Molecular Modelling and Synthesis of Certain Heterocyclic Compounds with Expected Biological Activity

Thesis

Presented by

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List of Abbreviations

ABL: Abelson tyrosine kinase

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity study

ALK: Anaplastic lymphoma kinase

ANLL: Acute Non-Lymphocytic Leukemia

Asp: Aspartate

ATP: Adenine-5'-triphosphate

BAECs : Bovine aortic endothelial cells

BBB: Blood brain barrier

BCR: breakpoint cluster region protein

BSA: Bovine serum albumin

BRMs: Biological response modifiers

C-Fms: Colony-Stimulating factor-1 receptor

C-kit: v-kit (Hardy-Zuckerman 4 feline) sarcoma viral oncogene

CHARMm: Chemistry at HARvard Macromolecular Mechanics

CTLA4 mab: Cytotoxic T-lymphocytes 4A monoclonal antibody

CYP 450: Cytochrome P450

Cys: Cysteine

D_2O: Deuterium oxide

DFG: Aspartate- Phenylalanine- Glycine

DIPEA: Diisopropyl ethylamine

DMF: Dimethyl formamide

DMSO: Dimethyl sulfoxide

DNA: Deoxyribonucleic acid

EC: Endothelial cell

EI-MS: Electron impact mass spectroscopy

EGFR: Epidermal growth factor receptor

5-FU: 5-Fluorouuracil

Fab: Fragment antigen-binding

FDA: Food and Drug Administration

FGFR: Fibroblast growth factor receptor

FLT: FMS-like receptor tyrosine kinase

FT-IR: Fourier transform-Infrared

Glu: Glutamate

HER-2: Human epidermal growth factor receptor-2

HIA: Human intestinal absorption

His: Histidine

Hrs: hours

HUVEC: Human umbilical vein endothelial cells

Hz: Hertz

IC_{50}: Half-maximal inhibitory concentration

IGFR: Insulin-like growth factor receptor

IRK: Insulin receptor kinase

JAK: Janus kinase

KDa: Kilo Dalton

KDR: Kinase insert domain receptor

Lys: Lysine

6-MP: 6-Mercaptopurine

m.p.: Melting point

Min: Minutes

MHz: Mega hertz

µM: Micromole

mmol: Millimole

µl: Microliter

MS: Mass spectroscopy

NCI: National Cancer Institute

NIH: National Institutes of Health

nM: Nanomole

NMR: Nuclear magnetic resonance

NRTK: Non-receptor tyrosine kinase

NSCLC: Non-Small Lung Cell cancer

PARP: Poly ADP ribose polymerase

Pd-C: Palladium on carbon

PDB: Protien data bank

PDGFR: Platelet derived growth factor receptor

PDT: Photodynamic therapy

Phe: Phenyl alanine

PM: Picometre

PPB: Plasma protein binding

Ppm: Part per million

PSA: Polar surface area

Raf: v-raf murine sarcoma viral oncogene

Ras: Rat sarcoma

RMSD: Root mean square deviation

RNA: Riboneucleic Acid

rt: Room temperature

RTK: Receptor tyrosine kinase

SAR: Structure activity relationship

SMART: string matching algorithms research tool

SRC: Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene

TEA: Triethyl amine

THF: Tetrahydrofuran

Tie-2: Tyrosine kinase with immunoglobulin-like and EGF-like domains 2

TK: Tyrosine kinase

TLC: Thin layer Chromatography

***TP53*:** Tumor protein 53

U.V: Ultra violet

VEGFR: Vascular endothelial growth factor receptor

Abstract

Title of thesis:

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Cancer, also known as a malignant tumor, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. A major problem in treating cancer is the fact that it is not a single disease. There are more than 200 different cancers resulting from different cellular defects. The growth of new blood vessels (angiogenesis) is one of the well established hallmarks in the process of carcinogenesis. Vascular endothelial growth factor receptor-2 (VEGFR-2) plays a crucial role in cancer angiogenesis. By targeting VEGFR-2, angiogenesis is greatly inhibited leading to the death of the tumor cells.

In this study, thienopyrimidine derivatives have been designed and synthesized as targeted angiogenesis inhibitors. The design focused on exploration of the previous revealed SAR studies, bioisosteric modifications of the lead compounds both in market and in clinical studies, and identification of the key interactions with the binding site *in silico.*

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-(4-Nitrophenyl)-3-phenylurea* ***(Ia)***
2) *1-(3-Methoxyphenyl)-3-(4-nitrophenyl)urea* ***(Ib)***
3) *1-(4-Nitrophenyl)-3-(m-tolyl)urea* ***(Ic)***
4) *1-(4-Acetylphenyl)-3-(4-nitrophenyl)urea* ***(Ie)***
5) *1-(4-Chlorophenyl)-3-(4-nitrophenyl)urea* ***(Ig)***
6) *N1-(3-Bromophenyl)-3-(4-nitrophenyl)urea* ***(Ih)***
7) *1-(4-Ethylphenyl)-3-(4-nitrophenyl)urea* ***(Ii)***
8) *1-(3,4-diChlorophenyl)-3-(4-nitrophenyl)urea* ***(Ij)***
9) *1-(3-trifluoromethyl-4-chlorophenyl)-3-(4-nitrophenyl)urea* ***(Ik)***
10) *1-(4-Aminophenyl)-3-phenylurea* ***(IIa)***
11) *1-(4-Aminophenyl)-3-(3-methoxyphenyl)urea* ***(IIb)***
12) *1-(4-Aminophenyl)-3-(m-tolyl)urea* ***(IIc)***
13) *1-(4-Aminophenyl)-3-(4-chlorophenyl)urea* ***(IIg)***
14) *1-(4-Aminophenyl)-3-(3-bromophenyl)urea* ***(IIh)***
15) *1-(4-aminophenyl)-3-(3,4-diChlorophenyl) urea* ***(IIj)***

16) *1-(4-aminophenyl)-3-(3-trifluoromethyl-4-chlorophenyl) urea* ***(IIk)***

17) *1-(4-Hydroxyphenyl)-3-phenylurea* ***(IIIa)***

18) *1-(3-Bromophenyl)-3-(4-hydroxyphenyl)urea* ***(IIIb)***

19) *1-(4-Hydroxyphenyl)-3-(3-methoxyphenyl)urea* ***(IIIc)***

20) *1-(4-Chlorophenyl)-3-(4-hydroxyphenyl)urea* ***(IIId)***

21) *11-(3,4-Dichlorophenyl)-3-(4-hydroxyphenyl)urea* ***(IIIf)***

22) *1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea* ***(IIIg)***

23) *5-Nitroindazole* ***(IV)***

24) *5-Aminoindazole* ***(V)***

25) 5-Amino benzimidazole ***(VI)***

26) N-(4-Nitrophenyl)-2-phenylacetamide ***(VII)***

27) *N-(4-aminophenyl)-2-phenylacetamide* ***(VIII)***

28) N-(4-Hydroxyphenyl)-2-phenylacetamide ***(IX)***

29) Diethyl (5-amino-3-methylthiophene)-2,4-dicarboxylate ***(X)***

30) Ethyl (5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine)-6-carboxylate ***(XI)***

31) Ethyl (4-chloro-5-methylthieno[2,3-*d*]pyrimidine)-6-carboxylate ***(XII)***

32) 3-((6-(Ethoxycarbonyl)-5-methylthieno[2,3-*d*]pyrimidin-4-yl)amino)benzoic acid ***(XXII)***

Also, it comprised the following new intermediates:

1) *1-(3-Acetylphenyl)-3-(4-nitrophenyl)urea* ***(Id)***
2) *1-(3-Chloro-4-methylphenyl)-3-(4-nitrophenyl)urea* ***(If)***
3) *1-(3-Acetylphenyl)-3-(4-aminophenyl)urea* ***(IId)***
4) *1-(4-Acetylphenyl)-3-(4-aminophenyl)urea* ***(IIe)***
5) *1-(4-Aminophenyl)-3-(3-chloro-4-methylphenyl)urea* ***(IIf)***
6) *1-(4-Aminophenyl)-3-(4-ethylphenyl)urea* ***(IIi)***
7) *1-(3-Chloro-4-methylphenyl)-3-(4-hydroxyphenyl)urea* ***(IIIe)***
8) *5-Methyl-4-((4-(3-phenylureido)phenyl)amino)thieno[2,3-d]pyrimidine-6-carboxylic acid* ***(XIVa)***
9) *4-((4-(3-(3-methoxyphenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylic acid* ***(XIVb)***

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

1) *Ethyl 5-methyl-4-((4-(3-phenylureido)phenyl)amino)thieno[2,3-d]pyrimidine-6-carboxylate* ***(XIIIa)***
2) *Ethyl 4-((4-(3-(3-methoxyphenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XIIIb)***
3) *Ethyl 5-methyl-4-((4-(3-(m-tolyl)ureido)phenyl)amino)thieno[2,3-d]pyrimidine-6-carboxylate* ***(XIIIc)***
4) *Ethyl 4-((4-(3-(3-acetylphenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XIIId)***
5) *Ethyl 4-((4-(3-(4-acetylphenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XIIIe)***
6) *Ethyl 4-((4-(3-(3-chloro-4-methylphenyl)ureido)phenyl)amino)-5-methylthieno [2,3-d]pyrimidine-6-carboxylate* ***(XIIIf)***
7) *Ethyl 4-((4-(3-(4-chlorophenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XIIIg)***
8) *Ethyl4-((4-(3-(3-bromophenyl)ureido)phenyl)amino)-5-methylthieno [2,3d] pyrimidine -6-carboxylate* ***(XIIIh)***
9) *Ethyl4-((4-(3-(4-ethylphenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylate* ***(XIIIi)***
10) *Ethyl4-((4-(3-(3,4-dichlorophenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylate* ***(XIIIj)***
11) *Ethyl4-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)amino)-5-methylthieno[2,3-d]pyrimidine-6-carboxylate* ***(XIIIk)***
12) *5-Methyl-4-((4-(3-phenylureido)phenyl)amino)-N-propylthieno[2,3-d]pyrimidine-6-carboxamide* ***(XVa)***
13) *4-((4-(3-(3-Methoxyphenyl)ureido)phenyl)amino)-5-methyl-N-propylthieno[2,3-d]pyrimidine-6-carboxamide* ***(XVb)***
14) *Ethyl 5-methyl-4-(4-(3-phenylureido)phenoxy)thieno[2,3-d]pyrimidine-6-carboxylate* ***(XVIa)***
15) *Ethyl 4-(4-(3-(3-bromophenyl)ureido)phenoxy)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XVIb)***
16) *Ethyl 4-(4-(3-(3-methoxyphenyl)ureido)phenoxy)-5-methylthieno[2,3-d] pyrimidine-6-carboxylate* ***(XVIc)***