Synthesis and Pharmacological Evaluation of 3-(3,4-Dichlorophenyl)-1-indanamine Derivatives as Nonselective Ligands for Biogenic Amine Transporters

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In our efforts toward developing a nonselective ligand that would block the effects of stimulants such as methamphetamine at dopamine (DA), serotonin (5-HT), and norepinephrine (NE) transporters, we synthesized a series of 3-(3,4-dichlorophenyl)-1-indanamine derivatives. Two of the examined higher affinity compounds had a phenolic hydroxyl group enabling preparation of a medium to long chain carboxylic acid ester that might eventually be useful for a long-acting depot formulation. The in vitro data indicated that (−)-(1*R*,3*S*)-*trans*-3-(3,4-dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-**11**) displays high-affinity binding and potent inhibition of uptake at all three biogenic amine transporters. In vivo microdialysis experiments demonstrated that intravenous administration of (−)-(1*R*,3*S*)-**11** to rats elevated extracellular DA and 5-HT in the nucleus accumbens in a dose-dependent manner. Pretreating rats with 0.5 mg/kg (−)-(1*R*,3*S*)-**11** elevated extracellular DA and 5-HT by approximately 150% and reduced methamphetamine-induced neurotransmitter release by about 50%. Ex vivo autoradiography, however, demonstrated that iv administration of (−)-(1*R*,3*S*)-**11** produced a dose-dependent, persistent occupation of 5-HT transporter binding sites but not DA transporter sites.

Introduction

The abuse of methamphetamine and other amphetamine-like stimulants has had a disturbing effect on public health in the United States.[1−3] Studies have shown that methamphetamine can act as a substrate for transporters of the biogenic amine neurotransmitters, dopamine (DA), serotonin (5-HT), and norepinephrine (NE), and can be transported by these transmembrane proteins into the nerve terminal.[4] The substrate activity of methamphetamine and related agents evokes the nonexocytotic release of biogenic amines transmitters. Increased release of DA in the central nervous system is thought to mediate the dependence-producing effects of methamphetamine, whereas increased release of NE in both the peripheral and central nervous system is thought to induce undesirable cardiovascular side effects.[5] However, recent data suggest that norepinephrine may play an important role in mediating amphetamine-induced subjective effects in humans.[6] There are, presently, no specific treatment agents available for stimulant abuse, although GBR 12909 is currently being evaluated as a potential pharmacotherapy for that purpose[7,8] and GBR 12935 has been considered for use as a treatment agent.

High-affinity dopamine uptake inhibitors, such as GBR 12909, selectively block the ability of methamphetamine[9] to increase extracellular dopamine. We believe that this effect follows in part from the ability of GBR 12909 to persistently occupy DA transporter binding sites.[9] However, a limitation of such agents is that they would not protect against the adverse effects of the amphetamine-like stimulants that are mediated by 5-HT and NE transporters. Therefore, we sought to develop a nonselective transporter ligand that would bind with high affinity to all three biogenic amine transporters. This type of medication would ideally neutralize the neurochemical effects of stimulants such as methamphetamine and not only attenuate the addictive effects of these agents but also block cardiovascular and neurotoxic effects.[10] Moreover, we wanted this agent to be amenable to formulation as a long-acting depot medication. One method that has been used to prepare an oil-soluble prodrug is to esterify a polar hydroxyl-containing compound with a medium to long chain alkanoic acid.[9]

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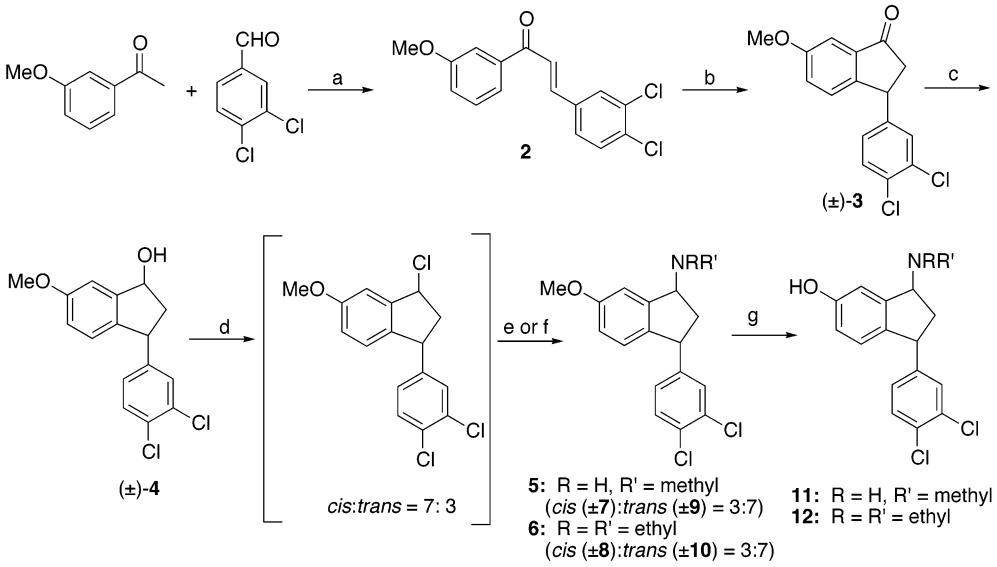
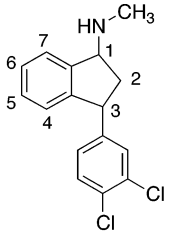
Scheme 1[a]



[a] Reagents and conditions: (a) KOH, EtOH/H_2O; (b) TFA, 130 °C; (c) $NaBH_4$, MeOH; (d) $SOCl_2$, 1,4-dioxane; (e) CH_3NH_2, toluene, 40 °C; (f) diethylamine, toluene, 40 °C; (g) 48% HBr, reflux or BBr_3, CH_2Cl_2, 0 °C.

Indatraline ((±)-*trans*-3-(3,4-dichlorophenyl)-*N*-methyl-1-indanamine, **1**) is an uptake inhibitor with high



1 ((±)-Indatraline (1,3-*trans*))

affinity for DA, 5-HT, and NE transporters.[10,11] It blocks the transport of methamphetamine into nerve terminals and therefore blocks the ability of methamphetamine to release these transmitters.[10] Since indatraline (**1**) does not contain a hydroxyl group that could serve as the anchor for the medium to long chain ester functionality, we synthesized a series of methoxyl and phenolic bearing analogues. We previously demonstrated[11] that the biological activity of indatraline is less sensitive to substitution on the aromatic ring of the indane than elsewhere in the molecule. Further, a methoxy substituent on the C6 position of the indane has the least negative effect on the binding affinity of indatraline **(1)**.[11] Therefore, our synthetic efforts were directed toward compounds with C6-monosubstituted oxygen-containing groups.

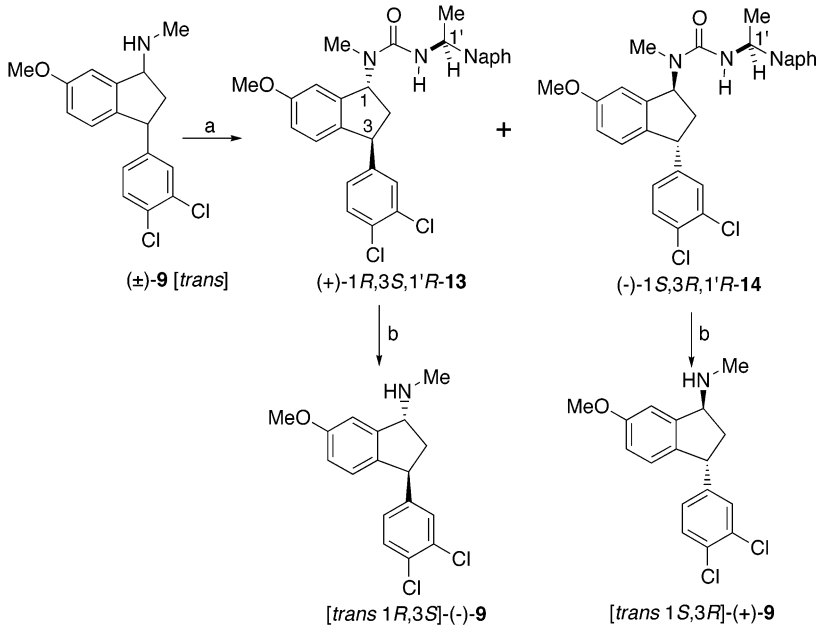
Chemistry

Initial attempts to prepare the needed intermediate, 3-(3,4-dichlorophenyl)-6-methoxylindan-1-one (**3**), following the procedure of Bogeso[12] gave us low yields. We then attempted to prepare **3** from the 1-(3,4-dichlorophenyl)-3-(3-methoxylphenyl)-1-propen-3-one (**2**, Scheme 1). Cyclizing ketone **2** with $AlCl_3$ or BF_3·OEt also gave a low yield of **3**. However, **3** was obtained in high yield by heating ketone **2** in neat trifluoroacetic acid at 120 °C in a sealed tube. Following a modification of the published procedure,[12] **3** was first reduced to 3-(3,4-dichlorophenyl)-6-methoxylindan-1-ol (**4**) as the cis diastereomer. The alcohol **4** was converted to the corresponding chloride with a cis/trans ratio of 7:3. Reacting the chloroindan mixtures with methylamine or diethylamine in toluene led to the inversion of the stereocenter to afford the *N*-methylamine **5** or *N*,*N*-diethylamine **6**, respectively, both in cis/trans ratios of 3:7. The cis and trans isomers of **5** and **6** were separated and purified by crystallization to give the racemic cis *N*-methylamine isomer **7** the cis *N*,*N*-diethylamine isomer **8**, the trans *N*-methylamine isomer **9** and the trans *N*,*N*-diethylamine isomer **10**. Cleavage of the methoxy group in the trans amine **9** gave the phenol **11**, and cleavage of the methoxy group in the trans diethylamine **10** afforded the phenolic compound **12**.

Optical resolution of **9** was initially accomplished through diastereomeric salt formation with *S*-(+)- and *R*-(−)-mandelic acids; however, the method was difficult to replicate. For the reproducible resolution of relatively small quantities, trans isomer **9** was reacted with (*R*)-(−)-1-(1-naphthyl)ethylisocyanate[13] to give chromatographically separable diastereomeric ureas (**13** and **14**, Scheme 2). The ureas **13** and **14** were converted to (−)-(1*S*,3*R*)-**9**·HCl and (+)-(1*R*,3*S*)-**9**·HCl, respectively, by transamination.[14] The optical purity of (−)-(1*S*,3*R*)-**9** and (+)-(1*R*,3*S*)-**9** was determined by 500 MHz NMR spectra of their diastereomeric ureas **13** and **14** to show 99.8% ee and 97.6% ee, respectively.[15]

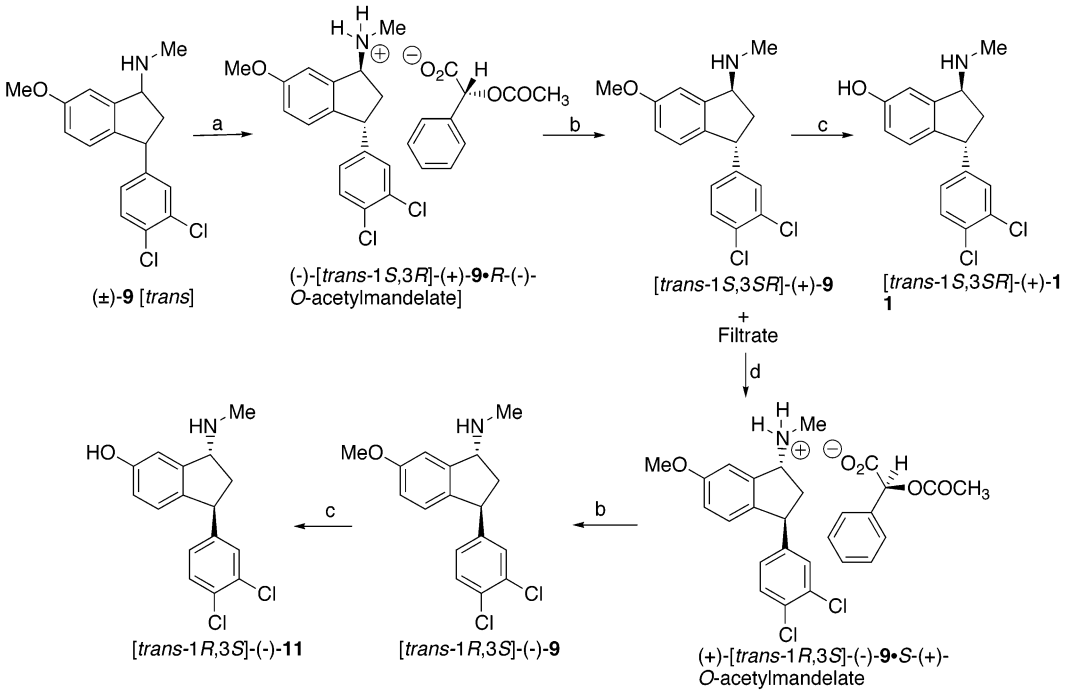
However, to obtain larger quantities of product for future pharmacological studies in the monkey, we developed an easily replicable chemical resolution of racemate **9** using (−)-(*R*)- and (+)-(*S*)-*O*-acetylmandelic acid (Scheme 3). This gave good yields, and multigram quantities, initially of a levorotatory *R*-(−)-*O*-acetylmandelate salt from which the trans-base (+)-(1*S*,3*R*)-*trans*-3-(3,4-dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-**9**) was obtained. A levorotatory hydrochloride salt was prepared from this (+)-base. The filtrates from the (−)-(*R*)-*O*-acetylmandelate salt were basified to give a base enriched with (−)-(1*R*,3*S*)-*trans*-3-(3,4-dichlorophenyl)-6-methoxyl-*N*-methyl-1-indan-

Scheme 2[a]



[a] Reagents and conditions: (a) (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, C_6H_6, room temp; (b) aniline, LiCl, 150 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) *R*-(−)-*O*-acetylmandelic acid, acetone; (b) 20% NH_4OH; (c) 48% HBr, reflux; (d) (1) NH_4OH, (2) *S*-(+)-*O*-acetylmandelic acid, acetone.

amine ((−)-(1*R*,3*S*)-**9**). Treatment with *S*-(+)-*O*-acetylmandelic acid, recrystallization of the dextrorotatory diastereomeric salt, and subsequent basification gave multigram quantities of the desired (−)-(1*R*,3*S*)-*trans*-**9** as the free base. It was converted to the dextrorotatory hydrochloride salt. The (−)-(1*R*,3*S*)-*trans*-**9** base was also converted to its ditoluoyl-D-tartaric acid salt for an X-ray crystallographic study (Figure 1). The optical purity of both enantiomers of trans amine **9** was found to be >99% ee, determined as described above in the chromatographic resolution of **9**.

Single-crystal X-ray diffraction analysis of the ditoluoyl-D-tartaric acid salt of (−)-(1*R*,3*S*)-*trans*-**9** gave definitive proof of the 1*R*,3*S* absolute configuration (Figure 1). The fact that the anion was a D-tartrate salt was used to determine the absolution configuration of the cation. The (−)-(1*R*,3*S*)-*trans*-**9** and (+)-(1*S*,3*R*)-*trans*-**9** were converted to the phenolic compounds (−)-(1*R*,3*S*)-*trans*-3-(3,4-dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-**11**) and (+)-(1*S*,3*R*)-*trans*-3-(3,4-dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-**11**), respectively, with HBr. Compounds **7**, **8**, and **10** were not resolved because of their weak affinity for the norepinephrine transporter (Table 1).

We found that in order to prepare a long-chain decanoate ester, it was necessary to first protect the

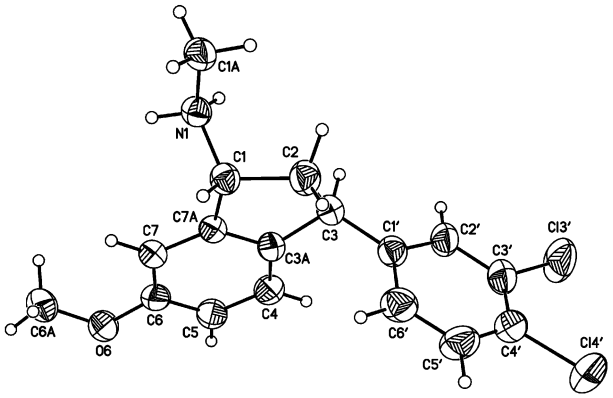


Figure 1. Results of the X-ray analysis on (−)-**9** drawn from the experimentally determined coordinates with the thermal parameters at the 20% probability level.

secondary amine with a BOC protecting group and then to react the resulting phenolic compound with 2.8 equiv of decanoic anhydride to form the decanoate ester. Removal of the BOC group under mild conditions (CAN, reflux)[16] afforded the decanoate ester **15** (Scheme 4). Ester **15** was stable for at least a month at room temperature.

Results and Discussion

The binding data shown in Table 1 indicate that all of the compounds have the highest affinity at the 5-HT transporter, followed by the DA and then the NE transporter. 3-(3,4-Dichlorophenyl)-6-methoxy-*N*, *N*-diethyl-1-indanamines **8**, **10**, and **12** bind poorly with the NE transporter. *N*-Methyl-1-indanamines are generally potent at all three transporters. As reported,[12] racemic trans amine **9** is more potent than the racemic cis amine **7**. Resolution of the trans amine **9** gave the two enantiomers (+)-(1*S*,3*R*)-**9** and (−)-(1*R*,3*S*)-**9**. The (−)-(1*S*,3*R*)-**9**·HCl is about twice as potent as the racemate at all of the transporters and considerably more potent than its enantiomer (+)-(1*R*,3*S*)-**9**·HCl. This trend was also observed for the trans phenolic enantiomers (−)-(1*R*,3*S*)-**11** and (+)-(1*S*,3*R*)-**11**, derived from the methoxy compounds (−)-(1*R*,3*S*)-**9** and (+)-(1*S*,3*R*)-**9**, respectively.

On the basis of the fact that there is a significant difference in the binding affinities of the two enantiomers, we next tested the effects of enantiomers (−)-(1*S*,3*R*)-**9**·HCl, (+)-(1*R*,3*S*)-**9**·HCl and (−)-(1*R*,3*S*)-**11**, (+)-(1*S*,3*R*)-**11** on the inhibition of DA, 5-HT, and NE uptake (Table 2). In the methoxy series, the (+)-(1*R*,3*S*)-**9**·HCl enantiomer is better able to inhibit the uptake of neurotransmitters at the DA, 5-HT, and NE transporters, and with the phenolic compounds, the (−)-(1*R*,3*S*)-**11** enantiomer was better. In both cases the enantiomer with the 1*R*,3*S* configuration was the more potent ligand.

The in vivo activity of (−)-(1*R*,3*S*)-**11** was assessed using in vivo microdialysis. As shown in Figure 2, iv administration of (−)-(1*R*,3*S*)-**11** produced significant dose-dependent elevations in extracellular DA (F[3,19] = 8.05, $P < 0.001$) and 5-HT (F[3,19] = 7.11, $P < 0.002$) in rat nucleus accumbens. The rise in both transmitters was slow in onset and persistent in duration, even with iv administration. Figure 3 shows the effects of pretreatment with (−)-(1*R*,3*S*)-**11** (0.5 mg/kg, iv) on methamphetamine-induced (0.5 mg/kg, iv) DA release. As expected, methamphetamine administration to saline-pretreated rats produced a rapid and robust increase in extracellular DA. (−)-(1*R*,3*S*)-**11** significantly blunted the peak effect of methamphetamine on dialysate DA (F[1,20] = 10.32, $P < 0.01$). Figure 4 shows the effect of (−)-(1*R*,3*S*)-**11** on methamphetamine-induced 5-HT release in the same rats. In contrast to the DA data, (−)-(1*R*,3*S*)-**11** pretreatment did not significantly affect the peak effect of methamphetamine. A valid interpretation of the effects of (−)-(1*R*,3*S*)-**11** pretreatment is complicated by the fact that (−)-(1*R*,3*S*)-**11** alone increases dialysate transmitter levels. In an attempt to account for this problem, the data in Figure 5 show the effects of (−)-(1*R*,3*S*)-**11** on methamphetamine-induced transmitter release expressed as a percent of preexisting baseline (i.e., baseline immediately prior to methamphetamine challenge). When the data are expressed in this manner, (−)-(1*R*,3*S*)-**11** pretreatment significantly reduced the peak effect of methamphetamine on the release of DA (F[1,20] = 13.13, $P < 0.001$) and 5-HT (F[1,20] = 4.27, $P < 0.05$) in vivo.

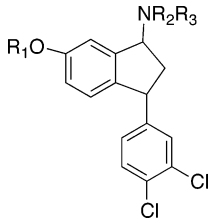
The ability of (−)-(1*R*,3*S*)-**11** to persistently occupy DA and 5-HT transporter binding sites was assessed using ex vivo autoradiography techniques. Rats were injected with saline and 1 or 3 mg/kg of (−)-(1*R*,3*S*)-**11** and were sacrificed 1 h later. Slide-mounted sections were prepared and labeled with [^{125}I]RTI-55 under conditions chosen to minimize dissociation of prebound (−)-(1*R*,3*S*)-**11**. As shown visually in Figure 6, (−)-(1*R*,3*S*)-**11** produced a dose-dependent reduction in 5-HT transporter, but not DA transporter, binding sites. When quantified, the effect on 5-HT transporters was quite striking, especially compared to the lack of effect seen with DA transporters (Figure 7).

Conclusions

In our efforts to develop a single molecular entity that would block the effects of methamphetamine at all three biogenic amine transporters, we synthesized a series of 3-(3,4-dichlorophenyl)-1-indanamine oxygen-containing derivatives. All of these compounds had high affinities at the 5-HT transporter. Their affinities at the NE transporter, however, were quite different. The relative and absolute stereochemistry at the C1 and C3 positions of the indane ring had profound effect on the pharmacological activity of the compound. The binding assays and uptake inhibition data indicated that (−)-(1*R*,3*S*)-*trans*-3-(3,4-dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-**11**) had high affinity and high uptake inhibition potency at all three transporters. Initial experiments indicated that *trans*-(−)-(1*R*,3*S*)-**11** blocked methamphetamine-induced release of DA, 5-HT, and NE.[17] Consistent with this observation, in vivo microdialysis experiments indicated that *trans*-(−)-(1*R*,3*S*)-**11** inhibited DA and 5-HT transporters, since iv administration of *trans*-(−)-(1*R*,3*S*)-**11** elevated extracellular DA and 5-HT in a dose-dependent manner. Although we did not measure extracellular NE in these experiments, we anticipate that *trans*-(−)-(1*R*,3*S*)-**11** will also elevate NE.

When assessing the effect of putative blocking agents on methamphetamine-induced neurotransmitter release, it is important to realize that the uptake inhibitor

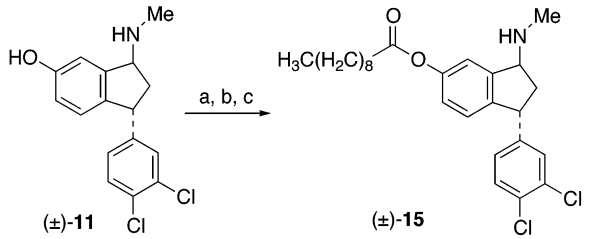
Table 1. Binding Affinities of 3-(3,4-Dichlorophenyl)-1-indanamines at the DA, 5-HT, and NE Transporters



compd	R_1	R_2	R_3	trans or cis	*R* or *S*	$K_i \pm$ SD,[a] nM DA[b]	5-HT[b]	NE[c]
8	CH_3	CH_2CH_3	CH_2CH_3	cis	racemate	1310 70	26 ± 2	>4700
10	CH_3	CH_2CH_3	CH_2CH_3	trans	racemate	140 ± 8	1.3 ± 0.1	1010 ± 57
12	H	CH_2CH_3	CH_2CH_3	trans	racemate	40 ± 4	0.7 ± 0.07	1330 ± 160
7	CH_3	H	CH_3	cis	racemate	96 ± 2	0.3 ± 0.03	170 ± 19
9	CH_3	H	CH_3	trans	racemate	12 ± 0.3	1.1 ± 0.08	15 ± 0.6
(+)-**9**·HCl	CH_3	H	CH_3	trans	1*R*, 3*S*	9 ± 0.3	0.7 ± 0.1	7 ± 0.7
(−)-**9**·HCl	CH_3	H	CH_3	trans	1*S*, 3*R*	600 ± 32	51 ± 4	820 ± 35
11	H	H	CH_3	trans	racemate	11 ± 0.2	3 ± 0.2	24 ± 1.4
(−)-**11**	H	H	CH_3	trans	1*R*, 3*S*	12 ± 0.7	2 ± 0.3	9 ± 1
(+)-**11**	H	H	CH_3	trans	1*S*, 3*R*	86 ± 2	43 ± 4	440 ± 30
indatraline (**1**)[d]						1.7 ± 0.2[e]	0.4 ± 0.04[e]	6 ± 0.4[e]

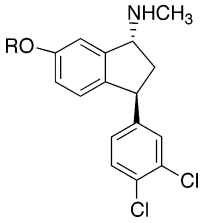
[a] The K_i values of the test agents were determined in the above assays as described in Biological Methods in ref 16. [b] Dopamine (DA) and serotonin (5-HT) transporter binding sites labeled with [^{125}I]RTI-55. [c] Norepinephrine (NE) transporter site labeled with [^{3}H]nisoxetine. [d] Physical data can be found in ref 10. [e] Data from ref 9.

Scheme 4[a]



[a] Reagents and conditions: (a) di-*tert*-butyl dicarbonate, Et_3N, MeOH; (b) decanoic anhydride, NaOH, 2-propanol/water; (c) ceric ammonium nitrate, MeCN, room temp, then reflux.

Table 2. Reuptake Inhibitory Activities of Indatraline Analogues at the DA, 5-HT, and NE Transporters



compd	R	*R* or *S*	Ki ± SD,[a] nM DA	5-HT	NE
(+)-**9**·HCl	CH_3	1*R*, 3*S*	12 ± 0.3	19 ± 1.9	34 ± 1.8
(−)-**9**·HCl	CH_3	1*S*, 3*R*	600 ± 23	109 ± 4	650 ± 33
(−)-**11**	H	1*R*, 3*S*	3 ± 0.1	2 ± 0.1	20 ± 2
(+)-**11**	H	1*S*, 3*R*	32 ± 1	41 ± 1	160 ± 12
indatraline (**1**)[b]			2 ± 0.10[c]	3 ± 0.16[c]	11 ± 1.3[c]

[a] The K_i value of the test agents were determined in the above assays as described in Biological Methods in ref 18. [b] Physical data can be found in ref 10. [c] Data from ref 9.

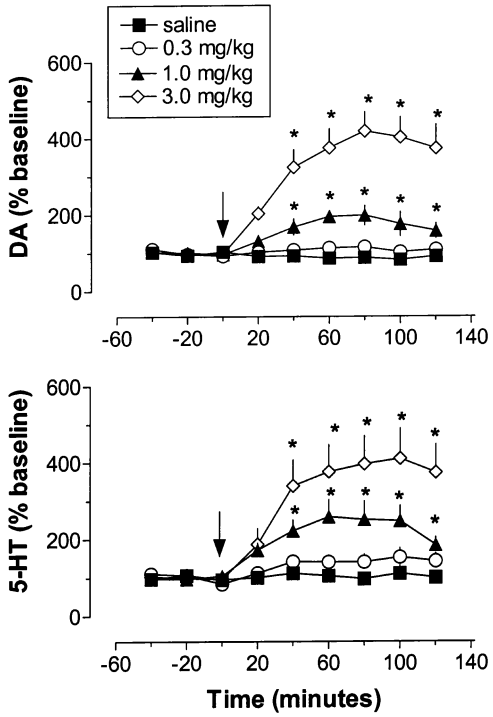


Figure 2. Effects of (−)-**11** on extracellular DA and 5-HT in rat nucleus accumbens. Rats received iv injections of saline or (−)-**11** at time zero, and dialysate samples were collected at 20 min intervals for 2 h postinjection. Data are the mean ± SEM for $n = 6$ rats/group expressed as % baseline. * = $P <$ 0.05 compared to saline-injected control rats.

itself will elevate extracellular neurotransmitter. The effect of the uptake inhibitor on methamphetamine-induced neurotransmitter release can be calculated in two ways. The first is the reduction in neurotransmitter release compared to the saline baseline (peak effect minus saline baseline, type 1 reduction) and second is the reduction in neurotransmitter release compared to the baseline observed in the presence of the uptake inhibitor (peak effect minus blocker baseline, type 2 reduction). On the basis of our experience with GBR 12909 and GBR 12909 decanoate, we expected that *trans*-(−)-(1*R*,3*S*)-**11** would decrease methamphetamine-induced neurotransmitter release by both measures. Instead, *trans*-(−)-(1*R*,3*S*)-**11** decreased methamphetamine-induced DA and 5-HT release only with the second measurement method (Figure 5). Also, on the basis of our experience with GBR 12909 and the

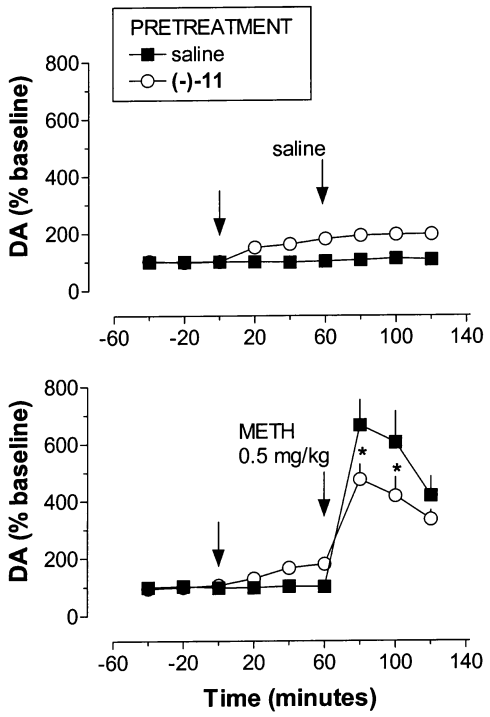


Figure 3. Effect of pretreatment with (−)-**11** (0.5 mg/kg, iv) on methamphetamine-induced (0.5 mg/kg, iv) DA release. * = $P < 0.05$ with respect to saline-pretreated rats.

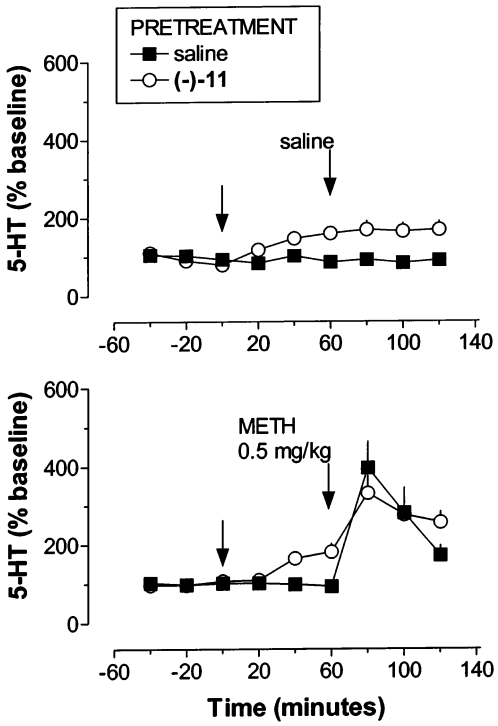


Figure 4. Effect of pretreatment with (−)-**11** (0.5 mg/kg, iv) on methamphetamine-induced (0.5 mg/kg, iv) 5-HT release.

similarly relatively high affinity of *trans*-(−)-(1*R*,3*S*)-**11** for DA transporters, we anticipated that administration of *trans*-(−)-(1*R*,3*S*)-**11** would persistently occupy DA transporters. We have speculated, for example, that the ability of GBR 12909 to persistently occupy DA transporters contributes to its ability to almost completely attenuate methamphetamine-induced DA release. The data (Figures 6 and 7) showed, however, that *trans*-(−)-(1*R*,3*S*)-**11** persistently occupies 5-HT but not

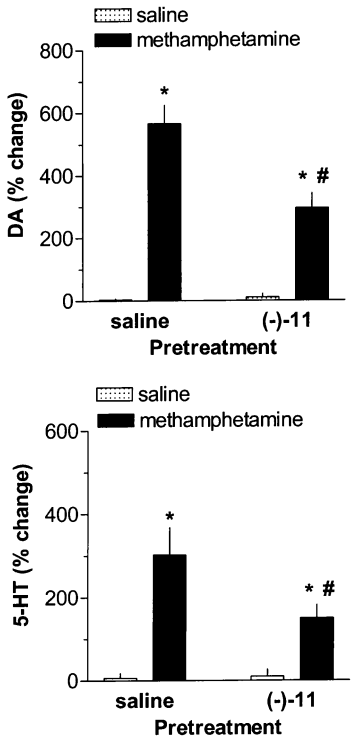


Figure 5. Effect of pretreatment with (−)-**11** (0.5 mg/kg, iv) on methamphetamine-induced (0.5 mg/kg, iv) DA and 5-HT release when expressed as % change in pre-existing baseline. * = $P < 0.05$ compared to acute saline challenge, and # = $P <$ 0.05 with respect to saline-pretreated rats.

DA transporters. The modest effect of *trans*-(−)-(1*R*,3*S*)-**11** on methamphetamine-induced neurotransmitter release and its inability to persistently block DA transporters in the rat suggest that further research will be needed to determine what properties of reuptake inhibitors predict high efficacy as inhibitors of methamphetamine-induced neurotransmitter release.

Viewed collectively, these data indicate that factors beyond ligand affinity contribute to the ability of an uptake blocker to attenuate methamphetamine-induced neurotransmitter release. Although 1*R*,3*S*-*trans*-(−)-**11** has high affinity for DA and 5-HT transporters, it persistently occupies only 5-HT transporters and has only a modest effect on methamphetamine-induced neurotransmitter release. This compound will be further evaluated in monkeys to see whether there are species differences, and the results will be reported in due course.

Experimental Section

Chemistry. Melting points were determined on a MEL-TEMP II capillary melting-point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on Varian Gemini-300 and Bruker DMX500 spectrometers. Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer in the chemical ionization mode (MS, CI-NH_3) and a JEOL SX102a mass spectrometer in the FAB mode with xenon gas. Optical rotations were obtained at 20 °C on a Perkin-Elmer 341 polarimeter. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220−240). Medium-pressure column chromatography (using silica gel) was carried out at 30 psi with an RT Scientific Co. (Manchester, NH) high-pressure chromatography system.

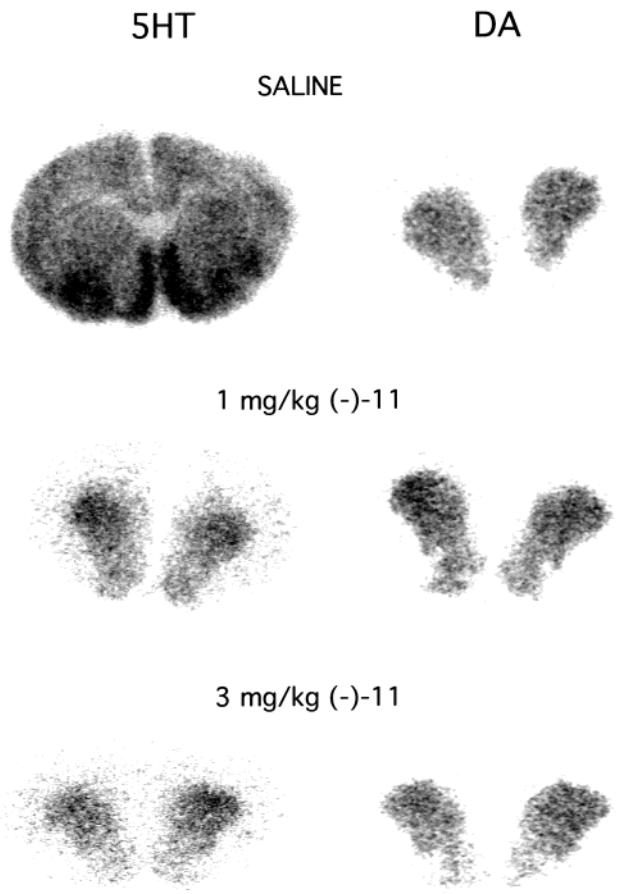


Figure 6. Ex vivo autoradiographic assessment of the ability of (−)-**11** to persistently occupy DA and 5-HT transporter binding sites.

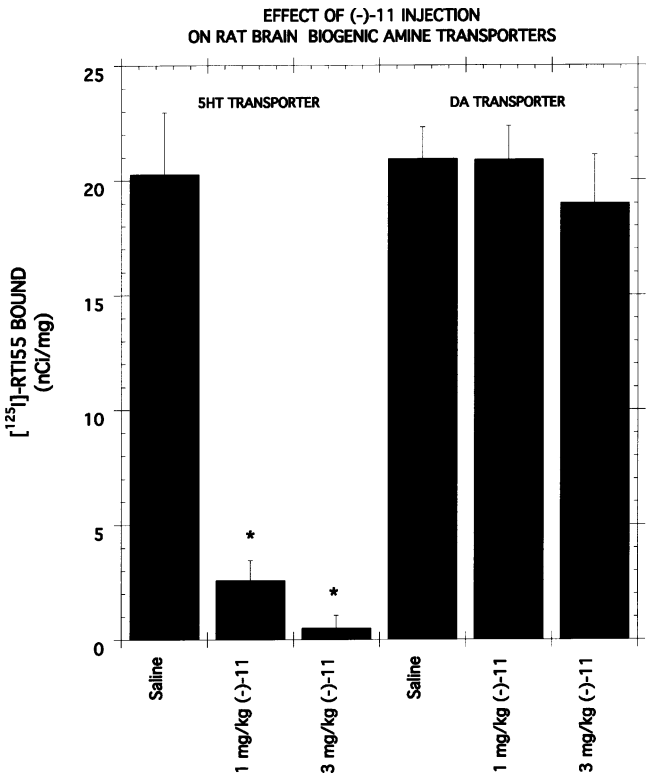


Figure 7. Effect of (−)-**11** on rat brain biogenic amine transporters. * = $P < 0.05$ compared to saline-injected control rats.

Atlantic Microlabs, Inc., Norcross, Georgia, performed elemental analyses, and the results were within ±0.4% of the theoretical values.

1-(3,4-Dichlorophenyl)-3-(3-methoxylphenyl)-1-propen-3-one (2). By use of a previously described procedure,[18,19] **2** was prepared[11] in 93% yield as a colorless solid from 3,4-dichlorobenzaldehyde and 3-methoxyacetophenone: mp 116 °C; ^{1}H NMR δ 7.74−7.14 (m, 8H), 3.89 (s, 3H).

3-(3,4-Dichlorophenyl)-6-methoxylindan-1-one ((±)-3). A solution of propenone **2** (34.0 g, 110.0 mmol) in trifluoroacetic acid (200 mL) was heated at 120 °C for 4 h in a sealed tube. The trifluoroacetic acid was removed in vacuo, and the resultant oil was poured into ice/water. The aqueous layer was separated and extracted with ethyl acetate (400 mL). The combined organic fractions were neutralized by washing with saturated $NaHCO_3$ solution. After the fractions were washed with brine and dried (Na_2SO_4), the solvent was removed in vacuo and the product was crystallized from isopropyl ether to afford 26.1 g (76.8%) of (±)-**3**: mp 81 °C (lit.[12] 67−69 °C); ^{1}H NMR δ 7.49−6.93 (m, 6H), 4.51−4.47 (m, 1H), 3.88 (s, 3H), 3.30−3.21 (m, 1H), 2.65−2.58 (m, 1H); EIMS *m*/*z* 307 $(M)^+$.

3-(3,4-Dichlorophenyl)-6-methoxylindan-1-ol ((±)-4). $NaBH_4$ (2.34 g, 62.0 mmol) was added portionwise to a solution of ketone (±)-**3** (19.15 g, 62.4 mmol) in MeOH (200 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and the MeOH was evaporated in vacuo. The resulting oil was partitioned between diethyl ether and H_2O. The aqueous layer was extracted with diethyl ether, the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Crystallization from a mixture of hexane (40 mL) and EtOAc (40 mL) gave (±)-**4** as a white solid (14.7 g, 76%): mp 102 °C (lit.[12] 104−106 °C); ^{1}H NMR δ 7.40−6.83 (m, 6H), 5.26−5.24 (m, 1H), 4.11 (t, J = 6.2 Hz, 1H), 3.84 (s, 1H), 3.06−2.97 (m, 1H), 1.89−1.83 (m, 1H); CIMS *m*/*z* 310 $(MH)^+$.

(±)-*cis*- and *trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((±)-7 and (±)-9). Thionyl chloride (17.32 g, 145.6 mmol) was added dropwise with stirring to a solution of (±)-**4** (30.0 g, 97.0 mol) in dioxane (500 mL) at 0−10 °C. The mixture was warmed to room temperature and was stirred for 3 h. Then it was quenched with saturated aqueous $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give an isomeric mixture of the crude cis and trans chlorides in a 7:3 ratio, respectively, that were dissolved in toluene (600 mL). This mixture was cooled in a dry ice/acetone bath, and methylamine was passed in until 80.0 g of amine was dissolved in the solution. The mixture was warmed at 40 °C in a sealed bottle for 60 h. After removal of the volatile material in vacuo, the residue was partitioned between H_2O and diethyl ether (400 mL each). The diethyl ether layer was separated and extracted with 10% aqueous citric acid (400 mL), and the extract was basified with concentrated NH_4OH and extracted with diethyl ether (400 mL). The diethyl ether was evaporated to give a mixture of the cis and trans bases ((±)-**7** and (±)-**9**, respectively) as a brown oil in a 3:7 ratio. This mixture of bases (20.0 g, 62.0 mmol) was dissolved in methanol (200 mL), and oxalic acid (2.79 g, 31 mmol, 1.0 acid equivalent) was added. After the mixture stood for 2 h at room temperature, the precipitate was collected and washed with methanol (50 mL). The solid was partitioned between 10% aqueous NH_4OH and diethyl ether (200 mL each). The aqueous layer was extracted with diethyl ether (75 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated. The resulting oil was dissolved in acetone (200 mL), and the solution was acidified with HCl in diethyl ether. The crystalline material that formed was recrystallized from a mixture of acetone (500 mL) and H_2O (70 mL) to afford 10.3 g (29.6% from (±)-**4**) of the trans salt, (±)-**9**·HCl: mp 248 °C; TLC (CH_2Cl_2/MeOH/concentrated NH_4OH, 24:1:0.05) R_f = 0.45; ^{1}H NMR δ 7.30−6.71 (m, 6H), 4.18 (t, J = 7.1 Hz, 1H), 4.06 (t, J = 6.9 Hz, 1H), 3.75 (s, 1H), 2.96−2.84 (m, 1H), 2.48 (s, 1H), 1.69−1.55 (m, 1H); CIMS *m*/*z* 323 $(MH)^+$. Anal. ($C_{17}H_{17}NOCl_2$·HCl) C, H, N, Cl.

The filtrate from the oxalate salt precipitation was evaporated, and the residue was partitioned between aqueous NH_4OH and diethyl ether. The organic portion was dried (Na_2SO_4) and evaporated. The residue was dissolved in acetone, and the solution was acidified with HCl in diethyl ether. The crystalline material was collected after 1 h at room temperature and recrystallized twice from 95% ethanol/diethyl ether to afford 1.3 g (3.7% from (±)-**4**) of the salt of the cis isomer, (±)-**7**·HCl: mp 267 °C (lit.[12] 262−264 °C); TLC (CH_2Cl_2/MeOH/concentrated NH_4OH, 24:1:0.05) $R_f = 0.57$; ^{1}H NMR δ 7.36−6.78 (m, 6H), 4.44 (t, $J = 7.2$ Hz, 1H), 4.26−4.23 (m, 1H), 3.82 (s, 3H), 2.51 (s, 3H), 2.49−2.40 (m, 1H), 2.30−2.21 (m, 1H); CIMS *m*/*z* 323 $(MH)^+$. Anal. ($C_{17}H_{17}NOCl_2$·HCl) C, H, N, Cl.

(±)-*cis*- and *trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*,*N*-diethyl-1-indanamine ((±)-8 and (±)-10). Thionyl chloride (2.60 g, 21.8 mmol) was added to a solution of (±)-**4** (4.5 g, 14.6 mmol) in dioxane at 0 °C. The mixture was warmed to room temperature and was stirred for 3 h. After the reaction was quenched with saturated aqueous $NaHCO_3$, the layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give an isomeric mixture of the crude cis and trans chlorides. The mixture was dissolved in toluene and diethylamine (8.0 g, 0.11 mol) and was heated at 40 °C for 60 h. The mixture was cooled and evaporated in vacuo. The residue was dissolved in diethyl ether, washed with H_2O, and extracted with 10% aqueous citric acid. The extract was basified with concentrated ammonium hydroxide and extracted with diethyl ether. The solvent was evaporated to give a mixture of cis and trans amines in a 3:7 ratio. The mixture was dissolved in MeOH and was acidified with a saturated solution of HCl in diethyl ether. The cis amine hydrochloride ((±)-**8**·HCl) crystallized as a white solid. It was recrystallized twice from a mixture of ethanol and diethyl ether to give (±)-**8**·HCl (954 mg, 2.63 mmol, 18% yield from (±)-**4**): mp 200 °C; ^{1}H NMR δ 7.39−6.75 (m, 6H), 4.54 (t, $J = 8.4$ Hz, 1H), 4.04 (t, $J = 9.3$ Hz, 1H), 3.83 (s, 1H), 2.73−2.39 (m, 5H), 1.88−1.77 (m, 1H), 1.12 (t, $J = 7.2$ Hz, 4H); CIMS *m*/*z* 365 (MH^+). Anal. ($C_{20}H_{23}NOCl_2$·HCl) C, H, N, Cl. The above filtrate was concentrated, basified, and extracted with diethyl ether. The diethyl ether extract was dried, and the solvent was removed in vacuo. The residue was dissolved in acetone and acidified with HCl in diethyl ether to give the trans amine (±)-**10**·HCl. The hydrochloride salt was recrystallized from a mixture of acetone and diethyl ether to give pure (±)-**10**·HCl (1.75 g, 4.82 mmol, 33% yield from (±)-**4**): mp 131 °C; ^{1}H NMR δ 7.32−6.77 (m, 6H), 4.67 (t, $J = 6.6$ Hz, 1H), 4.33 (dd, $J = 3.9$ Hz, $J = 13.2$ Hz, 1H), 3.83 (s, 1H), 2.62−2.37 (m, 5H), 2.03−1.95 (m, 1H), 1.06 (t, $J = 7.0$ Hz, 4H); CIMS *m*/*z* 365 $(MH)^+$. Anal. ($C_{20}H_{23}NOCl_2$·HCl) C, H, N, Cl.

(±)-*trans*-3-(3,4-Dichlorophenyl)-6-hydroxyl-*N*-methyl-1-indanamine ((±)-11). BBr_3 was added slowly to a solution of trans amine (±)-**9** (1.60 g, 4.98 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into a well-stirred mixture of ice (30 g) and concentrated NH_4OH (8 mL), and the two-phase system was kept at 0 °C overnight. The solid was collected to give 1.09 g (3.54 mmol, 71% yield) of (±)-**11**. The compound was recrystallized from EtOH/CH_2Cl_2 (1:1) to give a white solid: mp 214 °C (lit.[12] 206−210 °C); ^{1}H NMR δ 7.36−6.70 (m, 6H), 4.42 (t, $J = 7.8$ Hz, 1H), 4.22 (m, 1H), 2.50 (s, 3H), 2.50−2.41 (m, 1H), 2.27−2.17 (m, 1H); CIMS *m*/*z* 309 $(MH)^+$. Anal. ($C_{16}H_{15}NOCl_2$) C, H, N, Cl.

***trans*-1-[3-(3,4-Dichlorophenyl)-6-methoxy-indan-1-yl]-1-methyl-3-(1-naphthalen-2-yl-ethyl)urea ((+)-13 and (−)-14).** A mixture of racemic **9** (1.84 g, 5.7 mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (1.127 g, 5.7 mmol) in benzene (30 mL) was stirred at room temperature for 1 h. After removal of solvent, the compounds in the residue was separated with medium-pressure column chromatography (eluted with 20% ethyl acetate in hexanes) to give ureas (+)-**13** and (−)-**14** as white films in quantitative yield. (+)-**13**: mp 87−88 C; $[\alpha]^{20}_D$ +42.0 (*c* 0.98, $CHCl_3$); ^{1}H NMR 8.20 (d, $J = 8.1$ Hz, 1H), 7.89−7.85 (m, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.58−7.43 (m, 3H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 6.94−6.78 (m, 4H), 6.11 (t, $J = 7.5$ Hz, 1H), 5.96−5.78 (m, 1H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.34 (dd, $J = 8.4$ and 4.5 Hz, 1H), 3.81 (s, 3H), 2.57 (s, 3H), 2.49−2.28 (m, 2H), 1.71 (d, $J = 6.9$ Hz, 3H); MS (FAB) *m*/*z* 519 $(M)^+$. Anal. ($C_{30}H_{28}Cl_2N_2O_2$) C, H, N, Cl. (−)-**14**: mp 88−89 C; $[\alpha]^{20}_D$ −117.4 (*c* 0.89, $CHCl_3$); ^{1}H NMR 8.24 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.60−7.44 (m, 3H), 7.30 (d, $J = 8.1$ Hz, 1H), 7.14 (d, $J = 2.1$ Hz, 1H), 6.93 (d, $J = 7.8$ Hz, 1H), 6.87 (dd, $J = 8.4$ and 2.1 Hz, 1H), 6.78 (dd, $J = 8.1$ and 2.1 Hz, 1H), 6.68 (d, $J = 2.1$ Hz, 1H), 6.17 (t, $J = 8.1$ Hz, 1H), 5.96−5.86 (m, 1H), 4.72 (d, $J = 7.2$ Hz, 1H), 4.40 (dd, $J = 8.7$ and 3.9 Hz, 1H), 3.74 (s, 3H), 2.56 (s, 3H), 2.51−2.32 (m, 2H), 1.70 (d, $J = 6.6$ Hz, 1H); MS (FAB) *m*/*z* 519 $(M)^+$. Anal. ($C_{30}H_{28}Cl_2N_2O_2$·$0.5H_2O$) C, H, N, Cl.

(−)-(1*R*,3*S*)-*trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((−)-1*R*,3*S*-9) from (+)-*trans*-1-[3-(3,4-Dichlorophenyl)-6-methoxy-indan-1-yl]-1-methyl-3-(1-naphthalen-2-yl-ethyl)-urea ((+)-13), and (+)-(1*S*,3*R*)-*trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-9) from (−)-*trans*-1-[3-(3,4-Dichlorophenyl)-6-methoxy-indan-1-yl]-1-methyl-3-(1-naphthalen-2-ylethyl)urea ((−)-14). A mixture of urea (+)-**13** (129.3 mg, 0.248 mmol) and lithium chloride (12.7 mg, 0.3 mmol) in aniline (1.5 mL) was heated at 150 °C for 6 h. After removal of aniline in vacuo, the residue was diluted with ethyl acetate and washed with 2 N HCl. The aqueous layer was extracted with ethyl acetate (2×). The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified with column chromatography (eluted with 3% MeOH in $CHCl_3$ + 0.1% diethylamine) to give (−)-(1*R*,3*S*)-**9** (55.2 mg, 69%). A similar hydrolysis of urea (−)-*trans*-1-[3-(3,4-dichlorophenyl)-6-methoxyindan-1-yl]-1-methyl-3-(1-naphthalen-2-ylethyl)urea ((−)-**14**, 124.6 mg, 0.24 mmol) gave (+)-(1*S*,3*R*)-**9** (55.0 mg, 71%).

The enantiomeric excess of (−)-(1*R*,3*S*)-*trans*-3-(3,4-dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-**9**)- and (1*S*,3*R*)-(+)-*trans*-3-(3,4-dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-**9**) was determined as follows.[15,20,21] The (−)-(1*R*,3*S*)-**9** and (+)-(1*S*,3*R*)-**9** were converted to their diastereomeric ureas (+)-**13** and (−)-**14**, respectively, by reaction with (−)-(*R*)-1-(1-naphthyl)ethyl isocyanate. The ^{1}H NMR 500 MHz spectrum of a 1:1 mixture of **13** and **14** showed the methoxy group at 3.74 and 3.81 ppm in a ratio of 1:1. The baseline separation allowed quantitation of the signals. The ^{1}H NMR spectrum of (+)-**13** showed two singlets at 3.74 and 3.81 ppm in a ratio of 99.9:0.1 (99.8% ee), whereas that of (−)-**14** showed two singlets at 3.74 and 3.81 ppm in a ratio of 1.2:98.8 (97.6% ee). The addition of known amounts of (−)-**14** to (+)-**13** increased the size of the second singlet at 3.81 ppm in the spectrum of (+)-**13**. The size of the 3.74 ppm signal increased, again as expected, when a known amount of (+)-**13** was added to (−)-**14**.

1*R*,3*S*-(−)-*trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-9) and (−)-1*S*,3*R*-*trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-9) from Diastereomeric Optical Resolution of (±)-*trans*-3-(3,4-Dichlorophenyl)-6-methoxyl-*N*-methyl-1-indanamine ((±)-9). A solution of (±)-**9** (34.33 g, 0.107 mol), prepared from (±)-9·HCl, in acetone (500 mL) was treated with (−)-(*R*)-*O*-acetylmandelic acid (20.68 g, 0.107 mol). Crystallization occurred rapidly upon scratching. After 1 h at room temperature, the crystals were collected, washed with acetone, and dried to give 24.2 g of fine cotton-like needles, mp 174−175 °C. Recrystallization was accomplished by dissolving this solid in a minimum amount of boiling methanol (ca. 200 mL) and reducing the volume by boiling with efficient stirring until crystals appeared. At this point acetone (900 mL) was added and boiling continued until a thick slurry of needles was obtained (volume ca. 500 mL). This was repeated with 800 mL of acetone to give a thick slurry of crystals in ca. 600 mL of acetone. After addition of an additional 600 mL of acetone, the mixture was brought to room temperature and allowed to stand for 1 h. The crystals were

collected, washed with acetone, and dried to give the *R*-(−)-*O*-acetylmandelate salt of the (+)-(1*S*,3*R*)-**9** base (18.65 g, 67.8%): mp 176−177 °C; $[\alpha]^{20}_{D}$ −53.1° (*c* 1.1, MeOH). Anal. ($C_{27}H_{27}Cl_2NO_5$) C, H, N. The (+)-1*S*,3*R*-**9** base was obtained as an oil from its diastereomeric salt using 20% ammonium hydroxide and diethyl ether extraction, $[\alpha]^{20}_{365}$ +13.4° (*c* 1.2, MeOH). The (+)-(1*S*,3*R*)-**9** base from another preparation was rendered solvent-free by sparging with nitrogen at 60 °C until constant weight was reached. This material crystallized: mp 45−47 C; $[\alpha]^{20}_{365}$ +13.8° (*c* 1.365, MeOH). The optical purity of the (+)-(1*S*,3*R*)-**9** base, which was determined as above from the NMR of the urea obtained from reaction with (−)-*R*-1-(1-naphthyl)ethyl isocyanate, was >99.4% ee. The (−)-(1*S*,3*R*)-**9**·HCl salt was formed upon treatment of the (+)-(1*S*,3*R*)-**9** base with HCl in diethyl ether. It was recrystallized from 2-propanol isopropyl ether: mp 225−226 °C; $[\alpha]^{20}_{365}$ −16.4° (*c* 0.9, MeOH). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N.

The filtrates from the crystallization and recrystallization of the (+)-(1*S*,3*R*)-**9**·(−)-(*R*)-*O*-acetylmandelate salt were combined, evaporated, and converted to the free base (NH_4OH, diethyl ether) to give material enriched in (−)-(1*R*,3*S*)-**9** (21.75 g, 0.0675 mol). (+)-(*S*)-*O*-acetylmandelic acid (13.1 g, 0.068 mol) was added to the enriched material in acetone. After standing for 1 h at room temperature, a salt (24.1 g) was obtained that was recrystallized in a manner similar to its diastereomer (see above) to give 20.1 g (73.1%) of the (+)-(*S*)-O-acetylmandelic acid salt of (−)-(1*R*,3*S*)-**9**: mp 177.5−178.5 C; $[\alpha]^{20}_{D}$ +53.4° (*c* 0.91, MeOH). Anal. ($C_{27}H_{27}Cl_2NO_5$) C, H, N. (−)-(1*R*,3*S*)-**9** was obtained as an oil from the diastereomeric salt in a manner similar to its diastereomeric relative (see above): $[\alpha]^{20}_{365}$ −13.9° (*c* 1.68, MeOH). The optical purity of the (−)-(1*R*,3*S*)-**9** base, determined from the NMR of the urea obtained from reaction with (−)-*R*-1-(1-naphthyl)ethyl isocyanate, was found to be >99.8% ee. The (−)-(1*R*,3*S*)-**9** base was converted to its (+)-(1*R*,3*S*)·HCl salt: mp 225−226 °C; $[\alpha]^{20}_{365}$ +14.85° (*c* 0.93, MeOH). Anal. ($C_{17}H_{17}Cl_2NO$·HCl) C, H, N. The (−)-(1*R*,3*S*)-**9** base was also converted to its di-*p*-toluoyl-D-(+)-tartrate salt by addition of an equimolar amount of acid to the base in MeOH. Recrystallization from MeOH afforded the pure salt: mp 164−166 °C. Anal. ($C_{37}H_{35}Cl_2NO_9$·0.5H_2O) C, H, N.

(−)-(1*R*,3*S*)-*trans*-3-(3,4-Dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((−)-(1*R*,3*S*)-11). A mixture of (−)-(1*R*,3*S*)-**9** (6.3 g, 19.6 mol) and 48% HBr (85 mL) was heated at reflux for 45 min. Most of the HBr was removed in vacuo at 60 °C, the residual oil was dissolved in H_2O (150 mL), and the pH was adjusted to 9.5 with concentrated NH_4OH. The solid formed after standing at 4 °C overnight was recrystallized from 95% EtOH to give pure (−)-(1*R*,3*S*)-**11** (2.83 g). An additional amount of (1*R*,3*S*)-(−)-**11** was obtained by adjustment of the pH of the mother liquor from the above recrystallization to 9.5 with concentrated NH_4OH, followed by recrystallization from 95% EtOH (total yield 4.81 g, 79.6%): mp 202−203 °C; $[\alpha]^{20}_{D}$ −19.2° (*c* 0.9, MeOH); $[\alpha]^{20}_{365}$ −77.3° (*c* 0.9, MeOH). Anal. ($C_{16}H_{15}Cl_2NO$) C, H, N.

(+)-(1*S*,3*R*)-*trans*-3-(3,4-Dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine ((+)-(1*S*,3*R*)-11). The (+)-(1*S*,3*R*)-**11** isomer was prepared in 76% yield in a manner similar to (−)-(1*R*,3*S*)-**11** above: mp 200−202 °C; $[\alpha]^{20}_{D}$ +18.3° (*c* 1.1, MeOH); $[\alpha]^{20}_{365}$ +76.8° (*c* 1.1, MeOH). Anal. ($C_{16}H_{15}Cl_2NO$) C, H, N.

(±)-*trans*-3-(3,4-Dichlorophenyl)-6-hydroxyl-*N*,*N*-diethyl-1-indanamine ((±)-12). The compound was prepared from amine (±)-**10** using the procedure described for (±)-**11**: mp 239 °C; ^{1}H NMR δ 9.74 (s, 1H), 7.61−6.83 (m, 6H), 5.25−5.22 (m, 1H), 4.59 (t, J = 8.1 Hz, 1H), 3.32−2.80 (m, 5H), 2.40−2.29 (m, 1H), 1.31 (t, J = 6.9 Hz, 3H), 1.22 (t, J = 6.8 Hz, 3H); CIMS *m*/*z* 351 $(MH)^+$. Anal. ($C_{16}H_{15}NOCl_2$) C, H, N, Cl.

(±)-*trans*-3-(3,4-Dichlorophenyl)-6-decanoate-*N*-methyl-1-indanamine ((±)-15). To a solution of triethylamine (0.5 mL) in methanol (3 mL) at room temperature was added amine (±)-**11** (248 mg, 0.81 mmol) in 1 mL of methanol and then di-*tert*-butyl dicarbonate (351 mg, 1.61 mmol). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the product was extracted with CH_2Cl_2 (2 × 3 mL), washed with water (5 mL), and dried (Na_2SO_4). The mixture was concentrated to give an oil that was chromatographed to give *trans*-3-(3,4-dichlorophenyl)-6-hydroxyl-*N*-methyl-*N*-(*tert*-butoxycarbonyl)-1-indanamine (260 mg, 0.64 mmol, 79% yield) as a clear oil: TLC R_f = 0.40 (20% EtOAc/petroleum ether); ^{1}H NMR δ 7.38−6.71 (m, 6H), 6.01−5.88 (m, 1H), 4.45−4.35 (m, 1H), 2.79 (s, 3H), 2.79−2.41 (m, 1H), 2.38−2.22 (m, 1H), 1.51 (s, 9H); CIMS *m*/*z* 410 $(MH)^+$.

To the above amine (260 mg, 0.64 mmol) in 2-propanol (4 mL) was added a solution of NaOH (70 mg, 1.74 mmol) in 1 mL of H_2O. Decanoic anhydride (568 mg, 1.74 mmol) was gradually added, and the reaction mixture was stirred for 30 min at room temperature. Solvent was removed in vacuo, and the product was extracted with CH_2Cl_2 (2 × 3 mL), washed with H_2O (5 mL), and dried (Na_2SO_4). The mixture was concentrated and chromatographed in a mixture of CH_2Cl_2 and MeOH (9:1) to give *trans*-3-(3,4-dichlorophenyl)-6-decanoate-*N*-methyl-*N*-(*tert*-butoxycarbonyl)-1-indanamine (311 mg, 0.64 mmol, 87% yield) as a clear oil: TLC R_f = 0.48 (10% EtOAc/petroleum ether); ^{1}H NMR δ 7.35−6.89 (m, 6H), 6.03−5.78 (m, 1H), 4.48−4.43 (m, 1H), 2.62 (s, 3H), 2.60−2.42 (m, 3H), 2.39−2.23 (m, 1H), 1.80−1.69 (m, 2H), 1.58 (s, 9H), 1.57−1.21 (m, 12H), 0.89 (t, J = 5.9 Hz, 3H); CIMS *m*/*z* 565 $(MH)^+$.

To the above amine (311 mg, 0.64 mmol) in 2.5 mL of acetonitrile was added ammonium cerium nitrate (60 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 3 h, then was refluxed at 85 °C for another 3 h. The solvent was removed in vacuo and the residue was purified by chromatography to give the deprotected decanoate (±)-**15** (235 mg, 0.51 mmol, 92% yield) as a clear oil: TLC (50% EtOAc/petroleum ether) R_f = 0.42; ^{1}H NMR δ 7.41−6.92 (m, 6H), 4.98−4.88 (m, 1H), 4.68−4.62 (m, 1H), 3.01−2.91 (m, 1H), 2.75 (s, 3H), 2.51 (t, J = 5.9 Hz, 2H), 2.52−2.37 (m, 1H), 1.75−1.63 (m, 2H), 1.39−1.25 (m, 21H), 0.88 (t, J = 6.0 Hz, 3H); CIMS *m*/*z* 464 $(MH)^+$.

Biological Methods. [^{125}I]RTI-55 (0.01 nM, SA = 2200 Ci/mmol) was used in the binding assays for the DA (DAT) and 5-HT transporters (SERT).[22,23] [^{3}H]nisoxetine (1 nM, SA = 80 Ci/mmol) was used in the binding assays for the NE transporters (NET).[24] All binding assays were performed twice, each in triplicate, using membranes prepared from frozen rat caudate for the DAT and SERT assays and frozen whole rat brain membranes for NET. Briefly, 12 mm × 75 mm polystyrene test tubes were prefilled with 100 μL of drug, 100 μL of radioligand, and 50 μL of a blocker or buffer. Drugs and blockers were made up in 55.2 mM sodium phosphate buffer, pH 7.4 (with the addition of 5 mM KCl and 300 mM NaCl for NET binding), containing 1 mg/mL BSA (BB/BSA). Radioligands were made up in a protease inhibitor cocktail containing BB/BSA, chymostatin (25 μg/mL), leupeptin (25 μg/mL), EDTA (100 μM), and EGTA (100 μM). Membranes added in 750 μL of BB initiated the assay. The samples were incubated for 18−24 h at 4 °C (equilibrium) in a final volume of 1 mL. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM Tris-HCl/150 mM NaCl, pH 7.4, containing 2% PEI).

The [^{3}H]DA, [^{3}H]5-HT, and [^{3}H]NE uptake assays were run as previously reported.[25] All uptake assays were performed twice, each in triplicate, using crude synaptosomes prepared from rat caudate (for DA) or from rat whole brain minus caudate (for 5-HT and NE). Briefly, the assays were initiated by the addition of 100 μL of synaptosomes to 12 mm × 75 mm polystyrene test tubes, which were prefilled with 750 μL of [^{3}H]ligand in a Krebs phosphate buffer (pH 7.4) containing 1 mg/mL ascorbic acid and 50 μM pargyline. [^{3}H]NE assays were performed in the presence of 5 nM 3-(4-iodophenyltropane)-2-pyrrolidine carboxamide tartrate to prevent reuptake of [^{3}H]-NE into DA nerves. [^{3}H]5-HT uptake assays were performed in the presence of 100 nM nomifensine and 100 nM GBR 12935 to prevent reuptake into NE and DA nerves. The incubations were terminated after 15 min ([^{3}H]DA) or 30 min ([^{3}H]5-HT and [^{3}H]NE) by adding wash buffer (10 mM Tris-HCl/150 mM

NaCl, pH, 7.4) and rapidly filtering over Whatman GF/B filters on a Brandel cell harvester.

In vivo microdialysis studies followed published procedures.[26] For autoradiography experiments, rats received injections of vehicle ($n = 5$ animals), 1 mg/kg (−)-(1*R*,3*S*)-**11** ($n = 6$ animals), or 3 mg/kg (−)-(1*R*,3*S*)-**11** ($n = 5$ animals) and were sacrificed 1 h afterward. By use of published methods, 20 μm coronal sections taken at the caudate level were thaw-mounted onto subbed glass slides, vacuum-desiccated overnight, and stored at −80 °C until assayed. Slide-mounted sections were labeled with [^{125}I]RTI-55 for autoradiographic analysis of transporters. Slides were thawed at room temperature for 5 min, rinsed for 5 min (10 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mg/mL bovine serum albumin, 4 °C), and placed into cytomailers containing 10 mL of assay buffer, which consisted of 55.2 mM sodium phosphate buffer (pH 7.4), 1 mg/mL bovine serum albumin, 1 μg/mL chymostatin, 1 μg/mL leupeptin, 100 nM EDTA, 100 nM EGTA, 1 nM [^{127}I]RTI55, 0.01 nM [^{125}I]-RTI-55, and appropriate selective transporter blockers. Adjacent sections from each brain were incubated in the absence of blocking drug (total labeling), 100 nM citalopram to select for DA transporter labeling, 1 μM GBR 12909 to select for 5-HT transporter labeling, or 10 μM indatraline to determine nonspecific labeling. After 30 min at 4 °C, slides were rinsed five times for 1 min (10 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mg/mL bovine serum albumin, 4 °C) followed by a 10 s rinse in deionized water at 4 °C. Slides were vacuum-desiccated overnight and stored at room temperature until they were analyzed.

Autoradiographic distribution of 5-HT and DA transporters was revealed using a Cyclone storage phosphor system (Packard). Slides were placed into photographic film cassettes and apposed to storage phosphor screens of the supersensitive variety. Apposition times were 15 min for DA transporters and 6 h for 5-HT transporters. Transporter levels were quantified by NIH image software, using [^{125}]iodine microscale reference standards (Amersham). DA transporter levels were determined by subtracting nonspecific labeling from labeling in the presence of 100 nM citalopram. 5-HT transporter levels were determined by subtracting nonspecific labeling from labeling in the presence of 1 μM GBR 12909. Results were expressed as the mean SEM. Statistical significance was determine using the Students *t*-test.

Single-Crystal X-ray Diffraction Analysis of (1*R*,3*S*)-(−)-9·di-*p*-toluoyl-D-(+)-tartrate. $(C_{20}H_{17}O_8)^{-1}$, $(C_{17}H_{18}Cl_2NO)^{+1}$, (CH_4O), fw = 740.60 (0.06 mm^{-1} × 0.20 mm^{-1} × 0.32 mm^{-1}), orthorhombic space group $P2_12_12_1$, a = 8.0458(19) Å, b =14.451(3) Å, c = 31.537(5) Å, V = 3666.8(12) Å^3, Z = 4, dcalc = 1.34 mg mm^{-3}, λ(Cu Kα) = 1.541 78 Å, μ = 2.087 mm^{-1}, $F(000)$ = 1552, T = 198(2) K, R_1 = 0.0548 for 5650 observed ($I > 2\sigma I$) reflections and 0.0576 for the full set of 6095 reflections.

Data were collected on a Bruker SMART 6K CCD diffractometer using a Rigaku rotating anode source, which was equipped with Gobel mirrors in the incident beam. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved and refined with the aid of the programs in the Shelxtl Plus system of programs.[27] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. Most of the H atoms were included using a riding model. The fact that the anion was a d-tartrate salt was used to determine the absolution configuration of the cation. The Flack parameter refined to a value of 0.05(2) that confirms the correct absolute structure. Atomic coordinates have been deposited with the Cambridge Crystallographic Database (CCDC 212484), 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

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Supporting Information Available: Tables 1−6 of X-ray crystal data and structural refinement analysis, atomic coordinates, bond lengths and bond angles, anisotropic displacement parameters, hydrogen coordinates, and hydrogen bond lengths and angles of 1*R*,3*S*-(−)-**9**·di-*p*-toluoyl-D-(+)-tartrate. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) McCoy, C. B.; Inciardi, J. A. *Sex, Drugs, and the Continuing Spread of AIDS*; Roxbury Publishing Co.: Los Angeles, CA, 1995.
(2) McCoy, C. B.; Metsch, L. R.; Inciardi, J. A.; Anwyl, R. S.; Wingerd, J.; Bletzer, K. Sex, Drugs, and the Spread of HIV/AIDS in Belle Glade, Florida. *Med. Anthropol. Quart.* **1996**, *10*, 83−93.
(3) Goodkin, K.; Shapshak, P.; Metsch, L. R.; McCoy, C. B.; Crandall, K. A.; Kumar, M.; Fujimura, R. K.; McCoy, V.; Zhang, B. T.; Reyblat, S.; Xin, K.-Q.; Kumar, A. M. Cocaine Abuse and HIV-1 Infections: Epidemiology and Neuropathogenesis. *J. Neuroimmunol.* **1998**, *83*, 88−101 and references therein.
(4) Rudnick, G.; Clark, J. From Synapse to Vesicle: The Reuptake and Storage of Biogenic Amine Neurotransmitters. *Biochim. Biophys. Acta* **1999**, *1144*, 249.
(5) Wise, R. A. Neurobiology of Addiction. *Curr. Opin. Neurobiol.* **1996**, *6*, 243−251.
(6) Rothman, R. B.; Baumann, M. H.; Dersch, C. M.; Romero, D. V.; Rice, K. C.; Carroll, F. I.; Partilla, J. S. Amphetamine-Type Central Nervous System Stimulants Release Norepinephrine More Potently Than They Release Dopamine and Serotonin. *Synapse* **2001**, *39*, 32−41.
(7) Zhang, Y. The Identification of GBR 12909 as a Potential Therapeutic Agent for Cocaine Abuse. *Med. Chem. Res.* **1998**, *8*, 66−76.
(8) Preti, A. Vanoxerine. *Curr. Opin. Invest. Drugs* **2000**, *1*, 241−251.
(9) Baumann, M. H.; Ayestas, M. A.; Sharpe, L. G.; Lewis, D. B.; Rice, K. C.; Rothman, R. B. Persistent Antagonism of Methamphetamine-Induced Dopamine Release in Rats Pretreated with GBR 12909 Decanoate. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 1190−1197.
(10) Rothman, R. B.; Partilla, J. S.; Bauman, M. H.; Dersch, C. M.; Carroll, F. I.; Rice, K. C. Neurochemical Neutralization of Methamphetamine with High-Affinity Nonselective Inhibitors of Biogenic Amine Transporters: A Pharmacological Strategy for Treating Stimulant Abuse. *Synapse* **2000**, *35*, 222−227.
(11) Gu, X. H.; Yu, H.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; Flippen-Anderson, J. L.; Rice, K. C. Design, Synthesis, and Monoamine Transporter Binding Site Affinities of Methoxy Derivatives of Indatraline. *J. Med. Chem.* **2000**, *43*, 4868−4876.
(12) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. 3-Phenyl-1-indanamines. Potential Antidepressant Activity and Potent Inhibition of Dopamine, Norepinephrine, and Serotonin Uptake. *J. Med. Chem.* **1985**, *28*, 1817−1828.
(13) Pirkle, W. H.; Hoekstra, M. S. An Example of Automated Liquid Chromatography. Synthesis of a Broad-Spectrum Resolving Agent and Resolution of 1-(1-Naphthyl)-2,2,2-trifluoroethanol. *J. Org. Chem.* **1974**, *39*, 3904−3907.
(14) Van Landeghem, H.; De Aquirre, I. Relations between the Magnitude Kinetics and the Thermodynamics of Transformation of Urea. *Bull. Soc. Chim. Fr.* **1967**, 172−178.
(15) Rice, K. C.; Brossi, A. Expedient Synthesis of Racemic and Optically Active *N*-Norreticuline and *N*-Substituted and 6′-Bromo-*N*-norreticulines. *J. Org. Chem.* **1980**, *45*, 592−601.
(16) Hwu, J. R.; Jain, M. L.; Tsay, S. C.; Hakimelahi, G. H. Ceric Ammonium Nitrate in the Deprotection of *tert*-Butoxycarbonyl Group. *Tetrahedron Lett.* **1996**, *37*, 2035−2038.
(17) Partilla, J. S.; Dersch, C. M.; Yu, H.; Rice, K. C.; Rothman, R. B. Neurochemical Neutralization of Amphetamine-Type Stimulants in Rat Brain by the Indatraline Analog (−)-HY038. *Brain Res. Bull.* **2001**, *53*, 821−826.
(18) Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Owens, C. E.; Kula, N. S.; Baldessarini, R. J.; McPhail, A. T.; Mailman, R. B. Synthesis and Pharmacological Evaluation of 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as Ligands for a Novel Receptor with σ-Like Neuromodulatory Activity. *J. Med. Chem.* **1993**, *36*, 2542−2551.
(19) Southwick, P. L.; Sapper, D. I. 4-Styrylthiazoles. Synthesis and Relationships among Ultraviolet Absorption Spectra. *J. Org. Chem.* **1954**, *19*, 1926−1937.

(20) Greiner, E.; Folk, J. E.; Jacobson, A. E.; Rice, K. C. A Novel and Facile Preparation of Bremazocine Enantiomers through Optically Pure *N*-Norbremazocines. *Bioorg. Med. Chem.* **2004**, *12*, 232−238.
(21) Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V.; Simonds, W. F.; Streaty, R. A.; Klee, W. A. Probes for Narcotic Receptor Mediated Phenomena. 12. *cis*-(+)-3-Methylfentanylisothiocyanate, a Potent Site-Directed Acylating Agent for Opioid Recepors. Synthesis, Absolute Configuration, and Receptor Enantioselectivity. *J. Med. Chem.* **1986**, *29*, 1087−1093.
(22) Matecka, D.; Lewis, D.; Rothman, R. B.; Dersch, C. M.; Wojnicki, F. H. E.; Glowa, J. R.; DeVries, A. C.; Pert, A.; Rice, K. C. Heteroaromatic Analogs of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as High-Affinity Dopamine Reuptake Inhibitors. *J. Med. Chem.* **1997**, *40*, 705−716.
(23) Rothman, R. B.; Cadet, J. L.; Akunne, H. C.; Silverthorn, M. L.; Baumann, M. H.; Carroll, F. I.; Goodman, C. B.; Rice, K. C.; de Costa, B. R.; Partilla, J. S.; Wang, J.-B.; Uhl, G. R.; Glowa, J. R.; Dersch, C. M. Studies of the Biogenic Amine Transporters. IV. Demonstration of a Multiplicity of Binding Sites in Rat Caudate Membranes for the Cocaine Analog [^{125}i]RTI-55. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 296−309.
(24) Rothman, R. B.; Lewis, B.; Dersch, C.; Xu, H.; Radesca, L.; de Costa, B. R.; Rice, K. C.; Kilburn, R. B.; Akunne, H. C.; Pert, A. Identification of a GBR 12935 Homolog, LR 1111, Which Is Over 4,000-Fold Selective for the Dopamine Transporter, Relative to Serotonin and Norepinephrine Transporters. *Synapse* **1993**, *14*, 34−39.
(25) Rothman, R. B.; Katsnelson, M.; Vu, N.; Partilla, J. S.; Dersch, C. M.; Blough, B. E.; Baumann, M. H. Interaction of the Anorectic Medication, Phendimetrazine, and Its Metabolites with Monoamine Transporters in Rat Brain. *Eur. J. Pharmacol.* **2002**, *47*, 51−57.
(26) Baumann, M. H.; Phillips, J. M.; Ayestas, M. A.; Ali, S. F.; Rice, K. C.; Rothman, R. B. Preclinical Evaluation of GBR 12909 Decanoate as a Long-Acting Medication for Methamphetamine Dependence. *Ann. N. Y. Acad. Sci.* **2002**, 965, 92−108.
(27) Sheldrick, G. M. *Shelxtl Plus*, version 6.1; Bruker Analytical X-ray Instruments: 2000 Madison, WI.

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