Design, Synthesis, and Biological Evaluation of Novel Non-Piperazine Analogues of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines as Dopamine Transporter Inhibitors

Sung-Woon Choi,[†] David R. Elmaleh,[†] Robert N. Hanson,[‡] and Alan J. Fischman*[,†]

Division of Nuclear Medicine, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114, and Department of Pharmaceutical Sciences, Bouve College of Pharmacy and Health Sciences, Northeastern University, Boston, Massachusetts 02115

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A series of novel diamine, amine-amide, and piperazinone analogues of *N*-[2-(bisarylmethoxy)-ethyl]-*N′*-(phenylpropyl)piperazines, GBR 12909 and 12935, were synthesized and evaluated as inhibitors of presynaptic monoamine neurotransmitter transporters. The primary objective of the study was to determine the structural requirements for selectivity of ligand binding and potency for neurotransmitter reuptake inhibition. In general, the target compounds retained transporter affinity; however, structural variations produced significant effects on reuptake inhibition and transporter selectivity. For example, analogues prepared by replacing the piperazine ring in the GBR structure with an *N*,*N′*-dimethylpropyldiamine moiety displayed enhanced selectivity for binding and reuptake inhibition at the norepinephrine (NE) transporter site (e.g. **4** and **5**). Congeners in which the amide nitrogen atom was attached to the aralkyl moiety of the GBR molecule showed moderate affinity ($K_i = 51-61$ nM) and selectivity for the dopamine transporter (DAT) site. In contrast, introduction of a carbonyl group adjacent to either nitrogen atom of the piperazine ring (e.g. **25** and **27**) was not well tolerated. From the compounds prepared, analogue **16** was selected for further evaluation. With this congener, locomotor activity induced by cocaine at a dose of 20 mg/kg was attenuated with an AD_{50} (dose attenuating cocaine-induced stimulation by 50%) of 60.0 ± 3.6 mg/kg.

Introduction

Cocaine is one of the most powerful stimulant/reinforcer drugs, and its abuse is a major public health and social problem.[1] The primary pharmacological properties of cocaine have been associated with its propensity for binding to neurotransmitter transporters in the central nervous system (CNS), especially the dopamine transporter (DAT). According to the dopamine hypothesis, "cocaine receptors" located on the DAT in the mesolimbic system of the brain are believed to be responsible for the drug's reinforcing and self-administration properties and perhaps some of its euphorigenic effects. As a result, this protein has become a target for the development of the medications for treating cocaine addiction.[2−9] Over the past decade, several different classes of DAT-specific ligands have been identified. Of these compounds, 3β-aryltropanes[4,10] and *N*,*N′*-disubstituted piperazine derivatives[11] have been the most extensively evaluated.

In 1980, Van der Zee et al. developed the GBR series of compounds in which the tropine of benztropine was replaced by substituted piperazine.[11] Since the initial study which identified the GBR compounds as potent and highly selective DA reuptake inhibitors, numerous pharmacological,[12,13] neurochemical,[14−16] biological,[17,18] and molecular pharmacological[19] investigations have been conducted using these agents both to probe the DAT and to develop promising lead compounds for drug development.[20] Several structure−activity relationship (SAR) studies have been conducted to evaluate the three key structural features of the GBR compounds (Figure 1).[21] These studies suggested that the internal piperazine ring moiety plays a key role for modulating selective binding and in producing slow dissociation from the site.[22−24] Later studies evaluated the role of the piperazine ring and the tail-phenylpropyl moiety.[23,25−27] For example, the piperazine moiety was replaced by five-, seven-, or eight-membered rings, *trans*-2,5-dimethylpiperazine, homopiperazine, and ring-opened alkyldiamines. Although these studies failed to produce pure cocaine antagonists, a number of potent, selective, and high-affinity DAT inhibitors were identified.[24,28]

Two types of cocaine antagonists have been postulated, pure pharmacological antagonists and partial agonists (noncompetitive inhibitors).[29] Comparison of IC_{50} values for [^{3}H]DA uptake inhibition with IC_{50} values for inhibition of transporter ligand (e.g. [^{125}I]RTI-55) binding has been an important criterion for screening test ligands as cocaine antagonists.[22] In this context, good candidate cocaine antagonists are expected to display high "uptake-to-binding ratios" when both assays are performed under identical experimental conditions. On the basis of these ratios, GBR 12935 has been

* Requests for reprints should be addressed to Alan J. Fischman, M.D., Ph.D., Massachusetts General Hospital. Phone: (617) 726-8353. Fax: (617) 726-1650. E-mail: fischman@petw6.mgh.harvard.edu.
[†] Massachusetts General Hospital.
[‡] Northeastern University.

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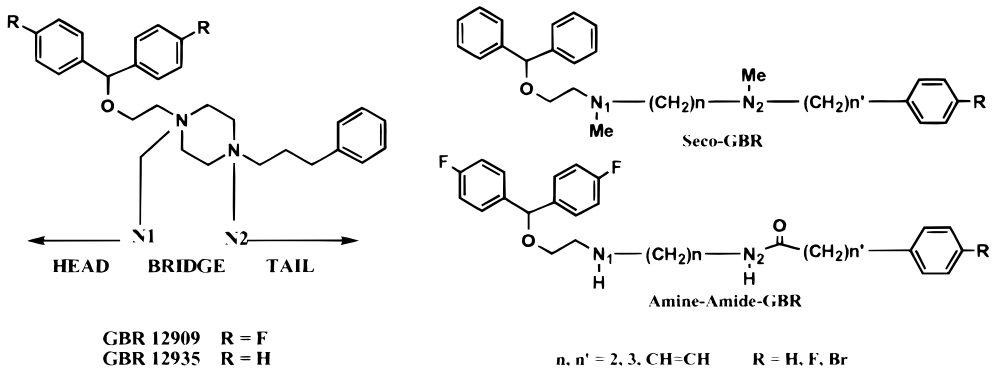


Figure 1. General structure of test ligands with modification sites indicated.

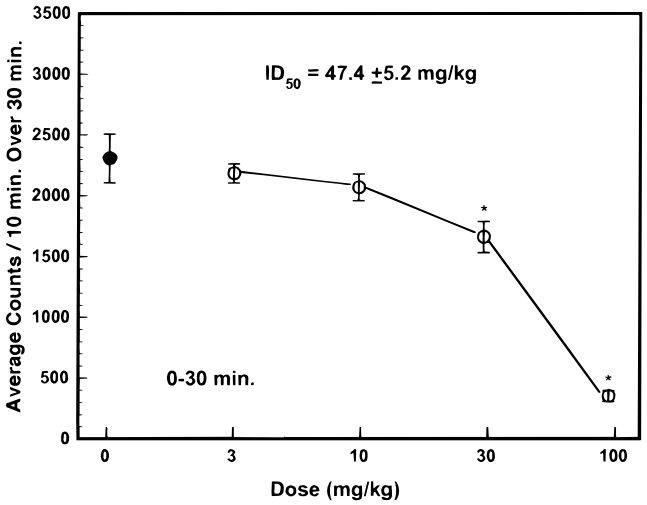


Figure 2. Average horizontal activity counts/10 min over 30 min as a function of dose, starting 20 min after pretreatment with **16**. The slope of the descending portion of the dose−effect curve (30−100 mg/kg dose range) indicated an ID_{50} of 47.4 ± 5.2 mg/kg.

considered to be a possible antagonist or partial agonist.[22] Previously published SAR studies with chiral piperazines related to GBR 12909 supported the notion of cocaine antagonism and established the feasibility of developing SAR studies of cocaine antagonists based on comparisons of binding and uptake inhibition.[23]

The goal of the present study was to develop and identify novel GBR analogues with sufficient structural variations to more precisely define the structural requirements for potent and selective binding to the DAT and to investigate the structural features for ligand interaction that block cocaine binding site(s), without interfering with DA uptake (cocaine antagonists). Previously, it was shown that the (bisphenylmethoxy)ethyl group (head, Figure 1) and diamine moiety are essential pharmacophores for retention of DAT binding.[24,32] Also, at least one nitrogen atom (N_2, Figure 1) connected to the tail-phenylpropyl moiety was shown to be required.[25,33] We began our investigation by opening the piperazine ring between the ethylenediamine and propylenediamine moieties with secondary and tertiary amines.[32] On the basis of previous findings, we decided to modify the ethylenediamine moiety of seco GBR analogues (Figure 2). To evaluate the effect of distance between the bridge and tail tether, length of the methylene tether (*n*, *n*′) was varied. Introduction of a carbonyl group external to the ring-opened diamine unit from the tail side was used to evaluate the effects of basicity at the N_2 nitrogen atom and its flexibility (Figure 1). Also, the amide present in these tail-amide analogues can serve as synthetic intermediates for the amine in seco GBR analogue **20**. Introduction of a carbonyl group into the piperazine ring (piperazinones) effectively eliminates the basicity of the adjacent nitrogen atom, and this modification was used to evaluate the effect of basicity of each nitrogen atom without significantly changing flexibility of the ring. This modification was also used to evaluate the possibility of different interactions at the binding sites with the DAT protein.

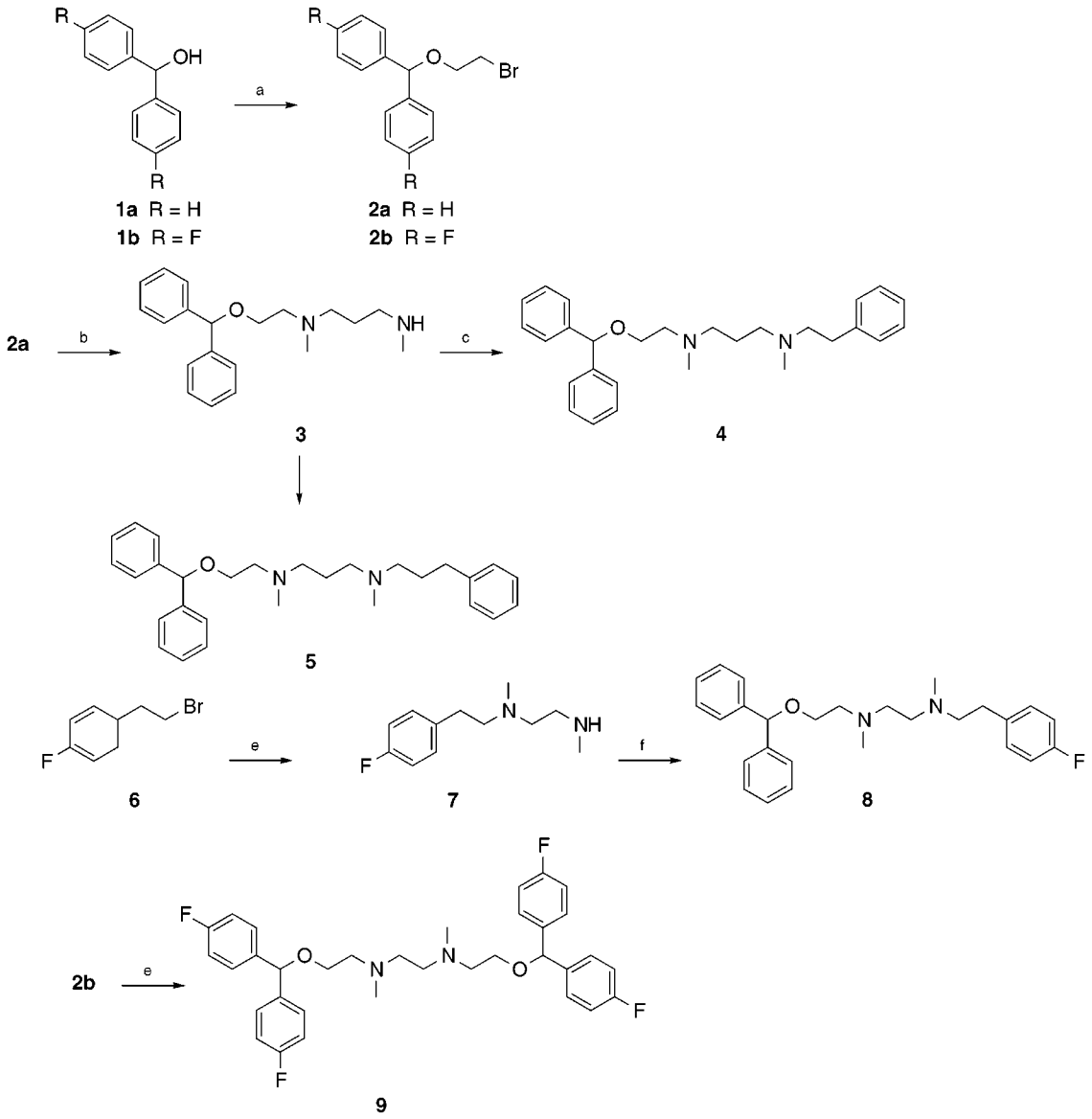
In this paper, we report the synthesis and the pharmacological evaluation of three series of GBR derivatives (Figure 1). In order to gain insight into some of the structural parameters which govern (1) binding selectivity at dopamine, norepinephrine, and serotonin (the three neurotransmitter transporters) and (2) potency of neurotransmitter reuptake inhibition, chemical modifications were systematically performed on these structures. Also, new functional groups were introduced to test for the possibility of additional modes of binding (additional primary recognition contacts) between the ligand and transporter which might have different effects on binding and reuptake inhibition at the DAT.

Chemistry

The requisite starting materials **2a**,**2b** in the first series of GBR analogues **4**, **5**, **8**, and **9** were prepared according to literature procedures with slight modifications.[11] For example, 2-bromoethanol was used instead of chloroethanol to synthesize the more reactive 2-bromoethyl diphenylmethyl ether **2a** or its bis(4-fluoro) derivative **2b**, and purification was achieved by using column chromatography instead of vacuum distillation. Commercially available *N*,*N*′-dimethylethylenediamine and *N*,*N*′-dimethyl-1,3-propanediamine were used as starting materials (10 equiv, excess) for the first monoalkylation step, and the final yields could be increased to 80% from the starting material (Scheme 1).

Synthesis of the second series of GBR analogues is shown in Scheme 2. Compounds **15**−**19** were prepared by monoacylation of ethylene- or propylenediamine with acid chlorides (22−35% yield) followed by mono-*N*-alkylation with **2b** (73−85% yield). Compound **14** was converted to GBR analogue **20** by alkylation with **2b** followed by LAH reduction. Because the monoacylated

Scheme 1[a]



[a] (a) $HOCH_2CH_2Br$, H_2SO_4, $PhCH_3$; (b) $MeNH(CH_2)_3NHMe$, K_2CO_3, DMF; (c) $Ph(CH_2)_2Br$; K_2CO_3, DMF; (d) $Ph(CH_2)_3Br$, K_2CO_3, DMF; (e) $MeNH(CH_2)_2NHMe$, K_2CO_3, DMF; (f) **2a**, K_2CO_3, DMF.

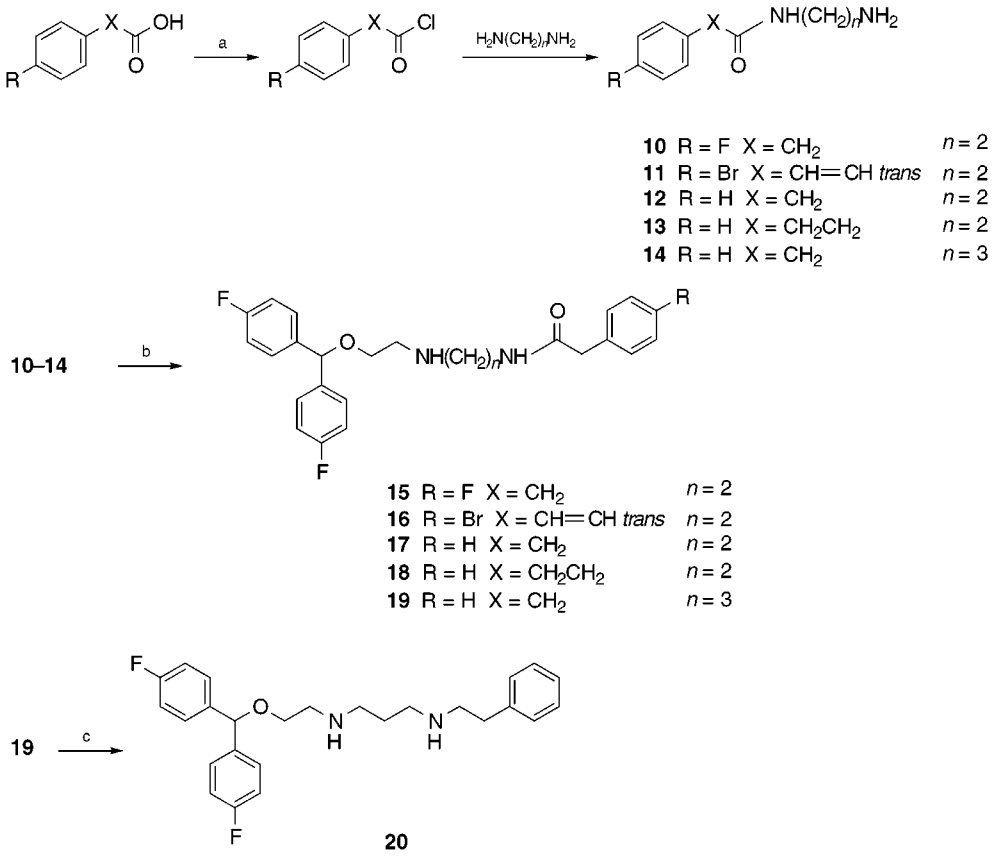
diamines were highly soluble in water, an extensive extraction process was used to improve yields.

The synthetic route for preparing piperazinone ring GBR analogues is shown in Scheme 3. The requisite ketopiperazine was synthesized in good yield (84%, crude) using the method described by Aspinal[31] with some modifications. Instead of using distillation for the cyclization of **22** and purification of **23**, the crude reaction mixture was stirred at ambient temperature for 24 h in DMF, the solvent was removed, and the resultant solid was purified by chromatography to give crude product **23**. The intermediate **23** was used in the following step without further purification. The *N*-alkylation step afforded amide ring intermediates **24** and **26** in moderate yields, which may be partially attributed to the impurity of ketopiperazine **23**. Subsequent alkylation of **24** and **26** with appropriate alkyl halides proceeded in moderate yields to give target GBR analogues **25** and **27**, respectively. The structures of all final products were confirmed by spectroscopic and analytic methods.

Biological Results

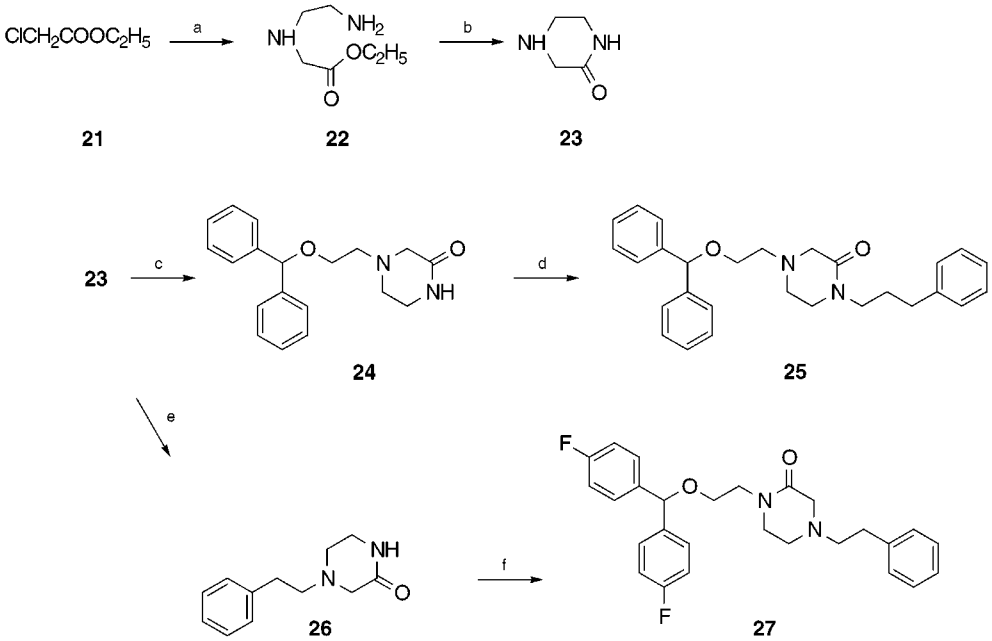
The final products were converted to oxalate or hydrochloride salts and submitted to the NIDA/MDD for the determination of binding affinity (K_i) and potency of reuptake inhibition (IC_{50}) at dopamine, serotonin, and norepinephrine transporter sites (Tables 1 and 2). The results shown in Table 2 indicate that most of the new seco compounds inhibited dopamine uptake at concentrations (120−830 nM) comparable to or lower than those reported for cocaine (190−300 nM). Interestingly, *N*,*N*′-dimethyl ring-opened GBR analogues such as **4** and **5**, with a propylene moiety between two nitrogen atoms, exhibited high affinity at the NET (K_i = 194, 30 nM) and inhibited [^{3}H]NE reuptake selectively (Tables 1 and 2). Because analogues containing acyclic diamine spacers exhibited NET activity, "linear" distance factors alone appear to produce NET selectivity. However, compound **20**, with a three-carbon spacer between the two basic nitrogens (secondary amines), showed selectivity for DAT binding and inhibi-

Scheme 2[a]



[a] (a) $SOCl_2$, $CHCl_3$, cat. DMF; (b) **2b**, K_2CO_3, DMF; (c) LAH, THF.

Scheme 3[a]



[a] (a) $H_2NCH_2CH_2NH_2$, abs. EtOH; (b) DMF, 60−70 °C; (c) **2a**, K_2CO_3, DMF; (d) $Ph(CH_2)_3Br$, NaH, DMF; (e) $Ph(CH_2)_2Br$, K_2CO_3, DMF; (f) **2b**, NaH, DMF.

tion of [^{3}H]DA reuptake. The other ring-opened congeners, **8** and **9**, with an ethylene moiety between two nitrogen atoms, retained high affinity (K_i = 26, 30 nM) at DAT sites and high selectivity for DAT vs SERT sites (18-, 30-fold). Interestingly, analogue **9** possessed a reuptake-to-binding ratio at the DAT site of about 32:1, similar to results reported by Matecka et al.[24] Insertion of one more carbon into the alkyl chain of the tail-phenylethyl group in **4** resulted in the tail-phenylpropyl moiety of **5** (three-carbon spacer between tail benzene ring and adjacent basic nitrogen atom). This modification improved binding affinity for NET (6-fold), DAT (3-fold), and SERT (4-fold) sites. However, activity as an inhibitor of reuptake was slightly improved only

Table 1. Affinities and Selectivities of GBR Analogues at the DA, 5-HT, and NE Transporters Measured by Inhibition of [^{125}I]RTI-55 Binding[a]

	binding ($K_i \pm$ SD, nM)			selectivity ratio	
compd	DAT	SERT	NET	SERT/DAT	NET/DAT
4	322 ± 57	1530 ± 421	194 ± 79	4.7	0.6
5	122 ± 12	438 ± 122	30 ± 5	3.6	0.2
8	30 ± 10	550 ± 70	370 ± 126	18.3	12.3
9	26 ± 7.8	770 ± 180	261 ± 81	30.1	10.2
15	54 ± 21	351 ± 81	844 ± 224	6.5	15.6
16	510 ± 160	590 ± 150	1760 ± 940	1.2	3.5
17	54 ± 23	556 ± 174	604 ± 234	10.3	11.2
18	51 ± 6	523 ± 28	545 ± 176	10.3	10.7
19	61 ± 11	1150 ± 212	477 ± 80	18.8	7.8
20	28 ± 7	125 ± 12	82 ± 12	4.5	2.9
25	8200 ± 1300	5900 ± 790	5850 ± 450	0.7	1.0
27	1430 ± 590	114 ± 49	7050 ± 2620	0.1	4.9
cocaine	759 ± 93	387 ± 88	1770 ± 369		
cocaine[b]	619 ± 93	204 ± 40	2040 ± 300		
cocaine[c]	960 ± 190	488 ± 67	2580 ± 260		

[a] The K_i values for the test ligands were determined with assays described in the Experimental Section. Results are mean ± SEM for three independent experiments assayed in triplicate. [b] Cocaine as reference for **9**. [c] Cocaine as reference for **16** and **25**.

Table 2. DA, 5-HT, and NE Reuptake Inhibition and Ratios of Reuptake to Binding of GBR Analogues at DA and 5-HT Transporters[a]

	reuptake inhibition ($IC_{50} \pm$ SD, nM)			ratio	
compd	[^{3}H]DA	[^{3}H]5-HT	[^{3}H]NE	[^{3}H]DA reuptake/DAT binding	[^{3}H]5-HT reuptake/SERT binding
4	349 ± 18	1700 ± 370	210 ± 33	1.1	1.1
5	237 ± 41	1700 ± 560	143 ± 27	1.9	3.9
8	119 ± 11	1050 ± 130	279 ± 67	4.0	1.9
9	830 ± 340	>10 μM	2600 ± 710	32.4	>13.0
15	47 ± 16	1990 ± 317	299 ± 82	0.9	5.7
16	1380 ± 390	4500 ± 1400	>10 μM	2.7	7.6
17	80 ± 22	1300 ± 66	399 ± 117	1.5	2.3
18	90 ± 24	1140 ± 392	205 ± 44	1.8	2.2
19	73 ± 17	1230 ± 135	192 ± 52	1.2	1.1
20	68 ± 8	249 ± 31	116 ± 52	2.4	2.0
25	>10 μM	>10 μM	>10 μM	>1.2	>1.7
27	>10 μM	3940 ± 856	>10 μM	>1.7	>34.5
cocaine	190 ± 21	336 ± 78	230 ± 41		
cocaine[b]	299 ± 61	301 ± 42	125 ± 8.6		
cocaine[c]	218 ± 29	217 ± 36	217 ± 60		

[a] IC_{50} values for the test ligands were determined with assays described in the Experimental Section. Results are mean ± SEM of three independent experiments assayed in triplicate. [b] Cocaine as reference for **9**. [c] Cocaine as reference for **16** and **25**.

at the NET sites (Table 2, **4** and **5**). Also, this structural change at the tail moiety exhibited a 2-fold improvement in the ratio of [^{3}H]DA reuptake inhibition to binding inhibition at the DAT. This finding suggests that the 3-phenylpropyl group may bind to domain(s) of the DAT which are more important for binding than for uptake inhibition.[23]

In previous studies it was shown that only one nitrogen atom attached to the phenylpropyl (tail) moiety of the GBR molecule was required for the retention of high-affinity DAT binding.[25] These new second-generation piperidine-based GBR-type compounds were more selective but equipotent compared to the original GBR 12909.[33] This was in contrast to the original notion, proposed by Van der Zee et al.,[11] that the 3-phenylpropyl substitution maximized the potency. Interestingly, initial evaluation of binding assay data (NOVA Screen) for ring-opened seco GBR analogues with a tail-amide function (compound **16**, Table 1), in which the N_2 nitrogen atom was replaced by a nonbasic amide function with one basic nitrogen atom (N_1) attached to the head moiety, demonstrated retention of DAT binding (IC_{50} = 450 nM, NOVA Screen not shown). This prompted a further evaluation of this series of compounds and four additional congeners were prepared and tested (Tables 1 and 2). This series of amine-amide GBR analogues showed moderate affinity (K_i = 51−61 nM, Table 1) and selectivity for the DAT, independent of the distance (*n*, Figure 1) between the basic nitrogen and the amide function of the tail moiety. Fluoro substitution at the benzene ring in the tail moiety improved potency for [^{3}H]DA reuptake inhibition about 2-fold without affecting binding affinity (IC_{50} = 47 nM, **15**−**17**). Introduction of a two-carbon (ethylene) linkage (*n*′, Figure 1) between the amide and tail benzene ring, congener **17**, had little effect at the DAT but produced a 2-fold improvement in reuptake inhibition at the NET. This modification produced a slight improvement in binding at all three transporters, similar to observations with seco GBR analogues (**4** and **5**, Tables 1 and 2). A three-carbon (propylene) linkage between the basic nitrogen atom and the amide function nitrogen atom, such as in congener **19**, produced 2-fold improvement in selectivity for DAT vs SERT binding affinity compared to compound **17**. However, DAT vs NET selectivity was decreased from 11.2 to 7.8-fold. These observations were in agreement with previous findings from seco GBR analogues, but the effects were minimal. This tolerance of an amide function may be attributable to a strong hydrogen-bonding interaction between the trans-

porter and the ligand's amide function as donor/acceptor in the ligand binding site(s) of the DAT.

Because we were trying to detect general trends in biological activity, multiple simultaneous changes were incorporated in the target compounds, e.g., fluorine for hydrogen on the aryl groups or the introduction of a different alkyl chain in the aralkyl tail. Previous studies[11,24,32] have described the individual effects of these changes on transporter inhibition. Introduction of a carbonyl group adjacent to each nitrogen atom on the piperazine ring produced the piperazinone ring GBR analogues **25** and **27** and showed a profound effect on biological properties. This modification which was used to evaluate the effect of basicity of each nitrogen atom without significantly changing flexibility of the ring was not successful in producing compounds with the desired properties. Introduction of a carbonyl group into the piperazine ring (piperazinone) significantly attenuated potency of reuptake inhibition at the DAT. Replacement of the phenylpropyl moiety by a phenylethyl moiety significantly shifted selectivity toward the SERT in these piperazinone ring GBR analogues. Interestingly, **27** possessed a reuptake-to-binding ratio at the SERT site of about 35:1. This analogue was practically inactive (>10 μM) for the inhibition of reuptake to the DAT and NET sites and had weak binding affinity (DAT 1.4 μM, NET 7.0 μM).

Based on the results in Tables 1 and 2, it appears that compound **16** has a reasonable ratio of [^{3}H]DA reuptake to DAT binding (2.7) with DAT binding comparable to that of cocaine. Although compounds **8** and **9** have superior selectivity ratios (4.0 and 32.4) both agents have much higher potency DAT binding compared with cocaine, similar to GBR 12909[34] (IC_{50}(DAT) = 43 ± 10 nM and IC_{50}(SERT) = 741 ± 56 nM). Thus, since our goal was to develop pure cocaine antagonists which have DAT binding similar to that of cocaine but reduced potency for [^{3}H]DA reuptake inhibition, compound **16** was selected for preliminary behavioral screening which involved testing of the compound alone and in combination with cocaine for its effect on locomotion activity in mice. Figure 2 shows average horizontal activity counts/10 min over 30 min as a function of dose, starting 20 min after ip administration of compound **16** without cocaine. Significant suppression of spontaneous locomotor activity was obtained at doses of 30 and 100 mg/kg. The mean average horizontal activity counts/10 min on the descending portion of the dose−effect curve (30−100 mg/kg dose range) for this 30-min period were fit to a linear function of $\log_{10}$ dose. Analogue **16** suppressed spontaneous locomotor activity with an ID_{50} (dose producing half-maximal depressant activity, where maximal depression = 0 counts/30 min) of 47.4 ± 5.2 mg/kg (mean ± SEM). Since this compound is not expected to significantly alter synaptic dopamine levels, the observed reduction in locomotor activity suggests that compound **16** may have other biological properties in addition to binding to the DAT.

Figure 3 shows the results of a cocaine/compound **16** interaction study. The period of 0−30 min was selected for analysis of dose−response data, because this is the time interval in which coicaine produces its maximal effects. Significant suppression of cocaine-induced locomotor activity was obtained only at a dose of 100 mg/kg. In contrast, at low doses of 3, 10, and 30 mg/kg, very weak stimulations of cocaine-induced locomotor activity were observed. Analogue **16** attenuated locomotor activity induced by 20 mg/kg cocaine with an AD_{50} (dose attenuating cocaine-induced stimulation by 50%) of 60.0 ± 3.6 mg/kg (mean ± SEM).

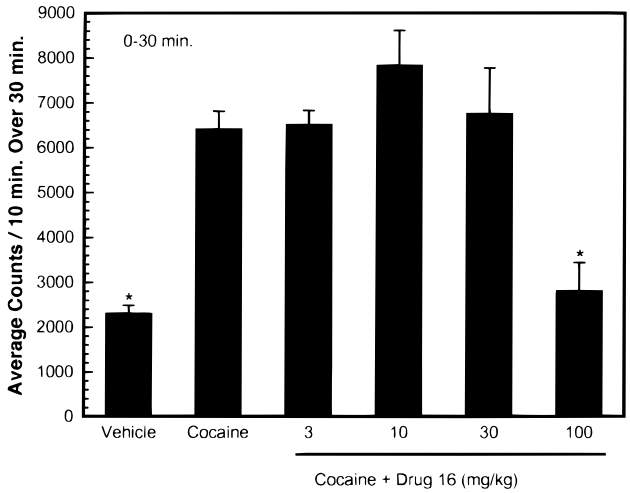


Figure 3. Average horizontal activity counts/10 min over 30 min as a function of dose condition, 20 min after pretreatment with **16**. The bar above "coc" represents the effect of vehicle 20 min prior to saline injection. The bars above "3, 10, 30, and 100" represent the effects of **16** at the designated doses 20 min prior to cocaine injection (20 mg/kg). The mean average horizontal activity counts/10 min on the descending portion of the dose−effect curve (10−100 mg/kg dose range) were fit to a linear function of log dose to yield an AD_{50} of 60.0 ± 3.6 mg/kg.

Conclusions

The rigid piperazine ring (bridge, Figure 1) of GBRs was substituted with conformationally flexible polymethylenediamines and amine-amide moieties without compromising biological activity. New analogues with a three-carbon linkage at the bridge portion of the structure displayed a tendency for NET site activities, and this bridge was proved to be a "selectivity controller" moiety. Tolerance of amide function at the N_2 (Figure 1) nitrogen atom may be due to strong hydrogen-bonding capabilities at the binding site(s) of the DAT protein. The current studies have provided additional information on pharmacophoric groups which are responsible for selective binding and potency of reuptake inhibition at the DAT. These acyclic analogues along with the results of in vivo studies with **16** may provide a basis for the design of novel probes and lead compounds which are structurally different DAT inhibitors with selective and strong binding to the DAT and weak potency for DA uptake.

Experimental Section

General Chemical Methods. All chemicals and solvents were obtained from commercial suppliers and were used without further purification. In general, all reactions were performed under atmospheric conditions and at ambient temperature unless otherwise noted. High boiling point solvents (DMF, DMSO, etc.) that are water-soluble were removed from the reaction mixture by first pouring into ethyl acetate and/or diethyl ether followed by washing with a saturated NaCl solution. All organic extracts were dried over $MgSO_4$ or Na_2SO_4 except where otherwise noted. The volatile solvents

were removed by rotary evaporation under reduced pressure. Melting points were determined on a Thomas-Hoover melting point apparatus or an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, for carbon, hydrogen, and nitrogen and were within ±0.4% of theoretical values unless noted otherwise. ^{1}H,^{13}C NMR spectra were determined on a Varian XL-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a TMS internal reference standard. In general, $CDCl_3$ was used for free bases and DMSO-d_6 was used for salts. Coupling constants (J values) are given in Hz. Thin layer chromatography (TLC) was performed on 250-μm thickness silica gel plates or alumina precoated plates (Whatman, AL SIL G/UV or J.T. Baker, Baker-flex, SILICA GEL IB-F) containing fluorescent indicator developed with appropriate solvent mixtures. Column separations were performed on silica gel (Baker, 40 μm flash chromatography). The collected fractions were analyzed by TLC and visualized by ninhydrin (0.5 g in 100 mL of methanol) for primary and secondary amine(s), ultraviolet light, or iodine vapor. For salt formation, free bases were dried and dissolved in ethyl acetate or/and diethyl ether and filtered. Oxalic acid solution in the same solvent or HCl in ether was added to the filtrates until no further turbidity or precipitation occurred. The resultant solids were collected by filtration and recrystallized from appropriate solvents. Unfilterable gels were evaporated to dryness and recrystallized.

1-[Bis(4-fluorophenyl)methoxy]-2-bromoethane (1b). A mixture of 2-bromoethanol (15.0 g, 120 mmol), 1 mL of concentrated sulfuric acid, and 4,4′-difluorobenzhydrol (4.4 g, 20 mmol) in 50 mL of toluene was heated at reflux for 6 h. The reaction mixture was cooled and washed successively with saturated sodium bicarbonate solution (50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. The resultant colorless oil was applied on a silica gel column for separation. Elution with 3% ethyl acetate/hexane afforded 5.3 g (17.0 mmol, 85%) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.45 (2H, t, J = 6.0), 3.70 (2H, t, J = 6.0), 5.36 (1H, s), 6.94−7.00 (4H, m), 7.26−7.31 (4H, m). ^{13}C NMR ($CDCl_3$): δ 30.55, 68.64, 82.27, 115.19, 115.30, 128.45, 128.55, 137.23, 137.27, 160.42, 163.68.

1-(Bisphenylmethoxy)-2-bromoethane (1a) was prepared as described for **1b** to give the title compound **1a** as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.42 (2H, t, J = 6.1), 3.69 (2H, t, J = 6.1), 5.37 (1H, s), 7.19−7.34 (10H, m). ^{13}C NMR (DMSO-d_6): δ 32.67, 68.71, 82.25, 126.59, 127.32, 128.28, 142.06.

***N,N′*-Dimethyl-*N*-[2-(bisphenylmethoxy)ethyl]-1,3-propanediamine (3).** To a mixture of amine (4.49 g, 44 mmol), *N*,*N*′-dimethyl-1,3-propanediamine, and K_2CO_3 (1.82 g, 13.2 mmol) in 15 mL of DMF was added dropwise 1-(bisphenylmethoxy)-2-bromoethane (1.28 g, 4.4 mmol) in 10 mL of DMF. The mixture was stirred for 48 h and poured into 200 mL of EtOAc. The organic phase was washed with saturated NaCl solution (60 mL × 3) dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography, eluted with $CHCl_3$:MeOH:NH_4OH (9:1:0.1) to give the desired product **3** (1.23 g, 3.94 mmol, 89%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.8 (1H, br s), 1.94 (3H, s), 2.01 (2H, quintet, J = 5.6), 2.35 (3H, s), 2.66 (2H, t, J = 5.1), 2.68 (2H, t, J = 4.8), 2.97 (2H, t, J = 5.5), 3.58 (2H, t, J = 5.1), 5.40 (1H, s), 7.25−7.42 (10H, m). Mp (HCl salt): 185−188 °C.

***N,N′*-Dimethyl-*N*-[2-(4-fluorophenyl)ethyl]-1,2-ethylenediamine (7)** was prepared as described for **3** to give the title compound **7** (88%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.73 (1H, br s), 2.28 (3H, s), 2.36 (3H, s), 2.49−2.62 (6H, m), 2.70−2.75 (2H, m), 6.93−7.00 (2H, m), 7.11−7.16 (2H, m). ^{13}C NMR ($CDCl_3$): δ 33.00, 36.41, 42.13, 49.32, 56.88, 59.52, 114.79, 115.07, 129.90, 130.00, 136.16, 136.21, 159.65, 162.87. Mp (bisoxalate salt): 207−209 °C.

***N,N′*-Dimethyl-*N*-[2-(bisphenylmethoxy)ethyl]-*N*′-(2-phenylethyl)-1,3-propanediamine (4)** was prepared as described for **3** to give the title compound **4** (83%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.65 (2H, quintet, J = 7.5), 2.27 (3H, s), 2.29 (3H, s), 2.40 (4H, t, J = 7.5), 2.56−2.61 (2H, m), 2.67 (2H, t, J = 6.1), 2.73−2.78 (2H, m), 3.56 (2H, t, J = 6.1), 5.36 (1H, s), 7.17−7.36 (15H, m). ^{13}C NMR ($CDCl_3$): δ 25.17, 33.76, 42.20, 42.91, 55.57, 56.13, 56.92, 59.60, 67.39, 83.92, 125.89, 126.93, 127.33, 128.30, 128.67, 140.52, 142.30. Mp (bisoxalate salt): 198−200 °C. Anal. Calcd for $C_{32}H_{40}N_2O_9$: C, 64.42; H, 6.76; N, 4.69. Found: C, 64.53; H, 6.77; N, 4.63.

***N,N′*-Dimethyl-*N*-[2-(bisphenylmethoxy)ethyl]-*N*′-(3-phenylpropyl)-1,3-propanediamine (5)** was prepared as described for **3** to give the title compound **5** (70%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.63 (2H, quintet, J = 7.5), 1.78 (2H, quintet, J = 7.7), 2.19 (3H, s), 2.26 (3H, s), 2.30−2.43 (6H, m), 2.61 (2H, t, J = 7.8), 2.67 (2H, t, J = 6.1), 3.56 (2H, t, J = 6.1), 5.36 (1H, s), 7.17−7.36 (15H, m). ^{13}C NMR ($CDCl_3$): δ 25.18, 28.98, 33.68, 42.17, 42.91, 55.71, 56.17, 56.90, 57.23, 67.38, 83.90, 125.66, 126.91, 127.31, 128.24, 128.28, 128.34, 142.28. Mp (bisoxalate salt): 191−193 °C. Anal. Calcd for $C_{33}H_{42}N_2O_9$: C, 64.90; H, 6.93; N, 4.59. Found: C, 64.76; H, 6.98; N, 4.55.

***N,N′*-Dimethyl-*N*-[2-(bisphenylmethoxy)ethyl]-*N*′-[2-(4-fluorophenyl)ethyl]-1,2-ethylenediamine (8)** was prepared as described for **3** to give the title compound **8** (85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.28 (3H, s), 2.29 (3H, s), 2.53−2.59 (6H, m), 2.69−2.75 (4H, m), 3.56 (2H, t, J = 6.1), 5.35 (1H, s), 6.91−6.97 (2H, m), 7.09−7.13 (2H, m), 7.19−7.36 (10H, m). ^{13}C NMR ($CDCl_3$): δ 32.92, 42.49, 43.24, 55.31, 55.74, 57.36, 60.09, 67.33, 83.96, 114.87, 115.15, 126.89, 127.33, 128.28, 129.90, 130.00, 136.01, 136.06, 142.25, 159.65, 162.88. Mp (bisoxalate salt): 225−230 °C. Anal. Calcd for $C_{31}H_{37}N_2O_9F$: C, 61.99; H, 6.21; N, 4.66. Found: C, 62.15; H, 6.26; N, 4.72.

***N,N′*-Dimethyl-1,2-bis[2-[bis(4-fluorophenyl)methoxy]-ethyl]ethanediamine (9)** was prepared as described for **3** to give the title compound **9** (85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.25 (3H, s), 2.52 (2H, s), 2.66 (2H, t, J = 6.0), 3.50 (2H, t, J = 6.1), 5.30 (1H, s), 6.96−7.02 (4H, m), 7.24−7.29 (4H, m). ^{13}C NMR ($CDCl_3$): δ 43.17, 55.81, 57.32, 67.32, 82.55, 115.08, 115.36, 128.44, 128.55, 137.83, 137.87, 160.46, 163.72. Mp (bisoxalate salt): 207−210 °C. Anal. Calcd for $C_{38}H_{40}N_2O_{10}F_4$: C, 60.00; H, 5.30; N, 3.68. Found: C, 60.11; H, 5.26; N, 3.67.

***N*-(4-Fluorophenylacetyl)-1,2-ethanediamine (10).** A mixture of thionyl chloride (11.9 g, 100 mmol) and 4-fluorophenylacetic acid (4.62 g, 30 mmol) in 40 mL of $CHCl_3$ was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo to give the acid chloride as a slightly yellow solid. This material was dissolved in 20 mL of anhydrous CH_2Cl_2 and was added over 2 h to the mixture of ethylenediamine (18.03 g, 300 mmol) and triethylamine (6.07 g, 60 mmol) in 50 mL of anhydrous CH_2Cl_2. The reaction mixture was allowed to stir for 24 h at ambient temperature. The solvent was removed using rotary evaporation. Ethyl acetate (200 mL) and saturated NaCl solution (30 mL) were added to the resultant crude product and stirred 2 h. The organic layer was separated, washed with saturated NaCl (30 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by chromatography on silica gel. Elution with $CHCl_3$:MeOH:NH_4OH (9:1:0.1) afforded 1.3 g (6.63 mmol, 22.1%) of desired product **10** as a slightly yellow sticky oil that solidified upon cooling. ^{1}H NMR ($CDCl_3$): δ 1.59 (2H, br s), 2.75 (2H, t, J = 5.9), 3.25 (2H, q, J = 5.9), 3.50 (2H, s), 6.57 (1H, br s), 6.98−7.04 (2H, m), 7.20−7.25 (2H, m). ^{13}C NMR ($CDCl_3$): δ 41.05, 42.07, 42.48, 115.27, 115.56, 130.56, 130.66, 160.12, 163.37, 171.10. Mp (oxalate salt): 147−150 °C.

***N*-[3-(4-Bromophenyl)-2-propenyl]-1,2-ethanediamine (11)** was prepared as described for **10** to give the product **11** (25%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.34 (2H, br s), 2.90 (2H, t, J = 5.9), 3.43 (2H, q, J = 5.8), 6.48 (1H, d, J_{trans} = 15.7), 6.85 (1H, br s), 7.29−7.32 (2H, m), 7.42−7.46 (2H, m), 7.54 (1H, d, J_{trans} = 15.6). ^{13}C NMR ($CDCl_3$): δ 41.26, 42.22, 121.49, 123.59, 129.02, 131.87, 133.65, 139.32, 165.91. Mp (free base): 129−132 °C, (oxalate salt) 183−186 °C.

***N*-(Phenylacetyl)-1,2-ethanediamine (12)** was prepared as described for **10** to give the product **12** (23%) as a slightly yellow oil, with the exception that the commercially available phenylacetyl chloride was used. ^{1}H NMR ($CDCl_3$): δ 1.32 (2H, br s), 2.75 (2H, t, J = 6.0), 3.25 (2H, q, J = 5.9), 3.57 (2H, s), 6.03 (1H, br s), 7.26−7.38 (5H, m). ^{13}C NMR ($CDCl_3$): δ 41.18, 42.18, 43.73, 127.18, 128.86, 129.26, 134.95, 171.26. Mp (oxalate salt): 135−138 °C.

***N*-(3-Phenylpropionyl)-1,2-ethanediamine (13)** was prepared as described for **10** to give the product **13** (28%) as a slightly yellow oil with the exception that the commercially available 3-phenylpropionyl chloride was used. ^{1}H NMR ($CDCl_3$): δ 1.29 (2H, br s), 2.48 (2H, t, J = 7.7), 2.72 (2H, t, J = 5.9), 2.97 (2H, t, J = 7.7), 3.24 (2H, q, J = 5.8), 6.06 (1H, br s), 7.17−7.31 (5H, m). ^{13}C NMR ($CDCl_3$): δ 31.73, 38.44, 41.21, 41.98, 126.15, 128.28, 128.42, 140.81, 172.29. Mp (oxalate salt): 127−132 °C.

***N*-(Phenylacetyl)-1,3-propanediamine (14)** was prepared as described for **10** to give the product **14** (35%) as a slightly yellow oil with the exception that the commercially available phenylacetyl chloride was used. ^{1}H NMR ($CDCl_3$): δ 1.30 (2H, br s), 1.54 (2H, quintet, J = 6.5), 2.68 (2H, t, J = 6.4), 3.31 (2H, q, J = 6.2), 3.55 (2H, s), 6.39 (1H, br s), 7.24−7.37 (5H, m). ^{13}C NMR ($CDCl_3$): δ 32.11, 37.95, 39.89, 43.78, 127.08, 128.79, 129.35, 135.05, 171.05. Mp (oxalate salt): 105−108 °C.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N′*-(4-fluorophenylacetyl)-1,2-ethanediamine (15).** (4-Fluorophenylacetyl)-1,2-ethanediamine (1.1 g, 5.6 mmol) (**10**) was dissolved in 20 mL of anhydrous DMF and stirred with K_2CO_3 powder (2.30 g, 16.8 mmol) for 0.5 h. To this turbid solution was added 1-[bis(4-fluorophenyl)methoxy]-2-bromoethane (1.2 g, 3.7 mmol) in 10 mL of DMF dropwise. The reaction mixture was stirred for 24 h at ambient temperature. The turbid reaction mixture was poured into 200 mL of ethyl acetate. The organic layer was separated, washed with saturated NaCl solution (60 mL × 3), dried over $MgSO_4$, and evaporated to dryness. The crude oil was applied to a silica gel column for purification. Elution with $CHCl_3$:MeOH:Et_3N (97:3:0.3) afforded the desired monoalkylated product **15** (1.20 g, 2.71 mmol) as a colorless oil. ^{1}H NMR ($CDCl_3$): 1.61 (1H, br s), 2.69 (2H, t, J = 5.9), 2.75 (2H, t, J = 5.2), 3.29 (2H, q, J = 5.8), 3.46 (2H, t, J = 5.2), 3.49 (2H, s), 5.30 (1H, s), 6.04 (1H, br s), 6.95−7.05 (6H, m), 7.17−7.29 (6H, m). ^{13}C NMR ($CDCl_3$): δ 39.07, 42.76, 48.01, 48.67, 68.34, 82.52, 115.18, 115.46, 115.75, 128.41, 128.52, 130.77, 130.88, 137.62, 137.66, 160.51, 163.77, 170.75. Mp (oxalate salt): 157−159 °C. Anal. Calcd for $C_{27}H_{27}N_2O_6F_3$: C, 60.90; H, 5.11; N, 5.26. Found: C, 60.74; H, 5.20; N, 5.16.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-N′-[3-(4-bromophenyl)-2-propenyl]-1,2-ethanediamine (16)** was prepared as described for **15** to give the product **16** (82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.64 (1H, br s), 2.80−2.88 (4H, m), 3.46 (2H, q, J = 5.7), 3.54 (2H, t, J = 5.1), 5.33 (1H, s), 6.32 (1H, br s), 6.34 (1H, d, J_{trans} = 15.6), 6.97−7.03 (4H, m), 7.25−7.33 (6H, m), 7.46−7.50 (2H, m), 7.54 (1H, d, J_{trans} = 15.6). ^{13}C NMR ($CDCl_3$): δ 39.13, 48.16, 48.75, 68.32, 82.55, 115.20, 115.49, 121.40, 123.68, 128.44, 128.55, 129.12, 131.97, 133.78, 137.63, 137.68, 139.50, 160.53, 163.80, 165.55. Mp (oxalate): 170−172 °C. Anal. Calcd for $C_{28}H_{27}N_2O_6F_2Br$: C, 55.55; H, 4.49; N, 4.63. Found: C, 55.56; H, 4.52; N, 4.66.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N′*-(phenylacetyl)-1,2-ethanediamine (17)** was prepared as described for **15** to give the product **17** (74%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.50 (1H, br s), 2.67 (2H, t, J = 6.0), 2.74 (2H, t, J = 5.2), 3.28 (2H, q, J = 5.8), 3.45 (2H, t, J = 5.4), 3.52 (2H, s), 5.30 (1H, s), 6.06 (1H, br s), 6.97−7.04 (4H, m), 7.21−7.32 (9H, m). ^{13}C NMR ($CDCl_3$): δ 39.07, 43.63, 48.01, 48.63, 68.29, 82.41, 115.08, 115.36, 127.03, 128.35, 128.45, 128.73, 129.20, 134.96, 137.59, 137.63, 160.41, 163.67, 170.92. Mp (oxalate salt): 143−145 °C. Anal. Calcd for $C_{27}H_{28}N_2O_6F_2$: C, 63.03; H, 5.48; N, 5.44. Found: C, 62.91; H, 5.48; N, 5.40.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N′*-(hydrocinnamoyl)-1,2-ethanediamine (18)** was prepared as described for **15** to give the title compound **18** (73%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.96 (1H, br s), 2.44 (2H, t, J = 7.8), 2.69 (2H, t, J = 5.8), 2.78 (2H, t, J = 5.2), 2.94 (2H, t, J = 7.8), 3.30 (2H, q, J = 5.7), 3.50 (2H, t, J = 5.2), 5.32 (1H, s), 5.98 (1H, br s), 6.97−7.05 (4H, m), 7.15−7.29 (9H, m). Mp (oxalate salt): 144−146 °C. Anal. Calcd for $C_{28}H_{30}N_2O_6F_2$: C, 63.63; H, 5.72; N, 5.30. Found: C, 63.42; H, 5.84; N, 5.25.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N′*-(phenylacetyl)-1,3-propanediamine (19)** was prepared as described for **15** to give the product **19** (85%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.57 (2H, quintet, J = 6.4), 1.60 (1H, br s), 2.60 (2H, t, J = 6.4), 2.70 (2H, t, J = 5.3), 3.30 (2H, q, J = 6.1), 3.44 (2H, t, J = 5.3), 3.50 (2H, s), 5.30 (1H, s), 6.50 (1H, br s), 6.96−7.05 (4H, m), 7.20−7.33 (9H, m). ^{13}C NMR ($CDCl_3$): δ 28.83, 38.84, 43.87, 47.88, 49.09, 68.21, 82.46, 115.15, 115.43, 127.08, 128.41, 128.52, 128.79, 129.34, 135.16, 137.67, 137.71, 160.49, 163.76, 170.90. Mp (oxalate salt): 148−149 °C. Anal. Calcd for $C_{28}H_{30}N_2O_6F_2$: C, 63.63; H, 5.72; N, 5.30. Found: C, 63.51; H, 5.68; N, 5.22.

***N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N′*-(2-phenylethyl)-1,3-propanediamine (20).** *N*-[2-[Bis(4-fluorophenyl)-methoxy]ethyl]-*N′*-(phenylacetyl)-1,3-propanediamine (0.76 g, 1.7 mmol) (**19**) in 10 mL of anhydrous ether was added dropwise to 6 mL (6 mmol) of 1 M solution of $LiAH_4$ in ether, and the mixture was stirred at room temperature for 24 h. After careful workup (water, 20% NaOH addition to destroy excess $LiAH_4$), the mixture was filtered and reextracted with ether from the filter cake. The combined organic filtrate and extracts were dried over $MgSO_4$, filtered, and evaporated to give an oil that was purified by silica gel column chromatography ($CHCl_3$:MeOH:Et_3N, 96:4:0.4). The reduced product **20** was purified as a colorless oil (0.36 g, 0.85 mmol, 50%) and converted to the bismalonate salt which was recrystallized from iPrOH-H_2O. ^{1}H NMR ($CDCl_3$): δ 1.49 (2H, br s), 1.66 (2H, quintet, J = 7.0), 2.64 (2H, t, J = 7.0), 2.68 (2H, t, J = 7.0), 2.76−2.89 (6H, m), 3.53 (2H, t, J = 5.3), 5.32 (1H, s), 6.97−7.04 (4H, m), 7.17−7.32 (9H, m). Mp (bismalonate salt): 153−155 °C. Anal. Calcd for $C_{32}H_{38}N_2O_9F_2$: C, 60.75; H, 6.05; N, 4.43. Found: C, 60.86; H, 6.12; N, 4.38.

2-Ketopiperazine (23). A solution of ethyl chloroacetate (**21**) (4.9 g, 40 mmol) in 40 mL of absolute ethanol was slowly added dropwise over a period of 3.5 h at ambient temperature to ethylenediamine (24 g, 400 mmol) in 100 mL of absolute ethanol. The reaction mixture was allowed to stand for 2 h after addition was completed. Sodium ethoxide (15 mL, 40 mmol, 21 wt % solution in denatured ethyl alcohol) was added. The precipitated sodium chloride was filtered off, the solvent was removed by evaporation, and 40 mL of DMF was added to the resultant red oil. The reaction mixture was allowed to stir for 24 h at ambient temperature and then heated at about 60−70 °C while removing the volatile materials with N_2 gas. The resultant yellow solid was applied to silica gel column for separation. The crude product (3.3 g, 33 mmol, 82%) was obtained by elution with a solvent mixture ($CHCl_3$:MeOH:NH_4-OH, 9:1:0.1). This crude yellow solid was used for next synthesis without further purification. Recrystalization three times from acetone gave well-defined, pure-white crystals. ^{1}H NMR ($CDCl_3$): δ 1.70 (1H, br s), 3.03 (2H, t, J = 5.4), 3.37 (2H, td, J = 2.3, 5.4), 3.52 (2H, s), 6.54 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 42.31, 43.05, 49.83, 170.00. Mp: 132−134 °C (uncorrected) (lit.[13] mp 136 °C, corrected).

4-[2-(Bisphenylmethoxy)ethyl]-2-ketopiperazine (24). A solution of 1-(bisphenylmethoxy)-2-bromoethane (1.97 g, 6.8 mmol) in 10 mL of DMF was added slowly to crude 2-ketopiperazine (1.0 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in 15 mL of DMF. The reaction mixture was stirred overnight at ambient temperature. About 30 mL of water was added slowly to the reaction mixture which was then extracted with ether (60 mL × 3). The ether layer was washed with 50% NaCl solution (60 mL × 1), dried over magnesium sulfate, and filtered. The slightly yellow solid which was obtained from evaporation of ether was applied for column chromatography on silica gel. Elution with a solvent mixture ($CHCl_3$:MeOH:

Et_3N, 97:3:0.3) afforded 1.85 g (5.96 mmol, 87.6%) of product **24** as fine white crystals. ^{1}H NMR ($CDCl_3$): δ 2.71 (2H, t, J = 5.4), 2.73 (2H, t, J = 5.6), 3.21 (2H, s), 3.28−3.33 (2H, m), 3.59 (2H, t, J = 5.6), 5.35 (1H, s), 7.14 (1H, br s), 7.20−7.36 (10H, m). ^{13}C NMR ($CDCl_3$): δ 41.11, 49.24, 56.69, 57.12, 66.74, 84.00, 127.00, 127.40, 128.29, 141.90, 169.81. Mp (free base): 93−94 °C.

4-(2-Phenylethyl)-2-ketopiperazine (26) was prepared as described for **24** to give the title compound **26** (67%) as a slightly yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.67−2.71 (4H, m), 2.78−2.83 (2H, m), 3.20 (2H, s), 3.33−3.37 (2H, m), 7.19−7.22 (3H, m), 7.27−7.31 (2H, m), 7.52 (1H, br s). ^{13}C NMR ($CDCl_3$): δ 33.34, 41.04, 48.97, 56.69, 59.12, 126.11, 128.33, 128.52, 139.51, 169.88. Mp (free base): 113−115 °C.

4-[2-(Bisphenylmethoxy)ethyl]-1-(3-phenylpropyl)-2-ketopiperazine (25). 4-[2-(Bisphenylmethoxy)ethyl]-2-ketopiperazine (**24**) (0.68 g, 2.2 mmol) was dissolved in 10 mL of anhydrous DMF and stirred with sodium hydride powder (0.06 g, 2.5 mmol) under a N_2 atmosphere. After 0.5 h, 1-bromo-3-phenylpropane (0.44 g, 2.2 mmol) in 5 mL of DMF was added dropwise to the turbid reaction mixture at ambient temperature. The reaction mixture was allowed to stir for 16 h under N_2 gas atmosphere. The remaining sodium hydride was destroyed with methanol. About 20 mL of water was added slowly to the reaction mixture which was then extracted with ether (50 mL × 3). The separated ether layer was dried over magnesium sulfate, filtered, and evaporated to yellow viscous oil. Silica gel column purification using a solvent mixture (hexane:EtOIAc:Et_3N, 50:50:2) afforded 600 mg (1.4 mmol, 64%) of pure product as a slightly yellow, viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.88 (2H, quintet, J = 7.7), 2.63 (2H, t, J = 7.8), 2.69 (2H, t, J = 5.7), 2.72 (2H, t, J = 5.4), 3.20 (2H, s), 3.26 (2H, t, J = 5.4), 3.41 (2H, t, J = 7.5), 3.58 (2H, t, J = 5.7), 5.35 (1H, s), 7.15−7.34 (15H, m). ^{13}C NMR ($CDCl_3$): δ 28.37, 33.11, 46.03, 46.45, 50.12, 56.73, 57.72, 66.79, 84.06, 84.09, 125.85, 126.88, 127.46, 128.23, 128.35, 141.47, 141.94, 166.77. Mp (oxalate salt): 126−128 °C. Anal. Calcd for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.55; H, 6.66; N, 5.43.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-phenylethyl)-2-ketopiperazine (27) was prepared as described for **25** to give the title compound **27** (65%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.62−2.68 (2H, m), 2.72 (2H, t, J = 5.4), 2.78−2.83 (2H, m), 3.21 (2H, s), 3.51 (2H, t, J = 5.4), 3.61 (4H, s), 5.31 (1H, s), 6.96−7.03 (4H, m), 7.19−7.31 (9H, m). ^{13}C NMR ($CDCl_3$): δ 33.49, 46.80, 48.50, 50.00, 57.36, 59.23, 67.10, 82.48, 82.52, 115.19, 115.48, 128.38, 128.46, 128.62, 137.57, 137.61, 139.57, 160.51, 163.77, 167.02. Mp (oxalate salt): 138−141 °C, (HCl salt) 150−152 °C. Anal. Calcd for $C_{29}H_{30}N_2O_6F_2$ (oxalate salt): C, 64.44; H, 5.59; N, 5.18. Found: C, 64.37; H, 5.60; N, 5.12. Anal. Calcd for $C_{27}H_{29}N_2O_2F_2Cl$ (HCl salt): C, 66.59; H, 6.00; N, 5.75. Found: C, 66.47; H, 6.03; N, 5.72.

Biological Methods. [^{125}I]RTI-55 binding assay: All drugs were prepared as 10 mM stock solutions in DMSO. The final DMSO concentration in the assay was 0.01%. Pipetting was performed with a Biomek 2000 robotic workstation. HEK 293 cell lines, transfected with NET, DAT, and SERT transporters,[35,36] were grown on 150-mm diameter tissue culture dishes. The medium was poured off, the cells were washed with 10 mL of phosphate-buffered saline (PBS), and 10 mL of lysis buffer (2 mM HEPES, 1 mM EDTA) was added. After 10 min, cells were scraped from plates, poured into centrifuge tubes, and centrifuged for 20 min at 30000*g*. The supernatant was removed, and the pellet was resuspended in 20−32 mL of 0.32 M sucrose, depending on the density of binding sites in a given cell line (i.e. resuspension volumes which bound ≤10% of the total radioactivity). The pellets were dispersed with a Polytron at setting 7 for 10 s. Each assay contained 50 μL of membrane preparation (approximately 15 μg of protein), 25 μL of drug, and 25 μL of [^{125}I]RTI-55 (40−80 pM final concentration) in a final volume of 250 μL. Krebs HEPES buffer was used as the assay diluent. The membranes were preincubated with drug for 10 min prior to addition of [^{125}I]RTI-55. The assay tubes were incubated for 90 min at room temperature in the dark, and the incubation was terminated by filtration onto GF/C filters using a Tom-tech harvester. Scintillation fluid was added to each square, and radioactivity remaining on the filter was measured using a Wallac μ- or β-plate reader. Competition experiments were conducted in duplicate. The results were analyzed using GraphPAD Prism and IC_{50} values converted to K_i values using the Cheng−Prusoff equation.

[^{3}H]Neurotransmitter uptake by HEK 293 cells expressing recombinant biogenic amine transporters: HEK 293 cell lines, transfected with NET, DAT, and SERT transporters,[35,36] were plated on 150-mm dishes and grown until confluent. The medium was removed, and the cells were washed twice at room temperature with PBS. Following addition of PBS (3 mL), the plates were placed in a 25 °C water bath for 5 min. The cells were gently scraped and then triturated with a pipet. One plate provided sufficient cells for 48 measurements, and cells from multiple plates were combined. Krebs HEPES buffer (350 μL) and drugs (50 μL) were added to a 1.0-mL assat vial and placed in a 25 °C water bath. Aliquots of cell suspension (50 μL) were added, incubation was continued for 10 min, and [^{3}H]DA, [^{3}H]5-HT, or [^{3}H]NE (50 μL, 20 nM final concentration) was added. After an additional 10 min of incubation, the reaction was terminated by filtration onto GF/C filters using a Tom-tech harvester using filters presoaked in 0.05% poly(ethylenimine). Scintillation fluid was added to each square, and radioactivity remaining on the filter was measured using a Wallac μ- or β-plate reader. All assays were performed in triplicate with 6 drug concentrations. The results were analyzed using GraphPAD Prism.

Locomotor activity: These measurements were performed with 16 Digiscan locomotor activity testing chambers (40.5 × 40.5 × 30.5 cm). Panels of infrared beams (16 beams) and corresponding photodetectors were located in the horizontal direction along the sides of each activity chamber. Twenty minutes prior to locomotor activity testing, groups of nonhabituated male Swiss Webster mice (n = 8 each) received an intraperitoneal (ip) injection of either vehicle (methylcellulose) or compound **16** (3, 10, 30, or 100 mg/kg). Immediately before placement in the apparatus, all animals were injected with saline (0.5 mL, ip). In all studies, horizontal activity (interruption of 1 photocell beam) was measured for 1 h within 10-min periods. Testing was conducted with one mouse per activity chamber. In the cocaine/compound **16** interaction study; 20 min following ip vehicle or **16** injections (3, 10, 30, or 100 mg/kg), groups of 8 nonhabituated male Swiss Webster mice were injected with either 0.9% saline or cocaine (20 mg/kg, ip) and placed in the Digiscan apparatus for a 1-h session.

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