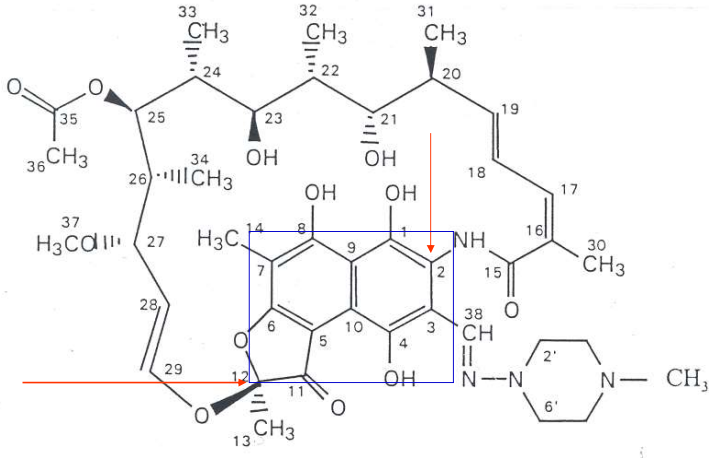
RIFAMYCINS

The introduction of rifampin in the late 1960s permitted a marked reduction in the treatment duration for tuberculosis, from 18-24 months to "just" 6-9 months.

PK/PD analysis in *in-vitro* and animal models indicates that rifampin is a concentration-dependent or area-under-the-concentration-curve-dependent drug: i.e., bacteriocidal kinetics increase in direct proportion to the dosage of rifampin administered.

This is in contrast to other first-line drugs, such as isoniazid, which are time-dependent, not concentration-dependent, drugs.

Rifampicin / Rifampin



Ansamycins characterised by a quinone or naphtoquinone-type element, the two extremes linked together by an aliphatic chain, called ansa.

RIFAMYCINS

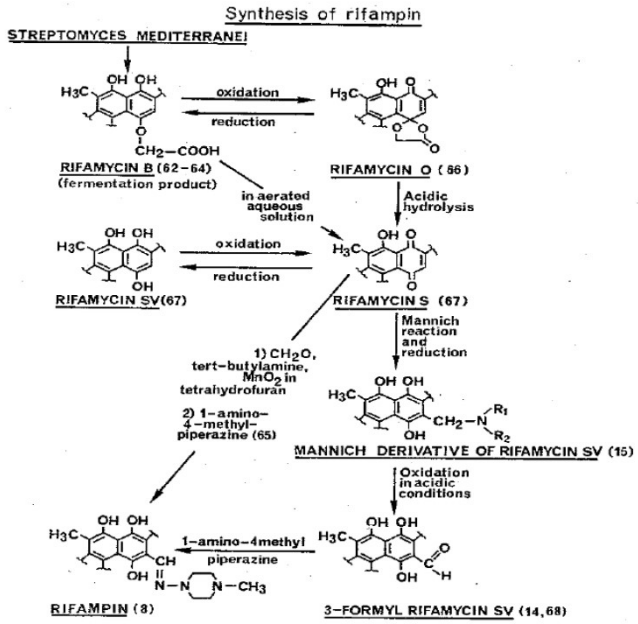
In 1957 Prof. Piero Sensi (1920-2013) and Dr. Maria Teresa Timbal (1925 - 1969) discovered a new bacterium.

After two years of attempts to obtain more stable semisynthetic products, a new molecule with high efficacy and good tolerability was produced in 1959 and was named "rifampicin".

There are various types of rifamycins, but the rifampicin form, with a 4-methyl-1-piperazinaminyl group, is by far the most clinically effective.

Rifampicin is an intensely red solid.

Rifampicin / Rifampin



Biosynthesis

Despite the fact that Rifamycin B is a mild antibacterial compound, it is known to be the precursor of various other clinically utilized potent derivatives.

The general scheme of biosynthesis starts with the uncommon starting unit, 3-amino-5-dihydroxybenzoic acid (AHBA), via type I polyketide pathway (PKS I) in which chain extension is performed using 2 acetate and 8 propionate units. AHBA is believed to have originated from the Shikimate pathway, however this was not incorporated into the biosynthetic mechanism. This is due to the observation that 3 amino-acid analogues converted into AHBA in cell-free extracts of *A. mediterranei*

Rifampicin / Rifampin

- **Rifampicin is not a true fermentation product according to the provisions of Ph. Eur. general monograph « fermentation products » (1468),**

  - **Rifampicin is a semi-synthetic antibiotic**

- **Rifamycin B or Rifamycin S, the starting materials of Rifampicin, are true fermenation products**

- **Rifamycin B obtained during growth of certain strains of *Amycolatopsis mediterranei***
- **Rifamycin S from *A. mediterranei* *mutants***

Rifampicin – starting material obtained from fermentation

- **Characterisation of the producer microorganism**

identification, source, purity and stability of master cell bank and working cell bank, deposition in a recognised culture collection

- **Details of fermentation process**

media ingredients and their specifications, their heat/sterilisation treatment, description of the process including conditions and controls accompagnied by a flow diagram

- In process controls to show **the reproducibility of the process**
- **Release and collection of the desired product**
- **Extraction and purification steps**
- Overview of the potential impurities and how they are removed (cellular residue, substrates, precursors and other media ingredients, unwanted metabolic products whether related substance or not)

Rifampicin / Rifampin - Properties

- Rifampicin is a Reddish-brown or brownish-red crystalline powder, slightly soluble in water

- Rifampicin presents the phenomenon of polymorphism: two crystalline forms I and II, an amorphous form and several solvates from different solvents (water, tetrahydrofuran, carbon tetrachloride)

- Commercial production is constituted of form II

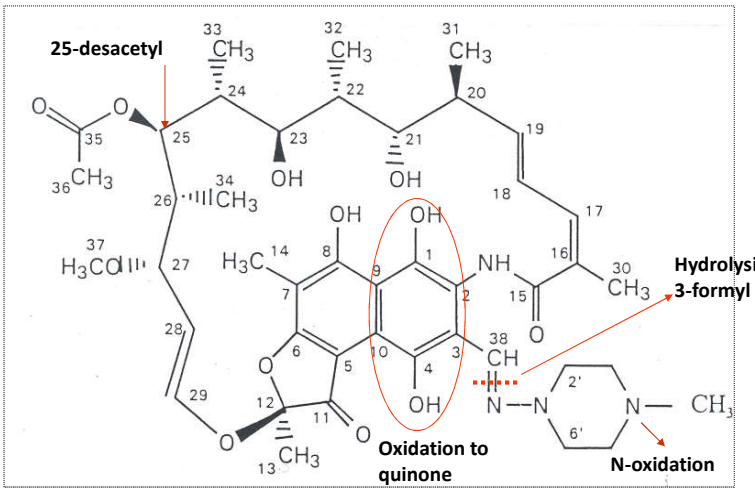
- Presence of amorphous form slows down dissolution characteristics of the solid dosage form

- The infrared (IR) test and differential scanning calorimetry (DSC) can distinguish between the different forms to be used as identification test

Rifampicin - Impurities

- Rifampicin quinone is the major degradation product of Rifampicin and arised from the oxidation of the naphtohyydroquinone moiety
- Rifampicin N-oxide is the other oxidation product/degradation product of rifampicin, arising from oxidation of the tertiary amine present on the piperazine moiety
- 3- formyl Rifamycin is synthesis impurity and degradation product by hydrolysis of the imine group in aqueous acidic media leading to loss of aminomethylpiperazine
- Desacetyl and transacetyl Rifampicins are obtained upon alkaline treatment: 25-desacetyl obtained by ester hydrolysis which may lead stepwise to C-21 and C-23

Rifampicin - Impurities



The utility of rifamycins is limited by three factors:

Rifamycin toxicity **prevents administration of rifamycins at concentrations that yield highest bacteriocidal and sterilizing kinetics and thus prevents greater reductions in treatment duration .**

Rifamycin tolerance **of *M. tuberculosis*--a reversible physiological state involving decreased sensitivity to rifamycins--limits bacteriocidal and sterilizing kinetics and thus prevents greater reductions in treatment duration.**

Rifamycin-tolerant *M. tuberculosis* cells exhibit low but detectable levels of RNAP activity in the presence of rifamycins.

RNAP activity in the presence of rifamycins is thought to be attributable to alternative RNAP holoenzyme species with

1. **decreased sensitivity to rifamycins**
2. **decreased cell permeability to rifamycins .**

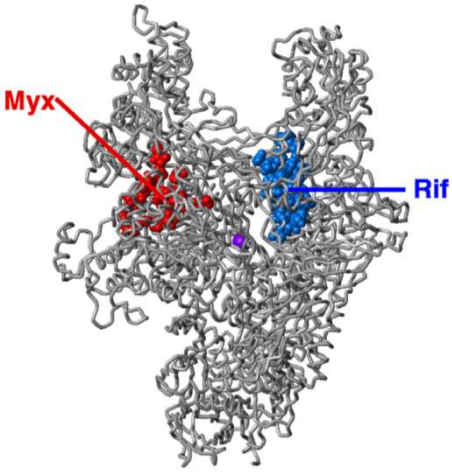
Rifamycin resistance **of *M. tuberculosis*--an irreversible genetic state involving decreased sensitivity to rifamycins--can result in frank failure of treatment. A significant and increasing percentage of tuberculosis cases are rifamycin-resistant (1.4% of new cases, 8.7% of previously treated cases, and 100% of cases designated multidrug-resistant, in 1999-2002).**

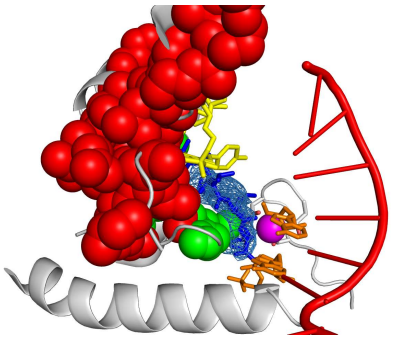
Rifamycin resistance is attributable to mutations that result in substitution of residues in or immediately adjacent to the rifamycin binding site on RNAP.

Mechanism of action

Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase.

Crystal structure and biochemical data indicate that rifampicin binds to RNA polymerase at a site adjacent to the RNA polymerase active center and blocks RNA synthesis by physically preventing extension of RNA products beyond a length of 2-3 nucleotides ("steric-occlusion" mechanism).





Pharmacologic Effects

Orally administered rifampicin results in peak plasma concentrations in about two to four hours.
4-Aminosalicylic acid (another antituberculosis drug) significantly reduces absorption of rifampicin.
Rifampicin is easily absorbed from the gastrointestinal tract; its ester functional group is quickly hydrolyzed in the bile; and it is catalyzed by a high pH and substrate-specific enzymes called esterases.
After about six hours, almost all of the drug is deacetylated. Even in this deacetylated form, rifampin is still a potent antibiotic; however..

Only about 7% of the administered drug will be excreted unchanged through the urine, though urinary elimination accounts for only about 30% of the drug excretion. About 60% to 65% is excreted through the feces.

Pharmacologic Effects

The half-life of rifampicin ranges from 1.5 to 5.0 hours, though hepatic impairment will significantly increase it.

Distribution of the drug is high throughout the body, and reaches effective concentrations in many organs and body fluids, including the CSF. About 60% to 90% of the drug is bound to plasma proteins.

Mechanism of resistance

Resistance to rifampicin arises from mutations that alter residues of the rifampicin binding site on RNA polymerase, resulting in decreased affinity for rifampicin. Resistant mutations map to the *rpoB* gene, encoding RNA polymerase beta subunit.

The mutations at codons 513 (5%), 526 (33%) or 531 (43%)

Clinical Uses

Rifampicin was introduced in 1967 as a major addition to the cocktail-drug treatment of tuberculosis and inactive meningitis, along with pyrazinamide, isoniazid, ethambutol, and streptomycin ("PIERS").

Rifampicin is also used in the treatment of cholestatic pruritus.

Clinical Uses

Rifampicin is used in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in combination with fusidic acid.

It is also used in prophylactic therapy against *Neisseria meningitidis* (meningococcal) infection.

Rifampicin is also recommended as an alternative treatment for infections with the tick-borne disease pathogens, *Borrelia burgdorferi* and *Anaplasma phagocytophilum*.
It is also used to treat infections by *Listeria* species, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and *Legionella pneumophila*.
The Enterobacteriaceae, and *Acinetobacter* and *Pseudomonas* species are intrinsically resistant to rifampicin.

Rifampicin has some effectiveness against vaccinia virus.

Adverse Effects

Hepatotoxic - hepatitis, liver failure in severe cases
Respiratory - breathlessness
Cutaneous - flushing, pruritus, rash, redness and watering of eyes
Abdominal - nausea, vomiting, abdominal cramps with or without diarrhea
Flu-like symptoms - with chills, fever, headache, arthralgia, and malaise, rifampin has good penetration into the brain, and this may directly explain some malaise and dysphoria in a minority of users.

Adverse Effects

Rifampicin has hepatotoxicity: patients receiving it often undergo baseline and frequent liver function tests to detect liver damage.

Rifampicin is an effective liver enzyme-inducer, promoting the upregulation of hepatic cytochrome P450 enzymes (such as CYP2C9 and CYP3A4), increasing the rate of metabolism of many other drugs that are cleared by the liver through these enzymes. As a consequence, rifampicin can cause a range of adverse reactions when taken concurrently with other drugs. For instance, patients undergoing long term anticoagulation therapy with warfarin have to be especially cautious. Failure to do so could lead to under-treating with anticoagulation, resulting in serious consequences of thromboembolism.

Interaction

Rifampicin is an inducer of many enzymes of the cytochrome P450 superfamily, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP3A7. Thus it will speed up the metabolism of any drug metabolized by any of these enzymes in the body.

Rifampicin is antagonistic to the effect of gentamycin and amikacin.

Advantage include

- **It is absorbed after either oral or intravenous administration**
- **It has both intracellular and extracellular anti-bacterial activity**

- Dosage

Generally, 10mg/kg, 600mg daily or twice weekly

- Adverse effects

The most common adverse event included gastrointestinal upset, hepatitis