“Design, Synthesis, and Biological Evaluation of Some New Heterocyclic Compounds"

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TO MY FAMILY WITH LOVE

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List of Abbreviations

- **ACCs:** atom centered charges
- **AKT:** protein kinase B
- **APAF-1:** apoptotic protease activating factor
- **Apo-1:** apoptosis antigen 1
- **ATRA:** all trans retinoic acid
- **BAD:** Bcl-2-associated death promotor
- **BAK:** Bcl-2 homologous antagonist killer
- **Bax:** Bcl-2-associated X protein
- **BBB:** blood brain barrier
- **Bcl-2:** B-cell lymphoma 2
- **Bid:** BH3 interacting domain
- **BIK:** Bcl-2 interacting killer
- **CACO cells:** Caucasian colon adenocarcinoma
- **CD-95:** cluster of differentiation 95
- **DMF:** dimethyl formamide
- **DMSO:** dimethyl sulfoxide
- **DRs:** death receptors
- **EI:** electron impact
- **FAP-1:** fibroblast activation protein 1
- **FasL:** fas ligand
- **HBA:** hydrogen bond acceptor
- **HBD:** hydrogen bond donor
- **HeLa:** cervical carcinoma cell line
- **HT29:** human colon adenocarcinoma
- **IAP:** inhibitors of apoptotic proteins
- **L1210:** mouse lymphocytic leukemia
- **MM:** molecular mechanics
- **NADH:** nicotinamide adenine dinucleotide
- **NFKB:** nuclear factor kappa-light-chain-enhancer of activated B cells)
- **PABA:** para amino benzoic acid
- **PBS:** phosphate buffered saline
- **PI3K:** phosphoinositide-3-kinase
- **QM:** quantum mechanics

- **RPMI:** Roswell park memorial institute medium
- **TLC:** thin layer chromatography
- **TMS:** Tetramethylsilane
- **TNF:** tumor necrosis factor
- **TRAIL:** TNF-related apoptosis inducing ligand
- **XED:** extended electron distribution

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Abstract

In this thesis, eighteen novel quinazolinone and triazinoquinazolinone derivatives were designed and synthesized as antineoplastic agents. Molecular modeling techniques were used to support the design. All the synthesized compounds were biologically evaluated for their cytotoxic activity in MCF-7 and HCT-116 cell lines. Most of the synthesized compounds showed excellent antiproliferative activity ranging from 0.35 µM to 3.8 µM in MCF-7 cell line and from 0.02 µM to 0.84 µM in HCT-116 cell line. Six compounds **(Va, VIa, VId, Xa, XIIa and XIId)** were further evaluated for their apoptotic activity as activators of caspases 3, 8 and 9 in HCT-116 cell line. Finally, compounds **VId**, **Xa** and **XIIa** showing potent effect on caspase 3,8, and 9 were further analyzed by cell cycle flow analysis where they showed cell cycle arrest mainly in G1/S phase.

The thesis included the following parts:

1. Introduction

This part is a comprehensive review for covering the therapeutic agents that target different pro-apoptotic proteins involved in the apoptotic process either through the extrinsic or intrinsic pathways, some agents interfere with both apoptotic pathways. Novel heterocyclic compounds based on quinazoline scaffold are reported to be promising agents as potent caspases activators and Bcl-2 inhibitors.

2. Aim and Rationale

The objective of this work was to design and synthesize new compounds as anti-cancer agents bearing quinazoline core with potential pro-apoptotic activity. The design of these compounds was based on structural modification of a selected lead compound and was supported by a molecular modeling study.

3. Discussion of the Synthetic Part

Synthesis of the target compounds was carried out adopting the chemical pathways in schemes (1 and 2). The chemical methods for preparing the starting materials and intermediates were mentioned. Also, this part a summarized data about the spectral methods adopted for verification of the structures of the prepared compounds

Reported synthetic intermediates: (5 compounds)

- 2-(2-Ethoxy-2-oxoacetamido)benzoic acid **(II)**

- Ethyl 4-oxo-4*H*-benzo[d][1,3]oxazine-2-carboxylate **(III)**
- 2-Aminobenzohydrazide **(VIII)**
- Ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate **(IX)**
- Ethyl(*E*)-3-((ethoxymethylene)amino)-4-oxo-3,4-dihydroquinazoline-2-carboxylate **(XI)**

New final compounds: (18 compounds)

- 4-(2-(Ethoxycarbonyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid **(IV)**
- Ethyl 4-oxo-3-(4-sulfamoylbenzyl)-3,4-dihydroquinazoline-2-carboxylate **(Va)**
- Ethyl 4-oxo-3-((4-sulfamoylphenyl)amino)-3,4-dihydroquinazoline-2-carboxylate **(Vb)**
- Ethyl 4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydroquinazoline-2-carboxylate **(VIa)**
- Ethyl3-(4-(*N*-(diaminomethylene)sulfamoyl)phenyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate **(VIb)**
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)-*N*-(pyridin-2-yl)benzenesulfonamide **(VIc)**
- Ethyl 4-oxo-3-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)-3,4-dihydroquinazoline-2-carboxylate **(VId)**
- Ethyl-3-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate **(VIe)**
- 3-Phenyl-1*H*-[1,2,4]triazino[6,1-b]quinazoline-2,4,10(3*H*)-trione **(Xa)**
- 3-(4-Chlorophenyl)-1*H*-[1,2,4]triazino[6,1-b]quinazoline-2,4,10(3H)-trione **(Xb)**
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)benzenesulfonamide **(XIIa)**
- *N*-(diaminomethylene)-4-(4,10-dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)benzenesulfonamide **(XIIb)**
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)-N-(pyridin-2-yl)benzenesulfonamide **(XIIc)**
- Ethyl 4-oxo-3-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)-3,4-dihydroquinazoline-2-carboxylate **(XIId)**
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide **(XIIe)**
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-b]quinazolin-3-yl)-*N*-(thiazol-2(3*H*)-ylidene)benzenesulfonamide **(XIIf)**