**BIOLOGICAL ACTIVITY:**

LY–411575 is a potent \(\gamma\)-secretase inhibitor with IC\(_{50}\) of 0.078 nM/0.082 nM (membrane/cell–based), and also inhibits Notch S3 cleavage with IC\(_{50}\) of 0.39 nM.

IC\(_{50}\) & Target: IC\(_{50}\): 0.078 nM (\(\gamma\)-secretase in membrane), 0.082 nM (\(\gamma\)-secretase cell–based), 0.39 nM (Notch S3 cleavage cell–based)\(^[1]\)

**In Vitro:** LY–411,575 blocks Notch activation, and results in apoptosis in primary and immortalized KS cells. LY–411,575 (500 μM) induces G2/M growth arrest SLK cells\(^[2]\). LY411575 treatment significantly decreases the amounts of intracellular HCV RNA with IC\(_{50}\) of 0.56 ± 0.20 μM and extracellular HCV particles. LY411575 (0–40 nM) alone or in combination with daclatasvir (0–40 pM) decreases supernatant infectious titers in a dose–dependent manner, and is synergistic regarding production of infectious virus. LY411575 (10 μM) treatment impairs ROS production in HCVcc–infected cells\(^[4]\). LY411575 significantly attenuates EMT by inhibiting the Notch signaling activation in vitro\(^[5]\).

**In Vivo:** LY–411,575 (10 mg/kg) decreases brain and plasma Aβ40 and –42 robustly when chronically administered to TgCRND8 mice\(^[1]\). LY411,575 reduces cortical Aβ40 in young transgenic CRND8 mice (ED\(_{50}\) appr 0.6 mg/kg) and produces significant thymus atrophy and intestinal goblet cell hyperplasia at higher doses (>3 mg/kg). The extent of intestinal goblet cell hyperplasia induced by LY411,575 (10 mg/kg) is similar in young and aged mice\(^[3]\). LY411575 inhibits mouse proliferative vitreoretinopathy (PVR) formation in vivo\(^[5]\).

**PROTOCOL (Extracted from published papers and Only for reference)**

**Animal Administration:** LY–411575 is formulated as 10 mg/mL solutions and diluted 1:10 with 0.4% methycellulose for oral administration; LY–411575 is formulated in 10 mg/mL stock solution and diluted 1:10 with 20% hydroxyl–propyl–β–cyclodextrin for subcutaneous dosing.\(^[3]\) Mice from the aged cohort (16–26 months old) are either retired breeders or experimentally naive mice. Before dosing begin and for the duration of the study, mice are singly housed with a plastic igloo and nesting material. Mice are sacrificed 2 to 4 h after their final dosing. For oral dosing, LY411,575 and LY–D are formulated as 10 mg/mL solutions and diluted 1:10 with 0.4% methycellulose. In the case of subcutaneous dosing, the 10 mg/mL stock solution is diluted 1:10 with 20% hydroxyl–propyl–β–cyclodextrin. If necessary, serial dilutions are made from the 1 mg/mL solution using the appropriate 1:10 vehicle. The dosing volume is 10 mL/kg. After oral administration of 10 mg/kg LY411,575, inhibition of plasma Aβ is still significant 24, but not 48, h after dosing, so in an effort to maintain continuous \(\gamma\)-secretase inhibition, LY411,575 and LY–D are dosed once per day in all studies.

**References:**


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

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA

www.MedChemExpress.com