Product Data Sheet

Product Name: XL-784 free base
Cat. No.: GC38871

Chemical Properties

Cas. No.	1356992-21-6		
SMILES	O=C(N1CC(C(NO)=O)N(S(=O)(C2=CC(F)=C(OC3=CC=C(Cl)C=C3)C(F)=C2)=O)CC1)OCCOC		
Formula	$C_{21}H_{22}ClF_2N_3O_8S$	M.Wt	549.93
Solubility	DMSO: 250 mg/mL (454.60 mM)	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	XL-784 free base		

Protocol

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Animal experiment:

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].

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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.

Background

XL-784 free base is a selective matrix metalloproteinases (MMP) inhibitor, with IC50s 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.

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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 IC50 values in the range of 1-2 nM. XL-784 also inhibits MMP-9 (IC50 ~20 nM) activity and ADAM17 (IC50 ~70 nM) also known as TACE. However, it exhibits low potency for inhibition of MMP-1 (IC50 ~2,000 nM)[1].

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].

[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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