

**DESIGN AND SYNTHESIS OF DIVERSITY-ORIENTED
PYRIMIDINE HETEROCYCLES AS ANTICANCER AGENTS**

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THESIS
SUBMITTED TO**



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**IN FULFILLMENT OF THE REQUIREMENTS
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**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 and Synthesis of Diversity-Oriented Pyrimidine Heterocycles As Anticancer Agents**” in fulfilment of the requirements of the award of the degree of Doctor of Philosophy in Faculty of **Pharmacy** and submitted in Maharaja Ranjit Singh Punjab Technical University, Bathinda is an authentic record of my own work carried out during a period from **August 2017** to **March 2022** under the supervision of **Dr. Raj Kumar Narang** and **Dr. Ravindra K. 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.

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LIST OF ABBREVIATIONS

$^{13}\text{CNMR}$	Carbon Nuclear Magnetic Resonance
$^1\text{HNMR}$	Proton Nuclear Magnetic Resonance
3D	Three Dimensional
ADMET	Absorption Distribution Metabolism Excretion and Toxicity
ALK	Anaplastic Lymphoma Kinase
ATP	Adenosine Triphosphate
BLBC	Basal-Like Breast Cancer
CADD	Computer-Aided Drug Design
CDCl_3	Deuterated Chloroform
CDKs	Cyclin Dependent Kinases
CH_3COOH	Acetic Acid
d	Doublet
dd	Doublet of Doublet
DFT	Density Functional Theory
DMSO	Dimethyl Sulphoxide
DNA	Deoxyribonucleic Acid
EDG	Electron-Donating Group
EGFR	Epidermal Growth Factor Receptor
eq.	Equivalent
ER	Estrogen Receptor
ERK	Extracellular Signal Regulated Kinase
ESI	Electrospray Ionization
EWG	Electron-Withdrawing Group
FBDD	Fragment Based Drug Discovery
FDA	Food and Drug Administration
FGFR-1	Fibroblast Growth Factor Receptor 1
FT-IR	Fourier Transform Infrared Spectrometer
GDP	Guanosine Diphosphate
GTP	Guanosine Triphosphate
H_2SO_4	Sulphuric Acid
HCl	Hydrochloric Acid

HER2	Human Epidermal Growth Factor Receptor
HOMO	Highest Occupied Molecular Orbital
HTS	High-Throughput Screening
Hz	Hertz
IC ₅₀	Half Maximal Inhibitory Concentration
IR	Infra-Red
JNKs	c-Jun N-Terminal Kinases
KBr	Potassium Bromide
KRAS	Kirsten Ras Oncogene
LBDD	Ligand Based Drug Design
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
m/z	Mass/Charge
MAPK	Mitogen-Activated Protein Kinase
MCF-7	Michigan Cancer Foundation-7
MD	Molecular Dynamics
MEK	Mitogen-Activated Protein Kinase Kinase
MeOH	Methanol
mg	Milligram
MHz	Megahertz
MM-GBSA	Molecular Mechanics Generalized Born Surface Area
MM-PBSA	Mechanics-Poisson Boltzman Surface Area
MS	Mass Spectroscopy
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
MW	Molecular Weight
NaOH	Sodium Hydroxide
nM	Nanomolar
OD	Optical Density
PDB	Protein Data Bank
PDGFR	Platelet-Derived Growth Factor Receptor
PI3K	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
ppm	Parts Per Million

PR	Progesterone Receptor
PTC	Papillary Thyroid Cancer
Q-TOF	Quad-Time of Flight
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat Sarcoma Virus
R _f	Retardation Factor
RMSD	Root-Mean-Square Deviation
RTKs	Receptor Tyrosine Kinases
s	Singlet
SAR	Structure-Activity Relationship
SBDD	Structure Based Drug Design
TLC	Thin Layer Chromatography
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TNBC	Triple-Negative Breast Cancer
TZD	Thiazolidinone
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization
δ	Chemical Shift Value
μM	Micromolar

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