

Product Data Sheet

Product Name: NMS-P715

Cat. No.: GC36752

Chemical Properties

Cas. No. 1202055-32-0

SMILES O=C(C1=NN(C)C2=C1CCC3=CN=C(NC4=CC=C(C(NC5CCN(C)CC5)=O)C=C4OC(F)(F)F)N=C23)NC6=C(CC)C=CC=C6CC

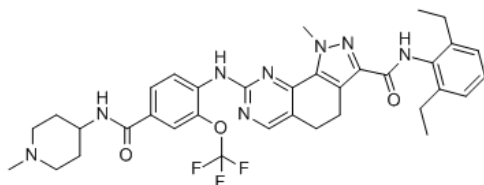
Formula $C_{35}H_{39}F_3N_8O_3$ M.Wt 676.73

Solubility DMSO: 2 mg/mL (2.96 mM) 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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Kinase experiment:	The potency of the compound towards MPS1 and 60 additional kinases belonging to kinase selectivity screening (KSS) panel is determined using either a strong anion exchanger based assay or P81 Multiscreen plate. MPS1 activity is measured using 5 nM of MPS1 recombinant protein in 50 mM HEPES pH 7.5, 2.5 mM MgCl ₂ , 1 mM MnCl ₂ , 1 mM DTT, 3 μM NaVO ₃ , 2 mM β-glycerophosphate, 0.2 mg/mL BSA, 200 μM P38-βtide substrate-peptide (KRQADEEMTGYVATR WYRAE) and 8 μM ATP with 1.5 nM 33P-γ-ATP. The assay is run in a robotized format, 10 serial 1:3 compounds dilutions (including NMS-P715, from 30 μM to 1.5 nM) are tested and IC ₅₀ determined[1].
Cell experiment:	Cells lines are seeded in 384 well-plates in the appropriate complete medium and treated with compounds (NMS-P715, etc.) dissolved in 0.1% DMSO 24 hours after seeding. The cells are incubated at 37°C and 5% CO ₂ and after 72 hours the plates are processed using CellTiter-Glo assay. Inhibitory activity is evaluated comparing treated versus control data using Assay Explorer software. IC ₅₀ of proliferation is calculated using sigmoidal interpolation curve fitting. Activity Ratio is calculated as the ratio of the single cell line IC ₅₀ and the IC ₅₀ average of all the cell lines tested[1].
Animal experiment:	Mice[1]Athymic nu-nu mice, 5-6 weeks of age (20-22 g) are used in the assay. A2780 ovary carcinoma and A375 melanoma cells are transplanted s.c. into female nu-nu mice. Mice bearing a palpable tumor (100-200 mm ³) are selected and randomized into control and treated groups. Treatment starts one day after randomization. NMS-P715 is typically administered by oral administration at doses of 90-100 mg/kg daily for more than seven days. Each group includes 8 animals. Tumor dimension is measured regularly by calipers during the experiments and tumor mass is calculated[1].

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References:

- [1]. Colombo R, et al. Targeting the mitotic checkpoint for cancer therapy with NMS-P715, an inhibitor of MPS1 kinase. Cancer Res. 2010 Dec 15;70(24):10255-64.
- [2]. Slee RB, et al. Selective inhibition of pancreatic ductal adenocarcinoma cell growth by the mitotic MPS1 kinase inhibitor NMS-P715. Mol Cancer Ther. 2014 Feb;13(2):307-315.

Background

NMS-P715 is a selective, ATP-competitive inhibitor of MPS1, with an IC₅₀ of 182 nM. Mps1|182 nM (IC₅₀)|CK2|5.7 μM (IC₅₀)|MELK|6.01 μM (IC₅₀)|NEK6|6.02 μM (IC₅₀)

NMS-P715 is a selective inhibitor of MPS1, with an IC₅₀ of 182 nM. NMS-P715 is highly specific for MPS1, with no other kinases inhibited below an IC₅₀ value of 5 μM and only 3 kinases inhibited below 10 μM (CK2, MELK, and NEK6). NMS-P715 promotes massive spindle assembly checkpoint (SAC) override with an EC₅₀ of 65 nM. NMS-P715 (1 μM) causes mitotic acceleration in U2OS cells overexpressing YFP-α-tubulin, induces aneuploidy and inhibits the proliferation of HCT116 cells. NMS-P715 (0.5, 1 μM) affects mitotic checkpoint complex (MCC) stability and cdc20 ubiquitylation[1]. NMS-P715 (1 μM) exhibits bypass of the spindle assembly checkpoint and apoptosis in pancreatic ductal adenocarcinoma (PDAC) cell lines. NMS-P715 (0-25 μM) also selectively inhibits growth of PDAC cells[2].

NMS-P715 (10 mg/kg) exhibits an oral bioavailability of 37% and good pharmacokinetic properties in nude mice bearing subcutaneous implanted human tumor cell xenografts. NMS-P715 (90 mg/kg, p.o.) is well tolerated and causes no signs of body weight loss or other overt toxicities in an A2780 ovary carcinoma xenograft model. NMS-P715 (100 mg/kg, p.o.) inhibits the tumor growth by approx 43% in the A375 melanoma xenograft model[1].

- [1]. Colombo R, et al. Targeting the mitotic checkpoint for cancer therapy with NMS-P715, an inhibitor of MPS1 kinase. Cancer Res. 2010 Dec 15;70(24):10255-64. [2]. Slee RB, et al. Selective inhibition of pancreatic ductal adenocarcinoma cell growth by the mitotic MPS1 kinase inhibitor NMS-P715. Mol Cancer Ther. 2014 Feb;13(2):307-315.

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