Original Article

Synthesis of Remdesivir Derivate as a Generation of Anti-COVID-19 Drugs Through Acetylation Reactions

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ABSTRACT

Remdesivir, a competitive inhibitor of viral RNA-dependent RNA polymerase, is the drug of choice for anti-COVID-19 treatment. However, the instability of these substances in plasma raises doubts about their therapeutic potency. Additionally, SARS-CoV-2-infected cells may exhibit a variety of antiviral behaviors due to intricate activation pathways. Therefore, this study aimed to develop a synthesis for the remdesivir derivative.

The remdesivir derivative was synthesized using acetyl chloride as a reagent in a ratio of 1:3 in dichloromethane and tetrahydrofuran solvent at 30°C for 6 h. Thin-layer chromatography and spectrophotometers (1H NMR and 13C NMR) were used to identify the produced molecule, which was a brownish-yellow crystalline powder. The results of the synthesis yielded 0.8 gr (77.34%), and the Rf value of the remdesivir derivate was 0.54. The characterization with 1H NMR at δ2.5 ppm (3H, s) indicated the presence of a proton in the H-C-C=O structure caused by the substitution of the acetyl group in the remdesivir structure. The 13C NMR data indicated the presence of aromatic carbons, alkenes, C≡N, and carbon bonds with electronegative O. This remdesivir derivate chemical can be a potential candidate for an anti-COVID-19 drug that has more potency because it has substitutions of acetyl groups at positions 2' and 3' in the structure of remdesivir.

Keywords: Acetylation, Acetyl chloride, COVID-19, Remdesivir, Remdesivir derivate, Synthesis

1. Introduction

There is still a need for efficient and economical treatments to address the COVID-19 pandemic brought on by the SARS-CoV-2 virus. Despite the fact that several vaccines have been developed and demonstrated to be effective in preventing transmission, antiviral therapy has been shown to play a significant role in hospitalized COVID-19 patients in reducing the risk of developing more severe disease and shortening the length of hospitalization (1).

Remdesivir was the first medication for COVID-19 that the Food and Drug Administration approved, and other related compounds, including galidesivir, sofosbuvir, and molnupiravir, have also shown promise. Remdesivir is licensed for use in adults and children (12 years of age and older) who are being treated in the hospital for COVID-19 on the basis of rapid clinical recovery (2).

There was clinical improvement in 36 of 53 (68%) patients with significant COVID-19 symptoms in a remdesivir treatment clinical trial conducted in the United States (3). Remdesivir exhibits antiviral activity against the SARS-CoV-2 virus with an EC50 value of 0.77 µM, which indicates that virus infection is inhibited at this smallest concentration (4). The effectiveness of remdesivir as an antiviral medication for COVID-19 patients is predicted to be 31% (95% CI, 1-18%) in lowering the risk of mortality and 10% (95% CI, 1-18%) in improving recovery chances. However, because these medications must be injected intravenously, their use ought to be restricted to people who need to be hospitalized for more severe conditions. Remdesivir is also unstable in plasma, and its complicated activation mechanism can have a highly varied impact on the antiviral activity in SARS-CoV-2-infected cells. As a result, efforts are being made to produce a more efficient remdesivir derivative (5).

Remdesivir derivative synthesis is still being developed. According to a study by Schooley (2021), three lipophilic products, including HDP-P-RVn, ODE-P-RVn, and ODBG-P-RVn, were produced from remdesivir nucleoside monophosphate and were found to have effective anti-SARS actions against CoV-2 in Vero E6 cells. In another study, El-Sayed (2021) created remdesivir derivatives by conjugating a fatty acyl group to the hydroxyl group (OH) in the remdesivir structure. Because the group was not crucial to the basic interaction of remdesivir at that position, the alteration was suited to boost permeability and potential antiviral activity. Twelve derivatives of five different fatty acyls were produced as a result of the reaction with remdesivir. The antiviral activity of remdesivir displayed a high selectivity index (>588 to >833), compared to all synthetically produced fatty acyl-conjugated remdesivir derivatives (>109 to >208), which was linked to the weak hydrolysis of the synthetic derivatives because of the lengthy carbon chain of the structure (6). As a result, acetyl chloride (CH3COCl) was used instead of acyl fatty reagents to generate remdesivir derivatives due to its short carbon chain. Remdesivir derivatives were then synthesized using the acetylation method to produce more potent derivative molecules.

The addition of acetyl chloride, which has a short carbon chain and is easily soluble, accessible, and capable of reacting with the hydroxyl group in remdesivir, is anticipated to boost the antiviral activity of the resulting remdesivir derivatives.

The goal of this acetylation procedure is to create a remdesivir derivative product by replacing the hydroxyl group of the parent chemical (remdesivir) with an acetyl group (CH3CO-) of acetyl chloride. The temperature needs to be kept low since the acetylation reaction is exothermic.

2. Materials and Methods

2.1.1. Synthesis of Remdesivir Derivatives

Remdesivir (30.5 mg, 0.05 mmol) was mixed in 20 mL of anhydrous dichloromethane and tetrahydrofuran in a 2:1 ratio, and then 70 µL of triethylamine was added. Additionally, 10 µL of

acetyl chloride was made, which is 1.5 equiv, 0.15 mmol, and dissolved in 5 mL of anhydrous dichloromethane. Drop by drop, the mixture was added to a solution of remdesivir with dichloromethane, tetrahydrofuran, and triethylamine for 60 min. The reaction mixture was then heated to 40°C and stirred for 6 h. The solvent was then evaporated over the water bath when the reaction was finished, and the reaction mixture was cooled to room temperature.

2.1.2. Thin-Layer Chromatography Analysis

Remdesivir and the synthetic compounds were spotted onto a silica gel 60 plate that had been heated to 110°C in an oven for 15 min before being eluted with a chloroform:methanol (2:3) solution. The spots were visible on the plates using UV light at 254 and 366 nm, and the Rf values of the remdesivir molecule and the synthetic chemical were then compared. The plate was exposed to UV light first, then 10% H2SO4 was sprayed on it, followed by burning to examine the immediate appearance of the stains. The intended pure compound would be produced if the synthesized chemical's stain on the thin-layer chromatography (TLC) plate was a single stain.

2.1.3. NMR-Based Characterization

1H NMR and 13C NMR spectroscopy were used to measure the number and type of hydrogen and carbon atoms in the remdesivir derivative compound, respectively. The remdesivir derivative compound weighing up to 2 mg was dissolved in an NMR tube with a special NMR solvent (CD3OD), and the volume was made up to 4 cm from the length of the tube.

3. Results

3.1.1. Remdesivir Derivate Reaction Mechanism

Remdesivir was used as the starting compound in a reaction with 0.15 moles of acetyl chloride in dichloromethane and tetrahydrofuran (2:1). Triethylamine was added as an organic base, and the reaction was stirred for 6 h at 40°C. The acetyl group of acetyl chloride was substituted for the hydroxyl group in the structure of remdesivir to produce the remdesivir derivate.

The hydroxyl group of remdesivir acts as a nucleophile and attacks the central carbon atom on the metallic acetyl (electrophilic) to produce a tetrahedral intermediate. The tetrahedral intermediate will then release transport, which is the leaving group forming an anion followed by the loss of a proton H, so that a synthesized compound is formed as a result of the acetyl group substitution.

3.1.2. Thin Layer Chromatography Analysis

A single spot (Figure 3) was obtained on the remdesivir-derived TLC plate from the results of TLC analysis using silica gel GF 60 as the stationary phase and a mixture of chloroform and methanol (2:3) as the fluid phase. It had a crescent shape and an Rf value of remdesivir derivate of 0.54, and an Rf value of remdesivir of 0.84 was observed in 254 nm UV light (Table 1). This indicated that the synthetic substance was a different substance from remdesivir in terms of structure.

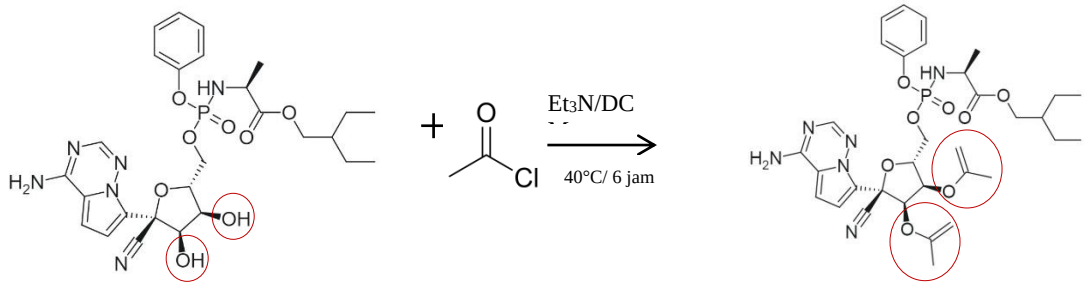

Figure 1. Synthesis of 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate

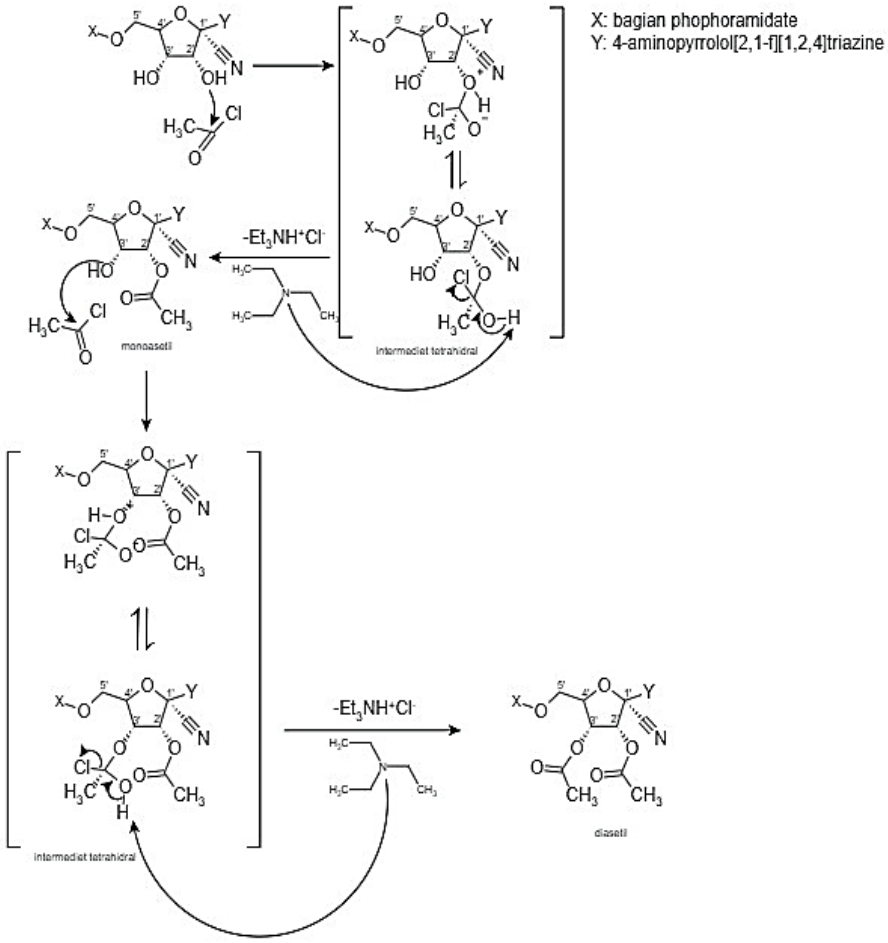

Figure 2. The mechanism of the acetylation reaction of the compound 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate

3.1.3. Spectrum Data 1H NMR and 13C NMR of Remdesivir Derivate

The results of 1H NMR analysis (Table 2, Figure 4) showed a peak in the remdesivir derivative 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate compound at the following positions: 7.91 ppm (triplet), 7.13 ppm (triplet), 6.87 ppm (triplet), 6.29 ppm (single), 5.64 ppm (single), 4.61 ppm (doublet), 4.15 ppm (quartet), 3.91 ppm (triplet of doublet of doublet), and 2.5 ppm (single). A chemical shift of 2.5 ppm is predicted to be a proton in a compound with the H-C-C=O structure. A chemical shift of 3.91 ppm and 4.15 ppm is predicted to be a proton in a methoxy compound. A chemical shift of 4.61 ppm is predicted

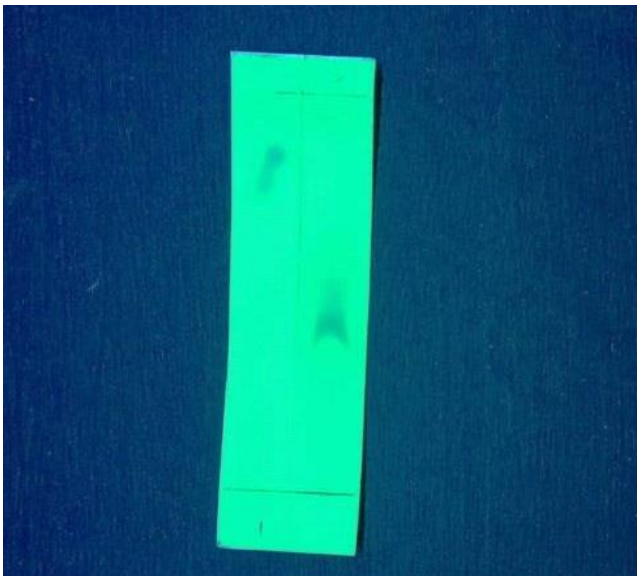

Figure 3. TLC results for remdesivir compounds (left) and remdesivir derivatives (right)

Table 1. Thin Layer Chromatography Results

Analysis	Remdesivir	Derivative of Remdesivir
Thin Layer Chromatography	Rf value: 0,84 Ratio of Eluent (Chloroform:Methanol= 2:3)	Rf value: 0,54 Ratio of Eluent (Chloroform:Methanol= 2:3)

to be a proton in a compound that bonds with amines (-NH). Chemical shifts of 5.64 ppm, 6.29 ppm, 6.87 ppm, 7.13 ppm, and 7.91 ppm are predicted to be protons in aromatic compounds and alkenes.

The results of 13C NMR analysis (Figure 5) showed a peak in the remdesivir derivative compound 2-ethyl butyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate at the δ positions of 155.59 ppm, 155.93 ppm, 153.88 ppm, 147, 83 ppm, 128.74 ppm, 123.95 ppm, 121.72 ppm, 119.98 ppm, 119.95 ppm, 117.16 ppm, 116.41 ppm, 110.39 ppm, 100.92 ppm, 83, 33 ppm, 83.27 ppm, 78.32 ppm, 74.41 ppm, 70.33 ppm, 64.60 ppm, and 64.56 ppm. Carbon with double bonds is predicted to have chemical shifts of 155.59 ppm, 155.93 ppm, 153.88 ppm, 147.83 ppm, 128.74 ppm, 123.95 ppm, 121.72 ppm, 119.98 ppm, 119.95 ppm, 117.16 ppm, 116.41 ppm, 110.39 ppm, and 100.92 ppm. Additionally, 56 ppm are predicted to be carbons that bond with electronegative O.

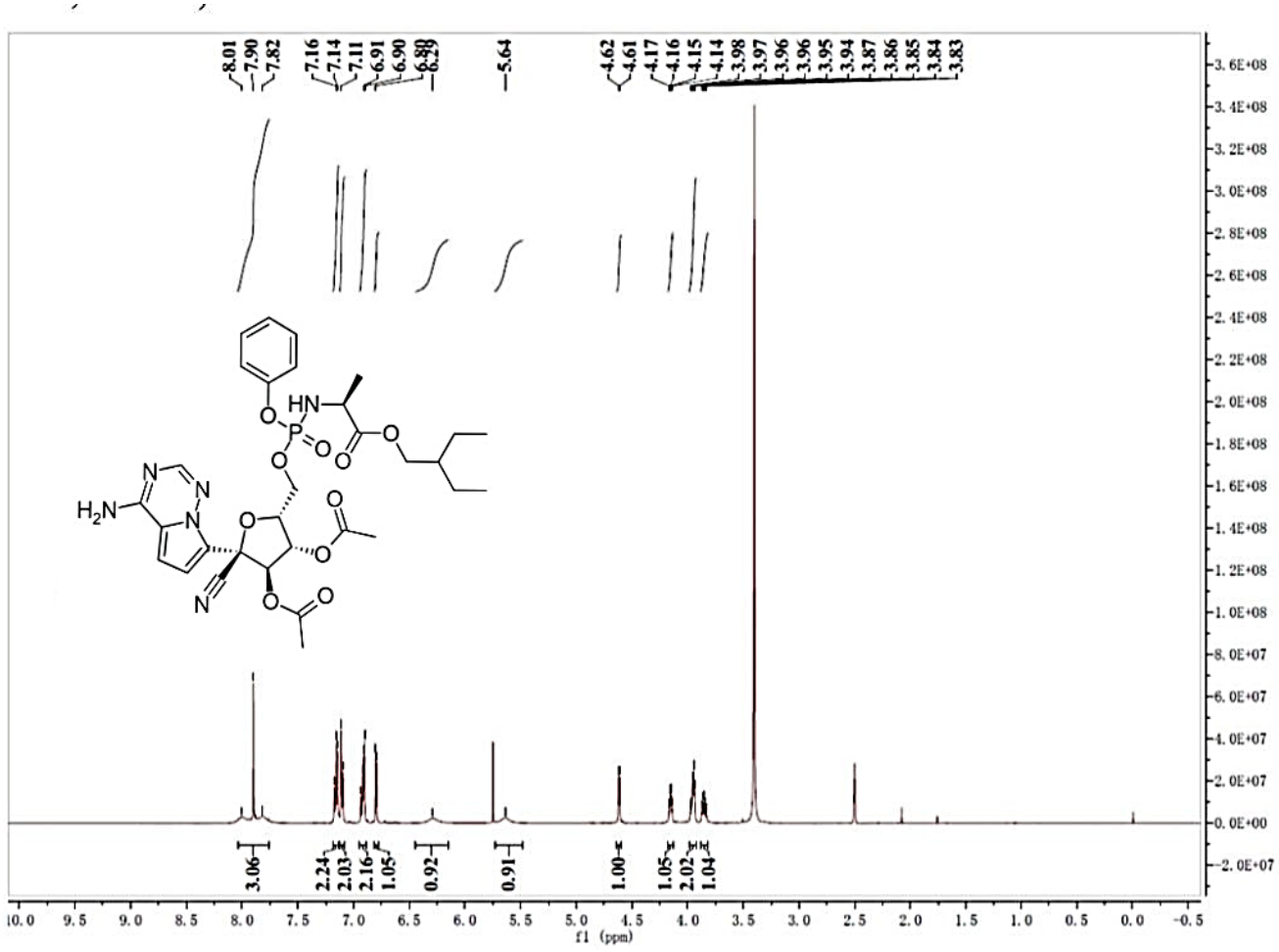

Figure 4. 1H NMR results for remdesivir derivatives

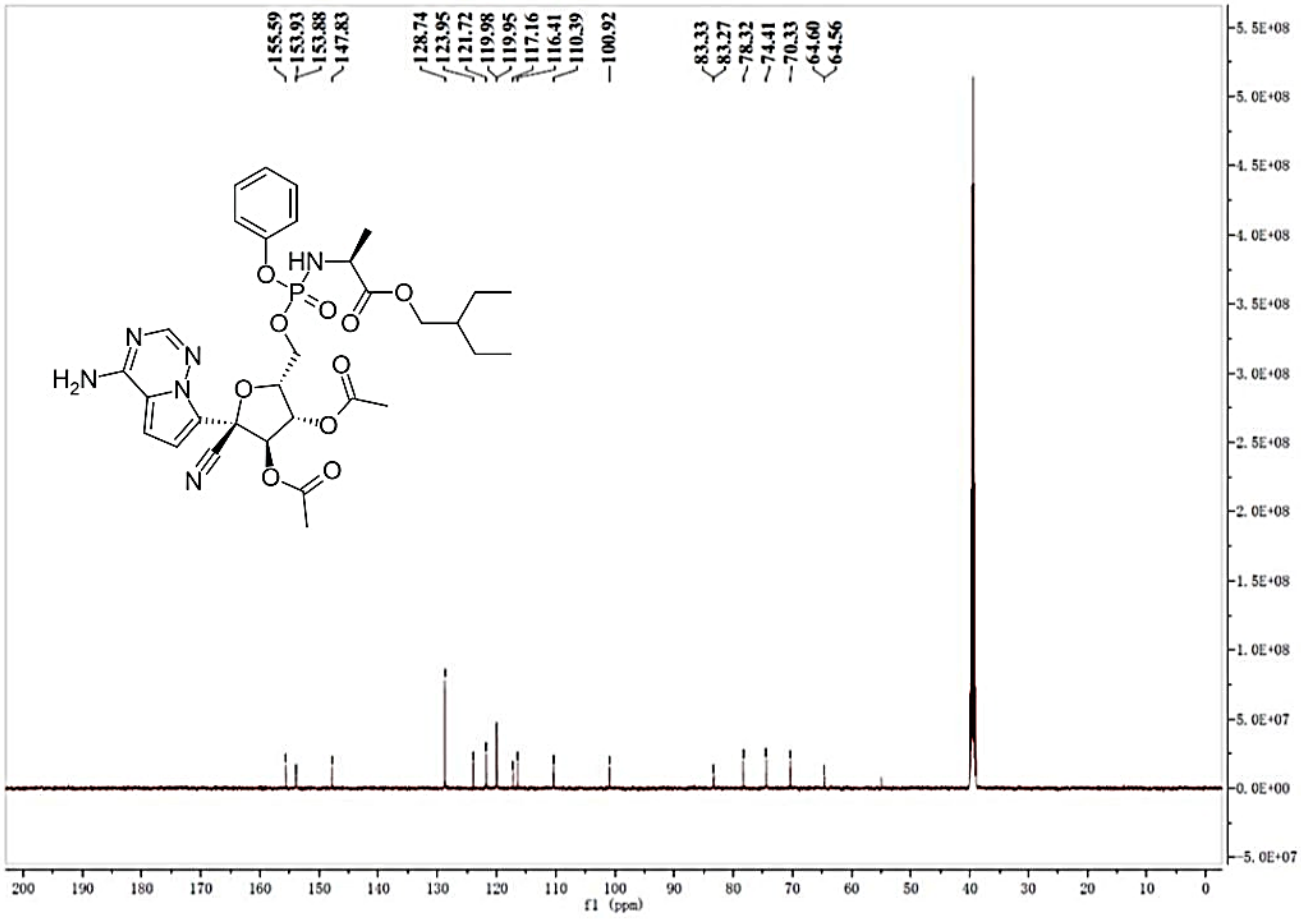

Figure 5. 13C NMR results for remdesivir derivatives

Table 2. Data from NMR measurements

	1H NMR	13C NMR
Chemical shift value (δ)	7.91 ppm (triplet) 7,13 ppm (triplet) 6,87 ppm (triplet) 6,29 ppm (singlet) 5,64 ppm (singlet) 4,61 ppm (doublet) 4,15 ppm (quartet) 3,91 ppm (triplet of doublet of doublet) 2,5 ppm (singlet)	155,59 ppm 155,93 ppm 153,88 ppm 147,83 ppm 128,74 ppm 123,95 ppm 121,72 ppm 119,98 ppm 119,95 ppm 117,16 ppm 116,41 ppm 110,39 ppm 100,92 ppm 83,33 ppm 83,27 ppm 78,32 ppm 74,41 ppm 70,33 ppm 64,60 ppm 64,56 ppm

4. Discussion

A chemical reaction called synthesis creates a complex molecule. The focus in pharmacy is on drug molecules. Although there are numerous chemical molecules, not all of them are medications. They must meet specific requirements to qualify as medications. Drugs are chemical substances that satisfy the criteria for having pharmacological activity, minimal toxicity, and storage stability (7). For the design of organic compound synthesis to be successful, it is necessary to have knowledge of dependable organic chemical processes and a comprehension of the reaction mechanisms, among other things. Having performed experiments involving organic chemicals, understanding stereochemistry, being familiar with the substances available, speeding up, and simplifying disconnect are

also necessary (8).

The USA Centers for Disease Control and Prevention and the USA Army Medical Research Institute for Infectious Diseases jointly own Gilead, which developed the first formulation of remdesivir (Veklury, GS-5734). Since nucleosides are known as cell-permeable substances, they are altered by molecules such as prodrug monophosphates, esters, and phosphoramides. Gilead Sciences researchers discovered that adenosine C-nucleoside with 1'-CN modification had potent anti-Ebola virus action in Hela cells and human umbilical vein endothelial cells. Remdesivir is the name of this potent substance (9). A nucleoside analogue called remdesivir (GS-5734; Gilead Sciences Inc., USA) functions as a competitive inhibitor of viral RNA-dependent RNA polymerase. The prodrug remdesivir has a precise mass of 602.23 Da and the chemical formula C27H35N6O8P. Remdesivir is transformed by the body into the active molecule GS-441524 with the chemical formula C12H13N5O4 (10). The complicated activation route and instability of remdesivir in plasma can have a very varied impact on its antiviral activity in SARS-CoV-2-infected cells (5).

Acetylation reactions, which include S_N2 reactions, such as mechanism reactions, are used to create 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxo lan-2-yl]methoxy-phenoxyphosphoryl]amino]propa noate compounds. This reaction is completed in a single step, during which the bond on the leaving group (loose group) begins to disintegrate and a nucleophilic bond is formed (11). Remdesivir is combined with acetyl chloride in dichloromethane and tetrahydrofuran solvents. These solvents are chosen because it is well known that the S_N2 reaction occurs when using a polar aprotic solvent (a polar solvent without OH and NH_2 groups). These two solvents speed up the S_N2 reaction by increasing the energy of the molecule. Triethyl amine is then employed as an organic base since the S_N2 reaction emits HCl, which could impede its development. This can be remedied by adding triethylamine base, which can also speed up the reaction, which is typical of the S_N2 reaction (11).

In this study, a remdesivir derivative compound, (2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxo lan-2-yl]methoxy-phenoxyphosphoryl]amino]propa noate), was created using a reagent comparison with the lead compound (3:1), in which 1 equivalent of remdesivir is reacted with 3 equivalents of acetyl chloride. In this compound, the hydroxyl group from remdesivir is substituted by an acetyl group (CH3CO) from acetyl chloride at positions 2' and 3' (Figure 1). In contrast, it is known that the free aromatic amine group in the remdesivir structure is less reactive than the hydroxyl groups in the 2' and 3' positions. The end product is a precipitate of brownish-yellow crystals with a distinct scent that dissolves well in distilled water and dimethyl sulfoxide (DMSO) but very slightly in ethanol and methanol. The synthetic precipitate has a mass of 0.8810 gr (77.34% yield). This outcome differs from the original component, remdesivir, which is a white powder with no scent.

According to the mechanism of the acetylation reaction (Figure 2), the hydroxyl group of remdesivir acts as a nucleophile and attacks the central carbon atom on the metallic acetyl (electrophilic) to produce a tetrahedral intermediate. The tetrahedral intermediate will then release transport, which is the leaving group forming an anion followed by the loss of a proton H, so that a synthesized compound is formed as a result of the acetyl group substitution. Cl and H combine to make HCl, and triethylamine heats up to create ammonium salt (Et3NH+Cl-).

Because El-Sayed (2021) employed fatty acyls as reagents, their technique of obtaining remdesivir derivatives through a conjugation reaction was distinct from the method used in this study to create remdesivir derivatives through an acetylation reaction. All remdesivir derivatives have a lengthy carbon chain, which prolongs the hydrolysis time.

The TLC can be used to monitor the development of a reaction, identify the compounds present in a

product, and analyze the purity of a substance. The struggle between the solute and the mobile phase for binding sites on the stationary phase is the basis for compound separation. For instance, silica gel used as the stationary phase can be regarded as polar in a normal-phase reaction. When two compounds with different polarities are present, the more polar molecule interacts with silica more strongly and is better able to remove the mobile phase from the binding sites (12).

An effective chromatographic method for separating organic substances is called TLC, which is frequently used to assess the purity of products and keep track of the development of organic reactions because it is quick and easy to use. The results of the TLC examination allowed for the product detection of chemical 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl] amino]propanoate. The stationary phase was silica gel GF 60, and the mobile phase, or eluting fluid, was a solution of chloroform and methanol (2:3). Stains were seen at UV 254 nm. As a result, one spot with a crescent shape and an Rf value of 0.54 was discovered in 254 nm UV light on the remdesivir-derived TLC plate (Figure 3). The obtained synthesized molecule had a different structure than remdesivir, as evidenced by the RF value, which is different from the RF value of 0.84 for remdesivir (lead compound). Evaluating this 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo [2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxo lan-2-yl]methoxy-phenoxyphosphoryl]amino]propano ate compound's ability to suppress the COVID-19 ability to replicate *in vitro* is the next step in the creation of a new medication.

The amount of each type of hydrogen and carbon in the compound under study can be determined using 1H NMR spectrophotometry and 13C NMR spectrophotometry, respectively. These techniques can also be used to learn more about the environmental characteristics of each type of hydrogen and carbon (12). The results of 1H NMR analysis showed a peak in the remdesivir derivative 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate compound at positions 7.91 ppm (triplet), 7.13 ppm (triplet), 6.87 ppm (triplet), 6.29 ppm (single), 5.64 ppm (single), 4.61 ppm (doublet), 4.15 ppm (quartet), 3.91 ppm (triplet of doublet of doublet), and 2.5 ppm (single). A chemical shift of 2.5 ppm is predicted to be a proton in a compound that has the H-C-C=O structure. A chemical shift of 3.91 ppm and 4.15 ppm is predicted to be a proton in a methoxy compound. A chemical shift of 4.61 ppm is predicted to be a proton in a compound that bonds with amines (-NH). Chemical shifts of 5.64 ppm, 6.29 ppm, 6.87 ppm, 7.13 ppm, and 7.91 ppm are predicted to be protons in aromatic compounds and alkenes.

The results of 13C NMR analysis showed a peak in the remdesivir derivative compound 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-diacetyloxyoxolan-2-yl] methoxy-phenoxyphosphoryl]amino]propanoate at the δ positions of 155.59 ppm, 155.93 ppm, 153.88 ppm, 147, 83 ppm, 128.74 ppm, 123.95 ppm, 121.72 ppm, 119.98 ppm, 119.95 ppm, 117.16 ppm, 116.41 ppm, 110.39 ppm, 100.92 ppm, 83, 33 ppm, 83.27 ppm, 78.32 ppm, 74.41 ppm, 70.33 ppm, 64.60 ppm, and 64.56 ppm. Carbon with double bonds is predicted to have chemical shifts of 155.59 ppm, 155.93 ppm, 153.88 ppm, 147.83 ppm, 128.74 ppm, 123.95 ppm, 121.72 ppm, 119.98 ppm, 119.95 ppm, 117.16 ppm, 116.41 ppm, 110.39 ppm, and 100.92 ppm. Moreover, 56 ppm are predicted to be carbons that bond with electronegative O.

The acetyl group from acetyl chloride was substituted in the 2' and 3' hydroxyl groups of remdesivir with a weight of 0.8810 gr (77.34% yield), resulting in the synthetic compound 2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4] triazin-7-yl)-5-cyano-3,4- diacetyloxyoxolan-2-yl] methoxy-phenoxyphosphoryl]amino]propanoate at 1H

NMR δ positions of 7.91 ppm (triplet), 7.13 ppm (triplet), 6.87 ppm (triplet), 6.29 ppm (singlet), 5.64 ppm (singlet), 4.61 ppm (doublet) 4.15 ppm (quartet), 3.91 ppm (triplet of doublet of doublet), and 2.5 ppm (singlet), and 13C NMR δ positions of 155.59 ppm, 155.93 ppm, 153.88 ppm, 147.83 ppm, 128.74 ppm, 123.95 ppm, 121.72 ppm, 119.98 ppm, 119.95 ppm, 117.16 ppm, 116.41 ppm, 110.39 ppm, 100.92 ppm, 83.33 ppm, 83.27 ppm, 78.32 ppm, 74.41 ppm, 70.33 ppm, 64.60 ppm, and 64.56 ppm, C31H39N6O10P (686.659 g/mol), which has the appearance of a yellow-brown crystal precipitate, a distinct aroma, and is well soluble in distilled water, DMSO, and slightly soluble in ethanol and methanol.

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Authors' Contribution

Study concept and design: R.S and Y.R
Drafting of the manuscript: R.S
Analysis and interpretation of data: R.S, Y.R, and G.A

Ethics

Ethics The study design was approved by the ethics committee of Hasanuddin University, Makassar, Indonesia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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