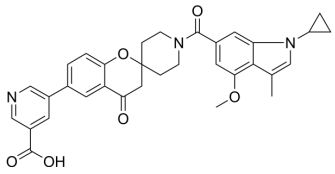
MK-4074

Cat. No.:	HY-107709
CAS No.:	1039758-22-9
Molecular Formula:	$C_{33}H_{31}N_3O_6$
Molecular Weight:	565.62
Target:	Acetyl-CoA Carboxylase
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (88.40 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7680 mL	8.8399 mL	17.6797 mL
	5 mM	0.3536 mL	1.7680 mL	3.5359 mL
	10 mM	0.1768 mL	0.8840 mL	1.7680 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MK-4074 is a liver-specific inhibitor of acetyl-CoA carboxylase ACC1 and ACC2 with IC_{50} values of approximately 3 nM.

IC_{50} & Target

IC50: 3 nM (Acetyl-CoA Carboxylase)[1]

In Vitro

MK-4074 strongly inhibits both ACC1 and ACC2 with IC_{50} values of approximately 3 nM. MK-4074 is highly liver specific because it is a substrate of organic anion transport protein (OATP) transporters that are present only in hepatocytes, and excretion of MK-4074 from hepatocytes into bile is dependent on the MRP2 efflux transporter[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

In male KKAy mice, a mouse model of obesity, type 2 diabetes, and fatty liver, a single oral dose of MK-4074 (0.3-3 mg/kg)

	significantly decreases DNL in a dose-dependent manner with an ID_{50} value of 0.9 mg/kg 1 hr post-administration. In a time course study, MK-4074 orally at 30 mg/kg reduces hepatic DNL by 83%, 70%, and 51% at 4, 8, and 12 hr post-dose, respectively. Single oral doses of MK-4074 at 30 and 100 mg/kg significantly increases plasma total ketones, a surrogate biomarker for hepatic FAO, by 1.5-fold to 3-fold for up to 8 hr[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Recombinant ACC protein is purified from FM3A or Sf9 cells expressing recombinant ACC by chelating chromatography or from liver by Softlink avidin resin chromatography. Purified ACC protein is incubated with MK-4074 in assay buffer containing 5 mM ATP, 250 mM acetyl-CoA, 4.1 mM $NaHCO_3$, 0.086 mM $NaH_{14}CO_3$, 20 mM potassium citrate, 20 mM $MgCl_2$, 2 mM DTT, 0.5 mg/mL BSA and 50 mM HEPES-Na (pH 7.5) for 40 min at 37°C[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	For cellular assays of DNL and FAO, cells are pre-incubated with MK-4074 for 1 hr. Then the cells are incubated for additional 1-3 hr with either 65-260 mM ^{14}C-labeled acetate or 0.018 mM ^{3}H-labeled palmitate for DNL or FAO assay, respectively. After incubation, intracellular ^{14}C-labeled lipids and released ^{3}H-labeled fatty acids are extracted and measured for DNL and FAO, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Studies are performed in male KKAy mice or C57BL/6J mice. KKAy mice are fed a chow diet while C57BL/6J mice are fed a high-fat diet (45% fat) for 3 weeks prior to study. Mice are treated for 7 days with vehicle (distilled water, 0.2 mL/mouse) before MK-4074 administration to acclimate mice to oral dosing. Animals are drug naive at the time of study. Mice are housed individually. Male KKAy mice (n=10-11/group) are administered a single oral dose of MK-4074 (0.3 to 3 mg/kg) prior to liver slice studies. Male KKAy mice (n=5/group) are administered a single oral dose of MK-4074 (3 to 30 mg/kg) prior to measurement of liver DNL rates. Male KKAy mice (n=8/group) are administered a single oral dose of MK-4074 (10 to 100 mg/kg) and plasma ketone bodies are measured at the indicated times. Male C57BL/6J mice (n=5, veh; n=10, MK-4074) are fed chow or a high-fat/high-sucrose (HF/HS) diet for 7 weeks and vehicle or MK-4074 is administered orally (10 or 30 mg/kg/day) for 4 weeks prior to study[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Research Square Print. December 20th, 2022.
- bioRxiv. 2021 Mar 8.
- bioRxiv. 2020 Jun.

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REFERENCES

[1]. Kim CW, et al. Acetyl CoA Carboxylase Inhibition Reduces Hepatic Steatosis but Elevates Plasma Triglycerides in Mice and Humans: A Bedside to Bench Investigation. Cell Metab. 2017 Aug 1;26(2):394-406.e6.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA