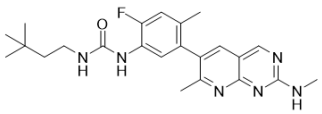
LY3009120

Cat. No.:	HY-12558
CAS No.:	1454682-72-4
Molecular Formula:	$C_{23}H_{29}FN_6O$
Molecular Weight:	424.51
Target:	Raf; Autophagy
Pathway:	MAPK/ERK Pathway; Autophagy
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



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

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

BIOLOGICAL ACTIVITY

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

PROTOCOL

Cell Assay [4]	Briefly, cells are grown in McCoy's 5A supplemented with 10% characterized fetal bovine serum at 37°C, 5% CO_2, 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% CO_2, 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% CO_2, 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 softwareto calculate IC_{50} values. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Briefly, 5×10^6 to 10×10^6 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 mm^3, 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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Syst. 2020 Oct 21;S2405-4712(20)30370-7.
- Oncogene. 2018 Oct;37(43):5719-5734.
- Clin Sci (Lond). 2019 Apr 16;133(8):919-932.
- Cancer Sci. 2018 Jan;109(1):121-131.
- bioRxiv. 2019 Sep.

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REFERENCES

[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

[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

[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

[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 tumo

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