

Product Data Sheet

Product Name: XL765
Cat. No.: GC12336

Chemical Properties

Cas. No. 1123889-87-1

Chemical Name N-[4-[[3-(3,5-dimethoxyanilino)quinoxalin-2-yl]sulfamoyl]phenyl]-3-methoxy-4-methylbenzamide

SMILES CC1=C(C=C(C=C1)C(=O)NC2=CC=C(C=C2)S(=O)(=O)NC3=NC4=CC=CC=C4N=C3NC5=CC(=CC(=C5)OC)OC)OC

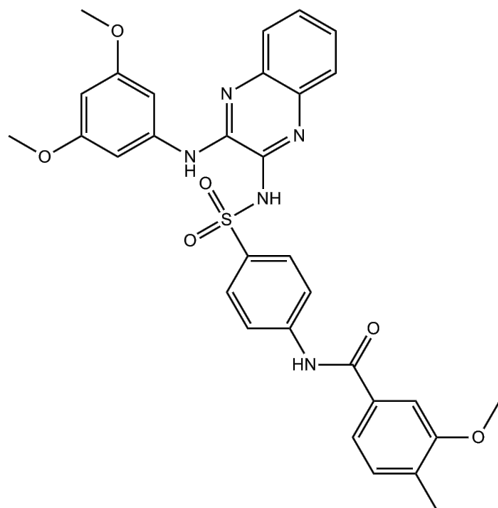
Formula $C_{31}H_{29}N_5O_6S$ M.Wt 599.67

Solubility DMSO : 16 mg/mL (59.20 mM; Need 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

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

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Cell experiment: Cellular proliferation is assessed using the Cell Proliferation ELISA, Bromodeoxyuridine Chemiluminescence Kit. Cytotoxicity is assessed using the ATP Bioluminescence Assay as follows: PC-3, MCF7, A549, LS174T, MDA-MB-468, U87-MG, and OVCAR-3 cells are plated at densities of 7×10^3 , 1.5×10^4 , 6×10^3 , 7×10^3 , 7×10^3 , 6×10^3 , 1.5×10^4 cells per well, respectively, onto 96-well microtiter plates in culture medium, incubated at 37°C, 5% CO₂ for 18 hours, and then treated with a serial dilution of compound in medium containing a final concentration of 0.3% DMSO. Triplicate wells are used for each compound concentration. Control wells receive 0.3% DMSO in media. Cultures are incubated at 37°C, 5% CO₂ for an additional 24 hours and cells are then assayed for viability using the ViaLight HS Kit[2].

Animal experiment: Mice[2] In vivo efficacy studies are performed in athymic nude mice. Tumor cells are cultured in DMEM supplemented with 10% FBS (20% for PC-3 and OVCAR-3 cells), Penicillin-Streptomycin, and nonessential amino acids at 37°C in a humidified 5% CO₂ atmosphere. On day 0, cells are harvested by brief trypsinization, and 1 to 5×10^6 cells in 0.1 mL ice-cold Hanks Balanced Salt Solution are implanted subcutaneously (OVCAR-3) or intradermally (MCF7 and U-87 MG) into the hind flank of female athymic nude mice. In the case of the MCF7 model, an estrogen pellet (IRA) is implanted subcutaneously at the nape of neck at the time of tumor cell implantation. A total of 3×10^6 PC-3 cells are similarly harvested and implanted subcutaneously into the hind-flank of 5- to 8-week-old male nude mice. Tumor growth is monitored weekly with calipers until staging and dose initiation. During the dosing period, body and tumor weights are assessed. Voxtalisib (XL-765) is formulated in sterile water/10 mM HCl or water and administered at the indicated doses and regimens by oral gavage at a dose volume of 10 mL/kg.

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References:

- [1]. Garcia-Echeverria C, et al. Drug discovery approaches targeting the PI3K/Akt pathway in cancer. *Oncogene*. 2008 Sep 18;27(41):5511-26.
- [2]. Yu P, et al. Characterization of the activity of the PI3K/mTOR inhibitor XL765 (SAR245409) in tumor models with diverse genetic alterations affecting the PI3K pathway. *Mol Cancer Ther*. 2014 May;13(5):1078-91.

Background

XL765 is a potent inhibitor of PI3Ks with IC₅₀ values 39, 113, 43, 9 nM for p110 α , β , δ , γ and 190, 908 nM for mTORC1, and mTORC2 respectively. [1]

The phosphoinositide-3 kinase (PI3K) pathway has been identified as an important target in breast cancer research. The PI3K pathway is integral to diverse cellular activities, including cellular metabolism and proliferation, survival, and differentiation. Besides, mTOR also acts as the nexus of signaling pathways regulating cell growth and proliferation. By inhibiting these targets, XL765 is thought to contribute to resistance to a variety of anticancer therapies. [2]

XL765 inhibits all four class I PI3K isoforms and mTOR with IC₅₀ values in the nanomolar range in biochemical assays, whereas is highly selective against a panel of over 130 other human kinases. XL765 exhibits inhibition of PI3K-dependent production of the second messenger PIP₃, and mTOR-dependent signaling stimulated by nutrient in cellular assays. Moreover, XL765 inhibits PI3K and mTOR-dependent phosphorylation of key components in the PI3K pathway including AKT, the substrates of AKT PRAS40 and GSK3 β , p70S6K, the p70S6K substrate S6, and 4E-BP1 in diverse cancer cells. [1,3]

Treatment of XL765 to mice bearing xenografts of PIK3CA mutant MCF-7 breast adenocarcinoma cells or PTEN-deficient PC-3 prostate adenocarcinoma cells resulted in significant inhibition of PI3K and mTOR signaling. XL765 significantly decreased tumor growth or caused tumor shrinkage in different xenograft tumor models, including brain, lung, breast, ovarian, and prostate cancers which were correlated with inhibition of tumor cell proliferation and tumor angiogenesis, and with induction of apoptosis. However, rapamycin inhibited proliferation caused little or no induction of apoptosis. These results demonstrate that a dual inhibitor strategy, targeting both PI3K and mTOR, may offer significant advantages over specifically targeting the mTOR/Raptor complex. XL765 is currently undergoing a Phase I clinical trial in patients with solid tumors.[3]

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1. Braña I, LoRusso P, Baselga J, et al. A Phase 1 dose-escalation study of the safety, pharmacokinetics and pharmacodynamics of XL765 (SAR245409), a PI3K/TORC1/TORC2 inhibitor administered orally to patients with advanced malignancies[J]. *bid*, 2010, 16: 5.
2. Baselga J. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer[J]. *The oncologist*, 2011, 16(Supplement 1): 12-19.
3. Laird A D. XL765 targets tumor growth, survival, and angiogenesis in preclinical models by dual inhibition of PI3K and mTOR[J]. *Molecular Cancer Therapeutics*, 2007, 6(11 Supplement): B250-B250.

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