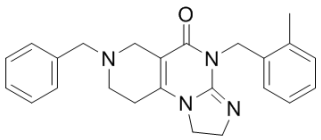
TIC10

Cat. No.:	HY-15615A
CAS No.:	1616632-77-9
Molecular Formula:	$C_{24}H_{26}N_4O$
Molecular Weight:	386.49
Target:	TNF Receptor; Apoptosis
Pathway:	Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 31.25 mg/mL (80.86 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5874 mL	12.9369 mL	25.8739 mL
	5 mM	0.5175 mL	2.5874 mL	5.1748 mL
	10 mM	0.2587 mL	1.2937 mL	2.5874 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 (6.47 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.47 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.47 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

TIC10 (ONC-201) is a potent, orally active, and stable tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) inducer which acts by inhibiting Akt and ERK, consequently activating Foxo3a and significantly inducing cell surface TRAIL. TIC10 can cross the blood-brain barrier[1].

IC_{50} & Target

TRAIL

In Vitro

TIC10 transcriptionally induces TRAIL in a p53-independent manner and crosses the blood-brain barrier[1].

	TIC10 induces a sustained up-regulation of TRAIL in tumors and normal cells that may contribute to the demonstrable antitumor activity of TIC10[1]. TIC10 inactivates kinases Akt and extracellular signal-regulated kinase (ERK), leading to the translocation of Foxo3a into the nucleus, where it binds to the TRAIL promoter to up-regulate gene transcription[1]. TIC10 is an efficacious antitumor therapeutic agent that acts on tumor cells and their micro-environment to enhance the concentrations of the endogenous tumor suppressor TRAIL[1]. TIC10 also causes a down-regulation of the total expression of ERK[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In DLD-1 colon cancer xenografts, TIC10 induces tumor stasis at 1 week after treatment, whereas TRAIL-treated tumors progress after a single dose. A single dose of TIC10 also induces a sustained regression of the SW480 xenograft and is equally effective when delivered by intraperitoneal or oral route, suggesting favorable oral bioavailability for TIC10. Titration of a single oral dose of TIC10 in the HCT116 xenograft model reveals sustained antitumor efficacy at 25 mg/kg. Exposure to oral TIC10 at 25 mg/kg weekly for 4 weeks in immunocompetent mice does not cause any changes in selected serum chemistry markers. The same oral dosing schedule is applied to Eμ-myc transgenic mice, which spontaneously develop meta-static lymphoma from weeks 9 to 12 of age, and TIC10 significantly (P=0.00789) prolongs the survival of these mice by 4 weeks[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Floating and adherent cells are analyzed on a Coulter-Beckman Elite Epics cytometer. For surface TRAIL experiments, adherent cells are harvested by brief trypsinization, fixed in 4% paraformaldehyde in phosphate-buffered saline (PBS) for 20 min, incubated with an anti-TRAIL antibody at 1:250 overnight, washed and incubated with anti-rabbit Alexa Fluor 488 for 30 min, and analyzed. Cells are gated on forward and side scatter to eliminate debris and dead cells from the analysis. Surface TRAIL data are expressed as median fluorescence intensity relative to that of control samples unless indicated otherwise. Surface DR5 is analyzed similarly with an antibody from Imgenex. For sub-G_1content and cell cycle profile analysis, all cells are pelleted and ethanol-fixed, followed by staining with propidium iodide in the presence of RNase. Cell viability assays are carried out in 96-well black-walled clear-bottom plates with CellTiter-Glo[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] For subcutaneous xenografts, 4- to 6-week-old female athymic nu/nu mice are inoculated with 1×10^6 cells (2.5×10^6 for T98G) of the indicated cell lines in each rear flank as a 200-μL suspension of 1:1 Matrigel (BD)/PBS. All subcutaneous tumors are allowed to establish for 1 to 4 weeks after injection until reaching a volume of ~125 mm^3 before treatment initiation. All intraperitoneal and intravenous injections are given at a total volume of 200 μL. Oral formulations of TIC10 are administered by oral gavage and given as a 200 μL suspension containing 20% Cremophor EL, 10% DMSO, and 70% PBS. Tumors are monitored with digital calipers at indicated time points. All subcutaneous tumors are allowed to establish for 1-4 weeks post-injection until reaching a volume of ~125 mm^3 before treatment initiation. Relief of tumor burden is monitored for 3 weeks after disappearance of the tumor and confirmed by visual inspection after euthanasia. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2019 May 13;35(5):721-737.e9.
- Oncotarget. 2018 Jan 10;9(15):12020-12034.

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REFERENCES

[1]. Allen JE, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. Sci Transl Med. 2013 Feb 6;5(171):171ra17.

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