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Synthesis and antimicrobial activity of some new N-acetyl pyrazoline derivatives from 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone

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ABSTRACT

The newly synthesized pyrazoline derivatives exhibited moderate to good antimicrobial activity respect to standard drugs. In present investigation, we report the synthesis of N-acetyl pyrazolines from chalcones and hydrazine hydrate using acetic acid for the reaction. These synthesized compounds were characterized on the basis of IR, ^{1}HNMR, Mass spectroscopic data. All synthesized new N-acetyl pyrazoline derivatives were screed for antibacterial and antifungal activity against different strains as compare to standard drugs Ciprofloxacin and Griseofulvin. Compound 3c and 3d were found to be active against selected antibacterial and antifungal strains.

KEYWORDS

N-acetyl pyrazoline;
1-(3,5-dibromo-2-hydroxy-4 methyl phenyl)ethanone;
Chalcone;
Antimicrobial Activity.

INTRODUCTION

The massive use of antibacterial drugs by mankind leads to a major problem i.e. drug resistance. The emergence of the drug resistance for major classes of antibacterial drugs is recognized by WHO and this became challenge for medicinal chemist to develop new class of antimicrobial agents. With increasing number of cases of pathogenic infection which suppress the immune system of human, medicinal chemist decided to move towards synthesis of small and novel molecule. Bromo acetophenone nucleus has received remarkable attention in medicinal science. There are many reports published in various journals regarding the derivatives of bromoacetophenone derivatives possess as antibacterial[1], anticancer[2], anti-HIV[3], anti-leishmanial[4] etc. The interest in research for chalcone by synthetic and medicinal chemist has been subject of reason due to its ease of synthesis, and variety of pharmacological activities[5]. Claisen-Schmidt condensation reaction is used for the synthesis of chalcone. Chalcones are intermediate for synthesis of various heterocycles like pyridine, pyrimidine, pyrazoline, isooxazoline, flavanoid, benzodiazepine, indazole, azetidinone etc. Pyrazoline and its derivatives are associated with diverse chemical and pharmacological properties such as antimicrobial[6], herbicidal[7], insecticidal, anti-inflammatory[8], anticonvulsant[9], antitumor[10], anti-oxidant etc. As far as the different pyrazoline isomers are concerned 2-pyrazoline derivatives have became the most frequently studied pyrazoline. The important features related to pharmacological activities of chalcone and pyrazoline and with our ongoing research strategy in the field of antimi-

crobial agents, we have undertaken the synthesis of chalcone and pyrazoline derivatives. From extensive literature survey we have identified that 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone and its derivatives are associated with many diverse therapeutic activity hence it is worthwhile to select as nucleus and synthesized antimicrobial activity and due to that, we have selected as nucleus and synthesized chalcones and its N-acetyl pyrazoline derivatives.

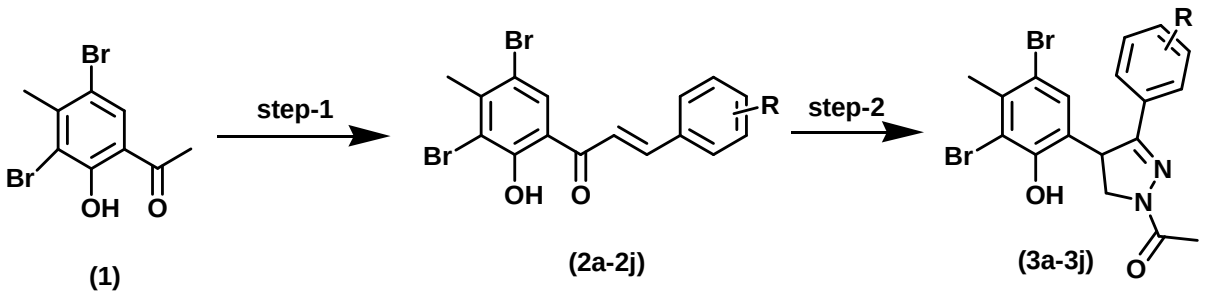
MATERIAL AND METHODS

The melting points were determined in open capillary tubes and are uncorrected.

IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and ^{1}H NMR spectra in DMSO- d_6 or in $CDCl_3$ (Chemical shift in δ ppm) on Bruker spectrometer (400 MHz) using TMS as an internal standard. The results are in good agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E. Merck G254) using.

Ethyl acetate : Hexane solvent system (7:3). Physical Constants and Spectral data of synthesized compounds (3a-3j) are recorded in TABLE – 1 and 2 respectively.

Reaction scheme



(1) (2a-2j) (3a-3j)

Reaction condition: (1) substituted aldehyde, 40% KOH, 25^{0}C, 18hrs, (R= different substitution.) (2) hydrazine hydrate, acetic acid, reflux, 6hrs

TABLE 1 : Physical constants 6-(1-acetyl-4-susbtituted phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2,4-dibromo-3-methylphenol (3a-3j)

Sr No.	Compound Name	R	Molecular Formula	Molecular Weight	Yield	Melting Point	R_f
1	3a	C_6H_5-	$C_{18}H_{16}Br_2N_2O_2$	452	71%	220^{0}C	0.54
2	3b	3-Br- C_6H_4-	$C_{18}H_{15}Br_3N_2O_2$	531	59%	190^{0}C	0.55
3	3c	2-Cl-C_6H_4-	$C_{18}H_{15}ClBr_2N_2O_2$	486	64%	160^{0}C	0.57
4	3d	4-Cl-C_6H_4-	$C_{18}H_{15}Br_2ClN_2O_2$	486	68%	198^{0}C	0.53
5	3e	4-N$(CH_3)_2$-C_6H_4-	$C_{20}H_{21}Br_2N_3O_2$	495	64%	154^{0}C	0.68
6	3f	4-OCH_3-C_6H_4	$C_{19}H_{18}Br_2N_2O_3$	482	77%	140^{0}C	0.74
7	3g	3,4-OCH_3-C_6H_4	$C_{20}H_{20}Br_2N_2O_4$	512	62%	170^{0}C	0.48
8	3h	2-NO_2-C_6H_4-	$C_{18}H_{15}Br_2N_3O_4$	497	55%	182^{0}C	0.32
9	3i	3-NO_2-C_6H_4-	$C_{18}H_{15}Br_2N_3O_4$	497	61%	198^{0}C	0.36
10	3j	4-OH-C_6H_4-	$C_{18}H_{16}Br_2N_2O_3$	468	72%	167^{0}C	0.57

General procedure for synthesis of (2E)-1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones (2a-2j)

To a well stirred solution of 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone (1) (0.01 mol) and substituted aldehyde (0.01 mol) in ethanol (25 ml), 40% KOH solution was added till the solution become basic. The reaction mixture was stirred for 24 hrs at 25^{0}C. Completion of reaction was monitored by TLC. Reaction mass was poured onto crushed ice, acidified using concentrated HCl. The product was filtered, dried in vacuo and crystallized using an appropriate solvent.

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General procedure for synthesis of 6-(1-acetyl-4-susbtituted phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2,4-dibromo-3-methylphenol (3a-3j)

To a solution of 2a-2j (0.01mol) in 25 ml ethanol, hydrazine hydrate (0.01mol) and glacial acetic acid (10 ml) were added and refluxed for 8 hrs. Completion of reaction was monitored by TLC. The reaction mass was poured onto crushed ice, filtered the product, dried in vacuo and crystallized using an appropriate solvent.

TABLE 2 : Spectroscopic data of 6-(1-acetyl-4-susbtituted phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2,4-dibromo-3-methylphenol (3a-3j)

Sr. No.	Compound No.	IR(KBr) ν(cm^{-1})	^{1}H NMR (δppm)
1	3a	1670 (C=O Str.), 1605 (C=N Str.), 1517 (C=C Str.), 760(C-Br)	2.32(3H,s,-COCH3), 2.82(3H,s, Ar-CH3), 4.15(1H,dd,pyrazoline-CH2), 4.28(1H, dd, pyrazoline -CHa), 4.35(1H,dd,-CHb), 6.92-7.31(5H,m,Ar-H), 8.06(1H,s, Ar-H)
2	3b	1668(C=O Str.), 1608(C=N Str.), 1518 (C=C Str.), 760 (C–Br)	2.32(3H,s,-COCH3), 2.82(3H,s-Ar-CH3), 4.11(1H,dd,-CH), 4.28(1H, dd, -CHa), 4.35(1H,dd,-CHb), 7.22(1H,m,Ar-H), 7.32(1H,m,Ar-H), 7.30(1H,m,Ar-H), 7.40(1H,m,Ar-H), 8.06(1H,s,Ar-H)
3	3c	1661 (C=O Str.), 1605 (C=N), 1520 (C=C Str.), 749 (C–Cl), 760(C-Br)	2.82(3H, s, Ar-CH3), 8.01(1H, s,Ar-H), 2.332(3H,s,-COCH3), 4.53(1H,dd,-CHa), 4.60(1H,dd, -CHb), 4.56(1H, dd,-CH),6.84(1, dd,Ar-H), 7.13(1H, dd, Ar-H), 6.99(1H, qd, Ar-H), 7.36(1H, dd, Ar-H)
4	3d	1661 (C=O Str.), 1605 (C=N), 1520 (C=C Str.), 760(C-Br)	2.82(3H, s, Ar-CH3), 8.06(1H, s, Ar-H), 2.32(3H,s,-COCH3), 4.28(1H, dd, -CHa), 4.35(1H, dd, -CHb), 4.15(1H, dd,-CH), 7.41(2H, dd, Ar-H), 7.18(2H,dd,Ar-H)
5	3e	1665 (C=O Str.), 1609(C=N Str.), 1518 (C=C Str.), 760(C-Br)	2.82(3H, s, Ar-CH3), 8.06(1H, s, Ar-H), 2.32(3H, s, -COCH3), 4.28(1H, dd, -CHa), 4.35(1H,dd, -CHb), 4.15(1H,dd,-CH), 6.72(2H,dd, Ar-H), 6.82(2H, dd, Ar-H), 2.90(6H, s, -N(CH_3)$_2$)
6	3f	1669 (C=O Str.), 1607(C=N Str.), 1510 (C=C), 1100(C-O)	2.82(3H,s,Ar-CH3), 8.06(1H,s, Ar-H), 2.32(3H,s,-COCH3), 4.28(1H,dd,-CHa), 4.35(1h,dd,-CHb), 4.15(1H,dd, -CH), 6.96(2H, dd, Ar-H), 7.12(2H, dd, Ar-H), 3.73(3H, s, -OCH3)
7	3g	1669 (C=O Str.), 1607(C=N Str.), 1510 (C=C), 1100(C-O)	2.82(3H,s,A r-CH3), 8.06(1H,s,Ar-H), 2.32(3H,s,-COCH3), 4.28(1H,dd,-CHa), 4.35(1H,dd,-CHb), 4.15(1H, dd,-CH), 3.82(6H, s, -OCH3), 6.23(1H,d,Ar-H), 6.51(1H,dd,Ar-H), 6.73(1H,dd,Ar-H)
8	3h	1669 (C=O Str.), 1607(C=N Str.), 1510 (C=C v), 1100(-NO2)	2.82(3H,s,Ar-CH3), 2.32(3H,s,-COCH3), 8.08(1H,s,Ar-H), 4.40(1H,dd,-CHa), 4.47(1H,dd,-CHb), 4.58(1H, dd, -CH), 6.98(1H,dd,Ar-H), 7.49(1H,td,Ar-H), 7.20(1H,td,Ar-H), 7.88(1H,dd,Ar-H)
9	3i	1669 (C=O Str.), 1607(C=N Str.), 1510 (C=C), 1100(-NO2)	2.82(3H,s,Ar-CH3), 2.32(3H,s,-COCH3), 4.28(1H,dd-CHa), 4.35(1H,dd,-CHb), 4.26(1H,m,-CH), 8.06(1H,s, Ar-H), 7.73(1H,t,Ar-H), 7.64(1H,qd,Ar-H), 7.48(1H,dd,Ar-H), 7.79(1H,qd,Ar-H)
10	3j	3400-3600(-OH), 1669 (C=O Str.), 1607(C=N Str.), 1510 (C=C)	2.82(3H,s,Ar-CH3), 8.06(1H,s,Ar-H), 2.32(3H,s,-COCH3), 4.25(1H,dd,-CHa),4.35(1H,dd,-CHb), 4.15(1H,dd,-CH), 9.32(1H,s,-OH), 6.67(2H,dd,Ar-H), 7.10(2H,dd,Ar-H)

Note : s (singlet), d(doublet),dd(double doublet), qd (quarteret of doublet), td(triplet of doublet), m(multiplet), Ar (Aryl)

Antimicrobial activity

The antimicrobial activity was assay by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains such *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and fungi strain *Aspergillus niger* at 40 μg/mL concentration. Standard drugs like Ciprofloxacin and Griseofulvin were used for the comparison purpose. The obtained results for compounds 3a-3j are recorded TABLE 3.

RESULTS AND DISCUSSION

N-acetyl pyrazolines have been synthesized by the reaction of (2E)-1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones (2a-2j) with hydrazine hydrate and acetic acid with 60 to 77% of good yield. N-acetyl pyrazolines having high melting points. The structure of compounds are confirmed by IR, NMR and Mass spectral data analysis. From the results of antimicrobial data, compounds 3c and 3d were active and compounds 3e and 3g were moderately ac-

tive against selected bacterial strains. While 3c,3d and 3h are shown good activity against fungi strain *A.niger*. From the structure activity relationship table, we found that phenyl ring substituted with chloro(3c) and flouro(3d) had shown an excellent result compare to standard drug Ciprofloxacin and Griseofulvin at concentration of 40µg/ml.

TABLE 3 : Antimicrobial screening results of compounds 3a-j

Compound No.	R	Zone of inhibition in mm				
		Antibacterial activity (%)				Antifungal activity % (%) activity
		S. aureus	*S.epidermisis*	*E.Coli*	*P.aeruginosa*	*A.niger*
3a	C_6H_5-	85	42	35	79	50
3b	3-Br C_6H_4-	65	65	88	82	64
3c	2-Cl-C_6H_4-	72	35	97	77	100
3d	4-Cl-C_6H_4-	79	90	74	94	83
3e	3-N$(CH_3)_2$-C_6H_4-	63	72	60	86	63
3f	4-OCH_3-C_6H_4-	78	52	72	53	67
3g	3,4-di OCH_3-C_6H_4-	65	70	85	77	50
3h	2-NO_2-C_6H_4-	68	46	38	62	83
3i	3-NO_2 -C_6H_4-	42	59	72	75	38
3j	4-OH-C_6H_4-	88	64	59	36	54
Ciprofloxacin	-	100	100	100	100	-
Greseofulvin	-	-	-	-	-	100

CONCLUSION

From the antimicrobial results, it worthwhile to say that, newly synthesized pyrazoline are showing good to moderate activity against bacterial and fungi strains From the structure activity relationship table and the results we found that, halogen substituted phenyl rings shows good activity as compare to other functional groups. This data give us idea to synthesized more compounds with different halogen substitution on the phenyl ring with different position, which may become good to excellent antimicrobial agents.

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