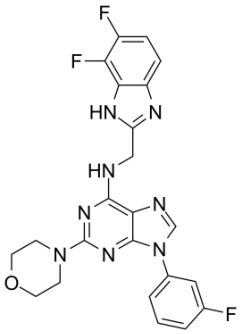
SR-3029

Cat. No.:	HY-100011
CAS No.:	1454585-06-8
Molecular Formula:	$C_{23}H_{19}F_3N_8O$
Molecular Weight:	480.45
Target:	Casein Kinase
Pathway:	Cell Cycle/DNA Damage; Stem Cell/Wnt
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 : ≥ 30 mg/mL (**62.44 mM**)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0814 mL	10.4069 mL	20.8138 mL
	5 mM	0.4163 mL	2.0814 mL	4.1628 mL
	10 mM	0.2081 mL	1.0407 mL	2.0814 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 (4.33 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.08 mg/mL (4.33 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SR-3029 is a potent and ATP competitive **CK1δ** and **CK1ε** inhibitor, with **IC_{50}**s of 44 nM and 260 nM, respectively, and **K_i**s of 97 nM for both kinases.

IC_{50} & Target				
	CKIδ 44 nM (IC_{50})	CKIε 260 nM (IC_{50})	CDK6/cyclin D3 427 nM (IC_{50})	CDK6/cyclin D1 428 nM (IC_{50})
	CDK4/cyclin D3	CDK4/cyclin D1	FLT3	

	368 nM (IC_{50})	576 nM (IC_{50})	3000 nM (IC_{50})
In Vitro	SR-3029 is a potent CK1δ/CK1ε inhibitor, with IC_{50}s of 44 nM and 260 nM, respectively. SR-3029 is ATP competitive, with K_is of 97 nM for CK1δ/CK1ε. SR-3029 also blocks CDK6/cyclin D3, CDK6/cyclin D1, CDK4/cyclin D3, CDK4/cyclin D1 and FLT3, with IC_{50}s of 427, 428, 368, 576, and 3000 nM, respectively. SR-3029 shows inhibitory effects on A375 cells, with an EC_{50} of 86 nM[1]. CK1δ is a necessary and sufficient driver of Wnt/β-catenin signaling in human breast cancer. SR-3029 shows less potent activities against MCF7 and T47D breast cancer cells and the MCF10A cell line, which express low amounts of CK1δ[2].		
In Vivo	SR-3029 (20 mg/kg daily i.p.) exibits anti-tumor effects in rthotopic MDA-MB-231, MDA-MB-468 (TNBC), SKBR3 and BT474 (HER2+) tumor xenografts with no overt toxicity in mice. SR-3029 (20 mg/kg daily i.p.) also effectively inhibits the growth of tumor in primary patient-derived xenograft (PDX) models. In addition, SR-3029 (20 mg/kg, i.p.) strongly reduces the expression of nuclear β-catenin in tumors of mice[2].		

PROTOCOL

Kinase Assay [1]

Briefly, final assay concentrations for **CK1δ**, Ulight peptide substrate (ULight-Topo-Ila(Thr1342) peptide) and ATP are 2 nM, 200 nM and 20 μM respectively. The reaction is performed at room temperature in a 10 μL final volume (384-well low volume plate) containing the following: 50 mM Hepes, pH 7.5, 5 mM $MgCl_2$, 0.1 mg/mL bovine serum albumin, 1 mM dl-dithiothreitol, 0.01% Triton X-100 and 1% DMSO. After 10 min, the reaction is terminated by addition of 10 μL of 4 nM Eu-anti-p-Topo-Ila in Lance Detection Buffer. The fluorescent signal is detected using a plate reader. 10 point does-response curves with 3-fold dilutions starting from **10 μM for each compound (SR-3029)** is generated in duplicate and data fit to a four parameter logistic[1].

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

Cell Assay [1]

Human A375 melanoma cells are cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin and 1× MEM Non-Essential Amino Acids at 37°C, 5% CO_2. To evaluate the anti-proliferative activity of newly synthesized CK1δ/ε inhibitors, each compound (**SR-3029**) is subjected to MTT assays against A375 melanoma cells and their EC_{50} values are determined. Briefly, A375 melanoma cells are plated into a 96-well plate and treated with a series of concentrations of each new inhibitor, vehicle (DMSO) or with SR-3029 or SR-1277 (positive controls). MTT assays are performed four days after treatment and data are analyzed using the GraphPad Prism5[1].

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Animal Administration [2]

Stable pools of **MDA-MB-231-Luc**, **MDA-MB-231**, **MDA-MB-468**, **SKBR3**, or **BT474 cells** are established by injection of **2 × 10^6 cancer cells** into the mammary fat pads of **6-week-old female athymic nude mice**. Establishment of **BCM-4013 patient-derived xenografts** is performed. Briefly, fresh xenograft tumor fragments (-1 mm^3) are transplanted into the cleared mammary fat pad of recipient SCID/Bg mice. Mice are treated with **SR-3029 or vehicle (10:10:80, DMSO:Tween-80:Water) at 20 mg/kg daily by i.p. injection**. Tumor volumes are measured as the indicated intervals using calipers or by luminescence imaging with the IVIS 100 imager after subcutaneous injection of luciferin (15 mg/mL). Average radiance (p/s/cm^2/sr) is determined from tumor region-of-interest (ROI) using Living-Image analysis software[2].

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CUSTOMER VALIDATION

- **Proc Natl Acad Sci U S A**. 2018 Aug 7;115(32):E7522-E7531.

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REFERENCES

[1]. Bibian M, et al. Development of highly selective casein kinase 1δ/1ε (CK1δ/ε) inhibitors with potent antiproliferative properties. Bioorg Med Chem Lett. 2013 Aug 1;23(15):4374-80.

[2]. Rosenberg LH, et al. Therapeutic targeting of casein kinase 1δ in breast cancer. Sci Transl Med. 2015 Dec 16;7(318):318ra202.

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