Abstract

Our lab has synthesized several novel compounds shown to inhibit replication of Hepatitis C virus (HCV). Three viral proteins (NS2, NS3, and NS5A) required for HCV replication contain or share structural zinc ions in order to maintain their function. Disruption of zinc binding within these proteins has been shown to inhibit their function, which has led to the hypothesis that inhibition results from the chelation of one or more structural zinc ions. Previously identified HCV inhibitors contain three Lewis-basic groups that have been shown to bind zinc. The specific goal of this research is to improve the efficacy of our lead compounds by synthesizing a series of analogs with an additional Lewis-basic group of an amine of varying length. With the additional Lewis-basic group we expect to see an increased affinity for zinc and, if the hypothesis is correct, increased HCV inhibitory activity.

Hepatitis C Virus

- Studies have shown an estimated 130-150 million people worldwide suffer from chronic hepatitis C infection with 500,000 people dying each year as a result of HCV related ailments.¹
- Current standard care is combination therapy of ombitasvir, paritaprevir and ritonavir (Technivie).²
- Technivie has been proven to cure HCV, but treatment last over 12 weeks with costs ranging from $92,000-$115,000.²
- Non-structural proteins (NS2, NS3, and NS5A) contain a structural zinc ion.³

Hypothesis

- Research has shown that inhibition may result from disruption of zinc binding within either NS2, NS3, or NS5A.³
- Lead compound 1a has shown an affinity for zinc chelation and efficacy for inhibition of HCV replication.
- Therefore we hypothesize inhibitory activity is due to the chelation of one or more structural zinc ions within NS2, NS3, and/or NS5A.
- If we increase affinity for zinc-binding then we might increase inhibition of HCV

References