

Artemisinin and Quinoline Hybrid Compounds Inhibit Replication of SARS-CoV-2 *In Vitro*

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Abstract: The newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause life-threatening diseases in millions of people worldwide and there is an urgent need for antiviral agents against this infection. While *in vitro* activities of artemisinins (containing endoperoxide moiety) and chloroquine (containing quinoline subunit) against SARS-CoV-2 have recently been demonstrated, no study of artemisinin- and quinoline-based hybrids has been reported yet. However, the hybrid drug's properties can be improved compared to its parent compounds and effective new agents can be obtained by modification/hybridization of existing drugs. In this study, fifteen artemisinin- and quinoline-containing hybrid compounds were synthesized and analyzed *in vitro* for the first time for their inhibitory activity against SARS-CoV-2 in a cytopathic effect reduction assay. All artesunic acid-containing hybrids display superior potency against SARS-CoV-2 (EC_{50} values 7.8 – 46 μ M) and show low or no cytotoxic effects on Vero E6 cells (CC_{50} up to 110 μ M). The most active artesunic acid-derived hybrid is significantly more potent *in vitro* (EC_{50} = 7.8 μ M) than its parent compound artesunic acid (EC_{50} >50 μ M). Among quinoline-based new compounds, quinoline-adamantane (EC_{50} = 1.5 μ M) is the most efficient *in vitro* outperforming the reference drugs chloroquine (EC_{50} = 3.8 μ M) and remdesivir (EC_{50} = 4.0 μ M).

Introduction

The novel human infection with the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is spreading rapidly across the world since it was first identified at the end of 2019. It is highly contagious and leads to serious disease COVID-19 (coronavirus disease 2019), which was declared as a pandemic

by the World Health Organization (WHO) on March 11th 2020.^[1] Several types of vaccines have already been developed, whereas effective antiviral treatments are lacking. Hence, development of novel efficient drugs against SARS-CoV-2 is highly desired.

One of the most frequent approaches is repurposing drugs already licensed for other diseases. While known repurposed drug Remdesivir (RDV) (Figure 1, A) showed activity *in vitro* against SARS-CoV-2^[2] and was first approved by the FDA for the use against SARS-CoV-2, there were insufficient clinical studies and since recently, due to low efficiency, its use for the treatment of COVID-19 is no longer recommended.^[3] Also chloroquine and hydroxychloroquine (Figure 1, A) - two antimalarial drugs that are active against several viruses,^[4] including HIV, hepatitis C and Ebola - were reported to be active against SARS-CoV-2.^[2, 5] These two drugs - both containing a quinoline subunit, showed high potency against SARS-CoV-2 - but neither *in vitro* studies nor clinical trials gave results consistent enough either in single use or in combination with other drugs like lopinavir or ritonavir.^[2, 5b, 6]

Recent studies demonstrated, that cyclic synthetic peroxides exhibit antiparasitic,^[7] anticancer^[8], antifungal,^[7e, 9] antitubercular^[10] and antiviral^[11] activities. Notably, synthetic peroxide arterolane (Figure 1, B), used in medical practice for treatment of malaria,^[12] has recently also been characterized for its *in vitro* activity against α -coronavirus NL63, β -coronaviruses OC43 and SARS-CoV-2.^[13]

Recently, it has been shown that plant extracts from *Artemisia annua*, which contain artemisinin - a sesquiterpene lactone with peroxide bridge, and used in traditional medicine as antimalarial drug, exhibit anti-viral activity against SARS-CoV-2 *in vitro*.^[14] These findings back the hypothesis, that African

countries have been hit later and weaker by the pandemic than expected, due to widespread use of artemisinin based traditional antimalarial medicine or artemisinin-based combination therapy (ACT).^[15] The anti-SARS-CoV-2 potential of artemisinins (Figure 1, C) was also determined in a pharmacokinetic model *in vitro*.^[16] Notably, artesunic acid, the API (active pharmaceutical ingredient) in FDA-approved malaria treatments, was demonstrated to show high *in vitro* potency against SARS-CoV-2.^[16b]

Despite these promising results, the WHO still advises to use artemisinins in ACT to prevent the development of drug resistances. The use of artemisinins is mainly focused on regions, where they are also applied for malaria treatment. In these regions, the risk is high that resistant malaria strains will spread due to use of artemisinins against SARS-CoV-2.^[14] Besides ACT, another powerful strategy to combat the emergence of drug resistances against artemisinins, is the use of hybrid molecules, which have been shown to not only prevent the development of new resistances, but also to have the ability to overcome these.^[17, 18] Furthermore, an improvement of anti-SARS-CoV-2 efficacy of artemisinins through their hybridization with selected bioactive

compounds is also expected. Thus, as alternatives to already studied known drugs, our ongoing quest for active hybrid molecules, which exceed their parent compounds in terms of activity against SARS-CoV-2, motivated the synthesis of new artemisinin- and quinoline-containing hybrid compounds **1-15** (Figure 2). Therefore, we set out to determine for the first time whether hybrids of artesunic acid and quinoline might be even more efficient against SARS-CoV-2 *in vitro*, in comparison to their already active parent compounds.

In the present study, we demonstrate that these new hybrid compounds are indeed highly efficacious in cultured-cell-based SARS-CoV-2 models. The most active artesunic acid-derived hybrid **7** ($EC_{50} = 7.8 \mu M$) is, e.g., significantly more potent *in vitro* than its parent compound artesunic acid ($EC_{50} > 50 \mu M$). Among the quinoline-based hybrids, quinoline-adamantane **15** ($EC_{50} = 1.5 \mu M$) is the most efficient agent *in vitro*, outperforming both reference drugs chloroquine ($EC_{50} = 3.8 \mu M$) and remdesivir ($EC_{50} = 4.0 \mu M$). Remarkably, the new hybrid compounds show low or no cytotoxic effects on Vero E6 cells (CC_{50} up to $110 \mu M$), which are used as a model for SARS-CoV-2 susceptible cells.

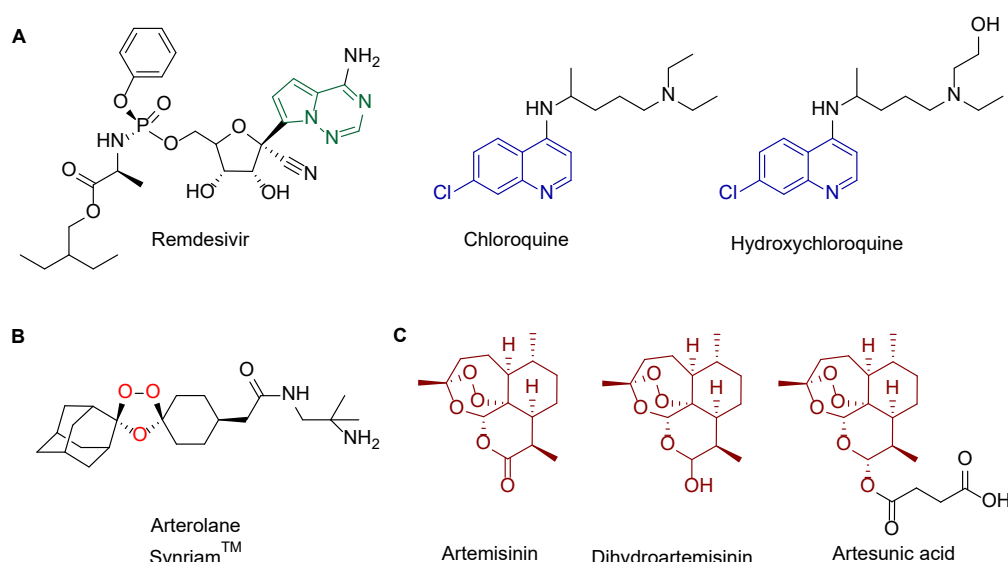


Figure 1. Structures of (A) antiviral Remdesivir and antimalarial/antiviral (Hydroxy)Chloroquine used as reference compounds in this study; (B) synthetic antimalarial and antiviral peroxide Arterolane; (C) Artemisinin (ARN, naturally occurring) and its semisynthetic derivatives Dihydroartemisinin (DHA) and Artesunic acid (ART).

Results and Discussion

Chemistry

Recently we reported the synthesis of different artesunic acid-quinoline hybrid compounds, which showed highly improved potencies against chloroquine-resistant and multidrug-resistant *P. falciparum* strains and strongly suppressed parasitemia in experimental malaria.^[18] We initiated the present research by screening those hybrid compounds for the first time for their inhibitory activity against SARS-CoV-2. To our delight, artesunic acid-quinoline hybrid **1** displayed superior potency against SARS-CoV-2 ($EC_{50} = 11 \pm 2.5 \mu M$), outperforming its parent compound artesunic acid ($EC_{50} > 50 \mu M$, Table 1, Figure 3). This remarkable result motivated us to further modify compound **1**, using its alkyne

linker and click reactions (Figure 2). This resulted in new artesunic acid-quinoline hybrids **2-7**, which have also been investigated for their activity against SARS-CoV-2 *in vitro*. Hybrids **2-7** were synthesized, starting from 4,7-dichloroquinoline, which was transformed over two steps to alkyne precursor **14** after a literature-known procedure, earlier reported by our team.^[18] From there on, triazole species **17-22** were synthesized via “click” copper-catalyzed alkyne azide cycloaddition reactions (CuAAC) in yields of 37-70%. Triazoles **17-22** were prepared in a two-phase solvent system using THF and water at room temperature under argon atmosphere. The chloroquinoline triazoles **17-22** underwent amide coupling reactions with EDCI and DMAP to form hybrid compounds **2-7** with artesunic acid. The reaction was performed in a mixture of DCM:THF due to poor solubility of the starting triazole compounds **17-22** in DCM. Corresponding hybrids **2-7** were obtained in 33-69% yields.

Quinoline-adamantane hybrid **15** was synthesized from 7-chloro-*N*-(2-chloroethyl)quinolin-4-amine and 1-adamantylamine in presence of Et₃N in DMF under argon atmosphere. Hybrid **15** was isolated in 54% yield. The acidic starting compounds, containing a bridged 1,2,4,5-tetraoxane and tricyclic monoperoxide fragment for the synthesis of hybrids **8-13**, were synthesized from corresponding β -diketones and β,δ' -triketones by their acid-catalyzed peroxidation in accordance with the known procedure published by our team.^[8c] In the next step, hybrids **8, 9, 11** and **13** were synthesized via an amide coupling reaction

between cyclic peroxide containing acid and an aminoquinoline under action of EDCI·HCl / DMAP system in DCM. Hybrids **8, 9, 11** and **13** were obtained in moderate to good yields (47-77%). For an acid, which contains a tricyclic monoperoxide moiety, yield of target hybrids was 17-30% higher, compared to an acid containing a bridged 1,2,4,5-tetraoxane moiety. Hybrids **10** and **13** were synthesized via an esterification reaction between corresponding acids and an alcohol containing quinoline moiety under the action of a DCC / DMAP system in DCM, which gave yields for **10** and **13** of 47% and 67%, respectively.

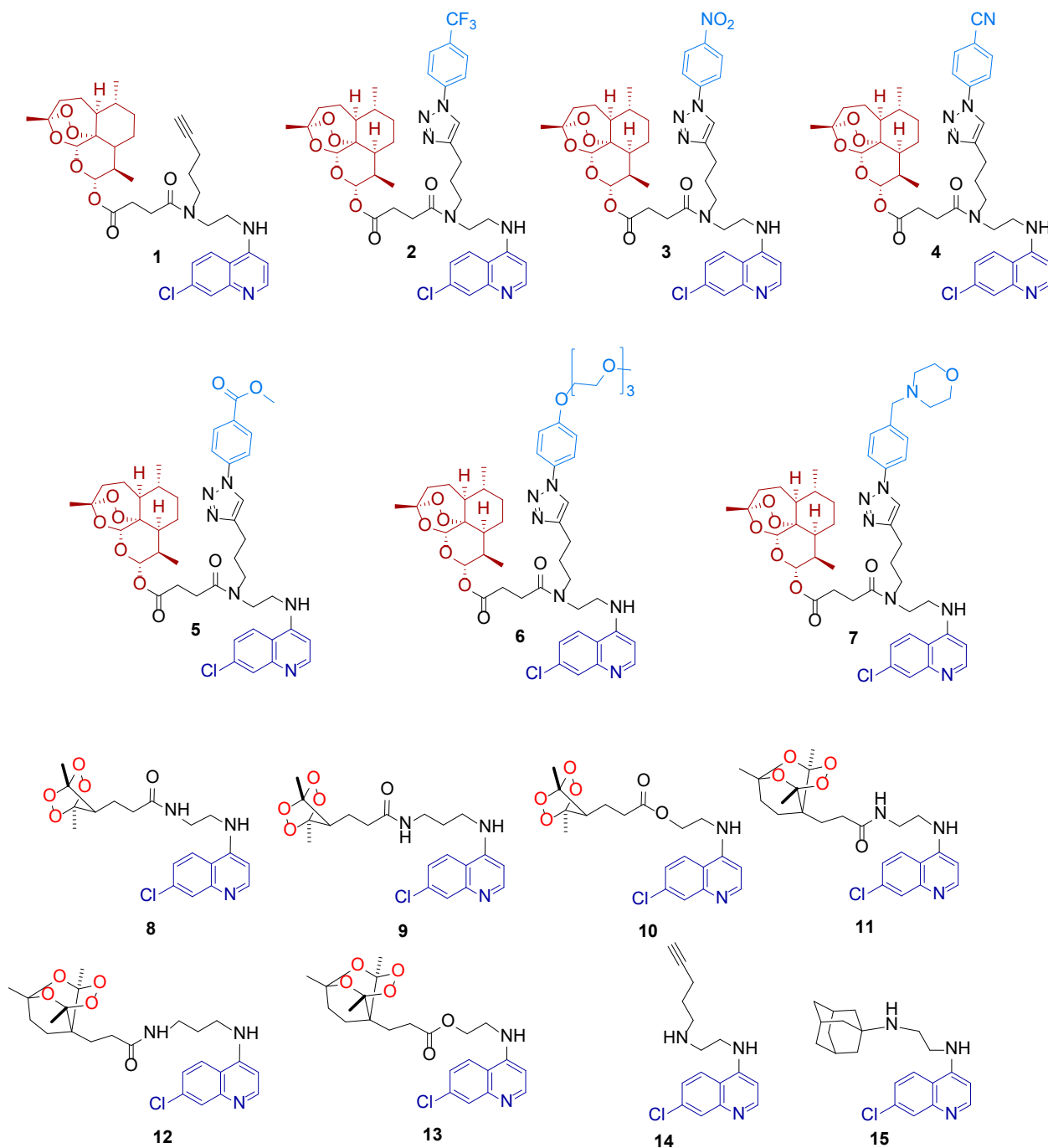
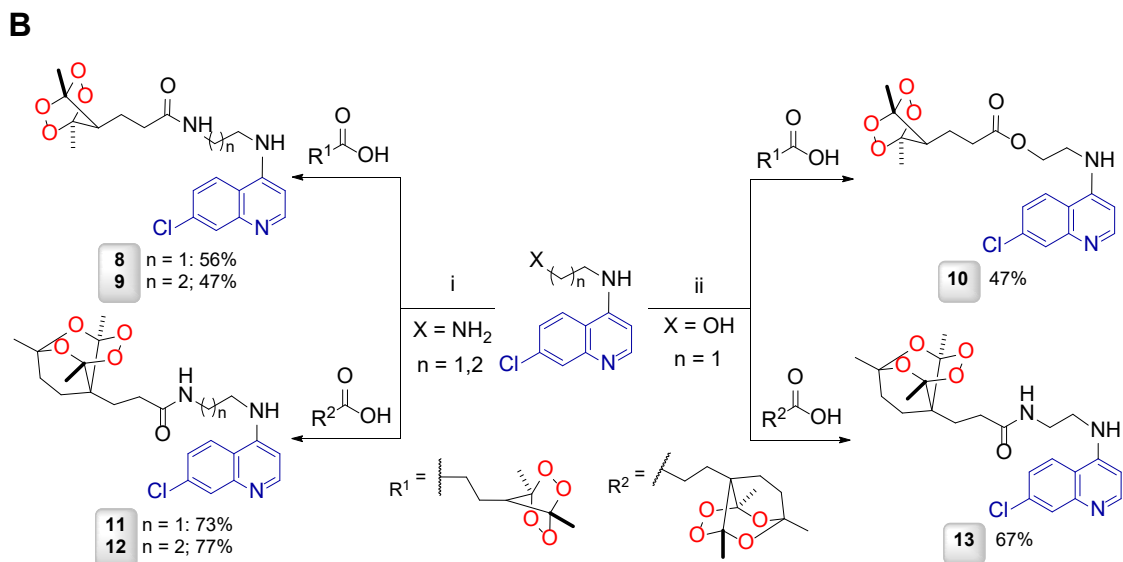
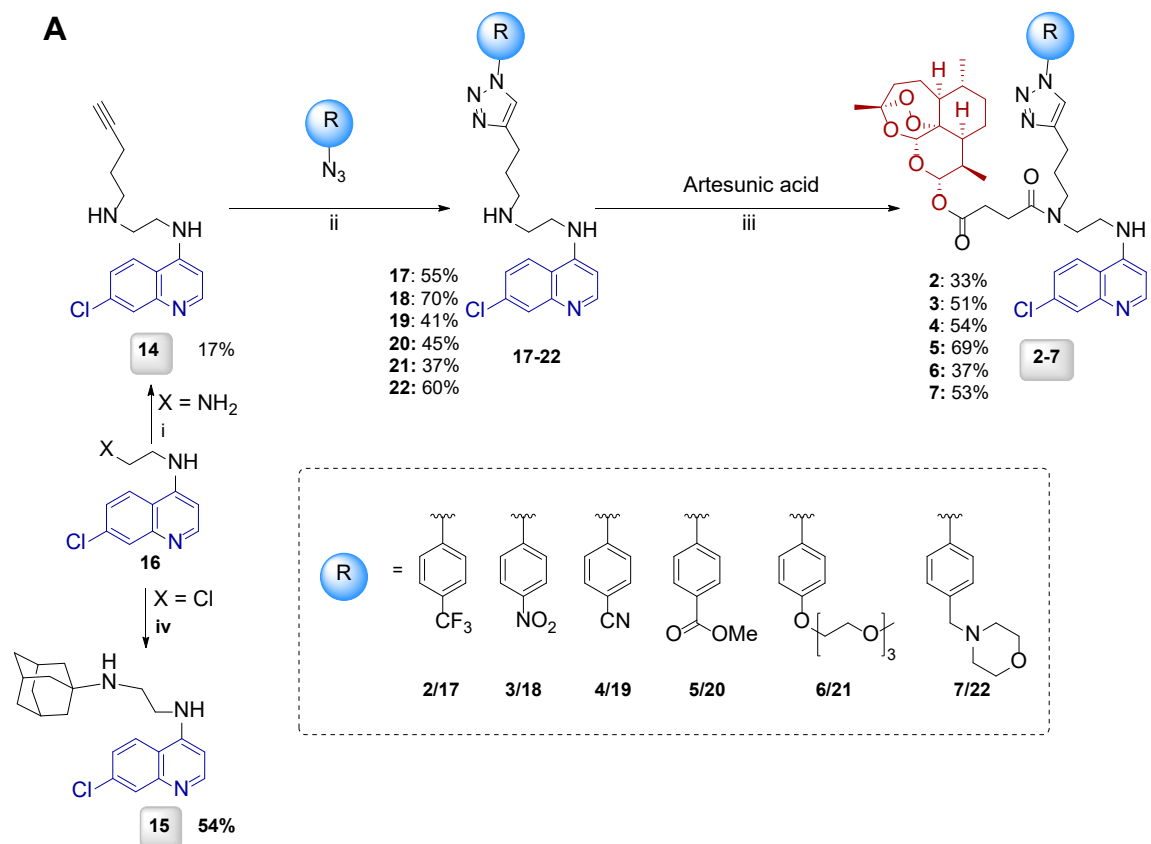


Figure 2. Artemisinin- and quinoline-based compounds **1-15**, designed for examination of their activity against SARS-CoV-2.



Scheme 1. (A) Synthesis of new artemisinin-based hybrids **2-7**. i) Chloropent-1-yne, K₂CO₃, CH₃CN, 115 °C, 25 h; ii) CuSO₄•5H₂O (20 mol%), sodium ascorbate (40 mol%), THF:H₂O (1:1), r.t., 2-3.5 h; iii) EDCI•HCl, DMAP, DCM, 0 °C to r.t., o/n; iv) 1-adamantylamine, Et₃N, DMF, 140 °C, 9 h. **(B)** Synthesis of novel peroxide based hybrids **8-13**: i) For **8**, **9**, **11** and **12**: EDCI•HCl, DMAP, DCM, 0 °C to r.t., o/n; ii) For **10** and **13**: DCC, DMAP, DCM, 0 °C to r.t., o/n.

Table 1. EC₅₀ values of hybrids **1–15** and of reference compounds artesunic acid (ART), chloroquine (CQ) and remdesivir, analyzed for anti-SARS-CoV-2 activities.

Compound	EC ₅₀ CPE [μM]	EC ₅₀ IF [μM]	CC ₅₀ [μM] Vero E6	SI
1	11 ± 2.5	~14*	~48*	4.4
2	24 ± 4.6	12 ± 7.0	30 ± 3.7	1.3
3	13 ± 1.1	33 ± 15	110 ± 30	8.5
4	13 ± 0.6	81 ± 23	>100	>7.7
5	19 ± 2.4	53 ± 8.0	>100	>5.3
6	46 ± 3.9	>100	>100	>2.2
7	7.8 ± 3.0	>16	25 ± 2.9	3.2
8	25 ± 1.4	~90*	~50*	2.0
9	13 ± 0.3	13 ± 3.1	28 ± 2.9	2.2
10	11 ± 0.3	30 ± 5.9	~37*	3.4
11	73 ± 5.3	>100	>100	>1.4
12	44 ± 3.2	59 ± 8.1	>100	>2.3
13	48 ± 4.0	72 ± 22	>100	>2.1
14	6.4 ± 0.2	9.5 ± 1.6	~60*	9.4
15	1.5 ± 0.1	>2.6	5.9 ± 1.6	3.9
artesunic acid	>50	n.d.	>50	-
chloroquine	3.8 ± 0.5	1.3 ± 0.3	~27*	7.1
remdesivir	4 ± 0.2	0.63 ± 0.06	>50	>13

*Estimate, standard deviation could not be determined due to incomplete 95% confidence interval;

n.d. = not determined;

SI (selectivity index) = EC₅₀ CPE / CC₅₀ Vero E6

Anti-SARS-CoV-2 Activity

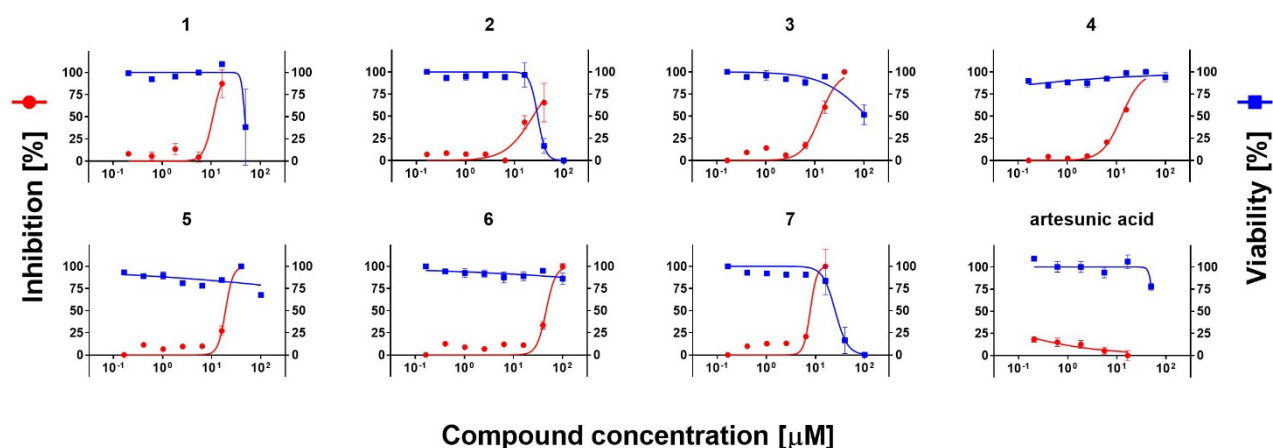
The *in vitro* anti-SARS-CoV-2 potency of novel hybrid drugs was confirmed using Vero E6 cells. The cytotoxicity of all hybrid compounds towards Vero E6 cells was assessed, too, to ensure that the antiviral effects were not caused by toxicity. These tests confirmed, that hybrid compounds **1–15** inhibit replication of SARS-CoV-2 viruses at levels at which there is only low or no toxicity to the cells at all (Figures 3 and 4, Table 1).

All new artesunic acid-containing hybrid compounds **2–7** show activity against SARS-CoV-2 (EC₅₀ values 7.8 – 46 μM) and low or no toxicity at the effective concentrations, indicated by SI (selectivity index) values up to 8.5. The morpholine-containing derivative **7** shows the highest activity (EC₅₀ = 7.8 ± 3.0 μM) with a SI value of 3.2. The morpholine moiety may improve the activity against SARS-CoV-2 due to its basic nature.^[19]

Among quinoline-based hybrids **8–15**, compound **15** was the most active (EC₅₀ = 1.5 ± 0.5 μM and SI = 3.9, see Table 1 and Figure 4).

Replacement of the adamantane fragment in **15** by 1-pentyne (see compound **14**) led to a decrease in activity, but to an increase in SI (EC₅₀ and SI are 6.4 ± 0.2 μM and 9.4, respectively). In the case of synthetic peroxide-containing hybrids **8–13**, compounds **8–10** with a 1,2,4,5-tetraoxane moiety were several times more active than compounds **11–13**, containing a tricyclic monoperoxide fragment. From the structural point of view, compounds with an ester group, like **10** and **13**, or with a chain of three carbon atoms between the amino group of quinoline and amido group such as in case of **9** and **12**, are more promising as components for the development of hybrids against SARS-CoV-2. Most active synthetic peroxide-quinoline hybrid was **10** (EC₅₀ and SI are 11.5 ± 0.3 μM and 3.4, respectively).

A



B

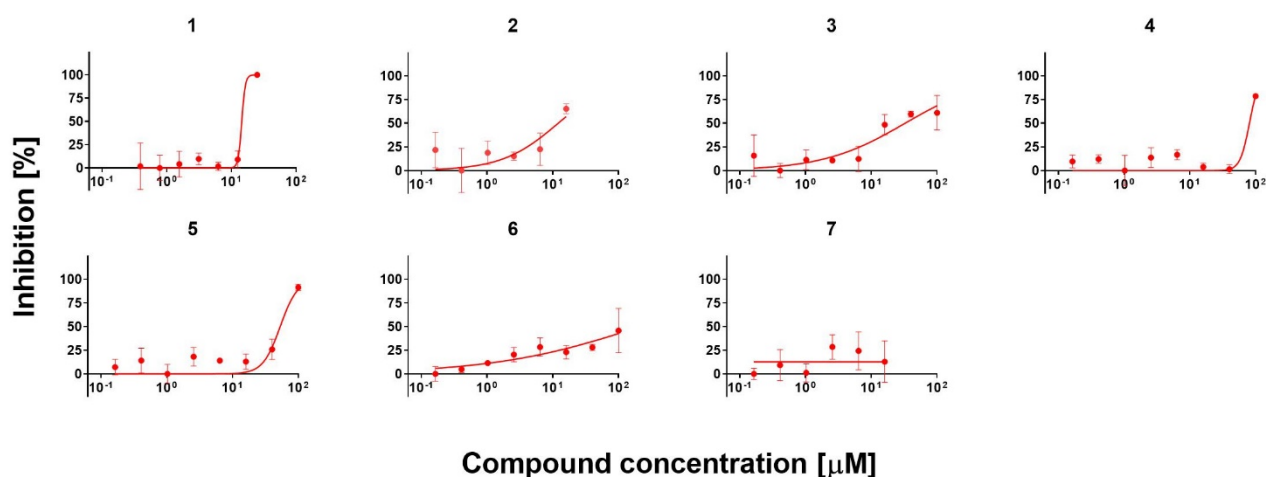
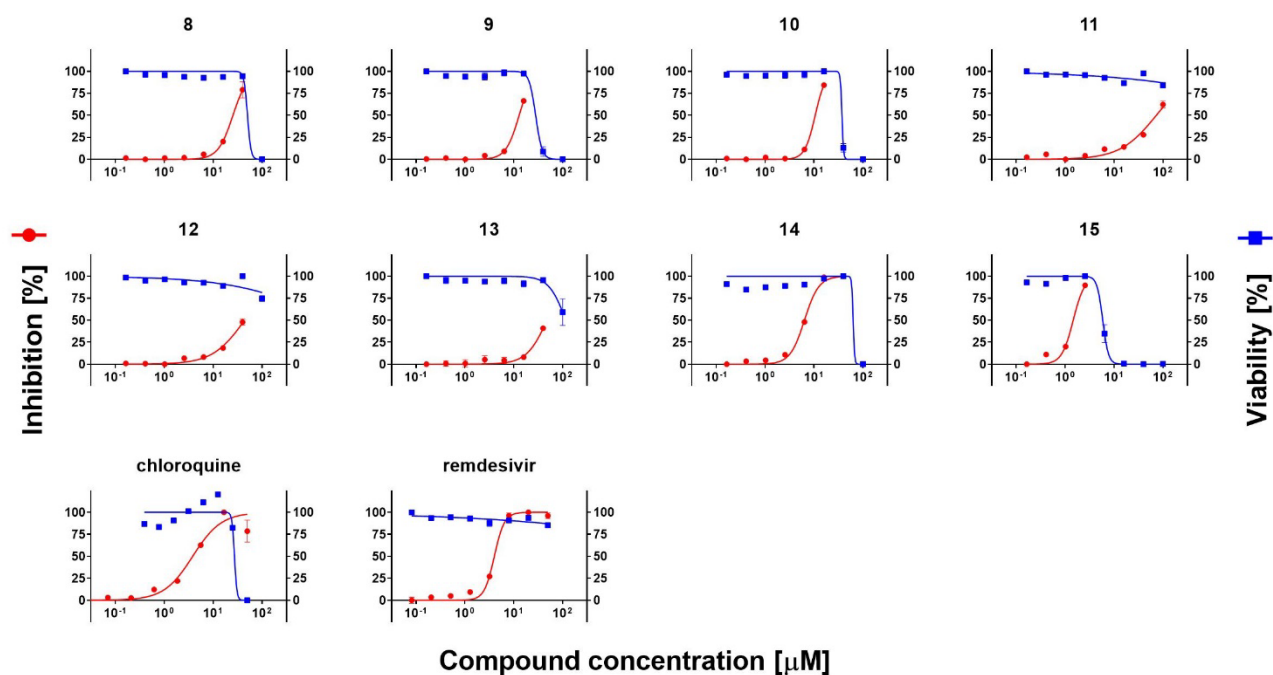


Figure 3. Dose-response curves of SARS-CoV-2 inhibition by different doses of artemisinin hybrids **1-7** and artesunic acid. **(A)** Graphical representation of CPE-based assay. Vero E6 cells were infected with SARS-CoV-2 at an MOI of 0.04 for 72 h and the inhibition of virus-induced cytopathic effect by 2.5 fold serial dilution of compounds **1-7** was determined by XTT assay (red circle). Same dilution of compounds **1-7** without SARS-CoV-2 were used to determine cell cytotoxicity (blue squares). **(B)** Graphical representation of immunofluorescence assay. Vero E6 cells were infected with SARS-CoV-2 at an MOI of 0.04 for 72 h and the inhibition of virus replication was determined by anti-SARS-CoV-2 nucleoprotein antibody. MOI = multiplicities of infection.

A



B

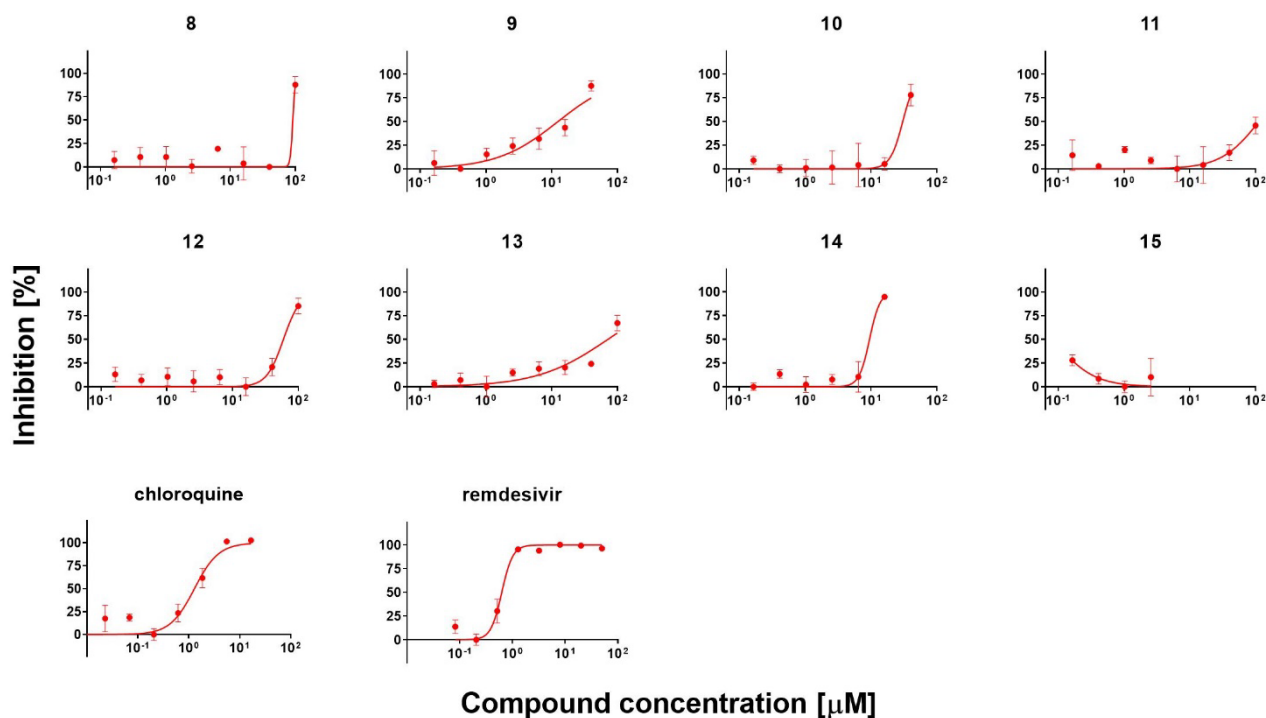


Figure 4. Dose-response curves of SARS-CoV-2 inhibition by different doses of quinoline hybrids **8-15**, chloroquine, and remdesivir control. **(A)** Graphical representation of CPE-based assay. Vero E6 cells were infected with SARS-CoV-2 at an MOI of 0.04 for 72 h and the inhibition of virus-induced cytopathic effect by 2.5 fold serial dilution of compounds **8-15** was determined by XTT assay (red circle). Same dilution of compounds **8-15** without SARS-CoV-2 were used to determine cell cytotoxicity (blue squares). **(B)** Graphical representation of immunofluorescence assay. Vero E6 cells were infected with SARS-CoV-2 at an MOI of 0.04 for 72 h and the inhibition of virus replication was determined by anti-SARS-CoV-2 nucleoprotein antibody. *MOI* = multiplicities of infection.

Molecular modeling

Further lead optimization and design of novel inhibitors of SARS-CoV-2 replication require knowledge about molecular targets and binding patterns of quinoline-based hybrids (chloroquine-like ligands). Based on crystallographic data collection deposited in the Protein Data Bank (PDB), possible quinoline binding sites were found in SARS-CoV-2 main protease and spike glycoprotein (see Supporting Information). A molecular docking approach was used for preliminary estimation of ligand binding in each possible binding site and results were subjected to protein-ligand structure refinement by MD simulation.^[20] According to molecular modeling, SARS-CoV-2 main protease (M^{pro}) was identified as the most probable binding partner for quinoline-based compounds (Figure 5). Hydrogen bonds between the quinoline moiety and His163, hydrogen bonds with Asn142, and a salt bridge with Glu166 are most important for high-affinity binding.

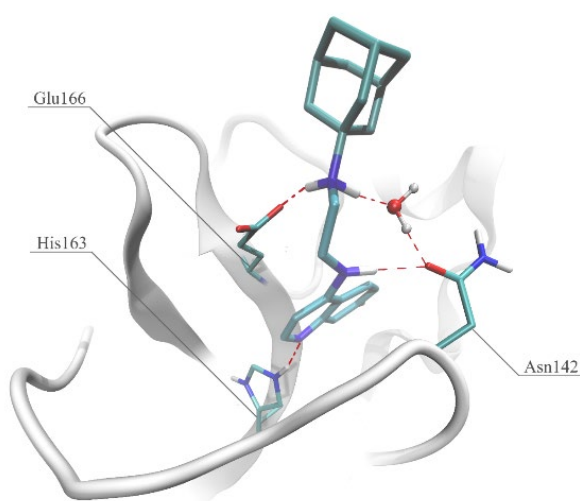


Figure 5. Essential interactions of quinolone-adamantane derivatives with SARS-CoV-2 main protease (M^{pro}) identified by molecular modelling. A representative binding pose from molecular dynamics simulations for ligand **15** is shown.

The found binding site is consistent with experimental data (Supporting Information, Figure S3), as well as with results of molecular modeling studies.^[21] High observed experimental activity of positively charged compounds can be explained by taking into account their electrostatic interaction with Glu166 (Figure 5).

Conclusions

In summary, these study reinforce our hypothesis that artemisinin and quinoline hybrid compounds could be effective as a COVID-19 treatment. We synthesized and explored the *in vitro* anti-SARS-CoV-2 activities of fifteen artemisinin- and quinoline-containing hybrid compounds **1-15**. All artemisinin-based hybrids **1-7** display superior potency against SARS-CoV-2 (EC_{50} values 7.8 – 46 μ M) outperforming artesunic acid. The most active artesunic acid-derived hybrid **7** (EC_{50} = 7.8 μ M) is also significantly more potent *in vitro* than its parent compound artesunic acid (EC_{50} >50 μ M) and shows low cytotoxic effects on benchmark Vero E6 cells. Notably, also synthetic peroxide-based hybrids **8-13** were remarkably potent against SARS-CoV-2. Most

active synthetic peroxide-quinoline hybrid was **10** (EC_{50} = 11.5 μ M). Among quinoline-based new compounds, quinoline-adamantane **15** (EC_{50} = 1.5 μ M) is the most efficient *in vitro*, outperforming chloroquine (EC_{50} = 3.8 μ M) and remdesivir (EC_{50} = 4.0 μ M), used as reference drugs. These promising results further underline the high potential of the hybridization concept for further investigations and hybrid-based drug design of efficient antiviral agents to treat SARS-CoV-2 infections.

Acknowledgements

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