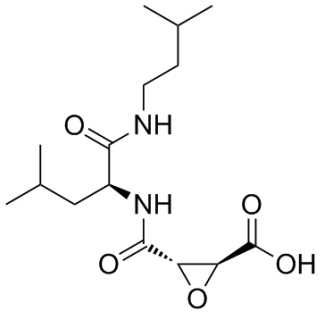
E 64c

Cat. No.:	HY-100227
CAS No.:	76684-89-4
Molecular Formula:	$C_{15}H_{26}N_2O_5$
Molecular Weight:	314.38
Target:	Cathepsin; SARS-CoV
Pathway:	Metabolic Enzyme/Protease; Anti-infection
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 : 250 mg/mL (**795.22 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1809 mL	15.9043 mL	31.8086 mL
	5 mM	0.6362 mL	3.1809 mL	6.3617 mL
	10 mM	0.3181 mL	1.5904 mL	3.1809 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 (6.62 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: ≥ 2.08 mg/mL (6.62 mM); Clear solution
3. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.08 mg/mL (6.62 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

E 64c is a derivative of naturally occurring epoxide inhibitor of **cysteine proteases**, a Calcium-activated neutral protease **(CANP)** inhibitor and a very weak irreversible **cathepsin C** inhibitor. E 64c exhibits entry-blocking effect for MERS-CoV.

IC_{50} & Target

Cysteine proteases[1], CANP[2], Cathepsin C[3].

In Vitro	E-64c, a derivative of naturally occurring epoxide inhibitor of cysteine proteases, with papain; especially with regard to the hydrogen bonding and hydrophobic interactions of the ligands with conserved residues in the catalytic binding site[1]. E 64c (k_2/K_i=140±5$M^{-1}s^{-1}$) is demonstrated to be a lead structure for the development of irreversible cathepsin C inhibitors[3].
In Vivo	The t-1/2 of plasma E-64c is 0.48 hours. The hemodynamic effects of E-64c are absent at this dose. Using two way analysis of variance, the effects of reperfusion (p=0.0016) or E-64c (p=0.0226) per se on infarct size are significant. In comparing Group A with Group B and Group C with Group D, the depletion of CPK in the E-64c treated groups (Groups A and C) is slightly less than in the vehicle-injected groups (Groups B and D). The insufficient effect of E-64c alone may be explained by the early administration and relatively short t-1/2. Since the effectiveness of NCO-700 has been established,6),7) our findings might indicate a small but beneficial effect of E-64c on infarct size and CPK content[2].

PROTOCOL

Animal Administration [2]	Dogs[2] Studies are carried out in 83 **mongrel dogs** with a mean weight of 11.2kg. They are anesthetized with intravenous sodium thiamylal (7mg/kg). An intravenous bolus of **E-64c (100mg/kg)**, dissolved in saturated sodium bicarbonate, is administered immediately before the occlusion and after reperfusion in Group A (n=17), whereas Group B (n=17) receive only the vehicle solution at these times. In the remaining 49 dogs (Groups C and D), the LAD is permanently ligated at the same level and an intravenous bolus of either Loxistatin acid (100mg/kg) (Group C; n=24) or vehicle only (Group D; n=25) is given immediately before and 1 hour after the ligation. The dose of E-64c is designed for its possible use in clinical practice and the estimated intramyocardial Loxistatin acid molecular concentration is 1,000 times that of total mCANP[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Khan MS, et al. Design, synthesis, evaluation and thermodynamics of 1-substituted pyridylimidazo[1,5-a]pyridine derivatives as cysteine protease inhibitors. PLoS One. 2013 Aug 5;8(8):e69982.

[2]. Toda G, et al. Calcium-activated neutral protease inhibitor (E-64c) and reperfusion for experimental myocardial infarction. Jpn Heart J. 1989 May;30(3):375-86.

[3]. Radzey H, et al. E-64c-hydrazide: a lead structure for the development of irreversible cathepsin C inhibitors. ChemMedChem. 2013 Aug;8(8):1314-21.

[4]. Ji Yeun Kim, et al. Safe, High-Throughput Screening of Natural Compounds of MERS-CoV Entry Inhibitors Using a Pseudovirus Expressing MERS-CoV Spike Protein. Int J Antimicrob Agents. 2018 Nov;52(5):730-732.

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