Mitapivat

Cat. No.: HY-12689

CAS No.: 1260075-17-9

Molecular Formula: $C_{24}H_{26}N_4O_3S$

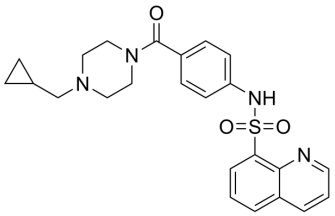
Molecular Weight: 450.55

Target: Pyruvate Kinase

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 : 20.83 mg/mL (46.23 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2195 mL	11.0975 mL	22.1951 mL
5 mM	0.4439 mL	2.2195 mL	4.4390 mL
10 mM	0.2220 mL	1.1098 mL	2.2195 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 (5.55 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.55 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Mitapivat (AG-348) is an orally active pyruvate kinase allosteric activator. Mitapivat increases enzymatic activity, protein stability, and ATP levels over a broad range of PKLR genotypes, shows the potential to restore the activity of PK (pyruvate kinase)-deficient glycolytic pathways. Mitapivat can be used in study of PK deficiency[1][2][3].

IC_{50} & Target

pyruvate kinase[1][2][3].

In Vitro

Mitapivat (0.1 nM-100 μM; 16 h) activates WT PK-R in RBCs from healthy donors[1].

Mitapivat (0.01 nM-10 μM; 16 h) promotes production of ATP in RBC cells in a dose-dependent manner[1].

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

Cell Viability Assay[1]

Cell Line:	RBC cells
Concentration:	0.1 nM-100 μM
Incubation Time:	16 h (incubate overnight)
Result:	Increased PK-R activity in a dose-dependent manner to ~2.5-fold of DMSO control with an AC_{50} of 62 nM.

Cell Viability Assay[1]

Cell Line:	RBC cells
Concentration:	0.01 nM-10 μM
Incubation Time:	16 h (incubate overnight)
Result:	Consistently increased ATP levels in a dose-dependent manner by an average of 60% over DMSO control with an AC_{50} of 10.9 nM.

In Vivo

Mitapivat (50 mg/kg; p.o.; twice daily for 21 days) improves anemia in a mouse model for β-thalassemia[2].

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

Animal Model:	WT C57B6 and $Hbb^{th3/+}$ mice (both are 2-month-old female mice; β-thalassemia model)[2].
Dosage:	50 mg/kg
Administration:	In animal feedings; single daily for 3 weeks.
Result:	Increased the expression of pyruvate kinase isoforms in both red cells and erythroid precursors from $Hbbth^{3/+}$ mice. Elevated pyruvate kinase activity in cells from $Hbbth^{3/+}$ mice, and markedly increased ROS level in erythrocytes. Increased the expression of PKM2 in polychromatic and orthochromatic erythroblasts of $Hbbth^{3/+}$ mice.

Animal Model:	WT C57B6 and $Hbb^{th3/+}$ mice (both are 2-month-old female mice; β-thalassemia model)[2].
Dosage:	50 mg/kg
Administration:	Oral gavage, twice daily for 21 days.
Result:	Ameliorated ineffective erythropoiesis and anemia in $Hbb^{th3/+}$ mice and increased ATP, reduced ROS production, as well as reduced markers of mitochondrial dysfunction associated with improved mitochondrial clearance.

REFERENCES

[1]. Kung C, et al. AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency. Blood. 2017 Sep 14;130(11):1347-1356.

[2]. Matte A, et al. The pyruvate kinase activator mitapivat reduces hemolysis and improves anemia in a β-thalassemia mouse model. J Clin Invest. 2021 May

17;131(10):e144206.

[3]. Rab MAE, et al. AG-348 (Mitapivat), an allosteric activator of red blood cell pyruvate kinase, increases enzymatic activity, protein stability, and ATP levels over a broad range of PKLR genotypes. Haematologica. 2021 Jan 1;106(1):238-249.

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