

DESIGN AND SYNTHESIS OF BIOACTIVE COMPOUNDS CONTAINING
THIAZOLIDINE AND THIAZOLIDINONE DERIVATIVES

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DEDICATION

This thesis is dedicated to my dear mother and father, Allah have mercy on them and make their abode the highest paradise. My father said: take the weapon of knowledge in your hand. With the help and success of Allah, I fulfilled my father's words. Also, it dedicated to my family and friends.

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ABSTRACT

Thiazolidine and thiazolidinone derivatives are important heterocyclic compounds which have varying biological activity in humans and have been shown to be effective against a variety of pathogens such as antimicrobial, antifungal, antioxidant, anti-inflammatory, anticancer, antidiabetic and anti-HIV. This study consists of three series of heterocyclic thiazolidine and thiazolidinone derivatives which have been synthesized from low to excellent yields. The first step in this study is to prepare a series of 2-(substituted phenyl)-thiazolidine-4-carboxylic acid and its derivatives in one step reaction of L-cysteine with different substituted of benzaldehyde in ethanol and water (3:1) to obtain sixteen compounds (28%-92%). All compounds were evaluated for their antifungal activity against *Candida albicans* and *Aspergillus niger*, using fluconazole as a reference drug. The assay revealed that, compound **172k** showed significant activity (14 mm ZOI, 64 µg/mL IC₅₀ and 15 mm ZOI, > 32 µg/mL IC₅₀) against *C. albicans* and *A. niger*, respectively. The issue of the high adaptability of HIV to the introduced drugs, as the retrovirus can easily mutate its active site has widely spread the interest of scientists to discover new compounds as candidate for the disease. Up to date, there is no commercial drug on HIV that contains thiazolidinone yet and there are a few previous researches that showed the high potential of the derivatives as drug candidates for anti-HIV. Thus, this study proposes the development of a novel HIV-1 RT drug based on the thiazolidinone chemical structure. The docking studies facilitated the identification of crucial interactions between the HIV-1 RT enzyme and thiazolidin-4-one inhibitors. The binding energy for new targeted second series of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethylthiazolidin-4-one and their derivatives (**194-216**) displayed strong binding energy values (binding energy of -10.54 to -9.07 kcal/mol). In addition, nine new compounds for the third series of 2-(4-hydroxy-3-methoxyphenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-one and their derivatives show moderate to strong binding energy values (binding energy of -9.14 to -8.40 kcal/mol). All compounds for the second series (**176-192**) and the third series (**194-216**) gave better activity than the standard drug (*Efavirenz*), which binding energy for the drug was (-8.30 kcal/mol). In the second and third series of the synthesized compounds, several thiazolidinone derivatives were produced by cyclization reaction using vanillin, mercaptoacetic acid and aromatic amine in the presence of toluene to form new 2,3-diaryl-1,3-thiazolidin-4-one derivatives. The second series of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethylthiazolidin-4-one and its derivatives were synthesized by reflux of reaction of the starting materials consisting of the amine and five groups (fluoro, chloro, bromo, nitro and methoxy), attached at *ortho*, *meta* and *para* position of 2-phenylethylamine ring with vanillin and thioacetic acid in the presence of dry toluene to obtain twelve new compounds (24%-89%). In the same way, the third series was synthesized by reacting vanillin, mercaptoacetic acid and 2-aminopyridine and two groups (chloro and methyl) attached at 3-,4-,5- and 6-position of 2-aminopyridine ring to obtain nine new compounds of 2-(4-hydroxy-3-methoxyphenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-ones and its derivatives (45%-75%). All the synthesized compounds were confirmed by FTIR, ¹H NMR, ¹³C NMR and MS.

ABSTRAK

Terbitan tiazolidina dan tiazolidinon ialah sebatian heterosiklik penting yang mempunyai pelbagai aktiviti biologi pada manusia dan telah terbukti berkesan terhadap pelbagai patogen seperti antimikrobial, antikulat, antioksidan, antiradang, antikanser, antidiabetik dan anti-HIV. Kajian ini terdiri daripada tiga siri terbitan heterosiklik tiazolidina dan tiazolidinon yang telah disintesis dalam hasil rendah hingga sangat baik. Langkah pertama dalam kajian ini adalah untuk menyediakan satu siri 2-(terbitan fenil)-tiazolidina-4-asid karboksilik dan terbitannya dalam tindak balas satu langkah L-sisteina dengan terbitan benzaldehid yang berbeza dalam etanol dan air (3:1) bagi mendapatkan enam belas sebatian (28%-92%). Semua sebatian dinilai bagi aktiviti antikulat terhadap *Candida albicans* dan *Aspergillus niger*, menggunakan *fluconazole* sebagai drug rujukan. Ujian tersebut memperlihatkan bahawa, sebatian **172k** menunjukkan aktiviti ketara (14 mm ZOI, 64 µg/mL IC₅₀ dan 15 mm ZOI, > 32 µg/mL IC₅₀) terhadap masing-masing *C. albicans* dan *A. niger*. Isu ketersesuaian HIV yang tinggi terhadap drug yang digunakan dimana retrovirus boleh dengan mudah bermutasi tapak aktifnya telah menyebarkan dengan meluas minat ahli sains untuk menemukan sebatian baharu sebagai calon bagi penyakit tersebut. Sehingga kini, belum ada drug komersial HIV yang mengandungi tiazolidinon dan terdapat beberapa kajian terdahulu menunjukkan potensi yang tinggi bagi terbitan tersebut sebagai calon drug untuk anti-HIV. Oleh itu kajian ini mencadangkan pembangunan drug HIV-1 RT baharu berdasarkan struktur kimia tiazolidinon. Kajian dok memudahkan pengenalanpastian interaksi penting antara enzim HIV-1 RT dan perencat tiazolidinon. Tenaga pengikat untuk sebatian sasaran baharu siri kedua 2-(4-hidroksi-3-metoksifenil)-3-fenetil-tiazolidin-4-on dan terbitannya (**194-216**) memaparkan nilai tenaga pengikat yang kuat (tenaga pengikat = -10.54 hingga -9.07 kcal/mol), dan sembilan sebatian baharu 2-(4-hidroksi-3-metoksi-fenil)-3-(piridin-2-yl)-1,3-tiazolidin-4-on dan derivatifnya menunjukkan nilai tenaga pengikat sederhana hingga kuat (tenaga pengikat = -9.14 hingga -8.40 kcal/mol) untuk derivatif siri ketiga. Semua sebatian bagi siri kedua (**176-192**) dan siri ketiga (**194-216**) memberikan aktiviti yang lebih baik daripada drug rujukan (Efavirenz), di mana tenaga pengikat untuk ubat adalah (-8.30 kcal/mol). Projek bagi siri kedua dan ketiga, beberapa terbitan tiazolidinon dihasilkan melalui tindak balas pensiklikan menggunakan vanilin, asid merkaptoasetik dan amina aromatik dengan kehadiran toluena untuk membentuk terbitan baharu 2,3-diaril-1,3-tiazolidin-4-on. Siri kedua 2-(4-hidroksi-3-metoksifenil)-3-fenetil-tiazolidin-4-on dan terbitannya telah disintesis melalui refluks bagi tindak balas bahan permulaan yang terdiri daripada amina dan lima kumpulan (fluoro, kloro, bromo, nitro dan metoksi) terikat pada kedudukan orto, para dan meta bagi gelang 2-feniletilamina dengan vanilin dan asid tio-asitik dengan kehadiran toluena kering untuk mendapatkan dua belas sebatian baru (24%-89%). Dengan cara yang sama, siri ketiga telah disintesis dengan tindak balas vanilin, asid merkaptoasetik dan 2-aminopiridina dan dua kumpulan (kloro dan metil) yang disambungkan pada kedudukan 3,4,5 dan 6 pada gelang 2-aminopiridina untuk mendapatkan sembilan sebatian baharu 2-(4-hidroksi-3-metoksifenil)-3-(piridin-2-yl)-1,3-tiazolidin-4-on dan terbitannya (45%-75%). Semua sebatian yang disintesis telah disahkan dengan FTIR, ¹H RMN dan ¹³C RMN dan MS.

TABLE OF CONTENTS

	TITLE	PAGE
	DECLARATION	iii
	DEDICATION	iv
	ACKNOWLEDGEMENT	v
	ABSTRACT	vi
	ABSTRAK	vii
	TABLE OF CONTENTS	viii
	LIST OF TABLES	xi
	LIST OF SCHEMES	xiv
	LIST OF FIGURES	xix
	LIST OF ABBREVIATIONS	xxii
	LIST OF APPENDICES	xxiv
CHAPTER 1	INTRODUCTION	1
	1.1 Background of research	1
	1.2 Problem statement	6
	1.3 Objectives of research	7
	1.4 Scope of research	7
	1.5 Significance of research	8
CHAPTER 2	LITERATURE REVIEW	11
	2.1 Introduction	11
	2.2 Synthesis of thiazolidine	13
	2.2.1 Synthesis of thiazolidine carboxylic acid derivatives	14
	2.3 Bioactivities of thiazolidine	15
	2.3.1 Antifungal of thiazolidine derivatives	15
	2.3.2 Antibacterial of thiazolidine derivatives	16
	2.3.3 Antiviral of thiazolidine derivatives	18

2.3.4	Antioxidant of thiazolidine derivatives	19
2.4	Molecular docking	25
2.5	Synthesis of thiazolidinone	28
2.6	Biological activities of thiazolidinone	36
2.6.1	Anti-HIV of thiazolidinone	36
2.6.2	Other bioactivities of thiazolidinone	60
CHAPTER 3	RESULTS AND DISCUSSION	69
3.1	The synthesis of thiazolidine derivatives	69
3.2	General reaction of proposed mechanism for the synthesis of series one compounds (172a-172p)	74
3.3	Synthesis of thiazolidine derivatives	75
3.4	General reaction of proposed mechanism for the synthesis of thiazolidinone derivatives	101
3.4.1	General synthetic procedure for compounds thiazolidine-4-one (176-192) Series 2	102
3.4.2	General synthetic procedure for compounds 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl-thiazolidin-4-one and its derivatives (194-216)	116
3.5	Antifungal biological activity of thiazolidine carboxylic acid (172a-p)	135
3.6	Molecular docking simulation	137
3.6.1	Molecular docking for compounds thiazolidine-4-one (176-192)	138
3.6.2	Molecular docking for compounds thiazolidine-4-one (194-216)	150
CHAPTER 4	EXPERIMENTAL	165
4.1	Material and instrumentation	165
4.2	Reagents and chemicals	165
4.3	Synthesis of heterocyclic compounds	166

4.3.1	General procedure for synthesis of heterocyclic thiazolidine-4-carboxylic acid derivatives (172a-p)	166
4.3.2	General procedure for synthesis of thiazolidin-4-one (176-192)	175
4.3.3	General procedure for synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194-216)	178
4.4	Bioactivity evaluation of compounds (172a-p) against antifungal	185
4.4.1	Antifungal activity of thiazolidine derivatives (172a-p)	185
4.4.2	Antifungal screening	185
4.5	Molecular docking Study	186
CHAPTER 5	CONCLUSION AND RECOMMENDATIONS	189
5.1	Conclusion	189
5.2	Recommendations	191
REFERENCES		192
PUBLICATION		208
APPENDICES	Appendix 1-96	209
	Appendix 97 -124 (e-thesis)	

LIST OF TABLES

TABLE NO	TITLE	PAGE
Table 2.1	In vitro fungicidal activities of compounds (9a-e) against 4 kinds of fungi	16
Table 2.2	Antimicrobial activity of compounds (11 and 13)	17
Table 2.3	The structures and urease inhibitory activity of some compounds (18-23)	19
Table 2.4	Inhibitory effects of kojic acid, Resveratrol and compound 25 on tyrosinase activity	21
Table 2.5	Some bioactive thiazolidine derivatives	21
Table 2.6	Recent data show the spread of HIV-1 infection in the world in 2019	23
Table 2.7	Anti-HIV activity and cytotoxicity of compounds (72a-e)	39
Table 2.8	Anti-HIV-1 activity and cytotoxicity in MT-4 cells of compounds (74a-f)	40
Table 2.9	<i>In vitro</i> anti-HIV-1 activity of the tested compounds (75a-g)	41
Table 2.10	Anti-HIV-1, anti-HIV-2 activity and cytotoxicity of titled compounds	42
Table 2.11	Anti-HIV-1 activity, cytotoxicity, and selectivity index in MT-4 cells	44
Table 2.12	Anti-HIV-1 activity and selectivity index in MT-4 cells (97-104)	46
Table 2.13	HIV-RT kit assay for compounds (105a-h and 106a-h)	47
Table 2.14	Anti-HIV-1 and -HIV-2 activity of thiazolidinones (108-111)	48
Table 2.15	Anti-HIV-1 activity, cytotoxicity in MT-4 cells for compounds (114-119)	50
Table 2.16	Anti-HIV-1 activity, cytotoxicity in MT-4 cells of compounds (120-123)	51
Table 2.17	Anti-HIV-1 activity, cytotoxicity, selectivity index, in MT-4 cells, and HIV-1RT inhibition by compounds (124-126)	52
Table 2.18	Anti-HIV-1 activity, cytotoxicity for compounds (127-130)	53
Table 2.19	HIV-1 RT Inhibitory action (131-135)	54

Table 2.20	Anti-HIV1 activity of the compounds against HIV-1 drug resistant	56
Table 2.21	Anti-HIV-1, anti-HIV-2 activity and cytotoxicity of compounds (148a–d) and (149a–d) in MT-4 cell culture	57
Table 2.22	Some studies for the most potent inhibitors of HIV-1 activity	58
Table 2.23	Antibacterial activity of the compounds (152a, 152d, 152h)	61
Table 2.24	In vitro anti-proliferative activity (GI50) of compound (160a-j) against human breast cancer cell line (MCF-7)	63
Table 2.25	Anti-cancer activity of 164a-g against MCF-7 and A549 cancer cell lines	64
Table 2.26	Ferric reducing antioxidant power (EC ₅₀ , mg/ mL) of compounds (169a-j)	66
Table 2.27	Examples of some bioactive thiazolidinone derivatives	67
Table 3.1	Derivatives of 2-phenyl thiazolidine-4-carboxylic acid (172a-p)	71
Table 3.2	Summarized IR spectrum of compounds (172a, 172d, 172e and 172 f)	83
Table 3.3	Summarized ¹ H NMR: Ratio of Major (Ma) and Minor (Mi)	83
Table 3.4	Summarized ¹³ C NMR of (172a, 172d, 172e, 172f)	84
Table 3.5	Summarized IR spectrum of compounds (172b, 172g, and 172 h)	87
Table 3.6	Summarized ¹ H NMR: Ratio of Major (Ma) and Minor (Mi)	87
Table 3.7	Summarized ¹³ C NMR of compounds (172b, 172g, and 172h)	88
Table 3.8	Summarized IR spectrum of compounds (172c, 172i, 172j)	91
Table 3.9	Summarized ¹ H NMR of compounds (172c, 172i, 17j)	91
Table 3.10	Summarized ¹³ C NMR of compounds (172c, 172i, 172j)	91
Table 3.11	Summarized IR spectrum of (172k, 172l, 172m)	96
Table 3.12	Summarized ¹ H NMR of (172k, 172l, and 172m)	96
Table 3.13	Summarized ¹³ C NMR of (172k, 172l, and 172m)	96
Table 3.14	Summarized IR spectrum of (172n, 172o, 172p)	100
Table 3.15	Summarized ¹ H NMR of (172n, 172o, 172p)	101
Table 3.16	Summarized ¹³ C NMR of (172n, 172o, 172p)	101
Table 3.17	Results of antifungal activity of the synthesized compounds (172a-p)	136
Table 3.18	Free binding energy values from docking results compounds (176-216)	139

Table 3.19	Illustration the interactions of compounds (176-192) and Efavirenz in the active site of HIV (PDB ID: 5CYQ)	140
Table 3.20	Illustration the interactions of compounds (194-216) and Efavirenz in the active site of HIV (PDB ID: 5CYQ)	151

LIST OF SCHEMES

SCHEME	TITLE	PAGE
Scheme 2.1	Synthesis of 2-substituted-2-phenylthiazolidine-4-carboxylic acid and thiazolidine-4-carboxylic acid derived from L-cysteine	13
Scheme 2.2	Synthesis of (4 <i>S</i>)-2-(4-hydroxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid	14
Scheme 2.3	Synthesis of quinoxaline thiazolidine-amino acid (8a-c)	15
Scheme 2.4	Synthesis of thiazolidine-4-carboxylic acids (9a-e)	16
Scheme 2.5	Synthesis of 3-(<i>tert</i> -butoxy carbonyl)-2-(5-fluoro-2-hydroxyphenyl)thiazolidine-4-carboxylic acid (11 and 13)	17
Scheme 2.6	Synthesis of thiazolidine derivatives (14a-g-17a-g)	18
Scheme 2.7	Synthesis of 2,4-dimethoxy phenyl thiazolidine-4-carboxylic acid (25)	20
Scheme 2.8	Mechanism formation of 1,3-thiazolidin-4-one	29
Scheme 2.9	Synthesis of 2,3-diaryl-1,3-thiazolidine-4-ones (27a-f)	30
Scheme 2.10	Synthesis route of 3-(3-morpholinopropyl) trifluoromethyl phenyl thiazolidine-4-one (30)	30
Scheme 2.11	Synthesis of 2,3-diaryl-1,3-thiazolidine-4-ones (32a-c)	30
Scheme 2.12	Synthesis route for thiazolidine-4-one compound (38a-d)	31
Scheme 2.13	Synthetic pathway for the compounds (42, 45 and 49)	32
Scheme 2.14	Synthesis of thiazolidine-4-one derivatives (56-58)	33
Scheme 2.15	Synthesis of the 2, 3-diaryl-1, 3-thiazolidin-4-ones (60a-e)	34
Scheme 2.16	Synthesis of 5-bromo-2-oxoindolin-(3-ylidene)hydrazineyl-methylene-4-thiazolidinone (63)	34
Scheme 2.17	General synthetic procedure for benzothiazolyl-4-thiazolidinones (65a-e)	35
Scheme 2.18	Synthesis of <i>N</i> -[(4-oxo-2-substituted aryl-1,3-thiazolidine)-acetamidyl]5-nitro-indazoles (70a-l)	36

Scheme 2.19	Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one (72a-e)	38
Scheme 2.20	Synthesis of 2,3-diaryl substituted 4-thiazolidinone derivatives (74a-f)	39
Scheme 2.21	Synthesized of 2,3-diaryl-1,3-thiazolidin-4-thione and dione	41
Scheme 2.22	Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one (79-83)	41
Scheme 2.23	Synthesis of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-one (84-88)	43
Scheme 2.24	Synthesis of 2,3-diaryl-1,3-thiazolidin-4-one (89, 90)	44
Scheme 2.25	Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one (91-96)	45
Scheme 2.26	Synthesis of 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidinone (97-104)	45
Scheme 2.27	Synthesis of 2-(2,6-dihalophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one (105a-h and 106a-h)	47
Scheme 2.28	Synthesis of 2-adamantyl-substituted thiazolidinone (108-111)	48
Scheme 2.29	Synthesis of 2-aryl-3-heteroaryl-2-ylmethyl-1,3-thiazolidinone	49
Scheme 2.30	Synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (114- 119)	50
Scheme 2.31	Synthesis of 2,3-diaryl/heteroaryl-1,3-thiazolidinone (120-123)	50
Scheme 2.32	Synthesis of 2,3-diaryl-1,3-thiazolidin-4-one (124-126)	51
Scheme 2.33	Synthesis of 2,3-diaryl/heteroaryl-1,3-thiazolidinone (127-130)	52
Scheme 2.34	General synthetic procedure for benzothiazolyl-thiazolidinone	53
Scheme 2.35	Synthesis of thiazolidin-4-one compounds (136-140)	55
Scheme 2.36	Synthesis of compounds 1,3-thiazolidine-4-one derivatives containing 3-(trifluoro-methyl)phenyl (147a-f)	56
Scheme 2.37	Synthesis of 1-aryl-3-methyl-thiazole-(3,4)-benzimidazoles (148a-d and 149a-d)	57
Scheme 2.38	Synthesis of 5-arylidene-3-substituted-1,3-thiazolidine-2,4-dione (152a-l)	60
Scheme 2.39	Synthesis of arylidene incorporated 4-thiazolidinone (157a-g)	62
Scheme 2.40	Synthesis of 5-(4-(5-phenyl-1,3,4-oxadiazol-2-yl)-benzylidene)thiazolidine-2,4-dione (160a -j)	63
Scheme 2.41	Synthesis of 5-substituted-thiazolidinone derivatives (164a-g)	64

Scheme 2.42	Synthesis of thiazolidine-2,4-dione derivatives (165a-g)	65
Scheme 2.43	Synthesis of thiazolidine-4-one derivatives with arginine moiety (169a-j)	66
Scheme 3.1	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-2-substituted phenyl thiazolidine-4-carboxylic acid (172g-p)	69
Scheme 3.2	Synthesis of <i>N</i> -(substituted benzoyl)-2-(substituted phenyl)-thiazolidine-4-carboxylic acid	74
Scheme 3.3	Proposed mechanism intramolecular cyclization of 2-(substituted phenyl)-thiazolidine-4-carboxylic acid (172a-p)	74
Scheme 3.4	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-2-phenyl thiazolidine-4-carboxylic acid (172a)	75
Scheme 3.5	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-2-hydroxyphenyl thiazolidine-4 carboxylic acid (172b)	76
Scheme 3.6	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-4-methoxyphenyl thiazolidine-4-carboxylic acid (172c)	77
Scheme 3.7	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-4-hydroxy-3-methoxy phenyl thiazolidine-4 carboxylic acid (172d)	79
Scheme 3.8	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-3-hydroxy-4-methoxyphenyl thiazolidine-4-carboxylic acid (172e)	80
Scheme 3.9	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-4-bromophenyl thiazolidine-4-carboxylic acid (172f)	82
Scheme 3.10	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-3-hydroxyphenyl thiazolidine-4-carboxylic acid (172g)	84
Scheme 3.11	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-4-hydroxyphenyl thiazolidine-4-carboxylic acid (172h)	86
Scheme 3.12	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-3-methoxyphenyl thiazolidine-4-carboxylic acid (172i)	88
Scheme 3.13	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-2-methoxyphenyl thiazolidine-4-carboxylic acid (172j)	89
Scheme 3.14	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-4-nitrophenyl thiazolidine-4-carboxylic acid (172k)	92
Scheme 3.15	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-3-nitrophenyl thiazolidine-4-carboxylic acid (172l)	93
Scheme 3.16	Synthesis of (<i>2R,4R</i> and <i>2S,4R</i>)-2-nitrophenyl thiazolidine-4-carboxylic acid (172m)	94

Scheme 3.17	Synthesis of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-chlorophenyl)thiazolidine-4-carboxylic acid (172n)	97
Scheme 3.18	Synthesis of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-3-chlorophenyl thiazolidine-4-carboxylic acid (172o)	98
Scheme 3.19	Synthesis of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-chlorophenyl thiazolidine-4-carboxylic acid (172p)	99
Scheme 3.20	General reaction of proposed mechanism of synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones and their derivatives (176-216)	102
Scheme 3.21	Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-ones (Series 2)	103
Scheme 3.22	Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-ones (176)	103
Scheme 3.23	Synthesis of 3-(6-chloropyridine-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (178)	105
Scheme 3.24	Synthesis of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (180)	107
Scheme 3.25	Synthesis of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4 one (182)	108
Scheme 3.26	Synthesis of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	109
Scheme 3.27	Synthesis of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	110
Scheme 3.28	Synthesis of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	112
Scheme 3.29	Synthesis of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	113
Scheme 3.30	Synthesis of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (192)	115
Scheme 3.31	2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl-thiazolidin-4-one and its derivatives (194-216)	116
Scheme 3.32	Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl-thiazolidine-4-one (194)	117

Scheme 3.33	Synthesis of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (196)	118
Scheme 3.34	Synthesis of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidine-4-one (198)	120
Scheme 3.35	Synthesis of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (200)	122
Scheme 3.36	Synthesis of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	123
Scheme 3.37	Synthesis of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	125
Scheme 3.38	Synthesis of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (206)	126
Scheme 3.39	Synthesis of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (208)	128
Scheme 3.40	Synthesis of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (210)	129
Scheme 3.41	Synthesis of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (212)	131
Scheme 3.42	Synthesis of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (214)	132
Scheme 3.43	Synthesis of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (216)	134

LIST OF FIGURES

FIGURE	TITLE	PAGE
Figure 1.1	Chemical structures of some drugs of antifungal inhibitor	2
Figure 1.2	Chemical structures of some HIV-1 RT inhibitor drugs	3
Figure 1.3	Structure of thiazolidine and thiazolidinone	4
Figure 1.4	2-(4-bromophenyl)thiazolidine-4-carboxylic acid	4
Figure 1.5	2-Aryl-3-heteroaryl-1,3-thiazolidin-4-one	5
Figure 2.1	Penicillin drug contain the thiazolidine ring	12
Figure 2.2	2 and 4 hydroxyl of thiazolidine derivatives	20
Figure 2.3	Global prevalence of HIV-1infection in 2019	22
Figure 2.4	The structure of the HIV	24
Figure 2.5	The onset AIDS as indicated by T-cell count	24
Figure 2.6	HIV Replication Cycle (National Institutes of Health, 2018)	25
Figure 2.7	Three-dimensional protein structure of HIV-1 RT	27
Figure 2.8	Docking flow chart overview	28
Figure 2.9	Chemical structures of some NNRTIs	37
Figure 2.10	Four 4-thiazolidinone derivatives (141-144)	55
Figure 3.1	¹ H NMR spectrum of compound (172n)	73
Figure 3.2	COSY spectrum of thiazolidinone derivatives (198)	122
Figure 3.3	Structural activity relationships for all compounds of series 2 (174-216) and 3 (194-216)	138
Figure 3.4	Two-dimensional representation of interactions of compound Efavirenz in the active site of HIV-1RT (PDB ID: 5CYQ)	141
Figure 3.5	Two-dimensional representation of interactions of compound 176 in the active site of HIV-1RT (PDB ID: 5CYQ)	142

Figure 3.6	Two-dimensional representation of interactions of compound (178) in the active site of HIV-1RT (PBD ID: 5CYQ)	143
Figure 3.7	Two-dimensional representation of interactions of compound (180) in the active site of HIV-1RT (PBD ID: 5CYQ)	144
Figure 3.8	Two-dimensional representation of interactions of compound (182) in the active site of HIV-1RT (PBD ID: 5CYQ)	145
Figure 3.9	Two-dimensional representation of interactions of compound (184) in the active site of HIV-1RT (PBD ID: 5CYQ)	146
Figure 3.10	Two-dimensional representation of interactions of compound (186) in the active site of HIV-1RT (PBD ID: 5CYQ)	147
Figure 3.11	Two-dimensional representation of interactions of compound (188) in the active site of HIV-1RT (PBD ID: 5CYQ)	148
Figure 3.12	Two-dimensional representation of interactions of compound (190) in the active site of HIV-1RT (PBD ID: 5CYQ)	149
Figure 3.13	Two-dimensional representation of interactions of compound (192) in the active site of HIV-1RT (PBD ID: 5CYQ)	150
Figure 3.14	Two-dimensional representation of interactions of compound (194) in the active site of HIV-1RT (PBD ID: 5CYQ)	153
Figure 3.15	Two-dimensional representation of interactions of compound (196) in the active site of HIV-1RT (PBD ID: 5CYQ)	154
Figure 3.16	Two-dimensional representation of interactions of compound (198) in the active site of HIV-1RT (PBD ID: 5CYQ)	155
Figure 3.17	Two-dimensional representation of interactions of compound (200) in the active site of HIV-1RT (PBD ID: 5CYQ)	156
Figure 3.18	Two-dimensional representation of interactions of compound (202) in the active site of HIV-1RT (PBD ID: 5CYQ)	157
Figure 3.19	Two-dimensional representation of interactions of compound (204) in the active site of HIV-1RT (PBD ID: 5CYQ)	158
Figure 3.20	Two-dimensional representation of interactions of compound (206) in the active site of HIV-1RT (PBD ID: 5CYQ)	159
Figure 3.21	Two-dimensional representation of interactions of compound (208) in the active site of HIV-1RT (PBD ID: 5CYQ)	160
Figure 3.22	Two-dimensional representation of interactions of compound (210) in the active site of HIV-1RT (PBD ID: 5CYQ)	161

Figure 3.23	Two-dimensional representation of interactions of compound (212) in the active site of HIV-1RT (PBD ID: 5CYQ)	162
Figure 3.24	Two-dimensional representation of interactions of compound (214) in the active site of HIV-1RT (PBD ID: 5CYQ)	163
Figure 3.25	Two-dimensional representation of interactions of compound (216) in the active site of HIV-1RT (PBD ID: 5CYQ)	164

LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
Å	Angstrom
C	Carbon
¹³ C NMR	Carbon-13 Nuclear Magnetic Resonance
CAS	Catalytic active site
δ	Chemical shift
CHCl ₃	Chloroform
CD4	Cluster of differentiation 4
<i>J</i>	Coupling constant
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
CDCl ₃	Deuterated chloroform
DMSO	Dimethyl sulfoxide
d	Doublet
dd	Doublet of doublets
Ddi	Didanosine
EFV	Efavirenz
ELI-MS	Electrospray ionization mass spectrometry
EtOH	Ethanol
EtOAc	Ethyl acetate
EMA	European medicine agency
Et ₃ N	Triethylamine
FDA	Food and drug administration
FTIR	Fourier transform infrared spectroscopy
H	Hydrogen
HIV	Human immunodeficiency virus
¹ H NMR	Proton Nuclear Magnetic Resonance
HCl	Hydrochloric acid
IR	Infrared
IC ₅₀	Half-maximal inhibition concentration

PPG	Poly propylene glycol
KBr	Potassium bromide
v_{\max}	Maximum absorbance
m.p	Melting point
MeOH	Methanol
mg	Milligram
mL	Millilitre
μL	Microlitre
$\mu\text{g/mL}$	Microgram per millilitre
MIC	Minimum inhibitory concentration
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
m	Multiplet
nM	Nanomolar
NaOAc	Sodium acetate
NaHCO ₃	Sodium bicarbonate
Na ₂ SO ₄	Sodium sulphate
NMR	Nuclear magnetic resonance
ppm	Part per million
π	Pi
Q	Quartet
R_f	Retention factor
S	Singlet
SAR	Structure activity relationship
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TBZ	Thiazole-benzimidazole
UCSF	University of california, san francisco
UV	Ultraviolet
WHO	World Health Organization
ZOI	Zone of inhibition

LIST OF APPENDICES

APPENDIX	TITLE	PAGE
Appendix 1	IR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-phenylthiazolidine-4-carboxylic acid (172a)	210
Appendix 2a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-phenylthiazolidine-4-carboxylic acid (172a)	211
Appendix 2b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-phenylthiazolidine-4-carboxylic acid (172a)	212
Appendix 3	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-phenyl thiazolidine-4-carboxylic acid (172a)	213
Appendix 4	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-hydroxyphenyl)thiazolidine-4-carboxylic acid (172b)	214
Appendix 5a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-phenyl thiazolidine-4-carboxylic acid (172a)	215
Appendix 5b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-hydroxyphenyl) thiazolidine-4-carboxylic acid (172b)	216
Appendix 6	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-hydroxyphenyl)thiazolidine-4-carboxylic acid (172b)	217
Appendix 7	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-methoxyphenyl)thiazolidine-4-carboxylic acid (172c)	218
Appendix 8a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-methoxyphenyl)thiazolidine-4-carboxylic acid (172c)	219
Appendix 8b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-methoxyphenyl) thiazolidine-4-carboxylic acid (172c).	220
Appendix 9	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-methoxyphenyl)thiazolidine-4-carboxylic acid (172c)	221
Appendix 10	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxy-3-methoxyphenyl)-thiazolidine-4-carboxylic acid (172d)	222
Appendix 11a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxy-3-methoxyphenyl)-thiazolidine-4-carboxylic acid (172d)	223

Appendix 11b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid (172d)	224
Appendix 12	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid (172d)	225
Appendix 13	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxy-4-methoxyphenyl) thiazolidine-4-carboxylic acid (172e)	226
Appendix 14a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxy-4-methoxyphenyl) thiazolidine-4-carboxylic acid (172e)	227
Appendix 14b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxy-4-methoxyphenyl) thiazolidine-4-carboxylic acid (172e)	228
Appendix 15	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxy-4-methoxyphenyl) thiazolidine-4-carboxylic acid (172e)	229
Appendix 16	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-bromophenyl) thiazolidine-4-carboxylic acid (172f)	230
Appendix 17a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-bromophenyl) thiazolidine-4-carboxylic acid (172f)	231
Appendix 17b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-bromophenyl) thiazolidine-4-carboxylic acid (172f)	232
Appendix 18	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-bromophenyl) thiazolidine-4-carboxylic acid (172f)	233
Appendix 19	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxyphenyl) thiazolidine-4-carboxylic acid (172g)	234
Appendix 20a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxyphenyl) thiazolidine-4-carboxylic acid (172g)	235
Appendix 2b'	Expansion ¹ H NMR spectrum of 2-(3-hydroxyphenyl) thiazolidine-4-carboxylic acid (172g)	236
Appendix 21	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-hydroxyphenyl) thiazolidine-4-carboxylic acid (172g)	237
Appendix 22	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxyphenyl) thiazolidine-4-carboxylic acid (172h)	238
Appendix 23a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxyphenyl) thiazolidine-4-carboxylic acid (172h)	239
Appendix 23b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-hydroxyphenyl) thiazolidine-4-carboxylic acid (172h)	240

Appendix 24	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)- 2-(4-hydroxyphenyl)thiazolidine-4-carboxylic acid (172h)	241
Appendix 25	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-methoxyphenyl)thiazolidine-4-carboxylic acid (173i)	242
Appendix 26a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-methoxyphenyl)thiazolidine-4-carboxylic acid (172i)	243
Appendix 26b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-methoxyphenyl) thiazolidine-4-carboxylic acid (172i)	244
Appendix 27	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-methoxyphenyl)thiazolidine-4-carboxylic acid (172i)	245
Appendix 28	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-methoxyphenyl)thiazolidine-4-carboxylic acid (172j)	246
Appendix 29a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-methoxyphenyl)thiazolidine-4-carboxylic acid (172j)	247
Appendix 29b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-methoxyphenyl) thiazolidine-4-carboxylic acid (172j)	248
Appendix 30	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-methoxyphenyl)thiazolidine-4-carboxylic acid (172j)	249
Appendix 31	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-nitrophenyl)thiazolidine-4-carboxylic acid (172k)	250
Appendix 32a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(4-nitrophenyl)thiazolidine-4-carboxylic acid (172k)	251
Appendix 32b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(4-nitrophenyl)thiazolidine-4-carboxylic acid (172k)	252
Appendix 33	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(4-nitrophenyl)thiazolidine-4-carboxylic acid (172k)	253
Appendix 34	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-nitrophenyl)thiazolidine-4-carboxylic acid (172l)	254
Appendix 35a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(3-nitrophenyl)thiazolidine-4-carboxylic acid (172l)	255
Appendix 35b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(3-nitrophenyl)thiazolidine-4-carboxylic acid (172l)	256
Appendix 36	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(3-nitrophenyl)thiazolidine-4-carboxylic acid (172l)	257

Appendix 37	FT-IR(KBr) spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(2-nitrophenyl)thiazolidine-4-carboxylic acid (172m)	258
Appendix 38a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(2-nitrophenyl)thiazolidine-4-carboxylic acid (172m)	259
Appendix 38b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(2-nitrophenyl)thiazolidine-4-carboxylic acid (172m)	260
Appendix 39	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(2-nitrophenyl)thiazolidine-4-carboxylic acid (172m)	261
Appendix 40	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-chlorophenyl)thiazolidine-4-carboxylic acid (172n).	262
Appendix 41a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(4-chlorophenyl)thiazolidine-4-carboxylic acid (172n)	263
Appendix 41b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-chlorophenyl)thiazolidine-4-carboxylic acid (172n)	264
Appendix 42	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(4-chlorophenyl)thiazolidine-4-carboxylic acid (172n)	265
Appendix 43	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2(3-chlorophenyl)thiazolidine-4-carboxylic acid (172o)	266
Appendix 44a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-chlorophenyl)thiazolidine-4-carboxylic acid (172o)	267
Appendix 44b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-chlorophenyl)thiazolidine-4-carboxylic acid (172o)	268
Appendix 45	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(3-chlorophenyl)thiazolidine-4-carboxylic acid (172o)	269
Appendix 46	ATR-FTIR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-chlorophenyl)thiazolidine-4-carboxylic acid (172p)	270
Appendix 47a	¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-chlorophenyl)thiazolidine-4-carboxylic acid (172p)	271
Appendix 47b	Expansion ¹ H NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-chlorophenyl)thiazolidine-4-carboxylic acid (172p)	272
Appendix 48	¹³ C NMR spectrum of (2 <i>R</i> ,4 <i>R</i> and 2 <i>S</i> ,4 <i>R</i>)-2-(2-chlorophenyl)thiazolidine-4-carboxylic acid (172p)	273
Appendix 49	IR spectrum of 2-(4-hydroxy-3-methoxy-phenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-ones (176)	274

Appendix 50a	¹ H NMR spectrum of 2-(4-hydroxy-3-methoxy-phenyl)-3-(pyridin-2-yl)-1,3- thiazolidin-4-ones (176)	275
Appendix 50b	Expansion ¹ H NMR spectrum 2-(4-hydroxy-3-methoxy-phenyl)-3-(pyridin-2-yl)-1,3- thiazolidin-4-ones (176)	276
Appendix 50c	Expansion ¹ H NMR spectrum 2-(4-hydroxy-3-methoxy-phenyl)-3-(pyridin-2-yl)-1,3- thiazolidin-4-ones (176)	277
Appendix 51	¹³ C NMR spectrum of 2-(4-hydroxy-3-methoxy-phenyl)-3-(pyridin-2-yl)-1,3- thiazolidin-4-ones (176)	278
Appendix 52	IR spectrum of 3-(6-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxy-phenyl) thiazolidin-4-one (178)	279
Appendix 53a	¹ H NMR spectrum of 3-(6-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (178)	280
Appendix 53b	Expansion ¹ H NMR spectrum of 3-(6-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxyphenyl) thiazolidin-4-one (178)	281
Appendix 53c	Expansion ¹ H NMR spectrum of 3-(6-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxyphenyl) thiazolidin-4-one (178)	282
Appendix 54	¹³ C NMR spectrum of 3-(6-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (178)	283
Appendix 55	IR spectrum of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxy-phenyl) thiazolidin-4-one (180)	284
Appendix 56a	¹ H NMR spectrum of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (180)	285
Appendix 56b	Expansion ¹ H NMR spectrum of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxyphenyl) thiazolidin-4-one (180)	286
Appendix 56c	Expansion ¹ H NMR spectrum of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (180)	287
Appendix 57	¹³ C NMR spectrum of 3-(5-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (180)	288
Appendix 58	IR spectrum of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3- methoxy-phenyl) thiazolidin-4-one (182)	289
Appendix 59a	¹ H NMR spectrum of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (182)	290
Appendix 59b	Expansion ¹ H NMR spectrum of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (182)	291

Appendix 59c	Expansion ¹ H NMR spectrum of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (182)	292
Appendix 60	¹³ C NMR spectrum of 3-(4-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (182)	293
Appendix 61	IR spectrum of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	294
Appendix 62a	¹ H NMR spectrum of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	295
Appendix 62b	Expansion ¹ H NMR spectrum of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	296
Appendix 62c	Expansion ¹ H NMR spectrum of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	297
Appendix 63	¹³ C NMR spectrum of 3-(3-chloropyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (184)	298
Appendix 64	IR spectrum of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	299
Appendix 65a	¹ H NMR spectrum of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	300
Appendix 65b	Expansion ¹ H NMR spectrum of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	301
Appendix 65c	Expansion ¹ H NMR spectrum of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	302
Appendix 66	¹³ C NMR spectrum of 3-(6-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (186)	303
Appendix 67	IR spectrum of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	304
Appendix 68a	¹ H NMR spectrum of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	305
Appendix 68b	Expansion ¹ H NMR spectrum of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	306
Appendix 68c	Expansion ¹ H NMR spectrum of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	307
Appendix 69	¹³ C NMR spectrum of 3-(5-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (188)	308

Appendix 70	IR spectrum of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	309
Appendix 71a	¹ H NMR spectrum of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	310
Appendix 71b	Expansion ¹ H NMR spectrum of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	311
Appendix 71c	Expansion ¹ H NMR spectrum of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	312
Appendix 72	¹³ C NMR spectrum of 3-(4-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (190)	313
Appendix 73	IR spectrum of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (192)	314
Appendix 74a	¹ H NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (192)	315
Appendix 74b	Expansion ¹ H NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (192)	316
Appendix 74c	Expansion ¹ H NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (192)	317
Appendix 75	¹³ C NMR spectrum of 3-(3-methylpyridin-2-yl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (192)	318
Appendix 76	IR spectrum of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	319
Appendix 77a	¹ H NMR spectrum of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	320
Appendix 77b	Expansion ¹ H NMR spectrum of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	321
Appendix 77c	Expansion ¹ H NMR spectrum of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	322
Appendix 78	¹³ C NMR spectrum of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	323
Appendix 79	MS of 2-(4-hydroxy-3-methoxyphenyl)-3-phenethyl thiazolidin-4-one (194)	324
Appendix 80	IR spectrum of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	325

Appendix 81a	¹ H NMR spectrum of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	326
Appendix 81b	Expansion ¹ H NMR spectrum of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	327
Appendix 81c	Expansion ¹ H NMR spectrum of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	328
Appendix 82	¹³ C NMR spectrum of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	329
Appendix 83	MS of 3-(2-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (196)	330
Appendix 84	IR spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	331
Appendix 85a	¹ H NMR spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	332
Appendix 85b	Expansion ¹ H NMR spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	333
Appendix 85c	Expansion ¹ H NMR spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	334
Appendix 86	¹³ C NMR spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	335
Appendix 87	MS of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	336
Appendix 88	COSY spectrum of 3-(3-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (198)	337
Appendix 89	IR spectrum of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (200)	338
Appendix 90a	¹ H NMR spectrum of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (200)	339
Appendix 90b	Expansion ¹ H NMR spectrum of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (200)	340
Appendix 90c	Expansion ¹ H NMR spectrum of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (200)	341
Appendix 91	¹³ C NMR spectrum of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (200)	342

Appendix 92	MS of 3-(4-fluorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (200)	343
Appendix 93	IR spectrum of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	344
Appendix 94a	¹ H NMR spectrum of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	345
Appendix 94b	Expansion ¹ H NMR spectrum of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	346
Appendix 94c	Expansion ¹ H NMR spectrum of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	347
Appendix 95	¹³ C NMR spectrum of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	348
Appendix 96	MS of 3-(2-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (202)	349
Appendix 97	IR spectrum of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	350
Appendix 98a	¹ H NMR spectrum of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	351
Appendix 98b	Expansion ¹ H NMR spectrum of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	352
Appendix 98c	Expansion ¹ H NMR spectrum of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	353
Appendix 99	¹³ C NMR spectrum of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	354
Appendix 100	MS of 3-(3-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (204)	355
Appendix 101	IR spectrum of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (206)	356
Appendix 102a	¹ H NMR spectrum of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (206)	357
Appendix 102b	Expansion ¹ H NMR spectrum of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (206)	358
Appendix 102c	Expansion ¹ H NMR spectrum of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (206)	359

Appendix 103 ¹³ C NMR spectrum of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (206)	360
Appendix 104 MS of 3-(4-chlorophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (206)	361
Appendix 105 IR spectrum of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	362
Appendix 106a ¹ H NMR spectrum of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	363
Appendix 106b Expansion ¹ H NMR spectrum of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	364
Appendix 106c Expansion ¹ H NMR spectrum of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	365
Appendix 107 ¹³ C NMR spectrum of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	366
Appendix 108 MS of 3-(2-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (208)	367
Appendix 109 IR spectrum of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	368
Appendix 110a ¹ H NMR spectrum of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	369
Appendix 110b Expansion ¹ H NMR spectrum of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	370
Appendix 110c Expansion ¹ H NMR spectrum of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	371
Appendix 111 ¹³ C NMR spectrum of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	372
Appendix 112 MS of 3-(3-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (210)	373
Appendix 113 IR spectrum of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	374
Appendix 114a ¹ H NMR spectrum of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	375
Appendix 114b Expansion ¹ H NMR spectrum of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	376

Appendix 114c Expansion ¹ H NMR spectrum of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	377
Appendix 115 ¹³ C NMR spectrum of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	378
Appendix 116 MS of 3-(4-methoxyphenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (212)	379
Appendix 117 IR spectrum of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	380
Appendix 118a ¹ H NMR spectrum of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	381
Appendix 118b Expansion ¹ H NMR spectrum of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	382
Appendix 118c Expansion ¹ H NMR spectrum of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	383
Appendix 119 ¹³ C NMR spectrum of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	384
Appendix 120 MS of 3-(4-bromophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (214)	385
Appendix 121 IR spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	386
Appendix 122a ¹ H NMR spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	387
Appendix 122b Expansion ¹ H NMR spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	388
Appendix 122c Expansion ¹ H NMR spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	389
Appendix 123 ¹³ C NMR spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	390
Appendix 124 MS spectrum of 3-(4-nitrophenethyl)-2-(4-hydroxy-3-methoxyphenyl) thiazolidin-4-one (216)	391

CHAPTER 1

INTRODUCTION

1.1 Background of Research

A fungus is a tiny organism that can live in the air, soil, water, plants or on the human body. About half of fungi are harmful. Despite the significance of fungi-caused diseases in humans and plants, they are still considered neglected topical diseases by public health authorities, despite the fact that the majority of deaths from fungal diseases are preventable (Larregieu *et al.*, 2014). Among, 43 published papers (2013-2017) that estimated the burden of fungal infections in each country, 39 of 43 articles included data on candidemia (Bongomin *et al.*, 2017). Pakistan was found to have the greatest prevalence of candidemia (38,795 cases) (Jabeen *et al.*, 2017) followed by Brazil (28,991 cases) (Giacomazzi *et al.*, 2016), Russia (11,840 cases) (Klimko *et al.*, 2015) and Vietnam (4540 cases) (Smith *et al.*, 2013). The two lowest cases were recorded in Jamaica (136 cases), (Gugnani *et al.*, 2015) and Portugal (231 cases) (Sabino *et al.*, 2017). The studies have not been used to publish the incidents in the three most populous countries, China, India, and the United States (Bongomin *et al.*, 2017).

Candida albicans causes the majority of fungal infections in humans. Fluconazole, Oxiconazole, Tioconazole, and Itraconazole are some of the medications used to treat this disease (Martin *et al.*, 1999). The chemical structure of these drugs, as shown in **Figure 1.1**. Fluconazole is well-known for treating and preventing *Candida albicans* infections as a first-line medication (Arendrup *et al.*, 2013). Fluconazole has predictable pharmacokinetics and is safe to use in most patients with *Candida albicans* infections, including children, the elderly, and those with compromised immunity (Campoy and Adrio, 2017); (Revie *et al.*, 2018). Fluconazole can be given prophylactically to patients receiving cytotoxic cancer therapy to help

prevent fungal infections. Fluconazole's increased usage for long-term prophylaxis and treatment of recurrent oral candidosis in AIDS patients has resulted in the establishment of *C. albicans* infections resistant to standard doses. If fluconazole fails, a wider-spectrum antifungal, such as itraconazole, should be used as a second-line treatment (Haria *et al.*, 1996).

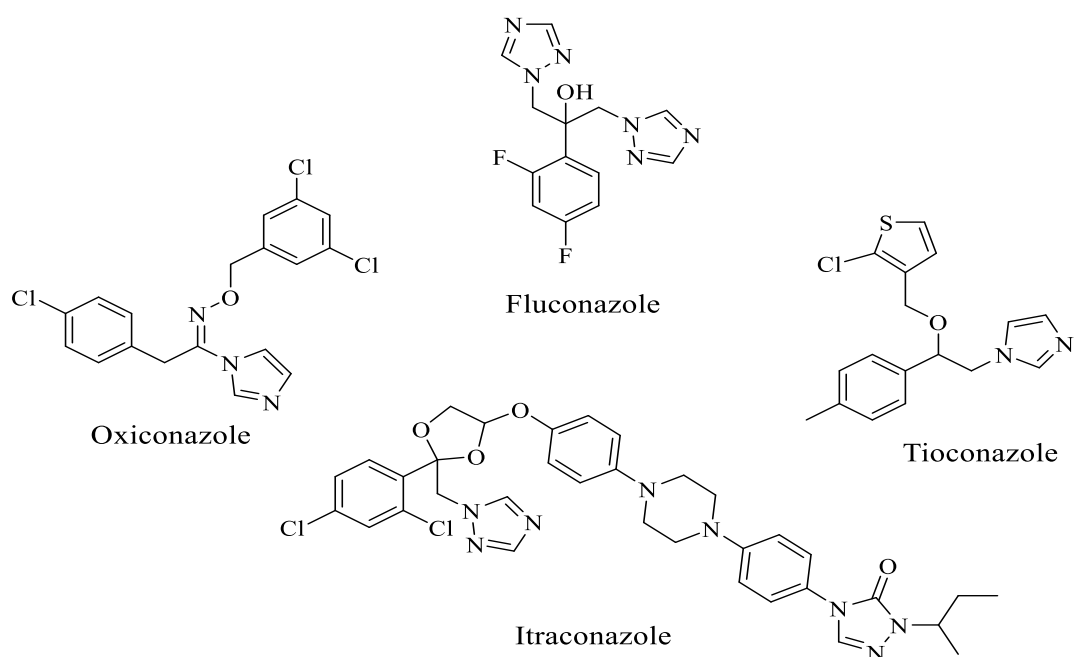


Figure 1.1. Chemical structures of some drugs of antifungal inhibitor

Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) is a retrovirus that infects numerous types of human white blood cells, especially the CD4 (cluster of differentiation 4) (T cell) and monocyte cells, thus causing a decrease in the immune system. AIDS, in fact, manifests in infected individuals as a collection of symptoms of the disease following infection by HIV (Kayabekir *et al.*, 2018). According to a report by the World Health Organization (WHO) published in 2020, a total of 38 million people were HIV positive and 26 million people were obtaining antiretroviral therapy as of the end of June 2020. WHO also reported 1.7 million of the global population were newly infected in 2019 and a mortality rate of 690,000 during 2019 (Global HIV & AIDS statistics-2020 fact sheet-UNAIDS).

Typically, the HIV retrovirus attacks human cells via adhering to the surface of the cell. The virus subsequently multiplies and spreads throughout the body by utilizing the metabolism of the host cell. The HIV life cycle is a seven-step process that passes through seven phases. Evans *et al.*, (2015), which was discussed further in Chapter 2. There are two types of HIV retrovirus (HIV-RT), namely, HIV-1 and HIV-2 RT. Specifically, research on the HIV-1 RT variant has garnered much interest. Many studies have been focused on this virus, which explain the reason behind the numerous developments of current HIV/AIDS antiretroviral therapies. Zidovudine (AZT) was initially described in 1964, and it received FDA approval in 1987, and was the first anti-HIV licensed drug for clinical use. It has a role as an antiviral drug and HIV-1 reverse transcriptase inhibitor. It works by preventing HIV from making DNA by inhibiting the enzyme reverse transcriptase. As a result, the virus's reproduction is reduced. Following that, so many of the other HIV-treatment therapies have been permitted by the Food and Drug Administration (FDA) and European Medicine Agency (EMA), including Efavirenz (I) which is widely used as a first generation NNRTI due to its desirable pharmacological properties and high potency. Its effectiveness is strongly dependent on ring-stacking interactions with RT hydrophobic amino acids (Bastos *et al.*, 2016). Other approved NNRTIs of second generation are included nevirapine (II) and delavirdine (III) as shown in **Figure 1.2** (Minuto *et al.*, 2008 and Rimsky *et al.*, 2015). With new effective potent antiviral drugs are used in the HIV treatment, the deaths related to AIDS have been decreased globally from 1.9 million in 2003 (Vernekar *et al.*, 2015) to 0.77 million in 2018 (Makurumidze *et al.*, 2020).

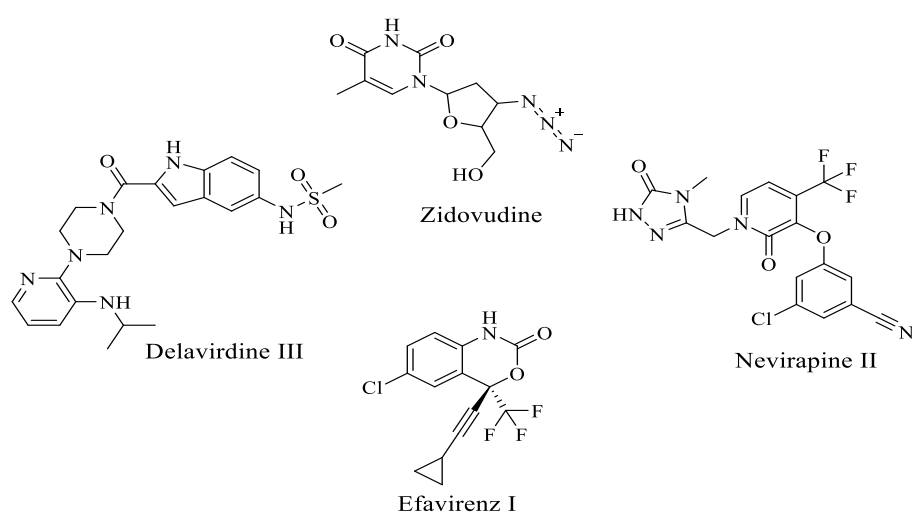


Figure 1.2. Chemical structures of some HIV-1 RT inhibitor drugs

However, current anti-retroviral therapies are largely comprised of RT inhibitors, in conjunction with the fact that the majority of drug resistant mutations occur in the RT region. In light of this, there have been concerted efforts into the development of newer strategies to counteract the RT of the HIV-1. Additionally, emergence of toxic side effects and poor patient adherence further emphasize the urgency for more variety of newer anti-HIV drugs to be developed. Correspondingly, to successfully produce effective anti-HIV drugs, novel mechanisms of action with the ability to inhibit drug resistant HIV-1 must therefore be developed (Vidya *et al.*, 2009).

The structures of thiazolidine and thiazolidinone as depicted in (Figure 1.3) have been reported biologically active against many diseases including antifungal (Lobo *et al.*, 2012) and HIV (Bielenica, *et al.*, 2017). For example, thiazolidine-4-carboxylic acid derivative (Figure 1.4) was prepared by Yang *et al.*, (2021) and tested on different groups of phylogenetic fungi. The results showed that thiazolidine derivatives have a broad-spectrum effect on fungi. So, this work study should be extended to other fungal microorganisms by replacing different types of aromatic rings in positions no. 2 and 3 of thiazolidine and thiazolidinone cores.

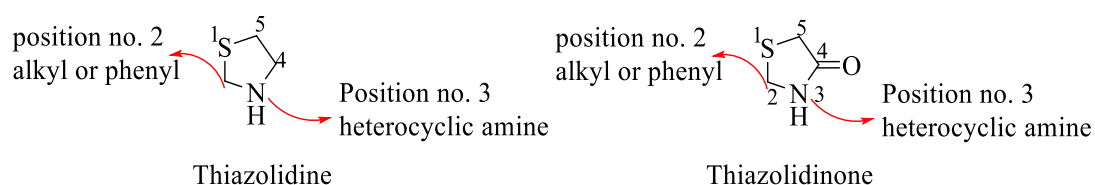


Figure 1.3 Structure of thiazolidine and thiazolidinone (Posner, M. R. *et al.*, 2007)

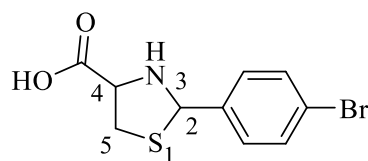


Figure 1.4 2-(4-bromophenyl)thiazolidine-4-carboxylic acid (Yang *et al.*, 2021)

Researchers have discovered a number of thiazolidinone compounds with anti-HIV efficacy. For example, Rawal *et al.*, (2008) synthesized and tested a number of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-one (**Figure 1.4**) with anti-HIV-1 RT inhibitory action and Murugesan *et al.*, (2014) synthesized a variety of thiazolidinone derivatives that have been investigated for anti-HIV-1 activity. Noteworthy, the myriad of biological activity of thiazolidinone derivative may be directly related to the existence of several substitution positions, giving rise to new functional attachments and thus, new corresponding biological activities.

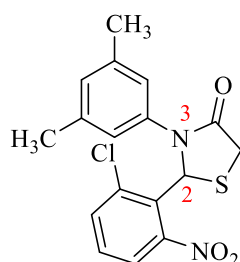


Figure 1.5 2-Aryl-3-heteroaryl-1,3-thiazolidin-4-one (Murugesan *et al.*, 2014)

Survey of the literature conveyed that substituent of thiazolidine and thiazolidinone at positions 2, 3 and 5 can be varied, but the group linked to the carbon atom in the 2-position exerts the greatest structural and property difference (Mistry and Desai, 2004). The R group at the 3-position of thiazolidine and thiazolidinone can be varied to harbour alkyl, aryl and heterocyclic groups, for example general chemical structure of 2-(substituted phenyl)-thiazolidine 4-carboxylic acid and 2,3-diaryl-1,3-thiazolidinone derivatives, have this property capable of varying biological activity in humans and have been shown to be effective against a variety of pathogens. This indicates that it has an anti-microbial (Shintre *et al.*,2017), antioxidant (De *et al.*, 2017), anti-inflammatory (Suthar *et al.*,2013), anti-cancer (Kumar *et al.*,2019), anti-diabetic (Bhutani *et al.*,2019), antifungal (Abid *et al.*, 2019), (Lobo *et al.*,2012) and anti-HIV (Barreca *et al.*,2001; Bielenica, *et al.*,2017; Suryawanshi *et al.*,2017). This variety in the biological reaction profile has drawn the interest of researchers to investigate the ability of this skeleton against various infections (Ashvini *et al.*,2015).

To accelerate the progress of the development of novel anti-HIV drugs, computer- aided drug design can be used for better explanation of the viral protein-

drug interaction and can also potentially lower research costs, time-saving and increase research efficiency (Panda *et al.*, 2015; Kumari and Singh, 2016). Among the computational approaches, molecular docking has been adopted to design new antiretroviral drugs (de Ruyck *et al.*, 2016; Tautermann *et al.*, 2015). Molecular docking study allows the behavioral characterization of small molecules in the binding site of target proteins (Ferreira *et al.*, 2015).

1.2 Problem Statement

More than 1.5 million individuals die each year from fungal diseases, which affect over a billion people around the world (Pilmis *et al.*, 2016). Despite the fact that the majority of deaths from fungal illnesses are preventable, they are still considered neglected topical diseases by public health authorities (Larregieu, C. *et al.*, 2014). Some of the most commonly used antifungal medications in clinical practice are clotrimazole, econazole, miconazole, terbinafine, fluconazole, ketoconazole and amphotericin (Pfaller *et al.*, 2012), that kill, weaken or inhibit fungi and other microbes. Yet, these drugs lead to the emergence of pathogens that are resistant to pharmaceutical drugs (Campoy and Adrio, 2017; Revie *et al.*, 2018). Moreover, there are many drugs against fungal but they have side effects such as phlebitis, rash, fever, nausea, vomiting, abdominal and diarrhea (Kathiravan *et al.*, 2012) and sometimes the drugs are inactive against certain kinds of fungal microorganisms (Ogundeji *et al.*, 2016). As a result, scientists are confronted with critical challenges such as microorganism treatment resistance and therapeutic adverse effects. Such issues have led to the development of novel antifungal medicines through the search, exploration, and modification of compounds. There are currently no antifungal medications that contain the thiazolidine ring. This encourages the synthesis and development of thiazolidine derivatives, which can kill the fungi without producing side effects.

Given the high rates of infection and mortality among HIV patients around the world, concerted efforts to design new potent anti-HIV drugs merits the attention of the scientific community. This issue is further exacerbated by the high adaptability of HIV to newly introduced drugs as the retrovirus can easily mutate its active site. Thus, the new drugs are rendered ineffective as they are incapable of deactivating the virus.

Moreover, there are some side effects of anti-HIV drugs that have been linked to combination therapy such as renal failure, hypokalemia, stomach pain, vomiting, diarrhea, nausea, decreased appetite, rash, headache, fatigue (Portman, 2018) as well as depression and suicidal ideation (Cihlar and Fordyce, 2016). In light of this, continuous development of new HIV inhibitors candidates with good resistance and a pharmacokinetic profile, must be further stepped up. Herein, this study proposes the development of a novel HIV-1 RT drug based on the thiazolidinone chemical structure. This group of compounds has shown to possess a wide spectrum of biological activities such as anti-cancer (Asati *et al.*, 2018), anti-virus (Abid *et al.*, 2014) and anti-HIV (Suryawanshi *et al.*, 2017). In conjunction with increasing interest in molecular biology, derivatives of thiazolidine or thiazolidinone can be modified by in silico or computational-assisted techniques, with respect to their ability to inactivate or inhibit HIV-RT.

1.3 Objectives of Research

The objectives of this study are:

1. To synthesize and characterize one series of thiazolidine derivatives.
2. To evaluate the bioactivity of the thiazolidine derivatives using antifungal assays.
3. To evaluate two new series of anti-HIV containing thiazolidinone derivatives by using molecular docking.
4. To synthesize and characterize the two targeted series of thiazolidinone derivatives.

1.4 Scope of Research

This thesis is divided into two parts. The synthesis of 2-(substituted phenyl)-thiazolidine-4-carboxylic acid and its derivatives were achieved in part one. In one step reaction of L-cysteine with different substituted of benzaldehyde in ethanol and water (3:1), sixteen compounds have been successfully synthesized. The biological

activities include antifungal of the thiazolidine derivatives (**172a-p**) series one. The antimicrobial activity was evaluated against antifungal by microdilution technique for determination of minimum inhibitory concentration (MIC) and zone of inhibition (ZOI), expressed in $\mu\text{g/mL}$ and mm terms, respectively were determined with fluconazole (FLC) as standard drug.

The second part of the study involved the design of new potential bioactive compounds using in silico methods and carried out molecular docking (Auto Dock). Thioazolidinone derivatives have been docked to the HIV-RT and estimated for binding energy between the ligand (drug) and the HIV- RT. The best results (lowest binding energy) of thiazolidinone derivatives with that of HIV-RT were selected. The targeted compounds have been synthesized by cyclization reaction using vanillin, mercapto-acetic acid and two different aryl amines in the presence of toluene according to a known procedure by Barreca *et al.*, (2001) to form new 2, 3-diaryl-1, 3-thiazolidin-4-one derivatives which carry different functional groups, namely halo, methoxy, methyl and nitro groups (series two and three) as potential HIV agents. The success of chemical reactions for all compounds were verified by Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR) and electrospray ionization mass spectrometry (ESI-MS).

1.5 Significance of Research

Through previous scientific researches, promising results have been shown for antifungals carried out on heterocyclic compounds, such as thiazolidine derivatives (Lobo *et al.*, 2012; Upadhyay *et al* 2010; Yang *et al* 2021). It has been observed that changing the substituents, functional groups as well as the homogeneous and heterogeneous aromatic rings connected to the thiazolidine or thiazolidinone core, has a different effect on the fungi. The development of these compounds may lead to the production of new drugs that are biologically active and eliminate fungi without side effects.

Previous research has focused on heterocyclic molecules, particularly those containing a sulphur atom, such as the thiazolidinone ring, which succeeded in the

manufacture of drugs that showed good biological activity against HIV. This was by inhibiting the virus from reproduction (Ravindra *et al.*, 2008a; Murugesan *et al.*, 2014; Pitta, Eleni *et al.*, 2013; Bielenica *et al.*, 2017; Suryawanshi *et al.*, 2017). Through the results of these studies, it was noted that thiazolidine or thiazolidinone compounds and their biological effects are based on the various aryl rings connected to the thiazolidinone core at positions 2 and 3, as well as on the functional groups substituted on the aryl rings. All the medicines discovered so far have not been able to eliminate or prevent HIV infection, but they do help keep it from reproducing. This study proposes the development of a novel HIV-RT drug based on the thiazolidinone chemical structure, by computational-assisted techniques, with respect to their ability to inactivate HIV-RT.

The researchers believe that employing a computational method to create and analyze new thiazolidine or thiazolidinone-based drugs could provide quick and reliable efficacy data due to the availability of knowledge about the structure of HIV-1 reverse transcriptase (RT). Furthermore, before undertaking empirical studies to determine their efficacy as an anti-HIV-RT agent, this technique can aid in acquiring a better knowledge of medicine and viral enzyme interactions. Furthermore, the study focused on the design and substitutions at positions 2 and 3 of the thiazolidinone to generate new derivatives of the thiazolidinone, and their efficacy as anti-HIV-1 RT drugs.

The *in-silico* method to design functional anti-HIV-RT proposed here may cut down on empirical testing and the time it takes to determine drug efficacy. Moreover, the *in-silico* investigation would aid in narrowing the scope of this study's search to only limited but fewer numbers of potentially efficacious anti-HIV drugs. The outcome of this work would impart new knowledge on the potential use of certain thiazolidine derivatives useful for averting further proliferation of the HIV in affecting individuals. Most importantly, the synthetic route to produce an effective thiazolidine or thiazolidinone-based anti-HIV drug may be discovered, which further contributes to the body of knowledge of anti-HIV drug design as well.

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