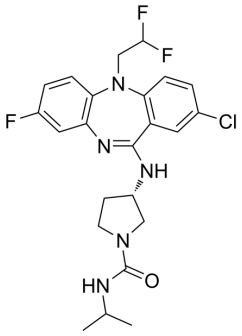
NVS-PAK1-1

Cat. No.:	HY-100519
CAS No.:	1783816-74-9
Molecular Formula:	$C_{23}H_{25}ClF_3N_5O$
Molecular Weight:	479.93
Target:	PAK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (208.36 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0836 mL	10.4182 mL	20.8364 mL
5 mM	0.4167 mL	2.0836 mL	4.1673 mL
10 mM	0.2084 mL	1.0418 mL	2.0836 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 (5.21 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

NVS-PAK1-1 is a potent and selective allosteric PAK1 inhibitor with an IC_{50} of 5 nM.

IC_{50} & Target

IC50: 5 nM (PAK1)[1]

In Vitro

NVS-PAK1-1 demonstrates high selectivity for inhibition of PAK1 over other PAK isoforms and the kinome in general. NVS-PAK1-1 has a biochemical PAK1 K_d of 7 nM and a PAK2 K_d of 400 nM. NVS-PAK1-1 shows excellent activity in biochemical assays and an exceptional selectivity profile against other known kinases. NVS-PAK1-1 at 6-20 μM inhibits the phosphorylation of the downstream substrate MEK1 Ser289. Consistent with the observation, NVS-PAK1-1 inhibits proliferation of Su86.86 cell line only above a concentration of 2 μM. In contrast, by applying a mixture of NVS-PAK1-1 and PAK2 shRNA, inhibition of downstream signaling and cell proliferation at a significantly lower 0.21 μM concentration are

	achieved[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	NVS-PAK1-1 shows a relatively poor stability in rat liver microsomes (RLM) and this would limit its application for in vivo studies ($t_{1/2}$ in RLM 3.5 min)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Inhibition of PAK1 kinase activity is measured using the Caliper assay. The assay is performed using 384-well microtiter plates. Compounds (NVS-PAK1-1) are tested as 8-point dose responses. The assays are prepared by addition of 50 nL of compound solution in 90% DMSO directly into the empty plate. Subsequently, 4.5 µL of the enzyme solution is added to each well and the resulting solution is pre-incubated at 30°C for 60 min, followed by addition of 4.5 µL of the peptide/ATP-solution. After 60 min incubation at 30°C, reactions are terminated by addition of 16 µL per well of the stop solution. Plates with terminated kinase reactions are transferred to the Caliper LC3000 workstations for reading. Product formation is measured in a microfluidic mobility shift assay. IC_{50} values are derived from percent inhibition values at different compound concentrations by non-linear regression analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- bioRxiv. 2023 Jun 11.

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REFERENCES

[1]. Karpov AS, et al. Optimization of a Dibenzodiazepine Hit to a Potent and Selective Allosteric PAK1 Inhibitor. ACS Med Chem Lett. 2015 May 22;6(7):776-81.

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