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Synthesis and Biological Evaluation of Bupropion Analogues as Potential Pharmacotherapies for Cocaine Addiction

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A series of bupropion (**1a**) analogues (**1b−1ff**) were synthesized, and their *in vitro* and *in vivo* pharmacological properties evaluated with the goal of developing a **1a** analogue that had better properties for treating addictions. Their *in vitro* pharmacological properties were examined by [^{3}H]dopamine ([^{3}H]DA), [^{3}H]serotonin ([^{3}H]5HT), and [^{3}H]norepinephrine ([^{3}H]NE) uptake inhibition studies, and by binding studies at the dopamine, serotonin, and norepinephrine transporters using [^{125}I]RTI-55 in cloned transporters. Several analogues showed increased [^{3}H]DA uptake inhibition with reduced or little change in [^{3}H]5HT and [^{3}H]NE uptake inhibition relative to bupropion. Thirty-five analogues were evaluated in a 1 h locomotor activity observation test and 32 in an 8 h locomotor activity observation test and compared to the locomotor activity of cocaine. Twenty-four analogues were evaluated for generalization to cocaine drug discrimination after i.p. administration, and twelve analogues were tested in a time course cocaine discrimination study using oral administration. 2-(*N*-Cyclopropylamino)-3-chloropropiophenone (**1x**) had the most favorable *in vitro* efficacy and *in vivo* pharmacological profile for an indirect dopamine agonist pharmacotherapy for treating cocaine, methamphetamine, nicotine, and other drugs of abuse addiction.

Introduction

Cocaine abuse continues to be a significant medical problem in the United States with an estimated 2.1 million current users of the drug by age 12 and older.[1] In addition to its direct effects, cocaine abuse has also contributed to the increase of the spread of human immunodeficiency virus (HIV) infection and drug-resistant tuberculosis. Even though considerable effort has been devoted to the development of a pharmacotherapy to treat patients addicted to cocaine, no effective medication is yet available for use in the clinic.[2]

Indirect dopamine agonists[3−10] are one class of compounds that have received considerable attention for treatment of cocaine addiction. Studies directed toward the development of indirect dopamine agonists have involved structurally diverse classes of compounds including analogues of 3-phenyltropane, 1,4-dialkylpiperazines (GBR), phenylpiperidine, benztropine, methylphenidate, and mazindol.[3,4,8,11]

Compound **1a** [(±)-2-*tert*-butylamino-3′-chloropropiophenone] is a well-known antidepressant. A sustained release (SR[a]) formulation of **1a** has proven to be highly useful for treating nicotine abuse.[12−14] Despite its use as an antidepressant for almost 30 years,[15] the neurochemical mechanism(s) underlying its action is still not well-defined.[16,17] Compound **1a** inhibits the reuptake of dopamine (DA) and norepinephrine (NE) but, unlike many other antidepressants, has very little effect on inhibiting serotonin (5HT) reuptake.[17,18] Its antidepressant effects have been attributed to its effects on the noradrenergic system.[17,19,20] This is based in part on the fact that **1a** is metabolized to an active metabolite (2*S*,3*S*)-3,5,5-trimethyl-2-phenylmorpholin-2-ol (**2**), which is a relatively more potent NE uptake inhibitor and is present at higher steady-state concentrations than those of **1a**.[17] However, some reports suggest that **1a** is a more potent DA reuptake inhibitor than an NE reuptake inhibitor.[21] Microdialysis studies showed that acute **1a** administration increased extracellular DA.[20] In animal behavioral pharmacology studies, **1a** induced locomotor activity,[22,23] generalized to cocaine and amphetamine in drug discrimination studies,[24,25] produced conditioned place preference (CPP),[26] and is self-administered in both rats[27] and nonhuman primates.[25] In addition, **1a** increased responding on a fixed interval (FI) schedule stimulus-shock termination study in squirrel monkey.[28] These effects likely reflect **1a**'s action as a DA reuptake inhibitor, and thus, **1a** has the properties of an indirect dopamine agonist.

In a clinical trial of **1a** for cocaine abuse, an exploratory analysis suggested that patients with depression may have benefited.[29] In another clinical study, **1a** augmented contingency management for cocaine dependence in methadone-maintained patients, but there was no evidence for efficacy of **1a** alone.[30] Compound **1a** has even greater

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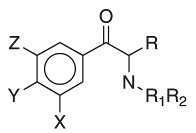
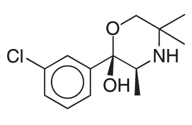
[a] Abbreviations: DA, dopamine; 5HT, serotonin; NE, norepinephrine; CPP, condition place preference; FI, fixed internal; SR, sustained release; DEG, diethylene glycol; PPA, polyphosphoric acid; ABSA, acetamidobenzenesulfonyl azide; DBU, 1,4-diazabicyclo[5.4.0]undec-7-ene; HEK, human embryonic kidney; DAT, dopamine transporter, SERT, serotonin transporter; NET, norepinephrine transporter.

efficacy for methamphetamine dependence. In one study, **1a** reduced methamphetamine-induced subjective effects and cue-induced craving.[31] In another study, **1a** reduced methamphetamine use in relatively light users.[32,33]

Given **1a**'s dopmainergic properties and its success in dependence studies for cocaine, methamphetamine, and nicotine, it is surprising that very few **1a** analogues have been synthesized and studied to identify an analogue with better overall pharmacological properties. The study presented here further examines the pharmacology of previously reported **1a** analogues and reports the pharmacology of several new **1a** analogues. The results are compared to the pharmacological properties of **1a** and cocaine. The study's goal was to develop a **1a** analogue with increased dopaminergic properties as determined by its DA uptake with reduced noradrenergic properties as determined by NE uptake properties to reduce the potential of cardiotoxicity.[34] Since the increased dopaminergic properties could also increase abuse potential, the desired analogue would need to have slow onset and long duration of action properties that are believed to reduce abuse potential.[35−38] Specifically, this study describes the synthesis of a number of **1a** analogues (**1a**−**1ff**, **3**−**7**) and reports their monoamine transporter binding properties, functional monoamine uptake inhibition efficacy, locomotor activity, and drug discrimination properties. 2-(*N*-*tert*-Butyl)-3′-chlorobutyrophenone (**1o**), 2-(*N*-*tert*-butyl)-3′-chloropentanophenone (**1p**), and 2-(*N*-*tert*-butyl)-3′-chlorohexanophenone (**1q**) were 31, 29, and 3.6 times more potent than **1a** as DA uptake inhibitors. 2-(*N*-Cyclopropylamino)-3-chloropropiophenone (**1x**), which was 4 times more potent as a DA uptake inhibitor, was also more potent than **1a** as a 5HT uptake inhibitor. When tested *in vivo*, **1o**, **1p**, and **1x** showed effects of long duration in a test of locomotor activity. When compared for generalization to cocaine in a drug discrimination test after oral administration, **1x** also had a slower onset and longer duration of action than **1a**.



1a–2ff
(see Table 1)



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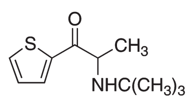

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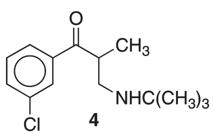

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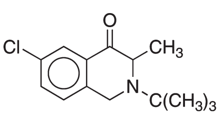

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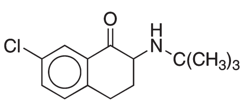

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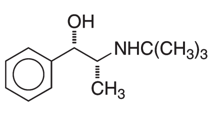

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Chemistry

Scheme 1 describes the general synthesis used for **1a**−**1ff**. In general, the original procedure used to prepare **1a**[39] and modified by Chenard and co-workers[40] was followed. This procedure provided an efficient way to the bromo intermediates **10** and the subsequent **1a** analogues **1b**−**1ff**. The procedure used to convert nitriles **8** to the corresponding ketones was similar to that of Birch and co-workers[41] or Bailey and co-workers.[42] 2-(*N*-*tert*-Butylamino)-1-(2′-thienyl)-1-propanone (**3**) was synthesized using a procedure similar to that used to synthesize the **1a** analogue **1bb** starting with ketone **11** (see Scheme 2). Syntheses of **1b**, **1d**, **1f**, **1h**, **1j**, **1o**, **1p**, and **1w** were reported in a communication as intermediates used in the synthesis of other compounds.[43] However, no experimental details and no characterization of the compounds were given.[43] The hydrochloride salt of **1b** has been reported.[44] This compound was characterized as the fumarate salt in this study.

Scheme 3 shows the procedure used for the synthesis of **4**. Subjection of 3′-chloropropiophenone (**10a**) to Mannich reaction conditions with aqueous formaldehyde and dimethylamine gave **13**. The methiodide **14** was obtained by alkylation of **13** with iodomethane. Treatment of **14** with *tert*-butylamine gave first a mixture of **15** and the desired **4**. Subjection of the mixture to excess *tert*-butylamine provided the desired target compound.

Compound **5** was synthesized by the route shown in Scheme 4. Ketone **17** was obtained in moderate yield by the addition of ethylmagnesium bromide to acid **16** in the presence of the catalyst bis(diphenylphosphinoethane)dichloronickel(II). Bromination of the ketone gave dibromo compound **18** and a small amount of monobromo derivative **19**. Treatment of the crude mixture with *tert*-butylamine in refluxing toluene gave the desired target compound **5**.

Scheme 5 outlines the synthesis of **1a** analogue **6**. Treatment of **20** with hydrazine and potassium hydroxide in refluxing diethylene glycol (DEG) afforded **21**. Compound **21** was cyclized to **22** using polyphosphoric acid (PPA). Subjection of **22** to acetamidobenzenesulfonyl azide (ABSA) in acetonitrile containing 1,4-diazabicyclo[5.4.0]undec-7-ene (DBU) yielded the diazo compound **23**. Treatment of **23** with *tert*-butylamine in dry toluene in the presence of ruthenium acetate provided **6**.

Compound **7** was prepared by reduction of **1a** as previously reported.[43]

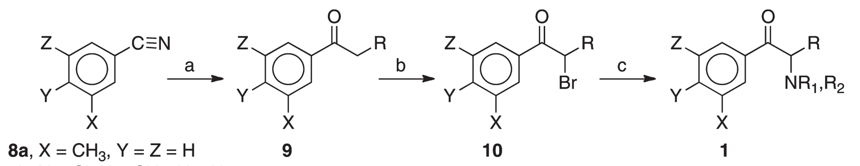
Biology

The competition binding assays were performed using (h)DAT, (h)SERT, and (h)NET, stably expressed in HEK293 cells, and the nonselective radioligand [^{125}I]RTI-55 for the analogues **1a**−**1ff** and **3**−**7** (Table 1).[45] The HEK-(h)DAT, -(h)SERT, and -(h)NET cells were also used to evaluate the compounds' ability to block the reuptake of [^{3}H]dopamine ([^{3}H]DA), [^{3}H]serotonin ([^{3}H]5HT), and [^{3}H]norepinephrine ([^{3}H]NE) (Table 1).[45]

The **1a** analogues were evaluated *in vivo* for their ability to increase locomotor activity of mice and to generalize to the discriminative stimulus effects of cocaine in rats, according to protocols established by the NIDA Cocaine Treatment Discovery Program. Each compound was first evaluated in a locomotor activity test[46−48] lasting 1 h, and compounds were reconsidered in a second test (lasting 8 h) if necessary to assess durations of effect longer than 60 min. The locomotor test results for each compound are listed in Table 2 in terms of the ED_{50} in mg/kg, each compound's maximal stimulant effect as a percent of cocaine's maximal effect, the 30 min time period in which the maximum locomotor stimulation occurred, and the duration of the locomotor stimulation.

Generalization to cocaine was subsequently evaluated for a subset of the **1a** analogues using rats trained to discriminate

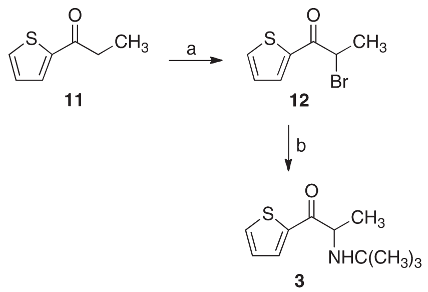
Scheme 1[a]



8a, X = CH_3, Y = Z = H
b, X = Cl, Y = CH_3, X = H
c, X = Z = Cl, Y = H
d, X = Cl, Y = Z = H
e, X = Y = Cl, Z = H

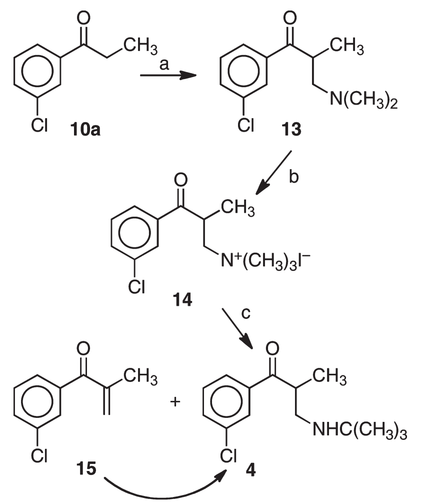
[a] Reagents: (a) RCH_2MgBr, $(C_2H_5)_2O$ or RLi, pentane/$(C_2H_5)_2O$; (b) Br_2, CH_2Cl_2; (c) R_1,R_2NH.

Scheme 2[a]



[a] Reagents: (a) Br_2, CH_2Cl_2; (b) $H_2NC(CH_3)_3$.

Scheme 3[a]



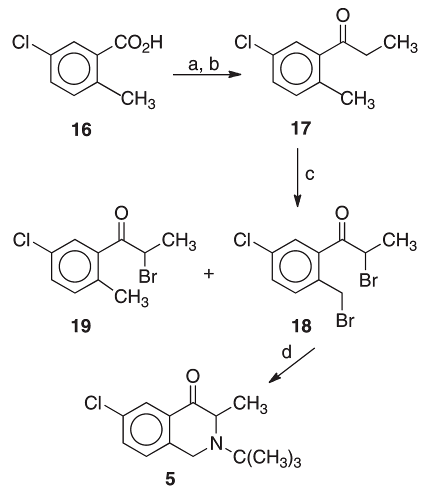
[a] Reagents: (a) CH_2O, $(CH_3)_2NH$; (b) CH_3I; (c) $(CH_3)_3CNH_2$.

cocaine from saline in a lever choice procedure.[47,49,50] Table 3 lists the percent of cocaine-appropriate responding following various intraperitoneal doses of the analogues along with ED_{50} values for cases when such responding reached at least 80%, suggesting generalization. Analogues were also evaluated for the time course of their generalization to cocaine when dosed p.o. in a volume of 1 mL/kg at 45, 90, 180, or 360 min before the generalization test. Table 4 lists the percent of cocaine-appropriate responding following various oral doses of the analogues at each time point, along with ED_{50} values for cases when such responding reached at least 80%.

Results and Discussion

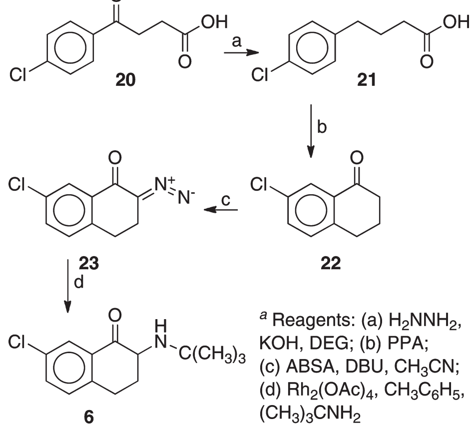
Compound **1a** is an approved drug for treating depression[15] and as a smoking cessation drug.[12−14] In addition, it has

Scheme 4[a]



[a] Reagents: (a) EtMgBr, $Ni(dppe)Cl_2$, THF; (b) HCl/H_2O; (c) Br_2, CH_2Cl_2; (d) $(CH_3)_3CNH_2$, toluene, reflux.

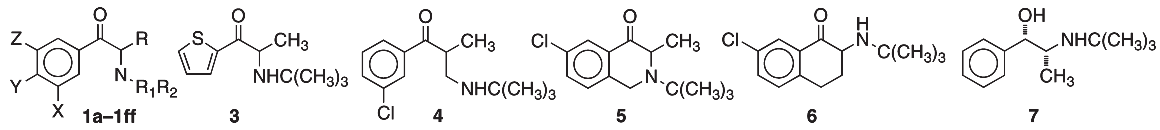
Scheme 5[a]



[a] Reagents: (a) H_2NNH_2, KOH, DEG; (b) PPA; (c) ABSA, DBU, CH_3CN; (d) $Rh_2(OAc)_4$, $CH_3C_6H_5$, $(CH_3)_3CNH_2$.

shown some positive effects in clinical trials for treatment of cocaine and methamphetamine dependence.[29−33] While **1a**'s precise mechanism of action is unknown, it is a weak inhibitor of DA uptake and has been shown to increase DA transmission in both the nucleus accumbens and the prefrontal cortex.[51] In addition, **1a** is a locomotor stimulant,[22,23] generalizes to cocaine,[24,25] produces CPP,[26] and is self-administered[27] in animal behavioral pharmacology studies. PET imaging studies show that administration of **1a** results in relatively low DAT occupancy.[52−54] Thus, the modest

Table 1. Comparison of Dopamine, Serotonin, and Norepinephrine Transporter Binding and Uptake Studies in C6hDAT, HEK-hSERT, and HEK-hNET Cells for **1a** Analogues



							binding,[a] K_i (nM)			uptake,[a] IC_{50} (nM)		
compd	R	R_1	R_2	X	Y	Z	DAT	SERT	NET	[^{3}H]DA	[^{3}H]5-HT	[^{3}H]NE
cocaine							272 ± 60	601 ± 130	830 ± 147	267 ± 47	318 ± 57	385 ± 40
1a	CH_3	H	$C(CH_3)_3$	Cl	H	H	871 ± 126	> 10 μM	6970 ± 2620	945 ± 213	[c]	443 ± 245
1b	CH_3	H	$C(CH_3)_3$	H	H	H	5730 ± 480	> 10 μM	5700 ± 150	2310 ± 750	[c]	8700 ± 1200
1c	CH_3	H	$C(CH_3)_3$	F	H	H	4510 ± 460	> 10 μM	> 10 μM	1460 ± 220	[c]	[c]
1d	CH_3	H	$C(CH_3)_3$	Br	H	H	4200 ± 1200	> 10 μM	> 7140 ± 640	950 ± 210	[c]	6500 ± 1000
1e	CH_3	H	$C(CH_3)_3$	CH_3	H	H	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
1f	CH_3	H	$C(CH_3)_3$	H	Cl	H	2195 ± 151	> 10 μM	> 10 μM	2319 ± 429	[c]	[c]
1g	CH_3	H	$C(CH_3)_3$	H	Br	H	1918 ± 221	4170 ± 730	> 10 μM	1295 ± 375	2520 ± 610	[c]
1h	CH_3	H	$C(CH_3)_3$	H	CH_3	H	> 10 μM	> 10 μM	6840 ± 1368	[c]	[c]	4100 ± 860
1i	CH_3	H	$C(CH_3)_3$	F	F	H	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
1j	CH_3	H	$C(CH_3)_3$	Cl	Cl	H	472 ± 81	1480 ± 310	5400 ± 1200	271 ± 96	> 10 μM	2100 ± 380
1k	CH_3	H	$C(CH_3)_3$	Cl	CH_3	H	1150 ± 370	2100 ± 510	5100 ± 860	650 ± 150	400 ± 190	900 ± 130
1l	CH_3	H	$C(CH_3)_3$	CH_3	Br	H	1740 ± 440	1215 ± 90	4600 ± 601	950 ± 310	473 ± 74	1623 ± 35
1m	CH_3	H	$C(CH_3)_3$	F	H	F	5660 ± 490	> 10 μM	> 10 μM	5600 ± 1800	[c]	[c]
1n	CH_3	H	$C(CH_3)_3$	Cl	H	Cl	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
1o	C_2H_5	H	$C(CH_3)_3$	Cl	H	H	459 ± 50	> 10 μM	3195 ± 145	31 ± 9	[c]	969 ± 410
1p	C_3H_7	H	$C(CH_3)_3$	Cl	H	H	96 ± 20	> 10 μM	1171 ± 260	33 ± 7	[c]	472 ± 93
1q	C_4H_9	H	$C(CH_3)_3$	Cl	H	H	350 ± 100	> 10 μM	3190 ± 850	69 ± 23	[c]	400 ± 190
1r	C_5H_{11}	H	$C(CH_3)_3$	Cl	H	H	709 ± 8.0	> 10 μM	4300 ± 1300	1570 ± 570	[c]	2000 ± 1000
1s	C_6H_{13}	H	$C(CH_3)_3$	Cl	H	H	510 ± 120	> 10 μM	2580 ± 700	135 ± 80	[c]	4890 ± 580
1t	$(CH_3)_2CHCH_2$	H	$C(CH_3)_3$	Cl	H	H	140 ± 14	6200 ± 1800	2300 ± 700	440 ± 180	> 10 μM	360 ± 190
1u	$(C_6H_{11})CH_2CH_2$	H	$C(CH_3)_3$	Cl	H	H	1700 ± 780	6200 ± 1500	3800 ± 1700	> 10 μM	> 10 μM	> 10 μM
1v	CH_3	H	$CH_2CH_2CH_3$	Cl	H	H	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
1w	CH_3	H	$CH(CH_3)_2$	Cl	H	H	3980 ± 230	> 10 μM	> 10 μM	2000 ± 516	[c]	[c]
1x	CH_3	H	$CH(CH_2CH_2)$	Cl	H	H	1150 ± 370	3420 ± 260	4000 ± 1200	265 ± 94	3180 ± 170	2150 ± 850
1y	CH_3	H	$CH(CH_2CH_2CH_2)$	Cl	H	H	343 ± 72	3450 ± 610	1800 ± 110	258 ± 46	185 ± 49	86 ± 32
1z	CH_3	H	$CH(CH_2CH_2CH_2CH_2)$	Cl	H	H	2200 ± 490	> 10 μM	5700 ± 400	980 ± 340	[c]	221 ± 94
1aa	C2H$_5$	H	$C(CH_3)_3$	Cl	Cl	H	278 ± 43	860 ± 230	2240 ± 510	175 ± 55	790 ± 320	135 ± 4.9
1bb	C3H$_7$	H	$C(CH_3)_3$	Cl	Cl	H	43.7 ± 6.5	842 ± 50	520 ± 100	84 ± 28	1580 ± 560	43 ± 14
1cc	CH_3	CH_3	$C(CH_3)_3$	Cl	H	H	6400 ± 1200	> 10 μM	> 10 μM	2060 ± 340	[c]	[c]
1dd	CH_3	CH_3	CH_3	Cl	H	H	4133 ± 548	> 10 μM	3090 ± 740	1534 ± 222	[c]	1260 ± 290
1ee	CH_3	CH_2CH_3	CH_2CH_3	Cl	H	H	2214 ± 308	> 10 μM	4476 ± 107	1744 ± 288	[c]	4603 ± 986
1ff	CH_3	$CH_2CH_2CH_2CH_2CH_2$		Cl	H	H	1148 ± 298	5479 ± 824	4760 ± 1540	1033 ± 287	970 ± 178	4798 ± 947
3							> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
4				Cl	H	H	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
5						H	> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
6							> 10 μM	> 10 μM	> 10 μM	[c]	[c]	[c]
7							> 10 μM	4000 ± 1400	> 10 μM	[c]	1240 ± 210	[c]

[a] Values for the mean ± standard error of three independent experiments, each conducted with triplicate determination. [b] Data taken from ref 43. [c] Not determined.

Table 2. Comparison of Locomotor Stimulant Effects for **1a** Analogues

compd	ED_{50}[a] mg/kg	95% conf[b]	% peak[c] cocaine	time of max effect[d] (min)	duration[e] (min)
cocaine	7.8 ± 0.45[f]		100	0−30	40−100
1a	5.5	(3.4−8.9)	87	0−30	130−270
1b	11.2	(6.0−21.4)	95	0−30	120
1c	17.5	(11.0−27.5)	80	0−30	150
1d	13.5	(8.5−21.4)	57	0−30	90−120
1e	31.0	NC[g]	76	10−40	50
1f	NE[h]				
1g	29.5	(18.6−46.8)	54	140−170	160
1h	3.8	(1.8−8.4)	26	30−60	60−140
1i	54.6	NC[g]	58	10−40	60
1j	26.9	(9.4−76.8)	61	270−300	140−240
1k	≥35.5[i]		≥77[i]	10−40	60
1l	12.6	(6.4−25.1)	36	50−80	240
1m	35.0	(22.4−54.3)	84	0−30	280
1n	NE[h]				
1o	18.6	(10.7−31.6)	62	0−30	360
1p	15.5	(10.5−22.9)	108	90−120	210−480
1q	10.2	(5.5−19.0)	136	0−30	40−460
1r	12.9	(5.5−29.5)	90	60−90	280−460
1s	5.6	(2.4−12.9)	94	110−140	130−400
1t	25.7	(8.7−74.1)	89	260−290	60
1u	14.1	(5.8−33.9)	33	60−90	160
1v	NE[h]				
1w	6.2	(2.8−14.1)	46	20−50	50−160
1x	16.6	(11.9−22.9)	82	0−30	350
1z	12.3	(9.1−16.2)	107	0−30	330−340
1aa	38.0	(14.8−95.5)	69	0−30	60
1bb	38.0	(24.0−61.7)	93	0−30	470
1cc	11.7	(8.3−16.6)	95	80−110	200−340
1dd	9.3	NC[g]	64	90−120	180−190
1ee	16.6	(10.5−26.3)	90	20−50	130−240
1ff	34.7	(16.2−74.1)	45	320−350	30−150
3	NE[h]				
4	NE[h]				
5	NE[h]				
6	2.6	NC[g]	41	150−180	390−480
7	NE[h]				

[a] Dose producing 50% of the compound's maximal effect. [b] 95% confidence interval based on logistic fit to ascending portion of dose response. [c] Compound's maximal effect as a percent of cocaine's maximal effect. [d] The 30 min period in which the maximal effect occurred. [e] Duration of stimulant effect for one or more doses on ascending portion of dose response. [f] Mean ± SD for 28 evaluations of cocaine's stimulant effect. [g] Could not be calculated. [h] No stimulant effect detected. [i] Peak effect not determined.

effect of **1a** could be in part due to its weak dopaminergic effects.

Much research, particularly in animals, suggests that repeated administration of cocaine produces disruption in brain dopamine (DA) functions that can lead to enhanced cocaine-seeking behavior. Reversal of these changes in DA activity can attenuate these cocaine-induced neurochemical and behavioral effects.[55,56] In the early 1990s, we and others hypothesized that a compound having good potency and selectivity for the dopamine transporter (DAT) combined with a slow onset and long-duration of activity relative to cocaine would reverse these changes in DA activity and would, therefore, be useful pharmacotherapy for cocaine addiction. An optimal compound would have no or low abuse potential itself.[4,6,9,55,56] While not exactly analogous, this is similar to the use of methadone for opiate addiction and varenicline or nicotine replacement therapy for tobacco smoking (nicotine addiction). Therefore, a **1a** analogue possessing increased dopaminergic properties may be able to reverse dopaminergic deficits in chronic cocaine users better than **1a**. This study identified **1a** analogues that had increased dopaminergic properties combined with slow onset and long duration of activity as determined by their DA uptake, locomotor, and drug discrimination properties.

In this study, we report that **1a** analogues with better DAT binding (lower K_i values) and [^{3}H]DA uptake (lower IC_{50} values) were obtained by (a) replacing the methyl group α to the ketone group with medium-sized alkyl groups; (b) changing the type and number of substituents on the 3-chlorophenyl ring; and (c) replacing the *N-tert*-butyl group with other *N*-alkyl groups. Since for the most part the rank order potency of the binding assays mirrors those of the uptake values, only the monoamine uptake values will be discussed.

Compound **1a** has IC_{50} values of 945 and 443 nM for DA and NE uptake inhibition, respectively (Table 1). Since the K_i value for binding to the SERT was > 10 μM, the 5HT uptake IC_{50} was not determined. Thus, **1a** is 3.5 times less potent as an inhibitor of DA uptake than cocaine. Compound **1a** and cocaine have almost equal potency for NE uptake, and cocaine with an IC_{50} value of 318 nM for 5HT uptake is much more potent than **1a**. Analogues **1o**−**1q** obtained by replacing the α-methyl group in **1a** with an ethyl, propyl, or butyl group had IC_{50} values of 31, 33, and 69 nM, respectively, compared to 945 nM for **1a**, and were the most DA efficacious analogues. Analogues **1s**−**1t** with larger hexyl and isobutyl

Table 3. Effect of **1a** Analogues in Rats Trained to Discriminate Cocaine after IP Administration

		dose (mg/kg), % cocaine-lever responding										
compd	pretreatment Time (min)	vehicle	cocaine	1	2.5	5	10	25	50	100	ED_{50} (mg/kg)	comments[a]
1a	15	0	83	24.1	0.7	0	67.1	66.3	66.7			A
1b	15	0	100		16	32.8	83.3	83.4			5.9 (3.8−9.1)	B
1c	15	1	83		17.6	0	50.2	100			10.0 (0.6−182.0)	B
1d	30	0	100		0.3	34.4	21	83.6			11.6 (6.0−22.6)	B
1f	15	0	83			0.1	32.7	18.1	0	33.3		B
1g	80	2	100				1.7	16.7	20	0.5		B
1h	15	0	83			0.6	0	16.7	66.7	100	39.6 (29.3−53.7)	C
1i	45	0	100				1.7	17	47	63.9		C
1j	240	0	100				0	16.7	22.4	2		B
1l	50	0	100				0	0	16.7	66.9		C
1m	30	0	100		0	43.6	16.7	50	83.3		17.3 (6.6−45.0)	B
1o	15	19	83		0.6	33.4	50	100			7.8 (4.9−12.5)	C
1p	15	0	100		0.2	17.2	33.3	83.3			12.2 (7.4−20.1)	D
1q	30	11	100		0	17.2	66.6	100			7.8 (5.7−10.7)	E
1r	45	17	100				0	1	50.9			F
1s	75	18	99			0	0	48.5	49.9	67.2		B
1u	60	0	100			0.2	0.7	69.6				B[b]
1w[c]	15	1	90	21.2	27	43.8	53.3	78.6	73.5	94.9	10.0 (3.6−27.4)	
1x[d]	15	1	100	21.5	39.5	67.2	66.7	66.3				F
1z	30	1	100	0.9	23.9	0	66.2	83.4			8.8 (6.1−12.5)	G
1aa	30	0	100	0	33.3	16.7	10	100			10.9[e]	B
1bb	30	0	100	0	41.8	33.3	33.3	100			6.3 (2.5−15.5)	B
1cc	15	0	100			0	49.4	75	66.7			F
1dd	15	3	100		0	83.3	83.2	100			3.9 (2.5−6.1)	G
1ee	15	2	83		0	16.7	98.6	74.8			5.9 (3.6−9.7)	H
1ff	335	0	100				7	16.5	32.7	33.7		B
cocaine (n = 66)		4.5	89.1	14.7	39.2	60.6	84.9				3.2 (2.7−3.8)	

[a] Response rate comments: A = The average response rate was increased relative to vehicle control following 5 to 25 mg/kg with a maximum effect at 5 mg/kg (127% of vehicle control). The average response rate decreased to 30% of vehicle control following 50 mg/kg **1a**. B = Response rate failed to show significant change. C = Response rate was decreased following 100 mg/kg. D = Response rate increased following 25 mg/kg. E = Response rate was increased following 5 mg/kg. F = Response rate was reduced following 50−100 mg/kg. G = Response rate was decreased following 25 mg/kg. H = Response rate was decreased following 25 mg/kg. [b] Adverse effects were seen at 50 mg/kg. [c] Compound **1w** was tested at 0.5 mg/kg and showed 0.3% cocaine-lever responding. [d] Compound **1x** was tested at 0.1, 0.25, and 0.5 mg/kg and showed % cocaine-lever responding of 9%, 24%, and 63%. [e] Confidence interval could not be calculated.

α substituents had IC_{50} values of 135 and 440 nM and, thus, were also better DA uptake inhibitors than **1a**. Replacement of the α-methyl group in **1a** with a much larger 2-(cyclohexyl)ethyl α substituent to give **1u** resulted in complete loss of DA uptake inhibition (IC_{50} value of $> 10\ \mu$M).

Changing the aromatic substituent pattern of **1a** also led to analogues with better IC_{50} values for DA uptake inhibition. For example, the 3,4-dichlorophenyl analogue **1j** and the 3-chloro-4-methylphenyl analogue **1k** with IC_{50} values of 271 and 650 nM, respectively, were 3.5 and 2 times more potent inhibitors than **1a**. The 3-bromophenyl and 4-bromo-3-methylphenyl analogues **1d** and **1l** with IC_{50} values of 950 nM were as potent as **1a**. Replacing the α methyl group of **1j** with an ethyl or propyl group gave analogues **1aa** and **1bb**, which had slightly lower IC_{50} values than **1j**. Replacement of the 3-chlorophenyl ring with a thiophene ring led to **3**, which had no efficacy for DA uptake inhibition.

Replacement of the *N-tert*-butyl group with an *N*-cyclopropyl or *N*-cyclobutyl group gave **1x** and **1y** with IC_{50} values of 265 and 258 nM for DA uptake inhibition, which are 3.6 and 3.7 times more potent than **1a**. The *N*-cyclopentyl analogue **1z** had an IC_{50} of 980 nM, almost identical to that of **1a**. The *N*-isopropyl analogue **1w** with an IC_{50} value of 2000 nM was 2 times less potent than **1a**. Surprisingly, the *N*-propyl analogue **1v** was inactive. None of the *N,N*-disubstituted analogues **1cc**−**1ff** had high efficacy for DA uptake inhibition. Of these, the most potent compound was the *N*-piperidino analogue **1ff**, which had an IC_{50} value of 1033 nM.

Overall, the DA uptake results show that changing the α-methyl group of **1a** to a larger ethyl (**1o**), *n*-propyl (**1p**), or

Table 4. Drug Discrimination Effects of **1a** and **1a** Analogues in Rats (p.o.) in a Time Course Study

	dose (mg/kg), % cocaine-lever responding										
compd	pretreat-ment time	vehicle	2.5	5	10	25	50	100	200	ED_{50} (mg/kg)	comments[a]
1a	45	0		33	17	50	83			22.8	A
	90			0	1	0	50			(12.0−43.2)	
	180			2.5	0	22	17				
	360			0	0	1	0				
1b	45	11	6	0	0	51	83			25.2	A
	90		1	0	0	33	33			(26.5−38.4)	
	180		0	33	3	20	50				
	360		0	0	0	34	4				
1c	45	0		17	17	49	67	95		25.3	B
	90			0	0	16	33	75		(13.7−46.9)	
	180			0	33	0	18	83			
	360			0	0	0	0	50			
1d	45	0	13	0	0	17	51	67	100	52.9	C, D
	90		0	15	0	0	21	56	100	(33.0−84.7)	
	180		0	0	0	0	0	34	5		
	360		33	7	0	0	0	14	34		
1m	45		0	31	0	4	67	18		41.5	E
	90	0	20	7	33	25	58	84		(23.4−73.6)	
	180		0	0	0	0	20	17			
	360		0	0	3	7	0	0			
1p	45	0	0	17	33	33[b]	50[c]	100[d]		23.2	F
	90		0	0	0	33[b]	17[c]	100[d]		(11.9−45.4)	
	180		0	22	33	0[b]	17[c]	50[d]			
	360		0	0	0	0[b]	16[c]	1[d]			
1q	45	0		17	0	0	83			46.9[e]	A
	90			0	0	0	17				
	180			26	29	0	17				
	360			0	0	0	0				
1s	45	0			0	0	83			46.9[e]	G
	90				0	0	17				
	180				0	0	25				
	360				0	0	0				
1x[e]	45		34	34	74	67				12.8	H
	90	0	0	0	33	83				(8.2−19.9)	
	180		34	0	33	99					
	360		0	0	0	0					
1z	45	1	17	50	60	67	100			6.6	A, I
	90		NT	0	33	67	83			(3.0−14.6)	
	180		NT	0	0	66	33				
	360		NT	0	0	34	16				
1aa	45	17	33	17	34	50	83			15.2	A
	90		17	1	0	33	67			(4.5−51.2)	
	180		50	0	0	2	50				
	360		17	0	2	33	16				
1bb[f]	45		0	0	33	58				22.8[e]	A
	90	17	0	13	0	84					
	180		0	0	5	17					
	360		0	0	0	0					
1dd	45	0	19	38	83					5.3	A
	90		0	0	100					(3.1−9.1)	
	180		33	0	33						
	360		0	0	18						

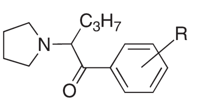
[a] Response rate comments: A = No significant change in response rate. B = Response rate was reduced at 50 and 100 mg/kg. C = Response rate was decreased at 200 mg/kg. D = Four of six rats failed to complete the first fixed ratio at 180 min following 200 mg/kg. E = Response rate was decreased 90 min following 50 mg/kg. F = Response rate was decreased following 2.5 and 5 mg/kg at 45 min. G = Response rate was increased relative to vehicle control 45 min following 10 mg/kg. H = Response rate failed to show significant change at the 90 min pretreatment interval. I = Decreased food consumption was observed following 25 mg/kg (1/24 rats) and 50 mg/kg (1/24 rats). [b] Dose = 20 mg/kg. [c] Dose = 40 mg/kg. [d] Dose = 80 mg.kg. [e] Confidence intervals could not be calculated. [f] Compound **1x** was also studied at other doses. At 0.25 mg/kg, the % cocaine lever responding was 0 for all time points except 360 min, when it was 34%. At 0.5 mg/kg, the % cocaine lever responding was 1, 16, 0, and 2 at 45, 90, 180, and 360 min, respectively. At 1 mg/kg, the % cocaine lever responding was 0 at all time points. [g] Compound **1f** was tested at 1 mg/kg and showed 0% lever pressing at all time points.

n-butyl (**1q**) group gave the greatest increase in [^{3}H]DA uptake inhibition relative to **1a**. In addition, adding a 4′-chloro (**1j**) group to **1a** gave an increase in [^{3}H]DA uptake inhibition relative to **1a**. Compounds with an α-ethyl or α-*n*-propyl substituent combined with a 4′-chloro substituent (**1aa**, **1bb**) did not show increased [^{3}H]DA uptake inhibition relative to **1o** and **1p**, respectively. Replacement of the *N*-*tert*-butyl group with an *N*-cyclopropyl (**1x**) or *N*-cyclopentyl (**1y**) resulted in a small increase in [^{3}H]DA uptake inhibition. Overall, 11 **1a** analogues from this study had lower IC_{50} values for DA uptake inhibition (IC_{50} = 31 nM to 650 nM) than **1a** (IC_{50} = 945 nM). The conformationally restricted **1a** analogues **5** and **6** had no efficacy at all three transporters.

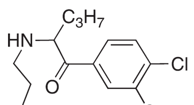
Similarly to **1a**, most of the **1a** analogues from this study showed little efficacy for 5HT uptake inhibition. The 3-chloro-4-methylphenyl, 3-methyl-4-bromophenyl, and *N*-cyclopentyl analogues **1k**, **1l**, and **1y** with IC_{50} values of 400, 473, and 185 nM for 5HT uptake inhibition, respectively, were the most potent.

Since there is concern that a pharmacotherapy having norepinergic activity might enhance the cardiotoxicity of cocaine, we hoped that our **1a** analogues would have reduced [^{3}H]NE uptake inhibition potency compared to that of **1a**. Several of the potent DA uptake inhibitors (**1o**−**1q**, **1s**, and **1x**) had lower efficacy for NE uptake inhibition than **1a**. However, analogues **1bb**, **1y**, and **1aa** with IC_{50} values of 43, 86, and 135 nM for NE uptake inhibition, respectively, were 34, 17, and 10 times better as NE uptake inhibitors than **1a**. While these analogues are not of interest for development of a cocaine pharmacotherapy, they would be of interest for the development of **1a** analogues as potential treatment for smoking cessation or possibly as antidepressants.

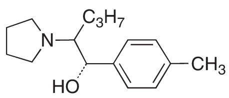
Meltzer and co-workers[57] used the DAT inhibitor pyrovalerone (**24a**) as a lead structure to develop new monoamine uptake inhibitors. In his study, Meltzer pointed out that pyrovalerone has structural features similar to **1a**. The *N*-cyclopentyl **1a** analogue **1z** in the present study is most similar to pyrovalerone. However, **1z** was not as potent as pyrovalerone as a DA and NE uptake inhibitor. Meltzer synthesized several analogues of **24a**, where the aromatic substituent, the amine group, and the substituent α to the carbonyl were changed. Several analogues had lower IC_{50} values for DA and NE uptake inhibition than **24a**.



24a, R = 4-CH_3
b, R = 4-$NHCOCH_3$
c, R = naphthyl
b, R = 3,4-diCl



25



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Replacement of the cyclopentyl group in **1z** with a cyclobutyl or cyclopropyl group to give **1y** and **1x**, respectively, resulted in significant changes in monoamine uptake properties. Compound **1z** had an IC_{50} value of 980 nM for DA uptake inhibition compared to 258 and 265 nM for **1y** and **1x**, respectively. Surprisingly, the IC_{50} value for NE uptake inhibition for **1z** of 221 nM improved to 86 nM for the cyclobutyl analogue **1y** but increased to 2150 nM for the cyclopropyl analogue **1x**. The cyclopentyl analogue **1z** was totally inactive as a 5HT uptake inhibitor, whereas the cyclobutyl analogue **1y** has an IC_{50} of 185 nM for this transporter, which is better than the other **1a** analogues studied (Table 1). Changing the cyclopentyl in **1z** to the cyclopropyl group in **1x** also resulted in improved 5HT uptake inhibition but only to an IC_{50} value of 3180 nM. Meltzer[57] found that opening the cyclopentyl ring of **24d** to give **25** resulted in a large loss in uptake inhibition at all three transporters. We found that **1v**, which can be viewed as the open ring analogue of **1x**, was inactive at all three transporters. Reduction of the carbonyl of **24a** to give alcohol **26** resulted in total loss of affinity at all three transporters. We found that reduction of the carbonyl of **1a** analogue **1b** to give 7 resulted in loss of affinity at the DAT and NET but gave a significant increase in potency for 5HT uptake from > 10 000 nM in **1a** to 1240 nM in **7**.

Thirty-five **1a** analogues were evaluated for their ability to increase locomotor activity, and the results were compared to results obtained for cocaine in separate studies conducted on a monthly basis. Cocaine had an ED_{50} value of 7.8 ± 0.45 mg/kg in 28 studies conducted over the period in which the **1a** analogues were evaluated, whereas the ED_{50} value for **1a** was 5.5 mg/kg. Cocaine's locomotor stimulant efficacy (maximum locomotor activity minus activity of vehicle control) was set at 100%, and efficacy of each analogue was expressed relative to that for cocaine as determined during the same month. Four analogues, **1q**, **1s**, **1w**, and **1dd**, yielded ED_{50} values similar to that of cocaine (ED_{50} = 5.6−10.2). The ED_{50} values for 28 compounds ranged from 2.6 mg/kg for **6** to 54.6 mg/kg for **1i**, whereas 7 analogues failed to yield locomotor stimulant effects at any time within 8 h following injection. Compound **1a** and ten analogues, **1b**, **1m**, **1p**, **1r**, **1s**, **1t**, **1z**, **1bb**, **1cc**, and **1ee**, showed locomotor stimulant efficacy similar to cocaine (84−107%). Compound **1q** with 136% was more stimulatory than cocaine. The remaining compounds had peak stimulant effects of 26−82% of that of cocaine. Several compounds, **1g**, **1j**, **1p**, **1r**, **1s**, **1t**, **1u**, **1cc**, **1dd**, **1ff**, and **6** had periods of maximum stimulatory effect at times of 1 h or greater following injection. The period of maximum stimulatory effect of **1a** was 0−30 min, which was similar to that of cocaine and analogues **1b**−**1d**, **1m**, **1o**, **1q**, and **1x**−**1bb**. Compounds **1j**, **1t**, and **1ff** yielded a very slow onset of stimulatory activity, with peak effects delayed by 260−320 min following injection. Compound **1a** had a stimulant effect of approximately 2−4.5 h duration. Sixteen of the analogues, **1b**, **1j**, **1l**, **1m**, **1o**, **1p**, **1q**, **1r**, **1s**, **1x**, **1z**, **1bb**, **1cc**, **1dd**, **1ee**, and **6**, had duration of locomotor activity greater than 3 h. Analogues **1o**−**1q**, which were 31, 29, and 14 times more potent than **1a** as DA uptake inhibitors, yielded very long durations of locomotor activity stimulation (360 to 480 min). In addition, analogue **1x**, which was 3.6 times more potent than **1a** as a DA uptake inhibitor with increased potency as a 5HT uptake inhibitor, possessed a duration of locomotor effect of 350 min, which is longer than **1a**. Analogue **1o** also had a much longer duration of effect compared with **1a**. It is also interesting to note that the conformationally rigid analogue **6** yielded a weak stimulant effect (31% of cocaine) that was of very slow onset and long duration.

Meltzer and co-workers[57] evaluated pyrovalerone analogues **14b** and **24c** for locomotor activity, which had IC_{50} values of 67.9 and 40 nM, respectively, for DA uptake inhibition. Compounds **24b** and **24c** had ED_{50} values of 0.21 and 2.2 mg/kg with long durations of action. The cyclopentyl **1a** analogue **1z** had an ED_{50} value of 12.3 mg/kg with long durations of action (Table 2).

Twenty-four **1a** analogues were evaluated using drug discrimination tests for generalization to cocaine after i.p. administration in rats using standard 2-lever operant chambers, with pretreatment intervals adjusted based on studies of locomotor activity (Table 3). Twelve analogues were also tested in a time course study using oral administration (Table 4). Fourteen **1a** analogues showed full generalization to cocaine with ED_{50} values of 3.9 mg/kg for **1dd** to 39.6 mg/kg for **1h** in the i.p. cocaine discrimination study. Compound **1a** substituted only partially for the discrimination stimulus effects of cocaine. The lowest dose yielding maximum substitution (10 mg/kg) resulted in 67% cocaine-appropriate responding. As pointed out in the Introduction, others have reported that **1a** shows full generalization in cocaine discrimination studies in animals including rats after i.p. administration.[24,58,59] However, response rate was decreased relative to vehicle control following 5−25 mg/kg doses. The failure to obtain full generalization was likely due to the greater response suppression observed in this sample of rats.

Compound **1dd** with an ED_{50} = 3.9 mg/kg was the most potent of the analogues, producing full generalization at doses of 5 to 25 mg/kg, even though its potency at all three transporters was relatively weak. Analogue **1b** fully generalized at 10 and 25 mg/kg. Analogues **1b**, **1c, 1d**, **1o**, **1p**, **1q, 1z**, **1aa**, **1bb**, and **1dd** all showed full generalization at a dose of 25 mg/kg. Analogue **1m** showed full generalization at a dose of 50 mg/kg and analogues **1h** and **1w** at 100 mg/kg. The *N*-cyclopropyl analogue **1x** produced partial generalization from 5 to 25 mg/kg, **1cc** from 10 to 50 mg/kg, and **1u** at 25 mg/kg. Higher doses were not tested due to decreases in response rate or adverse effects. Analogue **1s** produced partial generalization from 25 to 100 mg/kg, **1i** from 50 to 100 mg/kg, and **1l** at 100 mg/kg. Doses greater than 100 mg/kg were not tested in the i.p. studies.

All 12 analogues tested in the time-course study showed full generalization in at least one time point. ED_{50} values were calculated for the 45 min pretreatment with the exception of **1m**, **1x**, and **1bb**, which were calculated at the 90 min pretreatment. ED_{50} values ranged from 5.3 for **1dd** to 52.9 mg/kg for **1d**. Compound **1a** showed full generalization at 45 min following a 50 mg/kg dose and partial generalization at 90 min after a 50 mg/kg dose. The ED_{50} for drug-appropriate responding 45 min following **1a** was 22.8 mg/kg. Analogue **1dd** showed full generalization at 45 and 90 min after a 10 mg/kg dose. Analogue **1x** showed partial generalization at 45 min following a 10 mg/kg and 25 mg/kg dose and full generalization at 90 and 180 min at a 25 mg/kg dose. Analogue **1x** was the only compound to show full generalization at 180 min. Analogue **1bb** also showed full generalization at 90 min at a dose of 25 mg/kg. Similar to **1a**, analogues **1b**, **1q**, **1s**, and **1aa** showed full generalization at one time point at a dose of 50 mg/kg. Analogue **1z** showed full generalization at 45 and 90 min following 50 mg/kg. Analogues **1c** and **1p** showed full generalization at a dose of 100 mg/kg and **1d** at a dose of 200 mg/kg.

Even though most of the analogues that had low IC_{50} values for DA uptake also had low ED_{50} values for cocaine generalization, there were several exceptions. For example, the most potent analogue in the cocaine discrimination studies was **1dd** with an ED_{50} value of 3.9 mg/kg in the i.p. study and 5.3 mg/kg in the p.o. time course study. However, the IC_{50} value for **1dd** for DA uptake inhibition was 1534 nM compared to 943 nM for **1a**. Analogue **1j** with an IC_{50} value of 271 nM was 3.5 times more potent as a DA uptake inhibitor than **1a** but did not even show partial generalization to cocaine. In the Introduction, it was pointed out that **1a** is metabolized to yield the active metabolite **2** *in vivo* that likely contributes to its therapeutic effects. The nature of the metabolites associated with **1dd**, **1j**, and possibly other analogues is unknown, but it is conceivable that metabolites with different profiles of activity could account for the imperfect correlation between the *in vitro* and *in vivo* studies.

In summary, a number of **1a** analogues showed monoamine uptake inhibition efficacy and an animal behavior profile that suggested they might be better indirect dopamine agonists than **1a**. Analogues **1o**−**1q** and **1x** had the best overall profiles, with **1x** being the most interesting. Compound **1x** was four times more potent than **1a** in the DA uptake inhibition test and was more selective for DA uptake relative to NE uptake inhibition than **1a**. Compounds **1o**−**1q** were 30, 29, and 14 times more potent than **1a** as DA uptake inhibitors raising concern that they may have too much dopaminergic activity for treatment of cocaine addiction. Unlike **1a** and **1o**−**1q**, **1x** also has some efficacy as a 5HT uptake inhibitor. Studies from our laboratory as well as others have reported animal behavioral studies that show that reduction of cocaine self-administration can be enhanced by 5HT uptake inhibition.[60] Compound **1x** in the initial drug discrimination study showed partial generalization to cocaine at the dose of 5, 10, and 25 mg/kg compared to **1a**, which showed partial generalization at a dose of 10 and 25 mg/kg. Analogues **1o**−**1q** all showed full generalization at 25 mg/kg and, thus, were more cocaine-like. More importantly, **1x** was more potent than **1a** in the time-course discrimination study and had a slower onset and longer duration of action. The *in vitro* efficacy and animal behavioral properties thought to be necessary for an indirect dopamine agonist pharmacotherapy for treating abuse of cocaine, methamphetamine, and nicotine are both better for **1x** than for **1a**.

Experimental Section

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a 300 MHz (Bruker AVANCE 300) or 500 MHz (Varian Unity ANOVA) spectrometer. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal $(CH_3)_4Si$ (δ 0.0). Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Purity of compounds (>95%) was established by elemental analysis. Analytical thin-layer chromatography (TLC) was carried out on plates precoated with silica gel GHLF (250 μM thickness). TLC visualization was accomplished with a UV lamp or in an iodine chamber. All moisture-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Anhydrous solvents were purchased from Aldrich Chemical Co. or VWR.

Synthesis of 2-(*N-tert*-Butylamino)-3-chlorobutanophenone (1o) Fumarate. The synthesis of the title compound is given as a typical example used for the synthesis of **1a** analogues **1b**−**1ff**. Experimental details for the synthesis of each analogue can be found in Supporting Information.

Step 1. 3′-Chlorobutanophenone (9o). 3-Chlorobenzonitrile **8d** (3.0 g, 0.022 mol) and THF (75 mL) were placed in a 250 mL flask equipped with a magnetic stir bar. The flask was cooled to 0 °C with an ice−water bath. Propylmagnesium chloride (26.2 mL, 2 M in Et_2O) was syringed in over a 10 min period. The reaction was stirred under nitrogen at room temperature. After 96 h, the flask was cooled to 0 °C. The reaction was quenched by adding 0.1 M hydrochloric acid (75 mL). After stirring for 1 h at room temperature, the solution was transferred to a separatory funnel. Water (50 mL) and ammonium hydroxide (2 mL) were added to basify the reaction, and the aqueous layer was extracted 3× with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give 3.51 g (88%) of **9o** as a light-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.81−7.87 (d, 1H), 7.50−7.56 (d, 1H), 7.38−7.40 (t, 1H), 2.90−2.95 (t, 2H), 1.72−1.81 (m, 2H), 0.99−1.05 (t, 3H).

Step 2. 2-Bromo-3′-chlorobutanophenone (10o). Ketone **9o** (3.51 g, 0.01 mol) and methylene chloride (75 mL) were placed in a 500 mL flask equipped with a magnetic stir bar. The solution was stirred under nitrogen, and bromine (0.98 mL, 0.019 mol) was syringed into the flask. A small amount of bromine was added initially to catalyze the reaction. After reaction started, the remaining bromine was added over a 10 min period. After stirring for 14 h, the solution was transferred to a separatory funnel. A saturated sodium bicarbonate solution was added to basify the reaction. The aqueous layer was washed with a 1 M sodium thiosulfate solution and extracted 3× with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give 5.20 g of an oil. The orange oil was purified by flash chromatography on silica gel using 5:1 hexane−methylene chloride as eluent to afford 4.04 g (80%) of **10o** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.86−7.91 (d, 1H), 7.54−7.59 (d, 1H), 7.41−7.48 (t, 1H), 4.99−5.05 (t, 1H), 2.07−2.30 (m, 2H), 1.07−1.12 (t, 3H).

Step 3. 2-(*N-tert*-Butylamino)-3′-chlorobutanophenone (1o) Fumarate. Intermediate **10o** (3.90 g, 0.015 mol) and *tert*-butylamine (7.84 mL, 0.075 mol) were placed in a pressure tube equipped with a magnetic stir bar. The tube was sealed and heated at 75 °C with an oil bath. After 2 h, the reaction mixture was cooled to room temperature and transferred to a separatory funnel. A saturated sodium bicarbonate solution was added to basify the reaction, and the aqueous layer was extracted with methylene chloride (3×). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oil was dissolved in methanol, and the solvent was removed under reduced pressure to afford 3.51 g (93%) of **1o** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.84−7.89 (d, 1H), 7.53−7.58 (d, 1H), 7.40−7.48 (t, 1H), 4.04−4.10 (m, 1H), 2.04−2.24 (m, 2H), 1.02 (s, 9H), 0.92−0.99 (t, 3H).

Amine **1o** was converted to a fumarate salt by adding 1 equiv of fumaric acid to an Et_2O solution of **1o**. Recrystallization from methanol and Et_2O afforded 2.64 g of **1o**·fumarate as a white solid: mp 155−156 °C. ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 8.10−8.15 (d, 1H), 7.76−7.81 (d, 1H), 7.60−7.68 (t, 1H), 6.70 (s, 2H), 5.20−5.25 (t, 1H), 2.01−2.11 (m, 2H), 1.37 (s, 9H), 1.15−1.22 (t, 3H). Anal. ($C_{18}H_{24}NO_5$) C, H, N.

2-Methyl-3-(*N,N*-dimethylamino)-3′-chloropropiophenone (13). 3′-Chloropropiophenone **10a** (5.0 g, 0.03 mol) and methanol (50 mL) were placed in a pressure tube equipped with a magnetic stir bar. Aqueous formaldehyde (2.44 mL, 37% by weight) and aqueous dimethylamine (4.09 mL, 40% by weight) were added. The tube was sealed and refluxed in an oil bath at 75 °C. After 18 h, the reaction mixture was cooled to room temperature. Hydrochloric acid (4 mL) was added, and the reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure. The reaction mixture was transferred to a separatory funnel and extracted 3× with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to afford 5.73 g (86%) of **13** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.82−7.87 (d, 1H), 7.51−7.56 (d, 1H), 7.39−7.46 (t, 1H), 3.60−3.70 (q, 1H), 2.75−2.85 (m, 1H), 2.30−2.39 (m, 1H), 2.23 (s, 6H), 1.18−1.22 (d, 3H).

2-Methyl-3-(trimethylammonia)-3′-chloropropiophenone Iodide (14). Amine **13** (5.73 g, 0.025 mol) and methanol (50 mL) were placed in a pressure tube equipped with a magnetic stir bar. Iodomethane (1.74 mL, 0.03 mol) was added. After 2 days, more iodomethane (0.6 mL) was added. After stirring for 7 days at room temperature, the solution was filtered through a fritted funnel and washed with methanol. The solvent was removed under reduced pressure. The salt was recrystallized from isopropanol and Et_2O. The solution was filtered and washed with cold Et_2O. The solvent was removed under reduced pressure to afford 5.56 g (60%) of **14** as light-yellow crystals. ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 8.11−8.16 (d, 1H), 7.69−7.74 (d, 1H), 7.56−7.62 (t, 1H), 4.24−4.34 (m, 2H), 3.42−3.52 (m, 1H), 3.15 (s, 9H), 1.31−1.34 (d, 3H).

2-Methylene-3′-chloropropiophenone (15). Quaternary amine salt **14** (4.0 g, 0.011 mol), sodium carbonate (1.27 g, 0.01 mol), and DMF (50 mL) were placed in a pressure tube equipped with a magnetic stir bar. The mixture was stirred to dissolve the sodium carbonate. After 30 min, *tert*-butylamine (1.26 mL, 0.01 mol) was added. The tube was sealed and heated in an oil bath at 70 °C. After 5 h, the tube was cooled to room temperature, and the reaction mixture was transferred to a separatory funnel. Water (50 mL) and ammonium hydroxide (10 drops) were added to basify the reaction, and the aqueous layer was extracted 3× with Et_2O. The organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give 3.4 g of **14** and **15** as a light-yellow oil. ^{1}H NMR ($CDCl_3$): 2× as many aromatic peaks (thus, two compounds), alkene shown by δ 5.96 (s, 1H), 5.64 (s, 1H), 2.05 (s, 3H).

2-Methyl-3-(*N-tert*-butylamino)-3′-chloropropiophenone (4) Fumarate. The mixture of **14**/**15** (3.4 g) and an excess of *tert*-butylamine (6 mL) were placed in a pressure tube, and the reaction mixture was stirred at room temperature. The solution was transferred to a separatory funnel and basified with a saturated sodium bicarbonate solution. The aqueous layer was extracted 3× with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give 2.14 g (78%) of **4** as a light-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.82−7.87 (d, 1H), 7.52−7.57 (d, 1H), 7.39−7.46 (t, 1H), 3.52−3.60 (m, 1H), 3.01−3.10 (m, 1H), 2.60−2.69 (m, 1H), 1.20−1.25 (d, 3H), 1.11 (s, 9H).

Amine **4** was converted to a fumarate salt using the same procedures as for **1o**. Recrystallization from methanol and Et_2O afforded 2.53 g of **4**·fumarate as a white solid: mp 128−129 °C. ^{1}H NMR (CD_3OD) δ 8.01 (s, 1H), 7.94−7.99 (d, 1H), 7.63−7.68 (d, 1H), 7.51−7.58 (t, 1H), 6.65 (s, 2H), 3.85−3.96 (m, 1H), 3.50−3.60 (m, 1H), 3.04−3.11 (m, 1H), 1.41 (s, 9H), 1.27−1.30 (d, 3H). Anal. ($C_{18}H_{24}ClNO_5$) C, H, N.

3′-Chloro-6′-methylpropiophenone (17). To a stirred solution of 3-chloro-6-methylbenzoic acid **16** (12.5 g, 0.073 mol) in dry THF (100 mL) was added bis(diphenylphosphinoethane)-dichloronickel(II) catalyst (794 mg, 1.5 nmol). After stirring under nitrogen at 0 °C for 15 min, ethylmagnesium bromide (147 mL, 1 M in THF) was added via a cannula. After the initial exothermic reaction, the reaction mixture turned green, then black. Subsequently, the remaining ethylmagnesium bromide (100 mL, 3 M in THF) was added. After stirring for 16 h at room temperature, the reaction was quenched with 10% hydrochloric acid/water and extracted with Et_2O. The organic layer was washed with sodium bicarbonate, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give 13.02 g of an oil. The yellow oil was purified by flash chromatography on silica gel using 9:1 hexane−Et_2O as eluent to afford 6.87 g (51%) of **17** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.30−7.34 (d, 1H), 7.16−7.19 (d, 1H), 2.85−2.93 (q, 2H), 2.44 (s, 3H), 1.15−1.23 (t, 3H).

2-Bromo-3′-chloro-6′a-bromomethylpropiophenone (18). To a stirred solution of ketone **17** (4.79 g, 0.026 mol) in chloroform (100 mL) was added bromine (3.4 mL, 0.066 mol). The reaction mixture was heated with a heat gun until hydrogen bromide evolution began. Upon completion, the solvent was removed under reduced pressure to give 6.15 g (69%) of **18** as an orange oil. ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.48−7.54 (d, 1H), 7.23−7.27 (d, 1H), 5.11−5.19 (q, 1H), 4.66−4.76 (dd, 2H), 1.91−1.93 (d, 3H). The monobrominated product **19** was also formed. ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.34−7.38 (d, 1H), 7.24−7.27 (d, 1H), 5.08−5.16 (q, 1H), 2.44 (s, 3H), 1.87−1.90 (d, 3H).

2-*tert*-Butyl-6-chloro-3-methyl-4-oxo-1,2,3,4-tetrahydroisoquinoline (5) Hydrochloride. To a solution of **18** (6.15 g, 0.018 mol) in toluene (300 mL) was added *tert*-butylamine (4 mL, 38 mmol). After refluxing 4 h under nitrogen, the resulting slurry was basified with ammonium hydroxide and extracted with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered.

The solvent was removed under reduced pressure, and toluene was azeotroped with ethanol and water (5:3:1) to give the cyclized amine as an oil. The orange oil was purified by flash chromatography on silica gel using 9:1 hexane−Et_2O as eluent to afford 1.26 g (28%) of **5** as a pale-yellow oil. ^1H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.43−7.47 (d, 1H), 7.17−7.20 (d, 1H), 4.00−4.17 (m, 3H), 1.23−1.26 (d, 3H), 1.15 (s, 9H).

The isoquinoline **5** was converted to a hydrochloride salt and was recrystallized from methanol−Et_2O to afford 740 mg of **5**·HCl as an off-white solid: mp 182 °C (dec). ^1H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.68−7.71 (d, 1H), 7.35−7.38 (d, 1H), 4.88−4.95 (d, 1H), 4.55−4.62 (d, 1H), 4.42−4.44 (q, 1H), 1.94−1.97 (d, 3H), 1.47 (s, 9H). Anal. ($C_{14}H_{19}C_{12}NO$) C, H, N.

4-(4-Chlorophenyl)butyric Acid (21). A heterogeneous mixture of 4-(4-chlorophenyl)-4-oxobutanoic acid (5.00 g, 0.0235 mol), potassium hydroxide (3.5 g of 85%, 0.0522 mol), hydrazine monohydrate (2.57 g, 0.0514 mol), and diethylene glycol (21 mL) were heated in a flask equipped with a Dean−Stark trap and condenser. The mixture became homogeneous on heating. The heating of both was maintained at 120−130 °C for 1.5 h and then raised to 180 °C for 3 h. The reaction mixture was cooled to ambient temperature, diluted with water (25 mL), and poured into 2.5 M hydrochloric acid (30 mL). The mixture was allowed to stand for 16 h and the white amorphous solid collected by filtration. To remove the residual diethylene glycol, the solid was dissolved in saturated potassium carbonate (50 mL) and diluted with water (100 mL). The clear solution was poured carefully into stirred 2.5 M hydrochloric acid (50 mL). White crystals formed immediately and were collected by filtration, washed with water (2 × 200 mL), and dried under vacuum. This resulted in 3.9 g (83%) of **21**. ^1H NMR ($CDCl_3$) δ 7.26 (s, 2H), 7.12 (s, 1 H), 2.56 (t, 2H, J = 6 Hz), 2.37 (t, 2H, J = 9 Hz), and 2.13 (p, 2H, J = 6 Hz).

7-Chloro-1-oxo-1,2,3,4-tetrahydronaphthalene (22). Polyphosphoric acid (20 g, excess) was place in a beaker and heated to 90 °C on a steam bath. 4-(4-Chlorophenyl)butyric acid (**27**, 0.017 mol) was added in portions. The mixture was stirred for 5 min. An additional portion of polyphosphoric acid (20 g, excess) was added and heated to 90 °C for 5 min. The thick, homogeneous viscous orange oil was removed from the steam bath and cooled to 60 °C before water (200 mL) was added. When the reaction was complete (all the orange oil gone) and the mixture had cooled to ambient temperature, the mixture was extracted with ether (2 × 100 mL). The ethereal extracts were washed with water (2 × 100 mL), 1 N sodium hydroxide (2 × 100 mL), water (100 mL), aqueous acetic acid (100 mL of 3%), saturated sodium bicarbonate (100 mL), and finally with water (100 mL). The ethereal layer was dried ($MgSO_4$) and concentrated to give 2.52 g (82%) of **22** as a white amorphous solid. ^1H NMR ($CDCl_3$) δ 7.85 (d, 1H, J = 6 Hz), 7.42 (d, 1H, J = 6 Hz), 7.21 (d, 1H, J = 9 Hz), 2.94 (m, 2H), 2.63 (m, 2H), 2.15 (m, 2H).

7-Chloro-2-diazo-l-oxo-l,2,3,4-tetrahydronaphthalene (23). 7-Chloro-1-oxo-l,2,3,4-tetrahydronaphthalene **22**, (2.0 g, 0.011 mol) and acetamidobenzenesulfonyl azide (5.33 g, 0.022 mol) were dissolved in acetonitrile (50 mL) and cooled in an ice bath. A solution of 1,4-diazabicyclo[5.4.0]undec-7-ene (3.37 g, 0.0221 mol) in acetonitrile (5 mL) was added dropwise. The temperature was maintained at 0 °C for 2 h. The mixture was allowed to slowly warm to room temperature and stirred a total of 18 h. The purple solution was poured into 1 N sodium hydroxide (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated. The black solid was passed through silica gel eluting with hexane and gradually increasing the polarity by adding ethyl acetate (until a 1:1 mixture was obtained). Concentration of the product fraction afforded 1.6 g of **23** as a bright-yellow solid. ^1H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.39 (d, 1H, J = 6 Hz), 7.13 (d, 1H, J = 15 Hz), 2.99 (s, 4H).

2-(*tert*-Butylamino)-7-chlorotetralone (6) Fumarate. Ruthenium acetate (0.8 g, 0.0018 mol) and *tert*-butylamine (5 g, 0.668 mol) were dissolved in dry toluene (100 mL). The mixture was warmed in a 115 °C oil bath, creating a homogeneous light-purple solution. A solution of 7-chloro-2-diazo-l-oxo-1,2,3,4-tetrahydronaphthalene (l.50 g, 0.007 mol) in toluene (20 mL) was added dropwise over 20 min. The resulting dark-purple solution was cooled to ambient temperature and poured into 10% hydrochloric acid (50 mL), and the layers were separated. The aqueous layer was made alkaline by pouring it into a slurry of ice (20 g) and conc. ammonium hydroxide (20 mL). The resulting pink slurry was extracted with Et_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated to give 0.382 g of yellow resin, which quickly discolored to purple when exposed to air. The resin was promptly dissolved in acetone and poured into a solution of fumaric acid (0.176 mg, 0.0015 mol) in warm acetone. The resulting precipitate was collected by filtration, triturated with acetone (2 × 150 mL), and then dried, resulting in 461 mg of **6**·fumarate: mp softens 146 °C (dec) 196−199 °C. ^1H NMR (D_2O) δ 7.68 (s, 1H), 7.36 (d, 1H, J = 8 Hz), 7.09 (d, 1H, J = 8 Hz), 6.35 (s, 2H), 4.22 (dt, 1H, J = 10 Hz, J = 4.5 Hz), 2.99−2.87 (m, 2H), 2.3−2.07 (m, 2H), 1.14 (s, 9H). Anal. ($C_{18}H_{22}ClNO_5$) C, H, N.

Inhibition of Radioligand Binding of [^{125}I]RTI-55 to hDAT, hSERT, or hNET in Clonal Cells. Cell Preparation. HEK293 cells expressing hDAT, hSERT, or hNET inserts are grown to 80% confluence on 150 mm diameter tissue culture dishes and serve as the tissue source. Cell membranes are prepared as follows. Medium is poured off the plate, and the plate is washed with 10 mL of calcium- and magnesium-free phosphate-buffered saline. Lysis buffer (10 mL; 2 mM HEPES with 1 mM EDTA) is added. After 10 min, cells are scraped from plates, poured into centrifuge tubes, and centrifuged 30 000 × g for 20 min. The supernatant fluid is removed, and the pellet is resuspended in 12−32 mL of 0.32 M sucrose using a Polytron at setting 7 for 10 s. The resuspension volume depends on the density of binding sites within a cell line and is chosen to reflect binding of 10% or less of the total radioactivity.

Assay Conditions. Each assay tube contains 50 μL of membrane preparation (about 10−15 μg of protein), 25 μL of unknown, compound used to define nonspecific binding, or buffer (Krebs-HEPES, pH 7.4; 122 mM NaCl, 2.5 mM $CaCl_2$, 1.2 mM $MgS0_4$, 10 μM pargyline, 100 μM tropolone, 0.2% glucose, and 0.02% ascorbic acid, buffered with 25 mM HEPES), 25 μL of [^{125}I]RTI-55 (40−80 pM final concentration), and additional buffer sufficient to bring up the final volume to 250 μL. Membranes are preincubated with unknowns for 10 min prior to the addition of the [^{125}I]RTI-55. The assay tubes are incubated at 25 °C for 90 min. Binding is terminated by filtration over GF/C filters using a Tomtec 96-well cell harvester. Filters are washed for 6 s with ice-cold saline. Scintillation fluid is added to each square, and radioactivity remaining on the filter is determined using a Wallac μ- or β-plate reader. Specific binding is defined as the difference in binding observed in the presence and absence of 5 μM mazindol (HEK-hDAT and HEK-hNET) or 5 μM imipramine (HEK-hSERT). Two or three independent competition experiments are conducted with duplicate determinations. GraphPAD Prism is used to analyze the ensuing data, with IC_{50} values converted to K_i values using the Cheng-Prusoff equation ($K_i = IC_{50}/(1 + ([RTI - 55]/K_d\ RTI - 55))$).

Filtration Assay for Inhibition of [^{3}H]Neurotransmitter Uptake in HEK293 Cells Expressing Recombinant Biogenic Amine Transporters. Cell Preparation. Cells are grown to confluence as described above. The medium is removed, and cells are washed twice with phosphate buffered saline (PBS) at room temperature. Following the addition of 3 mL Krebs-HEPES buffer, the plates are warmed in a 25 °C water bath for 5 min. The cells are gently scraped and then triturated with a pipet. Cells from multiple plates are combined. One plate provides enough cells for 48 wells, which is required to generate data on two complete curves for the unknowns.

Uptake Inhibition Assay Conditions. The assay is conducted in 96 1-mL vials. Krebs-HEPES (350 μL) and unknowns, compounds used to define nonspecific uptake, or buffer (50 μL) are added to vials and placed in a 25 °C water bath. Specific uptake is defined as the difference in uptake observed in the presence and absence of 5 μM mazindol (HEK-hDAT and HEK-hNET) or 5 μM imipramine (HEK-hSERT). Cells (50 μL) are added and preincubated with the unknowns for 10 min. The assay is initiated by the addition of [^{3}H]dopamine, [^{3}H]serotonin, or [^{3}H]norepinephrine (50 μL, 20 nM final concentration). Filtration through Whatman GF/C filters presoaked in 0.05% polyethylenimine is used to terminate uptake after 10 min. The IC_{50}s are calculated applying the GraphPAD Prism program to triplicate curves made up of six drug concentrations each. Two or three independent determinations of each curve are made.

Locomotor Activity Studies.[61] Locomotor activity of mice within 10-min epochs was measured under dim illumination using a Digiscan apparatus (model RXYZCM-16, Omnitech Electronics, Columbus, OH) consisting of 40 testing chambers ($40.5 \times 40.5 \times 30.5$ cm^3) each surrounded by a panel of infrared beams and photodetectors. Compound **1a** analogues were initially evaluated for ability to increase locomotor activity of mice during a test lasting 1 h, following i.p. injection of the vehicle or 1 of 4−10 doses of the test compound (n = 8 mice per dose group). Incremental doses were tested until (i) a locomotor stimulant effect was evident and a peak or plateau of the dose−effect curve could be defined, (ii) a locomotor depressant dose−response could be defined, or (iii) there was no effect in doses up to 100 mg/kg. For analysis of stimulant potency and efficacy, the earliest 30 min period in which a maximal stimulant effect first appeared as a function of dose was considered. The maximal effect, measured in locomotor activity counts, was estimated by fitting a 3-parameter logistic peak or transition function (Tablecurve 2D v2.03; Jandel Scientific, San Rafael, CA) with the constant set to the mean activity counts of the vehicle control. Stimulant efficacy of each analogue (maximal activity counts−vehicle control counts) is reported as a percentage of that calculated for cocaine as determined monthly in a separate study. An ED_{50} was estimated as the center of a logistic dose−response function fit to the activity count data for the time period of maximal effect. A majority of the **1a** analogues yielded stimulant effects lasting longer than 1 h and were reconsidered in studies lasting a total of 8 h. The duration of the stimulant effect was estimated for all doses yielding a statistically significant stimulant effect that was equal to or less than the maximal effect, and reported as a range in Table 2.

Drug Discrimination Studies. These studies were conducted using standard behavior-testing chambers (Coulbourn Instruments, Allentown, PA) interfaced to computers programmed with MED-PC IV (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data. All rats were first trained to discriminate cocaine (10 mg/kg) from saline using a two-lever choice methodology. Ten minutes prior to each training session, the rats received an injection of either saline (S) or cocaine (C) and were placed in the test chamber which contained two response levers. A food pellet became available after every 10 responses on only one of the levers (a designated cocaine- or saline-appropriate lever). Each training session lasted until the rats earned 20 food pellets or for a maximum of 20 min. The rats received training sessions in a double alternating fashion (i.e., C−C−S−S−C, etc.) until they met a criterion of 85% or greater injection-appropriate responding during 9 of their last 10 sessions. All rats had received approximately 60 training sessions before they were used in the generalization experiments. In contrast to the training sessions, both levers were active during generalization tests, such that 10 consecutive responses on either lever yielded a pellet. Cocaine- and saline-appropriate responding was reconfirmed in standard training sessions conducted in between generalization tests. Different doses of **1a** analogues were injected i.p. prior to the generalization tests, using pretreatment times and starting doses adjusted based on the results of locomotor activity studies. Different doses of a given analogue were tested incrementally in the same group of six rats until (i) full generalization was evident, (ii) the rate of lever responding in the group was decreased to 20% of vehicle control, or (iii) toxicity was evident. Drug discrimination data were expressed as the mean percentage of responses on the cocaine-appropriate lever occurring in each generalization test, whereas the rates of responding were expressed as a function of the number of responses made divided by the total session time. Full generalization was defined as ≥80% cocaine-appropriate lever responding and partial generalization as ≥40% and <80% cocaine-appropriate responding. For all compounds yielding full generalization, an ED_{50} was estimated as the center of a logistic dose−response transition function fit to the percentage of cocaine-appropriate lever responding for all doses tested.

In studies of the time-course of generalization to cocaine, rats that had been trained for i.p. cocaine discrimination were administered **1a** analogues p.o., by gavage, in a volume of 1 to 6 mL/kg body weight. Generalization tests were then performed 45, 90, 180, or 360 min later in separate groups of 3−6 rats. Different doses of each analogue were tested incrementally beginning with starting doses determined by the i.p. discrimination studies, until full substitution was evident at one or more time points. A total of 6 rats were tested at each time point for the highest dose tested, and for vehicle and all doses tested at the shortest time point yielding full generalization (for which an ED_{50} value was calculated).

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Supporting Information Available: Experimental details for the synthesis of target compounds **1b**−**1ff** and results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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