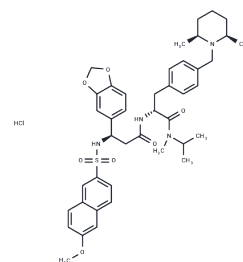


SSR240612

Chemical Properties

CAS No. : 464930-42-5
 Formula: C₄₂H₅₃ClN₄O₇S
 Molecular Weight: 793.41
 Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
 Actual storage temperature shall be subject to the COA.



Biological Description

Description	SSR240612 is a potent, orally active, specific non-peptide bradykinin B1 receptor antagonist (K _i = 0.48-0.73 nM for B1 receptors and 358-481 nM for B2 receptors, respectively).
Targets(IC ₅₀)	Bradykinin Receptor
In vitro	SSR240612 inhibited the binding of [(3)H]Lys(0)-des-Arg(9)-BK to the B(1) receptor in human fibroblast MRC5 and to recombinant human B(1) receptor expressed in human embryonic kidney cells with inhibition constants (K _i) of 0.48 and 0.73 nM, respectively. SSR240612 inhibited Lys(0)-desAr(9)-BK (10 nM)-induced inositol monophosphate formation in human fibroblast MRC5, with an IC(50) of 1.9 nM [1]. M. tuberculosis was not susceptible to the concentrations of antagonists tested, which suggests that the minimum inhibitory concentration values are larger than 250 μM for SSR240612 [2].
In vivo	SSR240612 inhibited des-Arg(9)-BK-induced paw edema in mice (3 and 10 mg/kg p.o. and 0.3 and 1 mg/kg i.p.). Moreover, SSR240612 reduced capsaicin-induced ear edema in mice (0.3, 3 and 30 mg/kg p.o.) and tissue destruction and neutrophil accumulation in the rat intestine following splanchnic artery occlusion/reperfusion (0.3 mg/kg i.v.). The compound also inhibited thermal hyperalgesia induced by UV irradiation (1 and 3 mg/kg p.o.) and the late phase of nociceptive response to formalin in rats (10 and 30 mg/kg p.o.). SSR240612 (20 and 30 mg/kg p.o.) prevented neuropathic thermal pain induced by sciatic nerve constriction in the rat [1]. SSR240612 blocked tactile and cold allodynia at 3 h (ID(50)=5.5 and 7.1 mg/kg, respectively) in glucose-fed rats but had no effect in control rats. The antagonist (10 mg/kg) had no effect on plasma glucose and insulin, insulin resistance (HOMA index) and aortic superoxide anion production in glucose-fed rats [3].
Kinase Assay	MRC5 human fibroblasts and transfected HEK-293 cells expressing human B1 receptors were routinely grown in Dulbecco's modified Eagle's medium (DMEM) with Glutamax-I supplemented with 10% fetal calf serum and antibiotics. MRC5 were incubated for 4 h in DMEM containing 0.5 μg/ml interleukin-1β (IL-1β) to induce B1 receptor synthesis. Cells were scraped and homogenized for 1 min using a Polytron (setting 8) in 25 mM TES-HCl containing 1 mM 1-10 phenantrolin. Homogenates were centrifuged at 40,000g for 15 min at 4°C, and pellets were resuspended in the same buffer using the Polytron (setting 8) for 1 min. Membranes were pelleted at 40,000g for 10 min at 4°C, resuspended in the same buffer, and conserved at 80°C. [3H]Lys0-des-Arg9-BK binding to cell membranes was performed in binding buffer of the following composition: 137 mM NaCl, 5.4 mM

Kinase Assay	KCl, 1.05 mM MgCl ₂ , 1.8 mM CaCl ₂ , 1.2 mM NaH ₂ PO ₄ , 15.5 mM NaHCO ₃ , 10 mM HEPES, 1 g/l bovine serum albumin (BSA), 140 mg/l bacitracin, and 1 μM captopril, pH 7.4. Membranes were incubated for 30 min at 25°C in 500 μl of binding buffer containing 1 nM [³ H]Lys0-des-Arg9-BK for competition curves or 0.1 to 10 nM for saturation isotherms. The reaction was terminated by filtration using a Brandel Harvester onto GF/B Whatman filters previously soaked for 2 h in 0.1% polyethyleneimine. Filters were washed three times with 5 ml of binding buffer, and radioactivity was determined by liquid scintillation spectrometry. Nonspecific binding was determined by the addition of 1 μM of unlabeled Lys0 -des-Arg9 BK [1].
Cell Research	[³ H]Inositol phosphate ₁ accumulation was measured in MRC5 fibroblasts labeled with [³ H]myoinositol according to the method described by Oury-Donat et al. Cells cultured in 6-well plates were labeled for 48 h with 5 μCi/ml [³ H]myoinositol added to the culture medium (DMEM). Cells were then incubated for 4 h in DMEM containing 0.5 μg/ml IL-1β to induce B1 receptor synthesis. Agonist stimulation of inositol phosphate ₁ accumulation was performed in DMEM containing 50 mM LiCl and test compounds. Antagonists were added 15 min before 10 nM Lys0-desArg10BK. After 30 min of incubation at 37°C, the medium was discarded, and the reaction was stopped by rapid addition of 1 ml of cold methanol and 1 N HCl (v/v). The cells were scraped, and the suspension was transferred to a glass tube with 1 ml of chloroform and 20 μl of 12 N HCl. The aqueous phase was neutralized by 350 μl of 1 M NaHCO ₃ and applied to 1 ml of Dowex AG1 × eight columns. [³ H]inositol phosphate ₁ was eluted with 0.2 M ammonium formate and 0.1 M formic acid. Radioactivity was measured by liquid scintillation spectrometry [1].
Animal Research	Groups of eight male albino mice under isoflurane anesthesia received a 20-μl intraplantar injection into the right hind paw of 5 μg of IL-1β in phosphate-buffered saline/0.1% BSA. Forty minutes later (T = 0), mice received, under anesthesia, a 20-μl intraplantar injection in the same paw of des-Arg9-BK (10 μg/paw) in water. SSR240612 or vehicle [5% (v/v) ethanol and 5% (v/v) Tween 80 in water] was administered by oral route at the doses of 1, 3, and 10 mg/kg 1 h before des-Arg9-BK injection and by intraperitoneal route at the doses of 0.1, 0.3, and 1 mg/kg 40 min before des-Arg9-BK injection. Paw volume was measured with a plethysmometer at T = -2 h (initial measurement) and at several times after edema induction (T = 20, 40, 60, and 120 min). Paw edema volume was expressed in milliliters as the difference between the paw volume at each time after edema induction and the initial paw volume. Results for each group are expressed as mean ± S.E.M. of individual paw edema volumes [1].

Solubility Information

Solubility	H ₂ O: Insoluble, DMSO: 100 mg/mL (126.04 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 4 mg/mL (5.04 mM),Sonication is recommended. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.2604 mL	6.3019 mL	12.6038 mL
5 mM	0.2521 mL	1.2604 mL	2.5208 mL
10 mM	0.126 mL	0.6302 mL	1.2604 mL
50 mM	0.0252 mL	0.126 mL	0.2521 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Gougat J, et al. SSR240612 [(2R)-2-(((3R)-3-(1,3-benzodioxol-5-yl)-3-[[[(6-methoxy-2-naphthyl)sulfonyl]amino]propanoyl)amino]-3-(4-[[[2R,6S)-2,6-dimethylpiperidinyl]methyl]phenyl)-N-isopropyl-N-methylpropanamide hydrochloride], a new nonpeptide antagonist of the bradykinin B1 receptor: biochemical and pharmacological characterization. *J Pharmacol Exp Ther.* 2004 May;309(2):661-9.

Rodrigues-Junior VS, et al. Effect of the bradykinin 1 receptor antagonist SSR240612 after oral administration in *Mycobacterium tuberculosis*-infected mice. *Tuberculosis (Edinb).* 2018 Mar;109:1-7.

Dias JP, et al. The kinin B1 receptor antagonist SSR240612 reverses tactile and cold allodynia in an experimental rat model of insulin resistance. *Br J Pharmacol.* 2007 Sep;152(2):280-7.

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