MOLECULAR MODELING STUDIES ON HIV-1 REVERSE TRANSCRIPTASE (RT) AND HEAT SHOCK PROTEIN (Hsp) 90 AS A POTENTIAL ANTI-HIV-1 TARGET

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(BSc.)

A thesis submitted to the College of Health Sciences, University of KwaZulu-Natal, Westville, in fulfillment of the requirements of the degree of Master of Medical Sciences

UNIVERSITY OF KWAZULU-NATAL

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A thesis submitted to the School of Health Science, University of KwaZulu-Natal, Westville Campus, for the degree of Master of Medical Science in Pharmaceutical Chemistry. This is the thesis in which the chapters are written as a set of discrete research publications, with an overall introduction and final summary. This is to certify that the contents of this thesis are the original research work of Miss Favourite Nontando Cele.

As the candidate's supervisor, I have approved this thesis for submission.

Supervisor:

Signed: ---------- Name: **Prof. Mahmoud E. Soliman** Date: ----------

ABSTRACT

Human immunodeficiency virus (HIV) infection is the leading cause of death globally. This dissertation addresses two HIV-1 target proteins namely, HIV-1 Reverse Transcriptase (RT) and Heat shock protein (Hsp) 90. More specifically for HIV-1 RT, a case study for the identification of potential inhibitors as anti-HIV agents was carried out. A more refined virtual screening (VS) approach was implemented, which was an improvement on work previously published by our group- "target-bound pharmacophore modeling approach". This study generated a pharmacophore library based only on highly contributing amino acid residues (HCAAR), instead of arbitrary pharmacophores, most commonly used in the conventional approaches in literature. HCAAR were distinguished based on free binding energy (FBE) contributions, obtained using calculation from molecular dynamics (MD) simulations. Previous approaches have relied on the docking score (DS) to generate energy-based pharmacophore models. However, DS are reportedly unreliable. Thus we present a model for a per-residue energy decomposition (PRED), constructed from MD simulation ensembles generating a more trustworthy pharmacophore model which can be applied in drug discovery workflow. This approach was employed in screening for potential HIV-1 RT inhibitors using the pharmacophoric features of the compound **GSK952**. The complex was subjected to docking and thereafter MD simulations confirmed the stability of the system. Experimentally determined inhibitors with known HIV-RT inhibitory activity were used to validate the proposed protocol. Two potential hits **ZINC46849657** and **ZINC54359621** showed a significant potential with regards to FBE. Reported results obtained from this work confirm that this new approach is favourable to the future of drug design process.

Hsp90 was recently discovered to play a vital role in HIV-1 replication. Thus has emerged, as a promising target for anti-HIV-1 drugs. The molecular mechanism of Hsp90 is poorly understood, thus the second study was aimed to address this issue and provide a clear insight to the inhibition mechanism of Hsp90. Reasonable continuous MD simulations were employed for both unbound and bound Hsp90 conformations, to understand the dimerization and inhibition mechanisms. Results demonstrated that coumermycin A1 (C-A1), a newly discovered Hsp90 inhibitor, binds at the CTD dimer of Hsp90 and lead

to a significant separation between orthogonally opposed residues, such as Arg591.B, Lys594.A, Ser663.A, Thr653.B, Ala665.A, Thr649.B, Leu646.B and Asn669A. A Large difference in magnitudes was observed in the radius of gyration (Rg), per-residue fluctuation, root-mean-square deviation (RMSD) and root-mean-square fluctuation (RMSF) confirming a completely more flexible state for the unbound conformation associated with dimerization. Whereas, a less globally correlated motion in the case of the bound conformer of Hsp90 approved a reduction of the dimeric process. This undoubtedly underlines the inhibition process due to ligand binding. The detailed dynamic analyses of Hsp90 presented herein are believed to give a greater insight and understanding to the function and mechanisms of inhibition of Hsp90. The report on the inhibitor-binding mode would also be of great assistance in the design of prospective inhibitors against Hsp90 as potential HIV target.

DECLARATION 1 – PLAGIARISM

I, **Favourite Nontando Cele,** declare that

1. The research reported in this thesis, except where otherwise indicated, is my original work.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a. Their words have been re-written, but the general information attributed to them has been referenced.

b. Where their exact words have been used, then their writing has been placed in italics and inside quotation marks, and referenced.

5. This thesis does not contain text, graphics or tables copied from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the references section.

A detail contribution to publications that form part and/or include research presented in this thesis is stated (include publications submitted, accepted, in *press* and published).

Signed: ----------

DECLARATION 2 - SUBMITTED ARTICLES

1. Favourite N. Cele, Ramesh Muthusamy and Mahmoud E.S Soliman (2015). Per-residue energy decomposition (PRED) pharmacophore model to enhance virtual screening (VS) in drug discovery: A case study for identification of Reverse transcriptase (RT) inhibitors as potential Anti-HIV agents (submitted and under review).

Contribution:

Favourite Nontando Cele: Author contributed to the project by performing all literature reviews, experimental work, and data analysis, interpretation of the results as well as manuscript preparation and writing.

Ramesh Muthusamy: The editing of the manuscript.

Mahmoud E. Soliman: Supervisor.

2. Favourite N. Cele, Hezekiel Kumalo, Mahmoud E. S. Soliman (2015). Mechanism of Inhibition of Hsp90 Dimerization by Gyrase inhibitor coumermycin A1 (C-A1) revealed by Molecular Dynamics Simulations and Thermodynamic Calculations (submitted and under review)

Contribution:

Favourite Nontando Cele: Author contributed to the project by performing all literature reviews, experimental work, and data analysis, interpretation of the results as well as manuscript preparation and writing.

Hezekiel Kumalo: Technical assistance.

RESEARCH OUTPUT

PUBLICATIONS

1. Favourite N. Cele, Ramesh Muthusamy and Mahmoud E.S Soliman (2015). Per-residue energy decomposition (PRED) pharmacophore model to enhance virtual screening (VS) in drug discovery: A case study for identification of Reverse transcriptase (RT) inhibitors as potential Anti-HIV agents (accepted for publication).

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DEDICATION

I would like to dedicate this work to the highest God, who made everything possible. Without the name 'JESUS CHRIST OF NAZARETH' this degree would not have been a great success it is now. This work is mostly dedicated to my mother, my brother and my fiancé. Their love and support enabled me to overcome challenges I encountered during the course of my degree.

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LIST OF ABBREVIATIONS

AZT	Azidothymidine
CADD	Computer aided drug design
CAMD	Computer aided molecular design
MVC	Maraviroc
PES	Potential energy surface
SIV	Simian immunodeficiency virus
T20	enfuvirtide
UNAIDS	United national programme on HIV/AIDS
WHO	World's health organization

CHAPTER 1

1.1. Background and rationale for this study

In this chapter, the background, rationale and novelty of this research project, which is associated to HIV-1 infection, is clearly and precisely conferred. Acquired Immune Deficiency Syndrome (AIDS) is an advancement of Human Immunodeficiency Virus (HIV) infection[1] and HIV is one of the leading cause of death globally[2]. Over 35 million people are affected with HIV/AIDS, of that, Sub-Saharan Africa being the most affected[3] with approximately 5.7 million are in South Africa[3]. Factors contributing to this high number is poverty, inequality and social instability, high levels of sexually transmitted infections, sexual violence, high mobility and limited access to quality medical care[4]. Though research shows great levels in the understanding of HIV transmission and prevention methods, preventative behavior are still not practiced. The HIV pandemic in South Africa has induced an international response in the assistance of HIV research in both prevention and treatments[5].

Thus far, there is no cure for HIV/ADS due to high mutation rates[6], which leads to drug resistance. Research has contributed much to improve current HIV treatment, which does not cure the virus but stops it from spreading and replicating[7]. A study by Ptak and collegues (2008) revealed that there has been 1448 human proteins identified that interact with HIV-1 involving 2589 distinctive HIV-1-to-human protein interactions[8]. There is currently more than twenty-five anti-HIV drugs which targets three known essential targets namely reverse transcriptase (RT), protease and intergrase (IN)[9]. These targets are crucial for different processes involved in HIV replication and survival. Reverse transcriptase consists of all vital enzymatic activity required for the conversion of HIV-1 single stranded RNA (ssRNA) into double stranded DNA (dsDNA) required for integration into the human genome[10,11]. Integrase enables the genetic material of the virus to be integrated into the DNA of an infected cell[12]. Protease is responsible for the maturation of the virus[6,13]. The anti-HIV drugs are divided into distinct classes namely nucleoside-analog RT inhibitors (NRTIs), non–nucleoside reverse transcriptase inhibitors (NNRTIs), Integrase inhibitors and Protease inhibitors (PIs)[14]. Reverse transcriptase is the target for more than half of the currently approved anti-AIDS drugs[15]. The efficacy of NNRTI drugs is reduced by the occurrence of drug-resistance mutations[16] due to the lack of exonucleolytic proofreading activity of HIV-RT[17] . As a results an abnormal strand is transferred into the DNA of the host cells[18]. Thus, the mutagenic virus replicate causing resistance to anti-HIV therapy[19]. Numerous studies have tried to improve NNRTI drugs' efficacy[20–24].

The use of computational tools have proved to be cost effective and less time consuming in the design and discovery of new drugs[25]. A number of studies have used computational tools such as molecular modelling, MD simulations, molecular docking, QSAR and virtual screening (VS) to improve existing drugs and to discover new RT inhibitor[26–32]. The use of VS has increased over the years in drug discovery industry[33–36]. A few studies have used phamarcophore models to identify novel and potent RT inhibitors[37–39]. Herein, we used a new approach to screen for NNRTIs. This approach is aimed to improve the conventional methods of VS, which will aid the drug design workflow to design more potent RT inhibitors.

Furthermore, Hsp90 has been recently reported as a potential target for HIV-1[40]. Gyrase B inhibitors has been confirmed to impair viral gene expression by binding to Hsp90[40,41]. To understand the dimerization process and the inhibition of Hsp90 by C-A1, MD simulations were employed for both the apo and bound conformations. Post-dynamics analysis including RMSD, RMSF, Rg, PCA and DCCM were used to understand the structural fluctuations of both apo and bound conformations. The structural and dynamic insights presented herein, can be implemented in the drug discovery and development of more potent HIV inhibitors against Hsp90.

In spite of the current treatment regimen, to date there is no cure or vaccination for HIV. Thus there is a great need for continued improvement on existing drugs as well as identification of novel and inhibitors.

1.2. Aims and objectives of this study

Broadly, the aims of this study were to investigate the inhibition of HIV-1 reverse transcriptase and the inhibition mechanism of Hsp90 by C-A1. These aims are further refined hereunder

A. The aim of this work was to identify more potential NNRTIs by exploiting the structural features of **GSK952** using a pharmacophore model approach. To accomplish this, the following specific objectives were outlined:

1. Download the crystal structure from Protein Data Bank (PDB) website

2. Prepare ligand and receptor from crystal structure

3. Run MD simulation

4. Select paharmacophore moieties based on highly contributing residues

5. Generate a library

6. Run molecular docking on above generated library

7. Run MD simulation on top ranked hits

8. Identify potential hits.

B. The aim of this work was to investigate the inhibition mechanism of Hsp90, a potential HIV-1 target protein, by the Gyrase B inhibitor C-A1. To accomplish this, the following specific objectives were outlined:

1. Download the crystal structure of Hsp90 protein.

2. To draw C-A1 from the SMILES using the Avogadro software.

3. To prepare both Hsp90 and C-A1 on chimera.

4. To dock C-A1 against Hsp90 from the PDB repository.

5. To Run MD simulation on docked Hsp90- C-A1 complex.

6. To do post-analysis from MD simulation.

1.3. Novelty and significance of this study

HIV-1 reverse transcriptase (RT) inhibition is a key focus of current anti-HIV drug discovery[42] as 17 of the 31 FDA-approved compounds target RT and it is a prominent target of many approved anti-HIV drugs that are key components of Highly Active Anti-Retroviral Therapies (HAART)[43]

Several computational screening tools are available for the mining of inhibitors having properties of significance[44]. Virtual screening is one of the most trusted and convenient tools in drug design[45]. Its reliability in the discovery of novel HIV-1 RT inhibitors has been confirmed in literature[45]. Virtual screening can be either ligand-based or structure based[46]. Ligand-based VS (LBVS) also known as pharmacophore-based VS, uses favorably features or properties of known bioactive ligands to build a pharmacophore model and searches for compounds with similar features[47]. Pharmacophore models is the best at discovering a range of chemical structures with possible features, thus the major method for the preliminary selection of compounds[48]. Ligand-based pharmacophore approaches generates libraries based on a set of known ligands illustrative of crucial interactions between the ligands and a particular target[49]. Whereas structure-based pharmacophore models are based on the knowledge of the 3D structure of the target[50]. A number of studies have combined LBVS and SBVS with the aim of improving the VS process[51–53]. Several studies have implemented approaches to improve VS and pharmacophore models[54–

[58]. A previous study proposed a target-bound ensemble generated pharmacophore model to further improve the pharmacophore-based VS. It has been confirmed that a target-bound pharmacophore-based VS is a more rational approach[59]. Yet to date, general standards for VS with regards to method evaluation are insufficient. An approach implemented in this study, aimed to improve and refine the current pharmacophore approach. Our approach was centered on the type of molecular interactions such as hydrogen bonding, charge, and hydrophobic interactions[60]. This approach searched for compounds that interact with highly contributing residues based on the Free Binding Energy. This work identified more potential NNRTIs by exploiting the structural features of **GSK952** using a pharmacophore model. Reported results obtained from this work see (**chapter 4**) confirm that the refinement of this approach is favorable to the future of drug design industry.

Hsp90 has been recently reported as a potential target for anti-HIV drugs[40]. It has also been found that the CTD demonstrate favorable activities within the binding pocket[61]. Coumermycin A1 (C-A1), a very potent Gyrase B inhibitor, was reported to disrupt the HIV-1 replication by targeting Hsp90 dimerization[40]. The understanding of the complex biological phenomena's involved in this process deserves great attention; hence the confirmation of the impairment of viral gene expression by C-A1 binding to Hsp90 is vital. This study validated these findings through computational methods. To the best of our knowledge this is the first report of the binding mechanism of C-A1 to Hsp90. The results reported for this study (see **Chapter 5**), which validates inhibition of viral gene expression, could also be implemented within the drug discovery industry to develop more potent HIV-1 inhibitors against Hsp90.

1.4. Overview of this thesis

This thesis has the total of six chapters, including this one:

Chapter 2: This chapter outlines endemic and therapy of HIV/AIDS infection. A historical background on HIV/AIDS is provided at the beginning of this chapter proceeding to most current statistics on the number of HIV-infected people globally including African continents. Details of HIV/AIDS are also highlighted which includes HIV virus structure; life cycle and the fundamental enzymes required for HIV lifecycle and targets anti-HIV therapy. The HIV-1 RT and Hsp90 enzymes are essential drug targets and are the principal focus of this work, which will be addressed in more detail. This will include the structure, inhibitor design strategies and the current FDA-approved inhibitors for each enzyme.

Chapter 3: A general introduction to computational chemistry, different molecular modeling and simulation techniques and their applications are provided in this chapter. Theoretical descriptions for some of the computational methods have been explained where applicable. Several computational tools employed in HIV research are also highlighted mainly focusing on MD simulations, quantum mechanics,

molecular mechanics, molecular docking and FBE calculations. Previous reports on computational studies on HIV-1 RT and reports on Hsp90 as potential HIV-1 target also formed part of this chapter.

Chapter 4: Published work –This chapter presents the research paper titled "Per-residue energy decomposition (PRED) pharmacophore model to enhance virtual screening (VS) in drug discovery: A case study for identification of Reverse transcriptase (RT) inhibitors as potential Anti-HIV agents." and it was accepted in the Dove Medical Press journal Objectives of this paper were addressed in **1.2.A** 1, 2, 3, 4, 5, 6, 7 and 8.

Chapter 5: Submitted work – This chapter presents the final and revised version of the submitted research paper from this study. The title of the paper is "Gyrase inhibitor coumermycin A1 (C-A1) inhibit Hsp90 Dimerization: Insights from Molecular Dynamics." Objectives of this paper were addressed in **1.2 .B** 1, 2, 3, 4, 5 and 6. **Chapter 6**: This chapter consists of the conclusion for the whole thesis and the possible future work plans.

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CHAPTER 2

2. Background on HIV/AIDS

2.1. Introduction

In this chapter a brief description on the background, life cycle and treatment of Human Immunodeficiency Virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS) is provided. The main focus will be on HIV-1 RT and it inhibitors. A brief discussion on Hsp90 as potential HIV-1 target will be included.

2.2. A brief history of HIV/AIDS

Human Immunodeficiency Virus is believed to have originated from a type of chimpanzee in West Africa, which was infected by simian immunodeficiency virus (SIV)[62]. The earliest known case of infection with HIV-1 in a human was in 1959 from a man in the Democratic Republic of the Congo, which was detected in his blood sample[63]. Acquired Immune Deficiency Syndrome was first documented as a new disease in 1981[62] and confirmed to be originated from HIV later in 1983[64]. There are two types of HIV, which are HIV-1 and HIV-2[65,66]. The HIV-1 infection is more virulent than HIV-2 and it is predominant across the globe[67]. The leading mode of HIV transmission is heterosexual transmission, which accounts for approximately 85% of all HIV-1 infections[68]. A number of factors have contributed on promoting the incidence of HIV, which includes migration, urbanization and family disruption, economic underdevelopment and poverty[69].

The HIV pandemic has not only affected people's health but also the economy growth. The economy has affected sectors such as the households, firms, health, transport, mining, education and water[70,71]. The global statistics by WHO reported that there were approximately 35 million people with HIV/AIDS infection all over the world, with Sub-Saharan Africa being the most affected region, with 24.7 million people living with HIV[72]. The current UNSAID statistic reported that there is a decrease in new HIV infection since 2001, decrease in AIDS related deaths since 2005 for both children and adults, a decrease in new HIV infections in children by 33%, 29% and 52% respectively[73]. South Africa has been recently reported to have the highest number of new HIV infections compared to the rest of the world[74].

2.3. Human immunodeficiency virus

Human immunodeficiency virus is associated with a group of viruses known as retroviruses[75]. The HIV virus is a virus that weakens the immune system by infecting the immune system cells[76]. The proteins involved in the HIV-I life cycle are shown if **Figure 2.1** below. The HIV genome is comprised of three

major genes, 5'gag-pol-env-3', encoding for key structural proteins, which includes the viral envelop (glycoprotein (gp) 120 and transmembrane gp41), the *gag* polyprotein such as gp17, the viral core capsule protein gp24, SP1 (spacer peptide 1, p2); NC (nucleocapsid protein, p7); SP2 (spacer peptide 2, p1) and P6 protein[77].These major genes also encode essential enzymes, which include RT, IN, Ribonuclease and Protease[77]. There are also accessory proteins, which assist HIV virus for an efficacious infection, which includes viral infectivity factor (Vif), negative regulation factor (Nef), viral protein R (Vpr) and viral protein (Vpu)[78,79].

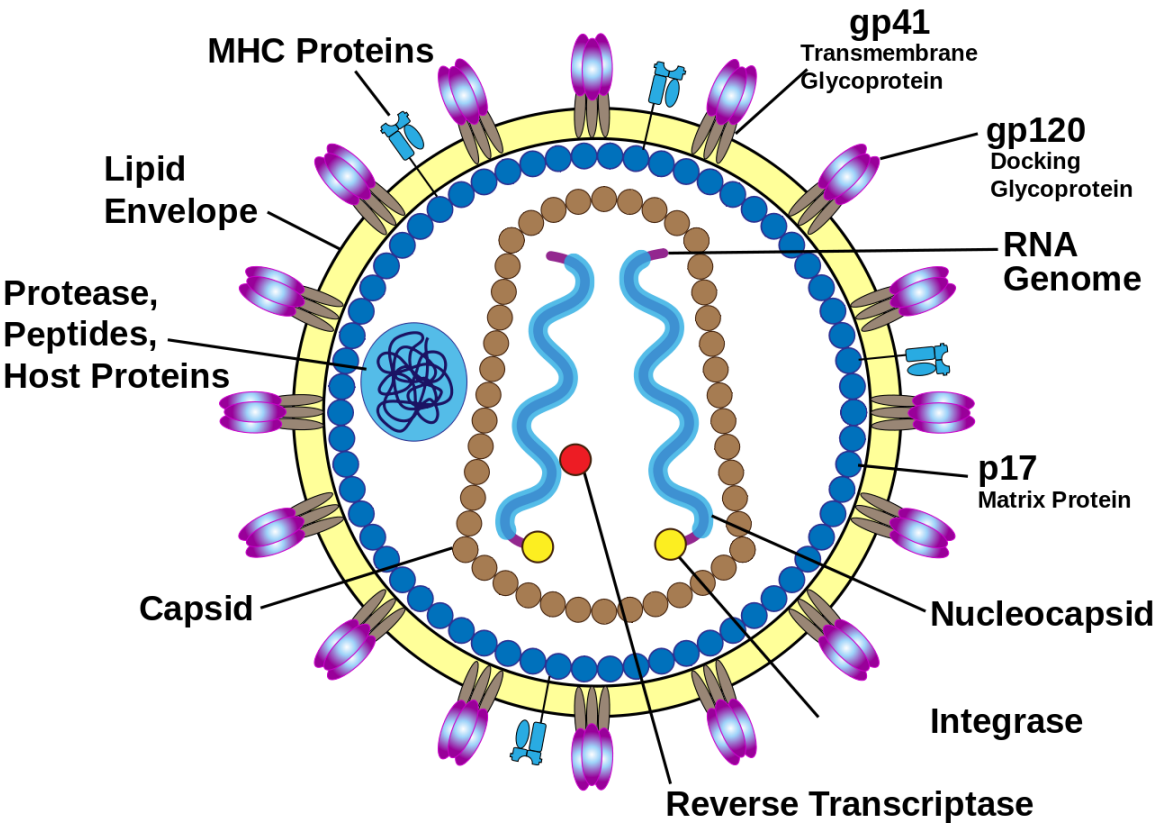


Figure 2.1: The structure of Human immunodeficiency virus adapted from[80].

2.4. The HIV-1 life cycle

Viruses need to infect cells to reproduce[81]. Like any other viruses, HIV does the same to human immune system cells[76]. The HIV infection involves a number of events, which are illustrated in the life cycle in **Figure 2.2** below. The HIV life cycle involves six stages known as binding and fusion, reverse transcription, integration, transcription, assembly and budding[82]. These stages are further elaborated below:

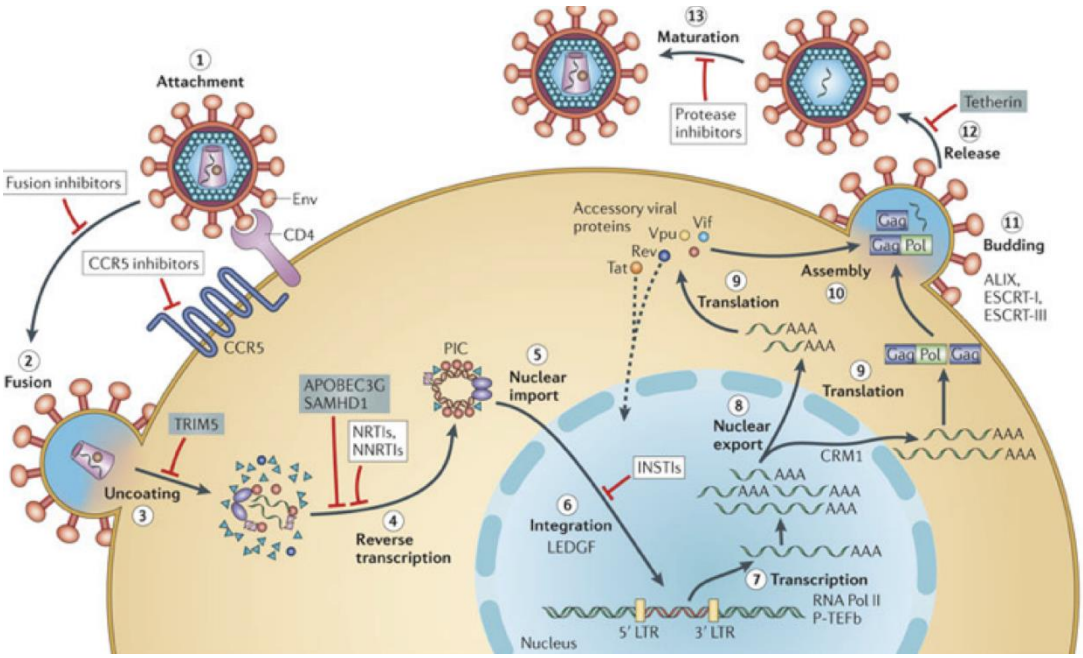


Figure 2.2: Systematic presentation of HIV replication cycle adapted from [83].

(i). Binding and fusion.

The initial step for HIV-1 life cycle is the binding and fusion of the virus into the host cell i.e. the human immune system[84]. The HIV-1 virus uses CD4 antigen for it entry into the host cell[84]. Chemokine receptors CCR5 and CXCR4 are believed to be the final trigger for HIV-1 virus fusion into the host cell

membrane[85]. This is achieved by the binding of envelop glycoproteins gp120 to CCR5 and CXCR4, which causes conformational changes to both gp120 and gp41 thus membrane fusion reaction is triggered which brings the viral core into the cytoplasm of the host cell[86]. Research have identified these three stages of viral entry as targets for the development of anti-HIV therapy. These include gp120 inhibitors[87–92], CCR5 inhibitors[93,94], CXCR4 inhibitors[95–99] and gp41 inhibitors[100–105].

(ii). Reverse transcription.

The reverse transcription process begins as soon as the viral particle move into the cytoplasm of the target host[10]. Reverse transcriptase is responsible for the conversion of RNA into a double-stranded DNA[43,106,107].

(iii). Integration.

The integration step occurs after RNA has been transcribed into a double stranded DNA. An enzyme called Integrase is required in this step to incorporate DNA copy (provirus) into the DNA of the host cell[108]. This is achieved by the cleaving of the viral DNA at each of the 3′ end creating the precursor ends for integration[109]. The cleaved fragments of viral DNA are joint into the host's DNA[110].

(iv). Transcription and translation.

After the integration stage the provirus acts as a template for transcription which is controlled at the transcriptional and posttranscriptional levels[111]. The spliced messenger RNA (mRNA) are produced which encodes viral regulatory proteins Tat and Rev[112]. Furthermore, the regulatory protein Tat stimulates transcription and Rev suppresses splicing and assist in the transportation of unspliced viral mRNA to the cytoplasm[113]. The unspliced mRNA encoding the viral structural proteins are translated and assembled into virus particles[114].

(v). Assembly.

The HIV genetic material gather together with new HIV proteins and enzymes to form new viral particle[115].

(vi). Budding and maturation.

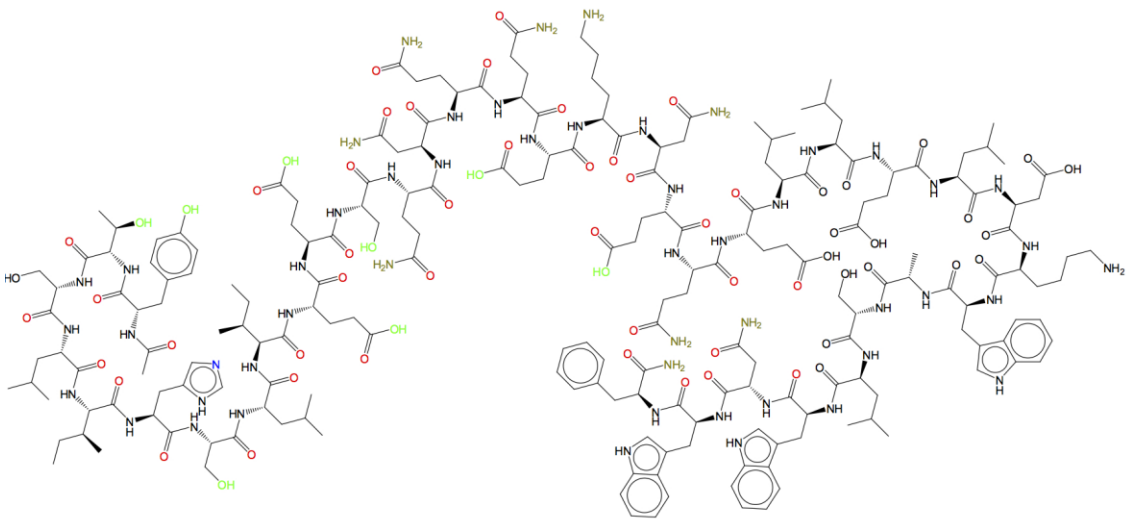
After the new viral particles have been assembled, they bud off the host cell, creating a new virus, which then matures and become infectious[116]. Each step of the HIV-1 cycle forms part of anti-HIV therapy and these are discussed further in the next sub-section.

2.5. The HIV-1 virus infection current treatments.

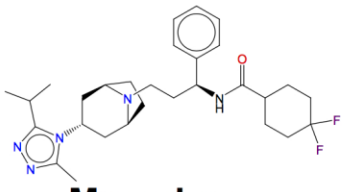
The fields of biology, pharmacology and clinical care have all greatly contributed in changing HIV infection from being a fatal illness to a chronic diseases that is manageable[117]. Combination of medicines are used in treating HIV infection[118]. The anti-HIV therapy does not cure HIV but controls the virus by decreasing the viral load in the blood[119]. Azidothymidine (AZT) was the first anti-HIV drug approved in 1987[120]. To date, 25 anti-HIV drugs have been approved[121], which include Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI), integrase inhibitors and entry inhibitors[122]. Fusion inhibitors are also part of anti-HIV drugs[123] and enfuvirtide (T20), Fuzeon is the only approved fusion inhibitor by far[124].

2.5.1 Fusion/entry inhibitors

The fusion of the HIV-1 virus is an early stage of the life cycle of HIV-1. To date there are two inhibitors inhibiting this stage namely T20 and Maraviroc (MVC) which were approved in 2003 and 2007 respectively[125]. The T20 inhibitor binds to gp41[126] while the MVC binds to CCR5-receptor antagonists[93].



Enfuvirtide



Maraviroc

Figure 2.3: FDA-approved fusion inhibitors

There are other agents, which are still under investigation for their ability to interact with the proteins involved in HIV entry and their possibility to serve as entry inhibitors[127]. These include Fostemsavir, Plerixafor, Epigallocatechin gallate, Vicriviroc, Aplaviroc, and VIR-576 (**Figure 2.3**).

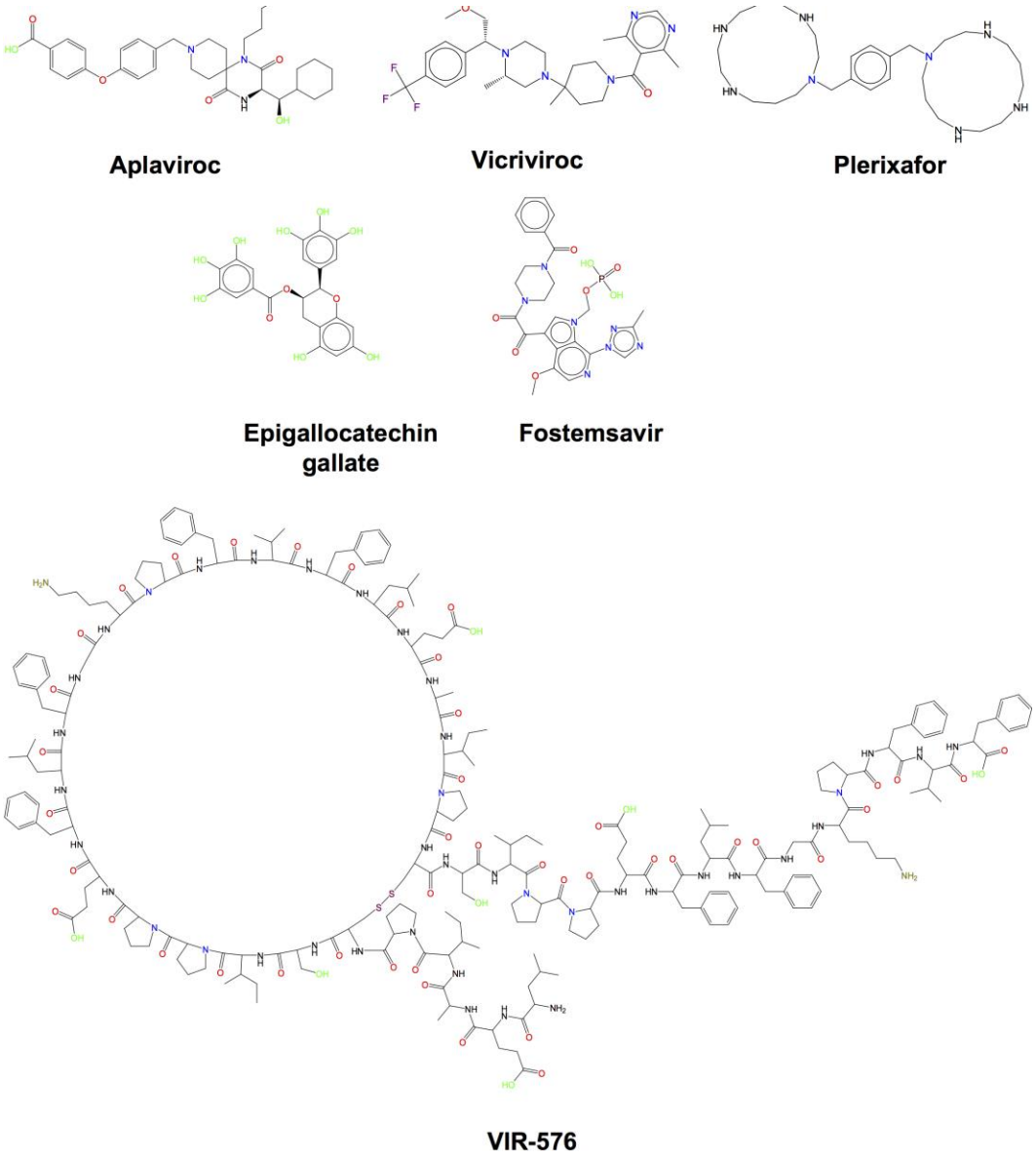


Figure 2.4: Agents under investigation as potential fusion inhibitors

2.5.2 Reverse transcriptase inhibitors

Reverse transcription is an essential step in the HIV-1 life cycle that involves the conversion of retroviral RNA to proviral DNA by the enzyme reverse transcriptase (RT)[128]. The two categories of RT inhibitors include NRTIs (**Figure 2.5**) and NNRTIs (**Figure 2.6**). The NRTIs binds to HIV-1 RT competitively, terminating the synthesis of proviral DNA[129]. Zidovudine is the first NRTI which was discovered in 1985[129]. Later, more NRTI were discovered which include didanosine, zalcitabine stavudine, lamiduvine, abacavir and acyclic nucleoside phosphonates (ANPs), such as adefovir and tenofovir[130].

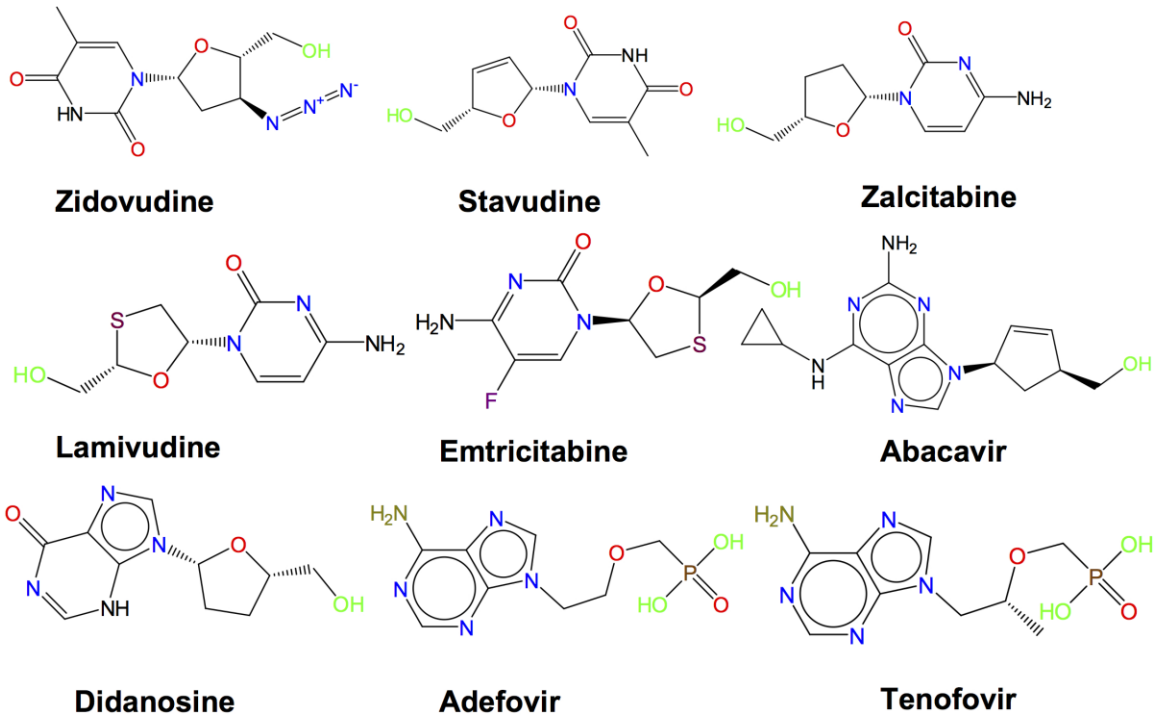


Figure 2.5: FDA-approved NRTIs

The NNRTIs were first reported between 1989 and 1990[131]. These inhibitors are said to inhibit HIV-1 RT in a non-competitive manner[132]. Nevirapine, Efarivenz and delavirdine are the first generation NNRTIs[132]. Etravirine is the second generation of NNRTIs[133], which was first approved in 2008[134] and Rilpivirine, which was approved in 2011 as the first line treatment for HIV-1[135].

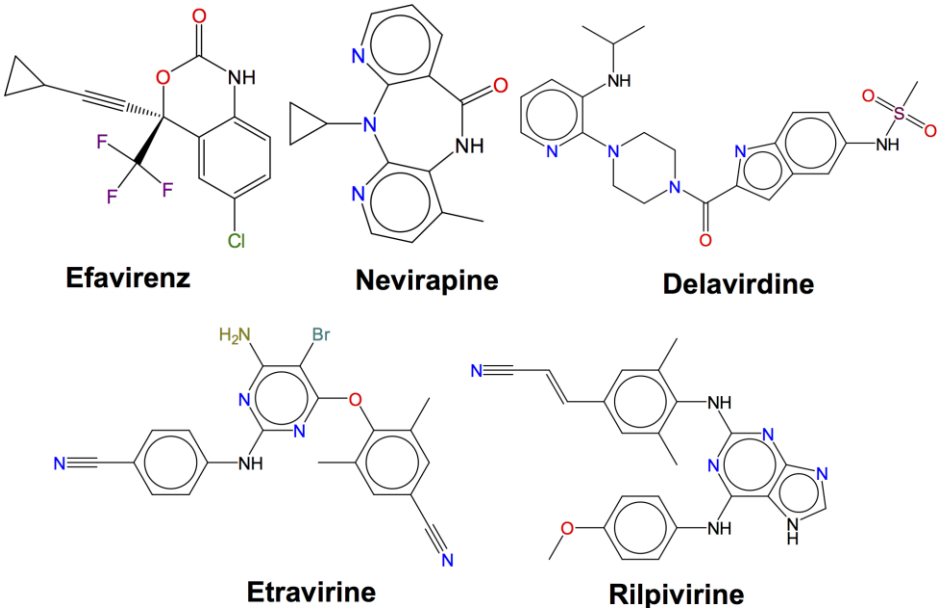


Figure 2.6: FDA-approved NNRTIs

The integration of HIV-1 genetic material into the host cell genome is a required replication step of the HIV life cycle Integrase is thus an essential target for therapeutic intervention[136]. The first FDA-approved Integrase inhibitor is Raltegravir in 2007[136,137] followed by Elvitegravir in 2012[138] and dolutegravir in 2013[139] (**Figure 2.7**).

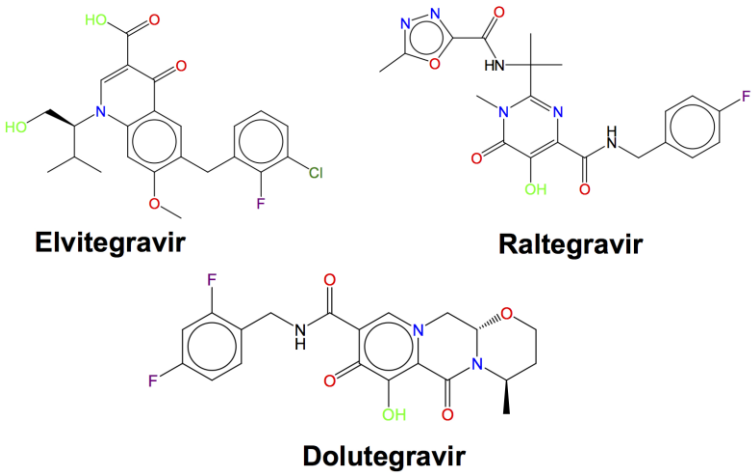


Figure 2.7: FDA-approved Intergrase inhibitors

2.5.4 Protease inhibitors

The HIV-1 protease cut the longer viral polypeptide chain precursor into individual mature and functional viral proteins[140]. Protease inhibitors are potent antiretroviral drugs and represent a fundamental component of highly active antiretroviral therapy (HAART)[141]. Protease inhibitors bind competitively to protease's active site[142], preventing the virus from reaching it infectious stage of maturity[143]. The FDA approve the first PIs between 1995 and 1996[144]. There are eleven PIs (**Figure 2.8**) exit in the market to date, namely saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, fosamprenavir, atazanavir, tipranavir and darunavir[145].

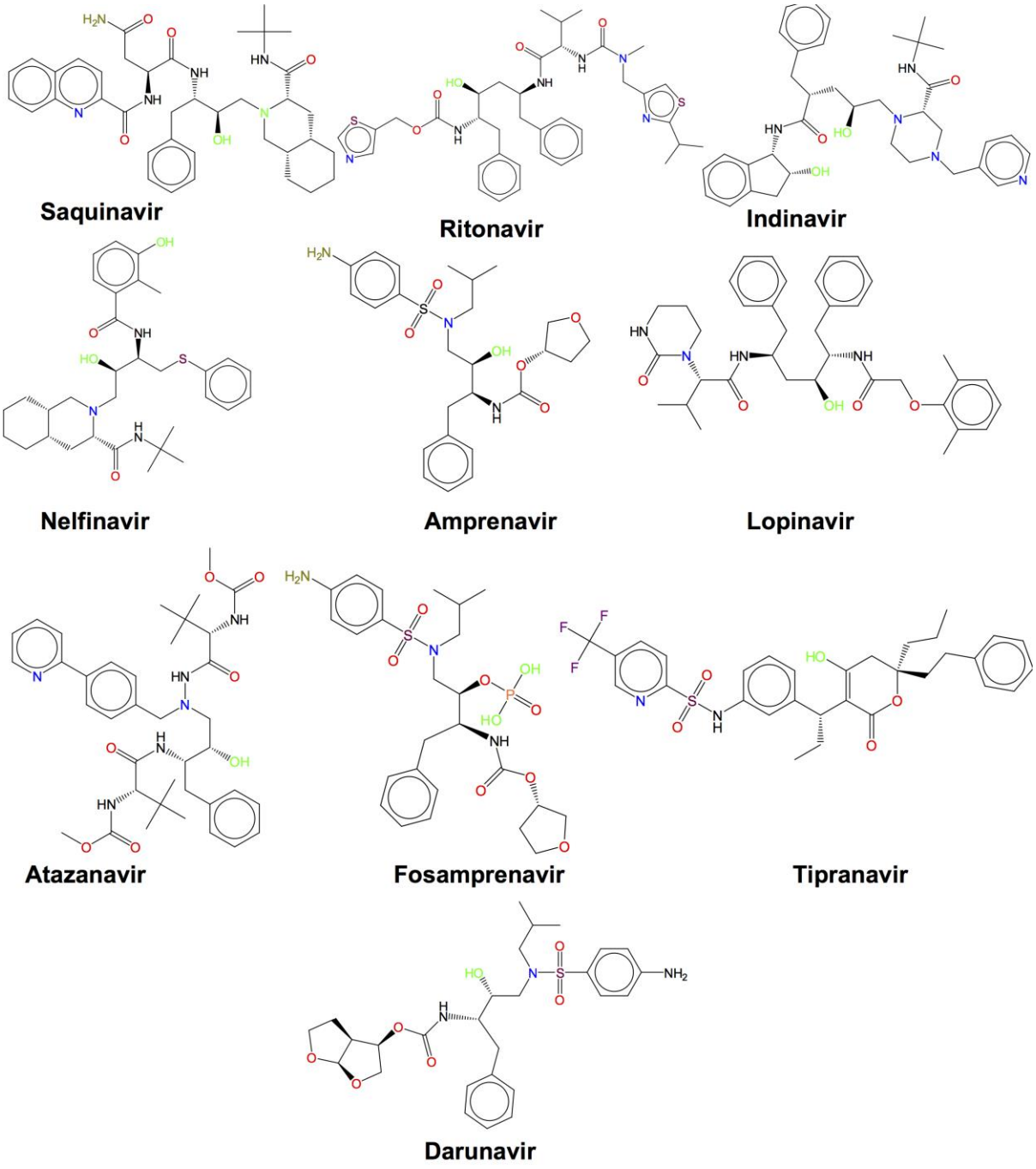


Figure 2.8: FDA-approved Protease inhibitors

2.6. The HIV-1 viral enzymes.

2.6.1. HIV-1 RT enzyme

A multifunctional enzyme, HIV-1 RT is responsible for copying the single-stranded viral RNA genome into double-stranded DNA[146]. The HIV-1 RT is one of the central targets in the anti-AIDS therapy[147] and It is a heterodimer comprised of two subunits namely p56 and p66[148]. The p56 is a smaller subunit consisting of 440 amino acid and p66 is a longer subunit with 560 amino acid[149]. It is comprised of four subdomains namely "fingers ","palm ","thumb ", and "connection " by comparison to a human right hand[146] illustrated in **Figure 2.9**.

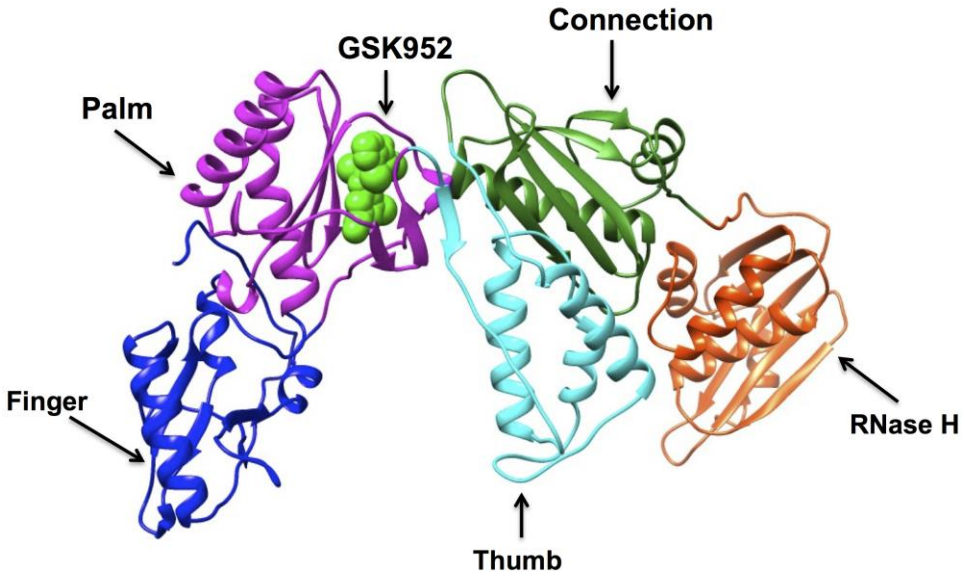


Figure 2.9: Ribbon representation of the HIV-1 RT-GSK952 complex (PDB code 2YNI[150]) with finger (blue), palm (magenta), thumb (cyan), connection (forest green) and RNase H (orange red) of p66 subunit and GSK952 (green).

The HIV-1 RT has two enzymatic activities, a DNA polymerase which uses RNA template to make a DNA strand and RNase H that cleaves the RNA strand, (both in the p66 subunit), after the DNA strand has been built[151]. The HIV-1 RT uses transfer RNA (tRNA) to build cDNA from sRNA to form DNA-RNA hybrid[152] (**Figure 2.10**). The tRNA binding to the 3' long terminal repeat, base paired to a complementary sequence near the 5′ end, of the viral RNA genome initiates the DNA synthesis process[106].

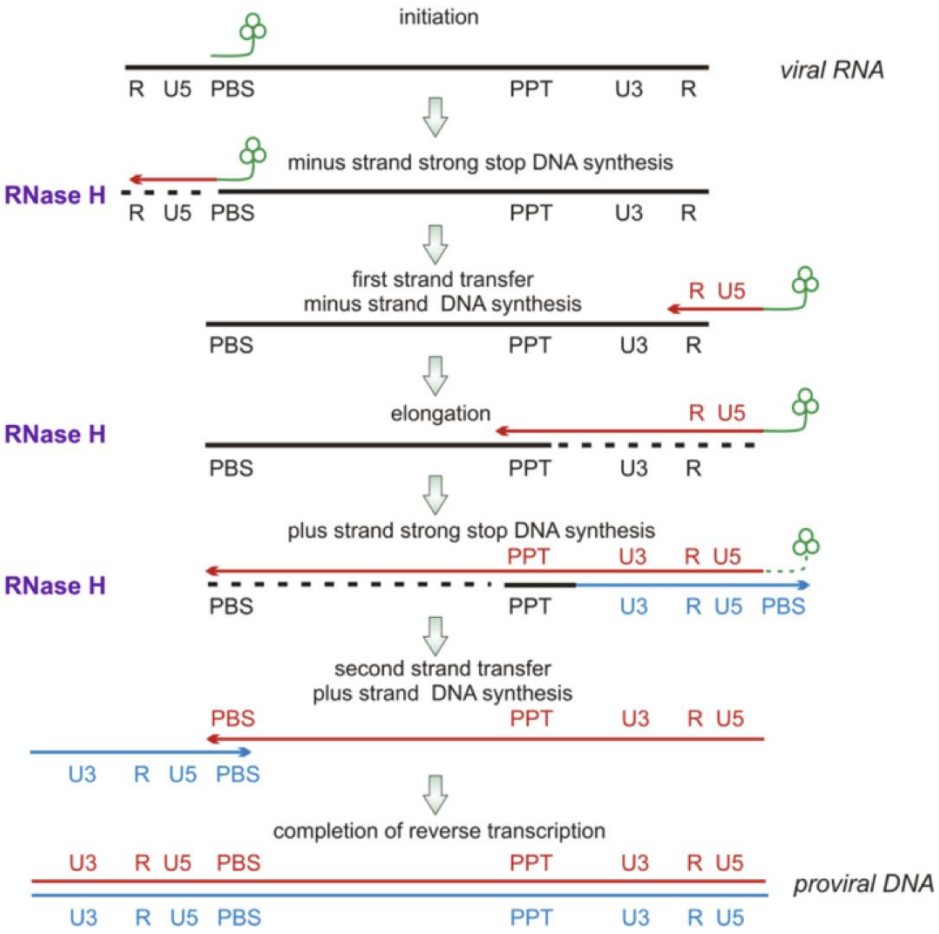


Figure 2.10: Schematic diagram of cDNA synthesis during transcription adapted from [26].

The RNase H degrades the 5′ end of the viral RNA, exposing the newly synthesized minus-strand DNA[153]. The two RNA fragments resistant to RNase H cleavage become templates for the synthesis of a plus-strand DNA[154,155]. A full-length double-stranded DNA copy is then produced by transfer step, which is incorporated into the host genome[156].

2.6.2. Heat shock protein (Hsp) 90.

Hsp90 is the fundamental constituent of a complex chaperone system[157]. Hsp90 is a vastly abundant, ATP-dependent molecular chaperon essential for the activation and stabilization of a variety of client proteins involved in cellular processes such as cell survival, hormone and cellular pathways[158,159]. Hsp90 is a highly flexible protein[160] and it functional diversity is generated from it conformational flexibility[161].

It is a homodimer consisting of two important isoforms: the Hsp90α and Hsp90β[162–165] entailing four domains[166] namely N-terminal ATP-binding domain (NTD), middle domain (MD), and a C-terminal dimerization domain (CTD) and charged linker that connects the N-terminal and middle domains[167–171], as illustrated in **Figure 2.11**. The NTD makes up the binding site of the nucleotide, MD is significant for the binding of several substrates and the CTD is primarily responsible for the dimerization of the protein[168]. Previous studies later discovered a second ATPase binding site in the CTD of Hsp90[172]. Chapter 5 entails an in-depth discussion about the Hsp90.

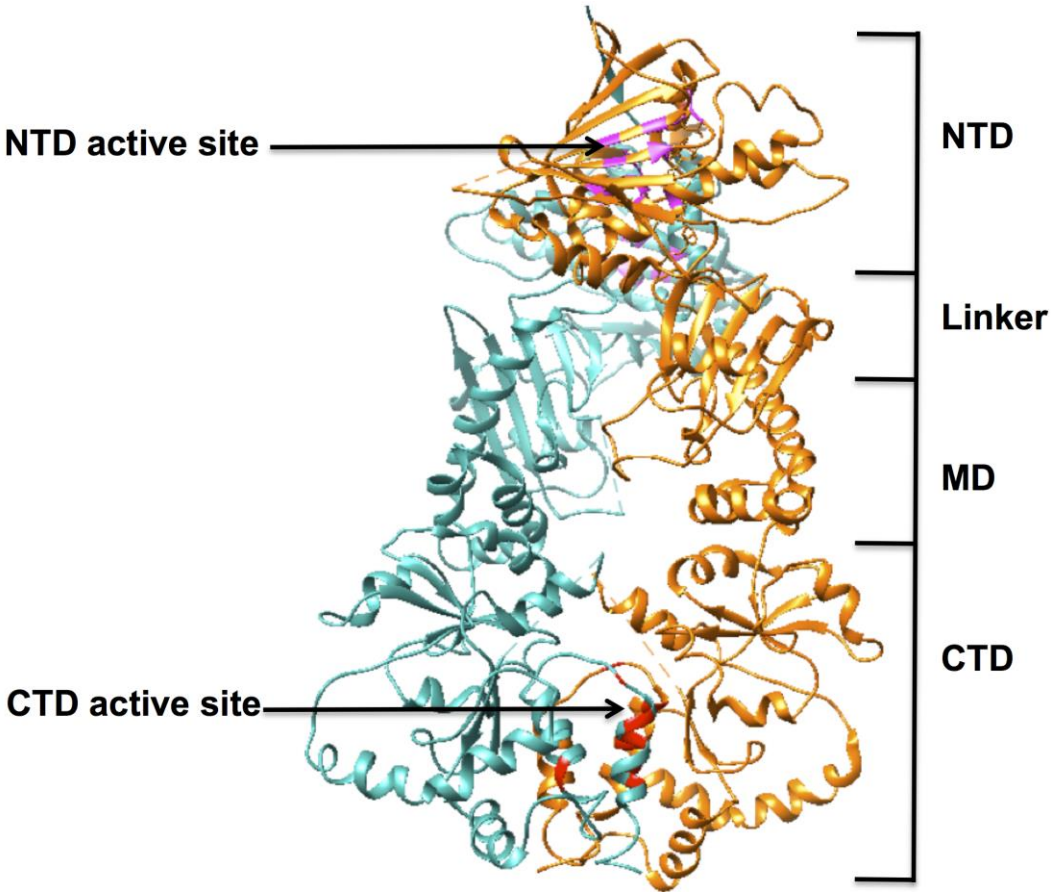


Figure 2.11: The crystal structure of Hsp90α and Hsp90β (PDB code 2CG9) in light sea green and orange respectively

Hsp90 was first and originally discovered for it potential as an anti-cancer drug target in the 1990's[173]. This resulted in great efforts and enthusiasm from researchers to develop potential small molecule which are clinically viable as Hsp90 inhibitors[174,175]. There are currently no FDA approved Hsp90 inhibitors[175]. Previously reported Hsp90 inhibitors include geldanamycin antibiotic[176], the first inhibitor to reach clinical stage[177], which was reported in 1994[178], later an anti-fungal, antibiotic radicicol was reported to

inhibit Hsp90 in 1998[179]. Novobiocin which inhibits the protein folding machinery of CTD of Hsp90 responsible for the conformational maturity of various proteins involved in cancer growth and survival[180]. Coumermycin A1 (C-A1) is a DNA Gyrase B inhibitor[181], which is naturally produced by *Streptomyces rishiriensis*[182]. The C-A1 binds to the N-terminal domain of Gyrase B DNA and inhibit the activity of it ATPase[183]. Recently C-A1 was reported as the inhibitor of Hsp90[184]. Another study confirmed that the C-A1 inhibitor hinders the dimerization process situated at the CTD of Hsp90. The identification and characterization of Hsp90 structure and dynamics and it mechanism of inhibition, form the heart of this study and in hope it can be implemented in the drug discovery and development of more potent HIV inhibitors against Hsp90.

2.5. References

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CHAPTER 3

3. Introduction to computational chemistry and molecular modeling

In this chapter, a broad-spectrum introduction to computational chemistry, different molecular modeling, simulation techniques and their uses are provided. Theoretical descriptions of the computational methods have been explained where applicable. A brief enlightenments of the various computational tools employed in HIV research with primary focus on molecular dynamics simulations, molecular mechanics, molecular docking, binding free energy calculations, pharmacophore model and virtual screening is also included.

3.1. Introduction to Computational Chemistry

Computational chemistry is a division of chemistry which uses computer as an experimental tool and is concentrated on obtaining results significant to chemical problems instead of directly emerging new theoretical methods[185]. The models used includes chem-informatics, molecular mechanics, semi-empirical methods and ab *initio* quantum chemistry which are dependent on experimental information such as parameters and energy levels[186]. Computer aided drug design (CADD), represents computational methods and resources that are used to enable the design and discovery of new therapeutic elucidations[187], and computer-aided molecular design (CAMD), generates compounds with desired properties[188], are methods which help escalate the effectiveness of the drug design process by using the available experimental data[188,189], thus identifying lead compounds and predicting their side-effects.

Molecular dynamics (MD) simulation, one of the two fundamental methods of computational chemistry, was used for the macromolecules-bound conformations to smaller molecules was used in this current research. This chapter will hence begin describing the computational chemistry theories found in both molecular mechanics (MM) and MD: Potential energy surface (PES); Born and Oppenheimer; the Schrödinger's equation, followed by the application of MM and MD methods used in our investigations.

3.2. Schrödinger's equation

The Schrödinger's equation is the principal equation of physics, which describes quantum mechanical behavior[190]. It defines the dynamics of physical systems for isolated quantum systems[191]. There are two sorts of Schrödinger equation: One which is time-dependent thus describes how the wave function of a particle changes over time[192] and the other one which is time-independent explain the permissible energies for the particle[193]. Hence the names time dependent Schrödinger equation and time independent Schrödinger equation respectively. Hamiltonian operator is defined by time dependent Schrödinger equation, a commonly used Schrödinger equation in computational chemistry, as the summation of both

the kinetic energy and the potential energy[194]. The sum of the kinetic energy and the potential energy are presented in the following equation:

$$H = T + V \qquad \text{Eq. 1}$$

Where *H* represents Hamiltonian operator, kinetic energy defined by *T* and the potential energy by *V*. H can alternatively be represented by the following equation:

$$H = -\frac{h^2}{8\pi^2} \sum i \frac{1}{mj} \left(\frac{a^2}{ax^2} + \frac{a^2}{ay^2} + \frac{a^2}{az^2} \right) + \sum i \sum < j \left(\frac{e_i e_i}{x_{ij}} \right) \qquad \text{Eq. 2}$$

3.3. Born-Oppenheimer approximation

The Born-Oppenheimer approximation is precisely a major part of an everyday quantum analysis of atoms and molecules[195], which was first introduced in 1927 post to the Schrödinger equation publication[196]. The Born-Oppenheimer approximation is centered on the nuclei being heavier than electrons by numerous thousand[197]. The molecular system's energy structure and the conditions of quantum can be merely determined in two steps[198] which involves the resolution of Schrödinger's equation. First step is to resolve Schrödinger's equation by holding the nuclei in space at a fixed position[194,199] and the second is by obtaining the PES based on resolving the Hamiltonian principle using the first step's energy[200]. These steps are well defined using the following equations:

Step1: $$(\boldsymbol{r},) = \boldsymbol{E^{eff}(R)\varphi^{elec}(r,R)} \qquad \text{Eq. 3}$$

and

Step 2: $$T^{elec} = \left[-\frac{h^2}{8\pi^2 m} \sum_i^{electrons} \left(\frac{a^2}{ax^2} + \frac{a^2}{ay^2} + \frac{a^2}{az^2} \right) \right] \qquad \text{Eq. 4}$$

3.4. Potential Energy Surface

A potential energy surface (PES) is a mathematical function that describes how the energy of a molecule is dissimilar to its geometry[201]. This energy is given as a function of stretches, bends and torsions by MM and QM gives an energy function, which can be the same in principle and works for any molecule[202]. Ab initio is a method used in determining PES and electronic structure calculation can be performed in a large number[203], which is relevant for accurately describing the whole PES[204]. The **Figure 3.1** below best describes the PES concept.

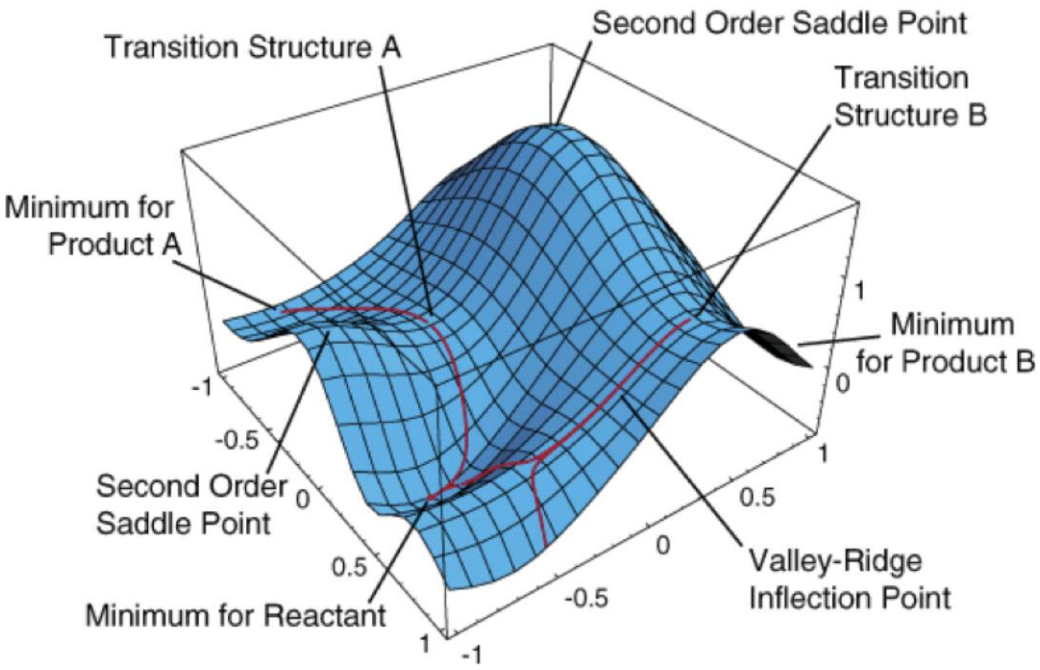

Figure 3.1: Three-dimensional structure of Potential energy surface adapted from[205].

3.5. Molecular Mechanics

Molecular mechanics (MM) is a model used in the calculation of the energy of the complex from which the energy of both the free ligand and the receptor can be obtained[206]. Force fields are used to calculate the potential energy of all systems in MM[207]. Small molecules as well as large biological systems or material assemblies with many thousands to millions of atoms can be studied using MM[208]. Molecular mechanics potential energy functions have been used to calculate binding constants[209], protein folding kinetics[210], protonation equilibria[211], active site coordinates[212] and to design binding sites[213]. The setbacks of MM are that it is circumscribed by parameters of equations (i.e. a different force-field for different types of atoms) and is not applicable for electronic properties[214–216]. Molecular mechanics articulates the total energy as a sum of Taylor series expansions for stretches for every pair of bonded atoms, and adds additional potential energy terms coming from *bending*, *torsional energy*, *van der Waals energy*, *electrostatics* and *cross terms*[217,218]:

$$E = E_{str} + E_{bend} + E_{torS} + E_{vdw} + E_{el} + E_{cross}. \qquad \text{Eq. 5}$$

Molecular mechanics attempts to make the remaining constants more transferrable among molecules than they would be in spectroscopic force fields by separating out the van der Waals and electrostatic terms.

3.5.1. Force fields

A force field is a mathematical function in combination with parameters that foretells the energy associated with the conformation of a molecule[217,219]. The widely used bio-molecular force fields include Amber, CHARMM, GROMOS, and OPLS-AA[220]. Each force-field is in possession of diverse parameters, therefore, they must be attuned to give results of the forces acting within a molecule. AMBER Force Field (GAFF) was used in our study to set parameters for the ligands while the standard AMBER force field was used for the human Hsp90 homologue and HIV-RT[221]. A comprehensive discussion about the AMBER force field is included in chapter 5.

3.6. Molecular Dynamics simulations

Molecular dynamics simulations have become a primary tool for the exploration of biomolecules[222]. Bio-molecular dynamics simulations, to date has three major areas of application which are to bring bio-molecular structures alive, calculates thermal averages of molecular properties and explores the thermally accessible conformations of a molecule or a complex[223]. The three commonly used simulation methods for molecular systems include Monte Carlo, Brownian dynamics and molecular dynamics[224,225]. Monte Carlo method is a vital tool for the estimation of the average properties of systems possessing a large number of accessible states[226]. Brownian dynamics technique is used to study the large-scale dynamics of macromolecules and nanoparticles diluted solution[227]. Molecular dynamics is proficient of simulating an enormous diverse systems both in and out of thermodynamic equilibrium[228] and codes such as LAMMPS[229], DLPOLY[230], GROMACS[231], NAMD[232] and ESPResSO[233]. The calculations for MD simulations are centered on MM principles, and the newton's laws of motion is incorporated to create conformations[234]. The results are in a form of trajectories that specifies how the particle position and velocity varies with time[235]. The trajectories results from determining the force (Fi) for each particle as a function of time, which is equivalent to the negative gradient of the potential energy

$$\boldsymbol{F_i} = -\frac{U}{ri} \qquad \text{Eq. 6}$$

The potential energy function is represented by U and the position of the particle by r, whereas acceleration ($\boldsymbol{a}$) of a particle is calculated by dividing the force by the mass of a particle represented by Newton's Laws of Motion equation below:

$$\boldsymbol{a_i} = -\frac{Fi}{mi} \qquad \text{Eq. 7}$$

The change in velocity is equal to the integral of acceleration over time and the change in position is equal to the integral of velocity over time, which is represented by an equation below:

$$\boldsymbol{dv} = \int \boldsymbol{adt}, \quad \text{Eq. 8}$$

$$\boldsymbol{dr} = \int \boldsymbol{vdt}, \quad \text{Eq. 9}$$

Lastly, the kinetic energy is equal to the velocities and momenta of the given particles:

$$(\boldsymbol{v}) = \frac{1}{2} \sum_{i=1}^{N} \boldsymbol{m_i v_i} \quad \text{Eq. 10}$$

Therefore, the sum of kinetic and potential energies gives the total energy of a given system and is called Hamiltonian (H):

$$(\boldsymbol{q},\boldsymbol{p}) = (\boldsymbol{p}) + \boldsymbol{U}(\boldsymbol{q}) \quad \text{Eq. 11}$$

A set of Cartesian coordinates is defined as *q*, momenta of the particles as *p* and the potential energy function as *U (q)*. The velocities, vi (*t*), are the first derivatives of the positions with respect to time:

$$(\boldsymbol{t}) = (\boldsymbol{t}) \quad \text{Eq. 12}$$

The atomic positions at a specific time (*t*) are defined by (*t*). New positions and velocities of the atoms at a given time (*t*) and the atoms will migrate to these new positions due to the initial atom coordinates of a particular system. Thus, the generation of new conformations and the system's temperature is directly proportional to the average kinetic energy[185,235].

3.7. Approaches for estimating binding affinities

3.7.1. Molecular docking

Molecular docking technique docks micro-molecules into the active site of the protein and try to detect the precise poses of the ligand in the active site of the protein at the same time predicting the binding affinity between the ligand and the protein[236]. The equation used in the calculation of ligand-receptor binding energy is as follows:

$$\boldsymbol{E_{binding}} = \boldsymbol{E_{target}} + \boldsymbol{E_{ligand}} + \boldsymbol{E_{target-ligand}} \quad \text{Eq. 13}$$

It has become a vital tool for drug discovery[237]. Docking can be accomplished over two interconnected steps: first by the selection of conformations of the ligand in the protein's active site; then ranking the conformations according to a scoring function[238]. A number of different docking programs, based on different algorithms, include DOCK[239], FTDOCK[240], FLOG[241], GOLD[242], FlexX[243], AutoDock[244], SANDOCK[245], which were established to perform molecular docking studies. All of these programs can be classified into four broader categories: stochastic Monte Carlo, fragment-based, evolutionary-based, and the shape complementary method[246]. The two types of docking include rigid body and flexible docking[247]. In this research study an advanced version of AutoDock (AutoDock Vina) was used as the docking method[248]. Different areas applies molecular docking including: virtual screening (hit identification), drug discovery (lead optimization), prediction of biological activity, de-orphaning of a

receptor, protein-protein interaction, structure-function studies, enzymatic reaction mechanisms, protein engineering and binding-site identification (blind docking)[249]. Protein-ligand docking is the most distinct docking, which is used to predict the biological activity of a ligand[250]. AutoDock however has some shortcomings including:

Posing: The process of determining the correct conformation and orientation of a ligand's binding mode into the target's active site.

Scoring: The pose score is a measure of the fit of a ligand into the active site. Scoring during the posing phase usually comprises of simple energy calculations such as electrostatic, Van der Waals and ligand strain. Furthermore, the re-scoring might attempt to estimate more accurately the binding free energy and perchance include properties like entropy and solvation.

Implementation of hybrid methods has been reported to create improved algorithms[251].

3.7.2. Binding free energy calculations

The binding free energy calculations allow a complete analysis of the amount of energies that are responsible for molecular stability or binding affinity. The Molecular Mechanics Poisson–Boltzmann Surface Area (MM/PBSA) method[252] was used in this study to estimate binding energies. Previous studies also documented that Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) calculates free binding energy better than MM/PBSA[253]. In the current study, the free binding energy of HIV-RT-ZINC54359621 complex and C-A1-Hsp90 was analyzed using the MM/GBSA method[254–257] to validate the docking studies. A brief description about free binding energy calculation is provided in both chapter 4 and 5.

3.7.3. Entropy calculations

Entropy can be defined as the vital information to measure the degree of disorder of a thermodynamic system[258]. Entropy forms a major role in all simulations hence if not accurate it causes a setback[259,260]. In drug design the binding affinity optimization of lead compounds or known drugs is normally accomplished by the substitution of atoms or groups of atoms in the molecule or by limiting the conformational freedom of the molecules as a result increasing the binding affinity, that is, induce a favorable change in binding free enthalpy (ΔG_{bind})[261]. The free energy of the system is equal to the sum of its enthalpy (H) plus the product of the temperature (Kelvin) and the entropy (S) of the system[262]. Gibbs free energy of reaction for calculating entropy is presented by the following equation:

$$\Delta G = \Delta H - T\Delta S \qquad \text{Eq. 14}$$

Thus

$$\Delta S = \frac{\Delta G}{\Delta H - T} \qquad \text{Eq. 15}$$

Where ΔG is free binding energy, and ΔH is enthalpy ΔS is entropy and T is the temperature.

3.8. Modeling tools used in this study

3.8.1. Per-residue energy decomposition analysis

Per-residue energy decomposition (PRED) defines the specific energy contributed by each amino acid residue in a protein towards the binding of the ligand[263]. The bond formation of the molecule-molecule interaction has been defined also by PRED[264,265]. The in-depth description of PRED is found in chapters 4 and 5.

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CHAPTER 4

Accepted article

Per-residue energy decomposition (PRED) pharmacophore model to enhance virtual screening (VS) in drug discovery: A case study for identification of Reverse transcriptase (RT) inhibitors as potential Anti-HIV agents.

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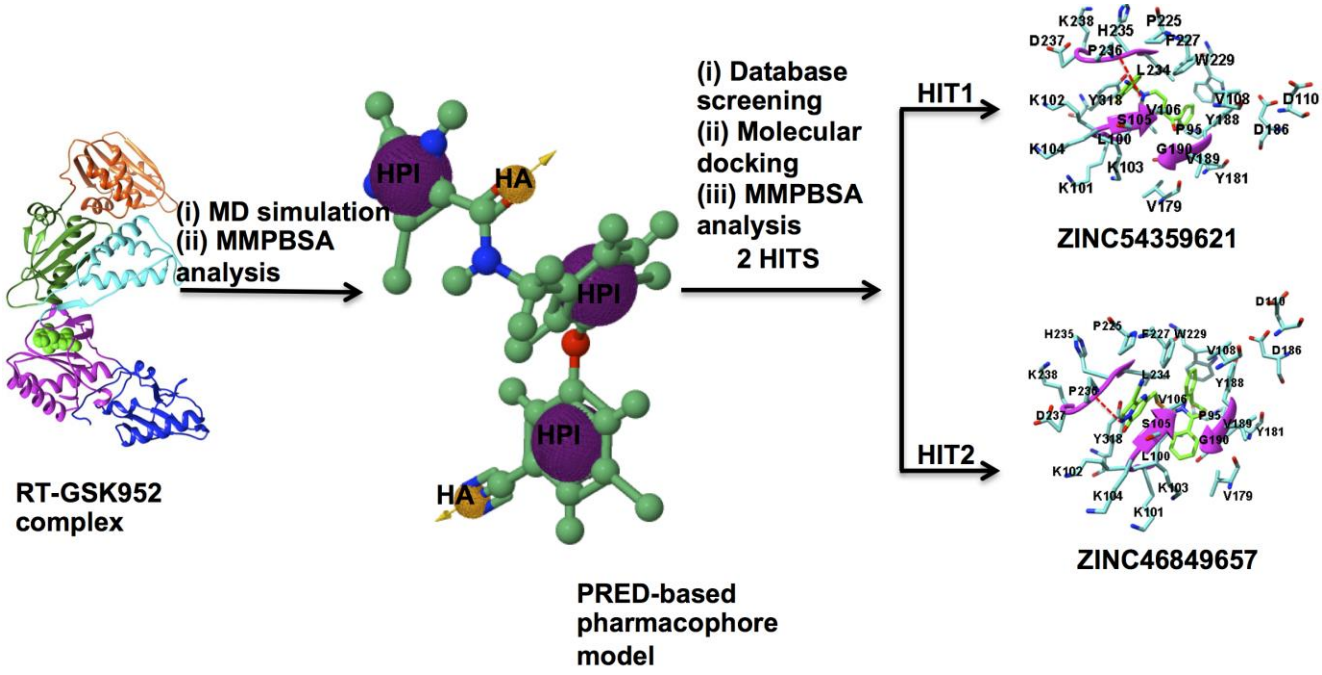
Graphical abstract



Abstract

A novel virtual screening (VS) approach is implemented herein, which is a further improvement of our previously published "target-bound pharmacophore modeling approach". The generated pharmacophore library is based only on highly contributing amino acid residues (HCAAR), instead of arbitrary pharmacophores, which is most commonly used in the conventional approaches in literature. HCAAR were distinguished based on free binding energy (FBE) contributions obtained from calculation from molecular dynamics (MD) simulations. To the best of our knowledge; this is the first attempt in the literature using such an approach; previous approaches rely on the docking score (DS) to generate energy-based pharmacophore models. However, DS are reportedly unreliable. Thus we present a model for a per-residue energy decomposition (PRED), constructed from MD simulations ensembles generating a more trustworthy pharmacophore model which can be applied in drug discovery workflow. This work is aimed at introducing a more rational approach to drug design field, rather than comparing the validity of this approach against those previously reported. We recommend additional computational and experimental work to further validate this approach. This approach was used to screen for potential reverse transcriptase (RT) inhibitors using the pharmacophoric features of compound **GSK952.** The complex was subjected to docking and thereafter MD simulation confirmed the stability of the system. Experimentally determined inhibitors with known HIV-RT inhibitory activity were used to validate the protocol. Two potential hits **ZINC46849657** and **ZINC54359621** showed a significant potential with regards to FBE. Reported results obtained from this work confirm that this new approach is favorable to the future of drug design industry.

Keywords: HIV-1; Reverse Transcriptase; **GSK952**; Molecular Dynamic simulations; Pharmacophore model; Molecular docking

1. Introduction

Human immunodeficiency virus (HIV) infection is the leading cause of death across the globe[266]. There are two strains of HIV, namely, HIV-1 and HIV-2. HIV-1 is the most infectious and prevalent globally[267]. Worldwide statistics by the American foundation for AIDS Research (amfAR) reported that sub-Saharan African is the most affected region, with approximately 70% of adults and 91% of children are HIV positive[268].

HIV-1 RT is currently an essential target for the United State Food and Drug Administration (FDA) approved HIV-1 therapy[2] and a prominent target of many approved anti-HIV drugs that are key components of Highly Active Anti-Retroviral Therapies (HAART)[43]. The HIV-1 RT enzyme catalyzes the conversion of viral RNA into cDNA which enters the host nucleus and it is incorporated into host chromosomal DNA of the host cell by the enzyme integrase (IN) enzyme[269]. It is the sole viral enzyme required for the catalytic formation of cDNA generated from viral RNA hence plays a central role in HIV replication[270] making it a prime target for HIV-1 therapy. HIV-1 RT is a heterodimer consisting of two subunits; a p66 subunit (DNA polymerization site and RNase H active site) responsible for the replication of the single stranded RNA genome found in virions into the double-stranded DNA; and a p51 subunit which is responsible for the proper folding of p66 rather than the catalytic subunit [12] (**Figure 1**).

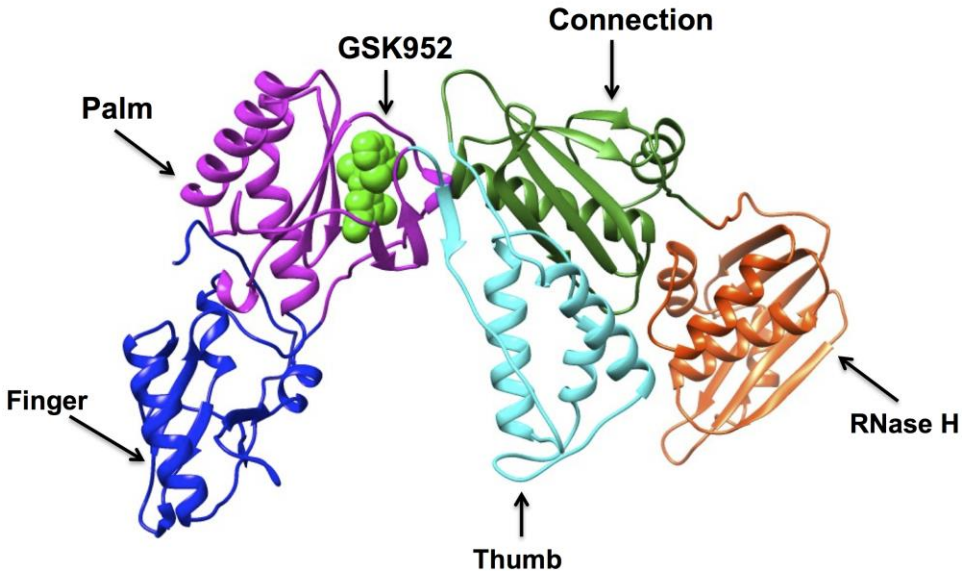


Figure 1: Ribbon representation of the HIV-1 RT-GSK952 complex (PDB code 2YNI[150]) with finger (blue), palm (magenta), thumb (cyan), connection (forest green) and RNase H (orange red) of p66 subunit and GSK952 (green).

HIV-1 RT does not possess any proofreading activity. Thus, DNA synthesis prone to errors can be carried out by HIV-1 RT, results in a higher mutation rate and the production of multiple HIV variants[267].

Etravirine (ETR) and rilpivirine (RPV) are the most recent non-nucleoside reverse transcriptase inhibitors (NNRTIs) resistant to which mutated RT viruses are resistant to[271]. To date, NNRTIs resistance still poses a challenge with regards to NNRTIs therapy. Thus, there is a clear need for the discovery of new drugs with greater resistance profiles capable of inhibiting HIV-I RT mutated viruses. Numerous studies have made a significant attempts in the discovery of new potent NNRTIs using a pharmacophore model approaches[272–274].

The potential anti-HIV drug needs to be effective against resistant strains. The present study looked at **GSK952**, a newly discovered NNRTI. The crystal structure (PDB 2YNI)[150] of the catalytic domain of HIV-1 RT enzyme bound to **GSK952** is available. **GSK952** shows high potency against the mutated Y188L strain as well as the mutated Y188C and K103N strains. Previous work on this compound confirmed it has a good inhibitory activity against HIV-1 RT, including the mutated viral Y188L HIV-1 RT strains[150]. It exhibited a high antiviral profiles when compared to a group of compounds sharing a common imidazole-amide biarylether scaffold[150]. It possesses a linear arrangement of a hydrogen bond acceptors (C=O) and donors (NH), which are required for binding to HIV-1 RT and to form hydrogen bonds with residues in the active site including K101, K103, and P236[275]. **GSK952** forms hydrogen bonds with NH and C=O groups (**S1**), which are positioned along the protein backbone rather than the side chains. This could explain the inhibitory activity against the K103N mutation[276].

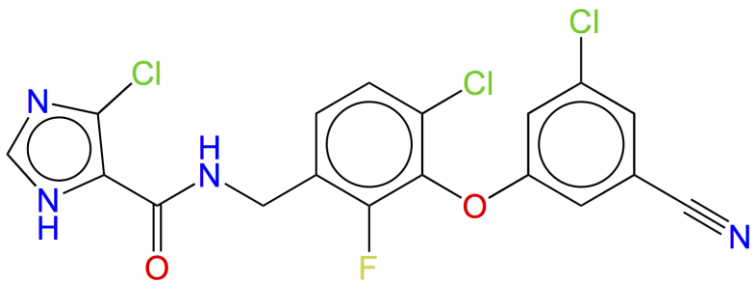


Figure 2: The 2D structure of ligand GSK952 used to generate the pharmacophore model.

In this mutation the side chain of K103 is tilted away from the inhibitor due to the mutation of the wild type to Asn103[150]. **GSK952** (**Figure 2**) has reveals an extraordinary antiviral activity against a wide range of NNRTI-resistant viruses[150] and forms favorable pharmacokinetic profiles across multiple species. We believe it has a great potential and deserves further exploration. Thus it is an ideal compound for the current study.

Computational tools and capability escalation have lead VS to become a routine method in pharmaceutical drug discovery[277]. Numerous computational screening tools are accessible for mining of inhibitors with properties of interest[278].VS is one of the most trusted and convenient tools in drug design. Literature confirms its reliability in the discovery of novel HIV-1 RT inhibitors through VS[279]. VS is either ligand-based or structure based[46]. Structure-based virtual screening (SBVS) uses the 3D structure of the receptor to search for potential ligands[59]. Ligand-based VS (LBVS) also known as pharmacophore-based VS explores features or properties of known bioactive ligands and searches for compounds with similarities[280] and favorable features of a known active are used to build a pharmacophore model. Amongst other models pharmacophore searches are finest at discovering a range of chemical structures with feasible features hence the principal method for the initial selection of compounds[48]. Ligand-based pharmacophore approaches generates libraries based on a set of known ligands illustrative of crucial interactions between the ligands and a particular target[49]. Whereas structure-based pharmacophore models are based on the knowledge of the 3D structure of the target[50]. Numerous studies have combined LBVS and SBVS with the aim of improving the VS process[51–53]. A number of studies have implemented on improving VS and pharmacophore model[54–58]. A previous study proposed a target-bound ensemble generated pharmacophore model to further improve pharmacophore-based VS. It has been confirmed that a target-bound pharmacophore-based VS is a more rational approach[59]. Yet to this date, general standards for VS with regards to method evaluation are insufficient. The aim of this work is to identify more potential NNRTIs by exploiting the structural features of **GSK952** using a pharmacophore model.

We propose implementing an approach aims at improving and refining the current pharmacophore approach. This approach is centered on the type of interactions witnessed at a molecular level which includes hydrogen bonding, charge and hydrophobic interactions[60]. This approach will search for compounds that interact with the highly contributing residues based on the FBE.

In this study we performed MD simulations, pharmacophore-based VS and PRED analysis for residues with the greatest FBE contributions. VS depends primarily on docking calculations although results based exclusively on docking calculations are rather questionable[281]. To test the validity of our proposed approach, we applied the same docking procedure to a set of experimentally determined inhibitors with known HIV-1RT inhibition activity. In our approach we intend to unshackle the limitations of previous approaches, such as using non-crucial residues, which retrieves a large number of hits with assumed activity. In an attempt to enhance the accuracy of the pharmacophore model we only selected HCAAR. A target-bound ensemble was employed in the current study, in the hope of implementing a better approach. A pharmacophore model was created using HCAAR in the protein's active site, whereas conventional

methods use pharmacophore maps created without considering the energy contributions of interacting residues. Only potential pharmacophore moieties were considered thus, the library of potential compounds generated is more concise and direct. In our approach the energy-based pharmacophore map is generated using the FBE calculated from MD, which is a more reliable approach, compared to the conventional approach using DC. We believe this approach will be of a greater advantage to the conventional approach due to these key factors highlighted above. The refinement of the method proposed in this study could be implemented as a potential tool for medicinal chemists in the search for more potent HIV-1 RT inhibitors.

2. Computational methodology

2.1 The computational tools implemented in this study are represented in the workflow in **Figure 3.**

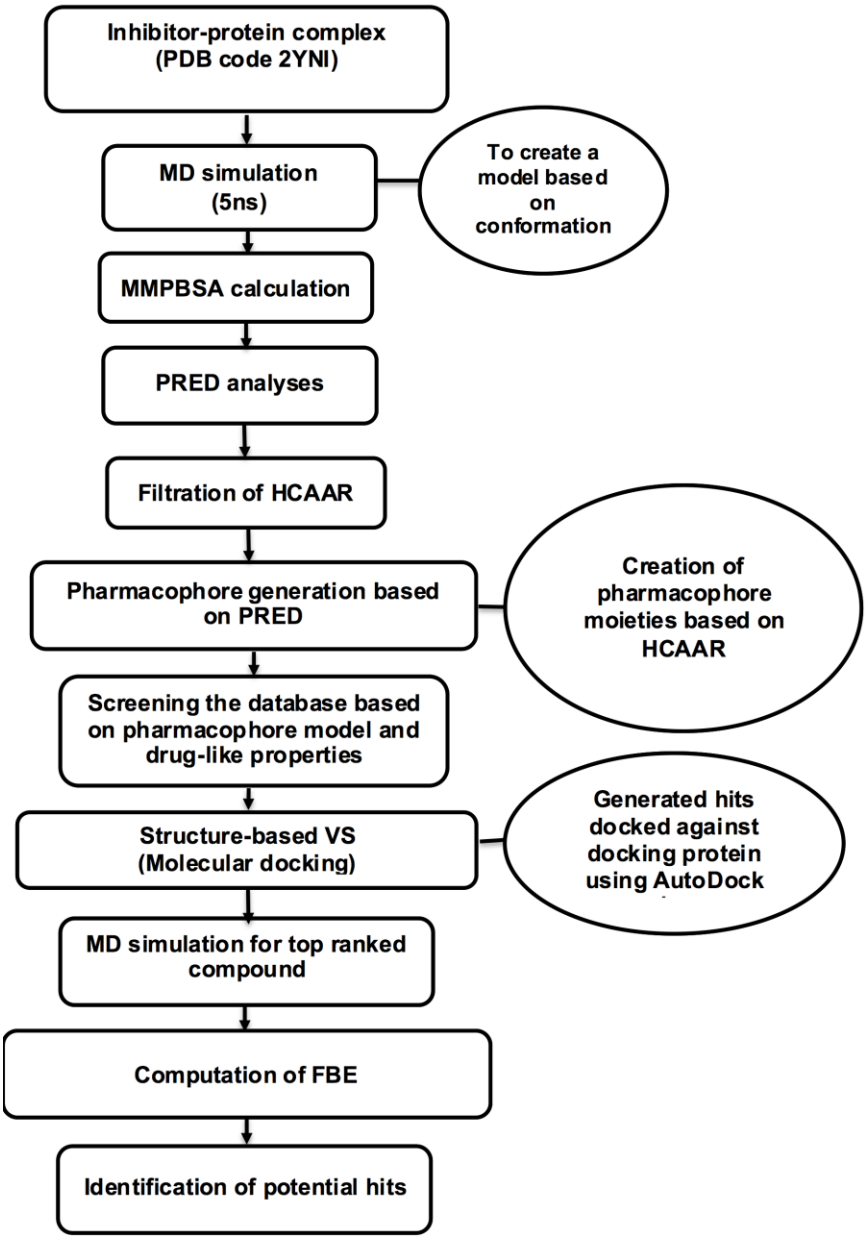


Figure 3: A schematic representation of the VS workflow used in the current study

2.2 A diagrammatic representation of the pharmacophore model used in this study is shown presented in **Figure 4**. The residues with the highest energy contributions are numbered and ranked from 1-6, with one being the highest FBE contributing residue (**Figure 4**). The highest ranked contributors were used to

select the corresponding pharmacophore moieties on the ligand to generate a pharmacophore model used to screen a database for potential hit compounds.

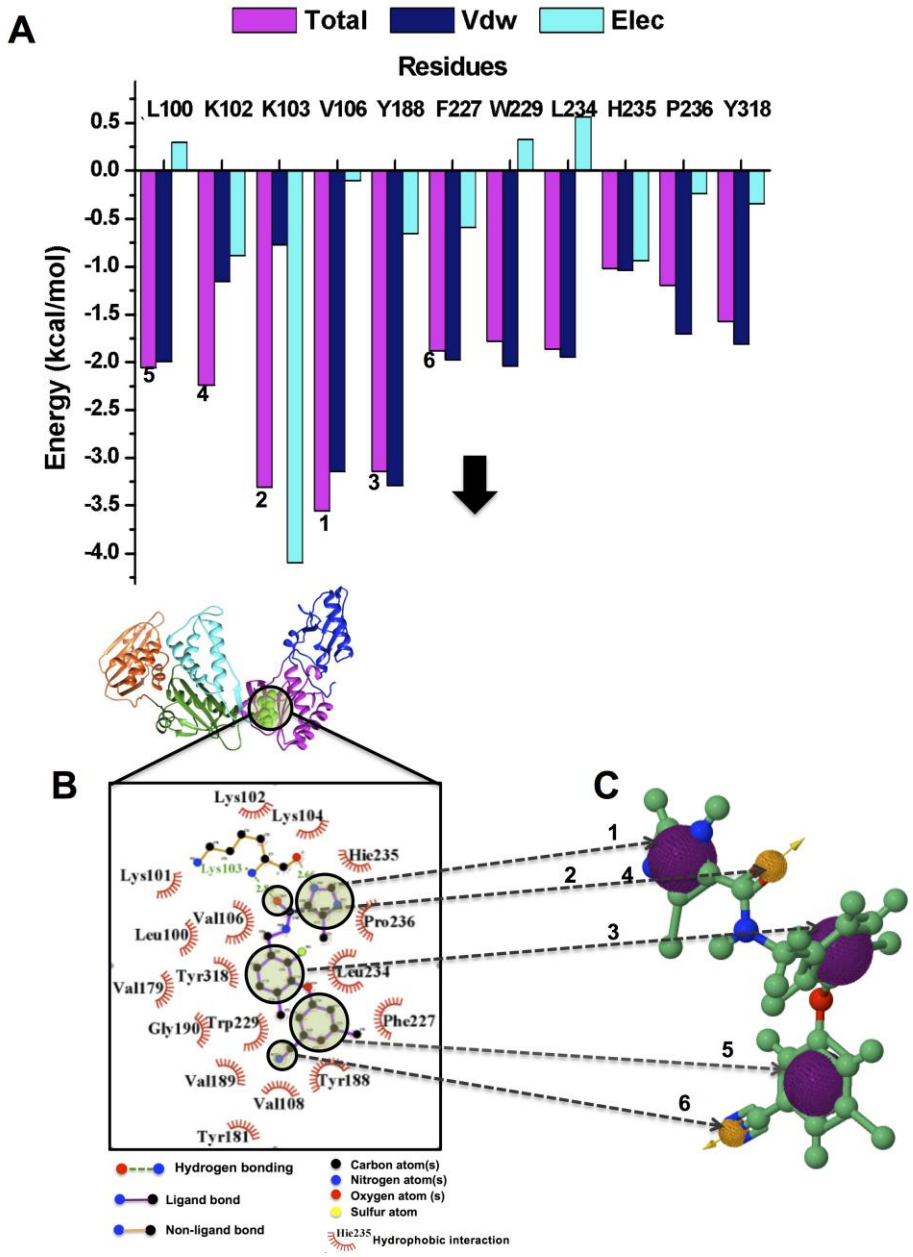


Figure 4: A diagrammatic representation of the pharmacophore model, a) PRED contributions, b) 2D ligand interaction plot and c) Pharmacophore features responsible for FBE contributions.

2.2 Ligand and receptor preparation

The crystal structure of HIV-1 RT-**GSK952** complex was obtained from Protein Data Base (PDB: 2YNI[150]). The steepest decent method and MMFF94S force field in Avogadro software[282] was used to minimize conformation HIV-1 RT-**GSK952** complex. The crystal structure was opened on UCSF chimera[283] to delete chain B and solvents (H_2O, MG, TAR). **GSK952** was selected and deleted. **GSK952** was prepared by adding hydrogen. The ligand was prepared using Antechamber and tLeap of Amber14[284] were used to optimize both HIV-1 RT (enzyme) and **GSK952** (ligand) respectively to ensure all parameters are present for MD simulations. Topology files generated were submitted for MD simulation.

2.3 Molecular dynamic simulations

Solvation of MD simulations[285] was performed on HIV-1 RT-**GSK952** using the GPU version of the PMEMD engine integrated with Amber14[284]. Leap module in Amber 14[284] was used to add hydrogen atoms to the proteins. The standard Amber force field was employed to treat the receptor for bioorganic systems (ff99sb)[286]. A box of equilibrated TIP3P[287] water molecules were arranged around the receptor at a distance of 10Å distance around the enzyme and Cl^- ions were added to neutralise the systems. Cubic periodic boundary conditions were employed and particle- mesh Ewald method[288] applied in Amber12 was used to treat the long-range electrostatic interactions with non-bonding at 2 fs integration step. The initial minimization of the system was carried out using the steepest descent method for 1000 steps. A canonical ensemble (NVT) MD was carried out for 50 ps, during which the system was progressively heated up from 0 to 300 K by means of a Langevin thermostat[289].The system was then equilibrated at 300 K under 1 atm pressure while preserving the force constants on the restrained solute. Throughout all MD simulations the SHAKE algorithm[290] was employed on all covalently bonded atoms to a hydrogen atom. A production run was achieved, with no restraints, for 5 ns in an isothermal isobaric (NPT) ensemble employing a Berendsen barostat.[291] Trajectory exploration including the RMSD, RMSF, and Rg were carried out using PTRAJ and CPPTRAJ modules applied in AMBER14[284].

The trajectory was saved every 1 ps and examined every 1 ps using the PTRAJ module applied in Amber14[284]. The structure was visualized using graphical user interface of UCSF Chimera package[283]. Data was plotted using the GUI of Microcal Origin data analysis software version6 (www.originlab.com).

2.5 Molecular docking.

AutoDock Vina was used for docking calculation[248]. Geister partial chargers were allocated during docking. AutoDock Graphical user interface provided by MGL tools were used to outline the AutoDock atom types[292]. The docked conformations were obtained using the Lamarckian Genetic Algorithm[293]. The magnitude of the grid box was x = 14 Å, y=14 Å, z=18 Å enclosing the anticipated active site residues

including the highest contributing Leu100, Lys102, Lys103, Val106, Try188 and Phe227 residues. The classification of the compounds was in accordance with their DS in a descending order.

Free binding energy calculations.

The FBE of the docked complexes was calculated to support the docking calculations and to predict the binding efficiencies of the HIV-1 RT against the targets. The FBE predictions are performed using MMPBSA that incorporates equation (1)[294] and MMGBSA method that incorporates equation (2)[295].

$$\Delta G_{bind} = G_{complex} - G_{protein} - G_{ligand} \quad (1)$$

$$= \Delta E_{MM} + \Delta G_{PB} + \Delta G_{non\text{-}polar} - T\Delta S$$

$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{solv} + \Delta G_{SA} \quad (2)$$

Here, ΔE_{MM} is the difference between the minimized energies of the HIV-1RT-**GSK952** complex and the total energies of the HIV-1 RT and HIV-1 RT inhibitor including the electrostatic and the van der Waals energies, $T\Delta S$ is the change in entropy of the ligand binding conformations, ΔG_{solv} is the difference in the P/GBSA solvation energies of the HIV-1 RT- **GSK952** complex and the sum of the solvation energies of the HIV-1 RT and HIV-1 RT inhibitor, ΔG_{SA} is the difference in the surface area energies for the HIV-RT enzymes and HIV-1 RT inhibitor. Both MMPBSA and MMGBSA methods have been realized to ensure the accurate ranking of inhibitors based on their FBE and hence can serve as a powerful tool in the drug design research.

3. Results and discussion

3.1 PRED-pharmacophore model.

The pharmacophore model exploits both the structural features of the proteins as well as the chemical features ligands. To generate a PRED based pharmacophore model, PRED decomposition was computed from MMPBSA calculations after 5ns MD simulations of the (2YNI-GSK952) complex. Residues Leu100, Lys102, Lys103, Val106, Try188 and Phe227 were found to be highest contributing residues that interact with the ligands (**S2**). The pharmacophoric features of the ligands hydrophobic interaction, hydrogen acceptor and hydrogen bond interactions (HPI, HA and HBI respectively) were found to interact with Leu100, Lys102, Val106, Try188, Lys103, Phe227 and Lys103 respectively. These ligand features were set as a query to generate a PRED-based pharmacophore model in ZINCpharmer[296].

Further the PRED-based pharmacophore model (**S3**) was used to screen the ZINC database[297] for compounds with similar features to obtain the novel hits. Additionally, a further selection criterion was implemented when screening ZincPharmer database. 788 hits were obtained from the ZINC database.

3.2 Molecular docking

All 788 hits were docked into the crystal structure (2YNI) to assess their chemical and physical feasibility. Thus the only with the correct pose and physical properties were selected for further consideration. This provided valuable insights into the nature of the binding site and the key ligand-protein interactions that are responsible for the molecular recognition and served as a validation step in the proposed workflow. A set of four compounds with experimentally determined activity (IC_{50} values) was selected to further validate our findings. These four compounds were docked into the crystal structure of 2YNI as described above in section **2.5.** Calculated DS were correlated against the inhibitors experimentally determined IC_{50} values (**Table 1**). DS are in correlation

(**R^2 = 0.62128**) (**Figure 5**) with the IC_{50} values. The comparison by means of correlation serves as an additional validation step and add robustness and validity to the docking protocol used in the current study. After the validation, molecular docking was carried out for all 788 hits.

Table 1: Validation of molecular docking approach.

Compound number	**Compound code**	**DS (kcal/mol)**	**IC_{50} (nM)**
1	3M8Q	-8.8	0.6
2	2BAN	-8.4	1
3	3IRX	-9.2	1
4	2RF2	-7.9	3.5

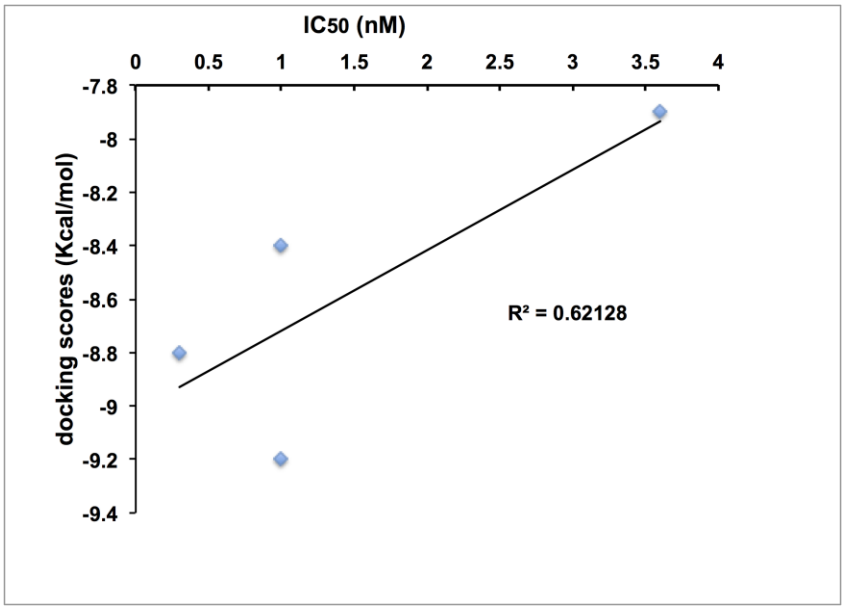
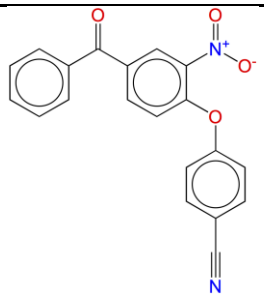
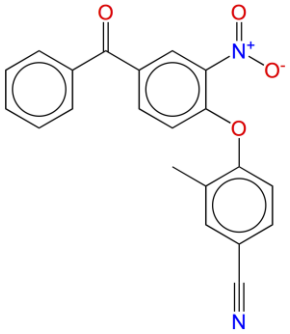
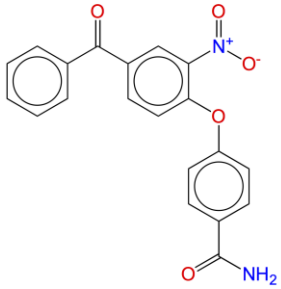
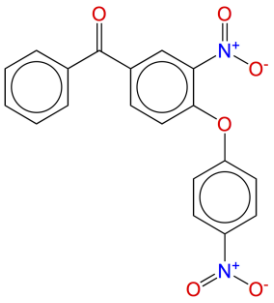
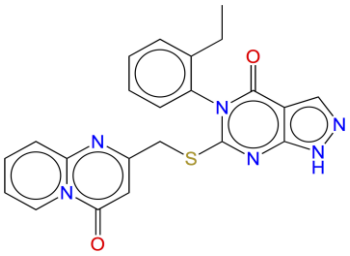
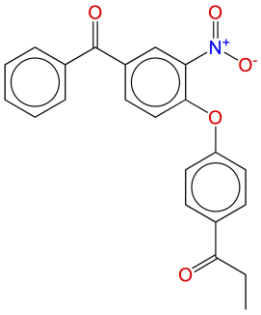
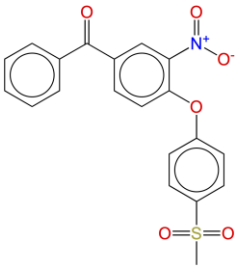


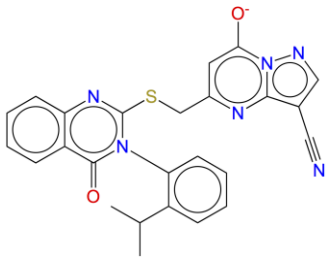
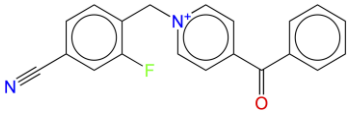
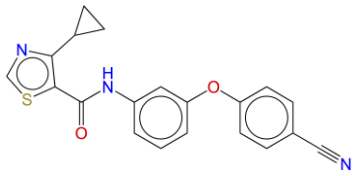
Figure 5: Validation of molecular docking: DS vs IC_{50}

The top 10 compounds with the highest docking scores were selected from the library of 788 hits. The docking scores for the top 10 compounds ranged from -11.5 to -12.4 kcal/mol (**Table 2**). It should be noted that there is not much difference in the binding energy of the top 10 compounds with the rough range of 0.9 kcal/mol. Hit compounds were found to be more stable due to conservation of vital pharmacophoric properties when generating the pharmacophore model.

Table 2: Representation of the top 10 compounds displaying 2D shapes, HBD, HBA, xlog*P*, MW and calculated DS and RB

Zinc ID	2D structure	xlog*P*	DS	HBA	HBD	MW	RB
ZINC15175251		4.79	-12.4	6	0	344.32	5
ZINC60349595		5.17	-12.3	6	0	358.35	5
ZINC07980692		5.17	-12.3	6	0	358.35	5

ZINC04952707		3.90	-12.0	7	0	397.40	6
ZINC09490236		4.07	-11.9	5	1	361.42	5
ZINC00868209		5.43	-11.7	6	0	375.3	7
ZINC60462497		3.90	-11.7	7	0	397.40	6

						
ZINC46849657	4.72	-11.6	8	0	467.53	5
						
ZINC54359621	-1.62	-11.6	3	0	317.34	4
						
ZINC89797911	4.07	-11.5	5	1	361.42	5

It is of high importance to consider residues that are directly accountable for the efficacy of HIV-1 RT when evaluating whether the molecules bind strongly with HIV-1 RT. This will ensure effective inhibition. Lig-plot analysis is best suited for displaying the 2D interaction between the ligand and the residue contributing to the ligand binding. Lig-plot shows the interacting residues with Leu100, Lys102, Lys103, Val106, Tyr188, and Phe227 with the highest FBE contributing to the ligand binding. Leu100, Lys102, Val106, Phe227, Pro229 and Y188 have hydrophobic interactions whereas Lys103 displays a hydrogen interaction with the inhibitor (**Figure 4**). The PRED calculations presented in this study are valuable tools that can be employed to highlight the most significant residues involved in the binding of the inhibitor serve as a guide to design drug candidates against HIV-RT.

The FDA-approved anti-HIV drugs were omitted throughout the entire screening process, this is to guarantee the design of compound libraries based on novel structural scaffolds. Such findings affirms the refined pharmacophore approach adopted in this work, rendering the suggested concept could be secure and dependable enough for the mining of novel drug candidates against the enzyme of interest. We believe the methodology in this current work can be applied to more biological drug targets with determined protein structures and binders that are recognized.

Molecular dynamic simulations and MMPBSA calculations.

As previously mentioned, docking alone cannot provide reliable results. Hence it is of high importance to correlate docking results with MD simulations. MD simulation (5ns) was performed on the top 10-screened hits from the molecular docking to confirm the change in mobility resulting from the binding of each hit to HIV-1 RT. Common MD-type force fields were employed to evaluate and rescore the docked complexes, this will lead to more accurate estimates of the binding affinities. All the free energy components are representative of averaged values over the 5 ns MD simulations calculated using the MM/PBSA approach shown below in **Table 3**. Amongst the top 10, **ZINC54359621** and **ZINC46849657** resulted with the highest FBE. The total calculated FBE (ΔG_{bind}) of **GSK952** against HIV-1 RT protein is -58.8 kcal/mol compared to -58.5 kcal/mol and -59.0 kcal/mol of **ZINC46849657** and, **ZINC54359621** respectively. These findings are more reliable than the energy contributions obtained from the docking calculations. It was also observed that the ΔE_{vdW} of **ZINC54359621** and **ZINC46849657** was higher (**Table 3**, **Figure 6**), which is advantageous and a contributing factor towards the high binding affinity[298]. Electrostatic forces contribute to inhibitor molecules to gain binding energy[299]. **ZINC54359621** and **ZINC46849657** electrostatic interactions are similar to that of **GSK952**, which explains their higher binding affinity and stability.

Table 3: A comparison of GSK952 binding affinity with that of top 2 hits ZINC54359621 and ZINC46849657

Ligand	ΔTotal	ΔEvdW	ΔEelec	ΔGbind	ΔGgas	ΔGsolv
GSK952	-58.8	-61.2	-21.4	30.9	- 82.6	23.8
ZINC46849657	-58.5	-67.1	-21.0	37.1	-88.1	29.6
ZINC54359621	-59.0	-67.6	-20.2	36.4	-87.9	28.8

PRED of the top 2 hits showed consistency compared to that of **GSK952**. The residues that contributed to the binding of **GSK952** to HIV-1 RT protein also contributed to the binding of the top two hits (**Figure 6**). The HCAAR for the **ZINC54359621** and **ZINC46849657** are included in **S4** and **S5** respectively.

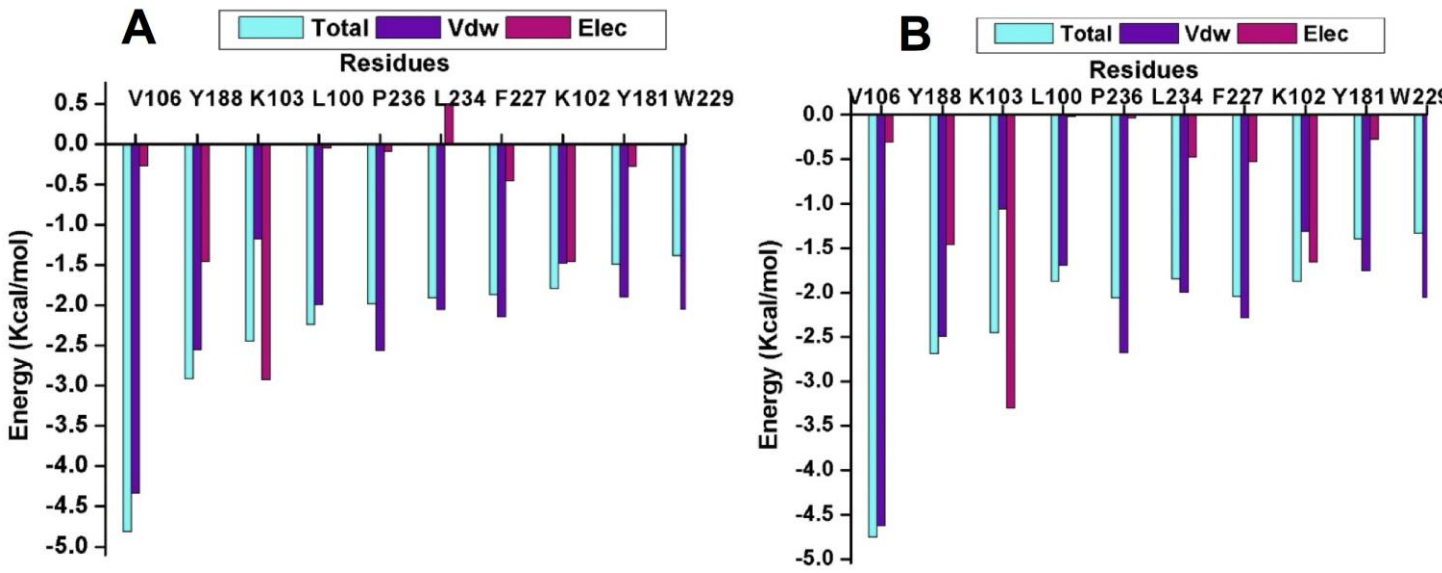


Figure 6: The per residue graphs A and B showing FBE contribution for both **ZINC54359621** and **ZINC46849657** respectively.

It is noted that **ZINC54359621** has a hydrogen bond between the oxygen atom of Pro236 and the NH group of the aromatic ring, NH group of Lys103 and the oxygen atom of the aromatic ring. **ZINC46849657** has a hydrogen bond between the oxygen atom of Pro236 and the NH group of the aromatic ring, the NH group of residue Lys103 and the oxygen atom of the aromatic ring (**Figure 7**). These are one of the key interactions required for the binding to HIV-1 RT. This indicates the compounds suitability as an RT inhibitor.

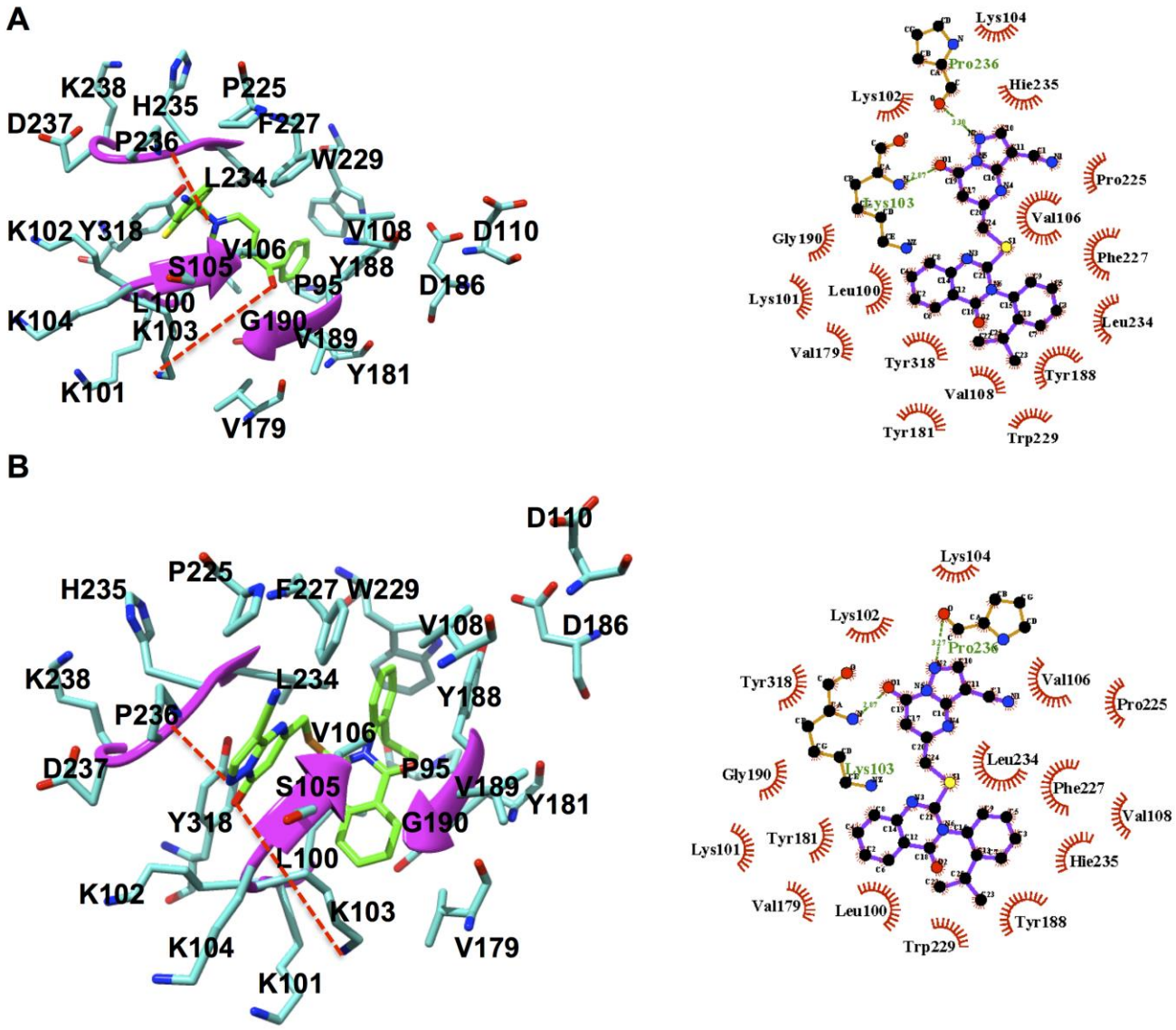


Figure 7: Binding mode of compound a) **ZINC54359621,** and b) **ZINC46849657** to HIV-1 RT enzyme respectively.

HIV-1 RT is highly flexible in nature[300,301] and therefore the stability of the system during MD simulation was analyzed by computing i) RMSD (**S6A**) and ii) RMSF (**S6B**). The average value of RMSD for **ZINC54359621** and **ZINC46849657** is 3.12 Å and 2.58 Å respectively. These RMSD values presented in **S6** have proven to be similar with the HIV-1 RT RMSD values presented in literature [302,303] thus, validating the stability of the system due to the high flexibility of HIV-RT protein. RMSF shows good stability of all residues interacting with the ligands from residues 100-236. The average RMSF for **ZINC54359621** and **ZINC4684965** are 1.87 Å and 1.53 Å respectively. Further, the compactness of the system was analyzed by computing Rg of the systems. The average Rg values for **ZINC54359621** and

ZINC46849657 is 51.2 Å respectively. Results show that the target protein folded correctly and was able to mantained a stable compact structure (**S 6c**).

Conclusion

Virtual Screening was carried out to identify the potential inhibitors against mutated HIV-1 RT based on (i) PRED-based pharmacophore model, (ii) molecular docking and (iii) MMPBSA approaches. The study identified two novel hits **ZINC54359621** and **ZINC46849657**. These compounds may be representatives of a new series of NNRTIs possessing high resistance profiles against mutated HIV viruses. They have the potential to inhibit the transcription of the viral RNA by binding to the active site of the RT's p66 subunit therefore the replication rate of the virus decreases. The pharmacophore approach was further refined, where the candidate molecules for structure-based VS were chosen based on their orientation and chemical features in relation to the 3D structure. The PRED was also calculated in order to obtain more insights into the crucial protein residues involved in ligand binding. This will potentially aid in the design of potent inhibitors that bind to these HCAAR. The results presented in this study present a map to the innovation and design of potent drug candidates against different biological targets. Results have shown that choosing highly contributing FBE candidates from a library of compounds generated from PRED target-bound pharmacophore map is a more reliable and accurate approach.

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Abbreviations

amFAR	American foundation for AIDS Research
DS	Docking Score
Elec	Electrostatic
FDA	Food and drug administration
HA	Hydrogen acceptor
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HBI	Hydrogen bond interaction
HCAAR	Highly contributing amino acid residues

HIV	Human Immunodeficiency Virus
HPI	Hydrophobic Interaction
IC	Inhibitory concentration
LBVS	Ligand based virtual screening
MD	Molecular dynamic
MMPB (GB) SA	Molecular Mechanics/ Poisson-Boltzmann (Generalized- Boltzmann) Surface Area
MW	Molecular Weight
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PDB	Protein Data Bank
Rg	Radius of gyration
RMSD	Root-mean-square deviation
RMSF	Root-mean-square fluctuation
RT	Reverse Transcriptase
SBVS	Structure-based virtual screening
vdW	van der Waals
VS	Virtual screening

Conflict of interests

The authors declare no conflict of interest to the above article.

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Supplementary Materials

Per-residue energy decomposition (PRED) pharmacophore model to enhance virtual screening (VS) in drug discovery: A case study for identification of Reverse transcriptase (RT) inhibitors as potential Anti-HIV agents.

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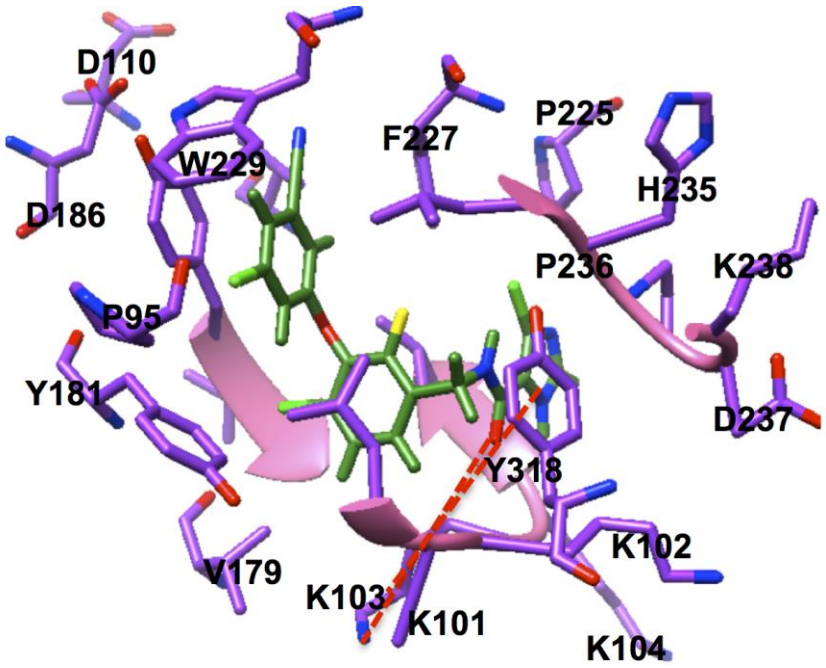
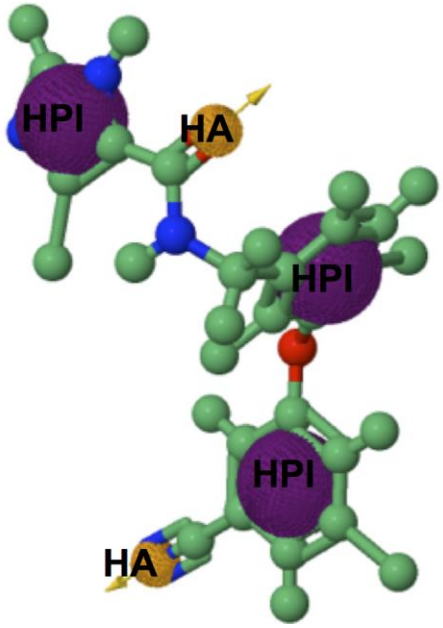


S1: Two key binding interactions exist between GSK952 and the backbone NH and C=O groups of Lys103 of HIV-1 RT.

S2: PRED of HCAAR for GSK952.

Residue number	Highly interacting residues	FBE (kcal/mol)
1	Val106	-3.556
2	Lys103	-3.311
3	Tyr188	-3.144
4	Lys102	-2.243
5	Leu100	-2.057
6	Phe227	-1.879



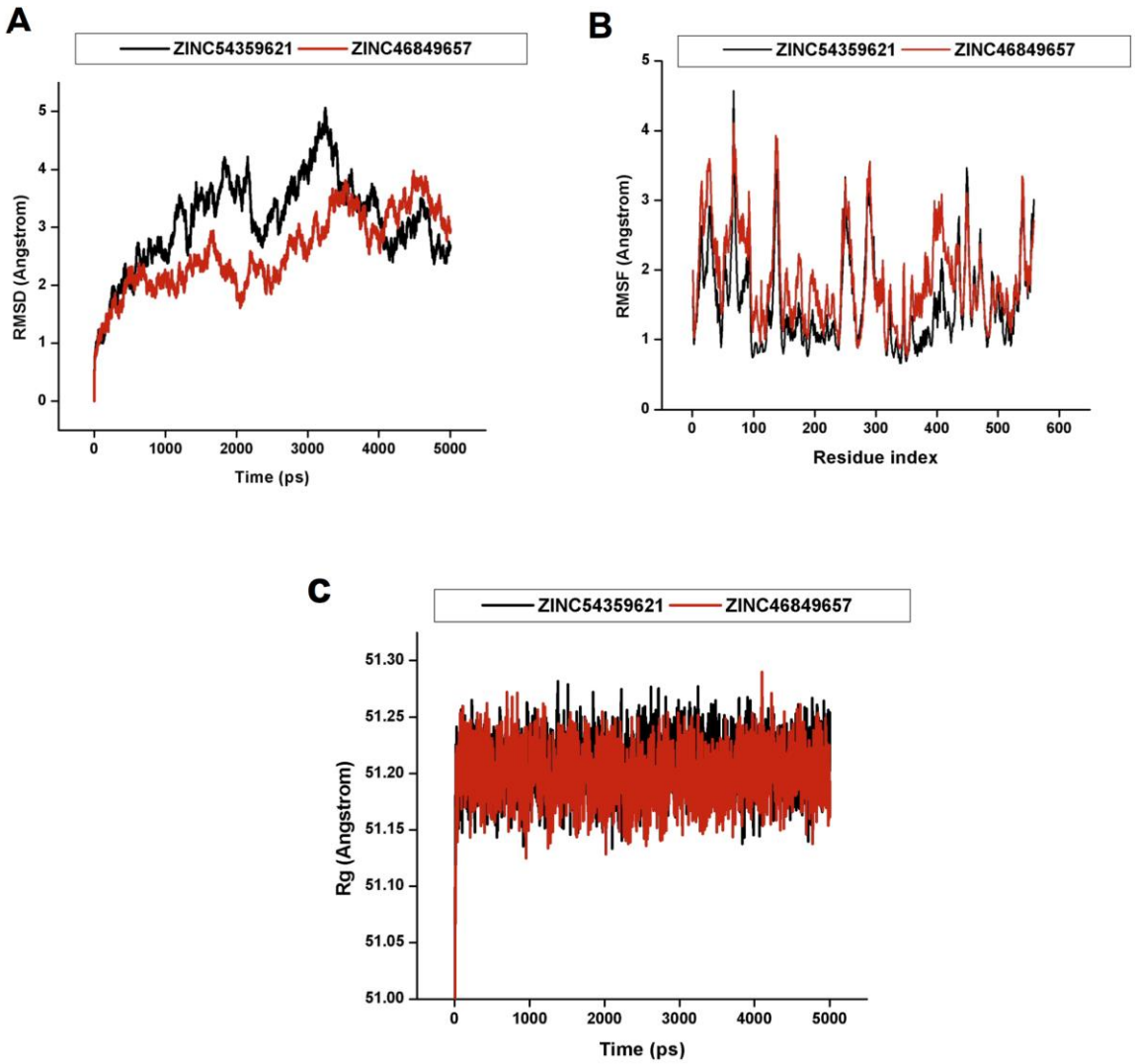
S3: PRED-based pharmacophore model.

S4: PRED of HCAAR for ZINC54359621

Residue name	Total Energy	vdW	Elec
Val106	-4.812	-4.342	-0.272
Lys103	-2.446	-1.176	-2.933
Tyr188	-2.919	-2.556	-1.459
Leu100	-2.242	-1.995	-0.048
Pro236	-1.986	-2.564	-0.093
Phe227	-1.873	-2.147	-0.450
Leu234	-1.906	-2.055	0.496
Lys102	-1.795	-1.480	-1.461
Tyr181	-1.488	-1.899	-0.277
Trp229	-1.380	-2.049	-0.446

S5: PRED of HCAAR for ZINC46849657

Residue name	Total Energy	vdW	Elec
Val106	-4.754	-4.262	-0.312
Lys103	-2.454	-1.058	-3.305
Tyr188	-2.692	-2.494	-1.461
Leu100	-1.876	-1.694	-0.023
Pro236	-2.062	-2.679	0.041
Phe227	-2.042	-2.287	-0.528
Leu234	-1.845	-1.996	0.477
Lys102	-1.865	-1.310	-1.660
Tyr181	-1.397	-1.753	-0.277
Trp229	-1.336	-2.054	-0.433



S6: MD Simulations results of **ZINC54359621** and **ZINC46849657** A) RMSD (Average of **3.12 Å** and **2.58 Å** respectively), B) RMSF (average of **1.87 Å** and **1.53 Å** respectively) and C) Rg (average of **51.2 Å** and **51.2 Å** respectively).

CHAPTER 5

Submitted Article

Mechanism of Inhibition of Hsp90 Dimerization by Gyrase B inhibitor coumermycin A1 (C-A1) revealed by Molecular Dynamics Simulations and Thermodynamic Calculations

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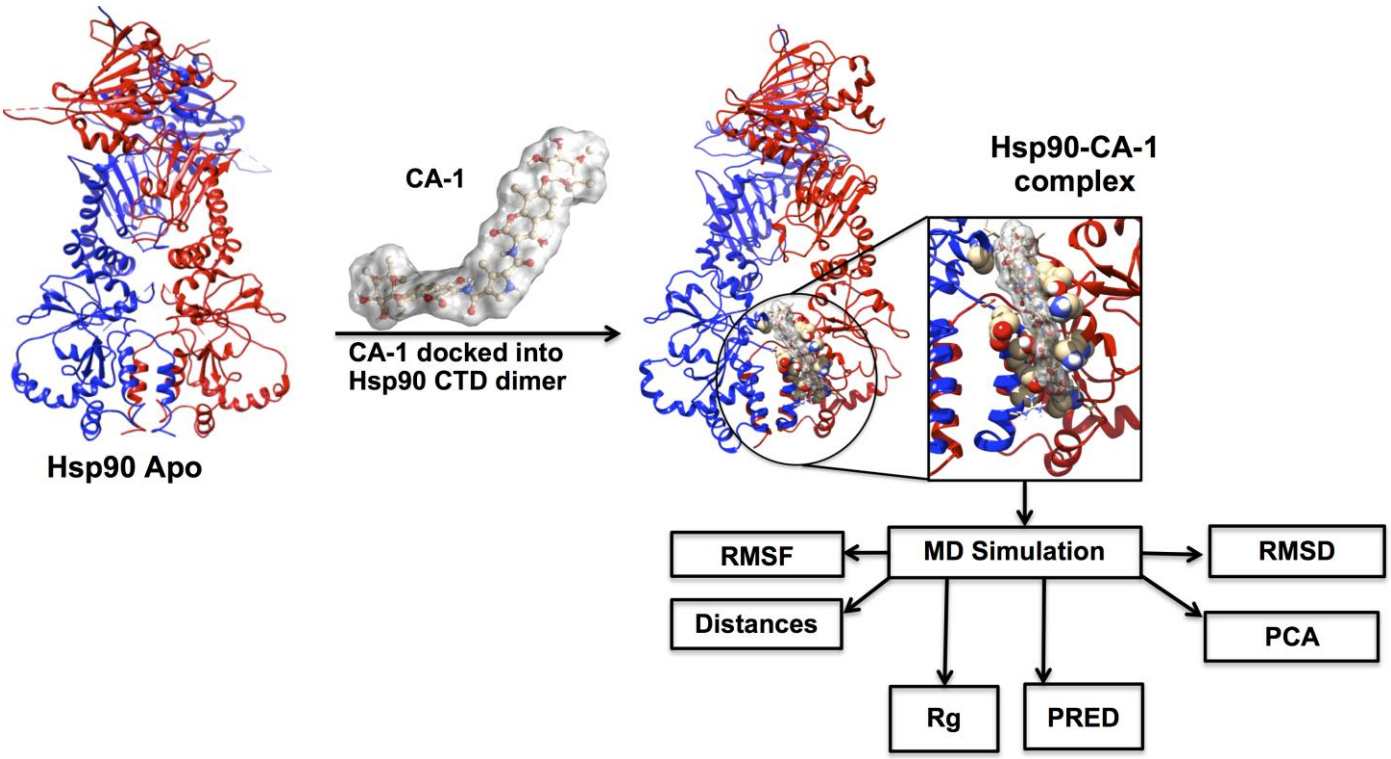
Graphical abstract



Abstract

Heat shock protein (Hsp) 90 is an emerging and attracting target in the anti-HIV drug discovery process due to this key role in the pathogenicity of HIV-1 virus. In this research study, long-range all-atom molecular dynamics (MD) simulations were carried out for both the bound and the unbound proteins to improve the understanding of the molecular mechanisms of the Hsp90 dimerization and inhibition. Results evidently show that coumermycin A1 (C-A1), a recently discovered Hsp90 inhibitor, binds at the dimer's interface of Hsp90 and leads to a substantial parting between dimeric opposed residues, which include Arg591.B, Lys594.A, Ser663.A, Thr653.B, Ala665.A, Thr649.B, Leu646.B and Asn669A. Significant differences in the magnitudes were observed in the radius of gyration (Rg), root-mean-square deviation (RMSD) and root-mean-square fluctuation (RMSF), which confirms a reasonably more flexible state in the apo conformation associated with it dimerization. In contrast, the bound conformer of Hsp90 showed less flexibility. This clearly highlights the importance of the inhibition process resulting from the binding of the ligand. These findings were further validated by Enhanced Molecular dynamics (EMD), also known as principal component analysis (PCA). We believe that the detailed dynamic analysis of Hsp90 presented in this study, would give an imperative insight and better understanding to the function and mechanisms of inhibition of Hsp90. Furthermore, information obtained from the binding mode of the inhibitor would also be of great assistance in the design of more potent inhibitors against the HIV target Hsp90.

Keywords: HIV-1; Hsp90; C-A1; MD simulations; Molecular docking.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is the most challenging disease outbreak thus far and is caused by the Human Immunodeficiency Virus (HIV)[153]. HIV/AIDS affected over 35 million people globally, and Sub-Saharan Africa is the most affected region with approximately 68% people affected[304]. Highly active antiretroviral therapy (HAART), approved by the Food and Drug Administration (FDA), is currently the most effective therapeutic regimen decreasing the viral load, which prolongs the survival of AID-free patients[305,306]. These drugs include inhibitors of three essential HIV enzymes protease, integrase (IN), reverse transcriptase (RT) as well as entry and progression enzyme inhibitors of in the HIV life cycle[307,308]. In spite of all currently existing anti-HIV therapies, resistant strains still poses a problem. This creates a demanding necessity for the identification of new antivirals that do not induce drug resistance.

Hsp90 is an ATP-dependent chaperone crucial for maintaining active forms of other proteins which are known as client proteins[175]. Hsp90 has also been reported to be responsible for the replication of nearly all kinds of viruses such as DNA, RNA viruses, and double-stranded RNA viruses[309]. Hsp90 is a homodimeric protein comprising a dimeric molecular weight of 90kDa. Each monomer shares a common domain organization which consists of a C-terminal dimerization domain (CTD) of ~12 kDa, a middle domain (MD) of ~40 kDa and an N-terminal domain (NTD) of ~25 kDa, which is found mostly in almost every part of eukaryotic cells[310–312]. Amongst other proteins, Hsp90 is one of the most profuse proteins found in the cytoplasm, where it makes up approximately 1–2% of the total protein levels[313]. It is responsible for the controls of activities, such as the maturation, localization of a selected large number of substrates called "client proteins" in the cytoplasm. These clients proteins are part of several processes including transcription, translation, mitochondrial function, kinetochore assembly, inflammation, immunology, cellular antiviral defense pathways, apoptosis, centrosome function and cell cycle[314–316]. Studies have demonstrated that the replication of viruses to be sensitive to Hsp90 inhibitors at very low concentrations without affecting cellular viability, due to their dependence in Hsp90 for their survival. Hsp90 is regarded as an essential protein for malignant transformation and progression, thus target protein for anti-cancer drugs[317,318]. A previous study in our laboratory gave a computational perspective of Hsp90 as an anti-cancer target[319]. Recently it has been reported as a potential target for anti-HIV therapy[320].

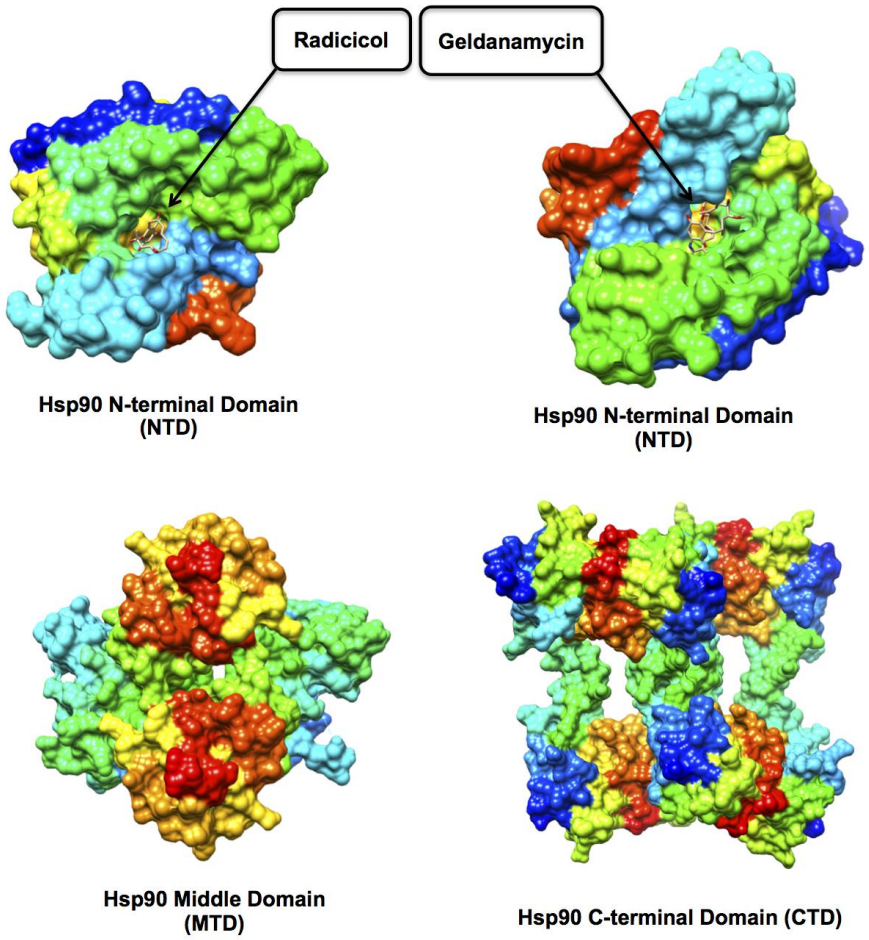


Figure 1: Hsp90 x-ray crystal structures accentuating different domains. The surface representations were generated using PDB co-ordinates of 1BGQ (NTD+RD), 1YET (NTD+GA), 1HK7 (MTD) and 1SF8 (CTD).

Recent studies revealed that the C-terminal domain (CTD) of Hsp90 protein has a crucial role in the dimerization of the chaperones with an additional binding site for inhibitors. It has also been reported that the nucleotide binding site situated at the CTD is more favorable to guanosine-5'-triphosphate (GTP) over ATP, which would possibly enhance the selectivity of the new inhibitors against this site[321–323]. Herein we focus on the C-terminal dimerization inhibitors because this domain is vital for the biological activity of Hsp90[307].

To date, a broad-spectrum of antivirals have been identified, including Hsp90 inhibitors[309,324–326] . Numerous antiviral activity of Hsp90 inhibitors have been proved against tissue culture of ill health conditions such as picornaviruses poliovirus, coxsackievirus, rhinovirus, influenza virus, paramyxoviruses, Hepatitis C virus (HCV), Ebola virus, vesicular stomatitis virus, severe acquired respiratory syndrome (SARS), Feline viral rhinotracheitis (FHV), human immunodeficiency virus (HIV),

vaccinia virus, and herpes viruses[320,324,327–333]. Gryase B inhibitors (novobiocin, coumermycin A1 (C-A1) and daunorubicin) have been reported to impair HIV-1 Replication the most, by targeting Hsp90[320]. It has been shown that they inhibit the formation Hsp90 dimer by binding in the C-terminal domain, which impairs viral gene expression[320].

The present study looked at C-A1, which has previously been screened for its antiretroviral activity by means of a chemical genetics (CG) approach[320]. This study confirmed the impairment of viral gene expression by C-A1 binding to Hsp90. C-A1 weakens both the HIV-1 integration and gene expression process.

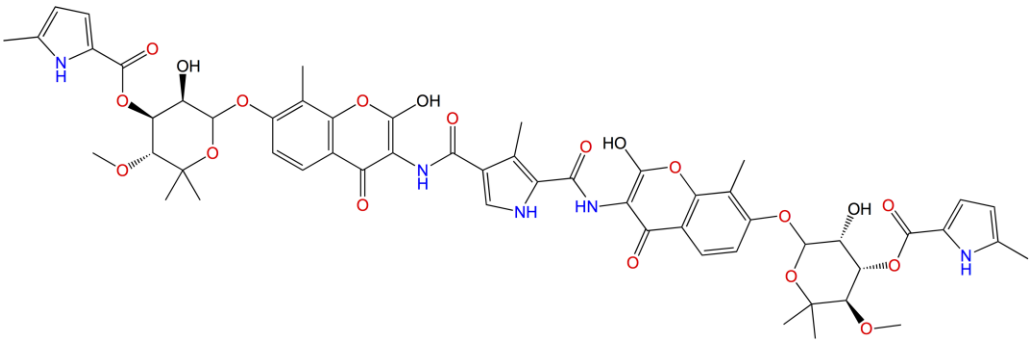


Figure 2: The 2D structure of coumermycin A1.

Molecular dynamic simulations and post-dynamics (PD) to be the closest methods to the actual wet lab experimentation and is of great help in the understanding of the complex biological phenomenas such as the binding mechanism of inhibitors to their target protein[334]. An application of continuous MD simulations to reveal folding and the unfolding activities of biological enzymes has made it convenient to fathom the dimerization process complexity of macromolecules [335–339]. The increased application of the PD methods in computational chemistry validates the usefulness of this technique in understanding the conformational dynamics aspects of biological macromolecules. The most broadly improved PD methodologies used to search for structural dissimilarities within distinctive biological phenomenas include PCA or essential dynamics (ED) analysis[307,340]. Although PCA has proved it competency to be implement in the comparison of motions of different macromolecules there are additional techniques to PCA analysis which were also applied to comprehend the of the biological phenomena's conformational behavior[321,341]. Such may include dynamic cross-correlation (DCC), which was valuable to gain insights on macromolecular motions in different biological systems[342]. To understand both the dimerization and the inhibition processes of Hsp90, virtual MD simulations were employed for the bound and the unbound conformations. To our understanding, this is the first report of comprehensive and extensive

computational insight on Hsp90 as a vital HIV target. Thus, we expect this study to significantly contribute towards an improved understanding of the Hsp90 protein structure, dynamics and its mechanism of inhibition. Herein, we presented the structural and dynamic insight that can be executed in the discovery of drugs and the development of more effective HIV inhibitors against Hsp90.

2. Computational methodologies

2.1. System Preparation

There is no available crystal structure of the human C-terminal portion of Hsp90, however structures of yeast (2CG9)[343] and *E. coli* (1SF8)[344] Hsp90 orthologues are available. 2CG9 was chosen for this study due to the fact there is very high sequence and structural conservation among Hsp90 proteins from prokaryotes to *Homo sapiens* [167]. The ligand and protein systems were prepared in the similar manner as mentioned in the previous reports[345,346]. Auto-Dock Vina[248] was used to generate docked conformation of C-A1 inside Hsp90's active site using a previously reported procedure[320].

2.2 Molecular dynamic simulations

The unbound and C-A1 bound models of Hsp90 proteins were exposed to all-atom, continuous MD simulations in precise solvent using the GPU version PMEMD engine integrated with Amber14[284]. The ff99sb force field[286] applied with Amber14 was employed in the description of the protein systems. To neutralize the system, missing hydrogen atoms and counter ions were added using the Leap module, integrated with Amber14. All the systems were submerged into an orthorhombic box with TIP3P[347] water molecules in a manner that none of the protein atoms were contained in 12 Å of any box edge prior to the set up. The Particle mesh Ewald (PME)[288] technique was employed to calculate the continuous electrostatic interactions and van de Waals cut-off of 12 Å. Initial minimization was implemented for 50000000 steps of steepest descent using conjugate gradients algorithm. CPU version of Amber 14 was used to perform all the minimization but before the minimization step, a gradual heating from 0 to 300 K by means of Langevin thermostat[289] with a collision frequency of 1/ps using an official ensemble (NVT) was used. All systems were successively equilibrated at 300k in a NPT ensemble for 100000 ps with no restrained and to uphold the pressure at 1 bar Berendsen barostat[291] was used. To restrict the bonds of all covalently bonded atoms to hydrogen atoms for all MD simulations runs the SHAKE algorithm[290] was used. The MD was run continuously in a NPT ensemble for 100 ns with a target pressure of 1 bar and a pressure-coupling constant of 2 ps. In every 1 ps the trajectories were examined and more analyses namely RMSD, RMSF, Rg, inter atomic distances, DCC and PCA were performed using PTRAJ and CPPTRAJ modules integrated in Amber14. All plots and visualization were performed in Chimera molecular modeling tool[283] and Origin data analysis software (www.originlab.com) respectively.

2.3 Free binding energy calculations.

The docked complex of Hsp90-C-A1 was calculated to predict the binding efficiencies and confirm the highly contributing amino acid residues (HCAAR) of C-A1 binding to Hsp90. The binding affinity predictions were executed using the MMPBSA with equation (1)[295] and MMGBSA method that with equation (2)[348].

$$\Delta G_{bind} = G_{complex} - G_{protein} - G_{ligand} \qquad (1)$$

$$= \Delta E_{MM} + \Delta G_{PB} + \Delta G_{non\text{-}polar} - T\Delta S$$

$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{solv} + \Delta G_{SA} \qquad (2)$$

Where, ΔE_{MM} is the differentiation between the minimized energies of the Hsp90-C-A1 complex and the total energies of the Hsp90 and Hsp90 inhibitor including the electrostatic and the van der Waals energies. The change in entropy of the ligand binding conformations is presented by $T\Delta S$, the variance in the P/GBSA solvation energies of the Hsp90-C-A1 complex and the summation of the solvation energies of the Hsp90 and Hsp90 inhibitor is represented by ΔG_{solv} and ΔG_{SA} is the difference in the surface area energies for the Hsp90 and Hsp90 inhibitor. Both MMPBSA and MMGBSA methods have been recognized to ensure the inhibitors are ranked accurately in accordance with their binding energy and thus can aid as a potent tool in the drug design research.

2.4 Principle Component Analysis (PCA)

Principle component analysis (PCA) is extensively used to effortlessly examine and identify data generated from MD simulations to highpoint principal modes accountable for changes in conformation[307]. The PTRAJ and CPPTRAJ modules were used in performing PCA C-alpha atoms[349] integrated with Amber 14[284]. The plots analysis showing the central conformational motions descriptive of each structure were created using Origin data analyses programme (www.originlab.com).

2.5 Dynamic cross correlation matrix

The DCCM between fluctuations based on the residues throughout the simulation was analyzed using the module called CPPTRAJ assimilated with Amber 14. The DCCM is best defined by the equation below[350]:

$$\mathrm{DCCM(I,j)} = \frac{<\Delta ri(t)\cdot\Delta rj(t)>t}{\sqrt{<\|\Delta ri(t)\|2>t}\sqrt{<\Delta rj(t)2>\mathrm{t}}} \qquad (3)$$

Where $\boldsymbol{r_i(t)}$ defines the vector of the atom's coordinates as a function of time t, $<\cdot>$ t measures the time ensemble average and $\Delta r_i\,(t) = r_{i(t)}-<r_i(t)>_t$. The backbone Cα atomic fluctuations were considered during the DCCM analysis.

3. Results and Discussion

3.1. Insights into coumermycin A1 bound with Hsp90

The lig-plot[351] analysis is best suited for displaying the 2D interaction between the ligand and the amino acid residue contributing to the ligand binding to the receptor. The structure of inhibitor C-A1 docked within the Hsp90 dimer's binding site gave essential evidence on the binding of the ligand inside the active site (**S1**). It was observed that C-A1 formed hydrogen bonds interactions with Arg591.B, Ala595.A, Glu660.A, Lys480.B, Ser663.A and Ser666.A (**S1**) residues of both Hsp90 dimer subunits. Interestingly, the binding of C-A1 is at the dimer of Hsp90 possessing multiple common residues from both sub-unit A and B in its active site. The averaged values of the calculated free energy, using MM/PBSA approach; over the 100 ns MD simulations for each CAAR to the binding of C-A1 to Hsp90 are illustrated in **Figure 8, S3**. The CAAR formed hydrogen bond interactions, which is one of the key interactions favorable and vital for binding of a ligand to its receptor, possess higher binding affinities.

The plot of the interaction (**Figure 3**) high spots the C-A1 location within the Hsp90 dimer and reciprocal residues' active site, together with the hydrogen bond interactions shown in red dotted lines, from each subunit.

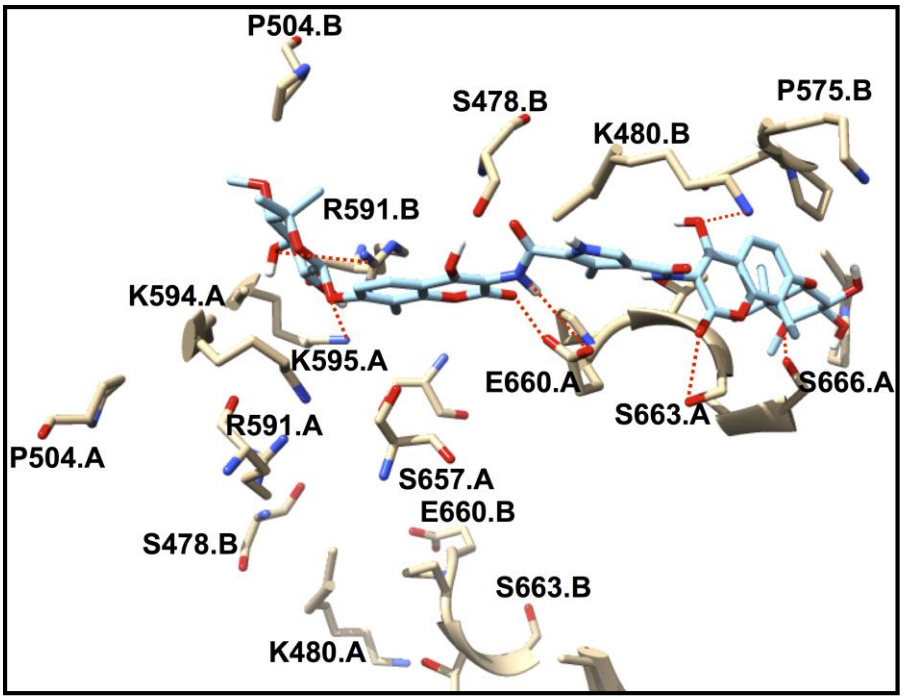


Figure 3: The binding mode of C-A1 to Hsp90 subunits.

The existence of hydrophobic/aromatic interactions, which promotes the appropriate binding of inhibitor into the dimer, consisting of key active site residues involved in dimer packing, including Ser595.A and Glu660.A, are visibly illustrated in the binding mode. It is assumed that binding of C-A1 in the Hsp90 dimer's active site results to the dimer inhibition of Hsp90. The dynamic insights of the dimerization mechanism process of Hsp90 through inhibition by C-A1 was obtained from the continuous MD simulations using the structure of Hsp90-C-A1 complex (docked) (**S2**).

3.2. Molecular dynamics simulations and Post-dynamics Analysis

3.2.1. RMSD, RMSF, and Rg.

Protein dynamics, structure, and function are highly interrelated. The conformational changes of Hsp90 are particularly critical for enzyme function[164,352]. Studying internal atomistic motions can unravel the dynamics nature of Hsp90, which is responsible for numerous biological functions as enzymes. Molecular dynamic simulations were performed for each enzyme (apo and bound) to establish the drug-binding pattern and to better understand the interaction of C-A1 with the CTD, to ensure the stability of the MD trajectories dynamic and the stabilities dissimilarities of MD simulations. The values of the RMSD for the protein backbone atoms and side chain atoms in relation to the initial minimized structure throughout the simulations were calculated for the Cα atoms for the dimer (**S4**) and whole protein (**Figure 4**).

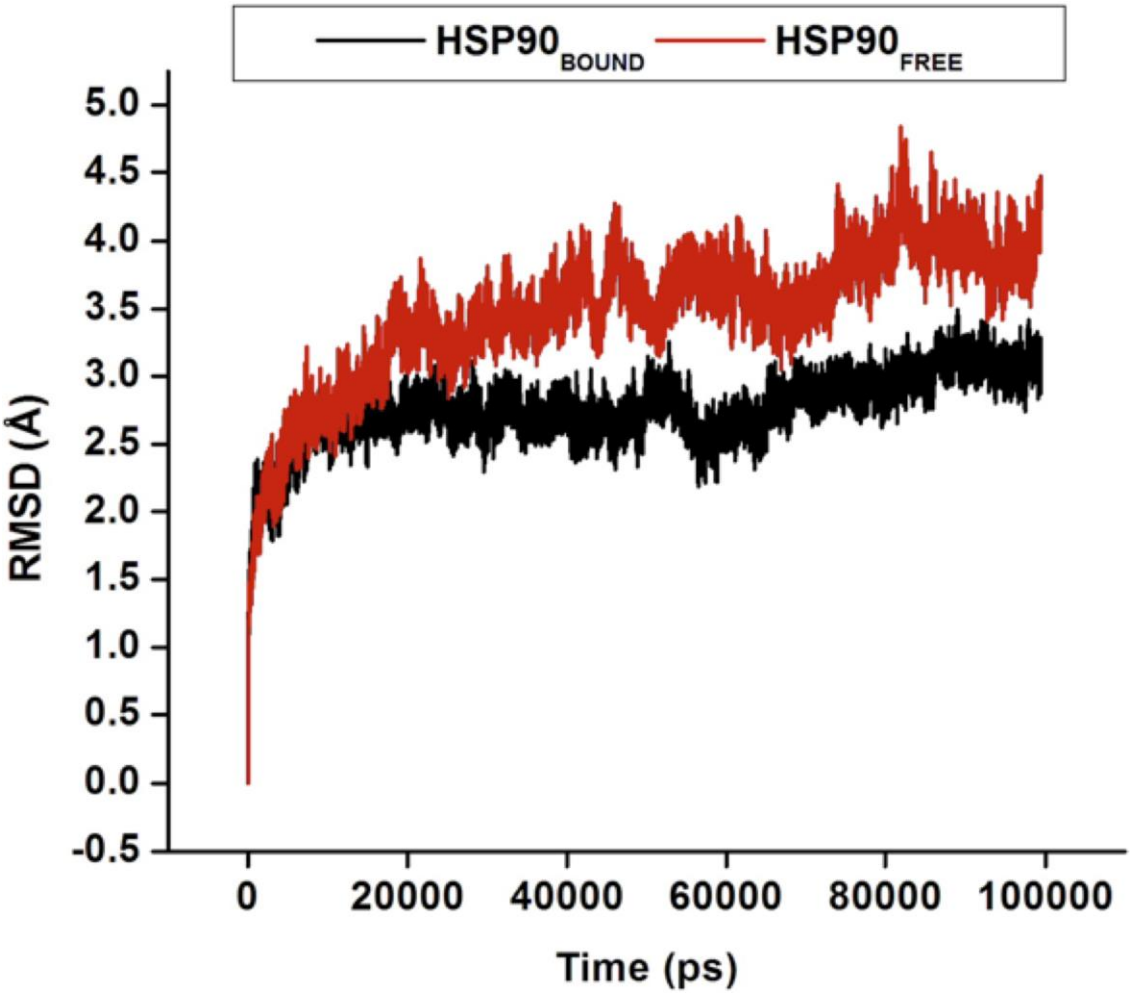


Figure 4: The (RMSD) values for the dimer atoms during continuous 100 ns MD simulation.

The average structure for the complete simulation was measured by calculating values for all residues of both in Apo and bound conformations (**Figure 5**) by means of the RMSF in order to obtain the system's subset movement. Residues between 400 to 600 have the highest RMSF values, this corresponds to CTD. The most stable areas are the areas with the lowest RMSF values. Overall the bound enzyme has slightly lower RMSF values of 1.88 Å compared to the apo with the value of 2.64 Å, which indicates that the backbone of the bound conformation is slightly more stable than that of the free enzyme.

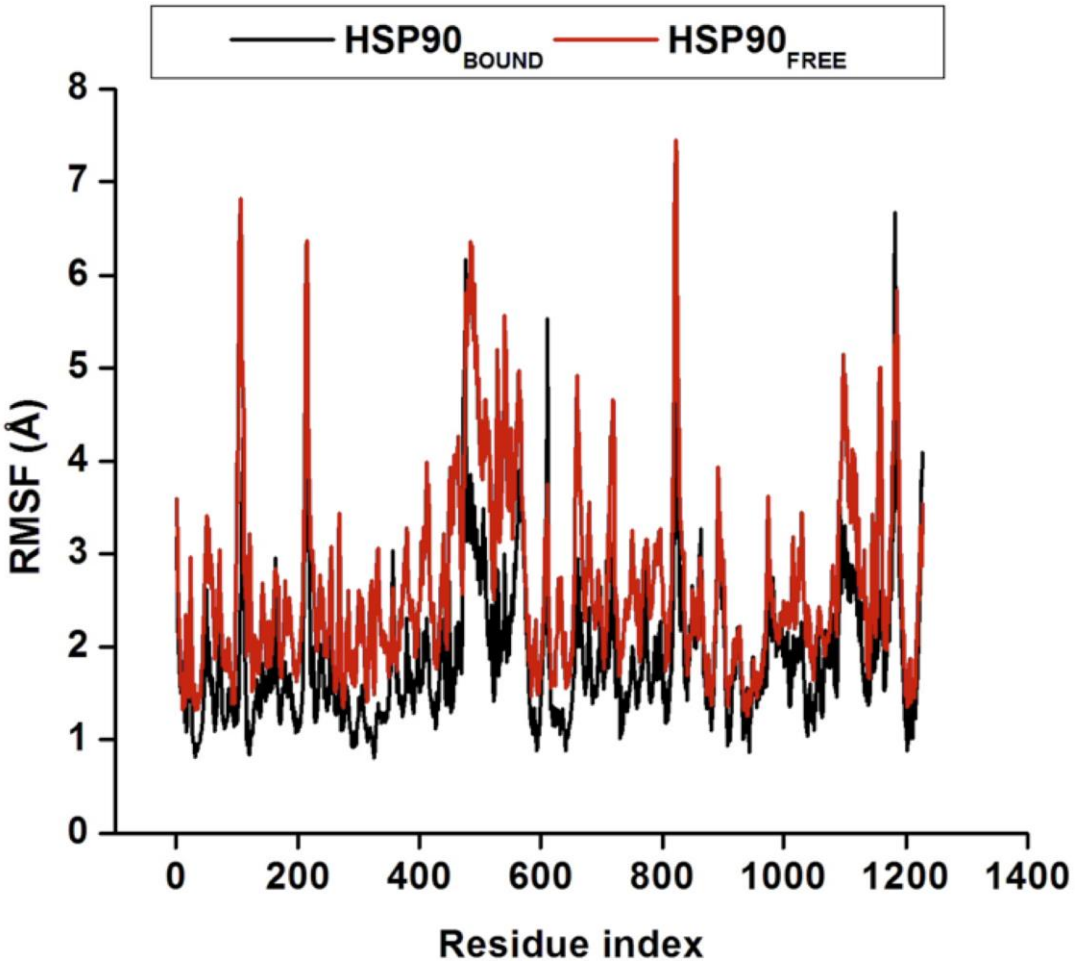


Figure 5: C-α atom RMSF values given for each residue number in both systems.

The mass-weighted root mean square distance of a collection of atoms from their common center of mass best describes the Rg. To measure for the compactness of a structure, the Rg was calculated. The analysis shown in **Figure 6, S5** provides us with an understanding into the dimensions of the dimeric cleavage and of the overall Hsp90 protein respectively. We observed the major fluctuations in both systems between 0 and 100000 ps. The Rg indicated higher structural deviations for the apo conformation in comparison to the bound conformation. The mean value of the bound is lower than that of the apo, which indicates that the bound protein is stable. This could be due to C-A1 inhibitory effect on the Hsp90 dimerization.

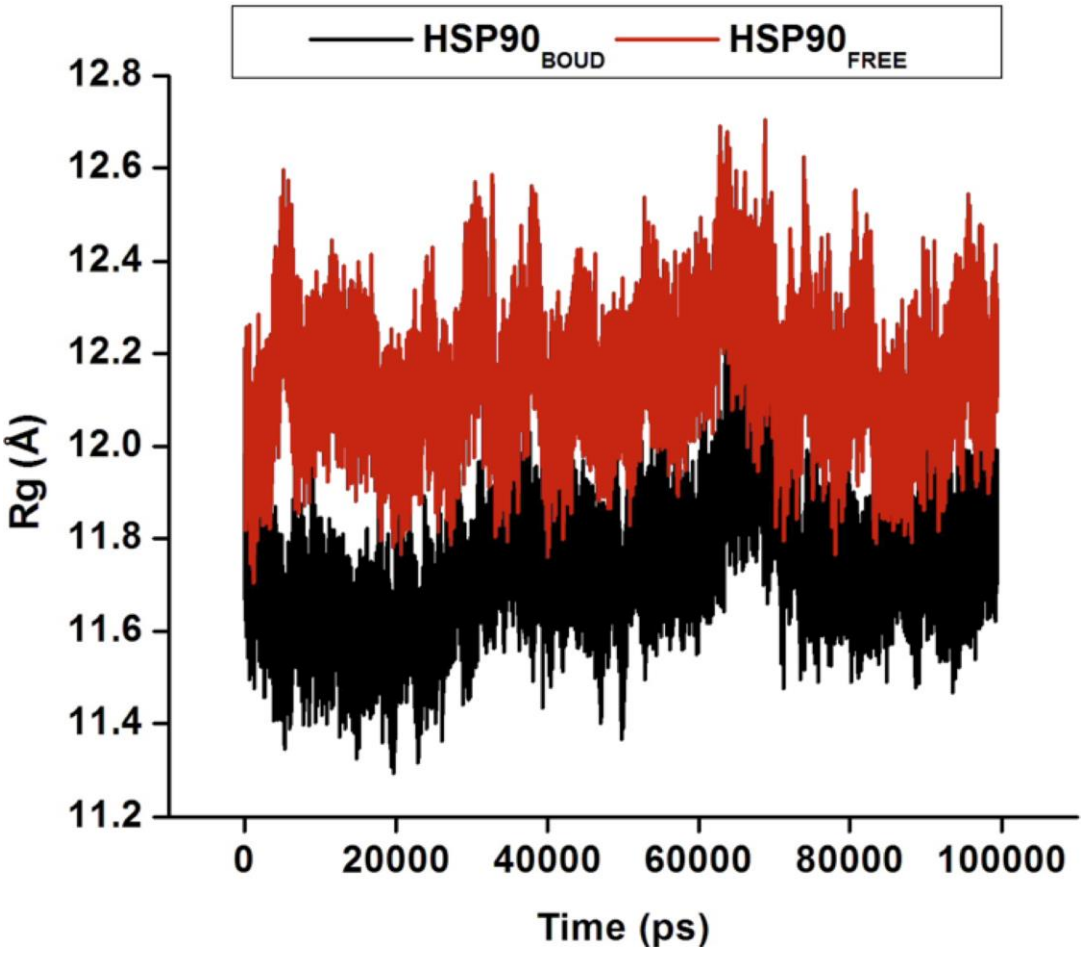


Figure 6: The radius of gyration (Rg) of the dimeric subunit during 100 ns MD simulation.

3.2.2. Principal Component Analysis

The trajectories' projection obtained at 300 K onto the first two principal components (PC1, PC2) presented the motion of two proteins in phase space. Clusters were better defined in the bound conformation than the apo conformation. Furthermore, the bound conformation covered a larger region of phase space particularly along PC1 and PC2 plane than the apo conformation as depicted in **Figure 7.**

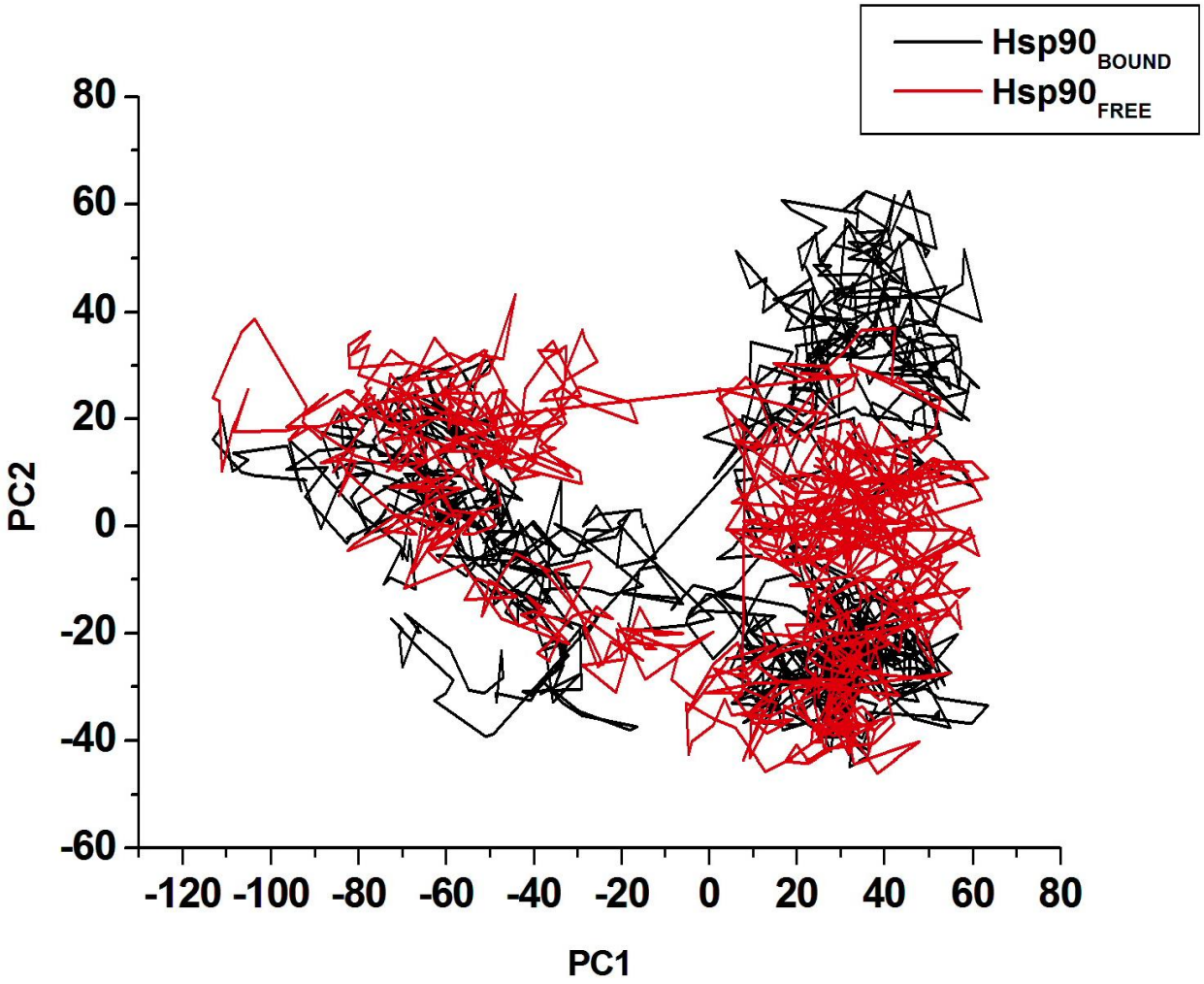


Figure 7: PCA projection of C-α atoms motion constructed by plotting the initial two principal components (PC1 and PC2) in conformational subspace.

3.2.3. Per-residue energy decomposition (PRED)

In an effort to offer more insight into the involvement of each amino acid residue toward the binding of C-A1, PRED was computed for the system. This helps us to observe the residues with the most contribution to the ligand binding, as seen from **Figure 8** the residues from both monomers showed interaction favorable to the ligand via different interactions. This further advocates that C-A1 inhibit dimerization. This information will ideally assist medicinal chemists in the design of inhibitors that precisely interrelate with these amino acid residues.

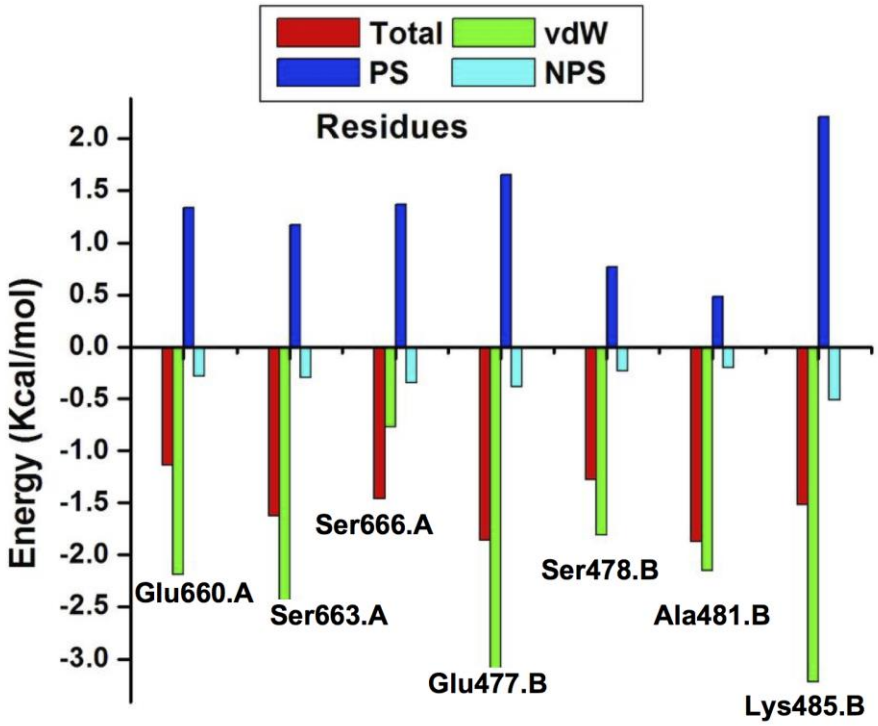


Figure 8: Graph showing binding energy (Total), van der Waals (vdW), polar solvation (PS) and non-polar solvation (NPS) contribution for each HCAAR.

3.2.3 Dynamic cross correlation

The DCCM is shown in **Figure 9, S7**, which has been calculated for both bound and unbound conformations of Hsp90 dimer subunits and Hsp90 as a whole. The free state of Hsp90 displayed a more correlated motion, which further justifies the occurrence of the dimerization process resulting in a more correlated residue-residue interaction. The bound state, on the contrary, showed a much greater reduction in correlated motions during simulations. With these findings we can thus conclude that C-A1 inhibited the dimerization mechanism of Hsp90. The suitability of C-A1 to inhibit dimerization mechanism is hence confirmed as Hsp90 ground state is stabilized.

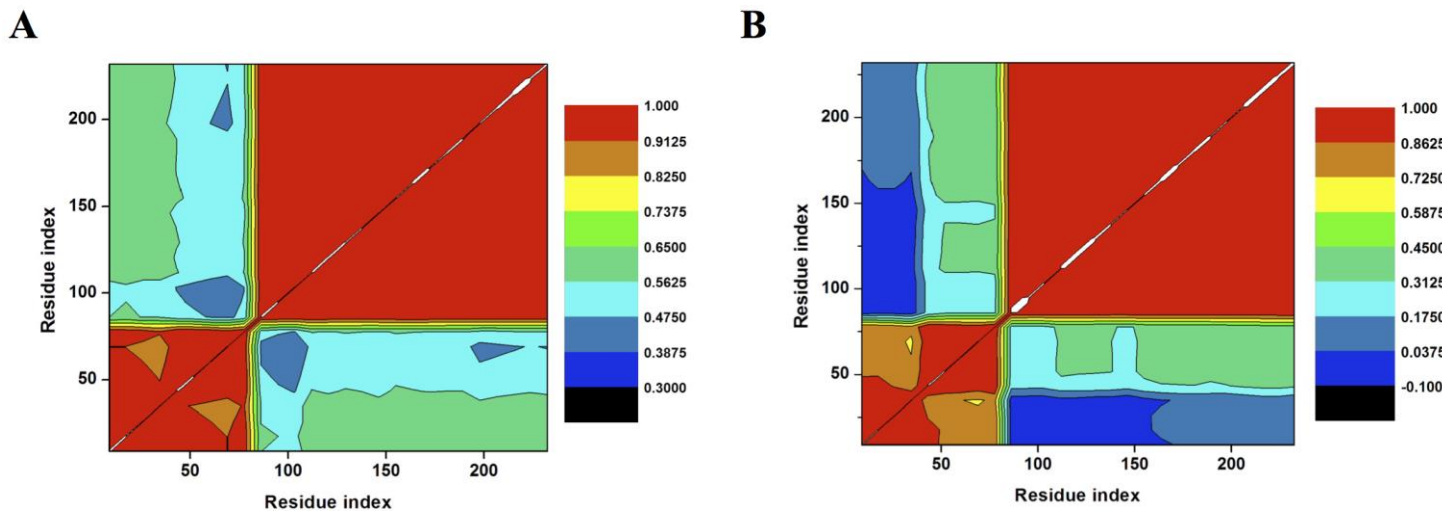


Figure 9: DCC matrix of the dimeric subunit during simulation taking into consideration C-α residues of Hsp90 ligand -bound (**A**) and free (**B**) conformations.

The distance between the dimer residues in each dimeric subunit were calculated by measuring the interatomic distances between the Cα atoms along the simulations to gain an in-depth insight of dynamics of the dimerization process. **Figure 10, S3** highlights these residues.

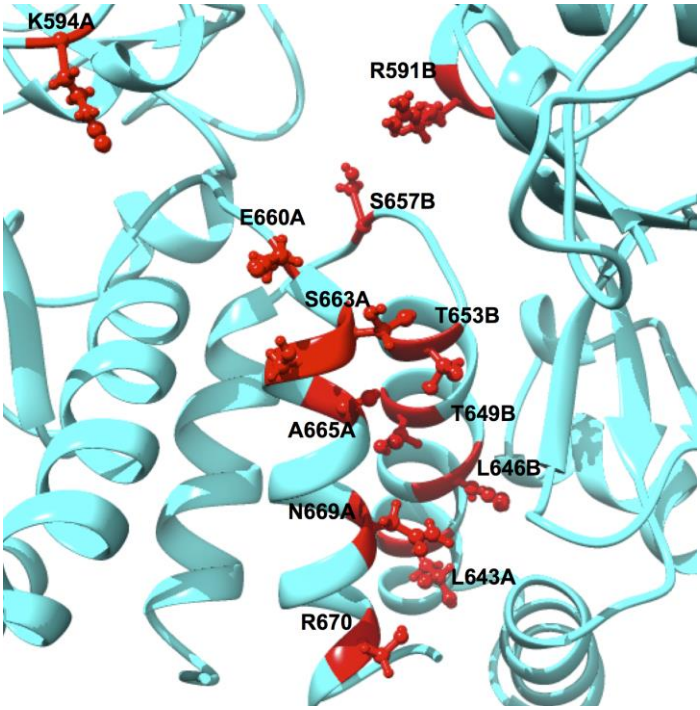


Figure 10. The dimeric region residues from both subunits assumed to be part of the Hsp90 dimerization process.

The distances between the orthogonal residues for the apo conformation were comparatively higher than that of the bound conformation as the average Cα distances specified on **Table 1**, **S6**. The standard deviation of distances for the apo conformation was higher than that of the bound conformation, indicating that the latter enzyme is more stable (agreeing with the RMSF, Rg and PCA studies).

Table 1. Residues involved in dimer packing and their averaged distances from each other throughout simulation.

Residues	**Apo/Å**	**Bound/ Å**
S663A-T653B	8.54 ± 0.40	8.46 ± 0.35
A665A-T649B	6.43 ± 0.57	5.55 ± 0.38
N669A-L646B	9.88 ± 0.72	7.32 ± 0.50
K594A-R591B	13.11 ± 0.91	12.44 ± 0.50

These substantial dissimilarities in distances between residues in the arranging of the dimer guaranteed the inhibitions of Hsp90 by C-A1 through the formation of a stable interaction with residues involved in the dimerization, preventing the dimer from opening and allowing the substrate from entering. This fact further correlates with previous biochemical analyses aimed at mapping the binding site of C-A1 in Hsp90 suggesting that the viral gene expression inhibited by C-A1 through the interference with Hsp90 dimerization[320].

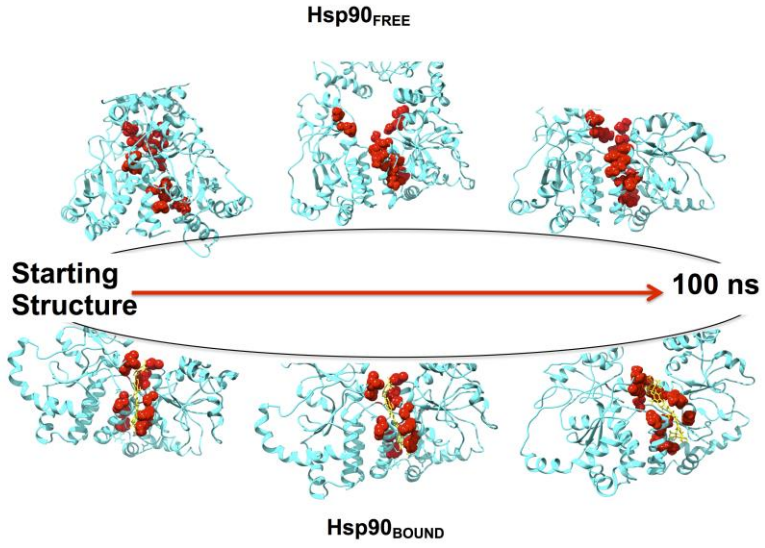


Figure 11: Snapshots of unbound and C-A1-bound conformations of Hsp90 at a definite frames during MD simulation.

Snapshots for the MD simulations for both the apo and the C-A1-bound conformations of Hsp90 were taken at specific time interval corresponding to the distances of orthogonal residues (**S6**) where it is evident for both conformations opening and closing. This further substantiate the lack of dimerization in the Hsp90-C-A1 complex (**Figure 11**).

4. Conclusion

Molecular dynamic simulations revealed differences in the dimerization mechanism of Hsp90 in its unbound and C-A1-bound conformations. Micro-molecule inhibitors such as C-A1 prevent the dimerization process by targeting the dimer of Hsp90. We believe a more conformational rigid system was due a dimerization process being delayed. This was indicated after the analysis of the RMSF and Rg proving a more conformational supple nature of unbound Hsp90, whereas the C-A1-bound conformation of Hsp90 was found to be more stable with a declined dimerization throughout the MD simulation. The binding of C-A1 to the Hsp90 dimer subunits inhibits the process of dimerization. This is further validated by observing the distance between the residues that are involved in the dimerization process. This is the first report emphasizing the important computational insight of the features of a crucial HIV target, which would also serve as an appropriate foundation in the process of designing new compounds against Hsp90 as future anti-HIV drugs.

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Abbreviations

ATP	Adenosine triphosphate
C-A1	Coumermycin A1
CAAR	Contributing amino acid residues
CTD	C-terminal domain
DCCM	Dynamic cross correlation matrix
DNA	Deoxyribonucleic acid
GTP	Guanosine-5'-triphosphate
IN	Integrase
NP	Polar solvation

NPS	Non-polar solvation
NTD	N-terminal domain
PCA	Principal Component Analysis
PRED	Per residue energy decomposition
Rg	Radius of gyration
RMSD	Root-mean-square deviation
RMSF	Root-mean-square fluctuation
RNA	Ribonucleic acid

Conflict of interests

The authors avow no conflict of interest to the above article.

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Supplementary material

Mechanism of Inhibition of Hsp90 Dimerization by Gyrase B inhibitor coumermycin A1 (C-A1) revealed by Molecular Dynamics Simulations and Thermodynamic Calculations

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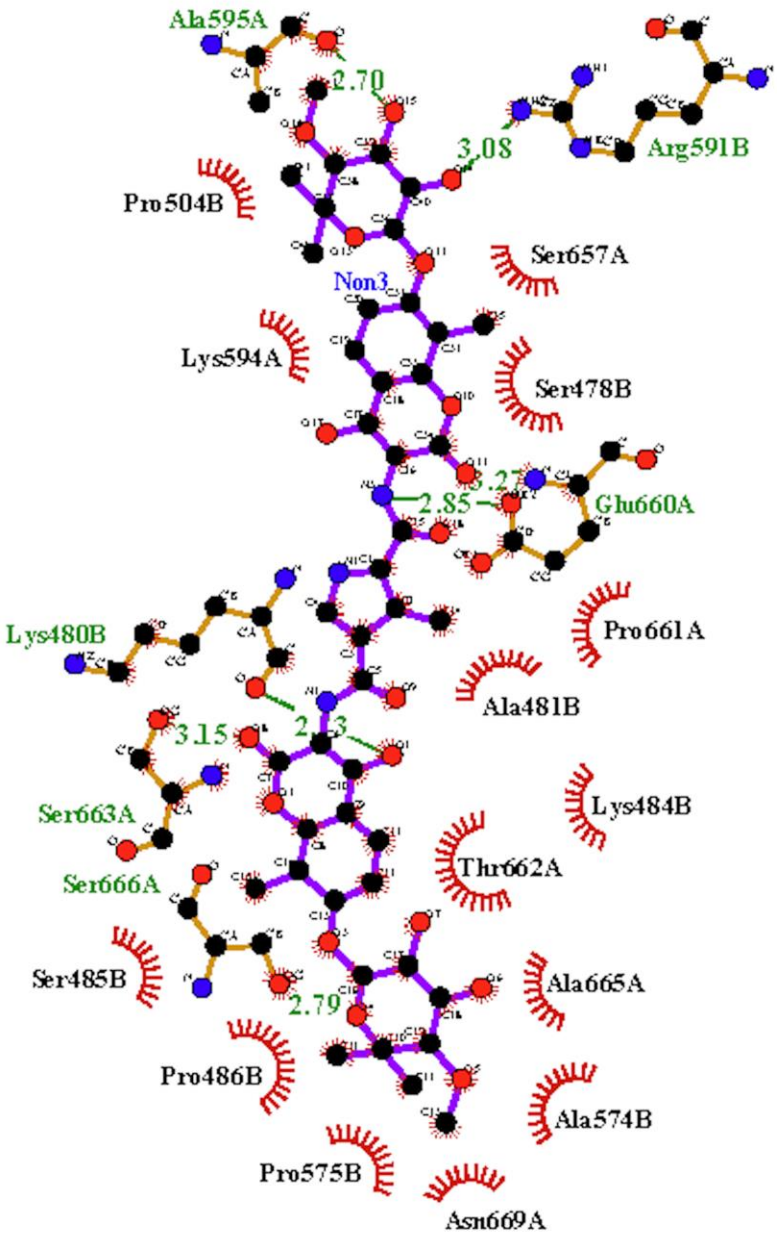
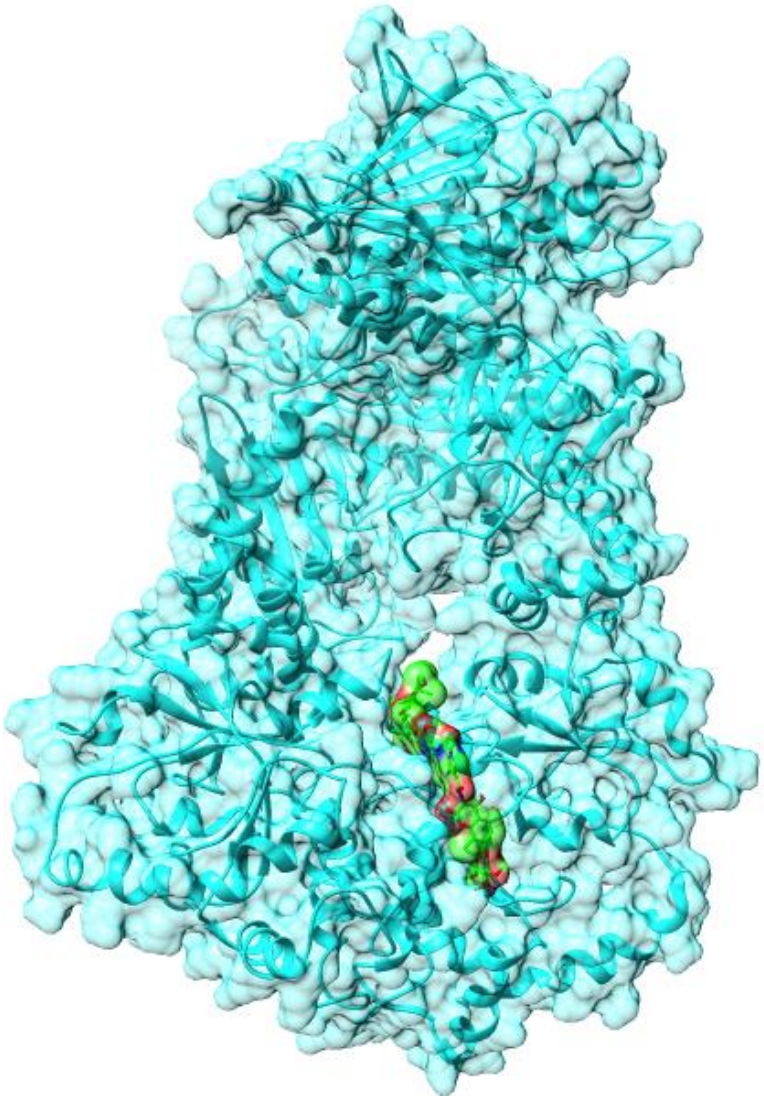


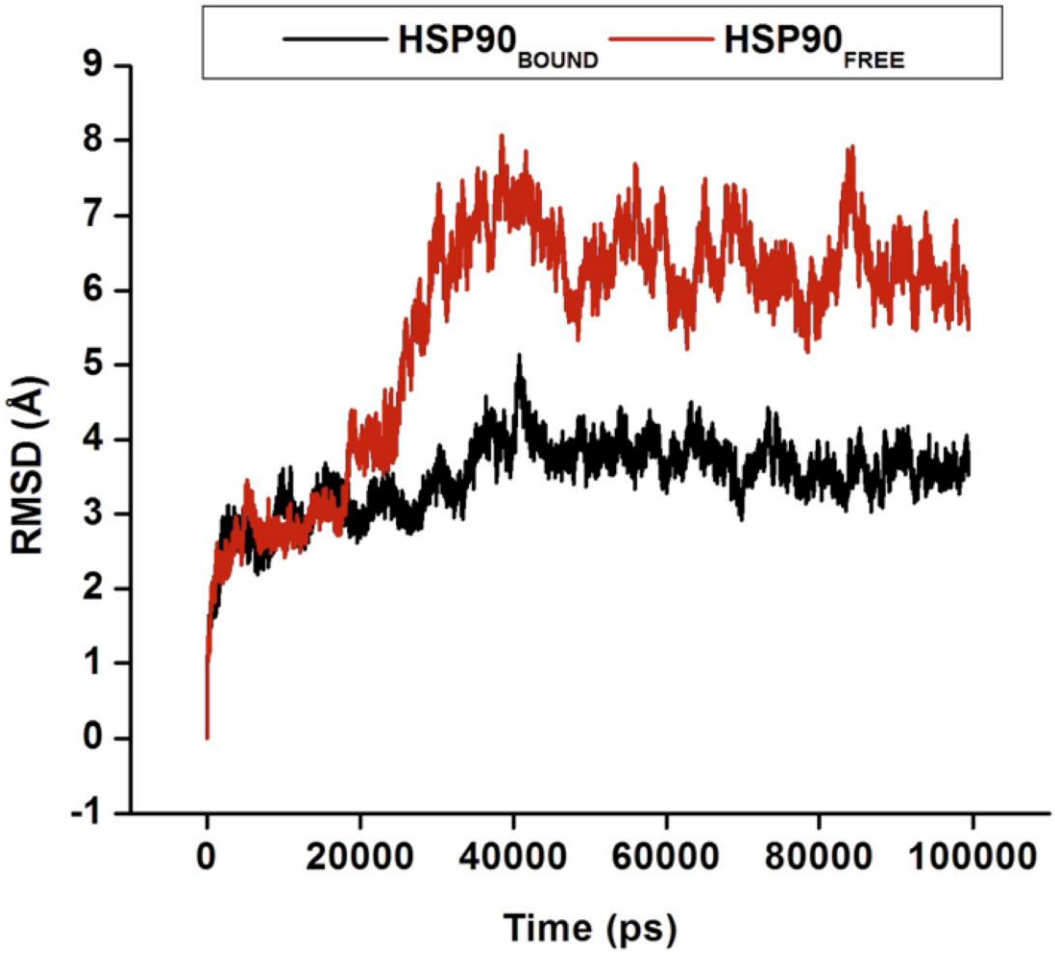
S1: Residue interaction lig-plot of C-A1 inside the active site of Hsp90. Hydrogen bond and hydrophobic interactions shown in green dotted lines and red eyelashes respectively.



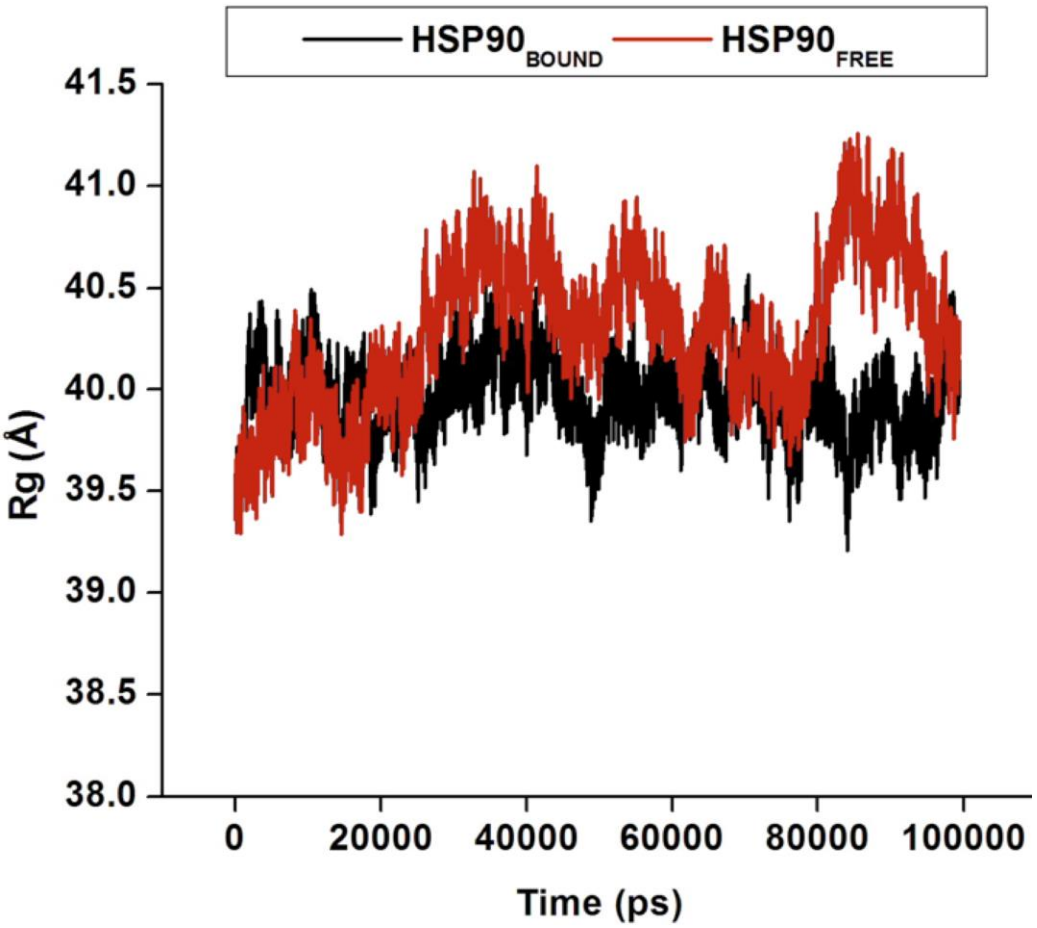
S2: The ribbon representation of the docked structure of Hsp90-C-A1 complex.

Residue name	Total Energy	Van der Waals	Polar Solvation	Non-Polar Solvation
Glu592	-1.136	-2.188	1.331	-0.279
Ser595	-1.626	-2.504	1.175	-0.297
Ser598	-1.461	-0.772	1.367	-0.347
Glu1040	-1.858	-3.124	1.651	-0.385
Ser1041	-1.275	-1.810	0.768	-0.232
Ala1044	-1.873	-2.154	0.484	-0.203
Lys1047	-1.519	-3.218	2.210	-0.512

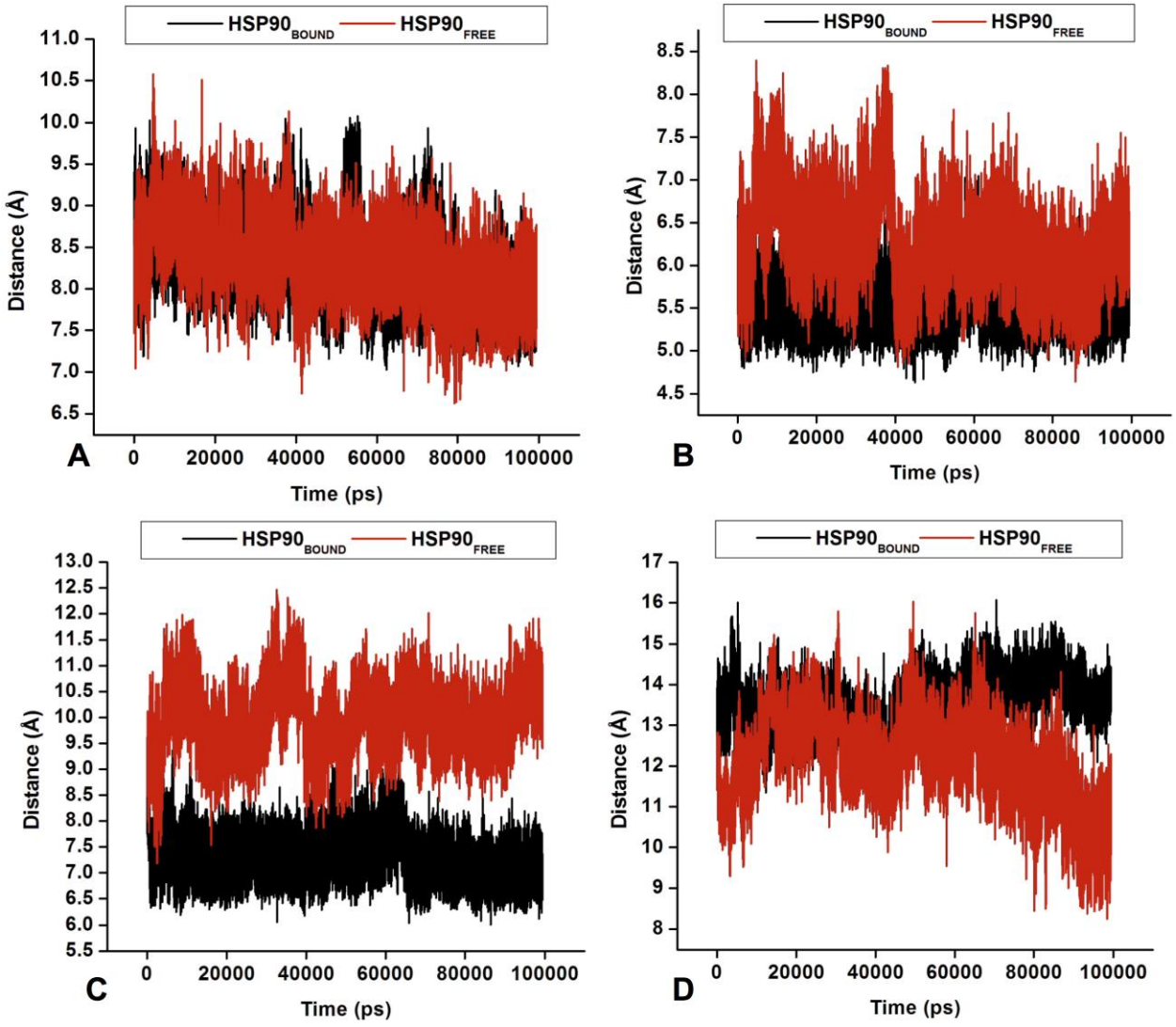
S3: Table of contributing amino acid residue to binding of C-A1.



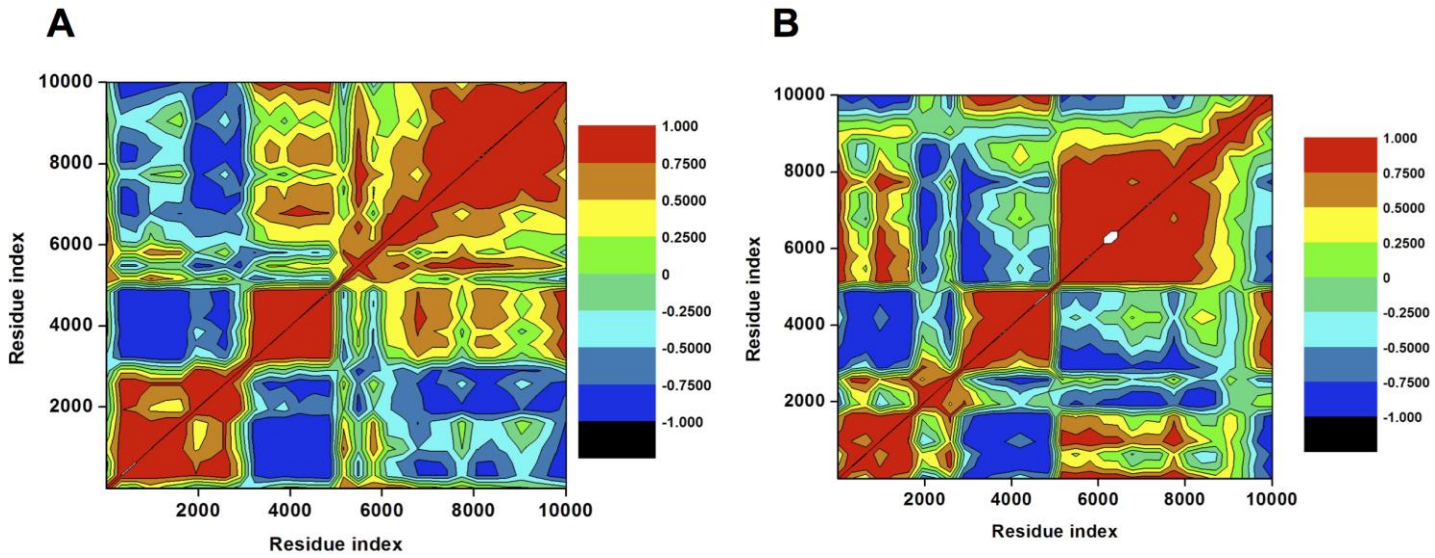
S4: Root-mean-square deviation (RMSD) values for backbone atoms along the 100 ns trajectory.



S5: Time evolution of the radius of gyration (Rg) during 100 ns MD simulation.



S6: Distances between residues involving (A) Ser663 and Thr653 (B) Ala665 and Thr649 (C) Asn669 and Leu646 (D) Lys594 and Arg591 for both apo and bound conformations.



S7: Dynamic cross correlation map of Hsp90-bound (A) and free (B) during simulation run of 100ns, considering Cα residues of both conformations.

CHAPTER 6

6.1 General conclusions and recommendations for future studies

A general conclusion of the study as well as recommendations for future research based on its findings will be outlined in this chapter.

6.1.1. General Conclusions

The reported research study reported herein is comprised of two aims: (i) To improve and refine the current pharmacophore approach, which will search for compounds that interact with the highly contributing residues based on the FBE for the HIV-1RT inhibition (ii) To study the mechanism of inhibition of Hsp90 dimerization by Gyrase B inhibitor C-A1. The aims of the studies were consummately accomplished and the results obtained from this work generated the listed conclusions below:

1) In this study the pharmacophore-based VS was used to screen for more potent HIV-1 RT inhibitors. This was an energy-based pharmacophore map, which was generated using the FBE calculated from MD. This approach was intended to unfetter the conventional pharmacophore approaches limitations. The compounds screened using this model were docked against HIV-1 RT. The docking method was successfully validated using known HIV-1 RT inhibitors and a reasonable R^2 value of 0, 62128 was obtained. Post to docking, MD simulation and MMPBSA were calculated for the top 10 compounds and two compounds showed a greater binding affinity compared to the prototype compound reported in literature[150]. Post-dynamic analysis proved our system to be stable throughout MD simulations.

2) This was a conformational study to investigate the C-A1 (Gyrase B inhibitor previously experimentally investigated[320]) mechanism of inhibition when bound to the CTD of Hsp90 protein (an emerging anti-HIV target). A continuous MD production, for both the bound and the unbound conformations, was run for 100ns and the post-dynamic analysis were carried out for both systems. The results were plotted using origin data analysis software[353].

3) The post-dynamic analysis such as RMSD, RMSF, Rg, PCA, inter atomic distances and DCC plots showed significant differences for both systems. The residue of the unbound conformation according to RMSF showed higher fluctuation in amino acid residues in the region of 400 to 600 CTD compared to the bound conformation amino acid residues which all revealed lower fluctuations.

4) It is also evident from RMSD that both the systems were equilibrated (not exceeding 2Å) towards the end of the simulation of 100 ns. The systems for bound and unbound conformations reached their stability after 60000 ps and 80000 ps respectively.

5) Results have shown that choosing highly contributing FBE candidates from a library of compounds generated from PRED target-bound pharmacophore map is a more reliable and accurate approach for the first study and the binding of C-A1 to the Hsp90 dimer subunits inhibits the process of dimerization for the second study. It can be concluded from the results obtained from both studies that the computational evidence from these present studies would serve as an appropriate foundation in the process of designing new compounds against both HIV-1 RT and Hsp90 as future anti-HIV drugs.

The results presented in these research studies shows us how promising these computational approaches and methods are for the discovery and development of drugs. They will eventually contribute to enhanced diagnosis and escalation of the rates of survival of HIV-1-infected patients. This is evident from previous successful computational studies on the HIV targets[354–359].

6.2. Recommendations and Future Studies

The computational chemistry methods employed in this study including VS, MD simulation, FBE calculation using MM/GBSA method (integrated in AMBER 14) and the post-dynamic analyses offer an inexpensive yet powerful tool for the design and drug discovery. These methods were involved in the inhibitory mechanism of compounds in the active site, determination of energy interactions of active site residues towards ligand binding and the authentication of results from docking studies.

6.3. The following may be included in the future studies:

1. To further validate the novel inhibitors, screened using an improved pharmacophore based VS approach, using an experimental approach.

2. Use the improved pharmacophore based VS approach to screen for more Hsp90 inhibitors using C-A1 as a prototype.

6.4. References

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