CA224

Cat. No.: HY-111207

CAS No.: 883561-04-4

Molecular Formula: $C_{24}H_{22}N_2O$

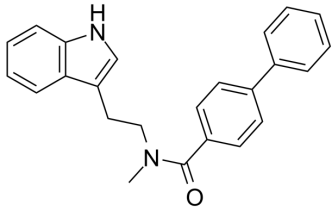
Molecular Weight: 354.44

Target: CDK; Apoptosis

Pathway: Cell Cycle/DNA Damage; Apoptosis

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 (282.14 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.8214 mL	14.1068 mL	28.2135 mL
5 mM	0.5643 mL	2.8214 mL	5.6427 mL
10 mM	0.2821 mL	1.4107 mL	2.8214 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.05 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CA224 (Compound 1) is a selective and orally active Cdk4–cyclin D1 inhibitor with an IC_{50} of 6.2 μM. CA224 induces cell apoptosis and shows antitumor activity[1].

IC_{50} & Target

cdk4-cyclin D1	cdk2-cyclin A
6.2 μM (IC_{50})	521 μM (IC_{50})

In Vitro

CA224 (Compound 1) (48 h) shows antiproliferation activity against human cancer cell lines[1].
CA224 (18-48 h) blocks the growth of cancer cells at G0/G1 and G2/M phase of the cell cycle, and selectively kills SV40 large T-antigen transformed normal mouse embryonic liver cells (BNL SV A.8)[1][2].
CA224 (0-4 μM, 30 min) inhibits tubulin polymerization and enhances the depolymerization of stabilized tubulin protein[1].
CA224 (0-72 h) induces cell apoptosis in cancer cells[1].
CA224 (10 μM) shows 50%, 14%, 51% and 19% inhibition of CYP3A4, CYP2D6, CYP2C9, and CYP2C19, respectively[1].

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

Cell Proliferation Assay[1]

Cell Line:	LS174T, PC-3, MiaPaCa, A549, Calu-1, NCI-H460, NCI-H1299, NCI-H358, BNL CL2 and BNL SV A.8
Concentration:	
Incubation Time:	48 h
Result:	Showed antiproliferation activity with IC_{50} values of 3.5, 6.2, 4.0, 3.5, 11.5, 2.0, 2.5, 2.2, 2.6 and 3.8 uM against LS174T, PC-3, MiaPaCa, A549, Calu-1, NCI-H460, NCI-H1299, NCI-H358, BNL CL2 and BNL SV A.8, respectively.

Cell Cycle Analysis[1][2]

Cell Line:	A549, NCI-H1299, NCI-H358, BNL CL2, BNL SV A.8 and Calu-1
Concentration:	IC_{50} concentration (IC_{70} for Calu-1)
Incubation Time:	24 h for A549, NCI-H1299 and Calu-1, 18 h for NCI-H358, 48 h for BNL CL2 and BNL SV A.8
Result:	Induced a profound block at G2/M in A549 and NCI-H1299 cells. Maintained nocodazole- and paclitaxel-induced G2/M block in NCI-H358 cells. Exhibited prominent G2/M arrest in BNL CL2 cells. 31% of cells were detected in sub-G1 phase (control: 0%) in BNL SV A.8 cells. Retained the G0/G1 block in serum-starved p53-null Calu-1 cells.

Western Blot Analysis[1]

Cell Line:	A549 and LS174T
Concentration:	IC_{50} concentration; 1, 2, 3 and 4 μM for tubulin polymerization
Incubation Time:	24 h; 30 min for tubulin polymerization in A549 cells
Result:	Induced p53, p21, and p27. Downregulated cyclin B1 and Cdk1. Inhibited tubulin polymerization in a dose-dependent manner and resulted in accumulation of unassembled tubulin in the supernatant.

Apoptosis Analysis[1]

Cell Line:	A549, NCI-H460, NCI-H358, and NCI-H1299
Concentration:	IC_{50} and IC_{70} concentration
Incubation Time:	24, 48 and 72 h
Result:	Induces apoptotic cell death in a dose- and time-dependent manner.

In Vivo

CA224 (Compound 1) (100 mg/kg; i.p.; once a day for 9 days) shows significant tumor growth inhibition without obvious toxicity[1].

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Animal Model:	The severe combined immunodeficient (SCID) mouse, lacking both T and B immune cells. Male mice weighing 18−25 g, 6−8 weeks of age for subcutaneous injection of HCT-116, female mice weighing 15−24 g, 6−8 weeks of age for subcutaneous injection of NCI-H460[1]

Dosage:	100 mg/kg
Administration:	Intraperitoneal injection, once a day for 9 consecutive days
Result:	Showed significant tumor growth inhibition in both HCT-116 and NCI-H460 tumor models without significant bodyweight loss.

Animal Model:	BALB/c mice[1]
Dosage:	10 mg/kg (oral administration) or 1.0 mg/kg (intravenous injection)
Administration:	Oral or intravenous injection (Pharmacokinetics Analysis)
Result:	Pharmacokinetics parameters determined for CA224 after IV and PO administration[1].

Parameter	IV (1 mg/kg)	Oral (10 mg/kg)
$t_{1/2,\beta}$ (h)	0.33	1.16
AUC_{0-t} (ng·h/mL)	187	172
$AUC_{0-\infty}$ (ng·h/mL)	189	182
$C_{max\ (ng/mL)}$	371	190
V_d (L/Kg)	2.52	nd
V_{dss} (L/Kg)	1.76	nd
CL (mL/min/kg)	88.3	nd
Bioavailability	-	9.6%
Time points considered for $t_{1/2,\beta}$ calculation	0.5-2 h	1-4 h

REFERENCES

[1]. Sachin Mahale, et al. Biphenyl-4-carboxylic acid [2-(1H-indol-3-yl)-ethyl]-methylamide (CA224), a nonplanar analogue of fascaplysin, inhibits Cdk4 and tubulin polymerization: evaluation of in vitro and in vivo anticancer activity. J Med Chem. 2014 Nov 26;

[2]. Sachin Mahale, et al. CA224, a non-planar analogue of fascaplysin, inhibits Cdk4 but not Cdk2 and arrests cells at G0/G1 inhibiting pRB phosphorylation. Bioorg Med Chem Lett. 2006 Aug 15;16(16):4272-8.

Caution: Product has not been fully validated for medical applications. For research use only.

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