

**DESIGN, SYNTHESIS AND EVALUATION OF COUMARIN  
FUSED/TETHERED NITROGEN CONTAINING HETEROCYCLES AS  
ANTICANCER AGENTS**

A  
THESIS  
SUBMITTED TO  
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IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY  
IN  
PHARMACEUTICAL SCIENCES**

By

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## CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis, entitled **“Design, Synthesis and Evaluation of Coumarin Fused/Tethered Nitrogen Containing Heterocycles as Anticancer Agents”** in fulfillment of the requirements of the award of the degree of Doctor of Philosophy in Faculty of Pharmaceutical Sciences and submitted in Maharaja Ranjit Singh Punjab Technical University, Bathinda is an authentic record of my own work carried out during a period from 2016 to 2021 under the supervision of **Dr. Raj Kumar Narang** and **Dr. Ravindra Kumar Rawal**.

The matter embodied in this thesis has not been submitted by me for the award of any other degree of this or any other University/Institute.

(ROHIT BHATIA)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.



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## LIST OF PUBLICATIONS

The designed 3 series of coumarin hybrid molecules has screened out compounds with significant anticancer potentials. So the strategy based on virtual screening of potent compounds utilizing molecular docking tools has been proven to be successful with good outcomes. This work will be helpful to the researchers for further exploration of these hybrids by making further modifications to their structure. Also adaptation of virtual screening approach will be helpful for the researchers to get more therapeutic benefits in less time and economic way. A few publications which have been contributed through this work are as follows:

### Research Articles

- **Rohit Bhatia**, Raj Kumar Narang, Ravindra Kumar Rawal. *In silico* investigation of therapeutic potentials of coumarin-quinoxaline hybrids against breast cancer, synthesis and *in vitro* activity. *Indian Journal of Heterocyclic Chemistry*, 2020, 30(4), 489.

**Impact Factor:** 0.339      **Indexing:** SCIE, SCOPUS.

- **Rohit Bhatia**, Raj Kumar Narang, Ravindra Kumar Rawal. Coumarin-dihydropyrimidinone hybrids: design, virtual screening, synthesis and cytotoxic activity against breast cancer. *Journal of Advanced Scientific Research*, 2020, 11(3), 220-233.

**Indexing:** UGC Care List.

### Review Articles

- **Rohit Bhatia**, Shelly Pathania, Virender Singh, R.K. Rawal. Metal catalyzed synthetic strategies toward coumarin derivatives. *Chemistry of Heterocyclic compounds*, 2018, 54 (3), 280-291.

**Indexing:** SCIE, SCOPUS      **Impact Factor:** 1.27

- **Rohit Bhatia**, R. K. Rawal. Coumarin Hybrids: Promising Scaffolds in the Treatment of Breast Cancer. *Mini Reviews in Medicinal Chemistry*, 2019, 19(17), 1443-1458.

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## LIST OF ABBREVIATIONS

%	Percentage
$\mu\text{M}$	Micro molar
$^{13}\text{CNMR}$	Carbon nuclear magnetic resonance
$^1\text{HNMR}$	Proton nuclear magnetic resonance
2D	Two dimensional
3D	Three diamensional
$\text{\AA}$	Angstrom
abs	Absorbance
ADME	Absorption, distribution, metabolism and excretion
ANOVA	Analysis of variance
BBB	Blood brain barrier
$\text{CDCl}_3$	Deuterated chloroform
$\text{CHCl}_3$	Chloroform
$\text{Cm}^{-1}$	Centimeter inverse
d	Doublet
dd	Doublet of doublet
DMSO	Dimethyl sulphoxide
EGFR	Epidermal growth factor receptor
FTIR	Fourier transform infra red
g	Gram
h	Hour
HER2	Human epidermal growth factor-2
HRMS	High resolution mass spectrometry
HSP90	Heat shock protein
Hz	Hertz
$\text{IC}_{50}$	Half maximal inhibitory concentration
IGF-1	Insulin like growth factor
IR	Infra red
m	Multiplet
M.P.	Melting point



m/z	Mass/charge
MeOH	Methanol
mg	Milligram
mL	Millilitre
MOE	Molecular operating environment
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NT	Not tested
°C	Degree Celsius
PDB	Protein data bank
ppm	Parts per million
RCSB	Research Collaboratory for Structural Bioinformatics
R <sub>f</sub>	Retardation Factor
RMSD	Root mean square deviation
s	Singlet
SAR	Structural activity relationship
t	Triplet
TLC	Thin layer chromatography
TNF- $\alpha$	Tissue necrosis factor- $\alpha$
WHO	World Health Organization
$\delta$	Chemical shift value