Rebastinib

Cat. No.: HY-13024

CAS No.: 1020172-07-9

Molecular Formula: $C_{30}H_{28}FN_7O_3$

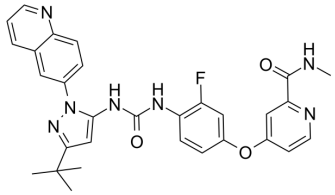
Molecular Weight: 553.59

Target: Bcr-Abl; FLT3; Src; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (90.32 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8064 mL	9.0320 mL	18.0639 mL
	5 mM	0.3613 mL	1.8064 mL	3.6128 mL
	10 mM	0.1806 mL	0.9032 mL	1.8064 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: ≥ 2.08 mg/mL (3.76 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Rebastinib (DCC-2036) is an orally active, non-ATP-competitive Bcr-Abl inhibitor for $Abl1^{WT}$ and $Abl1^{T315I}$ with IC_{50}s of 0.8 nM and 4 nM, respectively. Rebastinib also inhibits SRC, KDR, FLT3, and Tie-2, and has low activity to seen towards c-Kit.

IC_{50} & Target

IC50: 0.75±0.11 nM ($ABL1^{WT}$), 2±0.3 nM (FLT3), 4±0.3 nM (KDR), 6±0.3 nM (TIE2), 34±6 nM (SRC)[1]

In Vitro

Rebastinib potently (IC_{50} 0.82 nM) inhibits u-$ABL1^{native}$, which is thought to exist predominantly in the inactive type II conformation. In addition, Rebastinib also strongly inhibits p-$ABL1^{native}$ (IC_{50} 2 nM), which more readily adopts an active, Type I conformation[1].

Rebastinib potently inhibits both u-$ABL1^{T315I}$ (IC_{50} 5 nM) and p-$ABL1^{T315I}$ (IC_{50} 4 nM), both of which exist predominately in the Type I conformation due to stabilization of an activating hydrophobic spine by the T315I mutation[1].

	In addition to ABL1, Rebastinib also inhibits the SRC family kinases LYN, SRC, FGR, and HCK, and PDGFRα, and PDGFRβ with IC_{50} of 29±1, 34±6, 38±1, 40±1, 70±10 and 113±10 nM, respectively. Notably, Rebastinib spared c-KIT (IC_{50} 481 nM)[1]. Rebastinib effectively inhibits the proliferation of Ba/F3 cells expressing native BCR-ABL1^{native} (IC_{50} 5.4 nM). Rebastinib also inhibits proliferation of the Ph^+ cell line K562 (IC_{50} 5.5 nM)[1]. Rebastinib also inhibits proliferation of several common TKI-resistant mutants of BCR-ABL1, including G250E, Q252H, Y235F, E255K, V299L, F317L, and M351T, at IC_{50}s ranging from 6-150 nM. Rebastinib effectively inhibits autophosphorylation of BCR-ABL1^{native} (IC_{50} 29 nM) and BCR-ABL1^{T315I} (IC_{50} 18 nM), as well as the phosphorylation of STAT5 in both cell lines (IC_{50} 28 nM and 13 nM, respectively)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	A single dose of Rebastinib (DCC-2036; oral; 100 mg/kg) affords circulating plasma levels that exceeds 12 μM for up to 24 hours, and effectively inhibits BCR-ABL1 signaling for up to 8 hours in Ba/F3-BCR-ABL1^{T315I} leukemia cells isolated from BM and spleen of tumor-bearing mice[1]. Treatment of mice bearing Ba/F3-BCR-ABL1^{T315I} leukemia cells with Rebastinib at 100 mg/kg once daily by oral gavage significantly prolonged their survival, while STI571 at 100 mg/kg twice daily is ineffective[1]. In this aggressive allograft model, Rebastinib is as effective for treatment of BCR-ABL^{T315I} leukemia as STI571 at 100 mg/kg twice daily in BCR-ABL1^{native} leukemia, and reduces the leukemia cell burden in the spleens of treated mice[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Ba/F3 cells (3×10^3 cells/well) or primary Ph+ leukemia cells (5×10^4 cells/well) are plated in triplicate in 96-well plates containing test compounds (e.g., Rebastinib (DCC-2036)). After 72h, viable cells are quantified by resazurin or MTT assay. Results represent an average of at least three independent experiments[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Ba/F3 cells (1×10^6) transformed to interleukin-3 independence by transduction with either BCR-ABL1^{native} or BCR-ABL1^{T315I} retrovirus are injected intravenously into syngeneic Balb/c recipients. Beginning day 3 post-injection, mice are treated with STI571 (100 mg/kg in water twice daily via oral gavage) or with Rebastinib (DCC-2036) (100 mg/kg in 0.5% CMC/1% Tween-80, once daily via oral gavage) or with vehicle (0.5% CMC/1% Tween-80) alone. For induction of CML-like leukemia, bone marrow (BM) from male Balb/c donor mice is harvested 4d after intravenous administration of 150 mg/kg 5-FU, transduced with BCR-ABL1^{T315I} retrovirus, and 5×10^5 cells injected intravenously into sublethally irradiated (400 cGy) Balb/c recipients. Beginning at d5 post-transplant, cohorts are treated once daily by oral gavage with vehicle alone, or Rebastinib (DCC-2036) at 100 mg/kg. For induction of B-cell acute lymphoblastic leukemia, BM from donors not pretreated with 5-FU is transduced once with BCR-ABL1^{T315I} retrovirus and 1×10^6 cells injected into sublethally irradiated Balb/c recipients. Beginning at d8 post-transplant, cohorts are treated twice daily by oral gavage with vehicle alone, with Rebastinib (DCC-2036) at 60 mg/kg, with STI571 at 100 mg/kg (in water), or with BMS-354825 at 10 mg/kg (in 80 mM citric acid pH 3.1). 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.
- Nat Commun. 2021 Jan 25;12(1):504.
- J Exp Clin Cancer Res. 2022 Apr 21;41(1):149.
- J Med Chem. 2015 Jan 8;58(1):466-79.
- Anticancer Drugs. 2023 Jul 14.

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REFERENCES

[1]. Chan WW, et al. Conformational control inhibition of the BCR-ABL1 tyrosine kinase, including the gatekeeper T315I mutant, by the switch-control inhibitor DCC-2036. Cancer Cell. 2011, 19(4), 556-568.

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