XL228

Cat. No.: HY-15749

CAS No.: 898280-07-4

Molecular Formula: $C_{22}H_{31}N_9O$

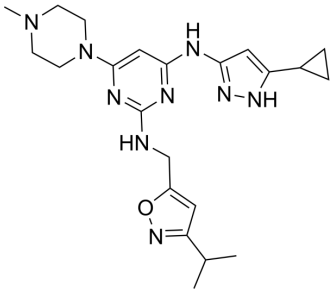
Molecular Weight: 437.54

Target: Aurora Kinase; Bcr-Abl; IGF-1R; Src

Pathway: Cell Cycle/DNA Damage; Epigenetics; Protein Tyrosine Kinase/RTK

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 : ≥ 83.33 mg/mL (190.45 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2855 mL	11.4275 mL	22.8551 mL
5 mM	0.4571 mL	2.2855 mL	4.5710 mL
10 mM	0.2286 mL	1.1428 mL	2.2855 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.75 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.75 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.75 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

XL228 is a multi-targeted tyrosine kinase inhibitor with IC_{50}s of 5, 3.1, 1.6, 6.1, 2 nM for Bcr-Abl, Aurora A, IGF-1R, Src and Lyn, respectively.

IC_{50} & Target

Aurora A 3.1 nM (IC_{50})	IGF-1R 1.6 nM (IC_{50})

In Vitro	XL228 shows a broad pattern of protein kinase inhibition, including the tyrosine kinases IGF1R, SRC, ABL, FGFR1-3, and ALK and the serine/threonine kinases Aurora A and Aurora B. A panel of kinase inhibitors including XL228 is profiled against a series of cancer cell lines with known alterations in major signaling pathways. Approximately 30% of the lines demonstrate XL228 IC_{50} values of <100nM in viability assays, including many lines with characterized ALK or FGFR mutations or amplifications. XL228 eliminates the phosphorylation of Aurora A and B at concentrations above 10 nM. Short-term treatment of HeLa cells leads to disruption of mitotic spindle formation, with the majority of mitotic cells exhibiting a unipolar spindle and disorganized chromosomes[2]. It displays low nanomolar biochemical activity against wild type Abl kinase (K_i=5 nM), as well as the T315I form of Abl resistant to imatinib and dasatinib (K_i=1.4 nM). XL228 inhibits phosphorylation of BCR-ABL and its substrate STAT5 in K562 cells in vitro with IC_{50}s of 33 and 43 nM, respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Single-dose pharmacodynamics studies demonstrate a potent effect of XL228 on BCR-ABL signaling in K562 xenograft tumors. Phosphorylation of BCR-ABL is decreased by 50% at XL228 plasma concentrations of 3.5 μM; a similar decrease in phospho-STAT5 occurred at 0.8 μM plasma concentration[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Nat Biomed Eng. 2018 Aug;2(8):578-588.
- Technical University of Munich. 24.01.2018.

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REFERENCES

[1]. Cortes J, et al. Preliminary Clinical Activity in a Phase I Trial of the BCR-ABL/IGF- 1R/Aurora Kinase Inhibitor XL228 in Patients with Ph++ Leukemias with Either Failure to Multiple TKI Therapies or with T315I Mutation. Blood 2008 112:3232

[2]. Douglas O, et al. Abstract C192: Characterization of the target profile of XL228, a multi-targeted protein kinase inhibitor in phase 1 clinical development. Mol Cancer Ther 2009;8(12 Suppl):C192.

[3]. Shah N, et al. Targeting Drug-Resistant CML and Ph+-ALL with the Spectrum Selective Protein Kinase Inhibitor XL228. Blood 2007 110:474;

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