Letter to Editor

Novel Indole-Derived Compounds for TB Treatment

A.S. Apt[1*], K.A. Kazarian[2], B.V. Nikonenko[1], A.E. Ergeshov[1], V.S. Velezheva[3]

1. Central TB Research Institute, Yauzskaya Alley 2, 107564 Moscow, Russia.
2. Institute for Molecular Medicine, 16371 Gothard str., Huntington Beach, CA 92647, USA.
3. A.N. Nesmeyanov Institute of Organoelement Compounds Russian Academy of Sciences, Vavilov str., 2, 117813 Moscow, Russia.

ABSTRACT

Tuberculosis (TB) is a serious threat for public health and major infectious cause of mortality worldwide: according to the WHO, international death toll due to *Mycobacterium tuberculosis* infection is approximately 2 million people each year, and about 8 million new infection cases are registered annually.

Keywords: Tuberculosis (TB), drug resistant, antibiotics

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***Address for correspondence**
AS. Apt,
Central TB Research Institute, Yauzskaya alley, 2, 107564 Moscow, Russia.
E-mail: asapt@aha.ru

INTRODUCTION

Mycobacteria are prone to develop genetic resistance to all drugs used for anti-TB treatment, thus multi drug resistant MDR (MDR-TB-the form of tuberculosis caused by mycobacterial strains resistant to treatment with isoniazide (INH) and rifampicin (RIF)-two first-line drugs most often used for TB treatment) and extra drug resistant XDR (XDR-TB-the form of MDR-TB caused by mycobacterial strains that acquired additional resistance to for-quinolones, or to at least one of the second-line drugs delivered in injections-amicacin, capreomycin or kanamycin (KAN)) mycobacterial strains are rapidly spreading in populations, especially where the burden of the disease is heavy [1]. To avoid selection of resistant mutants during treatment course, current medical strategy includes obligatory usage of complex chemotherapy based upon combination of at least four drugs inhibiting mycobacterial metabolism, with specific attention to blockage of cell wall biosynthesis. Regarding mechanisms of action, anti-TB drugs may be classified as inhibitors of cell wall biosynthesis (INH, ethionamide (ETH) and cycloserine (DCS)), inhibitors of protein biosynthesis (RIF, fluoroquinolones, streptomycin (STR), KAN) and inhibitors of trans-membrane transport (pyrazinamide (PZA)).

Mostly, TB patients can be cured using currently available drugs and treatment schemes; however, this takes a lot of time and effort: 4 different drugs are applied for at least 2 months, followed by 2 preparations for additional 4 months. Treatment of MDR- and, especially, XDR-TB normally requires more than 2 years and proscription of more toxic, less efficient and far more expensive drugs. In addition, in many countries availability of the second-line drugs is limited.

Another tremendous problem is treatment of latent TB. About 90 per cent of infected individuals without clinical manifestations comprise an enormous reservoir of latent tuberculosis infection (LTBI). In some of these latently infected individual's infection transits to the active state, becomes contagious and seriously affects epidemiological situation [2]. Apparently, LTBI may last asymptomatically for a very long time and represents the most common variant of tuberculosis infection [3]. Due to isolated location and depressed metabolism of mycobacteria, this form of infection is difficult to detect using standard biochemical and microbiological methods and to eliminate with common antibiotics.

Although a novel highly effective anti-TB drug-bedaquiline has been recently introduced to clinical practice [4,5] and despite a number of candidate compounds presently in clinical trials (e. g. OPC-67683, PA-824, Moxifloxacin, SQ109) [6,7], there is general consensus that we urgently need establishment of new candidate molecules for TB treatment. Specific requirements to

novel drug candidates include shortening of treatment course, acceptable level of adverse effects when treating MDR- and XDR-TB, efficacy against dormant TB and compatibility with anti-retrovirus therapies in HIV-positive patients.

Among several approaches to new drug discovery, those based upon studying privileged scaffolds have definite advantages over expensive and laborious high throughput techniques. Indole, pyridine, quinoline and related heterocyclic compounds belong to a relatively small family of privileged scaffolds-unique cyclic structures capable to establish high-affinity links with several endogenous sites. This property is very useful for predicting active medical preparations, including anti-mycobacterials.

Research teams from Nesmeyanov Institute and Central TB Institute in Moscow work on prediction, synthesis and preclinical evaluation of hybrid, multi-target molecules, in which electron donor (indole and ferrocene) and electron acceptor pyridine scaffolds, including INH, are linked via N-N-containing pharmacophore groups, either linear or within the heterocyclic structure. Using the structure of INH and its analogues that are active against INH-resistant mycobacterial strains (IQG607, pentacyano(isoniazid)ferrate(II), phtivazide, saluzide, phenazide, phtivazide, and metazide) as prototypes, we use the INH frame as a platform for designing hybrid compounds. According to molecular hybridization concept, hybrid preparations should bind more than one mycobacterial target, providing advantage over the existing drugs during treatment of MDR-TB. Apart from broadening the spectrum of heterocyclic scaffolds, we included novel metallocene frames by varying bonds between fragments via endocyclic or exocyclic N-N groups.

Initially the compounds were tested for the capacity to inhibit [^{3}H]-uracil incorporation (as preliminary screen) into *M. tuberculosis* H37Rv and INH-resistant human isolate CN-40 [8,9] followed by the MIC testing of the most active ones. MICs were determined by standard micro-dilution assay using micro-tubes with Dubos medium containing 0.05% Tween 80. The lowest concentration of a compound resulting in no visible growth of *M. tuberculosis* for 2 weeks was considered MIC [9-11]. All samples were tested twice in the triplicate setting. In addition, the samples were plated on Dubos agar for CFU counting and determination of MIC99. These efforts resulted in establishing a number of compounds with appreciable activity against *M. tuberculosis in vitro* and in infected macrophage cultures. Moreover, some compounds displayed activity against INH-resistant mycobacterial strain and against *M. avium*, an important pathogen of HIV-infected individuals. We also added to our panel of compounds new types of N-N-containing indoles and ferrocenes in which INH-like fragment is lacking. Importantly, among these compounds, whose activity is not due to action of the INH fragment by definition, some also displayed therapeutic effect against INH-resistant *M. tuberculosis* (with MIC 0.2 μg/ml to 0.5 μg/ml) and *M. avium* (0.05 μg/ml to 0.5 μg/ml) [12]. The most promising compounds with appropriate selectively index [13] are now studied in our refined mouse TB model.

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