# Slow-Onset, Long-Duration 3-(3′,4′-Dichlorophenyl)-1-indanamine Monoamine Reuptake Blockers as Potential Medications To Treat Cocaine Abuse

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A series of 3-(3′,4′-dichlorophenyl)-1-indanamine monoamine reuptake blockers have been synthesized in an effort to develop a compound that could be used as a maintenance therapy to treat cocaine abuse. Since the effects of cocaine on dopamine (DA) and serotonin (5HT) transporters are important components of its pharmacological activity, the focus was on nonselective inhibitors of monoamine transport. To reduce or eliminate the abuse potential of a DA reuptake blocker, the compounds were designed to be slow-onset, long-duration prodrugs whose *N*-demethylated metabolites would have increased activity over the parent compound with the ideal being a parent compound that has little or no activity. To achieve this, pairs of compounds with different groups on the amine nitrogen and with and without an additional *N*-methyl group were synthesized. All of the synthesized compounds were screened for binding and reuptake at the cloned human DA, 5HT, and norepinephrine (NE) transporters. As previously found, *trans* isomers are nonselective blockers of DA, 5HT, and NE reuptake, *cis* isomers with small *N*-alkyl groups are selective blockers of 5HT reuptake, and tertiary amines of the *trans* compounds are less potent than the corresponding *N*-demethylated secondary amines as blockers of DA reuptake. Larger *N*-alkyl groups in both the *trans* and *cis* series were found to reduce activity for the 5HT and NE transporters with less effect at DA transporters. Selected *trans* compounds were also screened for locomotor activity in mice and generalization to a cocaine-like profile in rats. With intraperitoneal administration, all of the *trans* isomers showed a slow onset of at least 20 min and an extremely long duration of action in the locomotor assays. Several of the *trans* compounds also fully generalized to a cocaine-like pharmacological profile. An initial lead compound, the *N*,*N*-dimethyl analogue *trans*-**1b**, was resolved into chirally pure enantiomers. Surprisingly, both enantiomers were found to have significant affinity for the DA transporter and to cause locomotor activation. This is in contrast to the *N*-methyl compound in which only the (+)-enantiomer had significant activity. The absolute configuration of the more active enantiomer was determined by X-ray crystallography to be 3*R*,1*S*.

## Introduction

The illicit abuse of cocaine is a major problem throughout the world. The ability of cocaine to bind to the dopamine (DA) transporter and, therefore, to block the reuptake of DA into presynaptic neurons that release DA appears to be responsible for its abuse potential.[1−3] For example, the potencies of cocaine-like drugs in self-administration studies correlate best with their affinities for binding to the DA transporter as labeled with tritiated mazindol or cocaine.[1,4] As a consequence, the acute use of cocaine increases synaptic DA, and this activates the brain reward loci that are believed to cause the euphoria associated with cocaine abuse.[2] With chronic use, however, it has been suggested that synaptic DA may become depleted during cocaine abstinence and that these reduced levels of synaptic DA may then be associated with craving and to result in drug-seeking behavior.[5] Indeed, intracranial microdialysis studies of rats trained to self-administer cocaine intravenously found reduced levels of extracellular nucleus accumbens DA during cocaine withdrawal though basal levels of DA were elevated in the cocaine-experienced rats as compared with drug-naïve controls.[6] Similarly, rats trained to self-administer cocaine intravenously were found to have elevated intracranial self-stimulation thresholds during cocaine withdrawal suggesting a "postcocaine anhedonia".[7,8] There is also evidence that there may be a genetic component to drug abuse vulnerability[9,10] and that some human abuse of drugs may be an effort at self-medication for depressed individuals.[11] A recent report, in which [$^{11}$C]PET imaging was used to quantitate the number of striatal DA D2 receptors in human subjects who had not previously abused drugs, reinforces the conclusion that genetic differences may account for different propensities to abuse drugs since individuals who reported "liking" the effects of intravenous methylphenidate were found to have significantly lower levels of D2 receptors than those that found the effects to be neutral or unpleas-

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ant.[12] For all of these reasons, a nonaddictive and nonabusable DA reuptake blocker that raises DA levels and relieves the dysphoria/craving that habitual users of cocaine feel may be useful in treating cocaine abuse.

Unlike the situation with other drugs of abuse, there are currently no safe and effective pharmacotherapies available to aid habitual users of cocaine who want to stop their usage of the drug. A number of possible pharmacotherapeutic approaches have been suggested.[13−15] One popular approach is to develop a cocaine antagonist that blocks cocaine binding to the DA transporter without inhibiting DA reuptake. Such a compound would antagonize cocaine binding without having a cocaine-like pharmacological effect. This kind of compound would have a high "uptake-to-binding ratio", though, as has been pointed out, this ratio may be highly dependent on the assay conditions.[16] There have been some claims of modest success with this approach.[17] A second possible approach is the development of a maintenance pharmacotherapy that would reduce the dysphoria that the chronic use of cocaine engenders which may then also reduce craving for cocaine and relapse to cocaine use. This approach has been most successful in the treatment of opiate and nicotine addicts. For a maintenance therapy to be beneficial, however, it should be less medically deleterious than the drug of abuse that it is replacing. For example, methadone and LAAM are orally active opioids that reduce the craving of heroin addicts who want to stop their intravenous injections of heroin. Similarly, nicotine patches allow the absorption of nicotine through the skin which is less deleterious than obtaining it by smoking cigarettes.

It is becoming increasingly clear that the pharmacodynamics of a drug of abuse is important for its abusability with those that have rapid onsets and short durations of action appearing to have the highest abuse potential.[18,19] Relevant to this is the recent report that humans who lack an enzyme that metabolically inactivates nicotine are less likely to become addicted to cigarette smoking.[20] Thus, our approach for a maintenance therapy for cocaine users has been to try to design slow-onset, long-duration DA reuptake blockers. In this, we were inspired by the development of LAAM for treating heroin addicts. While LAAM has been reported to have little intrinsic activity at opioid receptors, its two *N*-demethylated metabolites have significant activity,[21,22] and this offers advantages over methadone maintenance. Since LAAM has little or no initial activity, potential abusers do not get the "rush" associated with intravenous heroin or methadone. Nevertheless, its slow metabolism to more active compounds is sufficient to relieve the symptoms of opioid withdrawal. On the basis of the LAAM model, we have tried to design compounds that would require in vivo metabolism before they have their maximum effect. That is, they would be prodrugs whose activity would increase with time. An agonist therapy, by addressing the underlying dysphoric state, may be superior to an antagonist strategy by analogy to pharmacotherapies for heroin addiction since maintenance therapies, such as methadone and LAAM, are more widely accepted by addicts than opioid antagonists such as naltrexone. A similar approach is being tried with a decanoate ester of GBR

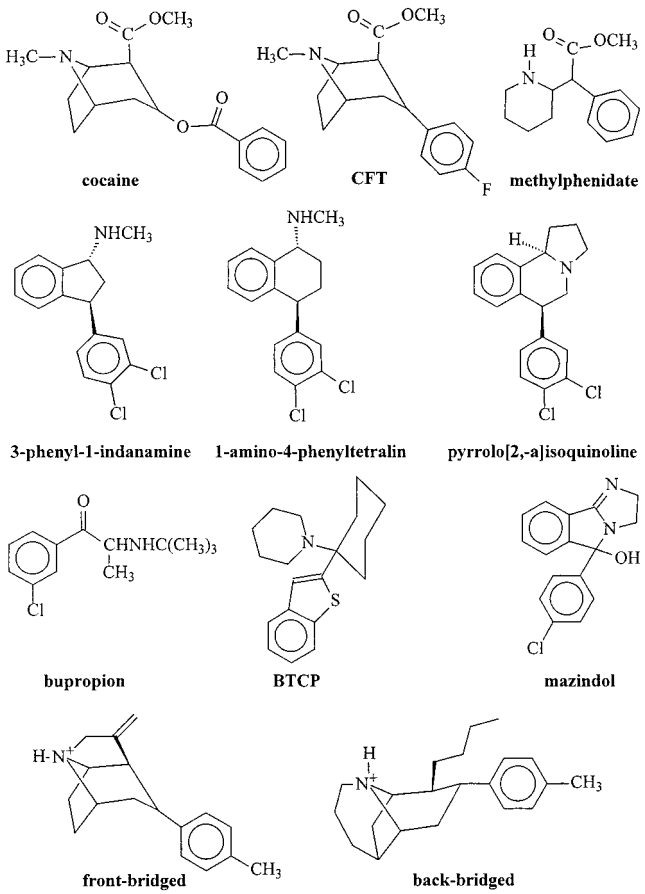


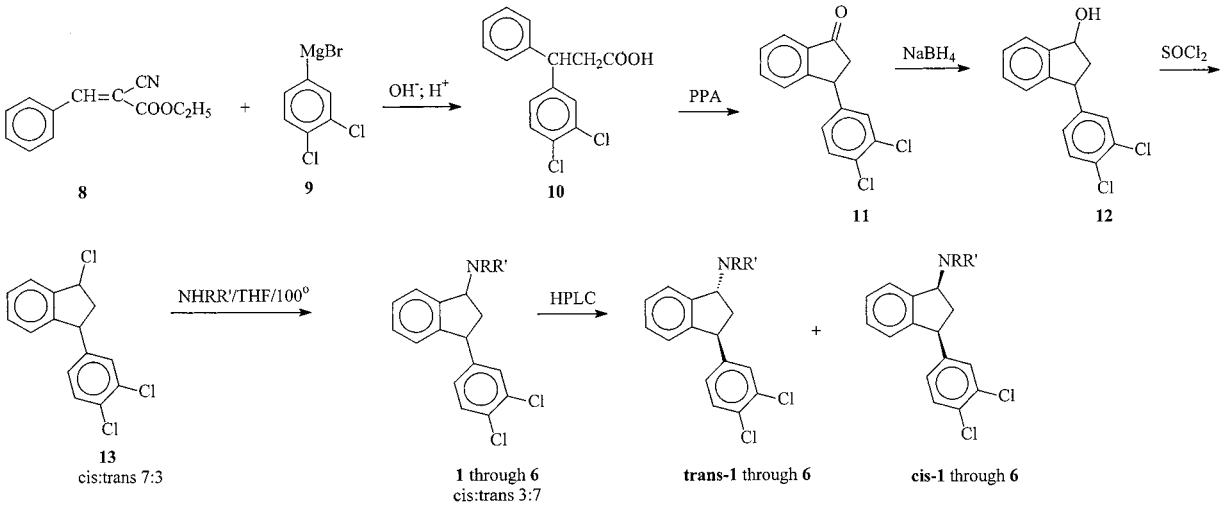

**Figure 1.** Dopamine reuptake blockers.

12909, a slow-release formulation, which has been reported to decrease cocaine self-administration for up to 1 month following a single injection.[23]

We were aided in our design of slow-onset compounds by a pharmacophore model developed for DA reuptake blockers of diverse structural classes.[24] Starting from cocaine and the related tropane CFT, the model encompasses other classes of compounds including 3-phenyl-1-indamines, 1-amino-4-phenyltetralins, and hexahydropyrrolo[2,1-*a*]isoquinolines (Figure 1). The model has been extended to include methylphenidate,[25] correctly predicting the decrease in potency of *N*-methyl derivatives of its analogues,[26] and to bupropion, in which both enantiomers fit the model equally well,[27] and this is consistent with the finding that the enantiomers have similar potencies as DA reuptake blockers.[28] Most recently, BTCP and its analogues have been incorporated into the pharmacophore model.[29]

We were further aided in our efforts by a report which indicated that the 3-aryl-1-indamine LU-19005 (also known as indatraline) is a slow-onset, long-duration DA reuptake blocker.[30] Based on the original report of compounds in this series,[31] it also appears that secondary amines in this series are consistently more potent than the corresponding tertiary amine. This can be understood with the pharmacophore model in that the additional methyl group of tertiary amines appears to be preferentially placed in the position required for an ammonium hydrogen.[24] Thus, we decided to synthesize a series of indanamines with different groups on the amine nitrogen with and without the additional methyl group. Specifically, we were looking for compounds in

**Scheme 1**

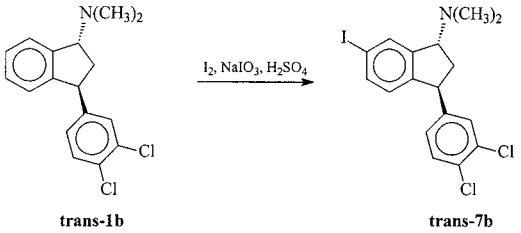



which the tertiary amine had minimal activity as a DA reuptake blocker but the corresponding secondary amine has potent activity. Since *N*-demethylation is one of the most common forms of human metabolism,[32] the tertiary amine would be expected to be a prodrug with the desired pharmacokinetic profile.

While the abuse potential of cocaine is primarily believed to be due to its action at the DA transporter, cocaine also has significant effects at serotonin (5HT) and norepinephrine (NE) transporters. There is evidence that the effect of cocaine on 5HT contributes to its discriminative and behavioral effects.[33,34] 5HT agonists and antagonists have also been shown to have important modulatory effects on DA levels.[35−37] This is one possible explanation for the finding that DA transporter knockout mice continue to self-administer cocaine.[38] For these reasons, it may be important for a pharmacotherapy that treats cocaine abuse to have a 5HT component. In any case, there do not appear to be any serious toxicity problems associated with 5HT reuptake blockers, and their antidepressant effects may be beneficial given the prevalence of depression in drug abusers.[11]

Analogues with a variety of substituents on the pendent phenyl ring have previously been made in the 3-phenyl-1-indanamine series.[31] The 3′,4′-diCl group was chosen here since this was optimal in this series. Interestingly, the same phenyl substitution is consistently optimal or near optimal in a variety of DA reuptake blockers including the 1-amino-4-phenyltetralins,[39] pyrroloisoquinolines,[40] 3-phenyltropanes,[41] methylphenidate analogues,[42] mazindol analogues,[43] and 3-phenylbicyclo[2.2.2]- and -[2.2.1]alkanes.[44] Similarly, a $CF_3$ phenyl substitution consistently *decreases* activity in all of these series in which it has been synthesized. This suggests that the phenyl ring is probably making similar interactions with the DA transporter in the various series. In the 3-aryl-1-indamine series, the *trans* isomers were generally found to be nonselective reuptake blockers at the DA, 5HT, and NE transporters whereas the *cis* isomers were selective for the 5HT transporter.[31] Since the Medications Development Division of the National Institute on Drug Abuse was interested in compounds with both pharmacological profiles, both isomers were synthesized and assayed.

**Scheme 2**

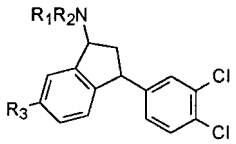



## Chemistry

Initial chemical syntheses were based on a published procedure shown in Scheme 1.[31] Intermediate **8** was produced by the reaction of benzaldehyde with ethyl cyanoacetate. This was coupled with the Grignard reagent **9** to produce the acid **10** after hydrolysis and decarboxylation. The acid **10** was cyclized with polyphosphoric acid to produce the ketone **11**. The ketone was reduced with $NaBH_4$ to produce the alcohol **12** which was converted to the chloride **13** with $SOCl_2$. Reflux in THF with the appropriate amine produced the desired amines **1**−**6**. To achieve high purity, HPLC was utilized to separate the *trans* and *cis* isomers with the former being the major product. The iodo derivative **7b** was synthesized by reacting *trans*-**1b** with $I_2$, $NaIO_3$, and $H_2SO_4$ in HOAc (Scheme 2).[45] The position of the iodine atom was determined by NMR and confirmed by X-ray crystallography. Chiral column Chiralcel OD was used to resolve *trans*-**1b** into its enantiomers using hexanes, 2-PrOH, and trifluoroacetic acid (90/10/0.1) as the mobile phase with the (+)-enantiomer being eluted first.

After *trans*-**1b** was chosen as an initial lead compound, process development was performed and a method developed for its large-scale synthesis as outlined in Scheme 3. This synthetic method produces the desired *trans* isomer without requiring chromatographic separation of the geometric and optical isomers. 3,4-Dichlorocinnamic acid (**14**) is reacted with $H_2SO_4$ and benzene to produce the acid **10** which was cyclized to produce the ketone **11** by treatment with $ClSO_3H$. $NaBH_4$ reduction produces the alcohol **12** with a *cis*/*trans* ratio of 92:7 (as measured by HPLC). After purification by crystallization from EtOAc/heptane, the ratio was 99.5:0.5. The *cis* alcohol **12** was then stereo-

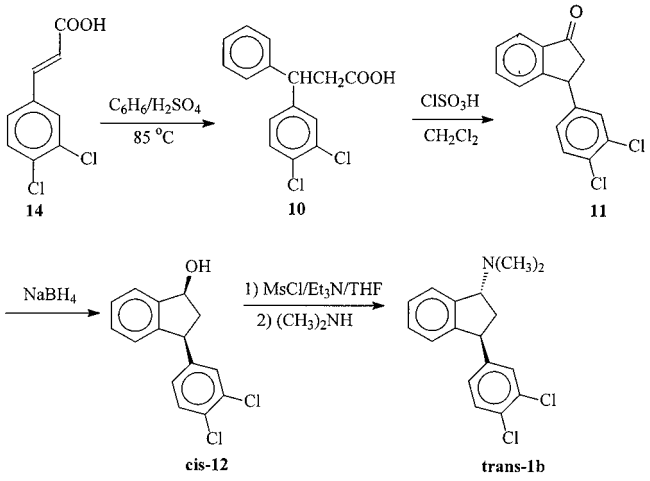
**Table 1.** Synthesized Compounds




| compd | $R_1$ | $R_2$ | $R_3$ | salt | mp, °C | anal. C,H,N,Cl |
|---|---|---|---|---|---|---|
| *trans*-**1a** | methyl | H | H | chloride | 175−177 | $C_{16}H_{16}NCl_3$ |
| *trans*-**1b** | methyl | methyl | H | hydrogen maleate | 155−156 | $C_{21}H_{21}NO_4Cl_2$ |
| (−)-*trans*-**1b** | methyl | methyl | H | chloride | 196−199 | $C_{17}H_{18}NCl_3$ |
| (+)-*trans*-**1b** | methyl | methyl | H | chloride | 195−197 | $C_{17}H_{18}NCl_3$ |
| *cis*-**1a** | methyl | H | H | chloride | 228−229 | $C_{16}H_{16}NCl_3$ |
| *cis*-**1b** | methyl | methyl | H | chloride | 204−207 | $C_{17}H_{18}NCl_3$ |
| *trans*-**7b** | methyl | methyl | I | hydrogen maleate | 122−123 | $C_{21}H_{20}NO_4Cl_2$ |
| *trans*-**2a** | ethyl | H | H | chloride | 217−225 | $C_{17}H_{18}NCl_3$ |
| *trans*-**2b** | ethyl | methyl | H | hydrogen oxalate | 96−102 | $C_{20}H_{21}NO_4Cl_2$ |
| *cis*-**2a** | ethyl | H | H | chloride | >240 | $C_{17}H_{18}NCl_3$ |
| *cis*-**2b** | ethyl | methyl | H | chloride | 196−198 | $C_{18}H_{20}NCl_3$ |
| *trans*-**3a** | propyl | H | H | chloride | 195−196 | $C_{18}H_{20}NCl_3$ |
| *trans*-**3b** | propyl | methyl | H | chloride | 182−184 | $C_{19}H_{22}NCl_3$ |
| *cis*-**3a** | propyl | H | H | hydrogen maleate | 188−189 | $C_{22}H_{23}NO_4Cl_2$ |
| *cis*-**3b** | propyl | methyl | H | chloride | >206 | $C_{19}H_{22}NCl_3$ |
| *trans*-**4a** | isopropyl | H | H | chloride | 147−150 | $C_{18}H_{20}NCl_3$ |
| *trans*-**4b** | isopropyl | methyl | H | chloride | 196−197 | $C_{19}H_{22}NCl_3$ |
| *cis*-**4a** | isopropyl | H | H | chloride | >212 | $C_{18}H_{20}NCl_3$ |
| *cis*-**4b** | isopropyl | methyl | H | chloride | >206 | $C_{19}H_{22}NCl_3$ |
| *trans*-**5a** | *tert*-butyl | H | H | chloride | >243 | $C_{19}H_{22}NCl_3$ |
| *trans*-**5b** | *tert*-butyl | methyl | H | chloride | 201−205 | $C_{20}H_{24}NCl_3$[a] |
| *cis*-**5a** | *tert*-butyl | H | H | chloride | >243 | $C_{19}H_{22}NCl_3$ |
| *cis*-**5b** | *tert*-butyl | methyl | H | chloride | 222−223 | $C_{20}H_{24}NCl_3$ |
| *trans*-**6a** | benzyl | H | H | chloride | >238 | $C_{22}H_{20}NCl_3$ |
| *trans*-**6b** | benzyl | methyl | H | chloride | 203−205 | $C_{23}H_{22}NCl_3$ |
| *cis*-**6a** | benzyl | H | H | chloride | 222−226 | $C_{22}H_{20}NCl_3$ |
| *cis*-**6b** | benzyl | methyl | H | chloride | 192−199 | $C_{23}H_{22}NCl_3$ |

[a] The elemental analysis could be made to fit the theoretical values by including 0.23 mol equiv of ethyl acetate and 0.021 mol equiv of diethyl ether that were observable by NMR and assuming 0.2 mol equiv of water.

**Scheme 3**




selectively converted to the desired *trans*-**1b** by converting the alcohol to the mesylate which was then reacted with the required amine via an $S_N2$ reaction. Purification of the final products was by crystallization of the hydrogen maleate salt. It was also possible to resolve the enantiomers of *trans*-**1b** by fractional crystallization with di-*p*-toluoyltartaric acid with the D-acid precipitating out the (+)-enantiomer. Unlike *trans*-**1b**, the HCl salts of the resolved enantiomers were solids.

## Results and Discussion

The results of the binding and reuptake assays for the monoamine transporters for the synthesized *trans* and *cis* isomers are shown in Tables 2 and 3, respectively. As previously reported,[31] the *trans* isomers were generally nonselective blockers of monoamine reuptake while the more potent *cis* isomers were selective for the 5HT transporter. Some of the *trans* isomers were considerably more potent in the DA assays than cocaine itself (Table 2). As previously noted, *trans* tertiary amines with an extra *N*-methyl group were consistently less potent than the corresponding secondary amines in blocking the reuptake of DA.[24,31] Larger *N*-alkyl groups reduced DA reuptake only slightly until the *N*-methyl, *N*-*tert*-butyl compound **5b** which had greatly decreased activity. For the 5HT and NE transporters, larger *N*-alkyl groups such as an *N*-*tert*-butyl or *N*-benzyl group reduced activity by greater amounts, particularly for the former. The deleterious effect of large groups on the nitrogen is also seen in the *cis* isomers and results in a loss of selectivity toward the 5HT transporter. The iodo compound *trans*-**7b** was synthesized as an intermediate in a procedure to produce tritiated compound. When the compound was submitted for biological testing, the effect of the iodine was found to greatly decrease the activity at the 5HT and NE transporters but to have a relatively small effect

**Table 2.** Binding of *Trans* Isomers to DA, 5HT, and NE Cloned Human Transporters Using 40−80 pM [$^{125}$I]RTI and Inhibition of [$^{3}$H]DA (20 nM), [$^{3}$H]5HT (20 nM), and [$^{3}$H]NE (20 nM) Uptake

| | binding $K_i$, nM | | | | | | | | | uptake $IC_{50}$, nM | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | dopamine | | | serotonin | | | norepinephrine | | | | |
| compd | binding | uptake | uptake/ binding | binding | uptake | uptake/ binding | binding | uptake | uptake/ binding | 5HT/DA | NE/DA |
| cocaine | 300 ± 10 | 330 ± 30 | 1.1 | 500 ± 50 | 310 ± 40 | 0.62 | 2700 ± 350 | 190 ± 50 | 0.07 | 0.94 | 0.58 |
| **1a** | 27 ± 6 | 23 ± 10 | 0.85 | 5.0 ± 0.8 | 4.8 ± 1.5 | 0.96 | 22 ± 7 | 15 ± 6 | 0.68 | 0.21 | 0.65 |
| **1b** | 19 ± 7 | 200 ± 70 | 11 | 0.33 ± 0.11 | 65 ± 12 | 200 | 95 ± 23 | 34 ± 8 | 0.36 | 0.033 | 0.17 |
| **(−)-1b** | 38 ± 12 | 650 ± 170 | 17 | 3.6 ± 1.5 | 130 ± 60 | 36 | 130 ± 35 | 130 ± 50 | 1.0 | 0.020 | 0.20 |
| **(+)-1b** | 8.7 ± 0.8 | 120 ± 33 | 14 | 0.06 ± 0.03 | 6.3 ± 2.4 | 110 | 52 ± 7 | 21 ± 6 | 0.40 | 0.053 | 0.18 |
| **7b** | 310 ± 210 | 290 ± 40 | 0.94 | 17 ± 7 | 3700 ± 1600 | 220 | 1400 ± 600 | 3200 ± 1100 | 2.3 | 13 | 11 |
| **2a** | 8.1 ± 1.3 | 61 ± 12 | 7.5 | 2.0 ± 0.8 | 13 ± 4 | 6.5 | 48 ± 29 | 28 ± 14 | 0.58 | 0.21 | 0.46 |
| **2b** | 39 ± 7 | 270 ± 30 | 6.9 | 16 ± 0.8 | 24 ± 7 | 1.5 | 250 ± 10 | 150 ± 50 | 0.60 | 0.089 | 0.56 |
| **3a** | 220 ± 20 | 53 ± 1 | 0.24 | 130 ± 40 | 480 ± 30 | 3.7 | 55 ± 28 | 130 ± 70 | 2.4 | 9.1 | 2.5 |
| **3b** | 250 ± 30 | 340 ± 10 | 1.4 | 91 ± 9 | 190 ± 40 | 2.1 | 400 ± 100 | 640 ± 330 | 1.6 | 0.56 | 1.9 |
| **4a** | 32 ± 6 | 51 ± 21 | 1.6 | 93 ± 9 | 240 ± 70 | 2.6 | 110 ± 50 | 75 ± 35 | 0.68 | 4.7 | 1.5 |
| **4b** | 180 ± 100 | 190 ± 60 | 1.1 | 44 ± 6 | 1500 ± 500 | 34. | 260 ± 80 | 420 ± 220 | 1.6 | 7.9 | 2.2 |
| **5a** | 130 ± 90 | 370 ± 170 | 2.8 | 740 ± 260 | 3100 ± 1200 | 4.2 | 150 ± 50 | 310 ± 50 | 2.1 | 8.4 | 0.84 |
| **5b** | 890 ± 280 | 2700 ± 1500 | 3.0 | 4700 ± 300 | >10 $\mu$M | | 440 ± 80 | 1000 ± 400 | 2.3 | | 0.37 |
| **6a** | 80 ± 20 | 130 ± 50 | 1.6 | 380 ± 140 | >10 $\mu$M | | 460 ± 180 | 2600 ± 240 | 5.7 | | 12 |
| **6b** | 120 ± 3 | 550 ± 200 | 4.6 | 180 ± 45 | 3700 ± 1300 | 21 | 2800 ± 1900 | 1600 ± 240 | 0.57 | 6.7 | 2.9 |

**Table 3.** Binding of *Cis* Isomers to DA, 5HT, and NE Cloned Transporters Using 40−80 pM [$^{125}$I]RTI and Inhibition of [$^{3}$H]DA (20 nM), [$^{3}$H]5HT (20 nM), and [$^{3}$H]NE (20 nM) Uptake

| | binding $K_i$, nM | | | | | | | | | uptake $IC_{50}$, nM | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | dopamine | | | serotonin | | | norepinephrine | | | | |
| compd | binding | uptake | uptake/ binding | binding | uptake | uptake/ binding | binding | uptake | uptake/ binding | 5HT/DA | NE/DA |
| **1a** | 290 ± 40 | 500 ± 110 | 1.7 | 38 ± 8 | 4.0 ± 2.0 | 0.11 | 600 ± 200 | 130 ± 70 | 0.22 | 0.008 | 0.26 |
| **1b** | 63 ± 16 | 550 ± 130 | 8.7 | 2.4 ± 1.0 | 5.5 ± 1.4 | 2.3 | 150 ± 40 | 86 ± 58 | 0.57 | 0.010 | 0.16 |
| **2a** | 140 ± 4 | 1000 ± 200 | 11. | 4.7 ± 1.0 | 19 ± 7 | 4.0 | | 170 ± 50 | | 0.02 | 0.17 |
| **2b** | 660 ± 190 | 530 ± 90 | 0.80 | 13 ± 1 | 72 ± 23 | 5.5 | 2400 ± 1200 | 4400 ± 2900 | 1.8 | 0.14 | 8.3 |
| **3a** | 280 ± 60 | 620 ± 60 | 2.2 | 500 ± 30 | 1300 ± 400 | 2.6 | 540 ± 210 | 630 ± 150 | 1.2 | 2.1 | 1.0 |
| **3b** | 1200 ± 300 | 1000 ± 60 | 0.83 | 200 ± 60 | 810 ± 120 | 4.0 | 2000 ± 600 | 540 ± 180 | 0.27 | 0.80 | 0.54 |
| **4a** | 450 ± 120 | 1400 ± 300 | 3.1 | 130 ± 30 | 300 ± 80 | 2.3 | 3500 ± 2100 | 1500 ± 500 | 0.43 | 0.21 | 1.1 |
| **4b** | 680 ± 210 | 960 ± 110 | 1.4 | 73 ± 11 | 1800 ± 600 | 25 | 650 ± 100 | 1800 ± 300 | 2.8 | 1.9 | 1.9 |
| **5a** | 650 ± 110 | 1500 ± 900 | 2.3 | 1700 ± 300 | >10 $\mu$M | | 1100 ± 500 | 1800 ± 20 | 1.6 | | 1.2 |
| **5b** | 2800 ± 900 | >10 $\mu$M | | >10 $\mu$M | | | 2200 ± 500 | >10 $\mu$M | | | |
| **6a** | 1100 ± 200 | 5300 ± 600 | 4.8 | 2100 ± 200 | >10 $\mu$M | | 4800 ± 400 | >10 $\mu$M | | | |
| **6b** | >10 $\mu$M | | | 300 ± 90 | 700 ± 240 | 2.3 | >10 $\mu$M | >10 $\mu$M | | | |

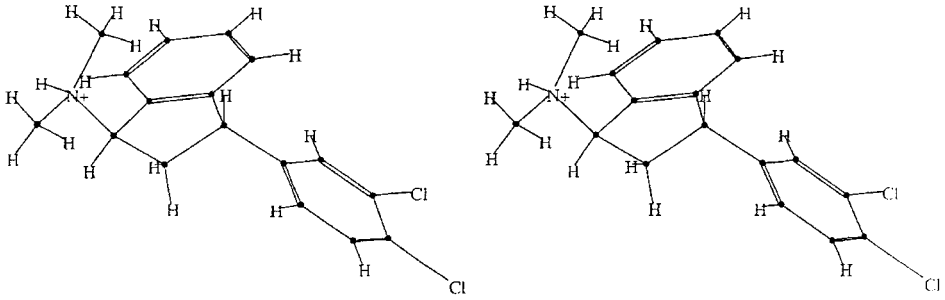



**Figure 2.** Stereoscopic image of the more active (+)-enantiomer of *trans*-**1b** showing the 3*R*,1*S* absolute configuration.

at the DA transporter. This suggests that large *N*-alkyl groups and steric bulk on the unsubstituted phenyl ring may be used to decrease activity at the 5HT and NE transporters in nonselective monoamine reuptake blockers if that is desired. As indicated above, our intention is to retain activity at the 5HT transporter since this component of the action of cocaine contributes significantly to its overall pharmacological effects.

For the resolved enantiomers of *trans*-**1b**, the (+)-enantiomer was the more potent one. Somewhat surprisingly, however, the (−)-enantiomer showed considerable affinity and potency in blocking the reuptake of all three monoamines. Given the 99.2% ee purity of the (−)-enantiomer, this is clearly not due to the presence of the (+)-enantiomer. This is unlike the situation for the *N*-methyl analogue *trans*-**1a** in which the (+)-enantiomer is about 50 times as potent as the (−)-enantiomer in blocking the reuptake of DA.[31] The absolute configuration of the more active (+)-enantiomer was determined by X-ray crystallography to be 3*R*,1*S* (Figure 2), as was also found previously for the more active enantiomer of the *N*-methyl analogue *trans*-**1a**.[31] The conformation of the *N*-methyl groups in the crystal structure is similar to the preferred conformation predicted by the MM2-87 calculations which was suggested to be unfavorable for binding to the transporter.[24]

In the previous study of 3-phenyl-1-indanamines,[31] among the compounds that were synthesized and as-

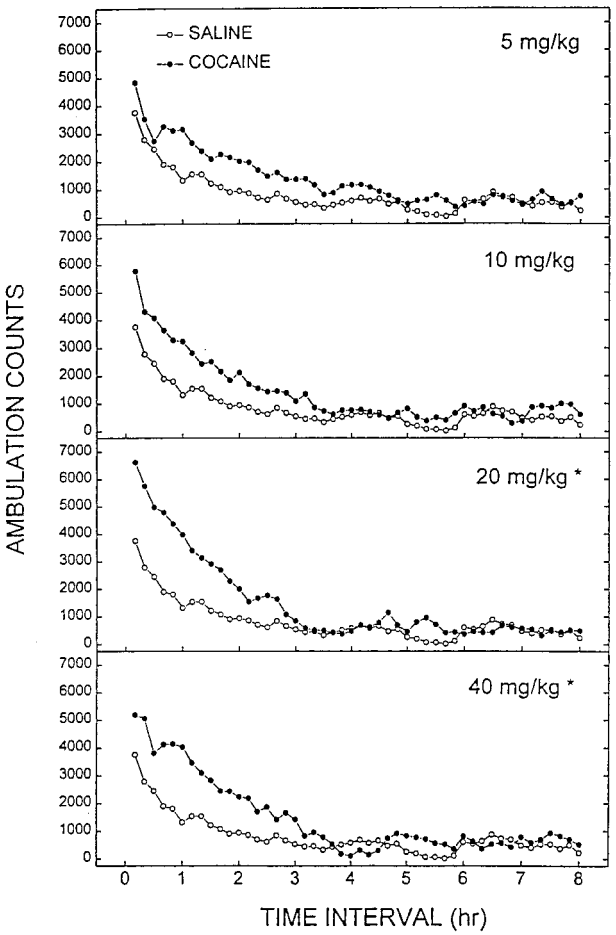



**Figure 3.** Effect of cocaine on horizontal activity counts/10 min as a function of dose and time during an 8-h session in mice; *$p < 0.05$ compared with vehicle (0−30 min).

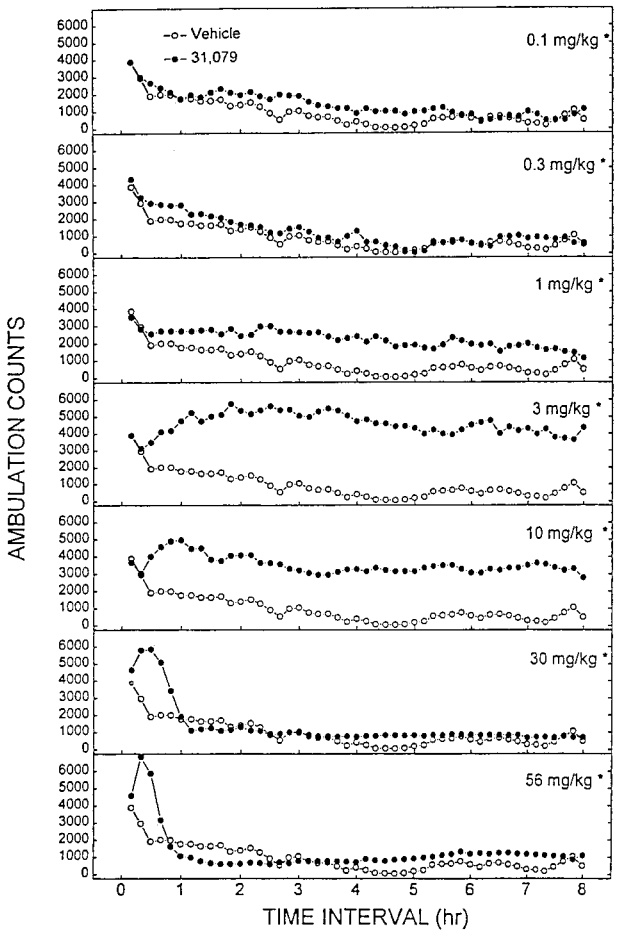



**Figure 4.** Effect of (+)-*trans*-**1b** on horizontal activity counts/10 min as a function of dose and time during an 8-h session in mice; *$p < 0.05$ compared with vehicle (210−240 min).

sayed for pharmacological activity were the *cis* and *trans* isomers of **1a**, **1b**, **2a**, and **3a**. In that study, the DA, NE, and 5HT reuptake assays utilized rat synaptosomal tissue, whereas the reuptake assays in this work used cloned human transporters. There was reasonable agreement for the common compounds in both studies.

The effects of cocaine and (+)-*trans*-**1b** on locomotor activity in mice are shown in Figures 3 and 4, respectively. It can be seen that the cocaine already has a substantial effect at the first data point of 10 min. In fact, the onset of cocaine is believed to be considerably faster than that. It can also be seen that most of its stimulatory effects are gone within 2 h. In contrast, (+)-*trans*-**1b** appears to have an onset of action of at least 20 min since locomotor activity is still going down at that point. Thereafter, the stimulatory effect appears to be present throughout the 8 h of the testing session. (The reduced activity at the highest doses appears to be due to stereotypy which occurs in rodents with high levels of released DA.) Thus, (+)-*trans*-**1b** can be seen to have the desired slow-onset, long-duration profile. The other *trans*-3-phenyl-1-indanamines synthesized also showed similar slow-onset, long-duration pharmacological profiles, and their $ED_{50}$ values are shown in Table 4. Most of the compounds in this class appear to be cocaine-like and produce maximum locomotor stimulation similar to that of cocaine. However, this is less true for the compounds with large groups on the ammonium nitrogen. Both enantiomers of *trans*-**1b** also produced locomotor stimulation in a 1-h locomotor assay with $ED_{50}$ values of 3.4 and 5.0 mg/kg for the (+)- and (−)-enantiomers, respectively (not shown). On the 8-h locomotor assay, the $ED_{50}$ value for the (+)-enantiomer was 0.96 mg/kg (Table 4). However, the less potent (−)-enantiomer showed considerably more toxicity at a high dose of 100 mg/kg than the (+)-enantiomer (not shown).

**Table 4.** $ED_{50}$ Values (±SEM) of Compounds on 8-h Locomotor Assay (Mice) and for Generalization to 10 mg/kg Cocaine (Rat)

| | $ED_{50}$, mg/kg | |
|---|---|---|
| compd | locomotor activity | generalization |
| cocaine | 7.92 ± 0.22[a] | 3.61 ± 0.14[b] |
| *trans*-**1a** | 1.2 ± 0.5 | |
| *trans*-**1b** | 2.4 ± 0.4 | 1.3 ± 0.5 |
| (+)-*trans*-**1b** | 0.96 ± 0.40 | |
| *trans*-**2a** | 1.0 ± 0.3 | |
| *trans*-**2b** | 2.7 ± 0.3 | |
| *trans*-**3a** | 8.1 ± 1.6 | 2.3 ± 0.5 |
| *trans*-**3b** | 1.7 ± 0.4 | 1.5 ± 0.5 |
| *trans*-**4a** | 3.1 ± 0.4 | |
| *trans*-**4b** | 2.9 ± 0.4 | 3.3 ± 0.4 |
| *trans*-**5a** | ≥28 | *c* |
| *trans*-**6a** | ≥20 | *d* |
| *trans*-**6b** | 5.7 ± 0.5 | |
| *trans*-**7b** | ≥17 | *e* |

[a] Standard error of the population of 72 independent determinations. [b] Standard error of the population of 88 independent determinations. [c] Partial substitution at 25 mg/kg. [d] Partial substitution at 5−10 mg/kg. [e] Partial substitution at 10−25 mg/kg.

This suggests that it may be toxicologically advantageous to use the (+)-enantiomer rather than the racemate.

Several of the compounds were also tested in an in vivo cocaine generalization assay in rats trained to discriminate cocaine from saline (Table 4). The compounds were perceived as being cocaine-like with racemic *trans*-**1b** being the most potent of these with an $ED_{50}$ of 1.3 mg/kg. This is interesting in that, while the compounds are perceived as being cocaine-like in this assay and reduce the self-administration of cocaine in both rodents[46,47] and primates,[48] they do not fully eliminate cocaine self-administration despite cocaine-like pharmacological profiles. The persistent, though reduced, self-administration of cocaine by these animals may be attributed to residual, rapid phasic fluctuations in DA levels superimposed on the tonic elevation of DA produced by the long-duration profile of the compounds. Interestingly, racemic *trans*-**1b** appears to be especially efficacious in reducing the self-administration of cocaine in Lewis rats, a hypodopaminergic strain which displays more self-administration and more conditioned place preferences than other strains of rats for drugs which increase levels of DA in brain reward regions.[49] Racemic *trans*-**1b** was also tested in rodents trained to self-administer cocaine to see if the compound, when substituted for cocaine, would itself be self-administered. Using a dose of racemic *trans*-**1b** that produces equivalent decreases of electrical brain stimulation reward thresholds and equivalent increases of nucleus accumbens DA as a dose of cocaine that is robustly self-administered, we found that the compound is only self-administered at levels comparable to their self-administration of saline.[46] This last result suggests that slow-onset, long-duration DA reuptake blockers will be nonabusable.

One potential problem with the use of a long-duration reuptake blocker as a medication for cocaine abuse is that a long-lasting stimulant effect may interfere with sleep in those that use it. For that reason, this approach will only work if the stimulatory effects can wear off by the end of the day or if substimulatory doses can have the desired therapeutic effects. To that end, our results with Lewis rats are promising. As indicated above, Lewis strain rats, due to a hypodopaminergic genetic fault, are believed to be a potential model for humans who have a propensity to abuse drugs. The effects of these slow-onset, long-duration compounds appeared to be particularly effective in reducing the self-administration of cocaine in this rat strain, and this occurred at doses which in themselves were *not stimulatory* to the animals.

As indicated above, a pharmacophore has been proposed for compounds that bind to the DA transporter.[24] After superposition of the key features of the molecules in their biologically active conformer, the direction of the ammonium hydrogen (or lone pair for the free base) was proposed as a crucial feature. However, there has recently been a drastic modification in thinking about the structural requirements of binding to the DA transporter with regard to the amine group. For example, introducing groups that reduce nitrogen basicity does not preclude high potency.[50,51] It has also recently been suggested that the cationic and neutral forms of DA reuptake blockers may have similar binding affinities.[52] It is even possible to achieve high potency in compounds in which the nitrogen of 3-phenyltropanes has been replaced by an oxygen or carbon atom.[53−56] This might argue against the pharmacophore model. Nevertheless, the importance of directionality of the ammonium hydrogen (or amine lone pair) was recently shown by the synthesis and testing of cocaine analogues in which additional rigidification produced defined directions of the ammonium hydrogen (or amine lone pair).[57] It was found that "back-bridged" analogues (Figure 1), in which the ammonium hydrogen was consistent with the pharmacophore model, had higher affinities for the DA transporter and were more selective for it relative to the 5HT transporter. In contrast, "front-bridged" analogues had higher affinities for the 5HT transporter and were more selective for it relative to the DA transporter. (Both classes of compounds had approximately equal high affinities for the NE transporter, suggesting that the differences in orientation of the ammonium hydrogen did not play a major role for the latter.) These preferences were not absolute, however, and "front-bridged" analogues still had considerable affinity at the DA transporter.

## Experimental Section

**Chemistry.** Column chromatography was carried out with Baker 40-$\mu$m silica gel. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are corrected. NMR spectra were recorded on a Bruker 300-MHz FT-NMR spectrometer. The HPLC system used contains an Eldex Duros Series pump as the feeding pump, two Rainin SD-1 pumps, a Rainin UV-1 detector, and a Rainin FC-1 fraction collector. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA, and were within ±0.4% of theoretical values.

**Synthesis of *trans*-1b by Scheme 3. 3-(3′,4′-Dichlorophenyl)-3-phenylpropanoic Acid (10).** A mixture of 3,4-dichlorocinnamic acid (**14**; 95% *trans*, 50 g, 0.23 mol), benzene (150 mL), and concentrated $H_2SO_4$ (100 mL) was stirred at 85−95 °C in a three-neck round-bottom flask. When the level of **14** was ≤1%, the reaction mixture was cooled to room temperature and slowly poured onto ice. The mixture was stirred for 30 min and then transferred into a separatory funnel. The aqueous layer was drained and extracted twice with EtOAc. The organic solutions were combined and washed five times with water and twice with brine. The solvent was then evaporated under reduced pressure and the residue dried under high vacuum at room temperature for 24 h. The desired acid **10** (65.8 g, 96% yield) was obtained as a thick oil: $^1$H NMR (DMSO-$d_6$) $\delta$ 12.23 (s, 1 H), 7.66 (d, 1 H, $J$ = 2 Hz), 7.54 (d, 1 H, $J$ = 9 Hz), 7.40−7.13 (m, 6 H), 4.49 (t, 1 H, $J$ = 9 Hz), 3.18−3.00 (m, 2 H); IR (KBr) 3500−2200, 1718 cm$^{-1}$.

**3-(3′,4′-Dichlorophenyl)indan-1-one (11).** Chlorosulfonic acid (66 mL, 0.99 mol) was added slowly to a solution of the acid **10** (65 g, 0.22 mol) in dichloromethane (330 mL) at room temperature. After the reaction was complete, the reaction mixture was slowly poured onto ice, stirred for 15 min, and transferred to a separatory funnel. The cloudy bottom layer was drained and the dichloromethane removed under reduced pressure to give a light yellow solid which was dissolved in EtOAc. The top aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water five times and twice with brine. The EtOAc solution was evaporated to dryness and the obtained solid was stirred for one hr with 100 mL of 1:9 EtOAc:heptane at room temperature. Stirring was continued for 4 h at 5−10 °C. The mixture was filtered and the filter cake washed twice with a cold solution of 1:9 EtOAc:heptane. After drying under high vacuum for 16 h, 45.6 g (71%) of the desired ketone **11** was obtained as an

off-white solid: 97% pure by HPLC; $^1$H NMR ($CDCl_3$) $\delta$ 7.85 (d, 1 H, $J$ = 9 Hz), 7.62 (t, 1 H, $J$ = 9 Hz), 7.50 (t, 1 H, $J$ = 9 Hz), 7.40 (d, 1 H, $J$ = 9 Hz), 7.30−7.20 (m, 2 H), 6.95 (dd, 1 H, $J$ = 9, 2 Hz), 4.56 (dd, 1 H, $J$ = 9, 4 Hz), 3.25 (dd, 1 H, $J$ = 21, 9 Hz), 2.62 (dd, 1 H, $J$ = 21, 4 Hz); IR (KBr) 1699 cm$^{-1}$.

***cis*-3-(3′,4′-Dichlorophenyl)indan-1-ol (12).** A solution of the ketone **11** (25 g, 0.09 mol) in 250 mL of THF was stirred at −5 °C. A solution of $NaBH_4$ (6.8 g, 018 mol) in water (28 mL) was cooled to 0 °C and then added dropwise while maintaining the temperature of the reaction mixture below 0 °C. After all of the $NaBH_4$ solution was added, the cooling bath was removed and the reaction mixture stirred for 2 h. The reaction mixture was diluted with ice-cold water and stirred for 1 h. THF was removed under reduced pressure and the mixture extracted twice with EtOAc. The EtOAc solution was washed twice with water, twice with brine, and then evaporated to dryness. The oily mixture that was obtained was stirred with a solution (100 mL) of 1:9 EtOAc:heptane for 1 h and at 5−10 °C for 4 h. The mixture was filtered and the filter cake washed with ice-cold solution of 1:9 EtOAc:heptane. After drying, 18.8 g (74%) of the *cis* alcohol **12** was obtained with a purity of 98.5% with the undesired *trans* alcohol being ≤1%: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.60 (d, 1 H, $J$ = 9 Hz), 7.50 (d, 1 H, $J$ = 2 Hz), 7.40 (d, 1 H, $J$ = 9 Hz), 7.30−7.15 (m, 3 H), 6.85 (d, 1 H, $J$ = 9 Hz), 5.53 (d, 1 H, $J$ = 9 Hz), 5.15−5.05 (m, 1 H), 4.25 (t, 1 H, $J$ = 9 Hz), 2.92−2.78 (m, 1 H), 1.86−1.73 (m, 1 H); IR (KBr) 3300 cm$^{-1}$.

***trans*-*N*,*N*-Dimethyl[3-(3′,4′-dichlorophenyl)indan-1-yl]amine (1b).** A solution of the *cis* alcohol **12** (22.7 g, 0.081 mol) and triethylamine (45 mL, 0.325 mol) in THF (350 mL) was stirred at −15 °C under argon. A solution of methanesulfonyl chloride (12.6 mL, 0.162 mol) in THF (150 mL) was cooled to −60 °C and then added slowly to the alcohol solution maintaining the temperature below 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then purged with dimethylamine gas (56 g, 1.21 mol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. THF was removed under reduced pressure and the mixture was extracted three times with EtOAc. The combined EtOAc solutions were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated to dryness to give 26 g of the desired *trans* amine (*trans*:*cis* ratio of 96.6:3.4) as a brown oil. The crude amine was stirred with 5 mL of EtOAc and then 45 mL of heptane was added. The mixture was stirred for 1 h at 15 °C, filtered, and the filter cake washed with 40 mL heptane. The solid was dried under high vacuum to give 14 g of the desired *trans*-**1b** (56%, first crop). The mother liquor was evaporated to dryness and the obtained oil was stirred with 10% EtOAc in heptane (15 mL) for 1 h at 15 °C. The formed solid was then filtered, the filter cake washed with heptane, and dried under high vacuum, to give 5.2 g of a second crop (21%). Both crops contained 0.6% of the undesired *cis* isomer as indicated by HPLC. After an additional washing, filter, and drying step, we obtained 15 g (60% yield) of the desired *trans*-**1b** amine that was 94% pure and contained 0.2% of the undesired *cis* isomer as determined by HPLC: $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (dd, 1 H, $J$ = 9, 2 Hz), 7.35 (d, 1 H, $J$ = 9 Hz), 7.30−7.20 (m overlapping $CHCl_3$ singlet, 2 H), 7.18 (d, 1 H, $J$ = 2 Hz), 6.98−6.90 (m, 2 H), 4.48−4.35 (m, 2 H), 2.72−2.60 (m, 1 H), 2.25 (s, 6 H), 2.05−1.90 (m, 1 H).

**HPLC Separation of *cis*- and *trans*-*N*,*N*-Dimethyl-[3-(3′,4′-dichlorophenyl)indan-1-yl]amine**. A Phenomenex Primesphere column (silica, 5 $\mu$m, 110 Å, 21.2 mm × 250 mm) was used with the UV detector set at 268 nm. The mixture of amines, which had been partially purified by chromatography, was dissolved in EtOAc (∼103 mg/mL) and filtered through a 0.2-$\mu$m filter. For each injection, ∼100 mg of the amine was loaded. The mobile phase contained EtOAc and $Et_3N$ in a ratio of 100/0.05 with a flow rate of 10 mL/min. The *cis* amine eluted out at 17 min and the *trans* amine at 20 min. Solvent evaporation afforded the desired *cis* and *trans* amines. Using this method, it was possible to obtain an essentially complete separation of the *cis* and *trans* isomers. The *cis* and *trans* isomers of other analogues with small *N*-alkyl groups could be separated in a similar fashion.

**HPLC Resolution of (+)- and (−)-*trans*-*N*,*N*-Dimethyl-[3-(3′,4′-dichlorophenyl)indan-1-yl]amine**. A Chiralcel OD column (10 $\mu$m, 10 mm × 250 mm) was used with the UV detector set at 260 nm. The purified *trans* amine was dissolved in 10% 2-PrOH/hexanes (∼2 mg/mL) and filtered through a 0.2-$\mu$L filter. For each injection, ∼1.5 mg of the amine was loaded. The mobile phase contained hexanes, 2-PrOH, and trifluoroacetic acid in a ratio of 90/10/0.1 with a flow rate of 4 mL/min. The (+)-salt eluted out at about 15 min and the (−)-salt at about 17 min. Fractions of each peak were combined, the solvent evaporated, treated with saturated $NaHCO_3$(aq) to produce the free bases, extracted with EtOAc, dried over $MgSO_4$, vacuum filtered, and the solvent evaporated. After conversion to the HCl salts, the optical purities were 100% ee for the (+)-salt and 99% ee for the (−)-salt, respectively, as measured by chiral HPLC.

**Chemical Resolution of (+)- and (−)-*trans*-*N*,*N*-Dimethyl-[3-(3′,4′-dichlorophenyl)indan-1-yl]amine**. To a solution of the racemate (10.5 g/100 mL of acetone) was added a solution of Di-*p*-toluoyl-L-tartaric acid (14.5 g/100 mL of acetone). A white solid formed immediately. The mixture was stirred at room temperature for 1 h and then filtered. The filter cake was washed with 50 mL of acetone and then stirred with 200 mL of acetone at room temperature for 12 h. Vacuum filtration gave 9.03 g of product. The obtained salt was stirred in 200 mL of acetone at room temperature for 12 h. The mixture was filtered and dried under reduced pressure to give 8.37 g of the di-*p*-toluoyl tartarate salt. This was converted to the free base by stirring with saturated $NaHCO_3$(aq) (50 mL). The free base was extracted with EtOAc (2 × 50 mL). The EtOAc layer was washed with water (100 mL) and brine (100 mL). After drying over anhydrous sodium sulfate, removal of solvent gave 3.71 g (71%) of the (+)-free base in 99.4% enantiomeric purity. The (−)-enantiomer was prepared similarly using di-*p*-toluoyl-D-tartaric acid.

**Novel Compounds Synthesized**. Note that most of the compounds with asymmetric alkyl groups on the amine showed two sets of NMR signals. We believe that this is due to significant concentrations of the different epimers in which the asymmetric *N*-alkyl groups are interchanged.

***trans*-*N*-Ethyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrogen oxalate (*trans*-2b)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 1.18 (3H, t, $J$ = 7.2 Hz), 3.09 (1H, dt, $J$ = 15.7 Hz, 8.3 Hz), 1.7−1.9 (2H, m), 2.9−3.3 (3H, m), 4.73 (1H, t, $J$ = 7.8 Hz), 5.19 (1H, d, $J$ = 7.6 Hz), 7.0 (1H, m), 7.17 (1H, d, $J$ = 8.3 Hz), 7.4 (2H, m), 7.47 (1H, s), 7.60 (1H, d, $J$ = 8.2 Hz), 7.7 (1H, m).

***cis*- *N*-Ethyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-2b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼35/65 were detected) $\delta$ 1.31 (1.05H, t, $J$ = 7.1 Hz), 1.42 (1.95H, t, $J$ = 7.1 Hz), 2.18 (0.35H, t, $J$ = 9.7 Hz), 2.22 (0.65H, t, $J$ = 9.7 Hz), 2.55 (1.95H, d, $J$ = 4.6 Hz), 2.8−3.1 (1.7H, m), 3.1−3.3 (1.35H, m), 4.42 (1H, t, $J$ = 8.9 Hz), 5.16 (0.35H, t, $J$ = 8.9 Hz), 5.24 (0.65H, t, $J$ = 8.3 Hz), 6.9 (1H, m), 7.3 (1H, m), 7.4 (2H, m), 7.4 (2H, m), 7.59 (1H, d, $J$ = 1.8 Hz), 7.65 (1H, d, $J$ = 8.3 Hz), 8.12 (0.35H, d, $J$ = 7.3 Hz), 8.19 (0.65H, d, $J$ = 7.0 Hz), 11.84 (1H, s).

***trans*-*N*-Methyl-*N*-propyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-3b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼1/1 were detected) $\delta$ 0.87 (1.5H, t, $J$ = 7.5 Hz), 0.92 (1.5H, t, $J$ = 7.5 Hz), 1.7−1.9 (2H, m), 2.3−2.5 (1H, m), 2.5 (1.5H, under DMSO-$d_5$), 2.69 (1.5H, d, $J$ = 4.6 Hz), 2.7−2.9 (0.5H, m), 2.9−3.1 (2H, m), 3.1−3.2 (0.5H, m), 4.76 (1H, q, $J$ = 8.5 Hz), 5.19 (0.5H, d, $J$ = 8.3 Hz), 5.29 (0.5H, d, $J$ = 8.3 Hz), 7.0 (1H, m), 7.18 (1H, dd, $J$ = 1.9 Hz, 8.3 Hz), 7.4 (2H, m), 7.48 (1H, d, $J$ = 1.9 Hz), 7.61 (1H, dd, $J$ = 1.1 Hz, 8.3 Hz), 7.9 (0.5H, m), 8.0 (0.5H, m), 10.98 (1H, s).

***cis*-*N*-Methyl-*N*-propyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-3b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼4/6 were detected) $\delta$ 0.87 (1.2H, t, $J$ = 7.5 Hz), 0.93 (1.8H, t, $J$ = 7.4 Hz), 1.7−1.9 (1.2H, m),

1.9−2.1 (0.8H, m), 2.1−2.3 (1H, m), 2.56 (1.8H, d, $J$ = 4.7 Hz), 2.83 (1.2H, d, $J$ = 4.6 Hz), 2.7−3.2 (3H, m), 4.42 (1H, t, $J$ = 8.8 Hz), 5.14 (0.4H, t, $J$ = 8.4 Hz), 5.23 (0.6H, t, $J$ = 8.5 Hz), 6.9 (1H, m), 7.28 (1H, dd, $J$ = 1.9 Hz, 8.3 Hz), 7.4 (2H, m), 7.6 (1H, m), 7.65 (1H, d, $J$ = 8.3 Hz), 8.08 (0.4H, d, $J$ = 6.5 Hz), 8.19 (0.6H, d, $J$ = 7.5 Hz), 11.72 (0.4H, s), 11.85 (0.6H, s).

***trans*-*N*-Isopropyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-4a):** $^1$H NMR (DMSO-$d_6$) $\delta$ 1.37 (3H, d, $J$ = 6.4 Hz), 1.41 (3H, d, $J$ = 6.4 Hz), 2.43 (1H, dt, $J$ = 14.1 Hz, 7.3 Hz), 3.5 (1H, m), 2.78 (1H, ddd, $J$ = 3.3 Hz, 8.2 Hz, 14.4 Hz), 3.5 (1H, m), 4.87 (1H, t, $J$ = 7.6 Hz), 5.0 (1H, m), 7.0 (1H, m), 7.17 (1H, dd, $J$ = 2.1 Hz, 8.4 Hz), 7.4 (2H, m), 7.44 (1H, d, $J$ = 2.0 Hz), 7.60 (1H, d, $J$ = 8.2 Hz), 7.9 (1H, m), 9.35 (1H, s), 9.48 (1H, s).

***trans*-*N*-Isoproyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-4b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼3/7 were detected) $\delta$ 1.32 (0.9H, d, $J$ = 6.5 Hz), 1.41 (2.1H, d, $J$ = 6.4 Hz), 1.47 (3H, d, $J$ = 6.5 Hz), 2.36 (0.3H, t, $J$ = 7.7 Hz), 2.41 (0.7H, t, $J$ = 8.0 Hz), 2.48 (2.1H, d, $J$ = 5.0 Hz), 2.51 (0.9H, d, $J$ = 3.9 Hz), 2.96 (0.7H, ddd, $J$ = 2.8 Hz, 8.5 Hz, 15.1 Hz), 3.04 (0.3H, dd, $J$ = 8.4 Hz, 15.3 Hz), 3.59 (0.7H, m, $J$ = 6.3 Hz), 3.7 (0.3H, m), 4.81 (0.7H, t, $J$ = 6.0 Hz), 5.03 (0.3H, t, $J$ = 8.4 Hz), 5.15 (0.3H, dd, $J$ = 5.3 Hz, 6.9 Hz), 5.4 (0.7H, m), 7.0 (1H, m), 7.17 (0.3H, dd, $J$ = 2.1 Hz, 8.4 Hz), 7.19 (0.7H, dd, $J$ = 2.1 Hz, 8.4 Hz), 7.4 (2H, m), 7.44 (0.3H, d, $J$ = 2.1 Hz), 7.47 (0.7H, d, $J$ = 2.0 Hz), 7.61 (0.7H, d, $J$ = 8.3 Hz), 7.62 (0.3H, d, $J$ = 8.3 Hz), 7.8 (0.3H, m), 8.1 (0.7H, m), 10.96 (0.3H, s), 11.13 (0.7H, s).

***cis*-*N*-Isopropyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-4a)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 1.41 (3H, d, $J$ = 6.2 Hz), 1.43 (3H, d, $J$ = 6.2 Hz), 2.16 (1H, q, $J$ = 10.7 Hz), 2.97 (1H, dt, $J$ = 12.5 Hz, 7.3 Hz), 3.5 (1H, m), 4.40 (1H, t, $J$ = 8.8 Hz), 4.96 (1H, q, $J$ = 6.8 Hz), 6.84 (1H, d, $J$ = 7.2 Hz), 7.4 (3H, m), 7.60 (1H, d, $J$ = 1.9 Hz), 7.66 (1H, d, $J$ = 8.3 Hz), 8.13 (1H, d, $J$ = 7.2 Hz), 9.28 (1H, t, $J$ = 9.0 Hz), 10.14 (1H, t, $J$ = 7.7 Hz).

***cis*-*N*-Isoproyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-4b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼1/9 were detected) $\delta$ 1.31 (0.3H, d, $J$ = 6.5 Hz), 1.44 (0.3H, d, $J$ = 6.6 Hz), 1.47 (2.7H, d, $J$ = 6.4 Hz), 1.54 (2.7H, d, $J$ = 6.4 Hz), 2.21 (1H, dt, $J$ = 12.9 Hz, 9.8 Hz), 2.58 (2.7H, d, $J$ = 4.9 Hz), 2.79 (0.3H, d, $J$ = 4.7 Hz), 2.84 (0.9H, dt, $J$ = 14.2 Hz, 7.4 Hz), 3.04 (0.1H, dt, $J$ = 13.1 Hz, 7.5 Hz), 3.48 (0.9H, m, $J$ = 6.5 Hz), 3.8 (0.1H, m), 4.36 (0.1H, t, $J$ = 8.9 Hz), 4.20 (0.9H, t, $J$ = 8.9 Hz), 5.19 (0.1H, t, $J$ = 9.1 Hz), 5.37 (0.9H, t, $J$ = 8.1 Hz), 6.9 (1H, m), 7.3−7.4 (3H, m), 7.9 (0.1H, m), 8.29 (0.9H, d, $J$ = 6.6 Hz), 11.26 (0.1H, s), 11.68 (0.9H, s).

***trans*-*N*-*tert*-Butyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-5a)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 1.47 (9H, s), 2.40 (1H, dt, $J$ = 14.2 Hz, 8.0 Hz), 2.99 (1H, ddd, $J$ = 1.6 Hz, 8.1 Hz, 13.9 Hz), 5.1 (2H, m), 7.0 (1H, m), 7.16 (1H, dd, $J$ = 2.1 Hz, 8.4 Hz), 7.4 (3H, m), 7.6 (2H, m), 8.43 (1H, d, $J$ = 12.2 Hz), 9.9 (1H, m).

***trans*-*N*-*tert*-Butyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-5b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼3/7 were detected) $\delta$ 1.66 (6.3H, s), 1.70 (2.7H, s), 1.9 (0.3H, m), 2.25 (2.1H, d, $J$ = 5.1 Hz), 2.3 (0.7H, m), 2.57 (0.9H, s), 2.84 (0.3H, bs), 3.74 (0.7H, dd, $J$ = 6.7 Hz, 14.2 Hz), 4.56 (0.3H, bs), 5.01 (0.7H, d, $J$ = 6.8 Hz), 5.12 (0.7H, dd, $J$ = 6.8 Hz, 9.7 Hz), 5.44 (0.3H, d, $J$ = 7.0 Hz), 6.85 (0.3H, d, $J$ = 7.0 Hz), 7.00 (0.3H, d, $J$ = 7.3 Hz), 7.1−7.5 (6.1H, m), 8.63 (0.3H, d, $J$ = 7.6 Hz), 11.63 (0.3H, s), 11.71 (0.7H, s).

***cis*-*N*-*tert*-Butyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-5a)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 1.49 (9H, s), 2.5 (1H, m), 3.07 (1H, dt, $J$ = 12.6 Hz, 7.7 Hz), 3.36 (1H, s), 4.38 (1H, t, $J$ = 9.0 Hz), 5.04 (1H, q, $J$ = 8.0 Hz), 6.87 (1H, d, $J$ = 7.3 Hz), 7.3−7.4 (3H, m), 7.60 (1H, d, $J$ = 2.0 Hz), 7.66 (1H, d, $J$ = 8.3 Hz), 8.05 (1H, d, $J$ = 7.3 Hz), 8.80 (1H, d, $J$ = 12.0 Hz), 9.63 (1H, t, $J$ = 10.4 Hz).

***cis*-*N*-*tert*-Butyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-5b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼16/84 were detected) $\delta$ 1.71 (7.56H, s), 1.74 (1.44H, s), 2.02 (1H, dt, $J$ = 13 Hz, 9.9 Hz), 2.65 (2.52H, d, $J$ = 5.2 Hz), 2.69 (0.48H, d, $J$ = 5.4 Hz), 2.93 (0.84H, dt, $J$ = 12.8 Hz, 7.6 Hz), 3.32 (0.16H, dt, $J$ = 7.3 Hz, 3 Hz), 4.15 (0.16H, dd, $J$ = 7.5 Hz, 10.0 Hz), 4.32 (0.84H, t, $J$ = 8.6 Hz), 5.09 (0.16H, dd, $J$ = 7.5 Hz, 10.0 Hz), 5.40 (0.84H, t, $J$ = 8.5 Hz), 6.94 (0.84H, d, $J$ = 7.7 Hz), 7.2 (1.32H, m), 7.3−7.5 (4.16H, m), 9.01 (0.84H, d, $J$ = 7.8 Hz), 11.89 (0.84H, s), 12.01 (0.16H, s).

***trans*-*N*-Benzyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-6a)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 2.6 (1H, m), 2.95 (1H, ddd, $J$ = 2.8 Hz, 8.2 Hz, 14.6 Hz), 4.21 (2H, s), 4.89 (1H, t, $J$ = 7.7 Hz), 5.36 (1H, d, $J$ = 6.0 Hz), 7.0 (1H, m), 7.26 (1H, dd, $J$ = 2.0 Hz, 8.3 Hz), 7.4−7.5 (6H, m), 7.61 (1H, d, $J$ = 8.2 Hz), 7.7 (2H, m), 7.9 (1H, m), 10.04 (2H, s).

***trans*-*N*-Benzyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*trans*-6b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼1/1 were detected) $\delta$ 2.30 (0.5H, t, $J$ = 7.9 Hz), 2.35 (0.5H, t, $J$ = 8.0 Hz), 2.44 (1.5H, d, $J$ = 4.8 Hz), 2.57 (1.5H, d, $J$ = 4.7 Hz), 3.18 (0.5H, d, $J$ = 8.4 Hz), 3.23 (0.5H, t, $J$ = 9.2 Hz), 4.2 (1H, m), 4.30 (0.5H, dd, $J$ = 6.5 Hz, 13.0 Hz), 4.43 (0.5H, dd, $J$ = 5.3 Hz, 13.0 Hz), 4.79 (0.5H, t, $J$ = 7.8 Hz), 4.90 (0.5H, t, $J$ = 7.9 Hz), 5.07 (0.5H, d, $J$ = 8.0 Hz), 5.28 (0.5H, d, $J$ = 8.4 Hz), 7.0 (1H, m), 7.20 (1H, dt, $J$ = 2.0 Hz, 8.9 Hz), 7.3−7.5 (6H, m), 7.6−7.7 (2H, m), 7.8 (1H, m), 8.0 (0.5H, m), 8.1 (0.5H, m), 11.61 (0.5H, s), 11.73 (0.5H, s).

***cis*-*N*-Benzyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-6a)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 2.35 (1H, dt, $J$ = 12.4 Hz, 10.0 Hz), 3.02 (1H, dt, $J$ = 12.6 Hz, 7.7 Hz), 4.30 (2H, s), 4.41 (1H, t, $J$ = 8.8 Hz), 4.83 (1H, s), 6.84 (1H, d, $J$ = 6.8 Hz), 7.3−7.5 (6H, m), 7.63 (1H, d, $J$ = 2.0 Hz), 7.67 (1H, d, $J$ = 8.3 Hz), 7.7 (2H, m), 8.09 (1H, d, $J$ = 6.7 Hz), 10.11 (1H, s), 10.51 (1H, s).

***cis*-*N*-Benzyl-*N*-methyl-3-(3′,4′-dichlorophenyl)-1-indanamine hydrochloride (*cis*-6b)**: $^1$H NMR (DMSO-$d_6$; two sets of signals in a ratio of ∼2/3 were detected) $\delta$ 2.4 (1H, m), 2.69 (1.2H, d, $J$ = 2.3 Hz), 2.8−3.0 (1H, m), 3.38 (1.8H, s), 4.18 (0.8H, s), 4.4 (2.2H, m), 5.02 (0.6H, t, $J$ = 7.4 Hz), 5.25 (0.4H, t, $J$ = 7.7 Hz), 6.91 (0.6H, d, $J$ = 6.0 Hz), 6.97 (0.4H, d, $J$ = 7.0 Hz), 7.2−7.7 (9H, m), 7.92 (1H, d, $J$ = 3.7 Hz), 8.23 (0.4H, d, $J$ = 6.8 Hz), 8.30 (0.6H, d, $J$ = 6.4 Hz), 11.92 (0.4H, s), 12.05 (0.6H, s).

***trans*-*N*,*N*-Dimethyl-3-(3′,4′-dichlorophenyl)-6-iodo-1-indanamine hydrogen maleate (*trans*-7b)**: $^1$H NMR (DMSO-$d_6$) $\delta$ 2.35 (1H, dt, $J$ = 7.8 Hz, 15.2 Hz), 2.7 (6H, bs), 2.91 (1H, dd, $J$ = 8.1 Hz, 14.4 Hz), 4.65 (1H, t, $J$ = 8.2 Hz), 5.08 (1H, d, $J$ = 6.8 Hz), 6.04 (2H, s), 6.82 (1H, d, $J$ = 8.1 Hz), 7.18 (1H, dd, $J$ = 2.5 Hz, 8.9 Hz), 7.48 (1H, d, $J$ = 1.7 Hz), 7.61 (1H, d, $J$ = 8.3 Hz), 7.76 (1H, d, $J$ = 7.8 Hz), 8.02 (1H, s).

**Crystallography.** $C_{17}H_{18}Cl_2N^+Cl^-$, fw = 342.67, monoclinic space group $P2_12_12_1$; $a$ = 5.747(1), $b$ = 11.397(1), $c$ = 26.484(3) Å; $V$ = 1734.7(3) Å$^3$, $Z$ = 4, $\rho_{calc}$ = 1.312 mg mm$^{-3}$; $\lambda$(Cu K$\alpha$) = 1.54178 Å, $\mu$ = 4.712 mm$^{-1}$, $F$(000) = 712, $T$ = 223 K.

A clear colorless crystal was used for data collection on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 40 centered reflections within 15° < 2$\theta$ < 56°. The data collection range had a $\{(\sin\theta)/\lambda\}_{max}$ = 0.55. Three standards, monitored after every 97 reflections, corrected for a decay of 3.2% during the data collection. A set of 1345 reflections was collected in the $\theta/2\theta$ scan mode, with an $\omega$-scan rate (a function of count rate) from 7.5 to 30.0°/min. There were 1282 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The maximum and minimum transmissions were 0.416 and 0.194, respectively. The structure was solved with SHELXTL[58] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on $F_o^2$ varied 194 atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96, H angles idealized, $U_{iso}$(H) were set to 1.2−1.5 $U_{eq}$(C)]. Final residuals were $R^1$ = 0.074 for the 1128 observed data with $F_o > 4\sigma(F_o)$ and 0.080 for all data. Final difference Fourier excursions of

0.66 and −0.35 eÅ$^{-3}$. The anomalous scattering was sufficiently accurate to determine the absolute configuration using the method of Flack,[59] and the absolute structure parameter was 0.01(6). Tables of coordinates, bond distances and angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge CB2 1EW, England.

**Binding and Reuptake Assays.** For the DA transporter assays, two different cell lines that express recombinant human DA (hDAT) transporters were utilized. Initially, C6 cells were used and HEK293 cells were used thereafter. A HEK293 cell line that expresses recombinant human serotonin (hSERT) and norepinephrine (hNET) transporters was used for all 5HT and NE transporter assays. The same cell lines were used for both the binding and reuptake assays. Test drugs (10 mM stock solution) were dissolved in DMSO. Pipetting was performed with a Biomek 2000 robotic workstation.

For the binding assays, C6-hDAT, HEK-hDAT, HEK-hSERT, or HEK-hNET cells were grown on 150-mm diameter tissue culture dishes. Medium was poured off the plate, the plate washed with 10 mL of phosphate-buffered saline (PBS), and 10 mL of lysis buffer (2 mM HEPES, 1 mM ETDA) added. After 10 min, cells were scraped from plates, poured into centrifuge tubes, and centrifuged for 20 min at 30000*g*. Supernatant was removed and the pellet was resuspended in 20−32 mL 0.32 M sucrose depending on the density of binding sites in a given cell line (i.e. a resuspension volume which results in binding ≤ 10% of the total radioactivity) with a Polytron at setting 7 for 10 s. Each assay contained 50 $\mu$L of membrane preparation (approximately 15 $\mu$g protein), 25 $\mu$L of test drug, and 25 $\mu$L of [$^{125}$I]RTI-55 (40−80 pM final concentration) in a final volume of 250 $\mu$L. Krebs HEPES was used for all assays. Membranes were preincubated with test drug for 10 min prior to addition of the [$^{125}$I]RTI-55. The mixture was incubated for 90 min at room temperature in the dark and was terminated by filtration onto GF/C filters using a Tomtech harvester. Scintillation fluid was added to each square and radioactivity remaining on the filter was determined using a Wallac $\mu$- or $\beta$-reader. Competition experiments were conducted with duplicate determinations. Data were analyzed using GraphPAD Prism with $IC_{50}$ values converted to $K_i$ values with the Cheng−Prusoff equation.

For the reuptake assays, C6-hDAT, HEK-hDAT, HEK-hSERT, or HEK-hNET cells were plated on 150-mm dishes and grown till confluent. The medium was removed and cells were washed twice with room-temperature PBS. Following the addition of 3 mL of PBS, the plates were placed in a 25 °C water bath for 5 min. The cells were gently scraped and then triturated with a pipet. Cells from multiple plates were combined. One plate provided enough cells for 48 wells which tested two drug curves. The assay was conducted in 96 1-mL vials and used the Tomtech harvester and betaplate reader. Krebs HEPES (350 $\mu$L) and test drugs (50 $\mu$L) were added to the vials and placed in a 25 °C water bath. Cells (50 $\mu$L) were added, preincubated for 10 min, and [$^3$H]DA, [$^3$H]5HT, or [$^3$H]-NE (50 $\mu$L, 20 nM final concentration) was added. Uptake was terminated after 10 min by filtration on the Tomtech harvester using filters presoaked in 0.05% polyethylenimine. Assays were conducted in triplicate with six test drug concentrations. Data were analyzed using GraphPAD Prism.

**Locomotor Assays**. These were conducted using 40 Digiscan locomotor activity testing chambers (40.5 × 40.5 × 30.5 cm$^3$) housed in sets of two within sound-attenuating enclosures. A panel of 16 infrared beams and corresponding photodetectors were located in the horizontal direction of each activity chamber. A 7.5-W incandescent light above each chamber provided dim illumination and fans provided an 80-dB ambient noise level. Separate groups of 8 nonhabituated male Swiss-Webster mice (Hsd:ND4, aged 2−3 months) were injected via the intraperitoneal route with either vehicle (0.9% saline), cocaine, or the test compound immediately prior to locomotor testing. Horizontal activity (interruption of photocell beams) was measured for 8 h within 10-min periods beginning at 0800 h (2 h after lights on). Testing was conducted with one mouse per activity chamber. $ED_{50}$ values, doses producing one-half maximal stimulant activity (maximum − mean control/10 min), were estimated from a linear regression against log doses of the ascending portion of the dose−response curves.

**Generalization Assays.** Six male Sprague−Dawley rats were trained to discriminate cocaine (10 mg/kg) from saline using a two-lever choice paradigm. Food was available as a reinforcer under a fixed ratio 10 schedule when responding occurred on the injection-appropriate lever. All tests were performed in standard, commercially available chambers (Coulbourn Instruments) using 45-mg food pellets (Bioserve) as reinforcers. Training sessions occurred in a double alternating fashion and tests were conducted between pairs of identical training sessions (i.e. between either two saline or two cocaine training sessions). Tests occurred only if, in the two preceding training sessions, subjects met the criteria of emitting 85% of responses on the injection-appropriate lever for both the first reinforcer (first fixed ratio) and the total session. Test sessions lasted for 20 min or until 20 reinforcers had been obtained. Intraperitoneal injections of test drug or its vehicle (methylcellulose) were performed 60 min prior to the start of the test session. A second injection of either saline or cocaine occurred 10 min prior to the start of the test session. The range of doses of the test compounds was chosen from inactive doses to those that had biological activity as evidenced by full substitution. $ED_{50}$ values were estimated from a linear regression against log doses.

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## References

(1) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters are Related to Self-Administration of Cocaine. *Science* **1987**, *238*, 1219−1223.
(2) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The Dopamine Hypothesis of the Reinforcing Properties of Cocaine. *Trends Neurosci.* **1991**, *14*, 299−302.
(3) Volkow, N. D.; Wang, G.-J.; Fischman, M. W.; Foltin, R. W.; Fowler, J. S.; Abumrad, N. N.; Vitkun, S.; Logan, J.; Gatley, S. J.; Pappas, N.; Hitzemann, R.; Shea, C. E. Relationship Between Subjective Effects of Cocaine and Dopamine Transporter Occupancy. *Nature* **1997**, *386*, 827−830.
(4) Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of Cocaine and Related Drugs in Non-Human Primates. III. Self-Administration by Squirrel Monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150−155.
(5) Dackis, C. S.; Gold, M. S. New Concepts in Cocaine Addiction: The Dopamine Depletion Hypothesis. *Neurosci. Biobehav. Rev.* **1985**, *9*, 469−477.
(6) Weiss, F.; Markou, A.; Lorang, M. T.; Koob, G. F. Basal Extracellular Dopamine Levels in the Nucleus Accumbens are Decreased During Cocaine Withdrawal After Unlimited-Access Self-Administration. *Brain Res.* **1992**, *593*, 314−318.
(7) Kokkinidis, L.; McCarter, B. D. Post-Cocaine-Depression and Sensitization of Brain Stimulation Reward: Analysis of Reinforcement and Performance Effects. *Pharmacol. Biochem. Behav.* **1990**, *36*, 463−471.
(8) Markou, A.; Koob, G.F. Postcocaine Anhedonia. An Animal Model of Cocaine Withdrawal. *Neuropsychopharmacology* **1991**, *4*, 17−26.
(9) George, F. R.; Goldberg, S. R. Genetic Approaches to the Analysis of Addiction Processes. *Trends Pharmacol. Sci.* **1989**, *10*, 78−83.

(10) Uhl, G. R.; Elmer, G. I.; Labuda, M. C.; Pickens, R. W. Genetic influences in drug abuse. In *Psychopharmacology: The Fourth Generation of Progress*; Bloom F. E., Kupfer D. J., Eds.; Raven Press: New York, 1995; pp 1793−1806.
(11) Markou, A.; Kosten, T. R.; Koob, G. F. Neurobiological Similarities in Depression and Drug Dependence: A Self-Medication Hypothesis. *Neuropsychopharmacology* **1998**, *18*, 135−174.
(12) Volkow, N. D.; Wang, G.-J.; Fowler, J. S.; Logan, J.; Gatley, S. J.; Gifford, A.; Hitzemann, R. J.; Ding, Y.-S.; Pappas, N. Prediction of Reinforcing Responses to Psychostimulants in Humans by Dopamine D2 Receptor Levels. *Am. J. Psychiat.* **1999**, *156*, 1440−1443.
(13) Johnson, D. N.; Vocci, F. J. Medications Development at the National Institute on Drug Abuse: Focus on Cocaine. In *Cocaine Treatment: Research and Clinical Perspectives*; Tims, F. M., Leukefeld, C. G., Eds.; NIDA Research Monograph No. 135; NIDA: Rockville, MD, 1993; pp 57−70.
(14) Mendelson, J. H.; Mello, N. K. Management of Cocaine Abuse and Dependence. *N. Engl. J. Med.* **1996**, *334*, 965−972.
(15) Carroll, F. I.; Howell, L. L.; Kuhar, M. K. Pharmacotherapies for Treatment of Cocaine Abuse: Preclinical Aspects. *J. Med. Chem.* **1999**, *42*, 2721−2736.
(16) Rothman, R. B.; Becketts, K. M.; Radesca, L. R.; de Costa, B. R.; Rice, K. C.; Carroll, F. I.; Dersch, C. M. Studies of the Biogenic Amine Transporters. II. A Brief Study on the Use of [$^3$H]DA-Uptake Inhibition to Transporter-Binding Inhibition Ratios for the in vitro Evaluation of Putative Cocaine Antagonists. *Life Sci.* **1993**, *53*, PL267−272.
(17) Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J.; Ball, R. G. Methoxylation of Cocaine Reduces Binding Affinity and Produces Compounds of Differential Binding and Dopamine Uptake Inhibitory Activity: Discovery of a Weak Cocaine 'Antagonist'. *J. Med. Chem.* **1993**, *36*, 3975−3977.
(18) Oldendorf, W. H. Some Relationships Between Addiction and Drug Delivery to the Brain. In *Bioavailability of Drugs to the Brain and the Blood-Brain Barrier*; Frankenheim, J., Brown, R. M., Eds.; NIDA Research Monograph No. 120; NIDA: Rockville, MD, 1992; pp 13−25.
(19) Volkow, N. D.; Ding, Y.-S.; Fowler, J. S.; Wang, G.-J.; Logan, J.; Gatley, J. S.; Dewey, S.; Ashby, C.; Lieberman, J.; Hitzemann, R.; Wolf, A. P. Is Methylphenidate Like Cocaine? Studies on Their Pharmacokinetics and Distribution in the Human Brain. *Arch. Gen. Psychiat.* **1995**, *52*, 456−463.
(20) Pianezza, M. L.; Sellers, E. M.; Tyndale, R. F. Nicotine Metabolism Defect Reduces Smoking. *Nature* **1998**, *393*, 750.
(21) Lukas, S. E.; Moreton, J. E.; Khazan, N. Comparative Study of the Electroencephalographic and Behavioral Effects of l-α-Acetylmethadol (LAAM), Two of its Metabolites and Morphine and Methadone in the Rat. *J. Pharmacol. Exp. Ther.* **1980**, *215*, 382−389.
(22) Misra, A. L.; Bartolomeo, J. G.; Bloch, R.; Mulé, S. J.; Bates, T. R. Pharmacokinetics and Metabolism of l-α-[O,O′-$^3$H$_2$]Acetylnormethadol (Nor-LAAM), the Active Metabolite of LAAM, in Acutely and Chronically Treated Rhesus Monkey. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 599−607.
(23) Glowa, J. R.; Fantegrossi, W. E.; Lewis, D. B.; Matecka, D.; Rice, K. C.; Rothman, R. B., Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazinyl Decanoate, a Long-Acting Ester Derivative of GBR 12909. *J. Med. Chem.* **1996**, *39*, 4689−4691.
(24) Froimowitz, M. Conformational Analysis of Cocaine, the Potent Analogue 2$\beta$-Carbomethoxy-3$\beta$-(4-fluorophenyl)tropane (CFT), and Other Dopamine Reuptake Blockers. *J. Comput. Chem.* **1993**, *14*, 934−943.
(25) Froimowitz, M.; Patrick, K. S.; Cody, V. Conformational Analysis of Methylphenidate and Its Structural Relationship to Other Dopamine Reuptake Blockers Such as CFT. *Pharm. Res.* **1995**, *12*, 1430−1434.
(26) Froimowitz, M.; Deutsch, H. M.; Shi, Q.; Wu, K.-M.; Glaser, R.; Adin, I.; George, C.; Schweri, M. M. Further Evidence for a Dopamine Reuptake Pharmacophore. The Effect of *N*-Methylation on threo-Methylphenidate and Analogues. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1213−1218.
(27) Froimowitz, M.; George, C. Conformational Analysis and a Crystal Structure of Bupropion, an Antidepressant with Dopamine Reuptake Blocking Activity. *J. Chem. Inform. Comput. Sci.* **1998**, *38*, 506−510.
(28) Musso, D. L.; Mehta, N. B.; Soroko, F. E.; Ferris, R. M.; Hollingworth, E. B.; Kenney, B. T. Synthesis and Evaluation of the Antidepressant Activity of the Enantiomers of Bupropion. *Chirality* **1993**, *5*, 495−500.
(29) Froimowitz, M.; Wu, K.-M.; Rodrigo, J., George, C. Conformational Preferences of the Potent Dopamine Reuptake Blocker BTCP and Its Analogues and Their Incorporation into a Pharmacophore Model. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 135−146.
(30) Rosenzweig-Lipson, S.; Bergman, J.; Spealman, R. D.; Madras, B. K. Stereoselective Behavioral Effects of Lu 19−005 in Monkeys: Relation to Binding at Cocaine Recognition Sites. *Psychopharmacology* **1992**, *107*, 186−194.
(31) Bøgesø, 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.
(32) Goldstein, A.; Aronow, L.; Kalman, S. *Principles of Drug Action: The Basis of Pharmacology*, 2nd ed.; Wiley & Sons: New York, 1974; pp 242−267.
(33) Spealman, R. D. Modification of Behavioral Effects of Cocaine by Selective Serotonin and Dopamine Reuptake Inhibitors in Squirrel Monkeys. *Psychopharmacology* **1993**, *112*, 93−99.
(34) Howell, L. L.; Byrd, L. D. Serotonergic Modulation of the Behavioral Effects of Cocaine in the Squirrel Monkey. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1551−1559.
(35) Chen, J.; van Praag; H. M.; Gardner, E. L. Activation of 5-HT$_3$ Receptor by 1-Phenylbiguanide Increases Dopamine Release in the Rat Nucleus Accumbens. *Brain Res.* **1991**, *543*, 354−357.
(36) Chen, J.; Paredes, W.; van Praag, H. M.; Lowinson, J. H.; Gardner, E. L. Presynaptic Dopamine Release is Enhanced by 5-HT$_3$ Receptor Activation in Medial Prefrontal Cortex of Freely Moving Rats. *Synapse* **1992**, *10*, 264−266.
(37) Benloucif, S.; Keegan, M. J.; Galloway, M. P. Serotonin-Facilitated Dopamine Release In Vivo: Pharmacological Characterization. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 373−377.
(38) Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S. R.; Ator, R.; Giros, B.; Miller, G. W.; Caron, M. G. Cocaine Self-Administration in Dopamine-Transporter Knockout Mice. *Nat. Neurosci.* **1998**, *1*, 132−137.
(39) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. Nontricyclic Antidepressant Agents Derived from *cis*- and *trans*-1-Amino-4-aryltetralins. *J. Med. Chem.* **1984**, *27*, 1508−1515.
(40) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortley, S. O.; Schneider, C. R.; Setler, P. E. Pyrroloisoquinoline Antidepressants. 2. In-Depth Exploration of Structure−Activity Relationships. *J. Med. Chem.* **1987**, *30*, 1433−1454.
(41) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-Phenyltropane Analogues of Cocaine: Synthesis, Inhibition of Binding at Cocaine Recognition Sites, and Positron Emission Tomography Imaging. *J. Med. Chem.* **1993**, *36*, 855−862.
(42) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. Synthesis and Pharmacology of Potential Cocaine Antagonists. 2. Structure−Activity Relationship Studies of Aromatic Ring-Substituted Methylphenidate Analogues. *J. Med. Chem.* **1996**, *39*, 1201−1209.
(43) Houlihan, W. J.; Boja, J. W.; Parrino, V. A.; Kopajtic, T. A.; Kuhar, M. J. Halogenated Mazindol Analogues as Potential Inhibitors of the Cocaine Binding site at the Dopamine Transporter. *J. Med. Chem.* **1996**, *39*, 4935−4941.
(44) Deutsch, H. M.; Collard, D. M.; Zhang, L.; Burnham, K. S.; Deshpande, A. K.; Holtzman, S. G.; Schweri, M. M. Synthesis and Pharmacology of Site-Specific Cocaine Abuse Treatment Agents: 2-(Aminomethyl)-3-phenylbicyclo[2.2.2]- and -[2.2.1]-alkane Dopamine Uptake Inhibitors. *J. Med. Chem.* **1999**, *42*, 882−895.
(45) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. Efficient Synthesis of a Phosphinate Bis-Amino Acid and Its Use in the Construction of Amphiphilic Peptides. *J. Org. Chem.* **1994**, *59*, 4206−4210.
(46) Froimowitz, M.; Wu, K.-M.; Paredes, W.; Giordano, A.; Spector, J.; Liu, X.; Lepore, M.; Gardner, E. L. Effects of a Slow-Onset, Long-Lasting Dopamine Reuptake Blocker on Cocaine Self-Administration and on Nucleus Accumbens Dopamine. Abstract 432.2, Society for Neuroscience, New Orleans, LA, October 1997.
(47) Hayes, R.; Spector, J.; Gardner, E. L.; Froimowitz, M.; Wu, K.-M.; Liu, X.; Paredes, W.; Ashby, Jr., C. R.; Lepore, M.; Hiroi, N. Slow-Onset, Long-Lasting Prodrugs as Potential Medications for Cocaine Addiction: Intravenous Cocaine Self-Administration Studies. Abstract 861.4, Society for Neuroscience, Los Angeles, CA, November 1998.
(48) Negus, S. S.; Brandt, M. R.; Mello, N. K. Effects of the Long-Acting Monoamine Reuptake Inhibitor Indatraline on Cocaine Self-Administration in Rhesus Monkey. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 60−69.
(49) Froimowitz, M.; Wu, K.-M.; Spector, J.; Hayes, R.; Vorel, S. R.; Paredes, W.; Ashby, Jr., C. R.; Gardner, E. L. Slow-Onset, Long-Lasting Prodrugs as Potential Medications for Cocaine Addiction: Intravenous Cocaine Self-Administration Studies in Rat Strains with Different Vulnerabilities to Drug-Seeking Behavior. Abstract 632.8, Society for Neuroscience, Miami Beach, FL, October 1999.

(50) Stoelwinder, J.; Roberti, M.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S. Differential binding and dopamine uptake activity of cocaine analogues modified at nitrogen. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 303−308.
(51) Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. Structure−Activity Relationship Studies of N-Sulfonyl Analogues of Cocaine: Role of Ionic Interaction in Cocaine Binding. *J. Med. Chem.* **1994**, *37*, 3440−3442.
(52) Xu, C.; Reith, M. E. A. Modeling of the pH dependence of the binding of WIN 35,428 to the dopamine transporter in rat striatal membranes: Is the bioactive form positively charged or neutral? *J. Pharmacol. Exp. Ther.* **1996**, *278*, 1340−1348.
(53) Madras, B. K.; Pristupa, Z. B.; Niznik, H. B.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Meltzer, P. C. Nitrogen-Based Drugs are not Essential for Blockade of Monoamine Transporters. *Synapse* **1996**, *24*, 340−348.
(54) Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George C.; Madras, B. K. 2-Carbomethoxy-3-ary-8-oxabicyclo-[3.2.1]octanes: Potent Non-Nitrogen Inhibitors of Monoamine Transporters. *J. Med. Chem.* **1997**, *40*, 2661−1673.
(55) Meltzer, P. C.; Blundell, P.; Chen, Z.; Yong, Y. F.; Madras, B. K. Bicyclo[3.2.1]octanes: Synthesis and Inhibition of Binding at the Dopamine and Serotonin Transporters. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 857−862.
(56) Kozikowski, A. P.; Simoni, D.; Roberti, M.; Rondanin, R.; Wang, S.; Du, P.; Johnson, K. M. Synthesis of 8-Oxa Analogues of Norcocaine Endowed with Interesting Cocaine-like Activity. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1831−1836.
(57) Miles, M. P.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J. L.; Kozikowski, A. P. Tuning the Selectivity of Monoamine Transporter Inhibitors by the Stereochemistry of the Nitrogen Lone Pair. *J. Am. Chem. Soc.* **1998**, *120*, 9072−9073.
(58) Sheldrick, G. M. *SHELXTL*, version 5.1; Bruker Analytical X-ray Instruments: Madison, WI, 1997.
(59) Flack, H. D. On Enantiomorph-Polarity Estimation. *Acta Crystallogr.* **1983**, *A39*, 876−881.

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