# UGC

# SUMMARY SHEET FOR MAJOR RESEARCH PROJECT

# NO. 42-676/2013(SR), Dated 30 December 2013


**Submitted by**

**Dr. Raj Kumar**

**(Principal Investigator)**

**Prof. P. Ramarao**

**(Co-principal Investigator)**

**Annexure – IX**

## Executive Summary of the Final Report

*of a major research project supported by*

**University Grants Commission**

**New Delhi – 110 002**

1. TITLE OF THE PROJECT:

**Design, Synthesis and Biological Screening of Novel Heterocycles as Inhibitors of Dual Tyrosine Kinase(s) and Histone Deacetylase as Potential Anticancer Agents**

2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR:

**Dr. Raj Kumar; Associate Professor and Head; Department of Pharmaceutical Sciences and Natural Products; Central University of Punjab. Bathinda; pin: 151001**

3. NAME AND ADDRESS OF THE INSTITUTION:

**Central University of Punjab**

**Mansa Road, Near Delhi Railway Crossing, Bathinda Punjab. Pin:151001**

4. UGC APPROVAL LETTER NO. AND DATE:

**F.No. 42-676/2013 (SR), Dated: 30 December 2013**

5. DATE OF IMPLEMENTATION: **28-2-2014**

6. TENURE OF THE PROJECT: **Three years (One year extended)**

7. TOTAL GRANT ALLOCATED **Rs. 1259800**

8. TOTAL GRANT RECEIVED: **Rs.700800**

9. FINAL EXPENDITURE: **Rs. 868421**

(An amount of **Rs. 136556** may be released in respect to salary for project fellow by University Grant Commission to settle the account)

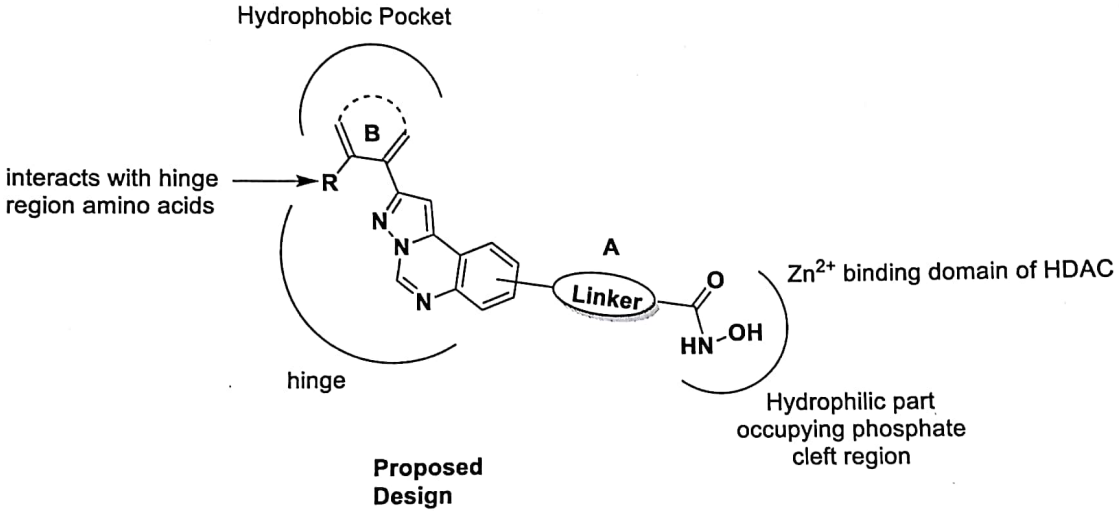
10. TITLE OF THE PROJECT:

**Design, Synthesis and Biological Screening of Novel Heterocycles as Inhibitors of Dual Tyrosine Kinase(s) and Histone Deacetylase as Potential Anticancer Agents**

11. **OBJECTIVES OF THE PROJECT**

The brief objectives of project are as follows

**Part 1.** To, design and synthesis of novel heterocycles derived from **pyrazolo [1,5-*c*]quinazoline** *via* rationally considering the common pharmacophoric features of EGFR, Her2 and HDAC inhibitors **(Figure 1)**




| Series | Linker A |
|---|---|
| 1 | —O—$(CH_2)n$— |
| 2 | —N(H)—$(CH_2)n$— |
| 3 | —NH—C(=O)—$(CH_2)n$— |

Where n can vary from one to six

Ring B: any aromatic, heteroaromatic with or without substitution

R= any alkyl, halogen or amino gp

**Figure 1.** Proposed Design for the target compounds

**Part 2.** *In vitro* biological screening of the synthetics against EGFR, and HDAC enzymes and against cancer cell lines.

## 12. WHETHER OBJECTIVES WERE ACHIEVED

**Yes.** The objectives have been fully realized as may be seen from the Summary, below, and detailed report which follows. The work has led to 10 papers in standard international journal of repute.

## 13. ACHIEVEMENTS FROM THE PROJECT

1. 10 papers in journals indexed on Thomson Reuter's Web of Science.

2. We have proposed newer, easy synthetic approach to synthesize the proposed molecules.

3. A trained professional in the field of medicinal chemistry to the society.

4. Provide the scope of development of drug regimen in one of the deadliest disease cancer.

5. Will contribute and enhance the scientific literature.

## 14. SUMMARY OF THE FINDINGS

Cancer is the second leading cause of death in India. Majority of the anticancer agents suffer from resistance to chemotherapy and have toxic nature. To overcome the resistance the possible solution is use of combined strategies and discovery of novel molecules having better efficacy, safety and potency. Heterocyclics have been known from the decades as medicinal compounds. Further pyrazoloquinazoline scaffold has already shown its potential as anticancer agent e.g. CUDC-101. We rationally synthesized compounds which are designed via merging pharmacophores from both EGFR inhibitors and HDAC inhibitors and based on the pyrazoloquinazoline scaffold as putative antiproliferative agents. The biological evaluation was performed on various cancer cell lines along with EGFR and HDAC enzymes. The compounds also portrayed their selectivity behavior towards cancer cell and also exhibited alteration in mitochondrial potential and significant increase in ROS levels inside the cancer cell. All the synthesized compounds exhibited good antiproliferative and enzymatic activity. Further the biological investigations were supported by *in-silico* studies.

The compounds further open the possibility of generation of the library of compounds and their evaluation against various cancer cell lines.

## 15. CONTRIBUTION TO THE SOCIETY

The present work is the actual bridge between the two *basic sciences* viz., chemical and biological sciences involving the exchange and thus imparting the knowledge to *applied* medical sciences for the treatment of cancer which requires *translational research* that focuses on multidisciplinary research skills needed to carry out bench to bedside research. The present work will stimulate cancer biologists to ponder on mechanistic interventions on unreported cross-talk(s) of epigenetics enzymes with other enzymes/proteins and their role in cancer development. The work will provide scope and opportunities to the medicinal chemists to discover and design novel and effective therapeutic strategies *via* dual or multiple inhibition of the targets.

Other significant contribution includes:

A. A trained professional in the field of medicinal chemistry to the society.
B. Provide the scope of development of drug regimen in one of the deadliest disease cancer.
C. Will contribute and enhance the scientific literature.

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

***Name:*** *Mr. Gaurav Joshi*
***Reg No.*** *15phdphm01*
*Department of Pharmaceutical Sciences and Natural Products*
*Central University of Punjab*

## 17. NO. OF PUBLICATIONS OUT OF THE PROJECT: 10


1. Microwave-assisted synthesis of pyrazolo [1,5-c] quinazolines and their derivatives. D. Kumar, R Kumar*. Tetrahedron Letters, 2014, 55, 2679-2683.
2. DNA Repair and Redox Activities and Inhibitors of APE1/Ref-1: A Comparative Analysis and their Scope and Limitations toward Anticancer Drug Development. G Kaur, R Cholia, AK Mantha, R Kumar*. Journal of Medicinal Chemistry, 2014. DOI:10.1021/jm500865u;
3. Chauhan, M., Joshi, G., Kler, H., Kashyap, A., Amrutkar, S. M., Sharma, P., ... & Kumar, R. (2016). Dual inhibitors of epidermal growth factor receptor and topoisomerase IIα derived from a quinoline scaffold. *RSC Advances*, *6*(81), 77717-77734.

4. Chauhan M, Sharma G, Joshi G, Kumar R. Epidermal Growth Factor Receptor (EGFR) and its Cross-Talks with Topoisomerases: Challenges and Opportunities for Multi-Target Anticancer Drugs. Current pharmaceutical design. 2016;22(21):3226-36.
5. Darpan, Joshi G, Amrutkar SM, Baviskar AT, Kler H, Singh S, Banerjee UC, et al. Synthesis and biological evaluation of new 2, 5-dimethylthiophene/furan based N-acetyl pyrazolines as selective topoisomerase II inhibitors. RSC Advances. 2016;6(18):14880-92.
6. Joshi G, Nayyar H, Alex J, Vishwakarma G, Mittal S, Kumar R. Pyrimidine-fused Derivatives: Synthetic Strategies and Medicinal Attributes. Current topics in medicinal chemistry. 2016. Current topics in medicinal chemistry, 16(28), 3175-3210.
7. Joshi G, Singh PK, Negi A, Rana A, Singh S, Kumar R. Growth factors mediated cell signalling in prostate cancer progression: implications in discovery of anti-prostate cancer agents. Chemico-biological interactions. 2015;240:120-33.
8. Negi A, Alex JM, Amrutkar SM, Baviskar AT, Joshi G, Singh S, et al. Imine/amide–imidazole conjugates derived from 5-amino-4-cyano-N1-substituted benzyl imidazole: Microwave-assisted synthesis and anticancer activity via selective topoisomerase-II-α inhibition. Bioorganic & medicinal chemistry. 2015;23(17):5654-61.
9. Muraleedharan, A, Joshi, G.,Kumar, R. (2016). Natural Products Based Ayurvedic Formulations: Chemical Constituents and Treatment in Neurodegenerative Disorders. Mini-Reviews in Organic Chemistry. Mini-Reviews in Organic Chemistry, 14(4), 280-287.
10. Joshi, G., Nayyar, H., Kalra, S., Sharma, P, Munshi, M., Singh S, Kumar R. Pyrimidine Containing Epidermal Growth Factor Receptor Kinase inhibitors: Synthesis and Biological Evaluation. Chemical Biology and Drug Design. 2017, 90(5);Pages 995-1006.

15/5/18.

(PRINCIPAL INVESTIGATOR)

for 06/6/18

(REGISTRAR/PRINCIPAL)

(Seal)

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15/5/18

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