Product Data Sheet

Product Name: TAK-659
Cat. No.: GC37723

Chemical Properties

Cas. No.	1312691-33-0		
SMILES	FC1=C(N[C@@H]2CCCC[C@@H]2N)N=C(C3=CN(C)N=C3)C4=C1CNC4=O		
Formula	$C_{17}H_{21}FN_6O$	M.Wt	344.39
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	TAK-659		

Background

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.

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[1]. 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 a broad kinase panel, TAK-659 demonstrates a more than 50-fold selectivity for SYK and FLT-3 over 290 other protein kinases[2]. 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-

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

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[3].

TAK-659 blocks anti-IgD (immune-globulin D antibody) stimulated CD86 expression in mouse peripheral B cells 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[1]. 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. Oral TAK-659 has an acceptable PK and safety profile in pts with solid tumors or lymphoma, supporting continuous oral QD dosing[4].

[1] Lam B, et al. Bioorg Med Chem Lett. 2016, 26(24):5947-5950. [2] Jie Yu, et al. Journal of Clinical Oncology. 2016, 34 (15_suppl). [3] Noelia Purroy, et al. Oncotarget. 2017, 8(1): 742-756.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA