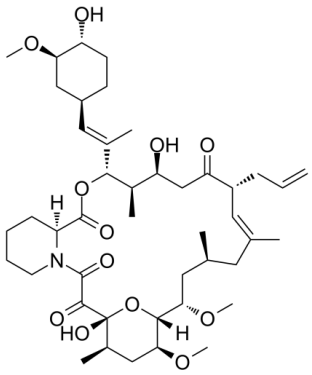
Data Sheet

Product Name:	Tacrolimus
Cat. No.:	CS-1507
CAS No.:	104987-11-3
Molecular Formula:	C44H69NO12
Molecular Weight:	804.02
Target:	Autophagy; FKBP; Phosphatase
Pathway:	Apoptosis; Autophagy; Immunology/Inflammation; Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 28 mg/mL (34.83 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

Tacrolimus (FK506; Fujimycin; FR900506) is a macrocyclic lactone with potent immunosuppressive properties, an immunosuppressant. Tacrolimus binds to **FK506 binding protein (FKBP)** to form a complex and inhibits **calcineurin phosphatase**, which inhibits T-lymphocyte signal transduction and IL-2 transcription[1]. IC50 & Target: PP2B (calcineurin phosphatase)[1]
Autophagy inducer[2] **In Vitro:** Tacrolimus (FK506) inhibits calcium-dependent events, such as IL-2 gene transcription, NO synthase activation, cell degranulation, and apoptosis. Tacrolimus also potentiates the actions of glucocorticoids and progesterone by binding to FKBPs contained within the hormone receptor complex, preventing degradation. The agent may enhance expression of the TGFβ-1 gene in a fashion analogous to that demonstrated for CsA. T cell proliferation in response to ligation of the T cell receptor is inhibited by Tacrolimus[1]. Treatment with a low concentration of Tacrolimus (FK506,10 μg/L) does not significantly affect the proliferation of MH3924A cells (P=0.135). Upon treatment with higher concentrations of Tacrolimus (100-1,000 μg/L), the proliferation of MH3924A cells is significantly enhanced (P<0.01). Treatment with AMD3100 at any concentration (10, 50 or 100 μg/L), has no obvious effect on MH3924A cell proliferation (P>0.05). However, when different concentrations of AMD3100 are combined with 100 μg/L Tacrolimus, the in vitro proliferation of MH3924A cells is increased (P<0.01)[3]. **In Vivo:** The therapeutic effect of Tacrolimus is investigated on progression and perpetuation of colitis by administering Tacrolimus to Dextran sulfate sodium (DSS)-treated mice from Days 10 to 16 or to 23. At Days 17 and 24, colon length is significantly shortened, and colon weight is significantly higher in DSS-treated control animals than in normal animals. In addition, colon weight per unit length in the control group is more than twice that in the normal group. While both 7 and 14 d treatment with Tacrolimus significantly suppresses increases in colon weight per unit length in DSS-treated animals compared with the control group, this treatment does not actually restore the colon shortening. In addition, this inhibitory effect of Tacrolimus on increases in colon weight per unit length is more pronounced with 14-d than 7-d treatment, as shown by the inhibitory percentages (59% vs. 28%)[4].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Tacrolimus (FK506; Fujimycin; FR900506) is dissolved in DMSO and stored, and then diluted with appropriate medium before use.[3]Tumor cell proliferation is determined by the MTT assay. Briefly, after **MH3924A cells** have reached the logarithmic growth phase, a 0.2-mL cell suspension at 1×10^4 cells/mL is added into each well of a 96-well plate and cultured in DMEM for 24 h. When adherent growth is established, different concentrations of **Tacrolimus (10, 100 and 1,000 μg/L)** , AMD3100 (10, 50 and 100 μg/L) and **Tacrolimus (0 and 100 μg/L)**+AMD3100 (0, 10, 50 and 100 μg/L) are added into the plates. Untreated cells cultured in medium alone are used as controls. After culturing for 48 h, 10 μL MTT (5 g/L) are added, and each well is incubated for 6 h; next, 150 μL/well DMSO are added, followed by measurements of the absorbance at 570 mm on a spectrophotometer reader. Each well is measured three times, and each sample is assayed in triplicate[3].
Animal Administration: [4]Mice[4]
Six-week-old **male C57BL/6J mice** are maintained in a temperature- and humidity-controlled room with a 12-h light-dark cycle. For

the multiple dosing study, colitic mice (n=10) are **orally administered Tacrolimus at 30 mg/kg** for 7 d (Days 10 to 16) or 14 d (Days 10 to 23). Control (n=10) and normal groups (n=5) are administered placebo using the same regimen. Tacrolimus or placebo is administered at 10 mL/kg. Mice are euthanized by CO_2 inhalation on the day following the final dosing. For the single dosing study, colitic mice are orally administered Tacrolimus at 30 mg/kg or placebo (n=8) once on Day 7, 10, 17, or 24. Normal mice (n=4) are administered placebo using the same regimen. Mice are euthanized by CO_2 inhalation eight hours after dosing[4].

References:

[1]. Thomson AW, et al. Mode of action of Tacrolimus (FK506): molecular and cellular mechanisms. Ther Drug Monit. 1995 Dec;17(6):584-91.

[2]. Vogel KR, et al. mTOR inhibitors rescue premature lethality and attenuate dysregulation of GABAergic/glutamatergic transcription in murine succinate semialdehyde dehydrogenase deficiency (SSADHD), a disorder of GABA metabolism. J Inherit Metab Dis. 2016 Nov;39(6):877-886.

[3]. Zhu H, et al. Tacrolimus promotes hepatocellular carcinoma and enhances CXCR4/SDF 1α expression in vivo. Mol Med Rep. 2014 Aug;10(2):585-92.

[4]. Okada Y, et al. Tacrolimus ameliorates dextran sulfate sodium-induced colitis in mice: implication of interleukin-1β suppression. Biol Pharm Bull. 2011;34(12):1823-7.

[5]. Yuwei He, et al. Drug targeting through platelet membrane-coated nanoparticles for the treatment of rheumatoid arthritis. Nano Res. 30 June 2018.

CAIndexNames:

15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propen-1-yl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-

SMILES:

O=C([C@@](CCCC1)([H])N1C(C([C@@]2(O)[C@H](C)C[C@H](OC)[C@@](O2)([H])[C@@H](OC)C[C@@H](C)C/C(C)=C/[C@H]3CC=C)=O)=O)O[C@H](/C(C)=C/[C@H]4C[C@@H](OC)[C@H](O)CC4)[C@H](C)[C@@H](O)CC3=O

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