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Research Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL PYRAZOLE DERIVATIVES

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ABSTRACT

Pyrazole derivatives are found to exhibit various pharmacological activities. On the basis of literature study the main objective of the present work was to synthesize new potent bioactive pyrazole derivatives. We have prepared 14 novel pyrazole derivatives. The newly synthesized compounds were analyzed by IR, ^{1}H-NMR and Mass spectral analysis. The entire series of the synthesized compounds was evaluated for their biological activities.

Keywords: Pyrazole Derivatives, Schiff Base, Biological Activities, MIC

1. INTRODUCTION

Pyrazole is a five member ring with two nitrogen atoms, separated by 1, 2 positions. It is also known as azoles. Pyrazole is an organic compound with the formula $C_3H_4N_2$. In the structure of pyrazole, there are three carbon atoms and two nitrogen atoms [1]. Pyrazole is a colorless solid with m.p. 69-70°C and boiling point 186-188°C.

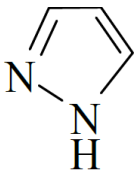

Fig. 1: Pyrazole Moiety

Pyrazoles have illustrious history. In 1883, a German chemist Ludwig Knorr was the first to discover antipyretic action of pyrazole derivative in man. He named the compound as antipyrine. When he attempted to synthesize quinoline derivatives with antipyretic activity, accidentally obtained antipyrine i.e. (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) (i.e. pyrazole derivative). It has analgesic, antipyretic and antirheumatic activities. Looking to pharmacological importance many researchers started working in the field of pyrazole chemistry.

Pyrazole derivatives are found to posses various biological activities such as anti-proliferative [2], anti-microbial [3], anti-viral [4], anti-tumor [5, 6], anti-histaminic [7], anti-depressant [8], insecticidal [9], etc.

2. MATERIAL AND METHOD

2.1. General

All chemicals used in the synthesis of the titled compounds were of analytical grade. Melting points were reported by the open capillary tube method and are uncorrected. Merck Kieselgel 60 F254 plates were used for TLC using mobile phase ethyl acetate: chloroform (4:1). IR spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pallets. The ^{1}H NMR spectra were recorded in DMSO d_6 solution in 5 mm tubes at room temperature, on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using broth dilution method to determine minimum inhibitory concentration (MIC).

2.2. Synthesis of 4-hydroxy methyl benzoate (I)

In a round bottom flask, a mixture of 4-hydroxy benzoic acid (0.26 mol) and 25 ml methanol was taken and sulphuric acid was added to it drop wise through a dropping funnel. The solution was heated to reflux for 6 hours. It was then cooled to room temperature and poured into ice cold water to form the product 4-hydroxy methyl benzoate. The product was filtered, washed and dried. Finally, the product was re-crystallized from ethanol. The progress and completion of the reaction were confirmed by TLC. Mobile phase for TLC toluene: acetone (8:2), Yield: 85 %, M.P.: 260°C - 263°C.

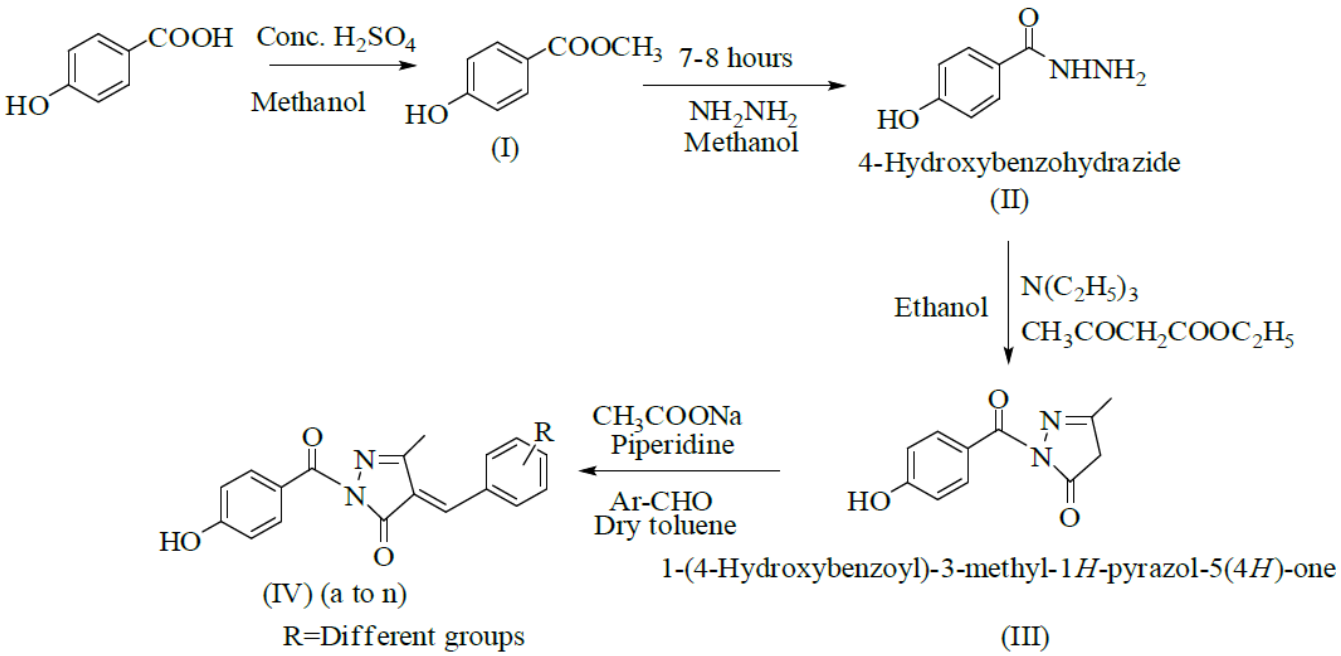

Fig. 2: Reaction scheme for the synthesis of the compounds IV(a-n)

2.3.Synthesis of 4-hydroxybenzo hydrazide (II)

In a round bottom flask a mixture of 4-hydroxy methyl benzoate (0.22 mol) and hydrazine hydrate (0.22 mol) in methanol was heated for 7-8 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The white precipitate was obtained to form 4-hydroxybenzo hydrazide. The product was filtered, washed and dried.

Finally, the product was re-crystallized from ethanol.The progress and completion of the reaction were confirmed by TLC.Mobile phase for TLC toluene: acetone (8:2), Yield: 75 %, M.P.: 220°C

2.4.Synthesis of 1-(4-hydroxybenzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (III)

In a round bottom flask, a mixture of 4-hydroxybenzohydrazide (0.01 mol), ethyl acetoacetate (0.01 mol), 20 ml absolute ethanol and catalytic amount of triethylamine (1 ml) were taken. The reaction mixture was refluxed for 12 hours at 78°C using reflux condenser equipped with magnetic stirrer. After completion of reaction, the resultant heavy reddish syrup was allowed to cool at room temperature. It was washed thoroughly with ether to remove impurities. After removal of ether layer the content was poured into ice cold water to form product. The product was filtered, washed and dried. Finally, the product was re-crystallization from ethanol. The reaction progress was monitored by TLC. Mobile phase for TLC hexane: ethyl acetate (8:2), Yield: 72%, M.P.: 252°C.

2.5. Synthesis of 1-(4-hydroxybenzoyl)-3-methyl -4-(arylidene)-1*H*-pyrazol-5(4*H*)-one (IVa-IVn)

In a round bottom flask, a mixture of 1-(4-hydroxybenzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (0.01 mol) and different aromatic aldehydes (0.01 mol) suspended in dry toluene were taken and catalytic amount of piperidine (0.5 ml) was added and the mixture was refluxed with stirring for 8 hours. The reaction mixture contents were poured into ice cold water. The solid products formed were filtered, washed and dried. Finally, the products were re-crystallized from ethanol or methanol. The reaction progress was monitored by TLC. **(IV a-IVn).**

Other compounds of this series I **(IVa-IVn)** were prepared by using the same method and their physical data are recorded in Table 1.

2.6. Anti Microbial Evaluation

All the synthesized compounds were screened for antibacterial and antifungal activities by broth dilution method with reference to standard drug Ampicillin and Amphotericin B.

Table 1: Physical properties of the synthesized compounds (IV a-n)

Compound Id	R	Molecular Formula	M.W.	M.P.	% Yield	Elemental Analysis			
						% of Carbon		% Nitrogen	
						Cal.	Obt.	Cal.	Obt.
IVa	-H	$C_{18}H_{14}N_2O_3$	306	242°C	75	70.58	70.85	9.15	9.25
IVb	-3-NO_2	$C_{18}H_{13}N_3O_5$	351	255°C	65	61.54	61.58	11.96	11.95
IVc	-4- Cl	$C_{18}H_{13}ClN_2O_3$	340	265°C	78	63.44	63.46	8.22	8.25
IVd	-4- OH	$C_{18}H_{14}N_2O_4$	322	252°C	61	67.07	67.08	8.69	8.88
IVe	-2-OH	$C_{18}H_{14}N_2O_4$	322	227°C	78	67.07	67.08	8.69	8.88
IVf	-4- OCH_3	$C_{18}H_{16}N_2O_4$	336	245°C	74	67.85	67.58	8.33	8.35
IVg	-4-C_8H_7	$C_{20}H_{16}N_2O_3$	332	256°C	59	72.28	72.58	8.43	8.45
IVh	-N$(CH_3)_2$	$C_{20}H_{19}N_3O_3$	349	273°C	62	68.75	68.58	12.03	12.13
IVi	-3,4,-$(OCH_3)_2$	$C_{20}H_{18}N_2O_5$	366	285°C	65	65.57	65.58	7.65	7.95
IVj	-2-Cl	$C_{18}H_{13}ClN_2O_3$	340	238°C	74	63.44	63.58	11.96	11.95
IVk	-2-NO_2	$C_{18}H_{13}N_3O_5$	351	248°C	72	61.54	61.58	8.22	8.25
IVl	-3-OCH_3, 4 –OH	$C_{19}H_{16}N_2O_5$	352	275°C	68	64.77	64.78	7.95	7.98
IVm	2,4-OH	$C_{18}H_{15}N_2O_5$	338	235°C	66	63.90	63.98	8.28	8.95
IVn	-5-Br	$C_{18}H_{13}N_2O_3Br$	338	245°C	70	56.12	56.58	7.27	7.95

3. RESULTS AND DISCUSSION

In the present work we have prepared a new series of pyrazole derivatives. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis. Compound (**IVc)** showed strong absorption at 1632 cm^{-1} due to carbonyl group. The compound (**IVj)** showed singlet at 2.2 δ ppm for three protons (CH_3) and one hydrogen at 6.2 ppm for =CH connected to pyrazole ring.

3.1.Spectral data of the synthesized compounds

3.1.1. 4-Benzylidene-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVa)

IR: (cm^{-1}, KBr): *1652(C=O), 1705(C=N), 3064(-O-H bending).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.8(3H, s, CH_3), 6.3(1H, s, CH) 6.7-7.9(9H, m, aromatic ring).* ***^{13}CNMR: (DMSO, δ ppm):*** *116.26-128.47 (Ar-C), 126.5(C=C) 147.8(C=N), 161.23(C-OH), 170.85(C=O).* ***Mass (m/z):*** *306.* ***Molecular formula:*** *$C_{18}H_{14}N_2O_3$,* ***Elemental Analysis:*** *Ana. Found: N-9.25%, C-70.85%.*

3.1.2. 4-(3-nitrobenzylidene)-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVb)

IR: (cm^{-1} KBr): *1655(C=O), 1708(C=N), 3026(-O-H bending).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.8(3H, s, CH_3), 5.3(1H, s, OH), 6.3(1H, s, CH), 6.7-7.9(8H, m, aromatic ring).* ***^{13}C NMR: (DMSO, δ ppm):*** *112.26-129.47 (Ar-C), 124.5(C=C), 145.2(C-NO2), 146.8(C=N), 162.23(C-OH), 171.85(C=O).* ***Mass:*** *(m/z): 351.* ***Molecular formula:*** *$C_{18}H_{13}N_3O_5$,* ***Elemental Analysis:*** *Ana. Found: N-11.95%, C-61.58%.*

3.1.3. 4-(4-Chlorobenzylidene)-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVc)

IR: (cm^{-1}, KBr): *775(C-Cl), 1632(C=O), 1701(C=N), 3066(-O-H bending).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.6(3H, s, CH_3), 5.5(1H, s, OH), 6.2(1H, s, CH), 6.7-7.8(8H, m, aromatic ring).* ***^{13}C NMR: (DMSO, δ ppm):*** *112.26-129.45 (Ar-C), 125.5(C=C), 145.8(C=N), 162.2(C-OH), 171.85(C=O).* ***Mass: (m/z):*** *340.* ***Molecular formula:*** *$C_{18}H_{13}N_2O_3Cl$,* ***Elemental Analysis:*** *Ana. Found: N-8.25%, C-63.46%*

3.1.4. 4-(4-Hydroxybenzylidene)-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVd)

IR: (cm^{-1}, KBr): *1658(C=N), 1677(C=O), 3016(-O-H bending).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.8(3H, s, CH_3), 5.2(2H, s, OH), 6.4(1H, s, CH), 6.6-7.9(8H, m, aromatic ring).* ***^{13}C NMR: (δ ppm, DMSO):*** *114.36-125.45 (Ar-C), 124.5(C=C), 144.8(C=N), 161.2(C-OH), 170.85(C=O).* ***Mass: (m/z):*** *322.* ***Molecular formula:*** *$C_{18}H_{14}N_2O_4$,* ***Elemental Analysis:*** *Ana. Found: N-8.88%, C-67.08%.*

3.1.5. 4-(2-Hydroxybenzylidene)-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVe)

IR: (cm^{-1}, KBr): *1667(C=O), 1708(C=N), 3160(-O-H bending).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.7(3H, s, CH_3), 5.1(2H, s, OH), 6.6-7.9(8H, m, aromatic*

ring), 6.5(1H, s, CH). **^{13}C NMR: (DMSO, δ ppm):** 111.16-128.45(Ar-C), 123.5(C=C), 143.8(C=N), 160.2(C-OH), 171.55 (C=O). **Mass: (m/z):** 322. **Molecular formula:** $C_{18}H_{14}N_2O_4$, **Elemental Analysis:** Ana. Found: N-8.88%, C-67.08%.

3.1.6. 4-(4-Methoxybenzylidene)-1-(4-hydroxybenzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVf)

IR: (cm^{-1}, KBr): 1608 (C=N), 1701(C=O), 2837(-OCH3), 3069(-O-H bending).**^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.8(3H, s, CH_3), 3.3(3H, s, OCH_3), 5.1(1H, s, OH), 6.4(1H, s, CH), 6.6-7.9(8H, m, aromatic ring). **^{13}C NMR: (DMSO, δ ppm):** 54.65(-OCH_3), 112.16-125.45(Ar-C), 122.5(C=C), 142.8(C=N), 171.55 (C=O). **Mass: (m/z):** 336. **Molecular formula:** $C_{18}H_{16}N_2O_4$, **Elemental Analysis:** Ana Found: N-8.35%, C-67.58%.

3.1.7. 1-(4-Hydroxybenzoyl)-3-methyl-4-phenyl-but-en-1-ylidene)-1H-pyrazole-5(4H)-one (IVg)

IR: (cm^{-1}, KBr): 1655 (C=N), 1704(C=O), 3065(-O-H bending). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.5(3H, s, CH_3), 4.3 (2H, s, CH), 5.3(1H, s, OH), 6.3(1H, s, CH), 6.5-7.9(9H, m, aromatic ring). **^{13}C NMR: (DMSO, δ ppm):** 110.15-126.55(Ar-C), 121.5(C=C), 141.8(C=N), 170.54(C=O). **Mass: (m/z):** 332. **Molecular formula:** $C_{20}H_{16}N_2O_3$, **Elemental Analysis:** Ana. Found: N-8.45%, C-72.58%.

3.1.8. 1-(4-Hydroxybenzoyl)-4-(4-dimethylamino-benzylidene)-3-methyl-1H-pyrazole-5-(4H)-one (IVh)

IR: (cm^{-1}, KBr): 1690(C=N), 1705(C=O), 2801(-NCH_3) 3071(-O-H bending).**^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.7(6H, s, NCH_3), 3.3(3H, s, CH_3), 5.1(1H, s, OH), 6.4(1H, s, CH), 6.6-7.9 (8H, m, aromatic ring). **^{13}C NMR: (DMSO, δ ppm):** 112.15-125.55 (Ar-C), 120.5 (C=C), 142.8 (C=N), 171.54(C=O). **Mass: (m/z):** 349. **Molecular formula:** $C_{20}H_{19}N_3O_3$, **Elemental Analysis:** Ana. Found: N-12.13%, C-68.58%.

3.1.9. 1-(4-Hydroxybenzoyl)-4-(3,4-dimethoxybenz-ylidene)-3-methyl-1H-pyrazole-5-(4H)-one (IVi)

IR: (cm^{-1}, KBr): 1605 (C=N), 1704(C=O), 2835(-OCH3), 3065(-O-H bending). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.6(6H, s, OCH_3), 3.2(3H, s, CH_3), 5.2(1H, s, OH), 6.4(1H, s, CH), 6.6-7.9(8H, m, aromatic ring). **^{13}C NMR: (DMSO, δ ppm):** 54.55(-OCH^3), 111.11-127.45(Ar-C), 120.5(C=C), 142.8(C=N), 171.44 (C=O). **Mass: (m/z):** 366. **Molecular formula:** $C_{20}H_{18}N_2O_5$, **Elemental Analysis:** Ana. Found: N-7.95%, C-65.58%

3.1.10. 1-(4-Hydroxybenzoyl)-4-(2-chlorobenzyli-dene)-3-methyl-1H-pyrazole-5-(4H)-one (IVj)

IR: (cm^{-1}, KBr): 655(C-Cl), 1605 (C=N), 1701(C=O), 3063(-O-H bending). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.2(3H, s, CH_3), 5.3(1H, s, OH), 6.2(1H, s, CH), 6.8-7.8(8H, m, aromatic ring). **^{13}CNMR (DMSO, δ ppm):** 62.55(CH-Cl), 112.11-126.45(Ar-C), 121.5(C=C), 141.8(C=N), 170.44(C=O). **Mass: (m/z):** 340. **Molecular formula:** $C_{18}H_{13}ClN_2O_3$, **Elemental Analysis:** Ana.Found: N-11.95%, C-63.58%.

3.1.11. 1-(4-Hydroxybenzoyl)-4-(2-nitrobenzyli-dene)-3-methyl-1H-pyrazole-5-(4H)-one (IVk)

IR: (cm^{-1}, KBr): 1604(C=N), 1735(C=O), 3026(-O-H bending). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.6(3H, s, CH_3), 5.2(1H, s, OH), 6.3(1H, s, CH), 6.7-7.8(8H, m, aromatic ring). **^{13}C NMR (DMSO, δ ppm):** 115.11-128.45(Ar-C), 121.5(C=C), 141.8(C=N), 148.9(-NO2), 171.44(C=O). **Mass: (m/z):** 351. **Molecular formula:** $C_{18}H_{13}N_3O_5$, **Elemental Analysis:** Ana. Found: N-8.25%, C-61.58%.

3.1.12. 1-(4-Hydroxybenzoyl)-4-(3-methoxy-4-hydroxybenzylidene)-3-methyl-1H-pyrazole-5-(4H)-one (IVl)

IR: (cm^{-1}, KBr): 1612 (C=N), 1701(C=O), 2837(-OCH_3), 3016(-O-H bending). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.6(3H, s, CH_3), 2.4(3H, s, OCH_3), 5.2(1H, s, OH), 6.3(1H, s, CH), 6.7-7.8(8H, m, aromatic ring). **^{13}C NMR: (DMSO, δ ppm):** 54.55(-OCH_3), 82.05(C-OH), 112.11-125.45(Ar-C), 121.5(C=C), 141.8(C=N), 172.44(C=O). **Mass: (m/z):** 352. **Molecular formula:** C19H16N2O5, **Elemental Analysis:** Ana Found: N-7.98%, C-64.78%.

3.1.13. 1-(4-Hydroxybenzoyl)-4-(2,4-di-hydroxy-benzylidene)-3-methyl-1H-pyrazole-5-(4H)-one (IVm)

IR: (cm^{-1}, KBr): 1250(C-OH), 1604(C=N), 1708(C=O). **^{1}H NMR: (DMSO, 400 MHz) (δ ppm):** 2.5(3H, s, CH_3), 5.1(3H, s, OH), 6.7-7.8(8H, m, aromatic ring), 6.2(1H, s, CH). **^{13}C NMR: (DMSO, δ ppm):** 81.05(C-OH), 111.16-125.35(Ar-C), 120.5(C=C), 142.8(C=N), 171.54(C=O). **Mass: (m/z):** 338. **Molecular formula:** $C_{18}H_{15}N_2O_5$, **Elemental Analysis:** Ana. Found: N- 8.95%, C-63.98%.

3.1.14. 4-(5-bromobenzylidene)-1-(4-hydroxybenz -oyl)-3-methyl-1H-pyrazole-5-(4H)-one (IVn)

IR: (cm^{-1}, KBr): *1206(C-OH), 1606 (C=N), 1751(C=O).* ***^{1}H NMR: (DMSO, 400 MHz) (δ ppm):*** *2.2(3H, s, CH_3), 5.3(1H, s, OH), 6.3(1H, s), 6.7-7.8 (8H m, aromatic ring).* ***^{13}C NMR: (DMSO, δ ppm):*** *111.11-126.35(Ar-C), 125.5(C=C), 142.8(C=N), 170.44(C=O).* ***Mass: (m/z):*** *338.* ***Molecular formula:*** *$C_{18}H_{13}N_2O_3Br$,* ***Elemental Analysis:*** *Ana. Found: N-7.95%, C-56.58%.*

3.2. Anti microbial Evaluation

All the synthesized compounds were screened for antibacterial and antifungal activities by broth dilution method. With reference to standard drug Ampicillin and Amphotericin B, from the bases of the biological activity data study of the synthesized compounds it was observed that compound, **(IVg)** exhibited good activity against *B. Cereus, and compound* **(IVm)** showed moderate activity against *B. cerus* and *Pseudomonas*. Similarly compound, **(IVk)** exhibited moderate activity against *E. coli* and compounds **(IVn)** showed moderate antifungal activity against *A. niger*.

Table 2: Biological activities in the terms of the MIC of the synthesized compounds (IV a-n)

Compound Id	Minimum inhibitory concentration (MIC) (µg/ml)				
	Anti-bacterial Activity				Anti-fungal activity
	Gram Positives bacteria		Gram Negative bacteria		Fungus
	Bacillus Cereus MTCC 430	*S. aureus* MTCC 737	*E. coli* MTCC 1687	*Pseudomonas* MTCC 1688	*A. niger* ATCC 16404
IVa	256	256	512	512	256
IVb	512	512	256	256	512
IVc	256	256	512	1024	256
IVd	>1024	>2048	>1024	256	>1024
IVe	512	512	256	512	512
IVf	256	>2048	512	256	>1024
IVg	64	256	512	>2048	256
IVh	>1024	>2048	1024	>2048	>1024
IVi	>1024	>2048	>1024	>2048	>1024
IVj	>1024	128	256	1024	1024
IVk	512	256	128	512	512
IVl	256	128	512	256	256
IVm	128	256	256	128	512
IVn	256	512	512	256	128
Ampicilline	10.0	12	2.0	8.0	-
Amphotericin B	-	-	-	-	0.05

S.aureus=Staphylococcus aureus, E. coli=Escherichia coli, Pseudomonas = Pseudomonas aeruginosa

4. CONCLUSION

From the present study it was observed that pyrazole moiety can be considered as promising pharmacophore for better antibacterial activities. It was found that varying the substitution in the final structure affect the biological activities. Final compounds with hydroxy, nitro and bromine group or atom were found to possess moderate antibacterial and moderate antifungal activities.

5. ACKNOWLEDGEMENT

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