Faculty of Pharmacy

Molecular design and synthesis of certain heterocycles based compounds as potential anti-cancer targeted agents

Thesis
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Elaborating piperazinyl-furopyrimidine based scaffolds as phosphoinositol-3-kinase enzyme alpha (PI3Kα) inhibitors to combat pancreatic cancer†

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Phosphoinositol-3-kinase enzyme (PI3K) plays a crucial role in driving oncogenic growth in various mammalian cells, particularly pancreatic cells. In the current study a series of novel furo[2,3-*d*]pyrimidine based-compounds were designed and synthesized as potential PI3K-α inhibitors. In accordance to the structure–activity relationship (SAR) studies of known PI3K-α inhibitors, different linkers including amide, urea and ether were attached to a piperazinyl furo[2,3-*d*]pyrimidine core. The synthesized compounds that revealed moderate PI3K-α inhibitory activity were tested for their anti-proliferative activities against pancreatic carcinoma on the PANC-1 cell line. Compounds **7b** and **8a** showed the highest anti-proliferative activity with IC_{50} values of 4.5 μM and 6 μM, respectively and relatively, the best *in vitro* PI3K inhibition ability within the newly synthesized compounds. Additionally, all the newly synthesized final compounds were tested on 60 human cancer cell lines. A docking study was carried out on the PI3K-α active site showing a comparable binding mode to that of FDA approved PI3K-α inhibitors. These newly discovered lipid kinase inhibitors could be considered as potential candidates for the development of new targeted anticancer agents.

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List of Abbreviations

5-FU	5-Fluorouracil
ADM	Acinar-to-Ductal Metaplasia
ADMET	Absorption, distribution, metabolism, excretion and toxicity
AKT	Ak strain transforming
ATP	Adenosine triphosphate
BBB	Blood brain barrier
CHARMM	Chemistry at *HAR*vard *M*acromolecular *M*echanics
CLL	Chronic lymphocytic leukemia
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DOX	Doxorubucin
EAT	Ehrlich ascites tumor
EGFR	Epidermal growth factor receptor
ErbB3	Erb-B2 Receptor Tyrosine Kinase 3
FDA	Food and drug administration
FL	Follicular lymphoma
FT-IR	Fourier transform infrared spectroscopy
FLT-3	fms like tyrosine kinase 3

GPCR	G protein-coupled receptor
GTPase	Guanosine triphosphatase
$G_{\beta\gamma}$	G protein betagamma
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HDI	Human Development Index
hrs	hours
IGF	Insulin-like growth factor
IGF1R	Insulin-like growth factor 1 receptor
IRS	insulin receptor substrate
JFCR39	Japanese Foundation for Cancer Research 39
KRAS	Kirsten rat sarcoma
MAPK	Mitogen-activated protein kinase
MD	molecular dynamics
mTOR	mammalian target of rapamycin
NSCL	Non-Small Cell Lung Cancer
PDAC	Pancreatic Ductal Adenocarcinoma
PDB	Protein data bank
PDGFR	Platelet-derived growth factor receptor
PDK-1	3′phosphoinositide- dependent kinase 1

PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol-4,5-bisphosphate.
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PSA	Polar surface area
PTEN	Phosphatase and TENsin homolog
RAS	Rat Sarcoma
rt	Room temperature
RTK	Receptor tyrosine kinases
RT-PCR	Reverse transcription polymerase chain reaction
SH2	Src Homology 2
SLL	Small Lymphocytic lymphoma
TEA	Triethyl amine
TGI	Tumor Growth inhibition
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TORC1	Target of rapamycin complex 1
TORC2	Target of rapamycin complex 2
Vps	vacuolar protein sorting

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Abstract:

Title of thesis:

"Molecular design and synthesis of certain heterocycles based compounds as potential anti-cancer targeted agents"

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Abstract

Cancer is considered rapidly propagating disease, in which the cells divide uncontrollably and abnormally, surpassing its usual boundaries and can as well extend to other organ and metastasize. In the meantime, pancreatic cancer is the seventh leading cause of cancer associated death, world widely, and predicted to be the second cause in the developed world by 2030.

PI3K family is involved in the normal physiological cell processes such as cell growth, proliferation, adhesion and survival through the production of lipid second messengers, binding to and activating downstream effector proteins. Among that family, the PI3K-α isoform was suggested to be the most frequently altered in human tumors; breast (27%), endometrial (23%), colorectal (14%), urinary tract (17%) and ovarian (8%) cancers. Meanwhile, overexpression of the upstream effectors of PI3K such as K-ras appeared within pancreatic ductal adenocarcinomas that consequently over activates the PI3K pathway, particularly the alpha isoform. Another member of the PI3K family is the PI3K-γ isoform was reported to be over activated by tumor-derived chemo-attractant signals, contributing in subsequent myeloid cell adhesion and invasion into tumors. Therefore, inhibiting such pathway represents an interesting class of rational targets for anticancer agents development.

The current study aimed to design novel Furo[2,3-*d*]pyrimidine based compounds targeting PI3K-α and PI3K-γ isoforms. The design focused on exploring the SAR studies, previously revealed by of the lead compounds possessing anti-cancer activity along with bioisosteric modifications to study the SAR of the newly designed series of compounds. The designed compounds were synthesized and their structures were confirmed by various spectral and micro-analytical methods.

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

1) 2-Chloro-N-phenylacetamide (**Ia**)
2) 2-Chloro-N-(p-tolyl)acetamide (**Ib**)
3) 2-Chloro-N-(4-methoxyphenyl)acetamide (**Ic**)
4) 2-Chloro-N-(4-nitrophenyl)acetamide (**Id**)