Bulletin of Faculty of Pharmacy, Cairo University (2015) **53**, 45–52

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ELSEVIER

Cairo University

Bulletin of Faculty of Pharmacy, Cairo University

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ORIGINAL ARTICLE

Synthesis and anti-mycobacterial evaluation of some new isonicotinylhydrazide analogues

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Received 21 August 2014; accepted 15 November 2014
Available online 5 December 2014

KEYWORDS

Isoniazid derivatives;
Synthesis;
Antitubercular activity

Abstract The synthesis of some new 3,4-disubstituted thiazolylideneisonicotinohydrazide derivatives **3a**–**k**, 2-substituted thiazolidinylisonicotinamide derivatives **4a**–**d** and pyrrolylisonicotinamide derivatives **5**, **6** and **7** is described. The resulted compounds are evaluated for their *in vitro* antitubercular activity. The minimum inhibitory concentration (MIC) of compound **3g** showed comparable *in vitro* activity to isoniazid against *Mycobacterium tuberculosis* H37Ra 7131 strain in concentration 9.77 μg/mL.

1. Introduction

Tuberculosis (TB) is a common and often deadly infectious disease caused by various strains of mycobacterium, mainly *Mycobacterium tuberculosis*. Members of *M. tuberculosis* complex are *M. tuberculosis*, *M. africanum*, *M. bovis* and the Bacillus Calmette-Guérin strain, *M. microti*, *M. canettii*, *M. caprae*, *M. pinnipedii*, and *M. mungi*. The species (*M. avium* complex, *M. gordonae*, *M. kansasii*, *M. simiae*, *M. chelonae*, *M. fortuitum*, etc.) other than *M. tuberculosis* complex does not cause tuberculosis in humans, TB usually attacks the lungs but can also affect other parts of the body. It was considered to be a disease of poverty for many years due to its rare occurrence in developed countries.[1] However, recently more people in the developed world are contracting TB because their immune systems are compromised by immunosuppressive drugs, substances abuse, or AIDS.[2–5] Several decades ago, effective anti-TB drugs were launched and one could hardly find a TB case demonstrated at medical universities. But the return of TB was declared by the World Health Organization (WHO) as a global emergency compared to a hypothetic third world war with 9 million TB cases and two million deaths reported each year; about one third of the world's population is already infected with *M. tuberculosis*.[6] Moreover, recent advances in diagnostics, drugs, and vaccines and enhanced implementation of existing interventions have increased the prospects for improved clinical care and global tuberculosis control.[7]

According to the 13th Annual Tuberculosis Report of the WHO published on the world TB day on March 24, 2009, there were 9.27 million new cases of TB estimated worldwide.[4,8] The terms associated with drug resistance in tuberculosis are very important. The stages of tuberculosis in terms of developing resistance are as follows: drug-sensitive tuberculosis, monodrug resistant tuberculosis, poly-drug resistant tuberculosis, multi-drug resistant (MDR) tuberculosis, extensively drug resistant (XDR) tuberculosis, and extremely drug resistant (XXDR) tuberculosis. MDR-TB is defined as resistance to

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Peer review under responsibility of Faculty of Pharmacy, Cairo University.

http://dx.doi.org/10.1016/j.bfopcu.2014.11.001

isoniazid and rifampicin, with or without resistance to other first-line anti-TB drugs. XDR-TB is defined as resistance to at least isoniazid and rifampicin from the first-line anti-tuberculosis drugs (the definition of MDR-TB) in addition to resistance to any fluoroquinolone, and to at least one of the three injectable second-line anti-tuberculosis drugs (kanamycin, capreomycin and amikacin). Multidrug Resistant Tuberculosis (MDR-TB) proved resistant to at least rifampicin and isoniazid, the two most frequently used anti-TB agents.[5,9,10] Current treatment programmes to combat TB are under threat due to the emergence of multi-drug and extensively-drug resistant TB. As part of our efforts towards the discovery of new anti-tubercular leads, a number of potent tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide(THPP) and *N*-benzyl-6′,7′-dihydrospiro [piperidine-4,4′-thieno[3,2-*c*]pyran](Spiro) analogues were recently identified against *M. tuberculosis* and *Mycobacterium bovis BCG* through a high-throughput whole-cell screening campaign.[11]

TB treatment strategy is tedious, long and has several side effects. The currently applied classical drugs used to treat TB include broad and narrow spectrum agents and different combinations targeting different types of TB. Such drugs are traditionally divided into two lines. First line drugs include fundamental chemotherapeutics of choice, like isoniazid and streptomycin. They are highly effective, but very susceptible to resistant strains and must be administered for 6–9 months. When these treatments fail, second line TB drugs are used. Second line tuberculostatics are the most commonly used. However, these drugs have far lower efficacy and require even longer administration periods up to 18–24.[12]

Isoniazid (Fig. 1) is one of the active and successful agents used to treat TB. It was considered as a starting point in the search for new active derivatives and analogues such as hydrazones which have been reported as active anti-TB drugs (Fig. 2).[13–16]

Nevertheless, the isoniazid therapy has two major drawbacks. The first one is its hepatotoxic effects. Isoniazid is metabolized in the liver mainly by acetylation and dehydrazination. The *N*-acetylhydrazine metabolite is believed to be responsible for the hepatotoxic effects. The second is its deactivation by the action of N-arylaminoacetyltransferases (NATs). These enzymes are found in both mycobacteria as well as mammalian hosts, they deactivate isoniazid by acetylation reaction at N^2 (terminal amino group) which is a step in the metabolism of isonicotinic acid hydrazide (INH). The literature survey demonstrated the synthesis of isoniazid derivatives such as hydrazones and Schiff's bases, where N^2 is blocked towards acetylation by NATs.[17] These derivatives are more effective and less hepatotoxic than isoniazid.[18]

On the other hand, several heterocyclic compounds were explored in the search for a reliable starting platform for anti-TB drug development such as pyrrole derivatives. The recently synthesized pyrrole LL-3858 (Sudoterb) (Fig. 3)

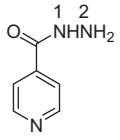

Figure 1 Isoniazid.

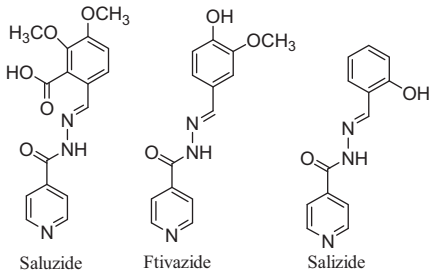

Figure 2 Some hydrazones of isoniazid.

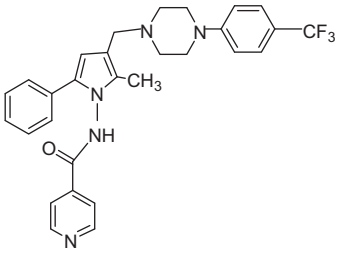

Figure 3 LL-3858 (Sudoterb).

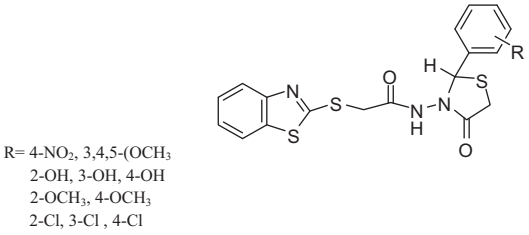

Figure 4 Some literature cited antituberculosis thiazolidine analogue.

showed higher bactericidal activity compared to isoniazid. Sudoterb is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs.[19,20]

Moreover, some drugs comprising a variety of ring systems exhibited bactericidal activity such as thiazolidine derivatives (Fig. 4).[21,22]

Guided by these findings, our rationale is to prepare new potent and safe isoniazid derivatives. Our strategy to construct new agents of isoniazid is based on the incorporation of various heterocyclic rings that possess anti-TB activity such as pyrrole and thiazolidine derivatives in the core structure of isoniazid with the aim of increasing their activity through blocking position NH_2 of the hydrazide group of isoniazid.

2. Materials and methods

2.1. Chemistry

Melting points were determined on Griffin apparatus and the values given are uncorrected. IR spectra were determined on Shimadzu IR 435 spectrophotometer (KBr, cm^{-1}). ^1H NMR