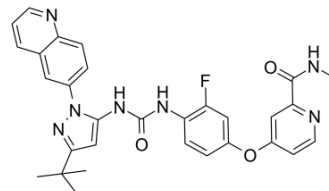


Rebastinib

Cat. No.:	HY-13024		
CAS No.:	1020172-07-9		
Molecular Formula:	C ₃₀ H ₂₈ FN ₇ O 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	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro	DMSO : 50 mg/mL (90.32 mM); ultrasonic and warming and heat to 80°C)				
		Solvent Concentration	Mass 1 mg	5 mg	10 mg
	Preparing Stock Solutions	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 a non-ATP-competitive Bcr-Abl inhibitor for Abl1 ^{WT} and Abl1 ^{T315I} with IC ₅₀ of 0.8 nM and 4 nM, also inhibits SRC, KDR, FLT3, and Tie-2, and low activity to seen towards c-Kit.
IC₅₀ & Target	IC ₅₀ : 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 (DCC-2036) inhibits ABL1 ^{native} and the gatekeeper mutant ABL1 ^{T315I} with IC ₅₀ of 0.8 nM and 4 nM, respectively. 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. More significantly, 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. Rebastinib also potently inhibits ABL1H396P (IC₅₀ 1.4 nM), which, like ABL1^{T315I}, is predisposed to exist predominately in a Type I activated conformation due to the restricted backbone torsional angles imposed by the mutant Pro396. In addition to ABL1, Rebastinib also inhibits the SRC family kinases LYN, SRC, FGR, and HCK, and PDGFR α , and PDGFR β with IC₅₀ of 29 \pm 1, 34 \pm 6, 38 \pm 1, 40 \pm 1, 70 \pm 10 and 113 \pm 10 nM, respectively. Notably, Rebastinib spared c-KIT (IC₅₀ 481 nM). Rebastinib effectively inhibits the proliferation of Ba/F3 cells expressing native BCR-ABL1^{native} (IC₅₀ 5.4 nM). Rebastinib also inhibits proliferation of the Ph⁺ cell line K562 (IC₅₀ 5.5 nM). REBASTINIB (DCC-2036) also inhibits proliferation of several common TKI-resistant mutants of BCR-ABL1, including G250E, Q252H, Y235F, E255K, V299L, F317L, and M351T, at IC₅₀s ranging from 6-150 nM. Rebastinib effectively inhibits autophosphorylation of BCR-ABL1^{native} (IC₅₀ 29 nM) and BCR-ABL1^{T315I} (IC₅₀ 18 nM), as well as the phosphorylation of STAT5 in both cell lines (IC₅₀ 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 oral dose of Rebastinib (DCC-2036) at 100 mg/kg afforded circulating plasma levels that exceeded 12 μ M for up to 24 hours (data not shown), and effectively inhibited 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, as assessed by intracellular flow cytometric staining for phospho-STAT5 and immunoblotting of tissue extracts for phospho-BCR-ABL1 and phospho-STAT5. 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. In this aggressive allograft model, Rebastinib (DCC-2036) is as effective for treatment of BCR-ABL^{T315I} leukemia as STI571 at 100 mg/kg twice daily is for treatment of BCR-ABL1^{native} leukemia, and reduced 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 \times 10³ cells/well) or primary Ph⁺ leukemia cells (5 \times 10⁴ 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 \times 10⁶) 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 \times 10⁵ 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 \times 10⁶ 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 Med Chem. 2015 Jan 8;58(1):466-79.
- Patent. US20170349880A1.

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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.

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

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