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4-Aminobicyclo[2.2.2]octanone Derivatives with Antiplasmodial and Antitrypanosomal Activities

Werner Seebacher[1,*], **Reto Brun**[2], **Robert Saf**[3], and **Robert Weis**[1]

[1] Institute of Pharmaceutical Chemistry and Pharmaceutical Technology, University of Graz, A-8010 Graz, Austria
[2] Swiss Tropical Institute, Basel, Switzerland
[3] Institute of Chemical Technology of Organic Materials, University of Technology, Graz, Austria

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Summary. 4-Aminobicyclo[2.2.2]octanones were converted to their *N*-oxides and to 4-aminobicyclo[2.2.2]octanes. Furthermore, the 6,7-bis-(4-methoxyphenyl) analogues were synthesized. All products were screened for their activities against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum*. The pharmacological results were compared with those of formerly tested bicyclo[2.2.2]octanones and bicyclo[2.2.2]octanols. Structure-activity relationships are discussed.

Keywords. Antiplasmodial activity; Antitrypanosomal activity; Bicyclo[2.2.2]octane derivatives; Reductions; Oxidations.

Introduction

Recently, we reported the synthesis of 4-aminobicyclo[2.2.2]octanones **1** and their stereoselective reduction to compounds **2** [1]. We investigated their activities against causative organisms of tropical deseases including *Trypanosoma cruzi*, *Leishmania donovani*, *Plasmodium falciparum*, and *Trypanosoma brucei rhodesiense*.

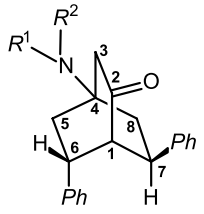
The bicyclo[2.2.2]octanones **1a**–**1d** and the corresponding bicyclo[2.2.2]octanols **2a**–**2d** showed antiprotozoal activities mainly against *Trypanosoma b. rhodesiense*, a causative organism of sleeping illness and *Plasmodium falciparum* K_1 (resistant against chloroquin and pyrimethamin), which is the causative organism of *Malaria tropica*. Therefore we synthesized further derivatives of 4-aminobicyclo[2.2.2]octanones and screened them for their antiplasmodial and antitrypanosomal activities to obtain data for the elucidation of structure-activity relationships.

* Corresponding author. E-mail: robert.weis@uni-graz.at

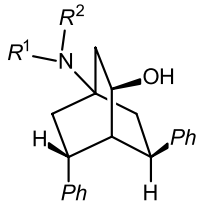
This paper deals with modifications of the amino function, the oxo group, and the aromatic ring system of the bicyclo[2.2.2]octan-2-ones **1**.

Results and Discussion

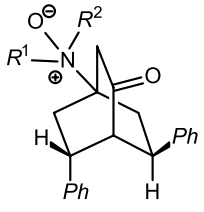
The data obtained so far indicate, that small alterations of the substituents of the amino group of **1** and **2** remarkably influence their biological activities. Some alkaloids with *N*-oxide structure have been reported to possess antiplasmodial activity [2–7]. Therefore we oxidized compounds **1a**–**1d** to their *N*-oxides **3a**–**3d** using 3-chloroperbenzoic acid in CH_2Cl_2 [8]. In the mass spectra of **3a**–**3d** we did not obtain a molecular peak due to cleavage of the N–O bond, however, their structures were established by NMR spectroscopy.



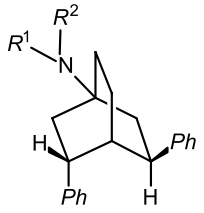
1a-1d



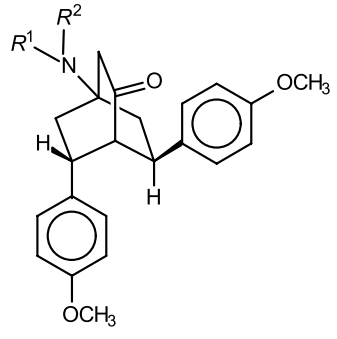
2a-2d



3a-3d



4a-4d



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

5a-5d

Fig. 1. Structures of compounds **1a**–**1d** to **5a**–**5d**

Due to *N*-oxide formation the signals of the NCH_3 and NCH_2 protons of **3a**–**3d** were split and shifted by about 0.8 ppm to lower field in comparison to the corresponding signals of **1a**–**1d**. The effect of *N*-oxide formation on the ^{13}C shifts of the neighbour carbons correlates well with published data [9]. In the ^{13}C NMR spectra of compounds **3a**–**3d** we found typical downfield shifts (11–18 ppm) for the resonances of C-4, the $N–CH_3$ and the $N–CH_2$ groups.

The bicyclo[2.2.2]octanols **2a**–**2d** showed in general higher antitrypanosomal and antiplasmodial activity than the bicyclo[2.2.2]octanones **1**. To investigate the contribution of the hydroxy and the keto group to the antiprotozoal activities we reduced compounds **1** to bicyclo[2.2.2]octanes **4**. Compounds **4a**–**4d** were prepared by a *Wolff-Kishner* procedure [10]. The formation of compounds **4** was indicated in their ^1H NMR spectra by the appearance of an additional CH_2 group. Furthermore, in the ^{13}C NMR spectra the signal of C-2 was shifted from *ca.* 215 ppm in compounds **1a**–**1d** to 22 ppm in compounds **4a**–**4d**. Besides, the resonances for C-1 and C-3 were shifted *ca.* 18 ppm to higher field.

Some antimalarial natural compounds own methoxyphenyl substituents, which are linked *via* an ethano bridge to a nitrogen atom [11–14]. Therefore we synthesized the bis-(4-methoxyphenyl) analogues **5** of the already investigated 4-aminobicyclo[2.2.2]octanones **1**. Compounds **5a**–**5d** were obtained following a

Table 1. Activities of **1a**–**1d** to **5a**–**5d**, expressed as IC_{50} ($\mu g/cm^3$)[a]

Compound[b]	*P. falciparum* K_1	*T. b. rhodesiense*	Cytotox. L6
1a	>4.0	3.78	9.3
1b	>5.0	48.9	n.t.
1c	0.48	3.25	10.7
1d	1.653	3.4	19.6
2a	>5.0	0.947	42.6
2b	0.881	7.56	n.t.
2c	0.832	1.48	9.3
2d	0.303	1.93	13.5
3a	>5.0	15.5	>90
3b	>5.0	14.8	>90
3c	2.234	9.0	>90
3d	>5.0	33.2	>90
4a	0.855	0.56	8.0
4b	2.215	5.7	18.5
4c	1.34	0.54	5.9
4d	0.593	0.571	4.4
5a	2.06	1.9	19.9
5b	>5.0	7.0	60.2
5c	1.365	1.5	17.0
5d	1.83	4.2	n.t.
standard	0.0018	0.00155	4.3

[a] values represent the average of four determinations (two determinations of two independent experiments), n.t. = not tested; [b] compounds **1** were tested as hydrorhodanides, compounds **4** as hydrochlorides

procedure reported for the preparation of octanones **1a**–**1c** [15]. As starting material we used 4-methoxybenzylidene acetone. In comparison to **1**, their bis-(4-methoxyphenyl) analogues **5** did not crystallize from the reaction mixture. For analytical and screening purposes, they were purified by means of repeated column chromatography.

The antiplasmodial and antitrypanosomal activities of compounds **1**–**5** are presented in Table 1. From the so far tested compounds, the bicyclo[2.2.2]octanol **2d** still has the highest activity against *Plasmodium falciparum*. The antiplasmodial activity of compounds **1** was decreased by *N*-oxide formation. The bicyclo[2.2.2]octanes **4** exhibit higher activity than their 2-oxo analogues **1** with the exception of the pyrrolidino derivatives. The influence of the methoxy groups of

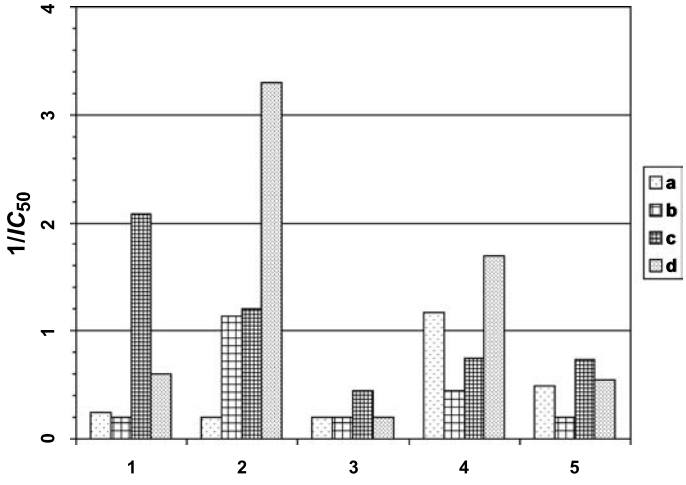


Fig. 2. Comparative presentation of the antiplasmodial activities of **1a**–**1d** to **5a**–**5d** as $1/IC_{50}$ values

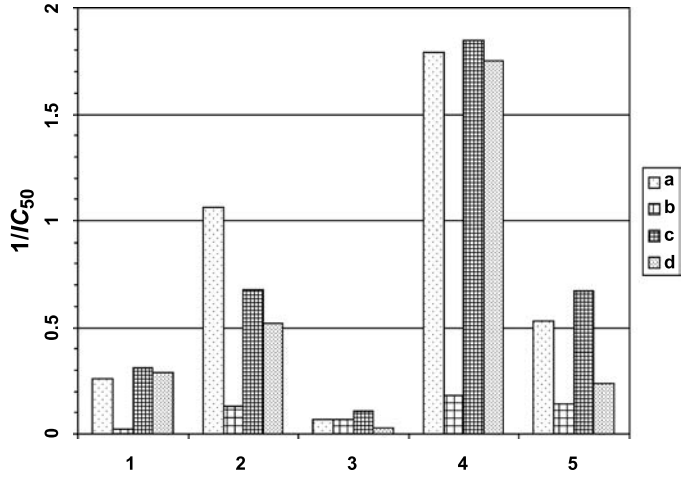


Fig. 3. Comparative presentation of the antitrypanosomal activities of **1a**–**1d** to **5a**–**5d** as $1/IC_{50}$ values

compounds **5** on the antimalarial activity is contradictory. Compound **5a** is more active than **1a**, whereas **5c** is less potent than **1c**. The activities of the dimethylamino and piperidino analogues remained unchanged (Fig. 2).

The activity of the *N*-oxides **3a**–**3d** against *Trypanosoma b. rhodesiense* is very low. The 4-aminobicyclo[2.2.2]octanes **4a**–**4d** possess the highest antitrypanosomal activity of all so far tested bicyclo[2.2.2]octane derivatives. In general compounds **5a**–**5d** are more active than **1a**–**1d** (Fig. 3).

Conclusion

N-Oxides exhibited only low activity, the bis(4-methoxyphenyl) analogues were more potent against *Trypanosoma b. rhodesiense* than the compounds without methoxy groups, and the antitrypanosomal activity was increased by reduction of the oxo group, which was, with one exception, also advantageous for the antimalarial activity. In a future study derivates of the most active compounds will be prepared.

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. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their values were in satisfactory agreement with the calculated ones. Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254}, 0.2 mm, 200 × 200 mm); column chromatography (CC): silica gel 60 (Merck 70–230 mesh, pore-diameter 60 Å); preparative TLC: PLC plates (Merck, silica gel 60 F_{254}, 1 mm, 200 × 200 mm); the substances were detected in UV light at 254 nm. The preparation of compounds **1a**–**1d** and **2a**–**2d** has already been reported [1, 15].

*Preparation of Compounds **3a**–**3d***

The bicyclo[2.2.2]octanone was dissolved in CH_2Cl_2 and *m*-chloroperbenzoic acid was added. The solution was stirred for two hours at room temperature. After evaporation of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel, using ether as eluent to remove *m*-chloroperbenzoic acid. Then CH_2Cl_2:*Me*OH = 8:2 and finally methanol were used for elution of the product, giving yellowish resins which gave white amorphous solids after recrystallization from heptane.

(6RS,7RS)-(±)-4-(N-Oxidodimethylamino)-6,7-diphenylbicyclo[2.2.2] octan-2-one (**3a**, $C_{22}H_{25}NO_2$)

Compound **1a** (1.16 g, 3.6 mmol) and 1.1 g (6.2 mmol) of *m*-chloroperbenzoic acid in 20 cm^3 of CH_2Cl_2 gave 1.2 g (98%) of **3a**. Mp 135°C; IR (KBr): $\bar{\nu}$ = 3406 (s), 1718 (s), 1601 (w), 1497 (w), 1452 (w), 754 (m), 699 (m) cm^{-1}; UV (CH_3OH): λ (log ε) = 211 (3.958) nm; ^{1}H NMR (CD_3OD, 400 MHz): δ = 2.09 (ddd, J = 12.4, 9.0, 2.9 Hz, 8-H), 2.53 (ddd, J = 12.2, 9.7, 2.4 Hz, 5-H), 2.57 (s,

1-H), 2.74 (ddd, $J = 12.9$, 10.2, 2.9 Hz, 5-H), 2.83 (ddd, $J = 12.9$, 10.7, 3.9 Hz, 8-H), 2.92 (dd, $J = 18.0$, 2.9 Hz, 3-H), 3.15 (dd, $J = 18.0$, 3.7 Hz, 3-H), 3.22, 3.23 (2s, $N(CH_3)_2$), 3.40–3.52 (m, 6-H, 7-H), 7.07–7.47 (m, 10aromatic H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 30.81$ (C-5), 36.51 (C-8), 37.25 (C-7), 39.46 (C-6), 44.57 (C-3), 54.60, 54.87 ($N(CH_3)_2$), 56.26 (C-1), 76.39 (C-4), 128.25, 128.51, 128.55, 128.94, 130.07, 130.25 (aromatic C), 141.97, 144.64 (aromatic C_q), 211.49 (C-2) ppm; MS (EI^+): m/z (%) = 319 (100.0) [M^+-O], 305 (40.0), 215 (68.5), 214 (60.2), 201 (36.9), 200 (64.8), 187 (57.3), 186 (43.7), 173 (59.6), 172 (46.5); HRMS (EI^+): calcd. for $C_{22}H_{25}NO_2$–O: 319.1936; found: 319.1949.

(6RS,7RS)-(±)-4-(N-Oxidomorpholino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**3b**, $C_{24}H_{27}NO_3$)

Compound **1b** (1.3 g, 3.6 mmol) and 1.1 g (6.2 mmol) of *m*-chloroperbenzoic acid in 20 cm^3 of CH_2Cl_2 gave 1.35 g (98.5%) of **3b**. Mp 150°C; IR (KBr): $\bar{\nu} = 3423$ (s), 1724 (s), 1497 (w), 1451 (w), 1117 (m), 754 (m), 701 (m), 553 (w) cm^{-1}; UV (CH_3OH): λ (log ε) = 210 (3.998) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.99$ (br, t, $J = 9.9$ Hz, 8-H), 2.45 (br, t, $J = 9.9$ Hz, 5-H), 2.76–2.84 (m, 3-H, 8-H), 2.89 (s, 1-H), 2.91 (br, t, $J = 11.0$ Hz, 5-H), 3.12 (d, $J = 11.0$ Hz, 1H of $N(CH_2)_2$), 3.18–3.24 (m, 3-H, 1H of $N(CH_2)_2$), 3.35 (ddd, $J = 14.1$, 11.1, 2.9 Hz, 1H of $N(CH_2)_2$), 3.41–3.48 (m, 6-H, 7-H, 1H of $N(CH_2)_2$), 3.82 (br, t, $J = 9.5$ Hz, 2H of $O(CH_2)_2$), 4.48–4.56 (m, 2H of $O(CH_2)_2$), 7.09–7.40 (m, 10aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 29.03$ (C-5), 35.50 (C-7), 35.79 (C-8), 37.13 (C-6), 43.02 (C-3), 52.69 (C-1), 57.88 ($N(CH_2)_2$), 61.62 ($O(CH_2)_2$), 75.77 (C-4), 126.74, 127.02, 127.08, 127.20, 128.83, 128.89 (aromatic C), 139.68, 142.48 (aromatic C_q), 209.13 (C-2) ppm; MS (EI^+): m/z (%) = 361 (66.6) [M^+-O], 360 (29.9), 359 (100.0), 257 (45.2), 255 (25.2), 229 (27.8), 215 (23.8), 213 (25.1), 131 (37.5), 91 (61.6); HRMS (EI^+): calcd. for $C_{24}H_{27}NO_3$–O: 361.2042; found: 361.2056.

(6RS,7RS)-(±)-4-(N-Oxidopyrrolidino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**3c**, $C_{24}H_{27}NO_2$)

Compound **1c** (1.25 g, 3.6 mmol) and 1.1 g (6.2 mmol) of *m*-chloroperbenzoic acid in 20 cm^3 of CH_2Cl_2 gave 1.3 g (99.9%) of **3c**. Mp 92°C; IR (KBr): $\bar{\nu} = 3407$ (m), 3028 (m), 2958 (m), 1724 (s), 1497 (m), 1450 (w), 755 (m), 701 (s) cm^{-1}; UV (CH_3OH): λ (log ε) = 214 (3.793) nm; ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 2.00$–2.10 (m, CH_2), 2.15 (ddd, $J = 12.0$, 8.8, 2.7 Hz, 8-H), 2.28–2.42 (m, CH_2), 2.52–2.60 (m, 1-H, 5-H), 2.75 (ddd, $J = 12.8$, 10.3, 2.5 Hz, 5-H), 2.81 (ddd, $J = 12.8$, 9.6, 3.4 Hz, 8-H), 2.92 (dd, $J = 17.7$, 2.5 Hz, 3-H), 3.18 (dd, $J = 18.1$, 3.4 Hz, 3-H) 3.20–3.30 (m, 1H of NCH_2), 3.30–3.38 (m, 1H of NCH_2), 3.46–3.51 (m, 6-H, 7-H), 3.53–3.62 (m, 1H of NCH_2), 3.70–3.78 (m, 1H of NCH_2), 7.06–7.46 (m, 10aromatic H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 22.30$, 22.56 ($(CH_2)_2$), 31.38 (C-5), 37.15 (C-8), 37.25 (C-7), 39.46 (C-6), 45.44 (C-3), 56.53 (C-1), 62.89, 63.48 ($N(CH_2)_2$), 74.20 (C-4), 128.21, 128.49, 128.53, 128.94, 130.06, 130.24 (aromatic C), 142.04, 144.75 (aromatic C_q), 211.75 (C-2) ppm; MS (EI^+): m/z (%) = 345 (69.5) [M^+-O], 343 (100.0), 241 (57.8), 240 (46.9), 231 (50.1), 226 (35.8), 211 (40.9), 199 (36.6), 197 (43.7), 91 (56.6); HRMS (EI^+): calcd. for $C_{24}H_{27}NO_2$–O: 345.2093; found: 345.2101.

(6RS,7RS)-(±)-4-(N-Oxidopiperidino)-6,7-diphenylbicyclo[2.2.2]octan-2-one
(**3d**, $C_{25}H_{29}NO_2$)

Compound **1d** (1.3 g, 3.6 mmol) and 1.1 g (6.2 mmol) of *m*-chloroperbenzoic acid in 20 cm^3 of CH_2Cl_2 gave 1.2 g (88.8%) of **3d**. Mp 118°C; IR (KBr) $\bar{\nu} = 3422$ (m), 3060 (w), 3028 (m), 2958 (m), 1724 (s), 1602 (w), 1497 (m), 1449 (m), 755 (s), 701 (s) cm^{-1}; UV (CH_2Cl_2): λ (log ε) = 234 (2.954) nm; ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.37$–1.44 (m, 1H of CH_2), 1.62–1.80 (m, 3H of CH_2), 2.06 (ddd,

$J = 12.3$, 9.1, 2.8 Hz, 8-H), 2.22–2.36 (m, CH_2), 2.52 (ddd, $J = 12.1$, 9.1, 2.8 Hz, 5-H), 2.59 (s, 1-H), 2.76 (ddd, $J = 12.8$, 10.1, 2.9 Hz, 5-H), 2.85 (ddd, $J = 12.9$, 10.4, 4.0 Hz, 8-H), 2.90 (dd, $J = 17.7$, 2.5 Hz, 3-H), 3.15 (dd, $J = 17.7$, 3.8 Hz, 3-H), 3.20–3.30 (m, NCH_2), 3.34–3.50 (m, 6-H, 7-H, NCH_2), 7.07–7.45 (m, 10aromatic H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 22.11$, 22.26, 23.18 ($(CH_2)_3$), 30.62 (C-5), 36.47 (C-8), 37.24 (C-7), 39.31 (C-6), 44.38 (C-3), 55.98 (C-1), 59.74, 59.87 ($N(CH_2)_2$), 77.96 (C-4), 128.24, 128.49, 128.53, 128.89, 130.06, 130.24 (aromatic C), 142.00, 144.67 (aromatic C_q), 211.61 (C-2) ppm; MS (EI^+): m/z (%) = 359 (34.0) [M^+-O], 358 (29.1), 357 (100.0), 255 (25.5), 253 (27.4), 252 (26.8), 225 (28.4), 211 (33.7), 131 (20.0), 91 (35.9); HRMS (EI^+): calcd. for $C_{25}H_{29}NO_2$–O: 359.2247; found: 359.2249.

*Preparation of Compounds **4a–4d***

The bicyclo[2.2.2]octanones **1a–1d** were dissolved together with KOH in diethylene glycol and heated to 100°C. At this temperature, hydrazine hydrate was added and the temperature was raised to 220°C. A quarter of the solvent was removed by distillation and the solution was stirred for 4 h at 220°C. After cooling, water was added and the resulting suspension was extracted five times with chloroform. The organic layers were washed with water, dried over Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The resulting yellowish resins are almost pure and can be purified to a colourless product by high-vacuum distilliation. The hydrochlorides were obtained by treating the bases with an excess of etheral HCl solution, subsequent evaporation, and crystallization from ethyl acetate. Melting points, IR and UV spectra, and elemental analyses were measured from the hydrochlorides.

(6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octane (**4a**, $C_{22}H_{27}N$)

Compound **1a** (1.7 g, 5.3 mmol), 2 g (35.6 mmol) of KOH, and 5 cm^3 (109 mmol) of hydrazine hydrate dissolved in 22 cm^3 of diethylene glycol gave 1.2 g (74%) of **4a**. Mp hygroscopic, therefore an exact melting point could not be determined; IR (KBr): $\bar{\nu} = 2951$ (s), 2678 (s), 1600 (m), 1496 (s), 1449 (s), 1349 (w), 1034 (m), 914 (w), 749 (s), 701 (s) cm^{-1}; UV (CH_3OH): λ (log ε) = 211 (3.981) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.62$–1.76 (m, 2-H, 3-H_2, 5-H*), 1.83–1.92 (m, 2-H, 8-H*), 1.98 (s, 1-H), 2.04–2.17 (m, 5-H, 8-H), 2.33 (s, $N(CH_3)_2$), 3.16 (t, $J = 9.5$ Hz, 6-H, 7-H), 7.16–7.38 (m, 10aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.26$ (C-2), 26.27 (C-3), 32.40 (C-5^x), 32.97 (C-8^x), 36.45 (C-1^y), 36.49 (C-6^{yz}), 38.32 ($N(CH_3)_2$), 41.77 (C-7^z), 55.87 (C-4), 125.75, 125.93, 127.35, 127.41, 128.21, 128.34 (aromatic C), 144.81, 145.05 (aromatic C_q) ppm; MS (EI^+): m/z (%) = 306 (23.8) [M+H^+], 305 (100.0) [M^+], 200 (68.6), 173 (79.9), 172 (48.1), 124 (18.3), 96 (28.6), 91 (16.4); HRMS (EI^+): calcd. for $C_{22}H_{27}N$: 305.2143; found: 305.2159.

(6RS,7RS)-(±)-4-Morpholino-6,7-diphenylbicyclo[2.2.2]octane (**4b**, $C_{24}H_{29}NO$)

Compound **1b** (10 g, 27.7 mmol), 10 g (178.2 mmol) of KOH, and 26.3 cm^3 (541.1 mmol) of hydrazine hydrate dissolved in 116 cm^3 of diethylene glycol gave 7.93 g (82%) of **4b**. Mp 254°C; IR (KBr): $\bar{\nu} = 2950$ (m), 2868 (m), 2368 (s), 1600 (w), 1495 (m), 1449 (s), 1361 (w), 1347 (w), 1262 (m), 1133 (m), 1112 (m), 1068 (s), 1047 (w), 907 (m), 753 (s), 699 (s) cm^{-1}; UV (CH_3OH): λ (log ε) = 212 (3.993) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.60$–1.76 (m, 2-H, 3-H_2, 5-H*), 1.82–1.93 (m, 2-H, 8-H*), 2.00 (s, 1-H), 2.06 (ddd, $J = 12.4$, 10.2, 2.2 Hz, 5-H*), 2.13 (ddd, $J = 12.5$, 10.0, 2.6 Hz, 8-H*), 2.59–2.72 (m, $N(CH_2)_2$), 3.15 (t, $J = 9.2$ Hz, 6-H, 7-H), 3.73–3.75 (m, $O(CH_2)_2$), 7.15–7.36 (m, 10aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.20$ (C-2), 26.40 (C-3), 32.65 (C-5^x), 33.40 (C-8^x), 36.46 (C-1^y), 36.56 (C-6^{yz}), 41.65 (C-7^z), 46.13 ($N(CH_2)_2$), 56.23 (C-4), 67.66 ($O(CH_2)_2$), 125.80, 125.97, 127.31, 127.36, 128.21, 128.35 (aromatic C), 144.59, 144.84 (aromatic C_q) ppm; MS (EI^+): m/z (%) = 347 (100.0) [M^+], 318 (7.0), 256 (20.9), 242 (48.1), 215 (55.8), 185 (10.1), 166 (12.4), 91 (11.6); HRMS (EI^+): calcd. for $C_{24}H_{29}NO$: 347.2249; found: 347.2266.

(6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octane (**4c**, $C_{24}H_{29}N$)

Compound **1c** (8.8 g, 25.5 mmol), 9.7 g (173 mmol) of KOH, and 24.2 cm^3 (497 mmol) of hydrazine hydrate dissolved in 106 cm^3 of diethylene glycol gave 6.75 g (80%) of **4c**. Mp 227°C; IR (KBr): $\bar{\nu} = 2958$ (m), 2922 (m), 2883 (m), 2554 (m), 2390 (s), 1600 (w), 1494 (m), 1450 (m), 1372 (w), 1348 (w), 1332 (w), 1075 (w), 920 (w), 798 (w), 760 (s), 705 (s) cm^{-1}; UV (CH_3OH): λ (log ε) = 211 (4.041) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.62–1.98$ (m, 1-H, 2-H_2, 3-H_2, 5-H, 8-H, $(CH_2)_2$), 2.06–2.19 (m, 5-H, 8-H), 2.68–2.78 (m, $N(CH_2)_2$), 3.18 (t, $J = 9.1$ Hz, 6-H, 7-H), 7.13–7.39 (m, 10aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.24$ (C-2), 23.55 ($(CH_2)_2$), 27.22 (C-3), 33.16 (C-5^x), 33.76 (C-8^x), 36.46 (C-6^y), 36.88 (C-1), 41.92 (C-7^y), 45.33 ($N(CH_2)_2$), 54.56 (C-4), 125.68, 125.87, 127.39, 127.44, 128.15, 128.30 (aromatic C), 144.88, 145.14 (aromatic C_q) ppm; MS (EI^+): m/z (%) = 331 (100.0) [M^+], 318 (22.5), 240 (43.8), 226 (72.1), 212 (14.0), 199 (91.5), 184 (16.3), 150 (30.2), 136 (16.3), 123 (24.0), 91 (20.5); HRMS (EI^+): calcd. for $C_{24}H_{29}N$: 331.2300; found: 331.2293.

(6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octane (**4d**, $C_{25}H_{31}N$)

Compound **1d** (2.6 g, 7.2 mmol), 2.8 g (50 mmol) of KOH, and 7 cm^3 (144 mmol) of hydrazine hydrate dissolved in 30 cm^3 of diethylene glycol gave 2.17 g (87%) of **4d**. Mp 298°C; IR (KBr): $\bar{\nu} = 2951$ (s), 2932 (s), 2883 (m), 2604 (m), 2571 (m), 2523 (s), 1601 (w), 1495 (m), 1449 (m), 1425 (w), 1370 (w), 1349 (w), 1332 (w), 1074 (w), 1028 (w), 753 (s), 698 (s) cm^{-1}; UV (CH_3OH): λ (log ε) = 212 (3.940) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.42–1.48$ (m, CH_2), 1.58–1.71 (m, 2-H, 3-H, $(CH_2)_2$), 1.74 (ddd, $J = 12.5$, 9.9, 2.6 Hz, 3-H, 5-H*), 1.86 (ddd, $J = 12.1$, 9.8, 2.4 Hz, 2-H, 8-H*), 1.99 (s, 1-H), 2.09 (ddd, $J = 12.2$, 10.3, 1.9 Hz, 5-H*), 2.15 (ddd, $J = 12.6$, 9.9, 2.7 Hz, 8-H*), 2.52–2.88 (m, $N(CH_2)_2$), 3.13 (t, $J = 9.6$ Hz, 6-H, 7-H), 7.09–7.40 (m, 10aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.35$ (C-2), 24.99 (CH_2), 26.62 (C-3), 26.84 ($(CH_2)_2$), 32.81 (C-5^x), 33.57 (C-8^x), 36.52 (C-6^{yz}), 36.59 (C-1^z), 41.70 (C-7^y), 46.71 ($N(CH_2)_2$), 54.50 (C-4), 125.68, 125.84, 127.35, 127.39, 128.15, 128.28 (aromatic C), 144.87, 145.10 (aromatic C_q) ppm; MS (EI^+): m/z (%) = 346 (27.1) [$M+H^+$], 345 (100.0) [M^+], 254 (52.5), 240 (69.1), 214 (20.9), 213 (73.3), 212 (33.3), 164 (23.2), 136 (24.0), 91 (23.1); HRMS (EI^+): calcd. for $C_{25}H_{31}N$: 345.2457; found: 345.2466.

*Preparation of **5a–5d***

4-Methoxybenzylidene acetone and the corresponding rhodanide were suspended in toluene and refluxed on a water separator for 4 h. The solvent was evaporated and the residue was purified by flash chromatography using benzene:chloroform:ethanol = 8:8:0.5 as eluent. The solvent of the fraction containing the product was evaporated, the residue was dissolved in $CHCl_3$ and shaken three times with 2*N* aqueous NaOH solution. The organic layer was washed twice with H_2O, dried over Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The residue was purified by CC using CH_2Cl_2:MeOH = 20:1.5 as eluent giving small amounts of pure product.

(6RS,7RS)-(±)-4-Dimethylamino-6,7-bis(4-methoxyphenyl)bicyclo[2.2.2] octan-2-one (**5a**, $C_{24}H_{29}NO_3$)

4-Methoxybenzylidene acetone (16.8 g, 95 mmol) and 5 g (48 mmol) of dimethylammonium rhodanide in 100 cm^3 of toluene gave 400 mg (2.2%) of **5a** as a resin. IR (KBr): $\bar{\nu} = 2955$ (w), 1725 (m), 1611 (m), 1514 (s), 1464 (w), 1250 (s), 1182 (m), 1033 (m), 830 (w); UV (CH_2Cl_2): λ (log ε) = 225 (4.271), 277 (3.552) nm; ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.53$ (ddd, $J = 12.0$, 8.5, 2.7 Hz, 8-H), 1.92 (ddd, $J = 11.8$, 8.5, 2.3 Hz, 5-H), 2.13 (ddd, $J = 13.0$, 10.1, 2.9 Hz, 5-H), 2.23 (s, $N(CH_3)_2$), 2.24–2.31 (m, 1-H, 3-H, 8-H), 2.50 (dd, $J = 18.4$, 3.5 Hz, 3-H), 3.09–3.21 (m, 6-H, 7-H), 3.58 (s, OCH_3), 3.66 (s, OCH_3), 6.64 (d, $J = 8.7$ Hz, 2aromatic H), 6.79–6.83 (m, 4aromatic H), 7.18 (d, $J = 8.7$ Hz, 2aromatic

H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 31.94$ (C-5), 36.36 (C-7), 37.95 (C-8), 38.90 (C-6), 38.98 ($N(CH_3)_2$), 45.07 (C-3), 55.95, 56.04 ($2OCH_3$), 57.20 (C-1), 59.84 (C-4), 115.26, 115.42, 129.40, 129.96 (aromatic C), 134.62, 137.67, 159.91, 160.21 (aromatic C_q), 215.30 (C-2) ppm; MS (EI^+): m/z (%) = 379 (90.6) [M^+], 245 (100.0), 230 (51.2), 217 (74.4), 202 (58.1), 188 (19.4), 161 (62.0), 133 (20.9), 121 (41.9), 96 (20.9), 85 (44.2), 70 (54.3); HRMS (EI^+): calcd. for $C_{24}H_{29}NO_3$: 379.2147; found: 379.2152.

(6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-morpholinobicyclo[2.2.2]octan-2-one
(**5b**, $C_{26}H_{31}NO_4$)

4-Methoxybenzylidene acetone (21 g, 120 mmol) and 17.4 g (120 mmol) of morpholinium rhodanide in 150 cm^3 of toluene gave 1.07 g (4.2%) of **5b** as a resin. IR (KBr): $\bar{\nu} = 2955$ (m), 2835 (w), 1719 (s), 1611 (m), 1514 (s), 1452 (w), 1306 (w), 1248 (s), 1181 (m), 1118 (s), 1033 (m), 831 (w) cm^{-1}; UV (CH_2Cl_2): λ (log ε) = 234 (4.101), 277 (3.541) nm; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.63$ (ddd, $J = 12.0$, 8.5, 2.7 Hz, 8-H), 2.04 (ddd, $J = 11.9$, 8.6, 2.2 Hz, 5-H), 2.26 (ddd, $J = 13.0$, 10.4, 2.6 Hz, 5-H), 2.32–2.42 (m, 3-H, 8-H), 2.53 (dd, $J = 18.1$, 3.1 Hz, 3-H), 2.60 (s, 1-H), 2.62–2.72 (m, $N(CH_2)_2$), 3.28 (t, $J = 9.4$ Hz, 6-H, 7-H), 3.73 (s, OCH_3), 3.75 (s, $O(CH_2)_2$), 3.81 (s, OCH_3), 6.78 (d, $J = 8.5$ Hz, 2aromatic H), 6.90 (d, $J = 8.5$ Hz, 2aromatic H), 6.97 (d, $J = 8.5$ Hz, 2aromatic H), 7.25 (d, $J = 8.7$ Hz, 2aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.87$ (C-5), 34.67 (C-7), 37.30 (C-6), 37.37 (C-8), 44.56 (C-3), 46.30 ($N(CH_2)_2$), 54.53 (C-1), 55.22, 55.28 ($2OCH_3$), 58.15 (C-4), 67.48 ($O(CH_2)_2$), 114.00, 114.08, 127.92, 128.40 (aromatic C), 132.95, 136.22, 158.15, 158.42 (aromatic C_q), 213.06 (C-2) ppm; MS (EI^+): m/z (%) = 421 (100.0) [M^+], 300 (21.7), 287 (97.7), 272 (45.0), 245 (53.5), 215 (11.6), 180 (17.4), 161 (85.7), 121 (58.1), 91 (12.8) ppm; HRMS (EI^+): calcd. for $C_{26}H_{31}NO_4$: 421.2253; found: 421.2263.

(6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-pyrrolidinobicyclo[2.2.2]octan-2-one
(**5c**, $C_{26}H_{31}NO_3$)

4-Methoxybenzylidene acetone (28.3 g, 161 mmol) and 11.0 g (84 mmol) of pyrrolidinium rhodanide in 150 cm^3 of toluene gave 913 mg (2.8%) of **5c** as a resin. IR (KBr): $\bar{\nu} = 2952$ (m), 2834 (w), 1719 (s), 1611 (m), 1514 (s), 1460 (m), 1333 (w), 1306 (w), 1248 (s), 1180 (m), 1114 (w), 1034 (m), 829 (m) cm^{-1}; UV (CH_2Cl_2): λ (log ε) = 234 (4.123), 278 (3.573) nm; ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.67$ (ddd, $J = 12.1$, 8.4, 2.5 Hz, 8-H), 1.75 (br, s, $(CH_2)_2$), 2.05 (ddd, $J = 12.7$, 10.6, 1.9 Hz, 5-H), 2.18 (ddd, $J = 12.7$, 10.6, 2.5 Hz, 5-H), 2.28–2.39 (m, 1-H, 3-H, 8-H), 2.58 (dd, $J = 18.2$, 3.3 Hz, 3-H), 2.66–2.80 (m, $N(CH_2)_2$), 3.18–3.28 (m, 6-H, 7-H), 3.62 (s, OCH_3), 3.71 (s, OCH_3), 6.69 (d, $J = 8.7$ Hz, 2aromatic H), 6.86 (d, $J = 8.7$ Hz, 2aromatic H), 6.87 (d, $J = 8.7$ Hz, 2aromatic H), 7.23 (d, $J = 8.7$ Hz, 2aromatic H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 24.83$ ($(CH_2)_2$), 33.07 (C-5), 36.39 (C-7), 38.81 (C-8), 39.07 (C-6), 45.73 (C-3), 47.25 ($N(CH_2)_2$), 56.05, 56.13 ($2OCH_3$), 57.51 (C-1), 59.05 (C-4), 115.38, 115.55, 129.52, 130.09 (aromatic C), 134.69, 137.78, 160.03, 160.35 (aromatic C_q), 214.86 (C-2) ppm; MS (EI^+): m/z (%) = 405 (85.3) [M^+], 362 (14.0), 284 (22.5), 271 (100.0), 256 (57.4), 243 (82.2), 229 (60.5), 216 (17.1), 175 (14.0), 161 (89.9), 150 (18.6), 134 (34.1), 121 (62.8), 111 (42.6); HRMS (EI^+): calcd. for $C_{26}H_{31}NO_3$: 405.2304; found: 405.2313.

(6RS,7RS)-(±)-6,7-Bis(4-methoxyphenyl)-4-piperidinobicyclo[2.2.2]octan-2-one
(**5d**, $C_{27}H_{33}NO_3$)

4-Methoxybenzylidene acetone (21 g, 119 mmol) and 17.2 g (119 mmol) of piperidinium rhodanide in 150 cm^3 of toluene gave 280 mg of the product which was purified additionally by preparative TLC using toluene:dichloromethane:methanol = 4:4:1 as eluent giving 110 mg (0.4%) of **5d** as a resin. IR (KBr): $\bar{\nu} = 2934$ (m), 1719 (s), 1611 (m), 1514 (s), 1464 (w), 1306 (w), 1248 (s), 1181 (m), 1112 (w),

1034 (m), 829 (m) cm^{-1}; UV (CH_2Cl_2): λ (log ε) = 236 (3.915), 278 (3.525) nm; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.44–1.50 (m, CH_2), 1.62–1.68 (m, 8-H, $(CH_2)_2$), 2.08 (t, J = 10.2 Hz, 5-H), 2.31 (ddd, J = 12.9, 10.4, 2.5 Hz, 5-H), 2.36–2.46 (m, 3-H, 8-H), 2.54–2.70 (m, 1-H, 3-H, $N(CH_2)_2$), 3.26 (t, J = 9.5 Hz, 6-H, 7-H), 3.75 (s, OCH_3), 3.81 (s, OCH_3), 6.78 (d, J = 8.6 Hz, 2aromatic H), 6.90 (d, J = 8.6 Hz, 2aromatic H), 6.97 (d, J = 8.6 Hz, 2aromatic H), 7.26 (d, J = 8.8 Hz, 2aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.70 (CH_2), 26.57 ($(CH_2)_2$), 32.04 (C-5), 34.84 (C-7), 37.40 (C-6), 37.77 (C-8), 44.56 (C-3), 46.97 ($N(CH_2)_2$), 54.50 (C-1), 55.22, 55.27 ($2OCH_3$), 58.67 (C-4), 113.96, 114.04, 127.94, 128.43 (aromatic C), 133.11, 136.38, 158.10, 158.35 (aromatic C_q), 213.82 (C-2) ppm; MS (EI^+): m/z (%) = 420 (29.3) [M+H^+], 419 [M^+] (100.0), 298 (29.3), 285 (86.3), 284 (59.6), 270 (41.3), 257 (42.4), 243 (31.6), 161 (27.3), 124 (22.2); HRMS (EI^+): calcd. for $C_{27}H_{33}NO_3$: 419.2460; found: 419.2437.

Biological Tests

The screening assays against *Plasmodium falciparum* K_1 and *Trypanosoma b. rhodesiense* where performed as reported [1].

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