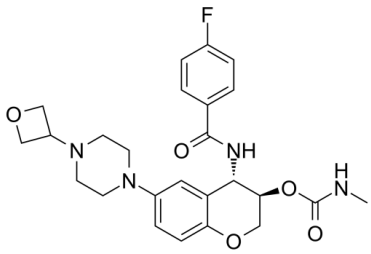
Data Sheet

Product Name:	LY 3000328
Cat. No.:	CS-1120
CAS No.:	1373215-15-6
Molecular Formula:	C25H29FN4O5
Molecular Weight:	484.52
Target:	Cathepsin
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 50 mg/mL (103.19 mM)



BIOLOGICAL ACTIVITY:

LY 3000328 is a potent and selective **Cathepsin S (Cat S)** inhibitor with **IC_{50}**s of 7.7 and 1.67 nM for hCat S and mCat S, respectively. IC50 & Target: IC50: 7.7±5.85 nM (hCat S), 1.67±1.17 (mCat S)[1] **In Vitro:** LY3000328 maintains excellent in vitro potency and selectivity. LY3000328 shows low in vitro CYP450 inhibition (<15% at 10 μM for CYP3A4, CYP2D6, and CYP2C9); low in vitro metabolism in mouse, rat, dog, and human liver microsomes (<20% after 30 min incubation at 4 μM); and good permeability (MDCK A-B>4%). At a 100 μM concentration of LY3000328 there is only 6% displacement of [^{3}H]-astemizole in an assay with HEK293 membrane preparation, indicating low potential of hERG blockade[1]. LY3000328 is a potent and specific inhibitor of cathepsin S (CatS). Inhibition of CatS activity in plasma would be 50% of maximal when LY3000328 plasma concentration is approximately 60 ng/mL[2]. **In Vivo:** The efficacies of LY3000328 is studied in a mouse model of abdominal aortic aneurysm (AAA). In this model, inflammation is induced using $CaCl_2$ applied to the ablumenal surface. It is shown that features of the disease state in this model resemble those of human AAA. LY3000328 exhibits a dose-responsive aortic diameter reduction at 1, 3, 10, and 30 mg/kg. At the lowest dose of 1 mg/kg of LY3000328, the aortic diameter is reduced by 58%, then 83% at 3 mg/kg, and 87% at 10 mg/kg. The exposure (AUC) for both compounds increased in a dose-dependent manner, suggesting that the drug disposition properties of LY3000328 are favorable[1].

References:

[1]. Jadhav PK, et al. Discovery of Cathepsin S Inhibitor LY3000328 for the Treatment of Abdominal Aortic Aneurysm. ACS Med Chem Lett. 2014 Aug 27;5(10):1138-42.

[2]. Payne CD, et al. Pharmacokinetics and pharmacodynamics of the cathepsin S inhibitor, LY3000328, in healthy subjects. Br J Clin Pharmacol. 2014 Dec;78(6):1334-42.

CAIndexNames:

Benzamide, N-[(3R,4S)-3,4-dihydro-3-[[(methylamino)carbonyl]oxy]-6-[4-(3-oxetanyl)-1-piperazinyl]-2H-1-benzopyran-4-yl]-4-fluoro-

SMILES:

O=C(C1=CC=C(F)C=C1)N[C@@H]2[C@@H](OC(NC)=O)COC3=CC=C(N4CCN(C5COC5)CC4)C=C32

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

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