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Original article

Design, diversity-oriented synthesis and structure activity relationship studies of quinolinyl heterocycles as antimycobacterial agents

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ABSTRACT

The current study reports design and diversity oriented synthesis of novel bis heterocycles with a common 2-methyl, C-4 unsubstituted quinoline moiety as the central key heterocycle. Employing reagent based skeletal diversity approach; a facile synthesis of bis heterocycles with different heterocyclic rings at C-3 position of the quinoline moiety has been accomplished. A broad range of heterocyclic frameworks thus obtained were evaluated for their antimycobacterial activity. The active scaffolds were further explored by a parallel library generation in order to establish SAR. Further, low cytotoxicity against A549 cell line enhances the potential of the synthesized molecules as promising antimycobacterial agents.

1. Introduction

Tuberculosis is a common chronic communicable disease caused by various strains of Mycobacterium. Mycobacteria are omnipresent intercellular pathogens which not only infect the oxygen rich macrophages of lung, but also affect other vital parts of the body. One third of world population is thought have been infected by TB. Emergence of drug resistant strains of TB (MDR-TB) bacteria is an alarming problem and is estimated to be 5% of the infections detected. About 40% of MDR-TB infections that are resistant to frontline treatment are also resistant to backup drugs leading to extensively drug resistant tuberculosis (XDR-TB). While MDR-TB is resistant to frontline drugs rifampcin and isoniazid, XDR TB is resistant to kanamycin, capreomycin or amikacin as well, making it virtually untreatable [1–3]. Alternative treatment options are highly toxic and expensive, especially since most MDR and XDR TB cases are reported in developing world. XDR TB also raises the concern of a possibility of a TB epidemic with restricted treatment options [1,4].

The absence of effective preventive measures like vaccines and development of drug resistance among the infectious bacterial strains, are the two major driving forces for design and development new potential drugs for treatment of TB. The most important challenge in this context is the problem in identifying suitable active new (small molecule) chemical entities. Small heterocyclic molecules exert powerful effects on the disease pathways in living systems and therefore find applications in betterment of human health [5]. Literature survey reveals that more efficacious new chemical entities can be envisaged by incorporating two or more highly active heterocyclic systems into a single molecule [6]. A simple synthetic design strategy would be based on analogues of known TB drugs or recently approved candidates (TMC207 [7], Fig. 1). Design of the title bis heterocycles is based on hybridization of isoniazid (Fig. 1). A rational approach for synthesis of bis heterocycles is envisaged by replacing pyridinyl ring of isoniazid with quinoline and incorporating the hydrazide fragment in various heterocyclic moieties [8]. A simple synthetic route was designed wherein a common 2-methyl, C-4 unsubstituted quinoline moiety was chosen as the central key heterocycle and various heterocyclic moieties built, at C3 position of the intermediate, employing diversity oriented synthesis.

2. Results and discussion

2.1. Chemistry

Diversity oriented synthesis is the latest tool in synthetic organic chemist's endeavour in simultaneous as well as efficient

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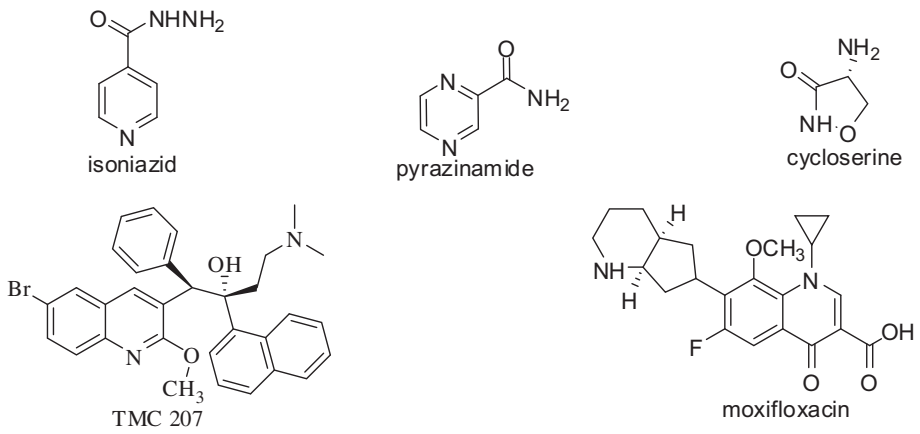

Fig. 1. Heterocyclic tuberculosis drugs.

synthesis of structurally diverse range of compounds [9]. A deliberate construction of diverse hybrid heterocycles by using different reagents to transform a common substrate is envisioned. This would lead to the availability of a collection of molecular frameworks that give the desired antimycobacterial action. The active bis heterocyclic frameworks can then be further extrapolated by rapid, simultaneous preparation of small molecule libraries of the hits generated for establishment of structure activity relationship.

A key challenge in the construction of hybrid heterocycles with quinoline core moiety is the design of sufficiently robust methods, allowing simultaneous preparation of diverse small molecule libraries, as well as arriving at common intermediate. 3-Acyl/carboxylate quinoline moiety has been chosen as common intermediate amenable for diversity oriented synthesis of bis heterocycles. A straight forward and efficient synthesis of quinolines *via* a BDMS ((bromodimethylsulfonium) bromide) catalysed solvent free Friedlander synthesis by condensation of 2-amino aryl/alkyl ketones with α-methylene containing carbonyls like, 1,3-dicarbonyls has already been developed and reported by this group [10]. The quinoline ester obtained from this protocol, however was not amenable to further reactions at C-3 position. This could probably be because all these derivatives invariably possess a C-4 substitution (aryl/alkyl) which sterically hampers reactions at C-3 carbon. An alternative quinoline moiety without C-4 substitution has been visualized starting from 2-nitrobenzaldehyde and 2-aminobenzaldehdye [11] or α-aminobenzyl alcohol [12]. α-Aminobenzyl alcohol was chosen, as it is readily available and could be effortlessly oxidized. Various oxidising reagents such as DMSO/HBr, BDMS, I_2, HTIB ([hydroxyl (tosyloxy)iodo] benzene), CAN (cerium(IV)ammonium nitrate, a single electron transferring reagent) etc., gave unsatisfactory results. MnO_2 oxidation was found to be cleanest and suitable method and core quinoline intermediates (**3a**–**c**) have been synthesized by this method as shown in Scheme 1.

3-(Dimethylamino)-1-(2-methylquinoline-3-yl) prop-2-one **6** (Scheme 1) was prepared by addition of DMF–DMA (*N*,*N*-dimethylformamide dimethylacetal) [13] to 3-acylquinoline **3a**, which is the key intermediate for construction of **7** and **8** (Scheme 1). On the other hand, 4-(2-methylquinoline-3-yl)pyrimidine-2-amine **7** and 2-methyl-3-(1*H*-pyrazol-3-yl)quinoline **8** skeletons were constructed from compound **6** by addition of guanidine hydrochloride [14] and hydrazine [15], respectively. Quinolinyl 2-aminothiazole **9** and imidazopyridine **10** (Scheme 1) rings were built by nucleophilic addition and condensation of thiourea [16] and 2-amino pyridine [17] respectively, on the 2-bromo-1-(2-methylquinoln-3-yl)ethanone **4** [18] (Scheme 1). The oxadiazole scaffold **12a** (Scheme 1) was formed by the oxidative cyclization of quinolinyl hydrazone **11** (Scheme 1). The 3-acyl quinoline **3a** was readily converted to the chalcone **13** by aldol condensation [19] with aldehyde (Scheme 1). Chalcones on addition of hydrazine gave corresponding *N*-acyl dihydropyrazoles **14f** (Scheme 1).

Preliminary screening to assess the antimycobacterial activity of the synthesized bis heterocycles was carried out against *Mycobacterium smegmatis*. This resulted in three active hits **8**, **12a**, **14f** (Table 1). Surprisingly, the quinolinyl hydrazide **5** (Table 1), which is similar to isoniazid, did not exhibit any antimycobacterial activity. Three active scaffolds had the hydrazide moiety incorporated into pyrazole **8**, oxadiazole **12a** and pyrazoline **14f** skeletons.

With diversity of the intermediates proven as well as the hits generated, the synthesis of a series of quinolinyl oxadiazoles, pyrazoles and pyrazolines was taken up starting from, 2-ethyl quinoline-3-carboxylate **3b** and 1-(2-methylquinolin-3-yl)ethanone **3a**, respectively. The ester **3b** was refluxed with hydrazine hydrate to obtain corresponding acylhydrazide **5**, which was condensed with various aldehydes to yield corresponding acyl hydrazones **11** (Scheme 2). Among the various oxidizing reagents available for oxidative cyclisation of hydrazones such as $POCl_3$ [20], CAN [21], Chloramine-T [22], solid phase synthesis with TFAA [23], etc., IBD (iodobenzene diacetate) [24] was found to be the most facile reagent. The oxidative cyclization of the quinolinyl hydrazones in the presence of IBD gave corresponding 2,5-disubstituted-1,3,4-oxadiazoles. A library of quinolinyl oxadiazoles was developed following the above protocol **12**(**a**–**o**) (Scheme 2).

Quinolinyl pyrazoles **16**(**a**–**b**) (Scheme 2) are obtained by refluxing acetylacetone or 3-(tetrahydro-2*H*-pyran-2-yl) pentane-2,4-dione [25] with corresponding acylhydrazide derivative in ethanol. *N*-Phenyl dihydropyrazoles **15**(**a**–**c**) (Scheme 2), are obtained by refluxing **13** with phenyl hydrazine in ethanol. 2-Methyl-3-(1*H*-pyrazol-3-yl)quinoline **8** (Scheme 1) was acylated with acetyl chloride to generate 1-(3-(2-methylquinolin-3-yl)-1*H*-pyrazol-1-yl)ethanone **17** (Scheme 2). All synthesized compounds were characterized completely by their spectral data.

The antimycobacterial activity of the synthesized quinolinyl oxadiazoles **12**(**a**–**o**), pyrazolines **14**(**a**–**n**), **15**(**a**–**c**) and pyrazoles **16**(**a**–**b**), **17** (Table 2) was evaluated against *M. smegmatis*. *M. smegmatis* is a fast grower and a suitable non-pathogenic strain for assessing activity of the compounds in primary screening. As reported in earlier literature on screening for antimycobacterial compounds, the *M. smegmatis* based screens showed 100% specificity and 78% sensitivity in comparison to MDR *Mycobacterium tuberculosis* screens [26].

In each series, the impact of the variation aryl/alkyl substitutions on the antimycobacterial activity was examined (Tables 1