# BI-882370

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| **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:**

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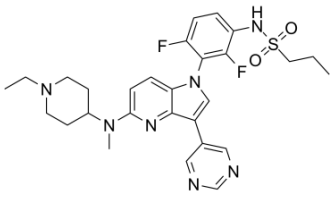
|---|---|---|
| Powder | -20°C | 3 years |
| | 4°C | 2 years |
| In solvent | -80°C | 6 months |
| | -20°C | 1 month |



## SOLVENT & SOLUBILITY

**In Vitro**

**DMSO : 5 mg/mL** (**8.78 mM;** ultrasonic and warming and heat to 60°C)
**$H_2O$ : < 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 | --- | --- | --- |

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].

**Cell Proliferation Assay[1]**

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| 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]**

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| 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].

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| **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.

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

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