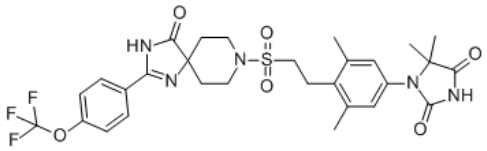
Product Data Sheet

Product Name: PCO371
Cat. No.: GC32415

Chemical Properties

Cas. No.	1613373-33-3		
SMILES	FC(F)(F)OC1=CC=C(C2=NC3(CCN(S(CCC4=C(C)C=C(N5C(NC(C5(C)C)=O)=O)C=C4C)(=O)=O)CC3)C(N2)=O)C=C1		
Formula	$C_{29}H_{32}F_3N_5O_6S$	M.Wt	635.65
Solubility	DMSO: 125 mg/mL (196.65 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure			



Protocol

Cell experiment [1]:

Cell lines	COS-7 cells (monkey kidney fibroblast-like cell line), UMR-106 cells (rat osteosarcoma cell line)

Product Data Sheet

Preparation Method	COS-7 cells were transfected to express human PTHR1 (hPTHR1). Cells were treated with PCO371 (0.1nM–0.1mM) in assay medium containing BSA and the phosphodiesterase inhibitor IBMX. UMR-106 cells expressing endogenous rat PTHR1 were also treated with PCO371 in similar assay medium for cAMP measurement or in DMEM with 0.2% BSA for gene expression analysis.
Reaction Conditions	0.1nM–0.1mM; 20 minutes or 6h
Applications	PCO371 dose-dependently stimulated cAMP production in hPTHR1-expressing COS-7 cells (EC_{50}=2.4μM) and also activated the phospholipase C signaling pathway (EC_{50}=17μM). In UMR-106 cells, PCO371 induced cAMP production and altered the expression of bone-related mRNAs.

Animal experiment [2]:

Animal models	Thyroparathyroidectomized (TPTX) rats
Preparation Method	TPTX rats with serum calcium levels <8.0mg/dL received a single oral administration of PCO371 (30mg/kg). Blood was collected from the jugular vein immediately before and at 0.5, 1, 2, 4, 6, 10, and 24 hours after administration to measure serum calcium and phosphate levels.
Dosage form	30mg/kg; p.o.; Single administration.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

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Applications	A single oral administration of PCO371 dose-dependently increased serum calcium concentration and decreased serum phosphate concentration. The calcemic action of PCO371 was more prolonged than that of its lead compound or a single subcutaneous administration of hPTH(1-34).

References:
[1] Tamura T, Noda H, Joyashiki E, et al. Identification of an orally active small-molecule PTHR1 agonist for the treatment of hypoparathyroidism. Nat Commun. 2016 Nov 18;7:13384.
[2] Nishimura Y, Esaki T, Isshiki Y, et al. Lead Optimization and Avoidance of Reactive Metabolite Leading to PCO371, a Potent, Selective, and Orally Available Human Parathyroid Hormone Receptor 1 (hPTHR1) Agonist. J Med Chem. 2020 May 28;63(10):5089-5099.

Background

PCO371 is an orally active small-molecule full agonist of the PTHR1, which binds to the intracellular interface of PTH1R and the Gs protein[1-2]. PCO371 can be used in research on PTH-related diseases such as hypoparathyroidism[3].

In vitro, PCO371 (0.1nM–0.1mM) stimulated COS-7 cells expressing human PTH1R and UMR-106 rat osteosarcoma cells expressing endogenous rat PTH1R for 20 minutes or 6 hours. PCO371 dose-dependently stimulated intracellular cAMP production and activated the phospholipase C signaling pathway. PCO371 dose-dependently increased the mRNA expression of Fos, osteocalcin, and RANKL, and decreased the mRNA expression of osteoprotegerin and sclerostin[4]. PCO371 (10nM–100μM) treated LLC-PK1 cells stably expressing the human parathyroid hormone 1 receptor (hPTHR1) for 5-120 minutes. PCO371 activated the receptor in a concentration-dependent manner and increased intracellular cAMP production[5].

In vivo, PCO371 (30mg/kg orally; once daily) was administered for 12 weeks to 32-week-old ovariectomized rats. PCO371 significantly increased bone turnover markers. PCO371 had limited effects on improving bone mineral density and bone strength[4]. A single oral administration of PCO371 (30mg/kg) was given to thyroparathyroidectomized (TPTX) rats. PCO371 significantly increased serum calcium concentration and decreased serum phosphate concentration in mice[5].

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References:

[1] Zhao LH, He Q, Yuan Q, et al. Conserved class B GPCR activation by a biased intracellular agonist. Nature. 2023 Sep;621(7979):635-641.
[2] Kobayashi K, Kawakami K, Kusakizako T, et al. Class B1 GPCR activation by an intracellular agonist. Nature. 2023 Jun;618(7967):1085-1093.
[3] Nishimura Y, Esaki T, Isshiki Y, et al. Synthesis and Biological Evaluations of Novel Human Parathyroid Hormone 1 Receptor (hPTHR1) Agonists Bearing Bicyclic Aromatic Moiety. ChemMedChem. 2024 Mar 1;19(5):e202300589.
[4] Tamura T, Noda H, Joyashiki E, et al. Identification of an orally active small-molecule PTHR1 agonist for the treatment of hypoparathyroidism. Nat Commun. 2016 Nov 18;7:13384.
[5] Nishimura Y, Esaki T, Isshiki Y, et al. Lead Optimization and Avoidance of Reactive Metabolite Leading to PCO371, a Potent, Selective, and Orally Available Human Parathyroid Hormone Receptor 1 (hPTHR1) Agonist. J Med Chem. 2020 May 28;63(10):5089-5099.

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