**Faculty of Pharmacy**

# Molecular Design and Synthesis of Certain Heterocycles as Targeted Anticancer Agents

Thesis
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اهدي ثمرة جهدي هذا الي اعز واغلي انسان في حياتي ، الذي انار دربي بنصائحه

والذي منحني القوة والعزيمة لمواصلة الدرب وكان سببا في مواصلة دراستي

الي من علمني الصبر والاجتهاد، الي الغالي علي قلبي

**اهداء الي روح استاذي الطاهرة رحمه الله عليه**

الي من علمني حرفا  سيبقي علمك

الذي استقيته منك شمعه

تضيء حياتي يا استاذي الغالي

ا.د.محمود علي حسن

## Pre-requisite Predoctoral Exams

The candidate has passed a comprehensive exam in organic and pharmaceutical chemistry and presented a research proposal with the title of “Design, Synthesis and Evaluation of Novel Hedgehog Pathway Inhibitors” and received grade: Excellent.

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# List of Abbreviation:

**ABL TK**: Abelson Tyrosine Kinase

**ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity study

**ALogP**: Atomic logP (the logarithm of 1-octanol/water partition coefficient)

**AMBER**: Assisted Model Building with Energy Refinement (force field)

**AQ Sol**: Aqueous Solubility

**ATP**: Adenine-5'-Triphosphate

**BBB LEV**: Blood–Brain Barrier Level

**BCR**: Breakpoint Cluster Region protein

**BRMs**: Biological Response Modifiers

**CAK: CDK** (Cyclin-Dependent Kinase)-Activating Kinase

**CDK:** Cyclin Dependent Kinase

**Cdc:** Cdc25 Phosphatases

**Cdk1**: Cyclin-Dependent Kinase 1

**CDOCKER**: CHARMm-based Docker

**C-Fms:** Colony-stimulating Factor-1 Receptor

**CHARMm**: Chemistry at HARvard Macromolecular Mechanics

**CHK1**: Checkpoint kinase 1

**CycB**: Cycline B

**CHK1**: Checkpoint kinase 1

**C-Kit:** Tyrosine-protein kinase KIT, CD117 (cluster of differentiation 117)

**C-Met:** Tyrosine-protein kinase Met or hepatocyte growth factor receptor

**DCC**: Dicyclohexylcarbodiimide

**DFG**: Aspartate- Phenylalanine- Glycine

**DIPEA**: Diisopropyl Ethyl Amine

**DMAC**: Dimethyl Acetamide

**DTP**: Developmental Therapeutics Program

**EGFR**: Endothelial Growth Factor Receptor

**EI-MS**: Electron Ionization Mass Spectrometry

**FGFR**: Fibroblast Growth Factor Receptor

**Flk-1**: Fetal liver kinase-1

**FLT-3**: Fetal liver Tyrosine kinase-3

**FP**: Fluorescence Polarization

**FPP**: Field Point Pattern

**FRET**: Fluorescence Resonance Energy Transfer

**G1**: GAP 1

**G2**: GAP 2

**GSK**: Glaxo Smith Kline

**HATU**: Hexafluorophosphate Azabenzotriazole Tetramethyl uronium

**HER-2**: The human Epidermal growth factor receptor 2

**HGF**: Hepatocyte Growth Factor

**HIA**: Human Intestinal Absorption

**HRD**: His- Arg- Asp

**HTS**: High Throughput Screening

**HUVEC**: Human Umbilical Vein Endothelial Cells

**$IC_{50}$**: Half-maximal inhibitory concentration

**Ig**: Immunoglobulin

**IGFR**: Insulin-like Growth Factor Receptors

**KDR**: Kinase Insert Domain Receptor

**Ki**: the inhibitor constant

**LC/MS**: Liquid Chromatography–Mass Spectrometry

**M/Z**: Mass-to-Charge ratio

**M**: Mitotic phase

**$M^+$:** Molecular ion

**MD**: Molecular Dynamics

**mTOR:** mammalian target of rapamycin

**MYT1**: **M**embrane-associated t**y**rosine- and **t**hreonine-specific cdc2-inhibitory kinase

**NIH**: National Institutes of Health

**NRTK**: Non-Receptor Tyrosine Kinase

**NSCLC**: Non-Small Cell Lung Cancer

**p53**: Tumor protein p53

**PDB**: Protein Data Bank

**Pd-C**: Palladium on Carbon

**PDGFR b**: Beta-type Platelet-Derived Growth Factor Receptor

**PDGFR**: Platelets Derived Growth Factor Receptor

**PDT**: Photodynamic Therapy

**PI3K:** phosphoinositide 3-kinase

**PLGF**: Platelet Growth Factor

**PPB LOG**: Logarithmic value of Plasma Protein Binding

**RCC**: Renal Cell Carcinoma

**RMSD**: Root Mean Square Deviation

**RTK**: Receptor Tyrosine kinase

**S**: Synthesis phase

**SRC**: Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene

**TKI**: Tyrosine Kinase Inhibitors

**TMS**: Tetramethyl silane

**TP53**: Tumor Suppression Genes

**VEGFR-2**: Vascular Endothelial Growth Factor Receptor-2

**WEE1**: Mitosis inhibitor protein kinase

# Abstract:

## *Title of thesis:*

## Molecular Design and Synthesis of Certain Heterocycles as Targeted Anticancer Agents

**Name of candidate:**

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According to American Cancer Society (ACS) statistics, cancer is the third most lethal disease following cardiovascular diseases, infectious diseases, and parasites. Cancer treatment tend to be one of the most important fields of scientific research.

Targeted therapy is a cancer treatment that uses drugs to target specific genes and proteins that are involved in the growth and survival of cancer cells; tyrosine kinase inhibitors (TKIs) are a type of targeted therapy. The formation of new blood vessels (angiogenesis) is one of the hallmarks well known in the carcinogenesis cycle. Vascular endothelial receptor-2 growth factor (VEGFR-2) plays a significant role in angiogenesis of cancer. Angiogenesis is greatly inhibited by targeting VEGFR which leads to tumor cell death. MYT1 (Membrane-associated tyrosine and threonine-specific cdc2-inhibitory kinase) is one of WEE kinase family that regulate and control cell cycle through phosphorylation of Cdk1/Cyclin B complex at G2/M transition which essential to entry into mitotic phase. Consequently, inhibition of MYT1 is promising target for synergistic action with convential cancer therapy to target cancer cell over non-cancerous cells.

In this study, quinazoline and quinoline derivatives were developed and synthesized as targeted inhibitors of VEGFR-2 and MYT1 kinases. The design centered on the scaffold hopping, redesign approach and analysis of previous SAR studies to approved lead compounds and in clinical studies ones;

Synthesis of the designed compounds was then achieved, and various spectral and microanalytical data validated their structures.

This study involved the synthesis of the following unavailable reported intermediates:

1) *1-(4-Nitrophenyl)-3-phenylurea* ***(Ia)***
2) *1-(3-Fluorophenyl)-3-(4-nitrophenyl)urea* ***(Ib)***
3) *1-(4-Fluorophenyl)-3-(4-nitrophenyl)urea* ***(Ic)***
4) *1-(3-Methoxyphenyl)-3-(4-nitrophenyl)urea* ***(Id)***
5) *1-(4-Methoxyphenyl)-3-(4-nitrophenyl)urea* ***(Ie)***
6) *1-(4-Chlorophenyl)-3-(4-nitrophenyl)urea* ***(If)***
7) *1-(4-Nitrophenyl)-3-(3-(trifluoromethyl)phenyl)urea* ***(Ig)***
8) *1-(3,4-Dichlorophenyl)-3-(4-nitrophenyl)urea* ***(Ih)***
9) *1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-nitrophenyl)urea* ***(Ii)***
10) *1-(4-Aminophenyl)-3-phenylurea* ***(IIa)***
11) *1-(4-Aminophenyl)-3-(4-fluorophenyl)urea* ***(IIb)***
12) *1-(4-Aminophenyl)-3-(4-fluorophenyl)urea* ***(IIc)***
13) *1-(4-Aminophenyl)-3-(3-methoxyphenyl)urea* ***(IId)***