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 IC_{50} and 15 mm ZOI, > 32 μg/mL IC_{50}) 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-methoxy-phenyl)-3-(pyridin-2-yl)-1,3-thiazolidin-4-ones and its derivatives (45%-75%). All the synthesized compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C 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 baias 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 IC_{50} dan 15 mm ZOI, > 32 μg/mL IC_{50}) 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 pengenalpastian 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, ^{1}H RMN dan ^{13}C RMN dan MS.

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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
J	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_3N	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
ν_{max}	Maximum absorbance
m.p	Melting point
MeOH	Methanol
mg	Milligram
mL	Millilitre
µL	Microlitre
µg/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_2SO_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

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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).

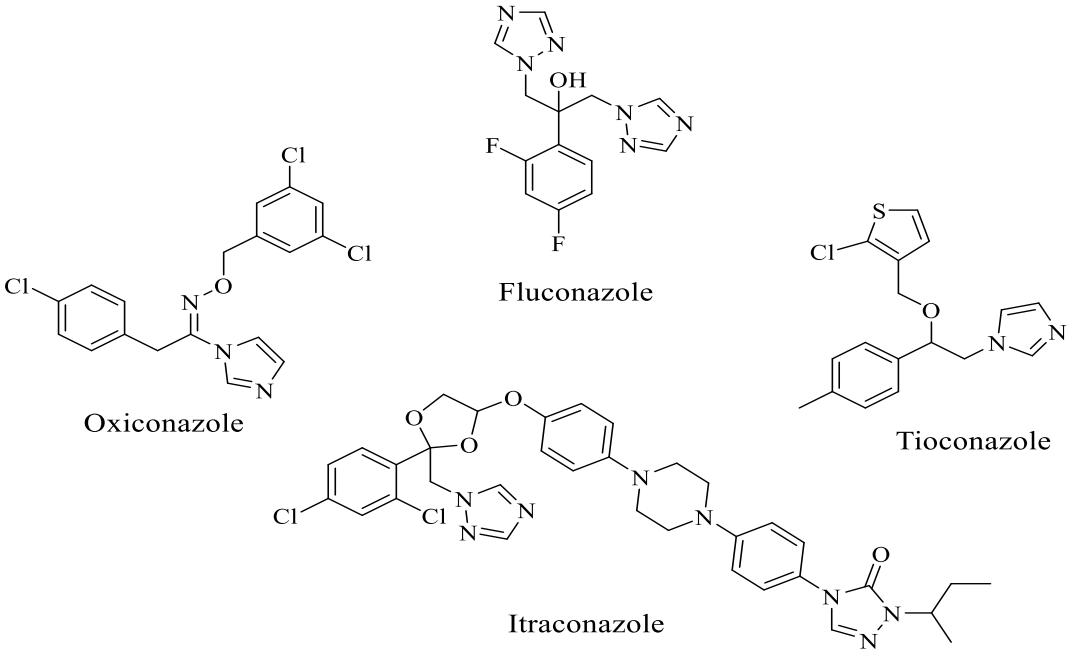

Figure 1.1. Chemical structures of some drugs of antifungal inhibitor

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).

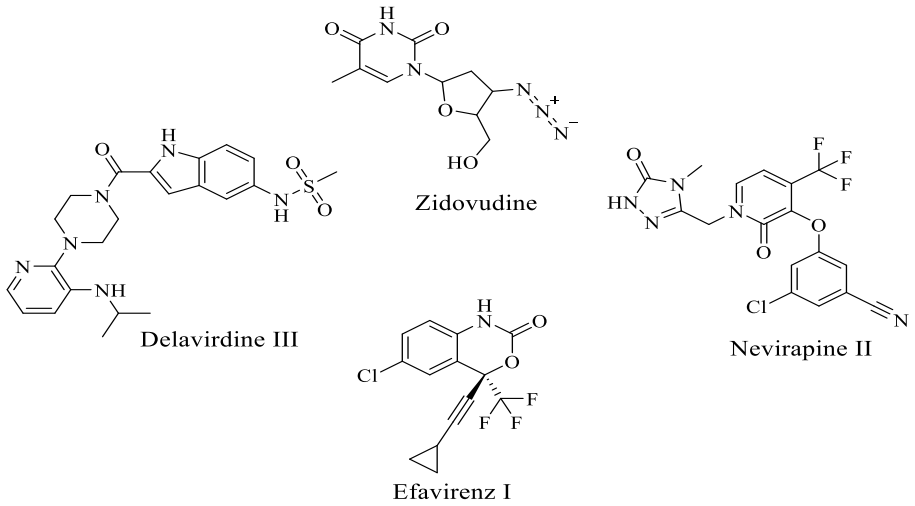

Figure 1.2. Chemical structures of some HIV-1 RT inhibitor drugs

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, three 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 phytogenic 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.

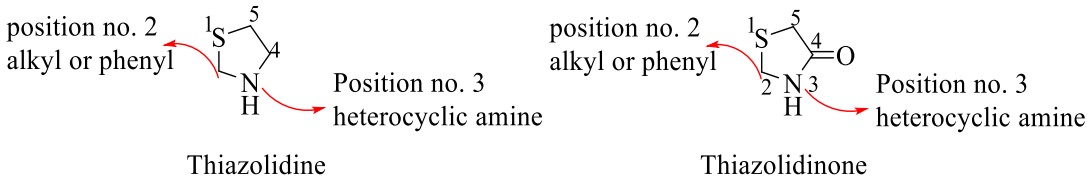

Figure 1.3 Structure of thiazolidine and thiazolidinone (Posner, M. R. *et al*., 2007)

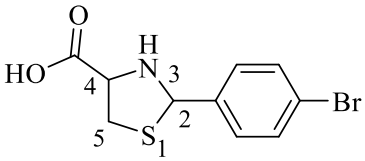

Figure 1.4 2-(4-bromophenyl)thiazolidine-4-carboxylic acid (Yang *et al*., 2021)

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. Noteworthily, the myriad of biologically 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.

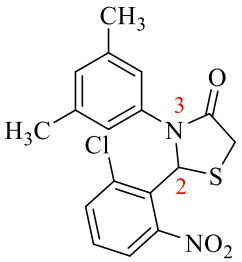

Figure 1.5 2-Aryl-3-heteroaryl-1,3-thiazolidin-4-one (Murugesan *et al.*, 2014)

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 candidaties 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 μg/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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