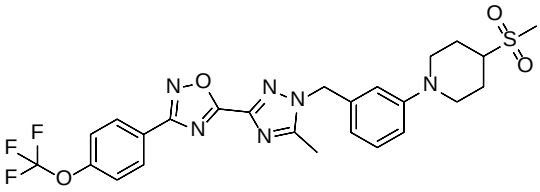
Product data sheet

MedKoo Cat#: 407917 Name: IACS-010759 free base CAS#: 1570496-34-2 (free base) Chemical Formula: $C_{25}H_{25}F_3N_6O_4S$ Exact Mass: 562.1610 Molecular Weight: 562.57	
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:
IACS-010759 or IACS-10759 is a potent and selective Oxidative Phosphorylation Inhibitor (IC50 < 10 nM) with potential antineoplastic activity. IACS-010759 binds to and inhibits complex I of the electron transport chain (NADH ubiquinone oxidoreductase), thereby selectively depriving tumor cells of nutrients, and energy, and inhibiting nucleotide and amino acid production, which induces autophagy, causes tumor cell death and inhibits cell proliferation. Mitochondrial complex I, which is hyperactivated in cancer cells to meet their increased demands for energy, plays a key role in the promotion of cancer cell proliferation.

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	24.23	43.07
DMF	0.10	0.18

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.78 mL	8.89 mL	17.78 mL
5 mM	0.36 mL	1.78 mL	3.56 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. Vangapandu HV, Alston B, Morse J, Ayres ML, Wierda WG, Keating MJ, Marszalek JR, Gandhi V. Biological and metabolic effects of IACS-010759, an OxPhos inhibitor, on chronic lymphocytic leukemia cells. Oncotarget. 2018 May 18;9(38):24980-24991. doi: 10.18632/oncotarget.25166. PMID: 29861847; PMCID: PMC5982765.
2. Liu F, Kalpage HA, Wang D, Edwards H, Hüttemann M, Ma J, Su Y, Carter J, Li X, Polin L, Kushner J, Dzinic SH, White K, Wang G, Taub JW, Ge Y. Cotargeting of Mitochondrial Complex I and Bcl-2 Shows Antileukemic Activity against Acute Myeloid Leukemia Cells Reliant on Oxidative Phosphorylation. Cancers (Basel). 2020 Aug 24;12(9):2400. doi: 10.3390/cancers12092400. PMID: 32847115; PMCID: PMC7564145.

In vivo study

1. Molina JR, Sun Y, Protopopova M, Gera S, Bandi M, Bristow C, McAfoos T, Morlacchi P, Ackroyd J, Agip AA, Al-Atrash G, Asara J, Bardenhagen J, Carrillo CC, Carroll C, Chang E, Ciurea S, Cross JB, Czako B, Deem A, Daver N, de Groot JF, Dong JW, Feng N, Gao G, Gay J, Do MG, Greer J, Giuliani V, Han J, Han L, Henry VK, Hirst J, Huang S, Jiang Y, Kang Z, Khor T, Konoplev

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S, Lin YH, Liu G, Lodi A, Lofton T, Ma H, Mahendra M, Matre P, Mullinax R, Peoples M, Petrocchi A, Rodriguez-Canale J, Serreli R, Shi T, Smith M, Tabe Y, Theroff J, Tiziani S, Xu Q, Zhang Q, Muller F, DePinho RA, Toniatti C, Draetta GF, Heffernan TP, Konopleva M, Jones P, Di Francesco ME, Marszalek JR. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. Nat Med. 2018 Jul;24(7):1036-1046. doi: 10.1038/s41591-018-0052-4. Epub 2018 Jun 11. PMID: 29892070.
2. Liu F, Kalpage HA, Wang D, Edwards H, Hüttemann M, Ma J, Su Y, Carter J, Li X, Polin L, Kushner J, Dzinic SH, White K, Wang G, Taub JW, Ge Y. Cotargeting of Mitochondrial Complex I and Bcl-2 Shows Antileukemic Activity against Acute Myeloid Leukemia Cells Reliant on Oxidative Phosphorylation. Cancers (Basel). 2020 Aug 24;12(9):2400. doi: 10.3390/cancers12092400. PMID: 32847115; PMCID: PMC7564145.

7. Bioactivity

Biological target: IACS-010759 (IACS-10759) is an inhibitor of complex I of oxidative phosphorylation (OXPHOS) with IC50 < 10 nM.

In vitro activity

CLL (chronic lymphocytic leeukemia) cells were incubated with 100 nM IACS-010759 for 24 h and later assayed for changes in mitochondrial OCR (oxygen consumption rate, a measure of OxPhos) and ECAR (a measure of glycolysis). Untreated cells showed the expected increase in spare respiratory capacity upon addition of uncoupler carbonylcyanide-4-trifluoromethoxyphenylhydrazone (FCCP). In drug-treated cells, basal OCR was greatly inhibited followed by a drastic decrease in spare respiratory capacity (after addition of FCCP) compared with the untreated control (Figure 2A). Similar assays were done in 10 patient samples where basal respiratory capacity (Figure 2B) and spare respiratory capacity showed a similar trend after incubation with the drug (Figure 2C). Glycolysis was measured simultaneously in these patient samples. An increase in glycolytic flux was observed in treated cells compared with untreated cells (Figure 2D). A similar increase in glycolytic flux was noted when an additional 11 samples were evaluated (Figure 2E). Because glycolytic flux increased, glucose consumption by the cells (substrate for glycolysis) was measured. 2-dG was used to measure glucose uptake in untreated and after a 24 h treatment with IACS-010759 (Figure 2F). Glucose uptake was significantly increased after treatment.

Reference: Oncotarget. 2018 May 18;9(38):24980-24991. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5982765/

In vivo activity

IACS-010759 is a mitochondrial complex I inhibitor that has demonstrated preclinical antileukemic activity. However, complex I deficiency has been reported to inhibit apoptotic cell death through prevention of cytochrome c release. Thus, combining IACS-010759 with a BH3 mimetic may overcome this mechanism of resistance leading to synergistic antileukemic activity against AML (acute myeloid leukemia). In a relatively OXPHOS-reliant AML cell line derived xenograft mouse model, IACS-010759 treatment significantly prolonged survival, which was further enhanced by treatment with IACS-010759 in combination with venetoclax. IACS-010759 treatment retained cytochrome c in mitochondria, which was completely abolished by venetoclax, resulting in Bak/Bax- and caspase-dependent apoptosis.

Reference: Cancers (Basel). 2020 Aug 24;12(9):2400. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7564145/