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RESEARCH PAPER

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Green synthesis, spectroscopic characterization of pyrazole derivatives by using Nano-catalyst and biological evaluation

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ABSTRACT

Substituted pyrazole title structures are eminent chemical backbones for the preparation of new drugs which are shows a broad biological application spectrum that directly influences the new way of an investigation by adopting new methodologies products consisting of substituted pyrazole core are found to be very biological activity and versatile of substituted pyrazoles derivatives have enormously attracted by great attention in the area of drug synthesis as a result in the new drug molecule development by the utility green solvent and Nanocatalyst for the implementation in this new aspects bioactivity of pyrazoles moieties provides a new research platform for latest development in sustainable green synthetic approach structurally diverse substituted pyrazoles were introduced. The new title structure is characterized by FT-IR and 1H and ^{13}C NMR Spectroscopy. Application of bioactive potential evaluation is covered by antibacterial and antifungal by agar well diffusion method.

Keywords: α, β, diketones, hydrazine hydrate, Phenyl hydrazine, microwave, Pyrazole

1. INTRODUCTION

Pyrazole is a simple aromatic ring an organic compound of the heterocyclic scaffolds viz are character five-membered structure whichever consist of two adjacent nitrogen and three carbon atoms respectively [1]. In present time it is very important to reduce environmental pollution from the synthetic reactions by the utility homogeneous catalyst and organic solvents in synthetic procedures [2-5]. Substituted pyrazole are successfully implemented in so many routes for antitumor, anti-inflammatory antipsychotic, antimicrobial and antifungal activities [6-10]. The expansive medicinal properties of substituted pyrazole moieties are still quite interesting. Substituted pyrazole moieties of five and six-membered heterocyclic compounds play crucial roles in the invention aimed drug to eradicating certain disorders which the human population suffers day to day life [11-15]. New substituted pyrazole structural drug discovery which are shows several biomedical features and their biological profile investigation including Antibacterial, Anti-inflammatory, Antitumor, Central nervous system activity grow very fast recent years [16]. The medicine development in the market covered only 58-63 % they are heterocyclic backbones [17]. In this consequence, a new research idea on the synthesis of multi-

functionalized substituted pyrazole derivatives has sustained remarkable attraction for the adaptation of a new "green synthetic method of investigation" [18-19]. Along with a hundred substitutes, pyrazole analogs have been derived for multidrug-resistant species which also contain double unsaturated five and six-membered hetero cyclic rings having adjacent nitrogen atoms [20].

The study focused to develop a green synthetic method for the synthesis of substituted pyrazole derivatives only because of their extensive medicinal as well as pharmaceutical applications has increases many a wide range of new investigations heterocyclic chemistry.

2. MATERIALS AND METHODS

2.1. Research design

Research ideology and on-going content related to microwave irradiated method of eco-friendly green synthesis of substituted pyrazole structures are clearly reported. Fragments are used to illustrate central themes about synthetic organic chemistry material bearing substituted pyrazole group. All the chemicals and solvents are purchased from Otto, SDNF Company. In reagents grade without purification reaction progress monitor TLC Chromatography in the ration 7:3 of acetyl acetone: petroleum ether. Precipitate transfer to ice cold water Compounds recrystallized by ethyl alcohol

As a MeOH, EtOH, EtOH, can be used are eco-friendly solvents only for hydrogen donors in transfer, particularly inhydrogenation reactions. Forth instance use as media for the cobalt oxide-catalyzed reduction of allylic alcohols has been reported in a number of Subsequent pyrazole moieties investigation transfer hydrogenation of the resulting substituted pyrazole derivatives (Scheme 1-3). The better results reflect in terms of yields up to 93% in EtOH, 82%, in CH2OH, and 51% in MeOH, were obtained when compared with other solvents like DMSO AND DMF with yields of 20 to 26 %. We have been confidently utilizing the solid-support and recyclable ability of Nanocatalyst (CoO) for the synthesis of substituted pyrazoles by the achievement of excellent and moderate expected yield. General Procedure for the synthesis of Pyrazole derivatives a solution of α, β-ketoesters (Ethyl Aceto acetate/ Ethyl cyanoacetate) (20 M mol) and Aryl hydrazines/hydrazine hydrate (20 M mol) were made to react in a round bottom flask. A catalytic amount of Nano-CoO and ethanol solvent (25-30 ml) were added. The reaction mixture was kept in a Microwave oven and run it for the reaction. The progress of the reaction was monitored by TLC (Pet Ether: Ethylacetate: 8:2). After the completion of the reaction, the mixture (color changed) contained the crude product, and was filtered off. The catalyst was separated from the crude by washing with hot water for 3-4 times (approx. 40-50 ml). After the separation, it was recrystallized with ethanol to get a pure product of pyrazole with finally dried and weighed.

The reaction between acetylacetone and 2, 4 dinitro phenyl hydrazine (4a-g) with CoO Nanocatalyst with MeOH as a solvent at 27°C for about 5 min afforded 1, 3-substituted pyrazole (5a-g).

The reaction between ethylacetoacetate and phenyl hydrazine and Diphenyl amine with solid-supported CoO Nanocatalyst in EtOH at 27°C yielded substitute Pyrazolones (5a-g).The reaction between substituted hydrazine's (5cg) with 1, 3, diketones (ethyl acetoacetate) with hydrazine hydrate and thioureain CoO Nanocatalyst in EtOH media which provided the substituted Product (5c-g) in good yields.

2.2. Selected spectra

Table 1. Different methods of organic synthesis

Methods	Time (Min)	Isolated yield (%)
Oil both	42	36
Stirring	25	45
Ultra sonication	18	75
Microwave	3	90

Table 2. Different solvents with nanocatalyst

Catalyst- Solvent	Time (Min)	Isolated yield (%)
CoO/DMF	20	20
CoO/DMSO	36	26
CoO/MeOH	5	51
CoO/CH_2OH	4	85
CoO/EtOH	3	90

Table 3. Productivity of scheme -o1(5a-g)

1.3, diketones	Precursors	Conventional		Microwave
		Time (min)	Time (min)	Yield in %
Acetyl acetone	Thiourea	25	5	89
Benzoin	Urea	25	5	87
Diethyl malonate	Diphenyl amine	25	5	88
Ethyl cyanoacetate	Hydroxyl amine	25	5	85
Ethyl acetoacetate	Semicarbazide	25	5	91
Methyl acetoacetate	Diethyl amine	25	5	85
Methyl cyano acetate	triphenylamine	24	5	91

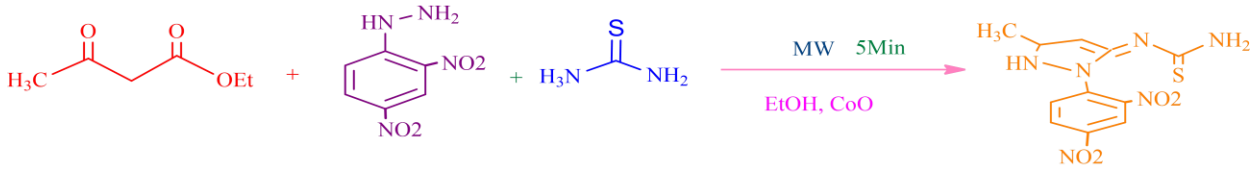


Figure 1. Scheme 01(5a-g)

3, 5-dimethyl-1-phenyl-1H-pyrazole: (5b1): White Solid, Yield, M.P. 273 °C, IR (KBr) Cm-1: 3428-3430 (N-H stretching, pyrazole ring Broad), 2867 (C-H stretching, medium, CH3), 1674 (C=C, stretching, Pyrazole), 1296-1299 (C=N, stretching, strengthening, Pyrazole rings). In 1HNMR data (DMSO-d6) of (5b1), the C=CH Proton displayed more down field signal in the range δ (H, 9.18 S) & (2H, Ar-H) 8.55 s, (3H, Ar-CH3), 9.42 to 10.25. bs and Besides this, C_5-H of the pyrazole ring resonates at around δ 7.51to 7.63. 1-[(3Z)-5-methyl-2, 4-dihydro-3H-pyrazol-3-ylidene] Urea: (5c1): White Solid, Yield M.P. 162 °C, IR (KBr) Cm^{-1} 3594 (N-H stretching, Pyrazole ring), 3389 (methyl group), 1772 (C=S stretch), 1676 (C=N urea, Pyrazole ring). In 1HNMR data (DMSO-d6) of (5b2) the C=CH Proton displayed more down field signal in the range δ (H, 9. 26 S) & (2H, Ar-H) 9.45 s, (3H, Ar-CH_3), 9.40to 7.55.bs and besides this, C_5-H of the pyrazole ring resonates at a round δ 7.51to 6.63. 1-[(3Z)- 5 - methyl - 2, 4- dihydro -3H –pyrazole – 3 ylidene] thiourea: (5c2): White Solid, Yield M.P. 142 °C, IR(KBr) Cm-1 3438 (N-H stretch, Pyrazole ring), 3378 (NH2, amine), 2174 (C=N stretch, Pyrazole ring)1616 (C=S thiourea). In the 1H NMR spectra of (5c3), the C=CH proton displayed more downfield signal in the range δ 10.18 to 10.25. Besides this, C_5-H of the pyrazole ring resonates at a round δ 7.51to 7.83.

3. RESULTS AND DISCUSSION

Synthetic route for preparation of substituted pyrazole moieties (5a, 5b, 5c) outline Schemes 1-3. Corresponding pyrazoles were systematically created with the help of earlier reported protocols by condensation of acetyl acetone/ethyl cyano acetate/1,3-diketones with appropriately substituted hydrazine hydrate. Finally, Knoevenagel condensation of appropriately different substituted pyrazole (5a-g) with substituted hydrazinein PEG as a solvent with Nano-CoO catalyst afforded the different substituted pyrazole derivatives (5c-g) an excellent yield. A synthesis was done corresponding substituted pyrazole with a 1, 3, diketones which is a precursor for an e-n withdrawing group. The replacement of hydrazine hydrate by Phenyl hydrazine in the presence of CoO Nanocatalyst in EtOH medium reaction completes in 4 min by the achievement

Table 4. Productivity of Scheme -02(5b-g)

1.3, diketones	Precursors	Conventional		Microwave
		Time (min)	Time (min)	Yield in %
Ethyl acetoacetate	Diphenyl amine	20	3	81
Acetyl acetone	Thiourea	20	3	82
Diethyl malonate	Urea	20	3	81
Ethyl cyanoacetate	Hydroxyl amine	20	3	85
Benzoin	Semicarbazide	20	3	81
Methyl acetoacetate	Diethyl amine	20	3	84
Methyl cyanoacetate	Triphenylamine	20	3	84

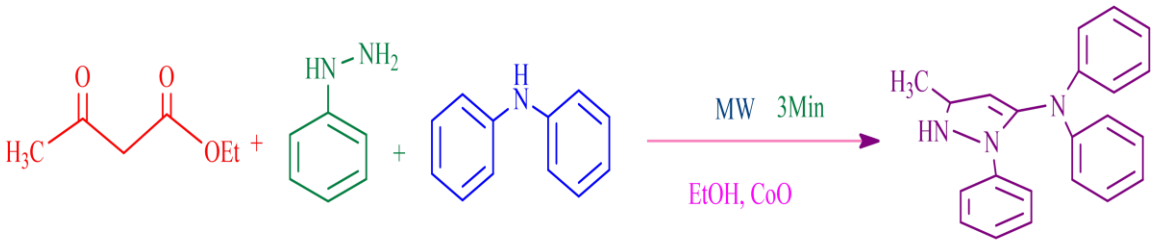


Figure 2. Scheme -02 (5b-g)

Table 5. Productivity of Scheme -03(5c-g)

1.3, diketones	Precursors	Conventional		Microwave
		Time (min)	Time (min)	Yield in %
Ethyl acetoacetate	Urea	18	3	90
Acetyl acetone	Thiourea	18	3	89
Diethyl malonate	Diphenyl amine	18	3	89
Ethyl cyanoacetate	Hydroxyl amine	18	3	85
Benzoin	Semicarbazide	18	3	81
Methyl acetoacetate	Diethyl amine	18	3	87
Methyl cyanoacetate	triphenylamine	18	3	81

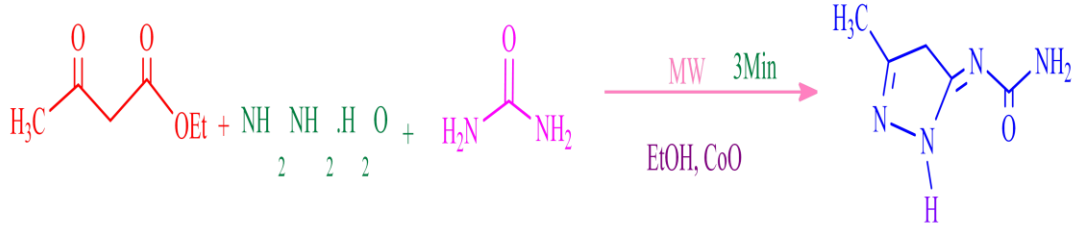


Figure 3. Scheme -03 (5c-g)

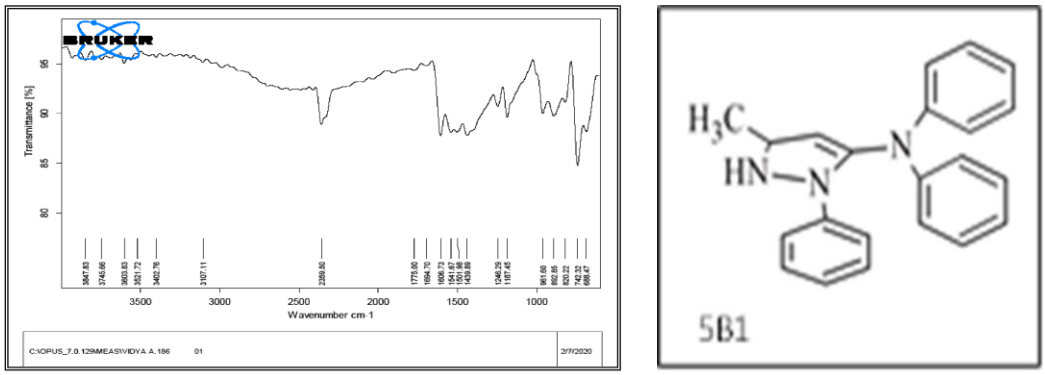


Figure 4. FT-IR Spectra (5b 1)

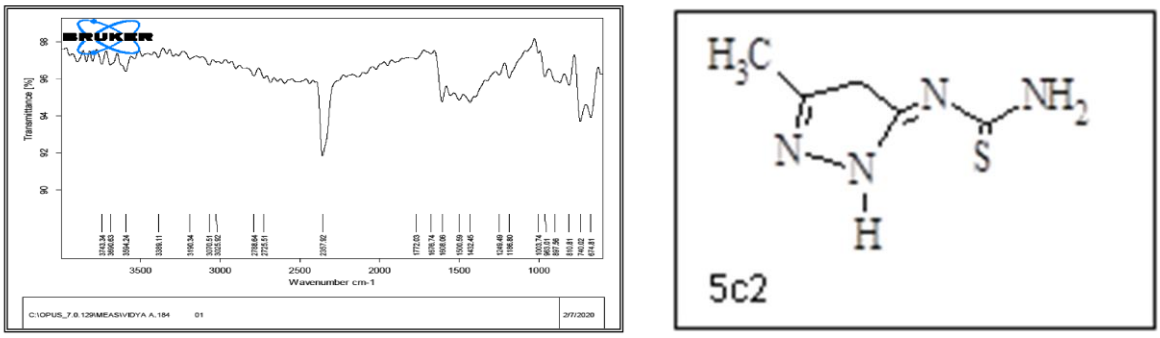


Figure 5. FT-IR Spectra (5c 2)

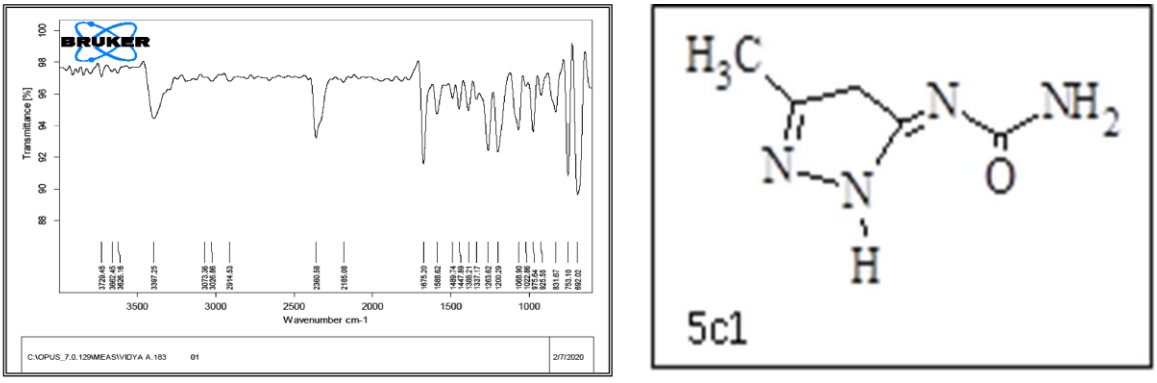


Figure 6. FT-IR Spectra (5c 1)

of 85% good yield.

At last 2, 4 dinitro phenyl hydrazine was introduced at the place of hydrazine in the presence of catalyst CoO and MeOH as a solvent reaction by the achievement of 45% expected yield. Spectral data (IR, 1H NMR, and 13C NMR) of the newly synthesized compounds 5a-5c were in full agreement with the proposed structures.

The IR spectra of 5b and 5c showed a characteristic absorption band around 1,674 to 1,682 cm-1 that was assigned to the C=O stretching, while the two absorptions bands around1, 304 to 1,335 and 1,149 to 1,165 cm^{-1}. This further supported the proposed structures of newly synthesized compounds displayed the SO_2 stretching's. In the 1H NMR spectra of 5b and 5c, the C=CH proton displayed more downfield signal in the range δ 10.18to 10.25. Besides this, C_5-H of the pyrazole ring resonates at a round δ 7.51to 7.63. Organic green synthesis by microwave-assisted has been the foremost and one of the most recent utility applications of microwave in chemical reactions. Literature survey reveals that CoO catalyst in EtOH solvent by the

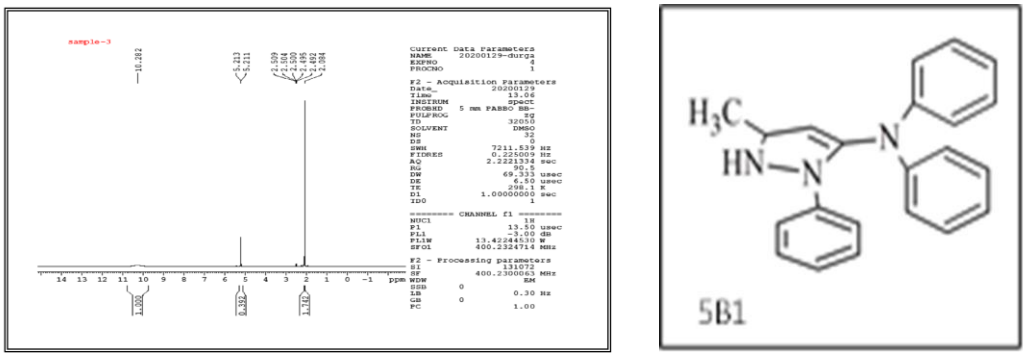


Figure 7. ^{1}H -NMR Spectra (5b 1)

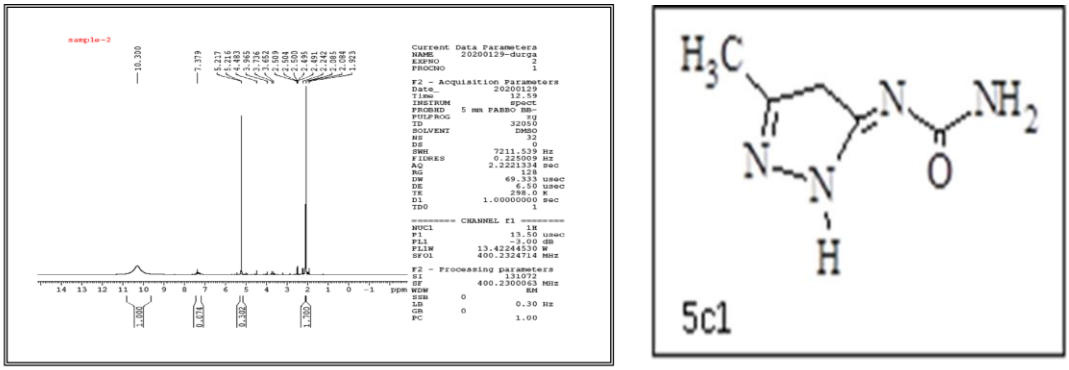


Figure 8. ^{1}H -NMR Spectra (5c 1)

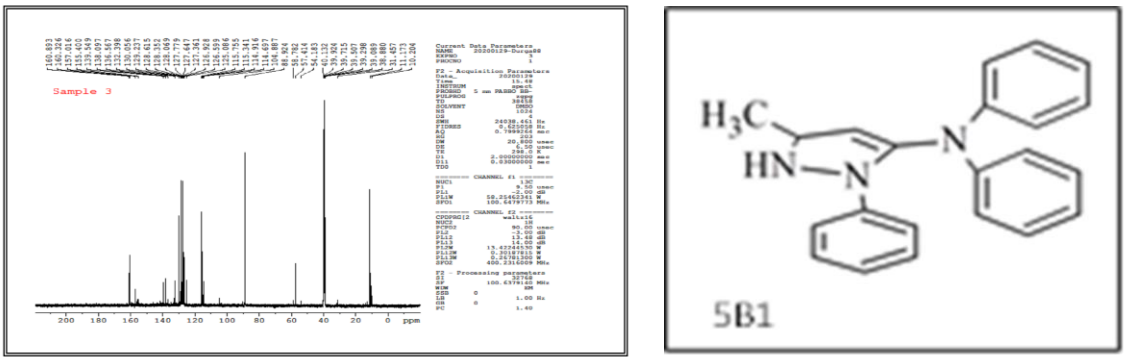
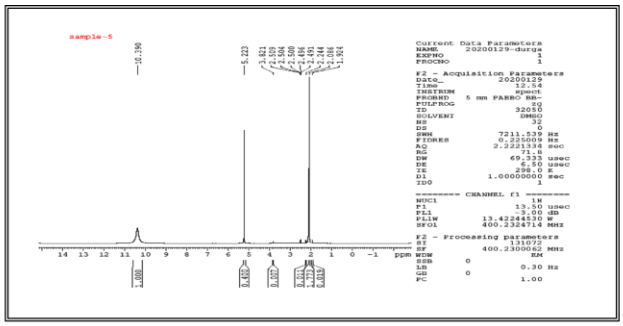


Figure 9. ^{13}C -NMR Spectra (5b 1)

combination of ethyl aceto acetate and hydrazine hydrates is an efficient one which influences the reactions to complete instantly and by the achievement excellent yield [21-22]. The study successfully conducted one more different series with phenyl hydrazine and another series with 2, 4, di nitrophenyl hydrazine. The comparison in different hydrazine and Nano-catalyst and different green solvents reactions are studied. These have differences in reaction timings to completed their reaction like 5 minutes in 2,4, dinitro phenyl hydrazine and 3 minutes phenyl hydrazine and 3 minutes in hydrazine hydrates in the presence PEG of under microwave method [16, 23]. It is more efficient and convenient for organic synthesis than for conventional magnetic stirring synthetic organic synthesis for substituted pyrazole.

4. CONCLUSION

In this, we have mentioned the three new method for the synthesis of substituted pyrazole derivatives. The first steps included condensation followed by cyclization or



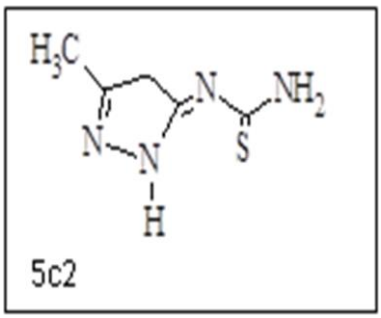
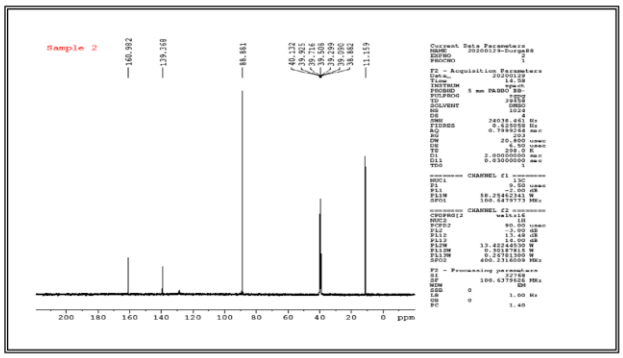


Figure 10. ^{1}H -NMR Spectra (5c 2)



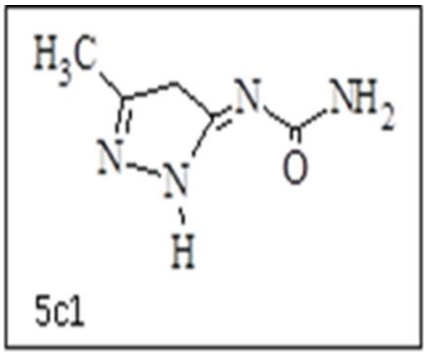


Figure 11. ^{13}C -NMR Spectra (5c 1)

Table 6. Antimicrobial activity of different molecules against various microorganisms using agar well diffusion method.

Samples	Inhibition zone diameter (mm/mg-sample)					
	A. fumigatus	C. albicans	S. aureus	B. subtilis	E. coli	S. Typhimurium
Tetracycline antibacterial	---	---	30	29	31	30
DMSO Control	0.0	0.0	0.0	0.0	0.0	0.0
Clotrimazole antifungal	24	22	--	--	--	--
$5c_1$	0.0	0.0	37	31	38	32
$5c_2$	0.0	0.0	35	30	37	30
$5c_3$	0.0	0.0	33	33	32	33
$5c_4$	20	21	37	0.0	0.0	0.0
$5c_6$	22	20	38	31	35	37
$5c_7$	19	0.0	0.0	0.0	0.0	0.0

multi-component reaction (MCR), in one pot green synthesis under microwave irradiation, which has been achieved successfully to obtain substituted the aforementioned class of hetero cycles under different conditions. Most of the preparative methods included Nanocatalysts in eco-friendly solvents and different hydrazine as common reagents or the synthesis of substituted pyrazole affix hetero cyclic backbone. Also, two more series of substituted pyrazole fused five and six-membered hetero cycles possessing N-S has been constructed by achieving excellent yields. Hence these short procedures provide convenient strategies for annulated different heterocyclic nuclei with pharmaceutically important pyrazole by extending the categories of heterocyclic derivatives.

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6. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

7. SOURCE/S OF FUNDING

NA

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