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Study of some new Substituted Pyrazole – Pyrimidine Derivatives as potential Anti Fungal Agents

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ABSTRACT

A number of 1-aroyl/aryloxyaceto-4-aryl-5-cyano-3-methyl pyrazolo[4,5-e]-pyridin-6-ones (3) 1-aroyl/aryloxyaceto-4-aryl-3-methyl pyrazolo[4,5-e]-pyrido[1,2-a]-pyrimidines (4) have been prepared by Michael addition between α, β –unsaturated ketone (2) and ethyl cyanoacetate / 2 –amino pyridine in presence of ammonium acetate. These compounds have been evaluated for their anti fungal activity against Pyricularia oryzae, Puccinia graminis , Alternaria solani , Pseudopernospora cubensis and Phytopthora infestans .

Introduction

Pyrazole ring system is associated with diverse biological activities like fungicidal [1,2], herbicidal [3-5], virucidal[6] and insecticidal[7-9]. Similarly pyridine ring system associated with herbicidal [10,11], acaricidal[12] and insecticidal[13] activities and pesticidal recognition of pyrimidine ring system is well documented [14,15].

Therefore it is thought of interest to combine either two or three of the above mentioned biolabile rings together in a molecular framework to see the additive effect of these rings towards the biological activities. The investigation was found to be of further interest because of compactness and planarity of such ring systems may be an additive factor for enhancing activities as it does with algicidal, herbicidal, fungicidal, antiallergenic, antiasthamatic and inflammation inhibitory activities.

The required pyrazolones (**1)** were prepared following the literature method[16]. Condensation of these pyrazolones with aromatic aldehydes through Knoevenagal condition furnished the corresponding arylidines (**2)**. The arylidines (**2)** were used as synthon for the preparation of the title compounds. In fact these pyrazolones with an α, β –unsaturated ketone (-CH=CH-CO-) function in their structure have been used as a component of Michael addition. The Michael addition between pyrazolo arylidines (**2)** and ethyl cyano acetate or 2 –amino pyridine followed by cyclo- dehydration furnished the title compounds (**3)** and (**4)** respectively. The details of which are given in **Table-I**.

Materials and method-

Procedure for one typical case for each step has been discussed. Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin –Elmer 881 Spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR spectra in DMSO-d6 on a Perkin-Elmer R-32(400 MHz) Spectrometer using TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on a Joel D-300 Spectrometer.

1-(4-Chlorobenzoyl)-3-methyl-5-pyrazolone (1a)-This compound was prepared following the literature method16 by refluxing a mixture of 4-chlorobenzoic acid hydrazide(0.01M) and ethyl acetoacetate (0.011 M)in methanol for 5 hours. The reaction mixture was poured into ice cold water. When solid mass precipitated out which was filtered, washed, dried and recrystallised from aqueous ethanol, mp 92^{0}C, yield 76%.

Other compounds of this type were prepared similarly and their melting points were recorded (R=2,4-$Cl_2C_6H_3$, 85^{0}C; 2-OHC_6H_4, 105^{0}C; 4-$NO_2C_6H_4$, 110-112^{0}C; $C_6H_5OCH_2$, 82-83^{0}C; 4-$ClC_6H_4OCH_2$, 117^{0}C)

1-(4-Chlorobenzoyl)-4-(4-chlorobenzylidene)-3-methyl-5-pyrazolone (2a)- A mixture of1-(4-chlorobenzoyl)-3-methyl-5-pyrazolone (1a) (0.01 M), 4-chlorobenzaldehyde(0.01M) and fused sodium acetate(0.013M) in glacial acetic acid was refluxed for 3 hours, cooled and poured into water. The solid thus obtained was filtered, washed, dried and re-crystallized from aqueous ethanol, mp 135^{0}C, yield 69%.

Analysis for $C_{18}H_{12}N_2O_2Cl_2$

Calcd: C 60.17; H 3.34; N 7.80 %.

Found: C 60.31; H 3.24; N 7.91%.

IR(KBr):1670(-CH=CH-C), 1700(C=O), 1610 (C=N), 1590, 1570, 1550, 1500 (Aromatic ring);

^1H NMR: 2.2(s, 3H, CH_3),4.5 (s,IH.CH),7.2-7.9(m,8H,ArH).

Other compounds of this type were prepared similarly and recorded in Table-1

1-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-5-cyano-3-methylpyrazolone [3,4-b]pyrid-6-one (3a)- A mixture of 2a (0.01M), ethyl cyano acetate (0.01M) and ammonium acetate (0.08M) was fused for 2 hrs, diluted with methanol and poured into water. The solid thus obtained was filtered, washed, dried and re-crystallized from aqueous ethanol, mp170^{0}C, yield 60%.

Analysis for $C_{21}H_{14}N_4O_2Cl_2$

Calcd: C 59.29; H 3.29; N13.18 %.

Found: C 59.20; H 3.19; N 13.37%.

IR(KBr):3200 (NH), 2240(C≡N), 1710(C=O), 1670 (CONH), 1620(C=N), 1600, 1580,1500 (Aromatic ring);

^1H NMR: 2.3(s, 3H, CH_3), 2.7(-CH-C=N), 3.0 (CH), 6.8-7.8(m,8H, ArH),9.8(s,1H,NH);

MS: m/z 424(M^+)

Other compounds of this type were prepared similarly and recorded in Table-1

1-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-3-methylpyrazolo[4,5-e] pyrido[1,2-a]pyrimidine (4a)- A mixture of 2a (0.01M), 2-aminopyridine (0.01M) and fused sodium acetate in glacial acetic acid was refluxed for 8 hours cooled and poured into water. The solid thus obtained was filtered, washed, dried and re-crystallized from aqueous ethanol, mp 205^{0}C, yield 67%.

Analysis for $C_{23}H_{16}N_4OCl_2$

Calcd: C 63.45; H 3.69; N 12.87 %.

Found: C 63.33; H 3.55; N 12.70%.

IR(KBr):1700(C=O), 1610(C=N),1600 1580,1500 (Aromatic ring);

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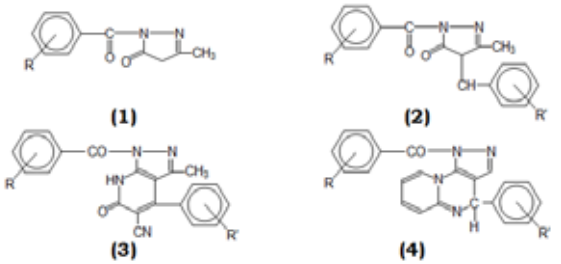
1H NMR: 2.4 (s, 3H, CH3), 7.2-8.6 (m,13H, ArH);

MS: m/z 434(M+)



Other compounds of this type were prepared similarly and recorded in Table-1

TABLE (1) Characterization data of the compounds 2, 3 and 4

Compd	R	R'	Mp °C	Yield (%)	Mol. Formula	Analysis					
						Carbon (%)		Hydrogen (%)		Nitrogen (%)	
						Found	Calcd	Found	Calcd	Found	Calcd
2a	4-Cl	4-Cl	135	69	$C_{18}H_{12}N_2O_2Cl_2$	60.31	60.17	3.49	3.34	7.98	7.80
2b	4-Cl	4-OCH_3	128	66	$C_{19}H_{15}N_2O_3Cl$	64.38	64.32	4.11	4.23	7.72	7.90
2c	2,4-Cl_2	4-OCH_3	112	72	$C_{19}H_{14}N_2O_3Cl_2$	58.78	58.61	3.73	3.60	7.35	7.20
2d	2-OH	4-OCH_3	192	66	$C_{19}H_{16}N_2O_4$	67.97	67.86	4.89	4.76	8.48	8.33
2e	4-NO_2	4-Cl	179	62	$C_{18}H_{12}N_3O_4Cl$	58.59	58.46	3.11	3.25	11.20	11.37
2f	4-NO_2	3,4-$(OCH_3)_2$	140	69	$C_{20}H_{17}N_2O_4$	60.62	60.76	4.43	4.12	7.77	7.90
3a	4-Cl	4-Cl	170	69	$C_{21}H_{14}N_4O_2Cl_2$	59.20	59.29	3.19	3.29	13.18	13.07
3b	4-Cl	4-OCH_3	197	66	$C_{22}H_{17}N_4O_3Cl$	62.89	62.78	3.90	4.04	13.07	13.32
3c	2,4-Cl_2	4-OCH_3	216	64	$C_{22}H_{16}N_4O_3Cl_2$	57.90	58.02	3.42	3.52	12.53	12.31
3d	2-OH	4-OCH_3	140	68	$C_{22}H_{18}N_4O_4$	65.88	65.67	4.60	4.48	14.07	13.93
3e	4-NO_2	4-Cl	210	67	$C_{21}H_{14}N_5O_4Cl$	57.80	57.86	3.15	3.21	16.27	16.07
3f	4-NO_2	3,4-$(OCH_3)_2$	146	69	$C_{23}H_{19}N_5O_6$	60.00	59.87	4.23	4.13	15.18	13.45
4a	4-Cl	4-Cl	205	67	$C_{23}H_{16}N_4OCl_2$	63.33	63.45	3.55	3.69	12.70	12.87
4b	4-Cl	4-OCH_3	182	65	$C_{24}H_{19}N_4O_2Cl$	66.78	66.90	4.29	4.41	13.18	13.00
4c	2,4-Cl_2	4-OCH_3	201	69	$C_{24}H_{18}N_4O_2Cl_2$	62.12	61.94	3.76	3.87	12.18	12.04
4d	2-OH	4-OCH_3	216	65	$C_{24}H_{20}N_4O_3$	70.10	69.90	4.99	4.85	13.75	13.59
4e	4-NO_2	4-Cl	225	70	$C_{23}H_{16}N_3O_3Cl$	62.09	61.95	3.70	3.59	15.87	15.71
4f	4-NO_2	3,4-$(OCH_3)_2$	192	53	$C_{25}H_{21}N_5O_5$	63.81	63.69	4.63	4.46	14.98	14.86

Evaluation of fungicidal activity-The anti fungal activity was evaluated by agar plate technique against *Pyricularia oryzae, Puccina graminis* , *Alternaria solani* , *Pseudopernospora cubensis* and *Phytopthora infestans* at concentrations 500 ppm and 100 ppm. The replications in each case were three. On the basis of growth recorded on 7th day of incubation the fungicidal activity of test compounds was calculated in terms of present inhibition of mycelial growth using the following formula.

Present inhibition of mycelial growth $= \frac{d - d}{d} \times 100$

Where dc = Average diameter growth of the colony in control sets on 7th day of incubation.

dt = Average diameter growth of the colony in treatment set on 7th day of incubation.

Diameter growth=apparent diameter of the colony−diameter of colony of the inoculums

The percentage inhibitions of various compounds are recorded in table -2

TABLE (2) Anti Fungal Activity Data Compounds 3 and 4

Compd.	Average % inhibition after 7 days									
	Pyricularia oryzae		Puccinia graminis		Alternaria solani		Pseudopernospora cubensis		Phytophthora infestans	
	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm
3a	62	45	63	46	64	47	63	46	62	46
3b	64	47	65	48	65	47	65	48	66	48
3c	68	49	69	50	69	51	69	50	67	48
3d	72	51	73	52	71	50	73	52	73	52
3e	74	52	75	53	74	51	75	53	76	54
3f	73	52	72	50	73	52	72	50	74	51
4a	76	53	77	54	77	54	76	52	77	54
4b	82	58	84	60	86	61	86	63	84	61
4c	80	56	79	55	80	56	79	55	80	56
4d	76	53	78	54	77	53	76	53	78	54
4e	82	58	84	60	86	61	86	63	84	61
4f	81	57	82	58	81	57	82	58	81	57
Carbendazim	100	78	100	79	100	78	100	79	100	78

Results and discussion-It is evident from the activity data that the all of the tested compounds have significant fungitoxicity at 500 ppm against all the fungi but their toxicity decreased considerably at lower concentration, although compounds having serial number 4a, 4b, 4c, 4d, 4e and 4f show greater anti fungal activity against all the organisms but the result are not very spectacular except for compounds 4b, 4e and 4f.

It is also evident from the fungicidal screening data of the tested compounds showed that pyrazolo-pyrido-pyrimidines are more effective than pyrazolo-pyridines. The most active compounds are 4b, 4e and 4f (>81%).

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