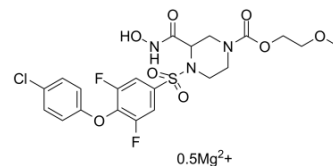


XL-784

Cat. No.:	HY-19485
CAS No.:	1224964-36-6
Molecular Formula:	C ₂₁ H ₂₂ ClF ₂ N ₃ O ₈ S
Molecular Weight:	549.93
Target:	MMP
Pathway:	Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the COA.



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.			
IC₅₀ & Target	MMP-1 1900 nM (IC ₅₀)	MMP-2 0.81 nM (IC ₅₀)	MMP-3 120 nM (IC ₅₀)	MMP-8 10.8 nM (IC ₅₀)
	MMP-9 18 nM (IC ₅₀)	MMP13 0.56 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, and ADAM10 [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] .			
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] .			

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
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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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Caution: Product has not been fully validated for medical applications. For research use only.

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