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Research paper

Design, synthesis and antimycobacterial activity of novel imidazo[1,2-*a*]pyridine-3-carboxamide derivatives

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ABSTRACT

We report herein the design and synthesis of "novel imidazo [1,2-*a*]pyridine-3-carboxamides (IPAs)" bearing a variety of different linkers, based on the structure of IMB-1402 discovered in our lab. Results reveal that 2,6-dimethyl-*N*-[2-(phenylamino)ethyl] IPAs with an electron-donating group on the benzene ring as a potent scaffold. Compounds **26g** and **26h** have considerable activity (MIC: 0.041–2.64 μM) against drug-sensitive/resistant MTB strains, and they have acceptable safety indices against MTB H37Rv with the SI values of 4395 and 1405, respectively. Moreover, *N*-[2-(piperazin-1-yl)ethyl] moiety was also identified as a potentially alternative linker (compound **31**), opening a new direction for further SAR studies.

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1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused mainly by Mycobacterium *tuberculosis* (MTB). The World Health Organization (WHO) 2015 TB report estimated that approximately one-third of the world population is infected with MTB, and 9.6 million people were infected and 1.5 million died from TB worldwide in 2014 [1]. The high prevalence of multidrug-resistant MTB (MDR-MTB) and the emergence of extensively drug-resistant MTB (XDR-MTB), together with coinfection with Human Immunodeficiency Virus (HIV), have intensified the need for new anti-TB drugs [2–4]. Bedaquiline (an ATP synthase inhibitor) was, for the first time since 1970s, approved by the US FDA for clinical management of MDR-TB in 2012 [5], but some adverse events have been noted [6]. Therefore, it is urgent to identify new molecules with alternative scaffolds as effective anti-TB drug candidates.

Recently, imidazo[1,2-*a*]pyridine-3-carboxamides (IPAs) as TB antibiotics have garnered great interest. Two candidates Q203 (Fig. 1) [7,8] and ND09759 (Fig. 1) [9,10] were reported to have strong inhibitory potency against drug-sensitive, MDR and XDR strains by targeting the QcrB subunit of the menaquinol cytochrome c oxidoreductase (bc1 complex) [8,11]. Structure–activity relationship (SAR) studies of IPAs demonstrated that the carboxamide linker with the *N*-benzylic group is critical for antimycobacterial activity [7]. However, many 2,6-dimethyl IPAs bearing a *N*-(2-phenoxy)ethyl moiety were also found to demonstrate highly potent activity (MIC: 0.025–0.054 μg/mL) against both drug-sensitive MTB and MDR-MTB strains in our lab. Among them, IMB-1402 (Fig. 1) displays acceptable safety and pharmacokinetic properties [12]. This suggests that other 3-carboxamide linkers between the imidazo[1,2-*a*]pyridine core and the benzene ring would be tolerated within the SAR of this IPA series. Accordingly, a series of novel 2,6-/2,7-dimethyl IPAs bearing a variety of different linkers were designed and synthesized as new anti-TB agents in this study (Scheme 2). Our primary objective was to identify alternative linkers with potent antimycobacterial activity. A preliminary SAR study was also explored to facilitate the further development of IPAs.

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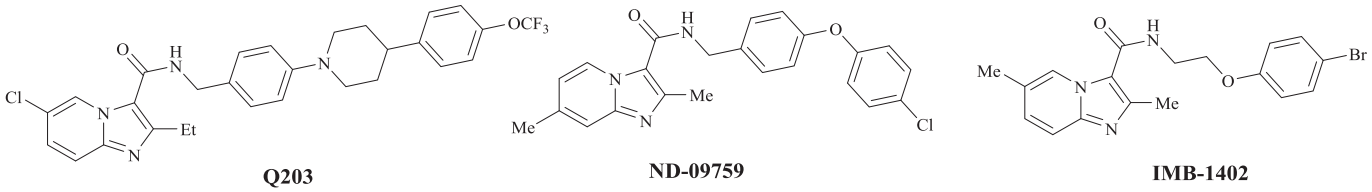


Fig. 1. Structures of Q203, ND-09759 and IMB-1402.

2. Results and discussion

2.1. Chemistry

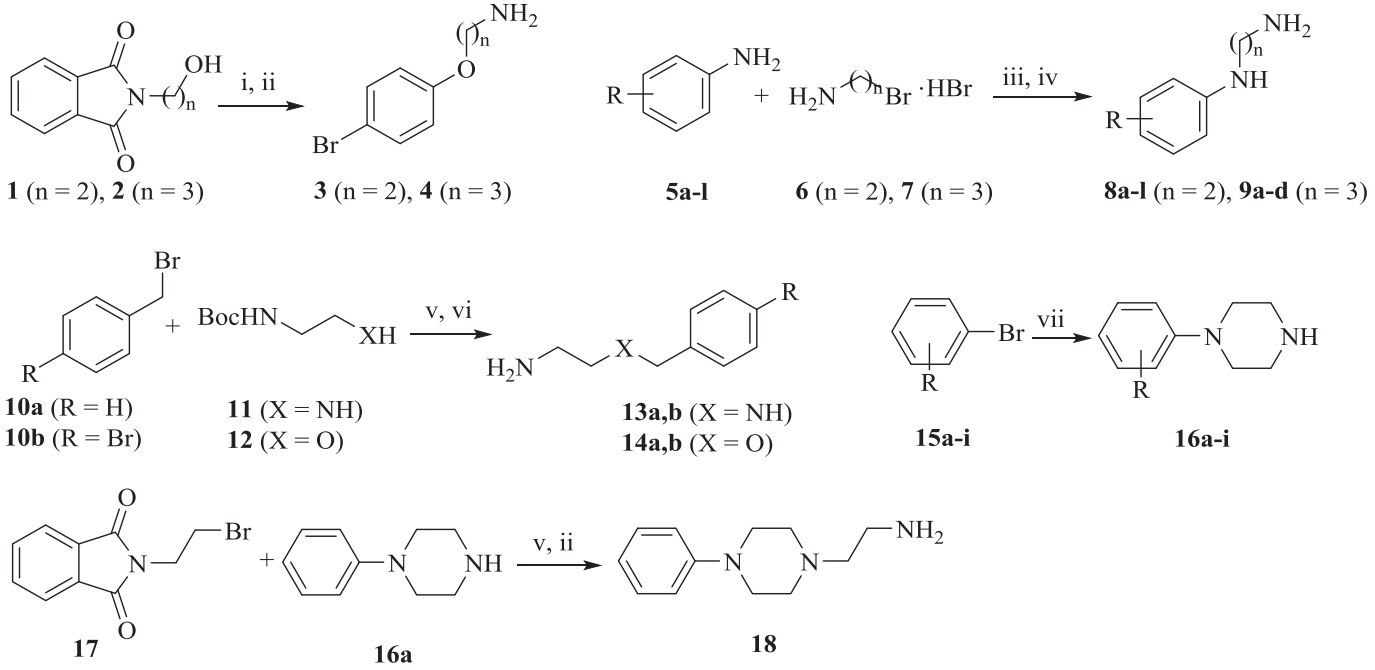
Detailed synthetic pathways to amine derivatives **3**, **4**, **8a-l**, **9a-d**, **13a-b**, **14a-b**, **16a-i**, and **18** which are commercially unavailable are depicted in Scheme 1. Coupling of 4-bromophenol with hydroxy phthalimide **1**, **2** in the presence of diethyl azodicarboxylate (DEAD) and PPh_3 followed by treatment with hydrazine hydrate in ethanol yielded amine **3**, **4**. Treatment of anilines **5a-l** with compounds **6**, **7** in toluene under reflux condition gave the desired 1, 2-diamines **8a-l** and 1,3-diamines **9a-d**. Nucleophilic substitution of benzyl bromides **10 a, b** with compounds **11, 12** followed by deprotection the Boc-group furnished *N*-benzylethane-1,2-diamines **13a, b** and 2-(benzyloxy)ethan-1-amines **14a,b**. Buchwald-Hartwig coupling of bromobenzenes **15a-i** with piperazine in toluene afforded compounds **16a-i**. Condensation of compound **16a** with *N*-(2-bormoethyl)phthalimide **17**, and then treatment of the resulting condensate with hydrazine hydrate in ethanol yielded 2-(4-phenylpiperazin-1-yl)ethan-1-amine **18.**

Core acids **21a, b** were obtained from 2-aminopyridines **19a, b** in two steps using our published procedures [13]. Direct amidation of the acids **21a, b** with the above amines **3**, **4**, **8a-l**, **9a-d**, **13a, b**, **14a, b**, **16a-i**, **18** and commercially available 1-(pyridine-2/4-yl) piperazines **22a, b** and 4-(4-fluorophenyl) piperidine **23** in the presence of Bis-(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) and triethylamine (Et_3N) gave target compounds **24-33** (Scheme 2).

2.2. Pharmacology

The target compounds **24-33** were initially screened for *in vitro* activity against MTB H37Rv ATCC 27294 strain using the Microplate Alamar Blue Assay (MABA) [14,15]. The minimum inhibitory concentration (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of >90% relative to the mean of replicate bacterium-only controls. The MIC values of the compounds along with isoniazid (INH) and rifampicin (RFP) for comparison are presented in Table 1.

Synthesized compound **25** exhibits significantly reduced activity (MIC: 0.62 μM) compared to IMB-1402 (**24**, MIC: 0.038 μM), suggesting that ethyl seems to be more favorable for activity than propyl. Therefore, structural modifications were focused on the *N*-(2-phenoxy)ethyl linker in this study. First, the linker was replaced by the isostere *N*-(2-phenylamino)ethyl one giving compounds **26a-k**, and SAR of the substitution on the benzene ring was investigated. It is clear that the anti-MTB potency is visibly influenced by the nature and position of the substitution on the benzene ring. For example, introduction of one or two halogen atoms on the



i) 4-bromophenol, DEAD, PPh_3, THF, 0-5 °C; ii) hydrazine hydrate, EtOH, reflux; iii) toluene, reflux;
iv) NaOH, rt; v) K_2CO_3, MeCN, reflux; vi) TFA, DCM, rt; vii) piperazine, $Pd(OAc)_2$, *t*-BuONa, BINAP, toluene, reflux

Scheme 1. Synthesis of compounds **3**, **4**, **8a-l**, **9a-d**, **13a-b**, **14a-b**, **16a-i**, and **18**.

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