ANTIVIRAL AGENTS (NON-RETROVIRAL)

- **Examples of DNA containing viruses**
  Herpes virus - HSV-1, HSV-2, Varicella zoster, Epstein Barr virus.
  Hepadnavirus - Hepatitis B
  Poxvirus- Variola (smallpox)
- **Examples of RNA containing viruses**
  Hepatitis A, C, Influenza, HIV.

ANTIHERPES VIRUS AGENTS

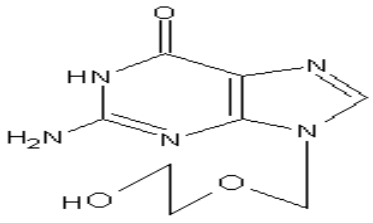
- Infection with herpes simplex virus type -1(HSV-1) typically causes disease of mouth, face, skin, esophagus, and brain.
- Herpes simplex virus type – 2(HSV-2) usually causes infection of the genital, rectum, skin, hands, and meninges.

ANTIHERPES VIRUS DRUGS

- Acyclovir
- Famciclovir
- Ganciclovir
- Idoxuridine
- Penciclovir
- Valacyclovir

S.A.R of Acyclovir and analogs

- Acyclovir though posses pronounced antiviral activity it has certain limitations. Acyclovir itself posses very poor oral bioavailability.
- Its antiviral spectrum is limited to herpes virus -1, 2 only.
- Modifications were made in the side chain of Acyclovir to overcome these drawbacks.



ACYCLOVIR

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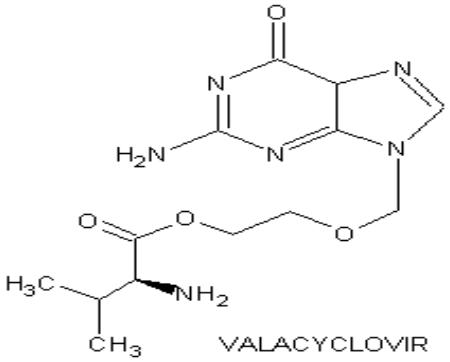
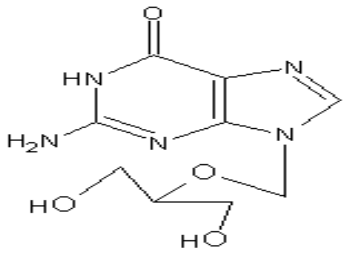
1. Introduction of L-valyl ester in place of acyclovir side chain improves the oral bioavailability 2-3 times that of acyclovir.



VALACYCLOVIR

Bioavailability of Acyclovir is 10-30%. Valacyclovir bioavailability increases above 55%

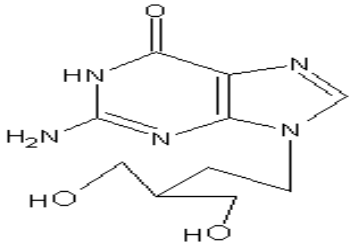
2. Additional hydroxymethyl group in the side chain of acyclovir improves the antiviral spectrum.



GANCICLOVIR

Antiviral spectrum increases 2-3 times as compared to acyclovir. Therapeutic indication- CMV retinitis

3. Introduction of carbon in place of oxygen and an additional hydroxy methyl group. Ex- Penciclovir.



PENCICLOVIR

Anti viral spectrum is same as acyclovir but have a better potency, faster onset and a longer duration of action.

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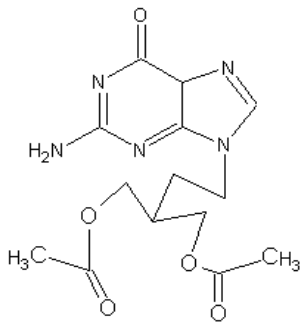
4. Penciclovir has a poor oral bioavailability therefore administered as a diacetyl ester prodrug. Example- Famciclovir



FAMCICLOVIR

Effective against VZV, HSV-1, HSV-2 Phase 3 trials for HBV

➢ **M.O.A OF ACYCLOVIR AND ANALOGS**

Acyclovir

↓ **Viral thymidine kinase**

Acyclovir-MP

↓ **Cellular GMP kinase**

Acyclovir- DP

↓ **Cellular protein kinase**

Acyclovir-TP (Competitive inhibitor of deoxyguanosine triphosphate)

↓

Competitively incorporates into primer strand

↓

DNA chain termination

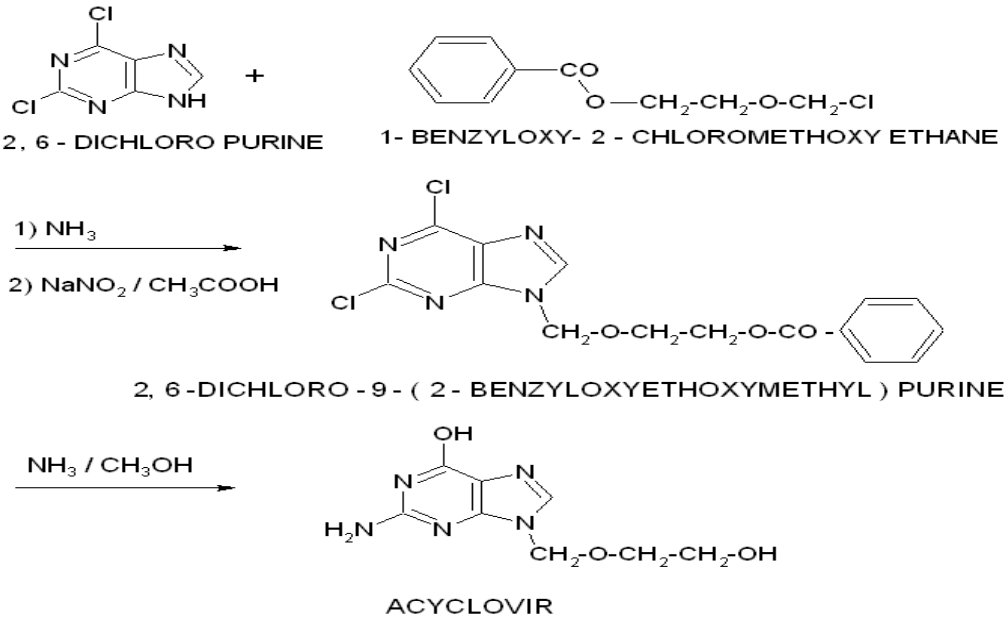
↓

Thus, inhibition of viral DNA polymerase

MP=MONOPHOSPHATE
DP=DIPHOSPHATE
TP=TRIPHOSPHATE

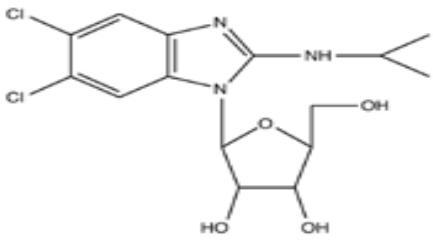
Ganciclovir, famciclovir, penciclovir, all possess the same mechanism as that of acyclovir.

Synthesis of Acyclovir



RECENT- MARIBAVIR

- For Herpes simplex cytomegalovirus
- The drug acts by inhibiting DNA synthesis



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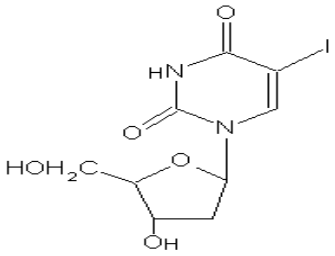
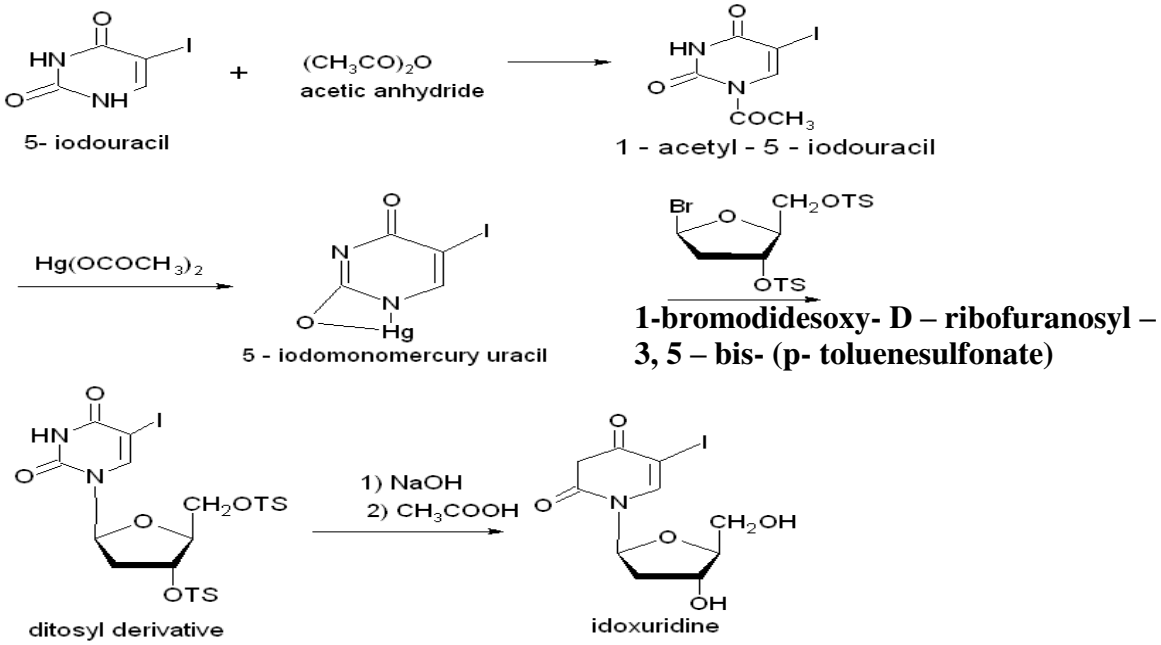
IDOXURIDINE

M.O.A-Inhibits replication of various DNA viruses.



IDOXURIDINE

SYNTHESIS OF IDOXURIDINE



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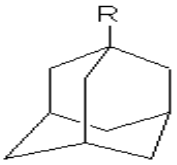
ANTI-INFLUENZA AGENTS

- AMANTADINE
- RIMANTADINE
- ZANAMIVIR

S.A.R OF AMANTADINE AND ANALOGS

Adamantane amines	**R**
Amantadine	-NH2
Rimantadine	-CH (CH_3)-NH_2
Tromantadine	-$NHCOCH_2OCH_2CH_2N$ (CH_3)$_2$



- N-alkyl and N, N-dialkyl derivatives of amantadine exhibit antiviral activity similar to that of amantadine hydrochloride.
- Replacement of amino group with an OH, SH, CN or halogen produced inactive compounds.
- Optical isomer and the racemic mixture of rimantadine are equally active.
- N-acyl derivatives show reduced antiviral activity except glycyl derivative. Ex- Tromantadine which posses efficacy against herpes labialis and herpes genitals.

- **M.O.A of amantadine and analogs:**
  - They inhibit an early step in viral replication probably viral uncoating.
  - The primary locus of action is influenza A virus M2 protein an integral membrane protein that functions as an ion channel.

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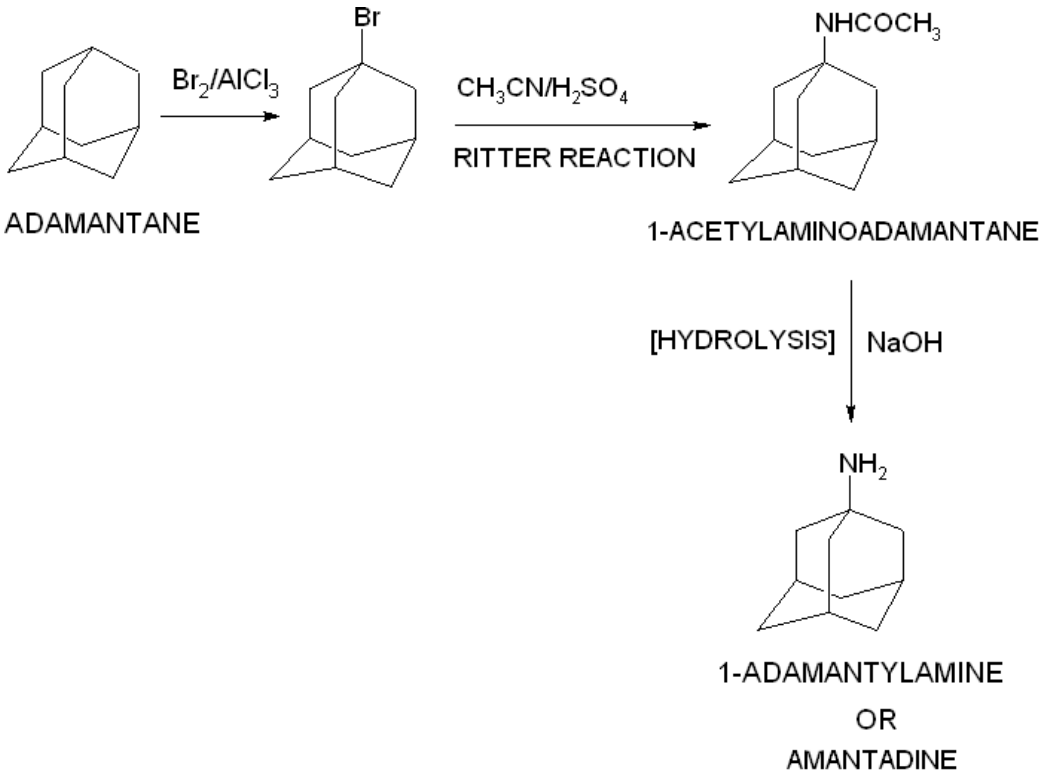
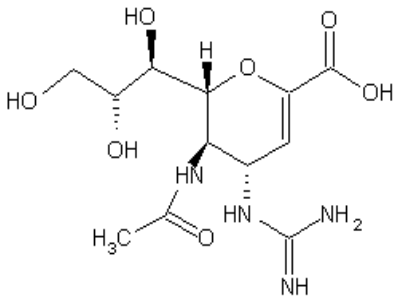


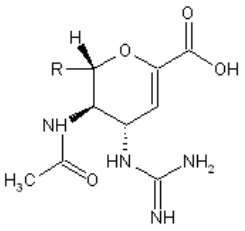
Neuraminidase inhibitors

- Neuraminidase plays a pivotal role in the spread of virus to new cells.
- It is also involved in the introduction of apoptosis to the infected cells.
- Examples- zanamivir, oseltamavir.
- **M.O.A** -
  - Zanamivir inhibits viral neuraminidase and thus causes viral aggregation at the cell surface and reduced spread of virus within the respiratory tract.
  - Zanamivir inhibits replication of influenza A and B virus.



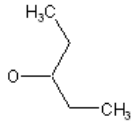
ZANAMIVIR

S.A.R of Zanamivir



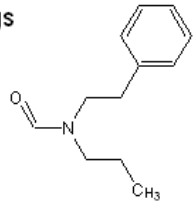
Zanamivir analogs

R=



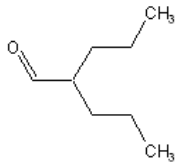
Ether

R=



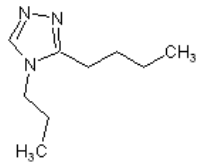
Carboxamide

R=



Ketone

R=



Heterocycle such as triazole

- Substitutions on the guanidino nitrogen generally resulted in much weaker inhibitors.
- 5 –Trifluoroacetamido and 5-sulphonamide derivatives of zanamivir remained the activity approaching to that of zanamavir.
- The C-6 moiety has been replaced by ether, ketone, carboxamide, or a heterocycle such as triazole. All these compounds showed a strong selectivity against Influenza A but worse activity against type B virus.

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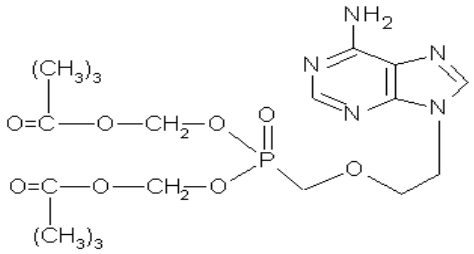
ANTIHEPATITIS AGENTS

- Adefovir
- Lamivudine
- Ribavirin
- Recent - Emtricitabine

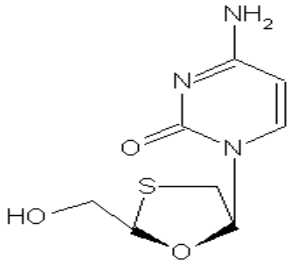
Adefovir Dipivoxil



ADEFOVIR DIPIVOXIL

M.O.A- Adefovir dipivoxil enters cells and is deesterified to adefovir it is converted by cellular enzymes to the diphosphate, which acts as competitive inhibitor of viral DNA polymerase followed by chain termination of viral DNA synthesis.

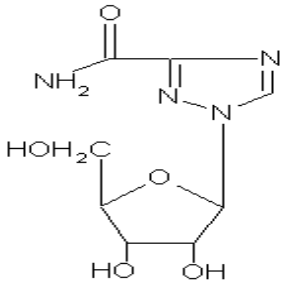
Lamivudine



LAMIVUDINE

- **M.O.A-** Cellular enzymes convert Lamivudine to triphosphate, which competitively inhibit HBV DNA polymerase and causes chain termination.

Ribavirin



RIBAVIRIN

M.O.A- The antiviral mechanism of ribavirin is incompletely understood but relates to alteration of cellular nucleotide pools and inhibition of viral messenger RNA synthesis.

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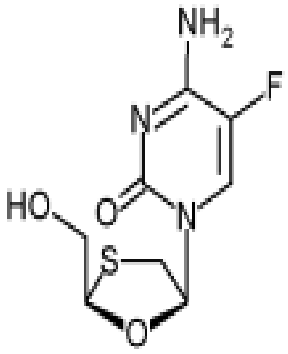
Recent- For treatment of hepatitis B virus
Nucleoside RT/ DNA polymerase inhibitor



EMTRICITABINE

ANTIRETROVIRAL AGENTS

- HIV are Lentiviruses a family of retroviruses evolved to establish chronic persistent infection with gradual onset of clinical symptom.
- Two major families- HIV-1 & HIV-2
- Reverse transcriptase are RNA-dependent DNA-polymerase which converts viral RNA into proviral DNA

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

- Nucleoside reverse transcriptase inhibitors (NRTI'**S**)
- Non- Nucleoside reverse transcriptase inhibitors (NNRTI'**S**)
- Protease inhibitors (PI'**s**)

Nucleoside Reverse Transcriptase inhibitors

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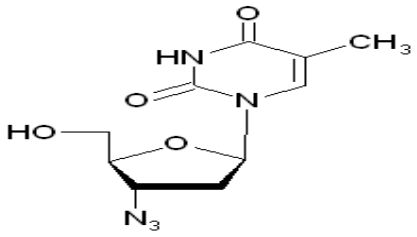
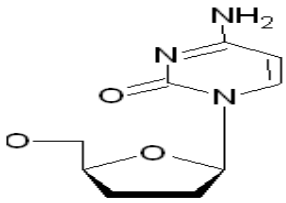
- **Classification of drugs**
  - Zidovudine (AZT)
  - Zalcitabine (ddc)
  - Stavudine (d4T)
  - Recent- Adefovir dipivixol

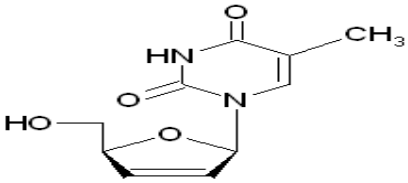
CURRENTLY APPROVED NRTI



ZIDOVUDINE (AZT)



ZALCITABINE (ddc)



STAVUDINE (d_4T)

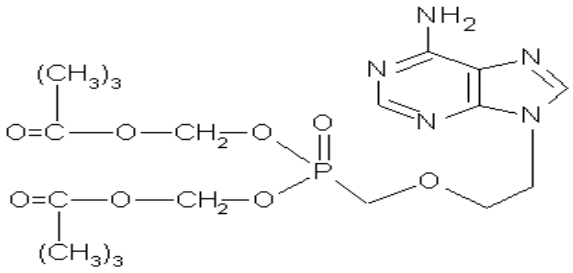
Members of this class act as irreversible competitive inhibitors for the HIV RT.

- **M.O.A-** They compete with normal substrates (Deoxyribonucleotide triphosphate or deoxynucleotides) at the enzyme catalytic site
  The compounds are converted to mono-, di-, and triphosphate by cellular kinases

.

<u>The structures of all NRTI'S lack the 3- hydroxyl group of the sugar which results in blocking DNA elongation</u>.

Newer second generation NRTIS are undergoing pre clinical phase-3 trial.

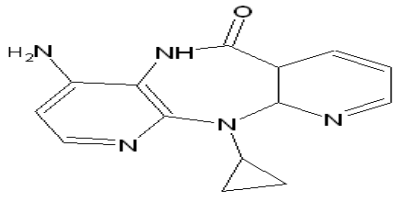


ADEFOVIR DIPIVOXIL

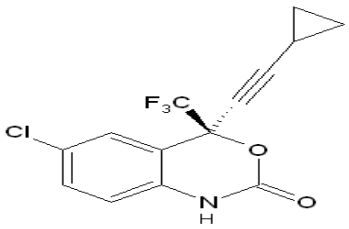
Classification of Non-nucleoside Reverse transcriptase inhibitors

- Nevirapine
- Delaviridine
- Efavirenz
- Recent- Emivirine

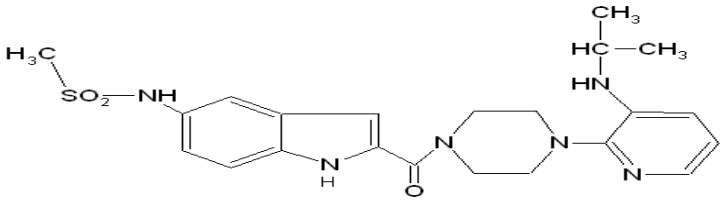
CURRENTLY APPROVED NNRTI'S



NEVIRAPINE



EFAVIRENZ

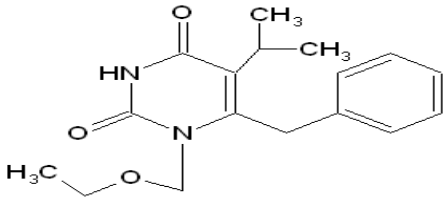


DELAVIRIDINE

NNRTIS target the allosteric non substrate binding sites.

- Members of this class are described as non-competitive, reversible inhibitors.
- **M.O.A-** The NNRTIS competitively inhibits binding to a site on the HIV RT that is distant from the active site inducing a conformational change that destroys catalytic activity.

Second-generation NNRTI Emivirine (MK- 442) is in Phase 3 clinical trial.



EMIVIRINE

HIV PROTEASE INHIBITORS

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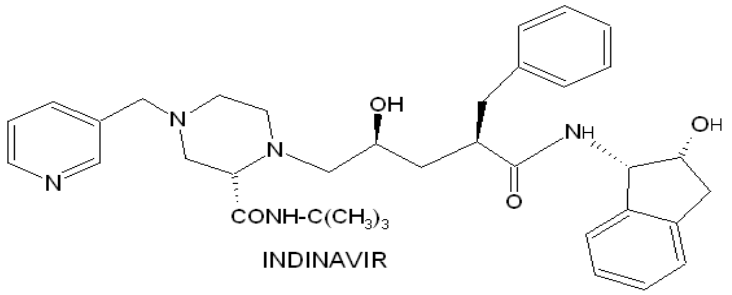
DESIGN OF PROTEASE INHIBITORS

- Three different approaches have been taken
  - Based on the transition state mimetic approach- act as the competitive inhibitor of the natural substrate (polyprotein) precursor binding to the enzyme.
  - Design based on disrupting the enzymes two fold rotational C-2 symmetry axis – forming specific hydrogen and hydrophobic interactions.
  - Fewer peptide characteristics- to improve pharmacokinetic properties**.**

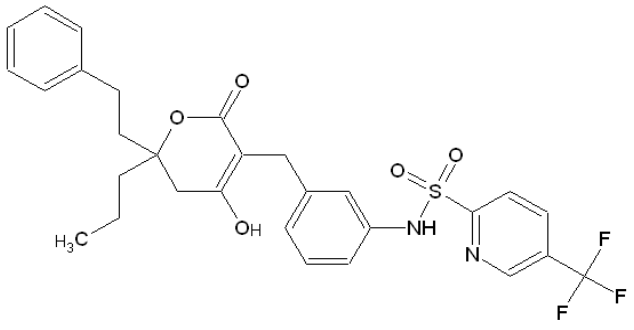
- **M.O.A-** Protease inhibitors reversibly bind to the active site of the HIV protease, preventing polypeptide processing and subsequent viral maturation.



INDINAVIR

Newer protease inhibitors

- Non peptide inhibitors- Tipranavir
- C-2 symmetric protease inhibitor- L- Mannaric acid.



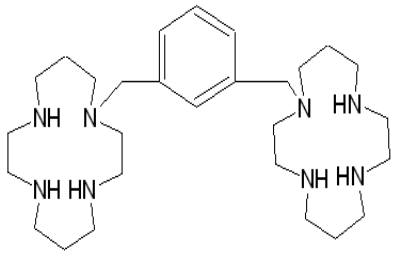
TIPRANAVIR

INHIDITORS OF OTHER TARGETS

- **Fusion inhibitor-** Enfuvirtide

  M.O.A- It is a polypeptide consisting of 36 amino acids which matches with the c-terminal end of the viral protein gp41. This prevents the process by which the virus enters the host cells.

- **CCR5 Antagonist-** Bicyclamines such as JM 3100



JM 3100