International Journal of Pharmacognosy and Pharmaceutical Sciences

ISSN Print: 2706-7009
ISSN Online: 2706-7017
IJPPS 2023; 5(1): 12-19
www.pharmacognosyjournal.net
Received: 13-04-2023
Accepted: 17-05-2023

Suresh HM
Research Scholar, Department of Chemistry, UBDT College of Engineering, Davanagere, Karnataka, India

Suresha Kumara TH
Associate Professor, Department of Chemistry, UBDT College of Engineering, Davanagere, Karnataka, India

Corresponding Author:
Suresh HM
Research Scholar, Department of Chemistry, UBDT College of Engineering, Davanagere, Karnataka, India

Green synthesis of pyrazole derivatives by using nano-catalyst

Suresh HM and Suresha Kumara TH

DOI: https://dx.doi.org/10.33545/27067009.2023.v5.i2a.127

Abstract
Background: 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. In present days very importance to reduce environment pollution from the synthetic reactions by the utility homogeneous catalyst and organic solvents in synthetic procedures our interest is to develop green synthetic protocol for synthesis of substituted pyrazole derivatives only because their extensive medicinal as well as pharmaceutical applications has increases many a wide range of new investigations in heterocyclic chemistry. Substituted Pyrazoles were also successfully implemented so many routes as antitumor, anti-inflammatory antipsychotic, antimicrobial and antifungal activities. Due to expansive medicinal properties of substituted pyrazole moieties till today quite interesting.
Methods: Research ideology and on-going content related to microwave irradiated green synthesis of substituted pyrazole structures are clearly report. Fragments are used illustrate central themes about synthetic organic chemistry material bearing substituted pyrazole derivatives.
Results: Brand new substituted α, β-Phenyl Pyrazoles and α, β-hydrazide Pyrazoles was synthesized by microwave heating directly from α, β-diketones and phenyl hydrazine, hydrazine hydrate via a cobalt oxide catalysed coupling reaction in green solvent medium,
Conclusion: Substituted pyrazoles were prepared via microwave irradiated using Nano catalyst solvent mediated at RMT. A green synthetic protocol which is zone-friendly and advisable method for the preparation of pyrazoles in the presence of heterogeneous catalyst in solvent medium. This method produced excellent yields in terms of minutes therefore; this simple method would be practical for green synthesis of potentially valuable derivatives.

Keywords: Diketones, α, β, hydrazine hydrate, phenyl hydrazine, microwave, pyrazole

Introduction
Substituted pyrazoles moieties of five and six membered heterocyclic compounds play crucial roles in the invention aimed drug to eradicate certain disorders in which human population suffer day today life. New substituted pyrazoles structural drug discovery which are shows several biomedical features and their biological profile investigation process including Antibacterial, Anti-inflammatory, Antitumor, Central nervous system activity grow very fast recent years. The medicine development in the market covered only 58-63% they are heterocyclic backbones. In this consequence not a surprising thought new research idea on the synthesis of multi-functionalized substituted pyrazole derivatives has sustain remarkable attraction for the adaptation of new “green synthetic method of investigation”. Along with a hundred of substitutes pyrazoles analogues have been derived for multidrug resistant species which also contains double unsaturated five and six membered heterocyclic ring having adjacent nitrogen atoms. Numerous utility of substituted pyrazoles features encourages the new ideal dreamed research scientist to creates new green synthetic approaches to synthesis of other new variety of substitutes pyrazole derivatives with similar characters but with for better pharmaceutical activity result. Now a day for one hours new several discover are going on in a small molecule which having pyrazoles backbone derivatives as drug will arises to social needs. It is important thoughts of research.

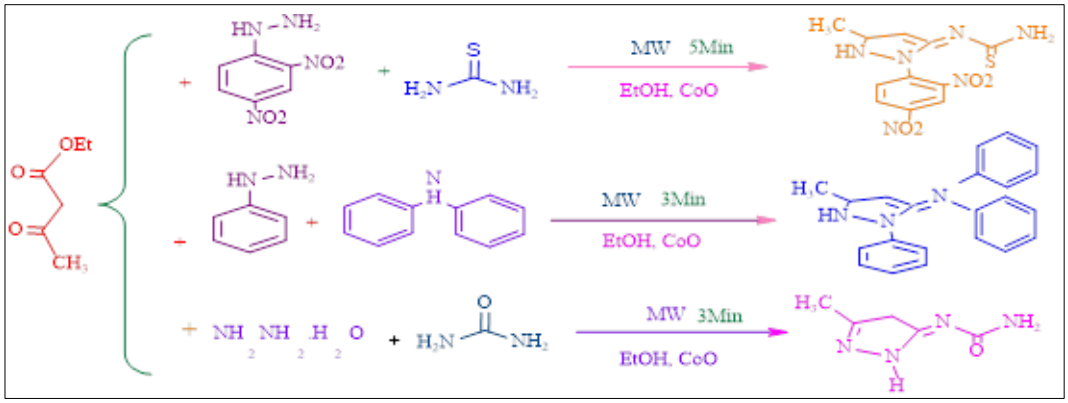

Fig 1: Graphical representation

Table 1: Present method compare with other

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

As a MeOH, EtOH, EtOH, can be uses are eco-friendly solvents only for hydrogen donor in transfer particularly in hydrogenation reactions. Forth instance use as media for the cobalt oxide-catalysed reduction of Allylic alcohols. Have been reported in numbers of Subsequent pyrazoles 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 CH_2OH, 51% in MeOH, were obtained when compared with other solvent like DMSO AND DMF with yield of 20 to 26%. We have been confidently utilizing the solid-support and recyclable ability of Nano catalyst (COO) for the synthesis of substituted pyrazoles by achieving of excellent and moderate and expected yield.

Reaction Protocols: (a) [2, 4, dinito phenyl hydrazine]

Kira *et al*. [5] denotes the reaction between acetyl acetone and 2, 4; dinitro phenyl hydrazine (4a-g) with COO Nano catalyst with MeOH as a solvent. 27 °C for about -5 Min afforded 1, 3-substituted pyrazole- (5a-g).

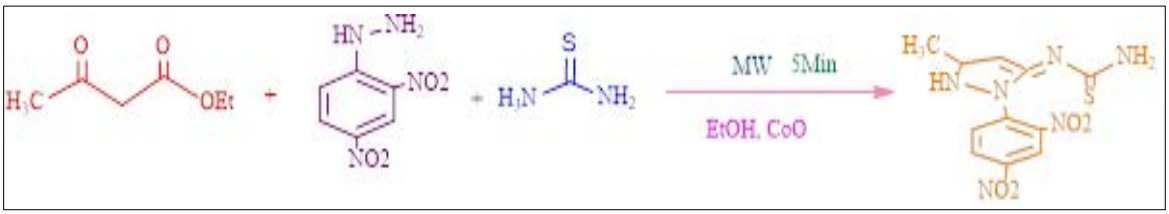

Fig 2: Scheme-01

Table 2: Result of Scheme -01

Sample	1.3, diketones	Precursors	Solvent and Catalyst	Conventional		Microwave	
				Time (Min)	Yield in%	Time (Min)	Yield in%
5a. 1	Acetyl acetone	Thiourea	MeOH/COO	25	51	5	89
5a. 2	Benzoin	Urea	MeOH/COO	25	51	5	87
5a. 3	Diethyl malonate	Diphenyl amine	MeOH/COO	25	51	5	88
5a. 4	Ethyl cyanoacetate	Hydroxyl amine	MeOH/COO	25	49	5	85
5a. 5	Ethyl acetoacetate	semicarbazide	MeOH/COO	25	50	5	91
5a. 6	Methyl acetoacetate	Diethyl amine	MeOH/COO	25	50	5	85
5a. 7	Methyl cyano acetate	triphenylamine	MeOH/COO	24	50	5	91

Reaction Protocols: (5b-g) [Phenyl hydrazine]

Main author Mariappan and *et al*. denoted the reaction protocol reaction between ethyl acetoacetate and phenyl hydrazine and Diphenyl amine with solid supported COO Nano catalyst in EtOH in 27 °C yielded substitute pyrazolones (5a-g). The pyrazolones upon reaction with different substituted aromatic diketones in presence of EtOH gives some substituted products (5b-g).

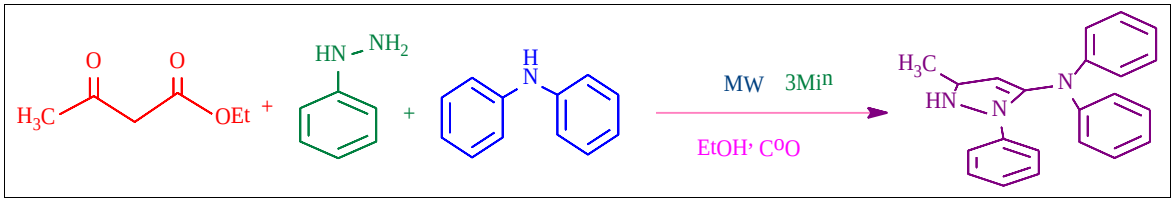

Fig 3: Scheme-02

Table 3: Result of Scheme-02

Entry	1.3, diketones	Precursors	Solvent & Catalyst	Conventional		Microwave	
				Time (min)	Yield in%	Time (min)	Yield in %
5b. 1	Ethyl acetoacetate	Diphenyl amine	EtOH/COO	20	45	3	81
5b. 2	Acetyl acetone	Thiourea	EtOH/COO	20	41	3	82
5b. 3	Diethyl malonate	Urea	EtOH/COO	20	49	3	81
5b. 4	Ethyl cyanoacetate	Hydroxyl amine	EtOH/COO	20	49	3	85
5b. 5	Benzoin	semicarbazide	EtOH/COO	20	5	3	81
5b. 6	Methyl acetoacetate	Diethyl amine	EtOH/COO	20	51	3	84
5b. 7	Methyl cyanoacetate	triphenylamine	EtOH/COO	20	57	3	84

Reaction Protocols: (5c-g) [hydrazine hydrates]

Isloor and *et al*. reported the reaction between substituted hydrazines (5c-g) with 1, 3, diketones (ethyl acetoacetate) with hydrazine hydrate and thiourea in COO Nano catalyst in EtOH media which provided the substituted Product (5c-g) in good yields.

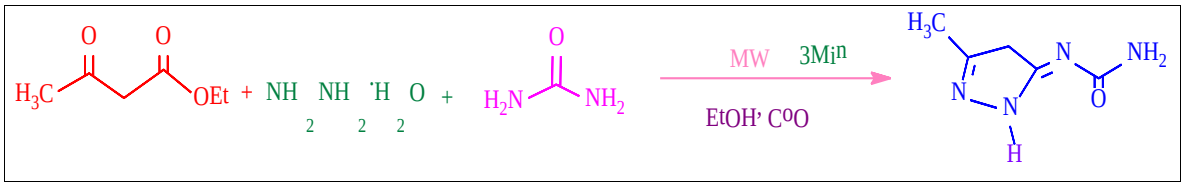

Fig 4: Scheme-03

Table 4: Result of Scheme-03

Entry	1.3, diketones	Precursors	Solvent & Catalyst	Conventional		Microwave	
				Time (Min)	Yield in%	Time (Min)	Yield in %
5c.1	Ethyl acetoacetate	Urea	EtOH/COO	18	51	3	90
5c.2	Acetyl acetone	Thiourea	EtOH/COO	18	59	3	89
5c.3	Diethyl malonate	Diphenyl amine	EtOH/COO	18	49	3	89
5c.4	Ethyl cyanoacetate	Hydroxyl amine	EtOH/COO	18	55	3	85
5c.5	Benzoin	semicarbazide	EtOH/COO	18	51	3	81
5c.6	Methyl acetoacetate	Diethyl amine	EtOH/COO	18	57	3	87
5c.7	Methyl cyanoacetate	triphenylamine	EtOH/COO	18	51	3	81

Selected spectra

3, 5-dimethyl-1-phenyl-1*H*-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, CH_3), 1674 (C=C, stretching, Pyrazole), 1296-1299 (C=N, stretching, strong, Pyrazole rings). In ^1H NMR data (DMSO-d6) of (5b1) the C=CH Proton displayed more downfield signal in the range δ (H, 9.18 S) & (2H, Ar-H) 8.55 s, (3H, Ar-CH_3), 9.42 to 10.25. BS and besides this, C_5-H of the pyrazole ring resonates at around δ 7.51 to 7.63. 1-[(3*Z*)-5-methyl-2, 4-dihydro-3*H*-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 ^1H NMR data (DMSO-d6) of (5b2) the C=CH Proton displayed more downfield signal in the range δ (H, 9.26 S) & (2H, Ar-H) 9.45 s, (3H, Ar-CH_3), 9.40 to 7.55. BS and Besides this, C_5-H of the pyrazole ring resonates at around δ 7.51 to 6.63.

1-[(3*Z*)-5-methyl-2, 4-dihydro-3 *H*-pyrazol-3-ylidene] thiourea

(5c2): White Solid, Yield M.P. 142 °C, IR (KBr) Cm^{-1} 3438 (N-H stretch, Pyrazole ring), 3378 (NH_2, amine), 2174 (C=N stretch, Pyrazole ring) 1616 (C=S Thiourea). In the H 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 around δ 7.51 to 7.83.

Spectra: FT-IR

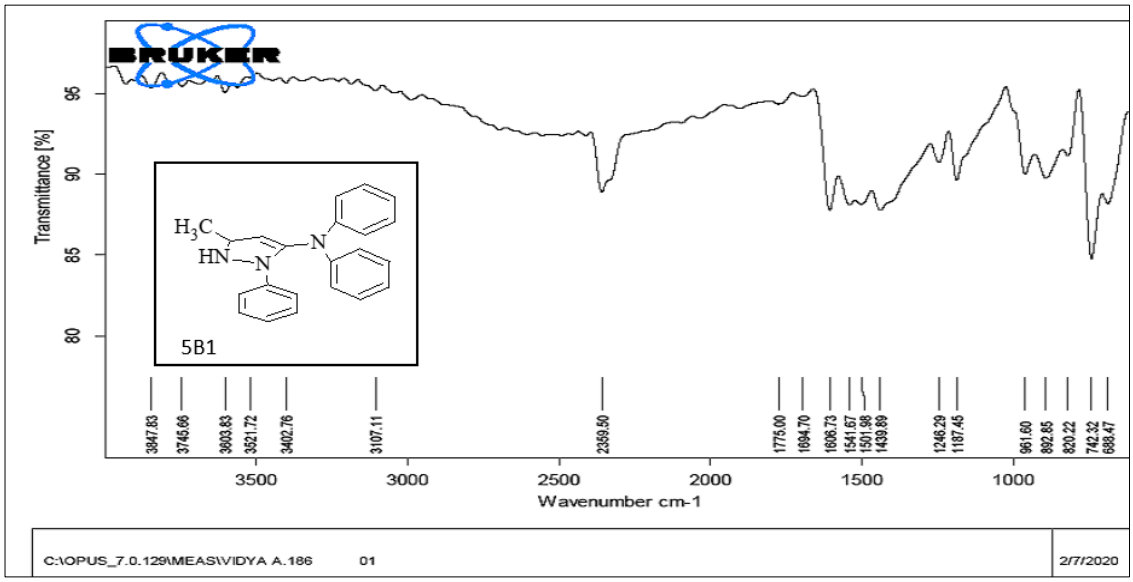

Fig 5: FTIR of 5B1 comp

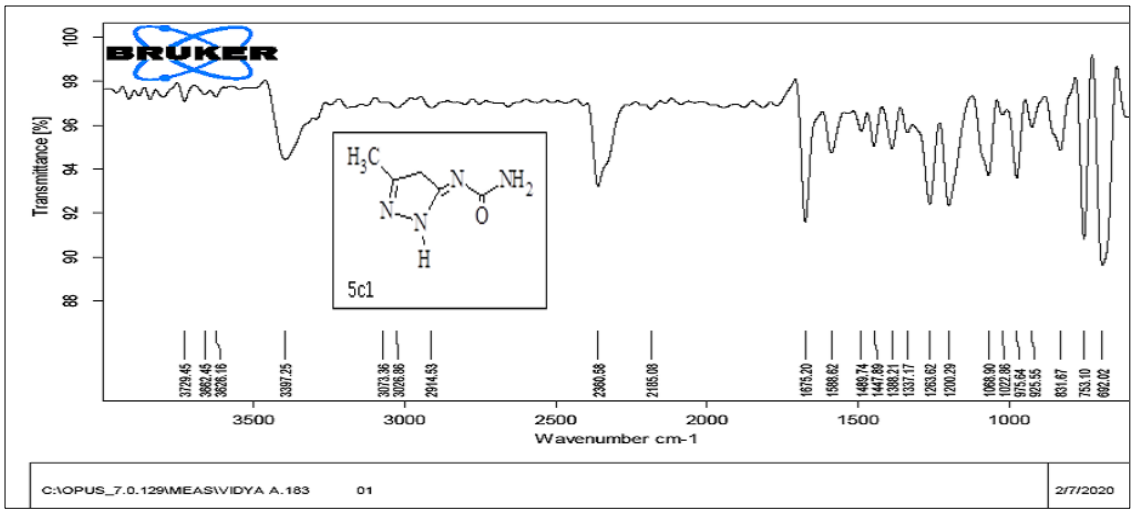

Fig 6: FTIR of 5C1 comp

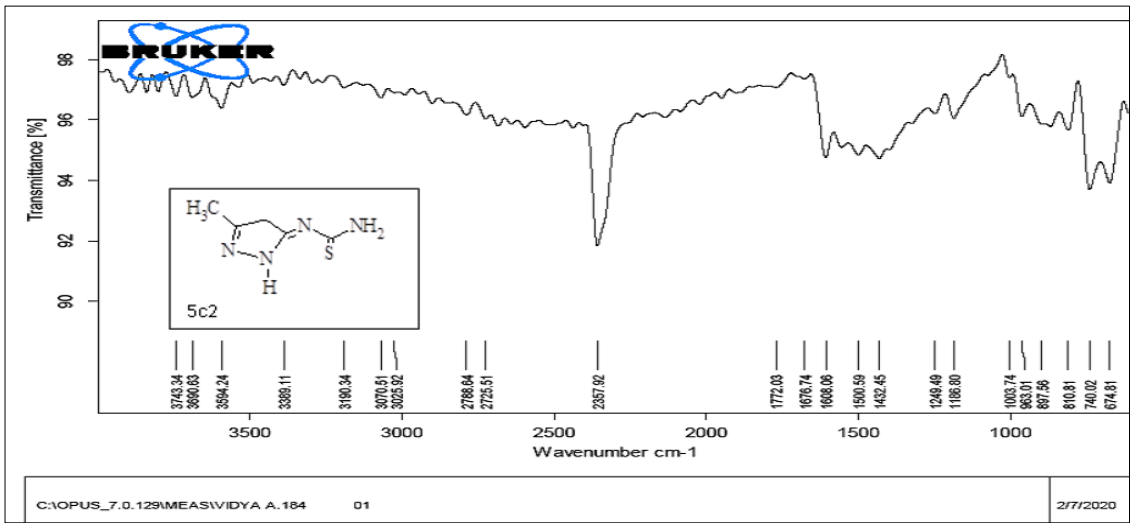

Fig 7: FTIR of 5C2 comp

Spectra-1 H and 13 C NMR

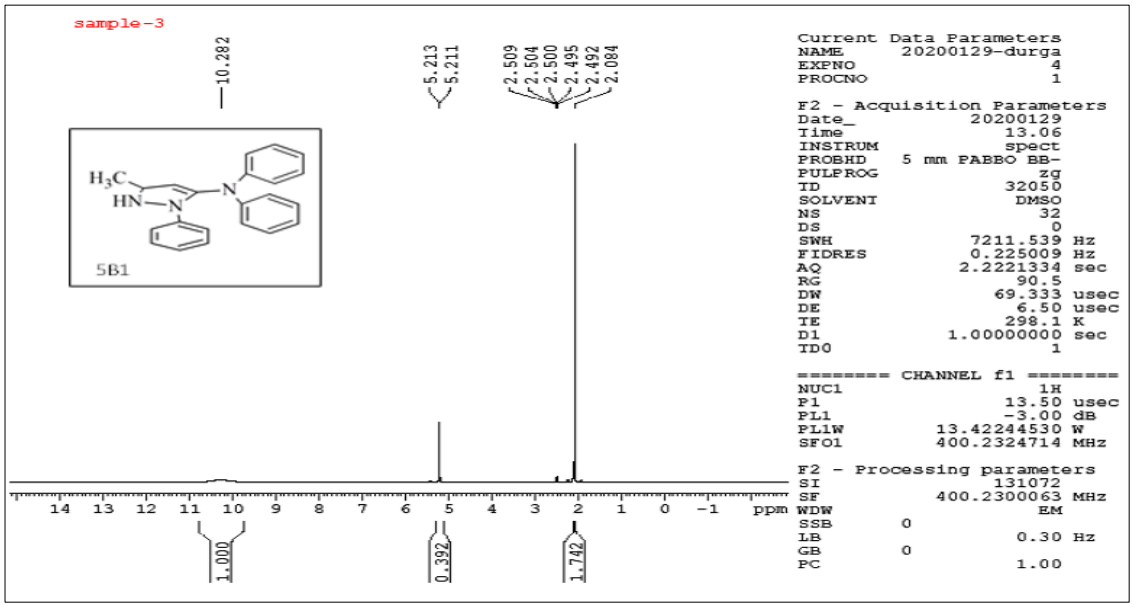

Fig 8: 1H NMR of 5B1 comp

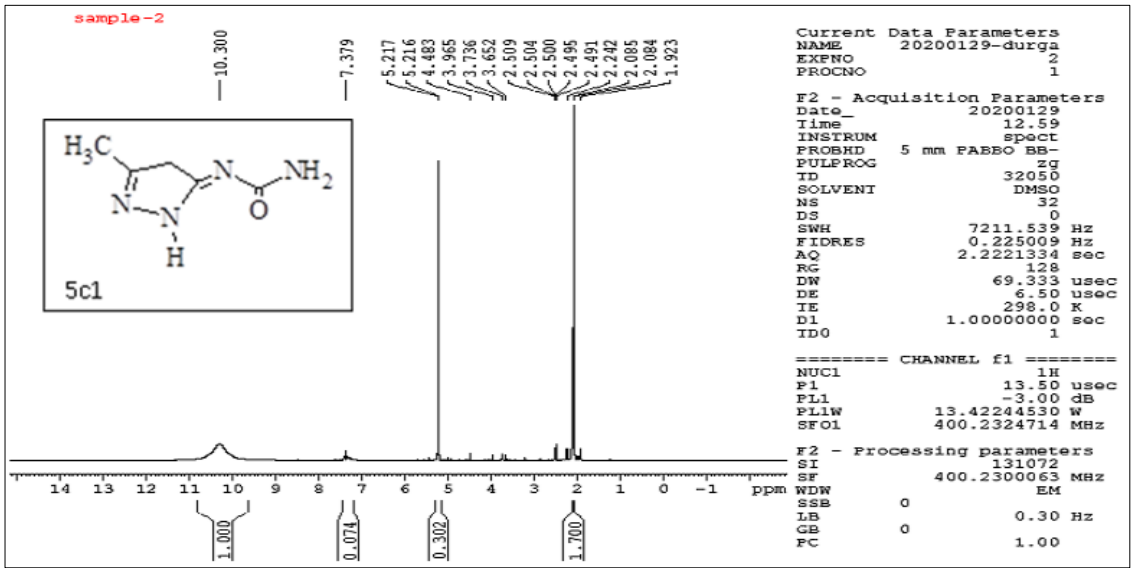

Fig 9: 1H NMR of 5C1 comp

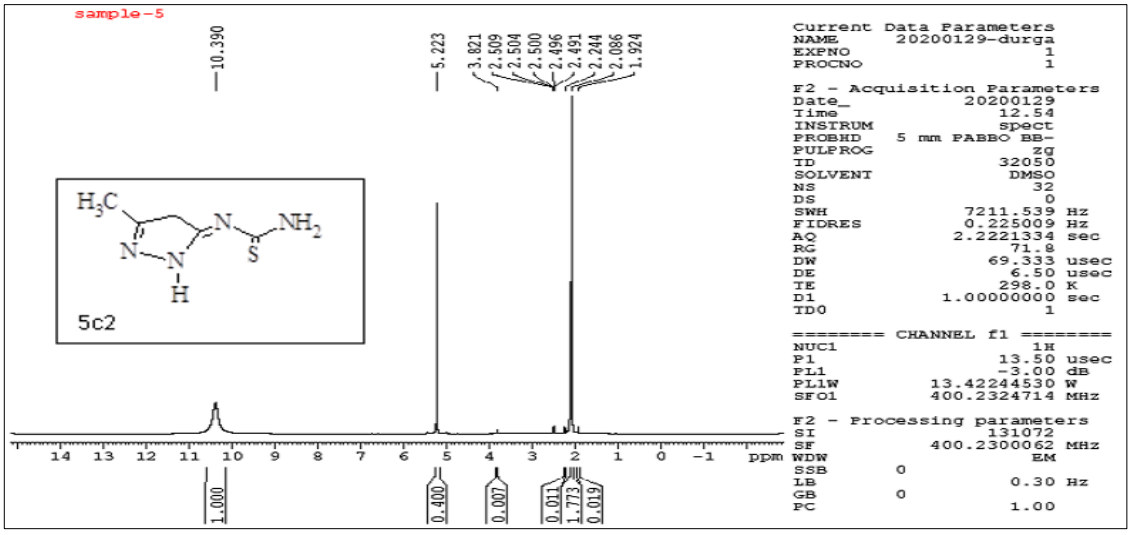

Fig 10: 1H NMR of 5C2 comp

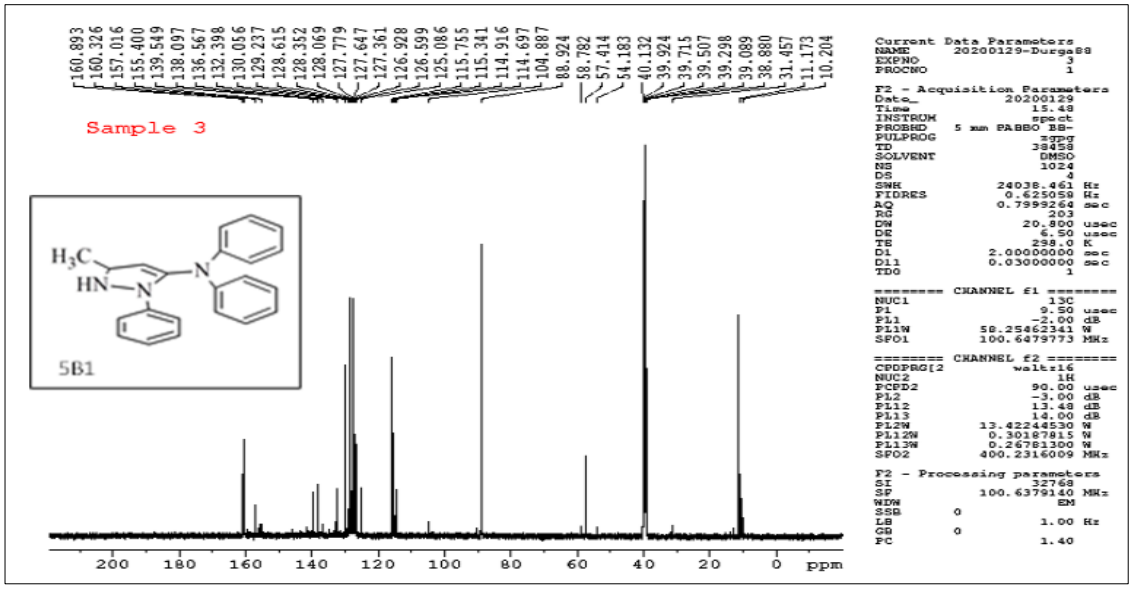

Fig 11: 13C NMR 5B1 comp

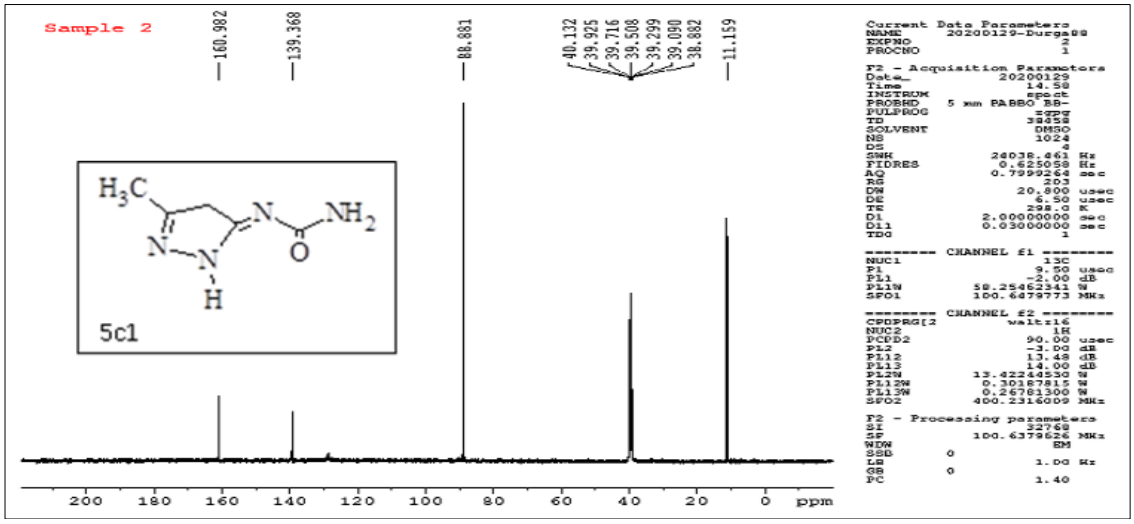

Fig 12: 13C NMR of 5C1 comp

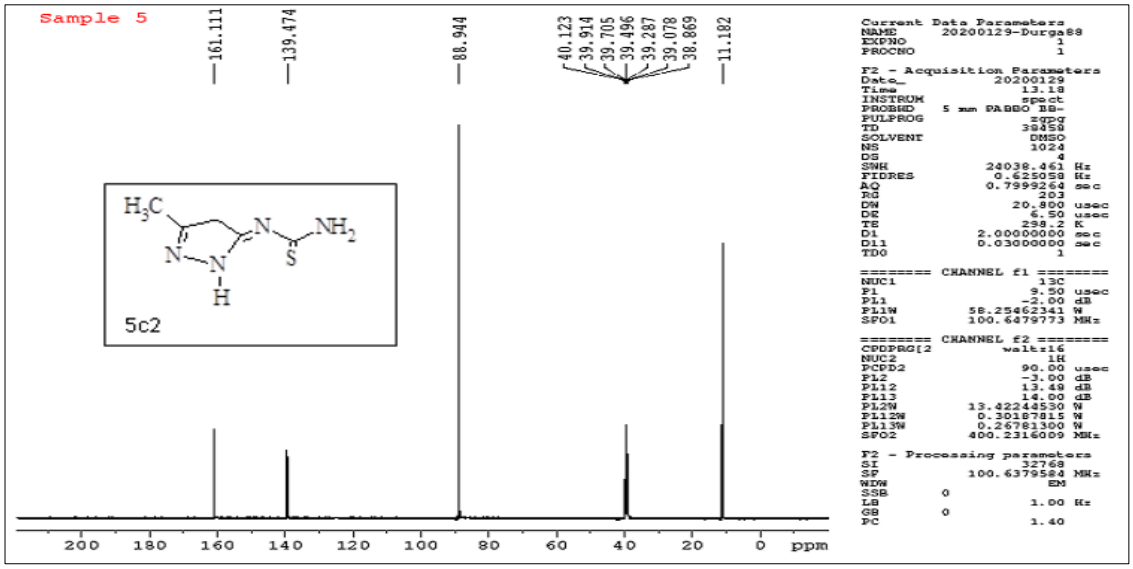

Fig 13: 13C NMR of 5C2 comp

Results and Discussion

Synthetic route for preparation of substituted pyrazole moieties (5a, 5b, 5c) outline Schemes 1-7. Corresponding Pyrazoles systematically created by the help of earlier reported protocols by condensation of acetyl acetone/ethyl cyano acetate/1, 3-diketones with appropriate substituted

hydrazine hydrate. Finally, Knoevenagel condensation of appropriately different substituted pyrazoles (5a-g) with substituted hydrazine in PEG as a solvent with Nano-COO catalyst afforded the different substituted pyrazole derivatives **(**5c-g**)** in excellent yield. We also decide to synthesized corresponding substituted pyrazoles with an 1, 3, diketones is a precursor as an e^{-n} with drawing group. By the replacement of hydrazine hydrate by Phenyl hydrazine in the presence of COO Nano catalyst in EtOH medium reaction completes 4 min by the achievement of 85% good yield. In Last 2, 4 dinitro phenyl hydrazine introduced in the place hydrazine in the presence of catalyst COO and MeOH as a solvent reaction by the achievement of 45% expected yield.

Spectral data (IR, ^{1}H NMR, and ^{13}C 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 around 1,304 to 1,335 and 1,149 to 1,165 cm^{-1} which further supported the proposed structures of newly synthesized compounds displayed the SO_2 stretching's. In the ^{1}H NMR spectra of 5b and 5c, 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 around δ 7.51 to 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 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. We have successfully conducted different one more series with phenyl hydrazine and another series with 2,4, di nitro phenyl hydrazine.We studied the comparison in different hydrazine's and Nano-catalyst and different green solvents reactions which have difference in reaction timings which are completed their reaction in 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 is more efficient and convenient for Organic synthesis for substituted pyrazoles.

Antibacterial and Antifungal activity of prepared compounds

Table 5: *In vitro* microbial activity of prepared compounds

Inhibition zone diameter (mm/mg-sample)						
Antimicrobial activity% (Inhibition zone %)						
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
$5c_7$	1 9	0.0	0.0	0.0	0.0	0.0

Conclusion

In this we have mentioned the three new protocols for the synthesis of substituted pyrazole derivatives. The first steps included condensation followed by cyclization or multi-component reaction (MCR), in one pot green synthesis under microwave irradiation, has been achieved successfully to obtain substituted the aforementioned class of heterocycles under different conditions. Most of the preparative methods included Nano catalysts in eco-friendly solvents and different hydrazine as common reagents or the synthesis of substituted pyrazole affix heterocyclic backbone. Also two more series of substituted pyrazole fused five and six membered heterocycles possessing N-, S have been constructed by achieving excellent yields. Hence these short procedures provide convenient strategies to annulated different heterocyclic nuclei with pharmaceutically important pyrazoles by extending the categories of heterocyclic derivatives.

Acknowledgement

Sincere Thanks to UBDT College of Engineering for providing Facility for Research Work and My Heart Full Thanks Dr. Manjanna professor Ranichennamma University DR. Vishwanath assistant Professor kuvempu university providing Nano catalyst. To SSM Institute of Medical Science and Research Centre, Davanagere providing Microbial Cultures. Honest thanks to BIET College of engineering, Davanagere. Providing Facility for biological investigation. Special thanks to social welfare department, Government of Karnataka, and Municipal Corporation, Davanagere for proving financial support.

References

1. Bougrin K, Loupy A. Microwave-assisted solvent-free heterocyclic synthesis. J Photochem. Photobiol C, Photochem. Rev. 2005;6:139-167.
2. Aggarwal VK, de Vicente. A novel one-pot method for the preparation of pyrazoles by 1, 3-dipolar Cyclo additions of Diazo compounds generated in Situ. J Org. Chem. 2003;68:5381-83.
3. Kost AN, Grandberg II. Progress in Pyrazole Chemistry. Adv. Heterocycl. Chem. 1966;6:347-429.
4. Padwa A. 1, 3-Dipolar Cycloaddition Chemistry; John Wiley & Sons: New York; c1984. p. 1.
5. Fulton JR, Aggarwal VK, de Vicente J. The use of Tosylhydrazone salts as a safe alternative for handling

Diazo compounds and their applications in organic synthesis. Eur. J Org. Chem; c2005. p. 1479-1492.
6. Bamford WR, Stevens TS. The decomposition of p-Tolylsulfonyl hydrazones by Alkali. J Chem. Soc; c1952. p. 4735-4740.
7. Brewbaker JL, Hart H. The Cyclization of 3-Diazoalkenes to Pyrazoles. J Am. Chem. Soc. 1969;91:711-715.
8. Doyle MP, Yan MJ. Effective and highly stereoselective coupling with vinyl diazomethanes to form symmetrical trienes. J Org. Chem. 2002;67:602-604.
9. Almirante N, Cerri A, Fedrizzi G, Marazzi G, Santagostino M. A General, [1+4] Approach to the Synthesis of 3(5)-Substituted pyrazoles from aldehydes. Tetrahedron Lett. 1998;39:3287-3290.
10. Grandi R, Messerotti W, Pagnoni UM, Trave R. Decomposition of Coniugated hydrazones in Base. Partition between Solvolysis and Cycloaddition Products. J Org. Chem. 1977;42:1352-1355.