产品名称：GDC-0152
产品别名：GDC-0152

生物活性：

Description	GDC-0152 is a potent IAPs inhibitor, and binds to the BIR3 domains of XIAP, cIAP1, cIAP2 and the BIR domain of ML-IAP with K_i values of 28 nM, 17 nM, 43 nM and 14 nM, respectively.
IC_{50} & Target	Ki: 28 nM (XIAP BIR3), 14 nM (MLIAP-BIR3), 17 nM (cIAP1-BIR3), 43 nM (cIAP2-BIR3)
In Vitro	GDC-0152 can block protein−protein interactions that involve IAP proteins and pro-apoptotic molecules. Using transiently transfected HEK293T cells, GDC-0152 is shown to disrupt XIAP binding to partially processed caspase-9 and to disrupt the association of ML-IAP, cIAP1, and cIAP2 with Smac. In melanoma SK-MEL28 cells, the endogenous association of ML-IAP and Smac is also effectively abolished by GDC-0152. GDC-0152 leads to a decrease in cell viability in the MDA-MB-231 breast cancer cell line, while having no effect on normal human mammary epithelial cells (HMEC). GDC-0152 is found to activate caspases 3 and 7 in a dose- and time-dependent manner. GDC-0152 is shown to induce rapid degradation of cIAP1 in A2058 melanoma cells. It effectively induces degradation of cIAP1 at concentrations as low as 10 nM, consistent with its affinity for cIAP1[1].
In Vivo	GDC-0152 has moderate predicted hepatic clearance based on metabolic stability assays conducted using human liver microsomes. Plasma−protein binding of GDC-0152 is moderate and comparable among mice (88−91%), rats (89−91%), dogs (81−90%), monkeys (76−85%), and humans (75−83%) over the range of concentrations investigated (0.1−100 μM); higher plasma−protein binding is observed in rabbits (95−96%). GDC-0152 does not preferentially distribute to red blood cells with blood−plasma partition ratios ranging from 0.6 to 1.1 in all species tested. The pharmacokinetics for GDC-0152 is achieved with a C max of 53.7 μM and AUC of 203.5 h·μM[1].
Solvent&Solubility	***In Vitro:*** **DMSO： ≥ 100 mg/mL (200.55 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0055 mL	10.0273 mL	20.0545 mL
5 mM	0.4011 mL	2.0055 mL	4.0109 mL
10 mM	0.2005 mL	1.0027 mL	2.0055 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 (5.01 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.01 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 (5.01 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.01 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 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 (5.01 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.01 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 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]. Flygare JA, et al. Discovery of a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152). J Med Chem. 2012 May 10;55(9):4101-13.

实验参考：

Cell Assay	Detached cells are washed with phosphate-buffered saline (PBS) and are resuspended in assay media (MDA-MB-231 cells: RPMI1640 supplemented with 10% fetal bovine serum and 2 mM L-glutamine [GlutaMAX-1]) or culture media (HMECs: MEBM® with MEGM SingleQuots®). Cells are placed in tissue culture-treated, white-wall or black-wall, clear-bottom, 96-well plates at 1×10^4 cells/well in a volume of 50 μL. The plates are incubated at 37°C and 5% CO_2 overnight, the media is removed, and GDC-0152 or it's enantiomer are added in assay media. Cells cultured in white-wall, clear-bottom plates are incubated at 37°C and 5% CO_2 for 3 days before cell viability is measured using the CellTiter-Glo® luminescent cell viability assay kit.［1］
Animal Administration	Cells are resuspended in PBS and the cell suspension is mixed 1:1 with Matrigel. The cells (1.5×10^7) are then implanted subcutaneously into the right flank of 130 female nude mice aged 6-8 weeks. Tumor volumes are calculated. Ten mice with the appropriate mean tumor volume are assigned randomLy to each of six groups. The mean tumor volume±the standard error of the mean (SEM) for all six groups is 168±3 mm^3 at the initiation of treatment (Day 0). Mice are dosed 1 or vehicle (PBS) by oral gavage with a dose volume of 4.0 mL/kg. The mice are observed on each day of the study, and tumor volumes and body weights are measured twice each week. Percent tumor growth inhibition is calculated using the formula %TGI=100× (1- Tumor Volumedose/Tumor Volumevehicle). [1]
Kinase Assay	Inhibition constants (K_i) for the antagonists are determined by addition of the IAP protein constructs to wells containing serial dilutions of the antagonists or the peptide AVPW, and the Hid-FAM probe or AVP-diPhe-FAM probe, as appropriate, in the polarization buffer. Samples are read after a 30-minute incubation. Fluorescence polarization values are plotted as a function of the antagonist concentration, and the IC_{50} values are obtained by fitting the data to a 4-parameter equation using software. K_i values for the antagonists are determined from the IC_{50} valued. [1]
References	[1]. Flygare JA, et al. Discovery of a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152). J Med Chem. 2012 May

	10;55(9):4101-13.