Lck Inhibitor

Cat. No.: HY-12072

CAS No.: 847950-09-8

Molecular Formula: $C_{31}H_{30}N_8O$

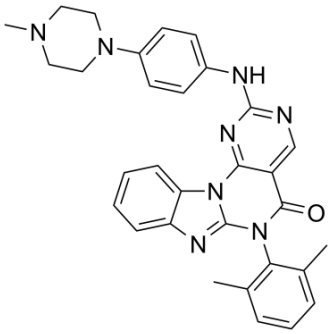
Molecular Weight: 530.62

Target: Src

Pathway: Protein Tyrosine Kinase/RTK

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (188.46 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8846 mL	9.4229 mL	18.8459 mL
	5 mM	0.3769 mL	1.8846 mL	3.7692 mL
	10 mM	0.1885 mL	0.9423 mL	1.8846 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: ≥ 2.5 mg/mL (4.71 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.71 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Lck Inhibitor is a potent, orally active Lck (lymphocyte specific kinase) inhibitor with IC_{50}s of 7, 2.1, 4.2 and 200 nM for Lck, Lyn, Src and Syk kinases, respectively. Lck Inhibitor shows >1000-fold selectivity for Lck over MAPK, CDK and RSK family representatives. Lck Inhibitor inhibits T cell proliferation and in vivo models of arthritis[1].

In Vitro

Lck Inhibitor (compound 25) exhibits good potency in the T-cell receptor-induced IL-2 secretion assay (IL-2, IC_{50}=0.46 μM) and also inhibits subsequent T-cell proliferation (T-cell prolif, IC_{50}=0.53 μM) in the same human T-cells. Lck Inhibitor also inhibits a human mixed lymphocyte reaction (huMLR) with a 10-fold increase in potency as compared to the other invitro cell assays utilizing purified human cells. Lck Inhibitor also displays inhibition of a mechanism-based biochemical cell assay probing Lck-dependent TCR-chain phosphorylation (TCR-chain). Lck Inhibitor shows a 10-fold reduction in potency when IL-2 is induced in a receptor-independent fashion by stimulating with phorbo lester and calcium ionophore (PMA/iono). Lck

Inhibitor exhibits a similar level of potency when tested in a general proliferation assay using the human T-cell line, Jurkat (JKT)[1].

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

In Vivo

Lck Inhibitor (0-60 mg/kg; p.o.; once daily; from day 9 today 17) shows a dose-dependent inhibition of arthritis[1].

Lck Inhibitor (p.o.; 5 mg/kg) treatment shows the C_{max}, $AUC_{0-\infty}$, t_{max} and F% are 82 ng/mL, 862 ng h/mL, and 17%, respectively[1].

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

Animal Model:	Male Lewis rat (adjuvant-inducedarthritis model) [1]
Dosage:	0, 30, and 60 mg/kg
Administration:	P.o.; once daily; from day 9 today 17
Result:	Showed a dose-dependent inhibition of arthritis, with an ED_{50} estimated at 24 mg/kg.

Animal Model:	Sprague-Dawley Rats[1]
Dosage:	P.o. (Pharmacokinetic Analysis)
Administration:	5 mg/kg
Result:	The C_{max}, $AUC_{0-\infty}$, t_{max} and F% were 82 ng/mL, 862 ng h/mL, and 17%, respectively.

REFERENCES

[1]. Martin, Matthew W.; Newcomb, John; Nunes, Joseph J.; et al. Structure-Based Design of Novel 2-Amino-6-phenyl-pyrimido[5',4':5,6]pyrimido[1,2-a]benzimidazol-5(6H)-ones as Potent and Orally Active Inhibitors of Lymphocyte Specific Kinase (Lck): Synthesis, SAR, and In Vivo Anti-Inflammatory Activity. Journal of Medicinal Chemistry (2008), 51(6), 1637-1648.

[2]. Liew, Chin Y.; Ma, Xiao H.; Liu, Xianghui; Yap, Chun W. SVM Model for Virtual Screening of Lck Inhibitors. Journal of Chemical Information and Modeling (2009), 49(4), 877-885.

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