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Supporting Information

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

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General information

All reactions were performed in distilled or HPLC grade solvents. The reagents supplied from commercial sources were used without further purification, if not expressly indicated otherwise. TLC chromatography was carried out on silica gel chromatography plates Macherey-Nagel Alugram UV254; Sorbent: Silica 60, specific surface (BET) ~ 500 m2/g, mean pore size 60 Å, specific pore volume 0.75 mL/g, particle size 5–17 µm; Binder: highly polymeric product, which is stable in almost all organic solvents and resistant towards aggressive visualization reagents. The detection occurred via fluorescence quenching or development in a phosphomolybdic acid solution (10% in EtOH). The compounds were purified via column chromatography and the hybrid compounds were re-precipitated from CH2Cl2 in n-pentane to obtain a pure compound for elemental analysis and further biological tests. All compounds were dried in high vacuum (10⁻³ mbar) or via freeze-drying (lyophilization). $^1$H-NMR and $^13$C-NMR spectra were recorded at room temperature, if not expressly noted otherwise, on a Bruker Avance or JEOL JNM GX 400 spectrometer operating at 300, 400, 500 or 600 MHz (respectively 76, 101, 126 or 151 MHz). The melting points were determined on a Kofler hot-stage apparatus. Chromatography of products was performed on silica gel (0.040-0.060 mm, 60 A, CAS 7631-86-9). All chemical shifts are given in the ppm-scale and refer to the nondeuterized proportion of the solvent. ESI and APPI mass spectra were recorded on a Bruker Daltonik maXis 4G or Bruker Daltonik micrOTOF II focus. Elemental analysis (C, H, N) was carried out with an Elementar vario MICRO cube machine and calculated values confirm a purity of > 95% for all biologically tested compounds. Artesunic acid was purchased from Acros Organics (Germany). Compound 3-azido-7-hydroxycoumarin was purchased from Biosynth Carbosynth (United Kingdom). Experimental details and the spectra of the hybrids and their precursors can be found below in this supporting information.

The substituted phenyl azide precursors (except 4-(4-azidobenzyl)morpholine) were synthesized after literature known procedures. Compound 7-Chloro-N-(2-chloroethyl)quinolin-4-amine, N¹-(7-chloroquinolin-4-yl)ethane-1,2-diamine, N¹-(7-chloroquinolin-4-yl)propane-1,3-diamine, 2-((7-chloroquinolin-4-yl)amino)ethan-1-ol, Tetraoxane acid (3-(1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]hept-7-yl)propanoic acid), and Monoperoxide acid (3-(3,6,7a-trimethylidydroxy-3H,4H-3,6-epoxy[1,2]dioxolo[3,4-b]pyran-3a-yl)propanoic acid) were synthesized according to known procedures.
Synthesis and characterization of new hybrid compounds

4-(4-azidobenzyl)morpholine: adapted from [1]

4-(morpholinomethyl)aniline (600 mg, 3.12 mmol, 1.0 equiv.) was cooled to 0 °C in a round-bottom flask with ice and subsequently suspended in HCl (konz., 3 mL). To this suspension, NaN₃ (323 mg, 4.68 mmol, 1.5 equiv.) in H₂O (8 mL) was slowly added under stirring. The reaction mixture was stirred for 30 min. at 0 °C before NaN₃ (304 mg, 4.68 mmol, 1.5 equiv.) in H₂O (6 mL) was added slowly. The reaction was stirred at r.t. for 2 h. The reaction mixture was neutralized with NaHCO₃ solution (sat. in H₂O) and extracted with EtOAc (3x 25 mL). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product was obtained as a light brown oil after drying under high vacuum without further purification (602 mg, 2.76 mmol, 88%). ¹H NMR (400 MHz, Acetone-d₆) δ [ppm]: 7.44-7.24 (m, 2H), 7.08-6.99 (m, 2H), 3.63-3.57 (m, 4H), 3.47 (s, 2H), 2.41-2.34 (m, 4H); ¹³C NMR (101 MHz, Acetone-d₆) δ [ppm]: 139.5, 136.4, 119.7, 67.48, 6.12, 54.4; HRMS (APPI) calculated for C₁₁H₁₄N₄O [M]+: 218.1162; found: 218.1162.

Synthesis of compound 14: adapted from [7]

Reactant N1-(7-chloroquinolin-4-yl)ethane-1,2-diamine (5.00 g, 22.6 mmol, 1.0 equiv.) was suspended in CH₃CN (150 mL) and heated to 115 °C. (solid dissolves completely). K₂CO₃ (15.6 g, 5.0 equiv.) was added, and the reaction was stirred for 1 h. Reactant 5-chloropent-1-yne (3.34 mL, 3.24 g, 31.6 mmol, 1.4 equiv.) was added to the reaction mixture and the mixture was stirred at 115 °C for 24 h. After the reaction was cooled to r.t., the suspension was filtered over Celite 577 and 100 mL of H₂O was added. The phases were separated, and the aqueous phase was extracted with DCM (3x 100 mL). The crude product was purified via column chromatography (DCM:MeOH / 10:1, silica deactivated with NEt₃) to obtain the product 14 as an off-white solid. (1.09 g, 22.6 mmol, 17%). ¹H NMR (400 MHz, CDCl₃) δ [ppm]: 8.52 (d, J = 5.4 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.37 (dd, J = 8.9, 2.2 Hz, 1H), 6.39 (d, J = 5.4 Hz, 1H), 5.93 (s, 1H), 3.40-3.26 (m, 2H), 3.10-3.02 (m, 2H), 2.82 (t, J = 6.9 Hz, 2H), 2.32 (td, J = 6.9, 2.7 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H); elemental analysis: calculated [%]: C, 66.78; H, 6.30; Cl, 12.32; N, 14.60; found: C, 66.49; H, 6.05; N, 14.45.

Preparation of the triazole precursors 15-20

![Chemical reactions for the synthesis of triazole precursors](image-url)
**General procedure A:**
The azide (1 equiv.) and the alkyne (1 equiv.) were dissolved in THF (bubbled with Ar for 10 min. under stirring). To the solution of CuSO₄•5 H₂O (0.2 equiv.) and sodium ascorbate (0.4 equiv.) were added in H₂O (bubbled with Ar for 10 min. under stirring). The reaction mixture was stirred vigorously for 2-3.5 h at r.t. under Argon. DCM:MeOH (10:1, 25 mL) and H₂O (15 mL) were added and the phases were separated. Subsequently, the aqueous phase was extracted with DCM:MeOH (10:1, 2x 25 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified via column chromatography (DCM:MeOH) to obtain the final products.

**Synthesis of triazole 15**
Product 15 was synthesized via general procedure A, using 1-azido-4-(trifluoromethyl)benzene (65.0 mg, 348 µmol, 1.0 equiv.) and alkyne 14 (100 mg, 348 µmol, 1.0 equiv.) with the catalyst system of CuSO₄•5 H₂O (17.4 mg, 69.5 µmol, 0.2 equiv.) and sodium ascorbate (27.5 mg, 139 µmol, 0.4 equiv.) in THF:H₂O (1:1; 10 mL). The reaction mixture was stirred for 3.5 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 8:1), the final product 15 was obtained as yellow solid (91.3 mg, 192 µmol, 55%). ¹H NMR (400 MHz, DMSO-d₆) δ [ppm]: 8.71 (s, 1H), 8.39 (d,  J = 5.4 Hz, 1H), 8.25 (d,  J = 9.0 Hz, 1H), 8.12 (d,  J = 8.5 Hz, 2H, 7.96 (d,  J = 8.5 Hz, 2H), 7.77 (d,  J = 2.2 Hz, 1H), 7.43 (dd,  J = 9.0, 2.3 Hz, 1H), 7.24 (s, 1H), 6.50 (d,  J = 5.4 Hz, 1H), 3.36 (t,  J = 6.5 Hz, 2H), 2.85 (t,  J = 6.5 Hz, 2H), 2.78 (t,  J = 7.6 Hz, 2H), 2.67 (t,  J = 7.0 Hz, 2H), 1.84 (p,  J = 7.3 Hz, 2H), 1.35 (s, 1H); ¹³C NMR (126 MHz, DMSO-d₆, 19F decoupled) δ [ppm]: 151.9, 150.1, 149.1, 148.5, 139.5, 133.4, 128.3, 127.5, 125.6, 125.6, 124.1, 124.0, 123.9, 120.3, 120.1, 117.5, 98.7, 48.3, 47.2, 42.4, 29.0, 22.8; ¹⁹F NMR (471 MHz, DMSO-d₆) δ [ppm]: -60.95; HRMS (APPI) calculated for C₂₃H₂₁ClF₃N₆ [M+H]⁺: 475.1619; found: 475.1627.

**Synthesis of triazole 16**
Product 16 was synthesized via general procedure A, using 1-azido-4-nitrobenzene (57.0 mg, 348 µmol, 1.0 equiv.) and alkyne 14 (100 mg, 348 µmol, 1.0 equiv.) with the catalyst system of CuSO₄•5 H₂O (17.4 mg, 69.5 µmol, 0.2 equiv.) and sodium ascorbate (27.5 mg, 139 µmol, 0.4 equiv.) in THF:H₂O (1:1, 10 mL). The reaction mixture was stirred for 3.5 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 8:1→6:1) the final product was obtained as yellow solid as a mixture of isomers (2.5:1; overall yield for both isomers: 110 mg, 243 µmol, 70%). Separation of the isomers was not possible with column chromatography or preparative thin layer chromatography. HRMS (APPI) calculated for C₂₂H₂₃ClN₇O₂ [M+H]⁺: 452.1596; found: 452.1606.

**Major isomer of 16:**

\[
\text{H NMR (600 MHz, DMSO-d₆) \delta [ppm]: 8.78 (s, 1H), 8.44-8.40 (m, 2H), 8.38 (d, J = 5.4 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.19-8.14 (m, 2H), 7.76 (d, J = 2.3 Hz, 1H), 7.45-7.38 (m, 1H), 6.50 (d, J = 5.4 Hz, 1H), 3.40-3.34 (m, 2H), 2.86 (t, J = 6.5 Hz, 2H), 2.78 (p, J = 6.3 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H), 1.85 (p, J = 7.3 Hz, 2H); ¹³C NMR (126 MHz, DMSO-d₆) \delta [ppm]: 151.9, 150.1, 149.1, 148.7, 146.4, 141.0, 133.4, 127.5, 125.6, 125.6, 124.1, 124.0, 117.5, 98.7, 48.2, 47.1, 28.8, 22.8.}\]
Minor isomer of 16:

\[
\text{H NMR (500 MHz, DMSO-d6) } \delta \text{ [ppm]}: 8.44-8.40 (m, 2H), 8.36 (d, } J = 5.4 \text{ Hz, 1H}), 8.22 (d, } J = 9.0 \text{ Hz, 1H}), 7.94-7.90 (m, 2H), 7.76 (d, } J = 2.3 \text{ Hz, 1H}), 7.45-7.38 (m, 1H), 6.45 (d, } J = 5.4 \text{ Hz, 1H}), 3.31-3.27 (m, 2H), 2.82 (t, } J = 7.7 \text{ Hz, 2H}), 2.75 (t, 2H), 2.57 (t, } J = 6.7 \text{ Hz, 2H}), 1.77-1.70 \text{ (m, 2H); 13C NMR (126 MHz, DMSO-d6) } \delta \text{ [ppm]}: 151.9, 150.1, 149.1, 147.4, 141.0, 138.8, 133.4, 132.8, 127.5, 125.9, 125.1, 124.1, 124.1, 117.4, 98.7, 47.9, 47.1, 27.7, 20.9.\]

Synthesis of triazole 17

Product 17 was synthesized via general procedure A, using 4-azidobenzonitrile (103 mg, 712 µmol, 1.0 equiv.) and alkyne 14 (205 mg, 712 µmol, 1.0 equiv.) with the catalyst system of CuSO\(\text{4} \times 5 \text{H}_2\text{O} \) (35.6 mg, 143 µmol, 0.2 equiv.) and sodium ascorbate (56.5 mg, 285 µmol, 0.4 equiv.) in THF:H\(\text{2O} \) (1:1, 20 mL). The reaction mixture was stirred for 3.5 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 6:1), the final product 17 was obtained as off-white solid (124 mg, 288 µmol, 41%). \(^1\)H NMR (400 MHz, DCM-d\(\text{2}/\text{MeOD} / 5:1\) ) \(\delta \) [ppm]: 8.35 (d, \( J = 5.6 \) Hz, 1H), 8.05 (s, 1H), 8.02 (d, \( J = 9.0 \) Hz, 1H), 7.93-7.87 (m, 2H), 7.86-7.82 (m, 2H), 7.81 (d, \( J = 2.1 \) Hz, 1H), 7.37 (dd, \( J = 9.0, 2.1 \) Hz, 1H), 6.45 (d, \( J = 5.6 \) Hz, 1H), 3.46 (t, \( J = 5.9 \) Hz, 2H), 3.30 (p, \( J = 1.6 \) Hz, 3H), 2.99 (t, \( J = 5.9 \) Hz, 2H), 2.87-2.81 (m, 2H), 2.74 (t, \( J = 7.4 \) Hz, 2H), 1.95 (p, \( J = 7.5 \) Hz, 2H), 1.86-1.79 (m, 1H); \(^{13}\)C NMR (101 MHz, DCM-d\(\text{2}/\text{MeOD} / 5:1\) ) \(\delta \) [ppm]: 151.6, 149.2, 148.6, 140.4, 135.8, 134.5, 134.2, 127.3, 126.1, 125.8, 123.1, 120.9, 120.1, 118.3, 117.9, 99.1, 68.3, 46.9, 42.5, 29.2, 23.3; HRMS (APPI) calculated for C\(_{23}\)H\(_{23}\)ClN\(_7\) [M+H]\(^+\): 432.1698; found: 432.1704.

Synthesis of triazole 18

Product 18 was synthesized via general procedure A, using methyl 4-azidobenzoate (61.5 mg, 348 µmol, 1.0 equiv.) and alkyne 14 (100 mg, 348 µmol, 1.0 equiv.) with the catalyst system of CuSO\(\text{4} \times 5 \text{H}_2\text{O} \) (17.4 mg, 69.5 µmol, 0.2 equiv.) and sodium ascorbate (27.5 mg, 139 µmol, 0.4 equiv.) in THF:H\(\text{2O} \) (1:1, 10 mL). The reaction mixture was stirred for 3 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 8:1), the final product 18 was obtained as white solid (73.1 mg, 157 µmol, 45%). \(^1\)H NMR (400 MHz, DMSO-d\(\text{6}\) ) \(\delta \) [ppm]: 8.69 (s, 1H), 8.39 (d, \( J = 5.4 \) Hz, 1H), 8.26 (d, \( J = 9.0 \) Hz, 1H), 8.17-8.09 (m, 2H), 8.08-8.00 (m, 2H), 7.77 (d, \( J = 2.3 \) Hz, 1H), 7.43 (dd, \( J = 9.0, 2.3 \) Hz, 1H), 7.25 (s, 1H), 6.50 (d, \( J = 5.5 \) Hz, 1H), 3.89 (s, 3H), 3.37 (t, \( J = 6.4 \) Hz, 2H), 2.85 (t, \( J = 6.5 \) Hz, 2H), 2.78 (t, \( J = 7.6 \) Hz, 2H), 2.67 (t, \( J = 7.0 \) Hz, 2H), 1.85 (h, \( J = 8.0, 7.3 \) Hz, 2H); \(^{13}\)C NMR (101 MHz, DMSO-d\(\text{6}\) ) \(\delta \) [ppm]: 165.4, 151.9, 150.1, 149.1, 148.4, 139.9, 133.4, 131.0, 129.0, 127.5, 124.1, 124.0, 120.2, 119.5, 117.5, 98.7, 52.4, 48.2, 47.2, 42.4, 28.9, 22.8; HRMS (APPI) calculated for C\(_{24}\)H\(_{26}\)ClN\(_6\)O\(_2\) [M+H]\(^+\): 465.1800; found: 465.1806.

Synthesis of triazole 19

Product 19 was synthesized via general procedure A, using 1-azido-4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzene (196 mg, 695 µmol, 1.0 equiv.) and alkyne 14 (200 mg, 695 µmol, 1.0 equiv.) with the catalyst system of CuSO\(\text{4} \times 5 \text{H}_2\text{O} \) (34.7 mg, 139 µmol, 0.2 equiv.) and sodium ascorbate (55.1 mg, 278 µmol, 0.4 equiv.) in THF:H\(\text{2O} \) (1:1, 20 mL). The reaction mixture was
stirred for 2 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 8:1), the final product 19 was obtained as a white solid (145 mg, 255 µmol, 37%). $^1$H NMR (400 MHz, acetone-d6) δ [ppm]: 8.45 (s, 1H), 8.15 (s, 2H), 7.83 (d, $J = 2.3$ Hz, 1H), 7.76-7.68 (m, 2H), 7.38 (dd, $J = 8.9, 2.0$ Hz, 1H), 7.16-7.09 (m, 2H), 6.55 (d, $J = 5.2$ Hz, 1H), 4.26-4.17 (m, 2H), 3.87-3.82 (m, 2H), 3.70- 3.64 (m, 2H), 3.64- 3.55 (m, 4H), 3.50-3.43 (m, 4H), 3.28 (s, 3H), 2.91-2.73 (m, 12H); 13C NMR (101 MHz, DMSO-d6) δ [ppm]: 158.9, 133.8, 130.9, 124.4, 123.1, 121.5, 119.5, 115.4, 71.8, 70.6, 70.4, 70.2, 69.4, 67.9, 57.9, 22.9; HRMS (APPI) calculated. for C$_{29}$H$_{38}$ClN$_6$O$_4$ [M+H]$^+$: 569.2638; found: 569.2649.

**Synthesis of triazole 20**

Product 20 was synthesized via general procedure A, using 4-(4-azidobenzyl)morpholine (152 mg, 695 µmol, 1.0 equiv.) and alkyne 14 (200 mg, 695 µmol, 1.0 equiv.) with the catalyst system of CuSO$_4$·5 H$_2$O (34.7 mg, 139 µmol, 0.2 equiv.) and sodium ascorbate (55.1 mg, 278 µmol, 0.4 equiv.) in THF:H$_2$O (1:1, 20 mL). The reaction mixture was stirred for 3 h at r.t. under Argon. After purification via column chromatography (DCM:MeOH / 3:1), the final product 20 was obtained as off-white solid (211 mg, 417 µmol, 60%). $^1$H NMR (400 MHz, acetone-d6): δ [ppm]: 8.45 (d, $J = 5.3$ Hz, 1H), 8.23 (d, $J = 0.7$ Hz, 1H), 8.12 (d, $J = 9.0$ Hz, 1H), 7.82 (d, $J = 2.2$ Hz, 1H), 7.81-7.74 (m, 4H), 7.56-7.47 (m, 2H), 7.37 (dd, $J = 9.0, 2.3$ Hz, 1H), 6.64 (s, 1H), 6.54 (d, $J = 5.3$ Hz, 1H), 3.66-3.58 (m, 4H), 3.55 (s, 2H), 3.46-3.40 (m, 2H), 3.00 (t, $J = 7.5$ Hz, 2H), 2.75 (t, $J = 6.8$ Hz, 2H), 2.45-2.39 (m, 4H), 1.98-1.85 (m, 2H); 13C NMR (101 MHz, acetone-d6) δ [ppm]: 153.0, 151.1, 150.6, 149.2, 139.7, 137.3, 134.7, 131.0, 129.2, 125.2, 123.8, 120.6, 120.2, 118.6, 99.9, 68.1, 67.5, 63.1, 54.5, 49.1, 48.3, 43.3, 26.2, 23.8; HRMS (APPI) calculated for C$_{27}$H$_{33}$ClN$_7$O $[M+H]^+$: 506.2430; found: 506.2444.

**Preparation of the artemisinin-quinoline hybrids 2-7**

![Diagram of artemisinin-quinoline hybrids]

**General procedure B:**

Artesunic acid (1 equiv.) was dissolved in DCM (dry) and cooled to 0 °C under N$_2$. EDCI·HCl (1.0 equiv.) was added and the solution was stirred for 5 min. The triazole precursor (1.0 equiv.) in dry DCM or DCM/THF (5:1) and DMAP (2.0 equiv.) were added. The reaction was stirred at r.t. for 24 h, quenched with the addition of H$_2$O (25 mL) and extracted with DCM (3 x 25 mL). The combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified with column chromatography (DCM:MeOH) to give the pure products as solids.

S6
Synthesis of hybrid 2

The hybrid compound 2 was prepared via general procedure B, using artesunic acid (66.1 mg, 172 µmol, 1.0 equiv.), amine 17 (81.6 mg, 172 µmol, 1.0 equiv. in 5 mL DCM:THF), EDCI (32.9 mg, 172 µmol, 1.0 equiv.) and DMAP (42.0 mg, 344 µmol, 1.0 equiv.) in DCM (dry, 5 mL). The crude product was purified via column chromatography (DCM:MeOH / 15:1) to obtain a white solid (42.2 mg, 50.2 µmol, 33%) as product. $^1$H NMR (500 MHz, DMSO-d6, 100 °C) δ [ppm]: 8.53 (s, 1H), 8.41 (d, $J = 5.4$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 8.5$ Hz, 2H), 7.77 (d, $J = 2.2$ Hz, 1H), 7.39 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.17-7.10 (m, 1H), 6.57 (d, $J = 5.4$ Hz, 1H), 5.66 (d, $J = 9.7$ Hz, 1H), 5.46 (s, 1H), 3.71-3.58 (m, 2H), 3.56-3.41 (m, 4H), 2.78 (s, 2H), 2.69-2.61 (m, 5H), 2.27-2.17 (m, 1H), 2.10-1.96 (m, 3H), 1.88-1.79 (m, 1H), 1.68-1.60 (m, 2H), 1.54 (dt, $J = 13.6, 4.3$ Hz, 1H), 1.46-1.25 (m, 7H), 1.20 (td, $J = 11.4, 6.6$ Hz, 1H), 1.02-0.92 (m, 1H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.76 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, DMSO-d6, 100 °C; $^{19}$F-decoupled) δ [ppm]: 171.4, 171.3, 170.6, 151.8, 150.0, 148.9, 148.1, 147.7, 139.5, 133.4, 128.4, 127.4, 127.2, 124.2, 123.9, 123.7, 120.5, 120.2, 117.3, 103.6, 98.5, 91.6, 90.6, 79.8, 51.1, 47.4, 44.5, 36.0, 35.9, 33.7, 31.7, 29.1, 27.8, 27.3, 25.5, 24.2, 22.1, 21.0, 20.0, 11.6; $^{19}$F NMR (471 MHz, DMSO-d6, 100 °C): δ -61.15; HRMS (APPI) calculated for C$_{42}$H$_{49}$ClF$_3$N$_6$O$_7$ [M+H]+:841.3298; found: 841.3309; elemental analysis: calculated: C, 59.96; H, 5.75; Cl, 4.21; F, 6.77; N, 9.99; O, 13.31, found: C, 60.07; H, 5.95; N, 9.85.

Synthesis of hybrid 3

The hybrid compound 3 was prepared via general procedure B, using artesunic acid (112 mg, 291 µmol, 1.0 equiv.), amine 18 (132 mg, 291 µmol, 1.0 equiv. in 6 mL DCM:THF), EDCI (55.8 mg, 291 µmol, 1.0 equiv.) and DMAP (71.2 mg, 582 µmol, 1.0 equiv.) in DCM (dry, 5 mL). The crude product was purified via column chromatography (DCM:MeOH / 15:1) to obtain an off-white solid (122 mg, 149 µmol, 51%) as product. $^1$H NMR (300 MHz, DMSO-d6, 100 °C) δ [ppm]: 8.60 (s, 1H), 8.45-8.36 (m, 3H), 8.18-8.10 (m, 3H), 7.76 (d, $J = 2.2$ Hz, 1H), 7.38 (dd, $J = 9.0, 2.3$ Hz, 1H), 7.12 (s, 1H), 6.60-6.53 (m, 1H), 5.66 (d, $J = 9.7$ Hz, 1H), 5.46 (s, 1H), 3.69-3.60 (m, 2H), 3.57 (s, 1H), 3.55-3.42 (m, 4H), 2.77 (d, $J = 7.7$ Hz, 2H), 2.69-2.60 (m, 4H), 2.40-2.30 (m, 1H), 2.29-2.16 (m, 1H), 2.07-1.93 (m, 4H), 1.59-1.48 (m, 1H), 1.48-1.14 (m, 8H), 1.06-0.81 (m, 4H), 0.77 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (76 MHz, DMSO-d6, 100 °C) δ [ppm]: 170.6, 151.4, 149.6, 148.8, 147.5, 146.3, 141.9, 140.6, 132.9, 127.1, 124.8, 123.6, 123.1, 120.0, 117.1, 103.1, 98.2, 96.7, 91.4, 90.3, 85.0, 83.5, 79.4, 73.7, 50.9, 44.3, 35.7, 35.6, 33.3, 31.2, 28.9, 28.5, 27.1, 26.9, 25.0, 23.7, 21.9, 20.7, 19.3, 11.0; HRMS (APPI) calculated for C$_{41}$H$_{49}$ClN$_7$O$_9$ [M+H]+:818.3275; found: 818.3278; elemental analysis: calculated: C, 59.96; H, 5.75; Cl, 4.21; F, 6.77; N, 9.99; O, 13.31, found: C, 59.69; H, 5.99; N, 11.77.

Synthesis of hybrid 4

The hybrid compound 4 was prepared via general procedure B, using artesunic acid (124 mg, 323 µmol, 1.0 equiv.), amine 19 (139 mg, 323 µmol, 1.0 equiv. in 8 mL DCM:THF), EDCI (61.8 mg, 323 µmol, 1.0 equiv.) and DMAP (78.8 mg, 645 µmol, 1.0 equiv.) in DCM (dry, 7 mL). The crude product was purified via column chromatography (DCM:MeOH / 30:1) to obtain a white solid (139 mg, 174 µmol, 54%) as product. $^1$H NMR (500 MHz, DMSO-d6, 100 °C) δ [ppm]: 8.56 (s, 1H), 8.41 (d, $J = 5.5$ Hz, 1H),
8.14 (s, 1H), 8.08-7.99 (m, 4H), 7.79 (d, J = 2.2 Hz, 1H), 7.41 (dd, J = 8.9, 2.3 Hz, 1H), 7.34 (s, 1H), 6.59 (d, J = 5.6 Hz, 1H), 5.66 (d, J = 9.7 Hz, 1H), 5.46 (s, 1H), 3.73-3.59 (m, 2H), 3.58-3.47 (m, 4H), 2.78 (s, 2H), 2.70-2.62 (m, 4H), 2.35 (s, 1H), 2.27-2.17 (m, 1H), 2.07-1.96 (m, 3H), 1.87-1.78 (m, 1H), 1.69-1.60 (m, 2H), 1.54 (dt, J = 13.8, 4.3 Hz, 1H), 1.46-1.30 (m, 3H), 1.29 (s, 3H), 1.19 (td, J = 11.4, 6.6 Hz, 1H), 1.02-0.93 (m, 1H), 0.91 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 7.1 Hz, 3H); 13C NMR (126 MHz, DMSO-d6) δ [ppm]: 171.4, 171.3, 170.6, 151.3, 151.0, 150.5, 150.2, 148.3, 148.2, 147.8, 147.8, 139.6, 139.6, 134.2, 133.8, 133.8, 126.9, 126.6, 124.4, 123.9, 123.9, 120.4, 120.3, 120.1, 120.0, 118.1, 117.2, 117.1, 110.7, 110.6, 103.5, 103.5, 98.6, 98.5, 91.6, 90.5, 79.8, 54.9, 51.1, 47.4, 45.4, 45.1, 44.5, 44.3, 40.9, 36.0, 35.9, 35.8, 33.6, 33.5, 31.6, 29.1, 29.0, 27.7, 27.2, 27.1, 26.7, 25.5, 24.1, 22.5, 22.1, 21.7, 21.0, 20.0, 13.9, 11.7, 11.6; HRMS (APPI) calculated for C42H49ClN7O7 [M+H]+: 798.3377; found: 798.3379; elemental analysis: calculated: C, 63.19; H, 6.06; Cl, 4.44; N, 12.28; O, 14.03; found: C, 63.08; H, 6.22; N, 12.10.

Synthesis of hybrid 5

The hybrid compound 5 was prepared via general procedure B, using artesunic acid (77.7 mg, 202 µmol, 1.0 equiv.), amine 20 (94.0 mg, 202 µmol, 1.0 equiv. in 6 mL DCM:THF), EDCI (38.8 mg, 202 µmol, 1.0 equiv.) and DMAP (48.4 mg, 404 µmol, 1.0 equiv.) in DCM (dry, 5 mL). The crude product was purified via column chromatography (DCM:MeOH / 20:1) to obtain a white solid (116 mg, 140 µmol, 69%) as product. 1H NMR (300 MHz, DMSO-d6, 100 °C) δ [ppm]: 8.51 (s, 1H), 8.41 (d, J = 5.5 Hz, 1H), 8.19-8.08 (m, 3H), 8.04-7.95 (m, 2H), 7.78 (d, J = 2.2 Hz, 1H), 7.40 (dd, J = 9.0, 2.3 Hz, 1H), 7.21 (t, J = 5.7 Hz, 1H), 6.58 (d, J = 5.5 Hz, 1H), 5.71-5.62 (m, 1H), 5.46 (s, 1H), 3.92 (s, 3H), 3.63 (d, J = 6.6 Hz, 2H), 3.58-3.42 (m, 4H), 2.78 (t, J = 7.4 Hz, 2H), 2.42-2.31 (m, 1H), 2.29-2.15 (m, 1H), 2.11-1.93 (m, 3H), 1.91-1.76 (m, 1H), 1.69-1.60 (m, 2H), 1.60-1.47 (m, 1H), 1.46-1.14 (m, 5H), 0.76 (d, J = 7.1 Hz, 3H); 13C NMR (76 MHz, DMSO-d6, 100 °C): δ [ppm]: 170.61, 164.9, 151.0, 149.7, 148.8, 148.1, 147.3, 139.6, 135.1, 133.1, 130.3, 129.0, 126.8, 123.7, 123.2, 119.7, 119.3, 117.0, 103.1, 98.2, 91.5, 90.3, 79.4, 51.6, 50.9, 44.3, 40.8, 35.7, 35.6, 33.3, 31.2, 28.9, 26.9, 25.0, 23.7, 21.9, 20.7, 19.3, 11.0; HRMS (APPI) calculated for C43H52ClN6O9 [M+H]+: 831.3479; found: 831.3495; elemental analysis: calculated: C, 62.12; H, 6.18; Cl, 4.26; N, 10.11; O, 17.32; found: C, 62.04; H, 6.36; N, 9.83.

Synthesis of hybrid 6

The hybrid compound 6 was prepared via general procedure B, using artesunic acid (94.6 mg, 246 µmol, 1.0 equiv.), amine 21 (140 mg, 188 µmol, 1.0 equiv. in 6 mL DCM:THF), EDCI (47.2 mg, 246 µmol, 1.0 equiv.) and DMAP (60.1 mg, 492 µmol, 1.0 equiv.) in DCM (dry, 5 mL). The crude product was purified via column chromatography (DCM:MeOH / 10:1) to obtain a white solid (85.7 mg, 91.6 µmol, 37%) as product. 1H NMR (500 MHz, DMSO-d6, 100 °C) δ [ppm]: 8.42 (d, J = 5.4 Hz, 1H), 8.27 (s, 1H), 8.13 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.74-7.67 (m, 2H), 7.41 (dd, J = 9.0, 2.2 Hz, 1H), 7.23 (s, 1H), 7.14-7.08 (m, 2H), 6.59 (d, J = 5.5 Hz, 1H), 5.67 (d, J = 9.7 Hz, 1H), 5.47 (s, 1H), 4.23-4.17 (m, 2H), 3.83-3.76 (m, 2H), 3.69-3.61 (m, 4H), 3.59-3.54 (m, 4H), 3.53-3.43 (m, 4H), 3.27 (s, 3H), 2.75 (s, 2H), 2.70-2.62 (m, 4H), 2.41-2.30 (m, 1H), 2.22 (ddd, J = 14.7, 13.4, 4.1 Hz, 1H), 1.88-1.79 (m, 1H), 1.64 (ddd, J = 13.4, 5.7, 3.5 Hz, 2H), 1.54 (dt, J = 13.7, 4.3 Hz, 1H), 1.44-1.25 (m, 7H), 1.20 (td, J = 11.4, 6.6 Hz, 1H), 1.02-0.94 (m, 1H), 0.91 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 7.1 Hz, 3H); 13C NMR
(126 MHz, DMSO-d6): δ [ppm] 171.4, 171.3, 171.3, 171.3, 170.6, 158.3, 158.3, 157.3, 151.7, 151.4, 150.3, 150.1, 149.7, 148.2, 147.4, 147.0, 146.6, 146.0, 145.1, 144.5, 144.4, 140.9, 140.5, 136.0, 135.9, 133.7, 133.5, 133.5, 131.7, 29.6, 29.2, 29.1, 27.9, 27.3, 21.7, 21.0, 20.1, 20.0, 13.9, 11.7, 11.7, 11.7, 11.3; HRMS (APPI) calculated for C₄₈H₆₄ClN₆O₁₁ [M+H]+: 935.4320; found: 935.4316; elemental analysis: calculated: C, 61.63; H, 6.79; Cl, 3.79; N, 8.98; O, 18.81, found: C, 61.22; H, 6.79; N, 9.05.

Synthesis of hybrid 7
The hybrid compound 7 was prepared via general procedure B, using artesunic acid (160 mg, 417 µmol, 1.0 equiv.), amine 22 (211 mg, 417 µmol, 1.0 equiv.) in 10 mL DCM:THF, EDCI (79.9 mg, 417 µmol, 1.0 equiv.) and DMAP (102 mg, 834 µmol, 1.0 equiv.) in DCM (dry, 10 mL). The crude product was purified via column chromatography (DCM:MeOH / 23:1) to obtain a white solid (194 mg, 223 µmol, 53%) as product. 1H NMR (500 MHz, DMSO-d6, at 100 °C) δ [ppm]: 8.41 (d, J = 5.4 Hz, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 7.78 (d, J = 2.2 Hz, 1H), 7.78-7.74 (m, 2H), 7.53-7.47 (m, 2H), 7.40 (dd, J = 9.0, 2.3 Hz, 1H), 7.20 (s, 1H), 6.58 (d, J = 5.4 Hz, 1H), 5.67 (d, J = 9.7 Hz, 1H), 5.47 (s, 1H), 3.72-3.58 (m, 6H), 3.56 (s, 2H), 3.54-3.44 (m, 4H), 2.76 (s, 2H), 2.71-2.64 (m, 4H), 2.45-2.42 (m, 4H), 2.41-2.30 (m, 1H), 2.22 (ddd, J = 14.6, 13.3, 4.0 Hz, 1H), 2.06-1.93 (m, 2H), 1.88-1.79 (m, 1H), 1.69-1.60 (m, 1H), 1.54 (dt, J = 13.6, 4.4 Hz, 1H), 1.48-1.26 (m, 7H), 1.20 (td, J = 11.4, 6.6 Hz, 1H), 1.05-0.93 (m, 1H), 0.91 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 7.1 Hz, 3H); 13C NMR (126 MHz, DMSO-d6): δ [ppm]: 70.6, 159.9, 151.0, 149.9, 137.9, 135.4, 133.2, 129.5, 126.7, 123.7, 123.2, 119.5, 119.4, 117.0, 103.1, 98.2, 91.4, 90.7, 90.3, 79.3, 65.8, 61.2, 55.9, 52.7, 51.0, 50.9, 44.3, 35.7, 35.7, 35.6, 33.3, 32.9, 31.2, 29.8, 28.9, 26.9, 25.0, 23.7, 21.9, 21.0, 20.7, 19.5, 19.3, 13.0, 11.0, 10.8; HRMS (APPI) calculated for C₄₆H₅₉ClN₇O₈ [M+H]+: 872.4108; found: 872.4116; elemental analysis: calculated:  C, 63.33; H, 6.70; Cl, 4.06; N, 11.24; O, 14.67, found: C, 63.58; H, 6.74; N, 10.95.

Synthesis of hybrid 8
Tetraoxane acid (150 mg, 0.73 mmol, 1.0 equiv.) was dissolved in dry CH₂Cl₂ (20 ml). The coupling agent EDCI (140 mg, 0.73 mmol, 1.0 equiv.) which was used to activate the carboxyl of tetraoxane acid, was added at 0 °C. DMAP (90.0 mg, 0.73 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (325 mg, 1.46 mmol, 2.0 equiv.) were added subsequently. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction was worked up with water (25 mL) and extracted with CH₂Cl₂ (3x 25 mL). The combined CH₂Cl₂ phase was evaporated, and the hybrid 8 (white crystals, 0.112 g, 0.27 mmol, 56%) was isolated by chromatography on SiO₂ using EtOAc : MeOH mixture as the eluent with a gradient of MeOH from 10 to 15 vol. %. Mp = 78-80°C. Rf = 0.23 (5:1, EtOAc:MeOH). 1H NMR (300.13 MHz, CDCl₃) δ [ppm]: 1.52 (s, 6H), 1.66-1.91 (m, 4H), 2.31 (dd, J = 8.7, 6.8 Hz, 2H), 2.48-2.52 (m, 4H), 2.73 (t, J = 5.9 Hz, 1H), 3.21 (q, J = 6.6 Hz, 2H), 3.26-3.39 (m, 4H), 6.48 (d, J = 5.5 Hz, 1H), 7.31 (t, J = 5.5 Hz, 1H), 7.46 (dd, J = 9.0, 2.3 Hz, 1H), 7.79 (d, J = 2.3 Hz, 1H), 8.02 (t, J = 5.6 Hz, 1H), 8.26 (d, J = 9.1 Hz, 1H), 8.40 (d, J = 5.4 Hz, 1H). 13C NMR (75.47 MHz, CDCl₃) δ [ppm]: 9.8, 19.7, 33.4, 38.9, 45.6, 58.4, 98.4, 110.9, 117.3, 122.3, 125.5, 127.8, 135.2, 148.8, 150.5, 151.7, 174.5; HRMS
Synthesis of hybrid 9
Tetraoxane acid (150 mg, 0.73 mmol, 1.0 equiv.) was dissolved in dry CH$_2$Cl$_2$ (20 ml). The coupling agent EDCI (140 mg, 0.73 mmol, 1.0 equiv.) which was used to activate the carboxyl group of tetraoxane acid, was added at 0°C. DMAP (90 mg, 0.73 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (346 mg, 1.46 mmol, 2.0 equiv.) were added subsequently. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction was worked up with water (25 mL) and extracted with CH$_2$Cl$_2$ (3x 25 mL). The combined CH$_2$Cl$_2$ phase was evaporated, and the hybrid 9 (white crystals, 0.147 g, 0.340 mmol, 47%) was isolated by chromatography on SiO$_2$ using EtOAc:MeOH mixture as the eluent with a gradient of MeOH from 10 to 15 vol. %. Mp = 149-151°C. R$_f$ = 0.20 (5:1, EtOAc:MeOH); $^1$H NMR (300.13 MHz, (CD$_3$)$_2$SO) $\delta$ [ppm]: 1.51 (s, 6H), 1.67-1.96 (m, 4H), 2.42 (t, J = 5.9 Hz, 2H), 2.66 (t, J = 5.9 Hz, 1H), 3.20 (q, J = 6.6 Hz, 2H), 3.61-3.74 (m, 2H), 6.25 (d, J = 5.5 Hz, 1H), 6.79 (d, J = 4.2 Hz, 1H), 7.30 (dd, J = 9.0, 2.2 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 5.5 Hz, 1H); $^{13}$C NMR (75.47 MHz, (CD$_3$)$_2$SO) $\delta$ [ppm]: 9.3, 19.6, 27.9, 32.8, 36.5, 58.1, 98.6, 110.6, 117.5, 123.9, 124.1, 127.5, 133.4, 149.1, 150.0, 151.9, 171.5; HRMS (ESI-TOF) calculated for C$_{20}$H$_{25}$ClN$_3$O$_5$ [M+H]$^+$: 422.1477; found: 422.1484; elemental analysis calculated: C, 56.94; H, 5.73; Cl, 8.40; N, 9.96; found: C, 57.12; H, 5.92; Cl, 8.62; N, 10.20.

Synthesis of hybrid 10
Tetraoxane acid (150 mg, 0.730 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (327 mg, 1.46 mmol, 2.0 equiv.) were dissolved in dry CH$_2$Cl$_2$ (20 mL) under argon atmosphere. DCC (167 mg, 0.81 mmol, 1.1 equiv.) and DMAP (180 mg, 1.46 mmol, 2.0 equiv.) were added at 0°C to the solution. The reaction mixture was warmed up to room temperature and stirred overnight. After filtration of the precipitated urea, solvent was evaporated, and the hybrid 10 (white crystals, 0.228 g, 0.55 mmol, 76%) was isolated by chromatography on SiO$_2$ using EtOAc:MeOH mixture as the eluent with a gradient of MeOH from 3 to 5 vol. %. Mp = 133-134°C. R$_f$ = 0.27 (10:1, EtOAc:MeOH); $^1$H NMR (300.13 MHz, (CD$_3$)$_2$SO) $\delta$ [ppm]: 1.48 (s, 6H), 1.66-1.78 (m, 2H), 2.55 (d, J = 7.7 Hz, 2H), 2.75 (t, J = 5.9 Hz, 1H), 3.58 (q, J = 5.7 Hz, 2H), 4.32 (t, J = 5.7 Hz, 2H), 6.58 (d, J = 5.4 Hz, 1H), 7.40 (t, J = 5.4 Hz, 1H), 7.46 (dd, J = 2.2, 9.0 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H); $^{13}$C NMR (75.47 MHz, (CD$_3$)$_2$SO) $\delta$ [ppm]: 9.6, 19.0, 31.5, 41.6, 58.1, 62.3, 99.3, 111.1, 117.9, 124.46, 124.70, 128.1, 133.9, 149.16 150.5, 152.4, 172.9; HRMS (ESI-TOF) calculated for C$_{19}$H$_{22}$ClN$_2$O$_6$ [M+H]$^+$: 409.1161; found: 409.1158; elemental analysis calculated: C, 55.82; H, 5.18; Cl, 8.67; N, 6.85; found: C, 55.99; H, 5.31; Cl, 8.91; N, 7.01.

Synthesis of hybrid 11
Monoperoxide acid (150 mg, 0.58 mmol, 1.0 equiv.) was dissolved in dry CH$_2$Cl$_2$ (20 ml). The coupling agent EDCI (111 mg, 0.58 mmol, 1.0 equiv.) which was used to activate the carboxyl group of monoperoxide acid, was added at 0°C. DMAP (71.0 mg, 0.58 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (258 mg, 1.16 mmol, 2.0 equiv.) were added subsequently. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction was worked up with water (25 mL) and
extracted with CH₂Cl₂ (3 × 25 mL). The combined CH₂Cl₂ phase was evaporated, and the hybrid 11 (white crystals, 0.196 g, 0.42 mmol, 73%) was isolated by chromatography on SiO₂ using EtOAc : MeOH mixture as the eluent with a gradient of MeOH from 10 to 15 vol. %. Mp = 113-115°C. Rf = 0.18 (5:1, EtOAc:MeOH); ¹H NMR (300.13 MHz, (CDCl₃) δ [ppm]: 1.36 (s, 3H), 1.41 (s, 6H), 1.66 (s, 4H), 1.74 – 1.88 (m, 2H), 2.42 – 2.53 (m, 2H), 3.38 (q, J = 4.9, 5.4 Hz, 2H), 3.67 (q, J = 5.8 Hz, 2H), 6.27 (d, J = 5.4 Hz, 1H), 6.61 (t, J = 6.2 Hz, 1H), 6.76 (t, J = 6.2 Hz, 1H), 7.34 (dd, J = 2.2, 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H); ¹³C NMR (75.47 MHz, (CDCl₃) δ [ppm]: 15.6, 20.9, 24.6, 27.1, 30.64, 30.96, 38.8, 45.5, 50.5, 94.3, 98.3, 106.8, 117.3, 122.0, 125.4, 128.3, 134.9, 149.0, 150.1, 159.9, 175.4; HRMS (ESI-TOF) calculated for C23H29ClN3O5 [M+H]+: 462.1790; found: 462.1780; elemental analysis: calculated: C, 59.80; H, 6.11; Cl, 7.67; N, 9.10; found: C, 59.98; H, 6.35; Cl, 7.98; N, 9.27.

Synthesis of hybrid 12
Monoperoxide acid (150 mg, 0.58 mmol, 1.0 equiv.) was dissolved in dry CH₂Cl₂ (20 ml). The coupling agent EDCI (111 mg, 0.58 mmol, 1.0 equiv.) which was used to activate the carboxyl group of monoperoxide acid, was added at 0°C. DMAP (71.0 mg, 0.58 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (274 mg, 1.16 mmol, 2.0 equiv.) were added subsequently. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction was worked up with water (25 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined CH₂Cl₂ phase was evaporated, and the hybrid 12 (white crystals, 0.215 g, 0.45 mmol; 77%) was isolated by chromatography on SiO₂ using EtOAc : MeOH mixture as the eluent with a gradient of MeOH from 10 to 15 vol. %. Mp = 77-79°C. Rf = 0.25 (5:1, EtOAc:MeOH); ¹H NMR (300 MHz, (CDCl₃) δ [ppm]: 1.36 (s, 3H), 1.43 (s, 6H), 1.68 (s, 4H), 1.75-1.88 (m, 4H), 2.30-2.52 (m, 2H), 3.28-3.41 (m, 4H), 6.34 (d, J = 5.4 Hz, 1H), 6.40 (t, J = 6.0 Hz, 1H), 6.66 (t, J = 6.0 Hz, 1H), 7.33 (dd, J = 2.2, 8.9 Hz, 1H), 7.81-7.93 (m, 2H), 8.43 (d, J = 5.4 Hz, 1H); ¹³C NMR (75 MHz, (CDCl₃) δ [ppm]: 15.8, 20.8, 24.7, 27.4, 28.3, 30.8, 31.2, 36.6, 39.4, 50.6, 94.4, 98.7, 106.9, 117.7, 122.1, 125.3, 128.3, 135.0, 149.3, 150.1, 159.9, 173.9; HRMS (ESI-TOF): calculated for C24H31ClN3O5 [M+H]+: 476.1947; found: 476.1953; elemental analysis: calculated: C, 60.56; H, 6.35; Cl, 7.45; N, 8.83; found: C, 60.80; H, 6.47; Cl, 7.62; N, 9.05.

Synthesis of hybrid 13
Monoperoxide acid (150 mg, 0.58 mmol, 1.0 equiv.) and 7-chloroquinoline derivative (259 mg, 1.16 mmol, 2.0 equiv.) were dissolved in dry CH₂Cl₂ (20 mL) under argon atmosphere. DCC (132 mg, 0.64 mmol, 1.1 equiv.) and DMAP (142 mg, 1.16 mmol, 2.0 equiv.) were added at 0°C to the solution. The reaction mixture was warmed up to room temperature and stirred overnight. After filtration of the precipitated urea, solvent was evaporated, and the hybrid 13 (white crystals, 0.180 g, 0.38 mmol, 67%) was isolated by chromatography on SiO₂ using EtOAc : MeOH mixture as the eluent with a gradient of MeOH from 3 to 5 vol. %. Mp = 60-62°C; Rf = 0.26 (10:1, EtOAc:MeOH); ¹H NMR (300 MHz, (CDCl₃) δ [ppm]: 1.39 (s, 3H), 1.44 (s, 6H), 1.58-1.71 (m, 2H), 1.75-1.90 (m, 2H), 2.52-2.67 (m, 2H), 3.59 (q, J = 5.2 Hz, 2H), 4.45 (t, J = 5.2 Hz, 2H), 5.50-5.61 (m, 1H), 6.41 (d, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.2, 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 5.4 Hz, 1H); ¹³C NMR (75 MHz, (CDCl₃) δ [ppm]: 15.8, 20.5, 24.8, 26.7, 29.5, 30.8, 42.9, 50.4, 62.7, 94.4, 99.1, 106.8, 117.3, 121.3,
125.8, 129.0, 135.2, 149.32, 152.2, 174.4. found: C, 59.90; H, 6.02; Cl, 7.82; N, 6.19; HRMS (ESI-TOF) calculated for C_{23}H_{28}ClN_{2}O_{8} [M+H]^+: 463.1630; found: 463.1626; elemental analysis: calculated: C, 59.68; H, 5.88; Cl, 7.66; N, 6.05.
Stability experiments using $^1$H-NMR Spectra

Stability testing of the hybrid compounds 2-7

To test the stability of the hybrid compounds, 3-4 mg were dissolved in DMSO-d6 and a $^1$H-NMR (400/500/600 MHz) was measured. The NMR tubes were then heated for at least 48 h at 60 °C in an oil bath or heated for at least 2 h at 100 °C. None of the compounds showed a decomposition ratio over 5%.
Hybrid 5 reference

Hybrid 5 after 6 h at 100 °C

Hybrid 4 reference

Hybrid 4 after 60 h at 60 °C
$^1$H/$^{13}$C-NMR spectra of new compounds

$^1$H NMR (400.35 MHz, acetone-d6) of 4-(4-azidobenzyl)morpholine

4-(4-azidobenzyl)morpholine
$^{13}$C NMR (100.68 MHz, acetone-d6) of 4-(4-azidobenzyl)morpholine

4-(4-azidobenzyl)morpholine
\(^1\text{H NMR (400.35 MHz, acetone-d6) of compound 14}\)
$^1$H NMR (400.35 MHz, DMSO-d$_6$) of compound 15
$^{19}$F NMR (376.62 MHz, DMSO-d6) of compound 15

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![Chemical structure of compound 15](image)
$^{13}$C NMR (125.82 MHz, acetone-d6) of compound 15
Complete NMR Analysis of compound 16 (mixture two isomers)
Complete NMR Analysis of compound 16 (major isomer)
Complete NMR Analysis of compound 16 (major isomer)
**Complete NMR Analysis of compound 16 (minor isomer)**

| Atom | Shift [ppm] | Multiplicity | Bound to | Correlation table |
|------|-------------|--------------|----------|-------------------|
| C19  | 1.72        | (C19)        | H13      |                   |
| C16  | 2.55        | (C16)        | H12      |                   |
| C17  | 2.75        | (C17)        | H11      |                   |
| C20  | 2.81        | (C20)        | H10      |                   |
| C18  | 3.28        | (C18)        | H9       |                   |
| C15  | 6.44        | (C15)        | H8       |                   |
| C13  | 7.4         | (C13)        | H7       |                   |
| C9   | 7.75        | (C9)         | H6       |                   |
| C8   | 7.8         | (C8)         | H5       |                   |
| C10  | 7.91        | (C10)        | H4       |                   |
| H14  | 7.91        | (C21)        | H14      |                   |
| C12  | 8.21        | (C12)        | H3       |                   |
| C1   | 8.35        | (C1)         | H2       |                   |
| C11  | 8.4         | (C11)        | H1       |                   |
**Complete NMR Analysis of compound 16 (minor isomer)**

| Atom | Shift [ppm] | # H's | Correlation table |
|------|-------------|-------|-------------------|
| C1   | 151.9       | 1     | C1                |
| C2   | 149.07      | 0     | C3                |
| C3   | 150.12      | 0     | C2                |
| C4   | 147.41      | 0     | C4                |
| C5   | 141.0       | 0     | C5                |
| C6   | 138.78      | 0     | C6                |
| C7   | 133.39      | 0     | C7                |
| C8   | 132.8       | 1     | C8                |
| C9   | 127.49      | 1     | C9                |
| C10  | 125.93      | 1     | C10               |
| C11  | 125.1       | 1     | C11               |
| C12  | 124.08      | 1     | C12               |
| C13  | 124.01      | 1     | C13               |
| C14  | 117.43      | 0     | C14               |
| C15  | 98.67       | 1     | C15               |
| C16  | 47.88       | 2     | C16               |
| C17  | 47.08       | 2     | C17               |
| C18  | 42.36       | 2     | C18               |
| C19  | 27.66       | 2     | C19               |
| C20  | 20.92       | 2     | C20               |

**13C table of assignments**
Atoms assigned to fragments are shown in italic.
$^1$H NMR (400.35 MHz, CD$_2$Cl$_2$/MeOD-d4) of compound 17
$^{13}$C NMR (100.67 MHz, acetone-d6) of compound 17
$^1$H NMR (400.30 MHz, DMSO-d4) of compound 18
$^{13}$C NMR (100.67 MHz, DMSO-d6) of compound 18
$^1$H NMR (400.35 MHz, acetone-d4) of compound 19

![NMR Spectrogram](image-url)
$^{13}$C NMR (100.67 MHz, acetone-d6) of compound 19
$^1$H NMR (400.35 MHz, acetone-d4) of compound 20

![Chemical Structure of Compound 20]

![NMR Spectra]

S32
$^{13}$C NMR (100.68 MHz, acetone-d6) of compound 20

![Chemical Structure](image)
$^1$H NMR (500.34 MHz, DMSO-d$_4$) of Hybrid 2 at 100 °C
$^{19}$F NMR (470.76 MHz, DMSO-d6) of Hybrid 2 at 100 °C
$^{13}$C NMR (100.67 MHz, DMSO-d6) of Hybrid 2 at 25 °C
$^1$H NMR (500.34 MHz, DMSO-d$_4$) of Hybrid 3 at 100 °C
$^{13}$C NMR (75.52 MHz, DMSO-d6) of Hybrid 3 at 100 °C
$^1$H NMR (500.34 MHz, DMSO-d4) of Hybrid 4 at 100 °C
$^{13}$C NMR (125.82 MHz, DMSO-d6) of Hybrid 4 at 100 °C
$^1$H NMR (300.30 MHz, DMSO-d$_4$) of Hybrid 5 at 100 °C
$^{13}$C NMR (75.52 MHz, DMSO-d$_6$) of Hybrid 5 at 100 °C
$^1$H NMR (500.34 MHz, DMSO-d$_4$) of Hybrid 6 at 100 °C
$^{13}$C NMR (125.82 MHz, DMSO-d6) of Hybrid 6 at 25 °C
$^1$H NMR (500.34 MHz, DMSO-d4) of Hybrid 7 at 100 °C
$^{13}$C NMR (125.82 MHz, DMSO-d6) of Hybrid 7 at 100 °C
$^1$H NMR (300.13 MHz, CDCl$_3$) of compound 8
$^{13}$C NMR (75.47 MHz, CDCl$_3$) of compound 8
$^1$H NMR (300.13 MHz, DMSO-d6) of compound 9
$^{13}$C NMR (75.47 MHz, DMSO-d6) of compound 9
$^1$H NMR (300.13 MHz, DMSO-d6) of compound 10
\[^{13}\text{C NMR (75.47 MHz, DMSO-d6) of compound 10}\]

![13C NMR spectrum of compound 10](image)

**ppm**

- 172.59
- 155.39
- 139.16
- 128.54
- 127.51
- 111.50
- 106.53
- 62.94
- 58.31
- 31.81
- 29.51
- 17.01

S52
$^1$H NMR (300.13 MHz, CDCl$_3$) of compound 11
$^{13}$C NMR (75.47 MHz, CDCl₃) of compound 11
$^1$H NMR (300.13 MHz, CDCl$_3$) of compound 12
$^{13}$C NMR (75.47 MHz, CDCl$_3$) of compound 12
$^1$H NMR (300.13 MHz, CDCl$_3$) of compound 13
$^{13}$C NMR (75.47 MHz, CDCl$_3$) of compound 13
Anti-SARS-CoV-2 activity determination

The anti-SARS-CoV-2 activity was measured by determining the extent the test compounds inhibited virus-induced CPE. Briefly, two-and-half-fold serial dilutions of compounds were added in triplicate in a 96-well plate with 15,000 Vero E6 cells seeded the day before in DMEM medium with 2% FBS, 100 U of penicillin/mL and 100 µg of streptomycin/mL (all Merck). After 1 h incubation, SARS-CoV-2 (strain hCoV-19/Czech Republic/NRL_6632_2/2020) was added at multiplicity of infection 0.04 IU/mL. Following 72 h incubation at 37 °C in 5% CO₂, the cell viability was determined by addition of XTT solution (Sigma-Aldrich). Drug concentrations required to reduce viral cytopathic effect by 50% (EC₅₀) were calculated using nonlinear regression from plots of percentage cell viability versus log₁₀ drug concentration using GraphPad Prism software.

Determination of compound cytotoxicity in Vero E6 cells

Cytotoxicity was evaluated by incubating two-and-half-fold serial dilutions of each compound from 100 µM concentration with Vero E6 cells in a 96-well plate. Following 72 h incubation at 37 °C in 5% CO₂, the cell cytotoxicity was determined by addition of XTT solution and the compound concentrations resulting in 50% reduction of absorbance (CC₅₀), corresponding to 50% reduction of viability, were calculated as above in the antiviral activity determination using CPE-based assay.

Figure S1. Dose-response curves of SARS-CoV-2 inhibition by different doses of artemisinin-based hybrids 1-7 and artesunic acid. 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). MOI = multiplicities of infection.
Figure S2. Dose-response curves of SARS-CoV-2 inhibition by different doses of synthetic peroxide-based hybrids 8-13, chloroquine, and remdesivir control. 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 8-13 was determined by XTT assay (red circle). Same dilution of compounds 8-13 without SARS-CoV-2 were used to determine cell cytotoxicity (blue squares). MOI = multiplicities of infection.

Anti-Cancer activity determination

Cell lines
All leukemia cell lines (CCRF-CEM, RPMI-8226, K562, HL-60, and MOLT-4) were obtained from NCI-DTP, NCI-Frederick, USA. Cells were cultured and maintained in RPMI-1640 (Corning, USA; #10-040-CV) media supplemented with 10% FBS (Corning, USA; #35-015-CV) and 1% penicillin-streptomycin–amphotericin B (GIBCO, USA; #15240-062) at 37 °C with 5% CO2. At 70-80% confluence cells were harvested and plated for cell viability assay.

Cell viability assay
Each leukemia cell line was plated at 3000 cells/well (in 100 µL complete media) in black-clear bottom 96-well plates (Corning, USA; #3603). After 24h cells were treated with respective compounds at 10 µM concentration. After 48 h treatment, cell viability was recorded using CellTiter-Blue cell viability assay (Promega, USA; #G8081) as per the manufacturer’s protocol.


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