Glucosidase inhibitors (Gluc-I) have antiviral properties against hepatitis B and C viruses. We have previously shown that glucosidase inhibitors derived from glucose (i.e., deoxynojirimycin (DNJ) derivatives) could inhibit HBV and HCV morphogenesis in cellulo via the inhibition of ER-glucosidases resulting in the perturbation of the folding and assembly of viral envelope glycoprotein. A pro-drug of castanospermine, another potent Gluc-I, has proven beneficial activity in a phase-II clinical trial on HCV-infected patients in combination with Peg-IFN/ribavirin. One of the main side effects of Gluc-I results from the inhibition of gastrointestinal (GI) osidases. Therefore the development of Gluc-I with a better selectivity toward ER-glucosidases would be of interest. Here we report the anti-HBV and anti-HCV activity of two alpha-1-C-alkyl-1-deoxynojirimycin derivatives, i.e. butyl and nonyl forms, (CB-DNJ and CN-DNJ), which differ from N-butyl-DNJ (NB-DNJ) and N-nonyl-DNJ (NN-DNJ) by the position of the alkyl chain on the ring. These molecules have different selectivity patterns against GI-related osidases compared to previously studied DNJ derivatives. We have used BVDV, HCVpp, and HCVcc models, as well as HepG2.2.15 cells or HBV-transfection systems to determine anti-HCV and anti-HBV activities. We showed that CB-DNJ and CN-DNJ have similar EC$_{50}$ and CC$_{50}$ than NB-DNJ and NN-DNJ against BVDV, HBV and HCV, while displaying slightly reduced EC$_{90}$. We confirmed that the antiviral effect was not due to the inhibition of genome synthesis, but was rather due to the inhibition of morphogenesis, secretion and infectivity of viruses. The reduced EC$_{90}$ of CB-DNJ and CN-DNJ derivatives over parental molecules was due to a reduced inhibition of ER-glucosidases in cellulo. The research of novel glucosidase inhibitors with improved selectivity towards ER glucosidases should be pursued.

Keywords: HCV, HBV, morphogenesis, ER-glucosidases