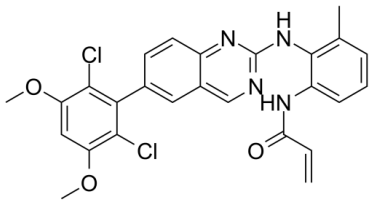
Data Sheet

Product Name:	BLU9931
Cat. No.:	CS-4139
CAS No.:	1538604-68-0
Molecular Formula:	C26H22Cl2N4O3
Molecular Weight:	509.38
Target:	FGFR
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 83.33 mg/mL (163.59 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

BLU9931 is a potent, highly selective, and irreversible **fibroblast growth factor receptor 4 (FGFR4)** inhibitor with an **IC_{50}** of 3 nM and a **K_d** of 6 nM. BLU9931 has significant antitumor activity[1]. IC50 & Target: IC50: 3 nM (FGFR4) **In Vitro:** BLU9931 inhibits proliferation of HCC cell lines that express an intact FGFR4 signaling complex, with **EC_{50}**s of 0.07 μM, 0.11 μM and 0.02 μM for Hep 3B, HuH7 and JHH7 cells, respectively[1].

BLU9931 (0.3-300 nM; 1 hour; MDA-MB-453 and Hep 3B cells) treatment demonstrates potent, dose-dependent reduction of phosphorylation of FGFR4 signaling pathway components, including fibroblast growth factor receptor substrate 2 (FRS2), MAPK, and AKT in MDA-MB-453 cells. BLU9931 shows dose-dependent inhibition of the signaling cascade downstream of FGFR4. BLU9931 exhibits potent inhibition of phosphorylation of the FGFR4 pathway components in Hep 3B cells. BLU9931 treatment leads to induction of caspase-3/7 activity, indicative of induction of apoptosis that results in inhibition of signaling downstream of FGFR4[1]. BLU9931 (100 nM; 0 -24 hours; Hep 3B cells) treatment increases CYP7A1 mRNA expression and the expression of the proliferative marker EGR1 is inhibited[1]. **In Vivo:** BLU9931 (10-100 mg/kg; oral administration; twice every day; for 21 days; mice) treatment demonstrates antitumor activity in HCC xenograft models[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]FGFR kinase inhibition assays are performed at KM for ATP. Picomolar to low nanomolar concentrations of FGFR proteins are incubated in 1× Kinase Reaction Buffer (KRB) with 1 μM of CSKtide and 50 to 250 of μM ATP at 25°C for 90 minutes in the presence or absence of a dosed concentration series of inhibitor. All reactions are terminated by the addition of Stop buffer, and plates are read on a Caliper EZReader2. IC_{50} values are fit with a four-parameter log[Inhibitor] versus response model with floating Hill Slope. **Cell Assay:** BLU9931 is dissolved in DMSO.[1]established and PDX-derived HCC cell lines are seeded in 96-well plates in respective growth media, allowed to attach overnight, and treated with a dilution series of test compounds for two cell-doubling times. Cell viability is determined by CellTiter-Glo, and results represented as background-subtracted relative light units normalized to a DMSO-treated control. Relative EC_{50} values are determined at 50% inhibition between the top and bottom plateau of the dose-response curve. **Animal Administration:** BLU9931 is formulated in 0.5% carboxymethylcellulose/1% Tween 80.[1]BLU9931 is formulated in 0.5% carboxymethylcellulose/1% Tween 80 and dosed orally as a suspension twice daily. Sorafenib is dissolved in Cremaphor:EtOH (1:1) and diluted with saline or water to yield the stock solution. Sorafenib is dosed orally once daily. All compound doses are expressed as mg/kg free base. For PK-PD studies, 3 mice are included in each treatment group. Mice receive four doses of compound or vehicle. Blood and tumors are collected 8, 12, 20, and 24 hours following the last dose. The concentration of BLU9931 in plasma is determined by LC/MS-MS. A section of each tumor is immediately frozen in liquid nitrogen and stored at −80°C.

References:

[1]. Hagel M, et al. First Selective Small Molecule Inhibitor of FGFR4 for the Treatment of Hepatocellular Carcinomas with an Activated FGFR4 Signaling Pathway. Cancer Discov. 2015 Apr;5(4):424-37.

CAIndexNames:

2-Propenamide, N-[2-[[6-(2,6-dichloro-3,5-dimethoxyphenyl)-2-quinazolinyl]amino]-3-methylphenyl]-

SMILES:

C=CC(NC1=CC=CC(C)=C1NC2=NC=C3C=C(C4=C(Cl)C(OC)=CC(OC)=C4Cl)C=CC3=N2)=O

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