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Zuschläge

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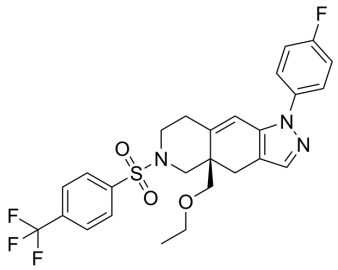
Cort108297

Cat. No.:	HY-15710
CAS No.:	1018679-79-2
Molecular Formula:	$C_{26}H_{25}F_4N_3O_3S$
Molecular Weight:	535.55
Target:	Glucocorticoid Receptor
Pathway:	Immunology/Inflammation; Vitamin D Related/Nuclear Receptor
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (186.72 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8672 mL	9.3362 mL	18.6724 mL
	5 mM	0.3734 mL	1.8672 mL	3.7345 mL
	10 mM	0.1867 mL	0.9336 mL	1.8672 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

Cort108297 is a specific glucocorticoid receptor (GR) antagonist. Cort108297 has a high affinity for GRs with a K_i of 0.45 nM.

IC_{50} & Target

Ki: 0.45 nM (glucocorticoid receptor)[1]

In Vitro

In LAPC4 cells, co-treatment with Dexamethasone induces steady-state SGK1 expression 1.7-fold compared to R1881/Enzalutamide (RE) treatment alone. Addition of CORT118335 (1μM) inhibits Dexamethasone-induced SGK1 expression 50% while Cort108297 completely blocks the Dexamethasone-mediated SGK1 increase ($p<0.05$). KLK3 expression is increased 2.5-fold by Dexamethasone compared to treatment with RE. Both Cort108297 and CORT118335 antagonize Dexamethasone-induced KLK3 expression (by 48% and 60%, respectively, $p<0.05$). Following 3 days of Dexamethasone±SGRMs in CWR-22Rv1 cells, SGK1 gene expression is dramatically induced by ~100-fold compared to RE-treated cells and this induction is completely abrogated by both Cort108297 and CORT118335 ($p<0.01$). KLK3 is also induced (7.5-fold) by Dexamethasone compared to RE in CWR-22Rv1 cells; Cort108297 and CORT118335 inhibits this induction by 70% and 75%, respectively ($p<0.01$)[2].

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

In Vivo	Ten-week-old, male, C57BL/6J mice are fed a diet containing 60% fat calories and water supplemented with 11% sucrose for 4 weeks. Groups (n=8) receive one of the following: Cort108297 (80 mg/kg QD), Cort108297 (40 mg/kg BID), Mifepristone (30 mg/kg BID), Rosiglitazone (10 mg/kg QD), or vehicle. Compared to mice receiving a high-fat, high-sugar diet plus vehicle, mice receiving a high-fat, high-sugar diet plus either Mifepristone or Cort108297 gain significantly less weight. At the end of the four week treatment period, mice receiving Cort108297 40 mg/kg BID or Cort108297 80 mg/kg QD also have significantly lower steady plasma glucose than mice receiving vehicle[3]. Male rats are treated for five days with Mifepristone (10 mg/kg), Cort108297 (30 mg/kg and 60 mg/kg), Imipramine (10mg/kg) or vehicle and exposed to forced swim test (FST) or restraint stress. Both doses of Cort108297 potently suppress peak corticosterone responses to FST and restraint stress. However, only the higher dose of Cort108297 (60mg/kg) significantly decreases immobility in the forced swim test (FST) [4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Steroid receptor competition binding assays are run in a buffer containing 20 mM HEPES buffer (pH=7.6), 0.2 mM EDTA, 75 mM NaCl, 1.5 mM $MgCl_2$, 20% glycerol, 20 mM sodium molybdate, 0.2 mM DTT, 20 μg/mL Aprotinin, and 20 μg/mL Leupeptin (assay buffer). Radiolabeled ligands are used to detect binding to cells expressing receptors including 0.25 nM [^{3}H]Aldosterone for mineralocorticoid receptor (MR) binding, 0.3 nM [^{3}H]Dexamethasone for GR binding, 0.36 nM [^{3}H]Methyltrienolone for aldosterone receptor (AR) binding, and 0.29 nM [3H]methyltrienolone for PR binding. Receptors are recombinantly expressed in human embryonic kidney 293 (HEK-293) cells, and 20 μg of 293-MR lysate, 20 μg of 293-GR lysate, 22 μg of 293-AR lysate, or 40 μg of 293-PR lysate are added per well. Competing test compounds (e.g., Cort108297) are added at various concentrations from 0.01 nM to 10 μM. Nonspecific binding is determined in the presence of 500 nM Aldosterone for MR binding, 500 nM Dexamethasone for GR binding, or 500 nM methyltrienolone for AR and PR binding. The binding reactions (140 μL) are incubated overnight at 4°C, then 70 μl of cold charcoal-dextran buffer (containing per 50 mL of assay buffer, 0.75 g of Charcoal, and 0.25 g of Dextran) is added to each reaction. Plates are mixed for 8 minutes on an orbital shaker at 4°C. The plates are then centrifuged at 3000 rpm at 4°C for 10 minutes. A 120 μL aliquot of the binding reaction mixture is then transferred to another 96-well plate, and 175 μL of Wallac Optiphase Hisafe 3 scintillation fluid is added to each well. The plates are sealed and shaken vigorously using an orbital shaker. After 2 hour incubation, the plates are counted using a Wallac MicroBeta counter[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	LAPC4 and CWR-22Rv1 cells are plated in standard media and incubated overnight. Cells are washed with PBS and placed into media containing charcoal stripped FBS, 10% for LAPC4 or 1%/10% for CWR-22Rv1. Cells are treated for indicated times with media changes every other day with either vehicle control or specified treatment: 1 nM R1881, 100 nM Dexamethasone, 10 μM Enzalutamide, 100 nM Mifepristone, 1 μM CORT118335, 1 μM Cort108297. For all experiments, equimolar vehicle (ethanol±DMSO) is added to every sample for equal treatment periods. Cells are plated and treated. At indicated days cells are washed, trypsinized, pelleted, and resuspended in media. Cells are then mixed 1:1 with trypan blue and viable cells are counted in a blinded fashion. Three biological replicates are assayed per condition per time point and the mean of the biological replicates is reported[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3][4]	Mice[3] Forty ten-week-old, male, C57BL/6J mice are fed ad libitum a diet containing 60% fat calories and water supplemented with 11% sucrose for 4 weeks. In addition, they receive one of the following five treatments: Cort108297 (80 mg/kg QD), Cort108297 (40 mg/kg BID), Mifepristone (30 mg/kg BID), Rosiglitazone, an oral glycemic medication (10 mg/kg QD), or vehicle (10% DMSO in 0.5% CMC). An additional control group (n=8) is fed a standard chow diet and tap water and does not receive any treatment. Rats[4] Male Sprague Dawley rats (250-275 g) are used. Forty-eight rats are matched by body weight and are administered, Cort108297 dissolved in DMSO (30mg/kg s.c.(n=10) or 60 mg/kg s.c. (n=10), Mifepristone dissolved in DMSO 10mg/kg s.c. (n=10), Imipramine dissolved in saline 10mg/kg i.p. (n=10) or vehicle DMSO s.c. (n=4) or saline i.p. (n=4). Control groups consist of both subcutaneous (s.c.) and intraperitoneal (i.p.) groups to control for the route of administration and both DMSO and saline to control for any potential differences between the compounds on neuroendocrine and behavioral stress

responsiveness.

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

REFERENCES

[1]. Sindelar DK, et al. LLY-2707, a novel nonsteroidal glucocorticoid antagonist that reduces atypical antipsychotic-associated weight gain in rats. J Pharmacol Exp Ther. 2014 Jan;348(1):192-201.

[2]. Kach J, et al. Selective Glucocorticoid Receptor Modulators (SGRMs) Delay Castrate-Resistant Prostate Cancer Growth. Mol Cancer Ther. 2017 Aug;16(8):1680-1692.

[3]. Asagami T, et al. Selective Glucocorticoid Receptor (GR-II) Antagonist Reduces Body Weight Gain in Mice. J Nutr Metab. 2011;2011:235389.

[4]. Solomon MB, et al. The selective glucocorticoid receptor antagonist CORT 108297 decreases neuroendocrine stress responses and immobility in the forced swim test. Horm Behav. 2014 Apr;65(4):363-71.

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