Poster Abstract P5

Novel dihydroquinolizinones for HBV surface antigen (HBsAg) reduction with liver targeting properties

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Background
Chronic hepatitis B (CHB) is characterized by high levels of hepatitis B virus (HBV) surface antigen (HBsAg) in blood circulation. A major goal of CHB interventions is to reduce or eliminate this antigenemia; however, the current standard of care medications with either pegylated interferon alpha or nucleos(t)ide analogues (NUCs) have failed to do this. A novel family of dihydroquinolizinone (DHQ) has been shown to reduce circulating levels of HBsAg in animals, representing a first small molecule with reliable and promising potential. Reductions of HBsAg were a result of the compound's effect on HBsAg mRNA levels. Since the first report of dihydroquinolizinone (DHQ) compound RG-7834 as an effective hepatitis B virus expression inhibitor in 2018, dozens of structurally diversified DHQs have been disclosed in both scientific journals and patent. However, the CNS liability observed for RG-7834 raised a safety concern for this compound. Commercial development by Roche of RG-7834 was stopped due to undisclosed toxicity issues.

Methods
Our rationale, contrary to the regular medicinal practice of pursuing a highly systemically bioavailable lead compound, is to convert a systemic RG-7834 to a liver selective new DHQs that have low to moderate bioavailabilities but high liver exposure and liver/plasma ratios. We believe that having drugs that are more selective for liver hepatocytes, which are the cells targeted by HBV, is one way to minimize or eliminate unnecessary side effects resulting from the inappropriate distribution of RG7834 to other tissues. Therefore, hepatoselective DHQ compounds should have great potential to improve the safety of this novel family of anti-HBV compounds. Here, we report our approach to develop liver targeting DHQ derivatives through the installation of a recognition element for organic anion transporting polypeptide protein 1B1 (OATP1B1) and 1B3 (OATP1B3) which are abundant on liver hepatocytes.

Results
we successfully developed RG-7834 derivatives as substrates of OATP1B1 and OATP1B3, resulting in a lead compound that is potent in biochemical and cellular assays, has low risk for penetrating blood-brain-barrier (BBB), and demonstrates high hepatoselectivity in liver versus plasma in a mouse pharmacokinetic (PK) study .

Conclusions
Based on the structure of RG7834 and the analysis of its ADME and PK profiles, we have incorporated an additional acid group into the side chain of RG7834. Through the increase in tPSA and the modulation of the cLogP/LogD of the new molecules, we have identified a new lead to be potent in both the PAPD 5 and 7 enzyme assays and HBV mRNA degradation cellular assay. Further evaluation showed that unlike RG7834, the new lead is a substrate of both OATP1B1 and OATP1B3, which may facilitate the absorption into the liver. This in vitro result was translated into an in vivo setting: the new lead demonstrated much better hepatoselective distribution in a mouse PK study than RG7834, with an average liver/plasma ratio of 37.8 over 8 h. More importantly, the new lead demonstrated a low risk for crossing the BBB in comparison to the moderate risk of RG7834.