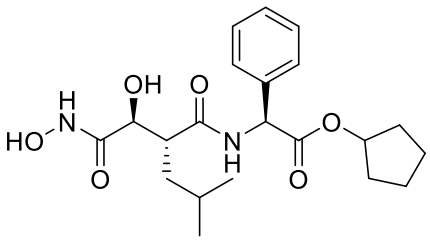
Product data sheet

MedKoo Cat#: 205648 Name: Tosedostat CAS#: 238750-77-1 Chemical Formula: $C_{21}H_{30}N_2O_6$ Exact Mass: 406.21039 Molecular Weight: 406.47	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Tosedostat is a proprietary orally bioavailable inhibitor of the M1 family of aminopeptidases with potential antineoplastic activity. Tosedostat is converted intracellularly into a poorly membrane-permeable active metabolite (CHR-79888) which inhibits the M1 family of aminopeptidases, particularly puromycin-sensitive aminopeptidase (PuSA), and leukotriene A4 (LTA4) hydrolase; inhibition of these aminopeptidases in tumor cells may result in amino acid deprivation, inhibition of protein synthesis due to a decrease in the intracellular free amino acid pool, an increase in the level of the proapoptotic protein Noxa, and cell death.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	42.0	103.33
Ethanol	28.0	68.89

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.46 mL	12.30 mL	24.60 mL
5 mM	0.49 mL	2.46 mL	4.92 mL
10 mM	0.25 mL	1.23 mL	2.46 mL
50 mM	0.05 mL	0.25 mL	0.49 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Krige D, Needham LA, Bawden LJ, Flores N, Farmer H, Miles LE, Stone E, Callaghan J, Chandler S, Clark VL, Kirwin-Jones P, Legris V, Owen J, Patel T, Wood S, Box G, Laber D, Odedra R, Wright A, Wood LM, Eccles SA, Bone EA, Ayscough A, Drummond AH. CHR-2797: an antiproliferative aminopeptidase inhibitor that leads to amino acid deprivation in human leukemic cells. Cancer Res. 2008 Aug 15;68(16):6669-79. doi: 10.1158/0008-5472.CAN-07-6627. PMID: 18701491.
2. Anbalagan S, Biasoli D, Leszczynska KB, Mukherjee S, Hammond EM. In Vitro Radiosensitization of Esophageal Cancer Cells with the Aminopeptidase Inhibitor CHR-2797. Radiat Res. 2015 Sep;184(3):259-65. doi: 10.1667/RR14150.1. Epub 2015 Aug 20. PMID: 26291737.

In vivo study

1. Krige D, Needham LA, Bawden LJ, Flores N, Farmer H, Miles LE, Stone E, Callaghan J, Chandler S, Clark VL, Kirwin-Jones P, Legris V, Owen J, Patel T, Wood S, Box G, Laber D, Odedra R, Wright A, Wood LM, Eccles SA, Bone EA, Ayscough A, Drummond AH. CHR-2797: an antiproliferative aminopeptidase inhibitor that leads to amino acid deprivation in human leukemic cells. Cancer Res. 2008 Aug 15;68(16):6669-79. doi: 10.1158/0008-5472.CAN-07-6627. PMID: 18701491.

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7. Bioactivity

Biological target:

Tosedostat (CHR-2797) is an orally active aminopeptidase inhibitor. CHR-2797 exerts antiproliferative effects against a range of tumor cell lines.

In vitro activity

he mechanistic link between aminopeptidase inhibition and antiproliferative effects was investigated by gene expression profiling in HL-60 cells treated with CHR-2797. Cells were treated with vehicle or 6 μmol/L CHR-2797, equivalent to 200× the IC50 for its inhibition of proliferation (30 nmol/L; Fig. 1A). Approximately, 40% of the genes represented on the microarray were expressed in HL-60 cells, and the expression of 2461 of these were increased or decreased by ⩾2-fold after treatment with CHR-2797.
CHR-2797 treatment also led to the up-regulation of a number of genes which have not previously been described as AADR genes. Treatment of HL-60 cells with CHR-2797 led to an increase in the secretion of STC2 protein into the growth medium (Supplementary Fig. S5).To determine whether the transcriptional effects of CHR-2797 were mediated by this signaling pathway, the levels of phosphorylated (Ser51) eIF2α were measured in HL-60 cells treated with the compound. Amino acid deprivation and treatment with CHR-2797 or bestatin caused an increase in phosphorylated eIF2α (Fig. 3A) In HL-60 cells, amino acid deprivation and treatment with bestatin or CHR-2797, but not its inactive analogue, CHR-3204, caused a decrease in the phosphorylation of both S6 kinase (Thr389) and 4E-BP1 (Thr37/46) at sites controlled by mTOR signaling (Fig. 3B and C) As CHR-2797 treatment inhibited the phosphorylation of key mTOR substrates, the effects of the compound on protein synthesis were measured. As expected, CHR-2797 treatment inhibited protein synthesis in HL-60 cells at concentrations as low as 0.06 μmol/L (Fig. 3D). These effects were much less pronounced in HuT 78 cells. The potential for synergy between CHR-2797 and agents targeting amino acid transporters is an obvious avenue to be explored.

Reference: Res. 2008 Aug 15;68(16):6669-79. https://cancerres.aacrjournals.org/content/68/16/6669.long

In vivo activity

The efficacy of CHR-2797 has been investigated in a range of in vivo tumor models, including syngeneic rat and human tumor xenografts. CHR-2797 is active as an anticancer agent in vivo in rodent cancer models, and a dose-response relationship has been shown in two models. The effect of CHR-2797 is less apparent when the tumor burden is higher before treatment (Supplementary Fig. S4).

Reference: Res. 2008 Aug 15;68(16):6669-79. https://cancerres.aacrjournals.org/content/68/16/6669.long

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.