ABSTRACT

6-Diazo-5-oxo-L-norleucine (DON, **1**) is a non-standard amino acid with proven antitumor activity found in soil bacteria of the genus *Streptomyces*. However, due to the considerable systemic toxicity manifested mainly in the gastrointestinal tract, DON alone is not a suitable clinical candidate for the treatment of cancer. One of the ways to solve the problem of its toxicity is the reversible structural modification of this molecule by protecting both its amino group and carboxyl functional group, by preparing the so-called prodrug of DON. The prepared prodrug may suitably alter the distribution of DON in the body and at the same time increase its permeability to brain tissue. Due to this structural modification, its side effects can be eliminated and a substance for the treatment of brain tumors, such as glioblastoma multiforme (GBM), can potentially be formed.

In my dissertation, five strategies for the specific delivery of DON to the brain using different types of its prodrugs are discussed. The new prodrugs are designed to be either capable of spontaneous penetration across the blood-brain barrier or of being a substrate for one of its influx transporters. At the same time, these prodrugs should be stable in other metabolically active organs and blood plasma in order to sufficiently reduce the already mentioned systemic toxicity of DON. Substituents on both the amino and carboxyl groups of DON in the prepared prodrugs should then be enzymatically easily cleaved in brain cells to release their own effective chemotherapeutic - unsubstituted DON. These biological studies with prepared prodrugs were performed in collaboration with the research team of Professor Barbara S. Slusher of Johns Hopkins Drug Discovery in Baltimore, USA.