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Research Article

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME 3, 5 DISUBSTITUTED PYRAZOLINE DERIVATIVES OF 2-ACETYL NAPHTHALENE

VARUN ARORA[1*], PRAGI ARORA[1] AND H.S. LAMBA[2]

[1] R.K.S.D. College of Pharmacy, Kaithal, Haryana, [2]H.R. Institute of Pharmacy, Gaziabad, U.P, India. Email: varunarora_knl@yahoo.co.in

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ABSTRACT

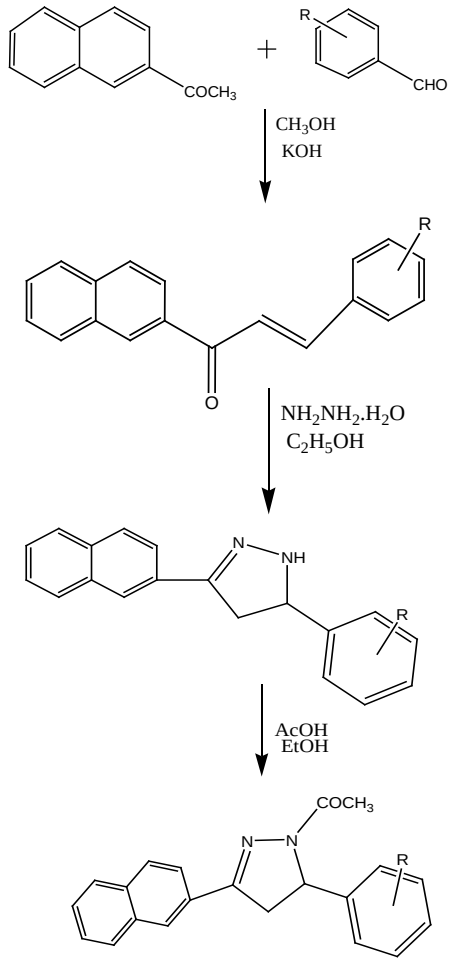
Synthesis and biological activities of a series of 1H-3,5-disubstituted-pyrazolines (II a-g) and 1-acetyl-3,5-disubstituted-pyrazolines (III a-g) are described. The structure of synthesized compounds have been established on the basis of IR and ^{1}H NMR and elemental analysis. The antimicrobial activity was evaluated against S.aureus, A. niger, A. flavus, E. coli and P.citrinum strains. All the tested compounds showed significant antibacterial and antifungal activity.

Keywords: Chalcones, Pyrazoline, Antimicrobial and Spectral studies.

INTRODUCTION

Pyrazole containing heterocyclic compound plays an important role in medicinal chemistry. Since a very long time the usefulness and great therapeutic value of pyrazole nucleus has been recognized and the wide range of biological activities of this nucleus evaluated.[1,2] Cox-2 inhibitory activity of pyrazole are well proved and many compounds containing pyrazole nucleus like celecoxib, sulphenazole, sulphinepyrazole & analgin are the well established in the market.[3] In the present study we have synthesized some 1H-3,5-disubstituted-Δ2-pyrazolines (IIa-g) by the cyclisation of different chalcones (Ia-g) in the presence of hydrazine hydrate.

The required chalcones (Ia-g) were prepared by the condensation of appropriate aromatic aldehyde & 2-acetyl naphthalene. 1H-3,5-disubstituted-2-pyrazolines (IIa-g) were further acetylated to 1-acetyl-3,5- disubstituted-2-pyrazolines (IIIa-g) with the help of acetic acid **(Scheme I).** These compounds were also evaluated for their antimicrobial activity.[4,5]



Scheme 1: 1H-3,5-Disubstituted--pyrazoline (IIa-g)

MATERIAL AND METHODS

The melting points were determined by open capillary method and are uncorrected.IR (KBr) spectra were recorded on a Shimadzu 8201PC infrared spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker DRX-300 spectrophotometer in DMSO using TMS as internal standard (Chemical shift are expressed in ppm).The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G coated plates and the spots were visualized by exposure to iodine vapors.

4-Substituted phenyl-4'-substituted chalcones (I a-g)

Potassium Hydroxide (0.1 mol) was dissolved in 20 ml of methanol and stirred in ice cold conditions. 2-acetyl naphthalene (0.1 mol) was dissolved in 20 ml of 95% v/v methanol and the solution was added drop wise with constant stirring under ice cold conditions. Pure benzaldehyde or substituted benzaldehyde (0.1 mol) was dissolved in 20 ml of 95% v/v methanol and added drop wise to the previous solution with constant stirring under ice cold conditions.

The stirring was continued till the TLC (Petether: Ethylacetate) had shown the disappearance of aldehyde spot and pH of the reaction mixture was made neutral by addition of dil. HCl. The product was filtered under vacuum, washed with excess distilled water and recrystallized.

General method

To 4-substituted phenyl-substituted chalcones (I a-g) (0.01 mol) in ethanol (25 ml) hydrazine hydrate (0.01 mol) was added. The reaction mixture was refluxed for 2 hr, concentrated and allowed to cool. The crystallized product was filtered and dried.

1-Acetyl-3,5-disubstituted--pyrazoline (IIIa- g)

General method

1H-3,5-disubstituted--pyrazoline (IIa-g) was dissolved in glacial acetic acid (10ml).The solution was refluxed for 2hr, concentrated and allowed to cool. The crystallized product was filtered, dried and recrystallised from ethanol.

Biological evaluation

Antimicrobial activity

Out of all the synthesized compounds(IIa,b,d,f and IIIa,b,d,f) were screened for their in vitro antibacterial activity against E.coli (gram-negative) and S.aureus (gram-positive) and antifungal activity against A. niger, A. flavus and P. citrinum using cup plate method[3] at 200,100 and 50 µg/ml concentration in DMSO. Ciprofloxacin and ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively at 50 µg/ml concentration in DMSO. (Table 4)

Table 1: Molecular formulae, molecular weights, reaction time, percentage yield, melting points and Rf values of compounds (IIa-IIg)

Compound No.	R[1]	Mol. Formulae	Mol. Weight	Reaction Time(hrs)	Yield (%)	m.pt. (^oC)	Analytical Calculation (%)
1Ia	H	$C_{19}H_{16}N_2$	272.34	2	89	125-127	C,83.79; H,5.92;N,10.29 found C,80.60, H,590 N,9.54
1Ib	4-Cl	$C_{19}H_{15}ClN_2$	306.78	3	90	189-191	C,74.28; H,4.93; N,9.13 found C,74.60,H,4.10 N,9.00
1Ic	4-Br	$C_{19}H_{15}BrN_2$	352	3	95	126-128	C,64.97; H,4.30; N,7.98 Br,22.75 found C,64.60,H,4.10 N,6.90; Br,21.90
1Id	4-F	$C_{19}H_{15}FN_2$	290.33	2	90	165-167	C,78.6; H,5.21; N,9.65;F,6.54 found C,77.20,H,5.00;N,9.00;F
1Ie	4-CH_3	$C_{20}H_{18}N_2$	286.37	2	85	198-200	C,83.88; H,6.34;N,9.78 found C,82.60,H,6.1;N,8.90
1If	4-OCH_3	$C_{20}H_{18}N_2O$	302.36	2	90	195-197	C,79.44; H,6.0;N,9.26;O,5.29 found C,77.60; H,6.0; N,8.95; O,5.00
1Ig	4-NO_2	$C_{19}H_{15}N_3O_2$	317.34	2	95	129-131	C,71.78; H,4.76;N,13.24; O,10.08 found C,71.90,H,4.70; N,13.00; O,9.95

Table 2: Spectral data of compounds (11a-11g)

Compound No.	I.R. data (cm^{-1})	1H NMR data (ppm)
1Ia	3455 (N-H), 1569 (C=N)	7.83-7.33 (m,12H+1H) 5.28-5.24 (dd,1H,H_A) 3.94-3.87 (dd,1H,H_B) 3.63-3.57 (dd,1H,H_X)
1Ib	3319 (N-H), 1514 (C=N), 840 (C-Cl)	7.89-6.97 (m,11H+1H) 5.40-5.10 (dd,1H,H_A) 3.60-3.49 (dd,1H,H_B) 3.76 (dd,1H,H_X)
1Ic	3350 (N-H), 1540 (C=N),586 (C-Br)	7.78-7.33 (m,11H+1H) 6.10--5.92 (dd,1H,H_A) 3.70-3.60 (dd,1H,H_B) 3.29-3.24 (dd,1H,H_X)
1Id	3364 (N-H), 1580 (C=N),1236 (C-F)	7.77-7.10 (m,11H+1H) 5.87-5.82 (dd,1H,H_A) 3.91-3.83 (dd,1H,H_B) 3.27-3.21 (dd,1H,H_X)
1Ie	3210 (N-H), 1520 (C=N), 1160 (C-C)	7.54-7.30 (m,11H+1H) 5.21-5.15 (dd,1H,H_A) 3.56-3.45 (m,3H+1H) 3.38-3.25 (dd,1H,H_X)
1If	3220 (N-H), 1542 (C=N), 1260 (C-O-C) 1170 (C-C)	6.82-6.72 (m,11H+1H) 5.82-5.72 (dd,1H,H_A) 3.76-3.65 (m,3H+1H) 3.63-3.52 (dd,1H,H_X)
1Ig	3450 (N-H), 1560 (C=N), 1165 (C-C) 870 (C-N), 610 (C-N-O)	7.70-7.60 (m,11H+1H) 5.80-5.72 (dd,1H,H_A) 3.90-3.81 (dd,1H,H_B) 3.20-3.16 (dd,1H,H_X)

Table 3: Spectral data of compounds (1I1a-1I1g)

Compound No.	I.R. data(cm^{-1})	1H NMR data(ppm)
1IIa	3052 (C-H, Ar), 2962 (C-H, Ali), 1666 (C=O)	7.80-7.35 (m,12H+1H) 5.20-5.20 (dd,1H,H_A) 3.94-3.87 (dd,1H,H_B) 3.67-3.57 (dd,1H,H_X) 2.50 (s, 3H, COCH3)
I1Ib	3200 (N-H), 3049 (C-H,Ar), 2962(C-H,Ali), 1660 (C=O), 1510 (C=N), 850 (C-Cl)	7.89-6.97 (m,11H+1H) 5.48-5.30 (dd,1H,H_A) 3.65-3.49 (dd,1H,H_B) 3.56 (dd,1H,H_X) 2.56 (s, 3H, COCH3)
IIIc	3350 (N-H), 3042 (C-H,Ar), 2944 (C-H,Ali), 1655 (C=O), 1545 (C=N), 586 (C-Br)	7.88-7.63 (m,11H+1H) 6.30--5.99 (dd,1H,H_A) 3.60-3.50 (dd,1H,H_B) 3.20-3.14 (dd,1H,H_X) 2.46 (s, 3H,COCH3)
IIId	3360 (N-H), 3050 (C-H,Ar), 2968(C-H,Ali), 1656 (C=O),1589 (C=N),1230 (C-F)	7.77-7.10 (m,11H+1H) 5.87-5.82 (dd,1H,H_A) 3.90-3.80 (dd,1H,H_B) 3.25-3.21 (dd,1H,H_X) 2.59 (s, 3H, COCH3)
IIIe	3210 (N-H), 3052 (C-H,Ar), 2962 (C-H,Ali), 1666 (C=O), 1520 (C=N), 1160 (C-C)	7.50-7.30 (m,11H+1H) 5.11-5.05 (dd,1H,H_A) 3.56-3.45 (m,3H+1H) 3.30-3.25 (dd,1H,H_X) 2.48 (s, 3H,COCH3).
IIIf	3229 (N-H), 3039 (C-H,Ar), 2960 (C-H,Ali), 1655 (C=O), 1532 (C=N), 1265 (C-O-C) 1179 (C-C)	6.72-6.62 (m,11H+1H) 5.92-5.82 (dd,1H,H_A) 3.70-3.65 (m,3H+1H) 3.60-3.52 (dd,1H,H_X) 2.99 (s, 3H, COCH3)
IIIg	3450 (N-H), 3100 (C-H,Ar), 2990 (C-H,Ali), 1559 (C=O), 1555 (C=N), 1160 (C-C) 875 (C-N), 615 (C-N-O)	7.77-7.65 (m,11H+1H) 5.85-5.72 (dd,1H,H_A) 3.93-3.81 (dd,1H,H_B) 3.25-3.16 (dd,1H,H_X) 2.55 (s, 3H, COCH3)

Table 4: Anti antibacterial and antifungal activity of selected compounds

Compound	Concentration (µg/ml)	E.coli	S.aureus	A.niger	A.flavus	P.citrinum
IIa	200	-	13	15	19	-
	100	-	14	15	19	-
	50	-	11	9	14	-
IIb	200	-	10	18	18	23
	100	16	11	16	11	18
	50	-	-	14	18	10
IId	200	-	11	10	19	11
	100	15	12	9	21	19
	50	-	9	15	17	-
IIf	200	16	11	19	18	-
	100	14	-	17	16	-
	50	11	-	15	10	-
IIIa	200	8	10	11	10	11
	100	-	9	14	19	10
	50	-	8	18	11	-
IIIb	200	10	7	17	18	8
	100	-	6	18	15	9
	50	-	9	16	16	11
IIId	200	8	11	12	18	-
	100	8	9	11	16	9
	50	9	10	11	21	12
IIIf	200	10	-	16	11	11
	100	9	-	14	10	-
	50	8	9	10	16	9
Ciprofloxacin	50	19	22	xx	xx	Xx
Ketoconazole	50	Xx	xx	18	16	20

(-) no zone of inhibition, (xx) not tested

RESULTS AND DISCUSSION

The results of antimicrobial studies have shown that four compounds out of seven were found to possess antimicrobial activity against all tested micro-organisms. Results have shown that all the compounds possess mild antifungal activity against all four tested strains. The structures of the synthesized compounds were confirmed on the basis of spectral and elemental analysis. The formulas, melting point, yield of the compounds are listed in Table 1.

Compounds with electron releasing groups such as methoxy and compounds having pharmacophores such as chloro, fluoro, bromo groups and both these groups are present in one moiety exhibited mild to moderate antimicrobial activity. Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

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