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PHARMACOTHERAPEUTIC EVOLUTION OF ANTITUBERCULOSIS DRUG-A REVIEW

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ABSTRACT

Tuberculosis is a cosmopolitan human lung infection caused by *Mycobacterium tuberculosis*. It represents one of the main causes of death worldwide. The therapeutic management of this disease by antituberculosis drugs faces several obstacles such as low adherence, the long duration of treatment, adverse effects of the drugs and the existance of the latent tuberculosis caused by dormant bacilli. Furthermore, the drug treatment of co-infection HIV and tuberculosis resistant is in a situation of therapeutic deadlock. Therefore, it seemed worthwhile to make an inventory of antituberculosis drugs and have a better understanding of future therapeutic options. This study highlighted the existance of many "doubtful" non-drug treatments proposed to treat tuberculosis before the discovery of modern tuberculosis chemotherapy. Some of them suggested prayers, incantations (heal power of kings), or a simple rest combined with a balanced diet. Others less gentle methods such as the injection of air into the lungs recommended surgical treatments like thoracoplasty. Various treatment based on gold salts, cod liver oil or the sanatorium cures were also tested. The discovery of streptomycin in the 1940, was the beginning of the current anti-tuberculosis therapy. Indeed, research aimed at finding an alternative treatment, to overcome the Streptomycin resistance, led to the introduction in therapy of many other antituberculosis like Para-aminosalicylic acid (1944), Isoniazid (1952), the ethambutol (1957), Rifampicin (1967), the pyrazinamide (1980) and fluoroquinolones (1982). Moreover, in order to shorten the duration of treatment and to limit the the emergence and spread of resistance, combination of antituberculous drugs has been proposed and the treatment of tuberculosis has evolved from

monotherapy to quadruple today. In addition, to deal with the appearance of poly-resistant strains and overcome the drawbacks existing tuberculosis drugs, research is underway to identify new biological targets and to develop antituberculosis of the future.

KEYWORDS: Antituberculosis drugs, tuberculosis, *Mycobacterium tuberculosis.*

INTRODUCTION

Tuberculosis is an infectious disease caused by the tubercular bacillus *Mycobacterium tuberculosis*, also called Koch Bacillus (BK). Tuberculosis is most commonly transmitted through the air when a person inhales droplet nuclei containing *M. tuberculosis* coming from the respiratory tract of another suffering from the respiratory form of the disease. This bacterial disease is a leading cause of infectious death in the world before HIV-AIDS, with 10.4 million people infected and 1.8 million deaths in 2015. It has become the leading killer of people living with HIV in 2015, with 35% of deaths in people with HIV. Undoubtedly, tuberculosis and HIV, each speeding the progression, form a lethal combination. HIV-AIDS, by weakening the immune system of patients, increases the risk of developing tuberculosis disease.[1,2] The medical management of tuberculosis based on a combination of several specific anti-tuberculosis antibiotics lasts 6 to 9 months. Contagiousness decreases rapidly at the initial phase of treatment, however respiratory isolation measures may be required in some cases.[1,3] While effective, the tubercular therapeutic faces factors that contribute to the spread of the disease. Indeed, the long duration of treatment associated with poly chemiotherapy causes many adverse effects, low therapeutic adherence, at the origin of the apparition of the relapse cases and the emergence of Multidrug-Resistant and ultraresistant bacillus forms. In 2015, WHO estimated 480 000 the number of people who have developed multidrug-resistant tuberculosis.[1,2] In addition, the increase in cases of co-infection of tuberculosis-HIV complicates the management of tuberculosis infection. To fight against the persistence or expansion of tuberculosis disease and relapse after antituberculosis treatment, several strategies have been developed throughout history in order to maximize the effectiveness of drug treatment. Thus, this literature review is an overview of past, current antituberculosis treatment and apprehends therapeutic solutions of the future. Specifically, it describes the empirical treatment of prehistory to the discovery of streptomycin, recounts the history of antituberculosis treatment while establishing the pharmacochemical evolution of current antituberculosis drugs.

I-EVOLUTION OF TUBERCULOSIS THERAPY

I.1-Old therapeutic tuberculosis

The former tuberculosis therapy aimed to alleviate the symptoms of the disease that were still unclear. Thus, ancient people were using the invocation of gods and magic to cure tuberculosis.[4,5] Then came the wave of medications with Hippocrates, the father of medicine, who proposed the use of "wine" between meals. The patients were further put to rest, subject to pleasant conditions, supposed to bring them healing. At that time indeed, patients were taking air and sun cures accompanied by dietary measures which consisted mainly drinking milk from cow, donkey and especially women. A young nurse was elected to feed the patient every day at the bedside.[4,5,6] Chinese doctors, meanwhile, advocated their urine as oral treatment.[4] The treatment by light, air and the sun was practiced until the 19th century. However, other treatments and beliefs existed. In the Middle Ages and until the late nineteenth century, the belief attributed to the kings the power to heal by touch "the illness of scrofula". Scrofula were outdated name of a tuberculous disease, causing festering fistula localized on lymph nodes of neck.[5,7] Cod liver oil-based treatments have also existed. In 1848, a study in a hospital in England has highlighted the properties of this oil on the tuberculosis patients who experienced an improvement in symptoms they suffered. This would be linked to the presence of vitamin D that would allow a better defense of the body[7,8] Similarly, Hermann Brehmer initiated in 1862, treatment in sanatoriums Gobersdorf which was first installed in Silesia (Germany). This method was to isolate patients and to subject them to clean air and sun baths and a good diet in a facility at altitude, offering a pleasant and peaceful stay in a view to obtaining a cure.[4,5,6,9,10] In addition, light therapy has been practiced to treat the disease. Dr Auguste Rollier was the instigator of this technique in the 20th century (from 1903 to 1945) at his clinic in Leysin. He was convinced that a sun-based treatment could cure the extra-pulmonary manifestations of the disease.[5] In the current 20 century, tuberculosis patients have been treated by several methods[4,5,6,10] such as chemotherapy based gold salts or calcium salts parenterally, the thoracoplasty, the lymph node dissection, the collapse therapy or pneumothorax, the lobectomy and the pneumonectomy. However, the collapse therapy was the only treatment available in Europe and the United States in the 1920. It consisted to put the lungs "at rest" by letting the air in or injecting an oily product between the leaves of the pleura in order to detach the ribs from the lung.

This maneuver has been so slightly, relieve the sick but many deaths occurred as a result of this surgical treatment.[5,7] This method relieved the patients, but many deaths have been observed as a result of this pulmonary treatment. Subsequently, these methods have disappeared by the end of the second world war. During this same period, treatment of tuberculosis was revolutionized by the discovery by Albert and Waksman in 1944 of streptomycin, first tuberculosis drug.[7,8,11]

I.2- Modern Therapeutic

The modern treatment of tuberculosis (TB) begins in 1944 with the discovery of Streptomycin. This molecule has treated properly and effectively, TB patients at that time. However, 3 years after its discovery, Streptomycin became less effective in monotherapy because *Mycobacterium tuberculosis* developed resistance and deaths were reported despite treatment.[7,8,12] Research undertaken to overcome drug resistance and find out more effective molecules have led to use Paraaminosalicylic acid (PAS) and Streptomycin in a synergic anti-tuberculosis combination in 1948.

This combination has enabled the reduction of resistance to Streptomycin but the high-dose of PAS required and its adverse reactions relating to digestive intolerance generated compliance problems.[7,8,12] Synthesized in 1912, Isoniazid was introduced in tuberculosis therapy in 1952. This new drug, low in toxicity and better tolerated, has been used very effectively in triple therapy with streptomycin and PAS to combat streptomycin resistance. But, it still required up to 24 months of treatment which has probably generated resistance and increased adverse effects of PAS.[7,8,12]

Thereafter, Ethambutol, active both on isoniazid and streptomycin resistant germs, replaced PAS in the triple combination in 1960 to shorten the duration of treatment to 18 months.[9,12,13]

However, resistance remained. To achieve the objective of reducing resistance and the duration of therapy required for cure from 18 months to 9 months with a better tolerance, quadritherapy was suggested. Thereby, in 1967 the association of Rifampicin, Isoniazid, Ethambutol, and Streptomycin was a major breakthrough because this combination were able to cure almost all patients with an important shortening of the treatment period.[4,7]

Finally, in 1980, the replacement of streptomycin which became inefficient[4,6,8] by Pyrazinamide (synthesized in 1954), was a major breakthrough that reduce the duration of the treatment from 9 to 6 months. This last quadritherapy is the first line treatment of tuberculosis currently use.[1,12,14]

Apart from these drugs, it should be noted the existence of other anti-tuberculosis drugs[4,6,14] such as Thiacetazone (appeared before isoniazid), Cycloserine, Ethionamide and Ofloxacin.

For efficient use of these medicines, WHO advocates their classification in terms of "first-line drugs" and "second-line drugs" involved in therapeutic diets. This classification was made in consideration of the criteria of efficiency, resistance, tolerance, and the price of the tuberculosis drugs available.[1,14] The first-line antituberculosis drugs are the most effective and their use in combination allow to avoid the development of resistance. As for second-line drugs, they are used after failure of treatment with first-line antituberculosis drugs because they have many disadvantage.[15]

I.2.1- First-line tuberculosis drugs

The first-line drugs are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol (**Figure 1**). Isoniazid and Pyrazinamide are prodrugs whose active derivatives are produced through the activity of catalase / peroxidase KatG[16,17] and PcnA pyrazinamidase[7,8] respectively.

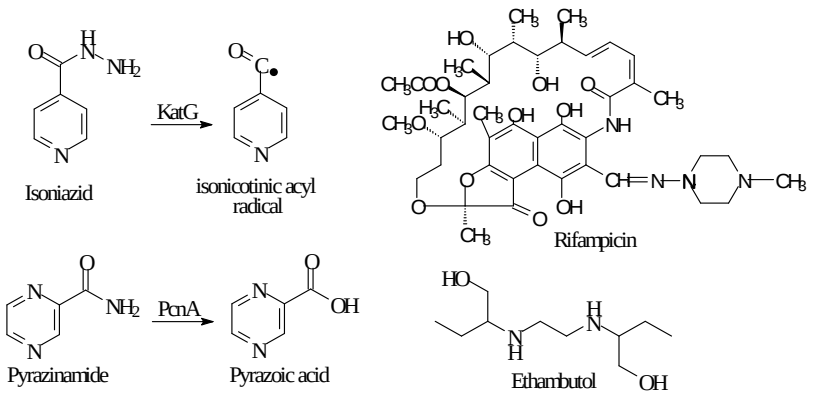

Figure 1: Chemical structures of first-line tuberculosis drugs.

I.2.2- Second-line tuberculosis drugs

The second-line drugs are characterized by limited sterilizing capabilities, and presence of major adverse side-effects and higher costs.[15] Their use requires medical assistance because some of these antibiotics should be injected into patients on a longer period of treatment ranging from 18 to 24 months. These drugs are primarily used for the treatment of cases of

tuberculosis related to proven multidrug-resistant bacilli.[18,19,20] These molecules can be classified into 6 families, namely the Aminoglycosides (Streptomycin), Fluoroquinolones (Ciprofloxacin), Thionamides (Ethionamide), Oxazolidinones (D-cycloserine), Para Amino Salicylates (PAS) and Thioamides (Thiacetazone).

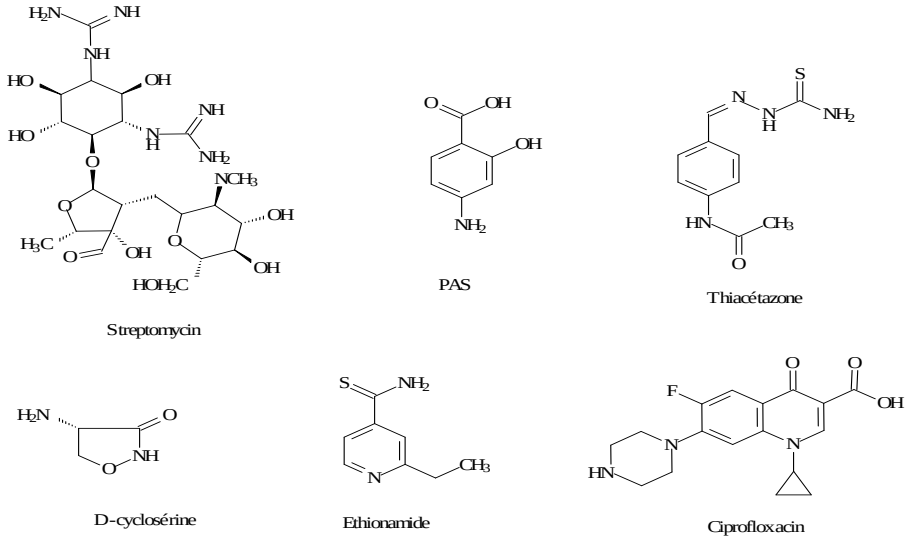

Figure 2: Chemical structures of second -line tuberculosis drugs

To these tuberculosis drugs of first and second line, must be added the very new tuberculosis drugs often classified as third-line drugs. This latest class contain the Bedaquiline and Delamanid[8,12] (**Figure 3**) respectively approved in 2012 and 2014 as specific tuberculosis antibiotics drugs.[17,21,22,23] These two molecules, administered orally, are recommended to treat cases of multidrug-resistant pulmonary tuberculosis in adults in combination with other tuberculosis drugs. However, their use is limited by the lack of data on their long-term sides effects.

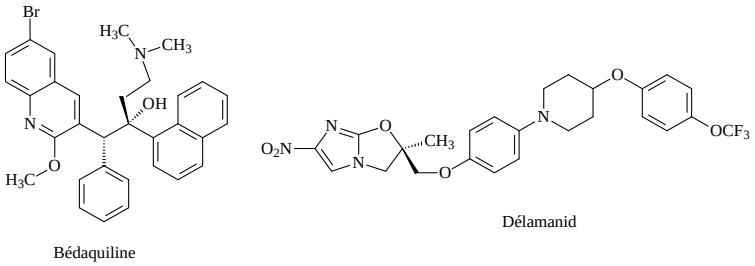

Figure 3: Chemical structure of Bedaquiline and Delamanid.

I.2.3-Mechanism of action of modern TB drugs

First, second or third line antibiotics deploy their antituberculosis activity by different mechanisms of action on different biological targets in *mycobacterium*. These biological mechanisms and targets are summarized in the table below.[24]

Table 1: Summary of the mechanism of action and biological targets of antituberculosis drugs.

Antituberculosis drugs		*Mechanism of action*	*Biological targets*
Antituberculosis drugs of 1st line	**Isoniazid**	Inhibition of the synthesis of the acid mycoliques, effects on DNA, lipids, and carbohydrates has Enoyl reductase (InhA)	Enoyl reductase (InhA)
	Rifampicin	Inhibition of the synthesis of RNA	RNA polymerase β subunit
	Ethambutol	Inhibition of the biosynthesis of arabinogalactan	Arabinosyl transferase
	Pyrazinamide	Blocking of membrane transport	Metabolism
Antituberculosis drugs of 2nd line	**Aminoglycosides**	Inhibition of the synthesis of proteins	Ribosomal RNA
	Fluoroquinolones	Inhibition of transcription and DNA replication	DNA gyrase
	Thionamides	Inhibition of the synthesis of mycoliques acids	Enoyl reductase (InhA)
	D-Cycloserine	Inhibition of the synthesis of the Peptidoglycan	D - alanine racemase
	PAS	Inhibition of the synthesis of folate acid, thymidilate synthase and transport of iron	Dihydrofolate reductase
	Thiacetazone	Inhibition of the synthesis of mycoliques acids	FAS - II dehydratase
Antituberculosis drugs of 3rd line	**Bedaquiline**	Inhibition of the production of energy	ATP synthase
	Delamanid	Inhibition of the synthesis of mycoliques, Production of radicals (NO•) toxic acids	Not fully elucidated

I.2.4 - Resistance and limits on use of the drugs first and second lines

Mycobacteria have developed resistance through various genetic mutation mechanisms to most antituberculous drugs. Thus, the resistance to Isoniazid comes from a mutation of KatG and inhA.[16,25,26,27,28] The Resistance to Rifampin and Ethambutol are expressed by a mutation respectively at the level of the gene rpoB[17,26] and embB.[17,26,29,30] Finally, the resistance to Pyrazinamide is the result of a mutation at the level of the gene PncA.[17,26,31] In

addition to this primary drug resistance, the Multidrug-Resistant and ultraresistances form of tuberculosis have emerged..

According to WHO, Multidrug-Resistant Tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to the 2 most potent anti-TB drugs; while Ultra-Resistant Tuberculosis (UR-TB) is defined as resistance to first and second-line drugs, particularly isoniazid, rifampin, fluoroquinolones and aminoglycosides.[17,26,29]

This drug resistance is associated with other limits of use of antituberculous drugs that are:
-The low sterilizing capacity causing their ineffectiveness on the dormant bacilli,
-The long duration of treatment leading treatment compliance problems and increase in adverse side effects,
-The harmful drug interactions due to multidrug therapy especially in case of tuberculosis-HIV co-infection.

To overcome all these limitations and to have new, more effective antituberculous drugs, different teams have undertaken new research around existing molecules and / or new chemical series.

II-PHARMACOMODULATIONS AND NEW ANTITUBERCULOSIS DRUGS

To obtain new molecules more effective and better tolerated, three main strategies have been developed across the pharmacomodulations. The first one focused with the review of existing antituberculosis drugs. The second strategy was to focus on molecules with high antituberculous potential. Finally, the last one concerned the development of new antituberculosis drugs with innovative mechanisms of action.[32]

II.1- Revival existing antituberculosis drugs

This first strategy is characterized by the pharmacomodulation of the structure of antituberculosis drugs to maximize therapeutic efficacy and reduced side effects.

II.1.1-Derivatives rifampicin: Rifapentine and Rifabutin

The pharmacomodulations carried out around Rifampicin made it possible to obtain Rifapentin and Rifabutin. Rifapentin (**Figure 4**) was obtained by replacing methyl piperazine of Rifampicin by cyclopentyl.[33] This chemical modulation reduced the duration of treatment from 6 months to approximately 3 months.[33] Rifapentin is currently in phase III clinical trials for the treatment of latent tuberculosis.[34]

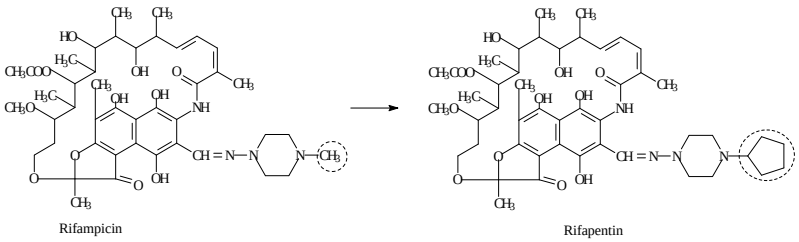

Figure 4: Pharmacomodulation of Rifampicin in Rifapentin.

As for Rifabutin (**Figure 5**), it results from a benzoxazimyl type cyclization of the hydroxyl at position 4 of Rifamycin SV. This modulation led to a compound that has a long half-life of 40 hours allowing to reduce the number of taking. In addition, it has been shown that Rifabutin has low harmful drug interactions, better tissue penetration and efficacy against MDR-TB patients living with HIV.[33]

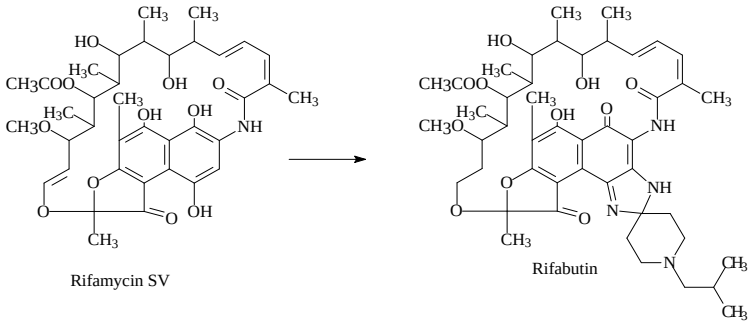

Figure 5: Pharmacomodulation of rifamycin SV in the rifabutin.

II.1.2-Derivatives Ethambutol: SQ109

The pharmacomodulations realized around Ethambutol led to the SQ109 derivative (**Figure 6**). This compound, belonging to the chemical class of ethylenediamine was obtained by replacing hydroxyethyl group of Ethambutol with alkyl groups. It demonstrated excellent activities against both drug susceptible and MDR strains of *Mycobacterium tuberculosis*.[17,35,36]

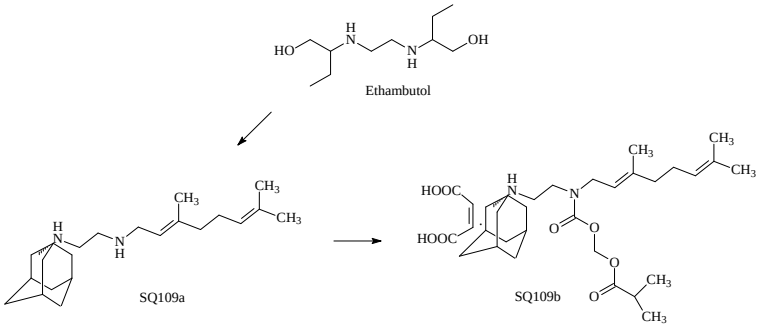

Figure 6: Pharmacomodulation of Ethambutol to the SQ109 derivatives

II.2-Molecules with high potential tuberculosis

In the second strategy, antibiotics that demonstrated activities against *Mycobacterium tuberculosis* including multi-resistant and ultraresistant strains were revivaled. These include the oxazolidinones, fluoroquinolones and dihydrophenazine derivatives.

II.2.1-Class of Oxazolidinones: Sutézolid and AZD5847

In this therapeutic class, we interested in Linezolid. The Linézolid is a synthetic antibiotic of the oxazolidinone family that inhibits the growth of *Mycobacterium tuberculosis*. This one has undergone a replacement of the morpholin present in its structure by a thiomorpholin. Such modulation led to Sutézolid (**Figure 7**) that showed a better tolerance than the Linezolid.[37,38] The AZD5847 (**Figure 7**) is another oxazolidinone obtained by pharmacodulation of Linezolid replacing the morpholine by an amide by tetrahydropyridine and isoxazol-3-yl.[32,39] These two molecules in phase II clinical trials demonstrated better tolerance than Linezolid doubled of reducing the duration of treatment.[32,39]

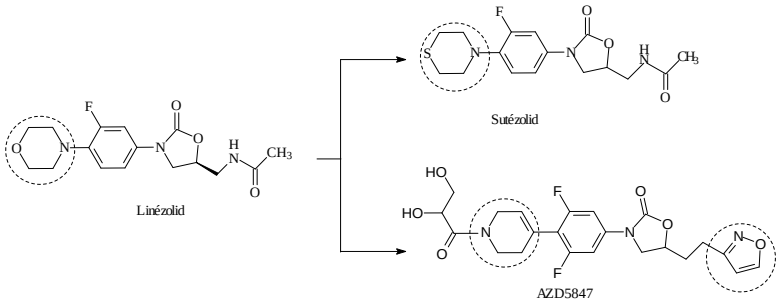

Figure 7: Pharmacomodulation of linezolid in the Sutezolid and the AZD5847

II.2.2- Class of fluoroquinolones: Moxifloxacin and DC 159

In this chemical series, two structural changes were performed on ciprofloxacin. The first derivative resulting from such modulation is Moxifloxacin **(Figure 8)**. It is the result of the replacement of C_7-piperazine of Ciprofloxacin by a piperidino-pyrrolidine and the addition of a methoxyl group in C_8. This molecule combines the advantages of having a long half-life, better solubility, efficacy on MDR-TB and a reduction in the duration of antituberculous treatment from 6 months to 4 months.[32,38,40] The second compund derived from Ciprofloxacin is DC159 (Figure 8). It is a fluoroquinolone in preclinical test phase, which carries in C7 to pyrrolidine, methoxyl group in C8 and the fluorocyclopropyl on the nitrogen atom in position 1. These structural features have allowed it to exhibit better antimycobacterial activity than Rifampicin and other Quinolones. In addition, it is effective

against Quinolone-resistant atypical bacilli and MDR strains of *Mycobacterium tuberculosis*.[41,42,43]

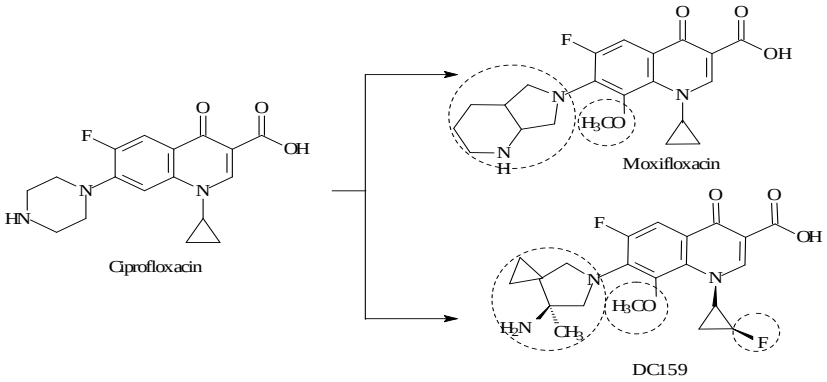

Figure 8: Pharmacomodulations of ciprofloxacin to Moxifloxacin and DC159

II.2.3-Class of dihydrophenazine: TBI-166

In exploring dihydrophenazine derivatives, Clofazimine, an anti-leprosy drug, was found to be active on *Mycobacterium tuberculosis*.[17,44] However, its low solubility and very long half-life are responsible for its accumulation in the tissues and the discoloration of the skin.[44,45] To overcome its limitations, TBI-166 (**Figure 9**) was developed by replacing *para*-chlorophenyl on the structure of Clofazimine with 2-methoxypyridin-3-yl. This derivative, which has the same efficacy as Clofazimine, has better physicochemical and pharmacokinetic properties to allowing avoid discoloration of the skin.[44,46]

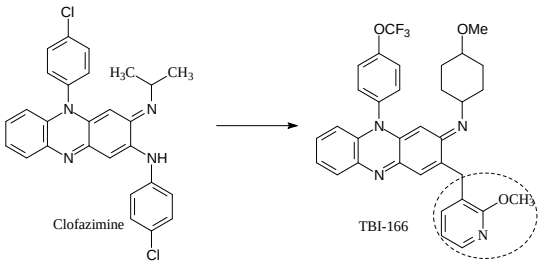

Figure 9: Pharmacomodulation of Clofazimine to TBI-166

II.3- New anti-tuberculosis drugs

The search for new molecules with innovative mechanisms of action triggered the development of new antituberculous drugs belonging to different chemical series.

II.3.1-Derivatives of diarylquinoléines: Bedaquiline

The diarylquinoléines were discovered as a result of a chemical screening, carried out with a view to obtain a structural model which inhibit the growth of *Mycobacterium smegmatis*

(non-pathogenic strain of *Mycobacterium* fast-growing). The Bedaquiline (**Figure 10**) currently marketed in the United States of America, has good anti-tuberculosis activity against the sensitive strains, multiresistant and ultraresistant of *Mycobacterium tuberculosis*. In addition, it has good oral bioavailability associated with a long half-life and and could act synergistically with pyrazinamide to reduce the duration of treatment. The Bedaquiline is characterized by its innovative mechanism of action, which consists in inhibiting bacterial ATP synthase. This inhibition causes a depletion of ATP reserves. Another advantage of this different mechanism of action is the absence of cross-resistance with other anti-TB drugs.[17,21,22]

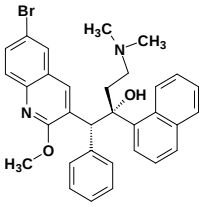

Figure 10: Structure of Bedaquiline.

II.3.2-Derivatives of nitroimidazopyran and nitroimidazooxazole

These are bicyclic structural analogues of the nitroimidazoles obtained by metronidazole pharmacomodulation. The research on these nitroimidazoles as antituberculous was born from an observation reporting the sterilization of latent strains of *Mycobacterium tuberculosis* when Metronidazole and Rifampicin were associated.[36,39,47] The nitroimidazopyran derivatives PA824 and TBA354 (Figure 11) are respectively in Phase II clinical trials and in the preclinical phase. These in addition to being active on MDR mycobacteria are effective on the intracellular and quiescent forms of tuberculosis bacilli.[36,39,47,48]

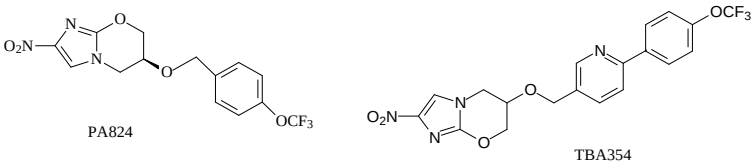

Figure 11: Structure of PA824 and TBA354.

As for the derivatives nitroimidazooxazole, they are represented by their leader, namely the OPC67683 or Delamanid (**Figure 12**). This molecule is currently used for the treatment of MDR-TB in combination with other anti-tuberculosis drugs. It is effective both on resistant mycobacteria, on quiescent and intracellular forms while allowing the reduction of the

duration of treatment. Its mechanism of action is innovative and highly dependent on aerobic or anaerobic conditions. Indeed, in aerobic conditions, these molecules activated by bioreduction would act by inhibiting the biosynthesis of proteins and lipids of the cell wall with growth arrest. In anaerobic conditions, it seems that their main metabolites formed after bioreduction have a harmful effect on the energy system of the *Mycobacterium*.[36,47,49]

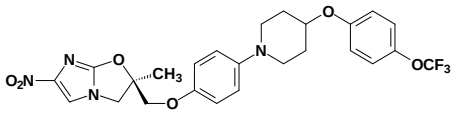

Figure 12: Structure of Delamanid.

II.3.3-Derivatives of imidazopyridine: Q203

The imidazopyridine amides are a new class of antituberculous drugs discovered following a specific and selective chemical screening using "phenotypic high content" technology performed directly on macrophages infected in vitro. The preclinical investigations undertaken have helped to highlight the antimycobacterial activities of Q203 derivative (**Figure 13**) on both extracellular and intracellular forms. The latter is distinguished by its paradoxically better performance on multi-drug resistant and ultraresistant strains than on susceptible strains. Q203 would in fact act by blocking the growth of *Mycobacterium tuberculosis* through its interaction with cytochrome bc1, an essential complex for the respiration of mycobacteria.[50,51]

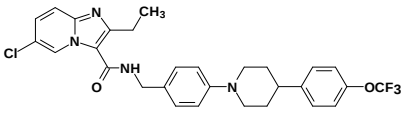

Figure 13: Structure of Q203.

II.3.4-Derivatives of dipiperidine: SQ609

The anti-tuberculous dipipéridines constitute a derived class ethylenediamines (pharmacophore of Ethambutol) wherein the diamine chain is included in two piperidine cycle, hence their name. The SQ609 (**Figure 14**) was identified as the most promising antimycobacterial of this series.[21,52,53] The SQ109 acts like the Ethambutol by inhibiting the biosynthesis of the cell wall. It would have a very good activity against *Mycobacterium tuberculosis* with a marked action on intracellular forms and low cytotoxicity. In combination with Isoniazid, Rifampicin and Pirazinamid, it would be more effective. It is currently being evaluated in preclinical trials.[54,52,53]

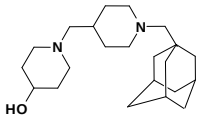

Figure 14: Structure of SQ609.

II.3.5-Derivatives of benzothiazinone: PBTZ169

The benzothiazinones are nitroaromatics compounds possessing a 2-piperazino benzothiazinone structure. They showed excellent activity vis-à-vis *Mycobacterium tuberculosis* and a new mechanism of action.[55,56] Benzothiazinones would act by inhibition of DprE1, essential enzymes involved in the synthesis of the cell wall. Among these compounds, PBTZ169 (**Figure 15**) stood out by its *in vivo* efficacy in the treatment of chronic tuberculosis in mice. Currently in phase I clinical trials, it would be more active on multirésistant and ultraresistant strains.[55,56]

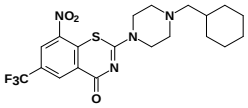

Figure 15: Structure of PBTZ169

II.3.6- Derivatives of nucleosides: SQ641 and CPZEN45

The nucleoside analogues SQ641 and CPZEN45 (**Figure 16**) are a class of anti-infective and anticancer drugs. These are natural products isolated from *Streptomyces* sp just like Streptomycin. They act by inhibition of translocase I, an essential enzyme involved in the biosynthesis of peptidoglycan. This translocase is an interesting target because of its unique presence in mycobacteria. Their singular mechanism of action justifies their action on the multiresistant and ultraresistant strains of *Mycobacterium tuberculosis*.[17,55]

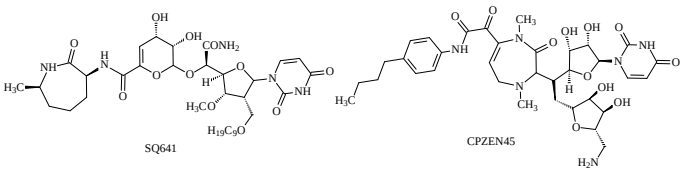

Figure 16: Structure of SQ641 and CPZEN45.

CONCLUSION

This review of the literature, whose purpose was to take stock of tuberculosis drugs, made it possible to understand that tuberculosis is a very old disease caused by *Mycobacterium tuberculosis* and that its treatment is constantly evolving. Indeed, before the discovery of

antituberculous drugs, non-medicinal "empirical" treatments have been proposed. Drug treatment began in the 1940s with the discovery of Streptomycin. Subsequently, various other antituberculous agents such as *Para*-Aminosalycilic acid (1944), Isoniazid (1952), Ethambutol (1957), Rifampicin (1967), Pyrazinamide (1980) and fluoroquinolones (1982) have been used to treat this infection. In addition, it took more than half a century to market a new anti-tuberculosis drug, Bedaquiline (2013). In addition, to limit the occurrence of resistance and reduce the duration of treatment, current tuberculosis treatment is in combination of several antituberculosis drugs. However, the challenge of tuberculosis control is not limited to a race against resistance, but it takes into account many other factors such as dormant bacilli involved in latent tuberculosis, interactions with HIV treatment and adverse effects. Some anti-tuberculosis drugs. To overcome the drawbacks of current anti-tuberculosis drugs, research focused on the optimization of existing drugs, the discovery of new biological targets, and even new molecules. Such research has triggered the development of new classes of antituberculous drugs, the most promising of which are diarylquinolines (Bedaquiline) and nitroimidazooxazoles (Delamanid).

Thus, the anti-tuberculosis drugs of the future under development will have to be able to solve certain difficulties encountered with the current drugs. These drugs will have to:

- Being active on highly drug-resistant TB strains,
- Have a new mechanism of original action,
- To be able to sterilize the sites where dormant bacilli persist,
- Allow to reduce the duration of treatments,
- Better tolerated with fewer interactions with antiretrovirals.

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