



## Synthesis of a novel series of highly functionalized Baylis–Hillman adducts of artemisinin with potent anticancer activity



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### ABSTRACT

A novel series of densely functionalized derivatives of artemisinin have been synthesized using Baylis–Hillman reaction and their further applicability has been demonstrated. The in vitro anticancer activity of these adducts against a panel of human cancer cell lines is summarized. Compound **10** (% GI of 100 against colon colo-205; % GI of 85 against Lung A-549), **7b** (% GI of 78 against prostate PC-3) and **9a**, **9b** (% GI of 71 against prostate PC-3) were especially potent in inhibiting the growth of certain human cancer cell lines and were comparable to that of clinically used anticancer drugs. These newly synthesized compounds can be further utilized as potential precursor for the synthesis of libraries of new artemisinin analogs including dimer.

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Artemisinin **1**, a sesquiterpene lactone, isolated from the Chinese medicinal plant *Artemisia annua*<sup>1</sup> and its derivatives, for example, artemether **2** and arteether **3**, are well known antimalarial agents especially against multidrug resistant malarial strains (Fig. 1). The 1,2,4-trioxane system is primarily responsible for its antimalarial activity.<sup>2</sup> In recent years, anticancer activity of artemisinin derivatives has gained attention as a new class of antimalarial and anticancer agents and several promising leads have also emerged from these analogs which are in different stages of development.<sup>3–8</sup>

Because of its sensitive nature, the artemisinin molecule offers very little scope for widespread derivatization. The sensitive nature of the pharmacophore, that is, 1,2,4-trioxane system also demands milder reaction conditions for synthetic manipulation. In this context, several authors have attempted functionalization in the deactivated centers of artemisinin using different microorganisms with limited success, but opened up further prospect of synthetic manipulation. The first generation derivatives of artemisinin viz. C-10 ether or ester derivatives having acetal linkage at C-10 position have been found to be metabolically unstable in the acidic environment of the stomach due to acetal linkage and offer limitation to this class of derivatives. As a result, more and more atten-

tion has been diverted to developing C-10 carba analogs to overcome this problem.

Baylis–Hillman reaction is one of the most important carbon–carbon bonds forming reaction with enormous synthetic utility, promise, and potential.<sup>9</sup> The Baylis–Hillman adducts contain at least three functional groups in close proximity which can easily undergo various transformations through appropriate tuning of these groups. The adducts can be tailored in different ways to generate an array of pharmacologically important compounds such as  $\gamma$ -lactam,  $\gamma$ -butyrolactone, epoxides, azides, etc.<sup>10–13</sup> More importantly, the Michael acceptor<sup>14</sup> group present in these adducts offers further scope for addition of various nucleophiles especially artemisinin derived nucleophiles to synthesize artemisinin dimers.

Having known this background and encouraged by the various reports of enhanced biological activity of 10-deoxo artemisinins, we were tempted to synthesize some functionalized artemisinin derivatives utilizing the 10-deoxo artemisinin aldehyde as a

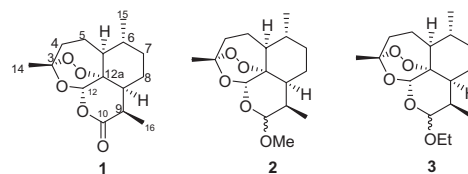
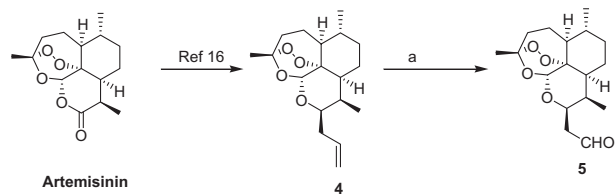


Figure 1.

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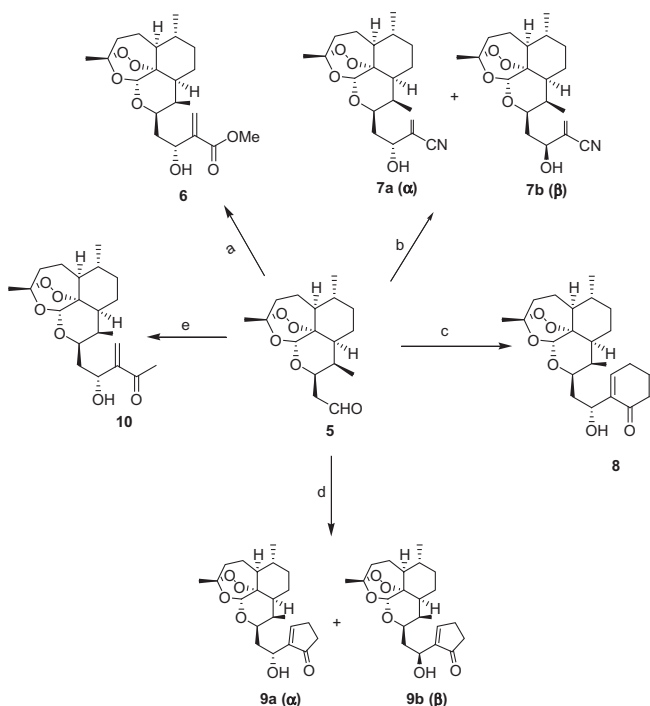
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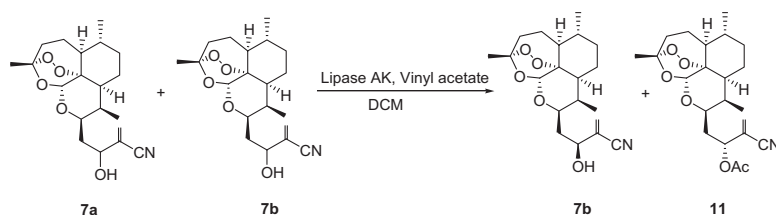
**Scheme 1.** Reagents and conditions: (a) osmium tetroxide, 2,6-lutidine, sodium periodate, dioxane–water (1:1), rt, 2 h, 60%.

precursor. As part of our ongoing project on value addition to phytochemicals,<sup>15</sup> we report herein the synthesis of a new series of 10-deoxy artemisinin derivatives along with their preliminary in vitro anticancer activity. It is worth mentioning that Baylis–Hillman reaction on sensitive artemisinin has not been attempted till date.

We designed a series of Baylis–Hillman reaction between 10-deoxy artemisinin aldehyde and different activated olefins in presence of a suitable base to synthesize highly functionalized artemisinin derivatives. We employed methyl acrylate, acrylonitrile, cyclohexenone, cyclopentenone, and methyl vinyl ketone as the activated olefins in this series of reactions to give rise to products **6**, **7a**, **7b**, **8**, **9a**, **9b**, and **10**, respectively.<sup>16</sup>



**Scheme 2.** Reagents and conditions: (a) methyl acrylate, DABCO, 31%; (b) acrylonitrile, DABCO, 67%; (c) cyclohexenone, DMAP, THF–water, 51%; (d) cyclopentenone, DMAP, THF–water, 60%; (e) methyl vinyl ketone, imidazole, L-proline, THF–water, 60%.



**Scheme 3.**

Our synthesis commenced with the three-step conversion of artemisinin to 10-β-allyldeoxy artemisinin **4** following the procedure reported by O'Neill.<sup>17</sup> It was then converted to the 10-deoxy artemisinin aldehyde **5** (Scheme 1) employing the one pot route of dihydroxylation and subsequent cleavage of the diol using osmium tetroxide in presence of 2,6-lutidine and sodium periodate as per procedure reported by Jin and co-workers in 60% yield.<sup>18</sup>

The aldehyde **5** was treated with a variety of activated olefins in presence of different bases (Scheme 2) to get hitherto unknown artemisinin derivatives **6**, **7a**, **7b**, **8**, **9a**, **9b**, and **10**. Treatment of the aldehyde with methyl acrylate in presence of 1, 4-diazabicyclo[2.2.2]octane (DABCO) in solvent free condition generated the adduct **6**. Under similar circumstances acrylonitrile furnished adduct **7**. In case of cyclohexenone and cyclopentenone, Kim and co-workers employed 4-dimethylaminopyridine (DMAP) as the base in catalytic amount.<sup>19</sup> We also tried these conditions with substrate **5** and after 3 days of continuous stirring we could isolate products **8** and **9** in 50–60% yield. Treatment of methyl vinyl ketone with **5** in presence of imidazole and L-proline furnished another densely functionalized artemisinin analog **10** in 60% yield.<sup>20</sup>

Two diastereomers were isolated in case of **7** (dr = 1.5:1; **7a**:**7b**) and **9** (dr = 2:1; **9a**:**9b**)<sup>21</sup> unlike the other cases where the other possible diastereomer was formed in very negligible amount and we did not isolate them. The major less polar isomer was arbitrarily assigned as α-isomer and the minor more polar compound as the β-isomer.<sup>22</sup> Initially, we tried to establish the stereochemistry by NOESY experiments. However, because of the flexibility of the side chain, although we observed indicative NOE cross peaks, it was not considered conclusive. Therefore, we decided to determine the stereochemistry by synthesizing the corresponding MTPA ester. To our surprise, attempts to synthesize MTPA-esters of these compounds were unsuccessful and hence empirical method of Lipase catalyzed kinetic resolution of alcohol put forward by Kazlauskas et al.<sup>23</sup> was adopted. To assign the absolute configuration to the carbinol carbon, an equimolar mixture of **7a** and **7b** was treated with *Pseudomonas fluorescens* Lipase from Amino (Lipase AK) in presence of vinyl acetate (Scheme 3).<sup>24</sup> The major less polar isomer **7a** was seen consumed to give acetylated product **11**. Since the α-isomer has (R)-configuration at carbinol carbon, this was in consonance with empirical rule predicted by Kazlauskas.

All the synthesized Baylis–Hillman adducts were tested for in vitro anticancer activity against different cell lines using Sulforhodamine B Assay and the results are summarized in Table 1. Some of the compounds showed encouraging results. Compound **10** showed 100% growth inhibition against colon colo-205 human cancer cell lines. Similarly, the same compound is also found to be promising against lung cancer cells of A-549 type, prostate PC-3, and neuroblastoma IMR-32 to an extent of 85, 81, and 79 (% GI) respectively. Among other compounds, **7b** showed glimpses of good activity against prostate PC-3 (% GI 78) and lung A-549 (% GI 77). Appreciable anticancer activities were also shown by **9b** against lung A-549 (% GI 70) and prostate PC-3 (% GI 71).

The Michael acceptor groups present in these adducts make them susceptible to be attacked by nucleophiles such as nitro

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