Towards targeting cancer therapy; design and synthesis of amide based scaffolds

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ACC: Acetyl-CoA carboxylase

ACL: ATP citrate lyase

AIBN: Azobisisobutyronitrile

AICAR: 5'-aminoimidazole- 4-carboxamide ribonucleoside

Akt: Protein kinase B (PkB)

AMP: Adenosine monophosphate

AMPK: Adenosine monophosphate activated protein kinase

Borane-DMS complex: Borane-dimethylsulfide complex

CA: Carbonic anhydrase

CAMKK2: Calcium/calmodulin-dependent protein kinase kinase 2

CBM: Carbohydrate binding module

ChoK: Choline Kinase

c-Myc: a regulator gene that codes for a transcription factor

COX-2: Cyclooxygenase-2

CPT1A: Carnitine palmitoyltransferase 1A

Dabco: 1,4-diazabicyclo[2.2.2]octane

DCM: Dichloromethane

DEAD: Diethyl azodicarboxylate

DIAD: Diisopropyl azodicarboxylate

DIBAL-H: Diisobutylaluminium hydride

DIPEA: Diisopropylethylamine

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

DMP: Dess–Martin periodinane

EMT: Epithelial-mesenchymal transition

ETFA: Ethyl trifluoroacetate

EtOAc: Ethyl acetate

EtOH: Ethanol

FASN: Fatty acid synthase

FH: Fumarate hydratase (fumarase)

GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

GLUT1: Glucose transporter 1

GLUT4: Glucose transporter 4

Her2: human epidermal growth factor receptor 2

HIF1α: hypoxia inducible factor 1α

HK: Hexokinase

IGFIR: Insulin-like growth factor receptor

IR: Insulin receptor

LDHA: Lactate dehydrogenase A

LKB1: Liver kinase B1

mCPBA: m-chloroperoxybenzoic acid

MCT4: Monocarboxylate transporter 4

mTOR: Mammalian target of rapamycin

mTORC1: mTOR complex 1

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide

NADPH: Reduced form of nicotinamide adenine dinucleotide phosphate

NBS: N-bromosuccinimide

NF1: Neurofibromin 1

NHE1: Sodium/hydrogen exchanger 1

NMP: *N*-Methyl-2-pyrrolidone

OXPHOS: Oxidative phosphorylation

p53: Tumor protein p53

p70S6K: Serine/Threonine kinase

PCC: Pyridinium chlorochromate

PDB: Protein Data Bank

PDC: Pyridinium dichromate

PDHs: Prolyl hydroxylases

PDK: Pyruvate dehydrogenase kinase

PFK: Phosphofructokinase

PGM: Phosphoglycerate mutase

PI3K: Phosphoinositide 3-kinase

PIP3: Phosphatidylinositol (3,4,5)-trisphosphate

PKM2: Pyruvate kinase isoform M2

PML: Probable transcription factor

PPP: Pentose phosphate pathway

PRAS40: Proline-rich Akt substrate of 40kDa

PTEN: Phosphatase and tensin homolog

RAPTOR: Regulatory-associated protein of mTOR

RAS: Class of protein called small GTPase and are involved in transmitting signals within cells

Rheb: Ras homolog enriched in brain

ROS: Reactive oxygen species

RTK: Receptor tyrosine kinase

SCO2: Cytochrome c oxidase assembly protein

SDHB, C and D: Succinate dehydrogenase subunits B, C and D

SREBP-1: Sterol regulatory element-binding protein 1

STK11: Serine/threonine kinase 11 (LKB1)

TBAB: Tetrabutylammonium bromide

TCA cycle: Tricarboxylic acid cycle

TEA-HCl: Triethylamine hydrochloride salt

TIGAR: TP53-inducible glycolysis and apoptosis regulator

TSC1: Tuberous sclerosis complex 1 (hamartin)

TSC2: Tuberous sclerosis complex 2 (tuberin)

ULK: Unc-51-like kinase

VDAC: Voltage dependent anion channel

VHL: Von Hippel–Lindau tumor suppressor

Abstract.

Title of thesis:

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Abstract

Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjacent parts of the body and spread to other organs, the latter process is referred to as metastasizing. Metastases are the major cause of death from cancer. Cancer is among the leading causes of death worldwide. In 2012, there were 14 million new cases and 8.2 million cancer-related deaths worldwide. The number of new cancer cases will rise to 22 million within the next two decades. More than 60% of the world's new cancer cases occur in Africa, Asia, and Central and South America; 70% of the world's cancer deaths also occur in these regions.

Knowledge about the causes of cancer, and interventions to prevent and manage the disease is extensive. Cancer can be reduced and controlled by implementing evidence-based strategies for cancer prevention, early detection of cancer and management of patients with cancer. Many cancers have a high chance of cure if detected early and treated adequately.

Adenosine monophosphate-activated protein kinase (AMPK) is a key player in maintaining energy homeostasis in response to metabolic stress. Beyond diabetes and metabolic syndrome, there is a growing interest in the therapeutic exploitation of the AMPK pathway in cancer treatment in light of its unique ability to regulate cancer cell proliferation through the reprogramming of cell metabolism.

Previously, a novel thiazolidinedione-based AMPK activator (**OSU-53**) was identified, which provided a proof-of-concept to highlight the important role of AMPK in regulating oncogenic signaling pathways associated with cell proliferation and epithelial-mesenchymal transition (EMT) in cancer cells. In this study, we used **OSU-53** as a scaffold to conduct lead optimization, which generated a library of eighty five derivatives. The design process focused on Identification of key interactions between AMPKα2β1 enzyme allosteric binding site and the reported activator **991**, modeling studies including docking of **OSU-53** into the active site of AMPKα2β1 enzyme and finally rational modification of the lead compound, **OSU-53** guided by modeling studies to help establish a clear SAR for this class of compounds.

Synthesis of the designed compounds was then accomplished & their structures were confirmed by various spectral and HPLC purity data.

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

1) *3-(Bromomethyl)benzamide* (**3a**)
2) *4-(Bromomethyl)benzamide* (**3b**)
3) 4-(Bromomethyl)benzensulfonamide (**6**)
4) *3-(Trifluoroacetyl)benzyl bromide* (**9a**)
5) *4-(Trifluoroacetyl)benzyl bromide* (**9b**)
6) *4-(Methylsulfinyl)benzyl bromide* (**11a**)
7) *4-(Trifluoromethyl sulfinyl)benzyl bromide* (**11b**)
8) *4- Isopropoxy benzyl alcohol* (**13a**)
9) *3,4-Bis(trifluoromethyl)benzyl alcohol* (**13b**)
10) *2-Chloro-4-nitrobenzaldehyde* (**17a**)
11) *2-(Trifluoromethyl)-4-nitrobenzaldehyde* (**17b**)
12) *2-Methoxy-4-nitrobenzaldehyde* (**17c**)
13) *3-Chloro-4-nitrobenzaldehyde* (**17d**)
14) *3-(Trifluoromethyl)-4-nitrobenzaldehyde* (**17e**)
15) *3-Methoxy-4-nitrobenzaldehyde* (**17f**)
16) *4-Methoxy-3-nitrophenyl isothiocyanate* (**19a**)
17) *3-Isothiocyanato benzenesulfonamide* (**19b**)
18) 5-(4-Nitrobenzylidene)-1,3-thiazolidine-2,4-dione (**26**)
19) *3-[[4-(Trifluoromethyl)phenyl]methyl]-5-(4-nitrobenzylidene)-1,3-thiazolidine-2,4-dione* (**27g**)
20) *3-[(4-Bromophenyl)methyl]-5-(4-nitrobenzylidene)-1,3-thiazolidine-2,4-dione* (**27j**)
21) *3-[(4-Tert-butylphenyl)methyl]-5-(4-nitrobenzylidene)-1,3-thiazolidine-2,4-dione* (**27m**)
22) *3-[(4-Methoxyphenyl)methyl]-1,3-thiazolidine-2,4-dione* (**28a**)
23) *3-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-1,3-thiazolidine-2,4-dione* (**28e**)
24) *3-[[4-(Trifluoromethyl)phenyl]methyl]-5-(4-aminobenzylidene)-1,3-thiazolidine-2,4-dione* (**30g**)