

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

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TO MY FAMILY WITH LOVE

Contents	Page
List of Abbreviations	I
List of Tables	III
List of Figures	IV
Abstract	VI
1. Introduction	1
1.1 Biological activity of quinazolines and quinazolinone derivatives	1
1.2. Apoptosis and different apoptotic pathways	2
1.2.1. The extrinsic pathway: Fas	3
1.2.2. The intrinsic pathway	4
1.2.3. The final way: Caspases	5
1.3. Regulation of proteins involved in apoptosis	6
1.3.1. P53	6
1.3.2. NFkB (Nuclear Factor Kappa-light-chain-enhancer of activated B cells)	7
1.3.3. The Ubiquitin/Proteosome system	7
1.3.4. PI3K (phosphoinositide-3-phosphate)	7
1.4. Therapeutic agents	8
1.4.1. Agents that target the extrinsic pathway	8
1.4.2. Agents that target the intrinsic pathway	8
1.4.3. Caspases activators	10
1.4.4. Quinazolines as activators of caspases	10
2. Aim and Rationale	16
2.1. lead compound	16
2.2. Design of target compounds	17
2.2.1. Identification of the potential binding features in the lead compound	17
2.2.2. Modification of the lead compound through the known techniques of lead optimization	18
2.2.2.1. Compounds IV , Va,b and Vla-e	18
2.2.2.2. Compounds Xa,b , XIIa-g and XIII	19
2.3. Field alignment study using FieldAlign module	19

2.3.2. Methodology	23
2.3.3. Results and discussion	23
3. Discussion of the Synthetic Part	28
3.1. Synthetic schemes adopted to prepare the target compounds	28
3.1.1. Scheme 1	28
3.1.2. Scheme 2	29
3.2. Synthesis of III , IV , V , and VI derivatives	30
3.2.1. Synthesis of ethyl 4-oxo-4 <i>H</i> -benzo[d][1,3]oxazine-2-carboxylate (III)	30
3.2.2. Synthesis 4-(2-(ethoxycarbonyl)-4-oxoquinazolin-3(4 <i>H</i>)-yl)benzoic acid (IV)	30
3.2.3. Synthesis of ethyl 4-oxo-3-(4-sulfamoylbenzyl)-3,4-dihydroquinazoline-2-carboxylate (Va), and ethyl 4-oxo-3-((4-sulfamoylphenyl)amino)-3,4-dihydroquinazoline-2-carboxylate (Vb)	31
3.2.4. Synthesis of ethyl 4-oxo-3-(4-(<i>N</i> -substitutedsulfamoyl)phenyl)-3,4-dihydroquinazoline-2-carboxylate (Vla-e)	32
3.2.5. Synthesis of ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate (IX)	33
3.2.6. Synthesis of 3-phenyl-1 <i>H</i> -[1,2,4]triazino[6,1- <i>b</i>]quinazoline-2,4,10(3 <i>H</i>)-trione (Xa) and 3-(4-chlorophenyl)-1 <i>H</i> -[1,2,4]triazino[6,1- <i>b</i>]quinazoline-2,4,10(3 <i>H</i>)-trione (Xb)	33
3.2.7. Ethyl (<i>E</i>)-3-((ethoxymethylene)amino)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (XI)	34
3.2.9. Synthesis of 4-((4,10-dioxo-4,10-dihydro-3 <i>H</i> -[1,2,4]triazino[6,1- <i>b</i>]quinazolin-3-yl)amino)benzenesulfonamide (XIII)	34
4. Biological Evaluation	36
4.1. Antiproliferative activity against MCF-7 human breast cancer cell line and HCT-116 human colon cell line	36
4.1.1. Principle	36
4.1.2. Measurement of cytotoxicity using MTT assay	37
4.1.3. Results	39
4.1.4. Discussion of the cytotoxic activity	41
4.1.4.1 MCF-7 IC ₅₀ Results discussion	41
4.1.4.2.HCT-116 IC ₅₀ Results discussion	41

4.2. Apoptotic evaluation of the synthesized compounds	42
4.2.1. Caspases enzyme assay	42
4.2.2. Effects of compounds Va, Vla, Vld, Xa, XIIa and XIId on caspases 3, 8 and 9	43
4.3. Cell cycle flow analysis	43
4.3.1. Principle	43
4.3.2. Cell staining procedures with PI	44
4.3.3. Cellular DNA content and expression of proliferation associated proteins	44
4.3.4. Results of cell cycle analysis	45
4.4.1. Assay protocol	48
4.4.2. Results	49
Experimental of the Synthetic Part	54
References	78
Arabic summary	82

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

List of Abbreviations

- **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

List of Tables

		Page
Table 1	Results of Field Align study for the designed compounds	24
Table 2	Cytotoxic activity of the synthesized compounds	39
Table 3	Effect of compounds Xa, Vla, Vld, Xlla, Vld, Va on caspase 3, 8, and 9	42
Table 4	Cell cycle flow cytometry results	45
Table 5	Results of P53 enzyme assay	50
Table 6	Results of Bax enzyme assay	51
Table 7	Results of Bcl-2 enzyme assay	52

List of Figures

	Page
Figure 1	The extrinsic & intrinsic pathways of apoptosis 3
Figure 2	Targeting Apoptosis Pathways in Cancer Therapy 6
Figure 3	The potential pharmacophoric features in the lead compound 17
Figure 4	Schematic presentation of the design of compounds IV , Va,b , and Vla-e 18
Figure 5	Schematic presentation of the design of compounds Xa,b , XI , and XIa-g 19
Figure 6:	The process followed for each database molecule in FieldAlign 20
Figure 7:	Steps in the creation of field points 21
Figure 8:	Interpretation o field point pattern 22
Figure 9:	The field points of <i>N</i> -methyl acetamide 22
Figure10:	The best aligned pose of compound IV (grey) overlaid with the reference ligand (12) (light green) 24
Figure 11:	The best aligned pose of compound Va (grey) overlaid with the reference ligand (12) (light green) 25
Figure 12:	The best aligned pose of compound Vla (grey) overlaid with the reference ligand (12) (light green) 25
Figure 13:	The best aligned pose of compound Xb (grey) overlaid with the reference ligand (12) (light green) 26
Figure 14:	The best aligned pose of compound XIib (grey) overlaid with the reference ligand (12) (light green) 26
Figure 15:	The best aligned pose of compound XIII (grey) overlaid with the reference ligand (12) (light green) 27
Figure 16:	MTT assay 37
Figure 17:	Images of cells before and after treatment 38

List of Figures

Figure 18:	Cell cycle flow cytometry of untreated HCT-116	46
Figure 19:	Cell cycle flow cytometry of HCT-116 after treatment with XIIa	46
Figure 20:	Cell cycle flow cytometry of HCT-116 after treatment with VId	47
Figure 21:	Cell cycle flow cytometry of HCT-116 after treatment with Xa	47
Figure 22:	The increase in P53 concentration in HCT-116 cells upon treatment with compounds Vlb , Xa , and XIIa	50
Figure 23:	The increase in Bax concentration in HCT-116 cells upon treatment with compounds Vlb , Xa , and XIIa	51
Figure 24:	The decrease in Bcl-2 concentration in HCT-116 cells upon treatment with compounds Vlb , Xa , and XIIa	52
Figure 25:	Illustrative diagram showing the relation between P53, BAX and Bcl-2 in apoptosis.	53

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**, **Vla**, **Vld**, **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 **Vld**, **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 (**Vla**)
- Ethyl 3-(4-(*N*-(diaminomethylene)sulfamoyl)phenyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**Vlb**)
- 4-(4,10-Dioxo-4,10-dihydro-3*H*-[1,2,4]triazino[6,1-*b*]quinazolin-3-yl)-*N*-(pyridin-2-yl)benzenesulfonamide (**Vlc**)
- Ethyl 4-oxo-3-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)-3,4-dihydroquinazoline-2-carboxylate (**Vld**)
- Ethyl-3-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**Vle**)
- 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(3*H*)-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 (**XIle**)
- 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**)