SB-649868

Cat. No.: HY-10806

CAS No.: 380899-24-1

Molecular Formula: $C_{26}H_{24}FN_3O_3S$

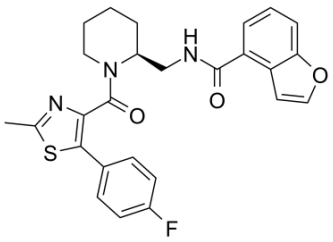
Molecular Weight: 477.55

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	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (209.40 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
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).

IC_{50} & 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 pKi 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.
In Vivo	Pharmacokinetic studies in the male CD rat, performed at 1 mg/kg, iv and 3 mg/kg, po, demonstrate an excellent pharmacokinetic profile for a hypnotic agent featuring moderate clearance in plasma (Cl_p=24 mL/min/kg), short half-life of (<0.6 h) and a low volume of distribution (V_{ss}=1.1 l/kg), coupled with excellent oral bioavailability (F=85%) and good exposure in plasma (C_{max}=333 ng/mL). A brain to blood ratio (B/B) of 0.1:1 is observed 1 h after iv administration, a value in line with the expected partition between the two compartments based on the lower tissue binding observed in vitro in brain tissues (fraction unbound/brain=5.28%) with respect to plasma proteins (fraction unbound/plasma=1.34%). SB-649868, administered orally 3 h before OX-A injection at doses of 1, 3 and 10 mg/kg, causes a dose-dependent reduction of OX-A induced grooming as measured by total time spent grooming and number of grooming bouts ($p < 0.01$ at 3 and 10 mg/kg po) [1]. From dissociation kinetic studies using [^{3}H]ACT-078573, the calculated long half-life, ($t_{1/2}$) supports the non-surmountability profile of SB-649868 ($t_{1/2}$=35.91 min) at OX_1 orexin receptor. The long or moderately long $t_{1/2}$values for SB-649868 at OX_2 orexin receptor ($t_{1/2}$=8.09 min)[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 μg/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 μg/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 μs 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 2receptor 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 OX1 and OX2 orexin receptorantagonists. Eur J Pharmacol. 2012 Oct 5;692(1-3):1-9.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA