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

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ABSTRACT

The present article reports the synthesis and antimicrobial studies of new pyrazoline derivatives. The structures of newly synthesized compounds were confirmed by various spectroscopic techniques. The antimicrobial study was carried out by disc diffusion methods. The results of antimicrobial data reveals that compounds **(3c)**, **(3d)**, **(3e)** and **(3g)** were active selected bacterial strains, while **(3c)**,**(3d)** and **(3h)** were shown good activity against fungi strain A.niger.

KEYWORDS

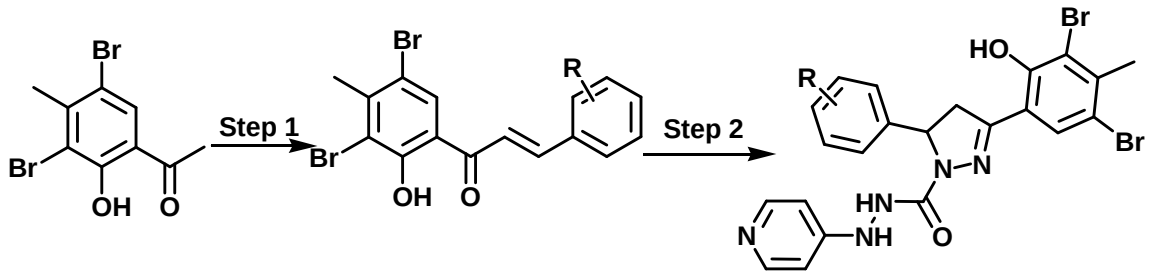
1-(3,5-Dibromo-2-hydroxy-4-methylphenyl)ethanone;
Pyrazoline, chalcone;
Antimicrobial activity.

INTRODUCTION

Multi Drug Resistant (MDR) is the major problem now a days associated with mankind health. The emergence of MDR, leads medicinal chemist to develop new class of antimicrobial agents, which are more superior with respect to current available therapies. Pyrazolines are on the most well known nitrogen-containing heterocycle which is associated with broad range of biological activities like antimicrobial[1], anticonvulsant[2], antiinflammatory[3] and antitumor[4] activities. Among different pyrazoline isomers 2-pyrazoline is most frequently studied pyrazoline. Various methods are reported in literature for synthesis of 2-pyrazoline derivatives, but the most common is reaction of α,β-unsaturated carbonyl system(chalcone) with hydrazine hydrate or hydrazine agents like phenyl hydrazine or phenyl carbohydrazide. Bromoacetophenone has received remarkable attention towards synthetic medicinal chemist. There were several reports published for the derivatives of bromoacetophenone which possess good antibacterial[5], anticancer[6], anti-HIV[7], anti-leishmanial[8] activities. Due to the biological activities associated with pyrazoline nucleus, and ease of synthesis from chalcone, we have decided to synthesized pyrazoline derivatives from chalcone of bromoacetophenone.

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 1H NMR spectra in DMSO-d_6 or in CDCl3 (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 synthesized compounds **(3a-3j)** are recorded in TABLE 1.



REACTION SCHEME

Reaction condition: (1) substituted aldehyde(R-CHO), 40% KOH, 25^{0}C, 18hrs, (R= different substitution) (2) pyridine-4-carbohydrazide, acetic acid, reflux, 6hrs

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

Sr No.	Com	R	Molecular Formula	M.W.	Yield	M.P^{0}C	R_f
1	3a	C_6H_5-	$C_{22}H_{17}Br_2N_3O_2$	515	71%	139	0.54
2	3b	3-Br- C_6H_4-	$C_{22}H_{16}Br_3N_3O_2$	558	59%	120	0.55
3	3c	2-Cl-C_6H_4-	$C_{22}H_{16}Br_2ClN_3O_2$	549	64%	133	0.57
4	3d	4-Cl-C_6H_4-	$C_{22}H_{16}Br_2ClN_3O_2$	549	68%	145	0.53
5	3e	4-$N(CH_3)_2$-C_6H_4-	$C_{24}H_{22}Br_2N_4O_2$	558	64%	137	0.68
6	3f	4-OCH_3-C_6H_4	$C_{23}H_{19}Br_2N_3O_3$	545	77%	124	0.74
7	3g	3,4-OCH_3-C_6H_4	$C_{24}H_{21}Br_2N_3O_4$	575	62%	118	0.48
8	3h	2-NO_2-C_6H_4-	$C_{22}H_{16}Br_2N_4O_4$	560	55%	115	0.32
9	3i	3-NO_2-C_6H_4-	$C_{22}H_{16}Br_2N_4O_4$	560	61%	135	0.36
10	3j	3-OC_6H_5-C_6H_4-	$C_{28}H_{21}Br_2N_3O_3$	607	72%	90	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.

General procedure for synthesis of 2,4-Dibromo-6-(1-isonicotinoyl-5-phenyl-4,5- dihydro-1H -pyrazol-3-yl)-3-methyl phenols (3a-3j)

To a solution of 2a-2j (0.01mol) in 25 ml ethanol, pyridine-4-carbohydrazide (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.

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 are recorded TABLE 2.

Spectroscopic data of 2,4-Dibromo-6-(1-isonicotinoyl-5-phenyl-4,5- dihydro-1H -pyrazol-3-yl)-3-methyl phenols (3a-3j)

(1) 2,4-Dibromo-6-(1-isonicotinoyl-5-phenyl-4,5-dihydro-1H-pyrazol-3- yl)-3-methylphenol (3a)

IR(KBr)cm^{-1} 3513(-OH str.), 3068(C-H str.), 2862(C-H str.),1644(C=O str.), 1592(C=N), 1568(C=C), 596(C-Br) 1H-NMR($CDCl_3$) δppm: 2.52(3H,s,-CH_3), 3.23(1H,dd,-CH_a), 3.79 (1H,dd,-CH_b), 5.81(1H,m,-CH), 7.19-7.44(5H,m,Ar-H), 8.06(1H,s,Ar-H), 7.91 (2H,m,Py-H),8.90(2H,m,Py-H), 8.15(1H,s,-OH) MS (ESI): m/z = 516[M+]

(2) 2,4-Dibromo-6-[5-(3-bromophenyl)-1-isonicotinoyl-4,5-dihydro-1H-pyrazol-3-yl]-3-methylphenol (3b)

IR(KBr)cm^{-1} 3500(-OH str.), 3050(C-H str.), 2850(C-H str.), 1640(C=O str.), 1585(C=N), 1530(C=C), 500(C-Br) 1H-NMR($CDCl_3$) δppm:2.50(3H,s,-CH_3), 3.24(1H,dd,-CH_a), 3.59 (1H,dd,-CH_b), 5.78(1H,m,-CH),7.13-7.61(4H,m,Ar-H),8.06(1H,smAr-H),7.95(2H,m,Py-H), 8.95(2H,m,Py-H), 8.2(1H,s,-OH) MS (ESI): m/z = 559[M+]

(3) 2,4-Dibromo-6-[5-(2-chlorophenyl)-1-isonicotinoyl-4,5-dihydro-1H- pyrazol-3-yl]-3-methylphenol (3c)

IR(KBr)cm^{-1} 3430(-OH str.), 3065 (C-H str.), 2870(C-H str.), 1650(C=O str.), 1590(C=N), 1560(C=C), 585(C-Br), 540(C-Cl) 1H-NMR($CDCl_3$)δppm: 2.50(3H,s,-CH_3), 3.03(1H,dd,-CH_a), 3.62 (1H,dd,-CH_b),5.81(1H,m,-CH),6.97-7.34(4H,m,Ar-H),8.06(1H,smAr-H),7.91(2H,m,Py-H), 8.90(2H,m,Py-H), 8.2 (1H,s,-OH) MS (ESI): m/z = 550 [M+]

(4) 2,4-Dibromo-6-[5-(4-chlorophenyl)-1-isonicotinoyl-4,5-dihydro-1H- pyrazol-3-yl]-3-methylphenol (3d)

IR(KBr)cm^{-1} 3465 (-OH str.), 3072 (C-H str.), 2852(C-H str.), 1668(C=O str.), 1606(C=N), 1523(C=C), 651(C-Br), 511(C-Cl) 1H-NMR($CDCl_3$)δppm: 2.52(3H,s,-CH_3), 3.07(1H,dd,-CH_a), 3.66 (1H,dd,-CH_b),5.84(1H,m,-CH),6.87-7.34(4H,m,Ar-H),8.11(1H,smAr-H),7.94(2H,m,Py-H), 8.92(2H,m,Py-H), 8.4 (1H,s,-OH) MS (ESI): m/z = 550 [M+]

(5) 2,4-Dibromo-6-{5-[4-(dimethylamino)phenyl]-1-isonicotinoyl-4,5- dihydro-1H-pyrazol-3-yl}-3-methylphenol (3e)

IR(KBr)cm^{-1} 3520(-OH str.), 3070(C-H str.), 2950(C-H str.), 1645(C=O str.), 1590(C=N), 1566(C=C), 592(C-Br) 1H-NMR($CDCl_3$)δppm: 2.52(3H,s,-CH_3), 3.96(6H,m,-$N(CH_3)_2$) 3.23(1H,dd,-CH_a), 3.75(1H,dd,-CH_b), 5.82(1H,m,-CH),7.2(2H,dd,Ar-H),7.25(2H,dd,Ar-H), 8.06 (1H,smAr-H),7.91(2H,m,Py-H), 8.90(2H,m,Py-H), 8.15 (1H,s,-OH) MS (ESI): m/z = 559[M+]

(6) 2,4-Dibromo-6-[1-isonicotinoyl-5-(4-methoxyphenyl)-4,5-dihydro- 1H-pyrazol-3-yl]-3-methylphenol (3f)

IR(KBr)cm^{-1} 3500(-OH str.), 3030(C-H str.), 2902(C-H str.),1655 (C=O str.), 1590(C=N), 1586(C=C), 1375(C-O-C), 610(C-Br), 1H-NMR($CDCl_3$) δppm: 2.42(3H,s,-CH_3), 3.86(3H,s,-OCH_3) 3.03 (1H,dd,-CHa), 3.59(1H,dd,-CH_b),5.81(1H,m,-CH),7.07(2H,dd,Ar-H), 6.69 (2H,dd,Ar-H),8.06(1H,sm, Ar- H),7.82 (2H,m,Py-H), 8.85 (2H, m, Py-H), 8.2 (1H,s,-OH) MS (ESI): m/z = 546 [M+]

(7) 2,4-Dibromo-6-[5-(3,4-dimethoxyphenyl)-1-isonicotinoyl-4,5- dihydro-1H-pyrazol-3-yl]-3-methylphenol (3g)

IR(KBr)cm^{-1}3480(-OH str.), 3025(C-H str.), 2890(C-H str.),1640(C=O str.), 1590(C=N), 1575(C=C), 1378(C-O-C), 615(C-Br), 1H-NMR($CDCl_3$)δppm: 2.45(3H,s,-CH_3), 3.96(6H,m,-$O(CH_3)_2$), 3.08(1H,dd,-CH_a),3.65(1H,dd,-CH_b),5.86(1H,m,-CH), 6.86(3H,m, Ar-H),7.91(2H,m,Py-H), 8.92 (2H, m, Py-H),8.5(1H,s,-OH) MS (ESI): m/z = 576[M+]

(8) 2,4-Dibromo-6-[1-isonicotinoyl-5-(2-nitrophenyl)-4,5-dihydro-1H- pyrazol-3-yl]-3-methylphenol (3h)

Yield: 55%, M. P. : 115^{0}C; TLC *Rf* value: 0.32 ; Solvent system: Hexane: Ethyl acetate, (6:4);1H-NMR($CDCl_3$) δppm: 2.62(3H,s,-CH_3), 3.24 (1H,dd,-CH_a), 3.59(1H,dd,-CH_b), 5.81(1H,m,-CH), 7.20-7.86(5H,m, Ar-H),7.91(2H,m,Py-H), 8.90 (2H, m, Py-H), 8.34 (1H,s,-OH) IR(KBr)cm^{-1} 3472(-OH str.), 3020(C-H str.), 2880(C-H str.),1665(C=O str.), 1590(C=N), 1545(C=C), 1530(N=O), 680(C-Br) MS (ESI): m/z = 561 [M+]

(9) 2,4-Dibromo-6-[1-isonicotinoyl-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazol-3 yl]-3-

methylphenol (3i)

IR(KBr)cm^{-1} 3497(-OH str.), 3030(C-H str.), 2890(C-H str.), 1650(C=O str.), 1590(C=N), 1585(C=C), 1395(C-O-C), 690(C-Br), 1H-NMR($CDCl_3$)δppm: 2.64(3H,s,-CH_3), 3.26 (1H,dd,-CH_a), 3.58(1H,dd,-CH_b), 5.82(1H,m,-CH), 7.18-7.84(5H,m, Ar-H),7.88(2H,m,Py-H), 8.85 (2H, m, Py-H), 8.36 (1H,s,-OH) MS (ESI): m/z = 561[M+]

TABLE 2 : Antimicrobial screening results of compounds 3a-j

Comp.	R	Antibacterial activity (%)				Antifungal activity (%)
		S.aureus	*S.epider*	*E.Coli*	*P.aerug*	*A.niger*
3a	C_6H_5-	83	42	35	81	51
3b	3-Br-C_6H_4-	63	66	89	83	65
3c	2-Cl-C_6H_4-	70	34	92	75	90
3d	4-Cl-C_6H_4-	81	91	72	92	81
3e	3-N(CH_3)-C_6H_4-	6-0	72	65	83	65
3f	4-OCH_3-C_6H_4-	77	55	73	55	61
3g	3,4-di OCH_3-C_6H_4-	64	75	85	71	45
3h	2-NO_2-C_6H_4-	69	47	39	62	75
3i	3-NO_2 -C_6H_4-	44	62	72	75	38
3j	3-OC_6H_5-C_6H_4-	88	64	55	36	51
Cipro.	-	100	100	100	100	-
Greseo.	-	-	-	-	-	100

S.aureus- Streptococcus aureus, S.epidermis- Streptococcus epidermis, E.Coli- Escherichia Coli, P.aerug- Pseudomonas aeruginosa, A.niger- Aspergillus niger, Cipro- Ciprofloxacin, Greseo.- Griseofulvin

(10) 2,4-Dibromo-6-[1-isonicotinoyl-5-(3-phenoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-3-methylphenol (3j)

IR(KBr)cm^{-1} 3515(-OH str.),3029(C-H str.), 2890(C-H str.),1650(C=O str.), 1590(C=N), 1585(C=C), 1395(C-O-C), 590(C-Br), 1H-NMR($CDCl_3$) δppm: 2.52(3H,s,-CH_3), 3.23 (1H,dd,-CH_a), 3.55(1H,dd,-CH_b), 5.75(1H,m,-CH), 6.74-7.13(5H,m,Ar-H), 7.20-7.43(5H,m,Ar-H), 7.90(2H,m,Py-H), 8.92 (2H, m, Py-H), 8.4(1H,s,-OH), MS (ESI): m/z = 608[M+]

RESULTS AND DISCUSSION

N-substituted pyrazolines **(3a-3j)** 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 pyridine-4-carbohydrazide in acetic acid in reflux condition to get the desired product with 60 to 77% of good yield. The structures 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 active 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, 3d) had shown an excellent result compare to standard drug Ciprofloxacin and Griseofulvin at concentration of 40μg/ml.

CONCLUSION

From the antimicrobial data, it is worthwhile to say that, newly synthesized N-substituted pyrazoline derivatives 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 results give us initiative to synthesize 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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