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Research paper

Synthesis and antimycobacterial screening of new thiazolyl-oxazole derivatives

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ABSTRACT

In the present study a series of 4-methyl-2-aryl-5-(2-aryl/benzyl thiazol-4-yl) oxazole (**4a-v**) have been synthesized and evaluated for their preliminary antitubercular, antimicrobial and cytotoxicity activity. Among all the synthesized compounds, **4v** reported comparable activity against dormant *M. tuberculosis* $H_{37}Ra$ and *M. bovis* BCG strains with respect to standard drug rifampicin.

The active compounds from the antitubercular study were further tested for anti-proliferative activity against HeLa, A549 and PANC-1 cell lines using MTT assay and showed no significant cytotoxic activity at the maximum concentration evaluated. Further, the synthesized compounds were found to have potential antibacterial activities with MIC range of 2.1–26.8 μg/mL. High potency, lower cytotoxicity and promising antimycobacterial activity suggested that these compounds could serve as good leads for further optimisation and development.

1. Introduction

Inspite of a large number of antibiotics and chemotherapeutics available for medical use, the treatment of infectious diseases still remains an important and challenging problem. Due to emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens in the last decades, a need for new classes of antimicrobial agents is warranted. The increase in antibiotic resistance due to multiple factors has encouraged the search for new compounds which are active against multi-drug resistant pathogens.

A large number of natural products from the marine environment and micro-organisms contain numerous bis- and trisoxazoles, as well as few oxazole–thiazoles and bisthiazole-containing natural products [1] reported promising antitumor, antibacterial, antiviral, antimalarial and anthelmintic activities [2–5]. The synthesis of motifs containing more than one heterocycle ring has received much attention in recent years [6]. Oxazole and thiazole rings are privileged scaffolds for the generation of target compounds for drug discovery (Fig. 1). The structural diversity and biological importance of oxazoles [7–23] and thiazoles [24–44] have made them attractive targets for synthesis. Oxazole and thiazole rings present in the same molecule could be convenient models for investigation of their biological activity.

Extensive efforts were invested in the discovery of novel anti-TB drugs in academic and pharmaceutical industry. So after thorough literature survey, we have designed several clubbed 4,5'-bisthiazole and oxazole derivatives as potential anti-tubercular and antibacterial agent [45]. The study indicated that substituted benzyl group at 2 or 2′ position of bisthiazole ring increase the activity. In view of these facts, we envisaged to design a scaffold containing oxazole and thiazole nucleus. By considering the importance of oxazole and thiazole derivatives and as part of search for compounds as candidates for antitubercular drugs employing molecular simplification, in this present work we described the synthesis of 4-methyl-2-phenyl/aryl-5-(2-aryl/benzylthiazol-4-yl) oxazole (**4a-v**) as potential antimycobacterial agents.

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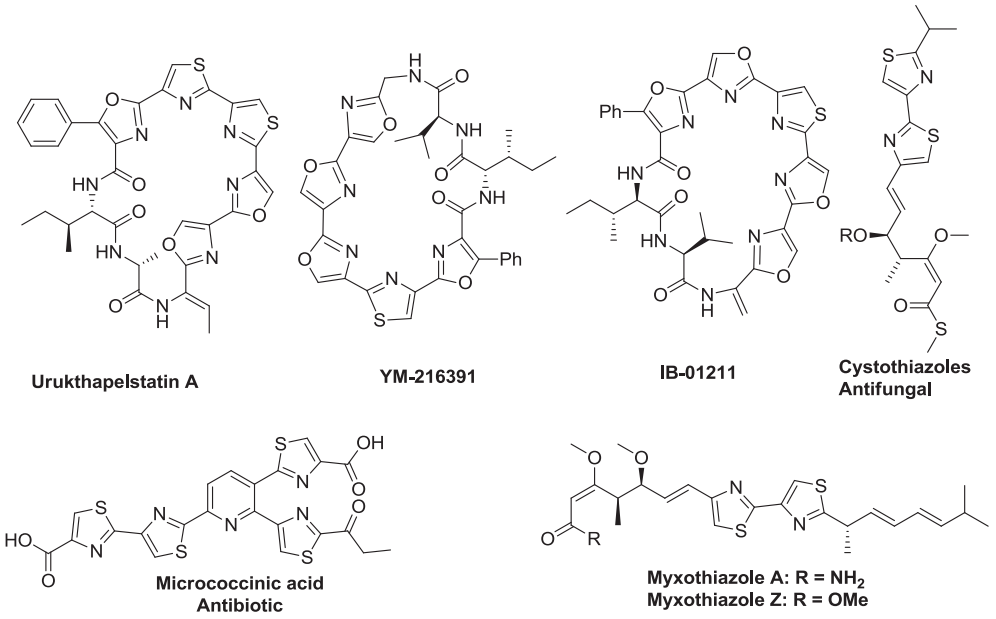


Fig. 1. Natural products containing thiazole and oxazole motifs.

2. Chemistry

The target compounds thiazolyl-oxazole were synthesized according to the synthetic route outlined in Scheme 1. 1-(4-methyl-2-aryloxazol-5-yl)ethanone, **1a-b** on selective bromination by using bromine and *p*-toluene sulphonic acid as catalyst in DCM resulted the formation of 2-bromo-1-(4-methyl-2-aryloxazol-5-yl)ethanone, **2a-b**. Compounds **2a-b** on cyclocondensation with aryl/benzyl thioamide, **3a-k** furnished 4-methyl-2-phenyl/aryl-5-(2-aryl/benzyl thiazol-4-yl)oxazole derivatives, **4a-v**. The structure of the title compounds, **4a-v** was confirmed by IR, NMR and MS.

3. Result and discussion

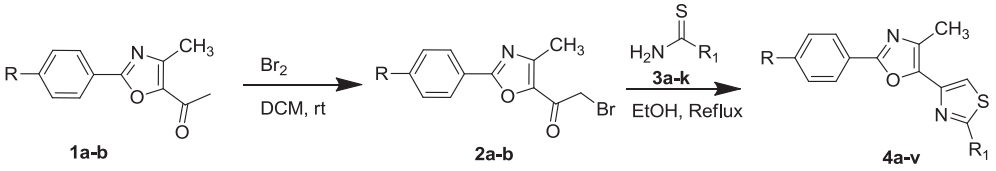
3.1. Anti-tubercular activity

The antitubercular activity for each synthesized compound was determined by measuring inhibition of growth against avirulent strain of *M. tuberculosis* H37Ra (MTB, ATCC 25177) and *M. bovis* BCG (BCG, ATCC 35743) in liquid medium. In a preliminary screening, the antimycobacterial activity of these compounds was assessed at concentrations of 30, 10, 3 μg/mL using first-line antitubercular drug rifampicin as reference standard. *In vitro* activity studies against MTB and *M. bovis* BCG were performed using the XRMA [46–49] and NR assays [46–49], respectively. The results of antimycobacterial activity are summarized in Table S1.

The compounds which showed more than 90% inhibition (Table S1) at 30 μg/mL were further studied for dose dependent effect using a range from 30 to 0.23 μg/mL to determine IC_{50} and MIC_{90} with serial dilution in DMSO of compounds (Table 1).

Analysis of anti-tubercular activity results provides some lead molecules with moderate to good antitubercular activity. The *in vitro* anti-tubercular activity results revealed that thiazolyl-oxazole compounds **4i**, **4j**, **4s**, **4t**, **4v** exhibited good anti-tubercular activity against dormant *M. tuberculosis* H37Ra and *M. bovis*. From the structure activity relationship of compounds **4a-v** it was noticed that, the replacement of hydrogen atom of phenyl ring A by fluorine and ring B by substituent like Br, Cl, F and CH_3 significantly affects the anti-tubercular activity (Fig. 2).

Further it was also noted that compounds **4a-g**, with un-



Comp.	R	R_1	Comp.	R	R_1	Comp.	R	R_1	Comp.	R	R_1
4a	H	C_6H_5	**4g**	H	4-$CH_3C_6H_4$	**4m**	4-F	4-BrC_6H_4	**4r**	4-F	4-$CH_3C_6H_4$
4b	H	4-BrC_6H_4	**4h**	H	$C_6H_5CH_2$	**4n**	4-F	3-ClC_6H_4	**4s**	4-F	$C_6H_5CH_2$
4c	H	3-ClC_6H_4	**4i**	H	3-$ClC_6H_4CH_2$	**4o**	4-F	4-ClC_6H_4	**4t**	4-F	3-$ClC_6H_4CH_2$
4d	H	4 -ClC_6H_4	**4j**	H	4-$ClC_6H_4CH_2$	**4p**	4-F	3-Cl,4FC_6H_3	**4u**	4-F	4-$ClC_6H_4CH_2$
4e	H	3-Cl,4FC_6H_3	**4k**	H	4-$FC_6H_4CH_2$	**4q**	4-F	4-FC_6H_4	**4v**	4-F	4-$FC_6H_4CH_2$
4f	H	4-FC_6H_4	**4l**	4-F	C_6H_5						

Scheme 1. Synthetic route of compounds **4a-v**.