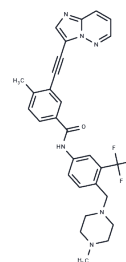


Ponatinib

Chemical Properties

CAS No. :	943319-70-8
Formula:	C ₂₉ H ₂₇ F ₃ N ₆ O
Molecular Weight:	532.56
Storage:	Powder: -20°C for 3 years In solvent: -80°C for 1 year Actual storage temperature shall be subject to the COA.



Biological Description

Description	Ponatinib (AP24534) is an orally available, multitargeted kinase inhibitor with IC ₅₀ values of 0.37 nM (Abl), 1.1 nM (PDGFR α), 1.5 nM (VEGFR2), 2.2 nM (FGFR1), and 5.4 nM (Src).
Targets(IC ₅₀)	FGFR,Bcr-Abl,Autophagy,c-Kit,PDGFR,Src,VEGFR
In vitro	Ponatinib (AP24534) potently inhibited native ABL (IC ₅₀ : 0.37 nM), ABL T315I (IC ₅₀ : 2.0 nM), and other clinically important ABL kinase domain mutants (IC ₅₀ : 0.30–0.44 nM). AP24534 also inhibited SRC (IC ₅₀ : 5.4 nM) and members of the VEGFR, FGFR, and PDGFR families of receptor tyrosine kinases. AP24534 did not inhibit Aurora kinase family members, nor did it inhibit the insulin receptor or CDK2/Cyclin E. AP24534 potently inhibited proliferation of Ba/F3 cells expressing native BCR-ABL (IC ₅₀ : 0.5 nM). All BCR-ABL mutants tested remained sensitive to AP24534 (IC ₅₀ : 0.5–36 nM) including BCR-ABL T315I (IC ₅₀ : 11 nM) [1]. Treatment with ponatinib efficiently inhibited the growth of CMPs expressing Hes1 with F/P, F/P-T674I, or F/P-D842V with an IC ₅₀ of 0.15 nM, 0.35 nM, or 1.71 nM, respectively. In accordance, ponatinib dose-dependently suppressed the activation of F/P and its downstream STAT5 and ERK in these cytokine-independent cells [2]. Ponatinib potently inhibits receptor phosphorylation and cellular proliferation with IC ₅₀ values comparable to those required for inhibition of BCR-ABL (0.3 to 20 nmol/L) [3].
In vivo	Daily oral treatment with 2.5 or 5 mg/kg AP24534 for 19 days prolonged median survival to 27.5 and 30 days, respectively. In a xenograft model of Ba/F3 BCR-ABL T315I cells, tumor growth was inhibited by AP24534 in a dose-dependent manner compared to vehicle-treated mice, with significant suppression of tumor growth upon daily oral dosing at 10 and 30 mg/kg. Daily oral dosing of 50 mg/kg AP24534 caused significant tumor regression, with a 96% reduction in mean tumor volume at the final measurement compared to the start of treatment [1]. Ponatinib (1–25 mg/kg, p.o.) was administered orally, once daily for 28 days, to mice bearing MV4-11 xenografts. ponatinib potently inhibited tumor growth in a dose-dependent manner. Administration of 1 mg/kg led to significant inhibition of tumor growth (TGI = 46%) and doses of 2.5 mg/kg or greater resulted in tumor regression. Dosing with 10 or 25 mg/kg led to complete and durable tumor regression [3].
Kinase Assay	AP24534 was profiled against >100 kinases by Reaction Biology Corporation using the Kinase Hotspot assay, which utilizes 10 μ M [33P]-ATP, recombinant kinase domain, peptide substrate, and a range of 10 concentrations of inhibitor to establish an IC ₅₀

Kinase Assay	value [1].
Cell Research	Ba/F3 cell lines were distributed in 96-well plates (4×10^3 cells/well) and incubated with escalating concentrations of AP24534 for 72 hr. The inhibitor ranges used were: 0-625 nM for cells expressing BCR-ABL and 0-10,000 nM for BCR-ABL negative cells. Proliferation was measured using an MTS-based viability assay. IC50 values are reported as the mean of three independent experiments performed in quadruplicate. For cell proliferation experiments with CML or normal primary cells, mononuclear cells were plated in 96-well plates (5×10^4 cells/well) over graded concentrations of AP24534 (0-1000 nM) in RPMI supplemented with 10% FBS, L-glutamine, penicillin/streptomycin, and 100 μ M β -mercaptoethanol. Following a 72 hr incubation, cell viability was assessed by subjecting cells to an MTS assay. All values were normalized to the control wells with no drug [1].
Animal Research	Briefly, tumor xenografts were established by the subcutaneous implantation of MV4-11 cells (1×10^7 in 50% Matrigel) into the right flank of female CB.17 severe combined immunodeficient mice and dosing was initiated when the average tumor volume reached approximately 200 mm ³ . Ponatinib was formulated in aqueous 25 mmol/L citrate buffer (pH = 2.75) and mice were dosed orally once daily for 4 weeks. The tumors were measured in 2 dimensions (length and width) with a caliper in millimeters. Tumor volume (mm ³) was calculated with the following formula: tumor volume = (length \times width ²)/2. Tumor growth inhibition (TGI) was calculated as follows: TGI = $(1 - \Delta T / \Delta C) \times 100$, where ΔT stands for mean tumor volume change of each treatment group and ΔC for mean tumor volume change of control group. The tumor volume data were collected and analyzed with a 1-way ANOVA test to determine the overall difference among groups. Each ponatinib treatment group was further compared to the vehicle control group for statistical significance using Dunnett's Multiple Comparison Test. A P-value less than 0.05 was considered to be statistically significant and a P-value less than 0.01 to be highly statistically significant [3].

Solubility Information

Solubility	Ethanol: 26.6 mg/mL (49.95 mM), Sonication is recommended. DMSO: 25 mg/mL (46.94 mM), Sonication and heating are recommended. H2O: < 1 mg/mL (insoluble) (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 5.33 mg/mL (10.01 mM), Suspension. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.8777 mL	9.3886 mL	18.7772 mL
5 mM	0.3755 mL	1.8777 mL	3.7554 mL
10 mM	0.1878 mL	0.9389 mL	1.8777 mL
50 mM	0.0376 mL	0.1878 mL	0.3755 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

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