The 8th International Electronic Conference on Medicinal Chemistry (ECMC 2022)
01–30 NOVEMBER 2022 | ONLINE

Design, synthesis and antimicrobial activities of quinoline-based FabZ inhibitors as promising antimicrobial drugs

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

Laurie Bibens [1,*], Jean-Paul Becker [1], Nadine Lemaitre [1], François Peltier [1], Virginie Morel [1], Céline Damiani [1], Nicolas Taudon [2], Alexandra Dassonville-Klimpt [1] and Pascal Sonnet [1]

[1] AGIR, UR 4294, Université de Picardie Jules Verne, Amiens, France;
[2] Unité de Développements Analytiques et Bioanalyse, IRBA, Brétigny-sur-Orge, France.

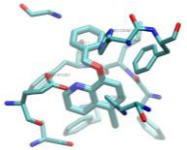
* Corresponding author: laurie.bibens@u-picardie.fr

Design, synthesis and antimicrobial activities of quinoline-based FabZ inhibitors as promising antimicrobial drugs

In silico evaluation of physico-chemical properties

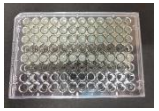
Molecular docking

Rational design
Structural analysis
Design of new quinolines



Synthesis of potential inhibitors

In vitro biological evaluations
MICs (*Sa*, *Ec* and *Pa*)
IC_{50} (*Pf* and HepG2)



Hit identification

Mode of action direct research
FabZ inhibitory potential

Mode of action indirect research
Lipidomic, metabolomic and proteomic analysis

ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE

Abstract:

Up to now, antimicrobial resistance is one of the biggest public health challenges. Multi-resistance is particularly worrying in both Gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli* for instance, and parasites such as *Plasmodium falciparum*.

Consequently, developing new compounds with original and selective antimicrobial modes of action is critical. Fatty acids are essential to maintain the vital integrity of the bacterial membrane. Their biosynthesis involves the fatty acid synthase-II (FAS-II) system which is exclusively found in germs. Furthermore, the amino-acid sequences of the FAS-II enzymes active site are well conserved in the microbial pathogens. As proves of concept, Isoniazid, a well-known antituberculous compound, and Afabicin – currently in clinical development to treat drug resistant staphylococci infections- target InhA or FabI, FAS-II enzymes. In this work, we focus on another important FAS-II enzyme, FabZ, to design new antimicrobials with limited side effects and minimal chances of cross resistance with existing drugs targeting other pathways.

In the Protein Data Bank (PDB), several FabZ 3D structures from different organisms have been reported. Among known FabZ inhibitors, the NAS91 family, with a quinoline core, inhibits *Pf*FabZ with IC_{50} in the micromolar range. Additionally, co-crystal NAS91 family-*Pf*FabZ complex structures are described in the PDB. Based on these data, we have started a FabZ-based drug design study to develop novel quinoline structures. Herein, the in silico study, synthesis of new quinolines and biological results will be exposed.

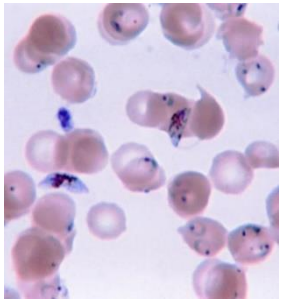
Keywords: antibioresistance; antimicrobial drugs; FabZ; fatty acid biosynthesis; quinolines.

Antimicrobial resistance

Public health issue:

2019: 1.3 M deaths due to antibioresistance worldwide
2050 forecast: 10 M deaths/year with new treatments
ESKAPEE bacteria:

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacter* spp.
- *Escherichia coli*



P. falciparum

2020: 627,000 deaths due to *Plasmodium* spp worldwide

Development of new treatments:

- Selective
- With original modes of action

→ New target: fatty acids biosynthesis *via* the enzymes type II *fatty acid synthase* system (FAS-II)

Murray *et al. The Lancet*, **2022**, 399, 629-655. O'Neill, *Review on Antimicrobial Resistance*, **2016**, Final report. *World Health Organization*, World Malaria Report 2021, **2021**.

Antimicrobial resistance

Public health issue:

2019: **1.3 M** deaths due to antibioresistance worldwide
2050 forecast: 10 M deaths/year with new treatments
ESKAPEE bacteria:

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacter* spp.
- *Escherichia coli*

P. falciparum

2020: **627,000** deaths due to ***Plasmodium* spp** worldwide

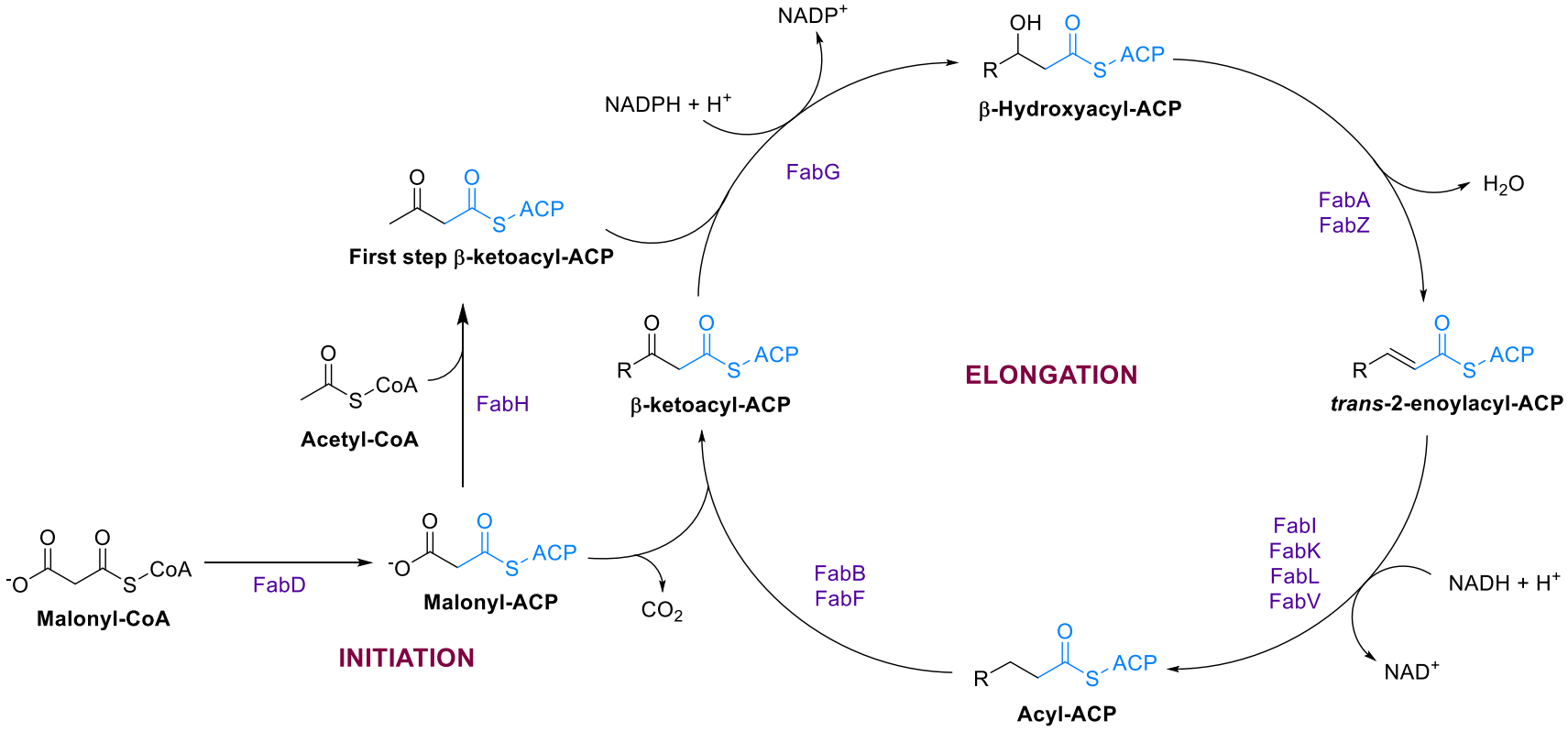
Development of new treatments:

- Selective
- With original modes of action

→ New target: fatty acids biosynthesis *via* the enzymes type II *fatty acid synthase* system (FAS-II)

Murray *et al. The Lancet*, **2022**, 399, 629-655. O'Neill, *Review on Antimicrobial Resistance*, **2016**, Final report. *World Health Organization*, World Malaria Report 2021, **2021**.

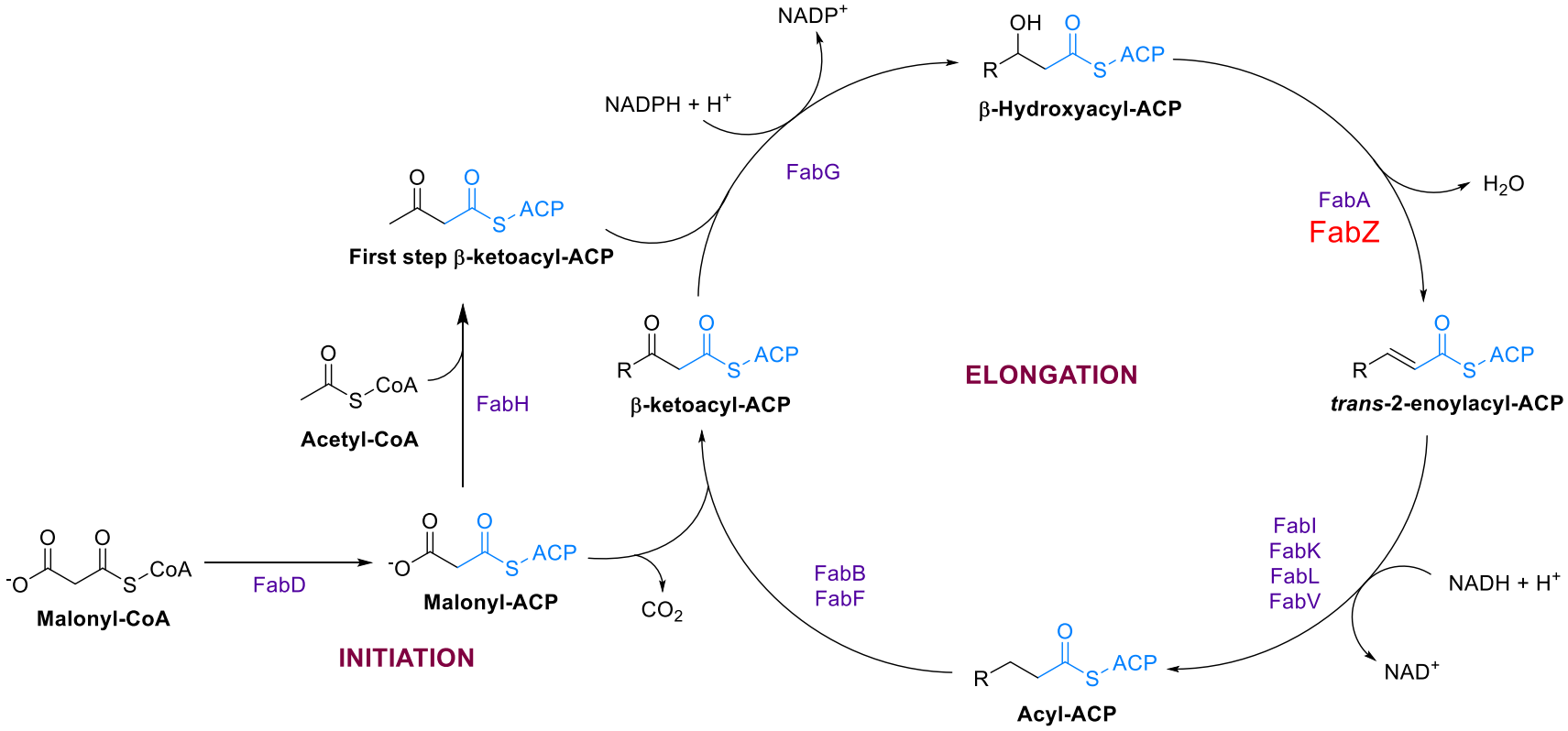
The FAS-II system



Role: Fatty acid biosynthesis

Essential to maintain the vital integrity of the bacterial membrane
Specific to pathogens: limited side effects

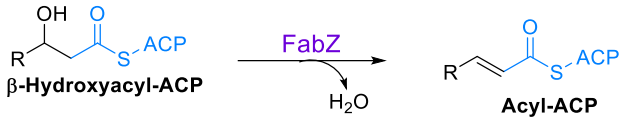
The FAS-II system



Role: Fatty acid biosynthesis

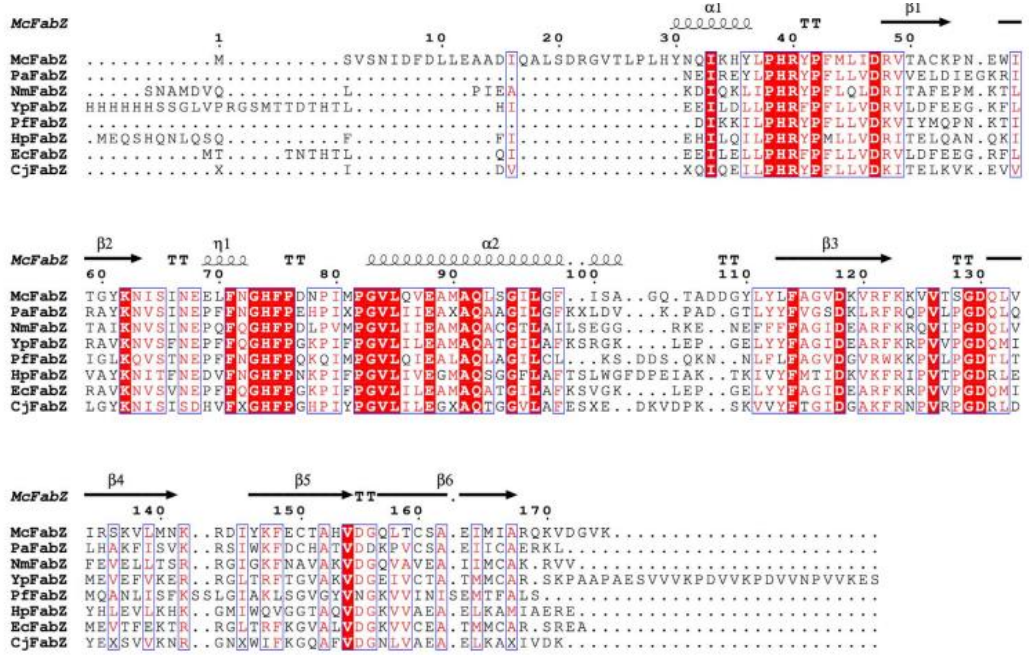
Essential to maintain the vital integrity of the bacterial membrane
Specific to pathogens: limited side effects

β-hydroxyacyl-ACP dehydratase (FabZ)



Ubiquitous in pathogens
→ broad-spectrum antibacterial

Protein Data Bank (PDB): crystal structures
→ rational design

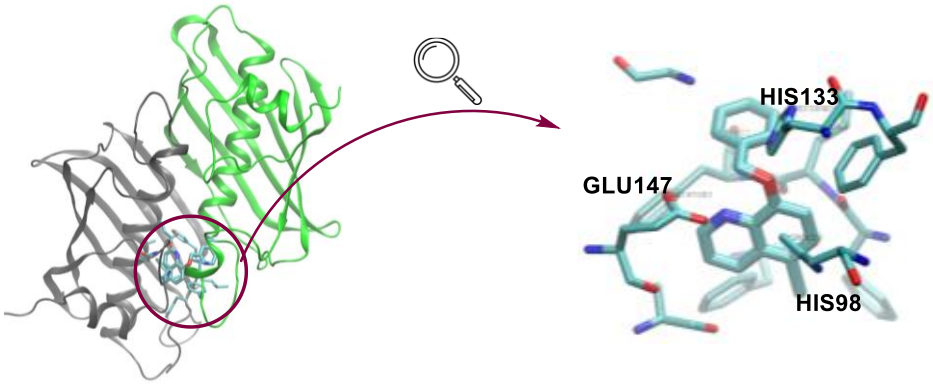


Amino-acid sequences of *Mc*FabZ, *Pa*FabZ, *Nm*FabZ, *Yp*FabZ, *Pf*FabZ, *Hp*FabZ, *Ec*FabZ and *Cj*FabZ

Crystal structures of *Hp*FabZ (PDB code: 2GLL)

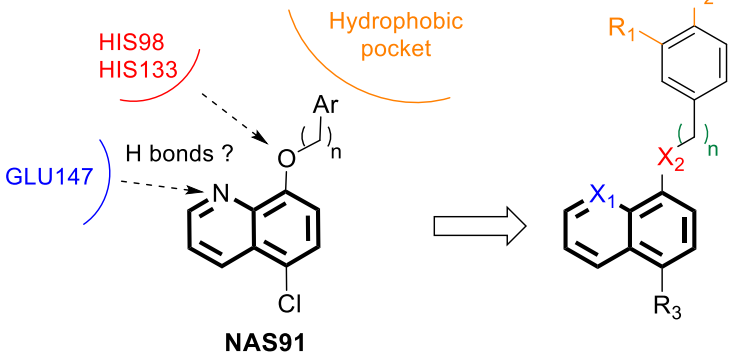
Zhang *et al.J. Biol. Chem.*, **2008**, 283, 5370-5379. Tasdemir *et al. J. Med. Chem.*, **2006**, 49, 3345-3353. Kumar *et al. BBA-General Subjects*, **2018**, 1862, 726-744.

Structural analysis and design of potential FabZ inhibitors



Active site of *Pf*FabZ-NAS91-10 co-crystal

Catalytic pocket of *Pf*FabZ-NAS91-10 co-crystal



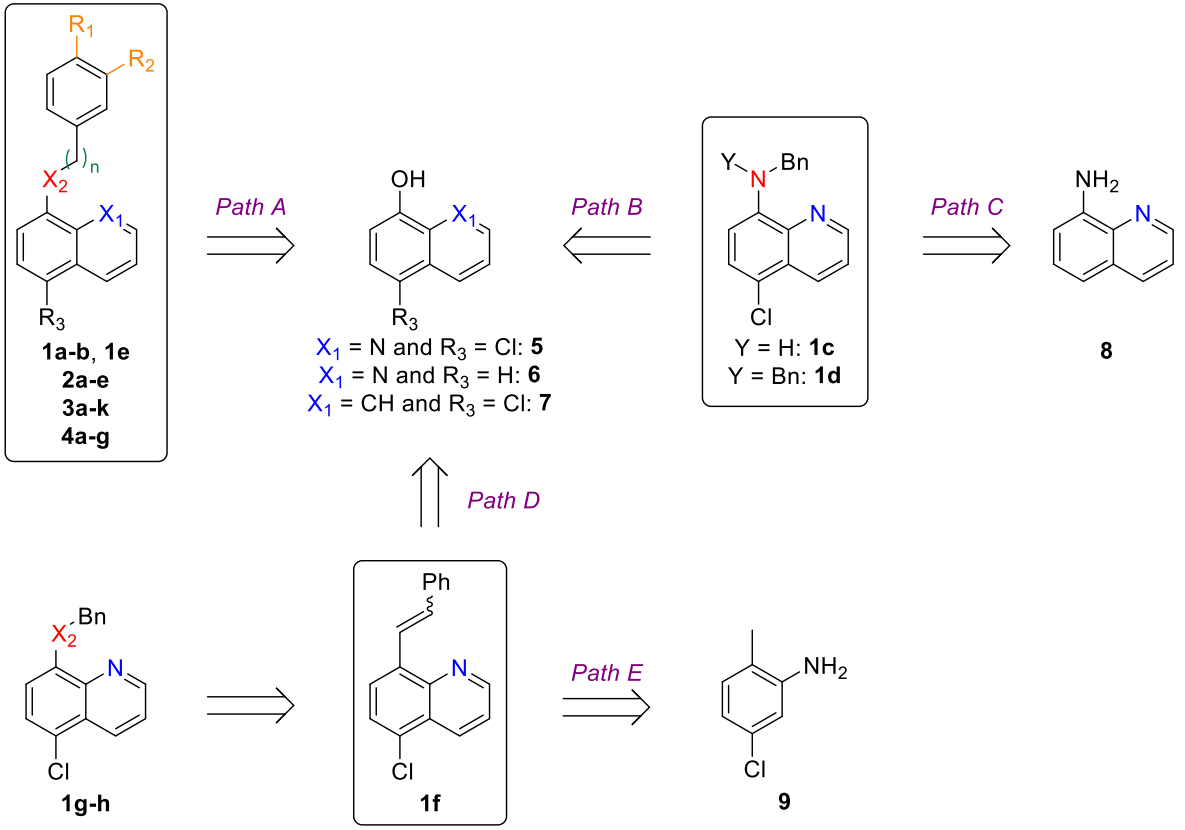
Series **1**:
X_1 = N or CH, X_2 = NH, O, NPh, CH_2 or CO
n = 1, R_1, R_2 = H, R_3 = Cl or H

Series **2**:
X_1 = N or CH, X_2 = O, n = 2 or 3,
R_1, R_2 = H, R_3 = Cl or H

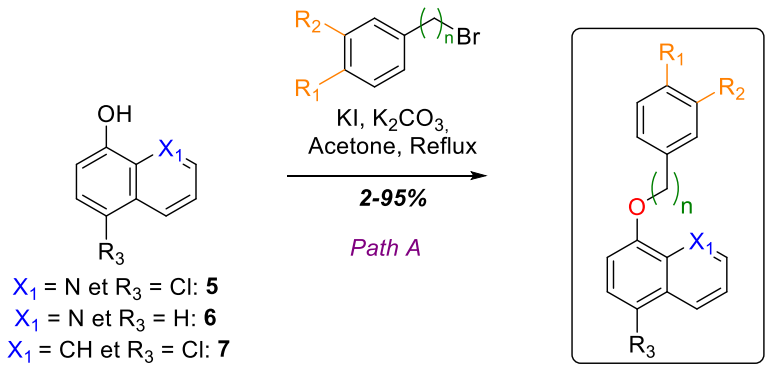
Series **3**:
X_1 = N, X_2 = O, n = 1,
R_1, R_2 = Cl, OMe, Me, CF_3, H,
R_3 = Cl or H

Series **4**:
X_1 = N, X_2 = O, n = 2
R_1, R_2 = Cl, CO_2Me, OMe or CF_3
R_3 = Cl or H

Retrosynthesis of series 1-4



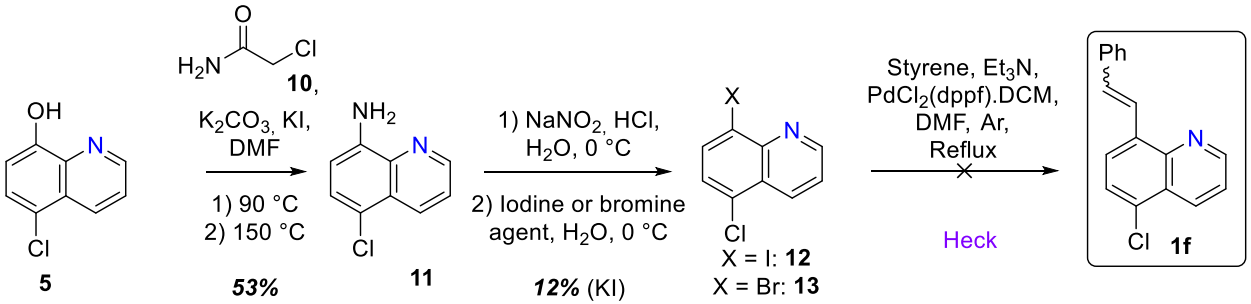
Synthesis of series 1-4 *via* path A



X_1 = N et R_3 = Cl: **5**
X_1 = N et R_3 = H: **6**
X_1 = CH et R_3 = Cl: **7**

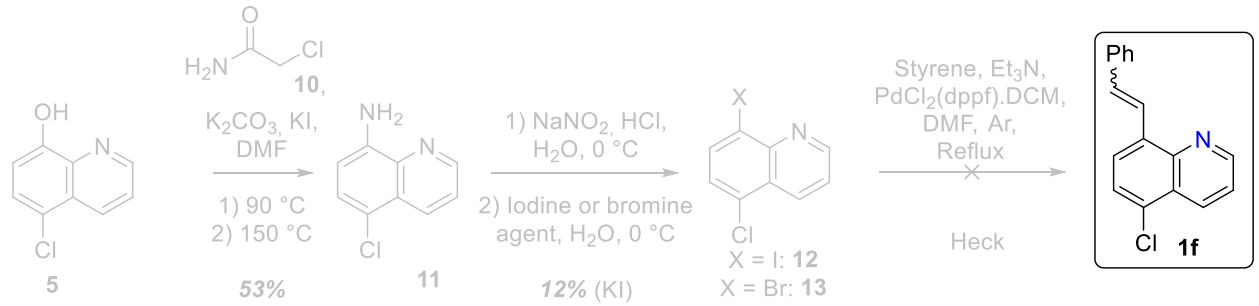
Series	Compounds	Yields
1	**1a-b, 1e**	74-88%
2	**2a-e**	21-95%
3	**3a-k**	48-96%
4	**4a-g**	20-47%

Synthesis of series 1-4 *via* path D

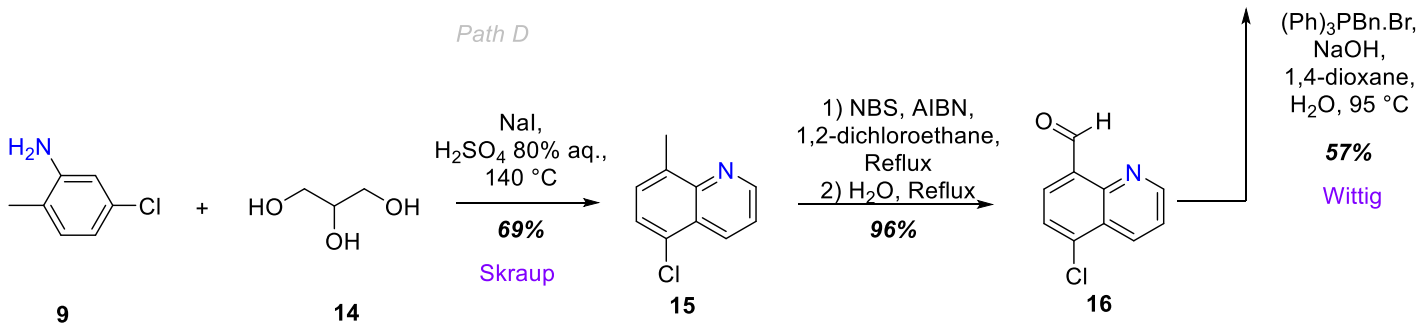


Path D

Synthesis of series 1-4 *via* path E

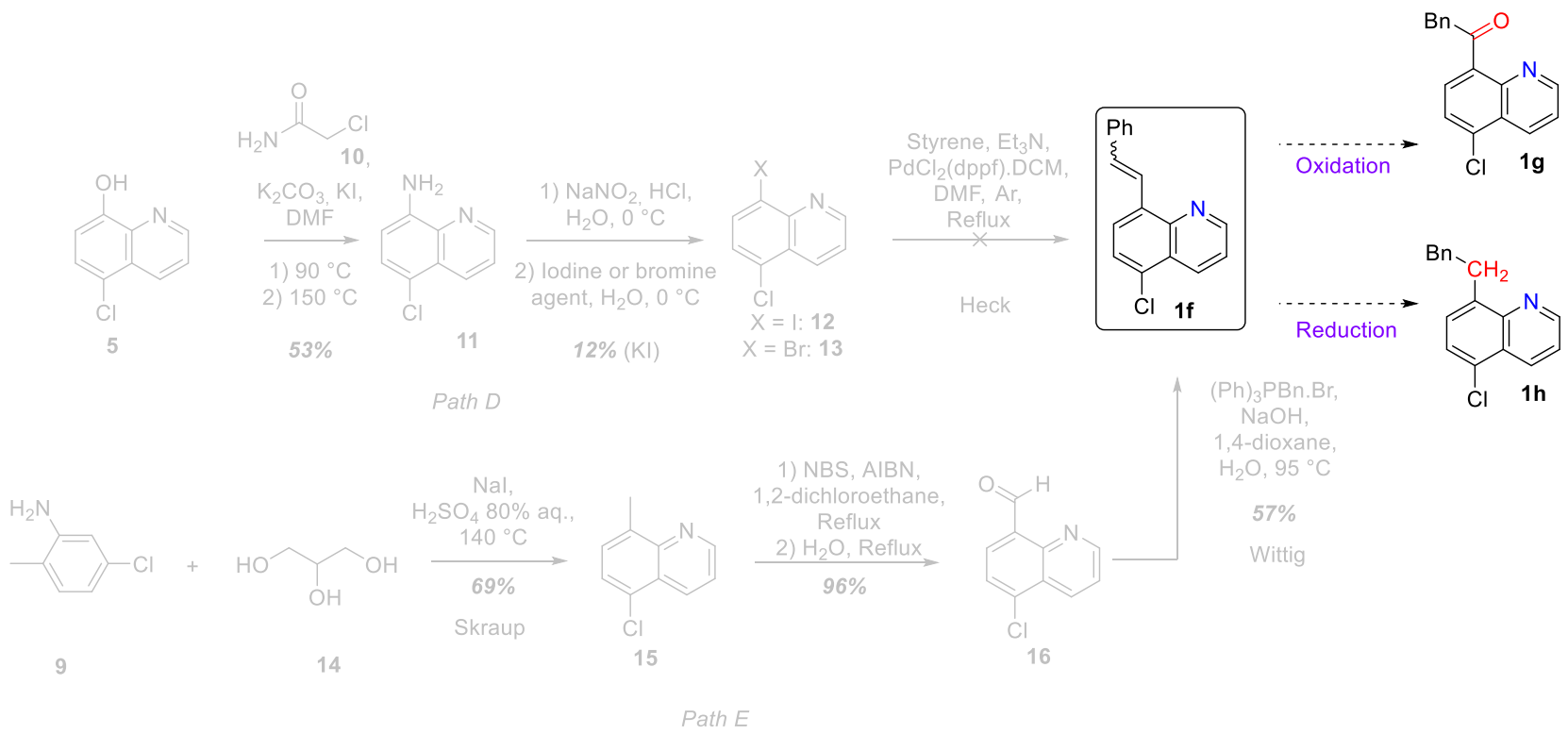


Path D

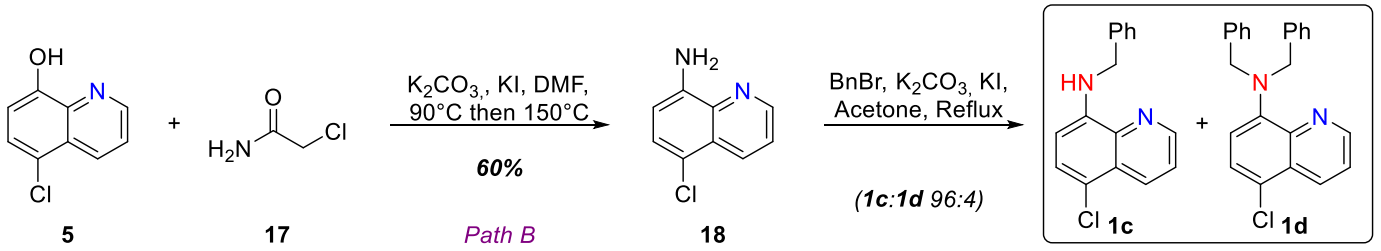


Path E

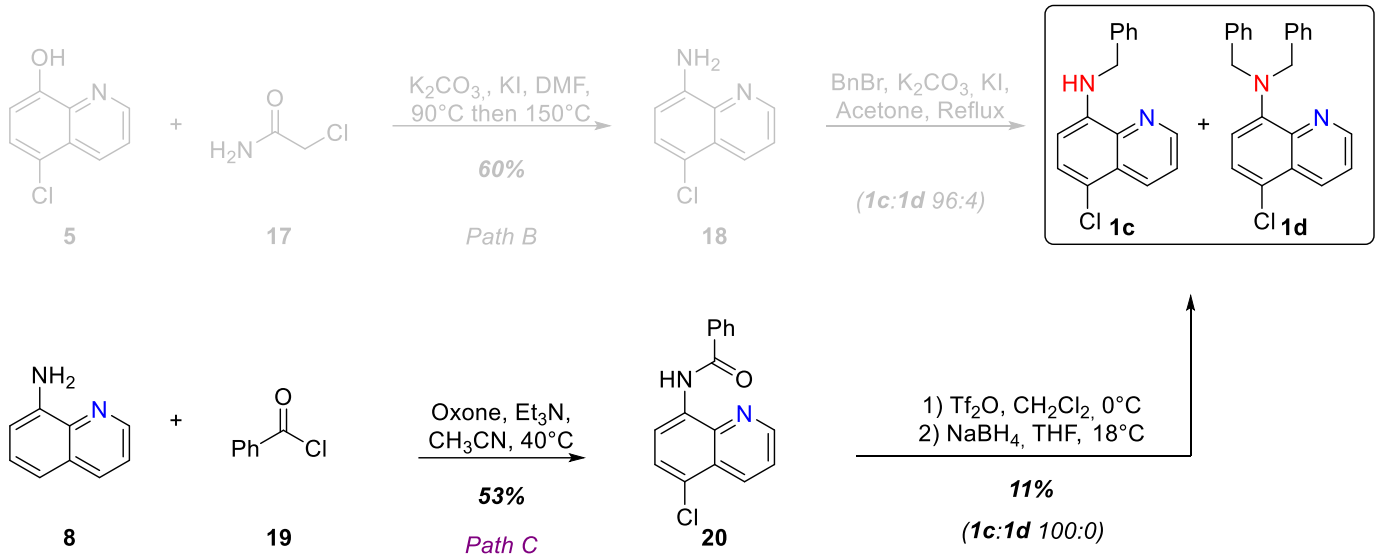
Synthesis of compounds 1g and 1h



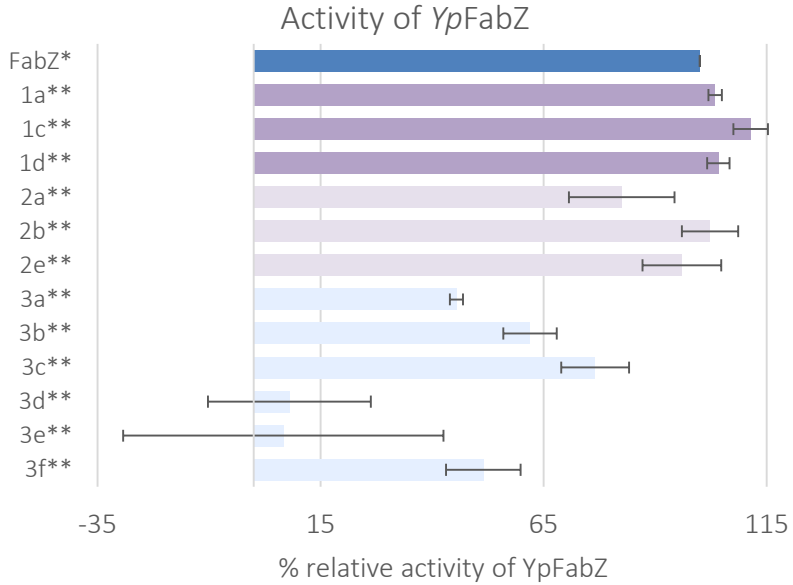
Synthesis of compounds 1c and 1d *via* paths B and C

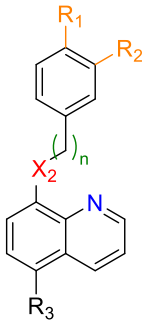


Synthesis of compounds 1c and 1d *via* paths B and C



Biological studies



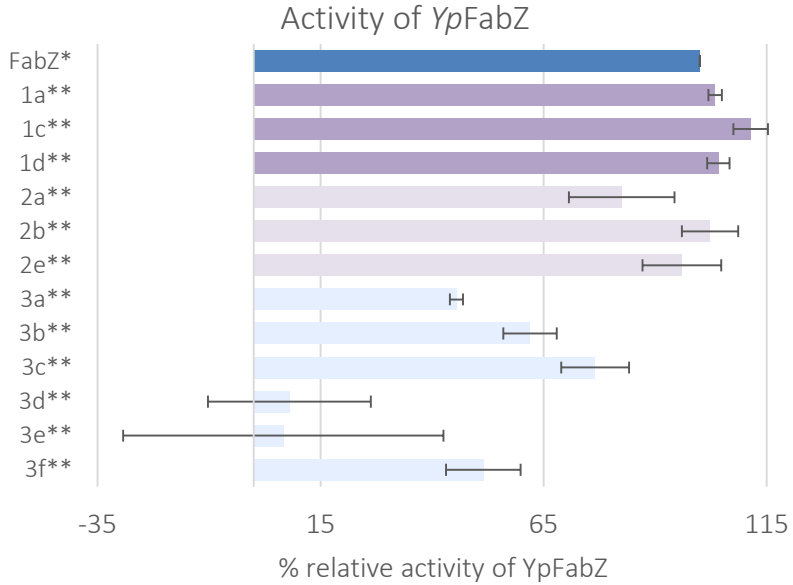


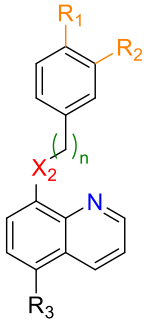
Compounds	X_2	n	R_1	R_2	R_3
1a	O	1	H	H	Cl
1c	NH	1	H	H	Cl
1d	NPh	1	H	H	Cl

* Activity of FabZ without inhibitor of presence of crotonyl-CoA
** Activity of FabZ with potential inhibitors at 100 µM in presence of crotonyl-CoA

Series	Most active compounds	Antibacterial activities (*Sa*, *Ec* and *Pa*)	Antiplasmodial activities (IC_{50})	Inhibition of *Yp*FabZ at 100 µM	Cytotoxicity IC_{50}(HepG2)
1	1d	None	15-19 µM (*Pf* W2/3D7)	None	ND

Biological studies



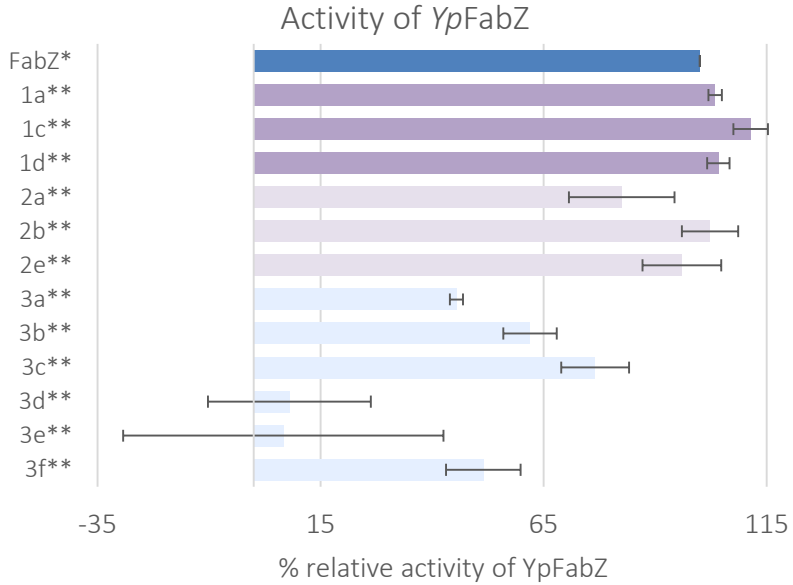


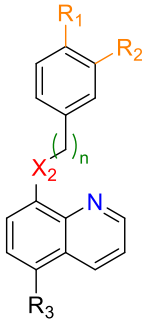
Compounds	X_2	n	R_1	R_2	R_3
1a	O	1	H	H	Cl
1c	NH	1	H	H	Cl
1d	NPh	1	H	H	Cl
2a	O	2	H	H	Cl
2b	O	3	H	H	Cl
2e	O	2	H	H	H

* Activity of FabZ without inhibitor of presence of crotonyl-CoA
** Activity of FabZ with potential inhibitors at 100 µM in presence of crotonyl-CoA

Series	Most active compounds	Antibacterial activities (*Sa*, *Ec* and *Pa*)	Antiplasmodial activities (IC_{50})	Inhibition of *Yp*FabZ at 100 µM	Cytotoxicity IC_{50}(HepG2)
1	1d	None	15-19 µM (*Pf* W2/3D7)	None	ND
2	2a	MIC(*Sa*) = 32 µg/mL MIC(*Ec*) = 128 µg/mL	15 µM (*Pf* W2)	17%	ND

Biological studies



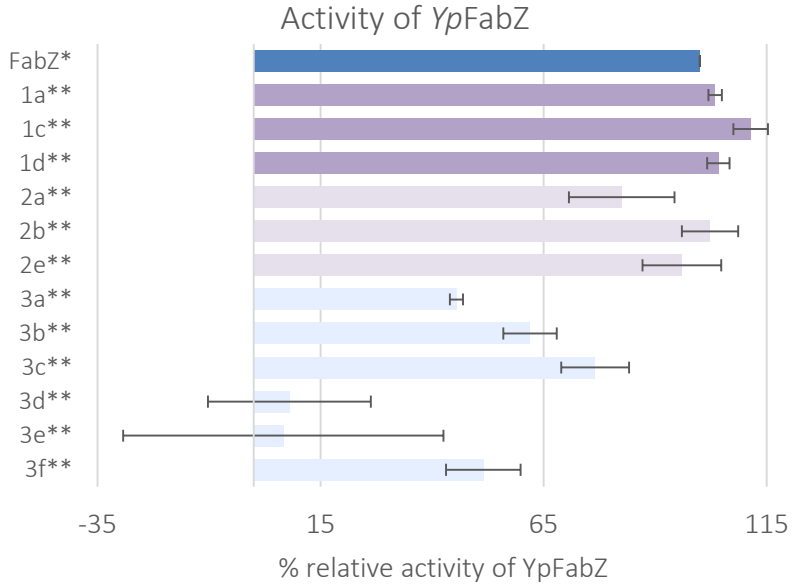


* Activity of FabZ without inhibitor of presence of crotonyl-CoA
** Activity of FabZ with potential inhibitors at 100 µM in presence of crotonyl-CoA

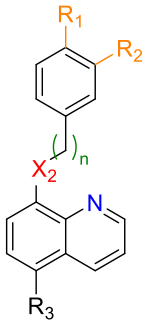
Compounds	X_2	n	R_1	R_2	R_3
1a	O	1	H	H	Cl
1c	NH	1	H	H	Cl
1d	NPh	1	H	H	Cl
2a	O	2	H	H	Cl
2b	O	3	H	H	Cl
2e	O	2	H	H	H
3a	O	1	Cl	H	Cl
3b	O	1	OMe	H	Cl
3c	O	1	Me	H	Cl
3d	O	1	Cl	Cl	Cl
3e	O	1	H	Cl	Cl
3f	O	1	H	Cl	H

Series	Most active compounds	Antibacterial activities (*Sa*, *Ec* and *Pa*)	Antiplasmodial activities (IC_{50})	Inhibition of *Yp*FabZ at 100 µM	Cytotoxicity IC_{50}(HepG2)
1	1d	None	15-19 µM (*Pf* W2/3D7)	None	ND
2	2a	MIC(*Sa*) = 32 µg/mL MIC(*Ec*) = 128 µg/mL	15 µM (*Pf* W2)	17%	ND
3	3a-f	None	≈ 20 µM (*Pf*W2, 3a, d, f)	23-93%	> 50 µM

Biological studies



* Activity of FabZ without inhibitor of presence of crotonyl-CoA
** Activity of FabZ with potential inhibitors at 100 µM in presence of crotonyl-CoA



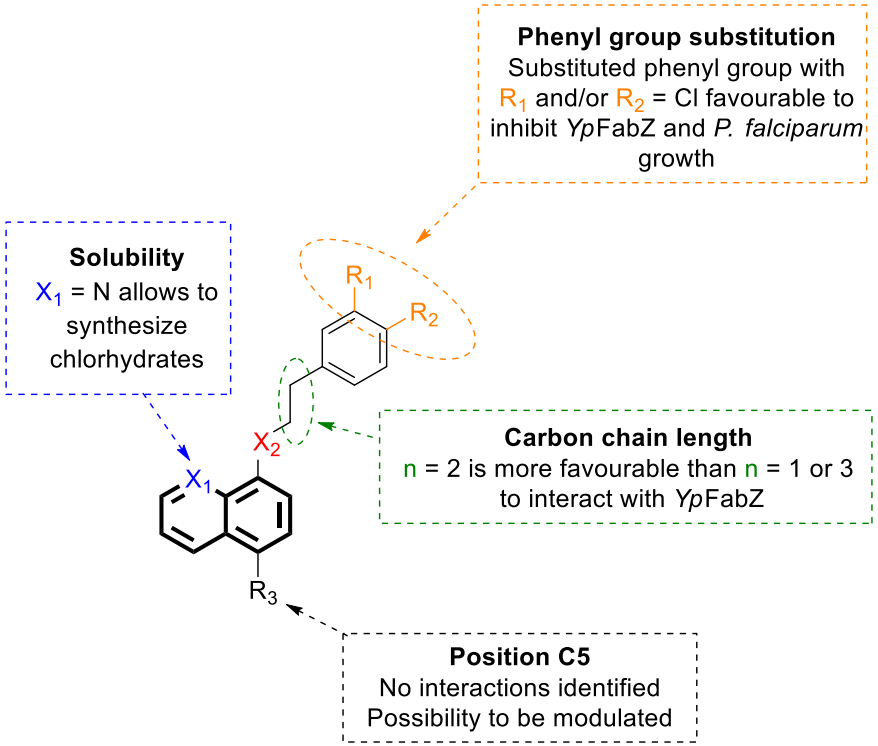
Compounds	X_2	n	R_1	R_2	R_3
1a	O	1	H	H	Cl
1c	NH	1	H	H	Cl
1d	NPh	1	H	H	Cl
2a	O	2	H	H	Cl
2b	O	3	H	H	Cl
2e	O	2	H	H	H
3a	O	1	Cl	H	Cl
3b	O	1	OMe	H	Cl
3c	O	1	Me	H	Cl
3d	O	1	Cl	Cl	Cl
3e	O	1	H	Cl	Cl
3f	O	1	H	Cl	H
4a	O	2	Cl	Cl	Cl
4b	O	2	OMe	H	Cl
4c	O	2	CO_2Me	H	Cl
4d	O	2	Cl	H	Cl
4e	O	2	Cl	H	H
4f	O	2	CO_2Me	H	H
4g	O	2	H	Cl	H

Series	Most active compounds	Antibacterial activities (*Sa*, *Ec* and *Pa*)	Antiplasmodial activities (IC_{50})	Inhibition of *Yp*FabZ at 100 µM	Cytotoxicity IC_{50}(HepG2)
1	1d	None	15-19 µM (*Pf* W2/3D7)	None	ND
2	2a	MIC(*Sa*) = 32 µg/mL MIC(*Ec*) = 128 µg/mL	15 µM (*Pf* W2)	17%	ND
3	3a-f	None	≈ 20 µM (*Pf*W2, **3a, d, f**)	23-93%	> 50 µM
4	4a, e, g	None	≈ 20 µM (*Pf*W2)	ND	ND

Conclusion

- 29 compounds of series **1-4** synthesized
- **3a-f** inhibit the activity of *Yp*FabZ at 100 µM (23-93%)
- **2a** slightly active against *Sa*, *Ec* and *Yp*FabZ
- **2a** slightly active against *Pf*

First Structure-Activity Relationships



Acknowledgments

AGENCE INNOVATION DÉFENSE

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DES ARMÉES

Région Hauts-de-France

UNIVERSITÉ de Picardie Jules Verne

AGIR
Agents Infectieux, Résistance et chimiothérapie