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Design, development of new synthetic methodology, and biological evaluation of substituted quinolines as new anti-tubercular leads

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ABSTRACT

Two series of quinoline-based compounds were designed, synthesised and evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294 strain). A new method for Friedländer quinoline synthesis has been developed in water under the catalytic influence of the Brønsted acid surfactant DBSA. Among the forty-two compounds tested for anti-TB activity, twenty-three compounds exhibited significant activity against the growth of *M. tuberculosis* (MIC 0.02–6.25 μg/mL). In particular, the compounds **3b** and **3c** displayed excellent anti-TB activity with MIC values of 0.2 and 0.39 μg/mL, respectively, and are more potent than the standard drugs E, Cfx and Z that are clinically used to treat TB. The cytotoxicity of the compounds with MIC ⩽6.25 μg/mL was evaluated against Human Embryonic Kidney 293T cell lines and all of the active compounds were found to be nontoxic (<50% inhibition). The results suggest that the synthesised substituted quinolines are promising leads for development of new drug to treat TB.

Tuberculosis (TB) is a disease of antiquity caused by infection with members of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis* (Mtb), *M. africanum*, *M. bovis*, *M. caprae*, *M. microti*, *M. pinnipedii* and *M. canetti* but the Mtb organism is the main pathogen infecting more than one-third of the world's human population [1]. It is an airborne disease affecting millions of people each year being the second leading cause of death worldwide, after the human immunodeficiency virus (HIV). In 1993, World Health Organisation (WHO) declared TB 'a global health emergency' [2]. According to WHO, 9.0 million people developed TB worldwide in the year 2013 out of which India and China accounted for 24% and 11% of the total cases, respectively, and approximately 1.5 million people died from the disease, 3,60,000 of whom were HIV-positive [3].

The recommended DOTS (Directly Observed Treatment, Short Course) therapy for TB is a regimen that consists of four drugs (Fig. 1) i.e., isoniazid (INH), rifampicin (R), pyrazinamide (Z), and ethambutol (E) taken daily for two months during the 'intensive' treatment phase, followed by two drugs – INH and R – taken daily for four months in the 'continuation' or 'sterilising' phase [4]. The lengthy treatment, lack of drug supply, underdeveloped health care and inappropriate drug prescription or dose leads to increasing the risk of resistance development [5]. All the existing drugs have acquired resistance and cross resistance [6]. The recalcitrant nature of persistence infection and increase in multi- and extensively-drug-resistant strains (MDR-TB and XDR-TB) are the main challenges for effective treatment of TB with the currently available anti-TB drugs. Thus, there is an urgent need for new anti-mycobacterial drugs that will shorten the duration of tuberculosis chemotherapy or overcome drug-resistant strains of the causative organism *M. tuberculosis* [7].

Quinoline derivatives have drawn considerable attention for the discovery of new anti-mycobacterial agents (Fig. 2) [8–16]. The well-known antimalarial drug mefloquine and its derivatives have been found to possess substantial activity against *Mycobacterium* species [17–24]. Fluoroquinolones (FQs), such as gatifloxacin and moxifloxacin are in phase III clinical trial and ciprofloxacin (Cfx), ofloxacin, lomefloxacin, and norfloxacin are used as second line anti-TB drugs for treatment of MDR-TB [25–27]. Quinoline moiety is the essential pharmacophoric feature of the recently approved anti-TB drug bedaquiline developed by Johnson & Johnson pharmaceutical company [28]. Bedaquiline acts by a novel mechanism by targeting proton pump of adenosine triphosphate (ATP) synthesis, leading to inadequate synthesis of ATP [29]. The WHO and the US Centers for Disease Control and Prevention suggested the use of bedaquiline for treatment of adult MDR-TB patients when an effective treatment regimen cannot otherwise be provided [30].

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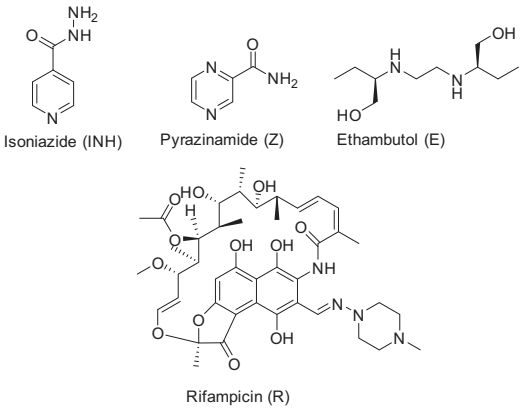

Fig. 1. First-line anti-tubercular drugs.

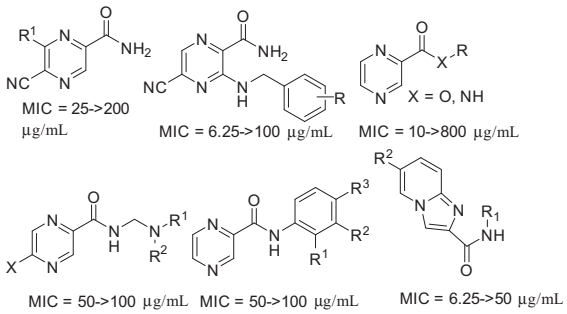

Figure 3. Various compounds bearing amide functionality with anti-tubercular activity.

On the other hand, many potential anti-TB compounds [31–38] and anti-TB drugs such as INH, PZA, PAS etc. has amide or carboxylic acid (Fig. 3) functionality as the essential structural feature.

As a part of investigation of new chemotherapeutic agents for tuberculosis [39], our research efforts have been focused towards the development of new scaffolds with potent anti-mycobacterial activity. Herein, we describe the synthesis and in vitro screening of substituted quinoline derivatives as potential anti-tubercular agents.

In the present study, we adopted scaffold hopping strategy [36–40] and incorporate amide group in the quinoline moiety for designing new anti-TB scaffold (Fig. 4). Two series of substituted quinolines have been designed by modifications on the quinoline core. In the first series various substitutions were made at C2, C3, C4, and C6 position of the quinoline nucleus in the Scaffold I (**3a**–**3u**) and in second series variations were made on quinoline-3-carboxamide (**5a**–**5u**) in Scaffold II.

The target compounds **3** can be obtained by Friedländer quinoline annulation through cyclo-condensation of 2-amino-substituted aromatic aldehydes/ketones with active-methylene group containing carbonyl derivatives (Scheme 1) [41]. However, the development of newer methodologies that would be useful addition to medicinal chemist's toolbox [42] and address the deficiency of ecofriendly need is in demand and subject of current interest due to the adverse effect of the manufacturing processes of drugs and pharmaceuticals on the environment [43].

The use of water as a reaction medium addresses adequately the aspect of maintaining greenness. Due to the unique physical and chemical properties, particularly hydrogen bond formation ability, water offers distinct advantages to increase the reaction rate unattainable in organic solvents that extend its role beyond the capacity of the reaction medium [44–51]. Although, the solubility of organic compounds in water is often a detrimental factor for using water as a reaction medium, the use of surfactants can overcome the issue [52–54]. However, the role of the surfactant may not be limited to solubility enhancer as surfactant exhibits new chemistry [55] and accelerates the reaction by generation of microreactor assemblies at the interface [56]. The reported methodologies of Friedländer quinoline synthesis utilize surfactant such as $Zr(DS)_4$ [57], dodecylphosphonic acid (DPA) [58] and $Sc(DS)_3$ [59] in water. These methodologies are associated with one or more drawback such as the requirement of higher reaction temperature, additional cost because of synthesis of catalyst, and long reaction time. Therefore, in order to develop a greener and more efficient methodology we started our systematic investigation by screening various cationic, anionic, and non-ionic surfactants (data provided in the Supporting information).

Herein, we describe the scope and limitations of surfactant catalysis with particular emphasis on DBSA as a catalyst for Friedländer annulation of **1** with **2** to form **3** in good to excellent yield in water (Scheme 2).

This method was found to be more advantageous as compared to other reported methodologies. The product was isolated by diluting the reaction mixture with cold water followed by filtration

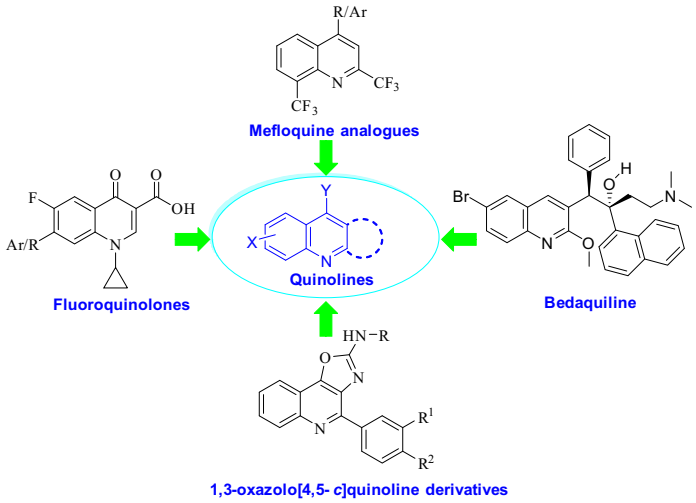

Fig. 2. Various quinoline-based compounds possessing anti-tubercular activity.