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New Derivatives of 4-Aminobicyclo [2.2.2]octanones and -ols as Potential Antiprotozoals

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Summary. New derivatives of 4-aminobicyclo[2.2.2]octanones and -ols were prepared. Their structures were established by means of NMR experiments. All new compounds were tested for their activities against *Plasmodium falciparum* and *Trypanosoma b. rhodesiense*. One of the bicyclooctanols showed promising antitrypanosomal activity.

Keywords. Acetylation; Oxidation; Hydrogenation; Amino alcohol; Structure-activity relationship.

Introduction

In subtropical and tropical zones of the world 0.7 to 2.7 million people per year die from malaria [1]. The disease is caused by four species of the malaria parasite of which *Plasmodium falciparum* is the most virulent and potentially deadly. Since multidrug-resistant strains of *Plasmodium* are becoming prevalent around the world [2–4], there is need of antimalarials with sufficient potency against these strains.

About 50000 deaths per year are caused by infection with *Trypanosoma b. rhodesiense*, the causative organism of sleeping sickness. The so far available trypanocidal drugs suramin, pentamidine, melarsoprol and eflornithine are not effective against all stages and against all strains and species of trypanosomes. Although they can cause severe side-effects [5, 6] they are used in medical therapy, because human African trypanosomiasis is, if untreated, a fatal disease. Therefore there is an urgent need for new antitrypanosomal drugs with less side-effects.

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Recently, we reported about the one-pot synthesis of 4-aminodiphenylbicyclo[2.2.2]octanones. These compounds were screened for their antiprotozoal properties revealing their activity against *Plasmodium falciparum* and *Trypanosoma b. rhodesiense*. As a result we prepared derivatives of the parent compounds modifying the oxo group, the amino group, and the aromatic ring system. Some of the new compounds exhibit increased antiplasmodial or antitrypanosomal activity compared to the starting compounds [7, 8]. This paper deals with the insertion of substituents, which were favouring the antiprotozoal activities of the so far synthesized bicyclo[2.2.2]octane derivatives. Besides, the polarity and the acidity of bicyclooctanones and -ols were varied by the preparation of *O*-acyl and *N*-acyl analogues.

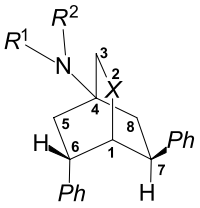
Results and Discussions

4-Aminodiphenylbicyclo[2.2.2]octanones **1** were prepared in a one-pot procedure from benzylidene acetone and dialkylammonium thiocyanates [9]. They were reduced to the bicyclo[2.2.2]octanols **2**, which possess higher antitrypanosomal activity. Furthermore, the 4-piperidino compound **2d** showed the highest antiplasmodial activity of all so far prepared bicyclooctane derivatives against the K1 strain of *P. falciparum*, which is resistant to chloroquine and pyrimethamine. The bis-(4-methoxyphenyl) analogues **3** were prepared from 4-methoxybenzylidene acetone and dialkylammonium thiocyanates. Most of them exhibit higher antitrypanosomal properties than compounds **1**. Besides, **3a** has enhanced antiplasmodial activity [8] (Fig. 1).

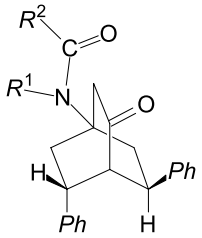
Consequently, we stereoselectively reduced the ketones **3a**–**3d** with $LiAlH_4$ at room temperature affording alcohols **4a**–**4d** in good yields. The characteristic shifts and couplings in their NMR spectra were in agreement with those of compounds **2** due to their analogous configuration. Unfortunately, the antiplasmodial and antitrypanosomal activities of most of the alcohols **4** were not significantly increased compared to the corresponding compounds **1**–**3**. However, the insertion of the methoxy groups contributes to the enhanced antiplasmodial activity of bicyclooctanol **4a** compared to that of **2a**. Compounds **4b**–**4d** exhibit lower antitrypanosomal activity than their analogues **1**–**3**. But the bicyclooctanol **4a** is the most active antitrypanosomal agent of compounds **1**–**4** (Table 1).

Moreover, we investigated the importance of the free hydroxy group for the antiprotozoal activities of **2** by their esterification. Excellent yields of the acetates **5** were achieved by treatment of the alcohols **2** with acetic anhydride in refluxing pyridine. In their ^{13}C NMR spectra two additional signals appeared at $\delta = 20$ and 170 ppm for the acetyl group. Characteristically, the signals for C-1 and C-3 were shifted to lower frequencies and the resonance for C-2 shifted downfield due to acylation. The esters **5** have lower antiprotozoal activities than the corresponding alcohols **2**, indicating the advantageous influence of the hydroxy group on these activities.

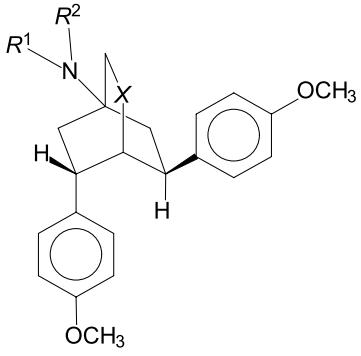
Likewise, the relevance of the basicity of the amino function of compounds **1** to their antiprotozoal activities was examined by their derivatization to amides. By treatment of bicyclooctanones **1** with $KMnO_4$ in acetone the methyl or methylene group adjacent to the nitrogen atom was regioselectively oxidized to give compounds **6**. Compound **6a** has been yielded as a mixture of (*E*) and (*Z*) diastereomers in the ratio of 7:3 (Fig. 2). The signal for the carbonyl carbons of the



1a-1d: X = C=O
2a-2d: X = HC-OH
5a-5d: X = HC-O*Ac*



6a: R^1 = *Me*, R^2 = H
6b: R^1+ R^2 = -$(CH_2)_2$-O-CH_2-
6c: R^1+ R^2 = -$(CH_2)_3$
6d: R^1+ R^2 = -$(CH_2)_4$-



3a-3d: X = C=O
4a-4d: X = HC-OH

1a-5a: $R^1 = R^2 = CH_3$
1b-5b: $R^1 + R^2 = –(CH_2)_2–O–(CH_2)_2–$
1c-5c: $R^1 + R^2 = –(CH_2)_4–$
1d-5d: $R^1 + R^2 = –(CH_2)_5–$

Fig. 1. Structures of compounds **1**–**6**

Table 1. Activities of compounds **1**–**6** expressed as IC_{50} ($\mu g/cm^3$)[a]

Compd.	*P. falciparum* K_1	*T.b. rhodesiense*	Cytotox. L6-cells
1a	>4.0	3.8	9.3
1b	>5.0	48.9	n.t.
1c	0.48	3.3	10.7
1d	1.7	3.4	19.6
2a	>5.0	0.95	42.6
2b	0.88	7.6	n.t.
2c	0.83	1.5	9.3
2d	0.30	1.9	13.5
3a	2.1	1.9	19.9
3b	>5.0	7.0	60.2
3c	1.4	1.5	17.0
3d	1.8	4.2	n.t.
4a	2.1	0.81	24.2
4b	>5.0	16.8	49.9
4c	1.1	3.1	7.3
4d	2.2	6.0	18.8

(*continued*)

Table 1 (*continued*)

Compd.	*P. falciparum* K_1	*T.b. rhodesiense*	Cytotox. L6-cells
5a	>5.0	1.9	17.9
5b	>5.0	18.0	n.t.
5c	>5.0	2.1	16.1
5d	>5.0	4.5	n.t.
6a	>5.0	18.6	55.9
6b	2.9	18.6	45.1
6c	4.5	16.0	47.3
6d	2.8	12.2	21.0
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

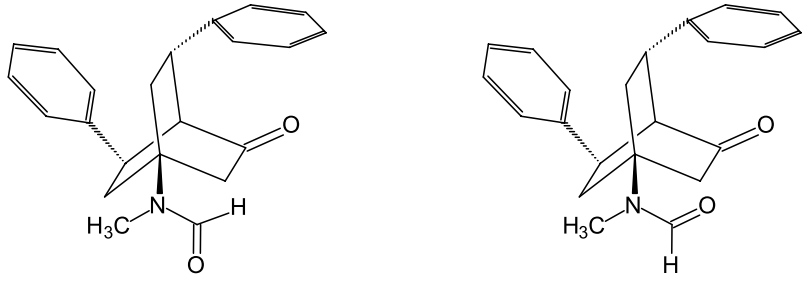


Fig. 2. Two diastereomers of **6a**

amides **6** appear at $\delta = 170$ ppm in their ^{13}C NMR spectra. The resonances of the neighbouring carbons were shifted to higher frequencies.

With the exception of the slightly active 2-oxomorpholinobicyclooctanone **6b**, which was formed from the inactive compound **1b**, the antiprotozoal activities of amides **6** are lower than those of the corresponding amino compounds **1**. This demonstrates the favourable contribution of the basic amino substituent to both the antiplasmodial and the antitrypanosomal activity of bicyclooctanone derivatives (Table 1).

Conclusion

Bis(4-methoxyphenyl) analogues of antiprotozoal bicyclooctanols were synthesized. One of the new compounds showed the highest antitrypanosomal activity compared to the so far prepared bicyclooctanones and -ols. In addition, esters of bicyclooctanols and amide analogues of bicyclooctanones were synthesized. Both modifications decreased the antiplasmodial and antitrypanosomal properties establishing the positive influence of the hydroxy substituent and a basic amino function on these antiprotozoal activities.

Experimental

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). 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 and superscript letters are interchangeable. MS, HR-MS: Kratos profile spectrometer 70 eV electron impact. GC-MS: HP-6890 (Hewlett-Packard) 70 eV electron impact. Compound **4d** was prepared for GC-MS by silylation with *N*-methyl-*N*-trimethylsilyltrifluoro acetamide (Fluka) in *tert*-butyl-methylether for 75 min at 70°C. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their results were in satisfactory agreement with the calculated values. 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 substances were detected in UV light at 254 nm.

*Preparation of **4a–4d***

On an ice bath dry ether was added dropwise under stirring to $LiAlH_4$. To this suspension an etheral solution of 4-amino-6,7-bis-(4-methoxyphenyl)-bicyclo[2.2.2]octan-2-ones **3a–3d** was added under the same conditions. The reaction mixture was stirred over night at room temperature. The reaction was quenched carefully by addition of ice-H_2O under stirring and cooling. After that, the reaction mixture was extracted four times with CH_2Cl_2. The organic layers were washed twice with H_2O and dried (Na_2SO_4). After filtration, the solvents were removed *in vacuo* at room temperature. The residue was recrystallized.

(2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-bis(4-methoxyphenyl)bicyclo[2.2.2]octan-2-ol (**4a**, $C_{24}H_{31}NO_3$)

Compound **3a** (489 mg, 1.3 mmol) in 30 cm^3 of dry ether gave with 1.0 g (26 mmol) of $LiAlH_4$ 302 mg (61%) of **4a** after crystallization from ether. Mp 138°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.48$ (br, s, OH), 1.70 (br, d, $J = 13.8$ Hz, 3-H), 1.81 (ddd, $J = 12.1$, 9.1, 2.5 Hz, 5-H), 1.92–2.01 (m, 3-H, 5-H), 2.05–2.12 (m, 2 8-H), 2.31–2.35 (m, 1-H, $N(CH_3)_2$), 2.83 (t, $J = 9.4$ Hz, 6-H), 3.12 (t, $J = 9.9$ Hz, 7-H), 3.74, 3.81 (2s, $2OCH_3$), 4.30 (dd, $J = 8.4$, 4.2 Hz, 2-H), 6.79 (d, $J = 8.9$ Hz, 2aromatic H), 6.91 (d, $J = 8.7$ Hz, 2aromatic H), 7.16 (d, $J = 8.7$ Hz, 2aromatic H), 7.30 (d, $J = 8.7$ Hz, 2aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.11$ (C-8), 31.89 (C-5), 34.00 (C-7), 37.39 (C-3), 38.36 ($N(CH_3)_2$), 38.70 (C-6), 44.15 (C-1), 55.19, 55.23 ($2OCH_3$), 56.40 (C-4), 71.99 (C-2), 113.63, 113.85, 128.13, 128.25 (aromatic C), 135.42, 137.05, 157.55, 157.93 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3002$, 2950, 2935, 2833, 1612, 1512, 1463, 1443, 1271, 1249, 1183, 1168, 1038, 1029, 825 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} ($\log\varepsilon$) = 237 (3.508), 277 (3.482) nm; MS (70 eV): $m/z = 381$ (M^+), 336, 246, 230, 203, 188, 161, 140, 121, 96, 70; HRMS (EI+): calcd. ($C_{24}H_{31}NO_3$): 381.23039, found: 381.23093.

(2SR,6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-morpholinobicyclo[2.2.2]octan-2-ol (**4b**, $C_{26}H_{33}NO_4$)

Compound **3b** (1.07 g, 2.5 mmol) in 40 cm^3 of dry ether gave with 1.3 g (34 mmol) of $LiAlH_4$ 793 mg (75%) of **4b** after crystallization from ether/heptane. Mp 139°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (d, $J = 3.3$ Hz, OH), 1.70 (br, d, $J = 13.7$ Hz, 3-H), 1.81 (ddd, $J = 12.0$, 9.2, 2.4 Hz, 5-H), 1.92–1.99 (m, 3-H, 5-H), 2.02–2.14 (m, 2 8-H), 2.36 (d, $J = 4.2$ Hz, 1-H), 2.63–2.76 (m, $N(CH_2)_2$), 2.83 (t, $J = 9.3$ Hz, 6-H), 3.13 (t, $J = 9.8$ Hz, 7-H), 3.73–3.77 (m, $2OCH_2$, OCH_3), 3.81 (s, OCH_3), 4.29 (dd, $J = 8.3$, 4.1 Hz, 2-H), 6.79 (d, $J = 8.7$ Hz, 2aromatic H), 6.91 (d, $J = 8.7$ Hz, 2aromatic H), 7.15 (d, $J = 8.2$ Hz, 2aromatic H), 7.29 (d, $J = 8.5$ Hz, 2aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

$\delta = 31.73$, 31.81 (C-5, C-8), 33.94 (C-7), 37.57 (C-3), 38.58 (C-6), 44.22 (C-1), 46.20 ($N(CH_2)_2$), 55.20, 55.23 ($2OCH_3$), 56.74 (C-4), 67.62 ($2OCH_2$), 71.89 (C-2), 113.66, 113.87, 128.06, 128.23 (aromatic C), 135.23, 136.89, 157.59, 157.97 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 2958$, 2943, 2855, 2821, 1612, 1513, 1446, 1286, 1262, 1247, 1221, 1170, 1125, 1023, 960, 825 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} ($\log\varepsilon$) = 237 (3.666), 278 (3.527) nm; MS (70 eV): $m/z = 423$ (M^+), 378, 302, 288, 272, 245, 182, 138, 121, 91, 77; HRMS (EI+): calcd. ($C_{26}H_{33}NO_4$): 423.24096, found: 423.24254.

(2SR,6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**4c**, $C_{26}H_{33}NO_3$)

Compound **3c** (913 mg, 2.3 mmol) in 30 cm^3 of dry ether gave with 1 g (26 mmol) of $LiAlH_4$ 734 mg (80%) of **4c** after crystallization from ether/heptane. Mp 164°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (br, s, OH), 1.70 (br, d, $J = 13.6$ Hz, 3-H), 1.80 (br, s, $2CH_2$), 1.86–2.19 (m, 3-H, 2 5-H, 2 8-H), 2.32 (d, $J = 4.0$ Hz, 1-H), 2.72–2.78 (m, $N(CH_2)_2$), 2.86 (t, $J = 9.2$ Hz, 6-H), 3.14 (t, $J = 9.8$ Hz, 7-H), 3.74, 3.81 (2s, $2OCH_3$), 4.29 (dd, $J = 7.9$, 3.7 Hz, 2-H), 6.78 (d, $J = 8.7$ Hz, 2aromatic H), 6.91 (d, $J = 8.6$ Hz, 2aromatic H), 7.15 (d, $J = 8.6$ Hz, 2aromatic H), 7.30 (d, $J = 8.6$ Hz, 2aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.52$ ($2CH_2$), 32.13 (C-8), 32.54 (C-5), 33.86 (C-7), 38.37 (C-3), 38.83 (C-6), 44.46 (C-1), 45.42 ($N(CH_2)_2$), 55.00 (C-4), 55.17, 55.21 ($2OCH_3$), 72.07 (C-2), 113.61, 113.81, 128.11, 128.29 (aromatic C), 135.49, 137.12, 157.51, 157.89 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 2946$, 2929, 2833, 2815, 1512, 1250, 1179, 1167, 1029, 824 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} ($\log\varepsilon$) = 235 (3.954), 278 (3.528) nm; MS (70 eV): $m/z = 407$ (M^+), 362, 286, 272, 256, 229, 166, 152, 139, 121, 91, 70; HRMS (EI+): calcd. ($C_{26}H_{33}NO_4$): 407.24604, found: 407.24567.

(2SR,6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-piperidinobicyclo[2.2.2]octan-2-ol (**4d**, $C_{27}H_{35}NO_3$)

Compound **3d** (60 mg, 0.14 mmol) in 10 cm^3 of dry ether gave with 144 mg (3.8 mmol) of $LiAlH_4$ 45 mg (75%) of **4d** after crystallization from ether. Mp 124°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (br, s, OH), 1.44–1.50 (m, CH_2), 1.63 (br, s, $2CH_2$), 1.72 (dd, $J = 13.7$, 1.4 Hz, 3-H), 1.84 (ddd, $J = 12.1$, 9.4, 2.4 Hz, 5-H), 1.95–2.02 (m, 3-H, 5-H), 2.07–2.12 (m, 2 8-H), 2.36 (d, $J = 4.1$ Hz, 1-H), 2.58–2.76 (m, $N(CH_2)_2$), 2.81 (t, $J = 9.4$ Hz, 6-H), 3.11 (t, $J = 10.0$ Hz, 7-H), 3.75, 3.81 (2s, $2OCH_3$), 4.29 (dd, $J = 8.5$, 4.4 Hz, 2-H), 6.79 (d, $J = 8.9$ Hz, 2aromatic H), 6.90 (d, $J = 8.6$ Hz, 2aromatic H), 7.15 (d, $J = 8.4$ Hz, 2aromatic H), 7.30 (d, $J = 8.6$ Hz, 2aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.93$ (CH_2), 26.75 ($2CH_2$), 32.01 (C-5, C-8), 33.98 (C-7), 37.61 (C-3), 38.68 (C-6), 44.10 (C-1), 46.78 ($N(CH_2)_2$), 55.19, 55.23 ($2OCH_3$), 57.08 (C-4), 72.11 (C-2), 113.64, 113.82, 128.06, 128.26 (aromatic C), 135.49, 137.17, 157.53, 157.90 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3427$, 2931, 2854, 2834, 1612, 1513, 1248, 1181, 1110, 1035, 824 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} ($\log\varepsilon$) = 237 (3.561), 277 (3.501) nm; GC-MS (70 eV): $m/z = 493$ (M^+-H + $Si(CH_3)_3$), 420 (M + -H), 358, 268, 225, 134, 119, 91, 73; HRMS (EI+): calcd. ($C_{27}H_{35}NO_3$): 421.26169, found: 421.26441.

*Preparation of **5a–5d***

To a solution of the bicyclooctanols in dry pyridine acetic anhydride was added dropwise under stirring and cooling. The ice bath was removed and the mixture was stirred over night at room temperature. After that, the reaction was quenched with ice-H_2O and extracted five times with CH_2Cl_2. The combined organic layers were washed twice with H_2O and dried (Na_2SO_4). The solvent was removed *in vacuo* and the brown residue was extracted with hot heptane giving a yellowish solution which was treated with charcoal and filtered. The solvent was evaporated giving almost pure bases of the bicyclooctyl esters. The hydrochlorides were prepared by treating the bases with an excess of etheral HCL solution, subsequent evaporation, and crystallization from ethanol/ethyl acetate. NMR spectra were collected from the bases, biological tests, elemental analyses, melting points, IR and UV spectra from the hydrochlorides.

(2SR,6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl acetate
(**5a**, $C_{24}H_{29}NO_2$)

Compound **2a** (700 mg, 2.2 mmol) in 10 cm^3 of pyridine gave with 5.9 g (57.8 mmol) of acetic anhydride 792 mg (99%) of **5a**. Mp 224°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (s, CH_3COO), 1.74 (d, $J = 14.1$ Hz, 3-H), 1.90 (ddd, $J = 12.4$, 9.6, 2.3 Hz, 5-H), 2.01–2.10 (m, 3-H, 5-H, 8-H), 2.17 (ddd, $J = 12.4$, 9.7, 3.0 Hz, 8-H), 2.38 (s, $N(CH_3)_2$), 2.78 (d, $J = 4.4$ Hz, 1-H), 2.99 (t, $J = 9.5$ Hz, 6-H), 3.18 (t, $J = 9.7$ Hz, 7-H), 5.22 (dd, $J = 9.0$, 4.4 Hz, 2-H), 7.08–7.42 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.22$ (CH_3COO), 31.06 (C-8), 31.43 (C-5), 33.96 (C-7), 34.54 (C-3), 38.36 ($N(CH_3)_2$), 38.61 (C-6), 39.51 (C-1), 56.09 (C-4), 72.76 (C-2), 125.20, 126.32, 126.50, 127.34, 127.87, 128.45, (aromatic C), 142.80, 144.50 (aromatic C_q), 170.63 (CH_3COO) ppm; IR (KBr): $\bar{\nu} = 2541$, 2510, 2449, 1742, 1499, 1489, 1452, 1365, 1232, 1175, 1024, 762, 744, 710, 697 cm^{-1}; UV-Vis (methanol): λ_{max} ($\log\varepsilon$) = 210 (4.131) nm; GC-MS (70 eV): $m/z = 363$ (M^+), 304, 276, 198, 172, 122, 91, 70.

(2SR,6RS,7RS)-(±)-4-Morpholino-6,7-diphenylbicyclo[2.2.2]octan-2-yl acetate
(**5b**, $C_{26}H_{31}NO_3$)

Compound **2b** (700 mg, 1.9 mmol) in 9 cm^3 of pyridine gave with 5.2 g (50.9 mmol) of acetic anhydride 750 mg (96%) of **5b**. Mp 251°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (s, CH_3COO), 1.76 (d, $J = 14.1$ Hz, 3-H), 1.92 (ddd, $J = 11.9$, 9.7, 2.3 Hz, 5-H), 2.05–2.12 (m, 3-H, 5-H, 8-H), 2.21 (ddd, $J = 12.2$, 9.3, 2.9 Hz, 8-H), 2.71–2.82 (m, $N(CH_2)_2$), 2.82 (d, $J = 4.3$ Hz, 1-H), 3.00 (t, $J = 9.5$ Hz, 6-H), 3.19 (t, $J = 9.6$ Hz, 7-H), 3.78–3.81 (m, $O(CH_2)_2$), 5.23 (dd, $J = 9.0$, 4.7 Hz, 2-H), 7.08–7.41 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.22$ (CH_3COO), 31.41, 31.44 (C-5, C-8), 33.93 (C-7), 34.57 (C-3), 38.45 (C-6), 39.49 (C-1), 46.13 ($N(CH_2)_2$), 57.00 (C-4), 67.21 ($O(CH_2)_2$), 72.55 (C-2), 125.34, 126.45, 127.32, 127.97, 128.53 (aromatic C), 142.53, 144.25 (aromatic C_q), 170.66 (CH_3COO) ppm; IR (KBr): $\bar{\nu} = 2517$, 2454, 1743, 1499, 1450, 1431, 1368, 1262, 1231, 1124, 1030, 1017, 756, 730, 702 cm^{-1}; UV-Vis (methanol): λ_{max} ($\log\varepsilon$) = 210 (4.075) nm; GC-MS (70 eV): $m/z = 405$ (M^+), 346, 254, 240, 215, 178, 164, 150, 128, 115, 104, 91, 78, 56.

(2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl acetate
(**5c**, $C_{26}H_{31}NO_2$)

Compound **2c** (700 mg, 2.0 mmol) in 9.2 cm^3 of pyridine gave with 5.4 g (53 mmol) of acetic anhydride 805 mg (94%) of **5c**. Mp 233°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (s, CH_3COO), 1.75 (d, $J = 14.2$ Hz, 3-H), 1.83 (br, s, 2 CH_2), 1.97 (ddd, $J = 12.0$, 9.1, 2.2 Hz, 5-H), 2.04–2.24 (m, 3-H, 5-H, 2 8-H), 2.76–2.80 (m, 1-H, $N(CH_2)_2$), 3.03 (t, $J = 9.4$ Hz, 6-H), 3.20 (t, $J = 9.9$ Hz, 7-H), 5.23 (dd, $J = 9.0$, 4.4 Hz, 2-H), 7.07–7.42 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.25$ (CH_3COO), 23.54 ($2CH_2$), 31.91 (C-5), 32.10 (C-8), 33.93 (C-7), 35.56 (C-3), 38.73 (C-6), 39.89 (C-1), 45.57 ($N(CH_2)_2$), 55.01 (C-4), 72.78 (C-2), 125.23, 126.35, 126.58, 127.43, 127.90, 128.48 (aromatic C), 142.85, 144.55 (aromatic C_q), 170.70 (CH_3COO) ppm; IR (KBr): $\bar{\nu} = 2545$, 2445, 1743, 1499, 1449, 1367, 1235, 1021, 760, 751, 701 cm^{-1}; UV-Vis (methanol): λ_{max} ($\log\varepsilon$) = 210 (4.140) nm; GC-MS (70 eV): $m/z = 389$ (M^+), 330, 302, 224, 199, 148, 128, 104, 78, 54.

(2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl acetate
(**5d**, $C_{27}H_{33}NO_2$)

Compound **2d** (500 mg, 1.4 mmol) in 7 cm^3 of pyridine gave with 3.8 g (37 mmol) of acetic anhydride 548 mg (90%) of **5d**. Mp 290°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (s, CH_3COO), 1.47–1.52 (m, CH_2), 1.65 (br, s, $2CH_2$), 1.76 (d, $J = 14.1$ Hz, 3-H), 1.92 (ddd, $J = 12.3$, 10.2, 2.1 Hz, 5-H), 2.03–2.13 (m, 3-H, 5-H, 8-H), 2.22 (ddd, $J = 12.6$, 9.2, 3.3 Hz, 8-H), 2.58–2.76 (m, $N(CH_2)_2$), 2.79 (d, $J = 4.6$ Hz,

1-H), 2.97 (t, $J = 9.5$ Hz, 6-H), 3.17 (t, $J = 9.9$ Hz, 7-H), 5.22 (dd, $J = 9.0$, 4.6 Hz, 2-H), 7.08–7.42 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.28$ (CH_3COO), 24.94 (CH_2), 26.76 (2 CH_2), 31.64 (C-5), 32.00 (C-8), 34.09 (C-7), 34.92 (C-3), 38.67 (C-6), 39.62 (C-1), 46.89 ($N(CH_2)_2$), 56.84 (C-4), 72.90 (C-2), 125.23, 126.35, 126.57, 127.43, 127.93, 128.50 (aromatic C), 142.95, 144.70 (aromatic C_q), 170.76 (CH_3COO) ppm; IR (KBr): $\bar{\nu} = 2944$, 2483, 1745, 1499, 1448, 1362, 1233, 1199, 1031, 752, 722, 699 cm^{-1}; UV-Vis (methanol): λ_{max} (logε) = 209 (4.113) nm; GC-MS (70 eV): $m/z = 403$ (M^+), 344, 312, 238, 213, 162, 136, 115, 91, 55.

Preparation of 4-N-Acyl-6,7-diphenylbicyclo[2.2.2]octan-2-ones ***6a–6d***

The 4-aminobicyclo[2.2.2]octan-2-ones were dissolved in acetone. $KMnO_4$ was added under stirring and cooling in portions. The reaction mixture was stirred over night at ambient temperature and the formed MnO_2 was filtered off. After evaporation of the solvent *in vacuo* the residue was dissolved in ether and extracted five times with diluted HCl and twice with H_2O. After drying (Na_2SO_4) the solution was filtered, and the solvent was evaporated *in vacuo*. The residue was purified by means of CC using CH_2Cl_2:CH_3OH = 20:1 as eluens giving colourless resins.

(6RS,7RS)-(±)-4-(N-Methylformamido)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**6a**, $C_{22}H_{23}NO_2$)

Compound **1a** (1.94 g, 6.1 mmol) in 75 cm^3 of acetone gave with 3.8 g (24 mmol) of $KMnO_4$ 1.16 g (58%) of the (*E*) isomer of **6a** and 0.44 g (22%) of the (*Z*) isomer of **6a** as a colourless resin. IR (KBr): $\bar{\nu} = 2948$, 1725, 1656, 1601, 1496, 1451, 1372, 1339, 1071, 756, 701 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (logε) = 232 (2.871), 253 (2.732) nm; MS (70 eV): $m/z = 333$ (M^+), 274, 228, 200, 183, 170, 142, 131, 103, 91, 78; HRMS (EI+): calcd. ($C_{22}H_{23}NO_2$): 333.17288, found: 333.17138;

6a(*E*): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.02$ (ddd, $J = 13.0$, 7.7, 2.9 Hz, 8-H), 2.39–2.53 (m, 2 5-H), 2.60–2.78 (m, 3-H, 8-H), 2.78 (s, 1-H) 2.86 (dd, $J = 17.9$, 3.7 Hz, 3-H), 2.98 (s, NCH_3), 3.45–3.49 (m, 6-H, 7-H), 7.03–7.43 (m, 10aromatic H), 8.50 (s, HC=O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.68$ (NCH_3), 34.42 (C-5), 35.00 (C-7), 37.80 (C-6), 39.63 (C-8), 47.41 (C-3), 53.63 (C-1), 57.57 (C-4), 126.77, 126.91, 127.28, 128.82, 128.93 (aromatic C), 139.87, 142.87 (aromatic C_q), 160.81 (HC=O), 209.43 (C-2) ppm;

6a(*Z*): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.11$ (ddd, $J = 13.0$, 7.7, 2.7 Hz, 8-H), 2.57–2.73 (m, 2 5-H), 2.71 (s, 1-H), 2.75–2.80 (m, 3-H, 8-H), 3.00 (s, NCH_3), 3.28 (dd, $J = 18.6$, 3.6 Hz, 3-H), 3.31–3.44 (m, 6-H, 7-H), 7.03–7.43 (m, 10aromatic H), 8.16 (s, HC=O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.95$ (C-5), 32.72 (NCH_3), 34.91 (C-7), 37.51 (C-8), 37.80 (C-6), 46.70 (C-3), 53.94 (C-1), 57.57 (C-4), 126.60, 126.94, 127.47, 128.66, 128.73 (aromatic C), 140.56, 143.46 (aromatic C_q), 163.94 (HC=O), 211.19 (C-2) ppm.

(6RS,7RS)-(±)-4-(2-Oxomorpholino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**6b**, $C_{24}H_{25}NO_3$)

Compound **1b** (1.0 g, 2.8 mmol) in 40 cm^3 of acetone gave with 1.75 g (11 mmol) of $KMnO_4$ 893 mg (86%) of **6b** as a colourless resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.11$ (ddd, $J = 12.8$, 7.7, 2.9 Hz, 8-H), 2.64 (ddd, $J = 13.0$, 8.0, 2.7 Hz, 5-H), 2.73 (s, 1-H), 2.76–2.85 (m, 3-H, 5-H), 2.90 (ddd, $J = 12.8$, 9.3, 3.8 Hz, 8-H), 3.39 (dd, $J = 18.6$, 3.6 Hz, 3-H), 3.46–3.55 (m, 6-H, 7-H, NCH_2), 3.83–3.94 (m, OCH_2CH_2N), 4.16 (s, OCH_2C=O), 7.06–7.40 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.13$ (C-5), 35.07 (C-7), 37.61 (C-8), 37.95 (C-6), 43.25 (NCH_2), 46.99 (C-3), 53.82 (C-1), 59.58 (C-4), 64.42 (OCH_2CH_2N), 69.20 (OCH_2C=O), 126.68, 126.98, 127.51, 128.72, 128.78 (aromatic C), 140.63, 143.47 (aromatic C_q), 168.29 (OCH_2C=O), 211.15 (C-2) ppm; IR (KBr): $\bar{\nu} = 1721$, 1648, 1497, 1468, 1426, 1344, 1329, 1143, 754, 701 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (logε) = 233 (2.762), 259

(2.728), 253 (2.709) nm; MS (70 eV): $m/z = 375$ (M^+), 347, 274, 242, 183, 155, 142, 128, 104, 91, 78; HRMS (EI+): calcd. ($C_{24}H_{25}NO_3$): 375.18344, found: 375.18525.

(6RS,7RS)-(±)-4-(2-Oxopyrrolidino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**6c**, $C_{24}H_{25}NO_2$)

Compound **1c** (2.29 g, 6.6 mmol) in 80 cm^3 of acetone gave with 4.2 g (27 mmol) of $KMnO_4$ 2.0 g (85%) of **6c** as a colourless resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.01$ (q, $J = 7.6$ Hz, CH_2–CH_2–CH_2), 2.09 (ddd, $J = 13.0$, 7.7, 3.1 Hz, 8-H), 2.41 (t, $J = 7.7$ Hz, CH_2–C=O), 2.55 (ddd, $J = 13.1$, 7.8, 2.8 Hz, 5-H), 2.66–2.73 (m, 1-H, 5-H), 2.78–2.85 (m, 3-H, 8-H), 3.23 (dd, $J = 18.7$, 3.5 Hz, 3-H), 3.38–3.48 (m, 6-H, 7-H), 3.53 (t, $J = 7.2$ Hz, NCH_2), 3.54 (t, $J = 7.5$ Hz, NCH_2), 7.05–7.40 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.16$ (CH_2–CH_2–CH_2), 32.25 (C-5), 32.78 (CH_2–C=O), 34.98 (C-7), 37.74 (C-8), 37.88 (C-6), 45.66 (NCH_2), 46.81 (C-3), 53.98 (C-1), 56.09 (C-4), 126.57, 126.90, 126.97, 127.51, 128.65, 128.73 (aromatic C), 140.72, 143.62 (aromatic C_q), 176.00 (C=O), 211.60 (C-2) ppm; IR (KBr): $\bar{\nu} = 2953$, 1722, 1677, 1601, 1496, 1451, 1409, 1341, 1286, 1261, 1188, 756, 701 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (logε) = 231 (2.937), 259 (2.706) nm; MS (70 eV): $m/z = 359$ (M^+), 274, 254, 226, 212, 170, 155, 142, 131, 103, 86, 78; HRMS (EI+): calcd. ($C_{24}H_{25}NO_2$): 359.18853, found: 359.18634.

(6RS,7RS)-(±)-4-(2-Oxopiperidino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**6d**, $C_{25}H_{27}NO_2$)

Compound **1d** (2.44 g, 6.8 mmol) in 80 cm^3 of acetone gave with 4.3 g (27 mmol) of $KMnO_4$ 2.1 g (84%) of **6d** as a colourless resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.70$–1.85 (m, NCH_2–CH_2, CH_2–CH_2–C=O), 2.07 (ddd, $J = 12.7$, 7.7, 2.8 Hz, 8-H), 2.42 (t, $J = 6.7$ Hz, CH_2–C=O), 2.62 (ddd, $J = 13.0$, 8.1, 2.8 Hz, 5-H), 2.70 (t, $J = 1.7$ Hz, 1-H), 2.75–2.82 (m, 3-H, 5-H), 2.92 (ddd, $J = 12.7$, 11.0, 3.6 Hz, 8-H), 3.36–3.46 (m, 3-H, 6-H, 7-H, NCH_2), 7.07–7.40 (m, 10aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.28$ (CH_2–CH_2–C=O), 24.06 (NCH_2–CH_2), 32.12 (C-5), 34.79 (CH_2–C=O), 35.18 (C-7), 37.84 (C-8), 38.05 (C-6), 44.31 (NCH_2), 47.23 (C-3), 53.83 (C-1), 59.52 (C-4), 126.48, 126.76, 126.98, 127.51, 128.58, 128.64 (aromatic C), 140.96, 143.78 (aromatic C_q), 171.73 (C=O), 212.01 (C-2) ppm; IR (KBr): $\bar{\nu} = 2947$, 1721, 1630, 1496, 1450, 1344, 1331, 1315, 757, 701 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (logε) = 232 (2.945), 253 (2.775) nm; MS (70 eV): $m/z = 373$ (M^+), 345, 268, 254, 241, 213, 192, 170, 138, 115, 91, 77; HRMS (EI+): calcd. ($C_{25}H_{27}NO_2$): 373.20418, found: 373.20328.

Antiprotozoal Tests

The activities against *Plasmodium falciparum* and *Trypanosoma b. rhodesiense* as well as the cytotoxicity were determined as reported [10]. The activity of the bicyclooctane derivatives was compared to commonly used drugs (chloroquine, suramine, mefloquine).

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