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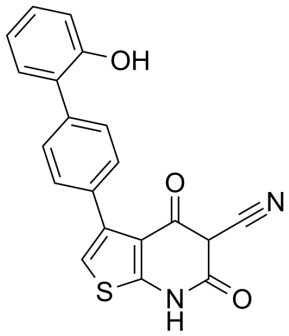
A-769662

Cat. No.:	HY-50662
CAS No.:	844499-71-4
Molecular Formula:	$C_{20}H_{12}N_2O_3S$
Molecular Weight:	360.39
Target:	AMPK
Pathway:	Epigenetics; PI3K/Akt/mTOR
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 (138.74 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7748 mL	13.8739 mL	27.7477 mL
	5 mM	0.5550 mL	2.7748 mL	5.5495 mL
	10 mM	0.2775 mL	1.3874 mL	2.7748 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 (6.94 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.94 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.94 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

A-769662 is a potent, reversible AMPK activator with EC_{50} of 0.8 μM.

IC_{50} & Target

AMPK
0.8 μM (EC50)

In Vitro

A-769662 is equally potent in activating the baculovirus expressed α1,β1,γ1 recombinant isoform of AMPK (EC_{50}=0.7 μM). A-769662 and A-592107 activate AMPK purified from multiple tissues and species in a dose-responsive manner with modest

	variations in observed EC_{50}s. EC_{50}s determined for A-769662 using partially purified AMPK extracts from rat heart, rat muscle, or human embryonic kidney cells (HEKs) are 2.2 μM, 1.9 μM, or 1.1 μM, respectively[1]. A-769662 activates endogenous AMPK in LKB1-expressing (HEK293) and LKB1-deficient (CCL13) cells. A-769662 allosterically activates AMPK complexes containing γ1 harboring a substitution of arginine residue 298 to glycine (R298G). A-769662 inhibits dephosphorylation of Thr-172 in the mutant γ1-containing complexes to a similar degree as seen in the wild-type complexes [2]. A769662 (300 μM) has toxic effects on MEF cells. A769662 reversibly inhibits the proteasomal activity[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	A-769662 (30 mg/kg, i.p.) significantly reduced the respiratory exchange ratio (RER) in the SD rat. There are 33% and 58% reductions of malonyl CoA levels in livers of animals treated with 30 mg/kg A-769662 (0.905 nmol/g) or 500 mg/kg metformin (0.574 nmol/g), respectively. A-769662 (30 mg/kg, b.i.d.) significantly decreases fed plasma glucose (30%-40% reduction), while the lower doses (3 and 10 mg/kg) of A-769662 had no effect on the in diabetic ob/ob mice[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	To assay glycogen phosphorylase b (GPb) activity, 1.5 μg/mL of rabbit GPb is added to a reaction mix containing 20 mM Na_2HPO_4 (pH 7.2), 2 mM $MgSO_4$, 1 mM β-NADP (β-nicotinamide adenine dinucleotide phosphate), 1.4 U/mL G-6-PDH (Glucose-6-Phosphate-Dehydrogenase) and 3 U/mL PGM (phosphoglucomutase). AMP or test compounds are added to the assay medium at the specified concentrations followed by the addition of glycogen (final concentration 1 mg/mL) to initiate the reaction. After incubating 10 min at 25°C, GPb activity is assessed by measuring absorbance at 340 nm. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	After acclimation ob/ob and lean mice are randomized to the various treatment groups by body weight and fed glucose levels (tail snip) at 8 AM. Baseline plasma insulin samples are also taken from a subset of the animals representing each treatment group (n=10 ob/ob and n=10 lean ob/+ littermates). Two separate ob/ob and lean littermate studies are completed: 1) an initial 5 day study, and 2) a 14 day study to examine efficacy and more completely characterize the body weight change observed in the 5 day study. Treatment groups for the 5 day study are as follows: ob/ob vehicle (0.2% hydroxypropyl methylcellulose [HPMC], i.p., b.i.d.), A-592107 (10 or 100 mg/kg, i.p., b.i.d.), A-769662 (3 or 30 mg/kg, i.p., b.i.d.), AICAR (375 mg/kg, s.c., b.i.d.), or metformin (450 mg/kg, p.o., q.d., with vehicle in PM), and lean littermates treated with vehicle (i.p., b.i.d.). Treatment groups for the 14 day ob/ob and lean littermate study are as follows: ob/ob vehicle (0.2% HPMC, i.p., b.i.d.), A-769662 (3, 10, or 30 mg/kg, i.p., b.i.d.), or metformin, and lean littermates treated with vehicle or 30 mg/kg of A-769662 (i.p., b.i.d.). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Nanotechnol. 2021 Jul;16(7):830-839.
- Cell Metab. 2019 Jul 2;30(1):157-173.e7
- Nat Commun. 2023 Dec 14;14(1):8316.
- Nat Commun. 2019 Feb 6;10(1):620.
- Mol Cell. 2017 Oct 19;68(2):336-349.e6.

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REFERENCES

[1]. Cool B, et al. Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome. Cell Metab, 2006, 3(6), 403-416.

[2]. Sanders MJ, et al. Defining the mechanism of activation of AMP-activated protein kinase by the small molecule A-769662, a member of the thienopyridone family. J Biol Chem, 2007, 282(45), 32539-32548.

[3]. Moreno D, et al, A769662, a novel activator of AMP-activated protein kinase, inhibits non-proteolytic components of the 26S proteasome by an AMPK-independent mechanism. FEBS Lett, 2008, 583(17), 2650-2654.

[4]. Yerra VG, et al. Adenosine Monophosphate-Activated Protein Kinase Abates Hyperglycaemia-Induced Neuronal Injury in Experimental Models of Diabetic Neuropathy: Effects on Mitochondrial Biogenesis, Autophagy and Neuroinflammation. Mol Neurobiol. 2017 Apr;54

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