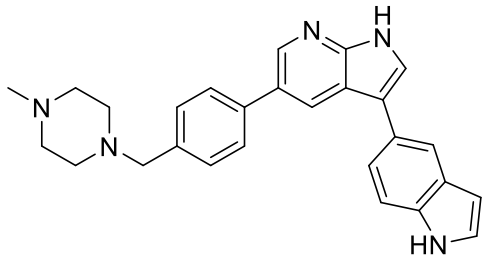
Product data sheet

MedKoo Cat#: 510349 Name: URMC-099 CAS#: 1229582-33-5 Chemical Formula: $C_{27}H_{27}N_5$ Exact Mass: 421.22665 Molecular Weight: 421.55	
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:

URMC-099 is an orally bioavailable, brain penetrant mixed lineage kinase (MLK) inhibitor with IC50 of 19 nM, 42 nM, 14 nM, and 150 nM, for MLK1, MLK2, MLK3, and DLK, respectively. MLK3 activation is associated with many of the pathologic hallmarks of HAND and therefore represents a prime target for adjunctive therapy based on small-molecule kinase inhibition. In vitro, URMC-099 treatment reduced inflammatory cytokine production by HIV-1 Tat-exposed microglia and prevented destruction and phagocytosis of cultured neuronal axons by these cells.

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	29.0	68.79
DMF	25.0	59.30
DMF:PBS (pH 7.2) (1:1)	0.5	1.19
Ethanol	1.0	2.37

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.37 mL	11.86 mL	23.72 mL
5 mM	0.47 mL	2.37 mL	4.74 mL
10 mM	0.24 mL	1.19 mL	2.37 mL
50 mM	0.05 mL	0.24 mL	0.47 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. Bellizzi MJ, Hammond JW, Li H, Gantz Marker MA, Marker DF, Freeman RS, Gelbard HA. The Mixed-Lineage Kinase Inhibitor URMC-099 Protects Hippocampal Synapses in Experimental Autoimmune Encephalomyelitis. eNeuro. 2018 Dec 3;5(6):ENEURO.0245-18.2018. doi: 10.1523/ENEURO.0245-18.2018. PMID: 30627663; PMCID: PMC6325567.
2. Saminathan P, Kevadiya BD, Marker DF, Gendelman HE, Gorantla S, Gelbard HA. Broad Spectrum Mixed Lineage Kinase Type 3 Inhibition and HIV-1 Persistence in Macrophages. J Neuroimmune Pharmacol. 2019 Mar;14(1):44-51. doi: 10.1007/s11481-018-09829-8. Epub 2019 Jan 7. PMID: 30617749; PMCID: PMC6391203.

In vivo study

1. Miller-Rhodes P, Kong C, Baht GS, Saminathan P, Rodriguiz RM, Wetsel WC, Gelbard HA, Terrando N. The broad spectrum mixed-lineage kinase 3 inhibitor URMC-099 prevents acute microgliosis and cognitive decline in a mouse model of perioperative

neurocognitive disorders. J Neuroinflammation. 2019 Oct 28;16(1):193. doi: 10.1186/s12974-019-1582-5. PMID: 31660984; PMCID: PMC6816182.
2. Calamaras TD, Baumgartner RA, Aronovitz MJ, McLaughlin AL, Tam K, Richards DA, Cooper CW, Li N, Baur WE, Qiao X, Wang GR, Davis RJ, Kapur NK, Karas RH, Blanton RM. Mixed lineage kinase-3 prevents cardiac dysfunction and structural remodeling with pressure overload. Am J Physiol Heart Circ Physiol. 2019 Jan 1;316(1):H145-H159. doi: 10.1152/ajpheart.00029.2018. Epub 2018 Oct 26. PMID: 30362822; PMCID: PMC6383356.

7. Bioactivity

Biological target:

URMC-099 is an orally bioavailable and potent mixed lineage kinase type 3 (MLK3) (IC50=14 nM) inhibitor with excellent blood-brain barrier penetration properties.

In vitro activity

URMC-099 (300 nM) blocked increases in JUN (expression as well as phosphorylation at serine residues 63 and 73 (Fig. 3C,D; n = 3 cultures per condition, p = 0.015 for P Ser 73 JUN in 099- vs vehicle-treated cultures at 8 h and p = 0.003 at 12 h, one-way ANOVA with Sidak post hoc testw,x), consistent with reduced JNK (c-Jun N-terminal kinase) activity downstream of MLK inhibition. Treatment with $CLFB_{1134}$ (a highly-specific MLK3 inhibitor with a different chemical scaffold) failed to provide protection or trophic support to NGF (nerve growth factor)-deprived neurons, which underwent neuritic beading and degeneration of cell bodies to an extent that precluded quantification of pyknotic versus healthy nuclei, suggesting that the neuroprotective effects of broad-spectrum MLK inhibition in vitro, like in vivo, are not reproduced by an inhibitor that is highly selective for MLK3. Thus, subsequent experiments focused on further characterizing the effects of URMC-099 in EAE (autoimmune encephalomyelitis) hippocampus.

Reference: eNeuro. 2018 Nov-Dec; 5(6): ENEURO.0245-18.2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325567/

In vivo activity

At 24 h post-surgery, hippocampal microgliosis was observed in vehicle-treated mice receiving orthopedic surgery relative to sham-treated controls using stereological analyses of F4/80+ cells (P = 0.0003; Fig. 1a, b). In contrast, URMC-099-treated mice exhibited a significant reduction (P = 0.0003) in the density of F4/80+ cells in the hippocampus relative to the sham-treated controls (Fig. 1b), indicating that our treatment paradigm effectively inhibited surgery-induced hippocampal microgliosis. BBB integrity was examined also using IgG immunostaining. There was significantly less IgG leakage in URMC-099-treated mice receiving surgery and sham-treated controls when compared to vehicle-treated mice receiving surgery (P values $\leqslant$ 0.044; Fig. 1c). Hence, URMC-099 was efficacious in preventing both microgliosis and leakage at the BBB.

Reference: J Neuroinflammation. 2019; 16: 193. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6816182/

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.