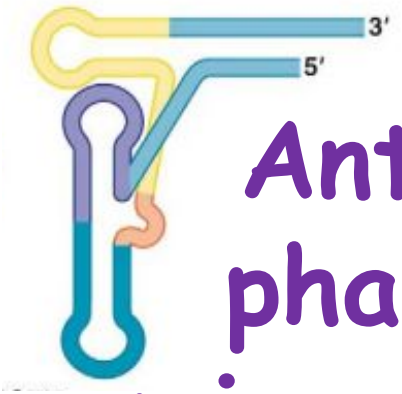
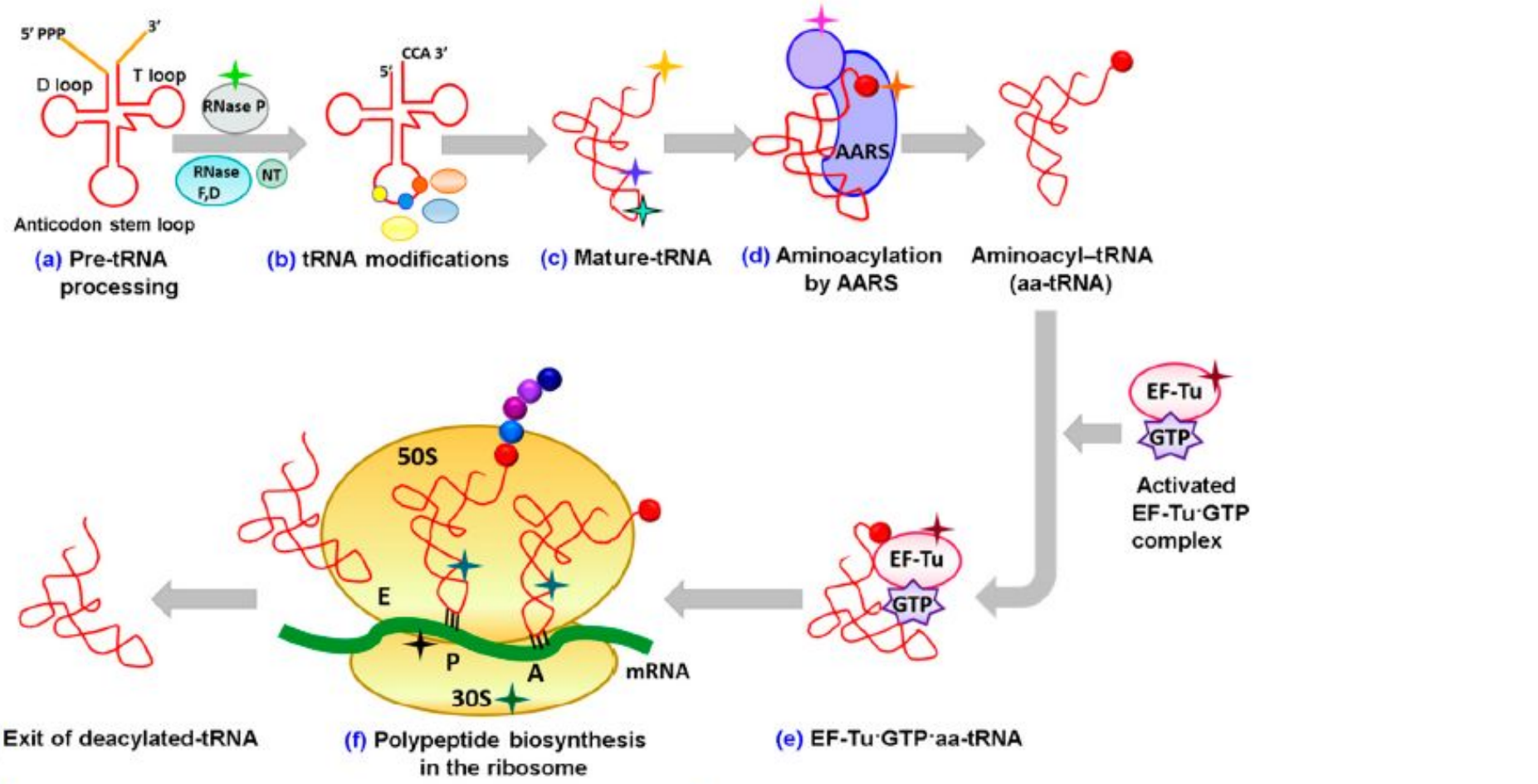


Antibiotics affecting codon phase-dependent binding of aminoacyl-tRNA to the ribosome.

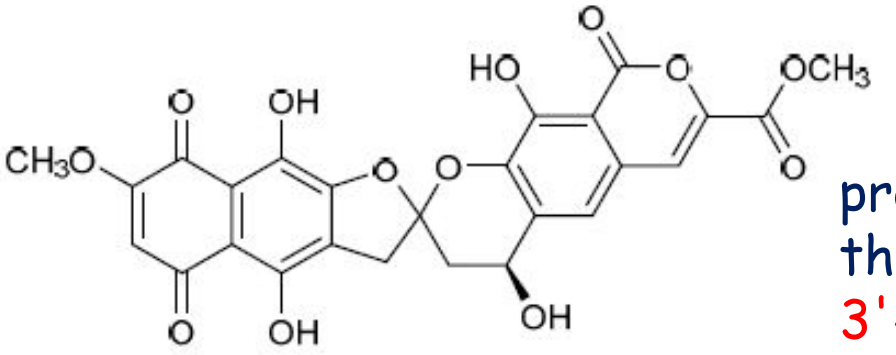
Done by: Maulenova R.,
Moldakozhayev A.,
Naizabayeva D.

Stages of tRNA modifications and functioning



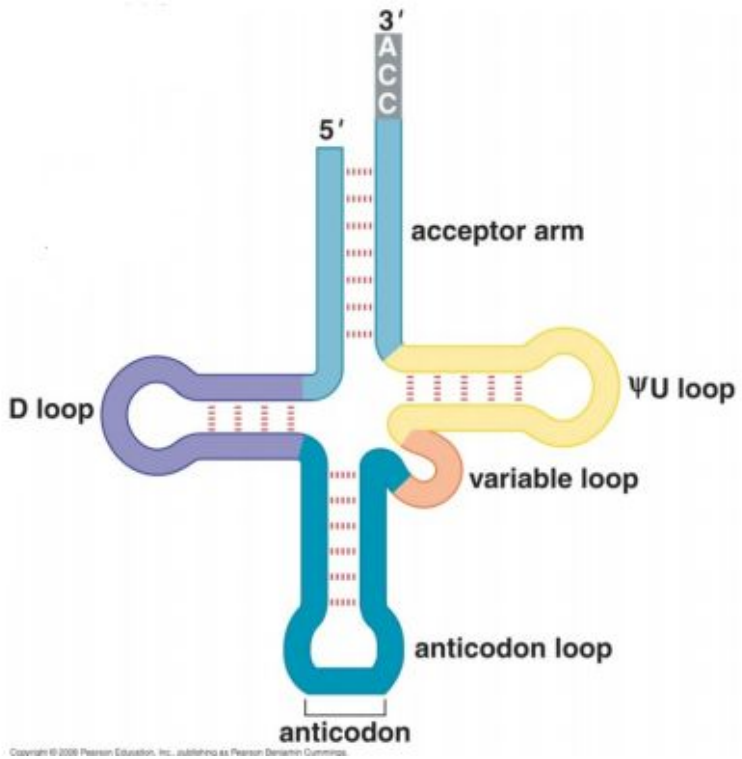
- Neomycin B, Bis-benzimidazole
- Purpuromycin
- Tobramycin
- Colicins, Anticodon Stem Loop Inhibitors
- AN2690
- Agrocin 84 (TM84)
- Aurodox, Encyloxin, GE2270A
- Tetracycline, Aminoglycosides (Streptomycin, Neomycin B, Tobramycin)
- Erythromycin, Chloramphenicol, Linezolid, Blasticidin S
- Viomycin, Thermorubin

Blocking the CCA 3'-End of tRNA



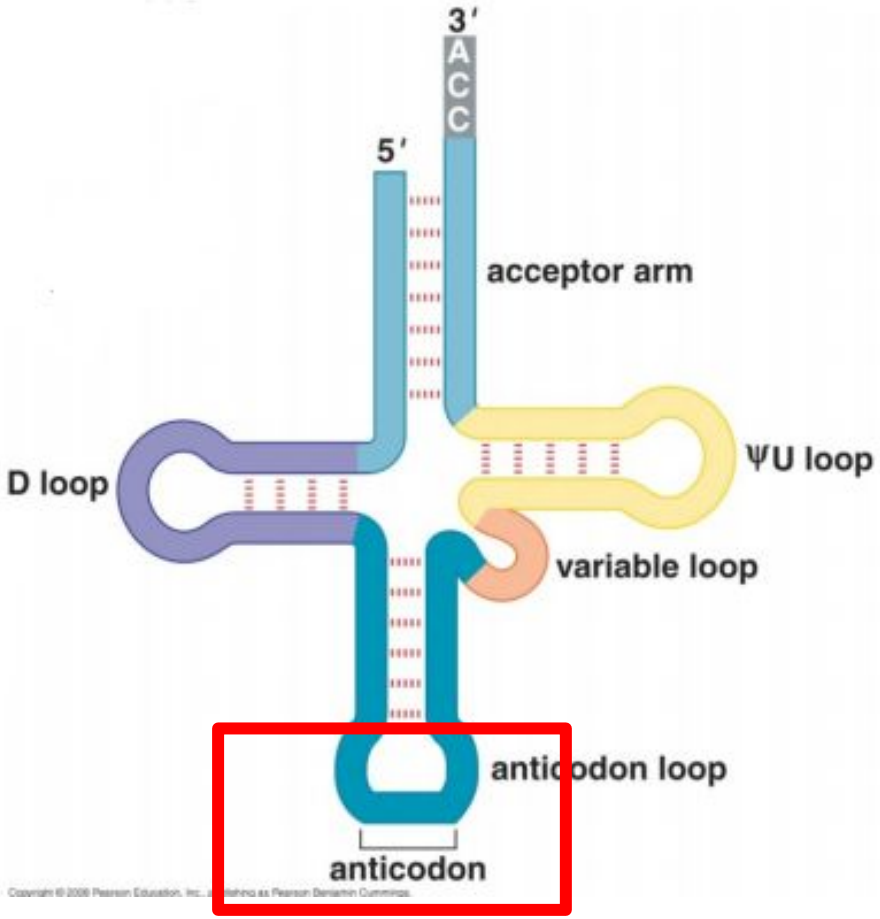
Purpuromycin

Purpuromycin is an antibiotic produced by *Actinoplanes ianthinogenes* that has been shown to bind to the 3'-acceptor stem of all tRNAs with high affinity thereby preventing the aminoacylation of tRNA by its cognate amino acid



Purpuromycin is active against Gram-positive bacteria, such as *Bacillus subtilis*, *Candida albicans* and protozoa, such as *Trichomonas* sp.

Cleavage of tRNAs



Colicins are antibacterial toxins secreted out into the extracellular medium by members of the enterobacteriaceae family, such as *E. coli* (about 30% of *E. coli* contain them).

Function: DNase activity, RNase activity, depolarization of the cytoplasmic membrane, and inhibition of murein synthesis.

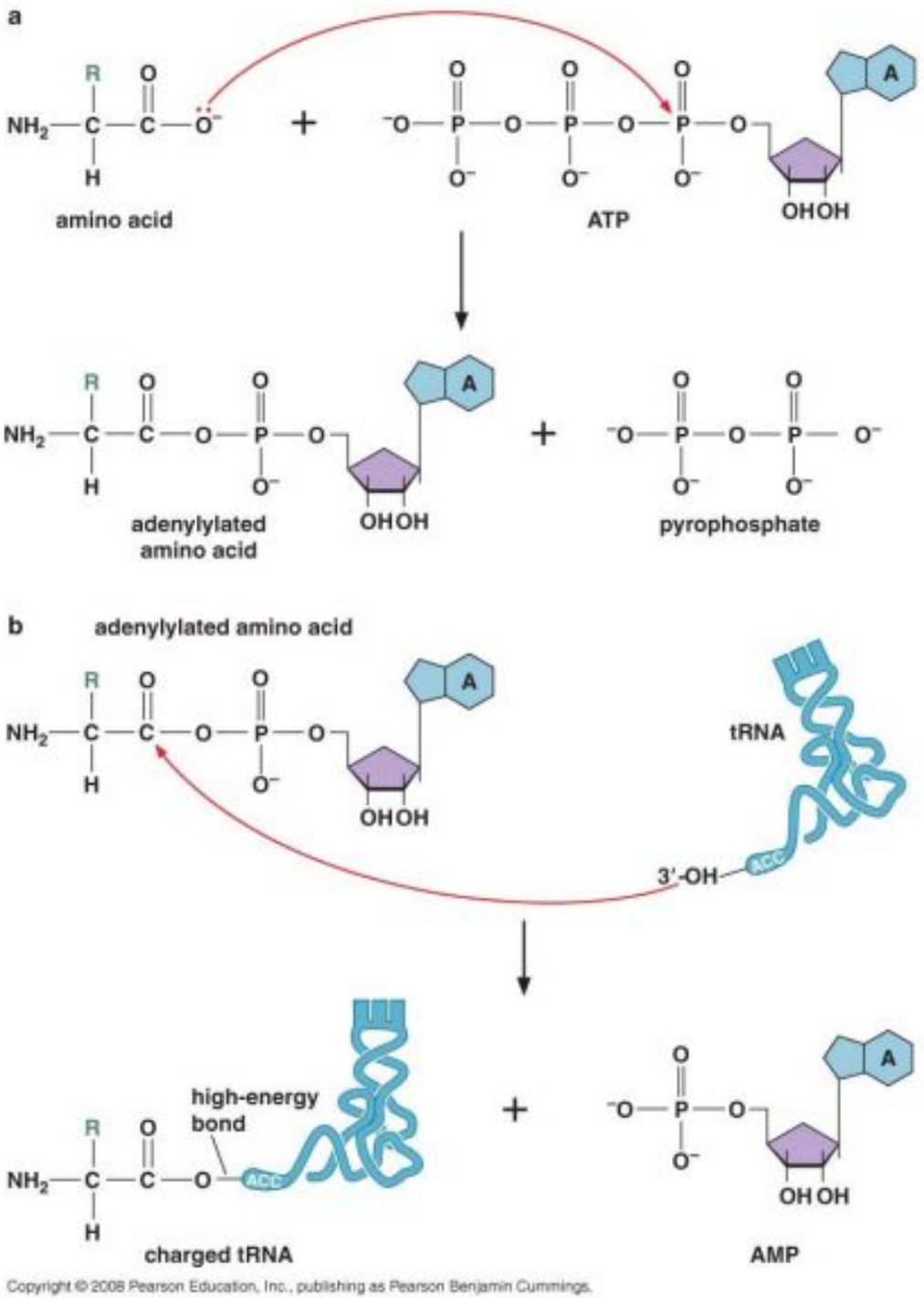
For example, Colicin E5 RNase targets tRNAs specific for tyrosine, histidine, asparagine and aspartic acid by cleaving anticodon QUN that contains the hyper-modified queuosine nucleotide (Q) at the wobble position 34.

Aminoacyl-tRNA formation

Aminoacyl-tRNA synthetases Charge tRNAs in two steps:

1)adenylylation: Amino acid react with ATP and AMP is transferred to amino acids

2)tRNA charging: transfer of aAmino acid to the 3' end of tRNA via 2'- or 3'-OH and release of AMP



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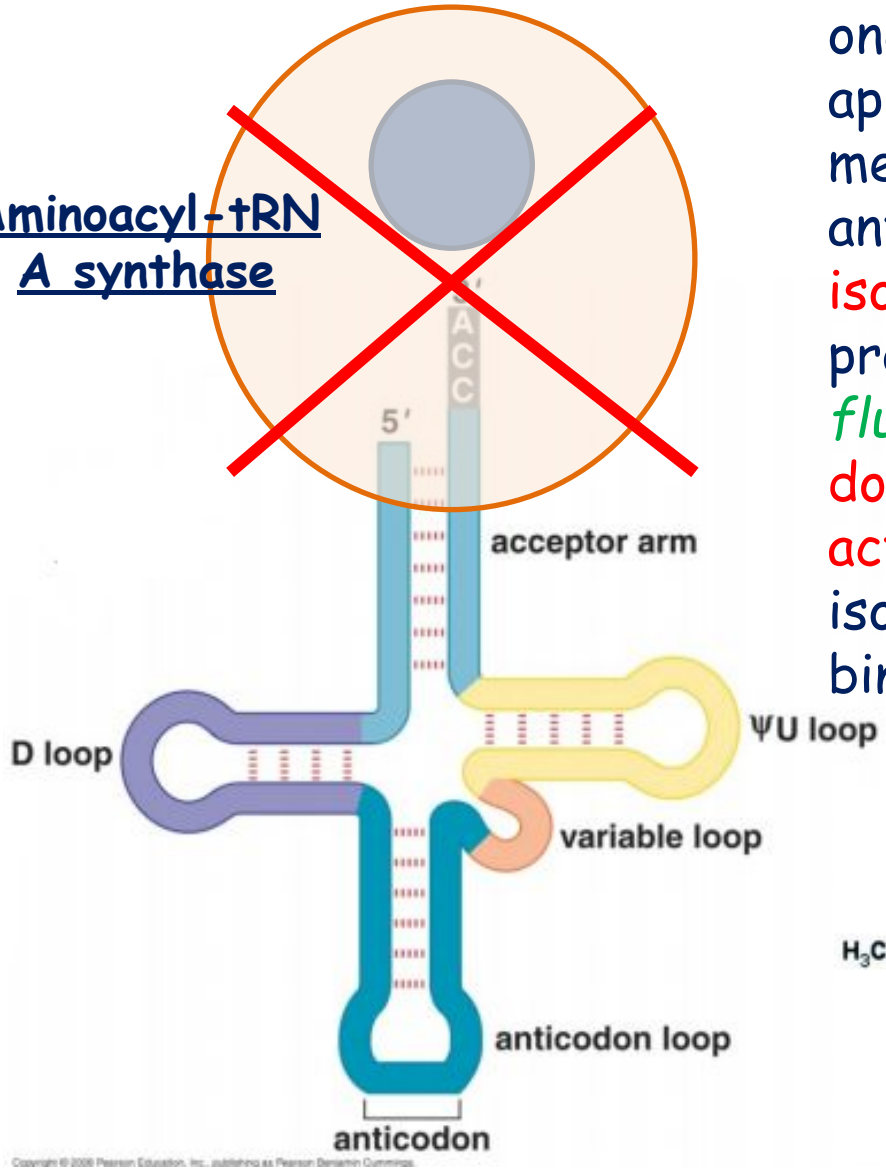
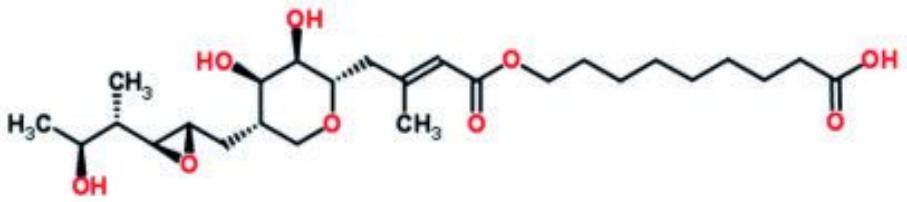
Antibiotics Inhibiting Aminoacylation of tRNA

Aminoacyl-tRNA A synthase



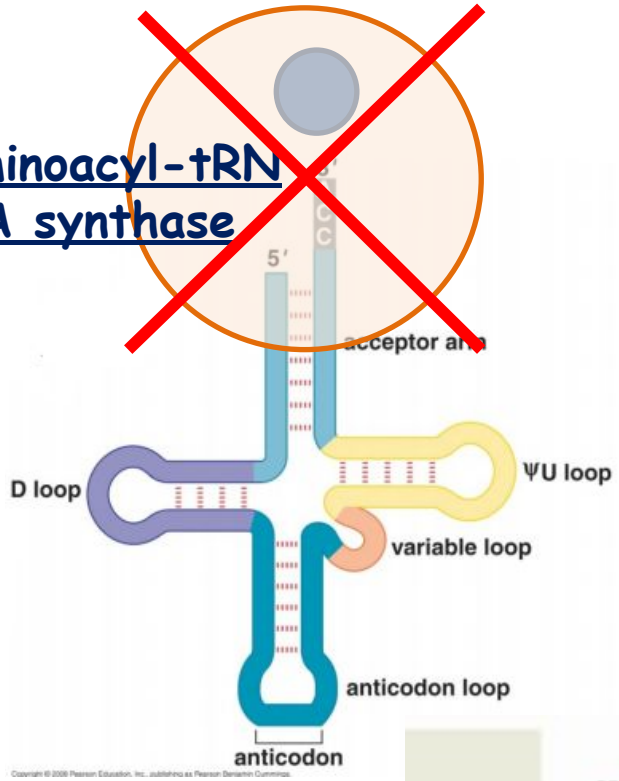
Pseudomonic acid or mupirocin is one of the most effective topically applied antibiotics used to combat methicillin resistant *S. aureus*. This antibiotic is a naturally occurring isoleucyl-tRNA synthetase inhibitor produced by *Pseudomonas fluorescens* strains and works by docking onto the enzyme catalytic active site and competing with the isoleucine and ATP substrates for binding.



Mupirocin

Inhibition by Trapping tRNA in a LeuRS Editing Domain

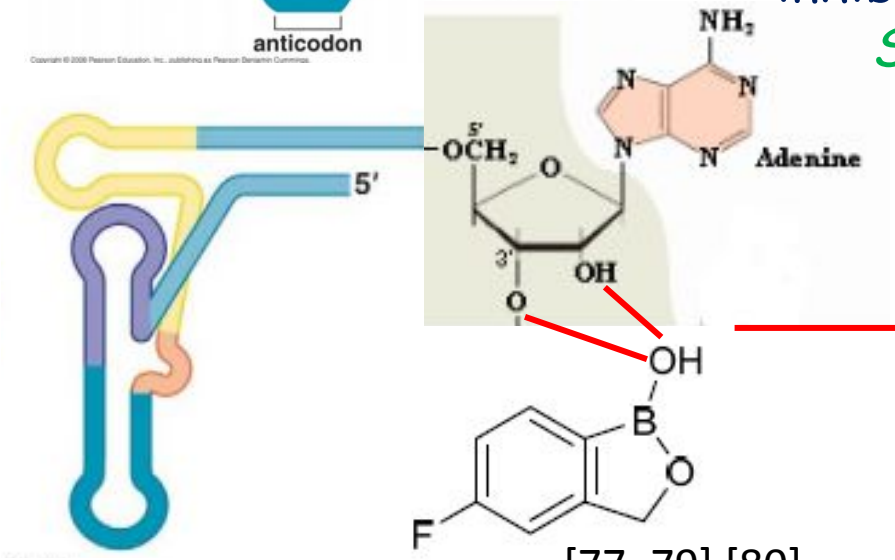
Aminoacyl-tRNA synthase



LeuRS, valyl-tRNA synthetase (ValRS) and IleRS, possess an additional proofreading domain called the CP1 domain.

Function: recognizing and hydrolyzing misacylated amino acids on the 3'-end of the tRNA.

Novel synthetic compound [Anchor company], AN2690 (5-fluoro-1,3 dihydro-1-hydroxy-2, 1-benzoxazole) inhibited a fungal LeuRS from the yeast *Saccharomyces cerevisiae*.



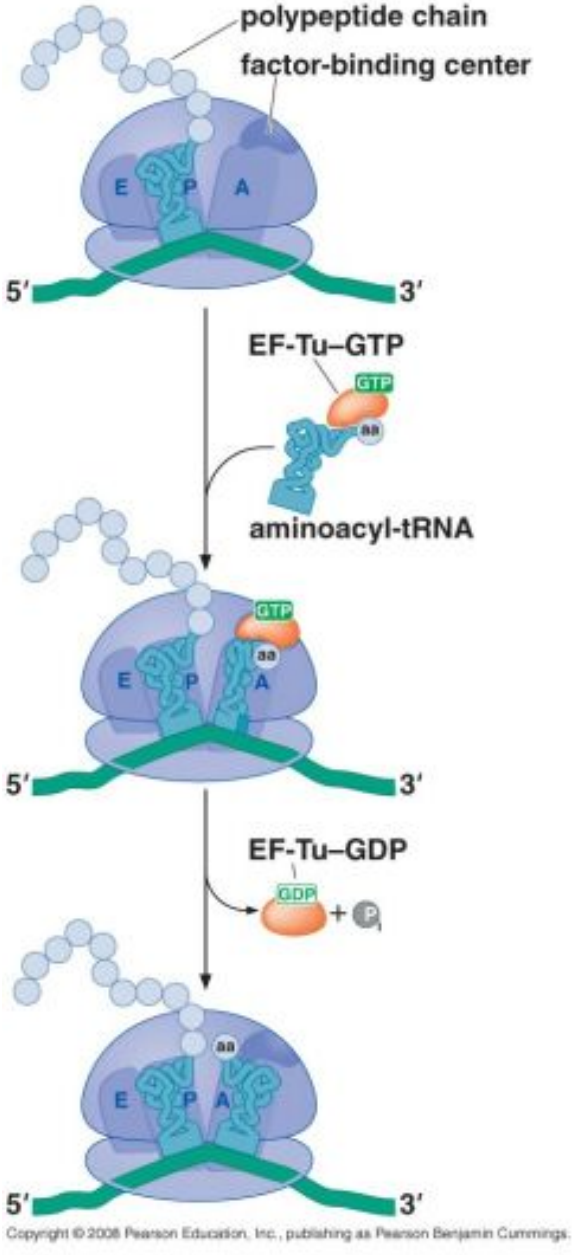
Contacts made with the 2' and 3'-oxygen atoms of the ribose of the 3'-terminal adenosine of tRNA leads to the formation of a stable tRNALeu-AN2690 adduct

[77–79] [80].

Antibiotics Affecting Elongation Factor EF-Tu

-aminoacyl-tRNA is escorted to the ribosome by elongation factor EF-Tu

-EF-Tu binds to tRNA's 3' end, masking the coupled amino acid ->
*prevent the bound aminoacyl-tRNA from participating in peptide bond formation
*affinity of EF-Tu is regulated by GTP status
*control of GTP hydrolysis by EF-Tu is critical to the specificity of translation



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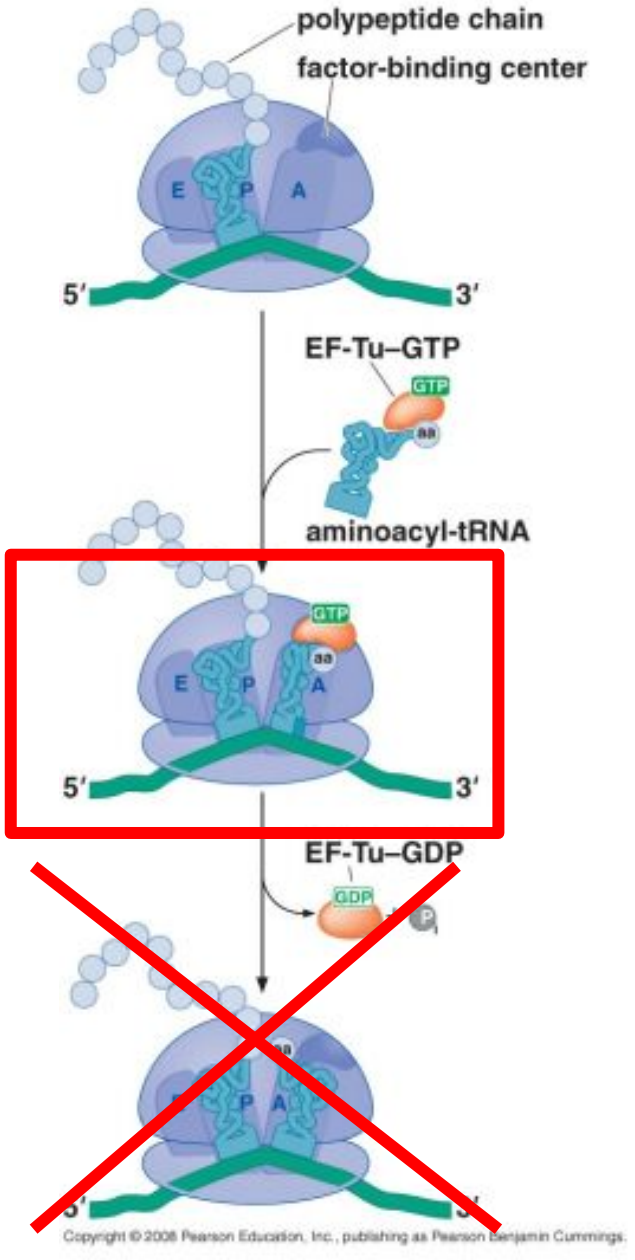
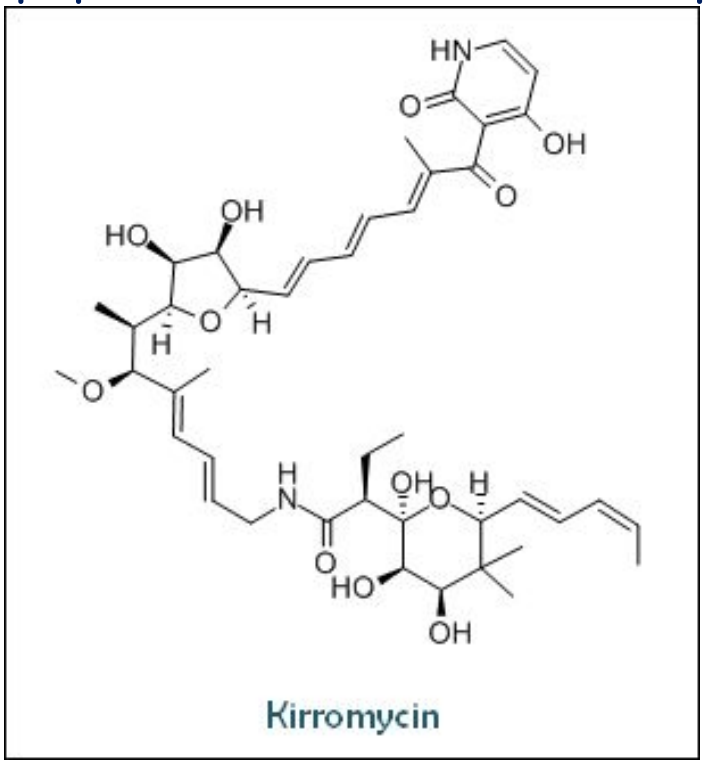
Antibiotics Affecting Elongation Factor EF-Tu

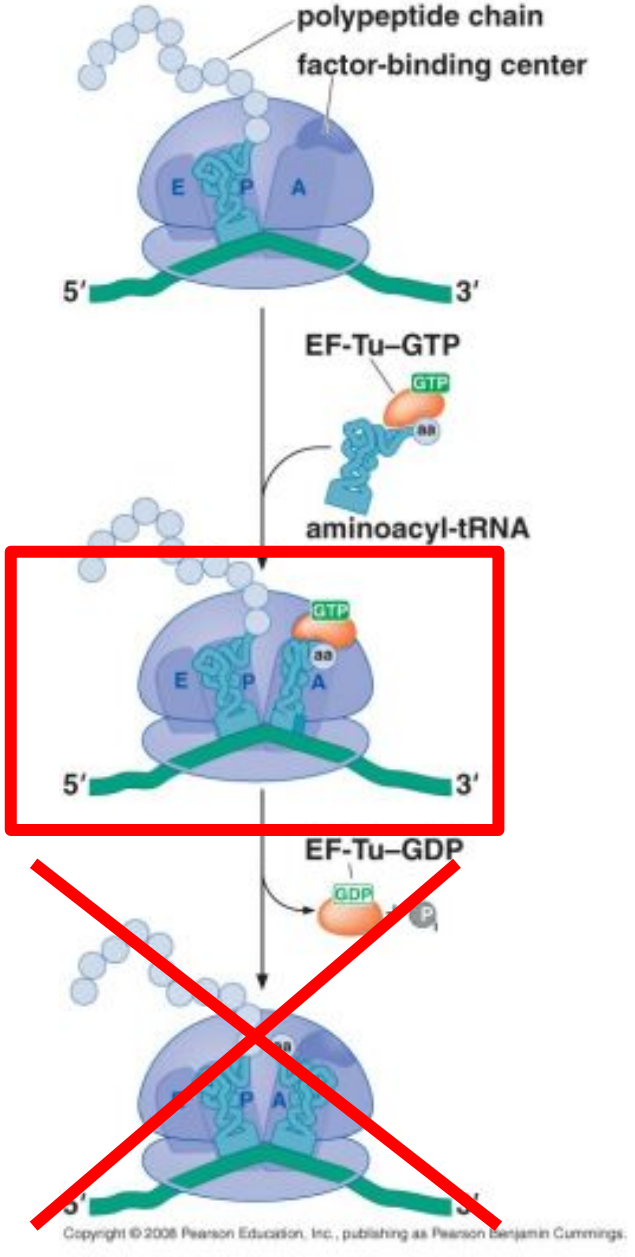


Kirromycin is an antibiotic that binds to the ribosome*aa-tRNA*EF-Tu*GDP complex. This results in inhibition of the release of the EF-Tu·GDP complex from the ribosome. Failure of the release of EF-Tu from the ribosome does not affect the binding of aminoacyl-tRNA to the A-site of the ribosome, but blocks the subsequent peptide bond formation step.

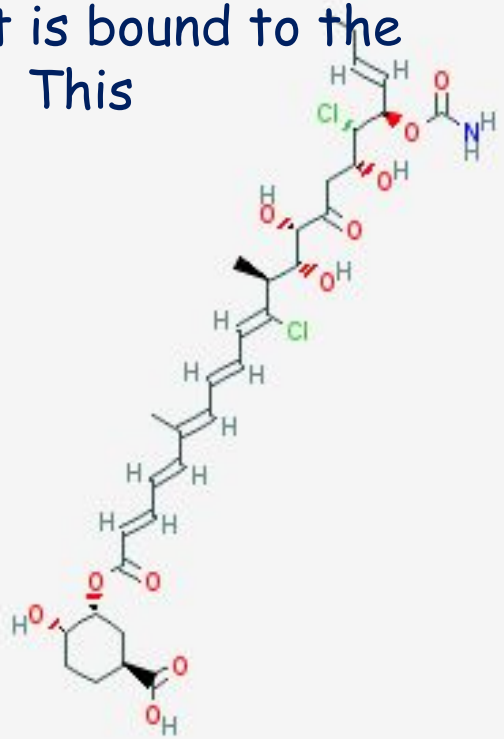


Kirromycin

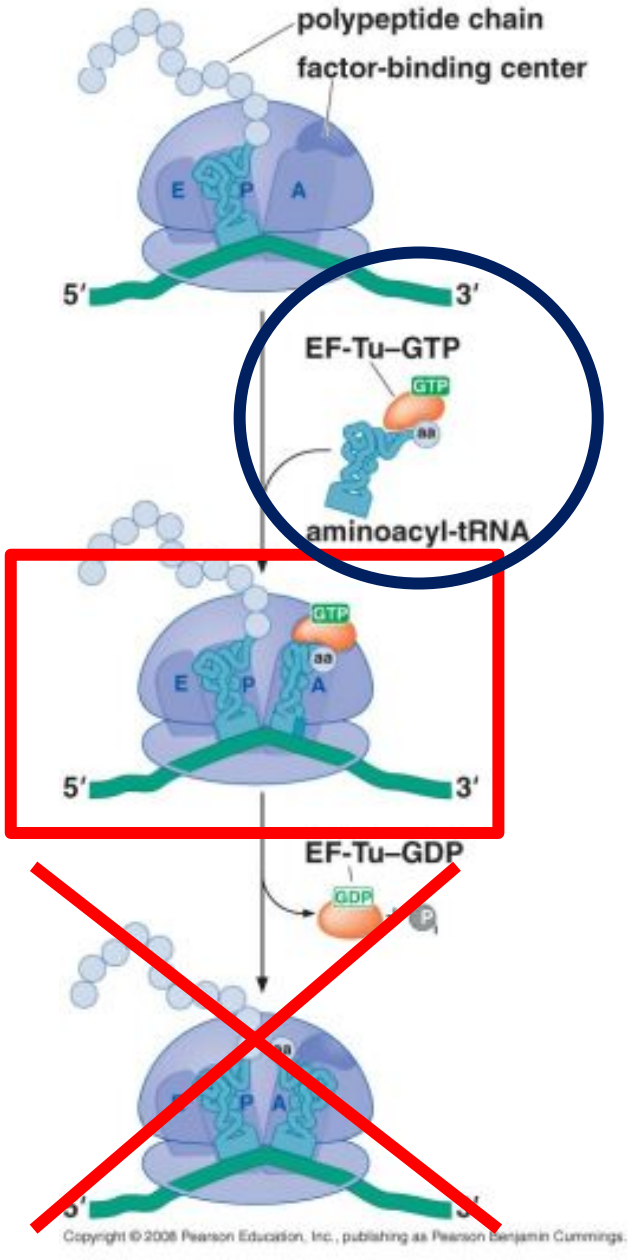
Antibiotics Affecting Elongation Factor EF-Tu



Enacyloxin IIa is produced by *Frateuria* sp. W-315 and is active against both Gram-positive and Gram-negative organisms. This antibiotic affects the interaction between EF-Tu and GTP by retarding the dissociation of GTP from the complex. This results in alteration of the conformation of aa-tRNA, thereby leading to the deacylation of the aa-tRNA that is bound to the EF-Tu·GTP complex. This consequently blocks polypeptide chain formation.



Antibiotics Affecting Elongation Factor EF-Tu



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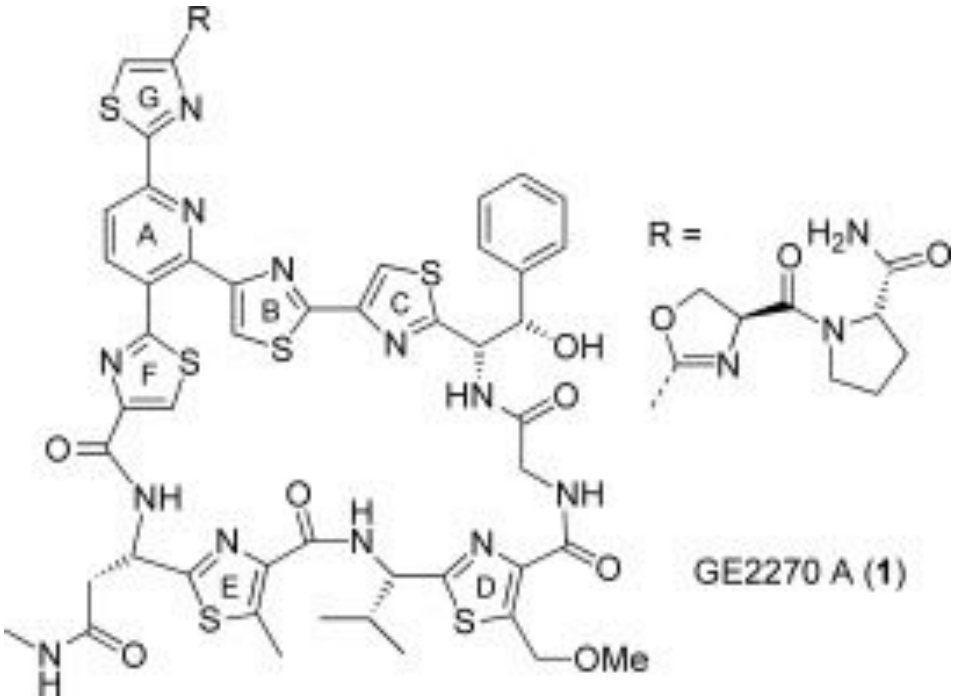
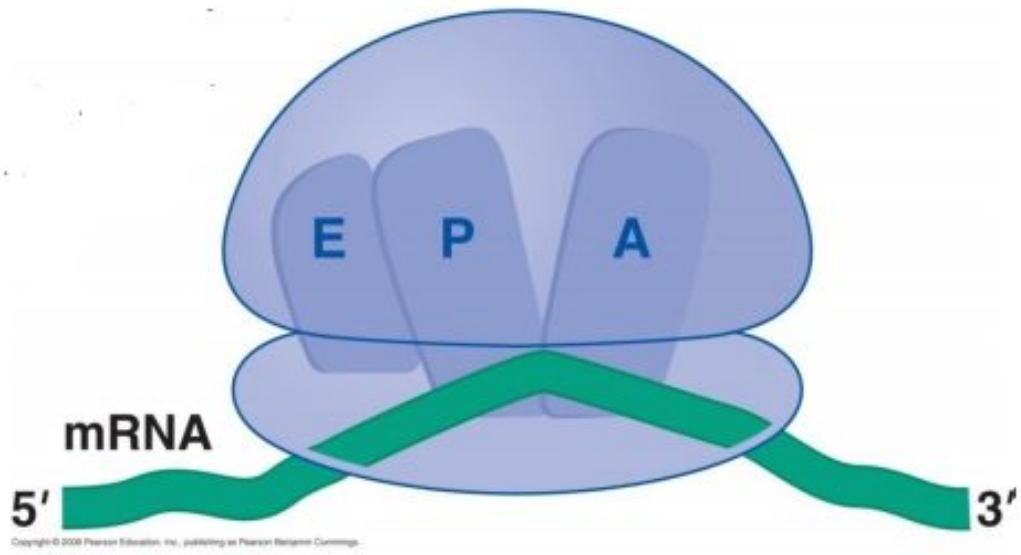
GE2270A is a thiazolyl peptide antibiotic that is active against Gram-positive bacteria. Crystal structure of *E. coli* EF-Tu*GDP*GE2270 complex has confirmed that this compound directly competes with aminoacyl-tRNA for the same binding site on EF-Tu. It also blocks the GTP to GDP conformational change in EF-Tu.



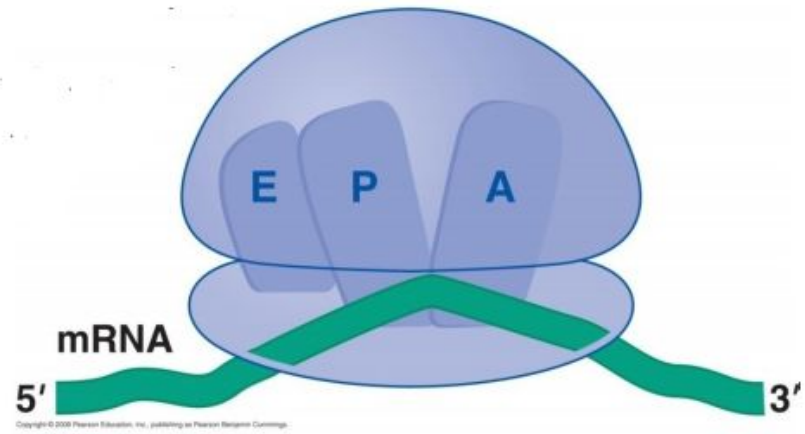
Targeting tRNAs in the Ribosome

The ribosome has three binding sites for tRNA

1)A site: binding site for aminoacyl-tRNA
2)P site: binding site for peptidyl-tRNA
3)E (denote exit) site: binding site for tRNA released after growing polypeptide chain has been transferred to the aminoacyl-tRNA

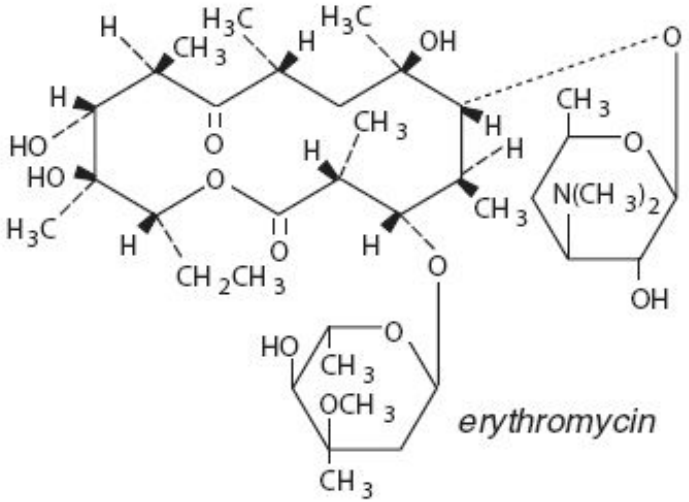


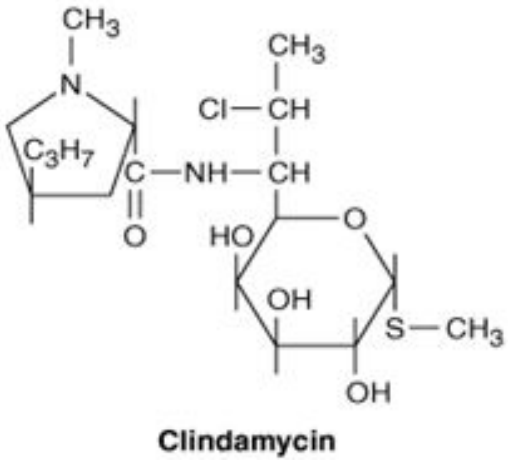
Targeting tRNAs in the Ribosome

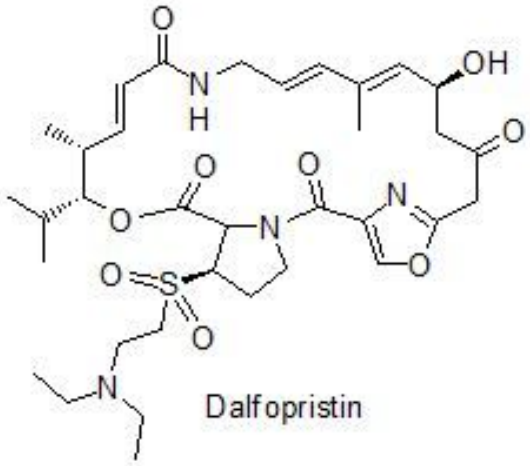


Inhibitors that prevent the binding of the initiator tRNA at the P-site - oxazolidines (linezolid)

Antibiotics that prevent peptide bond formation and/or the translocation of tRNA from the A-site to the P-site on the ribosome – macrolide (erythromycin), lincosamide (clindamycin) and streptogramin (dalfopristin) class of antibiotics).

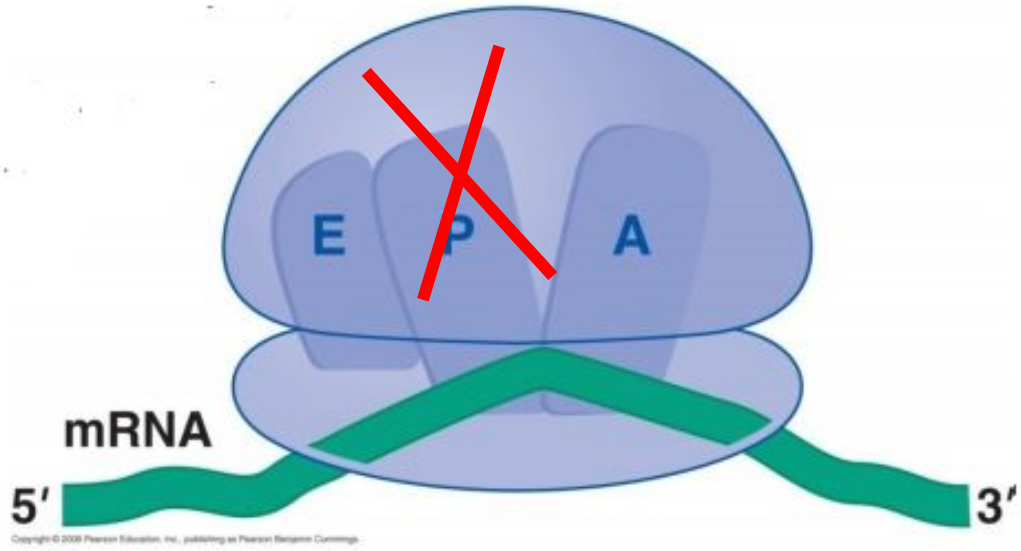


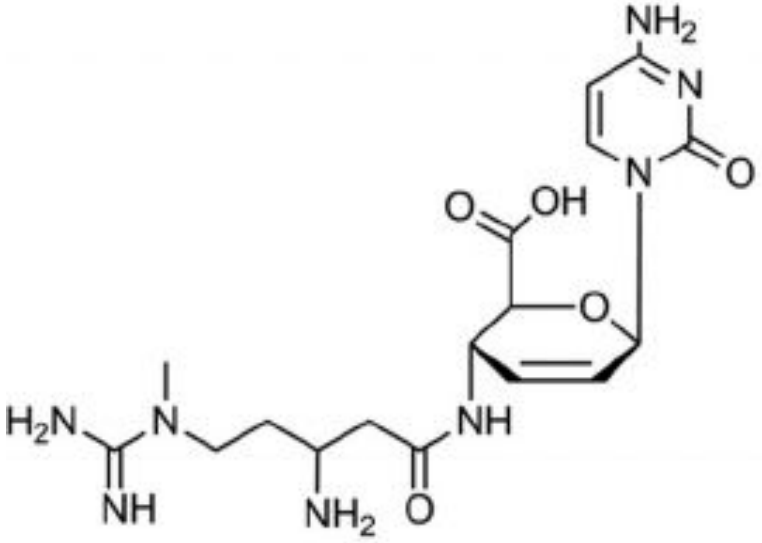




Targeting tRNAs in the Ribosome

Blasticidin S is an antibiotic produced by *Streptomyces griseochromogenes* . BlaS has been found to be a potent inhibitor of both prokaryotic and eukaryotic cells. BlaS binds to the 50S subunit of the ribosome at the P-site and not at the A-site like other Bla antibiotics. Upon binding the P-site, BlaS bends the CCA 3'-end of the tRNA bound at the P-site to the A-site resulting shift in the ribose phosphate backbone of the base C75 of the tRNA. This results in a decrease in the flexible movement of the CCA 3'-end of the tRNA, an important feature required by translation.





Blasticidin S

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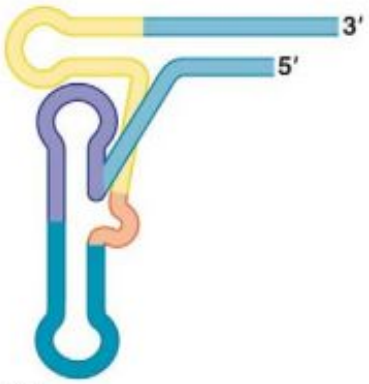

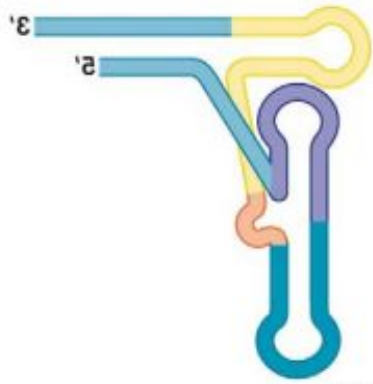

Thanks for attention!