كلية الصيدلة

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

Thesis Presented by

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(Pharmaceutical Chemistry)

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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

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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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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

GI_{50}, 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

^{1}H NMR, Proton Nuclear Magnetic Resonance

HOAt, 1-Hydroxy-7-azabenzotriazole

HOBt, *N*-Hydroxybenzotriazole

IC_{50}, 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

PLCγ, 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