Design and Synthesis of Small-molecule Hepatitis B Virus Capsid Self-assembly Inhibitors

Anda Sīpola [1*], Unda Nelda Dubova [2], Brigita Vīgante [1], Karīna Spunde [2], Tatjana Kozlovska [2], Gunārs Duburs [1]

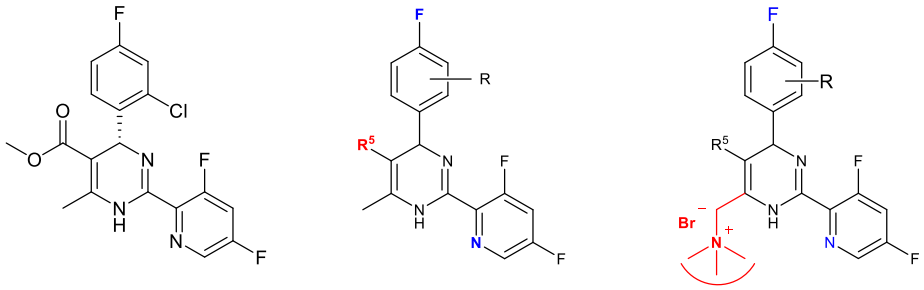
[1] Latvian Institute of Organic Synthesis, *Riga, Latvia*

[2]Latvian Biomedical Research and Study Centre, *Riga, Latvia*

Corresponding author: Anda Sīpola*, *Latvian Institute of Organic Synthesis, Aizkraukles str. 21, Riga LV-1006, Latvia. e-mail: anda.sipola@gmail.com*

An estimated 240 million persons worldwide are chronically infected with hepatitis B virus (HBV). Chronic hepatitis B (CHB) in up to 40% of cases progresses to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma, a leading cause of cancer-related morbidity and mortality worldwide [1]. We are focused on original antiviral strategy intended to suppress the self-assembly process of HBV core (HBc) protein as one of the promising ways to cure CHB without induction of drug resistance. Targeting the capsid protein of HBV and thus interrupting normal capsid formation have been an attractive approach to block the replication of HBV.

Heteroaryldihydropyrimidines (HAPs) were shown to bind the HBV core proteins and misdirect the assembly of the capsid *in vitro*. We carried out structural optimizations based on HAPs analogue Bay 41-4109 and structure-activity relationship studies [2].



Bay 41-4109 **1** **2**

Newly synthesized HAPs **1** and **2** were evaluated for their ability to disrupt the capsid assembly in cell culture, and promising candidates were selected for further evaluation of antiviral activity and discovery of mechanisms of compound action.

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References:

[1] World Health Organization (2016) *WHO Hepatitis B Fact Sheet* (World Health Organization, Geneva)

[2] Qiu, Z. *et.al.* (2016), Design and Synthesis of Orally Bioavailable 4-Methyl Heteroaryldihydropyrimidine Based Hepatitis B Virus (HBV) Capsid Inhibitors. *J. Med. Chem.* 59, 7651-7666