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Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-*b*]thiazole moiety

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ABSTRACT

A series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)methyl)-3*H*-1,2,4-triazole-3-thiones (**3a–i**) and 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)methyl)-1,3,4-thiadiazoles (**4a–c**) were synthesized starting from 6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-acetic acid hydrazide. The newly synthesized compounds were characterized by IR, ^{1}H NMR, mass and elemental analysis. All compounds were tested for antibacterial and antifungal activities. The antimicrobial activities of the compounds were assessed by the microbroth dilution technique. The compounds were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294). The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.

1. Introduction

Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immunocompromised patients. As known, not only biochemical similarity of the human cell and fungi forms a handicap for selective activity, but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungals. On the other hand, *Mycobacterium tuberculosis* remains a leading infectious cause of death in the world today. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly to the HIV/AIDS pandemic, which greatly increase the risk of infection proceeding to overt disease [1]. In particular, the appearance of multi-drug-resistant (MDR) strains of *M. tuberculosis*, which exhibit *in vitro* resistance to at least two major antituberculosis drugs (usually Isoniazide and Rifampicin) and cause intractable tuberculosis, has greatly contributed to the increased incidence of tuberculosis [2,3].

Moreover, the development of drug-resistant strains of mycobacterium species, has contributed to the inefficiency of the conventional antituberculosis therapy, thus, it is still necessary to search for new antimycobacterial agents.

1,2,4-Triazoles and their heterocyclic derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities. A large number of 1,2,4-triazole containing ring systems exhibits antibacterial [4–10], antifungal [7–11], antitubercular [12–14], analgesic [15,16], antiinflammatory [16–18], anticancer [19,20], anticonvulsant [21,22], antiviral [23,24], insecticide [25], antidepressant [26], central nervous system (CNS) [27] activities. In addition, 1,3,4-thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial [27–30], antifungal [29,30], antitubercular [31–33], analgesic [34], antiinflammatory [29,30,34], antidepressant [26], leishmanicidal [35] agents. In view of these facts and as a continuation of our research on the biological properties of 1,2,4-triazole and 1,3,4-thiadiazole containing derivatives [36–41], we have designed and synthesized a number of imidazo[2,1-*b*]thiazole substituted fused 1,2,4-triazole and 1,3,4-thiadiazole systems, as potential antibacterial, antifungal and antitubercular agents.

2. Chemistry

The key intermediate **1** was prepared from ethyl 6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-acetate and hydrazine hydrate following the literature method [42]. The synthetic route of the

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compounds is outlined in Scheme 1. 4-Alkyl/aryl-1-((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)-3-thiosemicarbazides (**2**) were obtained by the reactions of alkyl/arylisothiocyanates with 6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-acetatic acid hydrazide (**1**) whose synthesis was previously described [43]. Alkaline cyclisation of the compounds **2** using sodium hydroxide afforded the corresponding 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)methyl)-3*H*-1,2,4-triazole-3-thi ones (**3a–i**). Reacting thiosemicarbazides (**2**) with concentrated sulfuric acid at room temperature resulted in the formation of the corresponding 2-alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)methyl)-1,3,4-thiadiazoles (**4a–c**).

3. Results and discussion

The structures of the synthesized compounds were confirmed by analytical (Table 1) and spectral data (IR, ^{1}H NMR, EIMS). The IR spectra of **3a–i** and **4a–c** exhibited N–H bands in the 3440–3389 and 3428–3347 cm^{-1}, respectively. The absorption bands at 1616–1414 and 1600–1417 cm^{-1} are due to the presence of –C═N– stretch of the triazole and thiadiazole ring system, respectively. Absence of the C═O absorptions in **3a–i** and **4a–c** provided definitive proof for the formation of new products. The ^{1}H NMR of **3a**, **3b** and **3f** chosen as prototypes showed single NH resonances in the 13.74–13.52 ppm regions. In the ^{1}H NMR spectra of **4a**, **4b** and **4c**, the NH proton at 2-position of 1,3,4-thiadiazole ring appeared at 7.59–7.55, 7.62–7.55 ppm together with Ar–H as a multiplet and 10.31 ppm as a singlet, respectively. The exocyclic S–CH_2 protons of **3** and **4** resonated at 4.44–4.13 and 4.64–4.48 ppm, respectively. The protons of the imidazo[2,1-*b*]thiazole nucleus and the other protons resonated at the expected regions [44]. The EIMS of compounds **3a**, **3b**, **3f**, **4a**, **4b** and **4c** displayed molecular ions which confirmed their molecular weights. Fragmentation followed the route in accordance with literature [45].

4. Biological activity

All compounds to be tested were dissolved in DMSO at a stock concentration of 3200 μg cm^{-3} .The final desired concentration were prepared with RPMI 1640 medium for *Candida* species and dermatophytes and with Mueller–Hinton broth of bacteria. The final DMSO concentration was reduced to 1%.

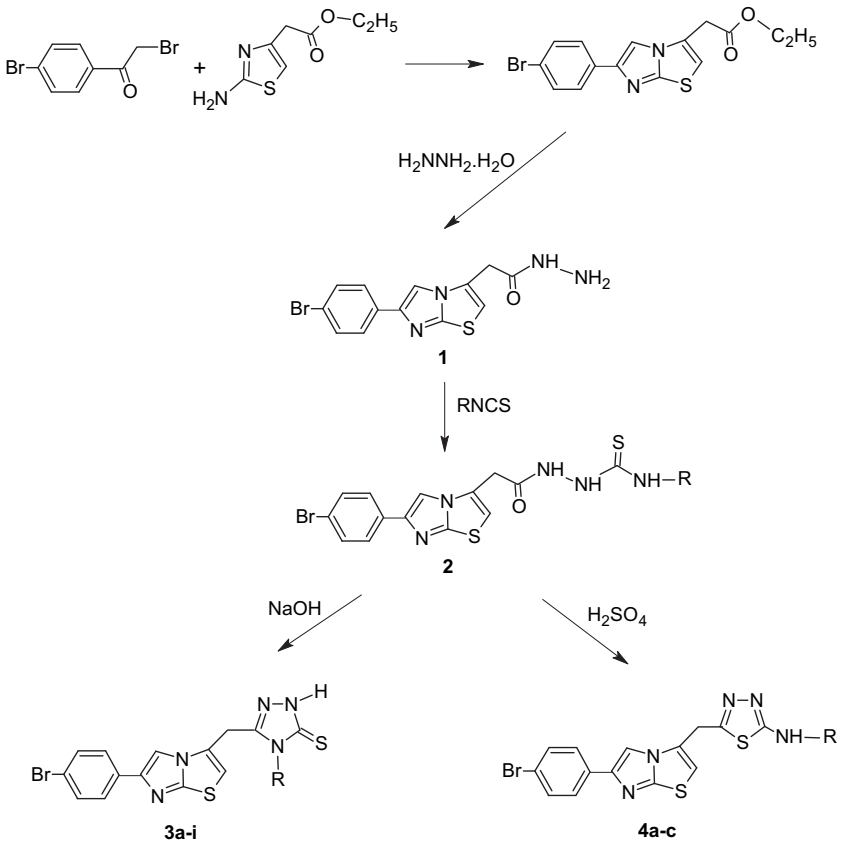
4.1. Antibacterial activity

MICs were determined by the microbroth dilution method using the National Committee for Clinical Laboratory Standards (NCCLS) recommendations [46]. Mueller–Hinton broth (Oxoid, Hemakim, Turkey) was used as the test medium. An inoculum of approximately 5×10^5 CFU cm^{-3} was delivered per well. Serial twofold dilutions of the test compounds (64–0.25 μg cm^{-3}) and extra dilutions (0.12–0.015 μg cm^{-3}) for antibiotic standards were prepared. Plates were incubated for 16–20 h at 35 °C in an ambient air incubator. The lowest concentration of the test compounds inhibiting visible growth was taken as the MIC value.

4.2. Antifungal activity

4.2.1. Antifungal activity for Candida species

MICs were determined by the microbroth dilution method using the NCCLS recommendations [47]. RPMI broth was prepared from RPMI 1640 medium (Sigma, St. Louis, Mo, USA) supplemented with



Scheme 1.