RIFAMPICIN
Sigma Prod. No. R3501

CAS NUMBER: 13292-46-1
SYNONYMS: Tubocin; Sinerdol; Rimactan; L-5103; Dione-21 Acetate; Archidyn; Arficin; 3-(4-Methylpiperazinyliminomethyl)-rifamycin SV; NSC 113926; Rifampin¹; Rifaldazine; Rifamycin AMP²

PHYSICAL PROPERTIES:

Appearance: Orange-brown to red-brown powder.³
Molecular formula: C₄₃H₅₈N₄O₁₂
Molecular weight: 823.0

$E_{\text{mm}}$ (max absorbance, phosphate buffer, pH 7.38): 33.20 (237 nm); 32.10 (255 nm); 27.00 (334 nm); 15.40 (475 nm)²,⁴

pKₐ (in water): 1.7 (4-hydroxyl group), 7.9 (4-piperazine nitrogen); in methylcellosolve-water (4:1): 3.6 (4-hydroxyl group), 6.7 (3-piperazine nitrogen)⁴

pI (in water): 4.84

Optical rotation: $\left[\alpha\right]_D^25 = +10.6^\circ$ (c=0.5% in CDCl₃)⁴

Melting point: 183-188°C (dec.)²,⁴

METHOD OF PREPARATION:

Methods of preparation have been reported.⁴,⁵ The NMR, UV, IR, Mass spectra, Thin-Layer chromatography and HPLC methods of detection have been reported.⁴,⁵,⁶ A colorimetric test for identification was reported.⁴

STABILITY / STORAGE:

Rifampicin (Rif) should be stable for at least two years when stored desiccated at -20°C and protected from light.³ Rif is stable as a solid at temperatures up to 70°C.⁴

SOLUBILITY / SOLUTION STABILITY:

Rif is soluble in dimethylsulfoxide (~100mg/mL), dimethylformamide, methanol (16 mg/ml, 25°C), chloroform (349 mg/ml, 25°C), ethyl acetate (108 mg/ml, 25°C), and acetone (14 mg/ml, 25°C).⁴,⁶,⁷,⁸,⁹ Rif is slightly soluble in water at 25°C: 2.5 mg/ml, pH 7.3; 1.3 mg/ml, pH 4.3; and in 95% ethanol (~10 mg/mL).⁴ Rif is soluble at 37°C: in 0.1 N HCl, 200 mg/ml and in phosphate buffer pH 7.4, 9.9 mg/ml.⁴
SOLUBILITY / SOLUTION STABILITY:

A 1% suspension in water has a pH of 4.5-6.5. Stock solutions in DMSO were diluted in 0.20 M potassium phosphate buffer to prepare working solutions of 10 µg/ml. Solution stabilities of Rif: DMSO, 10 mg/ml, about 8 months at 15°C; water-ethanol (8:2), 1 mg/ml, 8 weeks at 4°C or 20°C. In mildly basic aqueous solutions (pH 8.2, 20-22°C) in the presence of air, Rif is converted to rifampin quinone. Addition of sodium ascorbate can prevent its oxidation. Under basic conditions Rif undergoes desacetylation at 22°C forming the 25-desacetylrifampin (most of antibacterial activity is maintained). Rif decomposes rapidly in acidic or alkaline conditions at 25°C but slowly in neutral conditions, i.e. at 200 µg/ml, at pH 2.3 Rif is hydrolyzed to 3-formylrifampicin. It is best to prepare aqueous solutions with oxygen-free solvent and at neutral pH.

USAGE / APPLICATIONS:

Rif inactivates bacterial RNA polymerase (RNAP) at about 0.01-0.02 µg/ml (50% effective dose). Rif has activity against a wide range of microorganisms such as mycobacteria including Mycobacterium tuberculosis and M. leprae. Rif is highly active against Gram-positive bacteria, such as staphylococci, streptococci, pneumococci but is less active against Gram-negative organisms. The minimum inhibitory concentrations (MIC) for the most sensitive microorganisms (chlamydia, staphylococci) are in the range of about 0.01-0.02 µg/ml; and for the most sensitive mycobacteria, from about 0.1-2 µg/ml. Additional MIC values for different bacterial strains have been reported. The inhibitory activity of Rif remained practically unchanged between pH 5.5-8.0. Rif inhibits bacterial DNA-dependent RNA polymerase (the enzyme responsible for DNA transcription) by forming a stable enzyme-drug complex with the β-subunit of RNA polymerase (RNAP-Rif), rpoB gene (binding constant of 10-9 M at 37°C). Rif suppresses the initiation of chain formation (but not chain elongation) in RNA synthesis. The RNAP-Rif complex is locked on the promoter in the abortive initiation reaction, producing short oligoribonucleotides which diffuse out of the active site. There is some inhibition of mammalian RNA polymerases at much higher concentrations of Rif than that for bacterial RNA polymerases. Nuclear RNA polymerases from different eukaryotic cells are not inhibited by Rif.

Bacterial resistance to Rif is due to mutations which result in changes in the structure of the β subunit of RNA polymerase, i.e. studies of Rif resistance in Mycobacterium tuberculosis (M. tuberculosis) indicated that resistance is mostly, but not necessarily, associated with mutations on the rpoB gene in Mycobacterium tuberculosis. Rif (100 µg/ml) completely inhibited RNA synthesis in chloroplasts. Rif can penetrate into polymorphonuclear leucocytes and kill intracellular pathogens. Rif (100 µg/ml) is active against some viruses. Rif has antifungal activity probably due to some other mechanism of action than inhibition of a fungal RNA polymerase.
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USAGE / APPLICATIONS: (continued)

Rif inhibited Aβ1-40 (Amyloid β-peptide which deposits in the brains of Alzheimer’s disease patients) aggregation and neurotoxicity in rat PC12 cells in a concentration-dependent manner. Rif (25 µM) strongly induced the genes CYP3A4 and CYP3A7 mRNAs in adult human hepatocytes in culture. Rif strongly induced cytochrome P-450 3A-dependent enzyme and UDP-glucosyltransferase activities in female rat liver microsomes at dosage ≥250 mg/kg/day. Rif inhibited protein synthesis in rat thymocytes at >20 µg/ml.

GENERAL NOTES:

Rif is a semisynthetic derivative of rifamycin B and belongs to the rifamycin group of antibiotics. It functions as a bacteriostatic agent by interfering with the synthesis of nucleic acids by inhibiting microorganisms. The chemical, biological properties, activity studies (including microbiological assays methods), pharmacology, metabolism and mechanisms of action have been reported.

REFERENCES:

1. Sigma's Material Safety Data Sheet
2. The Merck Index 12:8382.
3. Sigma Quality Control data
REFERENCES: