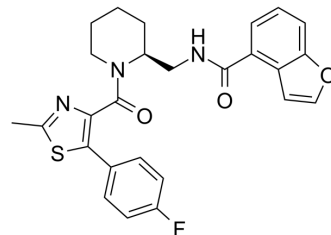


SB-649868

Cat. No.:	HY-10806		
CAS No.:	380899-24-1		
Molecular Formula:	C ₂₆ H ₂₄ FN ₃ O ₃ S		
Molecular Weight:	477.55		
Target:	Orexin Receptor (OX Receptor)		
Pathway:	GPCR/G Protein; Neuronal Signaling		
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 : 100 mg/mL (209.40 mM; Need ultrasonic)				
		Solvent Concentration	Mass 1 mg	5 mg	10 mg
	Preparing Stock Solutions	1 mM	2.0940 mL	10.4701 mL	20.9402 mL
		5 mM	0.4188 mL	2.0940 mL	4.1880 mL
10 mM		0.2094 mL	1.0470 mL	2.0940 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: ≥ 2.5 mg/mL (5.24 mM); Clear solution 2. Add each solvent one by one: 10% DMSO >> 90% corn oil Solubility: ≥ 2.5 mg/mL (5.24 mM); Clear solution				

BIOLOGICAL ACTIVITY

Description	SB-649868 is a potent and selective orally active orexin (OX) 1 and OX ₂ receptor antagonist (pK _i =9.4 and 9.5 at the OX ₁ and OX ₂ receptor, respectively).
IC₅₀ & Target	pKi: 9.4 (OX ₁), 9.5 (OX ₂) ^[1]
In Vitro	SB-649868 is identified as one the most in vitro potent dual OX ₁ and OX ₂ receptor antagonist known at that time (pK _i =9.4 and 9.5 at the OX ₁ and OX ₂ receptor, respectively) ^[1] . SB-649868 antagonizes orexin-A-induced inositol 1 phosphate (IP1) accumulation with the following pK _B value (OX ₁ =9.67; OX ₂ =9.64). SB-649868 displaces the [³ H]ACT-078573 receptor binding with the following pK _i values: OX ₁ =9.27; OX ₂ =8.91. Increasing concentrations of SB-649868 (0.3 nM-30 nM) induces a rightward shift of the orexin-A CRCs with a depression of the agonist efficacy suggesting a clear non-surmountable behavior.

The calculated apparent pK_b values are 9.67 ± 0.03 and 9.64 ± 0.07 for OX_1 and OX_2 ^[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay ^[2]

Chinese Hamster Ovary (CHO) cells stably transfected with human OX_1 orexin receptor are cultured in Dulbecco's modified Eagle's medium F12 Ham, supplemented with 10% fetal bovine serum (FBS), 2 mg/mL glutamine, 600 μ g/ml geneticin at 37 °C in an atmosphere of 95% air and 5% CO_2 . CHO cells stably transfected with human OX_2 orexin receptor are cultured in alpha-MEM supplemented with 10% FBS, 100 units/mL penicillin G, 100 units/mL streptomycin and 400 μ g/mL geneticin, at 37 °C in an atmosphere of 95% air and 5% CO_2 . Accumulation of IP1 is measured using IP-One HTRF terbium cryptate-based assay. OX_1 -CHO cells are seeded into white 384-well plate at the cell density of 1×10^4 cells per well and cultured for 24 h in the presence of 5 mM sodium butyrate while OX_2 -CHO cells are seeded at the cell density of 4×10^4 cells per well and cultured for 24 h in culture medium. After washings Hank's Balanced Salt Solution (HBSS) at room temperature containing 20 mM HEPES pH 7.4, 50 mM, LiCl and 0.1% Bovine Serum Albumin (BSA) cells are pre-incubated for 45 min with antagonist and then treated with agonist for 60 min at 37 °C. Detection reagents, IP1-d2 tracer and anti-IP1-cryptate are diluted in lysis buffer and added to the cells. Following 60 min incubation at room temperature, time-resolved fluorescence at 615 nm and 665 nm are measured with Envision Multilabel flash lamp reader with 100 flashes and 400 μ s integration time^[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

- [1]. Di Fabio R, et al. Discovery process and pharmacological characterization of a novel dual orexin 1 and orexin 2 receptor antagonist useful for treatment of sleep disorders. *Bioorg Med Chem Lett*. 2011 Sep 15;21(18):5562-7.
- [2]. Faedo S, et al. Functional and binding kinetic studies make a distinction between OX_1 and OX_2 orexin receptor antagonists. *Eur J Pharmacol*. 2012 Oct 5;692(1-3):1-9.
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Caution: Product has not been fully validated for medical applications. For research use only.

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