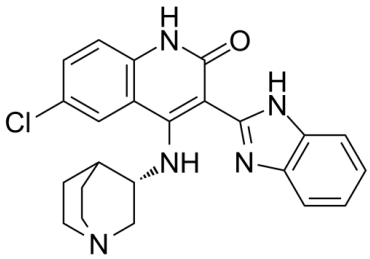
Data Sheet

Product Name:	CHIR-124
Cat. No.:	CS-0482
CAS No.:	405168-58-3
Molecular Formula:	C23H22ClN5O
Molecular Weight:	419.91
Target:	Apoptosis; Checkpoint Kinase (Chk); FLT3; PDGFR
Pathway:	Apoptosis; Cell Cycle/DNA Damage; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 14 mg/mL (33.34 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 0.3 nM (Chk1), 5.8 nM (FLT3), 6.6 nM (PDGFR)[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **Animal Administration:** CHIR-124 is prepared in captisol.[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.

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.

CAIndexNames:

2(1H)-Quinolinone, 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro-

SMILES:

ClC1=CC2=C(NC(C(C3=NC4=C(C=CC=C4)N3)=C2N[C@@H]5CN6CCC5CC6)=O)C=C1

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