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Acyl derivatives of 5-amino-2-azabicyclo[3.2.2]nonanes

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Abstract 5-Amino-2-azabicyclo[3.2.2]nonanes possess activity against the causative organisms of Human African trypanosomiasis and Malaria tropica. Their newly prepared *N*-acyl derivatives were inactive against *Trypanosoma b. rhodesiense*, but some of them showed good antiplasmodial activity against a multiresistant strain of *Plasmodium falciparum*. The results are compared to the activities of the *N*-unsubstituted compounds and *N*-sulfonyl analogues. The diastereomeric character of the formed amides was elucidated by NMR spectroscopy.

Keywords Amides; Antimalarial activity; Drug research; Isomers; NMR spectroscopy.

Introduction

5-Amino-2-azabicyclo[3.2.2]nonanes **1** exhibit activity against the causative organisms of Human African trypanosomiasis (HAT) and Malaria tropica [1]. About half a million people are infected with HAT and every year approximately 50,000 people die from the disease [2]. At the time, CNS infections with *Trypanosoma brucei rhodesiense* can only be cured with melarsoprol, however, its undesired effect of encephalopathy is killing 5–10% of the patients [3]. Since drug-resistance has become an additional problem, there is an urgent need for new compounds against HAT [4].

Malaria kills over 1 million people annually throughout the world [2, 5]. Furthermore, approximately 500 million people get infected with this disease every year [6]. The multidrug-resistant strains of the causative protozoon, *Plasmodium falciparum*, are becoming increasingly prevalent around the world [7–9]. Since traditional therapeutics have become ineffective in many parts of the world, there is great demand for new antimalarials with potency against drug-resistant strains [10, 11].

Recently, we reported the synthesis and the antiprotozoal potency of 5-amino-2-azabicyclo[3.2.2]-nonanes **1** [1]. Their 2-sulfonyl derivatives **2** and **3** have shown good activity against *T. b. rhodesiense* and a multiresistant strain of *P. falciparum* [12]. This paper deals with the synthesis and the antiprotozoal activities of the corresponding 2-acyl derivatives **4**–**7** (Fig. 1).

Results and discussion

Syntheses

Compound **1** was prepared in two steps from bicyclo[2.2.2]octan-2-ones **8**, which were obtained in good yields from the one-pot reaction of benzylidene acetone and dialkylammonium thiocyanates [13, 14]. The conversion of **8** to 2-azabicyclo[3.2.2]nonanes **1** succeeded *via* a *Beckmann* rearrangement and the

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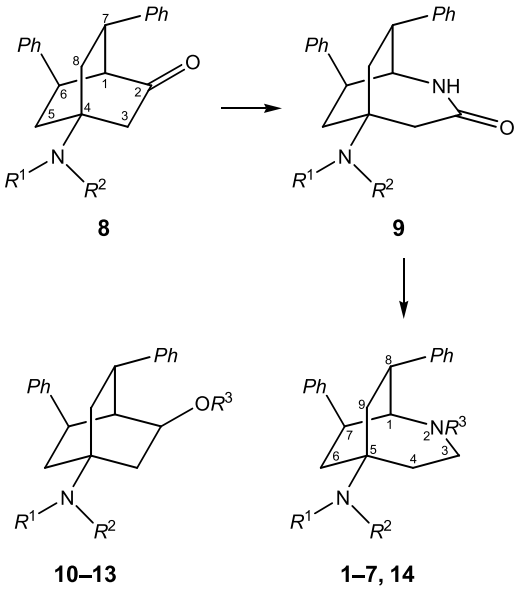

a: $R^1 = R^2 = Me$; **b:** $R^1+R^2 = -(CH_2)_4-$; c: $R^1+R^2 = -(CH_2)_5-$

	R^3
1	H
2	toluene-4-sulfonyl
3	biphenyl-4-ylsulfonyl
4,10	benzoyl
5,11	2-diethylaminoacetyl
6,12	2-pyrrolidinoacetyl
7,13	2-piperidinoacetyl
14	2-chloroacetyl

Fig. 1 Structures of compounds **1**–**9**

subsequent reduction of the formed 2-azabicyclo-[3.2.2]nonan-2-ones **9** with $LiAlH_4$ [1]. Benzamides **4** and aminoacetamides **5**–**7** were prepared from compounds **1**, due to the promising antiprotozoal activities of the benzoates **10** [15] and of the aminoacetates **11**–**13** [16] in the bicyclo[2.2.2]octane series. The acylation reactions with benzoyl chloride or chloroacetyl chloride proceeded in CH_2Cl_2 at room temperature giving amides **4** and **14**. The aminoacetamides **5**–**7** were prepared from the 2-chloroacetamides **14** upon treatment with the corresponding amines without use of a solvent. In the ^{13}C NMR spectra of compounds **4**–**7** the formation of an amide bond was obvious from the appearance of the carbonyl signal at *ca.* 170 ppm. The successful acylation of the nitrogen in ring position 2 was verified by long-range couplings from the protons in ring positions 1 and 3 to the carbonyl carbon in their HMBC spectra. Due to the partial double-bond character of the C(O)–N bond the rotation around this bond is restricted. Therefore two sets of signals for the (*E*)- and (*Z*)-diastereoisomers of compounds **4**–**7** were visable in their ^1H and ^{13}C NMR spectra (Fig. 2). The distinction between the (*E*)- and (*Z*)-isomers succeeded *via* ^{13}C NMR spectroscopy. Typically [17] the resonances for the C-1 and the C-3 in (*Z*)-relation to the carbonyl oxygen were shifted distinctly to lower frequencies in their ^{13}C NMR spectra. All other signals were assigned by means of two-dimensional NMR methods.

Antiprotozoal acitivities and cytotoxicity

The antiprotozoal activities of all new compounds **4**–**7** were tested against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum* K_1 using *in vitro* microplate assays. Their cytotoxicity was determined using L-6 cells. The results are presented in Table 1.

The antitrypanosomal potency of compounds **4**–**7** is negligible. Their antiplasmodial activities are similar to those of the formerly prepared sulfonamides **2** and **3**, but they are far less cytotoxic. The replacement of the benzoyl by an aminoacyl group has markedly improved the antiplasmodial activity and the selectivity indices (SI: IC_{50} cytotoxicity/IC_{50} activity) of structurally related esters in the bicyclo-[2.2.2]octane series [16]. Contrary to our expectations the aminoacylamides **5**–**7** are rather less active

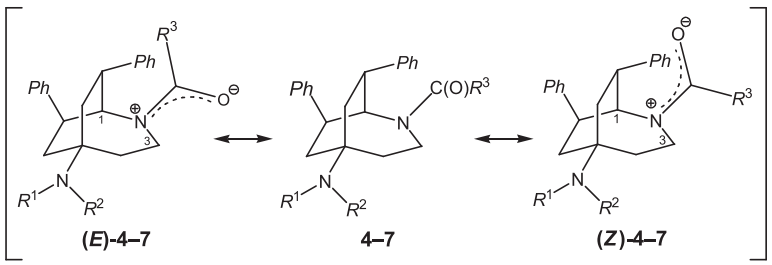

Fig. 2 Diastereomeric character (*E*/*Z*) of compounds **4**–**7**

Table 1 Activities of compounds **1**–**7** expressed as $IC_{50}/\mu M$[a]

Compd.	*T.b. rhodesiense*	*P. falciparum* K_1	Cytotox. L6-cells
1a	0.60	0.28	108.8
1b	1.16	0.56	120.4
1c	6.57	0.64	89.74
2a	0.76	0.43	9.27
2b	1.26	1.30	9.42
2c	2.65	1.26	10.50
3a	1.06	1.03	3.62
3c	1.45	0.85	7.33
4a	3.69	0.52	34.83
4b	5.59	0.49	80.06
4c	4.45	0.60	32.28
5a	5.21	1.30	89.57
5b	7.16	0.91	91.54
5c	18.59	0.94	102.19
6a	4.31	1.43	91.05
6b	9.85	1.26	74.20
6c	9.07	1.19	97.31
7a	9.47	1.72	141.4
7b	6.50	0.62	115.7
7c	6.83	0.78	102.8
chl		0.062	
sur	0.011		
mef			4.3

[a] Values represent the average of four determinations (two determinations of two independent experiments); *n.t.* not tested; *chl* chloroquine; *mef* mefloquine; *sur* suramine

against *P. falciparum* K_1 than the benzamides **4**, nevertheless, their selectivity is better due to their lower cytotoxicity. The favourable properties of the 2-unsubstituted 2-azabicyclo-nonane **1a** were not attained, however, the most active compounds **4a**–**4c** and **7b** exhibit good activities and selectivity indices.

Conclusion

Benzoyl and aminoacetyl derivatives of 2-azabicyclo[3.2.2]nonanes were prepared. Their structures were elucidated by NMR spectroscopy revealing the (*E*/*Z*)-character of the formed amide diastereoisomers. Their *in vitro* activities against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum* K_1 were determined. The antitrypanosomal activity was dramatically decreased by the acylation, whereas the antiplasmodial activities of the most active of the new compounds were similar to those of their parent 2-unsubstituted 2-azabicyclo-nonanes. The cytotoxicity of the sulfonamide analogues was markedly decreased by replacement of the sulfonyl substituent by an acyl group. The most promising of the new compounds were a single aminoacetamide and the benzamides, which will serve as leads for further studies.

Experimental

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200. IR spectra: infrared spectrometer system 2000 FT (*Perkin Elmer*). UV-VIS: Lambda 17 UV/VIS-spectrometer (*Perkin Elmer*). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, solvent resonance as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. Assignments marked with an asterisk are interchangeable between the (*E*)- and (*Z*)-isomers. HR-MS: Kratos profile spectrometer. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their values were in satisfactory agreement with the calculated ones. Materials: column-chromatography (CC): 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 compounds were detected in UV light at 254 nm.

The preparation of 2-azabicyclo[3.2.2]nonanes **1a**–**1c** [1] and their sulfonyl derivatives **2** and **3** has been reported [12]. The one-pot formation of compounds **8** was carried out as outlined in Refs. [13, 14].

*Preparation of 2-benzoyl-2-azabicyclo[3.2.2]nonanes **4a**–**4c***
In an atmosphere of *Ar* triethylamine and benzoyl chloride were added to a solution of the 2-azabicyclo[3.2.2]nonanes **1** in 5 cm^3 dry CH_2Cl_2. The mixture was stirred over night at room temperature. After dilution with 5 cm^3 CH_2Cl_2, 10 cm^3 2 *N* NaOH were added. The layers were separated and the aqueous phase was extracted 3 times with ether. The combined organic layers were washed 3 times with H_2O, dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The residue was purified by means of column chromatography.

(7RS,8RS)-(±)-2-Benzoyl-5-dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]nonane ((*E*)-**4a**, (*Z*)-**4a**, $C_{29}H_{32}N_2O$)
The reaction of 480 mg **1a** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 239 mg benzoyl chloride (1.7 mmol) gave a residue, which was chromatographed eluting with CH_2Cl_2:*Me*OH (9:1) and subsequently with ethyl acetate:*Me*OH (1:1). 234 mg (38%) of the isomers (*E*)-**4a** and (*Z*)-**4a** were obtained as a colorless resin. NMR: (*E*)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.76$–1.89 (m, 6-H), 2.03–2.39 (m, 4-H, 6-H, 9-H), 2.32 (s, $N(CH_3)_2$), 3.23 (ddd, $J = 10.1$, 10.0, 2.7 Hz, 8-H), 3.37 (dd, $J = 10.8$, 8.3 Hz, 7-H), 3.49–3.56 (m, 3-H), 3.95 (d, $J = 2.7$ Hz, 1-H), 4.58 (dd, $J = 15.0$, 3.4 Hz, 3-H), 6.56 (d, $J = 7.3$ Hz, aromatic H), 6.94 (t, $J = 7.8$ Hz, aromatic H), 7.07–

7.39 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 29.28$ (C-4), 32.36 (C-9), 37.89 (C-6), 37.95 ($N(CH_3)_2$), 41.37 (C-8), 41.65 (C-3), 46.21 (C-7), 57.28 (C-5), 62.67 (C-1), 126.26, 126.58*, 126.75, 126.97*, 127.01, 127.70, 127.84, 128.71, 128.82 (aromatic C), 136.25, 141.67, 143.43 (aromatic C_q), 171.75 (CO) ppm; (*Z*)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.67$–1.83 (m, 4-H), 2.03–2.47 (m, 6-H, 9-H), 2.30 (s, $N(CH_3)_2$), 3.11 (ddd, $J = 14.1$, 12.2, 4.0 Hz, 3-H), 3.40–3.52 (m, 7-H, 8-H), 3.66 (br, d, $J = 14.0$ Hz, 3-H), 5.14 (d, $J = 3.3$ Hz, 1-H), 7.18–7.39 (m, aromatic H), 7.66 (d, $J = 7.8$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 30.57$ (C-4), 34.93 (C-8), 35.32 (C-9), 36.40 (C-6), 38.03 ($N(CH_3)_2$), 45.24 (C-3, C-7), 55.84 (C-1), 57.82 (C-5), 126.26*, 126.33, 126.48, 126.58*, 126.97*, 127.84, 128.31, 128.48, 128.57, 129.47 (aromatic C), 136.77, 143.14, 143.27 (aromatic C_q), 170.52 (CO) ppm; (*E*)-**4a**, (*Z*)-**4a**: IR (KBr): $\bar{\nu} = 2983$, 2946, 2872, 1618, 1578, 1495, 1447, 1419, 1380, 1356, 1261, 1097, 1040, 937, 760, 721, 700 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log \varepsilon) = 232$ (3.728) nm; MS (base, EI$^+$): m/z (%) = 424 (44.6) [M$^+$], 319 (16.3), 275 (100.0), 215 (9.3), 173 (31.0), 105 (69.8), 96 (10.9), 77 (25.6); HR-MS (EI$^+$): calcd. ($C_{29}H_{32}N_2O$): 424.25146; found: 424.25246.

(7RS,8RS)-(±)-2-Benzoyl-7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]nonane ((*E*)-**4b**, (*Z*)-**4b**, $C_{31}H_{34}N_2O$)

The reaction of 382 mg **1b** (1.05 mmol), 127 mg triethylamine (1.25 mmol), and 176 mg benzoyl chloride (1.25 mmol) gave a residue, which was chromatographed eluting with ethyl acetate:*Me*OH (1:1). 209 mg (44%) of the isomers (*E*)-**4b** and (*Z*)-**4b** were obtained as a yellowish resin. NMR: (*E*)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.74$–1.84 (m, $(CH_2)_2$), 1.92 (t, $J = 12.0$ Hz, 6-H), 2.14–2.36 (m, 4-H, 6-H, 9-H), 2.68–2.78 (m, $N(CH_2)_2$), 3.27 (ddd, $J = 10.0$, 9.9, 2.2 Hz, 8-H), 3.38 (dd, $J = 10.4$, 8.6 Hz, 7-H), 3.49–3.60 (m, 3-H), 3.94 (d, $J = 2.8$ Hz, 1-H), 4.58 (dd, $J = 15.0$, 2.4 Hz, 3-H), 6.56 (d, $J = 7.4$ Hz, aromatic H), 6.94 (t, $J = 7.7$ Hz, aromatic H), 7.07–7.38 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.52$ ($(CH_2)_2$), 30.53 (C-4), 33.20 (C-9), 38.52 (C-6), 41.20 (C-8), 41.58 (C-3), 45.48 ($N(CH_2)_2$), 46.22 (C-7), 55.96 (C-5), 62.83 (C-1), 126.25, 126.58*, 126.67, 126.93, 126.95*, 127.66, 127.81, 128.65, 128.76 (aromatic C), 136.28, 141.66, 143.54 (aromatic C_q), 171.70 (CO) ppm; (*Z*)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.74$–1.84 (m, 4-H, $(CH_2)_2$), 2.16–2.40 (m, 6-H, 9-H), 2.54 (t, $J = 12.5$ Hz, 6-H), 2.68–2.78 (m, $N(CH_2)_2$), 3.14 (ddd, $J = 14.2$, 11.0, 5.3 Hz, 3-H), 3.42–3.50 (m, 7-H, 8-H), 3.64 (br, d, $J = 14.2$ Hz, 3-H), 5.14 (d, $J = 3.2$ Hz, 1-H), 7.14–7.38 (m, aromatic H), 7.67 (d, $J = 7.4$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.52$ ($(CH_2)_2$), 32.09 (C-4), 34.74 (C-8), 36.11 (C-9), 36.89 (C-6), 45.15 ($N(CH_2)_2$), 45.22 (C-7), 45.24 (C-3), 55.96 (C-1), 56.24 (C-5), 126.25*, 126.45, 126.52, 126.58*, 126.95*, 127.86, 128.27, 128.42, 128.52, 129.41 (aromatic C), 136.80, 143.11, 143.34 (aromatic C_q), 170.46 (CO) ppm; (*E*)-**4b**, (*Z*)-**4b**: IR (KBr): $\bar{\nu} = 2944$, 2875, 1626, 1599, 1496, 1433, 1389, 1351, 1259, 1113, 940, 776, 752, 737, 702 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log \varepsilon) = 232$ (3.809) nm; MS (base, EI$^+$): m/z (%) = 450 (46.6) [M$^+$], 345 (30.3), 301 (100.0), 241 (22.5), 212 (47.7), 199 (59.0), 184 (16.3), 122 (15.5), 105 (100.0), 91 (25.6), 77 (49.7); HR-MS (EI$^+$): calcd. ($C_{31}H_{34}N_2O$): 450.26711; found: 450.26729.

(7RS,8RS)-(±)-2-Benzoyl-7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]nonane ((*E*)-**4c**, (*Z*)-**4c**, $C_{32}H_{36}N_2O$)

The reaction of 500 mg **1c** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 239 mg benzoyl chloride (1.7 mmol) gave a residue, which was chromatographed eluting with ethyl acetate:*Me*OH (5:1). 397 mg (61%) of the isomers (*E*)-**4c** and (*Z*)-**4c** were obtained as a colorless resin. NMR: (*E*)-**4c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.40$–1.50 (m, CH_2), 1.54–1.68 (m, $2CH_2$), 1.76–1.84 (m, 6-H), 2.04–2.36 (m, 4-H, 6-H, 9-H), 2.50–2.70 (m, $N(CH_2)_2$), 3.23 (ddd, $J = 10.1$, 9.9, 2.7 Hz, 8-H), 3.35–3.47 (m, 7-H), 3.53 (dd, $J = 13.6$, 4.9 Hz, 3-H), 3.94 (d, $J = 2.7$ Hz, 1-H), 4.57 (dd, $J = 15.0$, 3.3 Hz, 3-H), 6.55 (d, $J = 7.4$ Hz, aromatic H), 6.95 (t, $J = 7.7$ Hz, aromatic H), 7.08–7.37 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.89$ (CH_2), 26.60 ($2CH_2$), 30.65 (C-4), 32.30 (C-9), 37.65 (C-6), 41.53 (C-8), 41.72 (C-3), 46.20 (C-7), 46.44 ($N(CH_2)_2$), 57.86 (C-5), 62.59 (C-1), 126.23, 126.52*, 126.66, 126.94, 126.96*, 127.64, 127.80, 128.64, 128.76 (aromatic C), 136.24, 141.72, 143.46 (aromatic C_q), 171.65 (CO) ppm; (*Z*)-**4c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.40$–1.50 (m, $2CH_2$), 1.54–1.68 (m, $2CH_2$), 1.70–1.82 (m, 4-H), 2.04–2.51 (m, 6-H, 9-H), 2.50–2.70 (m, $N(CH_2)_2$), 3.13 (ddd, $J = 13.8$, 12.9, 3.6 Hz, 3-H), 3.33–3.49 (m, 7-H, 8-H), 3.63 (br, d, $J = 14.3$ Hz, 3-H), 5.16 (d, $J = 3.2$ Hz, 1-H), 7.13–7.37 (m, aromatic H), 7.67 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.89$ (CH_2), 26.60 ($2CH_2$), 31.70 (C-4), 35.05 (C-9), 35.21 (C-8), 36.41 (C-6), 45.37 (C-3), 45.46 (C-7), 46.26, ($N(CH_2)_2$), 55.74 (C-1), 58.49 (C-5), 126.23*, 126.27, 126.48, 126.52*, 126.96*, 127.80, 128.27, 128.44, 128.49, 129.42 (aromatic C), 136.80, 143.17, 143.34 (aromatic C_q), 170.43 (CO) ppm; (*E*)-**4c**, (*Z*)-**4c**: IR (KBr): $\bar{\nu} = 2930$, 2850, 1630, 1601, 1577, 1496, 1447, 1421, 1380, 1352, 1259, 1150, 1103, 1031, 932, 738, 698 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log \varepsilon) = 233$ (3.769) nm; MS (base, EI$^+$): m/z (%) = 464 (50.4) [M$^+$], 373 (11.6), 359 (24.1), 315 (100.0), 275 (12.4), 255 (17.1), 239 (9.3), 213 (44.2), 198 (15.5), 136 (17.5), 105 (100.0), 91 (21.7), 77 (41.1), 51 (8.5); HR-MS (EI$^+$): calcd. ($C_{32}H_{36}N_2O$): 464.28276; found: 464.28192.

Preparation of 2-dialkylamino-1-(7,8-diphenyl-2-azabicyclo-[3.2.2]non-2-yl)ethanones ***5–7***

The 2-azabicyclo[3.2.2]nonanes were dried thrice by distillation with benzene. Then 10 cm^3 dry CH_2Cl_2, triethylamine and chloroacetyl chloride were added in an inert-gas atmosphere at 0°C. The mixture was stirred over night at room temperature. After dilution with 10 cm^3 CH_2Cl_2, 5 cm^3 2 *N* NaOH were added. The layers were separated and the aqueous phase was extracted 3 times with ether. The organic layers were washed 3 times with H_2O, dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The corresponding amine and a catalytic amount of KI were added to the residue and the mixture was stirred over night. Then most of the amine was removed *in vacuo*. The residue was dissolved in CH_2Cl_2, and ethyl acetate was added. The precipitate was sucked off and

the filtrate was repeatedly washed with H_2O. The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated *in vacuo* giving compounds **5**–**7**.

(7RS,8RS)-(±)-2-Diethylamino-1-(5-dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)ethanone ((*E*)-**5a**, (*Z*)-**5a**, $C_{28}H_{39}N_3O$)

The reaction of 480 mg **1a** (1.5 mmol), 182 mg triethylamine (1.8 mmol), and 203 mg chloroacetyl chloride (1.8 mmol) gave a resin, which was reacted with 1097 mg diethylamine (15 mmol). The afforded residue was chromatographed eluting with CH_2Cl_2:*Me*OH (6:1). 379 mg (58%) of the isomers (*E*)-**5a** and (*Z*)-**5a** were obtained as a colorless resin. NMR: (*E*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.61$ (t, $J = 7.1$ Hz, $2CH_3$), 1.86–1.92 (m, 6-H), 2.01 (dd, $J = 12.3$, 5.6 Hz, 4-H), 2.08–2.19 (m, 4-H, 9-H, NCH_2), 2.22–2.36 (m, 6-H, NCH_2), 2.33 (s, $N(CH_3)_2$), 2.47–2.55 (m, CH_2CO), 3.22–3.50 (m, 3-H, 7-H, 8-H), 4.35 (ddd, $J = 14.8$, 5.6, 2.7 Hz, 3-H), 4.48 (d, $J = 2.7$ Hz, 1-H), 7.13–7.42 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 10.79$ ($2CH_3$), 29.63 (C-4), 32.97 (C-9), 37.89 (C-6), 37.94 ($N(CH_3)_2$), 38.07 (C-6), 41.16 (C-3), 41.27 (C-8), 46.32 (C-7), 46.97 ($N(CH_2)_2$), 56.54 (CH_2CO), 57.64 (C-5), 60.02 (C-1), 126.77, 127.00, 127.02, 127.80, 128.73, 128.79 (aromatic C), 142.34, 144.42 (aromatic C_q), 170.96 (CO) ppm; (*Z*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.00$ (t, $J = 7.1$ Hz, $2CH_3$), 1.80 (td, $J = 13.4$, 4.0 Hz, 4-H), 1.87–1.94 (m, 4-H), 2.07–2.20 (m, 6-H, 9-H), 2.30–2.42 (m, 6-H, 9-H), 2.37 (s, $N(CH_3)_2$), 2.48–2.58 (m, $N(CH_2)_2$), 3.07 (td, $J = 13.3$, 3.2 Hz, 3-H), 3.22–3.36 (m, 7-H, 8-H, CH_2CO), 4.20 (br, d, $J = 13.5$ Hz, 3-H), 5.06 (d, $J = 3.4$ Hz, 1-H), 7.14–7.42 (m, aromatic H), 7.57 (d, $J = 7.9$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 11.56$ ($2CH_3$), 30.71 (C-4), 34.67 (C-8), 35.05 (C-6), 36.08 (C-9), 37.98 ($N(CH_3)_2$), 42.41 (C-3), 45.25 (C-7), 47.13 ($N(CH_2)_2$), 54.03 ($N(CH_2)_2$), 55.76 (C-1), 58.03 (CH_2CO), 58.25 (C-5), 126.18, 126.49, 126.52, 127.75, 128.40, 128.52 (aromatic C), 142.99, 143.31 (aromatic C_q), 169.55 (CO) ppm; (*E*)-**5a**, (*Z*)-**5a**: IR (KBr): $\bar{\nu} = 2966$, 1636, 1603, 1497, 1449, 1433, 1041, 933, 750, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log \varepsilon) = 230$ (3.574), 258 (2.930) nm; HR-MS (MALDI): calcd. ($C_{28}H_{40}N_3O$) [MH^+]: 434.3171; found: 434.3206.

(7RS,8RS)-(±)-2-Diethylamino-1-(7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)ethanone ((*E*)-**5b**, (*Z*)-**5b**, $C_{30}H_{41}N_3O$)

The reaction of 485 mg **1b** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 192 mg chloroacetyl chloride (1.7 mmol) gave a resin, which was reacted with 1024 mg diethylamine (14 mmol). The afforded residue was chromatographed eluting with CH_2Cl_2:*Me*OH (6:1). 431 mg (67%) of the isomers (*E*)-**5b** and (*Z*)-**5b** were obtained as a colorless resin. NMR: (*E*)-**5b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.62$ (t, $J = 7.2$ Hz, $2CH_3$), 1.78–1.86 (m, $(CH_2)_2$), 2.04–2.12 (m, 6-H), 2.10–2.20 (m, 4-H, NCH_2), 2.16–2.24 (m, 9-H), 2.22–2.34 (m, 6-H, 9-H, NCH_2), 2.47–2.55 (m, CH_2CO), 2.75–2.96 (m, $N(CH_2)_2$), 3.26–3.32 (m, 7-H), 3.41–3.53 (m, 3-H, 8-H), 4.35 (dt, $J = 14.8$, 4.1 Hz, 3-H), 4.49 (d, $J = 2.7$ Hz, 1-H), 7.16–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 10.75$ ($2CH_3$), 23.63 ($(CH_2)_2$), 30.82 (C-4), 33.79 (C-9), 38.23 (C-6), 40.84 (C-3), 40.90 (C-8), 45.56 ($N(CH_2)_2$), 46.19 (C-7), 46.93 ($N(CH_2)_2$), 57.23 (C-5), 56.50 (CH_2CO), 60.11 (C-1), 126.75, 126.95, 127.01, 127.74, 128.69, 128.73 (aromatic C), 142.14, 144.23 (aromatic C_q), 170.96 (CO) ppm; (*Z*)-**5b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.00$ (t, $J = 7.1$ Hz, $2CH_3$), 1.78–1.86 (m, $(CH_2)_2$), 1.93–1.98 (m, 4-H), 2.17–2.24 (m, 9-H), 2.30–2.37 (m, 6-H), 2.47–2.59 (m, 9-H, $N(CH_2)_2$), 2.75–2.96 (m, $N(CH_2)_2$), 3.10 (td, $J = 14.2$, 4.2 Hz, 3-H), 3.25–3.34 (m, 7-H, CH_2CO), 3.38 (ddd, $J = 11.6$, 8.4, 2.7 Hz, 8-H), 4.21 (br, d, $J = 14.2$ Hz, 3-H), 5.06 (d, $J = 3.4$ Hz, 1-H), 7.14–7.42 (m, aromatic H), 7.59 (d, $J = 7.8$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 11.52$ ($2CH_3$), 23.59 ($(CH_2)_2$), 32.35 (C-4), 34.34 (C-8), 35.57 (C-6), 36.17 (C-9), 42.19 (C-3), 45.12 (C-7), 45.56 ($N(CH_2)_2$), 47.09 ($N(CH_2)_2$), 55.82 (C-1), 58.05 (CH_2CO), 58.06 (C-5), 126.15, 126.41, 126.51, 127.74, 128.36, 128.50 (aromatic C), 142.73, 143.14 (aromatic C_q), 169.57 (CO) ppm; (*E*)-**5b**, (*Z*)-**5b**: IR (KBr): $\bar{\nu} = 2965$, 1635, 1602, 1496, 1433, 1032, 936, 748, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log \varepsilon) = 231$ (3.574), 258 (2.936) nm; HR-MS (MALDI): calcd. ($C_{30}H_{42}N_3O$) [MH^+]: 460.3328; found: 460.3360.

(7RS,8RS)-(±)-2-Diethylamino-1-(7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)ethanone ((*E*)-**5c**, *Z*-**5c**, $C_{31}H_{43}N_3O$)

The reaction of 504 mg **1c** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 192 mg chloroacetyl chloride (1.7 mmol) gave a resin, which was reacted with 1024 mg diethylamine (14 mmol) affording 398 mg (60%) of the isomers (*E*)-**5c** and (*Z*)-**5c** as a colorless resin. NMR: (*E*)-**5c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.59$ (t, $J = 7.1$ Hz, $2CH_3$), 1.41–1.51 (m, CH_2), 1.54–1.67 (m, $2CH_2$), 1.80–1.87 (m, 6-H), 1.93–2.01 (m, 4-H), 2.10–2.16 (m, 4-H, 9-H, NCH_2), 2.20–2.30 (m, 6-H, NCH_2), 2.46–2.70 (m, CH_2CO, $N(CH_2)_2$), 3.16–3.25 (m, 7-H), 3.31–3.39 (m, 3-H), 3.43 (br, td, $J = 9.9$, 2.5 Hz, 8-H), 4.35 (ddd, $J = 15.0$, 5.4, 2.5 Hz, 3-H), 4.47 (d, $J = 2.7$ Hz, 1-H), 7.18–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 10.82$ ($2CH_3$), 25.00, 26.72 ($3CH_2$), 30.85 (C-4), 33.02 (C-9), 37.97 (C-6), 41.52 (C-3), 41.63 (C-8), 46.44 ($N(CH_2)_2$), 46.50 (C-7), 46.95 ($N(CH_2)_2$), 56.59 (CH_2CO), 57.80 (C-5), 60.02 (C-1), 126.66, 126.92, 126.97, 127.79, 128.68, 128.77 (aromatic C), 142.55, 144.72 (aromatic C_q), 170.95 (CO) ppm; (*Z*)-**5c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.99$ (t, $J = 7.1$ Hz, $2CH_3$), 1.41–1.51 (m, CH_2), 1.54–1.67 (m, $2CH_2$), 1.80 (td, $J = 13.3$, 4.3 Hz, 4-H), 1.90–2.04 (m, 4-H, 6-H), 2.09–2.13 (m, 9-H), 2.31–2.40 (m, 6-H, 9-H), 2.46–2.70 (m, $2N(CH_2)_2$), 3.09 (td, $J = 13.7$, 3.0 Hz, 3-H), 3.14–3.21 (m, 7-H), 3.25–3.30 (m, 8-H, CH_2CO), 4.15 (br, d, $J = 13.7$ Hz, 3-H), 5.08 (d, $J = 3.2$ Hz, 1-H), 7.11–7.40 (m, aromatic H), 7.57 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 11.62$ ($2CH_3$), 25.00, 26.81 ($3CH_2$), 31.85 (C-4), 35.00 (C-6), 35.17 (C-8), 36.23 (C-9), 42.70 (C-3), 45.67 (C-7), 46.33 ($N(CH_2)_2$), 47.13 ($N(CH_2)_2$), 55.66 (C-1), 58.10 (CH_2CO), 58.34 (C-5), 126.10, 126.42, 126.57, 127.77, 128.36, 128.45 (aromatic C), 143.24, 143.60 (aromatic C_q), 169.57 (CO) ppm; (*E*)-**5c**, (*Z*)-**5c**: IR (KBr): $\bar{\nu} = 2931$, 1635, 1603, 1497, 1449, 1439, 1032, 919, 751, 734, 699 cm^{-1};

UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.647) nm; HR-MS (MALDI): calcd. ($C_{31}H_{44}N_3O$) [MH^+]: 474.3484; found: 474.3456.

(7RS,8RS)-(±)-2-Pyrrolidino-1-(5-dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)ethanone
((*E*)-**6a**, (*Z*)-**6a**, $C_{28}H_{37}N_3O$)
The reaction of 352 mg **1a** (1.1 mmol), 132 mg triethylamine (1.3 mmol), and 147 mg chloroacetyl chloride (1.3 mmol) gave a resin, which was reacted with 782 mg pyrrolidine (11 mmol). The afforded residue was chromatographed eluting with CH_2Cl_2:*Me*OH (9:1). 266 mg (56%) of the isomers (*E*)-**6a** and (*Z*)-**6a** were obtained as a colorless resin. NMR: (*E*)-**6a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.36$–1.52 (m, $(CH_2)_2$), 1.82 (br, t, $J = 12.5$ Hz, 6-H), 1.97 (dd, $J = 12.9$, 5.5 Hz, 4-H), 2.06–2.12 (m, 4-H), 2.09–2.18 (m, 9-H, NCH_2), 2.18–2.24 (m, 6-H, NCH_2), 2.30 (s, $N(CH_3)_2$), 2.59, 2.71 (2d, $J = 13.6$ Hz, CH_2CO), 3.20–3.29 (m, 7-H), 3.28–3.37 (m, 3-H), 3.37–3.45 (m, 8-H), 4.42 (ddd, $J = 14.8$, 5.1, 2.9 Hz, 3-H), 4.53 (d, $J = 2.7$ Hz, 1-H), 7.15–7.38 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.43$ ($(CH_2)_2$), 29.69 (C-4), 33.36 (C-9), 38.00 ($N(CH_3)_2$), 38.07 (C-6), 40.91 (C-3, C-8), 46.30 (C-7), 53.61 ($N(CH_2)_2$), 57.34 (C-5), 58.94 (CH_2CO), 59.71 (C-1), 126.63, 126.65, 126.88, 127.63, 128.78, 128.79 (aromatic C), 142.57, 144.69 (aromatic C_q), 170.12 (CO) ppm; (*Z*)-**6a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta =$ 1.75–1.82 (m, $(CH_2)_2$), 1.80 (td, $J = 13.4$, 4.0 Hz, 4-H), 1.88–1.94 (m, 4-H), 2.03–2.27 (m, 6-H, 9-H), 2.33 (s, $N(CH_3)_2$), 2.30–2.40 (m, 6-H, 9-H), 2.45–2.51 (m, NCH_2), 2.53–2.60 (m, NCH_2), 3.09 (td, $J = 13.4$, 3.2 Hz, 3-H), 3.26–3.33 (m, 7-H, 8-H), 3.29, 3.38 (2d, $J = 13.6$ Hz, CH_2CO), 4.02 (br, d, $J = 14.2$ Hz, 3-H), 5.05 (d, $J = 3.4$ Hz, 1-H), 7.13–7.39 (m, aromatic H), 7.57 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.69$ ($(CH_2)_2$), 30.66 (C-4), 34.82 (C-8), 35.10 (C-6), 36.15 (C-9), 37.97 ($N(CH_3)_2$), 42.44 (C-3), 45.33 (C-7), 54.03 ($N(CH_2)_2$), 55.76 (C-1), 57.87 (C-5), 59.54 (CH_2CO), 126.16, 126.48, 126.55, 127.76, 128.34, 128.49 (aromatic C), 143.13, 143.42 (aromatic C_q), 168.92 (CO) ppm; (*E*)-**6a**, (*Z*)-**6a**: IR (KBr): $\bar{\nu} = 2951$, 1638, 1602, 1497, 1434, 1041, 934, 752, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.573), 258 (2.815) nm; HR-MS (MALDI): calcd. ($C_{28}H_{36}N_3O$) [$M\text{-}H^+$]: 430.2858; found: 430.2861.

(7RS,8RS)-(±)-2-Pyrrolidino-1-(7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)ethanone
((*E*)-**6b**, (*Z*)-**6b**, $C_{30}H_{39}N_3O$)
The reaction of 381 mg **1b** (1.1 mmol), 132 mg triethylamine (1.3 mmol), and 147 mg chloroacetyl chloride (1.3 mmol) gave a resin, which was reacted with 782 mg pyrrolidine (11 mmol). The afforded residue was chromatographed eluting with CH_2Cl_2:*Me*OH (6:1). 348 mg (71%) of the isomers (*E*)-**6b** and (*Z*)-**6b** were obtained as a colorless resin. NMR: (*E*)-**6b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.37$–1.53 (m, $(CH_2)_2$), 1.72–1.82 (m, $(CH_2)_2$), 1.95–2.02 (m, 6-H), 2.05–2.14 (m, 4-H), 2.10–2.28 (m, $N(CH_2)_2$), 2.16–2.26 (m, 9-H), 2.26–2.34 (m, 6-H), 2.61, 2.73 (2d, $J = 13.8$ Hz, CH_2CO), 2.72–2.88 (m, $N(CH_2)_2$), 3.24–3.31 (m, 7-H), 3.32–3.40 (m, 3-H), 3.45 (br, td, $J = 10.0$, 2.5 Hz, 8-H), 4.41 (ddd, $J = 14.9$, 4.6, 3.5 Hz, 3-H), 4.53 (d, $J = 2.7$ Hz, 1-H), 7.14–7.37 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.43$ ($(CH_2)_2$), 23.60 ($(CH_2)_2$), 31.01 (C-4), 34.18 (C-9), 38.54 (C-6), 40.60 (C-8), 40.68 (C-3), 45.39 ($N(CH_2)_2$), 46.26 (C-7), 53.60 ($N(CH_2)_2$), 56.72 (C-5), 58.92 (CH_2CO), 59.83 (C-1), 126.61, 126.67, 126.83, 127.60, 128.75 (aromatic C), 142.47, 144.62 (aromatic C_q), 170.08 (CO) ppm; (*Z*)-**6b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.72$–1.86 (m, $2(CH_2)_2$), 1.87–1.97 (m, 4-H), 2.13–2.19 (m, 9-H), 2.23–2.34 (m, 6-H), 2.43–2.60 (m, 9-H, $N(CH_2)_2$), 2.72–2.88 (m, $N(CH_2)_2$), 3.13 (td, $J = 13.5$, 4.2 Hz, 3-H), 3.24–3.31 (m, 7-H), 3.30–3.36 (m, 8-H), 3.28, 3.38 (2d, $J = 13.7$ Hz, CH_2CO), 4.02 (br, d, $J = 13.5$ Hz, 3-H), 5.05 (d, $J = 3.4$ Hz, 1-H), 7.14–7.37 (m, aromatic H), 7.59 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.56$ ($(CH_2)_2$), 23.68 ($(CH_2)_2$), 32.34 (C-4), 34.58 (C-8), 35.75 (C-6), 36.40 (C-9), 42.35 (C-3), 45.28 (C-7), 45.39 ($N(CH_2)_2$), 54.00 ($(CH_2)_2$), 55.87 (C-1), 57.43 (C-5), 59.53 (CH_2CO), 126.12, 126.45, 126.51, 127.79, 128.31, 128.47 (aromatic C), 142.98, 143.40 (aromatic C_q), 168.88 (CO) ppm; (*E*)-**6b**, (*Z*)-**6b**: IR (KBr): $\bar{\nu} = 2960$, 1633, 1603, 1496, 1446, 1032, 925, 729, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) =$ 230 (3.5524), 259 (2.925) nm.

(7RS,8RS)-(±)-2-Pyrrolidino-1-(7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-ethanone ((*E*)-**6c**, (*Z*)-**6c**, $C_{31}H_{41}N_3O$)
The reaction of 504 mg **1c** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 192 mg chloroacetyl chloride (1.7 mmol) gave a resin, which was reacted with 996 mg pyrrolidine (14 mmol) affording 475 mg (72%) of the isomers (*E*)-**6c** and (*Z*)-**6c** as a colorless resin. NMR: (*E*)-**6c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.33$–1.50 (m, $3CH_2$), 1.54–1.65 (m, $2CH_2$), 1.75–1.84 (m, 6-H), 1.95–2.01 (m, 4-H), 2.08–2.16 (m, 4-H, 9-H, NCH_2), 2.18–2.30 (m, 6-H, NCH_2), 2.49–2.68 (m, $N(CH_2)_2$), 2.59, 2.73 (2d, $J = 13.7$ Hz, CH_2CO), 3.18–3.28 (m, 7-H), 3.25–3.31 (m, 3-H), 3.40 (br, td, $J = 10.1$, 2.7 Hz, 8-H), 4.42 (ddd, $J = 14.8$, 5.1, 2.6 Hz, 3-H), 4.53 (d, $J = 2.7$ Hz, 1-H), 7.14–7.36 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.44$ ($(CH_2)_2$), 25.00, 26.74 ($3CH_2$), 30.99 (C-4), 33.36 (C-9), 38.06 (C-6), 41.20 (C-3), 41.27 (C-8), 46.34 (C-7), 46.44 ($N(CH_2)_2$), 53.60 ($N(CH_2)_2$), 57.84 (C-5), 58.97 (CH_2CO), 59.70 (C-1), 126.56, 126.63, 126.84, 127.63, 128.75, 128.79 (aromatic C), 142.70, 144.89 (aromatic C_q), 170.09 (CO) ppm; (*Z*)-**6c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.44$–1.50 (m, CH_2), 1.54–1.65 (m, $2CH_2$), 1.70–1.82 (m, 4-H, $(CH_2)_2$), 1.91–2.06 (m, 4-H, 6-H), 2.09–2.14 (m, 9-H), 2.30–2.38 (m, 6-H, 9-H), 2.42–2.68 (m, $2N(CH_2)_2$), 3.11 (td, $J = 13.8$, 3.2 Hz, 3-H), 3.16–3.25 (m, 7-H, 8-H), 3.27–3.34 (m, 8-H), 3.27, 3.38 (2d, $J = 13.6$ Hz, CH_2CO), 4.00 (br, d, $J = 13.8$ Hz, 3-H), 5.08 (d, $J = 3.4$ Hz, 1-H), 7.12–7.36 (m, aromatic H), 7.58 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.72$ ($(CH_2)_2$), 25.03, 26.82 ($3CH_2$), 31.90 (C-4), 34.94 (C-6), 35.28 (C-8), 36.18 (C-9), 42.64 (C-3), 45.68 (C-7), 46.44 ($N(CH_2)_2$), 54.03 ($N(CH_2)_2$), 55.69 (C-1), 58.39 (C-5), 59.55 (CH_2CO), 126.12, 126.42, 126.61, 127.77, 128.33, 128.45 (aromatic C), 143.26, 143.58 (aromatic C_q), 168.87 (CO) ppm; (*E*)-**6c**, (*Z*)-**6c**: IR (KBr): $\bar{\nu} = 2931$, 1642, 1633, 1603, 1496, 1442,

1033, 910, 730, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.588), 258 (3.030) nm.

(7RS,8RS)-(±)-2-Piperidino-1-(5-dimethylamino-7,8-diphenyl-2-azabicyclo[3.2.2]non-2-yl)-ethanone ((*E*)-**7a**, (*Z*)-**7a**, $C_{29}H_{39}N_3O$)

The reaction of 352 mg **1a** (1.1 mmol), 132 mg triethylamine (1.3 mmol), and 147 mg chloroacetyl chloride (1.3 mmol) gave a resin, which was reacted with 937 mg piperidine (11 mmol). The afforded residue was chromatographed eluting with CH_2Cl_2:*Me*OH (6:1). 294 mg (60%) of the isomers (*E*)-**7a** and (*Z*)-**7a** were obtained as a colorless resin. NMR: (*E*)-**7a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.95$–1.08 (m, CH_2), 1.10–1.18 (m, $2CH_2$), 1.80 (br, t, $J = 13.6$ Hz, 6-H), 1.96–2.19 (m, 4-H, 9-H, $N(CH_2)_2$), 2.25–2.35 (m, 6-H), 2.31 (s, $N(CH_3)_2$), 2.40, 2.46 (2d, $J = 13.6$ Hz, CH_2CO), 3.26 (t, $J = 9.5$ Hz, 7-H), 3.36–3.40 (m, 3-H), 3.44 (ddd, $J = 12.6$, 9.9, 2.6 Hz, 8-H), 4.37 (ddd, $J = 14.6$, 5.1, 2.8 Hz, 3-H), 4.67 (d, $J = 2.7$ Hz, 1-H), 7.16–7.38 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.61$, 25.03 ($3CH_2$), 29.95 (C-4), 33.16 (C-9), 37.91 ($N(CH_3)_2$), 38.60 (C-6), 40.98 (C-3), 41.25 (C-8), 45.92 (C-7), 54.25 ($N(CH_2)_2$), 57.67 (C-5), 59.30 (C-1), 62.72 (CH_2CO), 126.55, 126.61, 126.93, 127.62, 128.77, 128.84 (aromatic C), 142.61, 144.78 (aromatic C_q), 170.02 (CO) ppm; (*Z*)-**7a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.35$–1.44 (m, CH_2), 1.48–1.56 (m, $2CH_2$), 1.79–1.95 (m, 4-H), 2.10–2.18 (m, 6-H, 9-H), 2.37 (s, $N(CH_3)_2$), 2.34–2.45 (m, 6-H, 9-H, $N(CH_2)_2$), 3.10 (td, $J = 13.8$, 3.2 Hz, 3-H), 3.16 (br, s, CH_2CO), 3.26 (t, $J = 9.5$ Hz, 7-H), 3.29–3.36 (m, 3-H), 4.06–4.13 (br, d, $J = 14.0$ Hz, 3-H), 5.03 (d, $J = 3.4$ Hz, 1-H), 7.15–7.37 (m, aromatic H), 7.57 (d, $J = 7.9$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.92$, 25.95 ($3CH_2$), 30.82 (C-4), 34.72 (C-8), 34.99 (C-6), 35.97 (C-9), 37.96 ($N(CH_3)_2$), 42.67 (C-3), 45.27 (C-7), 54.43 ($N(CH_2)_2$), 55.91 (C-1), 58.30 (C-5), 63.31 (CH_2CO), 126.13, 126.48, 127.72, 128.33, 128.47 (aromatic C), 143.00, 143.26 (aromatic C_q), 168.85 (CO) ppm; (*E*)-**7a**, (*Z*)-**7a**: IR (KBr): $\bar{\nu} = 2934$, 1636, 1602, 1496, 1440, 1040, 934, 750, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.585), 259 (2.973) nm; HR-MS (MALDI): calcd. ($C_{29}H_{38}N_3O$) [M-H^+]: 444.3015; found: 444.3049.

(7RS,8RS)-(±)-2-Piperidino-1-(7,8-diphenyl-5-pyrrolidino-2-azabicyclo[3.2.2]non-2-yl)-ethanone ((*E*)-**7b**, (*E*)-**7b**, $C_{31}H_{41}N_3O$)

The reaction of 485 mg **1b** (1.4 mmol), 172 mg triethylamine (1.7 mmol), and 192 mg chloroacetyl chloride (1.7 mmol) gave a resin, which was reacted with 1192 mg piperidine (14 mmol) affording 560 mg (85%) of the isomers (*E*)-**7b** and (*Z*)-**7b** as a colorless resin. NMR: (*E*)-**7b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.01$–1.11 (m, CH_2), 1.11–1.22 (m, $2CH_2$), 1.75–1.83 (m, $(CH_2)_2$), 1.84–1.90 (m, 6-H), 1.96–2.13 (m, $N(CH_2)_2$), 2.07–2.16 (m, 4-H), 2.13–2.24 (m, 9-H), 2.25–2.31 (m, 6-H), 2.41, 2.46 (2d, $J = 13.4$ Hz, CH_2CO), 2.58–2.85 (m, $N(CH_2)_2$), 3.22–3.30 (m, 7-H), 3.41–3.51 (m, 3-H, 8-H), 4.37 (ddd, $J = 14.9$, 4.7, 3.4 Hz, 3-H), 4.65 (d, $J = 2.7$ Hz, 1-H), 7.14–7.38 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.51$ ($(CH_2)_2$), 23.59, 25.02 ($3CH_2$), 31.19 (C-4), 34.06 (C-9), 39.30 (C-6), 40.97 (C-3), 41.11 (C-8), 45.19 ($N(CH_2)_2$), 45.95 (C-7), 54.22 ($N(CH_2)_2$), 56.81 (C-5), 59.44 (C-1), 62.67 (CH_2CO), 126.43, 126.59, 126.79, 127.58, 128.68, 128.74 (aromatic C), 142.71, 144.96 (aromatic C_q), 169.94 (CO) ppm; (*Z*)-**7b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.38$–1.43 (m, CH_2), 1.48–1.58 (m, $2CH_2$), 1.75–1.83 (m, $(CH_2)_2$), 1.90–1.98 (m, 4-H), 2.12–2.23 (m, 6-H, 9-H), 2.30–2.50 (m, 6-H, 9-H, $N(CH_2)_2$), 2.58–2.85 (m, $N(CH_2)_2$), 3.07–3.16 (m, 3-H), 3.15 (s, CH_2CO), 3.22–3.30 (m, 7-H), 3.35–3.41 (m, 8-H), 4.08 (br, d, $J = 12.7$ Hz, 3-H), 5.03 (d, $J = 3.4$ Hz, 1-H), 7.14–7.38 (m, aromatic H), 7.58 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.48$ ($(CH_2)_2$), 23.91, 25.92 ($3CH_2$), 32.22 (C-4), 34.60 (C-8), 35.99 (C-6), 36.49 (C-9), 42.76 (C-3), 45.12 ($N(CH_2)_2$), 45.34 (C-7), 54.39 ($N(CH_2)_2$), 56.00 (C-1), 56.18 (C-5), 63.27 (CH_2CO), 125.98, 126.33, 126.45, 127.74, 128.22, 128.36 (aromatic C), 143.09, 143.51 (aromatic C_q), 168.77 (CO) ppm; (*E*)-**7b**, (*Z*)-**7b**: IR (KBr): $\bar{\nu} = 2934$, 1637, 1602, 1496, 1439, 1037, 936, 748, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.651), 259 (3.135) nm.

(7RS,8RS)-(±)-2-Piperidino-1-(7,8-diphenyl-5-piperidino-2-azabicyclo[3.2.2]non-2-yl)-ethanone ((*E*)-**7c**, (*Z*)-**7c**, $C_{32}H_{43}N_3O$)

The reaction of 396 mg **1c** (1.1 mmol), 132 mg triethylamine (1.3 mmol), and 147 mg chloroacetyl chloride (1.3 mmol) gave a resin, which was reacted with 937 mg piperidine (11 mmol) affording 310 mg (58%) of the isomers (*E*)-**7c** and (*Z*)-**7c** as a colorless resin. NMR: (*E*)-**7c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.97$–1.06 (m, CH_2), 1.10–1.20 (m, $2CH_2$), 1.37–1.68 (m, $3CH_2$), 1.70–1.78 (m, 6-H), 1.90–2.18 (m, 4-H, 9-H, $N(CH_2)_2$), 2.24–2.31 (m, 6-H), 2.39, 2.45 (2d, $J = 13.6$ Hz, CH_2CO), 2.48–2.73 (m, $N(CH_2)_2$), 3.14–3.24 (m, 7-H), 3.38–3.45 (m, 3-H, 8-H), 4.38 (ddd, $J = 15.0$, 5.1, 2.5 Hz, 3-H), 4.66 (d, $J = 2.5$ Hz, 1-H), 7.18–7.36 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.66$, 25.07, 26.68 ($6CH_2$), 31.18 (C-4), 33.23 (C-9), 38.77 (C-6), 41.38 (C-3), 41.67 (C-8), 46.11 (C-7), 46.47 ($N(CH_2)_2$), 54.27 ($N(CH_2)_2$), 57.89 (C-5), 59.33 (C-1), 62.81 (CH_2CO), 126.49, 126.60, 126.91, 127.66, 128.77, 128.86 (aromatic C), 142.82, 145.08 (aromatic C_q), 170.05 (CO) ppm; (*Z*)-**7c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.37$–1.68 (m, $6CH_2$), 1.76–1.82 (m, 4-H), 1.91–1.98 (m, 4-H), 1.99–2.04 (m, 6-H), 2.09–2.14 (m, 9-H), 2.28–2.40 (m, 6-H, 9-H, $N(CH_2)_2$), 2.48–2.73 (m, $N(CH_2)_2$), 3.08–3.18 (m, 3-H, CH_2CO), 3.14–3.24 (m, 7-H), 3.27–3.32 (m, 8-H), 4.08 (br, d, $J = 14.5$ Hz, 3-H), 5.06 (d, $J = 3.5$ Hz, 1-H), 7.14–7.36 (m, aromatic H), 7.58 (d, $J = 7.6$ Hz, aromatic H), 7.58 (d, $J = 7.6$ Hz, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.00$, 26.02, 26.68 ($6CH_2$), 32.01 (C-4), 34.96 (C-6), 35.26 (C-8), 36.08 (C-9), 42.96 (C-3), 45.71 (C-7), 46.36 ($N(CH_2)_2$), 54.48 ($N(CH_2)_2$), 55.86 (C-1), 58.46 (C-5), 63.36 (CH_2CO), 126.11, 126.43, 126.60, 127.77, 128.34, 128.45 (aromatic C), 143.23, 143.53 (aromatic C_q), 168.84 (CO) ppm; (*E*)-**7c**, (*Z*)-**7c**: IR (KBr): $\bar{\nu} = 2924$, 1643, 1633, 1603, 1497, 1443, 1038, 909, 730, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.560), 258 (3.034) nm.

Antiprotozoal tests, cytotoxicity

A detailed description of the microplate assays against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhode-*

siense (STIB900) as well as the examination of the cytotoxicity using L6 cells has been reported [18].

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