Anti-HIV Drug Design

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The Human Immunodeficiency Virus

- First clinically observed in USA in 1981
- Causes AIDS, a condition in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive
- Most commonly spread via sexual contact
- Also transferred from infected mother to baby during pregnancy, by using infected needles & through blood transfusions

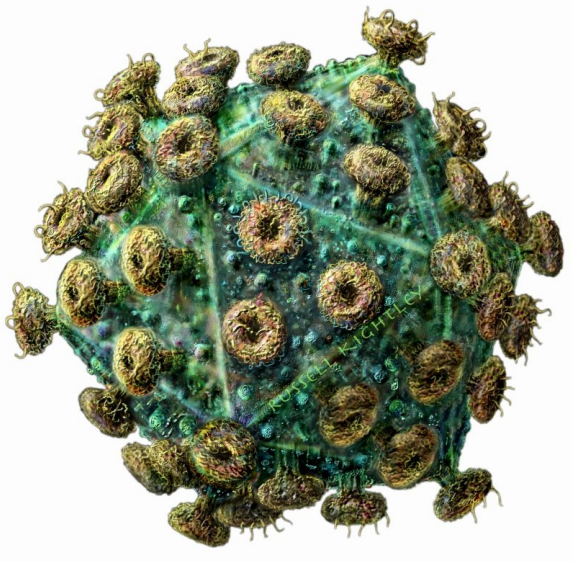


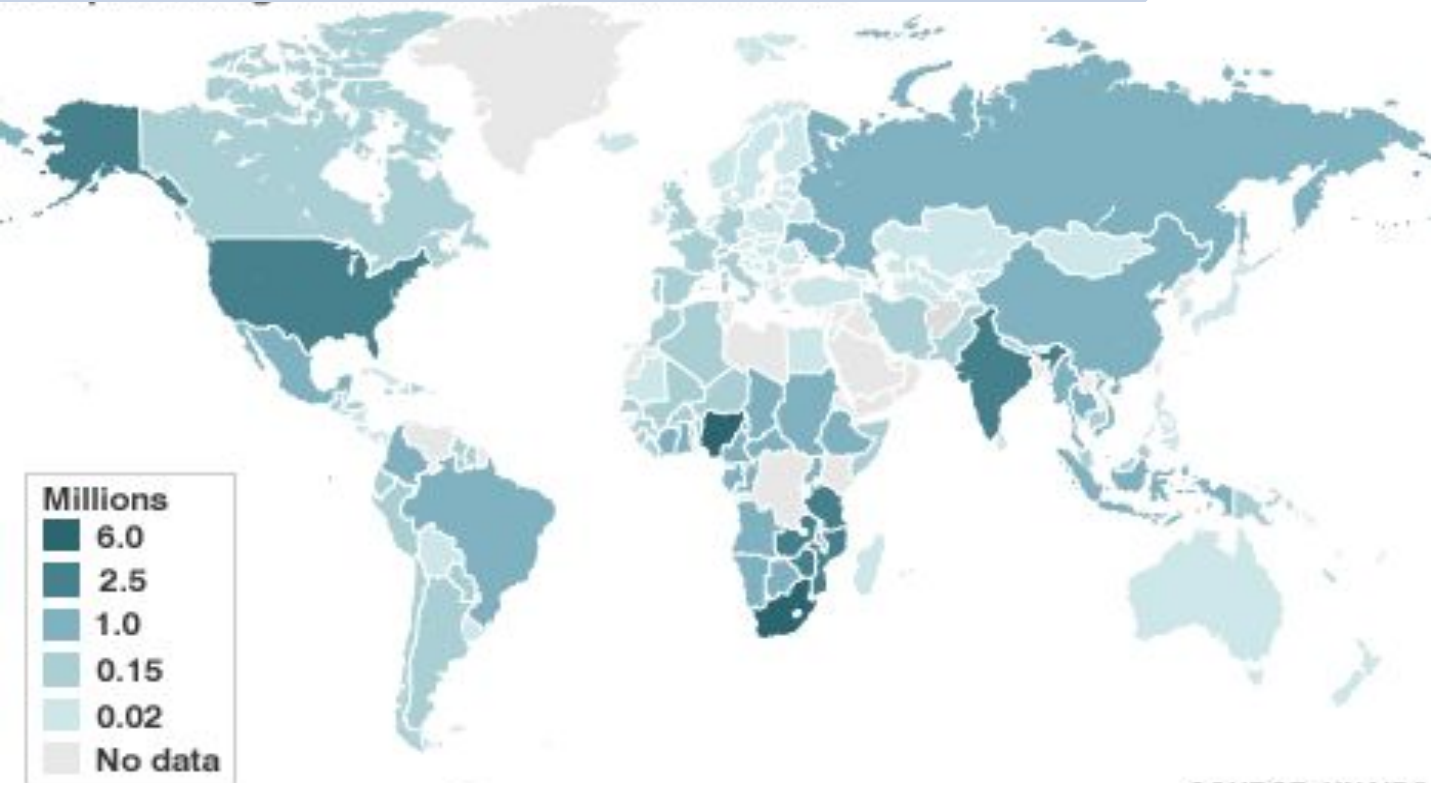
Fig: *The HIV Virus*

HIV/AIDS Statistics

- Approximately 36.7 million people living with HIV/AIDS at the end of 2016. Of these, around 2.1 million were children(<15 years)
- Around 5000 new cases reported everyday
- Only 60% of people infected know their statuses; remaining 40% don't even have access to HIV testing services
- 1 million people died from AIDS-related illnesses in 2016

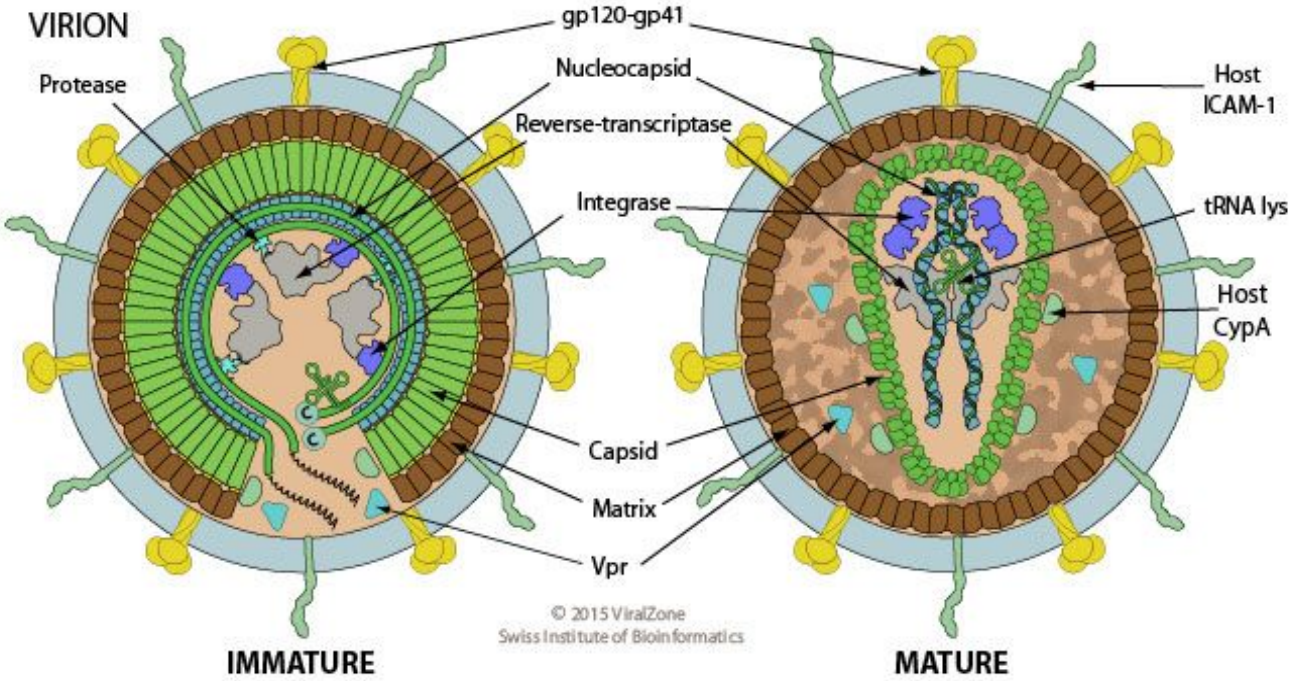
Source: *UNAIDS Foundation*

HIV Spread Map



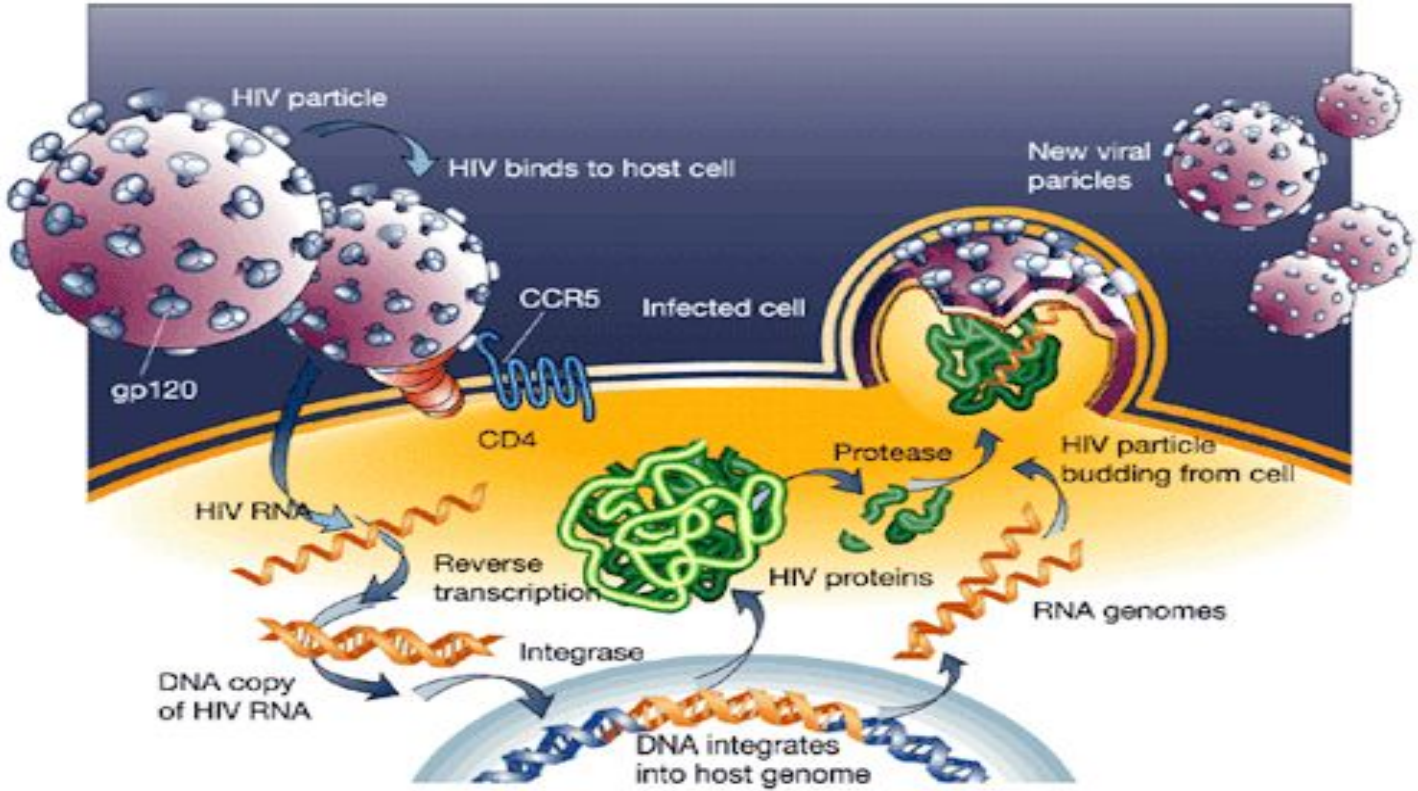
Source: *UNAIDS*

HIV Cell Structure



Ref: *https://viralzone.expasy.org/7?outline=all_by_species*

HIV Replication Life Cycle



Existing Treatment Methods

Antiretroviral Therapy

- **Entry Inhibitors:** Block entry of HIV into immune cells. Ex: Enfuvirtide
- **Nucleoside RT Inhibitors:** Block the reverse transcriptase proteins that HIV needs to multiply. Ex: Abacavir, Didanosine
- **Non-Nucleoside RT Inhibitors:** Bind to and disable the reverse transcriptase proteins that HIV needs to multiply. Ex: Delavirdine, Efavirenz
- **Integrase Inhibitors:** Block the enzyme that HIV needs to infect immune cells with its genetic material. Ex: Dolutegravir, Raltegravir
- **Protease Inhibitors:** Inhibit HIV Protease, that HIV needs to make copies of itself. Ex: Saquinavir, Darunavir

Target Molecule

HIV Protease

- Essential for life cycle replication of HIV
- Cleaves newly formed polyproteins at the appropriate locations to create mature components of an infectious HIV Virion
- Without effective HIV Protease, HIV Virions remain non-infectious

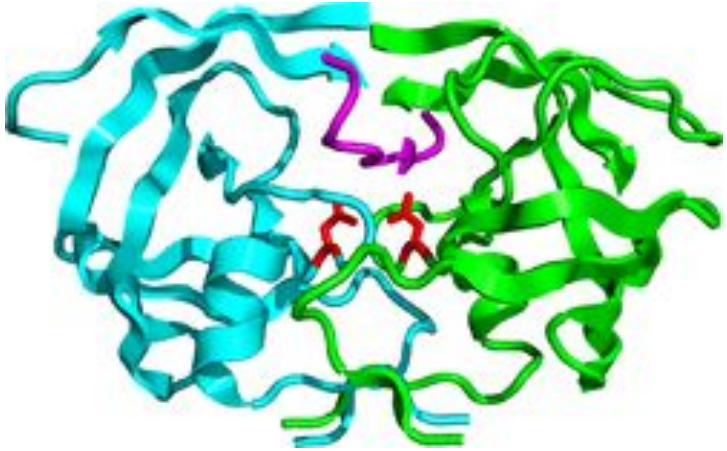


Fig: *HIV protease dimer(green & blue) with active site marked in red*

Target Molecule - Active Site

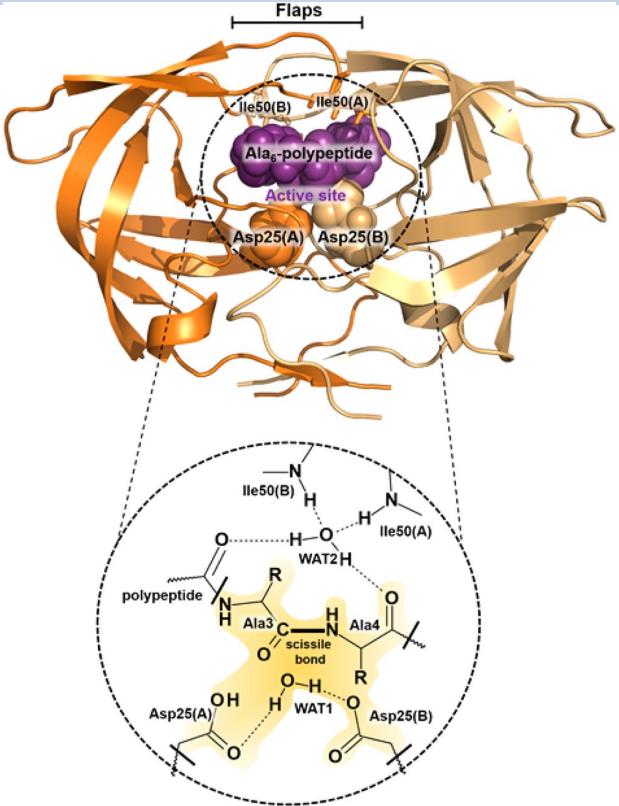
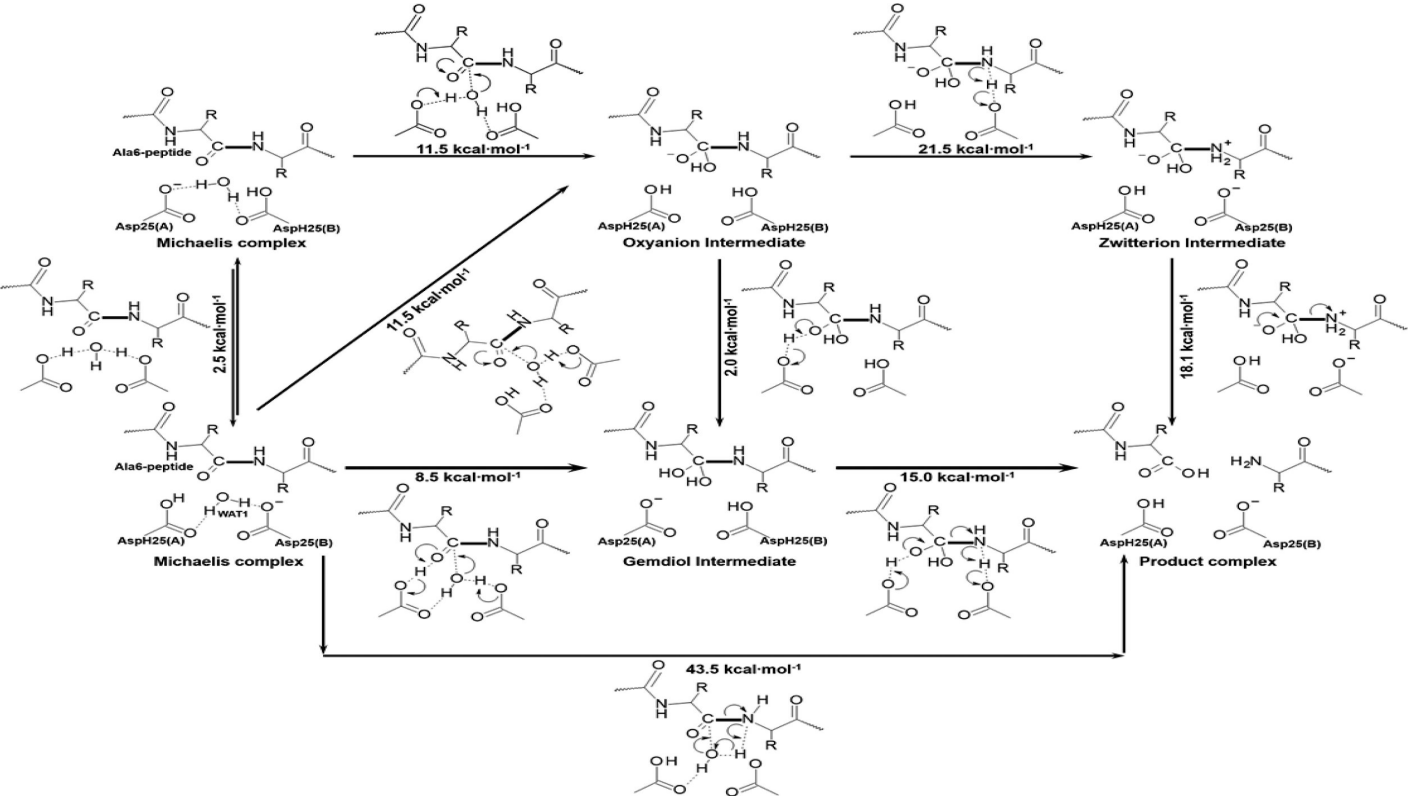


Fig:

Schematic representation of HIV Protease and detail of the active site, with protonated Asp-25(A), and Ala6 peptide as substrate

Action of HIV Protease



Ref: *Agnieszka Krzeminska, Vicent Moliner, Katarzyna Swiderek, "Dynamic and Electrostatic Effects on the Reaction Catalyzed by HIV-1 Protease", Journal of the American Chemical Society- 2016*

Methods of Drug Development

Lead Compound: Darunavir

- Darunavir was chosen as a base molecule from which analogues were constructed
- The docking of Darunavir was studied and possible analogues were designed considering gaps between the drug & the target as well as potential new interactions

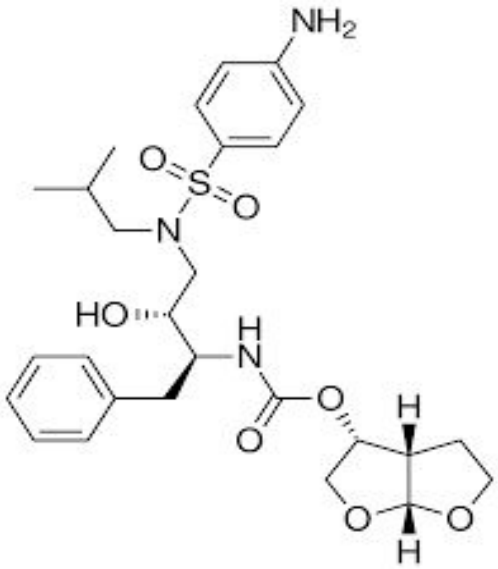
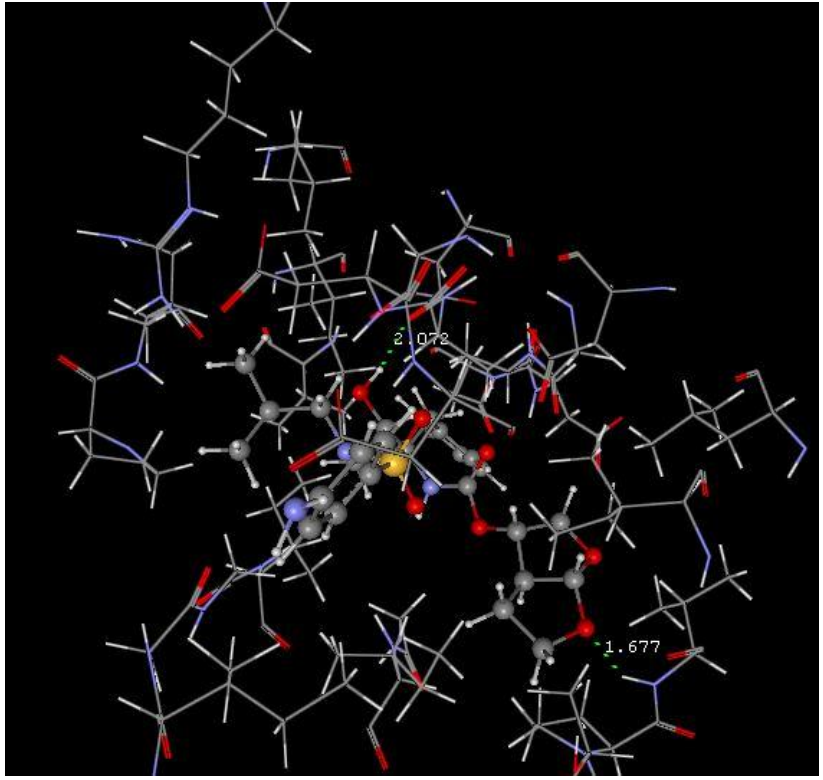


Fig: *Structure of Darunavir*

Docking of Darunavir



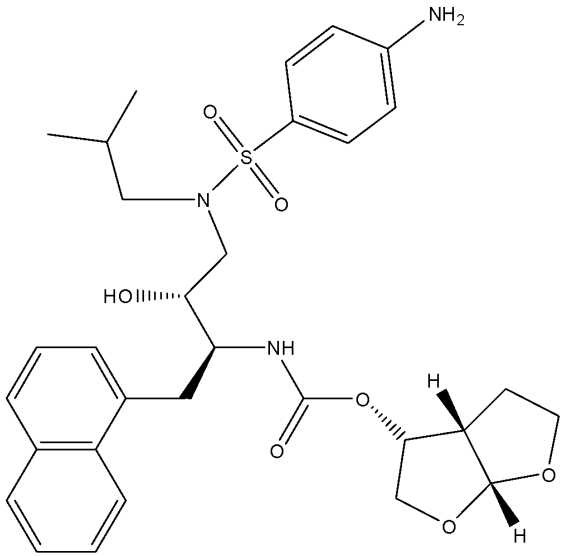
Interactions

- 2 Hydrogen Bonds
- No Pi-Pi Stacking

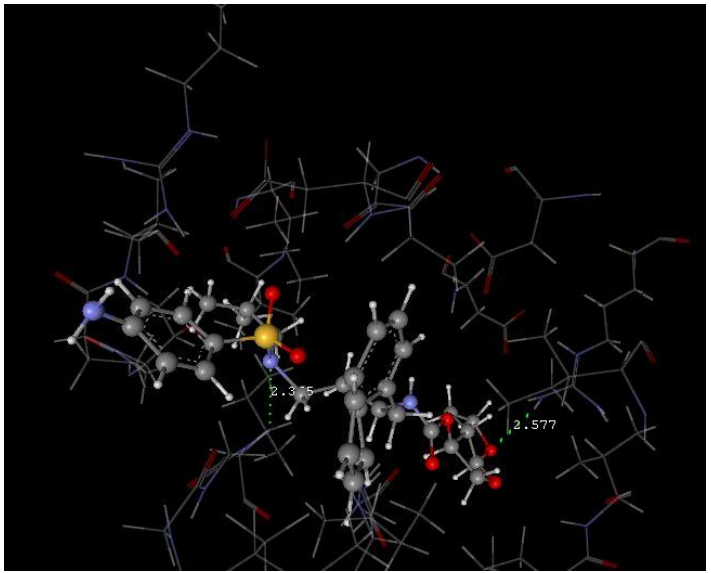
Docking Score:
-65.69

New Drug Design

Analogue 1



Docking Study



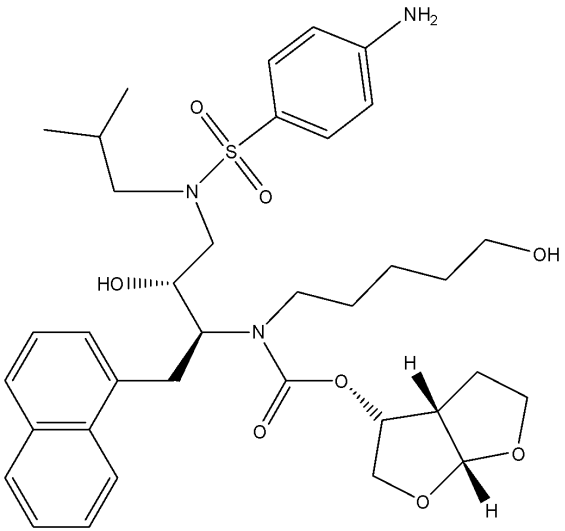
Interactions

- 2 Hydrogen Bonds
- No Pi-Pi Stacking

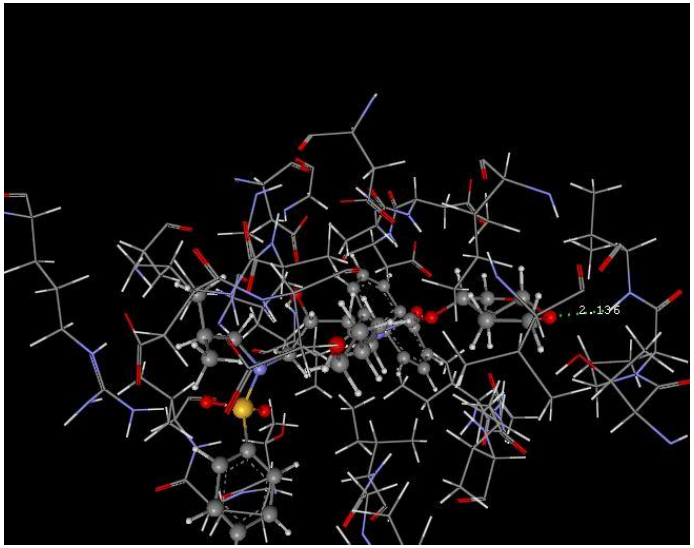
Docking Score:
-41.24

New Drug Design

Analogue 2



Docking Study



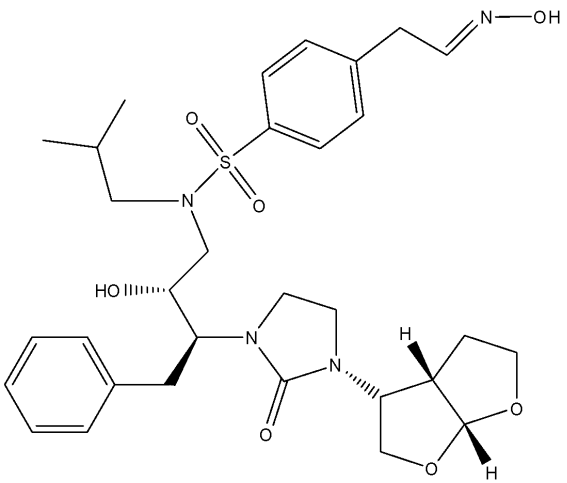
Interactions

- 1 Hydrogen Bond
- No Pi-Pi Stacking

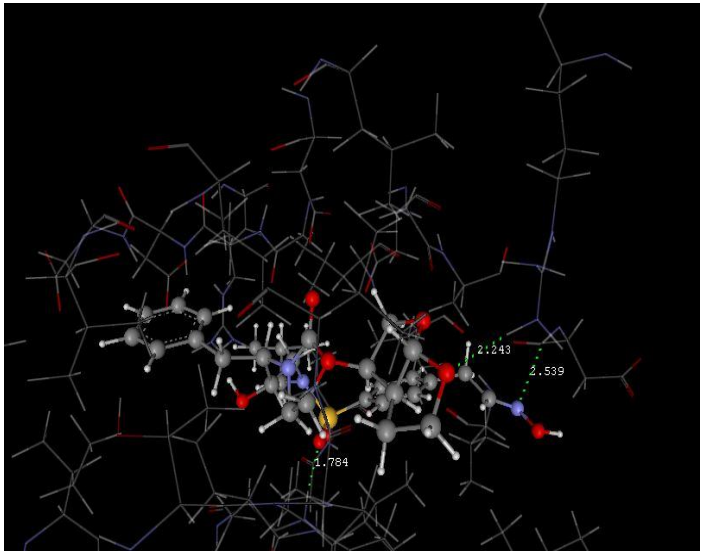
Docking Score:
-4.44

New Drug Design

Analogue 3



Docking Study



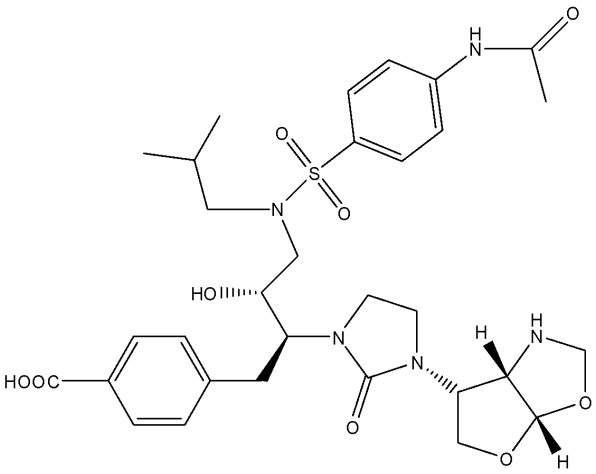
Interactions

- 3 Hydrogen Bonds
- No Pi-Pi Stacking

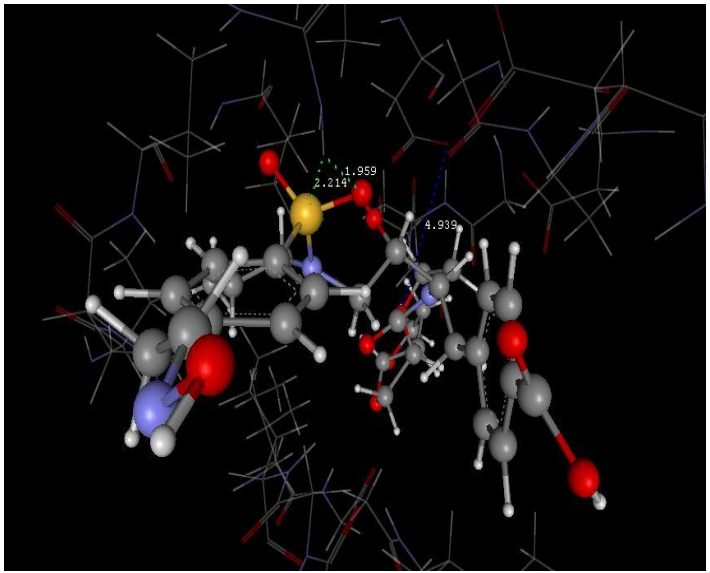
Docking Score:
-56.84

New Drug Design

Analogue 4



Docking Study



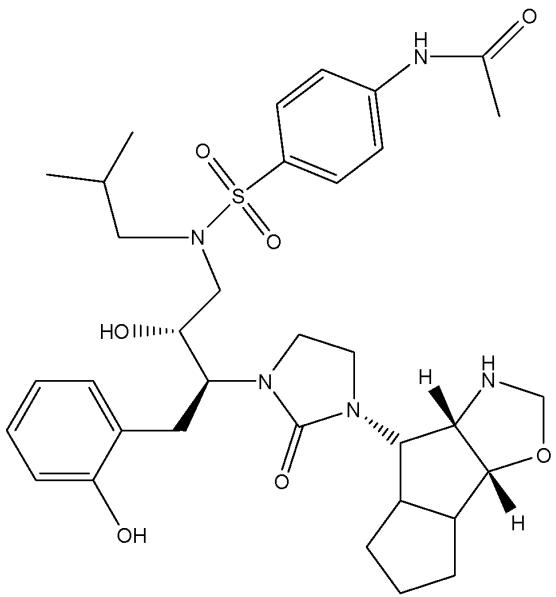
Interactions

- 2 Hydrogen Bonds
- No Pi-Pi Stacking

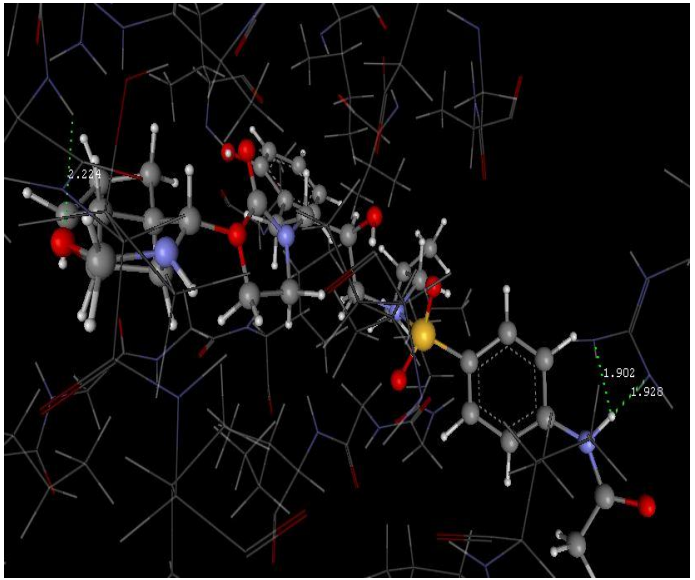
Docking Score:
-53.23

New Drug Design

Analogue 5



Docking Study

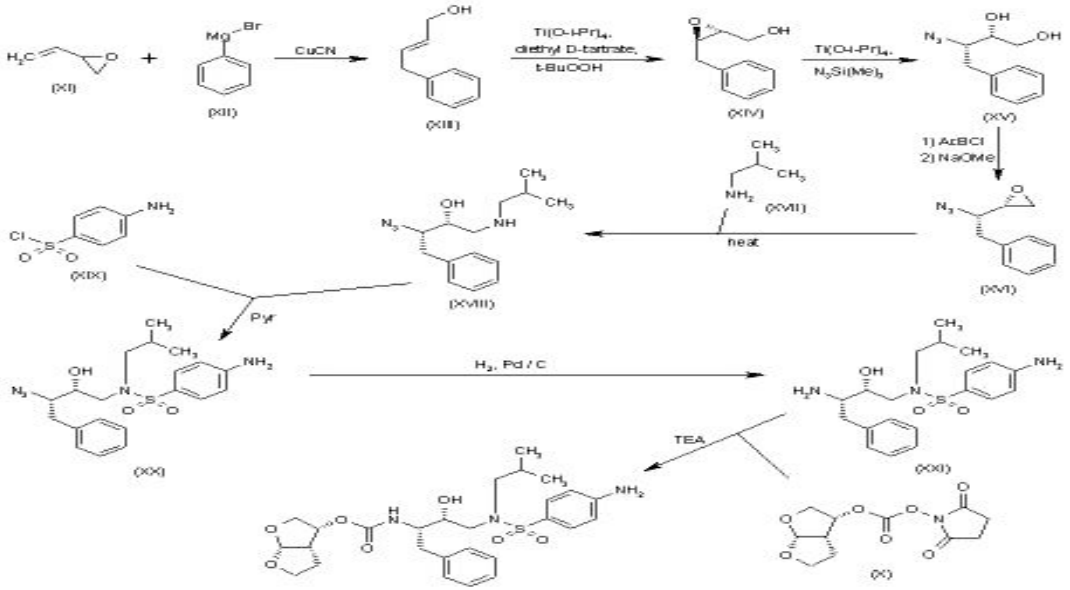


Interactions

- 3 Hydrogen Bonds
- No Pi-Pi Stacking

Docking Score:
-59.14

Synthesis of Drug Molecule



Ref: *US 7700645, Patent for preparation of amorphous Darunavir*

Drug Metabolism

- Darunavir is extensively metabolized by CYP enzymes, primarily CYP3A
- The terminal elimination half-life of darunavir is approximately 15 hours
- Around 48% Darunavir excreted unchanged from the human body

Ref:*Marc Vermeir, Sophie Lachau-Durand et al,"Absorption, Metabolism, and Excretion of Darunavir, a New Protease Inhibitor",Drug Metabolism & Disposition April 2009*

Conclusions

- HIV infection mechanism was studied & target HIV Protease was identified
- HIV Protease action was reviewed
- Mechanism of inhibition of Darunavir was examined
- Analogues of Darunavir were designed & their interactions were investigated


THANK YOU