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Effect of ring-constrained phenylpropyloxyethylamines on sigma receptors

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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.

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 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-D-aspartate (NMDA) receptors[14] 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 receptors[31] 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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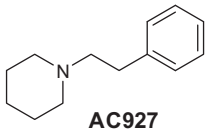
Earlier studies from our laboratory had shown that AC927 (*N*-phenethylpiperidine), a mixed σ_1 and σ_2 antagonist, demonstrated high selectivity for the σ receptors.[34] Additional studies showed that AC927 attenuated the behavioral and neurotoxic effects of cocaine in mice.[35] However, AC927 has a 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.



AC927

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

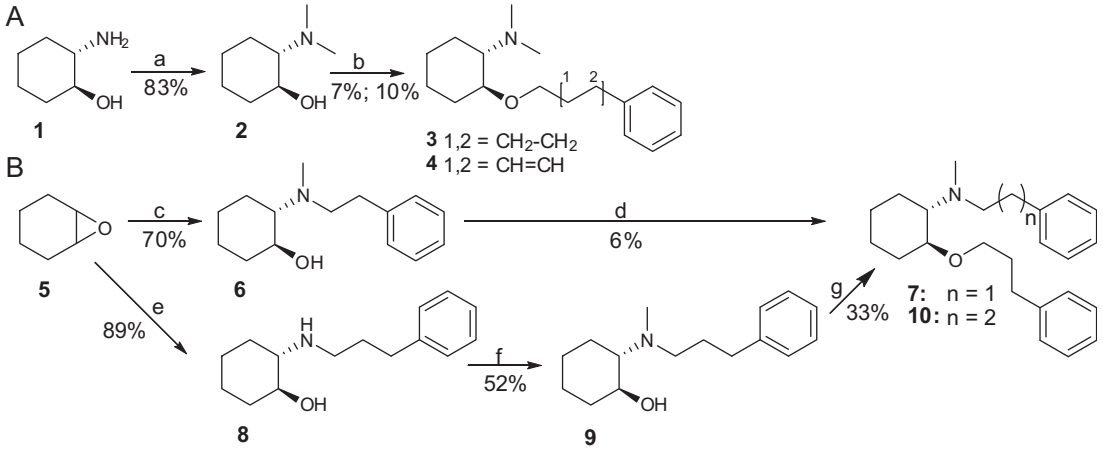
The synthetic sequences used to prepare compounds **3**, **4**, **6**, **7**, **9**, and **10** are displayed in Scheme 1. In brief, analogs **3** and **4** (Scheme 1A) were synthesized via *N*-methylation of *trans*-2-aminocyclohexanol hydrochloride (**1**) using the Eschweiler–Clark methylation[37] 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 reaction[37] 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 receptors[8] 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.