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Synthesis of novel 10-deoxoartemisinins

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Abstract—The synthesis of novel 10-deoxoartemisinin derivatives containing heterocyclic rings and hydrophilic groups, and their antimalarial activity assessment are described. Most of the synthesized derivatives are more potent than artemisinin, especially, some of them are 20–25 times more potent than artemisinin to two chloroquine-resistant and sensitive clones of *P. falciparum*.

Malaria, a deadly disease is now becoming an increasingly serious problem due to the development of drug resistance by many strains of *Plasmodium falciparum* to chloroquine (**1**) and mefloquine (**2**). These drug resistance strains have now spread to almost all areas where malaria is endemic. It is estimated that 2 billion people each year are affected by malaria, and the WHO predicts that this number will have been doubled by the year 2010[1,2] if there is no new antimalarial drug intervention. Therefore, the need for finding new molecules with novel modes of action is urgent. Artemisinin (**3**) (quinghaosu) and its derivatives such as artemether (**5a**), arteether (**5b**), and artesunate (**5c**) are now effectively used for the treatment of malaria (Fig. 1).

For more than a decade of using these derivatives in malaria treatment, shortcomings like poor bioavailability and rapid clearance are observed, principally as a result of the poor chemical and metabolic instability of the acetal function present in these derivatives. This is mainly due to oxidative dealkylation to the intermediate, dihydroartemisinin (**4**), a compound associated with toxicity[3] and short half-life.[4,5] Aspects regarding the chemistry, mechanism of action, metabolism, and toxicity of the endoperoxide class of drugs have been recently reviewed by Posner et al.[6] To solve the above mentioned problem, new derivatives of artemisinin in which the 10-acetal bond is replaced with 10-C–C, the so-called 10-deoxoartemisinins were synthesized.[7–14]

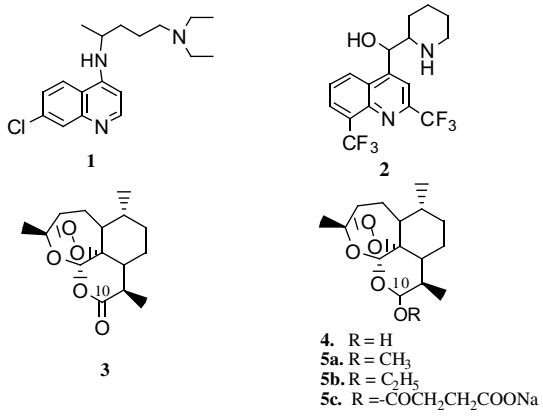

Figure 1.

These 10-substituted deoxoartemisinins have been proved to be more resistant to hydrolyses in simulated mixtures of stomach acid than the dihydroartemisinin derivatives currently in use.[15] Recently, we have reported the synthesis of novel 10-deoxoartemisinins containing heterocyclic rings, which showed in vitro antimalarial activity against two *P. falciparum* clones 10 times more than artemisinin.[16] In continuation of our interest to discover new derivatives of 10-deoxoartemisinins, now we present the synthesis of novel 10-deoxoartemisinins containing amino and hydrophilic groups.

The synthesis of 10-deoxoartemisinins (**12**) containing amino groups is outlined in Scheme 1. The key product, 10-β-allyldeoxoartemisinin (**7**) was previously

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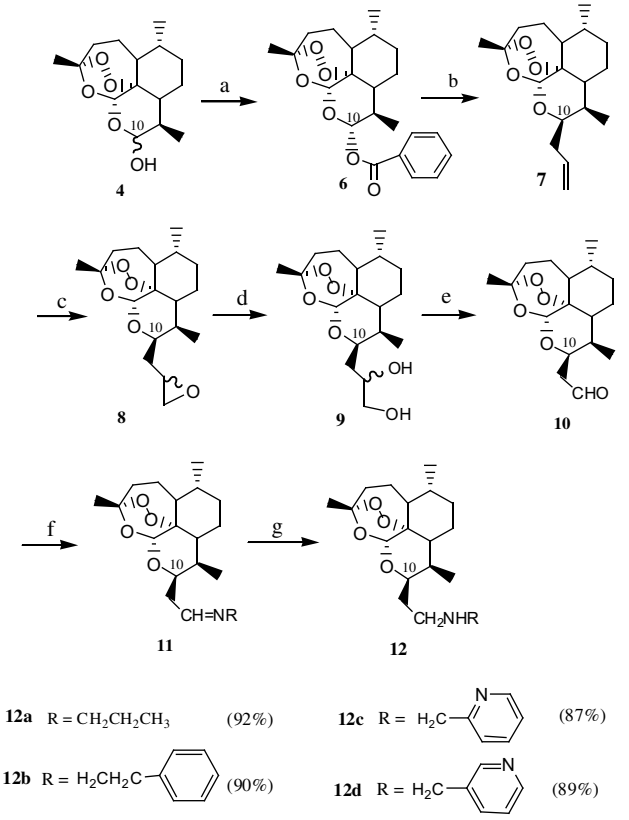
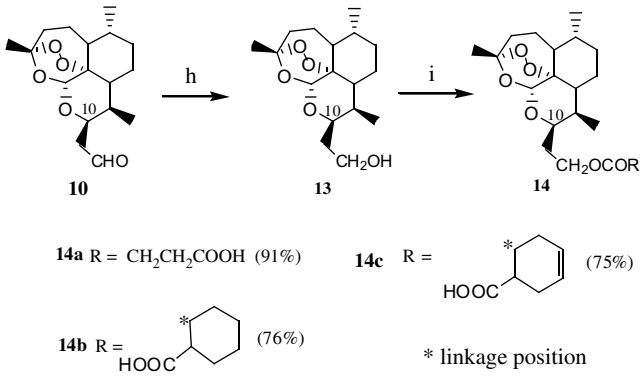


Scheme 1. Reagents and conditions: (a) benzoyl chloride, pyridine, CH_2Cl_2, rt, 16 h, 97%; (b) allyltrimethylsilane, $ZnCl_2$, 1,2-dichloroethane, 0 °C, 1 h, 90%; (c) *m*-CPBA, CH_2Cl_2, rt, 24 h, 85%; (d) (1) CF_3COOH, CH_2Cl_2, 0 °C, 1 h; (2) $NaHCO_3$ 5%, MeOH/H_2O, 1 h, 87%; (e) $NaIO_4$, MeOH, rt, 1 h, quant; (f) amines, Na_2SO_4, CH_2Cl_2, rt, 5 h; (g) $NaBH_4$, MeOH, rt, 2 h, 87–92% (three steps).

synthesized by treatment of dihydroartemisinin (**4**) with allyltrimethylsilane using catalytic Lewis acids as boron trifluoride etherate,[14,17] tin tetrachloride,[16] and zinc chloride.[18] This 10-β-allyldeoxoartemisinin (**7**) was directly ozonized to aldehyde **10**. However, the product was obtained as a reaction mixture, which is difficult to purify.[19] Later, Ziffer and co-workers[20] synthesized compound **10** by treatment of compound **7** with the mixture of osmium tetroxide and sodium periodate to afford compound **10** in 27% yield. In order to increase the yield of product **10** we modified the synthesis as shown in Scheme 1. The epoxidation of **7** by *m*-CPBA afforded a mixture of two isomers **8**. These isomers were then reacted with trifluoroacetic acid, followed by treatment with sodium hydrogencarbonate 5% to give the diol **9**, which after chromatography on silica gel was oxidized by sodium periodate in methanol and water to afford **10** in good yield. The condensation of aldehyde **10** with amines in the presence of sodium sulfate obtained imine **11**, followed by treatment with sodium borohydride in methanol afforded **12a**–**d** in high yield.[22]

The synthesis of 10-deoxoartemisinins containing the water-soluble carboxylic group is shown in Scheme 2. Reduction of aldehyde **10** by using sodium borohydride in methanol afforded compound **13** in very good yield, which was then treated with different anhydride carboxylic acids in the presence of pyridine and 4-(dimethylamino)pyridine to afford novel derivatives containing carboxylic group **14a**–**c** in good yield.[23]



Scheme 2. Reagents and conditions: (h) $NaBH_4$, MeOH, rt, 1.5 h, 95%; (i) pyridine, DMAP, anhydride carboxylic acids, CH_2Cl_2, rt, 24 h.

The antimalarial activity is assessed by known literature procedures.[21] Two strains of *P. falciparum*, the drug-sensitive GHA strain, derived from a Ghanese patient and the W-2 from CDC/Indochina III strain are used. The antimalarial activity of synthesized derivatives was evaluated and the results are summarized in Table 1.

Table 1 showed that all of the new derivatives were more potent than artemisinin to strains of *P. falciparum*. Among synthesized derivatives, the most potent derivatives, compounds **14a**, **14b**, and **14c** have shown very strong antimalarial potency. These compounds are about 25 times more potent to the resistant clone (W-2) and 20 times to the sensitive clone (Ghana) than artemisinin. In addition, other derivatives containing amino-alkyl and heterocycles were also highly potent against *P. falciparum*. These compounds are approximately 2.5–10 times more potent than artemisinin to both chloroquine-resistant and sensitive clones of *P. falciparum*. Compound **12d** is about 10 times more potent than artemisinin. The presence of carboxylic function and amino-alkyl heterocycles is beneficial to antimalarial activity.

In conclusion, a series of novel 10-deoxoartemisinins **12a**–**d** and **14a**–**c** was synthesized in good yield. These products were screened for the antimalarial activity on

Table 1. Antimalarial activities in vitro

Compds	W-2 IC_{50} (nM)	Ghana IC_{50} (nM)
12a	3	1
12b	20	11
12c	2	2
12d	1	1
13	1	1
14a	0.4	0.5
14b	0.4	0.5
14c	0.4	0.5
Chloroquine	110	18
Artemisinin	10	9

the two strains of *P. falciparum*. Almost all synthesized compounds exhibited the potent in vitro antimalarial activity. Some of them are 10–25 times more potent than artemisinin.

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22. Representative compound: 10β-[2′(*n*-propylamine-ethyl)]deoxoartemisinin (**12a**): 92%; mp: 158–160 °C; IR (KBr); ν (cm^{-1}): 3450; 2946; 2770; 2434; 1586; 1469; 1374; 1189; 1055; 878.
^{1}H NMR ($CDCl_3$; 400 MHz); δ (ppm): 5.46 (s, 1H, H-12); 4.35 (m, 1H, H-10); 3.08–3.28 (m, 2H); 2.92–3.05 (m, 1H); 2.75–2.90 (m, 1H); 2.60–2.74 (m, 1H); 2.21–2.44 (m, 2H); 1.82–2.20 (m, 6H); 1.60–1.80 (m, 3H); 1.41 (s, 3H, H-14); 1.85–1.34 (m, 3H); 0.96 (d, J = 6.25 Hz, 3H, H-15); 0.88 (d, J = 7.5 Hz, 3H, H-16).
^{13}H NMR ($CDCl_3$, 100 MHz); δ (ppm): 103.1; 89.3; 81.0; 74.3; 52.1; 49.7; 43.8; 37.2; 36.48; 36.4; 34.4; 30.2; 29.5; 26.0; 24.7; 24.7; 20.2; 19.5; 12.8; 11.3. CIMS: *m/z* 354 $[M+H]^+$.
23. Representative compound: 10β-[2′-(2″-carboxy-1″-ethylcarboxylate)-ethyl]deoxoartemisinin (**14a**): 91%; IR (KBr); ν (cm^{-1}): 3469; 2945; 1743; 1461; 1380; 1172; 1044; 836. ^{1}H NMR ($CDCl_3$; 400 MHz); δ (ppm): 5.40 (s, 1H, H-12); 4.31 (m, 1H, H-10); 4.18 (m, 2H, H-2′); 1.30–2.70 (m, 17H); 1.40 (s, 3H, H-14); 1.15–1.30 (m, 1H); 1.0 (d, J = 6.0 Hz, 3H, H-15); 0.92 (d, J = 7.5 Hz, 3H, H-16). ^{13}H NMR ($CDCl_3$, 100 MHz); δ (ppm): 176.1; 174.3; 104.5; 90.2; 82.3; 73.8; 63.8; 53.9; 45.8; 37.5; 37.4; 35.6; 31.4; 30.3; 26.1; 28.8; 25.7; 20.5; 13.2. CIMS: *m/z* 413 $[M+H]^+$.