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Synthesis and Antimicrobial Screening of New Pyrazolines Derived From Chalcones of Vanillin Analog

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ABSTRACT
In present study the new series of 3-(Aryl)-5-[4-(2, 4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4, 5-dihydro pyrazoline (2a-k) and 3-(Aryl)-5-[4-(2, 4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4, 5-dihydroacetyl pyrazoline (3a-k) derivatives were synthesized from various substituted 3-Methoxy-4-(2, 4-Dichlorophenyl methoxy) chalcones (1a-k). The new chalcones were synthesized using various acetophenones with newly synthesized aldehyde of vanillin analog by Claisen-Schmidt condensation. Characterization of pyrazoline derivatives have been established on the basis of IR, NMR, Mass and elemental analyses. The derivatives were screened for their *in vitro* antimicrobial Screening.

Keywords: Vanillin, Chalcone, Pyrazoline, Antimicrobial Screening.

INTRODUCTION

In recent times diseases due to antimicrobial infection have been reported to increase considerably worldwide and one of the major causes for that is suppressed immunity. Suppression of immunity has various malignancy,
immunosuppressive HIV-infection, surgeries and old age are major causes for catching microbial infections. The situation is further worsened by increasing incidence of microbial resistance to the majority of antibiotics available today. Antimicrobial resistance is a major disquiet and danger to the public health and warrants development of new and effective antibiotics to conflict drug resistance. [1] Currently available antifungal agents in the market are fewer in number and majority of them have number of disadvantages like toxicity, spectrum, lack of oral formulations, few drug targets, pharmacokinetics and higher cost of the drugs. [2]

Most of the heterocycles are well known due to their biological importance. Out of these pyrazolines are the five member heterocyclic compounds containing two nitrogen atoms, shows variety of biological applications such as anticonvulsant [3], diuretic [4], fungicidal [5], antitubercular [6], antinociceptive [7], anticonvulsant [8], anti-inflammatory [9]antimicrobial . [10-11] The pyrazoline ring contains N–N bond linkage and acetylpyrazoline ring contains N-N-CO moiety which is considered to be the key factor in their biological actions. In natural compounds having N–N bonds is rare because these bonds are constructed with a great difficulty by living organism. [12-13] The literature survey shows interesting biological activities of pyrazoline derivatives therefore; our interest to synthesize the new pyrazoline derivatives may have good biological importance. Among the methods employed in synthesis of pyrazolines, the standard procedure for the

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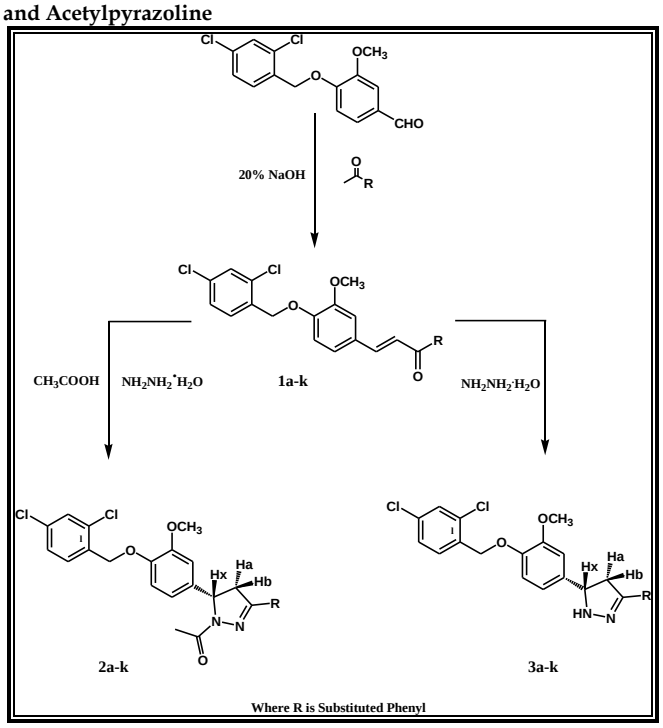
preparation of the pyrazolines involves the cyclocondensation of α, β-unsaturated compound (chalcone) and hydrazine derivatives. [14-18] Therefore we reported here the synthesis of some new pyrazolines for the first time using chalcones of vanillin analog [19] using glacial acetic acid as catalyst and methanol as a solvent media. The reaction is carried out in refluxing condition.

Scheme 1: General Reaction Scheme for Synthesis of Pyrazoline and Acetylpyrazoline



MATERIAL AND METHODS

The materials like hydrazine hydrate (Sigma Aldrich), glacial acetic acid (Renchem) and methanol (Renchem) are of analytical grade; used without further purification. Melting points of synthesized compounds were taken in open capillary method and are uncorrected. Elemental analyses (% of C, H & N) of the compounds were performed on a model 2400 Perkin–Elmer elemental analyzer. Infrared spectra (4000–400 cm^{-1}, using KBr discs) of the samples were recorded on Shimadzu-435 Spectrophotometer and ^1H NMR spectra on Bruker Advance 400MHz spectrometer with $CDCl_3$ as a solvent and tetramethyl silane (TMS) as internal standard. The chemical shift was measured in parts per million (ppm). The antimicrobial activity of purified compounds was done by Cup-plate agar diffusion method. Progress of the reaction and purity of the compounds is checked by thin layer chromatography (TLC) plates.

Experimental

Synthesis of Chalcone

General procedure for the synthesis of 3-Methoxy-4-(2, 4-dichlorophenylmethoxy) chalcones (1a-k)

To the alcoholic solution of 3-methoxy-4-(2, 4-Dichlorophenylmethoxy)benzaldehyde (3.11, 0.01 mol, 25 mL) was stirred with different substituted acetophenones (0.01 mol) and 20%(w/v) NaOH (5mL) for 12-17 h. Keep this reaction mixture aside for overnight, separated light green to brown color product was filtered and recrystallized from ethanol.

Synthesis of pyrazolines (2a-k)

General procedure for the synthesis of 3-(Aryl)-5-[4-(2, 4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4, 5-dihydropyrazoline

A mixture of 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy)chalcone(**1a-k**)(0.01 mol) and hydrazine hydrate (2.42 mL, 0.05 mol) was refluxed for 8-10 h in methanol in presence of glacial acetic acid as a catalyst. The solid product was separated out on cooling at room temperature, filtered and crystallized from ethanol.

Synthesis of Acetylpyrazolines (3a-k)

Synthesis of 3-(Aryl)-5-[4-(2, 4-Dichlorophenyl methoxy)-3-methoxyphenyl]-4, 5-dihydroacetyl pyrazoline

A mixture of 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy) chalcone (0.01mol) and hydrazine hydrate (2.42 mL, 0.05 mol) was refluxed for 5-7 h in glacial acetic acid as a solvent. The solid product was separated out on cooling at room temperature, filtered it and crystallized from ethanol.

Spectral Data of Synthesized Compounds

3-Methoxy-4-(2, 4-Dichlorophenylmethoxy)-4′-methoxy chalcone (1h): IR (KBr, cm^{-1}): ν 1652(-CO-CH=CH-), 1241(Ar-O-CH_2), 672(-C-Cl); ^1H-NMR ($CDCl_3$): δ 5.19(s, 2H, -O-CH_2-), 3.87(s, 3H, -OCH_3), 7.80-7.87 (d, 1H, 15.6Hz, =CH-Ar), 7.70-7.75(d, 1H, 16.4Hz, -CO-CH=), 7.13-8.12(m, 11H, Ar-H); Mass (m/z): 443(M^+).

3-(4-bromophenyl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydropyrazoline(2b): IR (KBr, cm^{-1}): 3441(-NH-), 1595 (C=N), 690 (C-Cl), 1257 (Ar-O-CH_2); ^1H NMR (DMSO-d_6): 5.19 (s, 2H,-O-CH_2-), 3.91 (s, 3H, -OCH_3), 3.02(1H, dd, -CH_A, Pyrazoline), 3.41 (1H, dd, -CH_B, Pyrazoline), 4.92(1H, dd, -CH_X, Pyrazoline), 6.79-7.56 (10H, m, Ar-H); Mass (m/z): 504(M^+).

3-(4-chloroophenyl)-5-[4-(2, 4-Dichlorophenyl methoxy)-3-methoxyphenyl]-4, 5-dihydropyrazoline (2c): IR (KBr, cm^{-1}):3438(-NH-), 1591(C=N), 692(C-Cl), 1261(Ar-O-CH_2); ^1H NMR (DMSO-d_6): 5.14 (s, 2H,-O-CH_2-), 3.87 (s, 3H, -OCH_3), 3.03(1H, dd, -CH_A, Pyrazoline), 3.40 (1H, dd, -CH_B, Pyrazoline), 4.94(1H, dd, -CH_X, Pyrazoline), 6.73-7.53 (10H, m, Ar-H); Mass (m/z): 461(M^+).

3-(4-methoxyphenyl)-5-[4-(2, 4-Dichlorophenyl methoxy)-3-methoxyphenyl]-4, 5-dihydropyrazoline (2h): IR (KBr, cm^{-1}):3440(-NH-), 1595(C=N), 690(C-Cl), 1257(Ar-O-CH_2); ^1H NMR (DMSO-d_6): 5.25 (s, 2H,-O-CH_2-), 3.84 (s, 3H, -OCH_3), 3.14(1H, dd, -CH_A, Pyrazoline), 3.79 (1H, dd, -CH_B, Pyrazoline), 5.16(1H, dd, -CH_X, Pyrazoline), 7.28-7.71 (10H, m, Ar-H); Mass (m/z): 456(M^+).

3-(4-bromophenyl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydroacetylpyrazoline(3b): IR (KBr, cm^{-1}):1659(-CO-CH_3), 1594(C=N), 693 (C-Cl),

1258(Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 5.17 (s, 2H,-O-CH_2-), 2.44 (s, 3H, -CO$\underline{CH_3}$), 3.87 (s, 3H, -OCH_3), 3.12(1H, dd, -CH_A, Pyrazoline), 3.67 (1H, dd, -CH_B, Pyrazoline), 5.23(1H, dd, -CH_X, Pyrazoline), 6.70-7.68 (10H, m, Ar-H); Mass (m/z): 548(M^++2).

3-(4-chlorophenyl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydroacetylpyrazoline(3c): IR (KBr, cm^{-1}):1661(-CO-CH_3), 1590(C=N), 687 (C-Cl), 1263(Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 5.19 (s, 2H,-O-CH_2-), 2.42 (s, 3H, -CO$\underline{CH_3}$), 3.88 (s, 3H, -OCH_3), 3.13(1H, dd, -CH_A, Pyrazoline), 3.63 (1H, dd, -CH_B, Pyrazoline), 5.43(1H, dd, -CH_X, Pyrazoline), 6.89-7.91 (10H, m, Ar-H); Mass (m/z): 502(M^+).

3-(4-methoxyphenyl)-5-[4-(2, 4-Dichlorophenyl methoxy)-3-methoxyphenyl]-4, 5-dihydroacetyl pyrazoline (3h): IR (KBr, cm^{-1}):1654(-CO-CH_3), 1597(C=N), 688 (C-Cl), 1260(Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 5.21 (s, 2H,-O-CH_2-), 2.40 (s, 3H, -CO$\underline{CH_3}$), 3.85 (s, 3H, -OCH_3), 3.11(1H, dd, -CH_A, Pyrazoline), 3.66 (1H, dd, -CH_B, Pyrazoline), 5.49(1H, dd, -CH_X, Pyrazoline), 6.72-7.69 (10H, m, Ar-H); Mass (m/z): 498(M^+).

Antimicrobial screening

The samples of synthesized pyrazolines (2a-k) and acetylpyrazolines (3a-k) derivatives for antimicrobial activity were prepared at concentration 40µg/ml in DMSO solvent. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against Gram positive bacteria *Staphylococcus aureus (S. aureus)* and *Bacillus subtilis (B. subtilis)*, *Gram negative* bacteria *Pseudomonas aeruginosa (P. aeruginosa)* and *Escherichia coli (E. coli)*. The antifungal activity was checked against fungi *Aspergillus niger (A. niger)* and *Candida albicans (C. albicans)*. The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.

RESULTS DISCUSSION

The new 3-(Aryl)-5-[4-(2, 4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4, 5-dihydropyrazoline (2a-k) and 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxy phenyl]-4, 5-dihydroacetylpyrazoline (3a-k) were synthesized by refluxing various substituted 3-Methoxy-4-(2, 4-Dichlorophenylmethoxy) chalcones with hydrazine hydrate derivatives results good to moderate yield. The analytical and physical data of the synthesized compounds are given (Table 1 & 3).

The FT−IR spectra of synthesized 3-(Aryl)-5-[4-(2, 4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4, 5-dihydropyrazoline shows a strong band at 3441-3445 cm^{-1} for (–NH-) and 1590-1597 cm^{-1} for (C=N) which is characteristic band for dihydropyrazoline moiety and additional strong band at 1654-1661 cm^{-1} for(C=O) support to acetyl(–$COCH_3$) group in acetyl pyrazoline. [20-21] The ^{1}HNMR also support the dihydropyrazoline moiety by chemical shift for protons of the pyrazoline and acetylpyrazoline ring, Ha, Hb & Hx, appeared as double of doublets at around 3.02-3.14, 3.40-3.79 and 4.91-5.49 δ respectively.

Table 1: Analytical and Physical data of 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydpyrazoline derivatives (2a-k)

Comp.	-R	Molecular formula	Mol. Wt.	M.P °C	% yield	Elemental analysis					
						Calculated (%)			Found (%)		
						C	H	N	C	H	N
2a	-C_6H_5	$C_{23}H_{20}Cl_2N_2O_2$	427	93	53	64.65	4.72	6.56	64.56	4.73	6.53
2b	-4-Br-C_6H_4	$C_{23}H_{19}BrCl_2N_2O_2$	504	116	78	54.57	3.78	5.53	54.53	3.76	5.54
2c	-4-Cl-C_6H_4	$C_{23}H_{19}Cl_3N_2O_2$	461	156	67	59.82	4.15	6.07	59.79	4.14	6.17
2d	-2-Cl-C_6H_4	$C_{23}H_{19}Cl_3N_2O_2$	461	147	72	59.82	4.15	6.07	59.74	4.17	6.11
2e	-2,4-Cl_2-C_6H_3	$C_{23}H_{18}Cl_4N_2O_2$	496	213	64	55.67	3.66	5.65	55.71	3.63	5.62
2f	-4-OH-C_6H_4	$C_{23}H_{20}Cl_2N_2O_3$	443	139	75	62.31	4.55	6.32	62.20	4.51	6.30
2g	-3-OH-C_6H_4	$C_{23}H_{20}Cl_2N_2O_3$	443	178	71	62.31	4.55	6.32	62.21	4.52	6.31
2h	-4-OCH_3-C_6H_4	$C_{24}H_{22}Cl_2N_2O_3$	456	78	76	63.03	4.85	6.13	63.12	4.83	6.17
2i	-4-NO_2-C_6H_4	$C_{23}H_{19}Cl_2N_3O_4$	472	188	45	58.49	4.05	8.90	58.54	4.02	8.92
2j	-3-NO_2-C_6H_4	$C_{23}H_{19}Cl_2N_3O_4$	472	173	53	58.49	4.05	8.90	58.45	4.04	8.94
2k	-4-NH_2-C_6H_4	$C_{23}H_{21}Cl_2N_3O_2$	442	126	69	62.45	4.79	9.50	62.51	4.81	9.46

Table 2: Antimicrobial Screening data of 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydropyrazoline derivatives (2a-k)

Comp	-R	Molecular formula	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
			S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*C. albicans*
2a	-C_6H_5	$C_{23}H_{20}Cl_2N_2O_2$	14	16	09	12	24	11
2b	-4-Br-C_6H_4	$C_{23}H_{19}BrCl_2N_2O_2$	15	12	12	13	12	13
2c	-4-Cl-C_6H_4	$C_{23}H_{19}Cl_3N_2O_2$	18	14	17	12	16	25
2d	-2-Cl-C_6H_4	$C_{23}H_{19}Cl_3N_2O_2$	13	15	13	11	10	06
2e	-2,4-Cl_2-C_6H_3	$C_{23}H_{18}Cl_4N_2O_2$	20	24	19	14	27	23
2f	-4-OH-C_6H_4	$C_{23}H_{20}Cl_2N_2O_3$	07	14	09	07	14	14
2g	-3-OH-C_6H_4	$C_{23}H_{20}Cl_2N_2O_3$	09	07	10	08	11	17
2h	-4-OCH_3-C_6H_4	$C_{24}H_{22}Cl_2N_2O_3$	09	12	07	11	12	13
2i	-4-NO_2-C_6H_4	$C_{23}H_{19}Cl_2N_3O_4$	08	13	08	06	15	11
2j	-3-NO_2-C_6H_4	$C_{23}H_{19}Cl_2N_3O_4$	10	08	07	09	09	21
2k	-4-NH_2-C_6H_4	$C_{23}H_{21}Cl_2N_3O_2$	11	12	09	12	19	18
	Sparfloxacin		24	25	25	22	-	-
	Benzyl penicillin		18	17	16	16	-	-
	Fluconazole		-	-	-	-	22	20

Table 3: Analytical and Physical data of 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydroacetylpyrazoline derivatives (3a-k)

Comp.	-R	Molecular formula	Mol. Wt.	M.P ˚C	% yield	Elemental analysis					
						Calculated (%)			Found (%)		
						C	H	N	C	H	N
3a	-C_6H_5	$C_{25}H_{22}Cl_2N_2O_3$	469	67	70	63.97	4.72	5.97	63.91	4.71	5.92
3b	-4-Br-C_6H_4	$C_{25}H_{21}BrCl_2N_2O_3$	546	107	68	54.77	3.86	5.11	54.68	3.82	5.14
3c	-4-Cl-C_6H_4	$C_{25}H_{21}Cl_3N_2O_3$	502	118	62	59.60	4.20	5.56	59.67	4.23	5.60
3d	-2-Cl-C_6H_4	$C_{25}H_{21}Cl_3N_2O_3$	502	129	66	59.60	4.20	5.56	59.65	4.21	5.57
3e	-2,4-Cl_2-C_6H_3	$C_{25}H_{20}Cl_4N_2O_3$	538	141	63	55.79	3.75	5.20	55.84	3.74	5.19
3f	-4-OH-C_6H_4	$C_{25}H_{22}Cl_2N_2O_4$	485	156	46	61.87	4.57	5.77	61.92	4.56	5.72
3g	-2-OH-C_6H_4	$C_{25}H_{22}Cl_2N_2O_4$	485	132	51	61.87	4.57	5.77	61.90	4.53	5.73
3h	-4-OCH_3-C_6H_4	$C_{26}H_{24}Cl_2N_2O_4$	498	86	69	62.53	4.84	5.61	62.51	4.81	5.61
3i	-2-NO_2-C_6H_4	$C_{25}H_{21}Cl_2N_3O_5$	514	171	47	58.38	4.12	8.17	58.45	4.12	8.12
3j	-4-NO_2-C_6H_4	$C_{25}H_{17}Cl_2N_3O_5$	514	198	49	58.38	4.12	8.17	58.39	4.14	8.20
3k	-4-NH_2-C_6H_4	$C_{25}H_{23}Cl_2N_3O_5$	484	121	55	61.99	4.79	8.68	70.03	4.81	8.57

Table 4: Antimicrobial Screening data of 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydroacetylpyrazoline derivatives (3a-k)

Comp	-R	Molecular formula	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
			S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*C. albicans*
3a	-C_6H_5	$C_{23}H_{18}Cl_2O_3$	12	16	10	14	09	12
3b	-4-Br-C_6H_4	$C_{23}H_{17}BrCl_2O_3$	23	13	18	15	18	10
3c	-4-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	18	16	08	08	17	09
3d	-2-Cl-C_6H_4	$C_{23}H_{17}Cl_3O_3$	12	11	07	11	23	19
3e	-2,4-Cl_2-C_6H_3	$C_{23}H_{16}Cl_4O_4$	07	09	10	06	12	18
3f	-4-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	13	17	30	13	11	18
3g	-2-OH-C_6H_4	$C_{23}H_{18}Cl_2O_4$	19	10	12	11	17	15
3h	-4-OCH_3-C_6H_4	$C_{24}H_{20}Cl_2O_4$	10	28	17	21	14	12
3i	-4-CH_3-C_6H_4	$C_{24}H_{20}Cl_2O_3$	07	13	11	12	13	09
3j	-2-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	10	19	09	09	12	16
3k	-4-NO_2-C_6H_4	$C_{23}H_{17}Cl_2NO_5$	16	12	13	11	10	18
	Sparfloxacin		24	25	25	22	-	-
	Benzyl penicillin		18	17	16	16	-	-
	Fluconazole		-	-	-	-	22	20

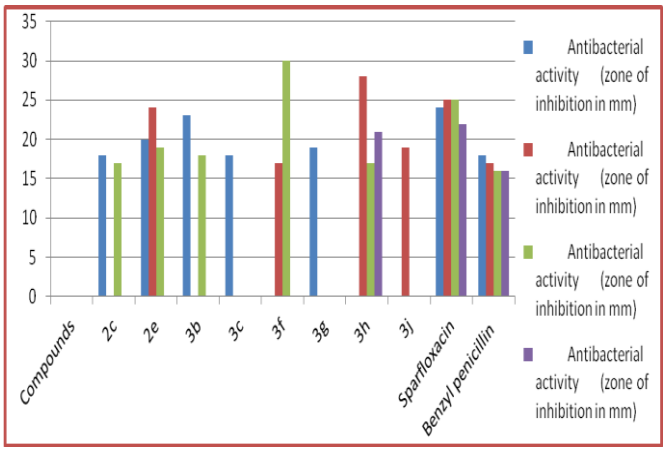


Fig. 1: Compounds having moderate to good antibacterial activity

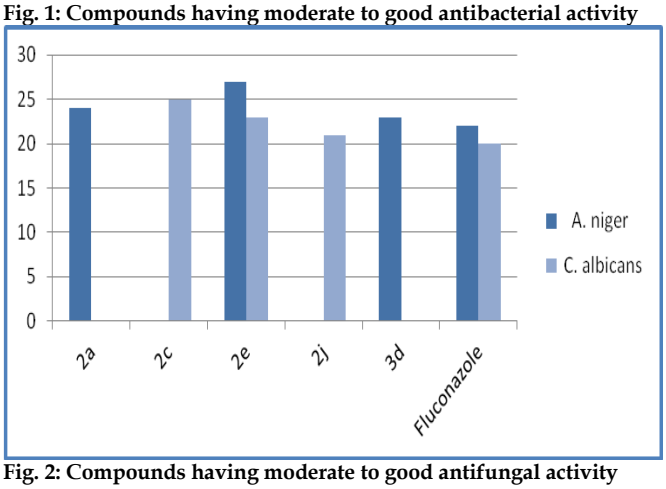


Fig. 2: Compounds having moderate to good antifungal activity

The doublet of doublet is due to germinal and vicinal coupling in pyrazoline ring. The 3H singlet at δ 2.38-2.46 for methyl protons confirmed the presence of acetyl (–$COCH_3$) in acetylpyrazoline.

The molecular ion peak (m/z) is equivalent to their molecular weight of proposed compounds and the fragmentation pattern of synthesized compounds matched with the typical fragmentation pattern of the pyrazoline moiety that further confirming the structures of the compounds. The elemental analysis (% of C, H and O) data found is equivalent to their calculated value.

From antimicrobial screening data (Table 2 & 4) of synthesized directives show that the compounds 2c, 2e, 3b, 3c, 3f, 3g, 3h and 3j have good antibacterial activity against *S. aureus, B. subtilis* (Gram positive bacteria) respectively compare to Benzyl penicillin. The compounds 2c, 2e, 3b, 3f and 3h have good antibacterial activity against *P. aeruginosa* (Gram negative bacteria) respectively compare to Benzyl penicillin and Sparfloxacin. The compounds 2c, 2e and 2j have very good antifungal activity against *C. albicans* and compounds 2a, 2e and 3d have good antifungal activity against *A. niger* compare to Flucanazole.

In the present work, a series of pyrazoline and acetylpyrazoline derivatives have been synthesized using new chalcones and hydrazine hydrate with moderate to good yield. The antimicrobial activities of

synthesized derivatives show that some derivatives have good results compared to standard drugs data. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products. The analytical data and spectral data support the structure and geometry of the pyrazoline derivatives.

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