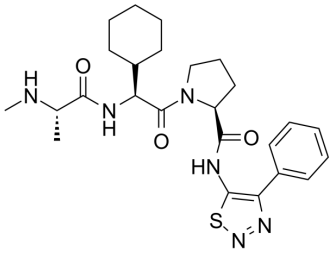
GDC-0152

Cat. No.:	HY-13638
CAS No.:	873652-48-3
Molecular Formula:	$C_{25}H_{34}N_6O_3S$
Molecular Weight:	498.64
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

Ethanol : 50 mg/mL (100.27 mM; Need ultrasonic)
DMSO : 50 mg/mL (100.27 mM; Need ultrasonic)

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

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 (5.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.01 mM); Clear solution

BIOLOGICAL ACTIVITY

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Immunol. 2018 Aug 24;3(26):eaat2738.
- Cell Death Differ. 2020 May;27(5):1569-1587.
- J Med Chem. 2019 Jun 13;62(11):5616-5627.

- Sci Signal. 2018 Jul 17;11(539). pii: eaao3964.
- J Taiwan Inst Chem Eng. June 2022, 104394.

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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.

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