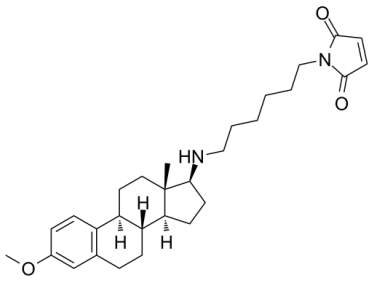
Data Sheet

Product Name:	U-73122
Cat. No.:	CS-2749
CAS No.:	112648-68-7
Molecular Formula:	C29H40N2O3
Molecular Weight:	464.64
Target:	Ferroptosis; Lipoxygenase; Phospholipase
Pathway:	Apoptosis; Metabolic Enzyme/Protease
Solubility:	DMSO : 12.5 mg/mL (26.90 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

U-73122 is a **phospholipase C (PLC)** and **5-LO (5-lipoxygenase)** inhibitor with an **IC_{50}**of 1-2.1 μM for PLC. **In Vitro:** U-73122 potently inhibits receptor-coupled activation of PLC in membranes isolated from PMNs[1]. U-73122 inhibits N-formyl-methionyl-leucyl-phenylalanine-induced aggregation of human polymorphonuclear neutrophils (PMN) and the associated production of IP_3 and diacyglycerol[2]. U-73122 markedly inhibits inositol phosphate release elicited by either oxotremorine-M or guanosine-5'-O-(3-thiotriphosphate) than that induced by added Ca^{2+} in digitonin-permeabilized cells[3]. **In Vivo:** U73122 significantly attenuates TNF-α mRNA expression, has no effect on sham animals, but significantly increases heart work and rate of contraction and relaxation without affecting heart rate in endotoxemic mice[4]. U73122 (400 nM/μL) significantly reduces total lordosis durations, compared to vehicle infusions to the VTA, of oestradiol and progesterone-primed hamsters. VTA infusions of U73122 do not alter motor behaviour of hamsters in the activity monitor, but there is a significant effect of muscimol to decrease total number of beam breaks compared to hamsters administered SKF38393[5].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: U-73122 is dissolved in DMSO.[2]Agonist-induced production of IP_3 in PMN is measured by use of the competitive radiobinding assy. PMN (2 x 10^6-10^7) in 0.2 mL of phosphate-buffered saline, pH 7.4 [NaC1 (138 mM), Na_2HPO_4 (8.1 mM), KH_2PO_4 (1.5 mM), KCI (2.7 mM), $CaCl_2$ (1.0 mM), $MgC1_2$ (1.0 mM) and glucose (0.1%, w/v)] are incubated in conical polypropylene tubes at 37°C in a shaking water bath. U-73122 or U-73343 is added (in 1 μL of DMSO) 3 min before the addition of agonist, FMLP (0.1 μM) plus cytochalasin B (5 μg/mL). FMLP and cytochalasin B are added in 1 μL each of DMSO and ethanol, respectively. Appropriate vehicle controls are included in each experiment. PMN incubation mixtures are quenched with the addition of 0.07 mL of ice-cold TCA (20%, w/v) and a portion (0.2 mL) of the TCA extract is processed for the measurement of IP_3 by competitive radiobinding as described above for platelets. **Animal Administration:** U-73122 is formulated in saline.[5]Hamsters are hormone-primed with 17β-oestradiol at h 0 and progesterone at h 45. At h 48, hamsters are pretested for motor behaviour, followed by sexual behaviour testing, and bilateral infusions of U73122 (400 nM/μL) or saline vehicle. Thirty minutes after infusions, hamsters are re-tested for sexual behaviour (post inhibitor infusion test) and, immediately after testing, infused bilaterally with SKF38393 (100 ng/μL), muscimol (100 ng/μL), or saline vehicle. Thirty minutes after the agonist or vehicle infusions, lordosis and motor behaviour of hamsters is reassessed (post agonist infusion test). All hamsters are assigned to one pretreatment condition, U73122 or vehicle, and are tested once a week for 3 weeks until all infusion conditions (SKF38393, muscimol or vehicle), are received. The order in which hamsters receive SKF38393, muscimol or vehicle infusions is counterbalanced across the group.

References:

[1]. Smith RJ, et al. Receptor-coupled signal transduction in human polymorphonuclear neutrophils: effects of a novel inhibitor of phospholipase C-dependent processes on cell responsiveness. J Pharmacol Exp Ther. 1990 May;253(2):688-97.

[2]. Bleasdale JE, et al. Selective inhibition of receptor-coupled phospholipase C-dependent processes in human platelets and polymorphonuclear neutrophils. J Pharmacol Exp Ther. 1990 Nov;255(2):756-68.

[3]. Thompson AK, et al. The aminosteroid U-73122 inhibits muscarinic receptor sequestration and phosphoinositide hydrolysis in SK-N-SH neuroblastoma cells. A role for Gp in receptor compartmentation. J Biol Chem. 1991 Dec 15;266(35):23856-62.

[4]. Peng T, et al. Disruption of phospholipase Cgamma1 signalling attenuates cardiac tumor necrosis factor-alpha expression and improves myocardial function during endotoxemia. Cardiovasc Res. 2008 Apr 1;78(1):90-7. Epub 2007 Dec 12.

[5]. Frye CA, et al. In the ventral tegmental area, the membrane-mediated actions of progestins for lordosis of hormone-primed hamsters involve phospholipase C and protein kinase C. J Neuroendocrinol. 2007 Sep;19(9):717-24.

[6]. Hörnig M, et al. Inhibition of 5-lipoxygenase by U73122 is due to covalent binding to cysteine 416. Biochim Biophys Acta. 2012 Feb;1821(2):279-86.

[7]. Xie W, et al. 3Beta-hydroxy-6-aza-cholestane and related analogues as phosphatidylinositol specific phospholipase C (PI-PLC) inhibitors with antitumor activity. Bioorg Med Chem. 2000 Apr;8(4):699-706.

CAIndexNames:

1H-Pyrrole-2,5-dione, 1-[6-[[(17b)-3-methoxyestra-1,3,5(10)-trien-17-yl]amino]hexyl]-

SMILES:

O=C(C=C1)N(CCCCCCN[C@H]2CC[C@@]3([H])[C@]4([H])CCC5=C(C=CC(OC)=C5)[C@@]4([H])CC[C@]23C)C1=O

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