

Product Data Sheet

Product Name: V-9302
Cat. No.: GC34852

Chemical Properties

Cas. No. 1855871-76-9

SMILES O=C(O)[C@H](N)CCN(CC1=CC=CC=C1OCC2=CC=CC(C)=C2)CC3=CC=CC=C3OCC4=CC=CC(C)=C4

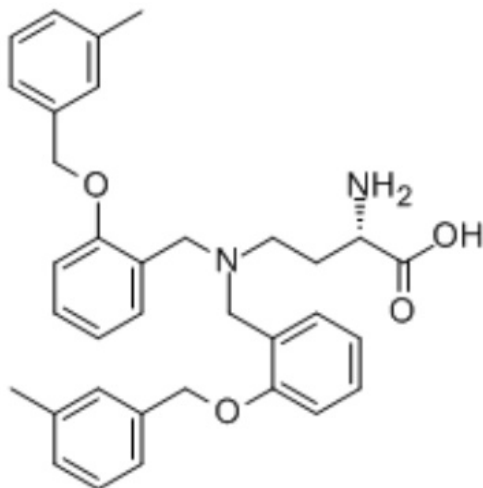
Formula $C_{34}H_{38}N_2O_4$ M.Wt 538.68

Solubility DMSO : 125 mg/mL (232.05 mM); Water : < 0.1 mg/mL (insoluble) 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

Cell experiment [1]:

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Cell lines HCC1806 cells

Preparation Method Cells were plated in 96-well plates for 24 h before the assay. Cells were treated with either vehicle or the indicated concentrations (25 μ M) of V-9302 hydrochloride for 48 h

Reaction Conditions 25 μ M, 48h

Applications Silencing of ASCT2 and V-9302 hydrochloride exposure in HCC1806 cells resulted in analogous downstream effects, including markedly decreased phosphorylated (p)-S6 levels and a modest decrease in p-ERK levels.

Animal experiment [2]:

Animal models 6-week-old female athymic nude mice

Preparation Method Chronic-exposure studies in tumor-bearing mice. Athymic nude mice (Hsd:Athymic nude-Foxn1nu) bearing HCT-116 (KRAS-G13D) or HT29 (BRAF-V600E) cell line xenografts were treated with 75 mg V-9302 hydrochloride per kg body weight per day for 21 d.

Dosage form 75 mg V-9302 hydrochloride per kg body weight per day for 21 day

Applications V-9302 hydrochloride led to significantly decreased expression of p-S6 in tumor tissue in both HCT-116 and HT29 xenografts. In addition to decreased p-S6 IHC staining, V-9302 treatment led to elevated levels of cleaved caspase 3 in both HCT-116 and HT29 xenografts.

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References:

[1]. Schulte ML, Fu A, et.al. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. Nat Med. 2018 Feb;24(2):194-202. doi: 10.1038/nm.4464. Epub 2018 Jan 15. PMID: 29334372; PMCID: PMC5803339.

Background

V-9302 hydrochloride is a competitive antagonist of transmembrane glutamine flux. V-9302 hydrochloride selectively and potently targets the amino acid transporter ASCT2 (SLC1A5) not ASCT1^[1].

V-9302 hydrochloride inhibits ASCT2-mediated glutamine uptake ($IC_{50}=9.6\ \mu M$) in HEK-293 cells. V-9302 hydrochloride inhibits ASCT2-mediated glutamine uptake in human cells in a concentration-dependent fashion. Treatment of HCC1806 cells with V-9302 hydrochloride resulted in a significant decrease in downstream levels including phosphorylated (P)-S6 and a moderate decrease in P-ERK levels, similar to knockdown of ASCT2^[1]. Pharmacological blockade of ASCT2 with V-9302 hydrochloride resulted in attenuated cancer cell growth and proliferation, increased cell death, and increased oxidative stress^[1]. The phosphorylation levels of the mTOR, S6K, and S6 proteins were reduced by treatment with 20 μM of V-9302 hydrochloride in SKOV3-TR cells, indicating that V-9302 hydrochloride effectively inhibited the mTORC1/S6K signaling pathway^[2]. As the glutamine transporter inhibitor, V-9302 hydrochloride suppresses tumor growth and increases T lymphocyte activation in a model of TNBC^[5]

In vivo, steady-state plasma concentrations were achieved at 4 h post-administration with a half-life of approximately 6 h in healthy mice. Besides, using anhyemic nude mice bearing HCT-116 or HT29 cell line xenografts, V-9302 hydrochloride prevented tumor growth. V-9302 hydrochloride led to significantly decreased expression of p-S6 in tumor tissue in both HCT-116 and HT29 xenografts. In addition to decreased p-S6 IHC staining, V-9302 hydrochloride treatment led to elevated levels of cleaved caspase 3^[1]. In vivo xenograft tumor model of MDA-MB-231 cells, tumor growth was inhibited by V-9302 hydrochloride alone, and further inhibited by combination of V-9302 hydrochloride with other inhibitor^[3]. The combination of CB-839 and V-9302 hydrochloride elicits a strong growth

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inhibition in both SNU398 and MHCC97H xenograft models, while single-drug treatment showed modest anti-tumor effects^[4]. ASCT2 inhibitor V-9302 hydrochloride may have influence in Alanine uptake in MRI^[7]. Blockade of glutamine uptake using V9302 hydrochloride combined mTORC1/2 inhibitor AZD2014 blocking the interaction between HDAC3 and GS not only significantly delayed the tumor growth but also resulted in partial or even complete tumor regression ^[6]

References:

- [1]. Schulte ML, Fu A, et.al. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. Nat Med. 2018 Feb;24(2):194-202. doi: 10.1038/nm.4464. Epub 2018 Jan 15. PMID: 29334372; PMCID: PMC5803339.
- [2]. Kim G, Jang SK, et.al. Inhibition of Glutamine Uptake Resensitizes Paclitaxel Resistance in SKOV3-TR Ovarian Cancer Cell via mTORC1/S6K Signaling Pathway. Int J Mol Sci. 2022 Aug 6;23(15):8761. doi: 10.3390/ijms23158761. PMID: 35955892; PMCID: PMC9369036.
- [3]. Zhou Q, Lin W, et.al. Neddylation inhibition induces glutamine uptake and metabolism by targeting CRL3SPOP E3 ligase in cancer cells. Nat Commun. 2022 May 31;13(1):3034. doi: 10.1038/s41467-022-30559-2. Erratum in: Nat Commun. 2022 Jun 14;13(1):3424. PMID: 35641493; PMCID: PMC9156729
- [4]. Jin H, Wang S, et.al. A powerful drug combination strategy targeting glutamine addiction for the treatment of human liver cancer. Elife. 2020 Oct 5;9:e56749. doi: 10.7554/eLife.56749. PMID: 33016874; PMCID: PMC7535927.
- [5]. Edwards DN, Ngwa VM, et.al. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. J Clin Invest. 2021 Feb 15;131(4):e140100. doi: 10.1172/JCI140100. PMID: 33320840; PMCID: PMC7880417.
- [6]. Zhang HL, Chen P, et.al. Targeting mTORC2/HDAC3 Inhibits Stemness of Liver Cancer Cells Against Glutamine Starvation. Adv Sci (Weinh). 2022 Jul;9(20):e2103887. doi: 10.1002/advs.202103887. Epub 2022 Feb 20. PMID: 35187863; PMCID: PMC9284171.
- [7]. Yang SH, Choi Y, et.al. MRI measurement of alanine uptake in a mouse xenograft model of U-87 MG glioblastoma. Magn Reson Imaging. 2022 Aug 24;93:189-194. doi: 10.1016/j.mri.2022.08.015. Epub ahead of print. PMID: 36029935.

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