Novel Gefitinib Analogues; Design, Synthesis and Anticancer Activity

Thesis

Presented by

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Master Degree

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(Pharmaceutical Chemistry)

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To whom it may concern

This is to certify that pharmacist / Mohamed Saad Abdullah Elsayed is registered for the Master degree in the department of Pharmaceutical Chemistry, and has successfully passed the Master's general & special courses in the academic year 2009/2010 with the general grade: Excellent .

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

The candidate hasn't fulfilled his master degree yet ; this letter is issued to him upon his request.

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To

My Parents

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List of Abbreviations:

3D QSAR: 3-Dimentional 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
CC_{50}: 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
EC_{50}: 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
GI_{50}: 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
IC_{50}: 50% Inhibitory concentration
Kcal: Kilocalories

LC_{50}: 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

Title of thesis:

"Novel Gefitinib Analogues; Design, Synthesis and Anticancer Activity"

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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 Gefitininb and Erlotininb 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 **(XVId)**
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)**