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AN AROMATIC MOIETY IS NOT ESSENTIAL FOR PHARMACOPHORE BINDING TO SIGMA BINDING SITES: SYNTHESIS OF N-ALKYLAZACYCLOHEPTANE DERIVATIVES AS POTENT SIGMA LIGANDS

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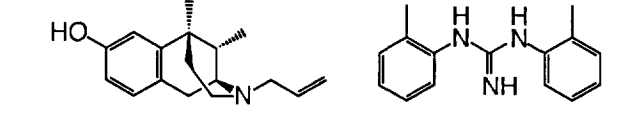
Abstract. Novel 3-(ω-(cycloalkyl)-alkyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octanes that had no aromatic rings were synthesized. Binding studies showed that these compounds were potent sigma ligands. Due to their simple structures without extra functional groups, they are suitable tools with which to identify pharmacophores capable of binding strongly to sigma binding sites. © 1997 Elsevier Science Ltd.

Sigma binding sites have been the focus of intense studies because of their important functions in several biochemical, physiological and behavioral processes.[1,2] Interest in sigma binding sites is largely motivated by the observation that these sites are high affinity binding sites for antipsychotics (e.g. haloperidol) and psychotropic drugs (e.g. (+)-SKF10047).[1,2] The existence of at least two distinct sigma binding subsites, designated as sigma-1 and sigma-2, has recently become evident based on the different binding profiles of structurally diverse ligands.[3]

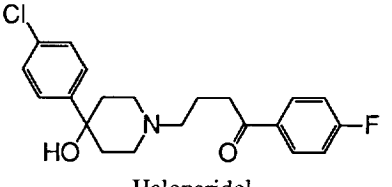
Despite much effort for the development of potent sigma ligands, the structural requirements of sigma ligands are not well understood. Many different classes of compounds exhibit high affinity for sigma binding sites. However, most known sigma ligands have several (at least two) functional groups.[1,2] For instance, (+)-SKF10047, DTG and haloperidol, representative sigma ligands, have aromatic ring(s), functional group(s)

Chart 1

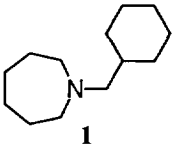


(+)-SKF10047

DTG

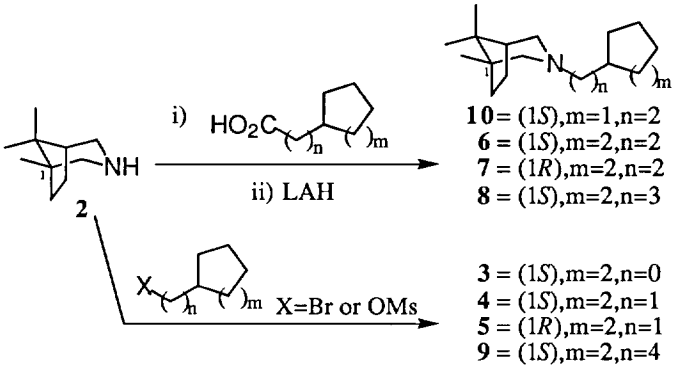


Haloperidol



1

Scheme 1



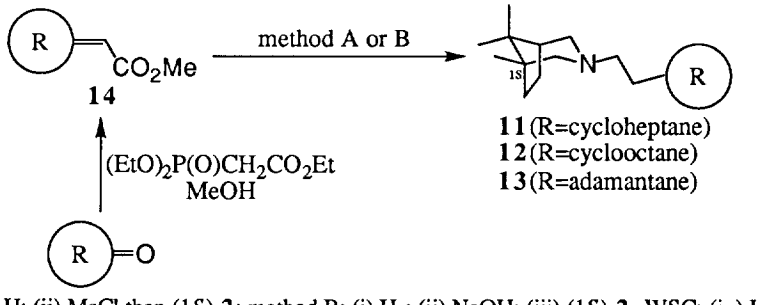
containing nitrogen atoms, and/or hydroxyl groups, respectively (Chart 1). The various functional groups of these molecules have made it difficult to identify of the pharmacophore and essential features of sigma ligand.

There have been a few previous studies of necessary conditions and tolerance limits of general structures that have high affinity for sigma binding sites.[4-6] In these articles, the authors reported various factors important for high affinity: 1) the active compounds may have one nitrogen atom that could be protonated, and 2) these may have two lipophilic parts that were admitted to rather bulky structures. However, there were no simple compounds with only one nitrogen and two rather bulky parts in these studys, and most of the compounds described had aromatic ring(s).

During the course of developing new antipsychotics, we found that amine **1** exhibited the strong affinity toward sigma-2 site (Ki 14nM, Chart 1). Interestingly, **1** has a quite simple structure and no special functional groups (e.g. aromatic rings) except for an amine group. Therefore, **1** is a valuable tool that can be used to research the pharmacophore of sigma binding sites. We report here the synthesis and results of binding studies of a series of novel monoazahydrocarbons based on **1**.

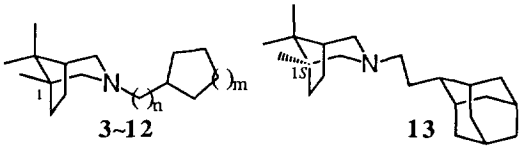
For preparation of bulkier analogues on the azepine part of **1**, we used 1,8,8-trimethyl-3-azabicyclo[3.2.1]octane (camphidine, **2**)[7], based on a 7-membered ring structure, as a starting material. The tertially amines (**6**, **7**, **8** and **10**) were synthesized by LAH reduction from corresponding amides, respectively. The alternative amines (**3**, **4**, **5** and **9**), analogues of **6** with different carbon chains, were easily prepared by standard N-alkylation reactions with appropriate bromides or mesylates (Scheme 1).

Scheme 2



• method A: (i) LAH; (ii) MsCl then (1*S*)-**2**; method B: (i) H_2; (ii) NaOH; (iii) (1*S*)-**2**, WSC; (iv) LAH.

Table 1 .Binding affinities of monoazahydrocarbons for the sigma binding subsites.[a]



3~12 13

compd[b]	configuration[c]	m	n	sigma-2 Ki([^{3}H]-DTG) (nM)[d]	sigma-1 Ki([^{3}H]-Pent) (nM)[d]	sigma-1 / sigma-2
3	*S*	2	0	1.10	3.00	2.73
4	*S*	2	1	3.14	1.33	0.42
5	*R*	2	1	3.54	1.08	0.31
6	*S*	2	2	0.28	2.17	7.75
7	*R*	2	2	0.23	1.35	5.87
8	*S*	2	3	0.56	2.53	4.52
9	*S*	2	4	6.79	1.20	0.18
10	*S*	1	2	0.70	1.67	2.39
11	*S*	3	2	0.25	2.87	11.48
12	*S*	4	2	0.33	2.87	8.70
13	-	-	-	0.77	4.30	5.58
DTG	-	-	-	16.8	27.40	1.63
haloperidol	-	-	-	69.6	0.44	0.006
(+)-SKF10047	-	-	-	14200	157	0.011

[a]Assays were performed by previously reported methods.[8,9] [b]All compounds were characterized by proton NMR and mass spectrometry and gave satisfactory elemental analyses. [c]Configuration of 1-position of camphidine. [d]Binding data are the means of at least two independent determinations.

For the syntheses of bulkier compounds at the cyclohexane part of **6**, we prepared larger cycloalkane analogues, **11** and **12**, and adamantane analogue **13**. Hornor-Emmons reaction of the commercially available cyclic ketones gave esters **14**, which were further converted to **11** via method A and to **12** and **13** by method B, as shown in Scheme 2.

Table 1 shows that expansion of the tetrahydroazepine part of **1** to camphidine (**4**) gave a 4.5-fold improvement in affinity for the sigma-2 site (Ki 3.1nM). Varying the alkyl chain length of **4** between the nitrogen atom and the cyclohexane ring (**3**, **4**, **6**, **8** and **9**) showed that the ethylene chain had the best characteristics; **6** was the most potent sigma-2 ligand in this series (Ki 0.28nM).

Optical isomeric pairs (**4** and **5**, **6** and **7**) had almost the same respective affinities, and variation of the cycloalkane ring size from C5 to C8 and adamantane (**6**, **10**, **11**, **12** and **13**) did not influence the affinity for the sigma-2 site.

It was unexpected that all camphidine derivatives described above had almost the same affinity for sigma-1 site (Ki 1.08-4.30nM), regardless of their differences in bulk and their various affinities for sigma-2 site. This result indicated that the bulk of these compounds and its location relative to the nitrogen atom are not important for sigma-1 binding affinity. Compound **11** was the most sigma-2-selective ligand in this series (sigma-2 / sigma-1 = 11).

Binding studies with our compounds shown in Table 1 indicated that sigma ligands do not need an aromatic ring or other special functional groups without an amine group. Also, sigma pharmacophores can admit to rather bulky structures (e.g. camphidine and adamantane).

In conclusion, we found novel potent sigma ligands that have quite unique structures without extra functional groups (aromatic rings). Using these compounds as starting materials, we are currently engaged in experiments to obtain pharmacophores of sigma subsites.

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