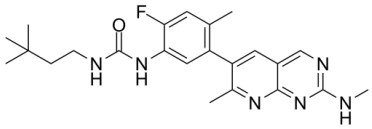
Data Sheet

Product Name:	LY3009120
Cat. No.:	CS-4147
CAS No.:	1454682-72-4
Molecular Formula:	C23H29FN6O
Molecular Weight:	424.51
Target:	Autophagy; Raf
Pathway:	Autophagy; MAPK/ERK Pathway
Solubility:	DMSO : ≥ 38 mg/mL (89.51 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 5.8 nM ($BRAF^{V600E}$), 9.1 nM ($BRAF^{WT}$), 15 nM ($CRAF^{WT}$)[1] **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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.

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

CAIndexNames:

Urea, N-(3,3-dimethylbutyl)-N'-[2-fluoro-4-methyl-5-[7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl]phenyl]-

SMILES:

O=C(NC1=CC(C2=CC3=CN=C(NC)N=C3N=C2C)=C(C)C=C1F)NCCC(C)(C)C

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA