

Product Data Sheet

Product Name: GDC-0152

Cat. No.: GC14451

Chemical Properties

Cas. No. 873652-48-3

Chemical Name (2S)-1-[(2S)-2-cyclohexyl-2-[(2S)-2-(methylamino)propanoyl]amino]acetyl]-N-(4-phenylthiadiazol-5-yl)pyrrolidine-2-carboxamide

SMILES CC(C(=O)NC(C1CCCCC1)C(=O)N2CCCC2C(=O)NC3=C(N=NS3)C4=CC=CC=C4)NC

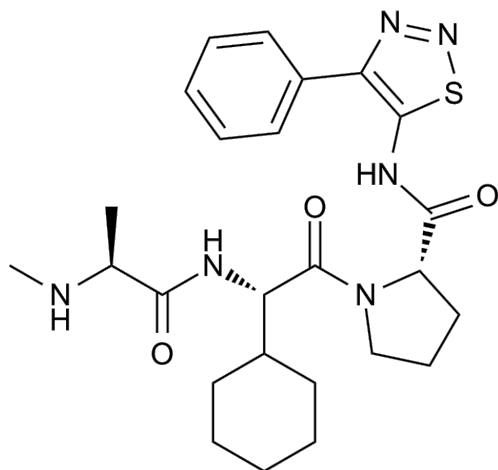
Formula $C_{25}H_{34}N_6O_3S$ M.Wt 498.64

Solubility ≥ 24.95 mg/mL in DMSO, ≥ 50.6 mg/mL in EtOH with ultrasonic and warming
Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Kinase experiment [1]:

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Fluorescence polarization-based competition assay

Inhibition constants (K_i) for the antagonists are determined by adding 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-min 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 KaleidaGraph software. K_i values for the antagonists are determined from the IC₅₀ values.

Cell experiment [1, 2]:

Cell lines

U87MG, GL261, GBM6, GBM9 cell lines, and MDA-MB-231 breast carcinoma cells

Preparation method

The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition

1 μ M or 100 μ M; 72h or 8 days; 10 nM-10 μ M; 3h-24h

Applications

GDC-0152 treatment triggered apoptosis and decreased IAP protein expression in glioblastoma cell lines. Moreover, GDC-0152 (10 nM-10 μ M) dose-dependently promoted degradation of cIAP1, induced caspase-3/7 activation, and lead to decreased viability of breast cancer cells.

Animal experiment [1, 2]:

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Animal models	100 000 U87MG-iRFP cells were injected into the corpus callosum of athymic nude mice; MDA-MB-231 breast cancer xenograft model;
Dosage form	10, 20, 50, and 100 mg/kg; intravenous injection or oral gavage; weekly for 2 months
Applications	GDC-0152 (10 mg/kg or 20 mg/kg) dose-dependently increased survival and slowed down tumor growth of mice bearing intracranial tumors. Moreover, GDC-0152 (10, 50, and 100 mg/kg) suppressed tumor growth in dose-dependent manner in the MDA-MB-231 breast cancer xenograft model.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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References:

1. Flygare, J. A., Beresini, M., Budha, N., Chan, H., Chan, I. T., Cheeti, S., Cohen, F., Deshayes, K., Doerner, K., Eckhardt, S. G., Elliott, L. O., Feng, B., Franklin, M. C., Reisner, S. F., Gazzard, L., Halladay, J., Hymowitz, S. G., La, H., LoRusso, P., Maurer, B., Murray, L., Plise, E., Quan, C., Stephan, J. P., Young, S. G., Tom, J., Tsui, V., Um, J., Varfolomeev, E., Vucic, D., Wagner, A. J., Wallweber, H. J., Wang, L., Ware, J., Wen, Z., Wong, H., Wong, J. M., Wong, M., Wong, S., Yu, R., Zobel, K. and Fairbrother, W. J. (2012) 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. 55, 4101-41132
2. Tchoghandjian, A., Souberan, A., Tabouret, E., Colin, C., Denicolai, E., Jiguet-Jiglaire, C., El-Battari, A., Villard, C., Baeza-Kallee, N. and Figarella-Branger, D. (2016) Inhibitor of apoptosis protein expression in glioblastomas and their in vitro and in vivo targeting by SMAC mimetic GDC-0152. Cell Death Dis. 7, e2325

Background

GDC-0152 is a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins, including ML-IAP, XIAP, cIAP1 and cIAP2, that binds to the BIR domain of ML-IAP and the BIR3 domains of XIAP, cIAP1 and cIAP2 with values of inhibition constant K_i of 14 nM, 28 nM, 17 nM and 43 nM respectively. GDC-0152 potentially inhibits tumor growth of breast cancer by promoting cIAP1 degradation and inducing caspase-3/7 activation which result in the decreasing of cell viability of breast cancer cells with normal epithelial cells unaffected. In recent studies, GDC-0152 shows its ability to disrupt the binding of XIAP to caspase-9 and the association of ML-IAP, cIAP1 and cIAP2 with Smac in HEK293T cells.

Reference

[1].Flygare JA, Beresini M, Budha N, Chan H, Chan IT, Cheeti S, Cohen F, Deshayes K, Doerner K, Eckhardt SG, Elliott LO, Feng B, Franklin MC, Reisner SF, Gazzard L, Halladay J, Hymowitz SG, La H, LoRusso P, Maurer B, Murray L, Plise E, Quan C, Stephan JP, Young SG, Tom J, Tsui V, Um J, Varfolomeev E, Vucic D, Wagner AJ, Wallweber HJ, Wang L, Ware J, Wen Z, Wong H, Wong JM, Wong M, Wong S, Yu R, Zobel K, Fairbrother WJ. Discovery of a potent small-molecule antagonist of

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inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152). J Med Chem. 2012;55(9):4101-4113

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