Product Data Sheet

Product Name: BLU-782
Cat. No.: GC19508

Chemical Properties

Cas. No.	2141955-96-4		
Chemical Name	1-Piperazinecarboxylic acid, 4-[6-[5-[4-ethoxy-1-(1-methylethyl)-4-piperidinyl]-2-pyridinyl]pyrrolo[1,2-b]pyridazin-4-yl]-, (3R)-tetrahydro-3-furanyl ester		
SMILES	O=C(N1CCN(C2=CC=NN3C2=CC(C4=NC=C(C5(OCC)CCN(C(C)C)CC5)C=C4)=C3)CC1)O[C@H]6COCC6		
Formula	$C_{31}H_{42}N_6O_4$	M.Wt	562.715
Solubility	Soluble in DMSO	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	BLU-782		

Protocol

Animal experiment [1]:

Animal models	$ALK2^{R206H}$ mice
Preparation Method	WT or ALK2R206H mice were untreated or dosed prophylactically with BLU-782 before receiving a pinch injury to one leg.
Dosage form	50 mpk QD BLU-782 for 19days
Applications	BLU-782 dampens edema early and prevents HO in ALK2R206H mice.

References:

[1]. A clinical update on BLU-782, an investigational ALK2 inhibitor in development for fibrodysplasia ossificans progressiva (FOP).

Background

BLU-782 is an oral precision therapy specifically designed to selectively target mutant ALK2[1].

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FOP is a rare genetic disorder characterized by the abnormal transformation of skeletal muscle, ligaments and tendons into bone, either spontaneously or as the result of physical trauma. FOP is caused by a mutation in the gene for ALK2, which is known as ACVR1, that causes hypersensitivity to certain bone morphogenetic proteins (BMP) and a neomorphic response to activins[4,5].

BLU-782 demonstrated exquisite selectivity for R206H mutant ALK2 in cellular assays, while sparing closely related anti-targets including ALK1, ALK3, and ALK6. Additionally, BLU-782 potently inhibited mutant ALK2 in vitro, regardless of the activating ligand, including Activin A, Activin B and BMP6. In vivo studies in a conditional knock-in ALK2R206H transgenic mouse model showed BLU-782 prevented the formation of injury-induced HO and edema, as measured by micro computed tomography and magnetic resonance imaging. Immunohistochemistry analyses also showed restoration of a healthy response to tissue injury in ALK2R206H mice, including skeletal myofiber regeneration. In addition, BLU-782 prevented the formation of surgery-induced HO following fibular osteotomy surgery in ALK2R206H mice[1]. BLU-782 dampens edema early and prevents HO in ALK2R206H mice[7].

The Phase I clinical trial BLU-782 in healthy volunteers to establish its safety of the investigational drug was recently completed (NCT03858075), and the result showed that BLU-782 is well tolerated with approximately 24 h of half-life and displays excellent properties of pharmacokinetics and pharmacodynamics[2,3].

Blu-782 selectively targets only mutant ALK2 with minimal interference to wild-type ALK2, which may be a good strategy for future FOP therapy[6].

References:
[1]: Blueprint medicines presents foundational preclinical data supporting the development of BLU-782, a highly selective ALK2 inhibitor, for the treatment of patients with fibrodysplasia ossificans progressive (2018)
[2]: Safety, tolerability, pharmacokinetics, and food effect of BLU-782 in healthy adults (2019). https://clinicaltrials.gov/ct2/show/NCT03858075. Accessed 14 Dec 2021
[3]: Alison DFA, Riadh L, Michael P, Cori AS, Sara G, Faith S, Sean K, Gordon W, Mark H, Robert S, Rachel S, Morgan L, Pauplis R, Vivek K, Andy B, Timothy L (2019) A clinical update on BLU-782, an investigational ALK2 inhibitor in development for fibrodysplasia ossificans progressiva (FOP). https://www.blueprintmedicines.com/wp-content/uploads/2019/09/Blueprint-Medicines-ASBMR-2019-BLU-782-Poster1.pdf.
[4]: Towler OW, Shore EM. BMP signaling and skeletal development in fibrodysplasia ossificans progressiva (FOP). Dev Dyn. 2022 Jan;251(1):164-177. doi: 10.1002/dvdy.387. Epub 2021 Jun 26. PMID: 34133058; PMCID: PMC9068236.
[5]: Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L, Delai P, Fastnacht-Urban E, Forman SJ, Gillessen-Kaesbach G, Hoover-Fong J, K?ster B, Pauli RM, Reardon W, Zaidi SA, Zasloff M, Morhart R, Mundlos S, Groppe J, Shore EM. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat. 2009 Mar;30(3):379-90. doi: 10.1002/humu.20868. PMID: 19085907; PMCID: PMC2921861.
[6]: Meng, X., Wang, H. & Hao, J. Recent progress in drug development for fibrodysplasia ossificans progressiva. Mol Cell Biochem 477, 2327-2334 (2022). https://doi.org/10.1007/s11010-022-04446-9
[7]: A clinical update on BLU-782, an investigational ALK2 inhibitor in development for fibrodysplasia ossificans progressiva (FOP)

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