(R)-CR8 trihydrochloride

Cat. No.: HY-18340A

CAS No.: 1786438-30-9

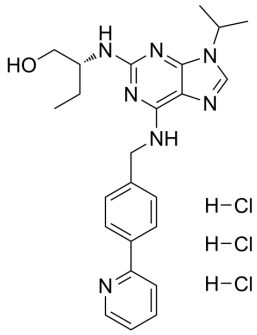
Molecular Formula: $C_{24}H_{32}Cl_3N_7O$

Molecular Weight: 540.92

Target: CDK; Apoptosis; Molecular Glues

Pathway: Cell Cycle/DNA Damage; Apoptosis; PROTAC

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (92.44 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8487 mL	9.2435 mL	18.4870 mL
	5 mM	0.3697 mL	1.8487 mL	3.6974 mL
	10 mM	0.1849 mL	0.9244 mL	1.8487 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: ≥ 2.17 mg/mL (4.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.17 mg/mL (4.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.17 mg/mL (4.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

(R)-CR8 (CR8) trihydrochloride, a second-generation analog of Roscovitine, is a potent CDK1/2/5/7/9 inhibitor. (R)-CR8 trihydrochloride inhibits CDK1/cyclin B (IC_{50}=0.09 μM), CDK2/cyclin A (0.072 μM), CDK2/cyclin E (0.041 μM), CDK5/p25 (0.11 μM), CDK7/cyclin H (1.1 μM), CDK9/cyclin T (0.18 μM) and CK1δ/ε (0.4 μM). (R)-CR8 trihydrochloride induces apoptosis and has neuroprotective effect[1][2]. (R)-CR8 trihydrochloride acts as a molecular glue degrader that depletes cyclin K[3].

IC_{50} & Target				
	CDK1/cyclinB1 0.09 μM (IC_{50})	cdk2/cyclin A 0.072 μM (IC_{50})	CDK2/cyclinE 0.041 μM (IC_{50})	Cdk5/p25 0.11 μM (IC_{50})
	CDK7/cyclin H	CDK9/Cyclin T	CK1δ/ε	

	1.1 μM (IC_{50})	0.18 μM (IC_{50})	0.4 μM (IC_{50})

In Vitro

(R)-CR8 (CR8) trihydrochloride (0.1-100 μM; 48 hours) is a potent inducer of apoptotic cell death with an IC_{50} of 0.49 μM for SH-SY5Y cell line[1].

(R)-CR8 trihydrochloride (0.25-10 μM) induces a dose-dependent induction of poly-(ADP-ribose)polymerase (PARP) cleavage [1].

The CDK-bound form of (R)-CR8 trihydrochloride has a solvent-exposed pyridyl moiety that induces the formation of a complex between CDK12-cyclin K and the CUL4 adaptor protein DDB1, bypassing the requirement for a substrate receptor and presenting cyclin K for ubiquitination and degradation

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

Apoptosis Analysis[1]

Cell Line:	SH-SY5Y cell line
Concentration:	0.1, 1, 10, 100 μM
Incubation Time:	24 hours
Result:	Reduced cell survival in a dose-dependent manner.

In Vivo

(R)-CR8 trihydrochloride (5 mg/Kg; i.p.) results in a significant reduction in lesion size at 28 days in histological assessment[2].

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

Animal Model:	Adult (10 to 12 weeks old) male Sprague-Dawley rats (310 to 330 g)[2]
Dosage:	5 mg/Kg
Administration:	i.p.
Result:	Resulted in a significant reduction in lesion size.

REFERENCES

[1]. Bettayeb K, et al. CR8, a potent and selective, roscovitine-derived inhibitor of cyclin-dependent kinases. Oncogene. 2008 Oct 2;27(44):5797-807.

[2]. Kabadi SV, et al. CR8, a novel inhibitor of CDK, limits microglial activation, astrocytosis, neuronal loss, and neurologic dysfunction after experimental traumatic brain injury. J Cereb Blood Flow Metab. 2014 Mar;34(3):502-13.

[3]. Słabicki M, et al. The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K [published online ahead of print, 2020 Jun 3]. Nature. 2020;10.1038/s41586-020-2374-x.

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