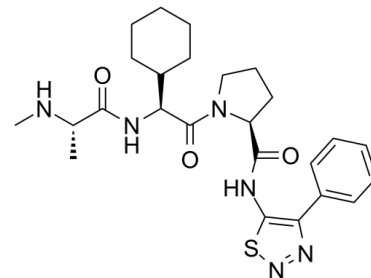


Data Sheet

Product Name:	GDC-0152
Cat. No.:	CS-3546
CAS No.:	873652-48-3
Molecular Formula:	C ₂₅ H ₃₄ N ₆ O ₃ S
Molecular Weight:	498.64
Target:	IAP
Pathway:	Apoptosis
Solubility:	Ethanol : 50 mg/mL (100.27 mM; Need ultrasonic); DMSO : ≥ 100 mg/mL (200.55 mM)



BIOLOGICAL ACTIVITY:

GDC-0152 is a potent **IAPs** inhibitor, and binds to the BIR3 domains of **XIAP**, **clAP1**, **clAP2** and the BIR domain of **ML-IAP** with **K_i** values of 28 nM, 17 nM, 43 nM and 14 nM, respectively. IC₅₀ & Target: Ki: 28 nM (XIAP BIR3), 14 nM (MLIAP-BIR3), 17 nM (clAP1-BIR3), 43 nM (clAP2-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, clAP1, and clAP2 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 clAP1 in A2058 melanoma cells. It effectively induces degradation of clAP1 at concentrations as low as 10 nM, consistent with its affinity for clAP1^[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].

PROTOCOL (Extracted from published papers and Only for reference)

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 IC₅₀ values are obtained by fitting the data to a 4-parameter equation using software. **K_i** values for the antagonists are determined from the IC₅₀ valued. **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 1×10⁴ cells/well in a volume of 50 μL. The plates are incubated at 37°C and 5% CO₂ 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% CO₂ for 3 days before cell viability is measured using the CellTiter-Glo[®] luminescent cell viability assay kit. **Animal Administration:** GDC-0152 is formulated in PBS.^[1]Cells are resuspended in PBS and the cell suspension is mixed 1:1 with Matrigel. The cells (1.5×10⁷) 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 \pm the standard error of the mean (SEM) for all six groups is $168 \pm 3 \text{ mm}^3$ 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 $\%TGI = 100 \times (1 - \text{Tumor Volume}_{\text{dose}} / \text{Tumor Volume}_{\text{vehicle}})$.

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.

CAIndexNames:

L-Prolinamide, N-methyl-L-alanyl-(2S)-2-cyclohexylglycyl-N-(4-phenyl-1,2,3-thiadiazol-5-yl)-

SMILES:

O=C(N1[C@H](C(NC2=C(C3=CC=CC=C3)N=NS2)=O)CCC1)[C@H](C4CCCCC4)NC([C@H](C)NC)=O

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 610-426-3128

Fax: 888-484-5008

E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA