PLX5622 hemifumarate

Cat. No.: HY-114153A

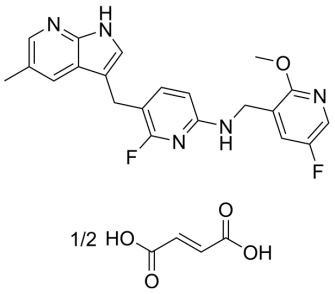
Molecular Formula: $C_{23}H_{21}F_2N_5O_3$

Molecular Weight: 453.45

Target: c-Fms

Pathway: Protein Tyrosine Kinase/RTK

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (220.53 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2053 mL	11.0266 mL	22.0531 mL
	5 mM	0.4411 mL	2.2053 mL	4.4106 mL
	10 mM	0.2205 mL	1.1027 mL	2.2053 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 (7.17 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3.25 mg/mL (7.17 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3.25 mg/mL (7.17 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PLX5622 hemifumarate is a highly selective brain penetrant and orally active CSF1R inhibitor (IC_{50}=0.016 μM; K_i=5.9 nM). PLX5622 hemifumarate allows for extended and specific microglial elimination, preceding and during pathology development. PLX5622 hemifumarate demonstrates desirable PK properties in varies animals[1][2].

IC_{50} & Target

CSF1R[1]

In Vitro

PLX5622 (1-20 μM; 3 days) hemifumarate effectively depletes microglia without affecting oligodendrocytes or astrocytes in cerebellar slices. PLX5622 (4 μM; 3 days) hemifumarate causes a 30-40% reduction in NG2+ or PDGFRα+ cells, and this increased to 90-95% at 20 μM. No reduction of NG2+ or PDGFRα+ OPCs is observed in slices exposed to 1 μM or 2 μM PLX5622

despite robust (~95%) depletion of the microglial cells[3].

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

In Vivo

Pharmacodynamics of PLX5622 hemifumarate in preclinical studies

PLX5622 (1200 ppm; chow; for 3 weeks or 3 days; adult C57/Bl6 wild type mice) hemifumarate leads to around 80% of microglia lost after 3 days of treatment and a 99% microglia loss after 3 weeks of treatment. PLX5622 (adult C57/Bl6 wild type mice aged 3 months; diet for 3 weeks) decreases microglia in cortex, striatum, cerebellum and hippocampus[4].

PLX5622 (50 mg/kg; intraperitoneal injection; once (neonatal rat) or twice (adult rat) a day; for a total of 14 days) hemifumarate depletes microglia by 80-90% within 3 days of treatment, which increases to > 90% by 7 days. After 14 days of PLX5622 treatment, microglia is depleted by > 96% in both neonates and adults while preserving baseline astrocyte quantity. (A single daily injection of 0.65% PLX5622 suspended in 5% dimethyl sulfoxide and 20% Kolliphor RH40 in 0.01 M PBS is sufficient for neonatal microglia depletion, adult depletion requires injections twice daily)[5].

PLX5622 (formulated in AIN-76A standard chow at 1200 mg/kg; for 28 days) hemifumarate leads to reduction in microglia throughout the CNS in 14-month-old 5xfAD mice[6].

Pharmacokinetics of PLX5622 hemifumarate in preclinical species[4]

Species	IV					PO (gavage)			
	Dose (mg/kg)	$AUC_{0-\infty}$ (ng•hr/mL)	CL (mL/min/kg)	Vss (L/kg)	$t_{1/2}$ (hr)	Dose (mg/kg)	$AUC_{0-\infty}$ (ng•hr/mL)	Cmax (ng/mL)	F
Mouse	1.92	15,500	2.1	0.34	2.6	45	215,000	26,300	59%
Rat (male)	1.13	2,630	7.7	1.2	2.3	45	99,600	12,000	95%
Rat (female)	1.13	5,110	3.7	1.0	3.9	45	181,000	15,600	89%
Dog	1.00	6,230	3.0	2.3	15	45	96,500	3,630	34%
Monkey	1.35	2,100	11	1.6	2.2	ND	ND	ND	ND

Preparation of gavage dosing suspensions for PLX5622 hemifumarate[4]

PLX5622 hemifumarate is dissolved in DMSO at a concentration that is 20x the final dosing solution. The compound stock is protected from light. A fresh stock is made each week.

The components of the diluent generally are prepared a day or more in advance because they take time to dissolve completely: a) 2% hydroxypropyl methyl cellulose (HPMC): 2.0 g powder was brought to 100 mL deionized water; b) 25% Polysorbate 80 (PS80): 25 g was brought to 100 mL deionized water. To make 100 mL diluent, add 25 mL of 2% HPMC stock (0.5% final) and 4 mL of 25% PS80 stock (1% final) to 71 mL deionized water to have final 100 mL. Final composition after mixing with compound: 0.5% HPMC, 1% PS80, 5% DMSO.

On each dosing day, the compound stock is diluted 20-fold as follows: 19 volumes of diluent are measured into the tube, and 1 volume of the 20x compound/DMSO stock is added. The cap is closed and the content of the tube is mixed by inversion and placed in a sonicating water bath to make a uniform suspension.

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

CUSTOMER VALIDATION

- Nature. 2021 Feb;590(7847):612-617.
- Cell. 2023 Sep 28;186(20):4454-4471.e19.

- J Exp Med. 2023 Mar 6;220(3):e20220857.
- Brain Behav Immun. 2023 Aug 28.
- EMBO Mol Med. 2022 Dec 21;e17175.

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REFERENCES

[1]. Spangenberg E, et al. Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model. Nat Commun. 2019 Aug 21;10(1):3758.

[2]. Lee S, et al. Targeting macrophage and microglia activation with colony stimulating factor 1 receptor inhibitor is an effective strategy to treat injury-triggered neuropathic pain. Mol Pain. 2018 Jan-Dec;14:1744806918764979.

[3]. Liu Y, et al. Concentration-dependent effects of CSF1R inhibitors on oligodendrocyte progenitor cells ex vivo and in vivo. Exp Neurol. 2019;318:32-41.

[4]. Badimon A, et al. Negative feedback control of neuronal activity by microglia. Nature. 2020;586(7829):417-423.

[5]. Andrew J. Riquier, et al. Astrocytic response to neural injury is larger during development than in adulthood and is not predicated upon the presence of microglia, Brain, Behavior, & Immunity-Health, Volume 1, 2020, 100010, ISSN 2666-3546.

[6]. Spangenberg EE, et al. Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology. Brain. 2016;139(Pt 4):1265-1281.

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