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Synthesis, Characterization and Antimicrobial Evaluation of Novel 2-Pyrazoline Derivatives Containing Morpholine Moiety

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ABSTRACT

A simple and efficient method for the synthesis of some novel 2-pyrazoline derivatives is reported. Chalcones were prepared by conventional Claisen-schmidt condensation of piperonal and substituted acetophenones. Some new N1-substituted diaryl pyrazoline derivatives have been prepared by condensation of 3,5-diaryl-2-pyrazolines with chloroacetyl chloride followed by the reaction with morpholine. The structures of the synthesized compounds were confirmed by FTIR, 1H NMR, mass spectral data. The synthesized compounds have been screened for their antimicrobial activity against different micro-organisms. A significant level of activity was observed.

Keywords: Chalcones, Pyrazolines, Morpholine, Antimicrobial activity.

INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. The most convenient methods are the Claisen-Schimdt condensation of equimolar quantities of an arylmethylketones with aryl aldehyde in the presence of alcoholic alkali. Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines, isoxazoles, pyrimidines, having different heterocyclic ring systems. In our present study, pyrazolines are synthesized by condensing chalcone with hydrazine hydrate. Piperonal, a naturally

occurring derivative of piperine compound (the pyrrolidine amide of piperic acid) is an aromatic aldehyde. In our present study, piperonal is the aldehyde moiety in the chalcone preparation. Methylenedioxy group in piperonal have some biological activity [1,2]. 2-Pyrazoline derivatives have also been reported in the literature to exhibit various pharmacological activities such as antimicrobial, [3-8] anti-inflammatory [9] and antihypertensive [10]. Its derivatives, possess a wide range of biological and physiological activities such as antitumor, antiarthritic, analgesic, anti-diabetic, fungicidal, bactericidal, immunosuppressive activities [6,8]. In the present study chalcones 1 (a-d) were treated with hydrazine hydrate to get corresponding 3,5-diaryl-2-pyrazolines 2 (a-d) . These pyrazolines were reacted with freshly prepared chloroacetyl chloride at room temperature to afford N1-chloroacetyl-3, 5-diaryl-2- pyrazolines 3 (a-d). The reaction of 3 (a-d) with morphine was carried out to get the title compounds 4 (a-d) in 80-90 % yields. In view of these observations and in continuation of our earlier work [11] some novel 2-pyrazoline derivative containing benzodioxole morpholine moiety are reported.

MATERIALS AND METHODS

Reagents

All the reagents were purchased from Aldrich and used as received. Dry solvents were supplied by Spectrochem, India. The 1H NMR was performed by 1H NMR chemical shift values were reported on the scale in ppm relative to TMS, The 1H NMR spectra were recorded in CDCl3 on Bruker AMX 400. Spectrometer (400MHz). IR spectra were recorded on Perkin Elmer spectrum 100 FT-IR model. Column chromatography was performed with silica gel 60-120 mesh (Merck, Mumbai, India.). All the compounds were routinely checked for their reaction on silica gel 60 F254 TLC plates and their spots were visualized by exposing them to iodine vapour or KMnO4 reagents. Melting points were determined by Buchi B-545 apparatus. Yield reported is the isolated yield after purification of the compounds.

Procedure for synthesis of 3, 5-diaryl-2-pyrazoline 2 (a-d)

A mixture of chalcone (0.01 mol) and hydrazine hydrate 99% (0.01 mol) was refluxed in absolute ethanol for 8 hours. Reaction was monitored by TLC, with eluent 8:2 petether: ethylacetate. Reaction was completed. Then the resulting solid obtained was dried and washed with water. The pure product was isolated by using column chromatography. The column was started at 10% ethyl acetate in petroleum ether and slowly increased to 70% ethyl acetate. The solid was dried and recrystallized from abs. ethanol.

(A) Synthesis of N1-chloroacetyl-3, 5-diaryl-2-pyrazoline 3 (a-d): To a solution of 3,5-diaryl-2-pyrazolines (0.01mol) in chloroform (20ml) was added freshly prepared chloroacetyl chloride (0.01 mol) with continuous stirring. A vigorous reaction takes place. After complete addition the reaction mixture was further stirred for 30 minutes at room temperature. The separated solid was filtered off and crystallized from ethanol to afford the product.

(B) Synthesis of N1-morpholino-ethanoyl-3, 5-diaryl-2-pyrazoline 4 (a-d): Compounds 3 (a-d) (0.01mol) and morpholine (0.01mol) were refluxed in absolute ethanol for 2 hours. After completion of the reaction the residue was cooled to room temperature. On standing at room temperature the solid separated was filtered and crystallized to get the solid of 4 (a-d).

RESULTS AND DISCUSSION

3,5-diaryl-2-pyrazolines 2 (a-d) is brown coloured powder whose yield is 80%. The IR (KBr) spectra exhibited 1564cm-1 (C=N), 1495 cm-1 (C=C),1130 cm-1 (C-N str) peaks. Condensation of 3,5-diaryl-2-pyrazolines with chloroacetyl chloride and morpholine afforded the title compounds, characterized as N1-morpholino ethanoyl-3,5-diaryl-2-pyrazolines. The structure of newly synthesized compounds was established on the basis of their analytical data and spectral analysis. The IR spectra (KBr,ν cm-1) of compounds 4 (a-d) exhibited 2950-2930 (-CH stret.), 1680-1660 (>C=O of COCH2Cl), and a high intensity broad band at 1590- 1570 (C=N and N-N combined vibrations). The IR spectra of compounds 4 (a-d) showedss 2960-2850 (-CH stret.), and a high intensity peak at 1660-1650 (>C=O). The 1H –NMR spectra (CDCl3, δ ppm) of compounds (4a-d) gave signals at δ 3.20-3-37 (dd, C4-Ha), δ 3.86-3.92 (dd, C4-Hb), δ 5.52-5.58 (C5-Hx) confirming the presence of typical ABX pattern of the pyrazoline ring. The aromatic protons gave a multiplet at δ 6.91-7.41. The methylene protons resulting from CH2-O-CH2 and CH2-N-CH2 grouping of morpholine nucleus appeared as singlet at δ 2.52, 2.60 respectively. The mass spectra of all the synthesized compounds gave molecular ion peaks and M+1 (chloro substituted) corresponding to their molecular masses.

Antimicrobial activity

We have investigated newly synthesised pyrazolines for their antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumonia bacterial strains by the disc diffusion method. Solvent and growth controls were kept, the zones of inhibition and minimum inhibitory concentrations (MIC) noted. Results of these studies are given in Table 1 and compared with the standard ciprofloxin. We have investigated newly synthesised pyrazolines were screened for their antifungal activity against Aspergillus niger, Candida albicans obtained. Antifungal activity was determined by

measuring the inhibition zone and (MIC) was noted. The results of these studies were given in Table 2 and compared with the standard Keta conazole.

Table 1: Antibacterial activities of the compounds 4 (a-d)

Compounds **(10 µg/ml)**	*S. aureus*	*E. coli*	*P. aeruginosa*	*Klebsilla pneumoniae*
4a	23 (6.25)	21.5 (6.25)	23.5 (6.25)	20 (6.25)
4b	23 (6.25)	21.5 (6.25)	23.5 (6.25)	20 (6.25)
4c	23 (6.25)	21.5 (6.25)	23.5 (6.25)	17 (6.25)
4d	21.5 (6.25)	23.5 (6.25)	19 (12.5)	23 (6.25)
Ciprofloxacin	24.5 (6.25)	25 (6.25)	24 (6.25)	25.5 (6.25)
Note: Zone of Inhibition in mm, Minimum inhibitory concentration in µg/ml given in parenthesis.				

Table 2: Antifungal activities of the compounds 4 (a-d)

Compounds **(10 µg/ml)**	*Aspergillus niger*	*Candida albicans*
4a	32 (6.25)	35.5 (6.25)
4b	30 (6.25)	32 (6.25)
4c	30 (6.25)	33 (6.25)
4d	35 (6.25)	36 (6.25)
Ketaconazole	38.5 (6.25)	34.5 (6.25)
Note: Zone of Inhibition in mm, Minimum inhibitory concentration in µg/ml given in parenthesis.		

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