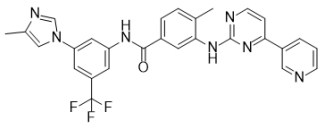
Nilotinib

Cat. No.:	HY-10159
CAS No.:	641571-10-0
Molecular Formula:	$C_{28}H_{22}F_3N_7O$
Molecular Weight:	529.52
Target:	Bcr-Abl; Autophagy
Pathway:	Protein Tyrosine Kinase/RTK; Autophagy
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 : 6 mg/mL (11.33 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8885 mL	9.4425 mL	18.8850 mL
	5 mM	0.3777 mL	1.8885 mL	3.7770 mL
	10 mM	0.1889 mL	0.9443 mL	1.8885 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: ≥ 0.6 mg/mL (1.13 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: ≥ 0.6 mg/mL (1.13 mM); Suspended solution
3. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 0.6 mg/mL (1.13 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Nilotinib is an orally available **Bcr-Abl** tyrosine kinase inhibitor with antineoplastic activity.
IC_{50} & Target	Bcr-Abl[1]
In Vitro	The novel, selective Abl inhibitor, Nilotinib (AMN107), is designed to interact with the ATP-binding site of BCR-ABL

	with a higher affinity than Imatinib. In addition to being significantly more potent compared with Imatinib (IC_{50}<30 nM), Nilotinib also maintains activity against most of the BCR-ABL point mutants that confer Imatinib resistance[1]. Nilotinib demonstrates significant antitumor efficacy against GIST xenograft lines and Imatinib-resistant GIST cell lines. The parent cell lines GK1C and GK3C show Imatinib sensitivity with IC_{50} of 4.59±0.97 μM and 11.15±1.48 μM, respectively. The Imatinib-resistant cell lines GK1C-IR and GK3C-IR show Imatinib resistance with IC_{50} values of 11.74±0.17 μM (P<0.001) and 41.37±1.07 μM (P<0.001), respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The percentage of tumor growth inhibition (TGI) is 83.8% for Imatinib and 69.6% for Nilotinib in the GK1X xenograft line (n.s.). In the GK2X xenograft line, TGI is 83.0% for Imatinib and 85.3% for Nilotinib (n.s.). Additionally, the GK3X xenograft line TGI is 31.1% for Imatinib and 47.5% for Nilotinib (n.s.). These results suggest that, except for the GK1X xenograft line, Nilotinib shows equivalent or higher antitumor effects than Imatinib[2]. Nilotinib has a significant healing effect on the macroscopic and microscopic pathologic scores and ensures considerable mucosal healing in the indomethacin-induced enterocolitis rat model. While Nilotinib decreased the PDGFR α and β levels and apoptotic scores in the colon, it did not have a significant effect on the weight and TNF-α levels. Further experimental investigations could provide more definitive evidence for humans[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The human GIST cell lines GK1C and GK3C, and the Imatinib-resistant cell lines GK1C-IR and GK3C-IR are plated in 96-well microplates and cultured for 12 h before exposure to Imatinib (1-100 μM) or Nilotinib (1-100 μM) for 72 h. The cells are quantified by the WST-8 assay. The optical density (OD) is determined with Sunrise rainbow. The rate of inhibition is calculated as follows: % of inhibition=(OD of treated group-blank)/(OD of control group-blank)×100%. The concentration of tested drugs resulting in 50% growth inhibition (IC_{50}) is calculated[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2][3]	Mice[2] The GIST xenograft lines GK1X, GK2X and GK3X in nude mice are used. These xenograft lines are maintained by continual passage in BALB/cSLc-nu/nu mice. Mice bearing GK1X, GK2X and GK3X tumors (6-8 mice per group) are treated daily with vehicle or 40 mg/kg Imatinib or Nilotinib for 4 weeks. Tumor volume (TV) is determined from caliper measurements of tumor length (L) and width (w) according to the formula $LW^2/2$. TV is determined every two to three days and on the day of evaluation. Mice are sacrificed and the percentage of tumor growth inhibition (TGI) is calculated as follows: TGI (%)=[1-(mean of treatment group tumor volume on evaluation day-mean of treatment group tumor volume on day 1)/(mean of control group tumor volume on evaluation day-mean of control group tumor volume on day 1)]×100. Rats[3] Female Wistar albino rats, weighing 226-243 g (mean weight, 241.09 g), for use in this study. Nilotinib, administered 20 mg/kg/d in two divided doses, is administered to the Nilotinib group of rats (n=7) for 13 d through an orogastric tube, beginning on the same day as indomethacin administration. Blood and tissue samples for pathological examination are obtained from all rats under ether anesthesia at the end of the 13-d period. All animals are then sacrificed by decapitation. 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). pii: eaaq1093.

- **Cell Syst**. 2018 Apr 25;6(4):424-443.e7.
- **Stem Cell Reports**. 2019 May 14;12(5):996-1006.
- **ACS Chem Biol**. 2016 Apr 15;11(4):992-1000.
- **Target Oncol**. 2020 Aug 11.

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REFERENCES

[1]. Weisberg E, et al. Beneficial effects of combining nilotinib and imatinib in preclinical models of BCR-ABL+ leukemias. Blood. 2007 Mar 1;109(5):2112-20.

[2]. Sako H, et al. Antitumor effect of the tyrosine kinase inhibitor Nilotinib on gastrointestinal stromal tumor (GIST) and Imatinib-resistant GIST cells. PLoS One. 2014 Sep 15;9(9):e107613.

[3]. Dervis Hakim G, et al. Mucosal healing effect of nilotinib in indomethacin-induced enterocolitis: A rat model. World J Gastroenterol. 2015 Nov 28;21(44):12576-85.

[4]. Fujita KI, et al. Involvement of the Transporters P-Glycoprotein and Breast Cancer Resistance Protein in Dermal Distribution of the Multikinase Inhibitor Regorafenib and Its Active Metabolites. J Pharm Sci. 2017 Sep;106(9):2632-2641.

[5]. Meirson T, et al. Targeting invadopodia-mediated breast cancer metastasis by using ABL kinase inhibitors. Oncotarget. 2018 Apr 24;9(31):22158-22183.

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