evropský sociální fond v ČR
EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Antituberculotics and antileprotics

TBC and lepra

- tuberulosis (consumption; TBC) – WHO report: 2.10^9 infected in 2009
- leprosy (Hansen disese, hanseniasis) – approx. $1.2 . 10^6$ infected in 2000, number of novel cases was 296 499 in 2005
- causing microorgansims: namely *Mycobacterium tuberculosis, M. leprae*
- also *M. bovis* and so called atypical strains (or facultatively pathogenic strains): *Mycobacterium avium, M. intracellulare, M. kansasii, M. paratuberculosis, M. scrofulaceum, M. simiae, M. habana, M. interjectum, M. xenopi, M. heckeshornense, M. szulgai, M. fortuitum, M. immunogenum, M. chelonae, M. marinum, M. genavense, M. haemophilum, M. celatum, M. conspicuum, M. malmoense, M. ulcerans, M. smegmatis, M. wolinskyi, M. goodii, M. thermoresistible, M. neoaurum, M. vaccae, M.palustre, M. elephantis, M. bohemicum* and *M. septicum*.

•slowly growing bacteria with a special cell wall structure; most of common antibacterial chemotherapeutics are ineffective

•the cell wall contains proteins, phenolic glycolipids, arabinoglycan, pepdidoglycan and mycolic acids (branched α-hydroxylated long-chain fatty acids; some containing cyclopropane fragment)

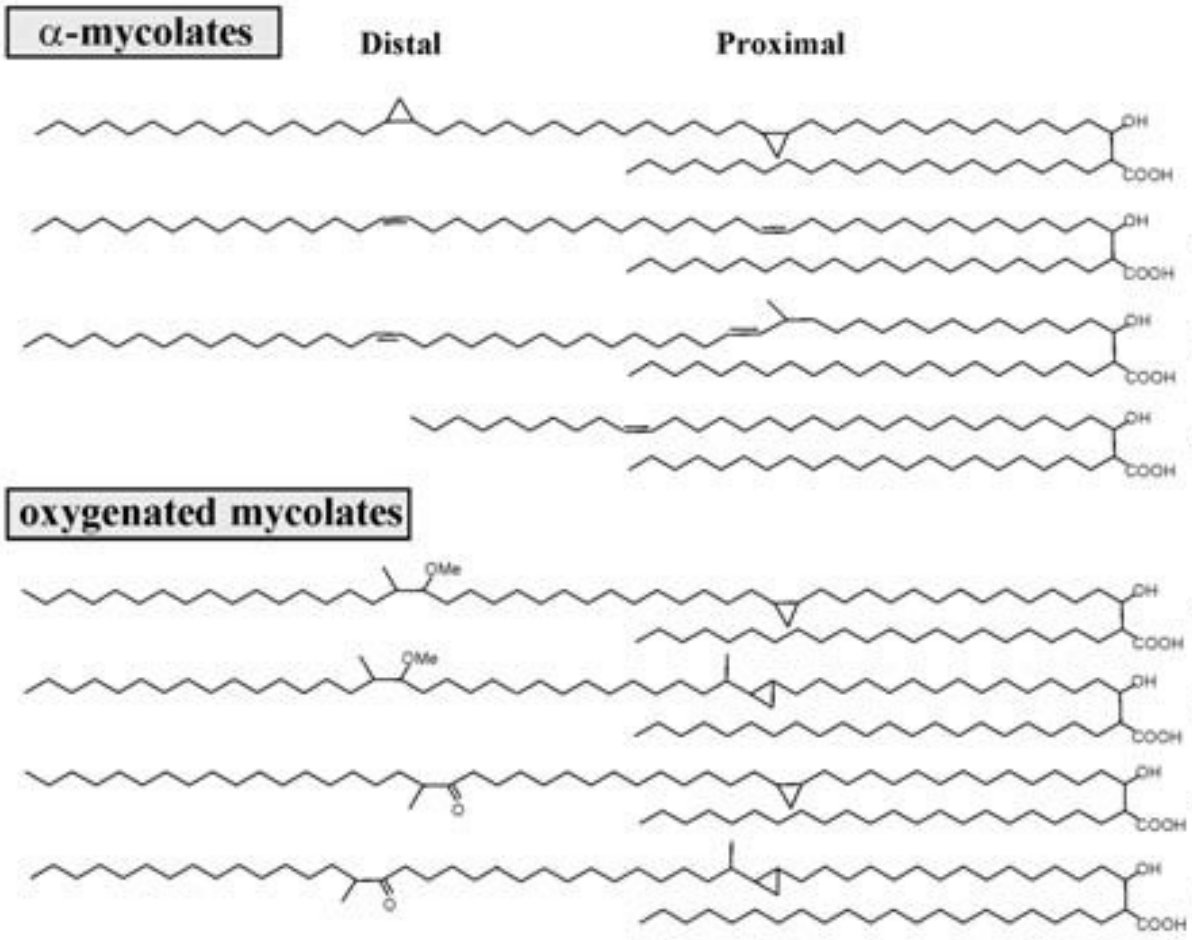
•cultivation of *M. tuberculosis in vitro* is difficult, cultivation of *M. leprae in vitro* is impossible

•*M. tuberculosis* discovered Robert Koch in 1882, *M. leprae* G. H. A. Hansen in 1874

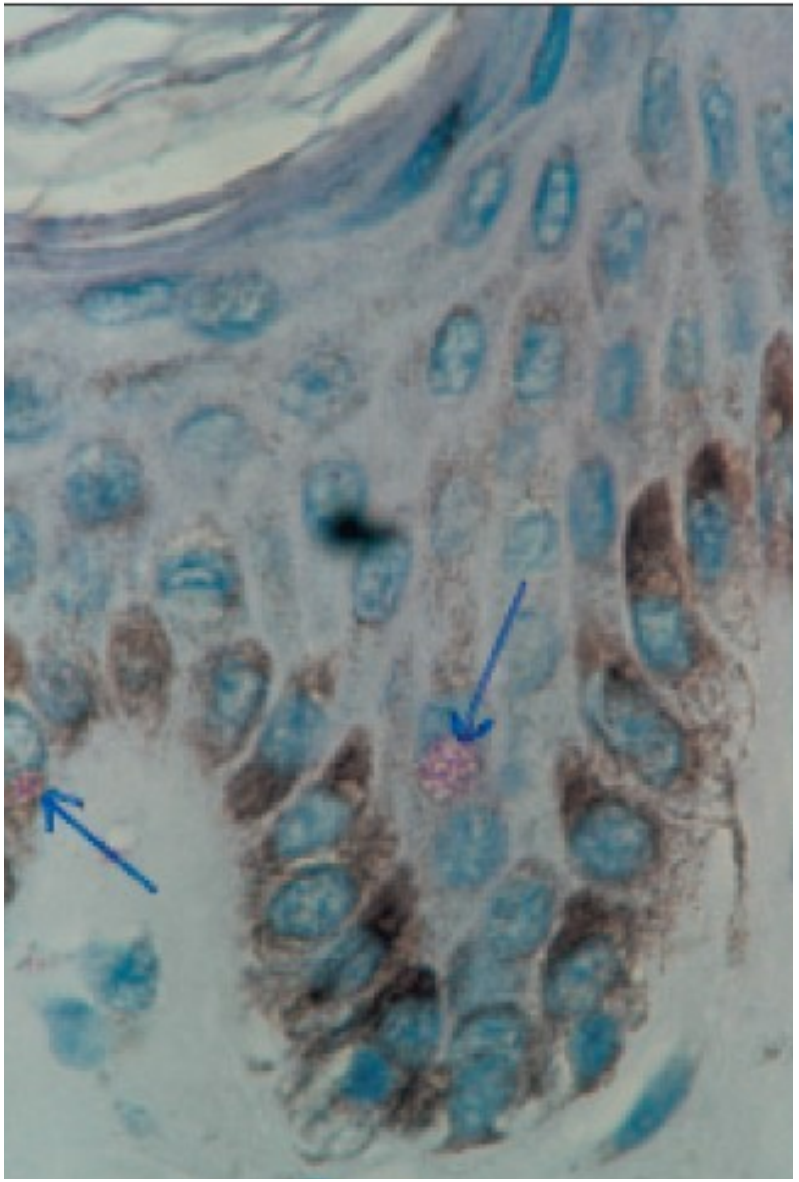
•leprosy is quite endemic, most of infected live in 11 countries, India is leading.

•“classical therapy” before discovery of effective chemotherapeutics: TBC – mountain environment, pneumothorax, Ca^{2+} compounds (calcification); leprosy – isolation of patients only - leprosaria

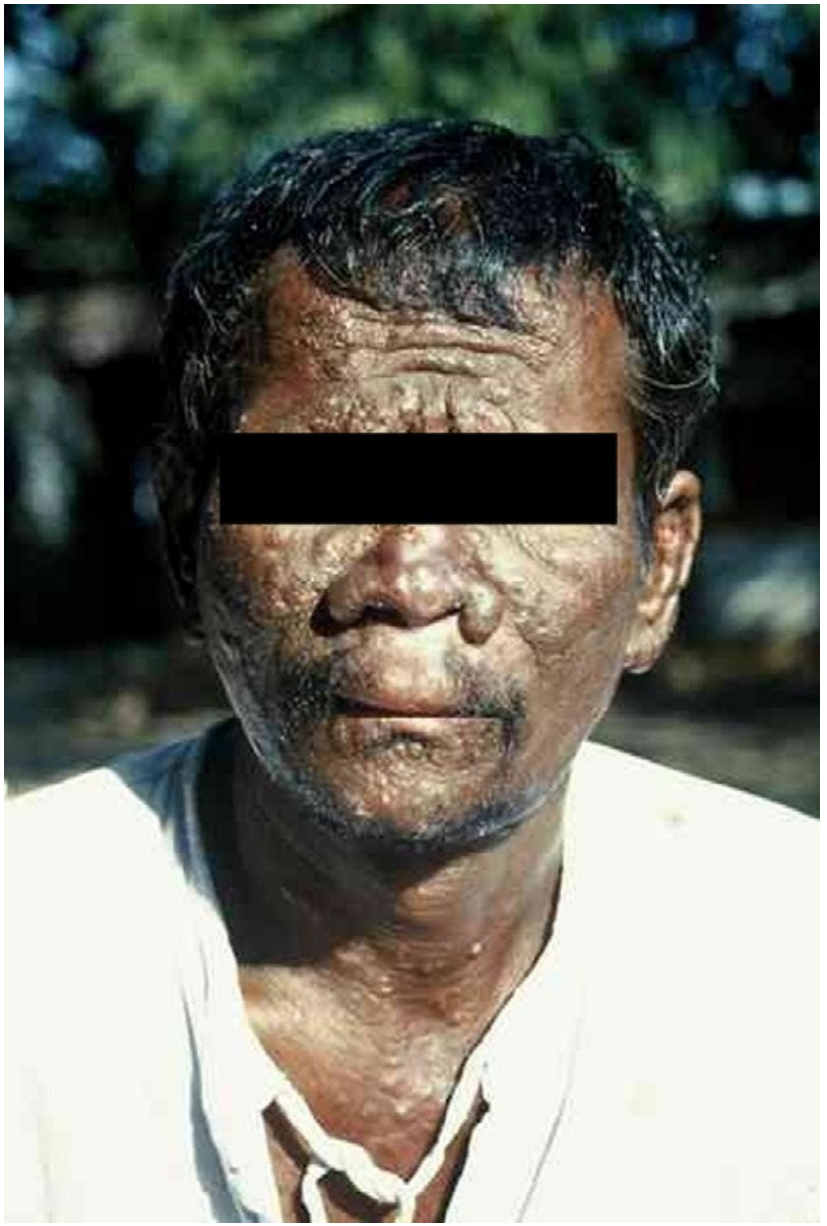
Structures of mycolic acids and their appearance in some species of *Mycobacterium* genus



	M. bovis BCG	*M. tb or M. marinum**	*M. chelonae*
α	+	+	+
α1	-	-	+
α2	-	-	+
α'	-	-	+
c-methoxy	-	+	-
t-methoxy	-	+	-
c-keto	+	+	-
t-keto	+	+	-

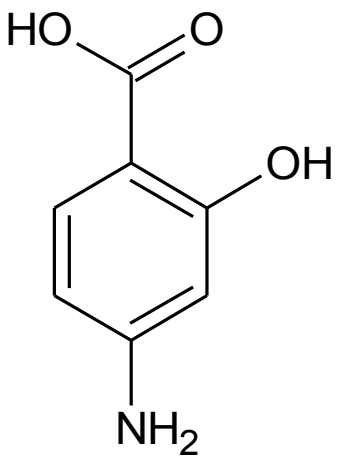


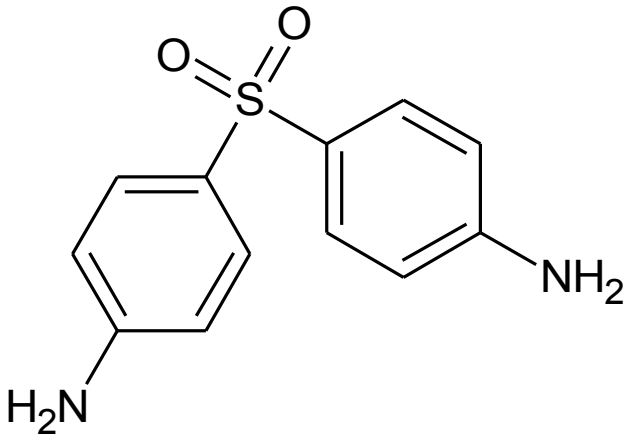
leprosy: aggregates of *M. leprae* in
in a basal cell and in a granulocyte



„Lion face“

1st used specific chemoterapeutics





4-amino-2-hydroxybenzoic acid

p-aminosalicylic acid

PAS

TBC

4,4'-sulfonyldianiline
1,1´-bis(4-aminophenyl)sulfone
1,1´-sulfonylbis(4-aminobenzene)
4,4´-diaminodiphenyl sulfone
dapson

leprosy

Classification of chemotherapeutics of mycobacterial infections

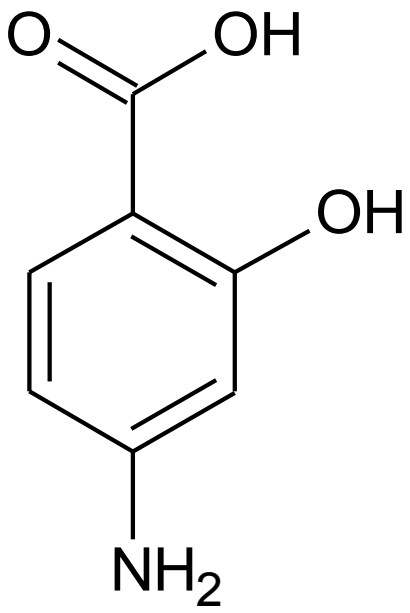
„Specific“ chemoterapeutics

PAS
Compouns derived from sulfonamides
Amides, hydrazide s and thioamides of heteroarenecarboxylic acids
1,2-diaminoethane derivatives
Thiacetazone
Tiocarlide
Phenazine derivatives
(Phenothiazines)
Peptide antibiotics

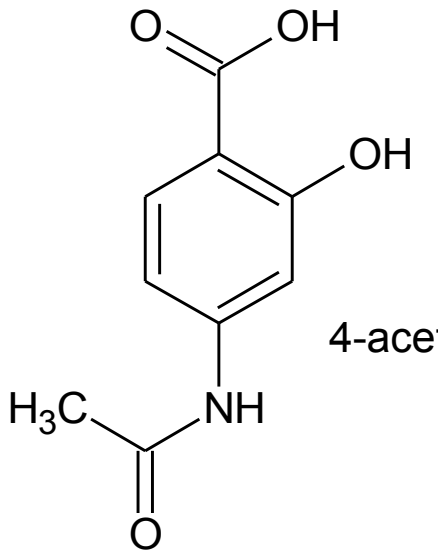
Broad spectrum chemoterapeutics

Rifamycins
Aminoglycosides
Cycloserin
Fluorinated quinolons
Tetracyclins
Macrolides
Oxazolidine-2-on derivatives

„Specific“ chemoterapeutics
PAS



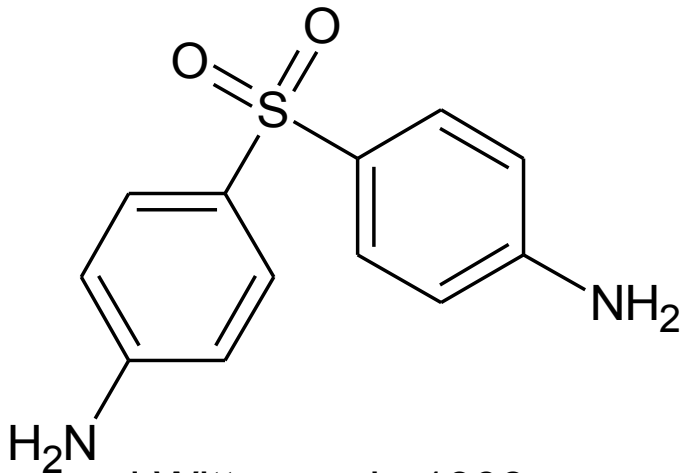
- 1946: inhibits growth of mycobacteria even in dilution 1 : 10^5 *in vitro*
- low toxicity enabled high doses 10 – 15 g/day
- stability: easily decarboxylates to 2-aminophenol in acid media
- metabolism: N-acetylation preferred
- bacteriostatic effect
- mode of action: dihydropteroate synthase inhibition (like sulfonamides)



4-acetamido-2-hydroxybenzooic acid, main PAS metabolit

Compounds derived from sulfonamides structure

Dapson



•prepared by Fromm and Wittmann in 1908

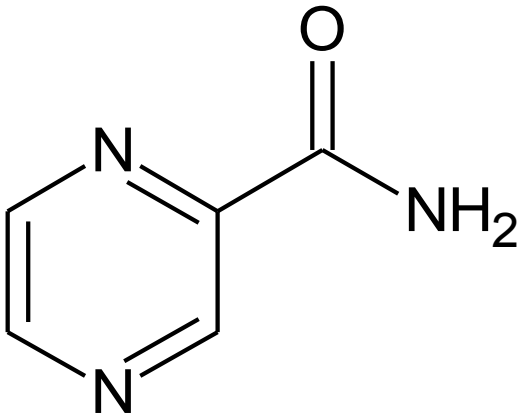
• antibacterial effects including antimycobacterial ones were discovered approx. in 1937, but originally was dapson supposed to be too toxic, after changed in dosing, it has been frequently used since 1940th .

•mode of action: inhibition of folic acid synthesis, inhibition of dihydropteroate synthase (like sulfonamides) in particular

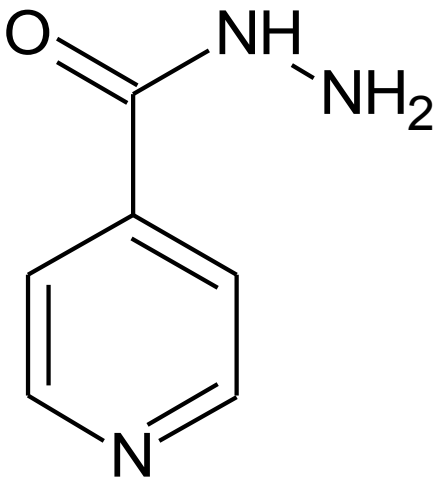
•also drug for malaria (in combinations) and skin infections including *acne vulgaris* and diseases linked with the excessive accumulation of neutrophils and eosinophils, also *lupus erythematodes, psoriasis* and ulcers after intoxication by a spider of *Loxosceles* genus

•adverse effects: methaemoglobinema, hemolysis, anaemia, agranulocytosis, nausea, vomitting, peripherial neuropathy, psychosis, rarely reversible eye disorders, photosensitivity

Amides, hydrazides and thioamides of heteroarencarboxylic acids



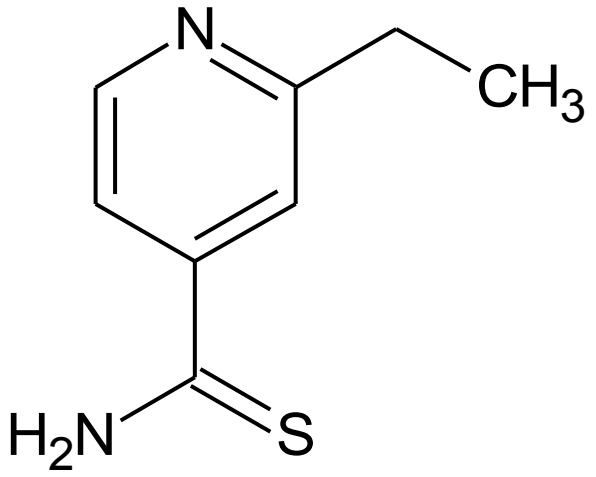
pyrazinamide
pyrazine-2-carboxamide
•strong synergy with isoniazid and rifampicin
•enabled shorten the treatment from initial 12 months or more to 6 months
•effect is dependent on the presence of bacterial amidase; pyrazinic acid (pyrazin-2-carboxylic acid) is its active form.
•*Meningitis tuberculosa*
Pyrazinamid Krka ® tbl.



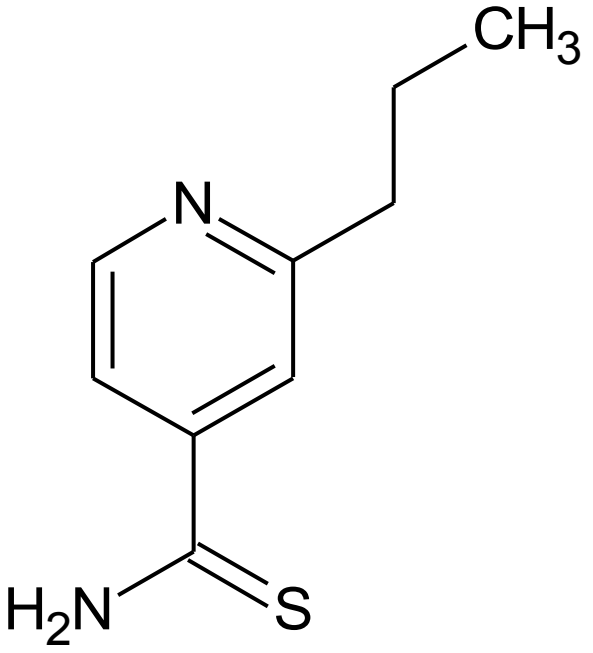
isoniazid
pyridine-4-carbohydrazide

•known since 1912, effect recognized in 1951
•effective *in vitro* even in dilution 1 : 10^7 (or MIC 0.02 – 0.06 μg/ml)
•mechanism of action: blocks mycolic acids synthesis by inhibition of mycolate synthetase and thus blocks cell wall building
Nidrazid ® tbl.

Amides, hydrazides and thioamides of heteroarencarboxylic acids
2-alkylpyridine-4-karbothioamides



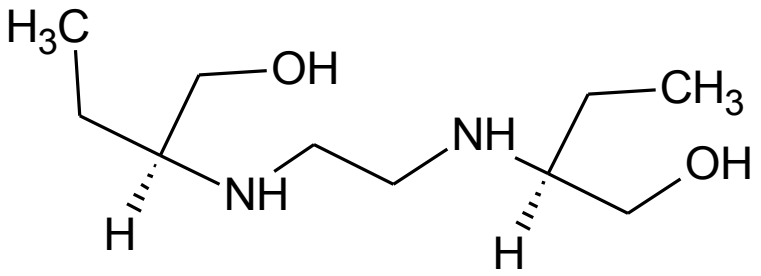
ethionamide



prothionamide

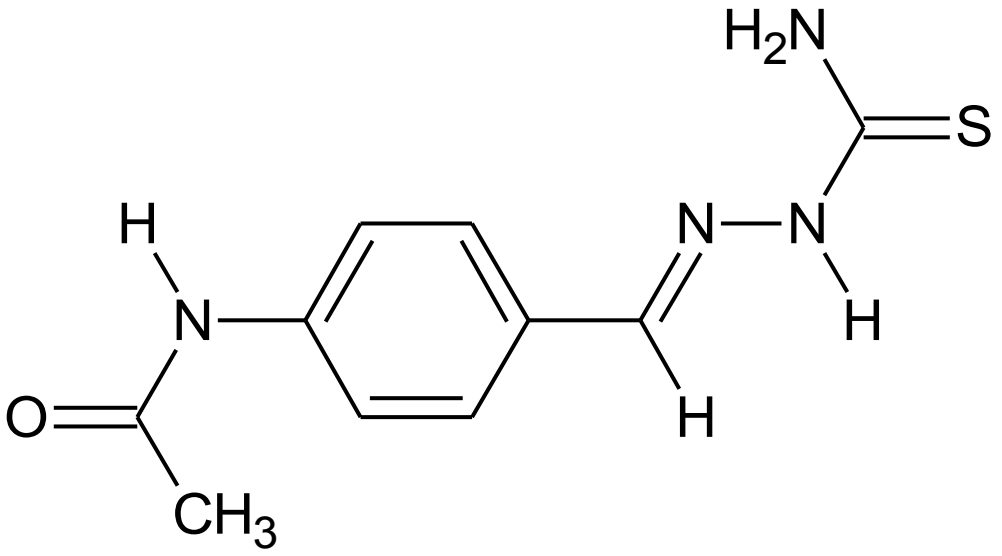
•mechanism of action: block synthesis of mycolic acids by inhibition of mycolate synthetase and thus block cell wall building

1,2-diaminoethane derivatives



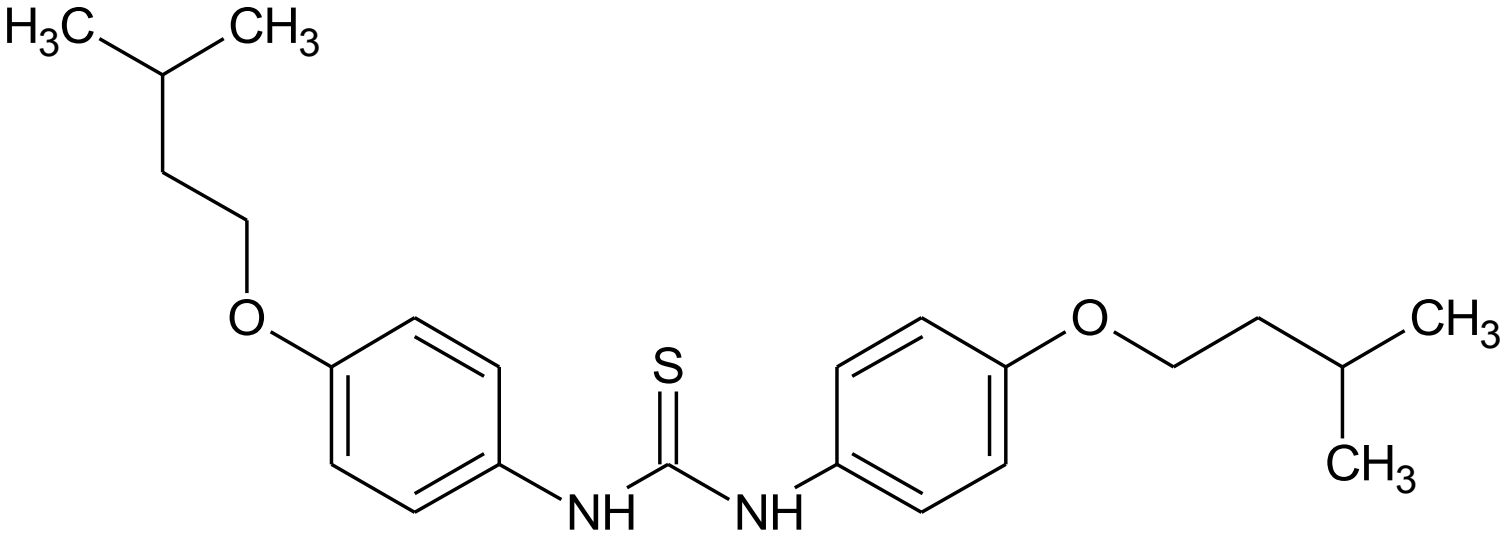
(S,S´)-N,N´-bis(1-hydroxybutane-2-yl)ethylenediamine
(+)-ethambutol
•(R,R)- a (R,S)- isomers are not effective
•used as dihydrochloride
•bacteriostatic
•mechanism of action: inhibits arabinosyl transferase which takes part in cell wall biosynthesis
•used since 1966
•administered always in combinations (e.g. with isoniazide or rifampicin) due to a risk of development of resistant mutants
•interaction with antacids based on $Al(OH)_3$
•toxicity: damage of visual nerve
•preparation from (S)-(+)-2-aminobutanol which is acquired by dividing of its racemate by crystallisation with tartaric acid
Sural ® tbl.

Thioacetazone



4-(acetamido)benzaldehyde thiosemicarbazone
•syn. thiacetazone
•bacteriostatic effect
•activated by mycobacterial monooxygenase EthA
•mechanism of action: inhibition of mycolic acids synthesis; probably by blocking of cyclopropanation of mycolic acids by inhibition of cyclopropane mycolic acid synthases (CMASs).
•combined with isoniasid
•cheap; used in Africa and Southern America

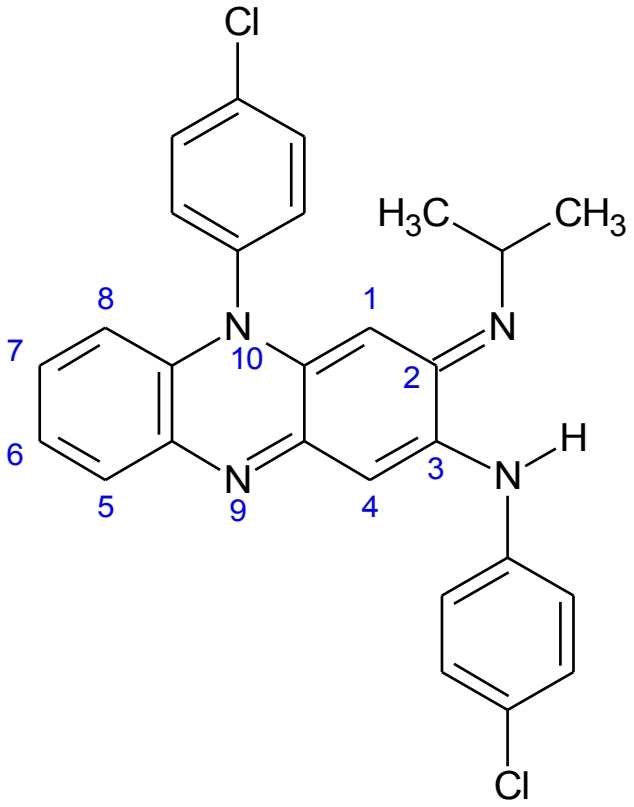
Tiocarlide



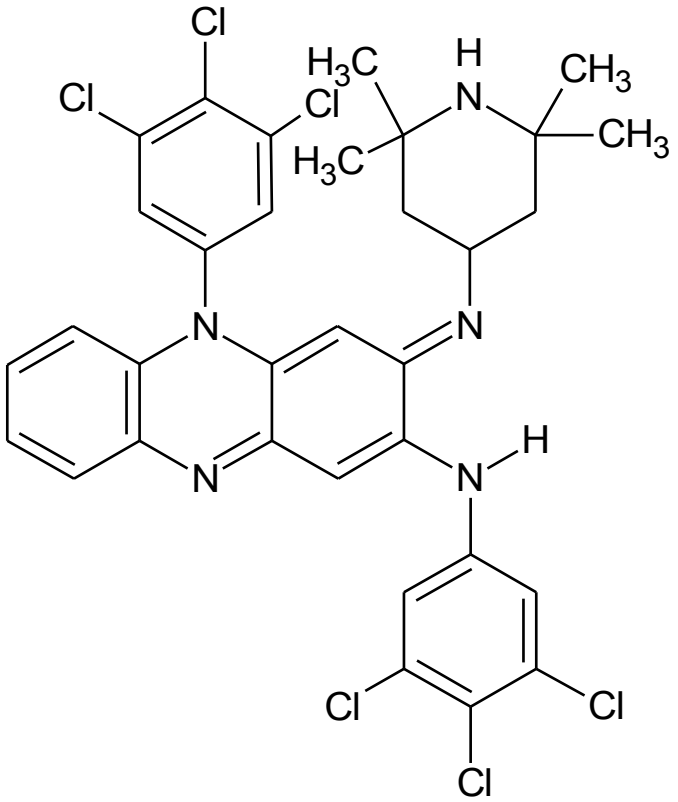
1,3-bis[4-(3-methylbutyloxy)phenyl]thiourea
4,4´-bis(isopentyloxy)thiokarbanilide

- syn. isoxyl
- mechanism of action: inhibition of membrane-bound $\Delta 9$ desaturase DesA3
  $\Rightarrow$ inhibition of syntheses of oleic acid and mycolic acids
- used in 1960th , then abandoned, after 2000, its efficacy against multiresistant strains was demonstrated and its mechanism of action was determined and it has started to be used again

Phenazine derivatives

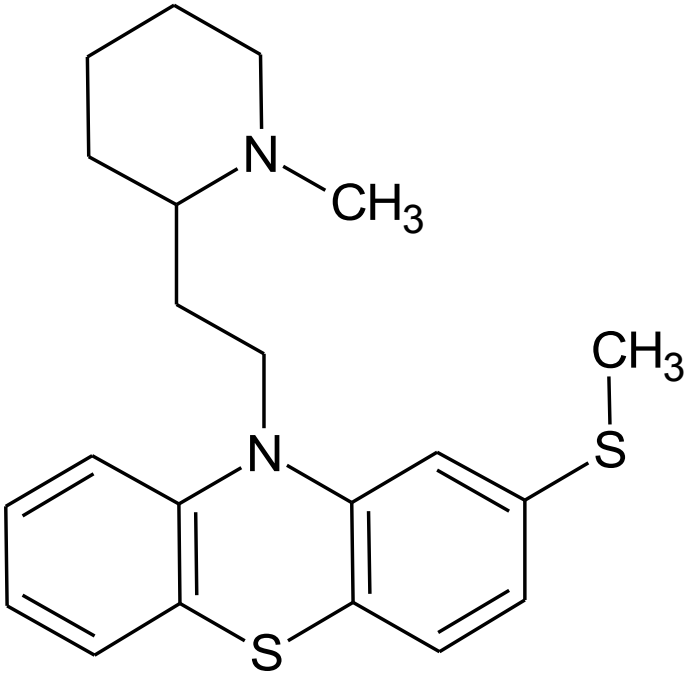


clofazimine
•dye
•leprosy
•also anti-inflammatory effect
•treatment of *erythema nodosum leprosum*
Lamprene ® por cps dur



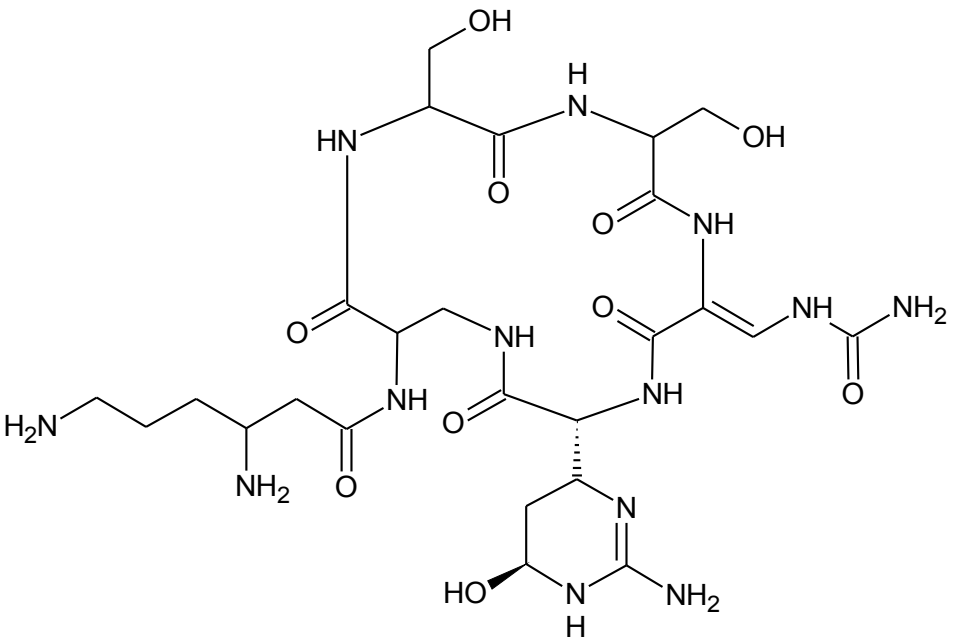
BM 4169
•greater activity against *M. tuberculosis* including multiresistant strains

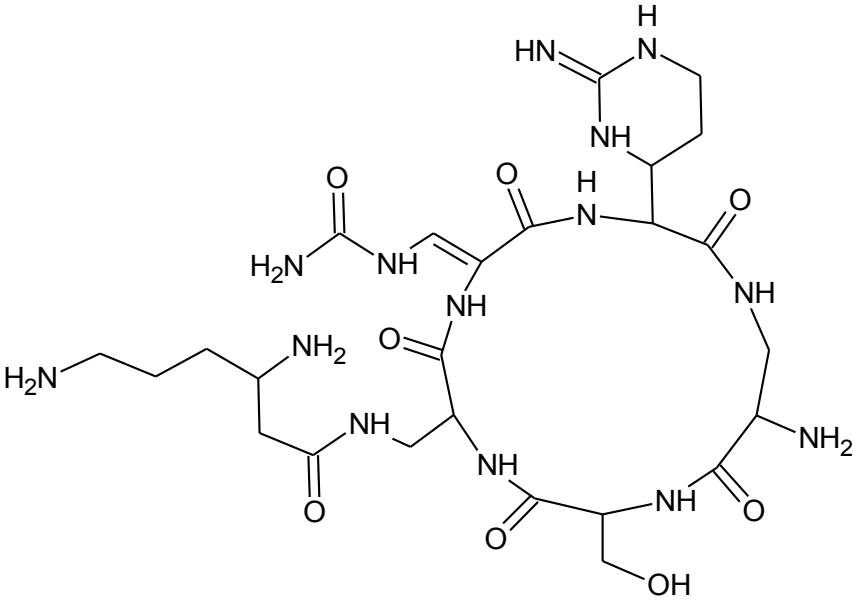
Phenothiazine derivatives



10-[2-(N-methyl-2-piperidyl)ethyl]-2-methylsulfanylphenothiazine
thioridazine
(normally used as an antipsychotic)
Supposed mechanisms of antituber. action:
1. calmoduline antagonist; genes of calmoduline type were found in *M. tuberculosis,* penothiazines are in general known by their calmoduline antagonist activity
2.phenothiazines inhibit succinate dehydrogenase and NADH-quinone oxidoreductase type II, cause depletion of ATP levels and change ratios NADH/NAD and menaquinol/menaquinone, which indicates an interference with oxidative phosphorylation
•expected usage in multiresistant strains

Peptide antibiotics





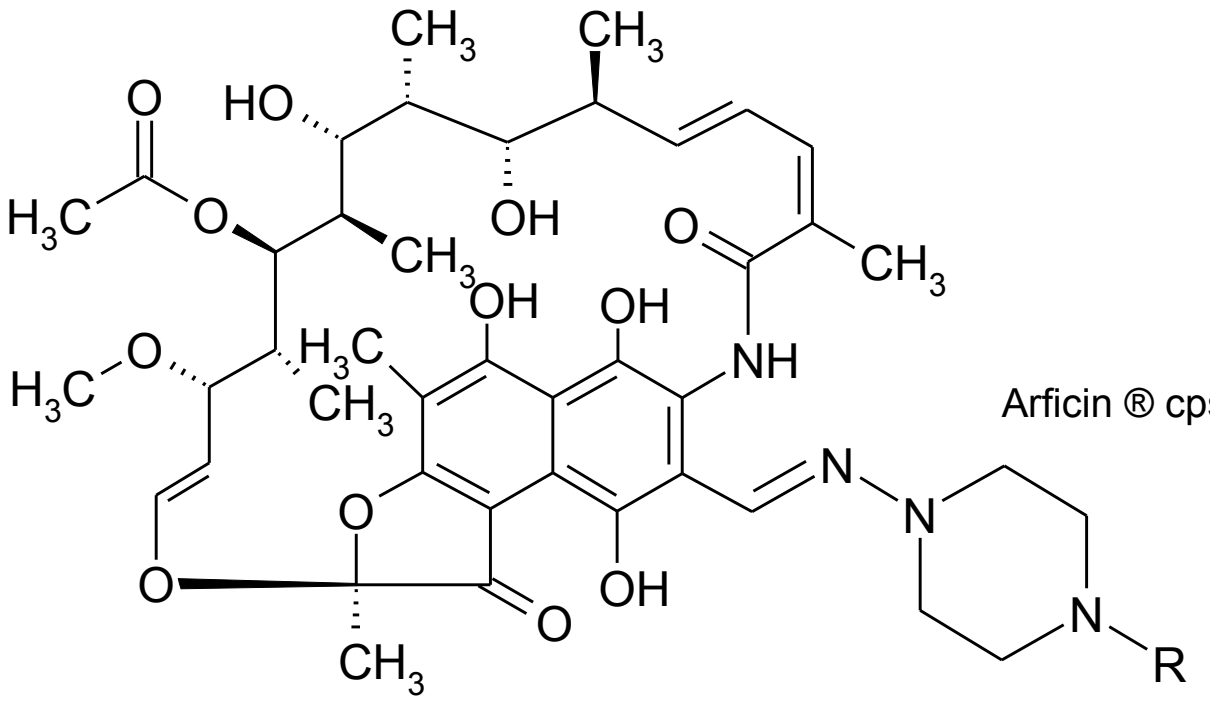
viomycin
•product of *Streptomyces puniceus*

capreomycin
•product of *Steptomyces capreolus*

•strongly basic peptides
•mechanismm of action: bound to RNA, they inhibit protheosynthesis and some types of splicing of RNA
•nephrotoxicity, neurotoxicity, ototoxicity, alergenicity

Broad spectrum antibacterial chemoterapeutics used for treatment of mycobakterioses

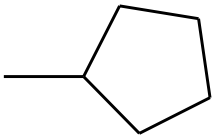
Rifamycins



R

-CH_3 **rifampicin**

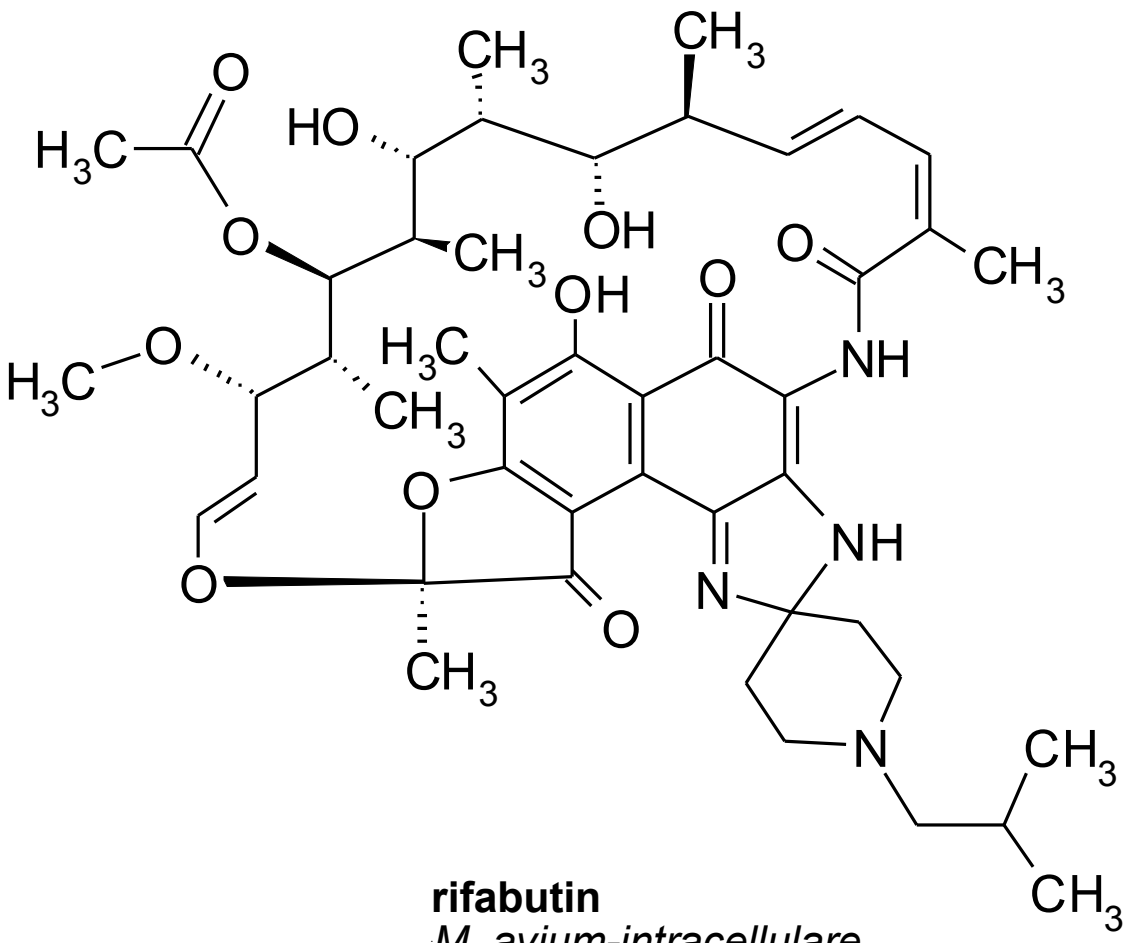
Arficin ® cps., Benemycin ® cps., Eremfat i.v. ® inj. plv. sol.



rifapentine

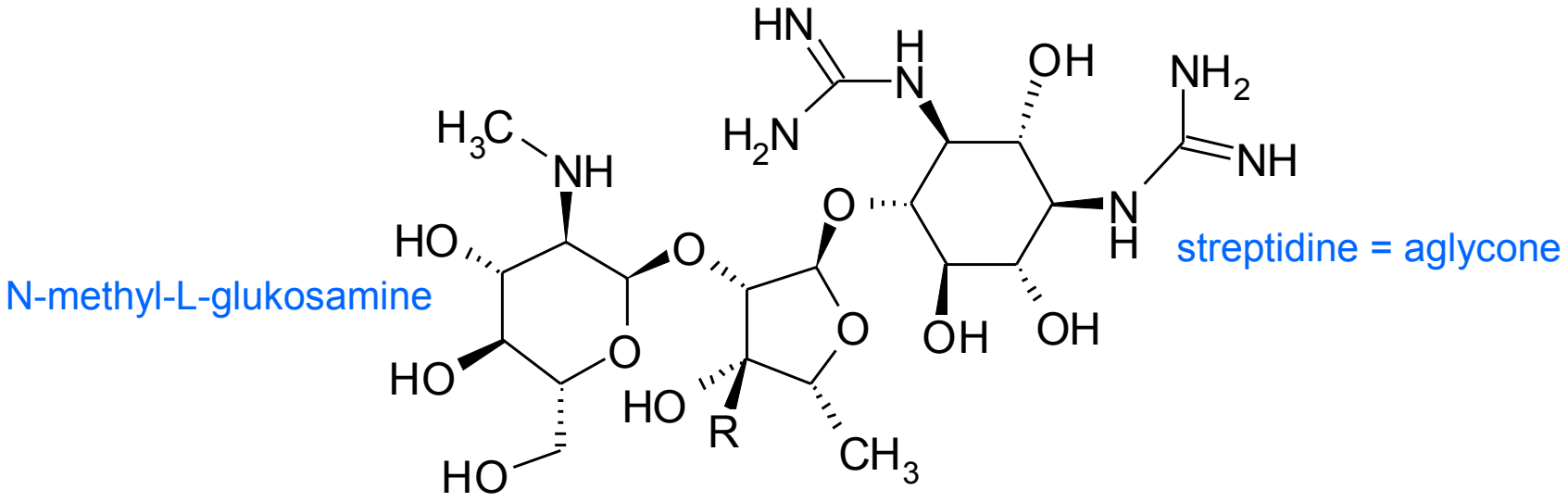
•mechanism of action: inhibition of DNA-dependent RNA polymerase

Rifamyciny



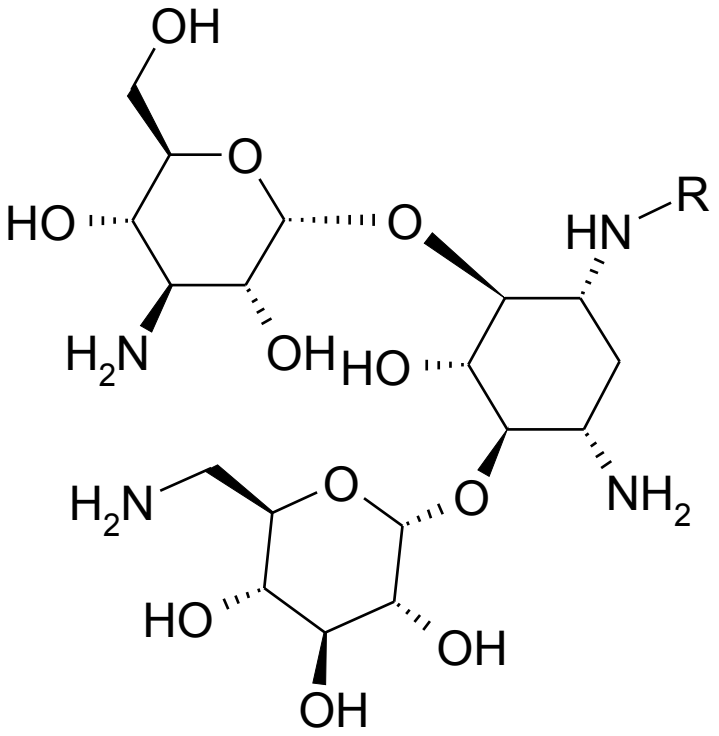
rifabutin
M. avium-intracellulare
Mycobutin cps.

Aminoglycosides of the 1st line

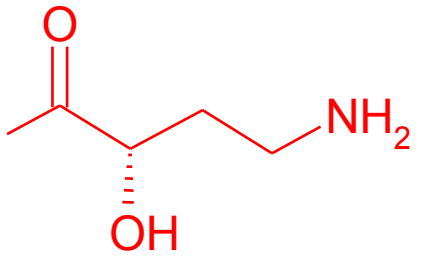


- 1st really active antituberculotic
- R = -CHO **streptomycin**
- used against *M. tuberculosis* in combination with other tuberculostatics
- isolated from *Streptomyces fradiae* in 1944
- bactericidal
- toxicity in both central and peripheral nervous system
- Streptomycin „Grünenthal“® inj. sic., Streptowerfft® a.u.v
- R = -CH_2OH **dihydrostreptomycin**
- formerly believed to be less toxic, however, damages 8th cranial nerve
- Depomycine® a.u.v. inj. (+ benzylpenicillin)
- mechanism of action: protheosynthesis inhibition

Aminoglycosides of 2nd line

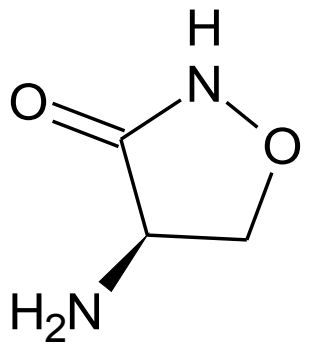


R = -H **kanamycin**

R =  **amikacin**

- mechanism of action: bound to the 30S subunit of a ribosome, they cause wrong reading of mRNA and thus block protheosynthesis
- serious multiresistantn infections
- damage kidneys and sense of hearing

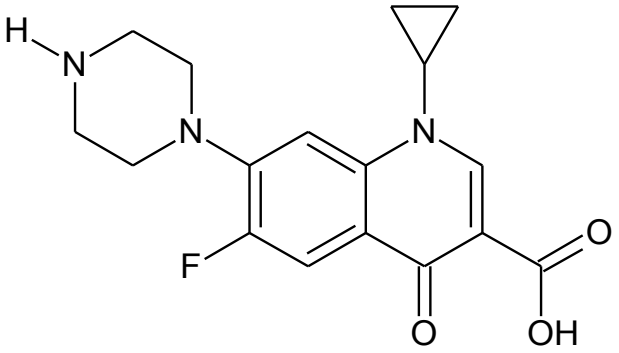
Cycloserine



(4*R*)-4-amino-1,2-oxazolidin-3-one
D-cycloserine

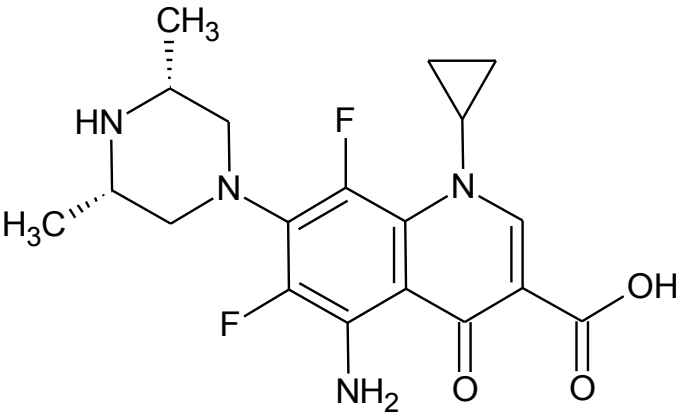
•antibiotic originally produced by *Streptomyces garyphalus*.
•mode of action: blocks cell wall building by inhibition of early stage peptidoglycane biosynthesis
•adverse effects: CNS: headaches, irritation, depression, convulsions

Fluorinated quinolones

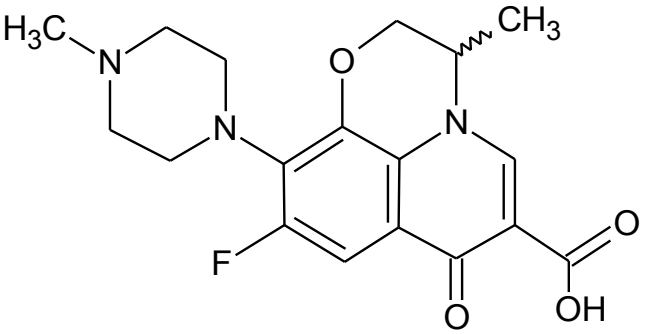


ciprofloxacin

Ciphin (r)



sparfloxacin

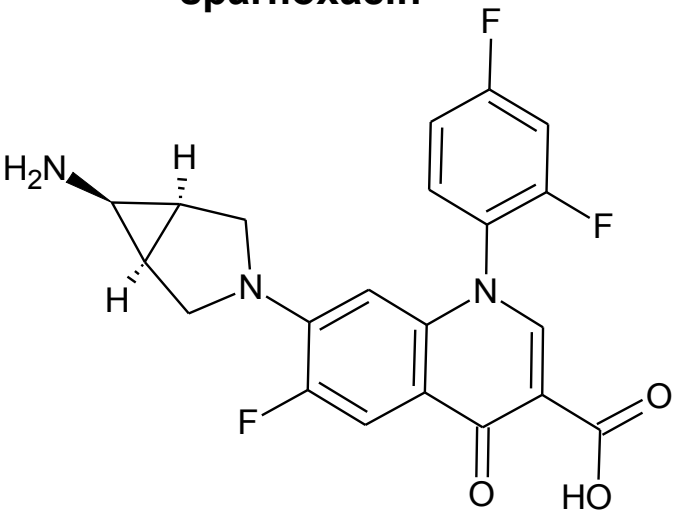


R/S: ofloxacin

Floxal (r)

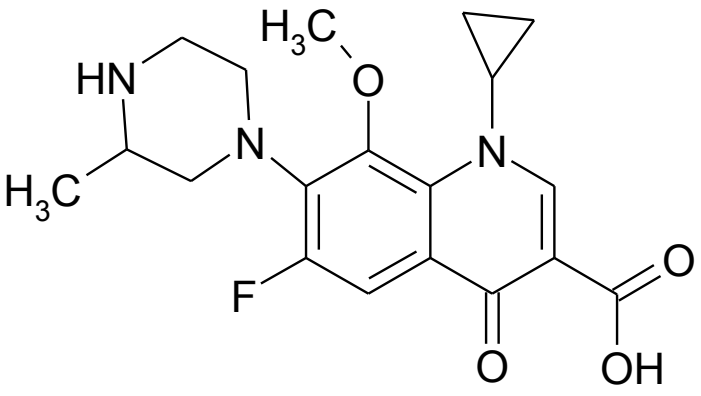
S: levofloxacin

Tavanic i.v.(r) inf sol

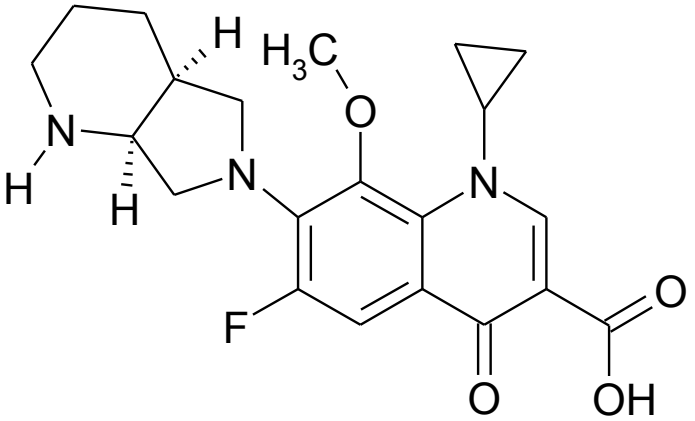


trovafloxacin

Fluorinated quinolones - continued

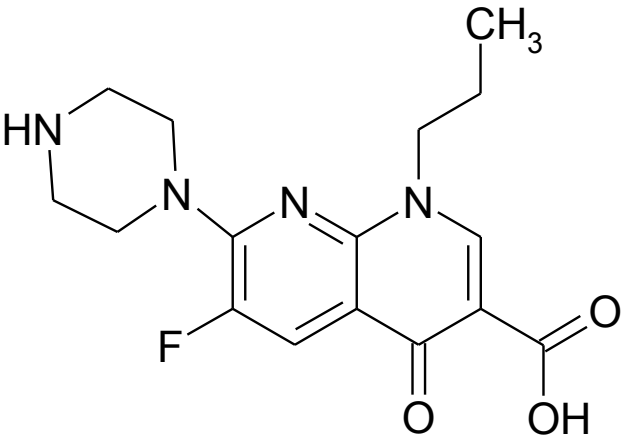


gatifloxacin



moxifloxacin

Avelox ® por tbl flm, inf sol

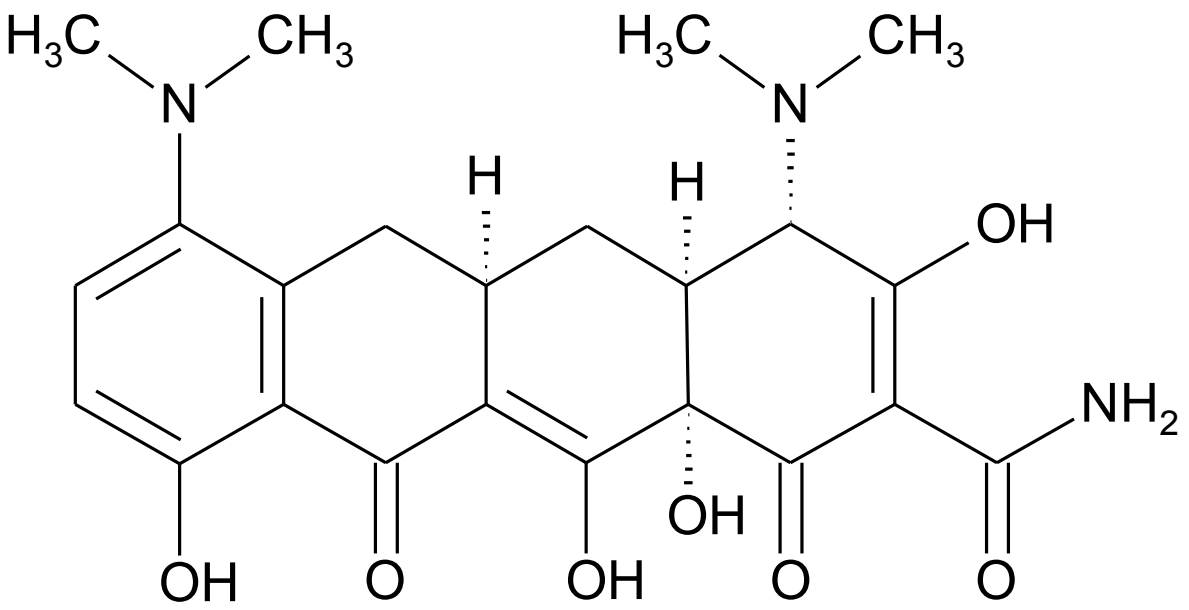


enofloxacin

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-**1,8-naphthyridine**-3-carboxylic acid

- mechanism of action: bacterial topoisomerase II (gyrase) and IV inhibition
- high incidence of resistance – usage only based on the determined susceptibility

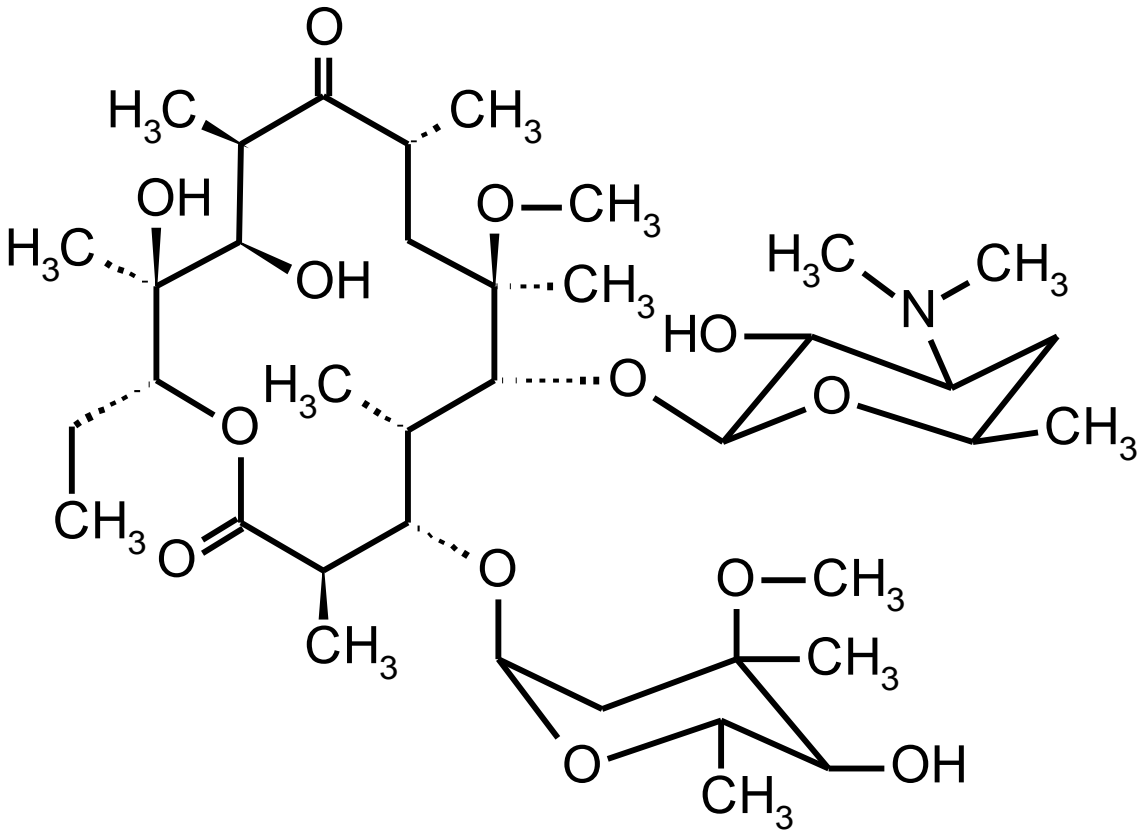
Tetracyclins



minocycline

•efficient to some strains of *M. tuberculosis, leprae, avium...*
•in combinations (rifampicin, ofloxacin ...)
•restoring to health from tuberculoid leprosy – single skin lesion by single dose administration has been referred
•mechanism of action: protheosynthesis inhibition
Skid ®

Macrolides



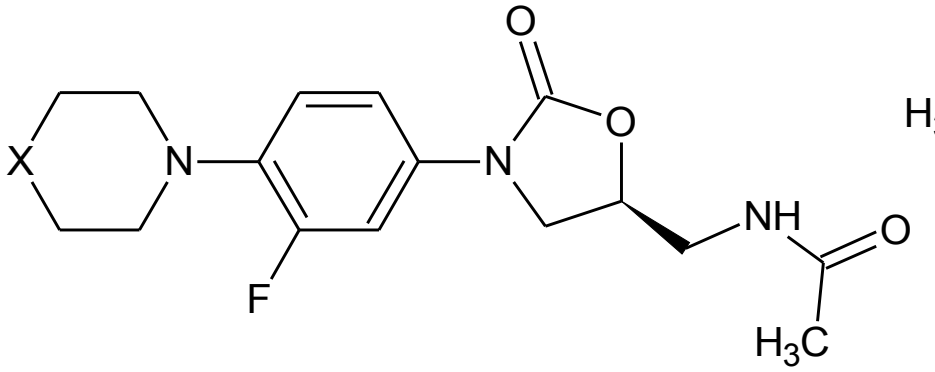
claritromycin

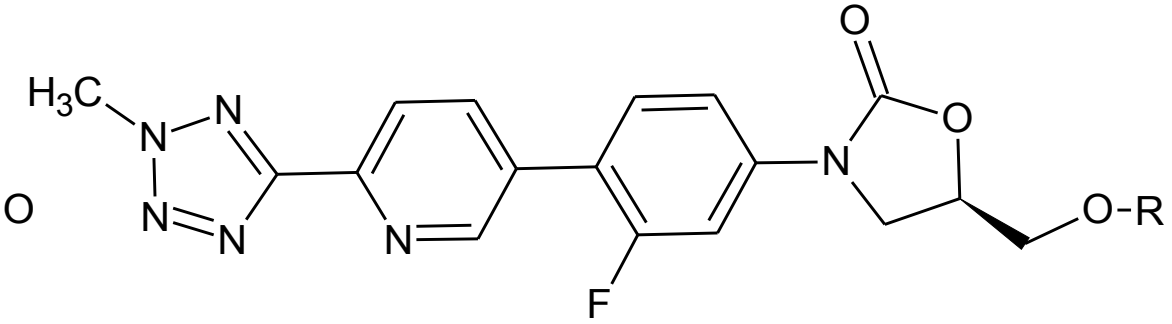
•against *M. avium complex* in patients with HIV

•bacteriostatic

•mechanism of action: inhibition of protheosynthesis – translation by binding to 50S ribosome subunit

Oxazolidin-2-one derivatives





X = S	U-100480	R = -P=O$(OH)_2$	DA-7218
X = O	**linezolid**	R = -H	DA-7157

- against multiresistant strains of *M. tuberculosis*
- mechanism of action: protheosynthesis inhibition by different way than other known antibacterial chemotherapeutics: bound to 23S subunit rRNA they inhibit the early stage of translation by preventing of correct binding of formyl-methionine tRNA
- they inhibit protheosynthesis also in mammal mitochondrias $\Rightarrow$ myelosupression, peripheral neuropathy as important adverse effects