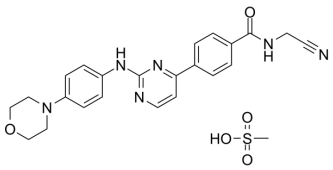
Momelotinib Mesylate

Cat. No.:	HY-10963
CAS No.:	1056636-07-7
Molecular Formula:	$C_{24}H_{26}N_6O_5S$
Molecular Weight:	510.57
Target:	JAK; Autophagy
Pathway:	Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt; Autophagy
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

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

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

In Vitro	Momelotinib Mesylate is an inhibitor of JAK1/JAK2 with IC_{50} of 11 nM/18 nM, appr 10-fold selectivity versus JAK3. Momelotinib inhibits the proliferation of parental Ba/F3 cells (Ba/F3-wt) stimulated by IL-3 with IC_{50} of 1400 nM. Furthermore, Momelotinib 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 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 inhibits PI3K/AKT and Ras/MAPK signaling induced by IL-6 and IGF-1. Moreover, Momelotinib induces apoptosis as a single agent and synergizes with the conventional anti-MM therapies bortezomib and melphalan 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 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

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[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal	Mice[3]

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 is dissolved in NMP (120 mg/mL final; 1-methyl-2-pyrrolidinone). Subsequently, the Momelotinib/NMP mix is diluted with 0.14 M Captisol to a concentration of 6 mg/mL and further diluted with 0.1 M Captisol to a final concentration of 4 mg/mL. All 3 groups of mice (n=12 per group) are administered Momelotinib 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 (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 treatment and followed for 45 additional days. For assessment of the effects of Momelotinib on normal blood counts, naive Balb/c mice are administered vehicle control, or 50 mg/kg, or 100 mg/kg Momelotinib in an identical fashion 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.
- J Pineal Res. 2019 Apr;66(3):e12552.
- Cancer Res. 2020 Jan 1;80(1):44-56.
- Cancer Immunol Res. 2016 Jun;4(6):520-30.

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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.

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