Product Data Sheet

Product Name: Dorsomorphin (Compound C) 2HCl
Cat. No.: GC12560

Chemical Properties

Cas. No.	1219168-18-9		
Chemical Name	6-[4-(2-piperidin-1-ylethoxy)phenyl]-3-pyridin-4-ylpyrazolo[1,5-a]pyrimidine;dihydrochloride		
SMILES	C1CCN(CC1)CCOC2=CC=C(C=C2)C3=CN4C(=C(C=N4)C5=CC=NC=C5)N=C3.Cl.Cl		
Formula	$C_{24}H_{25}N_5O.2HCl$	M.Wt	472.41
Solubility	≥100mg/mL in Water, ≥ 5.9mg/mL in DMSO, ≥ 11.34 mg/mL in 0.9% NS	Storage	Store at -20°C,protect from light
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			

Protocol

Kinase experiment [1]:

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AMPK partial purification and in vitro kinase assay	Liver AMPK is partially purified from male SD rats to the blue-Sepharose step. The 100-µl reaction mixture contains 100 µM AMP, 100 µM ATP (0.5 µCi 33P-ATP per reaction), and 50 µM SAMS in a buffer (40 mM HEPES, pH 7.0, 80 mM NaCl, 0.8 mM EDTA, 5 mM MgCl2, 0.025% BSA, and 0.8 mM DTT). The reaction is initiated with addition of the enzyme. After 30-minute incubation at 30°C, the reaction is stopped by addition of 80 µl 1% H3PO4. Aliquots (100 µl) are transferred to 96-well MultiScreen plates. The plate is washed three times with 1% H3PO4 followed by detection in a Top-count. The in vitro AMPK inhibition data obtained with compound C — (6-[4-(2-Piperidin-1-yl-ethoxy)-phenyl)]-3-pyridin-4-yl-pyyrazolo[1,5-a] pyrimidine — are fit to the following equation for competitive inhibition by nonlinear regression using a least-squares Marquardt algorithm in a computer program written by N. Thornberry of Merck Research Laboratories: Vi/Vo = (Km + S)/[S + Km × (1 + I/Ki)], where Vi is the inhibited velocity, Vo is the initial velocity, S is the substrate (ATP) concentration, Km is the Michaelis constant for ATP, I is the inhibitor (compound C) concentration, and Ki is the dissociation constant for compound C.

Cell experiment [2]:

Cell lines	mouse pulmonary artery smooth muscle cells (PASMCs), Hep3B cells
Preparation method	The solubility of this compound in DMSO is limited. General tips for obtaining a higher concentration: Please warm the tube at 37℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months.
Reacting condition	0.1-20 µM for 30 min

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Applications	Dorsomorphin (4 μM) inhibited osteogenic differentiation in C2C12 cells and suppressed BMP-mediated SMAD activation by blocking BMP type I receptor function. Moreover, treatment with dorsomorphin (1 μM) blocked BMP- and HJV-mediated hepcidin expression in cultured hepatoma-derived cells.

Animal experiment [2]:

Animal models	Zebrafish embryos model; Wild-type (WT) C57BL/6 adult mice model
Dosage form	10 mM dorsomorphin for 30 h; or 10 mg/ kg, intraperitoneal injection
Applications	Dorsomorphin induced dorsalization in zebrafish embryos model. Moreover, Dorsomorphin inhibited bone mineralization in vivo. Additionally, Dorsomorphin (10 mg/ kg) induced hyperferremia in mice.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

1. Zhou, G., Myers, R., Li, Y., Chen, Y., Shen, X., Fenyk-Melody, J., Wu, M., Ventre, J., Doebber, T., Fujii, N., Musi, N., Hirshman, M. F., Goodyear, L. J. and Moller, D.

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E. (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 108, 1167-1174

2. Yu, P. B., Hong, C. C., Sachidanandan, C., Babitt, J. L., Deng, D. Y., Hoyng, S. A., Lin, H. Y., Bloch, K. D. and Peterson, R. T. (2008) Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. Nat Chem Biol. 4, 33-41

Background

IC50: Dorsomorphin inhibited BMP4-induced phosphorylation of BMP-responsive SMADs in a dose-dependent manner (half maximal inhibitory concentration (IC50) =0.47 mM).
Bone morphogenetic protein (BMP) signals coordinate developmental patterning and have essential physiological roles in mature organisms. The first known small-molecule inhibitor of BMP signaling, dorsomorphin, were identified in a screen for compounds that perturb dorsoventral axis formation in zebrafish.

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In vitro: Previoius researchers found that dorsomorphin selectively inhibits the BMP type I receptors ALK2/ALK3/ALK6 leading to block BMP-mediated SMAD1/5/8 phosphorylation, osteogenic differentiation as well as target gene transcription. Using dorsomorphin, they examined the role of BMP signaling in iron homeostasis.dorsomorphin inhibited the systemic iron regulator hepcidin BMP-, hemojuvelin- and interleukin 6–stimulated expression, indicating that BMP receptors regulate hepcidin induction by all of these stimuli [1].
In vivo: The systemic challenge with iron rapidly induced SMAD1/5/8 phosphorylation and hepcidin expression in the liver, while dorsomorphin treatment could blocke SMAD1/5/8 phosphorylation, normalize hepcidin expression and increase serum iron levels. These suggest an crucial physiological role for hepatic BMP signaling in iron-hepcidin homeostasis [1].
Clinical trial: Dorsomorphin is still in preclinical development stage and no clinicl trial is ongoing currently.

Reference:

[1] Yu PB, Hong CC, Sachidanandan C, Babitt JL, Deng DY, Hoyng SA, Lin HY, Bloch KD, Peterson RT.Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. Nat Chem Biol. 2008;4(1):33-41.

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