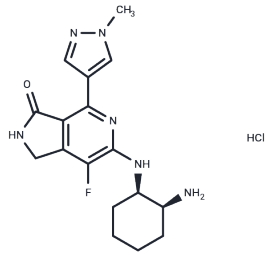
Data Sheet (Cat.No.T4209)

TargetMol
YOUR TARGET MOLECULES

TAK-659 hydrochloride

Chemical Properties



CAS No. : 1952251-28-3

Formula: C17H22ClFN6O

Molecular Weight: 380.85

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	TAK-659 hydrochloride (TAK-659) is a potent and selective inhibitor of spleen tyrosine kinase (SYK) with an IC50 value of 3.2 nM. It is selective against most other kinases, but potent toward both SYK and FLT3.
Targets(IC50)	VEGFR,FLT,Tyrosine Kinases,JAK,Syk
In vitro	In a broad kinase panel, TAK-659 demonstrates a more than 50-fold selectivity for SYK and FLT-3 over 290 other protein kinases. Treatment with TAK-659 inhibits Syk activation and BCR signaling in co-cultured primary CLL cells and Burkitt's lymphoma cells. In primary CLL cells in suspension culture, TAK-659 treatment results in a dose-dependent reduction in the phosphorylation of SykTyr525, Btk, NFκB, ERK1/2 and STAT3 after BCR stimulation. Inhibition of Syk by TAK-659 induces apoptosis of CLL cells and abrogates BCR and co-culture-derived survival signals. TAK-659 inhibits chemotaxis toward BMSC, CXCL12 and CXCL13 in primary CLL cells, and abrogates microenvironment-induced chemoresistance. TAK-659 does not inhibit TCR signaling and molecular features of T cell activation in primary T cells from patients with CLL. In a cell proliferation assay, TAK-659 shows inhibition toward a SYK-dependent cell line (OCI-LY10). the sensitivity to TAK-659 is associated with mutations impacting SYK activity in B cell lymphomas, whereas TAK-659 is not cytotoxic for adherent primary or solid tumor cell lines. In cell viability assays, TAK-659 is shown to be sensitive toward FLT3-ITD dependent cell lines, MV4-11 and MOLM-13 while the WT FLT3 RS4-11 (ALL cell line) and RA1 (Burkitt's Lymphoma cell line) are not sensitive toward TAK-659. In cultured human tumor cells, TAK-659 potently inhibits the growth of hematopoietic-derived cell lines, with a concentration producing half-maximal response (EC50) ranging from 11 to 775 nM in sensitive cell systems (eg, diffuse large B-cell lymphoma, and AML).
In vivo	In the FLT3-dependent MV4-11 xenograft model, TAK-659 shows tumor regression at 60 mg/kg daily after 20 days of dosing. Preliminary plasma and urine PK data show that TAK-659 was absorbed quickly (median Tmax 2-3 hrs), with moderate variability in steady-state exposures (40-50% CV for DN-AUCtau), mean peak/trough ratio of 3.2-4.2, and mean accumulation of 2.1- to 2.6-fold after 15 d QD dosing. Renal clearance (CLr) of unchanged drug accounts for 30-34% of apparent oral clearance, suggesting a CLr contribution of ≥30-34% to TAK-659 systemic clearance. TAK-659 blocks anti-IgD (immune-globulin D antibody) stimulated CD86 expression in mouse peripheral B cells in vivo.

Kinase Assay	Kinases are prepared in Base Reaction Buffer (20 mM Hepes pH 7.5, 10 mM MgCl2, 1 mM EGTA, 0.02% Brij35, 0.02 mg/mL BSA, 0.1 mM Na3VO4, 2 mM DTT, 1% DMSO) and substrate is added with 1.5 mM CaCl2, 16 μg/mL Calmodulin, and 2 mM MnCl2. Varying concentrations of SAR-20347 in DMSO are added to the kinase reaction along with 10 μM 33P-ATP (activity 0.01 μCi/μL final) for IC50 determination[1].
Cell Research	Cell lines: FLT3-dependent cell lines (MV4-11 and MOLM-13)Cells are maintained at 37°C in a humidified atmosphere containing 5-8% CO2. In a panel of hematological and solid tumor cell lines, inhibition of cell viability is determined using the soluble tetrazolium salt, MTS. Cells are seeded in 96-well tissue culture plates and are incubated at 37°C/5% CO2 for 24 hours prior to addition of compounds or DMSO vehicle. After 72 or 96 hours of incubation with compounds, MTS conversion by metabolically active cells is determined by measuring the OD490 nm of the wells using a Thermomax microplate reader. To generate concentration-response curves, cells are treated in duplicate with a range of serial compound dilutions. Prior to addition to cells, compound dilutions are prepared in DMSO. Equal amounts of DMSO are added to cells (final concentration is 0.5%). After background correction and normalization against DMSO-treated cells, EC50 values are calculated by curve-fitting these cell viability results using nonlinear regression analysis.
Animal Research	Animal Models: Athymic nude mice. Formulation: 0.5% carboxymethylcellulose (CMC). Dosages: 10,30,60 mg/kg QD. Administration: by oral gavage

Solubility Information

Solubility	DMSO: 1mg/ml,Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.6257 mL	13.1285 mL	26.2571 mL
5 mM	0.5251 mL	2.6257 mL	5.2514 mL
10 mM	0.2626 mL	1.3129 mL	2.6257 mL
50 mM	0.0525 mL	0.2626 mL	0.5251 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

Lam B, et al. Discovery of TAK-659 an orally available investigational inhibitor of Spleen Tyrosine Kinase (SYK). Bioorg Med Chem Lett. 2016 Dec 15;26(24):5947-5950.