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Antiprotozoal activities of new bis-chlorophenyl derivatives of bicyclic octanes and aza-nonanes

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Abstract—The in vitro activity of newly synthesized bis-(chlorophenyl)-azabicyclo[3.2.2]nonanes and bis-(chlorophenyl)-bicyclo[2.2.2]octanes against *Plasmodium falciparum* K_1 (resistant to chloroquine and pyrimethamine) and *Trypanosoma brucei rhodesiense* was investigated. Especially the bis-(chlorophenyl)-azabicyclo[3.2.2]nonanes exhibit promising antitrypanosomal activity and were tested in vivo against *Trypanosoma brucei brucei* featuring moderate activities.

Human African Trypanosomiasis is caused by the two protozoan parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. This disease is invariably fatal, if untreated[1], and a serious problem in sub-Saharan Africa with an estimated 100,000 deaths each year.[2] The drugs in use suffer from a number of disadvantages, including toxic side effects, poor clinical efficacy, partially painful parenteral administration and increasing problems with resistance.[3] Eflornithine is for 50 years the only new drug, but is ineffective against *T. b. rhodesiense*.[4] Therefore, there is an urgent need for new drugs against this protozoal parasite with less side effects.

At present malaria is considered to be the world's most important tropical parasitic disease, afflicting 300–500 million and killing 1–2 million people annually.[5] It is estimated that nearly 40% of the world's population lives in malaria endemic regions. *Plasmodium falciparum* is the most dangerous form of the disease-causing parasites, accounting for up to 95% of malaria-related deaths.[6]

A main problem in this species is drug resistance.[7] Drugs which were once highly effective such as chloroquine and the combination sulfadoxine-pyrimethamine are almost useless in many parts of the world.[8,9] Loss of sensitivity has been observed even for the most recently introduced artemisinine derivatives.[10–14] Therefore, there is great demand for new antimalarial drugs.

4-Dialkylaminobicyclo[2.2.2]octanones **1** which are available in a one-pot synthesis from cheap starting materials[15] and their alcohol analogues **2** have been screened for their activities against some causative organisms of tropical diseases such as malaria, leishmaniasis, Chagas' disease, and sleeping sickness.[16] Some of them exhibit antiplasmodial activity against the K1 strain of *P. falciparum* which is resistant to chloroquine and pyrimethamine. Additionally, those compounds show moderate potency against *T. b. rhodesiense*. Recently, we have synthesized 2-azabicyclo[3.2.2]nonan-3-ones **3** via a Beckmann rearrangement of **1**. Nonanes **4** which have been obtained by hydrogenation of **3** have promising antiprotozoal activities and low cytotoxicity.[17]

Keywords: Antiplasmodial activity; Antitrypanosomal activity; Bicyclo-octanones; Aza-bicyclononanes; In vitro and in vivo assays.
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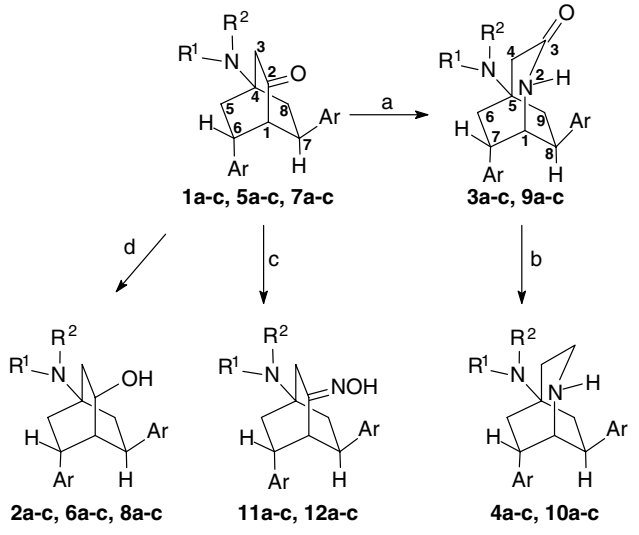
We decided to prepare analogues of **1**–**4** with varying electronic and lipophilic properties. The additional $-\sigma$ effect in position 4 of the phenyl rings of bis-(4-methoxyphenyl) analogues **5** and **6** did not significantly change the antiprotozoal activities.[18,19] Since activity usually increases with increasing π-values we synthesized the more lipophilic *p*-chloro analogues **7**–**10** as suggested by Topliss[20] (Scheme 1). The oximes **11** exhibit antiplasmodial activity which is comparable to that of chloroquine against sensitive strains.[21] Therefore, we prepared their 4-chlorophenyl analogues **12** from ketones **7**. The latter were available from 4-chlorobenzylidene acetone and dialkylammonium isothiocyanates[24] following a reported procedure.[15]

The alcohols **8** were obtained from a stereoselective reduction of **7** using $LiAlH_4$ as catalyst.[25] Ring enlargement to cyclic amides **9** succeeded by means of a Beckmann-rearrangement of ketones **7** with hydroxylamine-*o*-sulfonic acid[26] and the reduction of **9** with $LiAlH_4$ yielded diamines **10**.[27] The oximes **12** were prepared from **7** with hydroxylamine hydrochloride in the presence of sodium.[28] The structures of the new compounds were established using NMR spectroscopy. The structure of parent compounds **1** has been elucidated using a single crystal structure analysis.[15] The configuration in position 2 of compounds **2** has been determined by NOE measurements.[16]

Compounds **8**, **10** and **12** were investigated for their antiplasmodial and antitrypanosomal activities as well as for their cytotoxicity following reported procedures.[22] *T. b. rhodesiense* (STIB900) and *P. falciparum* K_1 (resistant to chloroquine and pyrimethamine) were used for the determination of the antitrypanosomal and antiplasmodial properties and L-6 cells for the cytotoxicity. Compounds **7** and **9** were not tested because of the poor antiprotozoal activity of their unsubstituted analogues **1** and **3**. The results are presented in Table 1.



Scheme 1. Reagents and conditions: (a) NH_2OSO_3H, glacial acetic acid, reflux, 18 h; (b) $LiAlH_4$, diethyl ether, reflux, 48 h; (c) $NH_2OH{\cdot}HCl$, C_2H_5ONa, EtOH, reflux, 18 h; (d) $LiAlH_4$, diethyl ether, reflux, 18 h.

The bis-chlorophenyl alcohols **8** exhibit a distinctly higher activity against *P. falciparum* K_1 than their unsubstituted analogues **2**. The antiplasmodial activity of **10** is comparable with that of the unsubstituted analogues **4** but unfortunately their selectivity is distinctly decreased. The antiplasmodial activity and the selectivity index of chlorophenyl-substituted oximes **12** are worse than those of their unsubstituted analogues **11**. The most active compound of this group is **12b′** (IC_{50} = 0.19 μM) showing *Z* configuration in the oxime function.

All of the 4-chlorophenyl derivatives have higher activity against *T. b. rhodesiense* than their unsubstituted analogues. Compared to their unsubstituted analogues **2** and **4** the alcohols **8** (IC_{50} = 0.32–0.44 μM) and the diamines **10** (IC_{50} = 0.061–0.066 μM) show a 10-fold increase of potency. Besides the selectivity index of the pyrrolidino and piperidino compounds **8b**,**c** and **10b**,**c** has improved. Compounds **10** show the highest antitrypanosomal activity (IC_{50} = 0.061–0.066 μM) of all so far synthesized bicyclo[2.2.2]octane and 2-azabicyclo[3.2.2]nonane derivatives. Besides, their selectivity (SI = 124–152) is distinctly pronounced.

Compounds **10** were tested in vivo against *Trypanosoma brucei brucei* using the following assay:

Female mice (NMRI), four mice per group, weighing 20–25 g were infected ip with 1×10^5 bloodstream forms of *T. b. brucei*. These bloodstream forms come from a stock of cryopreserved stabilates containing 10% glycerol. The stabilate was suspended in PSG (phosphate-saline-glucose) 6:4[23] to obtain a trypanosome concentration of 4×10^5/ml. Each mouse was injected with 0.25 ml. Compounds were prepared at appropriate concentrations in 100% DMSO and further diluted in distilled H_2O. They were daily administered ip in a total volume of 0.01 ml per g of body weight from day +3 to day +6 of the experiment. The day of death was recorded and the mean survival time calculated. The results are presented in Table 2.

Compounds **10a** and **10c** show moderate in vivo activity. In the case of the most active compound **10c** 75% of the mice lived at least 11 days.

Viewing at the increase of antitrypanosomal activity and selectivity of compounds **10b**,**c** compared to **4b**,**c** the insertion of chloro substituents in position 4 of the phenyl rings is advantageous and should be applied to other derivatives of the 2-azabicyclo[3.2.2]nonane and the bicyclo[2.2.2]octane series.

Table 1. Antiprotozoal activities of compounds **1**–**12**

Compound	Ar	R^1, R^2	*T.b. rhodesiense* IC_{50}[a] (μM) ± SD[c]	SI = IC_{50} (Cytotox.)/ IC_{50} (*T.b. rhodesiense*)	*P. falciparum* K_1 IC_{50}[a] (μM) ± SD[c]	SI = IC_{50} (Cytotox.)/IC_{50} (*P. falciparum*)	Cytotoxicity IC_{50}[a] (μM) ± SD[c]
1a	Ph	$R^1 = R^2 = CH_3$	9.99	2.46	>10.57	2.32	24.57
1b	Ph	$R^1 + R^2 = -(CH_2)_4-$	8.03	3.29	1.19	22.22	26.45
1c	Ph	$R^1 + R^2 = -(CH_2)_5-$	8.12	5.78	3.95	11.88	46.92
2a	Ph	$R^1 = R^2 = CH_3$	2.95	44.91	>15.55	8.52	132.5
2b	Ph	$R^1 + R^2 = -(CH_2)_4-$	4.26	6.28	2.39	11.20	26.76
2c	Ph	$R^1 + R^2 = -(CH_2)_5-$	5.34	6.99	0.84	44.45	37.34
3a	Ph	$R^1 = R^2 = CH_3$	37.97	7.09	1.40	192.2	>269.1
3b	Ph	$R^1 + R^2 = -(CH_2)_4-$	37.94	6.58	8.76	28.43	>249.7
3c	Ph	$R^1 + R^2 = -(CH_2)_5-$	36.60	6.38	13.00	17.97	233.6
4a	Ph	$R^1 = R^2 = CH_3$	0.60	181.3	0.28	388.6	108.8
4b	Ph	$R^1 + R^2 = -(CH_2)_4-$	1.16	103.8	0.56	215.0	120.4
4c	Ph	$R^1 + R^2 = -(CH_2)_5-$	6.57	13.66	0.64	140.22	89.74
5a	4-MeO–Ph	$R^1 = R^2 = CH_3$	5.01	10.47	5.43	9.66	52.44
5b	4-MeO–Ph	$R^1 + R^2 = -(CH_2)_4-$	3.70	11.34	3.37	12.44	41.92
5c	4-MeO–Ph	$R^1 + R^2 = -(CH_2)_5-$	10.01	—	4.36	—	nt
6a	4-MeO–Ph	$R^1 = R^2 = CH_3$	2.15	29.50	5.50	11.53	63.43
6b	4-MeO–Ph	$R^1 + R^2 = -(CH_2)_4-$	7.61	2.35	2.72	6.58	17.91
6c	4-MeO–Ph	$R^1 + R^2 = -(CH_2)_5-$	14.23	3.13	4.98	8.95	44.59
7a	4-Cl–Ph	$R^1 = R^2 = CH_3$	nt	—	nt	—	nt
7b	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	nt	—	nt	—	nt
7c	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_5-$	nt	—	nt	—	nt
8a	4-Cl–Ph	$R^1 = R^2 = CH_3$	0.32 ± 0.10	27.41	0.98 ± 0.20	8.95	8.77 ± 0.51
8b	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	0.37 ± 0.09	9.70	0.53 ± 0.13	6.77	3.59 ± 0.47
8c	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_5-$	0.44 ± 0.12	26.34	0.37 ± 0.09	31.32	11.59 ± 0.69
9a	4-Cl–Ph	$R^1 = R^2 = CH_3$	nt	—	nt	—	nt
9b	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	nt	—	nt	—	nt
9c	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_5-$	nt	—	nt	—	nt
10a	4-Cl–Ph	$R^1 = R^2 = CH_3$	0.061 ± 0.007	143.3	0.41 ± 0.050	21.32	8.74 ± 0.48
10b	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	0.066 ± 0.018	152.4	0.25 ± 0.035	40.24	10.06 ± 1.53
10c	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_5-$	0.065 ± 0.017	124.6	0.46 ± 0.034	17.61	8.10 ± 0.48
11a	Ph	$R^1 = R^2 = CH_3$	7.67	19.61	1.26	119.4	150.4
11b	Ph	$R^1 + R^2 = -(CH_2)_4-$	1.84	7.31	0.08	168.1	13.45
11c	Ph	$R^1 + R^2 = -(CH_2)_5-$	3.66	6.60	0.15	161.1	24.16
12a	4-Cl–Ph	$R^1 = R^2 = CH_3$	1.50 ± 0.09	5.21	1.00 ± 0.10	7.82	7.82 ± 1.17
12b	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	1.69 ± 0.55	7.49	0.51 ± 0.14	24.82	12.66 ± 1.25
12b′	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_4-$	1.51 ± 0.41	3.85	0.19 ± 0.07	27.26	5.81 ± 0.90
12c	4-Cl–Ph	$R^1 + R^2 = -(CH_2)_5-$	3.34 ± 0.22	2.62	0.50 ± 0.20	17.5	8.75 ± 0.08
mel	—	—	0.0039	1995	nt	—	7.78
sur	—	—	0.0075	629933	nt	—	4724.5
art	—	—	nt	—	0.0064	70390	450.5
chl	—	—	nt	—	0.12[b]	1570	188.5
mef	—	—	nt	—	nt	—	11.37

[a] Values represent the average of four determinations (two determinations of two independent experiments); art, artemisinin; chl, chloroquine; mel, melarsoprol; sur, suramine; mef, mefloquine; nt, not tested.
[b] Against sensitive *P. falciparum* strains.
[c] Standard deviation.

Table 2. In vivo antitrypanosomal activity of compounds **10a**–**c** against *Trypanosoma brucei brucei*

Compound	Appl.	Dose (mg/kg)	MSD	SD
10a	ip	4 × 50	9.00	3.5
10b	ip	4 × 50	5.75	0.6
10c	ip	4 × 50	10.25	2.9
ctrl	ip	—	6.00	0.6
mel	ip	4 × 0.5	42.50	—

ip, intraperitoneal; ctrl, control; mel, melarsoprol; MSD, mean survival days; SD, standard deviation.

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Supplementary data

Analytical data of compounds **7b**,**c**; **8b**,**c**; **9b**,**c**; **10b**,**c**; **12b**,**c** are reported in the supplementary material. Supplementary data associated with this article can be

found in the online version at doi:10.1016/j.bmcl.2006.07.057.

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24. *Experimental*. Melting points: digital melting point apparatus Electrothermal IA 9200, 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 Inova 400 (300 K) 5 mm tubes, in $CDCl_3$, TMS resonance as internal standard. ^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 (gCOSY, gHSQC, and gHMBC optimized on 8 Hz) and are numbered as given in the formula (br, broad; d, doublet; dd, double doublet; ddd, double double doublet; m, multiplet; t, triplet; s, singlet). MS: Kratos profile spectrometer 70 eV electron impact. *Microanalyses*. Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; EA 1108 CHNS-O apparatus (Carlo Erba). *Materials*. Column chromatography: 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. General procedure for the synthesis of (6RS,7RS)-(±)-4-dialkylamino-6,7-bis(4-chlorophenyl)bicyclo[2.2.2]octan-2-ones (**7a**–**c**). Dialkylammonium isothiocyanate (0.2 mmol) and 4-chlorobenzylidene acetone (0.2 mmol) were suspended in 125 mL of toluene. The mixture was refluxed for 4 h at 120 °C at a water separator and then cooled to room temperature. The solvent was evaporated in vacuo and the residue dissolved in hot ethanol and cooled in the refrigerator. After a few days, the product separated in form of brown crystals and was recrystallized from ethanol. The isothiocyanate was suspended in 2 N NaOH, stirred for 1 h and extracted five times with ether. The organic layers were combined, dried with Na_2SO_4, filtered and the solvent evaporated giving pure bases **7a**–**c**. Compound **7b**,**c** crystallized from EtOH. Analytical data of **7a**: orange oil, yield 14%. IR KBr (νcm^{-1}) 2948, 2872, 2829, 2783, 1721, 1493, 1466, 1404, 1345, 1093, 1041, 1012, 842, 823; UV CH_2Cl_2 (λ (log ε) nm) 231 (4.061), 269 (2.973); ^1H NMR (δ) ppm 1.62 (ddd, J = 13.1, 8.5, 2.7 Hz, 1H, 8-H), 2.03 (ddd, J = 13.1, 8.5, 2.4 Hz, 1H, 5-H), 2.27–2.44 (m, 9H, 3-H, 5-H, 8-H, $N(CH_3)_2$), 2.55 (dd, J = 18.5, 3.4 Hz, 1H, 3-H), 2.58 (s, 1H, 1-H), 3.24 (br t, J = 9.6 Hz, 1H, 7-H), 3.32 (br t, J = 9.5 Hz, 1H, 6-H), 6.97–7.36 (m, 8 aromatic H); ^{13}C NMR (δ) ppm 31.43 (C-5), 35.11 (C-7), 36.87 (C-8), 37.58 (C-6), 38.48 ($N(CH_3)_2$), 44.08 (C-3), 53.66 (C-1), 57.83 (C-4), 128.28, 128.72 128.76, 128.89 (aromatic C), 132.41,132.76, 139.46, 142.32 (aromatic C_q), 212.40 (C-2); HRMS (EI+): calcd ($C_{22}H_{23}Cl_2NO$): 387.11567; found: 387.11838.
25. General procedure for the synthesis of (6RS,7RS)-(±)-4-dialkylamino-6,7-bis(4-chlorophenyl)bicyclo[2.2.2]octan-2-ols (**8a**–**c**): Ketones **7a**–**c** (1.5 mmol) were dissolved under stirring and cooling on an ice bath in 15 mL of dry ether. $LiAlH_4$ (4.63 mmol) was added cautiously in portions and the mixture was stirred overnight at room temperature. 1 N NaOH was added dropwise under stirring and cooling to quench the reaction. The organic layer was removed and brine was added to the aqueous layer which was extracted subsequently several times with CH_2Cl_2 using total amount of 250 mL. The combined organic layers were washed two times with water and dried with sodium sulfate, filtered and the solvent evaporated in vacuo. The residue crystallized from CH_2Cl_2 or $CHCl_3$. Analytical data of **8a**: white crystals, yield 57%. mp (°C) 101; IR KBr (νcm^{-1}) 2976, 2876, 2839, 1492, 1093, 1060, 1012, 828, 818, 783, 755; UV CH_2Cl_2 (λ (log ε) nm) 231 (3.956), 270 (2.819); ^1H NMR (δ) ppm 1.32 (br s, 1H, OH), 1.70 (dd, J = 13.8, 1.9 Hz, 1H, 3-H), 1.82 (ddd, J = 12.6, 9.1, 2.6 Hz, 1H, 5-H), 1.95–2.02 (m, 2H, 3-H, 5-H), 2.05–2.09 (m, 2H, 8-H), 2.32 (d, J = 4.2 Hz, 1H, 1-H), 2.36 (s, 6H, $N(CH_3)_2$), 2.86 (br t, J = 9.3 Hz, 1H, 6-H), 3.06 (br t, J = 9.9 Hz, 1H, 7-H), 4.33 (dd, J = 8.5, 4.2 Hz, 1H, 2-H), 7.13–7.36 (m, 8 aromatic H); ^{13}C NMR (δ) ppm 30.94 (C-8), 31.56 (C-5), 34.69 (C-7), 37.29 (C-3), 38.38 ($N(CH_3)_2$), 38.93 (C-6), 44.16 (C-1), 56.33 (C-4), 71.64 (C-2), 128.22, 128.69 (aromatic C), 131.41, 132.12, 141.70,

143.55 (aromatic C_q); HRMS (EI+): calcd ($C_{22}H_{25}Cl_2NO$): 389.13132; found: 389.13214.

26. General procedure for the synthesis of (7RS,8RS)-(±)-5-dimethylamino-7,8-bis-(4-chlorophenyl)-2-azabicyclo[3.2.2]nonan-3-ones (**9a**–**c**). Ketones **7a**–**c** (12 mmol) and hydroxylamine-*O*-sulfonic acid (36 mmol) were suspended in 30 mL of glacial acetic acid and refluxed at 145 °C overnight. The brown solution was poured on ice, alkalized with 2 N NaOH and extracted five times with CH_2Cl_2. The combined organic layers were washed three times with water, dried over Na_2SO_4 and filtered. After evaporation of the solvent in vacuo, the residue was dissolved in the minimum amount of hot ethanol. The products crystallized overnight. Analytical data of **9a**: beige precipitate, yield 21%. mp (°C) 132; IR KBr (νcm^{-1}) 2950, 2874, 1650, 1492, 1466, 1413, 1330, 1109, 1091, 1013, 816, 794; UV CH_2Cl_2 (λ (log ε) nm) 230 (4.107); ^{1}H NMR (δ) ppm 1.91–2.02 (m, 2H, 6-H, 9-H), 2.19 (ddd, J = 13.7, 9.9, 1.4 Hz, 1H, 9-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.36 (dd, J = 13.1, 8.0 Hz, 1H, 6-H), 2.65 (dd, J = 17.8, 1.7 Hz, 1H, 4-H), 2.87 (d, J = 17.8 Hz, 1H, 4-H), 3.16 (d, J = 6.8 Hz, 1H, 1-H), 3.22 (br t, J = 9.6 Hz, 1H, 8-H), 3.42 (dd, J = 11.2, 8.2 Hz, 1H, 7-H), 6.89 (d, J = 6.8 Hz, 1H, N–H), 7.13–7.37 (m, 8 aromatic H); ^{13}C NMR (δ) ppm 35.51 (C-6, C-9), 37.84 ($N(CH_3)_2$), 40.68 (C-4), 40.88 (C-8), 45.78 (C-7), 54.95 (C-5), 57.49 (C-1), 128.08, 128.73, 129.14 (aromatic C) 132.89, 132.92, 140.19, 141.20 (aromatic C_q), 174.00 (C-3); HRMS (MALDI): calcd ($C_{22}H_{24}Cl_2N_2ONa$): 425.1163; found: 425.1147.

27. General procedure for the synthesis of (7RS,8RS)-(±)-(7,8-bis(4-chlorophenyl)-2-azabicyclo[3.2.2]non-5-yl)-dialkylamines **10a**–**c**: 2 mmol of (7RS,8RS)-(±)-5-dialkylamino-7,8-diphenyl-2-azabicyclo[3.2.2]nonan-3-ones **9a**–**c** was suspended in 40 mL of dry ether. Under cooling on an ice bath, $LiAlH_4$ (8 mmol) was added in portions. The reaction mixture was refluxed at 55 °C for 2 days. After cooling to room temperature, the reaction mixture was cooled with an ice bath and quenched carefully with ice water and 2 N NaOH. The mixture was extracted five times with ether, the combined organic layers were washed three times with water, dried over Na_2SO_4, filtered and the solvent evaporated. The dihydrochlorides were prepared by treatment of a solution of the base in CH_2Cl_2 with etheral HCl (2 M) and subsequent evaporation of the solvents in vacuo. The residue crystallized from ethanol/ethyl acetate or CH_2Cl_2/ethyl acetate. Analytical data of **10a**: white crystals, yield 81%. mp (°C) 251; IR KBr (νcm^{-1}) 3423, 2960, 2677, 2467, 1586, 1494, 1412, 1094, 1012, 830; UV CH_3OH (λ (log ε) nm) 223 (4.239); ^{1}H NMR (δ) ppm 1.80–1.91 (m, 3H, 4-H, 6-H), 2.10 (dd, J = 13.3, 10.9 Hz, 1H, 9-H), 2.17 (ddd, J = 13.3, 8.9, 2.4 Hz, 1H, 9-H), 2.30 (s, 6H, $N(CH_3)_2$), 2.34 (ddd, J = 13.0, 9.2, 2.1 Hz, 1H, 6- H), 3.01 (d, J = 2.4 Hz, 1H, 1-H), 3.08–3.13 (m, 2H, 3-H), 3.15 (ddd, J = 11.1, 8.4, 2.7 Hz, 1H, 8-H), 3.40 (br t, J = 9.4 Hz, 1H, 7-H), 7.22–7.32 (m, 8 aromatic H); ^{13}C NMR (δ) ppm 31.61 (C-4), 36.23 (C-9), 36.35 (C-6), 37.97 ($N(CH_3)_2$), 38.85 (C-8), 41.75 (C-3), 46.61 (C-7), 57.92 (C-5), 61.54 (C-1), 128.50, 128.51, 128.71, 128.84, 129.21 (aromatic C) 131.89, 142.62, 143.80 (aromatic C_q); HRMS (EI+): calcd ($C_{22}H_{26}Cl_2N_2$): 388.14730; found: 388.14811.

28. General procedure for the synthesis of (6RS,7RS)-(±)-4-dialkylamino-6,7-bis(4-chlorophenyl)bicyclo[2.2.2]octan-2-one oximes **12a**–**c**: sodium (10 mmol) was dissolved in 30 mL of dry EtOH and hydroxylamine hydrochloride (10 mmol) was added. The solution was refluxed for 1 h and ketones **7a**–**c** (3.4 mmol) were added. The mixture was refluxed overnight, the sodium chloride was filtered off and the solvent evaporated in vacuo. The residue was purified by means of CC using CH_2Cl_2/MeOH = 9:1 giving oximes **12a**–**c** as white resins. Analytical data of **12a**: yield: 10%. mp CH_2Cl_2 (°C) 234; IR (KBr) (νcm^{-1}) 2987, 2961, 2910, 2877, 2796, 1492, 1352, 1092, 1037, 1011, 948, 906, 852, 828, 798, 786; UV CH_2Cl_2(λ (log ε) nm) 231 (4.124); ^{1}H NMR (δ) ppm 1.58 (ddd, J = 12.5, 8.7, 2.4 Hz, 1H, 8-H), 1.95 (ddd, J = 13.0, 8.2, 2.7 Hz, 1H, 5-H), 2.18–2.29 (m, 2H, 5-H, 8-H), 2.38 (s, 6H, $N(CH_3)_2$), 2.54 (dd, J = 18.1, 3.4 Hz, 1H, 3-H), 2.58 (s, 1H, 1-H), 2.77 (dd, J = 18.1, 2.7 Hz, 1H, 3-H), 3.10 (br t, J = 9.4 Hz, 1H, 7-H), 3.23 (br t, J = 9.4 Hz, 1H, 6-H), 6.98–7.32 (m, 8 aromatic H), 9.22 (br s, 1H, NH); ^{13}C NMR (δ) ppm 30.57 (C-3), 31.63 (C-5), 35.74 (C-7), 36.62 (C-8), 38.39 ($N(CH_3)_2$), 39.98 (C-6), 43.68 (C-1), 56.89 (C-4), 128.40, 128.73, 128.79, 128.86 (aromatic C), 132.04, 132.38, 140.70, 142.92 (aromatic C_q), 159.73 (C-2); HRMS (EI+): calcd ($C_{22}H_{24}Cl_2N_2O$): 402.12657; found: 402.12597.