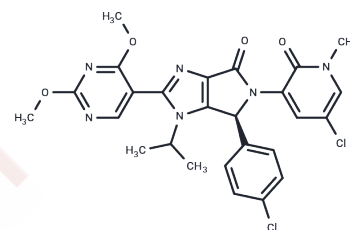


Siremadlin

Chemical Properties

CAS No. :	1448867-41-1
Formula:	C ₂₆ H ₂₄ Cl ₂ N ₆ O ₄
Molecular Weight:	555.41
Storage:	Powder: -20°C for 3 years In solvent: -80°C for 1 year Actual storage temperature shall be subject to the COA.



Biological Description

Description	Siremadlin (NVP-HDM 201) is a potent, orally bioavailable and highly specific p53-MDM2 interaction inhibitor.
Targets(IC50)	E1/E2/E3 Enzyme,MDM-2/p53
In vitro	Siremadlin inhibits both human and murine TP53- MDM2 interactions, with nanomolar cellular IC50 values, blocking TP53 degradation[1]
In vivo	Tumors are allografted in large cohorts of mice to assess the pharmacologic effects of Siremadlin (NVP-HDM201). Sixteen out of 21 allograft models are sensitive to Siremadlin (NVP-HDM201) but ultimately relapse under treatment[1]. Siremadlin has recently entered Phase 1 clinical trials in cancer patients[2]. Siremadlin (NVP-HDM201) administered either daily at a low dose or once at a high dose revealed a differentiated engagement of the p53 molecular response. In contrast to the daily low dose treatment regimen, the single high dose Siremadlin (NVP-HDM201) regimen results in a rapid and dramatic induction of p53-dependent PUMA expression and apoptosis. This is consistent with the finding that a single high dose Siremadlin (NVP-HDM201) treatment, administered orally or intravenously, results in a robust and sustained tumor regression. Overall, both daily and once every 3 weeks dosing regimen shows comparable long term efficacy in preclinical studies. The ongoing clinical trial is currently designed to compare both dosing regimens with regard to efficacy and tolerability[3].

Solubility Information

Solubility	DMSO: 150 mg/mL (270.07 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Saline: < 10 mg/mL (18 mM),Lower concentrations may be soluble, but exact solubility limit is unknown. 10% DMSO+40% PEG300+5% Tween 80+45% Saline: 10 mg/mL (18 mM),Solution. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.8005 mL	9.0024 mL	18.0047 mL
5 mM	0.3601 mL	1.8005 mL	3.6009 mL
10 mM	0.180 mL	0.9002 mL	1.8005 mL
50 mM	0.036 mL	0.180 mL	0.3601 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Chapeau EA, et al. Resistance mechanisms to TP53-MDM2 inhibition identified by in vivo piggyBac transposon mutagenesis screen in an Arf^{-/-} mouse model. *Proc Natl Acad Sci U S A*. 2017 Mar 21;114(12):3151-3156.

Furet P, et al. Discovery of a novel class of highly potent inhibitors of the p53-MDM2 interaction by structure-based design starting from a conformational argument. *Bioorg Med Chem Lett*. 2016 Oct 1;26(19):4837-41.

Stéphane F, et al. Abstract 1224: Insights into the mechanism of action of NVP-HDM201, a differentiated and versatile Next-Generation small-molecule inhibitor of Mdm2, under evaluation in phase I clinical trials. Insights into the mechanism of action of NVP-HDM201, a differentiated and versatile Next-Generation small-molecule inhibitor of Mdm2, under evaluation in phase I clinical trials. [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; *Cancer Res* 2016;76(14 Suppl):Abstract nr 1224.

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