1-Phenyl-3-azabicyclo[3.1.0]hexane derivatives as new ligands for sigma receptors

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Dedicated to Professor Vincenzo Tortorella in the occasion of his "Fuori Ruolo" status
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Abstract

A series of 1-phenyl-3-azabicyclo[3.1.0]hexanes were synthesized as more conformationally restricted prototypical σ ligands 3-phenylpiperidines with the aim to developing new σ ligands. Compared with 3-phenylpiperidines reported by Largent *et al*., binding data showed that conformational restriction was not detrimental for σ receptor affinity. Specifically, except for secondary amine **4**, all racemic 1-phenyl-3-azabicyclo[3.1.0]hexane derivatives (**12**-**19**) showed moderate to high affinity for both σ_1 and σ_2 receptors. Dextrorotatory isomers with the same configuration of 3-phenylpiperidines to C-1 carbon linked to the phenyl ring showed a better affinity and selectivity for σ_1 receptors compared to the respective levorotatory isomers. Compounds (+)-**14** and (+)-**15** displayed very high affinity for σ_1 (Ki = 0.9 and 2.3 nM respectively) but low selectivity for receptor subtypes. Compound (+)-**18** with *N*-phenethyl substituent embodies the highest selectivity for σ_1 receptors.

Keywords: 1-Phenyl-3-azabicyclo[3.1.0]hexane, sigma receptor, 3-phenylpiperidines

Introduction

Sigma (σ) receptors are typical binding sites interacting with several psychoactive drugs including haloperidol, benzomorphans and phencyclidine.[1-5] The σ_1 subtype exhibits high affinity for (+)-benzomorphans such as (+)-pentazocine and (+)-N-allylnormetazocine (SKF-10,047) and a reduced affinity for the respective (–)-enantiomers.

Based on animal model studies, this subtype seems to be involved in cocaine induced behavioral changes, in opiate induced analgesia, steroid-induced mental disturbances and alterations in immune functions.[6-8]

The σ_2 subtype showed low affinity for (+)-pentazocine and (+)-SKF-10,047 and (–)-isomers did not differentiate between the two sites.

Several pharmacological studies showed that σ_2 receptors are expressed in high concentration in tumor cell lines and that they are involved in proliferation and cell viability.[9] Thus, selective σ_1 and σ_2 ligands with agonist or antagonist properties might be potential drugs for clinical treatment of memory and learning disorders, psychoses, cocaine abuse, dyskinesia induced by classical antipsychotic therapy and cancer.

Recently, we have focused on the synthesis of substituted 1-phenyl-2-cyclopropylmethylamines as tools capable to providing new selective σ_1 and σ_2 ligands.[10-11] Taking into account these data and the synthetic opportunity to extend conformational restriction to prototypical σligands 3-phenylpiperidines[12] (Figure 1-2) we synthesized a series of 1-phenyl-3-azabicyclo[3.1.0]hexanes as possible new ligands for σ_1 and σ_2 receptors. Using a different synthetic approach, 1-phenyl-3-azabicyclo[3.1.0]hexanes were previously reported by Fanshawe et al. as non-narcotic analgesic compounds and as agents for treating depression and chemical dependencies.[13-15] Although some of these effects might be related to a possible interaction with σ receptors, to date no affinity binding data have been reported about these compounds.

In these studies we report our strategy to synthesize 1-phenyl-3-azabicyclo[3.1.0]hexane derivatives and structure affinity relationships for σ_1 and σ_2 receptors.

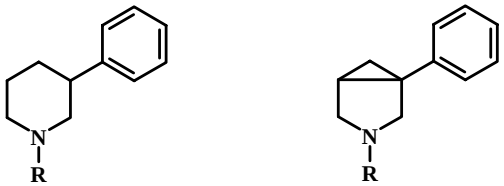


Figure 1. 3-Phenylpiperidines and conformational restricted 1-phenyl-3-azabicyclo[3.1.0]-hexanes.

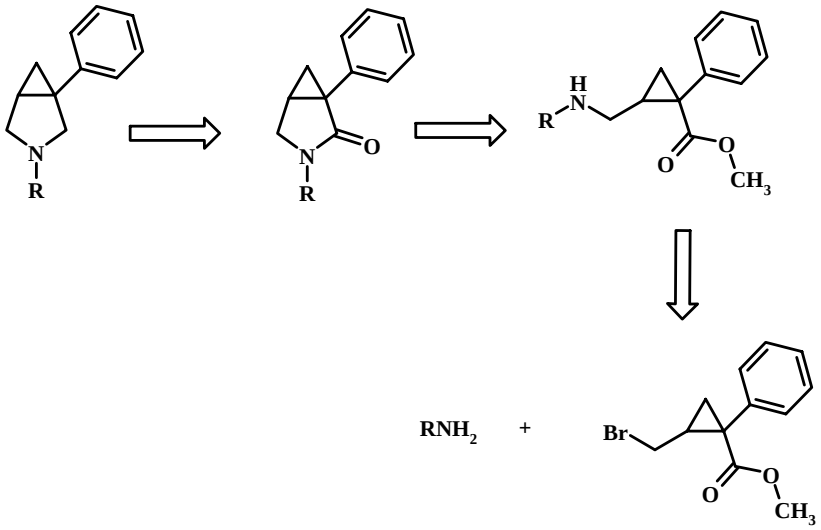


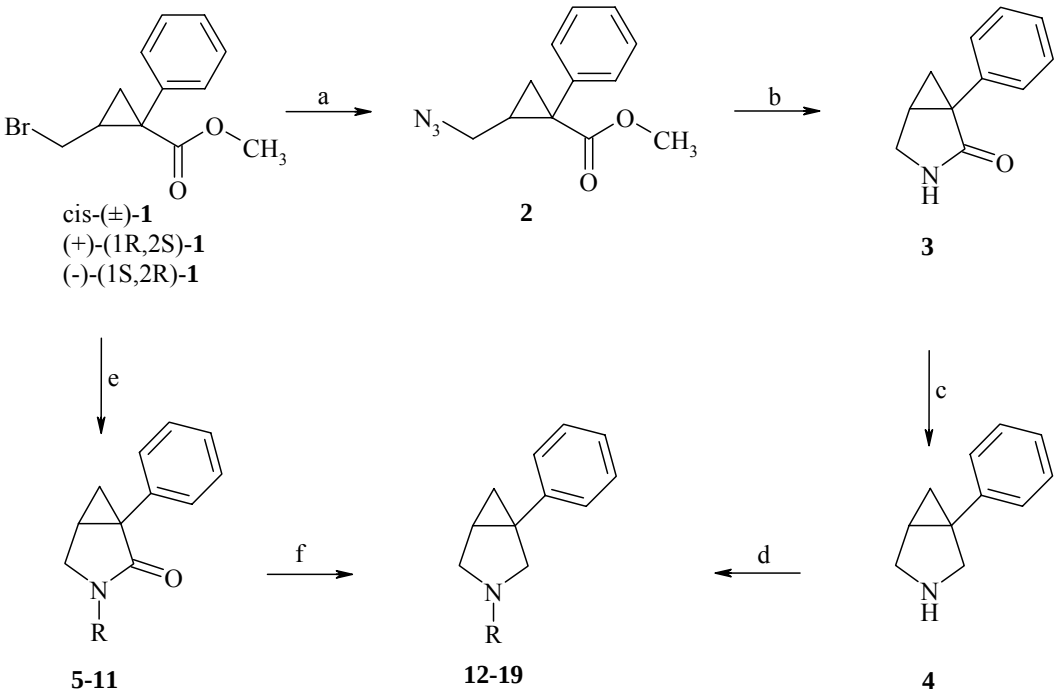
Figure 2. Retrosynthetic analysis for synthesis of 1-phenyl-3-azabicyclo[3.1.0]hexanes**.**

Results and Discussion

Chemistry

Racemic methyl 2-(bromomethyl)-1-phenylcyclopropanecarboxylate (±)-**1** and its enantiomers (+)- and (–)-**1** were synthesized according to a previously reported procedure.[11] Treatment of **1** with NaN_3 in DMF gave azido intermediate **2** (Scheme 1). Subsequently, reduction of **2** with sodium hydrogentelluride (NaTeH)[16] in ethanol and internal cyclization provided a good yield of lactam **3**. The NaTeH was readily prepared from tellurium and $NaBH_4$ as reported by Barton and McCombie.[17] Treatment of **3** with diborane in anhydrous THF gave 1-phenyl-3-azabicyclo[3.1.0]hexane **4**.

The final compound **12** was prepared by alkylation of **4** with commercially available 1-bromo-3-methylbut-2-ene. Intermediates **5-11** were synthesized by treatment of commercially available amines with methyl bromoester **1**. Compounds **13-20** were obtained by reduction with diborane in anhydrous THF of the respective lactams (**5-11**). All structures of synthesized compounds were fully consistent with ^{1}H-NMR and ^{13}C-NMR spectral data.



cis-(±)-**1**
(+)-(1R,2S)-**1**
(-)-(1S,2R)-**1**

2

3

5-11

12-19

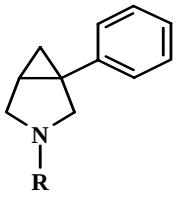
4

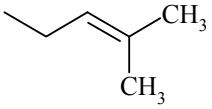
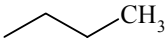
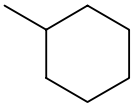
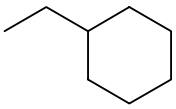
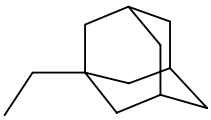
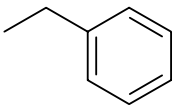
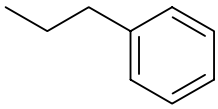
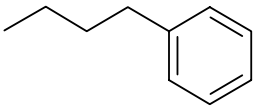
Scheme 1. a: NaN_3, DMF, 30 °C, 4 h; b: Te/$NaBH_4$, C_2H_5OH; c: B_2H_6/THF, reflux, 12 h; d: $BrCH_2CH{=}C(CH_3)_2$/$NaHCO_3$/DMF, 80° C, 12 h; e: RNH_2/CH_3OH, reflux, 6 h; f: B_2H_6/THF, reflux, 12 h.

The σ receptor affinities of racemic 1-phenyl-3-azabicyclo[3.1.0]hexanes **4** and **12-19** are reported in Table 1. These data show that secondary amine **4** did not interact significantly with σ_1 and σ_2 receptors (Ki > 10,000). However, nitrogen substitution with propyl or 2-methyl-2-butene led to compounds (**13** and **12** respectively) able to interact with σ receptors. Specifically,

compound **12** showed a good affinity with a slight preference for σ_1 receptor subtypes. *N*-cyclohexyl substitution gave compound **14** with the highest affinity in the racemic series.

Table 1. σ_1 and σ_2 binding affinities [*K*i ± SEM (nM)]



Compound	R	[^{3}H](+)Pentaz σ_1	[^{3}H]DTG σ_2
(±)-4	—H	>10,000	>10,000
(±)-12		12 ± 1	24 ± 3
(±)-13		84 ± 7	336 ± 23
(±)-14		2.1 ± 0.2	4.3 ± 0.3
(±)-15		12.4 ± 0.8	141 ± 4
(±)-16		369 ± 31	461 ± 36
(±)-17		261 ± 14	514 ± 27
(±)-18		88.3 ± 6	910 ± 35
(±)-19		191 ± 14	103 ± 12

These results were similar to the *N*-substitution on 3-phenylpiperidine, octahydrobenzo[*f*]quinoline and *cis*-benzomorphan derivatives[12, 18] which revealed an increase in binding affinity when nitrogen of the secondary amines was substituted with bulk alkyl substituents.

Compared to **14**, introduction of a methylene spacer between the nitrogen and cyclohexyl residue (**15**) decreased by six time the binding affinity for σ_1 receptors and to a greater extent for σ_2. The substitution of cyclohexane of **15** with more bulk adamantane (**16**) induced a strong reduction of σ_1 and σ_2 receptor affinity.

The benzyl derivative **17** revealed a lower σ binding affinity compared with the respective cycloalkyl **15**. Moreover, an increase of the methylenic chain in phenylethyl and phenylpropyl derivatives (**18** and **19** respectively) induced different effects on affinity and selectivity. In particular, **18** showed an improved affinity and selectivity for σ_1 subtypes, whereas compound **19** displayed a slight preference for σ_2 receptors.

Considering the better binding profile of racemic compounds **14**, **15**, **18** and **19** we also evaluated the affinity of the respective enantiomers (Table 2). The binding affinity data showed that (+)-(1*R*,5*S*)-isomers have higher affinity for the σ_1 receptor compared with (–)-(1*S*,5*R*)-isomers. Specifically, (+)-(1*R*,5*S*)-**14** displayed a slight improvement of affinity and selectivity for σ_1 receptors compared with the respective (–)-(1*S*,5*R*)-isomer which showed a little preference for σ_2 subtypes.

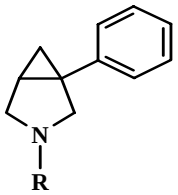
Enantiomers (+)-(1*R*,5*S*)- and (–)-(1*S*,5*R*)-**15** increased their binding affinity for both σ_1 and σ_2 subtypes and thus with no substantial increase of selectivity with respect to the racemic mixture.

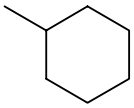
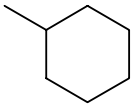
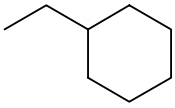
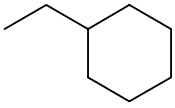
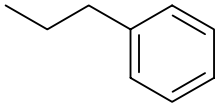
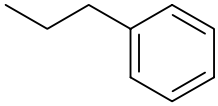
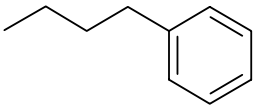
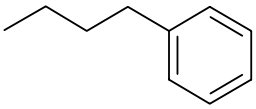
Conversely to these results, an improved selectivity for σ_1 receptors was obtained with *N*-phenethyl derivative (+)-(1*R*,5*S*)-**18** which had the highest selectivity of the series. The respective isomer (–)-(1*S*,5*R*)-**18** showing the same decrease of affinity for both σ_1 and σ_2 receptors did not provide significant results compared with racemic mixture.

The preference of (±)-**19** for σ_2 receptors was not confirmed in the respective enantiomers. In particular (+)-(1*R*,5*S*)- and (–)-(1*S*,5*R*)-**19** increased both σ_1 and σ_2 receptor affinity with a reversed selectivity compared to (±)-**19**. Moreover, the evaluation of binding affinity of *N*-phenethyl derivative (+)-(1*R*,5*S*)- and (–)-(1*S*,5*R*)-**18** and phenylpropyl (+)-(1*R*,5*S*)- and (–)-(1*S*,5*R*)-**19**, provided evidence that the increase of methylenic chain spacer was more critical for σ_2 with respect to σ_1 receptors.

In conclusion, in these paper we present novel 1-phenyl-3-azabicyclo[3.1.0]hexane derivatives capable of interacting with moderate to high affinity with sigma receptors. Conformational restriction of phenyl-3-azabicyclo[3.1.0]hexane derivatives compared with 3-phenylpiperidine did not produce compounds with high selectivity for σ receptor subtypes in this series but like (+)-and (–)-3-PPP (3-phenylpropylpiperidine) only a slight preference for σ_1 receptors. However, the very high affinity of compounds (+)-(1*R*,5*S*)-**14** and (+)-(1*S*,5*R*)-**15** gave a good starting point to design new potential σ_1 and σ_2 selective ligands.

Table 2. σ_1 and σ_2 binding affinities [*K*i ± SEM (nM)]



Compound	R	[^{3}H](+)Pentaz σ_1	[^{3}H]DTG σ_2
(+)-(1*R*,5*S*)-14		0.91 ± 0.2	5.8 ± 1
(–)-(1*S*,5*R*)-14		14.6 ± 1.3	9.6 ± 0.9
(+)-(1*R*,5*S*)-15		2.3 ± 0.4	33.8 ± 1.2
(–)-(1*S*,5*R*)-15		9.3 ± 1.7	46.6 ± 7
(+)-(1*R*,5*S*)-18		55 ± 11	1135 ± 75
(–)-(1*S*,5*R*)-18		164 ± 8	1765 ± 94
(+)-(1*R*,5*S*)19		16 ± 0.8	66 ± 16
(–)-(1*S*,5*R*)-19		48 ± 1.7	63 ± 4

Experimental Section

General Procedures. Reagents for organic synthesis were purchased from Aldrich & Sigma Chemicals Co. NMR spectra were recorded on a Varian Inova 200 spectrometer with TMS as

an internal standard. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{264} aluminum sheets (Merck); with visualization under UV light and in a iodine chamber. Melting points were determined in open capillary tubes on a Büchi melting point apparatus and are uncorrected. Infrared spectra (IR) were obtained using a 1600 FT-IR Perkin-Elmer spectrophotometer. All optical rotations were determined in CH_3OH solution (C = 1) employing an Optical Activity Ltd. automatic polarimeter type AA-10. Elemental analyses (C, H, N) were done on a Carlo Erba Model 1106 elemental analyzer.

Methyl c-2-(azidomethyl)-1-phenyl-r-1-cyclopropanecarboxylate (2). To a solution of methyl 2-(bromomethyl)-1-phenylcyclopropanecarboxylate (±)-**1** (200 mg, 0.74 mmol) in DMF NaN_3 at 0 °C was added (57.9 mg, 0.89 mmol) and the whole was stirred for 4 h. Water was added and the resulting mixture was evaporated under reduced pressure. The residue was partitioned between brine and AcOEt and the organic phase was dried (Na_2SO_4) and evaporated to give, as an oil, 171 mg (theoretical yield) of azide **2**.

The handling of NaN_3 and derivatives might be dangerous. For this reason, the reaction was repeated several time on a reduced scale in order to reduce the risk of explosion.

IR (KBr): 1718 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.45 (dd, 1H *J* = 4.6, 9.0 Hz), 1.72 (dd, 1H, *J* = 4.6, 7.2 Hz), 1.83-1.93 (m, 1H), 3.62 (dd, 1H, *J* = 10.0, 13.0 Hz), 3.65 (s, 3H), 3.68 (dd, 1H, *J* = 4.4, 13.0 Hz), 7.25-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 21.85, 33.57, 36.36, 51.95, 52.71, 125.30, 127.32, 128.65, 138.71, 172.61.

(±)-1-Phenyl-3-azabicyclo[3.1.0]hexan-2-one (3). A mixture of powdered tellurium (2.41 g, 18.58 mmol), $NaBH_4$ (1.69 g, 44.59 mmol) and ethanol (80 ml) was heated under reflux in a nitrogen atmosphere until the tellurium disappeared. After cooling to room temperature, a solution of azide **2** (3.42 g, 14.86 mmol) in ether (75 ml) was added to the dark red solution of sodium hydrogen telluride. The color turned black and after nitrogen evolution and precipitation of metallic tellurium, the mixture was left open to air with stirring for 12 h. The mixture was filtered through celite, heated to 60 °C and evaporated under reduced pressure to provide 1.7 g of lactam **3**, as a white solid.

(Yield 65.7%). m. p. 70-72 °C; IR (KBr): 1668 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.06 (dd, 1H *J* = 4.0, 4.6 Hz), 1.45 (dd, 1H, *J* = 4.6, 8.0 Hz), 1.93-2.20 (m, 1H), 3.25 (d, 1H, *J* = 10.4 Hz), 3.50 (dd, 1H, *J* = 5.6, 10.4 Hz), 7.15-7.42 (m, 5H), 7.64 (s, broad, 1H). ^{13}C NMR ($CDCl_3$) δ: 18.49, 22.15, 33.20, 42.75, 126.44, 127.76, 128.22, 135.64, 178.27.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.00; H, 6.45; N, 8.10.

(±)-1-Phenyl-3-azabicyclo[3.1.0]hexane (4). To a solution (1 M in THF) of 40 ml of diborane cooled to 0 °C and under nitrogen atmosphere, a solution of lactam **3** (1.7 g, 9.81 mmol) in anhydrous THF (5ml) was slowly added. The mixture was heated to reflux for 8 h and subsequently permitted to cool to room temperature. Twelve ml of a 6 M hydrochloric acid solution was slowly added through a dropping funnel. THF was removed by distillation at

atmospheric pressure and the mixture was basified with NaOH 2 M. The latter was extracted three times with a total of 100 ml of $CHCl_3$. The organic extract was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude base **4** which were purified on silica gel by flash chromatography using $CHCl_3$/cyclohexane/EtOH (50:48:2) as eluent. The purified compound **4** (1.4 g, yield 90%) was dissolved in ether and treated with an ether solution of oxalic acid to give the oxalate salts as a white solid. The analytically pure samples were obtained by recrystallization (EtOH/ether).

m. p. 180-182 °C; ^{1}H NMR (DMSO-d_6) δ: 1.08 (dd, 1H J = 5.4, 6.0 Hz), 1.55 (dd, 1H, J = 5.0, 5.4 Hz), 2.08-2.20 (m, 1H), 3.30-3.54 (m, 3H), 3.68 (d, 1H, 11.2 Hz), 7.15-7.42 (m, 5H), 8.00 (s, broad, 3H). ^{13}C NMR (DMSO-d_6) δ: 16.17, 23.85, 30.94, 47.30, 49.82, 127.04, 127.11, 129.00, 140.06, 165.45.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.87; H, 8.34; N, 8.85.

(±)-1-Phenyl-3-propyl-3-azabicyclo[3.1.0]hexan-2-one (5). A mixture of 2-(bromomethyl)-1-phenylcyclopropanecarboxylate (±)-**1** (400 mg, 1.48 mmol), 2 ml of propylamine (1.44 g, 24.3 mmol) and 2 ml of toluene was heated at 80 °C in a sealed reaction vessel for 6 h. After the recovery of the reaction mixture, the solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ and washed with a solution of 2 N HCl and subsequently dried over anhydrous Na_2SO_4. In vacuo evaporation of chloroform solution gave a crude product that was purified by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent.

(Yield 85 %); m. p. 73-75 °C; IR (KBr): 1671 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3H, J = 7.4), 1.45 (dd, 1H J = 6.0, 7.0 Hz), 1.38-1.70 (m, 3H), 2.06-2.19 (m, 1H), 3.25 (t, 2H, J = 7.8), 3.40 (d, 1H, J = 10.4 Hz), 4.02 (dd, 1H, J = 5.6, 10.2 Hz), 7.22-7.47 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 11.10,16.80, 19.06, 23.68, 32.27, 50.38, 53.27, 125.42, 126.47, 128.77, 137.75, 174.27.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.30; H, 8.00; N, 6.53.

The compounds **6-11** were prepared using the above procedure.

(±)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (6). (Yield 80 %); M. p. 90-92 °C; IR (KBr): 1672 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.06-1.80 (m, 10H) 2.07-2.12 (m, 3H), 3.03-3.23 (m, 1H), 3.93 (dd, 1H, J = 6.1, 10.6 Hz), 4.09 (d, 1H, J = 10.6 Hz), 7.18-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.57, 23.16, 23.30, 24.32, 27.91, 28.78, 52.63, 60.31, 124.38, 126.33, 128.78, 138.24, 177.10. Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.88; H, 8.48; N, 5.47.

(+)-(1R,5S)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (6). (Yield 75 %); M. p. 90-92 °C; $[\alpha]_D^{20}$ + 56.4°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.90; H, 8.20; N, 5.43.

(–)-(1S,5R)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (6). (Yield 78 %); M. p. 90-92 °C; $[\alpha]_D^{20}$ – 58.5°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.00; H, 8.45; N, 5.50.

(±)-3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7). (Yield 87 %); M. p. 94-96 °C; IR (KBr): 1684 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.80-1.38 (m, 7H),1.48 (dd, 1H, J = 4.6, 7.8 Hz), 1.57-1.85 (m, 5H), 2.13 (m, 1H), 3.01(dd, 1H, J = 6.8, 16.4 Hz), 3.13 (dd, 1H, J = 7.2,

16.4 Hz), 3.35 (d, 1H, *J* = 10.4 Hz), 3.61 (dd, 1H, *J* = 5.6, 10.3 Hz), 7.18-7.48 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 23.44, 24.33, 24.85, 27.31, 29.91, 30.42, 37.21, 53.32, 54.01, 123.15, 126.11, 129.32, 136.42, 180.22. Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.00; H, 8.50; N, 5.22.

(+)-(1R,5S)-3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7). (Yield 85 %); M. p. 94-96 °C; $[\alpha]_D^{20}$ + 65.2°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.55; H, 8.79; N, 5.26.

(–)-(1S,5R)3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (7). (Yield 90 %); M. p. 94-96 °C; $[\alpha]_D^{20}$ – 63.3°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.15; H, 8.49; N, 5.24.

(±)-3-(1-Adamantylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (8). (Yield 51 %); M. p. 138-140 °C; IR (KBr): 1676 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.03 (dd, 1H, *J* = 5.8, 7.4 Hz) 1.45-1.95 (m, 12H),1.97-2.05 (m, 4H), 2.10 (m, 1H), 2.80 (s, 2H), 3,51 (d, 1H, *J* = , 10.3 Hz) 3.73 (dd, 1H, *J* = 5.7, 10.3 Hz), 7.15-7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.99, 23.77, 28.41, 35.33, 37.01, 39.42, 42.21, 53.95, 56.97, 122.45, 126.71, 128.42, 136.77, 182.45.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.24; H, 8.40; N, 4.30.

(±)-3-Benzyl-1-phenyl-3-azabicyclo[3.1.0]hexan-2-one (9). (Yield 92 %); M. p. 86-88 °C; IR (KBr): 1674 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.00 (dd, 1H *J* = 5.4, 8.0 Hz), 1.48 (dd, 1H *J* = 4.8, 5.4, Hz) 1.98-2.18 (m, 1H), 3.30 (d, 1H, *J* = 10.4 Hz), 3.98 (dd, 1H, *J* = 5.9, 10.2 Hz), 4.37 (s, 2H), 7.12-7.60 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 22.55, 23.98, 34.73, 51.63, 53.48, 122.53, 126.12, 127.47, 127.53, 128.32, 128.95, 136.21, 137.45, 181.22. Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.04; H, 6.48; N, 5.30.

(±)-1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexan-2-one (10). (Yield 90 %); M. p. 91-93 °C; IR (KBr): 1664 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.20 (dd, 1H *J* = 4.8, 7.5 Hz), 1.48 (dd, 1H *J* = 7.5, 7.9, Hz) 2.00-2.20 (m, 1H), 2.88 (t, 2H, *J* = 6.8), 3.30 (t, 2H, *J* = 6.8), 3.49 (d, 1H, *J* = 10.2 Hz), 4.20 (dd, 1H, *J* = 6.0, 10.3 Hz), 7.12-7.60 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 23.71, 24.18, 34.13, 37.74, 50.22, 54.33, 122.11, 126.42, 126.78, 128.90, 128.94, 129.88, 136.41, 138.35, 182.02. Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.00; H, 6.88; N, 5.01.

(+)-(1R,5S)-1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexan-2-one (10). (Yield 87 %); M. p. 91-93 °C; $[\alpha]_D^{20}$ + 59.4°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.32; H, 6.98; N, 5.03.

(–)-(1S,5R)1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexan-2-one (10). Yield 88 %); M. p. 91-93 °C; $[\alpha]_D^{20}$ – 58.3 IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.15; H, 7.00; N, 5.00.

(±)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one (11). Yield 90 %); M. p. 100-102 °C; IR (KBr): 1683 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.35 (dd, 1H *J* = 4.5, 7.3 Hz), 1.53 (dd, 1H *J* = 7.3, 7.9, Hz) 1.80-2.10 (m, 3H), 2.70 (t, 2H, *J* = 6.9), 3.35 (t, 2H, *J* = 7.2), 3.51 (d, 1H, *J* = 10.6 Hz), 4.16 (dd, 1H, *J* = 5.8, 10.4 Hz), 7.05-7.45 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 2.32,

23.90, 27.72, 33.11, 36.24, 47.12, 51.11, 121.31, 126.14, 126.44, 128.11, 128.45, 129.96, 138.88, 139.90, 181.27. nal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.37; H, 7.28; N, 4.85.

(+)-(1R,5S)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one (11). (Yield 87 %); M. p. 100-102 °C; $[\alpha]_D^{20}$ + 57.7 IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. nal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.34; H, 7.20; N, 4.79.

(–)-(1S,5R)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexan-2-one (11). (Yield 85 %); M. p. 100-102 °C; $[\alpha]_D^{20}$ – 56.4°; IR, ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.48; H, 7.35; N, 4.80.

(±)-3-(3-Methylbut-2-enyl)-1-phenyl-3-azabicyclo[3.1.0]hexane (12). A mixture of (±)-1-phenyl-3-azabicyclo[3.1.0]hexane (**4**) (184 mg, 0.76 mmol), 4-bromo-2-methyl-2-butene (0.132 ml, 1.14 mmol), and $NaHCO_3$ (128 mg, 1.52 mmol) in dry DMF (15 ml) was stirred and heated to 80 °C for 6 h. The solvent was then removed under reduced pressure and the residue was extracted with $CHCl_3$ and water. The organic layers were dried over anhydrous Na_2SO_4 and after evaporation of the solvent the crude product was purified by flash column chromatography using $CHCl_3$/cyclohexane/EtOH (5:4:1) as eluent. The free base (103 mg, yield 60%) was dissolved in diethyl ether and treated with a solution of oxalic acid dihydrate in diethyl ether to give the oxalate salt as a white solid. The analytically pure sample was obtained by crystallization from methanol/diethyl ether.

M. p. 175-178 °C; ^{1}H NMR (DMSO-d_6) δ: 1.04 (dd, 1H J = 4.9, 8.0 Hz), 1.40 (dd, 1H, J = 3.8, 4.9 Hz), 1.70 (s, 3H), 1.75 (s, 3H) 2.09-2.18 (m, 1H), 3.20-3.90 (m, 6H), 4.90 (s, broad, 2H), 5.29 (t, 1H, J = 7.4), 7.12-7.42 (m, 5H). ^{13}C NMR (DMSO-d_6) δ: 16.25, 18.03, 23.24, 25.67, 30.06, 51.48, 54.10, 56.71, 115.42, 126.41, 126.49, 128.43, 139.82, 140.37, 164.38.

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.03; H, 7.55; N, 4.45.

Compounds **13-19** were synthesized using the same procedure reported for compound **4**.

(±)-1-Phenyl-3-propyl-3-azabicyclo[3.1.0]hexane (13). (Yield 95 %); M. p. 124-26 °C; ^{1}H NMR (DMSO-d_6) δ: 0.90 (t, 3H, J = 7.6), 1.04 (dd, 1H J = 8.1, 5.7 Hz), 1.42 (dd, 1H J = 4.8, 5.7 Hz), 1.55-1.70 (m, 2H), 2.00-2.20 (m, 1H), 3.03 (t, 2H, J = 8.6), 3.36 (dd, 1H, J = 4.0, 11.0 Hz), 3.45 (d, 1H, J = 10.8 Hz), 3.63 (d, 1H, J = 10.8 Hz), 3.91 (d, 1H, J = 10.8 Hz), 6.18 (s broad, 2H) 7.18-7.47 (m, 5H). ^{13}C NMR (DMSO-d_6) δ: 11.08, 16.52, 18.98, 30.18, 54.95, 56.08, 57.38, 126.42, 126.48, 128.43, 139.83, 164.49. Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.88; H, 7.45; N, 4.79.

(±)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexane (14). (Yield 93 %); M. p. 124-26 °C; ^{1}H NMR (DMSO-d_6) δ: 1.03-1.90 (m, 10H) 1.97-2.14 (m, 3H), 3.00-3.25 (m, 1H), 3.43 (m, 3H), 4.01 (d, 1H, J = 10.8 Hz), 5.16 (s broad, 4H), 7.20-7.42 (m, 5H). ^{13}C NMR (DMSO-d_6) δ: 22.99, 24.25, 24.59, 28.50, 28.55, 29.81, 53.30, 55.98, 64.46, 126.49, 126.52, 128.41, 139.64, 164.44.

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.56; H, 7.63; N, 4.20.

(+)-(1R,5S)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexane (14). (Yield 95 %); M. p. 123-25°C; $[\alpha]_D^{20}$ + 58.2°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.55; H, 7.58; N, 4.20.

(–)-(1S,5R)-3-Cyclohexyl-1-phenyl-3-azabicyclo[3.1.0]hexane (14). (Yield 97 %); M. p. 124-26°C; $[\alpha]_D^{20}$ – 60.4°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.58; H, 7.65; N, 4.25.

(±)-3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexane (15). (Yield 58 %); M. p. 140-43 °C; ^{1}H NMR (DMSO-d_6) δ: 0.78-1.38 (m, 7H), 1.49 (dd, 1H, *J* = 5.0, 5.4 Hz), 1.55-1.89 (m, 5H), 2.09 (m, 1H), 2.91 (d, 2H, *J* = 6.0 Hz), 3.21-3.43 (m, 2H), 3.60 (d, 1H, *J* = 10.4 Hz), 3.88 (d, 1H, *J* = 10.4 Hz), 5.87 (s broad, 4H), 7.18-7.48 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.90, 23.44, 25,16, 25,20, 25.68, 30.23, 30.51, 30.59, 34.52, 55.71, 58.07, 61.07, 126.40, 126.41, 128.38, 140.16, 164.10. Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.48; H, 7.66; N, 4.04.

(+)-(1R,5S)-3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexane (15). (Yield 53 %); M. p. 140-43 °C; $[\alpha]_D^{20}$ + 67.3°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.45; H, 7.66; N, 4.02.

(–)-(1S,5R)3-(Cyclohexylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexane (15). (Yield 55 %); M. p. 140-43 °C; $[\alpha]_D^{20}$ – 64.4°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.43; H, 7.55; N, 4.03.

(±)-3-(1-Adamantylmethyl)-1-phenyl-3-azabicyclo[3.1.0]hexane (16). (Yield 83 %); M. p. 240-42 °C; ^{1}H NMR (DMSO-d_6) δ: 1.01 (dd, 1H, *J* = 5.0, 7.6 Hz) 1.50-1.90 (m, 12H), 1.95-2.25 (m, 5H), 3,00 (d, 2H, *J* = , 4.6 Hz) 3.42-3.70 (m, 2H), 3.85 (dd, 1H, *J* = 4.6, 10.0 Hz), 4.20 (dd, 1H, *J* = 4.8, 10.0 Hz), 7.10-7.48 (m, 5H), 9.7 (s broad, 1H). ^{13}C NMR (DMSO-d_6) δ: 16.40, 23.21, 27.50, 30.61, 33.02, 35.85, 58.43, 60.60, 68.22, 126.64, 126.66, 128.44, 139.45. Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.30; H, 7.58; N, 3.50.

(±)-3-Benzyl-1-phenyl-3-azabicyclo[3.1.0]hexane (17). (Yield 93 %); M. p. 169-72 °C; ^{1}H NMR (DMSO-d_6) δ: 0.95 (dd, 1H *J* = 5.2, 8.2 Hz), 1.45 (t, 1H *J* = 5.0, Hz) 1.95-2.15 (m, 1H), 3.23 (dd, 1H, *J* = 3.8, 7.2 Hz), 3.25 (m, 2H), 3.58 (d, 1H, *J* = 10.0 Hz) 4.13 (s, 2H), 4.58 (s broad, 2H) 7.15-7.58 (m, 10H). ^{13}C NMR (DMSO-d_6) δ: 16.93,23.61, 30.21, 54.69, 57.42, 58.00, 126.30, 128.38, 128.56, 129.89, 134.18, 140.57, 163.47. Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.70; H, 6.28; N, 4.15.

(±)-1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexane (18). (Yield 68 %); M. p. 215-18 °C; ^{1}H NMR (DMSO-d_6) δ: 1.05 (dd, 1H *J* = 5.2, 8.0 Hz), 1.42 (dd, 1H *J* = 4.9, 5.2, Hz) 2.05-2.23 (m, 1H), 2.94 (dd, 2H, *J* = 5.2, 10.6), 3.27 (t, 2H, *J* = 9.0), 3.10-3.50 (m, 2H), 3.62 (d, 1H, *J* = 10.8 Hz), 3.90 (d, 1H, *J* = 10.6 Hz), 4.49 (s broad, 2H), 7.15-7.50 (m, 10H). ^{13}C NMR (DMSO-d_6) δ: 16.48, 23.26, 30.01, 31.89, 55.06, 55.52, 57.50, 126.46, 126.60, 126.65, 128.43, 128.57, 128.68, 137.76, 139.96, 164.30. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.07; H, 6.58; N, 3.93.

(+)-(1R,5S)-1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexane (18). (Yield 48 %); M. p. 215-18 °C; $[\alpha]_D^{20}$ + 60.4°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.12; H, 6.51; N, 3.91.
(–)-(1S,5R)1-Phenyl-3-(2-phenylethyl)-3-azabicyclo[3.1.0]hexane (18). (Yield 54 %); M. p. 215-18°C; $[\alpha]_D^{20}$ – 59.2°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.99; H, 6.48; N, 3.90.
(±)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane (19). (Yield 88 %); M. p. 159-62 °C; ^{1}H NMR (DMSO-d_6) δ: 1.09 (dd, 1H *J* = 5.2, 8.2 Hz), 1.40 (dd, 1H *J* = 4.9, 5.2, Hz) 1.80-2.03 (m, 2H), 2.04-2.12 (m, 1H) 2.59 (t, 2H, *J* = 7.4), 3.08 (t, 2H, *J* = 7.8), 3.36 (dd, 1H, *J* = 3.2, 10.4 Hz), 3.40 (d, 1H, *J* = 10.6 Hz), 3.60 (d, 1H, *J* = 10.8 Hz), 3.90 (d, 1H, *J* = 10.4 Hz), 5.25 (s broad, 2H) 7.09-7.48 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 16.45, 23.23, 27.16, 30.0, 32.18, 54.03, 55.0, 57.40, 126.06, 126.41, 126.44, 127.67, 128.28, 139.83, 140.73, 164.22. Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.00; H, 6.97; N, 3.85.
(+)-(1R,5S)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane (19). (Yield 90 %); M. p. 159-62 °C; $[\alpha]_D^{20}$ + 60.9°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.13; H, 6.98; N, 3.85.
(–)-(1S,5R)-1-Phenyl-3-(3-phenylpropyl)-3-azabicyclo[3.1.0]hexane (19). (Yield 90 %); M. p. 100-102 °C; $[\alpha]_D^{20}$ – 59.5°; ^{1}H NMR and ^{13}C NMR are identical to those of the racemate. Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.10; H, 6.95; N, 3.83.

Radiology and binding assays

σ_1-Site binding assays were carried out on guinea pig brain membranes as previously reported. [19] Briefly, each tube containing 500 μg of membrane protein was incubated for 150 min at 37 °C with [^{3}H]-(+)-pentazocine (3 nM) in 50 mM Tris-HCl pH 7.4. Non-specific binding was determined using 10 μM haloperidol. The final volume of the assay samples was 1.0 mL. After incubation the samples were filter through a Schleicher & Schnell GF 6 glass fiber filter which had been pre-soaked for 1 h in a 0.5% poly(ethylenimine) solution. Filters were washed twice with 4 ml of ice-cold buffer before transfer to scintillation vials.

σ_2-Site binding assays were carried out on guinea pig brain membranes, prepared as previously described by Mach *et al.* [20]. The membranes were incubated with [^{3}H]DTG [1,3-di-(2-tolyl)-guanidine] (3 nM) in the presence of 400 nM (+)-SKF10,047 (to block binding to σ_1 sites). The final volume of the assay sample was 0.5 mL. Incubations proceeded for 2 h at room temperature in 50 mM Tris-HCl, pH 8.0. Non-specific binding was evaluated in the presence of 5 μM DTG. Each assay was terminated by the addition of ice-cold 10 mM Tris-HCl pH 8.0, followed by filtration through a poly(ethylenimine) (0.5% w/v) treated GF 6 glass fiber filter which were washed twice with 4 ml of ice-cold buffer before transfer to scintillation vials. The Ki values were calculated using the EBDA/LIGAND program [21] purchased from Elsevier/Biosoft.

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