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Effect of ring-constrained phenylpropyloxyethylamines on sigma receptors

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1. Introduction

Finding effective pharmacotherapies to treat cocaine abuse and addiction remains a major challenge.¹ Considerable efforts have been put forth towards the development of potential anti-cocaine therapeutics that attenuate the toxic and addictive effects.² Our approach utilized the fact that cocaine interacts with sigma (σ) receptors^{3–5} and σ antagonists attenuate acute (convulsions, lethality, locomotor activity) and subchronic (sensitization, place conditioning) effects of cocaine, making these receptors a promising target for developing treatments for cocaine abuse.^{3,6–9} In addition, recent data from cocaine self administration studies suggests sigma receptor activation may have a role in stimulant abuse.^{10–13}

σ Receptors were initially proposed by Martin and co-workers as a subtype of opioid receptor to account for some benzomorphan activity.¹⁴ However, due to the inability of naloxone to antagonize σ-induced effects, σ receptors were later considered to be a unique class of receptors.¹⁵ σ Receptors are comprised of two subtypes, $σ_1$ and $σ_2$, with cocaine interacting with both subtypes.¹⁶ To date, $σ_1$ receptors are the only cloned σ receptor.¹⁷⁻²⁰ Studies have shown that $σ_1$ receptors are involved in intracellular signaling, synaptic transmission, modulation of inositol phosphates, protein kinases, and calcium.^{17,21-24} Though not yet cloned, $σ_2$ receptors appear to exist as heterodimers and are smaller in size

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ABSTRACT

A series of ring-constrained phenylpropyloxyethylamines, partial opioid structure analogs and derivatives of a previously studied sigma (σ) receptor ligand, was synthesized and evaluated at σ and opioid receptors for receptor selectivity. The results of this study identified several compounds with nanomolar affinity at both σ receptor subtypes. Compounds **6** and **9** had the highest selectivity for both σ receptor subtypes, compared to μ opioid receptors. In addition, compounds **6** and **9** significantly reduced the convulsive effects of cocaine in mice, which would be consistent with antagonism of σ receptors.

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compared to σ_1 .²⁵⁻²⁸ A recent study identified the σ_2 binding site as the progesterone receptor membrane component 1 (PGRMC-1).²⁹ In addition, σ_2 receptors are believed to be associated with the inhibition of cell proliferation and induction of apoptosis, producing transient and sustained release of calcium ions.³⁰

Prior to the discovery of the two subtypes, initial σ receptor– ligand structure-activity relationship (SAR) studies were performed on a range of opioid-related compounds and it was determined that (a) phenylpiperidine containing analogs had relatively high binding affinity at the σ receptor binding sites, (b) N-alkyl lipophilic substituents produce greater affinity for both σ subtypes, and (c) there is no predetermined set of rigid constraints for the intramolecular distances required for σ receptor binding.¹⁵ Though these initial σ ligands helped gain insight into the σ SAR, their interaction with other biological systems such as opioid receptors, dopamine transporters, or *N*-methyl-p-aspartate (NMDA) receptors¹⁴ impeded the understanding of theirtrue biological function. Subsequent studies included a partial opioid, *N*-phenylpropyl derivative of a ring opened benzomorphinan (PPAP), which had high selectivity for the σ receptor versus the phencyclidine (PCP) sites and dopamine D1 and D2 receptors³¹ and thus served as the lead compound for many years in detailed structure activity investigation. ^{20,32,33} Specifically, the effect of longer-chain, aryl substituents, as well as conformational constraint on PPAP derivates were examined.³³ These studies resulted in agents which were selective for σ over other biological systems while displaying equivalent or higher affinity for σ_1 and σ_2 receptor subtypes.33





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Earlier studies from our laboratory had shown that AC927 (*N*-phenethylpiperidine), a mixed σ_1 and σ_2 antagonist, demonstrated high selectivity for the σ receptors.³⁴ Additional studies showed that AC927 attenuated the behavioral and neurotoxic effects of cocaine in mice.³⁵ However, AC927 has a relatively narrow therapeutic window, which can result in deaths in mice at supratherapeutic doses (unpublished finding; R.R. Matsumoto, Morgantown, WV). Accordingly, analogs of AC927 and structurally similar compounds are required to determine the optimal substituents and structural backbone needed to improve selectivity for each σ subtype and to increase the therapeutic window for cocaine treatment.



The current series of compounds were initially synthesized to determine the minimal structural requirements for high affinity and efficacy at mu (μ) opioid receptors,³⁶ however they displayed low to negligible affinity for the μ opioid receptor. Their close resemblance to AC927 and their inability to bind to the opioid receptors prompted our decision to further investigate the partial opioid structures at the two established σ receptors subtypes (σ_1 , σ_2). The structural differences of the novel compounds will aid in the design of σ_1 and σ_2 ligands and ultimately provide insight into future drug development.

2. Results and discussion

2.1. Chemistry

The synthetic sequences used to prepare compounds **3**, **4**, **6**, **7**, **9**, and **10** are displayed in Scheme 1. In brief, analogs **3** and **4** (Scheme 1A) were synthesized via *N*-methylation of *trans*-2-aminocyclohexanol hydrochloride (**1**) using the Eschweiler–Clark methylation³⁷ followed by alkylation with the corresponding bromide in the presence of NaH.³⁸ Compound **6** and the intermediate of **9** (Scheme 1B) were synthesized by addition of the appropriate *N*-alkylamine to an epoxide under reflux conditions.³⁹ Eschweiler–Clark methylation reaction³⁷ was utilized again to obtain target **9**. Analogs **7** and **10** were achieved by alkylation with the appropriate phenylalkyl bromide in presence of NaH.³⁸ All

targets were converted to oxalate salts and characterized using NMR and MS. All elemental analyses of salts were within ±0.4%.

2.2. Opioid and σ receptor binding

All of the tested compounds exhibited low to negligible affinity (1000 to >10,000 nM) for the three opioid receptors subtypes μ , delta (δ) and kappa (κ). Among the tested compounds, compound **3** displayed the highest affinity for the σ_1 receptor (4.6 nM), with the greatest selectivity for the σ_1 receptor when compared to the σ_2 receptor (σ_2/σ_1 = 240). Reduction of a double bond on the cinnamyl group to give **4** decreased affinity at σ_1 and σ_2 receptors (59) and 3800 nM, respectively). Introduction of a phenylpropyl group on the oxygen position of compound **6** led to compound **7**, which displayed higher selectivity for σ_1 (compared to **6**) with 84 nM affinity. In contrast, introduction of a phenylpropyl group to give compound **10** resulted in dramatic decreases in both σ_1 and σ_2 receptor affinities, exhibiting low affinity at σ_1 receptors (790 nM) and negligible affinity at σ_2 receptors (>10,000 nM). In agreement with previous reports,³⁴ increasing the chain length from phenethyl (6) to phenylpropyl (9) gave rise to higher σ_1 and σ_2 affinities as indicated by **9**. These results suggest that the phenylpropylamines are required for σ_2 activity in the cyclohexanol series. Compounds 6 and 9 were selected, as they produced no affinity for the μ opioid receptor and had a similar σ binding profile to AC927, to undergo further in vivo testing in order to determine the ability of the compounds to block cocaine-induced convulsions (see Table 1).

2.3. Cocaine-induced convulsions

Based on their binding affinity for σ receptors, compounds **6** and **9** were investigated in vivo for anticonvulsant actions in cocaine-treated mice (Fig. 1). Results indicate that pretreatment of mice with compound **6** led to significant attenuation of cocaine-induced convulsions at the highest dose tested (30 mg/kg, ip; p < 0.05, Fisher's exact tests). Pretreatment with compound **9** significantly and dose-dependently attenuated cocaine-induced convulsions at lower doses (1 and 10 mg/kg, ip), likely due to its higher affinity for σ receptors when compared to **6**. Moreover, the additional methylene group in **9** causes the expected increase in cLog*P* of 0.3 units (ChemBioDraw Ultra 12.0, CambridgeSoft; Cambridge, MA), which indicates that potency may be related to lipophilicity due to greater brain penetration. Since cocaine interacts with σ receptors⁸ and our compounds display significant



Scheme 1. Synthesis of 3, 4, 6, 7, 9 and 10. Reagents and conditions: A, (a) HCHO, HCOOH, reflux; (b) cinnamyl bromide or 1-bromo-3-phenylpropane, NaH, DMF, 50 °C, 3 h. B, (c) *N*-methyl-phenethylamine, EtOH, reflux; (d) 1-bromo-3-phenylpropane, NaH, DMF, 50 °C, 3 h; (e) 3-phenylpropylamine, EtOH, reflux; (f) HCHO, HCOOH, reflux; (g) 1-bromo-3-phenylpropane, NaH, DMF, 50 °C.

Table 1				
Opioid and	σ	receptor	binding	affinities

Compd	0	Opioid binding ^a $K_i \pm SEM (nM)$			Sigma binding ^b $K_i \pm SEM (nM)$	
	μ	δ	к	$\sigma_1{}^a$	$\sigma_2{}^{\mathrm{b}}$	σ_2/σ_1
3	2300 ± 74	>10,000	>10,000	4.6 ± 0.20	1100 ± 29	240
4	4200 ± 140	>10,000	>10,000	59 ± 2.0	3800 ± 800	65
6	>10,000	>10,000	>10,000	120 ± 8.0	220 ± 6.0	2.0
7	1600 ± 41	>10,000	21,000 ± 93	84 ± 15	570 ± 31	7.0
9	>10,000	>10,000	>10,000	19 ± 0.90	6.7 ± 0.30	0.40
10	3100 ± 62	6200 ± 770	2200 ± 280	790 ± 76	>10,000	>13
AC927 ^c				30 ± 2.0	140 ± 18	5.0

^a Displacement of [³H](+)-pentazocine.

^b Displacement of [³H]di-o-tolylguanidine (DTG) in presence of (+)-pentazocine.

^c Citations reference previously known compounds and results Ref.³⁴.



Figure 1. Cocaine-induced convulsions. (A) Pretreatment of Swiss Webster mice with compound **6** (0–30 mg/kg ip), followed by a convulsive dose of cocaine (70 mg/kg ip) produced a reduction in the convulsive effects of cocaine. (B) Pretreatment of Swiss Webster mice with compound **9** (0–10 mg/kg ip), followed by a convulsive dose of cocaine (70 mg/kg ip) produced a dose-dependent reduction in the convulsive effects of cocaine. *p < 0.05; **p < 0.01; Fisher's exact test.

affinities for σ receptors, compounds **6** and **9** may in part produce their protective effects through these receptors. Recent evidence has suggested both σ_1 and σ_2 receptor antagonists possess anticocaine activity.^{2,3,15,21}

3. Conclusions

In the present study, we found that ring-constrained phenylpropyloxyethylamines exhibit low to negligible affinity for opioid receptors while displaying significant binding affinity for σ receptors. Binding studies showed that introduction of a cinnamyl group (compound **3**) resulted in an increase in selectivity for the σ_1 receptor when compared to the σ_2 receptor. Compounds **6** and **9** bind to σ receptors at nanomolar concentrations and in agreement with previous studies, increasing the chain length from phenethyl (**6**) to phenylpropyl (**9**) increased affinity at both σ receptor subtypes. Moreover, compounds **6** and **9** produced significant reductions in cocaine-induced convulsions, providing further evidence of σ involvement in the actions of cocaine and thus identifies compound **9** as a viable lead compound for the development of treatments for cocaine abuse.

4. Experimental methods

All reagents, solvents and compounds were purchased from Sigma Aldrich Inc. (St. Louis, MO) and used without further purification, unless stated otherwise. The radioligands were purchased from Perkin Elmer (Boston, MA).

4.1. Synthesis

All reactions were carried out under an atmosphere of nitrogen. Thin layer chromatography was performed on silica 60 F_{254} plated

(Analtech, Inc., Newark, DE). All compounds were purified using standard techniques (crystallization, etc.) and characterized using standard spectroscopic methods such as ¹H NMR (Varian Inova 500 MHz) and MS (ThermoFinnigan LCQ Classic, Waltham, MA). All optically active compounds were prepared as racemates and evaluated for their biological activities. Elemental analysis was performed by Atlantic Microlabs (Norcross, GA).

4.1.1. trans-2-(Dimethylamino)cyclohexanol (2)

A solution of *trans*-2-aminocyclohexanol (**1**, 1 g, 8.68 mmol, 1.0 equiv) 37% formaldehyde (HCHO) (14 mL, 471 mmol, 54.2 equiv) and formic acid (HCOOH) (14 mL, 365 mmol, 42.0 equiv) was refluxed overnight. The resulting crude mixture was concentrated and dissolved with ether and washed with 5 N NaOH. The organic extracts were combined, dried with K_2CO_3 , and evaporated. MS ESI m/z 144 (M+H⁺); yield 83% (1.03 g).

4.1.2. *trans-N,N*-Dimethyl-2-(3-phenylpropoxy)cyclohexanamine (3)

Compound **3** was prepared through alkylation of *trans*-2-(dimethylamino)cyclohexanol (**2**, 0.72 g, 5.03 mmol, 1.0 equiv) with 1-bromo-3-phenylpropane, (2.29 mL, 15.1 mmol, 3.0 equiv) in the presence of NaH (0.84 g, 35.2 mmol, 7.0 equiv) following the method described above. Yield 7% (0.092 g); ¹H NMR (500 MHz, D₂O) δ 7.41 (t, 7.67 Hz, 2H), δ 7.26–7.33 (m, 3H), δ 3.69–3.76 (m, 1H), δ 3.47–3.59 (m, 2H), δ 3.11–3.19 (m, 1H), δ 2.68–2.94 (m, 8H), δ 2.28–2.35 (m, 1H), δ 2.04–2.11 (m, 1H), δ 1.91–1.99 (m, 2H), δ 1.89 (d, 6.79 Hz, 1H), δ 1.75–1.81 (m, 1H); MS ESI *m*/*z* 262 (M+H⁺); Anal. (C₁₇H₂₇NO(C₂H₂O₄)₂) C, H, N.

4.1.3. trans-2-(Cinnamyloxy)-N,N-dimethylcyclohexanamine (4)

To a solution of DMF and NaH (1.21 g, 50.3 mmol, 7.0 equiv) was added *trans*-2-(dimethylamino)cyclohexanol (**2**, 1.03 g,

7.19 mmol, 1.0 equiv) dropwise and allowed to stir at room temperature for 30 min prior to adding cinnamyl bromide (4.25 g, 21.6 mmol, 3.0 equiv). The reaction was heated for 3 h at 50 °C. After the reaction reached completion, it was guenched with 20 mL of ethanol and the solvent was reduced under pressure. The crude product was dissolved in H₂O and extracted with Et₂O. The reaction mixture was then extracted into 6 M HCl and basified to pH 12-13 with 5 M NaOH (aq) and extracted with Et₂O. The combined organic layers were washed with brine solution and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, CHCl₃/5% MeOH/1% NH₄OH) followed by formation of an oxalate salt from ether. Yield 10% (0.18 g); ¹H NMR (500 MHz, D₂O) δ 7.52 (d, 3.56 Hz, 2H), δ 7.42 (t, 7.33 Hz, 2H), δ 7.33–7.38 (m, 1H), δ 6.73–6.79 (m, 1H), δ 6.36–6.44 (m, 1H), δ 4.36–4.41 (m, 1H), δ 4.20–4.26 (m, 1H), δ 3.65–3.72 (m, 1H), δ 3.15–3.22 (m, 1H), δ 2.80 (s, 6H), δ 2.38-2.44 (m, 1H), δ 2.07 (d, 5.86 Hz, 1H) δ 1.87 (d, 6.07 Hz, 1H), δ 1.76–1.81 (m, 1H), δ 1.41–1.51 (m, 1H), δ 1.19-1.38 (m, 4H); MS ESI m/z 260 (M+H⁺); Anal. (C₁₇H₂₅NO(C₂H₂₋ 0₄)₁) C, H, N.

4.1.4. trans-2-(Methyl(phenethyl)amino)cyclohexanol (6)

N-Methylphenethylamine (2.70 mL, 18.8 mmol, 1.0 equiv) and cyclohexene oxide (5, 3.70 mL, 36.6 mmol, 2.1 equiv) were dissolved in 50 mL of ethanol and refluxed overnight. The ethanol was evaporated under reduced pressure and purified by column chromatography (silica gel, CHCl₃/5% MeOH/1% NH₄OH). Yield 70% (3.04 g); ¹H NMR (500 MHz, D₂O) δ 7.44 (t, 7.23 Hz, 2H), δ 7.35–7.40 (m, 3H), δ 3.74–3.86 (m, 1H), δ 3.51–3.64 (m, 1H), δ 3.38–3.46 (m, 1H), δ 3.01–3.31 (m, 3H), δ 2.98 (s, 1H), δ 2.83 (s, 2H), δ 2.01–2.15 (m, 2H), δ 1.82–1.90 (m, 1H), δ 1.71–1.79 (m, 1H), δ 1.21–1.55 (m, 4H); MS ESI *m*/*z* 234 (M+H⁺); Anal. (C₁₅H₂₃-NO(C₂H₂O₄)₁) C, H, N.

4.1.5. *N*-Methyl-*N*-phenethyl-2-(3phenylpropoxy)cyclohexanamine (7)

Compound **7** was prepared through alkylation of *trans*-2-(methyl(phenethyl)amino)cyclohexanol (**6**) (1.5 g, 6.43 mmol, 1.0 equiv) with 1-bromo-3-phenylpropane (2.93 mL, 19.3 mmol, 3.0 equiv) in the presence of NaH (1.08 g, 45.0 mmol, 7 equiv) following the method described previously.³⁸ Yield 6% (0.14 g); ¹H NMR (500 MHz, D₂O) δ 7.33–7.47 (m, 6H), δ 7.26–7.33 (m, 4H), δ 3.59–3.69 (m, 3H), δ 3.39–3.48 (m, 1H), δ 3.25–3.32 (m, 1H), δ 3.16–3.24 (m, 1H), δ 3.09–3.15 (m, 1H), δ 2.27–2.33 (m, 1H), δ 2.01–2.14 (m, 1H), δ 1.73–1.90 (m, 4H), δ 1.44–1.56 (m, 1H), δ 1.11–1.39 (m, 4H); MS ESI *m*/*z* 352 (M+H⁺); Anal. (C₂₄H₃₃NO(C₂H₂-O₄)₁) C, H, N.

4.1.6. trans-2-(3-Phenylpropylamino)cyclohexanol (8)

Phenylpropylamine (1.58 mL, 11.1 mmol, 1.0 equiv) and cyclohexene oxide (**5**, 2.36 mL, 23.3 mmol, 2.1 equiv) were dissolved in 50 mL of ethanol and refluxed overnight. The ethanol was evaporated under reduced pressure and purified by column chromatography (silica gel, 94% CHCl₃/5% MeOH/1% NH₄OH). Yield 89% (2.30 g); MS ESI m/z 234 (M+H⁺).

4.1.7. trans-2-(Methyl(3-phenylpropyl)amino)cyclohexanol (9)

A solution of *trans*-2-(3-phenylpropylamino)cyclohexanol (**8**, 2.27 g, 9.73 mmol, 1.0 equiv) 37% formaldehyde (HCHO) (21 mL, 706 mmol, 72.6 equiv) and formic acid (HCOOH) (21 mL, 548 mmol, 56.3 equiv) was refluxed overnight. The resulting crude mixture was concentrated and dissolved with ether and washed with 5 N NaOH. The organic extracts were combined, dried with K₂CO₃, and evaporated. Yield 52.4% (1.26 g); ¹H NMR (500 MHz, D₂O) δ 7.41 (t, 7.41 Hz, 2H), δ 7.30–7.30 (m, 3H), δ 3.71–3.79 (m,

1H), δ 3.05–3.34 (m, 3H), δ 2.91–3.00 (m, 1H), δ 2.88 (s, 1H), δ 2.70–2.83 (m, 4H), δ 2.00–2.20 (m, 3H), δ 1.89–1.96 (m, 1H), δ 1.79–1.88 (m, 1H), δ 1.70–1.78 (m, 1H), δ 1.21–1.48 (m, 4H); MS ESI *m/z* 248 (M+H⁺); Anal. (C₁₆H₂₅NO(C₂H₂O₄)₁(H₂O)_{0.25}) C, H, N.

4.1.8. *trans-N*-Methyl-2-(3-phenylpropoxy)-*N*-(3-phenylpropyl)cyclohexanamine (10)

Compound **10** was prepared through alkylation of *trans*-2-(methyl(3-phenylpropyl)amino)cyclohexanol (**9**, 0.6 g, 2.43 mmol, 1.0 equiv) with 1-bromo-3-phenylpropane (1.84 mL, 12.13 mmol, 5.0 equiv) in the presence of NaH (0.41 g, 17.0 mmol, 7.0 equiv) following the method described previously.³⁸ Yield 33% (0.29 g); ¹H NMR (500 MHz, D₂O) δ 7.23–7.32 (m, 5H), δ 7.14–7.24 (m, 5H), δ 3.54–3.62 (m, 1H), δ 3.40–3.47 (m, 1H), δ 3.18–3.26 (m, 1H), δ 2.54–2.75 (m, 5H), δ 2.42–2.51 (m, 1H), δ 2.28–2.38 (m, 3H), δ 2.06–2.14 (m, 1H), δ 1.84–1.93 (m, 2H), δ 1.72–1.83 (m, 3H), δ 1.63–1.72 (m, 2H), δ 1.53–1.60 (m, 1H), δ 1.04–1.30 (m, 4H); MS ESI *m*/*z* 366 (M+H⁺); Anal. (C₂₅H₃₅NO(C₂H₂O₄)₁) C, H, N.

4.2. Receptor binding assays

The opioid receptor binding affinities of compounds were determined in membranes prepared from CHO cells stably transfected with and expressing each of the three human opioid receptor subtypes (μ , δ , and κ) using standard in vitro methods.^{36,40} Briefly, μ receptors were labeled with 1.3 nM [³H]DAMGO (53.4 Ci/mmol), δ receptors were labeled with 1.2 nM [³H]DPDPE (45 Ci/mmol), and κ receptors were labeled with 1.7 nM [³H]U69,593 (42.7 Ci/mmol). Nonspecific binding for the opioid receptor assays was determined in the presence of 1 μ M unlabelled DAMGO, DPDPE, or U69,593 for the respective subtypes.

The radioligand binding assays for σ receptors were performed in rat brain homogenates using methods previously described in detail. 41,42 Briefly, σ_1 receptors were labeled with 5 nM [3 H](+)-pentazocine and σ_2 receptors were labeled with 3 nM [3 H]di-o-tolylguanidine (DTG) in the presence of 300 nM (+)-pentazocine to block σ_1 receptors. Nonspecific binding for the σ receptor assays was determined in the presence of 10 μ M haloperidol.

The competition binding studies were performed in the presence of up to 12 concentrations of each test compound and were incubated for 120 min at 25 °C. Reactions were terminated by rapid vacuum filtration through Perkin Elmer Unifilter[®]-96, GF/B filters (Fisher Scientific, Hanover Park, IL) previously soaked in 0.5% polyethyleneimine (PEI). Bound radioactivity was quantified by liquid scintillation counting. Affinities (K_i) were calculated using the Cheng–Prusoff equation.⁴³

4.3. Cocaine-induced convulsions

To probe for anticonvulsant actions of compounds **6** and **9** against cocaine, male, Swiss Webster mice (n = 10/group) were pretreated (ip) with compounds **6** (0, 1, 10, or 30 mg/kg) or **9** (0, 0.1, 1, or 10 mg/kg) 15 min prior to administration of a convulsive dose of cocaine (70 mg/kg, ip), similar to previously described.²¹ The mice were observed for the occurrence of convulsions for 30 min following the cocaine injection and results were recorded. 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. Fisher's exact test was utilized to determine significant differences between each group.

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Supplementary data

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