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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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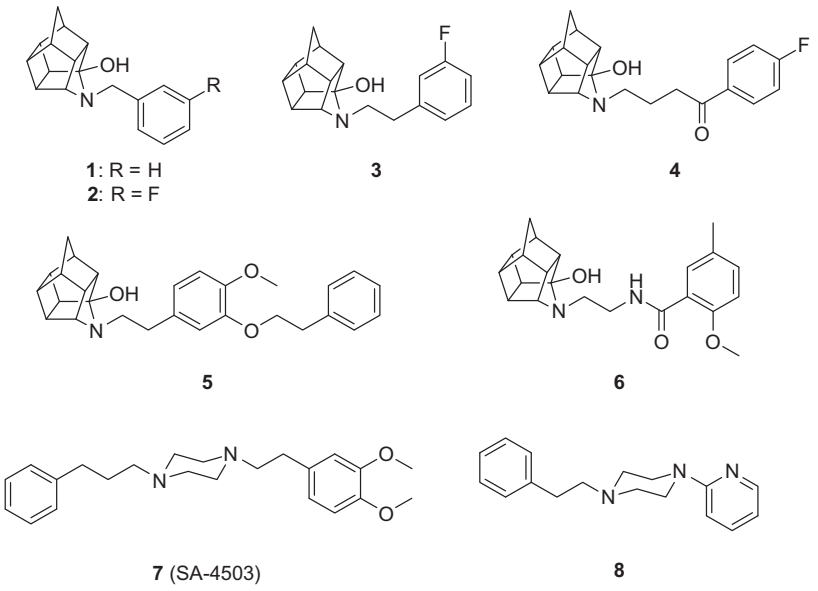


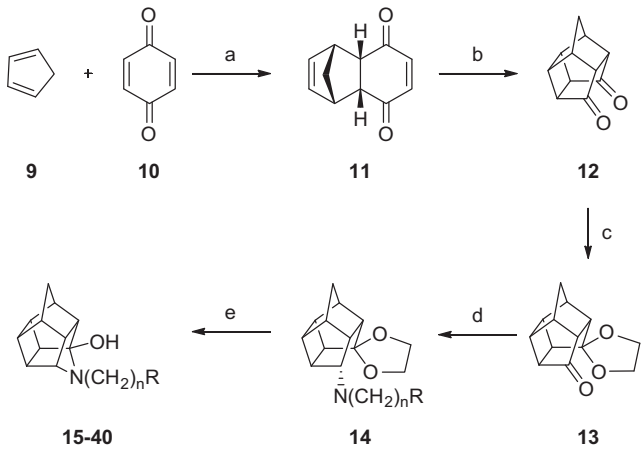
Figure 1. Selected σ receptor ligands.

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).

4, **5**, **6**, **38**, and **40**. The synthesis of **4**, **5**, and **6** has been previously described, but **38** and **40** required 3-(3-fluorophenyl)propylamine (**41**, Scheme 2) and 4-(3-fluorophenyl)butylamine (**42**, Scheme 3) respectively. The former was synthesized from 3-fluorocinnamic acid (**43**) via 3-fluorocinnamamide (**44**), with complete reduction of the α,β-unsaturated amide achieved by lithium aluminum hydride, to furnish **41** in 54% yield over 3 steps. The synthesis of the latter started with *N*-(3-bromopropyl)phthalimide (**45**), which was reacted with triphenylphosphine to give phosphonium bromide **46**. 3-Fluorobenzaldehyde was subjected to a Wittig reaction with **46** and the obtained distaereomeric mixture of alkenes (**47**) was hydrogenated over palladium on carbon to give saturated amine **48**. Removal of the phthalimide group was achieved by hydrazinolysis to give **42** in 57% overall yield.

The N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols **15**–**40** were subjected to protein binding assays against a panel of CNS receptors. The K_i values for **15**–**40** at σ_1 and σ_2 receptors are shown in Table 1. Rat brain homogenates were used as the source of σ_1 receptors, whilst PC12 cells were used as the σ_2 receptor source. The radioligands [^{3}H](+)-pentazocine and [^{3}H]DTG were used in the σ_1 and σ_2 receptor assays, respectively. Selected AHDs were comprehensively screened against major CNS receptors, transporters, and ion channels (see Table S1 of Supplementary data for full binding profiles). In general, compounds **15**–**40** showed negligible affinity for adrenergic, dopamine, GABA, histamine, 5-HT, muscarine, and opioid receptors, as well as monoamine transporters (DAT, NET, SERT), and ion channels (Ca^{2+}, NMDA/PCP), confirming the utility of AHD for the development of selective σ ligands.

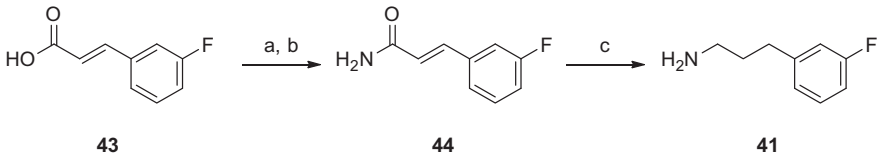
Consistent with the previously established SAfiRs, the benzylic derivatives **1** and **2** were both σ_2 selective ligands (Table 1). However, contrasting previous findings, the simple benzylic derivative **1** displayed the greatest σ_2 selectivity (K_i = 12.6 nM, σ_1/σ_2 = 26.7), with a 3-fluoro substituent (**2**) reducing σ_2 affinity (K_i = 31.0 nM) and diminished selectivity over σ_1 (σ_1/σ_2 = 4.9). The phenethyl derivative **27** showed a preference for σ_1 receptors (K_i = 26 nM, σ_2/σ_1 = 2.6) and a 3-fluoro substituent doubled σ_1 affinity, but produced little net improvement in selectivity over σ_2 (K_i = 12 nM, σ_2/σ_1 = 4.0). Increasing the distance between the trishomocubyl hemiaminal and aromatic ring led to improved binding at both σ_1 and σ_2 receptors, effectively abolishing σ subtype selectivity. Phenylpropyl derivative **37** (σ_1 K_i = 17 nM, σ_2 K_i = 26 nM) and its 3-fluoro analog, **38** (σ_1 K_i = 15 nM, σ_2 K_i = 6.3 nM), displayed almost equivalent affinity for the σ_1 and σ_2 receptor subtypes. Phenylbutyl derivative **39** displayed modest selectivity for the σ_1 receptor (σ_1 K_i = 10 nM, σ_2 K_i = 54 nM), but its 3-fluoro analog (**40**) was a high affinity, dual σ receptor ligand (σ_1 K_i = 5.5 nM, σ_2 K_i = 8.9 nM).

Substitution of the benzyl group of **1** with a single methoxy unit was equally well tolerated by σ_2 receptors at the 2-, 3-, and 4-positions (**15**, **16**, and **17** respectively). Like **1** itself, the methoxybenzyl regioisomers were selective for σ_2 receptors, and this was most pronounced for 3-methoxy analogue **16** (σ_1/σ_2 = 12.2). A 3,4-dimethoxy substitution pattern was optimal for σ_2 binding, with **19** possessing both the greatest affinity and subtype selectivity for the σ_2 receptor (K_i = 12.6 nM, σ_1/σ_2 = 18.1) within this series, and a 2,4-dimethoxy substitution pattern (**18**) was tolerated at both σ subtypes, but 3,5-dimethoxy analog **20** showed markedly

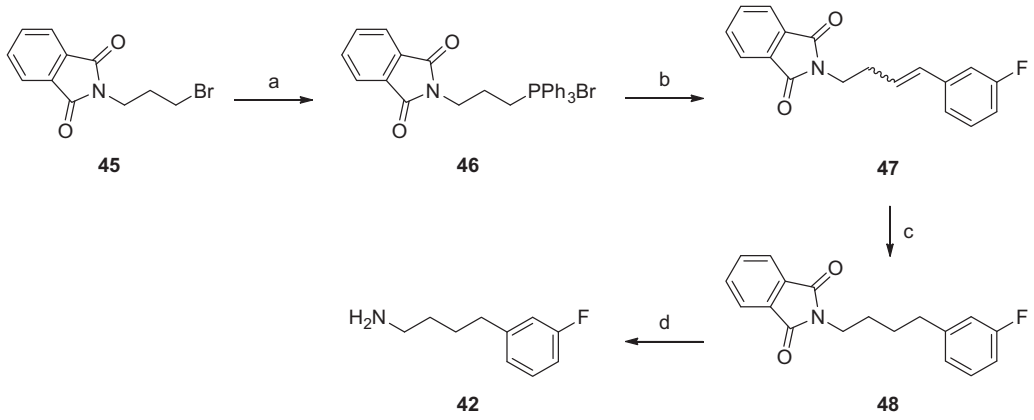
Table 1
Yields and binding affinities of compounds **1**–**6** and **15**–**39** for σ_1 and σ_2 receptors.

Cmpd	*n*	R	Yield[a] (%)	K_i (nM ± SEM)[b]		Selectivitiy	
				σ_1	σ_2	σ_1	σ_2
1	1	Ph	63	337 ± 21	12 ± 2		28
2[c]	1	3-FPh	34	153 ± 17	31 ± 6		4.9
3[c]	2	3-FPh	52	12 ± 1	48 ± 10	4.0	
4[d]	—	—	42	27 ± 2	55 ± 4	2.0	
5[d]	—	—	50	20 ± 1	93 ± 5	4.7	
6[d]	—	—	65	7.6 ± 1.0	225 ± 18	29.6	
15	1	2-(OCH_3)Ph	22	190 ± 22	27.3 ± 4.1		7.0
16	1	3-(OCH_3)Ph	53	327 ± 26	26.8 ± 3.7		12.2
17	1	4-(OCH_3)Ph	48	200 ± 26	27.3 ± 4.0		7.3
18	1	2,4-(OCH_3)$_2$Ph	61	66 ± 2	77 ± 7	1.2	
19	1	3,4-(OCH_3)$_2$Ph	41	228 ± 20	12.6 ± 2.2		18.1
20	1	3,5-(OCH_3)$_2$Ph	45	610 ± 34	125 ± 5		4.9
21	1	3,4-(OCH_2O)Ph	38	435 ± 51	259 ± 38		1.7
22	1	3,4,5-(OMe)$_3$Ph	61	4289 ± 395	>10 000	2.3	
23	1	Cyclohexane	38	6.7 ± 0.8	2.2 ± 0.3		3.0
24	1	2-Pyridine	36	1048 ± 30	20.0 ± 1.0		52.4
25	1	3-Pyridine	37	>10 000	3234 ± 397		3.1
26	1	4-Pyridine	39	1502 ± 148	514 ± 46		2.9
27	2	Ph	61	26 ± 2	68 ± 14	2.6	
28	2	2-(OCH_3)Ph	33	68.7 ± 6.0	56.9 ± 8.9	0.8	
29	2	3-(OCH_3)Ph	37	52.3 ± 4.0	100 ± 14	1.9	
30	2	4-(OCH_3)Ph	49	15.1 ± 1.1	56.9 ± 9.0	3.8	
31	2	2,3-(OCH_3)$_2$Ph	39	15.0 ± 0.7	107 ± 5	7.1	
32	2	3,4-(OCH_3)$_2$Ph	53	101 ± 13	259 ± 38	2.6	
33	2	3,4-(OCH_2O)Ph	41	26 ± 2	97 ± 10	3.7	
34	2	2-Pyridine	56	1170 ± 186	26.8 ± 4.1		43.7
35	2	3-Pyridine	48	815 ± 126	100 ± 14		8.2
36	2	4-Pyridine	33	68.0 ± 6.0	404 ± 32	5.9	
37	3	Ph	63	17 ± 1	26 ± 6	1.5	
38	3	3-FPh	55	15 ± 1	6.3 ± 0.7		2.4
39	4	Ph	58	10 ± 1	54 ± 13	5.4	
40	4	3-FPh	49	5.5 ± 1.0	8.9 ± 1.0	1.6	

[a] Un optimized yield over three steps.
[b] K_i values represent the mean ± SEM of four experiments.
[c] Data extracted from Ref.37.
[d] Data extracted from Ref.36.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, DMF (cat.), $CHCl_3$, reflux, 4 h; (b) 28% aq. NH_4OH, rt, 18 h, 66% over 2 steps; (c) $LiAlH_4$, Et_2O, reflux, 14 h, 81%.



Scheme 3. Reagents and conditions: (a) *p*-xylene, reflux, 45 h, 92%; (b) 3-FPhCHO, NaOMe, THF, 0 °C to rt, 41 h, 67%; (c) H_2, 10% Pd/C (cat.), THF-MeOH (50:50), rt, 18 h, 98%; (d) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 2 h, 95%.

reduced affinity for both σ receptors. Installation of a 3,4-methylenedioxy bridge (**21**) was detrimental to σ binding, as was further elaboration to 3,4,5-trimethoxybenzyl analogue **22**, with these analogs showing submicromolar and micromolar binding affinities respectively. The difference in σ affinity between **19** and **22** suggests that subtle steric or electronic alterations have a profound influence on σ_2 selectivity within this series.

Alkoxy-substituted phenethyl AHDs **28**–**33**, with the exception of **28**, showed a slight preference for σ_1 binding, with K_i values ranging from 15–101 nM, and generally low levels of subtype selectivity. Methoxy substitution in the 2- or 3-position (**28** and **29** respectively), imparted moderate affinity for both σ subtypes, with 4-methoxy derivative **30** displaying the greatest preference for σ_1 (K_i = 15.1 nM, σ_2/σ_1 = 3.8). Unlike its benzylic counterpart, the 3,4-dimethoxyphenethyl analog **32** displayed only low affinity for both σ receptors, with regioisomeric 2,3-dimethoxy **31** proving superior in terms of σ_1 affinity and subtype selectivity (K_i = 15.0 nM, σ_2/σ_1 = 7.1). Incorporation of a 3,4-methylenedioxy bridge (**33**) gave a modestly selective σ_1 ligand (K_i = 26 nM, σ_2/σ_1 = 3.7).

The 2-pyridylmethyl derivative **24** displayed high affinity for σ_2 receptors (K_i = 20.0 nM), and more than 50 times selectivity over the σ_1 receptor. The regioisomeric 3-pyridylmethyl (**25**) and 4-pyridylmethyl (**26**) analogs were much poorer σ_2 ligands, with submicromolar and micromolar binding affinities respectively. The same general trend was observed for the pyridylethyl regioisomers, with a 2-pyridyl group imaprting high σ_2 affinity and selectivity to **34** (K_i = 26.8 nM, σ_1/σ_2 = 43.7). The 3-pyridylethyl derivative **35** possessed moderate affinity and selectivity for σ_2, however, the 4-pyridylethyl derivative **36** showed moderate affinity for the σ_1 receptor (K_i = 68.0 nM, σ_2/σ_1 = 5.9).

AHD **23**, containing a cyclohexane ring in place of the phenyl ring of **1**, was prepared to investigate the hypothesis that HOMO density from aromatic π orbitals may be inversely correlated with σ receptor affinity. Confirming this hypothesis, **23** was found to possess high affinity for both σ receptor subtypes (σ_1 K_i = 6.7 nM, σ_1 K_i = 2.2 nM), making it the most potent σ receptor ligand identified within the AHD series to date.

With the exception of 3,4,5-trimethoxybenzyl derivative **22**, and 3- and 4-pyridine analogs **25** and **26** respectively, all N-substituted AHDs were found to interact with σ receptors with submicromolar affinity. The distance between the hemiaminal and the aromatic ring is the greatest determinant of σ subtype selectivity within this series; benzyl derivatives are σ_2 selective, phenethyl derivatives are σ_1 preferring. However, fewer high affinity, highly subtype selective σ_1 ligands were identified compared to σ_2 ligands. To understand the origin of subtype selectivity in N-substituted AHDs, and guide the development of increasingly potent and selective σ_1 ligands, a σ_1 pharmacophore model for the series of 32 N-substituted AHDs shown in Table 1 was developed using the Phase program provided in Maestro.[44,45]

The generated five feature pharmacophore represented as distances and angles is shown in Figures 2a and 2b respectively, and contained two hydrophobic regions (H6 and H11), one aromatic ring (R15), one positive ionizable feature (P14), and one hydrogen bond acceptor (A1). The distances between the central positive ionizable group and the two hydrophobic regions are in agreement with the few published σ_1 pharmacophores.[46–49] The distance between the positive ionizable *N* and hydrophobic region (H6) near the aromatic ring, which Glennon et al.[46] described as the primary hydrophobic region, is about 6.3 Å, whereas the distance between N and hydrophobic region (H11), near the hydrogen bond acceptor group, is 3.6 Å (secondary hydrophobic region).

Figure 3 shows the mapping of the generated pharmacophore with two of the best fitting σ_1 active compounds; **31** and **3**. The aromatic ring region is occupied by a phenyl ring in both compounds, with primary hydrophobic region (H6) occupied by a methoxy group in **31** and a fluorine atom in **3**. The other three pharmacophoric features, namely positive ionizable, hydrogen bond acceptor, and secondary hydrophobic region, are present in most of the dataset and are occupied by a basic nitrogen atom, hydroxy group, and the hexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane cage respectively. Figure 2 also includes yellow excluded volumes generated using the sterically unfavored regions of inactive compounds. Both depicted active compounds clearly do not overlap

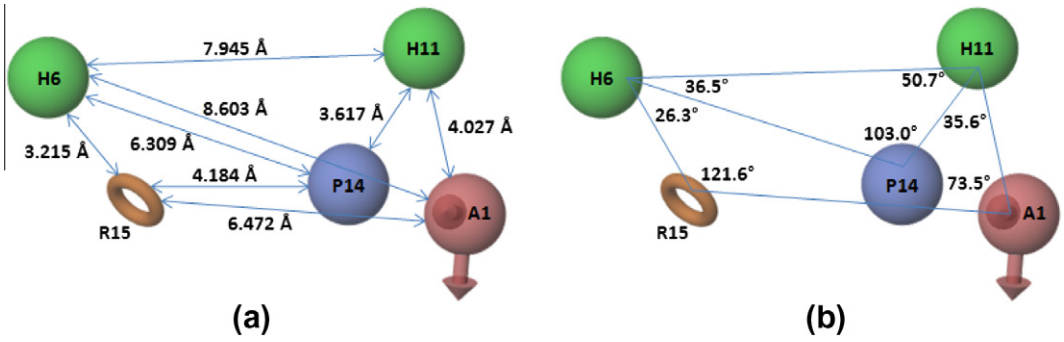


Figure 2. Best ranked five feature pharmacophoric hypothesis with (a) distances and (b) angles. Spheres represent favored hydrophobic regions (H6 and H11), positive ionizable region (P14), hydrogen bond acceptor (A1), and aromatic ring (R15).

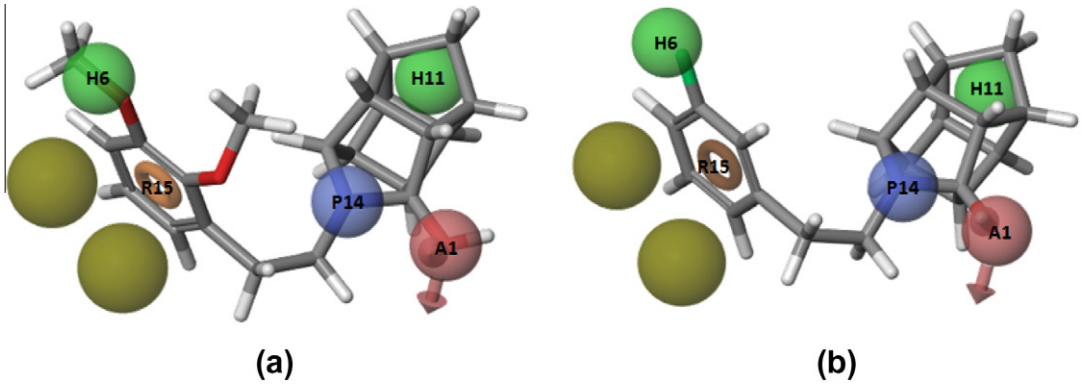


Figure 3. Five feature pharmacophore mapping to active compounds (a) **31** and (b) **3**. Yellow spheres represent sterically unfavored excluded volumes.

with these regions, indicating no unfavorable steric interactions with the receptor.

Figure 4 shows the mapping of the pharmacophore with the two least σ_1 active compounds of the dataset; **25** and **22**. Compound **25** (Fig. 4a) does not occupy the primary hydrophobic region (H6), and contains an electron deficient pyridine in place of the phenyl ring of **1**. Even though compound **22** (Fig. 4b) contains all the pharmacophoric features and maps well to the hypothesis, the two yellow excluded volumes are occupied by two methoxy groups, causing unfavorable steric interactions with the receptor. One of the limitations of the hypothesis is that compound **23**, one of the most active of the dataset, does not map properly due to the absence of an aromatic ring. However, its high affinity indicates that alicyclic hydrophobic groups are accepted in place of substituted phenyl rings.

The AHD scaffold represents an excellent platform for the development of highly selective, high affinity σ receptor ligands. Judicious selection of a suitable *N*-arylalkyl substituent has permitted the discovery of several selective σ_2 ligands (**1**, **19**, **24**, and **34**), and σ_1 ligands (**6**, **31**), as well many highly σ selective, dual subtype ligands (e.g. **23**, **38**, and **40**). Excluding **22**, **25**, and **26**, K_i values for N-substituted AHDs binding at the σ_1 receptor subtype ranged from 5.5–1170 nM, and from 6.3–404 nM at the σ_2 receptor. The proposed SAfiRs indicate that highly σ_2 selective ligands can be generated by appropriate ring substitution of the N-benzylic region of **1**, or substitution of this group with a 2-pyridinealkyl unit. Fewer σ_1 selective ligands have been generated from AHD, prompting the generation of a five feature pharmacophore to suggest a direction for the rational design of such agents in the absence of any structural information describing the σ_1 binding site. Ongoing

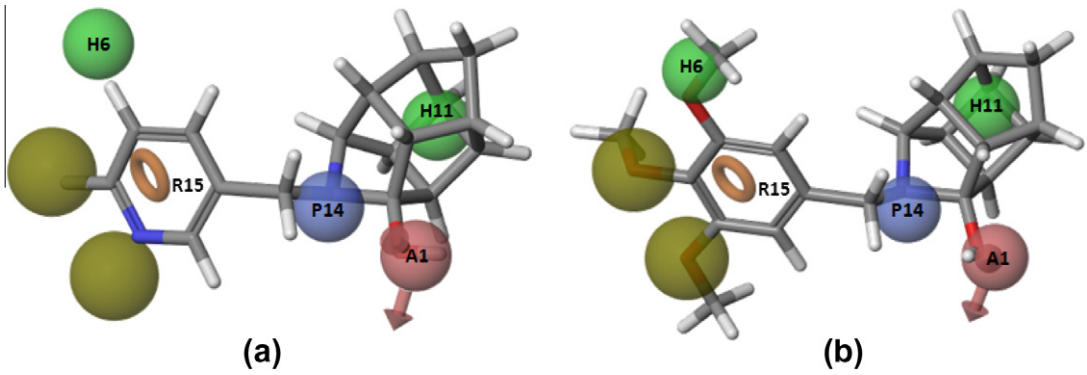


Figure 4. Five feature pharmacophore mapping to inactive compounds (a) **25** and (b) **22**. Yellow spheres represent sterically unfavored excluded volumes.

efforts to further elaborate the substituted AHDs will utilize the accumulated SAfiRs and five feature pharmacophore, ultimately providing increasingly selective ligands for either σ subtype from a common scaffold. These pharmacological tools demonstrably possess favourable in vivo properties, and will be used to delineate the functions of σ_1 and σ_2 receptors in CNS disease.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.046.

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