Trifluoromethoxyl Substituted Phenylethylene Diamines as High Affinity σ Receptor Ligands with Potent Anti-Cocaine Actions

Trudy A. Smith,[†] Xiaowen Yang,[†] Huifang Wu,[†] Buddy Pouw,[‡] Rae R. Matsumoto,[‡] and Andrew Coop*[,†]

Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Room 637 HSFII, Baltimore, Maryland 21201, and College of Pharmacy, University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, Oklahoma 73190

Received October 31, 2007

The phenylethylene diamines are a class of σ receptor ligands with excellent selectivity over other biological systems and with anti-cocaine actions that involve antagonism of σ_1 receptors. In order to increase the potency of the aromatic methoxyl substituted analogues, trifluoromethoxyl groups were introduced to prevent metabolic demethylation. The para-substituted trifluoromethoxyl substituted analogues were shown to have increased σ receptor affinity and represent the most potent anti-cocaine phenylethylene diamines yet described.

Introduction

Cocaine abuse remains a major public health problem[1,2] and is responsible for more serious intoxications and deaths than any other illicit drug, primarily as no effective treatments for cocaine overdose are currently available.[3] Previous studies aimed at developing anti-cocaine small molecule therapeutics have primarily focused on reversing the effects of cocaine on the dopaminergic system, yet success has been limited.[3–5] It is now becoming apparent not only that the behavioral effects of cocaine are due to actions at the dopamine transporter but that there is a contribution from other monoamine transporters and also receptors to which it binds.[6,7] Our approach to develop agents that attenuate the effects of cocaine is to prevent the access of cocaine to σ receptors, to which cocaine binds at concentrations that are achievable in vivo,[7–9] and because they are located in key organ systems (i.e., brain, heart) that mediate the drug's actions.[10]

The σ receptors were first postulated by Martin[11] and suffered from a complicated history, but they are now recognized as unique binding sites that are distinct from other known receptors[10,12] and have been shown to consist of σ_1 and σ_2 receptors through pharmacological methods.[13–16] The σ_1 receptor has been cloned,[17] and antisense oligodeoxynucleotides against σ_1 receptors attenuate the effects of σ_1 agonists.[18] Early generations of σ receptor antagonists were reported to attenuate cocaine-induced locomotor stimulation and convulsions with varying results, but newer generations of potent and selective σ-1 receptor antagonists and antisense oligodeoxynucleotides (to σ_1) unequivocally block the toxic and locomotor stimulatory effects of cocaine.[19]

Selective σ_1 agonists and antagonists have been described,[19] and the phenylethylenediamine class of ligands (typified by BD1008 (**1**) (Figure 1)) has been shown to be selective for σ receptors over all other biological systems, with some selectivity for σ_1 receptors over σ_2.[19] We have described the aromatic substituted methoxyl analogues (such as **2** and **3** (Figure 1)) as high affinity σ ligands that show high potency in reversing the effects of cocaine in mice, and it is also known that both *N*-methyl and *N*-ethyl substituted analogues are active.[20–22] As electron withdrawing groups have been shown to increase σ_1 affinity,[22] we considered that the introduction of electron withdrawing trifluoromethoxyl groups would prevent metabolic demethylation while increasing lipophilicity, thereby possibly leading to improved potency as anti-cocaine agents.

Synthesis

The synthesis of the analogues closely followed the procedures used for the methoxyl analogues reported previously.[21,22] The trifluoromethoxyl substituted analogues (Scheme 1) were prepared from the relevant trifluoromethoxyphenyl acetic acid through coupling with the relevant diamine[21] followed by reduction of the amide with alane. The intermediate amides were isolated and purified for the ortho and para analogues but were not isolated and purified in the case of the meta analogues (**23**–**26**). All compounds were converted to water soluble salts and evaluated in binding assays and mouse convulsion assays using procedures previously reported.[21,22]

Results and Discussion

Table 1 shows that all 12 compounds possess high affinity at σ_1 receptors with at least 4-fold preference over σ_2 receptors. All compounds show selectivity over a range of other biological targets, chosen because of interactions with cocaine and/or their involvement in the actions of stimulants,[21] but it should be noted that the ortho-substituted analogues (**18**–**21**) are not as selective because they possess affinity at dopamine D_2 receptors in the 100 nM range. However, the para-, ortho- and meta-substituted analogues all have higher affinity than their methoxyl substituted analogues reported previously (such as **3** Table 1).[21,22] It appears that the para- and meta-substituted trifluoromethoxylphenylethylenediamines possess the desired profile for anti-cocaine agents based on the binding assays. Cocaine-induced convulsions are a useful tool to assess σ-active compounds, as σ antagonists that attentuate cocaine-induced convulsions often attenuate cocaine-induced locomotor activity.[19] Data from our previously reported[21,23] anticonvulsion assays (Table 2) showed that the para-substituted analogues (**9**–**12**) were more potent than the ortho- and meta-substituted analogues. Indeed, the piperidine-based **11** and **12**, which have high affinity for σ_1, showed almost complete reversal of convulsions at 5 mg/kg, whereas the pyrrolidine-based **9** and **10** only showed activity in 50% of animals at this dose. The ortho-substituted analogues (**18**–**21**) were less potent, with only **19** and **21** attenuating convulsions in more than 50% of animals. The meta-substituted analogues

* To whom correspondence should be addressed. Phone: 410-706-2029. Fax: 410-706-5017. E-mail: acoop@rx.umaryland.edu.
[†] University of Maryland School of Pharmacy.
[‡] University of Oklahoma Health Sciences Center.

10.1021/jm7013666 CCC: $40.75
Published on Web 05/08/2008

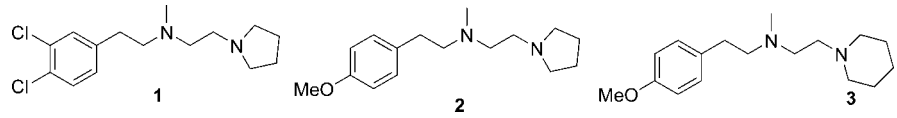
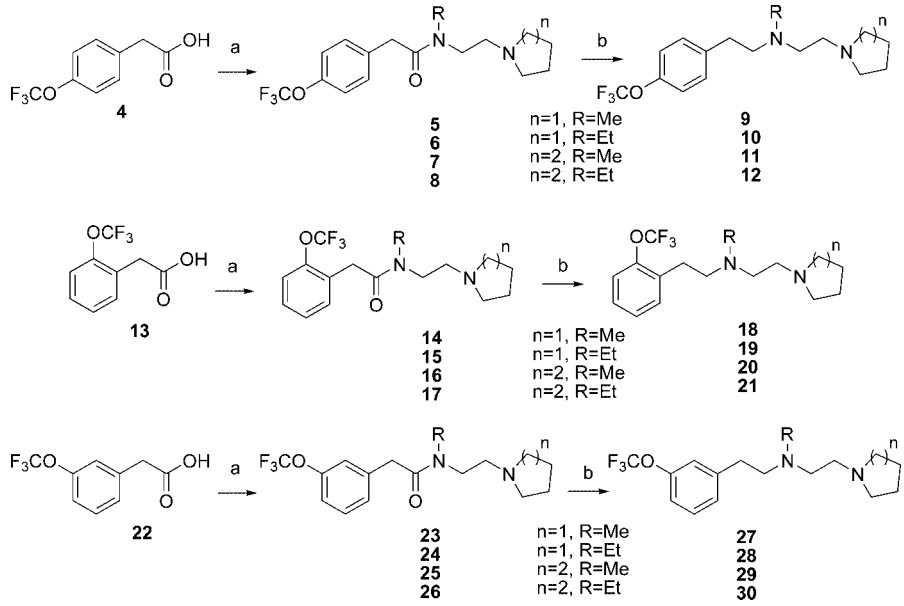


Figure 1. Phenylethylene diamine-based σ ligands.

Scheme 1[a]



[a] Conditions: (a) diamine, DCC; (b) AlH_3.

Table 1. Binding Affinities ($K_i \pm$ SEM, nM) at σ Receptors, Monoamine Transporters (DAT, SERT, NET), and Dopamine D_2 Receptors[a]

	σ_1	σ_2	DAT	SERT	NET	DA D_2
3[b]	21 ± 0.6	421 ± 99	12893 ± 1206	52647 ± 3286	19687 ± 2407	>10000
9	6 ± 1	36 ± 3	6331 ± 356	7105 ± 373	>100000	>10000
10	7 ± 1	32 ± 6	5525 ± 628	3791 ± 149	>100000	>10000
11	2 ± 0.2	25 ± 2	4123 ± 208	9465 ± 518	>100000	>10000
12	2 ± 0.2	26 ± 4	2389 ± 146	3303 ± 296	>100000	>10000
18	10 ± 1	43 ± 4	11970 ± 729	>100000	>100000	516 ± 39
19	17 ± 3	82 ± 8	13190 ± 1119	>100000	>100000	266 ± 13
20	3 ± 0.1	58 ± 2	11920 ± 868	>100000	>100000	146 ± 6
21	6 ± 0.1	55 ± 3	9530 ± 949	>100000	58100 ± 6400	213 ± 5
27	2 ± 0.4	40 ± 10	>10000	>10000	>10000	>10000
28	5 ± 0.8	43 ± 1	>10000	>10000	>10000	>10000
29	3 ± 0.1	31 ± 9	>10000	>10000	>10000	>10000
30	2 ± 0.6	15 ± 3	>10000	>10000	>10000	>10000

[a] At opioid, serotonin 5-HT-2, and NMDA receptors all compounds possessed a K_i of >10000 nM. [b] Data from ref 21.

(**27**–**30**) only showed attenuation of more than 50% of the animals in the piperidine-based **29** and **30**. Consistent with binding data, the para-substituted analogues show greater anti-cocaine activity in convulsion assays than their methoxyl analogues.[21,22] Whether an increase in anti-cocaine potency is due to increased affinity or decreased metabolism is yet to be determined, but the *p*-trifluoromethoxyl-substituted phenylethylenediamines represent the most potent members of this class in reversing the convulsive actions of cocaine. Though potent attentuation of convulsive effects is seen, the lack of a dose-related effect for several of the compounds indicates that further study is required to fully delineate the mechanism behind these effects, to allow the design and synthesis of potent pharmacotherapeutics for stimulant abuse.

Experimental Section

***N*-Methyl-*N*-(2-pyrrolidin-1-ylethyl)-2-[4-(trifluoromethoxy)-phenyl]acetamide (5).** To a stirred solution of DCC (3.1 g, 0.015 mol) in CH_2Cl_2 (20 mL), 4-(trifluoromethoxy)phenylacetic acid (2.2 g, 0.01 mol) in CH_2Cl_2 (10 mL) was added. After the mixture was stirred for 10 min, *N*-methyl-2-(1-pyrrolidinyl)ethylamine[24] (0.9 g, 0.007 mol) was added, and the mixture was stirred at room temperature for 20 min. The mixture was filtered, the filter cake was washed with CH_2Cl_2 (3 × 10 mL), and the filtrate was extracted with 10% aqueous citric acid (50 mL). The citric acid extracts were washed with CH_2Cl_2 (2 × 30 mL), basified with NH_4OH, and extracted into CH_2Cl_2 (3 × 40 mL). The organic layer was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated to give a colorless oil (1.68 g, 73%). ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 7.15 (m, 2H), 3.71 (m, 2H), 3.40 (m, 2H), 2.94 (d, 2H), 2.56 (m, 8H), 1.76 (s, 3H).

***N*-Ethyl-*N*-(2-pyrrolidin-1-ylethyl)-2-[4-(trifluoromethoxy)phenyl]acetamide (6).** Yield 77%; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.15 (m, 2H), 3.71 (m, 2H), 3.45 (m, 4H), 2.61 (m, 6H), 1.78 (m, 4H), 1.14 (m, 3H).

***N*-Methyl-*N*-(2-piperidin-1-ylethyl)-2-[4-(trifluoromethoxy)-phenyl]acetamide (7).** Yield 84%; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.16 (m, 2H), 3.72 (m, 2H), 3.50 (m, 2H), 3.00 (m, 3H), 2.38 (m, 6H), 1.54 (m, 4H), 1.43 (m, 2H).

Table 2. Number of Mice Convulsing with 60 mg/kg Cocaine after Pretreatment with Test Drug[a]

drug	pretreatment dose (mg/kg)	anticonvulsant effect (% convulsions)
9	5	5/10 (50%)
	10	1/10 (10%)
10	5	5/10 (50%)
	10	1/10 (10%)
11	5	2/10 (20%)
	10	3/10 (30%)
12	5	2/10 (20%)
	10	3/10 (30%)
18	5	7/10 (70%)
	10	6/10 (60%)
19	5	4/10 (40%)
	10	4/10 (40%)
20	5	8/10 (80%)
	10	7/10 (70%)
21	5	7/15 (47%)
	10	7/10 (70%)
27	5	5/10 (50%)
	10	6/10 (60%)
28	5	6/10 (60%)
	10	7/10 (70%)
29	5	8/10 (80%)
	10	3/10 (30%)
30	5	2/8 (25%)
	10	5/7 (71%)

[a] Control animals ($N = 10$) were pretreated with saline and then challenged 15 min later with cocaine, resulting in 100% of the mice exhibiting cocaine-induced convulsions. Values of ≤50% represent statistically significant reductions in cocaine-induced convulsions (Fisher's exact test).

***N*-Ethyl-*N*-(2-piperidin-1-ylethyl)-2-[4-(trifluoromethoxy)phenyl]acetamide (8).** Yield 87%; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 7.14 (m, 2H), 3.70 (m, 2H), 3.32 (m, 4H), 2.37 (m, 6H), 1.55 (m, 6H), 1.12 (m, 3H).

***N*-Methyl-2-pyrrolidin-1-yl-*N*-{2-[4-(trifluoromethoxy)phenyl]ethyl}ethanamine (9).** A solution of **5** (1.57 g, 0.0047 mol) in THF (5 mL) was added to a solution of AlH_3 (0.23 g, 0.023mol) in $PhCH_3$. About 5 min, the mixture was carefully poured into aqueous NaOH (15%, 30 mL). After cooling to room temperature, the mixture was extracted into $CHCl_3$ (3 × 30 mL). The organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography ($CHCl_3$/MeOH/NH_4OH = 95:5:0.1) gave a yellow oil (1.20 g, 81%): mp (dioxalate) 210–212 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 – 7.21 (m, 4H), 2.79 (m, 2H), 2.63 (m, 2H), 2.59 (m, 4H), 2.54 (m, 4H), 2.33 (s, 3H), 1.77 (m, 4H); LCMS 317 (M + 1). Anal. ($C_{20}H_{27}F_3N_2O_9$) C, H, N.

***N*-Ethyl-2-pyrrolidin-1-yl-*N*-{2-[4-(trifluoromethoxy)phenyl]ethyl}ethanamine (10).** Yield 61%; mp (dioxalate) 189–191 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 –7.40 (4H, m), 2.77–2.66 (6H, m), 2.62 (2H, m), 2.57 (2H, m), 2.52 (4H, m), 1.77 (4H, m), 1.05 (3H, m); LCMS 331 (M + 1). Anal. ($C_{21}H_{29}F_3N_2O_9$) C, H, N.

***N*-Methyl-2-piperidin-1-yl-*N*-{2-[4-(trifluoromethoxy)phenyl]ethyl}ethanamine (11).** Yield 83.5%; mp (dioxalate) 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 7.12–7.21 (4H, m), 2.78 (2H, m), 2.58−2.62 (4H, m), 2.43 (2H, m), 2.40 (4H, m,), 2.31 (3H, s), 1.58 (4H, m), 1.43 (2H, m); LCMS (M + 1) 331. Anal. ($C_{21}H_{29}F_3N_2O_9$) C, H, N.

***N*-Ethyl-2-piperidin-1-yl-*N*-{2-[4-(trifluoromethoxy)phenyl]ethyl}ethanamine (12).** Yield 86%; mp (dioxalate·0.25H_2O) 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (4H, m), 2.75 (2H, m), 2.69 (4H, m), 2.61 (2H, m), 2.42 (6H, m), 1.59 (4H, m), 1.43 (2H, m), 1.04 (3H, m); LCMS (M + 1) 345. Anal. ($C_{22}H_{31}F_3N_2O_9$·0.25H_2O) C, H, N.

***N*-Methyl-*N*-(2-pyrrolidin-1-ylethyl)-2-[2-(trifluoromethoxy)phenyl]acetamide (14).** Yield 87%; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 2H), 7.25 (m, 2H), 3.75 (m, 2H), 3.52 (m, 2H), 3.01 (m, 2H), 2.59 (m, 8H), 1.78 (s, 3H).

***N*-Ethyl-*N*-(2-pyrrolidin-1-ylethyl)-2-[2-(trifluoromethoxy)phenyl]acetamide (15).** Yield 82%; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 2H), 7.25 (m, 2H), 3.72 (m, 2H), 3.35 (m, 4H), 2.53 (m, 6H), 1.76 (m, 4H), 1.22 (m, 3H).

***N*-Methyl-*N*-(2-piperidin-1-ylethyl)-2-[2-(trifluoromethoxy)phenyl]acetamide (16).** Yield 86%; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 2H), 7.25 (m, 2H), 3.74 (m, 6H), 3.46 (m, 4H), 2.98 (m, 2H), 2.40 (s, 3H), 1.45 (m, 4H).

***N*-Ethyl-*N*-(2-piperidin-1-ylethyl)-2-[2-(trifluoromethoxy)phenyl]acetamide (17).** Yield 77%; ^{1}H NMR ($CDCl_3$) δ7.35 (m, 2H), 7.25 (m, 2H), 3.73 (m, 2H), 3.44 (m, 6H), 2.42 (m, 6H), 1.48 (m, 4H), 1.17 (m, 3H).

***N*-Methyl-2-pyrrolidin-1-yl-*N*-{2-[2-(trifluoromethoxy)phenyl]ethyl}ethanamine (18).** Yield 81%; mp (dioxalate) 217–219 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (4H, m), 2.85 (2H, m), 2.63 (6H, m), 2.52 (4H,m), 2.35 (3H, s), 1.77 (4H, m); LCMS (M + 1) 317. Anal. ($C_{20}H_{27}F_3N_2O_9$) C, H, N.

***N*-Ethyl-2-pyrrolidin-1-yl-*N*-{2-[2-(trifluoromethoxy)phenyl]ethyl}ethanamine (19).** Yield 66.5%; mp (dioxalate) 190–192 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (4H, m), 2.82 (2H, m), 2.70 (4H, m), 2.63 (2H, m), 2.59 (2H, m), 2.53 (4H,m), 1.78(4H, m), 1.07 (3H, m); LCMS (M + 1) 331. Anal. ($C_{21}H_{29}F_3N_2O_9$) C, H, N.

***N*-Methyl-2-piperidin-1-yl-*N*-{2-[2-(trifluoromethoxy)phenyl]ethyl}ethanamine (20).** Yield 85%; mp (dioxalate) 214–215 °C; ^{1}H NMR ($CDCl_3$) δ 7.21(4H, m), 2.84 (2H, m), 2.61 (4H, m), 2.46 (2H, m), 2.40 (4H, m), 2.34 (3H, s), 1.58 (4H, m), 1.43 (2H, m); LCMS (M + 1) 331. Anal. ($C_{21}H_{29}F_3N_2O_9$) C, H, N.

***N*-Ethyl-2-piperidin-1-yl-*N*-{2-[2-(trifluoromethoxy)phenyl]ethyl}ethanamine (21).** Yield 74.5%; mp (dioxalate) 179–181 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (4H, m), 2.80 (2H, m), 2.69 (4H, m), 2.63 (2H, m), 2.44 (6H, m), 1.59 (4H, m), 1.43 (2H, m), 1.06 (3H, m); LCMS (M + 1) 345. Anal. ($C_{22}H_{31}F_3N_2O_9$) C, H, N.

***N*-Methyl-2-pyrrolidin-1-yl-*N*-{2-[3-(trifluoromethoxy)phenyl]ethyl}ethanamine (27).** Yield 6%; mp (HCl) 237–241 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (4H, m), 2.76 (4H, m), 2.60 (4H, m), 2.50 (4H, m), 2.30 (3H, s), 1.70 (4H, m); LCMS (M + 1) 317.1. Anal. ($C_{16}H_{25}Cl_2F_3N_2O$) C, H, N.

***N*-Ethyl-2-pyrrolidin-1-yl-*N*-{2-[3-(trifluoromethoxy)phenyl]ethyl}ethanamine (28).** Yield 12%; mp (HCl) 180–183 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (4H, m), 2.74 (6H, m), 2.58 (6H, m), 1.76 (4H, m), 1.32 (3H, m), 1.16 (2H, m); LCMS (M + 1) 331.4. Anal. ($C_{17}H_{27}Cl_2F_3N_2O(H_2O)_{0.5}$) C, H, N.

***N*-Methyl-2-piperidin-1-yl-*N*-{2-[3-(trifluoromethoxy)phenyl]ethyl}ethanamine (29).** Yield 41%; mp (HCl) 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (4H, m), 2.79 (2H, m), 2.56 (6H, m), 2.40 (4H, m), 2.31 (3H, s), 2.24 (4H, m), 1.33 (2H, m); LCMS (M + 1) 331.4. Anal. ($C_{17}H_{27}Cl_2F_3N_2O$) C, H, N.

***N*-Ethyl-2-piperidin-1-yl-*N*-{2-[3-(trifluoromethoxy)phenyl]ethyl}ethanamine (30).** Yield 55%; mp (HCl) 250–253 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (4H, m), 2.80 (4H,m), 2.60 (4H, m), 2.40 (6H, m), 1.4 (4H, m), 1.23 (3H, m), 0.9 (2H, m); LCMS (M + 1) 345.4. Anal. ($C_{18}H_{29}Cl_2F_3N_2O$) C, H, N.

Radioligand Binding Assays. The assays were performed in rat brain homogenates using procedures previously published in detail. The σ_1 receptors were labeled with 5 nM [^{3}H](+)-pentazocine. The σ_2 receptors were labeled with 3 nM [^{3}H]DTG in the presence of 300 nM (+)-pentazocine to block σ_1 receptors. Nonspecific binding was determined in the presence of 10 μM haloperidol. K_i values were calculated using the Cheng−Prusoff equation.

Convulsion Assays. Male Swiss Webster mice were pretreated (ip) with saline or test compound, then challenged 15 min later with a convulsive dose of cocaine (60 mg/kg, ip). Mice were observed for the next 30 min for convulsions, which were defined as a loss of righting reflexes for at least 5 s combined with the presence of clonic limb movements or popcorn jumping.

Acknowledgment. The authors gratefully acknowledge NIDA (Grant DA 13978) for financial support of these studies. A.C. is the recipient of an Independent Scientist Award from NIDA (Grant K02 DA 19634).

Supporting Information Available: Elemental analysis results of final testing compounds and general procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Substance Abuse and Mental Health Services Administration National Household Survey on Drug Abuse: Main Findings 1997*; Department of Health and Human Services, U.S. Government Printing Office: Washington, DC, 1998.

(2) Community Epidemiology Work Group. *Epidemiological Trends in Drug Abuse*; NIDA, U.S. Government Printing Office: Washington, DC, 1996.

(3) Cartwright, W. S. Cocaine medications, cocaine consumption and societal costs. *Pharmacoeconomics* **2000**, *18*, 405–413.

(4) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. *J. Med. Chem.* **1999**, *42*, 2721–2736.

(5) Newman, A. H. Novel pharmacotherapies for cocaine abuse 1997–2000. *Expert Opin. Ther. Pat.* **2000**, *10*, 1095–1122.

(6) 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**, *237*, 1219–1223.

(7) Kuhar, M. J.; Ritz, M. C.; Sharkley, J. Cocaine receptors on dopamine transporters mediate cocaine-reinforced behavior. *NIDA Res. Monogr.* **1988**, *88*, 14–22.

(8) Mittleman, R. E.; Wetli, C. V. Death caused by recreational cocaine use: an update. *JAMA, J. Am. Med. Assoc.* **1984**, *252*, 1889–1893.

(9) Spiehler, V. R.; Reed, D. Brain Concentrations of cocaine and benzoylecgonine in fatal cases. *J. Forensic Sci.* **1985**, *30*, 1003–1011.

(10) Matsumoto, R. R.; Bowen, W. D.; Su, T. P. *Sigma Receptors: Chemistry, Cell Biology, and Clinical Applications*; Springer Press: New York, 2007.

(11) Martin, W. R.; Eades, G. C.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517–532.

(12) Quiron, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. A. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85–86.

(13) Booth, R. G.; Wyrick, S. D.; Baldessarini, R. J.; Kula, N. S.; Myers, A. M.; Mailman, R. B. New σ-like receptor recognized by novel phenylaminotetralins: ligand binding and functional studies. *Mol. Pharmacol.* **1993**, *44*, 1232–1239.

(14) Bowen, W. D.; Hellewell, S. B.; McGarry, K. A. Evidence for a multisite model of the rat brain σ receptor. *Eur. J. Pharmacol.* **1989**, *163*, 309–318.

(15) Codd, E. E.; Shank, R. P. 1,3-Di(2-[5-^{3}H]tolyl)guanidine labels more than one site in rat forebrain. *Eur. J. Pharmacol.* **1992**, *217*, 149–152.

(16) Hellewell, S. B.; Bruce, A.; Feinstein, G.; Orringer, J.; William, W.; Bowen, W. D. Rat liver and kidney contain high densities of sigma-1 and sigma-2 receptors: characterization by ligand binding and photoaffinity labeling. *Eur. J. Pharmacol.* **1994**, *268*, 9–18.

(17) Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H.-G.; Striessnig, J.; Kempner, E.; Glossman, H. Purification, molecular cloning, and expression of the mammalian sigma 1-binding site. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072–8077.

(18) Matsumoto, R. R.; McCracken, K. A.; Friedman, M. J.; Pouw, B.; de Costa, B. R.; Bowen, W. D. Conformationally restricted analogs of BD1008 and an antisense oligodeoxynucleotide targeting sigma-1 receptors produce anti-cocaine effects in mice. *Eur. J. Pharmacol.* **2001**, *419*, 163–174.

(19) Matsumoto, R. R.; Liu, Y.; Lerner, M.; Howard, E. W.; Brackett, D. J. Sigma receptors: potential medications development target for anti-cocaine agents. *Eur. J. Pharmacol.* **2003**, *469*, 1–12.

(20) Matasumoto, R. R.; McCraken, M. J.; Pouw, B.; Miller, J.; Bowen, W. D.; Williams, W. E.; de Costa, B. R. *N*-Alkyl substituted analogs of the σ receptor ligand BD1008 and traditional σ receptor ligands affect cocaine-induced convulsions and lethality in mice. *Eur. J. Pharmacol.* **2001c**, *411*, 261–273.

(21) Matsumoto, M. M.; Gilmore, D. L.; Pouw, B.; Bowen, W. D.; Williams, W.; Kausar, A.; Coop, A. Novel analogs of the σ receptor ligand BD1008 attenuate cocaine-induced toxicity in mice. *Eur. J. Pharmacol.* **2004**, *492*, 21–26.

(22) Zhang, Y.; Williams, W.; Bowen, W. D.; Rice, K. C. Synthesis and evaluation of aryl-substituted *N*-(arylethyl)-*N*-methyl-2-(1-pyrrolidinyl)ethylamines and corresponding arylacetamides for sigma receptor affinity. *J. Med. Chem.* **1996**, *39*, 3564–3568.

(23) Brackett, R. L.; Pouw, B.; Blyden, J. F.; Nour, M.; Matsumoto, R. R. Prevention of cocaine-induced convulsions and lethality in mice: effectiveness of targeting different sites on the NMDA receptor complex. *Neuropharmacology.* **2000**, *39*, 407–418.

(24) de Costa, B. R.; Radesca, L.; Di Paolo, L.; Bowen, W. D. Synthesis, characterization, and biological evaluation of a novel class of *N*-(arylethyl)-*N*-alkyl-2- (pyrrolidinyl)ethylamines: structural requirements and binding affinity at the sigma receptor. *J. Med. Chem.* **1992**, *35*, 38–47.

JM7013666