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Enhancement of the Antiplasmodial Activity of Quassin by Transformation into a γ-Lactone

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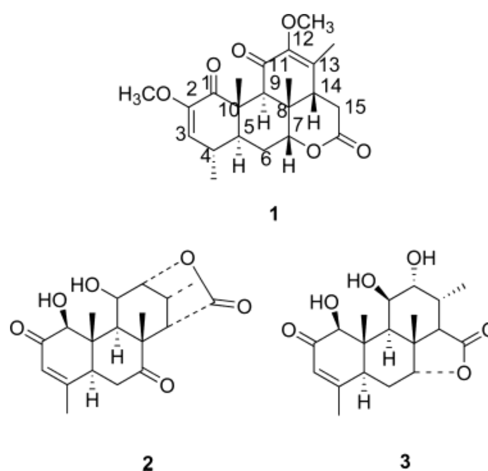
The naturally occurring bitter principle quassin (**1**) was converted chemically into the γ-lactone quassilactone (**13**) in an attempt to enhance its antiplasmodial activity. The in vitro antiplasmodial activity of **13** against *Plasmodium falciparum* (K1) (IC_{50} = 23 μM) was 40-fold greater than that of **1**. However, one of the intermediates, compound **8**, the 15β-hydroxy,16-*O*-*m*-chlorobenzoyl analogue of **1**, was 506-fold more active than **1** against *P. falciparum* (IC_{50} = 1.8 μM) and only 3-fold less potent than chloroquine. In addition, **8** displayed the best cytotoxic/antiplasmodial ratio (112) of all of the compounds tested. In the course of this work a dimer, neoquassin ether (**6**), linked at C-16 was also prepared; **6** was found to have weak antiplasmodial activity (IC_{50} = 9.7 μM).

Quassinoids are the bitter degraded triterpenoids of the Simaroubaceae plant family. Their name is derived from quassin (**1**), the first member of the group to be isolated.[1] Quassinoids have attracted much attention due to the wide spectrum of biological activities that they display (e.g., antileukemic, antimalarial, antiamebic, and antiviral[2]). The majority of isolated quassinoids have a C-20 skeleton and are δ-lactones, while the few C-19 skeletal type quassinoids that have been isolated are γ-lactones. The lactonic linkage may be at C-12 or at C-7, as exemplified by eurycomalactone[3] (**2**) and longilactone[4] (**3**), respectively. Interestingly, the latter compounds exhibit antiplasmodial and cytotoxic activities even though they do not possess some of the structural requirements such as an ester at C-6 or C-15 that have been shown to be essential for biological activities in other quassinoids.[5]

Quassin (**1**) itself does not have the latter structural requirements, and it does not possess potent antiplasmodial or cytotoxic activities. In our continuing work on synthetic quassinoids,[6,7] we now report the conversion of quassin (**1**) (a δ-lactone) into the γ-lactone analogue, quassilactone (**13**), to determine the effect of this modification on its biological activities. Compound **13** and the synthetic intermediates were assessed for antiplasmodial and cytotoxic activities.

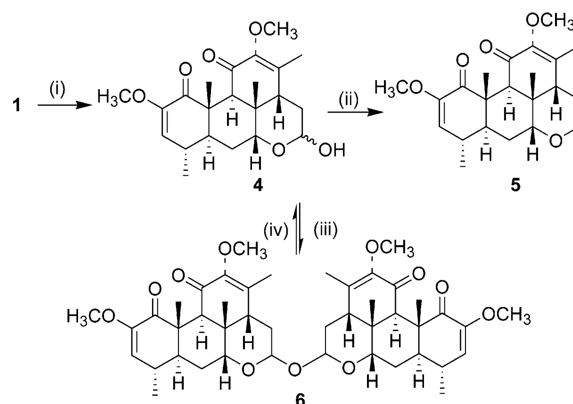


Results and Discussion

The reduction of **1** was carried out with sodium borohydride in absolute ethanol at room temperature as previously described[8] to afford neoquassin (**4**; yield 90%), as a mixture of diastereoisomers at C-16 (α,β ca. 1:1), determined by ^{1}H NMR spectroscopy (Scheme 1). The signal for H-16α appeared as a broad doublet at δ 4.7 (J = 9 Hz), while H-16β appeared as a doublet at δ 5.4 (J = 2.5 Hz); the keto groups at C-1 and C-11 were inert under these conditions.

Treatment of **4** with $POCl_3$ in pyridine at 110 °C gave the vinyl ether anhydroquassin (**5**) in 51% yield. The ^{1}H NMR spectrum of **5** showed three vinyl protons at δ 6.43

Scheme 1[a]



[a] (i) $NaBH_4$, EtOH, RT; (ii) $POCl_3$, pyridine 110 °C; (iii) excess $POCl_3$, pyridine, 110 °C; (iv) 10% HCl, THF.

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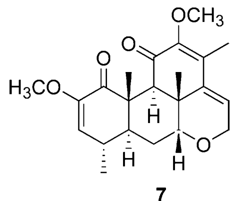
(dd, $J = 6.3$, 2.8 Hz, H-16), 5.29 (d, $J = 2.4$ Hz, H-3), and 4.60 (dd, $J = 6.2$, 2 Hz, H-15), and its mass spectrum revealed a molecular ion of *m/z* 372; the spectral data were in agreement with literature values[8] for **5**. When an excess of $POCl_3$ was used under the same conditions, a substitution product, neoquassin ether (**6**), was unexpectedly obtained instead of the dehydration product **5** (Scheme 1). At first it was thought that **6** might possibly be dehydroquassin (**7**), an isomer of **5**. However, **6** was found to be

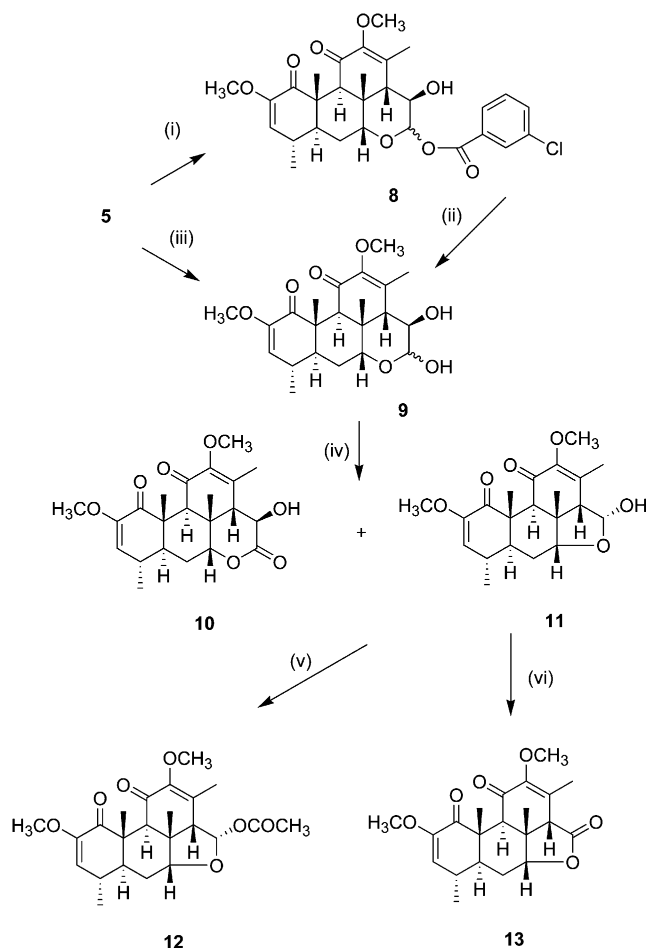


resistant to oxidation with *m*-chloroperbenzoic acid (MCPBA), and its UV spectrum did not show peaks at 272 and 290 nm[9] expected for **7**; instead it showed a single intense peak at 255 nm, which was also observed with **4** and **5** due to the two chromophoric groups absorbing at approximately the same wavelengths. The mass spectrum of **6** revealed a molecular ion at *m/z* 785 consistent with being a dimer. The ^1H NMR spectrum of **6** showed peaks at δ 5.20 and 5.30 ($J = 2$ Hz) corresponding to H-16 and H-3, respectively, while its ^{13}C NMR spectrum showed signals at 100 and 116 ppm for H-16 and H-3, respectively. This result suggests that the vinyl ether **5** initially formed reacts with **4** to give neoquassin ether (**6**). The structure of **6** was further confirmed after acid hydrolysis with 10% HCl–THF-generated **4**. The only other quassinoid dimers reported in the literature are the bis-brusatolyl esters which are linked together via ring A.[10]

Oxidation of anhydroquassin (**5**) with 50–60% *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature gave a diastereomeric mixture of 16-*O*-*m*-chlorobenzoylated hemiacetal (**8**) (α,β, ca. 1:3) as the major product (yield 47%) and hydroxyneoquassins (**9**) as the minor product (yield 6%) (Scheme 2). Treatment of **8** with 27% perchloric acid in THF furnished **9** as a mixture of diastereoisomers at C-16. Oxidation of **5** with osmium tetroxide in pyridine followed by hydrolytic cleavage of the osmate ester under reducing conditions with aqueous sodium bisulfite also yielded **9**.

Oxidation of the mixture of hemiacetals (**9**) by refluxing with excess Ag_2O in aqueous ethanol gave two products on TLC ($CHCl_3$–MeOH, 95:5; detected by spraying with *p*-anisaldehyde reagent); the less polar product ($R_f = 0.44$), 15β-hydroxyquassin (**10**) (41% yield), was a δ-lactone, and the more polar product ($R_f = 0.36$) was surprisingly a C_{19} skeletal type quassinoid, the γ-lactol quassilactol (**11**, 25% yield). The ^1H NMR spectrum of **10** displayed signals for H-14 and H-15 at δ 2.35 (1H, d, $J = 10.7$ Hz) and 4.50 (1H, d, $J = 10.7$ Hz), respectively, and was consistent with literature values for **10**.[8] The coupling constant between H-14 and H-15 was in agreement with a C-15 hydroxyl group in the β-configuration and is characteristic of the natural quassinoids.[8] The ^1H NMR spectrum of **11** revealed signals for H-14 and H-15 at δ 2.38 (1H, d, $J = 5.0$ Hz) and 5.53 (1H, d, $J = 5.0$ Hz), respectively, for which the coupling constants suggested the configuration of the hydroxyl at C-15 to be α. The mass spectrum of **11** showed a molecular ion at *m/z* 376, consistent with $C_{21}H_{28}O_6$, 28 mass units less than that of compound **10**, and consistent with the mass of a carbonyl group, the absence of which was confirmed by the ^{13}C NMR spectrum of **11**. The ^{13}C

Scheme 2[a]



[a] (i) MCPBA, CH_2Cl_2; (ii) 27% $HClO_4$, THF; (iii) OsO_4, pyridine, aq. $NaHSO_3^-$, (iv) Ag_2O, EtOH/H_2O; (v) $(CH_3CO)_2O$, DMAP, CH_2Cl_2; (vi) pyridinium chlorochromate.

NMR spectrum of **11** showed signals for 21 carbons, with the signals for C-14 and C-15 appearing at 64.1 and 100.8 ppm, respectively, which were considerably downfield compared with those of **10**, at 53.4 and 70.3 ppm, respectively. The structure of **11** was further confirmed by acylation with acetic anhydride, which furnished acetate **12** with the expected molecular ion of 419 $[M + 1]^+$. Its ^1H NMR spectrum revealed that the signals corresponding to H-15 and H-14 had shifted downfield to δ 6.31 ($J = 5$ Hz) and 2.59 ($J = 5$ Hz), respectively. Oxidation of quassilactol **11** with pyridinium chlorochromate in pyridine gave quassilactone **13**, as evidenced by the presence of two proton singlets at δ 2.92 and 2.93 for H-9 and H-14, respectively, in the ^1H NMR spectrum, while the mass spectrum revealed a molecular ion at *m/z* 374 ($C_{21}H_{26}O_6$).

The antiplasmodial and cytotoxic activities of the compounds tested together with their antiplasmodial/cytotoxic ratios are shown in Table 1. The antiplasmodial activity of quassilactone **13** ($IC_{50} = 23$ μM) was 40-fold higher than that of quassin **1** ($IC_{50} = 911$ μM), although **13** was 38-fold less potent than chloroquine ($IC_{50} = 0.6$ μM). Nevertheless, changing the δ-lactone of **1** into a γ-lactone as in **13** led to a significant enhancement of antiplasmodial activity. Interestingly, neoquassin ether (**6**) and the 16-*O*-*m*-chlorobenzoylated compound **8** were 94-fold and 506-fold, respectively, more active than **1** against *Plasmodium falciparum* ($IC_{50} = 9.7$ and 1.8 μM, respectively). Compound **8** is of comparable activity to chloroquine, but it must be remembered that a chloroquine-resistant strain

Table 1. Antiplasmodial and Cytotoxic Activities of Quassin Analogues in Vitro

compound	activity against KB cells: IC_{50} μM, $n = 2$ (A)	activity against KB cells: 95% CI	activity against *P. falciparum* (K1): IC_{50} μM, $n = 2$ (B)	activity against *P. falciparum* (K1): 95% CI	selectivity index A/B
1	>1000		911	773−1080	>1
4	615	390−1120	473	439−511	1.3
5	>1000		809	701−892	>1
6	149	120−220	9.7	7.8−12.0	15.3
8	232	190−420	1.8	1.5−2.0	112
9	NT[a]		68	60−120	
10	>1000		930	620−1390	>1.1
11	576	330−1110	65	32−140	8.9
13	406	320−520	23	20−28	17.7
emetine hydrochloride	0.96	0.18−1.68	NT[a]		
chloroquine diphosphate	NT[a]		0.60	0.40−0.90	

[a] NT: not tested.

(K1) of *P. falciparum* was used. Hydroxyneoquassin (**9**) was found to be 38-fold less potent against malaria parasites than **8**, indicating that the chlorobenzoyl ester of **9** contributes to its activity. Compared to the other compounds for which cytotoxic data are available, **8** displayed the best antiplasmodial/cytotoxic ratio (112), showing that there is some selective toxicity against *P. falciparum* compared with KB cells. In conclusion, the results of this study suggest that further modification of **1** and **8** may lead to compounds with enhanced antiplasmodial activities.

Experimental Section

General Experimental Procedures. UV spectra were recorded on a Perkin-Elmer 402 ultraviolet−visible spectrophotometer using spectroscopic grade methanol. Preparative column chromatography was carried out by flash technique using silica gel (Sorbsil C, 60-H (40−60 μM), Rhone-Poulenc), and analytical thin-layer chromatography was performed on precoated Kiesel gel 60_{F254} plates, 0.25 mm thick (Merck). ^{1}H NMR (^{1}H and ^{13}C) spectra ($CDCl_3$) were recorded on a Bruker WM 250, AMX 400, or AM 500 spectrometer. Electron-impact (EI) mass spectra were recorded on a VG Analytical LTD ZAB IF spectrophotometer. Fast-atom-bombardment (FAB) mass spectra were recorded on a VG analytical ZAB-SE spectrometer; samples were dissolved in a 2-nitrobenzyl alcohol plus sodium iodide matrix (MNOBA + NaI) unless otherwise stated. Chemicals were purchased from Sigma-Aldrich Chemical Co. Ltd., Poole, U.K.

Anhydroquassin (5). To an ice-cooled (0 °C) solution of **4** (3.3 g, 7.69 mmol), in dry pyridine (20 mL), was added $POCl_3$ (0.1 mL) with stirring. The mixture was allowed to warm to room temperature, then refluxed at 110 °C for 5 h. When cool, the mixture was diluted with $CHCl_3$ (100 mL) and poured into iced water (50 mL), and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$ (30 mL × 3), and the combined organic extracts were washed with 2 M HCl (100 mL × 2) and water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The product was chromatographed (Et_2O, 100%) to yield **5** (1.7 g, yield 52%), which crystallized out on standing.

Neoquassin Ether (6). To an ice-cold solution of **4** (2.5 g, 6.4 mmol) in dry pyridine (20 mL) was added phosphorus oxychloride (4 mL) with stirring. The solution was allowed to warm to room temperature, then refluxed at 110 °C for 5 h. When cool, the mixture was diluted with $CHCl_3$ (100 mL) and poured into iced water (50 mL), and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$ (30 mL × 2), and the combined organic extracts were washed with 2 M HCl (100 mL × 2) and water (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product was chromatographed (ether 100%) to afford 1.6 g (yield 33%) of **6**. Recrystallization from ethyl acetate yielded white needles: UV (MeOH) λ_{max} 255 nm; ^{1}H NMR ($CDCl_3$) δ 5.30 (2H, d, $J = 1.9$ Hz, H-3), 5.20 (2H, $J = 1.9$ Hz, d, H-16), 3.65 (6H, s, OCH_3-12), 3.64 (2H, m, H-7), 3.57 (6H, s, OCH_3-2), 3.19 (2H, s, H-9), 2.45 (2H, m, H-4), 2.30 (2H, m, H-14), 2.1−1.6 (10H, m, H-5, H-6, H-15), 1.90 (6H, s, CH_3-13), 1.55 (3H, s, CH_3-10), 1.10 (3H, d, CH_3-4); ^{13}C NMR ($CDCl_3$) δ 198.9 (C-1), 192.9 (C-11), 148.4 (C-12), 148.1 (C-2), 139.2 (C-13), 116.3 (C-3), 91.1 (C-16), 69.9 (C-7), 59.2 (O*C*H$_3$-12), 54.9 (O*C*H$_3$-2), 46.1 (C-9), 45.9 (C-14), 43.9 (C-10), 43.8 (C-5), 38.4 (C-8), 31.4 (C-4), 30.7 (C-15), 25.7 (C-6), 22.3 (*C*H$_3$-4), 19.6 (*C*H$_3$-8), 15.4 (*C*H$_3$-13), 12.98 (*C*H$_3$); FABMS *m*/*z* 785 (100) [M$^+$ + 23], 755 (4), 673 (4), 548 (2), 462 (6), 441 (9), 395 (23), 373 (9), 353 (6), 329 (22), 307 (6); HRFABMS *m*/*z* $C_{44}H_{58}O_{11}Na$, calcd 785.3877, found 785.3884.

Hydrolysis of Neoquassin Ether (6). A solution of **6** (40 mg, 0.0525 mmol) in THF (5 mL) and 10% HCl (5 mL) was stirred at room temperature for 16 h. The mixture was poured into water (10 mL) and extracted with ether (10 mL × 3), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ followed by brine, dried over Na_2SO_4, and evaporated under reduced pressure to yield 16 mg (yield 78%) of **4**, which was identical to an authentic sample (TLC, silica gel G, $CHCl_3$−MeOH, 95:5, and EtOAc−hexane, 75:25).

15β-Hydroxy-16-*m*-chlorobenzoyloxy-2,12-dimethoxypicrasa-2,12-diene-1,11-dione (8). To a cooled (−5 °C) solution of **5** (1.4 g, 3.76 mmol) in CH_2Cl_2 (40 mL) was added 50−60% MCPBA (1.4 g, 8.11 mmol), and the mixture was stirred for 1 h at room temperature. A solution of saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture stirred for 5 min. The organic layer was separated and evaporated under reduced pressure. The residue was dissolved in ether (30 mL), washed with more $NaHCO_3$ (20 mL × 2) and brine (20 mL), and dried ($MgSO_4$). Removal of the solvent followed by chromatography ($CHCl_3$−MeOH, 95:5) of the residue afforded 680 mg (yield 47%) of 16-*O*-*m*-benzoylated hemiacetal (**8**) and 96 mg (yield 6.6%) of hydroxyneoquassins (**9**).

Compound 8. ^{1}H NMR ($CDCl_3$): δ 8.10−7.40 (4H, m, aromatic-H), 6.45 (0.4H, d, $J = 3.7$ Hz, H-16), 5.75 (0.6H, d, $J = 8.2$ Hz, H-16), 5.30 (0.4H, d, $J = 2.3$ Hz, H-3), 5.25 (0.6H, d, $J = 2.4$ Hz, H-3), 4.40 (O.4H, t, H-15), 4.20 (0.6H, t, H-15), 3.90 (0.4H, m, H-7), 3.70 (3H, s, OCH_3-12), 3.65 (0.6H, m, H-7), 3.60 (1.5H, s, OCH_3-2), 3.55 (1.5H, s, OCH_3-2) 3.30 (0.6H, s, H-9), 3.20 (0.4H, s, H-9), 2.45 (1H, m, H-4), 2.30 (1H, m, H-14), 2.10 (3H, s, CH_3-13), 2.15−1.55 (3H, m, H-5, H-6), 1.50 (3H, s, CH_3-10), 1.10 (3H, s, CH_3-8), 1.05 (3H, d, CH_3-4); FABMS *m*/*z* 545 (43) [M$^+$], 478 (7), 460 (15), 403 (21), 389 (24), 373 (11), 329 (10), 307 (100), 289 (64), 279 (33), 259 (9); HRFABMS *m/z* $C_{29}H_{34}O_8Cl$, calcd 545.1942, found 545.1946.

Hydroxyneoquassins (9). To a solution of **8** (1.0 g, 2.58 mmol) in THF (20 mL) was added 27% perchloric acid (25 mL), and the mixture was stirred at room temperature for 21 h. The product was poured into water (25 mL) and extracted with CH_2Cl_2 (20 mL × 2). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (silica gel, $CHCl_3$−MeOH, 90:10) to afford 592 mg (yield 57%) of **9** as a mixture of diastereoisomers at C-16: TLC ($CHCl_3$−MeOH, 95:5), R_f =

0.17; ^{1}H NMR ($CDCl_3$) δ 5.30 (1H, d, H-3), 5.25 (0.5H, d, H-16), 4.51 (0.5H, bd, J = 7.5 Hz, H-16), 4.10 (0.5H, dd, H-15), 3.65 (3H, s, OC*H*$_3$-12), 3.60 (1.5H, s, OC*H*$_3$-2), 3.55 (1.5H, s, OC*H*$_3$-2), 3.50 (0.5H, m, H-7), 3.25 (0,5H, s, H-9), 3.15 (0.5H, s, H-9), 2.40 (1H, m, H-4), 2.20 (0.5H, bd, H-14), 2.10 (3H, s, C*H*$_3$-13), 2.95 (0.5H, bd, H-14), 2.90−1.60 (3H, m, H-5, H-6), 1.50 (1.5H, s, *CH*$_3$-10), 1.45 (1.5H, s, *CH*$_3$-10), 1.10 (3H, d, C*H*$_3$-4), 1.05 (3H, s, C*H*$_3$-8); EIMS *m/z* 407 (55) [M$^+$ + 1], 406 (23) [M$^+$], 388 (13), 373 (5), 360 (3), 329 (5), 315 (19), 302 (10), 255 (5), 203 (6), 179 (9), 165 (22), 152 (20), 127 (25), 105 (14), 91 (27), 77 (17), 69 (64), 55 (34), 43 (75), 28 (100); HREIMS *m/z* $C_{22}H_{30}O_7$ calcd 406.1992, found 406.1997.

Hydroxyneoquassins (9): Oxidation of (5) with Osmium Tetroxide. To a solution of **5** (405 mg, 1.1 mmol) in pyridine (15 mL) was added osmium tetroxide (277 mg, 1.09 mmol), and the mixture was stirred for 5.5 h at room temperature. A solution of sodium metabisulfite (0.5 g, 2.63 mmol), in water (20 mL) and pyridine (15 mL), was added to the reaction mixture and the resulting solution stirred at room temperature for 20 min. The mixture was extracted with $CHCl_3$ (20 mL × 3), washed with 2 M HCl (25 mL × 3), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was chromatographed (silica gel G, $CHCl_3$−MeOH, 90:10) to afford 192 mg (yield 43%) of **9** as a 1:1 mixture of diasteroisomers at C-16.

15*β*-Hydroxyquassin (10) and Quassilactol (11). To a solution of **9** (520 mg, 1.28 mmol) in ethanol (30 mL), and water (30 mL), was added freshly prepared Ag_2O (2.5 g, 20 mmol) and the mixture refluxed for 24 h. The warm mixture was passed through Celite, followed by washing with methanol (200 mL). The filtrate and washings were combined and concentrated to a volume of 30 mL. The mixture was poured into water (20 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue ($CHCl_3$−MeOH 95:5) yielded 210 mg (yield 41%) of **10** and 120 mg (yield 25%) of **11**. Recrystallization of **10** from ethyl acetate gave colorless prisms.

Quassilactol (11): ^{1}H NMR ($CDCl_3$) δ 5.53 (1H, d, J = 5 Hz, H-15), 5.33 (1H, d, H-3), 4.14 (1H, t, H-7), 3.74 (3H, s, OC*H*$_3$-12), 3.58 (3H, s, OC*H*$_3$-2), 3.25 (1H, bs, O*H*), 2.99 (1H, s, H-9), 2.46 (1H, m, H-4), 2.38 (1H, d, J = 5 Hz, H-14), 2.08 (1H, m, H-6), 1.86 (3H, s, C*H*$_3$-13), 1.53 (3H, s, C*H*$_3$-10), 1.13 (3H, s, C*H*$_3$-8), 1.09 (3H, d, C*H*$_3$-4); ^{13}C NMR ($CDCl_3$) δ 198.6 (C-1), 195.1 (C-11), 149.7 (C-12), 147 (C-2), 129.7 (C-13), 117.1 (C-3), 100.8 (C-15), 80.7 (C-7), 64.1 (C-14), 58.9 (O*C*H$_3$-12), 54.9 (O*C*H$_3$-2), 49.3 (C-9), 48.0 (C-10), 46.7 (C-8), 43.8 (C-5), 31.3 (C-4), 23.9 (C-6), 19.3 (*C*H$_3$-4), 18.3 (*C*H$_3$-8), 15.2 (*C*H$_3$-13), 11.9 (*C*H$_3$-10); EIMS *m/z* 376 (30) [M$^+$], 358 (15), 330 (100), 315 (18), 297 (12), 287 (16), 269 (7), 255 (8), 218 (18), 203 (12), 185 (7), 165 (19), 151 (7), 132 (22), 123 (9), 105 (10), 91 (19), 77 (13), 69 (38); FABMS *m/z* 377, (100) [M$^+$ + 1], 277 (53); HRFABMS *m/z* $C_{21}H_{28}O_6 + 1$ calcd 377.1964, found 377.1960.

15α-Acetoxyquassilactol (12). To a solution of **11** (20 mg, 0.0532 mmol) and DMAP (10 mg, 0.0815 mmol) in CH_2Cl_2 (1 mL) was added acetic anhydride (0.1 mL) with the mixture stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (EtOAc−hexane, 75:25) to afford 11.4 mg (yield 51%) of **12**: ^{1}H NMR ($CDCl_3$) δ 6.31 (1H, d, J = 5 Hz, H-15), 5.31 (1H, d, J = 2.4 Hz, H-3), 4.09 (1H, t, H-7), 3.75 (3H, s, OC*H*$_3$-12), 3.57 (3H, s, OC*H*$_3$-2), 3.02 (1H, s, H-9), 2.59 (1H, d, J = 5.0 Hz, H-14), 2.35 (1H, m, H-4), 2.12 (3H, s, COC*H*$_3$), 1.77 (3H, s, C*H*$_3$-13), 1.54 (3H, s, *CH*$_3$-10), 1.17 (3H, s, C*H*$_3$-8), 1.11 (3H, d, C*H*$_3$-4); EIMS *m/z* 419 [M + 1]$^+$ (72), 408 (10), 392 (12), 370 (37), 359 (19), 330 (13), 316 (100), 272 (83), 244 (34).

Quassilactone (13). To a solution of **11** (20 mg, 0.053 mmol) in CH_2Cl_2−pyridine (3 mL, 2:1) was added pyridinium chlorochromate (50 mg, 0.23 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O, filtered through a pad of silica gel, washed with Et_2O, and concentrated under reduced pressure. The crude product was chromatographed (EtOAc−hexane, 75:25) to afford 7 mg (yield 35%) of **13**: ^{1}H NMR ($CDCl_3$) δ 5.33 (1H, d, J = 2.4 Hz, H-3), 4.28 (1H, t, H-7), 3.76 (3H, s, OC*H*$_3$-12), 3.58 (3H, s, OC*H*$_3$-2), 2.92 (1H, s, H-14), 2.91 (1H, s, H-9), 2.45 (1H, t, H-4), 2.33 (1H, m, H-6), 2.29 (3H, s, OC*H*$_3$-13), 1.56 (3H, s, *CH*$_3$-10), 1.26 (3H, s, C*H*$_3$-8), 1.14 (3H, d, C*H*$_3$-4); EIMS *m/z* 374 [M$^+$] (37), 359 (4), 347 (5), 330 (8), 315 (15), 297 (19), 223 (11), 203 (17), 181 (41), 165 (34), 151 (34), 129 (21), 105 (23) 91 (100); HREIMS *m/z* $C_{21}H_{26}O_6$ calcd 374.1729, found 374.1735.

Biological Assays. Activity against *P. falciparum* (multidrug-resistant strain K1) was determined by measuring the inhibition of incorporation of [^{3}H]-hypoxanthine into red blood cells infected with malaria parasites.[11] Cytotoxicity against KB cells (human mouth cancer cells) was carried out using a microplate method as previously reported.[12]

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