Crenolanib

Cat. No.: HY-13223

CAS No.: 670220-88-9

Molecular Formula: $C_{26}H_{29}N_5O_2$

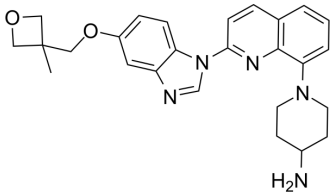
Molecular Weight: 443.54

Target: FLT3; PDGFR; Autophagy

Pathway: Protein Tyrosine Kinase/RTK; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (56.36 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2546 mL	11.2729 mL	22.5459 mL
	5 mM	0.4509 mL	2.2546 mL	4.5092 mL
	10 mM	0.2255 mL	1.1273 mL	2.2546 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: ≥ 3 mg/mL (6.76 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.43 mg/mL (3.22 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.43 mg/mL (3.22 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Crenolanib is a potent and selective inhibitor of wild-type and mutant isoforms of the class III receptor tyrosine kinases FLT3 and PDGFRα/β with K_ds of 0.74 nM and 2.1 nM/3.2 nM, respectively.

IC_{50} & Target

PDGFRα	PDGFRβ	FLT3
2.1 nM (Kd)	3.2 nM (Kd)	0.74 nM (Kd)

In Vitro

Crenolanib has 25-fold more affinity for PDGFRA/B compared with KIT, and is approximately 135-fold more potent than

	STI571 for inhibiting the PDGFRA D842V mutation. The IC_{50} for crenolanib for a KIT exon 11 deletion mutant kinase is greater than 1,000 versus 8 nM for STI571. Crenolanib has low nanomolar potency against the V561D + D842V-mutant kinase that is similar to its potency against the isolated D842V mutation. Both STI571 and crenolanib potently inhibit the kinase activity of the fusion oncogene with IC_{50} values of 1 and 21 nM, respectively, and inhibits PDGFRA activation in this cell line with IC_{50} values of 93 and 26 nM, respectively[1]. HL60/VCR and K562/ABCB1 cells, overexpressing ABCB1, are 6.9- and 3.6-fold resistant to crenolanib, respectively, in relation to parental HL60 and K562 cells. PSC-833 fully reverses resistance to crenolanib in both HL60/VCR and K562/ABCB1 cells. Crenolanib (1 nM-10 μM) stimulates ABCB1 ATPase activity in a concentration-dependent manner. Crenolanib treatment does not increase the cell surface expression of $ABCB_1$. Crenolanib inhibits [^{125}I]-IAAP photocrosslinking of ABCB1 at high concentrations, with 50 % inhibition at 10 μM, but has little effect at lower concentrations, below 1 μM[2]. Crenolanib decreases NSCLC cell viability, induces apoptosis in NSCLC cells, and inhibits cell migration in NSCLC cells[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Crenolanib (10 mg/kg and 20 mg/kg) suppresses non-small-cell lung cancer tumor growth in vivo and induces tumor cell apoptosis, and the dosage of crenolanib applied is well tolerated by recipient mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Viable cell numbers following drug treatment are measured using the WST-1 assay. Briefly, 1×10^3 cells are seeded in 100 μL complete medium per well in 96-well tissue culture plates and incubated with crenolanib (0-10 μM) at 37°C in 5% CO_2 for 96 h. 10 μL WST-1 reagent is then added to each well, incubation is continued for two additional hours and the color developed is quantified according to the manufacturer's instructions. Each experiment is performed in triplicate. IC_{50} concentrations are calculated by the least square fit of dose–response inhibition in a non-linear regression model using GraphPad Prism V software. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	A549 cells are injected into the axillary regions of mice (2×10^6 cells/mouse). When the tumor volumes reached 70 mm^3, the mice are randomLy allocated to the control group, low-dose crenolanib group (10 mg/kg), or high-dose crenolanib group (20 mg/kg) (n=6 per group). The vehicle for crenolanib treatment consists of 10% 1-methyl-2-pyrrolidinone and 90% polyethylene glycol 300. The tumor size and mouse body weight are measured every other day for about 2 weeks. The tumor volume is calculated as follows: (mm^3)=(width×width×length)/2. After treatment, the mice are euthanized using carbon dioxide, and the tumors are harvested and analyzed. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Blood. 2018 Jan 25;131(4):426-438.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Stem Cell Res Ther. 2015 Dec 10;6:243.
- J Med Chem. 2019 Mar 14;62(5):2428-2446.
- Br J Haematol. 2019 Nov;187(4):488-501.

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REFERENCES

[1]. Heinrich MC, et al.Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with STI571-resistant gastrointestinal stromal tumors. Clin Cancer Res, 2012, Jun 27.

[2]. Mathias TJ, et al. The FLT3 and PDGFR inhibitor crenolanib is a substrate of the multidrug resistance protein ABCB1 but does not inhibit transport function at pharmacologically relevant concentrations. Invest New Drugs. 2015 Apr;33(2):300-9.

[3]. Wang P, et al. Crenolanib, a PDGFR inhibitor, suppresses lung cancer cell proliferation and inhibits tumor growth in vivo. Onco Targets Ther. 2014 Sep 26;7:1761-8.

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