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RS-127445 hydrochloride

Cat. No.: HY-15419

CAS No.: 199864-86-3

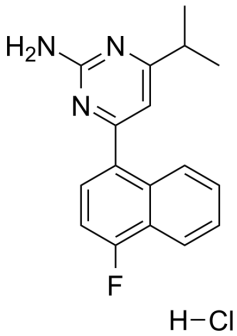
Molecular Formula: $C_{17}H_{17}ClFN_3$

Molecular Weight: 317.79

Target: 5-HT Receptor

Pathway: GPCR/G Protein; Neuronal Signaling

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (393.34 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.1467 mL	15.7337 mL	31.4673 mL
5 mM	0.6293 mL	3.1467 mL	6.2935 mL
10 mM	0.3147 mL	1.5734 mL	3.1467 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 (7.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

RS-127445 hydrochloride is a selective, high affinity, orally bioavailable 5-HT_{2B} receptor antagonist with a pK_i of 9.5. RS-127445 hydrochloride shows 1000 fold selectivity for this receptor as compared to numerous other receptor and ion channel binding sites[1].

IC_{50} & Target

sPLA2 5.5 (pKi)	5-HT_3 Receptor <6 (pKi)	5-HT_5 Receptor <6 (pKi)	5-HT_6 Receptor <6 (pKi)
5-HT_{2A} Receptor	5-HT_{2C} Receptor	5-HT_{2B} Receptor	

	6.3 (pKi)	6.4 (pKi)	9.5 (pKi)

In Vitro

RS-127445 is found to has nanomolar affinity for the 5-HT_{2B} receptor (pK_i=9.5±0.1) and 1,000 fold selectivity for this receptor as compared to numerous other receptor and ion channel binding sites. RS-127445 potently displaces [^{3}H]-5-HT from human recombinant 5-HT_{2B} receptors expressed in CHO-K1 cells. The affinity (pK_i value) of RS-127445 for the 5-HT_{2B} receptor is 9.5±0.1 (n=9). RS-127445 is selective for the 5-HT_{2B} receptor, having approximately 1000 fold lower affinity for the human recombinant 5-HT_{2A}, 5-HT_{2C}, 5-HT_5, 5-HT_6 and 5-HT_7 receptors, a 5-HT_{1A} receptor in rat brain membranes, a 5-$HT_{1B/D}$ receptor in bovine caudate, and a monoamine uptake site in rabbit platelets. RS-127445 potently blocks the 5-HT (10 nM) evoked increases in intracellular calcium concentrations in the HEK-293 cells expressing the 5-HT_{2B} receptor (pIC_{50} of 10.4±0.1). In cells expressing human recombinant 5-HT_{2B} receptors, RS-127445 potently antagonizes 5-HT-evoked formation of inositol phosphates (pK_B=9.5±0.1) and 5-HT-evoked increases in intracellular calcium (pIC_{10}=10.4±0.1). RS-127445 also blocks 5-HT-evoked contraction of rat isolated stomach fundus (pA_{2B}=9.5±1.1) and (±)α-methyl-5-HT-mediated relaxation of the rat jugular vein (pA_2=9.9±0.3)[1].

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

In Vivo

In rats, the fraction of RS-127445 that is bioavailable via the oral or intraperitoneal routes is 14 and 60% respectively. Intraperitoneal administration of RS-127445 (5 mg/kg) produced plasma concentrations predicted to fully saturate accessible 5-HT_{2B} receptors for at least 4 h.RS-127445 (5 mg/kg) is administered to rats by oral, intraperitoneal and intravenous routes. Peak plasma concentrations are rapidly achieved with the highest concentrations being found at the first time-point measured following intravenous and intraperitonael administration (0.08 h) and by 0.25 h following dosing by the oral route of administration. RS-127445 is cleared from plasma with an estimated terminal elimination half-life of approximately 1.7 h. The bioavailability of RS-127445, when administered by the oral and intraperitoneal routes is approximately 14 and 62% of that obtained by intravenous administration. Approximately 60% of an intraperitoneal dose and 14% of the oral dose of RS-127445 (5 mg/kg) is bioavailable[1]. RS-127445 (1-30 mg/kg), dose-dependently reduces faecal output, reaching significance at 10 and 30 mg/kg (n=6-11). In blood and brain, >98% of RS-127445 is protein-bound[2].

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PROTOCOL

Cell Assay [1]

HEK-293 cells expressing the human 5-HT_{2B} receptor are incubated with [^{3}H]-myoinositol (1.67 μCi/mL) in 162 cm^2 flasks overnight at 37°C in an inositol free Ham's F12 medium containing 10% dialyzed foetal bovine serum. The cells are harvested, washed five times with phosphate buffered saline and resuspended in inositol free Ham's F12 media at density of approximately 3×10^6 cells/mL. RS-127445 (10 μM) is initially dissolved in 10% (v/v) DMSO with 90% inositol free Ham's F12 medium. Subsequent dilutions are made with inositol free Ham's F12 medium. 5-HT is dissolved in inositol free Ham's F12 medium containing 100 mM LiCl and 1 mM ascorbate. RS-127445, vehicle or other antagonists are pre-incubated with 240 μL of cell suspension at 37°C for 20 min. The reactions are initiated by addition of 5-HT. Sixty minutes later, the reactions are terminated by adding 50 μL of ice-cold 20% perchloric acid, chilled in an ice-water bath for 10 min and then neutralized with 160 μL of 1 N KOH. Each sample is diluted with 2 ml of 50 mM Tris-HCl, pH 7.4 at room temperature. The aqueous portion (2.2 mL) is transferred onto Dowex AG1X8 columns (1 ml, 1 : 1, w/v) which had been washed with 5 ml of distilled water. The columns are then washed with 18 ml of distilled water and the inositol phosphates are eluted with 3 ml of 1 N HCl. The eluted radioactivity is determined by liquid scintillation spectroscopy using a Packard 1900CA analyzer[1].

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Animal Administration [1][2]

Rats[1]

Male Sprague-Dawley rats (200 g) are used. To compare the plasma kinetics of RS-127445 following different routes of administration, 90 rats are distributed into three treatment groups of 30 rats each. A single dose of RS-127445 (5 mg/kg) dissolved (2.5 mg/mL) in ethanol:propylene glycol : water (10 : 50 : 40, v:v:v), is administered to each rat. At 0.08, 0.25, 0.5, 1, 2, 4, 8 and 24 h after dosing, the rats are anaesthetized and blood samples are collected by cardiac puncture.

Mice[2]

Adult male C57BL/6J mice (25-30 g) are used. The effects of RS-127445 (1 nM-10 μM, single concentration per tissue, 15 min contact time) or vehicle (5 or 50 μL DMSO) are expressed as the percentage change in amplitude compared with the mean amplitude of four pre-drug, post-EFS contractile responses. The results are analysed using a two-sample equal variance t-

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

CUSTOMER VALIDATION

- Mol Neurobiol. 2023 Sep 25.
- Authorea. September 19, 2022.

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REFERENCES

[1]. Bonhaus DW, et al. RS-127445: a selective, high affinity, orally bioavailable 5-HT2B receptor antagonist. Br J Pharmacol. 1999 Jul;127(5):1075-82.

[2]. Bassil AK, et al. Inhibition of colonic motility and defecation by RS-127445 suggests an involvement of the 5-HT2B receptor in rodent large bowel physiology. Br J Pharmacol. 2009 Sep;158(1):252-8

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