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ProductInformation

RAPAMYCIN
Product Number **R0395**
Storage Temperature –20 °C

CAS #: 53123-88-9
Synonyms: Antibiotic AY 22989; NSC 2260804, Sirolimus , Rapamune[1]

Product Description

Appearance: Rapamycin is a powder[2]
The E1 %, 1 cm (maximum wavelength, 95% ethanol) is: 417 (267 nm); 541 (277 nm); 416 (288 nm).[1]
Molecular Formula: $C_{51}H_{79}NO_{13}$
Molecular Weight: 914.2

Rapamycin is extracted from a microbial fermentation of Streptomyces hygroscopicus.[2] The synthesis has been reported[3,4] Methods of preparation, purification and characterization have been reported.[5,6] HPLC quantitation [7] including in whole blood [8] has been reported .

Rapamycin exists as one isomer (structurally homogeneous) in the solid form as indicated by X-rays whereas in solution there are two conformational isomers (approx. 4:1) which exist in equilibrium. Through NMR analysis, the "isomerism is shown to be associated with the trans-cis rotation of an amidic bond within the 31-membered macrolide ring".[9,10]

Rapamycin is a macrocyclic-triene antibiotic possessing potent immunosuppressant activity. It has been found to be a useful probe for studying T-cell signal transduction.[11,12] Rapamycin exerts its immunosuppressant effect only after binding to the immunophilin proteins, FKBP12. Rapamycin inhibits growth factor- and mitogen-induced stimulation of proliferation of T lymphocytes by the binding of the Rapamycin-FKBP12 complex to an effector, and arresting the G_1 stage in the the G_1 to S transition of the cell cycle.[11,13] The effectors were identified as FRAP[12,13], (FKBP12 Rapamycin-associated protein, TOR protein) and RAFT1[14] (Rapamycin and FKBP12 target). The activity of FRAP and its relationship to the signaling events have not yet been delineated.[11] The Rapamycin-FKBP12-FRAP ternary complex (3 nM rapamycin)[15] induces rapid inactivation of p70s6 kinase as well as inhibition of cyclin A, the association of cyclin A with p34cdc2, and decreased p34cdc2 and p33cdk2 activities.[11,15-20] Rapamycin (IC_{50}=1 nM0 inhibited human peripheral blood mononuclear cell proliferation (induced by 0.1% phytohemagglutinin) and was about 50-100 fold more potent than cyclosporin A.[12]

Rapamycin (1.2 µm) inhibits protein kinase C activity and stimulates (10^{-5}M – 10^{-6}) ion transport in A6 cells.[21] Rapamycin inhibits the immune response in membrane and cytosolic preparations.[22] It exhibits distinct effects on translation of endogeneous mRNA's[23] and it (20 nM) suppresses 5'TOP mRNA translation through the inhibition of $p70^{s6k}$ activation in the signaling pathway.[24]

Rapamycin has been shown to have both antifungal (inhibits yeast and filamentous fungus) and antineoplastic properties.[25] Rapamycin is active mainly against Candida albicans having minimum inhibitory concentrations (MIC) against various strains from 0.02-0.2 µg/ml[5] Comparison of its activity (MIC concentration) with that of amphotericin B, nystatin and candicidin have been reported.[6]

The chemistry, pharmacology and mechanism of action have been reported.[5,6,11,12,26-31]

Storage/Stability

Rapamycin can dissolve in chloroform (5 mg/ml),[2] in methanol (25 mg/ml)[2], and in DMSO (25 mg/ml)[2]. Rapamycin is also soluble in ethanol, ether, acetone and N,N-dimethylformamide and is substantially insoluble in water.[1] It is very sparingly soluble in hexane and in petroleum ether.[1]

A 10 mg/ml solution in methanol (HPLC grade and degassed methanol) was kept at 2-8 °C for one week with no decomposition.[2] A 2 mM solution in ethanol was stored at -70°C and was diluted into a serum-free media before use.[21] For pancreatic acini cell studies, the final concentration of ethanol did not exceed 0.1%[15]. Unless otherwise indicated, solutions are probably best prepared fresh and protected from light.[1]

References

1. The Merck Index, 12th ed:8288
2. Sigma-Aldrich Production/Quality Control
3. Nicolaou, K.C. et al J. Am. Chem. Soc., 115, 4419 (1993).
4 Romo, D. et al. J. Am. Chem. Soc. 115, 7906, (1993).
5 Vezina, C. et al. J. Antibiotics, 28, 721, (1975).
6 Sehgal, S.N. et al. J. Antibiotics, 28, 727, (1975).
7 Napoli, K.L. and Kahan, B.D. Clin. Chem. 37, 294, (1991).
8. Yatscoff, R.W. et al. Therapeutic Drug Monitoring, 14, 138, (1992).
9. Findlay, J.A. and Radics, L. Canadian J. Chem. 58, 579, (1980).
10. Hughes, P. et al. Tetrahedron Letters, 33, 4739, (1992).
11. Vander Woude, A.C. et al. "Progress in Therapeutic Immunosuppression: Cyclosporine, Tacrolimus (FK506) and Rapamycin" in Therapeutic Immunology, Chapter 6, 71, eds. Austen, K.F., Burakoff, S.J., Rosen, F.S. and Strom T.B., Blackwell Science, 1996, Cambridge, MA
12. Sehgal, S.N. and Bansbach, C.C. Ann. N.Y. Acad. Sci. 685, 58, (1993).
13. Brown, E.J. et al. Nature 369, 756, (1994).
14. Sabatini, D.M. et al. Cell, 78, 35, (1994).
15. Bragado, M. et al. Am. J. Physiol. 273 (Cell Physiol. 42):C101, (1997).
16. Jayaraman, T. and Mark, A.R. J. Biol. Chem. 268, 25385, (1993).
17. Morice, W.G. et al. J. Biol. Chem. 268, 22737, (1993).
18. Morice, W.G. et al. J. Biol. Chem. 268, 3734, (1993).
19. Chung, J. et al. Cell 69, 1227, (1992).
20. Price, D.J. et al. Science, 257, 973, (1992).
21. Rokaw, M.D. et al. J. Biol. Chem. 271, 32, 468, (1996).
22. Martel, R.R. et al. Can. J. Physiol. Pharmacol. 55, 48, (1977).
23. Pedersen, S. et al. Eur. J. Biochem. 247, 449, (1997).
24. Jeffries, H.B.J. et al. The EMBO Journal, 16, 3693, (1997).
25. Martindale The Extra Pharmacopoeia, 30th, ed. 499.
26. Carlson, R.P. et al. J. Pharmacology and Exp. Therapeutics, 266, 1125, (1993).
27. Chang, J.Y. and Sehgal, S. British J. Rheumatology, 30, 62, (1991).
28. Brunn, G.J. et al. Science, 277, 99, (1997).
29. Sigal, N.H. and Dumont, F.J. Annu. Rev. Immunol. 10, 519, (1992).
30. Rejto, P.A. and Verkhivker, G.M. Proteins: Structure, Function and Genetics, 28, 313, (1997).
31. Sehgal, S.N. et al. Medicinal Research Reviews, 14,1, (1994).

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