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Design, synthesis and antimicrobial activities of potential FabZ inhibitors

Laurie Bibens [1,*], Jean-Paul Becker [1], Nadine Lemaitre [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

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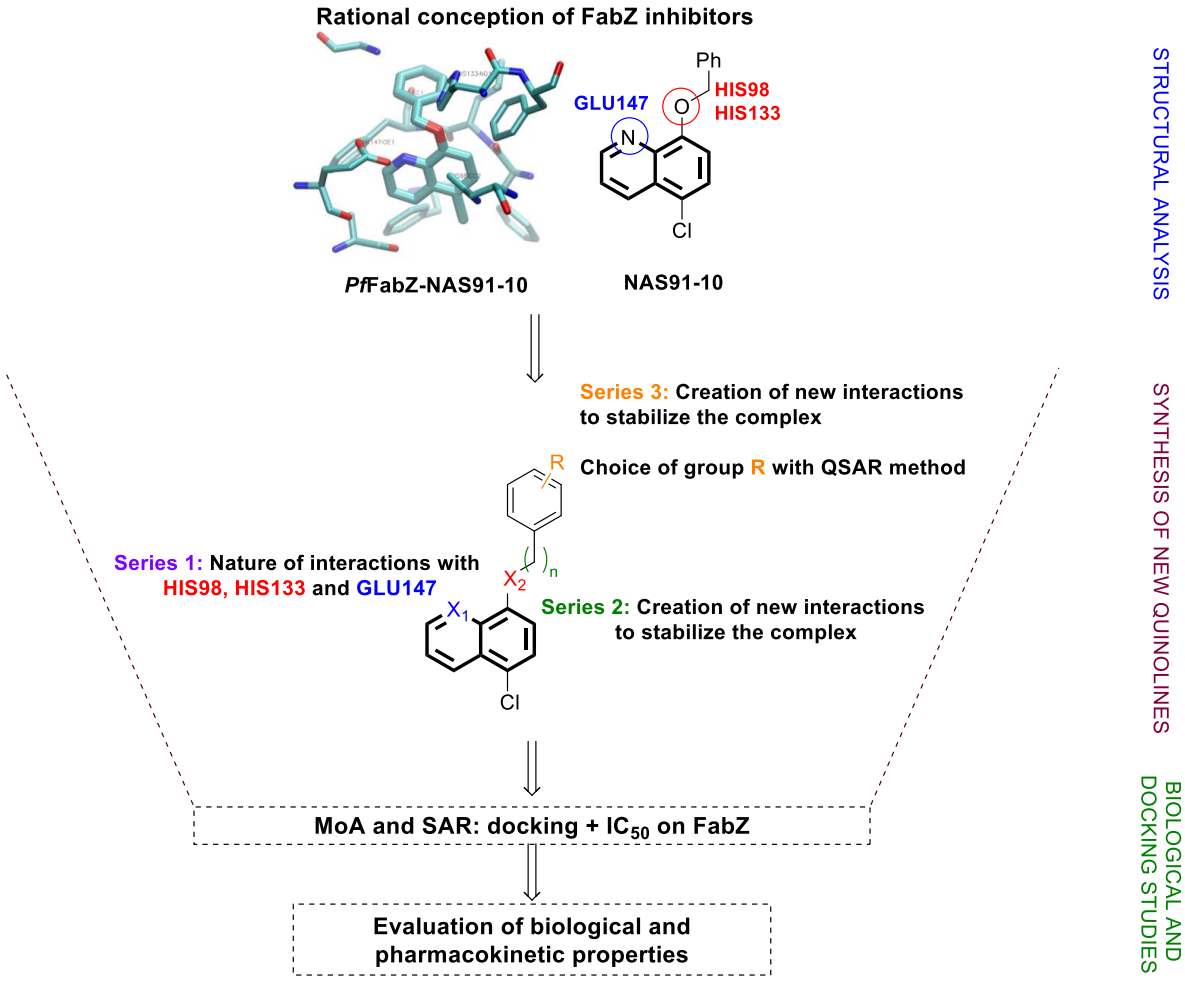
Design, synthesis and antimicrobial activities of potential FabZ inhibitors



Abstract:

To date, **antimicrobial resistance** is one of the biggest public health challenges. Multi-drug resistance is particularly worrying in both Gram-negative bacteria such as *P. aeruginosa* or *E. coli* and parasites such as *P. falciparum*.

Therefore, it is urgent to propose novel treatments with original and selective antimicrobial modes of action. Lipids are crucial to maintain the bacterial membrane integrity. Their biosynthesis involves both fatty acid synthase-I (FAS-I) and fatty acid synthase-II (**FAS-II**) systems. While FAS-I is present in both humans and microbes, FAS-II is uniquely found in germs. Furthermore, the FAS-II enzyme sequences have a high level of conservation in the microbial pathogens. Targeting these enzymes, especially **FabZ**, a β-hydroxyacyl-acyl carrier protein (ACP) dehydratase, represents a promising strategy to design **broad-spectrum antimicrobials** with **limited side effects** and offers **minimum chances of cross-resistance** with existing drugs targeting others pathways.

Few FabZ inhibitors were described while several FabZ 3D structures from different organisms such as *P. aeruginosa*, *P. falciparum* and *H. pylori* have been reported (Protein Data Bank: PDB). Among known FabZ inhibitors, the **NAS91 family**, with a quinoline core, inhibits *Pf*FabZ with IC_{50} in a micromolar range. Additionally, co-crystal NAS91 family-*Pf*FabZ complex structures are described in the PDB (3AZA, 3AZ9, 3AZB). Based on these data, we have started a **FabZ-based drug design study** to propose new **quinoline structures**. The *in silico* study, synthesis of some new quinolines and the first biological results will be exposed.

Keywords: Antimicrobials; drug design; FabZ; multi-drug resistance.

Introduction

PUBLIC HEALTH ISSUE

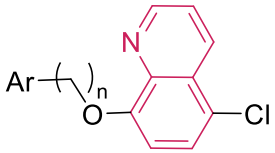
Antibiotic resistance: > 700,00 deaths/year worldwide[1]

Plasmodium spp.: 409,000 deaths in 2019 worldwide[2]

NEW TARGET

Type II fatty acid synthase system (**FAS-II**)

FabZ: β-hydroxyacyl-acyl carrier protein (ACP) dehydratase



n = 1 and Ar = Ph: **NAS91-10** (3AZA)
n= 2 and Ar = Ph: **NAS91-11** (3AZB)
n = 0 and Ar = 3-hydroxy-5-chlorophenyl: **NAS91** (3AZ9)

ORIGINAL PHARMACOPHORE

Few **quinoline**-based inhibitors: **NAS91 family**

NAS91-10: IC_{50}(*Pf*FAbZ) = 7.4 µM, IC_{50}(*Pf*) = 12 µM[3]

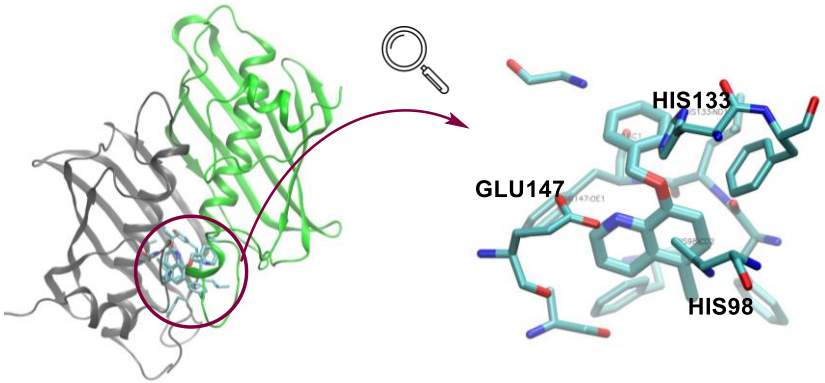
STRATEGY

FabZ-based drug design

Pharmacophore: **quinoline**

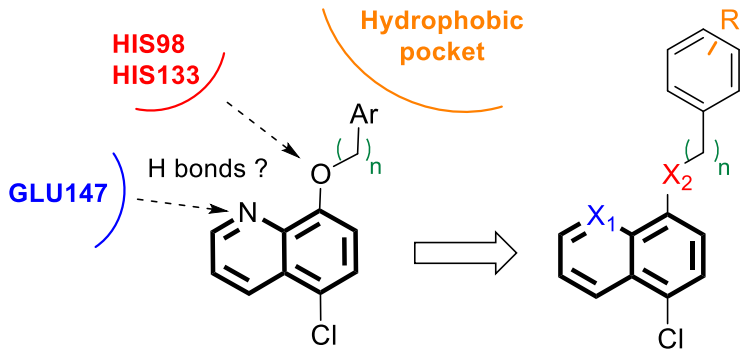
1. O'Neill, J., *Review on Antimicrobial Resistance,* **2016**, Final report. **2.** World Health Organization. Malaria. *www.who.int*, **2021**. **3.** Maity *et al*, Struct. *Biol.*, **2011**, 176, 238–249. **4.** Chen *et al*, *BMC Microbiology*, **2009**, *9*, 91–102.

Results and discussion: structural analysis and SAR study



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

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



STRUCTURAL ANALYSIS

Three main interactions between:

- HIS133 and O;
- HIS98 and O;
- GLU147 and quinolinic N.

Hydrogen bonds ?

STRUCTURE-ACTIVITY RELATIONSHIP STUDY

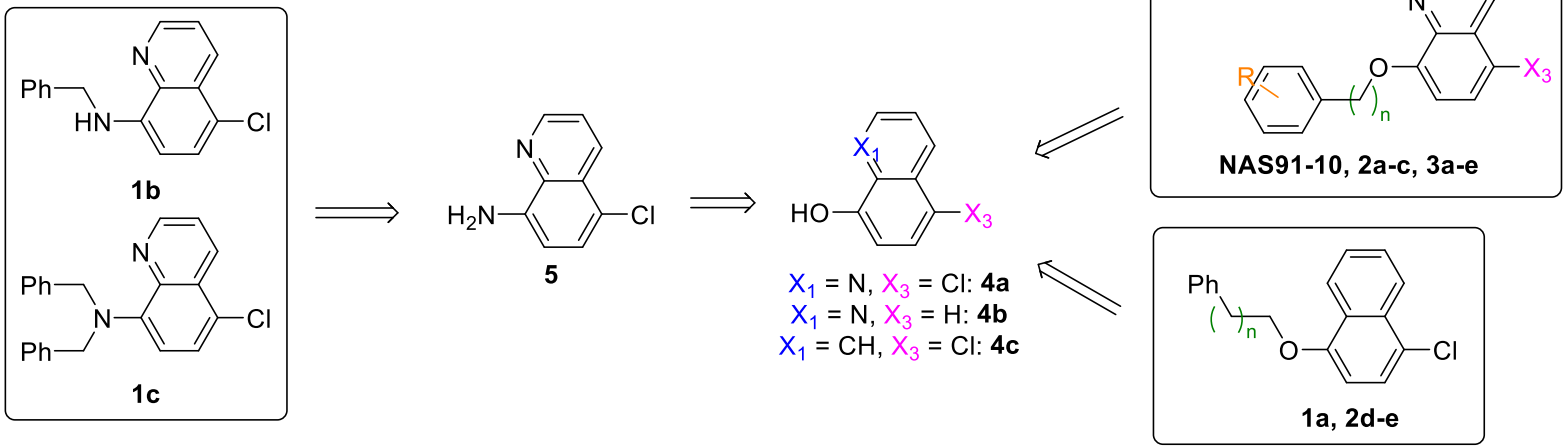
Pharmacomodulation of NAS91-10 to:

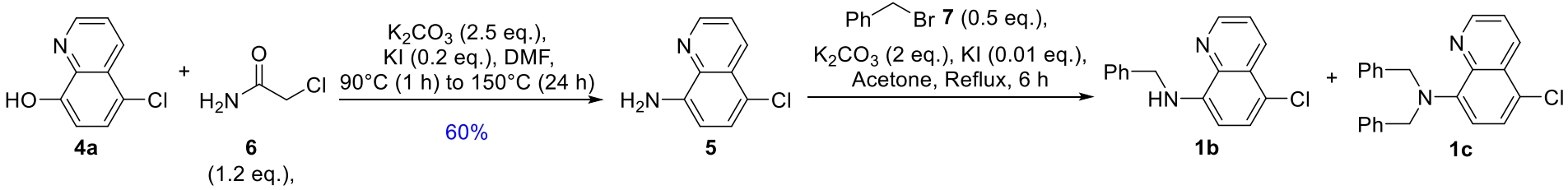
- Confirm the nature of interactions involved;
- Create new interactions and stabilize the complex.

→ Three series of new quinolines.

Results and discussion: synthesis of new quinolines

Fourteen compounds synthesized in one to three steps (7-95% yield)

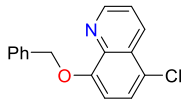
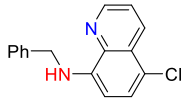
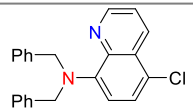
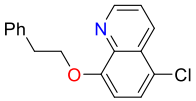
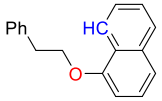
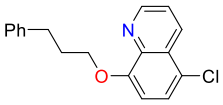




Best conditions : - 0.5 eq. of bromobenzene **7**
- 1b/1c : 95/5 (RMN ^{1}H)

Results and discussion: antimicrobial activities

→ All synthesized compounds were evaluated but only 2a showed antibacterial and antiplasmodial activities

Compounds		Purity (HPLC)	Antibacterial activity			Antiplasmodial activity	
			MIC (µg/mL)			IC_{50} (µM)	
Name	Structure		*P. aeruginosa* DSM 1117	*E. coli* DSM 1103	*S. aureus* CIP 103.429	*P. falciparum* 3D7	*P. falciparum* W2
NAS91-10		96%	> 256	> 256	> 256	> 40	> 40
1b		95%	> 256	> 256	> 256	> 40	> 40
1c		92%	> 256	> 256	> 256	15	19
2a		88%	> 256	128	32	29	> 40
2b		92%	> 256	> 256	> 256	23	> 40
2c		94%	> 256	> 256	> 256	> 40	> 40
Ciprofloxacine		/	0.0625	0.0625	0.0625	/	/
Mefloquine		/	/	/	/	0.032	0.010

Conclusions

- Three main interactions with FabZ: **O/HIS98**, **O/HIS133** and **N/GLU148**
- Fourteen compounds of series **I**, **II** and **III** synthesized
- Antibacterial activity: **2a** (*E. coli*, *S. aureus*) → FabZ inhibition ?
  Antiplasmodial activity: **2a**, **2b** and **1c** → *Pf*ACBP inhibition ?
- Prospects: enzymatic assays (*Yp*FabZ) and pharmacomodulation of **2a**

Acknowledgments

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