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Identification of novel 2-aminothiazole conjugated nitrofuran as antitubercular and antibacterial agents

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ABSTRACT

The emergence of antibiotic resistant pathogens is an ongoing main problem in the therapy of bacterial infections. In order to develop promising antitubercular and antibacterial lead compounds, we designed and synthesized a new series of derivatives of 2-aminothiazole conjugated nitrofuran with activities against both *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Eight compounds **12e**, **12k**, **12l**, **12m**, **18a**, **18d**, **18e**, and **18j** emerged as promising antitubercular agents. Structure–activity relationships (SARs) were discussed and showed that the derivatives substituted at the position-3 of benzene of 5-nitro-*N*-(4-phenylthiazol-2-yl)furan-2-carboxamide exhibited superior potency. The most potent compound **18e**, substituted with benzamide at this position, displayed minimum inhibitory concentrations (MICs) of 0.27 μg/mL against *Mtb* H37Ra and 1.36 μg/mL against *S. aureus*. Furthermore, compound **18e** had no obvious cytotoxicity to normal Vero cells (IC_{50} = 50.2 μM). The results suggest that the novel scaffolds of aminothiazole conjugated nitrofuran would be a promising class of potent antitubercular and antimicrobial agents.

Due to the widespread bacterial infection and the emergence of antibiotic resistant pathogens, the infectious diseases with high rate morbidity and mortality threaten public health seriously.[1,2] The major challenges of antibacterial drug discovery in the therapy are the phenomena of drug resistance, and the critical discussions about drug resistance are *Mycobacterium tuberculosis* (*Mtb*) and *Staphylococcus aureus* (*S. aureus*) infections.[3,4] In particular, tuberculosis (TB) that infecting approximately a third of world population has become the most dangerous disease among various deadly infections.[5] However, the standard clinical antitubercular drugs, like isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and pyrazinamide (PZA), have been used for decades. The consequent emergencies of multidrug-resistant and extensively drug resistant tuberculosis (MDR and XDR-TB) rendered the scanty drug supply to be tighter.[6] It was also clear from the WHO data that TB conjugating with AIDS lowered immunity and caused higher mortality rate, with 360,000 deaths amongst HIV-sufferers in 2013.[5] Unfortunately, there was a drop in the number of authorization of new antimicrobial agents by the regulatory agencies and there was low probability to discover a novel lead compound in the pre-clinical study.[7] Hence, there is a great need for increased drug discovery efforts in this important area.

Our endeavors to develop a novel series of antibacterial agents led to the study of privileged structure-based libraries. 2-Amino-1,3-thiazole derivatives were known to exhibit a broad range of biological activities, some thiazole-2-amine agents had been used in clinical antibacterial applications successfully (e.g., Sulfatizole, Cetraxone, Aztreonam, Riluzole).[8] Of interest were compounds possessing the 4-phenylthiazol-2-amine scaffold with a benzoyl substituent on the amino group that had the inhibitory activity against *S. aureus* and *Escherichia coli* by targeting *β*-Ketoacyl-acyl carrier protein (ACP) synthase III (FabH). One of the compounds, 3-bromo-*N*-(4-(4-bromophenyl)thiazol-2-yl)benzamide (**1**) (Fig. 1), exhibited a MIC of 6.25 μg/mL against *S. aureus* and FabH inhibitory activity IC_{50} of 5.8 μM.[9]

On another hand, nitrofuran derivatives were also precursors with a broad-spectrum activity against both Gram-negative and Gram-positive bacteria.[10,11] A recent literature survey revealed that nitrofuran containing compounds owed anti-TB potential.[12–16] Compound **2** (Lee-562)[13] and compound **3** (Lee-1106)[14] that generated from the nitrofuranylamides displayed nanomolar potency against H37Rv. On the basis of Lee's study, Yempalla and co-workers had rediscovered nitrofuranyl methyl piperazine **4** with optimal pharmacokinetic property and comparatively better aqueous

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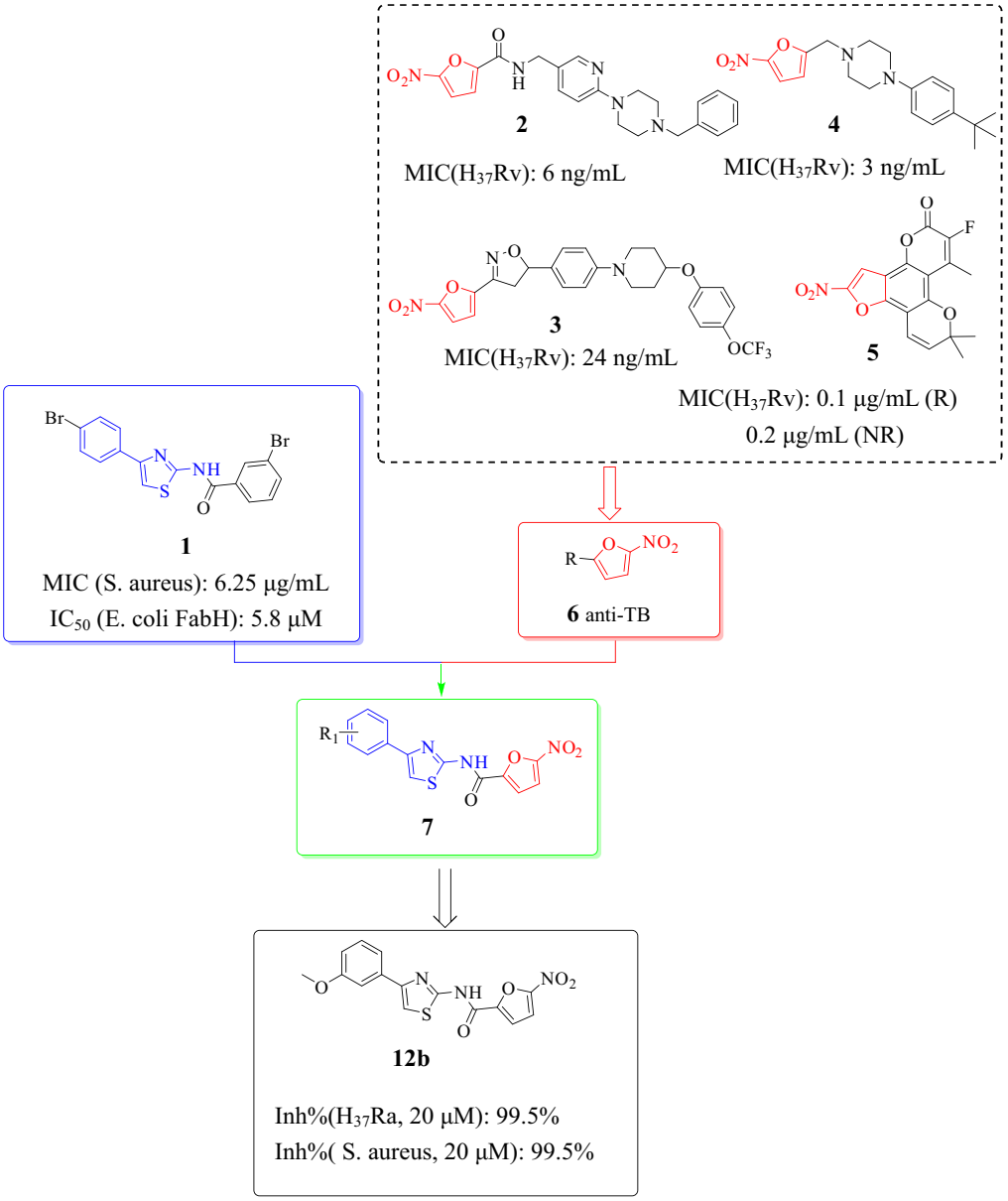

Figure 1. Aminothiazole and nitrofuranyl containing antimicrobial and antitubercular molecules.

solubility as an effective compound against sensitive and resistant strains of MTB.[15] Likewise, the nitrofuran introduction prompted calanolides **5** to eradicate both replicating (R) and nonreplicating (NR) *Mtb*.[16]

Motivated by these findings, we adopted the strategy of combinatorial chemistry and proposed the combination of 4-phenylthiazol-2-amine and 5-nitrofuran to generate novel structure **7** (Fig. 1), in anticipation of having the capacity of fighting both antimicrobial and anti-tubercular activity. The initial *N*-(4-(3-methoxyphenyl) thiazol-2-yl)-5-nitrofuran-2-carboxamide **12b** was found to exhibit the same inhibitory rate of 99.5% against *Mtb* and *S. aureus* at the concentration of 20 μM, which proved the practicability of our design strategy. In order to develop more potent agents, a series of 5-nitro-*N*-(4-phenylthiazol-2-yl)furan-2-carboxamide derivatives, compounds **11a–11b**, **12a–12m**, **13**, **16**, **17** and **18a–18j**, were designed, synthesized and evaluated for their antibacterial activities.

For synthesizing these designed compounds, we initially prepared a series of 4-phenylthiazol-2-amine analogs as shown in Scheme 1. Brominating of the commercially available acetophenone **8a–8l** with tetrabutylammonium afforded the α-brominated ketone **9a–9l** and Friedel–Crafts acylation of **8m–8n** generated **9m–9n**. Subsequently the classical Hantzsch synthesis of **9a–9n** with thiourea provided the desired aminothiazole **10a–10n**. Then condensation of **10a–10n** with the corresponding carboxylic acid afforded the products **11a–11b** and **12a–12n**. The product **13** was synthesized by nitro-reduction of **12b**.

Another series of compounds **18a–18j** were started from the above **10l** (Scheme 2), which was hydrolyzed firstly via hydrochloric acid to produce the de-acetylated **14**. After the process of *Boc*-protection, **15** condensed with 5-nitro-2-furoic acid to generate **16**. The de-protection of **16** afforded compound **17**. Finally, the uncovered phenylamine **17** was reacted with various alkyl, aromatic acyl chloride or sulfuryl chloride to generate the products **18a–18j**.

The structure–activity relationships of all compounds were studied for their inhibitory rate (%Inh) against *M. tuberculosis* H37Ra at the concentration of 10 μM and 1 μM in vitro, while