Synthesis and biological evaluation of new enantiopure 4-aminoalcohol-quinoline and -fluorene hybrids as antimalarial drugs

Camille Tisnerat [(1)], **Jérémy Schneider** [(1)], **René Pemha** [(1)], **Céline Damiani** [(1)], **Patrice Agnamey** [(1)], **Catherine Mullié** [(1)], **Anne Totet**[(1)], **Alexandra Dassonville-Klimpt** [(1)], **Pascal Sonnet** [(1)]

[(1)]AGIR, UR4294, UFR de Pharmacie, Université de Picardie Jules Verne, Amiens, France

camille.tisnerat@etud.u-picardie.fr

228 millions of cases (2018)[1]

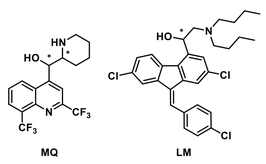
MALARIA

Deadly infection

Mainly caused by *Plasmodium falciparum*

Artemisinin-based combination therapy (ACT)[1,2]

as artemisinins + mefloquine (MQ) / lumefantrine (LM)



HOWEVER

Parasite resistance to antimalarials[3]

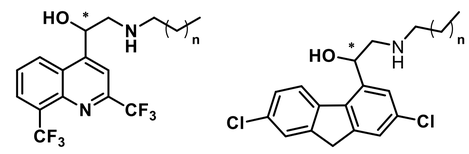
↓ sensibility to artemisinins + genic mutations - efflux pump to MQ / LM

P. falciparum

Covalent conjugation of antimalarial compounds with efflux pump inhibitors (EPI) can allow to struggle resistant parasites ?

Previous work

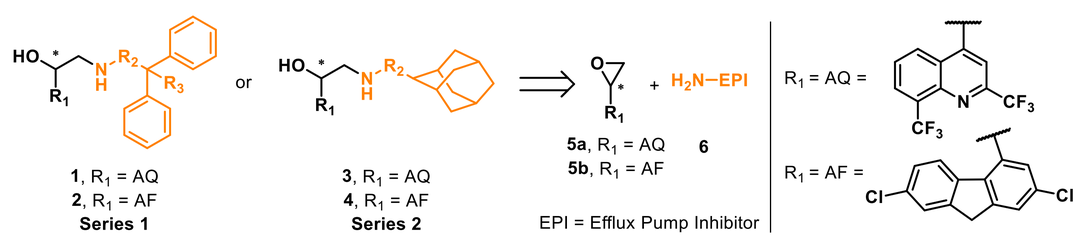
Our laboratory has developed an asymmetric synthesis to prepare 4-aminoalcohol-quinolines (AQ) and -fluorenes (AF) as enantiopure MQ and LM analogs from a key epoxyde **5**.[4-8]



IC_{50} : on nanomolar range
Eudysmic ratio : 1.0 to 22.9
Selectivity index > 145

Aim

Inspired from known reversal agents, [9] we designed new enantiopure AQ and AF **1-4** with EPI pattern under two series: benzhydryl/trityl (series 1) and adamantyl (series 2).



1, R_1 = AQ
2, R_1 = AF
Series 1

3, R_1 = AQ
4, R_1 = AF
Series 2

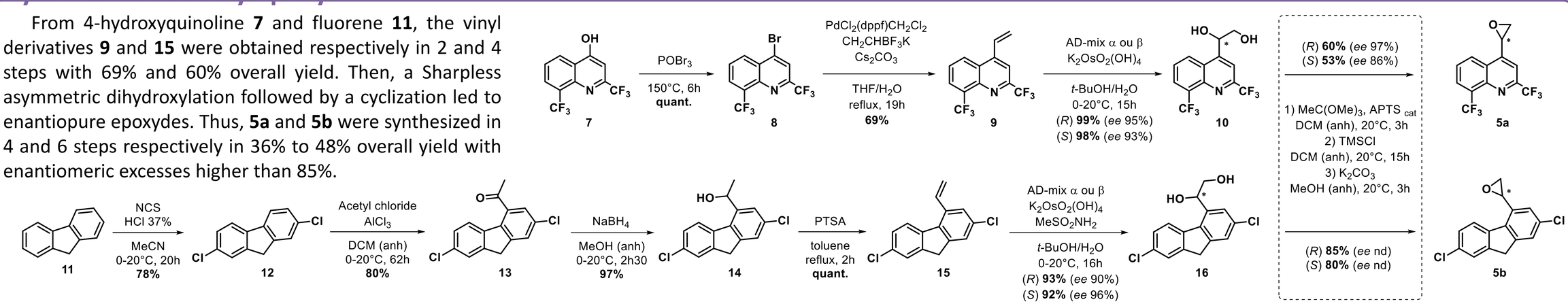
5a, R_1 = AQ
5b, R_1 = AF

6

EPI = Efflux Pump Inhibitor

Synthesis of the key epoxyde

From 4-hydroxyquinoline **7** and fluorene **11**, the vinyl derivatives **9** and **15** were obtained respectively in 2 and 4 steps with 69% and 60% overall yield. Then, a Sharpless asymmetric dihydroxylation followed by a cyclization led to enantiopure epoxydes. Thus, **5a** and **5b** were synthesized in 4 and 6 steps respectively in 36% to 48% overall yield with enantiomeric excesses higher than 85%.



7 **8** **9** **10** **5a** **11** **12** **13** **14** **15** **16** **5b**

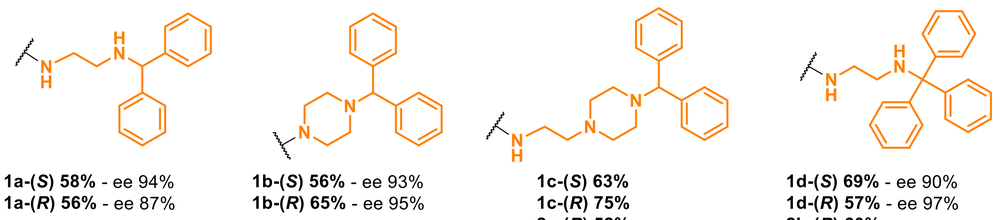
Synthesis of hybrids

Amino-moities IPE **6** were synthesized in one to five steps, in 35% to quantitative overall yields (not exposed herein). Hybrids were then obtained by a regioselective attack on 4-oxirane **5** under micro-waves with 1.5 to 3 equivalents of EPI **6**.

5 **1-4**

Nowadays, sixteen 4-AQ and seven 4-AF hybrids were obtained with a yield range from 41% to quantitative. First analysed compounds have suitable enantiomeric excesses, higher than 87%. Last syntheses and analyses are under progress.

Series 1



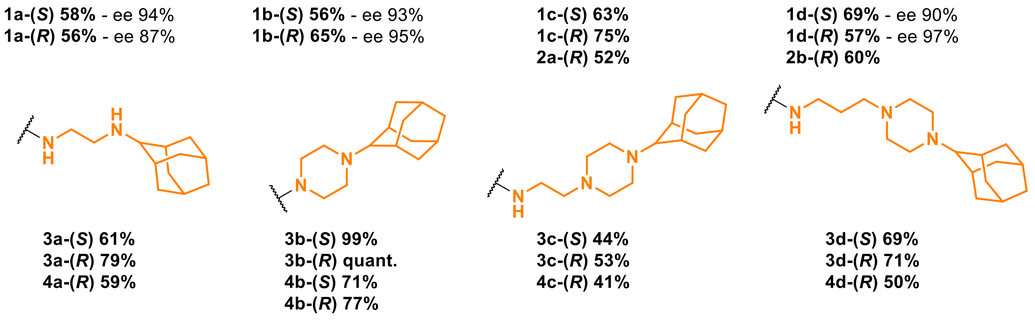
1a-(*S*) 58% - ee 94%
1a-(*R*) 56% - ee 87%

1b-(*S*) 56% - ee 93%
1b-(*R*) 65% - ee 95%

1c-(*S*) 63%
1c-(*R*) 75%
2a-(*R*) 52%

1d-(*S*) 69% - ee 90%
1d-(*R*) 57% - ee 97%
2b-(*R*) 60%

Series 2



3a-(*S*) 61%
3a-(*R*) 79%
4a-(*R*) 59%

3b-(*S*) 99%
3b-(*R*) quant.
4b-(*S*) 71%
4b-(*R*) 77%

3c-(*S*) 44%
3c-(*R*) 53%
4c-(*R*) 41%

3d-(*S*) 69%
3d-(*R*) 71%
4d-(*R*) 50%

Biological results

By a SYBR Green I fluorescence method, the *in vitro* antimalarial activity was evaluated against *Pf*3D7 and *Pf*W2 strains. Pleasingly, all IC_{50} were in nanomolar range, except for the compound **4c-(*R*)**. In series 1, compounds **1a** and **1d-(*R*)** present the better activity, proving the interest of benzhydryl- and trityl-ethane diamine as EPI. Equally for **3a** and the adamantyl-ethane diamine in series 2. Interestingly, **3b** shows the best eudysmic ratio, whatever the strain, and **3c** presents a good activity less than 15 nM. First results lead toward a better activity of 4-AQ moities than 4-AF. Evaluated against HepG2 cells, cytotoxicity (IC_{50}) was ranged from 2.5 to 28.1 µM, giving selectivity index (HepG2/*Pf*W2) superior to 110, except for **1c-(*R*)**, and closed to 4 170 for **1d-(*R*)**.

Compounds			Activity - IC_{50} (nM)		Eudysmic ratio	
Series	R_1		*Pf*3D7[a]	*Pf*W2[b]	*Pf*3D7	*Pf*W2
1	AQ	**1a-(*S*)**	5.0 ± 0.51	6.5 ± 1.26	1.4	2.1
		1a-(*R*)	6.8 ± 1.33	3.1 ± 0.38		
		1b-(*S*)	26.5 ± 1.61	9.2 ± 1.06	2.0	3.2
		1b-(*R*)	53.6 ± 5.08	29.3 ± 4.9		
		1c-(*S*)	75.7 ± 9.59	63.0 ± 3.74	1.7	1.2
		1c-(*R*)	45.1 ± 5.43	76.5 ± 5.06		
		1d-(*S*)	< 40	42.3 ± 10.5	nd	35
		1d-(*R*)	2.36 ± 0.2	1.2 ± 0.2		
	AF	**2a-(*R*)**	33.3 ± 4.06	16.7 ± 2.3	nd	nd
2	AQ	**3a-(*S*)**	6.8 ± 2.2	12.7 ± 5.8	1.7	2.0
		3a-(*R*)	11.4 ± 3.9	6.2 ± 0.2		
		3b-(*S*)	34.9 ± 2.0	18.5 ± 9.2	14.2	14.6
		3b-(*R*)	494.9 ± 176.7	271.2 ± 3.7		
		3c-(*S*)	14.1 ± 1.5	7.0 ± 0.8	2.3	1.9
		3c-(*R*)	6.2 ± 3.7	3.6 ± 0.4		
		3d-(*S*)	41.0 ± 6.4	19.6 ± 1.5	2.9	3.9
		3d-(*R*)	13.9 ± 7.1	5.0 ± 2.5		
	4-AF	**4a-(*R*)**	57.1 ± 8.12	55.3 ± 7.41	nd	nd
		4c-(*R*)	> 1 000	> 1 000	nd	nd
		4d-(*R*)	482.0 ± 110.9	> 500	nd	nd
Chloroquine			75.9 ± 3.0	198.8 ± 27.0		
Mefloquine			79.7 ± 8.5	31.8 ± 1.0		

[a]*Pf*3D7: CQ-S, MQ-diminished sensibility ; [b]*Pf*W2: CQ-R, MQ-S

Conclusion

Hybrids were synthesized with good yields following a synthesis in 5 to 7 steps. Most of evaluated compounds were more active than the CQ and MQ (whatever the strain). Interestingly, **1d-(*R*)** shows the best activity, inferior to 3 nM, and selectivity index. The benzhydryl- and trityl-ethane diamine turned out as the best EPI. The promising couple **1b** has a good selectivity index, higher than 980. Moreover, eudysmic ratio were found, and was even high for **1d** and **3b**, proving the added value of asymmetric synthesis.

Thanks to these first results, the covalent conjugation of enantiopure AQ and AF-based antiplasmodial compound with EPI is promising for next studies.

References: [1]World Malaria Report, WHO, **2019** ; [2]Guidelines for the Treatment of malaria, 3[RD] edition, WHO, 2015 ; [3]Saunders, Vanachayangkul, Lon, *N. Engl. J. Med*. **2014**, 371 (5), 484–485 ; [4]Burgess, Selzer, Kelly, *et al. J. Med. Chem*. **2006**, 49 (18), 5623–5625 ; [5]Jonet, Dassonville-Klimpt, Da Nascimento, *et al. Tetrahedron : Asymmetry*. **2011**, 22 (2), 138-148 ; [6a]Mullié, Taudon, Degrouas, *et al. Malaria Journal*. **2014**, 13:407 ; [6b]Jonet, Dassonville-Klimpt, Mullié-Demailly, *et al*. EP 11154229. Déposé le 11.02.2011 ; [7]Bentzinger, De Souza, Mullié, *et al. Tetrahedron : Asymmetry*. **2016**, 27 (1), 1-11 ; [8]Mullié, Jonet, Desgrouas, *et al. Malaria Journal*. **2012**, 11:65 ; [9]Bhattacharjee, Kyle, Vennerstrom, *et al. J. Chem. Inf. Comput. Sci*. **2002**, 42 (5), 1212-1220.

6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020
sponsored: MDPI *pharmaceuticals*