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ORIGINAL ARTICLE

Synthesis, antibacterial and antifungal activity of novel benzothiazole pyrimidine derivatives

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Abstract A new series of 5-amino-6-(benzo[*d*]thiazol-2-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)-7-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives (**7a–k**) were synthesized. All the newly synthesized compounds were screened for their *in vitro* antibacterial activity, against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Streptococcus pyogenes* and for antifungal activity against *Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium marneffei* and *Mucor*. Compounds **7b, 7e, 7f, 7g, 7h** and **7j** showed excellent *in vitro* antibacterial activity and antifungal activity than the standard drugs. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, LCMS mass and C, H, N analyses.

1. Introduction

Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties as effective bactericide and fungicide (Williams and Cline, 1936; Maddila and Jonnalagadda, 2012a,b). Many pyrimidine derivatives are known to exhibit analgesic (Regnier et al., 1972), antihypertensive (Winter et al., 1962), anti-tumour (Suguira et al., 1973), antimalarial (Brown and Evans, 1985), antioxidant (Stefani et al., 2006), antimitotic (Mayer et al., 1999), and anti-HIV activities (Okabe et al., 1991). Some dihydropyrimidines (DHPM) have emerged as integral backbones of calcium channel blockers, antihypertensive agents, adrenergic and neuropeptide antagonists (Pasha et al., 2005). Several alkaloids containing dihydropyrimidine isolated from marine sources such as batzelladine alkaloids are reported to be potent HIV-gp-120-CD4 inhibitors (Kappe et al., 2000; Kappe et al., 2000; Patil et al., 1995).

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In addition to their diverse biological activities, in association with other heterocyclics, pyrimidines are known to play a crucial role in several processes of chemical and pharmacological importance as therapeutics in clinical applications. A literature survey reveals that thiazole derivatives of pyrimidine have received much attention in recent years, due to their efficacy as analgesic, anti-inflammatory, ulcerogenic (Hafez and El-Gazzar, 2008), antifungal (Maddila et al., 2011a,b, 2016), antitubercular (Kapustina et al., 1991), antimalarial (Rosowsky et al., 1973), antitumour (Sasaki et al., 2003), cytotoxic (Suh et al., 2000), and anticancer agents (Skibo et al., 2002).

In the view of having a wide scope to find new potentially active agents, we have synthesized a new series of benzothiazole pyrimidine derivatives (**7a–k**) which is an extension of our previous reported work on biological studies of novel 2-(4-substitutedbenzylthio)-5-amino-6-(benzo[d]thiazol-2-yl)-7-(4-chlorophenyl)pyrido[2,3-*d*]-pyrimidin-4(3*H*)-one (Maddila et al., 2011). All the new compounds were characterized by elemental and spectral analyses and screened for their antibacterial and anti- fungal abilities.

2. Results and discussion

2.1. Chemistry

For the synthesis of the new materials, initially, 2-(benzo[*d*]thiazol-2-yl)acetonitrile **(1)** was treated with cyanoacetic acid in the presence of acetic anhydride to give their corresponding 2-(benzo[*d*]thiazol-2-yl)-3-oxopentane dinitrile (**2**). Compound **2** was reacted with *p*-chlorobenzaldehyde in the presence of piperidine to obtain 2-(benzo[*d*]thiazol-2-yl)-3-(4-chlorophenyl)-acrylonitrile **(3)** (Saito et al., 1983). Compound **3** by cyclization with 6-aminothiouracil in the presence of few drops of piperidine, was converted into 5-amino-6-(benzo[*d*]thiazol-2-yl)-7-(4-chlorophenyl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one **(4)** with good yield. Compound **4** was treated with benzyl bromide in the presence of K_2CO_3 and DMF medium to give its benzylthio derivative (**5**) in good yield (Maddila et al., 2011b).

The benzylthio compound was successfully reacted with hydrazine hydrate to afford its hydrazinyl derivative (**6**). The hydrazinyl derivative was condensed with a range of selected substituted aldehydes in the presence of DMF solvent, to yield a new series of corresponding Schiff bases in good yields (**7a**−**k**) (Scheme 1).

All the newly synthesized compounds gave moderate to high yields. Products were purified and characterized by various spectroscopic techniques. The IR spectra of compounds (7a–k) showed characteristic absorption bands at 3460–3387 cm^{-1}, 1679–1609 cm^{-1}, 1623–1561, and 1548–1520 cm^{-1} corresponding to the $N–H_{2str}$, $C{=}O_{str}$, $C{=}N_{str}$ and $C{=}C_{str}$ functions in the structures. The ^1H NMR spectra showed peaks in the range of δ 6.09–6.29 for NH_2, δ 8.01–8.71 for N=CH, δ 9.91–10.05 for hydrazinyl NH and δ 10.17–10.25 for pyrimidine NH. The mass spectrum of all the compounds showed a molecular ion peak at M^+, at M + H corresponding to its molecular formula, which confirmed its chemical structure. IR, ^1H NMR, LCMS mass spectra and elemental analysis confirmed the structure of various novel 5-amino-6-(benzo[d] thiazol-2-yl)-2-(2-(substitutedbenzylidene)hydrazinyl)-7-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives (**7a–k**).

3. Pharmacological assay

3.1. Antimicrobial activity

All the compounds were screened for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Streptococcus pyogenes* and antifungal activity against *Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium marneffei* and *Mucor*. Compounds **7b–k** with various substituents in the aromatic ring will give an insight into the steric and electronic effects on the biological activity.

3.2. Evaluation of antibacterial activity

The *in vitro* antibacterial activity of the compounds was tested in nutrient broth for bacteria by the twofold serial dilution method (Vincent and Vincent, 1944). The test compounds were dissolved in dimethyl sulphoxide (DMSO) to obtain 1 mg/ml stock solutions. Seeded broth (broth containing microbial spores) were prepared in NB from 24 h old bacterial cultures on nutrient agar at 37 ± 1 °C. The colony forming units (cfu) of the seeded broth were determined by the plating technique and adjusted in the range of 10^4–10^5 cfu/ml. The antibacterial assay was performed at pH 7.4 ± 0.2, with the final inoculum size of 10^5 cfu/ml. 0.20 ml of the solution of the test compound was added to 1.80 ml of seeded broth to form the first dilution. One millilitre of it was diluted with an equal volume of the seeded broth to give the second dilution. The dilution was continued in one ml increments to obtain six such dilutions. A set of assay tubes containing seeded broth were kept as controls and likewise solvent controls were also run simultaneously. The tubes were incubated in biochemical oxygen demand (BOD) incubators at 37 ± 1 °C for bacteria. The minimum inhibiting concentrations (MICs) were recorded by visual observations after 24 h. Ciprofloxacin was used as a standard for the antibacterial study.

For evaluating the antibacterial activity ciprofloxacin was used as the standard drug. The observed minimum inhibitory concentrations (MICs) are given in Table 1. In general, all the compounds exerted a modest to good antibacterial activity *in vitro* against the tested organisms. Compound **7a** without any substituent in the aryl moiety exhibited antibacterial activity *in vitro* at 100 μg ml^{-1} against *P. aeruginosa,* but its antibacterial activity against the other tested organisms was only at 200 μg ml^{-1}. However **7b**, in which the hydrogen at the para position of the aryl moiety is replaced by chlorine, showed a very good activity against all the tested organisms in the range of 25–50 μg ml^{-1}. Compound **7c**, which had the chlorine in the ortho position, exhibited similar activity as **7b**. Undeniably the compounds **7b–k**, bearing a substituent in the aryl group, are more active than the parent compound, **7a**. Compound **7a** and its isopropyl analogue **7k** have the similar moderate activity against *K. pneumoniae*. However, **7k** showed higher activity than **7a** against all the other tested organisms. Interestingly, **7**f with a nitro substituent, **7i** with an amide and **7g** with fluorine all in the para position, exhibited higher activity relative to Ciprofloxacin.