

Product Data Sheet

Product Name: LY2090314

Cat. No.: GC17187

Chemical Properties

Cas. No. 603288-22-8

Chemical Name 3-(9-fluoro-2-(piperidine-1-carbonyl)-1,2,3,4-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-7-yl)-4-(imidazo[1,2-a]pyridin-3-yl)-1H-pyrrole-2,5-dione

SMILES FC1=C([H])C2=C(C(C(C(C(N([H])C3=O)=O)=C3C4=C([H])N=C5N4C([H])=C([H])C([H])=C5[H])=C6[H])=C1[H])N6C([H])([H])C([H])([H])N(C(N7C([H])([H])C([H])([H])C([H])([H])C([H])([H])C7([H])[H])=O)C2([H])[H]

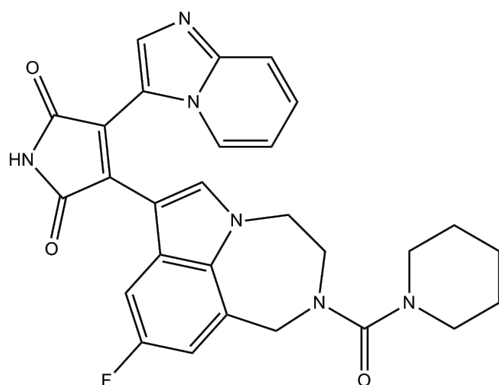
Formula $C_{28}H_{25}FN_6O_3$ M.Wt 512.53

Solubility ≥ 91 mg/mL in DMSO, ≥ 4.27 mg/mL in EtOH with ultrasonic and warming Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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

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Cell lines A panel of melanoma cell lines

Preparation method Soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition 20 nM

Applications LY2090314 potently induced apoptotic cell death in a panel of melanoma cell lines irrespective of BRAF mutation status. LY2090314 (20 nM) promoted a time-dependent stabilization of β -catenin total protein as well as an induction of Axin2. LY2090314 was highly selective towards GSK3 as demonstrated by its fold selectivity relative to a large panel of kinases. Cell death induced by LY2090314 was dependent on β -catenin and GSK3 β knockdown increased the sensitivity of cells to LY2090314. LY2090314 was active in cell lines resistant to Vemurafenib and showed an independent mechanism of action.

Animal experiment [1, 2]:

Animal models Athymic nude mice bearing A375 melanoma xenografts

Dosage form Intravenous injection, 25 mg/kg, every 3 days

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Application

LY2090314 (25 mg/kg Q3D, i.v.) elevated Axin2 gene expression in vivo, demonstrated single agent activity in the A375 xenograft model of melanoma and enhanced the efficacy of DTIC. LY2090314 exhibited high clearance (approximating hepatic blood flow) and a moderate volume of distribution (appr 1-2 L/kg) resulting in rapid elimination (half-life appr 0.4, 0.7, and 1.8-3.4 hours in rats, dogs, and humans, respectively). LY2090314 was rapidly cleared by extensive metabolism with negligible circulating metabolite exposures due to biliary excretion of metabolites into feces with no apparent intestinal reabsorption.

Other notes

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

- [1]. Atkinson J M, Rank K B, Zeng Y, et al. Activating the Wnt/ β -catenin pathway for the treatment of melanoma—application of ly2090314, a novel selective inhibitor of glycogen synthase kinase-3[J]. PLoS One, 2015, 10(4): e0125028.
- [2]. Zamek-Gliszczyński MJ, et al. Pharmacokinetics, metabolism, and excretion of the glycogen synthase kinase-3 inhibitor LY2090314 in rats, dogs, and humans: a case study in rapid clearance by extensive metabolism with low circulating metabolite exposure. Dr

Background

IC50: 1.5 nM (GSK-3 α); 0.9 nM (GSK-3 β)

LY2090314 (LY) is a potent inhibitor of glycogen synthase kinase-3 (GSK-3) which plays an important role in various pathways, such as protein synthesis initiation, cell proliferation/differentiation, and apoptosis.

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In vitro: LY2090314 selectively inhibits the activity of GSK-3 by inhibiting ATP binding. LY2090314 was reported to be able to stabilize β -catenin. As monotherapy, LY2090314 also showed limited efficacy. In solid tumor cancer cell lines, LY2090314 was found to enhance the efficacy of cisplatin and carboplatin [1].

In vivo: Even in Mdr1a-, Bcrp-, and Mrp2-knockout rats, the metabolites of LY2090314 did not appear in systemic circulation, and the urinary excretion was not found to be enhanced, since the hypothesized impaired biliary excretion of metabolites in the absence of these canalicular transporters was not observed. Dog metabolite disposition was similar, with the exception of LY2090314 glucuronide. Moreover, LY2090314 enhances the efficacy of cisplatin and carboplatin in solid tumor cancer xenografts [1]

Clinical trial: In advanced solid tumor patients (pts), LY2090314 (LY) was dosed intravenously as a lead-in 7 days prior to the first administration of the triplet combination with PC. Preliminary pharmacokinetic analyses showed that exposure increased as dose increased over the dose range studied with a short terminal elimination half-life calculated in the majority of patients. Large number of pretreated patients that experienced stable disease suggests continued evaluation of LY in NSCLC may be warranted.

Reference:

[1] Brail LH, et al. J Clin Oncol, 2011, 29, abstr 3030.

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