Plixorafenib

Cat. No.: HY-18972

CAS No.: 1393466-87-9

Molecular Formula: $C_{25}H_{21}F_3N_6O_3S$

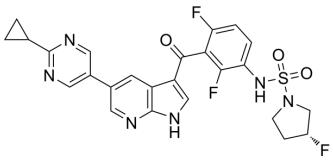
Molecular Weight: 542.53

Target: Raf

Pathway: MAPK/ERK Pathway

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 : ≥ 39 mg/mL (71.89 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8432 mL	9.2161 mL	18.4322 mL
5 mM	0.3686 mL	1.8432 mL	3.6864 mL
10 mM	0.1843 mL	0.9216 mL	1.8432 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 5 mg/mL (9.22 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.83 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PLX8394 is a potent and selective BRaf inhibitor, with an IC_{50} of appr 5 nM for $BRAF^{V600E}$.

IC_{50} & Target

$BRaf^{V600E}$

5 nM (IC_{50})

In Vitro

PLX8394 potently inhibits phosphorylation of ERK1/2 in PRT #3 and PRT #4 cells at >25 nM and in addition to parental cells at 10 nM. PLX8394 effectively reduces cyclin D3 and cyclin D1, phosphorylation of retinoblastoma protein, and expression of cyclin A2 in parental cells and PRT #3 and PRT #4 cells. PLX8394 inhibits ERK1/2 phosphorylation and the growth of PLX4032-resistant cells harboring either a BRAF V600K/L505H double mutation or an transposon-induced, N-terminal truncated form

	of BRAF[1]. PLX8394 significantly impairs tumor cell growth and suppresses MAPK signaling in LA cell lines expressing either endogenous V600E or non-V600 mutant forms of BRAF[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PLX8394 (150 mg/kg/d) substantially suppresses tumor growth, MAPK pathway signaling and tumor cell proliferation in these H1755 xenograft tumors without overt toxicity in mice. PLX8394 combines with CP-358774 yields plasma CP-358774 concentrations of >1 μM[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	For MTT assays, 2×10^3 cells are seeded in triplicate in 96 wells in their regular culture medium (containing PLX4720 for PRT lines). Next day, cells are washed twice with PBS and then the medium is replenished containing the indicated RAF inhibitor. Medium is changed 48 hours later and after a further 48 hours, 10 μL of 5 mg/mL MTT reagent is added to wells, and incubated for three hours. Formazan crystals are then solubilized overnight with a 1:10 dilution of 0.1 M glycine (pH 10.5) in DMSO. Wells are then analyzed at 450 nM in a Multiskan® Spectrum spectrophotometer. Results depicted are normalized to DMSO conditions and are a composite of three independent experiments. Error bars shown are representative of the standard error of mean (SEM). MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	H1755 tumor xenografts are generated by injection of 5×10^6 cells in a 50/50 mixture for matrigel and PBS into 6- to 8-wk-old female NOD/SCID mice. Mice are randomized to treatment groups once tumors reach an average size of 150 mm^3. H1755 cells are s.c. implanted and allowed to grow to appr 200 mm^3 (4 wk after implantation). Mice are then treated with vehicle, PLX4032, or PLX8394 for 15 d. The vehicle for daily oral gavage is PEG 400 [20% (vol/vol)], tocopheryl polyethylene glycol succinate (TPGS) [5% (vol/vol)], water [75% (vol/vol)]. PLX8394 is dissolved in PEG 400 [20% (vol/vol)], TPGS [5% (vol/vol)], and water [75% (vol/vol)] and vortexed continuously throughout the dosing period. PLX8394 is given daily by oral gavage at a dose of 150 mg/kg/d. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Discov. 2018 Sep;8(9):1130-1141.
- Nat Commun. 2022 Jul 15;13(1):4109.
- Nat Commun. 2021 Mar 19;12(1):1747.
- Nat Commun. 2018 Nov 14;9(1):4775.
- EMBO Mol Med. 2021 Mar 16;e13466.

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REFERENCES

[1]. Basile KJ, et al. Inhibition of mutant BRAF splice variant signaling by next-generation, selective RAF inhibitors. Pigment Cell Melanoma Res. 2014 May;27(3):479-484.

[2]. Okimoto RA, et al. Preclinical efficacy of a RAF inhibitor that evades paradoxical MAPK pathway activation in protein kinase BRAF-mutant lung cancer. Proc Natl Acad Sci U S A. 2016 Nov 22;113(47):13456-13461

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

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