

University of Karbala

College of veterinary medicine

Second semester

Pharmacology Lect. # 1

Antibacterial Drugs

Part three

Dr. Sattar K. Abdul-Hussain, Ph.D, DVM, DABT

I. TETRACYCLINES

The tetracyclines are polycyclic compounds that are amphoteric in nature. Most of tetracyclines are prepared as the hydrochloride salt. They chelate with cations such as Mg^{2+} , Ca^{2+} , Fe^{3+} to form insoluble complex. They accumulate in growing teeth and bones.

Mechanism of action:

Tetracyclines inhibit bacterial protein synthesis by binding to the 30S bacterial ribosome and preventing access of aminoacyl tRNA to the acceptor site on the mRNA-ribosome complex. They block the addition of amino acids to the growing peptide chain (Figure 8). They are bacteriostatic and broad spectrum. Their antimicrobial spectrum includes gram positive and *gram-negative aerobes and anaerobes*, *Rickettsiae*, *Spirochetes*, *Chlamydiae*, *Mycoplasma*, and some protozoans such as *Anaplasma* spp. and *Haemobartonella* spp. (Figures 6 and 8)

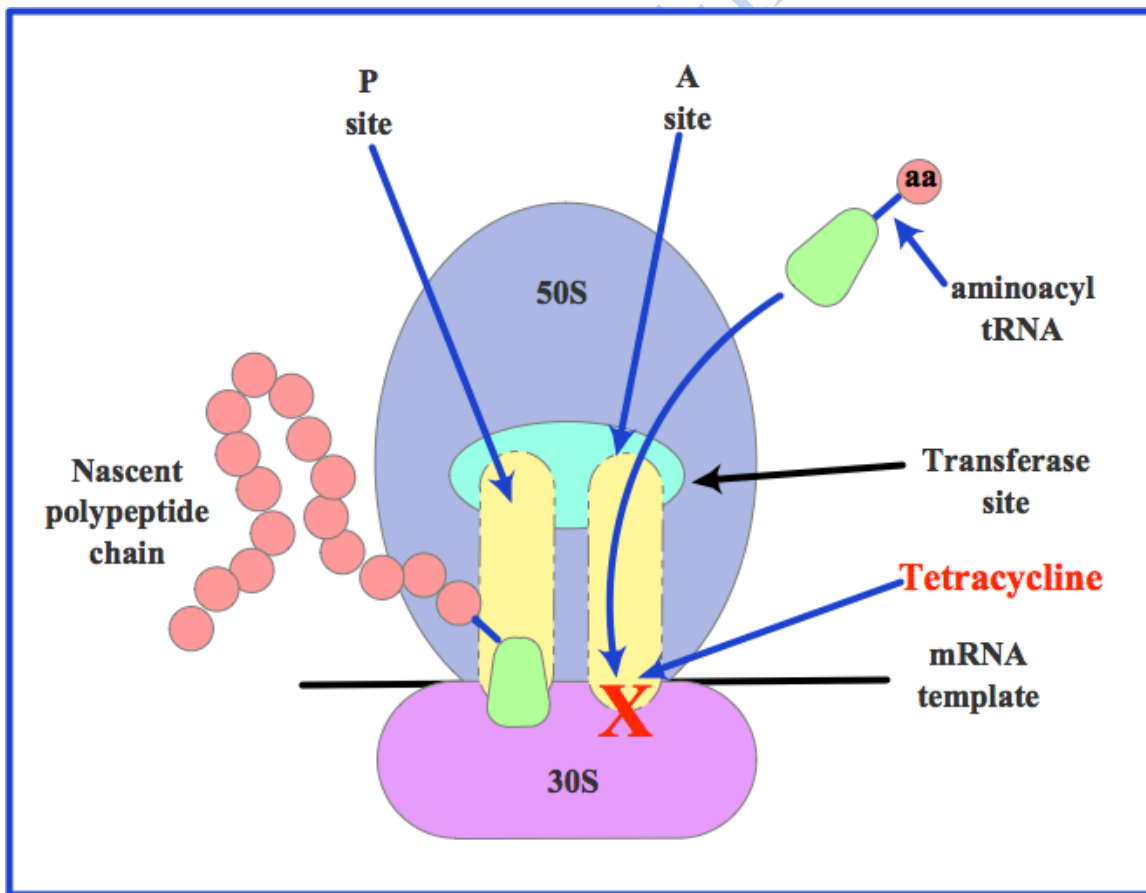


Figure 8. Inhibition of bacterial protein synthesis by tetracyclines. Messenger (mRNA) attaches to the 30S subunit of bacterial ribosomal RNA. The P (peptidyl) site of

the 50S ribosomal RNA subunit contains the nascent (the merging) polypeptide chain; normally, the aminoacyl tRNA charged with the next amino acid (aa) to be added to the chain moves into the A (acceptor) site, with complementary base pairing between the anticodon sequence of tRNA and the codon sequence of mRNA. Tetracyclines inhibit bacterial protein synthesis by binding to the 30S subunit and blocking tRNA binding to the A site (red X).

Therapeutic uses:

- a) **Large animals:** in cattle, sheep, horses, and swine, tetracycline, chlortetracycline, and oxytetracycline are used in the treatment of local and systemic bacterial, chlamydial, rickettsial, and protozoal infections.
- b) **Small animals:** in dogs and cats, doxycycline, minocycline, and tetracycline are used in the treatment of respiratory and urinary tract infections. Also can be used as specific treatment for *Borrelia* (Lyme disease), *Brucella*, *Haemobartonella*, and *Ehrlichia* species infections. They are also effective in the treatment of psittacosis in birds.

Administration:

Tetracyclines are given orally or IV every 8-12 hours. Oral therapeutic doses should be avoided in adult ruminants and used with caution in horses because of the danger of disrupting ruminal or colonic microflora, respectively.

Pharmacokinetics:

Oral absorption is fair for tetracyclines (range from 60-90%) of the given dose but not for chlortetracycline, which is only 35%. Since divalent ions chelate with tetracyclines, milk, antacids, or iron salts should be avoided 3 hours before and after oral administration. Tetracyclines distribute well in all body tissues except the CNS. However, doxycycline and minocycline are more lipid soluble than tetracycline, chlortetracycline, or oxytetracycline and penetrate the CNS, eye, and prostate at therapeutic concentrations.

Metabolism is minimal in domestic animals. Renal excretion by glomerular filtration is the major route of elimination for most tetracyclines.

Resistance:

Currently, resistance to tetracycline is widely spread because of the extensive use. Resistance may be developing due to decreased drug uptake or active transport of the tetracycline out of the bacterial cell.

Adverse effects:

- a) **Nephrotoxicity:** is common with tetracyclines except doxycycline and minocycline. Thus, they should be avoided if renal function is impaired.
- b) **Permanent teeth stain** may occur in young animals due to the formation of a tetracycline-calcium phosphate complex in enamel and dentine.
- c) Suprainfections of fungi, yeast, or resistant bacteria may occur in the GI tract with prolonged administration. **Oral tetracyclines should not be used with herbivores because of serious effects on ruminant digestion.**
- d) Antianabolic effect may develop with high doses due to binding to mitochondrial ribosomes.
- e) Although they are rare to occur, **photosensitivity and hepatotoxicity** can be developed with therapeutic use of tetracyclines.

Preslaughter withdrawal of oxytetracycline in food animals:

- a) The Food Animal Residue Avoidance Databank (FARAD) recommends, in cattle, an extralabel withdrawal of 28 days for intrauterine treatment. It also recommends testing milk after intrauterine treatment, as there is inter-cow variability in the residue eliminations profiled in milk.
- b) FARAD recommends an extralabel preslaughter withdrawal of 28 days in sheep and goats after IM or SC oxytetracycline administration. A milk withdrawal of 96 hours is recommended for sheep and goats.

II. CHLORAMPHENICOL GROUP

Chloramphenicol, an antibiotic produced by *Streptomyces venezuelae*, was introduced into clinical practice in 1948. With the drug's wide use, it became evident that chloramphenicol could cause serious and fatal blood disorders. For this reason, chloramphenicol is now reserved for treatment for life-threatening infections such as meningitis, rickettsia infections in patients who cannot take safer alternatives because of resistance or allergies. The compound is unique among natural compounds in that it contains a nitrobenzene moiety and is a derivative of dichloroacetic acid.

Mechanism of action:

Chloramphenicol and florfenicol inhibit protein synthesis in bacteria and to a lesser extent, in eukaryotic cells. The drugs readily penetrated bacterial cell by facilitated diffusion. They inhibit protein synthesis by binding reversibly to the 50S ribosomal subunit. Although binding of tRNA at the codon recognition site on the 30S ribosomal subunit is undisturbed, the drugs apparently prevent the binding of the amino acid-containing end of the aminoacyl tRNA to the acceptor site of the 50S ribosome subunit. The interaction between peptidyltransferase and its amino acid substrate cannot occur, and peptide bond formation is inhibited. Chloramphenicol and florfenicol are **bacteriostatic** and broad spectrum and are effective against most anaerobic bacteria (Figures 6 and 9).

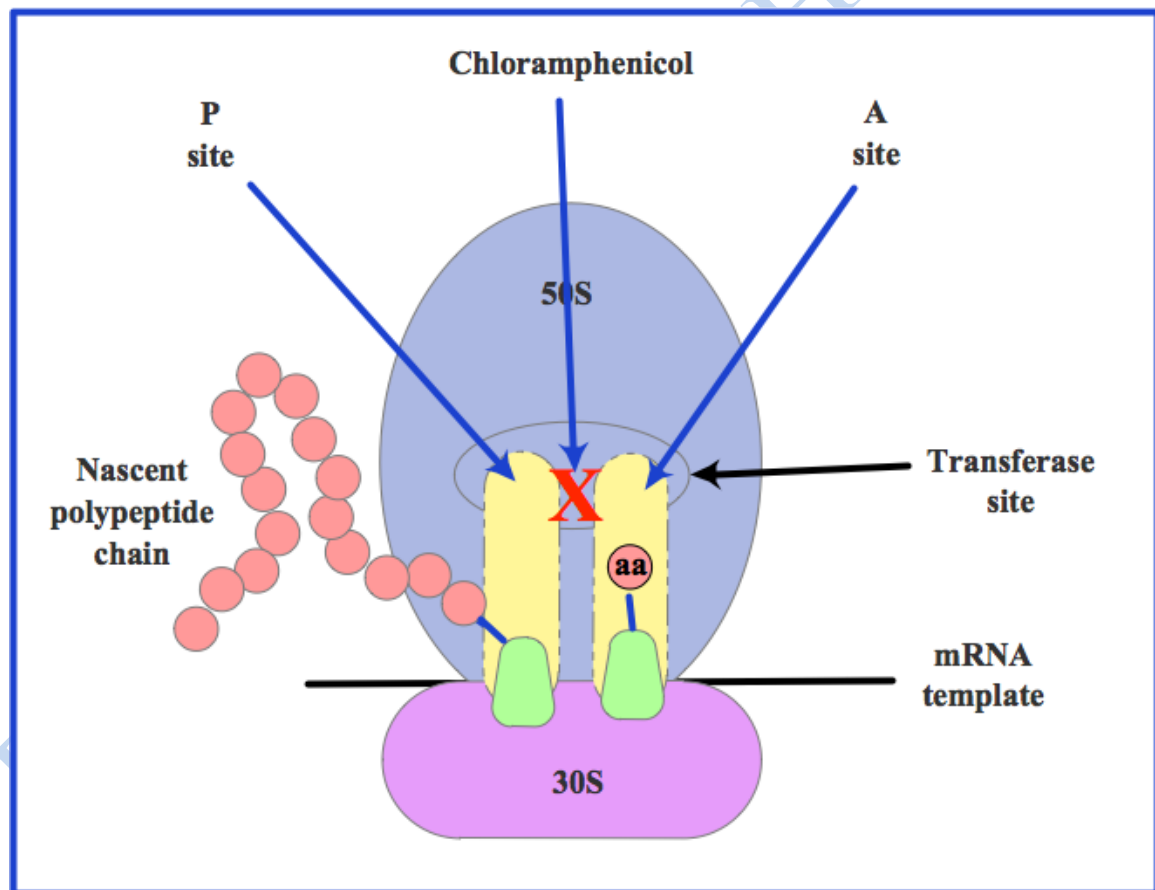


Figure 9. Inhibition of bacterial protein synthesis by chloramphenicol.

Chloramphenicol binds to the 50S ribosomal subunit near the site of action of clindamycin and the macrolide antibiotics. These agents interfere with the binding of chloramphenicol and thus may interfere with each other's if given at the same time.

Therapeutic uses: Chloramphenicol is not recommended for use in food-producing animals because the danger of the residue—induced toxicity in humans. In dogs, cats, horses and birds for local and systemic infections, caused by anaerobes and Salmonella species. Florfenicol is approved for use only in cattle for the treatment of bovine respiratory disease (BRD) caused by Pasturella species.

Pharmacokinetics:

- a) **Chloramphenicol:** Is rapidly absorbed from the GI tract and distributed to all body tissues including the CNS. It is metabolized by liver to metabolites that are eliminated by kidneys.
- b) **Florfenicol:** is absorbed orally in dogs and cats and from IM sites in cattle. It is like chloramphenicol, is widely distributed in all body tissues including CNS.

Administration: In dogs, birds, and horses, chloramphenicol is administered orally, IM, IV, or SC every 6-8 hours. Florfenicol is administered IM in cattle and repeated 48 hours later for a total of two doses of the slow-release preparation. In dogs and cats, it is administered IM or SC every 8 hours and every 12 hours, respectively.

Adverse effects:

- a) **Anemia:** it may occur in animals and humans. The anemia development is due to the **inhibition of iron uptake** by erythrocytes by chloramphenicol. The anemia development is dose-dependent. Another type of anemia may develop in humans by chloramphenicol, which is not dose related conditions.

This type of anemia is aplastic anemia which often fatal and it is the reason for the drug's ban in food-producing animals.

- b) **Anorexia and diarrhea** with high or prolonged dosage
- c) **Florfenicol is not known to produce aplastic anemia** admits use is permitted in beef cattle.

III. MACROLIDES

They are another group of antibiotics that includes erythromycin, azithromycin, clarithromycin, tulathromycin, tylosin, and tilmicosin. They are compounds

consisting of lactone rings to which are attached deoxy sugars. Preparations include sulfate salts or esterified salts of stearate, tartrate, estolate, or lactobionate.

Mechanism of action: They are **bacteriostatic** by inhibiting protein synthesis (Figure 6). They bind to the 50S ribosome to prevent translation of amino acids to the growing peptide chain. Binding sites on the 50S ribosome overlap with binding sites of chloramphenicol and the lincosamides (especially clindamycin) and combination therapy should be avoided. Their antimicrobial activity is primarily against gram-positive aerobes and anaerobes and *Mycoplasma* species. Tylosin and tiamulin are effective against some gram-negative pathogens, including *Pasteurella* and *Haemophilus* species (Figure 10).

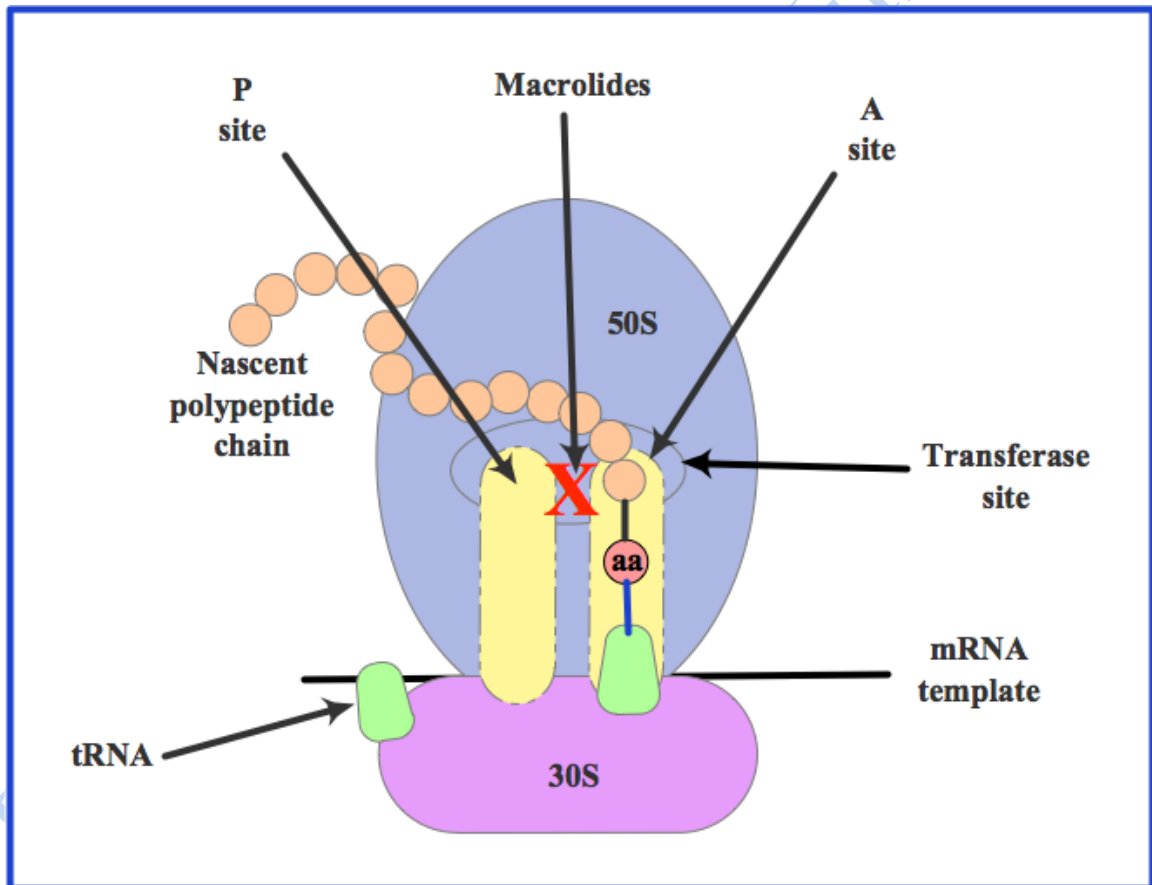


Figure 10. Inhibition of bacterial protein synthesis by the macrolide antibiotics erythromycin, clarithromycin, and azithromycin. *Macrolide antibiotics are bacteriostatic agents that inhibit protein synthesis by binding reversibly to the 50s bacterial ribosomal subunits. Erythromycin appears to inhibit the translocation step such that the nascent peptide chain temporarily residing at the A site of the*

transferase reaction fails to move to the P, or donor, site. Alternatively macrolides may bind and cause conformational change that terminates protein synthesis by indirectly interfering with transpeptidation and translocation.

Therapeutic uses:

- a) **Erythromycin:** In dogs, cats, and horses, it is an alternate to penicillin for infections caused by gram-positive aerobes and anaerobes.
- b) **Tylosin:** it is used in cattle, sheep, and swine for the treatment of local and systemic infections caused by *Mycoplasma* and gram-positive bacteria. It is also added to feed as a growth promotant in these species.
- c) **Tilmicosin:** is used in cattle for the treatment of respiratory disease. It has potentially fatal toxic effects in horses and humans.
- d) **Azithromycin:** It is used as alternative for erythromycin for *R. equi* pneumonia in foals.
- e) **Tulathromycin:** it is used for the treatment of bovine and swine respiratory diseases.
- f) **Clarithromycin:** is used in dogs and cats for the treatment of mycobacterial infections including canine leproid granuloma, feline leprosy, and for *Helicobacter* species in cats and ferrets, and for *R. equi* in foals.

Pharmacokinetics:

Macrolides are absorbed orally if protected from gastric acid destruction by enteric-coated preparations. They are widely distributed to all tissues except those of the CNS.

Administration:

- a) **Erythromycin:** is administered orally or IM three times a day to dogs, cats and foals and IM once a day in cattle, sheep, and swine.
- b) **Tylosin:** is administered SC to cattle every 72 hours
- c) **Tulathromycin:** it can be given IM to cattle as treatment for respiratory infections.
- d) **Azithromycin:** is administered orally once a day to dogs, cats, and foals
- e) **Clarithromycin:** is administered orally twice a day to dogs, cats, ferrets, and foals

Resistance:

Bacterial resistance to macrolide antibiotics may be chromosomal or plasmid mediated and is due to decreased drug binding by the 50S ribosome. Active efflux, or enzymatic inactivation by resistant bacteria may occur as mechanisms of resistances.

Adverse effects:

Drugs belong to this group of antibiotics have relatively few adverse effects. However, mild GI tract disturbances with oral doses and pain and irritation with IM injection sites may occur.

IV. LINCOSAMIDES

This group of antibiotics includes: (lincomycine, clindamycin, and pirlimycin). They are derivative of a sulfur-containing octose with an amino acid-like side chain and are highly lipid soluble.

Mechanism of action: Lincoasmides bind to the bacterial 50S subunit of bacterial ribosomes and suppresses protein synthesis (Figures 9 and 10). Since this is the same site for binding of chloramphenicol and the macrolides, combined therapy should be avoided. Binding one of these antibiotics to the ribosome may inhibit the interaction of the others. Lincomycin and clindamycin are bacteriostatic and are active against gram-positive aerobes and anaerobes, *Toxoplasma* species, *Neospora canis*, and *Mycoplasma* species.

Therapeutic uses:

Clindamycin is used in dogs and cats for periodontal disease, osteomyelitis, dermatitis, and deep soft tissue infections caused by gram-positive organisms. Prilimycin is prepared and used for the treatment of bovine mastitis.

Pharmacokinetics:

Oral absorption is 50% for lincomycin and 90% for clindamycin. Distribution is wide to include all body tissues with low penetration to CNS. They are metabolized by the liver microsomal enzymes into metabolites that are excreted in urine, bile, and feces.

Administration:

In dogs and cats, clindamycin is administered orally or IM twice a day. Pirlimucin is given by intramammary infusion.

Resistance:

Altered drug binding by bacterial ribosomes is the usual form of resistance. Cross-resistance between lincosamides and macrolides is common.

Adverse effects:

They are contraindicated in horses, rabbits, hamsters, and guinea pigs because they may produce a severe or fatal diarrhea due to altered GI flora.

V. MISCELLANEOUS ANTIBACTERIAL DRUGS

1. **Aminocyclitols:** Spectinomycin and apramycin are chemically related; they bind to the 30S ribosome and inhibit protein synthesis. Spectinomycin is used in dogs, cats, horses, calves, and poultry to treat enteric and respiratory infections.
2. **Metronidazole:** is used in veterinary medicine to treat infection caused by bacteria and protozoa by producing cytotoxic metabolites, which disrupt the DNA (Figure 6). Its use in food-producing animal is prohibited because of the potential carcinogenicity. It is used in dogs, cats, and horses for the treatment of severe infections. It is also used in treatment of protozoal infections such as giardiasis and trichomoniasis in dogs.
3. **Rifampin:** It inhibits DNA-dependent RNA polymerase, which prevents initiation of tRNA synthesis (Figure 6). It is effective against intracellular infections.
4. **Tiamulin:** It binds to the 50S bacterial ribosome to inhibit protein synthesis (Figure 6). Its mechanism of action and antibacterial spectrum are similar to macrolides. It is active against gram-positive cocci, mycoplasma, *Spirochetes*, and some gram-negative pathogens.
5. **Vancomycin:** It blocks the second step of bacterial cell wall synthesis by inhibiting polymer release from the cell membrane (Figure 6). It is bactericidal for gram-positive organisms. It is a reserved antibiotic that is administered IV over 30-60 min every 6-8 hours for methicillin-resistant staphylococcal infections of bone and soft tissue in dogs and cats.
6. **Bacitracin:** It inhibits the second step of cell wall synthesis (Figure 6). It is bactericidal for gram-positive bacteria and *Spirochetes*. It is used as an ointment for topical infection in combination with polymyxin B and/or neomycin. It is also added

to poultry rations for the prevention and treatment of clostridial enteritis and as a growth promotant.

7. **Polymyxin B:** It interacts with phospholipids in the bacterial cell membrane to produce a detergent-like effect and membrane disruption (Figure 6). It is used topically to treat gram-negative bacterial infection of the skin, eye, and ear in all species. It is not absorbed orally and it is too nephrotoxic for parenteral use.
8. **Nitrofurans:** They are reduced by the bacteria to reactive intermediates that inhibit nucleic acid synthesis (Figure 6). They produce DNA fragmentation and may also block mRNA translation. They are broad spectrum and bacteriostatic. Nitrofurazone is used topically as an antibacterial ointment, powder, and water-soluble wound dressings in all species.
9. **Novobiocin:** It is a coumarin antibiotic. It blocks binding of ATP to DNA gyrase to inhibit supercoiling of bacterial DNA (Figure 6). It is bacteriostatic for gram-positive cocci. It is used for wound treatment and the treatment of mastitis.
10. **Streptogramins:** Virginiamycin is used for poultry. It binds to the 50S ribosome to inhibit protein synthesis (Figure 6). It is administered as a medicated feed additive in broiler chickens as growth promotant. It is also used as a feed additive in cattle to increase feed efficiency and to reduce the incidence of liver abscesses.
11. **Ionophore antibiotics:** They are polyether antibiotics derived from *Streptomyces* used primarily in poultry for feed efficiency and anticoccidial activity. They include monensin, lasalocid, laidlomycin, salinomycin and narasin. They act as alkali metal ionophores by complexing with sodium in the cell membrane to reduce passive extracellular transport of potassium and intracellular influx of H^+ , which kills bacteria and coccidia by lowering intracellular pH. They are used as premixes or medicated feed for growth promotion and control of coccidiosis in cattle and broiler chickens.