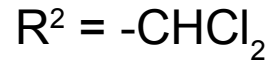
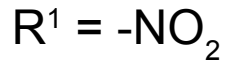


Antibiotics & other antibacterial chemotherapeutics of various structures

Chloramphenicol group (“amphenicols”)



chloramphenicol

- isolated from *Streptomyces venezuelae* in 1947, now prepared synthetically
- spectrum: both G^+ and G^- , e.g. *Salmonella*, *Rickettsia*, *Bordetella pertussis*, *Neisseria*, *Haemophilus*, *Klebsiela*, *Enterobacter*, *Staphylococcus aureus*, *Streptococcus* ...

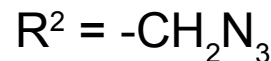
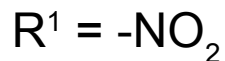
• mode of action: proteosynthesis inhibition: blocks peptidyltransferase

• **adverse effect: irreversible aplastic anaemia \Rightarrow systemic use strongly limited**

Chloramphenicolum PhEur

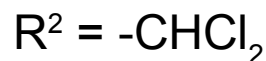
Ophthalmo-chloramphenicol Léčiva[®] ung., Spersadex[®] gtt. opht.

(+dexamethason)



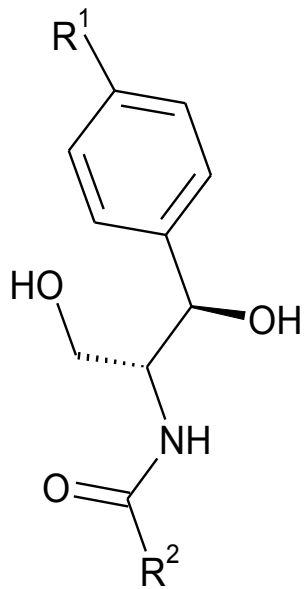
azidamphenicol

Ophthalmo-azaphenicol[®] oph. gtt.



thiamphenicol

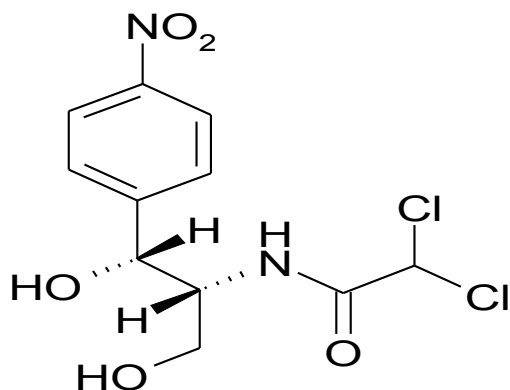
Thiamphenicolum PhEur



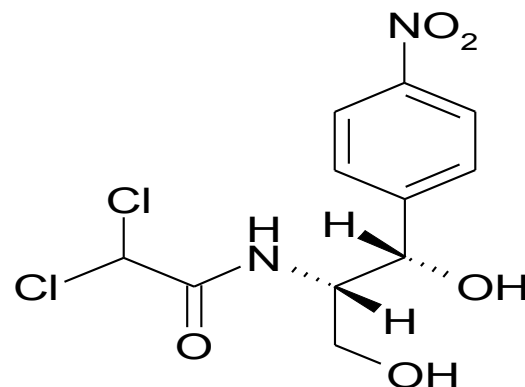
1R, 2R (= D-threo)

Stereochemistry and activity of chloramphenicol

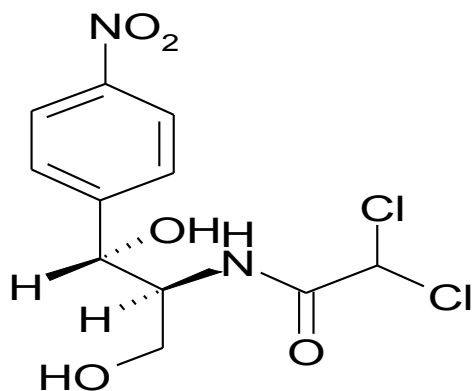
1R, 2R
D-(-)-threo
active
rel. activity 100



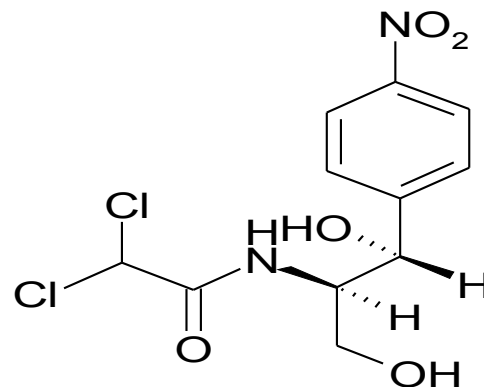
1S, 2S
L-(+)-threo
rel. activity < 0,4
also dextromycin



1R, 2S
D-(+)-erythro
rel. activity < 0,4



1S, 2R
L-(-)-erythro
rel. activity 1-2

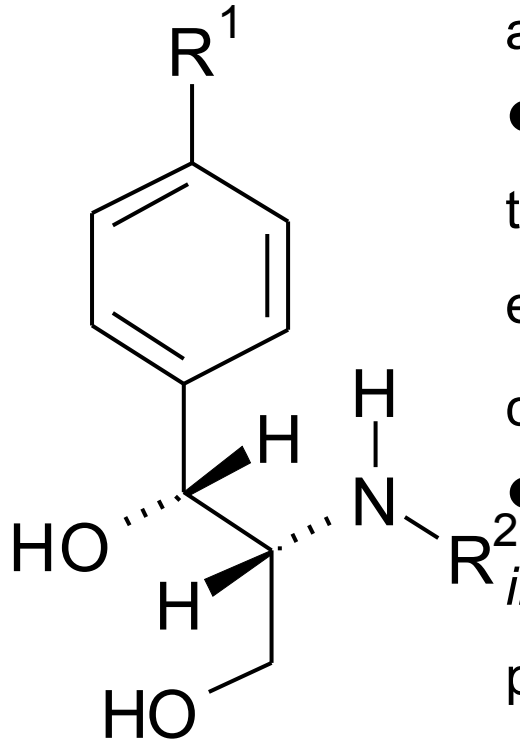


Structure-activity relationships (SAR) in amphenicols

- structural fragment necessary for the activity: (1R, 2R)-2-amino-1-phenyl-1,3-propanediol

- $R^1 = -NO_2$, but also $-SCH_3$ or $-SO_2CH_3$ (almost the same activity as in chloramphenicol)

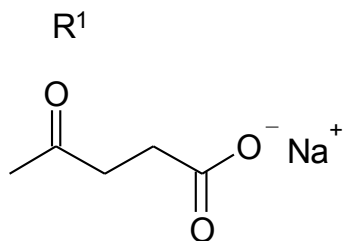
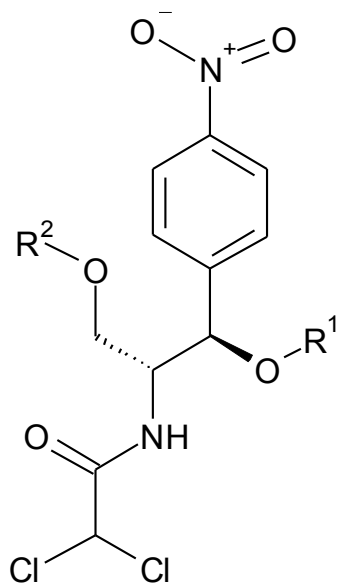
- the amide side chain must contain N-H; R^2 has an impact to the activity in accordance with its bulkiness and electronegativity ($R^2=OCCHBr_2$ retains 80 % of activity of chloramphenicol)



- esterification of primary -OH \Rightarrow loss or significant \downarrow of activity *in vitro*; esters are, however, rapidly hydrolysed (\Rightarrow ester prodrugs)

- absolute configuration is of fundamental importance for the activity; only 1R, 2R (= D-*threo*) is highly active, 1S, 2R (=L-*erythro*) retains minimal activity, while 1S, 2S (= L-*threo*) and 1R, 2S (=D-*erythro*) are nearly inactive \Rightarrow the activity depends more on the configuration on C1

Chloramphenicol prodrugs optimized for particular ways of administration

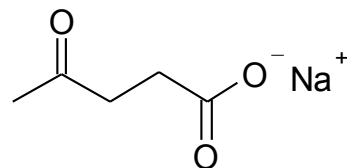


R²

H

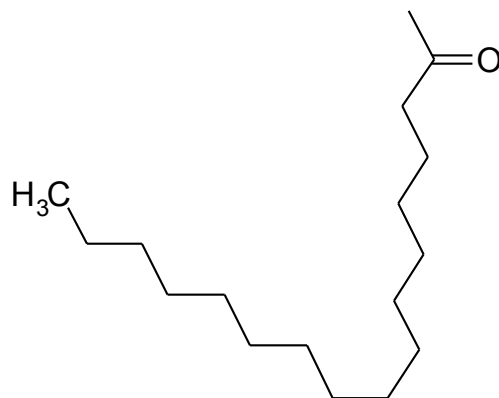
chloramphenicol sodium succinate
Chloramphenicoli natrii succinas
PhEur
Chloramphenicol® ICN plv. inj. sol.

or



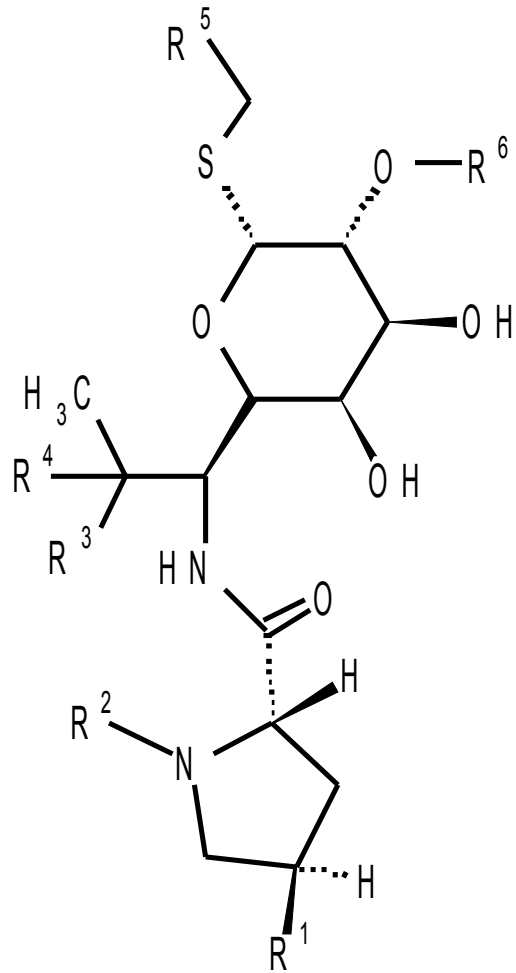
H

H



chloramphenicol palmitate
Chloramphenicoli palmitas PhEur
● nearly insoluble in water, bitter
taste suppressed

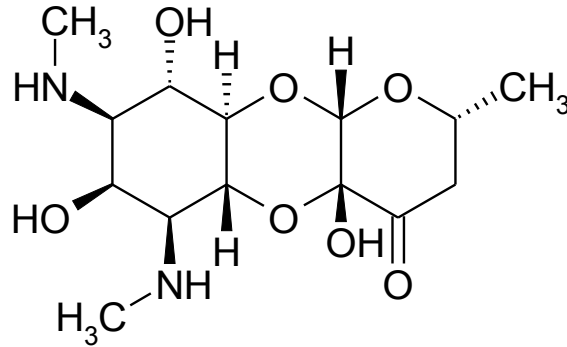
Lincosamides



R^1	R^2	R^3	R^4	R^5	R^6	
C_3H_7	CH_3	OH	H	H	H	<p>lincomycin</p> <p>isolated from <i>Streptomyces lincolnensis</i> var. <i>lincolnensis</i></p> <p><i>Lincomycini hydrochloridum</i> <i>monohydricum PhEur</i></p> <p>Lincocin[®] inj. sol., Lekomyacin P[®] a.u.v. plv. sol., Neloren[®] cps. (base)</p>
C_2H_5	CH_3	OH	H	H	H	<p>lincomycin B</p> <p>(up to 5 % in pharmacopoeial lincomycin)</p>
C_3H_7	CH_3	H	Cl	H	H	<p>clindamycin</p> <p><i>Clindamycini hydrochloridum PhEur</i></p>
C_3H_7	CH_3	H	Cl	H	$OPO(OH)_2$	<p>Clindamycin dihydrogen phosphate</p> <p><i>Clindamycini dihydrogenphosphas</i> Dalacin C[®]</p>
C_2H_5	CH_3	H	Cl	H	H	<p>clindamycin B</p> <p>(max. 2 % in pharmacopoeial clindamycin)</p>

- mode of action: protein synthesis inhibition by inhibition of peptide bond formation by peptidyl transferase
- bacteriostatic
- spectrum: narrow; G^+ and anaerobs, *Staphylococcus*, *Streptococcus*, *Clostridium*, *Bacteroides* ...

Spectinomycin



(2R,4aR,5aR,6S,7S,8R,9S,9aR,10aS)-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)decahydro-4H-pyran[2,3-b][1,4]benzodioxine-4-on

spectinomycin

➤ an antibiotic produced by *Streptomyces spectabilis*

● mode of action: protheosynthesis inhibition; in particular movement between mRNA and a ribosome

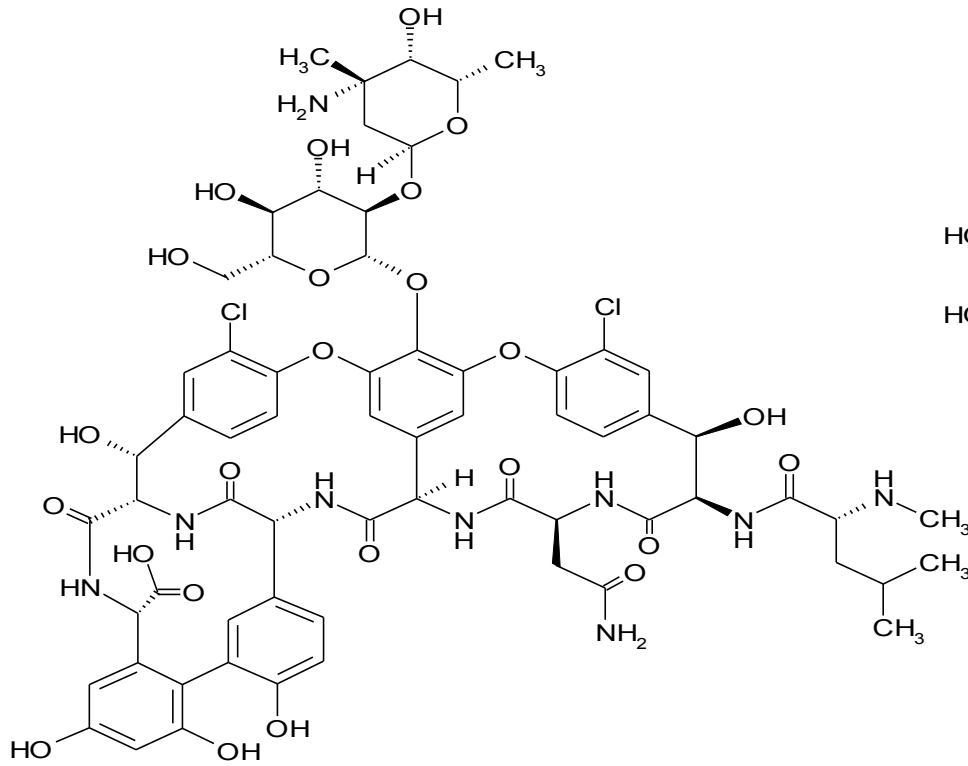
● bactericidal

● spectrum: ***Neisseria gonorrhoeae***, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *E. coli*, *Haemophilus*, *Proteus*, *Bacteroides*

formerly the only antibiotic for treatment of gonorrhoea

Spectam scour halt[®] a.u.v. gel, Mucospectom[®] a.u.v. (+linkomycin.HCl)

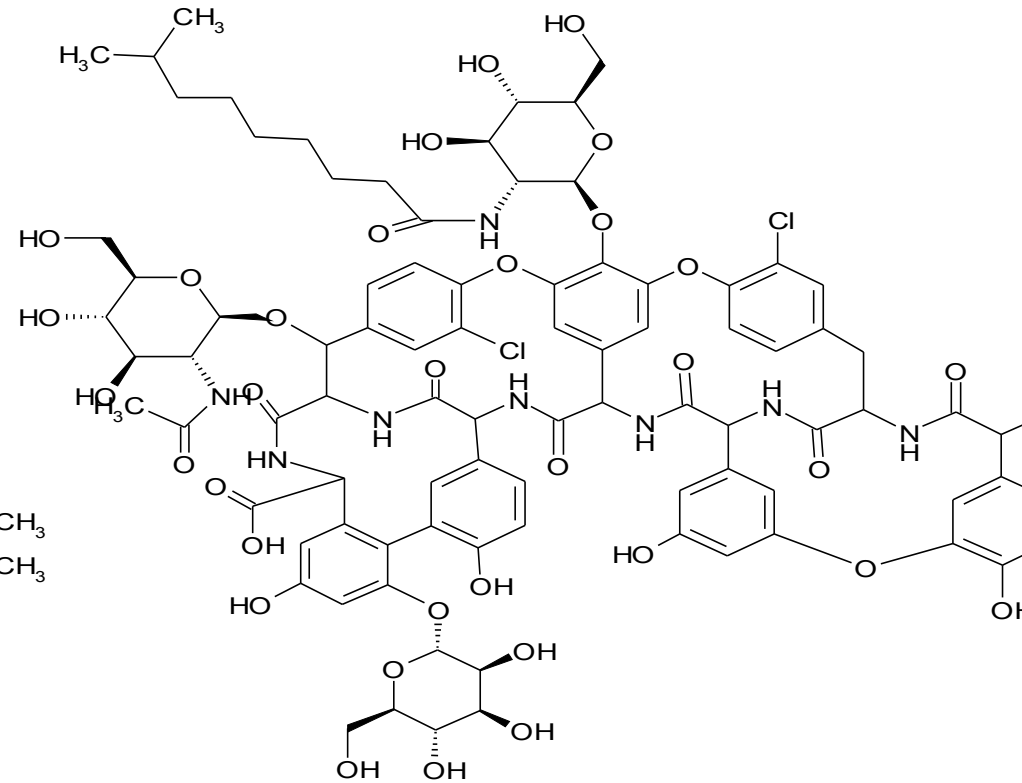
Glycopeptides



vancomycin

● isolated from *Streptomyces orientalis*
Edicin® inj. plv. sol., Vancocin CP® inj. sic.

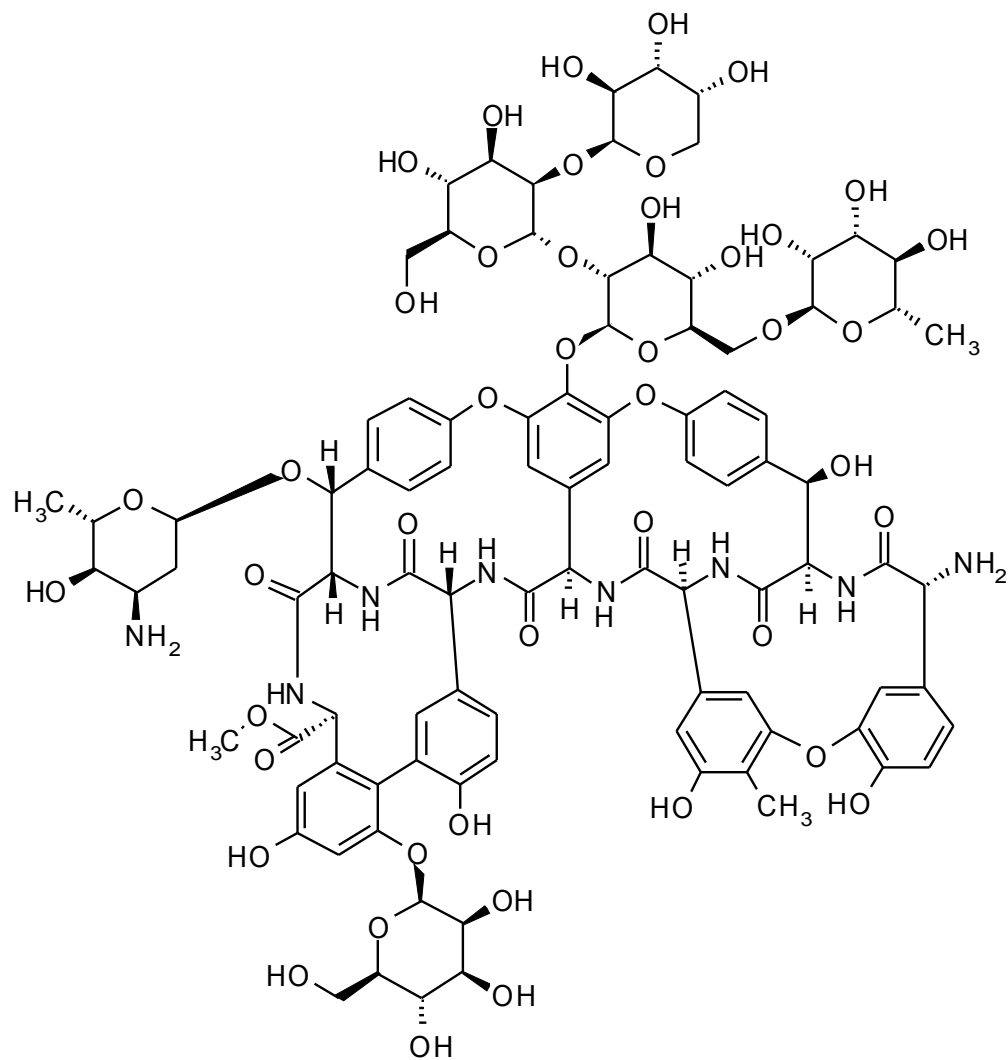
- mode of action: inhibition of bacterial cell wall building
- the resistance to them need not be crossed
- bactericidal
- parenteral administration only
- spectrum: narrow; G⁺: *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Clostridium* ...



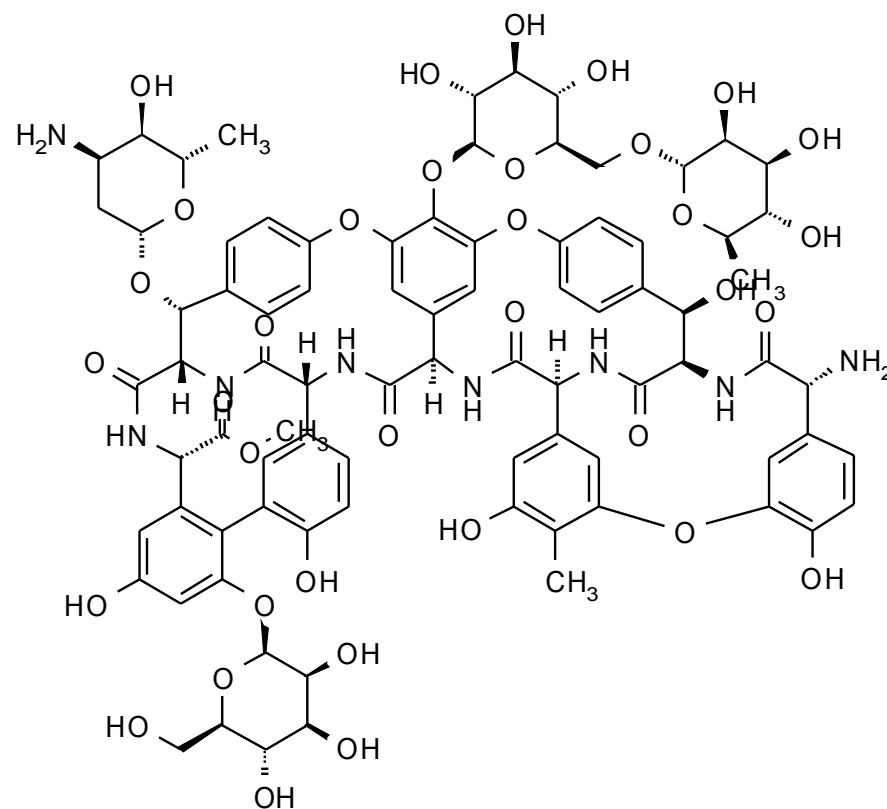
teicoplanin

● isolated from *Actinoplanes teichomyceticus*
Targocid® inj. sic.

Glycopeptides



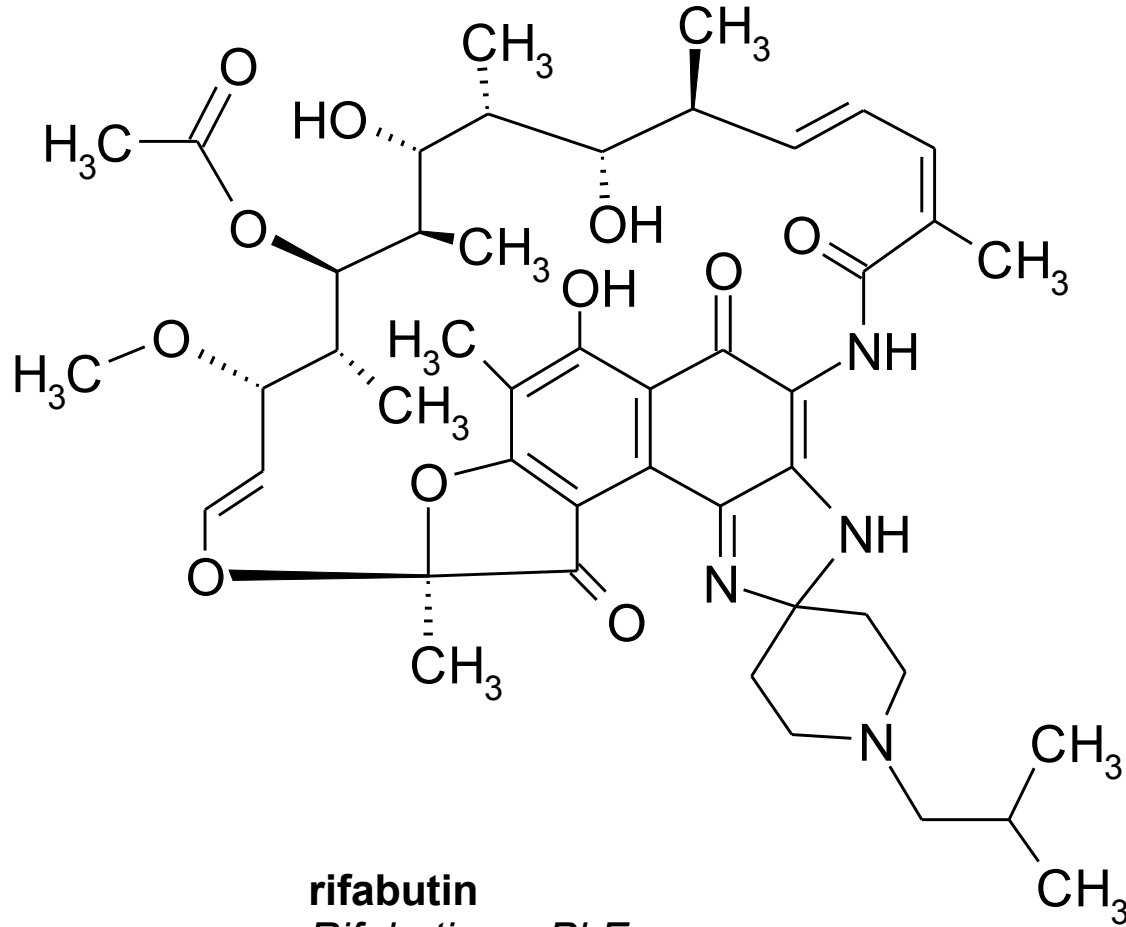
ristocetin A



ristocetin B

- a mixture isolated from *Nocardia lurida*
- toxic, agglutination of platelets, blood clotting

Rifamycins



rifabutin

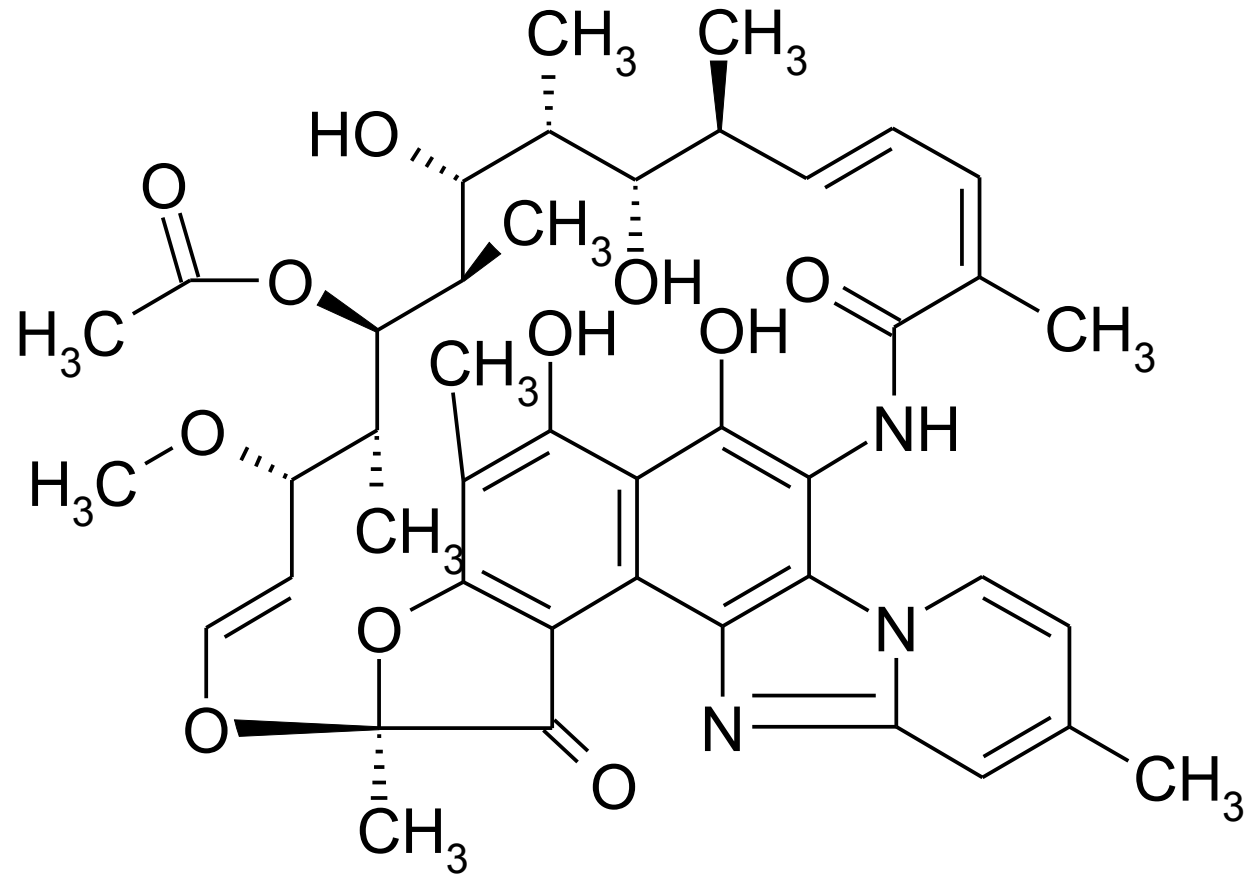
Rifabutinum PhEur

•semi-synthetic

●*M. avium-intracellulare*

Mycobutin® cps.

Rifamycins

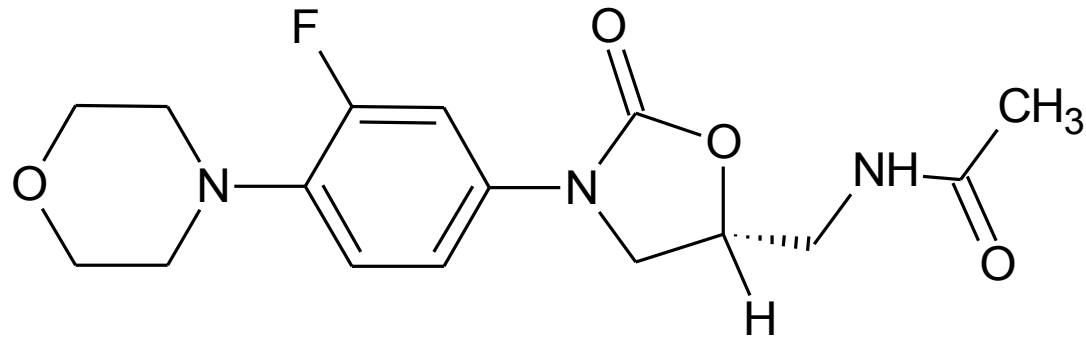


rifaximin

- non-absorbable antibiotic for treatment of infectious diarrhoea

Normix® tbl.

Oxazolidin-2-one derivatives



- fully synthetic antibacterial chemotherapeutic
 - mode of action: inhibits bacterial protein synthesis by binding to 23S rRNA of 50S subunit of ribosome and avoids formation of the functional 70S initiation complex which is a necessary part of the translation process
 - spectrum: G⁺ only: aerobs: *Enterococcus* , *Staphylococcus aureus*, *Streptococcus*; anaerobs: *Clostridium perfringens*, *Peptostreptococcus*
 - nosocomial (hospital) and community pneumonias, complicated skin and soft tissues infections
 - adverse effects: MAO inhibition
- Zyvoxid ® por tbl, inf sol