Development of Novel LAT1 Ligands as Potential Antitumor Agents

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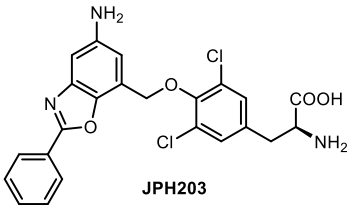
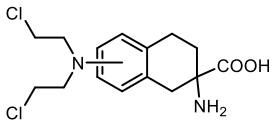
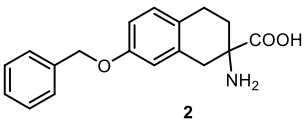
The human L-type amino acid transporter 1 (LAT1/SLC7A5) is responsible for the high affinity, sodium-independent cellular uptake of neutral amino acids with hydrophobic side chains, such as L-leucine or L-phenylalanine.[1] LAT1 is overexpressed on different types of tumor cells and high LAT1 expression levels correlate with poor cancer treatment prognosis. Therefore, LAT1 is considered as a promising target for new treatment modalities against cancer,[3] with the most advanced LAT1 inhibitor (**JPH203**) currently undergoing a Phase 2 clinical trial in biliary cancer in Japan. In general, however, very few potent and selective inhibitors of this transporter have been reported to date.



JPH203



1



2

Building on literature data on the binding of different bicyclic phenylalanine-based nitrogen mustards such as **1**,[4] we have synthesized and evaluated isomeric benzyloxy-substituted 2-amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acids and identified **2**, a conformationally constrained analog of *meta*-tyrosine. This compound inhibits LAT1-mediated L-[^{3}H]-leucine uptake into human colon carcinoma cells (HT-29) with an IC_{50} value of 600–800 nM. HT-29 cells are known to express high levels of LAT1 and, therefore, serve as a convenient system for the assessment of LAT1-inhibitory activity.
In this contribution we describe the synthesis and biological evaluation of a series of analogs of **2**. Structural changes investigated include variations of the benzyl motif, modification of the methylene-oxy linker, ring expansion in the saturated part of the bicyclic ring system and modifications of the carboxy group. These studies have led to the identification of new LAT1 inhibitors with IC_{50} values <100 nM for the inhibition of L-[^{3}H]-leucine uptake into HT-29 cells, thus exceeding the activity of **JPH203** in this system. Structural studies on LAT1-inhibitor complexes by cryo-EM have provided a rationale for the potent activity of these compounds, which bind to the transporter in an outward-occluded conformation.[5]

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