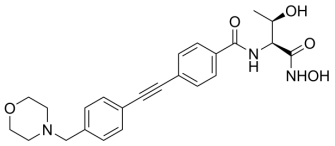
CHIR-090

Cat. No.:	HY-15460
CAS No.:	728865-23-4
Molecular Formula:	$C_{24}H_{27}N_3O_5$
Molecular Weight:	437.49
Target:	Bacterial; Antibiotic
Pathway:	Anti-infection
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 : 5 mg/mL (11.43 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2858 mL	11.4288 mL	22.8577 mL
5 mM	0.4572 mL	2.2858 mL	4.5715 mL
10 mM	0.2286 mL	1.1429 mL	2.2858 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: ≥ 0.5 mg/mL (1.14 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (1.14 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (1.14 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CHIR-090 is a potent, slow, tight-binding inhibitor of the LpxC deacetylase. It binds to E. coli LpxC with a K_i of 4.0 nM. CHIR-090 is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups.

IC_{50} & Target

Ki: 4 nM (Escherichia coli LpxC)[1]

In Vitro	CHIR-090 is a potent, slow, tight-binding inhibitor of the LpxC deacetylase from the hyperthermophile Aquifex aeolicus, and it has excellent antibiotic activity against P. aeruginosa and E. coli, as judged by disk diffusion assays. CHIR-090 is also a two-step slow, tight-binding inhibitor of Escherichia coli LpxC with K_i=4 nM. CHIR-090 at low nM levels inhibits LpxC orthologues from diverse Gram-negative pathogens, including Pseudomonas aeruginosa, Neisseria meningitidis, and Helicobacter pylori . In contrast, CHIR-090 is a relatively weak competitive and conventional inhibitor (lacking slow, tight-binding kinetics) of LpxC from Rhizobium leguminosarum (K_i=340 nM), a Gram-negative plant endosymbiont that is resistant to this compound. An E. coli construct in which the chromosomal lpxC gene is replaced by R. leguminosarum lpxC is resistant to CHIR-090 up to 100 μg/mL, or 400 times above the minimal inhibitory concentration for wild-type E. coli. CHIR-090, a very potent, slow, tight-binding inhibitor of Aquifex aeolicus LpxC, the sequence of which is 31 % identical to E. coli LpxC. CHIR-090 has remarkable antibiotic activity against E. coli and P. aeruginosa, comparable to ciprofloxacin, as judged by disk diffusion assays[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CHIR-090 is a potent antibiotic against E. coli and inhibits E. coli LpxC activity in vitro in the low nM range. E. coli W3110 colonies resistant to 1 μg/mL CHIR-090 are not observed without prior chemical mutagenesis. A strain of E. coli W3110 is able to grow on LB agar plates containing 1 to 10 μg/mL CHIR-090, which is 4 to 40 times above the MIC of 0.25 μg/mL under our conditions for wild-type E. coli W3110. The doubling time of W3110RL is 40 min in the presence of 1 μg/mL CHIR-090, which is exactly the same rate as wild-type in the absence of inhibitor. Wild-type cells stopped growing after about 2 h in the presence of 1 μg/mL CHIR-090[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Disk diffusion is conducted, except that 10 μg of each antibiotic compound is used per filter. Growth in liquid medium in the presence of CHIR-090 is evaluated as follows: cells from overnight cultures are inoculated into 50 mL portions of LB broth at an A_{600} of 0.02 and grown with shaking at 30°C. When the A_{600} reaches 0.15, parallel cultures are treated with either 6 μL of 500 μg/mL CHIR-090 in DMSO or 6 μL of DMSO. To assess cumulative growth, cultures are maintained in log phase growth by 10-fold dilution into pre-warmed medium, containing the same concentrations of DMSO or DMSO/CHIR-090, whenever the A_{600} reaches 0.4. The minimal inhibitory concentration is defined as the lowest antibiotic concentration at which no measurable bacterial growth is observed in LB medium containing 1% DMSO (v/v), when inoculated at a starting density of A_{600}=0.01. Cultures are incubated with shaking for 24 h at 30°C in the presence of CHIR-090. Experiments are performed in triplicate[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2018 Jul;559(7713):259-263.
- Cell Mol Gastroenterol Hepatol. 2021 Jul 6;12(5):1643-1667.
- Antimicrob Agents Chemother. 2017 Jun 27;61(7). pii: e02223-16.

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REFERENCES

[1]. Barb AW, et al. Inhibition of lipid A biosynthesis as the primary mechanism of CHIR-090 antibiotic activity in Escherichia coli. Biochemistry. 2007 Mar 27;46(12):3793-802.

[2]. Barb AW, et al. Structure of the deacetylase LpxC bound to the antibiotic CHIR-090: Time-dependent inhibition and specificity in ligand binding. Proc Natl Acad Sci U S A. 2007 Nov 20;104(47):18433-8.

[3]. Tan JH, et al. In Vitro and In Vivo Efficacy of an LpxC Inhibitor, CHIR-090, Alone or Combined with Colistin against Pseudomonas aeruginosa Biofilm. Antimicrob Agents Chemother. 2017 Jun 27;61(7). pii: e02223-16.

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