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Seeking potent anti-tubercular agents: Design, synthesis, anti-tubercular activity and docking study of various ((triazoles/indole)-piperazin-1-yl/1,4-diazepan-1-yl)benzo[*d*]isoxazole derivatives

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ABSTRACT

A series of thirty eight novel 3-(4-((substituted-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl/1,4-diazepan-1-yl)benzo[*d*]isoxazole and 1-(4-(benzo[*d*]isoxazol-3-yl)piperazin-1-yl/1,4-diazepan-1-yl)-2-(1*H*-indol-3-yl)substituted-1-one analogues were synthesised, characterised using various analytical techniques and evaluated for in vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain and two 'wild' strains *Spec. 210* and *Spec. 192*. The titled compounds exhibited minimum inhibitory concentration (MIC) ranging from 6.16 to >200 μM. Among the tested compounds, **7i**, **7y** and **7z** exhibited moderate activity (MIC = 24.03 – 29.19 μM) and **7j** exhibited very good anti-tubercular activity (MIC = 6.16 μM). Furthermore, **7i**, **7j**, **7y** and **7z** were found to be non-toxic against mouse macrophage cell lines when screened for toxicity. All the synthesised compounds were docked to pantothenate synthetase enzyme site to know deferent binding interactions with the receptor.

Tuberculosis (TB), a fatal contagious infectious disease caused by *Mycobacterium tuberculosis* (MTB), remains a global burden.[1] TB represents one of the crucial public health concerns worldwide after the human immunodeficiency virus (HIV).[2,3] It is one of the major causes of death in HIV patients, according to the World Health Organization (WHO).[1,4] If treatment is incomplete, it is dangerous and can be a cause of mortality.[4] It leads to drug resistance forms, such as multidrug resistant TB (MDR-TB), extensively drug resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB) or extremely drug resistant TB (XXDR-TB). In 2014, worldwide amongst 0.48 million individuals who suffered from MDR-TB, 0.21 million expired due to MDR-TB.[2,5] Pervasiveness of XDR-TB and TDR-TB has increased worldwide and hence, there is an urgent need to develop new anti-TB drugs with novel mechanism of action to cure all forms of TB regimens.[6,7] Since past few decades except for bedaquiline and delamanid which are used for healing pulmonary MDR-TB patients in severe or life-threatening conditions, no novel anti-TB drugs have surfaced out.[8,9]

Heterocyclic compounds play an important role in an untiring effort in development of new anti-tubercular agents. Mainly, benzisoxazoles and its derivatives hold wide range of activities viz., anti-cancer,[10,11] anti-diabetic,[12] antipsychotic,[13] anticonvulsant,[14] anti-HIV,[15] and antimicrobial.[16,17] In addition, importantly Naidu et al., recently published design, synthesis and biological evaluation of 5-(2-(4-(substituted benzo[*d*]isoxazol-3-yl)piperazin-1-yl)acetyl)indolin-2-one and 5-(2-(4-substitutedpiperazin-1-yl)acetyl)indolin-2-one analogues as novel anti-tubercular agents; design, synthesis and antimycobacterial activity of various 3-(4-(substituted sulfonyl)piperazin-1-yl)benzo[*d*]isoxazole derivatives was also published by them. Subash et al., reported 5-*tert*-butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives with excellent anti-TB activity and Ntie-Kang and his group published binding of pyrazole-based inhibitors to MTB pantothenate synthetase: docking and MM-GB(PB)SA analysis.[18–21] Inspired by the wide range of biological activities and in continuation to our ongoing research on novel anti-TB

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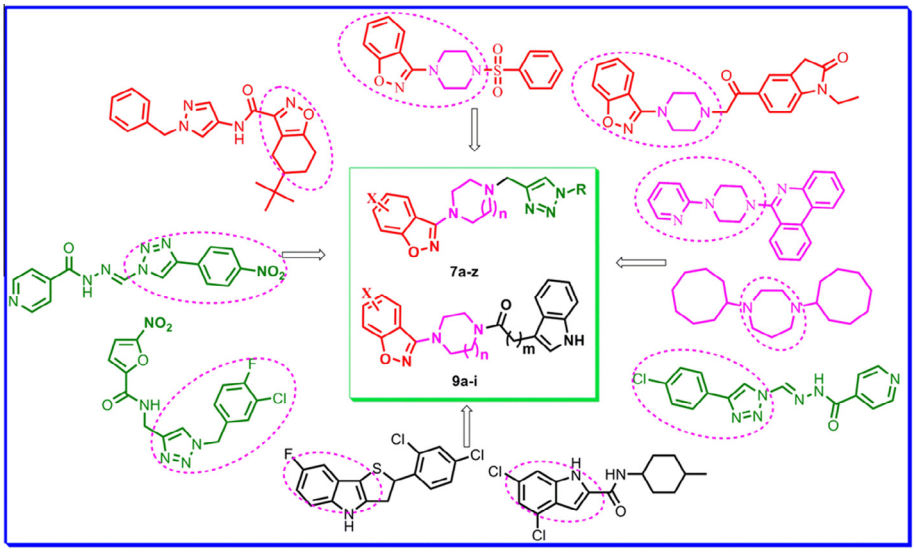
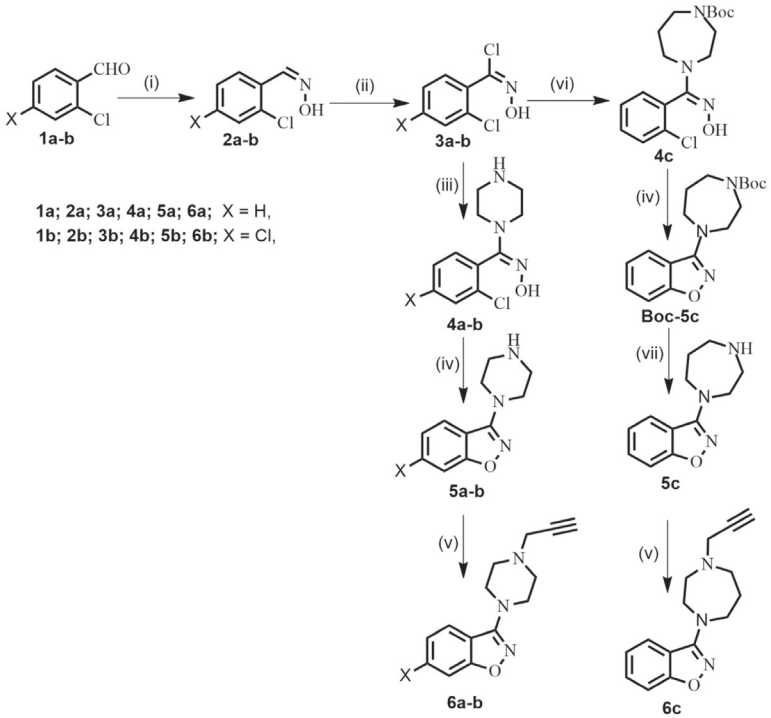


Figure 1. Design strategy to achieve title compounds.

agents[18,19,22] we extended our exploration on this heterocycle for anti-TB activity.

The indole moiety is the most widely spread nitrogen heterocycle in nature. The biological importance of indole heterocycles, their pharmacological and medicinal potential, have made indoles extremely attractive and rewarding research targets and have motivated countless researchers to study their synthesis, pharmacological and physiochemical properties. Particularly, some groups have published indole derivatives as anti-TB agents.[23–31] Yamuna et al., reported synthesis, antimicrobial, antimycobacterial and structure–activity relationship of substituted pyrazolo-, isoxazolo-, pyrimido- and mercaptopyrimidocyclohepta[*b*]indoles; Kondreddi et al., reported design, synthesis, and biological evaluation of forty one derivatives of indole-2-carboxamides. Synthesis, characterisation, and SAR studies of new (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide derivatives as possible antimicrobial and anti-tubercular agents was developed by Ranjith and his team.[23–25] These reports suggest, the importance of indole core motif and antimycobacterial activity, particularly, emphasising the fact that CF_3 substituted molecules have a significant role in medicinal chemistry.[23,32]

The lipophilicity of chemophores plays an important part in the physiochemical properties and biological activities. Attaching piperazine and homopiperazine analogues enriches the biological



Scheme 1. General synthetic route to achieve the cardinal synthons (**6a–c**). Reagents and conditions: (i) $NH_2OH{\cdot}HCl$ (1.2 equiv), CH_3COONa (2.0 equiv), EtOH, H_2O, 0 °C–rt, 1 h, (90–94%); (ii) *N*-chlorosuccinimide (1.2 equiv), CCl_4, 0 °C–rt, 45 min, (88–92%); (iii) piperazine (8.0 equiv), $N(C_2H_5)_3$ (2.0 equiv), CH_2Cl_2, rt, 2 h, (80–85%); (iv) KOH (3.0 equiv), dioxane/H_2O (3:1), 120 °C, 4 h, (70–80%); (v) propargyl bromide (1.1 equiv), $N(C_2H_5)_3$ (2.0 equiv), DMF, 0 °C–rt, 2 h, (90–95%); (vi) 1-Boc homo piperazine (1.0 equiv), $N(C_2H_5)_3$ (2.0 equiv), CH_2Cl_2, rt, 2 h, (92%); (vii) 4 N HCl in dioxane (1.0 equiv), CH_2Cl_2, 0 °C–rt, 1 h, (96%).