CGI-1746

Cat. No.: HY-11999

CAS No.: 910232-84-7

Molecular Formula: $C_{34}H_{37}N_5O_4$

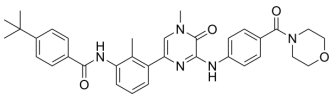
Molecular Weight: 579.69

Target: Btk; Autophagy

Pathway: Protein Tyrosine Kinase/RTK; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 50 mg/mL (86.25 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7251 mL	8.6253 mL	17.2506 mL
5 mM	0.3450 mL	1.7251 mL	3.4501 mL
10 mM	0.1725 mL	0.8625 mL	1.7251 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.31 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.31 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.31 mM); Suspended solution

BIOLOGICAL ACTIVITY

Description

CGI-1746 is a potent and highly selective inhibitor of the Btk with IC_{50} of 1.9 nM.

IC_{50} & Target

IC50: 1.9 nM (Btk)

In Vitro

CGI1746 is specific for Btk, with appr 1,000-fold selectivity over Tec and Src family kinases. In an ATP-free competition binding assay, the dissociation constant for Btk is 1.5 nM. CGI1746 inhibits Btk activity in a new binding mode that stabilizes

	an inactive nonphosphorylated enzyme conformation. CGI1746 inhibits both auto- and transphosphorylation steps necessary for enzyme activation. CGI1746 completely inhibits anti-IgM-induced murine and human B cell proliferation, with IC_{50}s of 134 nM and 42 nM, respectively, but has no effect on anti-CD3- and anti-CD28-induced T cell proliferation. CGI1746 potently inhibits the proliferation of CD27+IgG+ B cells isolated from the tonsils of four human donors with an average IC_{50} of 112 nM. In macrophages, CGI1746 abolishes FcγRIII-induced TNFα, IL-1β and IL-6 production. CGI1746 potently inhibits TNFα, IL-1β and, to a lesser extent, IL-6 (three- to eight-fold higher IC_{50}) production in human monocytes stimulated with immobilized or soluble immune complexes[1]. CGI-1746 does not kill cells as well as the irreversible BTK inhibitors at the same drug concentration. CGI-1746 significantly reduces phosphorylation of both the BTK-A and BTK-C proteins, indicating the auto-phosphorylation of the BTK-C isoform is inhibited in a manner similar to BTK-A. CGI-1746 does not kill LNCaP or DU145 prostate cancer cells at the same concentrations as Ibrutinib or AVL-292, but it demonstrates similar inhibition of BTK phosphorylation at tyrosine 233 in the SH3 domain[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CGI1746 abrogates B cell-dependent arthritis. CGI1746 treatment (100 mg/kg, s.c, twice-daily dosing) results in significant inhibition (97%) of overall clinical arthritis scores. CGI1746 treatment substantially reduces TNFα, IL-1β and IL-6, as well as MCP1 and MIP-1α on both the mRNA and protein level in the passive anti-collagen II antibody-induced arthritis (CAIA) model. CGI1746 shows comparable efficacy to TNFα blockade and significantly reduces clinical scores, as well as joint inflammation, in mice or rats with established arthritis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	5×10^3 DU145 cells or 10^4 LNCaP cells per well, grown on 96 well plates for 24h, are treated with 1 to 30 μM BTK inhibitors. Cells are fixed after 72h with 2.5% formaldehyde, and stained with Hoechst 33342. Control cells are treated with DMSO. Cell images are acquired using an IN Cell Analyzer 2200 high content imaging system, with a 20X objective. At least 9 fields are imaged per single well of each experiment. Cell numbers are determined and statistics performed using IN Cell Investigator 3.4 high content image analysis software. Each experiment is replicated 3 times, and data are presented as mean±SD. Results are considered significant if $p < 0.05$. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Leukemia. 2021 Feb 1.
- Mol Pharmacol. 2017 Mar;91(3):208-219.
- Patent. US20190040013A1.
- J Biomol Screen. 2015 Aug;20(7):876-86.

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REFERENCES

[1]. Di Paolo, Julie A. et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nature Chemical Biology (2011), 7(1), 41-50

[2]. Kokabee L, et al. Bruton's tyrosine kinase is a potential therapeutic target in prostate cancer. Cancer Biol Ther. 2015;16(11):1604-15

Caution: Product has not been fully validated for medical applications. For research use only.

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