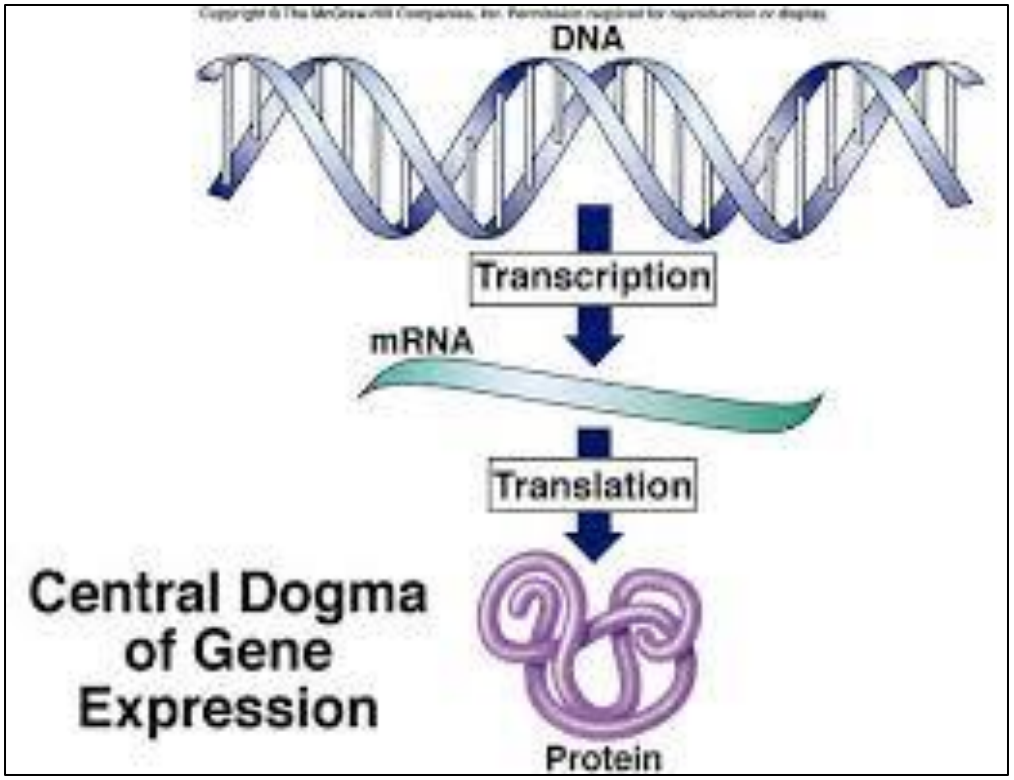
Inhibitors of Transcription

Courtesy:Satyam D Pawar

INTRODUCTION

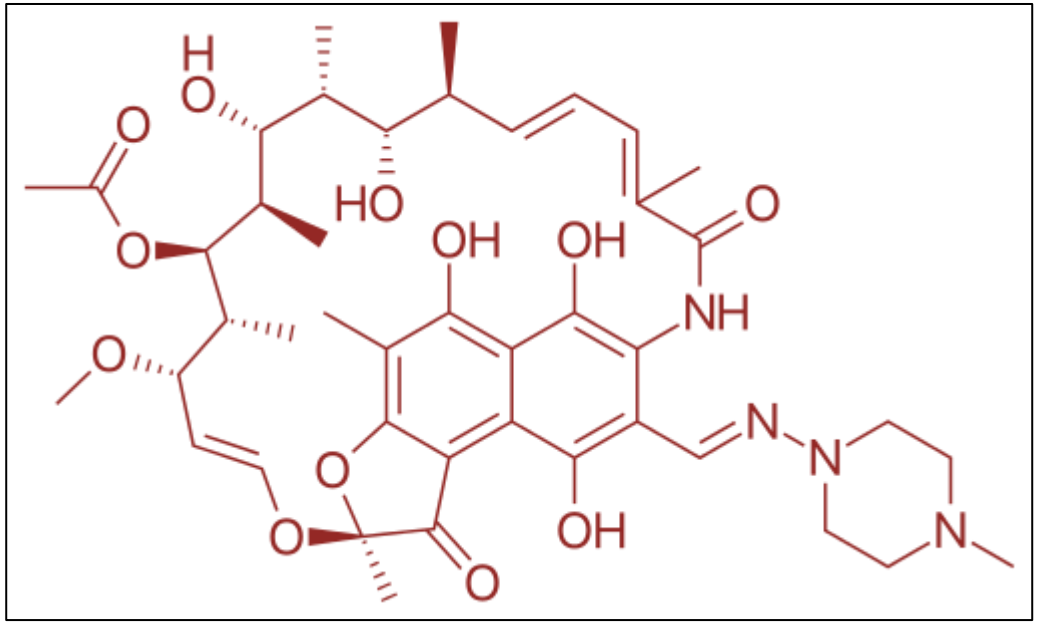
- Transcription is the process by which the DNA information is "copied" to an mRNA molecule, which will be further be the template for translation, process by which proteins are synthetized.
- Inhibition of Transcription can be done by –

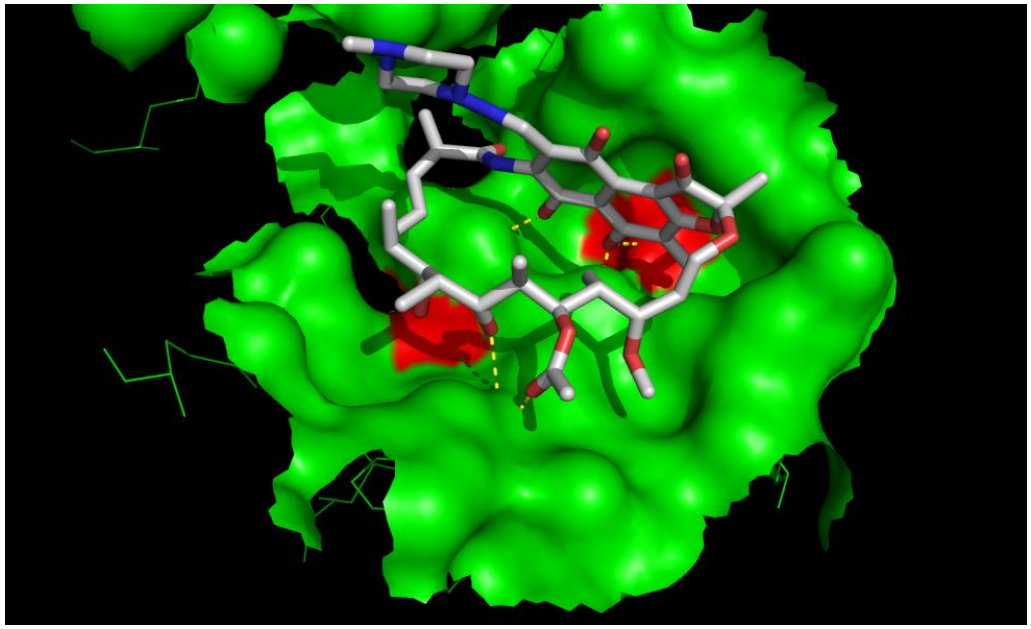
1. Targeting pIC assembly at promoter
2. Reducing DNA accessibility to transcriptional machinery through epigenetic modifications
3. Slowing down RNA elongation
4. Covalent/Non-covalent modifications of RNA Polymerases



Rifampicin :

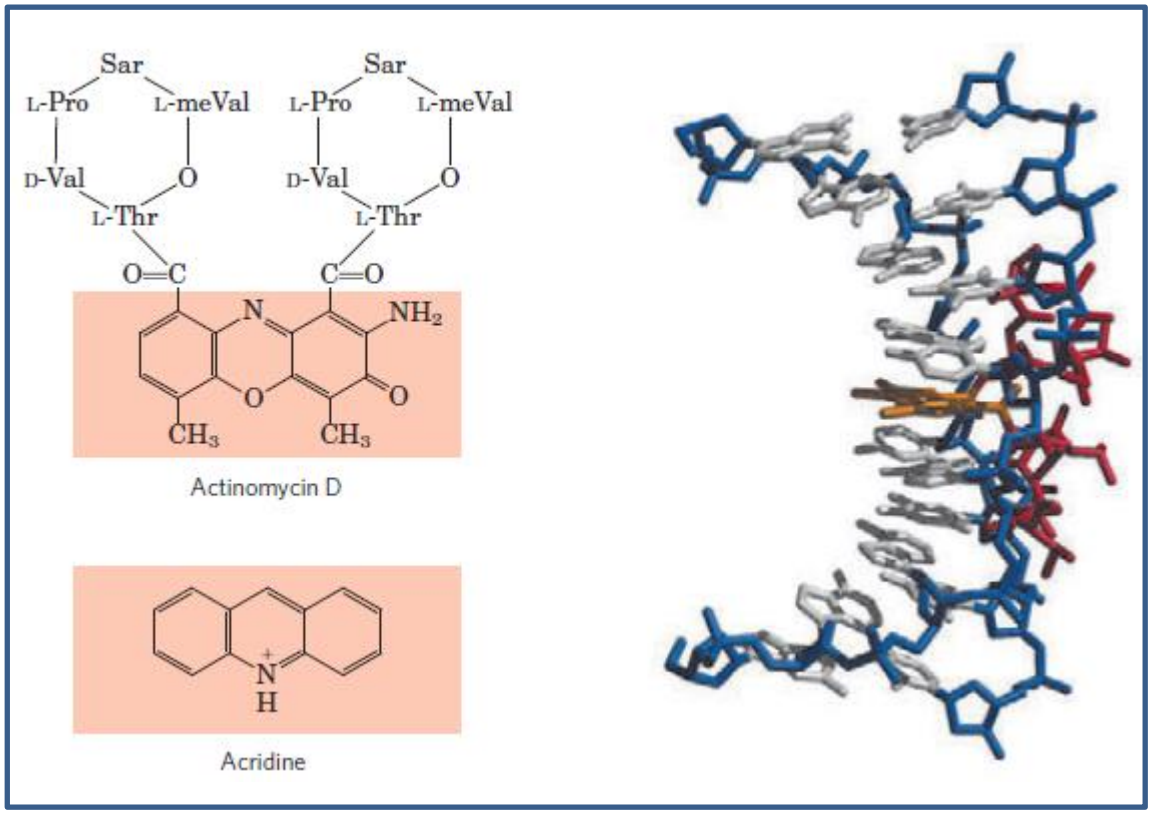
- **Rifampicin** binds with Beta subunit of prokaryotic RNA polymerase.
- It is an inhibitor of prokaryotic transcription initiation.
- It binds only to bacterial RNA polymerase but not to eukaryotic RNA polymerases.
- Therefore, Rifampicin is a powerful drug for treatment of bacterial infections.
- Used for the treatment of tuberculosis and leprosy.





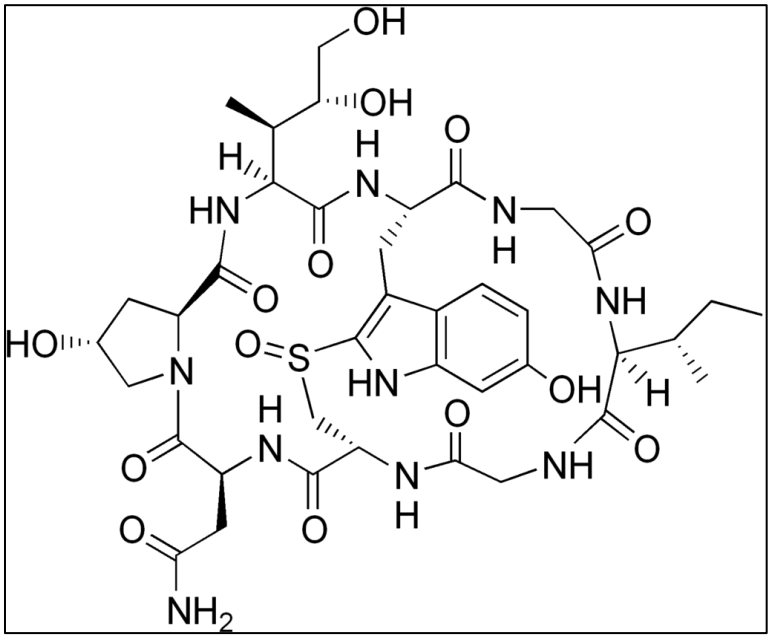
Actinomycin D :

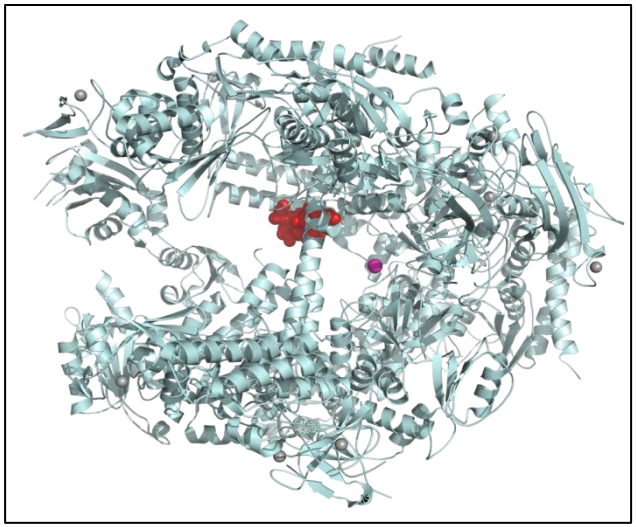
- Antibiotic, inhibits transcription in bacteria & eukaryotes
- The planar portion of this molecule inserts (intercalates) into the double helical DNA between successive GC base pairs, deforming the DNA.
- Inhibits RNA elongation by restricting RNA polymerase along the template
- Concentration dependent action
- Acridine also functions in a similar fashion.



α-Aminitin :

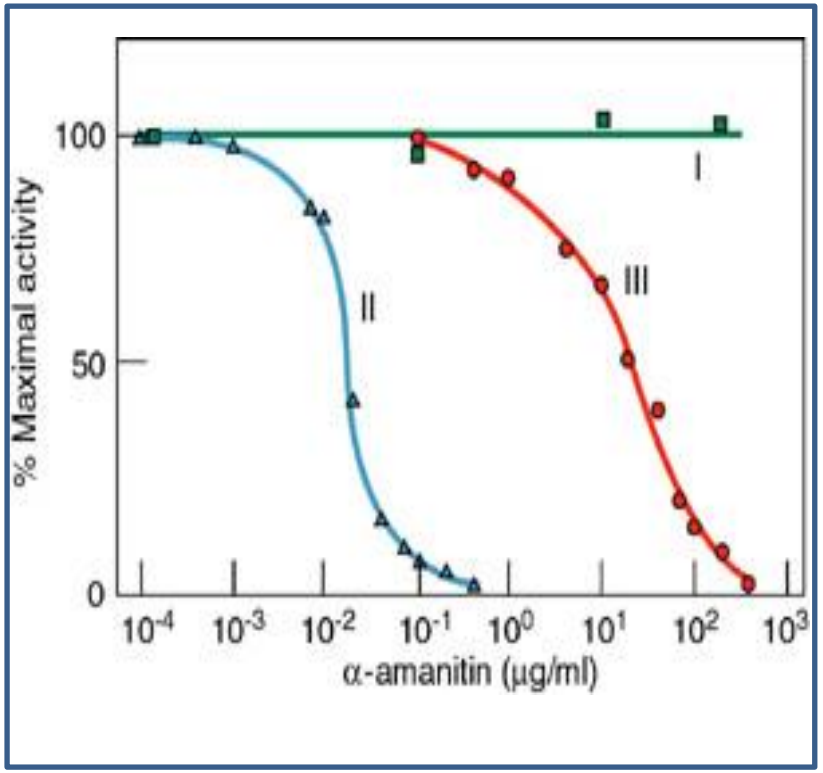
- a cyclic peptide of 8 amino acids
- a defense mechanism by *Amanita phalloides*
- Selective inhibitor of RNA Pol II & Pol III
- α-Amanitin interacts with the bridge helix in Pol II. This interaction interferes with the translocation of RNA and DNA needed to empty the site for the next round of RNA synthesis.
- No effect on affinity for NTPs & phosphodiester bond can be formed.
- Non-Competitive binding slows down rate of elongation





Pol II-Amanitin complex from yeast
Source : RCSB-PDB 1K83

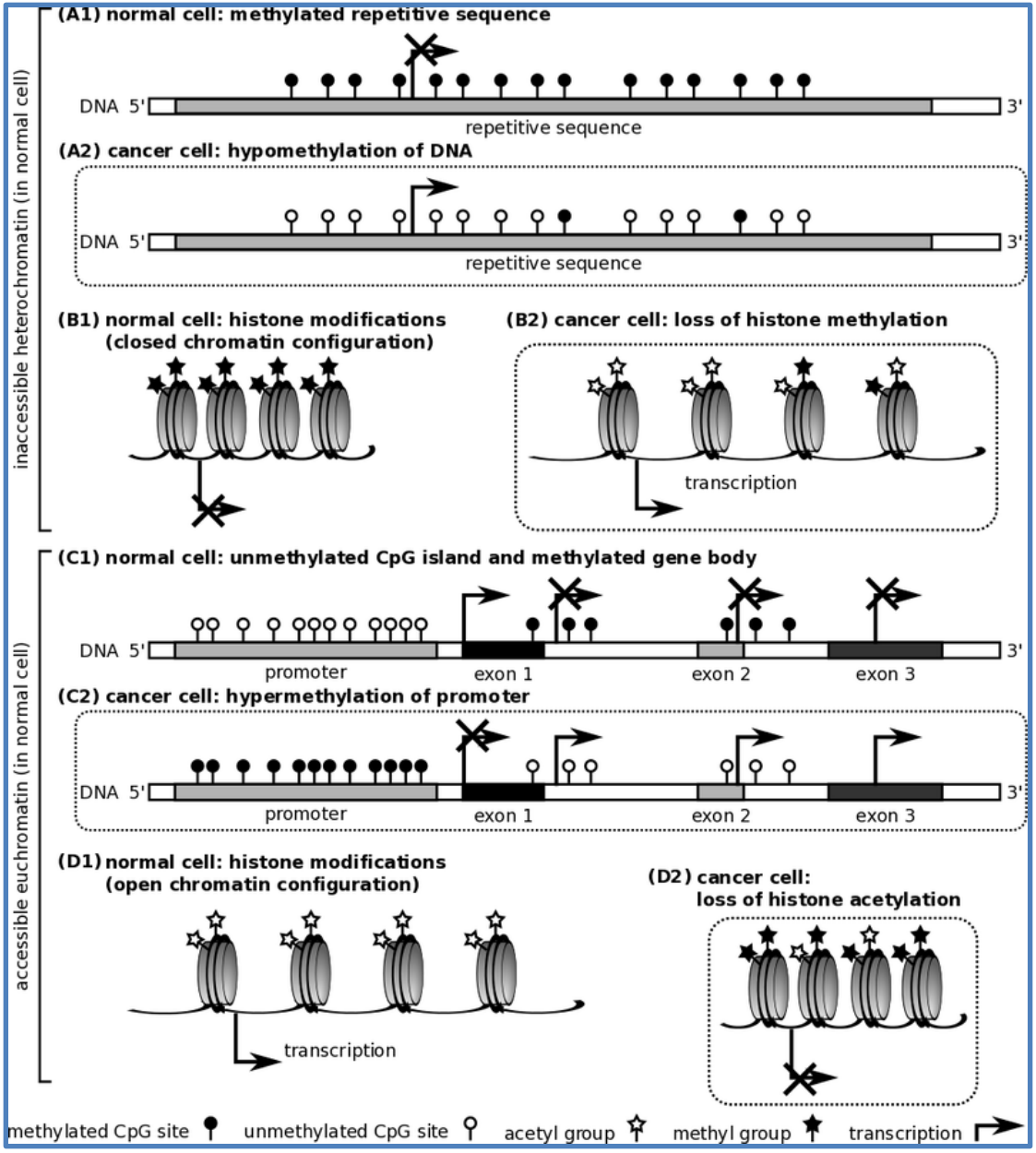
- α-Amanitin can also be used to determine which types of RNA polymerase are present. This is done by testing the sensitivity of the polymerase in the presence of α-amanitin. RNA polymerase I is insensitive, RNA polymerase II is highly sensitive (inhibited at 1μg/ml), RNA polymerase III is moderately sensitive (inhibited at 10μg/ml), and RNA polymerase IV is slightly sensitive (inhibited at 50μg/ml)
- Use in Antibody-Drug Conjugates
  - water soluble structure, low aggregation even at higher doses *in vivo*
  - very effective against MDR cells,
  - Inhibition by Amanitin induces apoptosis in targeted cells through Antibody
  - Studies in mouse models for prostrate cancer have been highly successful



RNA Pol activity in presence of α-Amanitin

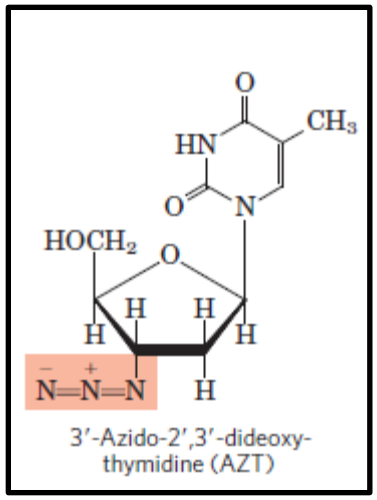
Endogenous Inhibitors

- Methylation pattern of CpG islands upstream of promoter
- Normally CpG islands other than those near promoters are methylated & those near promoter unmethylated.
- Cancer – Tumor suppressor genes & oncogenes
- Deacetylation of Lys residues of N-terminal of Histone octamer
- The accessibility of genes in euchromatin and those in heterochromatin reversed.

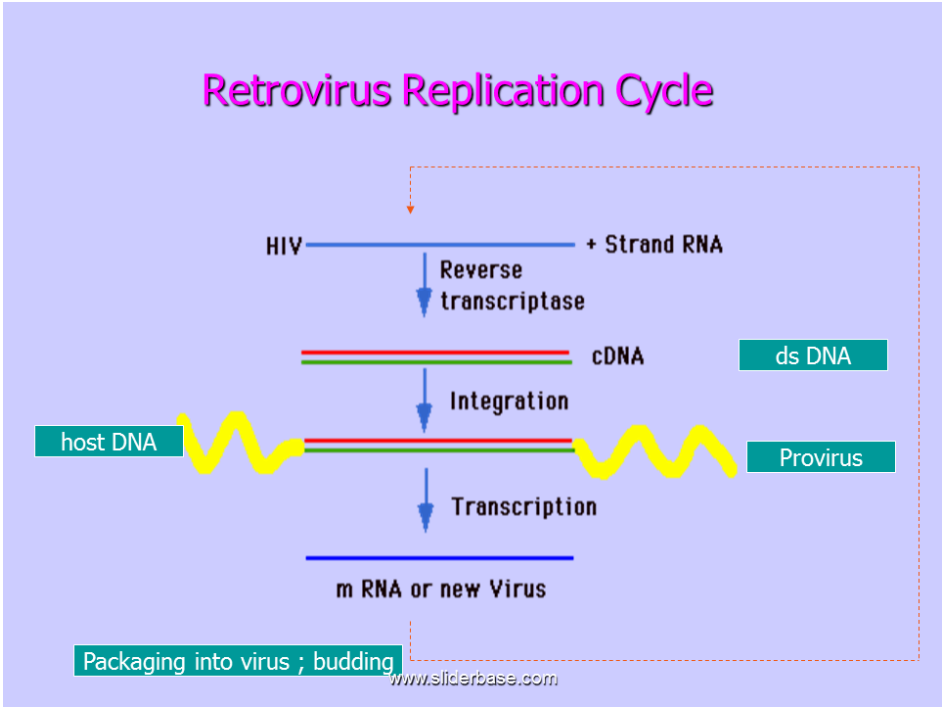


Reverse Transcriptase :

- A **reverse transcriptase** (RT) is an enzyme used to generate complementary DNA (cDNA) from an RNA template, a process termed reverse transcription.
- HIV infection – AZT used analog of dTTP
- AZT taken up by susceptible T lymphocytes
- Reverse Transcriptase has higher affinity for AZT triphosphate than dTTP unlike mammalian polymerases
- AZT triphosphate lacks 3'-OH group terminating viral replication.



3'-Azido-2',3'-dideoxy-thymidine (AZT)



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