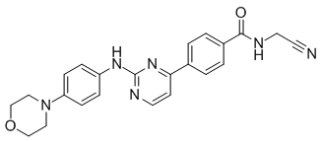
Data Sheet

Product Name:	CYT387
Cat. No.:	HY-10961
CAS No.:	1056634-68-4
Molecular Formula:	C23H22N6O2
Molecular Weight:	414.46
Target:	Autophagy; JAK
Pathway:	Autophagy; Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt
Solubility:	DMSO: ≥ 40 mg/mL



BIOLOGICAL ACTIVITY:

CYT387 is an ATP–competitive inhibitor of **JAK1/JAK2** with **IC_{50}** of 11 nM/18 nM, appr 10–fold selectivity versus JAK3.
IC50 & Target: IC50: 11 nM (JAK1), 18 nM (JAK2)
In Vitro: CYT387 inhibits the proliferation of parental Ba/F3 cells (Ba/F3–wt) stimulated by IL–3 with IC_{50} of 1400 nM. Furthermore, 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, 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]. CYT387 inhibits PI3K/AKT and Ras/MAPK signaling induced by IL–6 and IGF–1. Moreover, CYT387 induces apoptosis as a single agent and synergizes with the conventional anti–MM therapies bortezomib and melphalan in primary multiple myeloma (MM) cells[2].
In Vivo: In a murine MPN model, CYT387 normalizes white cell counts, hematocrit, spleen size, and restores physiologic levels of inflammatory cytokines[3].

PROTOCOL (Extracted from published papers and Only for reference)

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.
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.
Animal Administration: CYT387 is dissolved in NMP (120 mg/mL final; 1–methyl–2–pyrrolidinone).[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. 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 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 CYT387 (0 mg/kg group), 25 mg/kg CYT387, or 50 mg/kg 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 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 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.

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.

Caution: Product has not been fully validated for medical applications. For research use only.

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