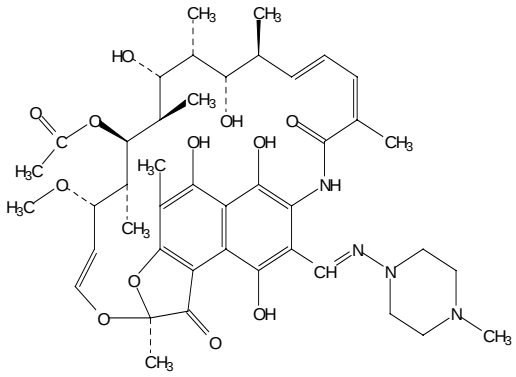
ProductInformation

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; Rifampin[1]; Rifaldazine; Rifamycin AMP[2]

PHYSICAL PROPERTIES:

Appearance: Orange-brown to red-brown powder.[3]
Molecular formula: $C_{43}H_{58}N_4O_{12}$
Molecular weight: 823.0
E_{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]
pK_a (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): 4.8[4]
Optical rotation: $[\alpha]_D^{25^\circ}$=+10.6° (c=0.5% in $CDCl_3$)[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]

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SOLUBILITY / SOLUTION STABILITY:

A 1% suspension in water has a pH of 4.5-6.5.[4,7] Stock solutions in DMSO were diluted in 0.20 M potassium phosphate buffer to prepare working solutions of 10 µg/ml.[8] Solution stabilities of Rif: DMSO, 10 mg/ml, about 8 months at 15°C[8]; water-ethanol (8:2), 1 mg/ml, 8 weeks at 4°C or 20°C.[2,4] 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).[4] 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.[4,5] 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 0.01-02 µg/ml (50% effective dose).[10,11] Rif has activity against a wide range of microorganisms such as mycobacteria including Mycobacterium tuberculosis[9] and M. leprae.[12] Rif is highly active against Gram-positive bacteria, such as staphylococci, streptococci, pneumococci but is less active against Gram-negative organisms.[13,14] 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.[7] Additional MIC values for different bacterial strains have been reported.[14,15] The inhibitory activity of Rif remained practically unchanged between pH 5.5-8.0.[14] Rif inhibits bacterial DNA-dependent RNA polymerase (the enzyme responsible for DNA transcription) by forming a stable enzyme-drug complex with the ß-subunit of RNA polymerase (RNAP-Rif), *rpoB* gene (binding constant of 10-9 M at 37°C).[10,16,17] Rif suppresses the initiation of chain formation (but not chain elongation) in RNA synthesis.[18] The RNAP-Rif complex is locked on the promoter in the abortive initiation reaction, producing short oligoribonucleotides which diffuse out of the active site.[19] There is some inhibition of mammalian RNA polymerases at much higher concentrations of Rif than that for bacterial RNA polymerases.[20] Nuclear RNA polymerases from different eukaryotic cells are not inhibited by Rif.[18,21]

Bacterial resistance to Rif is due to mutations which result in changes in the structure of the ß 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.[10,16] Rif (100 µg/ml) completely inhibited RNA synthesis in chloroplasts.[22] Rif can penetrate into polymorphonuclear leucocytes and kill intracellular pathogens.[18,23] Rif (100 µg/ml) is active against some viruses.[12,15,24,25] Rif has antifungal activity probably due to some other mechanism of action than inhibition of a fungal RNA polymerase.[26]

USAGE / APPLICATIONS: (continued)

Rif inhibited Aß1-40 (Amyloid ß-peptide which deposits in the brains of Alzheimer's disease patients) aggregation and neurotoxicity in rat PC12 cells in a concentration-dependent manner.[27] Rif (25 μM) strongly induced the genes CYP3A4 and CYP3A7 mRNas in adult human hepatocytes in culture.[28] Rif strongly induced cytochrome P-450 3A-dependent enzyme and UDP-glucosyltransferase activities in female rat liver microsomes at dosage ≥250 mg/kg/day.[29] Rif inhibited protein synthesis in rat thymocytes at >20 μg/ml.[30]

GENERAL NOTES:

Rif is a semisynthetic derivative of rifamycin B and belongs to the rifamycin group of antibiotics.[18] It functions as a bacteriostatic agent by interfering with the synthesis of nucleic acids by inhibiting microorganisms.[7] The chemical, biological properties, activity studies (including microbiological assays methods), pharmacology, metabolism and mechanisms of action have been reported.[4,10,15]

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