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Review

Current perspectives in drug discovery against tuberculosis from natural products

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ABSTRACT

Currently, one third of the world's population is latently infected with *Mycobacterium tuberculosis* (MTB), while 8.9–9.9 million new and relapse cases of tuberculosis (TB) are reported yearly. The renewed research interests in natural products in the hope of discovering new and novel antitubercular leads have been driven partly by the increased incidence of multidrug-resistant strains of MTB and the adverse effects associated with the first- and second-line antitubercular drugs. Natural products have been, and will continue to be a rich source of new drugs against many diseases. The depth and breadth of therapeutic agents that have their origins in the secondary metabolites produced by living organisms cannot be compared with any other source of therapeutic agents. Discovery of new chemical molecules against active and latent TB from natural products requires an interdisciplinary approach, which is a major challenge facing scientists in this field. In order to overcome this challenge, cutting edge techniques in mycobacteriology and innovative natural product chemistry tools need to be developed and used in tandem. The present review provides a cross-linkage to the most recent literature in both fields and their potential to impact the early phase of drug discovery against TB if seamlessly combined.

Contents

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Introduction

Tuberculosis (TB), an old, highly infectious disease, declared a global health emergency by the World Health Organization (WHO) in 1993, is still the second leading killer in the world, with an approximate 2 billion people being latently infected. These latently infected individuals with *Mycobacterium tuberculosis* (MTB) represent one third of the world's population. It still remains one of the world's deadliest infectious diseases. WHO estimates that there were approximately 9.0 million new cases and 1.5 million cases of mortality in 2013–360,000 of whom were positive for HIV [1]. TB treatment is generally comprised of 2 months with isoniazid, rifampicin, ethambutol and pyrazinamide (the intensive phase), followed by four additional months of isoniazid and rifampicin therapy (the continuation phase) [1]. Unfortunately, lack of adherence to prescribed treatment procedures and inefficient healthcare structures have contributed to the development of multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin, two front-line drugs used for the treatment of TB) that requires at least 20 months of treatment with second-line drugs comprised of capreomycin, kanamycin, amikacin and fluoroquinolones; these are more toxic and less efficient, with cure rates in the range of 60–75% [2]. Riccardi et al. [3] notes that in 2012, 450,000 people developed MDR-TB in the world. It is estimated that about 9.6% of these cases were extensively drug resistant (XDR-TB), showing additional resistance to at least one fluoroquinolone and one injectable second-line drug [1,4]. In patients affected by XDR-TB, the chances of successful treatment are quite low [3], underpinning the need for urgent discovery of novel compounds with activity against MTB strains resistant to second-line drugs. Recently, a few reports have claimed the emergence of a 'totally drug-resistant TB' strain with a limited chance of successful therapy [3,5–8]. Moreover, there is an urgent need to come to an agreement on the definition of these strains of MTB, mainly in terms of their severity [9]. Hence, the search for new antitubercular drugs is a priority so as to overcome the problem of drug resistance and to finally eradicate TB.

Trends in discovery of TB drugs

The four pioneer first-line drugs

Pyridine-4-carboxy hydrazide, isoniazid (INH; isonicotinyl hydrazide, Fig. 1a) was discovered at the same time in 1952 by three different pharmaceutical companies: BAYER