

Product Data Sheet

Product Name: GPNA hydrochloride

Cat. No.: GC39489

Chemical Properties

Cas. No. 67953-08-6

SMILES OC([C@@H](N)CCC(NC1=CC=C([N+])([O-])=O)C=C1)=O)=O.[H]Cl

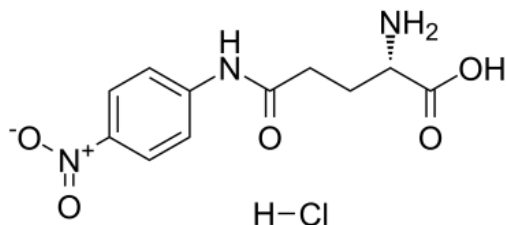
Formula $C_{11}H_{14}ClN_3O_5$ M.Wt 303.7

Solubility DMSO: 125 mg/mL (411.59 mM) Storage Store at 2-8°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]:

Cell lines Ishikawa, HEC1A, and KLE (human endometrial cancer cell lines)

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Cells were cultured in DMEM:F12 media containing 10% FBS at 37°C, 5% CO₂. For 3D spheroid culture, cells were plated in Matrigel-coated chambers with Preparation Method specific media for 8 days. The cell treatment with 1mM GPNA hydrochloride for 24 hours for cell viability and flow cytometry assays; 1mM GPNA hydrochloride during 8 days of spheroid culture for 3D spheroid assays.

Reaction Conditions 1mM; 24 hours or 8 day

Applications GPNA hydrochloride decreased cell viability in Ishikawa, HEC1A, and KLE cell lines. In 3D spheroid cultures, GPNA hydrochloride reduced spheroid cross-sectional area in Ishikawa and HEC1A cells.

Animal experiment [2]:

Animal models BALB/c nude mice

Preparation Method Mice were randomly divided into 4 groups (5 mice per group) and BGC803 cells ($\sim 5 \times 10^6$) were implanted subcutaneously at the right flanks of mice. Once the tumor volume reached $\sim 200\text{mm}^3$, the following treatments were administered: control group received PBS injection; cetuximab group received intraperitoneal injection of cetuximab at a dose of 1mg/mouse twice a week for 3 weeks; GPNA hydrochloride group received intraperitoneal injection of GPNA hydrochloride at a dose of 50mg/kg body weight every day; combined group received treatment with GPNA hydrochloride + cetuximab.

Dosage form 50mg/kg; i.p.

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Applications GPNA hydrochloride treatment significantly reduced tumor weight and volume in mouse xenografts with BGC803 cells. Combined treatment with GPNA hydrochloride and cetuximab further suppressed tumor growth compared to single treatment, demonstrating that combined blockage of glutamine uptake and EGFR significantly inhibited the proliferation of gastric cancer.

References:

- [1] Marshall AD, van Geldermalsen M, Otte NJ, et al. ASCT2 regulates glutamine uptake and cell growth in endometrial carcinoma. *Oncogenesis*. 2017 Jul 31;6(7):e367.
- [2] Ma H, Wu J, Zhou M, et al. Inhibition of Glutamine Uptake Improves the Efficacy of Cetuximab on Gastric Cancer. *Integr Cancer Ther*. 2021 Jan-Dec;20:15347354211045349.

Background

GPNA hydrochloride, as a substrate of γ -glutamyl transferase (GGT), can inhibit the activity of the glutamine (Gln) transporter ASCT2, with an IC₅₀ of 250 μ M^[1]. In addition, GPNA hydrochloride also inhibits the activity of the Na⁺-dependent carrier SNAT family proteins^[2] and leucine and other neutral amino acid transport carriers^[3]. Moreover, GPNA hydrochloride has the effect of inhibiting cancer development and metastasis^[4]

In vitro, treatment of Ishikawa, HEC1A, and KLE cell lines with GPNA hydrochloride (1mM) significantly inhibits cell growth. Also, GPNA hydrochloride significantly inhibits the growth of 3D spheroids in Ishikawa and HEC1A cells^[5]. When A549 cells are treated with GPNA hydrochloride (250 μ M), the compound exerts cytotoxic effects through GGT-mediated hydrolysis, resulting in reduced cell viability^[6].

In vivo, GPNA hydrochloride (50mg/kg) is intraperitoneally injected into mice to deplete endogenous glutamine levels, followed by airway challenge with ovalbumin (OVA) to induce an asthma response. Mice treated with GPNA hydrochloride show significantly enhanced airway inflammation, with significantly elevated levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Moreover, GPNA hydrochloride-treated mice also exhibit increased airway hyperresponsiveness, exacerbated

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lung tissue inflammation, and increased mucus production. GPNA hydrochloride significantly exacerbates asthma symptoms in mice, particularly neutrophil-mediated inflammatory responses^[7]. GPNA hydrochloride (50mg/kg) in combination with Cetuximab (1mg/mouse) is intraperitoneally injected twice a week for 3 weeks to treat BALB/c nude mice bearing gastric cancer cells. GPNA hydrochloride significantly inhibits the proliferation of gastric cancer cells and enhances the inhibitory effect of Cetuximab on gastric cancer^[8].

References:

- [1] Lyda BR, Leary GP, Farnsworth J, et al. Discovery and Synthesis of Hydroxy-L-Proline Blockers of the Neutral Amino Acid Transporters SLC1A4 (ASCT1) and SLC1A5 (ASCT2). *Molecules*. 2024 May 15;29(10):2330.
- [2] Freidman NJ, Briot C, Ryan RM. Characterizing unexpected interactions of a glutamine transporter inhibitor with members of the SLC1A transporter family. *J Biol Chem*. 2022 Aug;298(8):102178.
- [3] Chiu M, Sabino C, Taurino G, et al. GPNA inhibits the sodium-independent transport system L for neutral amino acids. *Amino Acids*. 2017 Aug;49(8):1365-1372.
- [4] Kong Y, Wu M, Wan X, et al. Lipophagy-mediated cholesterol synthesis inhibition is required for the survival of hepatocellular carcinoma under glutamine deprivation. *Redox Biol*. 2023 Jul;63:102732.
- [5] Marshall AD, van Geldermalsen M, Otte NJ, et al. ASCT2 regulates glutamine uptake and cell growth in endometrial carcinoma. *Oncogenesis*. 2017 Jul 31;6(7):e367.
- [6] Corti A, Dominici S, Piaggi S, et al. γ -Glutamyltransferase enzyme activity of cancer cells modulates L- γ -glutamyl-p-nitroanilide (GPNA) cytotoxicity. *Sci Rep*. 2019 Jan 29;9(1):891.
- [7] Kim JM, Im YN, Chung YJ, et al. Glutamine deficiency shifts the asthmatic state toward neutrophilic airway inflammation. *Allergy*. 2022 Apr;77(4):1180-1191.
- [8] Ma H, Wu J, Zhou M, et al. Inhibition of Glutamine Uptake Improves the Efficacy of Cetuximab on Gastric Cancer. *Integr Cancer Ther*. 2021 Jan-Dec;20:15347354211045349.

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