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Il Farmaco 57 (2002) 979–984

IL FARMACO

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Synthesis and binding affinities of 5-(3-pyridinyl)- and 5-(3-quinolinyl)-4-azahomoadamantanes to α7 nicotinic acetylcholine receptors

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Received 22 February 2002; accepted 28 April 2002

Abstract

A general synthetic route that can lead to nicotinic ligands bearing a variety of bulky aza-ring systems was developed. This methodology was applied to obtain 5-(3-pyridinyl)- and 5-(3-quinolinyl)-4-azahomoadamantanes **2a**, **3a** and **2b**, **3b**. The parent 5-(3-pyridinyl)-4-azahomoadamantane **2a** (Ki = 5.0 μM) binds with about 100 times lower affinity than (+)−epibatidine **1** (Ki = 0.045 μM) to α7 nicotinic acetylcholine receptors (nAChRs). *N*-methyl substitution of **2a** gives compound **3a** which has about nine times lower binding affinity. The replacement of pyridinyl with a quinolinyl ring (compounds **2b**, **3b**) results in a dramatic reduction in potency (Ki > 1000 μM).

Keywords: Synthesis; Azahomoadamantanes; α7 nAChRs; Epibatidine; Binding

1. Introduction

An intense research for the structure–activity relationships study of neuronal nicotinic acetylcholine receptor (nAChR) ligands has been noted in recent years in an effort aimed at the development of agents for the treatment of memory-related disorders. α4β2 and α7 types are the two major populations of brain nAChRs. Numerous agents have been developed and examined mainly against α4β2 nAChRs; the most potent known nAChR ligand is epibatidine **1** (Fig. 1). However, less is known about α7 subpopulations [1–3].

In an effort to find new nicotinic agents, we have synthesized the 5-(3-pyridinyl)- and 5-(3-quinolinyl)-4-azahomoadamantanes **2a**, **3a** and **2b**, **3b** in which the heteroaryl ring and sp^3 nitrogen pharmacophoric elements are mounted into the new homoadamantane scaffold (Fig. 1). The synthetic route followed can be generalized to obtain compounds with the nicotinic pharmacophore groups mounted into a bulky ring scaffold.

In this preliminary work, the synthesized compounds were tested against α7 nAChRs. These receptors are considered important in sensory processing and in the pathophysiology of schizophrenia. They are characterized by their high affinity for α-bungarotoxin.

2. Results−discussion

2.1. Chemistry

The synthesis of compounds **2a**, **b** and **3a**, **b** was accomplished according to Scheme 1. Reaction of 2-adamantanone **4** with 3-pyridinyl or 3-quinolinyl lithium afforded the tertiary alcohol **5a**, **b** which was then converted to the corresponding azide **6a**, **b** on treatment with a 4-fold excess of sodium azide in 75% H_2SO_4–$CHCl_3$ followed by aqueous 25% NH_3. Acid

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0014-827X/02/$ - see front matter
PII: S0014-827X(02)01273-9

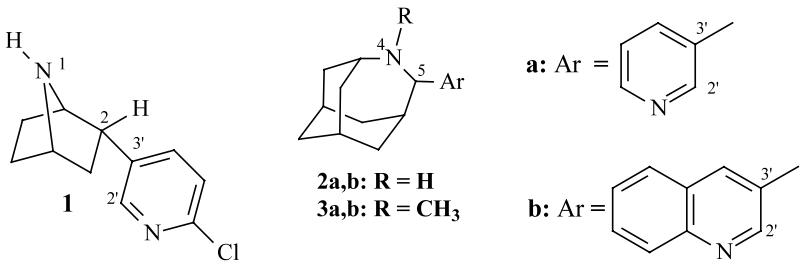
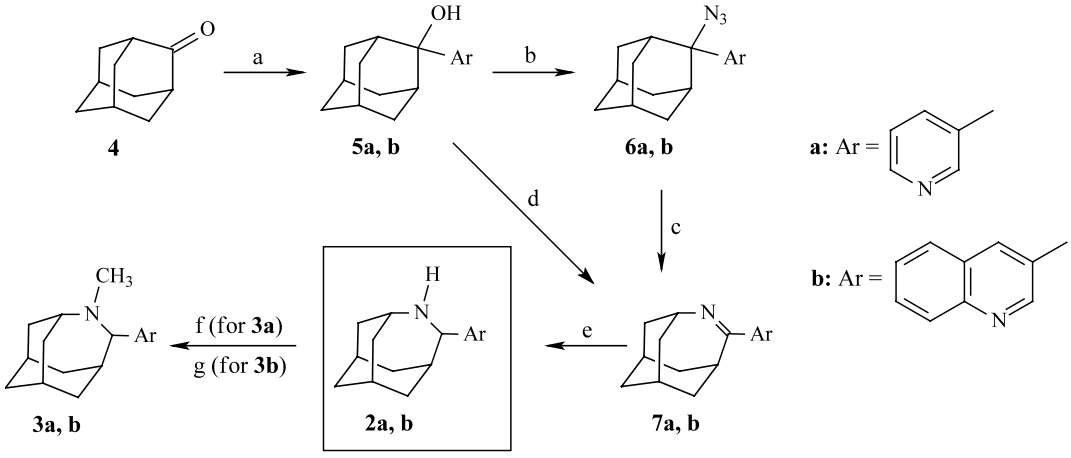


Fig. 1. Chemical structure of (+)−epibatidine **1** and synthesized 5-(3-pyridinyl)- and 5-(3-quinolinyl)-4-azahomoadamantanes **2a**, **b** and **3a**, **b**.



Scheme 1. Reagents (a) 3-pyridinyl lithium or 3-quinolinyl, Et_2O–THF, −65 °C and then HCl 10% (69 or 60%); (b) (i) H_2SO_4 75%, NaN_3, $CHCl_3$, 0 °C for 30 min and then 16 h at r.t. (ii) ice-NH_3 26% (80 or 94%); (c) conc. H_2SO_4, $CHCl_3$, 0 °C for 2 h and then NH_3 26%, 0 °C (95 or 86%); (d) conc. H_2SO_4, NaN_3, $CHCl_3$, 0 °C for 2 h and then ice-NH_3 26% (73 or 50.5%); (e) $NaBH_4$, MeOH, 0 °C for 6 h and then KOH 2N (96 or 93%); (f) (i) CH_2O 37%, MeOH, r.t. for 2 h and then $NaBH_4$, r.t. for 1.5 h. (ii) KOH 2N (85%); (g) (i) CH_2O 37%, MeOH, r.t. for 15 min and then $NaCNBH_3$, r.t. for 2 h at neutral pH (maintained by addition of AcOH). (ii) KOH 2 N (61%).

catalyzed breakdown of azide **6a**, **b** with 95% H_2SO_4 in a standard manner led to the substituted 4-azahomoadamant-4-ene **7a**, **b** formed by adamantane skeleton-expansion via the corresponding alkylnitrenium ion. The rearrangement product **7a**, **b** was also obtained through treatment of tertiary alcohol **5a**, **b** with 95% H_2SO_4 and sodium azide (5-fold excess) in $CHCl_3$ (Schmidt reaction) [4–7]. Reduction of cyclic imine **7a**, **b** with $NaBH_4$ gave the desired azahomoadamantane **2a**, **b**. The *N*-methyl derivative **3a**, **b** was prepared by reductive methylation of the amine **2a**, **b** with formaldehyde and sodium borohydride or sodium cyanoborohydride as reducing agent.

2.2. Binding studies

The affinity of the hydrochloride salts of the compounds **1**, **2a**, **b** and **3a**, **b** for the α7 receptor subtype was assayed using the displacement of ^{125}I-α bungarotoxin.

Table 1 shows the affinities of the new compounds for the α7 nAChRs, [8] as *K*i values. The binding results show some potency for pyridinyl analogue **2a** (*K*i = 5.0 μM). This compound binds with about 100-fold lower affinity than (+)-epibatidine **1** (*K*i = 0.045 μM). The superposition of the low energy conformers of the parent compound **2a** and epibatidine **1** shows that the two compounds have similar distances between sp^2 and sp^3 nitrogen atoms and pyridine ring alignments but differ in the aliphatic area around sp^3 nitrogen atom [9]. The decrease in the activity of **2a** with regards to epibatidine **1** can be possibly attributed to this difference.

N-methyl substitution of **2a** reduces about nine times the binding affinity (compound **3a**, *K*i = 43.5 μM). Quinolinyl instead of pyridinyl ring substitution results in a more than 200 times decrease in potency (compounds **2b** and **3b**, *K*i > 1000 μM).

Table 1
Binding affinities for α bungarotoxin, (+)−epibatidine and compounds **2a**, **b** and **3a**, **b** to α7 nAChRs

Comp.	*K*i (μM)
α-Bungarotoxin	0.00106 [8]
(+)-Epibatidine 1	0.045
2a	5.0
3a	43.5
2b	> 1000
3b	> 1000

3. Conclusion

Due to the potential therapeutic utility of the central nAChRs there is much interest in developing novel nAChRs ligands [2]. Thus, any new structure–activity relationships for the binding to α4β2 or α7 receptors, the major populations of brain nAChRs, is worth investigating. In this work, we have identified a general synthetic route that can lead to nicotinic ligands bearing a variety of bulky aza-ring systems as new scaffolds. We have applied this methodology to obtain 5-(3-pyridinyl)- and 5-(3-quinolinyl)-4-azahomoadamantanes **2a**, **3a** and **2b**, **3b**. The parent pyridinyl compound **2a** binds with 100 times lower affinity than (+)-epibatidine **1** to α7 receptors. *N*-methyl derivative **3a** has about nine times smaller binding affinity than the parent compound **2a** while quinolinyl analogs **2b**, **3b** lack a substantial binding to α7 receptors.

4. Experimental

4.1. Chemistry

Melting points (m.p.) were obtained on a Buchi Capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 833 instrument. NMR spectra were recorded on a Bruker AC 200 or a DRX 400 MHz machine using $CDCl_3$ or DMSO-d_6 as a solvent and TMS as an internal standard. Carbon multiplicities were established by DEPT experiments. 2D NMR Spectra (COSY and HMQC) were used to elucidate the structure of the derivatives. Elemental analyses were performed by the Service Central de Microanalyse (CNRS), France, and the results obtained had a maximum deviation of 0.4% from the theoretical values.

4.2. 2-(3-Pyridinyl)tricyclo[3.3.1.1.^{3,7}]decan-2-ol (**5a**)

To a 2.5 M solution of *n*-BuLi in hexane (8.5 ml, 21.1 mmol) was added dropwise with stirring at −75 °C over a 1 h period a solution of 3-bromopyridine (3.16 g, 20 mmol) in ether (25 ml) under argon atmosphere. After addition was completed, the reaction mixture was further stirred at −75 °C for 30 min. The mixture was then warmed to −65 °C and a solution of 2-adamantanone **4** (2 g, 13.3 mmol) in THF (10 ml) was added dropwise. Stirring was continued at −65 °C for 3 h and the reaction mixture was then allowed to gradually warm to ambient temperature. The reaction mixture was poured into a 10% hydrochloric acid solution (60 ml) under ice-cooling. The acidic aqueous phase was separated, washed with ether (1 × 50 ml) and basified with solid Na_2CO_3.The resultant solid was extracted with $CHCl_3$ (4 × 50 ml) and the combined organic phase was washed with water (4 × 50 ml), dried (Na_2SO_4), and evaporated under vacuum. The orange colored residue was purified by column chromatography on neutral aluminum oxide (70–230 mesh, Brockmann activity I) using $CHCl_3$–ether 1:1 as eluent, to give the pure alcohol **5a** (2.1 g, 69%): m.p. 144–146 °C (ether). IR (nujol): ν(OH) 3167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42–1.93 (complex m, 10H 4,5,6,7,8,9,10-adamantane H), 2.21–2.58 (m, 4H 1,3,4,9-adamantane H), 2.90–3.40 (br s, 1H, OH), 7.13–7.30 (m, 1H, 5-pyridine H), 7.79 (~ d, 1H, $J \approx 8.1$ Hz, 4-pyridine H), 8.35(~ s, 1H, 6-pyridine H), 8,54 (s, 1H, 2-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.77 (5-adamantane C), 27.36 (7-adamantane C), 32.65 (4, 9-adamantane C), 34.61 (8, 10–adamantane C), 35.26 (1, 3-adamantane C), 37.55 (6-adamantane C), 74.50 (2-adamantane C), 123.55 (5-pyridine C), 133.76 (4-pyridine C), 140.88 (3-pyridine C), 147.43 (2-pyridine C), 147.78 (6-pyridine C). *Anal.* Calc. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11%. Found: C, 78.17; H, 8.25; N, 5.90%.

4.3. 2-(3-Quinolinyl)tricyclo[3.3.1.1.^{3,7}]decan-2-ol (**5b**)

Compound **5b** was prepared by an analogous procedure to that described for the preparation of **5a** using 3-bromoquinoline instead of 3-bromopyridine. The crude solid obtained was triturated with three portions of ether to provide pure compound **5b** (60%): m.p. 233–234 °C ($CHCl_3$); IR (nujol: ν(OH) 3220 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.40–1.88 (complex m, 10H, 4,5,6,7,8,9,10-adamantane H), 2.40 (d, 2H, $J \approx$ 17.2 Hz, 4,9-adamantane H), 2.60 (br s, 2H, 1,3-adamantane H), 4.99 (s, 1H, OH), 7.42–8.04 (m, 4H, 5,6,7,8-quinoline H), 8.28 (d, 1H, $J \approx 2.2$ Hz, 4-quinoline H), 8.97 (d, 1H, $J \approx 2.2$ Hz, 2-quinoline H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 26.59 (5-adamantane C), 27.11 (7-adamantane C), 32.47 (4,9-adamantane C), 34.46 (8,10-adamantane C), 34.68 (1,3-adamantane C), 37.50 (6-adamantane C), 73.25 (2-adamantane C), 126.50, 127.62, 128.43, 129.13, 132.22 (4-quinoline C), 138.74, 146.39 (8a-quinoline C), 149.97 (2-quinoline C). *Anal*. Calc. for $C_{19}H_{21}NO$: C, 81.69; H, 7.58; N, 5.01%. Found: C, 81.49; H, 7.46; N, 4.89%.

4.4. 2-(3-Pyridinyl)tricyclo[3.3.1.1.^{3,7}]dec-2-ylazide (**6a**)

To a stirred mixture of alcohol **5a** (0.6 g, 2.62 mmol), 75% H_2SO_4 (4.2 ml) and $CHCl_3$ (4.5 ml), sodium azide (0.71 g, 10.92 mmol) was added in small portions at 0 °C over a 30 min period. After addition was completed, the reaction mixture was stirred at ambient temperature for 16 h, and was then basified by dropwise addition of a 26% aqueous ammonia solution under ice-cooling. The chloroform layer was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 15 ml).

The combined organic extracts were washed with water (3×10 ml), dried (Na_2SO_4) and evaporated under vacuum at ambient temperature. The residue was chromatographed on a column of aluminium oxide pH 9 ± 0.5 (70–230 mesh) using *n*-pentane-ether 6:1 as eluent, to give the azide **6a** as a colorless oil which was crystallized upon cooling (0.53 g, 80%): m.p. 56–58 °C (*n*-pentane); IR (nujol): $\nu(N_3)$ 2097 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50–2.00 (complex m, 10H 4,5,6,7,8,9,10-adamantane H), 2.29 ($\sim$d, 2H, $J \approx 12.1$ Hz, 4,9-adamantane H), 2.62 (br s, 2H, 1,3-adamantane H), 7.28–7.41 (m, 1H, 5-pyridine H), 7.74 (ddd, 1H, $J \approx$ 1.8, 2.6, 8.4 Hz, 4-pyridine H), 8.56 (dd, 1H, $J \approx 1.5$, 4.8 Hz, 6-pyridine H), 8.73 (d, 1H, $J \approx 2.2$ Hz, 2-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.45 (5-adamantane C), 27.14 (7-adamantane C), 32.58 (1,3-adamantane C), 32.95 (4,9-adamantane C), 33.65 (8,10-adamantane C), 37.36 (6-adamantane C), 68.99 (2-adamantane C), 123.55 (5-pyridine C), 133.21 (4-pyridine C), 135.68 (3-pyridine C), 147.64 (2-pyridine C), 148.91 (6-pyridine C). *Anal*. Calc. for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03%. Found: C, 70.76; H, 7.30; N, 22.14%.

4.5. 2-(3-Quinolinyl)tricyclo[3.3.1.1.^{3,7}]dec-2-ylazide (**6b**)

Compound **6b** was prepared from the alcohol **5b** by an analogous procedure to that described for the preparation of **6a**. The crude solid obtained was purified by column chromatography on aluminium oxide pH $9 \pm$ 0.5 (70–230 mesh) using *n*-pentane-ether 4:1 as eluent, to give the title compound as a white solid (94%): m.p. 126–128 °C (ether-*n*-pentane); IR (nujol): $\nu(N_3)$ 2095 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55–2.02 (complex m, 10H, 4,5,6,7,8,9,10-adamantane H), 2.35 ($\sim$d, 2H, $J \approx 12.6$ Hz, 4,9-adamantane H), 2.77 (br s, 2H, 1,3-adamantane H), 7.50–8.20 (m, 5H, 4,5,6,7,8-quinoline H), 9.04 (d, 1H, $J \approx 2.6$ Hz, 2-quinoline H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.50 (5-adamantane C), 27.20 (7-adamantane C), 32.77 (1.3-adamantane C), 33.00 (4,9-adamantane C), 33.78 (8,10-adamantane C), 37.38 (6-adamantane C), 69.25 (2-adamantane C), 126.93, 127.43, 128.16, 129.04, 129.76, 132.66, 132.90, 147.29 (8a-quinoline C), 148.80 (2-quinoline C). *Anal.* Calc. for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41%. Found: C, 74.67; H, 6.62; N, 18.12%.

4.6. 5-(3-Pyridinyl)-4-azatricyclo[4.3.1.1.^{3,8}]undec-4-ene (**7a**)

4.6.1. Acid catalyzed decomposition of the azide **6a**

To a stirred solution of the azide **6a** (0.4 g, 1.57 mmol) in $CHCl_3$ (5 ml), 96% H_2SO_4 (2 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and was then poured into a 26% aqueous ammonia solution (20 ml) under ice-cooling. The chloroform layer was separated and the aqueous phase was extracted with $CHCl_3$ (3×10 ml). The combined organic phase was washed with water (2×15 ml) and dried over Na_2SO_4. After evaporation of the solvent under vacuum, the oily residue was chromatographed on a column of aluminium oxide pH 9 ± 0.5 (70–230 mesh) using *n*-hexane-ether 1:1 as eluent, to give the rearrangement product **7a** as a colorless oil (0.34 g, 95%). IR (film): ν(C=N) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.65–1.92 (m, 10H, 2,7,9,10,11–azahomoadamantene H), 2.05–2.20 (m, 2H, 1,8-azahomoadamantene H), 3.25–3.35 (sym. m, 1H, 6-azahomoadamantene H), 4.22–4.33 (sym. m, 1H, 3-azahomoadamantene H), 7.18–7.29 (m, 1H, 5-pyridine H), 7.89 (dt, 1H, $J \approx 1.9$, 8.0 Hz, 4-pyridine H), 8.52 (dd, 1H, $J \approx 1.6$, 4.8 Hz, 6-pyridine H), 8.80 (d, 1H, $J \approx 2.1$ Hz, 2-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.76 (1,8-azahomoadamantene C), 31.19 (2,11-azahomoadamantene C), 32.72(7,10-azahomoadamantene C), 35.28 (9-azahomoadamantene C), 37.70 (6-azahomoadamantene C), 55.35 (3-azahomoadamantene C), 122.95 (5-pyridine C), 133.98 (4-pyridine C), 137.38 (3-pyridine C), 147.79 (2-pyridine C), 149.92 (6-pyridine C), 174.91 (5-azahomoadamantene C). Dipicrate: m.p. 168–170 °C (dec.) (MeOH). *Anal*. Calc. for $C_{27}H_{24}N_8O_7$: C, 47.59; H, 3.53; N, 16.44%. Found: C, 47.80; H, 3.58; N, 16.21%.

4.6.2. Schmidt reaction on the alcohol **5a**

To a vigorously stirred mixture of alcohol **5a** (0.6 g, 2.62 mmol), sodium azide (0.9, 13.84 mmol) and $CHCl_3$ (25 ml), 96% H_2SO_4 (6 ml) was added dropwise at 0 °C. After the stirring was continued at 0 °C for 2 h, the mixture was poured into a 26% aqueous ammonia solution (50 ml) under ice-cooling. The usual workup as above afforded the rearrangement product **7a** as colorless oil (0.43 g, 73%).

4.7. 5-(3-Quinolinyl)-4-azatricyclo[4.3.1.1.^{3,8}]undec-4-ene (**7b**)

Compound **7b** was prepared from the azide **6b** or alcohol **5b** by analogous procedures to those described for the preparation of **7a**. In both cases, the crude solid obtained was chromatographed on a column of aluminium oxide pH 9 ± 0.5 (70–230 mesh) using ether as eluent, to give the rearrangement product **7b** as colorless crystals (86% from the azide **6b** and 50.5% from alcohol **5b**): m.p. 117–118 °C (ether-*n*-pentane); IR (nujol): ν(C=N) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.65–2.00 (m, 10H, 2,7,9,10,11-azahomoadamantene H), 2.10–2.25 (m, 2H, 1,8-azahomoadamantene H), 3.40–3.57 (sym. m, 1H, 6-azahomoadamantene H), 4.30–4.48 (sym. m, 1H, 3-azahomoadamantene H), 7.45–8.15 (m, 4H, 5,6,7,8,-quinoline H), 8.30 (d, 1H, $J \approx 2.2$ Hz, 4-quinoline H), 9.21 (d, 1H, $J \approx 2.6$ Hz, 2-quinoline H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.88 (1,8-

azahomoadamantene C), 31.38 (2,11-azahomoadamantene C), 32.90 (7,10-azahomoadamantene C), 35.42 (9-azahomoadamantene C), 37.64 (6-azahomoadamantene C), 55.56(3-azahomoadamantene C), 126.81, 127.26, 128.31, 129.10, 129.82, 133.30(4-quinoline C), 134.35, 148.04 (8a-quinoline C), 149.44 (2-quinoline C), 174.76(5-azahomoadamantene C). *Anal*. Calc. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.13%. Found: C, 82.51; H, 7.23; N, 10.04%.

4.8. 3-(Pyridinyl)-4-azatricyclo[4.3.1.1.^{3,8}]undecane (**2a**)

To a stirred solution of cyclic imine **7a** (1.45 g, 6.4 mmol) in MeOH (35 ml), sodium borohydride (1 g, 25.6 mmol) was added in small portions at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and the solvent was then evaporated under vacuum. The residue was treated with a 2N KOH solution (40 ml) and the mixture was extracted with ether (3 × 25 ml). The combined ether extracts were washed with water (2 × 20 ml), dried (Na_2SO_4) and evaporated under vacuum, to give the azahomoadamantane **2a** as an oil which was crystallized upon cooling (1.39 g, 96%): m.p. 60–62 °C (ether-*n*-pentane); IR (nujol): ν(N–H) 3340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–2.22 (complex m, 14H, 1,2,6,7,8,9,10,11-azahomoadamantane H, NH), 3.37 (br s, 1H, 3-azahomoadamantane H), 4.32 (s, 1H, 5-azahomoadamantane H), 7.12 (m, 1H, 5-pyridine H), 7.81 (d, 1H, $J \approx 7.8$ Hz, 4-pyridine H), 8.37 (dd, 1H, $J \approx 1.7$, 4.7 Hz, 6-pyridine H), 8.63 (d, 1H, $J \approx 2$ Hz, 2-pyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.53, 26.82, 29.38, 36.13, 38.08, 39.96, 40.50, 41.43, 50.28 (3-azahomoadamantane C), 64.63 (5-azahomoadamantane C), 122.86 (5-pyridine C), 134.83 (4-pyridine C), 143.24 (3-pyridine C), 147.60 (6-pyridine C), 149.26 (2-pyridine C). Dihydrochloride: m.p. 250–251 °C (dec.) (EtOH–ether). *Anal*. Calc. for $C_{15}H_{22}Cl_2N_2$: C, 59.81; H, 7.36; N, 9.30%. Found: C, 59.97; H, 7.11; N, 9.11%.

4.9. 5-(3-Quinolinyl)-4-azatricyclo[4.3.1.1.^{3,8}]undecane (**2b**)

Compound **2b** was prepared from the cyclic imine **7b** by an analogous procedure to that described for the preparation of **2a**. The azahomoadamantane **2b** was obtained as colorless solid (93%): m.p. 130–131 °C (ether-*n*-pentane). IR (nujol): ν(N–H) 3376 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30–2.45 (complex m, 14H, 1,2,6,7,8,9,10,11-azahomoadamantane H, NH), 3.45 (br s, 1H, 3-azahomoadamantane H), 4.53 (s, 1H, 5-azahomoadamantane H), 7.40–8.10 (m, 4H, 5,6,7,8-quinoline H), 8.31 (t, 1H, $J \approx 1$ Hz, 4-quinoline H), 8.91 (d, 1H, $J \approx 2.2$ Hz, 2-quinoline H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.52, 26.81, 29.26, 36.08, 38.21, 39.71, 40.48, 41.38, 50.31 (3-azahomoadamantane C), 64.60 (5-azahomoadamantane C), 126.32, 127.74, 127.97, 128.48, 128.94, 133.35 (4-quinoline C), 140.67, 147.15 (8a-quinoline C), 151.49 (2-quinoline C). *Anal*. Calc. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.96 N, 10.06%. Found: C, 81.97; H, 8.02; N, 9.98%. Dihydrochloride: m.p. 254–257 °C (dec.) (EtOH–ether).

4.10. 4-Methyl-5-(3-pyridinyl)-4-azatricyclo-[4.3.1.1.^{3,8}]undecane (**3a**)

A solution of azahomoadamantane **2a** (0.5 g, 2.19 mmol) and 37% aqueous formaldehyde (1 ml) in MeOH (8 ml) was stirred for 2 h at ambient temperature. Sodium borohydride (0.29 g, 7.7 mmol) was then added in small portions over a 30 min period, and the reaction mixture was stirred for 1 h. After evaporation of the solvent under vacuum, the residue was treated with 2N KOH solution (15 ml) and the mixture was extracted with ether (3 × 15 ml). The combined ether extracts were washed with water (2 × 10 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on a column of aluminium oxide pH 9 ± 0.5 (70–230 mesh) using *n*-hexane-ether 5:1, to give the *N*-methyl derivative **3a** as an oil which was crystallized upon cooling (0.45 g, 85%): m.p. 61–63 °C (*n*-pentane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23–2.12 (complex m, 13H, 1,2,6,7,8,9,10,11-azahomoadamantane H) 2.27 (s, 3H, CH_3), 3.01 (br s, 1H, 3-azahomoadamantane H), 3.54 (s 1H, 5-azahomoadamantane H), 7.10–7.25 (m, 1H, 5-pyridine H), 7.81 (dt, 1H, $J \approx 1.6$, 7.9 Hz, 4-pyridine H), 8.39 (d, 1H, $J \approx 3.4$ Hz, 6-pyridine H), 8.62 (d, 1H, $J \approx 1.2$ Hz, 2-pyridine H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.19, 26.27, 29.42, 30.27, 35.98, 39.86, 40.69, 40.97, 44.89 (CH_3), 58.34 (3-azahomoadamantane C), 74.05 (5-azahomoadamantane C), 122.88 (5-pyridine C), 134.95 (4-pyridine C), 142.52 (3-pyridine C), 147.59 (6-pyridine C), 149.69 (2-pyridine C). *Anal*. Calc. for $C_{16}H_{22}N_2$: C, 79.30; H, 9.15; N, 11.56%. Found: C, 79.05; H, 8.91; N, 11.28%. Dihydrochloride: m.p. 247–249 °C (dec.) (EtOH–ether).

4.11. 4-Methyl-5-(3-quinolinyl)-4-azatricyclo-[4.3.1.1.^{3,8}] undecane (**3b**)

A solution of azahomoadamantane **2b** (0.475 g, 1.71 mmol) and 37% aqueous formaldehyde (1 ml) in MeOH (10 ml) was stirred for 15 min, and then sodium cyanoborohydride (0.25 g, 3.98 mmol) was added in one portion. After stirring for 30 min, the pH of the solution was adjusted to 7 by dropwise addition of acetic acid. Stirring was continued for an additional hour during which time the pH was maintained as neutral by addition of acetic acid. The solvents were evaporated under vacuum and the residue was treated with 2 N KOH solution (15 ml) under cooling. The resulting mixture was extracted with ether (3 × 15 ml), the ether

extracts were washed with water (2×10 ml) and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a column of aluminium oxide pH 9 ± 0.5 (70–230 mesh) using *n*-pentane-ether 25:1 and then *n*-pentane-ether 5:1 to give the *N*-methyl derivative **3b** as a crystalline product (0.305 g, 61%): m.p. 92–94 °C (ether-*n*-pentane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30–2.18 (complex m, 13H, 1,2,6,7,8,9,10,11-azahomoadamantane H), 2.36 (s, 3H, CH_3), 3.10 (br s, 1H, 3-azahomoadamantane H), 3.77 (s, 1H, 5-azahomoadamantane H), 7.43–8.12 (m, 4H, 5,6,7,8-quinoline H), 8.29 (br s, 1H, 4-quinoline H), 8.94 (br s, 1H, 2-quinoline H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.22, 26.32, 29.42, 30.36, 35.96, 39.70, 40.74, 41.00, 44.97 (CH_3), 58.44 (3-azahomoadamantane C), 74.23 (5-azahomoadamantane C), 126.23, 127.68, 128.16, 128.38, 128.99,133.53 (4-quinoline C), 139.83, 147.40 (8a-quinoline C), 151.85 (2-quinoline C). *Anal*. Calc. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.28; N, 9.58%. Found: C, 81.89; H, 8.09; N, 9.40%. Dihydrochloride: m.p. 256–258 °C (dec.) (MeOH–ether).

4.11.1. Biology

The human neuroblastoma cell line IMR32 was used as the α7 nAChRs source. The IMR32 cells were grown and the nAChR was extracted as described elsewhere [8]. Although this cell line produces additional neuronal nAChRs, the assays performed were with ^{125}I-α bungarotoxin, which binds only to α7 receptor. For the binding experiments, 15 μl of the IMR32 extract was incubated at 4 °C overnight in the presence of various concentrations of the compounds and 1 nM of ^{125}I-α bungarotoxin. At the end of the incubation the samples were diluted with 1 ml of 0.5% Triton X-100 in 20 mM Tris buffer, pH 7.5 and immediately filtered through two Whatman DE81 filters pre-soaked with the same buffer. The filters were then washed twice with 1 ml of the buffer and the bound radioactivity was counted on a γ counter. IC_{50} values were determined and the *K*i was calculated using the formula: $Ki = IC_{50}/\{1-([^{125}\text{I-}\alpha\text{ bungarotoxin}]/\text{Kd}\ ^{125}_{\text{I}-\alpha\ \text{bungarotoxin}})\}$, where Kd $^{125}_{\text{I}-\alpha\ \text{bungarotoxin}}$ is the Kd of ^{125}I-α bungarotoxin for the IMR32 α7 nAChR.

Acknowledgements

This research was supported (a) by a research grant from the Ministry of Industry, Energy and Technology of Greece (Program for the Promotion of Scientists) to the research group of Pharmaceutical Chemistry Department-University of Athens, and (b) by Contract ERBFMRXCT 970138 of the E.C. to S.J. Tzartos.

References

[1] M.W. Holladay, M.J. Dart, J.K. Lynch, Neuronal nicotinic acetylcholine receptors as targets for drug discovery, J. Med. Chem. 40 (1997) 4169–4194.
[2] M.J. Dart, J.T. Wasicak, K.B. Ryther, M.R. Schrimpf, K.H. Kim, D.J. Anderson, J.P. Sullivan, M.D. Meyer, Structural aspects of high affinity ligands for the α4β2 neuronal nicotinic receptor, Pharm. Acta Helv. 74 (2000) 115–123.
[3] R.A. Glennon, M. Dukat, Central nicotinic receptor ligands and pharmacophores, Pharm. Acta Helv. 74 (2000) 103–114 (and references cited there in).
[4] T. Sasaki, S. Eguchi, N. Toi, Synthesis of adamantane derivatives. Photochemical synthesis of 4-azahomoadamant-4-enes and further studies on their reactivity in some cycloadditions, J. Org. Chem. 44 (1979) 3711–3715 (and references cited there in).
[5] A. Astier, M.M. Plat, Synthesis of natural products via tertiary azides I 2-alkyl and *cis* 2,6 alkylpiperidine alkaloids, Tetrahedron Lett. 23 (1978) 2051–2052.
[6] G.F. Alberici, J. Andrieux, G. Adam, M.M. Plat, Synthesis of tobacco alkaloids via tertiary azides, Tetrahedron Lett. 24 (1983) 1937–1940.
[7] G. Fytas, G. Stamatiou, G.B. Foscolos, A. Kolocouris, N. Kolocouris, M. Witvrouw, C. Pannecouque, E. De Clercq, Synthesis and anti-HIV activity of some new aminoadamantane heterocycles, Bioorg. Med. Chem. Lett. 7 (1997) 1887–1890.
[8] B. Balestra, M. Moretti, R. Longhi, R. Mantegazza, F. Clementi, C. Gotti, Antibodies against neuronal nicotinic receptor subtypes in neurological disorders, J. Neuroimmunol. 102 (2000) 89–97.
[9] Molecular mechanics were performed using the MM+ force field provided by the Hyperchem program. Details of the overlay model will be presented in a future work.