

# **"Computer-aided design and synthesis of new 4,6-disubstituted quinazoline derivatives having potential anticancer activity"**

Thesis

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## ***DEDICATION***

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## **List of Abbreviations**

<b>3D structures</b>	: Three dimensional structures
<b>3-FPM</b>	: 3-Fluorophenylmethoxy.
<b>5-FU</b>	: 5-Fluorouracil .
<b>ABL</b>	: Abelson Murine Leukemia Viral Oncogene.
<b>ADEPT</b>	: Antibody-directed enzyme prodrug therapy.
<b>ALK</b>	: Anaplastic lymphoma kinase
<b>aPKs</b>	: Atypical protein kinases
<b>ATP</b>	: Adenosine triphosphate
<b>BCC</b>	: Basal cell carcinoma
<b>BMI</b>	: Body mass index.
<b>BSA</b>	: Bovine Serum Albumin
<b>CADD</b>	: Computer aided drug design
<b>CAMK</b>	: Calcium/calmodulin-dependent-like kinase
<b>CDK</b>	: Cyclin-dependent kinase
<b>CLK</b>	: CDC2-like kinase
<b>CK1</b>	: Casein kinase-1
<b>Cox-2</b>	: Cyclooxygenase-2
<b>c-SRC</b>	: C-terminal Src kinase
<b>DDT</b>	: Dichlorodiphenyltrichloroethane
<b>DFG</b>	: Aspartate- Phenylalanine- Glycine
<b>DFS</b>	: Disease free survival
<b>DMF-DMA</b>	: Dimethyl formamide dimethylacetal
<b>DNA</b>	: Deoxyribo Nucleic Acid
<b>DSKs</b>	: Dual-specificity kinases
<b>EGFR</b>	: Epidermal Growth Factor Receptor
<b>EGF</b>	: Epidermal Growth Factor
<b>ELISA</b>	: enzyme-linked immunosorbent assay
<b>ePKs</b>	: Eukaryotic protein kinases
<b>FAK</b>	: Focal adhesion kinase
<b>FDA</b>	: Food and Drug Administration
<b>FGFR</b>	: Fibroblast growth factor receptor

## *List of Abbreviations*

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<b>FLt-3</b>	: Fms-like tyrosine kinase 3
<b>FT-IR</b>	: Fourier transform-Infrared
<b>GSK-3</b>	: Glycogen synthase kinase 3
<b>H-Bond</b>	: Hydrogen Bond
<b>HER-2</b>	: Human epidermal growth factor receptor-2
<b>HIV</b>	: Humanimmunodeficiency virus
<b>Hks</b>	: Histidine kinases
<b>HBD</b>	: Hydrogen bond donor
<b>HYD</b>	: Hydrophobic
<b>IC<sub>50</sub></b>	: 50% Inhibitory concentration
<b>IL-2</b>	: Interleukin-2
<b>JAK</b>	: Janus kinase
<b>JNK</b>	: Jun nuclear kinase
<b>KDR</b>	: Kinase insert domain containing receptor
<b>KIT</b>	: Tyrosine-protein kinase Kit
<b>Lu</b>	: Luminescence
<b>MAPK</b>	: Mitogen activated protein kinase
<b>MET</b>	: Methionine
<b>mAB</b>	: monoclonal Antibodies
<b>MS</b>	: Mass spectroscopy
<b>mTOR</b>	: Mammalian target of rapamycin
<b>NDPK-B</b>	: Nucleoside diphosphate kinase B
<b>NRTK</b>	: Non- receptor tyrosine kinase
<b>Nrg B1</b>	: Neuregulin
<b>NSCLC</b>	: Non-small cell lung cancer
<b>OD</b>	: Optical Density
<b>PDB</b>	: Protein Data Bank
<b>PKA</b>	: Protein kinase A
<b>PKG</b>	: Protein kinase G
<b>PKC</b>	: Protein kinase C
<b>PLC<math>\gamma</math></b>	: Phosphoinositide phospholipase C
<b>PDGFR</b>	: Platelet-derived growth factor receptor
<b>PDT</b>	: Photodynamic therapy
<b>PI3K</b>	: phosphatidylinositol 3-kinase

## *List of Abbreviations*

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<b>ppm</b>	: Part per million
<b>PV</b>	: polycythemia Vera
<b>RGC</b>	: Receptor guanylate cyclase
<b>RIT</b>	: Radio-immunotherapy
<b>RMSD</b>	: Root mean square deviation
<b>RPMI</b>	: Roswell Park memorial institute
<b>RTK</b>	: Receptor tyrosine kinase
<b>SAR</b>	: Structure activity relationship
<b>siRNA</b>	: Small interfering ribonucleic acid
<b>SFDA</b>	: State food and drug administration
<b>TGF</b>	: Transforming growth factor
<b>TK</b>	: Tyrosine kinase
<b>TKL</b>	: Tyrosine kinase-like
<b>TP53</b>	: Tumor protein 53
<b>VDEPT</b>	: Virus-Directed Enzyme-Prodrug Therapy
<b>VEGF</b>	: Vascular endothelial growth factor
<b>VEGFR</b>	: Vascular endothelial growth factor receptor

# **Abstract**

Cancer is a medical term include group of diseases characterized by abnormal cell growth of uncontrolled division and which have the ability to invade tissues and destroy normal body tissues. It can spread all over the body at which the cells grow very rapidly forming malignant tumors that can transfer to different tissues through blood vessels and lymphatics.

As cancer cells are derived from normal ones most traditional therapies affect targets that present in both types of cells.

4-Anilinoquinazoline derivatives have been designed and its interaction energy and binding with EGFR enzyme has been studied, compounds of good results has been synthesized and evaluated as anticancer agents against MCF-7 breast cancer cell line. Also some of these compounds (**VIb, VIc, VIq, VIs, VIj, VIv, VIx, XIIIa, XIIIb, XIIIc, XIId**) have been evaluated against EGFR enzyme.

## **The thesis compromise six chapters:**

### **1. The introduction:**

This part describes cancer causes, discusses novel literature survey about its treatments and explains the different used mechanisms for designing different anticancer agents, this part gives a focus on EGFR inhibitors and clinically approved drugs by FDA.

### **2. Rational and design:**

Designing of new 4-anilinoquinazolines derivatives depending on the structure activity relationship and the essential groups for activity, also doking studies and binding energy scoring that gave best results for being synthesized according to scheme I,II

### **3. Results and discussion:**

#### **3.1. Molecular modeling**

It includes doking scores of hit compounds and its interaction energy calculations, as well as the binding modes inside EGFR enzyme binding site.

### 3.2. Chemistry:

This part includes all methods of synthesis the reported known and new compounds, synthesis of proposed compounds according to schemes I,II. All of synthesized compounds have been proved by different analytical and spectral data.

### 3.3. Biological evaluation

All designed compounds are evaluated as anticancer agent against MCF-7 breast cancer cell line, some of them evaluated for its %inhibition against EGFR enzyme.

### 4. Conclusion:

Based on the biological evaluation some of the hit compounds can be used for elucidation and designing of some new compounds as potent anticancer agents.

### 5. Experimental:

#### 5.1. Molecular modeling

Includes the procedure taken for calculation of docking the compounds in the enzyme and its binding energy calculation.

#### 5.2. Chemistry

It includes the detailed experimental methods used in preparation of intermediates and final compounds as well as physical and spectral properties (IR, mass spectrum,  $^1\text{H}$ NMR) and elemental analysis for C, H, N.

##### 5.2.1. Reported starting materials and intermediates:

1.  $N'$ -(2-Cyano-4-nitrophenyl)- $N,N$ -dimethylimidoforamide (**II**)
2. 6-nitro- $N$ -(3-(trifluoromethyl)phenyl)quinazolin-4-amine (**IIIa**)
3.  $N$ -(3-chlorophenyl)-6-nitroquinazolin-4-amine (**IIIb**)
4.  $N$ -(4-chlorophenyl)-6-nitroquinazolin-4-amine (**IIIc**)
5.  $N$ -(3-bromophenyl)-6-nitroquinazolin-4-amine (**IIId**)
6.  $N$ -(4-bromophenyl)-6-nitroquinazolin-4-amine (**IIIe**)
7.  $N$ -(4-chloro-3-(trifluoromethyl)phenyl)-6-nitroquinazolin-4-amine (**IIIf**)
8.  $N^4$ -(3-(Trifluoromethyl)phenyl)quinazoline-4,6-diamine (**IVa**)
9.  $N^4$ -(3-Chlorophenyl)quinazoline-4,6-diamine (**IVb**)