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Synthesis and antibacterial activity of some Pyrazoline derivatives

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ABSTRACT

Pyrazoline derivatives, being used as potential medicinal agents, a series P_1-P_5 containing 3,5-diphenylpyrazoline and N-phenyl-3,5-diphenylpyrazoline derivatives were synthesized, structures were confirmed using melting point, IR, NMR and MS and evaluated for their antibacterial activity using disc diffusion method at concentration 2mg/ml. The reference used was amikacin and mostly, all synthesized compounds exhibited a significant antibacterial activity against *Staphylococcus aureus* (MTCC No. 96) as Gram positive bacteria, *Staphylococcus epidermidis* (MTCC No. 435) as Gram positive and *Escherichia coli* (MTCC No. 739) as Gram negative bacteria. It was observed that P_1 and P_2 possess good antibacterial potential against *S. aureus*, P_5 against *S.epidermidis* and P_1 and P_4 against *E. coli*.

Key words: Pyrazoline, Disc diffusion method, Amikacin.

INTRODUCTION

For combating bacterial infection wide variety of anti-bacterial agents has been synthesized[1].

Pyrazolines are important nitrogen-containing five-member heterocyclic compounds. Several Pyrazoline derivatives possess important pharmacological activities and therefore they are useful materials in drug research. Pyrazolines are used as antitumour[2], immunosuppressive[3], antibacterial[4] and antitubercular agents. Some of the pyrazoline derivatives are reported to possess antiinflammatory[5], anticancer[6], antidiabetic[7] and antidepressant properties[8]. It also finds applications as dyestuffs, analytical reagents and agrochemicals[9]. Encouraged by its anti-bacterial activity, it was thought of interest to synthesize a new series of pyrazoline derivatives.

Aldol condensation between acetophenone and substituted benzaldehyde yields chalcone derivatives, a condensation product. These chalcone derivatives were reacted with phenyl hydrazine and hydrazine hydrate to form N-phenyl-3,5-diphenylpyrazoline & 3,5-diphenylpyrazoline derivatives respectively. The characterization of various synthesized compounds was done by TLC, melting point, IR, NMR & MS.

EXPERIMENTAL

Materials

Materials used in synthesis of compounds P_1-P_5 includes, benzaldehyde, chloro benzaldehyde,

o-methoxy benzaldehyde, acetophenone, potassium hydroxide pellets, phenyl hydrazine, hydrazine hydrate, glacial acetic acid, sulphuric acid and ethanol.

Synthesis

General procedure for synthesis of chalcone [P_1 and P_5]

Trituration was done on adding potassium hydroxide pellets (0.094mol) to the mixture of acetophenone (0.094mol) and benzaldehyde (0.094mol) at room temperature for 1h. The solid product 1,3-diphenyl-2-propen-1-one i.e. chalcone, so obtained was washed with water to remove excess of potassium hydroxide and then dried under UV light.

General procedure for synthesis of chalcone derivatives. [P_2, P_3, P_4]

[P_2] Trituration was done on adding potassium hydroxide pellets (0.072mol) to the mixture of acetophenone (0.072mol) and *o*-methoxy benzaldehyde (0.072mol) at room temperature for 1hr. The solid product 1-phenyl-3-(2-methoxy phenyl)-2-propen-1-one i.e. methoxy substituted chalcone so obtained was washed with water to remove excess of potassium hydroxide and then dried under UV light.

[P_3, P_4] Trituration was done on adding potassium hydroxide pellets (0.071mol) to the mixture of acetophenone (0.071mol) and *o*-chloro benzaldehyde (0.071mol) at room temperature for 1hr. The solid product 1-phenyl-3-(2-chloro phenyl)-2-propen-1-one i.e. chloro substituted chalcone so obtained was washed with water to remove excess of potassium hydroxide and then dried under UV light.

General procedure for synthesis of Pyrazoline derivatives from Chalcone and its derivatives

[P_1, P_5] To 1,3-diphenyl-2-propen-1-one i.e. chalcone (0.008mol) in 20ml of 1,4-dioxane, hydrazine hydrate (0.024mol) and phenyl hydrazine (0.024mol) were added for P_1 and P_5 respectively. To these mixtures 2-3 drops of sulphuric acid were

Table 1: Experimental data of synthesized Pyrazoline compounds

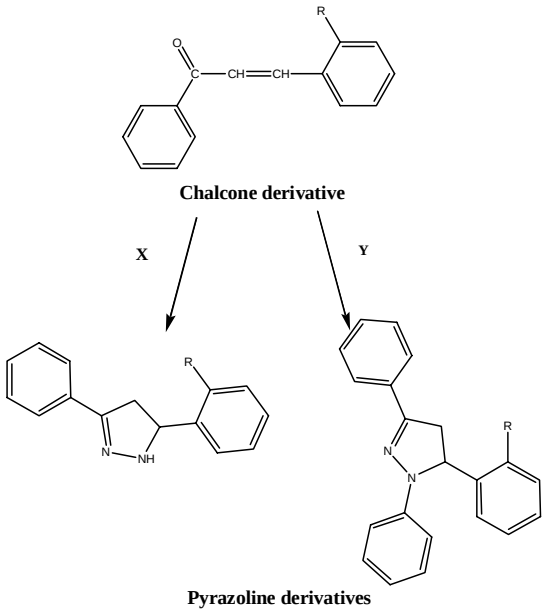
Compound	R	X/Y	Molecular formula	m.p. (°C)	% Yield
P_1	H	X	$C_{15}H_{14}N_2$	44-46	60
P_2	OCH_3	X	$C_{16}H_{16}ON_2$	52-54	30
P_3	Cl	Y	$C_{21}H_{17}N_2Cl$	129	53
P_4	Cl	X	$C_{15}H_{13}N_2Cl$	50-52	52
P_5	H	Y	$C_{21}H_{18}N2$	72-74	45

Table 2: Microbiological results of Pyrazoline compounds

Compound	MIC	% Inhibition		
	(mg/ml)	*S.aureus*	*E.coli*	*S.epidermidis*
P_1	2	59	54	50
P_2	2	62	-	45
P_3	2	-	48	52
P_4	2	51	56	52
P_5	2	51	48	56

(-) Indicates bacteria are resistant to the compounds at concentration 2mg/ml, MIC - minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

added and the contents were allowed to get reflux for 4h. 5ml glacial acetic acid was added to both the mixtures; again reflux was done for next 2h. On cooling to room temperature the contents were poured on crushed ice. As a result the solid products 3,5-diphenyl 4H-pyrazoline and 1,3,5-triphenyl 4H-pyrazoline were obtained which were recrystallized using ethanol.



Scheme 1: Synthesis route of Pyrazoline compounds

[P_2] To 1-phenyl-3-(2-methoxy phenyl)-2-propen-1-one (0.008mol) in 20ml of 1,4-dioxane, hydrazine hydrate (0.024mol) was added. To this mixture 2-3 drops of sulphuric acid was added and the contents were allowed to get reflux for 4hrs. 5ml glacial acetic acid was added to the mixture; again reflux was done for next 2hrs. On cooling to room temperature the contents were poured on crushed ice. As a result the solid product 3-phenyl-5-(2-methoxy phenyl) 4H-pyrazoline was obtained which was recrystallized using ethanol.

[P_3, P_4] To 1-phenyl-3-(2-chloro phenyl)-2-propen-1-one (0.008mol) in 20ml of 1,4-dioxane, hydrazine hydrate (0.024mol) and phenyl hydrazine (0.024mol) were added for P_3 and P_4 respectively. To these mixtures 2-3 drops of sulphuric acid were added and the contents were allowed to get reflux for 4hrs. 5ml glacial acetic acid was added to both the mixtures; again reflux was done for next 2hrs. On cooling to room temperature the contents were poured on crushed ice. As a result the solid products 1,3-diphenyl-5-(2-chloro phenyl) 4H-pyrazoline and 3-phenyl-5-(2-chloro phenyl) 4H-pyrazoline were obtained which were recrystallized using ethanol.

Antibacterial activity

The newly synthesized pyrazoline compounds were screened for antibacterial activity against *Staphylococcus aureus* (MTCC No. 96), *Escherichia coli* (MTCC No. 739) and *Staphylococcus epidermidis* (MTCC No.435) by disc diffusion method[10,11]. Discs measuring 10.0 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 discs were dispensed to each

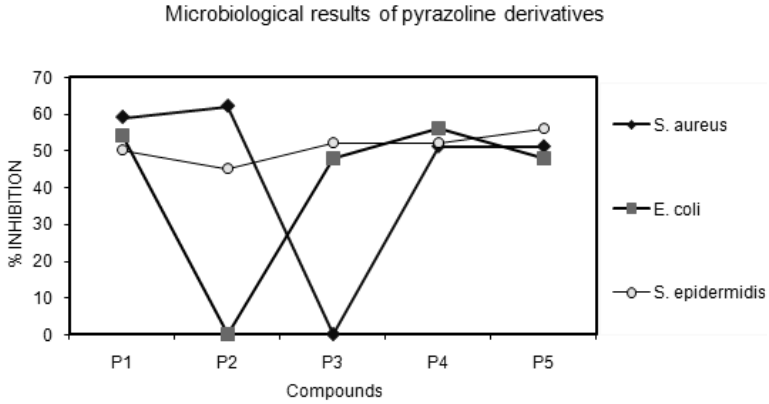


Chart 1: Microbiological results of Pyrazoline compounds

screw capped bottles and sterilized by dry heat at 50°C for 3hrs. Each disc containing full concentration (2mg/ml) were prepared using dimethylformamide (DMSO). The discs of each compounds was placed individually on nutrient agar medium seeded with fresh bacteria respectively using amikacin as the positive control. The nutrient agar plates were incubated at 37°C for 30min. before the discs were applied aseptically. The treated plates were incubated at 37°C for 48h. Minimum Inhibitory Concentrations (MIC) were noted and compared with positive control amikacin, the results of antibacterial studies are given:

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition action.

CONCLUSION

We have synthesized a series of 3,5-diphenylpyrazoline and N-phenyl-3,5-diphenylpyrazoline derivatives. The synthesized compound P_1 and P_2 shows significant antibacterial activity against *S. aureus,* P_1 and P_4 against *E. coli* and P_5 against *S. epidermidis.* Also P_3 compound shows adequate activity against *E. coli* and *S. epidermidis.* Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

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