产品名称：NMS-P118
产品别名：NMS-P118

生物活性：

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 (now marketed as Lynparza), a dual PARP-1/-2 inhibitor. NMS-P118 proves to be metabolically stable, it modestly inhibites two cytochrome P450 family members (CYP-2B6 IC50: 8.15 μM; CYP-2D6 IC50: 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].	
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].	

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

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.

实验参考：

Cell Assay	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].
Animal Administration	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].
Kinase Assay	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 IC50 values are found to be >10 μM for all enzymes tested[1].
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.