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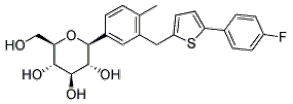
Canagliflozin Datasheet

Technical Data

Molecular Weight (MW)	444.52
Formula	$C_{24}H_{25}FO_5S$
CAS No.	842133-18-0, 928672-86-0 (0.5H2O)
Synonyms	N/A

Solubility (25°C)	DMSO 89 mg/mL	
	Water <1 mg/mL	
	Ethanol 89 mg/mL	
Storage	2 years	-20°C Powder
	2 weeks	4°C in DMSO
	6 months	-80°C in DMSO

Canagliflozin Chemical Structure



Biological Activity

Description	Canagliflozin is a highly potent and selective SGLT2 inhibitor for **CHO-hSGLT2**, **CHO-rSGLT2** and **CHO-mSGLT2** with **IC50** of 4.4 nM, 3.7 nM and 2 nM, respectively.					
Targets	hSGLT2	rSGLT2	mSGLT2			
IC50	4.4 nM	3.7 nM	2 nM[1]			
In vitro	Canagliflozin is a novel C-glucoside with thiophene ring. Canagliflozin inhibits Na^+-dependent ^{14}C-AMG uptake in a concentration-dependent fashion. Canagliflozin inhibits ^{14}C-AMG uptake in CHO-hSGLT1 and mSGLT1 cells with IC50 of 0.7 μM and >1 μM, respectively. Canagliflozin inhibits the facilitative (non-Na^+-linked) GLUT-mediated ^{2}H-2-DG uptake in L6 myoblasts by less than 50%. In sham-injected oocytes, Canagliflozin (10 μM) or phlorizin (3 mM) alone in the presence of 50 μM DNJ does not affect currents. In SGLT3-injected oocytes, DMSO and Canagliflozin 10 μM inhibits DNJ-induced currents by 15.6% and 23.4%, respectively.[1]					
In vivo	Canagliflozin shows pronounced anti-hyperglycemic effects in high-fat diet fed KK (HF-KK) mice. Oral administration at 30 mg/kg of Canagliflozin to male SD rats induces glucose excretion over 24 hours by 3,696 mg per 200 g body weight. Pharmacokinetic studies reveals a much higher exposure of Canagliflozin following oral administration. Following intravenous and oral doses of 3 and 10 mg/kg, respectively, to male SD rats, AUC_{0-inf}, po, $t_{1/2}$ and oral bioavailability are determined to be 35,980 ng·h/mL, 5.2 hours, and 85%, respectively. Thus, inhibition of SGLT2 in renal tubules after oral dosing of Canagliflozin is likely to continuously suppress reabsorption of glucose. The extensive UGE would reflect excellent pharmacokinetic properties of Canagliflozin in vivo as well as high potency of SGLT2 inhibition. Since most of the filtered glucose is reabsorbed by SGLT2 in the renal tubules, the novel compound would be useful for an anti-diabetic agent. Single oral administration of Canagliflozin at 3 mg/kg remarkably reduced blood glucose levels without influencing food intake in hyperglycemic high-fat diet fed KK (HF-KK) mice. There is a 48% reduction in blood glucose level versus vehicle at 6 hours. In contrast, Canagliflozin only slightly affects blood glucose levels in normoglycemic mice. Therefore, Canagliflozin would control hyperglycemia in the therapy of T2DM with low risk of hypoglycemia. [2]					
Clinical Trials	Canagliflozin has entered in a Phase III clinical trial for the treatment of diabetes mellitus and type 2 renal insufficiency.					
Features						

Protocol (Only for Reference)

Cell Assay: [1]

Cell Lines	L6 cell lines
Concentrations	0-10 μM
Incubation Time	24 hours
Methods	Cells from the rat skeletal muscle cell line, L6, is used to test the effect of Canagliflozin on glucose transporter 1 (GLUT1) activity. Cells are maintained in Dulbecco's modified Eagle's medium containing 5.6 mM glucose supplemented with 10% fetal bovine serum, are seeded in 24-well plates at a density of 3.0 × 10^5 cells/well and cultured for 24 hours in an atmosphere of 5% CO_2 at 37 °C. Cells are rinsed twice with Kreb's ringer phosphate HEPES buffer (pH 7.4, 150 mM NaCl, 5 mM KCl, 1.25 mM $MgSO_4$, 1.25 mM $CaCl_2$, 2.9 mM Na_2HPO_4, 10 mM HEPES) and are pre-incubated with the solutions of Canagliflozin (250 μL, 10 uM) for 5 minutes at room temperature. The transport reaction is initiated by adding 50 μL of 4.5 mM 2-DG (a substrate for GLUTs)/3H-2-DG (0.625 μCi) followed by incubation for 15 minutes at room temperature. The 2-DG uptake is halted by aspiration of the incubation mixture. Cells are immediately washed 3 times with ice-cold PBS. Samples are extracted with 0.3 N NaOH, and radioactivity is determined by liquid scintillation.

Animal Study:[2]

Animal Models	KK (HF-KK) mice
Formulation	0.2% CMC/0.2% Tween 80
Doses	10 mg/kg

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Administration	Oral administration

References

[1] Liang Y, et al. PLoS One. 2012, 7(2), e30555.
[2] Nomura S, et al. J Med Chem. 2010, 53(17), 6355-6360.

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