CHLORAMPHENICOL

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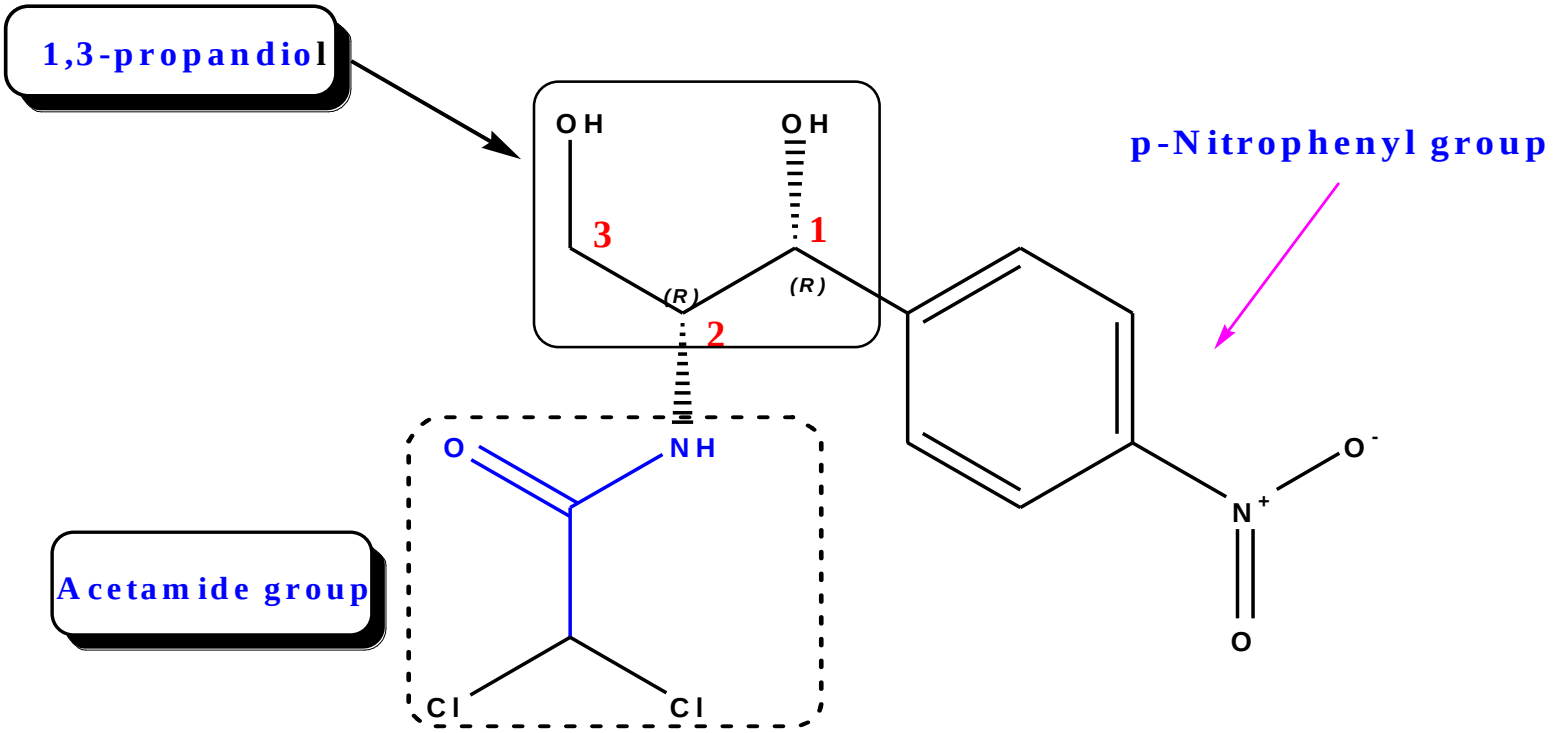


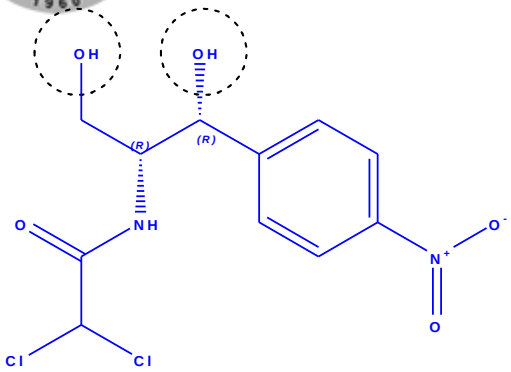
2-dichloroacetamide-1-(p-nitrophenyl)-1,3-propandiole

D-(-)Threo isomer

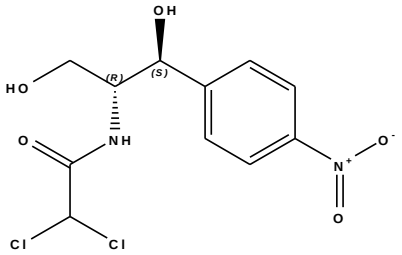
Mechanism of Action

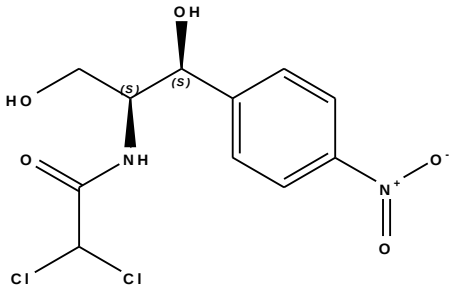
- inhibits protein synthesis.
- binds to 50 S r-RNA and inhibit formation of peptide bond.

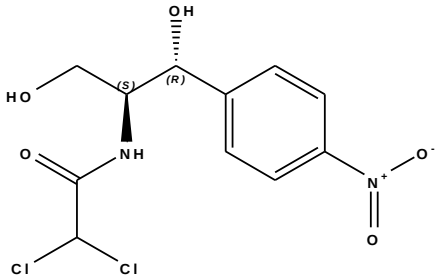
Stereochemistry of chloramphenicol

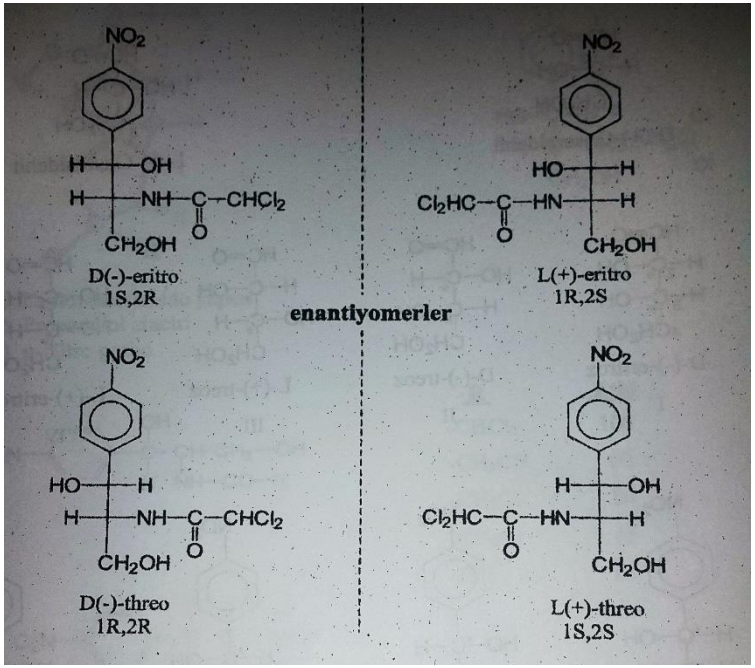


The active isomer







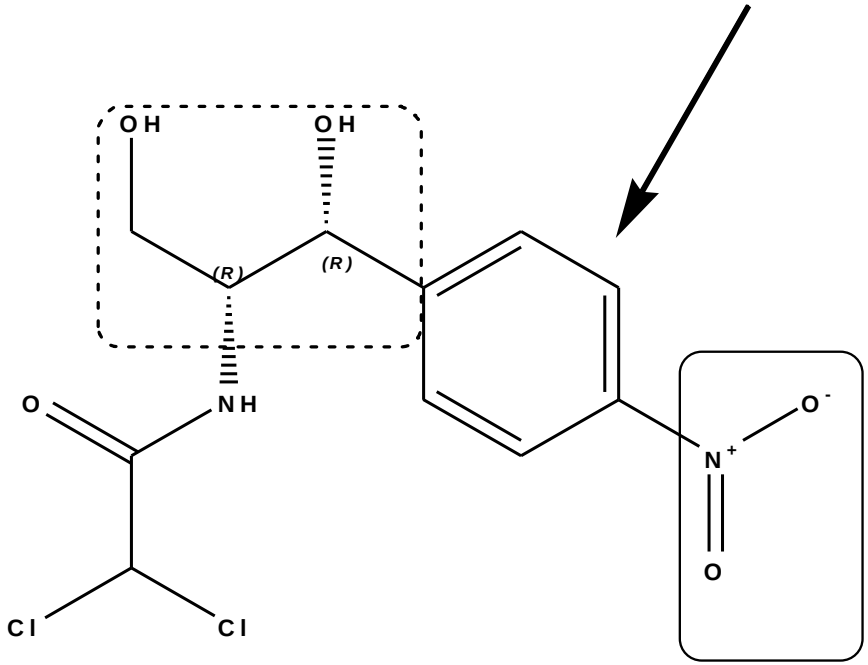


Konfigürasyon		Bakterisit Aktivite
(-) (1R,2R)	(-)-threo	100
(+) (1S,2S)	(+)-threo	0,4
(-) (1S,2R)	(-)-eritro	0,4
(+) (1R,2S)	(+)-eritro	2

The molecule of chloramphenicol contains two chiral centres and only one of the four diastereoisomers with 1R, 2R configuration is active. Total synthesis produces a mixture of all four isomers, the unwanted isomers are removed before use (refer to the synthesis). Its severe potential blood dyscrasia has greatly decreased its use.

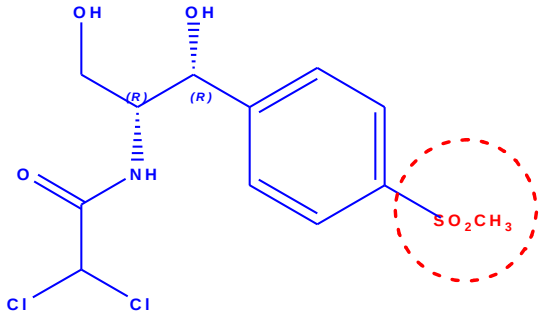
Structure Activity Relationship

- Replacement of phenyl group by other aromatic systems or cyclic systems e.g. cyclohexyl, furyl, naphthyl, pyridyl or thienyl results in loss of activity.
- Replacement of NO_2 by NH_2, NHR, OH, SO2R, CN results in loss of activity.
- Shifting of NO_2 from para-position leads to loss of activity.
- The propanediol moiety should be in D-(-) threo-isomer. Other isomers are inactive.
- Replacement of OH, and extension or suppression of terminal CH_2OH abolishes the activity.



Structure Activity Relationship

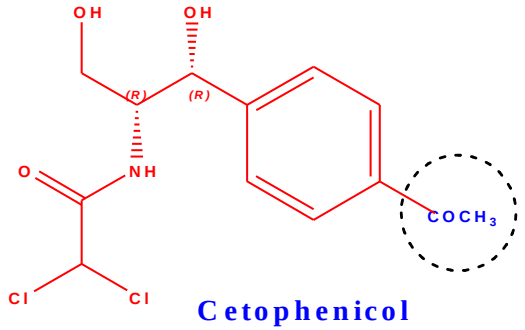
* Replacement of nitro group by other electron withdrawing groups gives active compounds as



Thiamphenicol

CH_3SO_2 (Thiamphenicol)

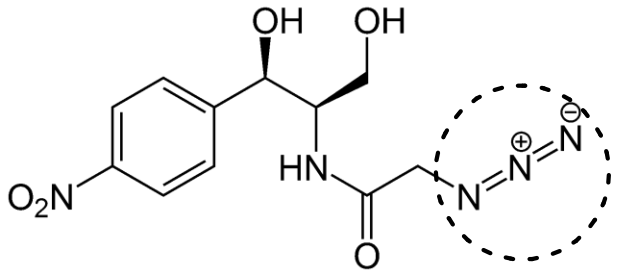
CH_3CO (Cetophenicol)



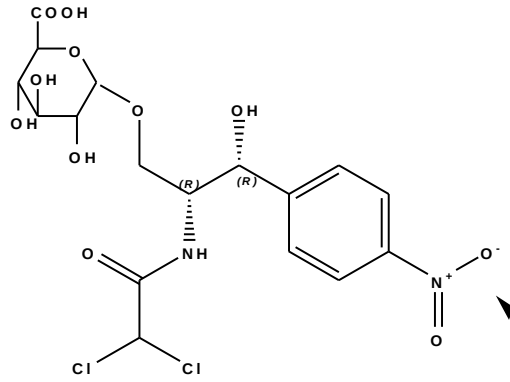
Cetophenicol

* Replacement of dichloro group by azido group gives active compounds as Azidamphenicol

Azidamphenicol

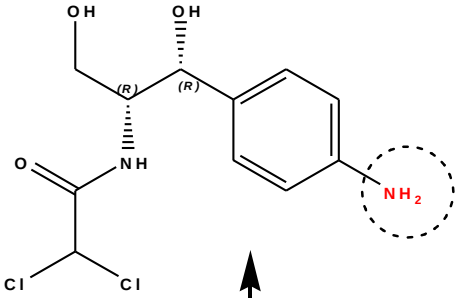


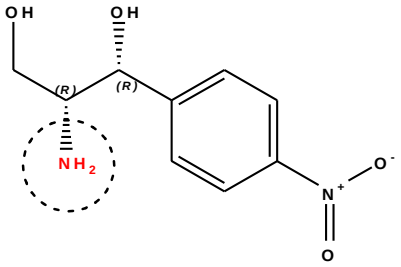
Metabolism of Chloramphenicol

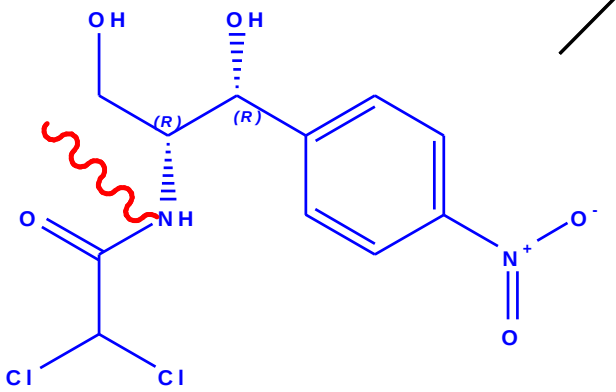


C-3 glucuronide conjugate

Major metabolite







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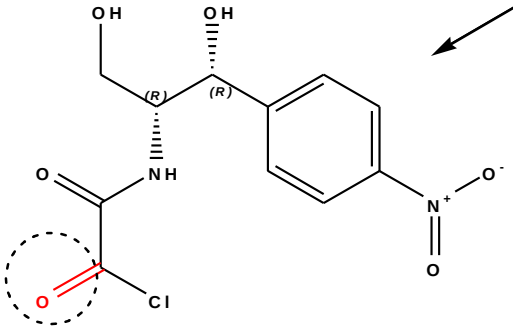
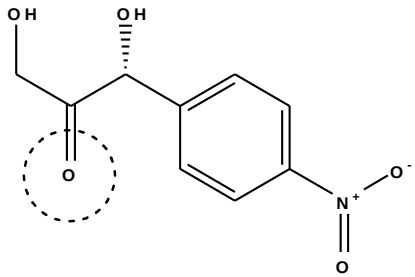




Toxicity of Chloramphenicol

- When used for a long time → reversible agranulocytosis and thrombocytopenia

- Hematoxicity is due to the formation of nitroso and hydroxyl amines due to the reduction of the aromatic nitro group (reversible when the drug is discontinued)

Gray baby syndrome: A syndrome due to toxicity of the antibiotic chloramphenicol in the newborn, especially the premature newborn

- because of lack the necessary liver enzymes to metabolize this drug.

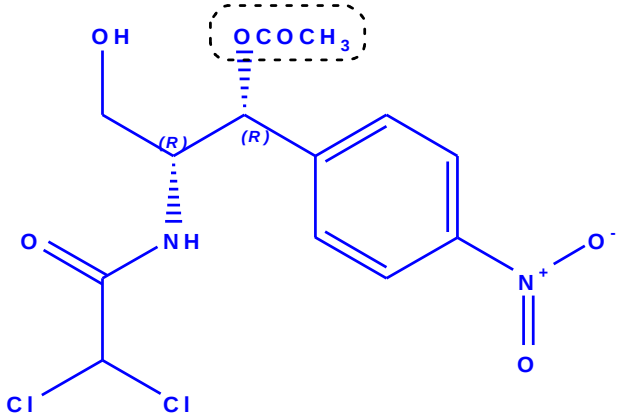
Chloramphenicol accumulates in the baby causing

- hypotension
- cyanosis (blue coloring of lips, nail beds, and skin from lack of oxygen in the blood),
- death

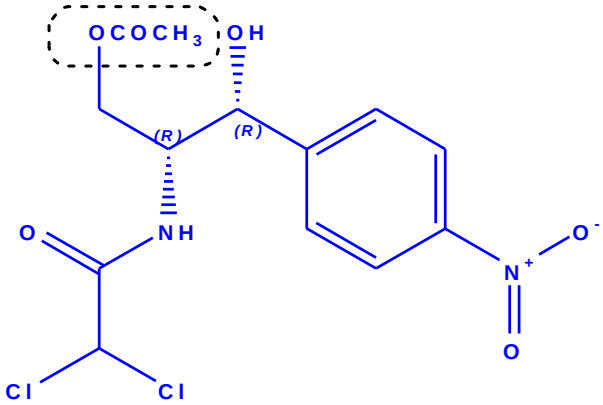
- Chloramphenicol is therefore usually not given to newborns or premature babies.

Bacterial Resistance

Bacterial resistance to chloramphenicol arises from the ability of certain strains of bacteria to produce chloramphenicol acetyltransferase, an enzyme that acetylates OH at C-1 and C-3 of the propanol moiety to produce 1-acetoxy and 3-acetoxy derivatives, respectively, which **are devoid of any activity**.



1-Acetoxy derivative

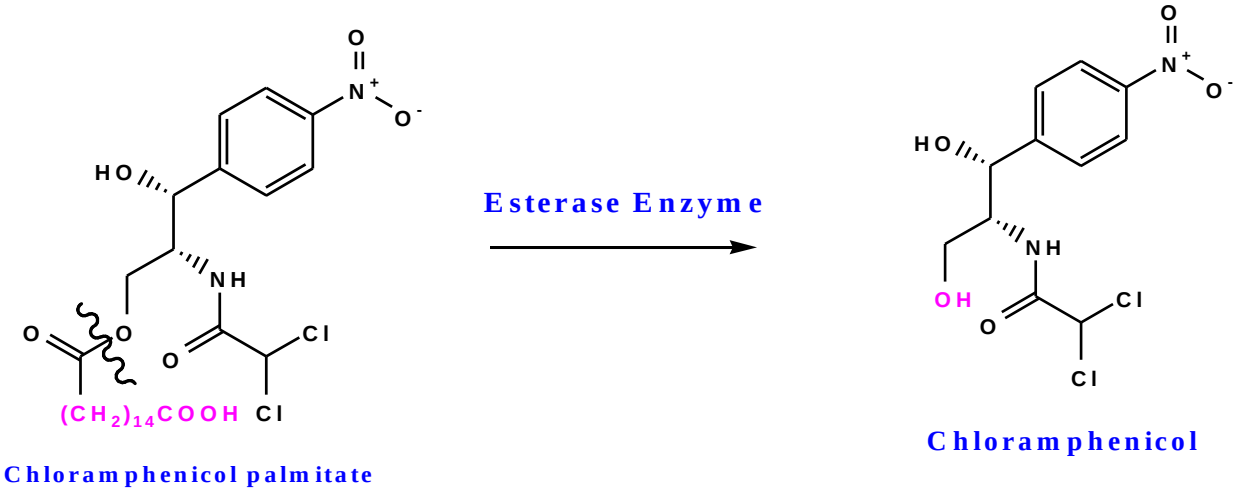


3- Acetoxy derivative

Latent forms of chloramphenicol (Prodrugs of chloramphenicol)

Chloramphenicol palmitate

- Since the drug is intensively bitter, this can be masked for use as a peadiatric oral suspension by use of the C-3 palmitate, which has extremely low solubility. The ester is cleared in the duodenum to liberate the drug.

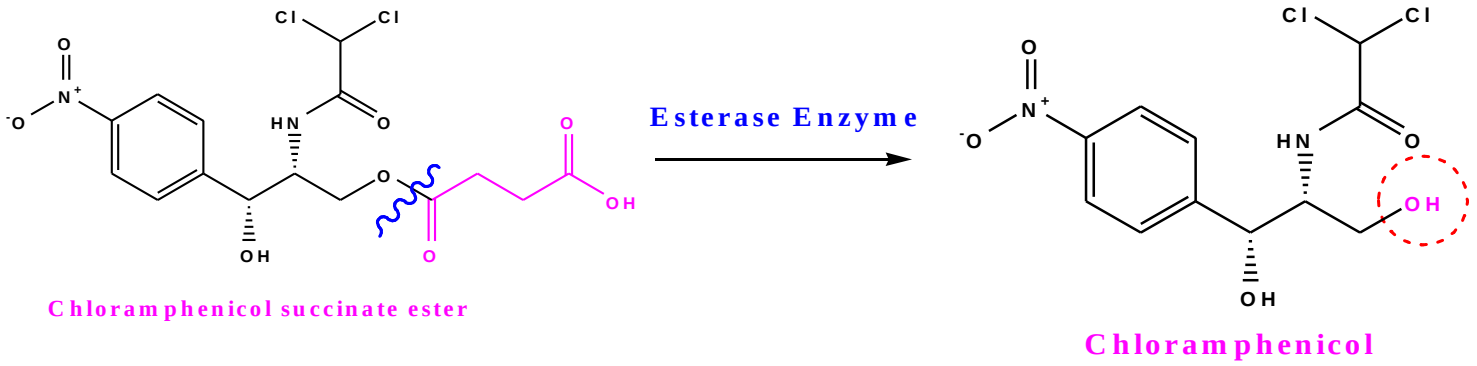


Latent forms of chloramphenicol (Prodrugs of chloramphenicol)

Chloramphenicol hemisuccinate

- Chloramphenicol has **poor water solubility** and, thus is largely overcome by conversion to the **3-hemisuccinyl ester**, which forms a water-soluble sodium salt suitable for parental preparation.

- This is cleaved in the body to produce active chloramphenicol. Because cleavage in muscles is too slow, this product is used intravenously rather than intramuscularly.



Chloramphenicol succinate ester

Chloramphenicol

Uses of Chloramphenicol

- Bacteriostatic or bactericidal (depending on an organism and dosage)
- The binding site is the same as the macrolide and the linkozamides.
- Because the sites of action are same, these 3 antibiotics prevent the antibacterial effect of each other; they should not be used together.
- Broad spectrum (especially against Gram (+) and anaerobes).
- Despite of potential serious limitations, chloramphenicol is an excellent drug when used carefully.
- It is of special value for treatment of **typhoid and parathyroid fevers, haemophilus infections, pneumococcal and meningococcal meningitis in beta lactam allergic patients**.
- Safer antibiotics should be used whenever possible.