For Research Use Only

Pictilisib

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Catalog Number: CM05949

产品信息

Catalog Number:
CM05949

CAS号:
957054-30-7

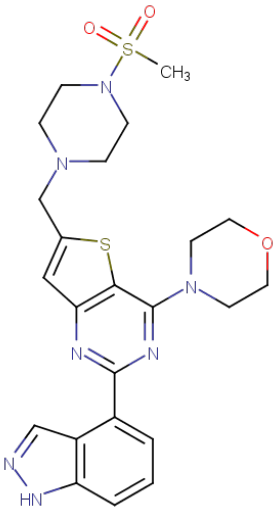
分子式:
$C_{23}H_{27}N_7O_3S_2$

主要靶点:
Apoptosis|Autophagy|PI3K

主要通路:
凋亡|PI3K/Akt/mTOR 信号通路|自噬

分子量:
513.64

溶解度:
Ethanol:< 1 mg/mL (insoluble or slightly soluble);H2O:< 1 mg/mL (insoluble or slightly soluble);DMSO:41 mg/mL (79.82 mM)



靶点活性

p110α:3 nM (cell free)|p110δ:3 nM (cell free)|p110β:33 nM (cell free)

体外活性

Pictilisib是这些细胞系中细胞增殖的强效抑制剂，具有亚μM级的IC50。在U87MG、PC3和MDA-MB-361细胞中观察到对Akt (Ser473) 磷酸化的强效抑制，其IC50分别为46、37和28 nM [1]。与单一化合物治疗相比，Pictilisib和多西他赛联合使用在体外测试的乳腺癌细胞系中减少了80%以上的肿瘤细胞存活率。在MDA-MB-453细胞系中计算出的Bliss和为0，表明了添加效应的组合效果，而其他肿瘤细胞系计算出的Bliss和>0，表明了协同效应 [2]。使用250 nM Pictilisib处理2小时，在所有测试的细胞系中pAKT的抑制率为40%-85%。Pictilisib通过剂量依赖性降低细胞增殖/存活率来抑制PI3K/AKT途径。Pictilisib抑制了曲妥珠单抗敏感和不敏感细胞的生长。Pictilisib的IC50值在150到950 nM之间，与曲妥珠单抗的敏感性无关 [3]。

体内活性

给携带MCF7-neo/HER2乳腺癌异种移植瘤的动物以7.5 mg/kg 的docetaxel或150 mg/kg的Pictilisib治疗，分别导致肿瘤生长延迟和肿瘤停滞。100 mg/kg的Pictilisib与docetaxel的联合使用在治疗期间导致肿瘤停滞，并在停药后持续维持[2]。AZD8055 (20mg/kg)或Pictilisib (75mg/kg)的给药引起血糖水平的短暂上升。无论是AZD8055还是Pictilisib的治疗均显著抑制了Akt的活性及其Thr308和Ser473的磷酸化。AZD8055或GDC-941还抑制了Akt底物PRAS40和Foxo-1/3a的磷酸化[4]。

动物实验

Female nu/nu mice were inoculated subcutaneously with MCF7-neo/HER2 or MX-1 breast cancer cells. When tumors reached a mean volume of 200 to 250 mm3, animals were size-matched and distributed into groups consisting of 10 animals per group. Docetaxel formulated in 3% EtOH, 97% saline was administered intravenously once weekly. GDC-0941, formulated in MCT (0.5% methylcellulose, 0.2% Tween-80) was dosed orally and daily. MAXF1162 is a HER2+/ER+/PR+ patient-derived breast cancer tumor xenograft model established by directly implanting tumors subcutaneously from patient to NMRI nu/nu mice. Tumor volume was calculated as follows: tumor size (mm3) = (longer measurement × shorter measurement2) × 0.5. Tumor sizes were recorded twice weekly over the course of a study. Following data analysis, P values were determined using the Dunnett t test. For pharmacodynamic studies, tumor samples (n = 4) were immediately frozen or fixed in 10% neutral-buffered formalin. Tumors were dissociated in cell extraction buffer, and lysates were analyzed by Western blotting as described above. Immunohistochemistry was conducted using 5- μm paraffin sections of formalin-fixed tissue on a Ventana Benchmark XT instrument by deparaffinization, treatment with antigen retrieval buffer, and incubation with anti-cleaved caspase-3 primary antibody at 37°C. Bound antibody was detected using DABMap technology, and sections were counterstained with hematoxylin [2].

细胞实验

All drug treatments were tested in quadruplicate during a 4-day incubation period, and the relative number of viable cells was estimated using CellTiter-Glo. Total luminescence was measured on a Wallac Multilabel Reader. Cells were treated simultaneously with docetaxel (dose range = 0.0003–0.020 μmol/L) or GDC-0941 (dose range = 0.083–5 μmol/L) in an 8 × 10 matrix of concentrations chosen to encompass clinically relevant doses (24). The concentration of drug resulting in EC50 was determined using Prism software. Combination synergy of GDC-0941 and docetaxel was determined by Bliss independence analyses. A Bliss expectation for a combined response (C) was calculated by the equation: C = (A + B) ? (A × B) where A and B are the fractional growth inhibitions of drug A and B at a given dose. The difference between the Bliss expectation and the observed growth inhibition of the combination of drugs A and B at the same dose is the 'Delta.Bliss.' Delta.Bliss scores were summed across the dose matrix to generate a Bliss sum. Bliss sum = 0 indicates that the combination treatment is additive (as expected for independent pathway effects); Bliss sum > 0 indicates activity greater than additive (synergy); and Bliss sum < 0 indicates the combination is less than additive (antagonism). Statistical analysis comparing the Bliss sums for each cell line was conducted by the Student t-test [2].

储存

Powder: -20°C for 3 years | In solvent: -80°C for 1 year | Shipping with blue ice.