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Antiplasmodial and antitrypanosomal activity of bicyclic amides and esters of dialkylamino acids

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ABSTRACT

Several bicyclic amides and esters of dialkylamino acids were prepared. Their activities against a multiresistant strain of *Plasmodium falciparum* and against *Trypanosoma brucei rhodesiense* (STIB 900) were examined. Structure–activity relationships were discussed. Particularly the ester compounds showed good antiplasmodial and antitrypanosomal activity and a single compound was tested in vivo against *Plasmodium berghei*.

1. Introduction

Malaria and Human African Trypanosomiasis (HAT) are dangerous diseases caused by infection with the corresponding eucaryotic parasites of the genera *Plasmodium* and *Trypanosoma*. Malaria is a global health problem killing more than 880,000 people in 2006. The *Plasmodium falciparum* subspecies, which is the most virulent and potentially deadly of the malaria parasites, is responsible in more than 90% of the cases.[1] Its multidrug-resistant strains are becoming prevalent around the world.[2] Uncomplicated *P. falciparum* infections are recommended to be treated with artemisinin-based combination therapy, however, possible in vitro and in vivo resistances have been demonstrated even against the most recently introduced artemisinin derivatives.[3–5] Therefore new drugs with activity against drug-resistant strains are urgently needed. Although HAT is mainly limited to Sub-Saharan Africa about half a million people are infected and about 50.000 people die from this disease annually.[6] The more virulent of the two causative species is *Trypanosoma brucei rhodesiense*. The only drug, which is capable of curing CNS infections with *T. b. r.* is the arsenic compound melarsoprol.[7] However, this drug causes an encephalopathy in more than 10% of the patients, killing half of them.[8,9] Hence, the discovery of new drugs against *T. b. rhodesiense* is indispensable.

The activity of bicyclo-octan-2-ols **1** against a multiresistant strain of *P. falciparum* and *T. b. rhodesiense* was increased by their esterification. Recently, we reported the activity of bicyclo-octyl esters **2–4** of 2-dialkylaminoacetic acids, which were far more active than formerly prepared analogues without amino substituent in the acid group.[10] A part of this paper deals with the presentation of a new series of such esters with a further tertiary amino group in the amino acid moiety. The bicyclo-octan-2-amines **5** as well as the structurally related 2-azabicyclo[3.2.2]nonanes **6** are more active than the alcohols **1**.[11,12] Therefore we additionally prepared several amide analogues of the esters **2–4**.

The new compounds were characterized and their biological activities were tested and investigated for structure–activity relationships (Scheme 1).

2. Results

2.1. Chemistry

The bicyclo-octyl esters **9** were synthesized from bicyclo-octanones **7** in two steps. The latter were reduced with $LiAlH_4$ giving selectively the (2-exo)-alcohols **1**.[13] Those were treated with 2-chloroacetyl chloride and 4-dimethylaminopyridine giving the 2-chloroacetates **8**. Finally, esters **9** were obtained by aminolysis of **8** with *N*-methylpiperazine.

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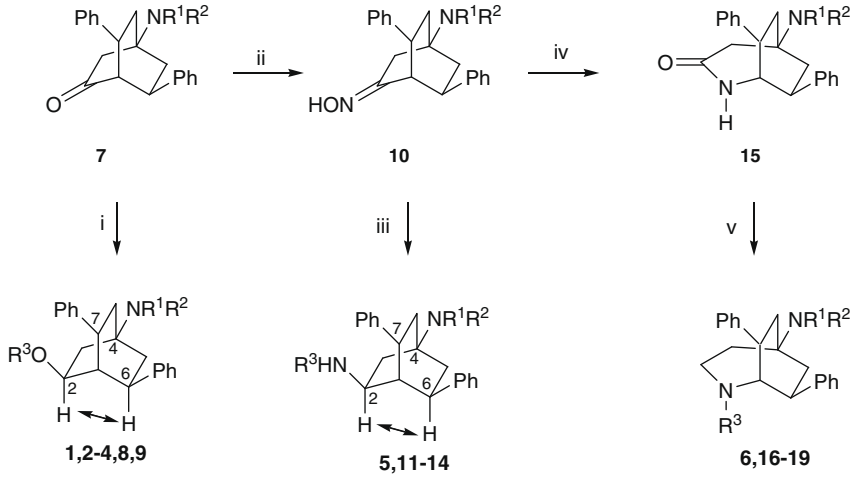


a: $R^1 = R^2 = CH_3$ **b:** $R^1 + R^2 = -(CH_2)_4-$ **c:** $R^1 + R^2 = -(CH_2)_5-$

1a-1c, **5a-5c**, **6a-6c**: R^3 = H

2a-2c: R^3 = N,N-diethylaminoacetyl

3a-3c: R^3 = N,N-pyrrolidinoacetyl

4a-4c: R^3 = N,N-piperidinoacetyl

8a-8c, **11a-11c**, **16a-16c**: R^3 = 2-chloroacetyl

9a-9c, **13a-13c**, **18a-18c**: R^3 = 2-(4'-methylpiperazin-1'-yl)acetyl

12a-12c, **17a-17c**: R^3 = 3-chloropropionyl

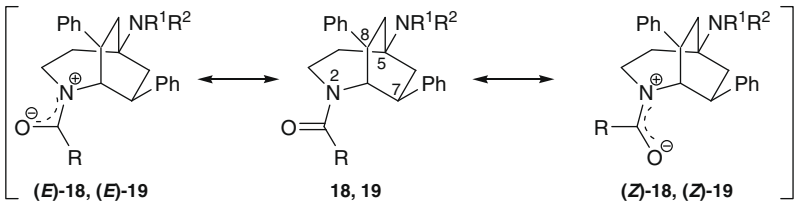
14a-14c, **19a-19c**: R^3 = 3-(4'-methylpiperazin-1'-yl)propionyl

Scheme 1. Preparation of esters and amides. Reagents and reaction conditions: (i) (1) $LiAlH_4$, ether, rt, 16 h; (2) ω-chloroacetyl chloride, CH_2Cl_2, 4-DMAP, rt, 16 h; (3) *sec*-amine, water, KI, 4 °C, 24 h; (ii) $NH_2OH{\cdot}HCl$, NaOEt, 110 °C, 16 h; (iii) (1) Raney nickel, EtOH, 50 psi (H_2), rt, 16 h; (2) ω-chloroalkanoyl chloride, CH_2Cl_2, $N(Et)_3$, rt, 16 h; (3) sec. amine, KI, rt, 40 h; (iv) H_2SO_4, 145 °C, 16 h; (v) (1) $LiAlH_4$, ether, 55 °C, 40 h; (2) ω-chloroalkanoyl chloride, CH_2Cl_2, $N(Et)_3$, rt, 16 h; (3) sec. amine, KI, rt, 40 h.

The corresponding amide analogues **13** and **14** were synthesized in four steps from bicyclo-octanones **7**. Those were converted to oximes **10**, which were hydrogenated with Raney nickel giving the (2-exo)-amines **5** in good yields.[11] Acylation of **5** with ω-chloroalkanoyl chlorides in the presence of triethylamine afforded ω-chloro amides **11**, **12** which were treated with *N*-methylpiperazine giving *N*-(bicyclo-octyl)amides **13**, **14** of ω-dialkylamino acids.

A series of *N*-(2-azabicyclo-nonyl)amides of ω-dialkylamino acids has already been published, however, the favorable properties of compounds **6** were not improved by acylation.[14] Nevertheless, we synthesized their ω-(*N*-methylpiperazinyl) analogues, because the newly prepared esters **9** with this substitution were more active than their formerly reported ω-dialkylamino analogues **2–4**. The 2-azabicyclo-nonan-3-ones **15** were prepared from compounds **7** in a Beckmann rearrangement via the oximes **10**.[12] The reduction of **15** with $LiAlH_4$ yielded the 2-azabicyclo-nonanes **6**, which were converted to *N*-(2-azabicyclo-nonyl)amides **18**, **19** by the above-mentioned two-step procedure via the ω-chloro amides **16**, **17** (Scheme 1).

The structures of all new compounds were elucidated by one- and two-dimensional NMR spectroscopy. The relative configuration in ring position 2 of the bicyclo-octanes **9** and **11–14** was confirmed by through-space couplings in their NOE spectra from the 2-H to the 6-H (Scheme 1). Due to their partial double-bond character and the restricted rotation around the C(=O)–N bond, two sets of signals were observed for compounds **18** and **19** in their ^1H and ^{13}C NMR spectra (Scheme 2). Typical upfield-shifts[15] for the C-1 or the C-3 in (*Z*)-relation to the carbonyl oxygen in their ^{13}C NMR spectra as well as the application of two-dimensional NMR methods allowed the exact assignment of all signals to the corresponding (*E*)- or (*Z*)-diastereomers of compounds **18** and **19**.



Scheme 2. (*E*/*Z*)-Character of compounds **18** and **19**.

Table 1
In vitro activities of compounds **2–6**, **9**, **13**, **14**, **18**, **19**, expressed as IC50 (μM)[a]

Compound	*Plasmodium falciparum* K_1	S.I. = IC_{50} (Cytotox.)/IC_{50} (*P. falc.*)	*Trypanosoma brucei rhodesiense*	S.I. = IC_{50} (Cytotox.)/IC_{50} (*T.b.r.*)	Cytotoxicity IC_{50} (μM)
2a[b]	2.72	11.08	0.61	49.41	30.14
2b[b]	0.20	245.0	0.72	68.06	49.00
2c[b]	0.25	95.68	0.56	42.71	23.92
3a[b]	0.71	46.00	0.21	155.5	32.66
3b[b]	0.70	61.34	0.23	186.7	42.94
3c[b]	0.47	34.85	0.32	51.19	16.38
4a[b]	0.52	56.27	1.99	14.70	29.26
4b[b]	0.37	38.43	0.37	38.43	14.22
4c[b]	0.18	335.5	0.87	69.41	60.39
5a[b]	0.61	67.02	0.35	116.8	40.88
5b[b]	0.65	58.62	0.41	92.93	38.10
5c[b]	0.55	63.55	0.27	129.4	34.95
6a[b]	0.28	388.6	0.60	181.3	108.8
6b[b]	0.56	215.0	1.16	103.8	120.4
6c[b]	0.64	140.2	6.57	13.66	89.74
9a	0.35	113.9	0.13	306.6	39.86
9b	0.54	45.54	0.14	175.6	24.59
9c	0.106	277.9	0.87	33.86	29.46
13a	2.58	25.66	1.60	41.37	66.19
13b	0.82	61.27	1.13	44.46	50.24
13c	0.38	151.4	0.69	83.36	57.52
14a	4.19	22.67	2.74	34.66	94.97
14b	2.08	41.68	4.15	20.89	86.69
14c	0.28	218.1	0.86	71.00	61.06
18a	2.37	82.44	45.80	4.27	195.4
18b	0.83	83.25	41.07	1.68	69.10
18c	0.62	286.1	92.01	1.93	177.4
19a	1.74	73.45	28.25	4.52	127.8
19b	0.90	83.81	31.93	2.36	75.43
19c	0.60	199.8	30.79	3.89	119.9
Mel			0.0039	1995	7.78
Art	0.0064	70391			450.5
Chl	0.15	1257			188.5

Art = artemisinin, chl = chloroquine, mel = melarsoprol, mef = mefloquine.
[a] Values represent the average of four determinations (two determinations of two independent experiments).
[b] Values are taken from Refs. 10–12.

2.2. Antiplasmodial and antitrypanosomal activity, cytotoxicity

The IC_{50} values for the antiplasmodial and antitrypanosomal activities as well as for the cytotoxicity of compounds **2–6**, **9**, **13**, **14**, **18** and **19** are presented in Table 1.

3. Discussion

The antiplasmodial potencies of compounds **9** (**9a–9c**: IC_{50} = 0.106–0.54 μM) are superior to that of their parent bicyclo-octanols **1** (**1a–1c**: IC_{50}: ⩾0.84 μM) due to acylation with dialkylamino acids. But also the activities of the formerly prepared bicyclo-octyl esters **2–4** (**2a–2c**, **3a–3c**, **4a–4c**: IC_{50} = 0.18–2.72 μM) were in general increased by the replacement of their 2-dialkylamino with the methylpiperazinyl group. With the exception of **2c** the 4-piperidino substituted bicyclo-octyl esters **3c**, **4c** and **9c** were the more active against *P. falciparum* K_1. The most active bicyclo-octyl acetate **9c** (IC_{50}: 0.106 μM, SI: 277.6) was even more active than chloroquine (IC_{50}: 0.12 μM, SI: 1571), but its selectivity index (SI) is still far from that of the traditional therapeutic agent. The in vivo activity of compound **9c** was determined against *Plasmodium berghei* in male mice. But only slight antiplasmodial activity (15%) was observed and an increase of mean survival days was not detectable. The antiplasmodial activity of the new amides was in the majority of cases lower than that of their parent amines. However, the most potent *N*-(bicyclo-octyl) derivatives **13c**, **14c** (**13c**: IC_{50}: 0.38 μM, **14c**: IC_{50}: 0.28 μM) and their *N*-(2-azabicyclo-nonyl) analogues **18c** and **19c** (**18c**: IC_{50}: 0.62 μM, **19c**: IC_{50}: 0.60 μM) exhibit improved or equal activities compared to their parent compounds **5c** (IC_{50}: 0.55 μM) and **6c** (IC_{50}: 0.64 μM). The antiplasmodial activity and the selectivity of the amides **13**, **14**, **18** and **19** is significantly increased by the piperidino substitution of the bridgehead of the bicyclic rings, as was already observed for the corresponding esters **9**. The selectivity indices of **13c** (SI: 151.4) and **14c** (SI: 218.1) were better than that of **5c** (SI: 63.55). Likewise amides **18c** (SI: 286.1) and **19c** (SI: 199.8) were less cytotoxic than **6c** (SI: 140.2), but the antiplasmodial activity and the selectivity of the 2-unsubstituted 2-azabicyclo-nonane **6a** (IC_{50}: 0.28 μM, SI: 388.6) remain unsurpassed.

The antitrypanosomal activities of the most potent ω-(*N*-methylpiperazinyl) substituted esters **9a** and **9b** (**9a**: IC_{50} = 0.13 μM, SI: 306.6; **9b**: IC_{50} = 0.14 μM, SI: 175.6) exceed those of their 2-dialkylamino analogues (**2–4**: IC_{50} ⩾0.21 μM, SI ⩽186.7). Moreover, **9a** and **9b** possess equal or improved selectivity. They will serve as leads for further structural modifications. Their *N*-(bicyclo-octyl) amide analogues **13**, **14** (**13**, **14**: IC_{50} ⩾0.69 μM, SI ⩽71.00) are hardly half as active as their parent compounds **5** (**5a–5c**: IC_{50} = 0.27–0.41 μM, SI = 92.93–129.4) and even so they are more cytotoxic. The corresponding *N*-(2-azabicyclo-nonyl) derivatives **18** and **19** are inactive against *T. b. rhodesiense* (Table 1).

4. Conclusion

This paper reports the synthesis, the antiplasmodial and the antitrypanosomal activities of new bicyclic amides and esters of ω-(4′-methylpiperazin-1′-yl)acids. In both series new compounds with increased antiplasmodial activities have been developed. Those with the piperidino substitution of the bicyclic bridgehead were always the more potent and the more selective representatives. Two of the amides showed good antiplasmodial activity

and improved selectivity. An ester analogue showed good selectivity and was in vitro even more potent than chloroquine, but its in vivo activity was only moderate. The antitrypanosomal potency of the amides was relatively weak, whereas some of the new esters were the most active of the so far prepared dialkylamino acid derivatives. They will serve as leads for further investigations.

5. Experimental

5.1. Instrumentation and chemicals

Melting points were measured on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. 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. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba) at the Microanalytical Laboratory at the Institute of Physical Chemistry, HRMS: Micromass Tofspec spectrometer. Materials: column chromatography (CC): silica gel 60 (Merck), thin-layer chromatography (TLC): TLC plates (Merck) silica gel 60 F_{254}.

5.2. Syntheses

5.2.1. (2*SR*,6*RS*,7*RS*)-(±)-4-Dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl 2-chloroacetates (8a–8c)

Their syntheses have already been reported.[10]

5.2.2. General procedure for the synthesis of (2*SR*,6*RS*,7*RS*)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl 2-(4′-methylpiperazin-1′-yl)acetates (9a–9c)

Compounds **8a–8c** were dissolved in excess *N*-methylpiperazine and a catalytical amount of KI in H_2O was added. Then the amine was removed in vacuo and the residue was dissolved in CH_2Cl_2, five times washed with water, dried over sodium sulfate and filtered. The solvent was removed in vacuo and the residue was purified by crystallization or by means of CC. Alternatively, hydrochlorides were afforded by treatment of the acetone solution of the residue with a small excess of a 1 M ethereal solution of hydrogen chloride. The precipitate was sucked off and washed with acetone.

5.2.2.1. (2*SR*,6*RS*,7*RS*)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 2-(4′-methylpiperazin-1′-yl)acetate (9a). Compound **8a** (0.47 g, 1.17 mmol) was dissolved in excess of *N*-methylpiperazine (2 mL) yielding **9a** (0.38 g, 0.83 mmol, 71%) as an oily residue. A small amount was purified for analytical purposes by CC over silica gel eluting with CH_2Cl_2/MeOH (49:1). IR (KBr): 2939, 2871, 2792, 1747, 1602, 1454, 1448, 1297, 1284, 1170, 1131, 745, 698 cm^{-1}. UV (MeOH, nm, (log ε)): 260 (3.019), 209 (4.193). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.73 (dd, J = 14.2, 2.2 Hz, 1H, 3-H), 1.91 (ddd, J = 12.3, 9.6, 2.2 Hz, 1H, 5-H), 1.94 (d, J = 17.0 Hz, 1H, CH–CO), 2.00–2.09 (m, 3H, 3-H, 5-H, 8-H), 2.17 (ddd, J = 12.0, 9.9, 3.0 Hz, 1H, 8-H), 2.25 (s, 3H, NCH_3), 2.25–2.34 (m, 4H, 2′-H, 6′-H), 2.34–2.42 (m, 4H, 3′-H, 5′-H), 2.39 (s, 6H, $N(CH_3)_2$), 2.61 (d, J = 17.0 Hz, 1H, CH–CO), 2.79 (d, J = 4.4 Hz, 1H, 1-H), 3.01 (t, J = 9.6 Hz, 1H, 6-H), 3.17 (t, J = 9.9 Hz, 1H, 7-H), 5.31 (dd, J = 9.0, 4.4 Hz, 1H, 2-H), 7.08–7.41 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 31.06 (C-8), 31.17 (C-5), 33.90 (C-7), 34.64 (C-3), 38.40 ($N(CH_3)_2$), 38.66 (C-6), 40.01 (C-1), 45.97 (NCH_3), 52.68 (C-2′, C-6′), 54.75 (C-3′, C-5′), 56.13 (C-4), 58.06 (CH_2–CO), 72.96 (C-2), 125.37, 126.41, 126.50, 127.36, 128.12, 128.52 (aromatic C), 142.73, 144.62 (aromatic C_q), 169.78 (COO). Anal. Calcd for $C_{32}H_{43}N_3O_2$: C, 76.61; H, 8.64; N, 8.38. Found: C, 76.28; H, 8.69; N, 8.19.

5.2.2.2. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 2-(4′-methylpiperazin-1′-yl)acetate (9b). Compound **8b** (0.22 g, 0.53 mmol) was dissolved in excess of *N*-methylpiperazine (2 mL) yielding **9b** (0.24 g, 0.49 mmol, 93%) as an oily residue. A small amount was purified for analytical purposes by CC over silica gel eluting with CH_2Cl_2/MeOH (49:1). IR (KBr): 2960, 2935, 2871, 2796, 1750, 1602, 1497, 1447, 1295, 1283, 1169, 1146, 749, 735, 698 cm^{-1}. UV (MeOH, nm, (log ε)): 262 (3.022), 209 (4.130). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.74 (dd, J = 14.1, 2.0 Hz, 1H, 3-H), 1.81–1.85 (m, 4H, $(CH_2)_2$), 1.94 (d, J = 17.0 Hz, 1H, CH–CO), 1.97–2.10 (m, 2H, 5-H), 2.12–2.21 (m, 3H, 3-H, 8-H), 2.24 (s, 3H, NCH_3), 2.27–2.43 (m, 8H, 2′-H, 3′-H, 5′-H, 6′-H), 2.60 (d, J = 17.0 Hz, 1H, CH–CO), 2.74–2.83 (m, 5H, 1-H, $N(CH_2)_2$), 3.04 (t, J = 9.4 Hz, 1H, 6-H), 3.18 (t, J = 9.8 Hz, 1H, 7-H), 5.31 (dd, J = 8.9, 4.4 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.53 ($(CH_2)_2$), 31.66 (C-5), 32.08 (C-8), 33.84 (C-7), 35.59 (C-3), 38.76 (C-6), 40.36 (C-1), 45.52 ($N(CH_2)_2$), 45.96 (NCH_3), 52.65 (C-2′, C-6′), 54.73 (C-3′, C-5′), 54.81 (C-4), 58.04 (CH_2–CO), 72.98 (C-2), 125.31, 126.37, 126.54, 127.41, 128.08, 128.49 (aromatic C), 142.79, 144.69 (aromatic C_q), 169.77 (COO). Anal. Calcd for $C_{31}H_{41}N_3O_2$: C, 76.35; H, 8.47; N, 8.62. Found: C, 76.20; H, 8.41; N, 8.43.

5.2.2.3. (2*SR*,6*RS*,7*RS*)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 2-(4′-methylpiperazin-1′-yl)acetate (9c). Compound **8c** (0.36 g, 0.83 mmol) was dissolved in excess of *N*-methylpiperazine (2 mL) yielding **9c** (0.32 g, 0.63 mmol, 76%) as an oily residue which was converted to its hydrochloride and recrystallized. Mp 194 °C (acetone). IR (KBr): 3422, 2949, 2664, 1746, 1600, 1497, 1450, 1287, 1224, 1181, 1129, 753, 701 cm^{-1}. UV (MeOH, nm, (log ε)): 258 (3.947), 209 (4.261). ^{1}H NMR (base, $CDCl_3$, 400 MHz) δ(ppm) 1.45–1.52 (m, 2H, CH_2), 1.63–1.69 (m, 4H, $2CH_2$), 1.75 (d, J = 14.0 Hz, 1H, 3-H), 1.89–1.94 (m, 1H, 5-H), 1.93 (d, J = 17.1 Hz, 1H, CH–CO), 2.03–2.12 (m, 3H, 3-H, 5-H, 8-H), 2.17–2.23 (m, 1H, 8-H), 2.24 (s, 3H, NCH_3), 2.25–2.34 (m, 4H, 2′-H, 6′-H), 2.31–2.42 (m, 4H, 3′-H, 5′-H), 2.59 (d, J = 17.1 Hz, 1H, CH–CO), 2.61–2.74 (m, 4H, $N(CH_2)_2$), 2.79 (d, J = 4.4 Hz, 1H, 1-H), 2.98 (t, J = 9.3 Hz, 1H, 6-H), 3.14 (t, J = 9.9 Hz, 1H, 7-H), 5.30 (dd, J = 8.9, 4.4 Hz, 1H, 2-H), 7.06–7.41 (m, 10H, aromatic H). ^{13}C NMR (base, $CDCl_3$, 100 MHz) δ(ppm) 24.94 (CH_2), 26.78 ($2CH_2$), 31.44 (C-5), 31.93 (C-8), 33.97 (C-7), 34.92 (C-3), 38.66 (C-6), 40.06 (C-1), 45.97 (NCH_3), 46.86 ($N(CH_2)_2$), 52.66 (C-2′, C-6′), 54.76 (C-3′, C-5′), 56.73 (C-4), 58.05 (CH_2–CO), 73.04 (C-2), 125.30, 126.35, 126.49, 127.38, 128.09, 128.49 (aromatic C), 142.84, 144.78 (aromatic C_q), 169.77 (COO). Anal. Calcd for $C_{29}H_{39}N_3O_2$: C, 75.45; H, 8.52; N, 9.10. Found: C, 75.42; H, 8.53; N, 9.12.

5.2.3. (2*SR*,6*RS*,7*RS*)-(±)-4-Dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl amines (5a–5c)

Their preparation has already been reported.[11]

5.2.4. General procedure for the synthesis of (2*SR*,6*RS*,7*RS*)-(±)-*N*-(4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl)-ω-chloroacylamides (11a–11c, 12a–12c)

The bicyclo-octanamine **5a–5c** and triethylamine were dissolved in dry CH_2Cl_2 (20 mL) and cooled with an ice-bath. Under stirring the ω-chloroacyl chloride was added. After 30 min the ice-bath was removed and the reaction batch was stirred over night at room temperature in an atmosphere of Ar. After that it was shaken with 1 N NaOH and the aqueous phase was exhaustively extracted with CH_2Cl_2. The organic phase was washed with water until the aqueous phase reacted neutral, dried over sodium sulfate, filtered and the solvent was evaporated in vacuo.

5.2.4.1. (2*RS*,6RS,7RS)-(±)-*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-2-chloroacetamide (11a). Compound **5a**

(0.24 g, 0.73 mmol) and triethylamine (0.11 g, 1.1 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.12 g, 1.1 mmol) compound **11a** (0.25 g, 0.63 mmol, 86%) as an oily residue.

5.2.4.2. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)-2-chloroacetamide (11b). Compound **5b** (0.38 g, 1.11 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.19 g, 1.66 mmol) compound **11b** (0.37 g, 0.88 mmol, 79%) as an oily residue.

5.2.4.3. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)-2-chloroacetamide (11c). Compound **5c** (0.40 g, 1.11 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.19 g, 1.66 mmol) compound **11c** (0.41 g, 0.93 mmol, 85%) as an oily residue.

5.2.4.4. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-3-chloropropionamide (12a). Compound **5a** (0.24 g, 0.73 mmol) and triethylamine (0.11 g, 1.1 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.14 g, 1.1 mmol) compound **12a** (0.22 g, 0.55 mmol, 74%) as an oily residue.

5.2.4.5. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)-3-chloropropionamide (12b). Compound **5b** (0.38 g, 1.11 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.21 g, 1.66 mmol) compound **12b** (0.37 g, 0.85 mmol, 77%) as an oily residue.

5.2.4.6. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)-3-chloropropionamide (12c). Compound **5c** (0.40 g, 1.11 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.21 g, 1.66 mmol) compound **12c** (0.40 g, 0.90 mmol, 81%) as an oily residue.

5.2.5. General procedure for the synthesis of (2*SR*,6*RS*,7*RS*)-(±)-*N*-(4-dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-ω-(4′-methylpiperazin-1′-yl)amides (13a–13c, 14a–14c)

The corresponding ω-chloroalkanoate **11a–11c**, **12a–12c** and a catalytical 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, washed with water until the aqueous phase reacted neutral, dried over sodium sulfate, filtered and finally the solvent was removed in vacuo.

5.2.5.1. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (13a). The reaction of compound **11a** (0.25 g, 0.63 mmol) with *N*-methylpiperazine (2.5 mL) and a catalytical amount of KI gave **13a** (0.26 g, 0.56 mmol, 90%). IR (KBr) 3057, 3025, 2937, 2869, 2821, 2789, 1675, 1600, 1497, 1446, 1291, 1167, 1138, 1014, 745, 698 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 229 (3.524). ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.34 (br dd, J = 13.6, 2.5 Hz, 1H, 3-H), 1.79 (ddd, J = 12.4, 9.9, 2.3 Hz, 1H, 8-H), 1.85 (ddd, J = 12.8, 9.3, 2.5 Hz, 1H, 5-H), 1.96–2.04 (m, 2H, 2′-H, 6′-H), 2.09 (ddd, J = 12.8, 9.3, 2.4 Hz, 1H, 5-H), 2.17–2.35 (m, 7H, 2′-H, 3-H, 3′-H, 5′-H, 6′-H), 2.24 (s, 3H, NCH_3), 2.26 (d, J = 16.2 Hz, 1H, CH–CO), 2.40 (s, 6H, $N(CH_3)_2$), 2.43 (ddd, J = 12.4, 9.9, 3.1 Hz, 1H, 8-H), 2.55 (d, J = 16.2 Hz, 1H, CH–CO), 2.83 (br d, J = 3.5 Hz, 1H, 1-H), 3.14 (t, J = 9.3 Hz, 1H, 6-H), 3.21 (t, J = 9.9 Hz, 1H, 7-H), 4.38–4.45 (m, 1H, 2-H), 6.81 (d, J = 8.1 Hz, 1H, NH), 7.10–7.40 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 29.16 (C-5), 33.65 (C-7), 33.81 (C-8), 36.94 (C-3), 38.34 ($N(CH_3)_2$), 38.58 (C-1), 40.33 (C-6), 45.91 (NCH_3), 48.15 (C-2), 52.85 (C-2′, C-6′), 54.85 (C-3′, C-5′), 56.30 (C-4), 60.86 (CH_2–CO), 125.68, 126.08, 126.30, 127.28, 128.44, 128.48 (aromatic C), 143.03, 144.54 (aromatic C_q), 169.44 (CO). HRMS (MALDI): calcd for $C_{29}H_{40}N_4O[MH^+]$: 461.3280; found: 461.3320.

5.2.5.2. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (13b). The reaction of compound **11b** (0.37 g, 0.88 mmol) with *N*-methylpiperazine (2.5 mL) and a catalytical amount of KI gave **13b** (0.38 g, 0.78 mmol, 90%). IR (KBr) 3049, 2937, 2868, 2823, 2793, 1682, 1598, 1517, 1497, 1445, 1290, 1169, 1136, 766, 754, 700 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 261 (3.028), 228 (3.545). ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.41 (br d, J = 13.4 Hz, 1H, 3-H), 1.83–1.89 (m, 4H, $(CH_2)_2$), 1.92–2.03 (m, 4H, 2′-H, 5-H, 6′-H, 8-H), 2.11 (ddd, J = 13.5, 9.3, 2.2 Hz, 1H, 5-H), 2.18–2.32 (m, 6H, 2′-H, 3′-H, 5′-H, 6′-H), 2.24 (d, J = 16.1 Hz, 1H, CH–CO), 2.25 (s, 3H, NCH_3), 2.36 (ddd, J = 13.4, 10.9, 3.4 Hz, 1H, 3-H), 2.42 (ddd, J = 13.2, 9.7, 3.4 Hz, 1H, 8-H), 2.54 (d, J = 16.1 Hz, 1H, CH–CO), 2.76–2.87 (m, 4H, $N(CH_2)_2$), 3.17 (t, J = 9.3 Hz, 1H, 6-H), 3.22 (t, J = 9.7 Hz, 1H, 7-H), 4.37–4.44 (m, 1H, 2-H), 6.75 (d, J = 8.2 Hz, 1H, NH), 7.09–7.41 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.56 ($(CH_2)_2$), 29.75 (C-5), 33.56 (C-7), 34.66 (C-8), 37.58 (C-3), 39.07 (C-1), 40.52 (C-6), 45.50 ($N(CH_2)_2$), 45.89 (NCH_3), 48.27 (C-2), 52.87 (C-2′, C-6′), 54.75 (C-3′, C-5′), 55.21 (C-4), 60.93 (CH_2–CO), 125.61, 126.12, 126.25, 127.31, 128.40, 128.44 (aromatic C), 143.38, 144.56 (aromatic C_q), 169.47 (CO). HRMS (MALDI): calcd for $C_{31}H_{42}N_4O[MH^+]$: 487.3437; found: 487.3468.

5.2.5.3. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (13c). The reaction of compound **11c** (0.41 g, 0.93 mmol) with *N*-methylpiperazine (2.5 mL) and a catalytical amount of KI gave **13c** (0.40 g, 0.80 mmol, 86%). IR (KBr) 3057, 3025, 2933, 2844, 2793, 1676, 1600, 1497, 1446, 1292, 1167, 1138, 1014, 744, 698 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 261 (3.070), 230 (3.627). ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.38 (br d, J = 13.5 Hz, 1H, 3-H), 1.47–1.52 (m, 2H, CH_2), 1.64–1.70 (m, 4H, $2CH_2$), 1.82 (ddd, J = 12.8, 9.9, 2.2 Hz, 1H, 8-H), 1.89 (ddd, J = 13.0, 9.4, 2.2 Hz, 1H, 5-H), 1.96–2.04 (m, 2H, 2′-H, 6′-H), 2.12 (ddd, J = 13.0, 9.4, 2.3 Hz, 1H, 5-H), 2.17–2.34 (m, 6H, 2′-H, 3′-H, 5′-H, 6′-H), 2.24 (d, J = 16.1 Hz, 1H, CH–CO), 2.25 (s, 3H, NCH_3), 2.32 (ddd, J = 13.5, 10.4, 3.3 Hz, 1H, 3-H), 2.44 (ddd, J = 12.8, 9.9, 3.3 Hz, 1H, 8-H), 2.54 (d, J = 16.1 Hz, 1H, CH–CO), 2.62–2.74 (m, 4H, $N(CH_2)_2$), 2.83 (d, J = 3.8 Hz, 1H, 1-H), 3.11 (t, J = 9.9 Hz, 1H, 6-H), 3.18 (t, J = 9.4 Hz, 1H, 7-H), 4.37–4.44 (m, 1H, 2-H), 6.76 (d, J = 8.1 Hz, 1H, NH), 7.09–7.40 (m, 10H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 24.84 (CH_2), 26.72 ($2CH_2$), 30.20 (C-5), 33.73 (C-8), 34.03 (C-7), 36.72 (C-3), 38.69 (C-1), 40.36 (C-6), 45.90 (NCH_3), 46.74 ($N(CH_2)_2$), 48.37 (C-2), 52.87 (C-2′, C-6′), 54.71 (C-3′, C-5′), 56.91 (C-4), 60.97 (CH_2–CO), 125.62, 126.11, 126.23, 127.29, 128.39, 128.42 (aromatic C), 143.35, 144.64 (aromatic C_q), 169.51 (CO). HRMS (MALDI): calcd for $C_{32}H_{44}N_4O[MH^+]$: 501.3593; found: 501.3650.

5.2.5.4. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (14a). The reaction of compound **12a** (0.22 g, 0.55 mmol) with *N*-methylpiperazine (2.5 mL) and a catalytical amount of KI gave **14a** (0.19 g, 0.40 mmol, 75%). IR (KBr) 3054, 2946, 2864, 2820, 2793, 2775, 1664, 1600, 1539, 1497, 1459, 1291, 1161, 1013, 744, 696 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 260 (2.939), 229 (3.535). ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.43 (dd, J = 13.8, 2.0 Hz, 1H, 3-H), 1.67–1.74 (m, 2H, CH–CO, NCH), 1.79 (ddd, J = 12.6, 9.9, 2.4 Hz, 1H, 8-H), 1.89 (ddd, J = 12.7, 9.5, 2.4 Hz, 1H, 5-H), 1.97–2.06 (m, 1H, CH–CO), 2.00–2.09 (m, 4H, 2′-H, 6′-H), 2.09–2.19 (m, 3H, 3-H, 5-H, NCH), 2.26 (s, 3H, NCH_3), 2.23–2.43 (m, 5H, 3′-H, 5′-H, 8-H), 2.40 (s, 6H, $N(CH_3)_2$), 3.06 (d, J = 3.7 Hz, 1H, 1-H), 3.14

(t, J = 9.5 Hz, 1H, 6-H), 3.21 (t, J = 9.9 Hz, 1H, 7-H), 4.40 (br ddd, J = 12.4, 7.3, 3.7 Hz, 1H, 2-H), 7.11–7.39 (m, 10H, aromatic H), 7.89 (d, J = 7.3 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 31.53 (CH_2–CO), 33.36 (C-5), 33.63 (C-8), 34.20 (C-3), 36.16 (C-1), 38.70 ($N(CH_3)_2$), 39.90 (C-6), 46.06 (NCH_3), 48.36 (C-2), 52.04 (C-2′,C-6′), 52.95 (NCH_2), 55.26 (C-3′, C-5′), 56.36 (C-4), 125.56, 125.97, 126.20, 127.31, 128.15, 128.43 (aromatic C), 143.40, 145.34 (aromatic C_q), 171.43 (CO). HRMS (MALDI): calcd for $C_{30}H_{42}N_4O[MH^+]$: 475.3437; found: 475.3489.

5.2.5.5. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]oct-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (14b). The reaction of compound **12b** (0.37 g, 0.85 mmol) with *N*-methylpiperazine (2.5 mL) and a catalytical amount of KI gave **14b** (0.30 g, 0.61 mmol, 71%). IR (KBr) 3048, 2943, 2796, 1660, 1599, 1539, 1496, 1444, 1288, 1162, 1137, 754, 700 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 260 (2.956), 229 (3.569). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.46 (br d, J = 13.5 Hz, 1H, 3-H), 1.67–1.75 (m, 1H, CH–CO, NCH), 1.82–1.91 (m, 5H, 8-H, $(CH_2)_2$), 1.95–2.06 (m, 2H, 5-H, CH–CO), 2.01–2.11 (m, 4H, 2′-H, 6′-H), 2.11–2.18 (m, 2H, 5-H, NCH), 2.18–2.44 (m, 5H, 3′-H, 5′-H), 2.27 (s, 3H, NCH_3), 2.44 (ddd, J = 12.4, 9.9, 3.0 Hz, 1H, 8-H), 2.77–2.86 (m, 4H, $N(CH_2)_2$), 3.04 (t, J = 9.4 Hz, 1H, 6-H), 3.23 (t, J = 9.9 Hz, 1H, 7-H), 4.37–4.44 (m, 1H, 2-H), 7.10–7.39 (m, 10H, aromatic H), 7.87 (d, J = 6.8 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.49 ($(CH_2)_2$), 31.54 (CH_2–CO), 33.56 (C-7), 34.08 (C-8), 34.23 (C-5), 35.29 (C-3), 36.62 (C-1), 39.97 (C-6), 45.84 ($N(CH_2)_2$), 46.03 (NCH_3), 48.37 (C-2), 52.00 (C-2′, C-6′), 52.89 (NCH_2), 55.22 (C-4, C-3′, C-5′), 125.54, 126.00, 126.18, 127.36, 128.14, 128.41 (aromatic C), 143.37, 145.36 (aromatic C_q), 171.34 (CO). HRMS (MALDI): calcd for $C_{32}H_{44}N_4O[MH^+]$: 501.3593; found: 501.3608.

5.2.5.6. (2*RS*,6*RS*,7*RS*)-(±)-*N*-(6,7-Diphenyl-4-piperidinobicyclo[2.2.2]oct-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (14c). The reaction of compound **12c** (0.40 g, 0.90 mmol) with *N*-methylpiperazine (2 mL) and a catalytical amount of KI gave **14c** (0.35 g, 0.69 mmol, 76%). A small amount was purified for analytical purposes by CC over silica gel eluting with CH_2Cl_2/MeOH (9:1). IR (KBr) 3050, 2933, 2795, 1660, 1600, 1542, 1496, 1446, 1289, 1161, 1013, 760, 747, 700 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 260 (2.877), 229 (3.593). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.45–1.54 (m, 3H, 3-H, CH_2), 1.63–1.72 (m, 6H, CH–CO, NCH, $2CH_2$), 1.82 (br dd, J = 12.5, 10.00 Hz, 1H, 8-H), 1.91 (br dd, J = 12.2, 9.4 Hz, 1H, 5-H), 1.98–2.19 (m, 8H, 2′-H, 3-H, 5-H, 6′-H, CH–CO, NCH), 2.27 (s, 3H, NCH_3), 2.45 (br dd, J = 12.5, 10.0 Hz, 1H, 8-H), 2.63–2.78 (m, 4H, $N(CH_2)_2$, 3.07 (d, J = 3.9 Hz, 1H, 1-H), 3.11 (t, J = 9.4 Hz, 1H, 6-H), 3.20 (t, J = 10.0 Hz, 1H, 7-H), 4.39 (ddd, J = 10.1, 6.6, 3.9 Hz, 1H, 2-H), 7.10–7.38 (m, 10H, aromatic H), 7.96 (d, J = 6.6 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 24.94 (CH_2), 26.66 ($2CH_2$), 31.46 (CH_2–CO), 33.33 (C-5), 33.69 (C-7), 34.63 (C-3), 34.83 (C-8), 36.14 (C-1), 39.83 (C-6), 46.02 (NCH_3), 47.28 ($N(CH_2)_2$), 48.31 (C-2), 51.97 (C-2′, C-6′), 52.86 (NCH_2), 55.19 (C-3′, C-5′), 56.58 (C-4), 125.52, 125.97, 126.16, 127.31, 128.11, 128.39 (aromatic C), 143.39, 145.48 (aromatic C_q), 171.35 (CO). HRMS (MALDI): calcd for $C_{33}H_{46}N_4O[MH^+]$: 515.3750; found: 515.3723.

5.2.6. (7*RS*,8*RS*)-(±)-5-Dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]nonanes (6a–6c)

Their preparation has already been reported.[12]

5.2.7. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-*N*-(5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-ω-chloroamides (16a–16c, 17a–17c)

The bicyclo-nonanamine **6a–6c** and triethylamine were dissolved in dry CH_2Cl_2 (20 mL) and cooled with an ice-bath. Under stirring the ω-chloroacyl chloride was added. After 30 min the ice-bath was removed and the reaction batch was stirred over night at room temperature in an atmosphere of Ar. After that it was shaken with 1 N NaOH and the aqueous phase was exhaustively extracted with CH_2Cl_2. The organic phase was washed with water until the aqueous phase reacted neutral, dried over sodium sulfate, filtered and the solvent was evaporated in vacuo.

5.2.7.1. (7*RS*,8*RS*)-(±)-*N*-(5-Dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-2-chloroacetamide (16a). Compound **6a** (0.34 g, 1.06 mmol) and triethylamine (0.16 g, 1.50 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.18 g, 1.50 mmol) compound **16a** (0.33 g, 0.83 mmol, 78%) as an oily residue.

5.2.7.2. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-2-chloroacetamide (16b). Compound **6b** (0.42 g, 1.21 mmol) and triethylamine (0.18 g, 1.73 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.20 g, 1.73 mmol) compound **16b** (0.39 g, 0.92 mmol, 76%) as an oily residue.

5.2.7.3. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-2-chloroacetamide (16c). Compound **6c** (0.38 g, 1.07 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with chloroacetyl chloride (0.19 g, 1.66 mmol) compound **16c** (0.40 g, 0.91 mmol, 85%) as an oily residue.

5.2.7.4. (7*RS*,8*RS*)-(±)-*N*-(5-Dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-3-chloropropionamide (17a). Compound **6a** (0.34 g, 1.06 mmol) and triethylamine (0.16 g, 1.59 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.20 g, 1.59 mmol) compound **17a** (0.28 g, 0.67 mmol, 63%) as an oily residue.

5.2.7.5. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-3-chloropropionamide (17b). Compound **6b** (0.40 g, 1.15 mmol) and triethylamine (0.18 g, 1.73 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.22 g, 1.73 mmol) compound **17b** (0.27 g, 0.62 mmol, 51%) as an oily residue.

5.2.7.6. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-3-chloropropionamide (17c). Compound **6c** (0.40 g, 1.11 mmol) and triethylamine (0.17 g, 1.66 mmol) in dry CH_2Cl_2 gave with 3-chloropropionyl chloride (0.19 g, 1.66 mmol) compound **17c** (0.40 g, 0.88 mmol, 80%) as an oily residue.

5.2.8. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-*N*-(5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-ω-(4′-methylpiperazin-1′-yl)amides (18a–18c, 19a–19c)

The corresponding ω-chloroamide **16a**–**16c**, **17a–17c** and a catalytical 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 sodium sulfate, filtered and finally the solvent was removed in vacuo.

5.2.8.1. (7*RS*,8*RS*)-(±)-*N*-(5-Dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (18a). The reaction of compound **16a** (0.33 g, 0.83 mmol) with *N*-methylpiperazine (1.8 mL) and a catalytical amount of KI gave after work-up **18a** (0.30 g, 0.65 mmol, 79%) as an oily residue. IR (KBr) 3059, 3026, 2935, 2873, 2792, 1637, 1601, 1496, 1449, 1291, 1164, 1138, 1012, 752, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 259 (3.207), 230 (3.659). Compound **(*E*)-18a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.76 (br t, J = 12.1 Hz, 1H, 6-H), 1.94–2.02 (m,

1H, 4-H), 2.06 (s, 3H, NCH_3), 2.05–2.20 (m, 5H, 2′H, 4-H, 6′-H, 9-H), 2.25–2.32 (m, 1H, 6-H), 2.29 (s, 6H, $N(CH_3)_2$), 2.37–2.55 (m, 6H, 2′-H, 3′-H, 5′-H, 6′-H), 2.45 (s, 2H, CH_2CO), 3.24 (br t, J = 9.5 Hz, 1H, 7-H), 3.34–3.47 (m, 2H, 3-H, 8-H), 4.38 (ddd, J = 14.8, 5.1, 2.6 Hz, 1H, 3-H), 4.56 (d, J = 2.7 Hz, 1H, 1-H), 7.16–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 29.94 (C-4), 32.96 (C-9), 38.05 ($N(CH_3)_2$), 38.83 (C-6), 41.30 (C-3), 41.60 (C-8), 45.77 ($N(CH_2)_2$), 46.09 (C-7), 52.91 (C-2′, C-6′), 54.06 (C-3′, C-5′), 57.36 (C-5), 59.64 (C-1), 61.75 (CH_2CO), 126.68, 126.69, 127.09, 127.70, 128.96 (aromatic C), 142.64, 145.00 (aromatic C_q), 169.49 (CO). Compound **(*Z*)-18a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.76–1.83 (m, 1H, 4-H), 1.89–1.96 (m, 1H, 4-H), 2.03–2.21 (m, 4H, 2′H, 6-H, 6′-H, 9-H), 2.27 (s, 3H, NCH_3), 2.30–2.37 (m, 2H, 6-H, 9-H), 2.34 (s, 6H, $N(CH_3)_2$), 2.37–2.55 (m, 6H, 2′-H, 3′-H, 5′-H, 6′-H), 3.12 (ddd, J = 14.3, 13.9, 3.3 Hz, 1H, 3-H), 3.19 (s, 2H, CH_2CO), 3.24 (br t, J = 9.5 Hz, 1H, 7-H), 3.26–3.29 (m, 1-H, 8-H), 3.95–4.04 (m, 1H, 3-H), 5.04 (d, J = 3.4 Hz, 1H, 3-H), 7.14–7.39 (m, 8H, aromatic H), 7.57 (d, J = 7.6 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 30.80 (C-4), 34.94 (C-8), 35.20 (C-6), 35.79 (C-9), 38.01 ($N(CH_3)_2$), 42.79 (C-3), 45.38 (C-7), 46.02 ($N(CH_2)_2$), 53.15 (C-2′, C-6′), 55.01 (C-3′, C-5′), 56.09 (C-1), 57.86 (C-5), 62.27 (CH_2CO), 126.20, 126.55, 126.57, 127.74, 128.38, 128.53 (aromatic C), 143.00, 143.37 (aromatic C_q), 168.30 (CO). HRMS (MALDI): calcd for $C_{29}H_{40}N_4O[MH^+]$: 461.3280; found: 461.3309.

5.2.8.2. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (18b). The reaction of compound **16b** (0.39 g, 0.92 mmol) with *N*-methylpiperazine (2 mL) and a catalytical amount of KI gave after work-up **18b** (0.30 g, 0.62 mmol, 67%) as an oily residue. IR (KBr) 3058, 3026, 2935, 2795, 1637, 1602, 1496, 1447, 1291, 1164, 1136, 748, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 260 (3.176), 230 (3.712). Compound **(*E*)-18b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.76–1.82 (m, 4H, $(CH_2)_2$), 1.85–1.94 (m, 1H, 6-H), 1.99–2.33 (m, 6H, 2′-H, 4-H, 6′-H, 9-H), 2.07 (s, 3H, NCH_3), 2.28–2.58 (m, 7H, 2′H, 3′-H, 5′-H, 6-H, 6′-H), 2.46 (s, 2H, CH_2CO), 2.69–2.85 (m, 4H, $N(CH_2)_2$), 3.25 (br t, J = 9.6 Hz, 1H, 7-H), 3.38–3.51 (m, 2H, 3-H, 8-H), 4.34–4.41 (m, 1H, 3-H), 4.55 (d, J = 2.6 Hz, 1H, 1-H), 7.16–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.56 ($(CH_2)_2$), 31.19 (C-4), 33.81 (C-9), 39.23 (C-6), 41.08 (C-3), 41.32 (C-8), 45.40 ($N(CH_2)_2$), 45.75 (NCH_3), 46.04 (C-7), 52.89 (C-2′, C-6′), 54.05 (C-3′, C-5′), 56.65 (C-5), 59.75 (C-1), 61.70 (CH_2CO), 126.52, 126.70, 127.03, 127.66, 128.92, 128.93 (aromatic C), 142.54, 144.91 (aromatic C_q), 169.45 (CO). Compound **(*Z*)-18b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.79–1.85 (m, 4H, $(CH_2)_2$), 1.86–1.98 (m, 2H, 4-H), 1.99–2.58 (m, 12H, 2′-H, 3′-H, 5′-H, 6-H, 6′-H, 9-H), 2.27 (s, 3H, NCH_3), 2.69–2.85 (m, 4H, $N(CH_2)_2$), 3.10–3.19 (m, 1H, 3-H), 3.19 (s, 2H, CH_2CO), 3.25 (br t, J = 9.6 Hz, 1H, 7-H), 3.31–3.40 (m, 1H, 8-H), 3.96–4.03 (m, 1H, 3-H), 5.04 (d, J = 3.2 Hz, 1H, 3-H), 7.12–7.38 (m, 8H, aromatic H), 7.58 (d, J = 7.8 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.60 ($(CH_2)_2$), 32.43 (C-4), 34.70 (C-8), 35.84 (C-6), 36.02 (C-9), 42.69 (C-3), 45.34 (C-7), 45.35 ($N(CH_2)_2$), 45.98 (NCH_3), 53.11 (C-2′, C-6′), 54.98 (C-3′, C-5′), 57.33 (C-5), 56.17 (C-1), 62.24 (CH_2CO), 126.16, 126.66, 126.70, 127.76, 128.28, 128.51 (aromatic C), 142.84, 143.34 (aromatic C_q), 168.21 (CO). HRMS (MALDI): calcd for $C_{31}H_{42}N_4O[MH^+]$: 487.3437; found: 487.3461.

5.2.8.3. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-piperidinobicyclo-[3.2.2]non-2-yl)-2-(4′-methylpiperazin-1′-yl)acetamide (18c). The reaction of compound **16c** (0.39 g, 0.91 mmol) with *N*-methylpiperazine (2.1 mL) and a catalytical amount of KI gave after work-up **18c** (0.32 g, 0.70 mmol, 70%) as an oily residue. A small amount was purified for analytical purposes by CC over silica gel eluting with CH_2Cl_2/MeOH (9:1). IR (KBr) 3059, 3026, 2932, 2841, 2794, 1638, 1601, 1496, 1439, 1291, 1282, 1164, 1013, 759, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 259 (2.914), 230 (3.704). Compound **(*E*)-18c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.41–1.50 (m, 2H, CH_2), 1.53–1.68 (m, 4H, $2CH_2$), 1.71–1.79 (m, 1H, 6-H), 1.98–2.03 (m, 1H, 4-H), 2.04 (s, 3H, NCH_3), 2.04–2.20 (m, 5H, 2′H, 4-H, 6′-H, 9-H), 2.20–2.28 (m, 1H, 6-H), 2.33–2.48 (m, 6H, 2′-H, 3′-H, 5′-H, 6′-H), 2.45 (s, 2H, CH_2CO), 2.48–2.68 (m, 4H, $N(CH_2)_2$), 3.14–3.24 (m, 1H, 7-H), 3.30–3.39 (m, 1H, 3-H), 3.42 (td, J = 9.7, 2.6 Hz, 1H, 8-H), 4.35–4.43 (m, 1H, 3-H), 4.56 (d, J = 2.6 Hz, 1H, 1-H), 7.16–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 25.00 (CH_2), 26.74 ($2CH_2$), 31.17 (C-4), 32.96 (C-9), 38.86 (C-6), 41.60 (C-3), 41.93 (C-8), 45.77 (NCH_3), 46.20 (C-7), 46.48 ($N(CH_2)_2$), 52.91 (C-2′, C-6′), 54.05 (C-3′, C-5′), 57.82 (C-5), 59.62 (C-1), 61.81 (CH_2CO), 126.60, 126.64, 127.04, 127.68, 128.93 (aromatic C), 142.75, 145.19 (aromatic C_q), 169.47 (CO). Compound **(*Z*)-18c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.41–1.50 (m, 2H, CH_2), 1.53–1.68 (m, 4H, $2CH_2$), 1.78–1.84 (m, 1H, 4-H), 1.92–2.01 (m, 2H, 4-H, 6-H), 2.04–2.20 (m, 3H, 2′-H, 6′-H, 9-H), 2.27 (s, 3H, NCH_3), 2.28–2.48 (m, 8H, 2′-H, 3′-H, 5′-H, 6-H, 6′-H, 9-H), 2.48–2.68 (m, 4H, $N(CH_2)_2$), 3.11–3.22 (m, 2H, 3-H, 7-H), 3.18 (s, 2H, CH_2CO), 3.26–3.36 (m, 1H, 8-H), 3.95–4.02 (m, 1H, 3-H), 5.08 (d, J = 2.8 Hz, 1H, 1-H), 7.12–7.39 (m, 8H, aromatic H), 7.57 (d, J = 7.8 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 25.07 (CH_2), 26.83 ($2CH_2$), 31.99 (C-4), 35.03 (C-6), 35.41 (C-8), 35.78 (C-9), 43.00 (C-3), 45.72 (C-7), 46.04 (NCH_3), 46.37 ($N(CH_2)_2$), 53.16 (C-2′, C-6′), 55.03 (C-3′, C-5′), 56.00 (C-1), 58.33 (C-5), 62.28 (CH_2CO), 126.17, 126.48, 126.64, 127.74, 128.36, 128.48 (aromatic C), 143.10, 143.52 (aromatic C_q), 168.25 (CO). HRMS (MALDI): calcd for $C_{32}H_{44}N_4O[MH^+]$: 501.3593; found: 501.3568.

5.2.8.4. (7*RS*,8*RS*)-(±)-*N*-(5-Dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (19a). The reaction of compound **17a** (0.28 g, 0.67 mmol) with *N*-methylpiperazine (1.5 mL) and a catalytical amount of KI gave after work-up **19a** (0.26 g, 0.54 mmol, 80%) as an oily residue. IR (KBr) 3026, 2936, 2874, 2791, 1636, 1496, 1448, 1283, 1163, 1012, 753, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 259 (3.141), 230 (3.668). Compound **(*E*)-19a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.69–1.82 (m, 1H, CH–CO), 1.83–1.98 (m, 2H, 4-H, 6-H), 2.02–2.21(m, 9H, 2′H, 4-H, 6′-H, 9-H, CH–CO, NCH), 2.21 (s, 3H, NCH_3), 2.22–2.35 (m, 5H, 2′-H, 5′-H, 6-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.38–2.48 (m, 1H, NCH), 3.26 (t, J = 9.9 Hz, 1H, 7-H), 3.35 (td, J = 13.5, 5.0 Hz, 1H, 3-H), 3.44 (td, J = 9.9, 2.8 Hz, 1H, 8-H), 3.97 (d, J = 2.8 Hz, 1H, 1-H), 4.42–4.48 (m, 1H, 3-H), 7.13–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 29.38 (C-4), 30.79 (CH_2–CO), 33.58 (C-9), 37.32 (C-6), 38.01 ($N(CH_3)_2$), 40.73 (C-3), 40.83 (C-8), 45.95 (NCH_3), 46.68 (C-7), 52.75 (C-2′, C-6′), 53.83 (NCH_2), 54.89 (C-3′, C-5′), 57.26 (C-5), 61.30 (C-1), 126.81, 127.06, 127.12, 127.70, 128.93, 129.17 (aromatic C), 142.24, 144.26 (aromatic C_q), 171.15 (CO). Compound **(*Z*)-19a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.71–1.77 (m, 1H, 4-H), 1.90–1.97 (m, 1H, 4-H), 1.98–2.17 (m, 2H, 6-H, 9-H), 2.28 (s, 3H, NCH_3), 2.33 (s, 6H, $N(CH_3)_2$), 2.33–2.66 (m, 12H, 2′-H, 3′-H, 5′-H, 6-H, 6′-H, 9-H, CH_2–CO), 2.67–2.79 (m, 2H, NCH_2), 3.10 (ddd, J = 13.7, 13.3, 3.3 Hz, 1H, 3-H), 3.25 (t, J = 9.2 Hz, 1H, 7-H), 3.26–3.36 (m, 1H, 8-H), 3.76–3.84 (m, 1H, 3-H), 5.08 (d, J = 3.1 Hz, 1H, 1-H), 7.13–7.38 (m, 8H, aromatic H), 7.55 (d, J = 7.7 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 30.75 (C-4), 31.99 (CH_2–CO), 34.80 (C-8), 35.22 (C-6), 36.18 (C-9), 38.01 ($N(CH_3)_2$), 42.52 (C-3), 45.12 (C-7), 46.04 (NCH_3), 53.16 (C-2′, C-6′), 54.11 (NCH_2), 55.10 (C-3′, C-5′), 55.42 (C-1), 57.79 (C-5), 126.22, 126.45, 126.51, 127.73, 128.44, 128.53 (aromatic C), 143.14, 143.46 (aromatic C_q), 170.25 (CO). HRMS (MALDI): calcd for $C_{30}H_{42}N_4O[MH^+]$: 475.3437; found: 475.3427.

5.2.8.5. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (19b). The reaction of compound **17b** (0.27 g, 0.62 mmol) with

N-methylpiperazine (2 mL) and a catalytical amount of KI gave after work-up **19b** (0.22 g, 0.44 mmol, 71%) as an oily residue. IR (KBr) 3058, 3025, 2935, 2874, 2793, 1635, 1496, 1447, 1425, 1163, 750, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 260 (3.163), 229 (3.702). Compound **(*E*)-19b**: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.70–1.78 (1H, CH–CO), 1.77–1.83 (m, 4H, $(CH_2)_2$), 1.97–2.07 (m, 1H, 6-H), 2.02–2.21 (m, 10H, 2′-H, 4-H, 6′-H, 9-H, CH–CO, NCH), 2.21 (s, 3H, NCH_3), 2.25–2.37 (m, 5H, 3′-H, 5′-H, 6-H), 2.41–2.49 (m, 1H, NCH), 2.68–2.82 (m, 4H, $N(CH_2)_2$), 3.28 (t, J = 9.2 Hz, 1H, 7-H), 3.35–3.44 (m, 1H, 3-H), 3.47 (td, J = 9.9, 2.8 Hz, 1H, 8-H), 3.97 (d, J = 2.8 Hz, 1H, 1-H), 4.41–4.48 (m, 1H, 3-H), 7.13–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.53 ($(CH_2)_2$), 30.63 (C-4), 30.77 (CH_2–CO), 34.36 (C-9), 37.98 (C-6), 40.58 (C-8), 40.63 (C-3), 45.29 ($N(CH_2)_2$), 45.91 (NCH_3), 46.64 (C-7), 52.72 (C-2′, C-6′), 53.80 (NCH_2), 54.85 (C-3′, C-5′), 56.33 (C-5), 61.45 (C-1), 126.82, 127.00, 127.07, 127.70, 128.88, 129.14 (aromatic C), 142.19, 144.27 (aromatic C_q), 171.12 (CO). Compound **(*Z*)-19b**: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.77–1.83 (m, 4H, $(CH_2)_2$), 1.87–1.97 (m, 2H, 4-H), 2.07–2.22 (m, 2H, 6-H, 9-H), 2.28 (s, 3H, NCH_3), 2.28–2.35 (m, 1H, 6-H), 2.38–2.60 (m, 11H, 2′-H, 3′-H, 5′-H, 6′-H, 9H, CH_2–CO), 2.68–2.82 (m, 6H, NCH_2, $N(CH_2)_2$), 3.09–3.16 (m, 1H, 3-H), 3.27 (t, J = 9.2 Hz, 1H, 7-H), 3.32–3.39 (m, 1H, 8-H), 3.75–3.82 (m, 1H, 3-H), 5.07 (d, J = 3.5 Hz, 1H, 1-H), 7.13–7.57 (m, 8H, aromatic H), 7.56 (d, J = 7.7 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 23.57 ($(CH_2)_2$), 31.94 (CH_2–CO), 32.32 (C-4), 34.63 (C-8), 35.90 (C-6), 36.53 (C-9), 42.50 (C-3), 45.10 (C-7), 45.24 ($N(CH_2)_2$), 46.00 (NCH_3), 53.11 (C-2′, C-6′), 54.07 (NCH_2), 55.05 (C-3′, C-5′), 55.51 (C-1), 56.99 (C-5), 126.15, 126.41, 126.46, 127.72, 128.39, 128.50 (aromatic C), 143.05, 143.53 (aromatic C_q), 171.12 (CO). HRMS (MALDI): calcd for $C_{32}H_{44}N_4O[MH^+]$: 501.3593; found: 501.3626.

5.2.8.6. (7*RS*,8*RS*)-(±)-*N*-(7,8-Diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-3-(4′-methylpiperazin-1′-yl)propionamide (19c). The reaction of compound **17c** (0.40 g, 0.88 mmol) with *N*-methylpiperazine (2 mL) and a catalytical amount of KI gave after work-up **19c** (0.30 g, 0.58 mmol, 66%) as an oily residue. A small amount was purified for analytical purposes by CC over silica gel eluting with CH_2Cl_2/MeOH (4:1). IR (KBr) 3058, 3026, 2932, 2793, 1636, 1602, 1496, 1448, 1282, 1163, 1012, 760, 699 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 259 (3.104), 230 (3.721). Compound **(*E*)-19c**: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.43–1.53 (m, 2H, CH_2), 1.58–1.78 (m, 5H, $2CH_2$, CH–CO), 1.88–2.01 (m, 3H, 4-H, 6-H, CH–CO), 2.05–2.21 (m, 7H, 2′-H, 4-H, 6′-H, 9-H, NCH), 2.22 (s, 3H, NCH_3), 2.23–2.33 (m, 6H, 3′-H, 5′-H, 6-H, 9-H), 2.36–2.47 (m, 1H, NCH), 2.48–2.68 (m, 4H, $N(CH_2)_2$), 3.18–3.27 (m, 1H, 7-H), 3.29–3.38 (m, 1H, 3-H), 3.45 (td, J = 9.9, 2.2 Hz, 1H, 8-H), 3.98 (d, J = 2.2 Hz, 1H, 1-H), 4.43–4.51 (m, 1H, 3-H), 7.12–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 24.66 (CH_2), 26.21 ($2CH_2$), 30.54 (C-4), 30.70 (CH_2–CO), 33.34 (C-9), 36.73 (C-6), 40.70 (C-3), 40.88 (C-8), 45.79 (NCH_3), 46.41 ($N(CH_2)_2$), 46.58 (C-7), 52.54 (C-2′, C-6′), 53.69 (NCH_2), 54.71 (C-3′, C-5′), 56.71 (C-5), 61.22 (C-1), 126.73, 127.02, 127.07, 127.63, 128.87, 129.11 (aromatic C), 142.04, 144.03 (aromatic C_q), 171.01 (CO). Compound **(*Z*)-19c**: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 1.43–1.53 (m, 2H, CH_2), 1.58–1.74 (m, 4H, $2CH_2$), 1.80–1.90 (m, 1H, 4-H), 1.93–2.01 (m, 1H, 4-H), 2.03–2.13 (m, 2H, 6-H, 9-H), 2.29 (s, 3H, NCH_3), 2.30–2.48 (m, 6H, 3′H, 5′-H, 6-H, 9-H), 2.50–2.75 (m, 12H, 2′-H, 6′-H, CH_2–CO, NCH_2, $N(CH_2)_2$), 3.14 (ddd, J = 14.2, 10.8, 2.6 Hz, 1H, 3-H), 3.17–3.26 (m, 1H, 7-H), 3.27–3.36 (m, 1H, 8-H), 3.75–3.84 (m, 1H, 3-H), 5.10 (d, J = 3.1 Hz, 1H, 1-H), 7.12–7.37 (m, 8H, aromatic H), 7.56 (d, J = 7.7 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 24.66 (CH_2), 26.21 ($2CH_2$), 31.80 (CH_2–CO), 31.97 (C-4), 34.61 (C-6), 35.08 (C-8), 35.65 (C-9), 42.44 (C-3), 45.23 (C-7), 45.88 (NCH_3), 46.41 ($N(CH_2)_2$), 52.95 (C-2′, C-6′), 53.94 (NCH_2), 54.86 (C-3′, C-5′), 55.28 (C-1), 57.63 (C-5), 126.21, 126.41, 126.47, 127.62, 128.39, 128.48 (aromatic C), 142.86, 143.25 (aromatic C_q), 170.05 (CO). HRMS (MALDI): calcd for $C_{33}H_{46}N_4O[MH^+]$: 515.3750; found: 515.3701.

5.3. Biological tests

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

Antiplasmodial activity was examined using the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). Viability is determined by the incorporation of [^{3}H]-hypoxanthine into living protozoal cells by a modification of a reported assay.[16] 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 Betaplate™ 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. Standard was artemisinin.

5.3.2. In vitro microplate assay against *T. b. rhodesiense*, cytotoxicity

Minimum Essential Medium (50 μL) supplemented according to a known procedure with 2-mercaptoethanol and 15% heat-inactivated horse serum was added to each well of a 96-well microtiter plate.[17] Serial drug dilutions were prepared covering a range from 90 to 0.123 μg/mL. Then 10^4 bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 μL were added to each well and the plate incubated at 37 °C under a 5% CO_2 atmosphere for 72 h. 10 μL of Alamar Blue (containing 0.0125 g resazurin dissolved in 1000 mL distilled water) were then added to each well and incubation continued for a further 2–4 h. The Alamar blue dye is an indicator of cellular growth and/or viability. The blue, non fluorescent, oxidized form becomes pink and fluorescent upon reduction by living cells. The plate was then read in a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and emission wavelength of 588 nm.[18] Fluorescence development was measured and expressed as percentage of the control. Data were transferred into the graphic program Softmax Pro (Molecular Devices) which calculated IC_{50} values. Melarsoprol served as standard. Cytotoxicity was assessed using the same assay and rat skeletal myoblasts (L-6 cells) with mefloquine as standard.

5.3.3. In vivo antimalarial activity of compound 9c

Male mice (Fü albino; specific pathogen free) weighing 20 ± 2 g were infected intravenously with 2×10^7 *P. berghei* ANKA strain-infected erythrocytes from donor mice on day 0 of the experiment. 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 5 mice. On day +3 (48 h after 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 drug. Solutions of

appropriate concentrations of compound **9c** contained 3% ethanol and 7% Tween 80. They were administered ip in a total volume of 0.01 mL per g of body weight 24 h after infection. In vivo studies were carried out by a protocol approved by an animal ethics committee.

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