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Design, synthesis and biological study of novel quinoline-based drugs targeting non-tuberculous mycobacteria

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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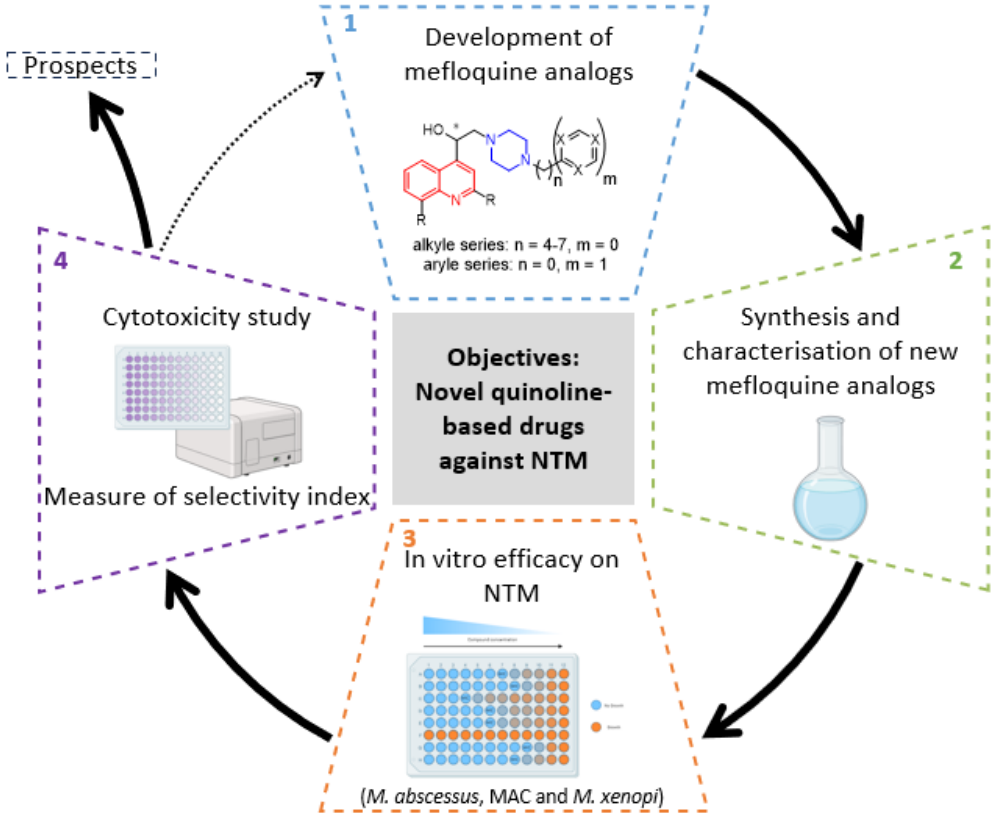
Design, synthesis and biological study of novel quinoline-based drugs targeting non-tuberculous mycobacteria



Abstract:

The emergence of non-tuberculous mycobacteria (NTM) infections, in Europe and North America, is higher than that of *M. tuberculosis* (*M. tb*). NTM are ubiquitous and opportunistic in persons with immunodeficiency or chronic lung disease. Among seven NTM with proven pulmonary pathogenicity, *M. avium* complex (MAC) and *M. abscessus* are the most common. Current NTM treatments are moderately efficient, as they were initially designed to cure *M. tb* infections. First-line treatments require the combination of at least three antibiotics with different mechanisms of action to limit cross-resistance over a long period (12 to 24 months). Consequently, it is urgent to develop new anti-NTM molecules more specific and more efficient to reduce treatment duration and overcome resistant strains. Two quinoline-based compounds, **bedaquiline** (**BQ**) and **mefloquine** (**MQ**) target the ATP synthase, a vital enzyme for mycobacteria. However, **BQ** is only used as a treatment of last resort due to many drug interactions and significant hepatic and cardiac side effects. **MQ** is safer than **BQ** but is moderately active against NTM (*e.g.*, MIC = 4 µg/mL on MAC). Recently, we developed a first series of **MQ** analogs active against MAC and *M. abscessus* with a better selectivity index (SI) than **MQ** (SI = 2.86 *vs* 0.38). In continuation of this work, new **MQ** analogs with piperazine core were designed, prepared by short asymmetric synthesis and characterized. The first *in vitro* antimycobacterial evaluations on several strains and cytotoxicity study were carried out.

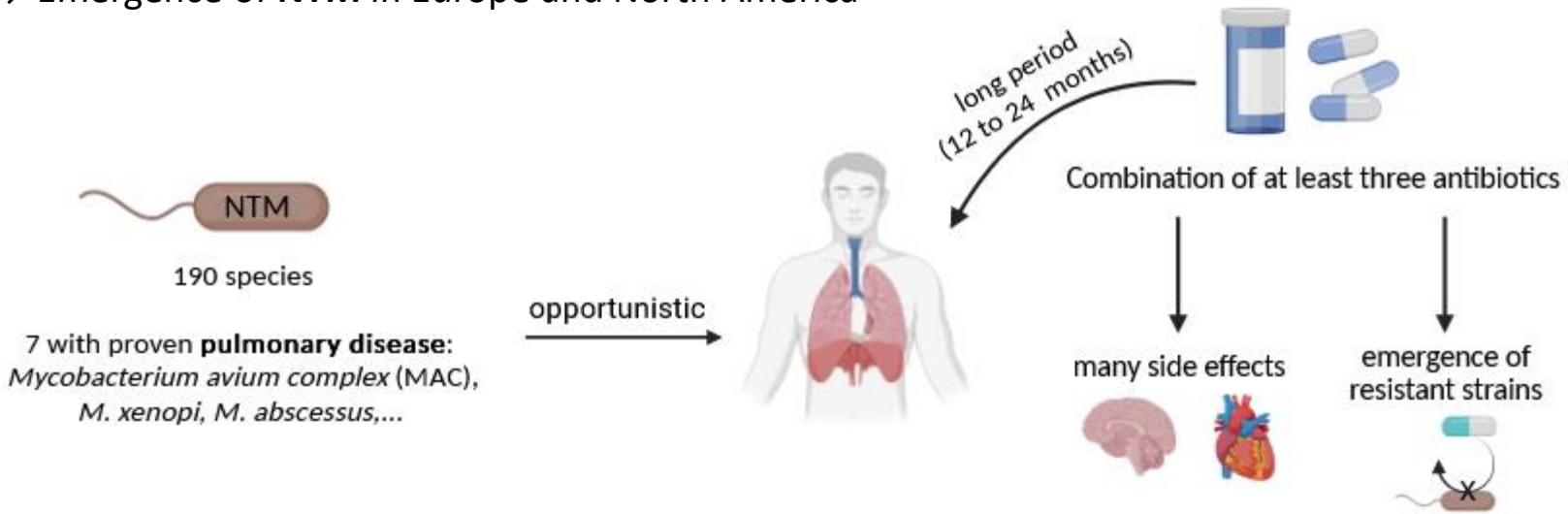
Keywords: amino-alcohol-quinolines; asymmetric synthesis; *in vitro* efficacy; non-tuberculous mycobacteria.

Introduction

Three categories of mycobacteria:

- tuberculosis mycobacteria
- leprae mycobacteria
- **non-tuberculous mycobacteria** (**NTM**)

→ Emergence of **NTM** in Europe and North America



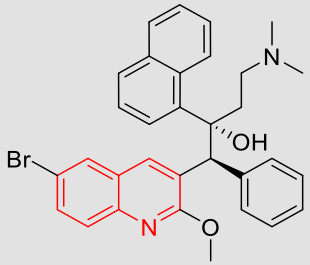
→ It is urgent to develop new anti-NTM molecules more specific and more efficient

References: Busatto, C. *et al*. *Tuberculosis,* **2019**, *114*, 127-134

Antimycobacterial quinolines

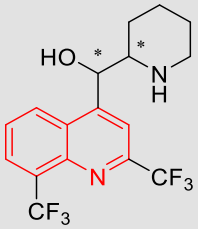
Two quinoline-based compounds: **bedaquiline** (**BQ**) and **mefloquine** (**MQ**)

(*R*,*S*)-BQ



MIC ≤ 0.015 μg/mL (MAC)
IC_{50} = 0.014 μg/mL (hERG)

MQ



MIC = 4 μg/mL (MAC)
IC_{50} = 1.5 ± 0.1 μg/mL (HepG2)

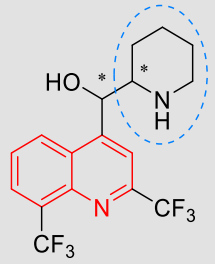
ATP synthase

BQ: treatment of last resort due to drug interactions and hepatic and cardiac side effects
MQ: safer than **BQ** but moderately activity against NTM

References: Brown-Eliott, B.A. *et al*. *Antimicrob. Agents and Chemother.*, **2017**, *61,* Patel, H. *et al*. *Tuberculosis*, **2019**, *117*, 79-84

Design of new amino-alcohol-quinolines (AAQ)

MQ



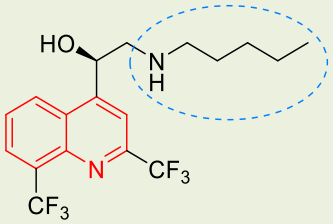
MIC = 4 µg/mL (MAC)
IC_{50} = 1.5 ± 0.1 µg/mL (HepG2)

SI = 0.4

modulation of amine moiety

conservation of quinoline pharmacophore

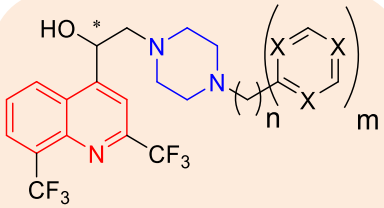
Previous work



Hit A
MIC = 4 µg/mL (MAC)
IC_{50} = 11.4 ± 0.4 µg/mL (HepG2)

SI = 2.9

addition of piperazine

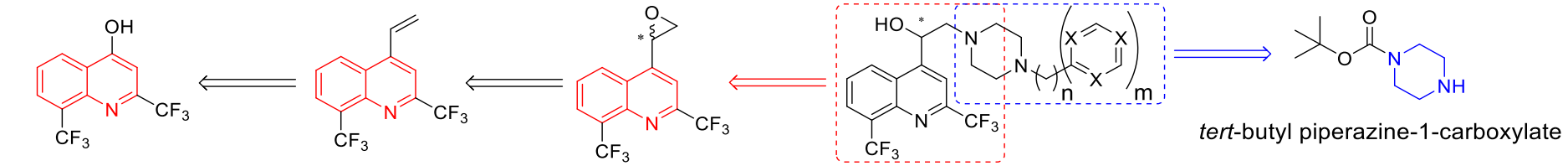


AAQ
aryl series: n = 0, m = 1
alkyl series: n = 4-7, m = 0

→ **Objectives: ↗ selectivity index (SI) of previous MQ-analogs**
→ **Synthesis of new AAQ including piperazine core**

References: Laumaillé, P. *et al*. *Pharmaceuticals*, **2019**, *12*, 91, Girase, P.S. *et al. Eur. J. Med. Chem.,* **2021**, *210*, 112967

Retrosynthesis of new AAQ



4-hydroxyquinoline — 4-vinylquinoline — epoxide — **AAQ**

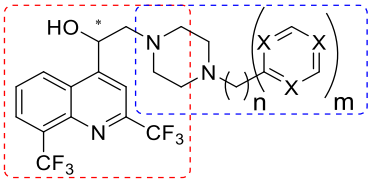
aryl series: n = 0, m = 1,
alkyl series: n = 4-7, m = 0

tert-butyl piperazine-1-carboxylate

→ Two key intermediates: epoxide and alkyl-piperazines

- Epoxide obtained from 4-hydroxyquinoline in 4 steps
- Alkyl-piperazines obtained from *tert*-butyl piperazine-1-carboxylate in 2 steps

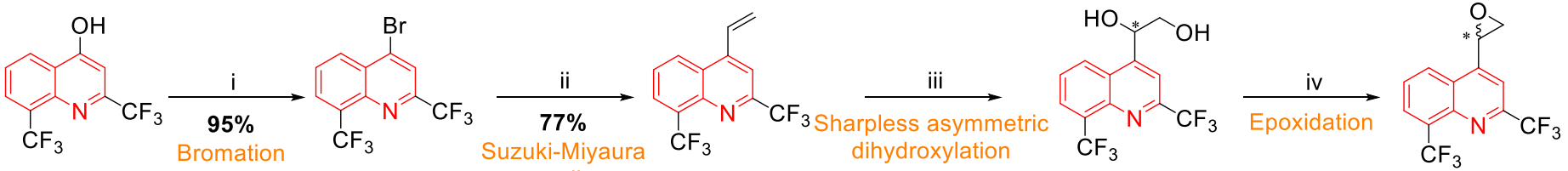
Results and discussion: synthesis of new AAQ



AAQ
aryl series: n = 0, m = 1,
alkyl series: n = 4-7, m = 0

Short asymmetric synthesis to obtain:

- Epoxides **5a/b** in 4 steps



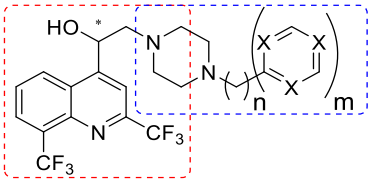
1 **2** **3**

4a (*R*): 95%, ee: 91%
4b (*S*): quant., ee: 91%

5a (*R*): 51%, ee: 91%
5b (*S*): 54%, ee: 93%

i: $POBr_3$, 150°C, ii: potassium vinyltrifluoroborate, Cs_2CO_3, $PdCl_2$(dppf).DCM, THF/H_2O 9/1, 70°C, iii: AD-mix α or β, $K_2[(OsO_2(OH)_4]$, *t*BuOH/H_2O 1/1,
iv: 1) $MeC(OMe)_3$, PTSA.H_2O,DCM, 2) TMSBr, DCM, 3) K_2CO_3, MeOH
ee: enantiomeric excess

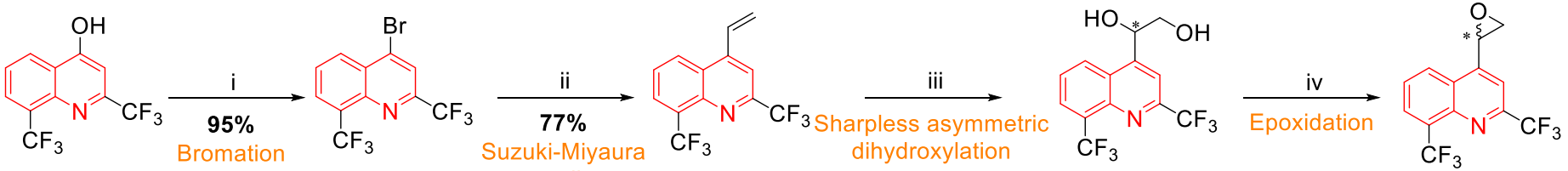
Results and discussion: synthesis of new AAQ



AAQ
aryl series: n = 0, m = 1,
alkyl series: n = 4-7, m = 0

Short asymmetric synthesis to obtain:

- Epoxides **5a/b** in 4 steps
- Alkyl-piperazines **8a/d** in 2 steps



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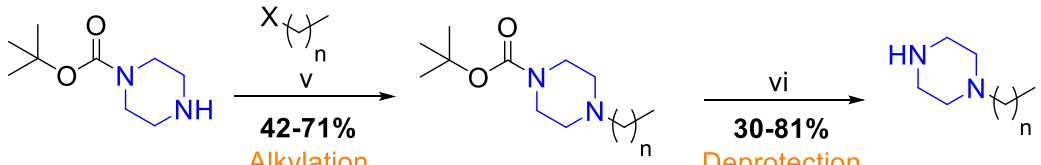
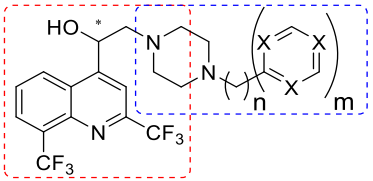


6 **7a-d** **8a-d**

i: $POBr_3$, 150°C, ii: potassium vinyltrifluoroborate, Cs_2CO_3, $PdCl_2$(dppf).DCM, THF/H_2O 9/1, 70°C, iii: AD-mix α or β, $K_2[(OsO_2(OH)_4]$, *t*BuOH/H_2O 1/1, iv: 1) $MeC(OMe)_3$, PTSA.H_2O,DCM, 2) TMSBr, DCM, 3) K_2CO_3, MeOH, v: DIPEA, MeCN, vi: 1) TFA, DCM, 2) NaOH, DCM
ee: enantiomeric excess

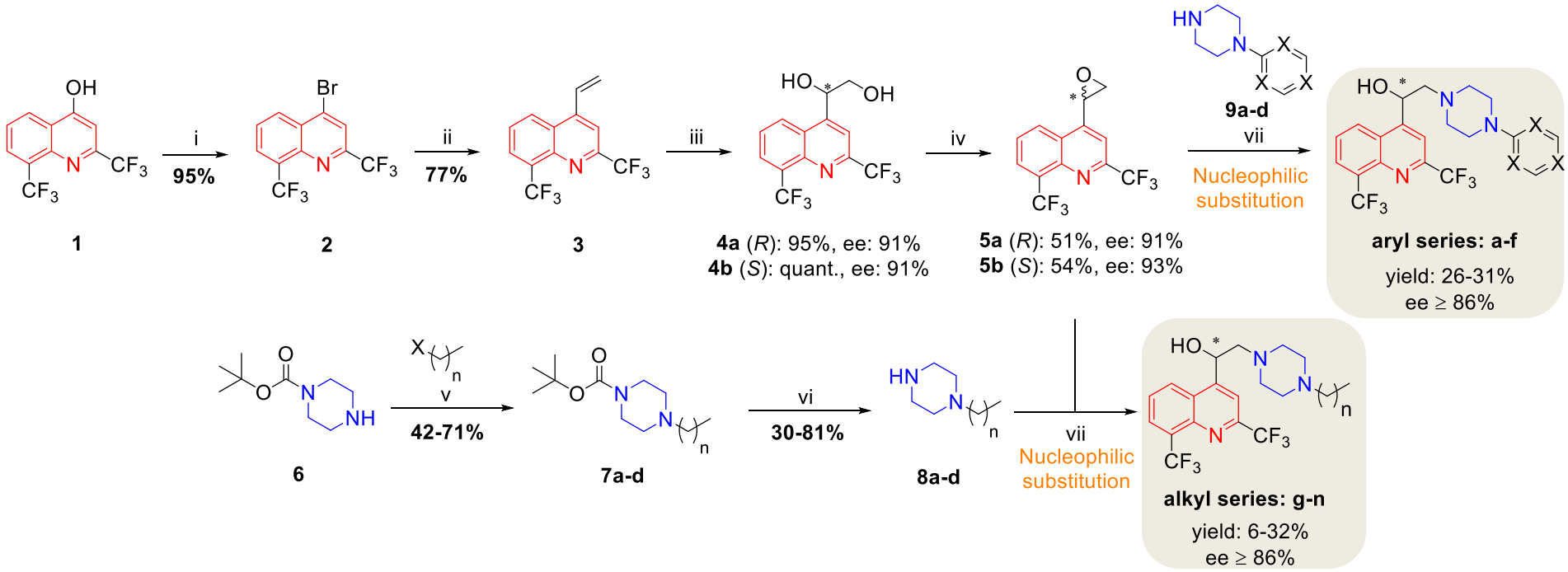
Results and discussion: synthesis of new AAQ



AAQ
aryl series: n = 0, m = 1,
alkyl series: n = 4-7, m = 0

Short asymmetric synthesis to obtain:

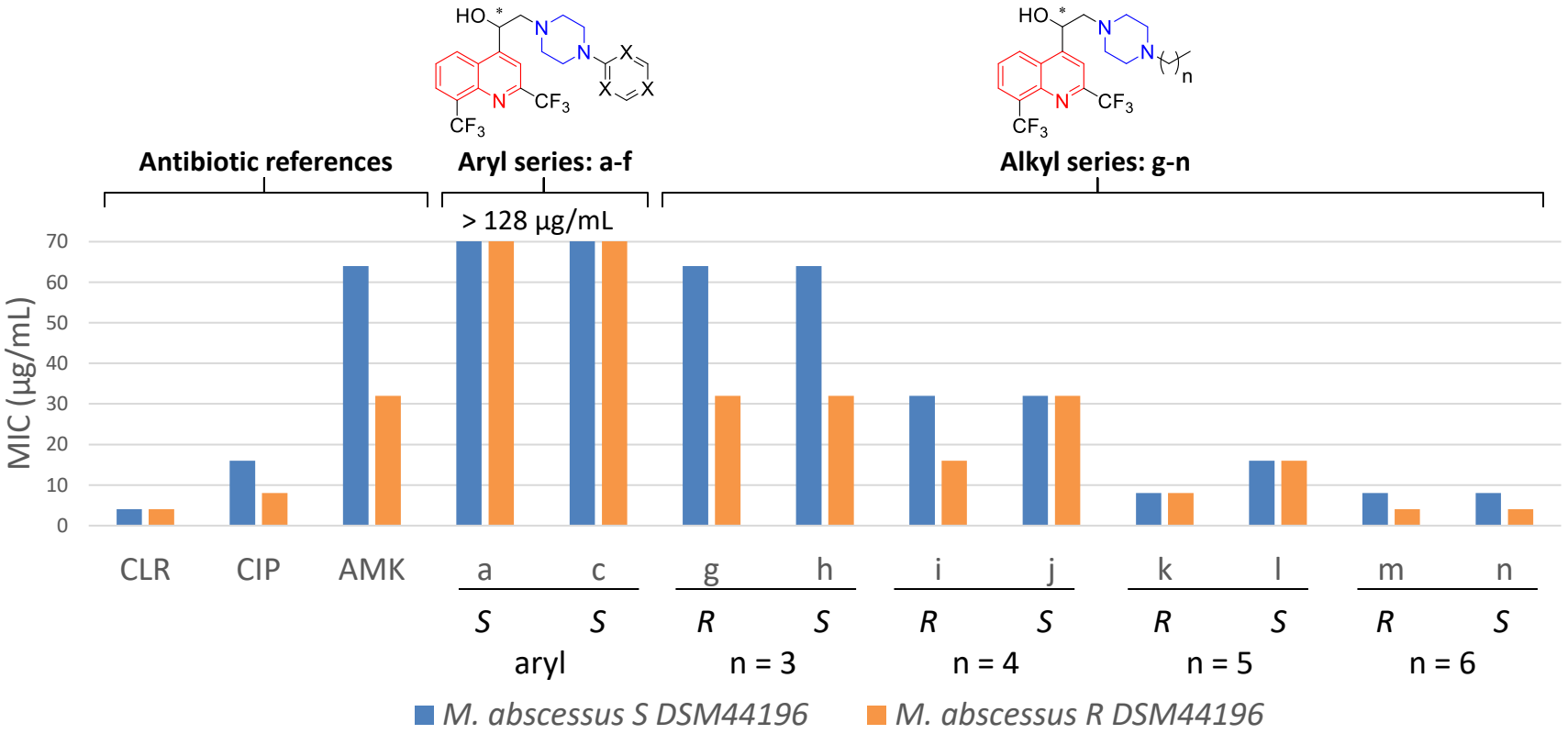
→ 14 piperazine-based AAQ a-n with 6 to 31% of global yields and 86% of ee in 5 or 7 steps



i: $POBr_3$, 150°C, ii: potassium vinyltrifluoroborate, Cs_2CO_3, $PdCl_2$(dppf).DCM, THF/H_2O 9/1, 70°C, iii: AD-mix α or β, $K_2[(OsO_2(OH)_4]$, *t*BuOH/H_2O 1/1, iv: 1) $MeC(OMe)_3$, PTSA.H_2O,DCM, 2) TMSBr, DCM, 3) K_2CO_3, MeOH, v: DIPEA, MeCN, vi: 1) TFA, DCM, 2) NaOH, DCM, vii:, 130°C, 150W, EtOH.
ee: enantiomeric excess

Antimycobacterial activity

Activity of aryl and alkyl series on *M. abscessus S and R*



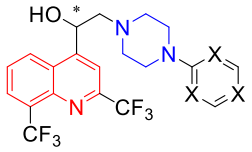
→ **Aryl series: No activity on *M. abscessus S* and *R***

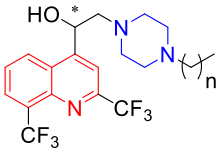
→ **Alkyl series: better activity with long chain alkyl (n ≥ 5) than short length of chain (n ≤ 4)**

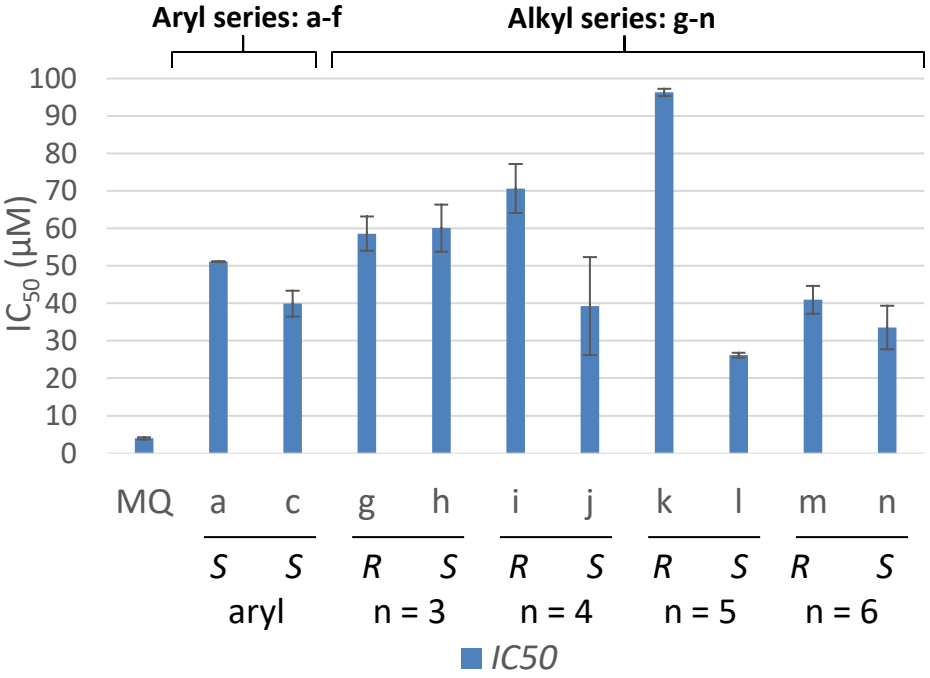
CLR: clarithromycin, CIP: ciprofloxacin, AMK: amikacin

Results and discussion: cytotoxicity on HepG2 cells (MTT test)

Cytotoxicity of aryl and alkyl series on HepG2

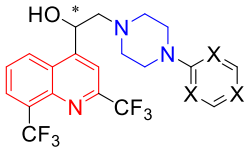


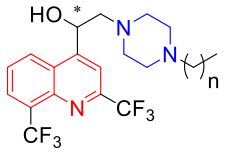


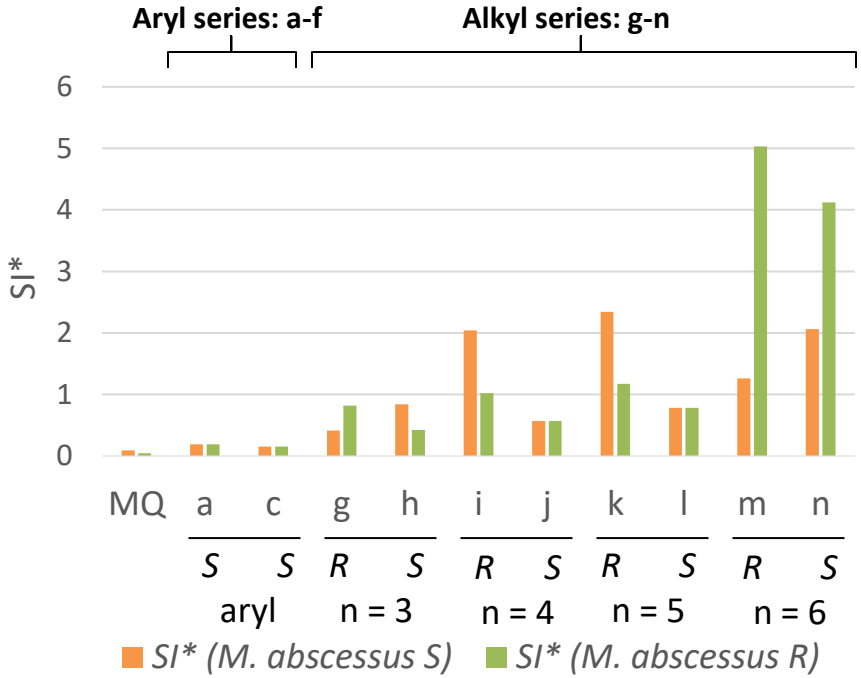


→ **Series are less toxic than MQ**

Selectivity index* of aryl and alkyl series



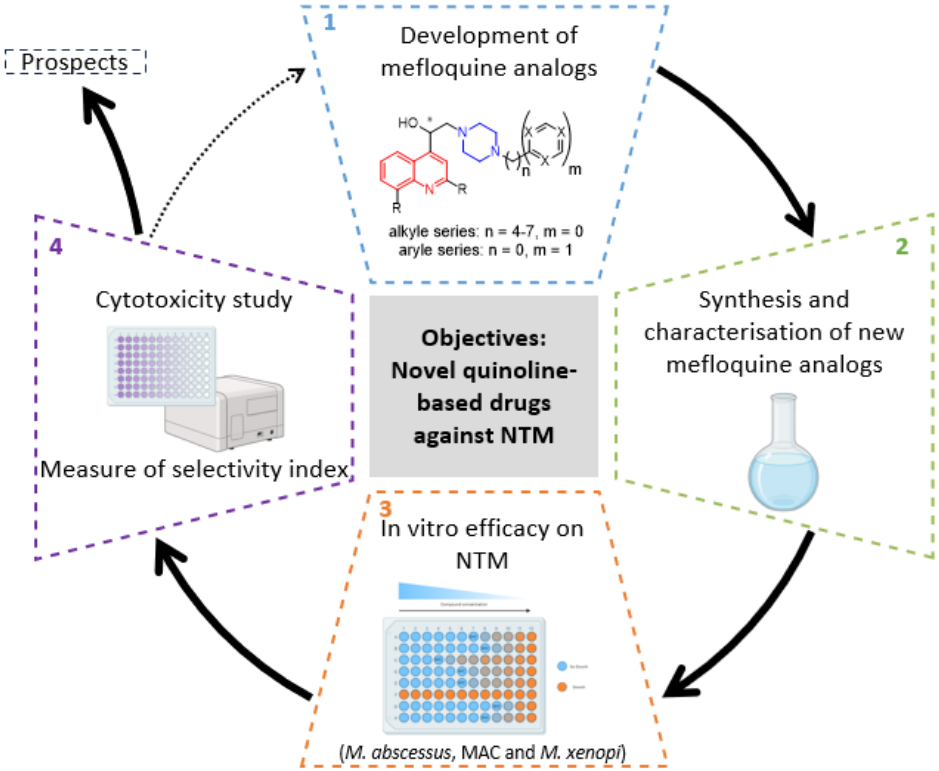




→ **SI of series are higher than that of MQ**

*SI = IC_{50} (µg/mL, HepG2) / MIC (µg/mL, *M. abscessus S* or *R*)

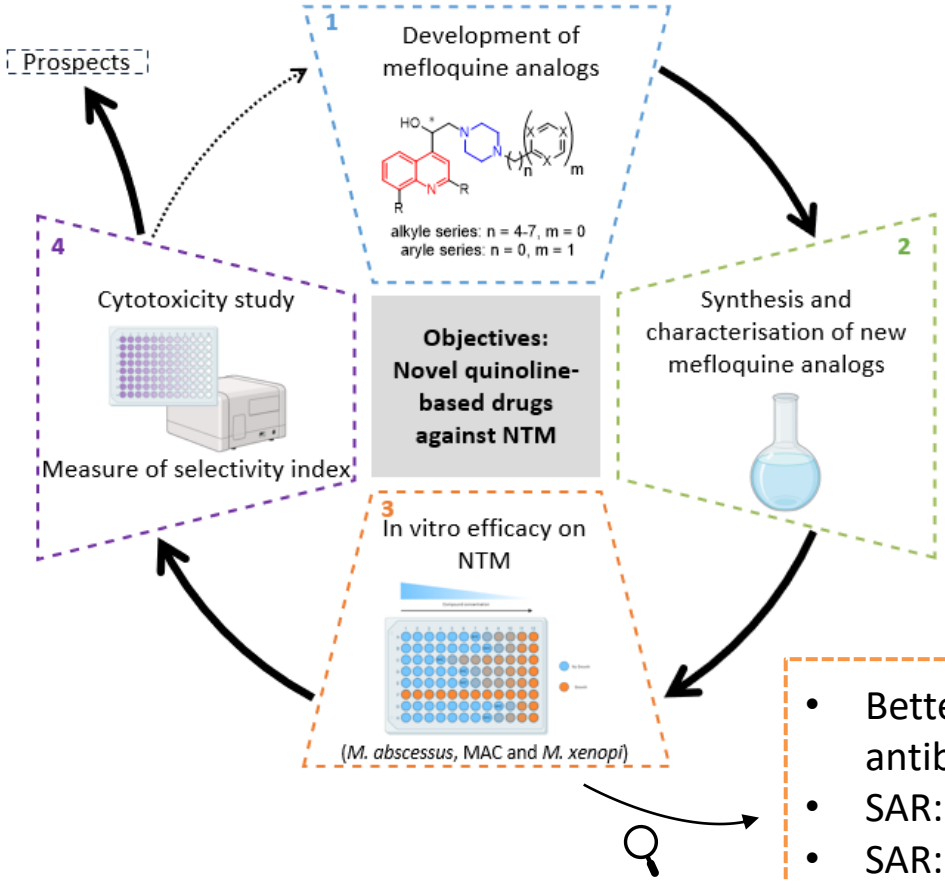
Conclusion



Development of short asymmetric synthesis

→ **14 synthetized compounds**

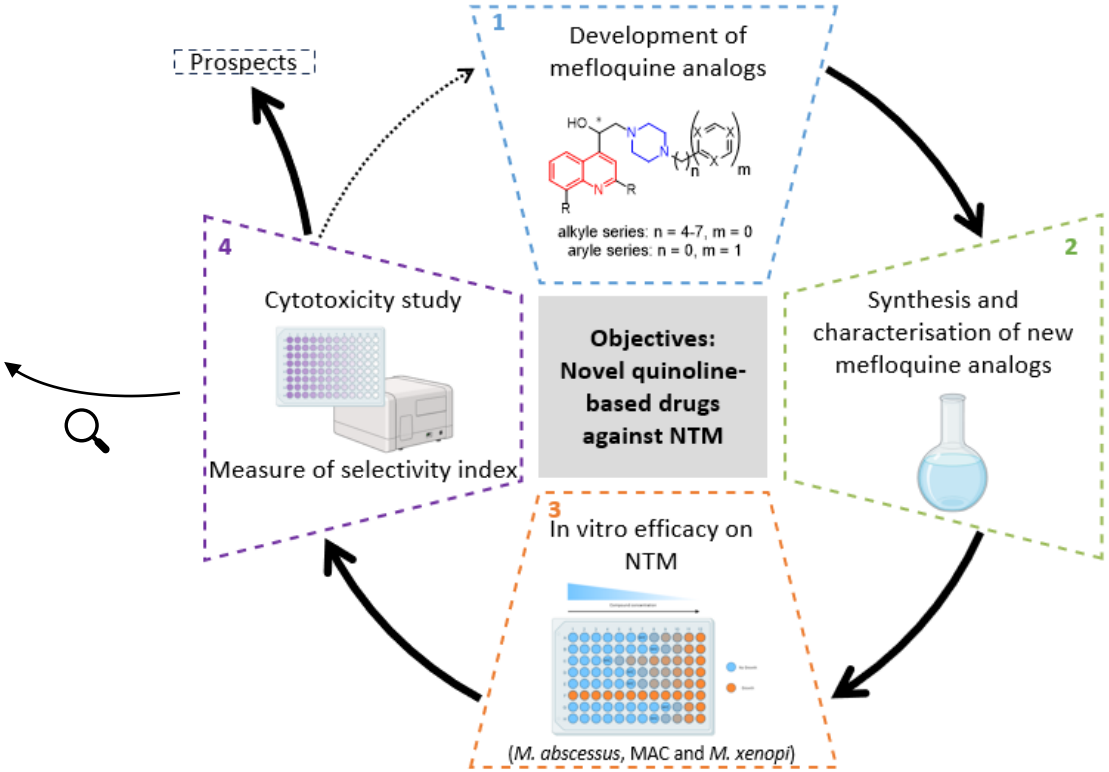
Conclusion



- Better activity of synthetized analogs than antibiotic references on *M. abscessus*
- SAR: alkyl series > aryl series
- SAR: long chain > short chain
- Evaluation on *M. avium* et *M. xenopi* in progress

Conclusion

- New series less toxic than **MQ** and SI higher than that of **MQ**
- SAR: long alkyl chain > short alkyl chain and aryl series
- SI can still be improve



Prospects

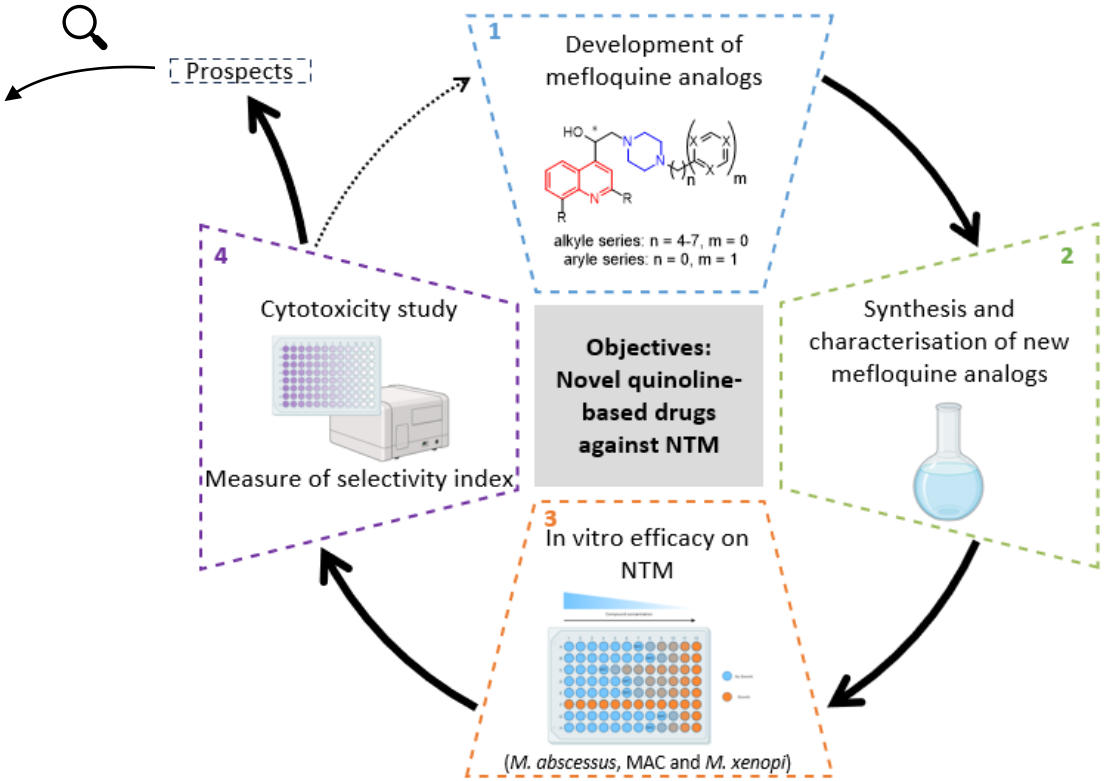
In the short-term:

- Continuation of *in vitro* efficacy
- Measure of selectivity index
- Explore new SAR

→ Selection of compounds with the higher SI

In the long-term:

- Research of action synergy with known antibiotics
- Determination of intracellular efficacy on THP-1 cells
- Determination *in vivo* efficacy on mouse model



Acknowledgments

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CHU AMIENS PICARDIE