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Synthesis and Biological Evaluation of Some Novel 1, 3, 5-Trisubstituted Pyrazolines

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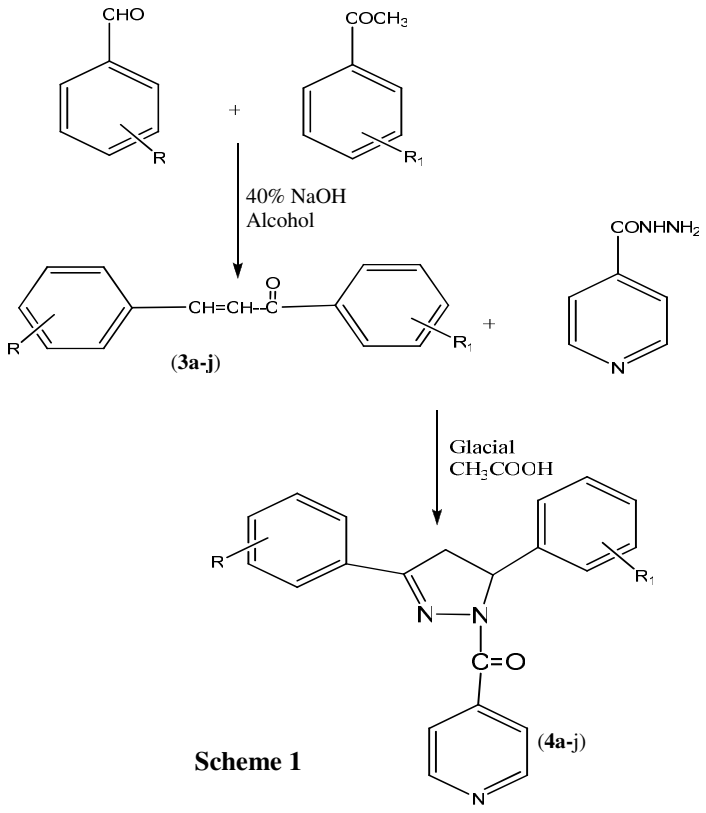
Abstract: A new series of chalcones **(3a-j)** were synthesized by condensation of simple aldehydes with substituted acetophenones in presence of alkali. The resulted chalcones upon cyclization in presence of glacial acetic acid with isoniazid (INH) will yields the title compounds **(4a-j).** The newly synthesized compounds were assigned on the basis of IR, ^{1}H NMR, and Mass spectral data. All the final compounds were evaluated for their *in vitro* antimicrobial activity.

Keywords: Pyrazolines, Chalcones, Antimicrobial activity.

Introduction

Nitrogen heterocyclic compounds like pyrazolines have received considerable attention in recent years due to their varied biological and pharmacological activities. Pyrazoline derivatives are well known for their anti-inflammatory[1], antiviral[2], herbicidal[3], antimicrobial[4], antifungal[5], anti-inflammatory[6] activities *etc*. Many class of chemotherapeutic agents containing pyrazoline nucleus are in clinical use such as orisul (bacterostatic), antipyrine (antipyretic), butazolidine (anti-inflammatory).

Based on the above biological activities exhibited by the pyrazoline compounds, we report here, the synthesis and biological evaluation of some novel pyrazoline derivatives. Chalcones **(3a-j)** were prepared from substituted aldehydes and ketones, in presence of alkali NaOH and alcohol as solvent medium. The later compounds **(3a-j)** were converted into the title compounds **(4a-j)** by reacting with isoniazid (INH) in glacial acetic acid medium. The structures of the newly synthesized compounds were established on the basis of IR, ^{1}H NMR, and mass spectral data. All the compounds were evaluated for their antibacterial and antifungal activities. The reaction sequence leading to the formation of the title compounds has been outlined in Scheme 1.



Scheme 1

Experimental

Melting points were determined in open capillary tubes and are uncorrected (Table 1). TLC (acetone: ethyl acetate 1:9) was used for monitoring the reaction and to check the purity. IR spectra were recorded on Shimadzu Perkin-Elmer 8201 FT-IR. The PMR spectra were recorded on BRUKER AVANCE II 400 NMR SPECTROMETER. Chemical shift values are reported as values in ppm relative to TMS (δ=0) as internal standard. The FAB mass spectra were recorded on JEOL SX- 102/DA-6000 Mass spectrometer using Argon/Xenon (6Kv, 10Ma) as the FAB gas operating at 70Ev. Elemental analyses were performed for C, N and were within ± 0.4% of theoretical values.

Table 1. Physical data of pyrazolines (**4a-j**).

Comp	R-CHO	R_1-$COCH_3$	m.p, ^{0}C	%, Yield
4a	2-Furfural	*p*-Cl	161-163	58
4b	*p*- CH_3	*p*-OH	120-122	59
4c	*p*-Cl	*p*-Cl	110-112	62
4d	C_6H_5	*p*-OH	130-132	68
4e	*p*-OCH_3	*p*-OH	103-105	59
4f	2-Thiophene	*p*-NO_2	147-149	68
4g	*m*-NO_2	C_6H_5	198-200	67
4h	m-NO_2	*p*-OH	119-121	57
4i	*p*-$(CH_3)_2$-N	*p*-Br	172-174	54
4j	*p*-OCH_3	*p*-Cl	188-190	67

*General procedure for the synthesis of chalcones (**3a-j**)*

To a solution of substituted aldehydes (0.01 mol) and ketones (0.01 mol) in ethanol (25 mL), a solution of NaOH (6 mL, 40%) was added. The reaction mixture was stirred at room temp for a period of 24 h, diluted with water (100 mL) and acidified with dil. HCl. The product obtained was filtered, washed with water and recrystallized from ethanol.

*General procedure for the synthesis of 1, 3, 5-trisubstituted pyrazolines (**4a-j**)*

A solution of chalcone (0.01 mol) and INH (0.01 mol) in glacial acetic acid (25 mL) was refluxed for about 36-48 h. Excess of solvent was removed under reduced pressure and the reaction mixture was poured into ice cold water. The product which was obtained is filtered, washed with water and recrystallized from ethanol.

4d: FTIR (KBr) (cm^{-1})**:** 3410 (OH), 3332 (NH), 1642 (C=O), 1513(C=N), 1489 (C=C). **^{1}H NMR** ($CDCl_3$) **:** δ 2**.**40 (3H, s, OCH_3)**,** 3.24-3.30 (1H, dd, Ha), 3.82-3.90(1H,dd, Hb), 5.74-5.78 (1H, dd, Hx),7.33-8.03 (13H, m, Ar-H), 8.79(1H, s,OH). **Mass** (m/z): Molecular ion peak at 373.

4e: FTIR (KBr) (cm^{-1}) **:** 3415(OH), 3396(NH), 1679 (C=O), 1585(C=N), 1486 (C=C). **^{1}H NMR** ($CDCl_3$) : δ 3.23-3.29 (1H, dd,Ha), 3.78-3.86(1H,dd, Hb), 5.72-5.80 (1H, dd, Hx), 7.24-8.00 (12H, m, Ar-H), 8.76(1H, s,OH). **Mass**(m/z): Molecular ion peak at 343.

4f: FTIR (KBr) (cm^{-1}): 3334(NH), 1646 (C=O), 1587(C=N), 1494 (C=C). 1514 (NO_2 asym)**,** 1330 (NO_2 sym) **^{1}H NMR** ($CDCl_3$):δ 3.22-3.28 (1H, dd, Ha), 3.54-3.61(1H, dd, Hb),5.16-5.20 (1H, dd, Hx), 6.87 -7.27(10H,m,Ar-H). **Mass** (m/z): Molecular ion peak at 378.

Antimicrobial activity

Antimicrobial screening was conducted using cup-plate method[7] at a conc of 100 µg/mL. All the compounds were assessed for their *in vitro* antimicrobial activity against different strains of bacteria such as *P.aeruginosa, E.coli* (gram negative), *B.subtilis, S.aureus* (gram-positive) and fungi like *A.niger, C.albicans.* Solvent DMF was used as solvent control. Standard drugs like streptomycin and griseofulvin were used for comparison purpose. After 24 h of incubation at 37 ^oC, the zones of inhibition were measured in mm. The biological data of the compound is given in Table 2.

Table 2. Antimicrobial activity of compounds **(4a-j).**

Comp	Diameter of zone of inhibition (mm) at 10 µg/mL concentration					
	S.aureus	*B.subtilis*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*
4a	13	12	11	14	14	15
4b	12	13	14	14	15	14
4c	14	14	15	12	16	16
4d	13	15	14	13	14	15
4e	12	14	15	14	13	13
4f	12	16	13	16	15	14
4g	10	15	14	14	13	16
4h	12	13	15	15	14	15
4i	13	13	16	14	15	14
4j	14	14	14	13	15	15
Streptomycin	24	21	22	22	-	-
Griseofulvin	-	-	-	-	23	22
Control(DMF)	-	-	-	-	-	-

Conclusion

All the newly synthesized pyrazoline compounds were screened for their antimicrobial activity. DMF is used as control and Streptomycin and Griseofulvin were used as standard drugs against bacteria and fungi organisms respectively. Among all the tested compounds **4f, 4i** displayed maximum activity against all the four pathogenic organisms. In the antifungal activity, compounds **4c, 4j** displayed maximum activity against both the fungi. From the results it is evident that most of the compounds are moderately active against both bacteria and fungi organisms.

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