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THE SYNTHESIS AND SPECTRAL STUDIES OF PYRAZOLE DERIVATIVES PROVEN EFFECTIVE AS ANTIBACTERIAL & ANTIFUNGAL ACTIVITY

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Abstract
Present work deals with the preparation of some pyrazole derivative which was prepared by using 2-hydroxyphenyl hydrazone derivatives by using DMF and $POCl_3$. After a complete addition of $POCl_3$. The structure of newly synthesized compounds are characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR analysis. The newly synthesized compounds were screened for antibacterial & antifungal activity. The investigation of biological screening data revealed that most of the tested compounds showed moderate to good antibacterial and antifungal activity.

Key words:
Hydrazone derivative, antibacterial, I.R. spectra, ^{1}H- NMR, antifungal, C^{13}- NMR, etc.

Introduction:
Pyrazole, itself, is a volatile, colourless, crystalline solid with a pyridine like odour. It is soluble in water, ethanol, and ether to lesser extent, benzene and cyclohexane. It is insoluble in petroleum ether. Much of the basic information obtained about the chemistry of the pyrazole moiety was its aromatic properties compared to those of benzene derivatives. The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. This is mainly due to the ease preparation and the important biological activity.

Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry. Pyrazole derivatives have been reported to wide range of biological activity. Pyrazoles have received a considerable interest in the field of drug discovery and therefore pyrazole ring constitutes a relevant synthetic target in pharmaceutical industry. In fact, such a heterocyclic moiety represents the core structure of a number of drugs. The wide range of biological activity of pyrazoles has made them popular synthetic targets. There are a number of book chapters and literature reviews dedicated to the synthesis of pyrazole and condensed pyrazoles. The

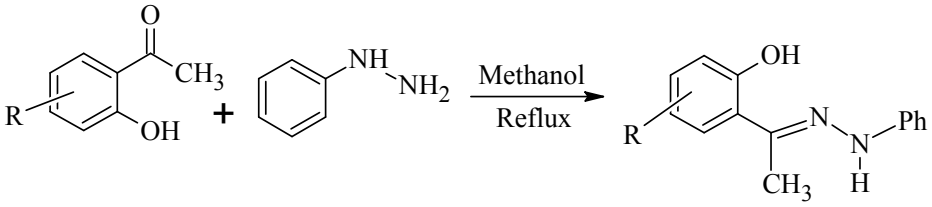
compounds containing pyrazole nucleus has wide applications in medicinal chemistry as well as considerable interest in the chemotherapeutic activity.

Pyrazole and their synthetic analogues have been found to exhibit industrial, agricultural and some biological application. For example some alkyl, aryl substituted pyrazoles have pronounced sedative action on the central nervous system. In recent experiment we have tried to decrease the reaction time required to complete the reaction for that purpose we had successfully driven our reaction, by Biginilli type of condensation in basic medium and those synthesized compounds were subjected to antibacterial and antifungal activity to compare their potentials.

General procedure for the preparation of phenyl hydrazones intermediate (I a-g)

To a solution of the appropriate 2-hydroxyacetophenone derivatives (24 mmol) in methanol (40 ml), phenyl hydrazine (24 mmol) was added and refluxed for two hours. After cooling the reaction mixture the phenyl hydrazone derivatives was crystallized and filtered, the higher yield intermediate was obtained.

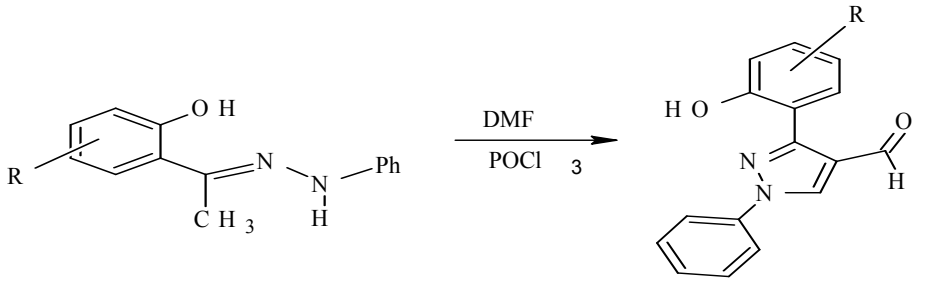
Scheme:



General procedure for the preparation of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehyde (II a-g):

The derivatives of2-hydroxyacetophenone phenylhydrazone (0.01 mol) was dissolved in DMF (15 ml) and then $POCl_3$ (0.03 mol) was added drop wise at 0 ^{0}C. After a complete addition of $POCl_3$, the reaction mixture warmed by hand at room temperature and heated at 60-70 ^{0}C for 2-3 hrs. The reaction was poured on to crushed ice and then neutralized with 10 % aqueous NaOH solution. The precipitate was filtered and washed with water and recrystallize from ethanol, this process give a high yield compounds.

Scheme:



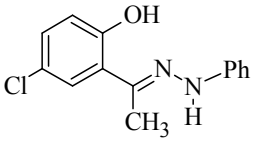
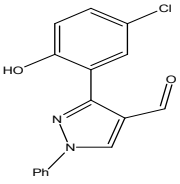
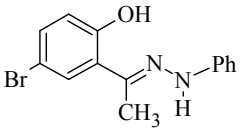
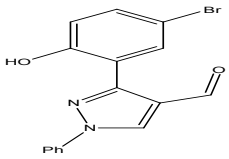
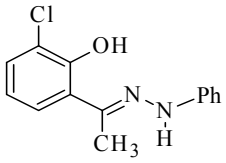
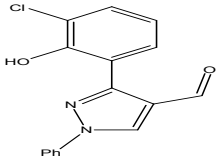
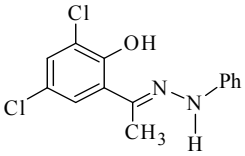
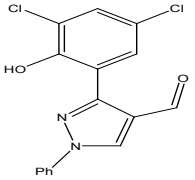
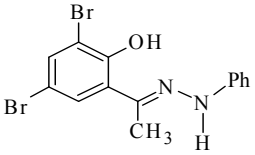
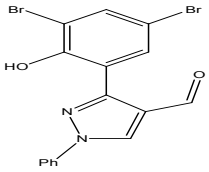
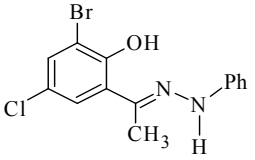
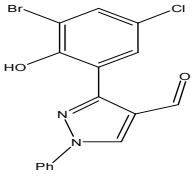
Experimental

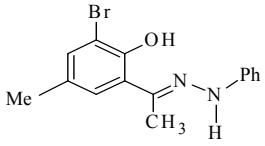
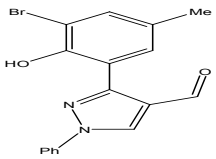
Material and Methods

All the chemicals and solvents were obtained from E-Merck and SD fine chemicals L.T.D. India (AR, LR grade) Melting points were determined in open capillaries in liquid paraffin bath and are uncorrected. Purity of the compound was routinely checked on silica gel TLC plates using $CHCl_3$ as solvent. ^{1}H NMR spectra were recorded on 200 MHz spectrometers in appropriate solvent using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scale. Multiplicities of ^{1}H NMR signals are

designated as- s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), quin (quintet), m (multiplet), etc. IR data were recorded an Alpha-T ATR-FTIR.

Table 1:Observation Table

Sr.No.	R	Intermediate	M.P. (^{0}C)	Yeild (%)	Product	M.P. (^{0}C)	Yeild (%)
1	Cl		170	91		132	82
2	Br		164	90		136	84
3	Cl		146	92		148	81
4	Cl		134	89		166	86
5	Br		152	93		172	88
6	Br,Cl		144	90		174	82

7	Br,Me		172	88		160	83

Antibacterial activity/Antifungal activity:

Antibacterial activity study was carried out by cup-plate agar diffusion method using nutrient agar by using sterile borer. The compounds were tested *in-vitro* for their antibacterial activityagainst microorganism viz. gram positive *Staphylococcus aureus & Bacillus subtilis, gram negative Escherichia coli & Proteus vulgaris.* Antifungal activity study was carried out by cup-plate agar diffusion method using nutrient agar. Fungal culture were made in the Sabouraud-Dextrose agar and the incubated at 37 ^{0}C for 18-24 hrs. The concentration was 200 µg/ml. The compounds were tested *in-vitro* for their antifungal activity against *viz. Aspergillusniger& Candida ablicans.* Standard drugs Ciprofloxacin and Griseofulvin were used.

Table 2:Zone of inhibition for minimal bactericidal conc. & minimal fungicidal conc.

Compound	Minimal bactericidal conc. µg/ml				Minimal fungicidal conc. µg/ml	
	S. aureus	***B.subtilis***	***E. coli***	***P.vulgaris***	***A. niger***	***C. ablicans***
II a	12	15	19	17	16	16
II b	17	18	16	14	17	19
II c	12	12	14	15	15	15
II d	18	19	21	16	20	17
II e	17	15	19	20	19	18
II f	14	16	20	19	18	17
II g	16	17	14	18	17	19
Ciprofloxacin	23	18	20	22	-	-
Griseofulvin	-	-	-	-	21	24

Results and discussion:

To overcome the resistance to antibacterial agents since last three decades promotes us to synthesize such a biologically active compound as second nitrogen in the five-membered ring

also influencesthe antibacterial or pharmacokinetic properties. And the synthesized compounds were screened for their *in vitro* antibacterial and antifungal activity. Some of the derivatives showed moderate to excellentactivity.

***Spectral Data for Intermediate (I a-g)**

a) 5-chloro-2-hydroxy acetophenone phenylhydrazone (I a)

Yield: 91%; **mp:** 170^{0}C;**IR (KBr)**ν = 3345, 3026, 1601 cm-1; **^{1}H NMR ($CDCl_3$) δ:** 2.30 (s, 3H) 6.93-7.03 (m, 4H) 7.16 (dd, 1HJ1= 8.4Hz, J2= 2.4Hz) 7.29-7.36 (m, 4H) 12.49 (s, 1H); **^{13}CNMR ($CDCl_3$)**δ **:**16.2, 115.4, 118.3, 119.8, 120.6, 128.1, 129.8, 130.5, 133.8, 145.1, 160.4, 170.1; **ms: m/z**262 (M^{+2}), 260 (M^+) 243.

b) **5-Bromo-2-hydroxy acetophenone phenylhydrazone (I b)**

Yield: 90%; **mp:** 164^{0}C ; **IR (KBr)** ν = 3354, 3049, 1600 cm^{-1} ; **^{1}HNMR($CDCl_3$)** δ:2.32(s, 3H) 7.01 (d, 1H, J= 7.5Hz)7.08- 7.12(m, 3H) 7.21 (dd, 1H J1= 7.8Hz, J2= 2.7Hz) 7.24-7.34 (m, 3H) 7.44 (d, 1H, J= 2.7Hz)12.61 (s, 1H); **^{13}CNMR ($CDCl_3$)δ:** 15.8, 114.9, 117.1,119.4, 119.8, 121.5, 128.2, 136.3, 137.1, 145.4, 159.2, 168.2; **ms: m/z** 306 (M^{+2}), 304(M^+)

c) **3-Chloro-2-hydroxy acetophenone phenylhydrazone (I c)**

Yield: 92% ; **mp:** 146 ^{0}C ; **IR (KBr)** ν = 3325, 3055, 1601 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 2.34 (s, 3H) 6.81(t, 1H, J= 8.1Hz) 6.94 (t, 1H, J= 7.2Hz) 7.31 (d, 2H, J= 8.1Hz), 7.27-7.33 (m, 4H) 12.63 (s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 16.1, 115.3, 119.2, 120.3, 122.8, 125.6, 129.7, 129.8, 134.5, 144.2, 158.6, 169.3; **ms: m/z** 262 (M^{+2}), 260 (M^+)

d) **3,5-Dicholro-2-hydroxy acetophenone phenylhydrazone (I d)**

Yield: 89%; **mp:** 134 ^{0}C; **IR (KBr)** ν = 3344, 3036, 1604 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ: 2.33 (s, 3H) 6.96 (t,1H, J= 7.5Hz) 7.02 (d, 2H, J= 7.5Hz) 7.28-7.33 (m, 4H) 7.39 (d, 1H, J=2.1Hz) 13.18 (s, 1H). **^{13}C NMR ($CDCl_3$)** δ: 15.9, 115.9, 119.8, 122.0, 126.7, 129.3, 129.5, 129.8, 135.6, 144.8, 157.8, 168.8; **ms: m/z** 296 (M^{+2}), 294 (M^+)

e) **3,5-Dibromo-2-hydroxy acetophenone phenylhydrazone (I e)**

Yield: 89%; **mp:** 134 ^{0}C; **IR (KBr)** ν = 3358, 3047, 1608 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ: 2.34(s, 3H) 6.99 (t, 1H, J= 8.1 Hz) 7.09 (d, 2H, J= 7.1Hz) 12.87(s, 1H) 7.31(s, 1H) 7.48(d, 1H, J= 2.4Hz) 7.32-7.36(m, 3H); **^{13}C NMR ($CDCl_3$)** δ : 115.9, 16.1, 116.0, 119.1, 119.4, 124.2, 128.1, 139.3, 134.2, 143.9, 159.1, 169.2 **ms: m/z** 386 (M^{+4}), 384 (M^{+2}), 382 (M^+)

f) **3-Bromo-5-chloro-2-hydroxy acetophenone phenylhydrazone (I f)**

Yield: 89%; **mp:** 134 ^{0}C; **IR (KBr)** ν = 1599, 3345, 3048 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 2.32 (s, 3H) 7.04(d, 2H, J= 7.2Hz) 6.98(t, 1H, J= 7.2Hz) 7.29(s, 1H) 7.32-7.34(m, 3H) 7.47 (d, 1H,J= 2.4Hz) 13.02 (s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 15.8, 114.1, 116.3, 118.1, 120.0, 128.2, 128.3, 128.6, 133.5, 142, 158.2, 169.1; **ms: m/z** 342(M^{+4}), 340(M^{+2}), 338(M^+)

g) **3-Bromo-5-methyl-2-hydroxy acetophenone phenylhydrazone (I g)**

Yield: 89%; **mp:** 134 ^{0}C ; **IR (KBr)** ν = 3344,3026, 1597 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 2.29 (s, 3H) 2.32 (s, 3H) 6.95 (t, 1H, J= 7.5Hz) 7.04 (D, 2H, 8.4Hz) 7.16 (s, 1H) 7.26-7.31 (m, 3H) 7.32 (d, 1H, J= 1.8Hz) 13.17 (s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 16.1, 22.9, 112.6, 115.8, 117.0, 122.1, 128.3, 128.9, 134.0, 138.2, 142.4, 157.7, 169.4; **ms: m/z** 320(M^{+2}), 318(M^+)

***Spectral Data for Product: (II a-g)**

a) 3-(5-chloro-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (a)
Yield: 82%; **mp:** 132 ^{0}C; **IR (KBr)** ν = 3450, 3159,1657,1683 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 7.02 (d, 1H, J= 8.4Hz), 7.25 (dd, 1H, J1= 8.7Hz, J2= 2.4Hz), 7.43 (t, 1H, J= 7.2Hz), 7.54 (t, 2H, J= 7.8Hz), 7.69 (d, 2H, J= 7.8Hz), 8.07 (d, 1H, J= 2.1Hz), 8.56 (s, 1H), 10.14 (s, 2H); **^{13}C NMR ($CDCl_3$)** δ : 116.4, 118.5, 119.3, 122.8, 124.2, 128.4, 129.0, 129.7, 130.6, 133.5, 137.6, 150.9, 154.4, 183.2; **ms: m/z** 298 (M^+)

b) 3-(5-bromo-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (b)
Yield: 84%; **mp:** 136 ^{0}C ; **IR (KBr)** ν = 3454, 3119, 1683, 1598 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 7.01 (d, 1H, J= 8.7Hz), 7.42-7.49 (m, 2H), 7.57(t, 2H, J= 8.4Hz), 7.72 (d, 2H, J= 8.4Hz), 8.23 (s, 1H), 8.59 (s, 1H), 10.18(s, 1H), 10.20(s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 117.2, 117.7, 118.0, 119.2, 124.8, 128.4, 131.2, 131.4, 133.7, 134.6, 141.8, 151.8, 153.6, 183.4; **ms: m/z** 342 (M^+)

c) 3-(3-Chloro-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (c)
Yield: 81%; **mp:** 148 ^{0}C; **IR (KBr)** ν = 3448, 3120, 1693, 1664 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ :6.97 (t, 1H, J= 7.8Hz), 7.41-7.45 (m, 2H), 7.53 (t, 2H, J= 7.5Hz), 7.71 (d, 2H, J= 8.1Hz), 7.98 (d, 1H, J= 7.8Hz), 8.58 (s, 1H), 10.13 (s, 1H), 10.65 (s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 119.2, 116.6, 119.5, 123.0, 121.9, 128.2, 128.4, 131.2, 129.8, 137.7, 133.4, 151.4, 183.5, 151.7; **ms: m/z** 298(M^+)

d) 3-(3,5-Dichloro-2hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (d)
Yield: 86%; **mp:** 166 ^{0}C; **IR (KBr)** ν = 1687, 3444, 3117, 1654 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 7.54 (t, 2H, J= 7.5Hz), 7.44-7.47 (m, 2H), 7.70 (d, 2H, J= 7.5Hz), 8.18 (s, 1H), 8.54 (s, 1H), 10.11 (s, 1H), 10.79 (s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 119.5, 117.4, 122.7, 124.4, 123.2, 127.9, 128.8, 130.0, 130.8, 134.2, 137.7, 150.4, 150.8, 183.0; **ms: m/z** 332(M^+)

e) 3-(3,5-dibromo-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (e)
Yield: 88%; **mp:** 172 ^{0}C; **IR (KBr)** ν = 3360, 3126, 1689, 1661 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 7.49 (t, 1H, J= 8.7Hz), 7.56 (t, 2H, J= 8.7Hz), 7.72 (d, 2H, J= 8.4Hz), 7.75 (d, 1H, J= 2.4Hz), 8.37 (d, 1H, J= 2.4Hz), 8.60 (s, 1H), 10.14 (s, 1H), 10.96(s, 1H); **^{13}C NMR ($CDCl_3$)** δ : 116.4, 117.1, 117.4, 121.3, 127.2, 128.4, 131.5, 132.1, 135.8, 136.4, 141.9, 151.6, 152.8, 182.8; **ms: m/z** 424(M^{+4}), , 422(M^{+2}), 420(M^+)

f) 3-(3-Bromo-5-chloro-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde
(f)Yield: 82%; **mp:** 174 ^{0}C; **IR (KBr)** ν = 3099, 3344, 1685, 1649 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 7.48 (t, 1H, J= 7.2Hz), 7.57 (t, 2H, J= 7.2Hz), 7.59 (d, 1H, J= 2.4Hz), 7.74 (d, 2H, J= 7.2Hz), 8.26 (d, 1H, J= 2.4Hz), 8.61 (s, 1H), 10.16 (s, 1H), 10.96 (s, 1H); **^{13}C NMR ($CDCl_3$)**δ : 117.2, 117.6, 119.2, 125.2, 128.4, 129.3, 131.4, 131.6, 132.1, 132.9, 139.7, 152.5, 154.7, 184.1; **ms: m/z** 380(M^{+4}), 376(M^+)

g) 3-(3-Bromo-5-methyl-2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde
(g)Yield: 83%; **mp:** 160 ^{0}C ; **IR (KBr)** ν = 3489, 3130, 1680, 1645 cm^{-1}; **^{1}H NMR ($CDCl_3$)** δ : 2.36 (s, 3H), 7.44-7.46 (m, 2H), 7.54 (t, 2H, J= 7.2Hz), 7.72-7.75 (m, 3H), 8.59 (s, 1H), 10.17 (s, 1H), 10.40 (s, 1H); **^{13}C NMR ($CDCl_3$)**δ : 22.8, 116.1, 115.5, 119.3, 123.7, 128.2, 131.4, 132.1, 133.0, 134.7, 135.3, 141.2, 151.0, 151.8, 182.8; **ms: m/z** 358(M^{+2}), 356(M^+)

Conclusion:

The main target of our reaction is to reduce the reaction time and efficiency of the product. Here, we have presented an operationally simple, suitable, fast, efficientmethod for the preparation of Pyrazole derivative. The main focus of this research work was to synthesize, purify, characterize and evaluate antibacterial & antifungal activities of the synthesized compounds & which shows good antibacterial as well as antifungal activity.

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