TG101209

Cat. No.: HY-10410

CAS No.: 936091-14-4

Molecular Formula: $C_{26}H_{35}N_7O_2S$

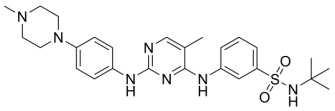
Molecular Weight: 509.67

Target: FLT3; JAK; RET; Autophagy; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt; Autophagy; Apoptosis

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 (98.10 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	1.9621 mL	9.8103 mL	19.6205 mL
5 mM	0.3924 mL	1.9621 mL	3.9241 mL
10 mM	0.1962 mL	0.9810 mL	1.9621 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: ≥ 2.75 mg/mL (5.40 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (5.40 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

TG101209 is a selective JAK2 inhibitor with IC_{50} of 6 nM, less potent to Flt3 and RET with IC_{50} of 25 nM and 17 nM, appr 30-fold selective for JAK2 than JAK3, and sensitive to JAK2V617F and MPLW515L/K mutations.

IC_{50} & Target

JAK2	JAK3	RET	FLT3
6 nM (IC_{50})	169 nM (IC_{50})	17 nM (IC_{50})	25 nM (IC_{50})

In Vitro

TG101209 is an orally bioavailable, small molecule, ATP-competitive inhibitor towards several tyrosine kinases. TG101209 inhibits growth of Ba/F3 cells expressing JAK2V617F or MPLW515L mutations with an IC_{50} of 200 nM. In a human JAK2V617F-

	expressing acute myeloid leukemia cell line, TG101209 induces cell cycle arrest and apoptosis, and inhibits phosphorylation of JAK2V617F, STAT5 and STAT3. TG101209 suppresses growth of hematopoietic colonies from primary progenitor cells harboring JAK2V617F or MPL515 mutations[1]. TG101209 significantly reduces STAT5 phosphorylation without affecting the total amount of STAT5 protein[2]. TG101209 inhibits survivin and reduces phosphorylation of STAT3 in HCC2429 and H460 lung cancer cells. TG101209 results in radio sensitization of HCC2429 and H460 lung cancer cells in vitro[3]. A recent study indicates TG101209 abrogates BCR-JAK2 and STAT5 phosphorylation, decreases Bcl-xL expression and triggers apoptosis of transformed Ba/F3 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	TG101209 (100 mg/kg) effectively prolongs the survival in JAK2V617F-induced disease (10 days). Compared with placebo-treated animals, TG101209-treated animals exhibit statistically significant, dose-dependent reduction in the circulating tumor cell burden at day +11 to 20%[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	In brief, approximately 2×10^3 cells are plated into microtiterplate wells in 100 mL RPMI-1640 growth media with indicated concentrations of TG101209. The relative growth of cells is quantified at 24-hour intervals using Cell Proliferation Kit II (XTT) as per manufacturer's guidelines. After incubation, 20 mL of XTT is added to the wells and allowed to incubate for 4-6 hours. The colored formazan product is measured spectrophotometrically at 450 nm with correction at 650 nm, and IC_{50} values are determined using the GraphPad Prism 4.0 software. Data are subjected to a non-linear regression-fit analysis and IC_{50} values are determined as the concentration that inhibits proliferation by 50%. All experiments are done in triplicate and the results normalized to growth of untreated cells. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Severe combined immunodeficiency (SCID) mice are intravenously injected with 10 times 10^6 sorted GFP-positive BaF/3 cells expressing JAK2V617F (Ba/F3-V617F-GFP). TG101209 is administered by oral gavage at the indicated doses beginning day +3 after tumor cell infusion and ending on day +20. On day +11 following tumor cell injection, 1 mL blood is collected by terminal cardiac bleeding from the mouse that receives vehicle, and 0.1 mL of blood is collected by non-lethal retro-orbital collection from each of the three six-mouse groups dosed with 10, 30 or 100 mg/kg b.i.d. (twice daily) of TG101209, and samples pooled within the dose groups. Blood mononuclear cells are isolated by a Ficoll cushion centrifugation method (600 RCF and 30 min). The isolated cells are subjected to FACS analysis to determine the percentage of GFP-positive tumor cells (that is, Ba/F3-V617F-GFP cells). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Elife. 2020 May 15;324:46-53.
- Biomed Pharmacother. 2020 Dec;132:110856.
- Eur J Pharmacol. 2021 Jan 15;891:173753.
- J Pharm Pharm Sci. 2021;24:1-15.

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REFERENCES

[1]. Pardanani A, et al. TG101209, a small molecule JAK2-selective kinase inhibitor potently inhibits myeloproliferative disorder-associated JAK2V617F and MPLW515L/K mutations. Leukemia. 2007 Aug;21(8):1658-68.

[2]. Ma AC, et al. A novel zebrafish jak2a(V581F) model shared features of human JAK2(V617F) polycythemia vera. Exp Hematol. 2009 Dec;37(12):1379-1386.e4.

[3]. Sun Y, et al. Inhibition of JAK2 signaling by TG101209 enhances radiotherapy in lung cancer models. J Thorac Oncol. 2011 Apr;6(4):699-706

[4]. Cuesta-Dominguez A, et al. Transforming and tumorigenic activity of JAK2 by fusion to BCR: molecular mechanisms of action of a novel BCR-JAK2 tyrosine-kinase. PLoS One. 2012;7(2):e3245

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA