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Dialkylaminoalkyl derivatives of bicyclic compounds with antiplasmodial activity

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ABSTRACT

Dialkylaminoalkyl derivatives of 2-azabicyclo[3.2.2]nonanes and of bicyclo[2.2.2]octanes were prepared and their activities determined in vitro against the multiresistant K_1 strain of *Plasmodium falciparum*. Several of the new compounds exhibited very promising antiplasmodial activity and selectivity. The results were compared to those of formerly synthesized analogues and of drugs in use. Structure–activity relationships were detected. Some of the more potent compounds were tested in vivo against *Plasmodium berghei* showing weak to moderate activity. A single compound was able to increase the mean survival days of infected mice.

1. Introduction

Malaria is a life-threatening disease caused by parasites of the species *Plasmodium*. Of the four types of malaria parasites the *Plasmodium falciparum* subspecies is the most deadly killing more than 850,000 people in 2008.[1] Due to increasing drug-resistance to previous antimalarial medicines, artemisinin derivatives are seen as the last defence against the disease, although drug-resistance has been demonstrated in vitro and in vivo.[2–5] Uncomplicated *P. falciparum* infections should be treated with artemisinin-based combination therapy (ACT).[6] But by now an alarming increase of the failure rate of ACTs has been observed in malaria parasites at the Cambodia–Thailand border, indicating emerging resistance even to artemisinin derivatives. Since half of the world's population is at risk of malaria this problem has to be rapidly countered by the discovery of new drugs with activity against drug-resistant strains.[1]

Several aminoacyl derivatives of 2-azabicyclo[3.2.2]nonanes **4** and **5** and the corresponding aminoacylamino analogues **13c** and **14c** of bicyclo[2.2.2]octanes **15** showed good antiplasmodial activity against a multiresistant strain of *P. falciparum* (Scheme 1).[7] Most recently compound **8c**, an aminoethyl derivative of a 2-azabicyclo-nonane was prepared, exhibiting significantly improved activity and very promising selectivity.[8]

In the present paper, derivatives of the aminoacyl- and aminoalkyl 2-azabicyclo-nonanes having other amino residues and differing chain length are described (compounds **7**, **9** and **10**). Moreover it deals with the preparation of analogues in the bicyclo-octane series possessing aminoalkyl and aminoacyl substituents equipped with the same amino residue as **8c** (compounds **15c**, **18** and **19**). The new compounds were characterized and their antiplasmodial activities were determined in vitro against the multiresistant K_1 strain of *P. falciparum*. The results were compared to the activities of the formerly prepared compounds and of drugs in use. Selected compounds were examined for their in vivo activities in a mouse model.

2. Results

2.1. Chemistry

The new 2-azabicyclo-nonane and bicyclo-octane derivatives were prepared from 4-aminobicyclo[2.2.2]octan-2-ones **1** which are accessible by a one-pot reaction of benzylidene acetone with thiocyanates of secondary amines.[9] The Beckmann rearrangement of compounds **1** afforded the 2-azabicyclo-nonan-3-ones **2** which were hydrogenated to compounds **3** using $LiAlH_4$.[10] The 2-azabicyclo-nonanes **3** were acylated with ω-chloroalkanoyl chlorides in the presence of triethylamine.[7] The formed ω-chloroamides were subsequently treated with secondary amines giving their ω-amino derivatives **6** and **7**. The latter were hydrogenated with $LiAlH_4$ giving the 2-aminoalkyl-2-azabicyclo-nonanes **9** and **10**.

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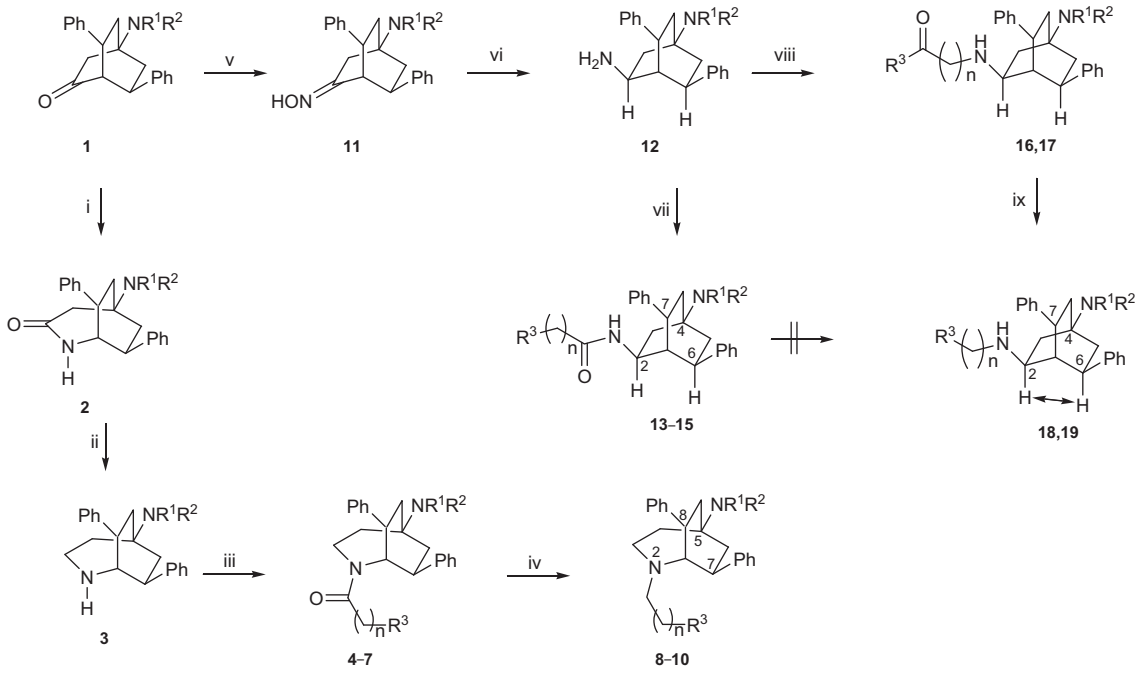


a: $R^1 = R^2 = CH_3$ **b:** $R^1 + R^2 = -(CH_2)_4-$ **c:** $R^1 + R^2 = -(CH_2)_5-$

4a–4c, 13a–13c: R^3 = 4-methylpiperazin-1-yl, n = 1

5a–5c, 14a–14c: R^3 = 4-methylpiperazin-1-yl, n = 2

6a–6c: R^3 = 4-acetylpiperazin-1-yl, n = 1

7a–7c, 10a–10c: R^3 = piperidino, n = 2

8a–8c: R^3 = pyrrolidino, n = 1

9a–9c: R^3 = 4-ethylpiperazin-1-yl, n = 1

15a–15c, 16a–16c, 18a–18c: R^3 = pyrrolidino, n = 1

17a–17c, 19a–19c: R^3 = pyrrolidino, n = 2

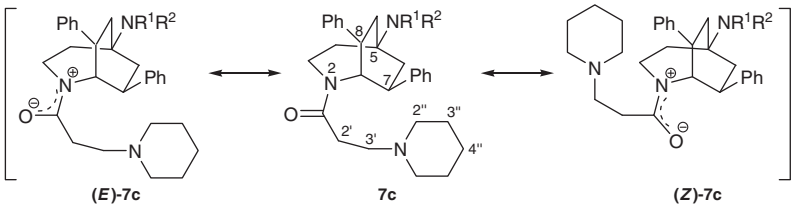
Scheme 1. Preparation of 2-aminoalkyl-2-azabicyclo-nonanes and bicyclo-octanes. Reagents and reaction conditions: (i) NH_2OSO_3H, glacial acetic acid, 145 °C, 16 h; (ii) $LiAlH_4$, ether, 55 °C, 40 h; (iii) (1) ω-chloroalkanoyl chloride, CH_2Cl_2, $N(Et)_3$, rt, 16 h, (2) sec. amine (1-methylpiperazine, 1-acetylpiperazine or piperidine), KI, rt, 48 h; (iv) $LiAlH_4$, ether, 55 °C, 16 h; (v) $NH_2OH{\cdot}HCl$, NaOEt, 110 °C, 16 h; (vi) Raney nickel, EtOH, 50 psi (H_2), rt, 16 h; (vii) (1) ω-chloroalkanoyl chloride, CH_2Cl_2, $N(Et)_3$, rt, 16 h, (2) sec. amine (1-methylpiperazine or pyrrolidine), KI, rt, 48 h; (viii) ω-chloroalkanoyl pyrrolidine, EtOH, KI, 110 °C, 16 h; (ix) $LiAlH_4$, ether, 55 °C, 16 h.

The ω-dialkylaminoalkyl derivatives **18** and **19** of 2-aminobicyclo-octanes were prepared from bicyclo-octan-2-ones **1** via the oximes **11**. Those were stereoselectively hydrogenated with Raney nickel giving the (2-exo)-amines **12**.[11] Their conversion to compounds **13**, **14** succeeded by the above-mentioned two-step procedure via the corresponding ω-chloro amides.[7] Compound **15c** had been prepared in the same way, however, we were not able to obtain **18c** by hydrogenation of **15c** using different hydrogenation catalysts. Most likely this was caused by sterical reasons. As a consequence we chose a different approach. We prepared *N*-(ω-chloroalkanoyl)pyrrolidines which were allowed to react with the 2-aminobicyclo-octanes **12**. The formed *N*-alkyl derivatives **16** and **17** were successfully hydrogenated to compounds **18** and **19** using $LiAlH_4$ (Scheme 1).

The structures of all new compounds were elucidated by one- and two-dimensional NMR spectroscopy. The appearance of two sets of signals in the ^1H and ^{13}C NMR spectra of compounds **4–7** indicated the restricted rotation around the C(=O)–N bond which is due to their partial double-bond character (Scheme 2). The exact distinction between the signals of the corresponding (*E*)- and (*Z*)-diastereomers of compounds **4–7** succeeded with the aid of the typical upfield-shifts[12] for the C-1 or the C-3 in (*Z*)-relation to the carbonyl oxygen in their ^{13}C NMR spectra. In addition, two-dimensional NMR techniques were applied. The relative configuration in ring position 2 of the bicyclo-octanes **18** and **19** was confirmed by through-space couplings in their NOE spectra from the 2-H to the 6-H (Scheme 1).

2.2. Antiplasmodial activity and cytotoxicity

In Table 1 the IC_{50} values for the antiplasmodial activities against the multiresistant K_1 strain of *P. falciparum* and for the cytotoxicity of the new compounds **7**, **9**, **10**, **15**, **18** and **19** are compared to data of formerly prepared analogues **4**, **5**, **8**, **13**, **14** and of drugs in use. Compounds **7b**, **7c**, **9b**, **9c**, **10b**, **10c**, **18c** and **19c** were tested via in vivo assays for their activity against *Plasmodium berghei* in mice. The results are given in Tables 1 and 2.



Scheme 2. (*E*/*Z*)-Character of compound **7c**.

Table 1
In vitro antiplasmodial activity against *Plasmodium falciparum* K_1 and cytotoxicity against rat skeletal myoblasts (L-6 cells) of compounds **4**–**10**, **13**–**15**, **18** and **19** expressed as IC_{50} (μM)[a]

Compound	*P. falc.*	Cytotoxicity	S.I.[b]
4b[c]	0.83	69.10	83.25
4c[c]	0.62	177.4	286.1
5b[c]	0.90	75.43	83.81
5c[c]	0.60	119.9	199.8
7a	1.07	128.3	119.9
7b	0.36	108.1	300.3
7c	0.19	63.89	336.3
8a[c]	0.59	80.41	136.3
8b[c]	0.50	58.22	116.4
8c[c]	0.092	155.7	1692
9a	0.34	57.98	170.5
9b	0.18	53.64	298.0
9c	0.14	67.50	482.1
10a	0.36	58.41	162.3
10b	0.10	28.68	286.8
10c	0.12	138.3	1152
13c[c]	0.38	57.52	151.4
14c[c]	0.28	61.06	218.1
15c	0.11	21.01	191.0
18a	1.01	69.32	68.63
18b	0.91	30.56	33.58
18c	0.076	42.98	565.5
19a	1.06	22.84	21.55
19b	1.09	28.38	26.04
19c	0.23	26.99	117.3
art	0.0064	450.5	70391
chl	0.15	188.5	1257

art = artemisinin, chl = chloroquine.
[a] Values represent the average of four determinations (two determinations of two independent experiments)
[b] S.I. = IC_{50} (cytotox.)/IC_{50} (*P. falc.*)
[c] Values are taken from Refs. 7,8.

Table 2
In vivo activities of compounds **7b**, **7c**, **9b**, **9c**, **10b**, **10c**, **18c**, **19c** against *Plasmodium berghei* expressed as IC_{50} (μM)

Compound	Application	Dose (mg/kg)	MSD	Activity (%)
7b	ip	4 × 30	6.7	27.2
7c	ip	4 × 50	6	36.5
9b	ip	4 × 30	7	8.90
9c	ip	4 × 30	7	0
10b	ip	4 × 30	7	31.0
10c	ip	4 × 50	8	30.4
18c	ip	2 × 50	Toxic after 2nd administration	
19c	ip	4 × 50	7	16.1
Control			6–7	
Chloroquine	ip	4 × 10	20	99.6

3. Discussion

In the 2-(ω-aminoacyl)-2-azabicyclo-nonane series compounds **7b** (IC_{50} = 0.36 μM; S.I. = 300.2) and **7c** (IC_{50} = 0.19 μM; S.I. = 336.3) showed good antiplasmodial activity. These compounds were more active and exhibited a higher selectivity index (S.I. = IC_{50} (cytotox.)/IC_{50} (*P. falc.*)) than their formerly prepared ω-(4-methylpiperazino) analogues **4b**, **4c**, **5b** and **5c** ($IC_{50} \geqslant 0.60$ μM; S.I. $\leqslant$ 286.1). The hydrogenation products **9** and **10** were in general more active than amides **7**. Compounds **9c** (IC_{50} = 0.14 μM; S.I. = 482.1) and **10c** (IC_{50} = 0.12 μM; S.I. = 1153) had very promising selectivity indexes, though they did not attain the superior selectivity of their *N*-(3-pyrrolidinopropyl) analogue **8c** (S.I. = 1692). Therefore the pyrrolidino substituent was chosen for the synthesis of bicyclo[2.2.2]octyl analogues. And indeed, the antiplasmodial activity of the *N*-(ω-pyrrolidino) substituted amide **15c** (IC_{50} = 0.11 μM) was increased compared to its ω-(4-methylpiperazino) analogues **13c** and **14c** ($IC_{50} \geqslant 0.28$ μM). However, since the cytotoxicity of **15c** was markedly higher we set the preparation of compounds **15a** and **15b** aside. The 2-pyrrolidinoethylaminobicyclo-octanes **18** exhibited better selectivity than their longer-chain analogues **19**, but the antiplasmodial activity of the majority of compounds **18** and **19** was low compared to their 2-azabicyclo analogues **8**. However, compound **18c** (IC_{50} = 0.076 μM; S.I. = 565.5) exhibited the highest activity of all tested bicyclic compounds and had a very good selectivity index (Table 1).

It is noticeable that the substituent of the bicyclic bridgehead had a remarkable influence on the antiplasmodial activity and the selectivity of the compounds. In the 2-azabicyclo[3.2.2]nonane series the 5-dimethylamino compounds were the least potent. Their 5-pyrrolidino and 5-piperidino analogues showed similar activity, but the 5-piperidino compounds exhibited higher selectivity in the majority of cases. However, in the bicyclo[2.2.2]octyl series the 4-piperidino derivatives showed by far the highest activity and selectivity. The acyl compounds were in general less active than their hydrogenated derivatives. A relatively high percentage of the new compounds was roughly as active as chloroquine (IC_{50} = 0.15 μM; S.I. = 1257) but only **10c** (S.I. $\geqslant$ 1152) had a comparable and **9c** and **18c** very good selectivity indexes (S.I. $\geqslant$ 482.1).

The in vivo activities of some of the more active compounds were determined against *P. berghei* in male mice. The in vivo results were quite disappointing. Only a couple of compounds was able to reduce parasitemia on day 4 by more than a quarter compared to the untreated control group. The 2-(2-piperidinopropionyl)-2-azabicyclo-nonane **7c** showed the highest activity (36.54%) of all tested compounds, however, only its hydrogenation product **10c** was able to increase the mean survival days of the group by at least one day. A future study will investigate if its higher activity (30.4%) compared to its analogue **9c** (0%) is rather caused by the longer alkyl chain or by the amino substitution of the chain (Table 2).

4. Conclusion

N-(Aminoacyl) and *N*-(aminoalkyl) derivatives of 2-azabicyclononanes and bicyclo-octanes were prepared and tested for their in vitro activity against a multiresistant strain of *P. falciparum*. Compounds with a piperidino substituent at a bridgehead atom were the most promising in both series. The *N*-(aminoalkyl) derivatives were more active than their acyl analogues. Several

compounds were approximately as potent as chloroquine and showed promising selectivity. Some of the more potent compounds were tested in vivo against *P. berghei* showing weak to moderate activity. Some compounds reduced the parasitemia in infected mice and one of them slightly increased their mean survival days. A future study will investigate the influence of the nature of the aminoalkyl substituent on this antiplasmodial effect.

5. Experimental

5.1. Instrumentation and chemicals

IR spectra: infrared spectrometer system 2000 FT (Perkin–Elmer). NMR spectra: Varian Unity Inova 400 (298 K) 5 mm tubes, TMS as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. ^{1}H NMR and ^{13}C NMR spectra are reported in ppm, ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra and are numbered as given in the formulas. Signal multiplicities are abbreviated as follows: br broad, d doublet, dd double doublet, ddd double double doublet, dt double triplet, m multiplet, s singlet, t triplet, td triple doublet, q quartet. HRMS: Micromass Tofspec spectrometer (MALDI), GCT-Premier, Waters (EI, 70 eV). Materials: column chromatography (CC): aluminum oxide B (Merck), thin-layer chromatography (TLC): TLC plates (Merck) aluminum oxide 60 F_{254} neutral.

5.2. Syntheses

Bicyclo-octan-2-ones **1a–1c** were prepared from benzylidene acetone and dialkylammonium isothiocyanates following reported procedures.[9,13]

The 2-azabicyclo-nonan-2-ones **2a–2c** were prepared from **1a–1c** as described.[10]

Nonanes **3a–3c** were prepared from **2a–2c** following reported procedures.[10]

Octyl-2-amines **12a–12c** were prepared from **11a–11c** following reported procedures.[11]

5.2.1. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-ω -amino-1-(5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]-non-2-yl)alkan-1-ones (6a–6c, 7a–7c)

The bicyclo-nonanes **3a–3c** and triethylamine were dissolved in dry CH_2Cl_2 and cooled with an ice-bath. Under stirring the chloroacyl chloride was added dropwise in an atmosphere of Ar. After 30 min the ice-bath was removed and the reaction batch was stirred overnight at room temperature. Subsequently 1 N aq NaOH was added and the layers were exhaustively extracted with CH_2Cl_2. The organic phase was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo giving the corresponding ω-chloroacylamide as an oily residue. The corresponding ω-chloroacylamide and a catalytic amount of KI were dissolved in an excess of secondary amine. The mixture was stirred for 48 h at room temperature in an atmosphere of Ar. Subsequently benzene was added and the reaction batch was evaporated. The residue was dissolved in CH_2Cl_2 and was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate and filtered. Finally, the solvent was removed in vacuo giving **6a–6c, 7a–7c**.

5.2.1.1. (7*RS*,8*RS*)-(±)-2-(4-Acetylpiperazin-1-yl)-1-(5-dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)ethanone (6a). Compound **3a** [0.500 g, 1.56 mmol] and triethylamine [0.236 g, 2.34 mmol] in 32 mL dry CH_2Cl_2 gave with chloroacetyl chloride [0.264 g, 2.34 mmol] the 2-chloroacetamide [0.586 g, 1.48 mmol, 95%] which reacted with excess 1-acetylpiperazine [0.950 g, 7.40 mmol] and a catalytic amount of KI in 20 mL dry CH_2Cl_2 to form **6a** [0.620 g, 86%] which was used without further purification for the synthesis of compound **9a**.

5.2.1.2. (7*RS*,8*RS*)-(±)-2-(4-Acetylpiperazin-1-yl)-1-(7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)ethanone (6b). Compound **3b** [0.700 g, 2.02 mmol] and triethylamine [0.306 g, 3.03 mmol] in 40 mL dry CH_2Cl_2 gave with chloroacetyl chloride [0.348 g, 3.03 mmol] the 2-chloroacetamide [0.760 g, 1.80 mmol, 89%] which reacted with excess 1-acetylpiperazine [1.15 g, 9.00 mmol] and a catalytic amount of KI in 20 mL dry CH_2Cl_2 to form **6b** [0.840 g, 91%] which was used without further purification for the synthesis of compound **9b**.

5.2.1.3. (7*RS*,8*RS*)-(±)-2-(4-Acetylpiperazin-1-yl)-1-(7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)ethanone (6c). Compound **3c** [0.360 g, 1.00 mmol] and triethylamine [0.152 g, 1.50 mmol] in 30 mL dry CH_2Cl_2 gave with chloroacetyl chloride [0.169 g, 1.50 mmol] the 2-chloroacetamide [0.350 g, 0.802 mmol, 80%] which reacted with excess 1-acetylpiperazine [0.514 g, 4.01 mmol] and a catalytic amount of KI in 20 mL dry CH_2Cl_2 to form **6c** [0.401 g, 95%] which was used without further purification for the synthesis of compound **9c**.

5.2.1.4. (7*RS*,8*RS*)-(±)-1-(5-Dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-3-piperidinopropan-1-one (7a). Compound **3a** [0.480 g, 1.50 mmol] and triethylamine [0.228 g, 2.25 mmol] in 25 mL dry CH_2Cl_2 gave with chloropropionyl chloride [0.285 g, 2.25 mmol] the 3-chloropropionamide [0.358 g, 0.871 mmol, 58%] which reacted with excess piperidine [1.49 g, 17.5 mmol] and a catalytic amount of KI to form **7a** [0.306 g, 76%]. IR (KBr): 3059, 3026, 2932, 2852, 2780, 1636, 1496, 1448, 1113, 1041, 753, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 259 (3.422), 230 (3.738). **(*E*)-7a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.27–1.36 (m, 2H, 4″-H), 1.37–1.46 (m, 4H, 3″-H, 5″-H), 1.86–1.98 (m, 3H, 2′-H, 4-H, 6-H), 1.98–2.18 (m, 9H, 2′H, 2″-H, 3′-H, 4-H, 6″-H, 9-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.24–2.37 (m, 2H, 3′-H, 6-H), 3.25–3.38 (m, 2H, 3-H, 7-H), 3.45 (td, *J* = 9.9, 2.6 Hz, 1H, 8-H), 3.99 (d, *J* = 2.6 Hz, 1H, 1-H), 4.43–4.50 (m, 1H, 3-H), 7.14–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.14 (C-4″), 25.74 (C-3″, C-5″), 29.34 (C-4), 30.91 (C-2′), 33.56 (C-9), 37.36 (C-6), 38.00 ($N(CH_3)_2$), 40.68 (C-3), 40.77 (C-8), 46.71 (C-7), 54.17 (C-2″, C-6″), 54.58 (C-3′), 57.24 (C-5), 61.16 (C-1), 126.85, 127.02, 127.10, 127.71, 128.89, 129.16 (aromatic C), 142.21, 144.22 (aromatic C_q), 171.42 (CO). **(*Z*)-7a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.40–1.48 (m, 2H, 4″-H), 1.55–1.61 (m, 4H, 3″-H, 5″-H), 1.71–1.81 (m, 1H, 4-H), 1.86–1.94 (m, 1H, 4-H), 1.98–2.13 (m, 2H, 6-H, 9-H), 2.33 (s, 6H, $(NCH_3)_2$), 2.30–2.45 (m, 7H, 2″-H, 3′-H, 6-H, 6″-H, 9-H), 2.53–2.63 (m, 2H, 2′-H), 2.64–2.73 (m, 1H, 3′-H), 3.09 (td, *J* = 13.5, 3.1 Hz, 1H, 3-H), 3.23–3.36 (m, 2H, 7-H, 8-H), 3.82 (br d, *J* = 13.5 Hz, 1H, 3-H), 5.07 (d, *J* = 3.1 Hz, 1H, 1-H), 7.14–7.38 (m, 8H, aromatic H), 7.56 (d, *J* = 7.6 Hz, 2H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.24 (C-4′), 25.96 (C-3″, C-5″), 30.62 (C-4), 32.10 (C-2′), 34.77 (C-8), 35.22 (C-6), 36.25 (C-9), 38.00 ($N(CH_3)_2$), 42.50 (C-3), 45.07 (C-7), 54.54 (C-2″, C-6″), 54.84 (C-3′), 55.38 (C-1), 57.76 (C-5), 126.20, 126.44, 126.49, 127.71, 128.42, 128.51 (aromatic C), 143.16, 143.47 (aromatic C_q), 170.54 (CO). HRMS (EI+) calcd for $C_{30}H_{41}N_3O$: 459.3250; found: 459.3246.

5.2.1.5. (7*RS*,8*RS*)-(±)-1-(7,8-Diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-3-piperidinopropan-1-one (7b). Compound **3b** [0.470 g, 1.36 mmol] and triethylamine [0.206 g, 2.04 mmol] in 25 mL dry CH_2Cl_2 gave with chloropropionyl chloride [0.259 g, 2.04 mmol] the 3-chloropropionamide [0.406 g, 0.929 mmol, 68%] which reacted with excess piperidine [1.59 g, 18.6 mmol] and a

catalytic amount of KI to form **7b** [0.282 g, 62%]. IR (KBr): 3058, 3026, 2932, 2851, 2799, 1636, 1496, 1423, 1155, 1118, 749, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 257 (3.567), 230 (3.815). **(*E*)-7b**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.27–1.36 (m, 2H, 4″-H), 1.37–1.46 (m, 4H, 3″-H, 5″-H), 1.67–1.86 (m, 5H, 2′-H, $(CH_2)_2$), 1.97–2.25 (m, 11H, 2′-H, 2″-H, 3′-H, 4-H, 6-H, 6″-H, 9-H), 2.26–2.40 (m, 2H, 3′-H, 6-H), 2.67–2.81 (m, 4H, $N(CH_2)_2$), 3.23–3.31 (m, 1H, 7-H), 3.32–3.40 (m, 1H, 3-H), 3.48 (td, *J* = 10.0, 2.5 Hz, 1H, 8-H), 3.99 (d, *J* = 2.5 Hz, 1H, 1-H), 4.43–4.50 (m, 1H, 3-H), 7.13–7.37 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.51 ($(CH_2)_2$), 24.14 (C-4″), 25.72 (C-3″, C-5″), 30.61 (C-4), 30.91 (C-2′), 34.40 (C-9), 38.09 (C-6), 40.58 (C-8), 40.62 (C-3), 45.25 ($N(CH_2)_2$), 46.73 (C-7), 54.16 (C-2″, C-6″), 54.58 (C-3′), 56.17 (C-5), 61.33 (C-1), 126.88, 126.96, 127.05, 127.69, 128.86, 129.12 (aromatic C), 142.23, 144.32 (aromatic C_q), 171.39 (CO). **(*Z*)-7b**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.39–1.48 (m, 2H, 4″-H), 1.54–1.62 (m, 4H, 3″-H, 5″-H), 1.76–1.86 (m, 4H, $(CH_2)_2$), 1.86–1.95 (m, 2H, 4-H), 2.10–2.22 (m, 2H, 6-H, 9-H), 2.26–2.33 (m, 1H, 6-H), 2.36–2.53 (m, 6H, 2″-H, 3′-H, 6″-H, 9H), 2.54–2.62 (m, 3H, 2′-H, 3′-H), 2.67–2.81 (m, 4H, $N(CH_2)_2$), 3.13 (td, *J* = 13.1, 3.4 Hz, 1H, 3-H), 3.21–3.29 (m, 1H, 7-H), 3.31–3.39 (m, 1H, 8-H), 3.81 (br d, *J* = 13.9 Hz, 1H, 3-H), 5.07 (d, *J* = 2.8 Hz, 1H, 1-H), 7.13–7.37 (m, 8H, aromatic H), 7.57 (d, *J* = 7.7 Hz, 2H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.51 ($(CH_2)_2$), 24.22 (C-4″), 25.93 (C-3″, C-5″), 32.07 (C-2′), 32.18 (C-4), 34.64 (C-8), 36.00 (C-6), 36.66 (C-9), 42.54 (C-3), 45.10 (C-7), 45.19 ($N(CH_2)_2$), 54.52 (C-2″, C-6″), 54.82 (C-3′), 55.49 (C-1), 56.79 (C-5), 126.14, 126.43, 127.75, 128.38, 128.48 (aromatic C), 143.14, 143.61 (aromatic C_q), 171.39 (CO). HRMS (EI+) calcd for $C_{32}H_{43}N_3O$: 485.3406; found: 485.3403.

5.2.1.6. (7*RS*,8*RS*)-(±)-1-(7,8-Diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-3-piperidinopropan-1-one (7c). Compound **3c** [0.457 g, 1.29 mmol] and triethylamine [0.196 g, 1.94 mmol] in 20 mL dry CH_2Cl_2 gave with chloropropionyl chloride [0.246 g, 1.94 mmol] the 3-chloropropionamide [0.358 g, 0.793 mmol, 61%] which reacted with excess piperidine [1.35 g, 15.9 mmol] and a catalytic amount of KI to form **7c** [0.283 g, 71%]. IR (KBr): 3058, 3026, 2931, 2851, 2797, 1637, 1496, 1438, 1153, 1110, 758, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 259 (3.480), 230 (3.764). **(*E*)-7c**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.28–1.36 (m, 2H, 4″-H), 1.37–1.49 (m, 10H, 3″-H, 5′′-H, $3CH_2$), 1.72–1.79 (m, 2H, 2′-H), 1.83–1.90 (m, 1H, 6-H), 1.92–1.99 (m, 1H, 4-H), 1.99–2.10 (m, 4H, 2″-H, 6″-H), 2.10–2.17 (m, 4H, 3′H, 4-H, 9-H), 2.23–2.29 (m, 1H, 6-H), 2.32–2.40 (m, 1H, 3′-H), 2.49–2.68 (m, 4H, $N(CH_2)_2$), 3.19–3.28 (m, 1H, 7-H), 3.29–3.38 (m, 1H, 3-H), 3.43 (td, *J* = 9.9, 2.5 Hz, 1H, 8-H), 3.99 (d, *J* = 2.4 Hz, 1H, 1-H), 4.45–4.53 (m, 1H, 3-H), 7.13–7.36 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.16 (C-4″), 24.99 (CH_2), 25.75 (C-3″, C-5″), 26.71 ($2CH_2$), 30.63 (C-4), 30.95 (C-2′), 33.52 (C-9), 37.27 (C-6), 40.99 (C-3), 41.14 (C-8), 46.41 ($N(CH_2)_2$), 46.85 (C-7), 54.17 (C-2‴, C-6″), 54.60 (C-3′), 57.77 (C-5), 61.16 (C-1), 126.81, 126.99, 127.03, 127.70, 128.89, 129.12 (aromatic C), 142.31, 144.38 (aromatic C_q), 171.38 (CO). **(*Z*)-7c**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.40–1.49 (m, 4H, 4″-H, CH_2), 1.54–1.67 (m, 8H, 3″-H, 5″-H, $2CH_2$), 1.77–1.87 (m, 1H, 4-H), 1.93–2.08 (m, 2H, 4-H, 6-H), 2.09–2.13 (m, 1H, 9-H), 2.30–2.47 (m, 7H, 2″-H, 3′-H, 6-H, 6″-H, 9-H), 2.49–2.71 (m, 7H, 2′-H, 3′-H, $N(CH_2)_2$), 3.11 (td, *J* = 13.6, 3.4 Hz, 1H, 3-H), 3.16–3.23 (m, 1H, 7-H), 3.30–3.38 (m, 1H, 8-H), 3.80 (br d, *J* = 13.6 Hz, 1H, 3-H), 5.10 (d, *J* = 3.2 Hz, 1H, 1-H), 7.13–7.36 (m, 8H, aromatic H), 7.55 (d, *J* = 7.7 Hz, 2H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.26 (C-4″), 24.99 (CH_2), 25.98 (C-3″, C-5″), 26.81 ($2CH_2$), 31.86 (C-4), 32.15 (C-2′), 35.03 (C-6), 35.29 (C-8), 36.18 (C-9), 42.72 (C-3), 45.41 (C-7), 46.32 ($N(CH_2)_2$), 54.55 (C-2″, C-6″), 54.86 (C-3′), 55.30 (C-1), 58.27 (C-5), 126.18, 126.43, 126.51, 127.70, 128.41, 128.47 (aromatic C), 143.24, 143.62 (aromatic C_q), 170.52 (CO). HRMS (EI+) calcd for $C_{33}H_{45}N_3O$: 499.3563; found: 499.3575.

5.2.2. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-2-(ω-alkylamino)-5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]-nonanes (9a–9c,10a–10c)

The corresponding acylnonane was suspended in dry diethyl ether and cooled with an ice-bath. Under stirring $LiAlH_4$ was added in portions. After 1 h the ice-bath was removed and the reaction batch was refluxed at 55 °C overnight, cooled to room temperature and was cautiously quenched with ice water. Then it was alkalized with 2 N aq NaOH and extracted five times with ether. The combined organic layers were washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate and filtered. Finally the solvent was removed in vacuo giving compound **9a–9c, 10a–10c**.

5.2.2.1. (7*RS*,8*RS*)-(±)-5-Dimethylamino-2-(4-ethylpiperazin-1-yl)ethyl-7,8-diphenyl-2-azabicyclo[3.2.2]nonane (9a). The reaction of compound **6a** [0.620 g, 1.27 mmol] and $LiAlH_4$ [0.193 g, 4.93 mmol] in 45 mL dry diethyl ether gave after work-up a residue **9a** [0.547 g, 93%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with CH_2Cl_2/MeOH (49:1). IR (KBr): 3083, 3024, 2941, 2808, 1653, 1600, 1494, 1450, 1269, 1165, 1128, 1033, 939, 757, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 234 (3.906). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (t, *J* = 7.2 Hz, 3H, CH_2–CH_3), 1.84–1.90 (m, 2H, 4-H), 1.93 (dd, *J* = 13.4, 9.0 Hz, 1H, 6-H), 2.01–2.14 (m, 3H, 2′-H, 9-H), 2.15–2.40 (m, 10H, 2″-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.35 (q, *J* = 7.2 Hz, 2H, CH_2-CH_3), 2.55 (t, *J* = 7.2 Hz, 2H, 1′-H), 2.88 (ddd, *J* = 12.5, 6.5, 5.8 Hz, 1H, 3-H), 2.90 (d, *J* = 2.9 Hz, 1H, 1-H), 2.96 (ddd, *J* = 12.5, 6.4, 5.9 Hz, 1H, 3-H), 3.13 (td, *J* = 9.7, 2.5 Hz, 1H, 8-H), 3.48 (t, *J* = 9.0 Hz, 1H, 7-H), 7.11–7.38 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 11.88 (CH_2–CH_3), 31.34 (C-4), 35.06 (C-6), 37.38 (C-9), 37.95 ($N(CH_3)_2$), 38.07 (C-8), 40.27 (C-7), 48.00 (C-3), 52.20 (CH_2-CH_3), 52. 64 (C-3″, C-5″), 53.37 (C-2″, C-6″), 55.01 (C-1′), 57.00 (C-2′), 57.44 (C-5), 68.50 (C-1), 125.78, 125.96, 127.49, 127.71, 128.48, 128.70 (aromatic C), 144.78, 145.87 (aromatic C_q). HRMS (EI+) calcd for $C_{30}H_{44}N_4$: 460.3566; found: 460.3567.

5.2.2.2. (7*RS*,8*RS*)-(±)-2-(4-Ethylpiperazin-1-yl)ethyl-7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]nonane (9b). The reaction of compound **6b** [0.840 g, 1.63 mmol] and $LiAlH_4$ [0.168 g, 4.43 mmol] in 40 mL dry diethyl ether gave after work-up a residue **9b** [0.700 g, 88%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with CH_2Cl_2/MeOH (79:1). IR (KBr): 3058, 3024, 2936, 2806, 1600, 1493, 1449, 1165, 1031, 943, 756, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 233 (3.958). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (t, *J* = 7.2 Hz, 3H, CH_2–CH_3), 1.73–1.81 (m, 4H, $(CH_2)_2$), 1.97 (t, *J* = 6.0 Hz, 2H, 4-H), 2.00–2.13 (m, 3H, 2-H, 6-H), 2.15–2.43 (m, 11H, 2″-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H), 2.35 (q, *J* = 7.2 Hz, 2H, CH_2–CH_3), 2.55 (t, *J* = 7.2 Hz, 2H, 1′-H), 2.71–2.79 (m, 4H, $N(CH_2)_2$), 2.90 (d, *J* = 2.8 Hz, 1H, 1-H), 2.89–3.00 (m, 2H, 3-H), 3.15 (td, *J* = 9.6, 2.4 Hz, 1H, 8-H), 3.50 (t, *J* = 9.2 Hz, 1H, 7-H), 7.11–7.39 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 11.91 (CH_2–CH_3), 23.64 ($(CH_2)_2$), 33.77 (C-4), 35.77 (C-6), 37.17 (C-9), 38.06 (C-8), 40.01 (C-7), 45.20 ($N(CH_2)_2$), 48.04 (C-3), 52.24 (CH_2-CH_3), 52.66 (C-3″, C-5″), 53.41 (C-2″, C-6″), 55.07 (C-1′), 57.00 (C-2′, C-5), 68.65 (C-1), 125.81, 125.98, 127.56, 127.74, 128.51, 128.75 (aromatic C), 144.76, 145.92 (aromatic C_q). HRMS (EI+) calcd for $C_{32}H_{46}N_4$: 486.3723; found: 486.3730.

5.2.2.3. (7*RS*,8*RS*)-(±)-2-(4-Ethylpiperazin-1-yl)ethyl-7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]nonane (9c). The reaction of compound **6c** [0.401 g, 0.758 mmol] and $LiAlH_4$ [0.168 g, 4.43 mmol] in 40 mL dry diethyl ether gave after work-up pure **9c** [0.348 g, 92%]. IR (KBr): 3058, 3024, 2929, 2806, 1600, 1494,

1450, 1164, 1098, 1012, 945, 756, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 233 (4.028). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (t, *J* = 7.2 Hz, 3H, CH_2–CH_3), 1.41–1.47 (m, 2H, CH_2), 1.56–1.65 (m, 4H, $2CH_2$), 1.85–1.96 (m, 3H, 4-H, 6-H), 2.08–2.41 (m, 13H, 2′-H, 2″-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H), 2.36 (q, *J* = 7.2 Hz, 2H, CH_2-CH_3), 2.56 (t, *J* = 7.2 Hz, 2H, 1″-H), 2.55–2.66 (m, 4H, $N(CH_2)_2$), 2.89 (ddd, *J* = 12.4, 6.4, 5.9 Hz, 1H, 3-H), 2.95 (d, *J* = 2.7 Hz, 1H, 1-H), 2.97 (ddd, *J* = 12.4, 6.7, 5.8 Hz, 1H, 3-H), 3.14 (td, *J* = 9.6, 2.4 Hz, 1H, 8-H), 3.45 (t, *J* = 9.0 Hz, 1H, 7-H), 7.11–7.39 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 11.92 (CH_2-CH_3), 24.98 (CH_2), 26.76 ($2CH_2$), 32.45 (C-4), 35.02 (C-6), 37.40 (C-9), 38.48 (C-8), 40.82 (C-7), 46.26 ($N(CH_2)_2$), 48.13 (C-3), 52.27 (CH_2-CH_3), 52.68 (C-3″, C-5″), 53.43 (C-2″, C-6″), 54.99 (C-1′), 57.12 (C-2′), 58.32 (C-5), 68.28 (C-1), 125.85, 126.00, 127.50, 127.84, 128.52, 128.61 (aromatic C), 144.84, 145.91 (aromatic C_q). HRMS (EI+) calcd for $C_{33}H_{48}N_4$: 500.3879; found: 500.3887.

5.2.2.4. (7*RS*,8*RS*)-(±)-5-Dimethylamino-7,8-diphenyl-2-(3-piperidinopropyl)-2-azabicyclo[3.2.2]nonane (10a). The reaction of compound **7a** [0.293 g, 0.638 mmol] and $LiAlH_4$ [0.096 g, 2.55 mmol] in 35 mL dry diethyl ether gave after work-up pure **10a** [0.236 g, 83%]. IR (KBr): 3059, 3024, 2932, 2852, 2777, 1601, 1494, 1450, 1155, 1040, 744, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 232 (3.981). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.25–1.40 (m, 4H, 2′-H, 4″-H), 1.48–1.54 (m, 4H, 3″-H, 5″-H), 1.84–1.89 (m, 2H, 4-H), 1.89–1.98 (m, 2H, 3′H, 6-H), 2.06–2.15 (m, 2H, 3′-H, 9-H), 2.15–2.29 (m, 6H, 2″-H, 6-H, 6″-H, 9-H), 2.29 (s, 6H, $N(CH_3)_2$), 2.29–2.43 (m, 2H, 1′-H), 2.79 (dt, *J* = 12.8, 6.0 Hz, 1H, 3-H), 2.83 (d, *J* = 2.2 Hz, 1H, 1-H), 2.95 (dt, *J* = 12.8, 6.0 Hz, 1H, 3-H), 3.14 (td, *J* = 9.6, 2.2 Hz, 1H, 8-H), 3.44 (t, *J* = 9.0 Hz, 1H, 7-H), 7.10–7.36 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.32 (C-4″), 25.46 (C-2′), 25.78 (C-3″, C-5″), 31.06 (C-4), 34.88 (C-6), 37.28 (C-9), 37.87 ($N(CH_3)_2$), 37.95 (C-8), 40.00 (C-7), 47.47 (C-3), 54.35 (C-2″, C-6″), 55.83 (C-1′), 57.03 (C-3′), 57.37 (C-5), 68.22 (C-1), 125.62, 125.86, 127.42, 127.62, 128.43, 128.65 (aromatic C), 144.75, 145.89 (aromatic C_q). HRMS (EI+) calcd for $C_{30}H_{43}N_3$: 445.3457; found: 445.3459.

5.2.2.5. (7*RS*,8*RS*)-(±)-7,8-Diphenyl-2-(3-piperidinopropyl)-5-pyrrolidino-2-azabicyclo[3.2.2]nonane (10b). The reaction of compound **7b** [0.260 g, 0.536 mmol] and $LiAlH_4$ [0.081 g, 2.14 mmol] in 35 mL dry diethyl ether gave after work-up a residue **10b** [0.220 g, 87%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (1:1:0.3). IR (KBr): 3058, 3024, 2931, 2851, 2799, 1600, 1493, 1450, 1157, 1032, 746, 698 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 233 (4.028). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.22–1.41 (m, 4H, 2′-H, 4″-H), 1.48–1.56 (m, 4H, 3″-H, 5″-H), 1.74–1.80 (m, 4H, $(CH_2)_2$), 1.90–1.98 (m, 3H, 3′-H, 4-H), 2.03–2.15 (m, 2H, 3′-H, 6-H), 2.15–2.26 (m, 7H, 2″-H, 6-H, 6″-H, 9-H), 2.31–2.43 (m, 2H, 1′-H), 2.70–2.77 (m, 4H, $N(CH_2)_2$), 2.77–2.83 (m, 1H, 3-H), 2.83 (d, *J* = 2.8 Hz, 1H, 1-H), 2.97 (dt, *J* = 12.5, 6.1 Hz, 1H, 3-H), 3.16 (td, *J* = 9.4, 2.8 Hz, 1H, 8-H), 3.47 (t, *J* = 9.1 Hz, 1H, 7-H), 7.11–7.38 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.63 ($(CH_2)_2$), 24.40 (C-4″), 25.53 (C-2′), 25.86 (C-3″, C-5″), 33.49 (C-4), 35.78 (C-6), 37.20 (C-9), 38.05 (C-8), 39.91 (C-7), 45.14 ($N(CH_2)_2$), 47.65 (C-3), 54.45 (C-2″, C-6″), 56.00 (C-1′), 56.75 (C-5), 57.17 (C-3′), 68.46 (C-1), 125.70, 125.94, 127.57, 127.72, 128.52, 128.77 (aromatic C), 144.89, 146.11 (aromatic C_q). HRMS (EI+) calcd for $C_{32}H_{45}N_3$: 471.3614; found: 471.3617.

5.2.2.6. (7*RS*,8*RS*)-(±)-7,8-Diphenyl-5-piperidino-2-(3-piperidinopropyl)-2-azabicyclo[3.2.2]nonane (10c). The reaction of compound **7c** [0.202 g, 0.404 mmol] and $LiAlH_4$ [0.061 g, 1.62 mmol] in 35 mL dry diethyl ether gave after work-up a residue **10c** [0.187 g, 95%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3058, 3025, 2930, 2851, 2796, 1601, 1493, 1452, 1157, 1097, 755, 699 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 233 (3.970). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.28–1.48 (m, 6H, 2′-H, 4″-H, CH_2), 1.50–1.61 (m, 8H, 3″-H, 5″-H, $2CH_2$), 1.84–1.95 (m, 3H, 4-H, 6-H), 1.98–2.03 (m, 1H, 3′-H), 2.06–2.19 (m, 2H, 3′-H, 9-H), 2.19–2.31 (m, 6H, 2″-H, 6-H, 6″-H, 9-H), 2.32–2.43 (m, 2H, 1′-H), 2.55–2.65 (m, 4H, $N(CH_2)_2$), 2.79 (dt, *J* = 12.7, 5.9 Hz, 1H, 3-H), 2.87 (d, *J* = 2.7 Hz, 1H, 1-H), 2.96 (dt, *J* = 12.7, 6.1 Hz, 1H, 3-H), 3.15 (td, *J* = 9.6, 2.7 Hz, 1H, 8-H), 3.42 (t, *J* = 9.2 Hz, 1H, 7-H), 7.11–7.37 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.17 (C-4″), 24.95 (CH_2), 25.25 (C-2′), 25.52 (C-3″, C-5″), 26.72 ($(CH_2)_2$), 32.21 (C-4), 34.85 (C-6), 37.09 (C-9), 38.43 (C-8), 40.62 (C-7), 46.13 ($N(CH_2)_2$), 47.71 (C-3), 54.18 (C-2″, C-6″), 55.64 (C-1′), 56.92 (C-3′), 58.17 (C-5), 68.02 (C-1), 125.67, 125.89, 127.40, 127.73, 128.45, 128.56 (aromatic C), 144.84, 145.97 (aromatic C_q). HRMS (EI+) calcd for $C_{33}H_{47}N_3$: 485.3770; found: 485.3778.

5.2.3. (2*SR*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-piperidinobicyclo-[2.2.2]oct-2-yl)-2-pyrrolidinoacetamide (15c)

Compound **12c** [0.279 g, 0.775 mmol] and triethylamine [0.118 g, 1.16 mmol] were dissolved in 20 mL of dry CH_2Cl_2 and cooled with an ice-bath. Under stirring chloroacetyl chloride [0.131 g, 1.16 mmol] was added in an atmosphere of Ar. After 30 min the ice-bath was removed and the reaction batch was stirred overnight at room temperature. Subsequently 1 N aq NaOH was added and the layers were exhaustively extracted with CH_2Cl_2. The organic phase was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo giving an oily residue [0.288 g, 0.659 mmol, 85%]. The obtained ω-chloroacetamide and a catalytic amount of KI were dissolved in an excess of pyrrolidine [2.16 g, 30.4 mmol]. The mixture was stirred for 48 h at room temperature in an atmosphere of Ar. Subsequently benzene was added and the reaction batch was evaporated. The residue was dissolved in CH_2Cl_2 and was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate and filtered. Finally, the solvent was removed in vacuo giving **15c** [0.230 g, 74%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with CH_2Cl_2/MeOH (19:1). IR (KBr): 3057, 3025, 2933, 2844, 2793, 1676, 1600, 1497, 1446, 1292, 1167, 1138, 1014, 744, 698 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 261 (3.070), 230 (3.627). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.43 (br d, *J* = 13.5 Hz, 1H, 3-H), 1.47–1.54 (m, 2H, CH_2), 1.54–1.60 (m, 4H, 3′-H, 4′-H), 1.61–1.75 (m, 4H, $2CH_2$), 1.84–1.95 (m, 2H, 5-H, 8-H), 2.03–2.16 (m, 3H, 2′-H, 5-H, 5′-H), 2.24–2.46 (m, 4H, 2′-H, 3-H, 5′-H, 8-H), 2.50 (d, *J* = 16.3 Hz, 1H, CH–CO), 2.63 (d, *J* = 16.3 Hz, 1H, CH-CO), 2.60–2.75 (m, 4H, $N(CH_2)_2$), 2.74 (d, *J* = 3.7 Hz, 1H, 1-H), 3.11 (t, *J* = 9.6 Hz, 1H, 6-H), 3.19 (t, *J* = 10.2 Hz, 1H, 7-H), 4.37–4.45 (m, 1H, 2-H), 6.86 (d, *J* = 7.9 Hz, 1H, NH), 7.10–7.41 (m, 10H, aromatic-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.76 (C-3′, C-4′), 24.77 (CH_2), 26.61 ($2CH_2$), 29.56 (C-5), 33.53 (C-8), 33.76 (C-7), 37.07 (C-3), 39.37 (C-1), 40.57 (C-6), 46.77 ($N(CH_2)_2$), 48.33 (C-2), 54.08 (C-2′, C-5′), 57.04 (C-4), 59.10 (CH_2-CO), 125.60, 126.17, 126.24, 127.30, 128.32, 128.43 (aromatic C), 143.34, 144.17 (aromatic C_q), 170.51 (COO). HRMS (E+) calcd for $C_{31}H_{41}N_3O$: 471.3250; found: 471.3260.

5.2.4. General procedure for the synthesis of chloroalkanoyl pyrrolidines

The chloroacyl chloride was dissolved in dry CH_2Cl_2 and cooled with an ice-bath. Then triethylamine diluted with dry CH_2Cl_2 and subsequently pyrrolidine in dry CH_2Cl_2 were added dropwise. After 30 min the ice-bath was removed and the reaction batch was

stirred overnight at room temperature in an atmosphere of Ar. Then 1 N aq NaOH was added, the organic layers were separated and the aqueous phase was exhaustively extracted with CH_2Cl_2 once again. The combined organic layers were washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo giving ω-chloroacyl pyrrolidine.

5.2.4.1. 2-Chloroacetyl pyrrolidine. Chloroacetyl chloride [1.69 g, 15.0 mmol], triethylamine [1.52 g, 15.0 mmol] and pyrrolidine [0.711 g, 10.0 mmol] dissolved in a total of 20 mL dry CH_2Cl_2 gave 2-chloroacetyl pyrrolidine [0.598 g, 41%].

5.2.4.2. 3-Chloropropionyl pyrrolidine. Chloropropionyl chloride [1.91 g, 15.0 mmol], triethylamine [1.52 g, 15.0 mmol] and pyrrolidine [0.711 g, 10.0 mmol] dissolved in a total of 20 mL dry CH_2Cl_2 gave 3-chloropropionyl pyrrolidine [0.737 g, 46%].

5.2.5. General procedure for the synthesis of (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(4-dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl) - amino)-1-pyrrolidinoalkan-1-ones (16a–16c, 17a–17c)

To a mixture of the corresponding bicyclo-octanamine **12** and a catalytic amount of KI in EtOH a solution of ω-chloroacyl pyrrolidine in EtOH was added dropwise under stirring. The reaction batch was refluxed overnight at 110 °C. The solution was acidified with 2 N aq HCl and extracted three times with diethyl ether. Subsequently the aqueous phase was alkalized with 2 N aq NaOH and extracted five times with diethyl ether. The combined organic layers were washed twice with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo giving **16a**–**16c**, **17a**–**17c** as a residue which was used without further purification for the synthesis of compounds **18a**–**18c**, **19a**–**19c**.

5.2.5.1. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidino-ethan-1-ones (16a). A mixture of compound **12a** [0.481 g, 1.50 mmol] dissolved in 20 mL EtOH, a catalytic amount of KI and a solution of ω-chloroacetyl pyrrolidine [0.222 g, 1.5 mmol] in 15 mL EtOH gave compound **16a** [0.452 g, 1.05 mmol, 70%].

5.2.5.2. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidino-ethan-1-ones (16b). A mixture of compound **12b** [0.732 g, 2.03 mmol] dissolved in 20 mL EtOH, a catalytic amount of KI and a solution of ω-chloroacetyl pyrrolidine [0.300 g, 2.03 mmol] in 20 mL EtOH gave compound **16b** [0.740 g, 1.62 mmol, 80%].

5.2.5.3. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidino-ethan-1-ones (16c). A mixture of compound **12c** [0.195 g, 0.540 mmol] dissolved in 5 mL EtOH, a catalytic amount of KI and a solution of ω-chloroacetyl pyrrolidine [0.246 g, 0.540 mmol] in 3 mL EtOH gave compound **16c** [0.197 g, 0.418 mmol, 77%].

5.2.5.4. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidinopropan-1-ones (17a). A mixture of compound **12a** [0.277 g, 0.80 mmol] dissolved in 10 mL EtOH, a catalytic amount of KI and a solution of ω-chloropropionyl pyrrolidine [0.186 g, 1.15 mmol] in 6 mL EtOH gave compound **17a** [0.340 g, 0.763 mmol, 95%].

5.2.5.5. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidinopropan-1-ones (17b). A mixture of compound **12b** [0.346 g, 1.00 mmol] dissolved in 10 mL EtOH, a catalytic amount of KI and a solution of ω-chloropropionyl pyrrolidine [0.290 g, 1.79 mmol] in 6 mL EtOH gave compound **17b** [0.427 g, 0.933 mmol, 93%].

5.2.5.6. (2*SR*,6*RS*,7*RS*)-(±)-ω-(*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)amino)-1-pyrrolidinopropan-1-ones (17c). A mixture of compound **12c** [0.361 g (1.00 mmol)] dissolved in 10 mL EtOH, a catalytic amount of KI and a solution of ω-chloropropionyl pyrrolidine [0.161 g, 1.00 mmol] in 6 mL EtOH gave compound **17c** [0.458 g, 0.943 mmol, 94%].

5.2.6. General procedure for the synthesis of (2*SR*,6*RS*,7*RS*)-(±)-4-dialkylamino-6,7-diphenyl-N-(ω-pyrrolidinoalkyl)bicyclo-[2.2.2]octan-2-amines (18a–18c, 19a–19c)

The corresponding bicyclooctyl-acylamide was suspended in dry diethyl ether and cooled with an ice-bath. Under stirring $LiAlH_4$ was added in portions. After 1 h the ice-bath was removed and the reaction batch was refluxed at 55 °C overnight, cooled to room temperature and was cautiously quenched with ice water. Then it was alkalized with 2 N aq NaOH and extracted with diethyl ether for five times. The combined organic layers were washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate and filtered. Finally the solvent was removed in vacuo giving compound **18a–18c, 19a–19c**.

5.2.6.1. (2*SR*,6*RS*,7*RS*)-(±)-4-Dimethylamino-6,7-diphenyl-*N*-(2-pyrrolidinoethyl)bicyclo[2.2.2]octan-2-amine (18a). The reaction of compound **16a** [0.187 g, 0.433 mmol] and $LiAlH_4$ [0.066 g, 1.73 mmol] in 70 mL dry diethyl ether gave after work-up compound **18a** [0.160 g, 89%]. IR (KBr): 3057, 3024, 2948, 2870, 2820, 2779, 1600, 1495, 1461, 1446, 1347, 1201, 1150, 1071, 1042, 794, 745, 697 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.708). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.48 (br d, J = 13.0 Hz, 1H, 3-H), 1.65–1.70 (m, 4H, 3″-H, 4″-H), 1.84 (ddd, J = 11.5, 7.4, 4.3 Hz, 1H, 2′-H), 1.95 (ddd, J = 12.8, 8.6, 2.6 Hz, 1H, 5-H), 1.96–2.08 (m, 3H, 3-H, 5-H, 8-H), 2.13–2.21 (m, 2H, 1′-H, 8-H), 2.21–2.32 (m, 5H, 2′-H, 2″-H, 5″-H), 2.39 (s, 6H, $N(CH_3)_2$), 2.40–2.45 (m, 2H, 1-H, 1′-H), 2.99 (t, J = 9.2 Hz, 1H, 6-H), 3.13 (t, J = 9.5 Hz, 1H, 7-H), 3.14 (dd, J = 9.6, 3.4 Hz, 1H, 2-H), 7.08–7.43 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.33 (C-3″, C-4″), 30.33 (C-8), 31.51 (C-5), 34.87 (C-7), 36.32 (C-3), 38.39 ($N(CH_3)_2$), 41.62 (C-1), 41.67 (C-6), 46.30 (C-1′), 54.16 (C-2″, C-5″), 55.89 (C-2′), 56.45 (C-4), 59.27 (C-2), 125.33, 126.09, 127.03, 127.40, 127.96, 128.39 (aromatic C), 144.20, 144.80 (aromatic C_q). HRMS (EI+) calcd for $C_{28}H_{39}N_3$: 417.3144; found: 417.3137.

5.2.6.2. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-pyrrolidino-*N*-(2-pyrrolidinoethyl)bicyclo[2.2.2]octan-2-amine (18b). The reaction of compound **16b** [0.740 g, 1.62 mmol] and $LiAlH_4$ [0.246 g, 6.47 mmol] in 100 mL dry diethyl ether gave after work-up a residue **18b** [0.617 g, 86%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3057, 3024, 2959, 2871, 2794, 1600, 1496, 1447, 1348, 1146, 1031, 794, 750, 697 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.687). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.50 (br d, J = 13.1 Hz, 1H, 3-H), 1.65–1.71 (m, 4H, 3″-H, 4″-H), 1.80–1.89 (m, 5H, 2′-H, $(CH_2)_2$), 1.98–2.09 (m, 3H, 5-H, 8-H), 2.09–2.19 (m, 2H, 1′-H, 3-H), 2.20–2.26 (m, 2H, 2′-H, 8-H), 2.23–2.36 (m, 4H, 2″-H, 5″-H), 2.41 (br s, 1H, 1-H), 2.41–2.47 (m, 1H, 1′-H), 2.78–2.85 (m, 4H, $N(CH_2)_2$), 3.02 (t, J = 9.1 Hz, 1H, 6-H), 3.16 (br d, J = 9.7 Hz, 1H, 2-H), 3.17 (t, J = 9.6 Hz, 1H, 7-H), 7.07–7.43 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.30 (C-3″, C-4″), 23.58 ($(CH_2)_2$), 31.11 (C-8), 32.13 (C-5), 34.73 (C-7), 37.23 (C-3), 41.69 (C-6), 41.82 (C-1), 45.47 ($N(CH_2)_2$), 45.94 (C-1′), 54.03 (C-2″, C-5″), 55.49 (C-4), 55.72 (C-2′), 59.16 (C-2), 125.33, 126.09, 127.03, 127.44, 127.97, 128.39 (aromatic C),

144.12, 144.79 (aromatic C_q). HRMS (EI+) calcd for $C_{30}H_{41}N_3$: 443.3300; found: 443.3312.

5.2.6.3. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-piperidino-*N*-(2-pyrrolidinoethyl)bicyclo[2.2.2]octan-2-amine (18c). The reaction of compound **16c** [0.197 g, 0.418 mmol] and $LiAlH_4$ [0.064 g, 1.67 mmol] in 35 mL dry diethyl ether gave after work-up a residue **18c** [0.171 g, 89%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3054, 3021, 2929, 2855, 2801, 1599, 1495, 1445, 1346, 1150, 1059, 1033, 796, 746, 697 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.865). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.44–1.50 (m, 2H, CH_2), 1.50 (d, J = 12.7 Hz, 1H, 3-H), 1.60–1.70 (m, 8H, $2CH_2$, 3″-H, 4″-H), 1.83 (ddd, J = 11.6, 7.3, 4.7 Hz, 1H, 2′-H), 1.97 (ddd, J = 12.7, 9.1, 2.0 Hz, 1H, 5-H), 2.00–2.09 (m, 3H, 3-H, 5-H, 8-H), 2.11–2.17 (m, 1H, 1′-H), 2.17–2.34 (m, 6H, 2′-H, 8-H, 2″-H, 5″-H), 2.39–2.45 (m, 1H, 1′-H), 2.42 (d, J = 3.2 Hz, 1H, 1-H), 2.61–2.73 (m, 4H, $N(CH_2)_2$), 2.96 (t, J = 9.1 Hz, 1H, 6-H), 3.11 (ddd, J = 10.0 Hz, 1H, 7-H), 3.12 (dd, J = 9.6, 3.2 Hz, 1H, 2-H), 7.07–7.43 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.33 (C-3″, C-4″), 24.97 (CH_2), 26.82 ($2CH_2$), 31.23 (C-8), 31.74 (C-5), 34.94 (C-7), 36.48 (C-3), 41.59 (C-6), 41.73 (C-1), 46.27 (C-1′), 46.79 ($N(CH_2)_2$), 54.17 (C-2″, C-5″), 55.84 (C-2′), 57.13 (C-4), 59.29 (C-2), 125.27, 126.04, 127.03, 127.43, 127.93, 128.28 (aromatic C), 144.27, 144.96 (aromatic C_q). HRMS (EI+) calcd for $C_{31}H_{43}N_3$: 457.3457; found: 457.3439.

5.2.6.4. (2*SR*,6*RS*,7*RS*)-(±)-4-Dimethylamino-6,7-diphenyl-*N*-(2-pyrrolidinopropyl)bicyclo[2.2.2]octan-2-amine (19a). The reaction of compound **17a** [0.340 g, 0.763 mmol] and $LiAlH_4$ [0.130 g, 3.43 mmol] in 60 mL dry diethyl ether gave after work-up a residue **19a** [0.276 g, 84%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3057, 3024, 2941, 2871, 2821, 2781, 1600, 1496, 1461, 1447, 1351, 1201, 1152, 1071, 1032, 796, 746, 698 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.769). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.11–1.21 (m, 1H, 2′-H), 1.28–1.39 (m, 1H, 2′-H), 1.45 (br d, J = 13.1 Hz, 1H, 3-H), 1.78–1.84 (m, 4H, 3″-H, 4″-H), 1.93–2.00 (m, 1H, 5-H), 2.01–2.12 (m, 4H, 3-H, 3′-H, 5-H, 8-H), 2.13–2.20 (m, 1H, 8-H), 2.19 (t, J = 7.9 Hz, 2H, 1′-H), 2.32 (dt, J = 10.8, 7.0 Hz, 1H, 3′-H), 2.42 (s, 6H, $N(CH_3)_2$), 2.44 (br s, 1H, 1-H), 2.55–2.62 (m, 4H, 2″-H, 5″-H), 2.99 (t, J = 9.1 Hz, 1H, 6-H), 3.09–3.15 (m, 1H, 2-H), 3.15 (t, J = 9.7 Hz, 1H, 7-H), 7.08–7.42 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.28 (C-3″, C-4″), 27.91 (C-2′), 30.35 (C-8), 31.10 (C-5), 34.60 (C-7), 36.27 (C-3), 38.15 ($N(CH_3)_2$), 41.22 (C-1), 41.46 (C-6), 45.30 (C-3′), 53.39 (C-2″, C-5″), 53.80 (C-1′), 56.94 (C-4), 59.07 (C-2), 125.45, 126.20, 126.84, 127.36, 128.05, 128.45 (aromatic C), 143.90, 144.78 (aromatic C_q). HRMS (EI+) calcd for $C_{29}H_{41}N_3$: 431.3300; found: 431.3286.

5.2.6.5. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-pyrrolidino-*N*-(2-pyrrolidinopropyl)bicyclo[2.2.2]octan-2-amine (19b). The reaction of compound **17b** [0.427 g, 0.905 mmol] and $LiAlH_4$ [0.142 g, 3.73 mmol] in 65 mL dry diethyl ether gave after work-up a residue **19b** [0.335 g, 81%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3057, 3024, 2934, 2872, 2790, 1600, 1496, 1447, 1351, 1149, 1031, 795, 750, 698 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.782). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.09–1.19 (m, 1H, 2′-H), 1.27–1.38 (m, 1H, 2′-H), 1.49 (br d, J = 13.1 Hz, 1H, 3-H), 1.76–1.82 (m, 4H, 3″-H, 4″-H), 1.84–1.90 (m, 4H, $(CH_2)_2$), 2.05–2.37 (m, 9H, 1′-H, 3-H, 3′-H, 5-H, 8-H), 2.44 (br s, 1H, 1-H), 2.45–2.53 (m, 4H, 2″-H, 5″-H), 2.84–2.91 (m, 4H, $N(CH_2)_2$), 3.03 (t, J = 9.0 Hz, 1H, 6-H), 3.11–3.16 (m, 1H, 2-H), 3.18 (t, J = 9.7 Hz, 1H, 7-H), 7.09–7.43 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.34 (C-3″, C-4″), 23.66 ($(CH_2)_2$), 28.27 (C-2′), 31.33 (C-8), 31.76 (C-5), 34.58 (C-7), 37.41 (C-3), 41.59 (C-1, C-6), 45.47 (C-3′), 45.73 ($N(CH_2)_2$), 53.87 (C-2″, C-5″), 54.21 (C-1′), 54.45 (C-4), 59.12 (C-2), 125.53, 126.24, 126.91, 127.46, 128.10, 128.50 (aromatic C), 143.83, 144.69 (aromatic C_q). HRMS (EI+) calcd for $C_{31}H_{43}N_3$: 457.3457; found: 457.3444.

5.2.6.6. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-piperidino-*N*-(2-pyrrolidinopropyl)bicyclo[2.2.2]octan-2-amine (19c). The reaction of compound **17c** [0.458 g, 0.943 mmol] and $LiAlH_4$ [0.142 g, 3.77 mmol] in 85 mL dry diethyl ether gave after work-up a residue **19c** [0.253 g, 57%]. A small amount was purified for analytical purposes by CC over aluminum oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR (KBr): 3058, 3024, 2930, 2853, 2787, 1600, 1496, 1448, 1350, 1153, 1074, 1032, 744, 697 cm^{-1}. UV (CH_2Cl_2, nm, (log ε)): 230 (3.877). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.97–1.08 (m, 1H, 2′-H), 1.21–1.31 (m, 1H, 2′-H), 1.43–1.51 (m, 3H, 3-H, CH_2), 1.60–1.65 (m, 4H, $2CH_2$), 1.69–1.75 (m, 4H, 3″-H, 4″-H), 1.91–1.99 (m, 1H, 5-H), 2.00–2.11 (m, 6H, 1′-H, 3-H, 3′-H, 8-H), 2.11–2.20 (m, 1H, 5-H), 2.27–2.36 (m, 5H, 2″-H, 3′-H, 5″-H), 2.44 (d, J = 3.0 Hz, 1H, 1-H), 2.59–2.74 (m, 4H, $N(CH_2)_2$), 2.94 (t, J = 9.2 Hz, 1H, 6-H), 3.07–3.13 (m, 1H, 2-H), 3.12 (t, J = 10.0 Hz, 1H, 7-H), 7.07–7.43 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.32 (C-3″, C-4″), 25.01 (CH_2), 26.87 ($2CH_2$), 29.35 (C-2′), 31.42 (C-5, C-8), 34.79 (C-7), 36.93 (C-3), 41.52 (C-1), 41.68 (C-6), 45.81 (C-3′), 46.81 ($N(CH_2)_2$), 54.11 (C-2″, C-5″), 54.48 (C-1′), 57.10 (C-4), 59.30 (C-2), 125.44, 126.08, 126.91, 127.46, 128.01, 128.39 (aromatic C), 144.33, 144.95 (aromatic C_q). HRMS (EI+) calcd for $C_{32}H_{45}N_3$: 471.3614; found: 471.3620.

5.3. Biological tests

5.3.1. In vitro microplate assay against *P. falciparum* K_1

Antiplasmodial activity was tested using the chloroquine- and pyrimethamine-resistant K_1 strain of *P. falciparum*. Viability was determined by the incorporation of [^{3}H]-hypoxanthine into living protozoal cells by a modification of a reported assay.[14] Briefly, infected human red blood cells in RPMI 1640 medium with 5% Albumax were exposed to serial drug dilutions ranging from 5 to 0.078 μg/mL in microtiter plates. After 48 h of incubation at 37 °C in a reduced oxygen atmosphere, 0.5 μCi ^{3}H-hypoxanthine were added to each well. Cultures were incubated for a further 24 h before they were harvested onto glass-fiber filters and washed with distilled water. The radioactivity was counted using a BetaplateTM liquid scintillation counter (Wallac, Zurich, Switzerland). The results were recorded as counts per minute (CPM) per well at each drug concentration and expressed as percentage of the untreated controls. IC_{50} values were calculated from the sigmoidal inhibition curves. Assays were run in duplicate and repeated once. Standards were artemisinin and chloroquine.

5.3.2. In vitro cytotoxicity assay

Briefly, 4000 rat skeletal myoblasts (L-6 cells) were seeded in RPMI 1640 medium supplemented with 2 mM L-glutamine, 5.95 g/L HEPES, 2 g/L $NaHCO_3$, and 10% fetal bovine serum in 96-well microtiter plates. Serial drug dilutions were incubated for 70 h at 37 °C under a humidified 5% CO_2 atmosphere. Then 10 μL of Alamar blue (12.5 mg resazurin dissolved in 100 mL of phosphate buffered saline) were added to each well and the plate was incubated for an additional 2–3 h. The plates were read in a Spectramax Gemini XS microplate fluorescence scanner (excitation wavelength 536 nm, emission wavelength 588 nm). The IC_{50} values were calculated from the sigmoidal inhibition curves using the SoftmaxPro software. The assay was carried out twice independently and in duplicate.

5.3.3. In vivo antimalarial activity

Male mice (Fü albino; specific pathogen free) weighing 20 ± 2 g were infected intravenously with 2×10^7 *P. berghei* ANKA strain-infected erythrocytes. For this purpose heparinized blood was taken from donor mice with approximately 30% parasitemia and was diluted in physiological saline to 10^8 parasitized erythrocytes/mL. Aliquots of 0.2 mL of this suspension were injected intravenously into experimental groups of 3 mice and a control group of five mice. The test compounds were dissolved in 10% DMSO. The drug concentrations were adjusted in a way that 0.01 mL per g of body weight had to be injected. 4, 24, 48 and 72 h post infection the experimental groups were treated ip with a single dose (30 or 50 mg/kg). 24 h after the last treatment blood smears of all animals were prepared and stained with Giemsa. Parasitemia was determined microscopically by counting 1000 red blood cells. For low parasitemias (<1%) 2000 RBC's had to be counted. The difference between the mean value for the control group (taken as 100%) and that for each experimental group was calculated and expressed as percent reduction (=activity). Furthermore, the mean survival days (MSD) were recorded as well as observations concerning side effects of the drugs. In vivo studies were carried out by a protocol approved by an animal ethics committee.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.07.046.

References and notes

1. World Malaria Report, 2009.
2. Meshnick, S. R. *Int. J. Parasitol.* **2002**, *32*, 1655.
3. Alker, A. P.; Lim, P.; Sem, R.; Shah, N. K.; Yi, P.; Bouth, D. M.; Tsuyuoka, R.; Maguire, J. D.; Fandeur, T.; Ariey, F.; Wongsrichanalai, C.; Meshnik, S. R. *Am. J. Trop. Med. Hyg.* **2007**, *76*, 641.
4. Afonso, A.; Hunt, P.; Cheesman, A.; Alves, A. C.; Chuna, C. V.; do Rosario, V.; Cravo, P. *Antimicrob. Agents Chemother.* **2006**, *50*, 480.
5. Jambou, R.; Legrand, E.; Niang, M.; Khim, N.; Lim, P.; Volney, B.; Ekala, M. T.; Bouchier, C.; Esterre, P.; Fandour, T.; Mercereau-Pujialon, O. *Lancet* **2005**, *366*, 1960.
6. Guidelines for the treatment of malaria, 2nd ed.; WHO, 2010.
7. Faist, J.; Seebacher, W.; Schlapper, C.; Kaiser, M.; Brun, R.; Saf, R.; Weis, R. *Bioorg. Med. Chem.* **2009**, *17*, 3595.
8. Faist, J.; Seebacher, W.; Kaiser, M.; Brun, R.; Saf, R.; Weis, R. *Eur. J. Med. Chem.* **2010**, *45*, 179.
9. Weis, R.; Brun, R.; Saf, R.; Seebacher, W. *Monatsh. Chem.* **2003**, *134*, 1019.
10. Seebacher, W.; Weis, R.; Kaiser, M.; Brun, R.; Saf, R. *J. Pharm. Pharm. Sci.* **2005**, *8*, 578.
11. Weis, R.; Berger, H.; Kaiser, M.; Brun, R.; Saf, R.; Seebacher, W. *Arch. Pharm. Res.* **2008**, *31*, 688.
12. Glaser, R.; Bernstein, M. A.; Balan, A. *Magn. Reson. Chem.* **1991**, *29*, 766.
13. Weis, R.; Schweiger, K.; Seebacher, W.; Belaj, F. *Tetrahedron* **1998**, *54*, 14015.
14. Matile, H.; Pink, J. R. L. In *Immunological Methods*; Lefkovits, I., Pernis, B., Eds.; Academic Press: San Diego, 1990; pp 221–234.