Design and Synthesis of Molecular Candidates for Kinase Inhibition as Potential Antiproliferative Agents

Thesis

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4) Physical Chemistry	Excellent
5) Pharmaceutical Chemistry	Excellent
6) Drug spectroscopy	Excellent
7) Selected Topics in Pharmaceutical Chemistry	Excellent
8) Drug Stereochemistry	Excellent

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List of Abbreviations:

Abl: Abelson

ADMET: absorption, distribution, metabolism, excretion and toxicity study

ATP: adenosine triphosphate

BCR: breakpoint cluster region protein

DCC: dicyclohexylcarbodiimide

DEE: diethyl ether

DIBAL: diisobutylaluminum hydride

DIPEA: N,N- Diisopropylethylamine

DMAP: 4- (Dimethylamino)pyridine

DMF: dimethyl formamide

DMSO: dimethyl sulfoxide

EDC.HCl: N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride

EGF: epidermal growth factor

EGFR: epidermal growth factor receptor

EtOAc: ethyl acetate

EtOH: ethanol

EU: European union

FDA: food and drug administration

FGFR: fibroblast growth factor receptor

FT-IR: fourier transform infrared spectroscopy

HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

HBA: hydrogen bond acceptor

HBD: hydrogen bond donor

HBTU: N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate

HDAC: histone deacetylases

HER2: human epidermal growth factor receptor 2

HOBT: hydroxybenzotriazole

hrs: hours

IRK: insulin receptor protein tyrosine kinase

JAK: janus kinase

KDR: kinase insert domain receptor

KRAS: kirsten rat sarcoma

MAPK: mitogen activated protein kinase

MEK: mitogen-activated protein kinase/extracellular signal-regulated kinase kinase

MeOH: methanol

NaOEt: sodium ethoxide

NIH: national institute of health

NRTKs: non-receptor tyrosine kinases

NSCLC: non-small cell lung cancer

PDB: protein data bank

PDGFR: platelet derived growth factor receptor

Ph : pleckstrin homology

PI3K: phosphoinositide 3 kinase

RMSD: root mean square deviation

rt: room temperature

RTKs: receptor tyrosine kinases

SCC: squamous cell carcinoma

SFDA: state food and drug administration

TEA: triethylamine

TGF: tumor growth factor

THF: tetrahydrofuran

TKI: tyrosine kinase inhibitor

TLC: thin layer chromatography

US: united states

VEGFR: vascular endothelial growth factor receptor

WT: wild type

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Cancer is characterized by the rapid creation of abnormal cells that grow beyond their usual boundaries and can then metastasize to other organs. Cancer is one of the leading causes of death worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012.

The HER family plays important roles in normal physiology and in cancer because of their essential role for intracellular signaling and cell transformation. Among this family, two members are particularly involved in cancer development; EGFR and HER2. EGFR overexpression is notable in many types of human cancers and it is responsible for poor prognosis. In particular, overexpression of EGFR has been found in 40-80% of NSCLC cases. NSCLC accounts for approximately 85% of primary malignant lung tumors and it remains the leading cause of cancer-related death worldwide. Meanwhile, HER2 has been identified as a prognostic and predictive factor in breast cancer (18–25%).Therefore, the HER family represents an attractive class of rational targets for anticancer drug development.

The current study aimed to design novel furo[2,3-*d*]pyrimidine derivatives targeting EGFR and HER2. The design focused on exploration of the previously revealed SAR studies and bioisosteric modifications of the lead compounds both in market and in clinical studies. Synthesis of the designed compounds was then accomplished & their structures were confirmed by various spectral and microanalytical data.

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

1) *1-(benzyloxy)-4-nitrobenzene (**Ia**)*
2) *1-fluoro-3-((4-nitrophenoxy)methyl)benzene (**Ib**)*
3) *1-chloro-3-((4-nitrophenoxy)methyl)benzene (**Ic**)*
4) *1-chloro-4-((4-nitrophenoxy)methyl)benzene (**Ie**)*
5) *1-methyl-4-((4-nitrophenoxy)methyl)benzene (**If**)*
6) *1,2-dichloro-4-((4-nitrophenoxy)methyl)benzene (**Ig**)*
7) *2-chloro-1-((3-fluorobenzyl)oxy)-4-nitrobenzene (**Ih**)*
8) *2-((2-chloro-4-nitrophenoxy)methyl)pyridine (**Ii**)*
9) *4-(benzyloxy)aniline (**IIa**)*
10) *4-((3-fluorobenzyl)oxy)aniline (**IIb**)*
11) *4-((3-chlorobenzyl)oxy)aniline (**IIc**)*

12) *4-((4-chlorobenzyl)oxy)aniline (**IIe**)*
13) *4-((4-methylbenzyl)oxy)aniline (**IIf**)*
14) *4-((3,4-dichlorobenzyl)oxy)aniline (**IIg**)*
15) *3-chloro-4-((3-fluorobenzyl)oxy)aniline (**IIh**)*
16) *3-chloro-4-(pyridin-2-ylmethoxy)aniline (**IIi**)*
17) *Ethyl 5-amino-4-cyano-2-methylfuran-3-carboxylate (**III**)*
18) *Ethyl 6-methyl-4-oxo-3,4-dihydrofuro[2,3-d]pyrimidine-5-carboxylate **(IV)***
19) *Ethyl 4-chloro-6-methylfuro[2,3-d]pyrimidine-5-carboxylate **(V)***

Also, it comprised the following new intermediates:

1) *1-methyl-3-((4-nitrophenoxy)methyl)benzene (**Id**)*
2) *4-((3-methylbenzyl)oxy)aniline (**IId**)*

And finally, the study involved the synthesis and the characterization of the following new-targeted compounds:

1) *Ethyl 6-methyl-4-(phenylamino)furo[2,3-d]pyrimidine-5-carboxylate (**VIa**)*
2) *Ethyl 4-((3-fluorophenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIb**)*
3) *Ethyl 4-((3-chlorophenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIc**)*
4) *Ethyl 4-((3-bromophenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VId**)*
5) *Ethyl 6-methyl-4-(m-tolylamino)furo[2,3-d]pyrimidine-5-carboxylate (**VIe**)*
6) *Ethyl 4-((3-methoxyphenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIf**)*
7) *Ethyl 4-((3-ethynylphenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIg**)*
8) *Ethyl 4-((4-fluorophenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIh**)*
9) *Ethyl 4-((3-chloro-4-fluorophenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIi**)*
10) *Ethyl 4-((4-(benzyloxy)phenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIIa**)*
11) *Ethyl 4-((4-((3-fluorobenzyl)oxy)phenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIIb**)*
12) *Ethyl 4-((4-((3-chlorobenzyl)oxy)phenyl)amino)-6-methylfuro[2,3-d]pyrimidine-5-carboxylate (**VIIc**)*