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MOLECULAR DOCKING STUDIES OF THIAZOLE SCHIFF'S BASES AS HIV1-PROTEASE INHIBITORS

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ABSTRACT

Structure-based drug design by use of structural biology remains one of the most logical and aesthetically pleasing approaches in drug discover paradigms. Managing AIDS, is the most challenging problems in the 21st century. Promising new agents may be developed by following targets. The concept of structure-based drug discovery combines information from several fields, X-ray crystallography and/or NMR, molecular modeling, synthetic organic chemistry, qualitative structure-activity relationships (QSAR), and biological evaluation. Thiazole Schiff bases are exhibit a wide range of biological activity such as antimicrobial, antituberculosis, anticancer & antiviral activities. HIV 1 Protease inhibitor effects were predicted by docking with use of cerius 2 software. From the Docking studies for HIV1 protease shows, out of 5 ligands compound 2 & 5 very well packed in to the active site of the protein like the standard Teliunavir. On the basis of Structure-based drug design, new lead structures were discovered for Rational drug designing for HIV–1 protease inhibitor and it will help full for further modification (molecular modeling) to obtained clinically useful novel entities for anti HIV drugs.

Key words: Thiazole Schiff bases, HIV1-Protease, Docking, Drug designing.

INTRODUCTION

HIV-1 Protease

HIV-1 protease (HIV PR) is an aspartic protease that is essential for the life-cycle of HIV, the retrovirus that causes AIDS. HIV PR cleaves newly synthesized polyproteins at the appropriate places to create the mature protein components of an infectious HIV virion. Without effective HIV PR, HIV virions remain uninfectious. Thus, mutation of HIV PR's active site or inhibition of its activity disrupts HIV's ability to replicate and infect additional cells, making HIV PR inhibition the subject of much pharmaceutical research.

Structure and Function

HIV PR's protein structure has been investigated using X-ray crystallography. It exists as a homodimer, with each subunit made up of 99 amino acids. The active site lies between the identical sub units and has the characteristic Asp-Thr-Gly (Asp25, Thr26 and Gly27) sequence common to aspartic proteases. The two Asp25 residues (one from each chain) act as the catalytic residues. According to the

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mechanism for HIV PR protein cleavage proposed by Jaskolski et al., water acts as a nucleophile, which acts in simultaneous conjunction with a well-placed aspartic acid to hydrolyze the scissile peptide bond. Additionally, HIV PR has two molecular "flaps" which move a distance of upto 7 Å when the enzyme becomes associated with a substrate.

HIV-1 Protease as a Drug Target

With its integral role in HIV replication, HIV PR has been a prime target for drug therapy. HIV PR inhibitors work by specifically binding to the active site by mimicking the tetrahedral intermediate of its substrate and essentially becoming "stuck," disabling the enzyme. However, due to the high mutation rates of retroviruses, and considering that a single amino acid change within HIV PR can render it invisible to an inhibitor, the active site of this enzyme can change rapidly when under the selective pressure of replication-inhibiting drugs. One approach to minimizing the development of drug-resistance in HIV is to administer a drug cocktail composed of drugs which inhibit several key aspects of HIV's replication cycle simultaneously, rather than one drug at a time. Other drug therapy targets include reverse transcriptase, virus attachment, membrane fusion, cDNA integration and virion assembly.

Protease Inhibitors

All currently licenced protease inhibitors for the treatment of HIV infection that is indinavir ritonavir, saquiomavir, neflinvir and amprenavir, share the same structural determinant, a hydroxyl ethylene group replacing the normal peptide bond. The hydroxyl ethylene group has a dual purpose. In addition to making the molecule nonscissile, it allows the molecule to bind to the catalytic site by hydrogen bonding, which can destabilize the enzyme dimmer. Other small size peptide inhibitors are reported to contain hydrophilic carboxyl groups as the hydrogen bonding destabilizer. Reports have appeared for peptidomimetic inhibitors with the sessile segment of the peptide substrate replaced with a 15-membered macrocylic peptide with stable substrate with suitable confirmation. Certain monoclonal antibodies were also studied as noncompetitive inhibitors for the enzyme acting through suppressing the dimerization process. In general, protease inhibitors are designed with the aim of driving the molecule to the active site, where in acts either as a competitive inhibitor with stronger hydrophobic end or hydrogen bonding or as a destabilizer to the enzyme dimeric structure through similar forces of interaction.

Some newer inhibitors with non-peptide structure have been developed, such as lopinavir the cyclic urea mozinavir, atazanavir, tipranavir and the C2-symmetric protease inhibitor L-mannaric acid depicts the structures of these newer protease inhibitors. Recently, other potential sites were targeted for HIV protease inactivation by peptides and peptidomimetics based on the terminal sequence of the enzyme. These terminal sequences exist at the enzyme surface and are believed to be less prone to mutations. Cupric ion was described to bind to such surface sequences rich in histidine and cysteine amino acid residues, leading to enzyme inhibition. Computer aided drug design and molecular modeling are used to analyze binding of the inhibitors to the enzyme and to debelop new agents based on a rationale drug design approach.

Theory and method

The concept of structure-based drug discovery combines information from several fields, X-ray crystallography and/or NMR, molecular modeling, synthetic organic chemistry, qualitative structure-activity relationships (QSAR) and biological evaluation.

Molecular modeling

Thiazole Schiff bases exhibit a wide range of biological activity such as antimicrobial, antituberculosis, anticancer & antiviral activities (PASS prediction of activity spectra for substances online software).

Table 1: Molecular Docking Results

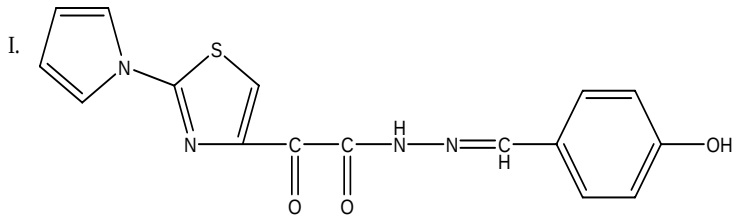
Structure name	Mol._Number	Conf._Number	PLP1_Dock
Comp. 2	2	1	109.65455
Comp. 2	2	2	98.8815
Comp. 2	2	3	98.57836
Comp. 8	8	1	116.07092
Comp. 8	8	2	114.93762
Comp. 8	8	3	104.79588
Teliunavir	10	1	124.88409
Teliunavir	10	2	120.67213
Teliunavir	10	3	118.59020

Methodology

* Selection of X-ray crystal structure of the target proteins (HIV1 protease 2 BPY-PDB) & minimizing the energy of the entire model.
* Identifying the active site of the protein (region around 5 Armstrong).
* Ligand building & energy minimization.
* Docking Ligands into the active site of the protein (ligand fit module by Cerius2).

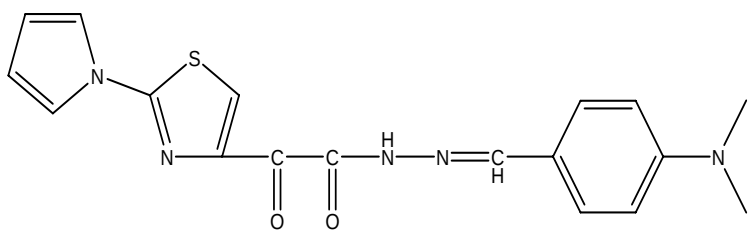
List of Compounds

I.



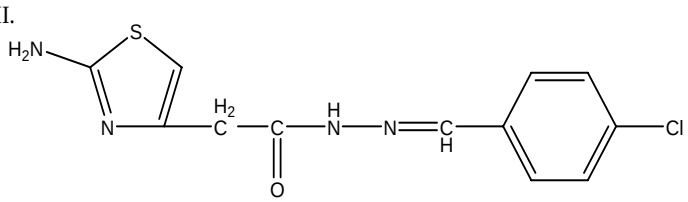
2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-hydroxybenzylidene)-2-oxoacetohydrazide

II



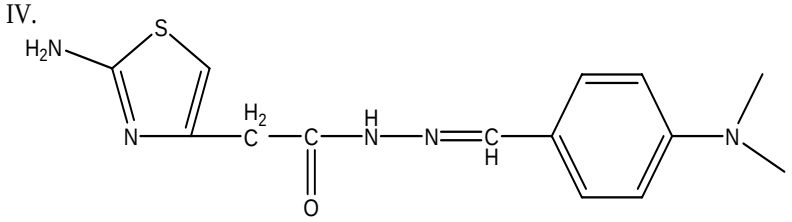
2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-(dimethylamino)benzylidene)-2-oxoacetohydrazide

III.



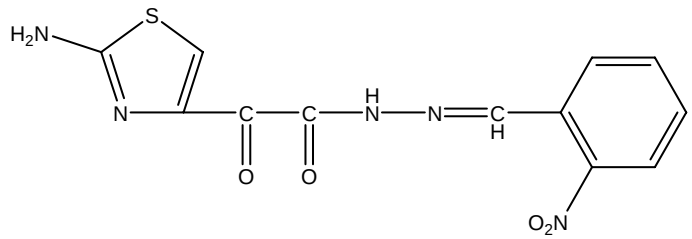
N'-(4-chlorobenzylidene)-2-(2-aminothiazol-4-yl)acetohydrazide

IV.



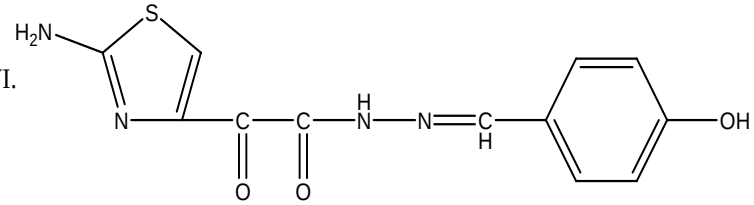
N'-(4-(dimethylamino)benzylidene)-2-(2-aminothiazol-4-yl)acetohydrazide

V.



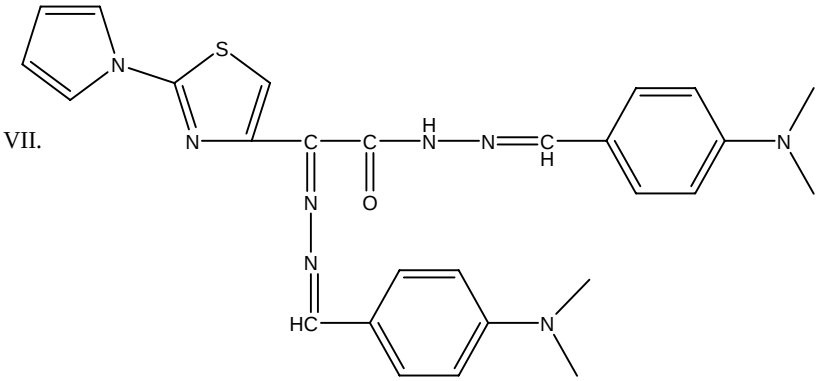
N'-(2-nitrobenzylidene)-2-(2-aminothiazol-4-yl)-2-oxoacetohydrazide

VI.



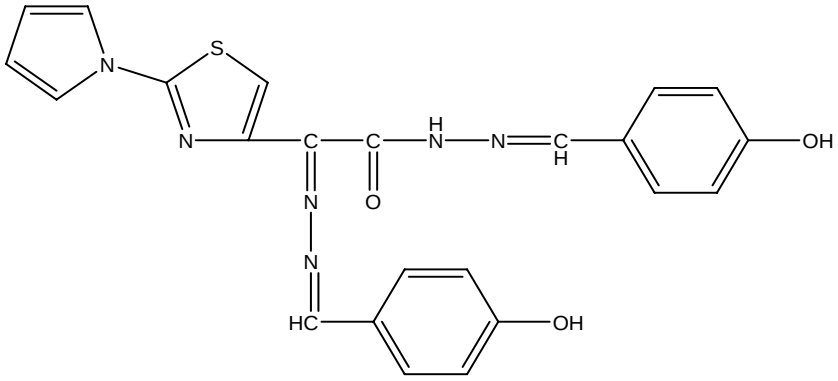
N'-(4-hydroxybenzylidene)-2-(2-aminothiazol-4-yl)-2-oxoacetohydrazide

VII.



2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-(dimethylamino)benzylidene)-2-(2-(4-(dimethylamino)benzylidene)hydrazono)acetohydrazide

VIII

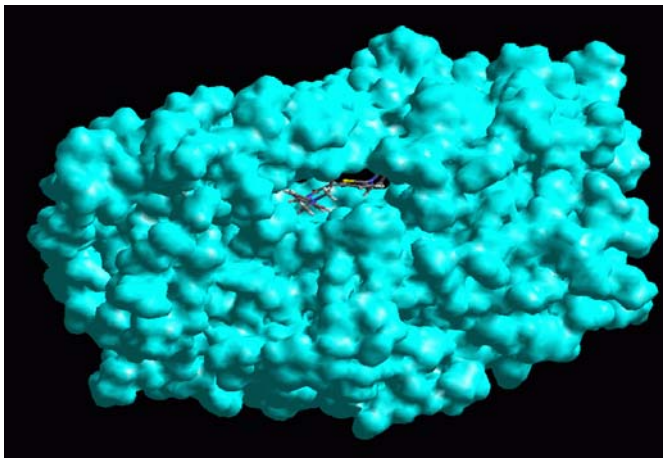


2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-hydroxybenzylidene)-2-(2-(4-hydroxybenzylidene)hydrazono)acetohydrazide

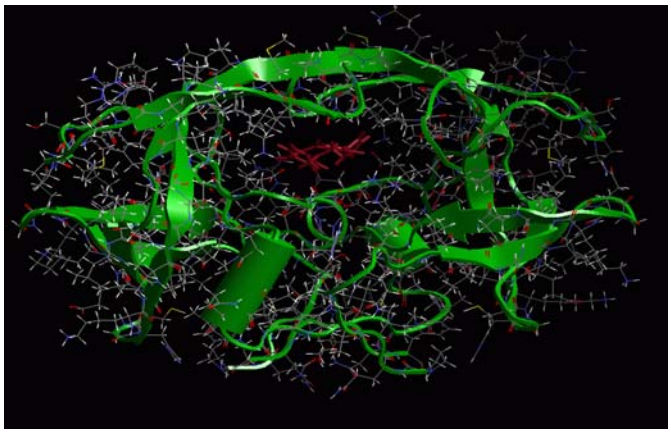
RESULTS AND DISCUSSION

From the Docking studies for HIV1 protease shows (Table 1), out of 8 ligands compounds; 2 & 8 very well packed into the active site of the protein like the standard Teliunavir.

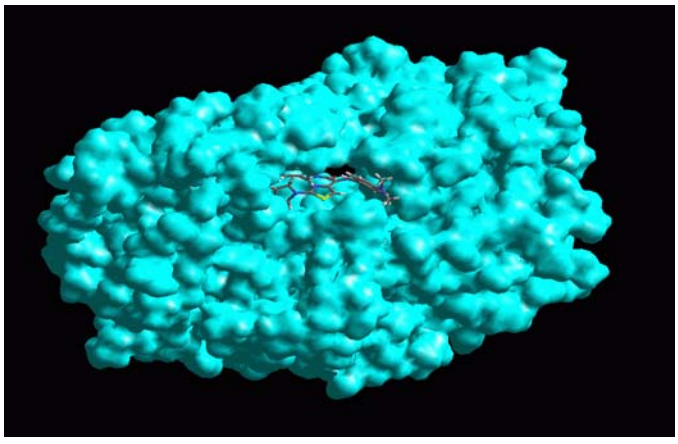
1. **Protein structure of HIV1 with a standard ligand inside the active site. Green colored is also the protein it's a different representation.**
2. **Docked Compound 2. Solid representation**



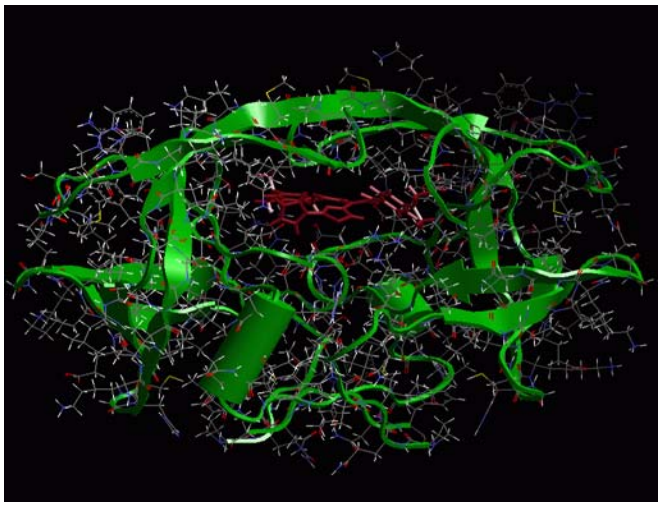
3. Docked Compound 2. Sheet representation



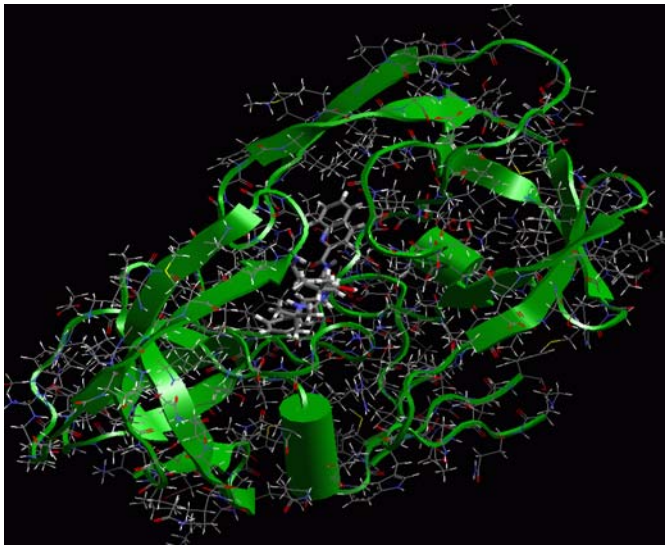
4. Docked Compound 8. Solid representation



4. Docked Compound 8. Sheet representation



4. Docked standard. Sheet representation



CONCLUSION

On the basis of Structure-based drug design, new lead structures were discovered for Rational drug designing for HIV–I protease inhibitor and it will help full for further modification (molecular modeling) to obtained clinically useful novel entities for anti HIV drugs.

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REFERENCES

1. Paola Vicini, Athina Geronikaki, Matteo Incerti and Paola La Colla, Bioorganic and Medicinal Chemistry, **11**, 4785-4789 (2003).

2. A. Brik, C. H. Wong, HIV-1 Protease: Mechanism and Drug Discovery, Org. Biomol. Chem., **1(1)**, 5–14, January (2003).

3. H. G. Kräusslich, R. H. Ingraham, M. T. Skoog and E. Wimmer, P. V. Pallai and C. A. Carter, Activity of Purified Biosynthetic Proteinase of Human Immunodeficiency Virus on Natural Substrates and Synthetic Peptides, Proc. Natl. Acad. Sci., U.S.A., **86(3)**, 807–11, February (1989).

4. N. E. Kohl, E. A. Emini and W. A. Schleif, et al., Active Human Immuno Deficiency Virus Protease is Required for Viral Infectivity, Proc. Natl. Acad. Sci., U.S.A., **85(13)**, 4686–90 July (1988).

5. S. Seelmeier, H. Schmidt, V. Turk and K. Von Der Helm, Human Immuno Deficiency Virus has an Aspartic-Type Protease that can be Inhibited by Pepstatin A, Proc. Natl. Acad. Sci., U.S.A., **85(18)**, 6612–6, September (1988).

6. F. McPhee, A. C. Good, I. D. Kuntz and C. S. Craik, Engineering Human Immuno Deficiency Virus 1 Protease Heterodimers as Macromolecular Inhibitors of Viral Maturation, Proc. Natl. Acad. Sci., U.S.A., **93(21)**, 11477–81, October (1996).

7. A. L. Perryman, J. H. Lin and J. A. McCammon, HIV-1 Protease Molecular Dynamics of a Wild-Type and of the V82F/I84V Mutant, Possible Contributions to Drug Resistance and a Potential New Target Site for Drugs, Protein Sci., **13(4)**, 1108–23, April (2004).

8. M. Jaskólski, A. G. Tomasselli, T. K. Sawyer and D. G. Staples, R. L. Heinrikson, J. Schneider and S. B. Kent, A. Wlodawer, Structure at 2.5-A Resolution of Chemically Synthesized Human Immuno Deficiency Virus Type 1 Protease Complexed with a Hydroxyethylene-Based Inhibitor, Biochemistry, **30(6)**, 1600–9, February (1991).

9. M. Miller, J. Schneider, B. K. Sathyanarayana and M. V. Toth, G. R. Marshall, L. Clawson and L. Selk, S. B. Kent and A. Wlodawer, Structure of Complex of Synthetic HIV-1 Protease with a Substrate-Based Inhibitor at 2.3 A Resolution, Science (Journal), **246(4934)**, 1149–52, December (1989).

10. T. Watkins, W. Resch, D. Irlbeck and R. Swanstrom, Selection of High-Level Resistance to Human Immuno Deficiency Virus Type 1 Protease Inhibitors, Antimicrob. Agents Chemother., **47(2)**, 759-69, February (2003).

11. J. P. Moore, M. Stevenson, New Targets for Inhibitors of HIV-1 Replication, Nat. Rev. Mol. Cell Biol., **1(1)**, 40–9, October (2000).

12. E. De Clercq, The Design of Drugs for HIV and HCV, Nat. Rev. Drug Discov., **6(12)**, 1001-18, December (2007).