Synthesis, Antibacterial and Antifungal Activities of 3-Aryl-5-(pyridin-3-yl)-4,5-dihydropyrazole-1-carbothioamide Derivatives

M. Shekarchi, M. Pirali-Hamedani, L. Navidpour, N. Adib and A. Shafiee*

aDepartment of Research and Development, Food and Drug Laboratory Research Center, Tehran, Iran
bDepartment of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14174, Iran

A new series of 3-aryl-5-(pyridin-3-yl)-1-thiocarbamoyl-2-pyrazoline derivatives (4a-j) were prepared by the reaction of azachalcons 3a-j with thiosemicarbazide in ethanolic sodium hydroxide. The structure of synthesized compounds were confirmed by 1H NMR and Mass spectral data. Their antibacterial activities against *Escherichia coli* (CTP 7624), *Staphylococcus aureus* (ATCC 6538), *Staphylococcus epidermidis* (ATCC 12229), *Pseudomonas aeruginosa* (ATCC 9027), *Bacillus subtilis* (ATCC 1156) and *Micrococcus luteus* (ATCC 9341) were investigated. Antifungal activity of compounds against *Candida albicans* and *Candida globrata* were found to be inactive. Compounds 4a-j were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) in BACTEC 12B using a broth microdilution assay and Microplate Alamar Blue Assay (MABA). The preliminary results showed that compounds 4e, 4d and 4g had 87%, 93% and 92% inhibitory effect respectively.

Keywords: Azachalcons, 2-Pyrazoline, Antimycobacterial agents, Antifungal

INTRODUCTION

Antibiotics are among the most prescribed drugs in the world today, and since their development and commercialization, have saved countless millions of lives. The ideal antimicrobial agents are selective in only targeting the microorganism but not host cells. Resistance to antimicrobial agents is now recognized as a major global public health problem. In addition, because of the increased number of immunocompromised patients (AIDS, cancer and transplants), primary and opportunistic fungal infections continue to increase rapidly, and as a consequence, invasive fungal infections constitute a major cause of mortality for these patients. Although there are new classes of compounds that are now frequently used to treat fungal infections, the frequency of deeply invasive microbial agents has increased 10 fold during the past decade. Moreover, many infections are actually refractory to antimicrobial therapy. With the emergence of new bacterial strain resistant to many currently available antibiotic treatments, there is increasing interest in the discovery of novel antibacterial agents [1,2]. Certain small heterocyclic molecules are known as pharmacophores of a number of biologically active and medicinally useful molecules [3,4]. Electron-rich nitrogen heterocycles play an important role in diverse biological activities. Introducing a pyrazolidine ring in place of β-lactam ring in penicillins and cephalosporins results in enhanced activity [5]. A second nitrogen in the five-membered ring also influences the...
antibacterial or pharmacokinetic properties [6,7].  

2-Pyrazoline derivatives [8-14] have been reported in the literature to exhibit various pharmacological activities such as antibacterial, antifungal, herbicidal and anticholinergic. Considering the above discussion and in continuation of our previous work in pyrazoline derivatives [15], herein we report the synthesis of novel pyrazoline derivatives (4a-j) with possible antimicrobial and antifungal activities.

**EXPERIMENTAL**

**Chemistry**

Melting points were determined on a Kofler hot stage apparatus, and are uncorrected. The Infrared spectra were acquired on a Nicolet 550-FT spectrograph (KBr disks). The mass spectra were run on a Finigan-MAT TSQ-70 spectrophotometer at 70 eV. 1H NMR spectra were recorded on a Varian unity plus 400 MHz instrument and tetramethylsilane was used as an internal standard.

**General procedure for the synthesis of 1-Aryl-3-(pyridin-3-yl)prop-2-ene-1-ones (3a-j).** To a mixture of 3-pyridinecarboxaldehyde (21.4 g, 0.2 mol) and 40 ml NaOH 10% in ethanol (20 ml), different acetophenone derivatives was added slowly under cooling (5 ºC) during 30 min. After addition was completed, reaction mixture was stirred for 4 h keeping the temperature below 10 ºC. The resulting solid was collected by filtration, washed thoroughly with ice-cold water, dried in a vacuum desiccator and recrystallized from ethanol-water to give 3a-j. Physical, analytical and spectral data for these compounds are given in Table 1.

**General procedure for the synthesis of 3-aryl-5-(pyridine-3-yl)-4,5-dihydropyrazole-1-carbothioamide derivatives (4a-j).** To a solution of NaOH (1 g, 0.025 mol)