CHIR-124

Cat. No.: HY-13263

CAS No.: 405168-58-3

Molecular Formula: $C_{23}H_{22}ClN_5O$

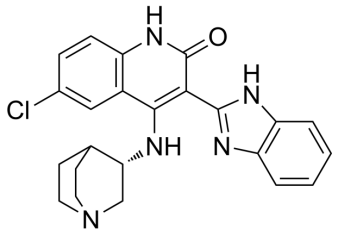
Molecular Weight: 419.91

Target: Checkpoint Kinase (Chk); FLT3; PDGFR; Apoptosis

Pathway: Cell Cycle/DNA Damage; Protein Tyrosine Kinase/RTK; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 7.14 mg/mL (17.00 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3815 mL	11.9073 mL	23.8146 mL
5 mM	0.4763 mL	2.3815 mL	4.7629 mL
10 mM	0.2381 mL	1.1907 mL	2.3815 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: ≥ 0.71 mg/mL (1.69 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.71 mg/mL (1.69 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CHIR-124 is a potent and selective Chk1 inhibitor with IC_{50} of 0.3 nM, and also potently targets PDGFR and FLT3 with IC_{50}s of 6.6 nM and 5.8 nM.

IC_{50} & Target

Chk1 0.3 nM (IC_{50})	Chk2 697.4 nM (IC_{50})	PDGFR 6.6 nM (IC_{50})	FLT3 5.8 nM (IC_{50})
Cdk4/cyclin D 2.05 μM (IC_{50})	CDC2/cyclin B 0.5057 μM (IC_{50})	Cdk2/cyclin A 0.1911 μM (IC_{50})	bFGFR 2.01 μM (IC_{50})
FGFR3	VEGFR2 FLK1	VEGFR1 FLT1	PKCα

	1.29 μM (IC_{50})	0.5779 μM (IC_{50})	0.4636 μM (IC_{50})	0.58 μM (IC_{50})
	PKAβ I 2.25 μM (IC_{50})	PKCβ II 0.58 μM (IC_{50})	PKCγ 0.11 μM (IC_{50})	ERK2 4.31 μM (IC_{50})
	PKA 0.1031 μM (IC_{50})	GSK3 0.0233 μM (IC_{50})		

In Vitro

CHIR-124 is 500- to 5,000-fold less active against other cell cycle kinases, such as cyclin-dependent kinase 2/cyclin A (0.19 μM), cdc2/cyclin B (0.51 μM), and cyclin-dependent kinase 4/cyclin D (2.1 μM). CHIR-124 (≥0.9 nM) in combination with SN-38 (≥0.42 nM) causes significant synergy or >10% deviation from additivity in human cancer cell lines expressing mutant p53, and these values overlap and fall below the IC_{50}s for SN-38 (1.2×10^{-7} M) and CHIR-124 (2.2×10^{-7} M), respectively. Moreover, CHIR-124 (100 nM) abrogates the SN-38-induced S and G2-M phase cell cycle checkpoints. CHIR-124 (200 nM) leads to a 2.5-fold elevated level of cdc25A above that of the untreated HCT116 $p53^{/}$ cells. The down-regulation of cdc25A induced by SN-38 is completely restored by concurrent or sequential treatment with CHIR-124, proving that CHIR-124 inhibits the Chk1-mediated destruction of cdc25A in whole cells[1]. CHIR-124 occupies the ATP-binding site, inhibits Chk1 (IC_{50}, 0.3 nM) 2,000-fold more potently than Chk2 (IC_{50}, 0.7 μM)[2].

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

In Vivo

CHIR-124 (10 or 20 mg/kg, p.o.) does not have a significant effect on tumor growth when compared with the vehicle-treated group, but it potentiates the growth inhibitory effect of CPT-11 in a human breast carcinoma xenograft model. The potentiation of the tumor growth inhibitory effect of CPT-11 by CHIR-124 is associated with an increase in apoptosis induction in the tumors. CHIR-124 reverses the suppression of phospho-H3 staining induced by CPT-11, indicating abrogation of the G2-M checkpoint by CHIR-124[1].

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PROTOCOL

Kinase Assay [1]

For the CHK1 assay, the kinase domain is expressed in Sf9 insect cells, and a biotinylated cdc25c peptide containing the consensus Chk1/Chk2 phosphorylation site (*)(biotin-[AHX]SGSGS*GLYRSPSMP-ENLNRPR[$CONH_2$]) is used as the substrate. A dilution series of CHIR-124 is mixed with a kinase reaction buffer containing a final concentration of 30 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, 2 mM DTT, 4 mM EDTA, 25 mM β-glycerophosphate, 5 mM $MnCl_2$, 0.01% bovine serum albumin, 1.35 nM CHK1 kinase domain, 0.5 μM peptide substrate, and 1 μM unlabeled ATP, plus 5 nM ^{33}P γ-labeled ATP (specific activity =2,000 Ci/mmol). Reactions and detection of the phosphate transfer are carried out by a radioactive method.

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

Animal Administration [1]

Severe combined immunodeficient mice harboring MDA-MD-435 tumor xenografts are randomized into the following treatment groups of 10: vehicle (captisol) alone, 5 mg/kg CPT-11, 10 mg/kg CHIR-124, 20 mg/kg CHIR-124, 5 mg/kg CPT-11 plus 10 mg/kg CHIR-124, or 5 mg/kg CPT-11 plus 20 mg/kg CHIR-124. Treatment is initiated on the day after randomization (day 1). CPT-11 is given i.p. daily (four times daily) ×5 on days 1 to 5, whereas CHIR-124 is given orally four times daily ×6 on days 2 to 7 in captisol. Percent tumor growth inhibition is defined as % T/C, where T = the treatment group mean, and C = the control group mean. In a similar study, tumors harvested from mice sacrificed on day 4 of treatment are examined for apoptosis by terminal deoxynucleotidyl transferase-mediated nick-end labeling staining and for mitotic index by immunofluorescence labeling with phospho-histone H3 antibody.

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

CUSTOMER VALIDATION

- Sci Rep. 2020 Jul 17;10(1):11921.

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REFERENCES

[1]. Tse AN, et al. CHIR-124, a novel potent inhibitor of Chk1, potentiates the cytotoxicity of topoisomerase I poisons in vitro and in vivo. Clin Cancer Res, 2007, 13(2 Pt 1), 591-602.

[2]. Dai Y, et al. New insights into checkpoint kinase 1 in the DNA damage response signaling network. Clin Cancer Res, 2010, 16(2), 376-383.

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