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Novel analogs of the σ receptor ligand BD1008 attenuate cocaine-induced toxicity in mice

Rae R. Matsumoto[a,*], Deborah L. Gilmore[a], Buddy Pouw[a], Wayne D. Bowen[b], Wanda Williams[b], Amina Kausar[c], Andrew Coop[c]

[a] *Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, P.O. Box 26901, CPB 337 Oklahoma City, OK 73190, USA*

[b] *Laboratory of Medicinal Chemistry, NIDDK/NIH, Bethesda, MD 20892, USA*

[c] *Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD 21201, USA*

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Abstract

Previous studies have shown that BD1008 (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine) and related analogs attenuate the toxicity and stimulant effects of cocaine through antagonism of σ receptors. In the present study, six analogs of BD1008 (UMB 98–103) were synthesized and evaluated in receptor binding and behavioral studies. Competition binding studies confirmed that all six compounds have high affinity for σ_1 receptors, moderate affinity for σ_2 receptors, and low to negligible affinity for monoamine transporters, opioid, *N*-methyl-D-aspartate, dopamine, and 5-HT receptors. In behavioral pharmacological studies, pretreatment of mice with UMB 100, UMB 101, or UMB 103 significantly attenuated cocaine-induced convulsions and lethality. Together with earlier studies, the data suggest that analogs of BD1008 are promising medication development leads for reducing the toxicity of cocaine.

Keywords: Cocaine; Convulsion; Lethality; σ Receptor; Toxicity

1. Introduction

Cocaine abuse is a serious health and societal problem. However, there are no effective medications to aid in its treatment (Carroll et al., 1999; Newman, 2000). Recently, accumulating evidence has suggested that σ receptors are promising medication development targets for cocaine abuse (cf. Matsumoto et al., 2003; Maurice et al., 2002). First, σ receptors are located in the brain and heart (Bouchard and Quirion, 1997; Gundlach et al., 1986; McLean and Weber, 1988; Novakova et al., 1995; Weissman et al., 1988), where they can influence the toxic and psychomotor effects of cocaine. Second, antagonizing σ receptors, using either pharmacological antagonists or antisense oligodeoxynucleotides, prevents cocaine-induced convulsions, lethality, locomotor activity, and reward in mice (Matsumoto et al., 2001b,c, 2002; McCracken et al., 1999a,b; Menkel et al., 1991; Romieu et al., 2000; Skuza, 1999; Witkin et al., 1993). Third, σ receptors can be targeted to modulate the activity of other neurotransmitter systems that are relevant to the actions of cocaine, such as dopamine (Booth and Baldessarini, 1991; Kobayashi et al., 1997; Patrick et al., 1993; Weiser et al., 1995) and serotonin (Bermack and Debonnel, 2001; Campbell et al., 1989). Fourth, a prototypic σ receptor antagonist has been reported to prevent cocaine-induced changes in gene expression (Matsumoto et al., 2003). Together, these data encourage further investigation of σ receptors as medication development targets for cocaine abuse.

Earlier studies have shown that the σ receptor ligand, BD1008 (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine), and several of its analogs possess anti-cocaine actions (Matsumoto et al., 2001b,c, 2002; McCracken et al., 1999a,b). Some of the structural modifications to BD1008 which yield favorable affinity for σ receptors and anti-cocaine actions include *N*-ethyl (e.g. BD1067) and methoxyphenyl (e.g. YZ-011, YZ-016, YZ-018) substitutions (Matsumoto et al., 2001c, 2002). Moreover, additional conformationally restricted analogs of

* Corresponding author. Tel.: +1-405-271-6593x47250; fax: +1-405-271-7505.

E-mail address: rae-matsumoto@ouhsc.edu (R.R. Matsumoto).

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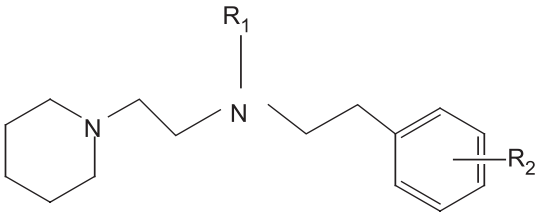

Compound	R_1 (N-alkyl)	R_2 (phenyl)
UMB 98	ethyl	*o*-OCH_3
UMB 99	ethyl	*m*-OCH_3
UMB 100	ethyl	*p*-OCH_3
UMB 101	methyl	*o*-OCH_3
UMB 102	methyl	*m*-OCH_3
UMB 103	methyl	*p*-OCH_3

Fig. 1. Structures of the novel ligands. The novel compounds possess a piperidine ring (six-membered ring incorporating one N). They also have either an *N*-methyl (CH_3) or *N*-ethyl (CH_2CH_3) substitution (indicated by R_1 in the figure). Finally, they have a methoxyl (OCH_3) group in the ortho, meta, or para position on the phenyl ring (indicated by R_2 in the figure).

BD1008 containing a piperidine ring (e.g. LR132) also possess significant affinity for σ receptors and produce anti-cocaine actions (Matsumoto et al., 2001b). Therefore, to further extend the structure–activity evaluation of analogs of BD1008, six new compounds were synthesized and characterized in receptor binding and behavioral studies for the present report.

The novel compounds (UMB 98–103) are shown in Fig. 1 and incorporate a piperidine ring, *N*-methyl or ethyl substitution, and methoxyphenyl substitutions. Since each of these structural features has been shown in earlier studies to convey favorable binding affinity for σ receptors and anti-cocaine actions (Matsumoto et al., 2001b,c, 2002), we hypothesized that optimal compounds could be developed by combining these features. The resulting composite compounds were evaluated in receptor binding assays and behavioral studies. For the receptor binding assays, the affinities of the novel compounds for the two established σ receptor subtypes were determined, and compared to their affinities for monoamine transporters and a select group of non-σ receptors to assess relative selectivity. For the behavioral studies, cocaine-induced convulsions and lethality were monitored as measures of toxicity because they are clinically relevant in an overdose situation.

2. Materials and methods

2.1. Drugs

UMB 98–103 were synthesized following a similar method to those of Zhang et al. (1996) and de Costa et al. (1992). Briefly, for UMB 101–103, *N*-(2-chloroethyl)piperidine·HCl was treated with methylamine to yield *N*-methyl-2-(1-piperidinyl)ethylamine. Coupling with the relevant methoxyl-substituted phenyl acetic acid through the use of dicyclohexylcarbodiimide (DCC), followed by alane reduction, gave the desired compounds. For UMB 98–100, (2-chloroethyl)piperidine·HCl was treated with ethylamine to yield *N*-ethyl-2-(1-piperidinyl)ethylamine, and coupling followed by reduction gave the desired products. All six compounds were converted to maleate salts, and spectral analysis was consistent with the assigned structures. All of the compounds were analyzed for purity through CHN analysis (Atlantic Microlabs, Atlanta, GA, USA) and are within ± 0.4% of calculated values. The compounds were dissolved in saline for the behavioral studies or stored as concentrated stock solutions dissolved in water for the receptor binding studies and subsequently diluted in buffer.

Cocaine hydrochloride was purchased from Sigma (St. Louis, MO, USA). The radioligands were acquired from Perkin Elmer (Boston, MA, USA). All other drugs and chemicals for the receptor binding assays were obtained from standard commercial suppliers (Sigma; St. Louis, MO Research Biochemicals International, Natick, MA).

2.2. Animals

Frozen guinea pig brains were purchased from Pel-Freeze (Rogers, AR). Male, Sprague Dawley rats (150–200 g) were obtained from Harlan (Indianapolis, IN). Male, Swiss Webster mice (22–32 g) were obtained from Harlan (Frederick, MD; Houston, TX; or Dublin, VA, USA) for the convulsion studies and from Charles River (Portage, MI, USA) for the lethality studies. Different vendors were used for the convulsion and lethality studies because earlier dose response characterizations for the toxicity of cocaine revealed that the variability in individual response between animals could be minimized by obtaining the mice from the respective vendors. All of the animals were housed in groups with a 12:12 h light/dark cycle and ad libitum food and water. Mice for the behavioral experiments were randomly assigned to their treatment groups, with animals from at least two different shipments being tested on different days to form the final data set for each dose/drug group. All procedures involving animals were performed as approved by the Institutional Animal Care and Use Committee at each institution where the studies were conducted.

2.3. Competition binding assays

The affinities of the novel ligands for σ receptors were determined in tissues that are enriched in the respective subtypes using methods previously published in detail (Bowen et al., 1993; Matsumoto et al., 1995). Briefly, σ_1 receptors were labeled in homogenates from guinea pig brain minus cerebellum using 3 nM [^{3}H](+)-pentazocine; σ_2 receptors were labeled in homogenates from rat liver with 3 nM

[^{3}H]DTG in the presence of 1 μM dextrallorphan to mask σ_1 receptors. Nonspecific binding was determined in the presence of 10 μM haloperidol. Twelve concentrations of test ligand (0.05–10,000 nM) were incubated for 120 min at 25 °C to evaluate their ability to displace the binding of the radioligand.

Since cocaine also interacts with monoamine transporters, the affinities of the novel compounds for dopamine, serotonin, and norepinephrine transporters were also determined. The membrane preparation and assay conditions were modified slightly from those previously described (Boja et al., 1994). Briefly, dopamine transporters were assayed in 2 mg wet weight rat striatal tissue using 0.5 nM [^{3}H]WIN35,428 [(−)-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester]; nonspecific binding was determined with 50 μM cocaine. Serotonin transporters were assayed in 1.5 mg wet weight rat brainstem tissue using 0.2 nM [^{3}H]paroxetine; nonspecific binding was determined with 1.5 μM imipramine. Norepinephrine transporters were assayed in 8 mg wet weight rat cerebral cortical tissue using 0.5 nM [^{3}H]nisoxetine; nonspecific binding was determined with 4 μM desipramine.

Since many historic σ receptor ligands are nonspecific, exhibiting interactions with dopamine, opioid, or phencyclidine sites on NMDA receptors, in addition to σ receptors (cf. Itzhak, 1994; Walker et al., 1990), the relative selectivities of the novel ligands were determined. The affinities of the compounds for 5-HT$_2$ receptors were also examined because antagonists at these sites are capable of attenuating the toxicity of cocaine (Ritz and George, 1997). The affinities of the novel ligands were measured in homogenates from rat brain minus cerebellum using previously published methods (Matsumoto et al., 1995). Briefly, dopamine receptors were labeled with 5 nM [^{3}H](−)-sulpiride; nonspecific binding was determined with 1 μM haloperidol. Opioid receptors were labeled with 2 nM [^{3}H]bremazocine; nonspecific binding was determined with 10 μM levallorphan. NMDA receptors were labeled with 5 nM [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine); nonspecific binding was determined with 10 μM cyclazocine. 5-HT$_2$ receptors were labeled with 2 nM [^{3}H]ketanserin; nonspecific binding was determined with 1 μM mianserin. The incubations were performed for 60 min at 25 °C for the dopamine and opioid receptor assays, 30 min at 37 °C for the 5-HT$_2$ receptor assays, and for 60 min at 4 °C for the NMDA receptor assays.

All of the assays were terminated with the addition of ice-cold buffer and vacuum filtration through glass fiber filters. Counts were extracted from the filters using Ecoscint cocktail (National Diagnostics, Manville, NJ, USA) for at least 8 h prior to counting.

2.4. Convulsions

To evaluate the effects of the ligands on cocaine-induced convulsions, mice were injected (i.p.) with saline (n = 11) or one of the following novel compounds: UMB 98 (1, 10, 20 mg/kg, n = 29), UMB 99 (1, 5, 10, 20 mg/kg, n = 40), UMB 100 (5, 10, 20, 30, 40 mg/kg, n = 50), UMB 101 (1, 5, 10, 20 mg/kg, n = 40), UMB 102 (1, 5, 10, 20 mg/kg, n = 40), or UMB 103 (1, 5, 10, 20, 30 mg/kg, n = 50). The mice were then injected 15 min later with a convulsive dose of cocaine (60 mg/kg, i.p.). In earlier studies, the 60 mg/kg, i.p. dose of cocaine used in this part of the study reliably produced convulsions in 100% of our animals obtained from Harlan, but no deaths (Brackett et al., 2000; McCracken et al., 1999a; Matsumoto et al., 2001a,b,c, 2002). After the injection with cocaine, the mice were placed in individual boxes and observed for the next 30 min for the occurrence of convulsions. Convulsions were operationally defined as clonic or tonic limb movements, which were accompanied by the loss of righting reflexes for at least 5 s, and/or popcorn jumping.

2.5. Lethality

To evaluate the effects of the novel σ receptor ligands on cocaine-induced lethality, mice were injected (i.p.) with saline (n = 10) or one of the following compounds: UMB 98 (10, 20, 30 mg/kg, n = 7), UMB 99 (10, 20, 30

Table 1
Binding affinities of novel ligands for σ receptors and other binding sites

σ Receptors

	σ_1	σ_2
UMB 98	25 ± 0.5	711 ± 64
UMB 99	16 ± 0.9	1015 ± 65
UMB 100	24 ± 0.04	955 ± 44
UMB 101	32 ± 0.8	387 ± 54
UMB 102	25 ± 0.7	379 ± 90
UMB 103	21 ± 0.6	421 ± 99

Monoamine transporters

	DAT	SERT	NET
UMB 98	5077 ± 477	7100 ± 471	24,875 ± 2235
UMB 99	12,220 ± 1378	>100,000	>100,000
UMB 100	10,136 ± 711	6362 ± 348	>100,000
UMB 101	4921 ± 341	14,653 ± 1397	>100,000
UMB 102	11,092 ± 875	>100,000	21,630 ± 1242
UMB 103	12,893 ± 1206	52,647 ± 3286	19,687 ± 2407

Other receptors

	Opioid	NMDA	Dopamine (D2)	5-HT$_2$
UMB 98	>10,000	>10,000	284 ± 12	4622 ± 207
UMB 99	>10,000	>10,000	>10,000	>10,000
UMB 100	>10,000	>10,000	>10,000	>10,000
UMB 101	>10,000	>10,000	608 ± 45	2188 ± 104
UMB 102	>10,000	>10,000	2368 ± 198	>10,000
UMB 103	>10,000	>10,000	>10,000	>10,000

Affinities (K_i in nM) were determined in competition assays, as described in Materials and methods. The values in the table represent the mean ± S.E.M. from three or more assays, each performed in duplicate. Values of >10,000 or 100,000 nM in the table signify that there was less than 30% displacement of the radioligand at that concentration. DAT = dopamine transporter, SERT = serotonin transporter, NET = norepinephrine transporter.

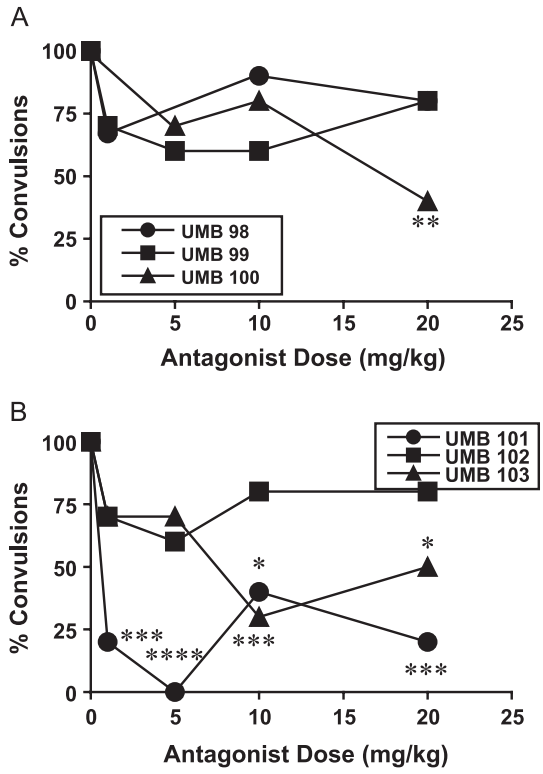

Fig. 2. Pretreatment with UMB 100, UMB 101, or UMB 103 attenuates cocaine-induced convulsions. Mice were pretreated with one of the novel compounds, followed 15 min later with a convulsive dose of cocaine (60 mg/kg, i.p.). The data for the *N*-ethyl substituted compounds (UMB 98–100) are shown in panel (A) and the data for the *N*-methyl substituted compounds (UMB 101–103) are shown in panel (B). The data are represented as the number of mice convulsing during the 30 min testing period/the total number of mice tested × 100%. *$P<0.05$, **$P<0.01$, ***$P<0.005$, ****$P<0.001$ using Fisher's exact tests.

mg/kg, $n=36$), UMB 100 (10, 20, 30 mg/kg, $n=30$), UMB 101 (5, 10, 20, 30 mg/kg, $n=39$), UMB 102 (10, 20, 30 mg/kg, $n=30$), UMB 103 (10, 20, 30 mg/kg, $n=30$). The mice were then injected 15 min later with a lethal dose of cocaine (125 mg/kg, i.p.). Similarly to the convulsion study, functional antagonism was tested against a single high dose of cocaine that produced lethality in 100% of our animals obtained from Charles River in earlier studies (Brackett et al., 2000; McCracken et al., 1999a; Matsumoto et al., 2001a,b, 2002). The mice were watched for 30 min following the cocaine injections and deaths were recorded.

2.6. Data analysis

The data from the binding assays were analyzed using GraphPad Prism (San Diego, CA, USA). Apparent K_i values were calculated using the Cheng–Prusoff equation and K_d values determined in saturation binding assays. The data from the toxicity studies were analyzed with Fisher's exact tests (GraphPad InStat, San Diego, CA, USA). $P<0.05$ was considered statistically significant.

3. Results

3.1. Binding affinities

The K_i values of the novel ligands for σ_1, σ_2, opioid, NMDA, dopamine (D2), and 5-HT_2 receptors and monoamine transporters are summarized in Table 1. All of the ligands had high affinities for σ_1 receptors, and moderate to low affinities for σ_2 receptors. In contrast to their significant affinities for σ_1 receptors, the compounds exhibited low to negligible affinities for the other receptors and monoamine transporters assayed.

3.2. Convulsions

Similar to earlier studies, pretreatment of mice with saline failed to prevent cocaine-induced convulsions (McCracken et al., 1999a; Matsumoto et al., 2001a,b,c, 2002). In contrast, pretreatment with UMB 100, UMB 101, or UMB 103 provided significant protection from cocaine-induced convulsions ($P<0.01$ at the best doses; Fig. 2).

3.3. Lethality

Pretreatment of mice with saline resulted in cocaine-induced lethality in all of the mice tested (McCracken et al., 1999a; Matsumoto et al., 2001b,c, 2002). Similar to the protective effects observed in the convulsion studies, UMB 100, UMB 101, or UMB 103 significantly attenuated cocaine-induced lethality ($P<0.001$ at the best doses; Fig. 3), while UMB 98, UMB 99 or UMB 102 failed to prevent cocaine-induced lethality.

4. Discussion

The novel BD1008 analogs, UMB 98–103, all have high affinities for σ_1 receptors. In contrast, they have moderate

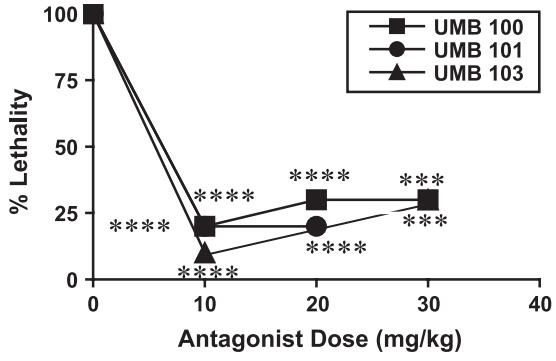

Fig. 3. Pretreatment with UMB 100, UMB 101, or UMB 103 attenuates cocaine-induced lethality. Mice were pretreated with one of the novel compounds, followed 15 min later with a lethal dose of cocaine (125 mg/kg, i.p.). The data are represented as the number of mice dying during the 30 min testing period/the total number of mice tested × 100%. ***$P<0.005$, ****$P<0.001$ using Fisher's exact tests.

affinities for σ_2 receptors and negligible interactions with monoamine transporters, and opioid, NMDA, dopamine D2, and 5-HT_2 receptors. The present study therefore confirms that BD1008 analogs with combinations of *N*-methyl or ethyl substitutions, methoxyphenyl substitutions, and piperidine rings retain high affinity and selectivity for σ receptors. Their 12- to 63-fold better affinity for σ_1 over σ_2 receptors suggests that they are advantageous for studying σ_1 receptor-mediated effects as there should be minimal influence from σ_2 receptors. This is consistent with the high affinity and selectivity of earlier reported analogs of BD1008 for σ receptors, particularly the σ_1 subtype (Matsumoto et al., 2001b,c, 2002; McCracken et al., 1999a).

Although the structural features of BD1008 analogs that convey favorable binding affinities for σ receptors appear consistent, it is still not totally clear which ones are associated with antagonist vs. agonist activity. In this study, compounds with *N*-methyl substitutions tended to be more favorable than *N*-ethyl substitutions in preventing cocaine-induced convulsions. However, there were compounds from both groups that were effective (i.e. UMB 100, UMB 101, UMB 103) and compounds from both groups that were ineffective (i.e. UMB 98, UMB 99, UMB 102), suggesting that *N*-alkyl substitutions alone are not the sole determinants of antagonist vs. agonist activity in this synthetic series.

In contrast, the increase in ring size from pyrrolidine (five-membered ring) in earlier compounds to piperidine (six-membered ring) in the present study may have compromised the anti-cocaine actions. Earlier compounds that were identical to UMB 101, UMB 102, and UMB 103, except that they contained a pyrrolidine instead of a piperidine ring (YZ-011, YZ-016, YZ-018), were all very effective in antagonizing the behavioral effects of cocaine (Matsumoto et al., 2002). Therefore, while the change from the pyrrolidine to piperidine ring does not have a significant influence on binding affinity for σ receptors, the pyrrolidine ring appears superior to the piperidine ring for conveying anti-cocaine actions.

With regard to the position of the aryl-substitution, both compounds with methoxyphenyl substituents in the para position (UMB 100, UMB 103) significantly attenuated the toxicity of cocaine. Compounds with methoxyphenyl substitutions in the meta position (UMB 99, UMB 102) were both ineffective at preventing the convulsive effects of cocaine. Therefore, it appears that the para-substitution is the favored position for conveying anti-cocaine actions. One caveat to this conclusion, however, is that earlier evaluations of other BD1008 analogs, namely aryl monosubstituted derivatives such as YZ-011 and its analogs (Matsumoto et al., 2002; Zhang et al., 1996) and *N*,*N*-disubstituted piperazines such as YZ-069 and its analogs (Matsumoto et al., 2004), revealed that the position of the aryl substitution had no significant influence on either binding affinity for σ receptors or anti-cocaine actions. All of the earlier synthetic series analyzed were comprised of compounds with pyrrolidine rings, suggesting that perhaps ring size affects the orientation of the compound when bound to the receptor. Thus, it appears that the position of the methoxyl substitution is important in the piperidine series, but not in the pyrrolidine series.

The data from UMB 98–103 suggest that small modifications to σ receptor ligands can influence agonist vs. antagonist actions. This was also observed in our pyrrolidine series with *N*-alkyl substitutions in which *N*-methyl and ethyl appeared to convey antagonist actions, *N*-propyl (BD1069) partial agonist actions, and *N*-allyl (BD1052) agonist actions (Matsumoto et al., 2001c; unpublished observations). This type of influence of small modifications is well known and has been reported in other fields as well. For example, in the opioid literature, *N*-methyl gives a mu agonist, whereas *N*-propyl gives a mu antagonist (Casey and Parfitt, 1986). It has also been reported that *N*-phenethyl substitutions produce some of the most potent mu agonists, whereas *N*-benzyl (one carbon less) are, at best, weak mu antagonists (May et al., 1998). Together, the data indicate that it will be important to continue characterizing the functional consequences of small changes in σ receptor ligands, such as the BD1008 analogs, in addition to their binding affinities.

In summary, UMB 100, UMB 101, and UMB 103 have high affinity for σ_1 receptors and significantly attenuate cocaine-induced convulsions and lethality in mice. When taken together with earlier studies, the data indicate that compounds related BD1008 are promising leads for the development of anti-cocaine medications.

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