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Original article

Synthesis, antimicrobial, antiquorum-sensing and cytotoxic activities of new series of benzothiazole derivatives

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ABSTRACT

New series of benzothiazole derivatives were designed and synthesized. The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus cereus*. Compounds **6j** and **6o** showed the highest activity against *E. coli* and *S. aureus*. The antifungal activity of these compounds was also tested against *Candida albicans* and *Aspergillus fumigatus* 293. Compounds **4c**, **4g** and **6j** exhibited the highest activity against *C. albicans*. In addition, compounds **4a** and **6j** displayed promising activity against *A. fumigatus* 293. The same compounds were examined for their antiquorum-sensing activity against *Chromobacterium violaceum* ATCC 12472, whereas compounds **4a**, **6j** and **6p** showed moderate activity. The *in vitro* cytotoxicity testing of the synthesized compounds was performed against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines. Results indicated that all tested compounds have IC_{50} values >50 μmol/L against both cell lines. Molecular properties, toxicities, drug-likeness, and drug score profiles of compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d** were also assessed.

1. Introduction

The traditional antibacterial agents either kill bacteria (bactericidal) or inhibit their growth (bacteriostatic). Typically, the targets for the conventional antibiotics are the essential cellular processes such as bacterial cell wall biosynthesis, bacterial protein synthesis, and bacterial DNA replication and repair [1]. The eventual growth arrest and cell death can be followed by rapid expansion of resistant subpopulations, making subsequent treatment difficult or impossible [2]. Therefore, new antibacterial strategies are required. An alternative to killing or inhibiting growth of pathogenic bacteria is the specific attenuation of bacterial virulence, which could be attained by targeting key regulatory systems that mediate the expression of virulence factors. One of the target regulatory systems is quorum sensing (QS) [1]. QS is a phenomenon used by bacteria for coordination of population-wide phenotypes, such as expression of virulence genes, antibiotic resistance and biofilm formation. QS disruption is one of the emerging anti-virulence strategies that promises a lower risk of resistance development [3]. Many quorum quenching methods have been developed against various clinically significant bacterial pathogens [4].

The benzothiazole nucleus is a unique scaffold for further molecular exploration to synthesize novel compounds. Literature survey revealed that benzothiazole analogs are associated with diverse pharmacological effects, including antimicrobial activity [5–9]. In addition, benzothiazoles incorporating pyrazole moiety demonstrated remarkable antimicrobial activity [10,11]. On the same line, benzothiazoles incorporating isatin moiety have received considerable attention owing to their diverse chemotherapeutic potentials, including antimicrobial activity [12,13]. In addition, various Schiff bases of 2-hydrazinobenzothiazole derivatives (Fig. 1) were previously synthesized and screened for their antimicrobial activity [14–16]. Some of these derivatives displayed promising activity.

Therefore, we found it interesting to design new compounds within the scope of synthetic procedures using the benzothiazole

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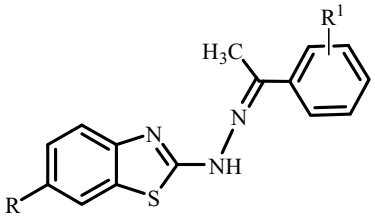

R = CH_3; F
R^1 = 2-F; 3-F; 2-Cl; 4-OH; 2,5-$(OH)_2$; 3,4-$(OCH_3)_2$

Fig. 1. Schiff bases of 2-hydrazinobenzothiazole derivatives with reported antimicrobial activity.

scaffold followed by suitable modifications to generate new series of compounds with expected antimicrobial activity. The manipulation strategy embraces the incorporation of pyrazole, isatin and arylidene moieties into the benzothiazole ring in order to verify the importance of these moieties for the antimicrobial activity (Fig. 2).

2. Experimental

A general approach for the synthesis of the designed compounds is outlined in Scheme 1. The starting compound, 2-amino-6-fluorobenzothiazole **(1)** was reacted with hydrazine hydrate in refluxing ethylene glycol in the presence of hydrochloric acid to produce the hydrazine derivative **2** [17]. Refluxing compound **2** with ethyl 3-oxo-2-((2-substituted phenyl)hydrazono)butanoates **3a–e** [18] in glacial acetic acid yielded the corresponding pyrazole analogs **4a–e**. In addition, the reaction of the key intermediate **2** with the appropriate isatin in ethanol in the presence of glacial acetic acid gave compounds **5a–c**. Reaction of **2** with the appropriate aromatic aldehyde in ethanol under microwave irradiation gave the corresponding Schiff bases **6a–r** in 64%–82% yields. Moreover, refluxing the hydrazine analog **2** with the appropriate acetophenone in ethanol in the presence of glacial acetic acid furnished compounds **7a–d** in 61%–73% yields. The newly synthesized compounds, **4a–e**, **5a–c**, **6a–r** and **7a–d** were screened for their *in vitro* antibacterial activity against two species of Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and one Gram-negative bacterium (*Escherichia coli*) [19,20]. Antifungal screening against *Candida albicans* and *Aspergillus fumigatus* 293 was also performed [20,21]. The same compounds were examined for their antiquorum-sensing activity against *Chromobacterium violaceum* ATCC 12472 [22]. Additionally, the *in vitro* cytotoxicity testing of compounds **4a–e**, **5a–c**, **6a–r** and **7a–d** was performed against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines adopting MTT assay [23–25].

The synthetic details and related spectra of the compounds as well as their biological testing are deposited in Supporting information.

3. Results and discussion

3.1. Chemistry

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. ^{1}H NMR spectra of compounds **4a–e** showed a characteristic singlet at δ 2.05–2.50 ppm for the methyl protons at the 3-position of the pyrazole ring. In the ^{1}H NMR spectra of compounds **6a–r**, a singlet at δ 7.95–8.83 ppm was due to CH=N proton. Regarding ^{1}H NMR spectra of compounds **7a–d**, methyl protons were observed as a singlet at δ 1.90–2.35 ppm.

3.2. Biological screening

The antimicrobial screening results (Table 1) were determined by measuring the average diameter of the inhibition zones, expressed in millimeters (mm) [19,21]. The minimum inhibitory concentration (MIC, μg/mL) of the most active compounds against *E. coli*, *S. aureus*, *C. albicans* and *A. fumigatus* 293 was carried out by broth microdilution method using 96-multiwell microtiter plates [20]. As shown in the results (Table 2), compound **6j** showed the highest activity against *E. coli* with MIC value of 312 μg/mL. Furthermore, compound **6j** exhibited good antibacterial activity against *S. aureus* with MIC value of 156.25 μg/mL. The results are compared to ampicillin as a reference antibacterial agent. Regarding the antifungal activity, compounds **4c**, **6g** and **6j** displayed the highest activity against *C. albicans* with MIC value of 312.5 μg/mL. In addition, compounds **4a** and **6j** demonstrated strong antifungal activity against *A. fumigatus* 293 with MIC value of 156.25 μg/mL (Table 2). The results are compared to fluconazole as a reference antifungal agent. *A. fumigatus* 293 was resistant to fluconazole [26]. These observations may promote further development of benzothiazole derivatives and may lead to compounds with potent antibacterial and antifungal activities.

While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors (QSIs) or quorum quenchers (QQs) attenuate bacterial virulence and appear to be a promising strategy to control bacterial resistance to antibiotics [27]. Thus, the same compounds were examined for their antiquorum-sensing activity

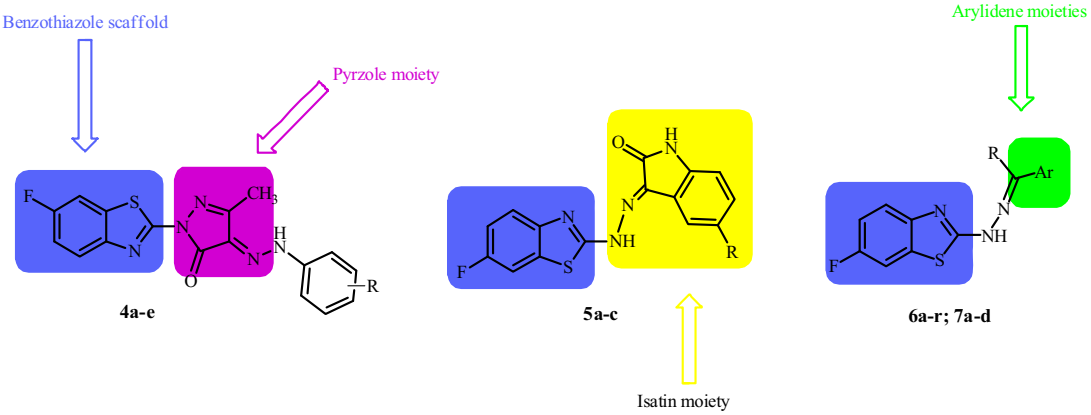

Fig. 2. Designed strategy of the titled compounds.