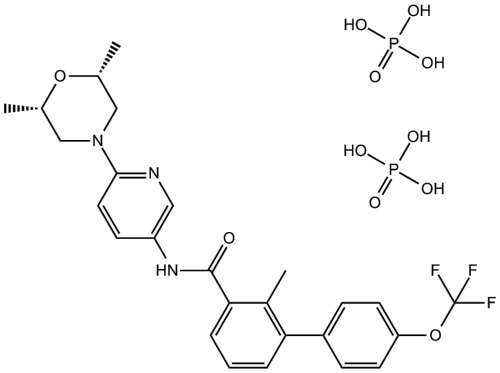
Product Data Sheet

Product Name: LDE225 Diphosphate
Cat. No.: GC14169

Chemical Properties

Cas. No.	1218778-77-8		
Chemical Name	N-[6-[(2S,6R)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl]-2-methyl-3-[4-(trifluoromethoxy)phenyl]benzamide;phosphoric acid		
SMILES	CC1CN(CC(O1)C)C2=NC=C(C=C2)NC(=O)C3=CC=CC(=C3C)C4=CC=C(C=C4)OC(F)(F)F.OP(=O)(O)O.OP(=O)(O)O		
Formula	$C_{26}H_{32}F_3N_3O_{11}P_2$	M.Wt	681.49
Solubility	≥ 27.85 mg/mL in DMSO	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

Cell experiment [1]:

Cell lines primary CD34+ CP-CML cells

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Preparation method	The solubility of this compound in DMSO is > 27.85 mg/mL. 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	10 nM, 100 nM, 72 hours
Applications	LDE225 (10 nM, 100 nM, 72 hours) inhibited downstream Hh signaling in primary CD34+ CP-CML cells. LDE225 (0.5-100 nM, 72h) significantly reduced colony forming cell (CFC) re-plating efficiency of primitive human CP-CML cells. LDE225 (10 nM) alone or in combination with nilotinib (5 μM) significantly reduced LTC-IC numbers in primary CD34+ CP-CML samples.

Animal experiment [1]:

Animal models	CP-CML murine model, BCR-ABL expressing mice
Dosage form	80 mg/kg by gavage, daily
Application	Treatment of Scl-tTa-BCR-ABL mice with LDE225+nilotinib resulted in inhibition of Gli1 in CP-CML BM LTHSC. LDE225 in combination with nilotinib on human CML LSC was capable of engrafting immunodeficient mice. LDE225+nilotinib administration significantly reduced leukaemia stem and progenitor cells in the spleen of BCR-ABL expressing mice.
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.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

References:

[1]. Irvine D A, Zhang B, Kinstrie R, et al. Deregulated hedgehog pathway signaling is inhibited by the smoothened antagonist LDE225 (Sonidegib) in chronic phase chronic myeloid leukaemia[J]. Scientific reports, 2016, 6: 25476.

Background

IC50: 1.3 and 2.5 nM for Mouse and Human Smo

LDE225 is a potent and selective smoothened antagonist. Smoothened (Smo) is a 7-pass transmembrane protein functioning as the key activator of the hedgehog (Hh) signaling pathway. Hh signaling is tightly controlled during cellular differentiation, proliferation, and embryonic morphogenesis. Hh signaling has been linked to tumorigenesis in several cancers.

In vitro: LDE225 was found to selectively bind to the Hedgehog (Hh)-ligand cell surface receptor Smo, which might result in the suppression of the Hh signaling pathway and, therefore, the inhibition of tumor cells in which this pathway was abnormally activated [1].

In vivo: In the subcutaneous medulloblastoma allograft mouse model, LDE225 demonstrated dose-related antitumor activity after 10 days of oral administration of a suspension. At a dose of 5 mg/kg/day qd, LDE225 inhibited tumor growth significantly, corresponding to a T/C value of 33%. When dosed at 10 and 20 mg/kg/day qd, LDE225 afforded 51 and 83% regression, respectively [1].

Clinical trial: In a phase I study, it was found that LDE225 had an acceptable safety profile in patients with advanced solid tumors and exhibited antitumor activity in advanced BCC and relapsed medulloblastoma, both of which were associated with hedgehog pathway strongly, as shown by gene expression [2].

References:

[1] Shifeng Pan,Xu Wu,Jiqing Jiang et al. Discovery of NVP-LDE225, a Potent and Selective Smoothened Antagonist. ACS Med Chem Lett. 2010 Jun 10; 1(3): 130–134.
[2] Rodon J,Tawbi HA,Thomas AL,Stoller RG,Turtschi CP,Baselga J,Sarantopoulos J,Mahalingam D,Shou Y,Moles MA,Yang L,Granvil C,Hurh E,Rose KL,Amakye DD,Dummer R,Mita AC. A phase I, multicenter, open-label, first-in-human, dose-escalation study of the oral smoothened inhibitor

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Sonidegib (LDE225) in patients with advanced solid tumors. Clin Cancer Res.2014 Apr 1;20(7):1900-9.