

产品名称: LY3009120

产品别名: DP-4978

生物活性:					
Description	LY3009120 is a pan RAF inhibitor which inhibits BRAF ^{V600E} , BRAF ^{WT} and CRAF ^{WT} with IC ₅₀ s of 5.8, 9.1 and 15 nM, respectively.				
IC ₅₀ & Target	BRAF ^{V600E}	Braf	CRAF		
	5.8 nM (IC ₅₀)	9.1 nM (IC ₅₀)	15 nM (IC ₅₀)		
In Vitro	In the whole-cell based KiNativ assay, LY3009120 shows affinity to each RAF isoform with the IC ₅₀ of 44, 31-47 and 42 nM for ARAF, BRAF and CRAF respectively. LY3009120 exhibits anti-proliferative effects on cell lines harboring BRAF ^{V600E} , KRAS ^{G13} and KRAS ^{G12} mutations. LY3009120 (1 μM) inhibits the phosphorylation of both MEK1/2 and ERK1/2 in cell lines with high basal levels of pMEK1/2 and pERK1/2 (RKO and HCT 116)[1]. LY3009120 shows inhibitory effect on tumor cells such as BxPC-3, NCI-H2405 and OV-90 cell lines. LY3009120 (0.01 μM) demonstrates potent and dose-dependent inhibition of phospho-MEK and ERK in all three cell lines. LY3009120 demonstrates a concentration-dependent cell growth inhibition with IC ₅₀ values of 0.04, 0.087, and 0.007 μM against H2405, BxPC-3, and OV-90 cells, respectively[2]. LY3009120 inhibits BRAF ^{WT} , CRAF ^{WT} , BRAF ^{V600E} , and BRAF ^{V600E+G468A} with the IC ₅₀ values of 9.1, 15, 5.8, and 17 nM, respectively. LY3009120 induces BRAF-CRAF dimerization but inhibits the phosphorylation of downstream MEK and ERK. LY3009120 also inhibits various forms of RAF dimers including BRAF or CRAF homodimers[3]. LY3009120 gives only very minor activation at very low doses, with near complete inhibition of phospho-ERK at concentrations above 100 nM[4].				
In Vivo	LY3009120 (20 mg/kg bid) displays significant activity in in vivo BRAF ^{mut} and KRAS ^{mut} CRC xenograft models. In Colo 205 xenografts (BRAF ^{mut}), LY3009120 results in statistically significant tumor regression, while treatment of HCT 116 xenografts (KRAS ^{mut}) results in statistically significant inhibition of tumor growth. LY3009120 treatment reduces pMEK1/2 in all HT-29 xenografts and reduces pERK1/2 in the majority of HT-29 xenografts[1]. LY3009120 (15 or 30 mg/kg) achieves almost complete tumor growth regression, and inhibits downstream phospho-MEK and ERK by approximately 70% and 60%, respectively, in the H2405 model[2].				
Solvent&Solubility	In Vitro:				
	DMSO : ≥ 38 mg/mL (89.51 mM)				
	* "≥" means soluble, but saturation unknown.				
	Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
		1 mM	2.3557 mL	11.7783 mL	23.5566 mL
		5 mM	0.4711 mL	2.3557 mL	4.7113 mL
10 mM		0.2356 mL	1.1778 mL	2.3557 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。					
	[1]. Vakana E, et al. LY3009120, a panRAF inhibitor, has significant anti-tumor activity in BRAF and KRAS mutant preclinical models of colorectal cancer. Oncotarget. 2017 Feb 7;8(6):9251-9266				

References	<p>[2]. Chen SH, et al. Oncogenic BRAF Deletions That Function as Homodimers and Are Sensitive to Inhibition by RAF Dimer Inhibitor LY3009120. Cancer Discov. 2016 Mar;6(3):300-15</p> <p>[3]. Peng SB, et al. Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers. Cancer Cell. 2015 Sep 14;28(3):384-98</p> <p>[4]. Henry JR, et al. Discovery of 1-(3,3-dimethylbutyl)-3-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)urea (LY3009120) as a pan-RAF inhibitor with minimal paradoxical activation and activity against BRAF or RAS mutant tumors</p>
实验参考:	
Cell Assay	<p>Briefly, cells are grown in McCoy's 5A supplemented with 10% characterized fetal bovine serum at 37°C, 5% CO₂, and 95% humidity. Cells are allowed to expand until 75-90% confluency at which point they are subcultured or harvested for assay use. A serial dilution of test compound is dispensed into a 384-well black clear bottom plate in triplicate. Six-hundred-twenty-five cells are added per well in 50 µL of complete growth medium in the 384-well plate. Plates are incubated for 67 h at 37°C, 5% CO₂, and 95% humidity. At the end of the incubation period, 10 µL of a 440 µM solution of resazurin in PBS is added to each well of the plate and plates are incubated for an additional 5 h at 37°C, 5% CO₂, and 95% humidity. Plates are read on a Synergy2 reader using an excitation of 540 nm and an emission of 600 nm. Data are analyzed using Prism software to calculate IC₅₀ values. [4]</p>
Animal Administration	<p>Briefly, 5×10⁶ to 10×10⁶ tumor cells in a 1:1 Matrigel mix (0.2 mL total volume) are injected subcutaneously into the right hind flank of female NIH nude rats. After tumors reach a desired size of approximately 300 mm³, animals are randomized into groups of 8 for efficacy studies. Drugs (LY3009120 or PLX4032) are administered orally (gavage) in 0.6-mL volume of vehicle with the dose schedules. Tumor growth and body weight are monitored over time to evaluate efficacy and signs of toxicity. [2]</p>
References	<p>[1]. Vakana E, et al. LY3009120, a panRAF inhibitor, has significant anti-tumor activity in BRAF and KRAS mutant preclinical models of colorectal cancer. Oncotarget. 2017 Feb 7;8(6):9251-9266</p> <p>[2]. Chen SH, et al. Oncogenic BRAF Deletions That Function as Homodimers and Are Sensitive to Inhibition by RAF Dimer Inhibitor LY3009120. Cancer Discov. 2016 Mar;6(3):300-15</p> <p>[3]. Peng SB, et al. Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers. Cancer Cell. 2015 Sep 14;28(3):384-98</p> <p>[4]. Henry JR, et al. Discovery of 1-(3,3-dimethylbutyl)-3-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)urea (LY3009120) as a pan-RAF inhibitor with minimal paradoxical activation and activity against BRAF or RAS mutant tumors</p>