Momelotinib

Cat. No.: HY-10961

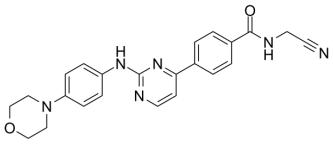
CAS No.: 1056634-68-4

Molecular Formula: $C_{23}H_{22}N_6O_2$

Molecular Weight: 414.46

Target: JAK; Autophagy; Apoptosis

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



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 : 10 mg/mL (24.13 mM; ultrasonic and warming and adjust pH to 3 with HCl and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4128 mL	12.0639 mL	24.1278 mL
5 mM	0.4826 mL	2.4128 mL	4.8256 mL
10 mM	0.2413 mL	1.2064 mL	2.4128 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: ≥ 1 mg/mL (2.41 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (2.41 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Momelotinib (CYT387) is an ATP-competitive inhibitor of JAK1/JAK2 with IC_{50}a of 11 nM and 18 nM,respectively. CYT387 shows much less activity against JAK3.

IC_{50} & Target

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

In Vitro

Momelotinib (CYT387) inhibits the proliferation of parental Ba/F3 cells (Ba/F3-wt) stimulated by IL-3 with IC_{50} of 1400 nM. Furthermore, Momelotinib (CYT387) also causes the inhibition of cell proliferation in cell lines constitutively activated by JAK2 or MPL signaling, including Ba/F3-MPLW515L cells, CHRF-288-11 cells and Ba/F3-TEL-JAK2 cells with IC_{50} of 200 nM, 1

	nM and 700 nM, respectively. In addition, Momelotinib (CYT387) has been shown to inhibit erythroid colony growth in vitro from JAK2V617F-positive PV patients with similar potency with IC_{50} of 2 μM-4 μM[1]. Momelotinib (CYT387) inhibits PI3K/AKT and Ras/MAPK signaling induced by IL-6 and IGF-1. Moreover, Momelotinib (CYT387) induces apoptosis as a single agent and synergizes with the conventional anti-MM therapies PS-341 and L-PAM in primary multiple myeloma (MM) cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In a murine MPN model, Momelotinib (CYT387) normalizes white cell counts, hematocrit, spleen size, and restores physiologic levels of inflammatory cytokines[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. 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. The TEL/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 hours at 37°C with 5% CO_2. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	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 had equivalent average body weight and blood counts. Momelotinib (CYT387) is dissolved in NMP (120 mg/mL final; 1-methyl-2-pyrrolidinone). Subsequently, the CYT387/NMP mix is diluted with 0.14 M 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 (CYT387), or 50 mg/kg Momelotinib (CYT387). 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 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[3]. 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]. Monaghan KA, et al. The novel JAK inhibitor CYT387 suppresses multiple signalling pathways, prevents proliferation and induces apoptosis in phenotypically diverse myeloma cells. Leukemia, 2011, 25(12), 1891-1899.

[3]. 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.

[4]. Kitajima S, et al.Overcoming Resistance to Dual Innate Immune and MEK Inhibition Downstream of KRAS.Cancer Cell. 2018 Sep 10;34(3):439-452.e6.

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