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Synthesis and cytotoxic activity of new artemisinin hybrid molecules against human leukemia cells

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ABSTRACT

A series of new artemisinin-derived hybrids which incorporate cholic acid moieties have been synthesized and evaluated for their antileukemic activity against sensitive CCRF-CEM and multidrug-resistant CEM/ADR5000 cells. The new hybrids **20**–**28** showed IC_{50} values in the range of 0.019 μM–0.192 μM against CCRF-CEM cells and between 0.345 μM and 7.159 μM against CEM/ADR5000 cells. Amide hybrid **25** proved the most active compound against both CCRF-CEM and CEM/ADR5000 cells with IC_{50} value of 0.019 ± 0.001 μM and 0.345 ± 0.031 μM, respectively. A relatively low cross resistance to hybrids **20**–**28** in the range of 5.7-fold to 46.1-fold was measured. CEM/ADR5000 cells showed higher resistance than CCRF-CEM to all the tested compounds. Interestingly, the lowest cross resistance to **23** was observed (5.7-fold), whereas hybrid **25** showed 18.2-fold cross-resistant to CEM/ADR5000 cells. Hybrid **25** which proved even more potent than clinically used doxorubicin against CEM/ADR5000 cells may serve as a promising antileukemic agent against both sensitive and multidrug-resistant cells.

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1. Introduction

Artemisinin (**1**) (Fig. 1), isolated from the Chinese plant *Artemisia annua* L., is a sesquiterpene lactone containing a 1,2,4-trioxane moiety, which has been proved a milestone in the treatment of malaria.[1–4] In an effort to improve the pharmacokinetic profile and efficacy of artemisinin, semi-synthetic derivatives[2,5,6] such as dihydroartemisinin (**2**),[7] artesunic acid (**3**)[8] and artemether (**4**)[9] (Fig. 1) have been developed and used in combination with other drugs for more than a decade. As a result, artemisinin-based combination therapies (ACTs)[10] have been considered the gold standard in the treatment of malaria caused by the drug-resistant *Plasmodium falciparum* strains, celebral malaria and malaria in children.[11,12] The bioactivity of artemisinins is strongly correlated with the presence of the endoperoxide bridge, which is implicated in the generation of reactive oxygen species (ROS) and peroxy free radicals inducing oxidative stress, DNA damage, alkylation of target proteins and apoptosis.[13–18]

Besides the antimalarial effects, the artemisinin compounds display a broad range of biological activities.[19,20] For example, artemisinin (**1**) and artesunic acid (**3**) have presented interesting antitumor[6,21–23] and antiviral properties.[24–28] More precisely, anticancer activities of artemisinins are mediated through inhibition of metastasis,[29] cancer-related signaling pathways[30–33] and angiogenesis.[34–36] Artemisinin compounds have shown cytotoxic activities against leukemia, colon, melanomas, breast, ovarian, prostate, central nervous system, and renal cancer cell lines.[37–39]

Various efforts to improve the effectiveness of artemisinins have led to the synthesis of artemisinin-derived hybrid molecules.[40–48] Interestingly, artemisinin-derived dimers and trimers have shown not only improved antimalarial and antiviral activities, but also great potency against leukemia cells in comparison with the corresponding parent artemisinin precursors or even the clinically used anticancer agent doxorubicin.[43] Additionally, hybrid molecules which combine the artemisinin pharmacophore with other bioactive natural product fragments via a linker, have been identified as promising anticancer drug candidates.[44,46,49]

In parallel, the insertion of the 1,2,4,5-tetraoxane motif in various cycloalkanes revealed an alternative pharmacophore group of synthetic antimalarials.[50–53] In an effort to address issues related to the lipophilicity and *in vivo* stability of this class of compounds, a series of bile acid-derived 1,2,4,5-tetraoxanes **5** (Fig. 2) have been synthesized and proved potent *in vitro* and *in vivo* antimalarials as well as *in vitro* antiproliferative agents.[54–56] Recently,

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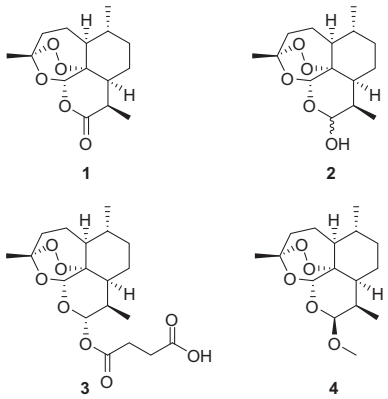


Fig. 1. Structures of artemisinin (**1**) and its derivatives.

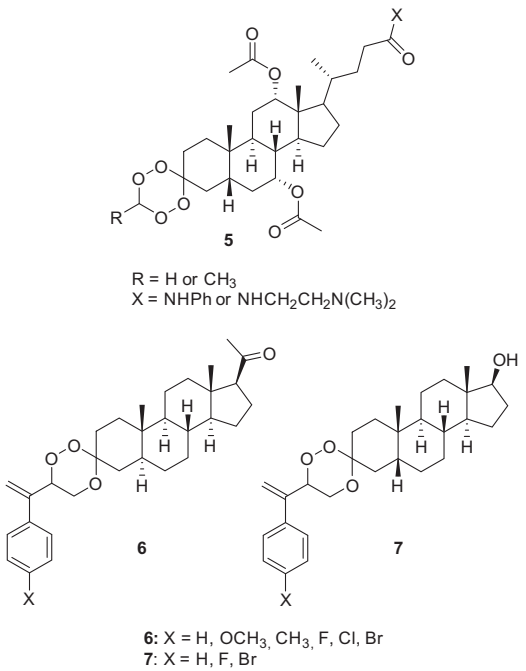


Fig. 2. Structures of bile acid-derived 1,2,4,5-tetraoxanes **5**, steroid-based **6** and bile acid-based 1,2,4-trioxanes **7**.

steroid-based **6**[57] and bile acid-based **7**[58] 1,2,4-trioxanes (Fig. 2) have shown significant *in vivo* antimalarial properties against multidrug-resistant *Plasmodium yoelii*. Additionally, the conjugation of nitrogenated bases with bile acid moieties has been applied as strategy to overcome chemotherapy drug resistance.[59]

Prompted by these data and due to our interest in the identification of new anticancer hybrid agents,[60–62] we decided to generate new artemisinin hybrid compounds which incorporate a bile acid moiety and investigate their anticancer activity. To gain insights into structure activity relationships, we use as building blocks of our new hybrids three C-10 substituted artemisinin derivatives with side chains of different length, the artesunic acid (**3**) as well as the artemisinin-derived carboxylic acid and alcohol, **8**[63] and **9**[64] (for chemical structures see Scheme 2), respectively. Precursors **8** and **9** were chosen based on literature data which indicated that C-10 non acetal artemisinin derivatives present greater stability and bioavailability than recently established drugs like artemether (**4**) and arteether.[65–68]

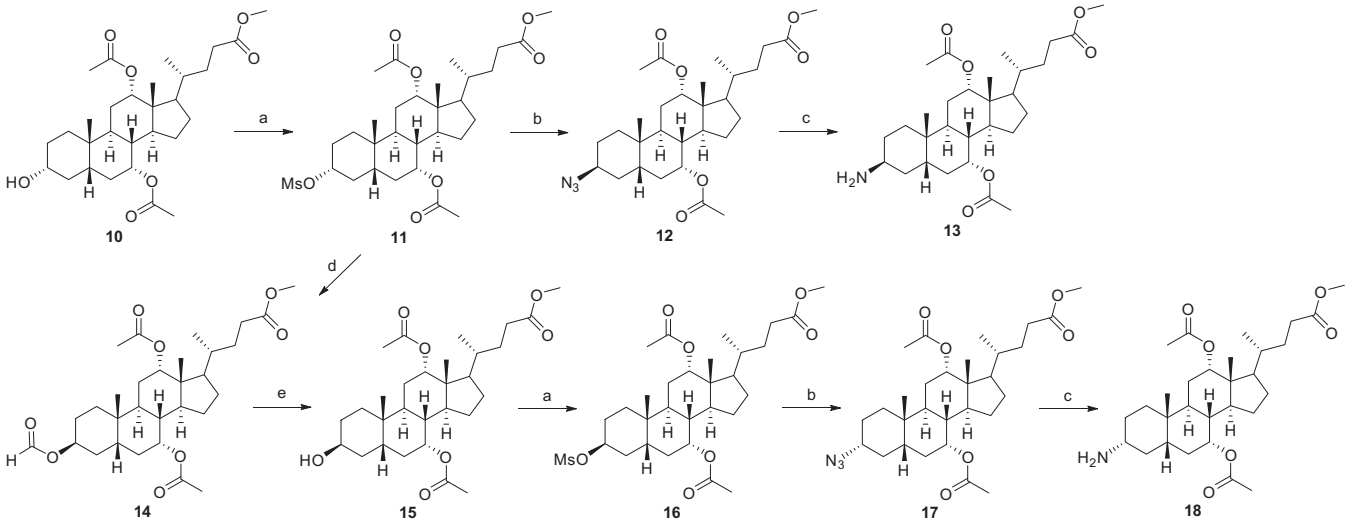
The diastereomers **10**[54] and **15**,[69] the corresponding 3-amino derivatives **18** and **13** and the 24-carboxy-cholic acid derivative **19**[54] were chosen as the bile acid fragments of the new hybrid molecules as the incorporation some of them in cholic acid-derived 1,2,4,5-tetraoxanes contributed significantly to the antimalarial and antiproliferative activity of the target molecules.[54]

Herein, we describe the synthesis of nine new artemisinin hybrid molecules and their biological activity against drug-sensitive CCRF-CEM leukemia cells and the multidrug-resistant leukemia sub-line CEM/ADR5000.

2. Results and discussion

2.1. Chemistry

Initially, the synthesis of the cholic acid derivatives **13**, **15** and **18** was performed (Scheme 1). Mesylation of **10** using methanesulfonyl chloride in the presence of triethylamine in DCM afforded the 3α-methanesulfonate **11** in excellent yield. Azidation of **11** furnished the corresponding 3β-azide derivative **12** which after Staudinger reduction provided the 3β-amino derivative **13**. Alternatively, prolonged heating of **11** in DMF, following the slightly modified method described by Chang[70] gave the 3β-formate **14**[69] which upon selective basic hydrolysis afforded the desired 3β-hydroxyl derivative **15**. The latter was transformed



Scheme 1. Synthesis of cholic acid derivatives **13, 15** and **18**. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, DCM, 0 °C, 1 h, yields: **11** = 94%, **16** = 96%; (b) NaN_3, DMF, 120 °C, 24 h, **12** = 91%, **17** = 93%; (c) Ph_3P, THF, H_2O, rt, 24 h, yields: **13** = 87%, **18** = 91%; (d) DMF, 80 °C, 144 h, 72%; (e) K_2CO_3, CH_3OH, rt, 1.5 h, 96%.

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