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Computational Approach Towards Designing Potential HIV Inhibitors

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Abstract

It is imperative to continue efforts to identify novel effective therapies that can assist in containing the spread of HIV. Recently acquired knowledge about the HIV entry process points to new strategies to block viral entry. For most HIV strains, the successful infection of their target cells is mainly dependent on the presence of the CD4 surface molecule, which serves as the primary virus receptor. The attachment of the viral envelope to this cellular CD4 receptor can be considered as an ideal target with multiple windows of opportunity for therapeutic intervention. Therefore, drugs that interfere with the CD4 receptor, and thus inhibit viral entry, may be promising agents for the treatment of AIDS. The CD4-targeted HIV entry inhibitors Cyclotriazadisulfonamides represent a novel class of small molecule antiviral agents with a unique mode of action. The lead compound, CADA, specifically interacts with the cellularCD4receptor and is active against a wide variety of HIV strains. CADA may also act synergistically in combination with other anti-HIV drugs.

This work includes study of interaction between CADA and CD4, mode of inhibition of CD4, designing a better drug against HIV also with antibacterial activity adding value to the entry inhibitor.

Keywords: HIV entry inhibitor; Drug designing; Autodock; Chemoffice; CADA

Introduction

In medicine, biotechnology and pharmacology, drug discovery is the process by which drugs are discovered and/or designed. The process of drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy based on their biological targets. The structure of the drug molecule can be modeled using computational tools.

Acquired immunodeficiency syndrome (AIDS) is a caused by the human immunodeficiency virus (HIV). HIV belongs to a subset of retroviruses called lentiviruses (or slow viruses) meaning that there is an interval — sometimes years — between the initial infection and the onset of symptoms. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV. Although treatments for AIDS and HIV exist to decelerate the virus' progression, there is currently no known cure. The different anti-HIV drugs available today are of three main types: NRTIs, NNRTIs and PIs. However, HIV Entry Inhibitors are being a major attention.

Considering these facts, the project was dedicated to designing HIV entry blocker by making the CD4 molecule unfavorable for interaction, moreover addition of antibacterial and antifungal properties to the drug designed. This work focuses on studying the involvement and role of CD4 receptor in HIV infection, its sequence and structural analysis, its binding site, site of interaction, inhibitors of CD4, their mode of action, and designing the drug molecule, etc.

Materials and Methods

Sequence analysis of CD4

The sequence of CD4 protein was obtained from NCBI (National Center for Biotechnology Information) which was submitted to Expasy Sequence Analysis Tools for sequence analysis for further detailed information about CD4 protein sequence.

The following data was obtained from the database

Number of amino acids: 458
Molecular weight: 51110.5
Theoretical pI: 9.60
Total number of negatively charged residues (Asp + Glu): 39
Total number of positively charged residues (Arg + Lys): 62
Formula: $C_{2282}H_{3717}N_{633}O_{657}S_{18}$
Total number of atoms: 7307
Estimated half-life: The N-terminal of the sequence considered is M (Met).
The estimated half-life is: 30 hours (mammalian reticulocytes, in vitro).
>20 hours (yeast, in vivo).
>10 hours (Escherichia coli, in vivo).
Instability index:
The instability index (II) is computed to be 41.78
This classifies the protein as unstable.
Aliphatic index: 94.67
Grand average of hydropathicity (GRAVY): -0.257

CADA Structure

ChemOffice 6.0

ChemOffice is a suite consisting various tools like ChemDraw Ultra, Chem3D Ultra, ChemFinder Ultra and few other tools that can be used for designing a molecule.

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ChemDraw ultra 6.0

ChemDraw is a tool to enable professional scientists, science students, and scientific authors to communicate chemical structures. It is designed to work according to conventions we found most intuitive for such users. Our goal has been to make ChemDraw as easy to use as possible while providing superior drawing quality.

Chem3D Ultra 6.0

Chem3D enables scientists to model their chemicals. Chem3D provides computational tools based on molecular mechanics to optimize models, conformational searching, molecular dynamics and calculating single point energies for molecules.

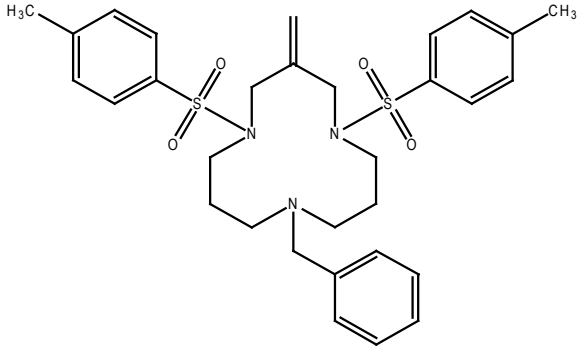
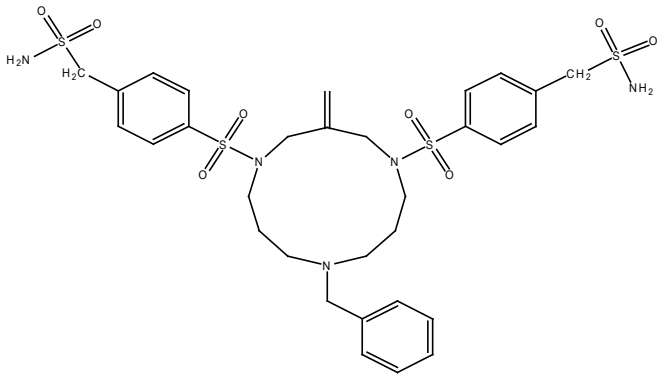


Figure 1: (a) Molecular structure of the lead compound Cyclotriazadisulfonamides (CADA = 9-benzyl-3-methylene-1, 5-di-p-toluenesulfonyl-1, 5, 9-triazacyclododecane).



{4-[9-Benzyl-3-methylene-5-(4-sulfamoylmethyl-benzenesulfonyl)-1,5,9triaza-cyclododecane-1-sulfonyl]
-phenyl}-methanesulfonamide

Figure 2: Structure of the drug designed and its nomenclature with two extra sulfonamide groups added at the two CH3 ends of CADA.

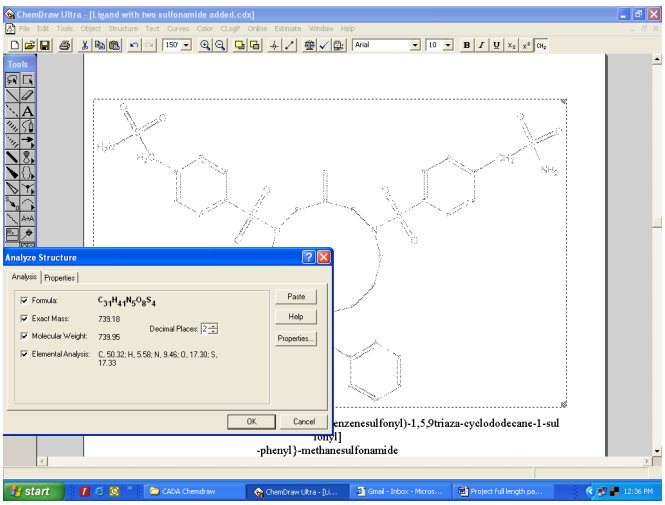


Figure 3: ChemDraw Ultra 6.0 sheet showing modified drug designed with its different properties computed using different options from toolbox.

The various physical properties of the drug/ligand were computed using the compute properties tools in Chem3D Ultra viz. Boiling point, Molar refractivity, LogP, etc which actually decide the ADME (Absorption, Distribution, Metabolism and Excretion) of the drug inside body. The different properties are discussed in results part of the report.

Modification of CADA using ChemOffice Ultra 6.0

CADA with two sulfonamide groups added

Autodock 3.0

AutoDock is a suite of automated docking tools designed to predict how small molecules bind to a receptor of known 3D structure. AutoDock consists of two main programs: AutoDock performs the docking of the ligand to a set of grids describing the target protein; AutoGrid pre-calculates these grids.

Properties of the drug

- Molecular formula = C31H41N5O8S4

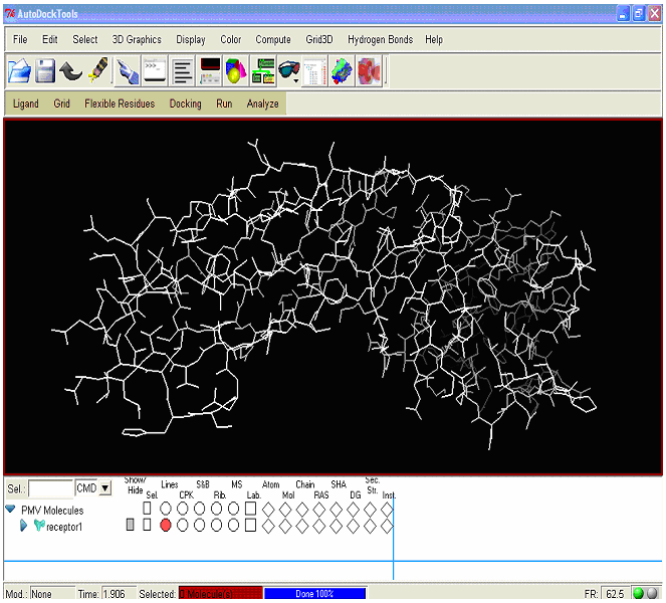


Figure 4: AutoDock page with receptor loaded.

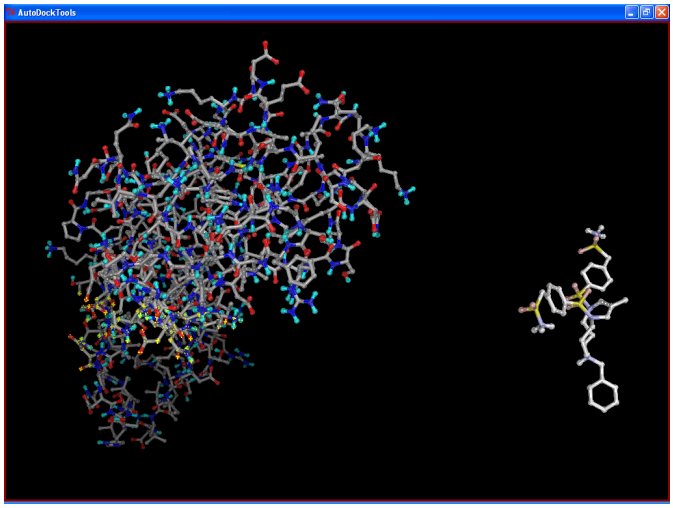


Figure 5: The receptor and the ligand read in AutoDock.

- Molecular weight = 739.965
- Boiling point = 975.263
- LogP value = 1.334
- Molar refractivity = 189.424 cm.cm.cm/mol
- Torsion energy = -6.032 kcal/mol
- Total energy = 27.61kcal/mol

The lower the logP value, more hydrophilic the drug is and vice-a-versa

Molar Refractivity is the measure of the probable volume occupied by a compound inside a phase or two and is dependent on temperature, pressure and index of refraction of the phase or the medium.

Lower the total energy of a molecule higher its stability

Docking results

No. of Hydrogen Bonds obtained – 2 - Binding energy - -3.34
Docking energy - -2.06 - Intermolecular energy - -6.45
Torsional energy – 3.11 - Internal energy – 4.4

Hydrogen bonds have a major role in molecular interactions. The two hydrogen bonds formed share Lysine at 1st and Serine at 79th position of the CD4 receptor with sulfonamide group and amino group attached to other sulfonamide group in the ligand molecule.

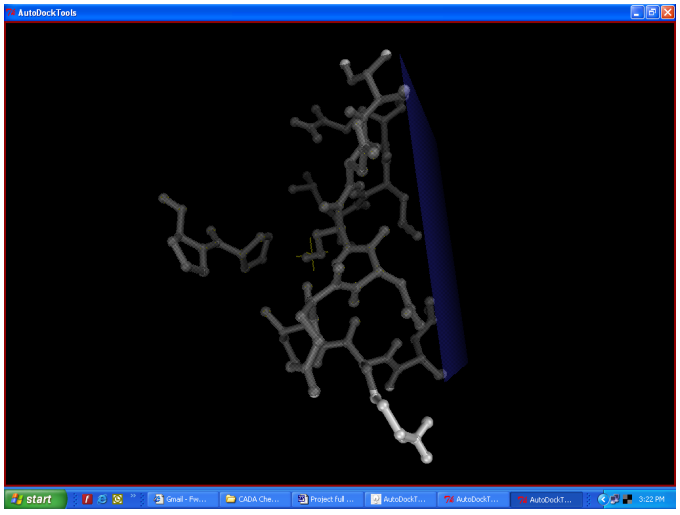


Figure 6: grid point setting.

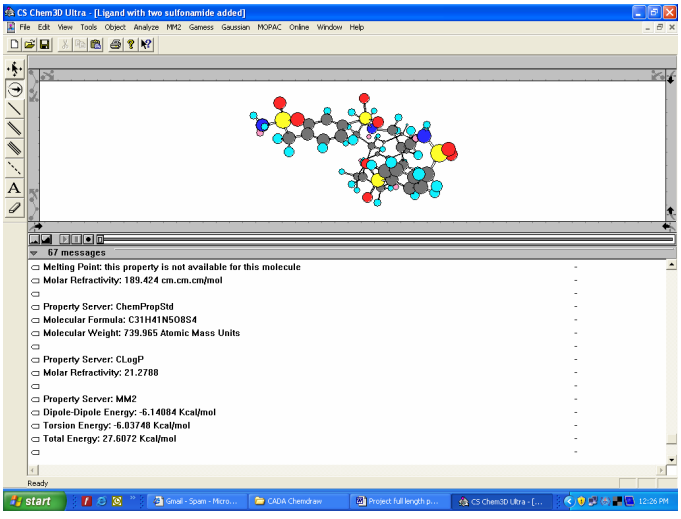


Figure 7: Chem3D showing properties of the ligand computed.

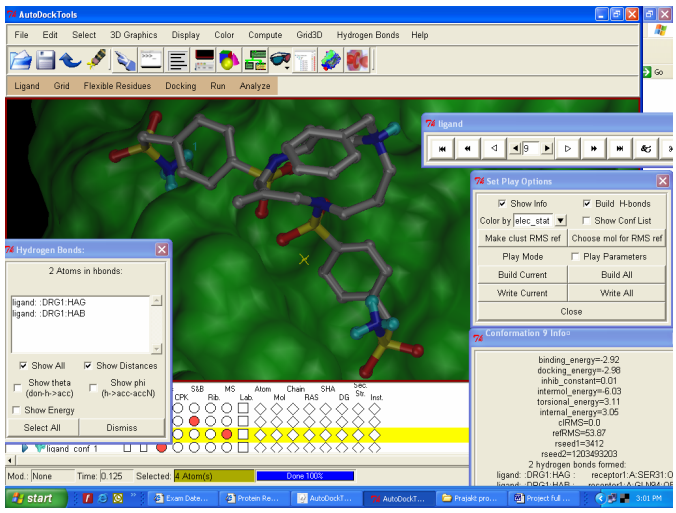


Figure 8: AutoDock docking analysis, windows with hydrogen bonds formed and the energies.

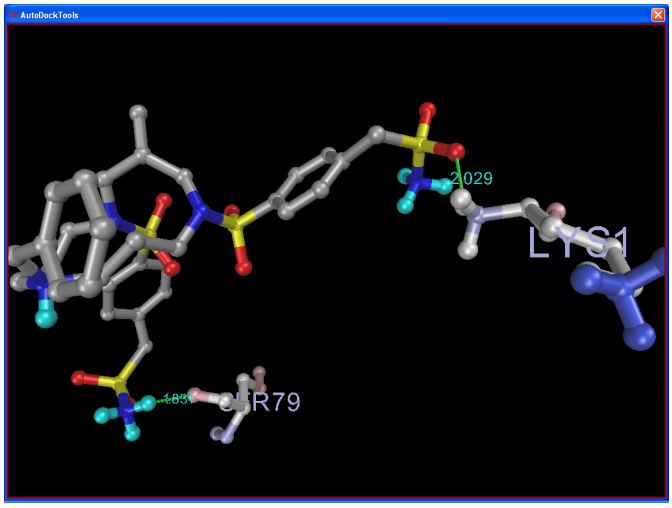


Figure 9: Hydrogen bonds.

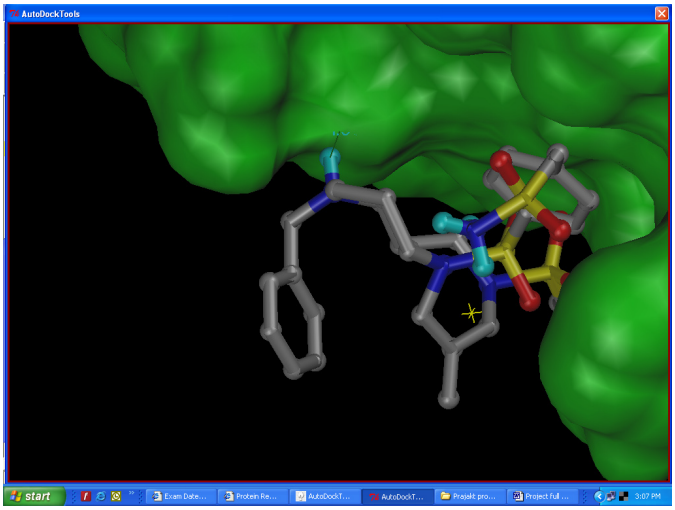


Figure 10: ligand lying in the cavity of CD4 receptor (close view).

The sulfur atom of sulfonamide group in the ligand has two electronegative oxygen atoms, one of which gets attracted towards the hydrogen atom of amino group at the side chain of the basic amino acid Lysine-1. The oxygen and nitrogen, share hydrogen in them forming a hydrogen bond. Bond length of 1.831A°.

The other hydrogen bond is formed between Serine residue at 79th position with amino group from the other sulfonamide group of the ligand Bond length - 2.029A^{o}.

Conclusion

The outcome drug named according to IUPAC naming system as {4-[9-Benzyl-3- methylene -5- (4 - sulfamoylmethyl - benzenesulfonyl) -1,5,9 triaza-cyclododecane-1-sulfonyl]-phenyl}-methanesulfonamide, contains two potent sulfonamide groups involved in strong interaction of the ligand with the CD4 receptor. The sulfonamide groups have very good antibacterial, antifungal activity in addition to the proven antiviral activity of the CADA molecule.

Thus, this drug is a value added product to the CADA class of compounds and can prove to be an efficient one against HIV and other major infections.

Reference

1. Chan DC, Kim PS (1998) HIV entry and its inhibition. Cell 93: 681-4. » CrossRef » PubMed » Google Scholar
2. Chesebro B, Buller R, Portis J, Wehrly K (1990) Failure of human immunodeficiency virus entry and infection in CD4-positive human brain and skin cells. J Virol 64: 215-21. » CrossRef » PubMed » Google Scholar
3. Kabat D, Kozak SL, Wehrly K, Chesebro B (1994) Differences in CD4 dependence for infectivity of laboratory-adapted and primary patient isolates of human immunodeficiency virus type 1. J Virol 68: 2570-7. » CrossRef » PubMed » Google Scholar
4. Kozak SL, Platt EJ, Madani N, Ferro FE Jr, Peden K (1997) CD4, CXCR-4, and CCR-5 dependencies for infections by primary patient and laboratory-adapted isolates of human immunodeficiency virus type 1. J Virol 71: 873-82. » CrossRef » PubMed » Google Scholar
5. Kwong PD, Wyatt R, Sattentau QJ, Sodroski J, Hendrickson WA (2000) Oligomeric modeling and electrostatic analysis of the gp120 envelope glycoprotein of human immunodeficiency virus. J Virol 74: 1961-72. » CrossRef » PubMed » Google Scholar
6. Layne SP, Merges MJ, Dembo M, Spouge JL, Nara PL (1990) HIV requires multiple gp120 molecules for CD4-mediated infection. Nature 346: 277-9. » CrossRef » PubMed » Google Scholar
7. Platt EJ, Madani N, Kozak SL, Kabat D (1997) Infectious properties of human immunodeficiency virus type 1 mutants with distinct affinities for the CD4 receptor. J Virol 71: 883-90. » CrossRef » PubMed » Google Scholar
8. Platt EJ, Wehrly K, Kuhmann SE, Chesebro B, Kabat D (1998) Effects of CCR5 and CD4 cell surface concentrations on infections by macrophagetropic isolates of human immunodeficiency virus type 1. J Virol 72: 2855-64. » CrossRef » PubMed » Google Scholar
9. Vermeire K, Bell TW, Choi HJ, Jin Q, Samala MF, et al. (2003) The anti-HIV potency of cyclotriazadisulfonamide analogs is directly correlated with their ability to down-modulate the CD4 receptor. Mol Pharmacol 63: 203-10. » CrossRef » PubMed » Google Scholar
10. Vermeire K, Princen K, Hatse S, De Clercq E, Dey K, et al. (2004) CADA, a novel CD4-targeted HIV inhibitor, is synergistic with various anti-HIV drugs in vitro. AIDS 18: 2115-25. » CrossRef » PubMed » Google Scholar
11. Vermeire K, Schols D (2003) Specific CD4 down-modulating compounds with potent anti-HIV activity. J Leukoc Biol 74: 667-75. » CrossRef » PubMed » Google Scholar
12. Vermeire K, Van Laethem K, Vandamme AM (2005) Resistance profile of human immunodeficiency virus to CADA, a novel HIV inhibitor that targets the cellular CD4 receptor. In: Abstracts of the Eighteenth International Conference on Antiviral Research, Barcelona, Spain. Antiviral Res 65: A43. » CrossRef » PubMed » Google Scholar
13. Vermeire K, Zhang Y, Princen K, Hatse S, Samala MF, et al. (2002) CADA inhibits human immunodeficiency virus and human herpesvirus-7 replication by downmodulation of the cellular CD4 receptor. Virology 302: 342-53. » CrossRef » PubMed » Google Scholar