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Synthesis and study of new antitubercular compounds

Pierre Laumailé ¹*, Alexandra Dassonville-Klimpt ², Pascal Sonnet ³

1 pierre.laumaille@etud.u-picardie.fr

2 alexandra.dassonville@u-picardie.fr

3 pascal.sonnet@u-picardie.fr

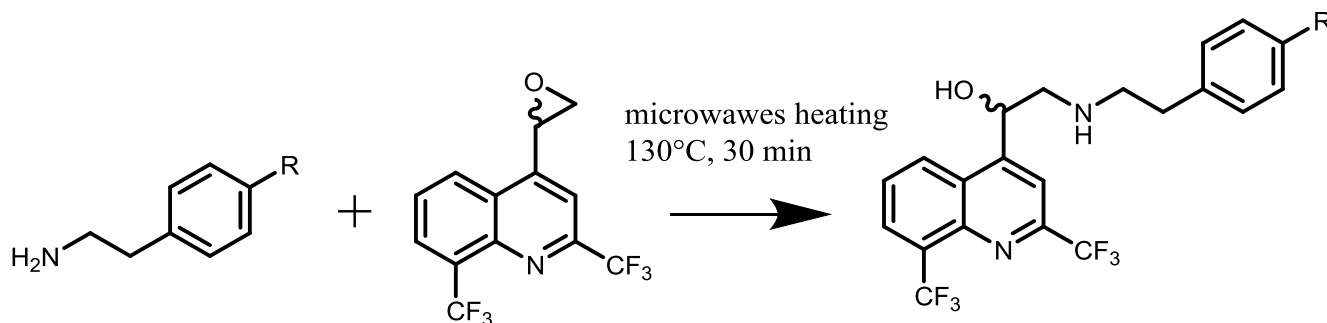
Team **AGIR** AGents antiInfectieux Résistances et chimiothérapie

Université de Picardie Jules Verne, UFR de Pharmacie, 1 rue des Louvels, 80037, Amiens cedex 1, France.

* Corresponding author: pierre.laumaille@etud.u-picardie.fr

Synthesis and study of new antitubercular compounds

Graphical Abstract



R= H, Me, OMe, Cl, CN, CO₂H
CONH₂, SO₂NH₂, NO₂, NH₂, CO₂Me.

MIC on *M. xenopi* from 8 to more than 64 mg/L. For R= Me, MIC= 8 mg/L
R= Me, OMe, OH > others => electron-donor groups give better biological activity
R enantiomer is more active.



Abstract:

Tuberculosis is regarded as one of the deadliest diseases in the world. It is a bacterial infection caused by some bacteria from the genus *Mycobacterium*, such as *Mycobacterium tuberculosis*. Some bacterial strains are multi-resistant or extensively-resistant against classical antibiotics. Consequently, there is a necessity to set up new strategies to prevent the spread of antibiotic resistant mycobacteria.

Quinoline core is present in some antitubercular compounds. Indeed, bedaquiline (one of the last commercialized antitubercular compounds) is a diarylquinoline, which acts by inhibiting selectively the mycobacterial ATP synthase. This enzyme is required for the energetic metabolism of the cell and is a critical target to kill dormant strains. Mefloquine is a quinoline used as antimalarial compound but this molecule shows also antimycobacterial properties. Mefloquine can inhibit ATP synthase of *Streptococcus pneumoniae*, this inhibition may explain its antimycobacterial activity.

The objectives of this work are designing, synthesizing, and evaluating new antitubercular compounds as quinoline derivatives (AQM). These molecules are expected to inhibit mycobacterial ATP synthase in order to fight latent forms of mycobacteria.

The previous works of the research team have allowed to identify a lead compound which shows an MIC of 1 μ M against *M. tuberculosis Mtb*_{H37Rv} strain. A pharmacomodulation of this lead compound will be shown here.

Keywords: Tuberculosis; Antitubercular; Quinoline



Introduction : generalities

Tuberculosis is caused mainly by *Mycobacterium tuberculosis* (Mtb).

Symptoms : cough, fever, weight loss, respiratory pain etc...

The principal targets are lungs (71,5 % cases in 2004) but all organs can be affected.

10.4 million of people infected and 1.7 million of death in 2017 → second cause of death among infectious diseases.

The co-infection by VIH and tuberculosis is a major issue: in 2016, 40% of death among seropositive people was attributable to tuberculosis. There is also a risk of interactions between antitubercular and antiretroviral drugs.



Introduction : antitubercular treatment

Treatment of sensitive tuberculosis : first line treatment

- Rifampicin, Isoniazid, Pyrazinamide et Ethambutol during 2 months → first line treatment
- then Rifampicin and Isoniazid during 4 months.

Treatment of resistant tuberculosis : second line treatment

Four to six drugs among which fluoroquinolones (Levofloxacin, Moxifloxacin etc...), and injectables aminosids (Amikacin, Kanamycin etc...) during 6 months, then a maintenance phase with three drugs during 12-18 months.

If the strain is resistant against Isoniazid and Rifampicin → Multi-Drug Resistant (MDR) strain

If the strain is resistant against first line treatment and some second line treatments → Extensively-Drug Resistant (XDR) strain



Introduction : resistance

There is a lack of safe therapeutical options to deal with MDR and XDR *Mtb* strains.

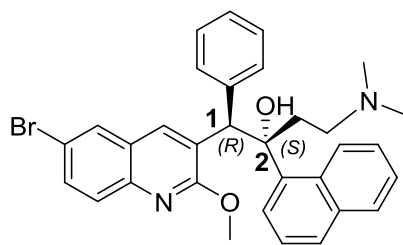
Only 2 antitubercular compounds have been commercialized since Rifampicin in 1971 : Bedaquiline (2012) and Delamanid (2014).

→ Urgent need of new antitubercular compounds

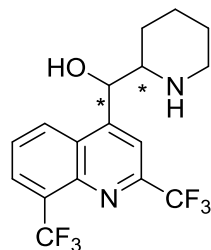


Introduction : biological target

- Bedaquiline, a diarylquinoline, target *Mtb* F1F0 ATP synthase.
- Mefloquine, an antimalarial quinoline, can inhibit *Streptococcus pneumoniae* ATP synthase



Bedaquiline



Méfloquine

→ Quinoline core seems to be effective to inhibit ATP synthase

ATP synthase is an interesting target to kill *Mtb*, especially in latent phase, because this enzyme is necessary for oxydative phosphorylation and so for the energetic metabolism of the cell.

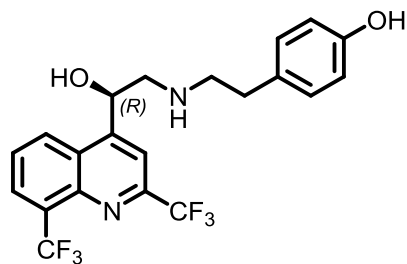
Inhibition of ATP synthase depends on stereochemistry: Bedaquiline (*1S,2R*) enantiomer is 630 fold less active than (*1R,2S*) enantiomer → an asymmetric synthesis is required



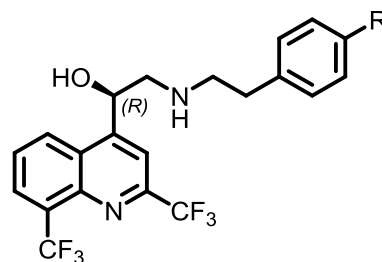
Introduction : objectives

The objectives of this project are designing, synthesising and evaluating new quinoline derivatives to treat replicating and latent form of *Mtb*.

Previous works of the team have allowed to identify a lead compound **1** which shows interesting activity against *Mtb* (MIC = 1 μ M). Only R enantiomer is active.



1



2

A first generation of Amino-Quinoline Methanol (AQM) **2** has been synthesized by pharmacomodulation of the phenyl group in para position of this lead compound.



Introduction : pharmacomodulation (1)

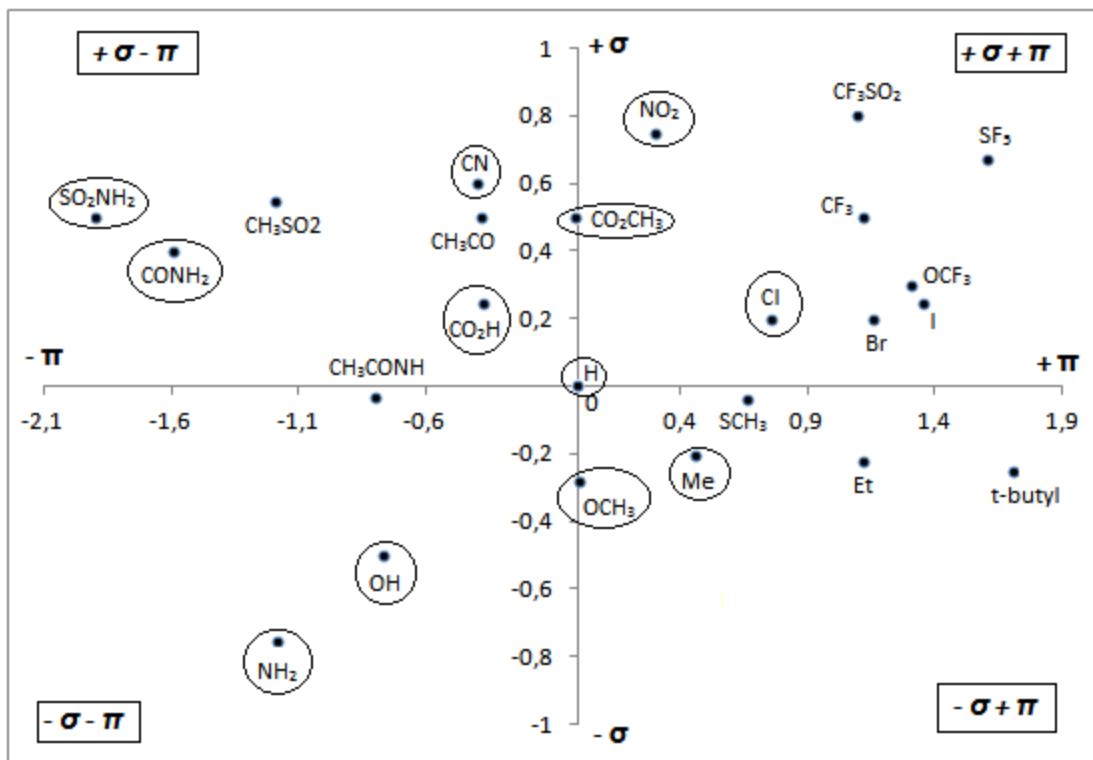
Pharmacomodulation was designed thanks to a Craig Plot. Craig Plot is a tool used in physical organic chemistry that allows to quantify electronic properties (with Hammett substituent constant σ) and lipophilicity properties (with partition coefficient π) of several chemical groups.

With this tool, we can choose some groups for this pharmacomodulation with different physico-chemical properties in order to maximize the probability of finding the best properties for effective pharmacodynamic interactions with the target.

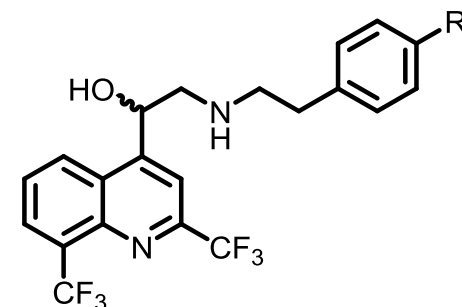
22 molecules (11 couples of enantiomers) have been chosen for this first generation of AQM.



Introduction : pharmacomodulation (2)



σ : Hammett substituent constant (electronic properties)
 π : partition coefficient (hydrophily/lipophily)



Structures considered:

- R= H
- R= Me
- R= OMe
- R= Cl
- R= CN
- R= COOH
- R= CONH₂
- R= NH₂
- R= NO₂
- R= COOMe
- R= SO₂NH₂

10



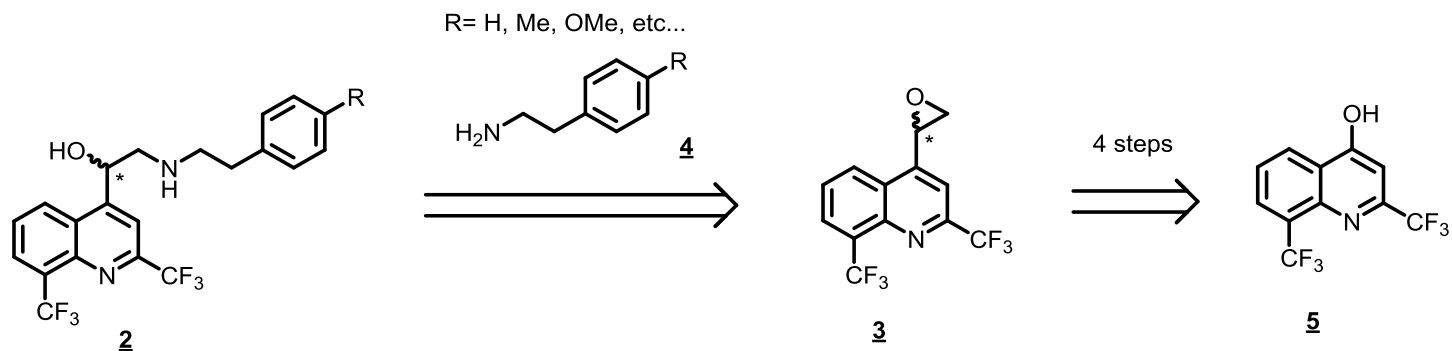
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Results and discussion : AQMs retrosynthesis

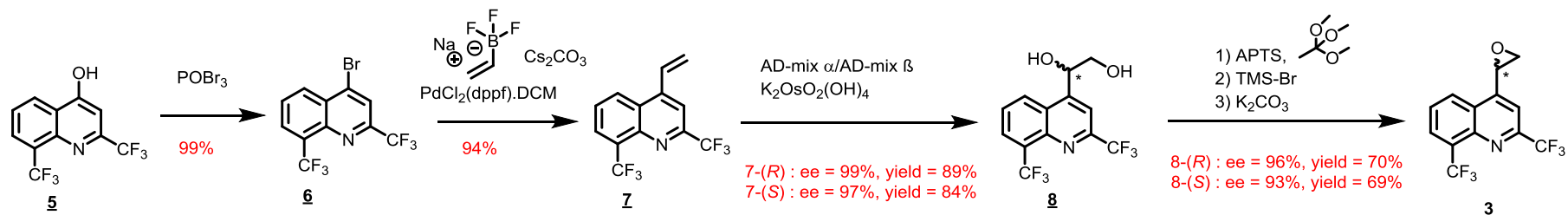


The desired AQMs **2** were obtained from a quinoline epoxyde **3** and the corresponding amine **4**. The quinoline epoxyde was obtained from an hydroxy-quinoline **5** in four steps.

This synthetic route is asymmetric, we have obtained a couple of enantiopur AQMs **5**.



Results and discussion : epoxyde synthesis

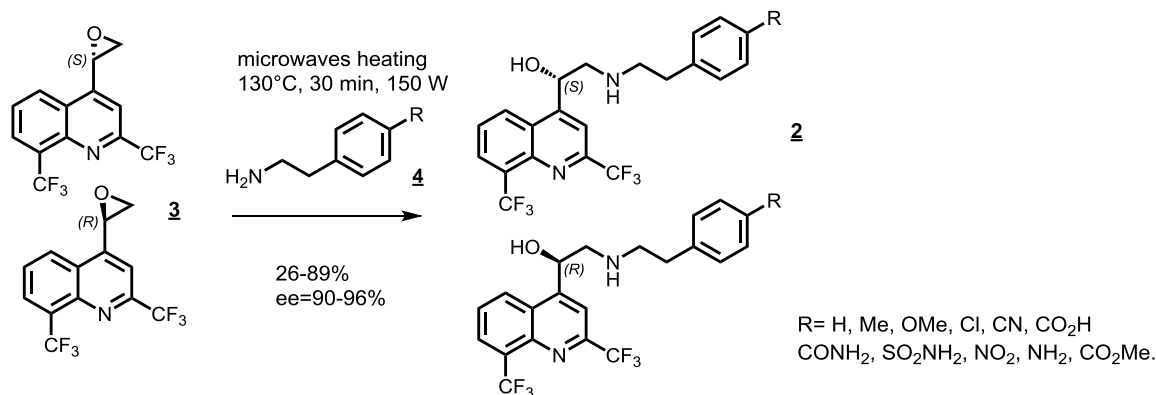


The hydroxy-quinoline **5** was reacted with POBr_3 to give the bromo-quinoline **6**. A Suzuki coupling with vinyl trifluoroborate allowed to obtain the vinyl quinoline **7**. A Sharpless dihydroxylation gave access to both enantiomers of diol **8**. A final reaction of one-pot/3-steps condensation gave both enantiomers of quinoline epoxyde **3** with retention of configuration.

This enantioselective synthetic route gave access to the *S* and *R* enantiomers of quinoline epoxyde **3** in four steps with a global yield of respectively **54%** and **58%**, and an enantiomeric excess of **93%** and **96%**.



Results and discussion : AQMs synthesis

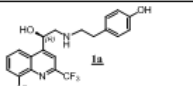
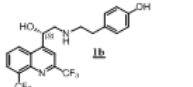
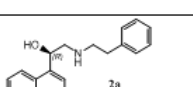
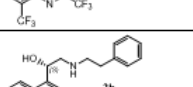
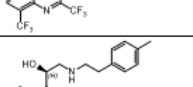
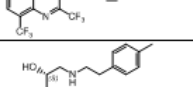
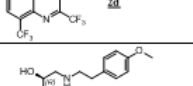
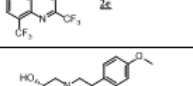


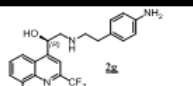
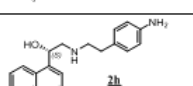
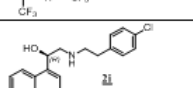
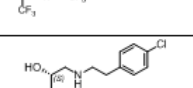
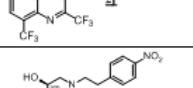
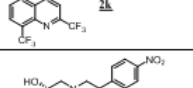
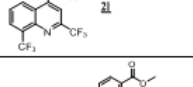
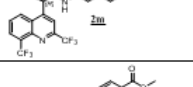
Each enantiomer of quinoline epoxyde **3** was reacted with the amine **4** to form the desired AQM **2** with 26-89% yield. The reaction took place under microwave heating, at 130 °C and 150 W during 30 min.

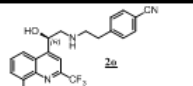
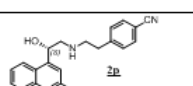
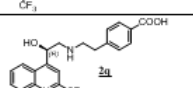
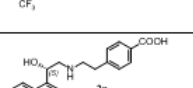
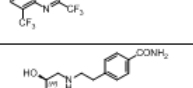
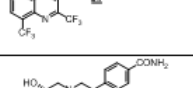
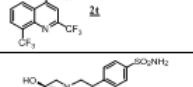
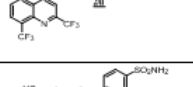
Twenty two molecules have been synthesized through this asymmetric synthetic route in **5 steps** with a global yield from **15 to 50 %** and an enantiomeric excess between 90 and 96%.



Results and discussion : biological activity

Compounds	CMI <i>M. avium</i> (mg/L)	CMI <i>M. xenopi</i> (mg/L)
Rifampicin	16	4
Bedaquiline	/	1
	32	8
	>32	16
	>32	>32
	>32	>32
	>64	8
	>64	16
	>64	16
	>64	32

Compounds	CMI <i>M. avium</i> (mg/L)	CMI <i>M. xenopi</i> (mg/L)
	64	/
	64	/
	>64	32
	>64	>32
	>64	>32
	>64	>32
	ND	>32
	ND	>32

Compounds	CMI <i>M. avium</i> (mg/L)	CMI <i>M. xenopi</i> (mg/L)
	>128	/
	>128	/
	>128	/
	>128	/
	64	/
	64	/
	64	/
	64	/

Some AQMs have been tested *in vitro*, on atypical mycobacteria *M. xenopi* and *M. avium*.

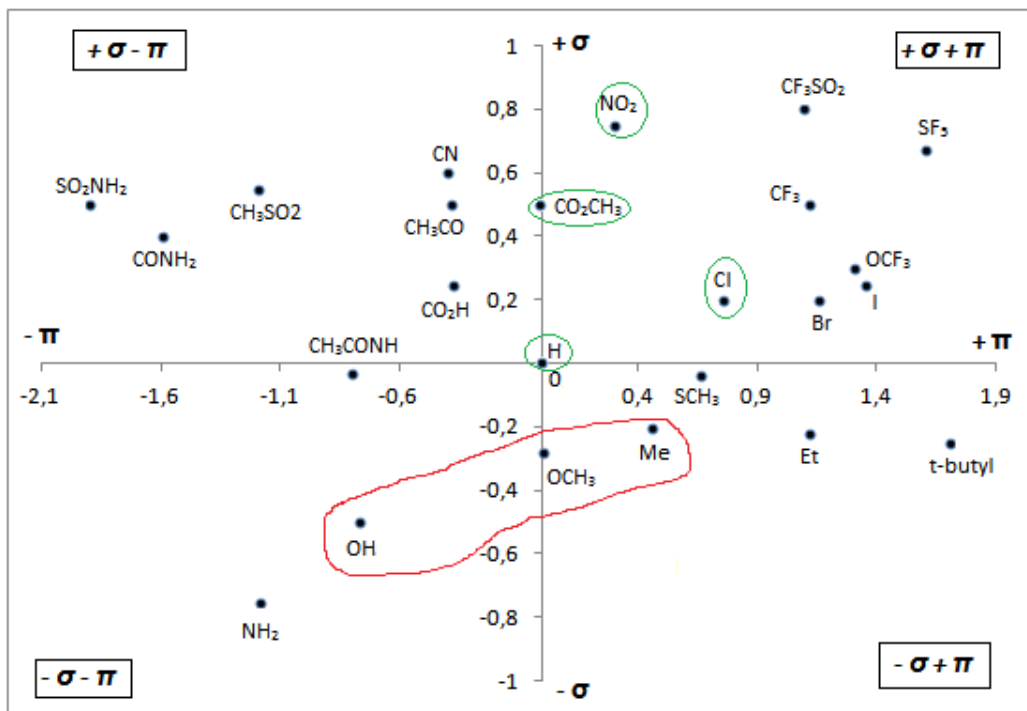
These compounds are less active than Rifampicin and Bedaquiline. They show MIC between 8 and more than 32 mg/L on *M. xenopi* and are few active on *M. avium* (MIC >64 mg/L).

2c is the most active molecule, with the same activity than **1a** on *M. xenopi* (8 mg/L).

Interestingly, we observe a difference of activity between *R* and *S* enantiomer : *R* is often more active.



Results and discussion : SAR



On the Craig Plot graph, we can circle in red the chemical groups corresponding to AQMs with the best antimycobacterial activity for *M. xenopi* (**8 to 16 mg/L**) and circle in green the others.

Hydrophobics and electron-withdrawings groups (upper right quadrant of the graph) seems to give compounds with low activity.

By contrary, electron-donor groups seems to allow to obtain quite good activity. Interestingly, the hydrophobicity of the group shows no or few difference concerning biological activity while the electron-donor effect is high enough.



Conclusions

Twenty two molecules have been synthesized with an enantioselective synthetic route in **5 steps** with a global yield from **15 to 50 %**. Some compounds (R= OH, Me and OMe) have shown encouraging activities (MIC = **8 to 16 mg/L** on *M. avium* and *M. xenopi*). The difference of biological activity between the *R* and *S* enantiomers justify the necessity of an asymmetric synthesis.

We will continue to explore the corresponding zone of the Craig plot (electron/donor groups) in order to increase the biological activity.

When the best group is found in this pharmacomodulation, a second generation of AQM will be synthesized. This second generation will differ by the introduction of a phenyl group between amino and hydroxy function of the AQM core, in order to get closer to Bedaquiline's structure and to increase the lipophilicity, which will allow the AQMs to reach latent bacteria.

Other ideas of pharmacomodulation consist of modified aliphatic chain length between amino group and aromatic part, and the nature of the aromatic moiety.



Acknowledgments

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