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

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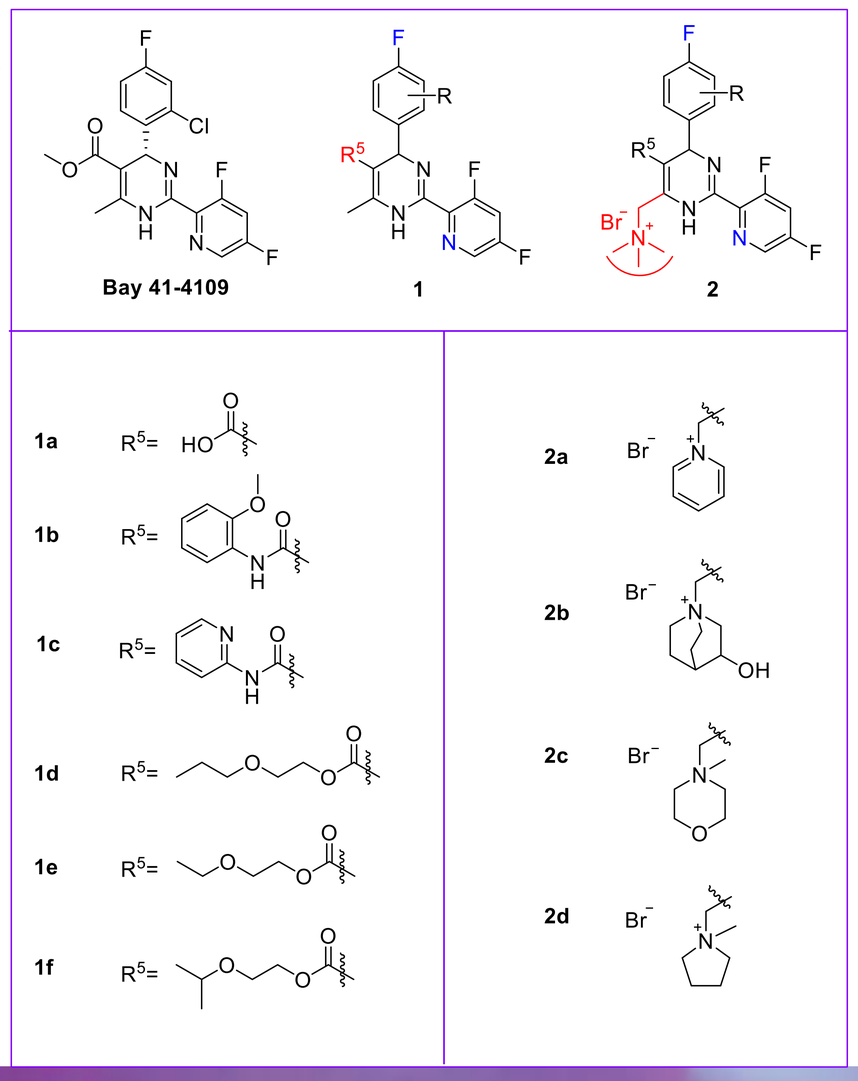
## 1. INTRODUCTION

An estimated 240 million people worldwide are chronically infected with hepatitis B virus (HBV). Hepatitis B surface antigen declines very slowly during nucleos(t)ide (NUC) therapy and the detection of anti-hepatitis B surface antibodies is a rare and late event [1]. That is the reason why life-long NUC administration is frequently required and there is a need to define novel therapeutic strategies for HBV infection. Heteroaryldihydropyrimidines (HAPs) are promising non-nucleos(t)ide HBV replication inhibitors. The first HAP compound **Bay 41-4109** promotes core protein assembly and leads to irregular particles and eventually causes core protein degradation [2].

## 2. NEWLY SYNTESIZED HAPs

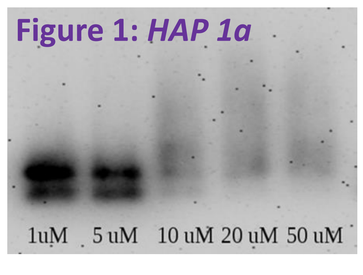
We carried out structural optimizations (shown in Table 1) based on the HAP analogue Bay 41-4109 and structure-activity relationship studies [3].

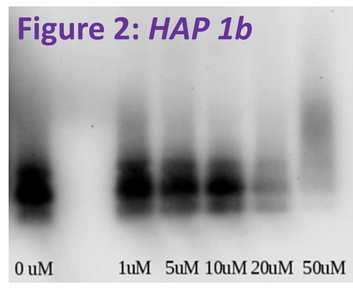
***Table 1***

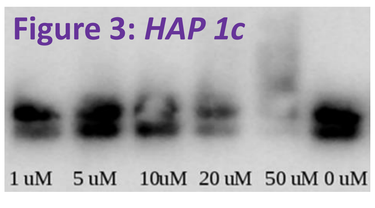


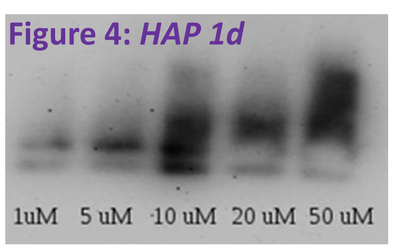

## 3. RESULTS

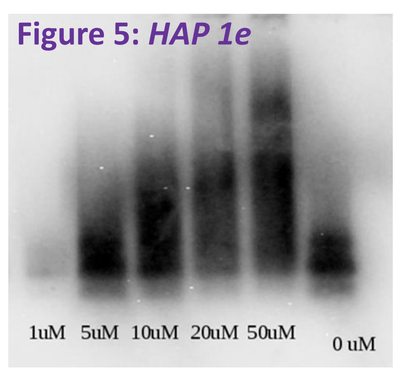
BHK-21 cells were infected with previously made Alphavirus. Infected cells were treated with newly synthesized HAPs and results are shown in Figure 1-6 (Native agarose gel electrophoresis and subsequent HBc specific immunoblotting pictures that show dose dependent effect of tested compounds on HBV nucleocapsid assembly).

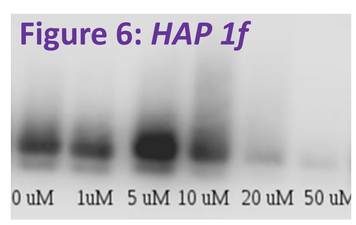



## 4. CONCLUSIONS

Compunds **1a, 1b** and **1f** showed a promising effect by inducing dose dependent decrement on the relative quantity of assembled capsids in concentrations less than those needed to affect cell viability.

Compounds **1e** and **1d** showed a dose dependent effect on HBc aggregation, possibly inducing disruption in capsid assembly.

Testing of HBV capsid self-assembly inhibition activity for compounds **2a-d** is in progress.

**REFERENCES:**

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