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An Efficient Synthesis of Pyrazole Derivatives Proven Effective as Antifungal and Antibacterial Activity

Archana D. Jadhav[1]*, Pankaj U. Barhate[1] and Ayesha Durrani[2]

1. Department of Chemistry, Loknete Ramdas Patil Dhumal Arts, Science and Commerce College Rahuri, Ahmednagar, Maharashtra, **INDIA**
2. Department of Chemistry, Dr. Rafiq Zakaria College of Womens, Naukhanda, Aurangabad, Maharashtra, **INDIA**

Email: archu1990jadhav@gmail.com

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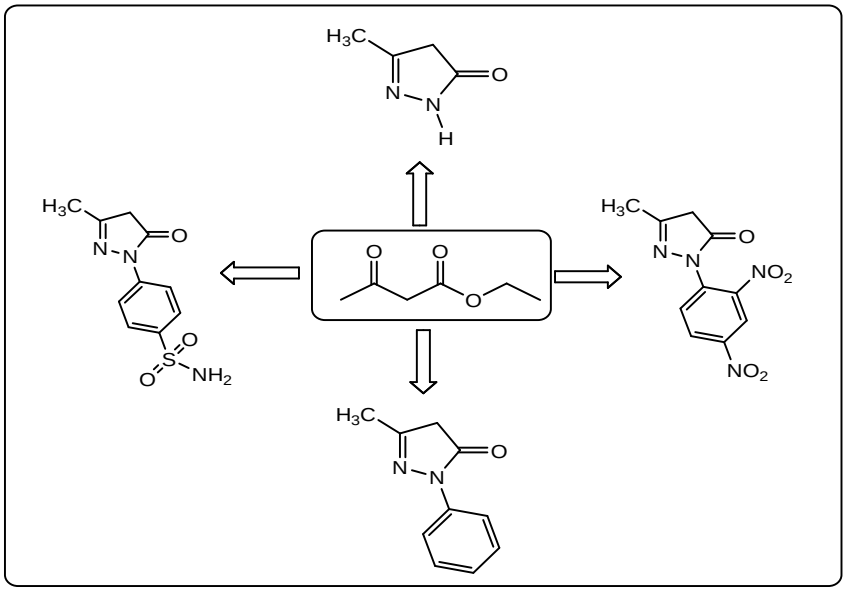
ABSTRACT

Present work deals with the preparation of some Pyrazole derivative which was prepared by using ethyl acetoacetate by using different hydrazine derivatives at room temperature. The reaction mixture was stirred on magnetic stirrer till colour change is observed and then product is separated out. The structures 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.

Graphical Abstract:



Keywords: Dicarbonyl compound, Hydrazine derivatives, Antifungal Activity, Antibacterial.

INTRODUCTION

Pyrazole is the five membered heterocyclic compounds involve two nitrogen with in ring system. There have been several major advances in synthetic organic chemistry, during the last decade [**1**]. In this new heterocyclic chemistry work on the advances of derivatives of pyrazole has some biological activities like antifungal, antibacterial, anti-cancerous, anti-inflammatory and analgesic drug activity, etc are observed [**2**]. Working with such types of pyrazole derivatives shows some important properties like simplifying criteria, minimum time requirement and role of importance in biological study [**3, 4**].

The role of medicinal chemistry is essential and sustainable for an empirical organic synthesis of new compound based on the modification of structure and identifies their biological activity [**5, 6**]. Many attempts have been made to synthesize, characterize and to study biological activity of pyrazole derivatives [**7**]. Combinatorial chemistry as a new method for the rapid generation of a great number of structurally diverse substances, being required widely a great impact of drug discovery [**8, 9**].

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. These derivatives have acquired versatile importance as drug substances in pharmaceutical industry. In this work the investigation of novel derivatives formation we use easily available starting materials and their broad range of antifungal and antibacterial activity was evaluated. The study was aimed at exploring our synthesis of some new biologically active pyrazole derivatives by the reaction of Ethyl acetoacetate and different hydrazine derivatives [**10-20**].

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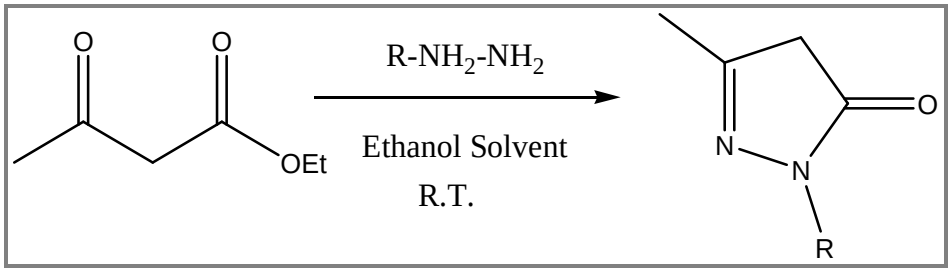
MATERIALS AND METHODS

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. ^1H NMR spectra were recorded on Bruker AV, 200 MHz spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scale. Multiplicities of ^1H 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 and also ^{13}C signals were recorded.

General Procedure for Preparation of Pyrazole Derivative: In present work we prepared the pyrazole derivative by using EAA (0.01mole) and hydrazine derivatives (0.01mole) dissolve in 10-15 mL of ethanol at room temperature till colour change is observed within the 10-20 h. time span to forms separation of crystalline compound then filter the product and recrystallize with organic solvents like ethanol/methanol.



Scheme. Preparation of pyrazole derivatives.

Table 1. Present Scheme observation

S.No.	R1	R2/ R3	Time (h)	M.P. (°C)	Yield (%)
C1E	-Ph-SO_2-NH_2	-CH_3	6	70	92
C2E	-Ph	-CH_3	9	172	90
C3E	-Ph$(NO_2)_2$	-CH_3	7	180	78
C4E	-H	-CH_3	9	168	88

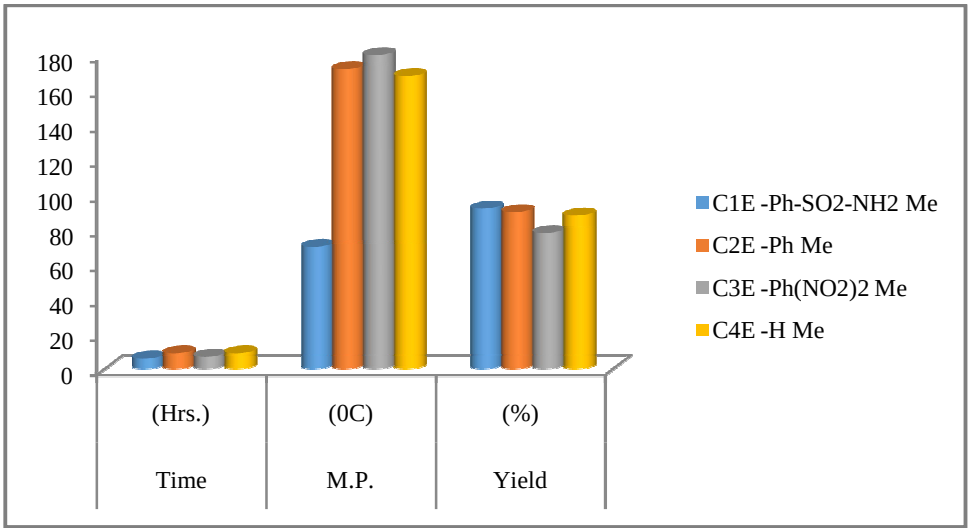


Figure 1. Graphical representation of observation.

RESULTS AND DISCUSSION

Antibacterial Activity: The plates were inoculated by specific microorganism by spread plate technique, bores were made in the solidified agar plate by using a sterile borer. The test solution of specified concentration was added in the bore by using sterile pipette and the plates were kept in freeze for 1 h for diffusion and then incubated at 37°C for 24 h. After 24 h the plates were examined and zone of inhibition were recorded. All the synthesized compounds were screened for antibacterial activity against both gram positive *S. aureus* and *Bacillus substilis* and gram negative E. coli & Proteus vulgaris bacteria at a concentration of 100 µg mL^{-1}, 200 µg mL^{-1}, 400 µg mL^{-1}, 800 µg mL^{-1}. Ampicillin Capsules is used as standard for comparison of antibacterial activity. In presence of base such as NaOH and ethanol is used as a solvent. The results of screening are given below.

Table 2. Zone Of Inhibition for Gram Positive Bacteria

Compound	Zone of inhibition (mm)							
	Staphylococcus aureus				*Bacillus subtilis*			
	100 µg	200 µg	400 µg	800 µg	100 µg	200 µg	400 µg	800 µg
C1E	10	12	15	17	12	15	16	19
C2E	10	12	14	15	08	11	13	15
C3E	09	11	13	16	10	13	15	18
C4E	08	10	13	15	09	12	14	16
Ampicillin	12	14	18	21	13	15	17	20

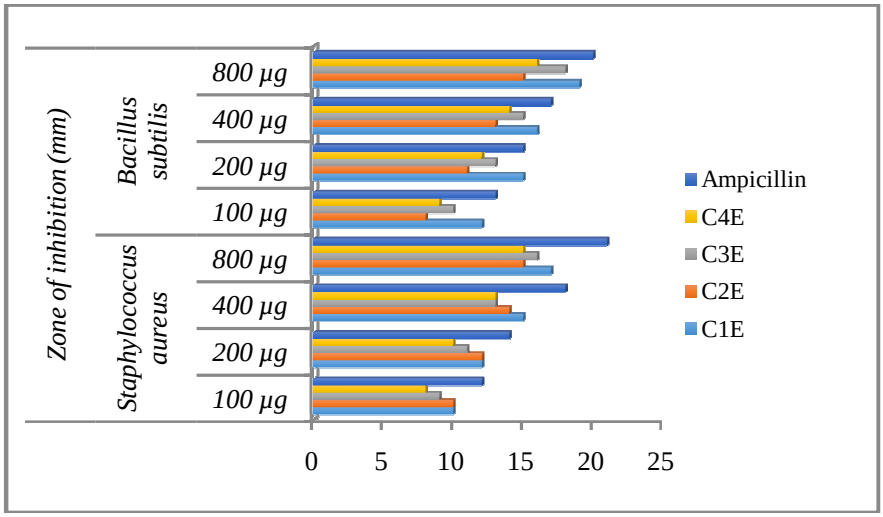


Figure 2. Graphical representation of Zone of inhibition for gram positive bacteria

Table 3. Zone of Inhibition for Gram Negative Bacteria

Compound	Zone of inhibition (mm)							
	Escherichia coli				*Proteus vulgaris*			
	100 µg	200 µg	400 µg	800 µg	100 µg	200 µg	400 µg	800 µg
C1E	10	12	14	16	10	13	15	17
C2E	07	10	12	14	09	11	13	14
C3E	08	10	13	15	07	08	10	12
C4E	10	11	13	14	10	11	14	15
Ampicillin	11	14	15	17	12	14	16	18

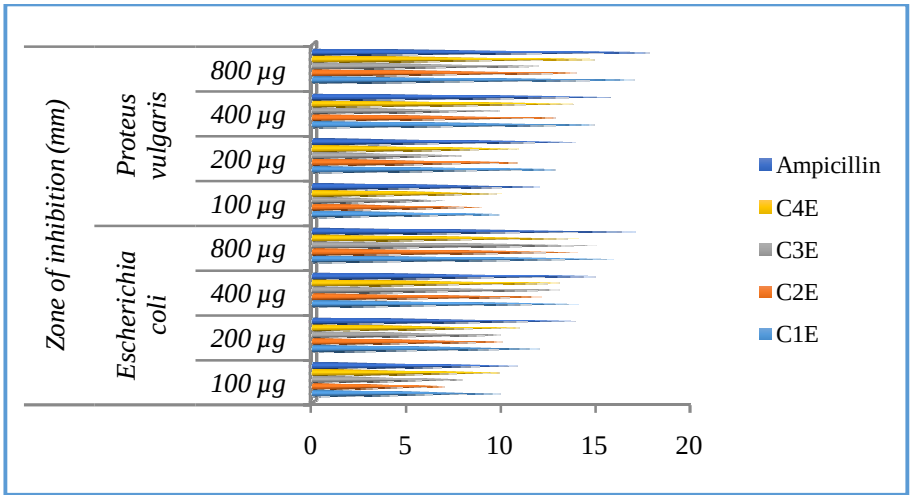


Figure 3. Graphical representation of zone of inhibition for gram negative bacteria.

Amongst all synthesized compounds **C1E** and **C3E** were found to be more potent as antibacterial *Staphylococcus aureus* and *Bacillus subtilis* agents. Whereas compound **C1E and C4E** was more active against antibacterial *Escherichia coli* and *Proteus vulgaris* as antibacterial. The zone of inhibition of synthesized compounds was compared with the standard drug Ampicillin at four different concentrations.

Antifungal Activity: The antifungal testing was carried out against *Aspergillus niger* and *Candida ablicans*, known antifungal drug Itraconazole as a standard. The zone of inhibition measured in mm, amongst all these synthesized compound shows significant activity.

Table 4. Zone of Inhibition for Antifungal Activity

Compound	Antifungal activity Zone of inhibition (mm)	
	A. niger	*C. ablicans*
C1E	15.6	12.4
C2E	13.2	11.4
C3E	14.4	11.7
C4E	10.6	10.8
Itraconazole	19.2	14.2

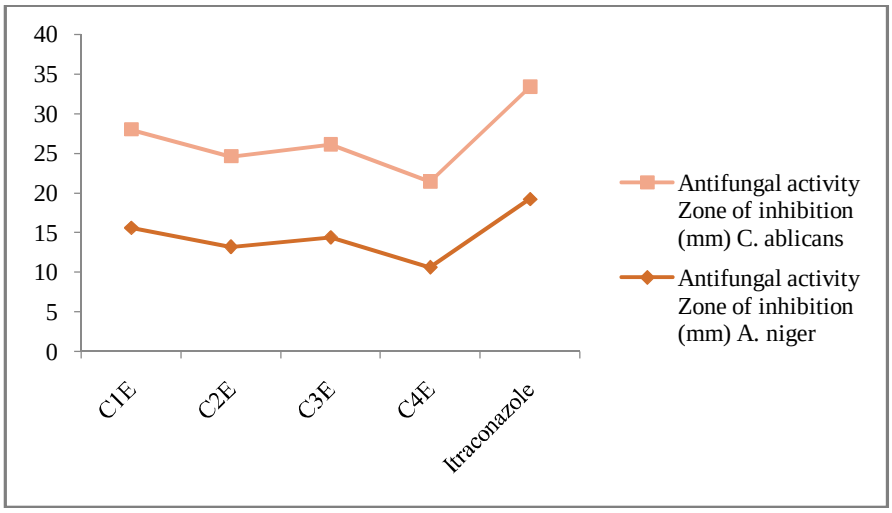
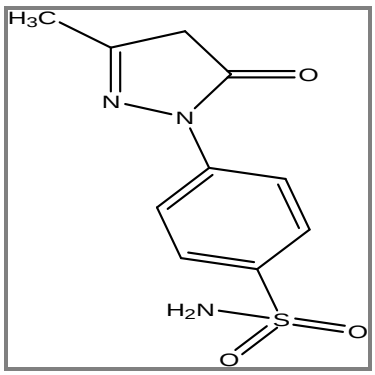


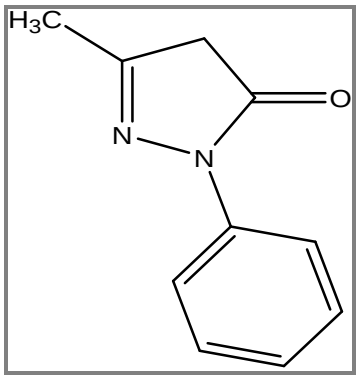
Figure 4. Graphical representation of zone of inhibition for antifungal activity.

Spectral Data: Spectral analysis of given Pyrazole can carry out by NMR spectra and IR spectroscopy.



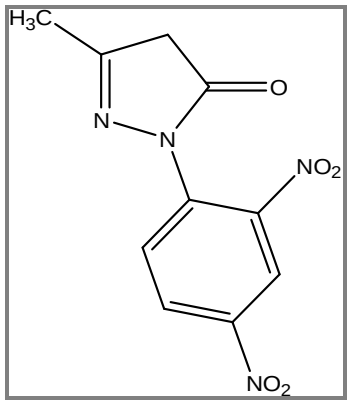
4-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl) benzenesulfonamide

C1E: Yield: 92%; **mp:** 70°C; **IR (KBr) ν** = 2950, 1640, 1375-1300, 1690-1640, 3500-3100 cm^{-1}; **^{1}H NMR (DMSO) δ :** 0.989 (s, 3H), 2.093 (s, 2H), 2.500 (s, 2H), 7.841 (d, 2H, J= 8 Hz), 7.865 (d, 2H, J= 8 Hz); **^{13}C NMR (DMSO) δ :** 153.63, 169.54, 44.39, 31.10, 145.05, 137.70, 123.43, 130.01



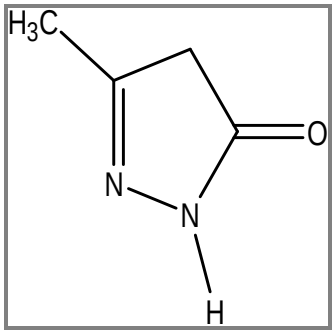
3-methyl-1-phenyl-1H-pyrazol-5(4H)-one

C2E: Yield: 90% ; **mp:** 172°C; **IR (KBr) ν** = 1600, 3000, 1550, 1640 cm^{-1}; **^{1}H NMR (DMSO) δ :** 0.938 (s, 3H), 2.198 (s, 2H), 6.941 (t, 1H), 7.274 (t, 2H), 7.649 (d, 2H) **^{13}C NMR (DMSO) δ :** 24.06, 40.02, 121.45, 123.43, 130.01, 137.70, 153.63, 169.54.



1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-5(4H)-one

C3E: Yield: 78% ; **mp:** 180°C; **IR (KBr) ν** = 1350, 3300-3200, 1550, 1640 cm^{-1}; **^{1}H NMR (DMSO) δ :** 1.024 (s, 3H), 2.283 (s, 2H), 8.160 (d, 1H, J= 8 Hz), 8.541 (d, 1H, J= 2 Hz), 9.141 (s, 1H, J= 0 Hz) **^{13}C NMR (DMSO) δ :** 24.06, 40.02, 121.45, 123.43, 127.04, 141.20, 142.03, 144.09, 159.63, 169.54.



3-methyl-1H-pyrazol-5(4H)-one

C4E: Yield: 88%; **mp:** 168°C; **IR (KBr) ν** = 3000-2850, 3100, 1640, 1550 cm^{-1} ; **^{1}H NMR (DMSO) δ :** 0.938 (s, 3H), 2.236-2.198 (s, 2H), 6.941 (s, 1H) ; **^{13}C NMR (DMSO) δ :** 23.31, 44.24, 159.45, 172.32.

APPLICATION

The application of our reaction is to obtained higher yield of the product within minimum time and great future opportunity for time being bioactivities like anticancer, antiviral, antidiabetic, etc. as relevant biological activities.

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, efficient method 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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