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NEW-GENERATION ANTIMALARIAL DRUGS

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ABSTRACT

Malaria is a disease that affects nearly 40% of the global population, and chemotherapy remains the mainstay of its control strategy. The global malaria situation is increasingly being exacerbated by the emergence of drug resistance to most of the available antimalarials, necessitating search for novel drugs. A recent rational approach of antimalarial drug design characterized as "covalent bitherapy" involves linking two molecules with individual intrinsic activity into a single agent, thus packaging dual-activity into a single hybrid molecule. Current research in this field seems to endorse hybrid molecules as the next-generation antimalarial drugs. If the selective toxicity of hybrid prodrugs can be demonstrated in vivo with good bioavailability at the target site in the parasite, it would offer various advantages including dosage compliance, minimized toxicity, ability to design better drug combinations, and cheaper preclinical evaluation while achieving the ultimate object of delaying or circumventing the development of resistance. This review is focused on several hybrid molecules that have been developed, with particular emphasis on those deemed to have high potential for development for clinical use.

INTRODUCTION

Malaria is caused by the bite of a female mosquito (*Anopheles*), resulting in the malaria parasite, *Plasmodium,* entering the human blood stream. Once a red blood cell has become invaded with the parasite, several rounds of asexual reproduction ensue, leading to its eventual rupture. It is the cyclic release of parasites from the red blood cells which causes the intermittent symptoms of fever, shivering and anaemia that are characteristic of malaria. Of the four species of *Plasmodium* that infect humans, the most dangerous is *P. falciparum*. This parasite accumulates in the capillaries of vital organs such as the brain, kidney, intestine and lungs. Cerebral malaria, the accumulation of *P. falciparum* in the brain, is responsible for most of the deaths associated with malaria. During the red-cell cycle, the parasite uses the host's haemoglobin as food. The haemoglobin protein is broken down by enzymes and the parasite assimilates the amino acids which are released. The digestive process also liberates haem, the iron-containing porphyrin which is normally buried within the haemoglobin molecule. In the past two decades, only a few compounds belonging to a new class of antimalarial drugs, including aminoalcohols (mefloquine, halofantrine, lumefantrine), sesquiterpenetrioxanes (artemisinin derivatives), and naphthoquinones (atovaquone) have been developed for clinical usage. One of the challenges of future malarial chemotherapy is to develop compounds that are innovative with respect to the chemical scaffold and molecular target. Many approaches to antimalarial drug discovery currently being deployed include optimization of therapy with available drugs including combination therapy, developing analogs of the existing drugs, evaluation of potent agents from natural products especially plants, use of compounds originally developed against other diseases, and evaluation of drug-resistance reversers (chemosensitizers) as well as new chemotherapeutic targets.Recently through rational drug design approach, single hybrid molecules with dual functionality and/or targets have been developed as novel antimalarial drugs. Some of these hybrid drugs have been demonstrated to be potent antimalarial agents, possessing no or minimum toxicity. However, so far none of these hybrid antimalarials have reached clinical application. In malaria drug combination therapy, the current trend is to co-formulate two or more agents into a single tablet, termed as multicomponent drug (e.g., Coartem®, lumefantrine-artemether) as opposed to the traditional cocktail therapy, so as to improve patient compliance. However, based on the wide interest in the hybrid molecules as well as numerous encouraging efficacy and toxicity reports, the next generation of antimalarials may as well be hybrid drugs as opposed to multi-component ones. There are numerous advantages of employing hybrid molecules over multicomponet drugs in malaria therapy.

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Compared to the latter, hybrid drugs may be less expensive since, in principle, the risks and costs involved may not be different from any other single entity. Another advantage is that of the lower risk of drug–drug adverse interactions compared to multicomponent drugs. The downside, however, is that it is more difficult to adjust the ratio of activities at the different targets.

Hybrid molecules can be classified as:

- *Conjugates*, in which the molecular frameworks, that contain the pharmacophores for each target are separated by a distinct linker group that is not found in either of the individual drugs. Most conjugates contain a metabolically stable linker.
- *Cleavage conjugates* have a linker designed to be metabolized to release the two drugs that interact independently with each target.
- *Fused hybrid* molecules have the size of the linker decreased such that the framework of the pharmacophores is essentially touching.
- *Merged hybrids* have their frameworks merged by taking advantage of commonalities in the structures of the starting compounds, which give rise to smaller and simpler molecules.

Quinine from Peruvian *Cinchona* trees provided the lead for the discovery and development of synthetic aminoquinolines, the most notable being CQ. Likewise, the discovery of artemisinin from the Chinese herb *Artemisia annua* has served as a template for development of semi-synthetic artemisinins including artesu-nate and artemether, which are being used extensively in ACT against drug-resistant malaria. The commercial availability of artemisinin(and hence its semi-synthetic derivatives) is limited by the fact that it is a natural product from *Artemisia annua*. Today, no fully synthetic peroxidic antimalarial drug has been made available for clinical application, which is unfortunate because of limitations associated with artemisinin semi-synthetics. The limitations include chemical (availability, purity, and cost), bio-pharmaceutical (poor bioavailability and limiting pharmacoki-netics), and treatment (non-compliance with repeated regimens and recrudescence) issues that limit their therapeutic potential. As a result, extensive research into synthetic endoperoxideantimalarials drugs has been undertaken in the last 15 years to produce molecules that are structurally simpler and synthetically accessible with a projected low cost of goods. Recently, fully synthetic peroxidicantimalarials are being developed, in which the pharmacophore of artemisinin is present within a 1,2,4-trioxalane, termed ozonide, rather than a 1,2,4-trioxane heterocycle of artemisinin. Synthetic 1,2,4-trioxolane derivatives being investigated as a new class of antimalarial peroxides offer the advantage of low cost of synthesis, improved biopharmaceutical properties, and excellent efficacy profiles compared with currently available artemisinin. Other synthetic cyclic endoperoxides being explored include 1,2-dioxanes, 1,2,4-trioxanes, and 1,2,4,5-tetraoxanes, all of which retain the critical endoperoxide bond, which confers activity to artemisinins. Recently, in a deliberate rational design of antimalarials acting specifically on multiple targets, several hybrid molecules have been developed in what has been termed "covalent bio therapy." One instance is where a trioxane or trioxolane motif is covalently linked to a quinoline entity, to form new modular molecules referred to as *trioxaquines*or *trioxolaquines*, respectively. The quinoline nucleus has been a chemical reference of highly active antimalarial drugs for many decades and several effective drugs containing this entity including CQ, mefloquine, amodiaquine, and primaquine have been developed. The trioxanes and trioxolanes contain a peroxide bridge, which is essential for the high activity of artemisinin and its semi-synthetics including arte-mether, arteether, dihydroartemisinin, and artesunate. As the trioxane or trioxolane moiety is a potential alkylating agent after reductive activation by heme, and the 4-aminoquioline entity easily penetrates into infected erythrocytes and then interacts with heme, such modular molecules are expected to combine the dual activity of both fragments. Trioxaquines are potent antimalarial drugs against both asexual and sexual malarial stages, and their potency is independent of CQ-sensitivity of the target parasite.

Artemisinin-Based Hybrids Trioxaquines and Trioxolaquines

Trioxaquines are synthetic hybrid molecules containing two covalently linked pharmacophores (1,2,4-trioxane and an aminoquinoline), a concept referred to as "covalent biotherapy", and thus possess a dual mode of action, namely heme alkylation with the trioxane entity, and heme stacking with the aminoquinolinemoeity and inhibition of haemozoin formation. Trioxolaquines are hybrid molecules similar to trioxaquines except that they contain a trioxolane motif, namely an ozonide, instead of a trioxane entity. The first series of trioxaquines were potent against both CQ and pyrimethamine-resistant *P. falciparum* strains, and Benoit-Vical and co-workers developed the second series of trioxaquines, that were highly potent in vitro against both CQ-sensitive and -resistant *P. falciparum* isolates.Thetrioxaquines had more improved antimalarial activity than their individual fragments, indicating a potential additive/synergistic effect of the hybrids. Quinoline-endoperoxide hybrids have been developed with both semi-synthetic artemisinin derivatives as well as synthetic analogs, and possess remarkable in vitro antiplasmodial activity. Incorporation of 4-aminoquinoline or 9-aminoacridine (a component of mepacrine) into the final hybrid drug enhanced drug accumulation in the digestive vacuole of the parasite thus inducing a greater turnover of potentially toxic-free radicals by endoperoxidebioactivation.

The potential advantage of both sets of compound lies in their capacity to target the parasite by two distinct mechanisms, thereby delaying or circumventing development of resistance. The synthetic peroxide hybrids (1,2,4-trioxalaquines) were generally more potent than their semi-synthetic (1,2,4-trioxaquines) counterparts. The most potent 1,2,4-trioxalaquine showed better *in vitro* antiplasmodial activity than either artemisinin or CQ against *P. falciparum* isolates. Although in some instances the hybrid molecule may lack a significant improvement of activity relative to the individual components of the hybrid, use of the hybrid drug would still be advantageous in several aspects. The derivatives may readily be converted into water-soluble salts making them suitable for oral or intravenous formulations. Also, when the peroxide component of the hybrid drug is "chemically consumed," the residual aminoquinoline or aminoacridine constituent can still act as an efficient antimalarial, provided it is not covalently bound to the protein.

Artemisinin-Dipeptidyl Vinyl Sulfone Hybrids

Cysteine proteases of the malarial parasite are of particular interest as therapeutic targets since they play major roles in parasite development. *P. falciparum* parasite expresses four cysteine proteases from the papain family known as falcipains, required for degradation of hemoglobin by erythrocytic malaria parasites, of which falcipain-2 and falcipain-3 are the most obvious as drug targets. Several falcipain inhibitors including fluoromethyl ketones and vinyl sulfones inhibit parasite development in cultures by blocking the hydrolysis of host hemoglobin, and to cure mice infected with lethal *P. vinckei* infection have developed a series of endoperoxide-dipeptidyl vinyl sulfone hybrid molecules possessing dual activity of endoperoxide activation and falcipain inhibition. The vinyl sulfone moiety is covalently linked to the endoperoxide entity via the N-terminus, using a 4-hydroxymethyl-benzoic acid linker. The conjugate inhibited CQ-resistance *P. falciparum* isolate (W2) in the range 2-5 nM being more active than artemisinin and equipotent with artelinic acid. When screened against *P. falciparum* isolates with different phenotypes, FCR3 (atovaquone-resistant), 3D7 (CQ-sensitive), V1/S (CQ-and pyrimethamine-resistant), and D6 (CQ-sensitive, mefloquine-resistant), compounds had superior activity when compared to CQ and artemisinin against all strains. Peptidyl vinyl sulfones are potent irreversible falcipain inhibitors, and hybrids that contained Leu-hPhe core inhibited falcipain-2 in the range 0.3–22 μM. The fact that the hybrid molecule falcipain inhibition was in the micromolar range implies that the endoperoxidepharmacophore contributed to the bulk of activity probably due to poor activity of the hybrids against falcipain-2 and/or their limited access to the food vacuole. However, this served as a proof of concept, and future work in this regard is required to optimize the bi-functional molecule enzyme-binding capabilities.

Quinoline-Chemosensitizer Hybrid Molecules

Dual-function acridones refer to hybrid molecules based on the aminoquinoline ring, using similar previously described "one-drug, two-targets approach" as for artemisinin hybrid molecules. It is widely accepted that the parasite heme-detoxification process after hemoglobin metabolism is the primary target of quinoline drugs. The present evidence indicates that CQ resistance is directly associated with mutations in the gene encoding the digestive vacuole (DV) membrane protein of the *P. falciparum* CQ-resistance transporter (PfCRT). The protein is predicted to function as an exporter of "metabolites" from the DV since it is a member of the drug/metabolite transporter superfamily. Efflux of quinoline drugs results in reduced drug concentration at the target but does not alter the he me target itself. Thus, the target remains vulnerable, and the parasite is susceptible if the drug availability to the target can be restored. This is in contrast to drug resistance on the basis of protein target mutation, such as those that confer resistance against antifolates. Several compounds referred to as resistance reversers or chemosensitizers have been studied including verapamil and imipramine that reverse quinolineresistance.Unfortunately, the chemosensitizers have not been embraced for clinical use due to potency and safety concerns as well as their lack of intrinsic antimalarial efficacy. Thus, their combination with quinolines will represent monotherapy.

In an attempt to surmount these limitations, several attempts have led to the design of novel chimeric compounds modeled on the concept that mutations in the parasite DV membrane protein PfCRT lead to excessive efflux of CQ, and that protein activity can be inhibited by reversal agents incorporated the acridonephramacophore of the quinolines into a chemosensitization moiety to synthesize twelve hybrid molecules, with T3.5 [3-chloro-6-(2-diethylamino-ethoxy)-10-(2-diethylaminol-ethyl)-acridone] being the most promising antimalarial drug. The heme-targeting tricyclic group with an ionizable side chain promotes drug accumulation in the DV while a chemosensitization moiety at the N10-position is provided to counteract quinoline resistance. The side-chain attachment at the central nitrogen provides a hydrogen bond acceptor required for a chemosensitization function, a feature that is a well-established component of the pharmacophore for effective chemosensitizers. T3.5 had remarkable *in vitro* and *in vivo*(in mice) activity. T3.5 (100 mg/kg/p.o.qd) for 3 days diminished *P. berghei*parasitaemia by 95% with an initial highdose being curative (256 mg/kg/day, p.o.) with no overt toxicity in mice. The drug had significant synergistic interaction with several quinolines including CQ, amodiaquine, quinine, and piperaquine against multi-drug-resistant *P. falciparum* isolate, The synergy between T3.5 and quinine was also observed *in vivo* against patent infection with quinine-sensitive *P. yoelii*. Hybrid drug uptake and accumulation in the DV was successful, and that drug interacted with heme thus interfering with hemozoin formation.

Quinoline-Novel Target Based Hybrid Molecules

Cysteine proteases play critical roles in parasite that include but are not limited to general catabolic functions and protein processing. As stated earlier, the *P. falciparum* cysteine protease falcipains are essential for degradation of hemoglobin during erythrocytic parasite development. A new class of 4-aminoquinoline-based isatin derivatives was designed on the basis of a multi-therapeutic strategy. Isatin can easily be functionalized with the thiosemicarbazone moiety that could inhibit *P. falciparum-derived* cysteine proteases.Thus, the quinoline entity could inhibit b-haematin formation whereas the isatin group inhibits *P. falciparum* cysteine proteases. Reports on the target compounds against both CQ-sensitive and -resistant *P. falciparum* strains, and against recombinant falcipain-2, demonstrated that the strategy is feasible. The hybrid molecules showed good in vitro antiplasmodial activity and inhibitory activity against falcipain-2, albeit modest. Thus, aminoquinoline-isatin hybrid molecules should be explored further as potential leads especially as regards the flexible ethylene linker and a thiosemicarbazone moiety. The ethylene linker increases the lipophilicity of the hybrid compound, which probably aids their passage through the parasite membranes to reach their presumed site of action, the acidic food vacuole synthesized chimeras of thiosemicarbazones and the new drug candidate, ferroquine, a new 4-aminoquinoline in which a ferrocenyl group is associated with CQ .Hybrid molecules of this type had in vitro antiplasmodial activity against both CQ-sensitive and -resistant *P. falciparum* isolates, activity that was independent of parasite CQ-susceptibility. Novel hybrids of phenolic Mannich bases linked to aminoquinoline fragment were synthesized and displayed significant antiplasmodial activity against *P. falciparum* isolate W2 (CQ-resistant) and inhibited cysteine protease falcipain-2.

However, some hybrid analogs had activity against cultured parasites as well as falcipain-2, while some were either equipotent with CQ, or had improved activity (up to 3 times the activity of CQ). However, the ability of these compounds to inhibit falcipain-2 and their antiplasmodial activity against W2 were not correlated developed 4-anilinoquinoline antimalarials based on the role reduced glutathione (GSH) plays in protecting *P. falciparum* from oxidative damage as well as in promoting heme detoxification. It was rationalized that increased GSH levels lead to increased CQ-resistance, and thus controlling levels of intracellular GSH by glutathione inhibitors could restore the efficacy of CQ and other 4-aminoquinoline analogues.Novel hybrid molecules based on aminoquinoline structures and 1,4-naphthoquinone ring were synthesized by esterification of naphthoquinolylalkanoic acids with the alcohol amodiaquine derivative in the presence of dicyclohexylcarboiimide and a 4-(dimethylamino)pyridine. It was anticipated that in the parasite, the molecule could be hydrolysed into two entities, with each product exerting its own action. The compounds displayed good in vitro antiplasmodial activity against CQ-resistant *P. falciparum* isolate, FcB1R (ED_{50}= 23–56 nM) and remarkable low in vitro percent cytotoxicity against hMRC-5 cells (25–35 μM). The ether analog affected the total glutathione content of the parasites. These hybrid molecules of a quinoline ring–glutathione reductase inhibitor can serve as a model for development of novel hybrids and need to be further explored.

Future prospects of "covalent biotherapy" strategy

The "Covalent bitherapy" strategy of drug design may find other future potential applications, which may include:

- **Novel antimalarial drugs:** The principle of rational drug design of hybrid molecules has the potential to be extrapolated to other antimalarial drugs with different targets and/or mechanisms of action other than the ones discussed in this review. Trioxaquines offer better antimalarial activity than the individual components in double combination. This may imply that interaction of the pharmacophores of two drugs in the single-hybrid molecule is better than that of individual drugs in a combination. It is also possible that hybrid molecules will possess superior bioavailability and/or different mode of action from that of individual drugs in combination. This is especially useful in designing drugs such as the aminoquinolines (e.g., CQ), where resistance is not due to an altered target but failure to access the target. It will be interesting to evaluate whether the principle of "covalent bitherapy" can be exploited to develop modular hybrid molecules that restore activity of other dug class such as antifolates (e.g.,sulfadoxine/pyrimethamine), which become ineffective due to resistance.
- **Drug-delivery system:** As the search for novel drugs continues, more drugs with novel targets are being developed, but many of these do not reach clinical trials due to associated toxicity. Hybrid molecules are essentially prodrugs that aid in improving the efficacy and reducing the toxicity and other adverse effects of drugs by controlling their pharmacokinetic properties. Although some drugs may be toxic, their pharmacophores may not be as toxic, and it may be possible to develop safer drugs by covalently linking these pharmacophores with those of other drugs into synergistic conjugates. For instance, 5-fluoroorotate (FOA) is an active antifolate that targets thymidylate synthase (TS) of P. falciparum , but its clinical usage is curtailed by toxicity concerns. It is noteworthy that there is no antimalarial antifolate in clinical use that targets TS, and all antifolate antagonists in malarial chemotherapy only target either dihydrofolatereductase or dihydropteroate synthase of the parasite folate metabolic pathway. Thus, clinical usefulness for FOA could be achieved by covalently linking it to another drug, ensuring safe delivery and selective toxicity to the malarial parasite cell, with no toxicity to the host cell. Primaquine, an 8-amino- quinoline, is a tissue schizontocide, which has serious side effects. Its toxicity limits its use in both prophylactic and therapeutic applications. It is known to induce hemolysis especially in glucose-6- phosphate dehydrogenase (G6PD)-deficient indivi duals. As described earlier, demonstrated that 8-quinolineamines conjugates as well as their "double prodrugs" had promising in vivo activity in mice. If these compounds, in which basic pharmacophore is primaquine, are modified to improve their blood schizontocide activity, they have the potential to be used as broad-spectrum (tissue and blood schizontocides) antimalarial agents. Conjugation of drugs may, therefore, serve as a useful tool to improve drug solubility and stability, and prolong drug release, reduce doses, dosing intervals, and drug toxicity, as well as to achieve.
- **Multiple (compound)-pharmacophoric hybrids:** Recently, a highly potent and promising ACT drug, a chlorproguanil hydrochloride-dapsone-artesunate (CDA, Dacart®) combination, was developed through collaborative work between WHO, MMV, and GSK. However, its Phase III trials and development were terminated prematurely because of toxicity concerns. Dapsone is known to induce hemolysis in G6PD-deficient individuals, who represent as much as 15% of the sub-Saharan Africa population, where over 90% of global malaria cases and deaths. For the same reason, Lapdap® (chlorproguanil-dapsone) developed by WHO/GSK/University of Liverpool collaboration was withdrawn from the market. The potential of hybrid molecules linking more than two pharmacophores could be explored, since such compound hybrids may increase efficacy while abrogating the underlying toxicity. It would be interesting to see whether a hybrid molecule linking the three pharmacophores of CDA will circumvent toxicity.
- **Tailor-made stage-specific hybrid molecules:** Covalently linking pharmacophores of antimalarial drugs that possess stage-specific action may have the potential of interrupting malaria transmission. For instance, drugs that target early asexual forms of the malarial parasite can be linked with the ones that target the late stages as well as the sexual forms (gametocytocides). Artemisinin semi-synthetics (e.g., artesunate), synthetic trioxaquines (e.g., DU1302), as well as primaquine have remarkable gametocytocidal activity. Artemisinins are also known to target early forms of the parasite, which is one of the main advantages of these drugs in ACT, reducing chances of development of resistance. In theory, therefore, it is

possible to design hybrid molecules that integrate the various pharmacophores of such drugs, which will not only lower the parasite load effectively (thus reducing chances of resistance development), but also targeting sexual parasite forms can go a long way in interrupting transmission especially in malariaendemic areas.

- **Elucidation of "drug mechanism of action" as well as "drug-resistance mechanisms":** The molecular basis of action of most antimalarial drugs in clinical use is poorly characterized, much less the mechanisms involved in their resistance. While CQ action is thought to mainly involve interference with hemoglobin digestion in the blood stages of the malaria parasite life cycle,the mechanism of action of artemisinins is a little controversial with various targets being reported although it is widely accepted that its activity is mediated via the endoperoxide function. It has been suggested that iron generates free radicals from artemisinins, which may lead to lipid peroxidation, protein oxidation, alkylation, and subsequent parasite death also reported that artemisinins exert their action in a similar manner to CQ, by interfering with the hemoglobin catabolic pathway and inhibition of heme polymerization. provided compelling evidence that after artemisinin activation by iron, it can inhibit P. falciparum sarco/endoplamic reticulum Ca^{2+}-ATPase (SERCA) ortholog (PfATP6) outside the food vacuole. PfATPase is the only SERCA-type Ca^{2+} ATPase sequence in the P. falciparum genome. CQ-resistance has been implicated with elevated levels of drug efflux mediated by PfCRT, a member of the drug/metabolite transporter superfamily located in the intraerythrocytic parasite DV.Although controversial, overexpression of the ATP-dependent drug transporter, P-glycoprotein, has also been implicated with CQ-resistance, and the pfmdr1 gene product, PGh-1 (a typical member of P-glycoprotein family), is localized to the membrane of the parasite food vacuole. It may be postulated that hybrid molecules may aid in clarifying both the mechanism of action of drugs as well as in elucidating the mechanisms of resistance.

REFERENCES

Atamna, H., Ginsburg, H. 1997. The malaria parasite supplies glutathione to its host cell: investigation of glutathione transport and metabolism in human erythrocytes infected with *Plasmodium falciparum*. *Eur J Biochem,* 250:670–679.

Araújo, N.C., Barton, V., Jones, M., Stocks, P.A., Ward, S.A., Davies, J., Bray, P.G., Shone, A.E., Cristiano, M.L., 2009. O'Neill PM. Semi-synthetic and synthetic 1,2,4-trioxaquines and 1,2,4-trioxolaquines: synthesis, preliminary SAR and comparison with acridineen doperoxide conjugates. *Bioorg Med Chem Lett.,* 19:2038–2043.

Barends, M., Jaidee, A., Khaohirun, N., Singhasivanon, P., Nosten, F. 2007. In vitro activity of ferroquine (SSR 97193) against *Plasmodium falciparum* isolates from the Thai-Burmese border. *Malar J.,* 6:81.

Basco, L.K., Dechy-Cabaret, O., Ndounga, M., Meche, F.S., Robert, A., Meunier, B. 2001. In vitro activities of DU-1102, a new trioxaquine derivative, against *Plasmodiumfalciparum* isolates. *Antimicrob Agents Chemother,* 45:1886–1888.

Becker, K., Rahlfs, S., Nickel, C., Schirmer, R.H. 2003. Glutathione: functions and metabolism in the malarial parasite *Plasmodium falciparum*. *Biol Chem.,* 384:551–566.

Bejon, P., Lusingu, J., Olotu, A., Leach, A., Lievens, M., Vekemans, J., Mshamu, S., Lang, T., Gould, J., Dubois, M.C., Demoitie, M.A., Stallaert, J.F., Vansadia, P., Carter, T., Njuguna, P., Awuondo, K.O., Malabeja, A., Abdul, O., Gesase, S., Mturi, N., Drakeley, C.J., Savarese, B., Villafana, T., Ballou, W.R., Cohen, J., Riley, E.M., Lemnge, M.M., Marsh, K., Von Seidlein, L. 2008. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. *N Engl J Med.,* 359:2521–2532.

Benoit-Vical, F., Lelievre, J., Berry, A., Deymier, C., Dechy-Cabaret, O., Cazelles, J., Loup, C., Robert, A. 2007. Magnaval JF, Meunier B. Trioxaquines are new antimalarial agents active on all erythrocytic forms, including gametocytes. *Antimicrob Agents Chemother,* 51:1463–1472.

Biot, C., Dessolin, J., Ricard, I., Dive, D. 2004. Easily synthesized antimalarial ferrocenetriazacyclononanequin oline conjugates. *J Organomet Chem.,* 689:4678–4682.

Biot, C., Pradines, B., Sergeant, M.H., Gut, J., Rosenthal, P.J., Chibale, K. 2007. Design, synthesis, and antimalarial activity of structural chimeras of thiosemicarbazone and ferroquine analogues. *Bioorg Med Chem Lett.,* 17:6434–6438.

Bloland, P.B. 2001. Drug resistance in malaria. Geneva: WHO, Malaria Epidemiology Branch, Centers for Disease Control and Prevention, pp. 1–23.

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