ANNEXURE - IX

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NEW DELHI – 110 002.

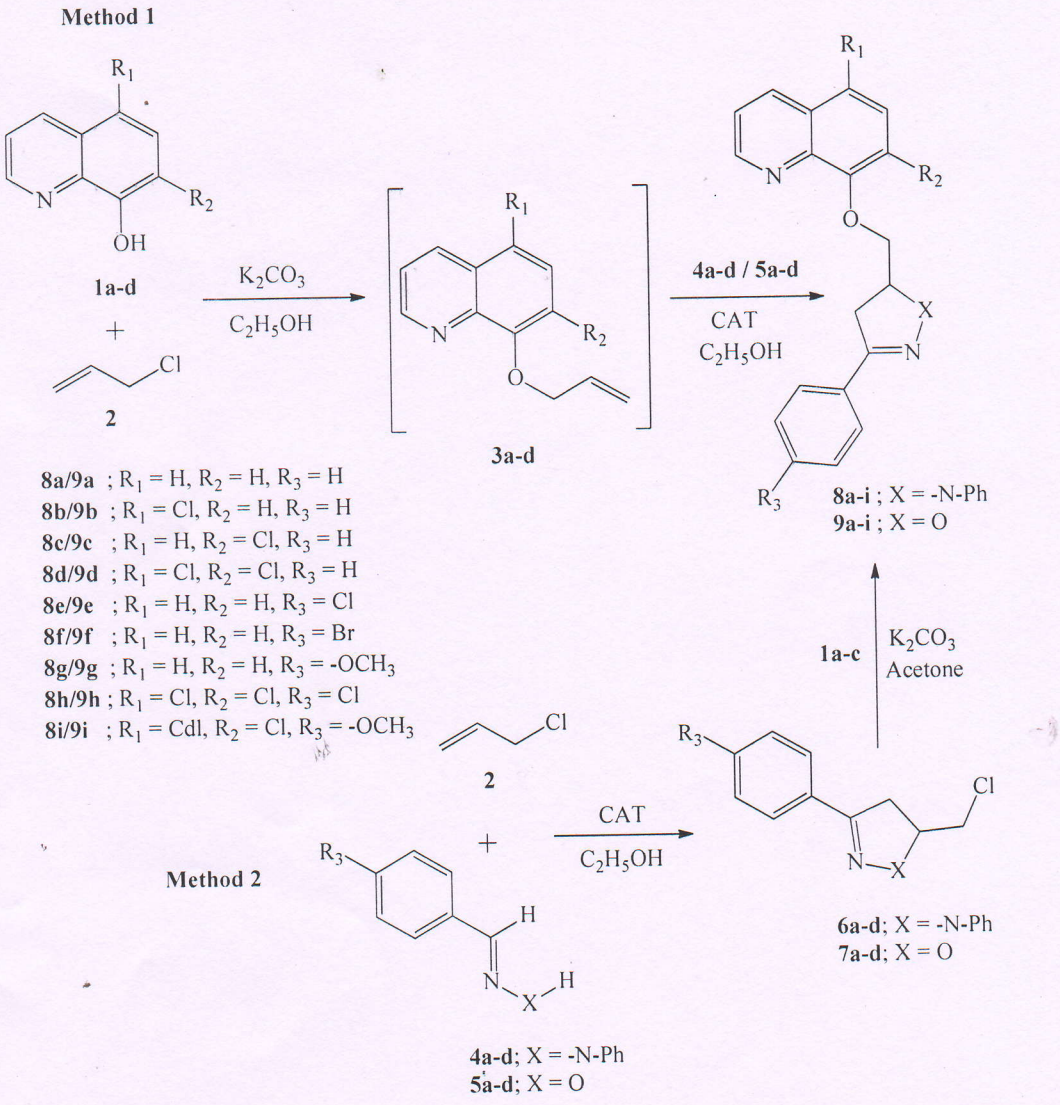
PROFORMA FOR SUBMISSOIN OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1	TIitle of the Project	**"Novel quinoline Allied Heterocycles: Synthesis And Structure Based Discovery of Lead for Breast Cancer Chemotherapy"**
2	NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR	**Dr. K. B. UMESHA** Department of Chemistry, Yuvaraja's College, Mysore.
3	NAME AND ADDRESS OF THE INSTITUTION	**YUVARAJA'S COLLEGE** UNIVERSITY OF MYSORE **MYSORE**–570 005
4	UGC APPROVAL LETTER NO. AND DATE	**No.F.2162-MRP/15-16/KAMY002/UGC-SWRO; Dated: 25 April 2016 and Dated: 11 Sep 2017**
5	DATEOF IMPLEMENTATION	**From 01–06–2016**
6	TENURE OF THE PROJECT	**TWO YEARS** **From 01–06–2016 to 30-09–2018**
7	TOTAL GRANT ALLOCATED	**Rs. 4,45,000/-** (Four lakh fifty five thousand)
8	TOTAL GRANT RECEIVED	**Rs. 4,23,275/-** (Four lakh twenty three thousand two hundred seventy five)
9	FINAL EXPENDITURE	**Rs. 4,31,116/-** (Four lakh thirty one thousand one hundred sixteen)
10	TITLE OF THE PROJECT	**"Novel quinoline Allied Heterocycles: Synthesis And Structure Based Discovery of Lead for Breast Cancer Chemotherapy"**

11. OBJECTIVES OF THE PROJECT:

A literature study reveals that quinoline moieties are the oldest compounds, which have been utilized for the treatment of a variety of diseases. Among quinoline analogs, 8-hydroxyquinoline (8HQ) is one of the most popular heterocyclic molecules with excellent pharmacological applications. Also nitrogen/oxygen containing five membered heterocyclic pyrazolines/isoxazolines has attracted attention of medicinal chemists and pharmacological activities because of their diversified biological applications in the area of pharmaceuticals and therapeutics. We focused on pyrazolines/isoxazolines and substituted pyrazolines/isoxazolines due to their interesting biological activities, we thought of synthesizing the 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)- methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole (**9a-i**) derivatives and screened for their breast cancer chemotherapeutic activity and also antimicrobial studies. We have

concentrated our efforts on enhancing the biological activities of quinoline bearing pyrazolines (**8a-i**)/isoxazolines (**9a-i**).



Scheme 1

12. WHETHER OBJECTIVES WERE ACHIEVED

-YES-

The investigator synthesized the samples 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)- methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole (**9a-i**) derivatives starting from one pot *O*-allylation of 8-hydroxyquinoline (**1a-d**) with allyl chloride (**2**) under mild basic medium using potassium carbonate in ethanol to gave 8-(allyloxy)quinoline (**3a-d**), then the reaction was continued by 1,3-dipolar cycloaddition reaction between previously generated dipolar species nitrile imines/nitrile oxides with carbon-carbon double bond in the compound 8-(allyloxy)quinoline (**3a-d**) to gave the target cycloadducts quinolinyl-4,5-dihdropyrazoles (**8a-i**)/quinolinyl-4,5-dihdroisoxazoles (**9a-i**).

13. ACHIEVEMENTS FROM THE PROJECT

The synthesized samples 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)- methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole (**9a-i**) derivatives. As per the present study quinoline bearing 4,5-dihydropyrazole (**8a-i**) and 4,5-dihydroisoxazole (**9a-i**) nucleus containing chlorine may intensifies the anti-breast cancer activity than the chlorine atoms on to quinoline moiety. All the compounds showed good antibacterial activity compared to standard chloramphinicol and also exhibit good antifungal activity using Fluconazole as a standard drug.

14. SUMMARY OF THE FINDINGS

The synthesized compounds 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole derivatives (**9a-i**) is a novel newer method by incorporating 4,5-dihydropyrazoles and 4,5-dihydroisoxazoles derivatives as the side chain in quinoline moiety. The molecules quinolinyl-4,5-dihydropyrazole (**8a-i**) and quinolinyl-4,5-dihydroisoxazole (**9a-i**) derivatives by two novel approached methods. When compare to second method, the first method was envisioned that the obtained yield was good (80-90%) than second method (40-50) due to the formation of undesired bicyclic adduct and other reasons. Therefore we, prompted us to follow method 1 to get target compounds target compounds 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole (**9a-i**) derivatives.

The synthesized compounds 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)-methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole derivatives (**9a-i**) were screened for their breast cancer chemotherapeutic activity against MCF7 cell line. As per the present study quinoline bearing 4,5-dihydropyrazole (**8a-i**) and 4,5-dihydroisoxazole (**9a-i**) nucleus containing chlorine are more potent compare to other moieties. So it was projected that, the integration of chlorine atom to intensifies the anti-breast cancer activity than the chlorine atoms on to quinoline moiety. The rate of cytotoxicity of compounds increases in the following order **8e>8h>8f>8d** of quinolinyl-4,5-dihydropyrazole with IC_{50} values 14, 18, 24, 30 µg/mL and **9e>9h>9f>9d** of quinolinyl-4,5-dihydroisoxazole with IC_{50} values 16, 20, 29, 32 µg/mL respectively. All other compounds showed low to moderate cytotoxicity. The IC_{50} for the standard drug *Doxorubicin (DOX)* was found to be 18µg/mL.

In addition, the synthesized compounds were also evaluated for antimicrobial activity by disc diffusion method and tested (dose of 100µg) for *in vitro* antibacterial activity against Gram-positive bacteria ***Bacillius cereus (B. cereus) and Staphylococcus aureus (S. aureus)***,

Gram-negative bacteria ***Escherichia coli (E. coli), Klebsiella pneumonia (K. pneumonia)*** and ***Shigella flexneri*** (***S. flexneri***) Chloramphenicol was used as a positive control standard drug. The *para* chloro and *para* methoxy substituent on benzene ring of five member heterocycle exhibited an excellent antibacterial activity compared to standard chloramphinicol drug. Also screened (dose of 100µg) for their antifungal activity against ***Aspergillus flavus (A. flavus)*** and ***Aspergillus niger (A. niger)*** using Fluconazole as a standard. All the compounds exhibit good antifungal activity against *A. Niger* and were weakly active against *A. flavus* compared to standard Fluconazole drug.

15. CONTRIBUTION TO THE SOCIETY

The synthesized compounds 8-[(1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)methoxy]-quinoline (**8a-i**) and 3-phenyl-5-(quinolin-8-yloxy)-4,5-dihydroisoxazole derivatives (**9a-i**) is a novel newer method by incorporating 4,5-dihydropyrazoles and 4,5-dihydroisoxazoles derivatives as the side chain in quinoline moiety. All the synthesized compounds were screened for their breast cancer chemotherapeutic activity against MCF7 cell line, the quinoline bearing 4,5-dihydropyrazole (**8a-i**)/4,5-dihydroisoxazole (**9a-i**) nucleus containing chlorine atom are more potent compare to other moieties. So it was projected that, the integration of chlorine atom in pyrazoline/isoxazoline ring to intensify the anti-breast cancer activity. All other compounds showed low to moderate anti-breast cancer activity using standard drug *Doxorubicin (DOX)*.

In addition, the synthesized compounds were also evaluated for antimicrobial activity; it shows an excellent antibacterial activity and antifungal activity compared to standard drug. On this basis the synthesized compounds shall be investigated towards clinical trial. After getting result from clinical trial evaluation it will be benefit for society towards anti-breast cancer, antibacterial and antifungal treatment.

16. WHETHER ANY Ph. D. ENROLLED/PRODUCED OUT OF THE PROJECT :-

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17. NO. OF PUBLICATIONS OUT OF THE PROJECT

Two research paper published and one more under progress.

1. A new approach for the synthesis of 8-((1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-5-yl)methoxy)quinoline: a novel lead for breast cancer chemotherapy., **K.B. Umesha**, N. Srikantamurthy, N.S. Lingegowda, B. Vrushabendra and D. Shridevi., *Biointerface Research in Applied Chemistry*, vol. 8, Issue 6, **2018**, 3744-50. [ISSN 2069-5837].
2. Noval Isoxazoline-1,2,4-oxadiazole: Synthesis, Characterization and Antimicrobial screening., **K.B. Umesha**, D. Shridevi and N. Srikantamurthy., *Journal of Chemical*

and Pharmaceutical Sciences, Issue 1, **2018**, 58-61. [ISSN (Print 0974-2115) (Online 2349-8552)].

3. Synthesis, Breast cancer chemotherapy and Antimicrobial screening of quinoline bearing isoxazoline derivatives via 1,3-dipolar cycloaddition reaction., **K.B. Umesha**, N. Srikantamurthy, B. Vrushabendra and D. Shridevi., Communicated to *Bulgarian Chemical Communications.*

15/2/19

SIGNATURE OF THE
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