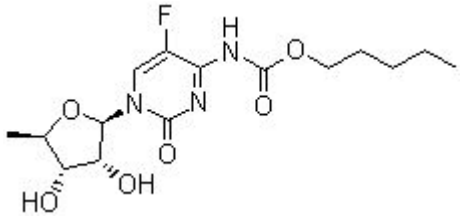
Product Introduction

CHIR-99021 (CT99021) HCl

CHIR-99021 HCl (CT99021) is hydrochloride of CHIR-99021, which is a **GSK-3α/β** inhibitor with **IC50** of 10 nM/6.7 nM; ability to distinguish between GSK-3 and its closest homologs Cdc2 and ERK2.

Technical Data:

Molecular Weight (MW):	501.8	
Formula:	$C_{22}H_{18}Cl_2N_8.HCl$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 93 mg/mL	
	Water 8 mg/mL	
	Ethanol 2 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	252917-06-9(free base)	

Biological Activity

CHIR-99021 shows greater than 500-fold selectivity for GSK-3 versus its closest homologs CDC2 and ERK2, as well as other protein kinases. Furthermore, CHIR-99021 shows only weak binding to a panel of 22 pharmacologically relevant receptors and little inhibitory activity against a panel of 23 nonkinase enzymes. CHIR-99021 induces the activation of glycogen synthase (GS) in insulin receptor-expressing CHO-IR cells with EC50 of 0.763 μM. [1] In addition to simulating the actions of insulin, inhibition of GSK-3 by CHIR-99021 (3 μM) increases free cytosolic β-catenin by 1.9-fold, mimicking the canonical Wnt signaling

pathway in 3T3-L1 preadipocytes. During any of the first 3 days of differentiation, CHIR-99021 treatment inhibits the preadipocyte differentiation with IC50 of 0.3 μM by blocking induction of CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ). [2] Unlike lithium chloride and AR-A014418, CHIR-99021 treatment does not reduce the viability of INS-1E cells even at high concentrations. Instead, CHIR-99021 robustly increases the rate of proliferation of INS-1E cells in a dose-dependent manner, and significantly inhibits INS-E cell death induced by high glucose and high palmitate in a concentration-dependent manner. CHIR-99021 promotes primary beta cell replication in isolated rat islets at concentrations as low as 1 μM, with 2-3 fold increase of cell replication at 5 μM of CHIR-99021 treatment. [3]

Oral administration of CHIR-99021 at 30 mg/kg enhances glucose metabolism in a rodent model of type 2 diabetes, with a maximal plasma glucose reduction of nearly 150 mg/dl 3-4 hours after administration, while plasma insulin remains at or below control levels. Oral administration of CHIR-99021 at 16 or 48 mg/kg 1 hour before oral glucose challenges in ZDF rats significantly improves glucose tolerance with 14% and 33% reduction in plasma glucose at 16 mg/kg and 48 mg/kg, respectively, and the higher dose of CHIR-99021 also reduces hyperglycemia before the oral glucose challenge. [1] Administration of CHIR-99021 significantly augments hematopoietic repopulation in recipient mice transplanted with mouse or human hematopoietic stem cells (HSCs), suggesting that GSK-3 is a specific modulator of HSC activity. [4]

References

[1] Ring DB, et al. Diabetes, 2003, 52(3), 588-595.
[2] Bennett CN, et al. J Biol Chem, 2002, 277(34), 30998-31004.
[3] Mussmann R, et al. J Biol Chem, 2007, 282(16), 12030-12037.

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