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Synthesis and Antibacterial Evaluation of Some Novel Acetonitrile and Immidazoline Derivatives

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ABSTRACT

A Series of Immidazolines and Acetonitriles derivatives have been synthesized and tested for in vitro antibacterial activity on different microorganisms. Synthesis have been carried out following methodology in excellent isolated yields. The structure and purity of the original compounds were confirmed by IR, NMR, MASS spectroscopy and element analysis. All compounds were tested for antibacterial and antifungal activity against S.Aureus, E.aerogenes, B. coccus, P. aeruginosa. A. nige, C. albicans. These preliminary result indicate that some of compound are exhibiting good activity.

Keywords: Different sub aryl amines, 1,N-Phenyl-3-*O*-methoxypohenyl-4-formyl pyrazole, Acetonitrile, Immidazoline, Microbial activity.

INTRODUCTION

The incidence of bacterial infections has increased dramatically in recent years [1]. The widespread use of antibacterial drugs and their resistance against bacterial infections has led to serious health hazards. The resistance of wide spectrum antibacterial agents has prompted discovery and modification towards new antifungal and antibacterial drugs [2-3]. The five membered heterocyclic ring system 5-oxo-imidazoline has two nitrogen atoms at 1- and 3-positions and a carbonyl group at 5-position.

2-Substituted-5-oxo-imidazolines have been reported for the first time in 1888. A. W. Hoffman [4] has prepared 2-methyl-5-imidazoline (lysidine) by heating N1-diacetylethylene diamine in a stream of dry hydrogen chloride. A. Ladenburg [5] has prepared the same compound by fusing two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride. Nitriles are reported to possess various thempentic activities, but due to their high toxicity, they have low thempentic importance. The first synthesis of nitrile has been reported by Wohler and Liebig [6] in 1832 and Pelouze [7] in 1834.They are very much useful as intermediate for various products such as acrylonitrile for plastic, synthetic rubber and fibers, pthalonitrile for dye stuff.

Among the various heterocyclic systems, Immidazoline nucleus is of great importance because of it's varies biological activities, Naphazoline and xylometazoline hydrochlorides are immidazolines derivatives, which have been used as adrenergic stimulants and tolazolines and phenotolamine as adrenergic blocking agents. Various immidazolines are known to exhibit a broad spectrum of biological activities such as anticonvulsant [8-9], sedative and hypnotics [10], Bactericidal [11-12], Fungicidal [13-14], antiparkinsonian [15-16], anthelmintic [17], antihistaminic [18],anticancer [19-20], antidiabetic [21], antitubercular [22], Potent CNS depressant [23-24], Insecticidal [25], antiviral [26], Hypertensive [27], anti inflammatory [28-30], Glucagon antagonists [31], Kolhe Vishnu [32],have investigated anti-AIDS, anticancer, anti bacterial and antifungal activity of immidazoloines. The development of efficient and selective synthesis of immidazoloines has attracted increasing attention because they often bring about unique Pharmacodynamic activities.

They show various therapeutic activities such as antihypertensive [33], antimicrobial [34],antihypoxic [35], anti-inflammatory [36],antiarrythemic [37],central nervous system agent [38], fungicidor [39], pesticidal nitriles and reported their antiviral activity. Looking to this reason their synthesis has always attracted the attention of organic chemists. These facts encourage us to prepare some new Acetonitrile derivatives.

MATERIALS AND METHOD

Experimental

Melting Points were determined on Gallen-Kamp melting point apparatus and are uncorrected. All the compounds were routinely checked for their homogeneity by TLC on silica gel-G plates, IR spectra were recorded in KBr on a Perkin-Elmer BX series FT-IR spectrophotometer, ^{1}H NMR spectra were recorded BRUKER Spectrometer on a 400 MH_z in $CDCl_3$ using TMS as internal standard and satisfactory C,H,N and S analyses were obtained for all the compounds. The mass spectra were recorded on (FAB mass), Spectromatery used to confirm their structure.

Antibacterial and anti-fungal activity (anti-microbial activity) was carried out by cup-plate agar diffusion method. The bacterial strains studied are identified strains and were obtained from National chemical laboratory (NCL), India.

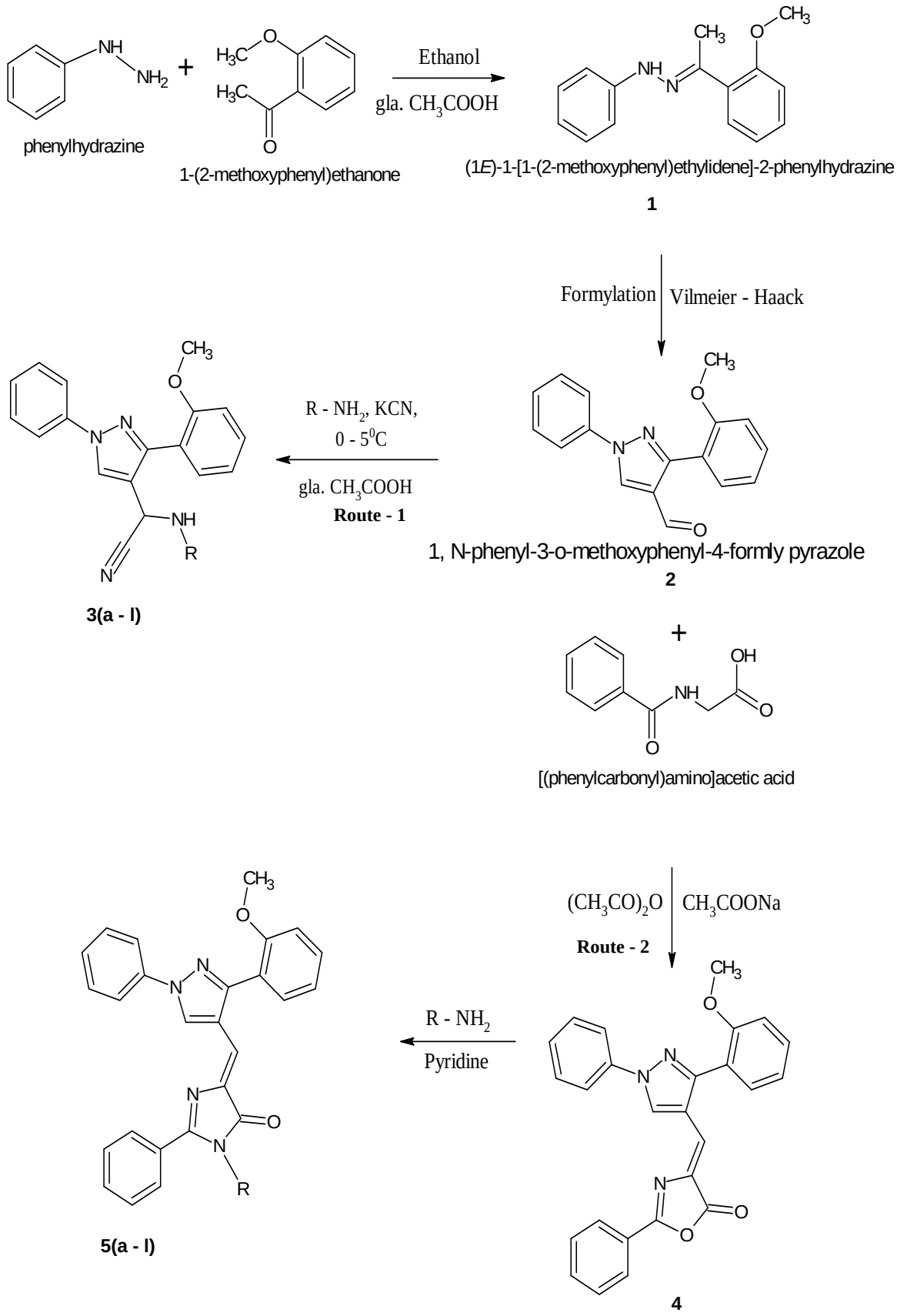
Synthesis of o-methoxyphenylhydrazone [A]:

A mixture of Phenyl hydrazine (1.08 g, 0.01 mole) and *o*-Methoxyacetophenone (1.64 g, 0.01 mole) in absolute ethanol was refluxed in water bath for 2 hrs. in the presence of 1ml of glacial acetic acid. Product obtained after cooling was crystallized from absolute ethanol. Yield 92%, m.p. 42^0C ($C_{15}H_{16}N_2O$; Calculated: C, 75.56;
H, 7.13, N, 11.01%; Found : C, 75.51; H, 7.09; N,10.95%.

Synthesis of 1, N-phenyl-3-0-methoxyphenyl-4-formly pyrazole [B]:

o-Methoxyphenylhydrazone (2.54 g, 0.01 mole) was added into a Vilsmeier-Haack reagent (prepared by drop wise addition of 3 ml $POCl_3$ in ice cooled 25 ml DMF) and refluxed for 6 hrs. The reaction mixture was poured on to crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from methanol. Yield 87%, m.p. 124^0C ($C_{17}H_{14}N_2O_2$; Calculated: C, 73.95; H, 5.52; N, 9.58; Found : C, 73.89; H, 5.48; N, 9.52%).

Reaction Scheme



When R= aryl amines

SCHEME (1 & 2) : Synthesis of Acetonitriles and Immidazolines Derivatives

Synthesis of α-p-Anisylamino-(1'- N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)acetonitrile [C]:

1,N-Phenyl-3-O-methoxypohenyl-4-formyl pyrazole (2.92 g, 0.01mole) dissolved in ethanol (25ml) was added to potassium ehanide (0.64g, 0.01mole) dissolved in water minutes to form cyanohydrins at 0 C p-Anisidine (1,23g, 0.0mole) dissolved in methanol was added to the reaction mixture, contents were stirred at room temperature for 24 hrs. The content was poured onto crushed ice. The solid product was filtered and crystallized form ethanol. Yield 58%, m.p. 146^0C ($C_{25}H_{22}N_4O_2$ calculated : C, 73, 56; H,5.70; N, 13.20; Found : C, 73.48; H, 5.63; N, 13.16%). *IR[KBR]* Vmax cm^{-1} : 2916, 2854, 1470-1435, 3060 [C-H str.(asym.), C-H str.(sym.), C-H i.p.def.(asym.), C-H str., -CH_3 alkane], 1502, 1064, 837 [C=C str., C-H i.p.def., C-H o.o.p.def., aromatic], 1595, 1159, 1232, 1064 [C=N str., C-N str., C-O-C str.(asym.), C-O-C str.(sym.), pyrazole moiety], 2216, 3355 [C ≡ N str., N-H str., nitrile]. *PMR Spectra* : [*δ DMSO*] : 3.97 [3H s,-OCH_3], 5.51 [1H s, CH], 6.39-6.42 [2H d, Ar-H], 6.85-6.88 [2H d, Ar- H], 6.97-7.02 [1H t, Ar-H], 7.19-7.22 [2H d, Ar-H], 7.29-7.35 [2H m, Ar-H], 7.38-7.43 [2H t, Ar-H], 7.48-7.50 [1H d, Ar-H], 7.66-7.69 [2H d, Ar-H], 8.17 [1H s, CH].

Similarly other substituted nitriles have been prepared. The physical data are recorded in Table No. 1

Synthesis of 2 -Phenyl-4-(1', N-phenyl-3'-o-methoxyphenyl-4'-pyrazolylmethino)Oxazolin -5-one [D]:

A mixture of 1, N-phenyl-3-*o*-methoxyphenyl-4-formyl pyrazole (2.92 g, 0.01 mole), acetic anhydride (7.6ml, 0.075 mole), sodium acetate (2.0 g, 0.025 mole) and hippuric acid (4.4g, 0.025 mole) was heated on water bath for four hrs. Resulting mass was poured onto crushed ice, filtered, washed with hot water and crystallized from ethanol. Yield 73%, m p. 146^0C, ($C_{26}H_{19}N_3O_3$: Calculated: C: 74.47; H: 4.86; N: 9.65; Found C: 74.41; H: 4.79; N: 9.61%).

Preparation of 1,N-Aryl-2-Phenyl-4-(1',N-Phenyl-3'-o-Methoxy-Phenyl-4' Pyrazolyl Methino)-Imidazolin-5-ones [E]:

A mixture of 2-Phenyl-4-(1', N-phenyl-3'-*o*-methoxyphenyl-4'-pyrazolylmethino)-oxazolin-5-one (4.35 g, 0.01 mole) and *p*-toludine (1.07g, 0.01 mole) in dry pyridine (20 ml) was refluxed for 12 hrs. Resulting mass was poured on to crushed ice and neutralized with HCl, filtered and crystallized from DMF. Yield, 63%, m.p. 156^oC ($C_{33}H_{26}N_4O_2$) Calculated: C: 77.84; H: 5.38; N: 10.68; Found : C: 77.76; H: 5.31; N: 10.64%). *IR[KBR]* Vmax cm^{-1} : 2964, 2879, 1434, 1363, 3053 [C-H str.(asym.), C-H str.(sym.), C-H i.p. def.(asym.), C-H o.o.p def.(sym.), C-H str., -CH_3 alkane], 1500, 1105, 833 [C=C str., C-H i.p. def., C-H o.o.p. def., aromatic], 1596, 1286, 1053, 1706 [C=N str., C-N str., C-O-C str.(sym.), C-O-C str.(sym.), pyrazole moiety ether], 1706, 1629, 1253 [C=O str., C=N str., C-N str., immidazoline ring]. *PMR Spectra* : [*δ DMSO*] : 2.42 [3H s, Ar-CH_3], 4.11 [3H s, -OCH_3], 7.02-7.09 [4H m, Ar-H], 7.20-7.22 [2H d, Ar-H], 7.33-7.37 [4H m, Ar-H, CH], 7.40-7.46 [2H m, Ar-H], 7.48-7.52 [2H t, Ar-H], 7.56-7.61 [3H m, Ar-H], 7.87-7.89 [2H d, Ar-H], 9.29 [1H s, CH].

Similarly, other imidazolin-5-ones have been prepared. The physical data are recorded in table – I.

TABLE-I : PHYSICAL CONSTANTS OF -ARYLAMINO-(1',N-PHENYL-3'-O- METHOXYPHENYL -4' -PYRAZOLYL- 4 YL)- ACETONITRILES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. °C	R_f* Value	Yield %	% of C,H,N Cal / Found		
							C	H	N
3a	C_6H_5-	$C_{24}H_{20}N_4O$	380	164	0.54	78	75.81	5.29	14.77
							75.78	5.26	14.73
3b	4-Cl-C_6H_4-	$C_{24}H_{19}ClN_4O$	414.5	172	0.49	67	69.49	4.61	13.54
							69.48	4.58	13.51
3c	3,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{18}C_{l2}N_4O$	449	184	0.44	54	64.19	4.03	12.51
							64.14	4.00	12.47
3d	4-Br-C_6H_4-	$C_{24}H_{19}BrN_4O$	459	127	0.61	81	62.74	4.09	12.15
							62.68	4.13	14.20
3e	4-F-C_6H_4-	$C_{24}H_{19}FN_4O$	398	140	0.72	75	72.39	4.80	14.10
							72.36	4.77	14.07
3f	3-Cl,4-F-C_6H_3-	$C_{24}H_{18}ClFN_4O$	432.5	124	0.55	66	66.61	4.19	12.97
							66.58	4.16	12.94
3g	2-OCH_3-C_6H_4-	$C_{25}H_{22}N_4O_2$	410	155	0.57	84	73.17	5.36	13.65
							73.12	5.32	13.61
3h	4-OCH_3-C_6H_4-	$C_{25}H_{22}N_4O_2$	410	146	0.63	58	73.17	5.36	13.65
							73.11	5.31	13.61
3i	2-CH_3-C_6H_4-	$C_{25}H_{22}N_4O$	394	169	0.48	64	76.19	5.63	14.25
							76.14	5.58	14.21
3j	4-CH_3-C_6H_4-	$C_{25}H_{22}N_4O$	394	115	0.59	80	76.25	5.67	16.21
							76.14	5.58	14.31
3k	2-NO_2-C_6H_4-	$C_{24}H_{19}N_5O_3$	425	137	0.73	72	67.67	4.47	16.47
							67.58	4.37	16.38
3l	4-NO_2-C_6H_4-	$C_{24}H_{19}N_5O_3$	425	158	0.64	78	67.76	4..47	16.47
							67.69	4.41	16.40

TABLE-1I : PHYSICAL CONSTANTS OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*O*- METHOXYPHENYL -4' -PYRAZOLYL- METHINO) -IMIDAZOLIN-5-ONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. °C	R_f* Value	Yield %	% of C,H,N Cal / Found		
							C	H	N
5a	C_6H_5-	$C_{32}H_{24}N_4O_2$	496	210	0.47	84	77.41	4.83	11.29
							77.36	4.78	10.92
5b	4-Cl-C_6H_4-	$C_{32}H_{23}ClN_4O_2$	530.5	230	0.52	74	72.38	4.33	10.55
							72.32	4.28	10.22
5c	3,4-$(Cl)_2$-C_6H_3-	$C_{32}H_{22}Cl_2N_4O_2$	565	180	0.56	58	67.96	3.89	9.91
							67.83	3.81	9.61
5d	4-Br-C_6H_4-	$C_{32}H_{23}BrN_4O_2$	575	144	0.62	64	66.78	4.00	9.73
							66.70	3.92	9.45
5e	4-F-C_6H_4-	$C_{32}H_{23}FN_4O_2$	528	160	0.48	71	72.72	4.35	10.60
							72.66	4.28	10.54
5f	3-Cl,4-F-C_6H_3-	$C_{32}H_{22}ClFN_4O_2$	548.5	175	0.64	83	70.00	4.01	10.20
							69.92	3.93	9.92
5g	2-OCH_3-C_6H_4-	$C_{33}H_{26}N_4O_3$	526	124	0.55	77	75.28	4.94	10.64
							75.19	4.86	10.31
5h	4-OCH_3-C_6H_4-	$C_{33}H_{26}N_4O_3$	526	223	0.51	65	75.28	4.94	10.64
							75.19	4.86	10.33
5i	2-CH_3-C_6H_4-	$C_{33}H_{26}N_4O_2$	510	129	0.65	68	75.29	5.09	10.98
							75.16	4.98	10.62
5j	4-CH_3-C_6H_4-	$C_{33}H_{26}N_4O_2$	510	156	0.46	63	75.29	5.09	10.98
							75.16	4.98	10.64
5k	2-NO_2-C_6H_4-	$C_{32}H_{23}N_5O_4$	541	184	0.64	70	70.97	4.25	12.93
							70.88	4.16	12.57
5l	4-NO_2-C_6H_4-	$C_{32}H_{23}N_5O_4$	541	192	0.73	78	70.97	4.25	12.93
							70.88	4.16	12.55

Biological Evaluation

Anti-bacterial activity of α-p-Anisylamino-(1'- N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl) acetonitrile:

It has been observed from the experimental data that all compounds of type (3a to 3l) tested their antibacterial activity against gram positive and gram negative bacteria *B. coccus, S. aureus, E. aerogenes, P. aeruginosa* by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMF and Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, Greseofulvin were used as a reference compound. The compound 3a, 3b, 3g, and 3k were shown significant activities and compound 3c, 3d, 3e, 3f, 3h, 3i, 3j and 3l have shown moderate activity. The plates were incubated at 37^{o} C for 24 hours and the control was also maintained with 0.04 ml of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded data in table-III.

Anti Fungal activity:

The same compound were tested for their antifungal activity against A. niger, and C. albicans. The compound 3b, 3g, 3h and 3l were shown significant activities and compound 3a, 3c, 3d, 3e, 3f, 3i, 3j and 3k have shown moderate activity.

Tabel - III :- Antibacterial and Antifungal activity

Compounds	Antibacterial and Antifungal activity MIC in µg/ml					
	B.coccus	P.aeruginosa	S.aureus	E.aerogenes	A.niger	C.albicans
3a	23	20	18	17	14	13
3b	18	19	19	18	23	18
3c	14	16	20	14	14	15
3d	17	13	15	16	17	16
3e	19	14	16	13	18	14
3f	18	23	17	21	16	11
3g	22	21	20	18	19	18
3h	17	18	22	14	22	19
3i	14	14	19	17	17	18
3j	16	17	16	13	16	09
3k	20	18	18	15	18	11
3l	13	20	17	17	19	17
Amoxicillin	25	22	25	20	00	00
Benzoylpenicillin	18	21	19	21	00	00
Erythromycin	22	23	21	19	00	00
Ciprofloxacin	20	16	15	22	00	00
Greseofulvin	00	00	00	00	26	27

Anti-bacterial activity of 1,N-Aryl-2-Phenyl-4-(1',N-Phenyl-3'-o-Methoxy-Phenyl-4' Pyrazolyl Methino)-Imidazolin-5-ones:

It has been observed from the experimental data that all compounds of type (5a to 5l) tested their antibacterial activity against gram positive and gram negative bacteria *B. coccus, S. aureus, E. aerogenes, P. aeruginosa* by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMF and Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, Greseofulvin were used as a reference compound. The compound 5b, 5e, 5f, 5h and 5l were shown significant activities and compound 5a, 5c, 5d, 5g, 5i, 5j and 5k have shown moderate activity.

The plates were incubated at 37^{o} C for 24 hours and the control was also maintained with 0.04 ml of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded data in table-IV.

Anti Fungal activity:

The same compound were tested for their antifungal activity against A. niger, and C. albicans. The compound 5c, 5i, 5j and 5l were shown significant activities and compound 5a, 5b, 5d, 5e, 5f, 5g, 5h and 5k have shown moderate activity.

Tabel - IV :- Antibacterial and Antifungal activity.

Compounds	Antibacterial and Antifungal activity MIC in µg/ml					
	B.coccus	P.aeruginosa	S.aureus	E.aerogenes	A.niger	C.albicans
5a	17	15	17	16	16	13
5b	23	18	16	17	19	12
5c	15	13	16	19	22	19
5d	18	23	24	14	15	17
5e	19	20	17	22	17	18
5f	19	16	17	18	18	11
5g	16	19	23	21	17	17
5h	21	18	17	18	19	10
5i	18	21	18	17	21	18
5j	14	17	22	17	20	19
5k	17	16	19	16	13	11
5l	20	16	18	20	23	19
Amoxicillin	25	22	25	20	00	00
Benzoylpenicillin	18	21	19	21	00	00
Erythromycin	22	23	21	19	00	00
Ciprofloxacin	20	16	15	22	00	00
Greseofulvin	00	00	00	00	26	25

RESULT AND DISCUSSION

New Acetonitrile and Immidazoline have been synthesized by the reaction of 1, N-phenyl-3-0-methoxyphenyl-4-formly pyrazole with various aryl groups in 54 to 84% and 58 to 84% yield. Acetonitrile and immidazoline having high melting points. The structure of compounds are confirmed by IR, NMR and Mass spectral data and are further supported by correct elemental analysis. Newly synthesized compounds of acetonitrile (3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l). The compound 3a, 3b, 3g, and 3k were shown significant activities and compound 3c, 3d, 3e, 3f, 3h, 3i, 3j and 3l have shown moderate activity against gram positive and gram negative bacteria. The same compounds were tested for their anti fungal activity against *A. niger and C. albicans* using cup-plate method. The compound 3b, 3g, 3h and 3l were shown significant activities and compound 3a, 3c, 3d, 3e, 3f, 3i, 3j and 3k have shown moderate activity.

Newly synthesized compounds of immidazoline (5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l) were inhibit the growth of gram positive bacteria and also gram negative bacteria. The compound 5b, 5e, 5f, 5h and 5l were shown significant activities and compound 5a, 5c, 5d, 5g, 5i, 5j and 5k have shown moderate activity. The same compounds were tested for their anti fungal activity against *A. niger and C. albicans* using cup-plate method. The compound 5c, 5i, 5j and 5l were shown significant activities and compound 5a, 5b, 5d, 5e, 5f, 5g, 5h and 5k have shown moderate activity.

CONCLUSION

Newly synthesized compounds of acetonitrile (3a to 3l) and immidazoline (5a to 5l) have been tested for their anti bacterial activity against gram positive bacteria *B. coccus, S. aureus, E. aerogenes* and gram negative bacteria *P. aeruginosa* by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMF. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, Greseofulvin were used as a reference compound. The compound 3a, 3b, 3g, and 3k were shown significant activities and compound 3c, 3d, 3e, 3f, 3h, 3i, 3j and 3l have shown moderate activity and compound 5b, 5e, 5f, 5h and 5l were shown significant activities and compound 5a, 5c, 5d, 5g, 5i, 5j and 5k have shown moderate activity. The compounds (3a to 3l) and (5a to 5l) were tested for their anti fungal activity against *A. niger and C. albicans* using cup-plate method. The compound 3b, 3g, 3h and 3l were shown significant activities and compound 3a, 3c, 3d, 3e, 3f, 3i, 3j and 3k have shown moderate activity and compound 5c, 5i, 5j and 5l were shown significant activities and compound 5a, 5b, 5d, 5e, 5f, 5g, 5h and 5k have shown moderate activity.

All the other compounds did not show significant activity against the fungi at the concentration used.

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