European Journal of Medicinal Chemistry 47 (2012) 510–519

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

New *N*-methylpiperazinyl derivatives of bicyclic antiprotozoal compounds

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ARTICLE INFO

Article history:
Received 20 April 2011
Received in revised form
7 October 2011
Accepted 10 November 2011
Available online 18 November 2011

Keywords:
5-(4-Methylpiperazinyl)-2-azabicyclo-nonanes
4-(4-Methylpiperazinyl)bicyclo-octanes
Plasmodium falciparum
Trypanosoma brucei rhodesiense

ABSTRACT

The 4-methylpiperazinyl group was inserted as substituent at the bridgehead of bicyclic compounds or as terminal group of their aminoacyl and aminoalkyl side chains. The new compounds were tested in vitro for their activities against the multidrug-resistant K_1 strain of *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* (STIB 900). The results were compared to those of formerly prepared analogues and of drugs in use. A couple of bicyclo-octyl ω-(4-piperazin-1-yl)alkanoates showed high antitrypanosomal ($IC_{50} \leq 0.087$ μM) and antiplasmodial activity ($IC_{50} \leq 0.06$ μM). The most active ω-(4-methylpiperazin-1-yl)alkyl-2-azabicyclo-nonane possessed higher antiplasmodial activity ($IC_{50} \leq 0.023$ μM) and selectivity (S.I. = IC_{50} (Cytotox.)/IC_{50} (*P. falciparum*) = 2188) than the antimalarial drug chloroquine ($IC_{50} = 0.15$ μM, S.I. = 1257).

1. Introduction

Eukaryotic parasites of the genera Plasmodium and Trypanosoma are responsible for Malaria and Human African Trypanosomiasis (HAT, sleeping sickness), respectively. Millions of people in 36 countries of Sub-Saharan Africa are threatened by sleeping sickness and around 30,000 actual cases of infected people are estimated [1]. The two sub-species *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are infectious in man. They are transmitted by the tsetse fly. The more virulent *T. brucei rhodesiense* causes East African sleeping sickness, whereas the West African form is elicited by *T. brucei gambiense*. Untreated the disease is always fatal. At the time there are five drugs in use (pentamidine, suramine, nifurtimox, eflornithine and melarsoprol) but only melarsoprol is effective against the late stage of East African sleeping sickness [2]. However, its administration is painful and causes an encephalopathy in 5–10% of the patients, killing half of them [3]. Therefore, the discovery of new drugs for the treatment of East African Trypanosomiasis is of special importance.

About 225 million cases of malaria have been estimated in 2009. Most of the 800,000 cases of death per year are due to infections with *Plasmodium falciparum* [4]. The efficacy of the antimalarial drugs in use is threatened by multidrug-resistant strains of *P. falciparum* which are becoming prevalent around the world [5]. Drug-resistance concerns particularly the most frequently used chloroquine but just as well the most recently introduced artemisinin derivatives [6–8]. Since half of the world's population is at risk of malaria there is an urgent need for new drugs with activity against drug-resistant strains [4].

The antitrypanosomal and antiplasmodial properties of several 2-azabicyclo-nonane and bicyclo-octane derivatives strongly depended on the amino substitution of the bridgehead atom and the terminal amino function of the side chain in ring position 2 [9–11]. The present study settled on the replacement of amino groups by an *N*-methylpiperazinyl group in this position and in the ω-amino position. The first representatives **18a**,**c** in the bicyclo-octyl acetate series had very promising antitrypanosomal and antiplasmodial activities [11]. In addition, this paper deals with the investigation of the influence of the spacer between the bicyclic ring system and the amino group. All new compounds were tested in vitro for their activities against *T. brucei rhodesiense* and the multiresistant K_1 strain of *P. falciparum*. The results were compared to those of their analogues and of drugs in use.

2. Chemistry

Compounds **1** are available from dialkylammonium thiocyanates and benzylidene acetone in a one-pot reaction [12,13]. 2-

Abbreviations: CC, column chromatography; 4-DMAP, 4-dimethylaminopyridine; EtOH, ethanol; MeOH, methanol.

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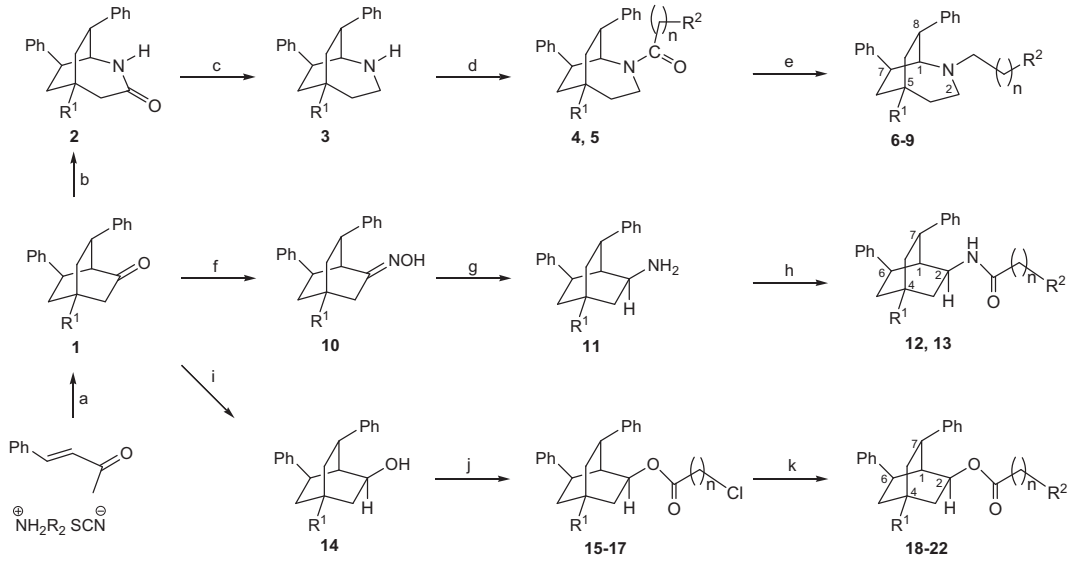
doi:10.1016/j.ejmech.2011.11.022

Azabicyclo-nonan-2-ones **2** were formed via a Beckmann rearrangement upon treatment of **1** with hydroxylamine-O-sulfonic acid in glacial acetic acid [14]. The reduction of **2** to 2-azabicyclo-nonanes **3** was accomplished with $LiAlH_4$. Compounds **3** were converted via ω-chloroacyl derivatives to their ω-(4-methylpiperazinyl)acyl analogues **4** and **5**. Those were hydrogenated with $LiAlH_4$ yielding their aminoalkyl analogues **6** and **7**. The (2-exo)-aminobicyclo-octanes **11** were prepared stereoselectively from compounds **1** via the oximes **10** [15]. Compounds **11** were converted to ω-(4-methylpiperazinyl)alkanamides **12** and **13** by acylation with ω-chloroalkanoyl chlorides and subsequent aminolysis with *N*-methylpiperazine. Bicyclo-octan-(2-exo)-ols **14** were stereoselectively synthesized by means of hydrogenation of **1** with $LiAlH_4$ [12]. They were converted to ω-chloroalkanoates **15**–**17**, which gave upon reaction with *N*-methylpiperazine the corresponding ω-amino analogues **18**–**20** (Scheme 1).

The structures of all new compounds were elucidated by one- and two-dimensional NMR spectroscopy. Evidence for the configuration in ring position 2 of compounds **12**, **13**, **19** and **20** was provided by through-space couplings from 2-H to 6-H in their NOE spectra (Fig. 1).

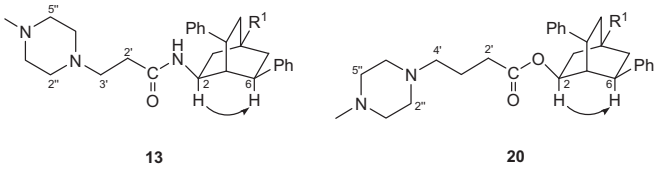
3. Antitrypanosomal and antiplasmodial activity

Routinely compounds were purified over small aluminium oxide columns. Subsequently they were tested via microplate



Scheme 1. Preparation of compounds **4**–**9**, **12**, **13** and **15**–**22**. Reagents and conditions: (a) toluene, 160 °C, 4–6 h; (b) Meth. A: NH_2OSO_3H, glacial acetic acid, 145 °C, 16 h; Meth. B: NH_2OSO_3H, glacial acetic acid, conc. H_2SO_4. 145 °C, 16 h; (c) $LiAlH_4$, ether, 55 °C, 48 h; (d) (1) ω-chloroalkanoyl chloride, triethylamine, CH_2Cl_2, rt, 16 h; (2) sec. amine, KI, rt, 48–72 h; (e) $LiAlH_4$, ether, 55 °C, 16–20 h; (f) $NH_2OH \cdot HCl$, NaOEt, 110 °C, 16 h; (g) Raney nickel, EtOH, 50 psi (H_2), rt, 16 h; (h) (1) ω-chloroalkanoyl chloride, triethylamine, CH_2Cl_2, rt, 16 h; (2) *N*-methylpiperazine, KI, rt, 48–72 h; (i) $LiAlH_4$, ether, 55 °C, 40 h; (j) 4-DMAP, ω-chloroalkanoyl chloride, CH_2Cl_2, rt, 20–48 h; (k) Meth. A: *N*-methylpiperazine, CH_2Cl_2, KI, rt, 48 h; Meth. B: *N*-methylpiperazine, KI, rt, 48 h.

Compounds	R^1	R^2	*n*
1a, **2a**, **3a**, **10a**, **11a**, **14a**	Dimethylamino	–	–
1b, **2b**, **3b**, **10b**, **11b**, **14b**	Pyrrolidino	–	–
1c, **2c**, **3c**, **10c**, **11c**, **14c**	Piperidino	–	–
1d, **2d**, **3d**, **10d**, **11d**	4-Methylpiperazinyl	–	–
4a, **6a**, **12a**, **18a**	Dimethylamino	4-Methylpiperazinyl	1
4b, **6b**, **12b**, **18b**	Pyrrolidino	4-Methylpiperazinyl	1
4c, **6c**, **12c**, **18c**	Piperidino	4-Methylpiperazinyl	1
12d	4-Methylpiperazinyl	4-Methylpiperazinyl	1
5a, **7a**, **13a**, **19a**	Dimethylamino	4-Methylpiperazinyl	2
5b, **7b**, **13b**, **19b**	Pyrrolidino	4-Methylpiperazinyl	2
5c, **7c**, **13c**, **19c**	Piperidino	4-Methylpiperazinyl	2
5d, **7d**, **13d**	4-Methylpiperazinyl	4-Methylpiperazinyl	2
8c	Piperidino	Pyrrolidino	1
9c	Piperidino	Piperidino	2
15a	Dimethylamino	–	1
15b	Pyrrolidino	–	1
15c	Piperidino	–	1
16a	Dimethylamino	–	2
16b	Pyrrolidino	–	2
16c	Piperidino	–	2
17a	Dimethylamino	–	3
17b	Pyrrolidino	–	3
17c	Piperidino	–	3
20a	Dimethylamino	4-Methylpiperazinyl	3
20b	Pyrrolidino	4-Methylpiperazinyl	3
20c	Piperidino	4-Methylpiperazinyl	3
21c	Piperidino	Piperidino	1
22a	Dimethylamino	Diethylamino	2



13 20

Fig. 1. NOE for compounds **13** and **20**.

assays for their activities against *T. brucei rhodesiense* and the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). The cytotoxicity was determined with rat skeletal myoblasts (L-6 cells). Melarsoprol, artemisinin and chloroquine were used as standards. Selected compounds were tested via in vivo assays against *Plasmodium berghei* and *T. brucei brucei* (STIB 795) in mice.

4. Results and discussion

In the 2-azabicyclo-nonane series the 2-unsubstituted 5-dimethylamino compound **3a** exhibited acceptable antitrypanosomal ($IC_{50} = 0.60$ μM) and antiplasmodial ($IC_{50} = 0.28$ μM) activities [14]. Its 5-(4-methylpiperazinyl) analogue **3d** showed slightly improved antitrypanosomal ($IC_{50} = 0.38$ μM), but decreased antiplasmodial ($IC_{50} = 1.50$ μM) activities (Table 1). Their 2-aminoacyl derivatives **4a**–**c** and **5a**–**c** possessed negligible antitrypanosomal ($IC_{50} \geq 28.25$ μM) and moderate antiplasmodial ($IC_{50} = 0.60$–2.37 μM) properties [11]. The antitrypanosomal potency was significantly improved by a 4-methylpiperazinyl group at the bridgehead atom. However, the activity of compound **5d** ($IC_{50} = 3.62$ μM) is still poor. Its antiplasmodial activity has been worsened compared to its analogues **4b**, **4c** ($IC_{50} = 0.62$–0.83) and **5b**, **5c** ($IC_{50} = 0.60$–0.90 μM). The antitrypanosomal properties of their corresponding 2-aminoalkyl derivatives **6** and **7** are not worth mentioning, but their antiplasmodial activities were promising. The antiplasmodial potency of the 2-(3-(4-methylpiperazinyl)propyl derivative **7c** ($IC_{50} = 0.11$ μM) was comparable to those of the most active of the formerly prepared compounds with similar structures **8c** ($IC_{50} = 0.092$ μM) and **9c** ($IC_{50} = 0.12$ μM). Its 2-aminoethyl analogue **6b** possessed the highest antiplasmodial activity of the whole compound class and moreover excellent selectivity ($IC_{50} = 0.023$ μM, S.I. = 2188). In general, compounds with a pyrrolidino or a piperidino group in ring position 5 exhibited higher antiplasmodial activity and better selectivity. At the time the influence of the 4-methylpiperazinyl group in ring position 5 cannot be assessed sufficiently, but viewing at the results for compound **7d** ($IC_{50} = 0.25$ μM, S.I. = 191) it can be said that the antiplasmodial activity was comparable to that of its pyrrolidino analogue **7b** ($IC_{50} = 0.27$ μM, S.I. = 101.7) and the selectivity was even better. Compounds **6b** and **7b** were tested in vivo against *P. berghei* showing up to 39% inhibition of the parasite and moderate prolongation of the mean survival time (control: 6.7 days, **6b**: 8.3 days, **7b**: 7.7 days). In the ω-aminoamide series the influence of the spacer length between ω-amino group and ring

Table 1
Activities of compounds **3**–**9**, **12**, **13** and **18**–**22** against *T. brucei rhodesiense*, *P. falciparum* K_1, and L-6 cells, expressed as IC_{50} (μM).[a]

Comp.	*T. brucei rhodesiense*	S.I. = IC_{50} (Cytotox.)/IC_{50} (*T. brucei rhodesiense*)	*P. falciparum* K_1[b]	S.I. = IC_{50} (Cytotox.)/IC_{50} (*P. falciparum*)	Cytotoxicity L-6 cells
3a [14]	0.60	181.3	0.28	388.6	108.8
3d	0.38	255.1	1.50	64.61	96.92
4c [11]	92.01	1.93	0.62	286.1	177.38
5c [11]	30.79	3.89	0.60	199.8	119.89
5d	3.62	44.47	1.95	82.55	160.98
6a	13.54	5.19	0.52	135.3	70.34
6b	6.35	7.93	0.023	2188	50.33
6c	43.66	2.91	0.30	423.9	127.18
7a	11.50	4.74	0.51	106.9	54.53
7b	6.99	3.93	0.27	101.7	27.45
7c	17.57	3.55	0.11	567.7	62.45
7d	6.67	7.16	0.25	191	47.75
8c [10]	25.56	6.09	0.092	1692	155.7
9c [10]	18.43	7.50	0.12	1152	138.3
12a [11]	1.60	41.37	2.58	25.66	66.19
12b [11]	1.13	44.46	0.82	61.27	50.24
12c [11]	0.69	83.36	0.38	151.4	57.52
12d	2.06	20.43	0.62	67.87	42.08
13a [11]	2.74	34.66	4.19	22.67	94.97
13b [11]	4.15	20.89	2.08	41.68	86.69
13c [11]	0.86	71.00	0.28	218.1	61.06
13d	3.30	20.57	0.55	123.4	67.88
18a [11]	0.13	306.6	0.35	113.9	39.86
18c [11]	0.87	33.86	0.106	277.9	29.46
19a	0.21	148.3	0.46	67.70	31.14
19b	0.45	47.36	0.26	81.96	21.31
19c	0.087	270.6	0.06	392.3	23.54
20a	0.08	248.1	0.24	82.71	19.85
20b	0.15	67.73	0.12	84.67	10.16
20c	0.16	139.3	0.05	445.8	22.29
21c [16]	0.87	69.41	0.18	335.5	60.39
22a [16]	0.11	214.6	0.43	54.91	23.61
art.			0.0064	70,391	450.5
chl.			0.15	1257	188.5
mel.	0.009	1945			7.78

art. = artemisinin; chl. = chloroquine; mel. = melarsoprol.
[a] Values represent the average of four determinations (two determinations of two independent experiments).
[b] Resistant to chloroquine and pyrimethamine.

nitrogen on the biological activities was non-uniform, whereas a 4-methylpiperazinyl substituent in ring position 4 of compounds **12d** ($IC_{50} = 0.62\ \mu M$) and **13d** ($IC_{50} = 0.55\ \mu M$) is the reason for their increased antiplasmodial activity compared to their 4-dimethylamino and 4-pyrrolidino analogues **12a**, **12b** ($IC_{50} = 0.82–2.58\ \mu M$) and **13a**, **13b** ($IC_{50} = 2.08–4.19\ \mu M$). The 4-piperidino analogues **12c** ($IC_{50} = 0.38\ \mu M$) and **13c** ($IC_{50} = 0.28\ \mu M$) remain the most active representatives in this compound series. Likewise the weak antitrypanosomal properties of compound **12c** and **13c** were not improved by the 4-methylpiperazinyl group at the bridgehead atom. In the bicyclo-octyl ester series the good antitrypanosomal and antiplasmodial activities of the 2-aminoacetates **18a–c** could be further improved via elongation of the spacer length between carbonyl and amino group of the acid moiety. The propionate **19c** ($IC_{50} = 0.087\ \mu M$) and the butyrate **20a** ($IC_{50} = 0.08\ \mu M$) showed very promising antitrypanosomal activity. Mice infected with *T. brucei brucei* (STIB 795) were only weak positive 24 h after treatment with compound **19c**, however, on day 10 after infection parasitaemia was comparable to control. The antiplasmodial activity of compounds **19c** ($IC_{50} = 0.06\ \mu M$) and **20c** ($IC_{50} = 0.05\ \mu M$) was excellent. Moreover, the selectivities (S.I. = 248.1–445.8) of these esters were pleasingly high. The piperidino substituent at the bridgehead atom of compounds **18c–20c** is responsible for their higher antiplasmodial activities compared to their analogues **18a–20a** and **18b–20b**. Their antitrypanosomal and antiplasmodial properties were improved in relation to the most active of their formerly prepared analogues **22a** (IC_{50} (*T. brucei rhodesiense*) = 0.11 μM) and **21c** (IC_{50} (*P. falciparum*) = 0.18 μM) which have no 4-methylpiperazinyl moiety.

Overall, the replacement of other ω-amino groups by a 4-methylpiperazinyl group afforded compounds with improved antitrypanosomal and antiplasmodial activity in the bicyclo-octylester series. In the aminoalkyl-2-azabicyclo-nonane series compounds with increased antiplasmodial activity were developed. Although the antitrypanosomal properties of several bicyclo-octyl esters were enhanced compared to their formerly prepared analogues, it should be mentioned that melarsoprol is twenty-times as potent. The antiplasmodial activities of a number of aminoalkyl-2-azabicyclo-nonanes and bicyclo-octyl ω-aminoalkanoates were equivalent to that of chloroquine. However, a single compound (**6b**: $IC_{50} = 0.023\ \mu M$) possessed considerably higher antiplasmodial potency and better selectivity than chloroquine. Compared to artemisinin the activity is still quite good, whereas the selectivity is significantly lower. The most active compounds will serve as leads in a future study dealing with the influence of a 4-methylpiperazinyl group at the bridgehead atom.

5. Conclusion

This paper reports the synthesis and the antitrypanosomal and antiplasmodial activities of new ω-aminoacyl and ω-aminoalkyl substituted derivatives of 2-azabicyclo-nonanes, bicyclo-octanamines and bicyclo-octanols with the emphasis on the 4-methylpiperazinyl group as amino component. Among the new compounds there were the so far most active in these series demonstrating the positive influence of this substituent. In the series of bicyclo-octyl ω-aminoalkanoates the tested biological properties were depending on the chain length of the acid moiety. The antiplasmodial activities of several compounds of the bicyclo-octane and 2-azabicyclo-nonane series were equivalent or even better than that of chloroquine. The most active compounds will serve as leads in a future study.

6. Experimental

6.1. Instrumentation and chemicals

The purity of compounds is generally checked with HPLC using UV detection. By default compounds are in addition purified prior to spectroscopic analysis over small aluminium oxide columns. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer) in KBr discs; frequencies are reported in cm^{-1}. UV/vis: Lambda 17 UV/vis-spectrometer (Perkin Elmer), maxima reported in nm. NMR spectra: Varian UnityInova 400, 5 mm tubes, 25 °C, internal standards: ^1H: TMS [$\delta = 0.00$ ppm] ^{13}C: centre of the solvent peak [$\delta = 77.0$ ppm for $CDCl_3$]. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra are reported in ppm, ^1H- and ^{13}C-resonances were assigned using $^1H,^1H$- and $^1H,^{13}C$-correlation spectra and are numbered as given in the formulae (br broad, d doublet, dd double doublet, ddd double double doublet, dt double triplet, m multiplet, q quartet, s singlet, t triplet, td triple doublet), resonances marked with a single quote belong to the alkyl chain of the compounds, those with a double quote belong to their ω-(4-methylpiperazinyl) group. HRMS: Micromass Tofspec 3E spectrometer (MALDI), GCT-Premier spectrometer, Waters (EI, 70 eV). Materials: column chromatography (CC): aluminium oxide for chromatography (pH: 9.5, Fluka); silica gel 60 (Merck 70–230 mesh, pore-diameter 60 Å); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254}, 0.2 mm, 200 × 200 mm); the substances were detected in UV light at 254 nm.

6.2. Syntheses

Bicyclo[2.2.2]octan-2-ones **1a–c** were synthesized following reported procedures [12,13].

The syntheses of the 2-azabicyclo[3.2.2]nonanes **3a–c** have already been reported [14].

The bicyclo[2.2.2]octan-2-amines **11a–c** were prepared following reported procedures [15].

Bicyclo[2.2.2]octanols **14a–c** were prepared according to reported procedures [12].

The syntheses of the chloropropionates **16a–c** have already been reported [16].

6.2.1. (6RS,7RS)-(±)-(4-Methylpiperazin-1-yl)-6,7-diphenylbicyclo[2.2.2]octan-2-one × HSCN (**1d**)

Benzylidene acetone [42.90 g (293 mmol)] and *N*-methylpiperazinium thiocyanate [23.25 g (146 mmol)] were suspended in 200 ml toluene and refluxed for 6 h at 160 °C using molecular sieve 4 Å. After cooling to room temperature the solvent was evaporated and the residue was recrystallised several times from EtOH yielding ketone **1d** [32.30 g (51%)]. IR = 3026, 2949, 2824, 2593, 2457, 1718, 1703, 1600, 1494, 1455, 1340, 1190, 1027, 755, 701; UV [CH_2Cl_2, (log ε)]: 231 (3.699); ^1H NMR (base, $CDCl_3$) $\delta = 1.68$ (ddd, $J = 12.2$, 8.5, 2.8 Hz, 1H, 8-H), 2.12 (ddd, $J = 13.0$, 8.6, 2.5 Hz, 1H, 5-H), 2.26–2.34 (m, 1H, 5-H), 2.29 (s, 3H, NCH_3), 2.38–2.55 (m, 6H, 3-H, $(N(CH_2)_2$, 8-H), 2.57 (dd, $J = 18.3$, 3.3 Hz, 1H, 3-H), 2.69 (s, 1H, 1-H), 2.66–2.79 (m, 4H, $(N(CH_2)_2)$, 3.32 (t, $J = 9.1$ Hz, 1H, 6-H), 3.33 (t, $J = 9.5$ Hz, 1H, 7-H), 7.05–7.39 (m, 10H, aromatic H); ^{13}C NMR (base, $CDCl_3$) $\delta = 31.79$ (C-5), 35.48 (C-7), 37.39 (C-8), 38.02 (C-6), 44.53 (C-3), 45.51 ($N(CH_2)_2$), 45.80 (NCH_3), 53.67 (C-1), 55.56 ($N(CH_2)_2$), 57.91 (C-4), 126.44, 126.79, 126.86, 127.37, 128.56, 128.64 (aromatic CH), 141.01, 144.06 (aromatic C), 212.98 (CO); HRMS (EI+) calcd for $C_{25}H_{30}N_2O$: 374.2358; found: 374.2356.

6.2.2. General procedure for the synthesis of (7RS,8RS)-(±)-5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]nonan-3-ones (**2a–d**)

Method A: 2-Azabicyclo[3.2.2]nonan-3-ones **2a–c** were prepared following the reported procedures [14].

Method B: To a mixture of ketone **1d** and hydroxylamine-O-sulfonic acid suspended in glacial acetic acid concentrated sulfuric acid was added. This reaction batch was refluxed overnight at 145 °C. Subsequently the solution was poured on ice, alkalized with 2 N aq NaOH and extracted five times with CH_2Cl_2. The organic layer was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate, filtered, evaporated and the residue was recrystallised from EtOH.

*6.2.2.1. (7RS,8RS)-(±)-5-(4-Methylpiperazin-1-yl)-7,8-diphenyl-2-azabicyclo[3.2.2]nonan-3-one (**2d**). Method B*: Base of compound **1d** [4.64 g (12.39 mmol)], hydroxylamine-O-sulfonic acid [4.20 g (37.17 mmol)] and concentrated sulfuric acid [1.26 g (12.34 mmol)] in a total of 50 ml glacial acetic acid gave after work-up **2d** [2.22 g (46%)] as a precipitate. IR = 3177, 3054, 2958, 2935, 2880, 2793, 1655, 1602, 1495, 1453, 1410, 1337, 1159, 1117, 1011, 7520, 702; UV [CH_2Cl_2, (log ε)]: 259 (3.438), 230 (3.670); ^{1}H NMR ($CDCl_3$) δ = 2.01 (t, *J* = 11.4 Hz, 1H, 6-H), 2.09 (dd, *J* = 11.8, 9.4 Hz, 1H, 9-H), 2.17–2.27 (m, 1H, 9-H), 2.30 (dd, *J* = 11.4, 8.0 Hz, 1H, 6-H), 2.31 (s, 3H, NCH_3), 2.48–2.64 (m, 4H, $N(CH_2)_2$), 2.73 (dd, *J* = 17.7, 2.0 Hz, 1H, 4-H), 2.67–2.88 (m, 4H, $N(CH_2)_2$), 2.96 (d, *J* = 17.7 Hz, 1H, 4-H), 3.25 (d, *J* = 6.9 Hz, 1H, 1-H), 3.34 (t, *J* = 9.4 Hz, 1H, 8-H), 3.46 (dd, *J* = 11.4, 8.0 Hz, 1H, 7-H), 6.20 (d, *J* = 6.9 Hz, 1H, NH), 7.22–7.40 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 35.35 (C-9), 35.67 (C-6), 41.79 (C-8), 42.60 (C-4), 44.87 ($N(CH_2)_2$), 45.64 (NCH_3), 46.37 (C-7), 55.19 (C-5), 55.63 ($N(CH_2)_2$), 57.77 (C-1), 126.72, 127.13, 127.16, 127.85, 128.72, 129.02 (aromatic CH), 141.87, 142.99 (aromatic C), 173.67 (CO); HRMS (EI+) calcd for $C_{25}H_{31}N_3O$: 389.2467; found: 389.2472.

*6.2.3. General procedure for the synthesis of (7RS,8RS)-(±)-5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]nonanes (**3a**–**d**)*

*6.2.3.1. (7RS,8RS)-(±)-5-(4-Methylpiperazin-1-yl)-7,8-diphenyl-2-azabicyclo[3.2.2]nonane (**3d**).* The 2-azabicyclo[3.2.2]nonan-3-one **2d** [3.13 g (8.05 mmol)] was suspended in 85 ml dry ether, cooled with an ice-bath and $LiAlH_4$ [1.22 g (32.20 mmol)] was added in portions. After 1 h the ice-bath was removed and the reaction batch was refluxed at 55 °C for 48 h. Subsequently the chemical reaction was quenched cautiously with ice-water. Then 2 N aq NaOH was added and the reaction mixture was exhaustively extracted with ether. 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 **3d** [1.87 g (62%)] as an oily residue. IR = 3058, 3024, 2930, 2837, 2793, 1600, 1495, 1451, 1377, 1292, 1159, 1010, 758, 737, 699; UV [CH_2Cl_2, (log ε)]: 231 (4.006); ^{1}H NMR ($CDCl_3$) δ = 1.88 (dd, *J* = 12.8, 10.3 Hz, 1H, 6-H), 1.93–1.97 (m, 2H, 4-H), 2.05–2.14 (m, 1H, NH), 2.11 (dd, *J* = 13.1, 10.7 Hz, 1H, 9-H), 2.21–2.37 (m, 2H, 6-H, 9-H), 2.28 (s, 3H, NCH_3), 2.42–2.53 (m, 4H, $N(CH_2)_2$), 2.62–2.78 (m, 4H, $N(CH_2)_2$), 3.07–3.19 (m, 2H, 3-H), 3.13 (d, *J* = 2.2 Hz, 1H, 1-H), 3.29 (td, *J* = 9.5, 2.2 Hz, 1H, 8-H), 3.42 (t, *J* = 9.4 Hz, 1H, 7-H), 7.17–7.40 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 32.25 (C-4), 35.44 (C-9), 36.11 (C-6), 39.30 (C-8), 41.48 (C-3), 44.47 ($N(CH_2)_2$), 45.52 (NCH_3), 46.56 (C-7), 55.42 ($N(CH_2)_2$), 57.66 (C-5), 61.04 (C-1), 125.77, 125.89, 126.73, 127.38, 128.09, 128.18 (aromatic CH), 143.64, 145.05 (aromatic C); HRMS (EI+) calcd for $C_{25}H_{33}N_3$: 375.2675; found: 375.2672.

*6.2.4. (7RS,8RS)-(±)-3-(4-Methylpiperazin-1-yl)-1-(5-(4-methylpiperazin-1-yl)-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl) propan-1-one (**5d**)*

To a cooled solution of 2-azabicyclo-nonane **3d** [0.247 g (0.658 mmol)] and triethylamine [0.100 g (0.987 mmol)] in 10 ml dry CH_2Cl_2 the chloropropionyl chloride [0.125 g (0.987 mmol)] was added under stirring in an atmosphere of Ar. After 30 min the ice-bath was removed and the reaction batch was stirred overnight at rt. Subsequently 1 N aq NaOH was added and the reaction mixture was exhaustively extracted with CH_2Cl_2. The organic layer 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 ω-chloropropionyl derivative [0.244 g (0.520 mmol)] of **3d**. The oily residue and a catalytic amount of KI were dissolved in an excess of *N*-methylpiperazine [0.520 g (5.20 mmol)] and were stirred for 72 h at rt in an atmosphere of Ar. Subsequently benzene was added and the reaction batch was evaporated. The residue was dissolved in CH_2Cl_2 and washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate and filtered. Finally, the solvent was removed in vacuo yielding pure **5d** [0.230 g (66%)]. IR = 3058, 3025, 2933, 2876, 2793, 1636, 1602, 1496, 1455, 1161, 1032, 1012, 754, 699; UV [CH_2Cl_2, (log ε)]: 265 (2.972), 230 (3.600); **(*E*)-5d**: ^{1}H NMR ($CDCl_3$) δ = 1.73 (ddd, *J* = 15.1, 12.0, 4.9 Hz, 1H, 2′-H), 1.87 (t, *J* = 12.1 Hz, 1H, 6-H), 1.90–2.03 (m, 2H, 2′-H, 4-H), 2.08–2.20 (m, 8H, 2″-H, 3′-H, 4-H, 6″-H, 9-H), 2.20, 2.26 (2s, 6H, $2NCH_3$), 2.21–2.32 (m, 5H, 3″-H, 5″-H, 6-H), 2.39–2.56 (m, 5H, 3′-H, $N(CH_2)_2$), 2.58–2.76 (m, 4H, $N(CH_2)_2$), 3.23–3.38 (m, 2H, 3-H, 7-H), 3.43 (td, *J* = 9.8, 2.7 Hz, 1H, 8-H), 3.98 (d, *J* = 2.7 Hz, 1H, 1-H), 4.45 (ddd, *J* = 12.3, 5.2, 2.7 Hz, 1H, 3-H), 7.12–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 30.45 (C-4), 30.68 (C-2′), 33.44 (C-9), 37.11 (C-6), 40.70 (C-3), 40.86 (C-8), 44.90 ($N(CH_2)_2$), 45.71 (NCH_3), 45.80 (NCH_3), 46.54 (C-7), 52.59 (C-2″, C-6″), 53.68 (C-3′), 54.73 (C-3″, C-5″), 55.57 ($N(CH_2)_2$), 57.22 (C-5), 61.16 (C-1), 126.63, 126.94, 126.99, 127.58, 128.81, 129.04 (aromatic CH), 142.05, 144.13 (aromatic C), 170.96 (CO); **(*Z*)-5d**: ^{1}H NMR ($CDCl_3$) δ = 1.79 (td, *J* = 13.5, 4.5 Hz, 1H, 4-H), 1.90–2.06 (m, 2H, 4-H, 6-H), 2.08–2.20 (m, 1H, 9-H), 2.27, 2.30 (2s, 6H, $2NCH_3$), 2.21–2.38 (m, 6H, 3″-H, 5″-H, 6-H, 9-H), 2.39–2.56 (m, 11H, 2′-H, 2″-H, 3′-H, 6″-H, $N(CH_2)_2$), 2.58–2.83 (m, 5H, 3′-H, $N(CH_2)_2$), 3.09 (td, *J* = 13.9, 3.1 Hz, 1H, 3-H), 3.21 (t, *J* = 10 Hz, 1H, 7-H), 3.26–3.34 (m, 1H, 8-H), 3.74–3.81 (m, 1H, 3-H), 5.10 (d, *J* = 3.3 Hz, 1H, 1-H), 7.12–7.37 (m, 8H, aromatic H), 7.55 (d, *J* = 8.0 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.49 (C-4), 31.88 (C-2′), 34.88 (C-8), 35.10 (C-6), 36.21 (C-9), 42.46 (C-3), 44.77 ($N(CH_2)_2$), 45.09 (C-7), 45.75 (NCH_3), 45.89 (NCH_3), 53.01 (C-2″, C-6″), 53.97 (C-3′), 54.95 (C-3″, C-5″), 55.27 (C-1), 55.65 ($N(CH_2)_2$), 57.72 (C-5), 126.11, 126.33, 126.38, 127.56, 128.32, 128.39 (aromatic CH), 142.94, 143.33 (aromatic C), 170.13 (CO); HRMS (EI+) calcd for $C_{33}H_{47}N_5O$: 529.3781; found: 529.3786.

*6.2.5. General procedure for the synthesis of (7RS,8RS)-(±)-5-dialkylamino-2-(ω-dialkylaminoalkyl)-7,8-diphenyl-2-azabicyclo [3.2.2]nonanes (**6a**–**c**, **7a**–**d**)*

The alkanones **4**, **5** were suspended in dry ether, cooled with an ice-bath and $LiAlH_4$ was added in portions. After 1 h the ice-bath was removed and the reaction batch was refluxed at 55 °C for 20 h. Subsequently the chemical reaction was quenched cautiously with ice-water. Then 2 N aq NaOH was added and the reaction mixture was exhaustively extracted with ether. 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 an oily residue **6a**–**c**, **7a**–**d**.

*6.2.5.1. (7RS,8RS)-(±)-5-Dimethylamino-2-(2-(4-methylpiperazin-1-yl)ethyl)-7,8-diphenyl-2-azabicyclo[3.2.2]nonane (**6a**).* The reaction of compound **4a** [0.117 g (0.254 mmol)] and $LiAlH_4$ [0.039 g (1.02 mmol)] in 40 ml dry ether gave after work-up **6a** [0.096 g (85%)]. A small amount was purified for analytical purposes by CC over aluminium oxide eluting with ethyl acetate/cyclohexane (3:1). IR = 3058, 3024, 2934, 2852, 2871, 2792, 1634, 1600, 1493, 1452, 1355, 1165, 1039, 757, 744, 699; UV [CH_2Cl_2, (log ε)]: 233 (4.002); ^{1}H NMR ($CDCl_3$) δ = 1.85–1.89 (m, 2H, 4-H), 1.93 (dd, *J* = 13.3, 9.1 Hz, 1H, 6-H), 1.98–2.15 (m, 3H, 2′-H, 9-H), 2.16–2.38 (m, 10H, 2″-H, 3″-

H, 5″-H, 6-H, 6″-H, 9-H), 2.23 (s, 3H, NCH_3), 2.31 (s, 6H, $N(CH_3)_2$), 2.54 (t, $J = 7.2$ Hz, 2H, 1′-H), 2.85–2.91 (m, 1H, 3-H), 2.89 (d, $J = 2.8$ Hz, 1H, 1-H), 2.97 (ddd, $J = 12.7, 6.6, 6.0$ Hz, 1H, 3-H), 3.14 (td, $J = 9.7, 2.8$ Hz, 1H, 8-H), 3.47 (t, $J = 9.1$ Hz, 1H, 7-H), 7.12–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 31.34$ (C-4), 35.12 (C-6), 37.34 (C-9), 37.99 ($N(CH_3)_2$), 38.13 (C-8), 40.35 (C-7), 46.01 (NCH_3), 48.06 (C-3), 53.39 (C-2″, C-6″), 54.98 (C-3″, C-5″), 55.05 (C-1′), 56.99 (C-2′), 57.54 (C-5), 68.55 (C-1), 125.87, 126.05, 127.55, 127.79, 128.57, 128.77 (aromatic CH), 144.79, 145.90 (aromatic C); HRMS (EI+) calcd for $C_{29}H_{42}N_4$: 446.3409; found: 446.3402.

*6.2.5.2. (7RS,8RS)-(±)-2-(2-(4-Methylpiperazin-1-yl)ethyl)-7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]nonane (**6b**).* The reaction of compound **4b** [0.150 g (0.308 mmol)] and $LiAlH_4$ [0.047 g (1.23 mmol)] in 50 ml dry ether gave after work-up **6b** [0.099 g (68%)]. A small amount was purified for analytical purposes by CC over silica gel starting with CH_2Cl_2/MeOH (5:1) as eluent. IR = 3058, 3024, 2931, 2871, 2793, 1636, 1600, 1493, 1454, 1165, 1030, 758, 746, 699; UV [CH_2Cl_2, (log ε)]: 233 (3.805); ^{1}H NMR ($CDCl_3$) $\delta = 1.76$–1.82 (m, 4H, $(CH_2)_2$), 1.96–2.00 (m, 2H, 4-H), 2.00–2.14 (m, 3H, 2′-H, 6-H), 2.15–2.31 (m, 7H, 2″-H, 6-H, 6″-H, 9-H), 2.23 (s, 3-H, NCH_3), 2.28–2.39 (m, 4H, 3″-H, 5″-H), 2.54 (t, $J = 7.1$ Hz, 2H, 1′-H), 2.76-2.84 (m, 4H, $N(CH_2)_2$), 2.91 (d, $J = 2.8$ Hz, 1H, 1-H), 2.91–3.01 (m, 2H, 3-H), 3.16 (br td, $J = 9.7, 2.8$ Hz, 1H, 8-H), 3.50 (t, $J = 9.1$ Hz, 1H, 7-H), 7.12–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.67$ ($(CH_2)_2$), 33.84 (C-4), 35.59 (C-6), 37.00 (C-9), 38.02 (C-8), 39.94 (C-7), 45.33 ($N(CH_2)_2$), 45.98 (NCH_3), 47.96 (C-3), 53.35 (C-2″, C-6″), 54.94 (C-3″, C-5″), 55.05 (C-1′), 56.92 (C-2′), 57.36 (C-5), 68.60 (C-1), 125.88, 126.04, 127.56, 127.78, 128.55, 128.76 (aromatic CH), 144.64, 145.80 (aromatic C); HRMS (EI+) calcd for $C_{31}H_{44}N_4$: 472.3566; found: 472.3582.

*6.2.5.3. (7RS,8RS)-(±)-2-(2-(4-Methylpiperazin-1-yl)ethyl)-7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]nonane (**6c**).* The reaction of compound **4c** [0.103 g (0.206 mmol)] and $LiAlH_4$ [0.035 g (0.926 mmol)] in 25 ml dry ether gave after work-up **6c** [0.083 g (83%)]. A small amount was purified for analytical purposes by CC over aluminium oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR = 3059, 3024, 2928, 2842, 2793, 1600, 1492, 1455, 1285, 1167, 1012, 743, 699; UV [CH_2Cl_2, (log ε)]: 233 (3.965); ^{1}H NMR ($CDCl_3$) $\delta = 1.41$–1.48 (m, 2H, CH_2), 1.55–1.62 (m, 4H, $2CH_2$), 1.84–1.93 (m, 3H, 4-H, 6-H), 2.07–2.18 (m, 3H, 2′-H, 9-H), 2.19–2.37 (m, 10H, 2″-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H), 2.23 (s, 3H, NCH_3), 2.56 (t, $J = 6.8$ Hz, 2H, 1′-H), 2.54–2.64 (m, 4H, $N(CH_2)_2$), 2.85–2.91 (m, 1H, 3-H), 2.94 (d, $J = 2.0$ Hz, 1H, 1-H), 2.97 (ddd, $J = 12.7, 6.6, 6.0$ Hz, 1H, 3-H), 3.14 (td, $J = 9.5, 2.0$ Hz, 1H, 8-H), 3.44 (t, $J = 9.2$ Hz, 1H, 7-H), 7.13–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 25.08$ (CH_2), 26.89 ($2CH_2$), 32.31 (C-4), 35.19 (C-6), 37.40 (C-9), 38.57 (C-8), 40.93 (C-7), 46.04 (NCH_3), 46.23 ($N(CH_2)_2$), 48.24 (C-3), 53.44 (C-2″, C-6″), 54.98 (C-3″, C-5″), 55.02 (C-1′), 57.11 (C-2′), 58.07 (C-5), 68.28 (C-1), 125.84, 125.99, 127.49, 127.85, 128.52, 128.61 (aromatic CH), 144.91, 146.02 (aromatic C); HRMS (EI+) calcd for $C_{32}H_{46}N_4$: 486.3723; found: 486.3737.

*6.2.5.4. (7RS,8RS)-(±)-5-Dimethylamino-2-(3-(4-methylpiperazin-1-yl)propyl)-7,8-diphenyl-2-azabicyclo[3.2.2]nonane (**7a**).* The reaction of compound **5a** [0.185 g (0.390 mmol)] and $LiAlH_4$ [0.067 g (1.76 mmol)] in 40 ml dry ether gave after work-up **7a** [0.092 g (51%)]. IR = 3058, 3024, 2934, 2872, 2791, 1600, 1493, 1457, 1283, 1168, 1014, 744, 699; UV [CH_2Cl_2, (log ε)]: 232 (3.875); ^{1}H NMR ($CDCl_3$) $\delta = 1.21$–1.34 (m, 2H, 2′-H), 1.86–2.08 (m, 6H, 2″-H, 3′-H, 4-H, 6-H, 6″-H), 2.08–2.20 (m, 2H, 3′-H, 9-H), 2.20–2.30 (m, 4H, 2″-H, 6-H, 6″-H, 9-H), 2.25 (s, 3H, NCH_3), 2.31 (s, 6H, $N(CH_3)_2$), 2.31–2.47 (m, 6H, 1′-H, 3″-H, 5″-H), 2.76–2.82 (m, 1H, 3-H), 2.82 (d, $J = 2.3$ Hz, 1H, 1-H), 2.97 (ddd, $J = 12.7, 6.6, 6.0$ Hz, 1H, 3-H), 3.15 (td, $J = 9.5, 2.3$ Hz, 1H, 8-H), 3.45 (t, $J = 9.1$ Hz, 1H, 7-H), 7.11–7.36 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 25.55$ (C-2′), 31.20 (C-4), 34.93 (C-6), 37.13 (C-9), 37.94 ($N(CH_3)_2$), 38.06 (C-8), 40.13 (C-7), 45.98 (NCH_3), 47.65 (C-3), 53.03 (C-2″, C-6″), 55.01 (C-3″, C-5″), 55.71 (C-1′), 56.26 (C-3′), 57.63 (C-5), 68.31 (C-1), 125.75, 126.00, 127.49, 127.72, 128.55, 128.74 (aromatic CH), 144.75, 145.91 (aromatic C); HRMS (EI+) calcd for $C_{30}H_{44}N_4$: 460.3566; found: 460.3569.

*6.2.5.5. (7RS,8RS)-(±)-2-(3-(4-Methylpiperazin-1-yl)propyl)-7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]nonane (**7b**).* The reaction of compound **5b** [0.174 g (0.348 mmol)] and $LiAlH_4$ [0.059 g (1.56 mmol)] in 40 ml dry ether gave after work-up **7b** [0.100 g (59%)]. IR = 3058, 3024, 2933, 2872, 2792, 1600, 1493, 1456, 1283, 1168, 1115, 1014, 746, 699; UV [CH_2Cl_2, (log ε)]: 230 (4.063); ^{1}H NMR ($CDCl_3$) $\delta = 1.19$–1.36 (m, 2H, 2′-H), 1.73–1.79 (m, 4H, $(CH_2)_2$), 1.93–2.03 (m, 3H, 3′-H, 4-H), 2.03–2.20 (m, 4H, 3′-H, 6-H, 2″-H, 6″-H), 2.20–2.31 (m, 5H, 2″-H, 6-H, 6″-H, 9-H), 2.25 (s, 3H, NCH_3), 2.31–2.44 (m, 6H, 1′-H, 3″-H, 5″-H), 2.71–2.77 (m, 4H, $N(CH_2)_2$), 2.77–2.86 (m, 1H, 3-H), 2.83 (d, $J = 2.4$ Hz, 1H, 1-H), 2.97 (ddd, $J = 12.7, 6.6, 6.0$ Hz, 1H, 3-H), 3.17 (td, $J = 9.4, 2.4$ Hz, 1H, 8-H), 3.46 (t, $J = 9.2$ Hz, 1H, 7-H), 7.10–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.60$ ($(CH_2)_2$), 25.58 (C-2′), 33.43 (C-4), 35.81 (C-6), 37.08 (C-9), 38.07 (C-8), 39.96 (C-7), 45.09 ($N(CH_2)_2$), 46.01 (NCH_3), 47.79 (C-3), 53.06 (C-2″, C-6″), 55.04 (C-3″, C-5″), 55.76 (C-1′), 56.30 (C-3′), 56.61 (C-5), 68.49 (C-1), 125.69, 125.93, 127.53, 127.69, 128.51, 128.76 (aromatic CH), 144.84, 146.10 (aromatic C); HRMS (EI+) calcd for $C_{32}H_{46}N_4$: 486.3723; found: 486.3706.

*6.2.5.6. (7RS,8RS)-(±)-2-(3-(4-Methylpiperazin-1-yl)propyl)-7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]nonane (**7c**).* The reaction of compound **5c** [0.069 g (0.134 mmol)] and $LiAlH_4$ [0.021 g (0.604 mmol)] in 25 ml dry ether gave after work-up **7c** [0.054 g (80%)]. A small amount was purified for analytical purposes by CC over aluminium oxide eluting with ethyl acetate/cyclohexane/MeOH (3:1:0.3). IR = 3058, 3024, 2931, 2848, 2791, 1600, 1493, 1455, 1282, 1168, 1095, 1014, 757, 699; UV [CH_2Cl_2, (log ε)]: 232 (4.026); ^{1}H NMR ($CDCl_3$) $\delta = 1.25$–1.40 (m, 2H, 2′-H), 1.42–1.48 (m, 2H, CH_2), 1.57–1.64 (m, 4H, $2CH_2$), 1.85–1.96 (m, 3H, 4-H, 6-H), 1.98–2.07 (m, 1H, 3′-H), 2.10–2.20 (m, 2H, 3′-H, 9-H), 2.26 (s, 3H, NCH_3), 2.21–2.45 (m, 12H, 1′-H, 2″-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H), 2.58–2.66 (m, 4H, $N(CH_2)_2$), 2.77–2.84 (m, 1H, 3-H), 2.88 (d, $J = 2.7$ Hz, 1H, 1-H), 2.97 (ddd, $J = 12.7, 6.7, 6.0$ Hz, 1H, 3-H), 3.16 (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 ($CDCl_3$) $\delta = 24.89$ (CH_2), 25.53 (C-2′), 26.59 ($2CH_2$), 32.32 (C-4), 34.77 (C-6), 36.84 (C-9), 38.46 (C-8), 40.74 (C-7), 45.84 (NCH_3), 46.17 ($N(CH_2)_2$), 47.78 (C-3), 52.87 (C-2″, C-6″), 54.84 (C-3″, C-5″), 55.52 (C-1′), 56.23 (C-3′), 58.50 (C-5), 68.04 (C-1), 125.75, 125.96, 127.42, 127.77, 128.51, 128.57 (aromatic CH), 144.74, 145.93 (aromatic C); HRMS (EI+) calcd for $C_{33}H_{48}N_4$: 500.3880; found: 500.3900.

*6.2.5.7. (7RS,8RS)-(±)-5-(4-Methylpiperazin-1-yl)-2-(3-(4-methylpiperazin-1-yl)propyl)-7,8-diphenyl-2-azabicyclo[3.2.2]nonane (**7d**).* The reaction of compound **5d** [0.164 g (0.310 mmol)] and $LiAlH_4$ [0.047 g (1.24 mmol)] in 20 ml dry ether gave after work-up **7d** [0.125 g (78%)]. IR = 3058, 3024, 2932, 2874, 2792, 1600, 1494, 1454, 1164, 1106, 1012, 758, 699; UV [CH_2Cl_2, (log ε)]: 233 (3.877); ^{1}H NMR ($CDCl_3$) $\delta = 1.25$–1.39 (m, 2H, 2′-H), 1.85–1.94 (m, 3H, 4-H, 6-H), 1.94–2.03 (m, 1H, 3′-H), 2.03–2.18 (m, 2H, 3′-H, 9-H), 2.21–2.51 (m, 16H, 2″-H, 1′-H, 3″-H, 5″-H, 6-H, 6″-H, 9-H, $N(CH_2)_2$), 2.26, 2.27 (2s, 6H, $2NCH_3$), 2.64–2.74 (m, 4H, $N(CH_2)_2$), 2.75–2.82 (m, 1H, 3-H), 2.86 (d, $J = 2.8$ Hz, 1H, 1-H), 2.95 (dt, $J = 12.3, 6.1$ Hz, 1H, 3-H), 3.15 (td, $J = 9.5, 2.8$ Hz, 1H, 8-H), 3.43 (t, $J = 9.2$ Hz, 1H, 7-H), 7.10–7.36 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 25.56$ (C-2′), 32.25 (C-4),

34.89 (C-6), 37.51 (C-9), 38.29 (C-8), 40.33 (C-7), 44.79 ($N(CH_2)_2$), 45.83 (NCH_3), 45.95 (NCH_3), 47.68 (C-3), 53.02 (C-2″, C-6″), 55.00 (C-3″, C-5″), 55.65 (C-1′), 55.84 ($N(CH_2)_2$), 56.24 (C-3′), 57.62 (C-5), 68.18 (C-1), 125.74, 125.96, 127.42, 127.73, 128.49, 128.62 (aromatic CH), 144.74, 145.91 (aromatic C); HRMS (EI+) calcd for $C_{33}H_{49}N_5$: 515.3988; found: 515.4008.

6.2.6. (2SR,6RS,7RS)-(±)-4-(4-Methylpiperazin-1-yl)-6,7-diphenylbicyclo[2.2.2]oct-2-ylamine (**11d**)

The mixture of a solution of soda [0.39 g (17.0 mmol)] in 60 ml dry EtOH and hydroxylamine hydrochloride [1.20 g (17.3 mmol)] was refluxed at 110 °C for 1 h. Then base of bicyclo[2.2.2]octan-2-one **1d** [2.1 g (5.61 mmol)] was added. The reaction batch was refluxed at 110 °C for 16 h. Subsequently the solution was filtered and evaporated giving the oxime **10d**. 15.0 g of Ni/Al alloy and 15.0 g of caustic soda were suspended in 75 ml of water. When the reaction ceased, the mixture was heated at 70 °C in a water bath for 30 min. The liquid was poured off and the residue was washed twice with 75 ml water and twice with 75 ml ethanol too. Afterwards the Raney nickel was suspended together with oxime **10d** [2.05 g (5.27 mmol)] in 125 ml ethanol. The reaction batch was allowed to shake overnight with H_2 at rt and a pressure of 50 psi on a Parr hydrogenation apparatus. On the next day the catalyst was sucked off and washed with ethanol. Combined washing solutions and the filtrate were evaporated giving a residue which was dissolved in CH_2Cl_2. The organic layer was carefully washed with water until the aqueous phase reacted neutral. After that it was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo giving 0.926 g of the bicyclo[2.2.2]oct-2-ylamine **11d** which was purified by CC over aluminium oxide using CH_2Cl_2/MeOH (19:1) as eluent yielding pure **11d** [0.500 g (24%)]. IR = 3352, 3276, 3055, 3023, 2930, 2882, 2791, 2697, 1599, 1495, 1447, 1377, 1353, 1164, 1012, 758, 745, 701; UV [CH_2Cl_2, (log ε)]: 225 (3.701); ^{1}H NMR ($CDCl_3$) δ = 1.45(br dd, J = 12.9, 2.4 Hz, 1H, 3-H), 1.90 (ddd, J = 12.7, 8.7, 2.4 Hz, 1H, 5-H), 2.04 (ddd, J = 12.7, 9.8, 2.3 Hz, 1H, 5-H), 2.06–2.22 (m, 3H, 3-H, 8-H), 2.32 (s, 3H, NCH_3), 2.43 (d, J = 3.4 Hz, 1H, 1-H), 2.45–2.62 (m, 4H, $N(CH_2)_2$), 2.69–2.86 (m, 4H, $N(CH_2)_2$), 3.02 (br t, J = 9.3 Hz, 1H, 6-H), 3.19 (br t, J = 9.8 Hz, 1H, 7-H), 3.44 (br dd, J = 9.8, 3.5 Hz, 1H, 2-H), 7.10–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.11 (C-5), 32.10 (C-8), 34.12 (C-7), 38.27 (C-3), 41.45 (C-6), 44.40 (C-1), 45.40 ($N(CH_2)_2$), 45.89 (NCH_3), 52.53 (C-2), 55.77 ($N(CH_2)_2$), 56.81 (C-4), 125.48, 126.11, 126.33, 127.27, 128.27, 128.41 (aromatic CH), 143.85, 145.45 (aromatic C); HRMS (EI+) calcd for $C_{25}H_{33}N_3$: 375.2675; found: 375.2666.

6.2.7. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-N-(4-dialkylamino-6,7-diphenylbicyclo[2.2.2]oct-2-yl)-ω-(4-methylpiperazin-1-yl)alkanamides (**12**, **13**)

A solution of the bicyclo-octylamine **11** and triethylamine in dry CH_2Cl_2 was cooled with an ice-bath. The chloroacyl chloride was added in an atmosphere of Ar under stirring. After 30 min the ice-bath was removed and the reaction batch was stirred overnight at rt. Subsequently 1 N aq NaOH was added and the reaction mixture was exhaustively extracted with CH_2Cl_2. The organic layer was washed with water until the aqueous phase reacted neutral, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo giving ω-chloroalkanamide as an oily residue. The ω-chloroalkanamide and a catalytic amount of KI were dissolved in an excess of secondary amine and were stirred for 48–72 h at rt 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.

6.2.7.1. (2SR,6RS,7RS)-(±)-2-(4-Methylpiperazin-1-yl)-N-(4-(4-methylpiperazin-1-yl)-6,7-diphenylbicyclo[2.2.2]oct-2-yl)acetamide (**12d**).

11d [0.759 g (0.965 mmol)], triethylamine [0.168 g (1.66 mmol)] and chloroacetyl chloride [0.188 g (1.66 mmol)] in 20 ml dry CH_2Cl_2 gave the chloroacetamide which reacted with 2.5 ml *N*-methylpiperazine [2.26 g (22.6 mmol)] within 48 h to compound **12d** [0.339 g (0.657 mmol)]. Yield: 68%. IR = 3366, 3057, 3025, 2934, 2872, 2793, 2693, 1676, 1600, 1497, 1453, 1376, 1166, 1140, 1013, 832, 746, 698; UV [CH_2Cl_2, (log ε)]: 230 (3.873), 263 (3.528); ^{1}H NMR ($CDCl_3$) δ = 1.38 (br d, J = 13.9 Hz, 1H, 3-H), 1.77–1.85 (m, 1H, 8-H), 1.90 (ddd, J = 12.8, 8.0, 2.2 Hz, 1H, 5-H), 1.97–2.05 (m, 2H, 2″-H, 6″-H), 2.06–2.15 (m, 1H, 5-H), 2.18–2.36 (m, 7H, 2″-H, 3-H, 3″-H, 5″-H, 6″-H), 2.25 (d, J = 16.1 Hz, 1H, 2′-H), 2.26, 2.35 (2s, 6H, $2NCH_3$), 2.42 (ddd, J = 12.1, 8.6, 3.1 Hz, 1H, 8-H), 2.55 (d, J = 16.1 Hz, 1H, 2′-H), 2.52–2.64 (m, 4H, $N(CH_2)_2$), 2.73–2.87 (m, 4H, $N(CH_2)_2$), 2.82 (d, J = 3.3 Hz, 1H, 1-H), 3.13 (t, J = 9.3 Hz, 1H, 6-H), 3.17 (t, J = 9.6 Hz, 1H, 7-H), 4.41 (ddd, J = 11.1, 8.0, 3.3 Hz, 1H, 2-H), 6.76 (d, J = 8.0 Hz, 1H, NH), 7.10–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 30.29 (C-5), 33.53 (C-7, C-8), 36.62 (C-3), 38.62 (C-1), 40.20 (C-6), 45.22 ($N(CH_2)_2$), 45.73 (NCH_3), 45.76 (NCH_3), 48.10 (C-2), 52.69 (C-2″, C-6″), 54.61 (C-3″, C-5″), 55.56 ($N(CH_2)_2$), 56.31 (C-4), 60.77 (C-2′), 125.53, 125.94, 126.14, 127.11, 128.12, 128.27 (aromatic CH), 143.05, 144.35 (aromatic C), 169.27 (CO); HRMS (EI+) calcd for $C_{32}H_{45}N_5O$: 515.3624; found: 515.3642.

6.2.7.2. (2SR,6RS,7RS)-(±)-3-(4-Methylpiperazin-1-yl)-N-(4-(4-methylpiperazin-1-yl)-6,7-diphenylbicyclo[2.2.2]oct-2-yl)propionamide (**13d**).

11d [0.195 g (0.520 mmol)], triethylamine [0.079 g (0.779 mmol)] and chloropropionyl chloride [0.099 g (0.779 mmol)] in 10 ml dry CH_2Cl_2 gave the ω-chloropropionamide which reacted with 2.5 ml *N*-methylpiperazine [2.26 g (22.6 mmol)] diluted with 1 ml dry CH_2Cl_2 within 72 h to compound **13d** [0.213 g (0.402 mmol)]. Yield: 77%. IR = 3425, 3219, 3052, 2934, 2871, 2795, 1661, 1600, 1545, 1496, 1455, 1377, 1355, 1291, 1163, 1012, 794, 749, 699; UV [CH_2Cl_2, (log ε)]: 230 (3.901), 261 (3.423); ^{1}H NMR ($CDCl_3$) δ = 1.45 (br d, J = 13.9 Hz, 1H, 3-H), 1.64–1.75 (m, 2H, 2′-H, 3′-H), 1.80 (ddd, J = 12.3, 9.9, 1.8 Hz, 1H, 8-H), 1.89 (ddd, J = 12.7, 9.4, 2.0 Hz, 1H, 5-H), 1.97–2.08 (m, 5H, 2′-H, 2″-H, 6″-H), 2.09–2.19 (m, 3H, 3-H, 3′-H, 5-H), 2.20–2.42 (m, 4H, 3″-H, 5″-H), 2.26, 2.33 (2s, 6H, $2NCH_3$), 2.44 (ddd, J = 12.3, 9.9, 2.9 Hz, 1H, 8-H), 2.48–2.63 (m, 4H, $N(CH_2)_2$), 2.73–2.88 (m, 4H, $N(CH_2)_2$, 3.09 (d, J = 3.5 Hz, 1H, 1-H), 3.12 (t, J = 9.6 Hz, 1H, 6-H), 3.21(t, J = 10.0 Hz, 1H, 7-H), 4.39 (ddd, J = 10.5, 6.8, 3.8 Hz, 1H, 2-H), 7.09–7.38 (m, 10H, aromatic H), 8.04 (d, J = 6.8 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ = 31.36 (C-2′), 33.32 (C-5), 33.61 (C-7), 34.63 (C-3), 34.68 (C-8), 36.00 (C-1), 39.75 (C-6), 45.77 ($N(CH_2)_2$), 45.85 (NCH_3), 46.10 (NCH_3), 48.19 (C-2), 51.92 (C-2″, C-6″), 52.83 (C-3′), 55.24 (C-3″, C-5″), 55.69 ($N(CH_2)_2$), 56.60 (C-4), 125.51, 125.87, 126.17, 127.26, 128.11, 128.39 (aromatic CH), 143.25, 145.28 (aromatic C), 171.35 (CO); HRMS (EI+) calcd for $C_{33}H_{47}N_5O$: 529.3781; found: 529.3779.

6.2.8. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl ω-chlorobutanoates (**17a**–**c**)

The bicyclo-octanol **14** and 4-DMAP were dissolved in dry CH_2Cl_2 and cooled with an ice-bath. Under stirring ω-chloroacyl chloride in dry CH_2Cl_2 was added dropwise in an atmosphere of Ar. After 1 h the ice-bath was removed and the reaction batch was stirred at room temperature for 20–48 h. Then it was carefully washed with water, subsequently the organic layer was once extracted with 1 N aq NaOH and washed with water again until the aqueous phase reacted neutral. Afterwards the organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo giving ω-chloroalkanoates **17a**–**c**.

*6.2.8.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo [2.2.2]octan-2-yl 4-chlorobutanoate (**17a**).* Bicyclo-octanol **14a** [2.50 g (7.80 mmol)] and 4-DMAP [0.194 g (1.55 mmol)] in 55 ml dry CH_2Cl_2 gave with 4-chlorobutanoyl chloride [1.65 g (15.50 mmol)] in 5 ml dry CH_2Cl_2 compound **17a** [2.44 g (74%)].

*6.2.8.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2] octan-2-yl 4-chlorobutanoate (**17b**).* Bicyclo-octanol **14b** [6.28 g (18.1 mmol)] and 4-DMAP [0.730 g (8.50 mmol)] in 75 ml dry CH_2Cl_2 gave with 4-chlorobutanoyl chloride [4.50 g (24.0 mmol)] in 5 ml dry CH_2Cl_2 compound **17b** [7.40 g (90%)].

*6.2.8.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2] octan-2-yl 4-chlorobutanoate (**17c**).* Bicyclo-octanol **14c** [3.50 g (11.0 mmol)] and 4-DMAP [0.472 g (5.50 mmol)] in 70 ml dry CH_2Cl_2 gave with 4-chlorobutanoyl chloride [4.12 g (22.0 mmol)] in 5 ml dry CH_2Cl_2 compound **17c** [4.60 g (90%)].

*6.2.9. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl ω-(4-methylpiperazin-1-yl)alkanoates (**19a–c**, **20a–c**)*

General method A: To a solution of 3-chloropropionate **16** and a catalytic amount of KI in dry CH_2Cl_2 an excess of secondary amine was added. The reaction batch was stirred under an atmosphere of Ar at rt for 48 h. Afterwards the main part of the solvent was evaporated. Then it was washed with water until the aqueous phase reacted neutral. Subsequently the organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo.

General method B: To the 4-chlorobutanoate **17** an excess of secondary amine and a catalytic amount of KI were added. The reaction batch was stirred under an atmosphere of Ar at rt for 48 h. Afterwards benzene was added and evaporated. The residue was dissolved in CH_2Cl_2 and washed with water until the aqueous phase reacted neutral. Subsequently the organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated in vacuo.

*6.2.9.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo [2.2.2]octan-2-yl 3-(4-methylpiperazin-1-yl)propionate (**19a**). Method A*: Compound **16a** [0.522 g (1.27 mmol) and *N*-methylpiperazine [2.30 g (23.0 mmol)] in 85 ml dry CH_2Cl_2 gave **19a** [0.223 g (37%)]. IR = 3059, 3026, 2939, 2792, 1730, 1602, 1497, 1180, 1162, 746, 698; UV [CH_2Cl_2, (log ε)]: 259 (2.869), 230 (3.378); ^{1}H NMR ($CDCl_3$) δ = 1.57 (ddd, *J* = 15.6, 9.5, 5.9 Hz, 1H, 2′-H), 1.65 (dd, *J* = 14.2, 2.2 Hz, 1H, 3-H), 1.85 (ddd, *J* = 15.6, 9.3, 5.9 Hz, 1H, 2′-H), 1.86–1.93 (m, 1H, 5-H), 2.01–2.08 (m, 3H, 3-H, 5-H, 8-H), 2.08–2.17 (m, 1H, 3′-H), 2.15–2.23 (m, 1H, 8-H), 2.26 (s, 3H, NCH_3), 2.24–2.45 (m, 9H, 2″-H, 3′-H, 3″-H, 5″-H, 6″-H), 2.39 (s, 6H, $N(CH_3)_2$), 2.79 (d, *J* = 4.4 Hz, 1H, 1-H), 3.01 (t, *J* = 9.5 Hz, 1H, 6-H), 3.18 (t, *J* = 9.9 Hz, 1H, 7-H), 5.24 (dd, *J* = 9.0, 4.4 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.13 (C-5), 31.39 (C-2′), 31.44 (C-8), 33.92 (C-7), 34.90 (C-3), 38.43 ($N(CH_3)_2$), 38.70 (C-6), 39.57 (C-1), 46.00 (NCH_3), 52.71 (C-2″, C-6″), 52.89 (C-3′), 55.00 (C-3″, C-5″), 56.15 (C-4), 72.96 (C-2), 125.37, 126.40, 126.48, 127.38, 127.96, 128.53 (aromatic CH), 142.81, 144.68 (aromatic C), 171.96 (CO); HRMS (MALDI) calcd for $C_{30}H_{41}N_3O_2$[MH^+]: 476.3277; found: 476.3259.

*6.2.9.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2] octan-2-yl 3-(4-methylpiperazin-1-yl)propionate (**19b**). Method A*: Compound **16b** [0.543 g (1.24 mmol) and *N*-methylpiperazine [2.20 g (22.0 mmol)] in 80 ml dry CH_2Cl_2 gave **19b** [0.474 g (76%)]. IR = 3087, 3058, 2938, 2795, 1730, 1601, 1497, 1181, 1162, 1012, 749, 698; UV [CH_2Cl_2, (log ε)]: 260 (2.948), 230 (3.398); ^{1}H NMR ($CDCl_3$) δ = 1.57 (ddd, *J* = 15.5, 9.5, 5.9 Hz, 1H, 2′-H), 1.74 (br d, *J* = 13.6 Hz, 1H, 3-H), 1.80–1.88 (m, 5H, 2′-H, $(CH_2)_2$), 1.95–2.03 (m, 1H, 5-H), 2.05–2.13 (m, 1H, 5-H), 2.08–2.18 (m, 3H, 3-H, 3′-H, 8-H), 2.18–2.24 (m, 1H, 8-H), 2.24–2.34 (m, 5H, 3′-H, 2″-H, 6″-H), 2.26 (s, 3H, NCH_3), 2.32–2.42 (m, 4H, 3″-H, 5″-H), 2.75–2.84 (m, 5H, 1-H, $N(CH_2)_2$), 3.04 (t, *J* = 9.5 Hz, 1H, 6-H), 3.20 (t, *J* = 9.8 Hz, 1H, 7-H), 5.24 (dd, *J* = 9.1, 4.6 Hz, 1H, 2-H), 7.07–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.56 (($CH_2)_2$), 31.40 (C-2′), 31.58 (C-5), 32.54 (C-8), 33.87 (C-7), 35.89 (C-3), 38.83 (C-6), 39.93 (C-1), 45.59 ($N(CH_2)_2$), 46.02 (NCH_3), 52.71 (C-2″, C-6″), 52.91 (C-3′), 55.01 (C-3″, C-4, C-5″), 73.03 (C-2), 125.35, 126.39, 126.55, 127.46, 127.96, 128.53 (aromatic CH), 142.90, 144.77 (aromatic C), 172.01 (CO); HRMS (MALDI) calcd for $C_{32}H_{43}N_3O_2$[MH^+]: 502.3434; found: 502.3488.

*6.2.9.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2] oct-2-yl 3-(4-methylpiperazin-1-yl)propionate (**19c**). Method A*: Compound **16c** [0.496 g (1.10 mmol) and *N*-methylpiperazine [1.96 g (19.5 mmol)] in 73 ml dry CH_2Cl_2 gave a residue which was purified by CC over silica gel using CH_2Cl_2/MeOH (9:1) as eluent yielding pure **19c** [0.138 g (24%)]. IR = 3058, 3026, 2934, 1730, 1601, 1497, 1180, 1162, 744, 698; UV [CH_2Cl_2, (log ε)]: 259 (2.883), 230 (3.420); ^{1}H NMR ($CDCl_3$) δ = 1.43–1.52 (m, 2H, CH_2), 1.56 (ddd, *J* = 15.6, 9.4, 5.9 Hz, 1H, 2′-H), 1.61–1.69 (m, 4H, $2CH_2$), 1.74 (dd, *J* = 14.1, 2.1 Hz, 1H, 3-H), 1.83 (ddd, *J* = 15.6, 9.4, 5.9 Hz, 1H, 2′-H), 1.91 (ddd, *J* = 12.6, 9.4, 2.1 Hz, 1H, 5-H), 2.03–2.16 (m, 4H, 3-H, 5-H, 8-H, 3′-H), 2.20–2.43 (m, 10H, 2″-H, 3′-H, 3″-H, 5″-H, 6″-H, 8-H), 2.26 (s, 3H, NCH_3), 2.58–2.76 (m, 4H, $N(CH_2)_2$), 2.80 (d, *J* = 4.7 Hz, 1H, 1-H), 2.98 (t, *J* = 9.4 Hz, 1H, 6-H), 3.16 (t, *J* = 10.0 Hz, 1H, 7-H), 5.23 (dd, *J* = 8.8, 4.7 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 24.94 (CH_2), 26.77 ($2CH_2$), 31.35 (C-2′), 31.38 (C-5), 32.29 (C-8), 33.98 (C-7), 35.21 (C-3), 38.69 (C-6), 39.58 (C-1), 46.02 (NCH_3), 46.89 ($N(CH_2)_2$), 52.71 (C-2″, C-6″), 52.90 (C-3′), 55.01 (C-3″, C-5″), 56.78 (C-4), 73.07 (C-2), 125.32, 126.35, 126.48, 127.39, 127.93, 128.50 (aromatic CH), 142.92, 144.84 (aromatic C), 171.99 (CO); HRMS (MALDI) calcd for $C_{33}H_{45}N_3O_2$[MH^+]: 516.3590; found: 516.3544.

*6.2.9.4. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo [2.2.2]octan-2-yl 4-(4-methylpiperazin-1-yl)butanoate (**20a**). Method B*: Compound **17a** [0.963 g (2.26 mmol)] and *N*-methylpiperazine [3.61 g (36.1 mmol)] gave a residue which was purified by CC over silica gel using CH_2Cl_2/MeOH (9:1) as eluent yielding pure **20a** [0.125 g (11%)]. IR = 3087, 3058, 3026, 2940, 2793, 1730, 1601, 1497, 1459, 1447, 1283, 1166, 745, 698; UV [CH_2Cl_2, (log ε)]: 260 (2.829), 230 (3.409); ^{1}H NMR ($CDCl_3$) δ = 1.27–1.48 (m, 3H, 2′-H, 3′-H), 1.65–1.71 (m, 1H, 2′-H), 1.72 (dd, *J* = 13.3, 1.9 Hz, 1H, 3-H), 1.91 (ddd, *J* = 12.8, 9.1, 2.2 Hz, 1H, 5-H), 2.03–2.12 (m, 5H, 3-H, 4′-H, 5-H, 8-H), 2.19 (ddd, *J* = 12.3, 9.7, 2.7 Hz, 1H, 8-H), 2.28 (s, 3H, NCH_3), 2.32–2.47 (m, 8H, 2″-H, 3″-H, 5″-H, 6″-H), 2.39 (s, 6H, $N(CH_3)_2$), 2.80 (d, *J* = 4.5 Hz, 1H, 1-H), 3.01 (t, *J* = 9.1 Hz, 1H, 6-H), 3.18 (t, *J* = 9.7 Hz, 1H, 7-H), 5.24 (dd, *J* = 9.0, 4.5 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 21.47 (C-3′), 31.28 (C-5, C-8), 31.49 (C-2′), 33.95 (C-7), 34.78 (C-3), 38.40 ($N(CH_3)_2$), 38.69 (C-6), 39.61 (C-1), 46.02 (NCH_3), 52.98 (C-2″, C-6″), 55.08 (C-3″, C-5″), 56.22 (C-4), 57.54 (C-4′), 72.77 (C-2), 125.26, 126.40, 126.51, 127.39, 127.93, 128.52 (aromatic CH), 142.81, 144.64 (aromatic C), 173.02 (CO); HRMS (MALDI) calcd for $C_{31}H_{43}N_3O_2$[MH^+]: 490.3434; found: 490.3472.

*6.2.9.5. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2] octan-2-yl 4-(4-methylpiperazin-1-yl)butanoate (**20b**). Method B*: Compound **17b** [1.19 g (2.63 mmol)] and *N*-methylpiperazine [4.1 g (40.9 mmol)] gave **20b** [0.530 g (39%)]. IR = 3086, 3058, 3025, 2937, 2794, 1730, 1601, 1497, 1447, 1164, 749, 698; UV [CH_2Cl_2, (log ε)]:

260 (3.047), 230 (3.451); ^{1}H NMR ($CDCl_3$) δ = 1.37–1.45 (m, 3H, 2′-H, 3′-H), 1.64–1.70 (m, 1H, 2′-H), 1.73 (dd, J = 14.2, 2.1 Hz, 1H, 3-H), 1.80–1.87 (m, 4H, $(CH_2)_2$), 1.97 (ddd, J = 12.3, 9.4, 2.2 Hz, 1H, 5-H), 2.03–2.18 (m, 5H, 3-H, 4′-H, 5-H, 8-H), 2.21 (ddd, J = 12.0, 9.9, 3.2 Hz, 1H, 8-H), 2.27 (s, 3H, NCH_3), 2.29–2.47 (m, 8H, 2″-H, 3″-H, 5″-H, 6″-H), 2.73–2.83 (m, 5H, 1-H, $N(CH_2)_2$), 3.03 (t, J = 9.4 Hz, 1H, 6-H), 3.19 (t, J = 9.9 Hz, 1H, 7-H), 5.24 (dd, J = 9.0, 4.6 Hz, 1H, 2-H), 7.06–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 21.49 (C-3′), 23.54 ($(CH_2)_2$), 31.51 (C-2′), 31.73 (C-5), 32.34 (C-8), 33.89 (C-7), 35.79 (C-3), 38.80 (C-6), 39.98 (C-1), 45.53 ($N(CH_2)_2$), 46.06 (NCH_3), 53.01 (C-2″, C-6″), 54.86 (C-4), 55.11 (C-3″, C-5″), 57.55 (C-4′), 72.79 (C-2), 125.20, 126.35, 126.56, 127.45, 127.89, 128.49 (aromatic CH), 142.90, 144.73 (aromatic C), 173.01 (CO); HRMS (MALDI) calcd for $C_{33}H_{45}N_3O_2$[MH^+]: 516.3590; found: 516.3581.

*6.2.9.6. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2] octan-2-yl 4-(4-methylpiperazin-1-yl)butanoate (**20c**). Method B*: Compound **17c** [1.36 g (2.93 mmol)] and *N*-methylpiperazine [4.2 g (41.9 mmol)] gave **20c** [0.389 g (25%)]. IR = 3087, 3056, 3025, 2935, 2791, 1733, 1600, 1497, 1446, 1282, 1168, 1133, 743, 697; UV [CH_2Cl_2, (log ε)]: 260 (3.015), 230 (3.476); ^{1}H NMR ($CDCl_3$) δ = 1.25–1.43 (m, 3H, 2′-H, 3′-H), 1.45–1.53 (m, 2H, CH_2), 1.62–1.70 (m, 5H, 2′-H, $2CH_2$), 1.74 (br d, J = 14.0 Hz, 1H, 3-H), 1.92 (br dd, J = 12.5, 9.3 Hz, 1H, 5-H), 2.04–2.13 (m, 5H, 3-H, 4′-H, 5-H, 8-H), 2.23 (ddd, J = 11.9, 9.9, 2.6 Hz, 1H, 8-H), 2.28 (s, 3H, NCH_3), 2.31–2.50 (m, 8H, 2″-H, 3″-H, 5″-H, 6″-H), 2.59–2.75 (m, 4H, $N(CH_2)_2$), 2.80 (d, J = 4.5 Hz, 1H, 1-H), 2.98 (t, J = 9.3 Hz, 1H, 6-H), 3.16 (t, J = 9.9 Hz, 1H, 7-H), 5.23 (dd, J = 8.9, 4.5 Hz, 1H, 2-H), 7.06–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 21.48 (C-3′), 24.92 (CH_2), 26.74 ($2CH_2$), 31.50 (C-5, C-2′), 32.13 (C-8), 34.02 (C-7), 35.06 (C-3), 38.70 (C-6), 39.66 (C-1), 46.05 (NCH_3), 46.88 ($N(CH_2)_2$), 53.01 (C-2″, C-6″), 55.10 (C-3″, C-5″), 56.88 (C-4), 57.57 (C-4′), 72.87 (C-2), 125.22, 126.36, 126.52, 127.42, 127.91, 128.50 (aromatic CH), 142.91, 144.79 (aromatic C), 173.04 (CO); HRMS (MALDI) calcd for $C_{34}H_{47}N_3O_2$[MH^+]: 530.3747; found: 530.3804.

6.3. Biological tests

6.3.1. In vitro microplate assay against T. brucei rhodesiense, cytotoxicity

Minimum Essential Medium (50 μl) supplemented with 2-mercaptoethanol and 15% heat-inactivated horse serum was added to each well of a 96-well microtiter plate according to a known procedure [17]. Serial drug dilutions were prepared covering a range from 90 to 0.123 μg/ml. Then 10^4 bloodstream forms of *T. brucei 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 were then added to each well and incubation continued for a further 2–4 h. 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 expressed as percentage of the control. Melarsoprol served as standard.

Cytotoxicity was assessed using the same assay and rat skeletal myoblasts (L-6 cells) with mefloquine as standard.

6.3.2. 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 [19]. 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, 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-fibre 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. Standards were artemisinin and chloroquine.

6.3.3. In vivo assay against P. berghei

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% parasitaemia 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. The test compounds were dissolved in 10% DMSO. The drug concentrations were adjusted in a way that 0.01 ml per gram of body weight had to be injected. 4, 24, 48 and 72 h post infection the experimental groups were treated i.p. 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. Parasitaemia was determined microscopically by counting 1000 red blood cells. For low parasitemias (<1%) 2000 rbcs 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 (MSDs) were recorded as well as observations concerning side effects of the drugs.

6.3.4. In vivo assay against T. brucei brucei (STIB 795)

Female mice (NMRI), 4 mice per group, weighing 20–25 g were infected i.p. with 1×10^5 bloodstream forms of *T. brucei brucei*. These bloodstream forms come from a stock of cryopreserved stabilates containing 10% glycerol. The stabilate was suspended in PSG (phosphate–saline–glucose) 6:4 [20] to obtain a trypanosome concentration of 4×10^5/ml. Each mouse was injected with 0.25 ml. Compounds were prepared at appropriate concentrations in 100% DMSO and further diluted in distilled H_2O. They were administered daily in a total volume of 0.01 ml per gram of body weight from day +3 to day +6 of the experiment. A control group was infected but not treated. Parasitaemia was monitored twice a week.

Acknowledgements

In vivo studies were carried out by a protocol approved by an animal ethics committee.

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