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ORIGINAL ARTICLE

# Design, synthesis and antimicrobial activities of some novel 1,3,4-thiadiazole, 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole

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1,3-Thiazolan-4-one;
Structure–activity relationship study;
Antimicrobial activity

**Abstract** A series of novel 1,3,4-thiadiazole; 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole were synthesized by nucleophilic substitution reaction of 2-substituted-1[*H*] benzimidazole. Compounds (1*H*-benzo[*d*]imidazol-2-yl)methanamine **3**, 2-(isothiocyanatomethyl)-1*H*-benzo[*d*]imidazole **4**, 4-(1*H*-benzo[*d*]imidazol-2-yl)benzenamine **6** and 4-(1*H*-benzo[*d*]imidazol-2-yl)benzenamine **7** are synthesized for the synthesis of targeted compounds. Structures of all the targeted synthesized compounds were evaluated by spectral and elemental methods of analysis. All the synthesized compounds were evaluated for antibacterial and antifungal activities. Some of the synthesized compounds showed good antibacterial and antifungal activities with 2.0 and 2.5 μg/mL MIC (minimum inhibitory concentration), respectively.


## 1. Introduction

Discovery of new drugs for systemic opportunistic microbial infections is a major challenge in infectious disease research. Microbial infections have increased in recent years, particularly those that are of nosocomial origin, leading to a broad use of agents with activity against pathogens [1]. Antimicrobial resistance of different pathogens also became widespread [2]. Among the most common Gram-positive resistant pathogens are *Streptococcus pneumoniae*, resistant to penicillin and macrolides, methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptides-intermediately resistant *S. aureus* (GISA), methicillin-resistant *Staphylococcus epidermidis*, glycopeptide-resistant enterococci and vancomycin-resistant enterococci (VRE) [3]. The response of the pharmaceutical industry to this challenge was the development of new antibiotics active against these pathogens [4]. Among these antibiotics, linezolid, an

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oxazolidinone; GAR-936, a tetracycline derivative; daptomycin, a lipopeptide; and ortivancin (LY-333328), a glycopeptide related to vancomycin are the novel antimicrobial agents [5]. Except for linezolid, which has been recently launched in many countries, all other agents are still at various developmental stages [6]. It is hoped that in the near future most of these agents will be approved and thus the grim outlook of patients infected with resistant Gram-positive bacteria, Gram-negative and fungus may improve [7].

Promising new compounds have recently been identified in an effort to supplement the relatively sparse portfolio of antifungal drugs. Many of these compounds have defined mechanisms of action against fungal cells and have, in some cases, aided the identification of new selective targets in fungi [8]. For most of these compounds, however, factors such as a narrow spectrum of activity, susceptibility to efflux pumps, protein binding, serum inactivation and poor pharmaceutical properties prevent their use in the clinic [9]. Even so, these compounds are novel substrates for synthetic modifications that could lead to the discovery of future antimicrobial drugs [10]. Corynecandin, Mer-WF3010, fusacandins and arthrichitin act as inhibitors of cell wall biosynthesis. Sordarins, cispentacin and azoxybacillin act as inhibitors of protein and amino acid synthesis. Aureobacidin, rustmicin and khafrefungin act as inhibitors of sphingolipid biosynthesis. UK2A and UK3A act as inhibitors of electron transport. New therapies such as addition of the iron chelator, deferasirox, in the treatment of zygomycosis in diabetic patients, appear promising but additional agents with new targets of action are urgently needed [11].

The 1,3,4-thiadiazole; 1,2,4-triazoles-5-thione and 1,3-thiazolan-4-one nucleus has been incorporated into a wide variety of therapeutically important agents, which mainly provides antimicrobial activities [12]. Moreover, the chemistry of 1,3,4-thiadiazole; 1,2,4-triazoles-5-thione; 1,3-thiazolan-4-one and their fused heterocyclic derivatives has shown potency to their synthetic and effective biological importance [13]. For example, a triazolothiadiazole system is a cyclic analog of two very important components such as thiosemicarbazide and biguanide, which often display antimicrobial, anticancer, antitubercular, anti-inflammatory or anticonvulsant activities [14]. In view of the above facts, in our present study, we have synthesized different 1,3,4-thiadiazole; triazole-5-thione and 1,3-thiazolan-4-one derivatives as benzimidazole derivatives for antimicrobial activities. These types of novel ring systems have not been studied yet as antimicrobial activities against multi-drug resistant microbial species [15,16].

## 2. Results and discussion

### 2.1. Chemistry

All the reagents were purchased from Sigma–Aldrich Chemicals (Bangalore, India) and were used without further purification. All solvents were distilled and dried using dry sieves as the usual manner. The moisture sensitive reactions were carried out under nitrogen atmosphere. TLC analysis was carried out on an aluminum foil pre-coated with silica gel 60 F254 (Sigma–Aldrich, Bangalore dealer). Melting points were determined on a Thomas micro hot stage apparatus and are uncorrected. Infrared spectra were determined as KBr solid disks + on a Shimadzu model 470 spectrophotometer. Mass spectra were recorded on a JEOL JMS-600H instrument using electro spray ionization (ESI) detector. $^1$H NMR spectra were recorded using a Jeol Eclipse 400 MHz spectrometer using $CDCl_3$ as NMR solvent and are reported in ppm down field from the residual $CDCl_3$. Elemental analysis was performed on a Elementar Vario Micro Cube analyzer and results were within ±0.4% of the predicted values for all compounds. IR (KBr) spectrum of all the synthesized compounds had strong C═C band at 1470–1575 $cm^{-1}$, which is similar as that of the ordinary C═C absorption (1400–1600 $cm^{-1}$). The formation of H-bond leads to an increase of their polarity, so the strength of their double bond decreased and absorption moved to lower wave number. The medium strong C–H band and C–N band in IR spectra of all the compounds appeared at 3000–3050 $cm^{-1}$ and 1160–1350 $cm^{-1}$ respectively which is similar as that of the ordinary C–H absorption (3000–3100 $cm^{-1}$). The $^1$H NMR spectrum exhibited different signals at different ppm which were assigned to the different types of protons. $^{13}$C NMR showed various types of signals at different ppm which were assigned for the different types of carbons of all the target compounds. The synthetic routes leading to the title compounds are summarized in schemes.

2-Aminomethyl-1[*H*] benzimidazole **3** was synthesized from *o*-phenylenediamine **1** and glycine **2** when refluxed with HCl and water at 70–73 °C [17]. Reaction of 2-methyl amino-1[*H*] benzimidazole **3**, dry pyridine and iodine at 0–5 °C gave 2-methylsulphonitrile-1[*H*]benzimidazole **4** when stirred for 3.5–4 h [18]. *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-isonicotinoyl hydrazine carbothioamide **9** was synthesized from 2-methylsulphonitrile-1[*H*] benzimidazole **4** and isoniazide **8** [19]. *N*-(4-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-amine **10** was synthesized from *N*-(4-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-2-isonicotinoyl hydrazine carbothioamide **9** when refluxed with 50 % $H_2SO_4$ [20]. (*Z*)-2-(4-(1*H*-benzo[*d*] imidazol-2-yl) methylimino)-3-isonicotinoyl thiazolidin-4-one **11** was synthesized from *N*-(4-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-2-isonicotinoyl hydrazine carbothioamide **9** and chloroacetylchloride when refluxed with chloroform for 6 h [21]. 4-(4-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-3-(pyridin-4-yl)-1*H*-1, 2, 4-triazole-5(4*H*)-thione **12** was synthesized from *N*-(4-(1*H*-benzo[*d*] imidazol-2-yl) methyl)-2-isonicotinoyl hydrazine carbothioamide **9** when refluxed with HCl and neutralization with NaOH [22] (Scheme 1). Physical properties of 1,3,4-thiadiazole; triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole are summarized in Table 1.

### 2.2. Antimicrobial activity

#### 2.2.1. Antibacterial activity

Pharmacological evaluation is one of the most important factors for the determination of activity of compounds. Evaluation part of the work should be variable and easy to perform. Since last few years, prevalence of infectious diseases has increased to a great extent [23]. Antimicrobial agents are the most commonly used to treat the different types of infectious diseases. Synthesized compounds were evaluated for their antibacterial activity against three Gram-positive organisms such as *Bacillus cereus* (MTCC-430), *Enterococcus faecalis* (MTCC-493), *S. aureus* (MTCC-737) and three Gram-negative