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Novel Azabicyclo[3.2.2]nonane derivatives and their activities against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhodesiense*

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ABSTRACT

New diaryl substituted 2-azabicyclo[3.2.2]nonane derivatives have been synthesized in order to investigate the influence of the aromatic substitution and of N substitution on the antiprotozoal activities of those compounds. Following a manual method for the Hansch approach, different 4-substituted aryl rings were systematically inserted, and moieties with varying basicity and polarity were attached to the ring nitrogen. All compounds were investigated for their activities against *Trypanosoma brucei rhodesiense* (STIB 900) and the K_1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine) and for their cytotoxicity using microplate assays. Some of the new compounds are amongst the most active antitrypanosomal agents in this series, and the selectivity index of a single derivative is superior in the 2-azabicyclo-nonane series.

1. Introduction

Malaria is estimated to cause the death of over one million people annually, mainly children in Africa. Moreover, despite intensive research, the overall burden arising from infections by the malaria parasite *Plasmodium falciparum* is increasing.[1] The emergence and spread of antimalarial drug resistance is one of the most important factors undermining malaria control programmes in most of the malaria endemic world.[2] As first line therapy artemisinine and its derivatives were introduced by many countries but even for these drugs stable resistance is reported from laboratory or field studies.[3–5] Therefore, there is still need for new drugs which are active against *Plasmodium falciparum* which causes the most fatal form of the disease, *Malaria tropica*.

Sleeping sickness is caused by two different sub-species of the protozoan *Trypanosoma brucei*: *T. b. rhodesiense* (in East and Southern Africa) and *T. b. gambiense* (mainly in West and Central Africa). The African trypanosomiasis is causing 65,000 deaths per year, and 66,000 new cases appear every year.[6] The disease is fatal if untreated and proceeds from a peripheral to a CNS infection. Only four drugs are in use for treatment of trypanosomiasis. Pentamidine and suramine are not able to cross the blood–brain barrier and therefore, will not cure CNS infections.[7] Melarsoprol is active against all strains of trypanosomes in all stages; however, encephalopathy, an undesired effect of this drug is usually fatal for up to 5% of the patients.[8] D,L-α-Difluoromethylornithine (Eflornithine®) is used as an alternative to melarsoprol but it is ineffective against *T. b. rhodesiense*.[9] Because of this, new agents with activity against *Trypanosoma brucei rhodesiense* and less side effects are in great demand.

Recently, we reported about the antiprotozoal activities of bicyclic aza-nonanes **1a–c** (Scheme 1), which show distinct antiplasmodial activity (IC_{50} = 0.28–6.84 μM).[10] Later we developed their bis-chlorophenyl derivatives **2**,[11] which exhibit a more than 10-fold antitrypanosomal activity (IC_{50} = 0.061–0.066 μM) than their unsubstituted parent compounds (Table 1). From this starting point we followed a 2-fold strategy. The bis-chlorophenyl derivatives **2a–c** were modified regarding their basicity and lipophilicity to compounds **3a,c** to **7a–c** by attachment of different side chains to the ring nitrogen. On the other hand, we tried to optimize the substitution pattern of the phenyl substituents by the application of the suggestions of Topliss[12] giving compounds **8a–c** to **14a**.

All new compounds were characterized and tested for their activity against *T. b. rhodesiense* and the K_1 strain of *P. falciparum* using in vitro assays and for their cytotoxicity against L-6 cells. The results were compared to activities of formerly synthesized 5-dialkylamino-2-azabicyclo[2.2.2]nonanes and drugs in use.

2. Results

2.1. Chemistry

The preparation of 5-dialkylamino-2-azabicyclo[2.2.2]nonanes starts from benzylidene acetone and dialkylammonium isothiocy-

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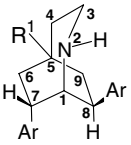
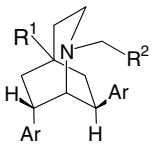


1a-1c, 2a-2c, 8a-8c, 9a, 10a, 11a, 12a, 13a, 14a



3a,c; 4c, 5c, 6a-6c 7a-7c

a: $R^1 = N(CH_3)_2$
b: R^1 = pyrrolidine-1-yl
c: R^1 = piperidine-1-yl

1a-**1c**: Ar = Ph	**8a**-**8c**: Ar = 3,4-diCl-Ph
2a-**2c**: Ar = 4-Cl-Ph	**9a**: Ar = 4-CH_3-Ph
3a,c: Ar = 4-Cl-Ph, R^2 = COOEt	**10a**: Ar = 4-OCH_3-Ph
4c: Ar = 4-Cl-Ph, R^2 = CH_2OH	**11a**: Ar = 4-CF_3-Ph
5c: Ar = 4-Cl-Ph, R^2 = COOH	**12a**: Ar = 4-Br-Ph
6a-**6c**: Ar = 4-Cl-Ph, R^2 = $CONH_2$	**13a**: Ar = 1-naphthyl
7a-**7c**: Ar = 4-Cl-Ph, R^2 = CH_2NH_2	**14a**: Ar = 4-F-Ph

Scheme 1. Structures of 2-azabicyclo[3.2.2]nonane derivatives.

Table 1
In vitro activities of **1–14**, expressed as IC_{50} (μM)[a]

Compound	*Trypanosoma brucei rhodesiense*	SI = IC_{50} (Cytotox.)/IC_{50} (*T.b.r.*)	*Plasmodium falciparum* K1	SI = IC_{50} (Cytotox.)/IC_{50} (*P.falc.*)	Cytotoxicity IC_{50} (μM)
1a	0.60	181.3	0.28	388.6	108.8
1b	1.16	103.8	0.56	215.0	120.4
1c	6.57	13.66	0.64	140.2	89.74
2a	0.061	143.3	0.41	21.32	8.74
2b	0.066	152.4	0.25	40.24	10.06
2c	0.065	124.6	0.46	17.61	8.10
3a	1.78	2.88	0.70	7.31	5.12
3c	2.19	5.97	1.01	12.94	13.07
4c	0.67	14.46	0.70	13.84	9.69
5c[b]	n.t.	—	n.t.	—	n.t.
6a	0.91	28.07	1.11	23.01	25.54
6b	0.76	31.45	0.83	28.80	23.90
6c	0.99	24.00	1.57	15.13	23.76
7a	0.50	20.44	0.90	11.36	10.22
7b	0.21	22.14	0.32	14.53	4.65
7c	0.076	44.34	0.15	22.47	3.37
8a	0.09	71.56	0.40	16.10	6.44
8b	0.15	45.80	0.28	24.54	6.87
8c	0.16	55.44	0.54	16.43	8.87
9a	0.12	337.2	0.45	89.91	40.46
10a	0.67	174.7	2.69	43.52	117.1
11a	0.08	118.0	0.85	11.11	9.44
12a	0.087	103.9	0.34	26.56	9.03
13a	0.11	58.82	0.48	13.48	6.47
14a	0.44	422.7	0.89	209.0	186.0
mel	0.0039	1995			7.78
art			0.0064	70391	450.5
chl			0.15	1571	188.5
mef					11.37

n.t.: not tested. art = artemisinin, chl = chloroquine, mel = melarsoprol, mef = mefloquine.
[a] Values represent the average of four determinations (two determinations of two independent experiments).
[b] **5c** was inactive in a preliminary screening against both parasites.

anates giving dialkylaminobicyclo[2.2.2]octan-2-ones in a one pot procedure.[13] Beckmann rearrangement and a subsequent reduction yielded 5-dialkylamino-2-azabicyclo[2.2.2]nonanes **1a–c**.[10] In the same way, compounds **2a–c** and **8a–c** to **14a** were prepared by the use of differently substituted arylidene acetones. The esters **3a**,**c** were prepared by N-alkylation of **2a**,**c** with ethyl 2-bromoacetate. Compound **4c** was yielded by the reduction of **3c** with $LiAlH_4$ and **5c** by acidic hydrolysis of **3c**. Compounds **6a–c** were obtained by treatment of **2a–c** with chloro acetamide. The triamines **7a–c** were synthesized by the reduction of **6a–c** with $LiAlH_4$.

2.2. Antiplasmodial and antitrypanosomal activity

The IC_{50} values for the antitrypanosomal and antiplasmodial activities and the cytotoxicity of compounds **1a–c** to **14a** are shown in Table 1.

3. Discussion

The antitrypanosomal activity of the 2-azabicyclo-nonanes **1a–c** has been markedly increased by 4-Cl substitution of their phenyl rings (**2a–c**: IC_{50} = 0.061–0.066 μM).[11]

The *N*-substituted derivatives **3a**,**c** to **7a**–**c** of compounds **2a**–**c** were less active. The most active of those compounds **7c** (IC_{50} = 0.076 μM) containing an additional basic centre in the side chain reaches almost the potency of compounds **2a**–**c** but is more toxic and therefore less selective.

For the antiplasmodial activity of compounds **3a**,**c** to **7a**–**c** we did not observe a distinct change due to N alkylation. The triamine **7c** (IC_{50} = 0.15 μM) was more active than the unsubstituted parent compounds **1a**–**c** and **2a**–**c** and was as active as chloroquine against the chloroquine-resistant K_1 strain of *Plasmodium falciparum*.

Since the *N*-substituted 2-azabicyclo-nonanes **3a**,**c** to **7a**–**c** were rather less active than their unsubstituted parent compounds **2a**–**c**, we decided to optimize the aromatic substitution of the latter. Following the suggestions of Topliss[12] we prepared a set of 4-substituted derivatives **8a**–**c** to **10a**. The antiplasmodial activity is affected by unfavourable steric effects from 4-substitution: The most active compound is the unsubstituted 5-dimethylamino-7,8-diphenyl-2-azabicyclo[2.2.2]nonane **1a** (IC_{50} = 0.28 μM) but the compound with the highest selectivity of this series is **14a** (IC_{50} = 0.89 μM, SI = 209).

The most active antitrypanosomal compound is the bis-(4-Cl-Ph) derivative **2a** (IC_{50} = 0.061 μM) followed by the bis-(3,4-Cl_2-Ph) compound **8a** (IC_{50} = 0.09 μM), the bis-(4-CH_3-Ph) derivative **9a** (IC_{50} = 0.12 μM), the 7,8-diphenyl compound **1a** and its bis-(4-OCH_3) derivative **10a**, which implies a 2π–π^2 dependency.

The most cytotoxic compound is the bis-(3,4-Cl_2-Ph) derivative **8a** (IC_{50} = 6.44 μM) followed by the bis-(4-Cl-Ph) analogue **2a** (IC_{50} = 8.74 μM), bis-(4-CH_3-Ph) derivative **9a** (IC_{50} = 40.46 μM), **1a** (IC_{50} = 108.8 μM) and the bis-(4-OCH_3) derivative **10a** (IC_{50} = 117.06 μM), which is most likely due to a 2π–π^2 dependency, although $\pi + \sigma$ or π dependencies have to be considered.

We synthesized the bis-(4-CF_3-Ph)-analogue **11a** and, according to the recommendations of Topliss,[12,14] the bis-(4-Br-Ph)-analogue **12a**. Both compounds showed similar antitrypanosomal activity (IC_{50} = 0.08, 0.087 μM) as their bis-(4-Cl-Ph) analogues **2a**–**c**. In order to verify the observed correlation between lipophilicity and cytotoxicity we prepared the bis-naphthyl derivative **13a**, which displayed—as expected—similar antitrypanosomal and cytotoxic properties as the bis-(3,4-Cl_2-Ph) compounds **8a**–**c**. To cover the section 'other' in Table III of Topliss,[12] we prepared the bis (4-F-Ph) compound **14a**, which is antitrypanosomal more active (IC_{50} = 0.44 μM) than **10a** (IC_{50} = 0.67 μM), but its selectivity (SI = 422.7) is much higher.

The highest antitrypanosomal activity of the new *N*-unsubstituted compounds exhibited **11a** (IC_{50} = 0.08 μM), but due to its selectivity index (SI = 337.2) **9a** (IC_{50} = 0.12 μM) is the most promising compound.

4. Conclusion

The synthesis of derivatives of antiprotozoal active diaryl substituted 5-dialkylamino-2-azabicyclo[2.2.2]nonanes is reported. On the one hand, *N*-alkylated compounds have been prepared introducing side chains with varying lipophilicity and basicity, on the other hand, the substitution pattern of the aryl moieties was diversified applying a manual method for the Hansch approach. The in vitro activity of the compounds against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhodesiense* as well as their cytotoxicity against L-6 cells has been determined using microplate assays. A single *N*-substituted compound shows improved antiplasmodial activity, whereas several of the new 7,8-diaryl derivatives possess good antitrypanosomal activity. Moreover, the 7,8-bis-(4-F-Ph)-substituted compound exhibits the best selectivity index of the so far prepared compounds of the 2-azabicyclononane series. Therefore, it will serve as a lead for further structural modifications.

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 were recorded on a Perkin-Elmer infrared spectrometer system 2000 FT on KBr discs. UV–vis spectra were recorded on a Perkin-Elmer Lambda 17 UV–vis-spectrometer. NMR spectra were recorded in 5 mm tubes at 25 °C on a Varian Unity Inova (400 MHz) using TMS as an internal reference. ^{1}H and ^{13}C resonances were assigned using ^{1}H, ^{1}H and ^{1}H, ^{13}C correlation spectra (gCOSY, gHSQC, gHMBC, optimized on 8 Hz) and are numbered as given in the formulas. Analyses were carried out at the Microanalytical Laboratory at the Institute of Physical Chemistry in Vienna on a Carlo Erba EA 1108 CHNS-O apparatus. HRMS: Kratos profile spectrometer. Materials: column chromatography (CC): aluminium oxide for chromatography (pH:9.5, Fluka) or 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 mm × 200 mm); the substances were detected in UV light at 254 nm.

5.2. Syntheses

5.2.1. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-ethyl 2-(7,8-bis-(4-chlorophenyl)-5-dialkylamino-2-azabicyclo[3.2.2]-non-2- yl)acetate (3a,c)

Azanonanes **2a**,**c**[11] were dissolved in ethanol and cooled on an ice bath. Ethyl bromoacetate was added dropwise under cooling and stirring using a syringe. The solution was stirred over night at room temperature, and water was added. Then it was alkalized with aqueous 2 M NaOH until turbidity persits. The mixture was extracted three times with ether, the combined organic layers were washed twice with water and dried using Na_2SO_4. After filtration the solvent was evaporated in vacuo and the residue purified using CC.

5.2.1.1. (7*RS*,8*RS*)-(±)-Ethyl 2-(7,8-bis-(4-chlorophenyl)-5-dimethylamino-2-azabicyclo[3.2.2]non-2-yl)-acetate (3a). Compound **2a** (2.53 g, 6.5 mmol) in ethanol (60 mL) gave with ethyl bromoacetate (1.085 g, 6.5 mmol) a residue which was purified by CC using CH_2Cl_2:MeOH = 4:1 as eluent yielding **3a** (2.1 g, 4.42 mmol, 68%). The dihydrochloride was prepared by repeated treatment of a solution of the base in CH_2Cl_2 with an excess of 2 M etheral HCl. Solvents were evaporated, and the dihydrochloride was precipitated from ethyl acetate. Mp(HCl): 147 °C. IR (KBr) 3433, 2931, 2866, 2825, 2780, 1736, 1491, 1461, 1190, 1090, 1025, 1013, 830 cm^{-1}. UV (CH_2Cl_2, nm, logε)): 234 (4.022). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.20 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.86–1.98 (m, 3H, 4-H, 6-H), 2.16 (br, t, J = 8.9 Hz, 2H, 9-H), 2.28 (br, t, J = 12.6 Hz, 1H, 6-H), 2.34 (s, 6H, $N(CH_3)_2$), 2.80–2.88 (m, 2H, 1-H, 3-H), 2.94 (ddd, J = 9.4, 8.2, 1.4 Hz, 1H, 8-H), 3.01, 3.30 (2d, J = 17.4 Hz, 2H, CH_2COO), 3.33–3.40 (m, 1H, 3-H), 3.96 (br, t, J = 9.0 Hz, 1H, 7-H), 4.05–4.12 (m, 2H, CH_2CH_3), 7.17–7.40 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.08 (CH_3), 32.02 (C-4), 33.64 (C-6), 37.23 (C-8), 37.79 ($N(CH_3)_2$), 38.98 (C-9), 39.64 (C-7), 46.03 (C-3), 58.15 (C-5), 60.17, 60.24 (CH_2CH_3, CH_2COO), 68.91 (C-1), 127.93, 128.43, 128.97, 129.72, 131.63, 131.66, 142.99, 143.75 (aromatic C), 171.75 (COO). Anal. Calcd for $C_{26}H_{32}Cl_2N_2O_2$: C, 65.68; H, 6.78; N, 5.89; Cl, 14.91. Found: C, 65.58; H, 6.68; N, 5.74; Cl, 14.76. HRMS (MALDI): calcd. for $C_{26}H_{32}Cl_2N_2O_2Na$ [MNa^+]: 497.1739; found: 497.1695.

5.2.1.2. (7*RS*,8*RS*)-(±)-Ethyl 2-(7,8-bis-(4-chlorophenyl)-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-acetate (3c). Compound **2c** (3.85 g, 9.0 mmol) in ethanol (80 mL) reacted with ethyl bromo acetate (1.54 g, 9.2 mmol) to a residue, which was purified by CC using CH_2Cl_2: MeOH = 19:1 as eluent yielding **3c** (2.18 g, 4.23 mmol, 47%). A small amount was purified for analytical purposes by CC over basic Al_2O_3 using CH_2Cl_2 as eluent. IR (KBr) 2932, 2852, 1739, 1492, 1189, 1093, 1013, 830, 701 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 233 (4.073). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.20 (t, J = 7.0 Hz, 3H, CH_3), 1.39–1.48 (m, 2H, CH_2), 1.54–1.64 (m, 4H, $2CH_2$), 1.78–1.95 (m, 3H, 4-H, 6-H), 2.07–2.16 (m, 2H, 9-H), 2.31 (br, t, J = 11.4 Hz, 1H, 6-H), 2.59 (br, s, 4H, $N(CH_2)_2$), 2.82–3.00 (m, 3H, 1-H, 3-H, 8-H), 3.05 (d, J = 17.4 Hz, 1H, CHCOO), 3.25–3.34 (m, 2H, 3-H, CHCOO), 3.87 (t, J = 8.9 Hz, 1H, 7-H), 4.04–4.11 (m, 2H, CH_2CH_3), 7.14–7.44 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.19 (CH_3), 25.05 (CH_2), 26.92 ($2CH_2$), 32.94 (C-4), 33.99 (C-6), 37.78 (C-8), 39.76 (C-9), 40.18 (C-7), 46.23 ($N(CH_2)_2$), 46.71 (C-3), 58.15 (C-5), 60.19, 60.27 (CH_2CH_3, CH_2COO), 68.88 (C-1), 128.08, 128.47, 129.05, 129.73, 131.66, 131.72, 143.38, 144.06 (aromatic C), 171.91 (COO). HRMS (MALDI): calcd. $C_{29}H_{35}Cl_2N_2O_2$ [M-H$^+$]: 513.2121; found: 513.2076.

5.2.1.3. (7*RS*,8*RS*)-(±)-2-(7,8-Bis(4-chlorophenyl)-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)ethanol (4c). Compound **3c** (724 mg, 1.40 mmol) was dissolved in dry ether (30 mL), and $LiAlH_4$ (211 mg, 5.6 mmol) was added in portions under stirring and cooling on an ice bath. The ice bath was removed after one hour and the mixture refluxed over night at 50 °C. The reaction was quenched cautiously by dropwise addition of aqueous 2 M NaOH under cooling. The mixture was extracted 5 times with ether, the combined organic layers were washed twice with water and dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo giving pure **4c** (458 mg, 0.97 mmol, 75%). IR (KBr) 3434, 2932, 1492, 1410, 1161, 1093, 1013, 912, 827, 698 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 231 (4.175). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.42–1.48 (m, 2H, CH_2), 1.56–1.66 (m, 4H, $2CH_2$), 1.83–1.94 (m, 3H, 4-H, 6-H), 2.09 (br, t, J = 12.0 Hz, 1H, 9-H), 2.26–2.31 (m, 2H, 6-H, 9-H), 2.46 (ddd, J = 12.8, 6.1, 4.1 Hz, 1H, NCH), 2.53–2.66 (m, 5H, NCH, $N(CH_2)_2$), 2.72 (d, J = 3.1 Hz, 1H, 1-H), 2.79 (ddd, J = 12.5, 7.0, 5.0 Hz, 1H, 3-H), 2.97 (ddd, J = 12.8, 7.0, 5.1 Hz, 1H, 3-H), 3.13–3.18 (m, 2H, 8-H, C*H*OH), 3.28 (ddd, J = 10.8, 6.0, 4.3 Hz, 1H, C*H*OH), 3.38 (br, t, J = 9.0 Hz, 1H, 7-H), 7.15–7.35 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 24.97 (CH_2), 26.78 ($2CH_2$), 31.85 (C-4), 34.86 (C-6), 35.75 (C-9), 38.06 (C-8), 41.04 (C-7), 46.21 ($N(CH_2)_2$), 48.04 (C-3), 57.91 (C-5), 58.67 (CH_2OH), 58.95 (NCH_2), 69.37 (C-1), 128.32, 128.66, 128.78, 129.53, 131.97, 142.45, 143.95 (aromatic C). Anal. Calcd for $C_{27}H_{34}Cl_2N_2O$: C, 68.49; H, 7.24; N, 5.92. Found: C, 68.71; H, 7.35; N, 5.77. HRMS (MALDI): calcd. $C_{27}H_{33}Cl_2N_2O$ [M−H$^+$]: 471.1970; found: 471.1939.

5.2.1.4. (7*RS*,8*RS*)-(±)-2-(7,8-Bis-(4-chlorophenyl)-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)acetic acid (5c). Compound **3c** (512 mg, 0.99 mmol) was suspended in aqueous HCl_{conc} (100 mL) and continuously, the third part of the solution was distilled off on an oil bath at 160 °C, which took 4–5 h. Then the reaction mixture was refluxed overnight and the solvent evaporated in vacuo. The white precipitate was washed with ethanol and dried under reduced pressure giving the pure dihydrochloride of **5c** (380 mg, 0.68 mmol, 69%). Mp (HCl, decomp.) 228 °C. IR (KBr) 3407, 2865, 2491, 1746, 1642, 1495, 1417, 1376, 1200, 1091, 1013, 944, 865, 848, 829, 686, 647 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 210 (4.366). ^1H NMR (CD_3OD, 400 MHz) δ (ppm) 1.52–1.66 (m, 1H, CH_2), 1.80–1.90 (m, 1H, CH_2), 1.97–2.10 (m, 4H, $(CH_2)_2$), 2.50–2.75 (m, 5H, 4-H, 6-H, 9-H), 3.02–3.10 (m, 3H, 9-H, CHCOO, NCH), 3.26 (ddd, J = 11.8, 11.1, 4.4 Hz, 1H, NCH), 3.62–3.80 (m, 3H, 3-H, NCH), 3.91–4.06 (m, 4H, 7-H, 8-H, CHCOO, NCH), 4.13 (d, J = 2.4 Hz, 1H, 1-H), 7.47 (br, d, J = 8.9 Hz, 6 aromatic H), 7.68 (br, d, J = 8.5 Hz, 2 aromatic H). ^{13}C (CD_3OD, 100 MHz) δ (ppm) 23.37 (CH_2), 24.93, 25.13 ($2CH_2$), 29.25 (C-9), 30.09 (C-4), 33.67 (C-6), 37.16 (C-8), 42.72 (C-7), 49.24, 49.72 ($N(CH_2)_2$), 50.73 (C-3), 57.11 (CH_2COO), 66.94 (C-5), 71.18 (C-1), 130.62, 130.75, 131.22, 135.37, 135.64, 137.21, 140.29 (aromatic C), 167.86 (COO). HRMS (MALDI): calcd. $C_{27}H_{33}Cl_2N_2O_2$ [MH$^+$]: 487.1919; found: 487.1945.

5.2.2. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-dialkylamino-2-azabicyclo[3.2.2]-non-2-yl]acetamides (6a–6c)

Compounds **2a–c** were dissolved in ethanol and cooled on an ice bath. Under cooling and stirring an ethanolic solution of 2-chloro acetamide was added dropwise using a syringe. The solution was refluxed for 48 h at 100 °C, and water was added. The mixture was alkalized with aqueous 2 M NaOH and extracted three times with ether, the organic phases were combined, washed twice with water and dried using Na_2SO_4. After filtration the solvent was evaporated yielding compounds **6** as yellowish resins.

5.2.2.1. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-dimethylamino-2-azabicyclo[3.2.2]non-2-yl]acetamide (6a). Compound **2a** (1.25 g, 3.25 mmol) dissolved in ethanol (30 mL) was treated with a solution of 2-chloro acetamide (310 mg, 3.32 mmol) in ethanol (15 mL) giving **6a** (773 mg, 1.73 mmol, 53%). For analytical purposes purification was done by CC over silica gel using CH_2Cl_2: CH_3OH = 7:3 as eluent. IR (KBr) 3423, 2935, 2871, 2828, 2783, 1685, 1492, 1461, 1409, 1151, 1091, 1012, 829 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 232 (4.121). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.83–1.96 (m, 3H, 4-H, 6-H), 2.10 (br, t, J = 12.5 Hz, 1H, 9-H), 2.28–2.36 (m, 8H, $N(CH_3)_2$, 6-H, 9-H), 2.70 (d, J = 3.4 Hz, 1H, 1-H), 2.70–2.77 (m, 1H, 3-H), 3.00–3.11 (m, 3H, 3-H, CH_2CO), 3.19–3.25 (m, 1H, 8-H), 3.38 (br, t, J = 8.9 Hz, 1H, 7-H), 5.43, 6.15 (2d, J = 4.2 Hz, 2H, NH_2), 7.16–7.34 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 29.81 (C-4), 35.21, 35.37 (C-6, C-9), 37.79 (C-8), 37.90 ($N(CH_3)_2$), 40.74 (C-7), 49.30 (C-3), 57.28 (C-5), 61.62 (CH_2CO), 70.65 (C-1), 128.48, 128.61, 128.91, 129.58, 132.12, 132.21, 142.17, 143.25 (aromatic C), 173.57 ($CONH_2$). HRMS (MALDI): calcd. $C_{24}H_{30}Cl_2N_3O$ [MH$^+$]: 446.1766; found: 446.1729.

5.2.2.2. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl]acetamide (6b). Compound **2b** (986 mg, 2.4 mmol) dissolved in ethanol (20 mL) was treated with a solution of 2-chloro acetamide (227 mg, 2.4 mmol) in ethanol (10 mL) giving **6b** (568 mg, 1.2 mmol, 50%). For analytical purposes purification was done by CC over silica gel using CH_2Cl_2: CH_3OH = 4:1 as eluent. IR (KBr) 3425, 2930, 2873, 1684, 1492, 1409, 1148, 1093, 1012, 828 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 232 (4.162). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.80 (br, s, 4H, $(CH_2)_2$), 1.91–2.06 (m, 3H, 4-H, 6-H), 2.20–2.30 (m, 3H, 6-H, 9-H), 2.70 (d, J = 3.4 Hz, 1H, 1-H), 2.72–2.82 (m, 5H, 3-H, $N(CH_2)_2$), 3.00–3.12 (m, 3H, 3-H, CH_2CO), 3.21–3.27 (m, 1H, 8-H), 3.40 (br, t, J = 8.9 Hz, 1H, 7-H), 5.38, 6.14 (2d, J = 3.5 Hz, 2H, NH_2), 7.16–7.36 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 23.52 ($(CH_2)_2$), 31.61 (C-4), 35.69 (C-6), 35.87 (C-9), 37.60 (C-8), 40.43 (C-7), 45.19 ($N(CH_2)_2$), 49.27 (C-3), 56.69 (C-5), 61.59 (CH_2CO), 70.91 (C-1), 128.46, 128.67, 128.89, 129.62, 132.09, 132.18, 142.15, 143.29 (aromatic C), 173.68 ($CONH_2$). HRMS (MALDI): calcd. $C_{26}H_{32}Cl_2N_3O$ [MH$^+$]: 472.1922; found: 472.1963.

5.2.2.3. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-piperidino-2-azabicyclo[3.2.2]non-2-yl]acetamide (6c). Compound **2c** (1.5 g, 3.5 mmol) dissolved in ethanol (30 mL) was treated with a solution of 2-chloro acetamide (333 mg, 3.6 mmol) in ethanol (15 mL) giving **6c** (1.12 g, 2.3 mmol, 66%). The residue was purified by CC over basic Al_2O_3 using CH_2Cl_2 as eluent. IR (KBr) 3425, 2930, 2851, 1686, 1492,

1409, 1156, 1093, 1012, 828 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 231 (4.150). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.42–1.48 (m, 2H, CH_2), 1.54–1.64 (m, 4H, $2CH_2$), 1.82–1.97 (m, 3H, 4-H, 6-H), 2.09 (br, t, J = 12.2 Hz, 1H, 9-H), 2.31 (br, t, J = 10.9 Hz, 2H, 6-H, 9-H), 2.52–2.68 (m, 4H, $N(CH_2)_2$), 2.71–2.77 (m, 2H, 1-H, 3-H), 3.00–3.11 (m, 3H, 3-H, CH_2CO), 3.21 (dd, J = 10.7, 7.8 Hz, 1H, 8-H), 3.35 (br, t, J = 8.9 Hz, 1H, 7-H), 5.36–5.38 (m, 1H, NH), 6.25 (d, J = 4.1 Hz, 1H, NH), 7.17–7.33 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 24.96 (CH_2), 26.77 ($2CH_2$), 31.18 (C-4), 34.91 (C-9), 35.26 (C-6), 38.22 (C-8), 41.46 (C-7), 46.21 ($N(CH_2)_2$), 49.54 (C-3), 57.82 (C-5), 61.49 (CH_2CO), 70.38 (C-1), 128.49, 128.56, 128.89, 129.12, 129.43, 132.11, 142.14, 143.38 (aromatic C), 173.62 ($CONH_2$). HRMS (MALDI): calcd. $C_{27}H_{34}Cl_2N_3O$ [MH^+]: 486.2079; found: 486.2084.

5.2.3. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-2-[7,8-bis-(4-chlorophenyl)-5-dialkylamino-2-azabicyclo[3.2.2]non-2-yl]ethylamines (7a–7c)

Compounds **6a-c** were suspended in dry ether and $LiAlH_4$ was added in portions at 0 °C under stirring. The mixture was refluxed over night at 55 °C on an oil bath, cooled to room temperature and was cautiously quenched with ice water. Aqueous 2M NaOH was added, and the mixture was extracted 5 times with ether. The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. Compounds **7** were yielded as yellowish resins.

5.2.3.1. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-dimethylamino-2-azabicyclo[3.2.2]non-2-yl]ethylamine (7a). Compound **6a** (75 mg, 0.17 mmol) reacted in dry ether (10 mL) with $LiAlH_4$ (50 mg, 1.3 mmol) to give **7a** (70 mg, 0.16 mmol, 96%). IR (KBr) 3424, 2927, 2823, 2780, 1491, 1460, 1410, 1091, 1039, 1012, 827 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 231 (4.022). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.84–1.89 (m, 3H, 4-H, 6-H), 2.09 (br, t, J = 12.2 Hz, 1H, 9-H), 2.18–2.32 (m, 9H, NCH_2, C*H*NH_2, $N(CH_3)_2$, 6-H, 9-H), 2.36–2.47 (m, 3H, NCH_2, C*H*NH_2), 2.66 (d, J = 3.1 Hz, 1H, 1-H), 2.74–2.80 (m, 1H, 3-H), 2.91–2.98 (m, 1H, 3-H), 3.10 (ddd, J = 10.9, 7.6, 3.0 Hz, 1H, 8-H), 3.42 (br, t, J = 10.0 Hz, 1H, 7-H), 7.17–7.34 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 30.83 (C-4), 34.85 (C-6), 37.17 (C-9), 37.45 (C-8), 37.98 ($N(CH_3)_2$), 39.39 (C-7), 39.92 (CH_2NH_2), 48.35 (C-3), 57.32 (C-5), 60.39 (NCH_2), 68.95 (C-1), 127.97, 128.75, 128.83, 130.08, 131.69, 131.83, 143.04, 144.25 (aromatic C). HRMS (MALDI): calcd. $C_{24}H_{32}Cl_2N_3$ [MH^+]: 432.1973; found: 432.2032.

5.2.3.2. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-pyrrolidino-2- azabicyclo[3.2.2]non-2-yl]ethylamine (7b). Compound **6b** (160 mg, 0.34 mmol) reacted in dry ether (10 mL) with $LiAlH_4$ (60 mg, 1.6 mmol) to give **7b** (130 mg, 0.28 mmol, 83%). For analytical purposes purification was done by CC over silica gel using CH_3OH as eluent. IR (KBr) 3441, 2929, 2871, 2813, 1629, 1492, 1460, 1092, 1012, 827, 700 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 231 (4.077). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.69 (br, s, 4H, $(CH_2)_2$), 1.86–1.95 (m, 3H, 4-H, 6-H), 2.10–2.38 (m, 7H, NCH_2, C$H_2$$NH_2$, 6-H, 9-H), 2.58 (d, J = 2.4 Hz, 1H, 1-H), 2.65–2.73 (m, 5H, $N(CH_2)_2$, 3-H), 2.84–2.89 (m, 1H, 3-H), 3.04 (ddd, J = 12.0, 10.0, 2.8 Hz, 1H, 8-H), 3.50 (br, t, J = 8.8 Hz, 1H, 7-H), 7.09–7.28 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 23.53 ($(CH_2)_2$), 32.79 (C-4), 35.48 (C-6), 37.32 (C-8, C-9), 39.06 (C-7), 39.85 (CH_2NH_2), 45.05 ($N(CH_2)_2$), 48.39 (C-3), 56.38 (C-5), 60.32 (NCH_2), 69.06 (C-1), 127.85, 128.63, 128.81, 130.04, 131.55, 131.67, 143.02, 144.33 (aromatic C).

5.2.3.3. (7*RS*,8*RS*)-(±)-2-[7,8-Bis-(4-chlorophenyl)-5-piperidino-2-azabicyclo[3.2.2]non-2-yl]ethylamine (7c). Compound **6c** (838 mg, 1.72 mmol) reacted in dry ether (20 mL) with $LiAlH_4$ (309 mg, 8.1 mmol) to give **7c** (439 mg, 0.93 mmol, 54%). For analytical purposes purification was done by CC over silica gel using CH_2Cl_2: CH_3OH = 1:1 as eluent. IR (KBr) 3423, 2929, 2850, 2798, 1491, 1409, 1151, 1092, 1012, 828 cm^{-1}. UV (CH_2Cl_2, nm, ($\log\varepsilon$)): 230 (4.124). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.42–1.48 (m, 2H, CH_2), 1.54–1.64 (m, 4 H, $2CH_2$), 1.80–1.92 (m, 3H, 4-H, 6-H), 2.10 (br, t, J = 12.0 Hz, 1H, 9-H), 2.20–2.36 (m, 3H, C*H*NH_2, 6-H, 9-H), 2.39–2.49 (m, 3H, C*H*NH_2, NCH_2), 2.59 (br, s, 4H, $N(CH_2)_2$), 2.71 (d, J = 2.8 Hz, 1H, 1-H), 2.74–2.81 (m, 1H, 3-H), 2.91–2.98 (m, 1H, 3-H), 3.09 (dd, J = 11.2, 8.0, 3.1 Hz, 1H, 8-H), 3.40 (br, t, J = 9.1 Hz, 1H, 7-H), 7.17–7.31 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 25.02 (CH_2), 26.85 ($2CH_2$), 32.05 (C-4), 34.78 (C-6), 36.95 (C-9), 37.90 (C-8), 39.97 (CH_2NH_2), 40.05 (C-7), 46.18 ($N(CH_2)_2$), 48.36 (C-3), 57.86 (C-5), 60.34 (NCH_2), 68.83 (C-1), 127.97, 128.67, 128.76, 129.90, 131.62, 131.73, 143.07, 144.32 (aromatic C). Anal. Calcd for $C_{27}H_{35}Cl_2N_3$: C, 68.63; H, 7.47; N, 8.89. Found: C, 68.32; H, 7.44; N, 8.33.

5.2.4. General procedure for the synthesis of (7*RS*,8*RS*)-(±)-5-dialkylamino-7,8-diaryl-2-azabicyclo[3.2.2]nonanes (8a–8c, 9a–14a)

The dialkylammonium isothiocyanate and the 4-arylbut-3-en-2-one were suspended in toluene and refluxed for 4 h at a water separator at 140 °C on an oil bath. The solvent was evaporated in vacuo and the residue was treated with ethanol, ethyl acetate or acetone. The afforded 6,7-diarylbicyclo[2.2.2]octan-2-one isothiocyanate was sucked off. Then it was stirred for 1 h with aqueous 2M NaOH and extracted with ether until the precipitate was completely dissolved. The combined organic phases were washed with water, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The resin was dried by distillation with dry benzene. Hydroxylamine-*O*-sulfonic acid was added and the mixture was suspended in glacial acetic acid and refluxed over night at 145 °C on an oil bath. After cooling to room temperature, the dark brown solution was poured on ice, alkalized with aqueous 2M NaOH and extracted 5 times with CH_2Cl_2. The combined organic phases were washed twice with water. After drying with Na_2SO_4, the solution was filtered, and the solvent was removed in vacuo. The residue was dissolved in acetone or ethanol and the product precipitated. It was filtered off and dried over phosphorus pentaoxide. Then ist was suspended in dry ether, and $LiAlH_4$ was added in portions under stirring and cooling on an ice bath. The mixture was refluxed for 48 h at 55 °C on an oil bath, cooled to room temperature and cautiously quenched with ice water under stirring and cooling on an ice bath. Aqueous 2M NaOH was added, and the mixture was extracted 5 times with $CHCl_3$. The organic layers were combined, washed with water, dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by means of CC or by extraction with hexane. The dihydrochlorides were prepared by treatment of a solution of the base in CH_2Cl_2 with 2M etheral HCl and subsequent evaporation of the solvents in vacuo. The residues crystallized from ethyl acetate, ethanol/ethyl acetate, ethanol, acetone, ether or acetone/ethanol.

5.2.4.1. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis-(3,4-dichlorophenyl)-2-azabicyclo[3.2.2]non-5-yl)-*N*,*N*-dimethylamine (8a). Dimethylammonium isothiocyanate (12.6 g, 120 mmol) and 3,4-dichlorobenzylidene acetone (44.3 g, 200 mmol) in toluene (113 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (6.2 g, 55 mmol) in glacial acetic acid (64 mL) and subsequently with $LiAlH_4$ (2.38 g, 63 mmol) in dry ether (100 mL). Compound **8a** (4.4 g, 9.6 mmol, 8%) was obtained by extraction of the residue with hexane. Mp (HCl, decomp.) 240 °C. IR (KBr) 3413, 2948, 2676, 2465, 1612, 1474, 1410, 1374, 1138, 1029, 903, 818 cm^{-1}; UV (CH_3OH, nm, ($\log\varepsilon$)): 206 (4.638). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.79 (dd, J = 13.3, 9.9 Hz, 1H, 6-H), 1.85–1.91 (m, 2H, 4-H), 2.11 (d, J = 9.9 Hz, 2H, 9-H), 2.29 (s, 6H, $N(CH_3)_2$), 2.35 (br, t, J = 6.7 Hz, 1H, 6-H), 3.00–3.14 (m, 4H, 1-H,

3-H, 8-H), 3.38 (br, t, J = 9.4 Hz, 1 H, 7-H), 7.13–7.45 (m, 6 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 31.51 (C-4), 35.90 (C-6), 36.75 (C-9), 37.93 ($N(CH_3)_2$), 38.41 (C-8), 41.50 (C-3), 46.41 (C-7), 57.78 (C-5), 61.02 (C-1), 126.47, 127.41, 129.22, 129.78, 130.15, 130.48 (aromatic C), 130.06, 130.26 132.28, 132.54, 144.47, 145.32 (aromatic C_q). HRMS (MALDI): calcd. $C_{22}H_{25}Cl_4N_2$ [MH^+]: 457.0772; found: 457.0815.

5.2.4.2. (7*RS*,8*RS*)-(±)-1-(7,8-Bis(3,4-dichlorophenyl)-2-azabicyclo[3.2.2]non-5-yl)pyrrolidine (8b). Pyrrolidinium isothiocyanate (5.83 g, 44.5 mmol), and 3,4-dichlorobenzylidene acetone (19.3 g, 89 mmol) in toluene (50 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (9.4 g, 83.1 mmol) in glacial acetic acid (84 mL) and subsequently with $LiAlH_4$ (3.5 g, 92.2 mmol) in dry ether (150 mL). Compound **8b** (4.8 g, 9.9 mmol, 22%) was obtained by extraction of the residue with hexane. Mp (HCl, decomp.) 227 °C. IR (KBr) 3422, 2949, 2869, 2613, 2486, 1589, 1475, 1411, 1137, 1028, 818 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 206 (4.629). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.77 (br, s, 4H, $2CH_2$), 1.89–1.97 (m, 3H, 4-H, 6-H), 2.11 (ddd, J = 13.3, 8.9, 2.1 Hz, 1H, 9-H), 2.20 (dd, J = 13.3, 10.6 Hz, 1H, 9-H), 2.30 (ddd, J = 13.1, 9.2, 1.9 Hz, 1H, 6-H), 2.66–2.78 (m, 4H, $N(CH_2)_2$), 3.02–3.16 (m, 4H, 1-H, 3-H, 8-H), 3.40 (br, t, J = 9.4 Hz, 1H, 7-H), 7.13–7.46 (m, 6 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 23.55 ($(CH_2)_2$), 33.27 (C-4), 36.81 (C-6), 36.98 (C-9), 38.32 (C-8), 41.60 (C-3), 45.16 ($N(CH_2)_2$), 46.41 (C-7), 56.81 (C-5), 61.27 (C-1), 126.58, 127.41, 129.24, 129.79, 130.04, 130.17, 130.49, 132.30, 132.55, 144.48, 145.47 (aromatic C). HRMS (MALDI): calcd. $C_{24}H_{27}Cl_4N_2$ [MH^+]: 483.0928; found: 483.1010.

5.2.4.3. (7*RS*,8*RS*)-(±)-1-(7,8-Bis(3,4-dichlorophenyl)-2-azabicyclo[3.2.2]non-5-yl)piperidine (8c). Piperidinium isothiocyanate (2.3 g, 22 mmol), and 3,4-dichlorobenzylidene acetone 8.06 g (38 mmol) in toluene (65 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (4.0 g, 35.3 mmol) in glacial acetic acid (41 mL) and subsequently with $LiAlH_4$ (1.5 g, 40 mmol) in dry ether (150 mL). Compound **8c** (4.24 g, 8.5 mmol, 39%) was obtained after extraction of the residue with hexane. Mp (HCl, decomp.) 225 °C. IR (KBr) 3425, 2947, 2867, 2648, 2529, 2362, 1726, 1635, 1587, 1475, 1409, 1371, 1254, 1137, 1028, 815 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 206 (4.612). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.42–1.50 (m 2H, CH_2), 1.56–1.66 (m, 4H, $2CH_2$), 1.77 (dd, J = 12.6, 10.6 Hz, 1H, 6-H), 1.84–1.96 (m, 2H, 4-H), 2.10–2.13 (m, 2H, 9-H), 2.34 (dd, J = 13.0, 9.2 Hz, 1H, 6-H), 2.50–2.66 (m, 4H, $N(CH_2)_2$), 3.00–3.13 (m, 4H, 1-H, 3-H, 8-H), 3.35 (br, t, J = 9.6 Hz, 1H, 7-H), 7.13–7.45 (m, 6 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 25.00 (CH_2), 26.76 ($2CH_2$), 32.64 (C-4), 35.72 (C-6), 36.68 (C-9), 38.82 (C-8), 41.81 (C-3), 46.25 ($N(CH_2)_2$), 46.90 (C-7), 58.34 (C-5), 61.01 (C-1), 126.51, 127.34, 129.15, 129.72, 130.21, 130.46, 132.34, 132.54, 144.52, 145.42 (aromatic C). HRMS (MALDI): calcd. $C_{25}H_{29}Cl_4N_2$ [MH^+]: 497.1085; found: 497.1091.

5.2.4.4. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis(4-methylphenyl)-2-azabicyclo-[3.2.2]non-5-yl)-*N*,*N*-dimethylamine (9a). Dimethylammonium isothiocyanate (2.4 g, 23 mmol), and 4-(4-methylphenyl)but-3-en-2-one (6.6 g, 42 mol) in toluene (35 mL) gave a resin which was treated with hydroxylamin-*O*-sulfonic acid (2.4 g, 21 mmol) in glacial acetic acid (80 mL) and subsequently with $LiAlH_4$ (1.58 g, 42 mmol) in dry ether (120 mL) giving **9a** (1.16 g, 3.3 mmol, 16%). Mp (HCl): 220–222 °C. IR (KBr) 3421, 3019, 2950, 2863, 2651, 2466, 1626, 1584, 1516, 1456, 1413, 1377, 1179, 1114, 1007, 903, 813 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 213 (4.324). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.83 (s, br, 1H, NH), 1.84–1.92 (m, 3H, 4-H, 6-H), 2.09 (dd, J = 13.2, 11.0 Hz, 1H, 9-H), 2.22 (ddd, J = 13.2, 8.8, 2.5 Hz, 1H, 9-H), 2.30–2.35 (m, 13H, 6-H, $2CH_3$, $N(CH_3)_2$), 3.06 (d, J = 2.5 Hz, 1H, 1-H), 3.07–3.15 (m, 2H, 3-H), 3.25 (ddd J = 11.0, 8.8, 2.2 Hz, 1H, 8-H), 3.39 (br, t, J = 9.3 Hz, 1H, 7-H), 7.10–7.29 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 20.87 ($2CH_3$), 31.67 (C-4), 35.72 (C-9), 36.79 (C-6), 37.95 ($N(CH_3)_2$), 39.23 (C-8), 41.89 (C-3), 46.69 (C-7), 57.97 (C-5), 61.75 (C-1), 127.02, 127.65, 129.10, 129.19 (aromatic C), 135.55, 135.66, 141.21, 142.59 (aromatic C_q). HRMS (MALDI): calcd. $C_{24}H_{33}N_2$ [MH^+]: 349.2644; found: 349.2670.

5.2.4.5. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis(4-methoxyphenyl)-2-azabicyclo-[3.2.2]non-5-yl)-*N*,*N*-dimethylamine (10a). Dimethylammonium isothiocyanate (4.1 g, 39 mmol), 4-(4-methoxyphenyl)but-3-en-2-one 12.5 g (71 mmol) in toluene (90 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (932 mg, 8.2 mmol) in glacial acetic acid (35 mL) and subsequently with $LiAlH_4$ (440 mg, 11.5 mmol) in dry ether (120 mL) giving **10a** (440 mg, 1.16 mmol, 3.3%). Mp (HCl) 209 °C. IR (KBr) 3421, 2958, 2836, 2676, 2464, 1611, 1582, 1515, 1461, 1418, 1251, 1183, 1030, 834 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 227 (4.407), 276 (3.768). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.26 (br, s, 1H, NH), 1.82–1.91 (m, 3H, 4-H, 6-H), 2.09 (dd, J = 13.2, 10.8 Hz, 1H, 9-H), 2.19 (ddd, J = 13.2, 8.9, 2.1 Hz, 1H, 9-H), 2.24–2.34 (m, 7H, 6-H, $N(CH_3)_2$), 3.00 (d, J = 2.6 Hz, 1H, 1-H), 3.08–3.13 (m, 2H, 3-H), 3.22 (ddd J = 10.9, 8.9, 2.3 Hz, 1H, 8-H), 3.37 (br, t, J = 9.4 Hz, 1H, 7-H), 3.77, 3.80 (2s, 6H, 2 OCH_3), 6.85 (d, J = 9.1 Hz, 2 aromatic H), 6.87 (d, J = 9.1 Hz, 2 aromatic H), 7.22 (d, J = 8.8 Hz, 2 aromatic H), 7.30 (d, J = 8.7 Hz, 2 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 31.58 (C-4), 35.88 (C-9), 36.67 (C-6), 37.90 ($N(CH_3)_2$), 38.63 (C-8), 41.80 (C-3), 46.05 (C-7), 55.18 (2 OCH_3), 58.00 (C-5), 61.99 (C-1), 113.81, 113.86, 128.05, 128.67 (aromatic C), 136.17, 137.60, 157.82, 157.92 (aromatic C_q). HRMS (MALDI): calcd. $C_{24}H_{33}N_2O_2$ [MH^+]: 381.2542; found: 381.2574.

5.2.4.6. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis(4-trifluoromethylphenyl)-2-azabicyclo[3.2.2]non-5-yl)-*N*,*N*-dimethylamine (11a). Dimethylammonium isothiocyanate (1.25 g, 12 mmol), and 4-trifluoromethylbenzylidene acetone (4.7 g, 22 mmol) in toluene (20 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (0.64 g, 5.7 mmol) in glacial acetic acid (40 mL) and subsequently with $LiAlH_4$ (400 mg, 10.5 mmol) in dry ether (40 mL) giving a residue which was purified by means of CC using CH_2Cl_2: MeOH = 1:1 as eluent yielding **11c** (480 mg, 1.1 mmol 9.4%). Mp (HCl) 226 °C. IR (KBr) 3423, 2950, 2854, 2683, 1620, 1467, 1419, 1328, 1168, 1122, 1070, 1016, 843 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 208 (4.260). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.81 (s, br, 1H, NH), 1.88–1.95 (m, 3H, 4-H, 6-H), 2.13–2.26 (m, 2H, 9-H), 2.32 (s, 6H, $N(CH_3)_2$), 2.39 (dd, J = 13.4, 8.9 Hz, 1H, 6-H), 3.11–3.18 (m, 3H, 1-H, 3-H), 3.24 (br, t, J = 9.5 Hz, 1H, 8-H), 3.51 (br, t, J = 9.3 Hz, 1H, 7-H), 7.40–7.61 (m, 8 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 31.56 (C-4), 36.00 (C-6), 36.22 (C-9), 37.90 ($N(CH_3)_2$), 39.31 (C-8), 41.62 (C-3), 47.03 (C-7), 57.90 (C-5), 61.08 (C-1), 125.30, 125.59 (2q, ^3J(C,F) = 3.8 Hz, 2 aromatic C), 127.46, 128.22 (aromatic C), 128.45, 128.77 (2d, ^2J(C,F) = 21.4 Hz, 2 aromatic C_q), 148.13 (d, ^1J(C,F) = 244.0 Hz, $2CF_3$), 148.23, 149.25 (aromatic C_q). HRMS (MALDI): calcd. $C_{24}H_{27}F_6N_2$ [MH^+]: 457.2078; found: 457.2066.

5.2.4.7. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis(4-bromophenyl)-2-azabicyclo [3.2.2]non-5-yl)-N,N-dimethylamine (12a). Dimethylammonium isothiocyanate (1.3 g,12.9 mmol), and 4-(4-bromophenyl)but-3-en-2-one (5.3 g, 24 mol) in toluene (40 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (1.8 g, 16 mmol) in glacial acetic acid (70 mL) and subsequently with $LiAlH_4$ (600 mg, 15.8 mmol) in dry ether (80 mL) giving **12a** (840 mg, 1.76 mmol, 25%). Mp (HCl, decomp.) 257 °C. IR (KBr) 3423, 2962, 2653, 2468, 1589, 1491, 1410, 1377, 1181, 1076, 1008, 903, 826 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 204 (4.453), 222 (4.401). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.84 (dd, J = 13.2, 9.9 Hz, 1H, 6-H), 1.88–1.91 (m, 2H, 4-H), 2.07–2.18 (m, 2H, 9-H), 2.31 (s, 6H,

$N(CH_3)_2$), 2.34 (ddd, J = 13.2, 9.5, 2.2 Hz, 1H, 6-H), 3.01 (d, J = 2.2 Hz, 1H, 1-H), 3.07–3.11 (m, 2H, 3-H), 3.13 (ddd, J = 10.6, 8.1, 2.6 Hz, 1H, 8-H), 3.39 (br, t, J = 9.3 Hz, 1H, 7-H), 7.18 (d, J = 8.4 Hz, 2 aromatic H), 7.24 (d, J = 8.4 Hz, 2 aromatic H), 7.41 (d, J = 8.8 Hz, 2 aromatic H), 7.45 (d, J = 8.4 Hz, 2 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 31.60 (C-4), 36.17, 36.20 (C-6, C-9), 37.95 ($N(CH_3)_2$), 38.86 (C-8), 41.68 (C-3), 46.61 (C-7), 57.99 (C-5), 61.41 (C-1), 119.96, 120.05 (aromatic C_q), 128.89, 129.63, 131.46, 131.66 (aromatic C), 143.10, 144.26 (aromatic C_q). HRMS (MALDI): calcd. ($C_{22}H_{27}Br_2N_2$) [MH^+]: 477.0541 found: 477.0533.

5.2.4.8. (7*RS*,8*RS*)-(±)-*N*-(7,8-Bis(naphthalen-1-yl)-2-azabicyclo-[3.2.2]non-5- yl)-N,N-dimethylamine (13a). Dimethylammonium isothiocyanate (1.6 g, 15 mmol), 4-(naphthalen-1-yl)but-3-en-2-one (5.43 g, 28 mmol) in toluene (20 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (1.25 g, 11 mmol) in glacial acetic acid (65 mL) and subsequently with $LiAlH_4$ (820 mg, 22 mmol) in dry ether (60 mL) gave a residue which was purified by means of CC using CH_2Cl_2: MeOH = 1:1 as eluent giving **13a** (650 mg, 1.55 mmol, 11.2%). Mp (HCl, decomp.) 291 °C. IR (KBr) 3405, 3048, 2942, 2661, 2455, 2380, 1600, 1586, 1511, 1457, 1408, 1373, 802, 776 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 224 (5.035), 283 (4.155). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.00–2.15 (m, 3H, 4-H, NH), 2.20 (dd, J = 13.4, 10.4 Hz, 1H, 9-H), 2.38–2.54 (m, 9H, 6-H, 9-H, $N(CH_3)_2$), 3.08 (s, 1H, 1-H), 3.28–3.34 (m, 1H, 3-H), 3.41–3.48 (m, 1H, 3-H), 4.11 (br, t, J = 9.6 Hz, 1H, 8-H), 4.37 (br, t, J = 9.2 Hz, 1H, 7-H), 6.83–8.23 (m, 14 aromatic H). ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 31.22 (C-4), 34.13 (C-6), 34.79 (C-8), 35.63 (C-9), 38.01 ($N(CH_3)_2$), 41.38 (C-7), 41.74 (C-3), 58.32 (C-5), 60.85 (C-1), 122.34, 122.48, 123.89, 123.96, 125.07, 125.14, 125.48, 125.67, 126.15, 126.85, 127.23, 128.72, 128.91, 131.56, 132.29, 133.95, 134.41, 139.05, 140.23 (aromatic C). HRMS (MALDI): calcd. $C_{30}H_{33}N_2$ [MH^+]: 421.2644; found: 421.2607.

5.2.4.9. (7*RS*,8*RS*)-(±)-(7,8-bis(4-fluorophenyl)-2-aza-bicyclo [3.2.2]non-5-yl)-dimethylamine (14a). Dimethylammonium isothiocyanate (8.46 g, 0.081 mol), 4-fluorobenzylidene acteone (24.2 g, 0.147 mol) in toluene (84 mL) gave a resin which was treated with hydroxylamine-*O*-sulfonic acid (6.68 g, 59.12 mmol) in glacial acetic acid (400 mL)) and subsequently with $LiAlH_4$ (1.9 g, 50.4 mmol) in dry ether (85 mL) gave a residue which was purified by means of CC using CH_2Cl_2: MeOH = 1:1 as eluent giving **14a** (1.02 g, 2.86 mmol, 3.9%). M.p. (HCl, decomp.): 282–286 °C; IR (KBr) 3510, 3374, 2946, 2659, 2473, 1606, 1586, 1510, 1482, 1456, 1414, 1222, 1164, 850 cm^{-1}. UV (CH_3OH, nm, ($\log\varepsilon$)): 207 (4.208), 265 (3.344), 349 (2.793). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)) 1.84 (dd, J = 13.2, 9.9 Hz, 1H, 6-H), 1.88 - 1.93 (m, 2H, 4-H), 2.11 (dd, J = 13.6, 10.6 Hz, 1H, 9-H), 2.18 (ddd, J = 13.2, 8.8, 2.0 Hz, 1H, 9-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.34 (ddd, J = 12.8, 11.0, 2.1 Hz, 1H, 6-H), 3.01 (d, J = 2.2 Hz, 1H, 1-H), 3.09 - 3.12 (m, 2H, 3-H), 3.19 (ddd, J = 10.8, 8.8, 2.0 Hz, 1H, 8-H), 3.41 (br, t, J = 9.3 Hz, 1H, 7-H), 6.96 - 7.37 (m, 8 aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz)δ (ppm) 31.57 (C-4), 36.39 (C-9), 36.56 (C-6), 37.91 ($N(CH_3)_2$), 38.59 (C-8), 41.72 (C-3), 46.45 (C-7), 57.90 (C-5), 61.68 (C-1), 115.09 (d, ^2J(C,F) = 21 Hz, aromatic C), 115.26 (d, ^2J(C,F) = 21 Hz, aromatic C), 128.45 (d, ^3J(C,F) = 7.6 Hz, aromatic C), 129.18 (d, ^3J(C,F) = 7.6 Hz, aromatic C), 139.81, 141.01 (aromatic C_q), 161.20 (d, ^1J(C,F) = 244 Hz, aromatic C_q), 161.30 (d, ^1J(C,F) = 243 Hz, aromatic C_q). HRMS (MALDI): calcd. ($C_{22}H_{27}N_2F_2$) [MH^+]: 357.2142; found: 357.2173.

5.3. Biological tests

5.3.1. In vitro microplate assay against Plasmodium falciparum K_1

Antiplasmodial activity was examined using the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). Viability was determined by the incorporation of [^{3}H]-hypoxanthine into living protozoal cells by a modification of a reported assay.[15] 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 was added to each well. Cultures were incubated for a further 24 h before they were harvested onto glass-fiber filters and washed with distilled water. The radioactivity was counted using a BetaplateTM liquid scintillation counter (Wallac, Zurich, Switzerland). The results were recorded as counts per minute (CPM) per well at each drug concentration and expressed as percentage of the untreated controls. From the sigmoidal inhibition curves IC_{50} values were calculated. Assays were run in duplicate and repeated once. Standard was artemisinin.

5.3.2. In vitro microplate assay against *Trypanosoma brucei 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.[16] Serial drug dilutions were prepared covering a range from 90 to 0.123 μg/mL. Then 10^4 bloodstream forms of *Trypanosoma 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. About 10 μl of Alamar Blue (containing 0.0125 g resazurin dissolved in 1000 mL distilled water) was 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.[17] Fluorescence development was measured and expressed as percentage of the control. Data were transferred into the graphic programme 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.

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