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Synthesis of some Pyrazole Derivatives via Knoevenagel Condensation Proven Effective as Antibacterial and Antifungal Activity

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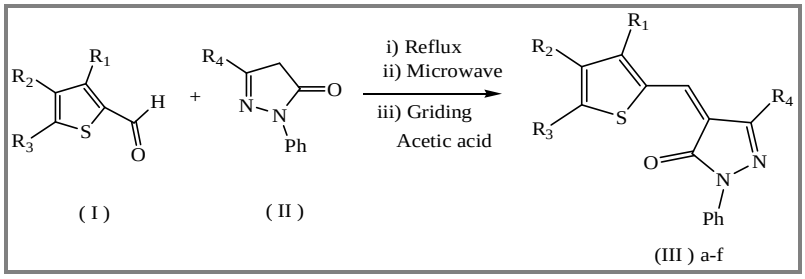
ABSTRACT

It deals with the preparation of pyrazole derivative synthesized by Knoevenagel condensation in acidic medium. The work represented by three different methods that is conventional, grinding and microwave assisted reaction. The entire synthesized compound was tested for their antibacterial activity against the Gram-positive and Gram-negative strains of bacteria. The investigation of antibacterial screening data revealed that most of the tested compounds showed less to moderate antibacterial and antifungal activity.

Graphical Abstract



Synthesis of Pyrazole Derivatives.

Keywords: Citric acid, thiophene-2-carbaldehyde, Antifungal, Antibacterial, Spectra, etc.

INTRODUCTION

Recently pyrazole containing compounds have attracted researchers because of their wide applications in the field of medicines. Pyrazolone is a derivative of pyrazole having an additional ketonic group. It is a heterocyclic nucleus incorporated in many drugs like Phenazone, Ampyrone, Propyphenazone which are potent antipyretics and analgesics [**1**]. It is an active pharmacophore due to various biological activities associated with it such as antimicrobial [**2**], antihyperlipidemic [**3**], anticonvulsant

[4], anti-inflammatory [5], antitumor [6], antiviral [7], antitubercular [8], antioxidant [9] and antidiabetic [10].

According to increasing microbial infections and the phenomenon of microbial resistance to current therapeutic agents due to mutations occurring at genetic level in micro-organisms are the too serious global problems. To overcome these problems there is a need of developing and designing new drug molecules with high potency. Currently much research is going on in this filed and heterocyclic compounds are dominating scaffolds owing to their interesting chemistry and bioactivity. There are various synthetic approaches in synthesizing new pyrazole derivatives. The most common synthetic method is conventional method. In recent experiment we were use other two methods that is microwave and simple grinding method for synthesis of pyrazole derivatives with higher yields of product. One of the major concerns is to exhibit simple routes for the synthesis of pyrazole derivatives [11, 12], by Knoevenagel condensation in acidic medium and those synthesized compounds were subjected to antibacterial and antifungal activity to compare their potentials.

MATERIALS AND METHODS

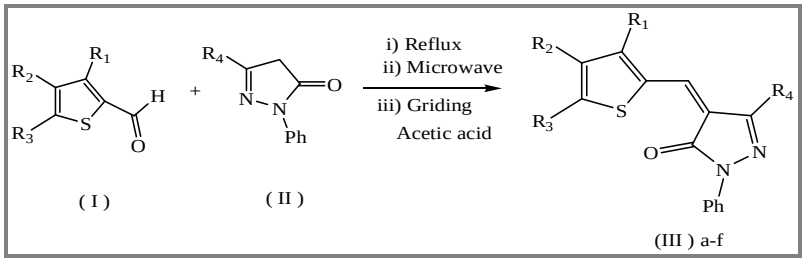
All the chemicals and solvents were obtained from E-Merck, and SD fine chemicals L.T.D. India (AR, LR grade). Melting points were determined in open capillaries in liquid paraffin bath and are uncorrected. Purity of the compound was routinely checked on silica gel TLC plates using $CHCl_3$ as solvent. ^1H NMR spectra were recorded on Bruker AV II, 400 MHz NMR spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shift was 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), m (multiplet), etc. IR data were recorded an Alpha-T ATR-FTIR.

Present work: In present work pyrazole derivatives were synthesized by Knoevenagel condensation in acidic medium, according to conventional as well as non-conventional methods for preparation.

Conventional method: Condensation of compounds by the equimolar amounts (0.002 mol) of thiophene-2-carbaldehyde (I) and substituted pyrazolone (II) were taken in glacial acetic acid (4 mL). The reaction mixture was refluxed for 2 to 3 h. The completion of reaction was checked by TLC. After completion of reaction the content were allowed to cool and solid obtained was filtered by Buchner funnel. It was recrystallizing from acetic acid to afford pure compound.

Microwave method: Condensation of compound by the equimolar amounts (0.002 mol) of thiophene-2-carbaldehyde (I) and substituted pyrazolone (II) were taken in glacial acetic acid (2 mL). The mixture was subjected to microwave irradiation at 300 W for about 10 min. till completion of reaction checked by colour change and TLC. After completion of reaction, contents were allowed to cool and solid obtained was filtered and purified by recrystallization from acetic acid to afford pure compound.

Experimental Scheme

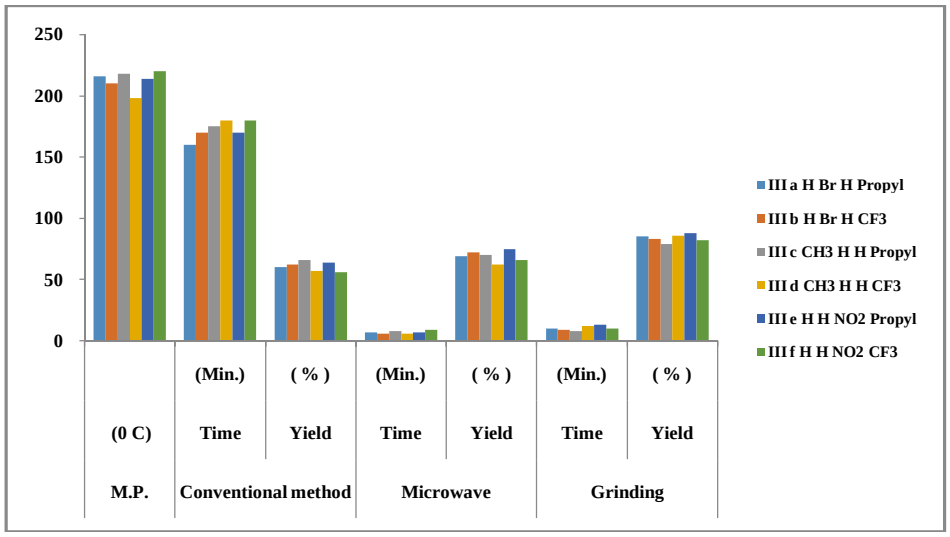


Scheme 1. Synthesis of some Pyrazole Derivatives.

Grinding method: Equimolar amounts (0.002 mol) of thiophene-2-carbaldehyde (I), substituted pyrazolone (II) and 2 gm of citric acid/tartaric acid were taken in morter and the whole reaction mixture was then grind with the help help of pestle for about 10 to 15 min. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was transferred into ice cold water, the solid was obtained filtered, dried and recrystallize from acetic acid to get pure compound.

Table 1. Experimental data

Comp.	R1	R2	R3	R4	M.P. (°C)	Conventional method		Microwave		Grinding	
						Time (Min.)	Yield (%)	Time (Min.)	Yield (%)	Time (Min.)	Yield (%)
III a	H	Br	H	Propyl	216	160	60	7	69	10	85
III b	H	Br	H	CF_3	210	170	62	6	72	09	83
III c	CH_3	H	H	Propyl	218	175	66	8	70	08	79
III d	CH_3	H	H	CF_3	198	180	57	6	62	12	86
III e	H	H	NO_2	Propyl	214	170	64	7	75	13	88
III f	H	H	NO_2	CF_3	220	180	56	9	66	10	82



Graphical representation of observation.

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 one hour 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 *Staphylococcus aureus* and *Staphylococcus epidermidis* and gram negative *E. coli* and *Proteus vulgaris* bacteria at a concentration of 1000 µg mL^{-1}. Azithromycin was used as internal standard for comparison of antibacterial activity.

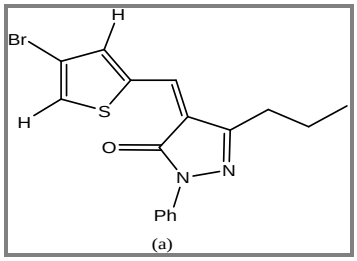
Antifungal activity: Antifungal activity study was carried out by cup-plate agar diffusion method using nutrient agar. Fungal culture were made in Sabouraud-Dextrose agar and incubated at 37°C for 18-24 h. The concentration was 1000 µg mL^{-1}. The compounds were tested *in-vitro* for their antifungal activity against *viz. Aspergillus niger* and *Candida albicans* at similar concentration as antibacterial. *Fluconazole* was used as internal standard for comparison of antifungal activity.

RESULTS AND DISCUSSION

All the synthesized compounds are less active or inactive towards used antibacterial and antifungal strains.

Spectral Data

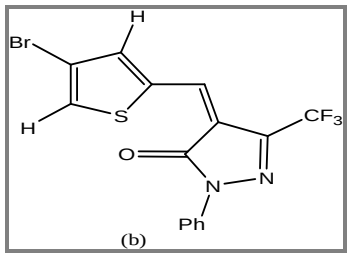
a). (Z)-4-((4-bromothiophen-2-yl)methylene)-1-phenyl-3-propyl-1H-pyrazol-5(4H)-one: IR: 1668 (C=O stretch.), 1593 (C=N stretch), 1112 (Ar-Br stretch.) cm^{-1}; **^{1}H NMR: (DMSO-d_6):** δ ppm 7.18 (t, 1H, Ar-H, J= 7.3 Hz), 7.42 (t, 2H, Ar-H, J= 7.5 Hz), 7.92- 7.94 (m, 2H, Ar-H), 1.05 (t, 3H, CH_3 of propyl, J= 7.32 Hz), 1.77 (q, 2H, CH_2 of propyl, J= 7.4 Hz), 2.69 (t, 2H, CH_2 of propyl, J= 7.4 Hz), 8.08 (s, 1H), 8.18 (s, 1H, =CH), 8.25 (d, 1H, J= 1.4 Hz); **LC/MS**m/z (M^{+1}) = 375.



(a)

(*Z*)-4-((4-bromothiophen-2-yl)methylene)-1-phenyl-3-propyl-1*H*-pyrazol-5(4*H*)-one

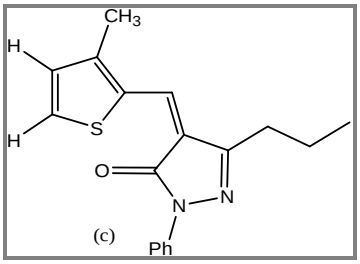
b). (Z)-4-((4-bromothiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one: IR: 1668 (C=O), 1591 (C=N), 1114 (Ar-Br) cm^{-1}; **^{1}H NMR (DMSO-d_6) δ:** 7.21 (t, 1H, Ar-H, J= 7.0 Hz), 7.49 (t, 2H, Ar-H, J= 7.4 Hz), 7.86 (d, 2H, Ar-H, J= 8.0 Hz), 8.29 (s, 1H, =CH), 8.39 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H); **MS:** m/z (M^{+1}) = 401.



(b)

(*Z*)-4-((4-bromothiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one

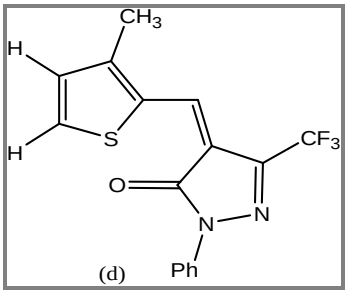
c). IR: 1665 (C=O), 1592 (C=N) cm^{-1}; **1H NMR (DMSO-d_6): δ** 1.08 (t, 3H, CH_3), 1.79 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.65 (t, 2H, CH_2), 7.20(t, 1H, Ar-H, J= 7.1), 7.40 (t, 2H, Ar-H, J=7.5 Hz), 7.96 (d, 2H, Ar-H, J= 8.2 Hz), 8.06 (s, 1H, =CH), 8.19 (d, 1H, Ar-H, J= 4.2 Hz), 8.27 (d, 1H, Ar-H, J= 4.2 Hz); **MS:** m/z (M^{+1}) = 311



(c)

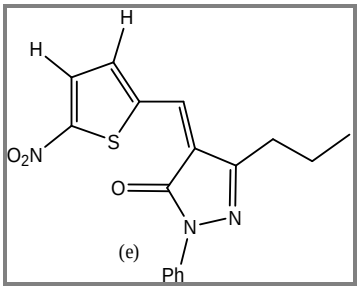
(*Z*)-4-((3-methylthiophen-2-yl)methylene)-1-phenyl-3-propyl-1*H*-pyrazol-5(4*H*)-one

d). (*Z*)-4-((3-methylthiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one: IR: 1667 (C=O), 1596 (C=N) cm^{-1}; **^{1}H NMR (DMSO-d_6): δ** 2.40 (s, 3H, CH_3), 7.32 (t, 1H, Ar-H, J= 7.2 Hz), 7.51 (t, 2h, Ar-H, J= 7.5 Hz), 7.98 (d, 2H, Ar-H, J= 8.1 Hz), 8.30 (s, 1H, =CH), 8.26 (d, 1H, Ar-H, J= 4.1 Hz), 8.39 (d, 1H, Ar-H, J= 4.1 Hz); **MS:** m/z (M^{+1}) = 337.



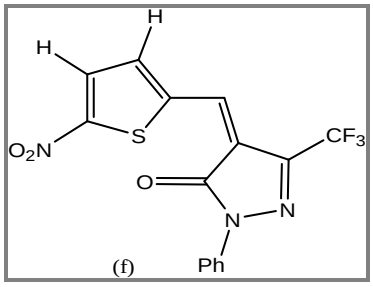
(*Z*)-4-((3-methylthiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one

e). (*Z*)-4-((3-nitrohiophen-2-yl)methylene)-1-phenyl-3-propyl-1*H*-pyrazol-5(4*H*)-one: IR: 1669 (C=O), 1609 (C=C), 1598 (C=N), 1540 (NO_2), cm^{-1}; **^{1}H NMR (DMSO-d_6): δ** 1.09(t, 3H, CH_3), 1.75 (m, 2H, CH_2), 2.62 (t, 2H, CH_2), 7.22 (t, 1H, Ar-H, J= 7.0 Hz), 7.44 (t, 2H, Ar-H, J= 7.4 Hz), 7.96 (d, 2H, Ar-H, J= 8.2Hz), 8.10 (s, 1H, =CH), 8.38 (d, 1H, Ar-H, J= 4.0 Hz), 8.49 (d, 1H, Ar-H, J= 4.0 Hz); **MS:** m/z (M^{+1}) = 342.



(*Z*)-4-((3-nitrohiophen-2-yl)methylene)-1-phenyl-3-propyl-1*H*-pyrazol-5(4*H*)-one

f). (*Z*)-4-((5-nitrohiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one: IR: 1665 (C=O), 1611 (C=C), 1594 (C=N), 1541 (NO_2) cm^{-1}; **^{1}H NMR (DMSO-d_6): δ** 7.35 (t, 1H, Ar-H, J= 7.3 Hz), 7.54 (t, 2H, Ar-H, J= 7.7 Hz), 7.92 (d, 2H, Ar-H, J= 8.4 Hz), 8.26 (s, 1H, =CH), 8.34 (d, 1H, Ar-H, J= 4.6 Hz), 8.45 (d, 1H, Ar-H, J= 4.6 Hz); **MS:** m/z (M^{+1}) = 368.

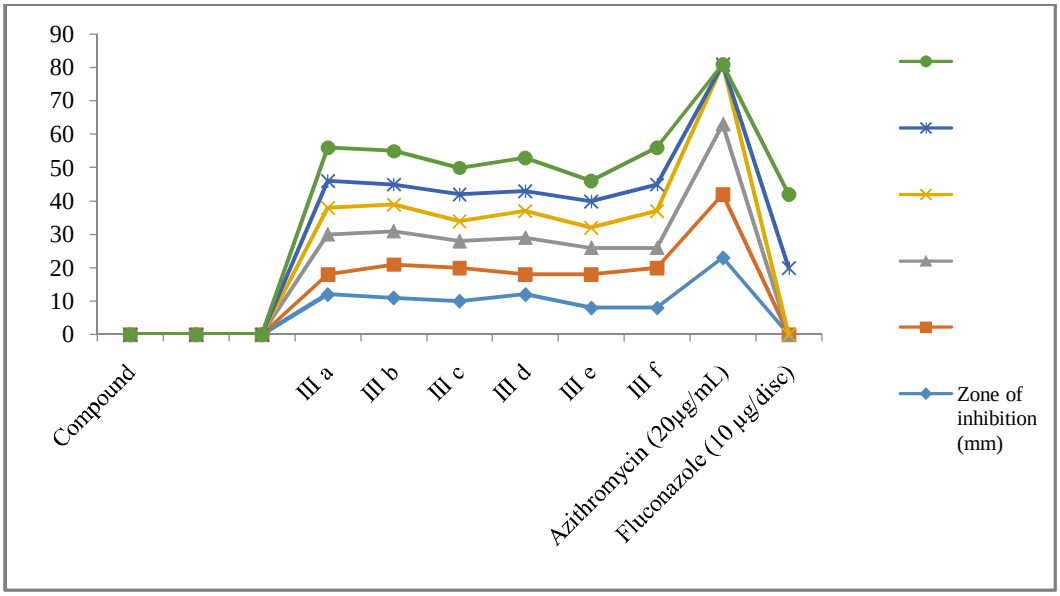


(*Z*)-4-((5-nitrohiophen-2-yl)methylene)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one

Antibacterial and Antifungal activity: The results of zone of inhibition of synthesized compounds are reported in table 2. It was observed that less to moderate antibacterial and antifungal activity compared to the control drug against all the tested species.

Table 2. Zone of inhibition for minimal bactericidal and fungicidal concentration

Compound	Zone of inhibition (mm)					
	Antibacterial test model				Antifungal test model	
	Gram positive		Gram negative			
	S. aureus	*S. epidermidis*	*E.coli*	*P. vulgaris*	*A. niger*	*C. albicans*
III a	12	06	12	08	08	10
III b	11	10	10	08	06	10
III c	10	10	08	06	08	08
III d	12	06	11	08	06	10
III e	08	10	08	06	08	06
III f	08	12	06	11	08	11
Azithromycin (20 µg mL^{-1})	23	19	21	18	-	-
Fluconazole (10 µg $disc^{-1}$)	-	-	-	-	20	22



Graphical representation for bactericidal and fungicidal concentration.

APPLICATION

The application of our reaction is to increase the product yield with minimum time span and in future it will apply for other bioactivities like anticancer, antiviral, etc. as relevant biological activity.

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 and antifungal activities of the synthesized compounds & which shows less to moderate antibacterial & antifungal activity.

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