Recent Advances in the Development of Salicylic Acid Analogues as Anti-Tubercular Agents

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ABSTRACT

Tuberculosis is still the second most crucial infectious disease globally. The effective treatment of tuberculosis is difficult due to the unusual cell wall structure and composition of mycobacteria, which makes many drugs ineffective and obstructs the entrance of drugs. The most essential cause for this is drug resistant tuberculosis, persistent infection and synergism of tuberculosis with HIV and also no any new effective chemical entity has come in last few decades. The modern drug design promises to bring significant development in the fight against tuberculosis. In this review, brief discuss on salicylic acid derivatives as anti-tubercular agent.

Keywords: Drug-resistant, tuberculosis, anti-TB drugs, *para*-aminosalicylic acids.

1. INTRODUCTION

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*Mtb*). It is the world's second regular cause of death from infectious diseases, after AIDS (Asif et al., 2014; Asif. 2014; Asif et al., 2013). According to the World Health Organization report, 2 million people die per year and at least 9 million are getting infected with TB, which support for the development of new active form of TB. The current treatment for TB is directly observed treatment short-course (DOTS) and DOTS-Plus (DOTS plus Second-line TB drugs) for multi drug resistant TB (MDR-TB) and extensively drug resistant (XDR-TB). In spite of the fact that it is curable and avoidable, the TB has been spreading at a balanced rate over the few years. Additionally, the reappearance of TB is alarming due to the development of pathogenic synergy with human immuno-deficient virus (HIV). The TB normally has a much earlier origin in AIDS patients than other pathogenic disorders. The frequency of TB in HIV positive patients is 50 times more than that of the rate for HIV negative patients (Asif et al., 2013; Asif et al., 2013; Asif et al., 2013; Asif. 2013). The emergence of MDR-TB and XDR-TB as a result of lengthy treatment makes patient observance difficult. The MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin). MDR-TB takes longer time to treat with second-line drugs (DOT-Plus), which are more

costly and have more adverse effects. The XDR-TB will expand when the second-line drugs are mishandled and then also become ineffective. This expansion of drug resistance in the people has amplified alarm that TB may once again become an untreatable disease. Particularly, in developing countries, the occurrence of XDR-TB is growing as an outcome of poor financial wealth (Asif. 2013; Asif. 2012; Asif. 2012; Ducati et al., 2006; Loddenkemper et al., 2002) and thus gives a strong inspiration for the development of effective and inexpensive anti-TB agents.

2. CURRENT CHEMOPTHERAPY OF TUBERCULOSIS

The **c**hemotherapy of TB started with discovery of anti-TB drug streptomycin. After that various drugs have been discovered and commenced in anti-TB therapy, such as *para*-aminosalicylic acid, isoniazid, cycloserine, pyrazinamide, rifampin, ethionamide and ethambutol. The most of these drugs were exposed through broad screening. The lack of accepting of drug action was compounded by a deep unawareness of the biochemistry of the *Mtb* bacillus. The short-course TB therapy used to treat drug-susceptible *Mtb* consists of 2 months treatment with four first-line drugs rifampin, isoniazid, pyrazinamide and ethambutol, followed by 4 months treatment with rifampin and isoniazid. The MDR-TB treatment require second-line drugs such as *p*-aminosalicylate, kanamycin, amikacin, capreomycin, fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin), ethionamide and cycloserine where treatments often extend for as long 2 years (Perri and Bonora. 2004; Bastian and Colebunders. 1999; Joshi et al., 2006).

3. PARA AMINOSALICYLIC ACID (*P*-AMINOSALICYLIC ACID, PAS)

P-Aminosalicylic acid is a bacteriostatic that inhibits most tuberculous mycobacteria. In terms of tuberculostatic activity it is inferior to isoniazid and streptomycin. It is nephro and hepatotoxic, and is rarely used. A synonym of this drug is apacizin. *In vitro,* most strains of *Mtb* are sensitive to a concentration of 1 µg/ml. The antimicrobial activity of aminosalicylic acid is highly specific and microbes other than *Mtb* are unaffected and most nontuberculous mycobacteria are not inhibited. It alone is of little value in the treatment of TB in humans. Strains of *M.tb* insensitive to numerous hundred times the usual bacteriostatic concentration of aminosalicylic acid can be produced *in vitro*. Resistant strains of *Mtb* also emerge in patients treated with aminosalicylic acid, but much more slowly than with streptomycin (Rattan et al., 1998; Gray. 1997; Janin. 2007; Asif. 2012). Aminosalicylic acid is an analog of *para*-aminobenzoic acid, and its mechanism of action similar to the sulfonamides. However, the sulfonamides are ineffective against *Mtb,* and aminosalicylic acid is inactive against sulfonamide-susceptible bacteria. This differential sensitivity most probably reflects differences in the enzymes responsible for folate biosynthesis in the various microbes. Aminosalicylic acid is a second-line anti-TB drug. Its importance in the treatment of pulmonary and other forms of TB has markedly decreased since more active and better-tolerated drugs, such as ethambutol and rifampin, have been developed. It is administered orally in a daily dose of 10 to 12 g. Because it is a gastric irritant, it is best administered after meals, with the daily dose being divided into 2 to 4 equal parts and children should receive 150 to 300 mg/kg per day in 3 to 4 divided doses. The occurrence of untoward effects linked with the use of aminosalicylic acid is about 10% to 30%. Gastrointestinal problems, including anorexia, nausea, abdominal distress, epigastric pain, and diarrhea are predominant and often limit patient adherence. Patients with peptic ulcers tolerate the drug poorly. Hypersensitivity reactions are seen in 5% to 10% of patients. High fever may develop abruptly, with irregular spiking. Generalized malaise, joint pains, and sore throat may be present at the same time. Skin eruptions of various types appear as isolated reactions or accompany the fever. Among the hematological abnormalities are leukopenia, agranulocytosis, eosinophilia, lymphocytosis, an atypical mononucleosis syndrome, and thrombocytopenia. Acute hemolytic anemia may appear (Asif. 2012; Asif. 2012; Asif. 2012).

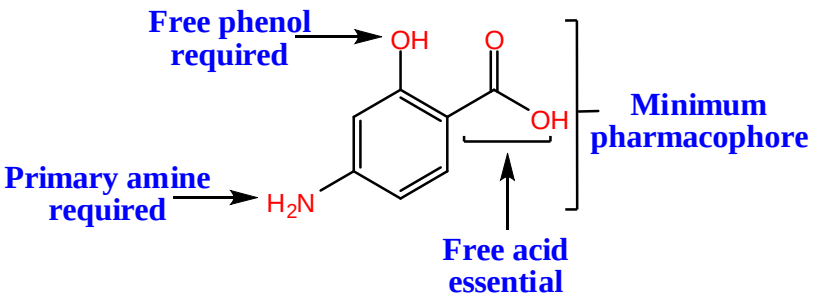
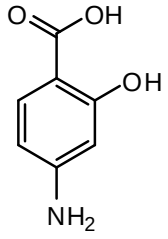


Figure 1
Structure activity relationship of p-aminosalicylic acid

3.1. Salicylic acid derivatives

The success of clinical trials of p-aminosalicylic acid in TB patients (Lehmann. 1949) prompted synthesis of analogs to enhance the activity of the parent compound. These analogs showed that p-aminosalicylic acid exhibits specific structural activity relationship (Doub et al., 1951). The mechanism of action of p-aminosalicylic acid is not fully understood, although folate biosynthesis has been proposed as the target, since inactivation of thymidylate synthase confers resistance (Rengarajan et al., 2004). The p-aminosalicylic acid is generally poorly tolerated in patients due to gastrointestinal disturbances often leading to discontinuation of p-aminosalicylic acid administration.

While in search of new potent anti-TB pyridines, a series of substituted *N*-pyridinyl salicylamides (**2**) and were evaluated for in vitro anti-TB activity against *Mycobacterium avium* and two strains of *M. kansasii*. Their moderate activity profile concludes that the 5-chloro-pyridin-2-yl and the substitution of the salicyl moiety by chlorine in position 4 or 5 had the strongest influence on the increase in anti-TB activity (Waisser et al., 2004). Salicylanilides derivatives have been of great interest in medicinal chemistry, although their mechanism of action still unknown. It is suggest that they serve as epidermal growth factor receptor protein kinase (EGFR PTK) inhibitors. These compounds have usually been designed to compete with adenosine triphosphate (ATP) in binding with the catalytic domain of tyrosine kinase. The selective inhibitors of interleukin-12p40 production also have a specific role in the initiation, expansion, and control of the cellular response to TB. The development of salicylanilide derivatives, a series of compounds (**3**) have activity similar to Isoniazid. Through a structure activity relationship study, the positions R_1 and R_2 showed Cl and Br atoms that are necessary for high activity against TB and that the benzyl and isopropyl substituent at R_3 increases activity (Imramovsky etal.,2009). Various salicylanilide derivatives that have been developed and showed electron withdrawing groups on the salicyloyl ring and hydrophobic groups on the anilide ring, as well as the 2-hydroxy group, are essential for optimal antimicrobial activity. Halogen substituted salicylanilides in both parties maintains the requirements and forms of more active derivatives that show anti-TB activity. However, its unsuitable physical properties led to the generation of prodrugs of salicylanilide derivatives with better bioavailability, and due to a high degree of lipophilicity, more efficient transport through *Mtb* cell membranes. Considering this, compound (**4**) was interesting activity against *Mtb*. The level of inhibition of is 89%-99% and an MIC of 3.13µg/mL. Although, the lipophilicity is a secondary parameter in anti-TB activity and demonstrated that in these compounds the stereoisomer effect is important for anti-TB activity; however, in this case the difference is not determined for individual R/S isomers (Imramovsky et al., 2009). Using the hybridization strategy, a series of derivatives with salicylanilides and carbamate groups, which have been used as antibacterial and antiviral agents. Thus the hybridization of two moieties could produce a new series with changes in their pharmacokinetic and pharmacodynamic properties. The carbamate could be protecting these molecules against first-pass metabolism, increasing their activity profile. The series obtained show that Cl atoms at 3 and 4-position on the aniline ring increase *Mtb* biological activity. Interestingly, the presence of an alkyl chain also increases the biological activity of these compounds, which suggests the importance of carbamate group (5). Although these compounds have high lipophilicity, high permeability for making of more effective drugs (Ferriz et al., 2009). Another strategy using salicylanilide derivatives has been the formation of cyclic derivatives, which could serve as antibacterial agents with a dual inhibition system.



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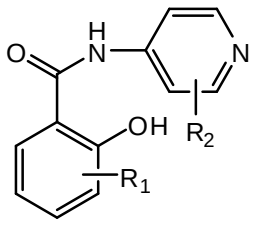

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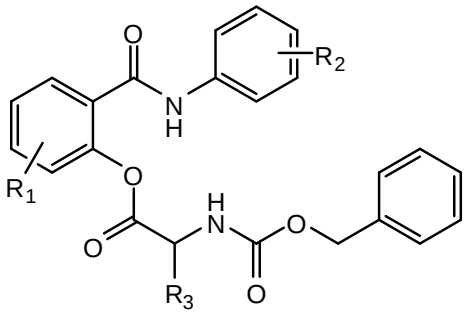

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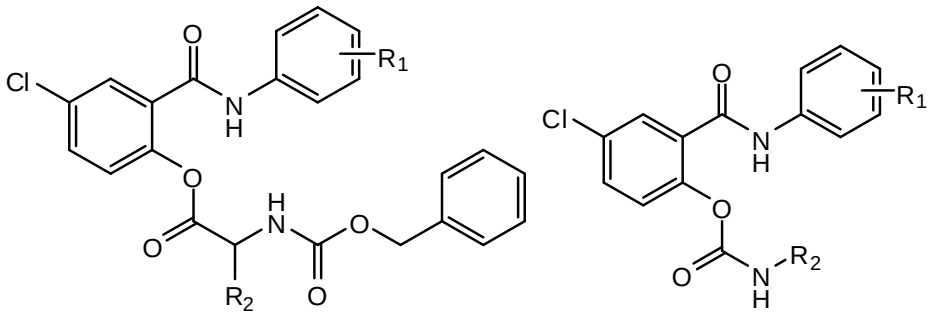

Figure 2
General structure of salicylanilide derivatives with anti-TB activity.

4. CONCLUSION

Tuberculosis is still the primary infectious cause of mortality in the globe, and many efforts have been done to improve the current therapy, allowing for the problem connected with the resistance concern. New introduced drugs, unfortunately, developed resistance upon prolonged treatment, so they can be used but only in combination with, at least, one antitubercular drug to which mycobacteria is susceptible. As consequence new multidrug regimens have been studied and some of them in used. Many new drugs are under clinical trials, and some of them are considered capable drugs for the future.

Peer-review
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Conflict of Interest
The authors declare that there are no conflicts of interests.

Data and materials availability
All data associated with this study are present in the paper.

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