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Original article

Synthesis of new esters and oximes with 4-aminobicyclo[2.2.2]octane structure and evaluation of their antitrypanosomal and antiplasmodial activities

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Abstract

New 4-amino-6,7-diphenylbicyclo[2.2.2]octane derivatives, esters of bicyclo[2.2.2]octan-2-ols and *O*-methyl oximes of bicyclo[2.2.2]octan-2-ones were synthesised. Their activities against *Trypanosoma brucei rhodesiense* (STIB 900) and their activity against the K1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine) were determined by use of microplate assays. The cytotoxicity was assessed using L6 cells. The antiprotozoal activities of the new compounds are compared with those of former prepared derivatives and drugs in use. Structure–activity relationships are discussed.

Keywords: 4-Aminobicyclo[2.2.2]octane derivatives; *Trypanosoma b. rhodesiense*; *Plasmodium falciparum*; In vitro assays; *O*-methyloximes; Aromatic esters

1. Introduction

Sleeping sickness has re-emerged as a serious problem in sub-Saharan Africa with an estimated 100,000 deaths each year [1]. The two protozoan parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense* are the causative organisms of this disease which is invariably fatal, if untreated [2]. The current drugs available for treatment suffer from a number of disadvantages, including toxic side effects, poor clinical efficacy, parenteral administration and increasing problems with resistance [3]. The latest introduced drug is eflornithine but it is unfortunately ineffective against *T. b. rhodesiense* [4]. Therefore, there is an urgent need for new drugs with less side effects and activity against the causative agent of East African Human Trypanosomiasis.

At present malaria is considered to be the world's most important tropical parasitic disease, afflicting 300–500 million people and killing 1–2 million annually [5]. It is estimated that nearly 40% of the world's population lives in malaria endemic regions. Of the four species of the disease-causing parasites, *Plasmodium falciparum* is the most dangerous form, accounting for up to 95% of malaria related deaths [6]. A main problem is drug resistance in this species [7]. Drugs in use such as chloroquine and the combination sulphadoxine–pyrimethamine which were once highly effective 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 potent new antimalarial drugs.

Recently we reported the antiprotozoal activities of some methyl thiosemicarbazones of dialkylaminobicyclo[2.2.2]octan-2-ones **1** and esters of dialkylaminobicyclo[2.2.2]octan-2-ols **2** [15]. Especially the esters seemed to be worthy of further investigations because they feature in addition to their enhanced antiplasmodial activity rather low cytotoxicity. In the mean time, we prepared oximes **3** of dialkylaminobicyclo[2.2.2]octan-2-ones which possess remarkable antimalarial potency and moderate toxicity [16]. Starting from these results we

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Abbreviations: CC, column chromatography; CH_2Cl_2, dichloromethane; DCC, dicyclohexylcarbodiimide; 4-DMAP, 4-dimethylaminopyridine; ether, diethylether; HCl, hydrochloric acid; MeOH, methyl alcohol; NaOH, sodium hydroxide.

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prepared a number of bicyclo[2.2.2]oct-2-yl esters of aromatic acids and *O*-methyl oximes of bicyclic ketones and investigated the new compounds **4–9** for their antitrypanosomal and antiplasmodial activity and their cytotoxicity using in vitro microplate assays (Fig. 1).

2. Chemistry

We described the synthesis of compounds **1** from acyclic starting material via a one-pot procedure and determined their structures with the aid of a single crystal structure analysis [17]. The reaction of ketones **1a**–**d** with *O*-methyl hydroxylamine was carried out in alkaline medium giving *O*-methyloximes **4**. Their structures were established using NMR spectroscopy. Typically, the signal for C-2 was shifted from 213 ppm to 160 ppm in their ^{13}C NMR spectra due to the formation of oximes **4**. Prior to chromatographic purification, at least traces of different isomers **4a**, **c**, **d** and **4a′**, **c′**, **d′** in the mixtures were detected. In the case of the piperidino compounds, we were able to separate the *E*-isomer **4d′** from its *Z*-isomer **4d**. Their distinction succeeded via the greater upfield shift of the signal for the α-syn carbons in their ^{13}C NMR spectra [18].

The alcohols **2a**–**d** which served as starting material for esterification were yielded stereospecifically by the reduction of **1a**–**d** with lithium aluminium hydride. The configuration in position 2 of compounds **2a–d** was determined by measurement of through space couplings (NOEs) from their 2-Hs to their 6-Hs [19].

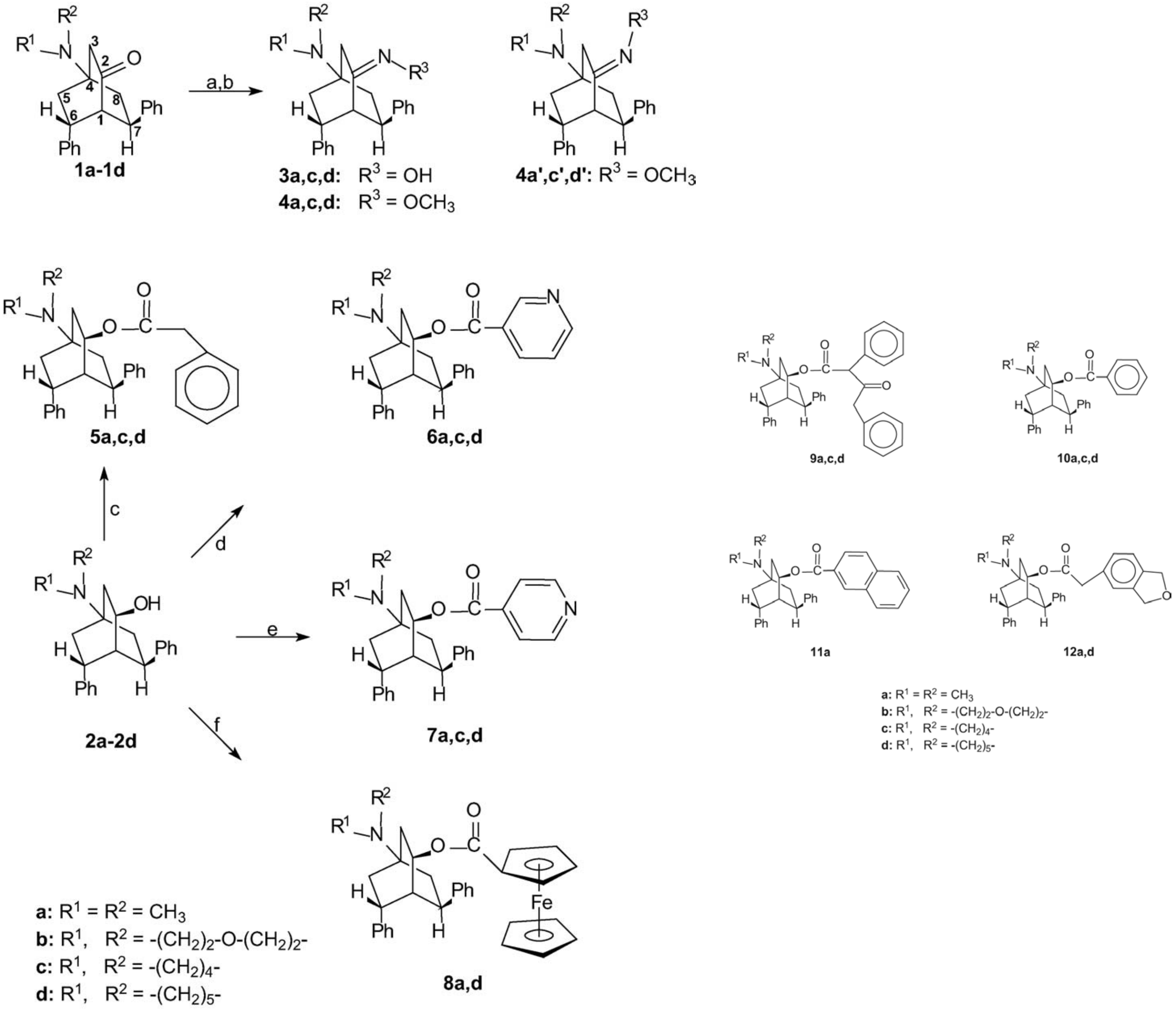

Fig. 1. (a) Hydroxylamine hydrochloride/NaOEt in refluxing EtOH (**3a**–**d**); (b) *O*-methyl hydroxylamine hydrochloride/NaOEt in refluxing EtOH (**4a**–**d**); (c) phenyl acetyl chloride/DMAP in CH_2Cl_2; (d) nicotinic acid/DCC/DMAP in CH_2Cl_2; (e) isonicotinic acid chloride/DMAP in CH_2Cl_2; (f) ferrocene carboxylic acid/DCC/DMAP in CH_2Cl_2.

The esters of phenylacetic acid **5** and isonicotinic acid **7** were prepared using the corresponding acid chlorides as reagent. The reactions were carried out in dichloromethane (CH_2Cl_2) at room temperature using 4-dimethylaminopyridine (DMAP) as catalyst. The esters of nicotinic acid **6** and ferrocene carboxylic acid **8** were synthesised using the corresponding acids as reagent, CH_2Cl_2 as solvent and DMAP as catalyst. Dicyclohexylcarbodiimide (DCC) was added to the reaction mixture to act as condensation agent removing the water formed during esterification by its reaction to dicyclohexylurea which precipitates from the reaction mixture. Esterification was proven by a long-range coupling from 2-H to the ester carbonyl carbon in their HMBC NMR spectra.

In the case of the reaction of the bicyclo[2.2.2]octan-2-ols **2a**, **c**, **d** with phenyl acetic acid chloride the 3-oxobutanoates **9a**, **c**, **d** were formed as by-products. Compound **9d** was isolated and its antiprotozoal activities were examined. The β-keto ester structure of **9d** was established by the long-range couplings from the methine proton to the ester and the oxo carbonyl carbon.

3. Antiprotozoal activity

The tests were performed as microplate assays using *Trypanosoma brucei rhodesiense* (STIB 900) and the K1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine). Cytotoxicity was assessed with rat skeletal myoblasts (L-6 cells) with the same assay which was used for the determination of the antitrypanosomal activity.

The following substances were used as standards: melarsoprol (*Trypanosoma b. rhodesiense*), artemisinin (*Plasmodium-falciparum*) and mefloquine for the determination of the cytotoxicity.

4. Results and discussion

The new compounds, *O*-methyloximes **4** and aromatic esters **5**–**9** were investigated for their antitrypanosomal and antiplasmodial activities and their cytotoxicity. The results are presented in Table 1.

Table 1
Activities of **1**–**12**, expressed as IC_{50} (μM)[a]

Compound	*T. b. rhodesiense*	SI	*P. falciparum K1*	SI	Cyt. L6
1a	9.99	2.46	> 10.57	2.32	24.57
1b	116.3	–	> 11.89	–	n.t.
1c	8.03	3.29	1.19	22.22	26.45
1d	8.12	5.78	3.95	11.88	46.92
2a	2.95	44.91	>15.55	8.52	132.5
2b	20.80	–	2.42	–	n.t.
2c	4.26	6.28	2.39	11.20	26.76
2d	5.34	6.99	0.84	44.45	37.34
3a	7.67	19.61	1.26	119.4	150.4
3c	1.84	7.31	0.08	168.1	13.45
3d	3.66	6.60	0.15	161.1	24.16
4a′	5.54	11.03	4.01	15.24	61.12
4c	4.64	6.33	2.90	10.13	29.37
4d′	11.42	5.49	6.37	9.85	62.74
4d	9.73	4.31	2.75	15.25	41.95
5a	1.25	3.37	0.89	4.73	4.21
5c	1.03	8.55	1.04	8.47	8.81
5d	6.88	2.65	0.36	50.64	18.23
6a	15.94	10.75	1.49	115.0	171.4
6c	0.62	39.35	0.20	122.0	24.40
6d	70.94	0.01	0.48	1.81	0.87
7a	3.16	8.27	1.14	22.92	26.14
7c	3.49	7.85	0.86	31.86	27.40
7d	16.92	6.69	0.65	174.2	113.2
8a	0.88	8.94	0.59	13.34	7.87
8d	21.10	3.40	1.50	47.89	71.83
9d	3.60	2.20	0.66	12.02	7.93
10a	1.53	6.46	2.47	4.00	9.88
10c	4.95	1.03	4.50	1.13	5.08
10d	14.99	6.49	0.66	147.4	97.29
11a	0.69	10.67	0.22	33.45	7.36
12a	0.66	9.85	0.24	27.08	6.50
12d	17.46	9.68	0.66	256.1	169.0
mel	0.0039	1995			7.78
sur	0.0075	629933			4724.5
art			0.0064	70390	450.5
chl			0.12[b]	1570	188.5
mef					11.37

n.t., not tested; art, artemisinin; chl, chloroquine; mel, melarsoprol; sur, suramine; mef, mefloquine.

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

[b] against sensitive *P. falciparum* strains.

In general, the *O*-methyloximes **4** exhibit distinctly decreased activities against both the protozoan parasites compared to their unsubstituted analogues **3a**, **c**, **d**. However, their cytotoxicity is lowered due to *O*-methylation too. Of the last series [15], the ester of homopiperonylic acid **12a** showed the highest antitrypanosomal activity ($IC_{50} = 0.66$ μM) followed by the naphthoic acid ester **11a** ($IC_{50} = 0.69$ μM). Both compounds are relatively toxic ($IC_{50} = 6.50$–7.36 μM). Of the new compounds, the ferrocenic carboxylate **8a** ($IC_{50} = 0.88$ μM) and the nicotinate **6c** ($IC_{50} = 0.62$ μM) are the most active ones. **6c** is even more active than **12a** and possesses much lower toxicity ($IC_{50} = 24.40$ μM).

The antiplasmodial activities of the new compounds do not reach the level of the already reported activity of oximes **3c**, **d** ($IC_{50} = 0.08$, 0.15 μM) but the most active compound **6c** ($IC_{50} = 0.20$ μM) is negligibly less active than **3d** and has comparable toxicity. Compared to benzoates **10** [16] the insertion of a methylene group between the aromatic ring and the carboxylic group to phenylacetates **5** increases both antiprotozoal activities but their toxicity too. Phenylacetate **5d** exhibits higher antiplasmodial activity ($IC_{50} = 0.36$ μM) than the ester of homopiperonylic acid **12d** ($IC_{50} = 0.66$ μM) with the same distance between the aromatic ring and the carboxylic group. Besides it shows only moderate toxicity ($IC_{50} = 18.23$ μM). The insertion of a nitrogen atom in position 3 of the aromatic ester residue of benzoates **10** to nicotinates **6** yielded compound **6c** with the highest antiplasmodial ($IC_{50} = 0.20$ μM) and antitrypanosomal ($IC_{50} = 0.62$ μM) potency of the new series. The toxicity of **6c** ($IC_{50} = 24.40$ μM) is acceptable. **7d** shows good antiplasmodial activity too ($IC_{50} = 0.48$ μM) but is rather toxic ($IC_{50} = 0.87$ μM). Insertion of a nitrogen in position 4 of the aromatic ester residue to isonicotinates **7** gives compounds **7c** and **7d** with good antiplasmodial activity ($IC_{50} = 0.86$, 0.65 µM). Especially **7d** has rather low toxicity (IC_{50} = 113.2 µM). Ferrocenic carboxylate **8a** possesses enhanced antitrypanosomal (IC_{50} = 0.88 µM) and antiplasmodial (IC_{50} = 0.59 µM) activities but is relatively toxic (IC_{50} = 7.87 µM). Compound **9d** exhibits good antiplasmodial activity (IC_{50} = 0.66 µM) but is toxic too (IC_{50} = 7.93 µM).

5. Conclusion

Considering the remarkable antiplasmodial activity of 4-aminobicyclo[2.2.2]octane oximes **3**, we synthesised the corresponding *O*-methyloximes **4** which show decreased activity. In contrast to that, the antiplasmodial activity of aromatic esters of bicyclo[2.2.2]octan-2-ols was increased by the insertion of a methylene group between the phenyl ring and the carboxylic group or by insertion of a nitrogen atom in position 3 or 4. Compound **6c** the nicotinate of (6*RS*, 7*RS*)-(±)-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol exhibits the strongest trypanocidal potency and the highest antiplasmodial activity of the newly synthesised compounds. Furthermore, it possesses acceptable toxicity. A racemic resolution of this compound and the investigation of the biological properties of pure isomers should be subject of a following study.

6. Experimental

6.1. Instrumentation and chemicals

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, 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, gHMBC optimised 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: Varian MAT 711 spectrometer 70 eV electron impact, Kratos profile spectrometer 70 eV electron impact. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; EA 1108 CHNS-O apparatus (Carlo Erba). pH: pH-meter 410 (Thermo Orion). 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, 20 0 × 200 mm); the substances were detected in UV light at 254 nm.

6.2. Syntheses

6.2.1. (6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ones (1a–d) and (2SR,6RS,7RS)-(±)4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ols (2a–d)

Ketones **1a**–**d** and the corresponding alcohols **2a**–**d** were prepared following reported procedures [17,19].

6.2.2. (6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one oximes (3a–d)

The synthesis of **3a**–**d** has already been reported [16].

6.2.3. General procedure for the syntheses of (6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one O-methyl-oximes (4a′, c, d, d′)

To a solution of sodium 230 mg (10 mmol) in ethanol (25 ml) *O*-methylhydroxylamine hydrochloride (12.24 mmol) was added in an atmosphere of Ar. The mixture was refluxed at 100 °C for 1 h. A concentrated solution of the ketones (3.2 mmol) **1a**, **c**, **d** in dry ethanol (10 ml) was added and the reaction mixture was refluxed over night. Then it was cooled, filtered and the filtrate was evaporated to dryness. The residue was purified by CC.

6.2.3.1. E-(6RS,7RS)-(±)-4-dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one O-methyl-oxime (4a′). 1030 mg of **1a** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 39:1 as eluent. Yield: 803 mg (72%) of **4a′** as a colourless oil; IR = 2948, 1602, 1495, 1464, 1454, 1048, 860, 754, 700; UV (CH_2Cl_2): $\lambda = 230, 259$; ^1H NMR ($CDCl_3$) $\delta = 1.61$ (ddd, $J = 13.0, 8.9, 2.7$ Hz, 1H, 8-H), 2.00 (ddd, $J = 13.2, 8.0, 2.6$ Hz, 1H, 5-H), 2.18–2.27 (m, 2H, 5-H, 8-H), 2.36 (s, 6H, $N(CH_3)_2$), 2.50 (dd, $J = 18.4, 3.5$ Hz, 1H, 3-H), 2.70 (dd, $J = 18.2, 2.7$ Hz, 1H, 3-H), 2.70 (s, 1H, 1-H), 3.22 (dd, $J = 10.4, 8.3$ Hz, 1H, 7-H), 3.29 (dd, $J = 10.2, 8.1$ Hz, 1H, 6-H), 3.86 (s, 3H, OCH_3), 7.09–7.36 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 31.02$ (C-3), 31.85 (C-5), 35.95 (C-7), 36.79 (C-8), 38.37 ($N(CH_3)_2$), 40.56 (C-6), 43.29 (C-1), 56.74 (C-4), 61.32 (OCH_3), 126.12, 126.42, 127.37, 127.39, 128.20, 128.46, 142.19, 144.56 (aromatic C), 159.85 (C = N); Anal. Calcd. for $C_{23}H_{28}N_2O$ (348.49): C 79.27, H 8.10, N 8.04; found: C 79.07, H 8.17, N 7.98; HRMS (EI+): calcd. ($C_{23}H_{28}N_2O$): 348.22016; found: 348.22116.

6.2.3.2. Z-(6RS,7RS)-(±)-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one O-methyl-oxime (4c). 1100 mg of **1c** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 29:1 as eluent. Yield: 455 mg (38%) of **4c** as a colourless oil; IR = 2933, 1602, 1496, 1450, 1047, 754, 700; UV (CH_2Cl_2): $\lambda = 231, 259$; ^1H NMR ($CDCl_3$) $\delta = 1.72$ (ddd, $J = 13.0, 8.4, 2.9$ Hz, 1H, 8-H), 1.77–1.83 (m, 4H, $(CH_2)_2$), 2.06 (dd, $J = 13.0, 8.2$ Hz, 1H, 5-H), 2.20–2.29 (m, 2H, 5-H, 8-H), 2.56, 2.60 (2d, $J = 18.0$ Hz, 2H, 3-H), 2.69–2.79 (m, 4H, $N(CH_2)_2$), 3.19–3.26 (m, 2H, 6-H, 7-H), 3.61 (s, 1H, 1-H), 3.68 (s, 3H, OCH_3), 7.13–7.38 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.55$ ($(CH_2)_2$), 32.88 (C-5), 34.33 (C-3), 36.12 (C-7), 36.61 (C-8), 37.99 (C-1), 39.04 (C-6), 45.75 ($N(CH_2)_2$), 56.56 (C-4), 60.91 (OCH_3), 126.18, 126.45, 126.96, 127.44, 128.17, 128.47, 142.10, 144.38 (aromatic C), 159.51 (C = N); HRMS (EI+): calcd. ($C_{25}H_{30}N_2O$): 374.23581; found: 374.23599.

6.2.3.3. Z- and E-(6RS,7RS)-(±)-6,7-diphenyl-4-piperidinobicyclo[2.2.2]octan-2-one O-methyl-oxime (4d and 4d′). 1150 mg of **1d** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 24:1 as eluent. For analytical and test purposes the isomers **4d** and **4d′**were separated by CC over silica gel using ethyl acetate as eluent. Yield: 516 mg (41%) of *E*-isomer **4d′** as a colourless oil; IR = 2933, 1601, 1495, 1451, 1049, 860, 753, 698; UV (CH_2Cl_2): λ = 231, 259; ^{1}H NMR ($CDCl_3$) δ = 1.41–1.48 (m, 2H, CH_2), 1.55–1.63 (m, 5H, 8-H, 2 CH_2), 2.00 (br, dd, J = 12.9, 8.6 Hz, 1H, 5-H), 2.18–2.29 (m, 2H, 5-H, 8-H), 2.49 (dd, J = 18.1, 2.9 Hz, 1H, 3-H), 2.56–2.68 (m, 4H, $N(CH_2)_2$), 2.70 (s, 1H, 1-H), 2.73 (dd, J = 18.1, 2.4 Hz, 1H, 3-H), 3.19 (br, t, J = 9.5 Hz, 1H, 7-H), 3.26 (dd, J = 11.2, 8.6 Hz, 1H, 6-H), 3.86 (s, 3H, OCH_3), 7.10–7.36 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) δ = 24.84 (CH_2), 26.78 (2 CH_2), 31.65 (C-3), 32.21 (C-5), 36.14 (C-7), 37.65 (C-8), 40.66 (C-6), 43.42 (C-1), 46.84 ($N(CH_2)_2$), 57.18 (C-4), 61.35 (OCH_3), 126.11, 126.40, 127.46, 128.22, 128.46, 142.38, 144.77 (aromatic C), 160.46 (C = N); Anal. Calcd. for $C_{26}H_{32}N_2O$ ● 0.25 H_2O (393.06): C 79.45, H 8.33, N 7.13; found: C 79.51, H 8.44, N 6.92; HRMS (EI+): calcd. ($C_{26}H_{32}N_2O$): 388.25146; found: 388.25069.

Yield: 463 mg (37%) of *Z*-isomer **4d** as a colourless oil; IR = 2930, 1602, 1495, 1453, 1047, 892, 751, 698; UV (CH_2Cl_2): λ = 231, 259; ^{1}H NMR ($CDCl_3$) δ = 1.43–1.50 (m, 2H, CH_2), 1.58–1.69 (m, 5H, 8-H, 2 CH_2), 2.00 (ddd, J = 13.0, 8.5, 1.8 Hz, 1H, 5-H), 2.21 (ddd, J = 12.9, 10.3, 2.7 Hz, 1H, 8-H), 2.28 (ddd, J = 12.9, 10.3, 2.9 Hz, 1H, 5-H), 2.50–2.70 (m, 6H, 5-H, 3-H, $N(CH_2)_2$), 3.16–3.21 (m, 2H, 6-H, 7-H), 3.63 (m, 1H, 1-H), 3.69 (s, 3H, OCH_3), 7.14–7.37 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) δ = 24.85 (CH_2), 26.74 (2 CH_2), 32.65 (C-5), 34.06 (C-3), 36.62 (C-7), 36.98 (C-8), 37.99 (C-1), 39.11 (C-6), 46.93 ($N(CH_2)_2$), 57.77 (C-4), 60.91 (OCH_3), 126.21, 126.43, 127.11, 127.50, 128.20, 128.50, 142.46, 144.65 (aromatic C), 160.41 (C = N); Anal. Calcd. for $C_{26}H_{32}N_2O{\cdot}0.5H_2O$ (394.36): C 79.19, H 8.43, N 7.10; found: C 79.21, H 8.58, N 6.77.

*6.2.4. General procedure for the syntheses of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl phenylacetates (**5a**, **c**, **d**) and of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl isonicotinates (**7a**, **c**, **d**)*

In an atmosphere of Ar the bicyclic alcohols **2a**, **c**, **d** (2 mmol) were dissolved in dry CH_2Cl_2 (10 ml) and the solution was cooled with an ice bath. Then DMAP (4 mmol) and phenylacetyl chloride (4 mmol) or isonicotinyl chloride (4 mmol) were added and the mixture was stirred for 1 h. The ice bath was removed and the mixture was stirred over night. The mixture was excessively extracted with water and NaOH. Then it was neutralised with water, dried over sodium sulphate and the solvent removed in vacuo. The residue was purified.

*6.2.4.1. (2SR,6RS,7RS)-(±)-4-dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl phenylacetate (**5a**)*. 643 mg of **2a** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 4:1 as eluent. The fractions contained a mixture of **5a** and **9a**. The latter was removed by CC using CH_2Cl_2/MeOH = 9:1 as eluent. Yield: 372 mg (40%) of **5a** as a colourless oil; IR = 2947, 1732, 1600, 1496, 1350, 1216, 1163, 744, 702; UV (CH_2Cl_2): λ = 232, 259; ^{1}H NMR ($CDCl_3$) δ = 1.69 (dd, J = 14.1, 2.0 Hz, 1H, 3-H), 1.90–1.97 (m, 1H, 5-H), 2.03–2.11 (m, 3H, 3-H, 5-H, 8-H), 2.19–2.30 (m, 1H, 8-H), 2.40 (s, 6H, $N(CH_3)_2$), 2.65 (d, J = 15.5 Hz, 1H, CH-C=O), 2.84 (d, J = 4.4 Hz, 1H, 1-H), 2.88 (d, J = 15.5 Hz, 1H, CH-C=O), 3.01 (t, J = 9.4 Hz, 1H, 6-H), 3.22 (t, J = 9.7 Hz, 1H, 7-H), 5.25 (dd, J = 9.1, 4.4 Hz, 1H, 2-H), 6.90 (d, J = 6.6 Hz, 2H, o-aromatic H), 7.14–7.41 (m, 13 aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.09 (C-5), 31.31 (C-8), 33.98 (C-7), 34.67 (C-3), 38.33 ($N(CH_3)_2$), 38.67 (C-6), 39.64 (C-1), 40.40 (CH_2-C = O), 56.74 (C-4), 73.20 (C-2), 125.50, 126.49, 126.63, 126.79, 127.38, 128.12, 128.27, 128.58, 129.28, 133.82, 142.59, 144.59 (aromatic C), 171.11 (C = O); Anal. Calcd. for $C_{30}H_{33}NO_2{\cdot}1.5H_2O$ (466.62): C 77.21, H 7.78, N 3.00; found: C 76.81, H 7.51, N 2.99.

*6.2.4.2. (2SR,6RS,7RS)-(±)-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl phenylacetate (**5c**)*. 695 mg of **2c** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 4:1 as eluent. The fractions contained a mixture of **5c** and **9c**. The latter was removed by CC using CH_2Cl_2/MeOH = 9:1 as eluent. Yield: 288 mg (30%) of **5c** as a colourless oil; IR = 3027, 2956, 1732, 1600, 1496, 1447, 1348, 1257, 1157, 749, 727, 697; UV (CH_2Cl_2): λ = 232, 259; ^{1}H NMR ($CDCl_3$) δ = 1.72 (d, J = 14.0 Hz, 1H, 3-H), 1.84–1.92 (m, 4H, $(CH_2)_2$), 2.02–2.32 (m, 5H, 3-H, 5-H, 8-H), 2.63 (d, J = 15.5 Hz, 1H, CH-C = O), 2.79–2.89 (m, 4H, $N(CH_2)_2$), 2.83 (d, J = 4.4 Hz, 1H, 1-H), 2.88 (d, J = 15.5 Hz, 1H, CH-C = O), 3.04 (br, t, J = 9.4 Hz, 1H, 6-H), 3.25 (br, t, J = 9.7 Hz, 1H, 7-H), 5.24 (dd, J = 8.9, 4.4 Hz, 1H, 2-H), 6.90 (d, J = 7.2 Hz, 2H, *o*-aromatic H), 7.15–7.41 (m, 13 aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.59 ($(CH_2)_2$), 31.55 (C-5), 32.18 (C-8), 33.87 (C-7), 35.47 (C-3), 38.68 (C-6), 39.96 (C-1), 40.34 (CH_2-C = O), 45.85 ($N(CH_2)_2$), 55.85 (C-4), 73.07 (C-2), 125.51, 126.50, 126.63, 126.78, 127.40, 128.11, 128.26, 128.57, 129.27, 133.77, 142.45, 144.40 (aromatic C), 171.09 (C = O); Anal. Calcd. for $C_{32}H_{35}NO_2{\cdot}H_2O$ (483.65): C 79.47, H 7.71, N 2.90; found: C 79.40, H 7.65, N 2.91.

*6.2.4.3. (2SR,6RS7RS) -(±)-6,7-diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl phenyl acetate (**5d**) and (±)-6,7-diphenyl-4-(piperidin-1-yl)bicyclo[2.2.2]oct-2-yl 3-oxo-2,4-diphenylbutanoate (**9d**)*. 723 mg of **2d** gave a residue which contained compounds **5d** and **9d**. Those were separated using CC over silica gel eluting with CH_2Cl_2/MeOH = 19:1 and finally recrystallised. Yield: 255 mg (27%) of **5d**; m.p. (ethanol) = 138 °C; IR = 2933, 1720, 1600, 1496, 1453, 1345, 1264, 1158, 997, 697; UV (MeOH): λ = 209, 258; ^{1}H NMR ($CDCl_3$) δ = 1.44 − 1.52 (m, 2H, CH_2), 1.59–1.69 (m, 4H, 2 CH_2), 1.70 (d, J = 15.8 Hz, 1H, 3-H), 1.87–1.96 (m, 1H, 5-H), 2.02–2.12 (m, 3H, 3-H, 5-H, 8-H), 2.19–2.26 (m, 1H, 8-H), 2.61 (d, J = 15.5 Hz, 1H, CH-C=O), 2.56–2.71 (m, 4H, $N(CH_2)_2$), 2.82 (d, J = 4.6 Hz, 1H, 1-H), 2.87 (d, J = 15.5 Hz, 1H, CH-C=O), 2.97 (br, t, J = 9.4 Hz, 1H, 6-H), 3.18 (br, t, J = 9.8 Hz, 1H, 7-H), 5.23 (dd, $J = 8.8$, 4.8 Hz, 1H, 2-H), 6.90 (d, $J = 7.6$ Hz, 2H, *o*-aromatic H), 7.11–7.42 (m, 13 aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.95$ (CH_2), 26.79 (2 CH_2), 31.36 (C-5), 32.15 (C-8), 34.03 (C-7), 34.98 (C-3), 38.69 (C-6), 39.78 (C-1), 40.35 (CH_2-C = O), 46.84 ($N(CH_2)_2$), 56.74 (C-4), 73.45 (C-2), 125.37, 126.36, 126.64, 126.74, 127.41, 128.05, 128.23, 128.50, 129.28, 133.86, 142.87, 144.91 (aromatic C), 171.17 (C = O); Anal. Calcd. for $C_{33}H_{37}NO_2$ (479.66): C 82.63, H 7.78, N 2.92; found: C 82.41, H 7.95, N 2.91.

Yield: 376 mg (31%) of **9d**; m.p. (ethanol) = 123 °C; IR = 2933, 1720, 1600, 1496, 1453, 1345, 1264, 1158, 997, 697; UV (MeOH): $\lambda = 209$, 259; ^{1}H NMR ($CDCl_3$) $\delta = 1.47$–1.54 (m, 2H, CH_2), 1.62–1.70 (m, 4H, 2 CH_2), 1.74 (d, $J = 14.4$ Hz, 1H, 3-H), 1.86–1.95 (m, 2H, 5-H, 8-H), 1.99–2.09 (m, 2H, 3-H, 5-H), 2.11–2.19 (m, 1H, 8-H), 2.56–2.71 (m, 4H, $N(CH_2)_2$), 2.73 (d, $J = 4.6$ Hz, 1H, 1-H), 2.95 (br, t, $J = 9.2$ Hz, 1H, 6-H), 3.10 (br, t, $J = 9.8$ Hz, 1H, 7-H), 3.46, 3.52 (2d, $J = 15.4$ Hz, 2H, CH-C = O), 3.68 (s, 1H, CH(-C = O)$_2$), 5.32 (dd, $J = 8.7$, 4.6 Hz, 1H, 2-H), 6.90–7.37 (m, 20 aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.97$ (CH_2), 26.82 (2 CH_2), 31.77 (C-5), 32.20 (C-8), 33.90 (C-7), 34.36 (C-3), 38.57 (C-6), 39.74 (C-1), 46.87 ($N(CH_2)_2$), 48.68 (CH_2-C = O), 56.64 (C-4), 62.40 (*C*H(-C = O)$_2$), 74.19 (C-2), 125.23, 126.35, 126.47, 127.24, 127.35, 128.04, 128.47, 128.67, 129.56, 129.70, 131.57, 133.17, 142.69, 145.08 (aromatic C), 167.73 (COO), 201.17 (C = O); Anal. Calcd. for $C_{41}H_{43}NO_3 \cdot 0.3H_2O$ (603.20): C 81.64, H 7.29, N 2.32; found: C 81.61, H 7.32, N 2.23.

6.2.4.4. *(2SR,6RS,7RS)-(±)-4-dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl isonicotinate (**7a**)*.

643 mg of **2a** gave a residue which was recrystallised from ethanol. Yield: 405 mg (47%) of **7a**; m.p. = 143 °C; IR =1732, 1601, 1498, 1284, 1124, 995, 753, 699; UV (CH_2Cl_2): $\lambda = 270$, 230; ^{1}H NMR ($CDCl_3$) $\delta = 1.82$ (dd, $J = 14.7$, 2.5 Hz, 1H, 3-H), 1.94 (ddd, $J = 12.1$, 9.2, 2.6 Hz, 1H, 5-H), 2.03–2.14 (m, 2H, 5-H, 8-H), 2.24 (ddd, $J = 14.4$, 9.1, 3.2 Hz, 1H, 3-H), 2.36 (ddd, $J = 12.6$, 9.2, 2.6 Hz, 1H, 8-H), 2.40 (s, 6H, $N(CH_3)_2$), 2.99 (d, $J = 4.3$ Hz, 1H, 1-H), 3.11 (t, $J = 9.2$ Hz, 1H, 6-H), 3.29 (t, $J = 9.7$ Hz, 1H, 7-H), 5.50 (dd, $J = 8.9$, 4.6 Hz, 1H, 2-H), 6.95–7.43 (m, 12H, aromatic H), 8.49 (dd, $J = 6.4$ Hz, 2H, heteroaromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 31.05$ (C-5), 32.31 (C-8), 33.52 (C-7), 35.36 (C-3), 38.43 ($N(CH_3)_2$), 38.69 (C-6), 38.89 (C-1), 56.16 (C-4), 74.68 (C-2), 122.57, 125.24, 126.14, 126.53, 127.31, 128.16, 128.62, 136.87, 142.62, 144.57, 149.94 (aromatic C), 164.62 (C=O); Anal. Calcd. for $C_{28}H_{30}N_2O_2$ (426.55): C 78.84, H 7.09, N 6.57; found: C 78.72, H 7.18, N 6.60.

6.2.4.5. *(2SR,6RS,7RS)-(±)-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-yl isonicotinate (**7c**)*.

695 mg of **2c** gave a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 29:1 as eluent. Yield: 151 mg (16%) of **7c** as a colourless oil; IR = 3026, 2940, 1721, 1599, 1561, 1496, 1446, 1406, 1324, 1281, 1122, 756, 697; UV (CH_2Cl_2): $\lambda = 274$, 230; ^{1}H NMR ($CDCl_3$) $\delta = 1.78$–1.87 (m, 5H, 3-H, $(CH_2)_2$), 2.03 (ddd, $J = 12.9$, 9.1, 2.1 Hz, 1H, 5-H), 2.12–2.20 (m, 2H, 5-H, 8-H), 2.28–2.44 (m, 2H, 3-H, 8-H), 2.75–2.86 (m, 4H, $N(CH_2)_2$), 2.98 (d, $J = 4.3$ Hz, 1H, 1-H), 3.14 (t, $J = 9.1$ Hz, 1H, 6-H), 3.31 (t, $J = 9.9$ Hz, 1H, 7-H), 5.49 (dd, $J = 8.8$, 4.6 Hz, 1H, 2-H), 6.95–7.44 (m, 12H, aromatic H), 8.48 (d, $J = 6.2$ Hz, 2H, heteroaromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 23.56$ ($((CH_2)_2)$), 31.32 (C-5), 33.44 (C-7, C-8), 36.45 (C-3), 38.80 (C-6), 39.19 (C-1), 45.59 ($N(CH_2)_2$), 54.94 (C-4), 74.69 (C-2), 122.59, 125.22, 126.18, 126.51, 127.37, 128.15, 128.61, 136.90, 142.68, 144.63, 149.93 (aromatic C), 164.64 (C=O); Anal. Calcd. for $C_{30}H_{32}N_2O_2 \cdot H_2O$ (470.61): C 76.57, H 7.28, N 5.95; found: C 76.48, H 7.04, N 5.74.

6.2.4.6. *(2SR,6RS,7RS)-(±)-6,7-diphenyl-4-piperidinobicyclo[2.2.2]octan-2-yl isonicotinate (**7d**)*.

723 mg of **2d** gave a residue which was recrystallised from ethanol. Yield: 311 mg (33%) of **7d**; m.p. = 161 °C; IR = 2932, 1721, 1599, 1560, 1498, 1446, 1406, 1327, 1283, 1132, 763, 743, 698; UV (CH_2Cl_2): $\lambda = 230$, 269; ^{1}H NMR ($CDCl_3$) $\delta = 1.46$–1.53 (m, 2H, CH_2), 1.60–1.69 (m, 4H, 2 CH_2), 1.83 (dd, $J = 14.1$, 2.1 Hz, 1H, 3-H), 1.94 (ddd, $J = 12.3$, 9.6, 2.5 Hz, 1H, 5-H), 2.04–2.18 (m, 2H, 5-H, 8-H), 2.67 (ddd, $J = 14.4$, 9.0, 3.1 Hz, 1H, 3-H), 2.41 (ddd, $J = 12.4$, 9.6, 3.1 Hz, 1H, 8-H), 2.60–2.76 (m, 4H, $N(CH_2)_2$), 3.00 (d, $J = 4.6$ Hz, 1H, 1-H), 3.08 (t, $J = 9.6$ Hz, 1H, 6-H), 3.27 (t, $J = 9.6$ Hz, 1H, 7-H), 5.49 (dd, $J = 9.0$, 4.6 Hz, 1H, 2-H), 6.95–7.43 (m, 12H, aromatic H), 8.48 (d, $J = 5.8$ Hz, 2H, heteroaromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.93$ (CH_2), 26.80 (2 CH_2), 31.18 (C-5), 33.24 (C-8), 33.59 (C-7), 35.83 (C-3), 38.67 (C-6), 38.84 (C-1), 46.89 ($N(CH_2.)_2$), 56.75 (C-4), 74.77 (C-2), 122.59, 125.21, 126.17, 126.47, 127.32, 128.13, 128.60, 136.94, 142.74, 144.74, 149.93 (aromatic C), 164.65 (C=O); Anal. Calcd. for $C_{31}H_{34}N_2O_2 \cdot 0.25H_2O$ (471.13): C 79.03, H 7.38, N 5.95; found: C 79.07, H 7.59, N 5.96.

6.2.5. *General procedure for the syntheses of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl nicotinates (**6a**, **c**, **d**)*

The bicyclic alcohols **2a**, **c**, **d** were dissolved in dry CH_2Cl_2. DCC, nicotinic acid and 4-DMAP were added and the solution stirred vigorously at room temperature for 2 days. The formed precipitate was filtered off and the filtrate was washed five times with 2 N NaOH and five times with water, dried over sodium sulphate and filtered. The solvent was evaporated in vacuo and the residue purified.

6.2.5.1. *(2SR,6RS,7RS)-(±)-4-dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl nicotinate (**6a**)*.

800 mg (2.5 mmol) of **2a** in 45 ml of dry CH_2Cl_2 gave with 646 mg (5.2 mmol) nicotinic acid, 1.3 g (6.3 mmol) DCC and 373 mg (3.1 mmol) 4-DMAP a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 8:2 as eluent. Yield: 800 mg (75%) of **6a** as a colourless resin; m.p. (ethanol) = 154 °C; IR = 2946, 2864, 2824, 2779, 1714, 1587, 1496, 1445, 1420, 1292, 1196, 1127, 1042, 1024, 744, 698; UV (CH_2Cl_2): $\lambda = 230$, 262; ^{1}H NMR ($CDCl_3$) $\delta = 1.84$ (d, $J = 14.3$ Hz, 1H, 3-H), 1.94 (ddd, $J = 12.0$, 9.8, 2.2 Hz, 1H, 5-H), 2.06–2.15 (m, 2H, 5-H, 8-H),

2.23 (ddd, J = 14.1, 9.1, 3.1 Hz, 1H, 3-H), 2.34 (ddd, J = 12.5, 9.4, 3.1 Hz, 1H, 8-H), 2.41 (s, 6H, $N(CH_3)_2$), 3.01 (d, J = 4.4 Hz, 1H, 1-H), 3.11 (br, t, J = 9.4 Hz, 1H, 6-H), 3.28 (br, t, J = 9.8 Hz, 1H, 7-H), 5.50 (dd, J = 8.9, 4.4 Hz, 1H, 2-H), 6.89–7.44 (m, 12 aromatic H), 8.51 (d, J = 1.8 Hz, 1H, aromatic H), 8.60 (dd, J = 5.0, 1.6 Hz, 1H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.13 (C-5), 32.14 (C-8), 33.48 (C-7), 35.23 (C-3), 38.39 ($N(CH_3)_2$), 38.66 (C-6), 39.01 (C-1), 56.15 (C-4), 74.22 (C-2), 122.58, 125.11, 125.59, 126.07, 126.45, 127.29, 128.02, 128.56, 136.69, 142.65, 144.39, 150.60, 152.74 (aromatic C), 164.70 (COO); Anal. Calcd. for $C_{28}H_{30}N_2O_2$ (426.55): C 78.84, H 7.09, N 6.57; found: C 78.63, H 7.36, N 6.49; HRMS (EI+): calcd. ($C_{28}H_{30}N_2O_2$): 426.23073; found: 426.22851.

*6.2.5.2. (2SR,6RS,7RS)-(±)-6,7-diphenyl-4-pyrrolidinobicyclo [2.2.2]octan-2-yl nicotinate (**6c**).* 685 mg (2.0 mmol) of **2c** in 45 ml of dry CH_2Cl_2 gave with 464 mg (3.8 mmol) nicotinic acid, 1.07 g (5.2 mmol) of DCC and 307 mg (2.5 mmol) of 4-DMAP a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 8:2 as eluent. Yield: 365 mg (70%) of **6c** as a colourless resin. IR = 2959, 1717, 1590, 1497, 1283, 1112, 1023, 743, 698; UV (CH_2Cl_2) λ = 231, 263, 335; ^{1}H NMR ($CDCl_3$) δ = 1.82–1.88 (m, 5H, 3-H, $(CH_2)_2$), 2.02 (ddd, J = 11.8, 9.9, 2.0 Hz, 1H, 5-H), 2.10–2.22 (m, 2H, 5-H, 8-H), 2.31 (ddd, J = 14.2, 9.0, 2.9 Hz, 1H, 3-H), 2.37 (ddd, J = 12.4, 9.5, 2.9 Hz, 1H, 8-H), 2.76–2.85 (m, 4H, $N(CH_2)_2$), 2.99 (d, J = 4.5 Hz, 1H, 1-H), 3.14 (br, t, J = 9.3 Hz, 1H, 6-H), 3.30 (br, t, J = 9.7 Hz, 1H, 7-H), 5.50 (dd, J = 9.0, 4.5 Hz, 1H, 2-H), 6.89–7.44 (m, 12 aromatic H), 8.50 (dd, J = 1.8, 0.8 Hz, 1H, aromatic H), 8.59 (dd, J = 4.7, 0.8 Hz, 1H, aromatic H); ^{13}C NMR ($CDCl_3$) δ = 23.52 ($(CH_2)_2$), 31.43 (C-5), 33.29 (C-8), 33.41 (C-7), 36.30 (C-3), 38.77 (C-6), 39.31 (C-1), 45.53 ($N(CH_2)_2$), 54.88 (C-4), 74.24 (C-2), 122.56, 125.07, 125.60, 126.11, 126.42, 127.34, 128.00, 128.53, 136.69, 142.72, 144.46, 150.61, 152.72 (aromatic C), 164.71 (COO); Anal. Calcd. for $C_{30}H_{32}N_2O_2{\cdot}0.7H_2O$ (465.21): C 77.46, H 7.24, N 6.02; found: C 77.27, H 7.19, N 5.96; HRMS (EI+): calcd. ($C_{30}H_{32}N_2O_2$): 452.24638; found: 452.24832.

*6.2.5.3. (2SR,6RS,7RS)-(±)-6,7-diphenyl-4-piperidinobicyclo [2.2.2]octan-2-yl nicotinate (**6d**).* 711 mg (2.0 mmol) of **2c** in 45 ml of dry CH_2Cl_2 gave with 267 mg (2.2 mmol) nicotinic acid, 1.04 g (5.0 mmol) of DCC and 282 mg (2.2 mmol) of 4-DMAP a residue which was purified using CC over silica gel and CH_2Cl_2/MeOH = 8:2 as eluent. Yield: 570 mg (61%) of **6d** as a colourless resin. m.p. (ethanol) = 169 °C; IR = 2933, 1718, 1591, 1497, 1291, 1126, 1112, 1025, 742, 701; UV (CH_2Cl_2) λ = 230, 262; ^{1}H NMR ($CDCl_3$) δ = 1.44–1.54 (m, 2H, CH_2), 1.60–1.72 (m, 4H, $CH_2)_2$ 1.85 (d, J = 14.6 Hz, 1H, 3-H), 1.95 (dd, J = 12.0, 10.0 Hz, 1H, 5-H), 2.07–2.17 (m, 2H, 5-H, 8-H), 2.26 (ddd, J = 14.6, 8.6, 2.6 Hz, 1H, 3-H), 2.39 (ddd, J = 12.0, 9.6, 2.6 Hz, 1H, 8-H), 2.60–2.76 (m, 4H, $N(CH_2)_2$), 3.01 (d, J = 4.3 Hz, 1H, 1-H), 3.09 (br, t, J = 9.4 Hz, 1H, 6-H), 3.27 (br, t, J = 9.9 Hz, 1H, 7-H), 5.50 (dd, J = 8.6, 4.4 Hz, 1H, 2-H), 6.90–7.44 (m, 12 aromatic H), 8.50 (s, 1H, aromatic H), 8.60 (d, J = 4.0 Hz, 1H, aromatic H); ^{13}C NMR ($CDCl_3$): δ = 24.92 (CH_2), 26.78 ($(CH_2)_2$), 31.27 (C-5), 33.10 (C-8), 33.56 (C-7), 35.70 (C-3), 38.66 (C-6), 38.98 (C-1), 46.86 ($N(CH_2)_2$), 56.73 (C-4), 74.32 (C-2), 122.57, 125.09, 126.10, 126.41, 127.32, 128.01, 128.54, 136.70, 142.79, 144.58, 150.64, 152.75 (aromatic C), 164.75 (COO); Anal. Calcd. for $C_{31}H_{34}N_2O_2$ (466.62): C 79.79, H 7.34, N 6.00; found: C 79.63, H 7.46, N 6.01; HRMS (EI+): calcd. ($C_{31}H_{34}N_2O_2$): 466.26203; found: 466.26620.

*6.2.6. General procedure for the syntheses of (2SR,6RS,7RS)-(±)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl ferrocenyl carboxylates (**8a, d**)*

2a or **2d**, ferrocenecarboxylic acid, DCC and 4-DMAP were dissolved in dry CH_2Cl_2 stirred at room temperature and filtered. CH_2Cl_2 was added and the solution was shaken five times with 2 N NaOH, three times with water, dried over Na_2SO_4, filtered and the solvent evaporated in vacuo. The excess of ferrocenecarboxylic acid was removed by CC over basic Al_2O_3 using CH_2Cl_2 as eluent. The residue was purified using CC over silica gel and CH_2Cl_2/MeOH = 9:1 as eluent.

*6.2.6.1. (2SR,6RS,7RS)-(±)-4-dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-yl ferrocenyl carboxylate (**8a**).* 527 mg (1.6 mmol) of **2a**, 415 mg (1.8 mmol) of ferrocenecarboxylic acid, 858 mg (4.2 mmol) of DCC and 236 mg (1.9 mmol) of 4-DMAP in 40 ml of dry CH_2Cl_2 gave after 20 days of stirring 300 mg (35%) of **8a** as a red resin which crystallised from ethanol in form of red needles. m.p. = 102 °C; IR = 2944, 1702, 1600, 1497, 1459, 1372, 1276, 1142, 1106, 1028, 744, 699; UV (CH_2Cl_2) λ = 231, 260, 310; ^{1}H NMR ($CDCl_3$) δ = 1.74 (d, J = 14.0 Hz, 1H, 3-H), 1.95 (ddd, J = 12.1, 9.8, 2.3 Hz, 1H, 5-H), 2.06 (ddd, J = 12.1, 10.2, 2.0 Hz, 1H, 8-H), 2.13 (ddd, J = 12.0, 10.4, 1.6 Hz, 1H, 5-H), 2.25 (ddd, J = 14.0, 8.6, 3.2 Hz, 1H, 3-H), 2.34 (ddd, J = 12.2, 9.3, 3.2 Hz, 1H, 8-H), 2.40 (s, 6H, $N(CH_3)_2$), 2.82 (d, J = 4.3 Hz, 1H, 1-H), 3.10 (t, J = 9.4 Hz, 1H, 6-H), 3.30 (t, J = 9.8 Hz, 1H, 7-H), 3.91 (t, J = 1.1 Hz, 1H, aromatic H), 4.05–4.21 (m, 8H, aromatic H), 5.38 (dd, J = 8.6, 4.5 Hz, 1H, 2-H), 7.13–7.42 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) δ = 31.46 (C-5), 32.78 (C-8), 34.00 (C-7), 35.66 (C-3), 38.36 ($N(CH_3)_2$), 39.00 (C-6), 39.21 (C-1), 56.53 (C-4), 69.47, 69.90, 70.12, 70.89, 71.02 (aromatic C), 72.93 (C-2), 125.25, 126.40, 126.42, 127.32, 128.09, 128.57, 142.80, 145.09 (aromatic C), 171.33 (COO); Anal. Calcd. for $C_{33}H_{35}NO_2Fe$ (533.49): C 74.30, H 6.61, N 2.63; found: C 74.11, H 6.70, N 2.63; HRMS (EI+): calcd. ($C_{33}H_{35}NO_2Fe$): 533.20173; found: 533.20029.

*6.2.6.2. (2SR,6RS,7RS)-(±)-6,7-diphenyl-4-piperidinobicyclo [2.2.2]octan-2-yl ferrocenyl carboxylate (**8d**).* 711 mg (2.0 mmol) of **2d**, 700 mg (3.0 mmol) of ferrocenecarboxylic acid, 1.04 g (5.0 mmol) of DCC and 282 mg (2.3 mmol) of 4-DMAP in 47 ml of dry CH_2Cl_2 gave after 14 days of stirring a residue which crystallised from ethanol giving 750 mg (65%) of **8d** as red needles. m.p. = 189 °C; IR = 2941, 1709, 1600, 1496, 1459, 1371, 1276, 1145, 1107, 1029, 820, 751, 743, 702; UV (CH_2Cl_2) λ = 231, 260, 309; ^{1}H NMR ($CDCl_3$) δ = 1.45–1.48 (m, 2H, CH_2), 1.58–1.70 (m, 4H, $2CH_2$), 1.75

(d, $J = 14.3$ Hz, 1H, 3-H), 1.94 (br, t, $J = 10.9$ Hz, 1H, 5-H), 2.07 (br, t, $J = 11.2$ Hz, 1H, 8-H), 2.15 (br, t, $J = 11.1$ Hz, 1H, 5-H), 2.24 (ddd, $J = 14.5$, 8.7, 3.9 Hz, 1H, 3-H), 2.35 (ddd, $J = 12.1$, 9.4, 2.7 Hz, 1H, 8-H), 2.60–2.74 (m, 4H, $N(CH_2)_2$), 2.83 (d, $J = 4.4$ Hz, 1H, 1-H), 3.07 (br, t, $J = 9.4$ Hz, 1H, 6-H), 3.28 (br, t, $J = 9.9$ Hz, 1H, 7-H), 3.95 (s, 1H, aromatic H), 4.07–4.17 (m, 8H, aromatic H), 5.38 (dd, $J = 8.5$, 4.6 Hz, 1H, 2-H), 7.11–7.43 (m, 10 aromatic H); ^{13}C NMR ($CDCl_3$) $\delta = 24.96$ (CH_2), 26.84 ($(CH_2)_2$), 31.77 (C-5), 33.75 (C-8), 34.07 (C-7), 35.91 (C-3), 39.04 (C-6), 39.28 (C-1), 46.86 ($N(CH_2)_2$), 56.82 (C-4), 69.50, 69.92, 70.16, 70.87, 70.88, 71.13 (aromatic C), 73.14 (C-2), 125.19, 126.36, 126.42, 127.38, 128.07, 128.54, 143.01, 145.38 (aromatic C), 171.39 (COO); Anal. Calcd. for $C_{36}H_{39}NO_2Fe$ (573.55): C 75.39, H 6.85, N 2.44; found: C 75.12, H 7.13, N 2.39; HRMS (EI+): calcd. ($C_{36}H_{39}NO_2Fe$): 573.23304; found: 573.23209.

6.3. Biological tests

A detailed description of the determination of antiplasmodial and antitrypanosomal activity and the cytotoxicity of compounds is reported [20].

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