Masitinib mesylate

Cat. No.: HY-10209A

CAS No.: 1048007-93-7

Molecular Formula: $C_{29}H_{34}N_6O_4S_2$

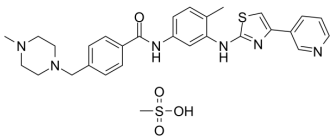
Molecular Weight: 594.75

Target: c-Kit; PDGFR; Src; FGFR; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 30 mg/mL (50.44 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.6814 mL	8.4069 mL	16.8138 mL
5 mM	0.3363 mL	1.6814 mL	3.3628 mL
10 mM	0.1681 mL	0.8407 mL	1.6814 mL

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

BIOLOGICAL ACTIVITY

Description

Masitinib mesylate (AB-1010 mesylate) is a potent, orally bioavailable, and selective inhibitor of c-Kit (IC_{50}=200 nM for human recombinant c-Kit). It also inhibits PDGFRα/β (IC_{50}s=540/800 nM), Lyn (IC_{50}= 510 nM for LynB), Lck, and, to a lesser extent, FGFR3 and FAK. Masitinib mesylate (AB-1010 mesylate) has anti-proliferative, pro-apoptotic activity and low toxicity [1][2][4].

IC_{50} & Target

IC50: 200 nM (Kit), 540 nM (PDGFRα), 800 nM (PDGFRβ), 510 nM (LynB)[1]

In Vitro

Masitinib is a competitive inhibitor against ATP at concentrations ≤500 nM. Masitinib also potently inhibits recombinant PDGFR and the intracellular kinase Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In contrast, masitinib demonstrates weak inhibition of Abl and c-Fms. Masitinib more strongly inhibits degranulation, cytokine production, and bone marrow mast cell migration than imatinib. In Ba/F3 cells expressing human wild-type Kit, masitinib inhibits SCF (stem cell factor)-induced cell proliferation with an IC_{50} of 150 nM, while the IC_{50} for inhibition of IL-3-stimulated proliferation is at approximately >10 μM. In Ba/F3 cells expressing PDGFRα, masitinib inhibits PDGF-BB-stimulated proliferation and PDGFRα tyrosine phosphorylation with IC_{50} of 300 nM. Masitinib also causes inhibition of SCF-stimulated tyrosine phosphorylation of

	human Kit in mastocytoma cell-lines and BMMC. Masitinib inhibits Kit gain-of-function mutants, including V559D mutant and Δ27 mouse mutant with IC_{50} of 3 and 5 nM in Ba/F3 cells. Masitinib inhibits the cell proliferation of mastocytoma cell lines including HMC-1α155 and FMA3 with IC_{50} of 10 and 30 nM, respectively[1]. Masitinib inhibits cell growth and PDGFR phosphorylation in two novel ISS cell lines, which suggest that Masitinib displays activity against both primary and metastatic ISS cell line and may aid in the clinical management of ISS[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Masitinib inhibits tumour growth and increases the median survival time in Δ27-expressing Ba/F3 tumor models at 30 mg/kg, without cardiotoxicity or genotoxicity[1]. Masitinib (12.5 mg/kg/d, p.o.) increases overall TTP (time-to-tumor progression) compared with placebo in dogs[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	A 96-well microtitre plateis coated overnight with 0.25 mg/mL poly(Glu,Tyr 4:1), rinsed twice with 250 µL of washing buffer (10 mM phosphate-buffered saline [pH 7.4] and 0.05% Tween 20) and dried for 2 hours at room temperature. Assays are performed at room temperature with a final volume of 50 µL in kinase buffer (10 mM $MgCl_2$, 1 mM $MnCl_2$, 1 mM sodium orthovanadate, 20 mM HEPES, pH 7.8) containing ATP at a concentration of at least twice the K_m for each enzyme and an appropriate amount of recombinant enzyme to ensure a linear reaction rate. Reactions are initiated upon introduction of the enzyme and terminated with the addition of one reaction volume (50 µL) of 100 mM EDTA per 5mol/Lurea mix. Plates are washed three times and incubated with 1:30,000 horseradish peroxidase-conjugated anti-phosphotyrosine monoclonal antibody, then washed three times and incubated with tetramethylbenzidine. The final reaction product is quantified by spectrophotometry at 450 nm. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	For the assay of Ba/F3 cell proliferation, microtitre plates are seeded with a total of 10^4 cells/well in 100 µL of RPMI 1640 medium with 10% foetal bovine serum at 37°C. These are supplemented, or not, with either 0.1% conditioned medium from X63-IL-3 cells or 250 ng/mL murine SCF. The murine SCF, which activates Kit, is purified from the conditioned medium of SCF-producing CHO cells. Cells are grown for 48 hours at 37°C with masitinib and then incubated with 10 µL/well of WST-1 reagent for 3 hours at 37°C. The amount of formazan dye formed is quantified by its absorbance at 450 nm using a scanning multiwell spectrophotometer. A blank well without cells is used as a background control for the spectrophotometer. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [4]	Male Nog-SCID mice (7 weeks old) are under specific pathogen-free conditions at 20±1°C in a 12-hour light/12-hour dark cycle and ad libitum access to food and filtered water. Mia Paca-2 cells are cultured as described above. At day 0 (D0), mice are injected with 10^7 Mia Paca-2 cells in 200 µL PBS into the right flank. Tumours are allowed to grow for 1.5 to 4 weeks until the desired tumour size is reached (appr 200 mm^3). At day 28, animals are allocated into four treatment groups (n=7 to 8 per group), ensuring that each group's mean body weight and tumour volume are well matched. Treatment is then administered for up to 4 weeks, after which time the animals are sacrificed. Treatments consisted of either: a) daily sterile water for the control group, b) an intraperitoneal (i.p.) injection of 50 mg/kg gemcitabine twice a week, c) daily gavage with 100 mg/kg masitinib, or d) combined i.p injection of 50 mg/kg gemcitabine twice a week and daily gavage with 100 mg/kg masitinib. Tumour size is measured with callipers and tumour volume is estimated using the formula: volume=(length×$width^2$)/2. The tumour growth inhibition ratio is calculated as (100)×(median tumour volume of treated group)/(median tumour volume of control group). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.

- Eur J Pharmacol. 2021 Oct 4;911:174549.
- BMC Vet Res. 2020 Feb 19;16(1):64.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Dubreuil P, et al. Masitinib (AB1010), a Potent and Selective Tyrosine Kinase Inhibitor Targeting KIT. PLoS One, 2009, 4(9), e7258.

[2]. Lawrence J, et al. Masitinib demonstrates anti-proliferative and pro-apoptotic activity in primary and metastatic feline injection-site sarcoma cells. Vet Comp Oncol, 2011, doi: 10.1111/j.1476-5829.2011.00291.x.

[3]. Hahn KA, et al. Masitinib is safe and effective for the treatment of canine mast cell tumors. J Vet Intern Med, 2008, 22(6), 1301-1309.

[4]. Marech I, et al. Masitinib (AB1010), from canine tumor model to human clinical development: where we are? Crit Rev Oncol Hematol. 2014 Jul;91(1):98-111.

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