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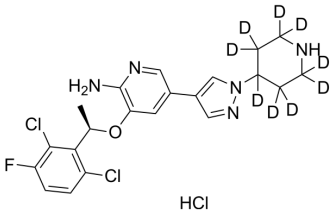
Crizotinib-d_9 hydrochloride

Cat. No.:	HY-50878AS
Molecular Formula:	$C_{21}H_{14}D_9Cl_3FN_5O$
Molecular Weight:	495.85
Target:	c-Met/HGFR; Autophagy; Anaplastic lymphoma kinase (ALK); ROS Kinase; Isotope-Labeled Compounds
Pathway:	Protein Tyrosine Kinase/RTK; Autophagy; Others
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Crizotinib-d_9 hydrochloride is deuterated labeled Crizotinib hydrochloride (HY-50878A). Crizotinib hydrochloride (PF-02341066 hydrochloride) is an orally bioavailable, selective, and ATP-competitive dual ALK and c-Met inhibitor with IC_{50}s of 20 and 8 nM, respectively. Crizotinib hydrochloride (PF-02341066 hydrochloride) inhibits tyrosine phosphorylation of NPM-ALK and tyrosine phosphorylation of c-Met with IC_{50}s of 24 and 11 nM in cell-based assays, respectively. It is also a ROS proto-oncogene 1 (ROS1) inhibitor. Crizotinib hydrochloride (PF-02341066 hydrochloride) has effective tumor growth inhibition[1][2][3].

In Vitro

Stable heavy isotopes of hydrogen, carbon, and other elements have been incorporated into drug molecules, largely as tracers for quantitation during the drug development process. Deuteration has gained attention because of its potential to affect the pharmacokinetic and metabolic profiles of drugs[1].

PF-2341066 displays similar potency against c-Met phosphorylation in mIMCD3 mouse or MDCK canine epithelial cells with IC_{50} of 5 nM and 20 nM, respectivly. PF-2341066 shows improved or similar activity against NIH3T3 cells engineered to express c-Met ATP-binding site mutants V1092I or H1094R or the P-loop mutant M1250T with IC_{50} of 19 nM, 2 nM and 15 nM, respectively, compared with NIH3T3 cells expressing wild-type receptor with IC_{50} of 13 nM. In contrast, a marked shift in potency of PF-2341066 is observed against cells engineered to express c-Met activation loop mutants Y1230C and Y1235D with IC_{50} of 127 nM and 92 nM, respectively, compared with wild-type receptor. PF-2341066 also potently prevents the phosphorylation of c-Met in NCI-H69 and HOP92 cells, with IC_{50} of 13 nM and 16 nM, respectively, which express the endogenous c-Met variants R988C and T1010I, respectively[2].

PF-2341066 also potently inhibits NPM-ALK phosphorylation in Karpas299 or SU-DHL-1 ALCL cells with an IC_{50} of 24 nM. PF-2341066 potently prevents cell proliferation, which is associated with G(1)-S-phase cell cycle arrest and induction of apoptosis in ALK-positive ALCL cells with IC_{50} of 30 nM, but not ALK-negative lymphoma cells[3].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

PF-2341066 reveals the ability to cause marked regression of large established tumors (> 600 mm^3) in both the 50 mg/kg/day and 75 mg/kg/day treatment cohorts, with a 60% decrease in mean tumor volume over the 43-day administration schedule in the GTL-16 model. In an another study, PF-2341066 displays the ability to completely inhibits GTL-16 tumor growth for >3 months, with only 1 of 12 mice exhibiting a significant increase in tumor growth over the 3-month treatment schedule at 50 mg/kg/day. A significant dose-dependent reduction of CD31-positive endothelial cells is observed at 12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day in GTL-16 tumors, indicating that inhibition of MVD shows a dose-dependent correlation to antitumor efficacy. PF-2341066 displays a significant dose-dependent reduction of human VEGFA and IL-8 plasma levels in both the GTL-16 and U87MG models. Marked inhibition of phosphorylated c-Met, Akt, Erk, PLCλ1, and STAT5 levels is observed in GTL-16 tumors following p.o. administration of PF-2341066[2].

Treatment of c-MET-amplified GTL-16 xenografts with 50 mg/kg PF-2341066 elicits tumor regression that is associated with a

slow reduction in 18F-FDG uptake and decreases expression of the glucose transporter 1, GLUT-1[5].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

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[5]. Russak EM, et al. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. Ann Pharmacother. 2019 Feb;53(2):211-216.

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