Synthesis and Antibacterial Activity of Some Novel 6-(1H-Benz[d]
imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]
triazolo[3,4-b][1,3,4]thiadiazepines

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A new series of novel 6-(1H-benz[d]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines 8a–d has been synthesized. These compounds were evaluated for their efficiency as antibacterial agents against two Gram-positive and Gram-negative strains of bacteria along with antifungal activity against two fungal organisms. The antibacterial and antifungal activities of the present compounds were not comparable with those of the standard drugs employed. However, all the test compounds could exhibit notable activities only at higher concentrations (250, 500 μg/ml). The chemical structures of these compounds were confirmed on the basis of spectral data.

Key words benzimidazole; triazole; thiadiazepine; antimicrobial activity

Benzimidazoles show significant activity against several viruses such as human cytomegalovirus (HCMV),1 human immunodeficiency virus (HIV),2 herpes (HSV-1),3 RNA4 and influenza.5 In view of the tremendous activities of benzimidazoles, their preparation has gained considerable attention. While many strategies are available for benzimidazole synthesis,6–9) Almost all benzimidazoles with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of drugs.

The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications.10) Many of them are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents.11–14) Some heterocycles containing benzodiazepines moiety were reported to possess anti inflammatory,15) antiviral,16) anti-HIV-1,17) antimicrobial18) and antitumor19) activities. It has been noticed that introduction of an extra ring to the benzodiazepine core tends to exert profound influence in conferring novel biological activities in these molecules.20 –24) Although many methods for synthesizing benzodiazepine ring systems have been reported, they continue to receive a great deal attention.25–27)

Another class of heterocycles used as scaffolds in medicinal chemistry is devoted to benzotriazole derivatives. They exhibit useful pharmacological properties and clinical applications.28–31) In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic synthesis.32)

Inspired with biological profile of benzimidazoles, triazoles and diazepines and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biologically active and pharmacologically important new heterocycles,33–38) it was thought worthwhile to synthesize the title compounds with a view to obtain certain new chemical entities with three active pharmacophores in a single molecular frame work in order to prepare molecules having with potentially enhanced biological activities and to have them evaluated for their antimicrobial activity. On the other hand, to the best of our knowledge, previously there is no report, on the synthesis of 6-(1H-benz[d]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines 8a–d skeleton system represented in Chart 1.

The key intermediate 4-amino-5-(4-pyridyl)-4H-1,2,4-triazol-3-ylhydroxysulfide 7, required for the synthesis of the title compounds was prepared by the cyclocondensation of 4-pyridinecarboxyhydrazide with hydrazine hydrate and CS2 in presence of potassium hydroxide and ethanol.39) 2-(α-Hydroxy)ethyl-benzimidazoles 3a–d was prepared by the reaction of substituted o-phenylenediamines 1 with α-hydroxy propionic acid 2 in presence of hydrochloric acid under reflux, followed by oxidation of compounds 3a–d in presence of potassium dichromate and sulfuric acid at room temperature yields 2-acetyl benzimidazoles 4 which on condensation reaction with 5-nitro furfural 5 at room temperature in presence of concentrated sulfuric acid and glacial acetic acid provides the formation of (E)-1-(1H-benz[d]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones 6a–d. These compounds 6a–d on cyclocondensation reaction with 4-amino-5-(4-pyridyl)-4H-1,2,4-triazol-3-ylhydroxysulfide 7 in presence of polyphosphoric acid afforded the compounds 6-(1H-benz[d]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines 8a–d. The synthetic route leading to the title compounds is summarized in Chart 1. The chemical structures of all the newly synthesized compounds were confirmed by their IR, 1H-NMR, and MS analysis and further the compounds were screened for their antibacterial and antifungal activities.

Antibacterial Activity The antibacterial activity of the synthesized compounds was evaluated against two Gram-positive bacteria viz., Bacillus subtilis and Staphylococcus aureus, and two Gram-negative bacteria viz., Escherichia coli and Klebsiella pneumoniae using streptomycin and benzyl penicillin as standard drugs, respectively by the ‘cup-plate method’40) using dimethyl sulfoxide (DMSO) as the solvent and the results are given in Table 1. The results of the test compounds could not be directly compared with those of the standard drugs, employed for a very simple reason that they vary greatly in their test concentrations, that is, 250 μg/ml and 500 μg/ml of test compounds against 40 μg/ml only of reference drugs. Hence, this data was used to compare the
relative antibacterial potencies of the test compounds only. Though all of the test compounds could cause inhibition of both Gram (+) and Gram (−) bacteria employed, effectively at a concentration of 500 mg/ml, the compound 8d with two nitro groups was found to be relatively more potent among the test compounds.

Antifungal Activity The newly prepared compounds were also screened for their antifungal activity against two fungi, viz., *Fusarium oxysporum* and *Aspergillus niger* by the ‘cup-plate method’ using Fluconazole as a standard drug and DMSO as the solvent and the results are summarized in Table 1. Similar to antibacterial activity the antifungal activity of the present compounds was also not comparable to that of the standard drug Fluconazole because of the concentration variation. But, however, the test compounds could also exhibit antifungal activity against both the fungi employed. Table 1 indicates once again the compound 8d with two nitro groups as the superior, relatively among the present new series.

**Experimental**

**General** All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60—120 mesh. IR spectra were obtained on a Perkin Elmer BX series FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for 1H-NMR. The chemical shifts were reported as ppm down field using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

**Typical Procedure** 2-(α-Hydroxy)ethyl Benzimidazoles (3) α-Phenylenediamine (0.01 mol) was mixed with lactic acid (0.01 mol) in presence of 4% hydrochloric acid (5 ml) and refluxed for 24 h. After completion of the reaction, (monitored by TLC) the reaction mixture was cooled and neutralized with NH₃ solution. The solid was separated through filter and recrystallized from ethanol.

2-Acetyl Benzimidazoles (4) To a solution of 2-(α-hydroxy)ethyl benzimidazoles 3 (0.01 mol) in dil. H₂SO₄ (5%, 40 ml) was drop wise added the solution of K₂Cr₂O₇ (0.15 mol) and aqueous H₂SO₄ (25%, 80 ml) with constant stirring at room temperature over a period of 20 min. Further the reac-
tion mixture was stirred at room temperature for 2 h. After completion of the reaction, (monitored by TLC), the reaction mixture neutralized with NH₄ solution (1:1) and formed orange solid was filtered, washed with water and dried, recrystallized from ethyl acetate.

(3)-1-(1H-benz[d]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones

(6) To a solution of 2-acyct benzimidazoles 4 (0.01 mol) and 5-nitrofuran (0.01 mol) in glacial acetic acid (20 ml) was added conc. sulfuric acid (2 ml). Then the reaction mixture stirred at 40 °C for 24 h. The solid formed was filtered and recrystallized from ethylacetate.

Amino-5-(4-pyridyl)-4H-1,2,4-triazol-3-ylhydrosulphide

7) 4-Pyridine carboxylic acid (0.01 mol) was dissolved in 10% alcoholic potassium hydroxide (25 ml) and stirred with an equimolar quantity of CdSO₄ slowlly while cooling in an ice bacht. The resultant bulk potassium diithiocarbazate was filtered and subjected to a reaction with excess of hydrazine hydrate. The product was filtered and recrystallized from alcohol to get a colorless crystalline solid.

(0.01 mol) was dissolved in 10% alcoholic potassium hydroxide (25 ml) and stirred with an equimolar quantity of CdSO₄ slowlly while cooling in an ice bacht. The resultant bulk potassium diithiocarbazate was filtered and subjected to a reaction with excess of hydrazine hydrate. The product was filtered and recrystallized from alcohol to get a colorless crystalline solid.

1-(1H-benz[d]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones

(6): Yellow solid, yield 40%, mp 208—210 °C. IR (KBr) cm⁻¹: 3278, 3026, 2919, 1687, 1526, 1032, 1014, 875. 1H-NMR (CDCl₃) δ: 8.77 (1H, s), 7.78 (1H, s), 7.79 (1H, d, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.58 (1H, d, J = 7.4 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.08 (1H, d, J = 7.8 Hz), 6.87 (1H, d, J = 7.6 Hz), 2.43 (3H, s). MS m/z: 298 (M⁺ + 1).

(1H-benz[d]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (6e): Yellow solid, yield 40%, mp 208—210 °C. IR (KBr) cm⁻¹: 3278, 3026, 2919, 1687, 1526, 1032, 1014, 875. 1H-NMR (CDCl₃) δ: 8.77 (1H, s), 7.78 (1H, s), 7.79 (1H, d, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.58 (1H, d, J = 7.4 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.08 (1H, d, J = 7.8 Hz), 6.87 (1H, d, J = 7.6 Hz), 2.43 (3H, s). MS m/z: 298 (M⁺ + 1).

(1H-benz[d]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (6d): Yellow solid, yield 30%, mp 193—195 °C. IR (KBr) cm⁻¹: 3279, 3012, 2921, 1669, 1512, 1018, 879. 1H-NMR (CDCl₃) δ: 9.09 (1H, s), 8.77 (1H, s), 8.30 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 7.8 Hz), 7.64 (1H, d, J = 7.4 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.08 (1H, d, J = 7.8 Hz), 6.87 (1H, d, J = 7.6 Hz), 2.43 (3H, s). MS m/z: 329 (M⁺ + 1).

References


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