Abstract

Background

Cancer remains a leading cause of death worldwide, with drug resistance accounting for nearly 90% of cancer-related fatalities showcasing the need for new drug targets for the treatment of cancer. The L-type amino acid transporter 1 (LAT1) is an essential amino acid transporter that is associated with overexpression in various tumors and plays an important role in tumor growth and metastasis through mTORC1 activation making it a promising anticancer target. However, current LAT1 inhibitors have many drawbacks that limit their clinical applications.

In this research paper, the goal was to develop a selective, noncompetitive LAT1 inhibitor by optimizing the structure of ESK242, a known inhibitor of LAT1 and LAT3 that displays allosteric binding, to overcome the shortcomings of current LAT1 inhibitors. The goal of this research is to provide insights into the structure-activity relationship of the binding of ESK242 to LAT1 to develop a minimal pharmacophore for LAT1 binding.

Methods

A series of compounds (eLI2, eLI4, eLI5, and eLI6) were synthesized and tested using an in vitro LAT1 transporter assay across four different cancer cell lines (HeLa, MCF-7, MDA-MB-231, and CHO).

Results

The results showed that eLI2 exhibited the highest percentage inhibition in the HeLa and MCF-7 cell lines (57% and 66%, respectively) but did not surpass the activity of ESK242. eLI5 demonstrated the best inhibition in the MDA-MB-231 cell line (93%) and both eLI2 and eLI5 surpassed the activity of ESK242 in the MDA-MB-231 cell line.

Discussion

Due to cell loss that occurred during the assay and with our assay lacking LAT1 specificity, it is difficult to interpret if our structural changes made to EKS242 were actually affecting LAT1 activity. Future work will focus on improving the assay conditions to accurately assess if structural changes increase LAT1 activity and synthesizing additional LAT1 inhibitors.