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A new approach for developing anti-malarial agents

Malaria is caused by the parasitic organism *Plasmodium falciparum* that invades and causes the destruction of red blood cells on which it feeds. According to the CDC (Centers for Disease Control and Prevention, www.cdc.gov), the disease affects 350–500 million individuals each year leading to over a million deaths, primarily in poor subtropical regions of the world. There have been drugs available to treat the disease for a number of years but, over the course of time resistance to these agents, especially the quinolines, has developed in certain strains of the pathogen. Therefore, new drugs are needed that are both effective against the resistant strains of the pathogen but which can be produced at low cost so that they are affordable in the areas of the world where the disease is endemic.

In a recent publication in *Nature* [1], a unique approach toward developing such agents is disclosed. Quinolines act in the digestive vacuole of *F. falciparum* by inhibiting the metabolism of hemoglobin that the parasite needs for survival and causing the buildup of a toxic heme precursor. Resistance to the quinoline class of compounds is caused by mutations in the gene encoding a protein, PfCRT (*P. falciparum* chloroquine resistance transporter), in the digestive vacuole membrane that leads to reduced uptake of the drug in the food vacuole. The actual target of the drug remains sensitive to inhibition but the organism escapes it by preventing access to the target. This type of resistance can be overcome by blocking the PfCRT transporter that is responsible for keeping the drug from accessing its target [2].

Taking advantage of this mechanism of resistance, the authors designed a series of compounds that are in essence multifunctional in that they consist of a central Heme-targeting core to which are attached a chemosensitizing moiety and a group that enhances the partitioning of the drug into the acidic digestive vacoule. Compound T3.5 is built upon an acridone core as the active agent. Attached to this are two ionizable amine-containing side chains, one that enhances accumulation of the compound in the acidic food vacuole and the other that acts as a chemosensitizer against quinoline resistance. By itself, this molecule was found to display favorable activity against both chloroquine sensitive and multidrug resistant (MDR) strains in *in vitro* assays and was effective in a mouse model of infection. Additionally, as expected when used in combination with other agents, T3.5 was able to sensitize MDR strains toward chloroquine, amodiaquinem quinine and piperaquine but no mefloquine, in the *in vitro* assay. Quite unexpectedly, T3.5 acts synergistically with quinine against drug-sensitive strains of *P falciparum*, an effect that has not previously been observed for chemosensitizers.
This suggests that T3.5 could be used in combination with quinine as front line therapy to treat infection and prevent the development of resistance (Figures 1 and 2).

Preclinical studies of the FXa inhibitor betrixaban

Late stage SAR studies leading up to the discovery of the Factor Xa (fXa) inhibitor betrixaban (PRT054021) were recently

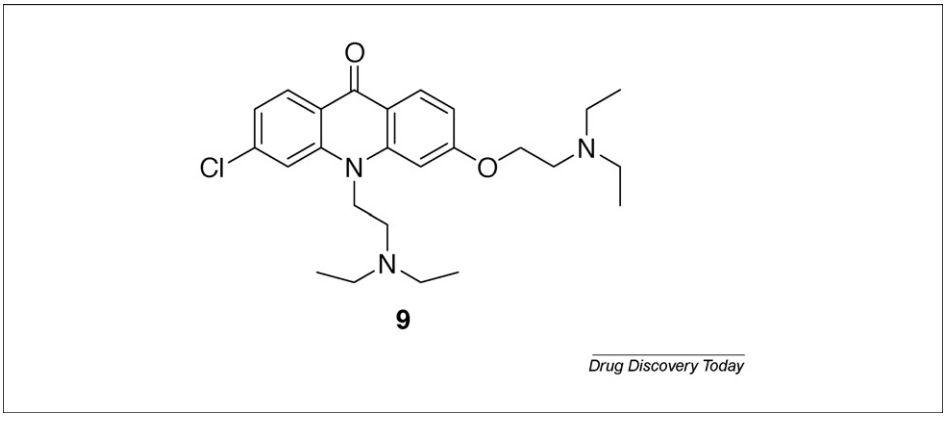

FIGURE 1
Multifunctional anti-malarial agent T3.3.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.06.006

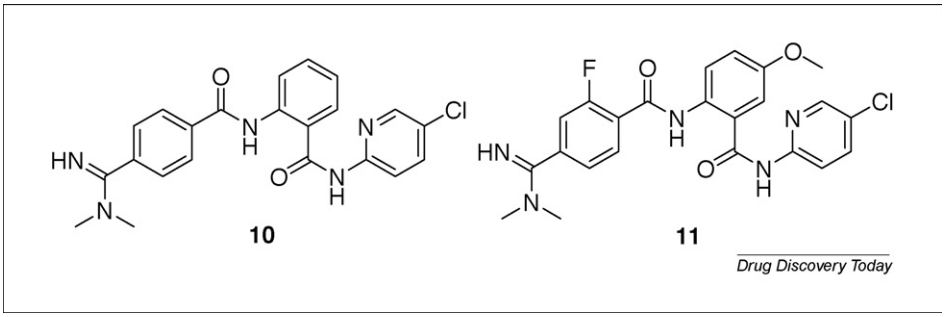

FIGURE 2

Factor Xa inhibitors (10) and betrixaban (11).

disclosed by researches at Millenium Pharmaceuticals [3]. Factor Xa catalyzes the conversion of prothrombin to thrombin and plays a major role in the blood coagulation cascade. Inhibitors of this enzyme can therefore be used for certain cardiovascular disorders without affecting the normal ability of the blood to clot. The anthranilide-based chemotype was identified as a favorable template, but the early lead series suffered from poor bioavailability due to the presence of a guanidine group. The search for an orally bioavailable compound led to the discovery of the amidine group as an acceptable replacement for guanidine. A SAR study around this group identified the dimethylamidine **10** as an advanced lead having very good *in vitro* activity (FXa IC_{50} = 3 nM, K_i = 1.4 nM) and potent functional activity in a plasma-based thrombin generation assay (2 × TG 0.54 μM). More importantly, **10** exhibited good exposure in animal PK studies where it displayed 31 % and 69% orally bioavailability in the rat and dog, respectively. Further improvements in activity were achieved by optimizing the substitution on the three phenyl rings. However, this also led inhibition of the hERG (human ether-a-go-go related gene) ion channel representing a potential off-target liability. In the end, the appropriate balance between hERG binding and fXa was achieved with the combination of phenyl ring substituents found in compound **11**, betrixiban (PRT054021) (fXa IC_{50} = 1.5 nM, K_i = 0.117 nM, 2 × TG 0.33 μM, hERG K_i = 1.8 μM). Favorable exposure in rat, dog and monkey were also found. As of January 2009, this compound was reported to be entering Phase II clinical trials for the prevention of VTE (venous thromboembolic events) after total knee replacement.

1 Kelly, J.A. *et al.* (2009) Discovery of dual function acridones as a new antimalarial chemotype. *Nature* 459, 270–273

2 Martin, S.K. *et al.* (1987) Reversal of chloroquine resistance in *Plasmodium Falciparum* by verapamil. *Science* 235, 899–901

3 Zhang, P. *et al.* (2009) Discovery of betrixiban (PRT054021), N-(5-chloropyridinyl-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor. *Bioorg. Med. Chem. Lett.* 19, 2179–2185

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