2014-08

2014 REU Poster: Synthesizing Antiviral Agents Effective Against Hepatitis C Virus

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http://hdl.handle.net/2144/12974

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Abstract
Chronic Hepatitis C Virus, or HCV, affects 120-150 million people worldwide. HCV causes liver disease and there is not a vaccine or an effective treatment\(^1\). Previous research indicated that compounds SL209 and SL205 inhibited the dimerization of core, the capsid protein of HCV responsible for assembling and releasing the infectious particle\(^2\). Current research is focused on testing the effect that the structure of these compounds has on their bioactivities, so analogues with similar structures to SL209 and SL205 are being synthesized.

Introduction
HCV is a bloodborne virus that can either be acute or chronic. Acute HCV usually is not life threatening and is usually asymptomatic. People with acute HCV can recover without treatment. Millions of people develop chronic HCV, which causes liver disease, such as liver cirrhosis, liver fibrosis, and even liver cancer. There is no vaccine and treatment is mostly ineffective. HCV can be contracted through needle sharing, inadequate sterilization of medical equipment, blood transfusions with untested blood, as well as sexually\(^1\).

Inhibiting Core Dimerization
Core is the capsid protein of HCV that assembles and packages the RNA genome of HCV, which then forms the viral nucleocapsid. Core is involved in the life cycle of HCV, including the assembly and release of the infectious particle. Inhibiting core could interfere with uncoating the viral particle, could prevent the formation of new viral particles, and could destabilize the entire virus particle. It was previously found that compounds SL209 and SL205 inhibit core dimerization, which is important because core has to dimerize to make HCV infectious\(^2\).

Analogue Type A
Analogue A compounds are being synthesized to test the effect of the size of the D-ring and the effect of substitutions on the A-ring on bioactivity. Some of these analogues will test how the D-ring size and angle to the aromatic core affect the bioactivities of compounds SL209 and SL205. Other analogues will test the significance of adding a methoxy group to carbon 5 on the A-ring to the bioactivities of SL209 and SL205.

Analogue B and C
Analogue B and C are being synthesized to test the significance of the D-ring in SL209 and SL205. Type B analogues have their D-ring reduced from a six-membered ring to a five-membered ring. Type C have the D-ring removed altogether. These changes can affect the activity of the compounds by flattening the core, while retaining its chirality.

Synthesizing Analogue B1
Analogue A compounds are being synthesized to test the effect of the size of the D-ring and the effect of substitutions on the A-ring on bioactivity. Some of these analogues will test how the D-ring size and angle to the aromatic core affect the bioactivities of compounds SL209 and SL205. Other analogues will test the significance of adding a methoxy group to carbon 5 on the A-ring to the bioactivities of SL209 and SL205.

Acknowledgments
• Dr. John Snyder
• Kyle Strom
• Boston University REU program
• Emory & Henry College, FOIS

References