Sotuletinib

Cat. No.: HY-12768

CAS No.: 953769-46-5

Molecular Formula: $C_{20}H_{22}N_4O_3S$

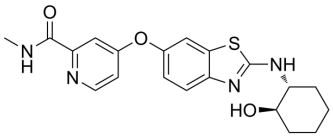
Molecular Weight: 398.48

Target: c-Fms

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 : 83.33 mg/mL (209.12 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5095 mL	12.5477 mL	25.0954 mL
	5 mM	0.5019 mL	2.5095 mL	5.0191 mL
	10 mM	0.2510 mL	1.2548 mL	2.5095 mL

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

In Vivo

1. Add each solvent one by one: 20% SBE-β-CD in saline
   Solubility: 10 mg/mL (25.10 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (5.22 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.22 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.22 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Sotuletinib (BLZ945) is a potent, selective and brain-penetrant CSF-1R (c-Fms) inhibitor with an IC_{50} of 1 nM, showing more than 1,000-fold selectivity against its closest receptor tyrosine kinase homologs[1].

IC_{50} & Target

IC50: 1 nM (CSF-1R), 3.2 μM (c-Kit), 4.8 μM (PDGFRβ), 9.1 μM (Flt3)[1]

In Vitro	Treatment of bone marrow-derived macrophages (BMDMs) with Sotuletinib inhibits CSF-1-dependent proliferation (EC_{50}=67 nM), and decreases CSF-1R phosphorylation, similar to CSF-1R antibody blockade. Sotuletinib also reduces viability of CRL-2467 microglia, Ink4a/$Arf^{?/?}$ BMDMs (PDG genetic background), and NOD/SCID BMDMs. Importantly, Sotuletinib treatment in culture does not affect proliferation of any PDG-derived tumor cell lines (all Csf-1r-negative), or U-87 MG human glioma cells, and PDG cell tumor sphere formation is unaffected. Thus, Sotuletinib has no direct effects on glioma cells, and perturbs macrophage survival through CSF-1R inhibition[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Mice are treated with Sotuletinib or vehicle, and evaluated for symptom-free survival. Median survival in the vehicle-treated cohort is 5.7 weeks. In striking contrast, Sotuletinib significantly improves long-term survival. This endpoint is chosen because Ink4a/$Arf^{?/?}$ mice develop spontaneous tumors, including lymphomas and sarcomas, beginning at ~30 weeks. Sotuletinib is well-tolerated over long-term treatment, with no visible side-effects, consistent with histopathological studies. Histological grading revealed high-grade, invasive gliomas in all vehicle-treated mice. By contrast, Sotuletinib-treated animals have significantly less-malignant tumors, and no detectable lesions in 55.6% of asymptomatic mice at the endpoint[1]. Mice receiving Sotuletinib shows reduced CSF1R staining in both cervical tumors and the associated stroma, with a significant decrease in $CSF1R^+$ stromal macrophages relative to vehicle-treated mice ($P<0.05$)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cell growth rate is determined using the MTT cell proliferation kit. Briefly, cells are plated in triplicate in 96-well plates: $1×10^3$ cells per well for glioma cell lines, $5×10^3$ cells per well for BMDM and CRL-2467, and $2.5×10^3$ cells per well for HUVEC and HBMEC cell lines. For all experiments, media is changed every 48 h. Cells are grown in the presence or absence of 6.7-6,700 nM of Sotuletinib, or 8 μg/mL of CSF-1R neutralizing antibody. To test the sensitivity to PDGFR inhibition, PDGC lines are cultured in the presence of 10,000 nM STI571 or 10,000 nM PTK787 (diluted from 10 mM stock solutions in DMSO). HUVEC and HBMEC cells are supplemented with ECGF supplied by the manufacturer unless otherwise indicated. Reduction of the MTT substrate is detected by colorimetric analysis using a plate reader as per the manufacturer's protocol. 10 μL of MTT labeling reagent is added to each well and then incubated for 4 h at 37°C, followed by the addition of 100 μL MTT solubilization reagent overnight. The mixture is gently resuspended and absorbance is measured at 595 nm and 750 nm on a spectraMax 340pc plate reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Tumors are measured using calipers and volumes calculated based on the formula: volume=$(width)^2$×length/2. In MMTV-PyMT mouse studies, 56-63 d old female mice are randomized into groups based on tumor volumes and dosed with either 20% Captisol vehicle or 200 mg/kg Sotuletinib. Dosing is administered by oral gavage once daily and tumor volumes are measured twice weekly. 5A1 rat anti-mouse CSF1 neutralizing antibody or rat IgG control is dosed at 10 mg/kg by intraperitoneal injection every 5 d. To calculate pulmonary metastasis in MMTV-PyMT transgenic mice, formalin-fixed paraffin-embedded lungs are serially sectioned and stained with hematoxylin and eosin. Tumor regions are scored by tumor burden (total tumor area divided by total lung area), size (tumor diameter), and according to the total number of individual metastases counted in a single-blind fashion. These values are averaged across the entire depth of the lung to obtain the final value. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Biomed Eng. 2018 Aug;2(8):578-588.
- Blood. 2019 Nov 28;134(22):1929-1940.
- Bioact Mater. 11 March 2022.

- J Exp Med. 2023 Mar 6;220(3):e20220857.
- J Exp Med. 2020 Nov 2;217(11):e20191820.

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REFERENCES

[1]. Pyonteck SM, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat Med. 2013 Oct;19(10):1264-72.

[2]. Strachan DC, et al. CSF1R inhibition delays cervical and mammary tumor growth in murine models by attenuating the turnover of tumor-associated macrophages and enhancing infiltration by CD8+ T cells. Oncoimmunology. 2013 Dec 1;2(12):e26968.

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