Developing novel inhibitors of the glutamine transporter ASCT2 to treat cancer

N.J. Freidman,[1] T. Rawling,[2] R.J. Vandenberg[1] and R.M. Ryan,[1] [1]Discipline of Pharmacology, Sydney Medical School, University of Sydney, NSW 2006, Australia and [2]Discipline of Pharmacy, Graduate School of Health, University of Technology, Ultimo, NSW 2007, Australia.

System Alanine-Serine-Cysteine is one of the four major neutral amino acid transport systems in the human body. The Alanine Serine Cysteine Transporter 2 (ASCT2) is the major route of delivery of the amino acid L-glutamine, which is conditionally essential in many cancer cell lines. Inhibitors of ASCT2 are sought as anticancer agents, as they may work to starve cancer cells of glutamine. In this study, analogues of the ASCT2 substrate L-asparagine were synthesized and tested for interaction with the transporter. We have identified novel L-asparagine analogues that bind selectively to ASCT2. Our results demonstrate that in the absence of a sidechain substitution, modification of the α-carboxyl group of the amino acid is not tolerated. However, in the presence of a sidechain substitution, modification at the α-carboxyl position may enhance the affinity and selectivity of the compounds. These results reveal the potential for the amino acid backbone to be modified in order to improve inhibition, potentially through exploration of a lipophilic binding pocket.