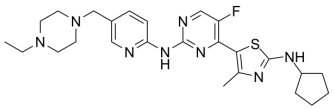
Ulecaciclib

Cat. No.:	HY-147409
CAS No.:	2075750-05-7
Molecular Formula:	$C_{25}H_{33}FN_8S$
Molecular Weight:	496.65
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Ulecaciclib is an orally activitive inhibitor of cyclin-dependent kinase (CDK), with K_i values of 0.62 μM (CDK2/Cyclin A), 0.2 nM (CDK4/Cyclin D1), 3 nM (CDK6/Cyclin D3), and 0.63 μM (CDK7/Cyclin H), respectively. Ulecaciclib can cross blood brain barrier and has good pharmacokinetic characteristics[1][2][3].

IC_{50} & Target

cdk2/cyclin A	Cdk4/cyclin D1	cdk6/cyclin D3	cdk7-cyclin H
0.62 μM (Ki)	0.2 nM (Ki)	3 nM (Ki)	0.63 μM (Ki)

In Vitro

Ulecaciclib (compound 2) (40 min) displays inhibitory effect on CDK kinase with K_i values of 0.62 μM (CDK2/A), 0.2 nM (CDK4/Cyclin D1), 3 nM (CDK6/Cyclin D3), 0.63 μM (CDK7/H), respectively[2].

Ulecaciclib (72 h) exhibits a strong antiproliferative activity against leukemia cells with a growth inhibition GI_{50} value of 10 nM[2].

Ulecaciclib (72 h) inhibits tumor growth with GI_{50}s range from 0.04-5.09 μM and inhibits Ovarian A2780 with an GI_{50} value of 40 nM, in particularly[2].

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

Cell Viability Assay[2]

Cell Line:	U87, U251, T98G (mycoplasma-free); and MB453, Colo205, H460, A2780, PANC1, LNC, M229
Concentration:	0-10 μM
Incubation Time:	72 hours
Result:	Inhibited cancer cells growth with GI_{50}s of 2.17 μM (U87), 5.09 μM (U251), 4.18 μM (T98G), 0.62 μM (MB453), 1.55 μM (Colo205), 0.41 μM (H460), 0.04 μM (A2780), 1.21 μM (PANC1), 0.28 μM (LNC), 0.83 μM (M229).

In Vivo

Ulecaciclib (compound 2) (2 mg/kg for i.v.; 10 mg/kg for p.o.) demonstrates a significantly propensity to cross the blood brain barrier in mice, with the brain/plasma ratios are >1.2 (i.v.) or >0.7 (p.o.), respectively[2].

Ulecaciclib (200 mg/kg; p.o.; daily; 21 d) displays in vivo anti-tumour efficacy in mice[2].

Ulecaciclib (25 mg/kg; p.o.; daily; 10 d) demonstrates significant anti-tumour efficacy at lower doses in combination with TMZ (5 mg/kg; p.o.; 5 d/week; 2 weeks) in mice[2].

Ulecaciclib (compound A) (50 mg/kg; p.o.) shows an oral bioavailability of about 21.8%, and good pharmacokinetic profile with T_{max} of 6.67 h and an half- of 8.34 h, while C_{max} =643 ng/mL, $AUC_{(0-24)}$ =9543 ng•h/mL in male cynomolgus monkeys[3].

Pharmacokinetic of Ulecaciclib in cynomolgus monkeys[3]

Route	Dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (h•ng/mL)	$AUC_{(0-\infty)}$ (h•ng/mL)	V_d (L/kg)	CL (mL/min/kg)	$MRT_{(0-t)}$ (h)	F (%)
i.v.	5	6.53	/	447	4187	4560	9.79	19.4	6.64	/
p.o.	50	8.34	6.67	643	9543	7305	/	/	10.4	21.8

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Animal Model:	CDl nu/nu female mice (5-6 weeks old; injected with U87 GBM cells, s.c.)[2]
Dosage:	200 mg/kg
Administration:	Oral gavage; daily; 21 days
Result:	Reduced tumour growth markedly without any overt toxicity.

Animal Model:	GBM orthotopic mouse xenograft models[2]
Dosage:	120 mg/kg
Administration:	Oral gavage; daily for 2 days
Result:	Inhibited tumor growth on day 21 and increased life span ratio (ILS) of 154.8% for teated mice. ILS = (DaysT - DaysC)/DaysC, where DaysC = days survived by control group and DaysT = days survived by treatment group.

REFERENCES

[1]. International Nonproprietary Names for Pharmaceutical Substances (INN). WHO Drug Information. 2022. 36(2):337.

[2]. Wang Shudong, et al. Treatment of proliferative diseases of the CNS using a class of thiazole-pyrimidine compounds that inhibit the activity of CDK4 and/or CDK6[P]. World Intellectual Property Organization, WO2021222967 A1 2021-11-11.

[3]. Wang Shudong, et al. Succinate and crystal form thereof as therapeutics[P]. World Intellectual Property Organization, WO2022099357 A1 2022-05-19.

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