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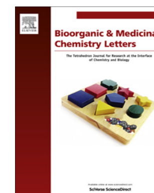

Synthesis of artemisinin dimers using the *Ugi* reaction and their in vitro efficacy on breast cancer cells

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ABSTRACT

The *Ugi* four-component reaction was used to prepare a series of artemisinin monomers and dimers. We found that the endoperoxide group in artemisinin remains intact during the reaction. The new artemisinin dimers showed potent anti-cancer activity against two human breast cancer cell lines, MDA-MB-231 and BT-474. One of the Ugi artemisinin dimers showed an IC_{50} value of 12 nM when tested on BT474 cells, more than 600 times more potent than artesunate. Furthermore, the same Ugi artemisinin dimer showed a low toxicity when tested on MCF10A, a nontumorigenic cell line, resulting in a selectivity index of more than 8000.

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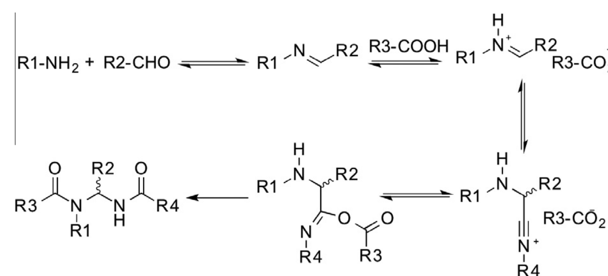
The *Ugi* four-component reaction was first reported in 1951, and has been widely used in organic synthesis.[1] In the *Ugi* reaction (Scheme 1), the initially formed imine reacts with isocyanide and carboxylic acid to form an intermediate that undergoes rearrangement to give the final dipeptide product. The *Ugi* reaction can tolerate a wide array of functional groups, and has been applied to generate compound libraries for activity screening.

Artemisinin is a naturally occurring peroxide, isolated from the Chinese medicinal plant, *Artemisia annua* L. Artemisinin and its simple derivatives have been widely used for malaria treatment in humans.[2,3] Human clinical trials have shown remarkable antimalarial activity of artemisinin derivatives and their excellent safety profile.[4,5] Artemisinin derivatives such as dihydroartemisinin and artesunate show modest anti-cancer activity. Both antimalarial and anti-cancer activities of artemisinin derivatives have been linked to iron-induced activation of the endoperoxide group of artemisinin to generate toxic radical species in the cells. We have shown that the anticancer activity of artemisinin is greatly enhanced by delivering the compound to the cellular iron uptake pathway.[6,7]

Recently, covalent dimers of artemisinin (ART dimers) have been shown to have remarkable anti-malaria and anti-cancer activities.[8–11] Some of the dimers are able to cure the malaria in a mouse model in a single administration.[12] These studies show that artemisinin dimers are an attractive class of compounds for further investigation.

We wish to report here the synthesis of new artemisinin monomers and dimers by using the *Ugi* reaction. We found that the endoperoxide group in artemisinin was compatible with the *Ugi* reaction. We also report the cytotoxicity of the new artemisinin derivatives on human breast cancer cell lines.

To prepare artemisinin dimers by using the *Ugi* reaction, we initially prepared two different artemisinin monomers as building blocks (Scheme 2). Moffatt oxidation[13] of artemisinin primary alcohol **1**[14] was furnished artemisinin aldehyde **2** in 91% chemical yield. Artemisinin amine, **4**, another component of *Ugi* reaction, was prepared by Mistunobu reaction.[15] Artemisinin primary alcohol **1** was first converted to artemisinin phthalimide **3** in 90% chemical yield by using triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD), followed by hydrazinolysis in EtOH at 50 °C, to give artemisinin amine **4** in 75% chemical yield. Two other



Scheme 1.

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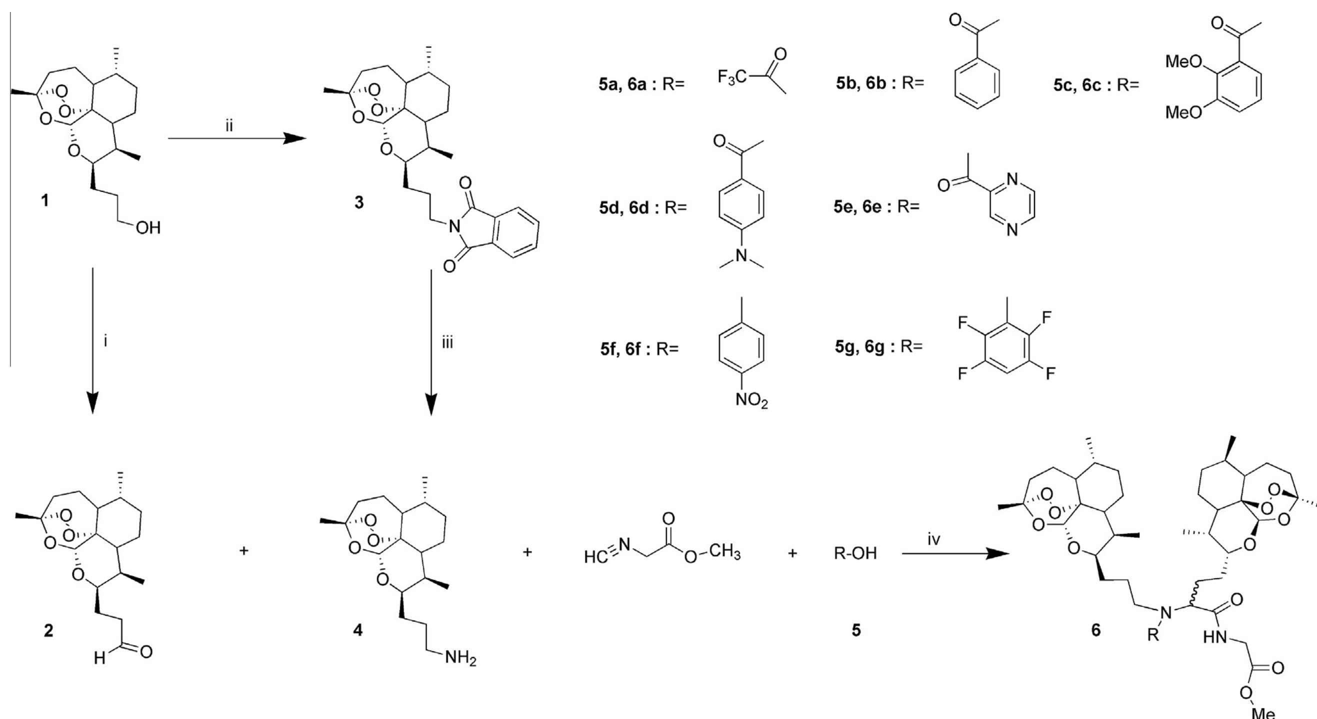
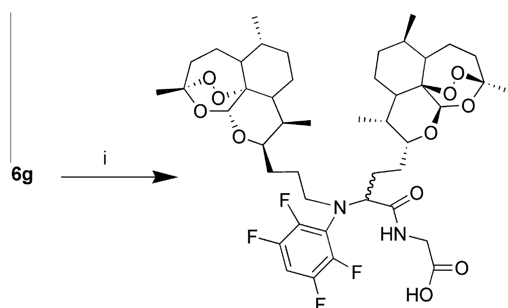


Scheme 2. Reagents and conditions: (i) benzene, dimethyl sulfoxide, pyridine, trifluoroacetic acid, *N*,*N*-dicyclohexylcarbodiimide, RT, 18 h; (ii) Ph_3P, phthalimide, DIAD, THF, 50 °C, 4 h; (iii) NH_2NH_2–H_2O, EtOH, 50 °C, overnight. The ratio of two diastereomeric products were determined by ^1H NMR; **6a**: 1:0.88; **6b**: 1:0.79; **6c**: 1:0.5; **6d**: 1:1.1; **6e**: 1:0.83; **6f**: 1:0.6; **6g**: 1:0.93.

components for the Ugi reaction are a carboxylic acid and an isonitrile. For carboxylic acid component, we included carboxylic acids **5a**–**e**. It has been reported that phenols with strong electrical withdraw group can be used as acid component in *Ugi* reaction, due to these phenols show significant acidity.[16,17] Thus, in addition to the carboxylic acids, we included *p*-nirophenol **5f** and 2,3,5,6-tetrafluorophenol **5g** in our synthesis of artemisinin dimers. A series of artemisinin dimers were synthesized by combining all the four components under the classic *Ugi* reaction conditions, that is, after stirring artemisinin aldehyde **2** and artemisinin amine **4** and acid component **5a**–**g**, respectively, in anhydrous methanol at room temperate for 30 min, methyl isocyanoacetate were added. The reaction was typically run overnight at room temperature.[18,19] After chromatographic purification we obtained six artemisinin dimers **6a**–**f** in 22–68% chemical yield. Interestingly, NMR and MS (MALDI-MS) indicated that artemisinin dimer **6g** underwent hydrolysis of methyl ester during the synthesis. This was probably due to the *trans*-esterification reaction with the phenol. Thus, we isolated the carboxylic acid **6h**, instead of **6g**, under our reaction conditions (Scheme 3). In addition to artemisinin dimers, we prepared an artemisinin monomer **7** as a control by using the same Ugi synthesis procedure (Scheme 4). Our attempts to synthesize artemisinin trimmers by using **2**, **4** and various artemisinin carboxylic acids failed, presumably due to steric interactions between the artemisinin cores.



Scheme 3. Reagents and condition: (i) methanol, RT, overnight.

We tested in vitro toxicity of new artemisinin derivatives on two breast cancer cell lines, MDA-MB-231 and BT-474. These cell lines represent triple negative and HER2-positive breast cancers, respectively. We used the standard MTT assay to determine the cell viability at 48 h after the drug was added to the culture medium. As a positive control, we included artesunate and artemisinin dimer succinate. Artemisinin dimer succinate has been shown to be up to 500 times more potent than artemisinin monomers such as artesunate when tested on a panel of NCI 60 cell lines. With MDA-MB-231 cell line, Ugi artemisinin dimers showed significantly higher potency than artesunate. Dimer **6f** was only five times less potent than artemisinin dimer succinate. With BT-474 cell lines, all the Ugi dimers showed remarkable activities. Especially, dimer **6h** showed an IC_{50} value of 12 nM, approximately eight times more potent than artemisinin dimer succinate. Artemisinin monomer **7** was completely inactive against both cell lines. We also tested the toxicity of artemisinin derivatives on MCF-10A, a nontumorigenic breast cell line, to determine the selectivity. As shown in Table 1, the selectivity of **6f** and **6h** was quite high, reaching more than 8000 for **6h**.

We have evaluated the cytotoxicity of artemisinin dimers, dimer-2Py, against a panel of four PCa cell lines, DU 145, PC-3, C4-2, and LNCaP.[20] While dimer-2Py was highly potent, dihydroartemisinin, a monomeric artemisinin, showed a negligible activity under the same conditions. Dimer-2y decreased survivin protein levels in all of the prostate cancer cell lines. Furthermore, dimer-2Py also induced the loss of androgen receptor (AR) and prostate specific antigen (PSA) expression in the C4-2 and LNCaP cells. Interestingly, dimer-ON-2Py, an analog of dimer-2Py where the hydrazone linkage is replaced by an oxime, showed significantly

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