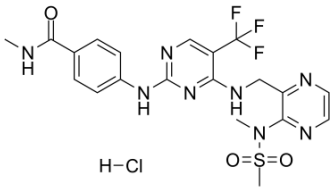
Defactinib hydrochloride

Cat. No.:	HY-12289A
CAS No.:	1073160-26-5
Molecular Formula:	$C_{20}H_{22}ClF_3N_8O_3S$
Molecular Weight:	546.95
Target:	FAK
Pathway:	Protein Tyrosine Kinase/RTK
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 : 30 mg/mL (54.85 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8283 mL	9.1416 mL	18.2832 mL
5 mM	0.3657 mL	1.8283 mL	3.6566 mL
10 mM	0.1828 mL	0.9142 mL	1.8283 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: ≥ 0.67 mg/mL (1.22 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.67 mg/mL (1.22 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.67 mg/mL (1.22 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Defactinib hydrochloride (VS-6063 hydrochloride; PF 04554878 hydrochloride) is a novel FAK inhibitor, which inhibits FAK phosphorylation at the Tyr397 site in a time- and dose-dependent manner.

IC_{50} & Target

FAK[1]

In Vitro

Defactinib (VS-6063) inhibits FAK phosphorylation at the Tyr397 site in a time- and dose-dependent manner. RPPA data

	shows that Defactinib reduces levels of AKT and YB-1 in taxane-resistant cell lines. The expression of pFAK (Tyr397) is statistically significantly inhibited by Defactinib in a dose-dependent manner in all cell lines. Defactinib inhibits pFAK (Tyr397) expression within 3 hours, with a gradual return of expression by 48 hours[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Defactinib (VS-6063) doses of 25 mg/kg twice a day or greater statistically significantly inhibits pFAK (Tyr397) at 3 hours, with return of expression noted by 24 hours. Therefore, administration of Defactinib at 25 mg/kg twice a day is selected as the dosing schedule for subsequent therapy experiments. For therapy experiments, female nude mice bearing HeyA8 tumors in the peritoneal cavity are randomly divided into 4 groups (n=10 per group): 1) vehicle orally twice daily and phosphate-buffered saline intraperitoneally weekly (control); 2) Defactinib 25 mg/kg orally twice daily; 3) PTX intraperitoneally weekly; and 4) both VDefactinib 25 mg/kg orally twice daily and PTX intraperitoneally weekly. There is an 87.4% reduction in tumor weight by PTX monotherapy in the HeyA8 model, and combination therapy resulted in the greatest tumor weight reduction, with a 97.9% reduction (P=0.05 compared with PTX). In the SKOV3ip1 model, a 92.7% tumor weight reduction is observed in the combination group compared with PTX (P<0.001)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] To determine the antitumor effects of Defactinib, SKOV3ip1, SKOV3-TR, HeyA8, and HeyA8-MDR cells are injected intraperitoneally. One week after tumor cell injection, mice are randomly assigned to 4 groups of 10 mice (control, PTX alone, Defactinib alone, and PTX with Defactinib); treatment is initiated at 3-4 weeks following injection. PTX at 2 mg/kg (SKOV3ip1 and SKOV3-TR) or 2.5 mg/kg (HeyA8 and HeyA8-MDR) is given intraperitoneally weekly; Defactinib at 25 mg/kg is given orally twice every day. Control mice received HBSS intraperitoneally once a week and vehicle orally twice every day. Mice are monitored daily for adverse effects of therapy and are killed on day 35 (SKOV3ip1 or SKOV3-TR), day 28 (HeyA8 or HeyA8-MDR), or when any of the mice seemed moribund. Total body weight, tumor incidence and mass, and the number of tumor nodules are recorded. Tumors are either fixed in formalin or embedded in paraffin or snap frozen in optimal cutting temperature (OCT) compound in liquid nitrogen. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367). pii: eaan4368.
- Nat Commun. 2019 Aug 16;10(1):3708.
- J Exp Clin Cancer Res. 2018 Jul 28;37(1):175.
- Mat Sci Eng C-mater. 2019 Oct.
- Sci Rep. 2019 May 20;9(1):7617.

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REFERENCES

[1]. Kang Y, et al. Role of focal adhesion kinase in regulating YB-1-mediated resistance in ovarian cancer. J Natl Cancer Inst. 2013 Oct 2;105(19):1485-95.

Caution: Product has not been fully validated for medical applications. For research use only.

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