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Synthesis and Antimicrobial activities of Various Pyrazolines from Chalcones

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Abstract: Some novel series of pyrazoline derivatives were synthesized from Chalcones. Chalcones were prepared by treatment of Furan-2-Carbaldehyde with different acetophenones by Claisen-Schimidt Condensation. Various Pyrazoline derivatives were prepared by reflux reaction of Chalcone with Phenyl Hydrazine/Hydrazine Hydrate in ethanolic solution. The structures of the newly synthesized Pyrazoline derivatives have been established on the basis of their spectral data. The synthesized selected compounds were screened for their antimicrobial activity.
Keywords: Pyrazoline, Chalcones, Furan-2-Carbaldehyde, Antimicrobial activity.

Introduction

Due to the rapid development of bacterial resistance to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity such as antibacterial[1], antitumour[2], anticancer[3], antitubercular[4], anti-inflammatory[5], antioxidant[6], antimalarial[7], antileishmanial[8] etc. The presence of reactive α, β-unsaturated keto group in chalcones is found to be responsible for their biological activity.

In the present work chalcones have been prepared according to claisen-schimidt condensation by condensing various ketones with aromatic aldehyde.

Available data suggest that N containing heterocyclic compounds from chalcones possesses wide variety of activities[9-17] such as potential cytotoxic agents, antimicrobial agents, antiviral, antiinflammatory, anesthetics, mydriatics etc.

Led by these considerations, it appeared of interest to synthesize novel pyrazoline derivatives and screened for their antimicrobial activities.

Materials and Methods

Chemicals and reagent

Furan-2-Carbaldehyde, Various Acetophenone, Phenyl Hydrazine, Hydrazine Hydrate, Ethanol, Ampicillin and Griseofulvin.

Experimental procedures

STEP.1

Chalcones By Claisen-Schimidt Condensation By Reaction Of Aldehyde With Various Acetophenone

Place a solution of 22g of sodium hydroxide in 200ml of water and 122.5ml of rectified spirit in a 500ml bolt-head flask provided with a mechanical Stirrer. Immerse the flask in a bath of crushed ice, pour in 0.43mol of freshly distilled Acetophenone, start the stirrer and then add 0.43mol of pure Furfuraldehyde. Keep the temperature of the mixture

at about 25^0C (the limits are 15- 30^0C) and stir vigorously until the mixture is so thick that stirring is no longer effective (2-3 hr). Remove the stirrer and leave the reaction mixture in an ice chest or refrigerator overnight. Filter the product with suction on a buchner funnel or a sintered glass funnel, wash with cold water until the washings are neutral to litmus and then with 20ml of icecold rectified spirit. The crude chalcone after drying in the air weigh 88g and melts at 50-54^0C. Recrystallized from rectified spirit warmed to 50^0C (about 5ml per gm). The yield of pure benzylideneacetophenone is 77 gm. [a pale yellow solid, mp 56-57^0C, 85%]. This substance should be handled with great care since it acts as a skin irritant**.**

STEP.2

Various Pyrazolines From Chalcones

The solution of appropriate Chalcone 0.01 mol and phenylhydrazine 0.02 mol in ethanolic sodium hydroxide 20 ml was refluxed for 4 hour. The product was poured into ice water and the crude product which was separated out was filtered and crystallised from proper solvent.

A-4 IR ($_{max}$): 3376.6(-NH_2), 3234.3(-NH), 3056.5(Ar-H), 1651.5(Ar-C=C), 1603.1 (C=N), 1441.6(CH_2 of Pyrazoline), 1235.8(C-O-C). ^{1}H NMR (DMSO): 8.51(1H,s, NH of Pyrazoline), 6.96-7.93(8H,m,Ar-H), 6.17-6.66(3H,m,Furan), 4.16-4.20(2H,d,CH2 of Pyrazoline), 3.68(2H,d, NH2), 2.48(1H,s,CH of Pyrazoline). Mass: m/z 303.2 (M^+)

B-4 IR (max): 3272.0(-NH), 3060.5(Ar-H), 1631.6(Ar-C=C), 1593.6 (C=N), 1401.8(CH_2 of Pyrazoline), 1236.6(C-O-C), 523.7(C-Br). ^{1}H NMR (DMSO): 7.50-7.90(8H,m,Ar-H), 6.67(1H,s,NH of Pyrazoline), 5.98-6.23(3H,m,Furan), 3.36-3.39(2H,d,CH2 of Pyrazoline), 2.57(1H,s,CH of Pyrazoline). Mass: m/z 367.2 (M+)

C-4 IR (max): 3291.0(-NH), 3069.2(Ar-H), 1621.6(Ar-C=C), 1602.2 (C=N), 1552.8(-NO_2), 1401.8(CH_2 of Pyrazoline), 1232.6(C-O-C). ^{1}H NMR (DMSO): 7.51-7.99(8H,m, Ar-H), 6.42(1H,s,NH of Pyrazoline) 6.02-6.25(3H,m,Furan), 3.45-3.50(2H,d, CH2 of Pyrazoline), 2.68(1H,s,CH of Pyrazoline). Mass: m/z 334.2 (M+1)

Hydrazine hydrate 0.02 mol was added to an ethanolic solution of appropriate chalcone (0.01 mol, 10 ml ethanol) and refluxed for 2 h. The solvent was evaporated at reduced pressure and the residue was crystallised from proper solvent.

A-5 IR ($_{max}$): 3349.3(-NH_2), 3211.0(-NH), 2985.3(Ar-H), 1685.7 (Ar-C=C), 1598.0(C=N), 1435.8(CH_2 of Pyrazoline), 1232.1(C-O-C). ^{1}H NMR (DMSO): 7.25-7.79(4H,m, Ar-H), 6.50(1H,s,NH of Pyrazoline), 6.18-6.19(3H,m,Furan), 4.66-4.80(2H,m,CH2 of Pyrazoline), 3.23(2H,d, NH2), 2.51(1H,s,CH of Pyrazoline). Mass: m/z 227.4 (M^+)

B-5 IR ($_{max}$): 3249.7(-NH), 3060.2(Ar-H), 1654.6 (Ar-C=C), 1599.3(C=N), 1471.3(CH_2 of Pyrazoline), 1217.5(C-O-C), 529.7(C-Br). ^{1}H NMR (DMSO): 7.83-7.87(4H,m,Ar-H), 7.58-7.62(3H,m,Furan), 7.48-7.52(1H,d,NH of Pyrazoline), 3.26(2H,s,CH2 of Pyrazoline), 2.51(1H,s, CH of Pyrazoline). Mass: m/z 291.9 (M^+)

C-5 IR ($_{max}$): 3223.9(-NH), 3173.8(Ar-H), 1692.7 (Ar-C=C), 1598.3(C=N), 1560.2(-NO_2), 1440.1 (CH_2 of Pyrazoline), 1231.7(C-O-C). ^{1}H NMR (DMSO): 7.27-7.80(4H, m, Ar-H), 6.87 (1H, s, NH of Pyrazoline), 6.08-6.44(3H,m,Furan), 4.73-4.82 (2H,m,CH2 of Pyrazoline), 2.58 (1H, s, CH of Pyrazoline). Mass: m/z 258.9 (M+1).

General procedures

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: s- singlet, d- doublet, t-triplet, q-quartet and m-multiplet. Mass spectra (MS) were recorded on MSroute JMS 600-H. All the synthesized compounds were purified by recrystallization. The reactions were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultraviolet light.

In vitro anti–microbial screening[18]

The synthesized compounds were subjected to antimicrobial screening by Cup plate method for zone of inhibition. The Antibacterial activity was tested against various gram positive and Gram negative bacteria and anti fungal activity against various fungal strains compared with standard drug (Ampicillin and Griseofulvin).

Antibacterial Activity

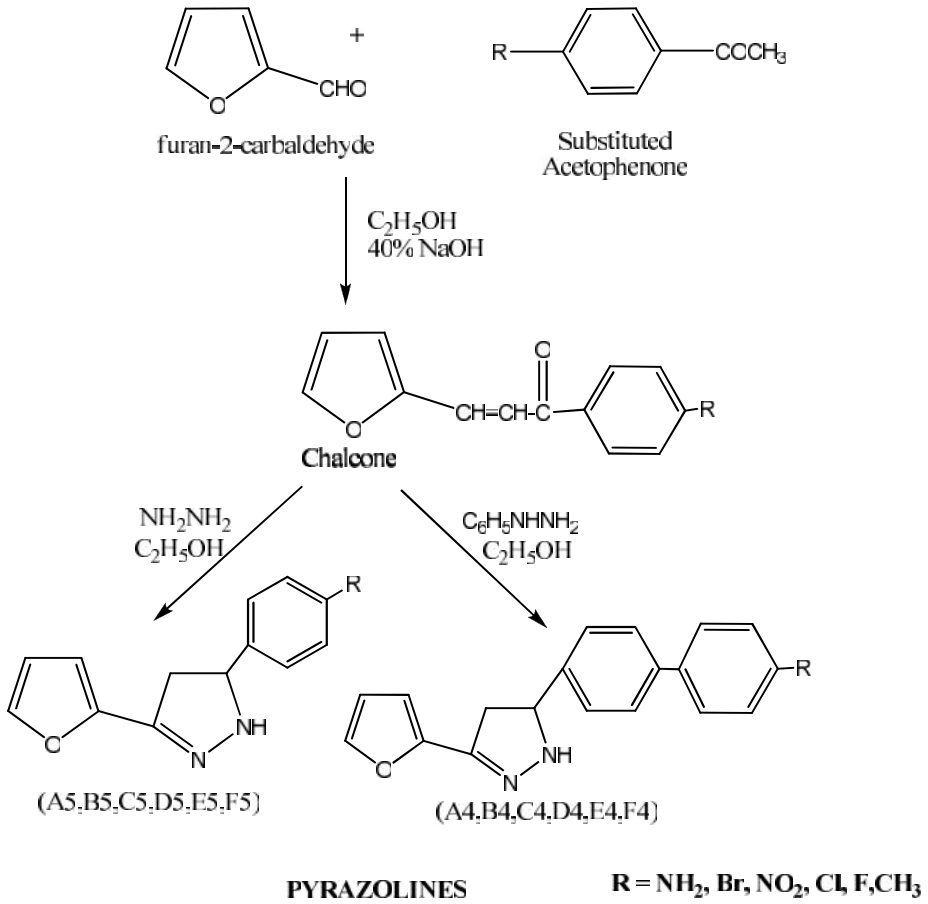
Each Petri dish containing Multer-Hinton agar medium was inoculated with one bacterial culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. In each plate cups of 6mm diameter were made at equal distances using sterile cork borer. One cup was filled wih 0.1 ml of standard drug ie., ampicillin, one was filled with 0.1

ml of DMF, others were filled with 0.1 ml of synthesized compound's solution in sterile DMF.
All plates were kept in the refrigerator for 30 minutes to allow the diffusion of sample to the surrounding agar medium. The Petri dishes were incubated at 37°C for 24 hrs. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameter obtained for the test samples were compared with that produced by standard ampicillin.

Antifungal Activity

oEach Petri dish containing nutrient agar medium was inoculated with one fungal culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. In each plate cups of 6mm diameter were made at equal distances using sterile cork borer. One cup was filled with 0.1 ml of standard drug ie., griseofulvin, one was filled with 0.1 ml of DMF, others were filled with 0.1 ml of synthesized compound's solution in sterile DMF.
oAll plates were kept in the refrigerator for 30 minutes to allow the diffusion of sample to the surrounding agar medium. The Petri dishes were incubated at 250C for 48 hours. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameter obtained for the test samples were compared with that produced by standard griseofulvin.
The results were described in the Table 2.

SCHEME



PYRAZOLINES **R = NH_2, Br, NO_2, Cl, F, CH_3**

TABLE 1: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound No.	Physical State	Melting point(^{o})	Yield (%)	Molecular Formula
A-4	Dark Yellow Crystals	158-160^{o}C	55.71%	$C_{19}H_{17}N_3O$
A-5	Dark Yellow Crystals	122-124^{o}C	55.40%	$C_{13}H_{13}N_3O$
B-4	Pale Yellow Crystals	192-195^{o}C	58.40%	$C_{19}H_{15}BrN_2O$
B-5	Pale Yellow Crystals	148-150^{o}C	68.21%	$C_{13}H_{11}BrN_2O$
C-4	Dark Yellow Crystals	153-155^{o}C	53.80%	$C_{19}H_{15}N_3O_3$
C-5	Yellow Crystals	110-112^{o}C	53.10%	$C_{13}H_{11}N_3O_3$
D-4	Pale Yellow Crystals	188-189^{o}C	56.15%	$C_{19}H_{15}ClN_2O$
D-5	Yellow Crystals	142-148^{o}C	63.12%	$C_{13}H_{11}ClN_2O$
E-4	Yellow Crystals	168-170^{o}C	70.55%	$C_{19}H_{15}FN_2O$
E-5	Dark Yellow Crystals	150-152^{o}C	73.22%	$C_{13}H_{11}FN_2O$
F-4	Pale Yellow Crystals	152-154^{o}C	50.32%	$C_{20}H_{18}N_2O$
F-5	Yellow Crystals	141-145^{o}C	47.83%	$C_{14}H_{14}N_2O$

TABLE 2: ANTIMICROBIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Sl. no.	Compound number	Diameter of zone of inhibition (mm)					
		S.aureus	***B.subtitis***	***E.coli***	***P.aeruginosa***	***A.Niger***	***C.albicans***
1	A-4	-	10	-	10	11	11
2	A-5	14	11	14	11	12	14
3	B-4	-	9	-	11	11	10
4	B-5	14	12	14	10	11	13
5	C-4	-	10	-	09	11	11
6	C-5	13	14	13	12	13	12
7	D-4	-	10	-	10	12	10
8	D-5	13	13	12	13	13	12
9	E-4	10	12	11	13	12	11
10	E-5	11	12	12	13	13	13
11	F-4	11	13	12	12	11	11
12	F-5	12	13	14	11	11	12
13	Ampicillin	15	15	16	16	-	-
14	Griseofulvin	-	-	-	-	15	15

- indicates no activity

Result and Discussion

In our study, new series of compounds namely substituted pyrzaolines (A-4,A-5,B-4,B-5,C-4,C-5,D-4,D-5,E-4,E-5,F-4,F-5) showed moderate to significant antibacterial and antifungal activity when compared with standard drugs. However it is less than standard drugs like Ampicillin and Griseofulvin but compounds A-5,B-5,C-5,D-5 Showed significant antibacterial activity and A-5,C-5,D-5,E-5 Showed significant antifungal activity when compared to standard drug.

The effect of synthesized pyrazolines on bacterial and fungal strains are summarized in Table 2.

Conclusion

Results of present study demonstrates that, a new class of different pyrazolines synthesized from chalcones and evaluated for antibacterial andantifungal activities. Among the tested A-5,B-5,C-5,D-5 compound showed better antibacterial activity while A-5,C-5,D-5,E-5 compound showed better antifungal activity. It can be concluded that Pyrazoline synthesized from chalcones certainly holds great promise towards good active leads in medicinal chemistry.

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