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A σ_1 receptor pharmacophore derived from a series of N-substituted 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols (AHDs)

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ABSTRACT

A library of N-substituted 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols (AHDs) was synthesized and subjected to competition binding assays at σ_1 and σ_2 receptors, as well as off-target screening of representative members at 44 other common central nervous system (CNS) receptors, transporters, and ion channels. Excluding 3 low affinity analogs, 31 ligands demonstrated nanomolar K_i values for either σ receptor subtype. Several selective σ_1 and σ_2 ligands were discovered, with selectivities of up to 29.6 times for σ_1 and 52.4 times for σ_2, as well as several high affinity, subtype non-selective ligands. The diversity of structures and σ_1 affinities of the ligands allowed the generation of a σ_1 receptor pharmacophore that will enable the rational design of increasingly selective and potent σ_1 ligands for probing σ_1 receptor function.

Sigma (σ) receptors are a neuromodulatory protein, widely expressed in the central nervous system (CNS) and certain peripheral organs.[1] The two currently defined subtypes, σ_1 and σ_2, differ in apparent molecular size, function, and ligand discrimination.[2] The σ_1 receptor has been cloned from numerous sources, including human brain tissue, and shows no sequence homology to any other mammalian protein.[3] The σ_1 receptor resides primarily at the mitochondria-associated endoplasmic reticulum membrane (MAM) where it acts as a molecular chaperone for type 3 inositol-1,4,5-triphosphate receptors to maintain correct interorganelle signalling and cytosolic Ca^{2+} concentrations.[4,5] However, σ_1 receptors are also known to undergo translocation to the nuclear envelope and plasma membrane, accounting for their modulation of various plasma membrane-bound proteins and maintenance of Ca^{2+} homeostasis by multiple mechanisms.[6–9] Historically, the elucidation of σ_2 receptor structure and function has proven more difficult, however, it was very recently proposed that the σ_2 receptor is actually progesterone receptor membrane component 1 (PGMRC1).[10]

The diverse, neuromodulatory pharmacology exhibited by σ receptors has implicated these proteins in virtually all major CNS diseases,[11,12] with compelling evidence that σ receptors play a central or ancillary role in anxiety and depression,[13–15] psychosis, [16,17] memory deficits,[18–21] and motor dysfunction.[22] Indeed, many clinically used antidepressants and antipsychotics from disparate mechanistic classes are known interact with σ receptors at therapeutically relevant concentrations.[23–27] σ Receptors are also involved in the physiological processes underlying addiction, and many drugs of abuse have been shown to interact with σ receptors, including cocaine, methamphetamine, and phencyclidine (PCP).[28–31]

While σ receptors remain a promising therapeutic target for multiple disorders of the CNS, the development of truly selective σ receptor ligands remains problematic. Many of the earliest σ receptor ligands were discovered serendipitously and were multifunctional 'dirty drugs', such as haloperidol. The structural heterogeneity of current σ ligands is extreme, and ligand promiscuity remains an impediment to understanding σ receptor pharmacology. Several selective ligands have been identified for both σ_1 and σ_2 subtypes, however, such compounds comprise relatively few distinct structural classes. The identification of new chemotypes with σ subtype selectivity and truly negligible off-target activity remains a goal for the development of pharmacological tools and potential therapeutic agents targeting these sites.

The 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol (AHD) scaffold confers affinity for σ receptors when judiciously appended at the nitrogen atom, as in **1** (Fig. 1), and analogous hemiaminals have demonstrated selectivity for σ receptors over 44 other major CNS receptors, transporters, and ion channels. Members of

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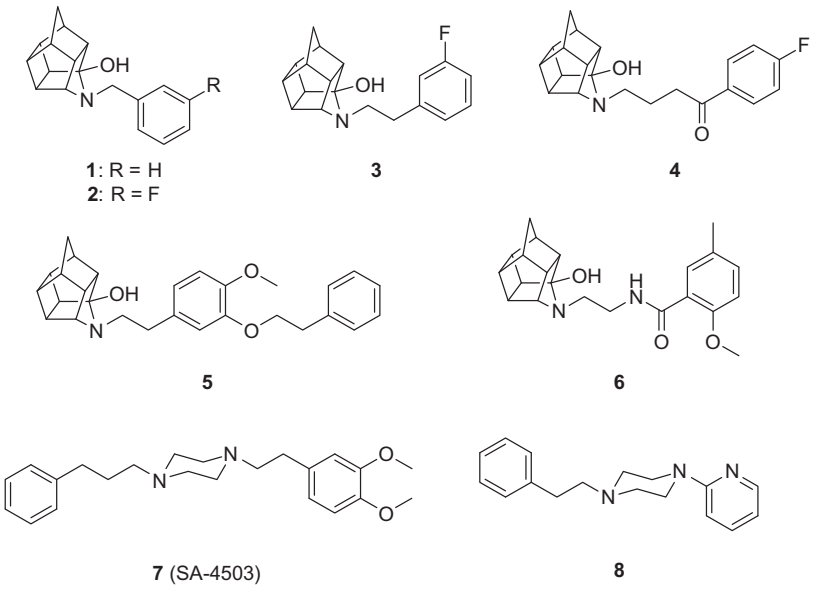


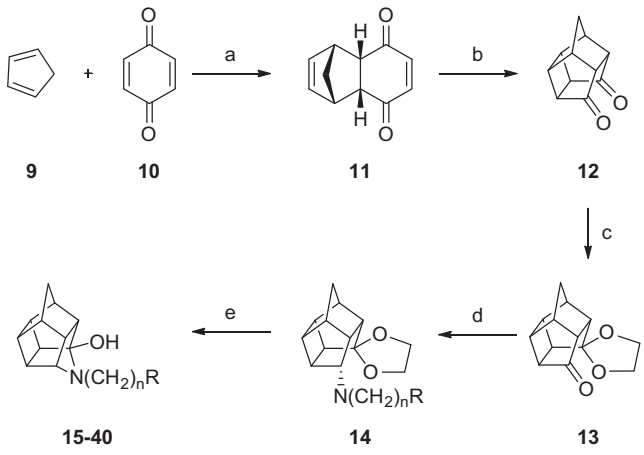
Figure 1. Selected σ receptor ligands.

this class, including **2** and **3**, have displayed promising anti-cocaine effects in mice,[32] but few structure-affinity relationships (SAfiRs) have been established for this class due to the limited structural variability of reported members.[33–35] Preliminary trends suggest that distance between the polycyclic hemiaminal and the aryl group is the primary determinant of σ subtype selectivity, with benzyl AHD derivatives generally preferring the σ_2 receptor and phenethyl AHD derivatives typically demonstrating selectivity for the σ_1 receptor, allowing the generation of ligands for either σ subtype from a common scaffold. Aromatic substitution patterns have been explored to a limited extent, and small, electronegative atoms in the 3-position appear to confer the greatest enhancement of affinity and subtype selectivity. A molecular hybridization strategy utilizing AHD produced **4**, **5**, and **6**, which demonstrated profound alterations of σ subtype selectivity and attenuated off-target interaction when compared to their respective parent compounds; haloperidol, NE-100, and RHM-2.[36]

Having recently explored the effect of hemiaminal isomerization[37,38] and expansion of the trishomocubane cage[39] of the AHD chemotype on σ binding, exploration of the N-substituent region would expand the SAfiRs for this class, potentially allowing the generation of σ subtype pharmacophores. The present study aimed to systematically explore the importance of (i) alkyl chain length, (ii) alkoxyaromatic substitution patterns, (iii) heteroaromatic incorporation, and (iv) aliphatic N-substitution. To address the first goal, analogs of **1** and **2** containing two to four methylene unit-spacers were envisaged. The second aim sought to explore the importance of substitution of the aromatic ring, given the frequent recurrence of the (poly)methoxyphenyl motif among σ ligands, such as SA-4503 (**7**, σ_1 K_i = 4.63 nM, σ_2/σ_1 = 13.6).[40] Such compounds may be amenable to the incorporation of carbon-11, thereby providing potential positron emission tomography (PET) tracers for imaging σ receptors in living systems. The incorporation of heteroaromatic rings has not been explored within the AHD class, however, the inclusion of certain pyridine regioisomers was shown to confer σ_2 selectivity to σ ligands such as **8** (σ_2 K_i = 4.91 nM, σ_1/σ_2 = 16.9).[41] Finally, molecular modeling of this class had indicated that π density on the aromatic ring of AHD analogs **2** and **3** may decrease σ receptor affinity.[37] Therefore, a similarly sized N-substituent that is alicyclic rather than aromatic may possess a more optimal highest occupied molecular orbital (HOMO) for σ receptor interaction.

The synthesis of target AHDs is depicted in Scheme 1. The Diels-Alder reaction of cyclopentadiene (**9**) and 1,4-benzoquinone (**10**) gave the well-precedented adduct **11**,[42] which underwent [2+2] photocyclization to give pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (Cookson's diketone, **12**).[43] Although cage diketone **12** is commercially available, the quantities required and the ease of synthesis deemed in-house production more economical, with up to 12 g produced in a single run from inexpensive precursors. Protection of a single ketone functionality of **12** as its ethylene acetal gave the racemic ketal **13**. Condensation of the remaining ketone of **13** with appropriate primary amines at high temperature (sealed tube) gave the corresponding imines, which were subsequently reduced by sodium borohydride to stereoselectively afford corresponding *endo*-amines of type (**14**). Acetal hydrolysis in aqueous acid with acetone as co-solvent and donor ketone, followed by basic work-up, furnished the transannularly-cyclized products **15**–**40**. The structures and yields of AHDs **15**–**39** are presented in Table 1.

The requisite amines for step (d) of Scheme 1 were generally commercially available, with the exception of those comprising



Scheme 1. Reagents and conditions: (a) PhMe,−10 °C–rt, 80%; (b) hν, hexane-Me_2CO (90:10), rt, 14 h, 93%; (c) $HOCH_2CH_2OH$, *p*-TsOH (cat.), PhMe, reflux, Dean-Stark, 5 h, 93%; (d)(i) $R(CH_2)_nNH_2$, EtOH, 100 °C, sealed tube, 18 h; (ii) $NaBH_4$, EtOH, 0 °C–rt, 8 h; (e) 4 M aq. HCl, Me_2CO, rt, 12 h, basic work-up, 22–65% (over 3 steps).