LY 3000328

**Cat. No.:** HY-15533  
**CAS No.:** 1373215-15-6  
**Molecular Formula:** C₂₅H₂₉FN₄O₅  
**Molecular Weight:** 484.52  
**Target:** Cathepsin  
**Pathway:** Metabolic Enzyme/Protease  
**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 : \(\geq 50\) mg/mL (103.19 mM)

* "\(\geq\)" means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Mass Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mM</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.0639 mL</td>
<td>10.3195 mL</td>
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<tr>
<td></td>
<td></td>
<td>5 mM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.4128 mL</td>
<td>2.0639 mL</td>
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<tr>
<td></td>
<td></td>
<td>10 mM</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.2064 mL</td>
<td>1.0319 mL</td>
</tr>
</tbody>
</table>

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: \(\geq 2.5\) mg/mL (5.16 mM); Clear solution

2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-\(\beta\)-CD in saline)  
   Solubility: \(\geq 2.5\) mg/mL (5.16 mM); Clear solution

3. Add each solvent one by one: 10% DMSO >> 90% corn oil  
   Solubility: \(\geq 2.5\) mg/mL (5.16 mM); Clear solution

### BIOLOGICAL ACTIVITY

**Description**  
LY 3000328 is a potent and selective Cathepsin S (Cat S) inhibitor with IC₅₀ 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 [³H]-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 CaCl₂ 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
