

Synthesis and evaluation of pentacyclic triterpenoids conjugates as novel HBV entry inhibitors targeting NTCP receptor

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Abstract

Chronic liver diseases caused by hepatitis B virus (HBV) are the accepted main cause leading to liver cirrhosis, hepatic fibrosis, and hepatic carcinoma. Sodium taurocholate cotransporting polypeptide (NTCP), a specific membrane receptor of hepatocytes for triggering HBV infection, is a promising target against HBV entry. In this study, pentacyclic triterpenoids (PTs) including glycyrrhetic acid (GA), oleanolic acid (OA), ursolic acid (UA) and betulinic acid (BA) were modified via molecular hybridization with podophyllotoxin respectively, and resulted in thirty-two novel conjugates. The anti-HBV activities of conjugates were evaluated in HepG2.2.15 cells. The results showed that 66% of the conjugates exhibited lower toxicity to the host cells and had significant inhibitory effects on the two HBV antigens, especially HBsAg. Notably, the compounds BA-PPT1, BA-PPT3, BA-PPT4, and UA-PPT3 not only inhibited the secretion of HBsAg but also suppressed HBV DNA replication. A significant difference in the binding of active conjugates to NTCP compared to the HBV PreS1 antigen was observed by SPR assays. The mechanism of action was found to be the competitive binding of these compounds to the NTCP 157–165 epitopes, blocking HBV entry into host cells. Molecular docking results indicated that BA-PPT3 interacted with the amino acid residues of the target protein mainly through π -cation, hydrogen bond and hydrophobic interaction, suggesting its potential as a promising HBV entry inhibitor targeting the NTCP receptor.

