

Novel Gefitinib Analogues; Design, Synthesis and Anticancer Activity

Thesis

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List of courses:

Subject	CR . HR	Grade in Semester (1)	Grade in Semester (2)
1- Statistics	1	Excellent	—
2-Instrumental Analysis	4	Excellent	—
3-Computer Sciences	2	Excellent	—
4- Physical Chemistry	2	good	—
5-Pharmaceutical Chemistry	3	—	Excellent
6- Drug Spectroscopy	3	—	Very good
7- Selected Topics in Pharmaceutical Chemistry	3	—	Excellent
8- Drug Stereochemistry	3	—	Very good

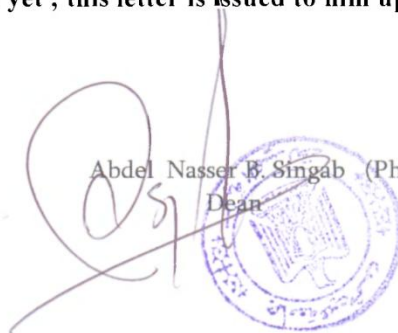
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To
My Parents

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List of Abbreviations:

3D QSAR: 3-Dimensional Quantitative Structure Activity Relationship

Å: Angstroms

Ac: Acetyl

ADP: Adenosine Di Phosphate.

ATP: Adenosine Tri Phosphate.

ATCC: American Type Culture Collection.

Bn: Benzyl

Bz: Benzoyl

CC₅₀: 50% Cytotoxicity concentration

CDK: Cycline Dependant Kinase

CMC: Critical Micelle Concentration

DFG: term used to describe three amino acid residues (Aspartate, Phenylalanine and Glycine)

DMAP: Di-Methyl Amino Pyridine

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

DMPK: Distribution metabolism pharmacokinetic properties.

DNA: Deoxyribo Neucleic Acid

EC₅₀: 50% Maximal effective concentration.

EGFR: Epidermal Growth Factor Receptor

ErbB-2: Human Epidermal Growth Factor Receptor 2

ESI-TOF: Electrospray ionization-Time of flight

EtOAc: Ethyl acetate

FBGF: Fibroblast Growth Factor

FDA: Food and Drug Administration

FT-IR: Fourier transform-Infrared

GI₅₀: Growth Inhibition

GOLD: Genetic optimization of ligand docking

Glide: Grid-based ligand docking with energetic

HIF: Hipoxia Inducible Factor

HIV: Human immunodeficiency virus

HMPA: Hexamethylphosphoramide

HRMS: High resolution mass spectroscopy

Hr: Hour

Hz: Hertz

IC₅₀: 50% Inhibitory concentration

Kcal: Kilocalories

LC₅₀: Lethal Dose
LDL: Low Density Lipoprotein
MAPk: Mitogen-activated protein kinase
MAP2K2: Mitogen-activated protein kinase kinase
MHz: Mega hertz
MS: Mass spectroscopy
MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazole
NCI: National Cancer Institute.
NMR: Nuclear magnetic resonance
NS: Non-structural
NTP: Nucleoside triphosphate
NSCLc: Non-small-cell lung carcinoma
PDB: Protein data bank
PDC: Pyridinium dichromate
PDGFR: Platelet-derived growth factor receptor
Pet ether: Petroleum ether
PK: Protein Kinase
RAF: Rapidly Accelerated Fibrosarcoma
Redox: Reduction-oxidation
RMSD: Root mean square deviation
rt: room temperature
siRNA: small interfering RNA
SRC: Sarcoma
TCA: Trichloro acetic acid
TEA: Triethyl amine
TFE: Trifluoro ethanol
THF: Tetrahydrofuran
TLC: Thin layer Chromatography
TGI: Total growth inhibition
TMS: Tetramethylsilane
TMEDA: Tetramethylethylenediamine
USA: United States of America
VEGFR: Vascular Endothelial Growth Factor Receptor
WHO: World Health Organization

Abstract

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Abstract

Cancer is considered a major health problem that requires urgent development of effective and safe medications. Cancer is the second major cause of death in the United States and worldwide exceeded only with cardiovascular disorders. Most of the current anticancer agents depend on the high rate of division and massive metabolism of cancerous cells. On the other hand, targeting anticancer therapy is directed towards some over-expressed molecular targets (enzymes and receptors) in cancer cells that are responsible for their mutations and cancerous nature. Epidermal growth factor receptor (EGFR) tyrosine kinase is one of these targets that is highly expressed in many kinds of cancers and responsible for poor prognosis of cancer patients.

In this study, scaffold hopping approach was utilized for the discovery of new ring system with new biological activity as an alternative for the quinazoline. Based on the crystal structure of Gefitinib and Erlotinib bounded to EGFR tyrosine kinase, compounds with benzo[d]isothiazole 1,1-dioxide core were designed as surrogates of quinazoline core of these drugs. In addition isoindolinone scaffold as bioisostere of benzo[d]isothiazole 1,1-dioxide was adopted to test the effect of this bioisosteric replacement. This new scaffold was adopted for the development of novel tyrosine kinase inhibitors of both type 1 and type 2 targeting EGFR and VEGFR-2 tyrosine kinases.

Synthesis of the designed benzo[d]isothiazole 1,1-dioxide compounds was accomplished and their structures were confirmed by various spectral and micro analytical data.

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

1. 2-Methyl-4-nitrobenzenesulfonamide **(II)**
2. 5-Nitrosaccharine (5-nitrobenzo[d]isothiazole 1,1-dioxide)**(III)**
3. 3-Chloro-5-nitrobenzo[d]isothiazole 1,1-dioxide **(IV)**
4. 3-Chlorobenzo[d]isothiazole 1,1-dioxide (3-chloropseudosaccharine)**(X)**
5. 3-(4-Nitrophenoxy)benzo[d]isothiazole 1,1-dioxide**(XI)**
6. 4-Nitrobenzoyl chloride **(XIV)**
7. 4-Nitrobenzoyl azide **(XV)**

8. 1-(4-Nitrophenyl)-3-phenylurea **(XVIa)**
9. 1-(4-Methoxyphenyl)-3-(4-nitrophenyl)urea **(XVIb)**
10. 1-(3-Bromophenyl)-3-(4-nitrophenyl)urea **(XVIc)**
11. 1-(2,4-Dichlorophenyl)-3-(4-nitrophenyl) urea **(XVI d)**
12. 1-(4-Aminophenyl)-3-phenylurea **(XVIIa)**
13. 1-(4-Aminophenyl)-3-(4-methoxyphenyl)urea **(XVIIb)**
14. 4-Nitro-N-(m-tolyl)benzamide **(XIXa)**
15. N-(2-Chlorophenyl)-4-nitrobenzamide **(XIXb)**
16. N-(4-Methoxyphenyl)-4-nitrobenzamide **(XIXc)**
17. 4-Amino-N-(m-tolyl)benzamide **(XXa)**
18. 4-Amino-N-(2-chlorophenyl)benzamide **(XXb)**
19. 4-Amino-N-(4-methoxyphenyl)benzamide **(XXc)**

Also, it comprises the following new intermediates:

1. 5-Nitro-3-(p-tolylamino)benzo[d]isothiazole 1,1-dioxide **(Va)**
2. 3-[(3-Bromophenyl) amino]-5-nitrobenzo[d]isothiazole 1,1-dioxide **(Vb)**
3. 3-[(4-Chlorophenyl)amino]-5-nitrobenzo[d]isothiazole 1,1-dioxide **(Vc)**
4. 3-[(2,4-Dichlorophenyl)amino]-5-nitrobenzo[d]isothiazole 1,1-dioxide **(Vd)**
5. 3-(4-Aminophenoxy)benzo[d]isothiazole 1,1-dioxide **(XII)**
6. 1-(4-Aminophenyl)-3-(3-bromophenyl)urea **(XVIIc)**
7. 1-(4-Aminophenyl)-3-(2,4-dichlorophenyl)urea **(XVIIe)**

Moreover, these new target compounds were synthesized:

1. 4-{{1,1-Dioxido-3-(p-tolylamino)benzo[d]isothiazol-5-yl}amino}-4-oxobutanoic acid **(VIIa)**
2. 4-{{3-[(3-Bromophenyl)amino]-1,1-dioxidobenzo[d]isothiazol-5-yl}amino}-4-oxobutanoic acid **(VIIb)**
3. Diethyl 2-{{[(3-[(4-chlorophenyl)amino]-1,1-dioxidobenzo[d]isothiazol-5-yl)amino]methylene}malonate **(VIIIa)**
4. Diethyl 2-{{[(3-[(3-bromophenyl)amino]-1,1-dioxidobenzo[d]isothiazol-5-yl)amino]methylene}malonate **(VIIIb)**
5. 1-{3-[(2,4-Dichlorophenyl)amino]-1,1-dioxidobenzo[d]isothiazol-5-yl}-3-phenylurea **(IXa)**