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Molecular Electrostatic Potential Analysis and Molecular Docking Studies of Anti-Viral Inhibitors

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Abstract:

Molecular electrostatic potential analysis and molecular docking studies play a crucial role in the development of anti-viral inhibitors for AIDS. These scientific methods help to understand the interactions between potential drugs and the viral targets associated with the human immunodeficiency virus (HIV).In this analysis, the electrostatic properties of molecules are examined. This analysis provides insights into the distribution of positive and negative charges within a molecule, which is essential for understanding its potential interactions with viral proteins. By studying the electrostatic potential, we can predict the regions of a molecule that are likely to interact with specific viral targets. Molecular docking studies involve the computational modeling of the binding process between a drug molecule and its target protein. In the case of AIDS, our research mainely focus on identifying inhibitors that can effectively bind to viral proteins involved in the replication and infection processes of HIV. By simulating the docking process, we predicted the binding affinity and orientation of potential inhibitors, providing valuable information for drug design and optimization. Current study is crucial for the development of effective anti-viral inhibitors for AIDS. By understanding the electrostatic properties of molecules and their interactions with viral targets, we can identify potential drug candidates with high binding affinity and specificity. This knowledge aids in the design of more potent and targeted therapies, which can inhibit the replication of HIV and slow down the progression of AIDS. Overall, molecular electrostatic potential analysis and molecular docking studies contribute significantly to the ongoing efforts in finding effective treatments for AIDS. These methods provide valuable insights into the molecular interactions between potential inhibitors and viral targets, ultimately leading to the development of novel anti-viral therapies for combating HIV/AIDS.

Key words: AIDS, HIV, antiretroviral therapy (ART), HAART, docking, modeling

Introduction

Acquired immunodeficiency syndrome (AIDS) is one of the most important infectious diseases leading to the mortality in many developed and developing countries. It is caused by the retrovirus Human Immunodeficiency Virus (HIV). According to NACO, it is estimated that there are currently 33.3 million people infected with HIV/AIDS worldwide. Even though 68% of the global burden of HIV infections is recorded from Sub-Saharan Africa with approximately 22.5 million infected people, globally the availability of antiretroviral therapy (ART) has declined the number of new infections by approximately 19% (*Gallo et al*, 1983).

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Human Immunodeficiency Virus (HIV-1) infection is universally considered by a long-time, chronic disease that slowly progresses to Acquired Immunodeficiency Syndrome (AIDS). HIV has a high genetic diversity due to the fast replication cycle of the virus coupled with the high error prone rate of its RT enzyme. RT also further increases HIV diversity by allowing for strains to recombine with each other. HIV-1 has been divided into four distinct groups M, non-M, non-O (N), outlier (O) and P with group M responsible for the worldwide pandemic we are facing today. More than Ninety percent of HIV-1 infections fit to group M. Nine genetically distinct subtypes (or clades) inclusive of A, B, C, D, F, G, H, J and K found in HIV-1 group M. HIV-1 subtype A, C, and D accounted for 65% of worldwide HIV-1 infections, but subtype C is responsible for a fifty percent of world-wide infections (*Popovic*, et al, 1984).

The HIV polyprotein precursor is encoded by relatively simple genomes consisting of gag, pol and env open reading frames. The gag gene encodes the structural capsid, nucleocapsid, and matrix protein; env undergoes multiple alternative splicing events to regulatory protein; while, pol encodes essential viral enzymes necessary for viral replication. The HIV-1 protease receptor (HIV-1 PR) is an aspartyl protease that is required for proteolytic processing of the gag and gag-pol polyprotein precursors to yield the viral enzyme and structural proteins and is absolutely indispensible for proper viron assembly and maturation. HIV-1 PR contains a homodimeric C-2 symmetric structure and each monomer contributes one catalytic aspartic residue along with threonine and glycine residues which are flexible and a flap that favors the binding of substrate and inhibitors (*Samgadharan* et al, 1984).

The highly active antiretroviral therapy (HAART) and protease inhibitors (PIs) along with reverse-transcriptase inhibitors have resulted in the unprecedented success of HIV/AIDS chemotherapy. However owing to the rapid emergence of drug-resistant HIV-1 variants and transmission of these resistant viral strains along with the adverse side effects of currently used HIV-1 PIs, are remain critical factors that limiting the clinical effectiveness of HAART.. Up to now, some clinically approved HIV-1 protease inhibitors including atazanavir, indivanir, nelfinavir and sequinavir are available in the market for HIV treatment but they are very peptide-like and have poor bio-availability (*Hemelaar* et al, 2004).

In the absence of an effective vaccine, drugs are the only therapeutic tools that can be used to treat HIV-1 infections. Unfortunately, HIV-1 infections cannot be cured, so that drug therapy, once initiated, must be continued for the life of the patient. This places a special burden on the design of anti-HIV drugs: They need to be relatively nontoxic so that they can be used in long-term therapy. HIV-1 replication is error prone and the errors that arise during the viral life cycle, together with the rapid replication of the virus in patients, allows the virus to escape the host's immune system and develop resistance to all of the available drugs. The virus evolves sufficiently rapidly that, unless the therapy is well-designed, resistance will develop in all treated patients (Coffin et al, 1997). The only way to stop the development of resistance is to completely block viral replication; this, in turn, stops the evolution of resistance. It takes a combination of drugs (usually three) to completely block viral replication; this is the reason that three-drug regimens are used in standard HIV-1 therapies. Of the approved drugs, most target two of the three virally encoded enzymes that carry out viral replication, reverse transcriptase (RT) and protease (PR). A new drug, raltegravir, that targets the third enzyme integrase (IN) has recently been approved (http://www.fda.gov/oashi/aids/virals.html). In addition to the drugs that target the viral enzymes, there are two approved drugs, enfurvitide and maraviroc, that target different aspects of viral entry.

Viral infections are initiated by the fusion of the viral and cellular membranes; this fusion reaction is caused by the interactions of the viral envelope glycoprotein with its receptor (CD4) and a co-receptor, usually either CCR5 or CXCR4. Binding the receptor and co-receptor causes changes in the structure of the envelope glycoprotein, this leads to membrane fusion. Membrane fusion places the

viral core, which contains RT, into the cytoplasm of the cell. A poorly understood process called "uncoating" modifies the core in ways that promote reverse transcription (Coffin, 1995).

Drug resistance remains a central challenge in HIV therapies. Because resistant viruses can be transmitted, the prevalence of resistant viruses is increasing in untreated HIV-1 patients. For the virus to replicate and be transmitted, HIV-1 RT must be able to complete viral DNA synthesis, and NRTI-resistant RTs must retain the ability to incorporate normal dNTPs with reasonable efficiency. This means that NRTI resistance involves enhanced discrimination between normal nucleosides and NRTIs. Two basic types of NRTI-resistance mechanisms are known for HIV-1 RT: 1) one resistance mechanism (exclusion) involves enhanced discrimination at the time the NRTI-TP is incorporated (Jacques et al, 1994). The M184V/I mutations provide a clear example of the exclusion mechanism, M184V/I selectively reduce the incorporation of 3TC and FTC by steric hindrance. 2) The second mechanism involves the selective removal of the NRTI from the end of the viral DNA after it has been incorporated by RT. This is the excision mechanism; a well-studied example involves AZT resistance caused by a set of mutations including M41L, D67N, K70R, L210W, T215F/Y, K219E/Q (these mutations will be collectively referred to as AZT resistant or AZTr; they are also referred to as thymidine-analog mutations, TAMs,or excision-enhancing mutations, EEMs). Although the HIV-1 RTs isolated from AZT-resistant viruses in patients do not ordinarily have all of the AZTr mutations, combinations of these mutations give rise to high levels of resistance to AZT and to much lower levels of resistance to some other NRTIs. HIV-1 RTs carrying the AZTr mutations can acquire additional mutations that enhance their ability to excise AZT, and allow these RTs to excise most other NRTIs more efficiently (Larder et al, 1987).

Therefore to overcome these problems, there is a need for the development of new PIs with improved activity against drug resistant variants and excellent pharmacokinetic and safety profiles. The pharmaco-informatics approaches including virtual screening and molecular docking have become pivotal techniques in the pharmaceutical industry for lead discovery. Many groups have applied the pharmacoinformatics approaches to identify inhibitors against HIV protease. Hence in the present study binding efficiencies of the inhibitory molecules of HIV protease in terms of space modelling study and virtual screening along with molecular docking and also the DFT studies were considered.

Materials And Methods

PUBMED

PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez system of information retrieval. This database is used to retrieve the article related to HIV-1 Protease. In this database the Simple searches on PubMed has been carried out by entering "HIV-1 Protease inhibitors and docking" as a key aspects of a subject into PubMed's search window and obtained 104 related articles (Pubmed website). Also some anti-viral compounds were selected as ligands.

PDB

The Protein Data Bank (PDB) is a crystallographic database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy are freely accessible in PDB. The 3D structure of HIV-1 protease receptor (HIV-1 PR) an aspartyl protease that is required for proteolytic processing of the gag and gag-pol polyprotein precursors to yield the viral enzyme and structural proteins and is absolutely indispensible for proper viron assembly and maturation is retrieved from PDB. The structure of this protein is determined by X-ray crystallography (1T3R) (PDB website).

ACD chemsketch

Chemsketch is a molecular modeling program used to create and modify images of chemical structures. This software allows molecules and molecular models to be displayed in two and three dimensions and also helps to understand the structure of chemical bonds and the nature of the functional groups. This software provided by Advanced Chemistry Development, Inc., (ACD/Labs) Software Company in support of small molecule chemistry. This software is used to sketch the 2D structures of selected HIV-1 protease inhibitors and obtained in mol format for further studies.

Online Smiles convertor

The simplified molecular-input line-entry system (SMILES) is a specification in form of a line notation for describing the structure of chemical species using short ASCII strings. SMILES strings can be imported by most molecule editors for conversion back into two-dimensional drawings or three-dimensional models of the molecules. The sketched 2D structures in mol format is converted into 3D structure and obtained in SD file format for further studies. This program is accessed at https://cactus.nci.nih.gov/translate/

DoGsite Scorer

DogSiteScorer is an automated pocket detection and analysis tool which can be used for protein druggability assessment. Predictions with DoGSiteScorer are based on calculated size, shape and chemical features of automatically predicted pockets, incorporated into a support vector machine for druggability estimation. Based on the 3D coordinates of a protein, its potential active sites on the protein surface are calculated with DoGSite. DoGSite is a grid-based function prediction method which uses a Difference of Gaussian filter to detect potential pockets on the protein surface and splits them into subpockets. The global properties, describing the size, shape and chemical features of the predicted pockets are calculated. To determine the binding affinities between different HIV-1 protease inhibitors and the HIV-1 protease protein the binding sites were predicted by submitting the structure to DoGSiteScorer: Active Site Prediction and Analysis Server. This program is accessed at http://dogsite.zbh.uni-hamburg.de/

FlexX

FlexX is a software package to predict protein-ligand interactions. FlexX accurately predicts the geometry of the protein-ligand complex within a few seconds. The intuitive GUI permits the set up of docking runs within a single minute and provides the instantaneous visual feedback. The retrieved compounds in SDF file format were docked with the amino acids in the predicted binding site of HIV-1 Protease by using the following parameters i) default general docking information's, ii) base placement using triangle matching, iii) scoring of full score contribution and threshold of 0,30 and No score contribution and threshold of 0,70.iv) chemical parameters of clash handling values for protein ligand clashes with maximum allowed overlap volume of 2.9 A03 and intra-ligand clashes with clash factor of 0.6 and considering the hydrogen in internal clash tests. v) default docking details values of 200 for both the maximum number of solutions per iteration and maximum number of solutions per fragmentation.

Pose view

The software tool PoseView automatically generates high-quality 2D structure-diagrams of protein-ligand complexes with known 3D structure according to chemical drawing conventions. The 2D depiction shows hydrogen bonds as dashed lines between the interaction partners on either side. Hydrophobic interactions are illustrated as smooth contour lines between the respective amino acids and the ligand. The interactions between 42 HIV-1 protease inhibitors and HIV-1 Protease in the docked complex were analyzed by the pose-view of LeadIT.

DFT studies

The molecular structure of best docked compound was computed using Gaussian software to retrieve the molecular geometric coordinates. Both density functional theory (DFT) and time-dependent density functional theory (TD-DFT) calculations were performed by using Gaussian 03W software. B3LYP hybrid functional 6-311G (d) basis set were used in the calculation methods. The models of electron density of various energy levels of the compound was visualized using Gauss View 3.0 (Suresh et al, 2013).

Results And Discussion

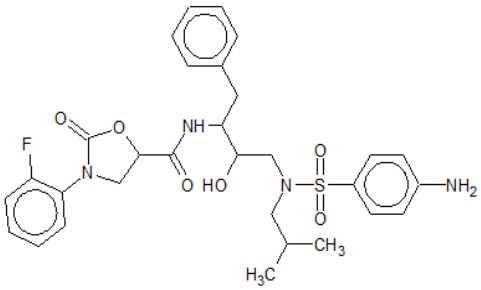
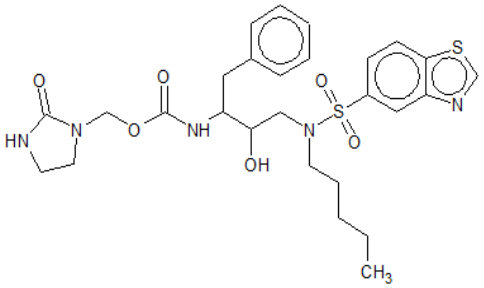
HIV drug resistance is one of the major hurdles for achieving and maintaining of successful viral suppression. Most data on the genetic mechanisms of HIV-1 drug resistance are from studies of subtype B viruses, the predominant subtype in the North American and Europe. Several of studies suggest that the currently available PR (Protease) and RT (Reverse Transcriptase) inhibitors are as active against non-B viruses as they are against subtype B viruses.

Thus to understand how the screened drug-like virtual hits bind to the receptor, in this study the potential HIV-1 protease ligands were analyzed using the ligand-receptor interactions by molecular docking. Molecular docking is one of the best filtering methods and a crucial technique in drug design process. The Molecular Docking protocol of the FlexX was used to dock the retrieved compounds by virtual screening. The protocol first analyses the provided cavity and then selects the region of the protein as the active site, and secondly dock the ligands to the selected site. 3D regular grids of points are employed for site detection and also for estimating the interaction energy of the ligand with the protein during docking. The protein receptor of the HIV protease was selected from RCSB Protein Data Bank (RCSB-PDB) for the molecular docking study. Among several HIV protease inhibitors PDB ID: 1T3R was selected based on the receptor size, resolution and deposited date. The 3D structure of the HIV-1 Protease is shown in Figure. 3.

Selection of compounds

A total of 20 anti-viral inhibitor molecules selected from the literature were shown as 2D structure in the Table.1

Table.1: Anti-HIV compounds selected for the study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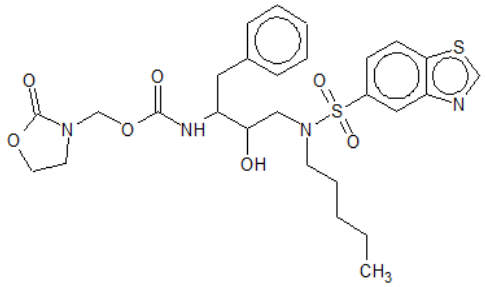	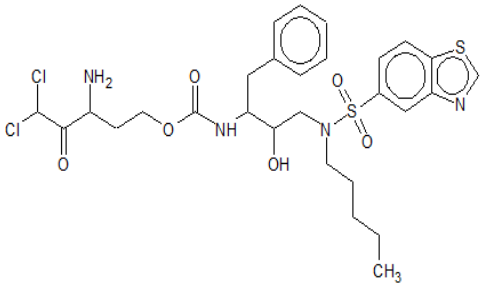
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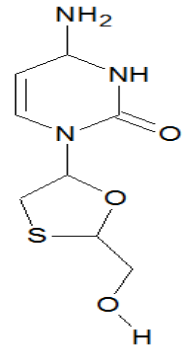	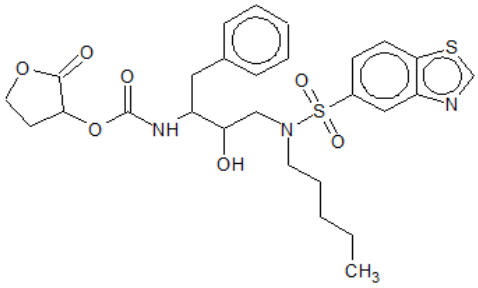
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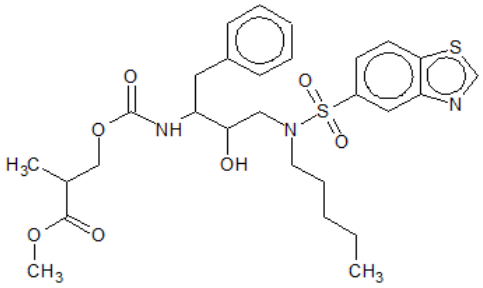	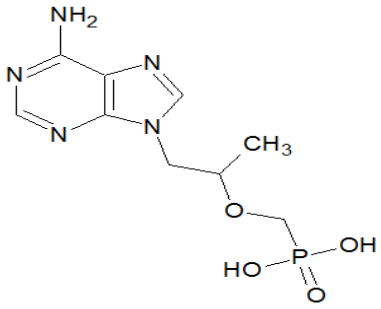
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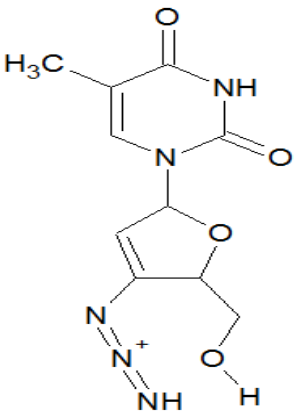	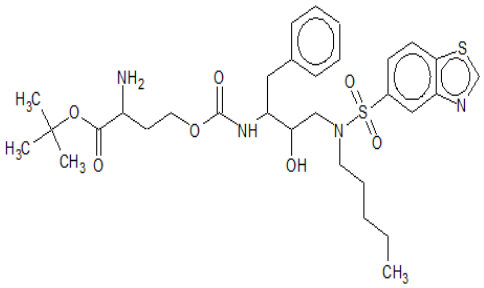
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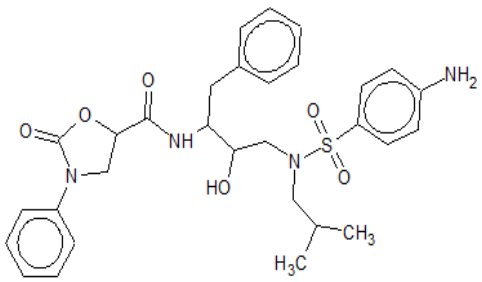	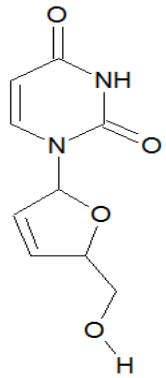
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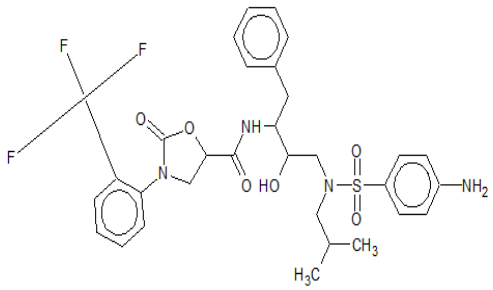	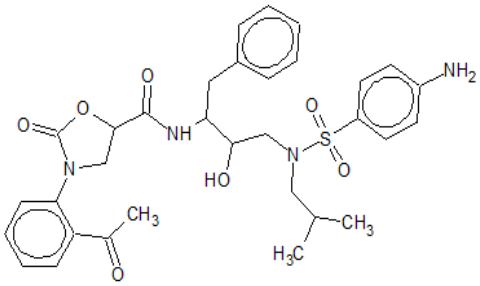
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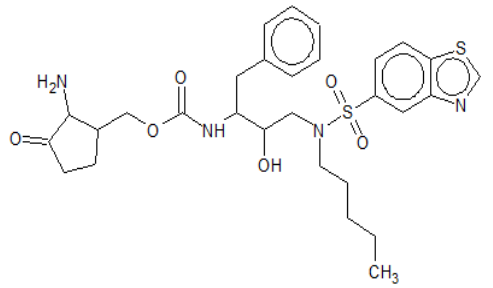	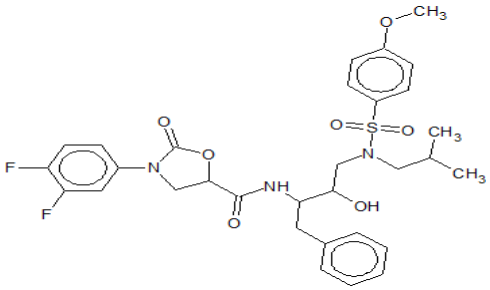
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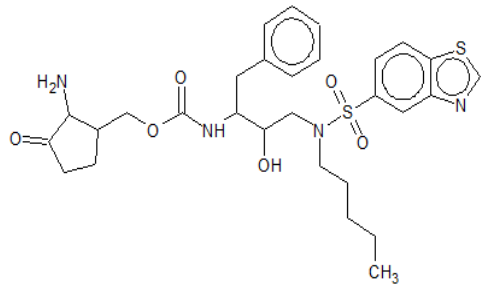	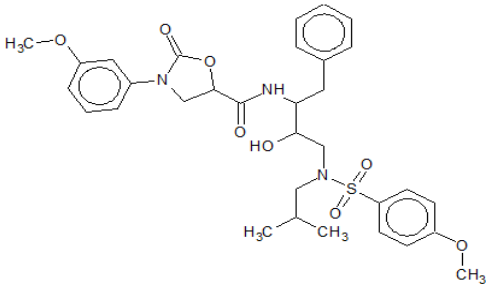
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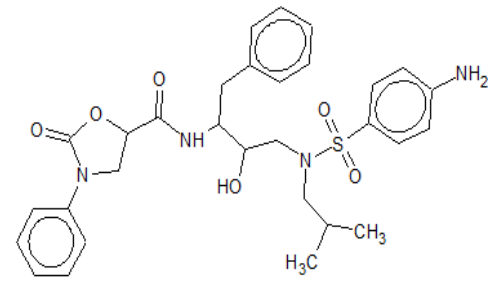
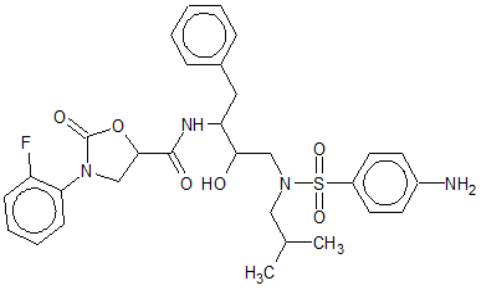
	
COMPOUND-19	COMPOUND-20

4.2 Docking Interactions

To infer possible occurrence of drug–drug interactions affecting combination therapy in HIV treatment, binding mode comparison studies were carried out to identify the competitive bindings among antiretroviral drugs with HIV-1 Reverse transcriptase. In this study, molecular docking interactions with 20 HIV-1 Reverse transcriptase inhibitors were reported and their potential drug–drug interactions with antiretroviral drugs were analyzed with their respective binding modes.

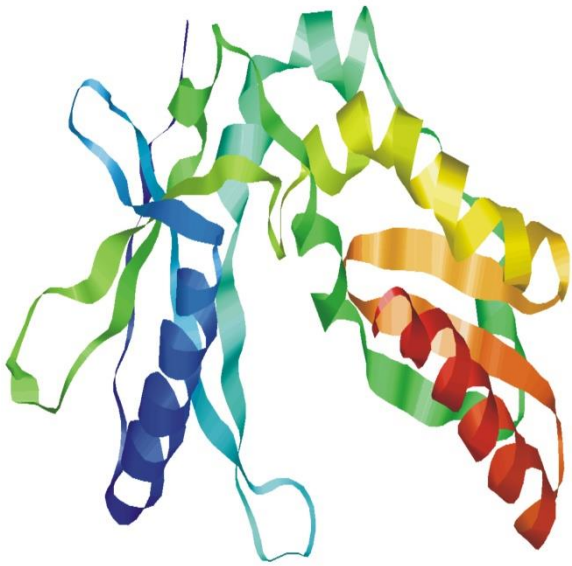


Figure.2: The 3D structure of the HIV-1 Reverse transcriptase

Eventually, it is assumed that the potential difference underlies in the drug interaction studies is significantly reflected by Reverse transcriptase binding site residues. From these docking studies it is observed that all the compounds considered in this study exhibited significant binding score with the active site of HIV-1 Reverse transcriptase. It is noteworthy to mention that all the compounds exhibited the binding interactions with the amino acids such as Asp25, Thr26, Asp29 and water molecule at Hoh 1023.

Among the 20 compounds, four compounds exhibited highest dock scores when compared to that of other compounds, The compounds 5,8,9 and 12 exhibited highest dock scores of -20.2777 kJ/mol, -21.5623 kJ/mol, -18.2542 kJ/mol and -19.5362 kJ/mol,.

Similarly, the studies of Islam et al, (2013) performed virtual screening using the Hypo 1 obtained one potential molecule, NCS70804 from NCI database which is already confirmed as active in anti-HIV screening. A number of hydrogen bonds and bump interactions were observed between potential HIV-Reverse transcriptase compounds and catalytic residues such as Leu24, Asp25, Thr26, Gly27, Asp29, Ile50 and Ile84. The potential HIV-Reverse transcriptase molecules will be subjected to experimental validation to obtain further confirmation.

The highest docking score of -21.5623 kJ/mol is exhibited by compound -8. This interaction is favored by amino acids Gly27, Asp29, Asp25, Asp30, Thr26 and water molecule Hoh1203 for the Hbond interactions and the non-bonded interactions are supported by Asp25, Gly27, gly49, ala28, Leu23, Ile50, Pro81 and Ile84. Thus this compound can be considered as potential HIV-Reverse transcriptase inhibitor molecule.

4.2.1 Docking interactions of Compound-8

The Compound -5 showed the highest docking score of -21.5623 kJ/mol with the HIV-1 Reverse transcriptase. It is observed that the Compound - 24 exhibited critical interactions with the catalytic amino acid residues present in the active site cavity of the HIV Reverse transcriptase by favoring the Hbond interactions and Non-bonded interactions. The amino acids Lys77, Lys75 and Cys155 favored the Hbond interactions and the non-bonded interactions are supported by Same and extra of Ile153. Thus this compound can be considered as potential HIV-Reverse transcriptase inhibitor molecule. The docking complex and docking interactions of Compound - 5 within the active site of HIV-1 Reverse transcriptase is shown in figure.3.

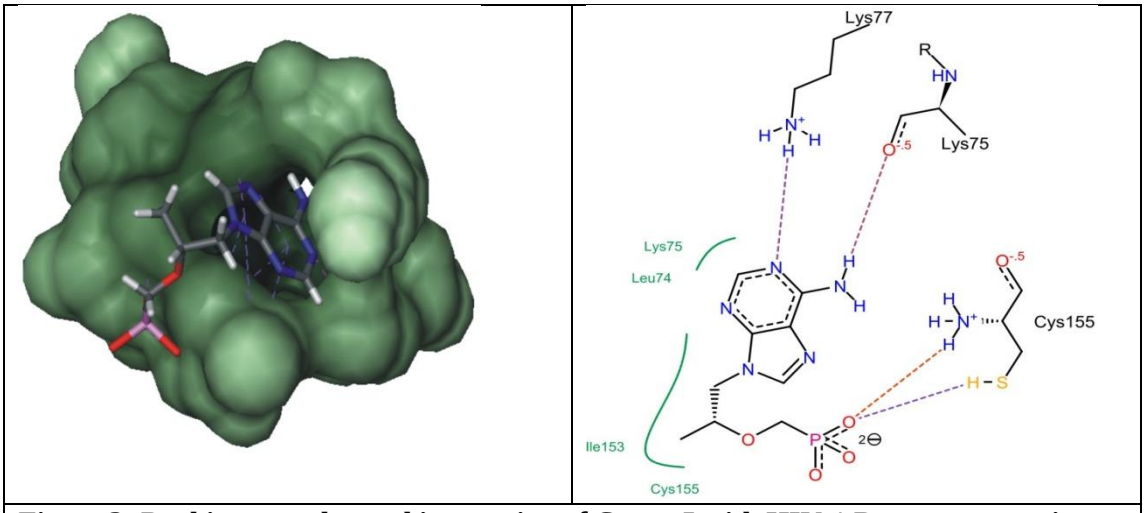


Figure.3: Docking complex and interaction of Comp-5 with HIV-1 Reverse transcriptase

Ungwitayatorn and Samee also performed studies on a series of non-peptide HIV-1 Reverse transcriptase (HIV-1 PR) inhibitors, chromone derivatives, were docked with the HIV-1 protease binding site for study the binding interaction. The orientation of chromone molecules showed the critical interaction which are important for the inhibition of the enzyme. The chromone molecules form hydrogen bonding interaction with Asp25, Asp25', Ile50 and Ile50' and hydrophobic interaction with Val32,Ile50,Pro81, Val82, and Ile84.

Thus the docking studies implies that the conserved amino acid Aspartic acid (Asp 25 and 29), Threonine (Thr26) and Glycine (Gly26) in the catalytic site of HIV-1Protease receptor are crucial in binding of anti-HIV-1 Protease inhibitors. These docking interactions implies that the NH group and =O present in the compounds favors the hbond interactions. Hence these findings throws light for the design of novel anti-HIV-1 protease inhibitors and also envisages that the amino acids Aspartic acid (Asp 25 and 29), Threonine (Thr26) and Glycine (Gly26) should be considered during its design for implying its action as a best anti-HIV-1 Protease compound against the potential target of HIV-1 Protease.

DFT studies

Vibrational analysis

The optimized structure of compound-8 is shown in figure.4.

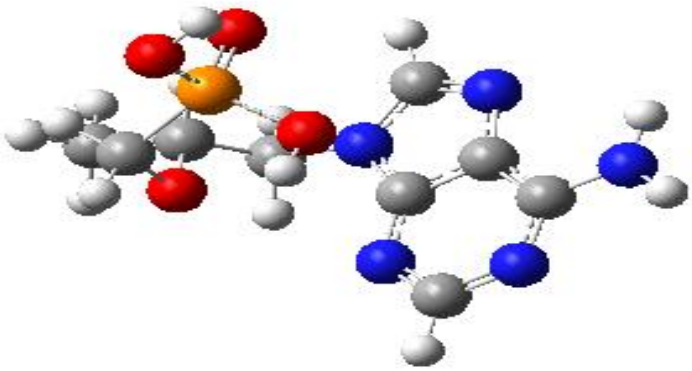


Figure.6: The optimized structure of Compound-8

The vibrational spectral analysis is performed on the basis of the characteristic vibrations of the amino group, hydroxyl group, carbonyl group and methyl group. The observed and simulated FT-IR and Raman spectra and selected vibrational normal modes are shown in Figure.5 and 6.

IR and Raman Spectral Analysis

The FT-IR spectrum of compound-24 was recorded in the region 400-4000 cm^{-1} on IFS 66V Spectrometer using KBr pellet technique .

Amino group vibrations

The fundamental modes involving the amino group are stretching and bending of NH bonds, torsion and inversion. The title molecule under investigation possesses one NH2 group and hence one expects one symmetric and one asymmetric N–H stretching vibrations. In all the primary aromatic amines the N–H stretching frequency occurs in the region 3300–3500 cm−1 and. The antisymmetric stretching mode appears to be higher wave number than the symmetric. In Compound-24 the NH2 asymmetric stretching vibration is observed in IR at 3250 as a medium band, the symmetric stretching vibration is observed in IR at 2850 cm−1 and in Raman at 3283 cm−1. The frequency lowering present in the molecule is due the intermolecular interaction. The characteristic frequency of the NH2 scissoring vibration is usually located in the range 1650–1600 cm−1. The very strong band observed in IR at 1296 cm−1 and weak band observed in Raman at 1576 cm−1 is assigned to the NH_2 scissoring vibration.

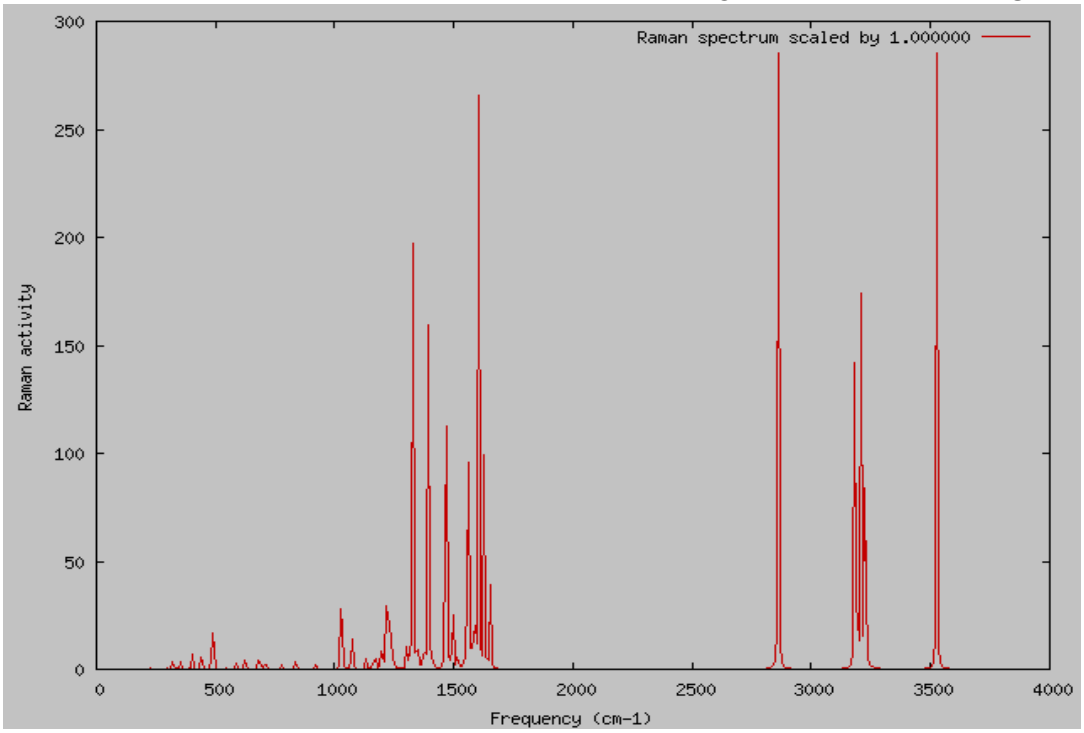


Figure.5: Theoretical FT-Raman Spectrum

Methyl group vibration

Methyl group vibrations are generally referred to as electron donating substituent in the aromatic rings system, the asymmetric C–H stretching mode of CH3 is expected around 2980 cm−1 and the CH3 symmetric stretching is expected at 2870 cm−1 and. The Me1 asymmetric stretching is observed as weak band in Raman at 2850 cm−1. The symmetric stretching mode of Me1 is observed 2881 cm−1 in IR. The shifting of the methyl stretching wave number is due to the influence of electronic effect resulting from the hyper conjugation and induction of methyl group in the aromatic ring. Hyper conjugation causes the interaction of the orbital of the methyl group with π orbital of an aromatic ring system.

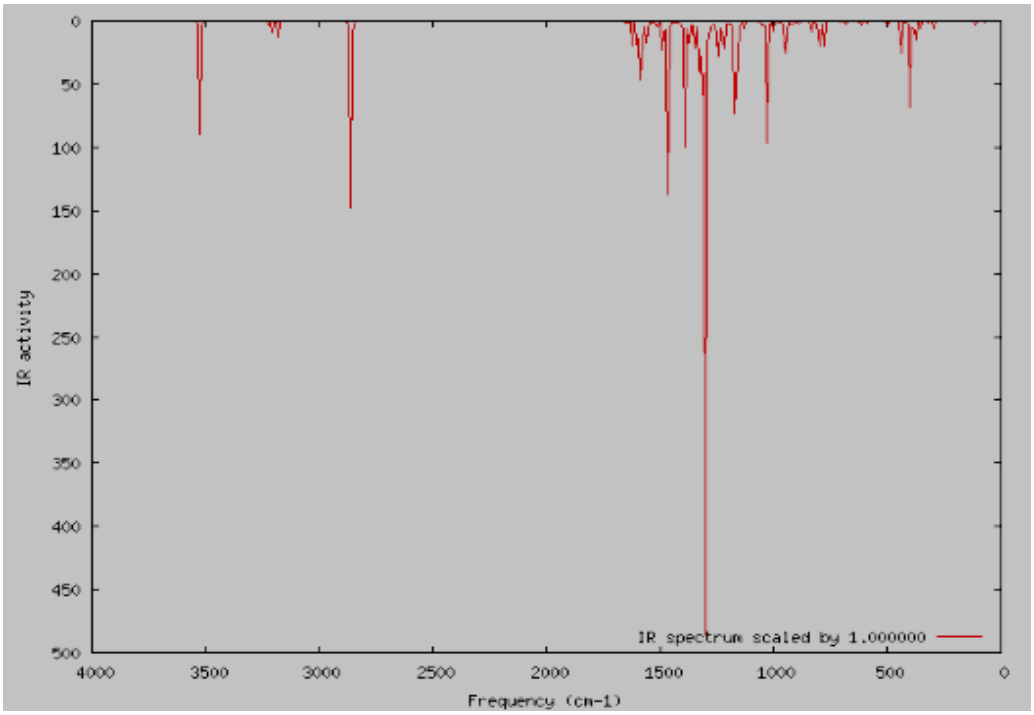


Figure.6: Theoretical FT-IR Spectrum of compound-24.

The asymmetric bending of Me2 is observed at 1397 cm−1 in IR and at 1398 cm−1 in Raman as a medium band. The asymmetric bending of Me1 is observed at 1383 cm−1 in IR as a medium band. These characteristic frequencies are in close agreement with those reported for the similar compounds. The Band observed at 935 cm−1 in IR and 1000 cm−1 in Raman is CH_3 out of plane bending modes. The bonds below 500 cm−1 in FT-Raman are assigned to methyl twisting mode.

Carbonyl group vibrations

The carbonyl group stretching vibrations give rise to the characteristic bands in IR and Raman. The intensity of these bands can increase because of the formation of hydrogen bonds. The carbonyl group vibration is observed in the region 1760–1730 cm−1 and. The strong band at 1648 cm−1 in IR and a weak band at 1655 cm−1 in Raman are assigned to carbonyl C28–O29 stretching mode. The C28–O27 stretching mode is observed in IR at 1629 cm−1 as a strong band and in Raman at 1630 cm−1 as a medium band. From that both C28–O27, and C28–O29 stretching vibrations are lowering from the normal value. The red shifting of carbonyl stretching mode is attributed to the fact that the carbonyl group chelate with the other nucleophilic group, thereby forming both intra- and intermolecular hydrogen bonding in the crystal. The C28–O27 stretching in lowering is due to the formation of N–H···O hydrogen bonding in the molecule. The C–O out of plane bending is identified as weak band in Raman at 142 cm−1.

C–N vibrations

The ring C–N stretching vibration occurs in the region 1310–1290 cm−1. Thus, the bands observed at 1314 cm−1 (IR) and 1312 cm−1 (Raman) is from the ring C–N stretching. The C–N bending is observed in IR at 846 cm−1 as a weak band.

Ring vibration

The carbon–hydrogen stretching vibrations give rise to bands in the region 3000–3100 cm−1 in all aromatic compounds. The intense band in Raman at 3069 cm−1 is assigned for ring C–H stretching wave number. The C–H in plane vibrations is appearing in the region 1000–1290 cm−1. The strong band observed in IR at 1337 cm−1 and in Raman at 1369 cm−1 is assigned the C–H in plane bending of compound-24. The series of bands observed in IR at 1170 and 1033 cm−1 and in Raman at 1199,

1167, 1115 and 1027 cm−1 are assigned to the ring C–H in plane bending ring. The C–H out of plane vibration of the ring is observed in the region 770–730 cm−1 and for the tri substituted ring is 800–760 cm−1. In Compound-24 the C–H out of plane vibration are observed in IR at 834, 791 cm−1 as medium band and is observed in Raman at 793 as a medium band. The C3–H21 stretching is observed as a weak band IR at 2916 cm−1 and as medium band in Raman at 2920 cm−1. The C3–H21 out of plane bending is observed at 761 cm−1 as a weak band in IR and Raman spectrum.

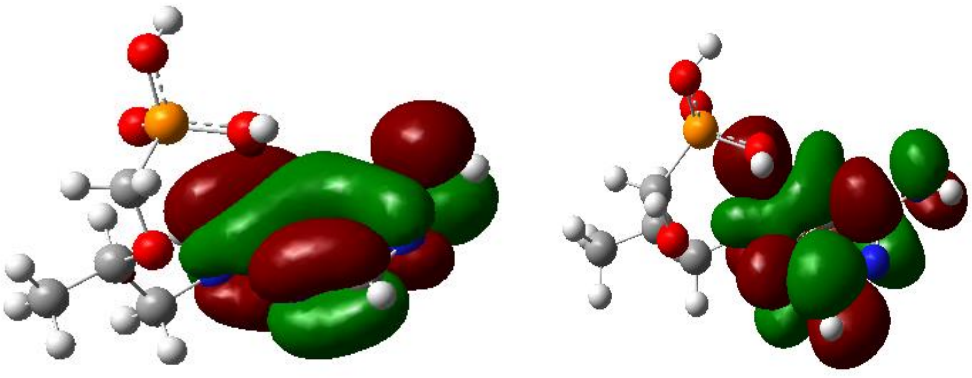
The ring C–C stretching vibration occurs in the region 1625–1430 cm−1. For six membered aromatic rings, there are two or three bands in this region due to skeletal vibration; the strongest usually being about 1500 cm−1. In the case where the ring is conjugated further, a band is about 1580 cm−1. The C–C stretching of ring is observed at 1513 cm−1 in IR as a medium band. The same band is observed in IR at 1478 cm−1 as a weak band and in Raman at 1473 cm−1 as the strong band. The aromatic ring deformation vibrations appear in the region of 625–605 cm−1 for the mono substituted ring and 475–425 cm−1 for the tri substituted ring. The series of weak band observed in IR at 666, 595, 539, 449 cm−1 and medium to strong band in Raman at 666, 546, 445 cm−1 are assigned to the C–C ring deformation.

Low-wave number hydrogen-bond vibrations

The attractive interaction between the hydrogen donor group and the acceptor moiety leads to the occurrence of new vibrational degrees of freedom, the so-called hydrogen bond modes. Such modes are connected with elongations changing the A···B distance and/or the relative orientation of the hydrogen-bonded groups. Thus, they provide direct insight into the structure of the hydrogen bonds and into the processes of bond formation and cleavage. As such modes are characterized by a high reduced mass of the oscillator and a small force constant determined by the comparably weak attractive interaction along the hydrogen bond, hydrogen bond modes occur at low wave numbers in the range between 50 and 300 cm−1. An interesting feature of these vibrations is the occurrence of an intense Raman band in the low-wave number region 164 cm−1 corresponding to the H···O stretching. This shows that there is a possibility of N–H···O hydrogen bonding present in the compound-8.

HOMO–LUMO energy gap

In general, there are several ways to calculate the excitation energies. The first, and the simplest one, involves the difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of a neutral system.



HOMO LUMO

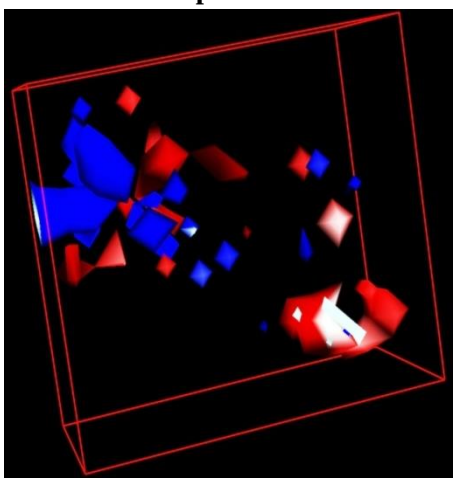
Figure.7: HOMO LUMO Plot of compound-8

This form corresponds to the frozen orbital approximation, as the ground state properties are used to calculate excitation values. The HOMO–LUMO energy gap for compound-8 has been calculated DFT level.

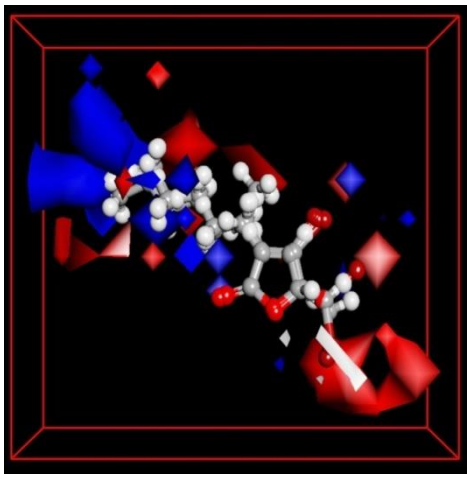
HOMO Energy = -5.2375 eV
LUMO Energy = -3.3547 eV
HOMO – LUMO energy gap = 1.88 eV

The Eigen values of LUMO–HOMO energy gap reflect the chemical activity of the molecule. The HOMO-LUMO plot is shown in Fig. 7. The decrease in the HOMO and LUMO energy gap explains the eventual charge transfer interaction taking place within the molecule, due to the strong electron-accepting ability of the electron-acceptor group. It is worth noting that HOMOs have an overall π bonding character along with a considerable non-bonding character and LUMOs have an anti-bonding π* character. The strong charge transfer interaction is responsible for the bioactivity of the molecule.

Molecular Electrostatic potentials



Electrostatic map



Electrostatic map with compound-8

The electrostatic contour map of the compound -8 is shown in figure.8 The blue contours indicate electro positive charges correlating with activity and the Hbond donor regions and the red contour indicates the relationship between negative charge and activity and also the Hbond acceptor regions. The increase in positive charge and H-bond donor regions are favored in blue region while increase in negative charge and H-bond acceptor regions are favored in red region. Blue-colored regions show areas where electropositive charged groups enhance inhibitory activity by the presence of H-bond donors, while red regions represent where electronegative charged groups improve the activity with the presence of H-bond acceptors.

Conclusions

HIV drug resistance is one of the major hurdles for achieving and maintaining of successful viral suppression. Most data on the genetic mechanisms of HIV-1 drug resistance are from studies of subtype B viruses, the predominant subtype in the North American and Europe. Several of studies suggest that the currently available PR (Protease) and RT (Reverse Transcriptase) inhibitors are as active against non-B viruses as they are against subtype B viruses. Thus to understand ligand-receptor interactions the protein receptor of the HIV protease was selected from RCSB Protein Data Bank (RCSB-PDB) and the set of 42 potential anti-HIV-1 Protease inhibitors reported from the studies of Islam were considered for the docking studies. Among several HIV protease inhibitors PDB ID: 1T3R was selected based on the receptor size, resolution and deposited date. From the docking studies it is observed that all the compounds considered in this study exhibited significant binding score with the active site of HIV-1 Protease. It is noteworthy to mention that all the compounds exhibited the binding interactions with the amino acids such as Asp25, Thr26, and Asp29 and water molecule at Hoh 1023.

The highest docking score of -30.6528 kJ/mol was exhibited by compounds-24. This interaction is favored by amino acids Gly27, Asp29, Asp25, Asp30, Thr26 and water molecule Hoh1203 for the

Hbond interactions and the non-bonded interactions are supported by Asp25, Gly27, gly49, ala28, Leu23, Ile50, Pro81 and Ile84. Thus it implies that the conserved amino acid Aspartic acid (Asp 25 and 29), Threonine (Thr26) and Glycine (Gly26) in the catalytic site of HIV-1Protease receptor are crucial in binding of anti-HIV-1 Protease inhibitors. Also it envisageds that the NH group and =O present in the compounds favors the hbond interactions. Hence these findings throws light for the design of novel anti-HIV-1 protease inhibitors and also envisages that the amino acids Aspartic acid (Asp 25 and 29), Threonine (Thr26) and Glycine (Gly26) should be considered during its design for implying its action as a best anti-HIV-1 Protease compound against the potential target of HIV-1 Protease.

Further, a complete vibrational analysis of compound-24 was performed using DFT calculations at B3LYP/6-31G* and B3LYP/6-31++G** levels in order to elucidate the structural activity relationship. FT-IR and FT-Raman spectra have been recorded and the detailed vibrational assignments were presented. The molecular geometry, vibrational frequencies, infrared intensities and Raman intensities of compound-24 in the ground state have been calculated by using density functional theory. The hydrogen bonds network has been thoroughly analyzed using NBO analysis. The molecular hydrogen bonding and charge transfer interaction present in the molecule gives the important of compound-24 that brings about most interesting Pharmaceutical activity. The natural bond orbital analysis confirms the hyper conjugation interaction and the possibility of N–H···O and C–H···O interaction. The lowering of carbonyl mode and the low wave number hydrogen bonds shows the occurrence of N–H···O hydrogen bonds. The assignment of most of the normal modes agrees well with the theoretical wave numbers.

The HOMO–LUMO energy gap has a substantial influence on the calculated value that is found to be 2.90 eV. The lowering of HOMO–LUMO energy gap, a quantum–chemical descriptor, explains the charge transfer interactions taking place within the molecule through strong N–H···O and C–H···O hydrogen bonding which is prove that the compound-24 is bioactive and pharmaceutical in nature.

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