

Product Data Sheet

Product Name: PLX7904

Cat. No.: GC10324

Chemical Properties

Cas. No. 1393465-84-3

SMILES O=C(C1=CNC2=NC=C(C3=CN=C(C4CC4)N=C3)C=C21)C5=C(F)C=CC(NS(=O)(N(CC)C)=O)=C5F

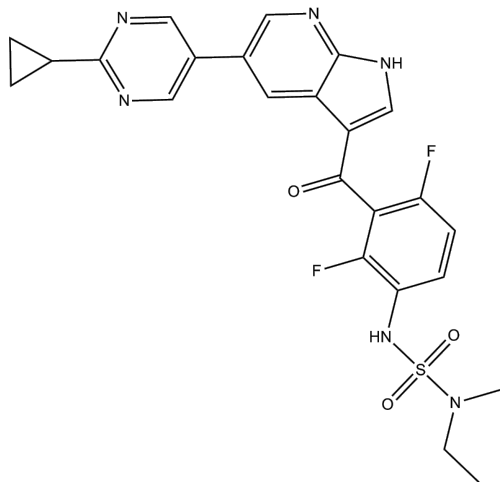
Formula $C_{24}H_{22}F_2N_6O_3S$ M.Wt 512.53

Solubility DMSO: >5mg/ml Storage Store at -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

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

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Cell experiment: For MTT assays, 2×10^3 cells are seeded in triplicate in 96 wells in their regular culture medium (containing PLX4720 for PRT lines). Next day, cells are washed twice with PBS and then the medium is replenished containing the indicated RAF inhibitor. Medium is changed 48 hours later and after a further 48 hours, 10 μ L of 5 mg/mL MTT reagent is added to wells, and incubated for three hours. Formazan crystals are then solubilized overnight with a 1:10 dilution of 0.1 M glycine (pH 10.5) in DMSO. Wells are then analyzed at 450 nm in a Multiskan® Spectrum spectrophotometer. Results depicted are normalized to DMSO conditions and are a composite of three independent experiments. Error bars shown are representative of the standard error of mean (SEM).

Animal experiment: COLO205 tumour cells are cultured in DMEM 10% FBS 1% penicillin/streptomycin supplemented with bovine insulin, at 37°C. Balb/C nude mice, female, 6-8 weeks old, weighing approximately 18-22 g, are inoculated subcutaneously at the right flank with COLO205 tumour cells (5×10^6) in 0.1 mL of PBS mixed with matrigel (50:50) for tumour development. The treatment is started when mean tumour size reach approximately 100 mm³, with eight mice in each treatment group randomized to balance the average weight and tumour size. B9 cells are expanded in DMEM 10% FBS 1% penicillin/streptomycin. Upon trypsinization the cells are washed three times with 20 mL RPMI, and after the final centrifugation are re-suspended, counted, and adjusted by volume to a final concentration of 5×10^7 cells per millilitre. B9 xenografts are started by injection of 5×10^6 cells subcutaneously in 6- to 7-week-old female nude Balb/c mice. Compound dosing starts when the average size of tumours reach 50-70 mm³. Animals are equally distributed over treatment groups (n=10) to balance the average tumour size and body weight. Animals are dosed orally for days 1-14 twice daily and days 15-28 once daily with vehicle, vemurafenib 50 mg per kg, or PLX7904 50 mg per kg. 12-O-tetradecanoylphorbol-13-acetate (TPA) is put on the skin of all mice twice a week during weeks 3 and 4 at a dose of 2 μ g in 200 μ L acetone.

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References:

- [1]. Zhang C, et al. RAF inhibitors that evade paradoxical MAPK pathway activation. Nature. 2015 Oct 22;526(7574):583-586.
- [2]. Basile KJ, et al. Inhibition of mutant BRAF splice variant signaling by next-generation, selective RAF inhibitors. Pigment Cell Melanoma Res. 2014 May;27(3):479-84
- [3]. Le K, et al. Selective RAF inhibitor impairs ERK1/2 phosphorylation and growth in mutant NRAS, vemurafenib-resistant melanoma cells. Pigment Cell Melanoma Res. 2013 Jul;26(4):509-17

Background

IC50: 0.17, 0.53, and 0.16 μ M for A375, COLO829 and COLO205 cell lines, respectively.

PLX7904 is a potent and selective BRAF inhibitor.

Oncogenic activation of BRAF leads to cancer growth by constitutively promoting RAS-independent mitogen-activated protein kinase pathway signalling. Therefore, BRAF inhibitors have provided substantially improved treatment of metastatic melanoma.

In vitro: Previous study showed that PLX7904 could inhibit the in-vitro growth of two melanoma cell lines (A375 and COLO829) and an additional human colorectal cancer cell line COLO205 expressed BRAFV600E. The gene expression changes in B9 cells treated with vemurafenib and PLX7904 were compared, and results demonstrated that vemurafenib could alter transcription of 191 mouse genes by at least 1.9-fold, while PLX7904 had minimal effects. Moreover, both vemurafenib and its analogue PLX4720 were able to stimulate B9 colony formation, whereas PLX7904 was not [1].

In vivo: Animal study showed that both PLX7904 and vemurafenib could produce similar anti-tumour effects in a subcutaneous COLO205 xenograft model with matching doses at 25 mg/kg twice daily and plasma exposures. In addition, when evaluated in vivo, subcutaneous B9-tumour growth was accelerated by vemurafenib but not by PLX7904 when administered at the same dose [1].

Clinical trial: Up to now, PLX7904 is still in the preclinical development stage.

Reference:

- [1] Zhang C et al. RAF inhibitors that evade paradoxical MAPK pathway activation. Nature. 2015 Oct 22;526(7574):583-6.

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