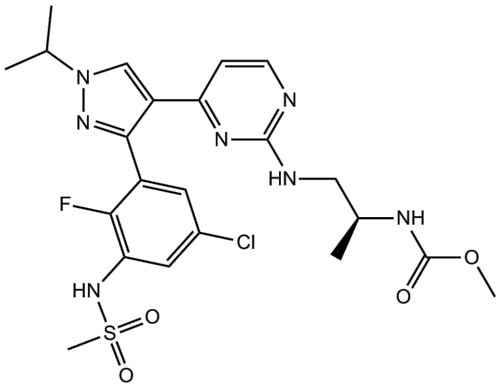
Product Data Sheet

Product Name: LGX818
Cat. No.: GC16576

Chemical Properties

Cas. No.	1269440-17-6		
Chemical Name	methyl N-[(2S)-1-[[4-[3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-propan-2-yl pyrazol-4-yl]pyrimidin-2-yl]amino]propan-2-yl]carbamate		
SMILES	CC(C)N1C=C(C(=N1)C2=CC(=CC(=C2F)NS(=O)(=O)C)Cl)C3=NC(=NC=C3)NCC(C)NC(=O)OC		
Formula	$C_{22}H_{27}ClFN_7O_4S$	M.Wt	540.01
Solubility	DMF: 25 mg/ml,DMF:PBS(pH 7.2) (1:1): 0.5 mg/ml,DMSO: 20 mg/ml,Ethanol: 15 mg/ml	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:

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Cell lines	Human melanoma A375 (BRAFV600E) cells
Preparation method	The solubility of this compound in DMSO is > 10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	3 ~ 900 nM
Applications	In human melanoma A375 (BRAFV600E) cells, LGX818 suppressed phospho-ERK (EC50 = 3 nM), thus potently inhibiting cell proliferation (EC50 = 4 nM). Meanwhile, LGX818 did not show any significant inhibition against a panel of 100 kinases (IC50 > 900 nM) as well as proliferation of > 400 cell lines expressing wild-type BRAF. In addition, biochemical assays showed that the dissociation half-life of LGX818 was >24 hrs. Thus, the inhibition effect of LGX818 remained following drug wash-out.

Animal experiment [1]:

Animal models	BRAF mutant or wild-type human tumor xenograft models
Dosage form	1 ~ 300 mg/kg; p.o.

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Applications	At an oral dose as low as 6 mg/kg, LGX818 potently (75%) and continuously (> 24 hrs) decreased phospho-MEK in human melanoma xenograft models (BRAFV600E). In nude mice and rats bearing multiple BRAF mutant human tumors, LGX818 induced tumor regression at the dose as low as 1 mg/kg. Moreover, for BRAF wild-type tumors, LGX818 did not show any activity at the dose up to 300 mg/kg (b.i.d.), with good tolerability and linear increase in exposure.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Stuart D D, Li N, Poon D J, et al. Preclinical profile of LGX818: A potent and selective RAF kinase inhibitor. Cancer Research, 2012, 72(8 Supplement): 3790.

Background

LGX818 is a potent and selective inhibitor of RAF kinase with EC50 value of 3nM in A375 cells [1].

The V600E mutation of B-Raf in the kinase domain results in constitutive activation of B-Raf and promotes cancer development. LGX818 is a RAF kinase inhibitor targeting V600E mutant B-Raf. It has little effect against wild-type BRAF. LGX818 has selective anti-proliferative and apoptotic activity ion in cells expressing BRAFV600E. It shows no significant activity against a panel of 100 kinases and no suppression of cell growth with more than 400 cell lines expressing BRAFV600E. In the A375 human melanoma cell line, LGX818 inhibits the phospho-ERK with EC50 value of 3nM and causes subsequent cell proliferation inhibition with EC50 value of 4nM. In human melanoma xenograft models, oral administration of LGX818 shows strong decrease in phospho-MEK and induces tumor regression [1, 2].

References:

[1] Stuart D D, Li N, Poon D J, et al. Preclinical profile of LGX818: A potent and selective RAF kinase

inhibitor. Cancer Research, 2012, 72(8 Supplement): 3790.
[2] Huang T, Karsy M, Zhuge J, et al. B-Raf and the inhibitors: from bench to bedside. J Hematol Oncol, 2013, 6(1): 30.

Caution: Product has not been fully validated for medical applications. For research use only.
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