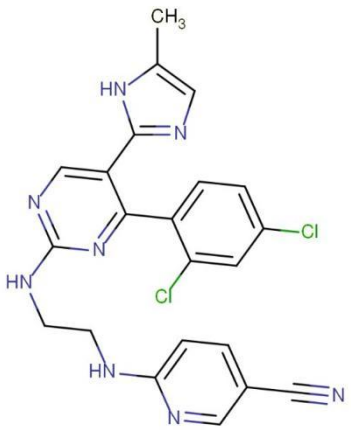
CHIR-99021 (GSK-3 抑制剂)

货号：RPM0009

◆ 产品信息

中文名称/Chinese Name:	CHIR-99021
别称/Synonyms:	6-[2-[4-(2,4-二氯苯基)-5-(4-甲基-1H-咪唑-2-基)嘧啶-2-基氨基]乙基氨基]吡啶-3-甲腈
CAS 号/CAS NO.:	252917-06-9
化学式/Formula:	$C_{22}H_{18}Cl_2N_8$
分子量/M.Wt:	465.34
外观/Appearance:	固体
保存条件/Storage:	Powder：-20℃，3 年 Insolvent：-80℃，1 年



◆ 溶解信息

溶解度/Solubility:	DMSO： 50 mg/mL (107.45 mM)

溶液配制参考/Preparing Stock Solutions:

	1 mg	5 mg	10 mg
1 mM	2.149 mL	10.7448 mL	21.4897 mL
5 mM	0.4298 mL	2.149 mL	4.2979 mL
10 mM	0.2149 mL	1.0745 mL	2.149 mL
50 mM	0.043 mL	0.2149 mL	0.4298 mL

◆ 生物活性

产品描述/Description	CHIR-99021 是一种 Wnt/β-catenin 信号通路激活剂，也是一种 GSK-3α/β抑制剂，可以诱导细胞自噬，增强小鼠和人类胚胎干细胞的自我更新。
靶点活性/Targets (IC_{50})	GSK-3α: 10 nM, GSK-3β: 6.7 nM
体外活性/In vitro	1.用 CHIR-99021（1-10 μM）处理小鼠干细胞 ES-D3 72 h，MTT 法检测细胞生长抑制情况。CHIR-99021 剂量依赖性地抑制细胞生长，IC_{50} 为 4.9 μM。[1] 2.用 CHIR-99021（3 μM）处理小鼠胚胎干细胞 J1 mESCs 和小鼠胚胎瘤细胞 F9 mEC 24 h，免疫荧光法检测靶点蛋白表达水平。CHIR-99021 处理后，J1-mESCs 和 F9-mEC 细胞的细胞质和细胞核中的β-连环蛋白增加。[2] 3.用 CHIR-99021（5 μM）处理人 Tenon 成纤维细胞 HTFs 48 h，Western Blot 检测靶点蛋白表达水平。CHIR-99021 处理使活性形式的 GSK-3β（p-GSK-3β (Y216)）的产生显著减少。[3]

体内活性/In vivo	1.将 CHIR-99021（37.5 mg/kg/第 0-3、6-10、13-17 和 20 天每天两次）口服给药和 paclitaxel（10 mg/kg/第 0 天单次给药）腹腔注射给携带人非小细胞肺癌肿瘤 H1975 的 Balb/c nude 小鼠，检测体内抗肿瘤活性。CHIR-99021 和 paclitaxel 在体内协同作用，抑制 NSCLC 肿瘤的生长。[4] 2.将 CHIR-99021（1-10 mg/kg）单次腹腔注射给有酒精或蔗糖自给药史的 C57BL/6J 小鼠，研究 GSK-3 的直接药理学抑制是否会改变酒精在小鼠体内的积极增强作用。CHIR-99021 剂量依赖性地增加了酒精强化反应，而对蔗糖自我给药或运动活性没有影响，显著降低了 pGSK-3β在所有测试脑区的表达，仅在 NAcb 中降低了 PICK1 并增加了 GluA2 的总表达。[5]
激酶实验/Kinase Assay	Kinases were purified from SF9 cells through the use of their His or Glu tag. Kinase assays were performed in 96-well plates with appropriate peptide substrates in a 300 μL reaction buffer (variations on 50 mM Tris-HCl, pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 1 mM dithiothreitol, 25 mM β-glycerophosphate, 1 mM NaF, and 0.01% bovine serum albumin). Peptides had Km values from 1 to 100 μM. CHIR 99021 or CHIR GSKIA was added in 3.5 μL of DMSO, followed by ATP to a final concentration of 1 μM. After incubation, triplicate 100 μL aliquots were transferred to Combiplate 8 plates containing 100 μL/well of 50 μM ATP and 20 mM EDTA. After 1 hour, the wells were rinsed five times with phosphate-buffered saline, filled with 200 μL of scintillation fluid, sealed, and counted in a scintillation counter 30 min later. All of the steps were at room temperature. The percentage of inhibition was calculated as 100 × (inhibitor-no enzyme control)/(DMSO control-no enzyme control) [4].

◆ 参考文献

[1] Naujok O, et al. Cytotoxicity and activation of the Wnt/beta-catenin pathway in mouse embryonic stem cells treated with four GSK3 inhibitors. BMC Res Notes. 2014 Apr 29;7:273.

[2] Wu Y, et al. GSK3 inhibitors CHIR99021 and 6-bromoindirubin-3'-oxime inhibit microRNA maturation in mouse embryonic stem cells. Sci Rep. 2015 Mar 2;5:8666.

[3] Lee SY, et al. The Effect of CHIR 99021, a Glycogen Synthase Kinase-3β Inhibitor, on Transforming Growth Factor β-Induced Tenon Fibrosis. Invest Ophthalmol Vis Sci. 2021 Dec 1;62(15):25.

[4] O'Flaherty L, et al. Tumor growth suppression using a combination of taxol-based therapy and GSK3 inhibition in non-small cell lung cancer. PLoS One. 2019 Apr 10;14(4):e0214610.

[5] Faccidomo S, et al. Pharmacological inhibition of glycogen synthase kinase 3 increases operant alcohol self-administration in a manner associated with altered pGSK-3β, protein interacting with C kinase and GluA2 protein expression in the reward pathway of male C57BL/6J mice. Behav Pharmacol. 2020 Feb;31(1):15-26.

◆ 注意事项

1. 请在收到本产品后立即按照说明书中推荐的条件保存，使用前进行离心，使粉末充分沉降至管底。
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