Abstract

Carbocyclic nucleoside analogs with norbornane moiety that have been synthesized at IOCB AS CR, represent new potential chemotherapeutic agents with significant activity against Coxsackieviruses. The main objective of this work was to study the metabolism and mechanism of action of the original analog carbocyclic nucleoside MS 254, which is characterized by its antiviral and cytostatic effects. The attention was partially paid also to the two structurally related substances (MS 255, MS 320). In this work, we determined cytotoxicity of these compounds in cell culture and the effect of MS 254 on the amount of total and oxidized glutathione, activity of glutathione-S-transferase (GST), glutathione reductase (GR) and the effect on cellular oxidative stress. The kinetics of the conjugation of MS 254 by human GST was also studied. It was found that of the three substances tested MS 255 was the most cytotoxic and MS 254 was the least cytotoxic compound. It was further found that MS 254 does not cause significant oxidative stress and that it increases the activity of GST and GR in a dose-dependent manner. Michaelis-Menten constant of the conjugation of MS 254 with the glutathione (main metabolic pathway) was determined in the milimolar range, indicating a relatively low affinity of MS 254 for GST.