HIV protease Inhibitors

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HIV Protease

HIV Protease is an Aspartyl protease of HIV
Aspartyl proteases Pepsin, Renin, Cathepsin D.
Catalyses cleavage of peptide bonds
Contains Aspartic acid residue in its active site.

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HIV Protease

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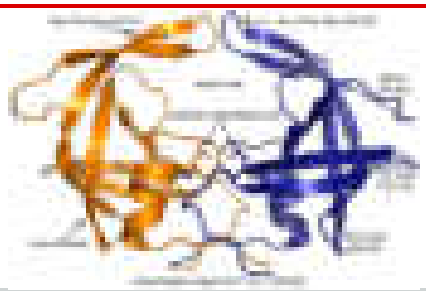
HIV Protease-Structure



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HIV Protease-Structure

➔It is a dimer made up of two identical protein units
➔each consists of 99 amino acids.
➔the active site lies within the interface between the protein units.
➔ It is symmetrical with two fold rotational symmetry.

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HIV Protease-Structure

The amino acids Asp-25, Thr-26 and Gly 27 from each monomer located on the floor of the active site.
each monomer provides a flap (Ile 50/ ile 50') act as ceiling.

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HIV Protease- Sub-Structure specificity

This enzyme can cleaves a variety of peptide bonds.

But crucially cleaves between a proline residue and an aromatic amino acid residue. (Phe/Tyr)

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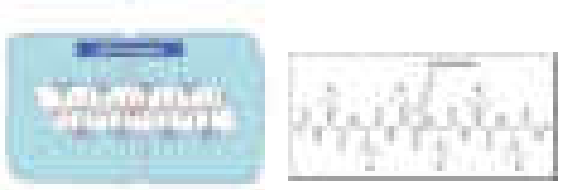
HIV Protease- Sub-Structure specificity



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HIV Protease- Binding subsites

There are 8 binding subsites on either side of the active site.

These subsites accepts the a. acid residue of the substrate.

N and O of each peptide bond of the substrate backbone is involved in a H-Bond interaction with the enzyme.

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HIV Protease- Binding subsites

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Catalysis

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Design of HIV-PI

Taken from the transition state inhibitors of Renin Research(Asp Prtease)

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Design of HIV-PI

★Transition state inhibitors mimic the transition state of the the enzyme catalysed reaction.

★Tran State likely to bound to the active site more strongly than either the substrate or product.

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Design of PI's

Ts structures are inherently unstable

necessary to design an inhibitor that contains tetrahedral centre to mimic the Tstate

it should be stable to hydrolysis.

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Design

➢ Most of the PI are designed to have core unit spanning spanning S1 and S1' subsites.

+

❖ Then substituents are added to either end to fit S2/S3 and S2'/S3'.

❖ Natural peptide fit for 8 subsites

❖ good interaction with enzyme

❖ ➠High MW + Poor oral Bioavailability(not advisable)

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Development of saquinavir

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Saquinavir interactions with HIV protease active site.

Blue = important hydrogen bond interactions.

Red = interactions with specificity sites of the protease.

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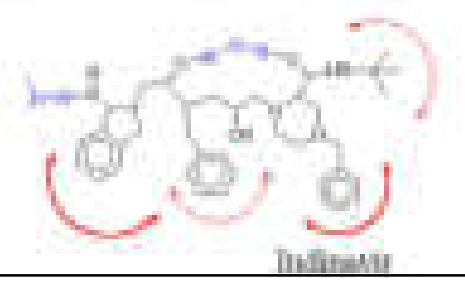

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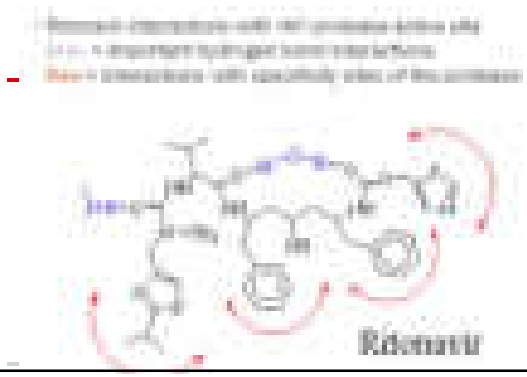

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Tipranavir

is a nonpeptidic protease inhibitor (PI)

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FUSION/ENTRY INHIBITORS

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Fusion / entry Inhibitors

- Entry inhibitors prevent HIV from entering human immune cells.
  There are several key proteins involved in the HIV
- entry process:
  - –CD4, a protein receptor found on the surface of Helper T cells in the human immune system, also called CD4+ T cells
  - –gp120, a protein on HIV surface that binds to the CD4 receptor
  - –CCR5, a second receptor found on the surface of CD4+ cells, called a chemokine coreceptor
  - –CXCR4, another chemokine coreceptor found on CD4+ cells
  - –gp41, a HIV protein, closely associated with gp120, that penetrates the cell membrane

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Fusion / entry Inhibitors

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Fusion / entry Inhibitors- Approved

- Maraviroc (brand-named Selzentry, or Celsentri outside the U.S.)
- Enfuvirtide (INN) is an HIV fusion inhibitor, It is marketed under the trade name Fuzeon (Roche).

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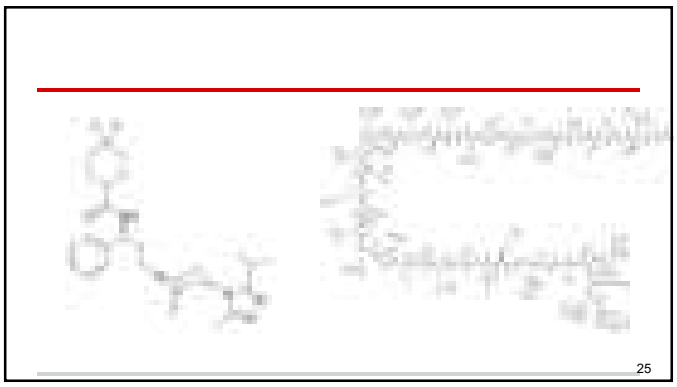

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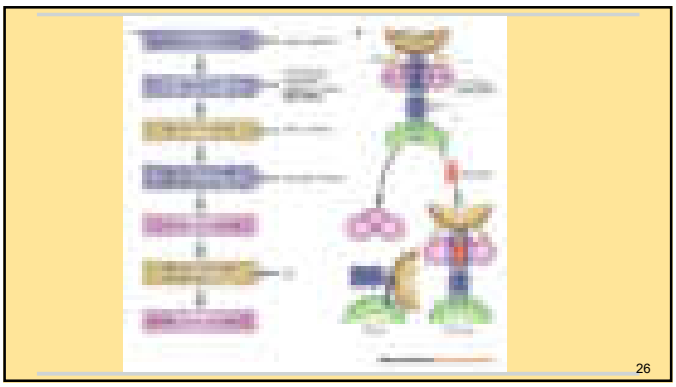

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