Abstract: 70O

Identification and characterization of a novel SNAT2 (SLC38A2) inhibitor reveals synergy with glucose transport inhibition in cancer cells.

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SNAT2 (SLC38A2) is a sodium-dependent neutral amino acid transporter, which is important for the accumulation of amino acids as nutrients, the maintenance of cellular osmolarity, and the activation of mTORC1. It also provides net glutamine for glutaminolysis and consequently presents as a potential target to treat cancer. A high-throughput screening assay was developed to identify new inhibitors of SNAT2 making use of the inducible nature of SNAT2 and its electrogenic mechanism. Using an optimized FLIPR membrane potential (FMP) assay, a curated scaffold library of 33934 compounds was screened to identify 3-(*N*-methyl(4-methylphenyl)sulfonamido)-*N*-(2-trifluoromethylbenzyl)thiophene-2-carboxamide as a potent inhibitor of SNAT2. In two different assays an IC_{50} of 0.8-3 µM was determined. The compound discriminated against the close transporter homologue SNAT1. MDA-MB-231 breast cancer and HPAFII pancreatic cancer cell lines tolerated the SNAT2 inhibitor up to a concentration of 100 µM but in combination with tolerable doses of the glucose transport inhibitor Bay-876, proliferative growth of both cell lines was halted. This points to synergy between inhibition of glycolysis and glutaminolysis in cancer cells.