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Sulfur rich 2-mercaptobenzothiazole and 1,2,3-triazole conjugates as novel antitubercular agents

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ABSTRACT

A series of benzfused heterocyclic derivatives such as amide conjugates of 2-(benzo[d]thiazol-2-ylthio) acetic acid with aromatic/aliphatic/cyclic secondary amines (**5a**–**5o & 8a**–**8m**); 1,2,3-triazole conjugates of 2-mercaptobenzothiazoles and amide conjugates of indole-3-glyoxalic acid with cyclic secondary amines (**14a**–**14g**) have been synthesized and were screened for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain by broth microdilution assay method. Compounds **8b, 8f, 8g** and **8l** inhibited the growth of the H37Rv strain at concentrations of 8 μg/mL. These compounds (**8b, 8f, 8g** and **8l**) have been further identified as bactericidal and are completely killing the microbes at 32–64 μg/mL concentrations. Molecular docking studies of the active compounds reveal that these compounds are targeting DprE1 and may act as DprE1 inhibitors.

1. Introduction

Despite being an ancient disease, tuberculosis (TB) remains the leading infectious disease killer in the world. The emergence of resistance to new generation TB drugs ("multiple drug resistant" *Mycobacterium tuberculosis*, MDR-TB) alarming the serious problem in TB control and demanding the need for new drugs more potent than earlier with safe ADME profile. The increasing number of MDR-TB cases has caused great concern because they are often associated with HIV infection. Due to the unusual structure and chemical composition of the mycobacterial cell wall, effective tuberculosis (TB) treatment is difficult, making many antibiotics ineffective and hindering the entry of new drugs [1]. No new chemical entity has been emerged in last 50 years after the discovery of rifampicin. Therefore new drugs are required to counter the tuberculosis (TB) pandemic. Several strategies are being pursued in order to identify new leads, although only a few leads are being optimized to generate drug candidates [2]. Most of the efforts have been directed towards identifying and validating drug targets and making derivatives of existing drugs [3].

Several heterocyclic moieties consisting of nitrogen, sulfur, oxygen hetero-atoms have been explored for the development of new generation anti-tubercular agents [1,4–7]. Azoles are one of the most important classes of nitrogen containing heterocycles that demonstrated the potential anti-tubercular activity. Azole derivatives inhibit the growth of bacteria by blocking lipid biosynthesis and/or additional mechanisms which is one of the most attractive strategies for effective anti-TB drug (development of cell wall biosynthesis inhibitors). From the literature it has been observed that sulfur is unusually common in most of the anti-tubercular drugs, therefore sulfur-containing heterocycles are being explored comprehensively [8]. Interestingly, it has also been observed that the introduction of sulfur atom in the cyclic systems along with nitrogen has resulted in the improved anti-tubercular activities [8b]. Thiazoles are five membered heterocycles of azole family consisting nitrogen and sulfur atoms, are one of the key building blocks in drug discovery that can be well illustrated by the

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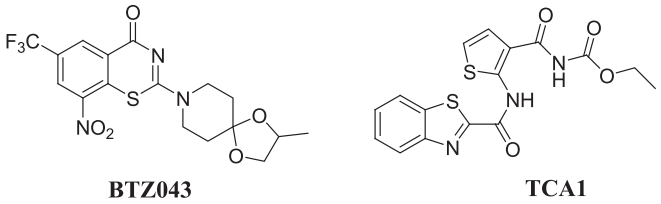
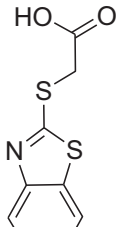
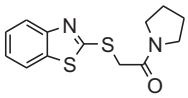
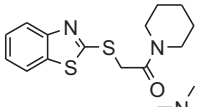
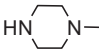
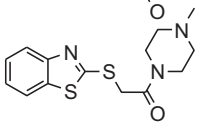
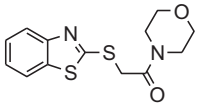
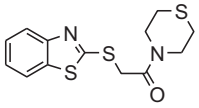
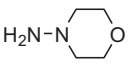
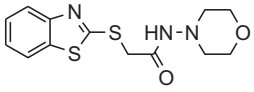
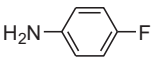
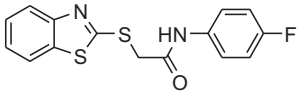
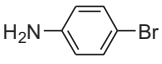
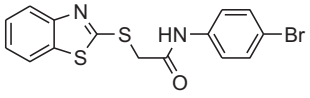
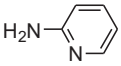
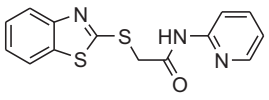
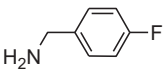
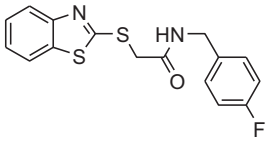
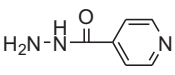
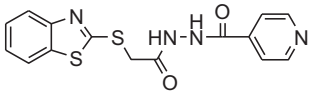


Fig. 1. Structures of BTZ043 & TCA1.

large number of drugs in the market [8]. Thiazoles are considered as important frameworks in the TB drug development and various derivatives of thiazoles have been made [8,9] including benzothiazole derivatives. Benzothiozoles are a kind of sulfur containing benzfused heterocycles showing a broad spectrum of biological properties including antitumor [10–12], antiviral [13], anti-HIV [14], antimicrobial [15] activities. In addition, the benzothiazole moiety has also been recognized for anti-TB design. Conjunction of benzothiazoles with 1,2,4-triazole system has resulted in the potential anti-tubercular activity [16a]. Benzo[*d*]isothiazole, Benzothiazole and Thiazole Schiff Bases have also been explored for their

Table 1
Amide conjugates of 2-mercaptobenzothiazoles.

Sr. No.	Carboxylic acid (**3**)	Amines (**4**)	Benzothiazole conjugates (**5**)	Yields[a] (%)
a				98
b				94
c				91
d				95
e				83
f				88
g				87
h				84
i				82
j				95
k				74

[a] Isolated yields.