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Original Article

Synthesis and Evaluation of Some New 3-(2'-hydroxy-phenyl)-5-(4'-substituted-phenyl)-2-Pyrazoline-N[1]-Carboxaldehydes as Antimicrobial Agents

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ABSTRACT

In the present investigation, a series of some novel 3-[substituted-2-hydroxy-phenyl]-5-(4'-dimethylamino-phenyl)-2-pyrazoline-1-carboxaldehydes **(2a-j)** have been synthesized by the treatment of 1-(substituted-2-hydroxy-phenyl)-3-(4'-dimethylamino-phenyl)-prop-2-en-1-one (chalcones) **(1a-j)** with hydrazine hydrate in hot formic acid using ethanol solvent by conventional method. In 85-95% yield with high purity, the structure of newly synthesized compounds was confirmed by the IR, ^{1}H NMR and Mass spectral analysis. All these newly synthesized compounds were evaluated for their *in vitro* antimicrobial activity. Most of the compounds showed potent activity.

Keywords: Halohydroxychalcones, hydrazine hydrae, formic acid, 2-pyrazoline-1-carboxaldehyde, antimicrobial activity.

INTRODUCTION

Pyrazoline is a class of compounds, which has many applications in different field. One of the methods for the synthesis of such compounds from α, β-unsaturated carbonyl compounds (chalcones) by the cyclization with hydrazine and substituted hydrazine hydrate. Pyrazoline and their derivatives are considered to be important for drugs and agricultural chemical[1]. Some substituted pyrazolines and their derivatives have been reported to possess several interesting biological activities such as Antimicrobial[2-4], Anti-inflammatory[5-6], Antitumor[7], Antioxidant[8], Antimalarial[9], Antidepressant[10], Anticonvulsant[11] and Antihistaminic[12] activities. Some of these compounds have also Antiviral, Analgesic, Antiamoebic, hypotensive, Anticancer and molluscicidal properties[13-18]. But to our knowledge very few synthetic pyrazoline

derivatives have been reported with halogens as substituent. Hence it was thought to be fruitful to synthesise and assess such new compounds for their antimicrobial properties.

We report here the synthesis of some novel halogen substituted pyrazoline derivatives **(2a-j)** from corresponding halohydroxychalcones **(1a-j)** and also evaluated them for their antimicrobial activities. In the present work substituted halohydroxychalcones were cyclized in the presence of hydrazine hydrate and hot formic acid to give 2-pyrazoline-1-carboxaldehyde derivatives. 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.

MATERIALS AND METHODS

All the melting points were determined by open capillary method and are uncorrected. The IR spectra in KBr were recorded on Shimadzu Spectrophotometer and 1H NMR spectra were recorded in DMSO on Avance 300 MHz Spectrometer using TMS as internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplet). Purity of the compounds is checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent in the ration of (6:4 v/v).

General procedure for the synthesis of 3-(substituted-2-hydroxy-phenyl)-5-(4'-substituted -phenyl)-2-pyrazole-1-carboxaldehydes (2a-j)

A mixture of substituted 2'-hydroxy chalcone (0.001mol) hydrazine hydrate (0.002mol) in 10ml ethanol was refluxed for 3 hrs. Then add 2ml of hot formic acid (0.10mol) in reaction mixture, continue refluxing further 2 hrs. After completion of reaction (checked by TLC), the reaction mixture was cooled and poured into ice cold water. The separated solid product was filtered, washed with cold water, dried and then recrystalized from ethanol to give corresponding 3-(substituted-2-hydroxy-phenyl)-5-(4'-dimethylamino-phenyl)-2-pyrazole-1-carboxaldehydes **(2a-j)** derivatives. The physical data of newly synthesized compounds is mentioned in **table 1.**

RESULTS AND DISCUSSION

In the present work, a series of novel halogen substituted pyrazoline **(2a-j)** were synthesized by cyclization of corresponding hydroxychalcones **(1a-j).** All these product of pyrazoline derivatives didn't give pink coloration with concentrated H2SO4 solution. The structures of newly synthesized compounds have been confirmed by IR, ^{1}H NMR and Mass spectral data. The IR spectrum of compound **2c** exhibited peaks due to group CHO, >C=N, OH and >C=C at 1606 cm^{-1} 1530 cm^{-1} 3097 cm^{-1} and 1442 cm^{-1} respectively. Its ^{1}H NMR spectrum showed pairs of doublets of doublet in the region δ3.3-3.4 (dd, 1H, H_A) and δ 3.7-3.9 (dd, 1H, H_B) respectively, due to germinal and vicinal coupling of CH_2 protons of the pyrazoline ring. Further, the CH proton of the ring resonated as a doublet of doublets at δ 5.3-5.5 (d, 1H, H_X) due to vicinal coupling with the two non-equivalent proton of the methylene group at position 4 of the pyrazoline ring, the presence of single peak at δ 8.50-9.20 (s, 1H, N-CHO), absence of singlet at δ 7.0-7.5 due to (N-H) and singlet at δ 11.10-12.50 due to proton of ortho hydroxyl group. These observations are in agreement with the spectral data reported by Priya Gothwal et al.[19] and Birbal Bajia *et al*[20].

All these newly synthesized compounds were screened for their

antibacterial activity against the selected four different selected pathogens, such as *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis*. The compounds, **2b, 2f,** and **2g** showed maximum activity against *E. coli*. All the compounds of 2-pyrazoline-1-carboxaldehyde do not biologically active against *S. typhi*.. The compounds **2c**, **2d, 2g** and **2h** showed moderate activity against *B. subtilis*, while **2a**, **2b, 2i** and **2i** showed significant activity in comparison with standard drugs (Penicilin).The more electronegative Chlorine atom substituted in pyrazoline 1-caboxaldehyde compound **2a** and **2f** are significant antibacterial activity against E. coli, as comparison with standard drug (peniciline). All the newly synthesized compounds were screened for their antifungal activity against the selected four different selected pathogens *Aspergillusnige, penicilliumchrysogenum, Fusariummoneliforme and Aspergillusflavus* In antifungal activity some compounds showed moderate activity. The presence of formyl pyrazoline moiety, the more electronegative atom substituent's particularly chloro, bromo, iodo, hydroxy and methyl groups in the phenyl ring of pyrazoline 1-caboxaldehyde compounds may be responsible for increases antimicrobial activity. The antimicrobial screening results are complementary to the earlier findings Seham Y. Hassan[21] and Jayanti Rajora *et al*[22]. for these types of compounds.

Spectroscopic data of synthesized compounds

3-(5-chloro-3-Bromo-2-hydroxy-phenyl)-5-(4'-(dimethylamino-phenyl)-4, 5-dihydro-2-pyrazoline-1-carboxaldehyde (2c)

IR (KBr): 1606 cm^{-1} (C=O), 3197 cm^{-1} (Ar-OH), 1530cm^{-1} (C=N), 1261 cm^{-1} (C-N);^{1}HNMR (DMSO): δ 2.85 (s, 6H, $(CH_3)_2$), δ 3.35 (dd, 1H, H_A), δ 3.90 (dd, 1H, H_B), δ 5.40 (d, 1H, H_X), δ 6.61-7.80 (m, 6H, Ar-H), δ 11.0 (s, 1H, OH), δ 8.95 (s, 1H, N-CHO), M.S. (m/z): = 423 [M+1]

3-(5, 3-dibromo-2-hydroxy-phenyl)-5-(4'-(dimethylamino-phenyl)-4, 5-dihydro-2-pyrazoline-1-carboxaldehyde (2d)

IR (KBr): 1608 cm^{-1} (C=O), 3213 cm^{-1} (Ar-OH), 1516 cm^{-1} (C=N), 1257 cm^{-1} (C-N);^{1}H NMR (DMSO): δ 2.86 (s, 6H, $(CH_3)_2$) δ 3.34 (dd, 1H, H_A), δ 3.89 (dd, 1H, H_B), δ5.41 (t, 1H, H_X), δ 6.6-7.9 (m, 6H, Ar-H), δ 11.0 (s, 1H, OH), δ 9.0 (s, 1H, N-CHO), M.S. (m/z): = 467 [M+1]

3-(5-bromo-2-hydroxy-phenyl)-5-(4'-(dimethylamino-phenyl)-4, 5-dihydro-2-pyrazoline-1-carboxaldehyde (2e)

IR (KBr): 1609 cm^{-1} (C=O), 3212 cm^{-1} (Ar-OH) 1528 cm^{-1} (C=N) 1220 cm^{-1} (C-N);^{1}H NMR (DMSO): δ 2.90 (s, 6H, $(CH_3)_2$), δ 3.32 (dd, 1H, H_A), δ 3.91 (dd, 1H, H_B), δ 5.45 (t, 1H, H_X), δ 6.60-7.9 (m, 6H, Ar-H), δ 11.01 (s, 1H, OH), δ 8.94 (s, 1H, N-CHO), M.S. (m/z): =388 [M+1]

3-(5-chloro-2-hydroxy-phenyl)-5-(4'-(dimethylamino-phenyl)-4, 5-dihydro-2-pyrazoline-1-carboxaldehyde (2f)

IR (KBr): 1608 cm^{-1} (C=O), 3221 cm^{-1} (Ar-OH) 1523 cm^{-1} (C=N) 1227 cm^{-1} (C-N);^{1}H NMR (DMSO): δ 2.85 (s, 6H, $(CH_3)_2$), δ 3.30 (dd,1H, H_A), δ 3.91 (dd,1H, H_B), δ 5.55 (t,1H, H_X), δ 6.65-8.0 (m, 6H, Ar-H), δ 11.05 (s, 1H, OH), δ 8.99 (s, 1H, N-CHO) M.S. (m/z): =343 [M+1]

ANTIMICROBIAL ACTIVITY

All the newly synthesized pyrazoline derivatives were assessed for their antibacterial and antifungal activities against different strains of bacteria such as E. coli, S. typhi, S. aureus and B. subtilis and fungi like Aspergillus niger, Penicillium chrysogenum, Fusariummoneliforme and Aspergillus flavus by using Cup Plate Method[23] at a concentration of 100µg/ml. Solvent DMSO

was used as solvent control. Standard drugs like Peniciline and Greseofulvin were used for comparison purpose. The biological data of compounds as shown in table 2.The chlorine substituted compounds, 2a, and 2f, showed significant activity against E.coli. All the compounds of 2-pyrazoline-1-carboxaldehyde do not biologically active against S. typhi. The compounds 2c, 2d, 2e and 2f showed maximum activity against B. subtilis as comparison with (penicilline) standard drug while 2a, 2b, 2g and 2i showed moderate activity. The more electronegative chlorine atom substituted in pyrazoline 1-caboxaldehyde compounds 2a, 2b, 2f, and 2h showed maximum antibacterial activity against S. aureus. The compounds 2c, 2d, and 2g exhibited moderate antibacterial activity against S. aureus. The results revealed that the newly synthesized compounds exhibited moderats to good antifungal activity as comparison with (Greseofulvinas) standard drugs against four different antifungal pathogen such as Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergillus flavus.

CONCLUSION

The present research work involved the newly synthesis of halogen substituted pyrazoline 1-caboxaldehyde compounds (**2a-j**) were screened for their *in vitro* antimicrobial activity. It is concluded from the result that halogen group substituted on the pyrazoline 1-caboxaldehyde compounds ring are responsible for the enhancement of the antibacterial activity. The chloro compounds **2a**, 2b, 2c, 2f, 2g and **2h** exhibited significant antibacterial activity against three pathogenic organisms. In the antifungal activity the halogen substituted compounds displayed potent activity against four fungi. From the results it is evident that most of chloro, bromo, iodo, hydroxyl and methyl groups exhibited good antimicrobial activity.

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Table 1. Physical data of N^1-carboxaldehyde-2-pyrazoline derivatives (2a-j)

Sr.No.	Entry	R_1	R_2	R_3	Molecular Formula	Yield (%)	M.P.^{0}C
1	**2a**	Cl	H	Cl	$C_{18}H_{17}O_2Cl_2N_3$	92	174
2	**2b**	I	H	Cl	$C_{18}H_{17}O_2ClIN_3$	90	162
3	**2c**	Br	H	Cl	$C_{18}H_{17}O_2BrClN_3$	88	185
4	**2d**	Br	H	Br	$C_{18}H_{17}O_2Br_2N_3$	94	192
5	**2e**	H	H	Br	$C_{18}H_{18}O_2BrN_3$	86	170
6	**2f**	H	H	Cl	$C_{18}H_{18}O_2ClN_3$	90	171
7	**2g**	Br	CH_3	Cl	$C_{19}H_{19}O_2BrClN_3$	91	172
8	**2h**	I	CH_3	Cl	$C_{19}H_{19}O_2IClN_3$	92	167
9	**2i**	Cl	H	CH_3	$C_{19}H_{20}O_2BrN_3$	88	153
10	**2j**	Cl	H	Br	$C_{18}H_{17}O_2BrIN_3$	85	172

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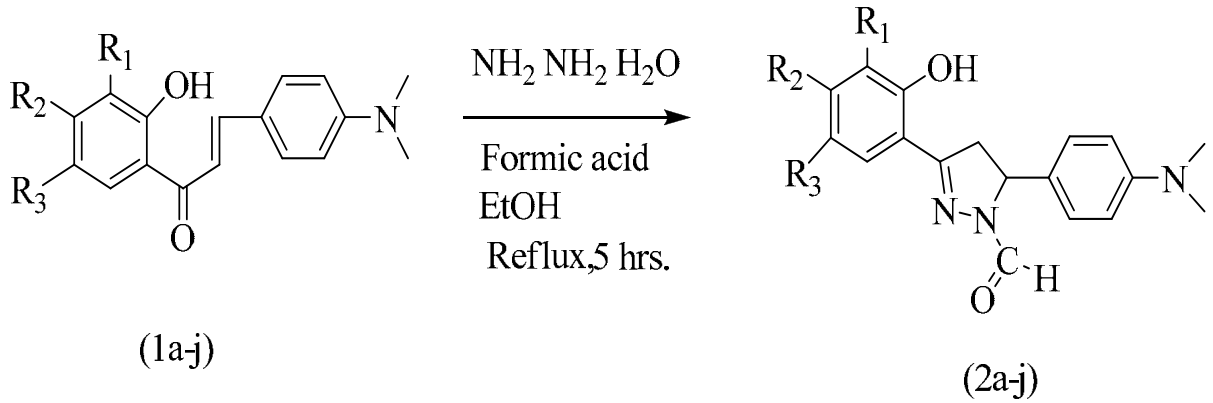
Table 2. Antimicrobial activity of N-carboxaldehyde-2-pyrazoline derivatives (2a-j)

		Bacteria (Zone of Inhibition in mm				Fungi (Zone of Inhibition in mm)			
Sr.No.	Product	*Escherichia coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*	*Aspergillus niger*	*penicilliumchrysogenum*	*Fusarium monelifo rme*	*Aspergillusflavus*
1	**2a**	14	--	22	12	RG	-ve	-ve	-ve
2	**2b**	13	--	23	11	-ve	-ve	-ve	-ve
3	**2c**	12	--	17	13	RG	-ve	-ve	-ve
4	**2d**	11	--	18	14	-ve	RG	-ve	-ve
5	**2e**	12	--	22	15	RG	RG	-ve	-ve
6	**2f**	14	--	21	16	RG	RG	-ve	-ve
7	**2g**	13	--	17	12	-ve	-ve	RG	-ve
8	**2h**	12	--	18	13	RG	-ve	-ve	-ve
9	**2i**	11	--	24	12	-ve	RG	RG	-ve
10	**2j**	11	--	21	12	RG	RG	-ve	-ve
+ve Conrol DMSO		-ve	-ve	-ve	-ve	+ve	+ve	+ve	+ve
Penicillin		12	20	34	22	X	X	X	X
-veControl (Griseofulvin)		X	X	X	X	-ve	-ve	-ve	-ve

Where -- = No Antibacterial activity, RG= Reduced Growth (Moderate Activity)
-ve = Growth (Antifungal Activity Observed)



Scheme-1 Synthesis of N-carboxaldehyde-2-pyrazoline derivatives