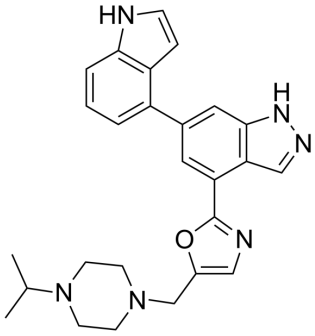
Nemiralisib

Cat. No.:	HY-19535A
CAS No.:	1254036-71-9
Molecular Formula:	$C_{26}H_{28}N_6O$
Molecular Weight:	440.54
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 33.33 mg/mL (75.66 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2699 mL	11.3497 mL	22.6994 mL
	5 mM	0.4540 mL	2.2699 mL	4.5399 mL
	10 mM	0.2270 mL	1.1350 mL	2.2699 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: ≥ 2.25 mg/mL (5.11 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.25 mg/mL (5.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Nemiralisib (GSK2269557 free base) is a potent and highly selective PI3Kδ inhibitor with a pK_i of 9.9.

IC_{50} & Target

PI3Kδ	PI3Kγ	PI3Kα	PI3Kβ
9.9 (pKi)	5.2 (pIC_{50})	5.3 (pIC_{50})	5.8 (pIC_{50})

In Vitro

Nemiralisib (GSK2269557 free base) is highly selective for PI3Kδ, with >1000-fold selectivity over the closely related isoforms PI3Kα (pIC_{50}=5.3), PI3Kβ (pIC_{50}=5.8) and PI3Kγ (pIC_{50}=5.2). Nemiralisib inhibits IFNγ in the peripheral blood mononuclear (PBMC) assay with an pIC_{50} of 9.7[1].

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

In Vivo	To assess the suitability of the series for inhaled delivery clearance data in rat microsomes and subsequently in vivo pharmacokinetic data from Sprague Dawley male rats is obtained. Compounds (e.g., Nemiralisib) are administered by the oral or intravenous routes, at a dose level of 3 and 1mg/kg respectively (n=2 rats/route). Nemiralisib free base is active in a disease relevant brown norway rat acute OVA model of Type 2 helper T-cells (Th2)-driven lung inflammation[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats[1] In vivo pharmacokinetics is tested in Sprague Dawley male rats. Compounds (e.g., Nemiralisib) are administered discretely by the oral or intravenous routes, at a dose level of 3 and 1 mg/kg respectively (n=2 rats/route). Compounds (e.g., Nemiralisib) are formulated as a solution in DMSO:PEG200:water (5:45:50 v/v/v) at a dose volume of 6 (oral) and 2 (intravenous) mL/kg. All animals are serially bled from the tail vein and blood samples collected over a time-course of 0-7 h are submitted to LC-MS/MS analysis for the quantification of the parent compound. The main pharmacokinetic parameters are estimated by non-compartmental analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Down K et al. Optimization of Novel Indazoles as Highly Potent and Selective Inhibitors of Phosphoinositide 3-Kinase δ for the Treatment of Respiratory Disease.J Med Chem. 2015 Sep 24;58(18):7381-99.

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