

Product Data Sheet

Product Name: Ponatinib (hydrochloride)

Cat. No.: GC52104

Chemical Properties

Cas. No. 1114544-31-8

SMILES O=C(C1=CC=C(C)C(C#CC2=CN=C3C=CC=NN23)=C1)N([H])C4=CC=C(CN5CCN(CC5)C)C(C(F)(F)F)=C4.Cl

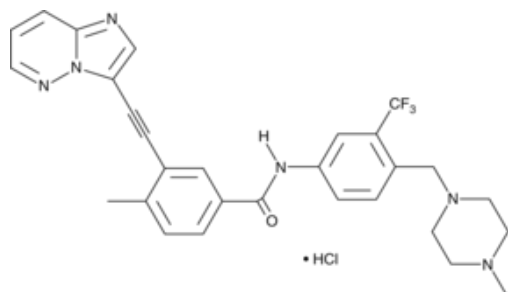
Formula C₂₉H₂₇F₃N₆O • HCl M.Wt 569

Solubility DMF: 2 mg/ml, DMSO: 11 mg/ml, Ethanol: Slightly soluble Storage -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

Cell lines SW26 (ALT-positive) and SW39 (telomerase-positive) isogenic cell lines derived from IMR90; osteosarcoma (OS) cell lines (SAOS-2, U2OS, T1000, CAL72); well-differentiated liposarcoma (LPS) cell lines; telomerase-positive cell lines (HT161, HOS); normal lung-derived IMR90 fibroblasts

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The cells were used in a comparative anti-cancer compound library screen and Preparation Method subsequent validation assays. ALT cell lines used in these experiments were ATRX-deficient. ALT cell lines were treated with Ponatinib at 125-250nM.

Reaction
Conditions 125-250nM; 24-72h

Applications Ponatinib exhibited enhanced killing of ALT-positive cells compared to telomerase-positive cells. Ponatinib induced an increase in extrachromosomal telomeric C-circles (a marker of ALT activity) in all tested ALT cell lines after 72 hours. Ponatinib provoked telomeric dysfunction, increased levels of telomere dysfunction-induced foci (TIFs), and caused specific telomere damage and replicative stress (evidenced by colocalization of pS33 RPA and telomeric DNA). Ponatinib interfered with telomeric replication and synthesis, decreasing newly BrdU-labelled telomeres and reducing ALT telomere DNA synthesis in APBs (ATSA assay). Ponatinib treatment also induced DNA damage (increased γ H2AX), promoted the formation of large telomere foci, and triggered senescence in ALT cell lines. Ponatinib inhibited an ABL1-JNK-JUN signaling circuit, reducing phosphorylation of JUN at Serine 63 and Threonine 91/93 and decreasing total JUN protein levels.

Animal experiment [2]:

Animal models Female C57BL/6J mice (for B16-F10 melanoma and GL261 glioblastoma models) and BALB/c mice (for 4T1 breast carcinoma model), 6-8 weeks old

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B16-F10 melanoma tumour model was established by injecting 2×10^5 cells with matrigel subcutaneously into the right flank of C57BL/6J mice. 4T1 breast carcinoma model was established by injecting 8×10^5 cells in the mammary pad Preparation Method of BALB/c female mice. GL261 glioblastoma model was established by implanting 1×10^6 cells in the right flank of C57BL/6 mice. Once the tumour volume reached 50–100mm³, mice were randomly divided into groups and the Ponatinib (15mg/kg) was administered daily for 10 days.

Dosage form 15mg/kg; i.p.; daily for 10day

Applications Ponatinib treatment significantly delayed the growth of B16-F10 melanoma and 4T1 breast tumours and reduced tumour weights. Ponatinib enhanced CD8⁺ T cell infiltration in the tumour microenvironment (TME), downregulated PD-L1 expression and downstream signalling molecules (p-P38, p-Erk, p-JNK), increased cleaved caspase-3 expression, regulated the Th1/Th2 balance (increased IFN- γ , decreased IL-4, increased Th1/Th2 ratio), increased IL-2 levels, lowered FoxP3 expression, and depleted tumour-associated macrophages (TAMs). Ponatinib also induced a favourable systemic antitumour immunity by enhancing CD8⁺ T cell population, tumour-specific CTL activity, balancing the Th1/Th2 ratio, and lowering PD-L1 expression.

References:

- [1] Kusuma FK, Prabhu A, Tio G, et al. Signalling inhibition by ponatinib disrupts productive alternative lengthening of telomeres (ALT). Nat Commun. 2023 Apr 6;14(1):1919.
- [2] Barnwal A, Tamang R, Sanjeev Das, et al. Ponatinib delays the growth of solid tumours by remodelling immunosuppressive tumour microenvironment through the inhibition of induced PD-L1 expression. Br J Cancer. 2023 Oct;129(6):1007-1021.

Background

Ponatinib (hydrochloride) is a multi-target tyrosine kinase inhibitor that inhibits the activity of Abl

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(IC₅₀=0.37nM), PDGFR α (IC₅₀=1.1nM), VEGFR2 (IC₅₀=1.5nM), FGFR1 (IC₅₀=2.2nM), and Src (IC₅₀=5.4nM). Ponatinib can be used in research related to chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia^[1-4].

In vitro, treatment of BIN67 and SCCOHT-1 cells with Ponatinib (1 μ M) for 1 hour significantly inhibited the phosphorylation of p38 and Akt^[5]. Ponatinib (125-250nM) was used to treat SAOS-2, CAL72, U2OS, and T1000 cells for 24-72 hours. Ponatinib significantly increased telomeric C-circle levels in cells and induced DNA damage and telomere dysfunction^[6].

In vivo, Ponatinib (5mg/kg) was administered to ob/ob mice via oral gavage for 8 weeks. Ponatinib significantly improved insulin sensitivity in obese mice^[7]. Ponatinib (15mg/kg) was administered intraperitoneally once daily to C57BL/6J or BALB/c mice for 10 days. Ponatinib significantly delayed the growth of B16-F10 melanoma and 4T1 breast cancer and reduced tumor weight^[8].

References:

- [1] O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009 Nov 6;16(5):401-12.
- [2] Gozgit JM, Wong MJ, Wardwell S, et al. Potent activity of Ponatinib (hydrochloride) in models of FLT3-driven acute myeloid leukemia and other hematologic malignancies. Mol Cancer Ther. 2011 Jun;10(6):1028-35.
- [3] Uchida T, Kitaura J, Nakahara F, et al. Hes1 upregulation contributes to the development of FIP1L1-PDGRA-positive leukemia in blast crisis. Exp Hematol. 2014 May;42(5):369-379.e3.
- [4] Dufies M, Cassuto O, Jacquelin A, et al. Ponatinib circumvents all types of imatinib resistance in chronic myelogenous leukemia cell lines. Cell Cycle. 2013 Jun 1;12(11):1645-6.
- [5] Lang JD, Hendricks WPD, Orlando KA, et al. Ponatinib Shows Potent Antitumor Activity in Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT) through Multikinase Inhibition. Clin Cancer Res. 2018 Apr 15;24(8):1932-1943.
- [6] Kusuma FK, Prabhu A, Tio G, et al. Signalling inhibition by ponatinib disrupts productive alternative lengthening of telomeres (ALT). Nat Commun. 2023 Apr 6;14(1):1919.
- [7] Lin Z, Lin X, Lai Y, et al. Ponatinib modulates the metabolic profile of obese mice by inhibiting adipose tissue macrophage inflammation. Front Pharmacol. 2022 Nov 15;13:1040999.
- [8] Barnwal A, Tamang R, Sanjeev Das, et al. Ponatinib delays the growth of solid tumours by remodelling immunosuppressive tumour microenvironment through the inhibition of induced PD-L1

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