PXS-5153A monohydrochloride

Cat. No.: HY-114286A

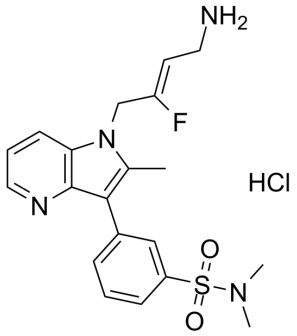
Molecular Formula: $C_{20}H_{24}ClFN_4O_2S$

Molecular Weight: 438.95

Target: Monoamine Oxidase

Pathway: Neuronal Signaling

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (284.77 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2782 mL	11.3908 mL	22.7816 mL
	5 mM	0.4556 mL	2.2782 mL	4.5563 mL
	10 mM	0.2278 mL	1.1391 mL	2.2782 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.74 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.74 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.74 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PXS-5153A monohydrochloride is a potent, selective, orally active and fast-acting lysyl oxidase like 2/3 enzymatic (LOXL2/LOXL3) inhibitor, with an IC_{50} of <40 nM for LOXL2 across all mammalian species and an IC_{50} of 63 nM for human LOXL3. PXS-5153A monohydrochloride could reduce crosslinks and ameliorates fibrosis.

In Vitro

PXS-5153A exhibits an IC_{50} of <40 nM for LOXL2 across all mammalian species tested. PXS-5153A also inhibits human LOXL3 with an IC_{50} value of 63 nM. PXS-5153A is >40-fold selective for LOXL2 over both LOX and LOXL1 and >700-fold selective over other related amine oxidases. PXS-5153A is a fast acting inhibitor, with enzymatic activity almost entirely blocked within 15 minutes [1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	As expected, rhLOXL2 dose-dependently induce oxidation of collagen with PXS-5153A dose-dependently impeding collagen oxidation. Therapeutic treatment of PXS-5153A substantially reduces immature crosslink formation compared with the CCl_4 treated animals. Mature crosslink formation is also reduced by PXS-5153A treatment. All groups with therapeutic treatment of PXS-5153A show a significant reduction in DHLNL formation compared to the CCl_4 treated animals. Treatment with PXS-5153A causes a significantly reduction in HYP compared to the CCl_4 group. In addition, the amount of fibrillar collagen is markedly augmented by disease as seen by the 2.2-fold increase in percentage coverage area by Picrosirius red staining, which is reduced by PXS-5153A[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats[1] Sprague Dawley rats are orally administered with 0.25 μL/g Carbon tetrachloride (CCl_4) in olive oil solution, starting from day 0, 3 times per week for 6 weeks. PXS-5153A is given by oral gavage after 3 weeks of CCl_4 administration and continued throughout the remainder of the study at 3 mg/kg (low dose) or 10 mg/kg (high dose) once a day or 10 mg/kg (high dose) three times a week. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were assessed in the plasma. Mice NASH is established in male C57/BL6 mice by a single subcutaneous injection of 200 μg streptozotocin after birth and with a high fat diet ad libitum after 4 weeks of age (day 28 ± 2) until 14 weeks of age. Mice are orally administered with 10 mg/kg PXS-5153A once daily from 8 to 14 weeks of age. ALT levels are assessed in the plasma. Mice Myocardial infarction (MI) is induced in C57/BL6 mice by occluding the left coronary artery. At 24 hours post-surgery, animals receive echocardiography. Infarcted mice with high cardiac function (FS > 40%) or low cardiac function (FS<10%) are excluded from the study. The remaining mice are treated q.d., p.o., with 25 mg/kg of PXS-5153A for 4 weeks. At the end of the experiment, echocardiography is performed on mice to assess left ventricular function and remodelling, followed by heart collection. The heart is fixed with 10% formalin. Fibrosis is assessed in the non-infarct area[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Schilter H, et al. The lysyl oxidase like 2/3 enzymatic inhibitor, PXS-5153A, reduces crosslinks and ameliorates fibrosis. J Cell Mol Med. 2018 Dec 9.

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