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Original article

Ultrasound-assisted one-pot four-component synthesis of novel 2-amino-3-cyanopyridine derivatives bearing 5-imidazopyrazole scaffold and their biological broadcast

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ABSTRACT

An alternative and environmentally caring way for the synthesis of novel 2-amino-3-cyanopyridine derivatives bearing 5-imidazopyrazole nucleus is reported by one-pot four-component cyclo-condensation reaction of substituted 5-(1*H*-imidazol/4-methyl-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a**–**b**), malononitrile (**4**), ammonium acetate (**5**) and aromatic (**6a**–**f**)/heterocyclic methyl ketones (**7a**–**d**) under ultrasonic irradiation. The newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against a panel of pathogenic stains of bacteria and fungi, *in vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv stain and *in vitro* antioxidant activity by ferric-reducing antioxidant power method. Compounds **8e**, **8h**, **8l**, **9c**, **9g** and **9h** exhibited excellent antibacterial activity and compounds **3a**, **8k**, **9a** and **9b**showed moderate antituberculosis activity as compared with the first line drugs. Majority of the compounds showed excellent antioxidant activity. This approaches claimed to be an environment friendly protocol as it afforded numerous advantages i.e. excellent yields, cleaner reaction profile and shorter reaction time.

1. Introduction

Mycobacterium tuberculosis is a deadly pathogen and contributory agent of tuberculosis (TB) which remains a chief reason of death worldwide [1–3]. Almost one third of the world's population is contaminated with TB bacilli and each year approximately 8 million people are added in the list suffering from active TB and 2 million die as a result [4]. HIV-positive patients are more likely to be infected with TB. The co-infection with HIV is considered accountable for these serious circumstances. The difficulty in treating drug-resistant TB, such as multidrug- resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) also contributes to the increased morbidity and mortality. There has been remarkable raise in the frequency of bacterial and fungal infections over the past few decades. These organisms possess the ability to withstand attack by currently available antimicrobial drugs. The uncontrolled rise in drug resistant pathogens have threatened lives [5]. Innovation of novel drug molecules for the action of complete mycoses is one of the most imperative challenges in infectious disease research. The investigation of new antimicrobial drugs is an evergreen area characterized by energetic search with the intention of conquering episode of abundant drug resistance. To establish preeminent ways to build up efficient therapy, the urgency for the need of novel, unique and persuasive antimicrobial and antitubercular agents attracts immediate attention.

Synthesis of the pyrazole ring system and its derivatives occupy an important place in the realm of synthetic organic chemistry, due to their pharmaceutical activities such as, anticancer [6], antibacterial [7], analgesic [8], antiviral [9] and anti-inflammatory [10] activities. Imidazole derivatives are known to be allied with diverse biological properties, such as antimicrobial [11], antitubercular [12], anti-inflammatory [13], anti-Parkinson [14], analgesic, anti-convulsant and anticancer activities [15]. In recent years, pyridine derivatives represent an imperative class of compounds which possesses high activity profile due to their therapeutic and pharmacological properties [16–18]. Pyridine ring is an essential part for the anticancer and anti-inflammatory agents [19,20]. The biologically active compounds having carbon–nitrogen bond especially the natural and synthetic compounds with cyanopyridine moiety are proved to display significant antifungal [21], antibacterial [22] and anticancer [23] activities.2-Amino-3-cyanopyridine motifs are known to have numerous biological activities, such as anti-microbial [24], anti-inflammatory [25],

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cardiotonic [26], anti-parkinsonism properties [27] and potent inhibitor of HIV-1 integrase [28].

Literature survey revealed that a number of 2-amino-3-cyanopyridine derivatives have been synthesized using a variety of aldehydes [25,26,29–31]. 5-(1*H*-imidazol/4-methyl-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes has not been reported so far for the purpose. Thus, with a view to obtain biologically more potent heterocyclic systems, our aim was focused on the prologue of chemical diversity in the molecular framework to synthesize pharmacologically interesting compounds of different composition by green protocol.

Ultrasonic-assisted organic synthesis (UAOS) offers a resourceful and too easy pathway for a large variety of scaffolds. The significant features of the ultrasound approach are formation of pure products in prominent yields, improved rate of reaction, easier handling and also considered as a processing aid in terms of energy conservation compared with conventional methods [32,33].

The single-pot synthesis proceeds over shorter reaction time without the need for isolation of the intermediates [34]. Hence, as a part of programme directed towards environmentally friendly methodologies for the preparation of heterocyclic compound [35–41], herein we report a simple, cost-effective, green and expeditious method for the synthesis of novel 2-amino-3-cyanopyridine derivatives bearing 5-imidazopyrazole moieties under ultrasound irradiation and investigation on their antimicrobial, antituberculosis and antioxidant activities (Scheme 1).

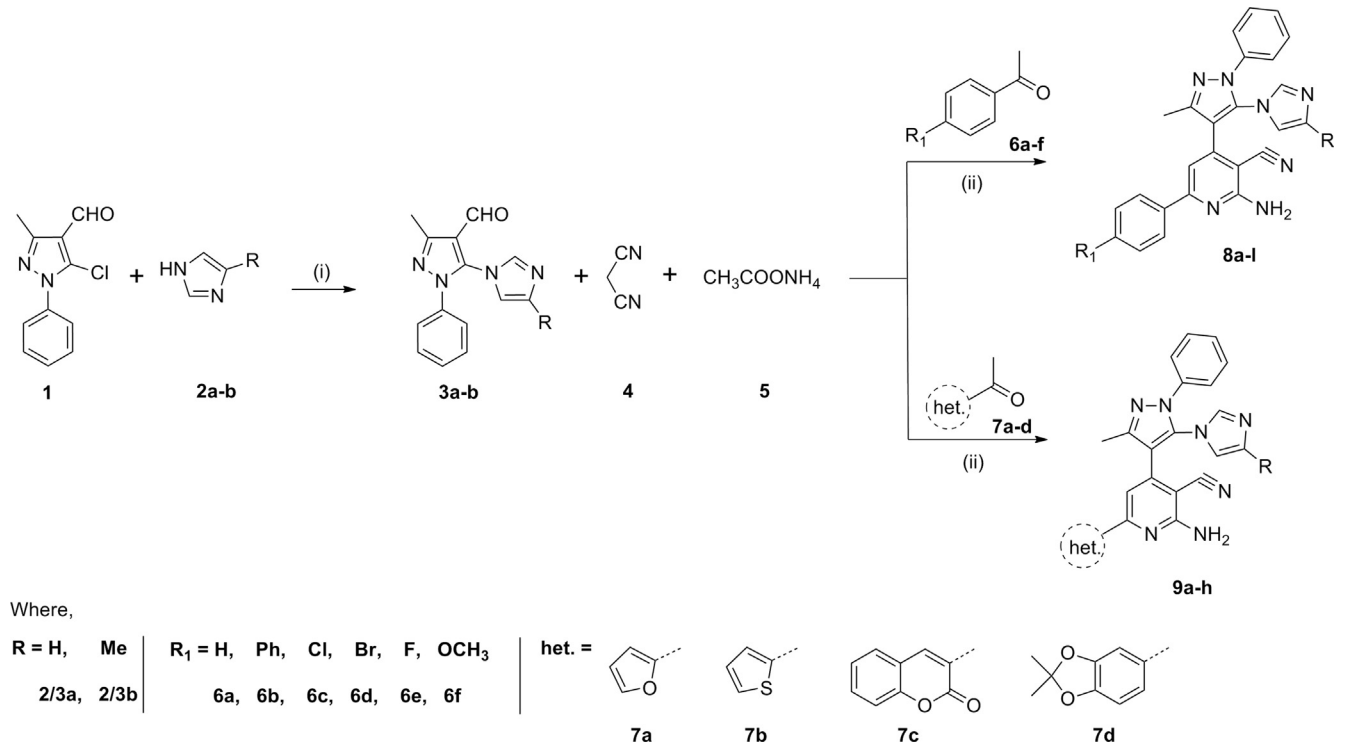
2. Chemistry

The synthetic approach adopted to acquire the targeted 4-(5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-aminonicotinonitrile derivatives **8a**–**l** and **9a**–**h** is summarized in Scheme 1. The starting material 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde **1** was prepared according to Vilsmeier–Haack reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one [42]. The final aldehydes 5-(1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **3a**–**b** were prepared by nucleophilic displacement of chloro group at C5 in 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with secondary amine of imidazole **2a**–**b**in refluxing DMF using anhydrous potassium carbonate as a base. The targeted compounds substituted 4-(5-(1*H*-imidazol/4-metyl-1-yl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-aminonicotinonitrile **8a**–**l** and **9a**–**h** were prepared in moderate to good yield (64–84%) by the reaction of substituted 5-(1*H*-imidazol/4-methyl-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **3a**–**b**, malononitrile **4**, ammonium acetate **5** and aromatic/heterocyclic methyl ketone **6a**–**f**/**7a**–**d** in absolute alcohol by one-pot four-component cyclocondensation reaction (Scheme 1 , Table 1). The formation of compounds **8a**–**l** and **9a**–**h** took place *via* imine formed from ketone and ammonium acetate. Imine reacted with alkylidene malononitrile formed from Knoevenagel condensation of aldehyde and malononitrile, followed by cycloaddition, isomerization and aromatization to give the targeted compounds **8a**–**l** and **9a**–**h**. The mechanism of compound **6c** is illustrated in Scheme 2.

3. Pharmacology

3.1. Antimicrobial activity

The minimal inhibitory concentration (MIC) of all the synthesized compounds **8a**–**l** and **9a**–**h** was determined by broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [43]. Antibacterial activity was screened against three Gram positive (*Streptococcus pneumoniae* MTCC 1936, *Clostridium tetani* MTCC 449 and *Bacillus subtilis* MTCC 441) and three Gram negative (*Escherichia coli* MTCC 443, *Vibrio cholerae* MTCC 3906 and *Salmonella typhi* MTCC 98) bacteria by



Scheme 1. Synthesis of the substituted 4-(5-(1H-imidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-aminonicotinonitrile **8a**–**l** and **9a**–**h**. (i) DMF, K_2CO_3, Reflux 2 h (ii) Ethanol, ultrasound irradiation, room temperature **Or** Ethanol, Reflux 1.5–3 h.