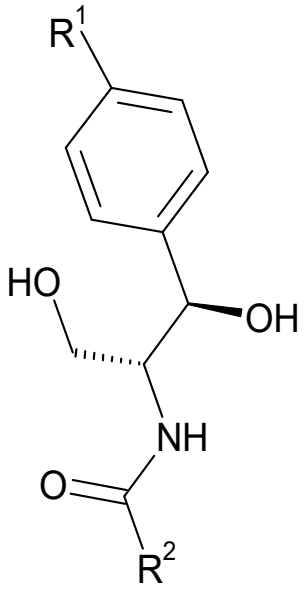
Antibiotics & other antibacterial chemotherapeutics of various structures

Chloramphenicol group (“amphenicols”)



1R, 2R (= D-threo)

$R^1 = -NO_2$ $R^2 = -CHCl_2$ **chloramphenicol**

- isolated from *Streptomyces venezuelae* in 1947, now prepared synthetically
- spectrum: both G^+ and G^-, e.g. *Salmonella, Ricketsia, Bordetella pertussis, Neisseria, Haemophilus, Klebsiela, Enterobacter, Staphylococcus aureus, Streptococcus ...*
- mode of action: proteosynthesis inhibition: blocks peptidyltransferase
- adverse effect: irreversible aplastic anaemia ⇒ systemic use strongly limited

Chloramphenicolum PhEur

Ophthalmo-chloramphenicol Léčiva® ung., Spersadex® gtt. opht. (+dexamethason)

$R^1 = -NO_2$ $R^2 = -CH_2N_3$ **azidamphenicol**

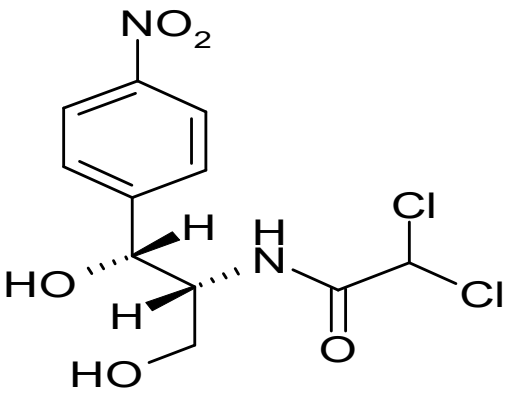
Ophthalmo-azaphenicol® oph. gtt.

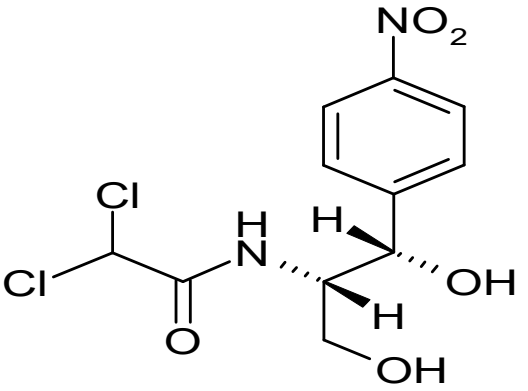
$R^1 = CH_3SO_2-$ $R^2 = -CHCl_2$ **thiamphenicol**

Thiamphenicolum PhEur

Stereochemistry and activity of chloramphenicol

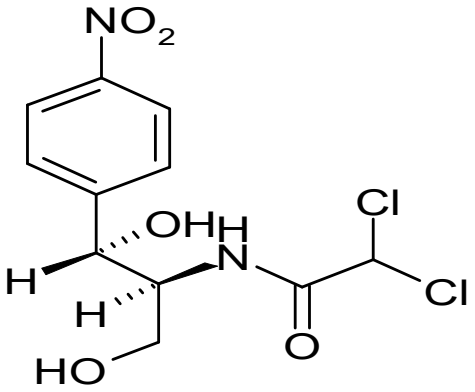
1R, 2R
D-(-)-threo
active
rel. activity 100

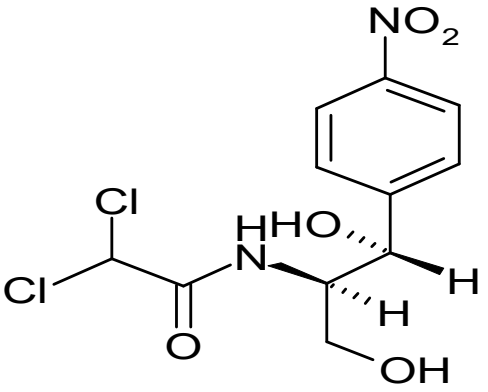




1S, 2S
L-(+)-threo
rel. activity < 0,4
also dextromycin

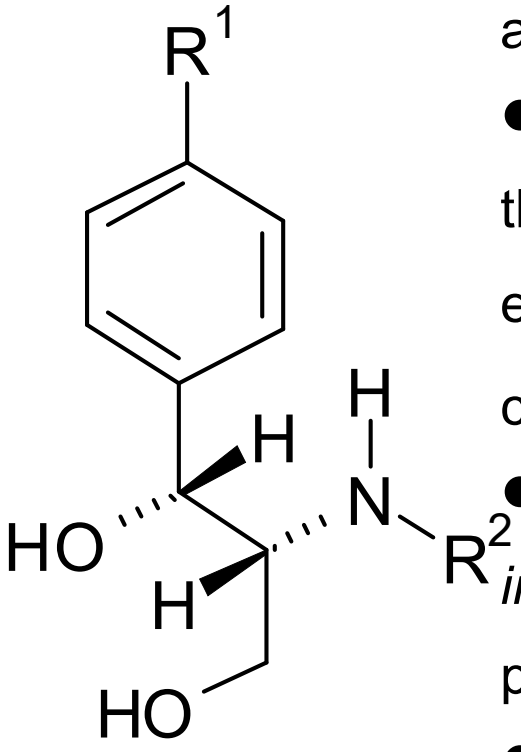
1R, 2S
D-(+)-erythro
rel. activity < 0,4





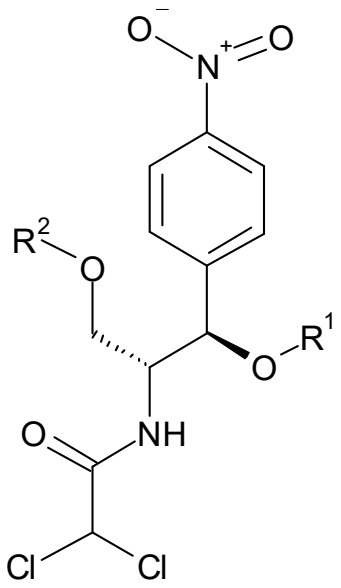
1S, 2R
L-(-)-erythro
rel. activity 1-2

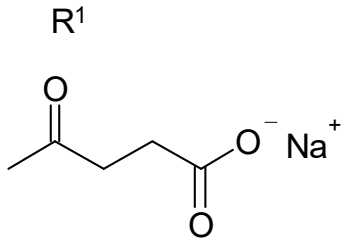
Structure-activity relationships (SAR) in amphenicols



- 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 higly 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

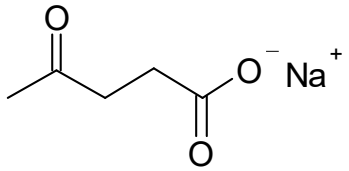
Chloramphenicol prodrugs optimized for particular ways of administration





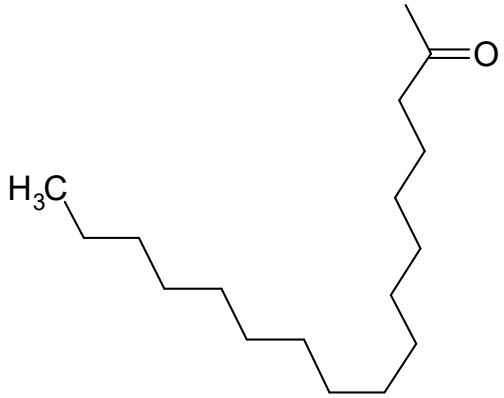
H

or



H

H



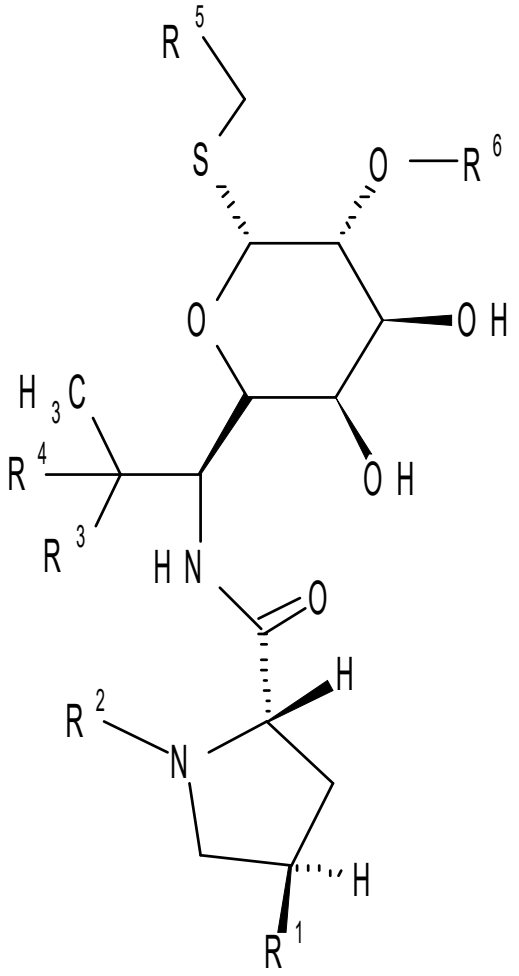
R2

H

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

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

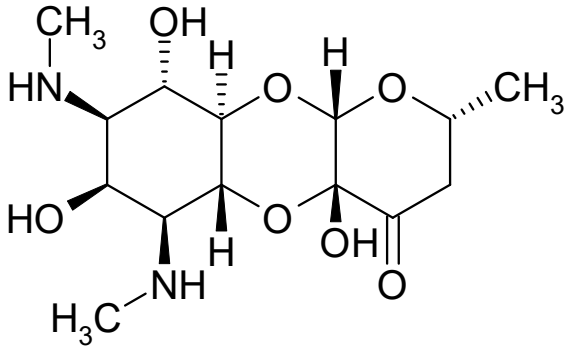
Lincosamides



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

- mode of action: protheosynthesis 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-pyrane[2,3-b][1,4]benzodioxine-4-on

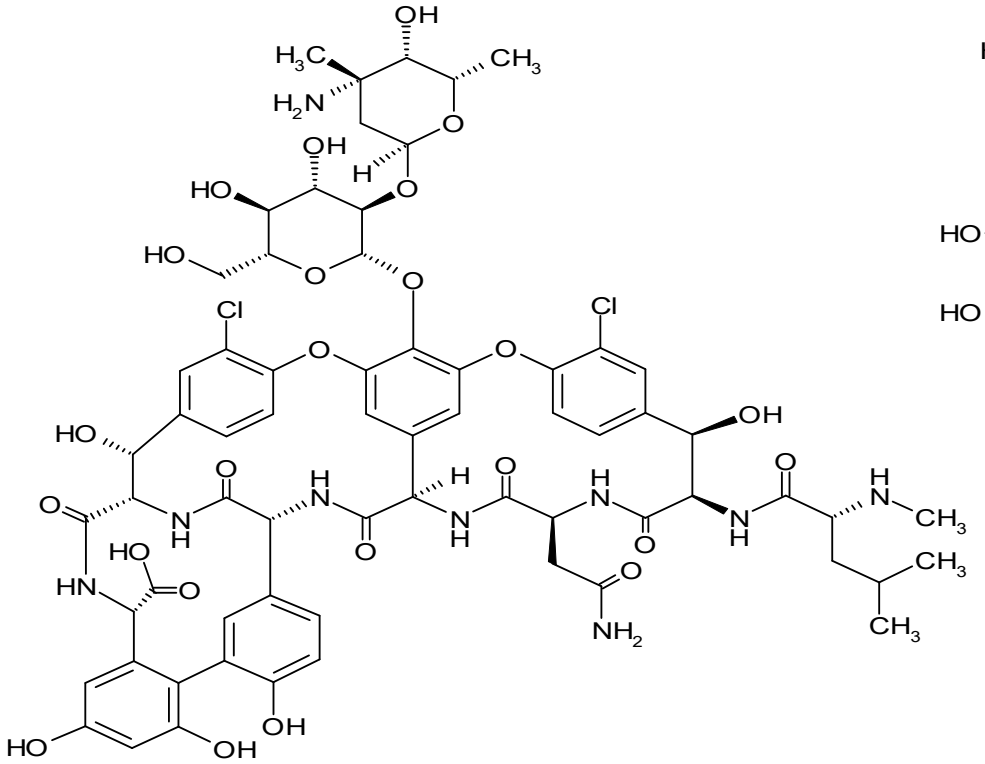
spectinomycin

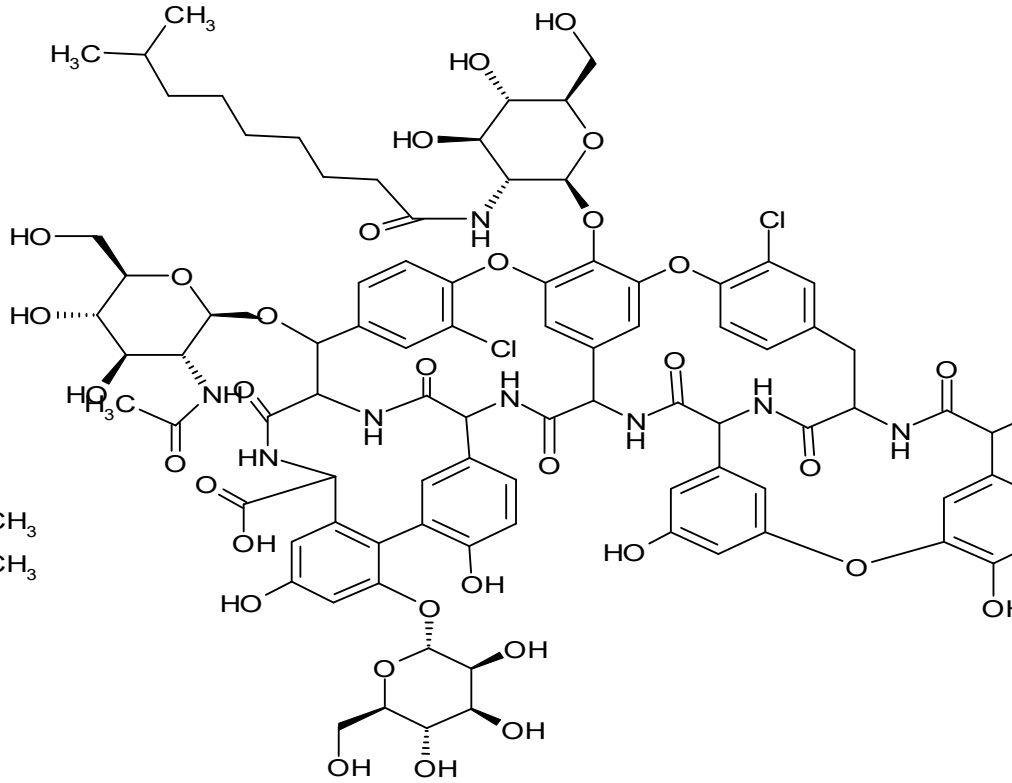
- an antibiotic produced by *Streptomyces spectabilis*
- mode of action: protheosynthesis inhibition; in particular movement between mRNA and a ribosome
- bactericidal
- spectrum: ***Neisseria gonorrhoeae***, *Staphylococcus, Streptococcus, Enterococcus, E. coli, Haemophilus, Proteus, Bacteroides*

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.

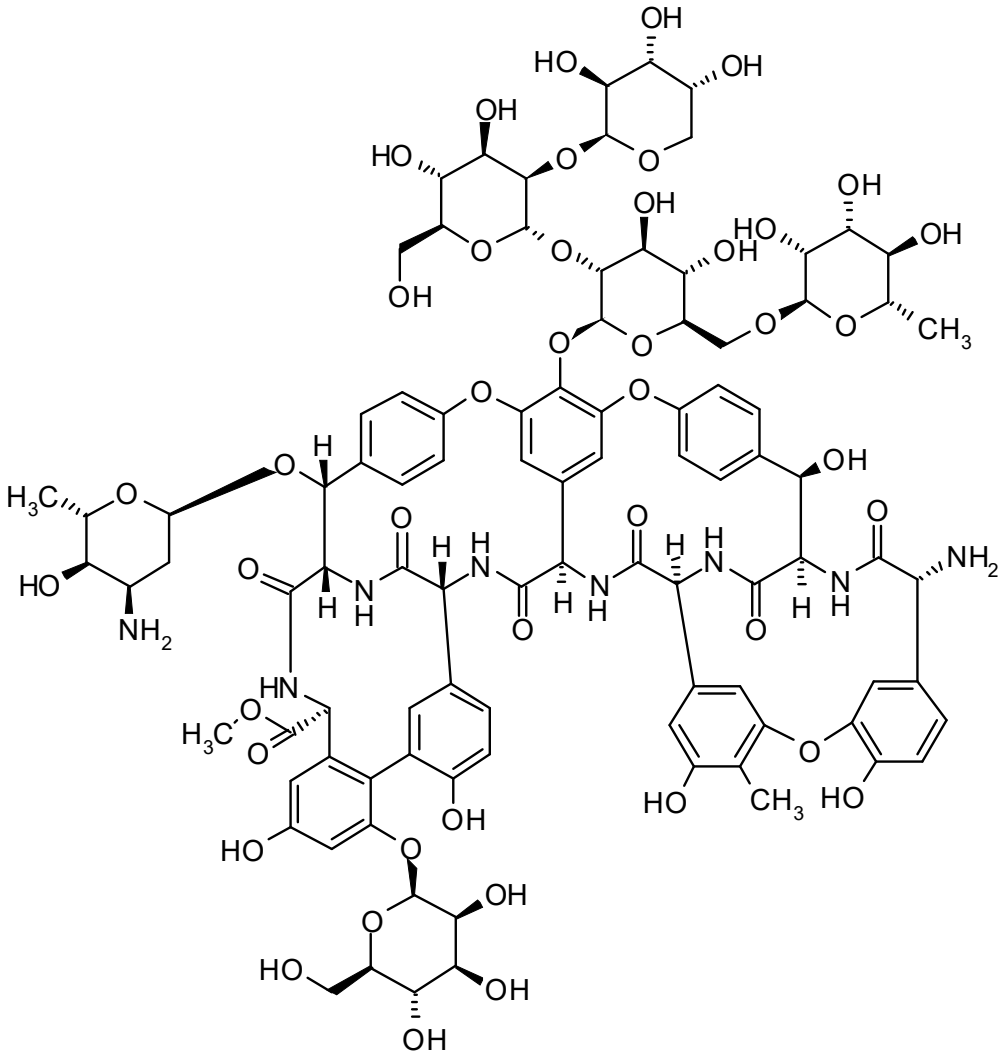
teicoplanin

- isolted from *Actinoplanes teichomyceticus*

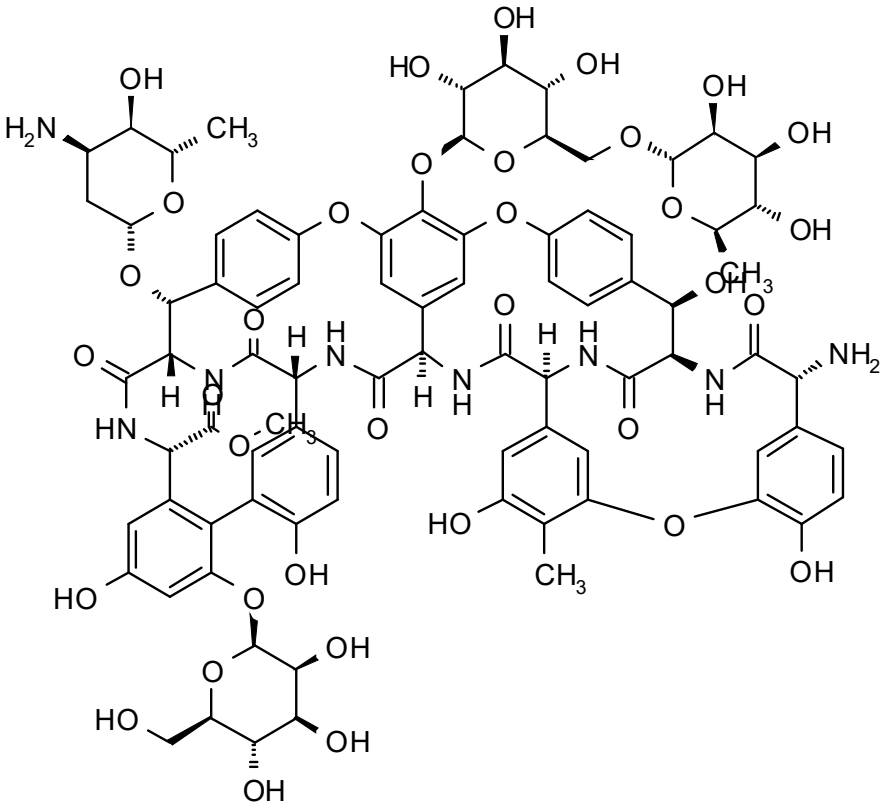
Targocid®inj. sic.

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

Glycopeptides



ristocetin A



ristocetin B

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

Ansamycins

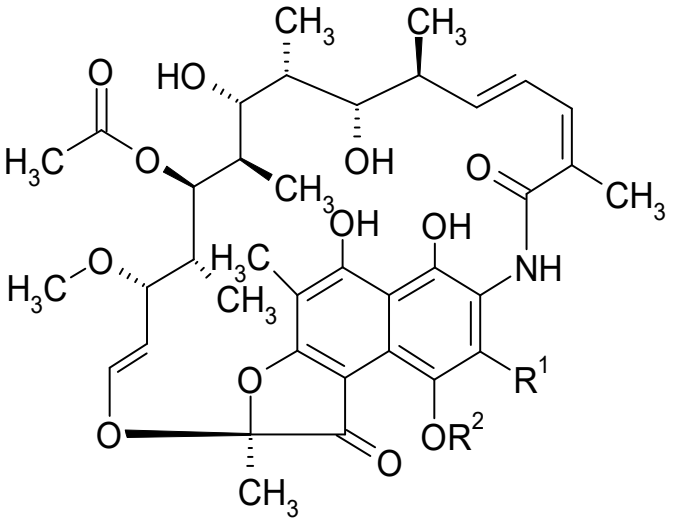
•contain an aromatic ring non-adjoining positions of which are linked with a macrocyclic lakctame ring

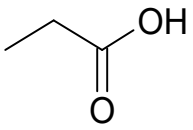
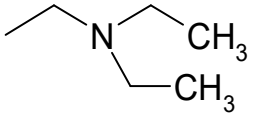
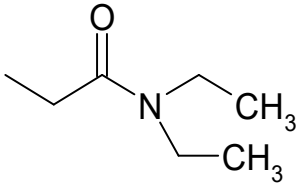
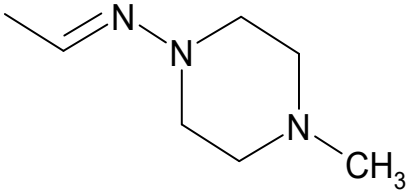
Rifamycins

•based on naphthalene ring

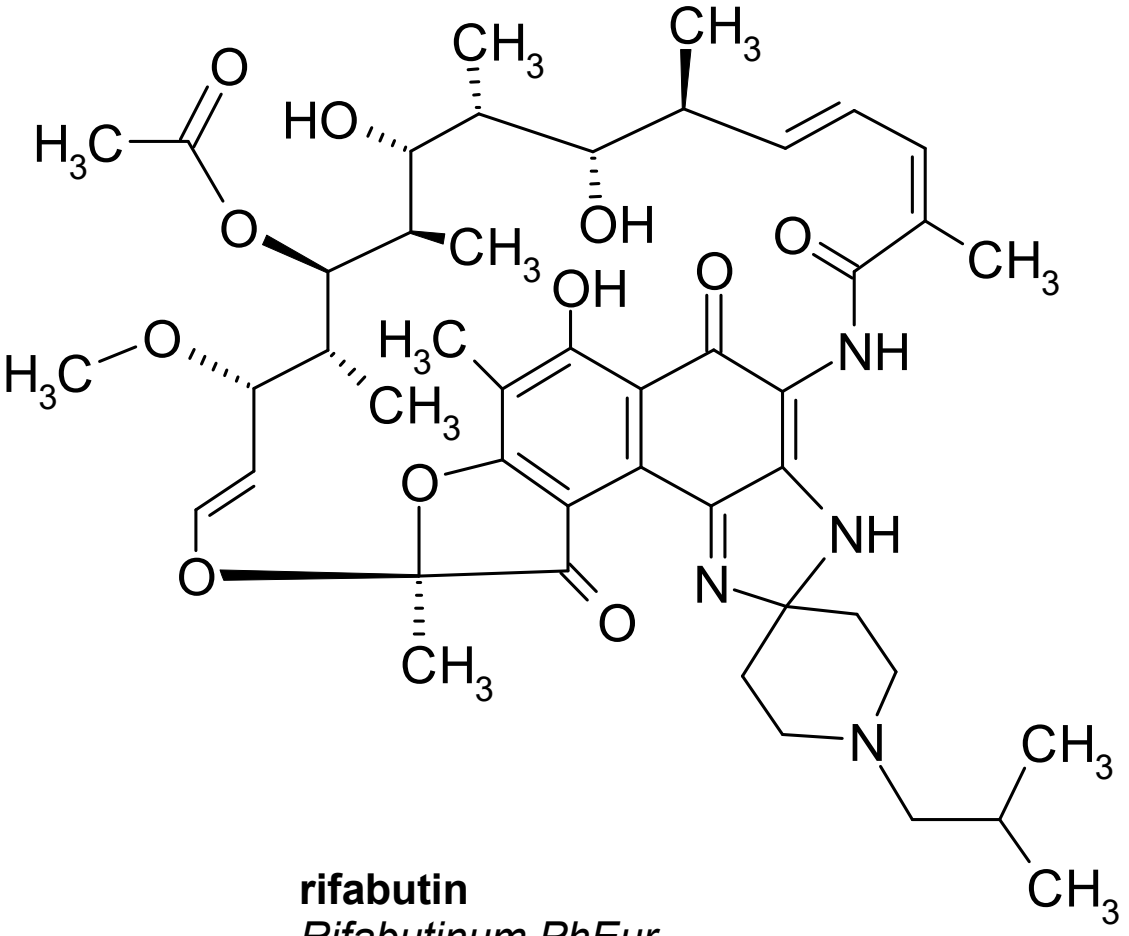
●mode of action: inhibition of RNA synthesis by blocking of DNA-dependent RNA-polymerase by forming a stable complex with the enzyme

●bacteriostatic, bactericidal in higher doses



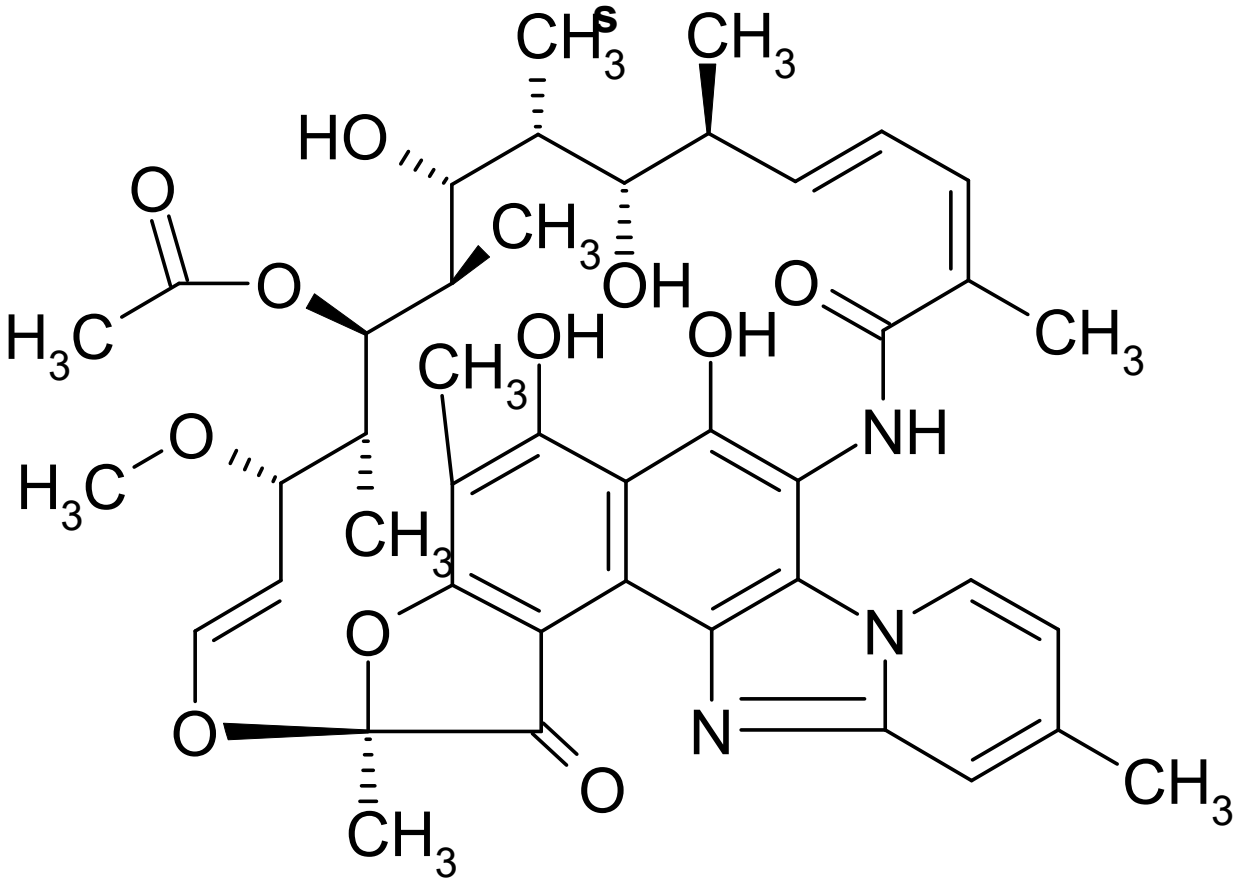
R^1	R^2	
-H		**rifamycin B** •natural antibiotic produced by *Amycolatopsis mediterranei*
	-H	**rifamycin SV** *Rifamycinum natricum PhEur*
-H		**rifamide**
	-H	**rifampicin** (syn. rifampin [USAN]) *Rifampicinum PhEur* ●*Mycobacterium tuberculosis, M. leprae* and other both G^+ and G^- Arficin®cps., Benemycin®cps.

Rifamycins



rifabutin
Rifabutinum PhEur
•semi-synthetic
●*M. avium-intracellulare*
Mycobutin ® cps.

Rifamycin S

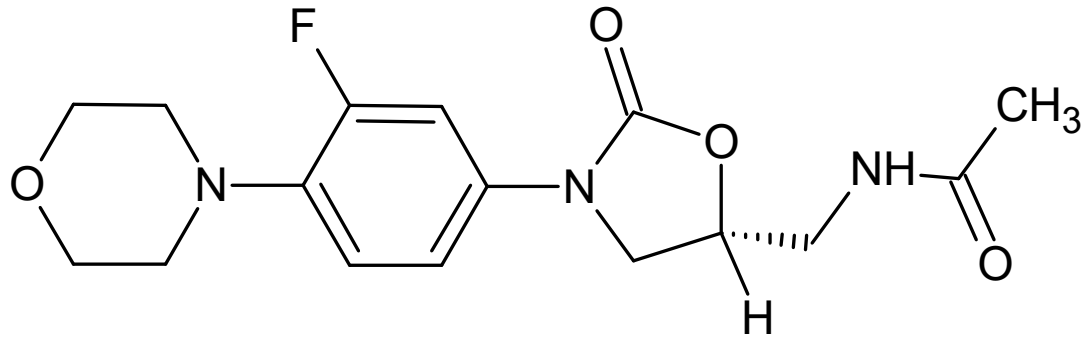


rifaximin

•non-absorbable antibiotic for treatment of infectious diarrhoea

Normix® tbl.

Oxazolidin-2-one derivatives



linezolid

•fully synthetic antibacterial chemotherapeutic

•mode of action: inhibits bacterial protein synthesis by binding to 23S rRNA of 50S subunit of ribozome 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; neutropenia

Zyvoxid ® por tbl, inf sol