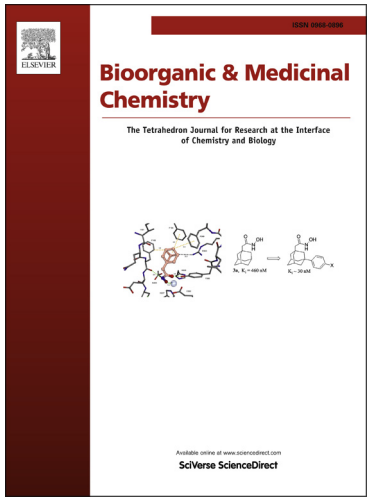


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# Structure-activity relationships of 2-aminothiazoles effective against *Mycobacterium tuberculosis*

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ABSTRACT

A series of 2-aminothiazoles was synthesized based on a HTS scaffold from a whole-cell screen against *Mycobacterium tuberculosis (Mtb)*. The SAR shows the central thiazole moiety and the 2-pyridyl moiety at C-4 of the thiazole are intolerant to modification. However, the N-2 position of the aminothiazole exhibits high flexibility and we successfully improved the antitubercular activity of the initial hit by more than 128-fold through introduction of substituted benzoyl groups at this position. *N*-(3-Chlorobenzoyl)-4-(2-pyridinyl)-1,3-thiazol-2-amine (**55**) emerged as one of the most promising analogues with a MIC of 0.024 μM or 0.008 μg/mL in 7H9 media and therapeutic index of nearly ~300. However, **55** is rapidly metabolized by human liver microsomes ($t_{1/2}$ = 28 min) with metabolism occurring at the invariant aminothiazole moiety and *Mtb* develops spontaneous resistance with a high frequency of ~$10^{-5}$.



## 1. Introduction

At the beginning of the 20th century tuberculosis (TB), also referred to as the White Plague and consumption in the middle ages, was a leading cause of mortality.[1] Poor public health and sanitation, inadequate diet as well as crowded housing and working conditions contributed to this endemic. The development of modern chemotherapy to treat TB began in 1943 with the momentous discovery of streptomycin, the first antibiotic effective against *Mycobacterium tuberculosis* (*Mtb*).[2] Dr. Selman Waksman predicted the end of the TB was "now virtually within sight" during his Nobel lecture in 1952 where he described his labs work that led to the isolation of streptomycin from soil microbes.[3] Indeed the discovery of other TB drugs followed in rapid succession with *para*-aminosalicylic acid (1946), pyrazinamide (1952), isoniazid (1952), ethambutol (1961), and rifampin (1965), among many others.[4] Introduction of these antibiotics led to a staggering drop in TB incidence in the developing world.

The standard treatment regimen in use today established over several decades through dozens of clinical trials by the British Medical Council (BMC) involves a 2-month intensive phase with isoniazid, rifampin, ethambutol, and pyrazinamide followed by a 4-month continuation phase of isoniazid and rifampin.[5] Combination therapy is required since the first clinical trials with streptomycin demonstrated that drug resistance rapidly developed to a single agent.[6] The extraordinarily long treatment course is necessary since *Mtb* is inherently slow growing, drug penetration into TB lessions is poor,[7] *Mtb* periodically switches its metabolism to a dormant state,[8] and a subpopulation of the bacteria exhibit reversible phenotypic drug tolerance.[9]

Unfortunately, the emergence of drug resistant strains is undermining the great advances made in the 20th century to control TB, which is now the second leading cause of infectious disease mortality with over 1.4 million deaths in 2011.[10] Multidrug resistant (MDR) TB is defined as resistance to the two most effective antitubercular drugs isoniazid and rifampin. Treatment of MDR-TB is typically accomplished by replacement of isoniazid and rifampin with an injectable aminoglycoside (i.e. amikacin), a fluoroquinolone (i.e. moxifloxacin), and other second-line drugs such as ethionamide, *para*-aminosalicylic acid, and cycloserine that are more toxic and less effective requiring 18–24 months of chemotherapy. Extensively drug resistant TB (XDR-TB) has been documented in 84 countries, which possesses the MDR phenotype and is additionally resistant to one of the injectable antibiotics and any fluoroquinolone.[10] Treatment options for XDR-TB are severely limited. The development of new TB drugs and ultimately of an entirely new treatment regimen for MDR- and XDR-TB is needed. The recent approval of Sirturo by the FDA (also known as bedaquiline, TMC-207, and R207910) as the first new TB drug in over forty years marks the first step toward this goal.[11]

There are two diametrically opposed strategies to antibacterial drug discovery: biased target-led approaches and un-biased screening using whole-cell assays.[12] In target-based strategies,