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Novel antimalarial enantiopure arylaminoalcohols as efflux pump substrates to fight resistant *P. falciparum*

Camille Tisnerat [1,2,*], Jérémy Schneider [1], Céline Damiani [1], Patrice Agnamey [1], Catherine Mullié [1], Anne Totet [1], Emmanuel Sevin [2], Alexandra Dassonville-Klimpt [1], Fabien Gosselet [2] and Pascal Sonnet [1]

[1] AGIR, UR4294, UFR de Pharmacie, Université de Picardie Jules Verne, Amiens, France
[2] LBHE, UR2465, Université d'Artois, Lens, France

* Corresponding author: camille.tisnerat@etud.u-picardie.fr

Abstract

Malaria still is one of the most threatening diseases in the world. In 2019, the WHO estimated 229 million of cases and 409,000 deaths mainly due to the most prevalent and lethal *Plasmodium* species: *P. falciparum* (*Pf*).

Fighting resistant *Pf* strains is henceforth one of the main challenges to eradicate malaria. Indeed, parasites have developed resistances against all the available therapeutic arsenal, including artemisinin-based combination therapies (ACT). Studies of resistance phenotypes identified efflux pumps involved in this phenomenom of which the multidrug resistance ABC transporter *Pf*MDR1. Its overexpression is partly responsible of the carrying of two ACT partner drugs, mefloquine (MQ) and lumefantrine (LM), into the food vacuole away from their cytosolic targets, leading to the efficacy decline of these arylaminoalcohol drugs.

In order to limit this efflux, our laboratory has developed efflux pump inhibitor (EPI) patterns based on previous described resistance reversing agents such as penfluridol. A library of novel arylaminoalcohols is easily affordable into a previously optimized synthesis to obtain MQ, LM and enpiroline analogs. This stereoselective and convergent synthesis requires a key arylvinyl converted to the corresponding enantiopure aryloxirane thanks to a Sharpless asymmetric dihydroxylation followed by a *one-pot* cyclization. Finally, a regioselective ring-opening by EPI moieties led to efflux pump substrate compounds.

Both design and synthesis of these arylaminoalcohols will be herein presented. *In vitro* efficacy against two *Pf* strains, cytotoxicity and preliminary results of P-gp, BCRP and MRPs efflux modulation in Caco-2 cells model will be reported. First structure-activity relationships will be discussed.

Keywords

Arylaminoalcools ; asymmetric synthesis ; efflux pump modulation ; malaria ; *Plasmodium falciparum*

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409,000 deaths
about **67% children** under five

94% of all malaria deaths
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World Malaria Report 2020; WHO, **2020**.

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Correlation between **arylaminoalcohols** (mefloquine – MQ, lumefantrine – LUM) and **the transporter *Pf*MDR1**

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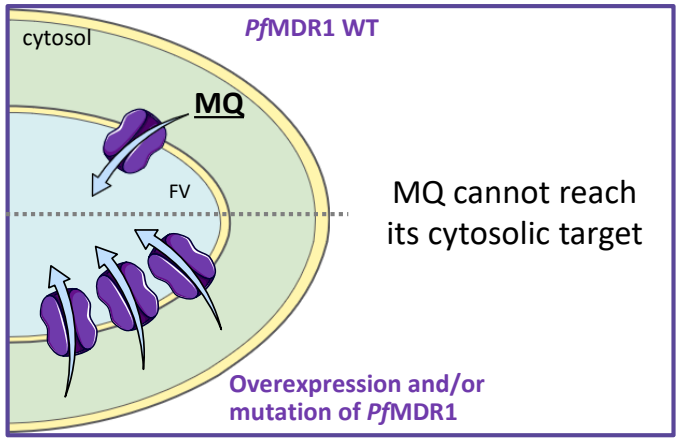

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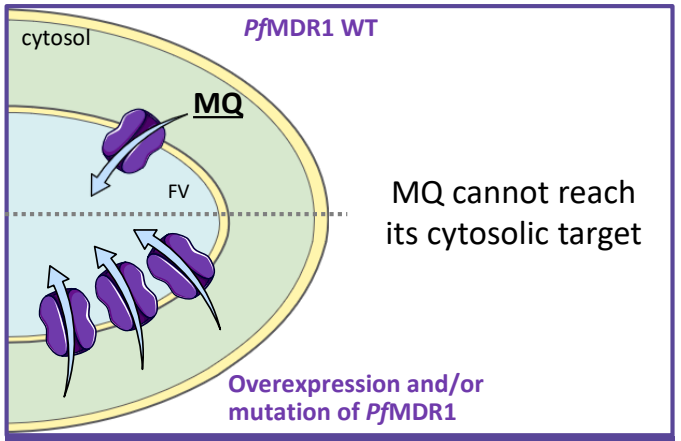

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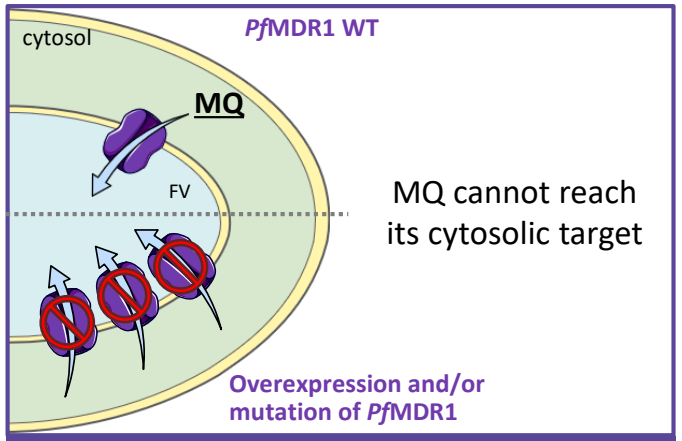

How to limit this efflux ?

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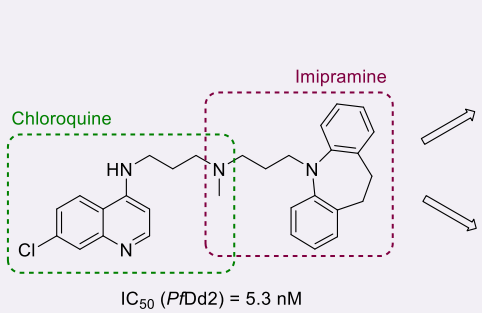
Hybrids strategy

Efflux pump inhibitor (EPI) moiety coupled with arylaminoalcohol pattern to block *Pf*MDR1

World Malaria Report 2020; WHO, **2020**.

Design and synthesis

Known hybrids in CQ-R strains



IC_{50} (*Pf*Dd2) = 5.3 nM

IC_{50} (*Pf*Dd2) = 1.8 nM

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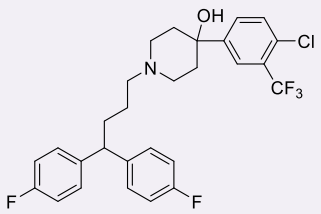
J. Med. Chem. (**2010**), 53, 6477–6489

Design and synthesis

In MQ-R strains, shift in sensitivity with penfluridol



Penfluridol

MQ alone
IC_{50} (*Pf*D6) = 33.7 nM

MQ + penfluridol (0.5 µM)
IC_{50} (*Pf*D6) = 13.7 nM

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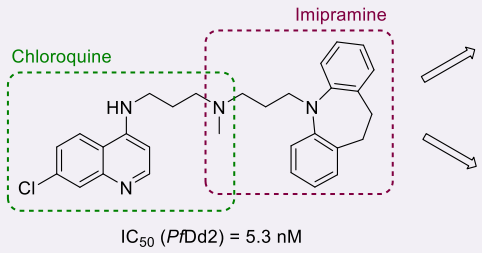

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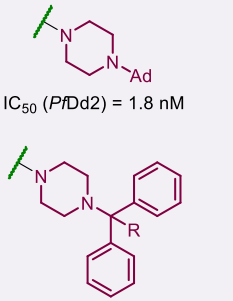

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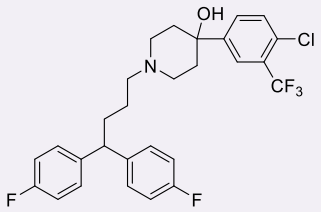

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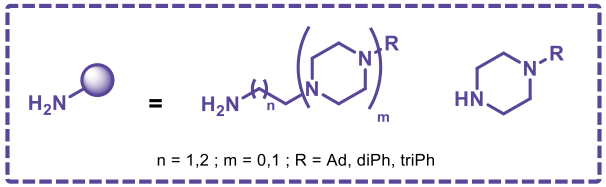

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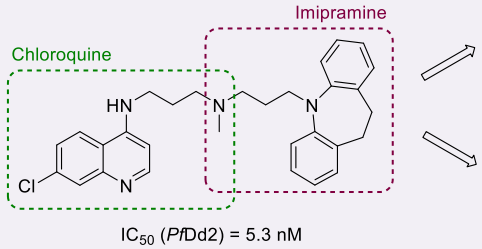

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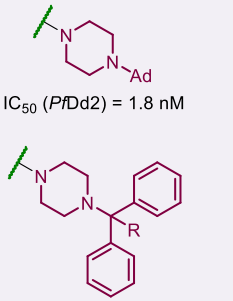

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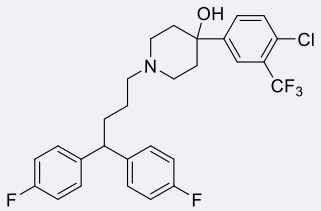

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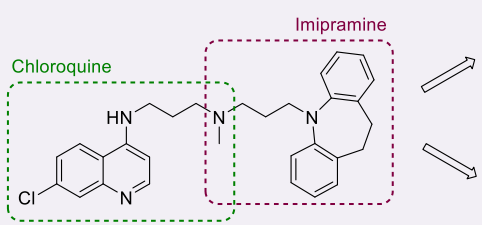

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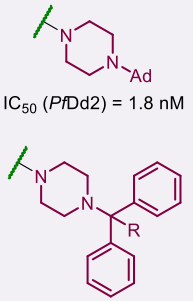

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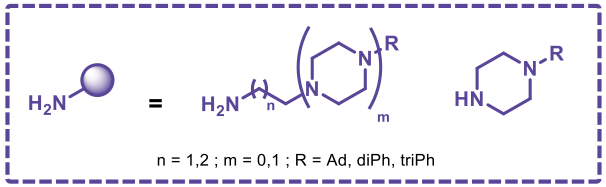
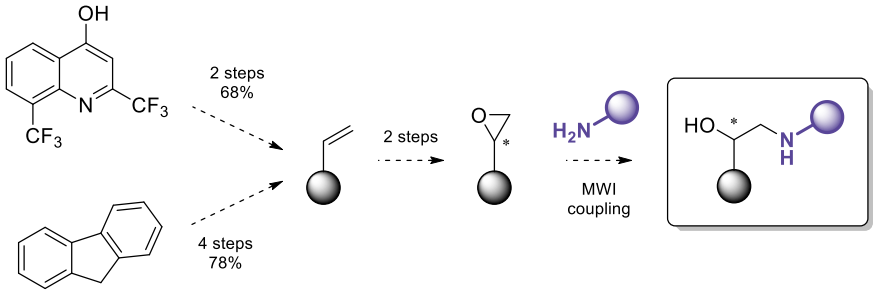
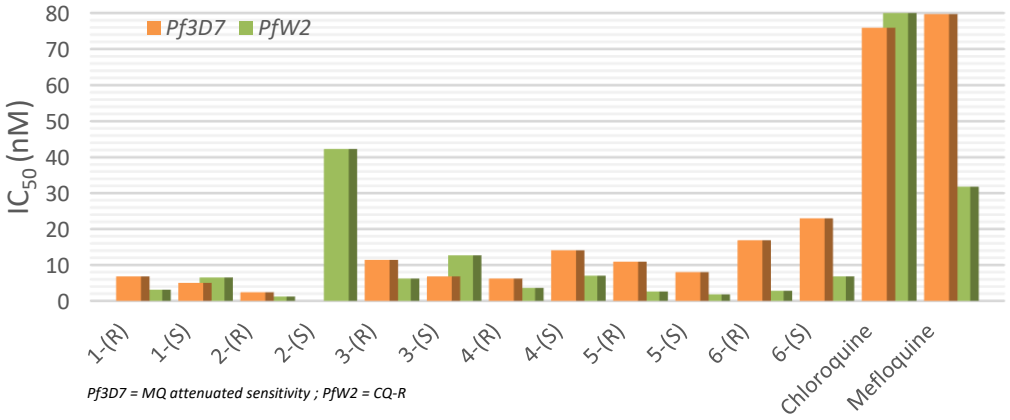


n = 1,2 ; m = 0,1 ; R = Ad, diPh, triPh

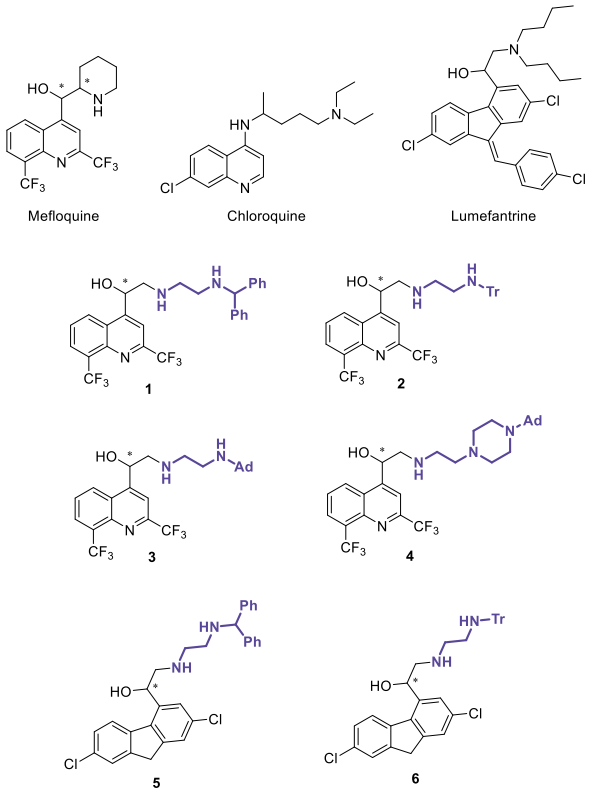


Biological properties

1 Nanomolar range activity



Pf3D7 = MQ attenuated sensitivity ; PfW2 = CQ-R



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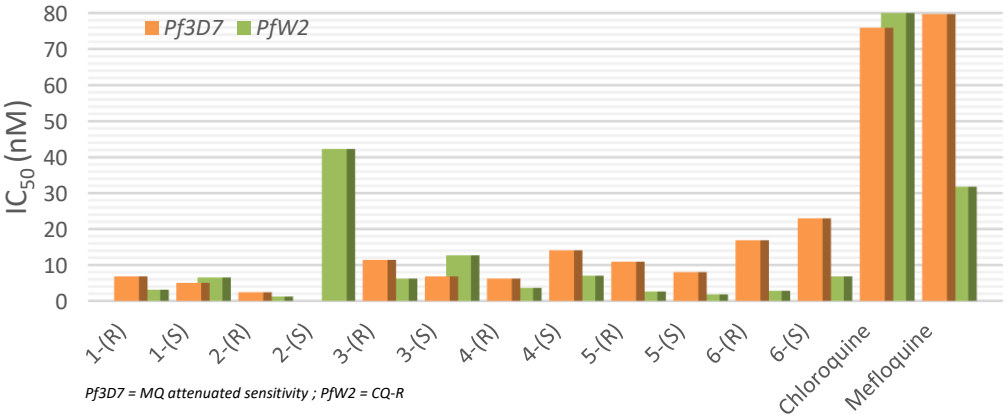

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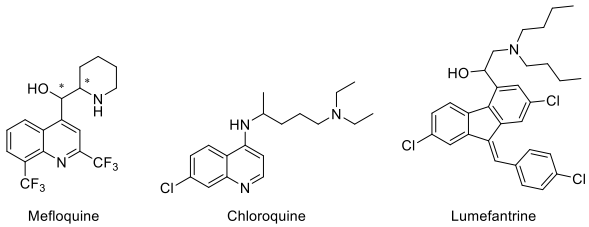
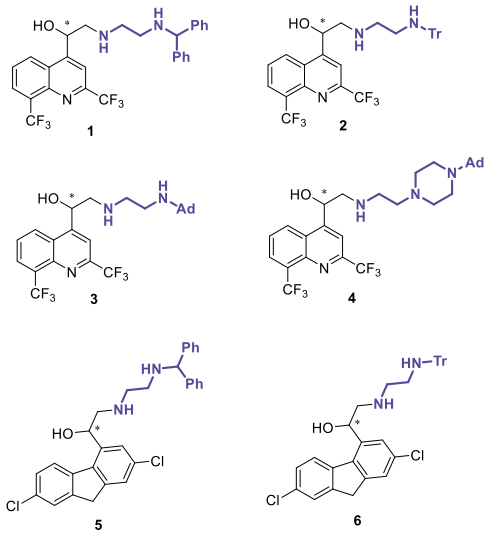
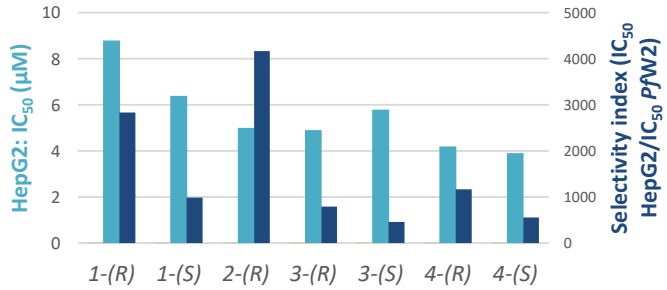




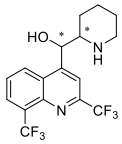
2 High selectivity index in quinoline series (> 450)



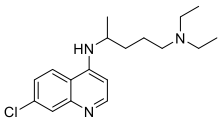
Modulation of *Pf*MDR1

3. **No MRPs modulation**
4. **Pgp/BCRP modulation**

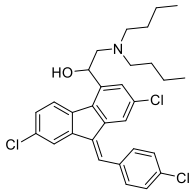
A miniaturized pump out method for characterizing molecule interaction with ABC transporters: *Int. J. Mol. Sci. (2019)*, **20** (*22*), 5529



Mefloquine



Chloroquine



Lumefantrine

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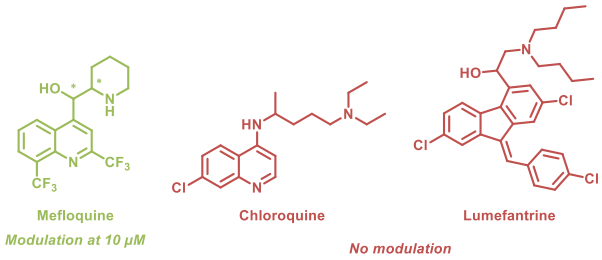

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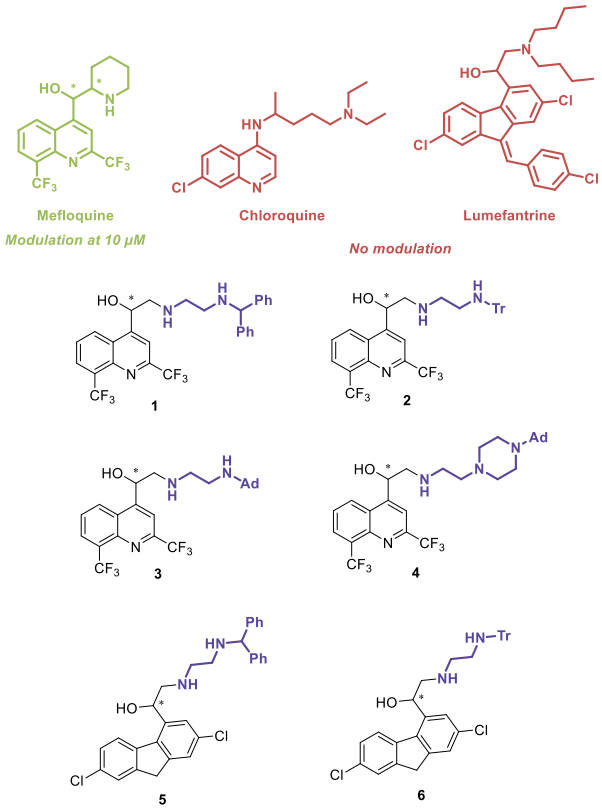

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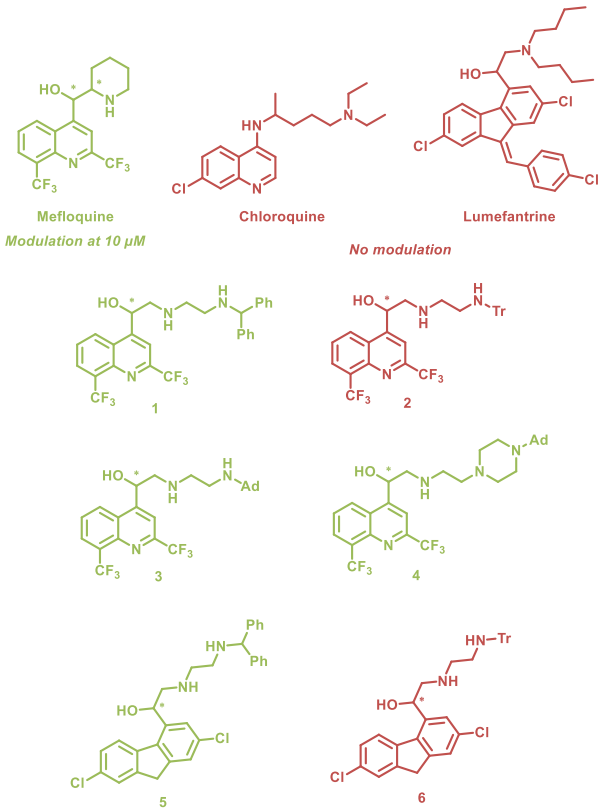

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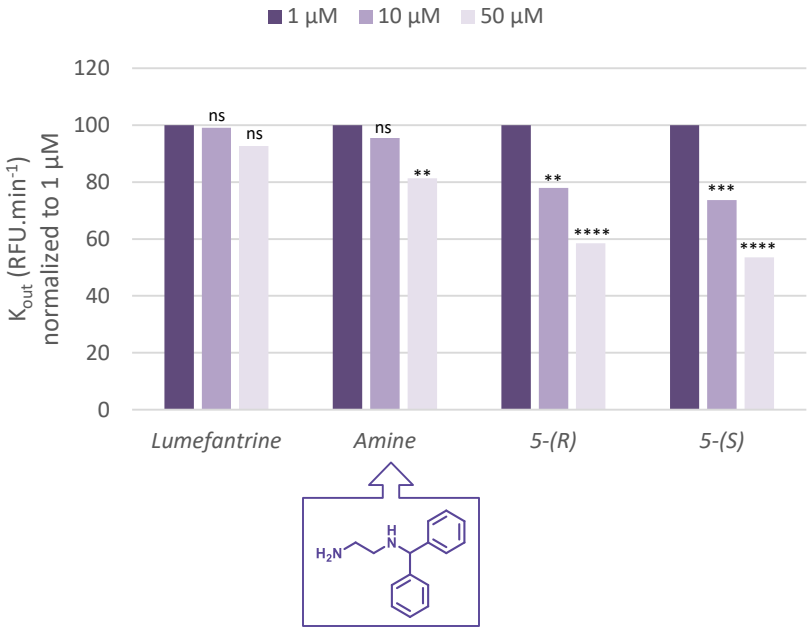

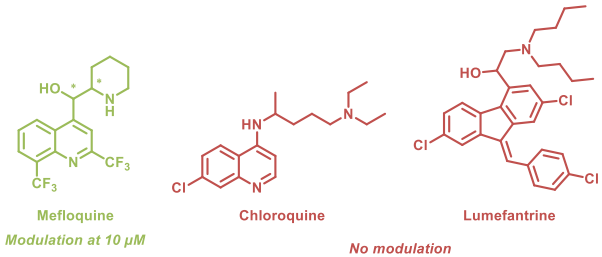

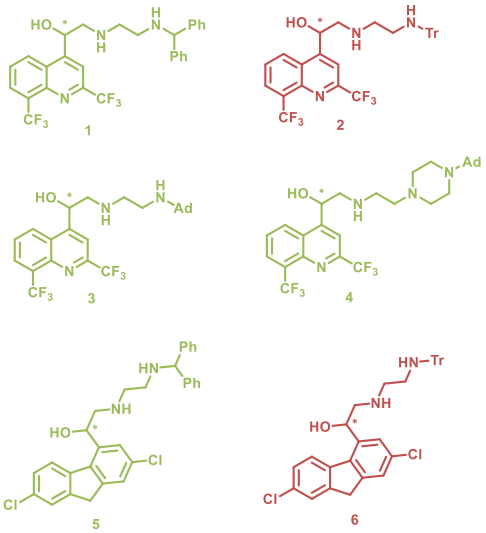

Conclusion & Prospects

❸ No MRPs modulation

❹ Pgp/BCRP modulation

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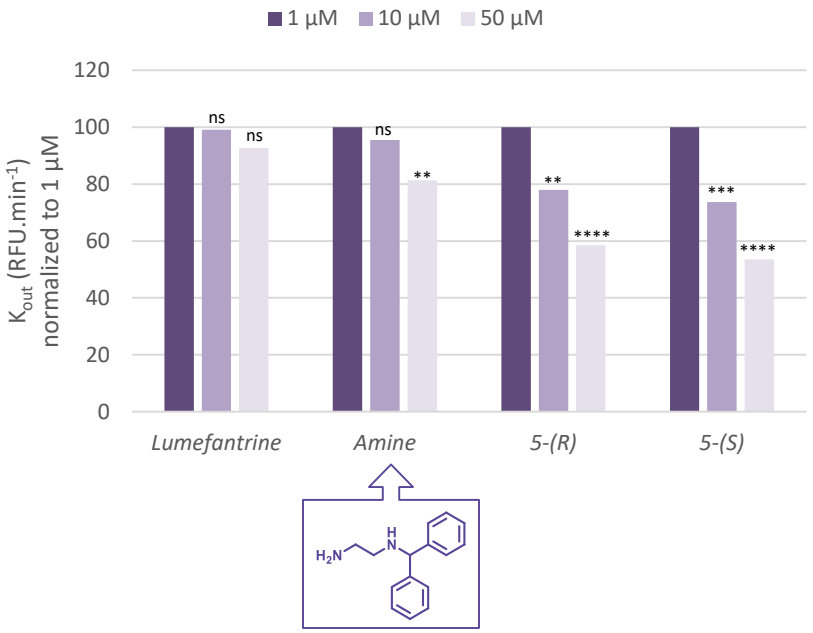

Support our strategy of hybrids synthesis

Next step: antimalarial activity against Dd2 strains

Aknowledgements

Région Hauts-de-France

UNIVERSITÉ de Picardie Jules Verne

UNIVERSITÉ D'ARTOIS

AGIR AGents Infectieux, Résistance et chimiothérapie

lb.h.e