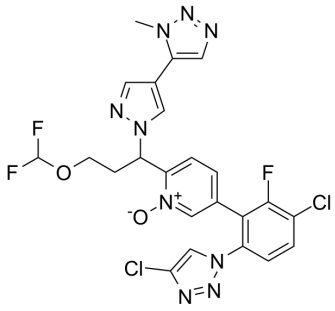
FXIa-IN-9

Cat. No.:	HY-150682
CAS No.:	2816108-87-7
Molecular Formula:	$C_{23}H_{18}Cl_2F_3N_9O_2$
Molecular Weight:	580.35
Target:	Factor Xa
Pathway:	Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

FXIa-IN-9 (compound 3f) is a potent and selective FXIa inhibitor. FXIa-IN-9 can bind with FXIa and form hydrogen bond (human FXIa K_i: 0.17 nM, rabbit FXIa K_i: 0.5 nM). FXIa-IN-9 also has anticoagulant activity, and can be used in the research of thromboembolic diseases such as atrial fibrillation, stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism[1].

IC_{50} & Target

Ki: 0.17 nM (human FXIa), 0.5 nM (rabbit FXIa)[1].

In Vitro

FXIa-IN-9 has anticoagulant activity, with $EC_{1.5x}$ values of 1.31 μM (human plasma aPTT) and 1.39 μM (rabbit plasma aPTT), respectively[1].

FXIa-IN-9 (10 μM, 5-15 min) is highly selective for FXIa against other human serine protease, except for plasma kallikrein (IC_{50} : 0.023 μM)[1].

FXIa-IN-9 shows the plasma protein binding ranges from 80.8 to 95.6%, and pharmacological profile is as follows[1].

property/assay	value
equilibrium solubility (pH 1.2; pH 6.8)	81.0 μM; 171.6 μM
PPB % (mouse/rat/dog/human)	91.2/91.6/80.8/95.6
hERG inhibition (IC_{50})	>10 μM
S9 aldehyde oxidase (AO)	$T_{1/2}$ > 180 min
hLM trapping assay	no GSH and CN adducts
AMES genotoxicity test	negative
in vitro micronucleus test	negative

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

In Vivo

FXIa-IN-9 (marginal ear intravenous injection, 1.7-10 mg/kg, dosing at 20 min prior to and 40 min during the AV shunt) achieves more than 50% thrombus reduction in the rabbit arteriovenous (AV) shunt thrombosis model[1].

FXIa-IN-9 (i.v. or p.o., 1-10 mpk) shows low clearance in rat and dog and moderate clearance in the monkey as well as good oral bioavailability[1].

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

Animal Model:	Rabbit AV shunt thrombosis model[1]
Dosage:	1.7 mg/kg bolus + 2.0 mg/kg/h infusion, or 8.5 mg/kg bolus + 10 mg/kg/h infusion.
Administration:	Intravenous dosing via the marginal ear vein 20 min prior to and 40 min during the AV shunt
Result:	Showed 36.5% (1.7 mg/kg bolus + 2.0 mg/kg/h infusion) and 62.2% (8.5 mg/kg bolus + 10 mg/kg/h infusion) inhibitions in thrombus weight, respectively.

Animal Model:	Rat, dog, monkey (pharmacokinetic assay)[1]
Dosage:	1 mpk, 2 mpk (i.v.); 5 mpk, 10 mpk (p.o.)
Administration:	Intravenous injection, oral administration.
Result:	Pharmacokinetic profile of FXIa-IN-9 in kinds of species.

animal species	clearance (mL/min/kg)	$T_{1/2}$ (h)	Vd_{ss} (L/kg)	F%	AUC (iv) (μM•h)	AUC (po) (μM•h)	Dose iv/po (mpk)
rat	10.7	1.4	0.8	36.4	5.5	10.0	2/10
dog	7.9	2.0	1.5	80.5	3.7	14.7	1/5
monkey	25.6	1.0	1.5	43.0	1.1	2.5	1/5

REFERENCES

[1]. Guozhang Xu, et al. Discovery of Potent and Orally Bioavailable Pyridine N-Oxide-Based Factor XIa Inhibitors through Exploiting Nonclassical Interactions. J Med Chem. 2022 Jul 21.

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