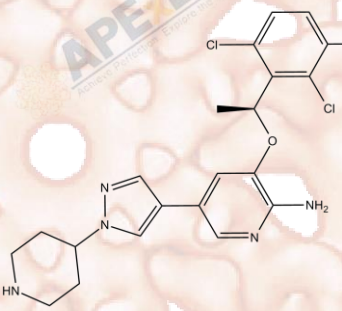
Product Data Sheet

(S)-Crizotinib



Cat. No.:	A8802
CAS No.:	877399-52-5;1374356-45-2
Formula:	C21H22Cl2FN5O
M.Wt:	450.34
Synonyms:	
Target:	DNA Damage/DNA Repair
Pathway:	MTH1
Storage:	Store at -20°C

Solvent & Solubility

In Vitro

⩾33.33 mg/mL in DMSO; insoluble in H2O; ⩾8.58 mg/mL in EtOH with ultrasonic

Preparing Stock Solutions

Mass / Solvent / Concentration	1mg	5mg	10mg
1 mM	2.2205 mL	11.1027 mL	22.2054 mL
5 mM	0.4441 mL	2.2205 mL	4.4411 mL
10 mM	0.2221 mL	1.1103 mL	2.2205 mL

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

Biological Activity

Shortsummary	Potent MTH1 inhibitor
IC_{50} & Target	72 nM (MTH1)

In Vitro

Cell Viability Assay

Cell Line:	BJ, H1437, H2122, H23, H358, H460, HCT116 and U2OS cells
Preparation method:	The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.
Reacting conditions:	BJ, SV40T, RASV12-cells (5 μM, 3h); U2OS cells (5 μM, 24h)

	Applications:	(S)-crizotinibthe selectively inhibited MTH1 catalytic activity with IC50 of 72 nM, while clinically used (R)-enantiomer of the drug was inactive with IC50 of 1375 nM. Furthermore, direct-binding assays (ITC) indicated a 16-fold higher affinity of the (S)-enantiomer towards MTH1 compared with (R)-enantiomer. By using Km concentrations of substrates, the average IC50 values for (S)-crizotinib and the MTH1 substrates 8-oxo-dGTP and 2-OH-dATP were 330 nM and 408 nM respectively. (S)-crizotinib efficiently inhibited colony formation of SW480 cells andKRAS-mutated PANC1 cells, similar to SCH51344. In addition, in vitro Kd measurements indicated that (S)-crizotinib was considerably less potent than the (R)-enantiomer against the established targets ALK,MET and ROS1. (S)-crizotinib did not lead to the detection of any significant effects on proliferation in SW480 cells and showed highest toxicity towards the SV40T and KRASV12 cells. (S)-crizotinib, in contrast to (R)-crizotinib, efficiently stabilized MTH1 validating the differential targeting within BJ-KRASV12 cells using a cellular thermal shift assay. (S)-crizotinib induced an increase in DNA single-strand breaks, activated DNA repair in human colon carcinoma cells, and effectively suppressed tumour growth in animal models as a result of disruption of nucleotide pool homeostasis via MTH1 inhibition.
In Vivo	**Animal experiment**	
	Animal models:	SCID mice (female, 5–6 weeks)
	Dosage form:	25 mg per kg,subcutaneously daily; 50 mg per kg, orally, daily
	Applications:	In vivo mouse xenograft studies showed (S)-crizotinib, but not the (R)-enantiomer, was able to impair overall tumour progression aswell as specifically reduce tumour volume by more than 50%.
	Other notes:	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

Product Citations

1. Qing X, Shao Z, et al. "Anticancer effect of (S)-crizotinib on osteosarcoma cells by targeting MTH1 and activating reactive oxygen species." Anticancer Drugs. 2018 Apr;29(4):341-352.PMID:29420337

2. Stewart E, Federico SM, et al. "Orthotopic patient-derived xenografts of paediatricsolid tumours." Nature. 2017 Sep 7;549(7670):96-100.PMID:28854174

3. Kawamura T, Kawatani M, et al. "Proteomic profiling of small-molecule inhibitors reveals dispensability of MTH1 for cancer cell survival." Sci Rep. 2016 May 23;6:26521.PMID:27210421

4. J Adachi, et al. "Proteome-wide discovery of unknown ATP-binding proteins and kinase inhibitor target proteins using an ATP probe." J Proteome Res. 2014 Sep 17.PMID:25230287

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References

1. Huber KVM, Salah E, Radic B, et al. Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy. NATURE,2014;508:222-227

Caution

FOR RESEARCH PURPOSES ONLY.

NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE.

Specific storage and handling information for each product is indicated on the product datasheet. Most APExBIO products are stable under the recommended conditions. Products are sometimes shipped at a temperature that differs from the recommended storage temperature. Shortterm storage of many products are stable in the short-term at temperatures that differ from that required for long-term storage. We ensure that the product is shipped under conditions that will maintain the quality of the reagents. Upon receipt of the product, follow the storage recommendations on the product data sheet.

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