"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

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

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

ppm	:	Part per million
PV	:	polycythemia Vera
RGC	:	Receptor guanylate cyclise
RIT	:	Radio-immunotherapy
RMSD	:	Root mean square deviation
RPMI	:	Roswell Park memorial institute
RTK	:	Receptor tyrosine kinase
SAR	:	Structure activity relationship
siRNA	:	Small interfering ribonucleic acid
SFDA	:	State food and drug administration
TGF	:	Transforming growth factor
TK	:	Tyrosine kinase
TKL	:	Tyrosine kinase-like
TP53	:	Tumor protein 53
VDEPT	:	Virus-Directed Enzyme-Prodrug Therapy
VEGF	:	Vascular endothelial growth factor
VEGFR	:	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, XIIId)** 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 doking 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, H^1NMR) and elemental analysis for C, H, N.

5.2.1. Reported starting materials and intermediates:

1. *N*′-(2-Cyano-4-nitrophenyl)-*N*,*N*-dimethylimidoformamide **(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-(Triflouromethyl)phenyl)quinazoline-4,6-diamine* **(IVa)**
9. *N^4-(3-Chlorophenyl)quinazoline-4,6-diamine* **(IVb)**