

产品名称: LY 303511

产品别名: LY 303511

生物活性:	
Description	LY303511 is a structural analogue of LY294002. LY303511 does not inhibit PI3K. LY303511 enhances TRAIL sensitivity of SHEP-1 neuroblastoma cells. LY303511 reversibly blocks K <sup>+</sup> currents (IC <sub>50</sub> =64.6±9.1 μM) in MIN6 insulinoma cells.
IC <sub>50</sub> & Target	TRAIL[2] IC50: 64.6±9.1 μM (K <sup>+</sup> currents, in MIN6 insulinoma cells)[3]
In Vitro	LY303511 is structurally identical to LY294002 except for a substitution of -O for -NH in the morpholine ring, and does not potently inhibit PI3K. Treatment of cells with LY303511 causes an increase in calcein spread similar to levels of LY294002. The ability of LY303511 to increase gap junctional intercellular communication (GJIC) does not occur concomitant with inhibition of phosphorylation of AKT as measured by immunoblotting[1]. LY303511 enhances TRAIL sensitivity of SHEP-1 neuroblastoma cells via H2O2-MAPK activation and up-regulation of death receptors. SHEP-1 cells are exposed to varying concentrations of LY303511 (LY30), TRAIL, and a combination of the two (1 h preincubation with LY303511 followed by TRAIL for 4 hours). SHEP-1 cells are responsive to TRAIL (~10%, ~15%, and ~30% reduction in the surviving fraction at 25, 50, and 100 ng/mL, respectively); however, treatment with LY303511 (12.5, 25, or 50 μM) has no effect on cell viability. However, incubation of cells with LY303511 (25 μM) for 1 hour followed by 4 hours exposure to 50 ng/mL of TRAIL has a strong synergistic effect (~40% reduction in viable cells with LY303511+TRAIL versus ~15% with TRAIL alone)[2]. LY303511 is a negative control compound with respect to PI3K activity. In MIN6 insulinoma cells, Wortmannin (100 nM) has no effect on whole-cell outward K <sup>+</sup> currents, but LY294002 and LY303511 reversibly block currents in a dose-dependent manner (IC <sub>50</sub> =9.0±0.7 μM and 64.6±9.1 μM, respectively). Kv2.1 and Kv1.4 are highly expressed in beta-cells, and in Kv2.1-transfected tsA201 cells, 50 μM LY294002 and 100 μM LY303511 reversibly inhibit currents by 99% and 41%, respectively. LY303511 blocks currents with an IC <sub>50</sub> of 64.6±9.1 μM, with a maximal inhibition of ~90% at 500 μM (n≥5 cells at each concentration)[3].
In Vivo	Intraperitoneal administration of vehicle or LY303511 (10 mg/kg/day) is performed when tumors reach a volume of ~150 mm <sup>3</sup> , at which time 35 mice have developed a tumor. After 21 days, >15% of the mice require euthanasia because of excessive tumor growth, and these data are censored due to unreliable estimates of average tumor volume. The administration of LY303511, 10 mg/kg/day, is sufficient to inhibit PC-3 tumor growth in vivo[4].
References	[1]. Bodenshtein TM, et al. Homotypic gap junctional communication associated with metastasis suppression increases with PKA activity and is unaffected by PI3K inhibition. Cancer Res. 2010 Dec 1;70(23):10002-11. [2]. El-Kholy W, Macdonald PE, Lin JH. The phosphatidylinositol 3-kinase inhibitor LY294002 potently blocks K(V) currents via a direct mechanism. FASEB J. 2003 Apr;17(6):720-2. [3]. Shenoy K, et al. LY303511 enhances TRAIL sensitivity of SHEP-1 neuroblastoma cells via hydrogen peroxide-mediated mitogen-activated protein kinase activation and up-regulation of death receptors. Cancer Res. 2009 Mar 1;69(5):1941-50. [4]. Kristof AS, et al. LY303511 (2-piperazinyl-8-phenyl-4H-1-benzopyran-4-one) acts via phosphatidylinositol 3-kinase-independent pathways to inhibit cell proliferation via mammalian target of rapamycin (mTOR)- and non-mTOR-dependent mechanisms. J Pharmacol Exp Ther. 2005



源叶生物