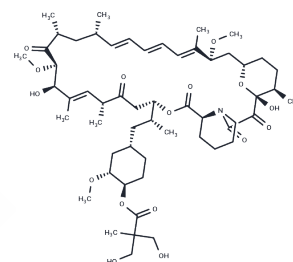


Temsirolimus

Chemical Properties

CAS No. :	162635-04-3
Formula:	C ₅₆ H ₈₇ N ₃ O ₁₆
Molecular Weight:	1030.29
Appearance:	no data available
Storage:	Powder: -20°C for 3 years In solvent: -80°C for 1 year



Biological Description

Description	Temsirolimus (CCI-779) is a specific mTOR inhibitor (IC ₅₀ : 1.76 μM), used in the treatment of advanced renal cell cancer.
Targets(IC ₅₀)	Apoptosis, Autophagy, mTOR
In vitro	Temsirolimus (CCI-779; 10 nmol/L to <5 μmol/L) exhibited a generally flat and cell-selective inhibition of cell proliferation. The most sensitive cell lines that were inhibited by ≥50% included LNCap, PC3MM2, MDA468, H446, and Caco2, whereas those with ≤25% inhibition were SW480, HT29, HCT116, and H460 [1]. Following a 3-day exposure to 100 nmol/L CCI-779, the numbers of colony-forming PC-3 and DU145 cells were 0.18 ± 0.09 and 0.37 ± 0.03, respectively, compared with controls [2].
In vivo	The growth of PC-3 tumors was inhibited by Temsirolimus in a dose-dependent manner and growth inhibition was greater than for DU145 tumors. Mean delay in growth to a volume of 500 mm ³ was 39 ± 5 and 17 ± 3 days, respectively, following treatment with Temsirolimus (20 mg/kg i.p.) five times weekly for 3 weeks. Mice were randomized to treatment with 5 to 10 mg/kg/d of Temsirolimus or vehicle alone as a control [2]. Mice were treated 6 days per week. A statistically significant improvement in disease burden was seen in all samples tested. Mice xenografted from 3 of the patients (96, 240, and 359) had a statistically significant decrease in splenic disease bulk [3]. Temsirolimus, given as 10 intraperitoneal injections, induced significant dose-dependent, antitumor responses against subcutaneous growth of 8226, OPM-2, and U266 cell lines. Effective doses of Temsirolimus were associated with modest toxicity, inducing only transient thrombocytopenia and leukopenia. Although Temsirolimus-mediated inhibition of the p70 mTOR substrate was equal in 8226 and OPM-2 tumor nodules, OPM-2 tumor growth was considerably more sensitive to inhibition of proliferation, angiogenesis, and induction of apoptosis [4].
Kinase Assay	The Flag-tagged wild-type human mTOR (Flag-mTOR) and Flag-mTOR-SI (S2035I, created by site-directed mutagenesis) DNA constructs were transiently transfected into HEK293 cells. Protein extraction and purification of Flag-mTOR and Flag-mTOR-SI were carried out 48 h later as described previously. In vitro kinase assays of purified Flag-mTOR and Flag-mTOR-SI without or with FKBP12 were done and detected by dissociation-enhanced lanthanide fluorescent immunoassay (DELFI) as described [1].
Cell Research	For all experiments, cells were plated in six-well plates in complete growth media for overnight. Various doses of CCI-779 or rapamycin analogs were added alone or with

FK506 for indicated periods of time. Total cellular lysates were prepared using NuPAGE-LDS sample buffer. Equal amounts of proteins were subjected to immunoblotting analysis using NuPAGE electrophoresis system. Immunoblots were probed with appropriate primary and secondary antibodies following the manufacturer's instructions and detected using enhanced chemiluminescence. β -Actin immunoblotting and/or reversible Ponceau-S staining of nitrocellulose membranes after the transfer was used to visualize the total protein loading [1].

Animal Research

Mice bearing PC-3 tumors were treated with CCI-779 (1, 5, 10, and 20 mg per kg per day), or vehicle solution for 3 or 5 days per week for 3 weeks. Mice bearing DU145 tumors were only treated with CCI-779 (20 mg per kg per day) or vehicle solution for 3 weeks. Mice bearing PC-3 tumors received the following treatments: (a) control, vehicle solution for CCI-779; (b) chemotherapy alone, mitoxantrone 1.5 mg/kg or docetaxel 10 mg/kg was injected i.p. weekly for 3 doses; (c) CCI-779 alone, 5 or 10 mg/kg was injected i.p. daily, three times a week for 3 weeks; (4) chemotherapy followed by CCI-779. The largest and perpendicular diameters of tumors were measured twice weekly, and animals were coded using ear tags so that the observer was unaware of their treatment history. Tumor volume was estimated and plotted against time to evaluate response to treatment [2].

Solubility Information

Solubility

H₂O: < 1 mg/mL (insoluble or slightly soluble),
Ethanol: 70 mg/mL (67.94 mM), Sonication is recommended.
(< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	0.9706 mL	4.853 mL	9.706 mL
5 mM	0.1941 mL	0.9706 mL	1.9412 mL
10 mM	0.0971 mL	0.4853 mL	0.9706 mL
50 mM	0.0194 mL	0.0971 mL	0.1941 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Reference

Shor B, et al. A new pharmacologic action of CCI-779 involves FKBP12-independent inhibition of mTOR kinase activity and profound repression of global protein synthesis. *Cancer Res.* 2008 Apr 15;68(8):2934-43.

Wu L, et al. Effects of the mammalian target of rapamycin inhibitor CCI-779 used alone or with chemotherapy on human prostate cancer cells and xenografts. *Cancer Res.* 2005, 65(7), 2825-2831.

Teachey DT, et al. The mTOR inhibitor CCI-779 induces apoptosis and inhibits growth in preclinical models of primary adult human ALL. *Blood*, 2006, 107(3), 1149-1155.

Frost P, et al. In vivo antitumor effects of the mTOR inhibitor CCI-779 against human multiple myeloma cells in a xenograft model. *Blood*. 2004 Dec 15;104(13):4181-7. Epub 2004 Aug 10.

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Tel: 781-999-4286 E_mail: info@targetmol.com Address: 36 Washington Street, Wellesley Hills, MA 02481