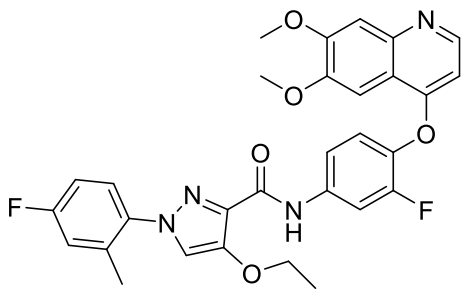
Product data sheet

MedKoo Cat#: 407188 Name: LDC1267 CAS#: 1361030-48-9 Chemical Formula: $C_{30}H_{26}F_2N_4O_5$ Exact Mass: 560.18713 Molecular Weight: 560.56	
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:

LDC1267 is a potent and selective TAM kinase inhibitor. LDC1267 displays lower activity against Met, Aurora B, Lck, Src, and CDK8. LDC1267 markedly reduced murine mammary cancer and melanoma metastases dependent on NK cells. The TAM tyrosine kinase receptors Tyro3, Axl and Mer (also known as Mertk) were identified as ubiquitylation substrates for Cbl-b. Treatment of wild-type NK cells with a newly developed small molecule TAM kinase inhibitor conferred therapeutic potential, efficiently enhancing anti-metastatic NK cell activity in vivo.

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	50.0	89.20

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.78 mL	8.92 mL	17.84 mL
5 mM	0.36 mL	1.78 mL	3.57 mL
10 mM	0.18 mL	0.89 mL	1.78 mL
50 mM	0.04 mL	0.18 mL	0.36 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. Paolino M, Choidas A, Wallner S, Pranjic B, Uribesalgo I, Loeser S, Jamieson AM, Langdon WY, Ikeda F, Fededa JP, Cronin SJ, Nitsch R, Schultz-Fademrecht C, Eickhoff J, Menninger S, Unger A, Torka R, Gruber T, Hinterleitner R, Baier G, Wolf D, Ullrich A, Klebl BM, Penninger JM. The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. Nature. 2014 Mar 27;507(7493):508-12. doi: 10.1038/nature12998. Epub 2014 Feb 19. PMID: 24553136; PMCID: PMC6258903.

In vivo study

1. Zou Z, Sun J, Kang Z, Wang Y, Zhao H, Zhu K, Wang J. Tyrosine Kinase Receptors Axl and MerTK Mediate the Beneficial Effect of Electroacupuncture in a Cuprizone-Induced Demyelinating Model. Evid Based Complement Alternat Med. 2020 Jul 4;2020:3205176. doi: 10.1155/2020/3205176. PMID: 32714402; PMCID: PMC7355344.
2. Paolino M, Choidas A, Wallner S, Pranjic B, Uribesalgo I, Loeser S, Jamieson AM, Langdon WY, Ikeda F, Fededa JP, Cronin SJ, Nitsch R, Schultz-Fademrecht C, Eickhoff J, Menninger S, Unger A, Torka R, Gruber T, Hinterleitner R, Baier G, Wolf D, Ullrich A, Klebl BM, Penninger JM. The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. Nature. 2014 Mar 27;507(7493):508-12. doi: 10.1038/nature12998. Epub 2014 Feb 19. PMID: 24553136; PMCID: PMC6258903.

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7. Bioactivity

Biological target:

LDC1267 is a highly selective TAM (Tyro3, Axl and Mer) kinase inhibitor with IC50s of <5 nM/8 nM/29 nM for Tyro3,Axl and Mer respectively.

In vitro activity

To assess whether modulation of the TAM/Cbl-b inhibitory pathway could be used for anti-tumor immunotherapy, a highly selective TAM kinase inhibitor, termed LDC1267. LDC1267 was developed and preferentially inhibits Tyro3, Axl, and Mer at low nanomolarity, as determined by tracer-based binding assays (Fig. 3d,e). Selectivity of LDC1267 was further assessed using a cell-free KINOMEscan assay covering 456 kinases (Fig. 3f, Supplementary Table 1). Cellular selectivity was confirmed employing a quantitative chemical proteomics approach, cell-based phosphorylation, and proliferation assays (Extended Data Fig. 9a-d). Treatment of NKG2D-activated NK cells with LDC1267 indeed abolished the inhibitory effects of Gas6 stimulation; LDC1267 had no apparent additional effect in Cbl-b deficient NK cells (Fig. 3g).

Reference: Nature. 2014 Mar 27; 507(7493): 508–512. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6258903/

In vivo activity

In vivo, wild-type mice treated with LDC1267 showed enhanced cytotoxicity towards RMA cells overexpressing the NKGD2 ligand Rae-1 (RMA-Rae1) to the same extent as C373AKI/KI mice, but had no effect on the already enhanced NK cytotoxicity in Cbl-b-deficient mice (Fig. 3h; Extended Data 9e). To provide definitive proof that LDC1267 treatment can license NK cells to kill, B16F10 melanoma-bearing mice were treated with NK cells that were either untreated or treated ex vivo with our TAM inhibitor (Extended Data Fig. 9f). Adoptive transfer of LDC1267-treated wild-type NK cells significantly increased the anti-tumor response to levels observed in mice transplanted with Cbl-b-/- NK cells, but did not increase the anti-metastatic efficacy of Cbl-b knock-out NK cells (Fig. 3i), reinforcing the notion that Cbl-b acts downstream of TAM receptors for NK cell inhibition. These results indicate that TAM receptor inhibition using LDC1267 unleashes NK cells to kill tumors cells in vivo.

Reference: Nature. 2014 Mar 27; 507(7493): 508–512. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6258903/