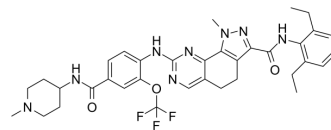


NMS-P715

| | | | |
|--------------------|--|-------|---------|
| Cat. No.: | HY-12382 | | |
| CAS No.: | 1202055-32-0 | | |
| Molecular Formula: | C ₃₅ H ₃₉ F ₃ N ₈ O ₃ | | |
| Molecular Weight: | 676.73 | | |
| Target: | Mps1 | | |
| Pathway: | Cell Cycle/DNA Damage; Cytoskeleton | | |
| Storage: | Powder | -20°C | 3 years |
| | | 4°C | 2 years |
| | In solvent | -80°C | 2 years |
| | | -20°C | 1 year |



SOLVENT & SOLUBILITY

| | | | | |
|---|--|--------------------------|-----------|-----------|
| In Vitro | DMSO : 2 mg/mL (2.96 mM); Need ultrasonic | | | |
| | | Solvent Concentration | Mass | |
| | | | 1 mg | 5 mg |
| | Preparing Stock Solutions | 1 mM | 1.4777 mL | 7.3885 mL |
| | | 5 mM | --- | |
| | | 10 mM | --- | |
| Please refer to the solubility information to select the appropriate solvent. | | | | |
| In Vivo | 1. Add each solvent one by one: 0.5% CMC/saline water Solubility: 3.33 mg/mL (4.92 mM); Suspended solution; Need ultrasonic | | | |

BIOLOGICAL ACTIVITY

| | | | | |
|---------------------------|--|-----------------------------------|-------------------------------------|-------------------------------------|
| Description | NMS-P715 is a selective, ATP-competitive inhibitor of MPS1, with an IC ₅₀ of 182 nM. | | | |
| IC ₅₀ & Target | Mps1 182 nM (IC ₅₀) | CK2 5.7 μM (IC ₅₀) | MELK 6.01 μM (IC ₅₀) | NEK6 6.02 μM (IC ₅₀) |
| In Vitro | NMS-P715 is a selective inhibitor of MPS1, with an IC ₅₀ of 182 nM. NMS-P715 is highly specific for MPS1, with no other kinases inhibited below an IC ₅₀ 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 EC ₅₀ 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] . | | | |

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

In Vivo

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].

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PROTOCOL

Kinase Assay ^[1]

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 MgCl₂, 1 mM MnCl₂, 1 mM DTT, 3 μM NaVO₃, 2 mM β-glycerophosphate, 0.2 mg/mL BSA, 200 μM P38-βtide substrate-peptide (KRQADEEMTGYVATRWYRAE) 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 IC₅₀ determined^[1].

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Cell Assay ^[1]

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% CO₂ 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. IC₅₀ of proliferation is calculated using sigmoidal interpolation curve fitting. Activity Ratio is calculated as the ratio of the single cell line IC₅₀ and the IC₅₀ average of all the cell lines tested^[1].

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Animal Administration ^[1]

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 mm³) 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].

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

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.

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

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