



Faculty of Pharmacy

Design and Synthesis of Benzothiazole Derivatives Having Potential Targeted Anticancer Activity

Thesis

Submitted in Partial Fulfillment of the
PhD's Degree in Pharmaceutical Sciences
(Pharmaceutical Chemistry)

Presented by

Hoda Sobhy Ibrahim Ismail

BSc in Pharmaceutical Sciences (July 2007)

MSc in Pharmaceutical Sciences (Pharmaceutical Chemistry) (2013)

Assistant Lecturer, Pharmaceutical Chemistry

Faculty of Pharmacy, Ain Shams University

Under Supervision of

Prof. Dr. Dalal A. Abou El Ella

Professor of Pharmaceutical Chemistry

Faculty of Pharmacy, Ain Shams University

Assoc. Prof. Dr. Rabah A. Taha

Associate Professor of Pharmaceutical Chemistry &

Head of the Pharmaceutical Chemistry Department,

Faculty of Pharmacy, Ain Shams University

Assoc. Prof. Dr. Deena S. Lasheen

Associate Professor of Pharmaceutical Chemistry

Faculty of Pharmacy, Ain Shams University

Faculty of Pharmacy

Ain Shams University

2020

Acknowledgments

*First and foremost, I would like to thank **ALLAH** Almighty for giving me the strength, knowledge, ability and opportunity to undertake this research study and to persevere and complete it satisfactorily. Without his blessings, this work would not been possible.*

*It's a pleasure to express my sincere appreciation to **Professor Dr. Dalal Abou El Ella**, Professor of Pharmaceutical Chemistry, for her scientific supervision, suggestion of the point of this research, innovative ideas, fruitful opinion, invaluable advices and continuous encouragement. I am indebted to her for her guidance and endless support throughout this work, which allowed this thesis to appear in its final form.*

*I owe my truthful gratitude to **Assoc. Prof. Dr. Rabah Taha**, Associate Professor of Pharmaceutical Chemistry and Deputy Head of the Pharmaceutical Chemistry Department, and **Assoc. Prof. Dr. Deena Lasheen**, Associate Professor of Pharmaceutical Chemistry, for their continuous encouragement and tremendous support. I am heartily grateful to their indispensable opinion, real interest, trust, eminent guidance and untiring help throughout the whole work.*

*Great thanks to **Professor Dr. Khaled A. M. Abouid**, Professor of Pharmaceutical Chemistry for his encouragement, guidance, and motivation to all the department members. I am extremely grateful to his sincere guidance, and tremendous support throughout the whole work.*

*I would also like to thank **Dr. Eman El Awady**, Lecturer of Pharmaceutical Chemistry, for her kindness, friendly cooperation, encouragement, continuous aid, and real support throughout the whole work.*

I acknowledge with thankfulness all my colleagues in the Pharmaceutical Chemistry Department, for their friendly cooperation, support and invaluable aid.

Also I would like to express my gratitude to the National Cancer Institute, Maryland, U.S.A for performing the in-vitro anticancer assay of the synthesized compounds.

Finally, I am profoundly indebted to my parents, my husband, my lovely sons and my sisters for their unconditional love and aid, endless patience, understanding, encouragement and full support all throughout the whole long way.

List of Contents

Title	Page NO.
Acknowledgements	I
List of Tables	V
List of Figures	VI
List of Abbreviations	VIII
Abstract	XI
1. INTRODUCTION	1
1.1. What is Cancer and it's Hallmarks?	1
1.2. Apoptosis: A promising target for anti-cancer therapy.	2
1.2.1. The Mechanistic basis & pathways of apoptosis.	3
1.2.1.1. The Extrinsic apoptotic pathway.	4
1.2.1.2. The Intrinsic apoptotic pathway.	5
1.3. The BCL-2 family proteins as the regulators of the intrinsic pathway.	6
1.3.1. How the BCL-2 family proteins interact to regulate apoptosis.	9
1.4. Targeting apoptosis (Selective anticancer therapeutic strategies).	11
1.4.1. Targeting the extrinsic pathway.	12
1.4.2. Targeting the intrinsic pathway.	13
1.4.2.1. Targeting inhibitors of apoptosis (IAPs).	13
1.4.2.2. Targeting the anti-apoptotic BCL-2 proteins.	19
1.4.2.2.1. Anti-sense oligonucleotides (ASOs).	19
1.4.2.2.2. Peptide and peptidomimetics.	19
1.4.2.2.3. Small Molecule BCL-2 Inhibitors (BH3 mimetics).	20
1.4.2.2.3.1. Pan- BCL-2 Inhibitors.	20
1.4.2.2.3.2. Dual BCL-2/BCL-XL Inhibitors.	22
1.4.2.2.3.3. BCL-2 Selective Inhibitors.	27
1.4.2.2.3.4. BCL-XL Selective Inhibitors.	30
1.4.2.2.3.5. MCL-1 Selective Inhibitors.	32
1.4.2.2.4. Non-canonical targeting of BCL-2 family of proteins.	37
1.4.2.2.4.1. BCL-2 BH4 antagonist.	37
1.4.2.2.4.2. Mcl-1 inhibitor/ degradation inducer.	38
1.4.2.2.4.3. MCL-1 allosteric and covalent inhibitors.	38
1.4.2.2.4.4. BAX agonist or activator.	39
2. RATIONALE AND DESIGN	40
2.1. Insights into BCL-2 protein structure and its BH3 binding groove.	41

2.2. Binding and (SAR) of some reported BCL-2 inhibitors.	43
2.3. Proposed design of novel benzothiazole based BCL-2 inhibitors.	49
2.4. Preliminary evaluation of the designed compounds using molecular modeling.	51
2.4.1. Molecular Field Alignment.	51
2.4.2. Docking study.	53
2.5. Synthetic Schemes of the designed compounds.	56
2.5.1. Scheme 1	56
2.5.2. Scheme 2	58
2.5.3. Scheme 3	59
2.5.3. Scheme 4	60
3. RESULTS AND DISCUSSION	61
3.1. Chemistry.	61
3.1.1. Scheme 1	61
3.1.2. Scheme 2	67
3.1.3. Scheme 3	74
3.1.4. Scheme 4	78
3.2. Biological Evaluation.	80
3.2.1 <i>In vitro</i> BCL-2 inhibitory activity.	80
3.2.1.1. Initial screening at single dose of 10 μ M concentration.	80
3.2.1.2. Measurement of potential enzyme inhibitory activity (IC ₅₀).	83
3.2.2 <i>In vitro</i> anti-proliferative activity against NCI 60-cell line.	84
3.3. Molecular Modelling.	89
3.3.1. Molecular docking study.	89
3.3.1.1. Validation of the docking protocol.	90
3.3.1.2. Results of docking of the target compounds into BCL-2 binding groove.	91
4. CONCLUSION	113
5. EXPERIMENTAL	115
5.1. Chemistry	115
5.1.1. Materials and instrumentation.	115
5.1.2. Synthesis.	116
5.2. Biological evaluation	158
5.2.1. <i>In vitro</i> BCL-2 inhibitory activity.	158
5.2.2. <i>In vitro</i> Anti-proliferative activity against 60 cell line panel.	159
5.3. Molecular Modelling study	161
5.3.1. Molecular docking.	161
5.3.2. Field alignment study.	164
6. SUPPLEMENTARY DATA	165
7. REFERENCES	202

List of Tables

Table NO.	Title	Page No.
Table 1	Prominent Smac mimetics undergoing clinical trials.	17
Table 2	Results of the molecular docking study of some of the designed compounds.	53
Table 3a	Percent inhibition of BCL-2 inhibitory activity achieved by the piperazine derivatives, XIa-i (Series 1) & XVIa-e (Series 2) at 10 μ M.	80
Table 3b	Percent inhibition of BCL-2 inhibitory activity achieved by the benzyloxy derivatives XIIa-f (Series 3) & XVIIa-d (series 4) at 10 μ M.	81
Table 3c	Percent inhibition of BCL-2 inhibitory activity achieved by the phenoxy derivatives XIIIa,b (Series 5) & XVIIIa,b (Series 6) at 10 μ M.	81
Table 3d	Percent inhibition of BCL-2 inhibitory activity achieved by the urea derivatives XXIIa-j (Series 7) at 10 μ M.	82
Table 4	The IC ₅₀ values for compounds (XIIId , XVIIb-d & XXIIIf).	83
Table 5	Cell growth percentage of NCI 60 cancer cell lines exhibited by investigated final compounds (XIf , XIIe , XIIIf , XVIa , XVIId , XVIIa , XVIIb , XVIIc , XVIIId , XVIIIa , XVIIIb , XXIIIf).	86
Table 6	The binding interactions of the designed compounds and their binding energies.	93

List of Figures

Figure NO.	Title	Page No.
Figure 1	Hallmarks of Cancer.	2
Figure 2	Apoptotic morphological changes.	3
Figure 3	The role of the three different types of caspases in apoptosis and inflammation.	4
Figure 4	The Extrinsic and Intrinsic Apoptotic Pathways	6
Figure 5	Classification of BCL-2 family according to conserved domains.	8
Figure 6	Interaction between BCL-2 family members to regulate apoptosis.	10
Figure 7	Binding profiles of BH3-only pro-apoptotic proteins to anti-apoptotic BCL-2 family proteins.	10
Figure 8	Schematic diagram of different targets of the extrinsic and intrinsic pathways of apoptosis.	11
Figure 9	Discovery of Venetoclax (ABT-199 (20)).	29
Figure 10	Structure of BCL-2 protein.	41
Figure 11	Interactions between anti-apoptotic BCL-2 proteins and BH3 ligands as exemplified by the BCL-2 -BAX BH3 complex.	42
Figure 12	Intermolecular interactions between BCL-2 and the BH3 domain of BAX	43
Figure 13	Co-crystal structure of Navitoclax (14) with BCL-2 (PDB: 4LVT) revealed the key interactions with BCL-2 protein.	44
Figure 14	Co-crystal structure of compound (43) with BCL-2 (PDB: 4AQ3); Right: 2D interaction diagram showing	45

	the key interactions with BCL-2.	
Figure 15	Replacement of the carbonyl group of acylsulfonamide inhibitor ABT-737 (13) with unsaturated ring systems.	46
Figure 16	Co-crystal structure of the lead compound (45) with BCL-2 (PDB: 4IEH) overlaid with the co-crystal structure of ABT-737 (13) with BCL-2; (Right): 2D interaction diagram of the lead compound (45) showing the key interactions with BCL-2.	47
Figure 17	The common structural features and the possible key interactions of prominent BCL-2 inhibitors with BCL-2 protein.	48
Figure 18	Proposed design of novel benzothiazole based small molecule BCL-2 inhibitors.	50
Figure 19	Representative designed compounds aligned to lead compound (45) using FieldAlign.	52
Figure 20	Béchamp Reduction, mechanism of metal-catalyzed nitro reduction.	65
Figure 21	Synthesis of 2-aminobenzothiazole by cyclization of arylthioureas.	68
Figure 22	Mechanism of one-pot synthesis of 2-aminobenzothiazole.	68
Figure 23	Copper-catalyzed tandem reaction of 2-haloanilines and isothiocyanates.	69
Figure 24	Mechanistic steps for EDC mediated coupling reaction.	72
Figure 25	Example of mean graph produced from NCI 60 cell line screening program. Mean graph of compound (XVIa) color codes are given for each cell line.	85
Figure 26	The alignment between the co-crystallized bioactive conformer of compound (45) and the pose of the same compound retrieved from docking using C-DOCKER	90

List of Abbreviations

Abbreviation	Full term
AcOH	Acetic acid.
AIF	Apoptosis Inducing Factor.
AML	Acute myeloid leukemia.
Apfa-1	Apoptotic protease activating factor 1.
Apo2L	Apoptosis-inducing ligand 2.
ATP	Adenosine triphosphate.
Bak	BCL-2 homologous antagonist/killer.
Bax	BCL2-associated protein.
BCL-2	Beta-cell chronic lymphocytic leukemia/lymphoma 2.
BH	BCL-2 Homolgy Domain.
BID	BH3-interacting domain death agonist.
BRD-4	Bromodomain-containing 4.
C-DOCKER	CHARMm-based docker.
CHARMm:	Chemistry at HARvard Macromolecular Mechanics.
CLL	Chronic lymphocytic leukemia.
¹³C NMR	Carbon-13 Nuclear Magnetic Resonance.
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide.
DCM	Dichloromethane.
DED	Death effector domain.
DEL	Double expressing lymphoma.
DIABLO	Direct IAP binding protein with low pI.
DISC	Death Inducing Signaling Complex.
DHL	Double hit lymphoma.
DMAP	4-Dimethylaminopyridine.
DMF	Dimethylformamide.

DMSO	Dimethylsulfoxide.
D₂O	Deuterium oxide.
DR	Death receptor
EDC.HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.
EI-MS	Electron Ionization Mass Spectrometry.
EtOAc	Ethyl acetate.
EtOH	Ethanol.
FADD	Fas associated death domain.
FDA	Food and Drug Administration.
FL	Follicular lymphoma.
FPP	Field Point Pattern.
HB	Hydrogen bond.
HBA	Hydrogen bond acceptor.
HBTU	N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate.
HCCs	Hepatocellular carcinoma cells.
¹H NMR	Proton Nuclear Magnetic Resonance.
HOBT	N-Hydroxybenzotriazole.
hrs	Hours.
Hz	Hertz.
IAPs	Inhibitor of apoptosis proteins.
IC₅₀	Half-maximal inhibitory concentration.
K_i	The inhibitor constant.
NHL	Non-Hodgkin lymphoma.
NSCLC	Non-small cell lung cancer.
MCL-1	Myeloid cell leukemia-1.
MeOH	Methanol.
MOMP	Mitochondrial outer membrane permeabilization.
m.p.	Melting Point.
m/z	Mass-to-charge ratio.

M+	Molecular ion.
μM	Micromole.
mmol	Millimole.
MS	Mass spectroscopy.
Mwt	Molecular Weight.
NCI	National Cancer Institute.
NMR	Nuclear Magnetic Resonance.
PDB	Protein Data Bank.
PARAs	Pro-apoptotic receptor agonists.
PPI	Protein-protein interaction.
Ppm	Part per million.
PUMA	P53-upregulated modulator of apoptosis.
RMSD	Root Mean Square Deviation.
rt	Room temperature.
SAR	Structure activity relationship.
SCLC	Small cell lung cancer.
SLL	Small lymphocytic lymphoma.
SMAC	Second mitochondria-derived activator of caspase.
TEA	Triethylamine.
THF	Tetrahydrofuran.
TLC	Thin layer Chromatography.
TMS	Tetramethylsilane.
TNF	Tumor necrosis factor.
TR-FRET	Time-resolved Fluorescence Energy Transfer.
TRAIL	Tumor necrosis factor related apoptosis-inducing ligand.

Abstract

Cancer is a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Normal cells are constantly subjects to signals that dictate whether the cell should divide and differentiate to another cell or die. Apoptosis is a normal physiological process which is very crucial to maintain tissue homeostasis. Dysregulated apoptosis can lead to various diseases as cancer. Thus, evasion of apoptosis stands out as a key hallmark of cancer cells. BCL-2 family of proteins is the key modulator of the mitochondrial apoptotic pathway. Therefore, the balance between the anti-apoptotic (BCL-2, BCL-XL and MCL-1) and pro-apoptotic (BAK, BAX, BAD, PUMA and NOXA) members of this family will govern cell fate. Overexpression of anti-apoptotic BCL-2 members is implicated in the progression of many human cancers as well as the emerging resistance to various anti-cancer agents including targeted therapies. Indeed, inhibition of the anti-apoptotic BCL-2 members by small molecule BH3 mimetics may provide an excellent approach in cancer therapy.

Herein, our research objective is to design, synthesize and biologically evaluate novel inhibitors targeting BCL-2 with a promising anti-cancer activity. The design process aimed to target BCL-2 BH3 binding groove and started by identification of the key interactions between BCL-2 binding groove and a previously reported BCL-2 inhibitors following, rational modification of the lead compound was proposed and a series of novel benzothiazole-based derivatives were suggested and finally molecular modeling studies including field alignment and docking were performed to investigate the predicted binding modes and binding affinities of the designed compounds.

The designed compounds were synthesized, purified and structurally confirmed by different analytical and spectral techniques.

The study involved the synthesis of the following reported intermediates:

- 1) Ethyl 4-fluoro-3-nitrobenzoate (**I**).
- 2) 1-((3-Fluorobenzyl)oxy)-4-nitrobenzene (**IVa**).
- 3) 1-((3-Chlorobenzyl)oxy)-4-nitrobenzene (**IVb**).

- 4) 1-((4-Chlorobenzyl)oxy)-4-nitrobenzene (**IVc**).
- 5) 1-((4-Bromobenzyl)oxy)-4-nitrobenzene (**IVd**).
- 6) 1-((4-Methylbenzyl)oxy)-4-nitrobenzene (**IVe**).
- 7) 4-((3-Fluorobenzyl)oxy) aniline (**Va**).
- 8) 4-((3-Chlorobenzyl)oxy) aniline (**Vb**).
- 9) 4-((4-Chlorobenzyl)oxy) aniline (**Vc**).
- 10) 4-((4-Bromobenzyl)oxy)aniline (**Vd**).
- 11) 4-((4-Methylbenzyl)oxy)aniline (**Ve**).
- 12) 4-Nitro-1-(4-bromophenoxy)benzene (**VIa**).
- 13) 4-Nitro-1-(3-fluoro-4-chlorophenoxy)benzene (**VIb**).
- 14) 4-(4-Bromophenoxy)aniline (**VIIa**).
- 15) 4-(3-Fluoro-4-chloro phenoxy) aniline (**VIIa**).
- 16) Ethyl 2-aminobenzo[*d*]thiazole-6-carboxylate (**VIII**).
- 17) 6-Nitrobenzo[*d*]thiazol-2-amine (**XIX**).
- 18) *N*-(6-Nitrobenzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XX**).
- 19) *N*-(6-Aminobenzo[*d*]thiazol-2-yl) naphthalene-2-sulfonamide (**XXI**).

Also, it comprised the synthesis of the following new intermediates:

- 1) Ethyl 3-nitro-4-(phenethylamino)benzoate (**II**).
- 2) 3-Nitro-4-(phenethylamino)benzoic acid (**III**).
- 3) 1-((4-Trifluoromethylbenzyl)oxy)-4-nitrobenzene (**IVf**).
- 4) 4-((4-Trifluoromethylbenzyl)oxy)aniline (**Vf**).
- 5) Ethyl 2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxylate (**IX**).
- 6) 2-(Naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxylic acid (**X**).
- 7) Ethyl 2-(3-nitro-4-(phenethylamino) benzamido)benzo[*d*]thiazole-6-carboxylate (**XIV**).
- 8) 2-(3-Nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxylic acid (**XV**).

Furthermore, the study involved the synthesis and characterization of the following new final compounds:

- 1) *N*-(6-(4-Phenylpiperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIa**).

- 2) *N*-(6-(4-(2-Fluorophenyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIb**).
- 3) *N*-(6-(4-(2-Methoxyphenyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIc**).
- 4) *N*-(6-(4-(4-Chlorophenyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XId**).
- 5) *N*-(6-(4-(3,4-Dichlorophenyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIe**).
- 6) *N*-(6-(4-Benzhydrylpiperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIf**).
- 7) (*E*)-*N*-(6-(4-Cinnamylpiperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIg**).
- 8) *N*-(6-(4-(Tetrahydrofuran-2-carbonyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIh**).
- 9) *N*-(6-(4-(Benzo[*d*]dioxol-5-ylmethyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XIi**).
- 10) *N*-(4-((3-Fluorobenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIa**).
- 11) *N*-(4-((3-Chlorobenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIb**).
- 12) *N*-(4-((4-Chlorobenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIc**).
- 13) *N*-(4-((4-Bromobenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIId**).
- 14) *N*-(4-((4-Methylbenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIe**).
- 15) *N*-(4-((4-Trifluormethylbenzyl)oxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIIf**).
- 16) *N*-(4-(4-Chloro-3-fluorophenoxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIIa**).
- 17) *N*-(4-(4-Bromophenoxy)phenyl)-2-(naphthalene-2-sulfonamido)benzo[*d*]thiazole-6-carboxamide (**XIIIb**).

- 18) *N*-(6-(4-(2-Methoxyphenyl) piperazine-1-carbonyl) benzo [*d*] thiazol-2-yl)-3-nitro-4-(phenethylamino)benzamide (**XVIa**).
- 19) *N*-(6-(4-(3,4-Dichlorophenyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)-3-nitro-4-(phenethylamino)benzamide (**XVIb**).
- 20) *N*-(6-(4-Benzhydrylpiperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)-3-nitro-(phenethylamino)benzamide (**XVIc**).
- 21) (*E*)-*N*-(6-(4-Cinnamylpiperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)-3-nitro-4-(phenethylamino)benzamide (**XVIId**).
- 22) 3-Nitro-4-(phenethylamino)-*N*-(6-(4-(tetrahydrofuran-2-carbonyl)piperazine-1-carbonyl)benzo[*d*]thiazol-2-yl)benzamide (**XVIe**).
- 23) *N*-(4-((3-Chlorobenzyl)oxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIIa**).
- 24) *N*-(4-((4-Bromobenzyl)oxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIIb**).
- 25) *N*-(4-((4-Methylbenzyl)oxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIIc**).
- 26) *N*-(4-((4-Trifluoromethylbenzyl)oxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIId**).
- 27) *N*-(4-(4-Chloro-3-fluorophenoxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIIa**).
- 28) *N*-(4-(4-Bromophenoxy)phenyl)-2-(3-nitro-4-(phenethylamino)benzamido)benzo[*d*]thiazole-6-carboxamide (**XVIIb**).
- 29) *N*-(6-(3-Phenylureido)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XXIIa**).
- 30) *N*-(6-(3-(3-Chlorophenyl)ureido)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XXIIb**).
- 31) *N*-(6-(3-(3-Bromophenyl)ureido)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XXIIc**).
- 32) *N*-(6-(3-(3-Methoxyphenyl)ureido)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XXIId**).
- 33) *N*-(6-(3-(*m*-tolyl)ureido)benzo[*d*]thiazol-2-yl)naphthalene-2-sulfonamide (**XXIIe**).