

Medicinal Chemistry/ CHEM 458/658

Chapter 10 – Nucleic Acids

Bela Torok

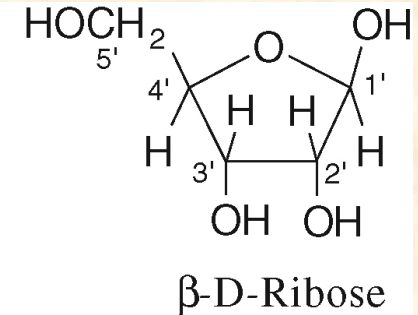
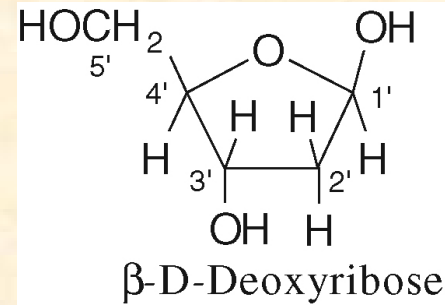
Department of Chemistry

University of Massachusetts Boston

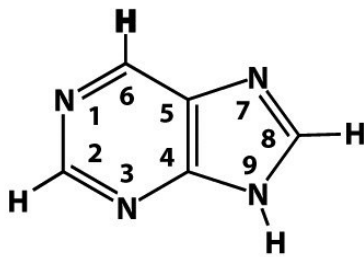
Boston, MA

Introduction

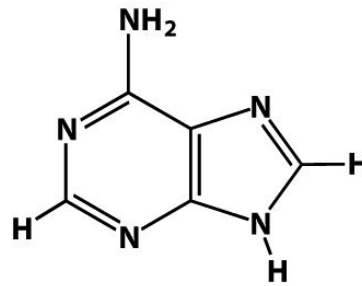
- Nucleic acids – major components
 - carbohydrate
 - base
 - phosphate



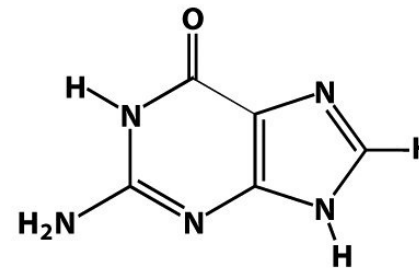
PURINES



Purine

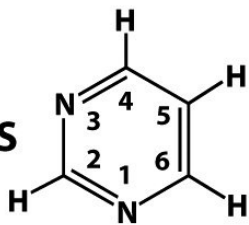


Adenine

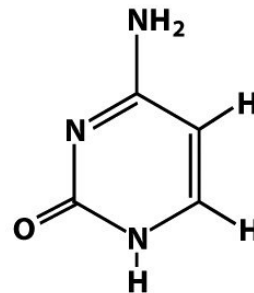


Guanine

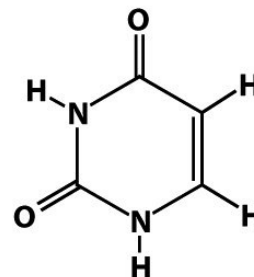
PYRIMIDINES



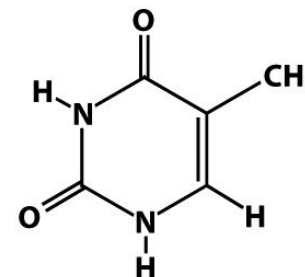
Pyrimidine



Cytosine



Uracil



Thymine

Introduction

- Nucleic acids – nucleosides, nucleotides

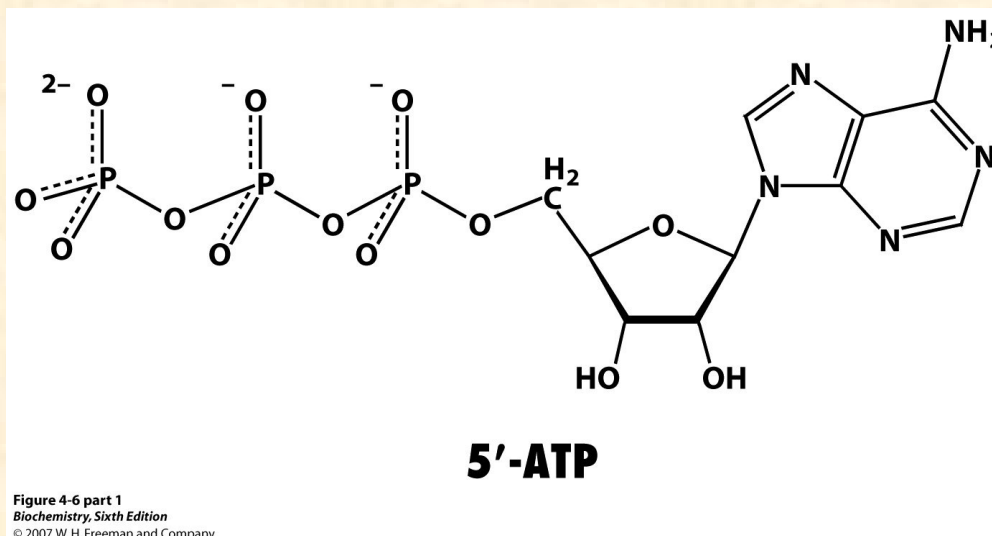
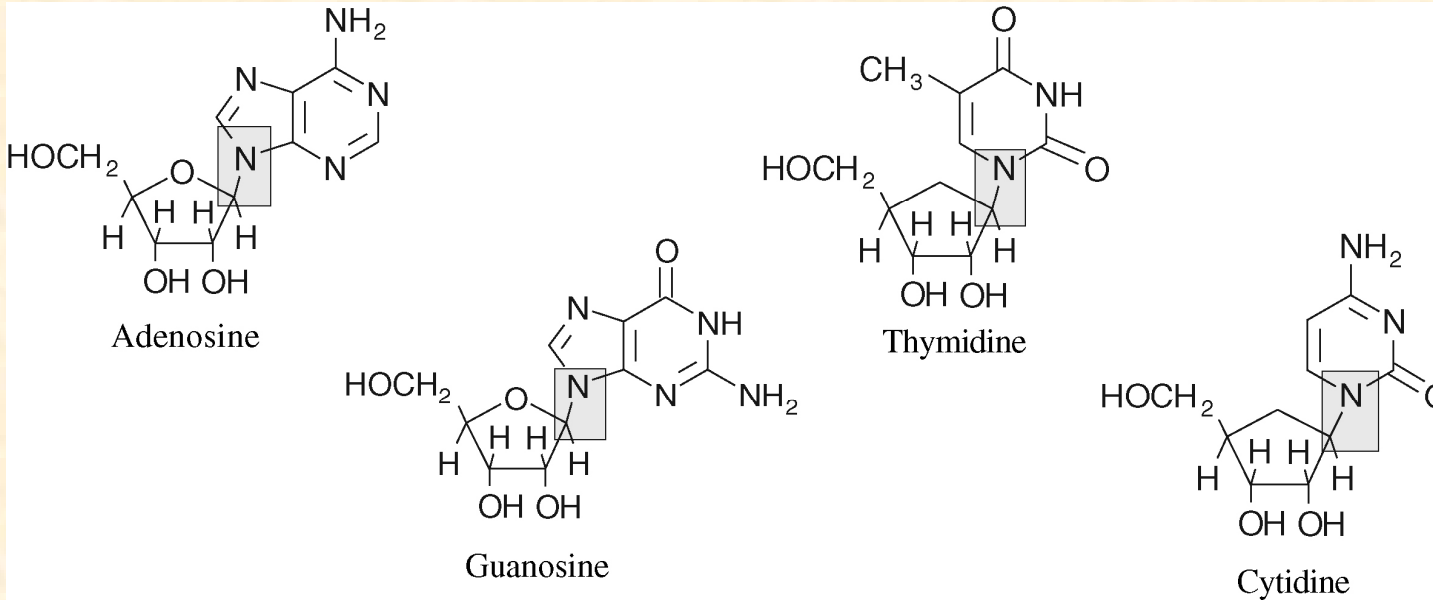


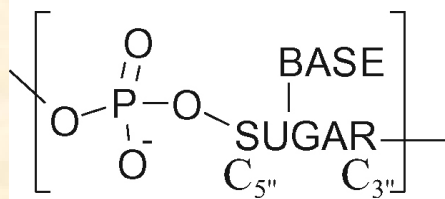
Figure 4-6 part 1
Biochemistry, Sixth Edition
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Introduction

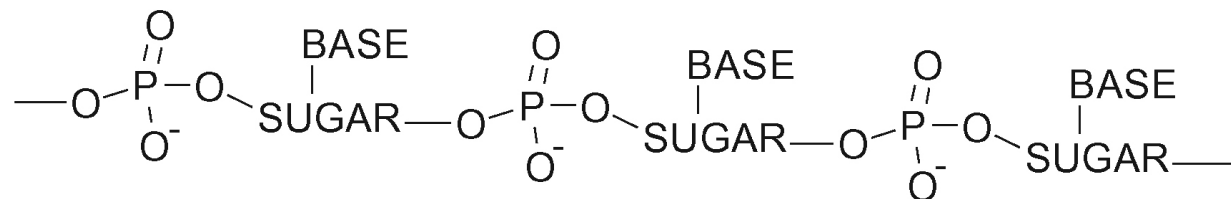
- Nucleic acids – nucleosides, nucleotides

TABLE 25.1 Nomenclature of bases, nucleosides, and nucleotides

RNA		
Base	Ribonucleoside	Ribonucleotide (5'-monophosphate)
Adenine (A)	Adenosine	Adenylate (AMP)
Guanine (G)	Guanosine	Guanylate (GMP)
Uracil (U)	Uridine	Uridylate (UMP)
Cytosine (C)	Cytidine	Cytidylate (CMP)
DNA		
Base	Deoxyribonucleoside	Deoxyribonucleotide (5'-monophosphate)
Adenine (A)	Deoxyadenosine	Deoxyadenylate (dAMP)
Guanine (G)	Deoxyguanosine	Deoxyguanylate (dGMP)
Thymine (T)	Thymidine	Thymidylate (TMP)
Cytosine (C)	Deoxycytidine	Deoxycytidylate (dCMP)



(a)



(b)

DNA

- Basic structure

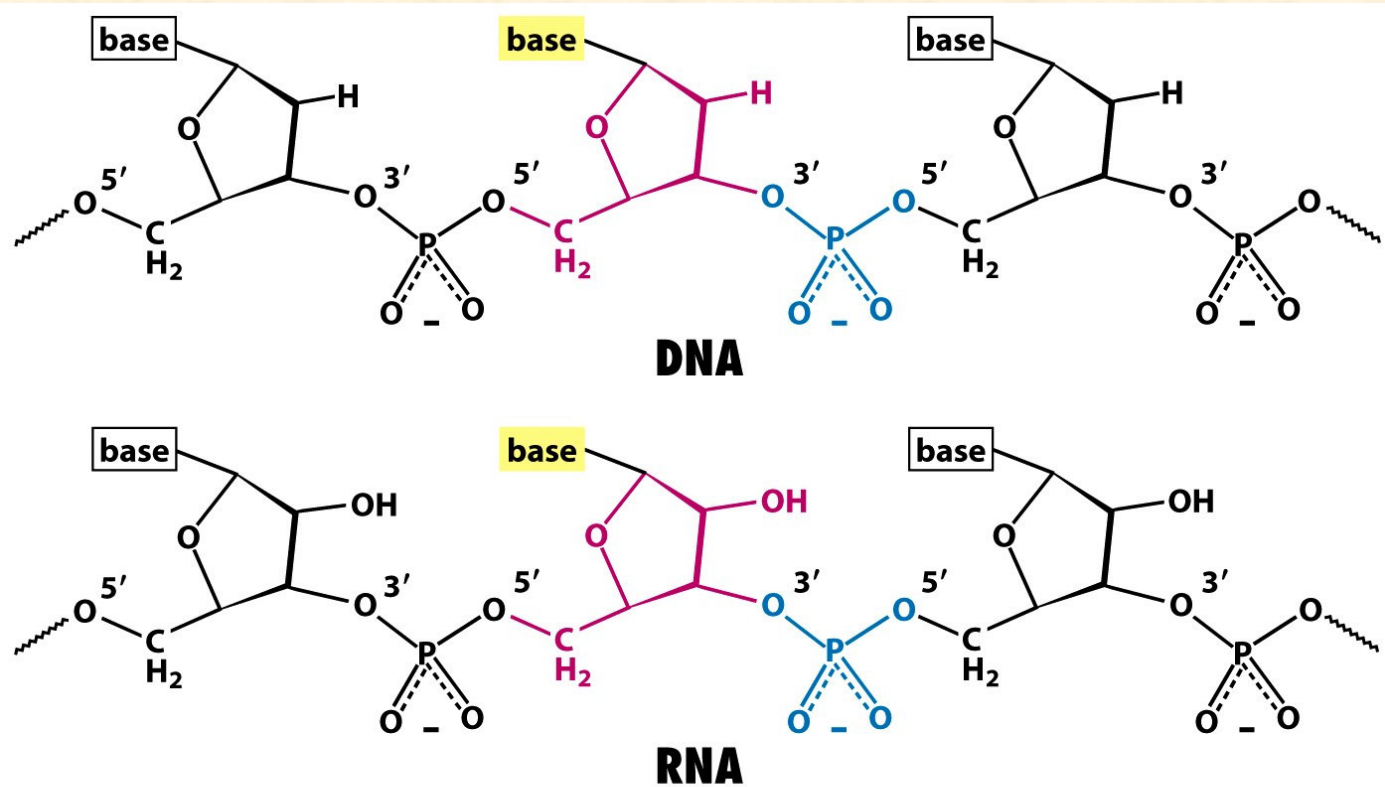
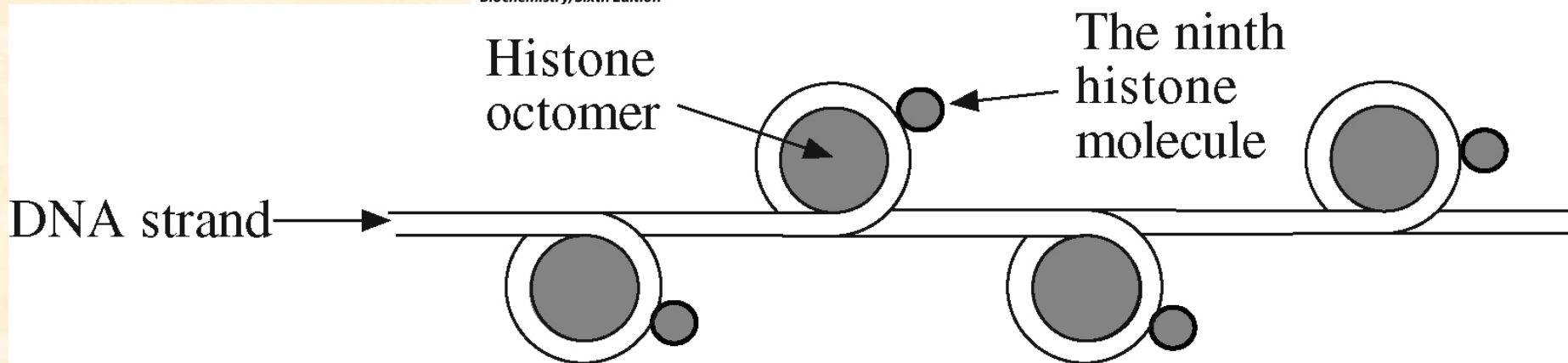


Figure 4-3
Biochemistry, Sixth Edition



DNA

- Structure

Table 10.4
Historical Landmarks in Early DNA Biochemistry

Date	Researcher(s)	Discovery
1868	Friedrich Miescher	Isolated and studied a phosphorus-containing substance from cell nuclei and salmon sperm cells. Miescher called the substance “nuclein” and suggested it was associated with cellular inheritance.
1928	Frederick Griffith	Defined a genetic “transforming principle” in the pneumococcus bacterium.
1929	Phoebus Levine	Used chemical analysis to determine four types of bases (A, T, G, C) as important building blocks of DNA.
1944	Oswald Avery Colin MacLeod Maclyn McCarty	Showed that Griffith’s bacterial transforming factor is not protein but DNA. The three published experimental evidence that DNA is a component in chromosomes and the principal agent involved in the transfer of genetic information.
1950	Alfred Hershey Martha Chase	Used viruses in experiments to confirm DNA is the genetic material.
1952	Erwin Chargaff	Studied the composition of DNA from different species and found the ratios of adenine to thymine and of guanine to cytosine to be 1.0.
1952	Maurice Wilkins Rosalind Franklin	Studied X-ray diffraction of DNA crystals and found periodic patterns implying repeating structural units in DNA.
1953	James Watson Francis Crick	Formulated a three-dimensional structure (double helix) for DNA that accounted for X-ray diffraction and A–T and G–C equivalence data.

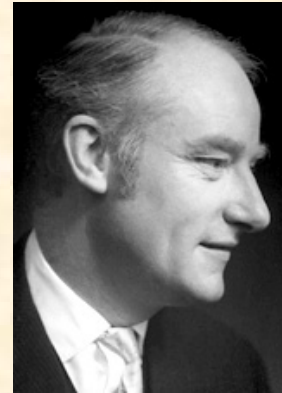
Table 10-4 Concepts in Biochemistry, 3/e
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DNA

- Structure



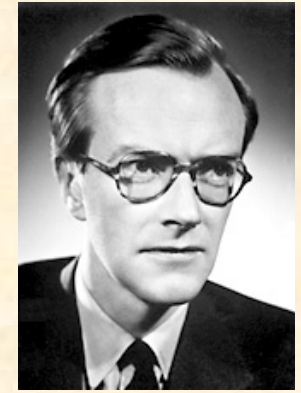
Nobel Prize
In Medicine
1962



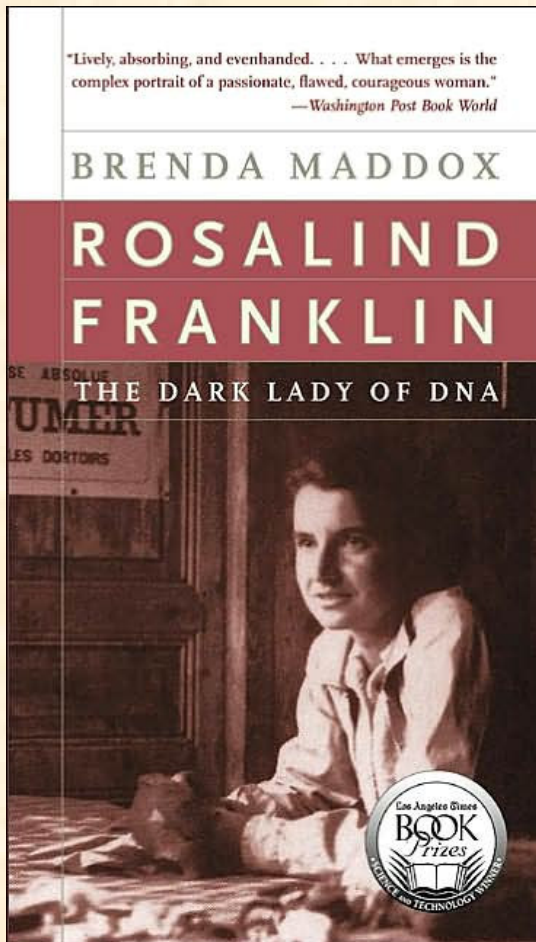
Francis H. C.
Crick



James D.
Watson

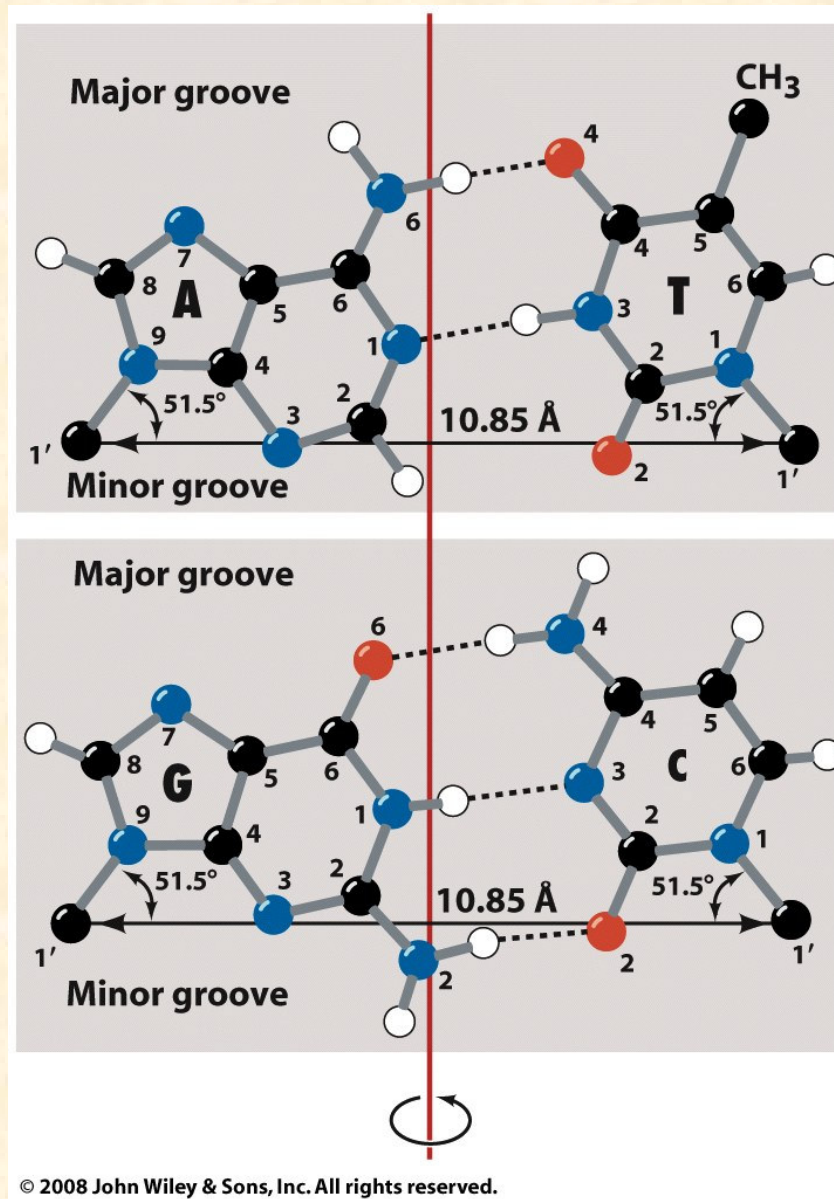
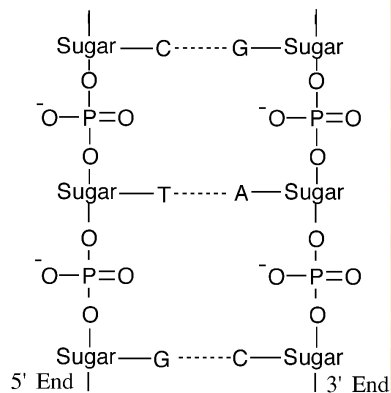
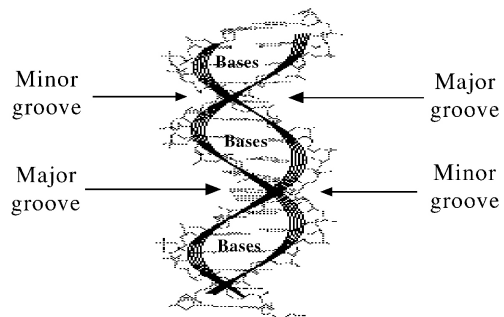


Maurice H. F.
Wilkins



DNA

- Structure

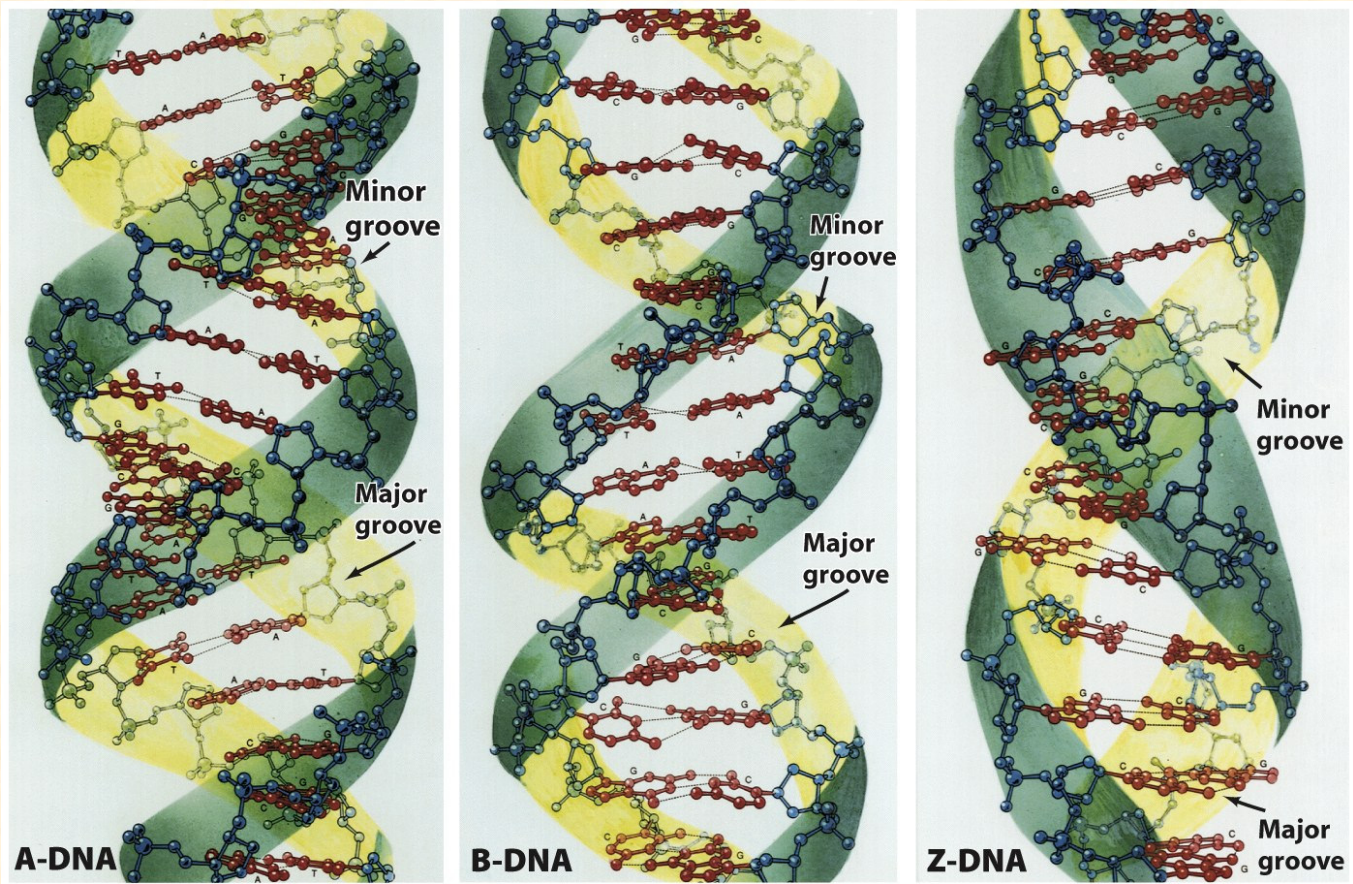


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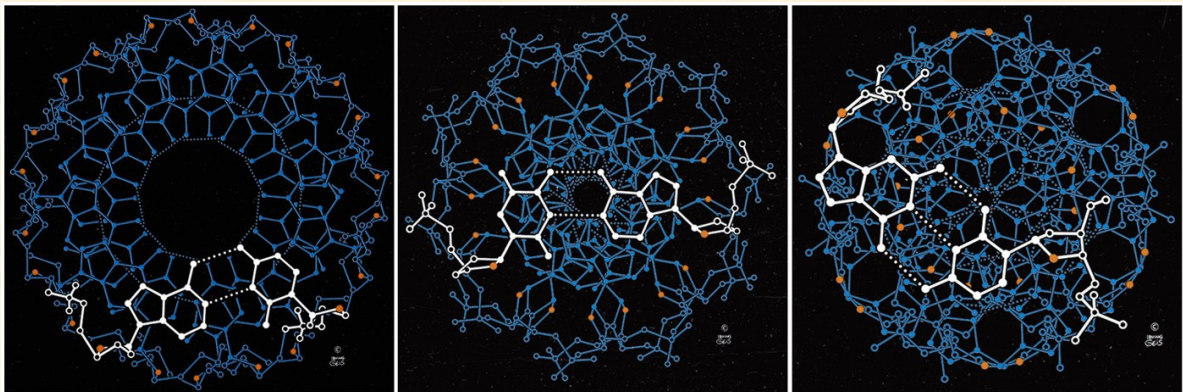


DNA

- Structure



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DNA

- Structure

Table 24-1 Structural Features of Ideal A-, B-, and Z-DNA

	A	B	Z
Helical sense	Right handed	Right handed	Left handed
Diameter	~26 Å	~20 Å	~18 Å
Base pairs per helical turn	11.6	10	12 (6 dimers)
Helical twist per base pair	31°	36°	60° (per dimer)
Helix pitch (rise per turn)	34 Å	34 Å	44 Å
Helix rise per base pair	2.9 Å	3.4 Å	7.4 Å per dimer
Base tilt normal to the helix axis	20°	6°	7°
Major groove	Narrow and deep	Wide and deep	Flat
Minor groove	Wide and shallow	Narrow and deep	Narrow and deep
Sugar pucker	C3'-endo	C2'-endo	C2'-endo for pyrimidines; C3'-endo for purines
Glycosidic bond conformation	Anti	Anti	Anti for pyrimidines; syn for purines

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DNA



- General Functions
 - repository for genetic information (genes)
 - to reproduce itself to maintain genetic information (replication)
 - to supply the information for protein synthesis (template)

DNA

- Genes
 - several hundred to 2000 bases
 - complete set : genome

	Exon	Intron	Exon	Intron	Exon	
	240	120	500	240	250	
	bases	bases	bases	bases	bases	

DNA

• Replication

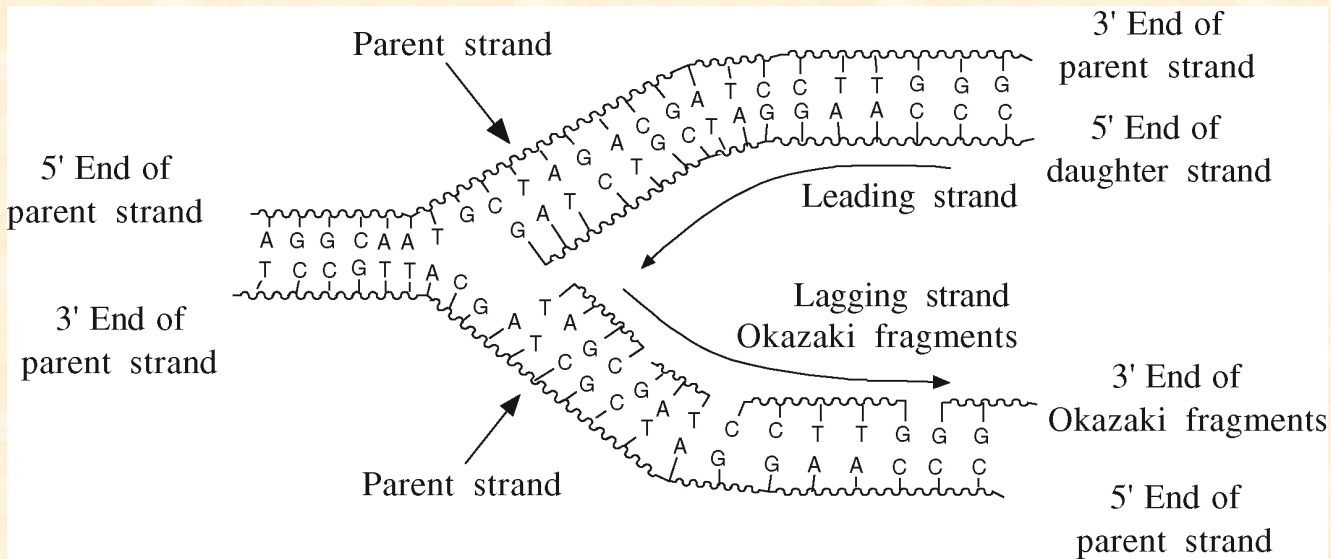
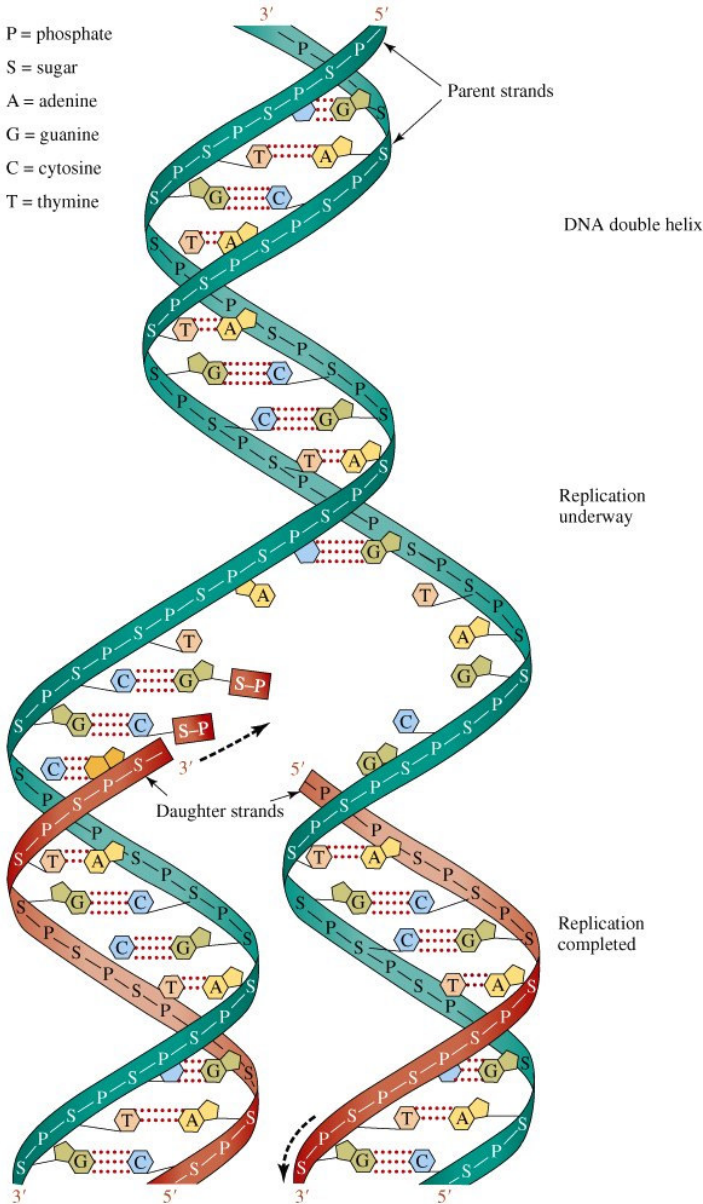
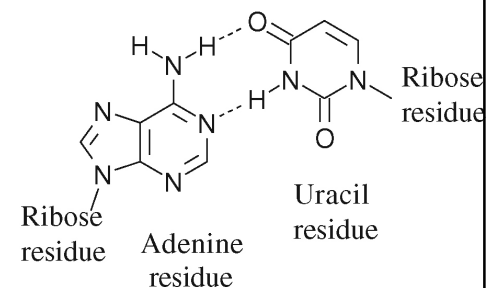
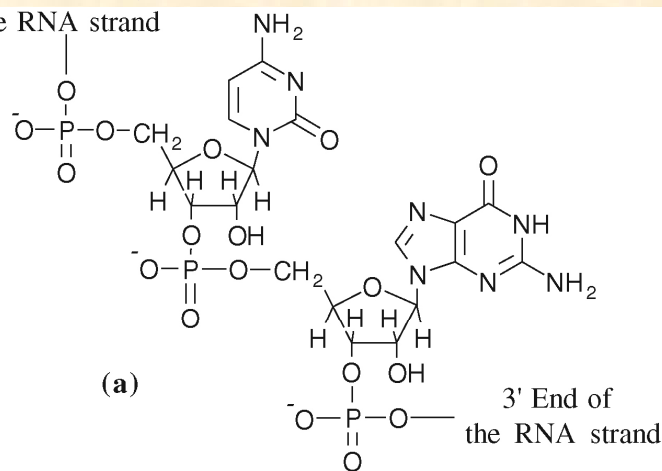
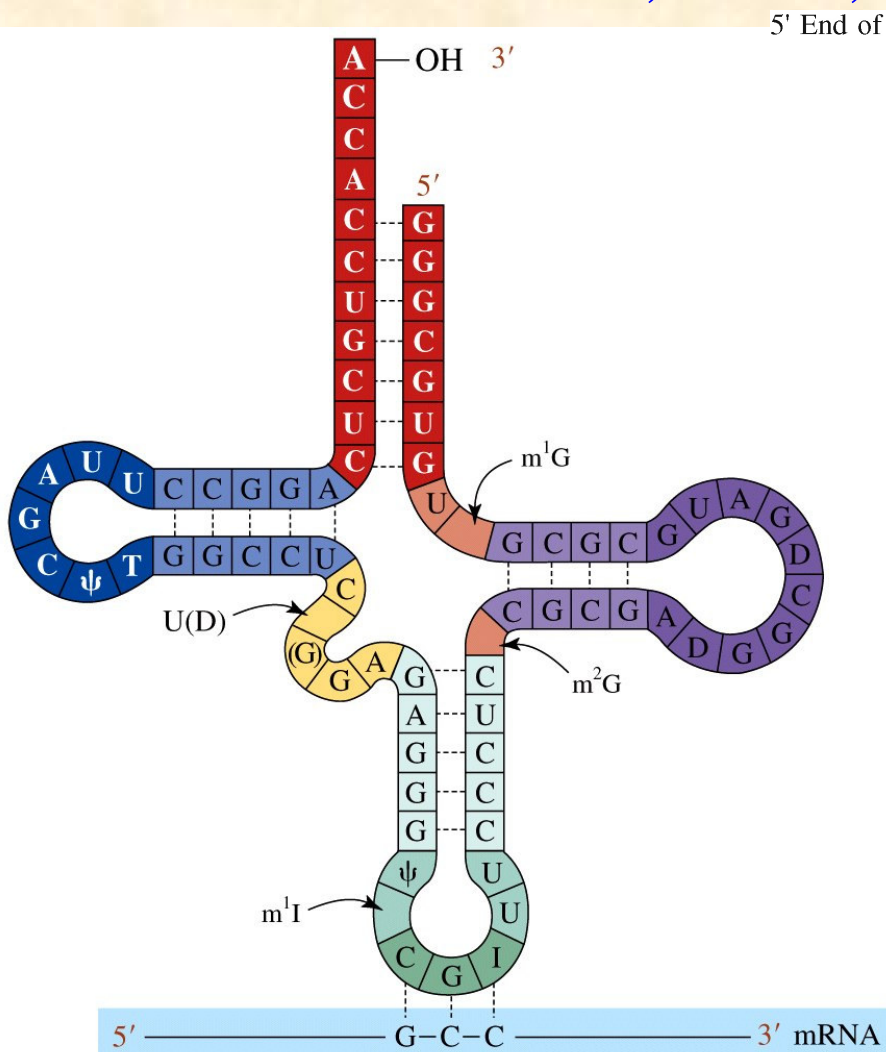


Figure 10-11 Concepts in Biochemistry, 3/e © 2006 John Wiley & Sons

RNA

- in nucleus and cytoplasm (ribosomes)
 - classified by the role in protein synthesis

mRNA, tRNA, rRNA,



Messenger RNA



- mRNA carries the genetic information
 - protein synthesis
 - produced from hnRNA by removal of introns – continuous sequence
 - code deciphered by Nirenberg (1960s)
 - the mRNA codon code is the genetic code

Messenger RNA

- the genetic code

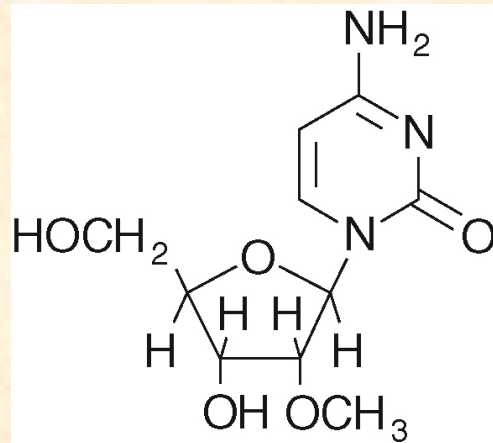
Table 12.2
The genetic code

		Second Base of Codon				
		U	C	A	G	
First Base of Codon	U	UUU } Phe	UCU } Ser	UAU } Tyr	UGU } Cys	U
		UUC } Leu	UCC } Ser	UAC } Tyr	UGC } Cys	C
		UUA } Leu	UCA } Ser	UAA } Stop	UGA } Stop	A
		UUG } Leu	UCG } Ser	UAG } Stop	UGG } Trp	G
	C	CUU } Leu	CCU } Pro	CAU } His	CGU } Arg	U
		CUC } Leu	CCC } Pro	CAC } His	CGC } Arg	C
		CUA } Leu	CCA } Pro	CAA } Gln	CGA } Arg	A
		CUG } Leu	CCG } Pro	CAG } Gln	CGG } Arg	G
	A	AUU } Ile	ACU } Thr	AAU } Asn	AGU } Ser	U
		AUC } Ile	ACC } Thr	AAC } Asn	AGC } Ser	C
		AUA } Ile	ACA } Thr	AAA } Lys	AGA } Arg	A
		AUG } Met	ACG } Thr	AAG } Lys	AGG } Arg	G
	G	GUU } Val	GCU } Ala	GAU } Asp	GGU } Gly	U
		GUC } Val	GCC } Ala	GAC } Asp	GGC } Gly	C
		GUA } Val	GCA } Ala	GAA } Glu	GGA } Gly	A
		GUG } Val	GCG } Ala	GAG } Glu	GGG } Gly	G

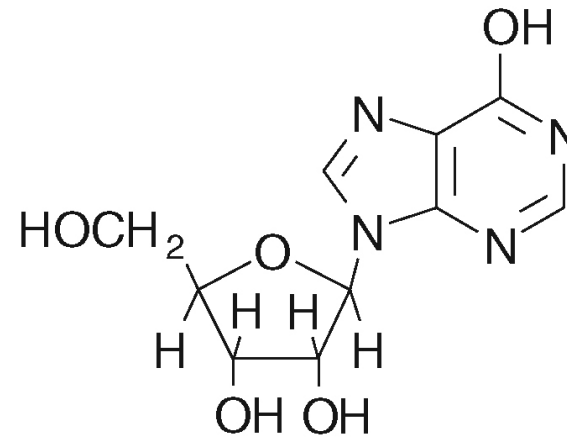
Note: AUG is the start codon and UAA, UAG, and UGA are stop codons as highlighted in table.

Transfer RNA

- tRNA carries amino acids to the ribosomes
 - protein synthesis
 - small, 73-94 nucleotides
 - each amino acid has its own tRNA
 - site recognition on mRNA – anticodon



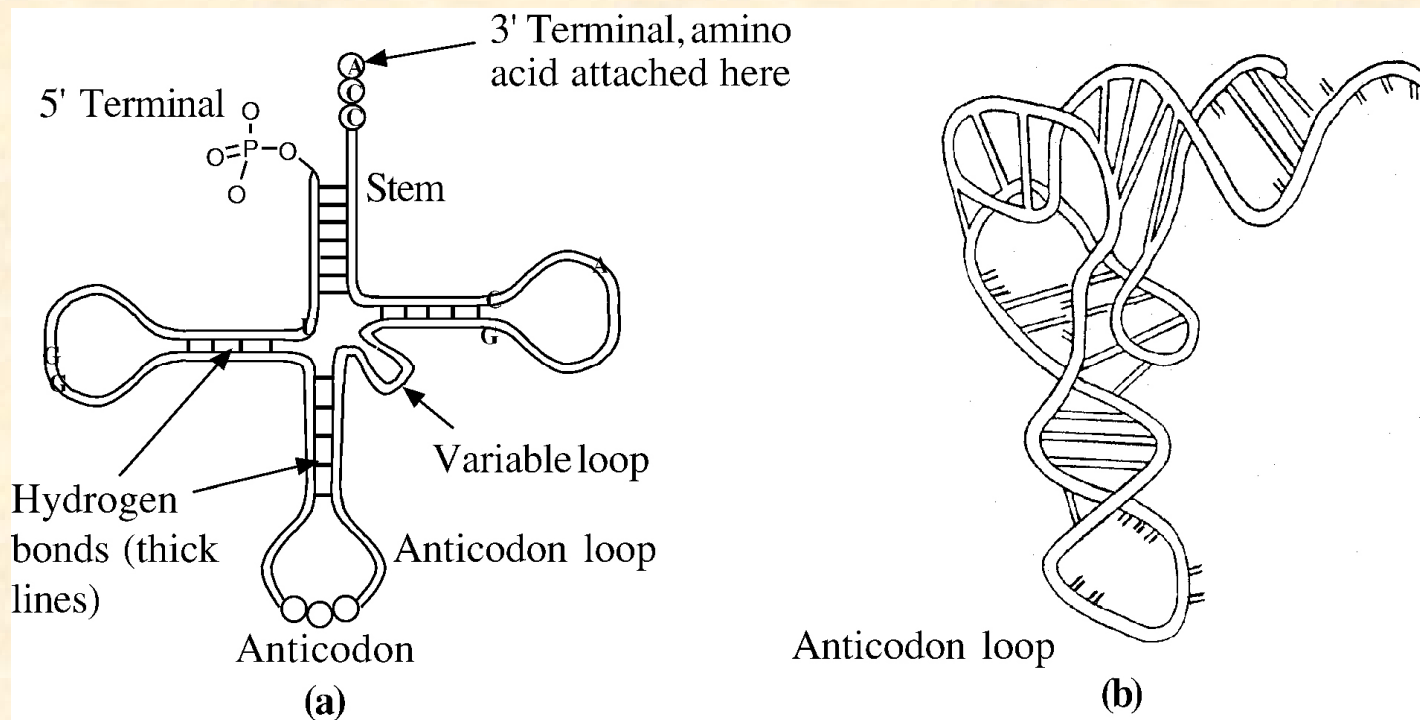
2'-*O*-Methylguanosine



Inosine

Transfer RNA

- tRNA carries amino acids to the ribosomes
 - protein synthesis
 - small, 73-94 nucleotides
 - each amino acid has its own tRNA
 - site recognition on mRNA – anticodon



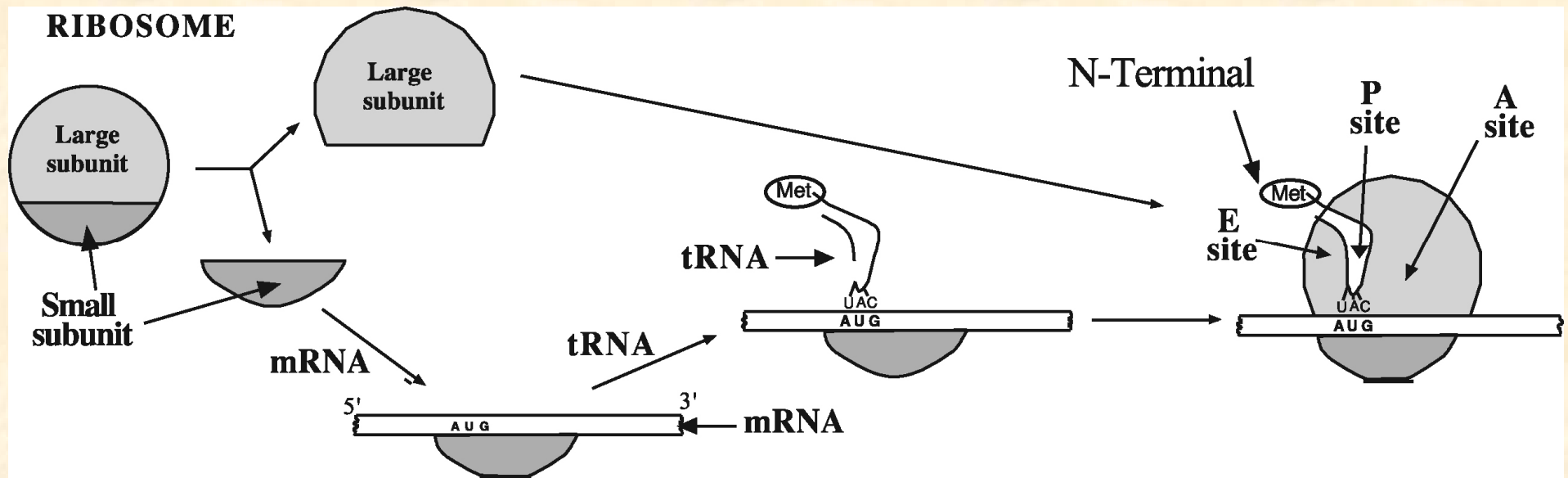
Ribosomal RNA



- Protein - rRNA mixture
 - 35% protein, 65% rRNA
 - 1500 – 2000 nucleotides

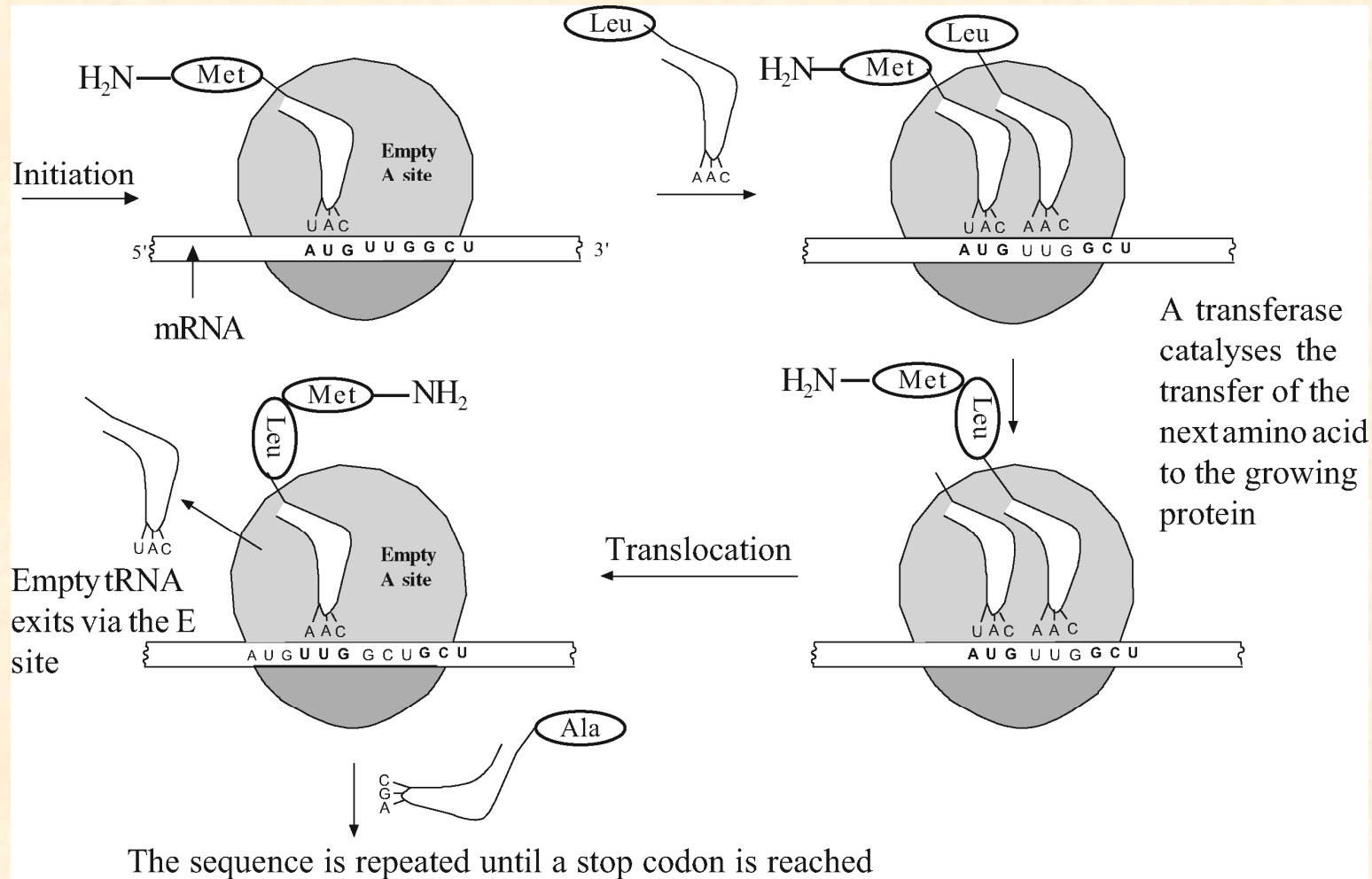
Protein Synthesis

- Initiation



Protein Synthesis

• Elongation



• Termination

Protein Synthesis

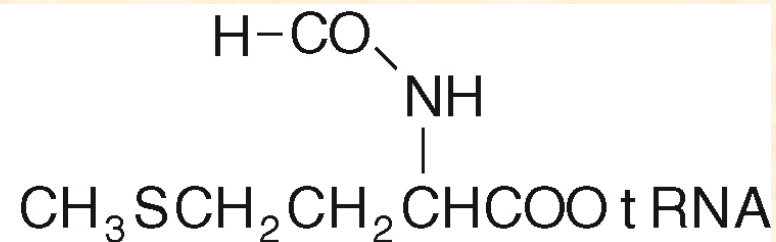


- Prokaryotic cells

- Shine-Dalgarno sequences

ϕ X174 phage A protein	-AAU-CUU- GGA-GGC -UUU-UUU- AUG -GUU-CGU-
Ribosomal protein S12	-AAA-ACC- AGG-AGC -UAU-UUA- AUG -GCA-ACA-
<i>trpL</i> . leader	-GUA-AAA- AGG-GUA -UCG-ACA- AUG -AAA-GCA-
<i>araB</i>	-UUU-GGA- UGG-AGU -GAA-ACG- AUG -GCG-AUU-

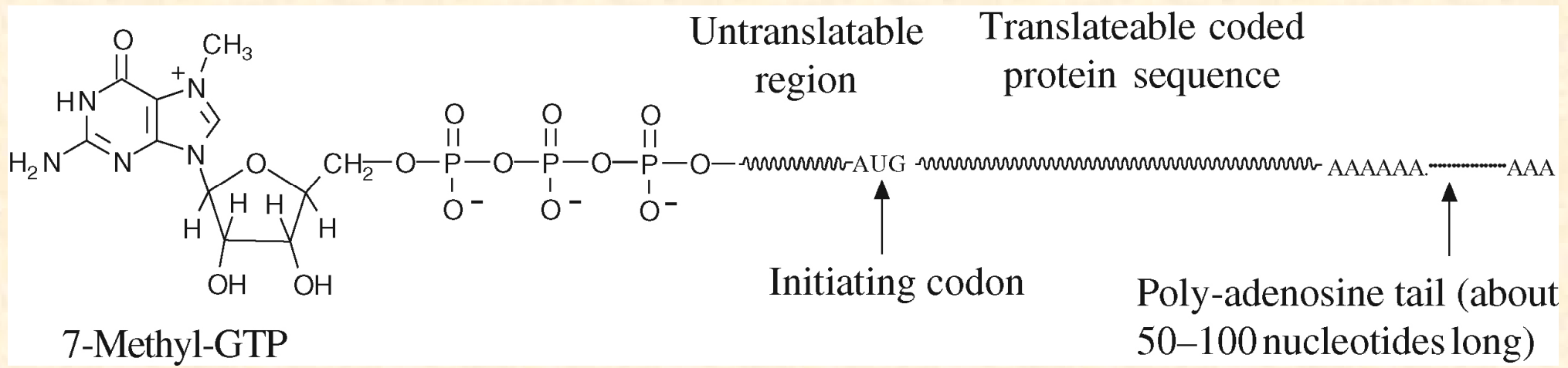
N -Formyl-methionine-tRNA_f^{Met}
(fMet-tRNA_f^{Met})



Protein Synthesis

- Eukaryotic cells

- No Shine-Dalgarno sequences

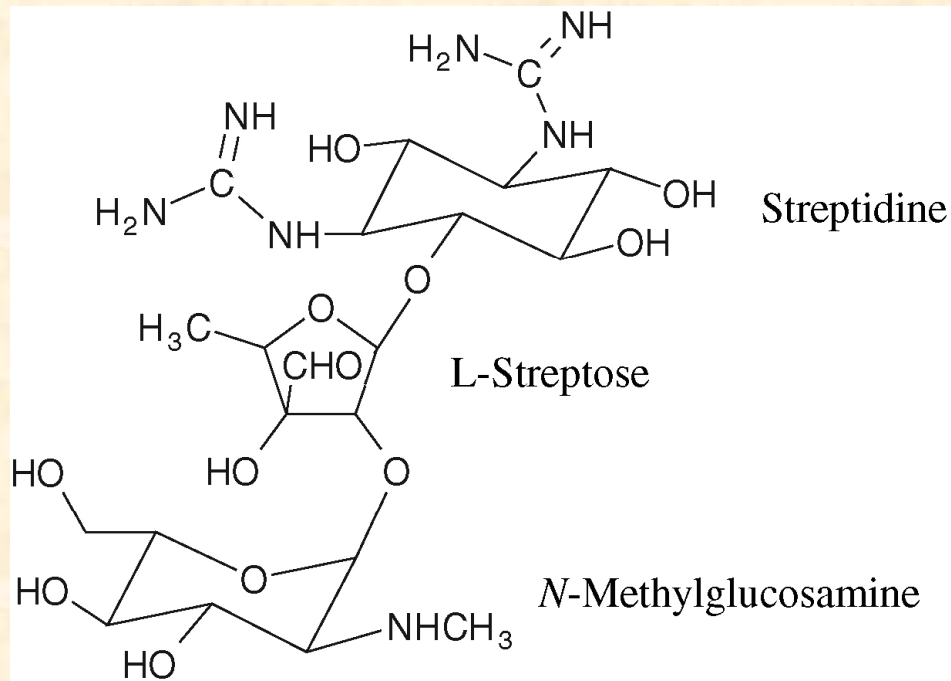


- initiating tRNA

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Aminoglycosides

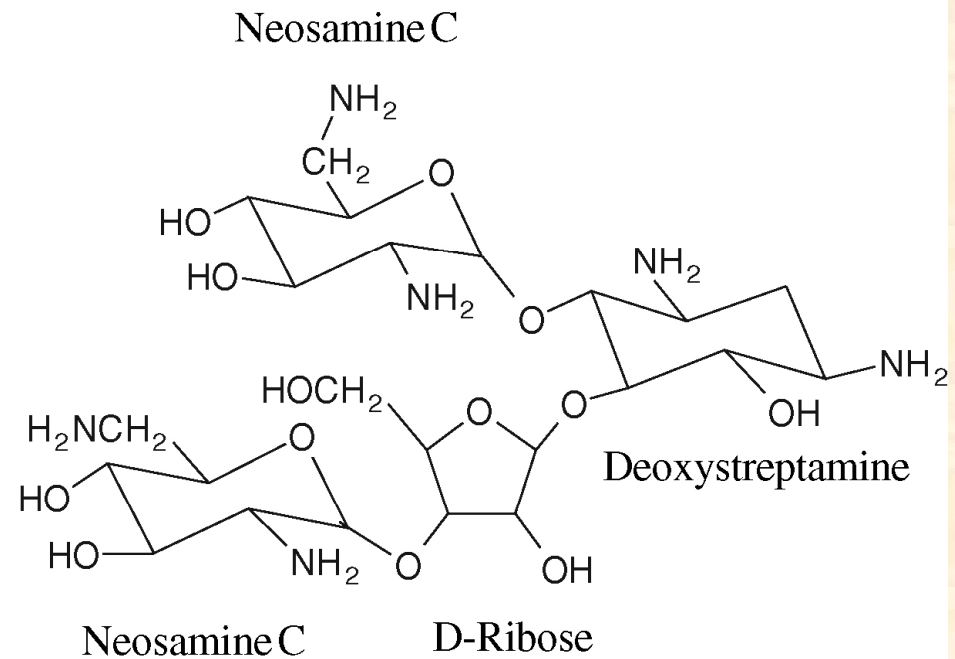
- Aminoglycosides

- aminosugar residues



(a)

streptomycin



(b)

neomycin

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Aminoglycosides



- Mode of action
 - inhibit protein synthesis in bacteria
 - bind to the 30S ribosome inhibits initiation
 - also causes of misreads of the mRNA codon
wrong protein – cell death
- Sources, characteristics
 - microorganisms
 - very well water soluble (used in inorg. salt form)
 - too polar, adsorb poorly, do not penetrate to CNS etc.
- Activity
 - broad spectrum antibiotics
 - usually for Gram negative infections

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Aminoglycosides

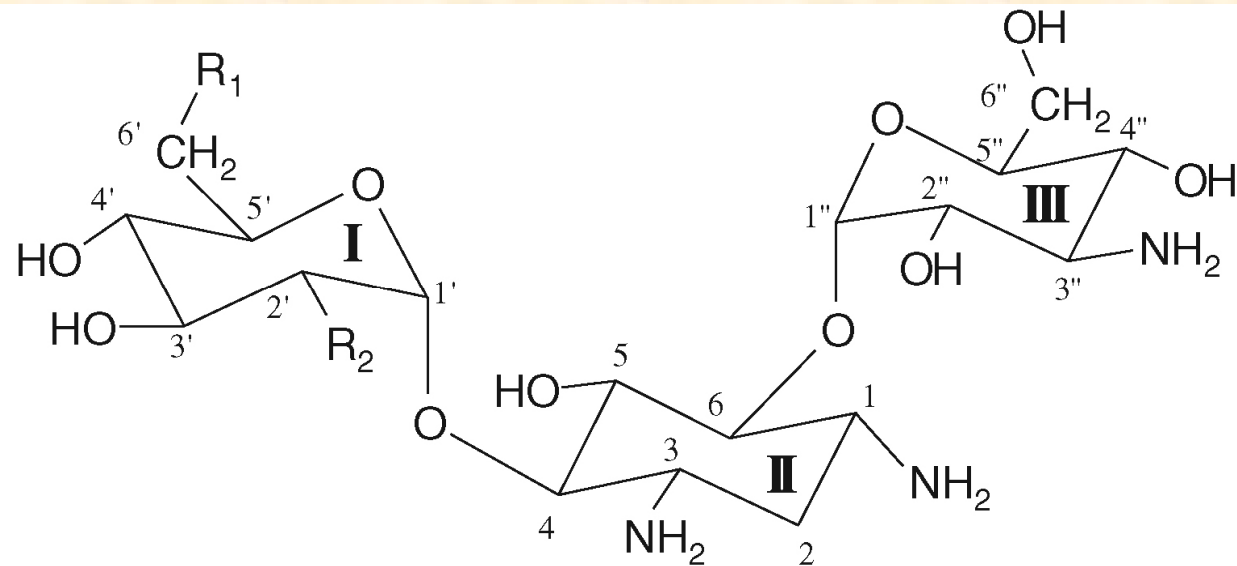
- Activity/potency – ring substituents case study – kanamycin

Key:

Kanamycin A: $R_1 = \text{NH}_2$; $R_2 = \text{OH}$

Kanamycin B: $R_1 = \text{NH}_2$; $R_2 = \text{NH}_2$

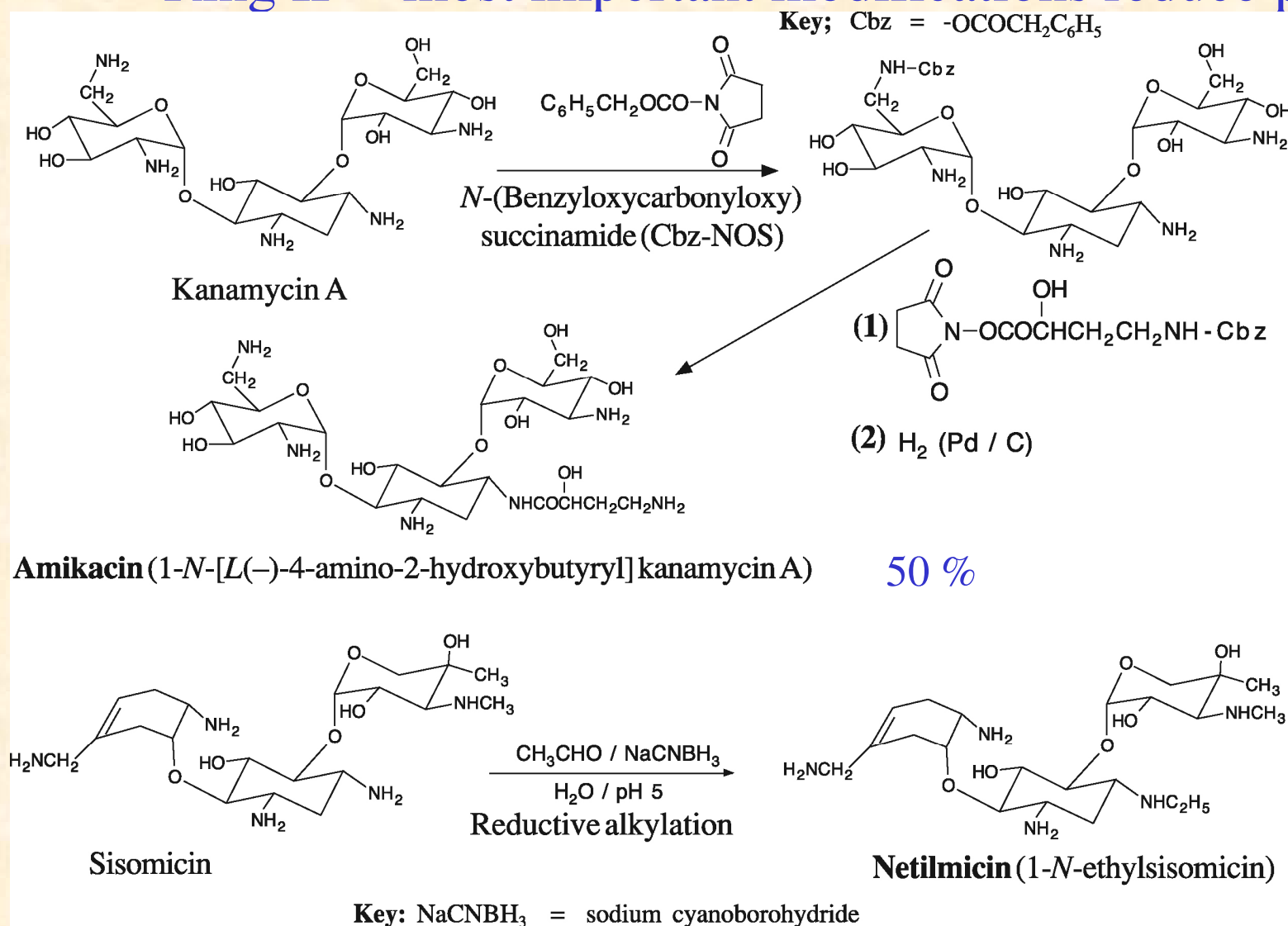
Kanamycin C: $R_1 = \text{OH}$; $R_2 = \text{OH}$



- Ring I 2' and 6' , 3' and 4' appears not important

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Aminoglycosides

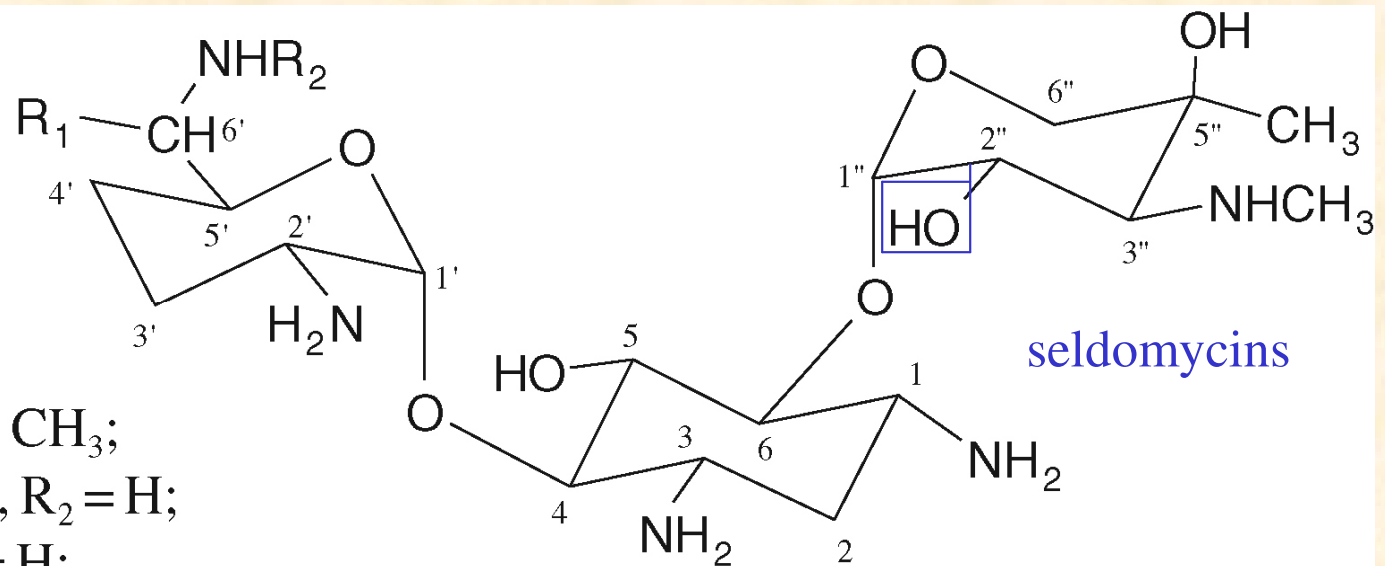
- Activity/potency – ring substituents case study – kanamycin
- Ring II most important modifications reduce potency



same potency

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Aminoglycosides

- Activity/potency – ring substituents case study – kanamycin
 - Ring III minor effect



Key:

Gentamicin C₁; R₁ = R₂ = CH₃;

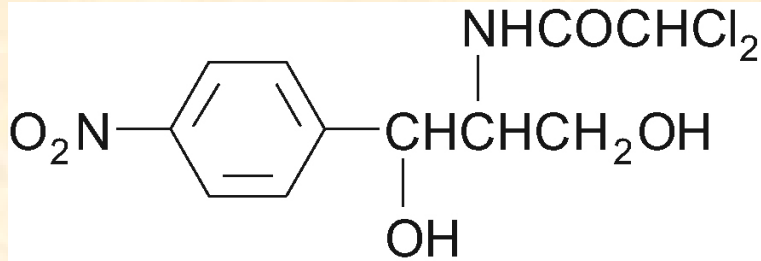
Gentamicin C₂; R₁ = CH₃, R₂ = H;

Gentamicin C_{1a}; R₁ = R₂ = H;

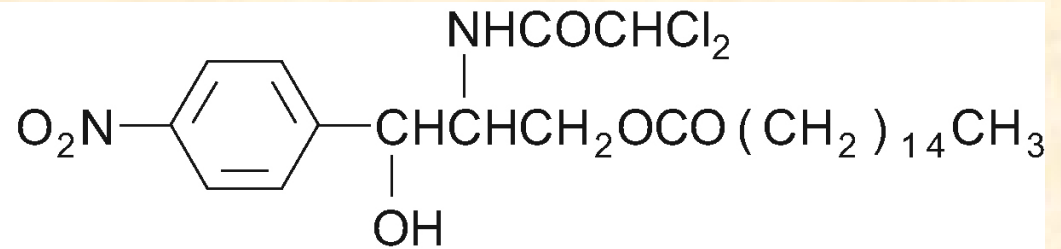
- resistance is a serious problem – usually via acylation/
phosphorylation, adenylation etc. by enzymes

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Chloramphenicol

- Isolation Erlich, 1947 (soil sample)
 - broad spectrum antibiotic
 - 4 isomers
 - inhibits the elongation, binds to 50S ribosome and inhibits the attachment of aminoacyl-tRNA to the ribosome



D-(-)-*Threo*-chloramphenicol



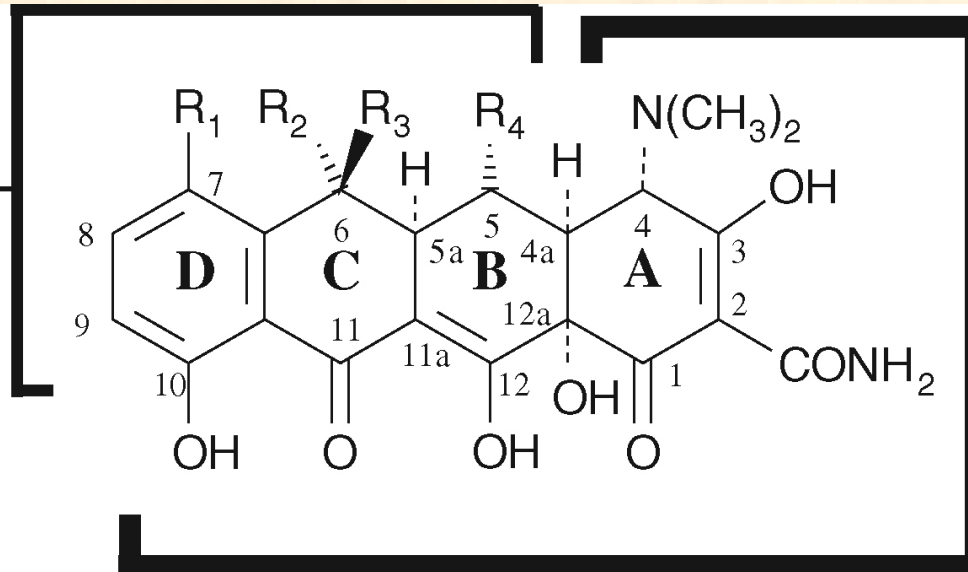
D-(-)-*Threo*-chloramphenicol palmitate

active

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Tetracyclines

- Isolation Duggar, 1948 (soil sample)
 - broad spectrum antibiotics: Gram +/-, mycoplasmas, chlamydiae, some protozoa
 - 6 chiral carbons (128 isomers just for one TC)
 - inhibits the elongation, binds to 30S ribosome and inhibits the attachment of aminoacyl-tRNA to the ribosome (Mg²⁺ ions are needed)

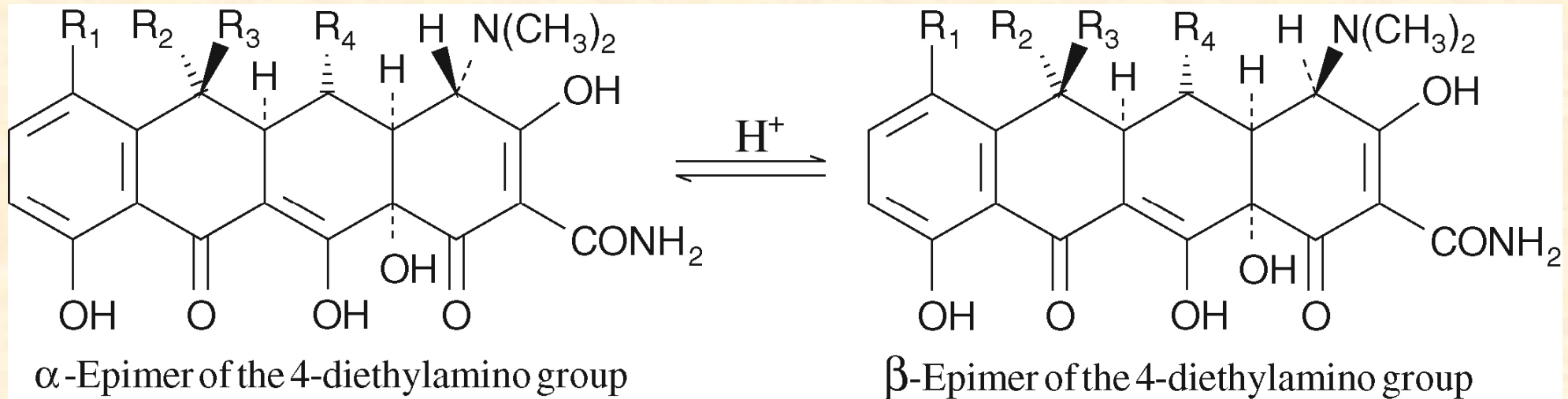
Modifications to these regions may result in compounds of similar or increased activity



Minor changes in these regions usually cause a significant reduction in activity

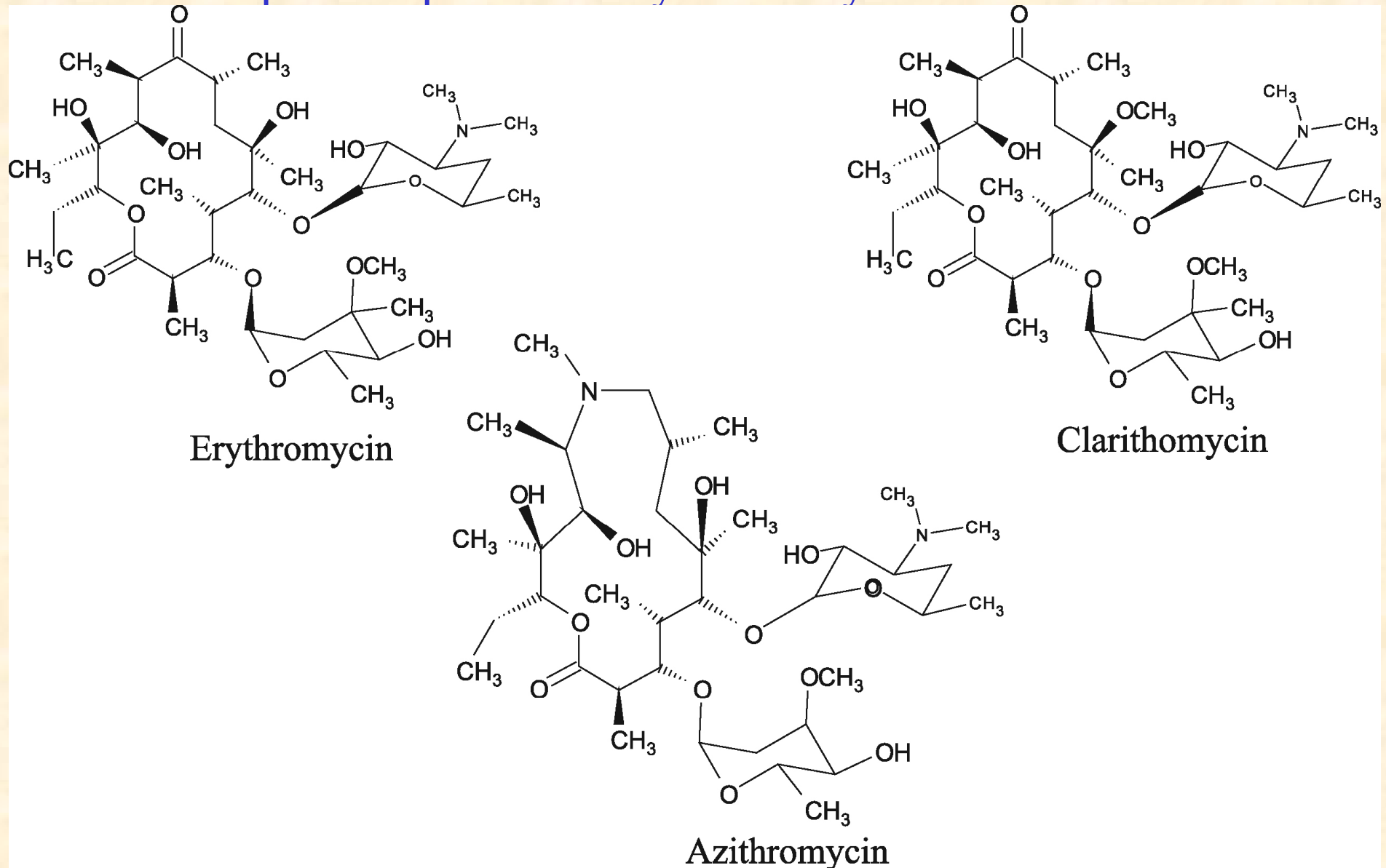
Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Tetracyclines

- importance of certain chiral centers



Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Macrolides

- natural compounds produced by a semisynthetic route



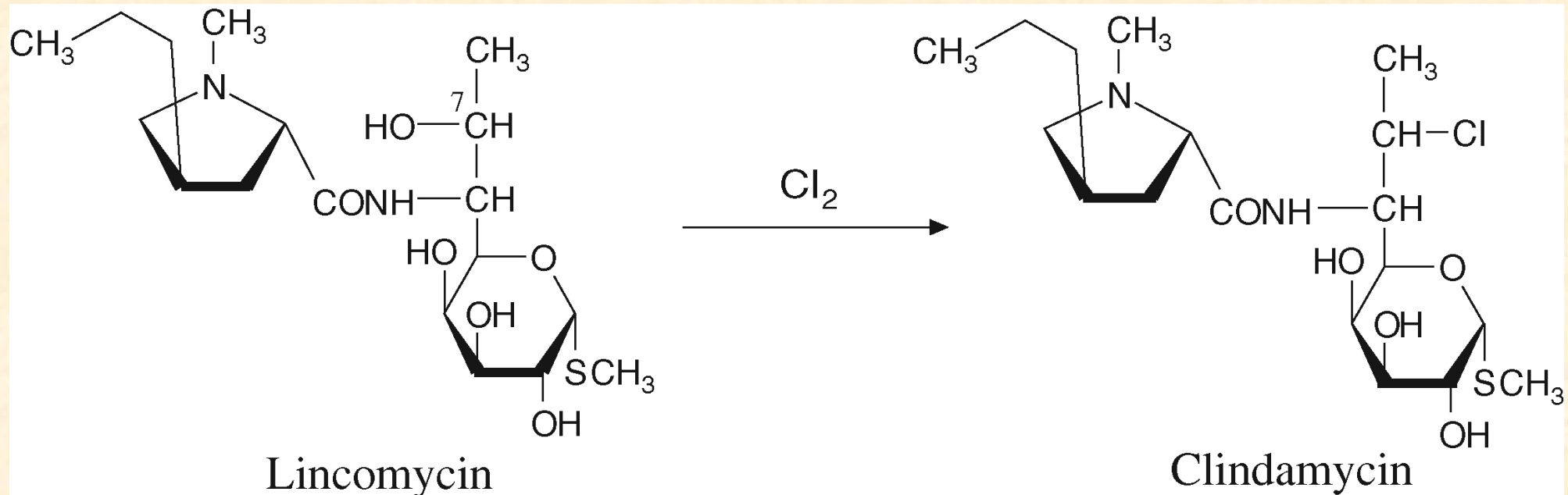
Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Macrolides



- spectrum similar to penicillins – active in penicillin resistance
- inhibits the elongation, binds to 50S bacterial ribosome and inhibits the attachment of aminoacyl-tRNA to the ribosome
- resistance common

Bacterial Protein Synthesis Inhibitors (Antimicrobials) - Lincomycins

- natural compounds but some produced by a semisynthetic route (1967)
 - active against Gram+
 - bind to 50S bacterial ribosome
 - both bacteriostatic and bactericidal



Drugs that Target Nucleic Acids

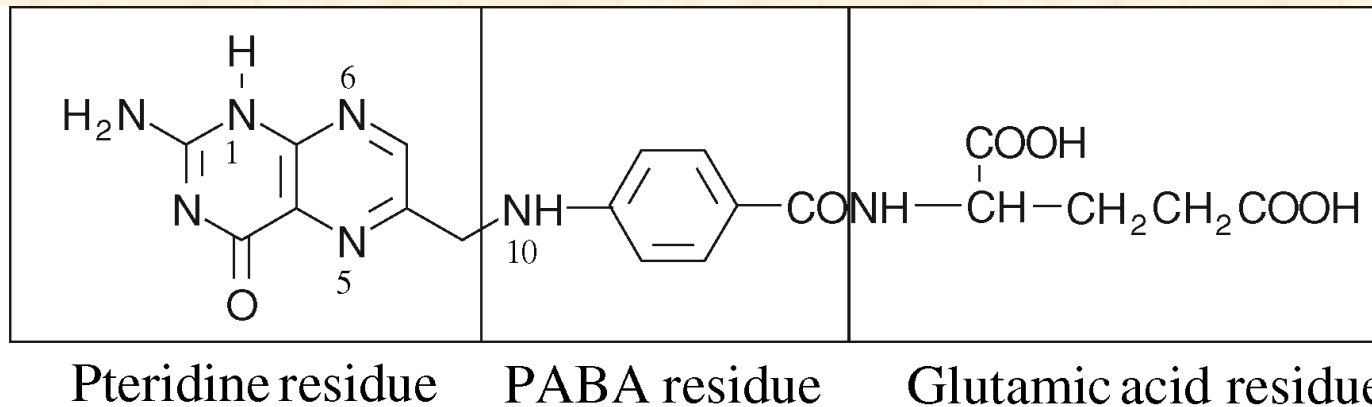


- Either DNA/RNA synthesis or act on existing NAs
 - antimetabolites or enzyme inhibitors
 - intercalating, alkylating, chain cleaving agents
 - applications: cancer, bacterial and other infections
- Antimetabolites
 - block normal metabolic pathways
 - replacing the endogenous ligand or enzyme inhibition
 - similar structure to the normal metabolites

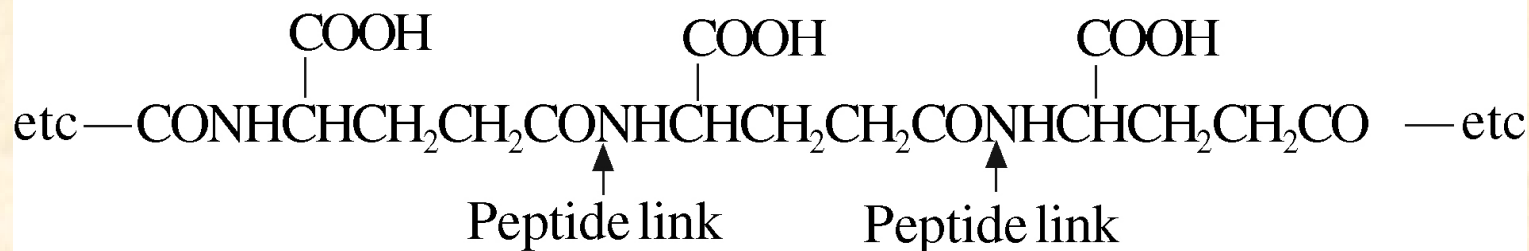
Drugs that Target Nucleic Acids - Antimetabolites

- Antifolates

- folic acid; parent compounds to folates
- 1930s Lewisohn



(a)

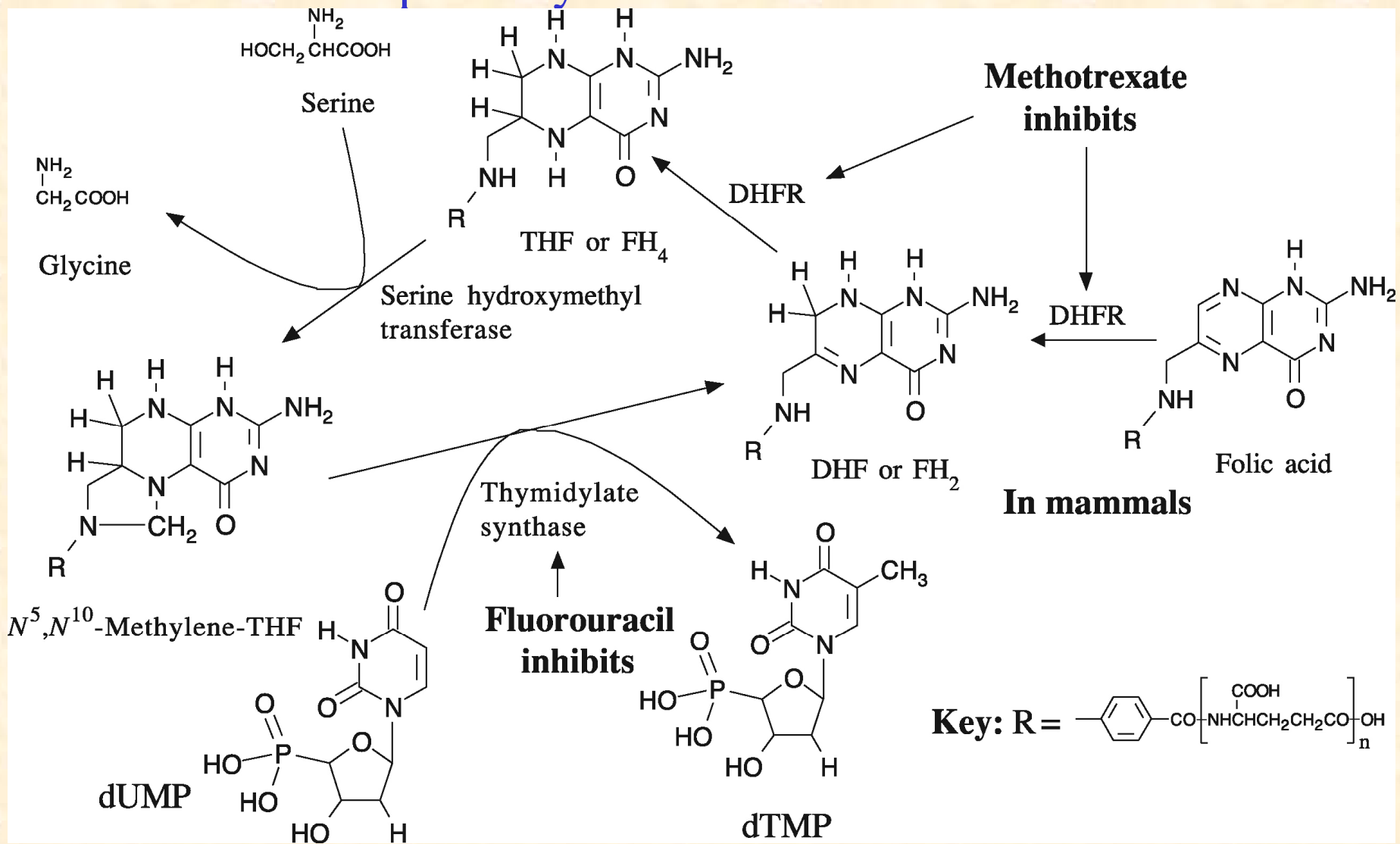


(b)

Drugs that Target Nucleic Acids - Antimetabolites

- Antifolates

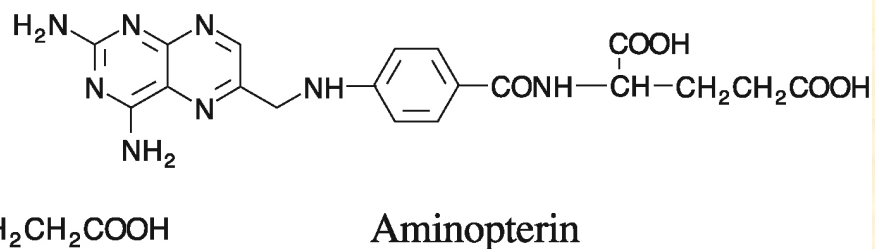
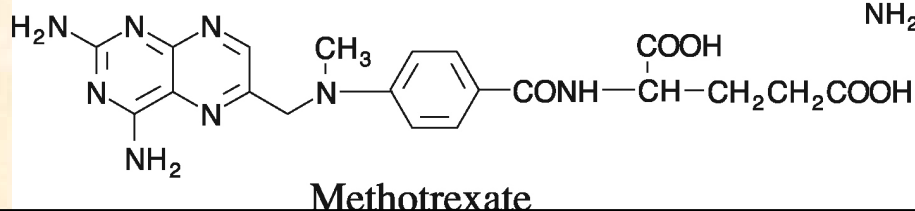
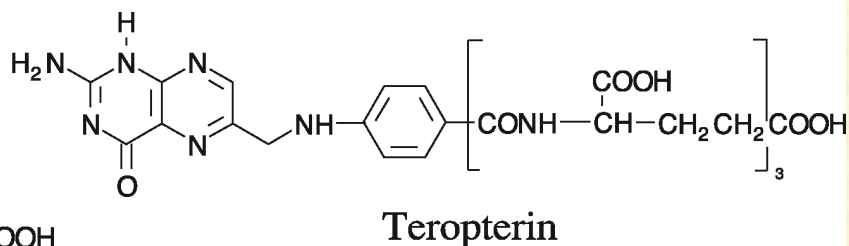
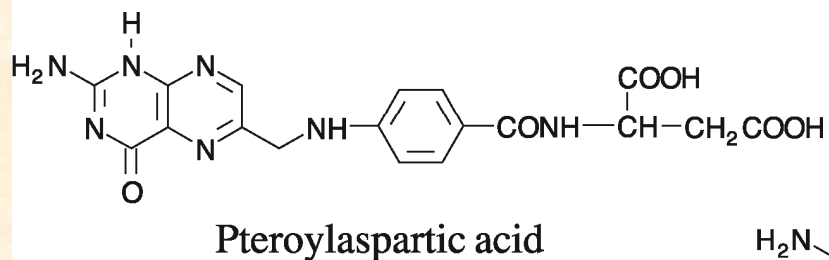
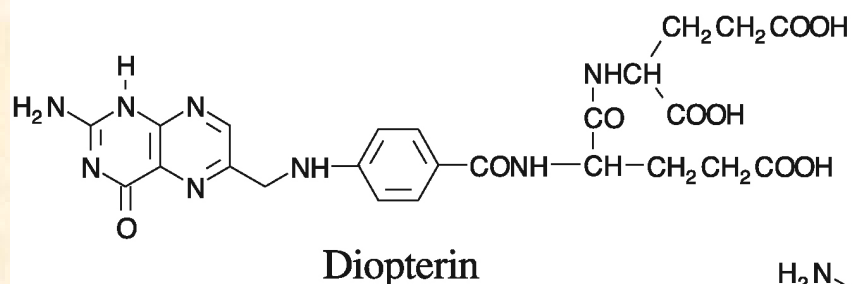
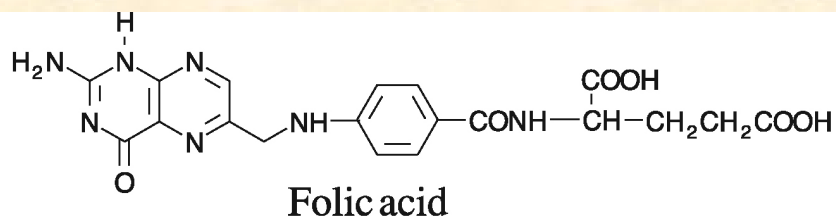
- metabolic pathway



Drugs that Target Nucleic Acids - Antimetabolites

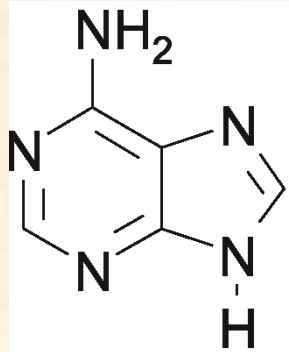
- Antifolates

- drugs and folic acid



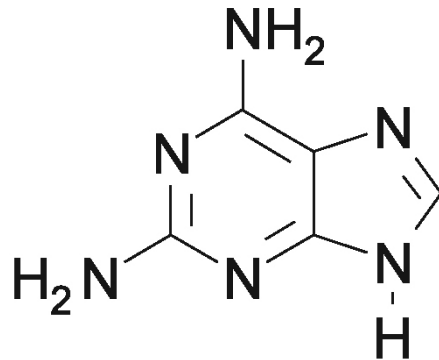
Drugs that Target Nucleic Acids - Antimetabolites

- Purine antimetabolites
 - Hitchings, 1942
 - active against leukemia



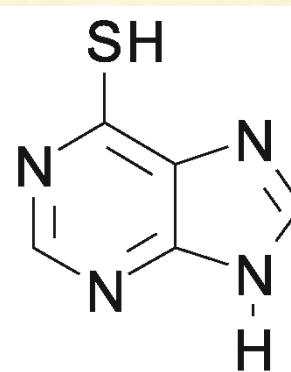
(a)

adenine



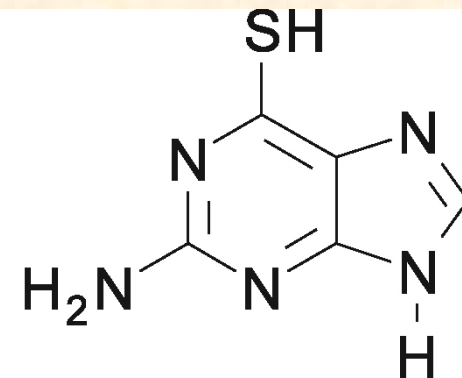
(b)

aminopurine



(c)

mercaptopurine

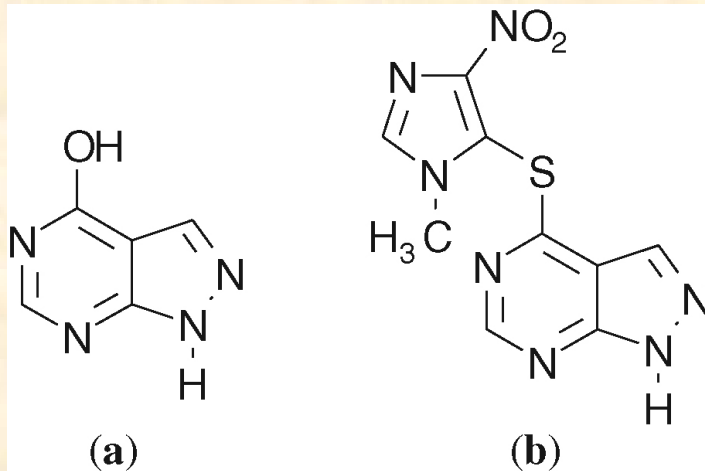


(d)

6-thioguanine

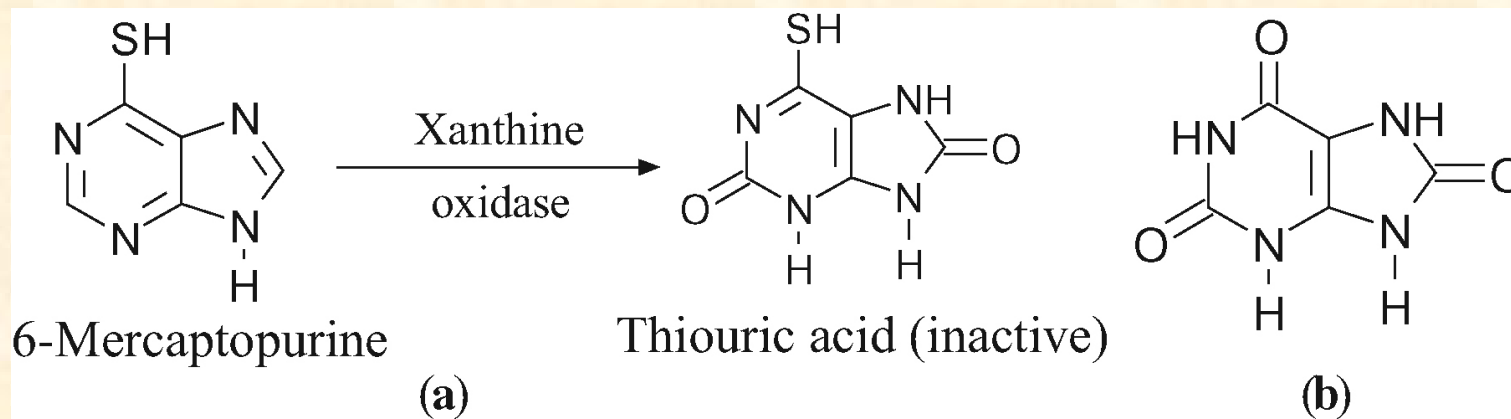
Drugs that Target Nucleic Acids - Antimetabolites

- Purine antimetabolites
 - further developments



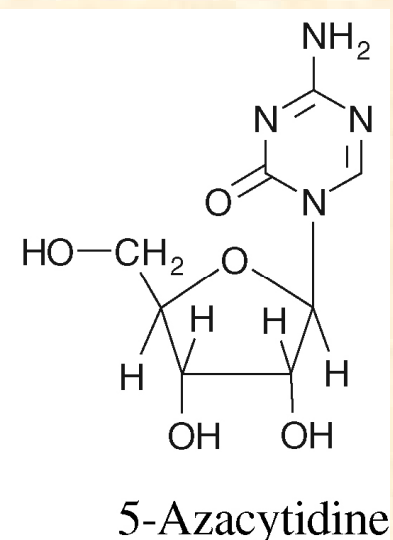
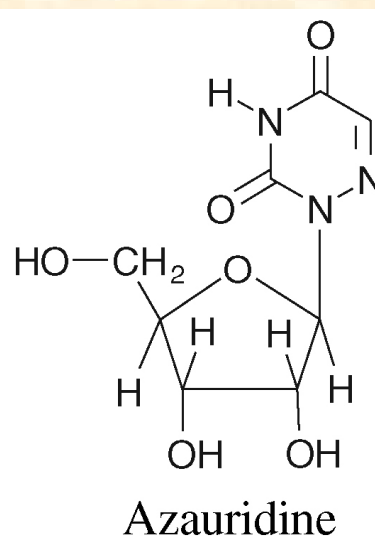
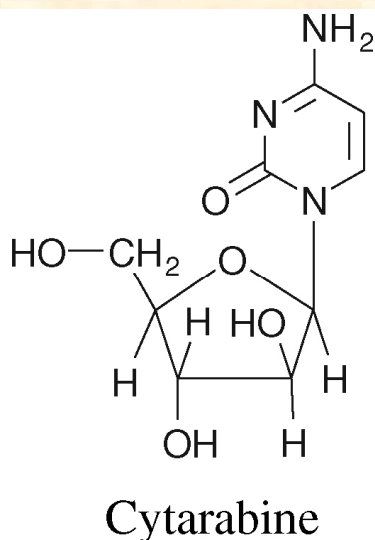
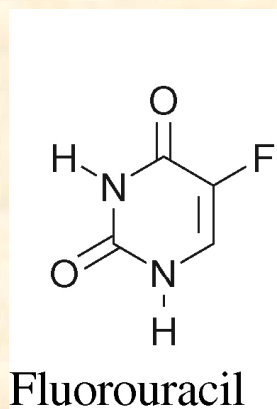
allopurinol

azathioprine



Drugs that Target Nucleic Acids - Antimetabolites

- Pyrimidine antimetabolites

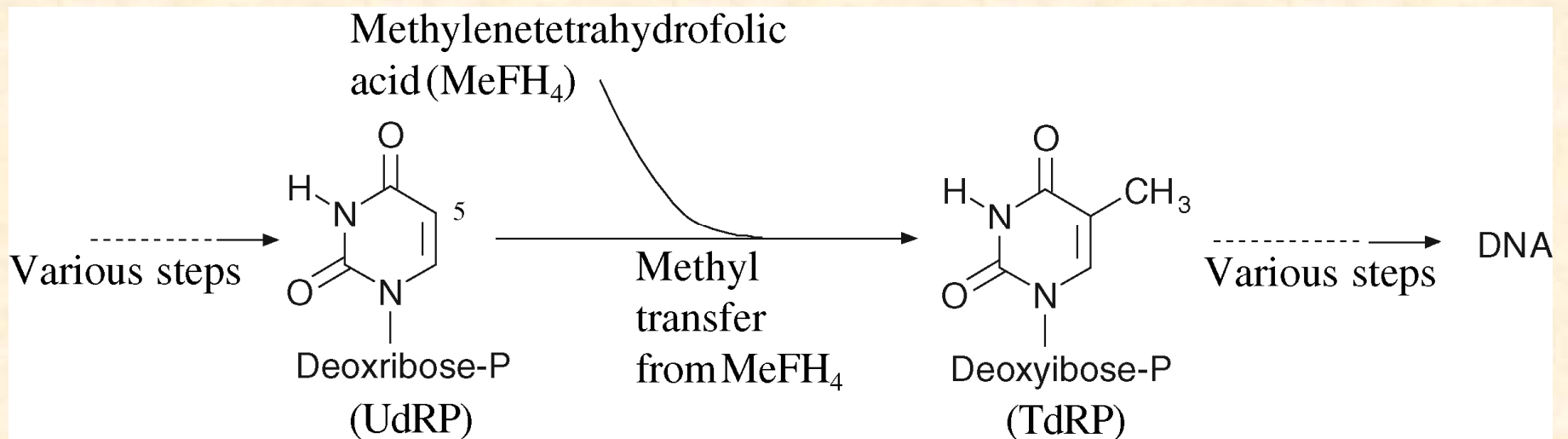


- first examples ; 1950s cancer research
- used against solid tumors
- inhibit enzymes that run the DNA synthesis

Drugs that Target Nucleic Acids - Antimetabolites

- Pyrimidine antimetabolites

- mode of action - fluorouracil

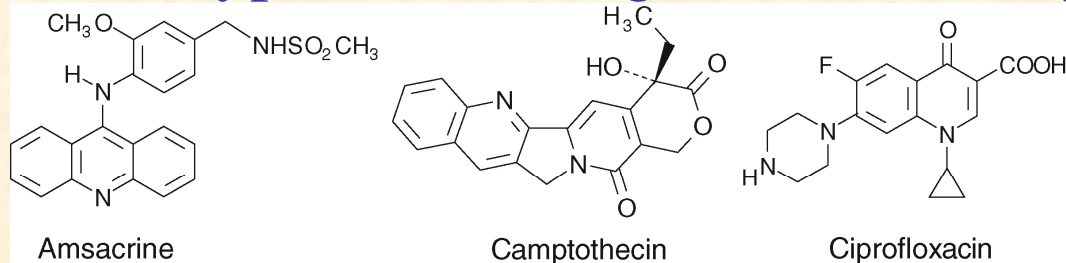


Drugs that Target Nucleic Acids – Enzyme Inhibitors

- Topoisomerase inhibitors

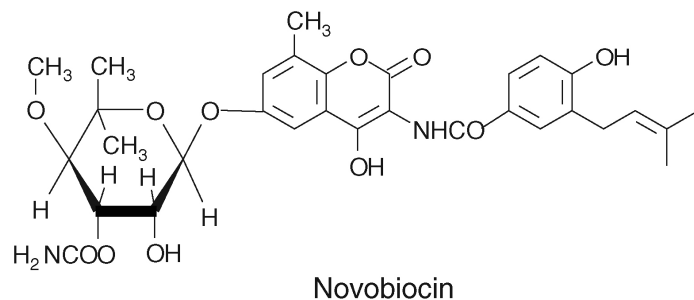
- topoisomerases (nicking or closing enzymes)

- Type I : breaking one strand; Type II: breaking both strands

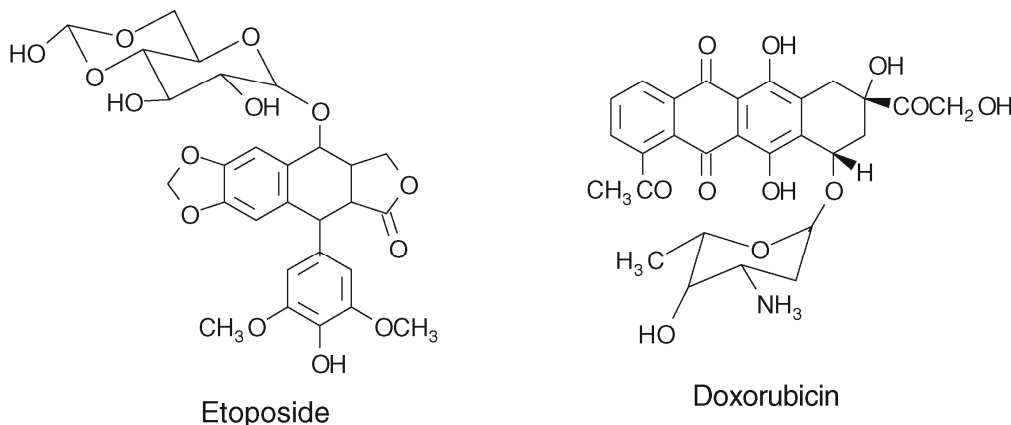


inhibit DNA replication

treatment of various cancers



Novobiocin



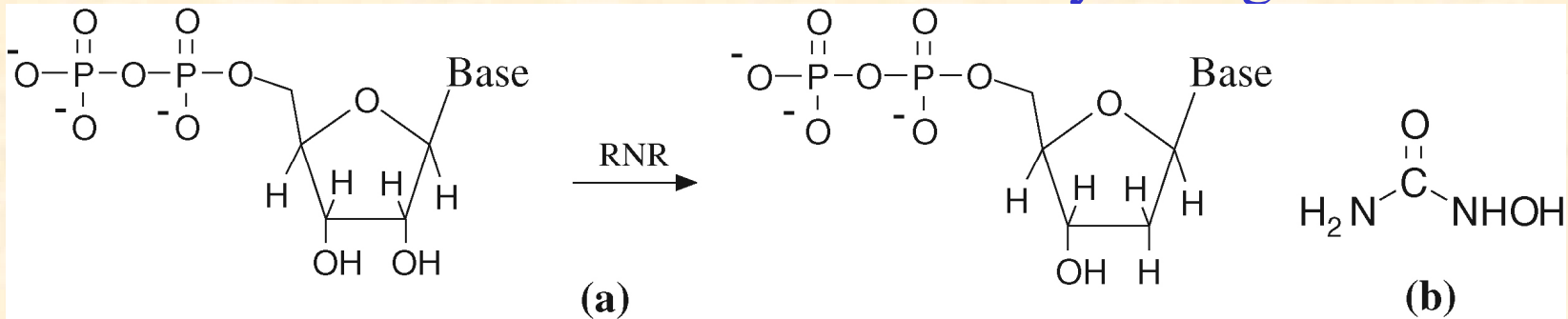
Etoposide

Doxorubicin

Drugs that Target Nucleic Acids – Enzyme Inhibitors

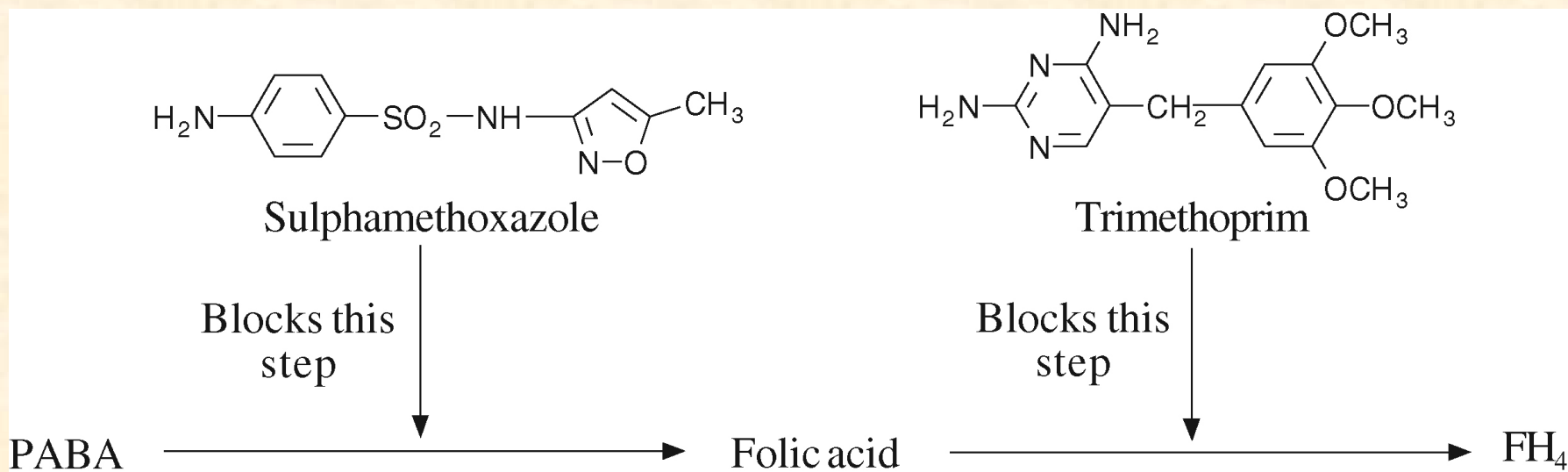
- Ribonucleotide reductase inhibitors

 - ribonucleotide reductase is in every living cell



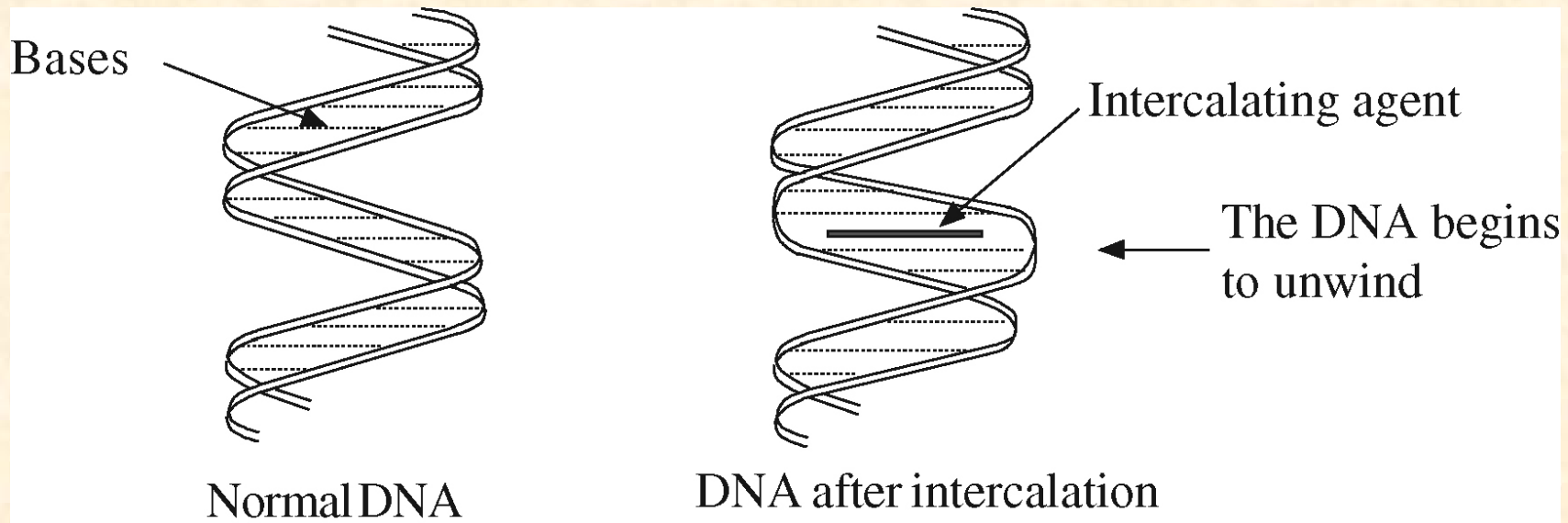
 - targets for new anticancer and antiviral drugs

- Enzyme inhibitors for pyrimidine/purine precursor systems



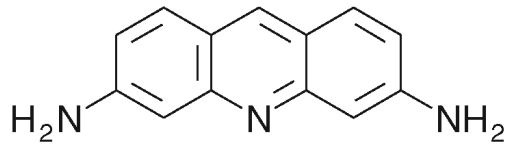
Drugs that Target Nucleic Acids – Intercalating Agents

- Intercalating agents – unwinds DNA – inhibits transcription
- both major and minor groove

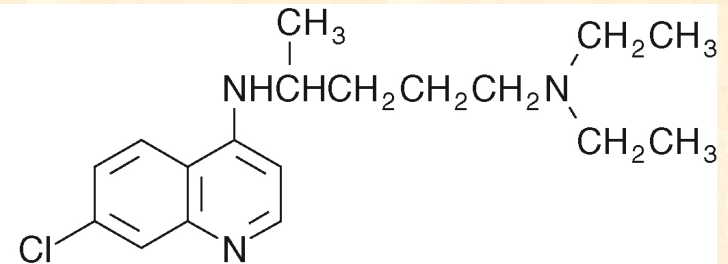


Drugs that Target Nucleic Acids – Intercalating Agents

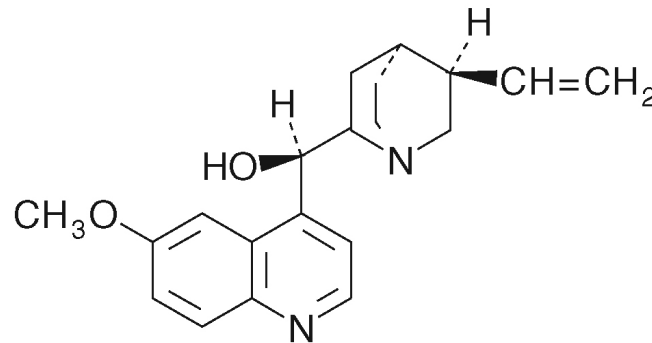
- Intercalating agents



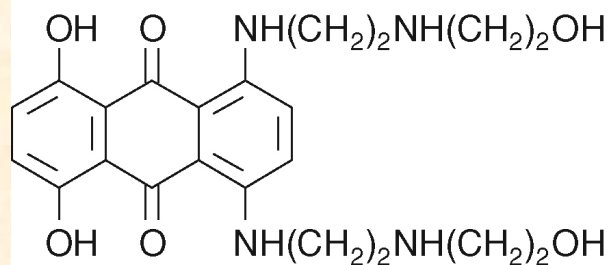
Proflavine (3,6-diaminoacridine)
(antibiotic)



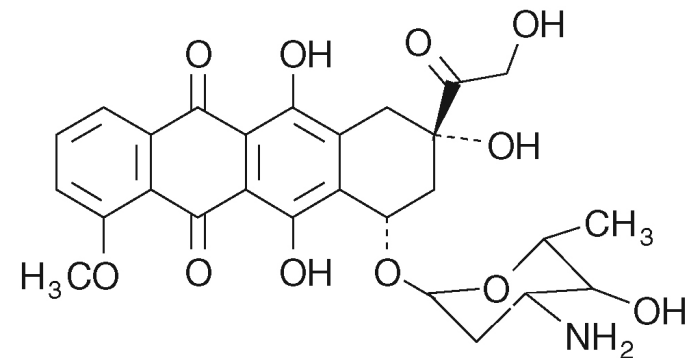
Chloroquine (antimalarial)



Quinine (antimalarial)



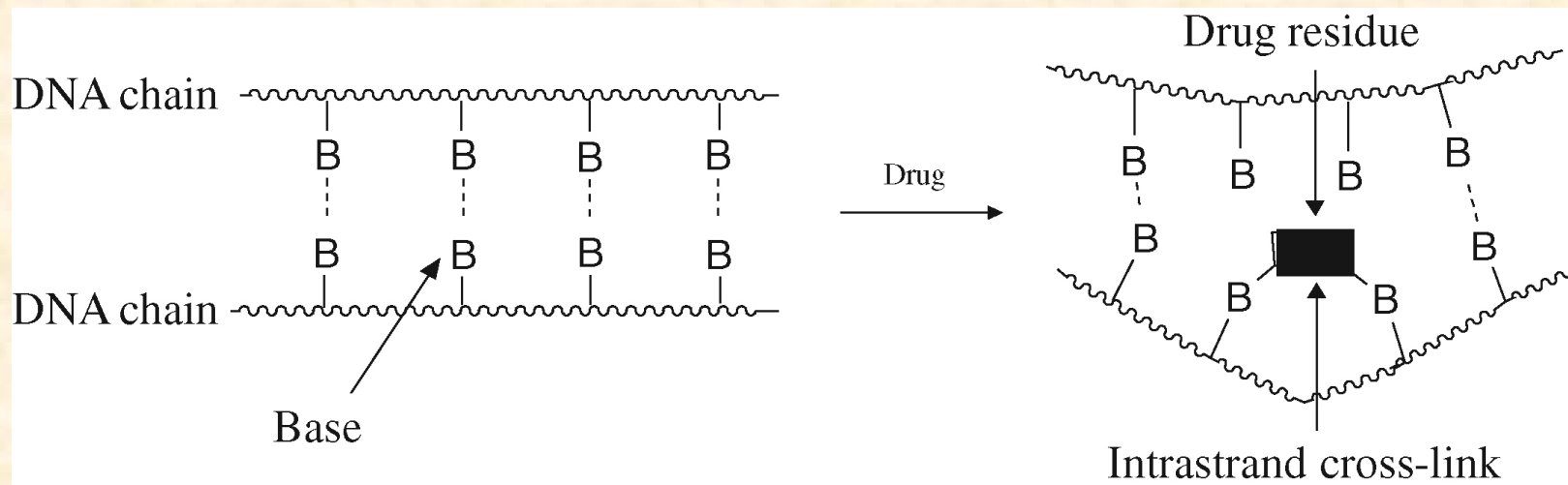
Mitoxantrone, Novanatrone*
(anticancer)



Doxorubicin, Adriamycin*
(anticancer)

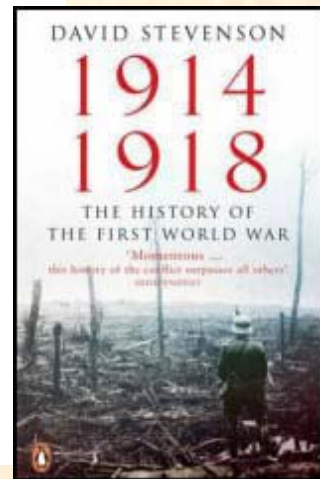
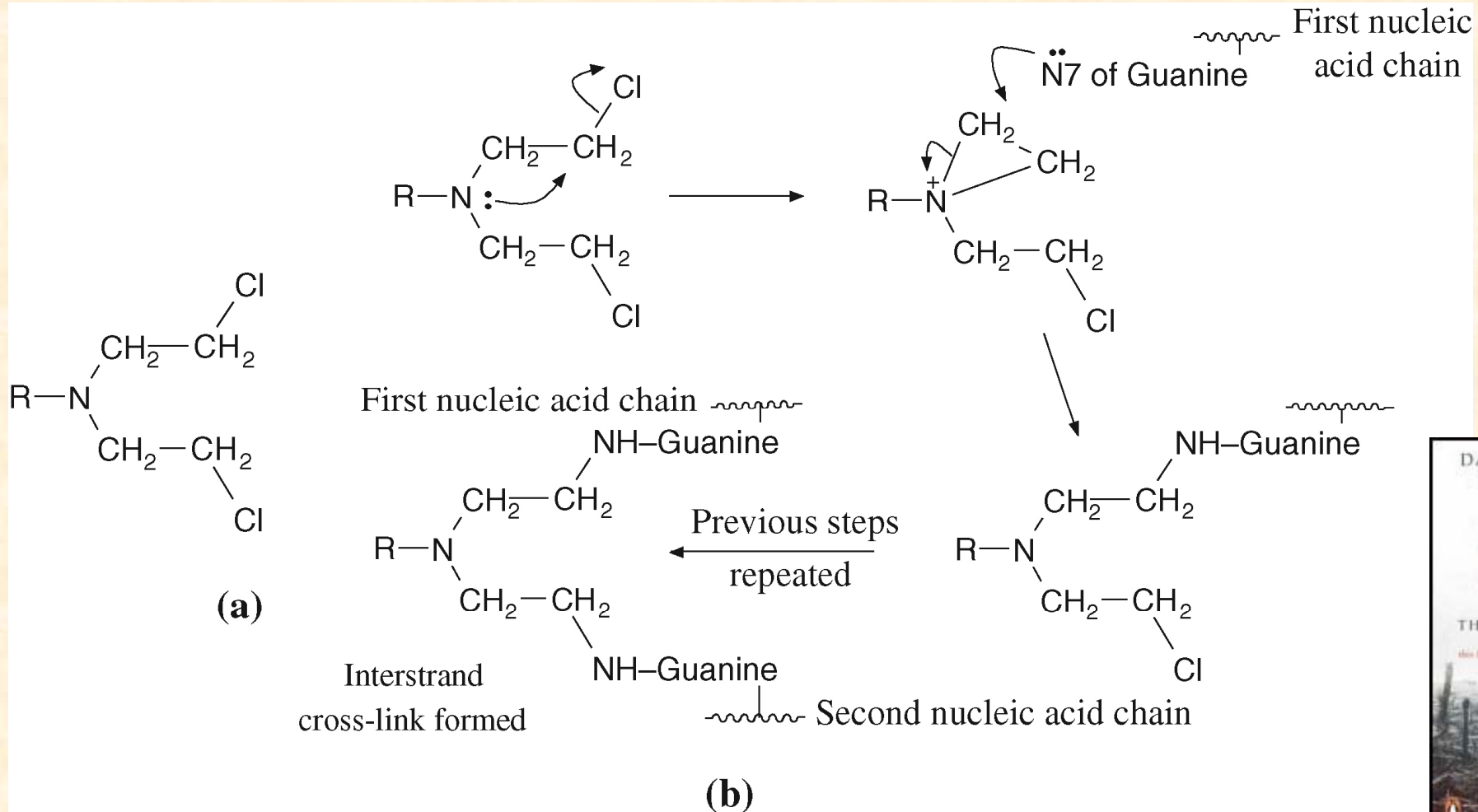
Drugs that Target Nucleic Acids – Alkylating Agents

- Alkylating agents - interstrand vs. intrastrand links



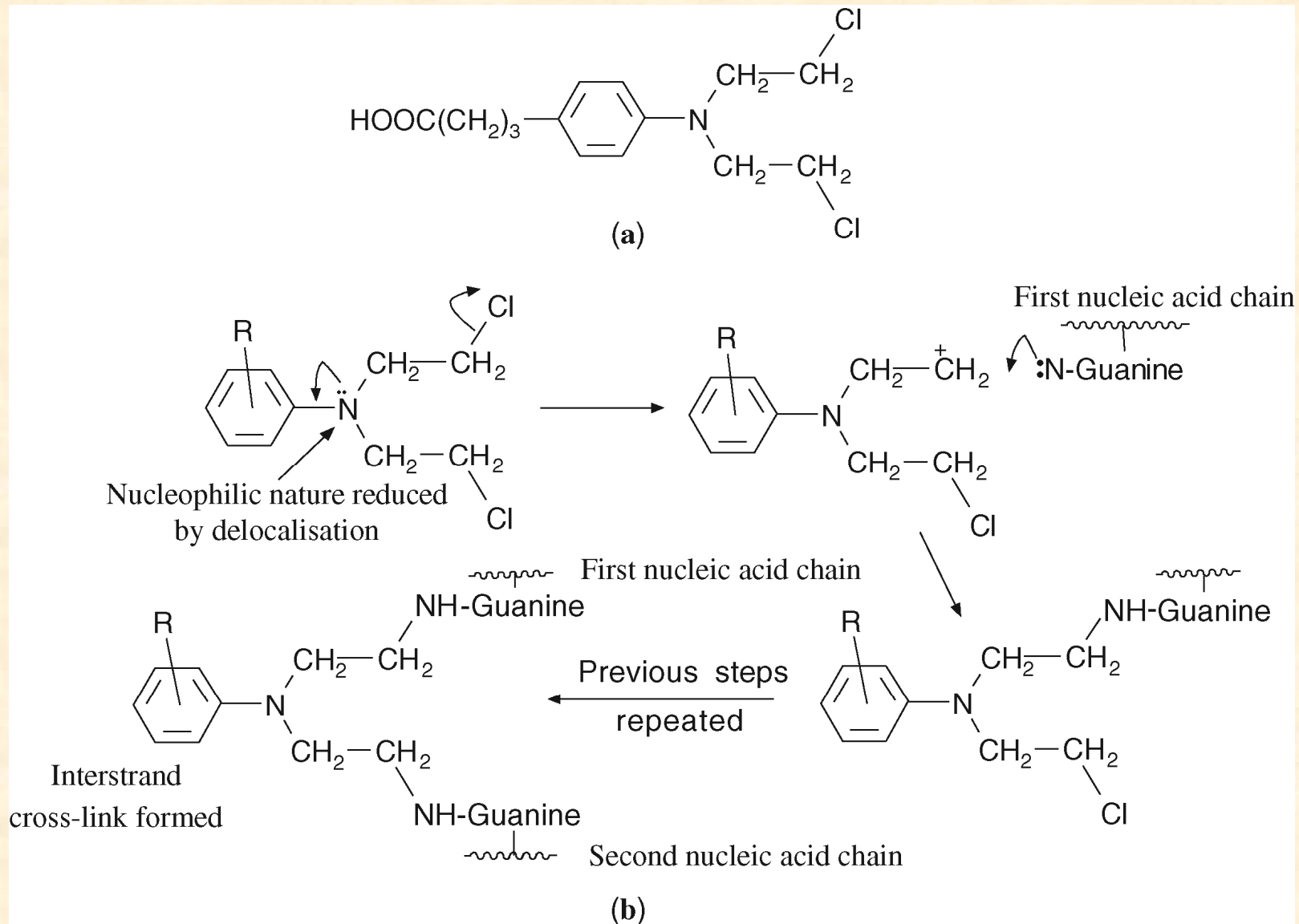
Drugs that Target Nucleic Acids – Alkylating Agents

- Alkylating agents - mustards

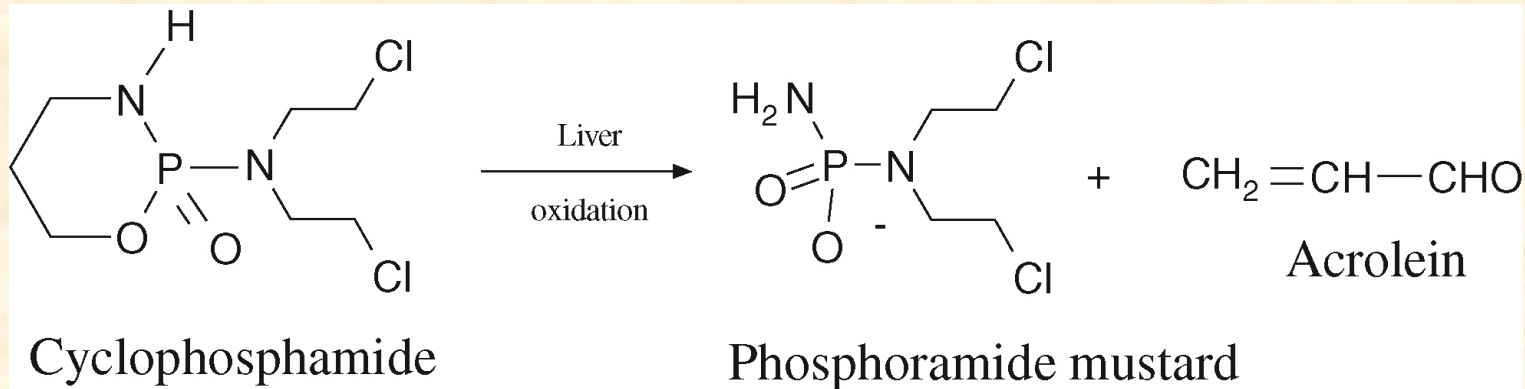


Drugs that Target Nucleic Acids – Alkylating Agents

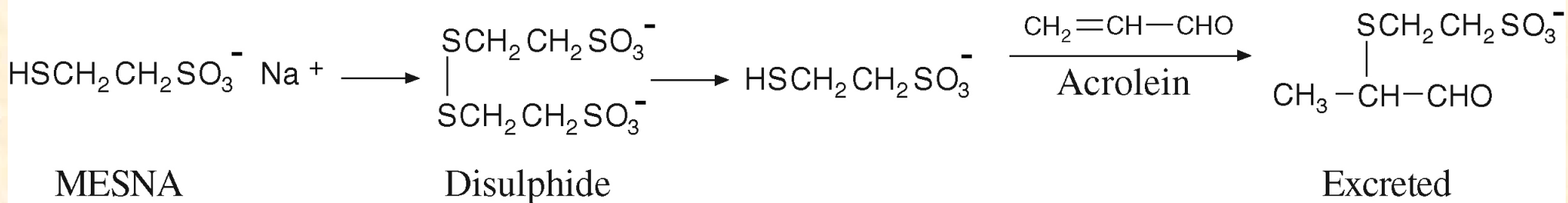
- Alkylating agents - mustards



Drugs that Target Nucleic Acids – Alkylating Agents

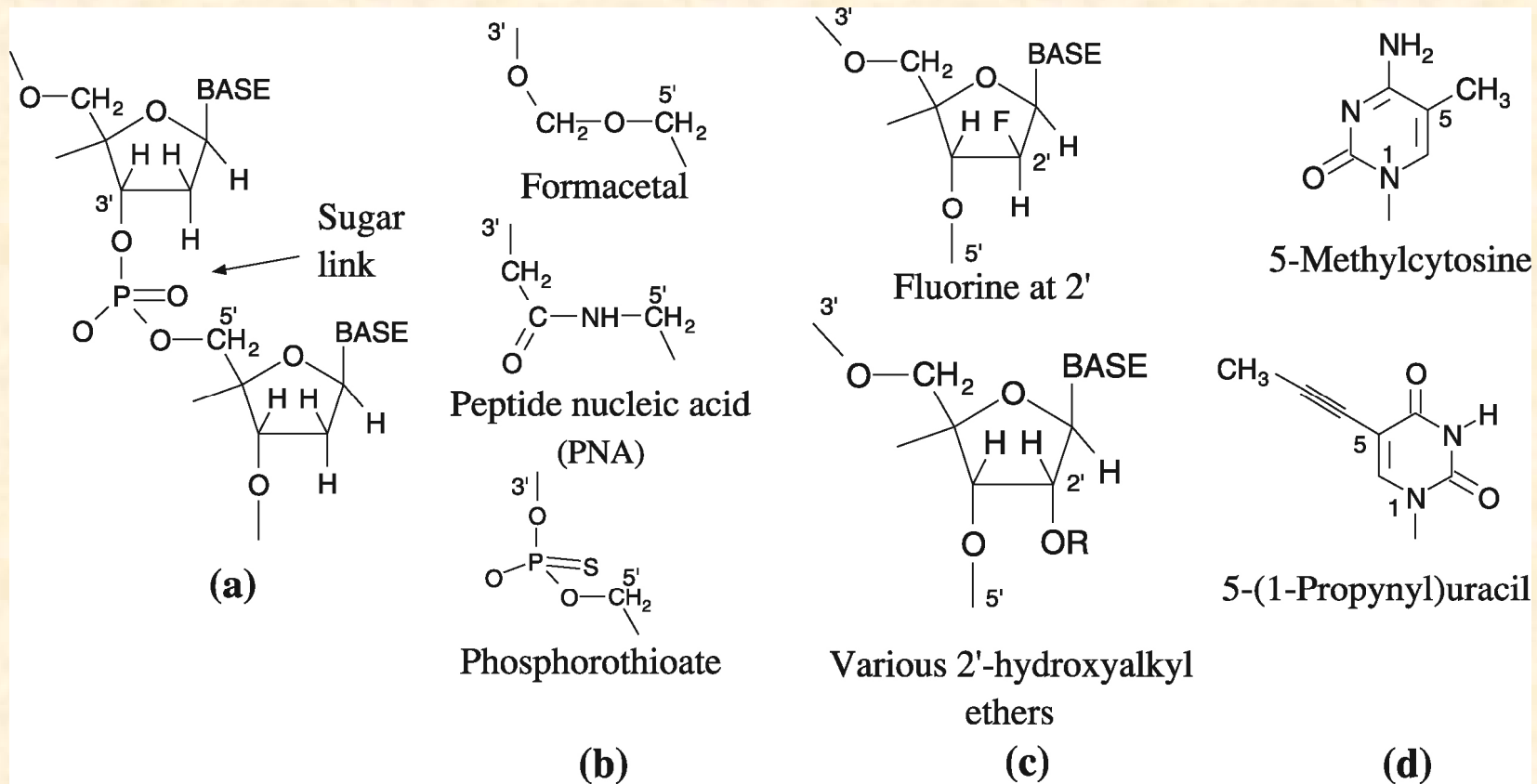


- Alkylating agents – mustards – Na-mercaptoethanesulfonate (MESNA)



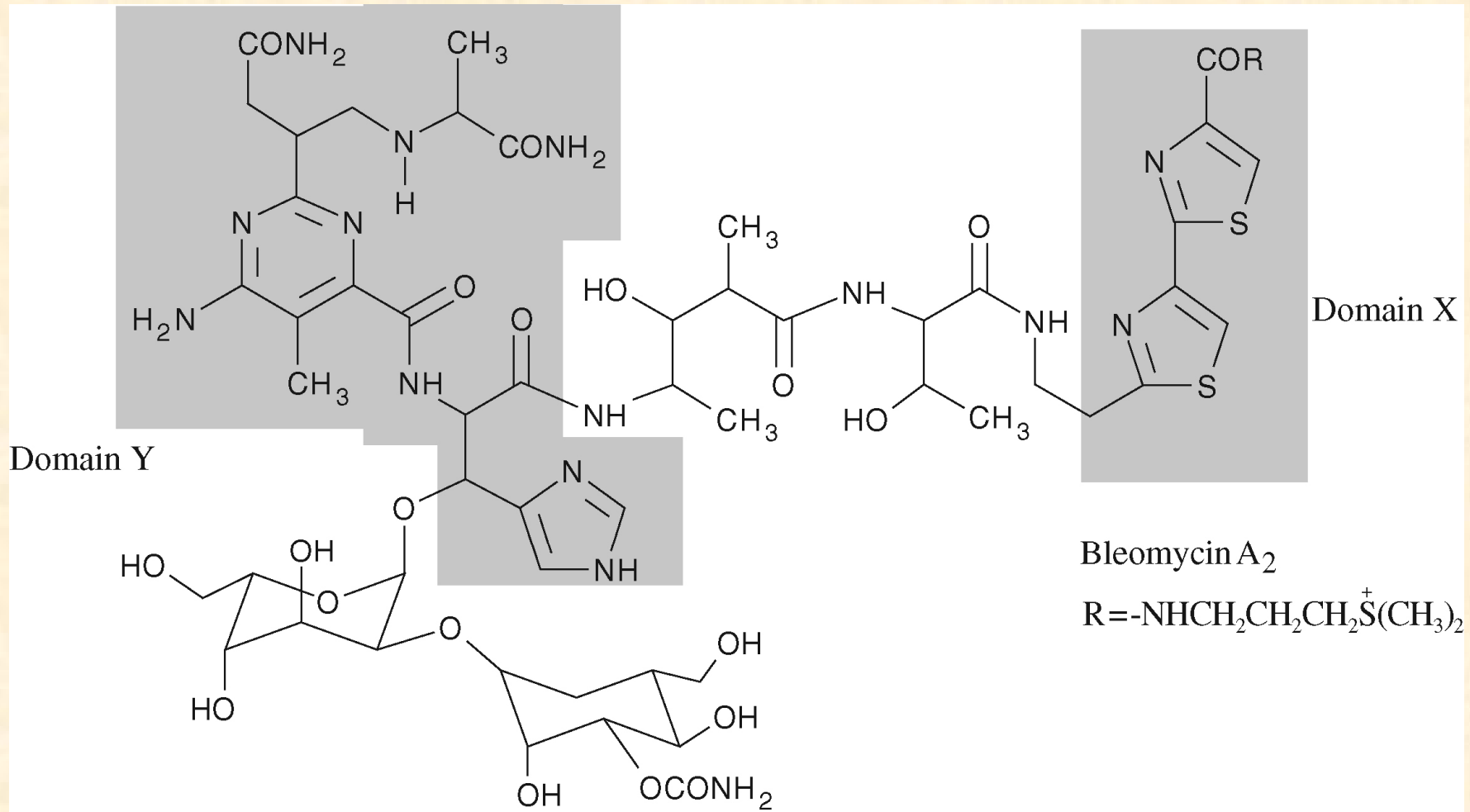
Drugs that Target Nucleic Acids – Antisense Drugs

- The antisense drug concept



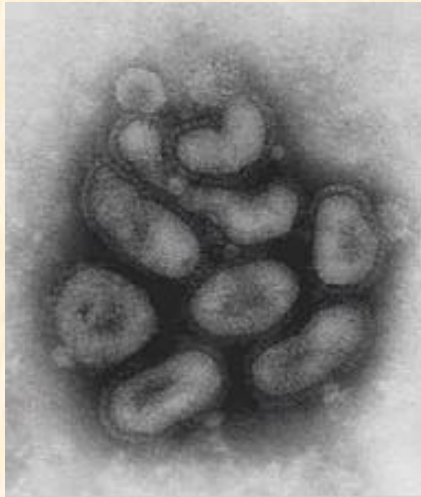
Drugs that Target Nucleic Acids – Chain Cleaving Agents

- Chain cleaving agents – break up the DNA (many side effects)

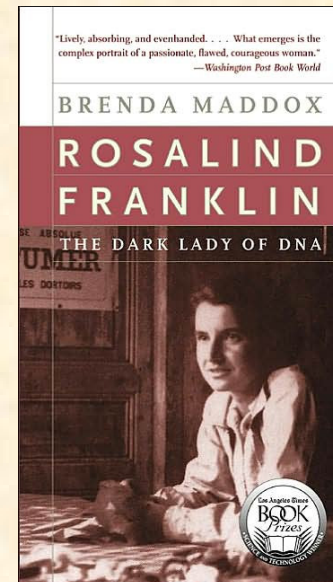
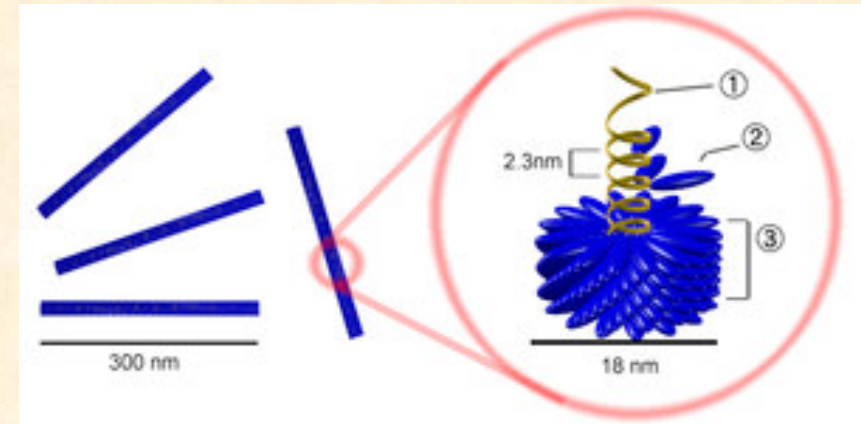
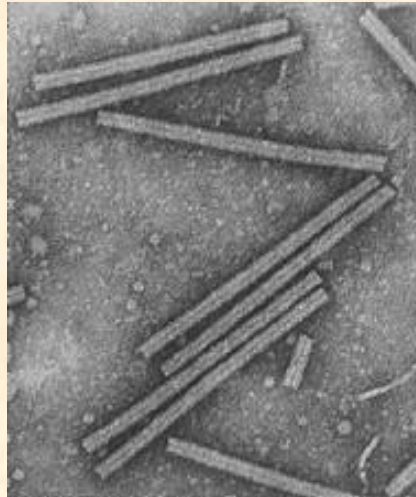


Viruses

- Friedrich Loeffler, Paul Frosch - foot-and-mouth disease 1898



influenza



Viruses

1908: Ilya Ilyich Mechnikov, Paul Ehrlich “in recognition of their work on immunity”.

1954: John F. Enders, Thomas H. Weller and Frederick C. Robbins “for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue”.

1965: François Jacob, André Lwoff and Jacques Monod “for their discoveries concerning genetic control of enzyme and virus synthesis”.

1966: Peyton Rous “for his discovery of tumour-inducing viruses”.

1975: David Baltimore, Renato Dulbecco and Howard Martin Temin “for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell”.

1978: Werner Arber, Daniel Nathans and Hamilton O. Smith “for the discovery of restriction enzymes and their application to problems of molecular genetics”.

1989: J. Michael Bishop and Harold E. Varmus “for their discovery of the cellular origin of retroviral oncogenes”.

1996: Peter C. Doherty and Rolf M. Zinkernagel “for their discoveries concerning the specificity of the cell mediated immune defence”.

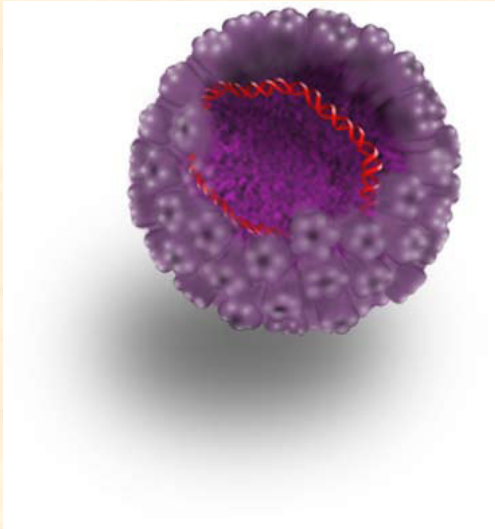


Nobel Prize In Medicine

Viruses

- Most recent

HIV - HPV



Harald zur Hausen



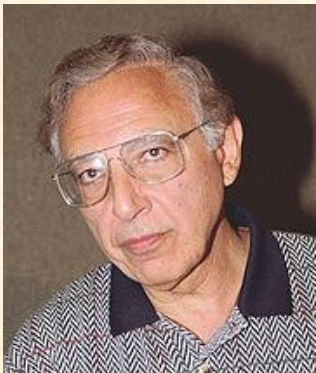
Françoise
Barré-Sinoussi



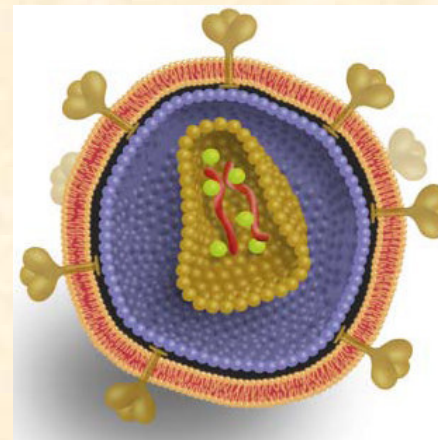
Luc Montagnier



Nobel Prize
In Medicine
2008

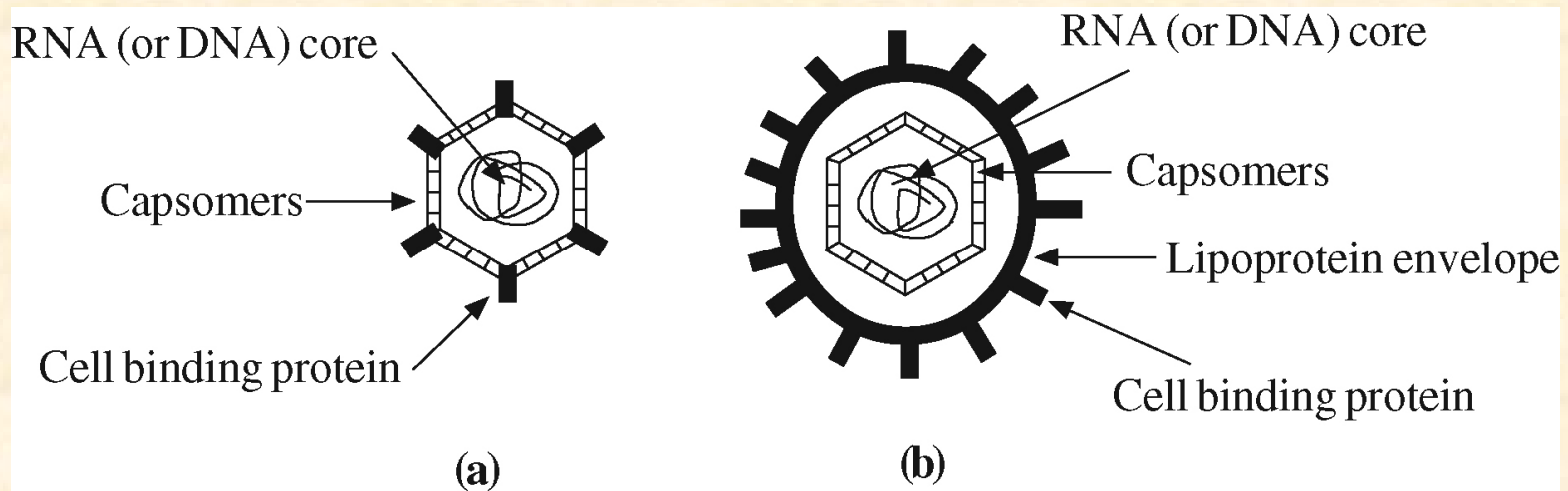


R. Gallo



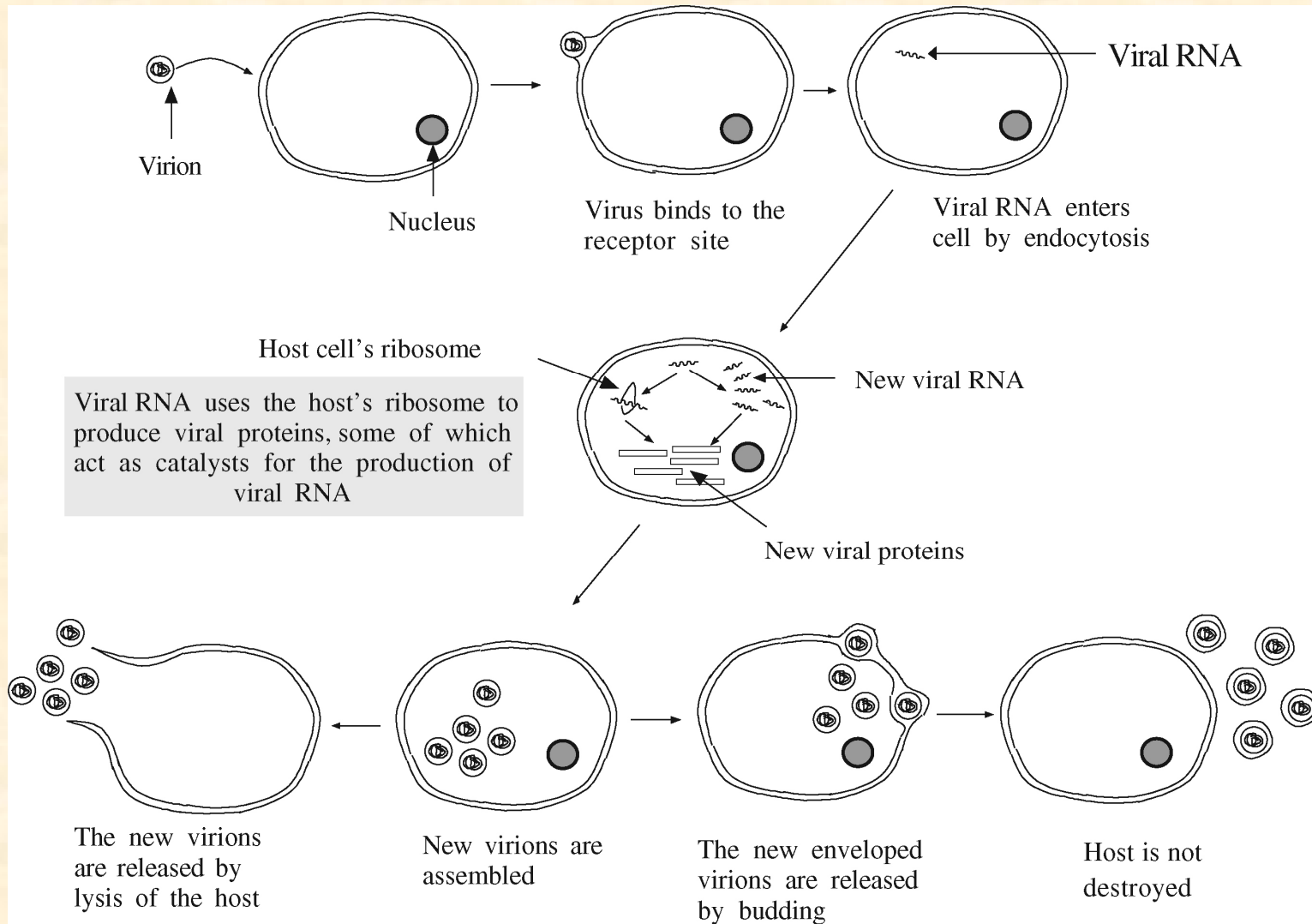
Viruses

- Structure



Viruses

• Replication



Viruses



- Classification

- RNA viruses

1. with single stranded antisense RNA, that is the complement of the message sense. (**negative-stranded RNA**). Examples: measles, Ebola
2. with single-stranded RNA, that has message sense (can act as a mRNA). (**positive-stranded RNA**). Examples: poliovirus
3. with genome made of **double-stranded RNA**. Example: reovirus

- RNA retroviruses

RNA (also single-stranded) is copied by **reverse transcriptase** into a DNA genome within the host cell. Example: HIV-1

- DNA viruses

1. genes on a double-stranded DNA molecule (dsDNA). Example: smallpox, varicella, herpes simplex, hepatitis B etc.
2. genes on a molecule of single-stranded DNA (ssDNA). Example: adeno associated virus (AAV).

Viruses

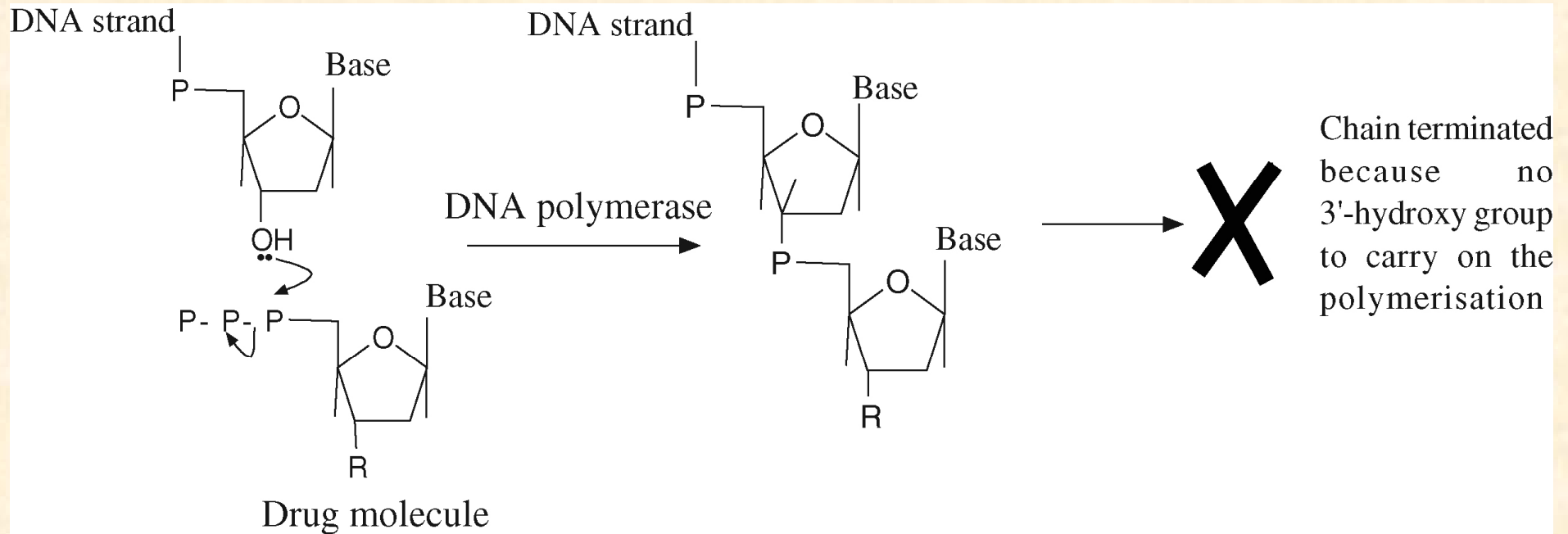


- Viral diseases
 - Parvovirus – Gastroenteritis
 - Herpes – Cold sores or genital
 - Picornavirus – Polio, hep A
 - Retrovirus – AIDS, leukaemia
 - Paramyxovirus – Measles, mumps, and para influenza
 - Rhabdovirus – Rabies

Viruses

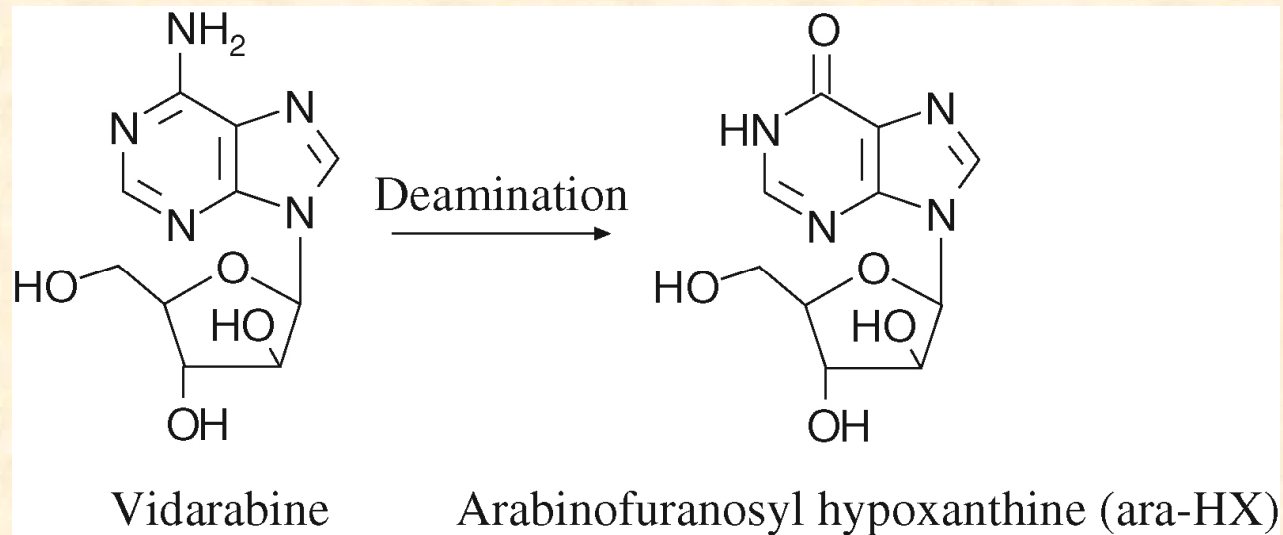
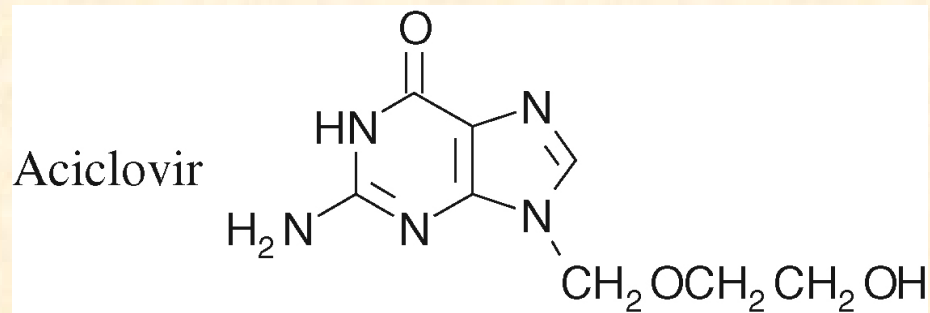
- Antiviral drugs

- Nucleic acid synthesis inhibitors



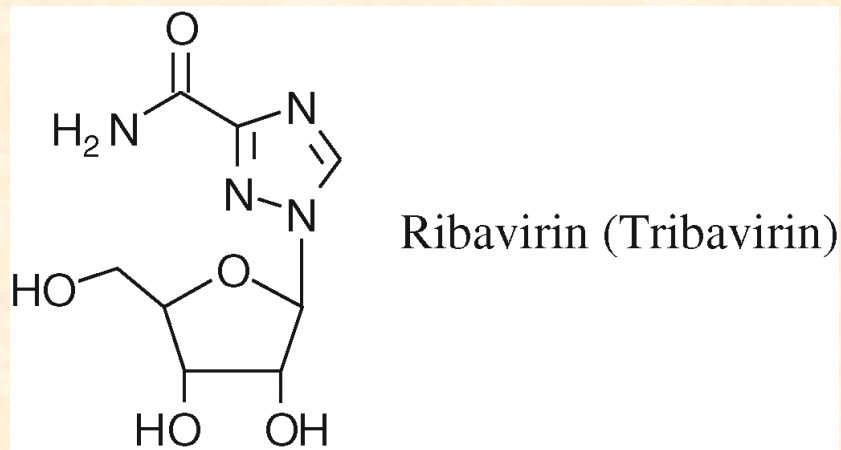
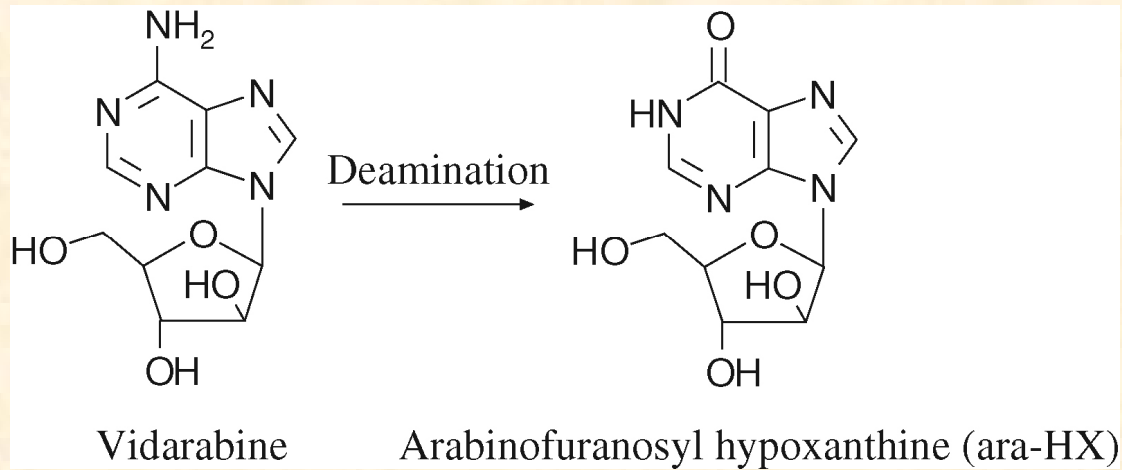
Viruses

- Antiviral drugs
 - Nucleic acid synthesis inhibitors



Viruses

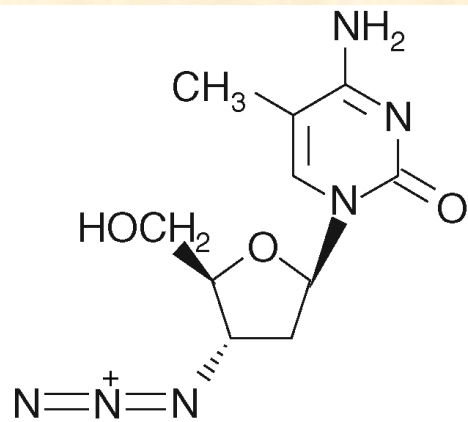
- Antiviral drugs
 - Nucleic acid synthesis inhibitors



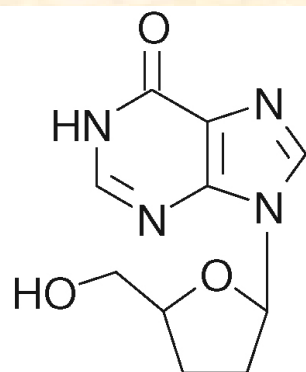
Viruses

- Antiviral drugs
 - Nucleic acid synthesis inhibitors

Zidovudine (AZT)

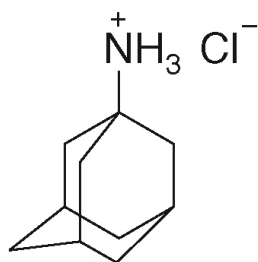


Didanosine

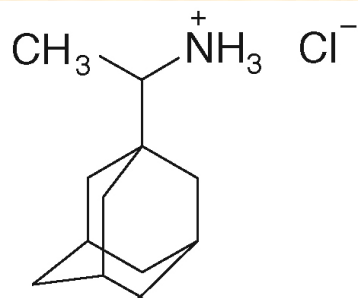


Viruses

- Antiviral drugs
 - Host cell penetration inhibitors

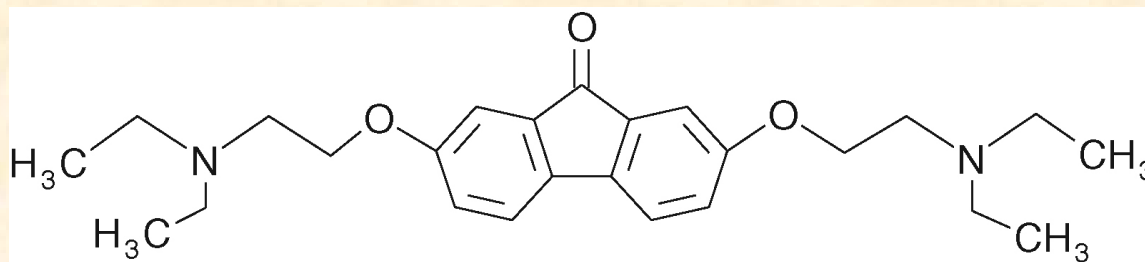


Amantadine hydrochloride



Rimantadine hydrochloride

- Inhibitors of viral protein synthesis



Tilorone