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Original article

Antiplasmodial and antitrypanosomal activities of aminobicyclo [2.2.2]octyl ω-aminoalkanoates

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Abstract

Several 4-aminobicyclo[2.2.2]octyl esters of ω-dialkylamino acids were prepared. Their activities against the multidrug-resistant K_1 strain of *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* (STIB 900) were determined using microplate assays and compared to those of formerly prepared analogues. The biological activity was influenced by the relative configuration in ring position 2, by the chain length of the acid moiety and by the amino substitution. The most active antiplasmodial ester was as active as chloroquine. One of the new compounds exhibited the highest antitrypanosomal activity and selectivity of all bicyclo-octane derivatives prepared so far.

Keywords: Bicyclo-octyl ester; 4-Aminobicyclo[2.2.2]octane derivative; In vitro assay; *Plasmodium falciparum*; *Trypanosoma brucei rhodesiense*

1. Introduction

Malaria and Human African Trypanosomiasis (HAT) are dangerous infectious diseases which are caused by eucaryotic parasites of the genera *Plasmodium* and *Trypanosoma*, respectively.

In 2004 malaria caused more than 1 million deaths [1]. From the four species of malarial parasites, the *Plasmodium falciparum* subspecies is the most virulent and potentially deadly organism. It is responsible for malaria tropica. Its multidrug-resistant strains are becoming prevalent around the world [1]. Possible in vitro and in vivo resistances have been demonstrated even against the most recently introduced artemisinin derivatives [2–4]. Therefore, new drugs with activity against drug-resistant strains are urgently needed.

In Sub-Saharan Africa about 40,000 people die annually because they fall ill with HAT [5]. More than 60 million people are at the risk of developing this disease, which is caused by the species of *Trypanosoma brucei* [6]. The more virulent *Trypanosoma brucei rhodesiense* causes East African sleeping sickness, whereas the West African form is elicited by *Trypanosoma brucei gambiense*. Without treatment every infection proceeds lethal. All four drugs in use (suramin, pentamidine, melarsoprol, eflornithine) cause severe side effects and have to be administered by partly painful injections. Melarsoprol, the only effective drug against the late stage of East African sleeping sickness, causes an encephalopathy in 10% of the patients, killing half of them [7]. Thus the development of new drugs against East African Trypanosomiasis is absolutely essential.

4-Aminobicyclo[2.2.2]octan-2-ols **2** have shown activity against a multiresistant strain of *P. falciparum* as well as against *T.b. rhodesiense* [8]. Compounds **2** were obtained in two steps from acyclic starting material via the corresponding ketones **1** [8,9]. Some of their ester derivatives **3** exhibit

Abbreviations: CC, column chromatography; CH_2Cl_2, dichloromethane; 4-DMAP, 4-dimethylaminopyridine; EtOH, ethanol; KI, potassium iodide; MeOH, methanol; NaOH, sodium hydroxide.

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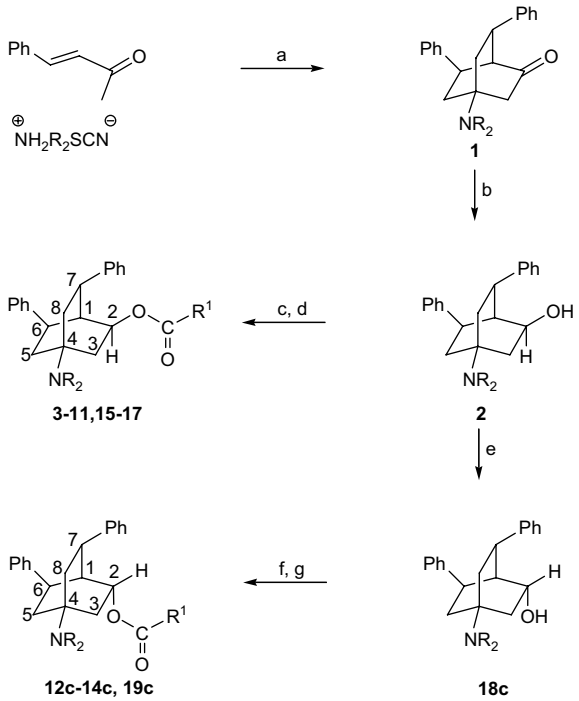
increased antiplasmodial and antitrypanosomal potencies [10–12]. So far the recently prepared bicyclo-octyl 2-aminoacetates **4**–**6** are the most potent in the ester series [13]. In order to investigate how the distance between the amino group and the bicyclic ring system influences the activities of these compounds, we inserted a methylene group into their carboxyl moiety synthesizing the corresponding 3-aminopropionates **7**–**9**. As a more hydrophilic alternative the ω-(4-hydroxypiperidino)alkanoates **10** and **11** were prepared. In addition selected epimers **12c**–**14c** of compounds **4**–**6** were synthesized. All new compounds were characterized and tested for their potencies against the K_1 strain of *P. falciparum* and *T.b. rhodesiense* using in vitro assays. Structure–activity relationships were derived from the comparison of the results with the activities of the corresponding 2-aminoacetates **4**–**6**.

2. Chemistry

The synthesis of bicyclo-octanones **1** from benzylidene acetone and dialkylammonium isothiocyanates succeeded via a one-pot procedure [8,9]. Their structures have been approved by a crystal structure analysis. Hydrogenation of compound **1** with lithium aluminium hydride gave stereoselectively the alcohols **2** which served as starting material for esterification. ω-Aminoalkanoates **4**–**11** were obtained from compound **2** via the corresponding ω-chloroalkanoates **15** and **16**. The latter were prepared by the treatment of compound **2** with the corresponding ω-chloroacyl chloride in the presence of 4-DMAP. Compounds **16** were always accompanied by a substantial quantity of secondary products, which were identified as acrylates **17** by means of NMR spectroscopy. However, a separation of chloropropionates **16** and acrylates **17** was not required. Both the compounds were smoothly converted to the 3-aminopropionates **7**–**9** by reaction with the corresponding secondary amine. The use of a solvent was sometimes required, whereupon the reaction period was considerably prolonged. In a likewise manner the 2-(4-hydroxypiperidino)alkanoates **10** and **11** were synthesized by the reaction of compounds **15** and **16** with 4-piperidinol using protic or polar-aprotic solvents (Scheme 1).

Bicyclo-octanol **18c** was prepared by the epimerization of compound **2c** in alkaline milieu in a two-step procedure [14]. The main part of alcohol **2c** was epimerized to **18c** upon heating with potassium *tert*-butoxide. The conversion was completed by the treatment of the isomeric mixture with sodium at ambient temperature. Acylation of compound **18c** with chloroacetyl chloride in the presence of 4-DMAP yielded compound **19c**, which was dissolved in excess amine to give the ω-aminoacetates **12c**–**14c**.

The configuration of compounds **7**–**11** was confirmed by through-space couplings from their 2-Hs to their 6-Hs in their NMR spectra. Likewise for compounds **12c**–**14c** NOEs were observed from aromatic *ortho*-protons to 2-H and 7-H. The bicyclic structure of compounds **7**–**14** was established by the typical w-couplings (2–3 Hz) between the protons in ring positions 3, 5 and 8 (Fig. 1).



Compounds	R^1
1, 2, 18c	----
3	*tert*-Bu, phenyl, naphthyl, benzyl, diphenylmethyl
4, 12c	diethylaminomethyl
5, 13c	pyrrolidinomethyl
6, 14c	piperidinomethyl
7	2-diethylaminoethyl
8	2-pyrrolidinoethyl
9	2-piperidinoethyl
10	4-hydroxypiperidinomethyl
11	2-(4-hydroxypiperidino)ethyl
15, 19c	chloromethyl
16	2-chloroethyl
17	vinyl

Scheme 1. Preparation of ω-aminoalkanoates **4**–**14**. Reagents and conditions: (a) toluene or DMF, 160 °C, 4 h; (b) $LiAlH_4$, ether, rt, 16 h; (c) ω-chloroalkanoyl chloride, 4-DMAP, CH_2Cl_2, rt, 2 days; (d) amine, KI, EtOH, rt, 30 min or amine, KI, CH_2Cl_2, rt, 16 h or amine, KI, rt, 30 min; (e) (1) potassium *tert*-butoxide, 200 °C, 24 h; (2) toluene, sodium, 100 °C to rt; (f) chloroacetyl chloride, 4-DMAP, CH_2Cl_2, rt, 16 h; (g) amine, KI, 4 °C, 2 days. **1a**–**11a**, **15a**–**17a**: NR_2 = dimethylamino; **1b**–**11b**, **15b**–**17b**: NR_2 = pyrrolidino; **1c**–**19c**: NR_2 = piperidino.

3. Antiplasmodial and antitrypanosomal activity

The new esters **7**–**14** were tested via microplate assays for their activities against the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine) and *T.b. rhodesiense*. The cytotoxicity was determined with rat skeletal myoblasts (L-6 cells). Chloroquine, melarsoprol and podophyllotoxine were used as standards.

4. Results and discussion

Due to their 2-dialkylamino-substitution acetates **4**–**6** exhibit far better antiplasmodial and antitrypanosomal properties than their 2-unsubstituted analogues. Compounds **4b**, **4c** and **6c**

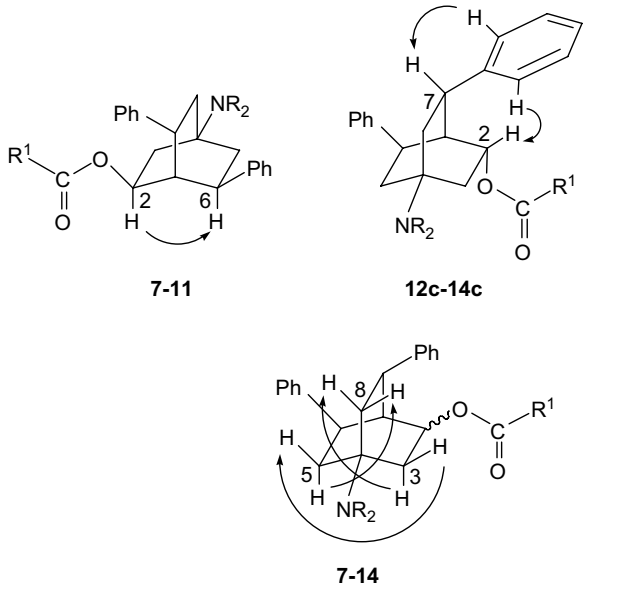


Fig. 1. NOEs and w-couplings for compounds **7**–**14**.

possess good antiplasmodial activity ($IC_{50} = 0.18–0.25$ μM), and compounds **5a** and **5b** were the most active antitrypanosomal compounds (**5a**: $IC_{50} = 0.21$ μM; **5b**: $IC_{50} = 0.23$ μM) in the bicyclo-octane series reported so far [13]. For their (2*RS*,6*RS*,7*RS*)-epimers **12c**–**14c** we observed decreased antiplasmodial ($IC_{50} = 0.74–1.41$ μM) and antitrypanosomal ($IC_{50} = 0.88–5.42$ μM) activities due to the inverted configuration in ring position 2.

In majority of the cases the propionates **7**–**9** were not only distinctly more active, but also more cytotoxic than their acetate analogues **4**–**6**. The most active antiplasmodial compound of the prepared propionates **7**–**9** is 3-diethylaminopropionate **7c** ($IC_{50} = 0.19$ μM), whereas compounds **7a**–**c**, **8a** and **8b** ($IC_{50} = 0.076–0.15$ μM) surpass the antitrypanosomal activities of the formerly most active bicyclo-octane derivatives **5a** and **5b**. Moreover, compound **8a** possesses the best selectivity index (SI = 341) in this series of compounds.

The 4-pyrrolidino and 4-piperidino bicyclo-octyl esters **4b**,**c**–**11b**,**c** are more active against *P. falciparum* K_1 than their dimethylamino analogues **4a**–**11a**. By contrast the 4-dimethylamino and 4-pyrrolidino analogues **4a**,**b**–**11a**,**b** exhibit higher antitrypanosomal activity with just a few exceptions (Table 1). Remarkably, the influence of the nature of the ω-dialkylamino substituent on the activities was much smaller for the propionates than in the acetate series.

2-(4-Hydroxypiperidino)alkanoates **10a**–**c**, **11a** and **11b** are far less cytotoxic than their corresponding piperidino analogues **6a**–**c**, **9a** and **9b**, however, their lower lipophilicity causes a substantial loss of antitrypanosomal activity. A sole exception is the properties of compound **11c**, which exhibits, compared to compound **9c**, increased antiplasmodial potency (**11c**: $IC_{50} = 0.17$ μM; **9c**: $IC_{50} = 0.26$ μM) and higher cytotoxicity (**11c**: $IC_{50} = 28.49$ μM; **9c**: $IC_{50} = 54.60$ μM).

A future study will investigate the influence of an additional chain extension in the acid moiety and of other acidic, basic or neutral substituents in the ω-dialkylamino residue.

Table 1
Activities of compounds **4**–**14** against *P. falciparum* K_1, *T.b. rhodesiense*, and L-6 cells, expressed as IC_{50} (μM)[a,b]

Compounds	*P. falciparum* K_1[c]	*T.b. rhodesiense*	Cytotoxicity of L-6 cells
4a	2.72	0.61	30.14
4b	0.20	0.72	49.00
4c	0.25	0.56	23.92
5a	0.71	0.21	32.66
5b	0.70	0.23	42.94
5c	0.47	0.32	16.38
6a	0.52	1.99	29.26
6b	0.37	0.37	14.22
6c	0.18	0.87	60.39
7a	0.43	0.11	23.61
7b	0.30	0.11	19.15
7c	0.19	0.15	22.92
8a	0.55	0.076	25.95
8b	0.37	0.12	21.90
8c	0.25	0.38	12.50
9a	0.40	0.21	25.83
9b	0.28	0.31	17.75
9c	0.26	0.91	54.60
10a	2.16	2.06	102.3
10b	0.86	1.05	93.38
10c	n.t.	3.81	>179.0
11a	2.25	0.95	89.23
11b	1.91	1.43	35.61
11c	0.17	0.98	28.49
12c	0.77	1.53	61.30
13c	0.74	0.88	52.04
14c	1.41	5.42	>184.9
Chl.	0.16		
Mel.		0.005	
Pod.			0.012

n.t.: Not tested due to low activity in a pre-screening; Chl. = chloroquine; Mel. = melarsoprol; Pod. = podophyllotoxine.

[a] Values represent the average of four determinations (two determinations of two independent experiments).

[b] Values for esters **4**–**6** [13].

[c] Resistant to chloroquine and pyrimethamine.

5. Conclusion

This paper reports the synthesis and the antiplasmodial and antitrypanosomal activities of new bicyclo[2.2.2]octyl esters of ω-dialkylamino acids. Compounds with (2*SR*,6*RS*,7*RS*)-configuration were much more active than their (2*RS*,6*RS*,7*RS*)-epimers. In most of the cases the insertion of a methylene group into the carboxyl moiety resulted in a remarkable increase of the determined activities of these compounds. 4-Pyrrolidino- or 4-piperidino-substituents in the bicyclo-octyl part of the esters support their antiplasmodial activity, whereas 4-dimethylamino and 4-pyrrolidino compounds were the more potent antitrypanosomal compounds. The antiplasmodial potency of the most active new compounds is in the range of chloroquine. Several of the new 3-dialkylaminopropionates show the highest antitrypanosomal activity of all bicyclo-octyl derivatives reported so far. The increase of both the investigated activities provides a basis for further structural modifications.

6. Experimental

6.1. Instrumentation and chemicals

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. 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: center 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 formulas (br broad, d doublet, dd double doublet, ddd double double doublet, m multiplet, q quartet, s singlet, t triplet), resonances marked with a prime belong to the 4-hydroxypiperidine moiety. MS: Kratos profile spectrometer. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna. 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

Ketones **1a–c** were prepared from benzylidene acetone and dialkylammonium isothiocyanates following the reported procedures [8,9], but solvent DMF was replaced by toluene and the reactions were carried out at 160 °C.

Alcohols **2a–c** were prepared by stereoselective hydrogenation with $LiAlH_4$ according to the reported procedures [8]. Alcohol **2c** was epimerized to **18c** in a two-step procedure as described [14].

(2*SR*,6*RS*,7*RS*)-(±)-4-Dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl ω-chloroacetates (**15a–c**) were prepared from alcohols **2a–c** and 2-chloroacetyl chloride following the reported procedures [13].

6.2.1. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 2-(4-hydroxypiperidino)acetates (*10a–c*)

The secondary amine was dissolved in EtOH (2 ml). Afterwards compounds **15a–c** and a catalytic amount of KI in H_2O were added at room temperature. After 30 min the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed five times with H_2O. The organic layer was dried over sodium sulfate, filtered and finally the solvent was removed in vacuo. The residue was purified by crystallization.

6.2.1.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 2-(4-hydroxypiperidino)acetate (*10a*).

Piperidin-4-ol [0.591 g (5.84 mmol)] in EtOH and chloroacetate **15a** [0.290 g (0.73 mmol)] yielded compound **10a** (0.250 g) as an oily residue. For analytical and test purposes it was recrystallized from acetone. Yield: 74%; m.p. 128–129 °C; IR = 2929, 2858, 2794, 1743, 1602, 1498, 1466, 1447, 1351, 1219, 1188, 1148, 1089, 1066, 753, 745, 697; UV [CH_2Cl_2 (log ε)]: 260 (2.825), 231 (3.132); ^1H NMR ($CDCl_3$) $\delta = 1.47–1.57$ (m, 2H, 3′-H, 5′-H), 1.73 (dd, $J = 14.2$, 2.5 Hz, 1H, 3-H), 1.78–1.84 (m, 2H, 3′-H, 5′-H), 1.91 (ddd, $J = 12.1$, 9.6, 2.6 Hz, 1H, 5-H), 1.98 (d, $J = 16.9$ Hz, 1H, CH–CO), 2.03–2.13 (m, 5H, 3-H, 5-H, 8-H, 2′-H, 6′-H), 2.12–2.22 (m, 1H, 8-H), 2.17 (s, 1H, OH), 2.39 (s, 6H, $N(CH_3)_2$), 2.46–2.55 (m, 2H, 2′-H, 6′-H), 2.62 (d, $J = 16.9$ Hz, 1H, CH–CO), 2.79 (d, $J = 4.6$ Hz, 1H, 1-H), 3.01 (t, $J = 9.6$ Hz, 1H, 6-H), 3.17 (t, $J = 9.8$ Hz, 1H, 7-H), 3.57–3.64 (m, 1H, 4′-H), 5.30 (dd, $J = 9.0$, 4.6 Hz, 1H, 2-H), 7.10–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 31.07$ (C-5), 31.17 (C-8), 33.93 (C-7), 34.30 (C-3′, C-5′), 34.69 (C-3), 38.41 ($N(CH_3)_2$), 38.70 (C-6), 40.04 (C-1), 50.27, 50.31 (C-2′, C-6′), 56.20 (C-4), 57.93 (CH_2–CO), 67.49 (C-4′), 72.97 (C-2), 125.32, 126.44, 126.53, 127.38, 128.11, 128.55 (aromatic C), 142.72, 144.64 (aromatic C_q), 170.07 (COO). Anal. Calcd for $C_{29}H_{38}N_2O_3 \cdot 0.25H_2O$ (467.14): C, 74.56; H, 8.31; N, 6.00; found: C, 74.70; H, 8.22; N, 5.83.

6.2.1.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 2-(4-hydroxypiperidino)acetate (*10b*).

Piperidin-4-ol [0.523 g (5.17 mmol)] in EtOH and chloroacetate **15b** [0.274 g (0.65 mmol)] yielded compound **10b** (0.260 g) as an oily residue. For analytical and test purposes it was recrystallized from acetone. Yield: 82%; m.p. 188–189 °C; IR = 2949, 2852, 2820, 1744, 1600, 1497, 1446, 1188, 1168, 1083, 755, 738, 699; UV [CH_2Cl_2 (log ε)]: 260 (2.824), 231 (3.222); ^1H NMR ($CDCl_3$) $\delta = 1.47–1.58$ (m, 2H, 3′-H, 5′-H), 1.74 (dd, $J = 14.0$, 1.7 Hz, 1H, 3-H), 1.78–1.86 (m, 6H, 3′-H, 5′-H, $(CH_2)_2$), 1.98 (d, $J = 17.1$ Hz, 1H, CH–CO), 1.97–2.23 (m, 7H, 3-H, 5-H, 8-H, 2′-H, 6′-H), 2.46–2.54 (m, 2H, 2′-H, 6′-H), 2.61 (d, $J = 17.1$ Hz, 1H, CH–CO), 2.74–2.82 (m, 5H, 1-H, $N(CH_2)_2$), 3.04 (t, $J = 9.5$ Hz, 1H, 6-H), 3.18 (t, $J = 9.8$ Hz, 1H, 7-H), 3.57–3.65 (m, 1H, 4′-H), 5.30 (dd, $J = 9.0$, 4.5 Hz, 1H, 2-H), 7.07–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.55$ ($(CH_2)_2$), 31.65 (C-5), 32.10 (C-8), 33.86 (C-7), 34.30 (C-3′, C-5′), 35.68 (C-3), 38.81 (C-6), 40.40 (C-1), 45.53 ($N(CH_2)_2$), 50.26 (C-2′, C-6′), 54.80 (C-4), 57.90 (CH_2–CO), 67.51 (C-4′), 73.00 (C-2), 125.27, 126.39, 126.59, 127.44, 128.07, 128.52 (aromatic C), 142.82, 144.75 (aromatic C_q), 170.07 (COO). Anal. Calcd for $C_{31}H_{40}N_2O_3$ (488.67): C, 76.19; H, 8.25; N, 5.73; found: C, 76.33; H, 8.22; N, 5.57.

6.2.1.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 2-(4-hydroxypiperidino)acetate (*10c*).

Piperidin-4-ol [0.684 g (6.76 mmol)] in EtOH and chloroacetate **15c** [0.370 g (0.84 mmol)] yielded compound **10c** (0.180 g) as an oily residue. For analytical and test purposes it was recrystallized from acetone. Yield: 43%; m.p. 201–202 °C; IR = 2936, 2847, 2817, 1746, 1720, 1599, 1497, 1447, 1191,

1170, 1083, 753, 744, 698; UV [MeOH (log ε)]: 258 (2.878), 209 (4.217); ^{1}H NMR ($CDCl_3$) δ = 1.37–1.42 (br s, 1H, OH), 1.43–1.58 (m, 4H, 3′-H, 5′-H, CH_2), 1.60–1.64 (m, 4H, 2 CH_2), 1.68 (br d, J = 14.3 Hz, 1H, 3-H), 1.74–1.84 (m, 2H, 3′-H, 5′-H), 1.87–1.95 (m, 1H, 5-H), 1.97 (d, J = 17.1 Hz, 1H, CH–CO), 2.03–2.15 (m, 5H, 3-H, 5-H, 8-H, 2′-H, 6′-H), 2.21 (t, J = 9.9 Hz, 1H, 8-H), 2.45–2.53 (m, 2H, 2′-H, 6′-H), 2.61 (d, J = 17.1 Hz, 1H, CH–CO), 2.58–2.74 (m, 4H, $N(CH_2)_2$), 2.78 (d, J = 4.6 Hz, 1H, 1-H), 2.98 (t, J = 9.4 Hz, 1H, 6-H), 3.14 (t, J = 9.9 Hz, 1H, 7-H), 3.58–3.66 (m, 1H, 4′-H), 5.29 (dd, J = 8.9, 4.6 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 24.96 (CH_2), 26.81 (2 CH_2), 31.40 (C-5), 31.97 (C-8), 34.00 (C-7), 34.32 (C-3′, C-5′), 34.99 (C-3), 38.71 (C-6), 40.12 (C-1), 46.88 ($N(CH_2)_2$), 50.24, 50.29 (C-2′, C-6′), 56.74 (C-4), 57.91 (*C*H_2–CO), 67.54 (C-4′), 73.05 (C-2), 125.27, 126.38, 126.54, 127.40, 128.08, 128.52 (aromatic C), 142.85, 144.82 (aromatic C_q), 170.06 (COO). Anal. Calcd for $C_{32}H_{42}N_2O_3 \cdot 0.3H_2O$ (508.10): C, 75.64; H, 8.45; N, 5.51; found: C, 75.49; H, 8.39; N, 5.35.

6.2.2. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-chloropropionates (**16a–c**)

Bicyclo-octanol **2** and 4-DMAP were dissolved in dry CH_2Cl_2 and cooled in an ice bath. Under stirring ω-chloropropionyl chloride in dry CH_2Cl_2 was added. After 1 h the ice bath was removed and the solution was stirred for 48 h at room temperature in an argon atmosphere. Then it was carefully washed five times with water, with 1 M NaOH and with water again, dried over sodium sulfate and filtered. Finally the solvent was removed in vacuo.

*6.2.2.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-chloropropionate (**16a**).* Bicyclo-octanol **2a** [5.786 g (18 mmol)] and 4-DMAP [0.592 g (4.8 mmol)] in 100 ml dry CH_2Cl_2 gave with 3-chloropropionyl chloride [6.151 g (48.0 mmol)] in 20 ml dry CH_2Cl_2 compound **16a** [5.1 g (69%)] as an oily residue.

*6.2.2.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 3-chloropropionate (**16b**).* Bicyclo-octanol **2b** [6.161 g (15.5 mmol)] and 4-DMAP [0.379 g (3.1 mmol)] in 100 ml dry CH_2Cl_2 gave with 3-chloropropionyl chloride [3.936 g (31.0 mmol)] in 20 ml dry CH_2Cl_2 compound **16b** [5.181 g (76%)] as an oily residue.

*6.2.2.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 3-chloropropionate (**16c**).* Bicyclo-octanol **2c** [1 g (2.76 mmol)] and 4-DMAP [0.068 g (0.553 mmol)] in 15 ml dry CH_2Cl_2 gave with 3-chloropropionyl chloride [0.702 g (5.53 mmol)] in 3 ml dry CH_2Cl_2 compound **16c** [1.1 g (89%)] as an oily residue.

6.2.3. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-(4-hydroxypiperidino) propionates (**11a–c**)

General method A. 3-Chloropropionate **16** was dissolved in dry CH_2Cl_2. Then a catalytic amount of KI and the secondary amine were added. The reaction batch was stirred overnight at room temperature in an atmosphere of Ar. Afterwards the main part of the solvent was evaporated. Then it was thoroughly shaken with water four times. The organic phase was dried over sodium sulfate and filtered. Ultimately the solvent was removed in vacuo.

General method B. An excess of secondary amine was dissolved in EtOH (2 ml). Then compound **16** and a catalytic amount of KI in H_2O were added at room temperature. After 30 min the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed four times with H_2O, dried over sodium sulfate and filtered. The solvent was evaporated in vacuo and the residue recrystallized.

*6.2.3.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-(4-hydroxypiperidino)propionate (**11a**). Method A*. Piperidin-4-ol [3 g (29.5 mmol)] and 3-chloropropionate **16a** [0.686 g (1.7 mmol)] in 110 ml dry CH_2Cl_2 gave a residue which was purified by CC over silica gel using CH_2Cl_2/MeOH = 19:1 as eluent yielding 0.596 g (74%) of compound **11a**. IR = 3087, 3059, 2942, 1729, 1602, 1497, 1185, 1073, 745, 698; UV [CH_2Cl_2 (log ε)]: 259 (2.694), 230 (3.294); ^{1}H NMR ($CDCl_3$) δ = 1.45–1.59 (m, 3H, 3′-H, 5′-H, CH–CO), 1.71 (br d, J = 14.1 Hz, 1H, 3-H), 1.79–1.92 (m, 4H, 3′-H, 5-H, 5′-H, CH–CO), 1.91–2.03 (m, 2H, 2′-H, 6′-H), 2.03–2.10 (m, 3H, 3-H, 5-H, 8-H), 2.08–2.23 (m, 2H, 8-H, NCH), 2.24–2.35 (m, 1H, NCH), 2.38 (s, 6H, $N(CH_3)_2$), 2.51–2.58 (m, 2H, 2′-H, 6′-H), 2.79 (d, J = 4.4 Hz, 1H, 1-H), 3.00 (t, J = 9.4 Hz, 1H, 6-H), 3.18 (t, J = 9.8 Hz, 1H, 7-H), 5.24 (dd, J = 8.9, 4.4 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.05 (C-5), 31.28 (C-8), 31.51 (*C*H_2–CO), 33.85 (C-7), 34.34 (C-3′, C-5′), 34.77 (C-3), 38.33 ($N(CH_3)_2$), 38.58 (C-6), 39.50 (C-1), 50.54, 50.73 (C-2′, C-6′), 52.71 (NCH_2), 56.12 (C-4), 67.55 (C-4′), 72.87 (C-2), 125.26, 126.33, 126.41, 127.30, 127.88, 128.46 (aromatic C), 142.70, 144.59 (aromatic C_q), 171.99 (COO); HRMS (MALDI) Calcd for $C_{30}H_{40}N_2O_3H$: 477.3117; found: 477.3153.

*6.2.3.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 3-(4-hydroxypiperidino)propionate (**11b**). Method A*. Piperidin-4-ol [2.6 g (25.6 mmol)] and 3-chloropropionate **16b** [0.631 g (1.44 mmol)] in 80 ml dry CH_2Cl_2 gave a residue which was purified by CC over silica gel using CH_2Cl_2/MeOH = 19:1 as eluent yielding 0.077 g (11%) of compound **11b**. IR = 3058, 3026, 2941, 1729, 1601, 1497, 1188, 1169, 750, 698; UV [CH_2Cl_2 (log ε)]: 259 (2.819), 230 (3.351); ^{1}H NMR ($CDCl_3$) δ = 1.47–1.59 (m, 3H, 3′-H, 5′-H, CH–CO), 1.73 (br d, J = 14.1 Hz, 1H, 3-H), 1.78–1.87 (m, 7H, 3′-H, 5′-H, CH–CO, $(CH_2)_2$), 1.93–2.02 (m, 3H, 2′-H, 5-H, 6′-H), 2.04–2.11 (m, 1H, 5-H), 2.10–2.25 (m, 4H, 3-H, 8-H, NCH), 2.29 (ddd, J = 15.3,

9.4, 6.0 Hz, 1H, NCH), 2.49–2.58 (m, 2H, 2′-H, 6′-H), 2.74–2.84 (m, 5H, 1-H, $N(CH_2)_2$), 3.04 (t, $J = 9.5$ Hz, 1H, 6-H), 3.20 (t, $J = 9.7$ Hz, 1H, 7-H), 3.59–3.67 (m, 1H, 4′-H), 5.24 (dd, $J = 8.8$, 4.4 Hz, 1H, 2-H), 7.07–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.51$ (($CH_2)_2$), 31.51 (C-5), 31.58 (CH_2–CO), 32.44 (C-8), 33.84 (C-7), 34.36 (C-3′, C-5′), 35.82 (C-3), 38.77 (C-6), 39.93 (C-1), 45.52 ($N(CH_2)_2$), 50.54, 50.72 (C-2′, C-6′), 52.76 (NCH_2), 54.89 (C-4), 67.73 (C-4′), 72.95 (C-2), 125.26, 126.35, 126.52, 127.40, 127.90, 128.49 (aromatic C), 142.83, 144.72 (aromatic C_q), 172.04 (COO); HRMS (MALDI) Calcd for $C_{32}H_{42}N_2O_3H$: 503.3274; found: 503.3314.

*6.2.3.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 3-(4-hydroxypiperidino)propionate (**11c**). Method B*. Piperidin-4-ol [0.440 g (4.35 mmol)], 3-chloropropionate **16c** [0.238 g (0.543 mmol)] in 2 ml EtOH and a catalytic amount of KI in two drops of H_2O gave a residue which was crystallized from acetone. Yield: 0.179 g (72%); m.p. 141–142 °C; IR = 2935, 1717, 1600, 1497, 1448, 1351, 1184, 1141, 1063, 743, 704, 697; UV [MeOH (log ε)]: 260 (3.500), 209 (4.349); ^{1}H NMR ($CDCl_3$) $\delta = 1.46$–1.58 (m, 5H, 3′-H, 5′-H, CH–CO, CH_2), 1.61–1.68 (m, 4H, 2 CH_2), 1.73 (dd, $J = 14.2$, 1.9 Hz, 1H, 3-H), 1.77–1.88 (m, 3H, 3′-H, 5′-H, CH–CO), 1.89–2.01 (m, 3H, 5-H, 2′-H, 6′-H), 2.03–2.16 (m, 4H, 3-H, 5-H, 8-H, NCH), 2.17 (s, 1H, OH), 2.19–2.34 (m, 2H, 8-H, NCH), 2.49–2.57 (m, 2H, 2′-H, 6′-H), 2.58–2.74 (m, 4H, $N(CH_2)_2$), 2.79 (d, $J = 4.6$ Hz, 1H, 1-H), 2.97 (t, $J = 9.5$ Hz, 1H, 6-H), 3.16 (t, $J = 9.8$ Hz, 1H, 7-H), 3.58–3.67 (m, 1H, 4′-H), 5.23 (dd, $J = 8.8$, 4.6 Hz, 1H, 2-H), 7.06–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.94$ (CH_2), 26.76 (2 CH_2), 31.32 (C-5), 31.61 (CH_2–CO), 32.24 (C-8), 34.00 (C-7), 34.39 (C-3′, C-5′), 35.19 (C-3), 38.68 (C-6), 39.64 (C-1), 46.85 ($N(CH_2)_2$), 50.54, 50.72 (C-2′, C-6′), 52.78 (NCH_2), 56.75 (C-4), 67.82 (C-4′), 73.06 (C-2), 125.26, 126.34, 126.50, 127.39, 127.92, 128.49 (aromatic C), 142.91, 144.85 (aromatic C_q), 172.08 (COO). Anal. Calcd for $C_{33}H_{44}N_2O_3 \cdot 0.3H_2O$ (522.13): C, 75.91; H, 8.61; N, 5.37; found: C, 75.71; H, 8.46; N, 5.19.

*6.2.4. General procedure for the synthesis of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-dialkylaminopropionates (**7–9**)*

General method A. To a mixture of 3-chloropropionate **16** and a catalytic amount of KI in dry CH_2Cl_2, amine was added dropwise. The reaction batch was stirred overnight at room temperature in an atmosphere of Ar. Afterwards most of the solvent was removed in vacuo. Then it was washed with water four times, dried over sodium sulfate and finally the solvent was evaporated.

General method B. Compound **16** was dissolved in excess secondary amine and a catalytic amount of KI in H_2O was added at room temperature. After 30 min the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O until the aqueous phase reached neutral. Then the organic layer was dried over sodium sulfate, filtered and the solvent removed in vacuo. The residue was purified by crystallization or by means of CC.

*6.2.4.1. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-diethylaminopropionate (**7a**). Method A*. 3-Chloropropionate **16a** [0.560 g (1.36 mmol)] in 80 ml dry CH_2Cl_2 was stirred with diethylamine [1.8 g (36.6 mmol)] for 40 h. After work-up the residue was purified by CC over aluminium oxide eluting with CH_2Cl_2/MeOH = 39:1 giving 0.470 g (77%) of compound **7a**. IR = 3059, 3026, 2967, 1730, 1601, 1497, 1195, 1170, 745, 698; UV [CH_2Cl_2 (log ε)]: 259 (2.862), 230 (3.412); ^{1}H NMR ($CDCl_3$) $\delta = 0.93$ (t, $J = 7.1$ Hz, 6H, 2 CH_3), 1.51 (ddd, $J = 15.5$, 9.5, 5.7 Hz, 1H, CH–CO), 1.72 (dd, $J = 14.1$, 2.5 Hz, 1H, 3-H), 1.78 (ddd, $J = 15.5$, 9.4, 5.9 Hz, 1H, CH–CO), 1.90 (ddd, $J = 12.1$, 9.5, 2.4 Hz, 1H, 5-H), 2.01–2.10 (m, 3H, 3-H, 5-H, 8-H), 2.20 (ddd, $J = 13.7$, 9.8, 3.1 Hz, 1H, 8-H), 2.26–2.33 (ddd, $J = 15.4$, 9.4, 5.9 Hz, 1H, NCH), 2.34, 2.35 (2q, $J = 7.1$ Hz, 4H, $N(CH_2)_2$), 2.39 (s, 6H, $N(CH_3)_2$), 2.44 (ddd, $J = 15.4$, 9.6, 5.9 Hz, 1H, NCH), 2.80 (d, $J = 4.5$ Hz, 1H, 1-H), 3.01 (t, $J = 9.5$ Hz, 1H, 6-H), 3.18 (t, $J = 9.8$ Hz, 1H, 7-H), 5.24 (dd, $J = 9.2$, 4.5 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 11.83$ (2 CH_3), 31.14 (C-5), 31.19 (CH_2–CO), 31.41 (C-8), 33.99 (C-7), 34.90 (C-3), 38.41 ($N(CH_3)_2$), 38.73 (C-6), 39.66 (C-1), 46.62 ($N(CH_2)_2$), 47.38 (NCH_2), 56.17 (C-4), 72.84 (C-2), 125.32, 126.38, 126.51, 127.39, 127.93, 128.51 (aromatic C), 142.86, 144.66 (aromatic C_q), 172.34 (COO); HRMS (MALDI) Calcd for $C_{29}H_{40}N_2O_2H$: 449.3168; found: 449.3208.

*6.2.4.2. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 3-diethylaminopropionate (**7b**). Method A*. 3-Chloropropionate **16b** [0.557 g (1.27 mmol)] in 80 ml dry CH_2Cl_2 was stirred with diethylamine [1.65 g (33.6 mmol)] for 40 h. After work-up 0.362 g (60%) of compound **7b** was yielded as a resin. IR = 3059, 3026, 2966, 1729, 1601, 1497, 1167, 750, 698; UV [CH_2Cl_2 (log ε)]: 260 (2.943), 230 (3.455); ^{1}H NMR ($CDCl_3$) $\delta = 0.94$ (t, $J = 7.1$ Hz, 6H, 2 CH_3), 1.50 (ddd, $J = 15.6$, 9.7, 5.7 Hz, 1H, CH–CO), 1.73–1.82 (m, 2H, 3-H, CH–CO), 1.82–1.87 (m, 4H, $(CH_2)_2$), 1.98 (ddd, $J = 12.2$, 9.5, 2.2 Hz, 1H, 5-H), 2.04–2.12 (m, 1H, 5-H), 2.12–2.25 (m, 3H, 3-H, 8-H), 2.29 (ddd, $J = 15.4$, 9.4, 5.7 Hz, 1H, NCH), 2.34, 2.35 (2q, $J = 7.1$ Hz, 4H, $N(CH_2)_2$), 2.44 (ddd, $J = 15.4$, 9.8, 5.9 Hz, 1H, NCH), 2.76–2.83 (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, $J = 8.9$, 4.4 Hz, 1H, 2-H), 7.06–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 11.77$ (2 CH_3), 23.56 (($CH_2)_2$), 31.12 (CH_2–CO), 31.59 (C-5), 32.42 (C-8), 33.90 (C-7), 35.81 (C-3), 38.81 (C-6), 39.98 (C-1), 45.57 ($N(CH_2)_2$), 46.60 ($N(CH_2)_2$), 47.34 (NCH_2), 54.99 (C-4), 72.87 (C-2), 125.30, 126.37, 126.55, 127.44, 127.91, 128.51 (aromatic C), 142.87, 144.68 (aromatic C_q), 172.31 (COO); HRMS (MALDI) Calcd for $C_{31}H_{42}N_2O_2H$: 475.3325; found: 475.3309.

*6.2.4.3. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 3-diethylaminopropionate (**7c**). Method B*.

3-Chloropropionate **16c** [0.323 g (0.710 mmol)] reacted with diethylamine (2 ml) in the presence of a catalytic amount of KI in H_2O to give an oily residue (0.304 g). The purification by CC over aluminium oxide eluting with CH_2Cl_2/EtOH = 49:1 gave 0.217 g (63%) of compound **7c**. IR = 2969, 2934, 1732, 1603, 1498, 1448, 1170, 743, 697; UV [MeOH (log ε)]: 260 (3.162), 210 (4.197); ^{1}H NMR ($CDCl_3$) δ = 0.93 (t, *J* = 7.1 Hz, 6H, 2 CH_3), 1.44–1.53 (m, 3H, CH–CO, CH_2), 1.61–1.68 (m, 4H, 2 CH_2), 1.71–1.81 (m, 2H, 3-H, CH–CO), 1.91 (ddd, *J* = 12.5, 9.4, 2.1 Hz, 1H, 5-H), 2.02–2.15 (m, 3H, 3-H, 5-H, 8-H), 2.19–2.34 (m, 2H, 8-H, NCH), 2.32, 2.33 (2q, *J* = 7.1 Hz, 4H, $N(CH_2)_2$), 2.37–2.46 (m, 1H, NCH), 2.58–2.73 (m, 4H, $N(CH_2)_2$), 2.80 (d, *J* = 4.6 Hz, 1H, 1-H), 2.97 (t, *J* = 9.4 Hz, 1H, 6-H), 3.15 (t, *J* = 9.8 Hz, 1H, 7-H), 5.23 (dd, *J* = 8.9, 4.6 Hz, 1H, 2-H), 7.06–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 11.80 (2 CH_3), 24.93 (CH_2), 26.76 (2 CH_2), 31.11 (CH_2–CO), 31.35 (C-5), 32.19 (C-8), 34.00 (C-7), 35.12 (C-3), 38.67 (C-6), 39.64 (C-1), 46.58 ($N(CH_2)_2$), 46.83 ($N(CH_2)_2$), 47.33 (NCH_2), 56.73 (C-4), 72.93 (C-2), 125.25, 126.30, 126.48, 127.38, 127.88, 128.46 (aromatic C), 142.94, 144.77 (aromatic C_q), 172.34 (COO); HRMS (MALDI) Calcd for $C_{32}H_{44}N_2O_2H$: 489.3481; found: 489.3456.

*6.2.4.4. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-pyrrolidinopropionate (**8a**). Method A.* 3-Chloropropionate **16a** [0.614 g (1.5 mmol)] and pyrrolidine [1.9 g (26.4 mmol)] were stirred in 100 ml dry CH_2Cl_2 overnight and gave a residue after work-up, which was purified by CC over silica gel eluting with CH_2Cl_2/MeOH = 39:1 in a first step. The fractions containing compound **8a** were chromatographed over aluminium oxide with CH_2Cl_2/MeOH = 29:1 as eluent giving 0.114 g (17%) of compound **8a**. IR = 3059, 3026, 2954, 1730, 1602, 1497, 1184, 746, 698; UV [CH_2Cl_2 (log ε)]: 260 (2.815), 230 (3.322); ^{1}H NMR ($CDCl_3$) δ = 1.61 (ddd, *J* = 15.7, 9.7, 5.9 Hz, 1H, CH–CO), 1.69–1.75 (m, 5H, 3-H, $(CH_2)_2$), 1.90 (ddd, *J* = 15.7, 9.5, 5.8 Hz, 1H, CH–CO), 1.90–1.94 (m, 1H, 5-H), 2.01–2.12 (m, 3H, 3-H, 5-H, 8-H), 2.15–2.24 (m, 2H, 8-H, NCH), 2.29–2.35 (m, 4H, $N(CH_2)_2$), 2.35–2.42 (m, 1H, NCH), 2.40 (s, 6H, $N(CH_3)_2$), 2.80 (d, *J* = 4.5 Hz, 1H, 1-H), 3.01 (t, *J* = 9.4 Hz, 1H, 6-H), 3.18 (t, *J* = 9.8 Hz, 1H, 7-H), 5.26 (dd, *J* = 9.0, 4.5 Hz, 1H, 2-H), 7.08–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.38 ($(CH_2)_2$), 31.12 (C-5), 31.44 (C-8), 33.39 (CH_2–CO), 33.97 (C-7), 34.93 (C-3), 38.42 ($N(CH_3)_2$), 38.73 (C-6), 39.61 (C-1), 50.79 (NCH_2), 53.86 ($N(CH_2)_2$), 56.18 (C-4), 72.90 (C-2), 125.37, 126.39, 126.51, 127.40, 127.97, 128.53 (aromatic C), 142.85, 144.66 (aromatic C_q), 171.98 (COO); HRMS (MALDI) Calcd for $C_{29}H_{38}N_2O_2H$: 447.3012; found: 447.3012.

*6.2.4.5. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl 3-pyrrolidinopropionate (**8b**). Method A.* 3-Chloropropionate **16b** [0.576 g (1.3 mmol)] in 80 ml dry CH_2Cl_2 was stirred with pyrrolidine [1.7 g (23.3 mmol)] overnight. After work-up 0.295 g (48%) of compound **8b** were obtained. IR = 3058, 3026, 2961, 1730, 1601, 1497, 1184, 1168, 749, 698; UV [CH_2Cl_2 (log ε)]: 260 (2.905), 230 (3.400); ^{1}H NMR ($CDCl_3$) δ = 1.60 (ddd, *J* = 15.8, 9.6, 5.9 Hz, 1H, CH–CO), 1.68–1.77 (m, 5H, 3-H, $(CH_2)_2$), 1.80–1.86 (m, 4H, $(CH_2)_2$), 1.88 (ddd, *J* = 15.8, 9.7, 5.9 Hz, 1H, CH–CO), 1.97 (ddd, *J* = 12.3, 9.5, 2.0 Hz, 1H, 5-H), 2.07 (br dd, *J* = 12.3, 9.5 Hz, 1H, 5-H), 2.13–2.27 (m, 4H, 3-H, 8-H, NCH), 2.29–2.35 (m, 4H, $N(CH_2)_2$), 2.37 (ddd, *J* = 15.9, 9.8, 5.9 Hz, 1H, NCH), 2.73–2.82 (m, 4H, $N(CH_2)_2$), 2.78 (d, *J* = 4.5 Hz, 1H, 1-H), 3.03 (t, *J* = 9.5 Hz, 1H, 6-H), 3.20 (t, *J* = 9.8 Hz, 1H, 7-H), 5.25 (dd, *J* = 9.0, 4.5 Hz, 1H, 2-H), 7.07–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.37 ($(CH_2)_2$), 23.54 ($(CH_2)_2$), 31.51 (C-5), 32.55 (C-8), 33.40 (CH_2–CO), 33.90 (C-7), 35.92 (C-3), 38.84 (C-6), 39.94 (C-1), 45.52 ($N(CH_2)_2$), 50.79 (NCH_2), 53.86 ($N(CH_2)_2$), 54.80 (C-4), 72.94 (C-2), 125.32, 126.35, 126.55, 127.45, 127.93, 128.50 (aromatic C), 142.94, 144.75 (aromatic C_q), 172.00 (COO); HRMS (MALDI) Calcd for $C_{31}H_{40}N_2O_2H$: 473.3168; found: 473.3187.

*6.2.4.6. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 3-pyrrolidinopropionate (**8c**). Method B.* The reaction of 3-chloropropionate **16c** [0.450 g (0.92 mmol)] with pyrrolidine (2 ml) in the presence of a catalytic amount of KI in H_2O gave compound **8c** (0.363 g) as an oily residue after work-up. For analytical and test purposes it was recrystallized from EtOH. Yield: 75%; m.p. 94 °C; IR = 2938, 2817, 1722, 1600, 1495, 1446, 1402, 1346, 1194, 1173, 1130, 756, 743, 701; UV [CH_2Cl_2 (log ε)]: 258 (2.794), 231 (3.417); ^{1}H NMR ($CDCl_3$) δ = 1.45–1.52 (m, 2H, CH_2), 1.55–1.76 (m, 10H, 4 CH_2, 3-H, CH–CO), 1.84–1.94 (m, 2H, 5-H, CH–CO), 2.02–2.13 (m, 3H, 3-H, 5-H, 8-H), 2.15–2.41 (m, 7H, 8-H, 3 NCH_2), 2.58–2.74 (m, 4H, $N(CH_2)_2$), 2.80 (d, *J* = 4.4 Hz, 1H, 1-H), 2.98 (br t, *J* = 9.4 Hz, 1H, 6-H), 3.16 (br t, *J* = 9.8 Hz, 1H, 7-H), 5.25 (dd, *J* = 9.0, 4.4 Hz, 1H, 2-H), 7.07–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.36 ($(CH_2)_2$), 24.94 (CH_2), 26.78 (2 CH_2), 31.32 (C-5), 32.26 (C-8), 33.37 (CH_2–CO), 34.01 (C-7), 35.22 (C-3), 38.70 (C-6), 39.61 (C-1), 46.84 ($N(CH_2)_2$), 50.78 (NCH_2), 53.85 ($N(CH_2)_2$), 56.77 (C-4), 72.98 (C-2), 125.30, 126.32, 126.49, 127.39, 127.92, 128.47 (aromatic C), 142.95, 144.80 (aromatic C_q), 171.99 (COO). Anal. Calcd for $C_{32}H_{42}N_2O_2 \cdot 0.9H_2O$ (502.91): C, 76.43; H, 8.78; N, 5.57; found: C, 76.59; H, 9.20; N, 5.50.

*6.2.4.7. (2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl 3-piperidinopropionate (**9a**). Method B.* The reaction of 3-chloropropionate **16a** [0.340 g (0.825 mmol)] with piperidine (2 ml) in the presence of a catalytic amount of KI in H_2O gave compound **9a** (0.336 g) as an oily residue after work-up. Yield: 88%. IR = 2935, 2825, 2790, 1732, 1602, 1497, 1447, 1354, 1170, 1154, 744, 698; UV [MeOH (log ε)]: 260 (3.072), 210 (4.167); ^{1}H NMR ($CDCl_3$) δ = 1.35–1.42 (m, 2H, CH_2), 1.48–1.54 (m, 4H, 2 CH_2), 1.58 (ddd, *J* = 15.7, 9.7, 5.9 Hz, 1H, CH–CO), 1.72 (dd, *J* = 14.1, 2.4 Hz, 1H, 3-H), 1.85 (ddd, *J* = 15.7, 9.4,

5.8 Hz, 1H, CH–CO), 1.86–1.93 (m, 1H, 5-H), 2.02–2.08 (m, 3H, 3-H, 5-H, 8-H), 2.09–2.16 (m, 1H, NCH), 2.16–2.25 (m, 5H, 8-H, $N(CH_2)_2$), 2.29 (ddd, $J = 15.4$, 9.6, 5.8 Hz, 1H, NCH), 2.38 (s, 6H, $N(CH_3)_2$), 2.79 (d, $J = 4.4$ Hz, 1H, 1-H), 3.01 (t, $J = 9.4$ Hz, 1H, 6-H), 3.18 (t, $J = 9.8$ Hz, 1H, 7-H), 5.24 (dd, $J = 8.9$, 4.4 Hz, 1H, 2-H), 7.09–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.24$ (CH_2), 25.89 (2 CH_2), 31.19 (C-5), 31.34 (CH_2–CO), 31.43 (C-8), 34.00 (C-7), 34.89 (C-3), 38.42 ($N(CH_3)_2$), 38.74 (C-6), 39.64 (C-1), 53.67 (NCH_2), 54.06 ($N(CH_2)_2$), 56.18 (C-4), 72.90 (C-2), 125.36, 126.40, 126.53, 127.40, 127.97, 128.53 (aromatic C), 142.85, 144.66 (aromatic C_q), 172.28 (COO); HRMS (MALDI) Calcd for $C_{30}H_{40}N_2O_2H$: 461.3168; found: 461.3181.

*6.2.4.8. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo [2.2.2]octan-2-yl 3-piperidinopropionate (**9b**). Method B*. The reaction of 3-chloropropionate **16b** [1.036 g (3.08 mmol)] with piperidine (2 ml) in the presence of a catalytic amount of KI in H_2O gave compound **9b** (1.036 g) as an oily residue after work-up. Yield: 69%. IR = 2936, 2873, 2855, 2806, 1732, 1602, 1497, 1447, 1355, 1167, 1153, 1115, 749, 698; UV [MeOH (log ε)]: 260 (3.397), 209 (4.331); ^{1}H NMR ($CDCl_3$) $\delta = 1.36$–1.42 (m, 2H, CH_2), 1.48–1.55 (m, 4H, 2 CH_2), 1.58 (ddd, $J = 15.6$, 9.6, 6.0 Hz, 1H, CH–CO), 1.74 (ddd, $J = 14.1$, 2.2, 1.5 Hz, 1H, 3-H), 1.72–1.90 (m, 5H, CH–CO, $(CH_2)_2$), 1.99 (ddd, $J = 11.9$, 9.6, 2.3 Hz, 1H, 5-H), 2.05–2.24 (m, 9H, 3-H, 5-H, 8-H, NCH, $N(CH_2)_2$), 2.29 (ddd, $J = 12.7$, 9.6, 5.8 Hz, 1H, NCH), 2.75–2.84 (m, 5H, 1-H, $N(CH_2)_2$), 3.04 (t, $J = 9.6$ Hz, 1H, 6-H), 3.20 (t, $J = 9.7$ Hz, 1H, 7-H), 5.24 (dd, $J = 8.6$, 4.5 Hz, 1H, 2-H), 7.07–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.56$ ($(CH_2)_2$), 24.20 (CH_2), 25.82 (2 CH_2), 31.28 (CH_2–CO), 31.63 (C-5), 32.45 (C-8), 33.91 (C-7), 35.80 (C-3), 38.81 (C-6), 39.97 (C-1), 45.60 ($N(CH_2)_2$), 53.63 (NCH_2), 54.04 ($N(CH_2)_2$), 55.10 (C-4), 72.89 (C-2), 125.32, 126.37, 126.55, 127.43, 127.94, 128.51 (aromatic C), 142.83, 144.65 (aromatic C_q), 172.22 (COO). Anal. Calcd for $C_{32}H_{42}N_2O_2 \cdot H_2O$ (504.71): C, 76.15; H, 8.79; N, 5.55; found: C, 75.92; H, 8.48; N, 5.39.

*6.2.4.9. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo [2.2.2]octan-2-yl 3-piperidinopropionate (**9c**). Method B*. The reaction of 3-chloropropionate **16c** [0.313 g (0.69 mmol)] with piperidine (2 ml) in the presence of a catalytic amount of KI in H_2O gave crude compound **9c** (0.305 g) after work-up, which was purified by CC over aluminium oxide eluting with CH_2Cl_2/EtOH = 29:1 giving 0.228 g (66%) of compound **9c**. IR = 2934, 2852, 1732, 1602, 1497, 1447, 1354, 1169, 1114, 744, 697; UV [CH_2Cl_2 (log ε)]: 258 (2.771), 232 (3.310); ^{1}H NMR ($CDCl_3$) $\delta = 1.34$–1.42 (m, 2H, CH_2), 1.44–1.55 (m, 6H, 3 CH_2), 1.57 (ddd, $J = 15.6$, 9.5, 5.7 Hz, 1H, CH–CO), 1.61–1.69 (m, 4H, 2 CH_2), 1.74 (br d, $J = 13.6$ Hz, 1H, 3-H), 1.84 (ddd, $J = 15.6$, 9.3, 5.7 Hz, 1H, CH–CO), 1.87–1.94 (m, 1H, 5-H), 2.03–2.16 (m, 4H, 3-H, 5-H, 8-H, NCH), 2.16–2.32 (m, 6H, 8-H, NCH, $N(CH_2)_2$), 2.58–2.74 (m, 4H, $N(CH_2)_2$), 2.79 (d, $J = 4.5$ Hz, 1H, 1-H), 2.98 (t, $J = 9.4$ Hz, 1H, 6-H), 3.16 (t, $J = 9.9$ Hz, 1H, 7-H), 5.23 (dd, $J = 8.8$, 4.5 Hz, 1H, 2-H), 7.06–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.25$ (CH_2), 24.95 (CH_2), 25.88 (2 CH_2), 26.79 (2 CH_2), 31.32 (CH_2–CO), 31.39 (C-5), 32.26 (C-8), 34.05 (C-7), 35.19 (C-3), 38.72 (C-6), 39.67 (C-1), 46.87 ($N(CH_2)_2$), 53.67 (NCH_2), 54.06 ($N(CH_2)_2$), 56.78 (C-4), 73.00 (C-2), 125.30, 126.34, 126.52, 127.41, 127.94, 128.50 (aromatic C), 142.96, 144.81 (aromatic C_q), 172.28 (COO). Anal. Calcd for $C_{33}H_{44}N_2O_2$ (500.72): C, 79.16; H, 8.86; N, 5.59; found: C, 78.87; H, 8.76; N, 5.76.

*6.2.4.10. (2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl acrylate (**17c**)*. Compound **17c** was formed as an intermediate during the synthesis of compound **16c**. It was separated by crystallization with EtOH. IR = 3058, 3030, 2982, 2964, 2937, 1712, 1616, 1602, 1497, 1285, 1050, 986, 974, 757, 743, 708, 696; UV [CH_2Cl_2 (log ε)]: 260 (2.861), 230 (3.400); ^{1}H NMR ($CDCl_3$) $\delta = 1.45$–1.52 (m, 2H, CH_2), 1.60–1.68 (m, 4H, 2 CH_2), 1.75 (dd, $J = 14.3$, 2.1 Hz, 1H, 3-H), 1.92 (ddd, $J = 12.5$, 9.4, 2.2 Hz, 1H, 5-H), 2.03–2.12 (m, 2H, 5-H, 8-H), 2.15 (ddd, $J = 14.3$, 8.9, 3.1 Hz, 1H, 3-H), 2.26 (ddd, $J = 11.8$, 9.7, 3.0 Hz, 1H, 8-H), 2.59–2.74 (m, 4H, $N(CH_2)_2$), 2.81 (d, $J = 4.5$ Hz, 1H, 1-H), 3.01 (t, $J = 9.4$ Hz, 1H, 6-H), 3.20 (t, $J = 9.7$ Hz, 1H, 7-H), 5.31 (dd, $J = 8.9$, 4.5 Hz, 1H, 2-H), 5.40 (dd, $J = 10.4$, 1.7 Hz, 1H, 3′-H), 5.50 (dd, $J = 17.1$, 10.4 Hz, 1H, 2′-H), 5.68 (dd, $J = 17.1$, 1.7 Hz, 1H, 3′-H), 7.04–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.97$ (CH_2), 26.82 (2 CH_2), 31.30 (C-5), 32.66 (C-8), 34.14 (C-7), 35.58 (C-3), 38.81 (C-6), 39.48 (C-1), 46.88 ($N(CH_2)_2$), 56.77 (C-4), 73.28 (C-2), 125.20, 126.37, 126.53, 127.41, 127.91, 128.53 (aromatic C), 128.01 (C-2′), 129.96 (C-3′), 142.97, 144.77 (aromatic C_q), 165.66 (COO); HRMS (MALDI) Calcd for $C_{28}H_{33}NO_2H$: 416.2590; found: 416.2579.

*6.2.5. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl chloroacetate (**19c**)*

Bicyclo-octanol **18c** [0.5 g (1.38 mmol)] and 4-DMAP [0.02 g (0.164 mmol)] were dissolved in dry CH_2Cl_2 (35 ml). Upon cooling in an ice bath 2-chloroacetyl chloride [0.312 g (2.76 mmol)] in dry CH_2Cl_2 (2 ml) was added under stirring. After 1 h the ice bath was removed and the solution was stirred overnight at room temperature in an argon atmosphere. Then it was carefully shaken five times with water. The organic layer was dried over sodium sulfate and filtered. The solvent was removed in vacuo. The ester **19c** [0.538 g (89%)] was converted to **12c–14c** without further purification.

*6.2.6. General procedure for the synthesis of (2RS,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo [2.2.2]octan-2-yl 2′-dialkylaminoacetates (**12c–14c**)*

Compound **19c** was dissolved in excess secondary amine (2 ml) and a catalytic amount of KI in H_2O was added. Then the solution was cooled to 4 °C in a fridge for 48 h. After that the amine was removed in vacuo and the residue was dissolved

in CH_2Cl_2. The organic phase was washed five times with H_2O, dried over sodium sulfate and filtered. Then the solvent was removed in vacuo and the residue was purified by means of CC.

*6.2.6.1. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 2′-diethylaminoacetate (**12c**).* Compound **19c** [0.147 g (0.34 mmol)] was dissolved in diethylamine giving an oily residue (0.132 g) after work-up, which was purified by means of CC using CH_2Cl_2/EtOH = 49:1 as eluent giving 0.106 g (66%) of compound **12c**. IR = 2969, 2934, 1739, 1604, 1497, 1451, 1178, 1158, 755, 699; UV [MeOH (log ε)]: 260 (3.208), 209 (4.254); ^{1}H NMR ($CDCl_3$) $\delta = 1.07$ (t, $J = 7.2$ Hz, 6H, 2 CH_3), 1.42–1.48 (m, 2H, CH_2), 1.55 (ddd, $J = 13.2$, 6.1, 2.7 Hz, 1H, 3-H), 1.56–1.65 (m, 4H, 2 CH_2), 1.66 (ddd, $J = 12.0$, 9.8, 2.1 Hz, 1H, 8-H), 1.86 (ddd, $J = 12.7$, 9.7, 1.8 Hz, 1H, 5-H), 2.13 (ddd, $J = 12.0$, 9.8, 2.7 Hz, 1H, 8-H), 2.24 (ddd, $J = 12.7$, 9.7, 2.1 Hz, 1H, 5-H), 2.30 (br s, 1H, 1-H), 2.40 (ddd, $J = 13.2$, 9.5, 1.8 Hz, 1H, 3-H), 2.52–2.67 (m, 4H, $N(CH_2)_2$), 2.67 (q, $J = 7.2$ Hz, 4H, 2 CH_2–CH_3), 3.18 (t, $J = 9.8$ Hz, 1H, 7-H), 3.34 (s, 2H, CH_2–CO), 3.50 (t, $J = 9.7$ Hz, 1H, 6-H), 5.20 (br dd, $J = 9.5$, 6.1 Hz, 1H, 2-H), 7.16–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 12.38$ (2 CH_3), 24.91 (CH_2), 26.76 (2 CH_2), 32.87 (C-5), 34.40 (C-7), 34.51 (C-8), 34.87 (C-3), 35.54 (C-6), 40.92 (C-1), 46.77 ($N(CH_2)_2$), 47.68 ($N(CH_2$–$CH_3)_2$), 54.24 (CH_2–CO), 57.23 (C-4), 70.17 (C-2), 126.11, 127.15, 127.37, 128.46, 128.49 (aromatic C), 143.53, 143.58 (aromatic C_q), 171.29 (COO); HRMS (MALDI) Calcd for $C_{31}H_{42}N_2O_2H$: 475.3325; found: 475.3301.

*6.2.6.2. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 2′-pyrrolidinoacetate (**13c**).* Compound **19c** [0.202 g (0.46 mmol)] was dissolved in pyrrolidine giving an oily residue (0.200 g) after work-up, which was purified by means of CC using CH_2Cl_2/MeOH = 49:1 as eluent giving 0.160 g (73%) of compound **13c**. IR = 2934, 2790, 1749, 1603, 1497, 1449, 1181, 1158, 754, 699; UV [MeOH (log ε)]: 259 (3.077), 209 (4.187); ^{1}H NMR ($CDCl_3$) $\delta = 1.42$–1.49 (m, 2H, CH_2), 1.54–1.71 (m, 6H, 3-H, 8-H, 2 CH_2), 1.78–1.87 (m, 5H, 5-H, $(CH_2)_2$), 2.13 (br dd, $J = 12.8$, 9.9 Hz, 1H, 8-H), 2.25 (br dd, $J = 12.0$, 9.7 Hz, 1H, 5-H), 2.31 (s, 1H, 1-H), 2.39 (br dd, $J = 12.5$, 9.5 Hz, 1H, 3-H), 2.50–2.71 (m, 8H, 2 $N(CH_2)_2$), 3.18 (t, $J = 9.9$ Hz, 1H, 7-H), 3.32, 3.38 (2d, $J = 16.8$ Hz, 2H, CH_2–CO), 3.49 (t, $J = 9.7$ Hz, 1H, 6-H), 5.21 (dd, $J = 9.5$, 7.1 Hz, 1H, 2-H), 7.14–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.77$ ($(CH_2)_2$), 24.89 (CH_2), 26.74 (2 CH_2), 32.74 (C-5), 34.38 (C-7), 34.70 (C-3, C-8), 35.49 (C-6), 40.83 (C-1), 46.80 ($N(CH_2)_2$), 54.01 ($N(CH_2)_2$), 56.97 (CH_2–CO), 57.29 (C-4), 70.33 (C-2), 126.15, 127.15, 127.40, 128.46, 128.49 (aromatic C), 143.48, 143.57 (aromatic C_q), 170.62 (COO); HRMS (MALDI) Calcd for $C_{31}H_{40}N_2O_2H$: 473.3168; found: 473.3207.

*6.2.6.3. (2RS,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl 2′-piperidinoacetate (**14c**).* Compound **19c** [0.276 g (0.63 mmol)] was dissolved in piperidine giving an oily residue (0.286 g) after work-up, which was purified by means of CC using CH_2Cl_2/MeOH = 49:1 as eluent giving 0.231 g (75%) of compound **14c**. IR = 2934, 2852, 2799, 1750, 1604, 1496, 1452, 1173, 1113, 754, 699; UV [MeOH (log ε)]: 260 (3.035), 209 (4.211); ^{1}H NMR ($CDCl_3$) $\delta = 1.39$–1.48 (m, 4H, 2 CH_2), 1.56 (ddd, $J = 12.6$, 6.1, 2.7 Hz, 1H, 3-H), 1.57–1.70 (m, 9H, 8-H, 4 CH_2), 1.84 (ddd, $J = 12.7$, 9.8, 2.3 Hz, 1H, 5-H), 2.13 (ddd, $J = 12.8$, 10.1, 2.7 Hz, 1H, 8-H), 2.24 (ddd, $J = 12.7$, 9.8, 2.2 Hz, 1H, 5-H), 2.30 (d, $J = 1.7$ Hz, 1H, 1-H), 2.39 (ddd, $J = 12.6$, 9.5, 2.3 Hz, 1H, 3-H), 2.48–2.58 (m, 6H, NCH_2, $N(CH_2)_2$), 2.61–2.68 (m, 2H, NCH_2), 3.18 (t, $J = 10.1$ Hz, 1H, 7-H), 3.17, 3.22 (2d, $J = 16.6$ Hz, 2H, CH_2–CO), 5.21 (ddd, $J = 9.5$, 6.1, 1.7 Hz, 1H, 2-H), 7.15–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.89$ (CH_2), 24.91 (CH_2), 25.85 (2 CH_2), 26.76 (2 CH_2), 32.75 (C-5), 34.41 (C-7), 34.63 (C-8), 34.80 (C-3), 35.50 (C-6), 40.87 (C-1), 46.78 ($N(CH_2)_2$), 54.32 ($N(CH_2)_2$), 57.24 (C-4), 60.32 (CH_2–CO), 70.26 (C-2), 126.13, 126.15, 127.15, 127.39, 128.46, 128.49 (aromatic C), 143.51, 143.58 (aromatic C_q), 170.42 (COO); HRMS (MALDI) Calcd for $C_{32}H_{42}N_2O_2H$: 487.3325; found: 487.3367.

6.3. Biological tests

A detailed description of the determination of antiplasmodial and antitrypanosomal activity and the cytotoxicity is reported [15].

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