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RESEARCH ARTICLE

NOVEL SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRAZOLINES AND ITS DERIVATIVES

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ABSTRACT

Biologically active Pyrazoline derivatives were efficiently synthesized in excellent yields and in less reaction time using ethanol via cyclization reaction of chalcones and Substituted hydrazines. These newly synthesized compounds were screened for their antimicrobial potencies which reflects moderate to good activity against different strains of bacteria and fungi employed. All the synthesized compounds were confirmed by IR, 1HNMR and Mass spectral data.

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INTRODUCTION

Due to the rapid development of bacterial resistance to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity such as antibacterial (Hogale *et al.,* 1986), antitumour (Yamakawa *et al.,* 1990), anticancer (Ahluwalia *et al.,* 1987), antitubercular (Bhatt *et al.,* 1972), anti-inflammatory (Mukherjee *et al.,* 2001), antioxidant (Indyah *et al.,* 2000), antimalarial (Chen *et al.,* 1997), antileishmanial (Nielsen *et al.,* 1998) etc. The presence of reactive α, β-unsaturated keto group in chalcones is found to be responsible for their biological activity. In the present work chalcones have been prepared according to claisen-schimidt condensation by condensing various ketones with aromatic aldehyde. Available data suggest that N containing heterocyclic compounds from chalcones possesses wide variety of activities (Vibhute, 2003; Bhat *et al.,* 2005; Edwards *et al.,* 1990; Kalirajan *et al.,* 2007) such as potential cytotoxic agents, antimicrobial agents, antiviral, antiinflammatory, anesthetics, mydriatics etc.

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Led by these considerations, it appeared of interest to synthesize novel pyrazoline derivatives and screened for their antimicrobial activities

MATERIALS AND METHODS

Section –A

Preparation of Acetophenone

The 2-Hydroxy-5-chloroacetophenone (IIa) was prepared by Fries migration of p-chlorophenol acetate (Ia) in presence of $AlCl_3$, mp. 55°C

Preparation of 2-Hydroxy- 3-bromo-5-chloroacetophenone (IIb)

The 2-Hydroxy- 3-bromo-5-chloroacetophenone (IIb) was prepared by the bromination of acetophenone (IIa) with bromine in acetic acid mp. 90°C.

Section –B

Preparation of Chalcones

Acetophenone (IIa-b) on condensation with aldehydes gave corresponding chalcones. The following chalcones were prepared.

Condensation with Anisaldehyde: 2-Hydroxy- 3-bromo-5-chloro-4-anisylchalcone (IIIa) mp. 172^{0}C

Condensation with Benzaldehyde: 2-Hydroxy- 3-bromo-5-chloro chalcone (IIIb). mp 124^{0}C

Section C

1. Preparation of 1-Phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline (IVa)

A mixture of 2-Hydroxy- 3-bromo-5-chloro-4-anisyl chalcone (IIIa) (0.01mole) and 99% Phenyl hydrazine (IIa) (0.015mole, 0.6 ml) in ethanol (60ml) was refluxed for about two hours. The reaction mixture was then concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and crystallized from ethanol to get yellow solid of 1-Phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(IVa) mp.142^{0}C ,Yield 75%

2. Preparation of 1-(2,4dinitro phenyl)-3- (2- hydroxy -3 -bromo- 5- chlorophenyl) -5-phenyl - 2- Pyrazoline (IVb)

A mixture of 2-Hydroxy- 3-bromo-5-chloro-chalcone (IIIb) (0.01mole, 3.37g) and 99% 2,4-dinitro phenyl hydrazine (IIa) (0.015mole, 0.6 ml) in ethanol (60ml) was refluxed for about two hours. The reaction mixture was then concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and crystallized from ethanol to get yellow solid of 1-(2,4dinitro phenyl)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-Pyrazoline(IVb) mp.175^{0}C, Yield 75%

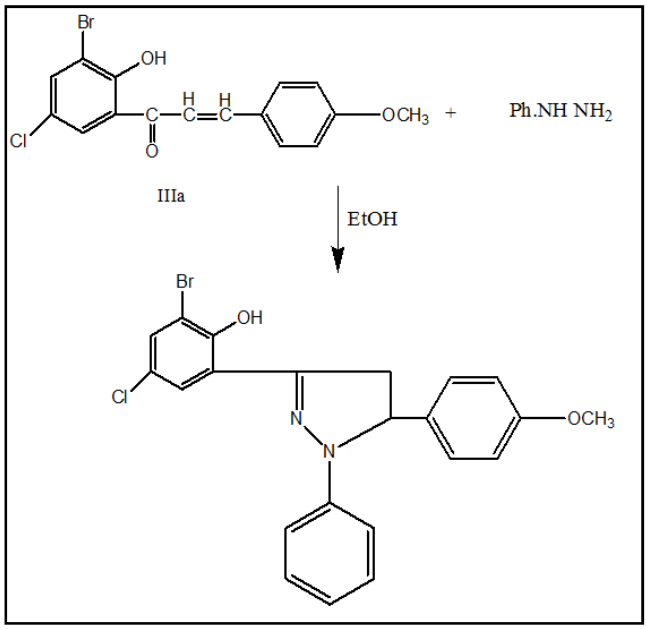
Section D
Preparation of Acetyl Derivative

1. Preparation of 1-(4-acetyl-benzene)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline (Va)

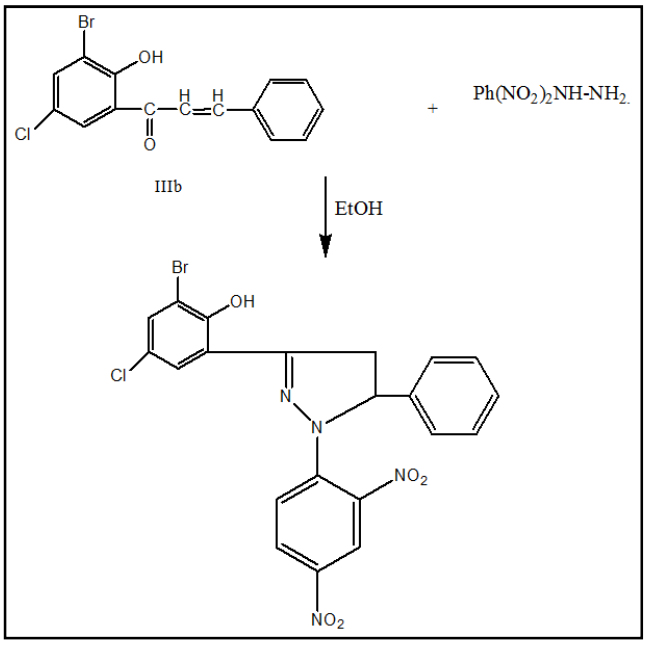
Mixture of 1 -phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-pyrazoline(IVa) (0.01mole, 3.81g) and acetic acid (15ml) was refluxed for 2 hours. The reaction mixture was then concentrated. On cooling the resulting solid was filtered,washed with water and crystallised from ethanol, to get (Va), mp 60^{0}C, Yield 68%

2. Preparation of 1-(5-acetyl,2,4dinitroPhenyl)-3-(2-hydroxy-3-bromo- 5-chlorophenyl)-5-phenyl -2-Pyrazoline (Vb)

Mixture of 1 -(2,4 dinitro phenyl)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-pyrazoline(IVb) (0.01mole, 3.51g)



IVa



IVb

Table 1.

Sr.No	Chalcone	Hydrazine	2-Pyrazoline	Mp^{0}C
1.	2-Hydroxy-3-bromo- 5-chloro-4-anisylchalcone (IIIa)	Phenyl hydrazine	1-Phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(IVa)	142
2	2-Hydroxy-3-bromo-5-chlorochalcone (IIIb)	2,4dinitroPhenyl hydrazine	1-(2,4 dinitro phenyl)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-Pyrazoline(IVb)	175

Table 2.

SR.NO	2-PYRAZOLINE	ACETIC ACID	ACETYL PYRAZOLINE	Mp^{0}C
1.	1-H-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(IVa)	Acetic acid	1-acetyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(Va)	60
2	1-H-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-Pyrazoline(IVb)	Acetic acid	1-acetyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-Pyrazoline(Vb)	55

and acetic acid (15ml) was refluxed for 2 hours. The reaction mixture was then concentrated .On cooling the resulting solid was filtered,washed with water and crystallised from ethanol, to get (Vb) ,mp 55^0C ,Yield 72%

RESULT AND DISCUSSION

1. Preparation of 1-phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(IVa)

2-Hydroxy- 3-bromo-5-chloro-4-methoxy chalcone (IIIa) and hydrazine hydrate in ethanol on refluxing gave yellow solid(IVa) mp 124^0C Yield-70%

The compound (IVa) is yellow coloured crystalline solid mp124C^0

2. It gives green colouration with neutral $FeCl_3$ solution indicating presence of free phenolic –OH group.
3. It gives deep blue colouration with concH_2SO_4 solution showing the absence of - C –CH = CH- linkage
5. From analytical data molecular formula of the compound (IVa) was found to be $C_{22}H_{19}O_2N_2BrCl$
4. Purity of the compound was tested by TLC

6 The I.R and NMR spectra of the compound (IVa)

Literature value cm-1	Observsd value	Assignment
3600-3000	3380	-NH stretching
1700-1550	1540-1550	-OH stretching
1300-1100	1240(s)	-C-N stretching
1470-1400	1400	-CH_2 stretching
1310-1320	1310	-OCH_3 stretching
800-700	790	C-Cl stretching
700-600	650	C-Br stretching

7. The PMR spectrum of the compound (IVa) was recorded as:

Peak observed	Multiplicity	Assignment
3.80	S	3H, -OCH_3
3.06	dd	1H, -CHH_A
3.48	dd	1H, -CH_BH
4.90	dd	1H, -CHX
6.8-7.8	m	1H , -NH and 6H, Ar -H .
11.92	s	1H, -OH

All these observation confirms the structure of compound(IVa)

II) 1. Preparation of 1-(4-acetyl benzene)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline(Va)

Mixture of 1 -phenyl-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-pyrazoline (IVa) and acetic acid was refluxed for 2 hours. The reaction mixture was then concentrated .On cooling the resulting solid was filtered,washed with water and crystallised from ethanol, to obtain (Va) ,mp 60^0C ,Yield 68%

The compound (Va) is orange coloured crystalline solid mp 60^0C

2.It gave deep blue colouration with neutral $FeCl_3$ solution indicating the presence of free phenolic –OH group.
3.It gives deep blue colouration with concH_2SO_4 solution showing the absence of - C –CH = CH- linkage.
4.Purity of the compound was tested by TLC.
5. From analytical data molecular formula of the compound (Va) was found to be $C_{24}H_{26}O_3N_2BrCl$

6. The I.R and NMR spectra of the compound (Va)

Literature value cm-1	Observsd value	Assignment
3600-3000	3380-3350	-OH stretching
3100-3000	3000	Ar-H
1720-1680	1680-1670	C=O stretching and N-C=O stretching
1700-1500	1640-1630	-C=N of Pyrazoline
1610-1590	1610-1600	Benzene ring
1310-1100	1230	C-N stretching
800-600	740	C-Cl stretching
700-600	650	C-Br stretching

7. The PMR spectrum of the compound (Va) was recorded as:

Peak observed	Multiplicity	Assignment
2.8	S	3H, -$COCH_3$
3.14	dd	1H, >CHHA JAB= 18HZ
3.6	dd	1H, >CHBH JAB= 18HZ JBX= 11HZ
3.88	s	3H, -OCH3
5.56	dd	1H, >CHX JAX= 4Hz JBX=11HZ
6.48 to7.44	m	7H, Ar-H
10.56	s	1H, -OH

All these observation confirms the structure of compound(Va)

Table 1. Minimum Inhibitory Concentration (MIC in %) of Chalcone

SR.NO	Name of the Compound	S. typhi	S.para typhi	P.vulgaris	X.sapp	F.solanii	B.cinerea
1	2-Hydroxy- 3-bromo-5-chloro-4-anisylchalcone **(IIIa)**	0.27	0.28	0.27	0.26	0.26	0.26
2	2-Hydroxy- 3-bromo-5-chloro chalcone **(IIIb).**	0.71	0.69	0.60	0.67	0.69	0.69

Table 2. Minimum Inhibitory Concentration (MIC in %) of Pyrazolines

Sr.No	Name of the Compound	S. typhi	S.para typhi	P.vulgaris	X.sapp	F.solanii	B.cinerea
1	1-phenyl-3-(2-hydroxy-3-bromo-5chlorophenyl)-5-anisyl-2-Pyrazoline**(IVa)**	0.20	0.20	0.20	0.20	0.22	0.22
2	1-(2,4 dinitro phenyl)-3-(2-hydroxy-3-bromo-5chlorophenyl)-5phenyl-2-Pyrazoline **(IVb)**	0.30	0.22	0.31	0.31	0.30	0.30

Table 3. Minimum Inhibitory Concentration (MIC in %) of Acetyl Pyrazolines

Sr.no	Name of the Compound	S. typhi	S.para typhi	P.vulgaris	X.sapp	F.solanii	B.cinerea
1	1-(4-acetyl-benzene)-3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-anisyl-2-Pyrazoline**(Va)**	0.09	0.11	0.10	0.12	0.92	0.09
2	1-(5-acetyl,2,4dinitroPhenyl)--3-(2-hydroxy-3-bromo-5-chlorophenyl)-5-phenyl-2-Pyrazoline**(Vb)**	0.20	0.21	0.21	0.23	0.23	0.23

Antimicrobial Activity of Synthesised Compounds

The pyrazoline when screened in vitro against the test organisms Salmonella typhi, Salmonella paratyphi, Proteus vulgaris, Xanthomonas, Fusarium solanii and Botrytis cinerea and it was noticed that most of all these compounds have shown remarkable inhibitory activity. An assay of newly synthesized Chalcones, pyrazoline S and Acety Pyrazolines revels that, almost all the compounds were strongly active against all the test pathogens. The minimum inhibitory concentration (MIC) values were determined by serial dilution method. The comparative study of MIC values of the compound are given in the Tables 1, 2and 3

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