6.95 (2H, t, J = 8.4 Hz, Ar-H), 4.39−4.32 (1H, q, J = 6.3 Hz, PhCHMe), 3.42 (2H, s, p-$FPhCH_2N$), 3.33−3.28 (2H, t, J = 6.2 Hz, OCH_2), 2.84−2.80 (2H, m, NCH_2), 1.95−1.84 (2H, dq, J = 2.1, 11.1 Hz, NCH_2), 1.64−1.33 (5H, m), 1.43−1.41 (3H, d, J = 6.0 Hz, CH_3), 1.28−1.13 (2H, m). Free base was converted into its oxalate salt: mp 155−157 °C. Anal. [$C_{22}H_{28}$-FNO·$(COOH)_2$·0.40H_2O] C, H, N.

Transporter Binding Assays. The affinity of test compounds for the rat DAT, SERT, and NET was assessed by inhibition of binding of [^{3}H]WIN 35,428, [^{3}H]citalopram, and

[^{3}H]nisoxetine, respectively. The general conditions for preparing membrane fractions from brain tissue and conducting the binding assays were as described in our previous studies.[35−37] Briefly, rat striatum was used for [^{3}H]WIN 35,428 (5.5 nM) binding assays and cerebral cortex for [^{3}H]citalopram (4.5 nM) and [^{3}H]nisoxetine (1.1 nM) binding assays. The incubation buffer for [^{3}H]WIN 35,428 and [^{3}H]citalopram assays was a sodium phosphate buffer at a final [Na^+] of 30 mM, pH 7.4 at room temperature; for [^{3}H]nisoxetine assays the same buffer contained, additionally, 225 mM NaCl and 4.5 mM KCl. 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 for 3 h for [^{3}H]nisoxetine binding. The total volume of the binding mixtures was 0.2 mL in all cases, and the average amount of protein per assay was 75 μg for [^{3}H]WIN 35,428 and [^{3}H]-citalopram measurements and 150 μg for [^{3}H]nisoxetine determinations. 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. Binding never exceeded 10% of the totally available radioligand. Assays were terminated by filtration with a MACH3-96 Tomtec harvester (Wallac Inc., Gaithersburg, MD) through 0.05% (v/v) polyethylenimine-presoaked glass fiber filtermats (Wallac Inc.). Filters were assayed for radioactivity in a Microbeta Plus liquid scintillation counter (Wallac Inc.).

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. The separation between individual points on the inhibition curves represented an approximately 3-fold difference in drug concentration. The IC_{50} value was estimated by nonlinear computer curve fitting to an equation for sigmoidal inhibition as described by us previously.[34]

DAT Uptake Assays. Measurement of uptake of [^{3}H]DA into rat striatal synaptosomes was based on our previously reported procedures.[45] Briefly, rat striatal P_2 membrane fractions were incubated with test drug for 8 min in uptake buffer (for composition see ref 45) followed by the additional presence of [^{3}H]DA (4 nM radiolabeled plus 46 nM unradioactive DA) for 4 min at 25 °C. The total volume was 0.4 mL, and nonspecific uptake was defined with 100 μM cocaine. The uptake assay was terminated by filtration through Watman GF/C glass fiber filters with a 24-pin Brandel cell harvester (Brandel Inc., Gaithersburg, MD), and filters were assayed for radioactivity with a liquid scintillation counter (Beckman model LS 6000IC). Construction of inhibition curves, dissolvement of test compounds, and calculation of IC_{50} values were as described above.

Locomotor Activity. Subjects: Adult male Swiss-Webster mice (Harlan Sprague Dawley, Inc., Indianapolis, IN) weighing 30−40 g were used. Mice were housed 5/cage and were provided continuous access to water and food except when in the activity chambers. All mice were drug-naive at the start of the study and did not have prior experience with the test chambers. The mice were housed in an AALAC-accredited animal facility with a controlled temperature (22−24 °C) on a 12-h light−dark cycle, and all testing occurred during the light component.

Apparatus and procedure: Four, commercially obtained, automated activity monitoring devices each enclosed in sound- and light-attenuating enclosures were used (AccuScan Instruments, Inc., Columbus, OH). The interior of each activity device was divided permitting the independent and simultaneous recording of two mice.[46] The solvents for the drugs were as follows: cocaine, GBR 12909, and compound **1b**: 0.05% sterile saline; compound **1a**: Alkamuls EL-620 (Rhone-Poulenc, North American Chemicals, Cranbury, NJ):water in 1:6 ratio; compound **17b**: Alkamuls EL-620:ethanol:water in 1:1:18 ratio; compound **21a**: sterile water. All drugs were administered ip in a volume equivalent to 10 mL/kg. The mice were injected ip with either vehicle or test compound and then placed into the test chambers where their activity was then measured for 60 min. A separate vehicle-control group was tested during tests with each compound. During tests, total distance traveled (cm) during the entire 60-min session was recorded for each mouse. A one-factor (dose) analysis of variance (ANOVA) was conducted for each drug and its vehicle accompanied by Dunnett's post-hoc tests when the initial ANOVA results were statistically significant. Comparisons between dosage groups were considered significant if $P = 0.05$.

Drug Discrimination. Subjects: The subjects used in the drug-discrimination studies were male adult Swiss-Webster mice (Harlan Sprague Dawley, Inc., Indianapolis, IN). Mice were individually housed in an AALAC-accredited animal facility with a controlled temperature (22−24 °C) on a 12-h light−dark cycle and provided continuous access to water except when in the operant chambers. Mice were brought into the laboratory and tested during the light cycle. The mice were maintained on a restricted diet by post-session feeding of rodent chow (Ralston-Purina, St. Louis, MO) in sufficient amounts to maintain their body weights at 35 ± 5 g.

Apparatus and procedure: Experimental sessions were conducted in eight, light- and sound-attenuated operant chambers equipped with two response levers separated by a trough into which a 0.01-mL dipper cup could be presented (Med Associates, Inc., St. Albans, VT; model ENV-307A). A triple cue lamp was positioned above each lever, and a house light was centered at the top of the front panel. Scheduling of dipper presentations, illumination of lights, and recording of lever presses were accomplished by a microcomputer system operating MED-PC software (Med Associates, Inc., St. Albans, VT; model SOF-700W). The drugs were administered ip in a volume equivalent to 10 mL/kg prior to the start of drug-discrimination sessions at the following times: cocaine, 10 min; compound **21a**, 20 min; all other compounds, 30 min. Solvents used were as described for the locomotor activity studies.

Subjects were initially trained to press one of the two levers under an FR 1 schedule of reinforcement in which the dipper cup filled with sweetened condensed milk (1 part granulated table sugar, 1 part powdered skim milk, and 2 parts water by volume) was presented following each lever press. The dipper cup remained raised into the trough except during refilling cycles. The response requirement was gradually increased to FR 20. Subsequently, and only during the next few sessions, the mice were reinforced for pressing the opposite lever until they pressed reliably under FR 20 conditions. Drug-discrimination training then began during the daily (Monday−Friday) 15-min experimental sessions. Cocaine-trained mice were injected with 10 mg/kg cocaine or saline ip 10 min prior to session start. For each subject, one lever was designated correct after training drug administration and the other as correct after saline administration. The lever upon which the mice initially acquired the lever press response was designated the saline-correct lever. Lever pressing produced milk delivery only on the injection-appropriate lever for that day; incorrect presses reset the response requirement on the correct lever. A pseudo-random sequence was used to determine which injection was administered, with the restriction that the same injection was not given on more than two consecutive sessions, and during each of the 30 training session blocks the number of saline and training drug injections was approximately equal.

Generalization testing began once a subject met the following criteria: (1) the first completed fixed-ratio (FFR) occurred on the lever designated correct on at least 8 of 10 consecutive training sessions; and (2) at least 80% of the total responses were made on the correct lever during those 8 sessions. After these initial training conditions were met, tests could occur on Tuesdays and Fridays provided that the subject completed the FFR on the correct lever during the most recent training drug and saline sessions; otherwise, a training session was administered. Test days were identical to training days except completions of the fixed ratio contingencies at either lever resulted in milk delivery. Dose−response curves were collected first with cocaine (0.3−30 mg/kg) followed by the test com-

pounds. Doses of test compounds were usually tested in an ascending order.

Percentage drug lever responding was calculated for each subject by dividing the number of lever presses emitted upon the training drug-designated lever by the total number of lever presses emitted upon both levers and then this quotient was multiplied by 100. Individual drug lever responding percentages were then averaged (±SEM). A dose of a test compound was considered to completely generalize from 10 mg/kg cocaine training stimulus if an average of 80% drug lever selection occurred. Mean response rates for each test condition were calculated by dividing the total number of lever presses emitted upon both levers by the duration of the test session in seconds (900 s) for each subject and then these rates were averaged (±SEM). In the data analysis, if a mouse failed to lever-press sufficiently to obtain at least one pellet delivery during a test, its data were excluded for calculations of mean drug lever responding for that test but were included in mean response rate expressions. This latter exclusion was made to minimize the exaggerated influence on expressions of drug lever selection by individual mice at doses which nearly totally suppressed lever pressing.

Acknowledgment. This work was supported by the National Institute on Drug Abuse, Grant No. DA 12449A (A.K.D.).

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JM000311K