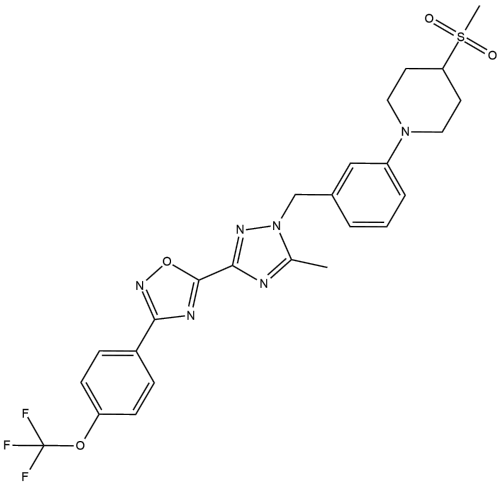
Product Data Sheet

Product Name: IACS-10759
Cat. No.: GC19194

Chemical Properties

Cas. No.	1570496-34-2		
SMILES	FC(F)(F)OC1=CC=C(C2=NOC(C3=NN(CC4=CC(N5CCC(S(=O)(C)=O)CC5)=CC=C4)C(C)=N3)=N2)C=C1		
Formula	$C_{25}H_{25}F_3N_6O_4S$	M.Wt	562.56
Solubility	DMSO : 62.5 mg/mL (111.10 mM);Water : < 0.1 mg/mL (insoluble)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:	
Cell lines	HCT116 cells

Product Data Sheet

Preparation Method	HCT116 cells were cultured in RPMI 1640 medium, supplemented with 10% fetal bovine serum (FBS), and 1% penicillin/streptomycin at 37°C in an incubator with 5% CO_2. Cells were seeded in a 96-well plate at a density of 1×10^4 cells/well overnight. Cells were treated with different concentrations of IACS-10759 (0, 0.1, 10, 100, and 1000nM) for 96h. Subsequently, the cell viability was detected.
Reaction Conditions	0, 0.1, 10, 100, and 1000nM; 96h
Applications	IACS-10759 treatment reduced the cell viability of HCT116 cells in a dose-dependent manner.
Animal experiment [2]:	
Animal models	Female NSG mice
Preparation Method	Female NSG mice (6 weeks old) were maintained on a 12:12h light-dark schedule in a temperature-controlled, specific pathogen-free facility and fed standard laboratory mouse chow. NB-1 cells were expanded in DMEM medium+20% FBS until ≥900 million cells were present, harvested, washed and resuspended at 5×10^6 cells/ml in PBS. A 1:1 mixture of 5×10^6 cells and matrigel (200μl) was injected into the right flank of anesthetized mice. When tumors grew to an average of $200mm^3$, mice received daily oral doses of 10mg/kg IACS-10759 for 21 days. Tumor sizes were measured every week.
Dosage form	10mg/kg/day; 21 days; p.o.

Product Data Sheet

Applications	IACS-10759 treatment inhibited tumor growth in the NB-1 xenograft mouse model.

References:

[1] Zhou Y, Zou J, Zhong X, et al. Synthesis and biological evaluation of novel pyrazole amides as potent mitochondrial complex I inhibitors[J]. European Journal of Medicinal Chemistry, 2023, 258: 115576.

[2] Molina J R, Sun Y, Protopopova M, et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability[J]. Nature medicine, 2018, 24(7): 1036-1046.

Background

IACS-10759 (IACS-010759) is an oxidative phosphorylation inhibitor, IACS-10759 is a potent inhibitor of complex I of oxidative phosphorylation (OXPHOS)[1].

IACS-010759 targets glycolysis-deficient tumor cells, In most cell lines, IACS-010759 treatment modestly increased apoptosis by up to twofold[1]. IACS-010759, like known quinone-site inhibitors, suppresses chemical modification by the tosyl reagent AL1 of Asp160 in the 49-kDa subunit, located deep in the interior of a previously proposed quinone-access channel[2]. IACS-010759 in complex I is the membrane-embedded ND1 subunit because amino acid substitution at Leu55 (to Phe) in this subunit, which faces the proposed ubiquinone-access channel interior[3].Treatment of primary CLL cells with IACS-010759 greatly inhibited OxPhos but caused only minor cell death at 24 and 48 h. In the presence of stroma, the drug successfully inhibited OxPhos and diminished intracellular ribonucleotide pools[4]. Inhibition of OxPhos(by IACS-010759) induced transfer of mitochondria derived from mesenchymal stem cells (MSCs) to AML cells via tunneling nanotubes under direct-contact coculture conditions. Inhibition of OxPhos also induced mitochondrial fission and increased functional mitochondria and mitophagy in AML cells[5]. Systems analysis of IACS-010759-induced changes in RTS osteoblasts revealed that chemical inhibition of mitochondrial respiratory complex I impaired cell proliferation, induced senescence, and decreased MAPK signaling and cell cycle associated genes, but increased H19 and ribosomal protein genes[8]. In vitro, the combination of

Product Data Sheet

AZD3965 and IACS-010759 is synergistic and induces DLBCL cell death, whereas monotherapy treatments induce a cytostatic response[9].

IACS-010759 also suppressed tumor growth in zebrafish and mouse xenograft models of high-risk neuroblastoma[6].Changes in blood glucose level with single or repeated doses of IACS-010759 did not observe. However, at 2 h after the first or fifth dose, plasma insulin levels transiently decreased and returned to control levels by 24 h postdose[1]. IACS-010759 as an OXPHOS inhibitor currently in early-phase clinical trials, improved survival of mice bearing MAPK inhibitor-resistant intracranial melanoma xenografts and inhibited melanoma brain metastases (MBM) formation in the spontaneous MBM model[7].

References:

[1]. Molina JR, Sun Y, et,al. 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]. Tsuji A, Akao T, et,al.IACS-010759, a potent inhibitor of glycolysis-deficient hypoxic tumor cells, inhibits mitochondrial respiratory complex I through a unique mechanism. J Biol Chem. 2020 May 22;295(21):7481-7491. doi: 10.1074/jbc.RA120.013366. Epub 2020 Apr 14. PMID: 32295842; PMCID: PMC7247293.
[3]. Zhu J, Vinothkumar KR, et,al. Structure of mammalian respiratory complex I. Nature. 2016 Aug 18;536(7616):354-358. doi: 10.1038/nature19095. Epub 2016 Aug 10. PMID: 27509854; PMCID: PMC5027920.
[4]. Vangapandu HV, Alston B, et,al.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.
[5]. Saito K, Zhang Q, et,al.Exogenous mitochondrial transfer and endogenous mitochondrial fission facilitate AML resistance to OxPhos inhibition. Blood Adv. 2021 Oct 26;5(20):4233-4255. doi: 10.1182/bloodadvances.2020003661. PMID: 34507353; PMCID: PMC8945617.
[6]. Anderson NM, Qin X, et,al. Metabolic Enzyme DLST Promotes Tumor Aggression and Reveals a Vulnerability to OXPHOS Inhibition in High-Risk Neuroblastoma. Cancer Res. 2021 Sep 1;81(17):4417-4430. doi: 10.1158/0008-5472.CAN-20-2153. Epub 2021 Jul 7. PMID: 34233924; PMCID: PMC8577318.
[7]. Fischer GM, Jalali A, et,al. Molecular Profiling Reveals Unique Immune and Metabolic Features of Melanoma Brain Metastases. Cancer Discov. 2019 May;9(5):628-645. doi: 10.1158/2159-

Product Data Sheet

8290.CD-18-1489. Epub 2019 Feb 20. PMID: 30787016; PMCID: PMC6497554.
[8]. Jewell BE, Xu A, et,al.Patient-derived iPSCs link elevated mitochondrial respiratory complex I function to osteosarcoma in Rothmund-Thomson syndrome. PLoS Genet. 2021 Dec 29;17(12):e1009971. doi: 10.1371/journal.pgen.1009971. PMID: 34965247; PMCID: PMC8716051.
[9]. Noble RA, Thomas H, et,al.Simultaneous targeting of glycolysis and oxidative phosphorylation as a therapeutic strategy to treat diffuse large B-cell lymphoma. Br J Cancer. 2022 Sep;127(5):937-947. doi: 10.1038/s41416-022-01848-w. Epub 2022 May 26. PMID: 35618788; PMCID: PMC9428179.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA