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Original Article

Synthesis, characterization and evaluation for antifungal activity of substituted diaryl imidazo [2, 1, b]-benzothiazole

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ABSTRACT

Aims: To synthesis substituted diaryl imidazole [2, 1, b] benzothiazole derivatives and evaluate for their antifungal activity.

Method: The synthesis of a series of substituted diaryl imidazo [2, 1-b] benzothiazole derivatives by reacting 2-amino benzothiazole with an appropriately substituted α-bromo-1,2-(*p*-substituted) diaryl-1-ethanones. All synthesized compounds were examined for their antifungal activity by disc diffusion method against pathogenic strains of *Aspergillus flavus* (MTCC 277), *Aspergillus niger* (MTCC 1344) and *Candida albicans* (MTCC 227) with the standard drug Clotrimazole.

Results: The diaryl imidazo [2, 1-b] benzothiazole derivatives were synthesized and characterized by spectral studies using IR, ^{1}H NMR, ^{13}C NMR, Mass ^{1}H NMR spectra **(8a–y)**. All synthesized compounds examined for their antifungal activity and compounds **8k**, **8l**, **8m**, **8n**, **8q**, **8r**, and **8y** exhibited excellent an antifungal activity profile as compared with the standard.

Conclusion: All synthesized compounds showed mild to moderate activity against *A. flavus* and *A. niger* and this indicate that some of the newly synthesized title compounds exhibited promising antifungal activities and they warrant more consideration as prospective antimicrobials.

1. Introduction

Invasive fungal infections, particularly in immunosuppressed patients, have continued to increase in incidence during the past 20 years and are now significant causes of morbidity and mortality.[1] Long before mankind discovered the existence of microbes, the idea that various synthetic compound had healing potential, that they contained what we would currently characterize as antimicrobial principles, was well accepted. Since antiquity, man has employed the synthetic to treat common infectious diseases and some of these traditional medicines are still included as part of the habitual treatment of various maladies.[2] Autopsy data indicate that more than half of the patients who die with malignancies are infected with *Candida* spp., approximately one-third with *Aspergillus* spp., and increasing numbers

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with *Cryptococcus* spp. or other fungi such as *Fusarium* spp.[3–5] Major factors which predispose patients to invasive fungal diseases include: prolonged neutropenia (chemotherapy induced); defective T-lymphocyte function (associated with organ transplantation and HIV infection); impaired macrophage function, particularly of pulmonary macrophages (associated with high doses and prolonged administration of corticosteroids); and barrier defects (associated with invasive medical procedures, vascular catheters, parenteral nutrition, hemodialysis and peritoneal dialysis) in compromised patients.[6–10] Although invasive fungal diseases are now more frequent than during the first half of the century, they are still difficult to diagnose clinically. During the latter half of the century, particularly during the past two decades, a number of different classes of antifungal agents have been discovered.[11–13] Despite advances in antifungal therapies, many problems remain to be solved for most antifungal drugs available. Clotrimazole[14,15] was used as the standard drug for the present study. The use of azoles, such as fluconazole, ketoconazole and miconazole, has resulted in clinically resistant strains of *Candida* spp.[16,17] A 3.6–7.2% of vaginal isolates of *Candida albicans* from women with *Candidal vaginitis* is resistant to fluconazole.[18] This situation highlights the need for advent of safe, novel and effective antifungal compounds. Recently, some new, imidazo [2, 1-b]-benzothiazole and their derivatives have been synthesized as antibacterial, diuretic, antifungal and anti-HIV agents. Imidazole [2,1,b], thiazole,[19] imidazo [2, 1-b]-benzothiazole[20,21] and their bio-isosteric derivatives are also regarded as safer and better drug molecules.[22] In view of the previous study and in continuation of an ongoing program aiming at finding new structure leads with potential antifungal activity, new series of substituted diaryl Imidazole [2, 1-b]-benzothiazole derivatives have been synthesized and screened for antifungal activity.

2. Chemistry

The 2-amino-6, 7-disubstituted benzothiazoles **(3a–h)** were synthesized by the reaction of substituted aniline **(1a–h)** and potassium thiocyanate in the presence of glacial acetic acid at 0 °C by following the literature procedure.[23] The synthesis of 1, 2-(4-substituted) diaryl-1-ethanones **(6a–i)** was carried out by reacting appropriate phenylacetic acid **(4a–c)** with various substituted aromatic hydrocarbons in the presence of orthophosphoric acid and trifluoroacetic anhydride **(5a–c)**. The resulting intermediates **(6a–i)** were subjected to bromination using liquid bromine in chloroform to obtain α-bromo-1,2-(4-substituted) diaryl-1-ethanones **(7a–i)** as show in Scheme 1.[19] The synthesis of substituted diaryl imidazo [2, 1-b]-benzothiazoles **(8a–y)** was carried out by condensation of 2-amino benzothiazole **(3a–h)** with substituted α-bromo-1, 2-(*p*-substituted) diaryl-1-ethanones **(7a–i)** in suitable solvent. This method provides required substituents at 2-, 5- and 6- position by starting with appropriately substituted synthons. The resulting free bases are obtained by neutralization of the salts with sodium carbonate solution.

3. Antifungal activity

Series of substituted 2,3-diaryl substituted imidazo [2,1-b] benzothiazoles (8a-y) have been examined for activity against pathogenic strains of *Aspergillus flavus*, *Aspergillus niger* and *C. albicans*.[24] The anti-candida activity of all the synthesized compounds (8a-y) and investigated by microbroth dilution assay[25] The concentrations of the tested compounds (10 μg/mL) were used according to a modified disk diffusion method. The sterile discs were impregnated with 10 μg/disc of the tested compound. Each tested compound was performed in triplicate. The solvent DMSO was used as a negative control and Clotrimazole was used as standard calculated average diameters (for triplicates) of the zone of inhibition (in mm) for tested samples with that produced by the standard drugs[26] and the results are given in Table 1. Among the series tested, seven compounds (8k, 8l, 8m, 8n, 8q, 8r and 8y) exhibited excellent antifungal activity against pathogenic strains of *A. flavus*, *A. niger* and *C. albicans*. However, all other compounds in the series were found to have moderate to good antifungal activity as compared to the standard. Minimum inhibitory concentration (MIC) was recorded as the lowest concentration of a compound that inhibits the growth of the tested microorganisms. In comparing the MIC values with the standard Clotrimazole (MIC = 0.1 μg/mL), compounds 8k, 8l, 8m, 8n, 8q, 8r and 8y exhibit the most potent antifungal activity against all evaluated organisms. Especially compounds 8l (MIC = 0.15–2 μg/mL), 8n (MIC = 0.15–0.25 μg/mL), and 8y (MIC = 0.15–0.20 μg/mL) showed high antifungal activity while compounds 8k (MIC = 0.2–0.5 μg/mL), 8m (MIC = 0.15–0.25 μg/mL), and 8q (MIC = 0.15–0.20 μg/mL) showed respectable antifungal activity.

A brief investigation of the structure-activity relationship (SAR) revealed that the compounds with a methyl, nitro (-NO2), or carboxylic acid functional group at position C-6 and C-7 of the imidazo [2, 1-b]-benzothiazole nucleus contributed to a better antifungal activity. Presence of electron withdrawing group on the C-7 and phenyl ring at C-3 and of the imidazo [2, 1-b]-benzothiazole nucleus favors the activity Hence, compounds 8k, 8l, 8m, 8n, 8q, 8r and 8y have exhibited excellent antifungal activity against all the test organisms and have emerged as active antifungal agents.

4. Results and discussion

We have synthesized a series of substituted diaryl imidazo [2, 1-b]-benzothiazole derivatives by reacting 2-amino benzothiazole with an appropriately substituted α-bromo-1,2-(*p*-substituted) diaryl-1-ethanones as illustrated in Scheme 1. The derivatives were characterized by spectral studies using IR, ^{1}H NMR, ^{13}C NMR, Mass.^{1}H NMR spectra the synthesized compounds **(8a–y)** showed prominent signals for the aromatic protons between δ 6.83 and 8.26 ppm. Compounds showed a singlet between δ 3.90–3.84 ppm indicating the presence of–OCH_3 group. The peaks appearing at around δ 1.22, 1.96–2.03, 3.10 and 3.78–3.88 ppm confirm the presence of CH_3, SCH_3 and OCH_3 groups, respectively. In ^{13}C NMR spectrum we have observed most characteristic signals