XL-784

Cat. No.: HY-19485

CAS No.: 1224964-36-6

Molecular Formula: $C_{21}H_{21}ClF_2N_3O_8S$-

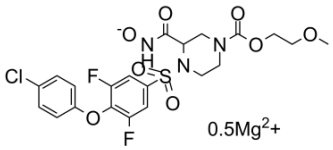
Molecular Weight: 548.92

Target: MMP

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 110 mg/mL (200.39 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8218 mL	9.1088 mL	18.2176 mL
5 mM	0.3644 mL	1.8218 mL	3.6435 mL
10 mM	0.1822 mL	0.9109 mL	1.8218 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: ≥ 2.75 mg/mL (5.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (5.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (5.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

XL-784 is a selective matrix metalloproteinases (MMP) inhibitor, with IC_{50}s of ~1900, 0.81, 120, 10.8, 18, 0.56 nM for MMP-1、MMP-2、MMP-3、MMP-8、MMP-9、MMP-13、respectively.

IC_{50} & Target

MMP-2 0.81 nM (IC_{50})	MMP13 0.56 nM (IC_{50})	MMP-8 10.8 nM (IC_{50})	MMP-9 18 nM (IC_{50})
MMP-3	MMP-1		

	120 nM (IC_{50})	1900 nM (IC_{50})
In Vitro	XL-784 is a highly potent, low-molecular-weight (1,122 g/mol) inhibitor of MMPs that has very limited aqueous solubility (20 μg/mL). XL-784 potently inhibits MMP-2, MMP-13, andADAM10 [TNF-α-converting enzyme (TACE)] activity in vitro, with IC_{50} values in the range of 1-2 nM. XL-784 also inhibits MMP-9 (IC_{50} ~20 nM) activity and ADAM17 (IC_{50} ~70 nM) also known as TACE. However, it exhibits low potency for inhibition of MMP-1 (IC_{50} ~2,000 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	All mice tolerate the treatments similarly. Control mice all developed aneurysms with a mean %△AD of 158.5%±4.3%. Treatment with all doses of XL-784 and doxycycline are effective in inhibiting aortic dilatation. There is a clear dose-response relationship between XL-784 and reductions in aortic dilatation at harvest (50 mg/kg 140.4% ±3.2%; 125 mg/kg 129.3% ±5.1%; 250 mg/kg 119.2%±3.5%; all Ps<0.01 compared to control). This continues with the higher doses (375 mg/kg 88.6%±4.4%; 500 mg/kg 76.0%±3.5%). The highest 2 doses of XL-784 tested are more effective than doxycycline (112.2%±2.0%, P<0.05) in inhibiting maximal dilatation of the aorta after elastase perfusion[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Animal Administration [2]	Mice[2] A total of 89 mice undergo aortic perfusion. Beginning the day of perfusion, animals are treated with the study drug (e.g., XL-784), a negative control, or doxycycline. 76 animals survive to sacrifice and are included in the analysis. Animals treated with the experimental agent, XL-784, receive gavage daily with the agent diluted in 0.1 mL of Cremophor, a nonionic castor oil-based solubilizer and emulsifying agent. Three doses of the drug are used, 50 (n=17), 125 (n=17), and 250 mg/kg per d (n=18) administered as a single daily dose. The fifth group of mice do not receive a gavage treatment but are treated with doxycycline (n=19) in their drinking water at a concentration 100 mg/kg per d of the animals. In the second treatment protocol, a total of 50 animals underwent aortic perfusion and 47 animals survive for analysis at 14 days. The 5 treatment groups are XL-784 at 250, 375, or 500 mg/kg, Cremaphor diluent alone, or doxycycline 100 mg/kg. Animals are assigned in groups of 3 to a treatment group rotating randomly through each treatment group until there are 9 animals in each group except for the 500 mg/kg per d group which totaled to 14 animals[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Williams JM, et al. Evaluation of metalloprotease inhibitors on hypertension and diabetic nephropathy. Am J Physiol Renal Physiol. 2011 Apr;300(4):F983-98.

[2]. Ennis T, et al. Effect of novel limited-spectrum MMP inhibitor XL784 in abdominal aortic aneurysms. J Cardiovasc Pharmacol Ther. 2012 Dec;17(4):417-26.

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