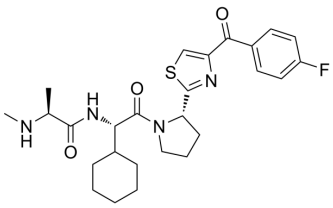
LCL161

Cat. No.:	HY-15518
CAS No.:	1005342-46-0
Molecular Formula:	$C_{26}H_{33}FN_4O_3S$
Molecular Weight:	501
Target:	IAP
Pathway:	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 : 100 mg/mL (199.60 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9960 mL	9.9800 mL	19.9601 mL
5 mM	0.3992 mL	1.9960 mL	3.9920 mL
10 mM	0.1996 mL	0.9980 mL	1.9960 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 (4.99 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.99 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.99 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LCL161 is a IAP inhibitor which inhibits XIAP in HEK293 cell and cIAP1 in MDA-MB-231 cell with IC_{50}s of 35 and 0.4 nM, respectively.

IC_{50} & Target

IC50: 35 nM (XIAP, in HEK293 cell), 0.40 nM (cIAP1, in MDA-MB-231)[1]

In Vitro

LCL161 shows anti-proliferative effects and reduces cell viability significantly in Hep3B (IC_{50}=10.23 μM) and PLC5 (IC_{50}=19.19 μM) cells in a dose-dependent manner. LCL161 induces apoptosis significantly in both the sensitive cell lines in a dose-

	dependent manner. LCL161 significantly down regulates the expression of cIAP1, starting at very low concentrations. LCL161 at low concentrations inhibits cIAP1 starting at the concentration of 0.5 nM[2]. LCL161 is a small molecule oral IAP antagonist in development for use in combination with cytotoxic agents. The effect of LCL161 on CYP3A4/5 (CYP3A) activity is investigated in vitro. Results in human liver microsomes indicated LCL161 inhibited CYP3A in a concentration- and time-dependent manner (K_I of 0.797 μM and K_{inact} of 0.0803 min^{-1}). LCL161 activates human PXR in a reporter gene assay and induced CYP3A4 mRNA up to ~5-fold in human hepatocytes[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Tumor-bearing mice are treated with vehicle or LCL161 p.o. at a dose of 50 mg/kg/day, or SC-2001 p.o. at a dose of 10 mg/kg/day, 5 days a week, or in combination for the duration of the study. Tumor growth is significantly inhibited by co-treatment with SC2001 and LCL161 and tumor size in the co-treatment group is only one third of that of the control group at the end of the study[2]. LCL161 is a first-in-class oral Smac mimetic shown to induce degradation of cIAP1 and cleavage of caspase 3 in mouse xenograft models[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	Cells are plated (3×10^4 viable cells/well) in 96-well clear bottom white plates and the plates are incubated for ~24 hours at 37°C (5% CO_2/95% air) in a humidified incubator. The cells (six replicate wells) are then treated with various concentrations (0.5, 1, 2.5, 5, 10, 25, or 50 μM) of LCL161, or vehicle control (0.1% DMSO, final concentration) for 24 hours in Puracyp dosing media. After the incubation period, the cells are washed with PBS, lysed and the luciferase substrate is added according to the vendor instructions. An aliquot of each well is transferred to the identical wells of black 96-well plates. The luminescence of each well is measured with a TopCount NXT Microplate Scintillation and Luminescence Counter. Cell viability is measured in separate plates treated identically to the PXR-reporter gene assay plates by measurement of ATP content of the cells using the CellTiter-Glo® Luminescent Cell Viability Assay kit. Cell viability is >80% for all treatments[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2][4]	Mice[2] Male NCr athymic nude mice (5-7 weeks of age) are used. Each mouse is inoculated s.c. in the dorsal flank with 1×10^6 Huh-7 cells suspended in 0.1 mL of serum-free medium containing 50% Matrigel. When tumors reach 200-300 mm^3, mice receives LCL161 (50 mg/kg) or SC-2001 (10 mg/kg) p.o., or a combination of LCL161 and SC-2001, once daily. Controls receive vehicle. Tumors are measured weekly using calipers and their volumes calculated using the following standard formula: $width^2\times length\times0.52$. LCL161 is a first-in-class oral Smac mimetic shown to induce degradation of cIAP1 and cleavage of caspase 3 in mouse xenograft models . Rats[4] LCL161 is administered orally, once weekly in 21-day cycles, at a starting dose of 10 mg (calculated by using one tenth of the dose that caused severe toxicity in 10% of rats and converted to a human-equivalent dose). In the MDA-MB-231 triple-negative breast cancer xenograft model, once-weekly and twice-daily LCL161 dosing are similarly efficacious. Once weekly is better tolerated, with reduced weight loss. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Res. 2023 Aug 14.
- Immunity. 2021 Aug 10;54(8):1758-1771.e7.
- Adv Mater. 2022 Nov 25;e2208782.
- Nat Commun. 2023 Oct 30;14(1):6908.
- Theranostics. 2023 Jul 31;13(13):4376-4390.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Maria Ahn, et al. Potent, Dual cIAP1/XIAP Antagonists Induce Apoptosis in a Melanoma Stem Cell Population.

[2]. Chen KF, et al. Inhibition of Bcl-2 improves effect of LCL161, a SMAC mimetic, in hepatocellular carcinoma cells. Biochem Pharmacol. 2012 Aug 1;84(3):268-77.

[3]. Dhuria S, et al. Time-dependent inhibition and induction of human cytochrome P4503A4/5 by an oral IAP antagonist, LCL161, in vitro and in vivo in healthy subjects. J Clin Pharmacol. 2013 Jun;53(6):642-53.

[4]. Infante JR, et al. Phase I dose-escalation study of LCL161, an oral inhibitor of apoptosis proteins inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2014 Oct 1;32(28):3103-10.

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