222 Glucose Transporter Inhibitors (GLUT1 Inhibitors)

Asset Overview

Product Type	Small molecule
Indication	Oncology
Current Stage	Preclinical
Target(MoA)	Glucose Transporter Inhibitors (GLUT1 Inhibitors)
Brief Description	The Ohio State University researchers, led by Dr. Ching-Shih Chen, developed and synthesized a novel class of anticancer agents that suppress the ability of cancer cells to utilize glucose, resulting in cellular death in the cancer cells. These agents take advantage of the differences between glucose uptake rate in non-malignant and malignant cancer cells. The agents exhibited anticancer activity against androgen-insensitive prostate cancer cells, breast cancer cells, and pancreatic cancer cells. Currently, this class of glucose transporter inhibitors is in early preclinical evaluations with initial in vivo evaluations of tumor-suppressive activities in human xenograft tumor models beginning.
Organization	The Ohio State University

Differentiation

□ **The Need**

- A fundamental property of neoplastic cells is the shift in cellular metabolism from oxidative phosphorylation to aerobic glycolysis. This glycolytic shift, called the Warburg effect, enables cancer cells to adapt to low-oxygen microenvironments, to generate biosynthetic building blocks for cell proliferation, to acidify the local environment, to facilitate tumor invasion, and to generate NADPH and glutathione through the pentose phosphate shunt to increase resistance to oxidative stress. Thus, the targeting of glucose metabolism is considered an attractive therapeutic approach for cancer

□ **Benefits/Features**

- Does not exhibit cytotoxicity in non-malignant cells
- Suppresses glucose uptake in cancerous cells Influences apoptotic activity in malignant cells
- The IC-50 of the lead compound (30) has been found to be 4 uM

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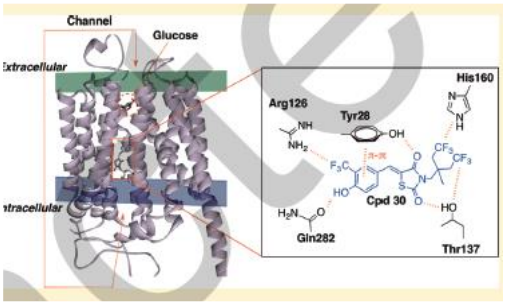
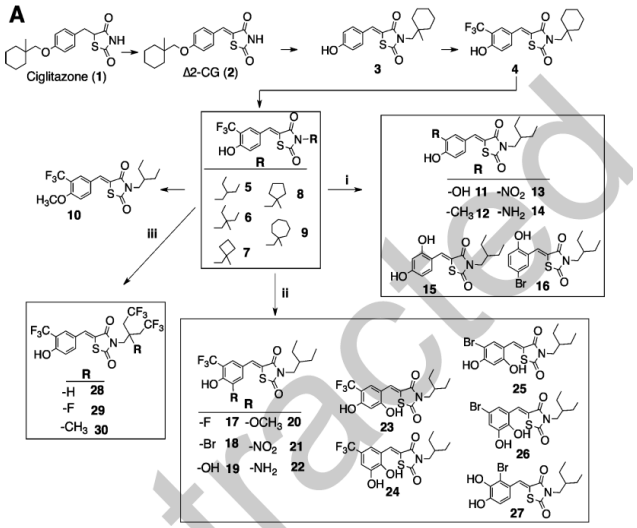
Key Data

Development of a Novel Class of Glucose Transporter Inhibitors



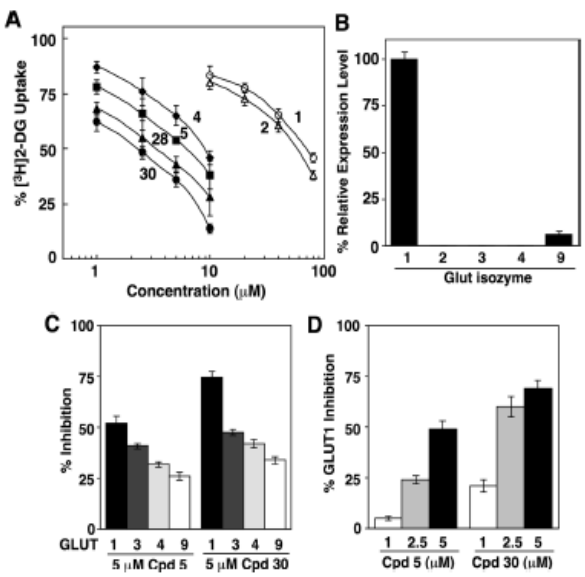


PPARγ-inactive analogue to develop a novel class of glucose transporter (GLUT) inhibitors.

Chemical compopunds 1-30 in the 5-{4-[(1-methylcyclohexyl)methoxy]benzyl}thiazolidine-2,4-dione-based focused compound.

J Med Chem. 2012 Apr 26;55(8):3827-36.

Suppression of Glucose Uptake through the Inhibition of Glucose Transporters



(A) Dose-dependent inhibitory effects of compounds 1, 2, 4, 5, 28, and 30 on the uptake of [3H]-2-DG into LNCaP cells in Krebs−Ringer phosphate buffer at 37 °C after 30 min of drug treatment. Points, mean; bars, SD (N = 3). (B) Quantitative real-time PCR analysis of the differential expression of GLUT1−4 and GLUT9 in LNCaP cells. Column, mean; bars, SD (N = 3). (C) Suppressive effects of compounds 5 and 30, each at 5 μM, on [3H]-2-DG uptake into LNCaP cells overexpressing GLUT1, GLUT3, GLUT4, or GLUT9. The analysis was carried out in Krebs−Ringer phosphate buffer at 37 °C after 30 min of drug treatment. Column, mean; bars, SD (N = 3). (D) Dose-dependent suppressive effects of compound 5 and 30 on [3H]-2-DG uptake into LNCaP cells overexpressing GLUT1. Column, mean; bars, SD (N = 3).

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Cancer selectivity and regulation of signaling pathway

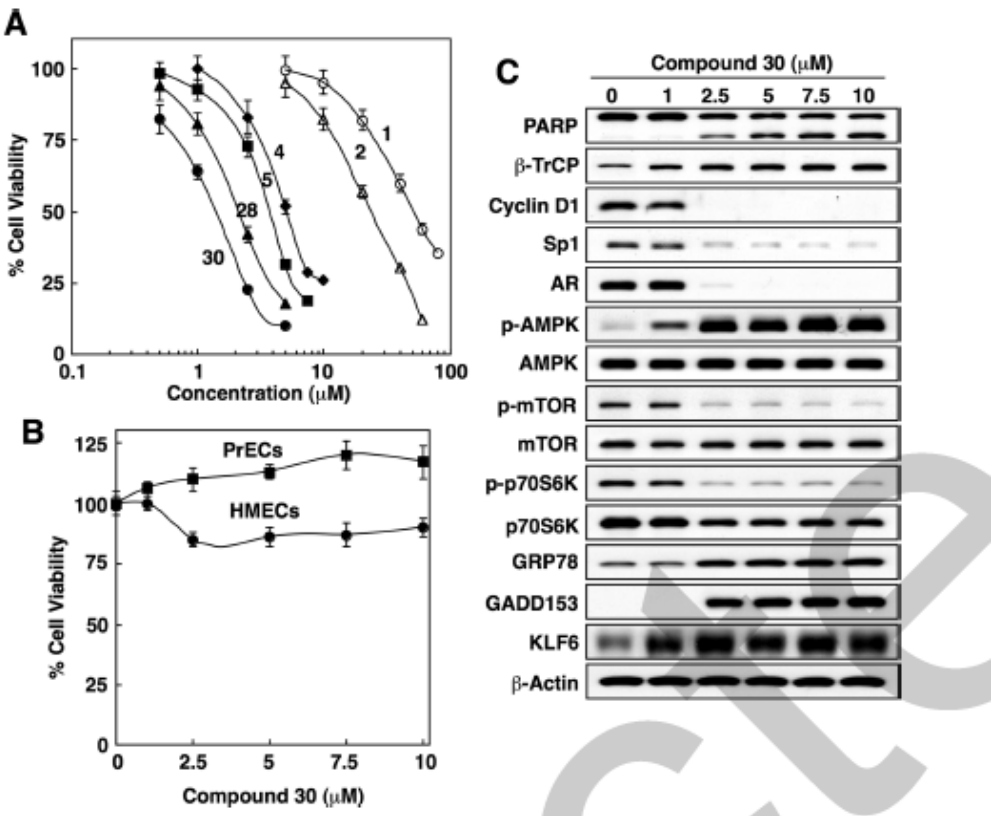

Figure 4. (A) Dose-dependent suppressive effects of compounds 1, 2, 4, 5, 28, and 30 on the viability of LNCaP cells by MTT assays in 10% FBS containing RPMI 1640 medium after 72 h of drug treatment. Points, mean; bars, SD (N = 6). (B) Dose-dependent effect of compound 30 on the viability of normal prostate epithelial cells (PrECs) and human mammary epithelial cells (HMECs) after 72 h of treatment. Points, mean; bars, SD (N = 6). (C) Western blot analysis of the dose-dependent effects of compound 30 on markers associated with apoptosis (PARP cleavage), β-TrCP mediated protein degradation (β-TrCP, cyclin D1, Sp1, and AR), AMPK activation (p-AMPK, p-mTOR, and p-p706SK), ER stress (GRP78 and GADD153), and epigenetic activation of KLF6. Journal of Medicinal Chemistry Article 3832 dx.doi.org/10.1021/jm300015m| J. Med. Chem. 2012, 55, 3827−3836

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Intellectual Property

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Country	US, EP, JP, CA, AU

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