Medicinal Chemistry

(Iso)Quinoline–Artemisinin Hybrids Prepared through Click Chemistry: Highly Potent Agents against Viruses

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Abstract: Viral infections cause life-threatening diseases in millions of people worldwide every year and there is an urgent need for new, effective antiviral drugs. Hybridization of two chemically diverse compounds into a new bioactive effector product is a successful concept to improve the properties of a hybrid drug relative to the parent compounds. In this study, (iso)quinoline–artemisinin hybrids, obtained through copper-catalyzed azide–alkyne cycloaddition or metal-free click reactions (in organic solvents or in the presence of water), were analyzed in vitro, for the first time, for their inhibitory activity against human cytomegalovirus (HCMV), relative to their parent compounds and the reference drug ganciclovir. EC₅₀ (HCMV) values were obtained in a range 0.22–1.20 μM, which indicated highly potent antiviral properties in the absence of cytotoxic effects on normal cells (CC₅₀ > 100 μM). The most active hybrid, 1 (EC₅₀ = 0.22 μM), is 25 times more potent than its parent compound artemisinic acid (EC₅₀ = 5.41 μM) and 12 times more efficient than the standard drug ganciclovir (EC₅₀ = 2.6 μM). Interestingly, hybrid 1 also shows inhibitory activity against hepatitis B virus in vitro (EC₅₀ (HBeAg) = 2.57 μM).

Introduction

Human cytomegalovirus (HCMV) is an opportunistic viral pathogen, which can take severe and sometimes life-threaten-
fungal, and antibacterial. Furthermore, quinolines are also active against a wide range of viruses, such as coronaviruses, human immunodeficiency virus (HIV), respiratory syncytial virus, hepatitis C virus, West Nile virus, Zika virus, and Dengue virus. Known representatives in the field of antiviral agents containing an (iso)quinoline core structure are depicted in Figure 1A, namely, the protease inhibitors Paritaprevir (a drug against hepatitis C virus), saquinavir (an anti-HIV drug), FGI-104 (a drug candidate against Ebola virus), and chloroquine (an antimalarial drug that is active against several viruses, including HIV, hepatitis C virus, Ebola virus; and, as recently reported, against coronaviruses, including newly emerged SARS-CoV-2).

ARN is an enantiopure sesquiterpene lactone/trioxane (Figure 1B), which is an approved antimalarial drug originally been isolated from the plant Artemisia annua L. The herb has been used since ancient times; however, structural identification of ARN was first possible in 1972 through X-ray crystal structure analysis by Tu. Artesunate (the sodium salt of ART (Figure 1B)), a semisynthetic derivative of ARN, has recently been characterized as an active compound against wild-type, recombinant, GCV-sensitive, and GCV-resistant HCMVs, lacking cross-resistance with HCMV drugs in vitro. In addition to artemesine, other derivatives, such as DHA and artemether (Figure 1B), have been widely investigated as potential antiviral agents.

As alternatives to standard drugs, our ongoing search for highly active hybrid molecules, which exceed their parent compounds in activity against HCMV and malaria parasites, has resulted in the synthesis of novel (iso)quinoline–ARN hybrids (Figure 2). Notably, in our recent study, we reported that these hybrids were able to combat multidrug-resistant malaria. Herein, we focus on their activities against HCMV. Twelve (iso)quinoline–ARN hybrids from our previous work were, therefore, analyzed, for the first time, for their potency as quinoline–ARN HCMV agents. The hybrid compounds exhibited high anti-HCMV activities, without toxic effects on normal cells, and were more active than their parent compounds and more efficient than the standard drug GCV. In addition, the most potent anti-HCMV hybrid also showed inhibition activity against HBV in vitro.

**Results and Discussion**

**Chemistry**

The synthesis of hybrid compounds 1–12 (Figure 2) was described in our previous work (in which the compounds were studied against chloroquine-resistant malaria parasites). Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions were applied to couple the corresponding (iso)quinolines with ARN derivatives in vitro. In addition to artemesine, other derivatives, such as DHA and artemether (Figure 1B), have been widely investigated as potential antiviral agents.

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trimethylsilylacetylene.\(^{[21]}\) Additionally, hybrid 3 was isolated as a side product of hybrid 2 because the peroxide bridge of ARN was hydroxylated at the C3 position in the presence of copper(I) species, resulting in desoxydehydromarselfpinin (Scheme 1A).\(^{[22]}\) Hybrids 4–12 were obtained by coupling ART-\((18–21)\) or ARN-derived \((23–27)\) alkynes with 4-azido-7-chloroquinoline (22) in the presence of the catalyst system \(\text{CuSO}_4\cdot\text{H}_2\text{O}\) and sodium ascorbate (Scheme 1B and C).

To open up the opportunity to apply the formation of our hybrid compounds in future research in the field of bioorthogonal chemistry and, for example, enable the generation of hybrids in situ directly in living cells, we additionally applied an alternative metal-free pathway, leading to the selected hybrid compounds 8, 10, and 12. The first metal-free click reaction, which was reported independently in 2014 by the groups of Ramachary\(^{[23]}\) and Paixão,\(^{[24]}\) is a green method that might allow toxic copper(I) species\(^{[25]}\) to be replaced with DBU. The mechanism of regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles by applying a DBU/malononitrile co-catalyzed 1,3-dipolar cycloaddition strategy was proposed by Paixão et al.\(^{[24]}\) It starts with a Knoevenagel condensation of malononitrile with the aliphatic aldehyde, giving the alkylidene malononitrile A, which is subsequently deprotonated by DBU, forming vinlogous carbamion B (Scheme 2). Electron-rich olefin B thereafter reacts with the aryl azide, proceeding via proposed transition-state TS1, to give cycloaddition adduct D after protonation. Hypothetical transition-states TS2, which could lead to isomer F (not observed), and TS3, which could give zwitterionic intermediate E, might be disfavored energetically. Finally, a syn-elimination step results in the 1,4-disubstituted-1,2,3-triazole products and recovers the malononitrile.\(^{[24]}\)

Aldehydes are used as substrates instead of alkynes, which are applied in CuAAC. Thus, for metal-free click reaction, we used ARN-derived aldehydes 31–33 and the previously applied azide 22 to form hybrids 8, 10, and 12. The aldehydes were obtained by etherification of DHA with the corresponding alco-
A) Synthesis of isoquinoline–ARN hybrids 1–3 through the CuAAC reaction. B) Synthesis of 7-chloroquinoline–ARN hybrids 4–7 through the CuAAC reaction. C) Synthesis of 7-chloroquinoline–ARN hybrids 8–12 through the CuAAC reaction. D) Synthesis of hybrids 8, 10, and 12 through metal-free click reactions. Reagents and conditions: A) i) [Co(CO)Cp*] (10 mol%), CuCl (1 mol%), Ph$_3$P (1 mol%), 1,2-dichloroethane, 120°C, 1 h; ii) 1) [PdCl$_2$(PPh$_3$)$_2$] (1.0 mol%), trimethylsilylacetylene, triethylamine, 50°C, 2 h; 2) K$_2$CO$_3$, MeOH, 25°C, 4 h; iii) CuSO$_4$·5H$_2$O (5 mol%), sodium L-ascorbate (10 mol%), CH$_3$Cl/H$_2$O (1:1), RT, 1h; iv) Ph or nBu. B) i) CuSO$_4$·5H$_2$O (20 mol%), sodium ascorbate (40 mol%), CH$_3$Cl/H$_2$O (1:1), RT, 1h; ii) Dess–Martin periodinane (1.2 equiv), CH$_2$Cl$_2$; 28: n = 3 (C-10β); 28α: n = 3 (C-10α); 29: n = 4 (C-10β); 30: n = 6 (C-10β); iii) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 1 equiv), malononitrile (1 equiv), DMSO, RT, 4h; 31: n = 3 (C-10β); 32: n = 4 (C-10β); 33: n = 6 (C-10β).

hols, catalyzed by H$_2$PW$_2$O$_7$·H$_2$O (Scheme 1D), and subsequent Dess–Martin oxidation reaction to obtain aldehydes. Because a mixture of both DHA isomers was used, the alpha and beta isomers of the ARN-derived alcohols were formed. In the case of compound 28, a mixture of both isomers (28β (C-10β)//28α (C-10α) = 5:4) were isolated and used further. In the case of compounds 29 and 30, the β isomers were separately isolated in moderate yields (29: 40%, 30: 44%). The corresponding Dess–Martin oxidation gave the ARN-derived aldehydes 31–33 (31: 86%, 32: 65%, 33: 14%).

The DBU-mediated 1,3-dipolar cycloaddition was performed by stirring 22 with the corresponding ARN-derived aldehydes 31–33 at RT in DMSO in the presence of malononitrile (1 equiv) and DBU (1 equiv). Hybrids 8, 10, and 12 were obtained in 43, 30, and 36% yields, respectively (Scheme 1D). Comparing the outcomes of the CuAAC and for metal-free cycloaddition reactions in organic solvents (Scheme 2 and Table 1), the CuAAC catalysis gives hybrid 8, with the shortest linker, in a better yield (70%) than entry 1 through metal-free click reaction (43%, entry 5). If the linker contains more CH$_2$ groups, the yields of hybrids 10 and 12 obtained in organic solvents through both synthetic pathways are almost identical: yields of CuAAC reactions were 35 (for hybrid 10, entry 2) and 32% (for hybrid 12, entry 3), whereas yields of the corresponding metal-free click reactions were 30 (hybrid 10, entry 6) and 36% (hybrid 12; Table 1, entry 7), respectively.

As an initial test case for a metal-free click reaction as a potential bioorthogonal reaction, we evaluated the tolerance of both catalytic systems to water as a solvent and studied how the yield of hybrid 8 was influenced by changing the solvent system from H$_2$O/CH$_2$Cl$_2$ (CuAAC; Table 1, entry 4) and DMSO (metal-free click reaction; Table 1, entry 8) to H$_2$O. The experiments showed that, for the formation of quinoline–ARN hybrid 8 under aqueous conditions, the metal-free system resulted in better yield (30% yield, Table 1, entry 8) than that of the CuAAC reaction system (9% yield, Table 1, entry 4). This higher yield of product 8, obtained through the metal-free click reaction in the presence of water, could be explained by higher...
polarity of the aldehyde, relative to the alkyne, and thus, its higher solubility in water. In summary, such a metal-free click reaction in water has the potential to be developed as a bioorthogonal metal-free reaction under live-cell conditions or in live cells.

**Antiviral activity**

In our previous study, the set of hybrids 1–12 enabled us to investigate variation of the antimalarial activities, depending on the type of linkage between ARN and (iso)quinolones. Herein, the extension of this study to the in vitro quinoline–ARN HCMV activity is presented (Table 2).

Reference drug GCV; two quinoline compounds (34 and 35; see Table S1 in the Supporting Information); and the parent drugs ARN, ART, DHA, and artemether were used as comparative compounds in this analysis. Anti-HCMV EC_{50} values of the hybrids and of precursor 13 were determined. GCV and ART showed EC_{50} values of (2.60 ± 0.5) and (5.41 ± 0.61) µM (Table 2), respectively, whereas ARN, DHA, and artemether were mostly inactive against HCMV. Similarly, quinoline compounds 34 and 35, as well as parent compound 13, only comprising the 7-chloroquinoline unit, had no measurable effect on HCMV replication. Contrary to the antimalarial results, this antiviral analysis showed that dihydroartemisinin-7-chloroquinoline-based hybrids 8–12 and isooquinoline–ARN hybrids 1 and 2 achieved the highest activity, with EC_{50} values ranging from (0.22 ± 0.04) to (1.20 ± 0.11) µM, even exerting higher in vitro activities than those of the parent and reference compounds. Isomers 8 (C-10β-isomer) and 9 (C-10α-isomer) exhibited a similar structure–activity relationship against HCMV to that observed for the antimalarial activity; the β-isomer was

### Table 1. A comparison of CuAAC and metal-free cycloaddition reactions.

| Entry | Catalytic system[a] | Solvent[a] | Product | Yield[a] [%] |
|-------|---------------------|------------|---------|--------------|
| 1     | CuSO_4·5H_2O (20 mol %), sodium ascorbate (40 mol %) | CH_2Cl_2/H_2O (1:1) | 8 | 70 |
| 2     | CuSO_4·5H_2O (20 mol %), sodium ascorbate (40 mol %) | CH_2Cl_2/H_2O (1:1) | 10 | 35 |
| 3     | CuSO_4·5H_2O (20 mol %), sodium ascorbate (40 mol %) | CH_2Cl_2/H_2O (1:1) | 12 | 32 |
| 4     | CuSO_4·5H_2O (1 equiv), sodium ascorbate (4 equiv) | H_2O | 8 | 35 |
| 5     | DBU (1 equiv), malononitrile (1 equiv) | DMSO | 8 | 83 |
| 6     | DBU (1 equiv), malononitrile (1 equiv) | DMSO | 10 | 30 |
| 7     | DBU (1 equiv), malononitrile (1 equiv) | DMSO | 12 | 36 |
| 8     | DBU (1 equiv), malononitrile (1 equiv) | H_2O | 8 | 30 |

[a] Reaction conditions and product yields correspond to the reaction mechanism depicted in Scheme 2.
more active than the \( \alpha \)-isomer. \( \beta \)-Isomer 8 showed an EC\(_{50} \) value of (0.71 ± 0.03) \( \mu \)M, whereas \( \alpha \)-isomer 9 showed (1.20 ± 0.11) \( \mu \)M. Hybrids 10, 11, and 12 were particularly active, with EC\(_{50} \) values of (1.08 ± 0.18), (0.30 ± 0.02), and (0.38 ± 0.03) \( \mu \)M (Table 2). The two longest linkers (hybrids 11 and 12), as spacers between pharmacophores, improved the activity; this was likely as a result of providing increased intramolecular flexibility.

Surprisingly, isoquinoline–ARN hybrids 1 and 2 showed 8- to 25-fold higher activities than that of ART, with EC\(_{50} \) values of (0.22 ± 0.04) and (0.67 ± 0.03) \( \mu \)M, respectively, whereas none of the other ART-based hybrids 4–7 were found to be active against HCMV (or the EC\(_{50} \) values could not be determined due to the induction of cytotoxicity). Of the three isouquinoline–ARN hybrids, only one, namely, hybrid 3, was inactive; this can be ascribed to hydroxylation of the peroxide bridge of the ARN unit. This finding was comparable to the antimarial activity of 3, for which bioactivation was putatively based on the peroxide bridge. Notably, all active compounds were similar or even more active, in terms of in vitro anti-HCMV efficacy, than that of the parent compounds and reference drugs. Moreover, none of these compounds exerted acute cytotoxicity, according to the LDH release assay, with CC\(_{50} \) values of >100 \( \mu \)M (Table 2).

Recently, the activities of ARN, artemesane, and whole extract of Chinese herb Artemisia capillaris were determined in HBV-transfected HepG2.2.15 cells.[32] Artemesane was shown to inhibit the HBV’s antigen (HBsAg), with an IC\(_{50} \) value of 2.3 \( \mu \)M, and reduced the amount of HBV-DNA secreted from HepG2.2.15 cells to the culture medium. On the other hand, HBsAg reduction by ARN was weaker, with an IC\(_{50} \) value of around 50 \( \mu \)M, and no reduction in HBV-DNA was observed.[34]

Inspired by these results, we decided to assess the inhibitory potential of a selected subset of ARN-derived hybrid compounds 1, 2, 5, 7, 11, and 12 against HBV. Inhibition of HBV was evaluated by measuring the extent to which the test compounds reduced the release of HBV e antigen (HBeAg) and HBV-DNA after infection of HepG2-hNTCP cells for 14 days.

The reference compounds TAF, DHA, and ART were used for comparison in the assays. Isoquinoline–ARN hybrid 1, containing \( n \)-butyl moieties, inhibited HBeAg secretion in cell-free supernatant, with EC\(_{50} \) = (2.57 ± 1.51) \( \mu \)M, and showed a reduction in HBV-DNA, with an IC\(_{50} \) value of approximately 10 \( \mu \)M. This compound exhibited cytotoxicity in HepG2-hNTCP cells, with CC\(_{50} \) = (29.9 ± 1.1) \( \mu \)M. The reference compound TAF showed similar cytotoxicity and reduction in HBeAg secretion, but, as a selective inhibitor of reverse transcriptase activity, it showed 10000 times better inhibition of HBV-DNA secretion in a medium than that of compound 1. The introduction of phenyl moieties in the place of \( n \)-butyl in compound 2 abolished the anti-HBV activity. Similarly, there was no anti-HBV activity for dihydroartemisinin-7-chloroquinoline-based hybrids 11 and 12.

### Conclusion

Although HCMV infection is mostly inapparent in immunocompetent persons, it can be life-threatening for immunonaıve or immunocompromised individuals, so that anti-HCMV-specific drug research is an ongoing issue investigated worldwide. To this end, the present study characterized new (iso)quinoline–ARN hybrid compounds for anti-HCMV activity in vitro. Thus, three isoquinoline–ARN and nine quinoline–ARN hybrids, together with their precursors and reference drugs, were phar-

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**Table 2.** EC\(_{50} \) values for reference compounds GCV, ART, ARN, DHA, artemether, tenofovir alafenamide fumarate (TAF); parent compound 13, and hybrids 1–12, which were analyzed for anti-HCMV and anti-HBV activities.[26]

| Compound | HCMV EC\(_{50} \) [\( \mu \)M] | LDH CC\(_{50} \) [\( \mu \)M] | HepG2-hNTCP CC\(_{50} \) [\( \mu \)M] | HBeAg ELISA EC\(_{50} \) [\( \mu \)M] | HBV DNA qPCR EC\(_{50} \) [\( \mu \)M] |
|----------|-------------------------------|-----------------------------|--------------------------------|---------------------------------|-------------------------------|
| 1        | 0.22 ± 0.04                   | >10*                        | 29.9 ± 1.1                     | 2.57 ± 1.51                     | ≈10                           |
| 2        | 0.67 ± 0.03                   | >100                        | >50                            | >10                             | >10                           |
| 3        | none                          | n.d.                        | n.d.                           | n.d.                            | n.d.                          |
| 4        | none (strong cytotox. **)     | >100**                      | n.d.                           | n.d.                            | n.d.                          |
| 5        | none (strong cytotox. **)     | >100**                      | >50                            | >10                             | >10                           |
| 6        | none (strong cytotox. **)     | >100**                      | n.d.                           | n.d.                            | n.d.                          |
| 7        | none (strong cytotox. **)     | >100**                      | >50                            | >10                             | >10                           |
| 8        | 0.71 ± 0.03                   | n.d.                        | n.d.                           | n.d.                            | n.d.                          |
| 9        | 1.20 ± 0.11                   | >100                        | >50                            | >10                             | >10                           |
| 10       | 1.20 ± 0.18                   | >100*                       | n.d.                           | n.d.                            | n.d.                          |
| 11       | 0.30 ± 0.02                   | >100                        | >50                            | >10                             | >10                           |
| 12       | 0.38 ± 0.03                   | >100                        | >50                            | >10                             | >10                           |
| 13       | >10                           | n.d.                        | n.d.                           | n.d.                            | n.d.                          |
| ARN[29]  | >10                           | >100                        | >50                            | >10                             | >10                           |
| ART[28]  | 5.41 ± 0.61                   | n.d.                        | >50                            | >10                             | >10                           |
| DHA[26]  | >10                           | >100                        | >50                            | >10                             | >10                           |
| artemether | >10                           | >100                        | >50                            | >10                             | >10                           |
| GCV[27]  | 2.60 ± 0.5                    | >100                        | n.d.                           | n.d.                            | n.d.                          |
| TAF      | –                             | –                           | 27.2 ± 0.7                     | 3.9 ± 0.8                       | 0.00024 ± 0.00004             |

[a] ***: Microscopic inspection of cell morphology or cell lysis after 6–8 days, long-term cytotoxicity (‘moderate,’ ‘strong’) LDH: lactate dehydrogenase release assay, 24 h, acute cytotoxicity; ‘n.d.’—not determined. [b] IC\(_{50} \) values have been previously reported.[34, 26] [c] EC\(_{50} \) values have been previously reported.[31]
Additionally, hybrids 8, 10, and 12 were, for the first time, synthesized through a metal-free cycloaddition reaction, with DBU and malononitrile as cocatalysts. Additionally, preliminary experiments of both cycloaddition reactions (CuAAC and metal-free) were performed to analyze their suitability for future application in the context of living cells, by performing the selected reactions in the presence of water. Metal-free click reaction proved to be more promising, since hybrid 8 could be isolated in 30% yield, whereas CuAAC catalysis gave the hybrid product in only 9% yield.

Remarkably, hybrids 1, 2, 8, 11, and 12 demonstrated pronounced activity against HCMV, that is, in vitro EC_{50} values in the sub-micromolar range (down to 0.22 μM for hybrid 1). Notably, hybrid 1 also exhibited low micromolar activity against HBV (EC_{50} (HEBaG) = 2.57 μM). Moreover, the cytotoxicity profiles of all hybrids were almost negative within the relevant range of antiviral concentrations in primary HFFs, that is, EC_{50} values were low or undetectable at concentrations up to 100 μM. Thus, these compounds, exhibiting high antiviral activities combined with a low toxicity/high selectivity profile, illustrate the potential of the hybridization concept as an alternative drug-discovery approach, which can also be applied for current anti-coronavirus drug development.

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Conflict of interest

The authors declare no conflict of interest.

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