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From the design to the biological evaluation of quinoline-based carboxamides targeting non-tuberculous mycobacteria

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INTRODUCTION & AIM

In Europe and in North America, non-tuberculous mycobacterial (NTM) infections accounts from 1.0 to 1.8 case per 100,000 people. Several thousands people die each year from NTM infections. Intrinsic and acquired resistances pose a public health challenge and explain part of the difficulties to treat these infections.

For few years, the macrolide resistance has been known as a major problem for clinical specialists and their patients. NTM are commonly found in the environment and are especially harmful to high-risk people, such as those with weakened immune system or pre-existing lung diseases(1). Some NTM species are pulmonary pathogens and are found in 75 % of respiratory clinical isolates. NTM can be distinguished according to their growth: slow-growing species including MAC complex, *M. xenopi*, *M. kansasii* and *M. marinum*; and also rapid-growing species such as *M. abscessus* (*Mab*) complex and *M. fortuitum*(2).

In this context, the promising quinoline scaffold allowed us to design a novel series of quinoline-based carboxamides as potential antimycobacterial agents.

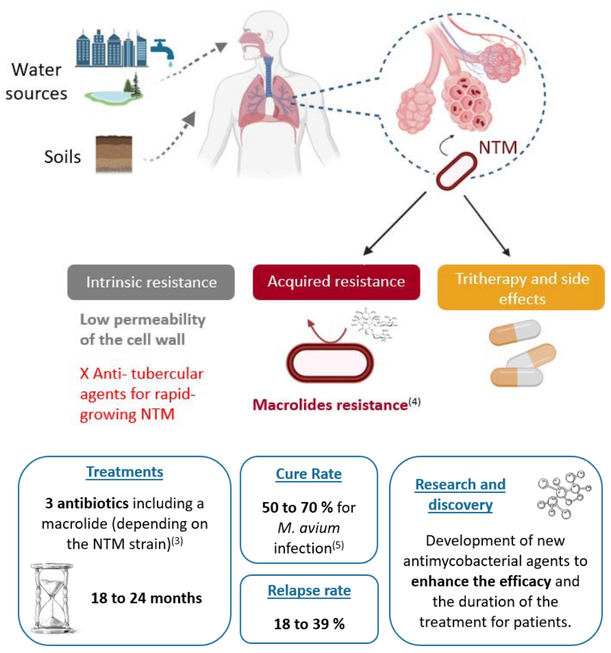
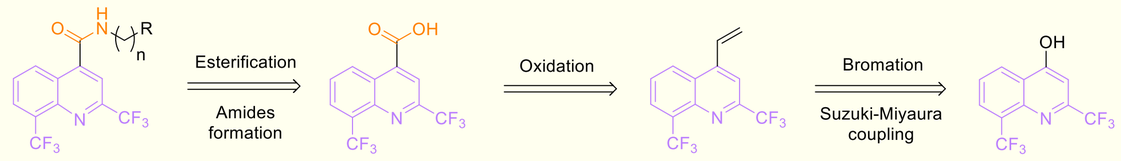


Figure 1 : Development of NTM infections, main health challenges and objectives.

METHOD

Retrosynthesis of quinoline-based carboxamides:

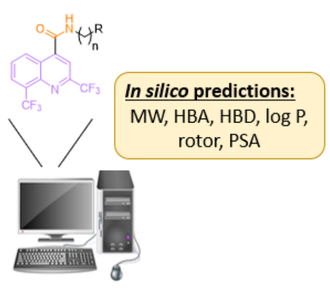
Final carboxamides were designed following a five-step synthesis. These compounds were obtained *via* an amidation of ester intermediates, which resulted in two oxidation and esterification reactions. Ester precursors were produced from a carboxylic acid intermediate, synthesized from a vinyl compound, obtained via a bromination of 2,8-*bis*(trifluoromethyl)quinolin-4-ol, followed by a Suzuki-Miyaura coupling (Scheme 1).



Scheme 1: Retrosynthesis of quinoline-based carboxamides.

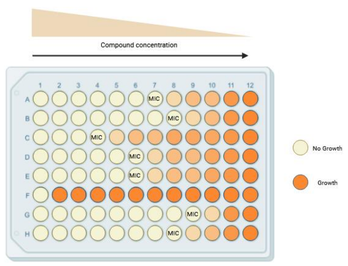
Determination of physico-chemical properties of carboxamides:

To predict the pharmacokinetics properties, the Lipinski's and Veber's rules were calculated using QikProp and Pallas softwares. This includes standard ranges for the molecular weight (MW < 500), the number of hydrogen bonds donor (HBD < 5), the number of hydrogen bonds acceptor (HBA < 10), the predicted octanol/water partition coefficient (clogP < 5), the rotary connections (rotor <10) and the polar surface area (PSA < 140 Å^2).



Testing the antimycobacterial activity of carboxamides:

Minimal Inhibitory Concentrations (MICs) were determined against 7 NTM strains: *Mab* smooth and rough morphotypes, *M. fortuitum*, *M. avium*, *M. xenopi*, *M. marinum* and *M. kansasii*. Amikacine (AMK), clarithromycin (CLR) and rifampicin (RIF) were used as 3 antibiotics references.



RESULTS & DISCUSSION

- **Synthesis of quinoline-based carboxamides**

The first two steps consisted in a bromination of **1**, followed by a Suzuki-Miyaura coupling to give the 2,8-*bis*(trifluoromethyl)-4-vinylquinoline **3** with 85 % yield. To afford the acid **4**, an oxydation was realized to obtain it with 67 % yield. Then, direct couplings of **4** with amines have been tested with different coupling agents (EDCI/HOBt, COMU or HOBt/HBTU) but without success. The activation of **4** to the corresponding esters **5a** and **5b** was necessary to facilitate the formation of amides **6a** and **6b**.

A first hydrazide-hydrazone **6a** was obtained from the methylic ester in 51 % yield. After optimized conditions, the reaction between the ethylic ester **5b** and the pentylamine in a microwave irradiation gave the compound **6b** in 80 % yield.

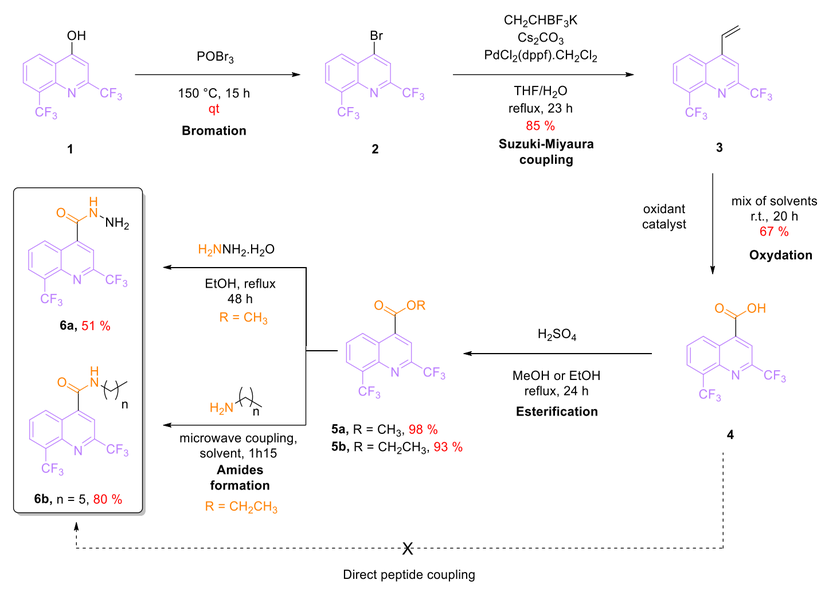


Figure 2 : Synthesis of 2,8-*bis*(trifluoromethyl)quinoline-4-carboxamides 6a and 6b.

- **Physico-chemical properties**

According to the results, compounds **6a** and **6b** satisfied drug-likeness conditions, except a value for **6a** (red line). It slightly exceeds the desirable lipophilicity value (clogP = 5.15) for a good oral administration but this property seems to be advantageous for penetrating the NTM lipophilic membrane.

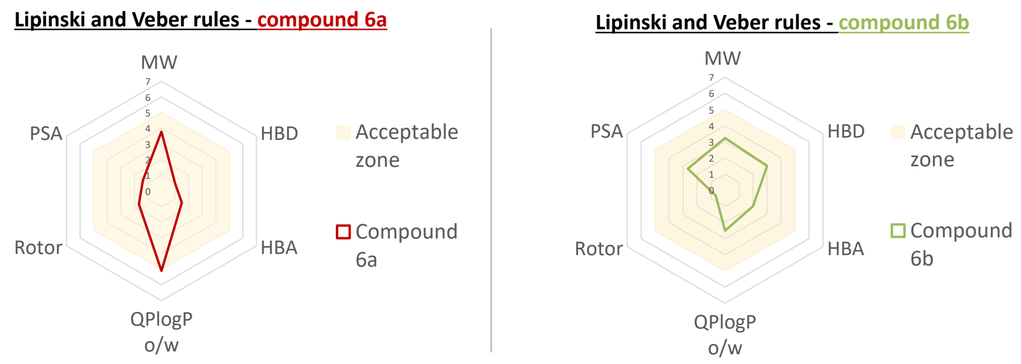


Figure 3 : Radar diagrams of final compounds 6a and 6b and acceptable values for oral bioavailability (beige zone).

- **Antimycobacterial activities**

Unfortunately, compounds **6a** and **6b** on both slow-growing and rapid-growing species were inactive, with MIC values above 128 µg/mL.

MIC (µg/mL)	NTM species						
	Mab (R)	*Mab* (S)	*M. fortuitum*	*M.avium*	*M. xenopi*	*M. marinum*	*M. kansasii*
6a	>128	>128	>128	>128	>128	>128	128
6b	>128	>128	>128	>128	>128	>128	>128
AMK	8	8	ND	2-16	ND	1-4	ND
CLR	Inductible R	Inductible R	Inductible R	0.5-2	≤ 0.25	0.5-2	ND
RIF	ND	ND	ND	0.5-4	< 0.05	≤ 0.5-2	ND

Table 1 : Antimycobacterial activities against different NTM species. R : resistance, ND : not determined.

CONCLUSION / FUTURE WORK

- ✓ Two final compounds **6a** and **6b** were obtained with 28 % and 23 % global yields.
- ✓ They satisfied drug-likeness conditions and **6b** showed a good lipophilicity value (clogP > 5 for **6b**) compatible to cross the NTM membrane.
- ✓ Further pharmacomodulations and optimizations are underway to complete these series and the structure-activity relationships.

REFERENCES

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