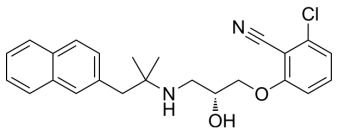
NPS-2143

Cat. No.:	HY-10007
CAS No.:	284035-33-2
Molecular Formula:	$C_{24}H_{25}ClN_2O_2$
Molecular Weight:	408.92
Target:	CaSR
Pathway:	GPCR/G Protein
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 : 17.86 mg/mL (43.68 mM; ultrasonic and adjust pH to 2 with HCl)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4455 mL	12.2273 mL	24.4547 mL
	5 mM	0.4891 mL	2.4455 mL	4.8909 mL
	10 mM	0.2445 mL	1.2227 mL	2.4455 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 (6.11 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

NPS-2143 (SB-262470A), an orally active calcilytic agent, is a selective and potent calcium ion-sensing receptor (CaSR) antagonist. NPS-2143 (SB-262470A) blocks increases in cytoplasmic Ca^{2+} concentrations (IC_{50}=43 nM) elicited by activating the Ca^{2+} receptor in HEK 293 cells expressing the human Ca^{2+} receptor[1][2].

IC_{50} & Target

IC50: 43 nM (Ca^{2+} receptor)

In Vitro

NPS-2143 (SB-262470A) stimulates parathyroid hormone (PTH) secretion from bovine parathyroid cells with EC_{50} of 41 nM. Moreover, NPS 214 also blocks the inhibitory effects of calcimimetic NPS R-467 on PTH secretion from bovine parathyroid cells and the inhibitory effects of extracellular Ca^{2+} on isoproterenol-stimulated increases in cyclic AMP formation[1].
?In HEK 293 cells transiently expressing hCaSRs, NPS-2143 significantly suppresses the kokumi taste by effectively inhibiting

	the activity of both GSH and γ-Glu-Val-Gly[3].?A recent study shows that NPS-2143 treatment suppresses low molecular weight fractions of azuki hydrolysate-induced cholecystokinin (CCK) secretion in CaSR-transfected HEK 293 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	NPS-2143 (SB-262470A) results in a rapid 4- to 5-fold increase in plasma PTH levels in rats[1]. ?In normotensive rats, NPS-2143 administration (1 mg/kg, i.v.) markedly increases mean arterial blood pressure (MAP) in the presence of parathyroid glands[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	This clonal cell line, referred to as HEK 293 4.0-7 cells, are used in a high-throughput screening format to detect agonists and allosteric activators of the Ca^{2+} receptor. Changes in the concentration of cytoplasmic $[Ca^{2+}]i$ provide a quantitative and functional assessment of Ca^{2+} receptor activity in these cells and the results using this assay parallel those obtained using a homologous expression system of bovine parathyroid cells. On-line continuous measurements of fluorescence in fluo-3- or fura-2-loaded HEK 293 4.0-7 cells are obtained using a custom-built spectrofluorimeter or a fluorescence imaging plate reader instrument. NPS-2143 is incubated with cells for 1 minute before increasing the concentration of extracellular Ca^{2+} from 1.0 mM to 1.75 mM. NPS-2143 is tested individually at a concentration of 100 μg/mL (20 μM-80 μM) and those causing more than a 40% inhibition of the control response are considered to be biologically active. To determine the potencies (IC_{50}) of NPS-2143 with biological activity, concentration-response curves are obtained and then, as an initial assessment of selectivity, the effects of NPS-2143 on $[Ca^{2+}]i$ evoked by other G protein-coupled receptors are examined at a concentration several times their IC_{50}. Wild-type HEK 293 cells (and HEK 293 4.0-7 cells) express receptors for thrombin, bradykinin, and ATP, which couple to the mobilization of intracellular Ca^{2+}. These responses can be studied to quickly assess any nonselective action of compounds on G protein-coupled receptors. Additional assays for selectivity include HEK 293 cells engineered to express receptors most homologous in sequence and topology to the Ca^{2+} receptor. These include native or chimeric receptors for various metabotropic glutamate and γ-aminobutyric acid type B receptors (GABABRs). Chimeric receptors are created using partial sequences of metabotropic glutamate receptors and Ca^{2+} receptors, engineered to couple to activation of phospholipase C and release of intracellular Ca^{2+} in HEK 293 cells. NPS-2143 lacking pan-activity are then subjected to structural modifications and their potencies and selectivities monitored using these HEK 293 4.0-7 cell assays in an iterative process. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats: On the day of study, the rats are infused intravenously (0.1 mL/kg·min) for 120 min with NPS-2143 (0.1 μmol/kg·min) or vehicle, a 20% aqueous solution of 2-hydroxypropyl-β-cyclodextrin. Blood samples (0.5 mL) are collected before and at various times after the start of the infusion for measurements of plasma levels of PTH and Ca^{2+}. To prevent excessive blood volume loss during the course of the experiment, for each blood sample the erythrocyte pellet is resuspended in an equal volume of normal rat plasma and reinjected. Plasma levels of Ca^{2+} are measured immediately after collection using a model 634 ionized calcium analyzer. PTH levels are measured using the Immutopics rat PTH(1-34) immunoradiometric assay kit. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Phytomedicine. 2021, 153507.
- Acta Physiol. 2023 Jan 6;e13926.
- Food Funct. 2022 May 19.
- Int J Mol Sci. 2023 Mar 3.
- Front Pharmacol. 2022 Feb 23;13:816133.

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REFERENCES

[1]. Nemeth EF, et al. Calcilytic compounds: potent and selective Ca2+ receptor antagonists that stimulate secretion of parathyroid hormone. J Pharmacol Exp Ther. 2001 Oct;299(1):323-31.

[2]. Rybczynska A, et al. Hypertensive effect of calcilytic NPS 2143 administration in rats. J Endocrinol. 2006 Oct;191(1):189-95.

[3]. Ohsu T, et al. Involvement of the calcium-sensing receptor in human taste perception. J Biol Chem. 2010 Jan 8;285(2):1016-22

[4]. Nakajima S, et al. Calcium-sensing receptor mediates dietary peptide-induced CCK secretion in enteroendocrine STC-1 cells. Mol Nutr Food Res. 2012 May;56(5):753-60

[5]. Sun J, et al. Calcium-sensing receptor: a sensor and mediator of ischemic preconditioning in the heart. Am J Physiol Heart Circ Physiol. 2010 Nov;299(5):H1309-17.

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