Synthesis and Antimalarial Activity of Febrifugine Derivatives

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The regioisomers (2a,b) of the piperidine ring of febrifugine (1a) and isofebrifugine (1b) were synthesized from 4-allyl-3-piperidone (5). Reduction of 5 afforded a mixture of the *trans* and *cis* alcohols (6a,b) without diastereoselectivity; this result differentiated it from the reduction of 2-allyl-3-piperidone (14). The antimalarial activity of 2a,b and related compounds was tested.

Key words antimalarial activity; febrifugine; synthesis; structure–activity relationship

Febrifugine (**1a**) is an antimalarial agent which was isolated from *Dichroa febrifuga* or *Hydrangea umbellata* with isofebrifugine (**1b**).[1)] Recently Kobayashi *et al.* corrected the error in the absolute structures of **1a**,**b**, as shown in Fig. 1, by achieving the asymmetric syntheses of all the stereoisomers.[2)] We have developed a new synthetic method for **1a**,**b**,[3)] and our interest next focused on the structure–activity relationship (SAR) of **1a**,**b**. The difficulty in the purification or antimalarial screening of **1a**,**b** is isomerization[4)] between **1a** and **1b**, which occurs *via* a reversible Michael reaction. We thought that a derivative in which isomerization did not occur might be a more potent compound. Although much is reported on the SAR of substituents[5)] on the 4(3*H*)-quinazolinone ring, the only known modification of the piperidine ring involves regioisomers of the hydroxy group.[6)] In this report, we describe the synthesis and antimalarial activity of derivatives (**2a**,**b**) that are regioisomers of the nitrogen atom on the piperidine ring of **1a**,**b**.

We prepared **2a**,**b** from 1-benzyl-3-hydroxypyridinium chloride (**3**) in seven isolated steps by modifying our method for synthesizing **1a**,**b** (Chart 1). The successive *O*-allylation, reduction,[7)] and replacement[8)] of the benzyloxycarbonyl (Cbz) group from **3** afforded benzyl 1-(3-allyloxy-1,2,5,6-tetrahydropyridine)carboxylate (**4**) in 47% yield. The Claisen rearrangement of **4** by heating at 140 °C in xylene proceeded smoothly to give benzyl 4-allyl-3-oxo-1-piperidinecarboxylate (**5**) in 99% yield. Reduction of **5** with sodium borohydride ($NaBH_4$) afforded *trans* (**6a**) and *cis* (**6b**) benzyl 4-allyl-3-hydroxy-1-piperidinecarboxylate as an inseparable mixture.

Purification and structural determination of the inseparable mixture of **6a** and **6b** were achieved as shown in Chart 2. Although *trans* (**12a**) and *cis* (**12b**) benzoate produced from **6a**,**b** were separated by column chromatography, the existence of rotomers[9)] in the ^{1}H-NMR spectrum made the structural analysis of **12a**,**b** difficult. Hydrogenolysis of **12a**,**b** produced *trans* (**13a**) or *cis* (**13b**) 4-propyl-3-piperidinyl benzoate, respectively. In the ^{1}H-NMR spectrum, the proton at the 3 position on the piperidine ring of **13a** was observed at 4.73 ppm with a coupling constant of 4.0 and 9.5 Hz. The proton on **13b**, on the other hand, was observed at 5.10 ppm as a single broad peak. Pure **6a** and **6b** were prepared by hydrolysis of **12a** and **12b** and led to **7a** and **7b**, respectively.

We previously found that reduction of benzyl 2-allyl-3-oxo-1-piperidinecarboxylate (**14**) with $NaBH_4$ at room tem-

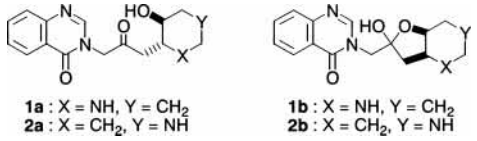

Fig. 1. Febrifugine Derivatives

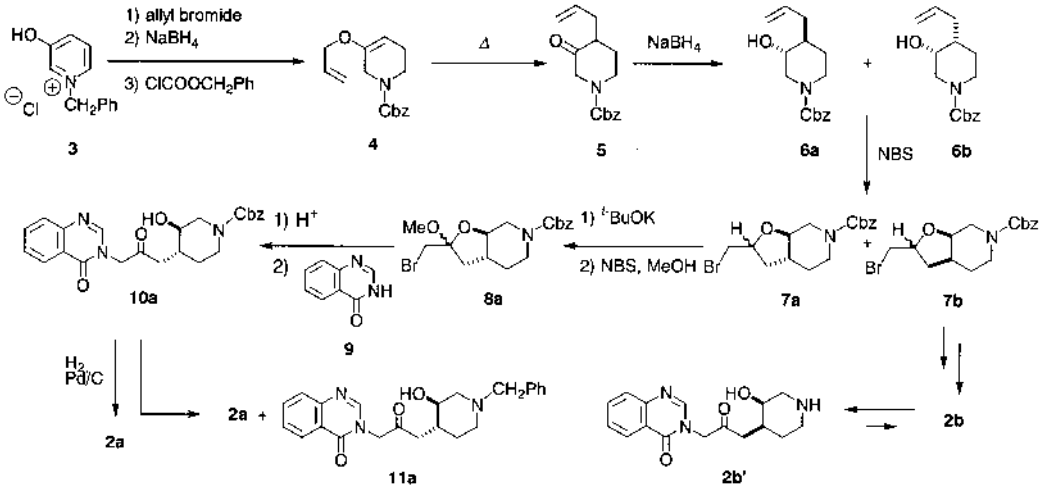

Chart 1

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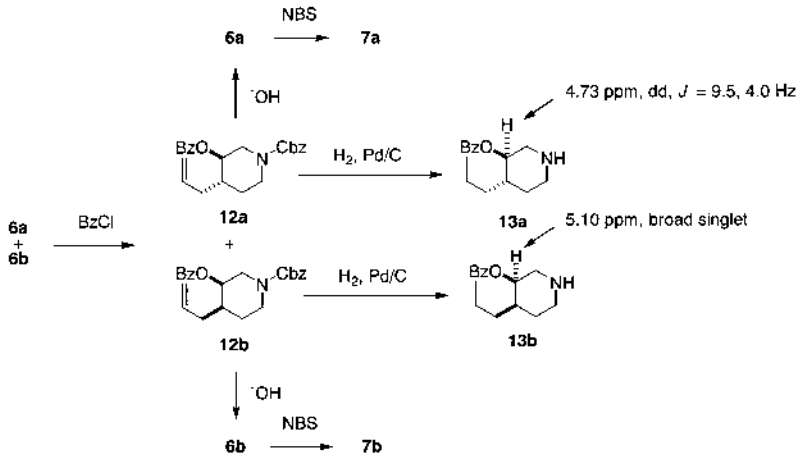
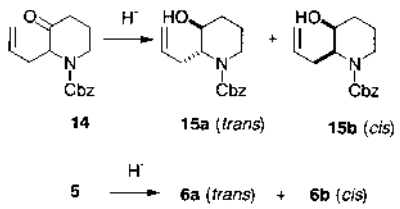


Chart 2

Table 1. Reduction of **5** and **14** with Boron Hydride



Ketone	Reducing agent	Products	
		Yield (%)[a]	*trans* : *cis*[b]
14	$NaBH_4$	100	1 : 499
14	$LiBEt_3H$	87	1 : 77
14	$LiB^{i-}Bu_3H$	79	1 : 39
5	$NaBH_4$	97	2 : 1
5	$LiBEt_3H$	84	1 : 2
5	$LiB^{i-}Bu_3H$	29	1 : 71

a) Yield of *trans* and *cis* compound. *b*) Determined from HPLC.

perature gave *cis*-benzyl 2-allyl-3-hydroxy-1-piperidinecarboxylate (**15b**) in high yield as the sole product, without involving the diastereomeric isomer.[3a,b] As an additional experiment, we attempted reduction of **14** with super hydride® ($LiBEt_3H$) or L-selectride® ($LiB^{i-}Bu_3H$) (Table 1). The high *cis* selectivity in the reduction was maintained, although it decreased in the order $NaBH_4$, $LiBEt_3H$, $LiB^{i-}Bu_3H$. In contrast, reduction of the 4-allyl derivative (**5**) with $NaBH_4$ afforded *trans* selectivity to generate a mixture of **6a** and **6b**.

We predicted *cis* selectivity in the reduction of **14** with hydride from a conformational analysis of **14** using molecular calculations.[3a,b] In order to confirm our prediction, we calculated[10] the stable conformers of **16** and **17**, which were selected as convenient models of **5** and **14** (Fig. 2). The difference in the heat of formation (H.F.) between the minimized conformer (**16b**) having the allyl group at the axial position and the optimized conformer (**16a**) having the allyl group at the equatorial position was about 3.0 kcal/mol; between **17**b and **17a** it was −0.6 kcal/mol. Considering the generation of *cis* alcohol from **16b** or **17b**, our prediction is consistent with experimental determinations of selectivity.

The reaction of a mixture of **6a**,**b** with *N*-bromosuccinimide (NBS) gave a mixture of separable intramolecular bromoetherified products (**7a**,**b**). The HPLC data for **7a** indicated that this was a 3.6 : 1 mixture of the diastereomeric isomers. The methoxy compound (**8a**) could be prepared in high yield (83%) as a 1 : 2 mixture of the diastereomeric isomers by dehydrobromination using potassium *tert*-butoxide and bromoetherification using NBS and methanol. Deacetalization of **8a** followed by a coupling reaction with 4(3*H*)-quinazolinone (**9**) afforded **10a** in 81% yield. The hydrogenolysis of **10a** gave **2a** in 37% yield as a crystalline solid. To increase the yield of hydrogenolysis, we treated **10a** with acid in an unsuccessful attempt to give the *N*-benzylated compound (**11a**) of **2a** along with **2a**. Similarly, the diastereomer (**2b**) of **2a** was synthesized from **7b**. Contrary to our expectations, the ^{13}C-NMR spectrum made it clear that **2b** was present in the keto form, not the hemi-acetal form (**2b′** in Chart 1).

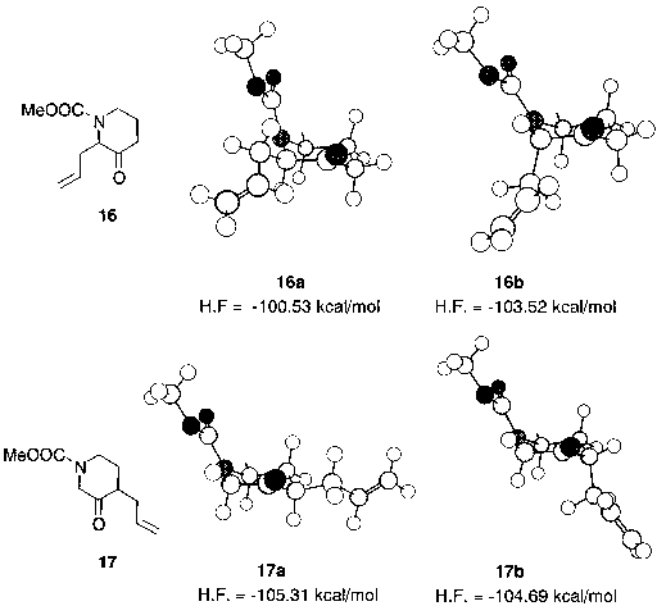


Fig. 2. Minimized and Optimized Conformers of **16** and **17**

The *in vitro* antimalarial activities of compounds **1a**,**b**, **2a**,**b**, **10a**,**b**, and **11a** against *Plasmodium falciparum* were

Table 2. Antimalarial Activity and Toxic Selectivity

Compound	FM3A EC_{50}, μM	*P. falciparum* EC_{50}, μM	Toxic selectivity
dl-Febrifugine (**1a**)	0.17	0.00070	243
2a	–	–[a)]	–
10a	33	0.52	63
11a	82	2.6	32
dl-Isofebrifugine (**1b**)	0.94	0.012	78
2b	–	–[a)]	–
10b	72	4.4	16
Quinine	100	0.11	909
Chloroquine	32	0.018	1778
Pyrimethamine	0.12	0.0010	120
Artemisinin	10	0.0079	1266

a) >10 μM.

tested (Table 2).[11] Both **2a**,**b** regioisomers of the nitrogen atom in the piperidine ring of **1a**,**b** were inactive, while the Cbz derivatives of **2a**,**b** exhibited very weak activity compared to **1a**,**b**.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ^{1}H- and ^{13}C-NMR spectra were run on a JASCO MY 60FT or a Varian VXR-500 spectrometer. Analytical HPLC was performed with a Shimadzu SPD-6A instrument on a silica gel column, Chemcosorb 5Si-U (Chemco). Merck Silica gel 60 (230—400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography.

Benzyl 1-(3-Allyloxy-1,2,5,6-tetrahydropyridine)carboxylate (4) NaH (4.40 g, 0.11 mol as 60% dispersion in mineral oil) was added portionwise to an absolute MeOH (50 ml). To the solution, 1-benzyl-3-hydroxypyridinium chloride (22.17 g, 0.10 mol) and allyl bromide (9.6 ml, 0.11 mol) were added. After reflux for 4 h, the mixture was cooled and $NaBH_4$ (3.78 g, 0.10 mol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then was acidified with aqueous 10% HCl solution and basified with aqueous saturated $KHCO_3$ solution. The mixture was poured into water and extracted with AcOEt. The combined organic layers were washed with brine, dried, and then the solvent was removed. Benzyl chloroformate (28.5 ml, 0.20 mol) was added dropwise to a solution of the residue in dry tetrahydrofuran (THF) (50 ml) at 0 °C. The mixture was stirred at room temperature for 2.5 h and the solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 15) to give **4** (12.83 g, 47%) as colorless needles. This compound was identified by spectral comparison with authentic samples obtained by our previous method.[3a,b)]

Benzyl 4-Allyl-3-oxo-1-piperidinecarboxylate (5) A solution of **4** (10.93 g, 40.0 mmol) in xylene (50 ml) was stirred at reflux for 2 h and the solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 5) to give **5** (10.80 g, 99%) as light yellow oil. This compound was identified by spectral comparison with authentic samples obtained by our previous method.[3a,b)]

Reduction of 5 with $NaBH_4$ $NaBH_4$ (0.51 g, 13.5 mmol) was added portionwise to a solution of **5** (7.39 g, 27.0 mmol) in abs. MeOH (50 ml) at 0 °C. The mixture was stirred at the same temperature for 15 min and poured into aqueous 10% HCl solution, then was extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed to give an almost pure mixture of *trans* (**6a**) and *cis* (**6b**) benzyl 4-allyl-3-hydroxy-1-piperidinecarboxylate (7.25 g, 97%) as colorless oil. HPLC conditions: column, Chemcosorb 5Si-U; temperature, room temperature; solvent, AcOEt : hexane = 1 : 5; flow rate, 1.0 ml/min; wavelength, 254 nm; retention time, t_R = 16.2 and 18.7 min (31 : 63). IR (neat) cm^{-1}: 3440, 1700, 1680, 1240. ^{1}H-NMR (500 MHz, $CDCl_3$, rotomers) δ: 1.10—1.20 (1/2H, m), 1.43—1.51 (1H, m), 1.52—1.58 (1/2H, m), 1.75 (1H, br d, J = 13.5 Hz), 1.90—2.04 (1H, m), 2.18—2.24 (1H, m), 2.50 (1H, br s), 2.60—2.68 (1H, m), 2.76 (1H, br s), 3.30—3.38 (1H, m), 4.00—4.13 (1H, m), 4.14—4.30 (1H, m), 5.02—5.12 (4H, m), 5.74—5.84 (1H, m), 7.28—7.36 (5H, m). FAB-MS *m/z*: 276 $(M+1)^+$.

Reduction of 5 with $LiBEt_3H$ $LiBEt_3H$ (1.0 M solution in THF, 3.0 ml, 3.0 mmol) was added dropwise to a solution of **5** (0.818 g, 3.0 mmol) in dry THF (5 ml) at 0 °C. The mixture was stirred at the same temperature for 1 h and quenching of the reaction was performed by the methods described above to give an almost pure mixture of **6a** and **6b** (0.694 g, 84%) as colorless oil.

Reduction of 5 with $LiB^{i-}Bu_3H$ $LiB^{i-}Bu_3H$ (1.0 M solution in THF, 1.0 ml, 1.0 mmol) was added dropwise to a solution of **5** (0.274 g, 1.0 mmol) in dry THF (1 ml) at 0 °C. The mixture was stirred at the same temperature for 4 h and quenching of the reaction was performed by the method described above to give an almost pure mixture of **6a** and **6b** (0.080 g, 29%) as colorless oil.

Reduction of 14 with $NaBH_4$ $NaBH_4$ (0.07 g, 1.85 mmol) was added portionwise to a solution of **14**[3a,b)] (1.00 g, 3.66 mmol) in MeOH (10 ml) at 0 °C. The mixture was stirred at the same temperature for 1 h and poured into aqueous 10% HCl solution, then extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed to give an almost pure mixture of *trans* (**15a**) and *cis* (**15b**) benzyl 2-allyl-3-hydroxy-1-piperidinecarboxylate (1.00 g, 100%) as colorless oil. HPLC conditions: column, Chiralcel OJ; temperature, room temperature; solvent, isopropyl alcohol : hexane = 3 : 37; flow rate, 1.0 ml/min; wavelength, 254 nm; retention time, t_R = 5.6, 6.2, and 8.1 min (1 : 499). The compounds were identified by spectral comparison with authentic samples obtained by our previous method.

Reduction of 14 with $LiBEt_3H$ $LiBEt_3H$ (1.0 M solution in THF, 7.32 ml, 7.32 mmol) was added dropwise to a solution of **14**[3a,b)] (1.00 g, 3.66 mmol) in dry THF (5 ml) at 0 °C. The mixture was stirred at the same temperature for 2 h and quenching of the reaction was performed by the method described above to give an almost pure mixture of **15a** and **15b** (0.88 g, 87%) as colorless oil.

Reduction of 14 with $LiB^{i-}Bu_3H$ $LiB^{i-}Bu_3H$ (1.0 M solution in THF, 10.98 ml, 10.98 mmol) was added dropwise to a solution of **14** (1.00 g, 3.66 mmol) in dry THF (5 ml) at 0 °C. The mixture was stirred at the same temperature for 2 h and quenching of the reaction was performed by the method described above to give an almost pure mixture of **15a** and **15b** (0.79 g, 79%) as colorless oil.

***trans*- (12a) and *cis*- (12b) Benzyl 4-Allyl-3-benzoyloxy-1-piperidinecarboxylate** Benzoyl chloride (1.95 ml, 16.8 mmol) was added dropwise at 0 °C to a mixture of **6a** and **6b** (4.13 g, 15.0 mmol), 4-(dimethylamino)pyridine (DMAP) (1.84 g, 15.1 mmol), and Et_3N (2.3 ml, 16.5 mmol) in CH_2Cl_2 (25 ml). The mixture was stirred at room temperature for 2.5 h and poured into aqueous 10% HCl solution, extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 15) to give *trans* (**12a**, 61%) and *cis* (**12b**, 34%).

12a: Colorless oil. IR (neat) cm^{-1}: 1720, 1700, 1270. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.50—2.40 (5H, m), 2.80—3.24 (2H, m), 3.82—4.39 (2H, m), 4.69—5.20 (3H, m), 5.13 (2H, s), 5.46—6.20 (1H, m), 7.25—7.55 (3H, m), 7.33 (5H, s), 7.96—8.13 (2H, m). FAB-MS *m/z*: 380 $(M+1)^+$. FAB-HR-MS: *m/z*: 380.1862 $(M+1)^+$ (Calcd $C_{23}H_{26}NO_4$: 380.1862).

12b: Colorless oil. IR (neat) cm^{-1}: 1700, 1270, 1230. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.40—2.30 (5H, m), 2.70—3.10 (2H, m), 4.20—4.50 (2H, m), 4.50—5.25 (3H, m), 5.10 (2H, s), 5.30—6.00 (1H, m), 7.00—7.60 (8H, m), 7.90—8.07 (2H, m). FAB-MS *m/z*: 380 $(M+1)^+$. FAB-HR-MS *m/z*: 380.1864 $(M+1)^+$ (Calcd for $C_{23}H_{26}NO_4$: 380.1862).

***trans*-Benzyl 4-Allyl-3-hydroxy-1-piperidinecarboxylate (6a)** A mixture of **12a** (1.60 g, 4.22 mmol) and NaOH (0.451 g, 11.3 mmol) in MeOH (55 ml) was stirred at room temperature for 1.5 h. The mixture was concentrated, poured into water, and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and then solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 7) to give **6a** (1.16 g, 100%) as colorless oil. IR (neat) cm^{-1}: 3420, 1680, 1240, 1220. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.20—2.20 (6H, m), 2.20—2.90 (2H, m), 3.10—3.50 (1H, m), 3.80—4.40 (2H, m), 4.90—5.20 (2H, m), 5.11 (2H, s), 5.55—6.10 (1H, m), 7.34 (5H, s). FAB-MS *m/z*: 276 $(M+1)^+$. FAB-HR-MS *m/z*: 276.1610 $(M+1)^+$ (Calcd for $C_{16}H_{22}NO_3$: 276.1600).

***cis*-Benzyl 4-Allyl-3-hydroxy-1-piperidinecarboxylate (6b)** A mixture of **12b** (0.708 g, 1.87 mmol) and NaOH (0.340 g, 8.5 mmol) in MeOH (20 ml) was stirred at room temperature for 21.5 h. The mixture was concentrated, and poured into water, and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and then solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 4) to give **6b** (0.48 g, 93%) as colorless oil. IR (neat) cm^{-1}: 3440, 1680, 1240. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.45—1.57 (3H, m), 1.90—2.25 (3H, m), 2.55—3.03 (2H, m), 3.70—4.45 (3H, m), 4.92—5.25 (2H, m), 5.15 (2H, s), 5.52—

6.07 (1H, m), 7.35 (5H, s). FAB-MS *m/z*: 276 $(M+1)^+$. FAB-HR-MS *m/z*: 276.1584 $(M+1)^+$ (Calcd for $C_{16}H_{22}NO_3$: 276.1600).

***trans*-4-Propyl-3-piperidinyl Benzoate (13a)** A mixture of **12a** (0.380 g, 1.00 mmol) and 10% Pd/C (78 mg) in MeOH (5 ml) was stirred at room temperature for 9 h under a balloon of H_2 gas. The mixture was filtered and the solvent was removed to give almost pure **13a** (0.244 g, 99%) as colorless oil. IR (neat) cm^{-1}: 3320, 1720, 1270. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7.5 Hz), 1.15—1.29 (3H, m), 1.39—1.46 (1H, m), 1.53—15.9 (1H, m), 1.71—1.79 (1H, m), 1.77 (1H, br s), 1.89—1.95 (1H, m), 2.55—2.64 (2H, m), 3.03 (1H, dt, J=12.7, 4.0 Hz), 3.33 (1H, dd, J=12.3, 4.0 Hz), 4.73 (1H, td, J=9.5, 4.0 Hz), 7.43—7.46 (2H, m), 7.54—7.58 (1H, m), 8.04—8.06 (2H, m). FAB-MS *m/z*: 248 $(M+1)^+$. FAB-HR-MS *m/z*: 248.1637 $(M+1)^+$ (Calcd for $C_{15}H_{22}NO_2$: 248.1651).

***cis*-4-Propyl-3-piperidinyl Benzoate (13b)** A mixture of **12b** (0.192 g, 0.51 mmol) and 10% Pd/C (51 mg) in MeOH (2.5 ml) was stirred at room temperature for 20 h under a balloon of H_2 gas. The mixture was filtered and the solvent was removed to give almost pure **13b** (0.119 g, 95%) as colorless oil. IR (neat) cm^{-1}: 3320, 1720, 1270. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, J=7.5 Hz), 1.22—1.39 (3H, m), 1.57—1.62 (2H, m), 1.72—1.76 (2H, m), 1.88 (1H, br s), 2.66—2.72 (1H, m), 2.82 (1H, dd, J=14.3, 2.0 Hz), 3.15 (1H, br d, J=13.5 Hz), 3.29 (1H, dt, J=14.3, 1.3 Hz), 5.10 (1H, br s), 7.43—7.48 (2H, m), 7.56—7.59 (1H, m), 8.07—8.09 (2H, m). FAB-MS *m/z*: 248 $(M+1)^+$. FAB-HR-MS *m/z*: 248.1639 $(M+1)^+$ (Calcd for $C_{15}H_{22}NO_2$: 248.1651).

(3a*R,7a*R**)-Benzyl 2-(Bromomethyl)-2,3,3a,4,7,7a-hexahydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate (7a)** At 0 °C, NBS (0.392 g, 2.2 mmol) was added to the solution of **6a** (0.552 g, 2.0 mmol) in MeCN (5 ml). The mixture was stirred at room temperature for 1.5 h and poured into aqueous 10% $Na_2S_2O_3$ solution, then extracted with AcOEt. The AcOEt layer was washed with saturated $KHCO_3$ solution and brine, dried, and the solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane=1 : 5) to give **7a** (0.692 g, 98%) as colorless oil. HPLC conditions: column, Chemcosorb 5Si-U; temperature, room temperature; solvent, AcOEt : hexane=1 : 5; flow rate, 1.0 ml/min; wavelength, 254 nm; retention time, t_R=7.5 and 9.2 min (19 : 75). IR (neat) cm^{-1}: 1700, 1240, 1230. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.10—2.10 (5H, m), 2.50—3.30 (2H, m), 3.30—3.50 (2H, m), 4.10—4.80 (4H, m), 5.12 (2H, s), 7.34 (5H, s). FAB-MS *m/z*: 354 $(M+1)^+$, 356 $(M+3)^+$. FAB-HR-MS *m/z*: 354.0707 $(M+1)^+$ (Calcd for $C_{16}H_{21}BrNO_3$: 354.0705).

(3a*R,7a*S**)-Benzyl 2-(Bromomethyl)-2,3,3a,4,7,7a-hexahydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate (7b)** At 0 °C, NBS (0.042 g, 0.23 mmol) was added to the solution of **6b** (0.058 g, 0.21 mmol) in MeCN (0.5 ml). The mixture was stirred at room temperature for 1 h, poured into aqueous 10% $Na_2S_2O_3$ solution, and extracted with AcOEt. The AcOEt layer was washed with saturated $KHCO_3$ solution and brine, dried, and the solvent was removed. The residue was purified by column chromatography (Al_2O_3, AcOEt : hexane=1 : 5) to give **7a** (0.073 g, 99%) as colorless oil. HPLC conditions: column, Chemcosorb 5Si-U; temperature, room temperature; solvent, AcOEt : hexane=1 : 5; flow rate=1.0 ml/min; wavelength, 254 nm; t_R=15.1 and 16.8 min (62 : 27). IR (neat) cm^{-1}: 1700, 1210. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.20—2.20 (5H, m), 2.50—3.30 (2H, m), 3.30—3.70 (3H, m), 3.80—4.50 (3H, m), 5.15 (2H, s), 7.35 (5H, s). FAB-MS *m/z*: 354 $(M+1)^+$, 356 $(M+3)^+$. FAB-HR-MS *m/z*: 354.0690 $(M+1)^+$ (Calcd for $C_{16}H_{21}BrNO_3$: 354.0705).

(3a*R,7a*R**)- (7a) and (3a*R**,7a*S**)- (7b) Benzyl 2-(Bromomethyl)-2,3,3a,4,7,7a-hexahydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate from a Mixture of 6a and 6b** At 0 °C, NBS (1.96 g, 11.0 mmol) was added to the solution of a mixture of **6a** and **6b** (2.75 g, 10.0 mmol) in MeCN (20 ml). The mixture was stirred at room temperature for 2 h and poured into aqueous 10% $Na_2S_2O_3$ solution, then extracted with AcOEt. The AcOEt layer was washed with saturated $KHCO_3$ solution and brine, dried, and the solvent was removed. The residue was purified by column chromatography (Al_2O_3, AcOEt : hexane=1 : 9) to give **7a** (2.13 g, 60%) and **7b** (0.96 g, 27%).

(3a*R,7a*R**)-Benzyl 2-(Bromomethyl)-2-methoxy-2,3,3a,4,7,7a-hexahydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate (8a)** Potassium *tert*-butoxide (3.00 g, 26.7 mmol) was added at 0 °C to a solution of **7a** (4.72 g, 13.3 mmol) in THF (15 ml) and the mixture was stirred at the same temperature for 1 h. Methanol (25 ml) and NBS (2.84 g, 16.0 mmol) were added and the mixture was stirred at room temperature for 1.5 h, then poured into aqueous 10% $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane=1 : 9) to give **8a** (4.23 g, 83%) as colorless oil. IR (neat) cm^{-1}: 1700, 1230. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.05—2.20 (5H, m), 2.30—2.95 (2H, m), 3.31 (3H, s), 3.42—3.57 (3H, m), 4.20—4.80 (2H, m), 5.14 (2H, s), 7.35 (5H, s). FAB-MS *m/z*: 352 $(M-OMe)^+$, 354 $(M+2-OMe)^+$, 384 $(M+1)^+$, 386 $(M+3)^+$. FAB-HR-MS *m/z*: 352.0536 $(M-OMe)^+$ (Calcd for $C_{16}H_{19}BrNO_3$: 352.0548).

(3a*R,4a*S**)-Benzyl 2-(Bromomethyl)-2-methoxy-2,3,3a,4,7,7a-hexahydrofuro[2,3-*c*]pyridine-6(5*H*)-carboxylate (8b)** Potassium *tert*-butoxide (1.46 g, 13.0 mmol) was added at 0 °C to a solution of **7b** (2.30 g, 6.50 mmol) in THF (7 ml) and the mixture was stirred at the same temperature for 1 h. Methanol (15 ml) and NBS (1.39 g, 7.80 mmol) were added and the mixture was stirred at room temperature for 2 h. It was then poured into aqueous 10% $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed. The residue was purified by column chromatography (SiO_2, AcOEt : hexane=1 : 9) to give **8b** (2.14 g, 86%) as colorless oil. HPLC conditions: column, Chemcosorb 5Si-U; temperature, room temperature; solvent, AcOEt : hexane=1 : 4; flow rate=1.0 ml/min; wavelength, 254 nm; t_R=8.9 and 10.1 min (17 : 66). IR (neat) cm^{-1}: 1700, 1220. ^{1}H-NMR (60 MHz, $CDCl_3$, rotomers) δ: 1.24—2.59 (7H, m), 3.22 (3H, s), 3.15—3.40 (2H, m), 3.52 (2H, s), 3.99—4.26 (1H, m), 5.13 (2H, s), 7.35 (5H, s). FAB-MS *m/z*: 384 $(M+1)^+$, 386 $(M+3)^+$. FAB-HR-MS *m/z*: 384.0859 $(M+1)^+$ (Calcd for $C_{17}H_{23}BrNO_4$: 384.0810).

(3*R,4*R**)-Benzyl 3-Hydroxy-4-[2-oxo-3-(4-oxo-3(4*H*)-quinazolinyl)-propyl]-1-piperidinecarboxylate (10a)** Aqueous 10% HCl solution (6 ml) was added to a solution of **8a** (2.89 g, 7.5 mmol) in MeCN (18 ml) and the mixture was stirred at room temperature for 0.5 h, then poured into water and extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and solvent was removed. Quinazolinone (**9**, 1.09 g, 7.5 mmol) and anhydrous K_2CO_3 (2.07 g, 15.0 mmol) were added to the solution of the residue in *N*,*N*-dimethylformamide (DMF) (10 ml) and the mixture was stirred at room temperature for 1 h, poured into water and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and then solvent was removed. The residue was recrystallized from AcOEt to give **10a** (2.67 g, 81%) as colorless needles, mp 191—192 °C (AcOEt). IR (KBr) cm^{-1}: 3440, 1720, 1700, 1660, 1280. ^{1}H-NMR (500 MHz, $CDCl_3$, rotomers) δ: 1.24—1.40 (1H, m), 1.75 (1H, s), 1.80 (1H, dd, J=13.5, 3.5 Hz), 2.02—2.10 (1H, m), 2.44—2.54 (1H, m), 2.54—2.65 (1H, m), 2.66—2.93 (2H, m), 3.22—3.38 (1H, m), 4.04—4.22 (1H, m), 4.24—4.37 (1H, m), 4.86 (2H, dd, J=37.0, 12.3 Hz), 5.11 (2H, br s), 7.30—7.38 (5H, m), 7.51 (1H, t, J=7.5 Hz), 7.72 (1H, d, J=7.5 Hz), 7.77 (1H, td, J=7.5, 1.3 Hz), 7.90 (1H, s), 8.27 (1H, dt, J=7.5, 1.3 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$, rotomers) δ: 30.62, 40.63, 43.50, 43.97, 50.34, 54.36, 67.23, 70.82, 121.68, 126.67, 127.33, 127.41, 127.75, 128.01, 128.44, 134.54, 136.41, 146.58, 146.58, 147.89, 155.11, 160.89, 202.52. FAB-MS *m/z*: 436 $(M+1)^+$. *Anal.* Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.06; H, 6.05; N, 9.66.

(3*R,4*S**)-Benzyl 3-Hydroxy-4-[2-oxo-3-(4-oxo-3(4*H*)-quinazolinyl)-propyl]-1-piperidinecarboxylate (10b)** Aqueous 10% HCl solution (7 ml) was added to a solution of **8b** (2.14 g, 5.57 mmol) in MeCN (15 ml) and the mixture was stirred at room temperature for 0.25 h, poured into water and extracted with AcOEt. The AcOEt layer was washed with aqueous saturated $KHCO_3$ solution and brine, dried, and then solvent was removed. Quinazolinone (**9**, 0.814 g, 5.57 mmol) and anhydrous K_2CO_3 (1.54 g, 11.1 mmol) were added to the solution of the residue in DMF (10 ml) and the mixture was stirred at room temperature for 3.5 h, then was poured into water and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and solvent was removed. The residue was recrystallized from CH_2Cl_2 to give **10b** (1.48 g, 61%) as colorless needles, mp 205—207 °C (CH_2Cl_2). IR (KBr) cm^{-1}: 3440, 1720, 1690, 1660, 1280. ^{1}H-NMR (500 MHz, $CDCl_3$, rotomers) δ: 1.35—1.42 (1H, m), 1.48—1.58 (1H, m), 2.07—2.14 (1H, m), 2.50 (1H, s), 2.50—2.54 (1H, m), 2.72 (1H, dd, J=16.8, 6.3 Hz), 2.82—3.10 (2H, m), 3.63 (1H, br s), 3.83—3.91 (2H, m), 4.86 (2H, dd, J=17.5, 3.5 Hz), 5.07 (2H, br s), 7.30—7.38 (5H, m), 7.57 (1H, td, J=8.0, 1.5 Hz), 7.72 (1H, d, J=8.0 Hz), 7.86 (1H, ddd, J=8.0, 8.0, 1.5 Hz), 8.14 (1H, dd, J=8.0, 1.5 Hz), 8.21 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.51, 25.76, 35.34, 42.95, 49.80, 54.87, 65.35, 66.17, 121.61, 126.26, 127.40, 127.48, 127.64, 127.86, 128.57, 134.73, 137.38, 148.23, 148.28, 155.36, 160.20, 203.70. FAB-MS *m/z*: 418 $(M-H_2O+1)^+$, 436 $(M+1)^+$. *Anal.* Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.02; H, 5.73; N, 9.57.

***trans*-3-[3-(3-Hydroxy-4-piperidinyl)-2-oxopropyl]-4(3*H*)-quinazolinone (2a)** A mixture of **10a** (1.09 g, 2.50 mmol) and 10% Pd/C (157 mg) in MeOH (5 ml) and THF (15 ml) was stirred at room temperature for 48 h under a balloon of H_2 gas. The mixture was filtered and the solvent was removed. The residue was purified by column chromatography (MeOH : Et_3N=200 : 1) to give **2a** (0.28 g, 37%) as colorless needles, mp

163—164 °C (AcOEt). IR (KBr) cm^{-1}: 3400, 3260, 1720, 1690. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.24—1.35 (3/2H, m), 1.81 (1/2H, dd, J=13.5, 3.3 Hz), 1.90 (2H, br s), 1.98—2.04 (1H, m), 2.43 (1H, t, J=11.5 Hz), 2.50 (1H, dd, J=15.8, 5.3 Hz), 2.57 (1H, td, J=12.0, 2.5 Hz), 2.82 (1H, dd, J=15.8, 8.0 Hz), 2.98 (1H, br d, J=12.0 Hz), 3.20 (1H, dd, J=11.5, 4.5 Hz), 3.31 (1H, td, J=10.0, 4.5 Hz), 4.89 (2H, dd, J=49.5, 17.3 Hz), 7.51 (1H, td, J=8.0, 1.5 Hz), 7.73 (1H, d, J=8.0 Hz), 7.77 (1H, td, J=8.0, 1.5 Hz), 7.90 (1H, s), 8.28 (1H, dd, J=8.0, 1.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 31.99, 41.02, 43.54, 45.71, 54.12, 54.77, 71.18, 121.60, 126.22, 127.32, 127.42, 134.65, 148.18, 148.22, 160.16, 203.98. FAB-MS *m/z*: 302 $(M+1)^+$, 603 $(2M+1)^+$. FAB-HR-MS *m/z*: 302.1539 $(M+1)^+$. (Calcd for $C_{16}H_{20}N_3O_3$: 302.1505). *Anal.* Calcd for $C_{16}H_{19}N_3O_3$ 1/2 H_2O: C, 61.92; H, 6.50; N, 13.54. Found: C, 62.01; H, 6.22; N, 13.56.

***trans*-3-[3-(1-Benzyl-3-hydroxy-4-piperidinyl)-2-oxopropyl]-4(3*H*)-quinazolinone (11a)** The mixture of **10a** (871.0 mg, 2.0 mmol) and 6 N HCl aq. (25 ml) was heated at reflux for 2 h. After being cooled, the mixture was made basic with aqueous 6 N NaOH and 20% K_2CO_3 solution. The Et_2O layer, which was continuously extracted for 4 d, was dried over anhydrous $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography (MeOH) to give **11a** (0.215 g, 28%) as colorless needles, mp 153.5—156 °C (EtOH). IR (KBr) cm^{-1}: 3440, 1720, 1660. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.43 (1H, ddd, J=21.5, 11.5, 4.0 Hz), 1.67 (1H, br s), 1.78 (1H, ddd, J=13.5, 7.0, 3.0 Hz), 1.87 (1H, t, J=10.0 Hz), 1.88—1.96 (1H, m), 2.02 (1H, td, J=11.5, 2.5 Hz), 2.50 (1H, dd, J=15.5, 5.5 Hz), 2.80 (2H, dd, J=17.5, 7.5 Hz), 3.02 (1H, dd, J=10.0, 4.0 Hz), 3.45 (1H, td, J=10.0, 4.0 Hz), 3.52 (2H, dd, J=27.5, 13.5 Hz), 4.87 (2H, dd, J=46.0, 18.0 Hz), 7.25—7.33 (5H, m), 7.50 (1H, td, J=7.8, 1.0 Hz), 7.72 (1H, d, J=7.5 Hz), 7.77 (1H, td, J=7.5, 1.5 Hz), 7.90 (1H, s), 8.27 (1H, dd, J=8.0, 1.5 Hz). FAB-MS *m/z*: 392 $(M+1)^+$. FAB-HR-MS *m/z*: 392.1904 $(M+1)^+$. (Calcd for $C_{23}H_{26}N_3O_3$: 392.1974). *Anal.* Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.49; H, 6.09; N, 10.79.

***cis*-3-[3-(3-Hydroxy-4-piperidinyl)-2-oxopropyl]-4(3*H*)-quinazolinone (2b)** A mixture of **10b** (0.103 g, 0.24 mmol) and 10% Pd/C (28.7 mg) in MeOH (3 ml) and CH_2Cl_2 (5 ml) was stirred at room temperature for 32 h under a balloon of H_2 gas. The mixture was filtered and the solvent was removed. The residue was recrystallized from EtOH to give **2b** (0.528 g, 82%) colorless needles, mp 233—235 °C (dec.). IR (KBr) cm^{-1}: 3300, 1720, 1690. ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.73 (1H, dd, J=14.0, 3.5 Hz), 1.90 (1H, ddd, J=22.5, 13.0, 4.0 Hz), 2.27—2.34 (1H, m), 2.66 (1H, dd, J=17.5, 7.0 Hz), 2.87 (1H, dd, J=17.5, 7.0 Hz), 3.02 (1H, td, J=13.0, 3.5 Hz), 3.13 (1H, dd, J=12.8, 1.3 Hz), 3.23—3.28 (1H, m), 3.28—3.32 (3H, m), 4.02 (1H, br s), 4.83—4.98 (2H, m), 7.57 (1H, t, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 7.85 (1H, td, J=8.0, 0.8 Hz), 8.17 (1H, s), 8.21 (1H, dt, J=8.0, 0.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.01, 35.04, 42.85, 45.04, 51.18, 56.00, 64.46, 122.80, 127.40, 128.08, 128.72, 135.99, 149.23, 149.24, 162.49, 203.73? FAB-MS *m/z*: 302 $(M+1)^+$, 604 $(2M+2)^+$. FAB-HR-MS *m/z*: 302.1527 $(M+1)^+$. (Calcd for $C_{16}H_{20}N_3O_3$: 302.1505).

Antimalarial Activity Assays and evaluation of siderophore activities were carried out according to the methods described previously.[11)]

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