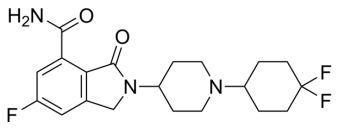
NMS-P118

Cat. No.:	HY-18954
CAS No.:	1262417-51-5
Molecular Formula:	$C_{20}H_{24}F_3N_3O_2$
Molecular Weight:	395.42
Target:	PARP
Pathway:	Cell Cycle/DNA Damage; Epigenetics
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 : 16 mg/mL (40.46 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5290 mL	12.6448 mL	25.2896 mL
	5 mM	0.5058 mL	2.5290 mL	5.0579 mL
	10 mM	0.2529 mL	1.2645 mL	2.5290 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

NMS-P118 is a potent, orally available, and highly selective PARP-1 Inhibitor for cancer therapy.

IC_{50} & Target

PARP-1	PARP-2
9 nM (Kd)	1390 nM (Kd)

In Vitro

NMS-P118 is found to be less myelotoxic in vitro than olaparib, a dual PARP-1/-2 inhibitor. NMS-P118 proves to be metabolically stable, it modestly inhibits two cytochrome P450 family members (CYP-2B6 IC_{50}: 8.15 μM; CYP-2D6 IC_{50}: 9.51 μM) out of eight isoforms tested. Its ability in hampering the proliferation of bone marrow cells is from 5 to > 60 times lower then olaparib according to the species[1].

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

In Vivo

NMS-P118 is a potent (K_D=0.009 μM) PARP-1 inhibitor, showing 150-fold selectivity over PARP-2 (K_D=1.39 μM). NMS-P118 possesses excellent pharmacokinetic profile and nearly complete oral bioavailability both in mice and rats. It proved to be highly efficacious in vivo both as single agent in MDA-MB-436 human breast cancer tumors and in combination with temozolomide in CAPAN-1 human pancreatic tumors growing as xenografts in the mouse. The compound is well tolerated at

	highly efficacious doses and is endowed with an excellent ADME profile[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	NMS-P118 is profiled on 56 different kinases (ABL, ACK1, AKT1, ALK, AUR1, AUR2, BRK, BUB1, CDC7/DBF4, CDK2/CYCA, CHK1, CK2, EEF2K, EGFR1, ERK2, EphA2, FAK, FGFR1, FLT3, GSK3beta, Haspin, IGFR1, IKK2, IR, JAK1, JAK2, JAK3, KIT, LCK, LYN, MAPKAPK2, MELK, MET, MNK2, MPS1, MST4, NEK6, NIM1, P38alpha, PAK4, POLYDATINGFRb, POLYDATINK1, PERK, PIM1, PIM2, PKAalpha, PKCbeta, PLK1, RET, SULU1, Syk, TLK2, TRKA, TYK2, VEGFR2, ZAP70). The IC_{50} values are found to be >10 μM for all enzymes tested[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	NMS-P118 is dissolved in DMSO and diluted with appropriate medium before use. Cellular activity of PARP-1 inhibitors is assessed by measuring the inhibition of the hydrogen peroxide induced PAR formation in HeLa cells (ECACC). Cellular PAR levels are measured by immunocytochemistry, and quantified using an ArrayScan vTi instrument[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	The pharmacokinetic profile and the oral bioavailability of the compounds have been investigated in rat in ad hoc pharmacokinetic studies. NMS-P118 is formulated for intravenous bolus administration in 20% DMSO + 40% PEG 400 in 5% dextrose. Oral administration is performed using a NMS-P118 suspension in 0.5% methylcellulose. A single administration at the dose of 10 mg/kg for each route and a single oral administration at the dose of 100 mg/kg are given. Three male animals for each study are used[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Dis. 2023 Aug 15;14(8):524.
- J Mol Med (Berl). 2019 Aug;97(8):1183-1193.

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REFERENCES

[1]. Papeo G, et al. Discovery of 2-[1-(4,4-Difluorocyclohexyl)piperidin-4-yl]-6-fluoro-3-oxo-2,3-dihydro-1H-isoindole-4-carboxamide (NMS-P118): A Potent, Orally Available, and Highly Selective PARP-1 Inhibitor for Cancer Therapy. J Med Chem. 2015 Sep 10;58(17):6875-98.

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