Momelotinib sulfate

Cat. No.: HY-10962

CAS No.: 1056636-06-6

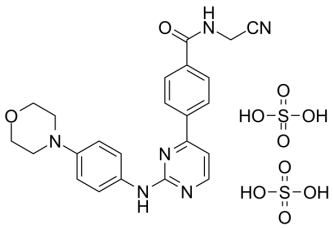
Molecular Formula: $C_{23}H_{26}N_6O_{10}S_2$

Molecular Weight: 610.62

Target: JAK; Autophagy; Apoptosis

Pathway: Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt; Autophagy; Apoptosis

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 220 mg/mL (360.29 mM; Need ultrasonic)
H_2O : 100 mg/mL (163.77 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6377 mL	8.1884 mL	16.3768 mL
	5 mM	0.3275 mL	1.6377 mL	3.2754 mL
	10 mM	0.1638 mL	0.8188 mL	1.6377 mL

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

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 100 mg/mL (163.77 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 5.5 mg/mL (9.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 5.5 mg/mL (9.01 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 5.5 mg/mL (9.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Momelotinib sulfate (CYT387 sulfate salt) is an ATP-competitive inhibitor of JAK1/JAK2 with IC_{50} of 11 nM/18 nM, 10-fold selectivity versus JAK3 (IC_{50}=155 nM).

IC_{50} & Target	JAK1	JAK2	JAK3
	11 nM (IC_{50})	18 nM (IC_{50})	155 nM (IC_{50})

In Vitro	Momelotinib sulfate (CYT387 sulfate salt) inhibits growth of Ba/F3-JAK2V617F and human erythroleukemia (HEL) cells (IC_{50} =1.5 μM) or Ba/F3-MPLW515L cells (IC_{50}=200 nM), but has considerably less activity against BCR-ABL harboring K562 cells (IC_{50}=58 μM) and FLT3 mutation harboring MV4-11 cells (IC_{50}=3 μM). Proliferation of parental Ba/F3 cells (Ba/F3-wt) stimulated with IL-3 is inhibited with an IC_{50} value of 1.4 μM, consistent with the established role of IL-3-dependent signaling in the parental cell line[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Momelotinib sulfate (CYT387 sulfate salt) at twice the dose used in disease model (50 and 100 mg/kg) has little to no effect on peripheral blood counts over a period of 8 weeks. Median plasma peak concentrations are 7.1 μM with the lower dose and 32.1μM with the higher dose, with a half-life of approximately 2 hours. Trough levels at 12 hours are 10nM for the 25 mg/kg and 900nM for the 50 mg/kg dose. At day 34 after transplantation, the mean white blood cell counts and hematocrit values of the entire cohort exceeded the normal range for Balb/c mice by more than 1 SD. At this point, 6 mice are sacrificed and subjected to autopsy. In the remaining animals, treatment is initiated with 25 mg/kg Momelotinib sulfate (CYT387 sulfate salt), 50 mg/kg Momelotinib sulfate (CYT387 sulfate salt), or vehicle, administered twice daily by oral gavage (12 mice per treatment group). A rapid drop of the white cell counts is apparent in both dose cohorts as early as 6 days after initiation of treatment and a decline of the hematocrit is apparent after 20 days[2]. After oral dosing, Momelotinib sulfate (CYT387 sulfate salt) exhibits high plasma concentrations (C_{max}= 40.4 μM; T_{max}=4 h), with quantitative absolute oral bioavailability and an apparent half life of 2.4 h. The high oral bioavailability, can likely be partly ascribed to the low blood clearance of Momelotinib sulfate (CYT387 sulfate salt) (6.3 mL/min/kg) and therefore low susceptibility to hepatic first pass metabolism [3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Glutathione-S-transferase (GST)-tagged JAK kinase domains expressed in insect cells are purified before use in a peptide substrate phosphorylation assay. Assays are carried out in 384-well optiplates using an Alphascreen Protein Tyrosine Kinase P100 detection kit and a PerkinElmer Fusion Alpha instrument[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Ba/F3 cells expressing JAK2V617F (Ba/F3-JAK2V617F) and MPLW515L (Ba/F3-MPLW515L) mutants, as well as CHRF-288-11 (JAK2T875N) and CMK (JAK3A572V) cells are used. The TEL/JAK2 and TEL/JAK3 fusions are generated and introduced into Ba/F3 murine cells. TheTEL/JAK2- or TEL/JAK3-transfected cells are cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum (FCS). Ba/F3 wild-type cells are cultured in RPMI containing 10% FCS supplemented with 5 ng/mL murine IL-3. Proliferation is measured using the Alamar Blue assay after incubating for 72 h at 37°C with 5% CO_2[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] On day 32 after bone marrow transplantation (when all mice exhibit severe leukocytosis and erythrocytosis), mice are assigned to 3 groups such that each group has equivalent average body weight and blood counts. Momelotinib (CYT387) is dissolved in NMP (120 mg/mL final; 1-methyl-2-pyrrolidinone, Chromasolv Plus). Subsequently, the Momelotinib/NMP mix is diluted with 0.14M Captisol to a concentration of 6 mg/mL and further diluted with 0.1M Captisol to a final concentration of 4 mg/mL. All 3 groups of mice (n=12 per group) are administered Momelotinib (CYT387) by oral gavage twice daily at 10- to 12-hour intervals from day 34 after bone marrow transplantation to day 82 (end of experiment). Mice receive NMP/Captisol without Momelotinib (CYT387) (0 mg/kg group), 25 mg/kg Momelotinib, or 50 mg/kg Momelotinib. At day 82 after bone marrow transplantation, all mice are euthanized for analysis except for 2 mice each from the 50 mg/kg and 25 mg/kg groups, which are taken off Momelotinib (CYT387) treatment and followed for 45 additional days. For assessment of the effects of Momelotinib (CYT387) on normal blood counts, naive Balb/c mice are administered vehicle control, 50 mg/kg, or 100 mg/kg Momelotinib (CYT387) in an identical fashion as described for the bone marrow transplant experimental mouse cohort. Peripheral blood is drawn at day 14, 28, 42, and 56 and levels of red cells, white cells, reticulocytes, granulocytes, lymphocytes, and monocytes are analyzed.

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

CUSTOMER VALIDATION

- Cancer Cell. 2018 Sep 10;34(3):439-452.e6.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Leukemia. 2012 Oct;26(10):2233-44.
- Cancer Res. 2020 Jan 1;80(1):44-56.
- J Pineal Res. 2019 Apr;66(3):e12552.

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REFERENCES

[1]. Pardanani A, et al. CYT387, a selective JAK1/JAK2 inhibitor: in vitro assessment of kinase selectivity and preclinical studies using cell lines and primary cells from polycythemia vera patients. Leukemia, 2009, 23(8), 1441-1445.

[2]. Tyner JW, et al. CYT387, a novel JAK2 inhibitor, induces hematologic responses and normalizes inflammatory cytokines in murine myeloproliferative neoplasms. Blood, 2010, 115(25), 5232-5240.

[3]. Burns CJ, et al. Phenylaminopyrimidines as inhibitors of Janus kinases (JAKs). Bioorg Med Chem Lett. 2009 Oct 15;19(20):5887-92.

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