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# Thiazolopyridone ureas as DNA gyrase B inhibitors: Optimization of antitubercular activity and efficacy

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ABSTRACT

Scaffold hopping from the thiazolopyridine ureas led to thiazolopyridone ureas with potent antitubercular activity acting through inhibition of DNA GyrB ATPase activity. Structural diversity was introduced, by extension of substituents from the thiazolopyridone N-4 position, to access hydrophobic interactions in the ribose pocket of the ATP binding region of GyrB. Further optimization of hydrogen bond interactions with arginines in site-2 of GyrB active site pocket led to potent inhibition of the enzyme ($IC_{50}$ 2 nM) along with potent cellular activity (MIC = 0.1 μM) against *Mycobacterium tuberculosis* (Mtb). Efficacy was demonstrated in an acute mouse model of tuberculosis on oral administration.



Tuberculosis (TB) continues to remain one of the major causes of death, claiming close to 1.5 million patients per year.[1] The standard treatment is six months long and for drug-resistant TB, this extends to 18–24 months. There is a high medical need for a shorter, better tolerated regimen for the treatment of drug-sensitive TB, as well as a combination therapy that will be more effective in the treatment of drug-resistant TB. Cure rates for patients with extensively drug resistant (XDR) TB are very low and the advent of totally drug resistant TB (TDR) leaves very little hope for patients infected with such strains.[2–4]

A new drug must have a novel mechanism of action to be effective against drug resistant forms of TB. DNA gyrase maintains the topological state of DNA in the bacterial cell, which is important for transcription. A second topoisomerase, toposiomerase IV, decatenates DNA and plays a critical role in DNA replication and cell division. *M. tuberculosis* (Mtb), however, lacks topoisomerase IV and the function of decatenation is performed by DNA gyrase,[5] making Mtb DNA gyrase a very attractive drug target. DNA gyrase is also clinically validated as a target for the discovery of new antibacterial agents since the fluoroquinolones, which target this enzyme, are used extensively for treatment of bacterial infections and are the mainstay of second line treatment of TB.[6] However, the emergence of resistance to the fluoroquinolones may limit their effectiveness in the long term.[7] The fluoroquinolones inhibit DNA cleavage and reunion, one of the two activities present in DNA gyrase. A second mechanism, hitherto

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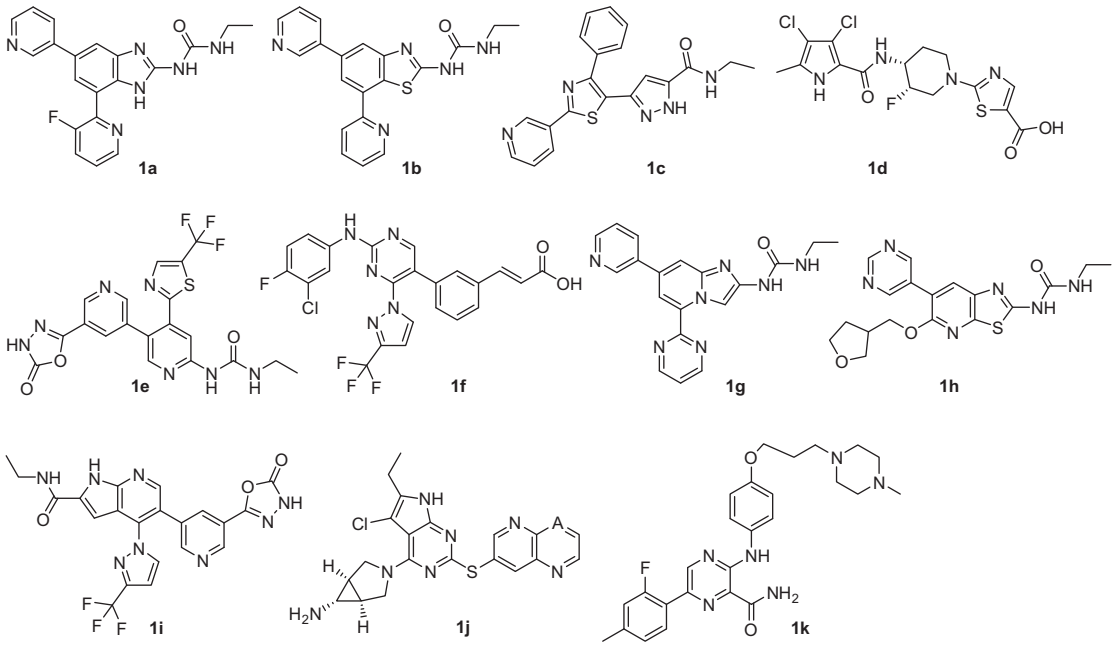
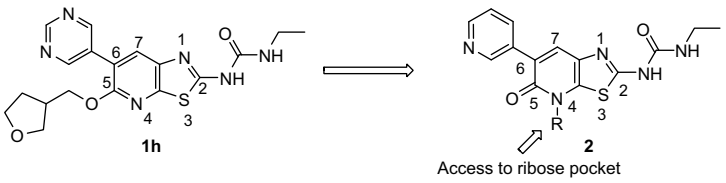



**Figure 1.** Known GyrB inhibitors.



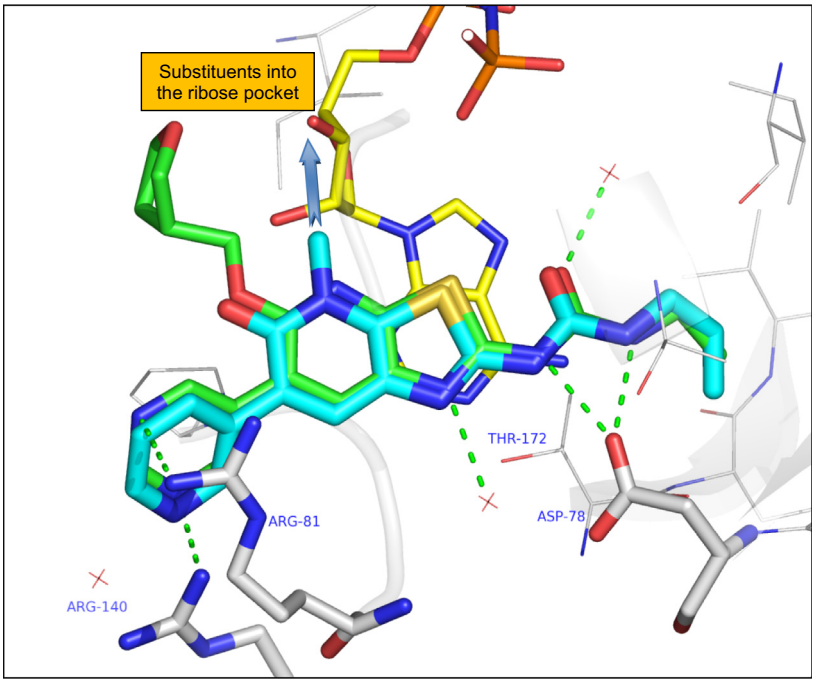




**Figure 2.** Overlay of ATP (yellow) and thiazolopyridone **2** (cyan) on to the crystal-bound conformation of thiazolopyridine **1h** (green) in Spn-ParE (PDB ID: 4mb9).[15b]

underexploited, is the ATPase activity of DNA gyrase which resides in the GyrB subunit. The ATPase activity can be uncoupled from the supercoiling activity, which needs both GyrA and GyrB subunits, and measured in isolation. Resistance studies to date have indicated that there is little likelihood of cross resistance between inhibitors of the ATPase and the fluoroquinolones[8]