A Dissertation

entitled

Synthesis of Novel Nucleoside Analogs Targeting HCV

by

Bader Saleh Alabdullah

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Doctor of Philosophy Degree in

Medicinal Chemistry

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Dr. Amanda Bryant-Friedrich, Committee Chair

_____
Dr. James Slama, Committee Member

_____
Dr. Viranga Tillekeratne, Committee Member

_____
Dr. Malathi Krishnamurthy, Committee Member

_____
Dr. Amanda Bryant-Friedrich, Dean
College of Graduate Studies

The University of Toledo
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Despite all the advancement that has been produced in the clinic for treating HCV infection, it is nevertheless a major causal agent of liver disease due to its silent nature. With 7 genotypes and many subtypes, the search for a pan-genotypic treatment is challenging and leads in many cases to the use of combination treatments to tackle the infection.

Ribavirin (RBV) and Pegylated Interferon alfa-2b (pegIFNα-2b) represented the standard of care (SoC) for a long period. Sustained Virologic Response (SVR) was only achieved in low percentage of patients with this SoC. Also, the SoC was associated with severe side effects that resulted in the termination of treatment in many cases. So, it is necessary to find a treatment that is pan-genotypic and has fewer side effects than that of the SoC. Identification of multiple points to disrupt the HCV viral life cycle and to halt viral protein synthesis was enabled through determination of the crystal structure of the viral proteins and a better understanding of the viral life cycle. Most notably the determination

of the crystal structure of the HCV NS5B RdRp as it is the catalytic machinery for viral replication.

The conserved nature of the HCV NS5B active site across viral species, as compared to other HCV viral proteins, along with the fact that there is no human NS5B made NS5B a primary target for drug design and development.

In this project, we synthesized 2′-C-acetyl and 2′-C-(1-hydroxyethyl) uridine and started the synthesis of 2′-C-formyl and 2′-C-aminomethyl uridine analogs. Based on the approval of Sofosbuvir, which is 2′-modified uridine that act as an NS5B inhibitor, we assume that these compounds will work as non-obligate chain terminators for the synthesis of the viral RNA by the NS5B enzyme.