

Product Data Sheet

Product Name: XL147
Cat. No.: GC12709

Chemical Properties

Cas. No. 956958-53-5

Chemical Name N-[3-(2,1,3-benzothiadiazol-5-ylamino)quinoxalin-2-yl]-4-methylbenzenesulfonamide

SMILES CC1=CC=C(C=C1)S(=O)(=O)NC2=NC3=CC=CC=C3N=C2NC4=CC5=NSN=C5C=C4

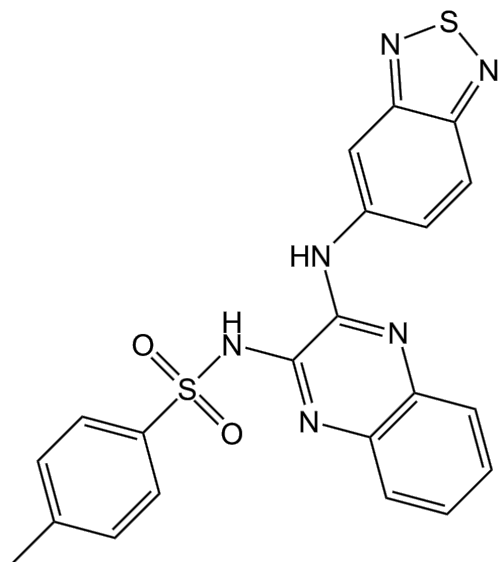
Formula $C_{21}H_{16}N_6O_2S_2$ M.Wt 448.52

Solubility $\geq 22.45\text{mg/mL}$ in DMSO with gentle 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

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

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Cell experiment [1]:

Cell lines Rhabdomyosarcoma cell lines, neuroblastoma cell lines

Limited solubility. General tips for obtaining a higher concentration: Please warm Preparation method 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 10 nM-100 µM, 6–12 h

Applications In PPTP cell lines, XL147 (100 µM) demonstrated cytotoxic activity with the IC50 values ranged from 2.7 µM (CHLA-10) to 24.5 µM (TC-71). There was a trend for lower values for the rhabdomyosarcoma panel (median rIC50 5.6 µM) and higher values for the neuroblastoma panel (median rIC50 19.5 µM). XL147 showed higher sensitivity for the rhabdomyosarcoma cell lines and lower sensitivity for the neuroblastoma cell lines.

Animal experiment [1,2]:

Animal models Solid glioma xenografted mouse model

Dosage form Oral administration, 100 mg/kg, daily for 14 days

Application In BALB/c nu/nu mice, Pilaralisib (100 mg/kg, p.o.) induced tumor growth inhibition for solid glioma xenografts. Pilaralisib was well tolerated, with only 0.7% toxicity rate in the treated groups. In athymic female mouse, Pilaralisib (100 mg/kg, p.o.) significantly delayed tumor growth without significant drug-related toxicity.

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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]. Reynolds C P, Kang M H, Carol H, et al. Initial testing (stage 1) of the phosphatidylinositol 3' kinase inhibitor, SAR245408 (XL147) by the pediatric preclinical testing program[J]. Pediatric blood & cancer, 2013, 60(5): 791-798.
- [2]. Chakrabarty A, Sánchez V, Kuba M G, et al. Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors[J]. Proceedings of the National Academy of Sciences, 2012, 109(8): 2718-2723.

Background

XL147 is a potent and orally active inhibitor that targets Class I PI3Ks with IC₅₀ values in the nanomolar level. It has PI3K inhibition activities with IC₅₀ of 39,383,36, and 23nM for PI3K α , PI3K β , PI3K δ ,PI3K γ , respectively.[1]

PI3Ks are a family of enzymes, which phosphorylate the 3'- OH position of the inositol ring of phosphoinositides.PI3Ks are divided into three classes based on structural features and in vitro lipid substrate specificity. The three class-Ia PI3K (p110 α / β / δ) and the sole class-Ib PI3K (p110 γ) couple growth factor receptors and G-protein-coupled receptors, respectively, to a wide range of downstream pathways. Signal transduction via the PI3K/Akt pathway is essential for regulating cellular functions, including proliferation, survival, migration, motility and tumorigenesis, in a variety of cell types. XL147 is a reversible ATP-competitive inhibitor, yet is highly selective against over 130 human protein kinases.[1]

MCF7 and PC-3 cell lines were treated with XL147 led to a reduction in the levels of phosphatidylinositol-3,4,5-tris-phosphate (PIP3) and decline in phosphorylation of AKT and ribosomal S6 protein, which are two downstream effectors of PI3K signaling. Furthermore, XL147 demonstrates potent anti-angiogenic effects in tubule formation driven by vascular endothelial growth factor and potent inhibition of cell migration stimulated by hepatocyte growth factor . [1]

Oral administration of XL147 results in eminent inhibition of tumor growth in mice bearing xenografts

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in which PI3K signaling is activated, including the PTEN-deficient PC-3 prostate adenocarcinoma and MDA-MB-468 breast adenocarcinoma models, and the K-Ras activated Calu-6 non-small cell lung carcinoma model. These effects on pathway signaling correlate with inhibiting tumor cell proliferation, inhibiting tumor angiogenesis, and inducing apoptosis as determined by immunohistochemical analysis. Moreover, combining XL147 in these models with other mTOR/Raptor inhibitors, such as the chemotherapeutic agents paclitaxel and carboplatin, results in enhanced anti-tumor efficacy associated with a substantial increase in apoptosis when compared to the individual agents alone. [2]

References:

1. Shapiro G, Edelman G, Calvo E, et al. Targeting aberrant PI3K pathway signaling with XL147, a potent, selective, and orally bioavailable PI3K inhibitor[J]. *Proc 97th Annu Meet AACR*, 2007: 14-18.
2. Traynor A M, Kurzrock R, Bailey H H, et al. A phase I safety and pharmacokinetic (PK) study of the PI3K inhibitor XL147 (SAR245408) in combination with paclitaxel (P) and carboplatin (C) in patients (pts) with advanced solid tumors[J]. *J Clin Oncol*, 2010, 28(15s): 3078.

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