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ORIGINAL ARTICLE

2-(5-Chlorobenzo[*d*]thiazol-2-ylimino)thiazolidin-4-one derivatives as an antimicrobial agent

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Abstract A series of 2-(5-chlorobenzo[*d*]thiazol-2-ylimino)-5-((3-(*p*-substituted phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazolidin-4-ones (**3a**–**h**) were prepared from 2-(5-chlorobenzo[*d*]thiazol-2-ylimino)thiazolidin-4-one (**1**) and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (**2a**–**h**). All compounds were characterized using elemental analytical (C, H, and N) and spectral (FT-IR, ^{1}H NMR, ^{13}C NMR and GC–MS) data. These compounds were screened for their antibacterial, antifungal and antimycobacterial activities. Antimicrobial activity was evaluated against the bacterial strains e.g., *Eschericha coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), H37Rv strain of *Mycobacterium tuberculosis*, and the antifungal activity was observed against strains e.g., *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). All the synthesized compounds were found to possess moderate to excellent activity against selected strains.

1. Introduction

The widespread use of antifungal and antibacterial drugs and the fast development of pathogen resistance to most of the known antibiotics is becoming a serious problem (Chu et al., 1996). So, it has become quite difficult to eradicate these microbial infections (Patterson, 2005). Heterocyclic compounds are reported to be effective against many of these pathogens up to some extent. A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring and the most common hetero atoms are nitrogen, oxygen, and sulfur. Heterocyclic compounds are very widely distributed in nature and are essential to life as they play a very important role in the metabolism of many living cells, e.g., amino acids, vitamins, DNA base (purines and pyrimidines) (Achson, 2009).

Benzothiazole moieties are known to be weak base heterocyclic compounds, having diverse biological activities and are of great scientific interest nowadays. They are widely studied in the areas of bioorganic and medicinal chemistry with many applications in drug discoveries. Drugs containing benzothiazole moiety are reported to possess numerable biological activities such as antimicrobial (Gupta et al., 2009; Kumbhare and Ingle, 2009; Lacova et al., 1989; Rajeeva et al., 2009; Maharan et al., 2007), anticancer (Linhong et al., 2006; Kamal et al., 2006; Kini et al., 2007; Stanton et al., 2008), anthelmintic

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(Sreenivasa et al., 2009), antidiabetic (Pattan et al., 2005; Hermenegilda et al., 2008), anti tuberculosis (Abdel-Rahman and Morsy, 2007; Nandy et al., 2006), antiviral (Shingare et al., 1996; Mane et al., 1996), as well as antitumor (Yoshida et al., 2005; Cedric et al., 2006). Predominantly, 4-thiazolidinones are known to possess various important biological activities such as anti-inflammatory (Ottana et al.,2005), antitubercular (Srivastava et al., 2005), antimicrobial (Mistry and Desai, 2004), anticonvulsant (Kaur et al., 2010), antiviral (Terzioglu et al., 2006), and anti-HIV (Balzarini et al., 2009). Besides these compounds, pyrazole derivatives are also associated with many biologically important activities like antimicrobial (Damljanovic et al., 2009), anti-inflammatory (Bekhit et al., 2008), antitubercular (Chovatia et al., 2007), antitumor (Joksovic et al., 2009), antiangiogenesis (Abadi et al., 2003), antiparasitic (Rathelot et al., 2002), and antiviral (Hashem et al., 2007).

Therefore, it is envisaged that chemical entities with benzothiazole, pyrazole and 4-thiazolidinone moieties would result in compounds of interesting biological activities. In view of these findings, we have attempted to incorporate all these three biologically active components together to give a confined structure like the titled compounds for evaluating their antimicrobial and anti mycobacterial activities.

2. Experimental

2.1. General

The melting points of the products were determined by open capillary method using Mettler Toledo FP 62 melting point apparatus (Metter Toledo-Switzerland) and were used without correction. The FT-IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR System (USA) in a KBr disk. ^{1}H and ^{13}C spectra were recorded on 200 and 500 MHz Bruker Avance DPX NMR spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. The mass spectra were recorded on a Shimadzu QP2010 spectrometer (equipped with a direct inlet probe) operated at 70 eV. Elemental analysis was carried out on Perkin Elmer CHNS (O) analyzer (PE-2400 Series II-USA). Homogeneity of compounds was checked by analytical TLC on a silica gel GF 254 plate using ethyl acetate/methanol (10:90) as a solvent system.

2.2. Biological assay

2.2.1. Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (*MTCC-96*) and *Streptococcus pyogenes* (MTCC-442) and gram negative *Escherichia coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688). Thiazole inhibits protein synthesis in bacteria by binding to the complex formed between 23S rRNA and ribosomal protein L11, thereby restricting the action of GTP dependent elongation factors (Porse et al., 1998). Antibacterial activity was carried out by serial broth dilution method (Ghalem and Mohamed, 2009). The standard strains used for the antimicrobial activity was procured from the Institute of Microbial Technology, Chandigarh. The compounds (**3a**–**h**) were screened for their antibacterial activity in triplicate against *E. coli*, *S. aureus*, *P. aeruginosa,* and *S. pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25, 12.5 μg/ml as shown in (Figs. 3 and 4). The growths of bacterial cultures were monitored after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 cells/ml. The standard drug used was 'ampicillin' for evaluating antibacterial activity and it showed 100, 100, 250, and 100 μg/ml MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes*, respectively.

2.2.2. Antifungal activity

Same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus* at various concentrations of 1000, 500, 200, and 100 μg/ml as shown in (Figs. 5 and 6). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 μg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as MIC and the test mixture was found to contain 10^8 spores/ml. "Griseofulvin" was used as a standard drug for antifungal activity and it recorded 500, 100 and 100 μg/ml MIC for *C. albicans*, *A. niger*, and *A. clavatus*, respectively.

2.2.3. Antimycobacterial

The screening of antimycobacterial activity of novel synthesized compound was carried out *in vitro* against a highly virulent H37Rv strain of *Mycobacterium tuberculosis*. Antimycobacterial activity was performed as per the LJ Medium (conventional method). The media were incubated for four weeks. The screening was performed in triplicate at 250 μg/ml concentration of compound. "Isoniazid" was used as a standard drug for antimycobacterial activity, which showed 0.2 μg/ml MIC against $H_{37}Rv$ *M. tuberculosis* strains. The data are as shown in (Figs. 7 and 8).

2.3. General synthesis method

2.3.1. Synthesis of 2-(5-chlorobenzo[d]thiazol-2-ylimino) thiazolidin-4-one (*1*)

The titled compound was prepared according to the method reported earlier (Ameya and Nandini, 2007). Characterization data of the compounds matched well with the reported values.

To the cold glacial acetic acid (20 ml), potassium thiocyanate (0.08 mol) and 4-chloro aniline (0.01 mol) were added and mixture was placed in freezing mixture of ice with continuous mechanical stirring. Bromine (1.6 ml) was added at controlled temperature, when all the bromine was added (105 min), the solution was stirred for 2 h below room temperature and then for 10 h at room temperature, and resultant mixture was kept for overnight. Yellow precipitate so obtained was filtered out and the filtrate was neutralized with ammonia to give 2-amino-6-chloro methyl benzothiazole, which was further reacted with chloroacetyl chloride and ammonium thiocyanate to give 2-(5-chlorobenzo[*d*]thiazol-2-ylimino)thiazolidin-4-one. Product was filtered, washed with water and recrystallized from glacial acetic acid.

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