



Design, Synthesis and Biological Evaluation of Heterocyclic Compounds As Potential Targeted Anticancer Agents

Thesis Presented by

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"Thanks be to God for His indescribable gift,
'For in Him we live and move and have our being',
Who is able to do immeasurably more than all we ask or
imagine, according to His power that is at work within us."

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Transcript of Master's Courses



To whom it may concern

This is to certify that pharmacist /**Sandra Nabil Mourad Milik** 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 **2012/2013** with the general grade: **Excellent**

List of courses:

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

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Table of Contents

Acknowledgements	I
Transcript of Master's Courses	III
Table of Contents	IV
List of Figures	VI
List of Tables	X
List of Abbreviations	XII
Abstract	XV
1. Introduction	1
1.1. <i>Get to know your enemy: What is Cancer?</i>	1
1.2. <i>The target of this study: Epidermal Growth Factor Receptor (EGFR)</i> <i>tyrosine kinase</i>	3
1.2.1. What are kinases?	3
1.2.2. Epidermal Growth Factor Receptor (EGFR) family.....	6
1.2.3. Dual EGFR/HER2 inhibitors: a literature review	18
2. Rationale and Design	49
2.1. <i>The Rationale behind targeting EGFR</i>	49
2.2. <i>The Rationale behind dual EGFR/HER2 targeting</i>	51
2.2.1. Potentiate EGFR signaling pathway blockade	51
2.2.2. Overcome EGFR inhibitors resistance.....	53
2.3. <i>Rational Design of the Dual EGFR/HER2 Inhibitors</i>	56
2.3.1. Analyzing the binding site.....	56
2.3.2. Structure-activity relationship (SAR) of reported dual EGFR/HER2 inhibitors	57
2.3.3. Proposed design of novel thieno[2,3- <i>d</i>]pyrimidine-based dual EGFR/HER2 inhibitors	60
2.3.4. In silico evaluation of the validity of the design.....	62
2.4. <i>Synthetic Schemes of the designed compounds</i>	67
2.4.1. Scheme 1: Preparation of 3,4-disubstituted aniline intermediates.	67
2.4.2. Scheme 2: Preparation of <i>N</i> -substituted-6-(4- nitrophenyl)thieno[2,3- <i>d</i>]pyrimidin-4-amine (XIII - XXI).....	69

2.4.3. Scheme 3: Preparation of 6-(4-((substituted)amino)phenyl)-N-(3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)thieno[2,3-d]pyrimidin-4-amine (XXII - XXVIII)	70
3. Results and Discussion.....	71
3.1. Chemistry	71
3.1.1. Scheme 1	71
3.1.2. Scheme 2	77
3.1.3. Scheme 3	90
3.2. Biological Evaluation	98
3.2.1. Screening for the optimum aniline derivative.....	99
3.2.2. Screening for the optimum solubilizing group.....	111
3.3. Molecular Modeling Study	118
3.3.1. Docking Study conforming to the observed enzymatic activity.....	118
3.3.2. Identifying the Molecular properties affecting the cellular activity.....	128
4. Conclusion.....	132
5. Experimental.....	134
5.1. Chemistry	134
5.1.1. Materials and instrumentation	134
5.1.2. Synthesis.....	135
5.2. Biological Evaluation	165
5.2.1. <i>In vitro</i> EGFR/HER2 tyrosine kinase inhibitory activity	165
5.2.2. <i>In vitro</i> antiproliferative activity against NCI panel of 60 cell lines	166
5.2.3. <i>In vitro</i> antiproliferative activity against A431 and MDA-MB-361 cell lines	168
5.3. Molecular Modeling Protocols.....	169
5.3.1. Molecular Field Alignment	169
5.3.2. Ligand-Pharmacophore Mapping.....	169
5.3.3. Molecular Docking	170
6. Supplementary Materials	171
7. References	217

List of Figures

Figure 1 Hallmarks of Cancer.....	2
Figure 2 Mechanisms for sustaining the proliferative signaling in Cancer cells ...	3
Figure 3 Kinase-catalyzed phosphorylation of proteins	4
Figure 4 the phylogenetic tree of the Human Kinome.	5
Figure 5 Classification of Protein Kinases.....	6
Figure 6 Receptor Tyrosine Kinases (RTKs), 20 families.	6
Figure 7 Epidermal Growth Factor Receptor (EGFR) family members, mechanism of activation and downstream signaling pathways.	7
Figure 8 EGFR Structure.	8
Figure 9 Structural differences between EGFR Family members, and different Growth factor groups that bind to each receptor.	9
Figure 10 EGFR extracellular domain structure, and mechanism of receptor dimerization.	10
Figure 11 EGFR Intracellular Kinase domain activation.	11
Figure 12 EGFR kinase domain: Active vs Inactive conformations.....	12
Figure 13 EGFR active conformation: Stabilization of the α C-in conformation by hydrogen bonding with the α E-helix.....	13
Figure 14 EGFR Kinase domain: ATP binding site. (a) EGFR with AMP-PNP (b) EGFR with Erlotinib (c) EGFR with TAK-285 (d) HER2 with TAK-285	14
Figure 15 EGFR (3POZ) and HER2 (3RCD) sequence alignment.	15
Figure 16 The inability to stabilize the α C-in conformation in HER2 kinase domain due to absence of hydrogen bonding between α C-helix and α E-helix.	16
Figure 17 Therapeutic targeting approaches of EGFR and HER2.	17
Figure 18 FDA-approved EGFR inhibitors	17
Figure 19 General layout of dual EGFR/HER2 inhibitors.....	19
Figure 20 EGFR kinase domain co-crystallized with Lapatinib (PDB: 1XKK)	21
Figure 21 Design Strategy of Pyrrolo[3,2-d]pyrimidine dual inhibitors.....	22
Figure 22 Proposed binding mode in HER2 back pocket	24
Figure 23 Pyrimidine-based dual inhibitors (21-23) binding mode	28
Figure 24 Pyrimidine-based inhibitors binding mode.....	31
Figure 25 Proposed binding mode of compound (23)	31

Figure 26 Compound (24)-(25) aligned to Lapatinib bioactive conformation ..	32
Figure 27 Compound (27)-(28) aligned to Lapatinib bioactive conformation ..	32
Figure 28 EGFR kinase domain complexed with Compound (29) (3W33)	33
Figure 29 Conserved Cysteine in the solvent-accessible region in the ATP binding site of EGFR family	36
Figure 30 Design and Binding mode of covalent irreversible inhibitors	36
Figure 31 Mechanism of base-catalyzed Michael addition.....	39
Figure 32 Mutant EGFR vs WT EGFR kinase domain.....	40
Figure 33 T790M EGFR kinase domain complexed with Dacomitinib (35)	40
Figure 34 Afatinib (5) binding mode.	43
Figure 35 Covalent modification by alkynyl thienopyrimidines.....	44
Figure 36 A compilation of fragments used in dual EGFR/HER2 inhibitors reported in the literature.	48
Figure 37 Cancers overexpressing EGFR/HER2.....	50
Figure 38 the 10 Most Common Causes of Cancer Death: 2012 Estimates.	50
Figure 39 Homo- and Heterodimers of the EGFR family of kinases.....	52
Figure 40 Proposed endocytic model of heterodimerization-mediated tuning of mitogenic signals.	52
Figure 41 Prevalence rates of the mechanisms of resistance to EGFR inhibitors	53
Figure 42 Summary of mechanisms of resistance to EGFR TKIs	55
Figure 43 EGFR Kinase domain: ATP binding site.....	57
Figure 44 TAK-285 (10) interactions with EGFR (PDB: 3POZ).	58
Figure 45 TAK-285 (10) interactions with HER2 (PDB: 3RCD).	58
Figure 46 Proposed design of novel dual EGFR/HER2 inhibitors	61
Figure 47 Design of dual inhibitors. R ¹ = Library of selected anilines. R ² = Library of selected solubilizing groups.....	61
Figure 48 Representative designed compounds (pink, blue and violet) aligned to TAK-285 (grey) using FieldAlign.	63
Figure 49 Representative designed compounds (pink, cyan and violet) aligned to Lapatinib (3) (light green) using FieldAlign.	63
Figure 50 Pharmacophore model assembly.....	65

Figure 51 Aligned Pharmacophore models of EGFR (PDB:3POZ) and HER2 (PDB: 3RCD).	65
Figure 52 Representative designed compounds mapped to the pharmacophore model representing the features of dual EGFR/HER2 inhibitors.	66
Figure 53 Williamson Ether Synthesis	71
Figure 54 Béchamp Reduction, mechanism of metal-catalyzed nitro reduction.	73
Figure 55 Nucleophilic Aromatic Substitution (S_NAr)	74
Figure 56 The mechanism of Enamine formation using DMF-DMA.....	77
Figure 57 Gewald Amino thiophene Synthesis	79
Figure 58 Mechanism of Gewald Amino thiophene Synthesis using an Enamine	80
Figure 59 Proposed mechanism for cyclizing the 2-amino thiophene-3-carboxylate into thieno[2,3-d]pyrimidine using formamide	81
Figure 60 Proposed mechanism of chlorination of thieno[2,3-d]pyrimidin-4-one using $POCl_3$	82
Figure 61 Mechanism of Amide formation through EDC/DMAP-assisted coupling	95
Figure 62 Mechanism of mixed anhydride-mediated amide formation.....	95
Figure 63 Urea preparation through isocyanate using triphosgene	97
Figure 64 Abstract scenario for the development of dual EGFR/HER2 inhibitors	98
Figure 65 An outline of the stages of development of dual EGFR/HER2 inhibitors	99
Figure 66 One-Dose Mean Graph from the NCI-60 cell lines screening program for compound (XVIIIa) showing the growth percent of each of the 60 cell lines after treatment with compound (XVIIIa) at 10 μ M concentration.....	105
Figure 67 One-Dose Mean Graph from the NCI-60 cell lines screening program for compound (XX) showing the growth percent of each of the 60 cell lines after treatment with compound (XX) at 10 μ M concentration.....	106
Figure 68 Mean graph plots of GI_{50} values for Gefitinib (NSC 715055) and Lapatinib (NSC 745750) against NCI-60 cell lines	107
Figure 69 Expression of EGFR and HER2 in different cancer cell lines.....	109
Figure 70 Cytotoxic activity of compounds (XIVa, XV, XVIIa, XVIIIa) and their reduced NH_2 derivatives (XXII, XIX, XX) against A431 cell line	110

Figure 71 Cytotoxic activity of compounds (XIVa , XV , XVIIa , XVIIIa) and their reduced NH ₂ derivatives (XXII , XIX , XX) against MDA-MB-361 cell line	111
Figure 72 Cytotoxic activity of compounds (XXII-XXVIII) against A431 cell line	116
Figure 73 Cytotoxic activity of compounds (XXII-XXVIII) against MDA-MB-361 cell line	116
Figure 74 The alignment between the co-crystallized bioactive conformer of TAK-285 (green) and the pose of TAK-285 retrieved from docking using CDOCKER	119
Figure 75 A heat map representing the Correlation Matrix between different molecular properties and cellular activity.....	130
Figure 76 The correlation between the cellular activity and ALogP of the compounds.....	131
Figure 77 The correlation between the cellular activity and PSA of the compounds	131
Figure 78 A summary of the design, screening and identification of dual EGFR/HER2 inhibitors	133

List of Tables

Table 1 Biological Data for Pyrrolo[3,2- <i>d</i>]pyrimidines (10-13)	23
Table 2 Biological Data for Pyrrolo[2,1- <i>f</i>][1,2,4]triazines (17-19)	26
Table 3 Biological Data for Compound (20)	27
Table 4 Biological Data for Pyrimidine-based inhibitors (21-28)	29
Table 5 Biological Data for Compound (29)	33
Table 6 Biological Data for miscellaneous dual inhibitors (30-32)	34
Table 7 Biological Data for Quinoline-3-carbonitriles (33-34)	38
Table 8 Biological Data for Quinazoline irreversible dual inhibitors (35-41)	41
Table 9 Biological Data for Thienopyrimidine irreversible dual inhibitors (42-44)	45
Table 10 Biological Data for Compound (45)	47
Table 11 Gewald Aminothiophene Synthesis: Components and Conditions	79
Table 12 Summary of reported chlorinating agents and conditions for chlorinating thieno[2,3- <i>d</i>]pyrimidinones	82
Table 13 Summary of reported conditions for nucleophilic substitution of 4- chlorothieno[2,3- <i>d</i>]pyrimidine with aniline derivatives	83
Table 14 Summary of reagents and conditions for acetylation of amino groups	89
Table 15 Reagents and conditions for Sulfonation of amines	91
Table 16 Reagents and conditions for Carbamate synthesis	92
Table 17 Reagents and conditions for amide synthesis	94
Table 18 Approaches, reagents and conditions for Urea synthesis	97
Table 19 % inhibitory effect of compounds (XIII-XVIII) on EGFR/HER2 kinase activities at 10 μ M	100
Table 20 % inhibitory effect of compounds (XIVa, XVIIa, XVIIIa) and their reduced NH ₂ derivatives (XXII, XIX, XX) on EGFR/HER2 kinase activities at 10 μ M	108
Table 21 Cytotoxic activity (IC ₅₀) of compounds (XIVa, XV, XVIIa, XVIIIa) and their reduced NH ₂ derivatives (XXII, XIX, XX) against A431 and MDA-MB-361	110
Table 22 % inhibitory effect of compounds (XXII-XXVIII) on EGFR/HER2 kinase activities at 10 μ M	112

Table 23 Cytotoxic activity (IC ₅₀) of compounds (XXII-XXVIII) against A431 and MDA-MB-361	115
Table 24 IC ₅₀ values of compounds (XXII-XXIV, XXVIIIa,b) against EGFR/HER2	117
Table 25 Results of the Molecular Docking Study of compounds (XIII-XVIII, XXIV) in EGFR (PDB: 3POZ) and HER2 (PDB: 3RCD) binding sites compared to TAK-285 (10)	122
Table 26 Calculated Molecular properties and Cellular activities of the compounds tested on A431 cell line	129
Table 27 Biological activities of the three identified dual EGFR/HER2 inhibitors	133

List of Abbreviations

ADMET, Absorption Distribution Metabolism Excretion and Toxicity

ADP, Adenosine diphosphate

Akt, Protein kinase B (PKB), also known as Akt

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

AMBER, Assisted Model Building with Energy Refinement (force field)

AMP-PNP, Adenylyl-imidodiphosphate, an adenosine triphosphate analog
containing a P-N-P linkage, ATP[β,γ -NH]

ATP, Adenosine triphosphate

BOP, (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium
hexafluorophosphate

BRAF, v-Raf murine sarcoma viral oncogene homolog B

BSA, bovine serum albumin

Cbl, Casitas B-lineage Lymphoma

CDI, 1,1'-Carbonyldiimidazole

CDOCKER, CHARMM-based docker

CHARMm, Chemistry at Harvard Macromolecular Mechanics (force field)

c-MET, cellular mesenchymal to epithelial transition factor

^{13}C NMR, Carbon-13 Nuclear Magnetic Resonance

DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC, *N,N'*-Dicyclohexylcarbodiimide

DCM, dichloromethane

DIEA, synonym for DIPEA (*N,N*-Diisopropylethylamine, or Hünig's base)

DIPEA, *N,N*-Diisopropylethylamine, or Hünig's base

DM, double mutant

DMAP, 4-(Dimethylamino)pyridine

DMF, Dimethylformamide

DMF-DMA, *N,N*-dimethylformamide dimethyl acetal

DMSO, Dimethyl sulfoxide

DPPA, Diphenylphosphoryl Azide

DTT, Dithiothreitol

EDCI, *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide

EGFR, Epidermal Growth Factor Receptor
EI-MS, Electron-Impact Ionization Mass Spectrometry
ErbB, avian erythroblastosis oncogene B
EWG, Electron Withdrawing Group
FDA, Food and Drug Administration
GI₅₀, concentration for 50% of maximal inhibition of cell proliferation
HATU, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HB, hydrogen bond
HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HER2, human epidermal growth factor receptor 2
¹H NMR, Proton Nuclear Magnetic Resonance
HOAt, 1-Hydroxy-7-azabenzotriazole
HOBt, *N*-Hydroxybenzotriazole
IC₅₀, half maximal inhibitory concentration
K-RAS, Kirsten rat sarcoma oncogene
m/z, mass-to-charge ratio
M⁺, Molecular ion
MAPK, mitogen-activated protein kinase
MD, Molecular Dynamics
MeCN, Acetonitrile
MEK, MAPK/ERK kinase
MP, melting point
mTOR, mechanistic target of rapamycin
Mwt, Molecular Weight
NSCLC, non-small cell lung cancer
Nü, Nucleophile
OD, Optical Density
PDB, protein data bank
PI, Pseudo-irreversible
PI3K, Phosphoinositide 3-kinase
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha

PK, Pharmacokinetic
PLC γ , phospholipase C gamma
ppm, parts per million
PSA, Polar Surface Area
PTEN, Phosphatase and tensin homolog
PyBOP, (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RAF, Rapidly Accelerated Fibrosarcoma proto-oncogene
RAS, Rat sarcoma oncogene
RMSD, Root Mean Square Deviation
RTK, receptor tyrosine kinase
SAR, structure-activity relationship
S_N2, bimolecular nucleophilic substitution
S_NAr, nucleophilic aromatic substitution
SOS, Son of Sevenless genes
SRB, sulforhodamine B
T3P, Propylphosphonic anhydride
TBTU, 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TEA, Triethylamine
THF, Tetrahydrofuran
TKIs, tyrosine kinase inhibitors
TLC, Thin-layer chromatography
TMLR, T790M/L858R
TMS, Tetramethylsilane
Tris, tris(hydroxymethyl)aminomethane
WT, wild type