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Molecular Modeling and Synthesis of Certain 2-Thiopyrimidine Derivatives with Expected Biological Activity

Thesis
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List of Abbreviations

2D: 2-Dimensional
3D: 3-Dimensional.
A°: Angstrom.
A_{2A}R:Adenosine A_{2A} receptor
AIDS: Acquired immune deficiency syndrome
Ala: Alanine
AMPA: Alpha amino-3-hydroxy-5-methyl-4-isoxazole propionate
APE: Ala-Pro-Glu
Asp: Aspartic acid
ATP: Adenosine triphosphate
CAK: Cdk activating kinase
CDK: Cyclin dependent kinase
CDKI: Cyclin dependent kinase inhibitors
Cdc25c: Cell division cycle phosphatase
CML:Chronic myeloid leukemia
CMV: Cytomegalovirus
CNS: Central nervous system
D_2: Dopaminergic receptor
DFG: Asp-Phe-Gly
DHFR: Dihydrofolate reductase
DMF: Dimethyl formamide
DNA: Deoxyribonucleic acid
EGFR: Endothelial growth factor receptor
ERK: Extracellular regulated kinase
FTase: Farnesyl transeferase
FTIs: Farensyl transeferase inhibitors
G_1, G_2,G_0: Gap
GABA: Gamma aminobutyric acid
GF: Growth factor
GIST: Gastrointestinal stromal tumor
Gln: Glutamine
Glu: Glutamic acid
Gly: Glycine
h: Hour

HCl: Hydrochloric acid
HIV: Human immune deficiency virus
His: Histidine
HSV: Herpes simplex virus
IC_{50}: Concenteration of compound causing 50% mortality
Ile: isoleucine
Ink_4/ ARF: Inhibitor of kinase 4 / Alternative Reading Frame
Leu: Leucine
Lys: Lysine
mAb: Monoclonal antibody
MAP: Mitogen activated protein
Met:Methionine
MIC: Minimum inhibitory concenteration
MRSA: Methicillin resistant strain of Staphylococcus aureus
NMR: Nuclear magnetic resonance.
NSAID: Non steroidal anti-inflammatory drugs
PDB: Protein data bank
Phe: Phenylalanine
PK: Protein kinase
Ppm: Part per million
pRb: Retinoblastoma tumor suppressor protein
RNA: Ribonucleic acid
r.t.: Room temperature
SAR: Structure activity relationship
Ser: Serine
SRB:Sulforhodamine B
TCA: Trichloroacetic acid
TEA: Triethylamine
Thr: Threonine
TK: Tyrosine Kinase
TLC: Thin Layer Chromatography
Tyr: Tyrosine
UV: Ultraviolet
Val: Valine

Abstract

Title of Thesis:

Molecular Modeling and Synthesis of Certain 2-Thiopyrimidine Derivatives with Expected Biological Activity.

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Abstract:

This study involves a survey covering the synthesis and biological significance of some compounds containing pyrimidine nucleus.

A number of new 2,4,5,6- tetrasubstituted pyrimidine derivatives were designed, synthesized, and some of them were biologically evaluated as anti-cancer. The design of these agents was based on the molecular modeling simulation, by direct molecular modeling method comprising docking study on cyclin- dependent kinase 2 enzyme using Discovery Studio software.

Preliminary screening of the anticancer activity against cervix carcinoma (Hela cell lines) for some of these compounds which gave promising results in molecular modeling study was fulfilled.

This thesis comprises the synthesis of the following unavailable reported starting material:

1) 6-(3,4-Dimethoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carbonitrile **(I)**.

In addition, the study comprises the synthesis of the following new intermediate:

2) 4-Chloro-6-(3,4-dimethoxyphenyl)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile**(II)**

Furthermore, the study involves the synthesis of the following new targeted compounds:

3) 7-(3,4-Dimethoxyphenyl)-5-thioxo-5,6-dihydrotetrazolo[1,5-c]pyrimidine-8- carbonitrile **(III)**.

4) 4-(8-Cyano-7-(3,4-dimethoxyphenyl) tetrazolo[1,5-c]pyrimidin-5-ylamino)benzeesulfonamide **(IV).**

5) 7-(3,4-Dimethoxyphenyl)-3-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2c]pyrimidine-8-carbonitrile **(V).**

6) 4-(8-Cyano-7-(3,4-dimethoxyphenyl) -3-oxo-2,3-dihydroimidazo[1,2-c]pyrimidin-5-ylamino) benzenesulfonamide **(VI).**

7) 6-(3,4-Dimethoxyphenyl)-4-hydrazinyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile **(VII).**

8) 7-(3,4-Dimethoxyphenyl)-3-methyl-5-thioxo-5,6-dihydro-[1,2,4]triazolo[4,3-c]pyrimidine-8-carbonitrile**(VIII).**

9) 4-(8-Cyano-7-(3,4-dimethoxyphenyl)-3-methyl-[1,2,4]trizolo[4,3-c]pyrimidin-5-ylamino)benzenesulfonamide **(IX).**

10) 6-(3,4-Dimethoxyphenyl)-4-(3,5-dimethyl-1H-pyrazol-1-yl)-2-thioxo- 1,2-dihydropyrimidine-5-carbonitrile **(X).**

11) 4-(5-Cyano-4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino) benzenesulfonamide **(XI).**

12) 6-(3,4-Dimethoxyphenyl)-4-(3-substituted-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile **(XIIa,b).**

13) 4-(5-Cyano-4-(3,4-dimethoxyphenyl)-6-(3-substituted-5-oxo-4,5-dihydro-1H-pyrazo-1-yl)pyrimidin-2- ylamino) benzenesulfonamide **(XIIIa,b).**

14) 4-(5-Amino-4-cyano-1H-pyrazol-1-yl)-6-(3,4-dimethoxyphenyl)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile **(XIV).**

15) 4-(4-(5-Amino-4-cyano-1H-pyrazol-1-yl)-5-cyano-6-(3,4-dimethoxyphenyl)pyrimidin-2-ylamino) benzenesulfonamide **(XV).**

16) 7-(3,4-Dimethoxyphenyl)-3-oxo-5-thioxo-2,3,5,6,-tetrahydro-[1,2,4]triazolo[4,3-c]pyrimidine-8-carbonitrile **(XVI).**

17) 4-(8-Cyano-7-(3,4-dimethoxyphenyl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]pyrimidin-5-ylamino) benzenesulfonamide **(XVII).**

The structures of these compounds were confirmed by microanalytical and spectral data.The biological evaluation was promising, as all selected compounds showed cytotoxic activity against cervix canceroma (Hela cell lines). Detailed descriptions of the synthesis, molecular modeling, and biological evaluation were discussed in this thesis.

A. Introduction

A.Introduction

1-Chemistry of 2-thiopyrimidines

Pyrimidine derivatives have been very well known in medicinal chemistry for their therapeutic applications [1]. One possible reason for their activity is the presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids [2], DNA and RNA. One important class of pyrimidines is 2-thiopyrimidine and its derivatives, which are also well known as 2-mercaptopyrimidine compounds [3]. In 2-thiopyrimidine ring sulfur atom serves as an interesting replacement for the existing oxygen atom bonded to C-2 in uridine base[4]. Considering this assumption, 2-thiopyrimidines have attracted substantial interest of synthetic-biochemists [5]. This was revealed [6] for their application as cardiotonic drugs. Pathak [7] evaluated its activity against tuberculosis. Also, 2- thiopyrimidines serve as important precursors for asymmetric synthesis of allylic sulfides /sulfonates [8]. Thus synthesis[9] as well as biological[10] studies of 2-thiopyrimidine derivatives have been topics of interest for chemists. 2-Thiopyrimidines serve as important precursors for synthesis of novel, potent and selective derivatives to substitute drugs having major side effects [11].

1-Structure of 2-thiopyrimidine

2-Thiouracil is an example of six-membered ambident heterocyclic system possessing several possible tautomeric structures [12] but found predominantly in the oxothione form (**1**).