Rigosertib

Cat. No.: HY-12037A

CAS No.: 592542-59-1

Molecular Formula: $C_{21}H_{25}NO_8S$

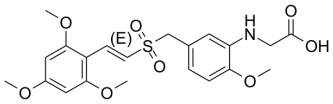
Molecular Weight: 451.49

Target: Polo-like Kinase (PLK); PI3K; Apoptosis

Pathway: Cell Cycle/DNA Damage; PI3K/Akt/mTOR; Apoptosis

Storage: -20°C, stored under nitrogen

* The compound is unstable in solutions, freshly prepared is recommended.



SOLVENT & SOLUBILITY

In Vitro

DMSO : 75 mg/mL (166.12 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2149 mL	11.0744 mL	22.1489 mL
	5 mM	0.4430 mL	2.2149 mL	4.4298 mL
	10 mM	0.2215 mL	1.1074 mL	2.2149 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 (5.54 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.54 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.54 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Rigosertib (ON-01910) is a multi-kinase inhibitor and a selective anti-cancer agent, which induces apoptosis by inhibition the PI3 kinase/Akt pathway, promots the phosphorylation of histone H2AX and induces G2/M arrest in cell cycle[1][2]. Rigosertib is a selective and non-ATP-competitive inhibitor of PLK1 with an IC_{50} of 9 nM[3].

IC_{50} & Target

PLK1 9 nM (IC_{50})	PLK2 260 nM (IC_{50})	PDGFR 18 nM (IC_{50})	Src 155 nM (IC_{50})
BCR-ABL 32 nM (IC_{50})	Cdk1 260 nM (IC_{50})	Flt1 42 nM (IC_{50})	Fyn 182 nM (IC_{50})

In Vitro	Rigosertib is non-ATP-competitive inhibitor of PLK1 with IC_{50} of 9 nM. Rigosertib also exhibits inhibition of PLK2, PDGFR, Flt1, BCR-ABL, Fyn, Src, and CDK1, with IC_{50} of 18-260 nM. Rigosertib shows cell killing activity against 94 different tumor cell lines with IC_{50} of 50-250 nM, including BT27, MCF-7, DU145, PC3, U87, A549, H187, RF1, HCT15, SW480, and KB cells. While in normal cells, such as HFL, PrEC, HMEC, and HUVEC, Rigosertib has little or no effect unless its concentration is greater than 5-10 μM. In HeLa cells, Rigosertib (100-250 nM) induces spindle abnormalities and apoptosis[3]. Rigosertib also inhibits several multidrug resistant tumor cell lines, including MES-SA, MES-SA/DX5a, CEM, and CEM/C2a, with IC_{50} of 50-100 nM. In DU145 cells, Rigosertib (0.25-5 μM) blocks cell cycle progression in G2/M phase, results in an accumulation of cells containing subG1 content of DNA, and activates apoptotic pathways. In A549 cells, Rigosertib (50 nM-0.5 μM) induces loss of viability and caspase 3/7 activation[4]. Rigosertib sodium (2 μM) induces apoptosis in chronic lymphocytic leukemia (CLL) cells without toxicity against T-cells or normal B-cells. Rigosertib sodium (2 μM) also abrogates the pro-survival effect of follicular dendritic cells on CLL cells and reduces SDF-1-induced migration of leukemic cells[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Rigosertib (250 mg/kg, i.p.) markedly inhibits tumor growth in mouse xenograft models of Bel-7402, MCF-7, and MIA-PaCa cells[3]. Rigosertib (200 mg/kg, i.p.) shows inhibition on tumor growth in a mouse xengraft model of BT20 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Recombinant PLK1 (10 ng) is incubated with different concentrations of Rigosertib in a 15 μL reaction mixture (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA, 2 mM Dithiothreitol, 0.01% NP-40 [pH 7.5]) for 30 min at room temperature. Kinase reactions are performed for 20 min at 30°C in a volume of 20 μL (15 μL enzyme + inhibitor, 2 μL 1 mM ATP), 2 μL of γ^{32}P-ATP (40 μCi), and 1 μL of recombinant Cdc25C (100 ng) or casein (1 μg) substrates. Reactions are terminated by boiling for 2 min in 20 μL of 2× Laemmli buffer. Phosphorylated substrates are separated by 18% SDS-PAGE. The gels are dried and exposed to X-ray film for 3-10 min. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Tumor cells are plated into six-well dishes at a density of 1×10^5 cells/mL/well, and Rigosertib is added 24 hours later at various concentrations. Cell counts are determined from duplicate wells after 96-hour of treatment. The total number of viable cells is determined by trypan blue exclusion. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Bel-7402 tumor models: twenty female athymic (NCR-nu/nu) nude mice are injected with 1×10^7 Bel-7402 tumor cells subcutaneously, and 10-14 days later, when the tumor volumes reach 200-250 mm, the mice are divided into four groups such that each group harbors tumors of the same volume. Rigosertib (ON01910, 250 mg/kg) dissolved in PBS is administered alone or in combination with NSC 266046 (100 mg/kg) intraperitonially on alternate days. Tumor measurements are done two times/week using traceable digital vernier calipers. Body weight is determined during each measurement. The animals are observed for signs of toxicity[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Oncol Res. 2021 Feb 11.
- Int J Biol Sci. 2020 Jun 27;16(13):2382-2391.
- Sci Rep. 2017 Aug 17;7(1):8629.
- Harvard Medical School LINCS LIBRARY

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[1]. Xu F, et al. Rigosertib as a selective anti-tumor agent can ameliorate multiple dysregulated signalingtransduction pathways in high-grade myelodysplastic syndrome. Sci Rep. 2014 Dec 4;4:7310.

[2]. Hyoda T, et al. Rigosertib induces cell death of a myelodysplastic syndrome-derived cell line by DNA damage-induced G2/M arrest. Cancer Sci. 2015 Mar;106(3):287-93.

[3]. Gumireddy K, et al. ON01910, a non-ATP-competitive small molecule inhibitor of Plk1, is a potent anticancer agent. Cancer Cell. 2005 Mar;7(3):275-86.

[4]. Reddy MV, et al. Discovery of a clinical stage multi-kinase inhibitor sodium (E)-2-{2-methoxy-5-[(2',4',6'-trimethoxystyrylsulfonyl)methyl]phenylamino}acetate (ON 01910.Na): synthesis, structure-activity relationship, and biological activity. J Med Chem. 2011 Sep 22;54(18):6254-76.

[5]. Chapman CM, et al. ON 01910.Na is selectively cytotoxic for chronic lymphocytic leukemia cells through a dual mechanism of action involving PI3K/AKT inhibition and induction of oxidative stress. Clin Cancer Res. 2012 Apr 1;18(7):1979-91

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