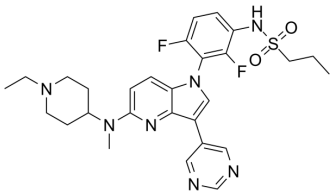
BI-882370

Cat. No.:	HY-107779
CAS No.:	1392429-79-6
Molecular Formula:	$C_{28}H_{33}F_2N_7O_2S$
Molecular Weight:	569.67
Target:	Raf
Pathway:	MAPK/ERK Pathway

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 17.86 mg/mL (31.35 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7554 mL	8.7770 mL	17.5540 mL
5 mM	0.3511 mL	1.7554 mL	3.5108 mL
10 mM	0.1755 mL	0.8777 mL	1.7554 mL

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

BIOLOGICAL ACTIVITY

Description

BI-882370 is a potent and selective RAF kinase inhibitor that binds to the ATP binding site of the kinase positioned in the DFG-out (inactive) conformation of the BRAF kinase. BI-882370 (BI 882370) inhibits the oncogenic $BRAF^{V600E}$-mutant, the WT BRAF and CRAF kinases with IC_{50}s of 0.4, 0.8, and 0.6 nM, respectively. BI-882370 also inhibits SRC family kinases[1].

IC_{50} & Target

Braf	c-Raf	$BRaf^{V600E}$
0.6 nM (IC_{50})	0.8 nM (IC_{50})	0.4 nM (IC_{50})

In Vitro

BI-882370 (0.9-6000 nM; 3 days) inhibits the BRAF-mutant human melanoma and colorectal cancer cells proliferation with a EC_{50} range of 1-10 nM[1].

BI 882370 (0.1-100 nM, 0.1-3000 nM; 2 hours) results in a reduction of p-MEK1/2, p-ERK1/2 and cyclin D1/D2 expression in $BRAF^{V600E}$-mutant A375 cells; induces phosphorylation of MEK1/2 and enhanced phosphorylation of ERK1/2 in WT BRO cells (3-300 nM)[1].

BI 882370 (0.1-100 nM, 0.1-3000 nM; 24 hours) suppresses cyclin D1/D2 expression, induces Kip1/p27 expression at concentrations of 1 nM or higher in $BRAF^{V600E}$-mutant A375 cells, expression of cyclins D1/D2 or Kip1/p27 is not affected in

WT BRO cells[1].

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

Cell Proliferation Assay[1]

Cell Line:	BRAF-mutant and WT melanoma cell lines (A101D, A375, SK-MEL-28, G-361, and BRO); Colorectal cancer cell lines (COLO 205, HT-29, LS411N, and HCT-116)
Concentration:	0.9-6000 nM
Incubation Time:	3 days
Result:	Showed a EC_{50} range of 1-10 nM in an extended panel of BRAF-mutant human melanoma and colorectal cancer cell; while proliferation of BRAF WT cells was inhibited with EC_{50} >1 μM.

Western Blot Analysis[1]

Cell Line:	$BRAF^{V600E}$-mutant A375 cells; BRAF WT, NRAS-mutant BRO (WT BRO) cells
Concentration:	0.1-100 nM; 0.1-3000 nM
Incubation Time:	2 hours; 24 hours
Result:	Resulted in a reduction of phospho-MEK1/2 signals and cyclin D1/D2 expression in $BRAF^{V600E}$-mutant A375 cells.

In Vivo

BI-882370 (deliver orally; 25 mg/kg, 50 mg/kg; twice daily; 2 weeks) is efficacious in multiple mouse models of BRAF-mutant melanomas and colorectal carcinomas, shows superior efficacy compared with Vemurafenib, Dabrafenib, or Trametinib[1].

BI-882370 (deliver orally; 25 mg/kg; twice daily; 40 days) developes resistance within 3 weeks, but resistance is not observed during 5 weeks of second-line therapy in combination with trametinib[1].

BI-882370 (deliver orally; 60 mg/kg; once daily; 2 weeks) indicates lack of toxicity in terms of clinical chemistry, hematology, pathology, and toxicogenomics in rats[1].

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

Animal Model:	Human melanoma xenografts in nude mice with BRAF-mutant melanomas and colorectal carcinomas cells (A375, COLO 205; G-361, HT-29 cells)[1]
Dosage:	25 mg/kg; 50 mg/kg
Administration:	Deliver orally; 25 mg/kg, 50 mg/kg; twice daily; 2 weeks
Result:	Regressed tumors partially, upon discontinuation, tumor regrowth was markedly delayed.

REFERENCES

[1]. Waizenegger IC, et al. A Novel RAF Kinase Inhibitor with DFG-Out-Binding Mode: High Efficacy in BRAF-Mutant Tumor Xenograft Models in the Absence of Normal Tissue Hyperproliferation. Mol Cancer Ther. 2016 Mar;15(3):354-65.

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