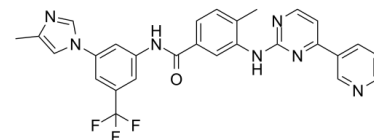


## Data Sheet

<b>Product Name:</b>	Nilotinib
<b>Cat. No.:</b>	CS-0102
<b>CAS No.:</b>	641571-10-0
<b>Molecular Formula:</b>	C <sub>28</sub> H <sub>22</sub> F <sub>3</sub> N <sub>7</sub> O
<b>Molecular Weight:</b>	529.52
<b>Target:</b>	Autophagy; Bcr-Abl
<b>Pathway:</b>	Autophagy; Protein Tyrosine Kinase/RTK
<b>Solubility:</b>	DMSO : 6 mg/mL (11.33 mM; Need ultrasonic); H <sub>2</sub> O : < 0.1 mg/mL (insoluble)



### BIOLOGICAL ACTIVITY:

Nilotinib is a second generation tyrosine kinase inhibitor (TKI), is significantly more potent against **BCR-ABL** than Imatinib, and is active against many Imatinib-resistant BCR-ABL mutants. IC<sub>50</sub> & Target: Bcr-Abl<sup>[1]</sup> **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<sub>50</sub><30 nM), Nilotinib also maintains activity against most of the BCR-ABL point mutants that confer Imatinib resistance<sup>[1]</sup>. 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<sub>50</sub> 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<sub>50</sub> values of 11.74±0.17 μM (P<0.001) and 41.37±1.07 μM (P<0.001), respectively<sup>[2]</sup>. **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<sup>[2]</sup>. 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<sup>[3]</sup>.

### PROTOCOL (Extracted from published papers and Only for reference)

**Cell Assay:** Nilotinib is prepared in 100% DMSO (10 mM) and then diluted to final concentration in medium<sup>[2],[2]</sup> 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<sub>50</sub>) is calculated<sup>[2]</sup>.

**Animal Administration:** Nilotinib is dissolved in N-methyl-2-pyrrolidone (NMP) at 100 mg/mL and diluted 1:10 (10 plus 90 v/v) with polyethylene glycol 300 (PEG300) to final 10 mg/mL (Mice)<sup>[2]</sup>. ;Nilotinib is prepared in DMSO and then dioluted with saline (Rats)<sup>[3]</sup>.<sup>[3]</sup>Mice<sup>[2]</sup>

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:  $TGI (\%) = [1 - (\text{mean of treatment group tumor volume on evaluation day} - \text{mean of treatment group tumor volume on day 1}) / (\text{mean of control group tumor volume on evaluation day} - \text{mean of control group tumor volume on day 1})] \times 100$

control group tumor volume on day 1)] $\times 100$ .

#### Rats<sup>[3]</sup>

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.

#### 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.

#### CAIndexNames:

Benzamide, 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-

#### SMILES:

O=C(NC1=CC(C(F)(F)F)=CC(N2C=NC(C)=C2)=C1)C3=CC=C(C)C(NC4=NC=CC(C5=CC=CN=C5)=N4)=C3

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

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