Bioorganic & Medicinal Chemistry Letters 22 (2012) 4059–4063

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

7-Azabicyclo[2.2.1]heptane as a scaffold for the development of selective sigma-2 (σ_2) receptor ligands

Samuel D. Banister [a,b], Louis M. Rendina [a], Michael Kassiou [a,b,c,*]

[a] School of Chemistry, The University of Sydney, NSW 2006, Australia
[b] Brain and Mind Research Institute, Sydney, NSW 2050, Australia
[c] Discipline of Medical Radiation Sciences, The University of Sydney, NSW 2006, Australia

ARTICLE INFO

Article history:
Received 14 March 2012
Revised 11 April 2012
Accepted 16 April 2012
Available online 30 April 2012

Keywords:
Azanorbornanes
Pyrrolidines
Sigma receptors
CNS
Structure–activity relationships

ABSTRACT

A series of N-substituted 7-azabicyclo[2.2.1]heptanes (**12**–**17** and **22**–**25**) and similarly substituted pyrrolidines (**32**–**36** and **41**–**44**) were synthesized as sterically-reduced, achiral analogs of adamantane- and trishomocubane-derived σ ligands. In vitro competition binding assays against σ receptors revealed that arylalkyl N-substituents conferred selectivity for the σ_2 subtype, while alicyclic or polycarbocyclic substituents imparted high affinity for both subtypes. The σ_2 binding and subtype selectivities of *N*-arylalkyl-7-azanorbornanes was generally greater than the analogously-substituted pyrrolidines, indicating that steric bulk and conformational restriction around the nitrogen atom are likely important for subtype discrimination.

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More than 35 years after their discovery, sigma (σ) receptors remain widely studied due to their involvement in virtually all major central nervous system (CNS) diseases.[1] Two σ receptor subtypes have been defined, σ_1 and σ_2, differing in size, ligand selectivity, and anatomical distribution.[2,3] The σ_1 receptor has been cloned from numerous tissues and species, and its predicted 223 amino acid sequence shares no homology with any other mammalian protein.[4] Primarily, σ_1 receptors reside at the mitochondria-associated enoplasmic reticulum membrane (MAM), where their ability to act as chaperones for type 3 inositol-1,4,5-triphosphate (IP3) receptors assists the maintenance of Ca^{2+} homeostasis under conditions of cellular stress.[5,6] However, σ_1 receptors may undergo unidirectional translocation to the plasmalemma where they modulate the activity of K^+ and Ca^{2+} channels, as well as other components of membrane-bound signal transduction.[7–9]

In contrast, the pharmacology of σ_2 receptors remains less well-defined. The σ_2 receptor has not been cloned, but photoaffinity studies have suggested it is smaller than the σ_1 receptor, approximately 21.5 kDa.[10] Fluorescent probes have indicated that the subcellular localization of σ_2 receptors resembles that of σ_1, with high concentrations found in mitochondria, endoplasmic reticulum, and plasma membrane.[11] It was very recently proposed that the hitherto unknown identity of the σ_2 binding site may be progesterone receptor membrane component 1 (PGRMC1), or a protein complex thereof.[12]

The implication of both σ receptors subtypes in the pathophysiologies of multiple affective disorders, including anxiety, depression, and schizophrenia, as well as dysfunctions of memory (Alzheimer's disease) and movement (Parkinson's disease), has prompted the development of increasingly selective σ ligands for the potential treatment of CNS disorders.[1,13] Indeed, many clinical antidepressants and antipsychotics have demonstrated activity at σ receptors at therapeutically-relevant concentrations.[14–17] Cocaine and methamphetamine also interact with σ receptors at physiologically-relevant concentrations, and there is extensive evidence that σ receptors are involved in both the toxic and rewarding effects of these widely abused stimulants, making σ receptors a promising target for the treatment of substance abuse.[18–21]

Despite the therapeutic utility of σ receptors, the design of drugs acting selectively at σ binding sites remains challenging. No tertiary structural information is available for either σ subtype, and the structural heterogeneity of known σ ligands is extreme.[22,23] A pharmacophore for the σ_1 receptor has been proposed and its simplicity allows it to encompass the majority of σ_1 ligands, albeit at the expense of predictive utility.[22] However, no such consensus model exists for σ_2 binding, and truly selective σ_2 ligands are far outnumbered by those with selectivity for σ_1. As a result, the use of relatively subtype non-selective σ ligands in animal models of disease has often obscured the independent roles of σ receptor subtypes in such models.

In an effort to delineate the roles of σ_1 and σ_2 receptors in substance abuse in vivo,[24] we sought to develop chemotypes with improved selectivity for each σ receptor subtype. Our efforts have

* Corresponding author.
E-mail address: michael.kassiou@sydney.edu.au (M. Kassiou).

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http://dx.doi.org/10.1016/j.bmcl.2012.04.077

focused on the development of increasingly subtype-selective σ receptor ligands based on heterocyclic[25–27] and heteropolycyclic scaffolds,[24,28–30] resulting in the generation of several classes of highly selective σ_1 ligands with negligible off-target activity.

It was recently reported that deoxygenation of *N*-arylalkyl-2-azaadamantan-1-ols (**1**) to the corresponding N-substituted 2-aza-adamantanes (**2**) resulted in improved σ_1 binding and subtype selectivity Figure 1. It was anticipated that an analogous transformation might enhance the well-established in vitro and in vivo σ receptor-mediated pharmacology of trishomocubanes of type **3**.[24,31] However, the synthesis of similarly deoxygenated analogs (**4**) proved extremely difficult. To further explore the steric contribution of such polycarbocyclic amines to σ receptor binding and subtype selectivity, a series of ligands was envisaged incorporating 7-azabicyclo[2.2.1]heptane (**5**), the simplest aza-bridged bicyclic subunit of compound **4** (Fig. 1).

The synthesis of this series of N-substituted 7-azanorbornanes is shown in Scheme 1. The amine of *trans*-4-aminocyclohexanol (**6**, Scheme 1) was protected as its benzyl carbamate (**7**) and the remaining alcohol converted to the toluenesulfonate (**8**). Carbamate cleavage using hydrogen bromide in glacial acetic acid gave hydrobromide salt **9**. Dissolution of **8** in aqueous ethanol containing sodium hydroxide furnished transannularly-cyclized **5** as its free base. The volatility of solid free base **5** necessitated immediate conversion to the hygroscopic hydrochloride salt, which was purified by recrystallization. Thus, **5**·HCl was obtained in 69% yield over four steps without chromatographic purification, providing several grams of this common precursor.

The synthesis of *N*-benzylic 7-azabicyclo[2.2.1]heptanes was achieved by liberating the hydrochloride salt of **5** with triethylamine in situ, and treating the solution with the appropriate aroyl chloride. In this way the theoretically-interesting non-planar benzamide **10**,[32,33] and 3-fluorobenzamide **11**, were synthesized in excellent yield. Reduction of the amide group, using lithium aluminum hydride in each case, gave the amines **12** and **13** in 88% and 89% yield, respectively. Although this route provided the desired amines in 79–82% yield over two steps from a common precursor, a more direct approach was reductive alkylation of **5**, using the appropriately substituted aldehyde and sodium triacetoxyborohydride, to give the desired amines **12**–**17** in 65–95% yield in a single step. Azanorbornamides **18**–**21** were prepared by activating the appropriate arylalkanoic acids with carbonyl diimidazole followed by treatment with **5**. Reduction of the amide group, to give the desired amines **22**–**25**, was achieved using lithium aluminum hydride (**22**, **23**, and **25**), or borane (**24**).

The synthesis of the azanorbornane analog containing a cubylmethyl moiety (**17**) required the preparation of cubanecarboxaldehyde (**26**, Scheme 2). Cyclopentanone was converted to dimethyl cubane-1,4-dicarboxylate (**27**) in 19% yield over six steps using the previously reported procedure of Bliese and Tsanaktsidis.[34] Diester **27** was monohydrolysed to acid-ester **28**, which was subjected to a Moriarty reaction, with subsequent saponoification of the remaining ester furnishing 4-iodocubanecarboxylic acid (**29**).[35,36] Reduction of iodo-acid **29** with borane dimethylsulfide complex gave iodo-alcohol **30**, which underwent lithium–halogen exchange and subsequent methanol quench to provide cubylcarbinol **31**. Parikh–Doering oxidation[37] of **31** gave cubanecarboxaldehyde in comparable yield to the previously reported Swern oxidation.[38,39]

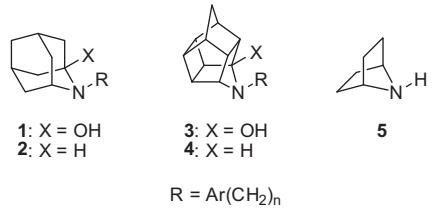


Figure 1. Azapolycarbocyclic σ receptor ligand scaffolds.

A series of N-substituted pyrrolidines analogous to azanorbornanes **12**–**16** and **22**–**25** was also synthesized, as shown in Scheme 3, to investigate the σ receptor binding of the simplest possible heterocyclic subunit of frameworks such as **3** and **4**. Thus, pyrrolidines **32**–**36** were prepared by reductive alkylation with the appropriate benzaldehyde using sodium triacetoxyborohydride. Coupling suitably substituted arylalkanoic acids with pyrrolidine using carbonyl diimidazole gave amides **37**–**40**, which were reduced by lithium aluminum hydride to give **41**, **42**, and **44**, or borane in the case of **43**.

The synthesized azanorbornanes and pyrrolidines were routinely converted to their hydrogen oxalate salts, and subjected to in vitro competition binding assays. Rat brain homogenates were used as the source of σ_1 receptors, while 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. The K_i values for **12**–**17**, **22**–**25**, **32**–**36**, and **41**–**44** at σ_1 and σ_2 receptor subtypes are shown in Table 1. Selected compounds were also screened for off-target activity against a panel of 42 common CNS sites, and generally displayed negligible affinity for all sites tested (see Table S1 for complete binding data).

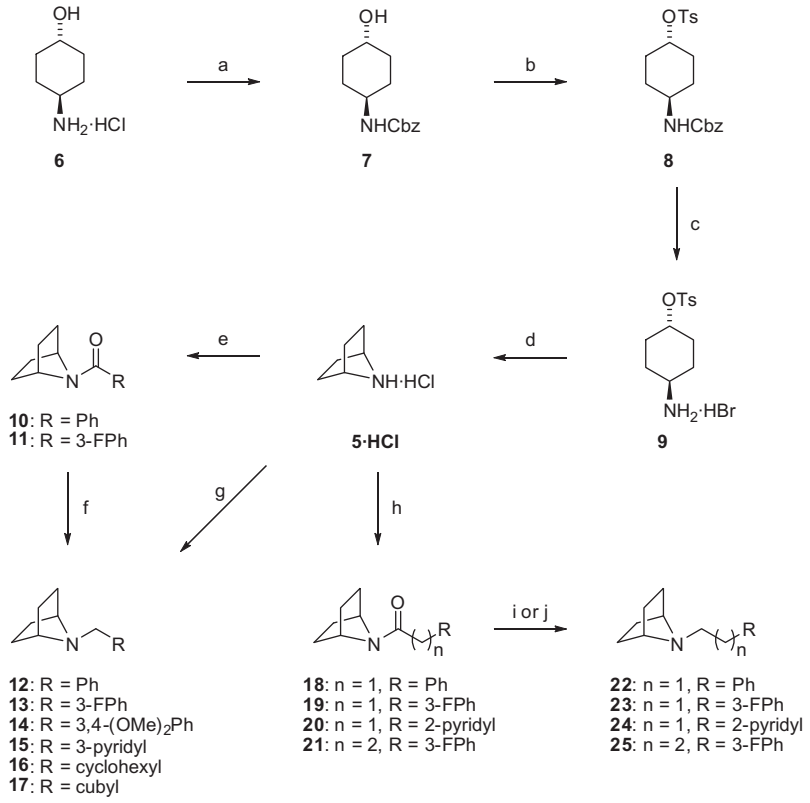
N-Benzyl-7-azabicyclo[2.2.1]heptane (**12**) possessed moderate affinity for the σ_2 receptor (K_i = 399 nM), and was essentially devoid of affinity for the σ_1 receptor (K_i >10000 nM). Introduction of a fluorine atom at the 3-position slightly improved σ_2 affinity (**13**, K_i = 251 nM), but had no effect on σ_1 binding. A 3,4-dimethoxy-substitution pattern (**14**) conferred high affinity for σ_2 (K_i = 43.1 nM) without altering σ_1 affinity, resulting in more than 230-fold selectivity for the σ_2 subtype.

Incorporation of a heteroaromatic ring was detrimental to σ binding, with **15** demonstrating only micromolar affinity for both σ subtypes. Saturation of the aromatic ring, as in cyclohexyl derivative **16**, resulted in unexpectedly high affinity for both σ receptor subtypes (σ_1 K_i = 22 nM, σ_2 K_i = 18 nM), and substitution with a cubane moiety (**17**) bestowed further improvement to σ_1 binding (σ_1 K_i = 7 nM, σ_2 K_i = 18 nM).

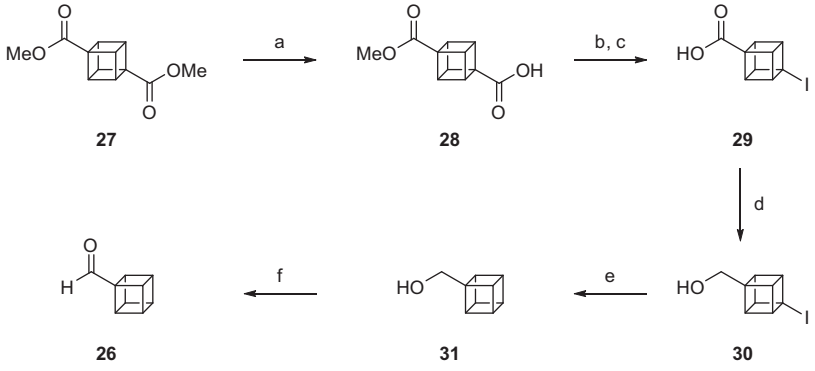
Extending the distance between the bicyclic amine group and the aromatic ring introduced significant affinity for σ_1 receptors. The simple phenethyl derivative (**22**) had submicromolar affinity for the σ_2 receptor (K_i = 131 nM) but also interacted with the σ_1 receptor (K_i = 276 nM), and binding at both σ receptor subtypes was improved by a 3-fluorophenethyl substituent (**23**; σ_1 K_i = 103 nM, σ_2 K_i = 29.5 nM). Further homologation of **23** to give 3-(3-fluorophenyl)propyl analog **25** produced a high affinity σ_2 ligand with moderate subtype selectivity (σ_2 K_i = 11.9 nM, σ_2/σ_1 = 10). A pyridine ring within this homologous series imparted low affinity for both σ subtypes, with **24** demonstrating submicromolar affinity for σ_2 receptors, but only micromolar σ_1 affinity.

When compared to the corresponding 7-azabicyclo[2.2.1]heptanes, the substituted pyrrolidines (**32**–**36**, **41**–**44**) generally showed a reduction in both σ_1 and σ_2 binding. *N*-Benzylpyrrolidine (**32**) displayed barely submicromolar affinity for σ_2 receptors (K_i = 852 nM), a greater than two-fold reduction in binding compared to the corresponding 7-azanorbornane, and was similarly devoid of σ_1 affinity (K_i >10 μM). Substituting the benzyl group with 3-fluorobenzyl (**33**) or 3,4-dimethoxybenzyl (**34**) moiety had little effect on σ_2 affinity (K_i values of 1611 and 661 nM, respectively), although both compounds interacted more poorly with σ_2 than their 7-azabicyclo[2.2.1]heptane counterparts.

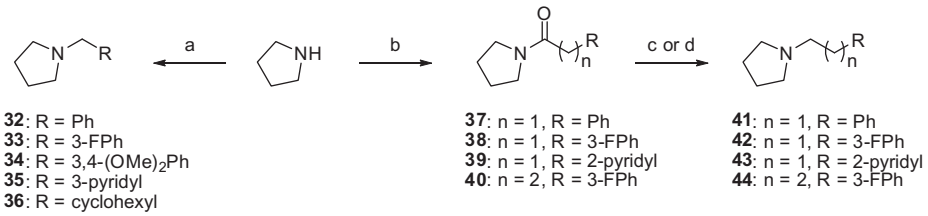
The cyclohexyl subunit, which had conferred high σ_1 and σ_2 affinity in the 7-azanorbornane series, produced low σ_2 affinity within the pyrrolidine series, although moderate σ_1 affinity was retained (**36**; σ_1 K_i = 51 nM, σ_2 K_i = 410 nM).



Scheme 1. Reagents and conditions: (a) $BnOC(O)Cl$, Na_2CO_3, $THF–H_2O$, 0 °C to rt, 2 h, 97%; (b) TsCl, C_5H_5N, 0 °C to rt, 24 h, 94%; (c) 33% HBr in AcOH, rt, 1 h, 97%; (d) NaOH, $EtOH–H_2O$, rt, 24 h, 78%; (e) $RC(O)Cl$, Et_3N, CH_2Cl_2, 0 °C, 4.5 h, 90–92%; (f) $LiAlH_4$, THF, reflux, 20 h, 88–89%; (g) RCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 14–22 h, 65–95%; (h) $R(CH_2)_nCOOH$, CDI, Et_3N, THF, rt, 12–20 h, 83–93%; (i) $LiAlH_4$, THF, reflux, 20 h, 87–91% (**22**, **23**, **25**); (j) $BH_3·SMe_2$, THF, reflux, 23 h, 57% (**24**).



Scheme 2. Reagents and conditions: (a) NaOH in MeOH, THF, rt, 14 h, 92%; (b) $PhI(OAc)_2$, I_2, PhMe, 80 °C, 8 h; (c) aq NaOH, MeOH, THF, rt, 14 h, 74% over two steps; (d) $BH_3·SMe_2$, THF, 0 °C to rt, 4.5 h, 93%; (e) *n*-BuLi, THF, −78 °C, 1 h, then MeOH, rt, 1 h, then 25% w/v NaOMe in MeOH, reflux, 1 h, 76%; (f) DMSO, $SO_3·C_5H_5N$, Et_3N, CH_2Cl_2, 0 °C to rt, 18 h, 77%.



Scheme 3. Reagents and conditions: (a) RCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 14–22 h, 90–96%; (b) $R(CH_2)_nCOOH$, CDI, THF, rt, 12–20 h, 86–92%; (c) $LiAlH_4$, THF, reflux, 20 h, 86–97% (**41**, **42**, **44**); (d) $BH_3·SMe_2$, THF, reflux, 17 h, 66% (**43**).

Table 1
Binding affinities and σ_2 subtype selectivities of N-substituted 7-azabicyclo[2.2.1]heptanes and pyrrolidines for σ receptors

Compound	K_i (nM ± SEM)[a]		σ_2 Selectivity
	σ_1	σ_2	
12	NA	399 ± 21	>25
13	NA	251 ± 38	>39
14	NA	43.1 ± 7.2	>232
15	NA	6352 ± 342	>1.6
16	22 ± 1	18 ± 1	1.2
17	7.0 ± 0.3	18 ± 1	0.39
22	276 ± 47	131 ± 5	2.1
23	103 ± 8	29.5 ± 5.1	3.5
24	3826 ± 364	517 ± 103	7.4
25	120 ± 9	11.9 ± 2.3	10
32	NA	852 ± 35	>11
33	NA	1611 ± 47	>6.2
34	NA	661 ± 27	>15
35	NA	NA	—
36	51 ± 5	410 ± 30	0.12
41	NA	658 ± 25	>15
42	NA	246 ± 32	>40
43	NA	3516 ± 165	>2.8
44	NA	39 ± 1	>260

[a] K_i values represent the mean ± SEM of four experiments. NA = less than 50% inhibition of specific binding at 10 μM.

Phenethylpyrrolidine (**41**) showed a five-fold reduction in σ_2 affinity (K_i = 658 nM) when compared to corresponding 7-azabicyclo[2.2.1]heptane, however, the reduction in σ_1 affinity was much more pronounced (K_i >10 μM). The same trend was observed for 3-fluorophenethyl-substituted pyrrolidine (**42**), which showed approximately eight times lower affinity for σ_2 (K_i = 246 nM) than the analogous 7-azanorbornane, but negligible affinity for σ_1 (K_i >10 μM). Compound **44**, *N*-(3-(3-fluorophenyl)propyl)pyrrolidine, showed a marked improvement in σ_2 binding (K_i = 39 nM), but was still devoid of σ_1 affinity (K_i >10 μM), resulting in an anomalously selective σ_2 ligand (σ_1/σ_2 = 256) for the series.

Replacement of the phenyl ring of **32** with a 3-pyridine ring (**35**) abolished affinity for either σ receptor subtype (K_i > 10 μM in each case), and homologation to 2-pyridylethyl-substituted pyrrolidine (**43**) did little to improve σ binding. Although the pyridine-containing **15** and **24** were the least active azanorbornanes, the σ binding of pyridine-derived pyrrolidines **35** and **43** was even poorer, consistent with the observed trend for reduced σ affinities when moving the pyrrolidine unit.

Several structure–affinity relationships can be identified from the σ binding data presented in Table 1. In the context of previously reported σ binding profiles of trishomocubanes of type **3**, steric reduction of the polycyclic framework was detrimental to binding at both σ subtypes. Removal of a single ethylene bridge from the 7-azanorbornane analogs, to give the corresponding pyrrolidines, significantly attenuated σ_2 binding. Within the 7-azabicyclo[2.2.1]heptane series, benzylic substituents conferred the greatest σ_2 selectivities, while increasing the distance between the aryl group and the nitrogen atom increased affinity for both σ_1 and σ_2 (particularly the former), resulting in σ_2 ligands with low levels of subtype discrimination.

The high σ_1 affinity of cyclohexyl-derived azanorbornane **16**, containing an aliphatic rather than aromatic group, indicates that electronic factors are more important for σ_1 than σ_2 binding. This is further supported by the anomalous σ_1 affinity of the cyclohexyl-bearing **36** within the pyrrolidine series. However, the possibility of multiple binding orientations for non-aromatic σ ligands cannot be excluded and may contribute to the observed binding profiles. Aliphatic compound **17**, the first σ receptor ligand comprising a cubane subunit, showed remarkably high affinity for both σ subtypes, warranting the further investigation of cubane for the design of potent, but subtype non-selective, σ receptor ligands.

The 7-azabicyclo[2.2.1]heptane scaffold represents a promising candidate for the development of selective σ_2 ligands, particularly when substituted with electron-rich benzylic systems, as in **14**. In order to further improve σ_2 receptor affinity and selectivity, future work will focus on the exploration of alkoxy substitution patterns (as well as alternative electron-donating substituents) around the benzyl ring of **14**. The development of potent and highly σ_2-selective 7-azanorbornanes will enable the delineated investigation of the role of the σ_2 receptor in CNS disorders such as anxiety, depression, and substance abuse.

Acknowledgments

K_i determinations for targets included in Table 1 and in the SI were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract #NO1MH32004 (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP web site http://pdsp.med.unc.edu/.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.077.

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