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SYNTHETIC APPROACH TO SOME PROSPECTIVE ANTIMICROBIAL PYRAZOLONES AND THEIR DERIVATIVES

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ABSTRACT

Substituted pyrazolones are known to exhibit significant biological activities, viz; bactericidal and fungicidal etc. Three series of substituted and fused pyrazolones have been synthesize [A] 5-methyl-2-[2-(aryloxy) propanoyl]-2,4-dihydro-3H-pyrazol-3-one have been synthesised by condensation reaction of ethylacetoacetate and glacial acidic acid. Series [B] (4E)-4-(4-chlorobenzylidine)5-methyl -2-[aryloxy] propanoyl-2,4dihydro-3H-pyrazol-3-one have been synthesized by condensation of p-chlorobenzaldehyde in presence of fused sodium hydroxide and glacial acetic acid. Seris [C] 1-[4-(-chlorophenyl)-3methyl-4,5-dihydropyrazolo(3,4-c)pyrazol-1(3aH)-yl]-2-(aryloxy) propane-1-one have been synthesised in presence of hydrazine hydrate. The entire newly synthesized compound has been screened for their antimicrobial and antifungal activities against E.coli and A.flavous. The compounds characterised by ir, nmr method and antimicrobial study revealed that all that all the compounds screened showed good or moderate activities.

KEYWORDS: Anti-fungal, Anti-bacterial, Chlorobenzaldehyde, hydrazinehydrate, Pyrazolone.

INTRODUCTION

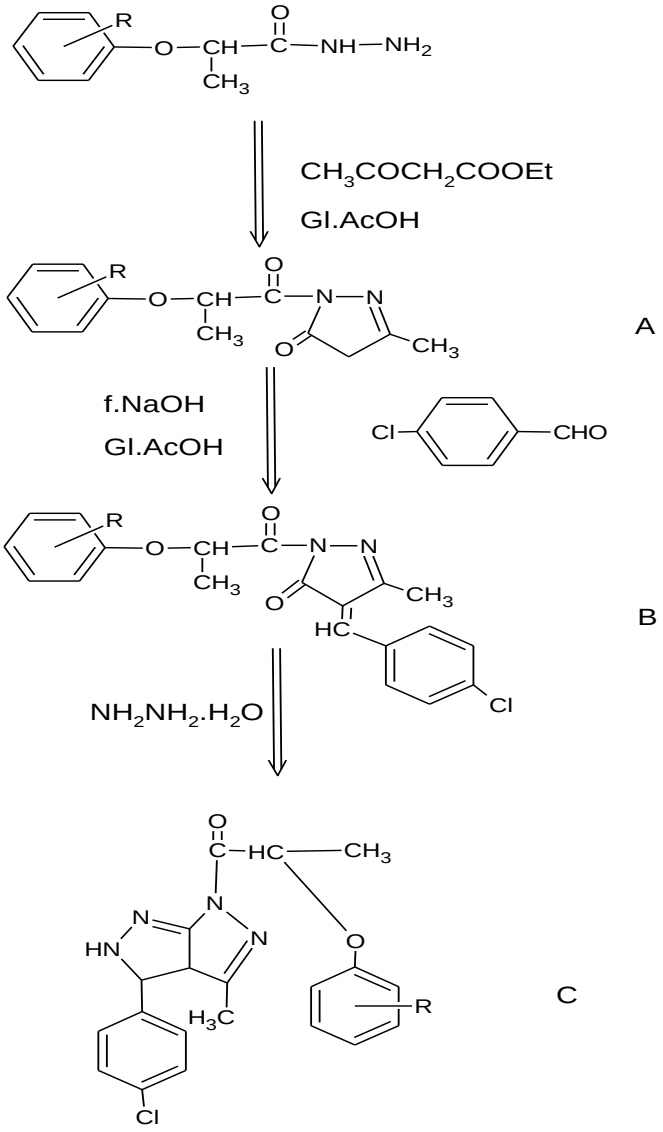
Compounds classified as 'heterocyclic' probably constitute the largest and most varied family of organic compounds. Heterocyclic ring system have been found to be potent in many biological assessment because of their biological activities and properties, heterocyclic compounds have been studied by the several research groups. Pyrazolone and its derivative are of interest to synthetic and medicinal chemists because of their versatile biological activities e.g. Antimicrobial Analgesics Anti-inflamatory and Anti-cancer . They are also used as intermediates in the dye industries.

The purpose of this study is to synthesize some new pyrazolones and

derivatives and to investigate their Anti-microbial activities the antimicrobial activity against pyrazolones derivatives against E.coli and A.flaves. Pyrazolones possess various biological activities. Pyrazolones have been reported to possess anticancer, analgesics, antidiabetic , antitumour , antipyretic , antineoplastic , activities.

Pesticidal properties, are also prominently associated with pyrazolones. Several compounds containing 5-pyrazolones ring are well known for fungicidal, bactericidal, herbicidal, virucida activities.

SCHEME

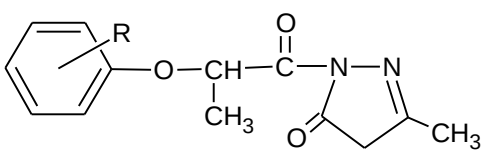


1. Instrumentation and methodology

Charactrised by elemental analysis (Carlo Erba 1108 Heraeus), Infrared (KBr, Nujol, perkin Elmer-R-32- spectrometer, 90MHZ, TMS) and mass (jeol D-300) spectra, melting point were taken in open capillaries. Due to limited facilities available compounds were screened for their antifungal against A.fiavus and antibacterial against E.coli activities. Their antifungal activities against A.flavous involving mixing of toxicants with agar medium and then inoculating a fungus colony on such poisoned food to grow. The antifungal activity of each compound was screened at three different concentrations viz., 1000, 100, and 10ppm. The compounds were tested in acetone solution. One standered solution (1% w/v) of each compound was prepared and 1.0 solution of this solution was diluted by 9.0ml and 99.0ml of the solvent. In this way three solutions of concentrations 1000,100,10 were obtained.

2. General method of preparation of compound A:

A mixture of 2-(aryloxy)propanehydrazide (0.01M) and ethylacetoacetate (0.01M) in acetic acid (5.0ml) was refluxed for four hour, cooled and poured into cold water. The solid separating out was filtered , washed and recrystallised from aqous ethanol.



3. General method of preparation of compound B:

A mixture of 5-methyl-2-[2-(4-methylphenoxy) propanoyl]-2,4-dihydro-3H-pyrazol-3-one(0.01M), fused sodium acetate and p-chlorobenzaldehyde (0.01) in acetic acid was refluxed for four hour, cooled and poured into cold water. The resulting solid was filtered washed and recrystallised.

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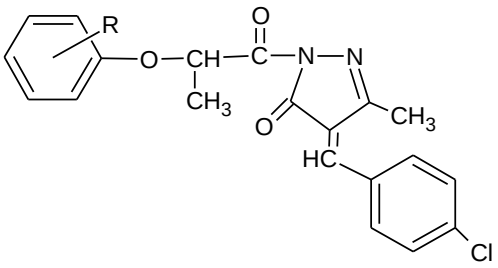

4. General method of preparation of compound C:

A mixture of (4E)-4-(4-chlorobenzylidine)5-methyl -2-[2-aryloxy] propanoyl -2,4dihydro-3H-pyrazol-3-one was refluxed with methanol (10.00ml) for eight hour, methanol evaporated off and residue poured into cold water the solid thus obtained was filtered washed and recrystallized.

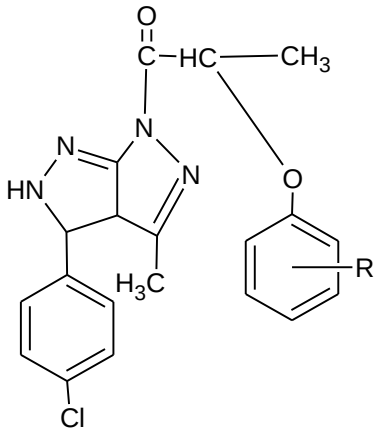

Table 1. Characterisation

SERIES	COMPOUND	MELTING POINT	YIELD IN GRAM
A.1	R=2-Cl	185^0	1.91
A.2	R=2,4-Cl_2	232^0	2.15
A.3	R=2-CH_3	194^0	1.63
B.1	R=2-Cl	180^0	2.27
B.2	R=2,4-Cl_2	250^0	1.52
B.3	R=2-CH_3	200^0	1.53
C.1	R=2-Cl	93^0	1.28
C.2	R=2,4-Cl_2	155^0	1.93
C.3	R=2-CH_3	80^0	0.43

Table 2. Screening

S.No.	Series	Compound No.	R	Average % inhibition after 168 hour. Organism: *A.flavus* concentrations (ppm)			Average % inhibition after 36 hours. Organism: *E.coli* concentrations (ppm)		
				1000	100	10	1000	100	10
1.	A	1	-Cl	69	**50**	32	27	19	0
		2	-2,4-Cl	77	**64**	49	44	35	10
		3	-CH_3	63	47	29	25	17	0
2.	B	4	-Cl	77	52	35	30	20	0
		5	-2,4-Cl	84	69	55	51	38	15
		6	-CH_3	70	49	28	28	18	0
3.	C	7	-Cl	96	55	38	50	25	0
		8	-2,4-Cl	115	75	60	70	45	17
		9	-CH_3	95	51	34	40	22	0

Evaluation and discussion of antimicrobial activities:

Nine compounds of this series have been screened against *A.flaves* and *E.coli* in table. The antifungal activity of each compound was screened at three different concentration viz. 1000, 100, 10ppm. The compounds were tested in acetone solution. One standard solution (1%w/v) of each compound was prepared at 1.0ml of this solution was diluted

by 9.0ml and 99.0ml the solvent. In these way three solutions of concentration 1000,100, 10ppm was obtained.

9,0ml of the medium was taken in several test tubes, plugged with cotton and autoclave for half an hour at pressure of 120 lbs. To this (kept 400) 1.0ml of test solution was added mixed well and sterilized petriplates. The fungus was incubated. The experiment is repeated in triplicates in each case and six numbered of the control were provide.

RESULT AND DISCUSSION

The elemental analysis has been carried out for each compound in all three series. The percentage of C, H and N shows close coherence with the expected molecular formula of the compounds predicted to be formed from the known procedures. Formation of [A] group of compounds are clearliy indicated by ir, and nmr spectra. IR spectra exibit at δmax 1700 cm-1 which corresponds to cyclic ketone another peak is seen at 1620 cm-1 which corresponds to cyclic carbonyl group is present and characteristic peak C=N(1479), C-N(1300). Nuclear magnetic resonance (1H NMR) spectra were recorded by use of perkin Elmer –R- 32 90 MHz spectrometer in deuterated dimethyl sulphoxide (DMSO-d6) with tetra methyl silane as internal refrence; chemical shift (δ) are given in ppm. 1H NMR spectra of compound A has been obtained Ar-H (4H) (m) (6.7-7.4), Ar-CH3 (6H) (s) and (3-CH3) are 2.4 and –CH3 (3H) (d) 1.6-1.7. Formation of compound [C] group of compounds have been again synthesised by ir spectra, which give prominent peak at δmax cm-1 for exocyclic (C=C) 2920 with other usual peaks C=O for cyclic ketone 1700, acyclic C=O(1620), C=N (1500) and C-N (1300). As we proceed the formation of series [C] the peaks of cyclic ketone disappear and one CO group remains isolated giving peak at 1600 cm-1 along with other usual peaks C=N (1570), C-CH3 (1390), =C-O-C (1260). The NMR peaks very well fit in the proposed structure of these compounds proving that the compounds have been actually formed.

a. Antifungal screening:

All the compounds show bearable level of antifungal activity. In the aryloxy moiety a chloro group in place of a methyl has been found to enhance the activity. Fused pyrazolones show highest level of activity.

b. Antibacterial activity:

All nine compounds screened show average Antibacterial activity. Increase in the number of –Cl group increases activity to greater extent.

CONCLUSION

Pyrazolones are promising anti-microbial agents. Toxophores like –Cl and –CH3 enhance the activity substantially. Fused pyrazoles are found to be far – far more active towords both bacteria and fungus. The work has lots of scope in preparing rare derivatives encluding –OCH3, -OH and –CHO groups increasing the numbers of toxophores also provide wider scope to the present work.

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