Product Data Sheet

Product Name: PIM447 (LGH447)
Cat. No.: GC25743

Chemical Properties

Cas. No.	1210608-43-7(freebase)		
Formula	C24H23F3N4O.HCl	M.Wt	476.92
Solubility	DMSO: 88 mg/mL (184.52 mM);Water: Insoluble;Ethanol: 88 mg/mL (184.52 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	PIM447 (LGH447)		

Background

PIM447 (LGH447) is a novel pan-PIM kinase inhibitor with Ki values of 6 pM, 18 pM, 9 pM for PIM1, PIM2, PIM3 respectively. It also inhibits GSK3β, PKN1, and PKCτ, but at a significantly lower potency with IC50 between 1 and 5 μM (>105-fold differential relative to the Ki on PIMs). PIM447 induces apoptosis.

The kinase selectivity of PIM447 is first determined in biochemical assays for a panel of 68 diverse protein kinases that included PIM2 as well as 9 lipid kinases. In this panel, only PIM2 is significantly inhibited by PIM447 with an IC50 of <0.003 μM, the lowest sensitivity range for the assay. PIM447 also inhibits GSK3β, PKN1, and PKCτ, but at a significantly lower potency with IC50 between 1 and 5 μM (>105-fold differential relative to the Ki on PIMs). The biochemical IC50 for all other kinases tested in this panel is >9 μM. In follow-up cellular assays of GSK3β inhibition, PIM447 is tested up to 20 μM and is not active[1]. PIM447 is cytotoxic for myeloma cells due to cell-cycle disruption and induction of apoptosis mediated by a decrease in phospho-Bad (Ser112) and c-Myc levels and the inhibition of mTORC1 pathway. PIM447 also inhibits in vitro osteoclast formation and resorption, downregulates key molecules involved in these processes, and partially disrupts the F-actin ring, while increasing osteoblast activity and

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

mineralization[2].

Low to moderate in vivo CL is observed for PIM447 across species, as CL values of 20, 28, and 8 mL/min/kg are observed in mouse, rat, and dog, respectively. The volume of distribution is consistently large across species, with Vss of 5.3, 6.4, and 3.6 L/kg observed in mouse, rat, and dog, respectively. Additionally, PIM447 exhibits high oral bioavailability across species, as 84%, 70%, and 71% is observed in mouse, rat, and dog, respectively. The stability of PIM447 in human plasma is high, >90% after a 3 h incubation, and the human plasma protein binding of PIM447 is 95%. With the combination of potent in vitro activity and low to moderate CL, PIM447 demonstrates in vivo target modulation (pS6RP), single agent antitumor activity in a KG-1 AML mouse xenograft model, and druglike properties suitable for development[1]. PIM447 significantly reduces the tumor burden and prevents tumor-associated bone loss in a disseminated murine model of human myeloma[2].

[1] Burger MT, et al. J Med Chem. 2015, 58(21):8373-86. [2] PaÍno T, et al. Clin Cancer Res. 2017, 23(1):225-238.

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Address: 10292 Central Ave. #205, Montclair, CA, USA