产品名称：LCL161
产品别名：LCL161

生物活性：

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 (IC50=10.23 μM) and PLC5 (IC50=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 (KI of 0.797 μM and Kinact 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].
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].
Solvent&Solubility	***In Vitro:*** **DMSO : DMSO : 100 mg/mL** (**199.75 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9975 mL	9.9874 mL	19.9748 mL
	5 mM	0.3995 mL	1.9975 mL	3.9950 mL
	10 mM	0.1997 mL	0.9987 mL	1.9975 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:

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 (4.99 mM); Clear solution、

此方案可获得 ≥ 2.5 mg/mL (4.99 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。

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.

实验参考：

Cell Assay	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% CO2/95% 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].
Animal Administration	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×length×0.52. 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.
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.