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Azoalkyl ether imidazo[2,1-*b*]benzothiazoles as potentially antimicrobial agents with novel structural skeleton

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ABSTRACT

A series of new azoalkyl ether imidazo[2,1-*b*]benzothiazoles were developed *via* a convenient synthetic procedure. The antimicrobial assays showed that a good number of the prepared derivatives exhibited significant inhibitory properties against most of the tested strains. Especially 2-methyl-5-nitroimidazole derivative **5a** presented superior inhibit activity against MRSA and *B. typhi* with MIC = 4 μg/mL and MIC = 1 μg/mL, respectively. The highly active compound **5a** showed low toxicity against mammalian cells without obvious triggering of the development of bacterial resistance, and it also possessed rapid bactericidal efficacy. Molecular docking study exposed that the active molecule **5a** could interact with the active site of *S. aureus* gyrase through hydrogen bond. Quantum chemical studies were also performed to explain the high antibacterial activity. Further investigation revealed that compound **5a** could significantly associate with gyrase–DNA complex by mean of hydrogen bonds and could efficiently intercalate into MRSA DNA to form **5a**–DNA supramolecular complex, which impart potent bioactivity.

Infectious diseases instigated by the invasion of the pathogenic microorganisms continue to be a major health threat due to increased resistance to the existing antimicrobial drugs, even with substantial progress in the antimicrobial treatment.[1,2] The prevalence of bacterial resistance to various antibacterial agents such as sulfonamides, glycopeptides, nitroimidazoles, β-lactams, quinolones, chloramphenicols, macrolides, and tetracyclins are of foremost concern. Methicillin Resistant Staphylococcus aureus (MRSA) is one of the most nosocomial pathogens with the properties of antibiotic resistance in the recent times. MRSA could be any strain of *Staphylococcus aureus* that has acquired multiple drug resistance to β-lactam class of antibiotics by means of horizontal gene transfer and natural selection.[3] In addition, MRSA has the characteristic ability to sustain penicillin-like antibiotics which usually inhibit bacterial growth by impeding cell wall synthesis. However, this is brought about by mecA, a resistance gene, which obstructs β-lactam antibiotics from disabling the crucial enzymes for cell wall synthesis like transpeptidases.[4] Accordingly, the infections caused by MRSA associated with excessive morbidity and mortality are now treated as a global challenge.[5] As a consequence of these facts, the research on novel drugs bearing high competence for these pathogens and less toxicity to the host which may be different from existing resistant drugs is of considerable exploration.[3]

Benzothiazole is an aromatic heterocyclic system having various biological activities such as antimicrobial, anticancer, anticonvulsant, anti-inflammatory, anti-alzheimer, anti-psychotic, antidiabetic, diuretic and protein tyrosine inhibitor activities.[6] Additionally, imidazo[2,1-*b*]benzothiazole derivatives are fused tricyclic sulfur and nitrogen-containing heterocycles, frequently encountered in pharmaceutical chemistry as bioactive molecules and reported to be associated with promising biological activities such as antitumor, antimicrobial, antibacterial and antiallergic agents.[7–9] Also, imidazo[2,1-*b*]benzothiazoles demonstrated a large extent of pharmacological properties like antimicrobial activity and potentiality to combat drug resistance.[10–12]

Azoles such as imidazoles and triazoles are a significant class of nitrogen heterocycles with multiple heteroatoms, aromaticity and

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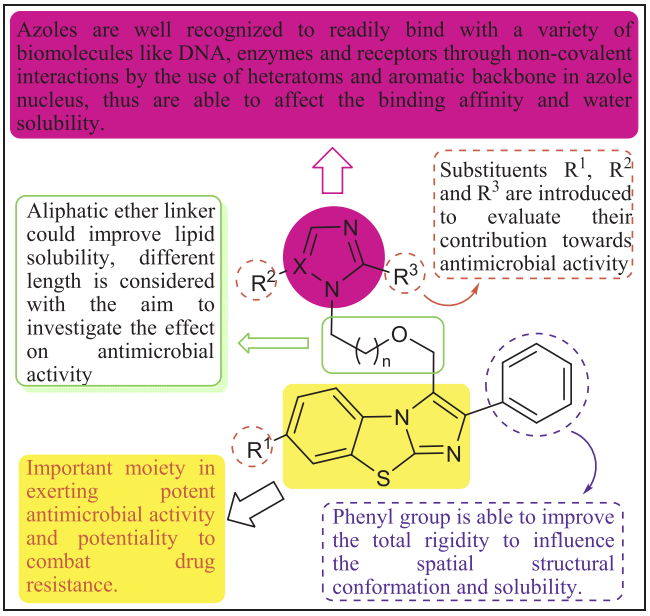


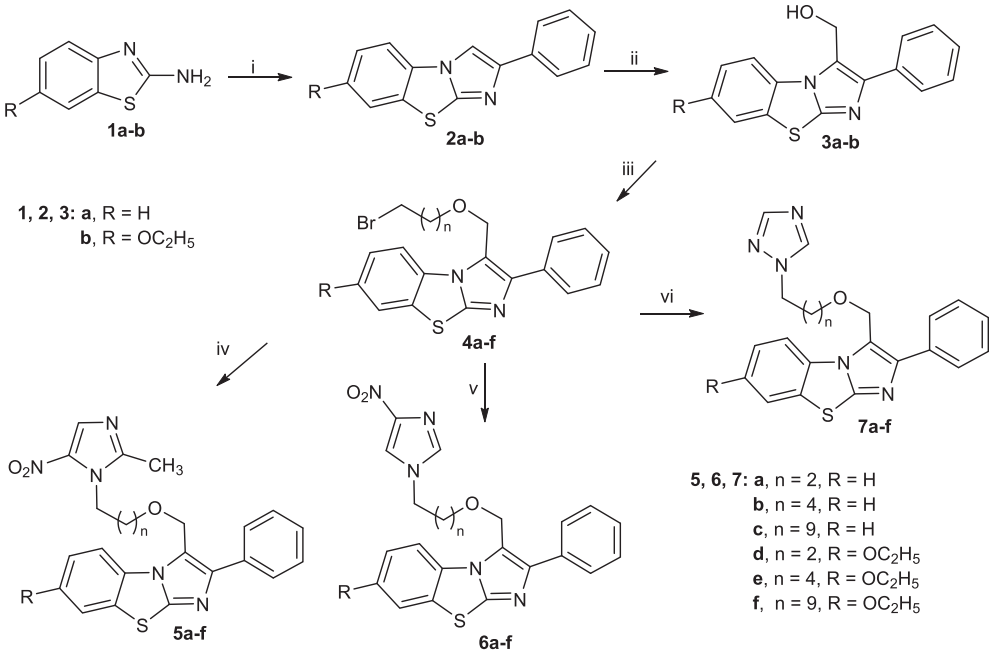
Fig. 1. Design of novel target hybrids of azoalkyl ether imidazo[2,1-*b*]benzothiazoles.

electron rich properties.[13,14] The exceptional structure makes azole-based derivatives not only bind effortlessly through noncovalent interactions like coordination and hydrogen bonds with enzymes and receptors in living organisms, but also affect the binding affinity and water solubility of conjugated system, thus allow azoles imparting diverse applications in the scope of medicinal chemistry.[15] Thereby this privileged class exert wide pharmacological profile like antibacterial, antifungal, antitubercular, anticancer, antiviral, antiproliferative, antihistaminic, anticonvulsant, antihypertensive and other properties.[16] Consequently we intended to design novel potential drugs with enhanced antimicrobial efficacy by combining two active pharmacophores *via* a linker bridge (Fig. 1).

Aiming to better understand the structure–activity relationship and increase flexibilities, various lengths of alkyl chains were introduced. Researches provide evidence that aliphatic ether linker could improve lipid solubility, meanwhile different alkyl linkers have the ability to modulate lipid solubility and physicochemical properties.[17–19] The antibacterial and antifungal potencies of all the newly synthesized compounds were evaluated in *vitro* against four Gram-positive bacteria, six Gram-negative bacteria and five fungi. The preliminary antimicrobial mechanism was investigated by evaluating the interactions of the prepared highly active compounds with calf thymus DNA. Bactericidal kinetic assay and resistance developing ability were also investigated. Moreover, the molecular modeling and experimental investigation of the highly active compound with DNA were further studied to explore the possible antibacterial mechanism.

The intended azoalkyl ether imidazo[2,1-*b*]benzothiazole derivatives **5–7** were prepared by involving multiple step reactions starting from commercially available benzothiazol-2-amine and/or 6-ethoxybenzothiazol-2-amine as represented in Scheme 1. Condensation of benzothiazol-2-amine and/or 6-ethoxybenzothiazol-2-amine and phenacyl bromide in the presence of ethanol at 70 °C produced compounds **2a–b** in 90–92% yield, which was then subjected to hydroxyl methylation using acetic acid and sodium acetate at 60 °C to afford compounds **3a–b** with 74–76%.[20] The prepared intermediates **3a–b** were treated with different alkyl dibromides and sodium hydride in THF at room temperature for several hours to achieve the desired compounds **4a–f** in yields of 84–89%. Finally, the target imidazo[2,1-*b*]benzothiazole azoles **5a–f**, **6a–f** and **7a–f** were conveniently and efficiently obtained in 80–94% yields by the reaction of *O*-alkyl bromides **4a–f** with 2-methyl-5-nitroimidazole, 4-nitroimidazole, 1,2,4-triazole in acetonitrile at 50 °C in the presence of potassium carbonate, respectively. All the prepared compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS spectra. However, the compound purity was estimated through the aid of quantitative nuclear magnetic resonance (Q NMR) technique with 1,3,5-trioxane as internal standard. All the synthesized compounds were uncovered to be more than 95% pure and the spectral information was listed in the Supporting Information.

Twofold serial dilution technique was used to investigate the antimicrobial activity as recommended by the Clinical and Laboratory Standards Institute (CLSI).[21] The results are shown in Table 1. It is revealed that a good number of the tested compounds could significantly obstruct the growth of tested bacterial strains. Excitingly, compounds **4a**, **5a–b** and **6b** could successfully inhibit the growth of MRSA at the concentrations of 4–8 μg/mL, which were more effective than chloromycin (MIC = 16 μg/mL). Especially, 2-methyl-5-nitroimidazole



Scheme 1. Synthetic routes of target azoalkyl ether imidazo[2,1-*b*]benzothiazoles. Reagents and conditions: i) Phenacyl bromide, C_2H_5OH, 70 °C; ii) CH_3COOH, CH_3COONa, 50 °C; iii) Alkyl dibromides, NaH, THF, rt, 6 h; iv) 2-Methyl-5-nitroimidazole, K_2CO_3, CH_3CN, 50 °C, 5 h; v) 4-Nitroimidazole, K_2CO_3, CH_3CN, 50 °C, 5 h; vi) Triazole, K_2CO_3, Acetonitrile, 50 °C, 5 h.