292 GLUT 1/3 inhibitor

Asset Overview

Product Type	Small Molecule
Indication	Oncology, Immunology
Current Stage	Hit
Target(MoA)	GLUT1 and GLUT3 inhibition
Brief Description	Inhibition of glucose transporters (such as GLUT1 and GLUT3) can increase proliferation of effector T cells while immunosuppressive regulatory T cells are not affected. Simultaneous inhibition of more than one glucose transporter target is critical for achieving adequate immunoregulatory function by inhibitors as GLUTX response regulation makes single-target inhibitor insufficient. Inhibition of glucose transporter can lead to starvation and eventual cancer cell death.
Organization	Lead Discovery Center

Differentiation

□ **Target rationale**

- Immunometabolism of T effector cells allows to reduce proliferation by blocking glucose transporters , while T regulatory cells are not impacted
- Selective Glut1 inhibition is not sufficient due to GlutX response regulation → need for dual Glut1/3

□ **Key achievements**

- Identification of selective small molecule inhibitors of glucose uptake (2 prioritized hit series)
- Effect on T cell proliferation shown in vitro
- PK of early frontrunner compound looks promising

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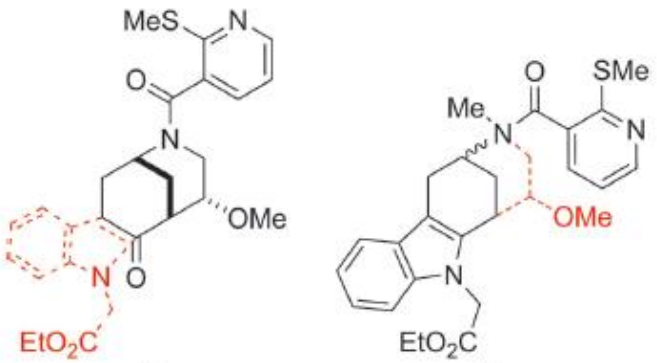
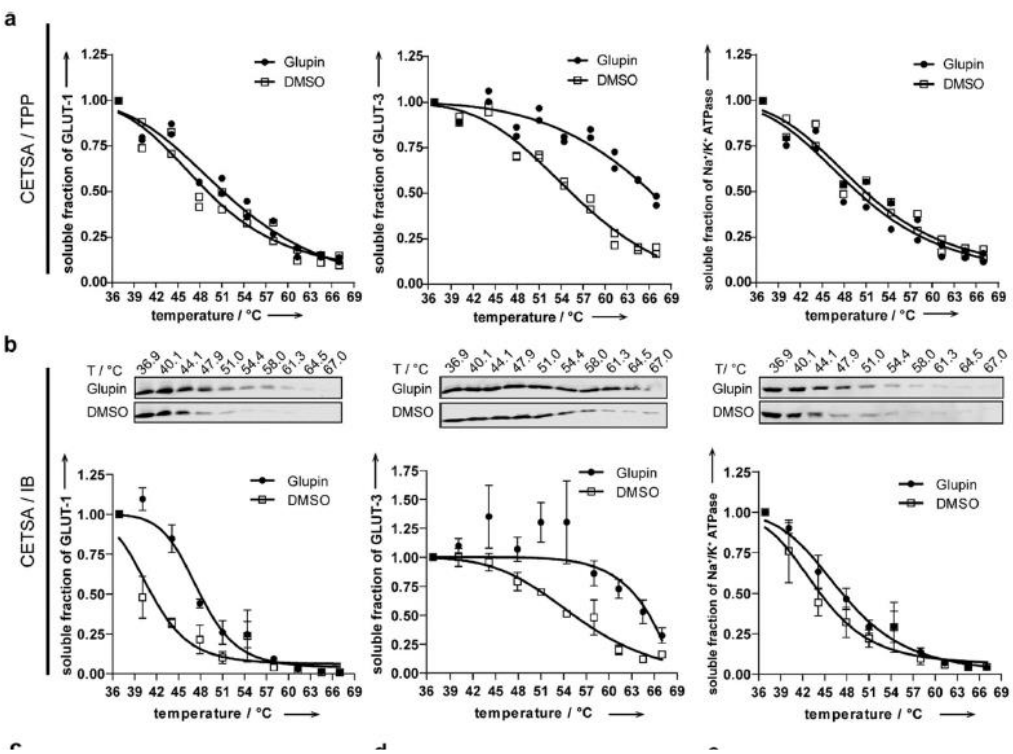
Key Data

Structure and activity of the Glupin-based fragment analogues



Structure and activity of the Glupin-based fragment analogues 6 and 7. Red dashed lines show the fragments missing from the indomorphan core, with R1 to R4 overall shown as in Glupin.



Target engagement of GLUT-1 and GLUT-3 by Glupin. The cellular thermal shift assay was performed with lysates from SW480 cells in the presence of 1 mm Glupin or DMSO using mass spectrometry (a) or immunoblotting (b) to detect GLUT-1 or GLUT-3 and Na+/K+-ATPase as a control. Data of two biological replicates (a) or mean values SD and representative of n=3 (b) are shown.

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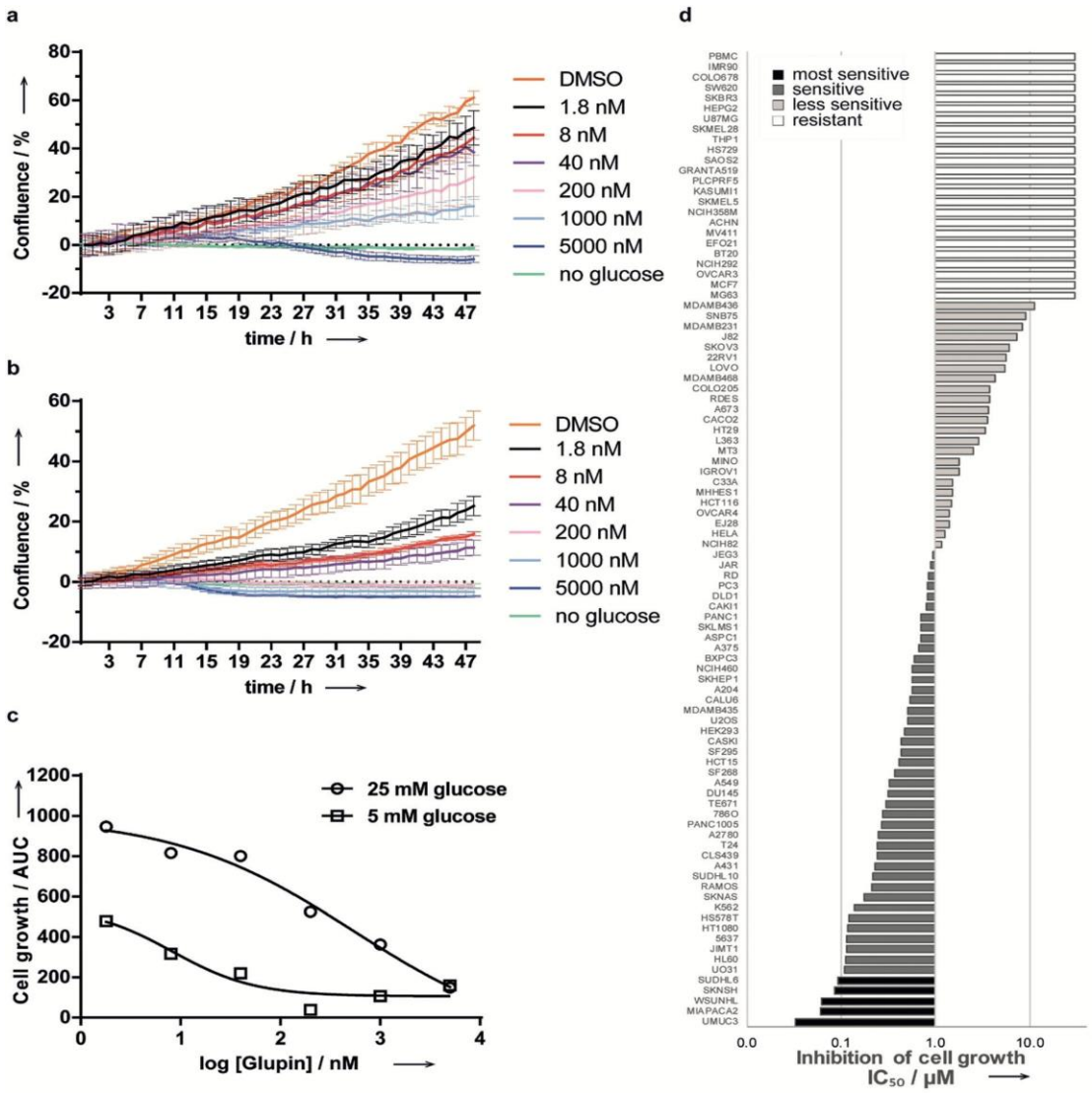
Cancer cell killing effect of GLUT 1/3 inhibitor



Inhibition of cancer cell growth by Glupin. a–c) The growth of MDA-MB-231 cells in 25 mm (a) or 5 mm glucose (b) was monitored in the presence of Glupin or DMSO by means of live-cell kinetic analysis and confluence as a measure. Data are mean values (N=3)±SD and representative of n=3. c) Comparison of cell growth at 5 and 25 mm glucose. The area under the curve (AUC) was calculated for the curves in (a) and (b). d) Glupin inhibits the growth of various cancer cell lines. 94 cell lines were treated with different concentrations of Glupin for 72 h followed by the sulforhodamine B assay and IC_{50} determination.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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