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Synthesis and in vitro Study of Artemisinin/Synthetic Peroxide-Based Hybrid Compounds against SARS-CoV-2 and Cancer

Lars Herrmann,[a] Ivan A. Yaremenko,[b] Aysun Çapcı,[a] Julia Struwe,[c] Dhanir Tailor,[d] Arpit Dheeraj,[d] Jan Hodek,[e] Yulia Yu. Belyakova,[b] Peter S. Radulov,[b] Jan Weber,[e] Sanjay V. Malhotra,[d] Alexander O. Terent'ev,*[b] Lutz Ackermann,*[c, f] and Svetlana B. Tsogoeva*[a]

The newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause life-threatening diseases in millions of people worldwide, in particular, in patients with cancer, and there is an urgent need for antiviral agents against this infection. While *in vitro* activities of artemisinins against SARS-CoV-2 and cancer have recently been demonstrated, no study of artemisinin and/or synthetic peroxide-based hybrid compounds active against both cancer and SARS-CoV-2 has been reported yet. However, the hybrid drug's properties (e.g., activity and/or selectivity) can be improved compared to its parent compounds and effective new agents can be obtained by modification/hybridization of existing drugs or bioactive natural products. In this study, a series of new artesunic acid and synthetic peroxide based new hybrids were synthesized and analyzed *in vitro* for the first time for their inhibitory activity against SARS-CoV-2 and leukemia cell lines. Several artesunic acid-derived hybrids exerted a similar or stronger potency against K562 leukemia cells (81–83% inhibition values) than the reference drug doxorubicin (78% inhibition value) and they were also more efficient than their parent compounds artesunic acid (49.2% inhibition value) and quinoline derivative (5.5% inhibition value). Interestingly, the same artesunic acid-quinoline hybrids also show inhibitory activity against SARS-CoV-2 *in vitro* (EC_{50} 13–19 μM) and no cytotoxic effects on Vero E6 cells (CC_{50} up to 110 μM). These results provide a valuable basis for design of further artemisinin-derived hybrids to treat both cancer and SARS-CoV-2 infections.

Introduction

The novel human infection with the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has spread globally since its discovery in late 2019.[1] It has been found that the patients with cancer have been disproportionately affected by this pandemic.[2] Moreover, increasing evidence worldwide suggests that patients with malignancies are highly susceptible to severe infections and mortality from COVID-19.[3] Although, the molecular interplay that involves the tight relationship between COVID-19 and cancer is not fully understood, these observations do suggest the possibility of designing drugs, which could be effective against molecular targets common to both these diseases.

Natural products have always been important hit and lead compounds for drug discovery.[4] Artemisinin (Figure 1), a highly effective natural product, is an enantiopure sesquiterpene lactone, used in traditional Chinese medicine as antimalarial agent, and occurs in *Artemisia annua* L.[5] Its discoverer Youyou Tu was awarded the 2015 Nobel Prize in physiology or

[a] *L. Herrmann, Dr. A. Çapcı, Prof. Dr. S. B. Tsogoeva*
Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM)
Friedrich-Alexander-University Erlangen-Nürnberg
Nikolaus Fiebiger-Straße 10, 91058 Erlangen (Germany)
E-mail: svetlana.tsogoeva@fau.de
[b] *Dr. I. A. Yaremenko, Y. Y. Belyakova, Dr. P. S. Radulov, Prof. Dr. A. O. Terent'ev*
N. D. Zelinsky Institute of Organic Chemistry
Russian Academy of Sciences
47 Leninsky prosp., 119991 Moscow (Russian Federation)
E-mail: terentev@ioc.ac.ru
[c] *J. Struwe, Prof. Dr. L. Ackermann*
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstraße 2, 37077 Göttingen (Germany)
E-mail: lutz.ackermann@chemie.uni-goettingen.de
[d] *D. Tailor, A. Dheeraj, Prof. Dr. S. V. Malhotra*
Department of Cell, Developmental and Cancer Biology
Center for Experimental Therapeutics, Knight Cancer Institute
Oregon Health and Science University
97201 Portland, OR (USA)
[e] *Dr. J. Hodek, Dr. J. Weber*
Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Flemingovo namesti 2, 16610 Prague (Czech Republic)
[f] *Prof. Dr. L. Ackermann*
German Center for Cardiovascular Research (DZHK)
Potsdamer Str. 58, 10785 Berlin (Germany)

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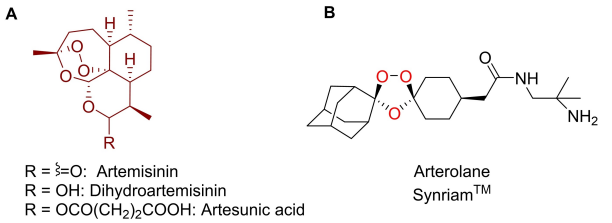


Figure 1. Structures of **(A)** Artemisinin (ARN, naturally occurring) and its semisynthetic derivatives Dihydroartemisinin (DHA) and Artesunic acid (ART); **(B)** synthetic antimalarial and antiviral peroxide Arterolane.

medicine.[6] Artemisinin is also known to possess impressive anticancer,[7] and antiviral activity.[8] Recently, it has also been shown that plant extracts from *Artemisia annua*, which contain artemisinin, exhibit antiviral activity against SARS-CoV-2 *in vitro*.[9]

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 anti-malarial medicine or artemisinin-based combination therapy (ACT).[10] The anti-SARS-CoV-2 potential of artemisinins (Figure 1A) was also determined in a pharmacokinetic model *in vitro*.[11] 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.[11b] Moreover, in those treatment assays, *artesunic acid* proved most potent, followed by artemether, *A. annua* extracts and artemisinin.

Over the past decade, the hybridization of natural products turned out to be a highly fruitful strategy for medicinal chemistry and drug design.[12] This powerful concept attracts attention in terms of improved pharmacological properties of parent compounds. For that reason and also motivated by our previous studies applying the hybridization concept using artemisinin derivatives,[13] we recently synthesized a series of novel artesunic acid-quinoline hybrids and demonstrated that they are highly efficient against multidrug-resistant malaria and human cytomegalovirus (HCMV) outperforming their parent compounds.[14] Following these studies, we herein present the synthesis of new artesunic acid-quinoline hybrids (Figure 2A) and investigate for the first time all compounds against SARS-CoV-2 and cancer. In particular, we explored the activities of our new hybrid compounds against leukemia cells, since the worldwide numbers regarding leukemia are sobering: e.g., 437033 new cases and 309006 deaths caused by leukemia in 2018.[15]

Recent studies demonstrated, that cyclic synthetic peroxides exhibit antiparasitic,[16] anticancer,[17] antifungal,[18] antitubercular[19] and antiviral[18] activities. Notably, synthetic peroxide arterolane (Figure 1B), used in medical practice for treatment of malaria,[16,20] has recently also been characterized for it's *in vitro* activity against α-coronavirus NL63, β-coronaviruses OC43 and SARS-CoV-2.[21] Therefore, we prepared for the first time also synthetic peroxide-quinoline hybrid compounds (Figure 2B).

In the present study, we demonstrate that most of hybrid compounds are indeed potent in cultured-cell-based SARS-CoV-2 models and different leukemia cell lines. Notably, artesunic acid-quinoline hybrids **3**–**5** and synthetic peroxide-quinoline hybrids **9**, **10** were more efficient against K562 leukemia cell line (81–83% inhibition values, Table 1) than their parent compounds: quinoline **14** (5.5% inhibition value) and artesunic acid (49.2% inhibition value). Remarkably, these novel hybrids showed a similar or higher potency against K562 leukemia cells

Table 1. EC_{50} values of hybrids **1**–**13** and of reference compounds (quinoline **14**, chloroquine, artesunic acid and remdesivir), analyzed for anti-SARS-CoV-2 activities; and % inhibition values of hybrids **1**, **3**–**13** and reference compounds (quinoline **14**, artesunic acid and doxorubicin) analyzed for anti-leukemia activities.

Compound	anti-SARS-CoV-2 activities		anti-leukemia activities				
	EC_{50} CPE [μM]	CC_{50} Vero E6 [μM]	CCRF-CEM	RPMI-8226	K562	HL-60	MOLT-4
1	11 ± 2.5	~48[a]	43.5 ± 2.5	35.8 ± 1	48.5 ± 3.9	62.8 ± 1.5	21.8 ± 4.8
2	24 ± 4.6	30 ± 3.7	n.d.	n.d.	n.d.	n.d.	n.d.
3	13 ± 1.1	110 ± 30	52.3 ± 1	42.7 ± 0.9	81.2 ± 1.3	63.1 ± 0.7	33.4 ± 0.3
4	13 ± 0.6	> 100	34.0 ± 0.8	23.3 ± 1.6	82.8 ± 0.9	65.4 ± 0.6	35.7 ± 0.7
5	19 ± 2.4	> 100	53.0 ± 0.6	44.4 ± 0.4	82.5 ± 0.9	63.4 ± 0.2	33.5 ± 0.4
6	46 ± 3.9	> 100	36.9 ± 4.8	23.9 ± 3.2	47.3 ± 1.7	72.2 ± 1.5	33.3 ± 3.6
7	7.8 ± 3.0	25 ± 2.9	33.3 ± 3.5	27.2 ± 4.6	60.1 ± 7	63.0 ± 0.6	29.8 ± 1.6
8	25 ± 1.4	~50[a]	52.8 ± 5.9	24.5 ± 7	37.3 ± 7.6	74.0 ± 1.6	33.6 ± 1.5
9	13 ± 0.3	28 ± 2.9	37.8 ± 4.8	16.3 ± 5.6	83.0 ± 4	67.4 ± 4.1	30.8 ± 2.7
10	11 ± 0.3	~37[a]	36.1 ± 4.3	24.4 ± 5.2	82.6 ± 4	65.2 ± 4.6	37.7 ± 4.9
11	73 ± 5.3	> 100	16.0 ± 3.9	19.6 ± 3.9	7.5 ± 4.1	0	12.7 ± 6.7
12	44 ± 3.2	> 100	22.9 ± 6.5	22.7 ± 1.4	22.3 ± 3.9	6.3 ± 12.1	16.3 ± 5.3
13	48 ± 4.0	> 100	34.1 ± 2.2	31.9 ± 4.2	6.5 ± 3.2	9.9 ± 6	12.9 ± 4.1
14	6.4 ± 0.2	~60[a]	4.2 ± 2.5	13 ± 1.7	5.5 ± 7.6	8.1 ± 3.7	0
chloroquine	3.8 ± 0.5	~27[a]	–	–	–	–	–
artesunic acid	> 50	> 50	9.4 ± 4	27.3 ± 6.1	49.2 ± 1.2	44.3 ± 7.4	9.9 ± 4.8
remdesivir	4 ± 0.2	> 50	–	–	–	–	–
doxorubicin	–	–	92.3 ± 1.3	84.1 ± 3.2	78.2 ± 4.1	91.5 ± 0.6	93.2 ± 2.6

[a] Estimate, standard deviation could not be determined due to incomplete 95% confidence interval; n.d. = not determined. CPE = cytopathic effect; EC_{50} = 50% effective concentration; CC_{50} = 50% cytotoxic concentration.

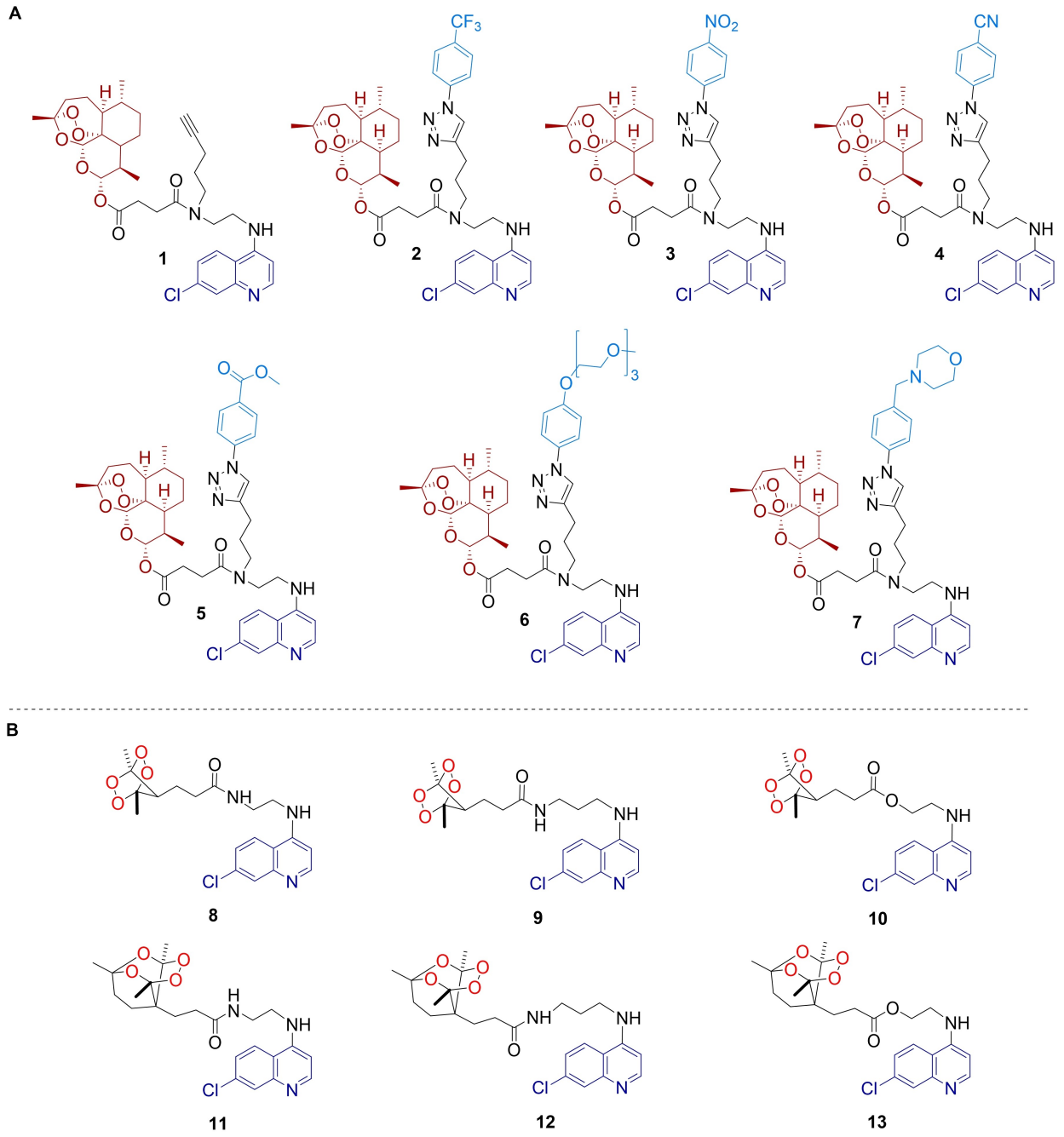


Figure 2. Artemisinin- and synthetic peroxide-based hybrid compounds, designed for examination of their activity against SARS-CoV-2.

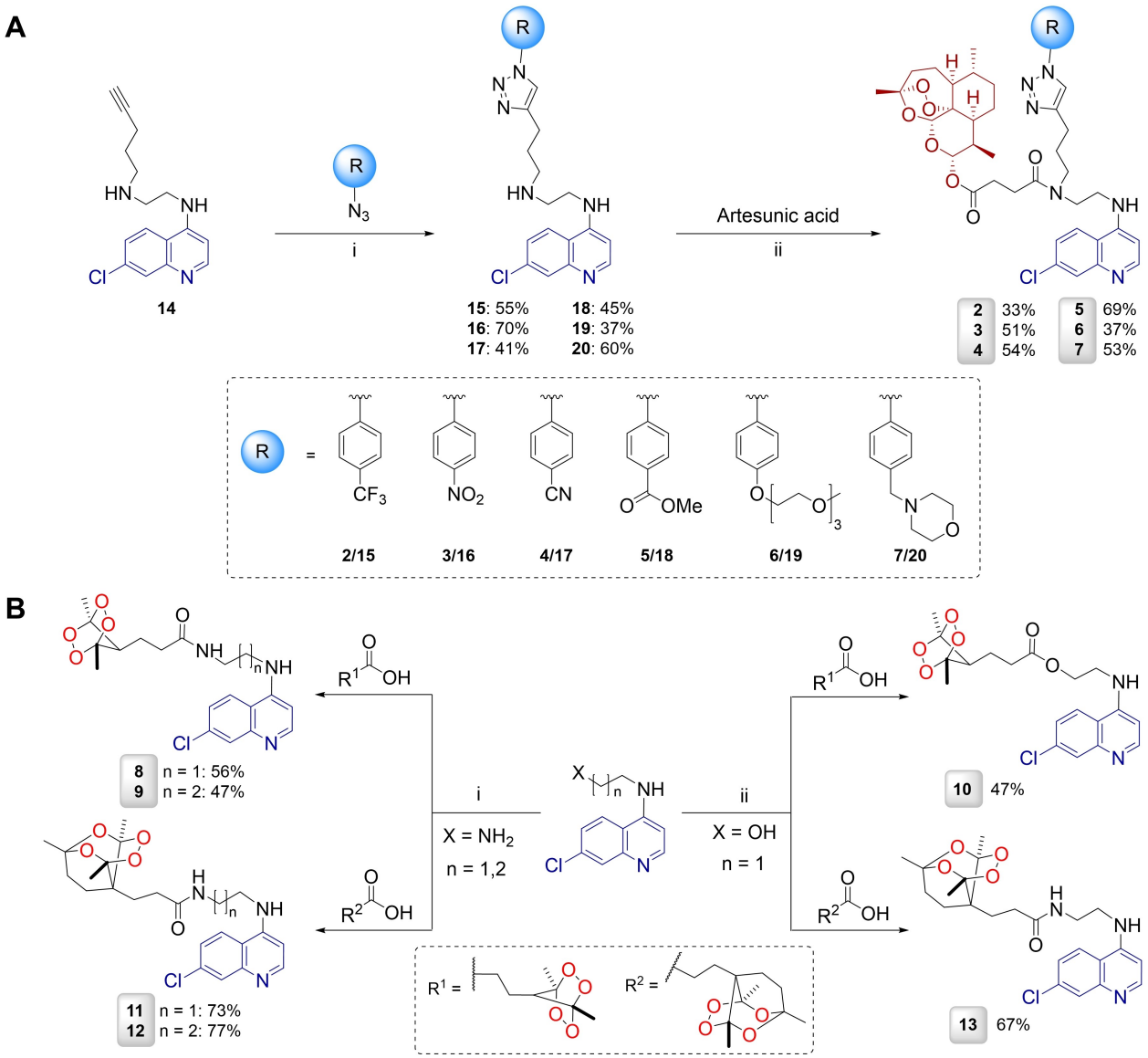
than the reference anti-leukemia drug doxorubicin (78% inhibition value, Table 1). Interestingly, the artesunic acid-quinoline hybrids **3**–**5** also show inhibitory activity against SARS-CoV-2 *in vitro* (EC_{50} 13–19 μM) and no cytotoxic effects on Vero E6 cells (CC_{50} up to 110 μM, Table 1), which are used as a model for SARS-CoV-2 susceptible cells. Overall, our findings are highly relevant towards the future development of drugs suitable to effectively tackle both cancer and COVID-19.

Results and Discussion

Recently we reported the synthesis of different artesunic acid-quinoline hybrid compounds, which showed highly improved potencies against multidrug-resistant *P. falciparum* strains[14a] and against HCMV.[14b] We initiated the present research by screening those hybrid compounds for the first time for their inhibitory activity against SARS-CoV-2. Artesunic acid-quinoline hybrid **1** displayed superior potency against SARS-CoV-2 (EC_{50} = 11 ± 2.5 μM; CC_{50} ~ 48 μM), outperforming its parent compound artesunic acid (EC_{50} > 50 μM; CC_{50} > 50 μM, see Table 1). This

result motivated us to further modify compound **1**, by performing click reactions at its alkyne linker with aromatic azides (Scheme 1). This resulted in new artesunic acid-quinoline hybrids **2**–**7**, which have also been investigated for their activity against SARS-CoV-2 and cancer *in vitro*. Hybrids **2**–**7** were synthesized, starting from quinoline derivative **14**, prepared *via* procedure, earlier reported by our team.[14a] From there on, triazole species **15**–**20** were synthesized *via* "click" copper(I)-catalyzed azide–alkyne cycloaddition reactions (CuAAC) in yields of 37–70%. Those triazoles were prepared in a two-phase solvent system using THF and water at room temperature under argon atmosphere. The chloroquinoline triazoles **15**–**20** underwent amide coupling reactions with artesunic acid utilizing EDCI and DMAP to form hybrid compounds **2**–**7** in moderate to good yields (33–69%, Scheme 1). The reaction was performed in a mixture of DCM:THF due to poor solubility of the starting triazole compounds **15**–**20** in DCM. 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.[17] In the next step, hybrids **8**, **9**, **11** and **12** were synthesized *via* an amide coupling reaction between cyclic peroxide containing acid and an aminoquinoline under action of EDCI·HCl/DMAP system in DCM (Scheme 1).

Hybrids **8**, **9**, **11** and **12** were obtained in moderate to good yields (47–77%). For an acid, which contains a tricyclic monoperoxide moiety, yields of target hybrids (**11**–**13**) were 17–30% higher, compared to an acid containing a bridged



Scheme 1. (A) Synthesis of new artemisinin-based hybrids **2**–**7**. i) $CuSO_4 \cdot 5H_2O$ (20 mol%), sodium ascorbate (40 mol%), THF:H_2O (1 : 1), RT, 2–3.5 h; ii) EDCI·HCl, DMAP, DCM, 0 °C to RT, overnight. **(B)** Synthesis of novel peroxide based hybrids **8**–**13**: i) For **8**, **9**, **11** and **12**: EDCI·HCl, DMAP, DCM, 0 °C to RT, overnight; ii) For **10** and **13**: DCC, DMAP, DCM, 0 °C to RT, overnight.

1,2,4,5-tetraoxane moiety, and which resulted in target hybrids **8**–**10** (see Scheme 1). 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.

Anti-SARS-CoV-2 and anti-cancer activities

The *in vitro* anti-SARS-CoV-2 potency of novel hybrid drugs was confirmed using Vero E6 cells. In addition, the cytotoxicity of all hybrid compounds towards Vero E6 cells was determined. All new artesunic acid-quinoline hybrid compounds **2**–**7** show *in vitro* activity against SARS-CoV-2 (EC_{50} values 7.8–46 μM) and moderate or no cytotoxicity at the effective concentrations (CC_{50} values 25–110 μM). The morpholine-containing derivative **7** showed the highest activity ($EC_{50} = 7.8 \pm 3.0$ μM), which might be due to the morpholine moiety that may enhance the activity against SARS-CoV-2 because of its basic nature.[22] While compound **7** is the most active, it shows moderate toxicity to the Vero E6 cells ($CC_{50} = 25 \pm 2.9$ μM). In 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. Whereas most active synthetic peroxide-quinoline hybrids are **9** and **10** (EC_{50} values 13 ± 0.3 and 11 ± 0.3 μM, respectively, Table 1), they show also moderate cytotoxicity to the Vero E6 cells (CC_{50} 28–37 μM). While hybrids **3**–**5** show no higher anti-SARS-CoV-2 activity (EC_{50} down to 13 ± 1.1 μM) than parent compound **14** (EC_{50} 6.4 ± 0.2 μM), they are significantly more active *in vitro* than their parent compound artesunic acid ($EC_{50} > 50$ μM). Furthermore, the parent compounds **14**, artesunic acid and a reference drug chloroquine are comparably more cytotoxic (CC_{50} values down to ~27, Table 1). Therefore, artesunic acid-quinoline hybrids **3**–**5** showing EC_{50} values in the range of 13 ± 1.1 to 19 ± 2.4 μM and no cytotoxic effects on Vero E6 cells (CC_{50} 100–110 μM, Table 1) can be considered as the most promising among the studied hybrid compounds.

Anticancer activity of the same hybrid compounds **1**, **3**–**13** was determined using a cell viability assay[23] on five different leukemia cell lines (CCRF-CEM, RPMI-8226, K562, HL-60, MOLT-4). K562 cells were most sensitive to compound treatment. 3000 Cells were plated in black-clear bottom 96-well plates and treated with respective compounds (10 μM) after 24 h. Cell viability was recorded after 48 h of treatment using CellTiter-Blue assay and % inhibition was calculated for each cell line (Table 1). The obtained data suggest that artesunic acid-quinoline hybrids **3**–**5** and synthetic peroxide-quinoline hybrids **9**, **10** are the most active compounds against K562 leukemia cell line *in vitro* (Figure 3 and Table 1). Overall, cell viability data (81–83% inhibition values) and anti-SARS-CoV-2 activities (EC_{50} down to 13 ± 1.1 μM and CC_{50} up to 110 μM, Table 1) suggest that artesunic acid-quinoline hybrids **3**–**5** have the potential for further development of novel therapeutic agents against both diseases.

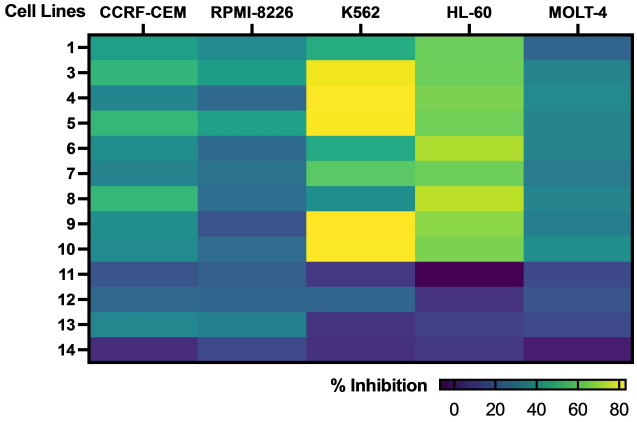


Figure 3. % inhibition heatmap of compounds **1**, **3**–**14**, analyzed for anti-cancer activities.

Conclusion

In summary, we synthesized and explored for the first time the *in vitro* anti-cancer and anti-SARS-CoV-2 activities of a series of new artesunic acid- and synthetic peroxide-containing hybrid compounds **1**–**13**. All artesunic acid-based hybrids **1**–**7** display remarkable activity against SARS-CoV-2 (EC_{50} values 7.8–46 μM). Notably, also synthetic peroxide-based hybrids **8**–**13** were potent against SARS-CoV-2 (EC_{50} values 11–73 μM). Among studied hybrid compounds, artesunic acid-quinoline hybrids **3**–**5** and synthetic peroxide-quinoline hybrids **9**, **10** showed highest potency against K562 leukemia cells (81–83% inhibition values), comparable to the standard anti-leukemia drug doxorubicin (78% inhibition value, Table 1). Interestingly, the artesunic acid-quinoline hybrids **3**–**5** show also high inhibitory activity against SARS-CoV-2 *in vitro* (EC_{50} 13–19 μM) and no cytotoxic effects on Vero E6 cells (CC_{50} up to 110 μM). These studies reinforce our hypothesis that new artesunic acid-quinoline hybrid compounds could be promising as a treatment for cancer and/or COVID-19. The obtained results provide a valuable basis for design of further hybrid-based drug candidates to treat cancer and SARS-CoV-2 infections.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: artemisinin based hybrids · anti-SARS-CoV-2 compounds · anti-cancer compounds · anti-leukemia agents

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