# 产品名称：NPS-2143
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## 生物活性：

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| **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 Ca2+ concentrations (IC50=43 nM) elicited by activating the Ca2+ receptor in HEK 293 cells expressing the human Ca2+ 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 EC50 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 Ca2+ on isoproterenol-stimulated increases in cyclic AMP formation[1].<br>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]. |
| **In Vivo** | NPS-2143 (SB-262470A) results in a rapid 4- to 5-fold increase in plasma PTH levels and also a transient increase in plasma Ca2+ levels in rats[1].<br>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]. |
| **Solvent&Solubility** | ***In Vitro:***<br>**DMSO : ≥ 100 mg/mL (244.55 mM)**<br>* "≥" means soluble, but saturation unknown. |

**Preparing Stock Solutions**

| Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
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| 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 |

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

***In Vivo:***

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.11 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；

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| | 向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。<br><br>2.请依序添加每种溶剂： 10% DMSO →90% corn oil<br>Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (6.11 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。<br>以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。 |
| **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.<br>[2]. Rybczynska A, et al. Hypertensive effect of calcilytic NPS 2143 administration in rats. J Endocrinol. 2006 Oct;191(1):189-95.<br>[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<br>[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<br>[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. |

**实验参考：**

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| **Animal Administration** | 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. [1] |
| **Kinase Assay** | 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 |

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