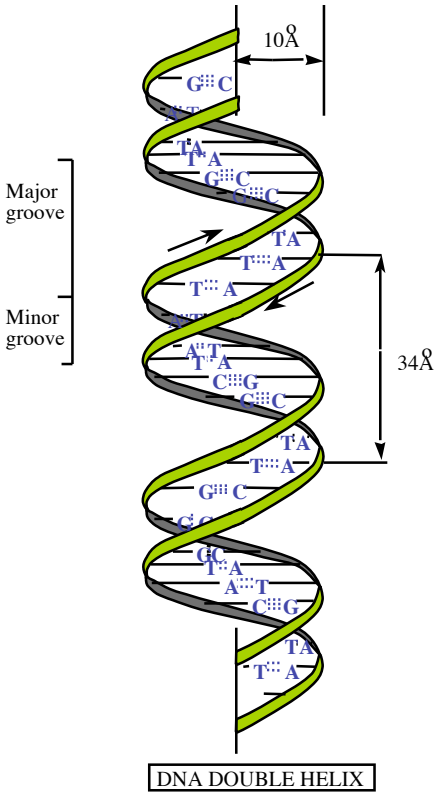
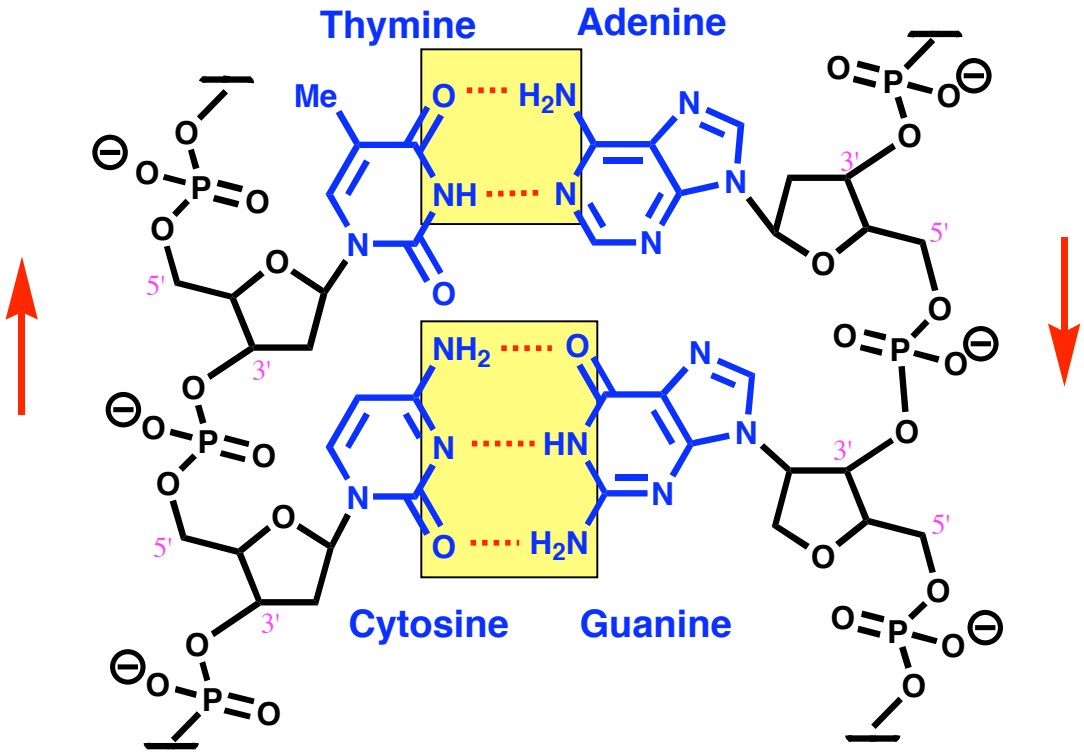
Topic 5 Nucleic Acids as Drug Targets

Nucleic Acids-Chapter 7 Patrick and Corey 187, 188, 193-194, 198-199

1. DEOXYRIBONUCLEIC ACID (DNA)

1.2 Secondary Structure - Double Helix





Base Pairing

G-C base pairing involves 3 H-bonds

A-T base pairing involves 2 H-bonds

1. DEOXYRIBONUCLEIC ACID (DNA)

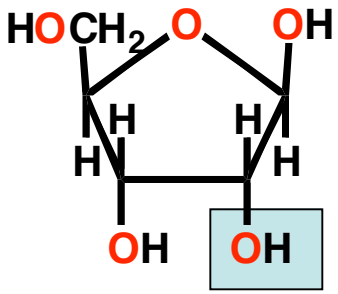
1.3 Tertiary Structure

- **Double helix coils into a 3D shape - supercoiling**
- **Double helix has to unravel during replication**
- **Unravelling leads to strain**
- **Relieved by enzyme catalysed cutting and repair of DNA chain**
- **Important to the activity of the quinolone and fluoroquinolone antibacterial agents which act as enzyme inhibitors**

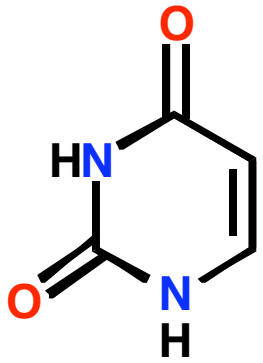
2. RIBONUCLEIC ACID (RNA)

2.1 Primary structure

- **Similar to DNA with the following exceptions**
- **Ribose is used instead of deoxyribose**
- **Uracil is used rather than thymine**



Ribose



Uracil

2. RIBONUCLEIC ACID (RNA)

2.2 Secondary structure

- **Single stranded**
- **Some regions of helical secondary structure exist due to base pairing within the same strand (see t-RNA)**
- **Adenine pairs to uracil; guanine pairs to cytosine**

2. RIBONUCLEIC ACID (RNA)

2.3 Tertiary structure

- **Three types of RNA are involved in protein synthesis:**

- **Messenger RNA (mRNA)**
  Relays the code for a protein from DNA to the protein production site

- **Transfer RNA (tRNA)**
  The adapter unit linking the triplet code on mRNA to specific amino acids

- **Ribosomal RNA (rRNA)**
  Present in ribosomes (the production site for protein synthesis). Important both structurally and catalytically

2. RIBONUCLEIC ACID (RNA)

2.3 Tertiary structure

3'p end

5'p end

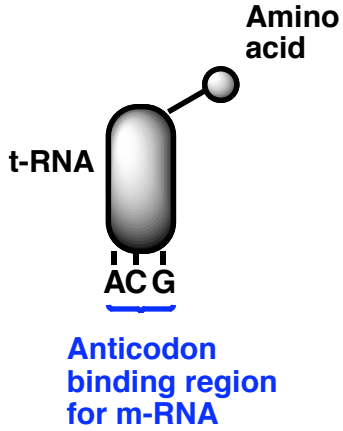
AMINO ACID

Base Pairing

mI	Methylinosine
I	Inosine
UH2	Dihydrouridine
T	Ribothymidine
Ps	Pseudouridine
mG	Methylguanosine
m2G	Dimethylguanosine

Yeast alanine-tRNA

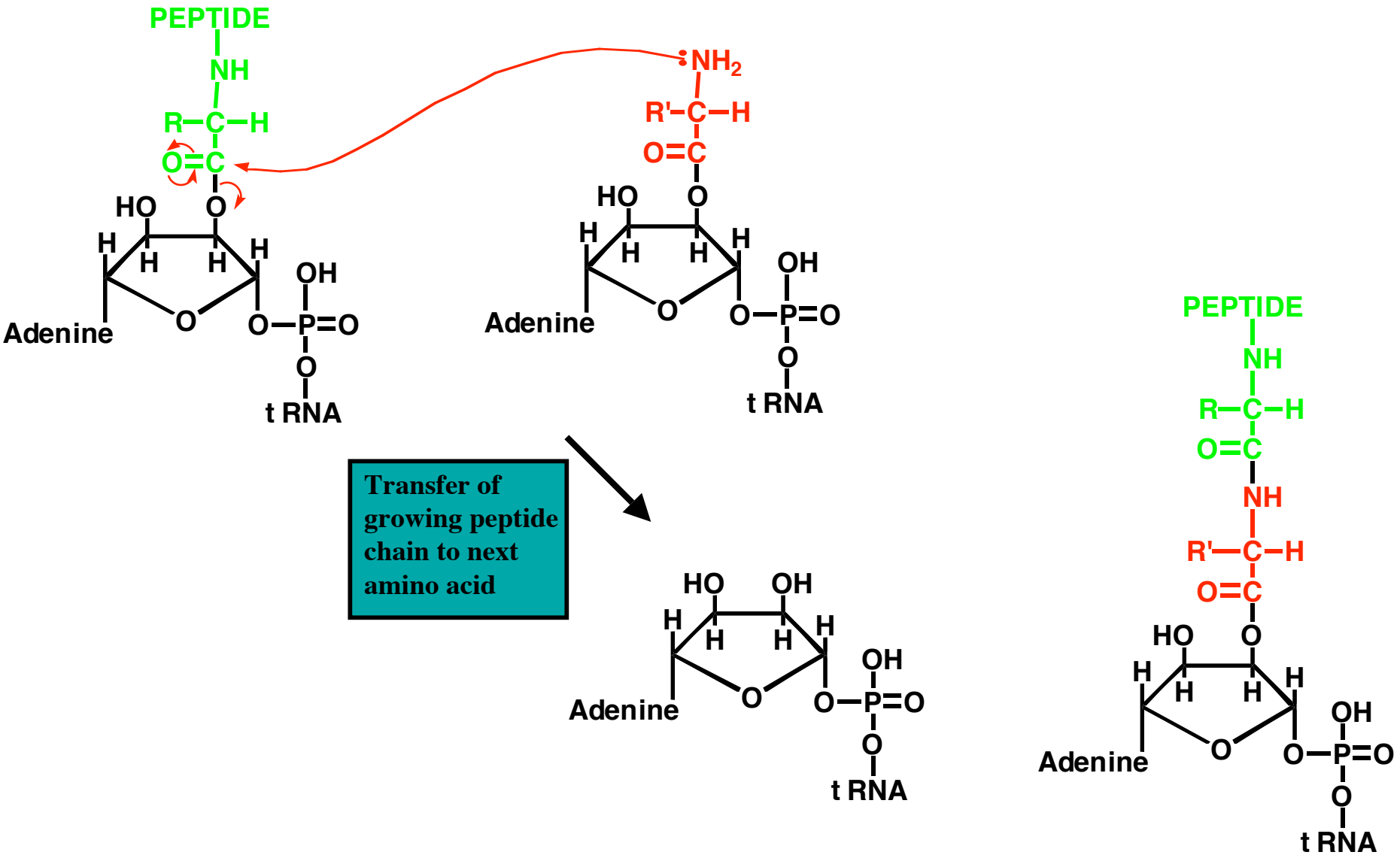
ANTICODON



Anticodon - the 3 bases are specific for the attached amino acid
- base pair to the complementary triplet code on m-RNA (the codon)

2. RIBONUCLEIC ACID (RNA)

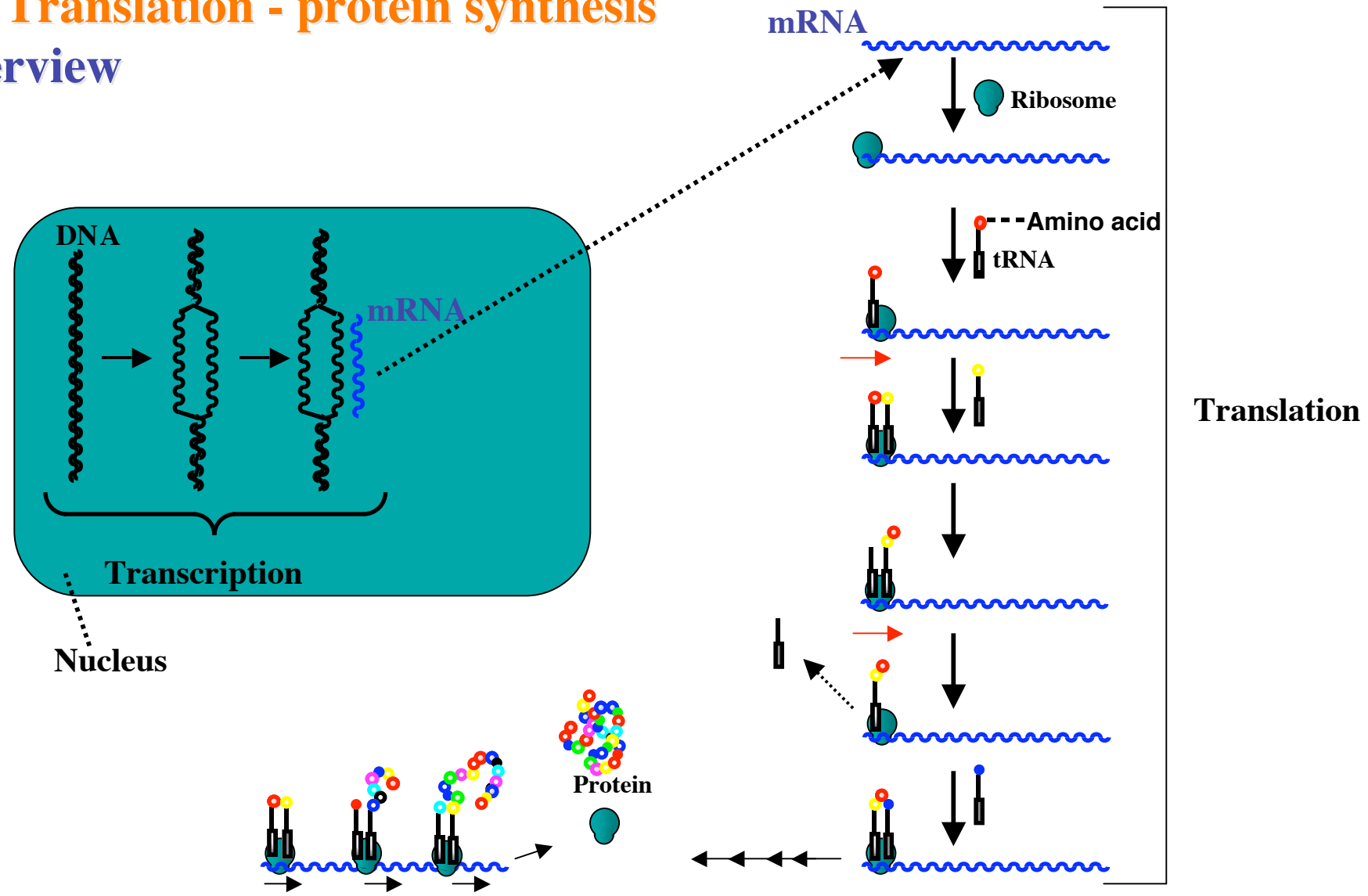
2.5 Translation - protein synthesis



2. RIBONUCLEIC ACID (RNA)

2.5 Translation - protein synthesis

Overview



Contents

Part 2: Section 7.3 (Drugs acting on DNA)

3. DRUGS ACTING ON DNA

3.1 Intercalating agents

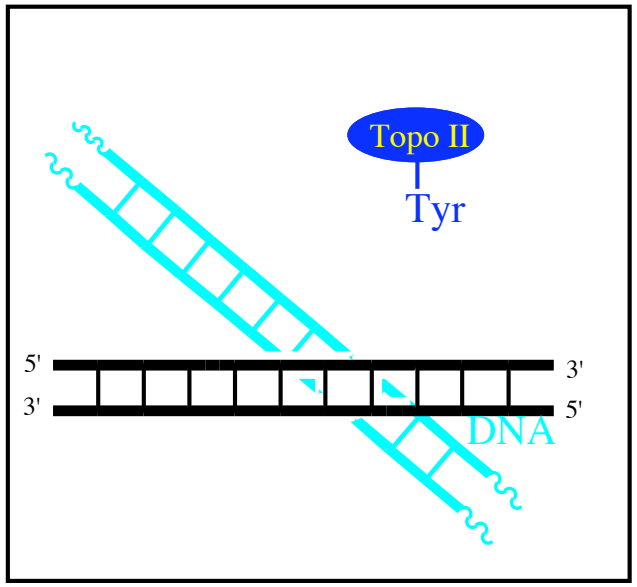
Mechanism of action

- **Contain planar aromatic or heteroaromatic ring systems**
- **Planar systems slip between the layers of nucleic acid pairs and disrupt the shape of the helix**
- **Preference is often shown for the minor or major groove**
- **Intercalation prevents replication and transcription**
- **Intercalation inhibits topoisomerase II- see Doxorubicin, p.198 *Corey*.**

3. DRUGS ACTING ON DNA

Topoisomerase II

- **Relieves the strain in the DNA helix by temporarily cleaving the DNA chain and crossing an intact strand through the broken strand**



- **Tyrosine residues in the enzyme are involved in the chain breaking process**
- **The residues form covalent bonds to DNA**

3. DRUGS ACTING ON DNA

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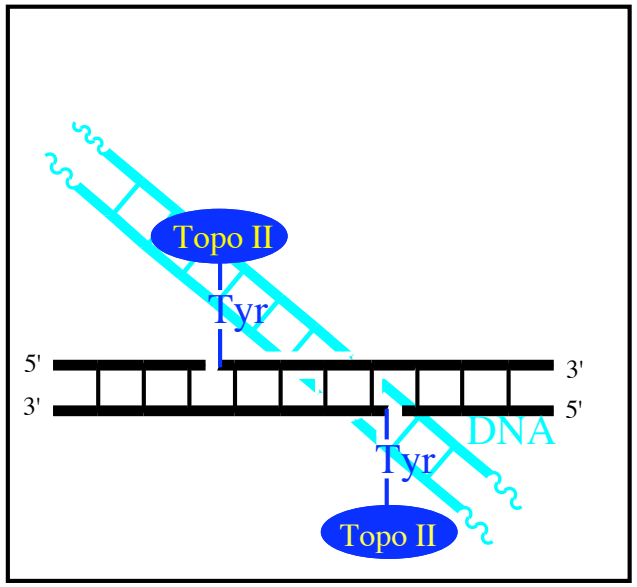

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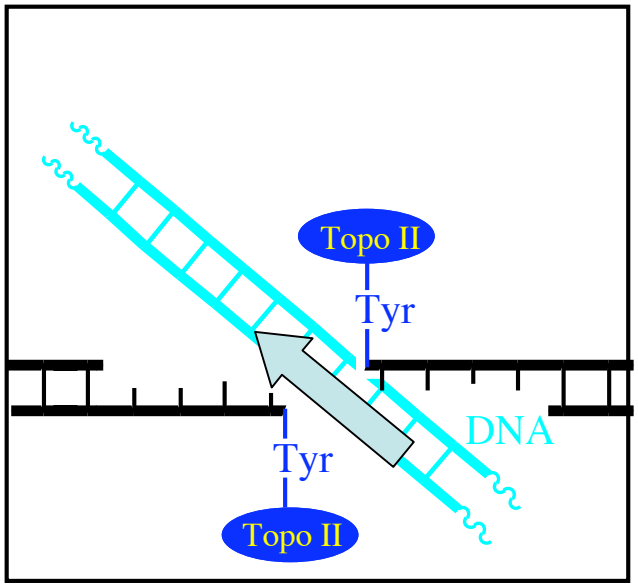

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3. DRUGS ACTING ON DNA

Topoisomerase II

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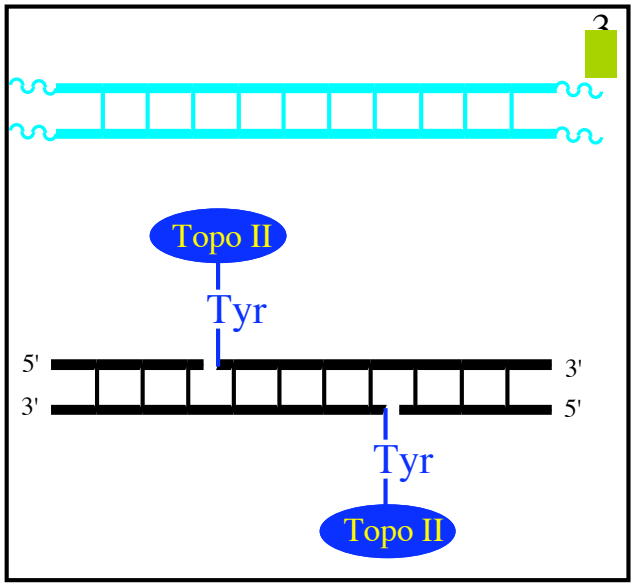

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- **The break is resealed**

3. DRUGS ACTING ON DNA

Topoisomerase II

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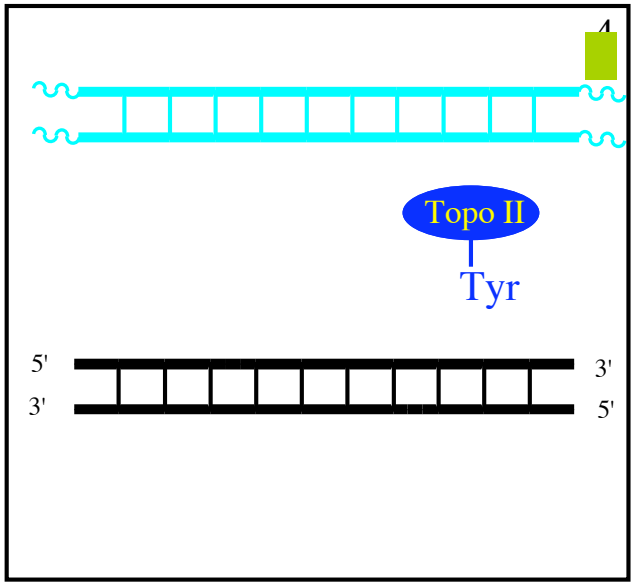

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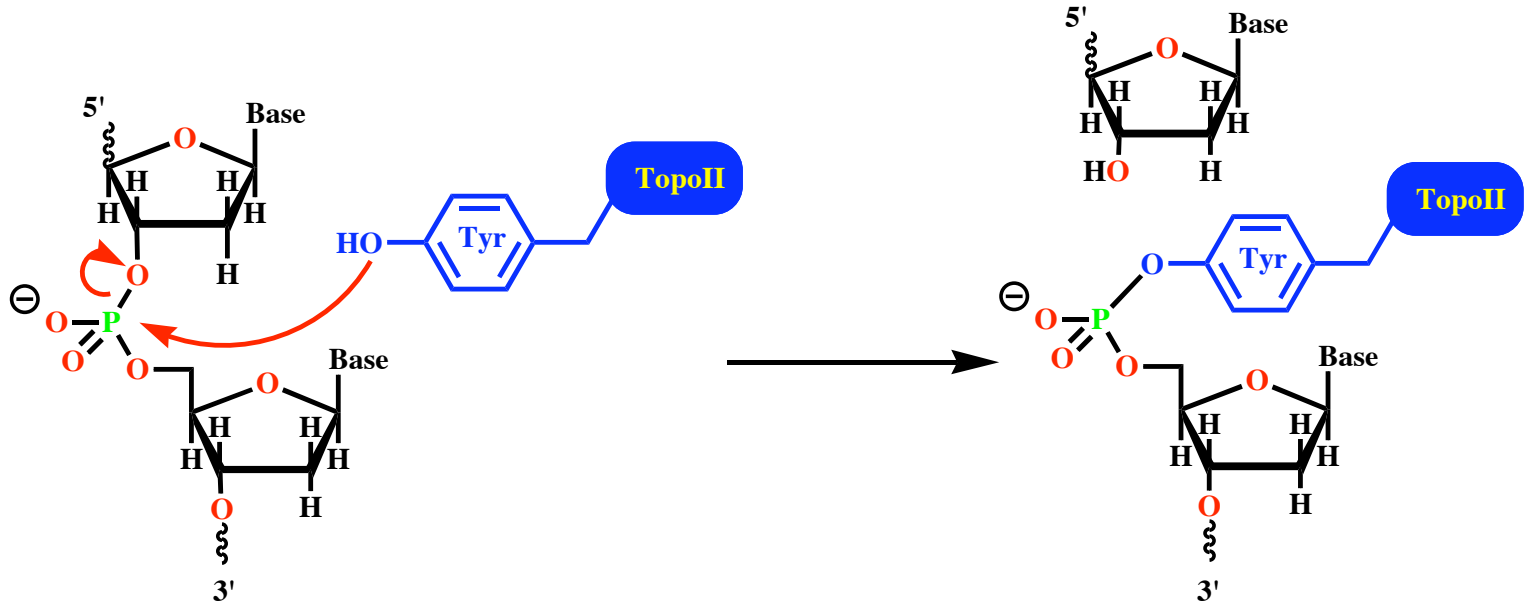
3. DRUGS ACTING ON DNA

Topoisomerase II

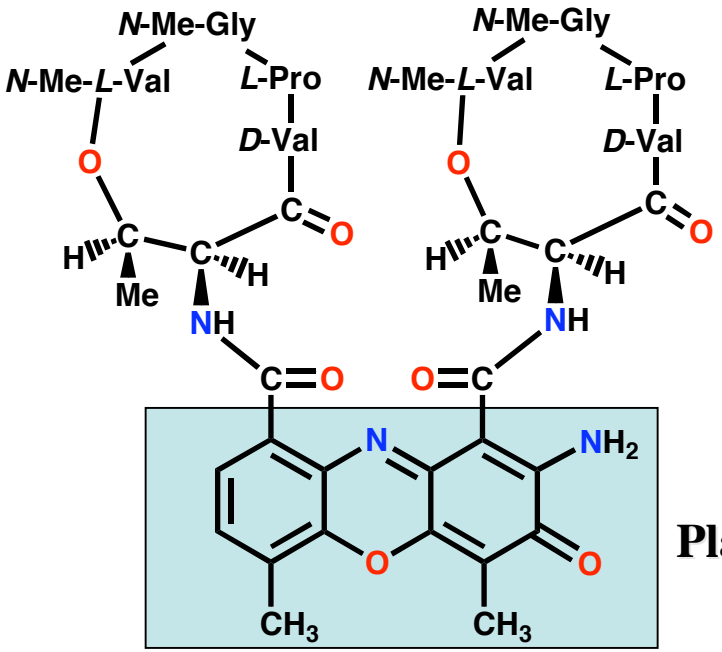
Mechanism of chain cutting



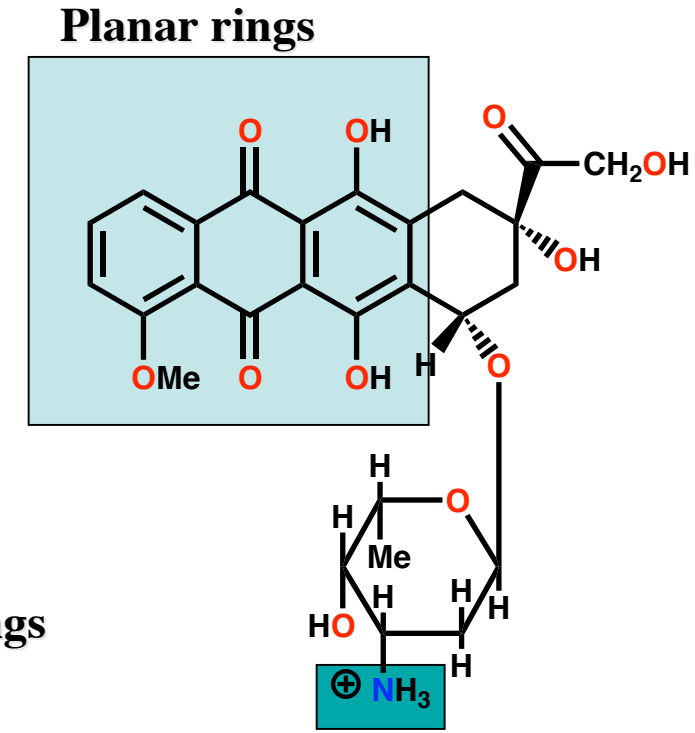
3. DRUGS ACTING ON DNA

3.1 Intercalating agents

Examples



Planar rings



Dactinomycin

Extra binding to sugar phosphate backbone by cyclic peptide

Doxorubicin (Adriamycin)

Extra binding to sugar phosphate backbone by NH_3

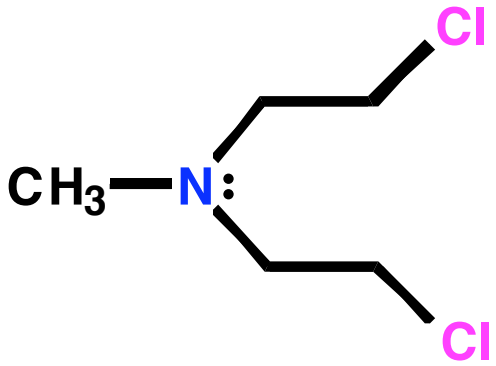
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

- Contain highly electrophilic groups
- Form covalent bonds to nucleophilic groups in DNA (e.g. 7-N of guanine)
- Prevent replication and transcription
- Useful anti-tumour agents
- Toxic side effects (e.g. alkylation of proteins)

Example

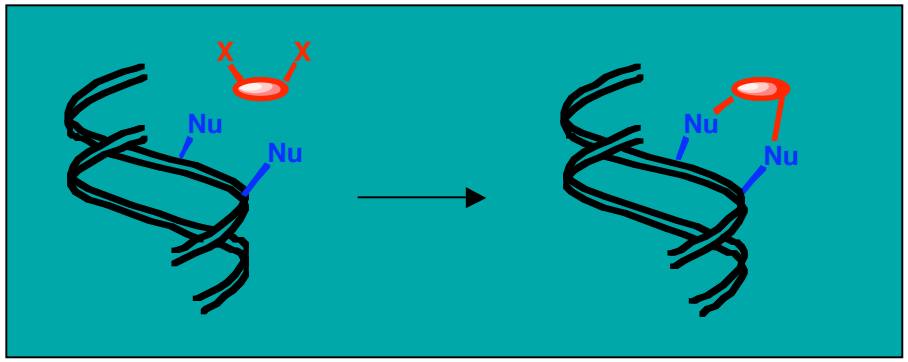
Mechlorethamine (nitrogen mustard)



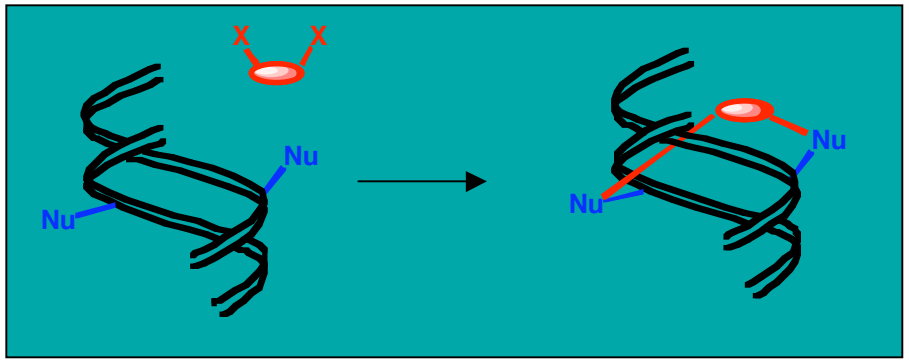
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

Cross linking



Intrastrand cross linking

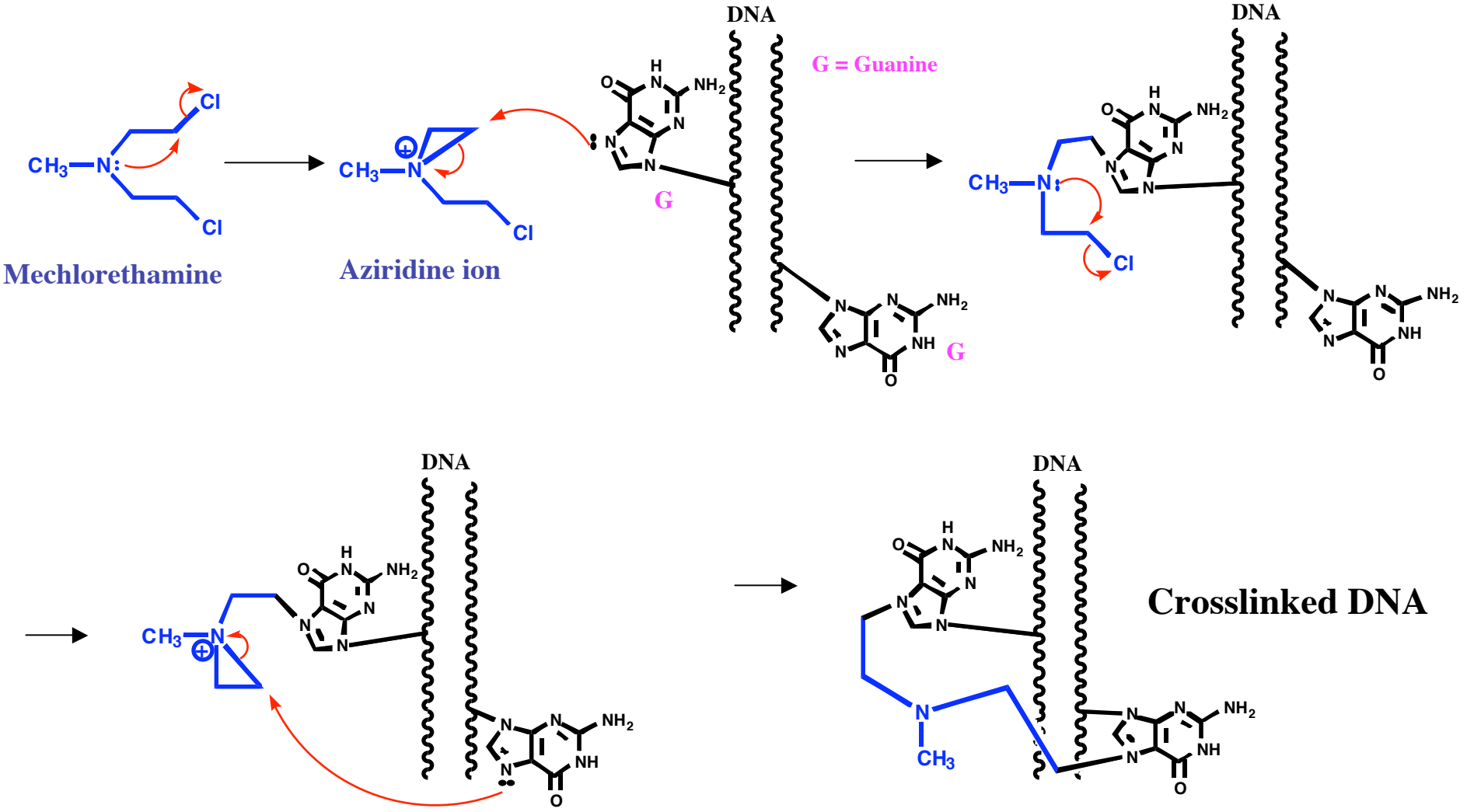


Interstrand cross linking

3. DRUGS ACTING ON DNA

3.2 Alkylating agents

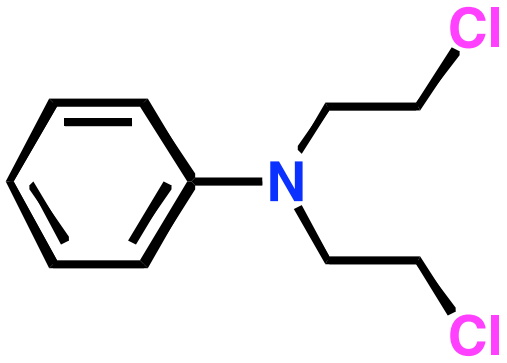
Mechanism of action

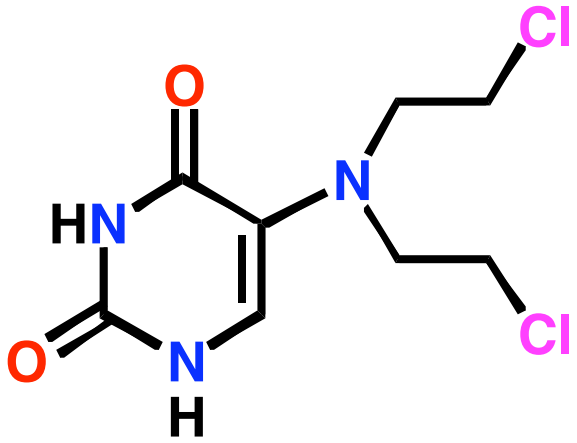


3. DRUGS ACTING ON DNA

3.2 Alkylating agents

Mechlorethamine analogues





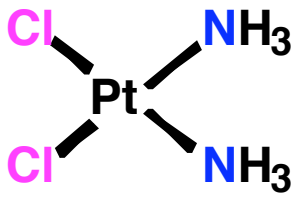
Aromatic ring - e withdrawing effect
N is less nucleophilic
Less reactive alkylating agent
Selective for stronger nucleophiles (e.g. guanine)

Uracil mustard
Used vs leukemia
Attached to a nucleic acid building block
Concentrated in fast growing cells (tumours)
Some selectivity

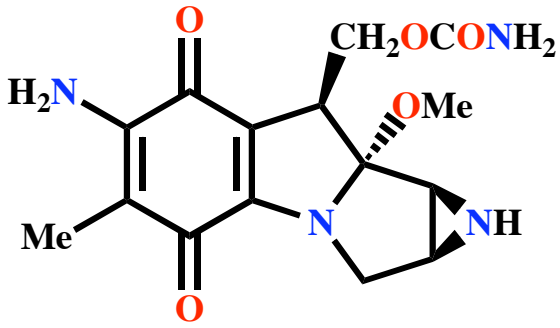
3. DRUGS ACTING ON DNA

3.2 Alkylating agents

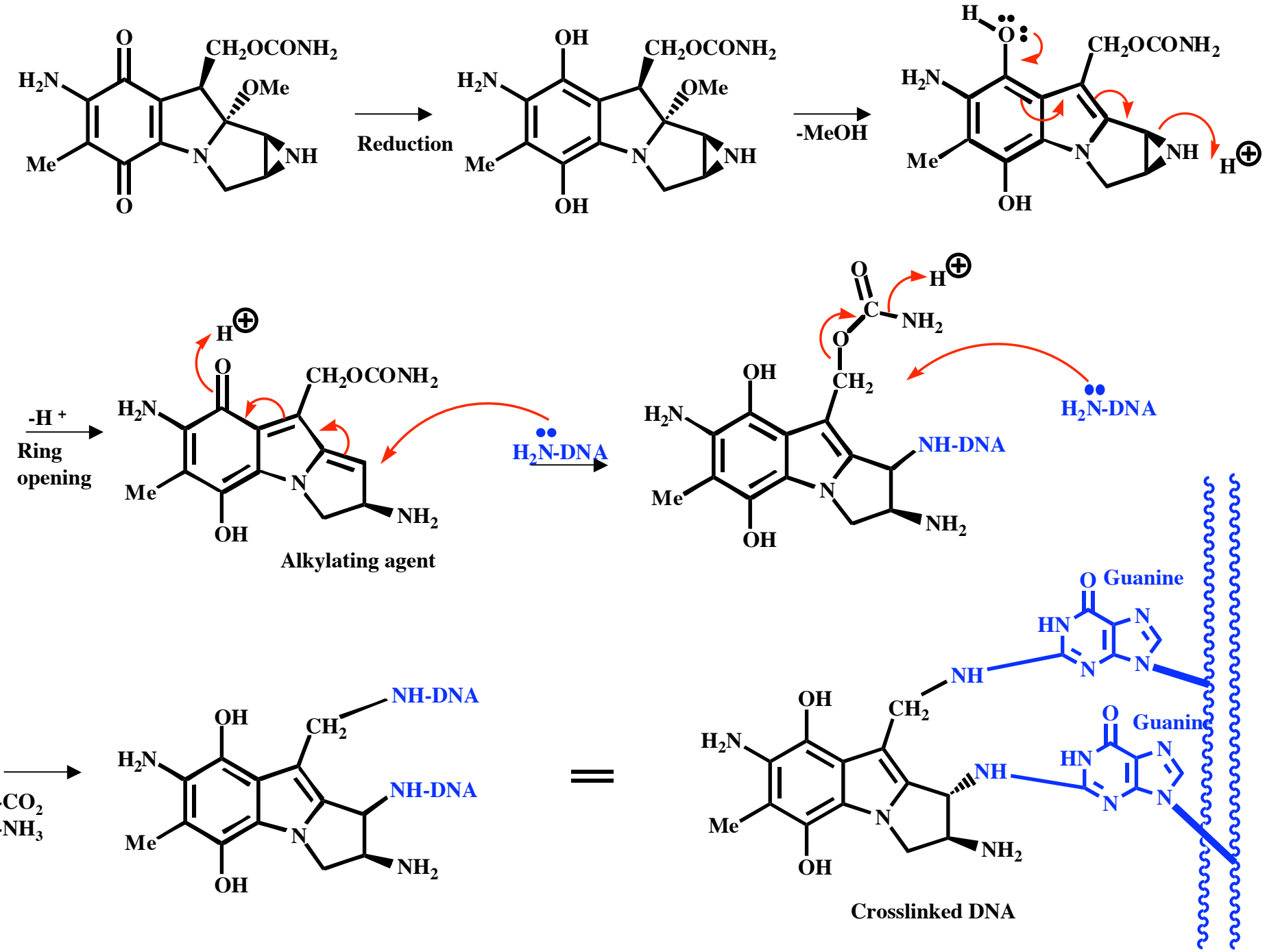
Cisplatin



Mitomycin C

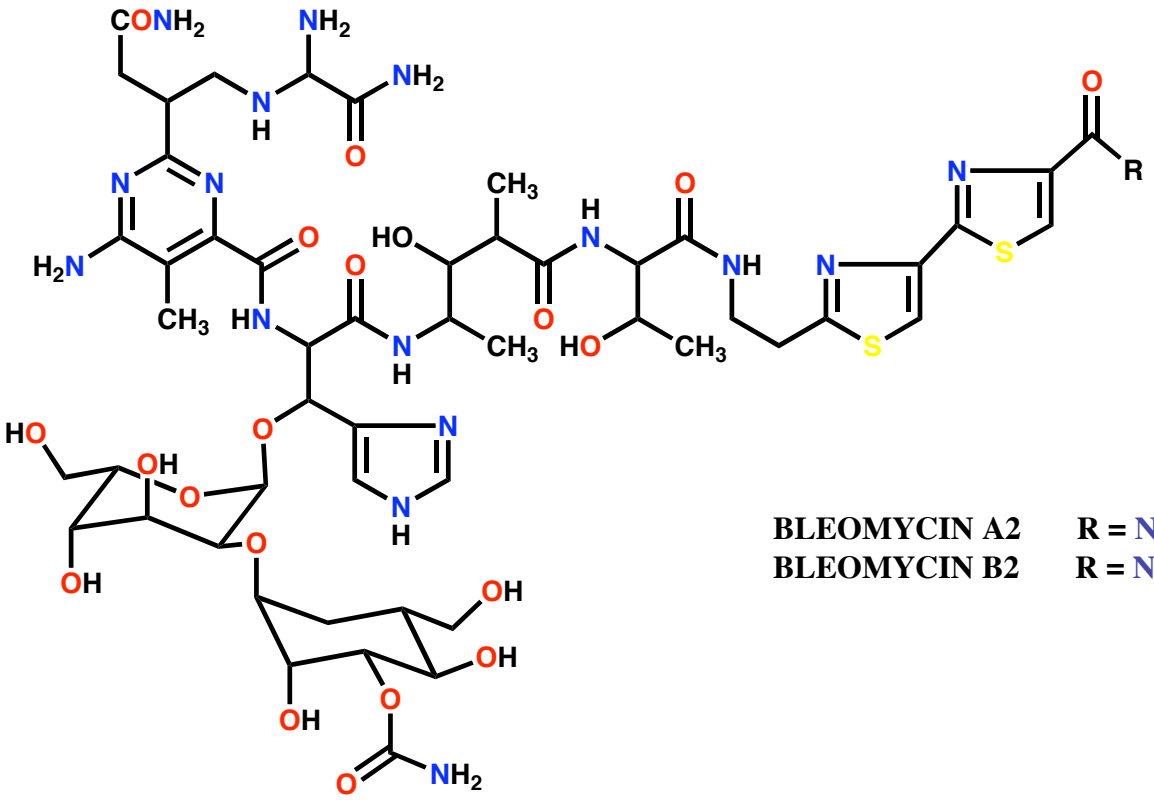


Binds to DNA in regions rich in guanine units Intrastrand links rather than interstrand Inhibits transcription	Converted to alkylating agent in the body


Reduction
-MeOH
-H +
Ring opening
Alkylating agent
H2N-DNA
NH-DNA
-CO2
-NH3
Guanine
Crosslinked DNA

3. DRUGS ACTING ON DNA

3.3 Chain cutters



Bleomycin
Used vs skin cancer

BLEOMYCIN A2 R = $NHCH_2CH_2CH_2SMe_2$
BLEOMYCIN B2 R = $NHCH_2CH_2CH_2CH_2NHC(NH_2)=NH$

- **Abstracts H from DNA to generate radicals**
- **Radicals react with oxygen resulting in chain cutting**
- **Bleomycin also inhibits repair enzymes**

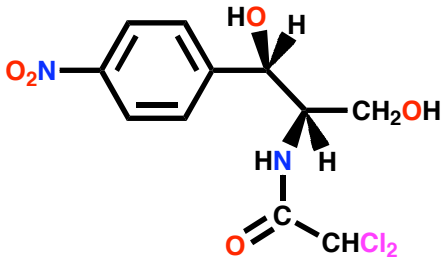
Contents

Part 3: Section 7.3 (Drugs acting on RNA)

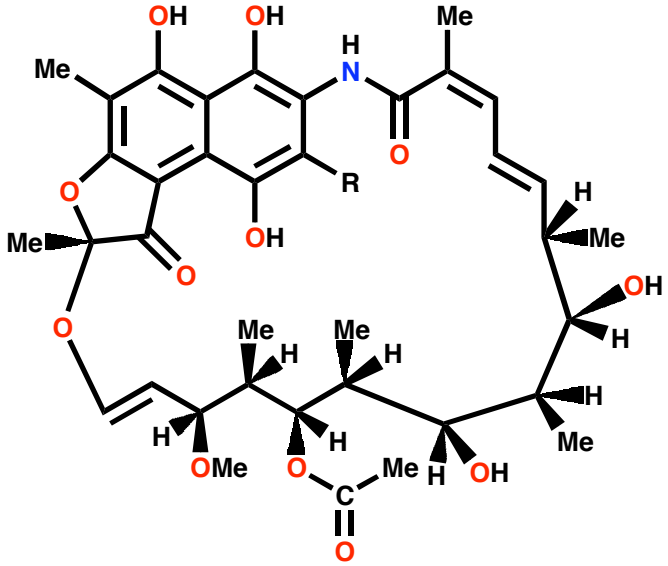
4. Drugs Acting On rRNA
   - Antibiotics
5. Drugs Acting On mRNA
   - Antisense Therapy
   - siRNA
6. Drugs related to nucleic acid building blocks
   - Examples: Antiviral agents
   - Examples

4. DRUGS ACTING ON rRNA

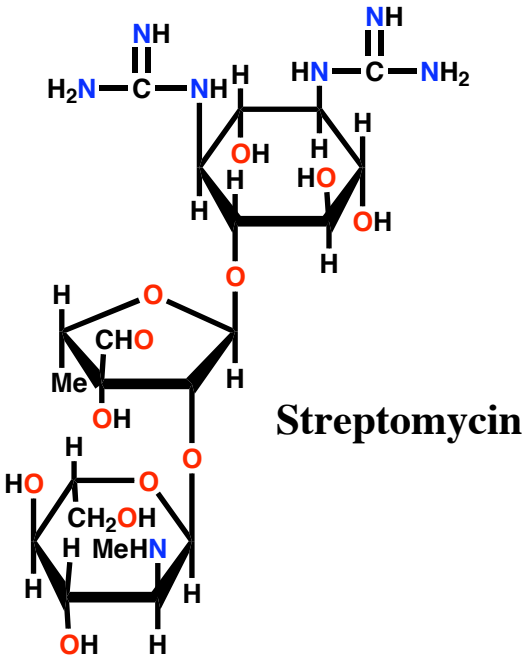
Antibiotics



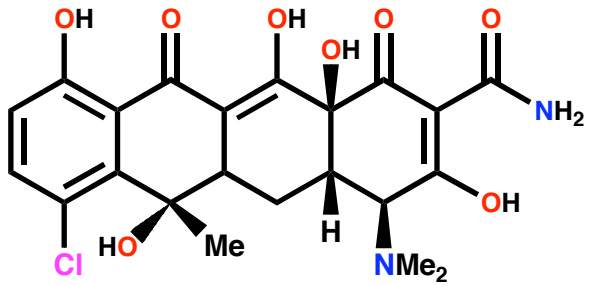
Chloramphenicol
(vs typhoid)



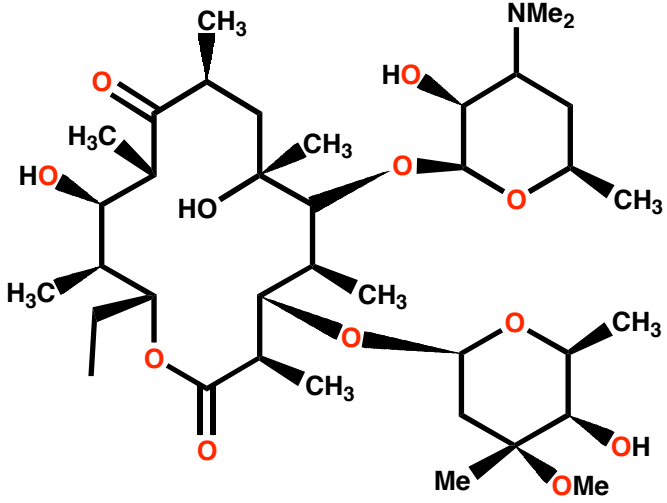
Rifamycins



Streptomycin



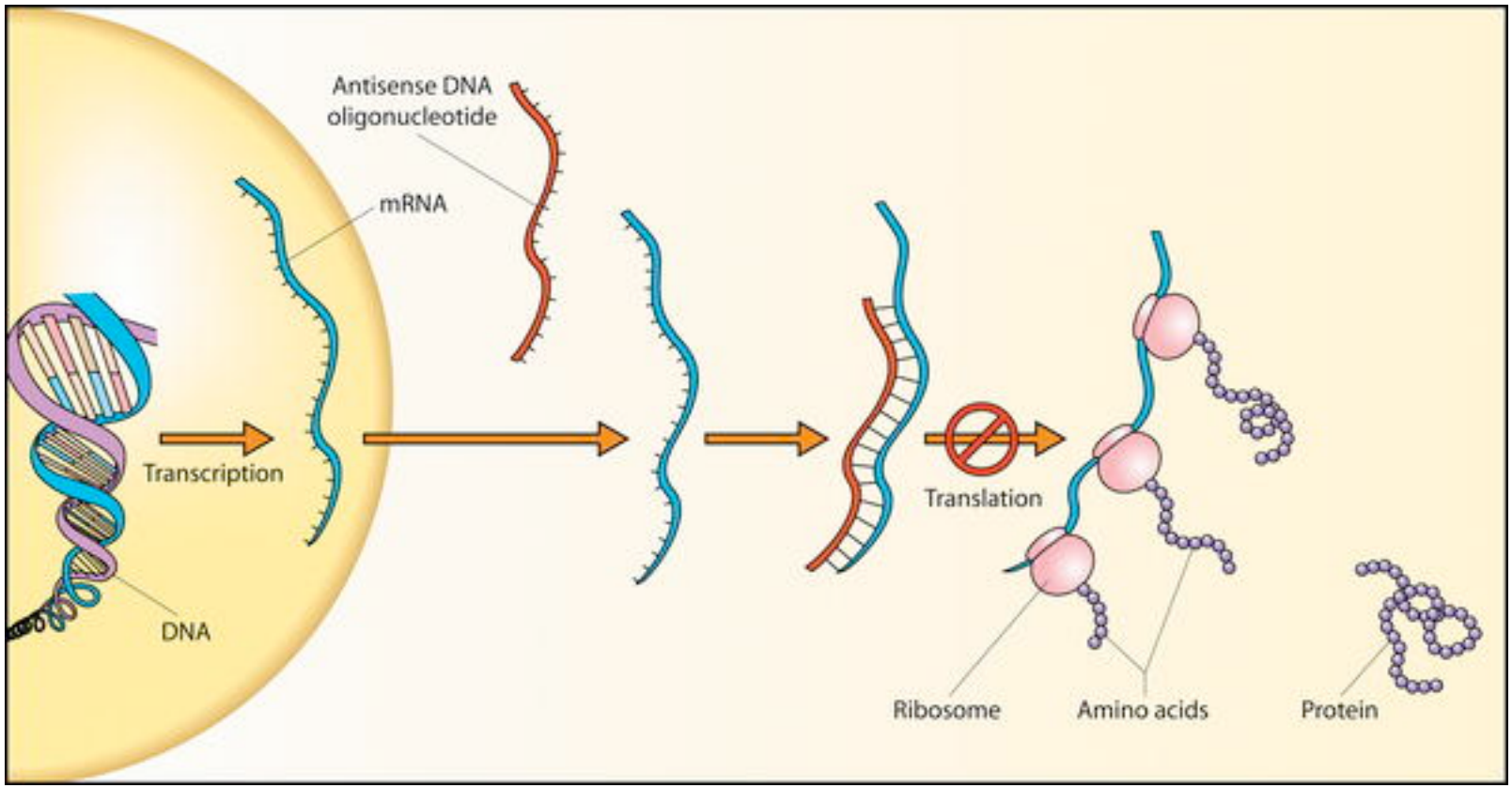
Chlortetracycline
(Aureomycin)



Erythromycin

5. DRUGS ACTING ON mRNA

Antisense RNA Therapy



5. DRUGS ACTING ON mRNA

Antisense Therapy

Advantages

- Same effect as an enzyme inhibitor or receptor antagonist
- Highly specific where the oligonucleotide is 17 nucleotides or more
- Smaller dose levels required compared to inhibitors or antagonists
- Potentially less side effects

Disadvantages

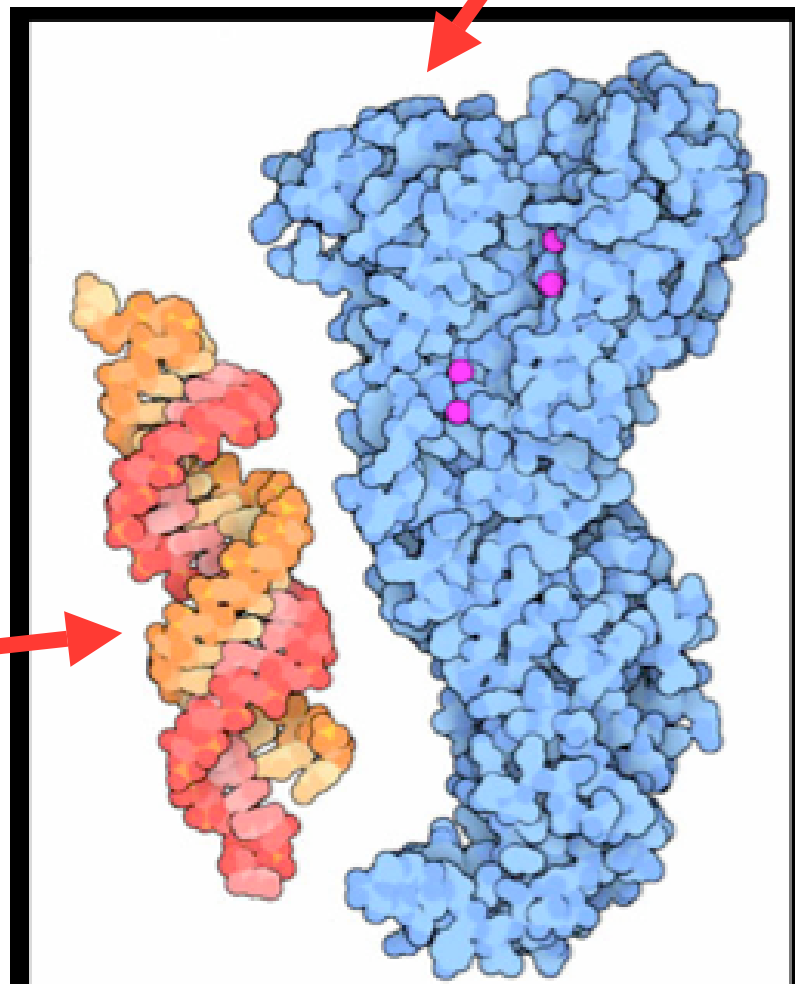
- 'Exposed' sections of mRNA must be targeted
- Instability and polarity of oligonucleotides (pharmacokinetics)
- Short lifetime of oligonucleotides and poor absorption across cell membranes

5. DRUGS ACTING ON *or through* RNA

Small Interfering RNA-siRNA

Targets specific RNA sequences for destruction

si RNA-
ds, ~21BP, 2 base overhang + phosphate



5. DRUGS ACTING ON *or through* RNA

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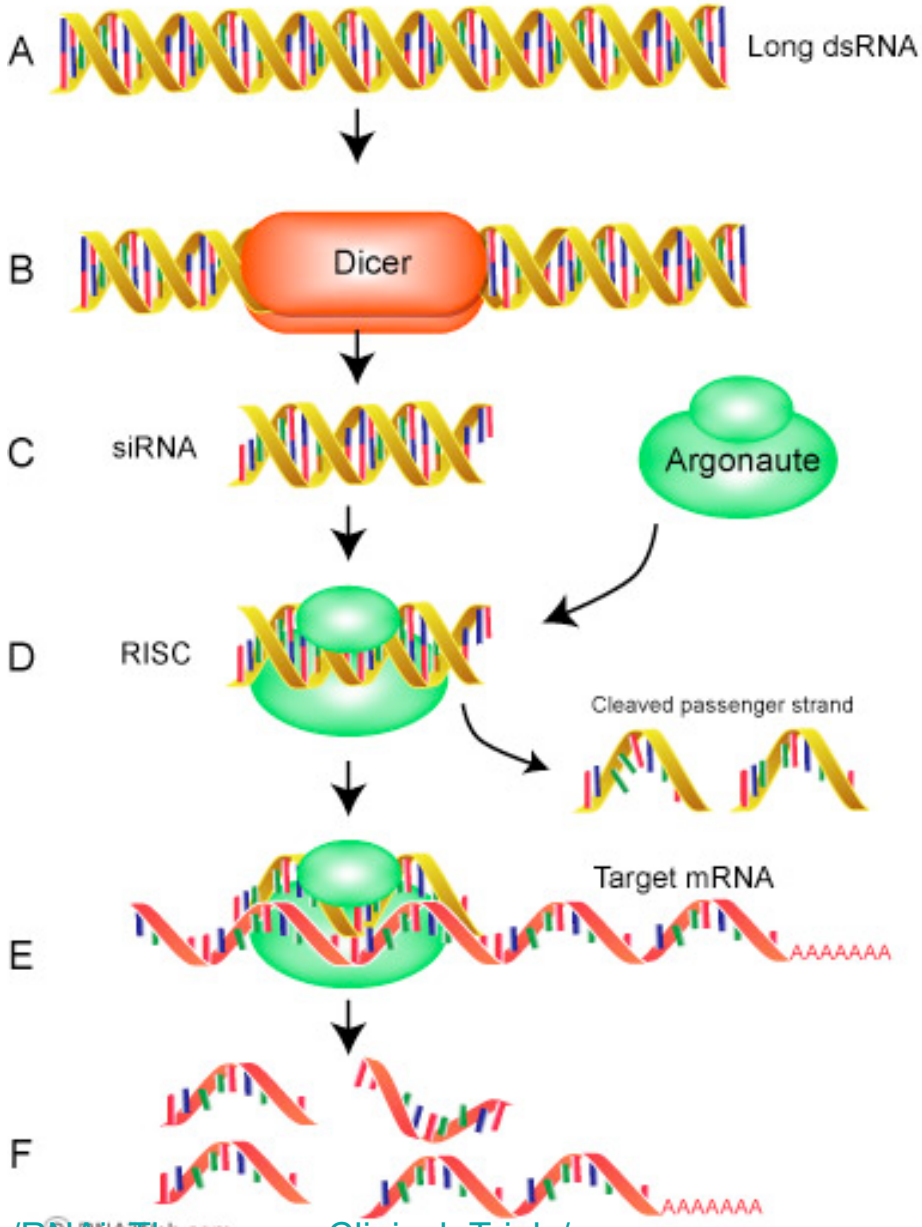
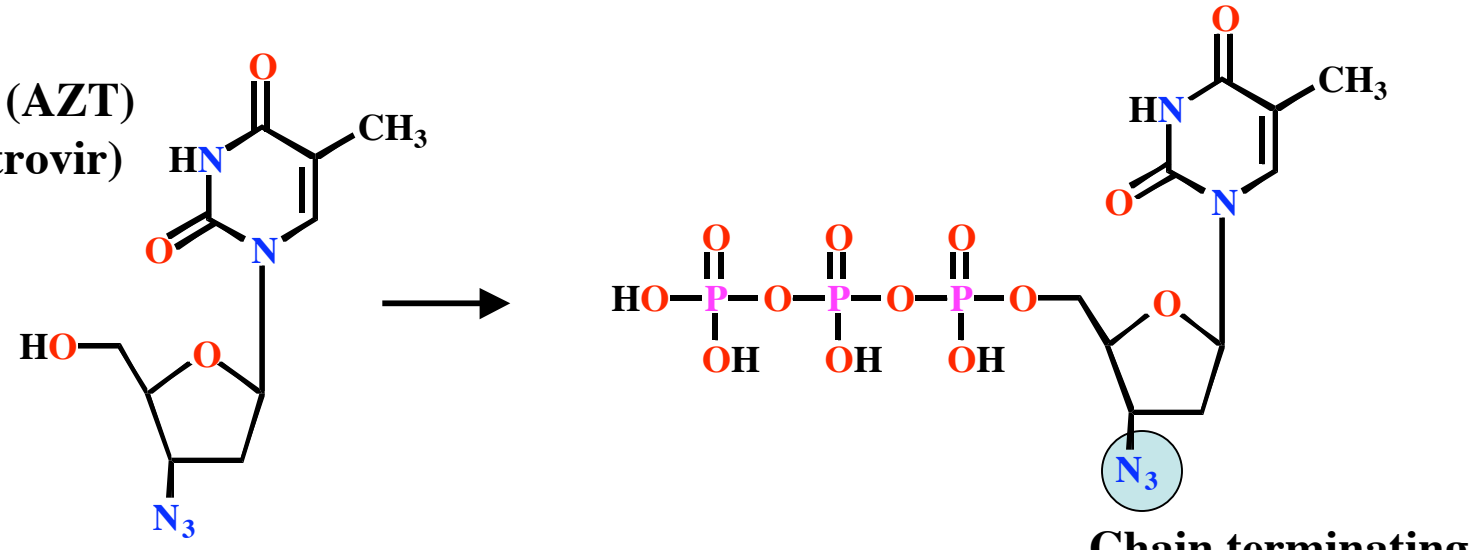


http://www.rnaiweb.com/RNAi/RNAi_Web_Resources/RNAi_Therapy___Clinical_Trials/

6. Drugs related to nucleic acid building blocks

Examples: Antiviral agents

Azidothymidine (AZT)
(Zidovudine;Retrovir)

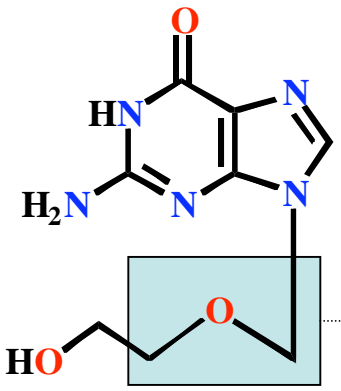


Chain terminating group

- Enzyme inhibitor
- AZT is phosphorylated to a triphosphate in the body
- Triphosphate has two mechanisms of action
  - inhibits a viral enzyme (reverse transcriptase)
  - added to growing DNA chain and acts as chain terminator

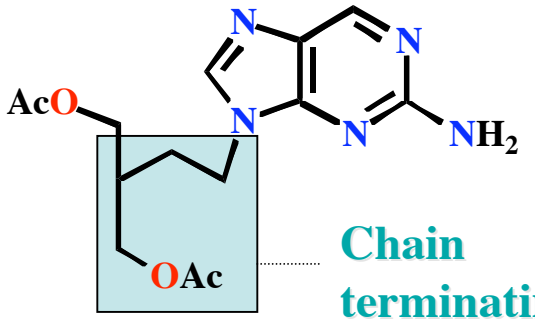
6. Drugs related to nucleic acid building blocks

Examples: **Antiviral agents**



Chain terminating group

Acyclovir
(Zovirax)



Chain terminating group

Famciclovir
(Famvir)

Notes:

Same mechanisms of action as AZT

Used vs herpes simplex and shingles