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Novel molecule combinations and corresponding hybrids targeting artemisinin-resistant *Plasmodium falciparum* parasites

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ABSTRACT

Malaria is still considered as the major parasitic disease and the development of artemisinin resistance does not improve this alarming situation. Based on the recent identification of relevant malaria targets in the artemisinin resistance context, novel drug combinations were evaluated against artemisinin-sensitive and artemisinin-resistant *Plasmodium falciparum* parasites. Corresponding hybrid molecules were also synthesized and evaluated for comparison with combinations and individual pharmacophores (e.g. atovaquone, mefloquine or triclosan). Combinations and hybrids showed remarkable antimalarial activity (IC_{50} = 0.6 to 1.1 nM for the best compounds), strong selectivity, and didn't present any cross-resistance with artemisinin. Moreover, the combination triclosan + atovaquone showed high activity against artemisinin-resistant parasites at the quiescent stage but the corresponding hybrid lost this pharmacological property. This result is essential since only few molecules active against quiescent artemisinin-resistant parasites are reported. Our promising results highlight the potential of these combinations and paves the way for pharmacomodulation work on the best hybrids.

Malaria is one of the leading causes of mortality by infectious diseases, killing >400 000 people each year, mainly in tropical and subtropical regions.[1] The disease is caused by the *Plasmodium* parasite, transmitted through the bite of an infected mosquito of the genus *Anopheles*. A notable decrease of malaria mortality has been observed for the 20 last years due in part to the introduction of artemisinin and its derivatives (ARTs) in the antimalarial therapeutic arsenal. To reduce the risk of drug resistance, ARTs are used in combination with one or two other antimalarial drugs having different modes of action and pharmacokinetic properties. These Artemisinin-based Combination Therapies (ACTs) have been recommended by the WHO, since 2001, as first-line treatments of uncomplicated *falciparum* malaria worldwide.[2] However, the efficacy of the ACTs rapidly declined in South-East Asia, due to the emergence of *P. falciparum* resistance to ARTs[3–7] but also to partner drugs,[8,9] and is now threatening malaria eradication. Targeting ARTs-resistant parasites is thus an urgent concern.

ART-resistance is based on an original mechanism relying on a parasite quiescence state induced by ARTs exposure.[10–12] Indeed, this state of quiescence is characterized by a drastically lowered metabolism that allows parasites to limit ART-induced cellular damages.[13,14] However, quiescent parasites still possess a maintained mitochondrial activity and an implemented fatty acid synthesis type II (FAS-II) pathway in the apicoplast that enable parasites to restart their cell cycle after drug elimination.[10,13,14] Interestingly, the antimalarial drug atovaquone (ATQ, Table 1), which targets the bc_1 complex of mitochondrial electron transport chain,[15] was reported to kill dihydroartemisinin-induced quiescent parasites.[16,17] Similarly, triclosan (TCS) and haloxyfop, which inhibit the FabI and acetyl-CoA carboxylase of the *Plasmodium* FAS-II pathway respectively, delayed the recrudescence of quiescent parasites after dihydroartemisinin treatment.[13] Simultaneously targeting the mitochondrion with ATQ and the apicoplast with TCS would thus be of valuable interest to face the issue of ART-resistance. Compound GW844520 reported, like ATQ, as an inhibitor of the bc1 complex of the mitochondrial electron transport chain,[18] was also selected to be studied in the context of ART-resistance. Finally, the antimalarial drug mefloquine (MQ) was picked out as a relevant compound for drug

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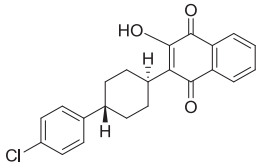
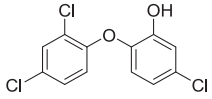
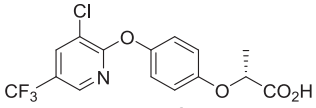
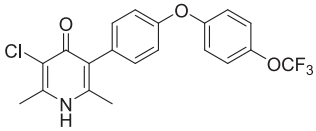
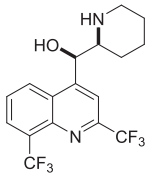
combinations studies because it is one of the only two partner drugs used in ACTs to be reported as active on quiescent ART-resistant parasites.[17] We report here the evaluation of different combinations of two of these compounds, each targeting one essential pathway for quiescence survival: ATQ + TCS, ATQ + MQ, GW844520 + TCS. This evaluation was performed first on proliferating parasites then in an artemisinin resistance context on dihydroartemisinin (DHA)-induced quiescent state, thanks to two specific tests, the recrudescence assay,[19] and the Quiescent-stage Survival Assay (QSA) for the best combination.[17] In addition, the very high antiplasmodial activities reported with these combinations lead us to a hybridization strategy. Hybrid molecules, combining at least two pharmacophoric subunits with distinct modes of action, are considered as original compounds which offer the potential of improved biological activity, reduced risk of drug resistance emergence and better patient compliance. Compared to simple drug combinations, they also offer easier formulation, as well as more predictable pharmacokinetic and pharmacodynamic relationships.[20,21] Several reviews dealing with recent development of antimalarial hybrids are available in the literature.[22,23] Combinations of selected compounds that showed activity both on proliferating parasites and on quiescent parasites were thus translated to corresponding hybrid molecules: ATQ-TCS, ATQ-MQ and GW844520-TCS. The synthesis of these original compounds is reported herein, together with their evaluation for *in vitro* antiparasitic activity against ART-susceptible and ART-resistant strains of *P. falciparum* (chemosensitivity, recrudescence assay, and QSA for the best hybrid).

Drug combinations targeting different pathways were first evaluated for antiplasmodial effect on proliferating *P. falciparum.* With an IC_{50} value of 2 nM, atovaquone (ATQ) displayed a very high activity on proliferating parasites. GW844520 and mefloquine (MQ) also confirmed their antiplasmodial activity with IC_{50} values in the 40–90 nM range (Table 2). Significantly less active, triclosan had a low antiplasmodial activity with an IC_{50} of 5 μM. Interestingly the 1:1 combination ATQ + MQ supports the strategy to target different parasite pathways, with an IC_{50} value of 0.9 nM, corresponding to a more potent anti-proliferative effect than the two compounds alone. This combination appeared as the best one tested. The combination ATQ + TCS also had a good antiplasmodial activity but its IC_{50} value (1.8 nM) close to the ATQ one suggests that the result is mainly due to ATQ activity. The same reasoning can be made for the combination GW844520 + TCS. The low efficacy of TCS, alone and in combination, can be explained by the fact that it targets lipid metabolism, while this metabolism is absent in proliferating parasites. By contrast, it has been shown that parasite lipid metabolism takes place during induced quiescence of the parasites by dihydroartemisinin treatment.[13] In these conditions, TCS would inhibit the FabI enzyme of the *Plasmodium* FAS-II pathway and delay the recrudescence of quiescent parasites.[13] Moreover, good selectivity of these molecules towards mammalian cells (Table 2) led us to pursue their evaluation in an artemisinin resistance context.

The *Plasmodium* artemisinin resistance mechanism consists in a quiescence phenomenon based on a cell cycle arrest of a sub-population of the parasites during artemisinin or its derivatives treatment. When the drug is eliminated, the parasites are able to develop again normally.[10,32] This quiescence is characterized by a DNA and RNA synthesis arrest under treatment.[13] A standard chemosensitivity assay, based on the measurement of the inhibition of parasite proliferation, is thus not relevant for the evaluation of compounds against artemisinin-resistant parasites. Indeed, there is no difference in IC_{50} values between artemisinin-resistant and artemisinin-susceptible strains.[10,19] In this context, the recrudescence assay, based on the comparison of recrudescence capacities between the artemisinin-resistant strain F32-ART5 and its twin artemisinin-sensitive strain F32-TEM after 48 h of exposure with the molecule of interest, was used to determine if a cross-resistance exists with artemisinin. Potential cross-resistance is evidenced by a faster resumption of the ART-resistant strain (F32-ART5) compared to the sensitive F32-TEM parasites. Interestingly, no significant differences of recrudescence were observed between F32-ART5 and F32-TEM neither for the compounds tested alone nor for the three

Table 1
Structures and targets of compounds reported as active on ART- or DHA-induced quiescent parasites (ATQ, TCS, haloxyfop)[13,16] or which have showed activity on ARTs-resistant parasites maintained in a quiescent state[a] (ATQ, MQ, GW844520).[17]

Drug	Structure	Main targets (*P. falciparum*)	Ref
Atovaquone (ATQ)		Mitochondrial electron transport chain (ETC) Cytochrome bc_1 (Q_o site)	15,24
Triclosan (TCS)		Apicoplast FAS-II pathway FabI	25,26
haloxyfop		Apicoplast FAS-II pathway Acetyl-CoA carboxylase	27
GW844520		Mitochondrial electron transport chain (ETC) Cytochrome bc_1 (Q_i site)	28
Mefloquine (MQ)		Metacaspase; Phospholipids/Ferriprotoporphyrin IX; 80S-ribosome	29,30,31

[a] Activity measured by Quiescent-stage Survival Assay (QSA).

Table 2
Antimalarial and cytotoxic activities of selected molecules and their (1:1) combinations.

Compound	Hybrid pharmacophoric units	Antiplasmodial activity on *P. falciparum* IC_{50} ± SEM (nM)	Cytotoxicity on Vero Cells CC_{50} ± SEM (μM)	Selectivity index CC_{50} (Vero Cells) / IC_{50} (*P. falciparum*)
ATQ	–	2.1 ± 0.6	0.5 ± 0.1	257
GW844520	–	42 ± 10.5	8 ± 1	190
MQ	–	87 ± 18	21 ± 7	241
TCS	–	5 10^3 ± 1 10^3	25 ± 9	5
ATQ + TCS	–	1.8 ± 0.8	–	
GW844520 + TCS	–	38 ± 6	–	
ATQ + MQ	–	0.9 ± 0.3	–	
Hybrid **4**	ATQ/TCS	0.6 ± 0.5	6 ± 2	10 000
Hybrid **8**	GW844520/TCS	169 ± 37	>120	>710
Hybrid **12**	ATQ/MQ	0.6 ± 0.3	4 ± 1	6660
Hybrid **13**	ATQ/MQ	1.1 ± 1.0	5 ± 2	4545
Artemisinin	–	18 ± 2.5	130	7222

IC_{50} values on *Plasmodium falciparum* F32-TEM strain were obtained using SYBR Green assay. Cytotoxicity activities were evaluated against Vero cell line. Artemisinin was used as antiplasmodial control drug.
ATQ: atovaquone; MQ: mefloquine; TCS: triclosan.
Number of different independent experiments performed: n = 4 for the cytotoxicity assay; at least n = 4 for the antiplasmodial activity. For each one, a triplicate (technical repeats) was carried out.

combinations (Table 3), thus demonstrating the absence of cross-resistance with artemisinin.

The good IC_{50} values for the three combinations, associated with good selectivity indexes and absence of cross-resistance with artemisinin, motivated the design of hybrid compounds inspired from such combinations. The first hybrid was thus based on the association of ATQ and TCS bound *via* an 8-carbon chain, in order to limit steric hindrance. Since ester derivatives of ATQ and TCS have shown antimalarial activities comparable to the one of their parent drugs, [33,34] the free –OH groups of both drugs were selected for linker attachment through ester bonds from octanedioic acid. Ethers or carbamate bonds have also been considered for linker attachment to the –OH groups. However, El Hage *et al.* reported that ester analogues of atovaquone were more active than the corresponding ethers[33] and carbamate derivatives of atovaquone were not selected because such compounds are reported as chemically unstable.[35,36] Hybrid **4** was thus prepared in a four steps synthesis (Scheme 1). Octanedioic acid was monoprotected *via* a Steglich esterification reaction performed with benzylic alcohol, in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 3,4-dimethylaminopyridine (DMAP), with a yield of 71%. The remaining carboxylic acid function of **1** was then activated in the presence of thionyl chloride and reacted with TCS, to afford the intermediate **2** in 61% yield. Finally, quantitative deprotection of the benzylic ester by catalytic hydrogenation on Pd/C, activation of the resulting carboxylic acid with thionyl chloride and subsequent esterification with ATQ afforded hybrid **4**, which was isolated in 89% yield.

A second hybrid, for which the ATQ moiety of **4** was replaced by the GW844520 unit, was prepared according to a similar sequence (Scheme 2). GW844520 (**7**)[37] was first prepared *via* a Suzuki-Miyaura cross-coupling reaction between 3-chloro-5-iodo-2,6-dimethylpyridin-4(1*H*)-one **5** [38] and boronic acid **6**, [37] under microwave conditions. Compound **7** was then treated with sodium hydride and the resulting pyridinolate intermediate was reacted with the acyl chloride of compound **3**, to give hybrid **8** with a yield of 30%.

The two last hybrids **12** and **13** were designed by associating the two antimalarial drugs ATQ and MQ, bound *via* a diester linker, as for the ATQ-containing hybrid **4**. The selection of an ester bond for MQ linking allowed the direct transposition of the previous synthesis scheme using a symmetrical linker, and was supported by the antiplasmodial and antimalarial activity of a trifluoromethylartemisinin–mefloquine hybrid displaying similar linker attachment.[39] Our first attempts to use octanedioic acid as linker precursor, as for hybrids **4** and **8**, having been unsuccessful, we envisaged shorter linkers accessible from sucininc and glutaric anhydrides. The synthesis pathway for hybrids **12** and **13** is presented in Scheme 3. The first step consisted in the protection of the piperidinyl amine of MQ by a Boc group, followed by treatment of the resulting Boc-mefloquine **9** with succinic or glutaric anhydride to give compounds **10**[39] and **11**, with overall yields of 94% and 92%. The free carboxylic acids of these two compounds were then esterified by ATQ after an activation step with thionyl chloride. During the course of the reaction, the piperidinyl amine was (partially) deprotected, affording hybrids **12** (and **12-Boc**) and **13**, respectively. **12-Boc**, isolated with a yield of 21%, was finally converted to hybrid **12** by treatment with HCl.

Hybrids were first evaluated for their activity on proliferating parasites. Hybrid **4** (ATQ/TCS) showed a sub-nanomolar IC_{50} value (0.6 nM) against *P. falciparum*, better than the corresponding pharmacophores alone and their combination (Table 2). Similarly, hybrids **12** and **13** (ATQ/MQ) displayed IC_{50} values of 0.6 and 1.1 nM, respectively, comparable to the one of the ATQ + MQ combination and better than the activities of the individual drugs. By contrast hybrid **8,** resulting from the association of GW844520 and TCS, was significantly less active than the corresponding combination and GW844520 alone (Table 2). One explanation for this reduced activity could be a default of aqueous solubility of the hybrid, lower than the one of GW844520, which was already described as poorly soluble.[40] Otherwise, the linker attachment in hybrid **8** compared to GW844520 may affect target interaction. Indeed, the modification introduced in hybrid **8** locked the 4-pyridone moiety in the less favored pyridinol tautomeric form,[37] preventing H-bond formation between the pyridine carbonyl group and Ser35 residue of cytochrome bc_1.[28]

Interestingly, the cytotoxicity of the four hybrids was very low (Table 2), resulting in excellent selectivity indexes.

The recrudescence assay (Table 3) showed a loss of activity of all hybrids compared to their corresponding combinations with more days necessary for parasites to reach initial parasitemia when they are treated by combinations than for parasites treated by the corresponding hybrids. Surprisingly, this activity decrease of hybrids is only noted when high concentrations are tested (recrudescence assay, Table 3) but not for lower ones (IC_{50} values, Table 2). This result could indicate that the hybrids are less soluble than the corresponding combinations. Interestingly, for all the hybrid compounds, no cross-resistance with artemisinin was reported since no significant difference in recrudescence capacity of the parasites was observed between the two strains, like for the compounds alone and their combinations. The difference of 12.5 days between the two strains, F32-ART5 and F32-TEM, can be noted for the control drug artemisinin as the sign of the resistance of the strain F32-ART5 (Table 3).

As the mitochondrial electron transfer chain and the apicoplast FAS-

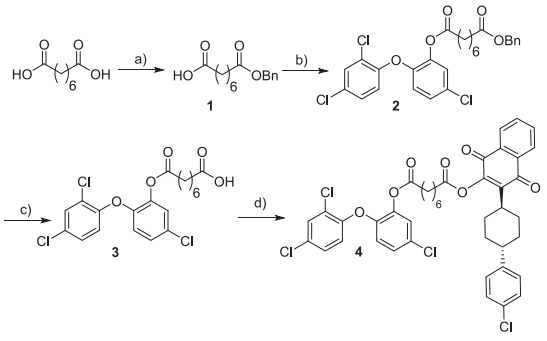
Table 3
Recrudescence capacity of *Plasmodium falciparum* F32-ART5 and F32-TEM parasites after 48 h of drug exposure.

Compounds	Doses	Median recrudescence days		Delay in recrudescence time [a] Mean ± SEM	*P*-value [b]
		F32-ART5	F32-TEM		
ATQ	1 μM	11	14	3	–
	7 μM	21	23	1 ± 0.6	0.486
GW844520	7 μM	2	8	3 ± 1.2	0.325
MQ	1 μM	>30	>30	–	–
TCS	7 μM	5	6	0.8 ± 0.9	0.417
ATQ + TCS (1:1)	7 μM	17	19.5	2.3 ± 1.1	0.175
GW844520 + TCS (1:1)	7 μM	8	12	3.3 ± 1.4	0.418
ATQ + MQ (1:1)	1 μM	>30	>30	–	–
Hybrid **4** (ATQ/TCS)	7 μM	9	12	4 ± 2.4	0.265
Hybrid **8** (GW844520/TCS)	7 μM	3	4	0.6 ± 0.4	0.093
	20 μM	2	3	1	–
Hybrid **12** (ATQ/MQ)	1 μM	14	14	0	–
Hybrid **13** (ATQ/MQ)	1 μM	14	14	0	–
Artemisinin [c]	18 μM	9	22	12.5 ± 1.8	< 0.0001

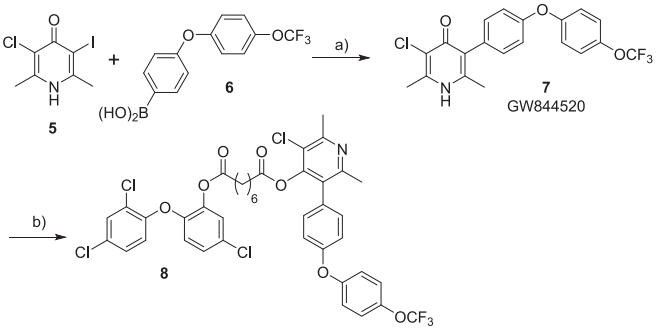
Each experiment was performed for F32-ART5 and F32-TEM cultivated in parallel in the same conditions (adjusted to the same initial parasitemia and cultivated with the same batch of erythrocytes and same batch of human serum) to generate paired results.
Synchronized ring-stage parasites have undergone 48 h of drug treatment. After culture washing, the parasitemia was monitored during 30 days or until reaching the initial parasitemia, defined as the recrudescence day. If no parasites were observed at the end of the experiment, the culture was considered as no recrudescent, and the recrudescence day was noted as > 30. The doses tested for ATQ correspond to concentrations pharmacologically relevant in patients. The same doses were then used for all the compounds tested. The results correspond to data obtained in at least 3 independent experiments except for the molecules **12**, **13**, ATQ (1 μM), MQ and ATQ + MQ (1:1), 1 time. The same number of experiments was performed for each parasite lineage and statistically analyzed.
ATQ: atovaquone; MQ: mefloquine; TCS: triclosan.
[a] The delay of recrudescence days corresponds to the mean of the differences, obtained for each experiment, between the day of recrudescence of F32-ART5 compared to F32-TEM, after 48 h of molecule exposure.
[b] A log-rank (Mantel-Cox) test was used for statistical analysis of recrudescence days; a significant difference between F32-ART5 and F32-TEM is validated for $P < 0.05$.
[c] The concentration of artemisinin at 18 μM was shown as the most relevant to discriminate both strains F32-ART5 and F32-TEM regarding artemisinin sensitivity.[19]

II pathway are described as maintained active during dihydroartemisinin-induced quiescence,[13] and because of their very high antiplasmodial activity reported, the ATQ + TCS combination ($IC_{50} = 1.8$ nM) and its corresponding hybrid molecule **4** ($IC_{50} = 0.6$ nM) were selected for evaluation on artemisinin-resistant quiescent parasites, using the Quiescent-stage Survival Assay (QSA) (Table 4). The parent molecules (ATQ and TCS) were also evaluated for comparison. In the QSA, quiescence is first induced with 6 h-DHA treatment then parasites are exposed to the drug to be tested for 48 h in the presence of DHA to maintain the quiescence state. QSA interpretation is based on the difference in recrudescence days after exposure of DHA-induced quiescent parasites to the compound being tested (DHA 6 h/(DHA + molecule) 48 h) compared to DHA alone treatment (DHA 6 h/DHA 48 h).[17] A cut-off of 6 days-delay is reported as significant.[17] The control drug chloroquine shows that a molecule can be active on proliferative parasites (Table 4, third column) but lose its activity on quiescent parasites, with no significant difference between the two first columns. The delay of 13 days in the recrudescence time observed between DHA 6 h/(DHA + (ATQ + TCS) 48 h) compared to DHA (DHA 6 h/DHA 48 h) means that the 1:1 combination ATQ + TCS is active on quiescent parasites. This can be correlated with the activity on quiescent parasites of ATQ alone with a difference of 12 days between (DHA 6 h/(DHA + ATQ) 48 h) compared to DHA (DHA 6 h/DHA 48 h) and the maintained mitochondrial activity under the quiescence state.[13,16,17] TCS alone didn't show any activity neither on proliferating parasites, nor on quiescent parasites with no delay observed between both first conditions. At the same dose tested (7 μM), hybrid **4**, compared to the 1:1 ATQ + TCS combination, showed a reduced activity in the quiescent parasites evidenced by a delay of only 3 days between conditions (DHA 6 h / (DHA + **4**) 48 h) and DHA (DHA 6 h/DHA 48 h). This loss of activity of the hybrid **4** is also illustrated, on proliferating parasites, by 10 days necessary for parasites to reach initial parasitemia comparatively to 20 days when they are treated by the corresponding combination ATQ + TCS (Table 4, third column).

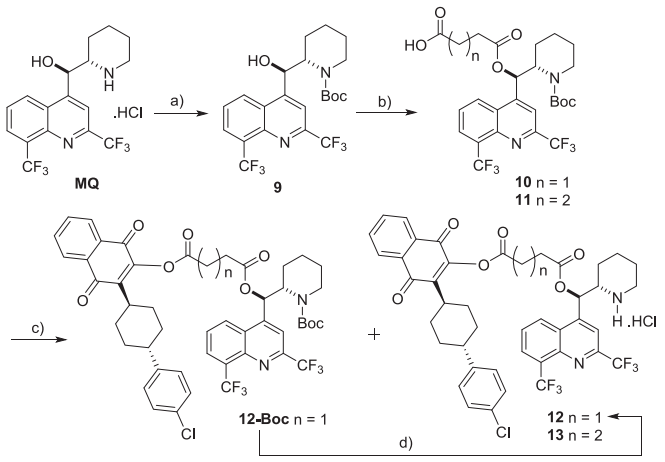
In conclusion, 1:1 combinations of three compounds having good antiplasmodial activities, atovaquone, mefloquine, GW844520, and of triclosan, an inhibitor of the lipid metabolism, were evaluated against



Scheme 1. Synthesis of hybrid 4. Reagents and reaction conditions: (a). Benzyl alcohol, DMAP, DCC, DCM, rt, 1 h, 71%; (b). i) $SOCl_2$, 50 °C, 3 h, ii) TCS, pyridine, DCM, 0 °C to rt, 8 h, 61%; (c). H_2, Pd/C, EtOAc, rt, overnight, 100%; (d). i) $SOCl_2$, 50 °C, 3 h, ii), ATQ, pyridine, DCM, rt, overnight, 89%.



Scheme 2. Synthesis of hybrid 8. Reagents and reaction conditions: (a). Pd $(OAc)_2$, K_2CO_3, *n*-Bu_4NBr, EtOH, 100 °C, 1 h, MW, 29%; (b). i) NaH, THF, rt, 10 min, ii) (**3** + $SOCl_2$), THF, rt, overnight, 30%.



Scheme 3. Synthesis of hybrids 12 and 13. Reagents and reaction conditions: (a). Boc_2O, Et_3N, DCM, 95%; (b) succinic anhydride or glutaric anhydride, Et_3N, $CHCl_3$, 99% and 97%, respectively; (c). i) $SOCl_2$, ii) ATQ, pyridine, DCM, 11% for **12** (+21% **12-Boc**), 27% for **13**; (d). HCl, MeOH, 96%.

P. falciparum parasites. Corresponding hybrid molecules combining atovaquone and triclosan, GW844520 and triclosan and, atovaquone and mefloquine were synthesized, focusing on rapid and efficient drugs linking, and studied in similar conditions to allow a first comparison between drug combination and drug hybridization. All combinations and hybrids showed high activity on proliferative *P. falciparum* parasites, with IC_{50} values in the low- or sub-nanomolar range for ATQ + TCS, GW844520 + TCS, ATQ + MQ and hybrids **4**, **12** and **13**, together with very good selectivity towards mammalian cells. Interestingly, in a context of artemisinin resistance, no cross-resistance with artemisinin was observed for these combinations and hybrids. Moreover, the combination ATQ + TCS showed a strong activity against parasites at the DHA-induced quiescence state. However, at high concentrations, the corresponding hybrid **4** showed a weaker activity than the combination on proliferative and on quiescent parasites, suggesting a lower solubility. This result does not call into question the value of using hybrid molecules to combat resistant parasites. Indeed, the combination of two molecules, each having different targets and presenting no cross-resistance with artemisinin, in a hybrid compound would be a good approach to prevent cross-resistance and kill quiescent parasites. That is why, based on the very promising results obtained with all combinations tested, further studies will be carried out on these hybrids focusing on linker pharmacomodulation. Thus, varying the nature of the linker with an oxygenated chain, modifying its length and the nature of the chemical bond for drug linkage (e.g. *O*-alkylation versus *O*-esterification) would certainly impact the solubility, the stability and more generally the activity of the resulting hybrids. Furthermore, the use of a combination active on quiescent parasites such as atovaquone combined with triclosan represents an encouraging prospect for the development of effective treatment of malaria cases caused by artemisinin-resistant parasites.

Table 4
QSA: Recrudescence time of the *P. falciparum* ART-resistant line F32-ART5.

Compounds	Median recrudescence days		
	DHA 6 h then DHA 48 h	DHA 6 h then (DHA + Molecule) 48 h	Nothing 6 h then Molecule 48 h
ATQ	6	18	17
TCS	7	7	6
ATQ + TCS (1:1)	7	20	20
Hybrid **4**	7	10	10
Chloroquine (200 nM) [a]	6	8	>30

Synchronized ring-stage parasites have different drug treatment during 54 h. After culture washing, the parasitemia was monitored until reaching the initial parasitemia, defined as the recrudescence day. Delay in recrudescence times corresponds to the difference between the recrudescence day after DHA 6 h / (DHA + molecule) 48 h exposure and the recrudescence day after DHA alone (54 h) treatment. All the molecules were tested at 7 μM (except chloroquine at 200 nM), in 3 independent experiments. The control condition (nothing 6 h / molecule 48 h) allowed the confirmation of the antiplasmodial activity of the molecules tested alone at this concentration.
ATQ: atovaquone; TCS: triclosan.
[a] data from reference[17].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127884.

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