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Alkylated/aminated nitroimidazoles and nitroimidazole-7-chloroquinoline conjugates: Synthesis and anti-mycobacterial evaluation

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ABSTRACT

The success in exploring anti-tubercular potency of nitroimidazole and quinoline, the core moieties of recently approved anti-tubercular drugs instigated us to synthesize a series of alkylated/aminated 2-methyl-5-nitroimidazoles and nitroimidazole-7-chloroquinoline conjugates and to evaluate them for their activities against *Mycobacterium tuberculosis* as well as for their cytotoxicity towards the J774 murine macrophage cell line. Although the synthesized compounds did not surpass the activity of the standard drug Isoniazid, they have appreciable activities with minimal cytotoxicity. The synthesized nitroimidazole-7-chloroquinoline conjugate, **11c,** having butyl chain as linker, proved to be the most potent among the series with an MIC_{50} value of 2.2 μg/mL.

Tuberculosis (TB), caused by *Mycobacterium tuberculosis (Mtb)*, remains one of the deadliest diseases worldwide. According to the latest WHO Global Tuberculosis Report in 2017, an estimated 10.4 million people fell ill with TB, leading to 1.3 million TB deaths among HIV-negative people and an additional 374,000 deaths among HIV-positive people.[1] Despite a boost in the medical field and Research & Development sector, treating TB continues to be a great challenge as the rate of decline in TB incidence worldwide remained at only 1.5% from 2014 to 2015. The WHO estimated that if the prevailing trend continues, 30 million people will be infected by TB between the years 2000 and 2020.[2,3] For more than 60 years, various groups of drugs have been used for treating TB, which include (A) first-line oral anti-TB drugs, Isonaizid (INH), Rifampicin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA); (B) injectable anti-TB drugs, Streptomycin, Kanamycin, Amikacin, Capreomycin; (C) fluoroquinolones, Levofloxacin, Moxifloxacin, Gatifloxacin, Ofloxacin and (D) oral bacteriostatic second-line anti-TB drugs *viz* Ethionamide, Prothionamide, Cycloserine, Terizidone and *p*-Aminosalicylic acid.[4] Inspite of having this vast availability of medical assistance, a grave concern is required over the TB menace due to the emergence of various types of drug resistance viz. multi-drug resistance (MDR) and extensive drug resistance (XDR).[5] Besides, the long duration of current treatment (6–9 months), adverse side effects owing to the cytotoxic tendency of available drugs provide strong impetus for the introduction of new anti-TB agents.

There are around nine drugs in advanced phases of clinical trials for the treatment of drug-susceptible TB, drug-resistant TB or latent TB infections.[4] Among these drugs under trial, Bedaquiline (TMC-207), **1** and Delamanid (Deltyba™;OPC-67683), **2** have been approved by the US Food & Drug Administration (FDA) and by the European Medicines Agency (EMA) to include them in the combination therapy for the treatment of patients affected by MDR-TB.[6–8] According to the latest survey, 89 countries and territories have already started using Bedaquiline while 54 countries have used Delamanid by June 2017 as part of efforts to improve outcomes for MDR/XDR-TB.[1]

Nitroimidazoles are pro-drugs that are highly effective against both the replicating and non-replicating persistent forms of *Mtb*.[9] The use of the antibiotic Metronidazole in the management of anaerobic bacterial and protozoan infections has aroused interest in the nitroimidazole scaffolds over the past decade.[10,11] Currently available Delamanid (possessing a nitro-dihydroimidazooxazole core) and Pretomanid (PA-824), **3** (possessing a nitroimidazopyran core) are nitroimidazole based anti-TB agents which are under phase II and III clinical trials.[12] The anaerobic activity of these drugs is due to the vital presence of the nitroimidazole fragment

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whose mode of action includes the release of reactive nitrogen species *viz* nitric oxide causing respiratory poisoning.[13]

Enormous utilization of the quinoline nucleus in the areas of medicine, food, catalysts, dyes, materials, refineries, electronics etc. as well as its numerous biological applications as in antimalarial, antimicrobial, antimycobacterial, antidepressant, anticancer, and anti-HIV compounds have given this pharmacophore a prominent status in the field of pharmaceuticals for further exploration. Bedaquiline belongs to the diarylquinoline class of antibiotics whose pharmacologically active site consists of a quinoline central heterocyclic nucleus and side chains of tertiary alcohol and tertiary amine groups which are the main cause of its anti-tubercular action.[14] But this drug is accompanied by a black box warning due to serious adverse effects like increased mortality and QT (electrical depolarization and repolarization of the ventricles) prolongation, which limits its clinical application (Fig. 1).[15]

Chemical modifications of biologically active pharmacophores are key to drug discovery, resulting in improved therapeutic effects while minimizing the side effects. Recent reports from our lab on anti-mycobacterial evaluation of quinoline based hybrids *viz* 4-aminoquinoline-ferrocenylchalcone conjugates showed good activities with non-cytotoxicity.[16] In continuation of our endeavours towards synthesizing new anti-TB scaffolds,[17–20] the present manuscript describes the synthesis of alkylated and aminated nitroimidazoles with extension towards nitroimidazole-7-chloroquinoline conjugates. The synthesized scaffolds were evaluated against the mc^{2}6230 strain of *M. tuberculosis* along with their cytotoxic evaluation against the J774 murine macrophage cell line.

The first set of target scaffolds **5a–e**, was synthesized *via* base promoted alkylation of commercially available 2-methyl-5-nitroimidazole **4**, using various dibromo alkanes in anhydrous DMF at room temperature.[22] Interestingly, the alkylation of **4** with dibromo ethane afforded a mixture of two compounds **7** and **5a** as evident from the ^{1}H NMR of crude reaction mixture. The appearance of **7** as the major product could be attributed to the facile β-elimination in 1-(2-Bromo-ethyl)-2-methyl-5-nitro-1H-imidazole, **5a**. The structure of **7** was assigned on the basis of ^{1}H NMR spectra, which showed appearance of a pair of doublet of doublet at δ5.2 (J = 2.2 Hz, 8.7 Hz) and 5.4 (J = 2.2 Hz, 15.5 Hz) corresponding to olefinic protons H^1 and H^2 respectively. The appearance of an absorption peak at δ 107.71 in the ^{13}C NMR (DEPT) spectrum further corroborated the assigned structure. The alkylated nitroimidazoles **5a–e** were reacted with various secondary amines (listed in Table 1) in the presence of activated potassium carbonate in anhydrous DMF to yield the desired compounds **6b–j**.[23] The inability of **5a** to yield the desired aminated derivative, **6a** proved its vulnerability to undergo β-elimination in the presence of even a mild base. The complete reaction sequence is outlined in Scheme 1.

The work was further extended to synthesize nitroimidazole-7-chloroquinoline conjugated **11b–e** by reacting **5b–e** and **10**, prepared by heating overnight 4,7-dichloroquinoline **8** with an excess of piperazine **9** and triethylamine at 120 °C (Scheme 2)[21], using sodium hydride as base in dry DMF at room temperature (Scheme 3).[24] The success in hybrid formation was revealed by spectral and analytical data. For instance, High Resolution Mass spectrometry (HRMS) of **11c** showed a molecular ion peak at m/z = 428.1715 [M]$^+$ while in its ^{1}H NMR spectrum, the appearance of singlets at δ 2.7 and 3.2, corresponding to piperazine protons, two multiplets and two triplets at δ 1.6, 1.8, 2.5, 3.9 respectively because of methylene protons along with requisite aromatic protons as well as a characteristic singlet at δ 7.7 corresponding to a proton of nitroimidazole ring.

The whole series of synthesized compounds was evaluated for their anti-tubercular activities against the mc^{2}6230 strain of *M. tuberculosis* and the activities are listed in Table 1. Although the compounds were not as active as the standard drug Isoniazid, some of the compounds exhibited substantial anti-tubercular activity. Evaluating the structure–activity relationship (SAR) among the alkylated nitroimidazoles showed a decrease in activity with increase in spacer length, except for **5e** (n = 6) exhibiting an MIC_{50} of 4.9 μg/mL. The replacement of the bromo functional group with a secondary amine resulted in loss of anti tubercular activity. Among the three secondary amines introduced, namely morpholine, piperidine and pyrrolidine, pyrrolidine appeared to improve the activities with compounds **6g** and **6c** exhibiting MIC_{50} values in the range of 12.3–19.3 μg/mL. The introduction of a quinoline ring resulting in the nitroimidazole-7-chloroquinoline conjugate substantially improved the activity profiles with activity being independent upon the alkyl chain length introduced as spacer. The conjugate **9c** with a butyl chain as linker proved to be the most potent among the series exhibiting a MIC_{50} of 2.2 μg/mL. The anti-mycobacterial potential of precursor viz. 4-piperazinyl-7-chloroquinoline **10** was also evaluated in order to justify the rationale behind the hybridization approach. As evident, the compound exhibited poor activity with MIC_{50} of 92 μg/mL, which is much lower than the synthesized scaffolds, further strengthens the logic of conjugating a quinoline-nucleus with nitroimidazole-core for enhancing anti-TB activities.

Cytotoxicity of the synthesized scaffolds was determined using J774 murine macrophage cells in order to ascertain whether the observed activities were due to their anti-tubercular efficacy or their cytotoxic tendency and the results are enlisted in Table 1. As evident, most of these compounds were not cytotoxic except **11e** and exhibited high selectivity index.

In conclusion, a series of alkylated/aminated nitroimidazoles and nitroimidazole-7-chloroquinoline conjugates were synthe-

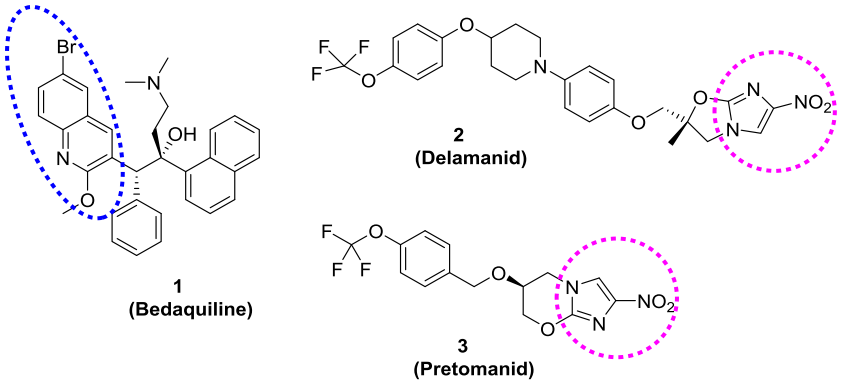

Fig. 1. Structures of quinoline and nitroimidazole based some anti-TB drugs which are under advanced phase of clinical trial.