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Systematic Review of New Trends in Antitubercular Synthesis and Analysis

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Abstract

Many researches are undertaken to develop antibiotics to treat resistant tuberculosis. This review discusses new trends in research undertaken on new antituberculars reported to date, with a particular attention on their synthesis and analysis.

Keywords

Review, Antituberculars, Synthesis, Analysis

1. Introduction

Tuberculosis still remains a major worldwide Public health concern [1] despite the significant progress in the fight against TB worldwide over 25 years. Its high mortality and morbidity rates are enhanced by Multidrug resistance and Human Immunodeficiency Virus infection [1]. HIV/AIDS pandemic provoked the re-emergence of TB from middle 1980s. In 1993, WHO declared tuberculosis (TB) as a global public health emergency. This declaration has stimulated many efforts in order to decrease and eliminate TB worldwide. Currently several antibiotics are combined to treat it and patients endure some adverse effects and stay long under observation [2] [3] [4] and [5]. In addition, some scholars point out the stability issue when antituberculars are administrated simultaneously. For example, Rifampicin degrades in presence of Isoniazid [6].

Recently, two new compounds, bedaquiline and delamanid were approved in combination to the actual MDR-TB chemotherapy [7]. Nevertheless, there is always the possibility that the tubercle bacillus can quickly develop resistance related to the mechanism of action of these new drugs.

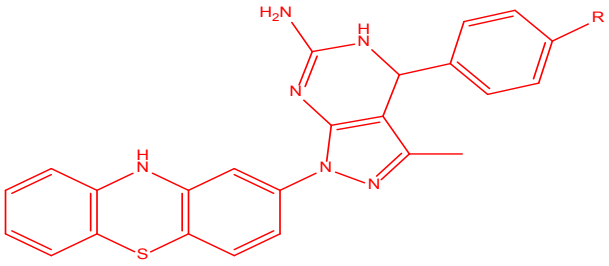
To face the multifactorial grow in tuberculosis epidemiology leading to an economical impact there is an emergency to discover and develop new antibiotics with new mechanisms of action having one target and less toxicity [2] [5]. Therefore, the actual therapeutic arsenal must be strengthened by other TB drugs. To meet this crucial need, several promising candidates are in process [4]-[20]. The developed strategies are used to shorten the treatment time, improve patient safety and/or overcome drug resistance issues.

This study explored and discussed strategies developed in the recent pass in synthesis and analysis of new antibubercular compounds.

2. Results and Discussions

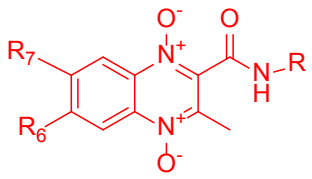
Tuberculosis (TB) is one of the oldest human diseases, but not a disease of the past. The discovery of *Mycobacterium tuberculosis* as the etiologic agent of tuberculosis has accelerated research and development of treatment and prevention of this disease. In 1921, the TB vaccine bacillus Calmette-Guerin (BCG) was firstly used in clinics. After the discovery of streptomycin as the first antituberculosis drug in 1944, many other antituberculosis drugs were then developed, e.g. isoniazid, rifampicin, ethambutol and pyrazinamide. Consequently, quadri-therapy regimens have been started for the treatment of TB in 1967. Tuberculosis became curable by chemotherapy and for that reason many people have believed that this disease could almost be defeated. Unfortunately, in the mid-80s, with the epidemic of acquired immune deficiency syndrome (AIDS), Tuberculosis has returned as one of the most threatening infectious diseases.

The current treatment regimen of Tuberculosis has some limitations. Decades of widespread and uncontrolled application of antibiotics in clinical has resulted in the emergence of drug resistant strains of *Mucobacterium tuberculosis* [7]. Phenothiazine derivatives for example, inhibit the NADH II of the respiratory chain of mycobacteria, are synthesized by Biginelli multicomponent reaction, but are known as antipsychotics that display lots of adverse events and studies are still limited to *in vitro* tests [8].



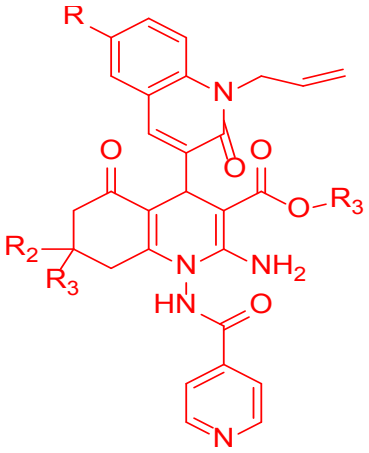
Scheme 1. General structure of potential antituberculars containing Phenothiazine nucleus [8].

Many studies of Quinoxalines showed interesting biological properties and the structure-activity relationship (SAR), good *Mycobacterium tuberculosis* activity and less reduction potentials but little is known about their mechanism of action [9].



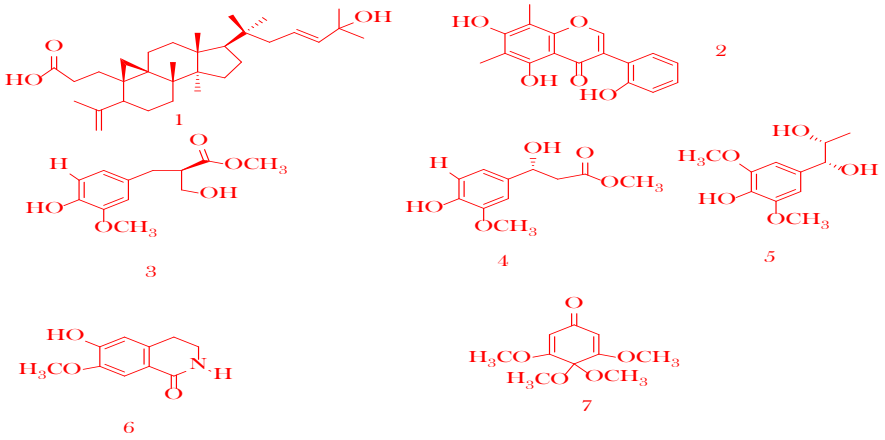
Scheme 2. General structure of quinoxalines [9].

Isoniazid and quinolones are combined by multicomponent cyclocondensation to give new active and less toxic potential antituberculars but the mechanism of action is not discussed [10].



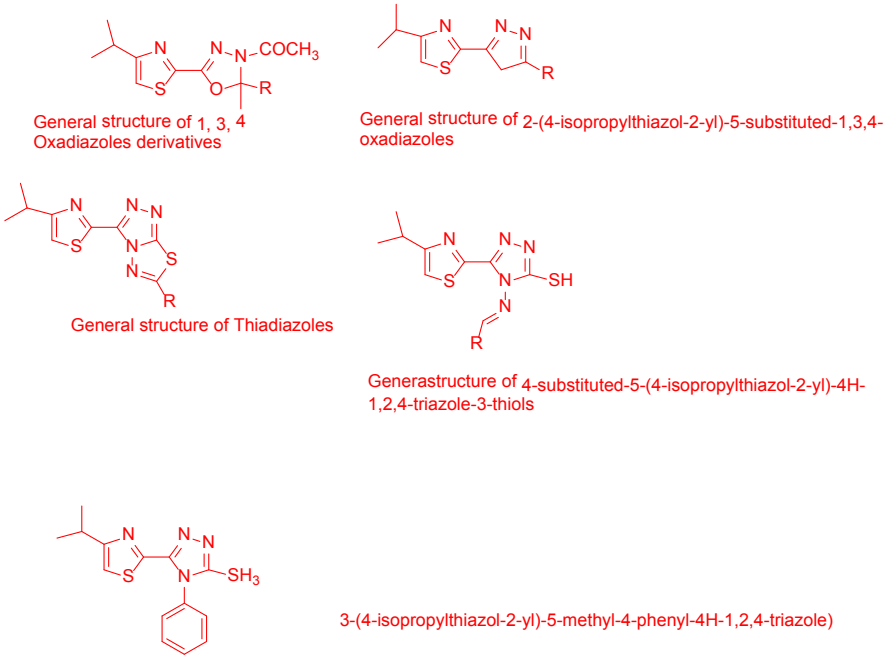
Scheme 3. General structure of biquinolone-isoniazide hybrids [10].

Fatty acid biosynthesis enzyme inhibitors appear to be attractive molecules for the design of news antitubercular agents but only *in vitro* [14]. Kuo *et al.* performed the structural elucidation of new compounds isolated from the stem of *Pisonia umbellifera* and their antitubercular activity on the H37Rv stain of *Mycobaterium tuberculosis* [15].



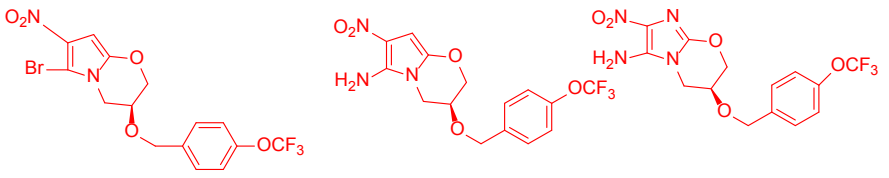
Scheme 4. Antitubercular compounds of *Pisonia umbellifera* [15].

Azoles inhibit the lipid biosynthesis of the cell-wall of the pathogen agents made of complex fatty acids like mycocerosic acids, arabinogalactans and peptidoglycans are lipophilic, and this key property influences their ability to reach their target by transmembrane diffusion and show promising activity against drug resistant tuberculosis. Clubbed 1, 2, 4-triazoles and 1, 3, 4-oxadiazoles are new class of azole antituberculars that are proved to be highly active both *in vitro* and *in vivo*. Propylthiazoles coupled with other heterocyclic rings provide novel biologically active compounds that could be explored as potent antimicrobial and antitubercular agents. The study was limited to the preliminary step of cytotoxicity, antimicrobial and antitubercular activities [16].



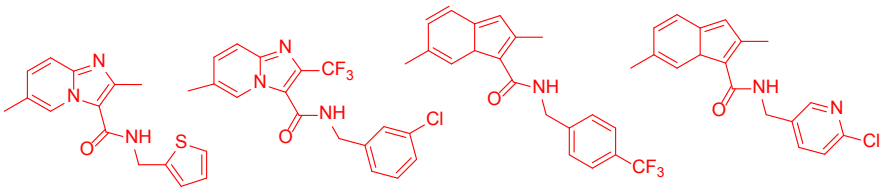
Scheme 5. General Strutucres of antitubercular Oxazoles, Thiadiazoles and triazoles compounds synthesized [16].

An important aspect is that the presence of nitro-imidazole ring in antibiotics influences reduction and the stability of the corresponding nitro radical anion and tend to be a key element to overcome the resistance of bacteria [17].



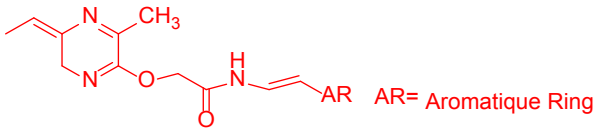
Scheme 6. Structures of antitubercular Nitroimidazoles [17].

Imidazole [1, 2-*a*] pyridine inhibitors compounds of resistant antituberculosis pathogens inhibiting the DNA synthesis are also explored and further investigation are needed for confirmation [3].



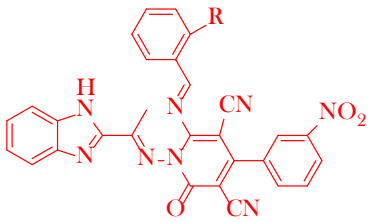
Scheme 7. New Imidazole [1, 2α] pyridine inhibitors [3].

Microwave assisted synthesis can improve reaction yields in less time and friendly to the environment comparatively to traditional heating method [11].



Scheme 8. General structure of Microwaze-Assisted Synthesized new antitubercular Quinoxaline-Incorporated Schiff Bases [11].

Benzimidazole compound are not only none cytotoxic but also release good antitubercular activities, and one of them is shown to give better activity than chloramphenicol and ketoconazole but the tested cytotoxic of these molecules is none neglected [4].



Scheme 9. General structure of Facile Synthesized Benzimidazole bearing 2 pyridones new antituberculars compounds [4].

The shikimate kinase inhibition is a newly discovered mechanism of action of some new antitubercular medicines, results are limited to in silico-designs until, and *in vitro* tests and clinical trials are needed for a final conclusion [18]. Deoxysugars are a group of compound candidate antituberculars that inhibit Alpha-Monnosidase enzymes [19]. Some inorganic compounds and compounds containing Metal are also discussed. ZnO nanoparticles have antibacterial activity and may have future applications [20]. Ni (II) and Co (II) complexes of heterocyclic hydrazine ligands were synthesized, and the yielded compounds shown antioxidant and antibacterial properties [21]. Some Ruthenium (II) Complexes with polypyridines showed remarkable antitubercular activities [22]. Some innovations are made in synthesizing antituberculars to produce best yield, to reduce reaction time and use less catalyst without losing the catalytic activity [13].

Computational chemists have also showed by using software, some peptides can display antibacterial activities [23]. Docking studies of nitro-aromatic compounds indicated that the presence of most negative potential regions above the oxygen atoms of nitro groups extending laterally towards the isoxazole ring or amide bond are essential for potent antitubercular activity [24]. Fragment-based drug discovery (FBDD) approach has emerged among many strategies that are actually used in the drug development, as a promising strategy. This method relies on the screening of small chemical entities that can probe biological targets more effectively than drug-like molecules. Identified hits are then rapidly optimized using rational design to lead-like compounds [7].

Concerning methods used for antitubercular analysis, HPLC-RRS was reported to be a suitable method to detect fluoroquinolones in human urine and in water [25]. It was also reported that UPLC-MS-MS was suitable to monitor dosage froms and to performe pharmacokinetic analysis of antituberculars [26]. Electrochemistry and voltammetry are also used to analyze antituberculars. Among the reported methods voltammetry seems to be the more popular both in pharmaceutical dosage forms and in biological fluids analysis [14]. Electrochemical methods like Polarography and Electrochemical stripping techniques are precise, accurate, and economic for the analysis of quinolones in pharmaceutical dosage forms, biological fluids and in low level media [27]. Nanoelectrochemistry, precisely nanovoltametry is very famous in antitubercular analysis [28]. The new trends in antibacterial and antitubercular analyses are Nano electrochemical methods [29]. Electrochemical sensors and biosensors are applicable to any scientific field including anti-tuberculosis analysis [23]. Electrochemical Nano sensors are also usable in coulometry [30]. The addition of surfactants to electrolyte that contain Isoniazid can enhance the oxidation current signals in voltametric analysis of the analytical method and improve the limit of detection [31]. Structural determinations are performed by IR and H-NMR and Mass spectrometry, elemental analyses and X-ray crystallography [12]. Various phthalides synthetized from 2-carboxy-benzaldehydes and aromatic methyl ketones in presence of methane sulphonic acid are reported to have antitubercular activities. Their antitubercular activities are characterized by spectral techniques, namely by the XRMA and 4 of the screened compounds showed an IC50 ranging from 0.81 - 1.24 μg, thereby providing potential lead compounds for future drug discovery studies [32].

3. Conclusion

We have critically examined the strategies developed in the last decades for antibubercular compounds synthesis and analysis. Decades of widespread and uncontrolled application of antibiotics in clinical has resulted in the emergence of drug resistant strains of *M. tuberculosis.* To face drug resistance, several methods are developed for the synthesis of new antitubercular compounds. Among many strategies that are actually used in the drug development, fragment-based drug discovery (FBDD) approach has emerged as a promising strategy. Azoles

are more discussed than any other antitubercular. Many analytical methods are used to characterize antitubercular antibiotics. Liquid chromatography and voltammetry are mostly preferred for the determination of antitubercular compounds. The redox (oxidation/reduction) properties of antituberculars make them analyzable by electrochemical methods. The quantification of the categories of antibiotics by voltammetry in both dosages forms and human body fluids seems to be the cheapest for developing countries. This analytical method is not only precise, accurate and with low limit of detection but also less difficult to perform comparably to the others.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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