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Studies on Cyanopyridones and Isoxazoles ring system in the synthesis of Novel bioactive compounds

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ABSTRACT

Heterocyclic compounds have been indispensable in the recent far reaching developments in science and technology embracing a vast spectrum of advances of both theoretical and practical relevance. Endowed with unique properties, they are well recognized for their multifaceted pharmacological, medicinal and biochemical behaviors. Heterocyclic compounds offer many opportunities for synthetic organic chemists. Cyanopyridone and Isoxazole derivatives have been prepared from condensation of chalcones (I) with acetate and hydroxylamine hydrochloride respectively. The structural assignments of the products have been made on the basis of their elemental analyses, spectral analyses and other physico-chemical investigations, antimicrobial activities of the synthesized compounds have been determined qualitatively against different pathogenic bacteria.

Keywords : Cyanopyridones, Isoxazoles, Synthesis, Characterization, and Biological activities.

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]. Pyridone derivatives have remarkable many biological, pharmaceutical and therapeutic activities. Pyridones, with carbonyl group at position- 2 have been the subjected of extensive study in the resent years. The addition reaction between ethylcyano acetate and α, β - unsaturated ketone give cyanopyridone via Michael addition . Pyridone derivatives have been found to possess variety of therapeutic activities as anti-cancer[4], antimicrobial[5], angiotensin II antagonist[6], anti-viral[7], anti-HIV[8], Herbicidal[9], pesticidal[10] and in many other ways.

Pednekar[11] synthesized some new fused 2-pyridenes as useful Hetrocyclic moieties as they possess a broad spectrum of biological activities such as anti-viral CNS depressant, bactericidal and ulcer inhibiter. Upadhyay et.al.[12] have synthesised Cyanopyridone derivatives which showed anti-fungal and anti-leishmanial activities. 3-Cyano Pyridone derivatives showing high

antimicrobial activities[13]. Anti-cancer activity of 2-Pyridones have been reported by Abon El-Fotooh and co-workers[14]. Recently, Devdas B. et.al.[15] have synthesized Pyridone derivatives which are useful for treating diseases and conditions caused or exacerbated by unregnlated P38MAP kinase and/or TNF activity, such as inflammation, ischemia, viral infections and autoimmune diseases.

Thus the important role played by Cyanopyridone nucleus for various physiological activities prompted us to explore Cyanopyridone ring system by synthesized its derivatives bearing Pyrazole ring systems of therapeutic importance, in order to achieving compounds having better drug potential which has been prepared.

Isoxazoles possess typical properties of and aromatic system but under certain reaction conditions, particularly in reducing or basic media, its become highly labile. Well know sulpha drug. Sulphamethoxazole, anti-inflammatory drug isoxicam, anti-tumor drug acivicin bears Isoxazole type of nucleus which suggest Isoxazole and its derivatives have better therapeutic values in the field of medicinal chemistry. Isoxazoles have various medicinal application such as anti-inflammatory[16-19], anticonvulsant[20,21], muscle relaxant[22], antipyretic[23], anticholestermic, antidiabetic[24], antibacterial[25,26], nematocidal[27], fungicidal[28,29], antiviral[30], herbicidal[31,32], anthelmintics[33], antileukemic[34], anti-tumour[35], hypoglycemic[36], analgesic[37] etc..

With view to getting better therapeutic value, it was contemplated to synthesized isoxazole derivatives in corporating pyrazole as parent molecule, to enhance the overall activity of resulting compounds which have been synthesized.

MATERIALS AND METHODS

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 on 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), Spectrometer used to confirm their structure.

Antibacterial and anti-fungal activity (anti-microbial activity) were carried out by cup-plate agar diffusion method[38]. The bacterial strains studied are identified strains and were obtained from National chemical laboratory (NCL), India.

General procedure for synthesis of 1-(p-chlorophenyl)-3-(1',N-phenyl-3'-o-mehoxyphenyl-pyrazole-4'-yl)-2-propen-1-one

Synthesis of o-Methoxyphenylhydrazone [1]:

A mixture of Phenylhydrazine (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-o-methoxyphenyl-4-formyl pyrazole [2]:

o-Methoxyphenylhydrazone(2.54 g, 0.01 mole) was added into a Vilsmeier-Haack reagent (prepared by drop wise addition of 3 ml PoCl3 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 filtrated and crystallised from methanol. Yield 87%, m.p. 124^{0}C ($C_{17}H_{14}N_2O_2$; Calculated: C, 73.95; H, 5.52; N, 9.58; Found : C, 73.89; H, 5.48; N, 9.52%).

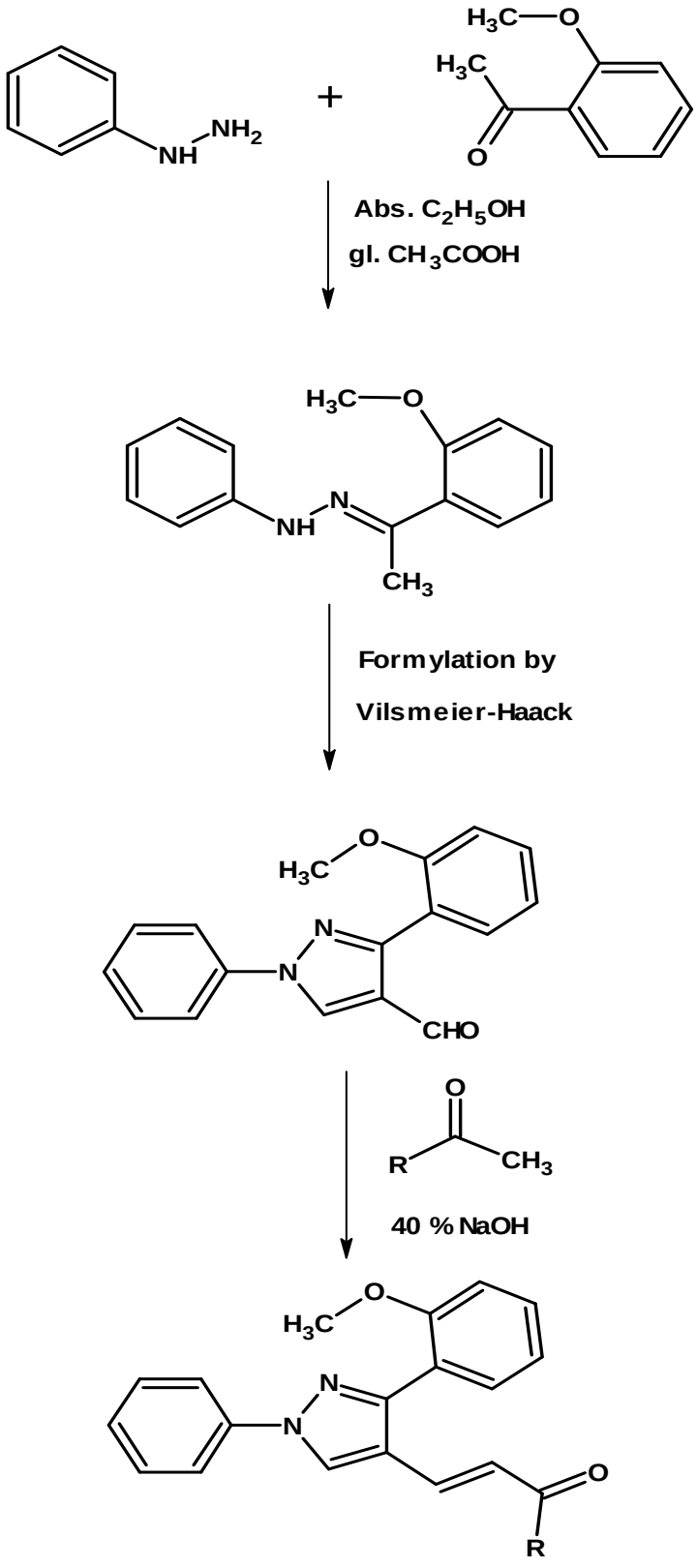
Synthesis of 1-(p-chlorophenyl)-3-(1',N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)-2-propen-1-one [3]:
To a solution of 1,N-phenyl-3-*o*-methoxyphenyl-4-formyl pyrazole (2.92 g, 0.01 mole), *p*-bromoacetophenone (1.99 g, 0.01 mole) in ethanol (25 ml) and 40% NaOH was added till the solution becomes basic. The reaction mixture was stirred for 24 hrs. The contents were poured on to crushed ice. Upon neutralization, the solid was separated and crystallized from ethanol. Yield 65%, m.p.160^{0}C ($C_{25}H_{19}BrN_2O_2$; Calculated : C, 65.97; H, 4.47; N, 5.92; Found : C, 65.91; H, 4.41; N, 5.87%).

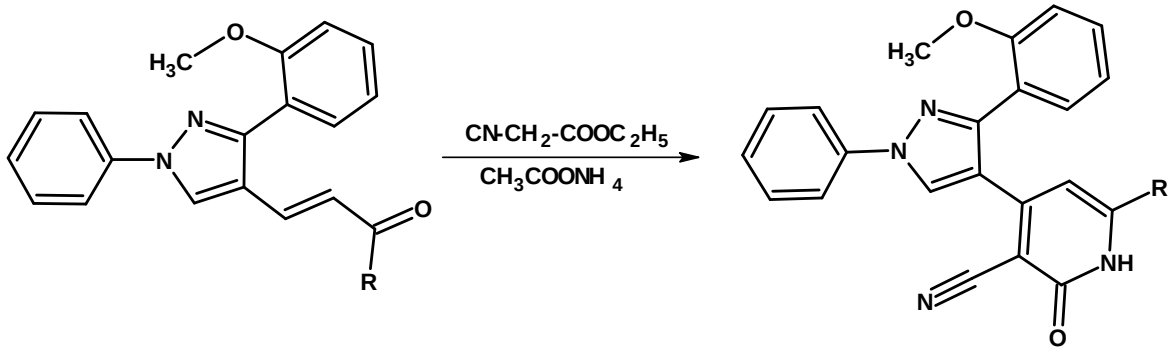
Synthesis of 3-cyano-4-(1',N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)-6-(p-chlorophenyl)-1,2-dihydro-2-pyridone [4]:
A mixture of 1-(*p*-chlorophenyl)-3-(1',N-phenyl-3'-*o*-methoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.28 g, 0.01 mole), ethylcyano acetate (1.13 g, 0.01 mole) and ammonium acetate (6.16 g, 0.08 mole) in Absolute alcohol was refluxed for 12 hrs. The reaction mixture was poured on to crushed ice and product was isolated and crystallized from Ethanol. Yield 74%, m.p. 260^{o}C ($C_{28}H_{19}ClN_4O_2$; Calculated : C, 70.66; H, 4.29; N, 11 .37; Found : C, 70.59; H, 4.23; N, 11.32%). *IR[KBr]* V_{max} Cm^{-1} : 2923, 2854, 1458, 1392 [C-H stretching(asym.), C-H stretching(sym.), C-H i p.def.(asym.), C-H o.o.p.def. (sym.), -CH_3alkane], 1535, 1535, 1095, 821 [C=C stretching, C-H i p.def., C-H o.o.p.def, aromatic], 1604, 1157, 1242 [C=N stretching, C-N stretching, C-O-C stretching(asym.), pyrazole moiety ether], 1037, 2214, 1639, 3413, 1604 [C-O-C stretching(sym.), C=N stretching, C=O stretching, N-H stretching, N-H def., pyridone ring]. *PMR Spectra :* [δ $CDCl_3$], 3.86[3H s, OCH_3], 6.18[1H s, CH], 6.92-6.95[1H d, Ar], 7.10-7.15[1H t, Ar], 7.24-7.27[2H d, Ar], 7.32-7.39[3H m, Ar], 7.43-7.54[3H m, Ar], 7.61-7.64[2H d, Ar], 7.82-7.85[2H d, Ar], 8.75[1H s, CH].
Similarly other substituted Pyridones have been prepared. The physical data are recorded in table-I.

Synthesis of 3-(p-bromophenyl)-5-(1',N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)-isoxazole [5]:
A solution of anhydrous sodium acetate (1.46g, 0.02 mole) in a minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (1.4 g, 0.02 mole) in ethanol (20 ml). This solution was added to a solution of 1-(*p*-bromophenyl)-3-(1',N-phenyl-3'-*o*-methoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.73 g, 0.01 mole) in Ethanol (25 ml). The mixture was heated under reflux on water bath for 12 hrs. The product was isolated and recrystallized from ethanol. Yield 68%, m.p. 119°C ($C_{25}H_{18}BrN_3O_2$; Calculated : C, 64.21; H, 4.14; N, 8.64; Found : C, 64.14; H, 4.08; N, 8.58%). *IR[KBr]* Vmax Cm^{-1}: 2931, 2835, 1436, 1382 [C-H stretching(asym.), C-H stretching(sym.), C-H i p.def.(asym.), C-H o.o.p.def. (sym.), -CH_3 alkane], 3060, 1558, 1101, 829 [C-H stretching, C=C stretching, C-H i p.def., C-H o.o.p.def, aromatic], 1596, 1174, 1249, 1058 [C=N stretching, C-N stretching, C-O-C stretching(asym.), C-O-C stretching(sym.), pyrazole moiety ether], 1558, 1596, 806 [C=C stretching, C=N stretching, N-O stretching, isoxazole]. *PMR Spectra* : [δ $CDCl_3$], 4.04 [3H s, OCH_3], 7.02-7.10 [1H t, Ar], 7.17-7.19 [1H d, Ar], 7.36-7.41 [1H t, Ar], 7.45-7.49 [2H t, Ar], 7.54-7.60 [2H t, Ar], 7.66 [1H s, CHy], 7.76-7.79 [2H d, Ar], 7.85-7.97 [4H m, Ar], 9.34 [1H s, CHx].

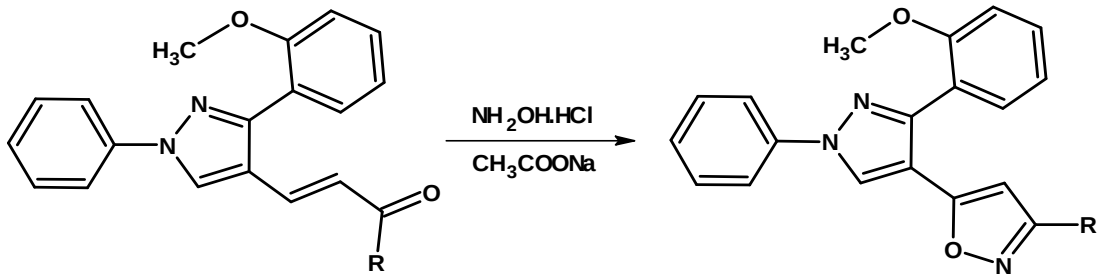
Similarly other substituted Isoxazoles have been prepared. The Physical data are recorded in table-II.

REACTION SCHEME





Scheme-1 **1,2-dihydro-2-pyridone**



Scheme-2 **Isoxazole**

Biological Evaluation

Anti-bacterial activity of 3-cyano-4-(1',N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)-6-(p-chlorophenyl)-1,2-dihydro-2-pyridone:

Newly synthesized compound (1a to 1l)have been 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 1b,1c,1g,1i,1l were shown significant activities and compound 1a,1d, 1e, 1f, 1h, 1j and 1k 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 1c, 1d, 1e, 1g and 1i were shown significant activities and compound 1a, 1b, 1f, 1h, 1j, 1k and 1l have shown moderate activity

Table – I : Physical constants of 3-cyano-4-(1',N-phenyl-3'-*O*-methoxyphenyl-pyrazole-4'-yl)-6-aryl-1,2-dihydro-2-pyridone

Sr. No	R	Molecular Formula	Molecular Weight	M.P. °C	R_f* Value	Yield %	% of C,H,N,S Cal / Found			
							C	H	N	S
1a	C_6H_5-	$C_{28}H_{20}N_4O_2$	444	188	0.61	82	75.71	4.54	12.66	-
							75.67	4.50	12.61	-
1b	4-NH_2-C_6H_4-	$C_{28}H_{21}N_5O_2$	459	202	0.46	66	73.24	4.61	15.29	-
							73.20	4.57	15.25	-
1c	4-Cl-C_6H_4-	$C_{28}H_{19}ClN_4O_2$	478.5	260	0.65	74	70.16	3.92	11.66	-
							70.21	3.97	11.70	-
1d	4-Br-C_6H_4-	$C_{28}H_{19}Br\ N_4O_2$	523	208	0.48	76	64.20	3.59	10.66	-
							64.24	3.63	10.70	-
1e	4-F-C_6H_4-	$C_{28}H_{19}FN_4O_2$	462	258	0.73	62	72.77	4.17	12.18	-
							72.72	4.11	12.12	-
1f	2-OH-C_6H_4-	$C_{28}H_{20}N_4O_3$	460	241	0.56	73	73.08	4.38	12.21	-
							73.04	4.34	12.17	-
1g	4-OH-C_6H_4-	$C_{28}H_{20}N_4O_3$	460	192	0.52	80	73.07	4.37	12.20	-
							73.04	4.34	12.17	-
1h	4-OCH_3-C_6H_4-	$C_{29}H_{22}N_4O_3$	474	148	0.60	76	73.36	4.55	11.76	-
							73.41	4.60	11.81	-
1i	4-CH_3-C_6H_4-	$C_{29}H_{22}N_4O_3$	458	203	0.64	70	75.91	4.74	12.17	-
							75.98	4.80	12.22	-
1j	3-NO_2-C_6H_4-	$C_{28}H_{19}N_5O_4$	489	142	0.54	68	68.75	3.92	14.35	-
							68.71	3.88	14.31	-
1k	4-NO_2-C_6H_4-	$C_{28}H_{19}N_5O_4$	489	156	0.62	84	68.74	3.91	14.34	-
							68.71	3.88	14.31	-
1l	2-C_4H_3S-	$C_{26}H_{18}N_4O_2S$	450	174	0.47	72	69.30	3.98	12.40	7.08
							69.33	4.00	12.44	7.11

Table – II : Physical constants of 3-aryl-5-(1',N-phenyl-3'-*O*- methoxyphenyl –pyrazol-4'-yl)-isoxazoles

Sr. No	R	Molecular Formula	Molecular Weight	M.P. °C	R_f* Value	Yield %	% of C,H,N,S Cal / Found			
							C	H	N	S
2a	C_6H_5-	$C_{25}H_{19}N_3O_2$	393	105	0.56	72	76.39	4.87	10.72	-
							76.33	4.83	10.68	-
2b	4-NH_2-C_6H_4-	$C_{25}H_{20}N_4O2$	408	98	0.62	64	73.58	4.95	13.78	-
							73.52	4.90	13.72	-
2c	4-Cl-C_6H_4-	$C_{25}H_{18}ClN_3O_2$	427.5	183	0.55	75	70.22	4.28	9.88	-
							70.17	4.21	9.82	-
2d	4-Br-C_6H_4-	$C_{25}H_{18}BrN_3O_2$	472	119	0.61	68	63.50	3.79	8.78	-
							63.55	3.81	8.89	-
2e	4-F-C_6H_4-	$C_{25}H_{18}FN_3O_2$	411	165	0.49	57	72.91	4.31	10.15	-
							72.99	4.37	10.21	-
2f	2-OH-C_6H_4-	$C_{25}H_{19}N_3O_3$	409	147	0.58	81	73.39	4.71	10.31	-
							73.34	4.64	10.26	-
2g	4-OH-C_6H_4-	$C_{25}H_{19}N_3O_3$	409	150	0.64	73	73.38	4.70	10.30	-
							73.34	4.64	10.26	-
2h	4-OCH_3-C_6H_4-	$C_{26}H_{21}N_3O_3$	423	120	0.72	65	73.70	4.90	9.88	-
							73.75	4.96	9.92	-
2i	4-CH_3-C_6H_4-	$C_{26}H_{21}N_3O_2$	407	134	0.48	84	76.60	5.11	10.28	-
							76.65	5.15	10.31	-
2j	3-NO_2-C_6H_4-	$C_{25}H_{18}N_4O_4$	438	159	0.57	76	68.53	4.14	12.82	-
							68.49	4.10	12.78	-
2k	4-NO_2-C_6H_4-	$C_{25}H_{18}N_4O_4$	438	164	0.46	72	68.52	4.13	12.81	-
							68.49	4.10	12.78	
2l	2-C_4H_3S	$C_{23}H_{17}N_3O_2S$	499-	114	0.62	58	55.28	3.38	8.38	6.37
							55.31	3.40	8.41	6.41

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*
1a	13	15	17	16	16	13
1b	21	17	18	16	14	12
1c	19	19	16	17	19	18
1d	16	20	17	19	18	17
1e	15	18	15	15	19	18
1f	14	13	12	14	16	11
1g	19	17	16	19	18	17
1h	14	16	17	20	16	10
1i	20	15	19	17	18	18
1j	14	14	14	20	17	09
1k	15	16	14	18	13	11
1l	20	19	21	17	17	10
Amoxicillin	25	22	25	20	00	00
Benzoylpenicillin	19	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 3-(p-bromophenyl)-5-(1',N-phenyl-3'-o-methoxyphenyl-pyrazol-4'-yl)-isoxazole:

Newly synthesized compound (2a to 2l)have been tasted 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 2b, 2e, 2g, 2i, 2k were shown significant activities and compound 2a, 2c, 2d, 2f, 2h, 2j and 2l 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*
2a	18	19	16	17	17	15
2b	19	21	17	17	16	17
2c	13	10	18	12	14	13
2d	15	12	17	18	19	21
2e	19	19	14	17	18	18
2f	14	22	18	15	15	13
2g	22	15	17	16	22	21
2h	20	20	19	22	19	16
2i	21	16	18	17	12	11
2j	15	19	12	15	10	10
2k	22	14	18	19	21	17
2l	10	16	17	15	17	09
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

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 tasted for their antifungal activity against A. niger, and C. albicans. The compound 2d, 2g, 2h and 2k were shown significant activities and compound 2a, 2b, 2c, 2e, 2f, 2i, 2j and 2l have shown moderate activity.

RESULTS AND DISCUSSION

New Pyridones and Isoxazoles have been synthesized by the reaction of 1-(*p*-chlorophenyl)-3-(1',N-phenyl-3'-*o*-methoxyphenyl-pyrazole-4'-yl)-2-propen-1-one with various aryl groups in 62 to 84% and 57 to 84% yield. pyridones and isoxazoles 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 pyridones (1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1l). The compound 1b, 1c, 1g, 1i, 1l were shown significant activities and compound 1a, 1d, 1e, 1f, 1h, 1j and 1k have shown moderate activity.

Newly synthesized compounds of isoxazoles (2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2l) were inhibit the growth of gram positive bacteria and also gram negative bacteria. The compound 2b, 2e, 2g, 2i, 2k were shown significant activities and compound 2a, 2c, 2d, 2f, 2h, 2j and 2l have shown moderate activity.

CONCLUSION

Newly synthesized compounds of pyridon (1a to 1l) and isoxazole (2a to 2l) 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 1b,1c,1g,1i,1l were shown significant activities and compound 1a,1d, 1e, 1f, 1h, 1j and 1k have shown moderate activity and compound 2b, 2e, 2g, 2i, 2k also were shown significant activities and compound 2a, 2c, 2d, 2f, 2h, 2j and 2l have shown moderate activity. The compounds (1a to 1l) and (2a to 2l) were tested for their anti fungal activity against *A. niger and C. albicans* using cup-plate method. The compound 1c, 1d, 1e, 1g and 1i were shown significant activities and compound 1a, 1b, 1f, 1h, 1j, 1k and 1l have shown moderate activity and compound 2d, 2g, 2h and 2k were shown significant activities and compound 2a, 2b, 2c, 2e, 2f, 2i, 2j and 2l have shown moderate activity. All the other compounds did not show significant activity against the fungi at the concentration used.

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