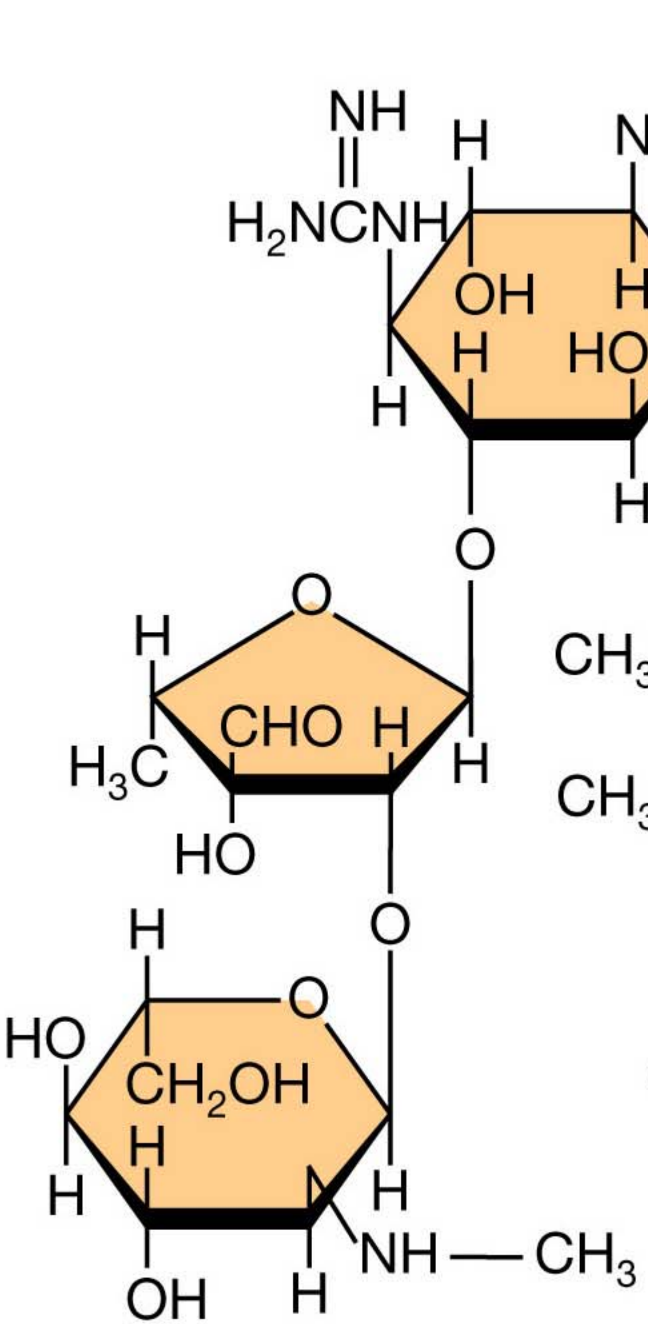
Classification of Antibiotics:

1. Inhibit growth – “stat”
   Kill bacterium – “cide”

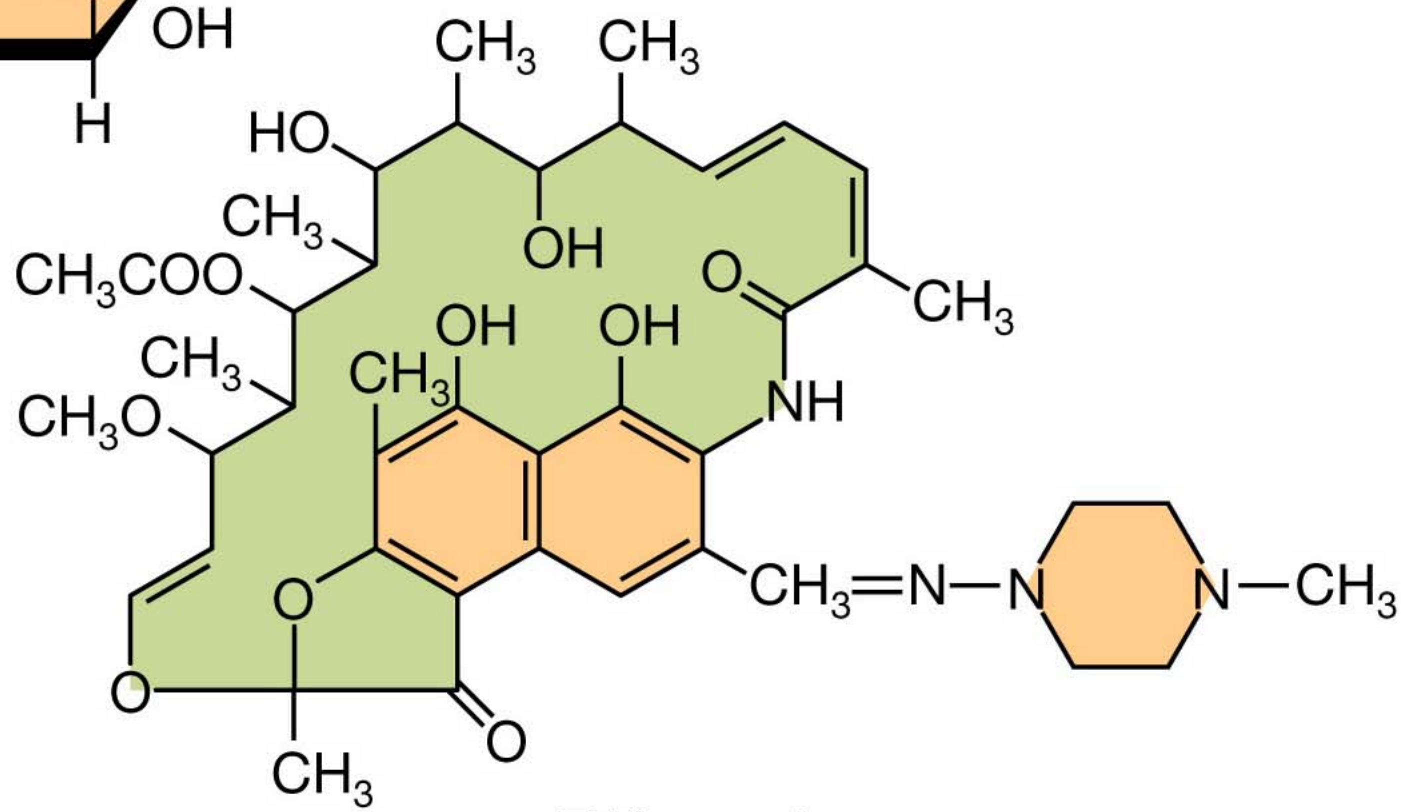
2. Broad and Narrow spectrum

3. Production Types:
   - Natural
   - Synthetic
   - Semi-synthetic

Representative structure

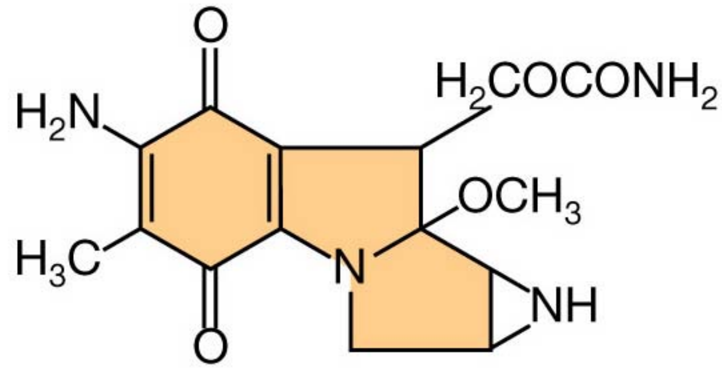


Streptomycin

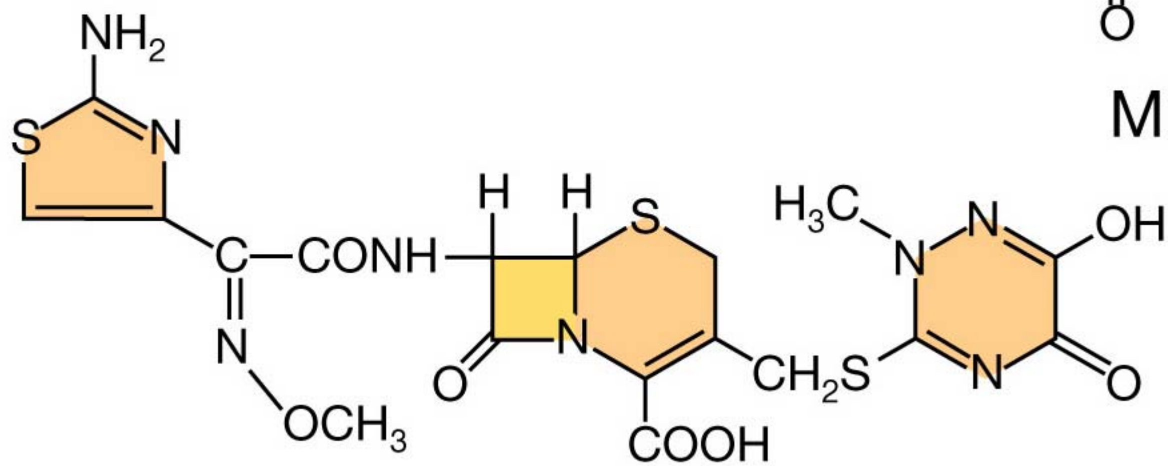


Rifampin

Representative structure

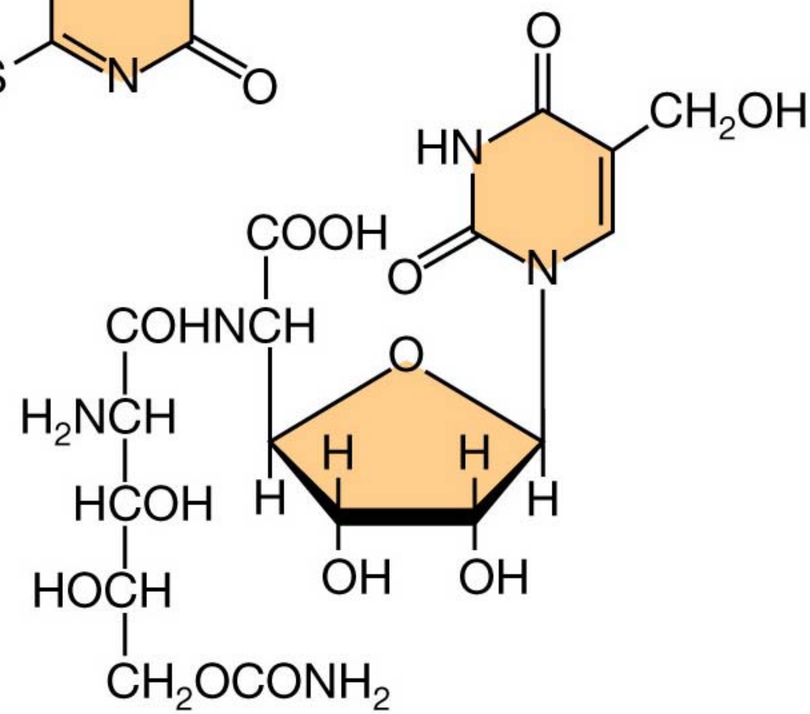


Mitomycin C



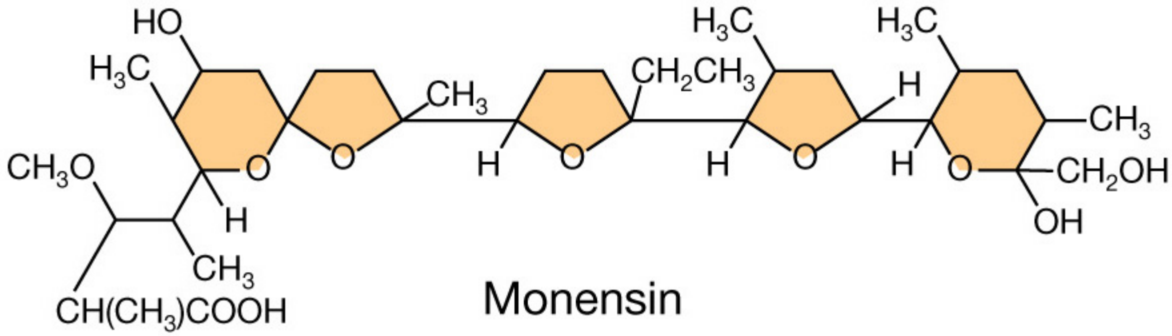
Ceftriaxone

Fancy synthetic cephalosporin,
Note β-lactam box

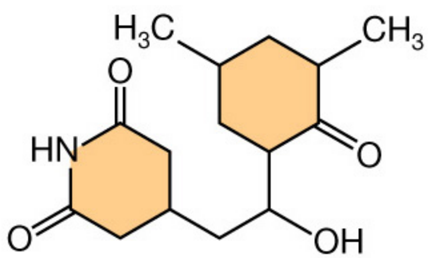


Polyoxin B

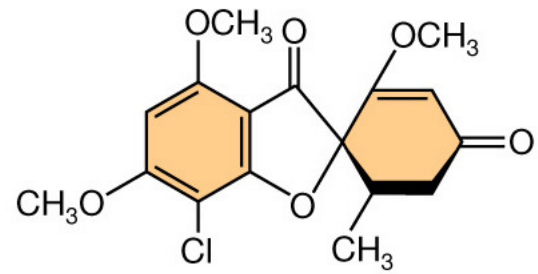
Representative structure



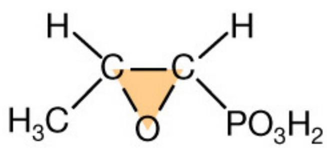
Monensin



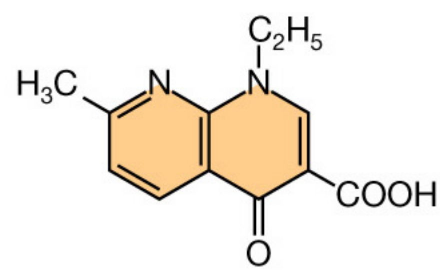
Cycloheximide



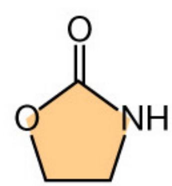
Griseofulvin



Fosfomycin

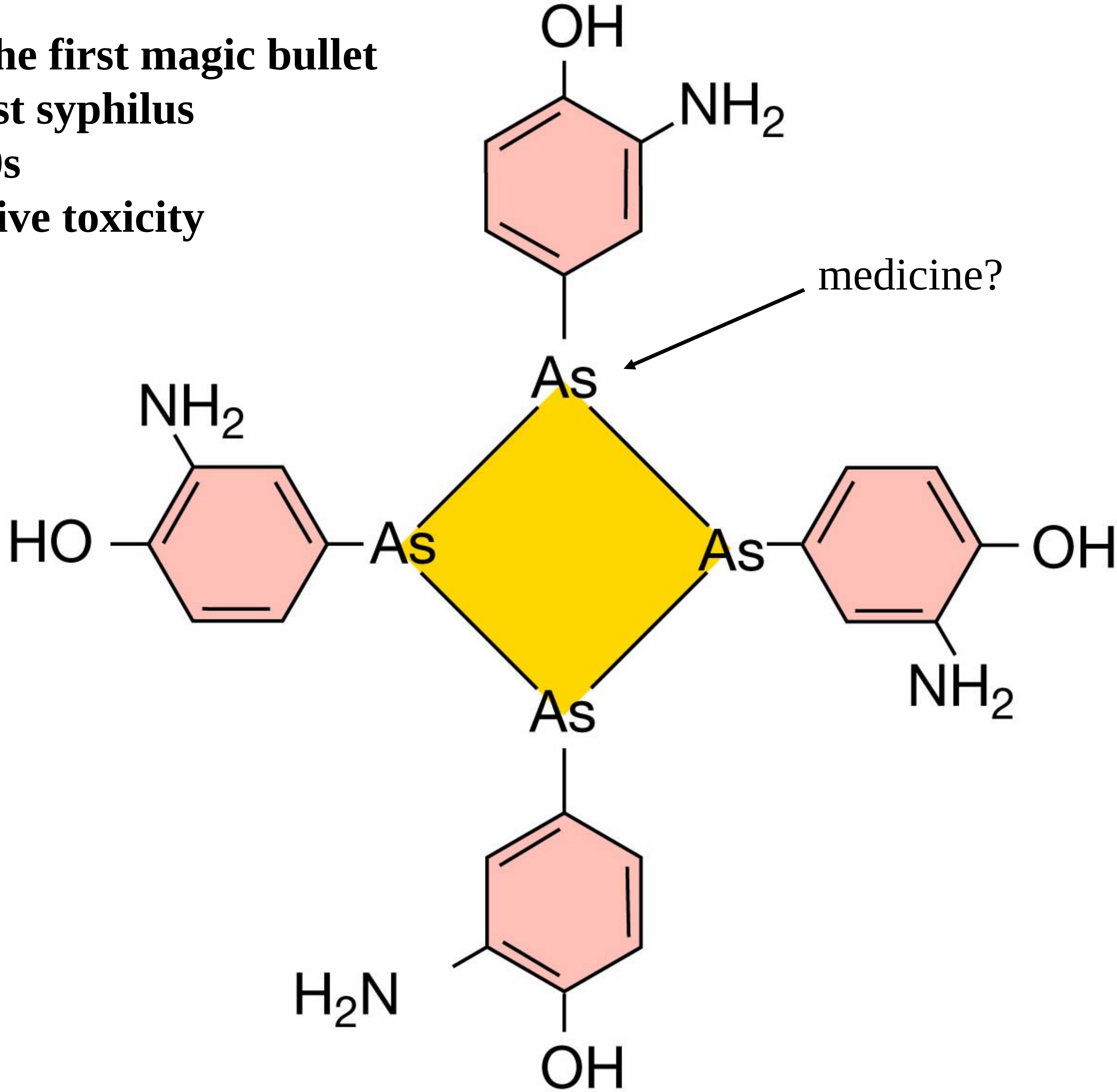


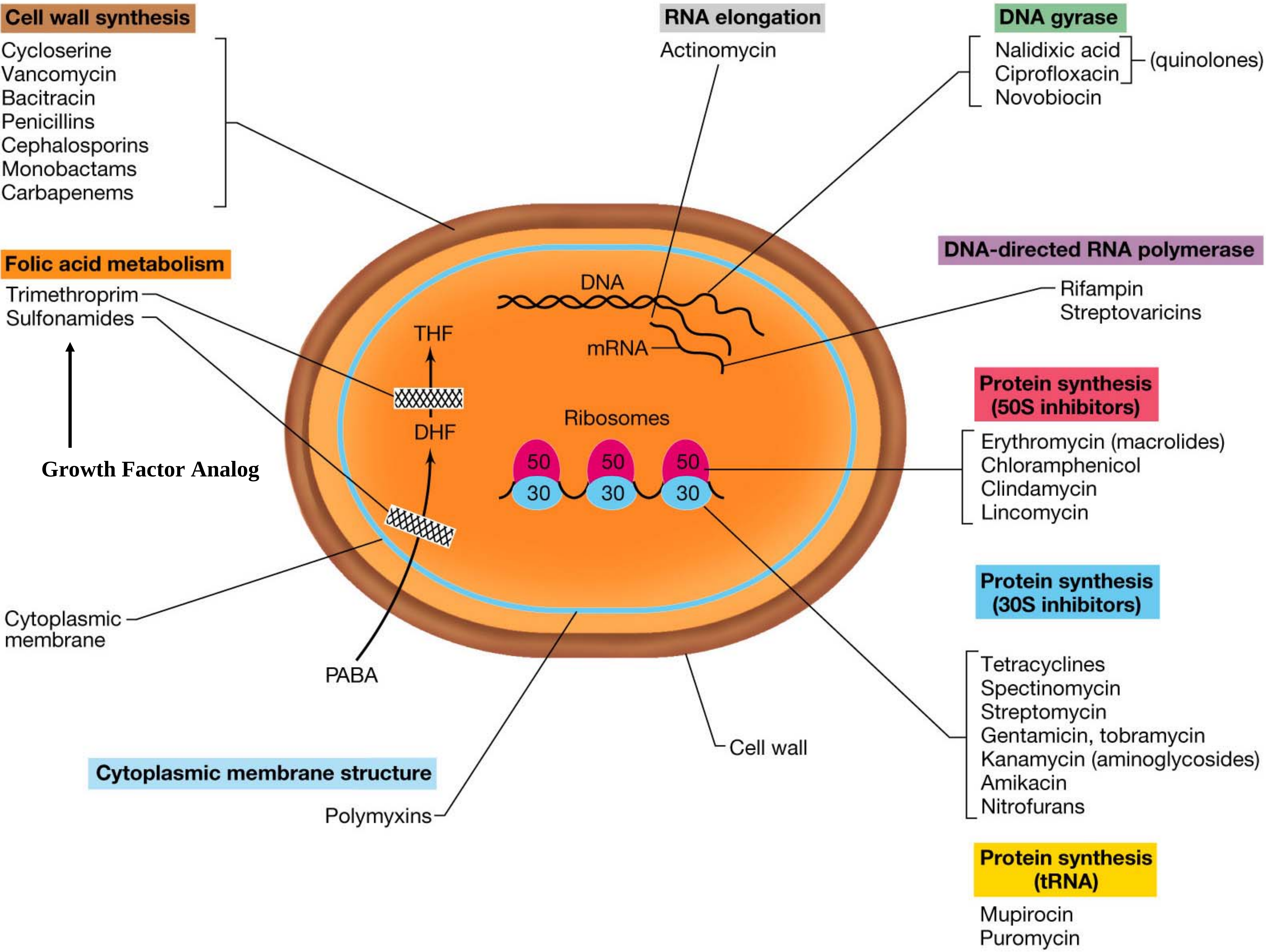
Nalidixic acid



2-Oxazolidinone

Salvarsan: The first magic bullet
Works against syphilus
Ehrlich, 1900s
Idea of selective toxicity





Cell wall synthesis
Cycloserine
Vancomycin
Bacitracin
Penicillins
Cephalosporins
Monobactams
Carbapenems
RNA elongation
Actinomycin
DNA gyrase
Nalidixic acid
Ciprofloxacin
Novobiocin
(quinolones)
Folic acid metabolism
Trimethroprim
Sulfonamides
Growth Factor Analog
THF
DHF
PABA
DNA
mRNA
Ribosomes
50
30
DNA-directed RNA polymerase
Rifampin
Streptovaricins
Protein synthesis (50S inhibitors)
Erythromycin (macrolides)
Chloramphenicol
Clindamycin
Lincomycin
Protein synthesis (30S inhibitors)
Tetracyclines
Spectinomycin
Streptomycin
Gentamicin, tobramycin
Kanamycin (aminoglycosides)
Amikacin
Nitrofurans
Protein synthesis (tRNA)
Mupirocin
Puromycin
Cytoplasmic membrane
Cell wall
Cytoplasmic membrane structure
Polymyxins

Antibiotics Affecting Replication, Transcription, & Translation

DNA replication:

Nalidixic Acid & Novobiocin – Inhibits DNA gyrase

Transcription:

Rifampin – Beta subunit of RNA polymerase

Actinomycin – DNA binding, blocks elongation

Translation:

Streptomycin – Blocks initiation on SSU of ribosome

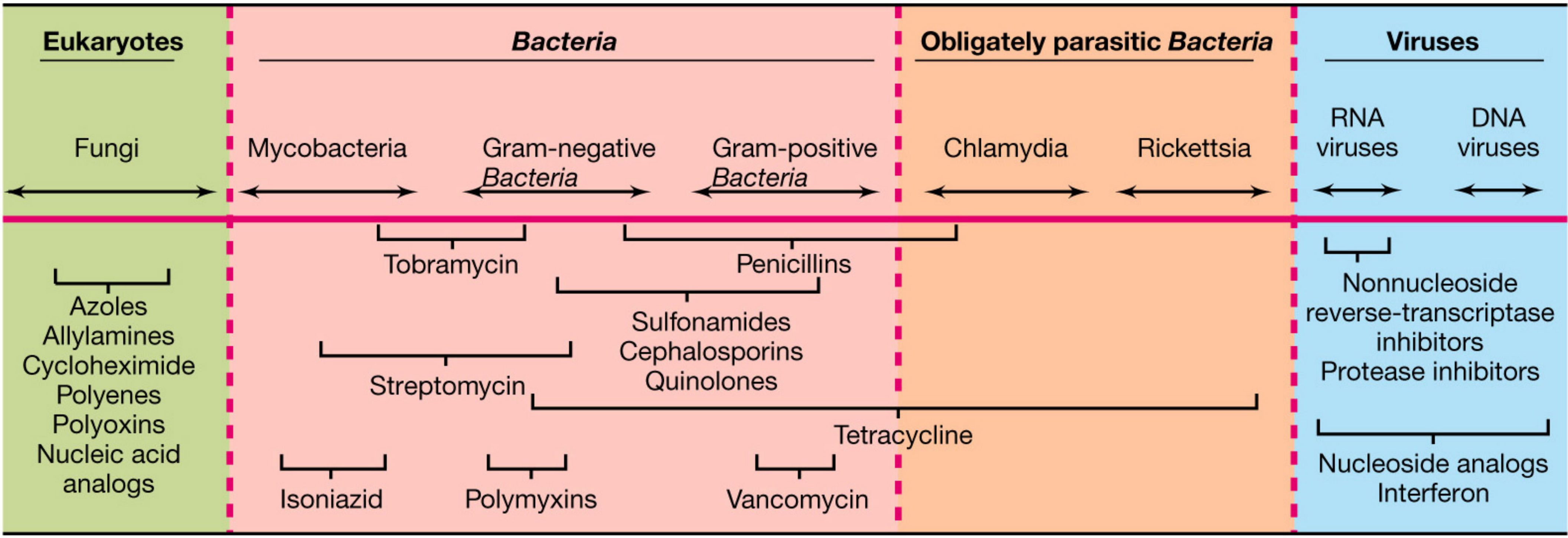
Chloramphenicol – Blocks elongation on LSU via peptide bond

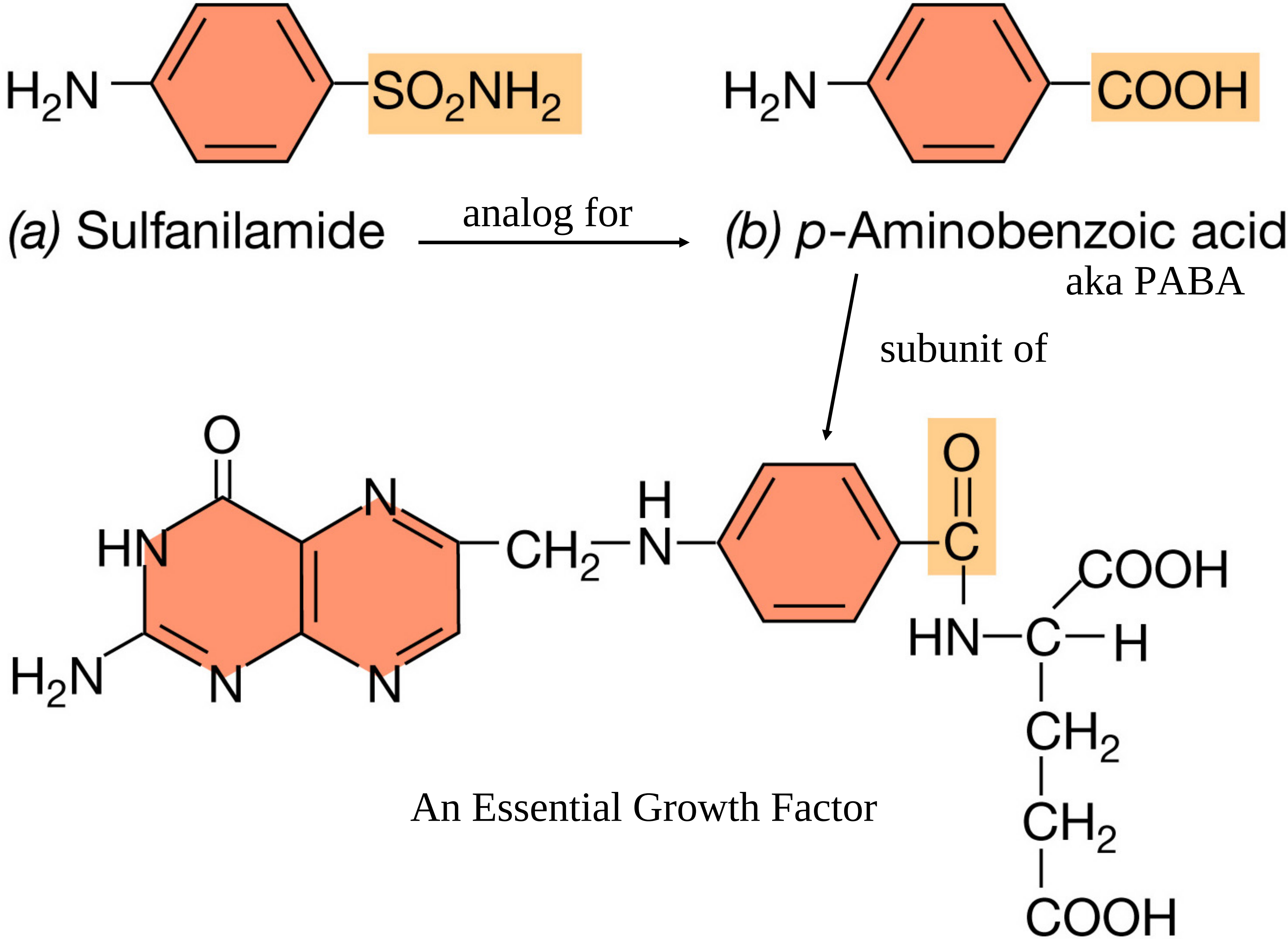
Tetracycline – Blocks elongation SSU

Cycloheximide – Eucarya ribosome specific

Diptheria Toxin – EF blocker; both Archaea and Eucarya

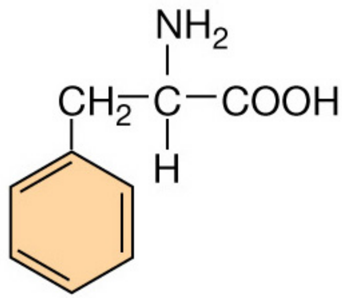
Antimicrobial spectrum of action for selected chemotherapeutics



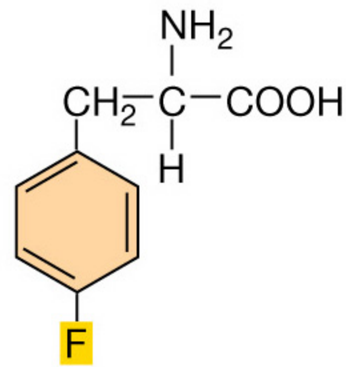

H2N
SO2NH2
(a) Sulfanilamide
analog for
H2N
COOH
(b) p-Aminobenzoic acid
aka PABA
subunit of
O
HN
H2N
N
N
N
CH2
H
N
O
C
COOH
HN
C
H
CH2
CH2
COOH
An Essential Growth Factor

(c) Folic acid

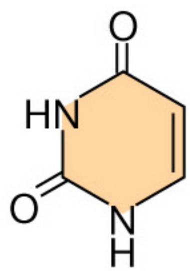
Growth factor | **Analog**



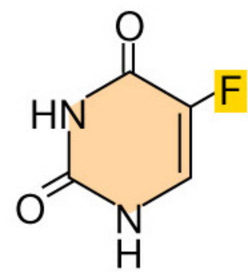
Phenylalanine
(an amino acid)



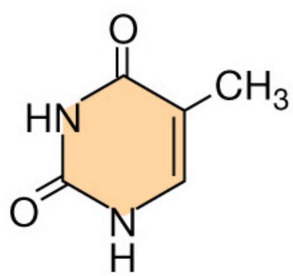
p-Fluorophenylalanine



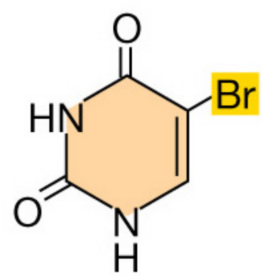
Uracil
(an RNA base)



5-Fluorouracil
(a uracil analog)

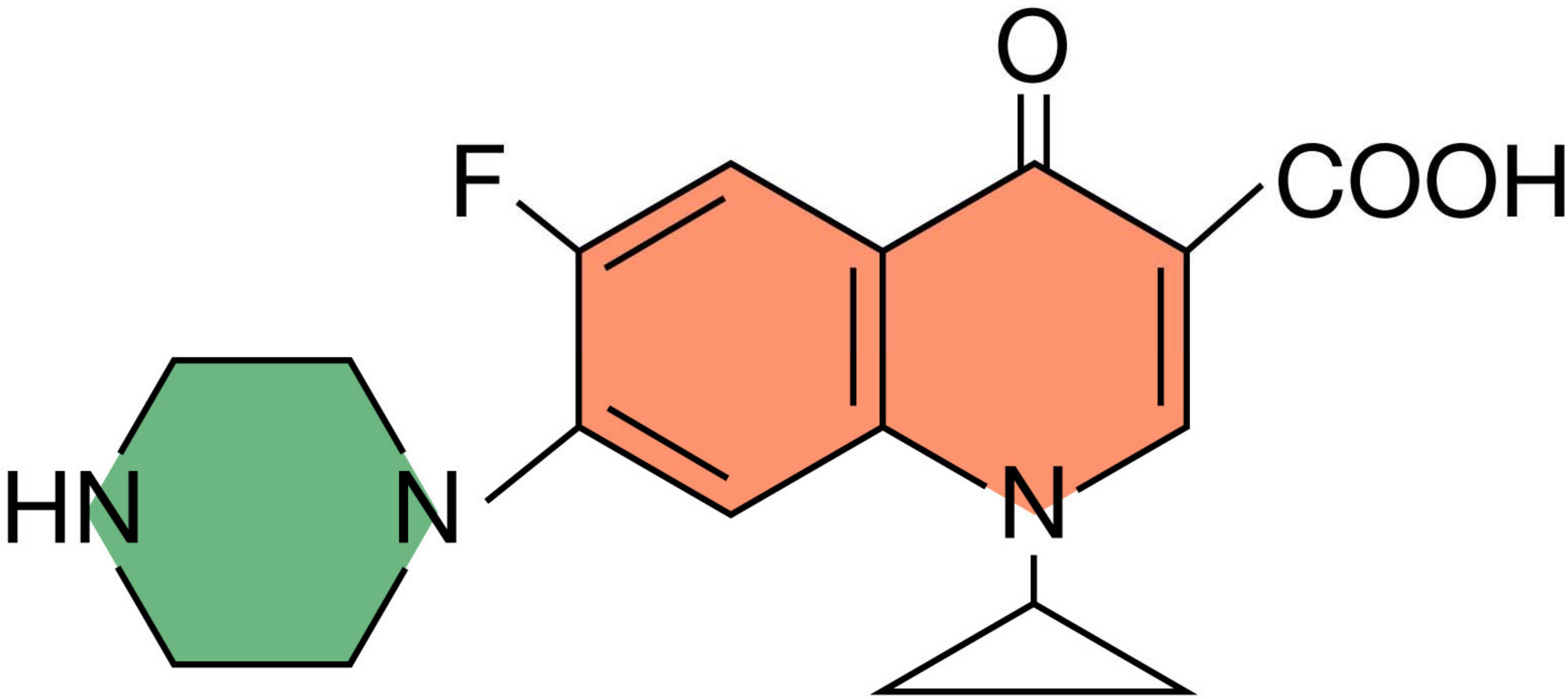


Thymine
(a DNA base)

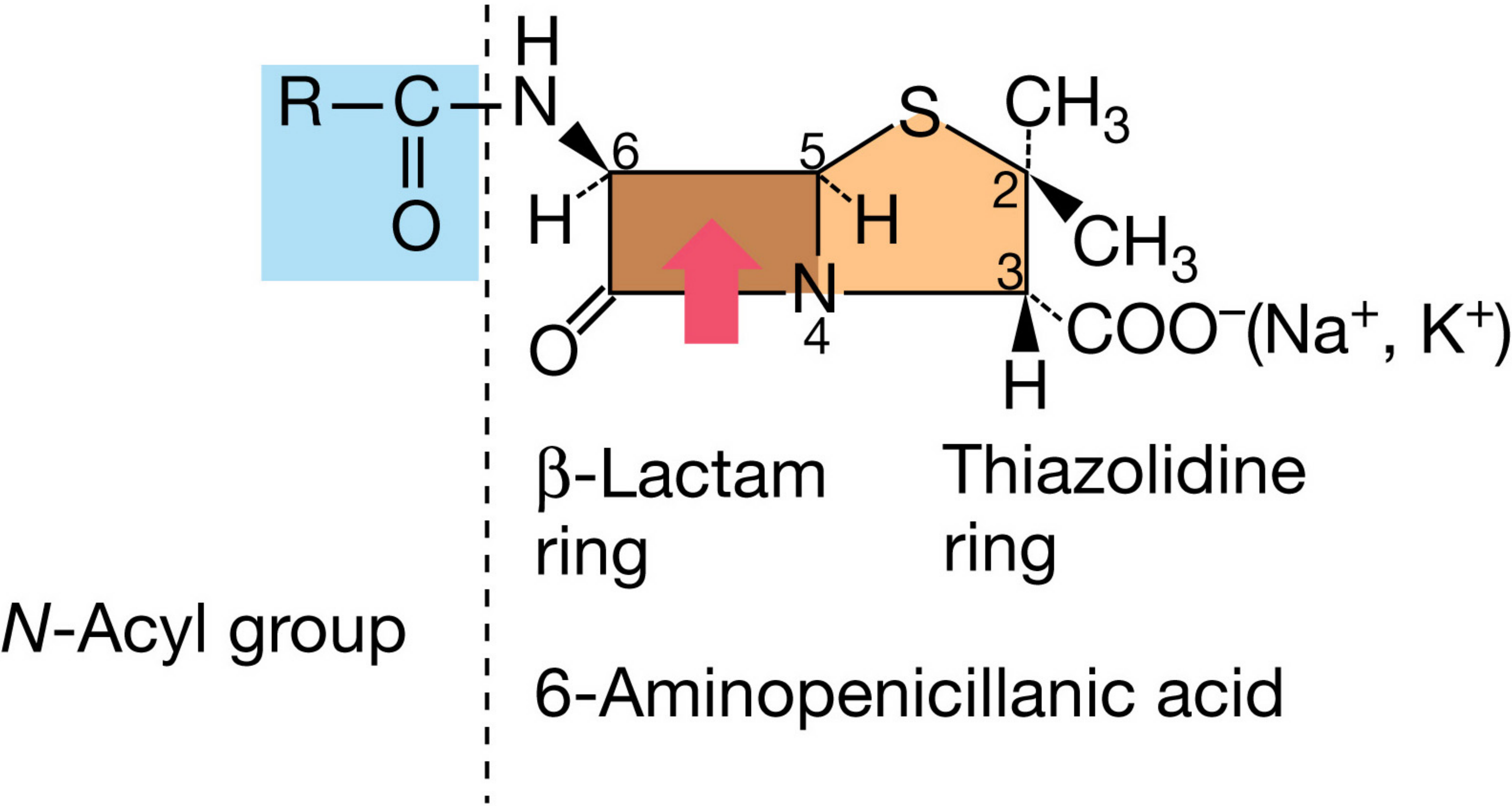


5-Bromouracil
(a thymine analog)

Cipro or ciprofloxacin, a quinoline
Not a growth factor!
Prevents DNA gyrase from supercoiling
Used for anthrax, etc.



How to build a better mouse trap: Penicillin
A β-lactam antibiotic



Inhibits transpeptidation of peptidoglycan chains
Forms the old 1-2-punch with autolysins

Semi's are made
to be acid-stable and
more broad spectrum

Difference b/t ampicillin
and penicillin is only
one amino group.

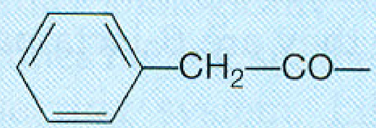
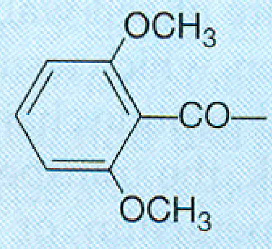
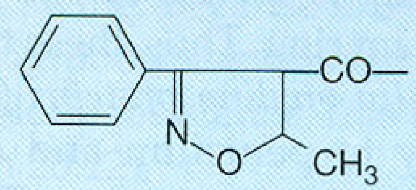
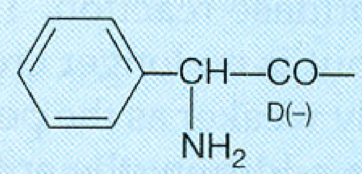
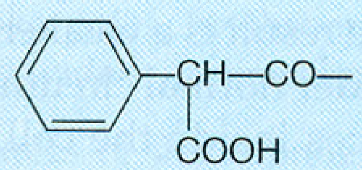
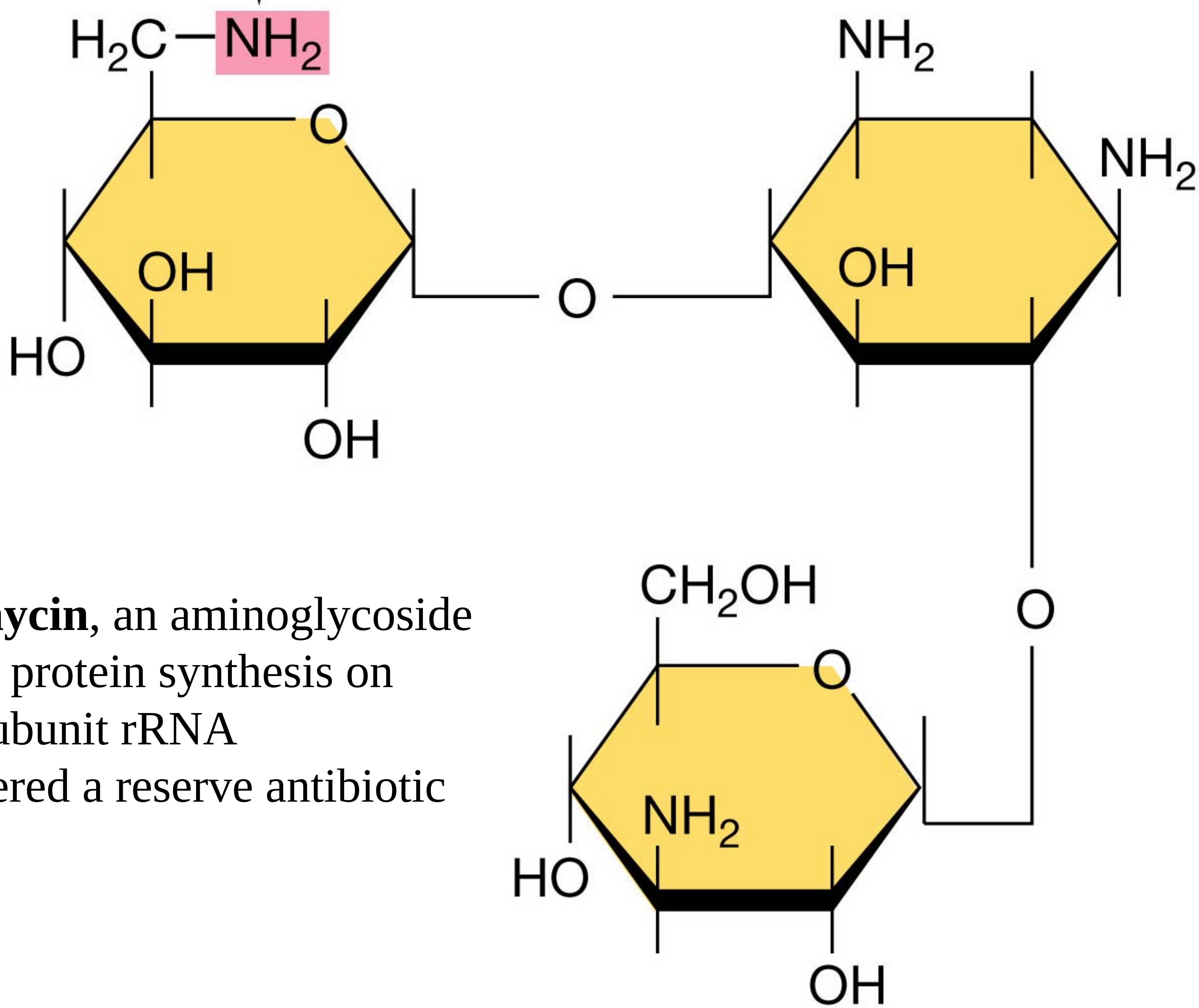
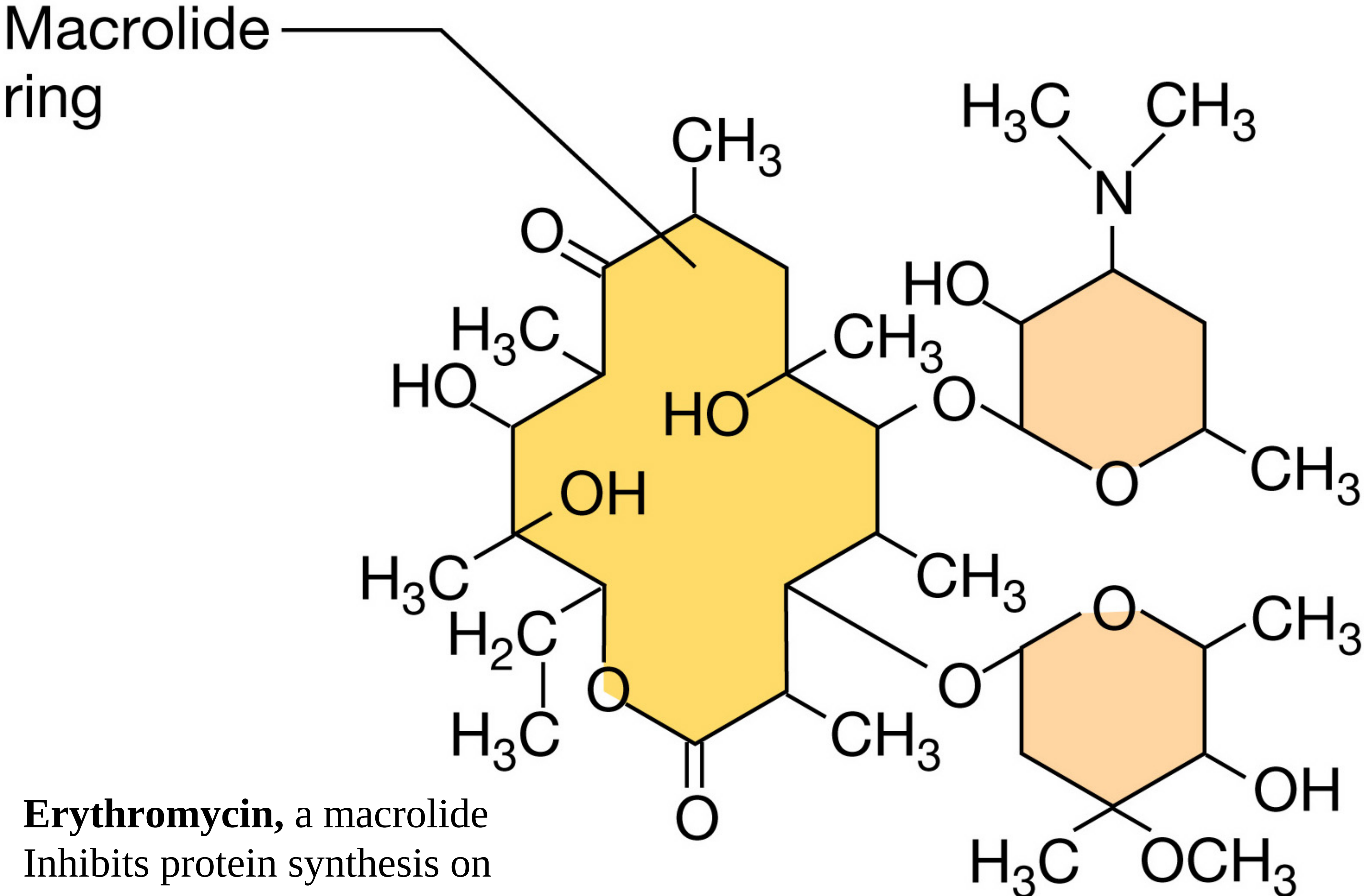
Designation	*N*-Acyl group
NATURAL PENICILLIN	
Benzylpenicillin (penicillin G) Gram-positive activity β-lactamase-sensitive	
SEMISYNTHETIC PENICILLINS	
Methicillin acid-stable, β-lactamase-resistant	
Oxacillin acid-stable, β-lactamase-resistant	
Ampicillin broadened spectrum of activity (especially against gram-negative bacteria), acid-stable, β-lactamase-resistant	
Carbenicillin broadened spectrum of activity (especially against *Pseudomonas aeruginosa*), acid-stable but ineffective orally, β-lactamase-sensitive	

Figure 20.19 The structures of some important penicillins.

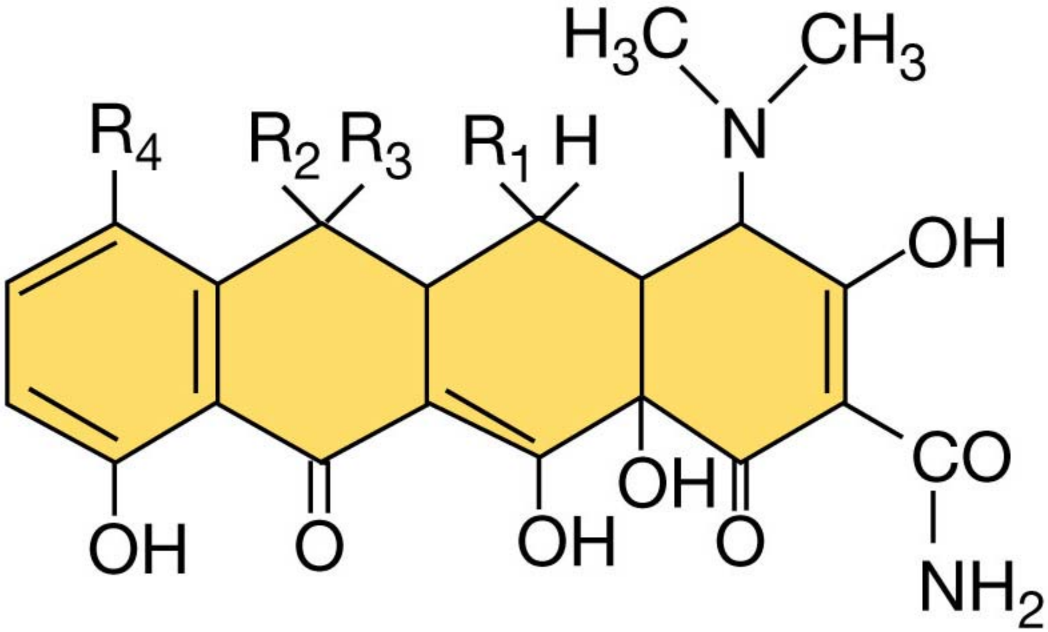
N-Acetyltransferase ← R-plasmid born resistance



Kanamycin, an aminoglycoside
Inhibits protein synthesis on
small subunit rRNA
Considered a reserve antibiotic



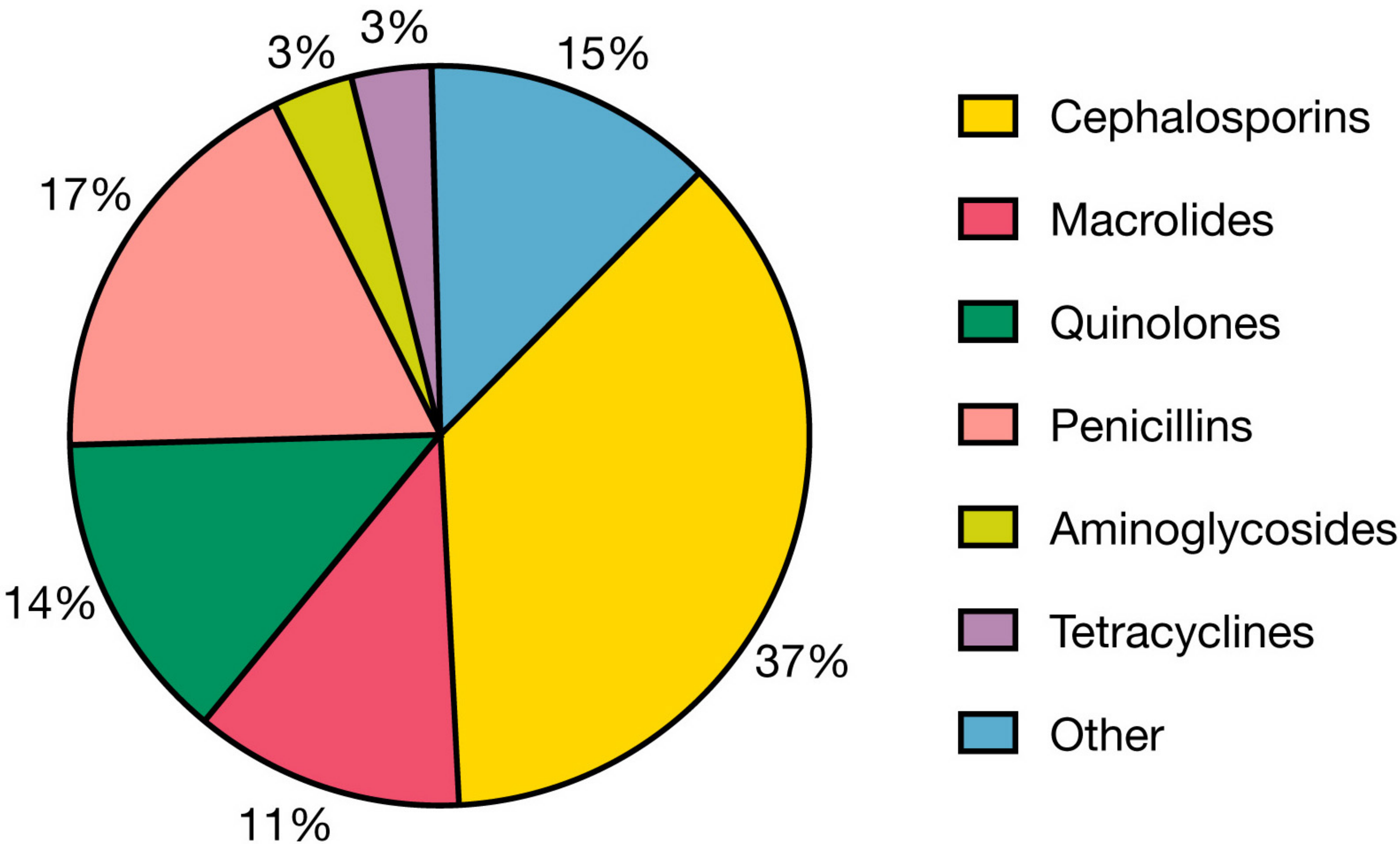
Erythromycin, a macrolide
Inhibits protein synthesis on
large subunit rRNA
Often works when allergic to β-lactams



Tetracyclines
Inhibits protein synthesis on small subunit rRNA
Along with β-lactams make up the majority used

Tetracycline analog	R_1	R_2	R_3	R_4
Tetracycline	H	OH	CH_3	H
7-Chlortetracycline (aureomycin)	H	OH	CH_3	Cl
5-Oxytetracycline (terramycin)	OH	OH	CH_3	H

Annual Worldwide Production of Antibiotics



Overall more than 500 metric tons!

Mechanisms of Antibiotic Resistance

1. Lacks structure antibiotic inhibits:
   Mycoplasms lack a typical cell wall

2. Impermeable to the antibiotic:
   Gram - bacteria impermeable to penicillin G

3. Alteration of antibiotic:
   β-lactamase degrades antibiotic e.g., springs open the mouse trap

4. Modifies the target of the antibiotic

5. Genetically modifies the pathway that the antibiotic affects

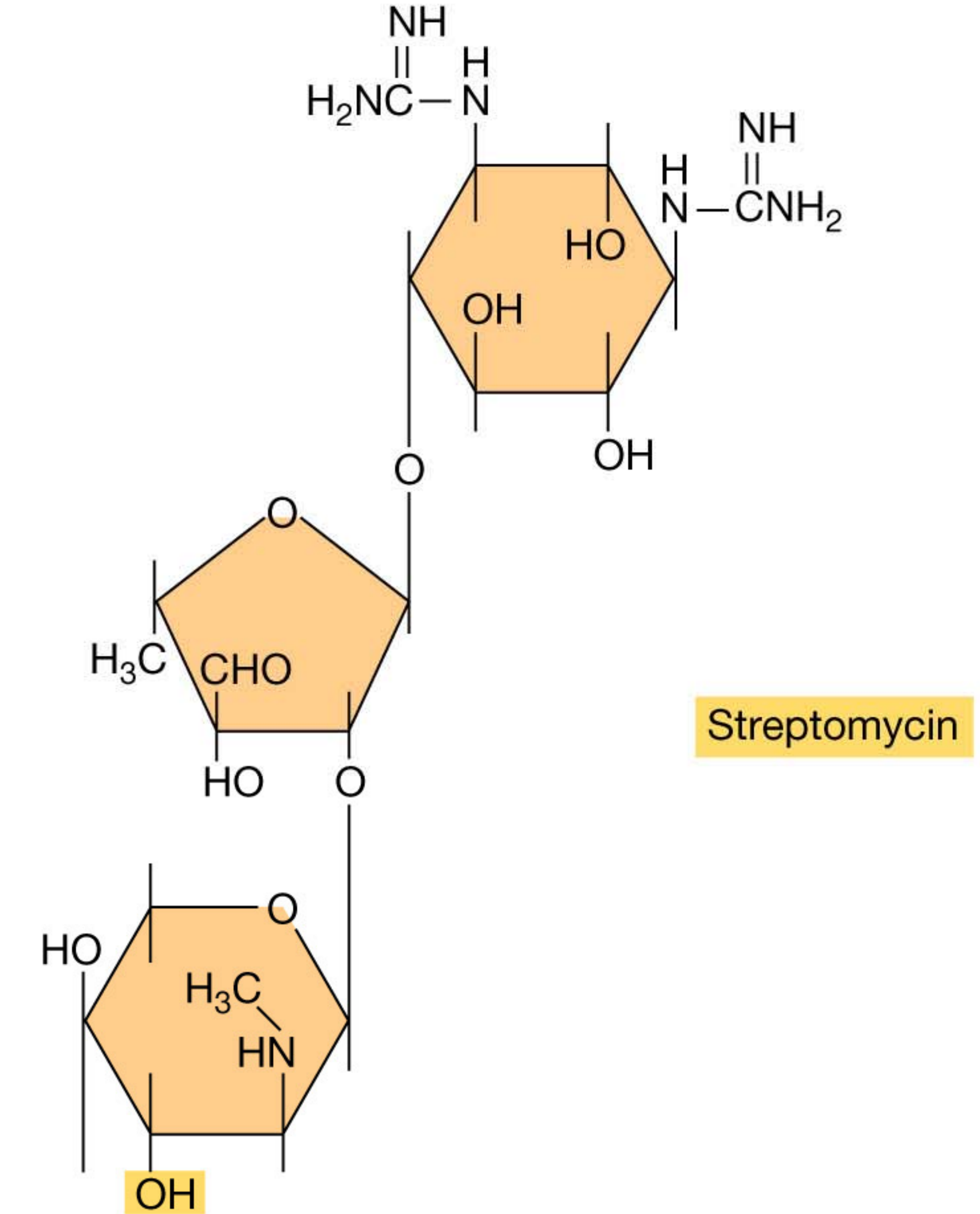
6. Efflux of the antibiotic:
   Tetracycline gets pumped back out of the cell

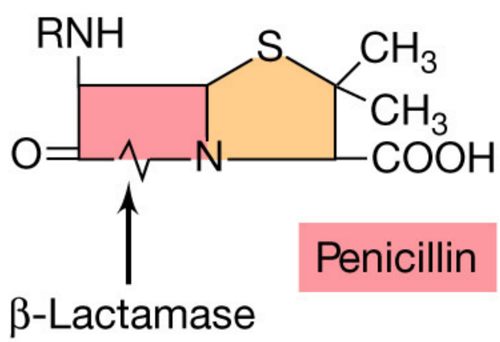
TABLE 20.7 Mechanisms of bacterial resistance to antibiotics

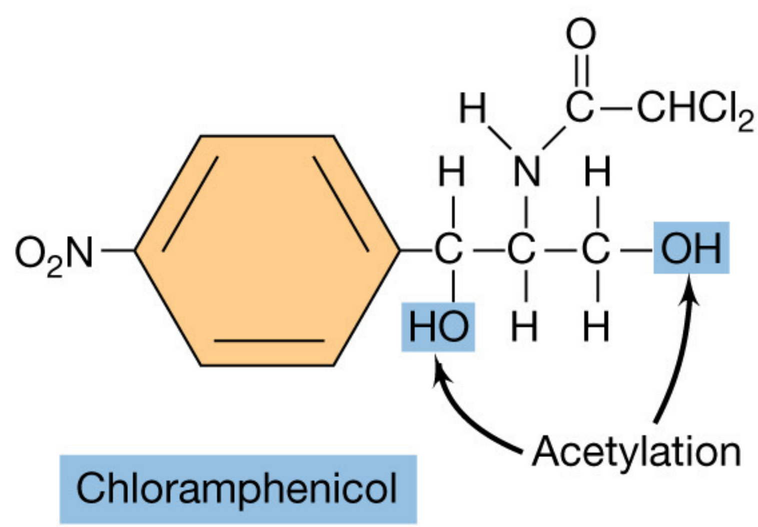
Resistance mechanism	Antibiotic example	Genetic basis of resistance	Mechanism present in:
Reduced permeability	Penicillins	Chromosomal	*Pseudomonas aeruginosa* Enteric *Bacteria*
Inactivation of antibiotic (for example, penicillinase; modifying enzymes methylases, acetylases, and phosphorylases; and others)	Penicillins	Plasmid and chromosomal	*Staphylococcus aureus* Enteric *Bacteria* *Neisseria gonorrhoeae*
	Chloramphenicol	Plasmid and chromosomal	*Staphylococcus aureus* Enteric *Bacteria*
	Aminoglycosides	Plasmid	*Staphylococcus aureus*
Alteration of target (for example, RNA polymerase, rifamycin; ribosome, erythromycin, and streptomycin; DNA gyrase, quinolones)	Erythromycin	Chromosomal	*Staphylococcus aureus*
	Rifamycin		Enteric *Bacteria*
	Streptomycin		Enteric *Bacteria*
	Norfloxacin		Enteric *Bacteria* *Staphylococcus aureus*
Development of resistant biochemical pathway	Sulfonamides	Chromosomal	Enteric *Bacteria* *Staphylococcus aureus*
Efflux (pumping out of cell)	Tetracyclines	Plasmid	Enteric *Bacteria* *Staphylococcus aureus*
	Chloramphenicol	Chromosomal	*Bacillus subtilis*

R plasmid encoded enzymes attack these various sites.

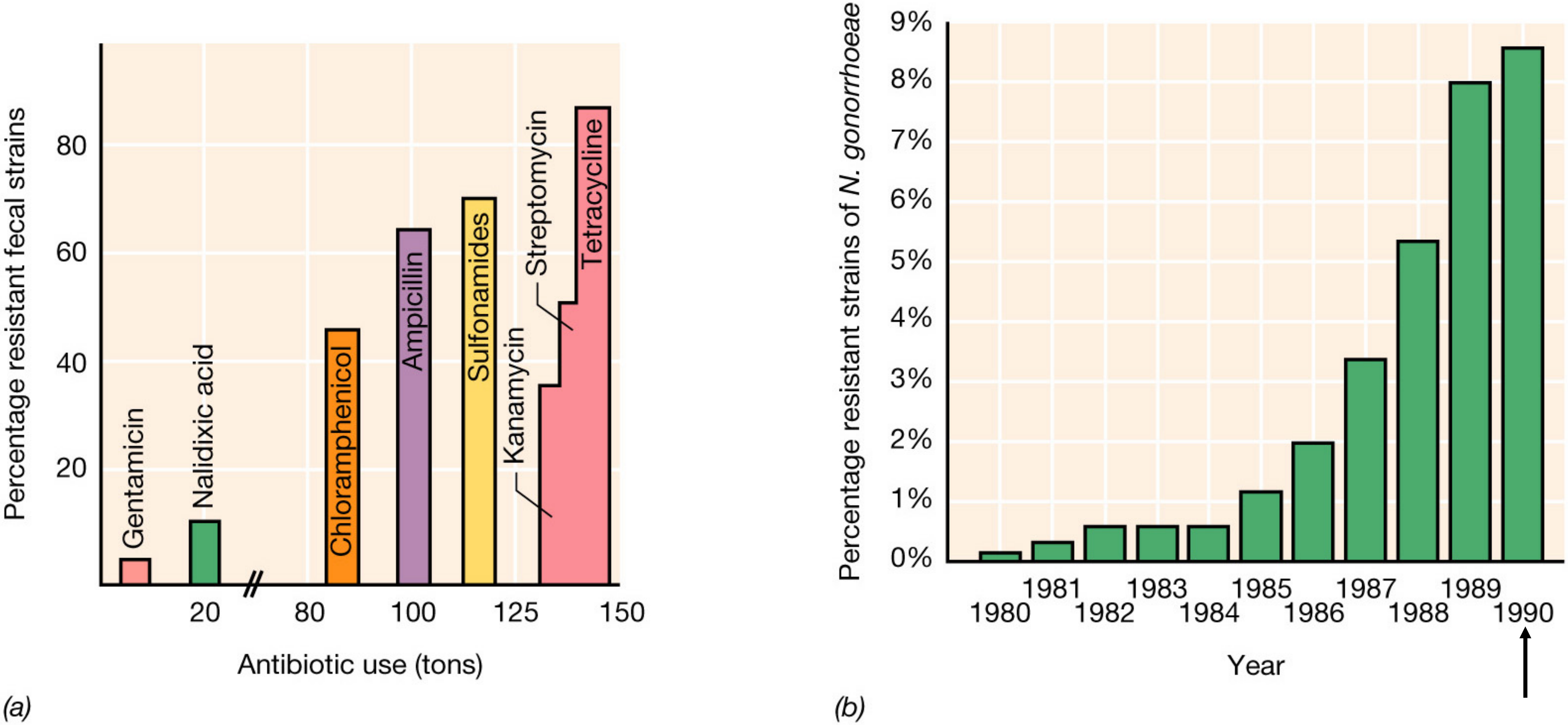
Rem: N-acetylation in Aminoglycosides too!



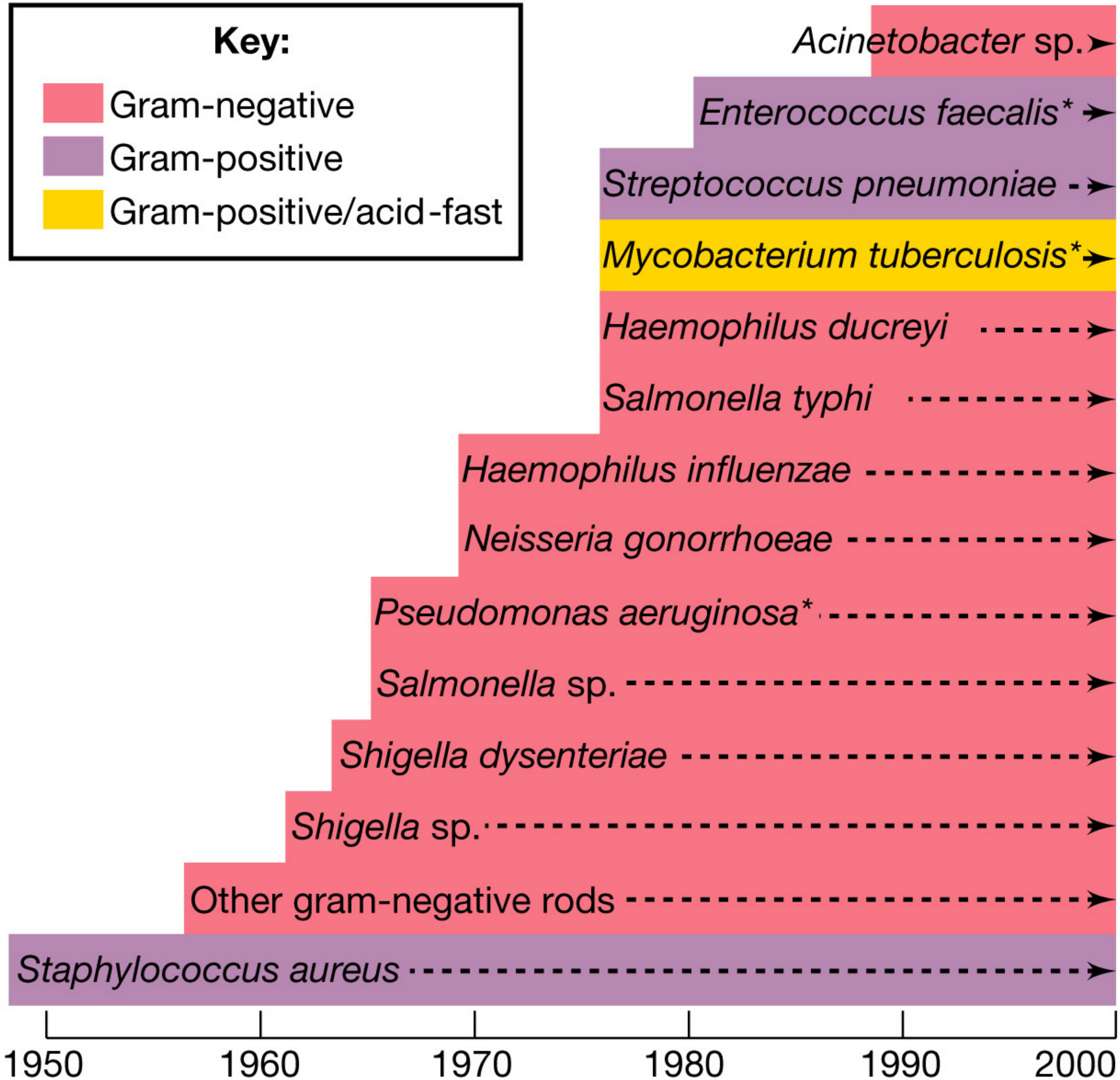




The emergence of antimicrobial drug-resistant bacteria

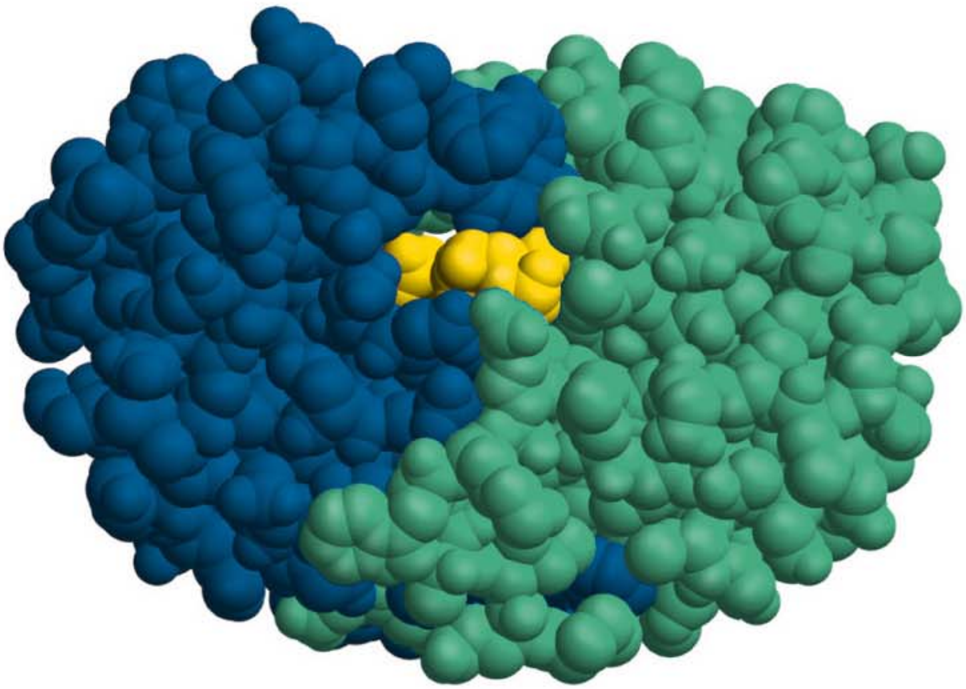


Stopped using penicillin

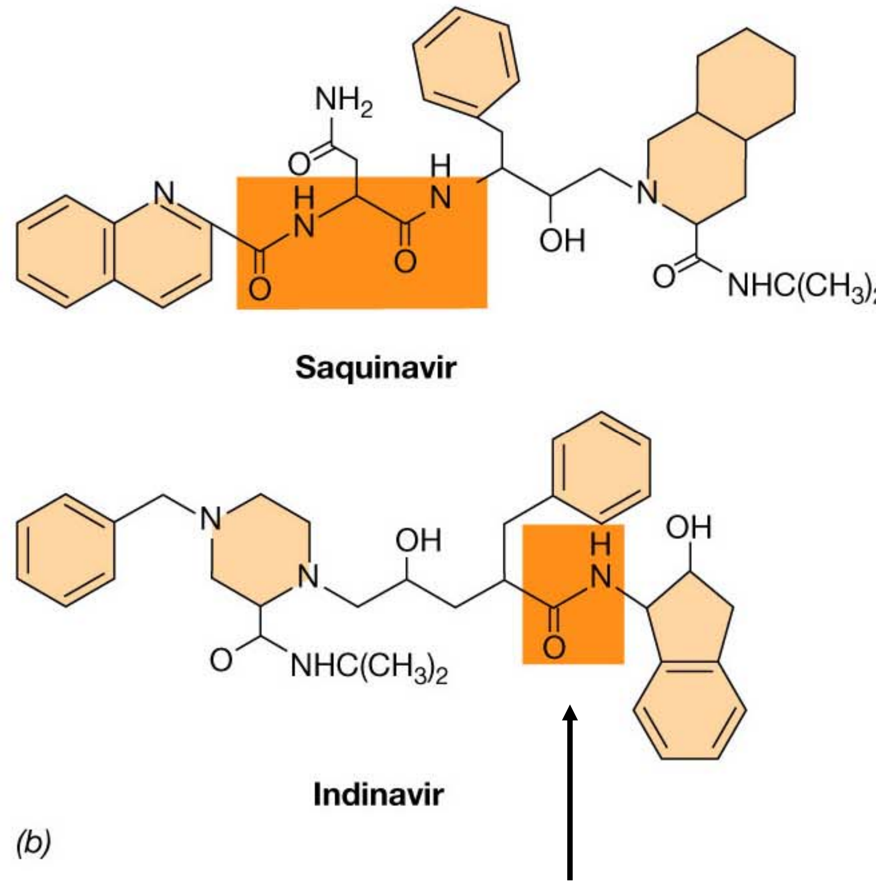


Key:
Gram-negative
Gram-positive
Gram-positive/acid-fast
Acinetobacter sp.
Enterococcus faecalis*
Streptococcus pneumoniae
Mycobacterium tuberculosis*
Haemophilus ducreyi
Salmonella typhi
Haemophilus influenzae
Neisseria gonorrhoeae
Pseudomonas aeruginosa*
Salmonella sp.
Shigella dysenteriae
Shigella sp.
Other gram-negative rods
Staphylococcus aureus
1950
1960
1970
1980
1990
2000

Computerized Drug Design



(a)



(b)

HIV protease homodimer
required for HIV maturation

Peptide bond analogs &
non-nucleoside RT inhibitors

Microbial Sources of Antibiotics

Microorganism	Antibiotic
Bacteria:	
***Streptomyces* spp.**	**chloramphenicol**
	erythromycin
	kanamycin
	rifampin
	streptomycin
	tetracyclines
***Bacillus* spp.**	**bacitracin**
	polymyxin
Fungi:	
***Penicillium* spp.**	**penicillin**
***Cephalosporium* spp.**	**cephalosporins**

Production of Antibiotics:

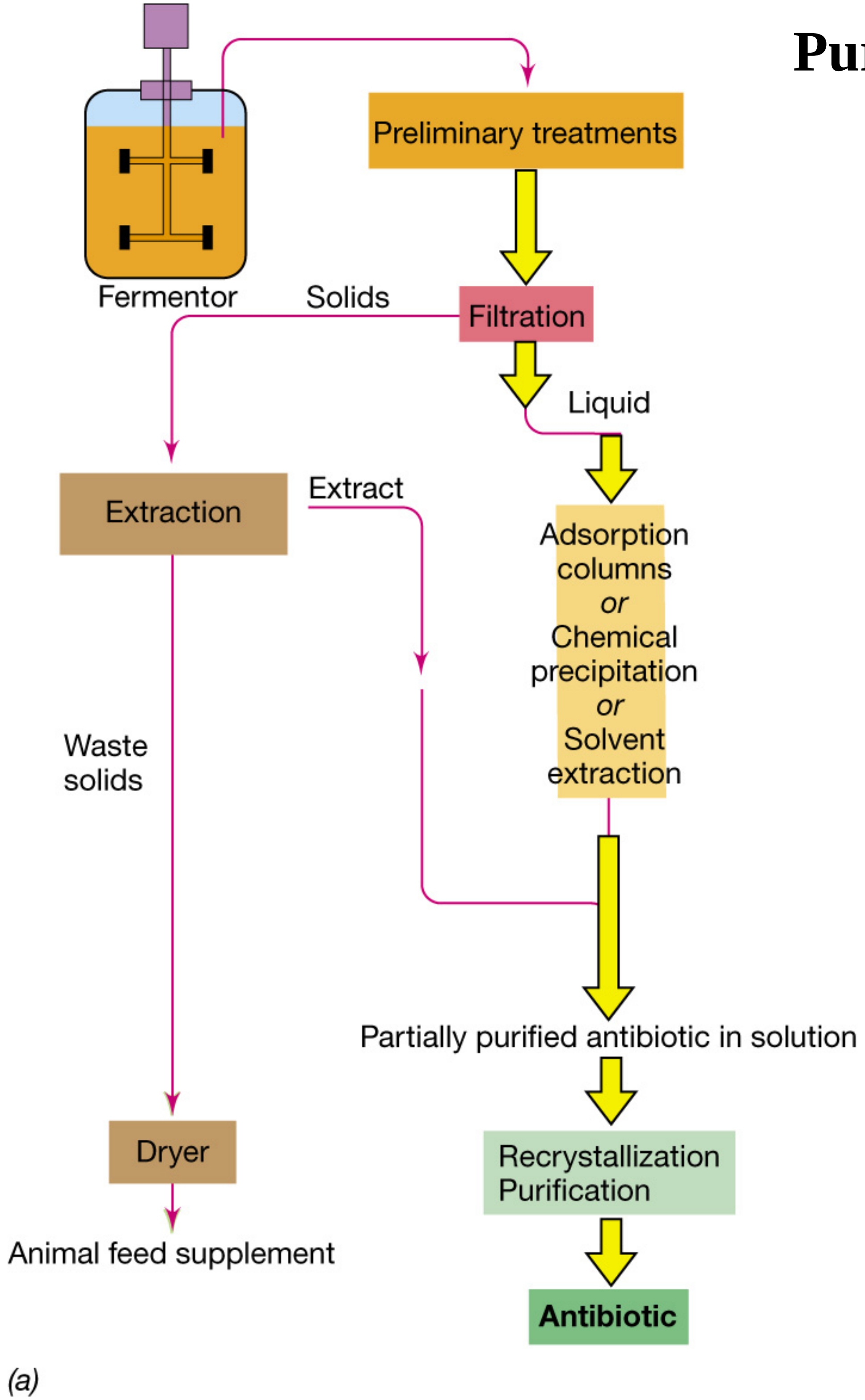
Secondary Metabolites produced near the end of a bacterium or fungus life cycle:

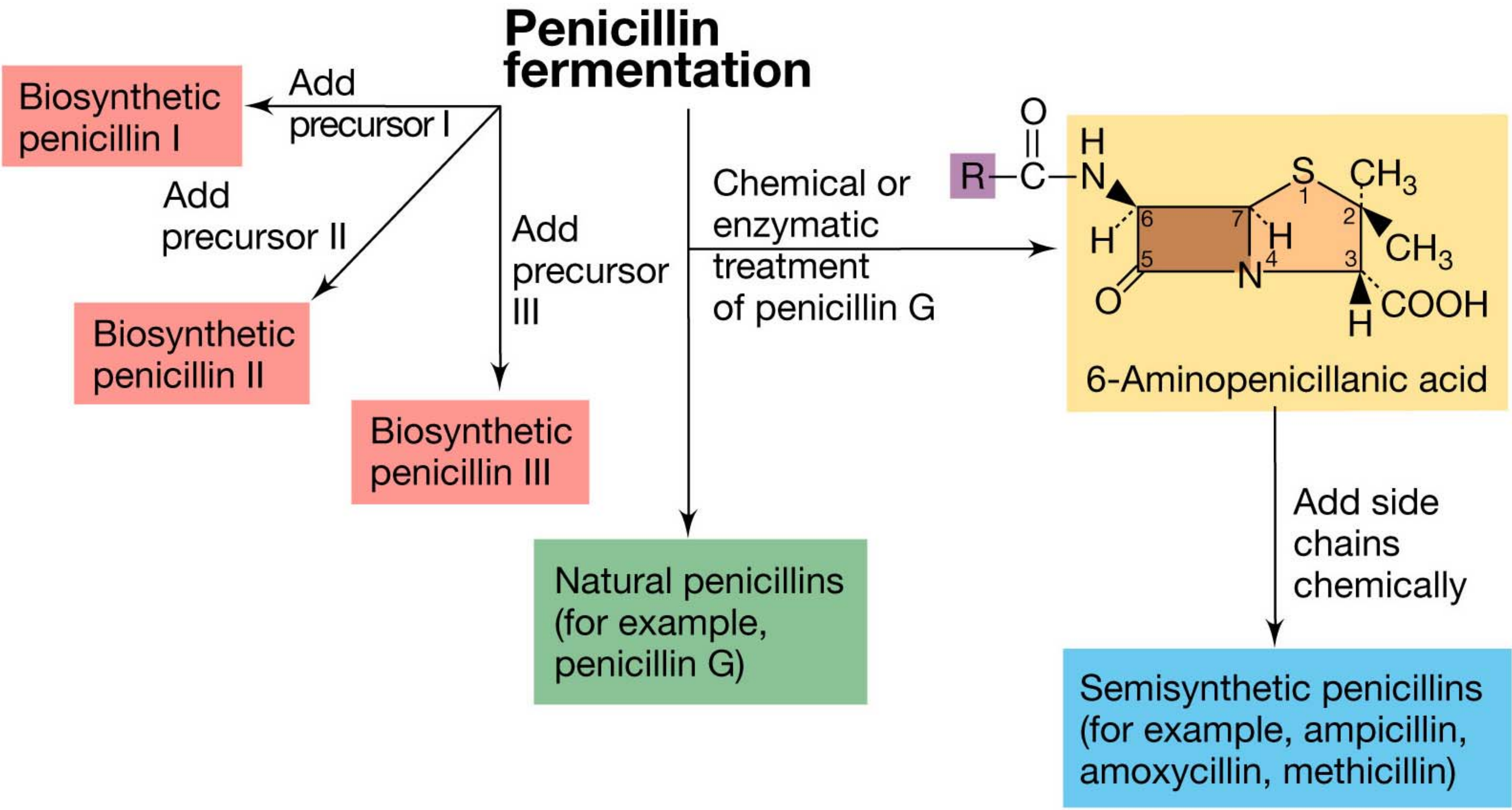
1. Formed @ end of stationary phase of growth

2. Not essential for growth or viability

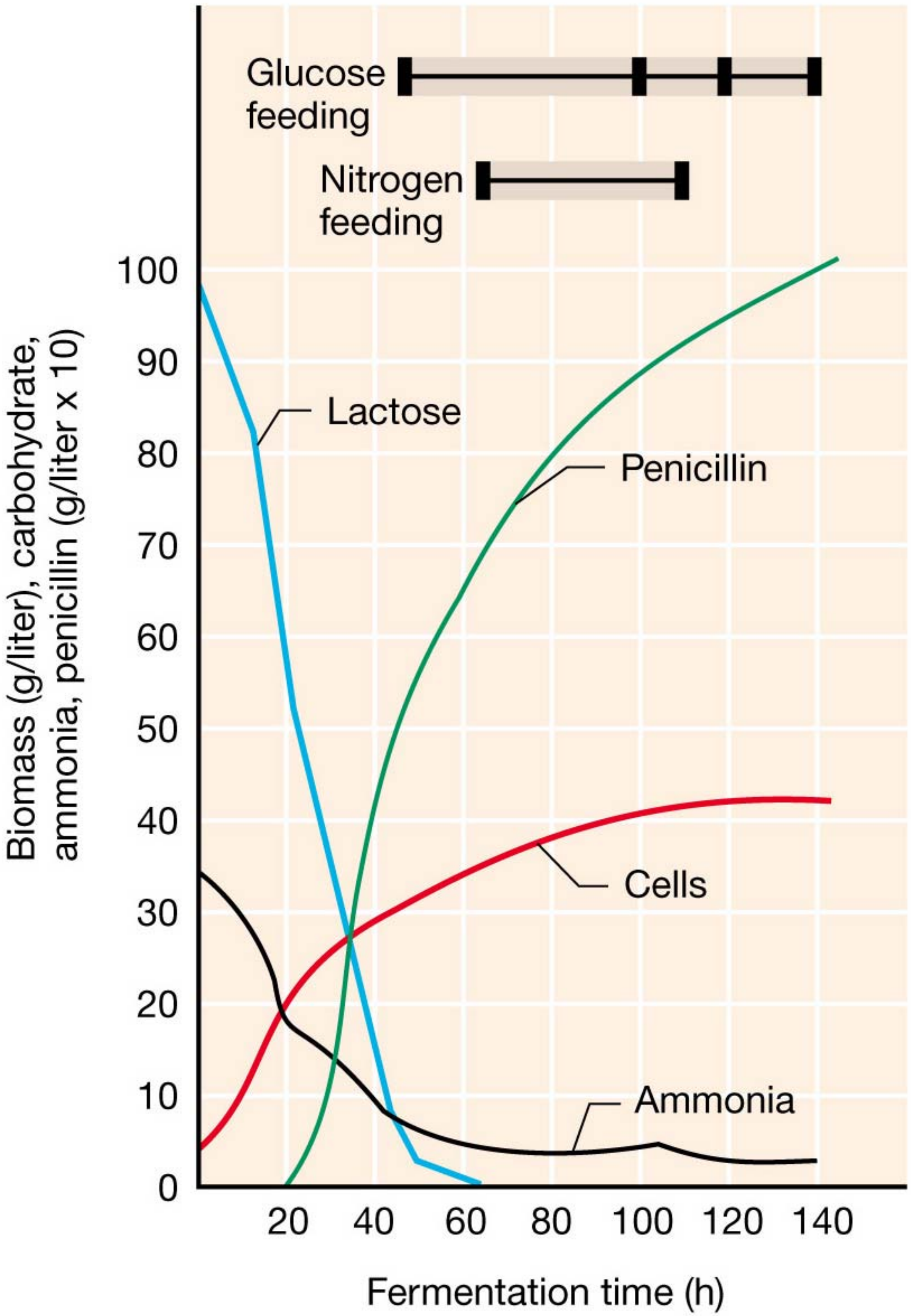
3. Formation depends upon the media, possible over production

Purification of an antibiotic



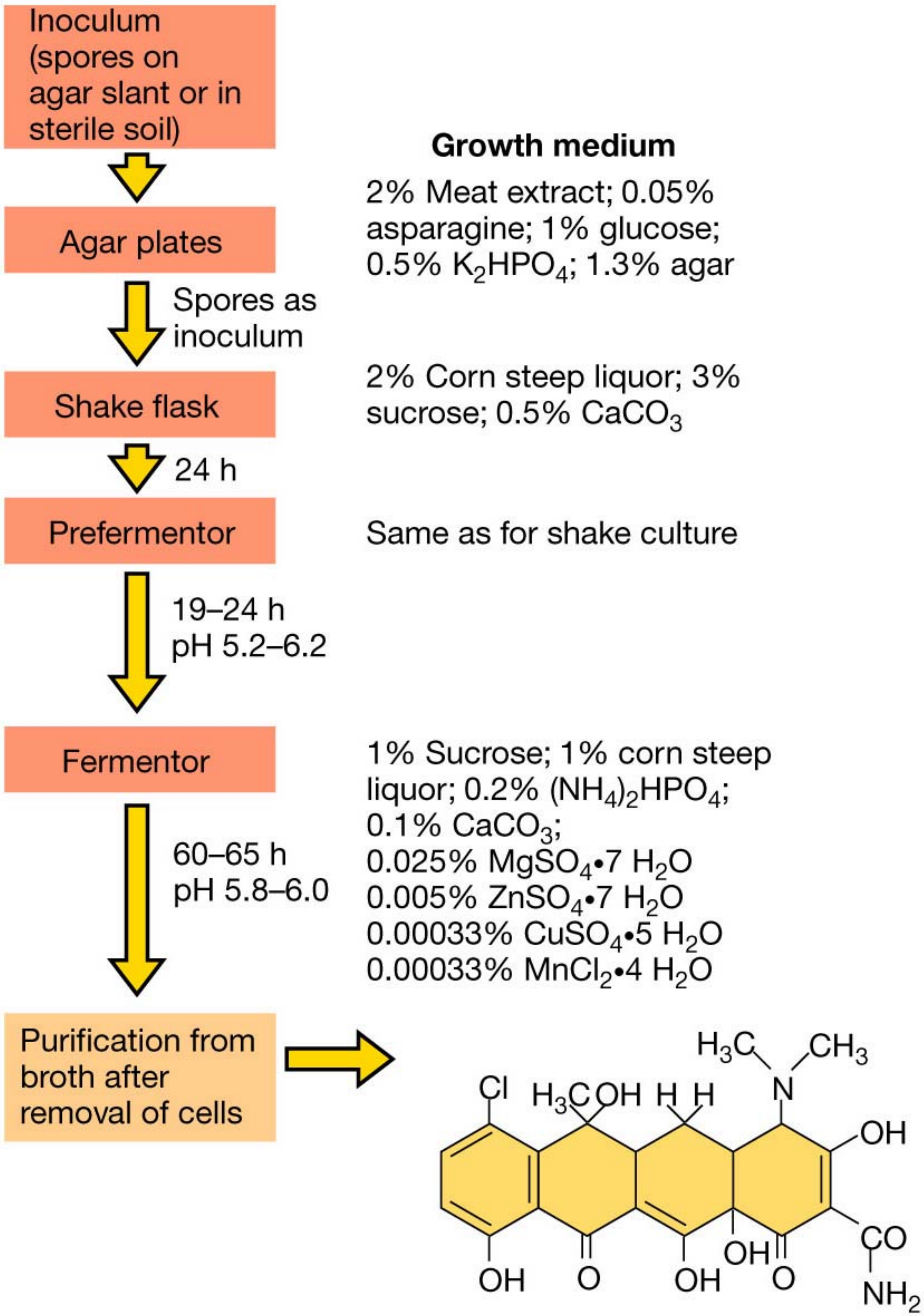


Penicillin fermentation
Add precursor I
Biosynthetic penicillin I
Add precursor II
Biosynthetic penicillin II
Add precursor III
Biosynthetic penicillin III
Natural penicillins (for example, penicillin G)
Chemical or enzymatic treatment of penicillin G
R
O
C
H
N
S
CH3
CH3
COOH
H
H
H
N
O
1
2
3
4
5
6
7
6-Aminopenicillanic acid
Add side chains chemically
Semisynthetic penicillins (for example, ampicillin, amoxycillin, methicillin)



Kinetics of penicillin fermentation

Production scheme for chlortetracycline



>300 genes involved

~72 intermediate products

Glucose avoided due to catabolite repression