

## Product Data Sheet

Product Name: (R)-GNE-140

Cat. No.: GC19012

### Chemical Properties

Cas. No. 2003234-63-5

Chemical Name (13E,14E,22R,6R)-35-fluoro-6-methyl-7-aza-1(5,3)-pyrazolo[1,5-a]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one

SMILES O=C1N[C@@](C2=CSC=C2)(C3=CC=C(N4CCOCC4)C=C3)CC(O)=C1SC5=CC=CC=C5Cl

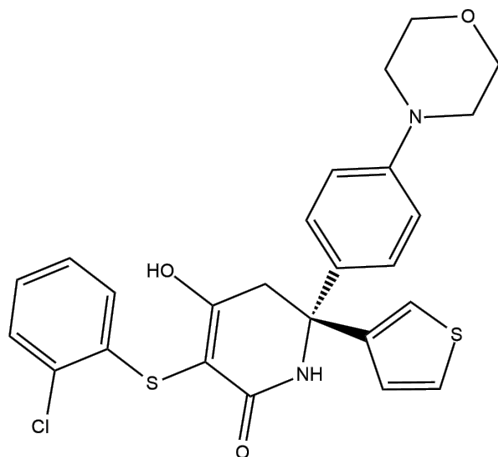
Formula  $C_{25}H_{23}ClN_2O_3S_2$  M.Wt 499.04

Solubility DMSO :  $\geq 14.43$  mg/mL (28.92 mM); Water :  $< 0.1$  mg/mL (insoluble) Storage Store at  $-20^{\circ}\text{C}$

General tips For obtaining a higher solubility, please warm the tube at  $37^{\circ}\text{C}$  and shake it in the ultrasonic bath for a while. Stock solution can be stored below  $-20^{\circ}\text{C}$  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          | NCI-237UTSW, XTC.UC1 (Hurthle cell carcinoma, HTC), TPC-1, and UTSW-354 (papillary thyroid carcinoma, PTC) cells                                                                                                                    |
| Preparation Method  | Cells were maintained in physiologic human plasma-like media (HPLM) or RPMI-1640 medium supplemented with 2% fetal bovine serum (FBS) at 37°C, 5% CO <sub>2</sub> . Cells were treated with (R)-GNE-140 at 0.041-30µM for 72 hours. |
| Reaction Conditions | 0.041-30µM; 72h                                                                                                                                                                                                                     |
| Applications        | (R)-GNE-140 treatment caused a dose-dependent decrease in proliferation and viability across all cell lines.                                                                                                                        |

### Animal experiment [2]:

|                    |                                                                                                                                                                    |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Animal models      | BALB/c mice (breast cancer model)                                                                                                                                  |
| Preparation Method | Mice were subcutaneously inoculated with 4T1 breast cancer cells and treated with (R)-GNE-140 (2.5mg/kg or 5mg/kg) via intragastric administration every two days. |
| Dosage form        | 2.5mg/kg or 5mg/kg; intragastric administration; every two days for seven doses.                                                                                   |

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### Applications

(R)-GNE-140 treatment significantly reduced tumor volume and weight in a dose-dependent manner, with the high-dose group (5mg/kg) showing more pronounced inhibition of tumor progression compared to the low-dose group (2.5mg/kg). Immunohistochemical staining of mouse tumor tissues revealed a gradient downregulation in global lactylation (Kla) levels compared to the control group.

### References:

- [1] Lee SO, Li X, Hedrick E, et al. Diindolylmethane analogs bind NR4A1 and are NR4A1 antagonists in colon cancer cells. *Mol Endocrinol*. 2014 Oct;28(10):1729-39.
- [2] Liu J, Zhao L, Yan M, et al. H4K79 and H4K91 histone lactylation, newly identified lactylation sites enriched in breast cancer. *J Exp Clin Cancer Res*. 2025 Aug 23;44(1):252.

### Background

(R)-GNE-140 is an orally active lactate dehydrogenase A (LDHA) inhibitor. (R)-GNE-140 exhibits inhibitory activity against both LDHA ( $IC_{50}=3nM$ ) and LDHB ( $IC_{50}=5nM$ ), with its (R)-isomer demonstrating higher activity compared to the S-isomer<sup>[1-2]</sup>. (R)-GNE-140 can reduce intracellular lactate levels while upregulating pyruvate content, thereby affecting the proliferation and survival of glycolysis-dependent cancer cells. (R)-GNE-140 is primarily utilized in cancer-related research<sup>[3-4]</sup>.

In vitro, pretreatment of periodontal ligament stem cells (PDLSCs) and bone marrow stromal cells (BMSCs) with (R)-GNE-140 (10 $\mu$ M) for 12 hours, followed by induction of osteogenic differentiation, (R)-GNE-140 significantly reduced cell proliferation and decreased the expression of osteogenic differentiation proteins<sup>[5]</sup>. Treatment of thyroid cancer cell lines with (R)-GNE-140 (0.041-30 $\mu$ M) for 72 hours, (R)-GNE-140 caused a dose-dependent decrease in proliferation and viability across all cell lines<sup>[6]</sup>.

In vivo, BALB/c mice inoculated with KRASG12V/MYC tumor cells were treated with low-dose (2.5mg/kg) and high-dose (5mg/kg) (R)-GNE-140 via intragastric administration (once every two days for a total of seven doses). (R)-GNE-140 (5mg/kg) significantly inhibited tumor volume and weight and reduced the expression levels of lactylated proteins (Kla)<sup>[7]</sup>. In 4T1 breast cancer-bearing

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BALB/c mice, treatment with (R)-GNE-140 (2.5mg/kg or 5mg/kg) via intragastric administration (once every two days), (R)-GNE-140 significantly reduced tumor growth rates and downregulated histone H4K79 and H4K91 lactylation modifications (H4K79la/H4K91la)<sup>[8]</sup>.

### References:

- [1] Purkey HE, Robarge K, Chen J, et al. Cell Active Hydroxylactam Inhibitors of Human Lactate Dehydrogenase with Oral Bioavailability in Mice. ACS Med Chem Lett. 2016 Aug 26;7(10):896-901.
- [2] Gong Y, Ji P, Yang YS, et al. Metabolic-Pathway-Based Subtyping of Triple-Negative Breast Cancer Reveals Potential Therapeutic Targets. Cell Metab. 2021 Jan 5;33(1):51-64.e9.
- [3] Huang Q, Sun Y, Kuang P, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles Modulate the Course of Peritoneal Inflammation Through Metabolic and Epigenetic Regulation. Adv Sci (Weinh). 2025 Nov 26:e08645.
- [4] Feng Y, Pathria G, Heynen-Genel S, et al. Identification and Characterization of IMD-0354 as a Glutamine Carrier Protein Inhibitor in Melanoma. Mol Cancer Ther. 2021 May;20(5):816-832.
- [5] Yang W, Guo Q, Quan S, et al. Impaired mitochondrial metabolism is a critical cancer vulnerability for MYC inhibitors. Sci Adv. 2025 Jul 18;11(29):eadw5228.
- [6] Frank AR, Li V, Shelton SD, et al. Mitochondrial-Encoded Complex I Impairment Induces a Targetable Dependency on Aerobic Fermentation in Hürthle Cell Carcinoma of the Thyroid. Cancer Discov. 2023 Aug 4;13(8):1884-1903.
- [7] Liu J, Wang J, Wang Z, et al. PGC-1 $\alpha$ /LDHA signaling facilitates glycolysis initiation to regulate mechanically induced bone remodeling under inflammatory microenvironment. Bone. 2024 Aug;185:117132.
- [8] Liu J, Zhao L, Yan M, et al. H4K79 and H4K91 histone lactylation, newly identified lactylation sites enriched in breast cancer. J Exp Clin Cancer Res. 2025 Aug 23;44(1):252.

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