Web: www.taiclone.com
Tel: +886-2-2735-9682
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Rebastinib

Catalog No: tcsc1038

Available Sizes

Size: 5mg

Size: 10mg

Size: 50mg

Specifications

CAS No:
1020172-07-9

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

Pathway:
Protein Tyrosine Kinase/RTK;Protein Tyrosine Kinase/RTK;Protein Tyrosine Kinase/RTK

Target:
Src;Bcr-Abl;FLT3

Purity / Grade:
>98%

Solubility:
DMSO : ≥ 320 mg/mL (578.05 mM)

Alternative Names:
DCC-2036

Observed Molecular Weight:
553.59

Product Description

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Rebastinib (DCC-2036) is a conformational control **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: 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 (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 (IC_{50} 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 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). 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). 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 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].

In Vivo: A single oral dose of Rebastinib (DCC-2036) at 100 mg/kg afforded circulating plasma levels that exceeded 12 μM 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 imatinib 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 imatinib 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].