上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：CGI-1746
产品别名：CGI-1746

生物活性：

Description	CGI-1746 is a potent and highly selective inhibitor of the Btk with IC50 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 IC50s 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 IC50 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 IC50) 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].
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].

In Vitro:

DMSO : ≥ 50 mg/mL (86.25 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" 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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

Solvent&Solubility	请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (4.31 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.31 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (4.31 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (4.31 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.31 mM); Suspended solution 此方案可获得 ≥ 2.5 mg/mL (4.31 mM，饱和度未知) 的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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 $p < 0.05$. [2]
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.