ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Editorial

Perspectives in Multidrug-Resistant Tuberculosis Drug Discovery

Guilherme Felipe Dos Santos Fernandes[1,2]* and Jean Leandro Dos Santos[1,2]

[1]São Paulo State University (UNESP), Institute of Chemistry, Araraquara, Brazil
[2]São Paulo State University (UNESP), School of Pharmaceutical Sciences, Araraquara, Brazil

***Corresponding Author**: Guilherme Felipe Dos Santos Fernandes, São Paulo State University (UNESP), Institute of Chemistry, Araraquara, Brazil.

Received: May 25, 2017**; Published:** June 09, 2017

Tuberculosis (TB) has become one of the most important infectious diseases worldwide responsible for 10 million of new cases and 1.3 million of deaths worldwide according to World Health Organization (WHO) [1]. Currently, there is an increased number of new cases of multidrug multidrug-resistant (MDR; defined as resistant at a minimum to rifampicin and isoniazid), extensively drug-resistant (XDR; defined as MDR plus additional resistance to at least one fluoroquinolone and one second-line injectable drug) and totally drug-resistant tuberculosis (TDR-TB) strains of *Mycobacterium tuberculosis* [2-4]. The last WHO's report reported around 480.000 new cases of MDR-TB and approximately 190.000 deaths around the world [1]. Despite this alarming worldwide scenario, the discovery of new drugs for the treatment of resistant tuberculosis presents some challenges to be overcome. For instance, bedaquiline (Sirturo®, Janssen Therapeutics) approved by the U.S. Food and Drug Administration (FDA) in 2012 and delamanid (Deltyba®, Otsuka Pharmaceutical) approved in 2014 in Europe, Japan, and South Korea were the last drugs for MDR-TB treatment. Nonetheless, strains resistant to these new molecules have been reported [3,4]. Current, we have observed some advances in the development of new drug candidates for MDR-TB treatment. For instance, the current anti-tuberculosis drug pipeline presents several molecules in clinical trials, including sutezolid, pretomanid, clofazimine and levofloxacin [5,6]. Despite approved by regulatory agencies, both bedaquiline and delamanid are still under evaluation in clinical trials (phase 3 and 4).

Although there are advanced drug candidates in clinical trials, the rate of failure in the development of anti-tuberculosis drugs is still high. Why? What are the reasons for these failures? The ongoing research and development of new bioactive compounds that may be useful in the treatment of resistant tuberculosis plays an important role [7]. Advances in relation to promising compounds have been achieved in recent years and several molecules reached MIC_{90} values at nanomolar concentration against MDR-TB strains. For instance, Roh and coworkers have identified an oxadiazole derivative (1) with MIC_{90} of 0.03 μM and selective index above to 600 [8]. In another work, a pyrazolo[1,5-a]pyridine-3-carboxamide derivative (2) was discovered through a phenotypic screening evaluation and it exhibited MIC90 of 0.01 μM against several MDR-TB strains. In addition, this compound was able to reduce the bacterial burden in a mouse model infected with the selectable marker-free autoluminescent *M. tuberculosis* H37Ra, a non-virulent strain [9]. The quinoline derivative (3) was reported with a better antituberculosis activity. This compound presented an outstanding MIC_{90} of 0.001 μM against a clinical isolate MDR-TB strain [10]. Luoting Yu and coworkers have reported a benzothiazinethione derivative (4) with a MIC_{90} of 0.03 μM against several MDR and XDR-TB clinical isolates strains. This compound demonstrated *in vivo* efficacy in a mice model, which was able to reduce the MTB burden in lungs by 3.4 logs CFU [11]. Moreover, compound (4) showed good pharmacokinetics. More recently, Kozikowski and coworkers have identified a potent indole-2-carboxamide derivative (5) with MIC90 values ranging from 0.006 to 0.047 μM against MDR and XDR-TB strains. Furthermore, this compound was able to reduce the bacterial burden of 2.12 $\log_{10}$ CFU in the lungs after 4 weeks of treatment in a mouse infection model [12].

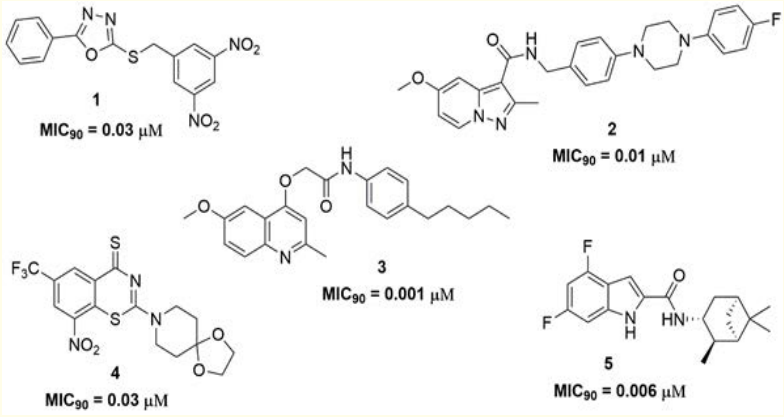

Figure 1: *Compounds with antitubercular activity against MDR-TB.*

These interesting results pointed out some of these compounds as promising drug candidates for human clinical trials. Nevertheless, detailed pharmacokinetic studies and the determination of the mechanism of action should be performed in order to ensure greater safety in clinical trials. The global scenario for MDR-TB drug discovery has been expanding and every year new bioactive compounds from several classes of heterocyclics have been reported as promising derivatives. The major challenge is to bring the most promising compounds to advanced stages of development, especially for clinical studies. For this, the partnerships between university and pharmaceutical industry are essential. Moreover, the continuing flow of investment in R and D by governments, research funding agencies and non-governmental organizations plays a vital role throughout the process.

Bibliography

1. World Health Organization, Global Tuberculosis Report, 2015.

2. World Health Organization, Global tuberculosis report 2014.

3. S Zhang., *et al*. "Mycobacterium tuberculosis Mutations Associated with Reduced Susceptibility to Linezolid". *Antimicrobial Agents and Chemotherapy* 60.4 (2016): 2542-2544.

4. E Segala., *et al*. "New mutations in the mycobacterial ATP synthase: New insights into the binding of the diarylquinoline TMC207 to the ATP synthase C-Ring structure". *Antimicrobial Agents and Chemotherapy* 56.5 (2012): 2326-2334.

5. M Pai., *et al*. "Tuberculosis". *Nature Reviews Disease Primers* 2 (2016): 16076.

6. RS Wallis., *et al*. "Tuberculosis-advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers". *Lancet Infectious Diseases* 16.4 (2016): e34-e46.

7. GFS Fernandes., *et al*. "Current Advances in Antitubercular Drug Discovery: Potent Prototypes and New Targets". *Current Medicinal Chemistry* 22.27 (2015): 3133-3161.

8. G Karabanovich., *et al*. "Development of 3,5-Dinitrobenzylsulfanyl-1,3,4-oxadiazoles and Thiadiazoles as Selective Antitubercular Agents Active Against Replicating and Nonreplicating Mycobacterium tuberculosis". *Journal of Medicinal Chemistry* 59.6 (2016): 2362-2380.

9. J Tang., *et al*. "Design, Synthesis, and Biological Evaluation of Pyrazolo1,5-apyridine-3-carboxamides as Novel Antitubercular Agents". *ACS Medicinal Chemistry Letters* 6.7 (2015): 814-818.

10. BC Giacobbo., *et al*. "New insights into the SAR and drug combination synergy of 2-(quinolin-4-yloxy): acetamides against Mycobacterium tuberculosis". *European Journal of Medicinal Chemistry* 126 (2017): 491-501.

11. C Gao., *et al*. "Benzothiazinethione is a potent preclinical candidate for the treatment of drug-resistant tuberculosis". *Scientific Reports* 6 (2016): 29717.

12. J Stec., *et al*. "Indole-2-carboxamide-based MmpL3 Inhibitors Show Exceptional Antitubercular Activity in an Animal Model of Tuberculosis Infection". *Journal of Medicinal Chemistry* 59.13 (2016): 6232-6247.

Volume 8 Issue 4 June 2017