VX-11e

Cat. No.: HY-14178

CAS No.: 896720-20-0

Molecular Formula: $C_{24}H_{20}Cl_2FN_5O_2$

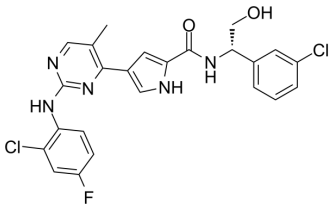
Molecular Weight: 500.35

Target: ERK

Pathway: MAPK/ERK Pathway; Stem Cell/Wnt

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 : ≥ 100 mg/mL (199.86 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9986 mL	9.9930 mL	19.9860 mL
5 mM	0.3997 mL	1.9986 mL	3.9972 mL
10 mM	0.1999 mL	0.9993 mL	1.9986 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: ≥ 3.25 mg/mL (6.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3.25 mg/mL (6.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

VX-11e is a potent, selective, and orally bioavailable inhibitor of ERK with K_i < 2 nM.

IC_{50} & Target

ERK2	GSK3	AURA	CDK2
2 nM (Ki)	395 (Ki)	540 (Ki)	852 (Ki)

In Vitro

VX-11e is active in the HT29 cell proliferation assay (IC_{50}=48 nM)[1].

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

In Vivo

VX-11e is orally bioavailable in both rat and mice[1]. VX-11e (50 mg/kg, p.o.) results in robust inhibition of pRSK, and inhibits

	tumor growth in NSG mice bearing human melanoma RPDX tumors. VX-11e with BKM120 significantly improves tumor growth inhibition[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Compounds are assayed for the inhibition of ERK2 by a spectophotometric coupled-enzyme assay. In this assay, a fixed concentration of activated ERK2 (10 nM) is incubated with various concentrations of the compounds in DMSO (2.5%) for 10 min. at 30°C in 0.1 mol/L HEPES buffer, pH=7.5, containing 10 mM $MgCl_2$, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase and 200 μM erktide peptide. The reaction is initiated by the addition of 65 μM ATP. The rate of decrease of absorbance at 340 nM is monitored. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cell proliferation is measured by ^{3}H-thymidine incorporation. The cells are plated at a concentration of 10,000 cells/well in a 96-well plate using growth media, RPMI 1640 containing 10% FBS. Serially diluted compounds are added. The cells and compounds are incubated for 48 hours at 37°C incubator. After 48 hours, 0.4 μCi of ^{3}H-thymidine is added to each wells for 8 hours and returned to the 37°C incubator. The cells are harvested using a Tomtec 96-well cell harvester and the CPM is determined using the Wallac 1205 BETAPLATE liquid scintillation counter. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Human melanoma RPDX tumors are expanded in vivo using NSG mice prior to the therapy experiments. Pooled tumor chunks banked from early mouse passages are implanted into 50 NSG mice (1:10 expansion). These tumors are harvested when reaching the maximum volume allowed on the protocol (1,000 mm^3), digested, and banked as live cells. The larger part of this stock is retained as a master bank, and the other part is implanted at a 1:5 ratio into NSG mice to use in the therapy experiments. The expansion phase is under continuous drug pressure with PLX4720 200 ppm chemical additive diet at approximately clinical plasma levels. The plasma levels of PLX4720 (103.7 μg/mL ±3.2 after 7 days) are similar to steady-state levels in patients treated with vemurafenib 960 mg twice a day (130.6 μg/mL±71.78). When tumors have reached 200 mm^3 per caliper measurement, animals are randomized into treatment groups followed by a 3-day ishout phase. Tumor size is assessed twice weekly per caliper measurement. Mice are sacrificed after two weeks of treatment or when necessary for animal welfare. Dosing is prolonged when tumor control is achieved as indicated. Tumor tissue is conserved in formalin (for FFPE) and snap-frozen in liquid N2 for protein extraction. Treatment groups are sacrificed 4 hours after last dose. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cell Death Dis. 2022 May 12;13(5):451.
- J Invest Dermatol. 2020 Sep 9;S0022-202X(20)32055-8.
- Stem Cells Dev. 2020 Jul 1;29(13):863-875.
- ACS Comb Sci. 2019 Dec 9;21(12):805-816.

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REFERENCES

[1]. Aronov, Alex M., et al. Structure-Guided Design of Potent and Selective Pyrimidylpyrrole Inhibitors of Extracellular Signal-Regulated Kinase (ERK) Using Conformational Control. Journal of Medicinal Chemistry (2009), 52(20), 6362-6368.

[2]. Krepler C, et al. Personalized Preclinical Trials in BRAF Inhibitor-Resistant Patient-Derived Xenograft Models Identify Second-Line Combination Therapies. Clin Cancer Res. 2016 Apr 1;22(7):1592-602.

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