Annexure - VIII

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1. Title of Project: ***"Microwave Assisted Synthesis and Biological Evaluation of Heterocyclic Compounds"***
2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR: **Shri. Kiran Neminath Patil, Department of Chemistry, Dr.Ghali College, Gadhinglaj.**
3. NAME AND ADDRESS OF THE INSTITUTE: **Dr.Ghali College, Gadhinglaj. Tal – Gadhinglaj, Dist Kolhapur. Pin- 416 502.**
4. UGC APPROVAL LETTER NO. AND DATE:

   F. 47-1160/14(WRO) dated 28th Dec 2015

   F.47-1160/14(WRO) dated 30th March 2016
5. DATE OF IMPLEMENTATION: **01/04/2016**
6. TENURE OF THE PROJECT: **Two years (01/04/2016 to 31/03/2018)**
7. TOTAL GRANT ALLOCATED: **3,60,000/-**
8. TOTAL GRANT RECEIVED: **2,50,000/-**
9. FINAL EXPENDITURE: **3,63,486/-**
10. TITLE OF THE PROJECT: ***"Microwave Assisted Synthesis and Biological Evaluation of Heterocyclic Compounds"***
11. OBJECTIVES OF THE PROJECT:

    1. **To study the synthesis of diverse and complex heterocyclic molecules by multicomponent reactions (MCR)**
    2. **To synthesize nanoparticles as green catalyst and employed to carry MCR**
    3. **Microwave strategy used to synthesize heterocyclic compounds in green approach**
    4. **Carried out**
       a) **Synthesis of functionalized 1H-pyrazolo [1,2-b] phthalazine-5,10- dione derivatives**
       b) **Microwave assisted one pot synthesis of bowl shaped molecular architecture from**

Phloroglucinol and Ninhydrin.

c) **Multicomponent one pot synthesis of highly substituted pyridines with ZnO Nanoparticles as catalyst.**

d) **Microwave assisted efficient synthesis of 5H-dibenzo [b, i] xanthene-tetraones and its Biological Evaluation.**

5. **Further synthesized compounds characterized by IR, NMR and Mass spectroscopy techniques**
6. **Synthesized compounds screened for Biological activity like Anti-bacterial, Anti-fungal, anti-tuberculosis etc.**

13. ACHIEVEMENTS FROM THE PROJECT

- The research paper entitled "Microwave assisted green synthesis of 1H-Pyrazolo [1, 2-b] Phthalazine-5, 10-Dione Derivatives with CTAB capped ZnO nanoparticles as catalyst" presented in International Conference on Advances in Materials Science at Raje Ramrao Mahavidyalaya, Jath on 07 & 08 Dec 2016 with **ISBN 978-93-5254-490-5** (Best Poster Presentation award for this research paper)
- The research paper entitled "Microwave Assisted One-Pot Synthesis of Bowl Shaped Molecular Architecture from Phloroglucinol and Ninhydrin" presented in National Conference on Emerging Trends in Chemical and Physical Sciences at Yashwantrao Chavan Warana Mahavidyalaya, Warananagar on 14 Feb 2017.**(Third Prize for Oral Presentation)**
- Two students from B.Sc. III (Chemistry) has done their project work in this field.
- The research paper entitled "Multicomponent, one –pot synthesis of highly substituted pyridines with Zinc Oxide nanoparticles as catalyst" published in **Indian Journal of Heterocyclic Chemistry** .Vol.27, No.2, June 2017,157-164 with ISSN 0971-1627.
- The research paper entitled "Oxalic acid dihydrate-proline(LTTM) as a new generation designer solvent for efficient three-component synthesis of 3-methyl-4(hetero)aryl methylene isoxazole-5(4H)-ones" presented in National Conference on **Recent Trends in Chemical Sciences and Its Interdisciplinary Applications** at Yashwantrao Patil Science College, Solankur on 06 Jan 2018.

- The research paper entitled "Microwave assisted green and efficient synthesis of 2-aryl-1, 3-benzothiazoles catalysed by *Lemon juice*" presented in National Conference on **Recent Trends in Chemistry** at G.I Bagewadi Arts, Science & Commerce College, Nipani, Karnataka on 03 Feb 2018.
- The research paper entitled "Synthesis of Pyranopyrazoles by using Chitosan Hydrogel as a green and recyclable catalyst" submitted to **Asian Journal of Research in Chemistry, Manuscript ID:** 18113165958645125, 13 January 2018.**(Accepted for Publication)**

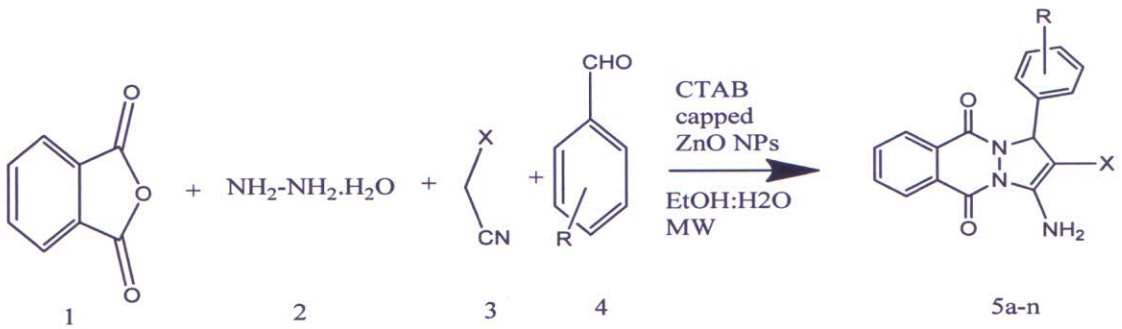
14. SUMMARY OF THE FINDINGS

1) Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. After World War II, there was an enormous explosion research in the field of heterocycles. About one half of over six million compounds recorded in Chemical Abstracts are heterocyclic. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.

2) Extensive literature survey were done on the synthesis of functionalized 1H-pyrazolo [1,2-b] phthalazine-5,10- dione derivative, bowl shaped molecular architecture, synthesis of nanoparticles and microwave irradiation techniques. To carry out experimental work, purchased chemicals, glass wares and equipments.

3) In this study multicomponent reactions (MCR) gained more importance for the rapid and highly efficient synthesis of diverse and complex heterocyclic molecules. Multi-component reactions constitute a very powerful tool to synthesize more classical drug-like, heterocyclic core structures. Microwave provides a powerful way to do synthetic chemistry in green approach.

4) In the research work of multicomponent reactions , herein described the preparation of functionalized 1H-pyrazolo[1,2-b]phthalazine-5,10- dione derivatives from four-component condensation reaction of hydrazine monohydrate, phthalic anhydride, malononitrile or ethyl cyanoacetate, and aromatic aldehydes in the presence of CTAB capped ZnO nanoparticles as catalyst and which were irradiated by microwaves.



X= -CN,-COOEt

Scheme 1. Synthesis of 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives

General procedure for the preparation of 1H-pyrazolo [1,2-b] phthalazine-5,10-dione Derivatives:

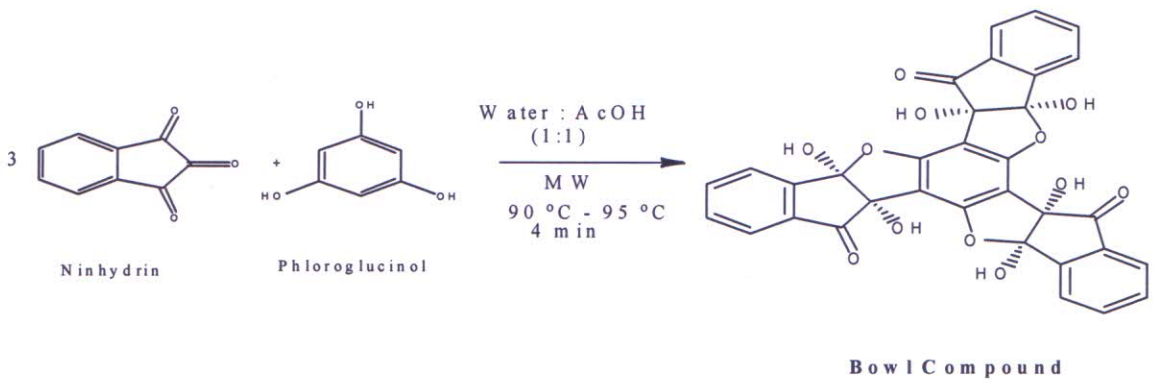
a) Thermal Method: Hydrazine monohydrate (1 mmol), phthalic anhydride (1 mmol) and CTAB capped ZnO nanoparticles (0.03g) as catalyst was mixed at 70°C (15 min). Then, aromatic aldehydes (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and ethyl alcohol: water (1:1), was added and stirred at 70°C for 50 min. After completion of the reaction, the reaction mixture was recrystallized from MeOH to afford the pure product.

b) Microwave Irradiation Method: Hydrazine monohydrate (1 mmol), phthalic anhydride (1 mmol) and CTAB capped ZnO nanoparticles (0.03g) as catalyst was mixed and irradiated in microwave synthesizer system(CATA R) for 60 sec (560W) at 65°C . Then, aromatic aldehydes (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and ethyl alcohol: water (1:1), was added and irradiated at 65°C for 60 sec (560W). After completion of the reaction, the reaction mixture was recrystallized from MeOH to afford the pure product.

5) Carried out this scheme by using CTAB capped ZnO nanoparticles as catalyst. ZnO

nanoparticles capped with surfactant like cetyltrimethylammonium bromide (CTAB). CTAB capped zinc oxide has smallest particle size, due to this fine particle size which provides large surface area and reaction proceeds faster and gives excellent yield in shorter time.

6) In another study, microwave assisted one pot reaction has been established for the synthesis of bowl shaped molecular architecture from phloroglucinol and ninhydrin. The reaction promoted by acetic acid as catalyst was carried out by using readily available and inexpensive materials in water under microwave irradiation.



Scheme 2 Synthesis of bowl compound

Synthesis of bowl compound

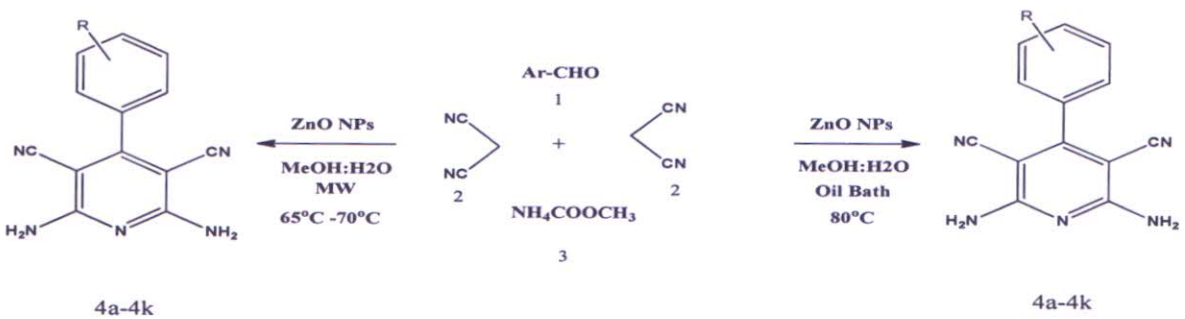
A mixture of Ninhydrin (3 mmol) and Phloroglucinol (1 mmol) in acetic acid: water (1:1) were irradiated in microwave synthesizer system at 560W (90°C-95°C) for 240 sec with 10 sec pulse rate interval. The reaction was monitored by TLC with MeOH: $CHCl_3$ (9:1) as solvent system. After completion of the reaction, the reaction mixture was recrystallized from EtOH to afford the pure product. (Scheme 2)

7) Prepared ZnO Nanoparticles were characterized by using SEM,TEM,XRD etc

8) Synthesized heterocyclic compounds were characterized by using IR, ^{1}H & ^{13}C NMR, Mass spectral techniques.

9) In another scheme, ZnO nanoparticles was used for a highly efficient one pot synthesis of highly substituted pyridines by the three component condensation reaction of aromatic aldehydes, malononitrile and ammonium acetate in the mixture of methanol and water as solvent under classical heating. Using microwave heating, reaction times were shortened from 3 hr to 3 min.

The advantage of this method includes the use of green catalyst, short reaction time, easy work-up and excellent yields.



4a-4k

4a-4k

Scheme 3 Synthesis of substituted pyridine derivatives

General Procedure -

c) Thermal Method for the preparation of Substituted Pyridine Derivatives:

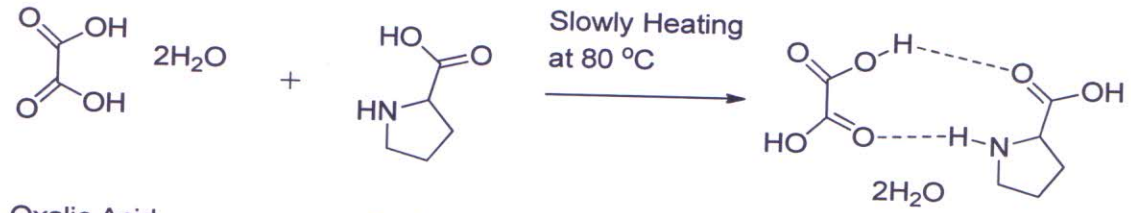
A mixture of aromatic aldehyde (1 mmol), malononitrile (2 mmol), ammonium acetate (1.5 mmol) and ZnO nanoparticles (0.4 mmol) as catalyst in methanol: water (6:1) were mixed and magnetically stirred at 80°C for 3 hr. After completion of the reaction, the reaction mixture was recrystallized from EtOH to afford the pure product.

d) Microwave Irradiation for the preparation of Substituted Pyridine Derivatives:

A mixture of aromatic aldehyde (1 mmol), malononitrile (2 mmol), ammonium acetate (1.5 mmol) and ZnO nanoparticles (0.4 mmol) as catalyst in methanol: water (6:1) were irradiated in microwave synthesizer system at 560W (65°C-70°C) for 180 sec. After completion of the reaction, the reaction mixture was recrystallized from EtOH to afford the pure product.

10) A rapid and highly efficient one-pot, three component synthesis of 3-methyl-4 (hetero) aryl methylene isoxazole-5(4*H*)-ones from aromatic aldehydes, ethyl acetoacetate and hydrazine hydrate using LTTM as green reaction medium. The advantages of this method includes, good to excellent yields, operational simplicity, short reaction time, easy work up procedures, easy of

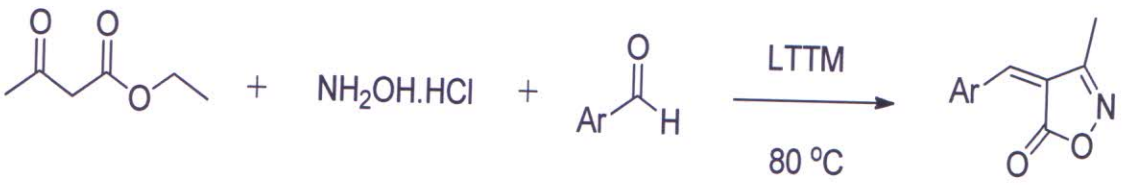
separation of pure products avoiding chromatographic purification. The method is operationally simple and ecofriendly.



Oxalic Acid Dihydrate

Proline

LTTM



Scheme 4 LTTM catalysed synthesis of 3-methyl-4 (hetero) aryl methylene isoxazole-5(4*H*)-ones

c) Preparation of LTTM

As per reported method in literature [21] the LTTM were synthesized. It is prepared by mixing of oxalic acid dihydrate (12.6 g, 100 mmol) and proline (11.5 g, 100 mmol) in the equimolar ratio of 1:1 and then heated slowly and maintained at 80 °C for 1 hr resulting in the formation of yellowish viscous liquid (LTTM) .

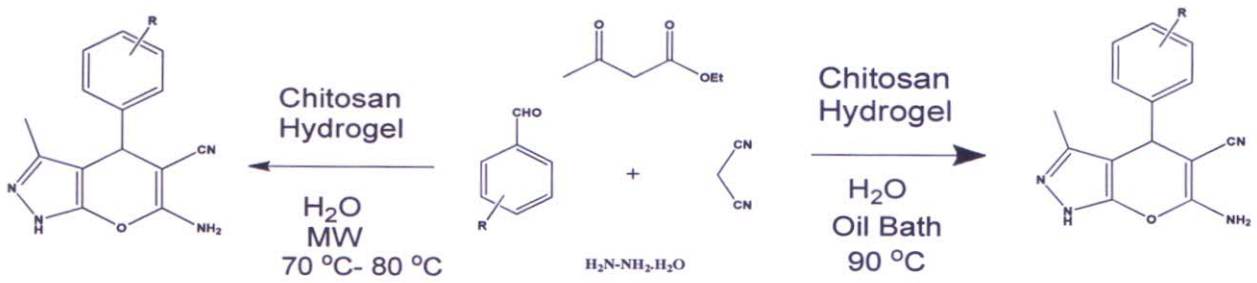
d) General procedure for the synthesis of 3-methyl-4-(hetero) arylmethylene isoxazole-5(4H)-ones.

A mixture of equimolar quantities of hydroxylamine hydrochloride (1 mmol) and ethyl acetoacetate (1 mmol were mixed in oxalic acid: proline (5ml) as solvent was stirred at 80 °C in an oil bath. Then, added aromatic/heterocyclic aldehyde (1 mmol) and the reaction mixture was stirred. The reaction was monitored by TLC. After completion of the reaction, the mixture. After the completion of the reaction indicated by TLC, 5 ml distilled water was added. The insoluble crude product was filtered, washed with distilled water and recrystallized from ethanol as shown in scheme 4.

11) A rapid, simple, efficient, and environmentally benign one-pot three-component protocol for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)- ones with good to excellent yields. Instead of toxic solvents the LTTM is simple, highly efficient and recyclable

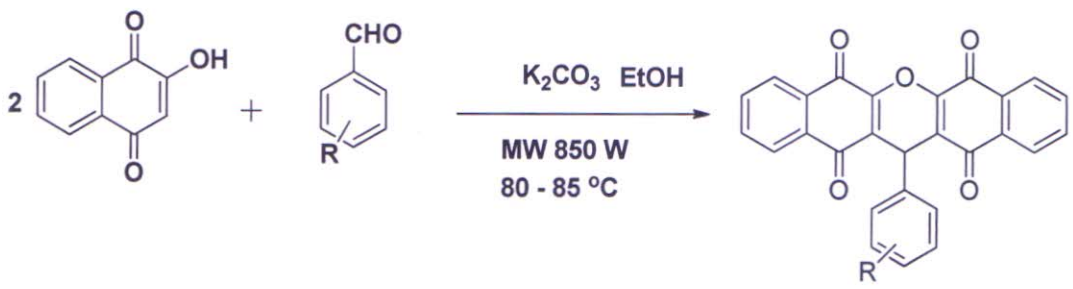
in this protocol. . Satisfactory yield of products and easy workup make this a useful protocol for green synthesis of this class of compounds.

12) In another scheme, Chitosan Hydrogel was used for a highly efficient one-pot, four component synthesis of 6-amino-3-methyl-5-cyano-4-aryl-1, 4-dihydropyrano [2, 3-c] pyrazoles from aromatic aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate in water as solvent under classical heating. Using microwave heating, reaction times were shortened from 1hr to 2 min. The advantages of this method includes the use of water as a green solvent ,use of recyclable chitosan hydrogel as a green catalyst, short reaction time, easy work up, and excellent yields.



Scheme 5 Synthesis of Pyranopyrazoles

13) In another scheme, a rapid and highly efficient one pot synthesis of 5H-dibenzo [b, i] xanthene-tetraones from aromatic aldehydes and 2-hydroxy 1, 4-naphthaquinone using K_2CO_3 as base catalyst. The advantages of this method includes, good to excellent yields, operational simplicity, short reaction time, easy work up procedures. The method is operationally simple and ecofriendly.



Scheme-6 : Synthesis of 13-aryl-5*H*-dibenzo [b,i] xanthene-5,7,12,14(13*H*)-tetraones

14) We have reported efficient one-pot protocol for the preparation of various 5H-dibenzo [b, i] xanthene-tetraones derivatives using basic K_2CO_3 as catalyst in a microwave irradiation as a green pathway. Clean reaction, low reaction times was the main advantages of this method. Satisfactory yield of products and easy workup make this a useful protocol for green synthesis of this class of compounds.

15. CONTRIBUTION TO THE SOCIETY

Two research papers published and one accepted. Four students from B.Sc. III (Chemistry) has done their project work in this field. One of them presented their research work in **Avishkar Research Competition 2017** on 26 Dec 2017 at Shivaji University, Kolhapur and got **third prize** for his work. The proposed work was utilized for training the B.Sc. students in handling the various chemicals at the milimole level and developing the skills of the students in monitoring the reactions at the various levels using the TLC techniques. The students were also trained in the isolation and purification techniques such as extraction, column chromatography and crystallization. This opportunity was also utilized in the developing the skills of the students in characterization technique by studying the IR & NMR spectra of the various compounds those synthesized.

16. WHETHER ANY PH. D. ENROLLED/ PRODUCED OUT OF THE PROJECT: **YES**

I have registered my Ph.D. degree in concern with the project that I have recently completed.

17. NO. OF PUBLICATIONS OUT OF THE PROJECT: **Two (Publications are attached)**

PRINCIPAL INVESTIGATOR

PRINCIPAL

Principal
Dr. Ghali College
Gadhinglaj, Dist. Kolhapur

(Seal)

DR. GHALI COLLEGE Estd. 1984 GADHINGLAJ