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Synthesis and anticancer activity of novel aza-artemisinin derivatives

Sampad Jana [a,d], Shabina Iram [b,d], Joice Thomas [a], Sandra Liekens [c,*], Wim Dehaen [a,*]

[a] Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
[b] Department of Plant Biotechnology, Atta-Ur-Rahman School of Applied Biosciences (ASAB), National University of Sciences and Technology (NUST), H-12 Islamabad, Pakistan
[c] Rega Institute for Medical Research, Department of Microbiology and Immunology, KU Leuven, 3000 Leuven, Belgium

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ABSTRACT

Three series of aza-artemisinin derivatives were synthesized for studies of anticancer activity. The first series of compounds were prepared via copper(I)-catalyzed azide alkyne cycloaddition, so called "click reaction", starting from propargyl derivatives of 11-aza-artemisinin and various azides, whereas the second and third series of compounds were prepared by triazolization reaction starting from enolizable ketones and primary amines connected to artemisinin. In vitro studies of the 23 synthesized artemisinin derivatives unveiled that 9 compounds displayed antiproliferative activity in the low micromolar range, with **5d** being the most promising compound showing 50% inhibition of Cem and HeLa cell growth at 0.92 and 1.2 μM, respectively.

1. Introduction

Artemisinin, which is a naturally occurring 1,2,4-trioxane sesquiterpene, is best known for its antimalarial activity.[1,2] Artemisinin and its derivatives have shown an excellent safety profile. Recently it has been discovered that artemisinin derivatives also possess anticancer activity with low toxicity.[3–11] Although the mechanism of action is still not clear, one of the believed reasons behind both the anticancer and antimalarial activity is the generation of highly cytotoxic carbon-centred free radicals by reaction of iron ions with the endoperoxyl moiety of artemisinin.[11] In order to increase the therapeutic value, several derivatives of artemisinin have been prepared in recent years.[3–10] However, poor water solubility, bio degradation by liver, and short half live undermine the therapeutic value of artemisinin.[11] Artemisinin derivatives which are devoid of these deficiencies will have a high chance to go into clinical trials. Thus, an urgent investigation is needed to improve the pharmacological properties of artemisinin derivatives.

The applications of the click reaction have grown significantly since the discovery by Sharpless and Meldal.[12] Due to the mild reaction conditions and the high functional group tolerance, the click reaction has been used in diverse fields of chemistry for linking two partners via a triazole.[13,14] Beside the click reaction several synthetic strategies have been discovered toward triazoles.[15,16] Recently, the triazolization strategy developed by our group has drawn considerable attention. This metal-free strategy enables the synthesis of various previously inaccessible 1,5-disubstituted and fused 1,2,3-triazole derivatives from commercially and readily available starting materials such as unactivated enolizable ketones and primary amines.[17–19]

Several heterocyclic derivatives of artemisinin were developed in order to increase the anticancer properties.[3–10] Almost all the modifications were done at the C-10 carbon atom. In contrast, only a limited number of modifications at O-11 were reported.[20] Among these, 11-aza-artemisinin and its derivatives were mostly studied and are known to possess various biological activities. However, the lack of an efficient functional handle for further diversification of aza-artemisinin limits its application in pharmaceutical chemistry.[21] Hence the development of a synthetic route by which a series of diverse derivatives of artemisinin could be prepared is necessary. Here we would like to disclose the synthesis and anticancer activity of a series of 11-aza-artemisinin derivatives, which were prepared by general click reactions, as well as dihydroartemisinin derivatives, prepared *via* triazolization strategies.[22]

2. Results and discussion

2.1. Chemistry

First, 11-aza-artemisinin **2** has been prepared starting from artemisinin by a previously reported method (Scheme 1).[20] In accordance to that method, 11-aza-artemisinin **2** was obtained by immersion of artemisinin in liquid ammonia at −15 °C. The 11-aza-artemisinin **2** was then treated with propargyl bromide in

* Corresponding authors.
E-mail address: wim.dehaen@chem.kuleuven.be (W. Dehaen).
[d] These author contributed equally.

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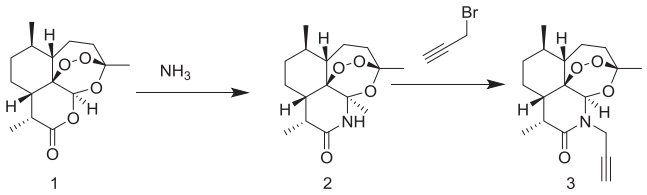

Scheme 1. Synthesis of propargyl derivative of 11-aza-artemisinin.

the presence of a base resulting in the propargyl derivative of 11-aza-artemisinin **3** (scheme 1), which readily undergoes click reaction with various azides **4** to form a library of 1,4-disubstituted triazoles (**5a**–**5g**) in excellent yield (Table 1).

Next, two series of compounds were prepared *via* triazolization strategy.[17–19] Out of three series, the second one was based on the variation of ketones and third one was about the variation of amines. In the second strategy, the amine **7** was synthesized in three steps starting from dihydroartemisinin.[22] The amine functionalized dihydroartemisinin **7** was subsequently treated with various enolizable ketones **6** and 4-nitrophenyl azide, yielding the desired 1,5-disubstituted or fused 1,2,3-triazoles **8a**–**l** (Table 2). Products from the third strategy were obtained by varying amines. The starting ketone **9** was synthesized from dihydroartemisinin in a one-step fashion. The dihydroartemisinin functionalized ketone was then treated with amine **10** and 4-nitrophenyl azide resulting in the formation of fused 1,2,3-triazoles **11a**–**d** (Table 3).

2.2. Biological activity

The anti-proliferative activity of the synthesized compounds was evaluated in 2 tumor cell lines: human T-lymphoblastic leukemia (CEM) and human cervical carcinoma (HeLa) cells, and in human dermal microvascular endothelial HMEC-1 cells. Data are expressed as IC_{50} (50% inhibitory concentration), which is defined as the compound concentration that reduces cell proliferation by 50%, and are shown in Table 4.

Aza-artemisinin (**2**) did not inhibit the growth of the cell lines tested ($IC_{50} > 150\ \mu M$). Also, its propargyl derivative (**3**) only showed a cytostatic effect at 100 μM. However, several 1,4-disub-

Table 1
List of compounds from click reaction.