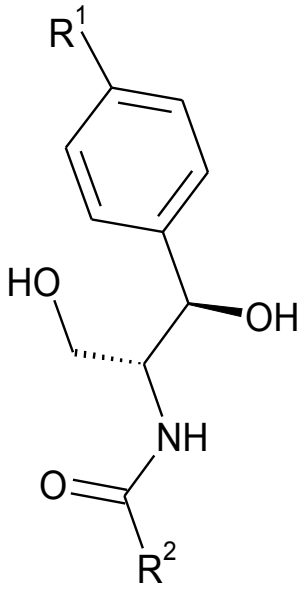
# Antibiotics & other antibacterial chemotherapeutics of various structures

# **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**

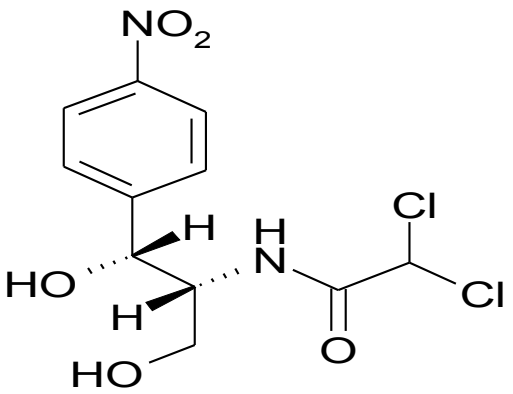
Ophthalmo-azaphenicol® oph. gtt.

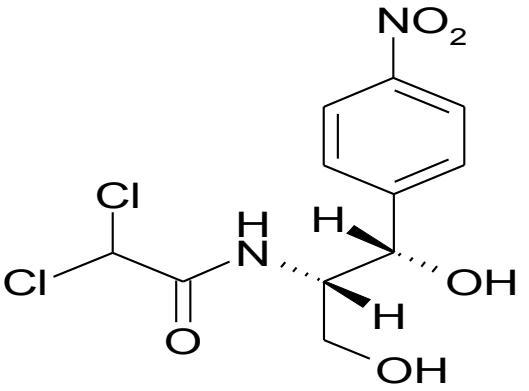
$R^1 = CH_3SO_2-$ $R^2 = -CHCl_2$ **thiamphenicol**

*Thiamphenicolum PhEur*

# Stereochemistry and activity of chloramphenicol

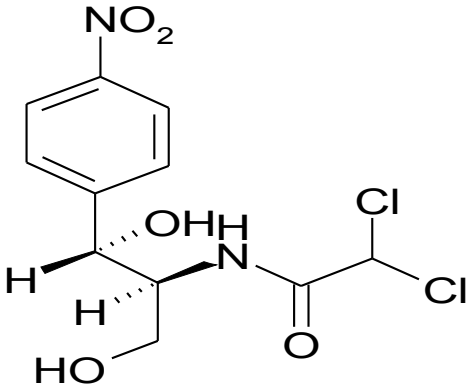
1R, 2R
D-(-)-threo
active
rel. activity 100

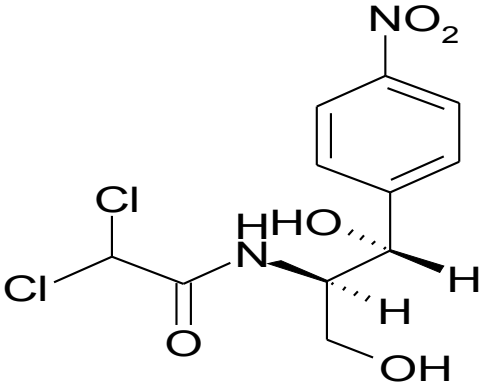



1S, 2S
L-(+)-threo
rel. activity < 0,4
also dextromycin

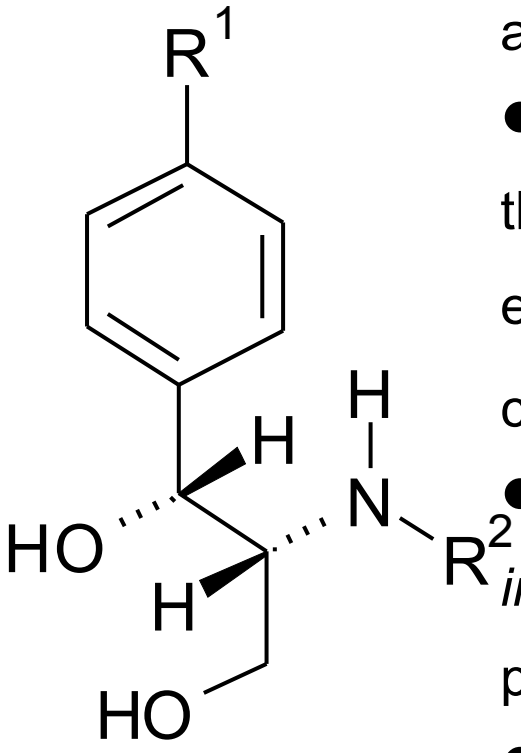
1R, 2S
D-(+)-erythro
rel. activity < 0,4



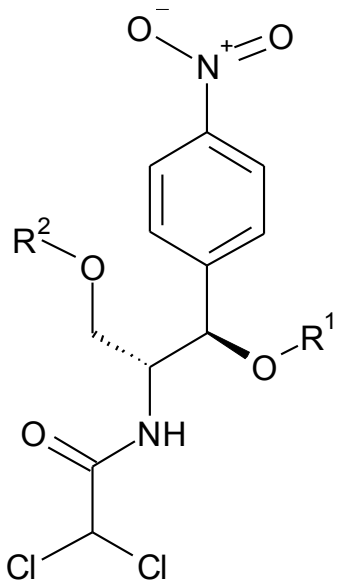

1S, 2R
L-(-)-erythro
rel. activity 1-2

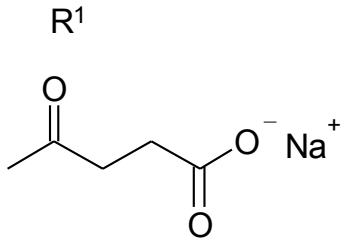
## Structure-activity relationships (SAR) in amphenicols




- 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

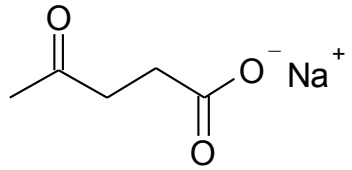
# Chloramphenicol prodrugs optimized for particular ways of administration



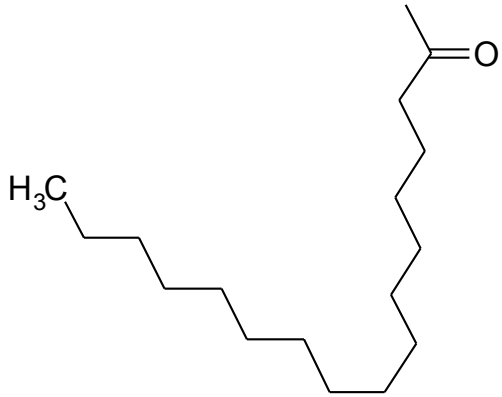

chloramphenicol sodium succinate
*Chloramphenicoli natrii succinas PhEur*
Chloramphenicol® ICN plv. inj. sol.

or



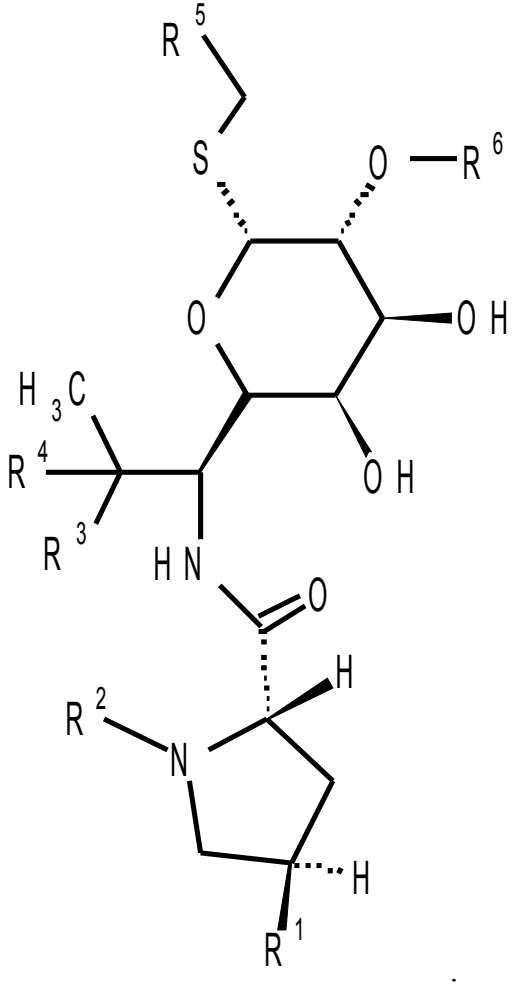

H

H




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

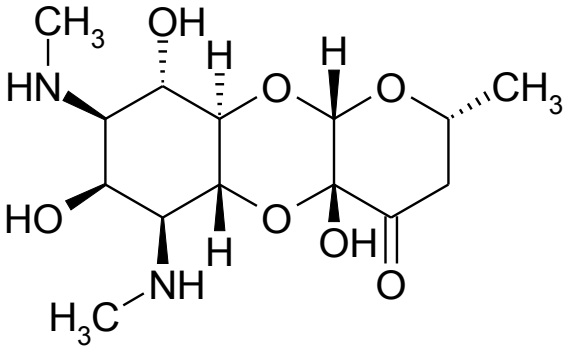
# Lincosamides




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

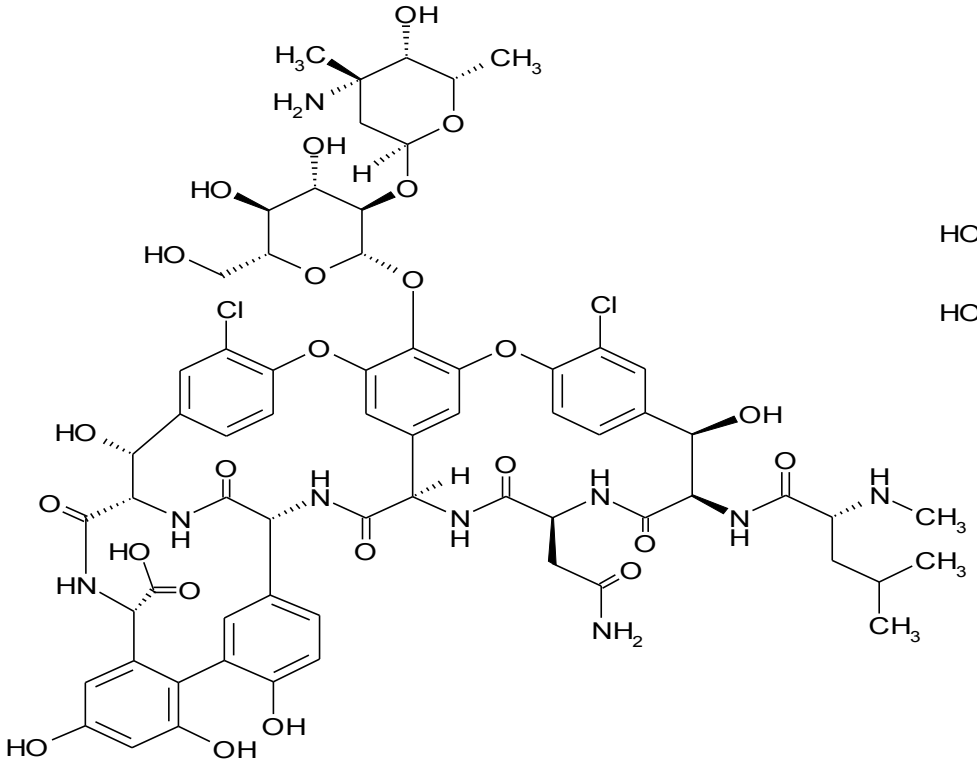
**spectinomycin**

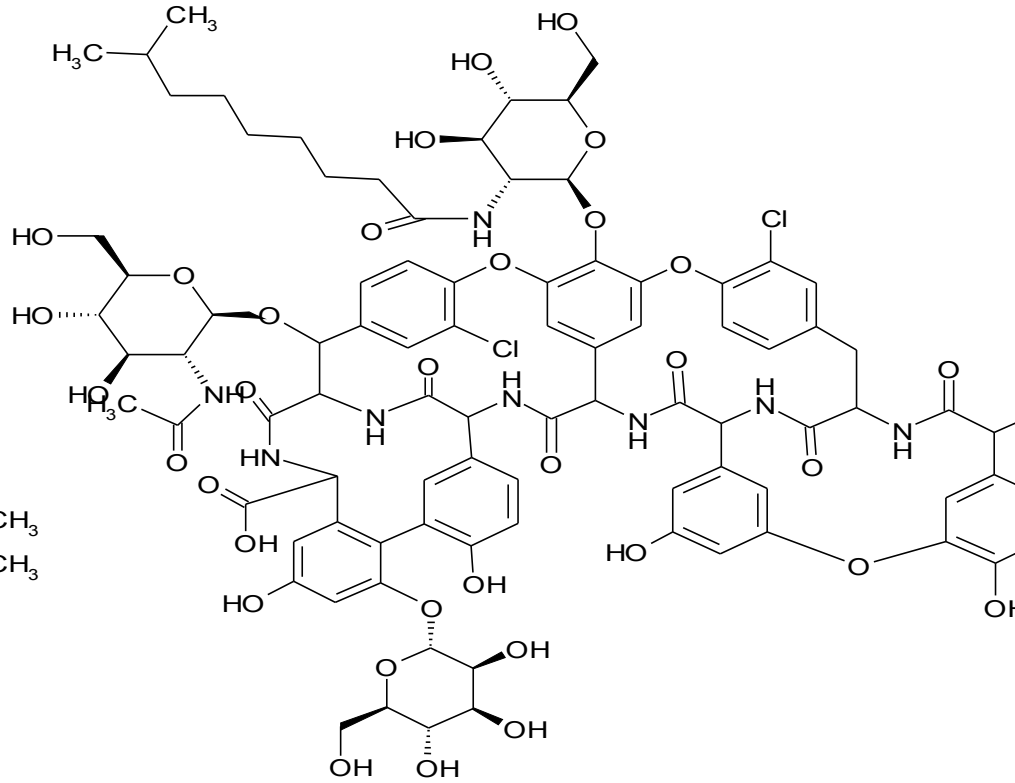
- an antibiotic produced by *Streptomyces spectabilis*
- mode of action: protheosynthesis inhibition; in particular movement between mRNA and a ribosome
- bactericidal
- spectrum: ***Neisseria gonorrhoeae****, Staphylococcus, Streptococcus, Enterococcus, E. coli, Haemophilus, Proteus, Bacteroides*

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.

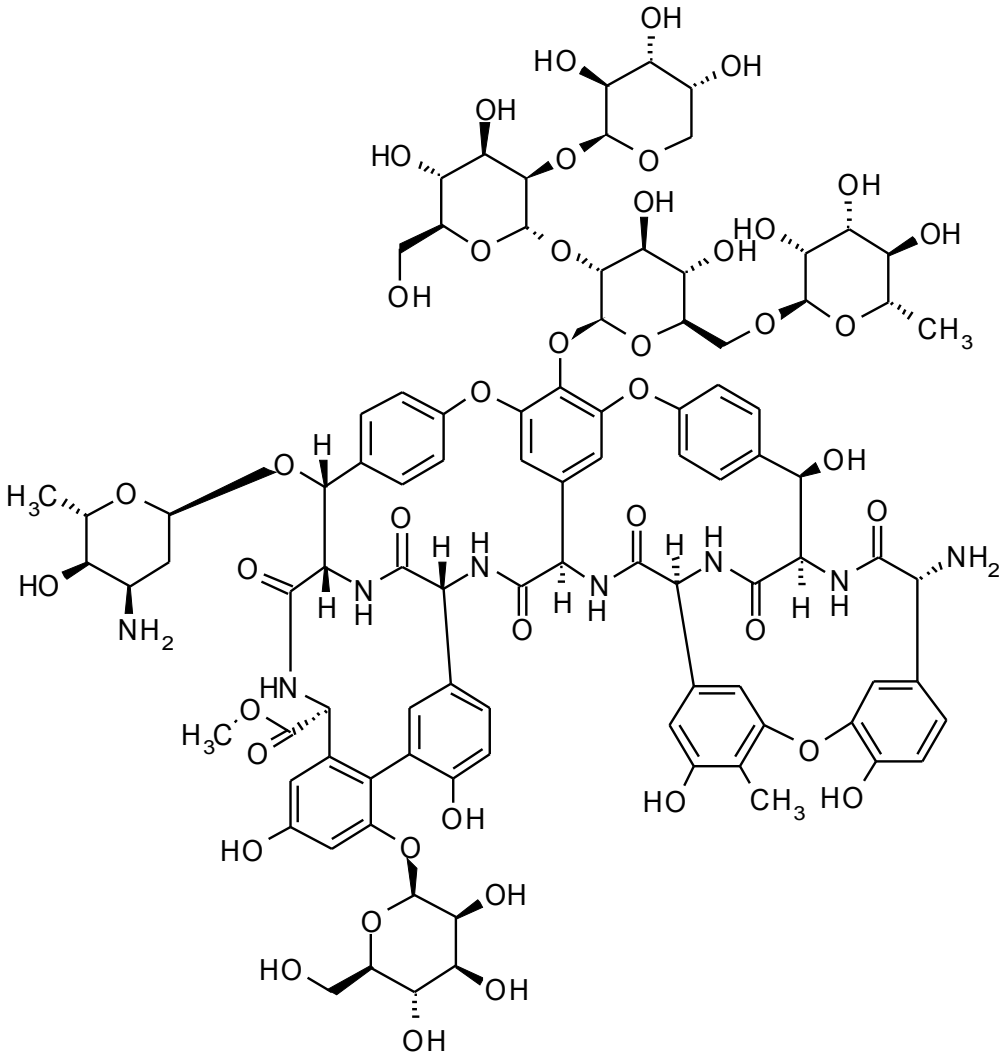
**teicoplanin**

- isolted from *Actinoplanes teichomyceticus*

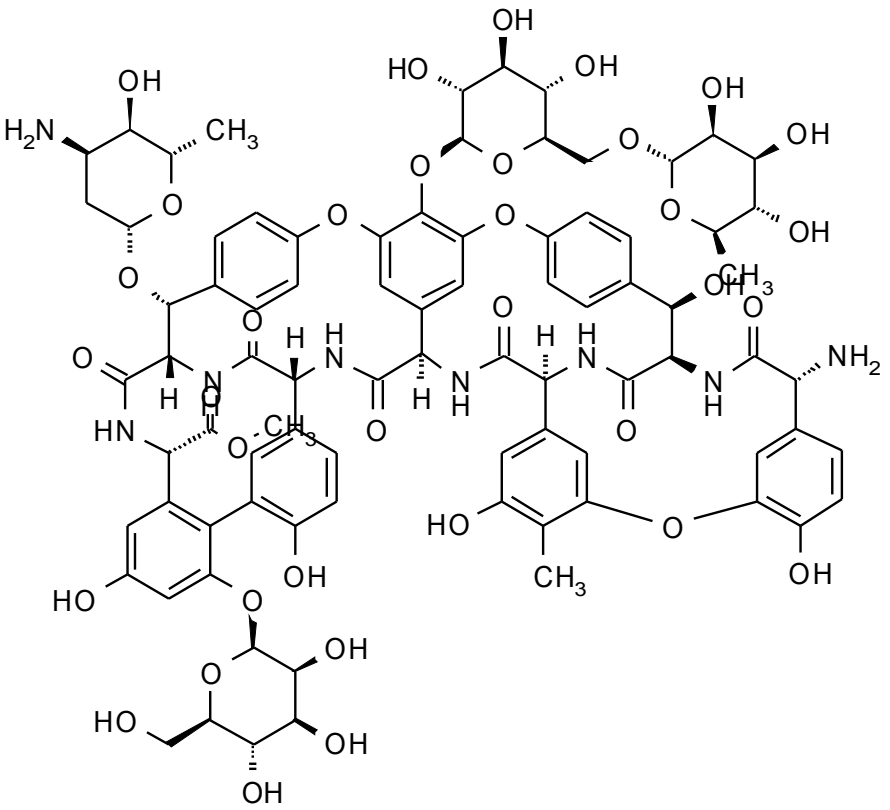
Targocid®inj. sic.

- 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

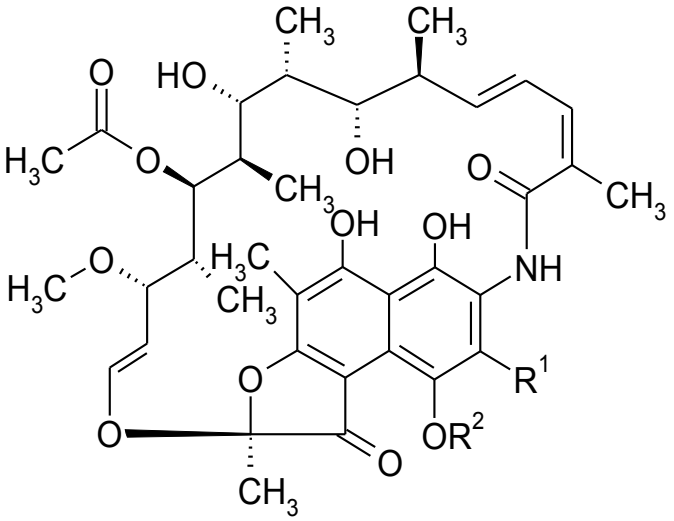
•contain an aromatic ring non-adjoining positions of which are linked with a macrocyclic lakctame ring

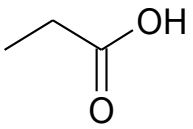
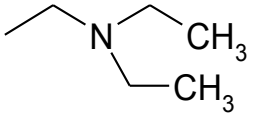
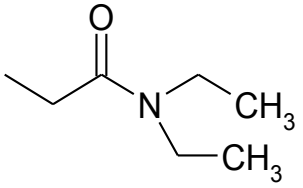
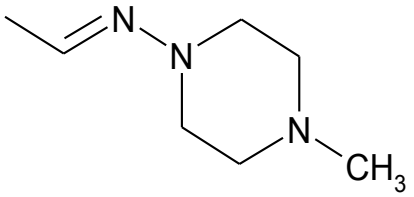
## Rifamycins

•based on naphthalene ring

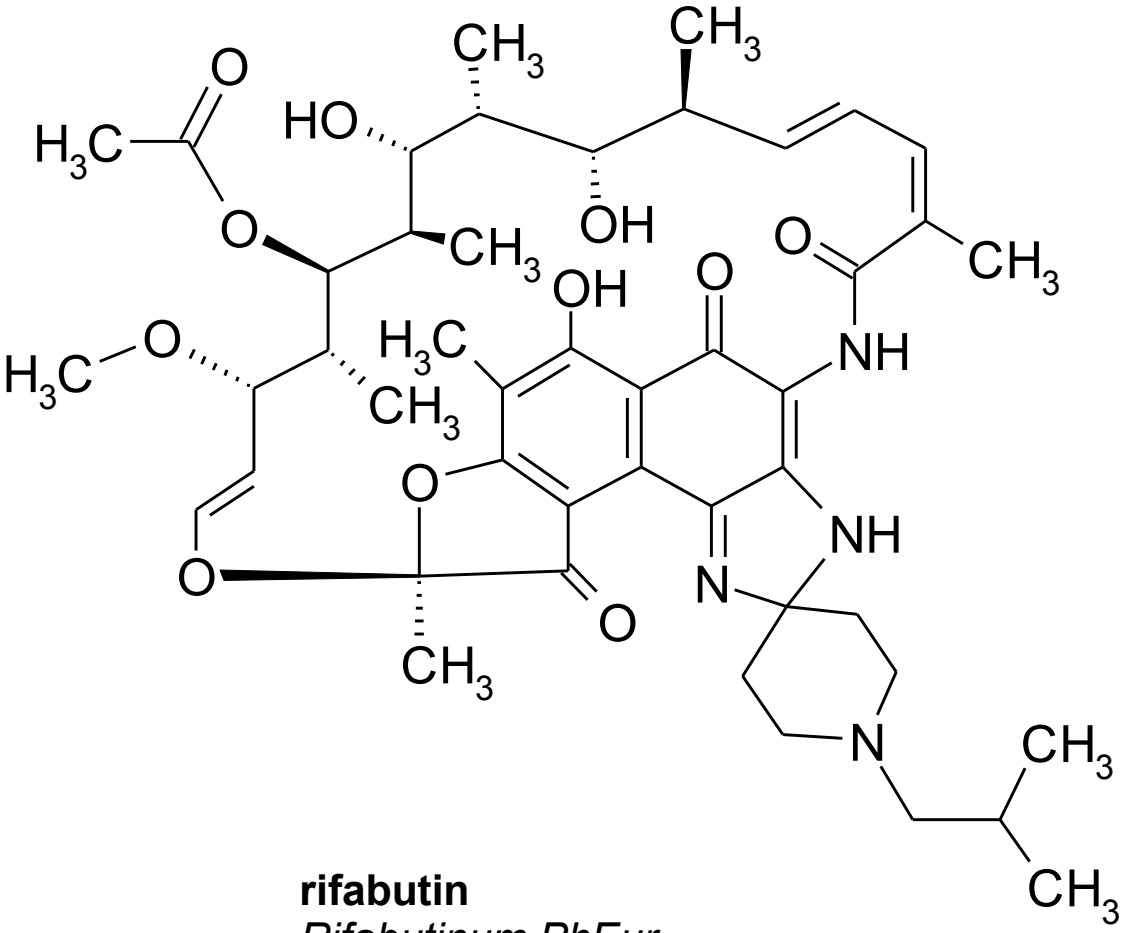
●mode of action: inhibition of RNA synthesis by blocking of DNA-dependent RNA-polymerase by forming a stable complex with the enzyme

●bacteriostatic, bactericidal in higher doses



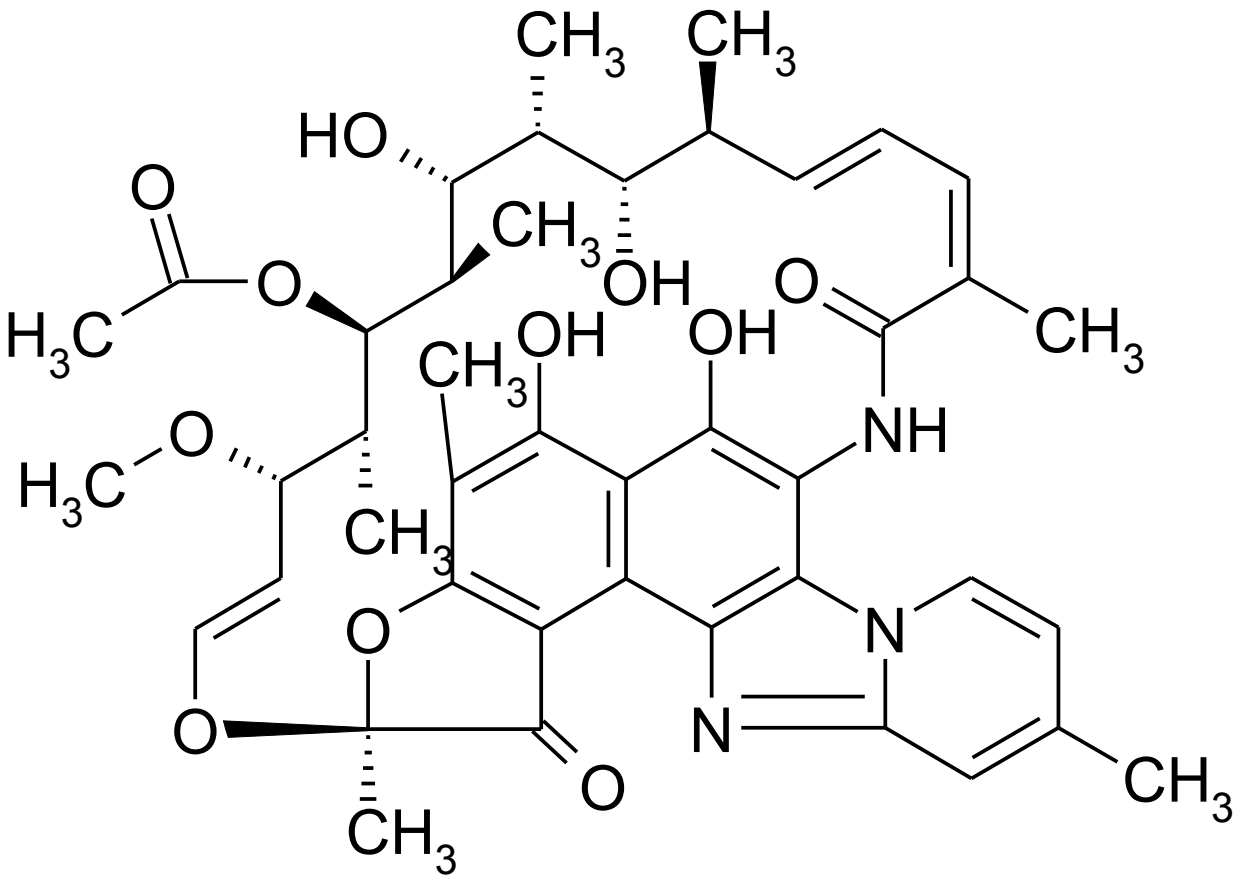
| $R^1$ | $R^2$ | |
|---|---|---|
| -H |  | **rifamycin B**<br>•natural antibiotic produced by *Amycolatopsis mediterranei* |
|  | -H | **rifamycin SV**<br>*Rifamycinum natricum PhEur* |
| -H |  | **rifamide** |
|  | -H | **rifampicin** (syn. rifampin [USAN])<br>*Rifampicinum PhEur*<br>●*Mycobacterium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

# Rifamycins



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

**Rifamycins**

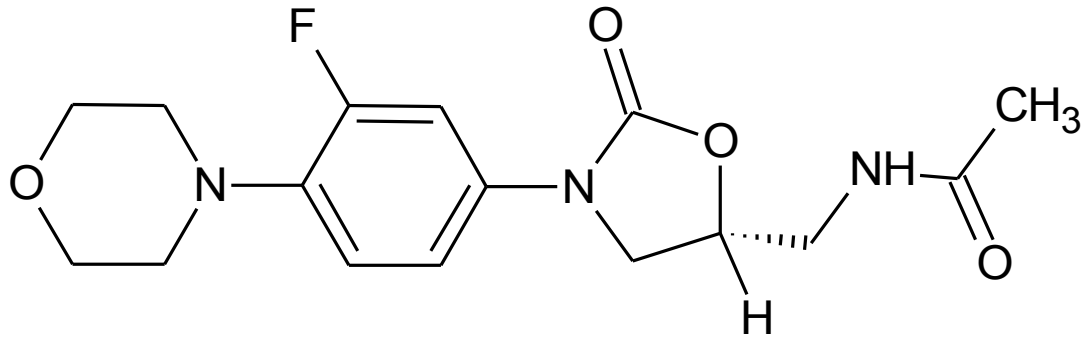


**rifaximin**

•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 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
Zyvoxid ® por tbl, inf sol