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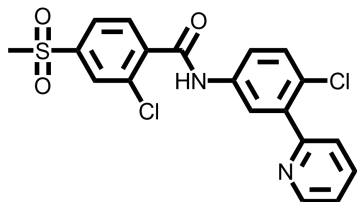
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GDC-0449 (Vismodegib) --- Hedgehog Antagonist

Chemical Name: 2-Chloro-N-(4-chloro-3-pyridin-2-ylphenyl)-4-methylsulfonylbenzamide



Molecular Weight:	421.30
Formula:	C ₁₉ H ₁₄ Cl ₂ N ₂ O ₃ S
Purity:	≥98%
CAS#:	879085-55-9
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

Vismodegib (GDC-0449) is a potent and specific hedgehog pathway inhibitor with an IC₅₀ of 3 nM. It has been approved by FDA to treat BCC, and also in multiple clinical trials to treat advanced solid tumors. It blocks the activities of the Hedgehog-ligand cell surface receptors PTCH and/or SMO and suppressing Hedgehog signaling. It prevents multiple ATP-binding cassette (ABC) transporters. GDC-0449 also exhibited efficacy in medulloblastoma animal models and primary pancreatic cancer xenograft models. It was shown to inhibit cell growth in cisplatin-resistant lung cancer cells.

How to Use:

In vitro: GDC-0449 was used at 5-10 μM concentration in the cellular assays.

In vivo: GDC-0449 was dosed orally 12.5 mg/kg twice per day (lowest dose), up to 100 mg/kg twice per day (formulated as a suspension in 0.5% methylcellulose, 0.2% Tween-80 (MCT))

Reference:

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2. Yauch RL, et al. Smoothed mutation confers resistance to a Hedgehog pathway inhibitor in medulloblastoma. (2009) *Science* 326(5952):572-4.
3. LoRusso PM, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. (2011) *Clin Cancer Res.* 17(8):2502-11
4. Giannetti AM, et al. Identification, characterization, and implications of species-dependent plasma protein binding for the oral Hedgehog pathway inhibitor vismodegib (GDC-0449). (2011) *J Med Chem.* 54(8):2592-601
5. Lorusso PM, et al. Pharmacokinetic dose-scheduling study of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors. (2011) *Clin Cancer Res.* 17(17):5774-82
6. Philips GM, et al. Hedgehog signaling antagonist promotes regression of both liver fibrosis and hepatocellular carcinoma in a murine model of primary liver cancer.(2011) *PLoS One.* 6(9):e23943.
7. Metcalfe C, et al. Hedgehog fights back: mechanisms of acquired resistance against Smoothed antagonists. (2011) *Cancer Res.* 71(15):5057-61.
8. Singh BN, et al. Hedgehog signaling antagonist GDC-0449 (Vismodegib) inhibits pancreatic cancer stem cell characteristics: molecular mechanisms. (2011) *PLoS One.* 6(11):e27306
9. Tian F, et al. The hedgehog pathway inhibitor GDC-0449 alters intracellular Ca²⁺ homeostasis and inhibits cell growth in cisplatin-resistant lung cancer cells. (2012) *Anticancer Res.* 32(1):89-94

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