OPEN ACCESS

GAVIN PUBLISHERS

Educational Research Applications

Review Article

Abebe M, et al. Educ Res Appl 5: 175.
DOI: 10.29011/2575-7032.100175

Teaching Students Synthesizing Molecules Mimicking an Existing Drug against Covid-19

Moges Abebe[1*], Lashan Eloise Knowles[1], Bisrat Hailemeskel[2]

[1]Department of Biological and Physical Sciences, Saint Augustine University, Raleigh, NC, USA

[2]Department of Clinical & Administrative Pharmacy Sciences, College of Pharmacy, Howard University, NW Washington, DC, USA

[*]**Corresponding author:** Moges Abebe, Department of Biological and Physical Sciences, Saint Augustine University, Raleigh, NC 27610, NC, USA

Citation: Abebe M, Knowles LE, Hailemeskel B (2020) Teaching Students Synthesizing Molecules Mimicking an Existing Drug against Covid-19. Educ Res Appl 5: 175. DOI: 10.29011/2575-7032.100175

Received Date: 26 May 2020; **Accepted Date:** 01 June, 2020; **Published Date:** 06 June, 2020

Abstract

End of semester organic chemistry course projects are valuable learning assessment tools while giving students a creative opportunity and sparking interest for further research investigations. The purpose of this year's project was to teach students how to synthesize a molecule that potentially mimics an existing drug that works against the COVID-19. The available drugs chosen for the project are those that are proposed to work either by prohibiting the easy entry of the virus into respiratory tissues or those who deprive the virus's ability to reproduce once they enter the cell. An investigative search in historical literature and the current conditions of the virus enabled students to create a unique and innovative product that requires a cumulative learned knowledge. History has shown that when a new virus becomes pandemic it takes time for researchers to create a drug, test the results, and gets approved by the Food and Drug Administration (FDA) for public availability. If given an opportunity, students can offer their untapped imagination and resourcefulness to produce the groundwork for a drug that will fight the COVID-19 virus. In this project, three drugs that are in clinical trials against Covid-19 were studied. Their structure activity and active functional group were reviewed. Based on their structure using their proposed active functional group, a chemical molecule was synthesized using phenol as a starting molecule and adding butanoic acid with an amino group as an attachment. The final functional groups in the molecule are a hydroxide group, benzene ring, amine, an ester, and two methyl groups. By mimicking the active functional groups in drugs that are in clinical trail at the time this review, we hopefully achieved our goal of teaching students a strategy that potentially leads to new drug discovery.

Introduction

Every year a semester project is assigned to Organic Chemistry II (CHEM142) students to design a molecule that will be an effective drug for the disease of their choice. The course is a four-credit hour mandatory course for biology and chemistry majors in our University. Students have to complete the basic organic chemistry course (CHEM341) before registering for this course. This year, a few of the students chose to develop a molecule that will potentially mimic existing drugs that have been shown to stop the spread of the COVID-19 in a laboratory setting. The first part of the assignment was to study the nature of existing drugs to determine the effectiveness of their functional groups and potentially to synthesize a similar molecule to mimic its chemical structure. The drugs considered for the project were Hhydroxychloroquine, lopinavir/ritonavir (Kaletra®), and remdesivir. Designing a molecule requires background knowledge of the mechanism of organic reactions and the interactions of functional groups in medicine. These students have been exposed to the following basic information in their CHEM 142 lectures.

First, functional groups in organic chemistry are a group of atoms that are, combined part of the collectives, that will give the molecule its functional characteristics. Using computer modeling and later in clinical trials, these molecules are designed to interact with the human body for a variety of purposes including to heal the sickness or to kill bacteria and viruses acting as antibacterial and antivirus drugs.

Second, it is believed that living organisms have two important mechanisms for identifying molecules. The first is the shape of the molecules and the second is the functional groups

that are found on the surface of the molecules. The shape of the molecule is subject to the functional groups that determine the form and behavior of the molecule towards the molecule in question. The most important functional groups in medicine are the oxygenated carbons, the nitrogen compounds, the sulfur compounds, phosphorous compounds, and the groups that have halogens as part of their assembly. Examples of most common oxygenated singly bonded carbon compounds are alcohols and ethers, while the double-bonded carbonyl compounds are aldehydes, ketones, carboxylic acids, and esters. The most common nitrogen compounds are amines, amides, and cyanides while the phosphates and the sulfates have the resemblance of amino acids. Third, when it comes to the intermolecular attraction of the molecule the functional groups are either hydrophobic or hydrophilic, acidic or basic, reactive or unreactive, and with or without stereogenic centers.

Methodology

The semester project exposed students first asked to perform online research on the historical background of the many faces of the coronavirus which is not new to the world. In their presentation students reported that the first time that pandemic coronavirus appeared was as the Spanish flu of 1918 infecting half of the world population and killing over 20 million victims worldwide. They also reported that the second well-documented appearance of the Coronavirus was transmitted from bats to other animals and then to humans. Severe Acute Respiratory Syndrome (SARS) which appeared in China in 2003 was transmitted from bats to civets and was contained that same year preventing a pandemic level outbreak. Middle Eastern Respiratory Syndrome was detected in Saudi Arabia and again transmitted from bats to camels and then to human and took the lives of over 800 victims.

Next, students researched the present plague caused by the COVID-19 virus and the seriousness of the pandemic and the urgency for searching for an effective remedy. Lack of available drug that is approved by the FDA has caused the loss of millions of lives. The spread of COVID-19 was so fast, and the infections were so severe that it took by surprise the lives of many elderly people and infants. To protect their citizen many countries have passed regulations to stop the spread of the virus and the students were under the stay at home quarantine when they were doing their research. Many lives could have been saved with the right kind of medication in place.

The students also assigned to research currently active drugs that are in clinical trials for Covid-19. The available medications [1-3] that are being used in the hospitals currently are Hydroxychloroquine, Lopinavir-Retinovir, and Remdesivir. Table 1 lists the functional groups found in the study drugs. Hydroxychloroquine contains chloride, hydroxide, amine groups, and benzene ring attached to a pyrimidine. Remdisvir has a phosphate group, nitrile, hydroxides, benzene ring, pyridine, and imidazole combined in a ring. Lopoinavir/reinovir, on the other hand contains these functional groups: a complex ring structure with several hydroxides, methyl groups, acetals and hemiacetal, and amino groups. In addition, the hydroxides, the amines, and carboxylic acids are hydrophilic creating a hydrogen bonding site to enhancing solubility in water, while methyl, benzene, and cyclic hydrocarbons are hydrophobic and inhibit solubility in water for delayed reactions.

Name	Alkyl Halides	Ether & Alcohol	Aldehydes & Ketones	Carboxylic acid & Esters	Amines & Amides	Thionyl & Phosphides	Benzene
Hydroxychloroquine	X	X			X		X
Kaletra® (Lopinavir-Retinovir)			X	X	X		X
Remdesivir		X	X	X	X	X	X

Table 1: list of functional groups in three different COVID-19 drugs.

Developing the Drug

In the developmental process of any medicinal drug, the first and the most important part is determining the drug target in the virus. COVID-19 has many protein spikes on the exterior surface surrounding the virus. The drug target is the protein spikes which are large molecules composed of many amino acids.

It is proposed that the lock and key model of enzymes apply here with the small molecule drug finding its way into a large protein molecule and binding itself to the binding site. In other words, the right combination of these functional groups is essential for the success of the drug. Figure 1 shows a drug that was designed in this research work, 2-(4-hydroxyl-phenyl)-3-amino-ethyl butanoate [1], to fight COVID-19. The functional groups in the molecule are a hydroxide group, benzene ring, amine, an ester, and two methyl groups. The amine and the hydroxide group create an opportunity for the benzene ring to be polar as well as hydrogen bond with the protein.

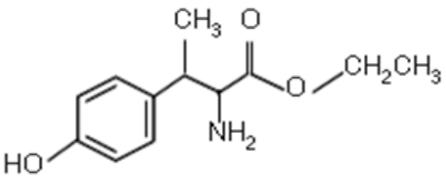

Figure 1: The designed, 2-(4-hydroxyl-phenyl)-3-amino-ethyl butanoate.

The reaction mechanism to synthesize the drug is as follows; the starting material is phenol which can be acquired commercially from chemical supply companies. Since the hydroxide group is an electron donor it enhances the o-p substitution on the benzene ring thus boosting the bonding of the amine group. Adding an amino-butanoic acid to the benzene ring can be accomplished via a Grignard Reaction. The last step is the condensation of methanol with a carboxylic acid. After the synthesis is completed, students are asked to predict the chemical and physical properties of the molecule synthesized.

Results

The final product is a water-soluble oral drug. This is important because it is hypothesized that once it gets in the body, it is expected to hydrolyze into two byproducts that are soluble in water. The first product is the carboxylic acid and the second product is ethanoic acid. The synthesized drug is hypothesized to be eliminated from the body primarily through the liver utilizing the reverse reaction of the hydrolysis of the ester. However, this requires pharmacokinetic studies in model animals to determine the enzyme system that will be involved in the metabolism or excretion of the drug molecule. Based on the laboratory testing, the byproduct is expected to be ethanol which can easily be broken down by cytochrome p450 enzyme system and excreted through urine.

The carboxylic group, assuming a suitable route of administration method is developed that allows the molecule to reach the target site as an intact molecule, can bind with receptors, and form an amide with an amine via a peptide bond in the protein spikes of Covid-19. The hydrophobic side of the drug is supported by the hydrophobic ligand of the protein and it is hypothesized to further strengthen the binding of the drug.

The actual molecule synthesized, and its active functional groups are shown in Figures 1 and 2. The molecular weight of the molecule is about 223 g/mole and the physical properties are slightly soluble in water with an estimated melting point of 120°C. One of the limitations of this study is that the molecules synthesized were not tested to determine its effectiveness against the Covid-19 virus in a petri dish or other laboratory mechanisms. Since this is an organic chemistry course, the project ended once a molecule in question was synthesized.

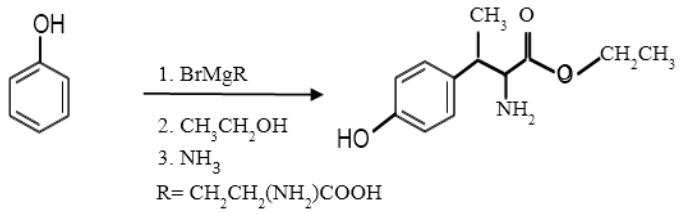

Figure 2: The reaction mechanism for synthesizing the proposed drug.

Discussion

The current antiviral drugs currently in clinical trials against Covid-19 are designed with a specific purpose either to prohibit virus entry into the cell or to stop replication and duplication of the virus in the viral sequence. Some drugs are designed to uncoat the virus proteins after it has penetrated the cell. These drugs have an amino group as a solitary functional group in their hydrocarbon backbone (Figure 3). The designed drug that is proposed here has an amino group that potentially has a role in removing the sticky protein from the virus and crippling it from fusing to the host receptors. If this is done outside the cell possible outbreak of the virus in the host cells can be eliminated.

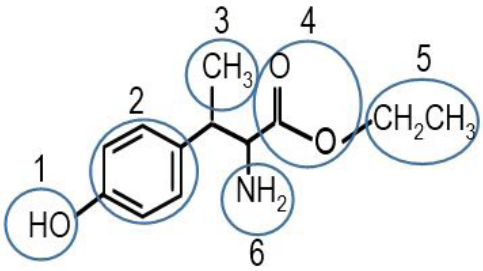

Figure 3: Similarities of the designed drug with an amino acid.

Furthermore, the proposed synthesized drug has the same functional groups found in the current antiviral drugs (Figure 4). Table 1 also lists the functional groups that are found in antiviral medications. The hydroxide group (1) is found in hydroxychloroquine and Remdesivir while the benzene ring (2) and the amino group (6) are both found in Hydroxychloroquin, Kaletra®, and Remdesivir. The hydrocarbon backbone is found in every organic medicine and the carboxylic acid is found in Kaletra® and Remdesivir. These functional groups enable the prospective drug to function as a competitive antiviral option.

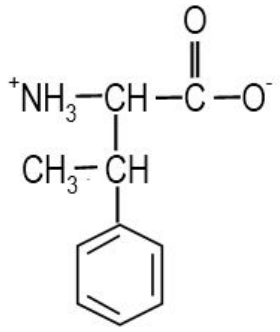

Figure 4: Important functional groups.

The third property is the shape of the molecule. Figure 4 shows the structure of the prospective antivirus drug that has a similar structure to amino acids. Redrawing the hydrolyzed ionic molecule shows its strong resemblance to Tyrosine, the amino acid the body prepares from phenylalanine. The potential drug is soluble in water (*in vivo*) which potentially enables it to enter the cell. If this is true and when it reaches the target site of action and stays chemically intact, it can mimic as an amino acid simulator to synthesize the virus protein and disrupt the amino acid sequence. If the proposed drug succeeds to disrupt the protein sequence of the virus, mutation may not occur in Covid-19. The three properties of the potential drug, its functional groups that have shown in currently existing drugs that can block virus fusion to cell receptors and potentially dissolve the protein spikes in the virus, and its potential to disrupt the protein synthesis of the virus make it a very good prospect for preclinical studies.

Conclusion

This study was conducted to teach organic chemistry students by assigning them to synthesize a molecule against Covid-19 as an end-of-semester project. Observations were also made during student oral and written presentations to determine their comprehension of the material learned from the lecture and their independent literature search. The semester project played a significant role in creating awareness of the Covid-19 virus, in communicating urgency for the development of an effective molecule that mimics currently used drugs against the virus. We also believe that it built the student's confidence and sparked interest in drug development as a career choice. This year's students were successful in their choice of functional groups, the naming of the molecule, the mechanism that is required to create the drugs, as well as their predictions of the physical and chemical properties of the potential drug. This proves the point that the end of the semester project in our course was a valuable tool to enable students to apply theory and to assess their learning. The future semester project will investigate computer-aided drug design.

References

1. Knowles, L. E., (2020) Research towards the Creation of Antiviral Drug for 2019 Novel Corona Virus.
2. Sterling T, Irwin JJ (2015) ZINC 15 – Ligand Discovery for Everyone. J Chem Inf Model 55: 2324-2337.
3. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, et al. (2006) Drugbank: A Comprehensive Resource For In Silico Drug Discovery And Exploration. Nucleic Acids Res 34: D668-D672.