

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

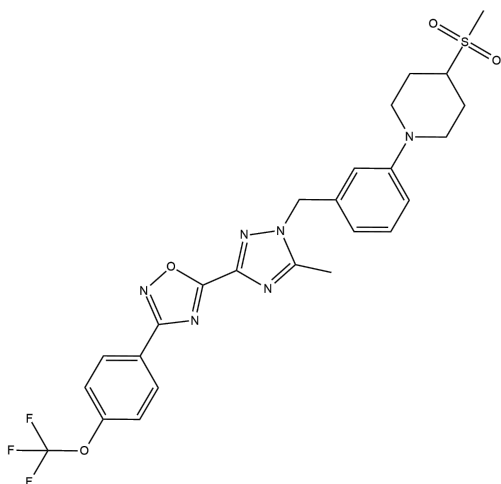
Formula $C_{25}H_{25}F_3N_6O_4S$ M.Wt 562.56

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

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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 (200 μ l) 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.

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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

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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:

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- [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.
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