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Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds

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ABSTRACT

In search of more potent and safe new antitubercular agents, here new 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazoles (**6a**–**o**), have been designed and synthesized using thionicotinamide as a starting, following novel multistep synthetic route. An intermediate, pyridinyl substituted thiazolyl acid hydrazide (**4**) when condensed with benzoic acids/nicotinic acids (**5a**–**o**) in the presence of silica supported $POCl_3$ yielded better to excellent yields of the title compounds. All the synthesized compounds (**6a**–**o**) and intermediate acid hydrazide (**4**) have been screened for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Ra (MTB) and *Mycobacterium bovis* BCG. Amongst them, **6f**, **6j**, **6l** and **6o** have revealed promising activity against *M. bovis* BCG at concentrations less than 3 μg/mL. These compounds have shown low cytotoxicity (CC_{50}: >100 μg/mL) towards four human cancer cell lines. Molecular docking study has also been performed against mycobacterial enoyl reductase (InhA) enzyme to gain an insight into the binding modes of these molecules and recorded good binding affinity. The ADME properties the title products have also been analyzed.

Tuberculosis has become a serious global health problem as it is second leading cause of death amongst infectious diseases.[1] Though first line and second line multicomponent pattern of treatments for tuberculosis are practiced but now they are facing serious threats.[2] The patterns need longer duration for treatment and therefore the pathogenic strains responsible for tuberculosis are found to be acquiring resistance to the drugs[3] and new forms of tuberculosis like multidrug resistant tuberculosis (MDR TB) and extensively drug resistant tuberculosis (XDR TB) are found to be emerging as new challenge for medicinal chemists.[4] Nowadays population of patients having HIV and TB as coinfections is increasing. To address the above threats now more attention is found to be paid on the search of appropriate drugs for treating both the diseases simultaneously and efficiently.[5] Therefore chemists are paying their more focus on creation of library of new analogues of existing drugs or new chemical entities with hope to obtain the agents with potential antitubercular activity with reduced toxicity and treatment duration.[6]

Recently, in search of the newer effective antitubercular agents, various new sulfur, nitrogen, and oxygen containing heterocyclic scaffolds like thiazole, pyridine, 1,3,4-oxadiazole, oxazoline and imidazole have been synthesized and evaluated.[7] The potential of the pyridine derivatives has been well explored and are found to display antitubercular,[8] anti-inflammatory,[9] insecticidal,[10] and anticancer,[11] activities. Novel isoniazid–amidoether derivatives, reported by Rawat et al. have shown considerable antitubercular activity.[9b] Thiazoles are well established as building blocks for generating leads and have displayed broad spectrum of therapeutic activities.[12] Thiazole is seen as a key scaffold in various clinical agents.[13] There is a brief review on thiazoles possessing antitubercular activity.[14] New bisthiazoles have also been recently reported and found to exhibit noteworthy antitubercular and antimicrobial activities.[15] Balkan and co-workers have synthesized some amino thiazoles and thiazolylhydrazones and reported their antitubercular activity.[16]

Azole class of compounds are gaining importance because of their key property liphophilicity that influence the ability of the drug to reach the target by transmembrane diffusion.[17] 1,3,4-Oxadiazoles have exhibited wide range of biological activities such as-antibacterial,[18] antitubercular,[19] antitumor,[20] antifungal,[21] anti-inflammatory.[22] Oxadiazole derivatives have also shown wide spectrum of antimicrobial activities and are key component of antibiotic furamizole[23] and antiretroviral raltegravil.[24] 1,3,4-Oxadiazole scaffold is found to work as bioisosteres of

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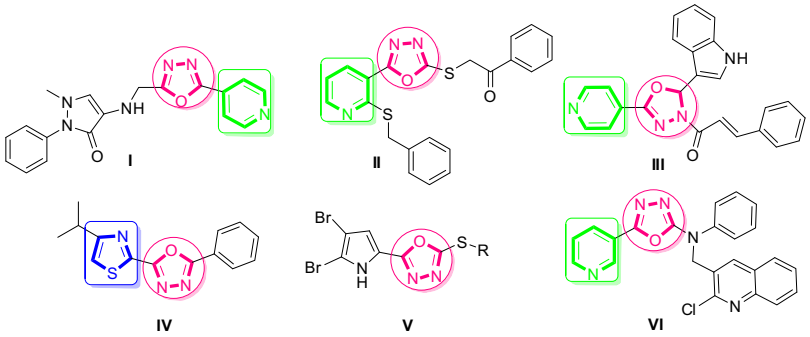


Figure 1. Some of the active pyridine, thiazole and 1,3,4-oxadiazole based anti-TB derivatives.

amides and esters which helps substantially to enhance therapeutic activities by participating in hydrogen bonding interactions with respective receptors.[25] Literature reveals that there is a scanty information on the molecules having scaffolds like thiazole, 1,3,4-oxadiazole and pyridine in one molecular framework.

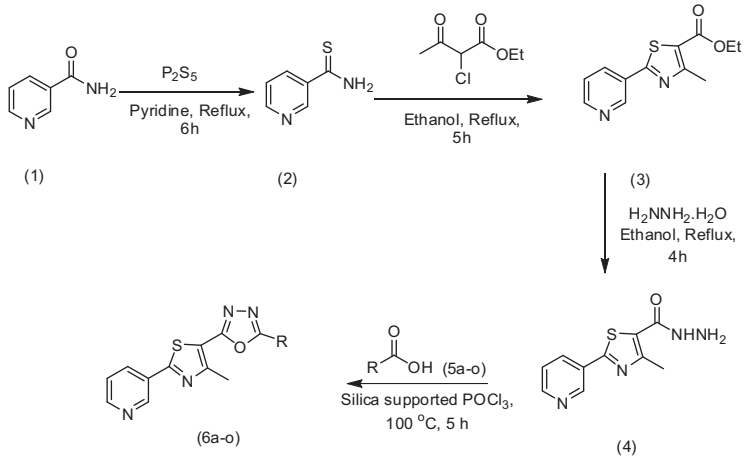
1,3,4-Oxadiazoles clubbed separately with thiazoles,[26] pyridines,[27] indoles,[28] quinolines,[29] and pyrrols[30] have shown enhanced in vivo and in vitro antimycobacterial activity (Fig. 1). Literature reveals that 1,3,4-oxadiazoles clubbed with thiazole having pyridyl moiety are not reported.

Considering the urgent need of preparing library of new antitubercular agents and highly impressed by the antimicrobial activities, displayed by coupled azoles especially 1,3,4-oxadiazoles, here we thought worthwhile to design and synthesize new hybrid 1,3,4-oxadiazoles with thiazolyl and pyridyl ring systems in a single molecular framework with hope to obtain the new molecules with enhanced antimycobacterial activity.

Mycobacterium bovis BCG is gaining importance as a *Mycobacterium tuberculosis* surrogate for rapid and safer screening.[31] BCG is manipulated safely and its genome sequence is more than 99% identical to the *M. tuberculosis* H37Rv.[32] Therefore here we have reported a multistep synthesis of new 2-pyridinylsubstituted thiazolyl-5-aryl-1,3,4-oxadiazoles (**6a**–**o**) and their antimycobacterial evaluation against *Mycobacterium tuberculosis* H37Ra (MTB) and *Mycobacterium bovis* BCG. Molecular docking study and in silico ADME predictions have been carried of the synthesized compounds and results are discussed.

The title compounds, 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazoles (**6a**–**o**) have been synthesized by following multistep route, starting from nicotinamide (Scheme 1). Thionicotinamide (**2**) was freshly prepared by digesting nicotinamide (**1**) and phosphorus pentasulfide in pyridine.[33] Thionicotinamide was then condensed with 2-chloro-ethylacetoacetate in refluxed ethanol and obtained 5-carboethoxy-4-methyl(nicotinyl-2-yl)thiazole (**3**) by following Hantzsch Synthesis. A mixture of hydrazine hydrate and the carboethoxythiazole (**3**) was dissolved in ethanol and the solution was refluxed for getting the respective acid hydrazide (**4**). When cyclocondensation of the acid hydrazide (**4**) and benzoic acids/nicotinic acids (**5a**–**o**) was carried in silica supported $POCl_3$ at 100 °C gave the title compounds, 2-pyridinylsubstituted thiazolyl-5-aryl/pyridinyl-1,3,4-oxadiazoles (**6a**–**o**) with moderate to better yields. The physical data of oxadiazoles (**6a**–**o**) is incorporated in Table S1 (Supporting information).

All the newly synthesized compounds have been characterized using their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. The IR spectrum of compound (**6a**) indicates the formation of product as it shows a characteristic absorption peak at 1577 cm^{-1} which corresponds to the C=N of azole. The ^{1}H NMR spectrum of compound (**6a**) displays peaks, a singlet at δ 2.95 ppm, due to the CH_3 and multiplets in the region at δ 7.41–8.10 and 8.15–9.22 ppm for five phenyl protons and four pyridyl protons, respectively. The presence of three characteristics carbon signals are observed at δ 17.61, 165.27 and 165.93 ppm in ^{13}C NMR spectrum of (**6a**) owing to the signals of carbons of CH_3 and the two oxadiazol ring carbons respectively, confirming the presence of a 1,3,4-oxadiazole ring in (**6a**). The HRMS spectrum further strengthen the structure assigned to (**6a**) as 2-pyridinylsubstituted thiazolyl-5-phenyl-1,3,4-oxadiazole as it displays $[M+H]^+$ ion peak at *m*/*z* 321.0805 for the molecular formula $C_{17}H_{12}N_4OS$. Experimental procedures



Scheme 1. 2-pyridinylsubstituted thiazolyl-5-aryl-1,3,4-oxadiazoles (**6a**–**o**).