

RESEARCH MONOGRAPH . COMPOUND PROFILE

Rapamycin (Sirolimus)

A bacterial macrolide isolated from Streptomyces hygroscopicus, FDA-approved as an immunosuppressant and increasingly investigated for longevity applications through mTOR inhibition.

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ABSTRACT

Rapamycin (Sirolimus, Rapamune; CAS 53123-88-9; molecular formula $C_{51}H_{79}NO_{13}$; molecular weight 914.17) is a macrolide compound isolated in 1972 from *Streptomyces hygroscopicus* from Easter Island (Rapa Nui, providing the name). The compound was approved by the FDA in 1999 as an immunosuppressant for renal transplantation. Mechanism is selective inhibition of mTORC1 (mammalian target of rapamycin complex 1) through binding to FKBP12 and forming a complex that allosterically inhibits mTOR kinase activity. Beyond immunosuppression, rapamycin extends lifespan in multiple model organisms (yeast, worms, flies, mice) when administered late in life, making it the most extensively documented pharmacological intervention for lifespan extension. The Interventions Testing Program (ITP) at NIA showed reproducible lifespan extension in genetically heterogeneous mice. Mechanisms of lifespan extension include reduced cellular senescence, improved autophagy, attenuation of age-related inflammation, and reduced age-related cancer incidence. The compound is increasingly used off-label for longevity applications by physicians and patients pursuing geroscience interventions; intermittent dosing schedules (5 to 10 mg weekly or monthly) are used to reduce immunosuppressive effects. Pharmacokinetics: plasma half-life 60 to 70 hours; high oral bioavailability; CYP3A4 metabolism.

1. Compound Identification

Rapamycin (Sirolimus) is described as mtor inhibitor / immunosuppressant. A bacterial macrolide isolated from *Streptomyces hygroscopicus*, FDA-approved as an immunosuppressant and increasingly investigated for longevity applications through mTOR inhibition.

1.1 Class summary

mTOR inhibitor / immunosuppressant

1.2 Subtitle

A bacterial macrolide isolated from *Streptomyces hygroscopicus*, FDA-approved as an immunosuppressant and increasingly investigated for longevity applications through mTOR inhibition.

2. Abstract

Rapamycin (Sirolimus, Rapamune; CAS 53123-88-9; molecular formula $C_{51}H_{79}NO_{13}$; molecular weight 914.17) is a macrolide compound isolated in 1972 from *Streptomyces hygroscopicus* from Easter Island (Rapa Nui, providing the name). The compound was approved by the FDA in 1999 as an immunosuppressant for renal transplantation. Mechanism is selective inhibition of mTORC1 (mammalian target of rapamycin complex 1) through binding to FKBP12 and forming a complex that allosterically inhibits mTOR kinase activity. Beyond immunosuppression, rapamycin extends lifespan in multiple model organisms (yeast, worms, flies, mice) when administered late in life, making it the most extensively documented pharmacological intervention for lifespan extension. The Interventions Testing Program (ITP) at NIA showed reproducible lifespan extension in genetically heterogeneous mice. Mechanisms of lifespan extension include reduced cellular senescence, improved autophagy, attenuation of age-related inflammation, and reduced age-related cancer incidence. The compound is increasingly used off-label for longevity applications by physicians and patients pursuing geroscience interventions; intermittent dosing schedules (5 to 10 mg weekly or monthly) are used to reduce immunosuppressive effects. Pharmacokinetics: plasma half-life 60 to 70 hours; high oral bioavailability; CYP3A4 metabolism.

3. Mechanism of Action

Selective mTORC1 inhibitor through FKBP12-rapamycin complex. Reduces senescence, improves autophagy, attenuates age-related inflammation.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

1 to 5 mg daily (immunosuppression); 5 to 10 mg weekly intermittent (longevity, off-label).

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Harrison DE, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 2009.
2. Mannick JB, et al. mTOR inhibition improves immune function in the elderly. Sci Transl Med 2014.

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