

FINAL CONCLUSION

Conclusions

The recently reported potential emergence of resistance of artemisinin in western Cambodia has the potential to spread to different parts in the region, subsequently becoming a global threat for malaria control and treatment. Thus, highlighting the need for new chemotherapeutic approaches to treat *P. falciparum* infections as there are currently no alternative drugs to replace artemisinin derivatives (Dondorp *et al.*, 2009; Dondorp *et al.*, 2010; Phyo *et al.*, 2012). A major drawback of the artemisinin derivatives is their very rapid half-life and susceptibility for recrudescence, when given as monotherapy results in resistance (Ashton *et al.*, 1998). Autoinduction of CYP-mediated metabolism is the underlying mechanism of the appearance of recrudescence (Asimus *et al.*, 2007; Liu *et al.*, 2011).

Hybrid molecules, as described by Meunier (Meunier, 2008), are composed of two distinct moieties joined covalently, which will act as two distinct pharmacophores. The risk of treatment failure is reduced and the partner drug may be protected from the spread of resistance. The concept of the formation of a hybrid, especially in the treatment of malaria, was already taken up by various researchers all over the world (Meunier, 2008; Dechy-Cabaret *et al.*, 2004; Singh, Malik & Puri, 2004; Grelepois *et al.*, 2005; Benoit-Vical *et al.*, 2007; Cosledan *et al.*, 2008).

In this study a series of novel artemisinin-quinoline hybrids were synthesized. DHA was reacted with bromoethanol in the presence of boron trifluoride etherate and yielded 2-(10 β -dihydroartemisininoxy)ethylbromide which was treated with different quinoline based primary/secondary amines. These aminoquinolines were obtained by the condensation of various diamines with 4, 7-dichloroquinoline. Under specified conditions, disubstitution took place when a second DHA-moiety bound to the most available N-atom obtaining hybrid-dimers.

These synthesized hybrids and hybrid-dimers displayed potent low *in vitro* antiplasmodial activities with no notable toxicity. Subsequently, the promising compounds were selected for further investigation to ascertain whether potent low nanomolar *in vitro* antiplasmodial activity would be carried over *in vivo* against *P. vinckei*.

The dimer featuring the aliphatic 1,3-diaminopropyl linker, had overall superior antimalarial activity and pharmacokinetic characteristics and displayed potent anticancer activities against all 3 cell lines. Although the attachment of a long acting drug moiety (quinoline) did not appear to increase the

half-life of the artemisinin pharmacophore, prolonged antimalarial drug activities did occur and were expected to be due to active metabolites.

The selected artemisinin-quinoline hybrids displayed potent and rapid *in vivo* antimalarial activity when optimum dosages were applied, resulting in recrudescence if otherwise applied. Despite a short half-life and moderate oral bioavailability of the parent drug, this class of compounds was able to cure malaria in mice at very low dosages, implying that the compounds were metabolized to active metabolites. At 15 mg/kg ip and 50 mg/kg po two of the hybrids, featuring non-methylated and methylated two-carbon diaminoalkyl linkers, provided a complete clearance of parasitaemia and a total cure of malaria, whereas artesunate is able to provide a complete cure at only 30 mg/kg ip and 80 mg/kg po. Long term monitoring showed 100% survival on day 30, with no observed recrudescence.

In this study the optimum linker length for *in vivo* antimalarial activity was found to be a diamino-aliphatic linker consisted of two carbon atoms either unmethylated or bearing a single methyl group. Lengthening the linker by adding another carbon atom in the chain resulted in a reduction of parasites survival rate from 100% to 66% at the same dosages.

In view of all the results, these compounds may provide a new class of antimalarial drugs.

Recommendations

The next step will be to conduct a comprehensive pharmacokinetic study, including metabolite identification.

Chemical modifications could be introduced to the structure of these compounds to replace the metabolic unstable C-10 acetal functionality resulting in compounds that will not be easily metabolized. For these compounds to be used as oral antimalarial treatment, modifications to improve bioavailability are necessary.

The dimer featuring the aliphatic 1,3-diaminopropyl linker might be potentially interesting for further research in search for better anticancer drugs.

References

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