For Research Use Only

Vismodegib

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Catalog Number: CM00628

产品信息

Catalog Number:
CM00628

CAS号:
879085-55-9

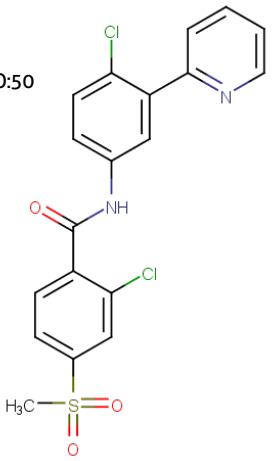
分子式:
$C_{19}H_{14}Cl_2N_2O_3S$

主要靶点:
ABC|Hedgehog/Smoothened|Autophagy

主要通路:
干细胞|G 蛋白偶联受体|离子通道|自噬

分子量:
421.3

溶解度:
Ethanol:Insoluble;H2O:Insoluble;DMSO:50 mg/mL (118.68 mM)



靶点活性

Hedgehog:3 nM (cell free)|P-gp:3.0 μM|ABCG2:1.4 μM

体外活性

Vismodegib (GDC-0449) 是针对两种ABC转运蛋白，ABCG2/BCRP 和 ABCB1/Pgp 的强效抑制剂，并对 ABCC1/MRP1 表现出温和的抑制作用。在过表达ABCG2 的HEK293细胞中，Vismodegib 增加了荧光ABCG2底物BODIPY-prazosin的保留，并使这些细胞重新对抗肿瘤药物mitoxantrone敏感。此外，Vismodegib 还使过表达ABCG2的人类非小细胞肺癌细胞 NCI-H460/par 和 NCI-H460/MX20 对mitoxantrone、topotecan 或 SN-38 重新敏感。Vismodegib 抑制ABCG2 和 Pgp 的IC(50) 值分别约为1.4 μM 和约 3.0 μM [2]。在对顺铂敏感和耐药的细胞中，GDC-0449 均抑制了细胞生长。在这两种细胞类型中，GDC-0449 增加了[Ca(2+)](cyto) 并减少了内质网中的[Ca(2+)](ER) [3]。

体内活性

经口给予vismodegib在Ptch(+/-)同种异体移植的小脑髓质瘤模型中，当剂量≥25 mg/kg时可引起肿瘤退缩。在两种配体依赖的CRC模型D5123和1040830中，vismodegib剂量高达92 mg/kg并每日两次给药时可抑制肿瘤生长。通过分析Hh通路活性和PK/PD建模显示，vismodegib在这两种模型中抑制Gli1的IC(50)相似（分别为0.165 μmol/L ±11.5%和0.267 μmol/L ±4.83%）。该路径调控与疗效的关联通过一个整合的PK/PD模型揭示，其中vismodegib活性> 50%与Hh路径>80%的抑制呈陡峭关系[4]。

动物实验

Female CD-1 nude mice (weighing 25–28 g) were administered oral doses of 5, 15, 50, and 100 mg/kg (free base equivalent) of vismodegib hydrochloride salt in 0.5% methylcellulose/0.2% Tween 80 (MCT). Blood samples (~1 mL) were collected up to 24 hours postdose via cardiac puncture (terminal collection) into tubes containing potassium ethylenediaminetetraacetic acid (K2EDTA) anticoagulant. Immediately on the collection, the blood was mixed with K2EDTA and stored on ice. Within 30 minutes, blood samples were centrifuged at approximately 1000 to 1500 × g for 5 minutes at 4°C, and plasma was harvested. The plasma samples were stored at ?80°C until analysis. Concentrations of vismodegib were determined by LC/MS/MS as described previously [4].

细胞实验

MDCKII cells were plated into 24-well plates at a density of 3 x 10^5 cells per well and were allowed to attach. The medium was then changed to that containing different drugs (50 μM VP, 50 μM indomethacin, or 20 μM Vismodegib) in DMSO or DMSO alone as control, and nonfluorescent calcein-AM was added to a final concentration of 1.0 μM and incubated at 37°C for 2 hours. Cells were then washed twice with Ca2+, Mg2+-containing Hank's balanced salt solution buffer and lysed by shaking in 0.01% Triton X-100 in PBS buffer for 1 hour at room temperature or overnight at 4°C. The lysate was then transferred into 96-well plates, and the fluorescence signal caused by the cell-derived calcein was quantified spectrophotometrically with a SpectraMax M5 Multi-Detection Reader using an excitation wavelength of 495 nm and an emission wavelength of 515 nm. All manipulations were performed in the dark. All readings are expressed as mean ± SEM normalized to the control [2].

储存

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