# NEW ARTEMISININ HYBRIDS WITH 1,2,3-TRIAZOLE LINKERS

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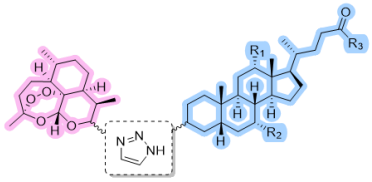
Artemisinin is a natural sesquiterpene lactone, widely used for the treatment of malaria.[1] Besides malaria, artemisinin and its derivatives have shown inhibitory effects against viruses, bacteria, fungi and various cancer cell lines.[2] Oxidative stress, induction of apoptosis, inhibition of angiogenesis, arrest of cell cycle at $G_0/G_1$ and ferroptosis are the most commonly reported mechanisms of artemisinin's anticancer activity.[3] Notably, artemisinin has been reported to decrease the viability of the prostate cancer cells through ubiquitin-26S proteasome-mediated degradation of the human androgen receptor.[4] Conjugation of artemisinin to a wide range of bioactive molecules has been applied as an approach for the improvement of its biological activities. Interestingly, artemisinin-derived hybrids have been identified as promising anticancer drug candidates, while artemisinin-bile acid hybrids have been studied on various cancer cell lines, mostly against hepatocarcinoma and leukemia.[5]

In an attempt to discover new agents with potential activity against prostate cancer, we designed and synthesized new artemisinin-derived hybrids containing cholic acid moieties and utilizing a 1,2,3-triazole linker (**I**). We have previously reported on the anticancer activity of several artemisinin-derived hybrids containing cholic fragments connected to various artemisinin derivatives through amide or ester bonds.[6] In the present study, we focus on the modification of the linker with the aim to attain optimized compounds.

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Appropriately modified $C_{10}$ artemisinin and $C_3$ cholic acid derivatives were synthesized and introduced to a Cu(I) catalyzed 1,3-cycloaddittion reaction for the generation of the 1,2,3-triazole containing, target hybrid molecules. The new artemisinin-derived hybrids exhibited promising antiproliferative and cell migration inhibitory activity in PC-3 prostate cancer cells when compared with previously synthesized, by our group, hybrids bearing an ester or amide linkage between the artemisinin and the cholic acid fragment. Furthermore, the tested molecules did not show toxic activity against NIH-3T3 fibroblast cells. Herein, the synthesis and the results of preliminary biological evaluation of these new hybrids will be presented.

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