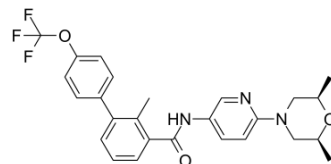


Sonidegib

Cat. No.:	HY-16582A		
CAS No.:	956697-53-3		
Molecular Formula:	C ₂₆ H ₂₆ F ₃ N ₃ O ₃		
Molecular Weight:	485.5		
Target:	Smo		
Pathway:	Stem Cell/Wnt		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (102.99 mM; Need ultrasonic)

Concentration	Solvent	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	2.0597 mL	10.2987 mL	20.5973 mL
	5 mM	0.4119 mL	2.0597 mL	4.1195 mL
	10 mM	0.2060 mL	1.0299 mL	2.0597 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.5 mg/mL (5.15 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: 2.5 mg/mL (5.15 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (5.15 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Sonidegib (Erismodegib) is a potent and selective Smo antagonist with IC₅₀ of 1.3 nM and 2.5 nM for mouse and human Smo in binding assay, respectively^[1].

IC₅₀ & Target

IC₅₀: 1.3 nM (mSmo), 2.5 nM (hSmo)^[1]

In Vitro

The IC₅₀ values for Sonidegib (NVP-LDE225) for the major human CYP450 drug metabolizing enzymes is greater than 10 μM^[1]. Sonidegib (LDE225), a small molecule, clinically investigated SMO inhibitor, used alone and in combination with Nilotinib,

inhibits the Hh pathway in CD34⁺ chronic phase (CP)-chronic myeloid leukaemia (CML) cells, reducing the number and self-renewal capacity of CML leukaemia stem cell (LSC). Sonidegib interacts directly with SMO, in a similar fashion to cyclopamine, to reduce expression of downstream Hh signaling targets. Primary CD34⁺ CP-CML cells are cultured in serum free media (SFM)±Sonidegib for 6, 24 and 72 hours (h). At 72 h, while there is variability between the biological samples, GLI1 is significantly downregulated following exposure to Sonidegib (10 nM; 0.78-fold and 100 nM; 0.73-fold, respectively (p<0.01) [2].

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

In Vivo

Sonidegib (NVP-LDE225) is a weak base with a measured pK_a of 4.2 and exhibits relatively poor aqueous solubility. In the subcutaneous Ptch^{+/-}p53^{-/-} medulloblastoma allograft mouse model, Sonidegib demonstrates dose-related antitumor activity after 10 days of oral administration of a suspension of the diphosphate salt. At a dose of 5 mg/kg/day qd, Sonidegib significantly inhibits tumor growth, corresponding to a T/C value of 33% (p<0.05 as compared to vehicle controls). When dosed at 10 and 20 mg/kg/day qd, Sonidegib affords 51 and 83% regression, respectively^[1]. Bone marrow cells and spleen cells from a subset of treated mice are transplanted into secondary recipient mice. Transplantation of either bone marrow (BM) or spleen cells from mice treated with Sonidegib (LDE225)+Nilotinib results in reduced white cell count (WCC) and reduces leukaemia development in secondary recipients compared to Sonidegib or Nilotinib alone^[2].

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PROTOCOL

Cell Assay [2]

CD34⁺ CP-CML cells are seeded in SFM alone±Sonidegib±Nilotinib and cultured for 24-72 h prior to assessment. Proliferation is measured using colorimetric assessment of BrDU incorporation. Proportion of viable cells versus those in early and late apoptosis is assessed by flow cytometry using annexin V-FITC and 7-amino-actinomycin D (7-AAD, Via-Probe solution). Cell cycle status is assessed using Ki67 (FITC) expression and 7-AAD incorporation.

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Animal Administration [2]

Mice^[2]

The transgenic EGFP⁺/SCLtTA/TRE-BCR-ABL mouse model is used to investigate the effect of Sonidegib treatment on CML LSC in vivo. Scl-tTa-BCR-ABL mice in the FVB/N background are crossed with transgenic GFP-expressing mice. Bone marrow cells are obtained 4 weeks post induction, GFP⁺ cells are selected by flow cytometry and transplanted by tail vein injection (10⁶ cells/mouse) into wild-type FVB/N recipient mice, irradiated at 900 cGy, generating a large cohort of mice with similar time of onset of leukemia. Blood samples obtained 4 weeks post transplantation confirmed a neutrophilic leukocytosis in recipient mice. Mice are treated with Nilotinib (50 mg/kg by gavage, daily), Sonidegib (80 mg/kg by gavage, daily), Sonidegib+Nilotinib, or with vehicle alone (control). After 3 weeks of treatment, animals are euthanised and marrow content of femurs and tibiae, spleen cells and blood obtained. Total white cell count (WCC), GFP-expressing WCC, myeloid cells, and GFP⁺ progenitors and stem cells are measured by flow cytometry. Survival is assessed in a subset of mice for 120d post discontinuation of treatment. Spleen and BM cells from a subset of mice in each arm are pooled and 5×10⁶ cells/mouse (8 mice/condition) are transplanted into wild-type FVB/N recipient mice irradiated at 900 cGy. Engraftment is monitored by drawing peripheral blood (PB) every 4 weeks. The percentage of GFP⁺ cells in PB is analyzed by flow cytometry.

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

CUSTOMER VALIDATION

- Nat Med. 2018 Nov;24(11):1752-1761.
- J Genet Genomics. 2018 May 20;45(5):237-246.
- Patent. US20180263995A1.
- Cell Physiol Biochem. 2018;47(4):1352-1364.

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REFERENCES

- [1]. Pan S, et al. Discovery of NVP-LDE225, a Potent and Selective Smoothed Antagonist. ACS Med Chem Lett. 2010 Mar 16;1(3):130-4.
- [2]. Irvine DA, et al. Deregulated hedgehog pathway signaling is inhibited by the smoothed antagonist LDE225 (Sonidegib) in chronic phase chronic myeloid leukaemia. Sci Rep. 2016 May 9;6:25476.
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Caution: Product has not been fully validated for medical applications. For research use only.