Bioorganic & Medicinal Chemistry Letters 21 (2011) 5289–5292

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

N-Arylalkyl-2-azaadamantanes as cage-expanded polycarbocyclic sigma (σ) receptor ligands

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ARTICLE INFO

Article history:
Received 14 June 2011
Revised 4 July 2011
Accepted 6 July 2011
Available online 14 July 2011

Keywords:
Adamantanes
Polycarbocyclic
Sigma receptors
CNS
Structure–activity relationships

ABSTRACT

A series of racemic *N*-arylalkyl-2-azaadamantan-1-ols (**9**–**15**) and the corresponding deoxygenated, achiral *N*-arylalkyl-2-azaadamantanes (**23**–**29**) were synthesized and screened in competition binding assays against a panel of CNS targets. Adamantyl hemiaminals **9**–**15** displayed generally low affinity for both σ_1 (K_i values = 294–1950 nM) and σ_2 receptors (K_i values = 201–1020 nM), and negligible affinity for 42 other CNS proteins. Deoxygenation of 9–15 to give the corresponding achiral azaadamantanes **23**–**29** greatly improved affinity for σ_1 (K_i values = 8.3–239 nM) and σ_2 receptors (K_i values = 34–312 nM).

The σ receptors are a unique class of mammalian proteins widely distributed in the central nervous system (CNS) and peripheral organs, and two subtypes have been defined: σ_1 and σ_2 receptors, differing in size, anatomical distribution, and ligand selectivity.[1–3] While the human σ_1 receptor has been cloned from various tissues, and shows no sequence homology with any known mammalian protein, the σ_2 receptor has not been cloned from any species.[4,5]

σ_1 receptors primarily reside at the interface between the endoplasmic reticulum (ER) and the mitochondrion, where they mobilize ER Ca^{2+} stores by acting as a molecular chaperones for type 3 inositol (1,4,5)-triphosphate receptors.[6] However, σ_1 receptors can also translocate to the plasma membrane where they modulate Ca^{2+} flux via K^+ channels and voltage-dependent Ca^{2+} channels.[7,8] The role of σ_1 receptors in the maintenance of Ca^{2+} homeostasis may partially account for their diverse pharmacology. Indeed, σ_1 receptors may regulate adrenergic, cholinergic, dopaminergic, glutamatergic, and serotonergic neurotransmissions.[9–15]

Relatively less is known about the structure and function(s) of the σ_2 receptor. The σ_2 receptor is also believed to regulate intracellular Ca^{2+} concentrations, however, the precise mechanisms involved are yet to be elucidated.[16] The over-expression of σ_2 receptors in several cancer cell lines suggests that they may represent potential biomarkers of tumor cell proliferation, potentially allowing selective σ_2 ligands to act as diagnostic probes.[17,18]

An interest in σ receptors persists more than 35 years after their discovery due to their implication in virtually all major CNS diseases.[19,20] Some of the earliest σ receptor ligands identified were clinical antipsychotics, such as haloperidol, which binds to σ_1 and σ_2 receptors with nanomolar affinity.[21] In addition to structurally diverse antipsychotics, several antidepressants from disparate pharmacological classes were also found to interact with σ_1/σ_2 receptors with high affinity.[22,23] The implication of σ receptors in anxiety disorders,[24] depression,[25] Alzheimer's disease,[26] and drug addiction[27] is well accepted, however, elucidation of the precise mechanistic role of σ receptors in many of these diseases has been hampered by the historical lack of truly selective ligands.

A myriad of structurally dissimilar ligands are known to interact with σ_1 and σ_2 receptors. The finding that adamantine (**1**, Fig. 1), used in the treatment of Parkinson's disease, interacts with σ receptors at therapeutically-relevant concentrations prompted the investigation of alternate polycarbocyclic 'cage' amines with potential activity at σ receptors.[28,29] *N*-Arylalkyl-4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols (**2**), derived from the trishomocubane scaffold, can be modified to provide compounds with selectivity for either σ_1 or σ_2 receptors.[30–32] Moreover, congeners of **2** were able to modulate amphetamine-stimulated dopamine release in vitro, and have shown promising alteration of cocaine-mediated effects in behavioral assays.[33,34]

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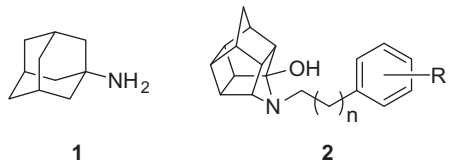
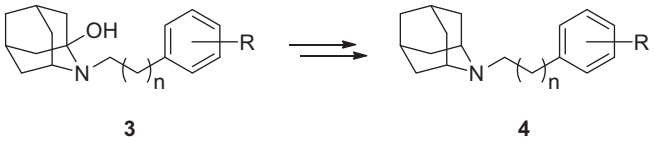
doi:10.1016/j.bmcl.2011.07.028



1 2

Figure 1. Polycarbocyclic 'cage' amines with σ receptor activity.



3 4

Figure 2. Proposed *N*-arylalkyl-2-azaadamantan-1-ols and the corresponding *N*-arylalkyl-2-azaadamantanes.

Table 1
Binding affinities, and subtype selectivities, of compounds **9**–**15** and **23**–**29** for σ_1 and σ_2

Compound	R	*n*	X	K_i[a] (nM ± SEM)		Selectivity	
				σ_1	σ_2	σ_1	σ_2
9	H	0	OH	1450 ± 170	1020 ± 91		1.4
10	3-F	0	OH	862 ± 150	705 ± 66		1.2
11	4-F	0	OH	650 ± 55	826 ± 19	1.3	
12	3-OMe	0	OH	1950 ± 91	353 ± 29		5.5
13	4-OMe	0	OH	1240 ± 100	426 ± 28		2.9
14	3-F	1	OH	234 ± 20	250 ± 28	1.1	
15	4-F	1	OH	246 ± 55	201 ± 19		1.2
23	H	0	H	29 ± 5	95 ± 11	3.3	
24	3-F	0	H	22 ± 2	132 ± 5	6.0	
25	4-F	0	H	12.0 ± 0.4	90 ± 6	7.5	
26	3-OMe	0	H	239 ± 9	64 ± 2		3.7
27	4-OMe	0	H	12.4 ± 0.8	54 ± 7	4.4	
28	3-F	1	H	8.3 ± 0.6	40 ± 2	4.8	
29	4-F	1	H	12.8 ± 0.8	34 ± 3	2.7	

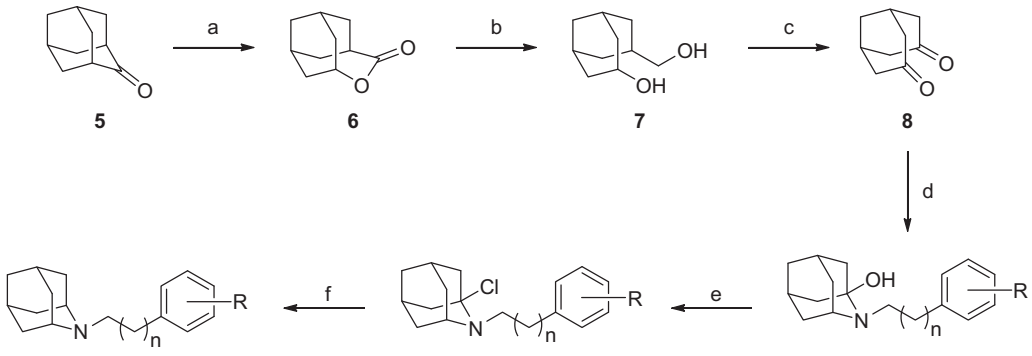
[a] K_i values represent the mean ± SEM of four experiments.

To further explore the structure–affinity relationships of polycarbocyclic amines acting at σ receptors, we sought to synthesize and screen a series of *N*-arylalkyl-2-azaadamantan-1-ols (**3**, Fig. 2) as cage-expanded analogs of trishomocubane hemiaminals like **2**. Furthermore, these adamantyl hemiaminals could be deoxygenated to give the corresponding N-substituted 2-azaadamantanes (**4**), thereby providing information about the steric and electronic tolerance of the postulated hydrophobic region surrounding the basic nitrogen atom at the σ receptor binding site.[35]

Commercially available 2-adamantanone (**5**, Scheme 1) was subjected to a Baeyer–Villiger oxidation to generate lactone **6**. Chromatographic purification of **6** afforded an analytical sample, but the crude material was sufficiently pure for use in further reactions. Complete reduction of **6** with lithium aluminum hydride gave diol **7**, requiring no further purification. Treatment of **7** with excess pyridinium dichromate (PDC) furnished diketone **8** as the result of an unusual oxidation.[36] Stirring a solution of **8**, acetic acid, and the appropriate arylalkylamine with sodium triacetoxy borohydride at ambient temperature afforded the desired *N*-arylalkyl-2-azaadamantan-1-ols **9**–**15**.

Like **4** and it congeners, **9**–**15** were synthesized as racemates. However, deoxygenation of **9**–**15** gives the corresponding achiral, azaadamantanes, providing information about the importance of the hydroxy group to this class of σ receptor ligands. The adamantyl hemiaminals **9**–**15** were converted to the corresponding alkyl chlorides (**16**–**22**) by refluxing in thionyl chloride. Alkyl chlorides **16**–**22** underwent reductive dehalogenation with lithium aluminum hydride to give the symmetrical *N*-arylalkyl-2-azaadamantanes **23**–**29**.

The synthesized azaadamantanols **9**–**15** and azaadamantanes **23**–**29** were routinely converted to their hydrochloride salts, and subjected to in vitro binding assays. The K_i values for **9**–**15** and **23**–**29** at σ_1 and σ_2 receptor subtypes are shown in Table 1. Guinea pig brain membrane homogenates were used as the source of σ_1 receptors, while rat liver membrane homogenates 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 σ_2 receptor binding assay was conducted in the presence of 1 μM (+)-pentazocine to mask ligand binding to σ_1 receptors. To confirm the selectivity of these chemotypes for σ receptors, representative compounds (**9**, **10**, **23**, and **24**) were screened against a panel of 42 other CNS proteins, and showed negligible affinity at all sites tested (see Table S1 for full binding profiles).



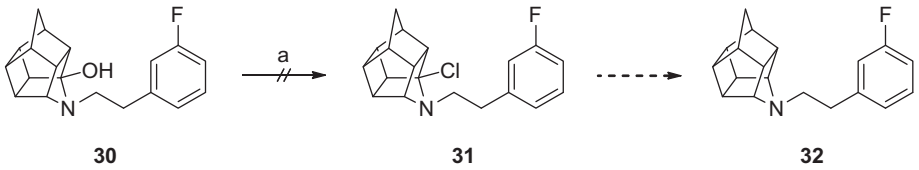
5 6 7 8

23: n = 0, R = H
24: n = 0, R = 3-F
25: n = 0, R = 4-F
26: n = 0, R = 3-OMe
27: n = 0, R = 4-OMe
28: n = 1, R = 3-F
29: n = 1, R = 4-F

16: n = 0, R = H
17: n = 0, R = 3-F
18: n = 0, R = 4-F
19: n = 0, R = 3-OMe
20: n = 0, R = 4-OMe
21: n = 1, R = 3-F
22: n = 1, R = 4-F

9: n = 0, R = H
10: n = 0, R = 3-F
11: n = 0, R = 4-F
12: n = 0, R = 3-OMe
13: n = 0, R = 4-OMe
14: n = 1, R = 3-F
15: n = 1, R = 4-F

Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 18 h, 97%; (b) $LiAlH_4$, Et_2O, reflux, 19 h, 99%; (c) PDC, CH_2Cl_2, rt, 66 h, 40%; (d) $Ar(CH_2)_nNH_2$, AcOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 18 h, 94–100%; (e) $SOCl_2$, reflux, 1 h, 91–99%; (f) $LiAlH_4$, 1,4-dioxane, reflux, 18 h, 62–92%.



30 31 32

Scheme 2. Reagents and conditions: (a) $SOCl_2$, reflux, 8 h.

The simple benzylic adamantyl hemiaminal (**9**) showed only micromolar affinity for σ_1 (K_i = 1.45 μM) and σ_2 receptors (K_i = 1.02 μM). The introduction of a fluorine atom to the phenyl ring of **9** produced a small increase in σ receptor affinity, regardless of substitution position; 3-fluorobenzyl derivative **10** (σ_1 K_i = 862 nM, σ_2 K_i = 705 nM) showed a similar binding profile to that of the 4-fluoruobenzyl congener **11** (σ_1 K_i = 650 nM, σ_2 K_i = 826 nM). Although **9**–**11** displayed negligible subtype selectivity, a methoxy substituent was able to introduce a small degree of σ_2 selectivity. The 3-methoxybenzyl analog **12** showed a slight preference for σ_2 receptors (σ_2 K_i = 353 nM, σ_1/σ_2 = 5.5), comparable in magnitude to the 4-methoxy isomer **13** (σ_2 K_i = 426 nM, σ_1/σ_2 = 2.9).

Extending the distance between the polycyclic cage and the aryl group produced the greatest increase in σ receptor binding. The 3-fluorophenethyl adamantyl hemiaminal **14** showed increased affinity for both σ receptor subtypes (σ_1 K_i = 234 nM, σ_2 K_i = 250 nM) when compared to **10**, but subtype selectivity was similarly negligible. Much like the corresponding benzylic analogs, the binding profile of the 4-fluoruophenethyl derivative **15** (σ_1 K_i = 246 nM, σ_2 K_i = 201 nM) largely resembled that of **14**, demonstrating that positional isomerism is similarly unimportant for these ethylene-spaced congeners. Overall, **9**–**15**, showed only micromolar or submicromolar affinity for σ_1 receptors (K_i values 234–1950 nM), and similar σ_2 binding (K_i values 234–1020 nM).

Deoxygenation of hemiaminals **9**–**15** to the corresponding azaadamantanes **23**–**29** generally produced a dramatic increase in σ_1 binding, but a less pronounced increase in σ_2 affinity. When compared to hemiaminal **9**, the simple *N*-benzyl-2-azaadamantane (**23**) demonstrated a 50-fold improvement in σ_1 affinity (K_i = 29 nM), and a greater than 10-fold increase in σ_2 affinity (K_i = 95 nM). The 3-fluorobenzyl-substituted azaadamantane **24** showed a similar level of improvement over hemiaminal **10**, furnishing a moderately σ_1-selective ligand (σ_1 K_i = 22 nM, σ_2/σ_1 = 6), and the same trend was observed for 4-fluorobenzyl congener **25** (σ_1 K_i = 12 nM, σ_2/σ_1 = 7.5) when compared to **11**.

The 3-methoxybenzyl-substituted **26** represented the sole instance in which deoxygenation imparted similar increases in both σ_1 (K_i = 239 nM) and σ_2 affinity (K_i = 64 nM) when compared to the parent compound, producing a net retention of the σ_2-selectivity of parent compound **12**. By contrast, 4-methoxy isomer **27** showed a 100-fold increase in σ_1 affinity (σ_1 K_i = 12.4 nM) compared to the corresponding hemiaminal **13**, and was a moderately selective σ_1 ligand (σ_2/σ_1 = 4.4).

Since hemiaminals **14** and **15** showed the greatest σ receptor affinity within that series, the relative improvement arising from deoxygenation to the corresponding 3- and 4-fluorophenethyl-substituted azaadamantanes **28** and **29**, was less dramatic. Compounds **28** and **29** both interacted with σ_1 receptors with high affinity (σ_1 K_i = 8.3 and 12.8 nM, respectively), and showed a preference for this σ receptor subtype (σ_2/σ_1 = 4.8 and 2.7, respectively).

The enhancement of σ receptor affinity conferred by the deoxygenation of adamantyl hemiaminals prompted attempts to effect the analogous transformation in trishomocubyl hemiaminal **30** (σ_1 K_i = 12 nM, σ_2 K_i = 48 nM)[30] using the aforementioned conditions (Scheme 2). Unfortunately, refluxing **30** in $SOCl_2$ for several hours returned only starting material, and alkyl chloride **31** could not be obtained.

Due to the relatively increased rigidity of the trishomocubane scaffold compared to that of adamantane, the hemiaminal carbon of trishomocubane **30** is likely unable to adopt a sufficiently planar configuration in order to stabilize the carbocation-like transition state required for chlorination to occur. Investigation of alternative direct and indirect deoxygenation approaches to achiral azatrishomocubanes like **32** are currently underway.

Taken together, the results of the binding assays suggest that deoxygenation of *N*-arylalkyl-2-azaadamantanols to the corresponding achiral, *N*-arylalkyl-2-azaadamantanes, increases σ_1 affinity by up to two orders of magnitude, and improves σ_2 binding by as much as a single order of magnitude. Excluding compound **26**, all N-substituted 2-azaadamantanes showed a preference, albeit slight, for σ_1 receptors (σ_1 selectivity = 2.7–7.5). Most deoxygenated compounds showed low nanomolar affinity for σ_1 receptors, and excellent selectivity over 42 other CNS targets. Although structural refinement is required to improve σ subtype selectivity, the *N*-arylalkyl-2-azaadamantane chemotype represents a novel lead for the development of potent, selective σ_1 receptor ligands.

Acknowledgements

K_i determinations for targets included 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 M.D., Ph.D. 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 doi:10.1016/j.bmcl.2011.07.028.

References and notes

1. Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. *Trends Pharmacol. Sci.* **1992**, *13*, 85.
2. Leonard, B. E. *Pharmacopsychiatry* **2004**, *37*(Suppl 3), S166.
3. Guitart, X.; Codony, X.; Monroy, X. *Psychopharmacology (Berl)* **2004**, *174*, 301.
4. Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H. G.; Striessnig, J.; Kempner, E.; Glossmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072.
5. Kekuda, R.; Prasad, P. D.; Fei, Y. J.; Leibach, F. H.; Ganapathy, V. *Biochem. Biophys. Res. Commun.* **1996**, *229*, 553.
6. Hayashi, T.; Su, T.-P. *Cell* **2007**, *131*, 596.
7. Aydar, E.; Palmer, C. P.; Klyachko, V. A.; Jackson, M. B. *Neuron* **2002**, *34*, 399.
8. Monnet, F. P. *Biol. Cell* **2005**, *97*, 873.
9. Matsuno, K.; Matsunaga, K.; Senda, T.; Mita, S. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 851.
10. Gonzalez-Alvear, G. M.; Werling, L. L. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 212.
11. Gonzalez-Alvear, G. M.; Werling, L. L. *Brain Res.* **1995**, *673*, 61.
12. Debonnel, G.; de Montigny, C. *Life Sci.* **1996**, *58*, 721.
13. Gonzalez, G. M.; Werling, L. L. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *356*, 455.
14. Bermack, J. E.; Debonnel, G. *Br. J. Pharmacol.* **2001**, *134*, 691.
15. Lucas, G.; Rymar, V. V.; Sadikot, A. F.; Debonnel, G. *Int. J. Neuropsychopharmacol.* **2008**, *11*, 485.
16. Vilner, B. J.; Bowen, W. D. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 900.

17. Mach, R. H.; Smith, C. R.; al-Nabulsi, I.; Whirrett, B. R.; Childers, S. R.; Wheeler, K. T. *Cancer Res.* **1997**, *57*, 156.
18. al-Nabulsi, I.; Mach, R. H.; Wang, L. M.; Wallen, C. A.; Keng, P. C.; Sten, K.; Childers, S. R.; Wheeler, K. T. *Br. J. Cancer* **1999**, *81*, 925.
19. Maurice, T.; Su, T.-P. *Pharmacol. Ther.* **2009**, *124*, 195.
20. Hayashi, T.; Stahl, S. M. *Drugs Future* **2009**, *34*, 137.
21. Tam, S. W.; Cook, L. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5618.
22. Itzhak, Y.; Kassim, C. O. *Eur. J. Pharmacol.* **1990**, *176*, 107.
23. Narita, N.; Hashimoto, K.; Tomitaka, S.; Minabe, Y. *Eur. J. Pharmacol.* **1996**, *307*, 117.
24. Kulkarni, S. K.; Dhir, A. *Expert Rev. Neurother.* **2009**, *9*, 1021.
25. Bermack, J. E.; Debonnel, G. *J. Pharmacol. Sci.* **2005**, *97*, 317.
26. Maurice, T. *Drug News Perspect.* **2002**, *15*, 617.
27. Maurice, T.; Martin-Fardon, R.; Romieu, P.; Matsumoto, R. R. *Neurosci. Biobehav. Rev.* **2002**, *26*, 499.
28. Kornhuber, J.; Schoppmeyer, K.; Riederer, P. *Neurosci. Lett.* **1993**, *163*, 129.
29. Peeters, M.; Romieu, P.; Maurice, T.; Su, T. P.; Maloteaux, J. M.; Hermans, E. *Eur. J. NeuroSci.* **2004**, *19*, 2212.
30. Banister, S. D.; Moussa, I. A.; Jordan, M. J. T.; Coster, M. J.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 145.
31. Banister, S. D.; Moussa, I. A.; Beinat, C.; Reynolds, A. J.; Schiavini, P.; Jorgensen, W. T.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 38.
32. Banister, S. D.; Moussa, I. A.; Jorgensen, W. T.; Chua, S. W.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3622.
33. Liu, X.; Nuwayhid, S.; Christie, M. J.; Kassiou, M.; Werling, L. L. *Eur. J. Pharmacol.* **2001**, *422*, 39.
34. Liu, X.; Banister, S. D.; Christie, M. J.; Banati, R.; Meikle, S.; Coster, M. J.; Kassiou, M. *Eur. J. Pharmacol.* **2007**, *555*, 37.
35. Glennon, R. A. *Mini-Rev. Med. Chem.* **2005**, *5*, 927.
36. Zalikowski, J. A.; Gilbert, K. E.; Borden, W. T. *J. Org. Chem.* **1980**, *45*, 346.