E-ISSN: 2664-6773
P-ISSN: 2664-6765
Impact Factor: RJIF 5.6
IJCBS 2025; 7(2): 19-25
www.chemicaljournal.org
Received: 16-06-2025
Accepted: 19-07-2025
Published: 27-07-2025

Nabaa Abdul-Rasool Mahmood
Department of Chemistry, College of Science, University of Kirkuk, Kirkuk, Iraq

Hala Mohammed Ghareeb
Department of Chemistry, College of Science, University of Kirkuk, Kirkuk, Iraq

Corresponding Author:
Nabaa Abdul-Rasool Mahmood
Department of Chemistry, College of Science, University of Kirkuk, Kirkuk, Iraq

Synthesis and characterization of alanine-derived nucleoside analogues

Nabaa Abdul-Rasool Mahmood and Hala Mohammed Ghareeb

DOI: https://www.doi.org/10.33545/26646765.2025.v7.i2a.142

Abstract
In this work, a series of new nucleoside analogues derived from alanine were synthesized using a multistep method involving Schiff base formation, Pictet–Spengler-type cyclization, glycosylation with protected fructose, and subsequent deacetylation. This synthetic approach enabled the construction of fused heterocyclic systems incorporating both amino acid and sugar moieties, resembling natural nucleoside structures. TLC, melting point analysis, FT-IR, and detailed ^{1}H and ^{13}C NMR spectroscopy were employed to characterize the key intermediates and final products. The inclusion of alanine introduced pharmacophoric functionality, facilitating ring closure and potentially enhancing biological selectivity. Additionally, the use of a per acetylated fructose derivative improved glycosylation efficiency and structural stability. The resulting deprotected compounds exhibited well-defined structures, rendering them suitable for future bioactivity screening. Overall, the proposed methodology offers a promising synthetic platform for the development of structurally diverse and biologically relevant nucleoside mimics.

Keywords: Alanine, protected sugar, nucleoside analogues, Schiff base, cyclization

1. Introduction
Nucleosides analogs are a significant family of antiviral and therapeutic drugs that are frequently used to treat persistent viral infections and some types of cancer. Their importance stems from their capacity to imitate natural nucleosides and obstruct the synthesis and replication of viral DNA or RNA. Because of this mechanism, nucleoside analogues are very effective against viruses like the hepatitis B virus (HBV), slowing the course of the disease and lowering the risk of hepatocellular carcinoma, which is one of the world's leading causes of cancer-related death [1]. In addition to their antiviral properties, some nucleoside analogues, such as cladribine, are used to control the immune system in diseases including multiple sclerosis [2]. These medications work by targeting certain lymphocyte populations, which reduces disease activity. When paired with other treatment options, their therapeutic benefit extends to the control of extrahepatic viral infections as well as improved clinical outcomes [3]. Despite their demonstrated usefulness, continuing research seeks to improve their usage, reduce resistance, and create safer and more effective counterparts [4]. In drug development, amino acids such as alanine play a critical role in enhancing biological activity and selectivity [5]. Their unique chemical properties strengthen antioxidant defenses by mediating molecular interactions, improving the solubility and bioavailability of bioactive compounds, and modulating cellular pathways such as NRF2–KEAP1 [6]. Co-amorphous systems that include amino acids (e.g., arginine and lysine) have been demonstrated to improve the potency of drugs such as genistein. Furthermore, proline and other amino acids have important structural roles in crucial biological activities such as immune responses and signal transmission. Because of their many functions, amino acids are essential for optimizing treatment efficacy [7].

Alanine, in particular, plays an important function in increasing biological activity and selectivity in a variety of biochemical and pharmacological applications. It has been demonstrated that structural modification of natural chemicals with amino acids increases their biological potency, solubility, and selectivity. Conjugation with amino acids, for example, can produce derivatives with increased antiproliferative action against cancer cells while reducing damage to normal cells, as seen by investigations on 23-hydroxybetulinic acid derivatives [8]. Additionally, alanine plays a role in vital metabolic functions that affect biological function and cellular energy balance, including gluconeogenesis and glycolysis control. Furthermore, via modifying signaling pathways such as mTOR, which controls protein synthesis and cell

proliferation, amino acids support certain physiological responses [9]. The ability of amino acids to improve biological performance is further demonstrated by their significance in promoting psychosocial and cognitive health in aging populations. All things considered, adding or supplementing with amino acids such as alanine can greatly increase the effectiveness and specificity of physiological functions and medicinal substances [10].

Sugar derivatives based on alanine have garnered a lot of attention because of their unique chemical and biological characteristics. These derivatives combine sugar moieties with the structural characteristics of alanine, an essential amino acid, to create molecules that may find use in biomolecular research, medicinal chemistry, and metabolic engineering. Numerous studies have been conducted on their synthesis, structural description, and biological activities, such as metabolic activity and enzyme inhibition.

The asymmetric synthesis of α-alanine derivatives using Michael addition reactions has been the subject of recent research, which has shown encouraging biological activities including aldose reductase inhibition, which is pertinent to diabetic problems [11]. Furthermore, studies on the chemical reactivity of N, N-diglycated alanine derivatives have provided insight into their distinct reactivity as well as the creation of new heterocyclic structures that are pertinent to the chemistry of the Maillard reaction [12]. Their conformational characteristics and possible application as artificial peptide building blocks have been revealed by structural investigations of sugar amino acids with amino acid moieties affixed to hexose backbones [13].

The metabolic significance of alanine derivatives has also been investigated, in addition to their synthetic chemistry. For example, alanine has been demonstrated to improve glucose metabolism in pancreatic β-cells, and L-alanine metabolism is essential for cellular processes like insulin synthesis. All of these studies highlight the interest in alanine-based sugar derivatives from a variety of fields, including synthetic organic chemistry, metabolic biochemistry, and structural biology [14].

The synthesis and characterization of novel alanine-derived nucleoside analogues is a potential avenue in medicinal chemistry for generating bioactive compounds with better therapeutic characteristics. Nucleoside analogues are structurally modified copies of natural nucleosides that have gained popularity as antiviral, anticancer, and antibacterial medicines due to their potential to alter nucleic acid metabolism and function [15]. The chemical synthesis of these analogues frequently employs tactics that allow for selective alterations of the sugar or base moieties, such as the use of achiral starting materials and catalytic approaches to increase efficiency and stereo selectivity [16].

Recent advances have demonstrated the efficacy of proline-catalyzed enantioselective aldol reactions and intramolecular cyclizations in swiftly producing varied nucleoside analogues from simple precursors, facilitating the development of chemical libraries for drug discovery. Alanine-derived analogues with amino acid motifs may have distinct bioactive profiles because they combine nucleoside pharmacophores with amino acid functions, hence increasing both biological activity and target selectivity [17]. These new compounds are often described using spectroscopic methods and biologically evaluated to determine their efficacy against relevant medicinal targets [18].

The aim of this article is to develop a multi-step synthetic strategy for the synthesis of new alanine-derived nucleoside analogues through Schiff base formation and cyclization, glycosylation with protected fructose, and deacetylation; to create fused heterocyclic systems that mimic natural nucleosides by incorporating both sugar and amino acid moieties; to characterize the synthesized intermediates and final products using FT-IR, TLC, melting point analysis, and detailed ^{1}H and ^{13}C NMR spectroscopy; and, finally, to create a flexible synthetic platform for producing structurally diverse and biologically relevant nucleoside mimics.

2. Materials and Methods

2.1 Materials

All materials were obtained from Merck® and utilized without additional purification.

2.2 Procedures

2.2.1 Schiff Base Synthesis

An equimolar mixture (0.01 mol) of one of the aromatic aldehydes (*p*-hydroxybenzaldehyde, *p*-bromobenzaldehyde, or *p*-chlorobenzaldehyde) dissolved in 10 mL of 100% ethanol was combined with aniline (0.01 mol) in a 150-mL round-bottom flask. After adding a few drops of glacial acetic acid, the mixture was refluxed and stirred constantly for 12 hours at 70-80 °C. After completion, the reaction mixture was allowed to cool, forming a precipitate. The solid result was then filtered, washed, and recrystallized with 100% ethanol, as illustrated in the equation below. Thin-layer chromatography (TLC) was performed to validate the production of products (1, 2, and 3), with a 7:3 (v/v) solvent system of hexane and ethyl acetate [19].

2.2.2 Cyclization Procedure

0.01 mol of Schiff bases (1, 2, and 3) were dissolved in 15 mL of tetrahydrofuran (THF), and then 0.01 mol of alanine was added. Following that, the reaction mixture was refluxed for 48 hours. After the reflux was finished, the mixture was cooled, and the precipitate that formed was collected and recrystallized using ethanol. Thin-layer chromatography (TLC) was utilized to track the reaction's development and completion using a methanol: benzene solvent solution in a 4:1 (v/v) ratio [20]. allowing for the isolation of pure compounds (4, 5, and 6).

^{1}H NMR for Compound (4) (250 MHz, $CDCl_3$) δ (ppm): 8.*58* (s, 1H), 7.32 (m, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 7.22 (m, 1H), 6.78 (m, 1H). 5.98 (s, 1H), 3.92 (q, 1H) and 1.21 (d, 3H) ^{13}C NMR (250 MHz, CDCl3) δ (ppm):18.00, 53.93, 87.29, 114.80, 123.90, *126.2*6, 129.70, 133.99, 137.33, 157.87and 170.48.

^{1}H NMR for Compound (5) (250 MHz, $CDCl_3$) δ (ppm): 7.48 (m, 1H), 7.34 (m, 1H), 7.30 (m, 1H), 7.23 (m, 1H), 7.14 (m, 1H), 7.01 (m, 1H). 5.99 (s, 1H), 3.93 (q, 1H) and 1.21 (d, 3H) ^{13}C NMR (250 MHz, CDCl3) δ (ppm):25.03, 52.18, 80.81, 121.51, 126.75, *1*29.42, 129.69, 130.74, 132.34, 136.55,142.09and 174.58.

^{1}H NMR for Compound (6) (250 MHz, $CDCl_3$) δ (ppm): 7.50 (m, 1H), 7.32 (m, 1H), 7.28 (m, 1H), 7.26 (m, 1H), 7.25 (m, 1H), 7.19 (m, 1H). 6.00 (s, 1H), 3.92 (q, 1H) and 1.21 (d, 3H) ^{13}C NMR (250 MHz, CDCl3) δ (ppm):18.00, 53.93, 77.94, 123.80, 126.26, *1*28.11, 128.87, 129.70, 134.95, 137.34,139.19 and 170.48.

2.2.3 Fructose Protection Procedure

Fructose (1 g, 0.006 mol) and anhydrous sodium acetate (0.8

g, 0.0097 mol) were mixed in 6 mL of acetic anhydride. The reaction mixture was then cooked in a water bath for three hours, stirring continuously. After completing the acetylation, the reaction product was extracted with chloroform, and the solvent was evaporated to produce a dark syrup. TLC was performed to monitor the reaction and confirm the synthesis of α-D-fructofuranoside pentaacetate (Compound 7), using a chloroform: methanol solvent mixture (4:1, v/v) [21].

^{1}H NMR for Compound (7) (250 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H), 7.42 (m, 1H), 7.28 (m, 1H),6.79 (s, 1H) and 3.90 (q, 2H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 20.70, 20.75, 20.88, 20.96, 21.46, 64.47, 64.97, 73.56, 75.43, 77.40, 107.72, 169.87 and 170.83.

2.2.4 General Procedure for the Preparation of 2-Bromo Acetyl Sugar Compound 8

After dissolving Compound **7** (0.006 mol) of acetylated sugar, add 3 mL of 50% hydrogen bromide in glacial acetic acid dropwise at 5 °C. After one hour of stirring at 5 °C, pour the solution into 35 mL of chloroform and let it rest at room temperature for 15 minutes. After washing with ice-cold water (2 × 15 mL), the mixture was neutralized with saturated aqueous sodium bicarbonate to remove any leftover acid. The organic layer was dried over anhydrous magnesium sulfate ($MgSO_4$) following a final wash with 20 mL of cold water. The solvent was evaporated, leaving Compound 8 as an oily residue. The reaction was tracked by TLC in a chloroform: methanol (4:1, v/v) solvent solution. The isolated bromo sugar was used directly for the synthesis of nucleoside analogues [22].

1H NMR for Compound (8) (250 MHz, CDCl3) δ (ppm): 5.53 (d, 1H), 5.32 (t, 1H), 4.82 (dd, 2H), 4.75 (q, 1H), 4.37 (q, 2H) and 2.03 (m, 12H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 20.72, 20.76, 20.89, 21.09, 64.44, 67.41, 74.13, 76.35, 77.53, 92.66, 169.98, 170.44, 170.65 and 170.71.

2.2.5 Synthesis of Protected Nucleoside Analogs Derivatives (9, 10, 11)

Acetylated sugar bromide (0.001 mol) was mixed with a solution of one of the compounds (4, 5, or 6) in 25 milliliters of dry o-xylene. The mixture was swirled for an hour. The organic layer was then rinsed with two milliliters of water and dried on anhydrous sodium sulfate. The solvent was then evaporated to get the acetylated nucleosides. Thin Layer Chromatography (TLC) was used to monitor the progress and completion of the reaction, with the mobile phase being a 4:1 combination of chloroform and methanol [23].

^{1}H NMR for Compound (9) (250 MHz, $CDCl_3$) δ (ppm): 8.58 (s, 1H), 7.32 (m, 1H), 6.78 (m, 1H), 5.82 (s, 1H), 5.32 (m 1H), 4.65 (m, 2H), 4.11 (q, 1H), 2.06 (q, 12H), and 1.37 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 16.20, 20.90, 58.54, 78.16, 99.03, 115.84, 125.20, 126.26, 129.70, 130.25, 134.53, 138.48, 157.86, and 173.88.

^{1}H NMR for Compound (10) (250 MHz, $CDCl_3$) δ (ppm): 7.50 (m, 1H), 7.32 (m, 1H), 5.83 (s, 1H), 4.53 (m 1H), 4.43 (m, 2H), 4.12 (q, 1H), 2.05(q, 12H), and 1.37 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 18.97, 21.49, 63.39, 77.72, 97.53, 123.43, 129.10, 129.43, 131.65, 133.77, 135.30, 139.77, 144.64, and 172.54.

^{1}H NMR for Compound (11) (250 MHz, $CDCl_3$) δ (ppm): 7.42 (m, 1H), 7.29 (m, 1H), 5.82 (s, 1H), 4.51 (m 1H), 4.48 (m, 2H), 4.11 (q, 1H), 2.04 (q, 12H), and 1.36 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 16.18, 20.90, 58.54, 63.76, 76.72, 99,03, 125.20, 129.06, 129.70, 130.27, 134.94, 138.49, 140.15 and 173.88.

2.2.6 Hydrolysis for Protected Nucleosides Analog Derivatives (12, 13, 14)

A solution comprising 0.003 mol of the protected nucleoside analogs (9, 10, 11) was heated in seven milliliters of 0.1 M sodium methoxide and stirred for 30 minutes. The reaction mixture was then neutralized with acetic acid and evaporated until dry. After dividing the residue between water and chloroform, the aqueous layer was vacuum-dried to extract the nucleoside analogs. TLC was used to monitor the progress and completion of the reaction in a chloroform-methanol solvent combination (4:1, v/v) [24].

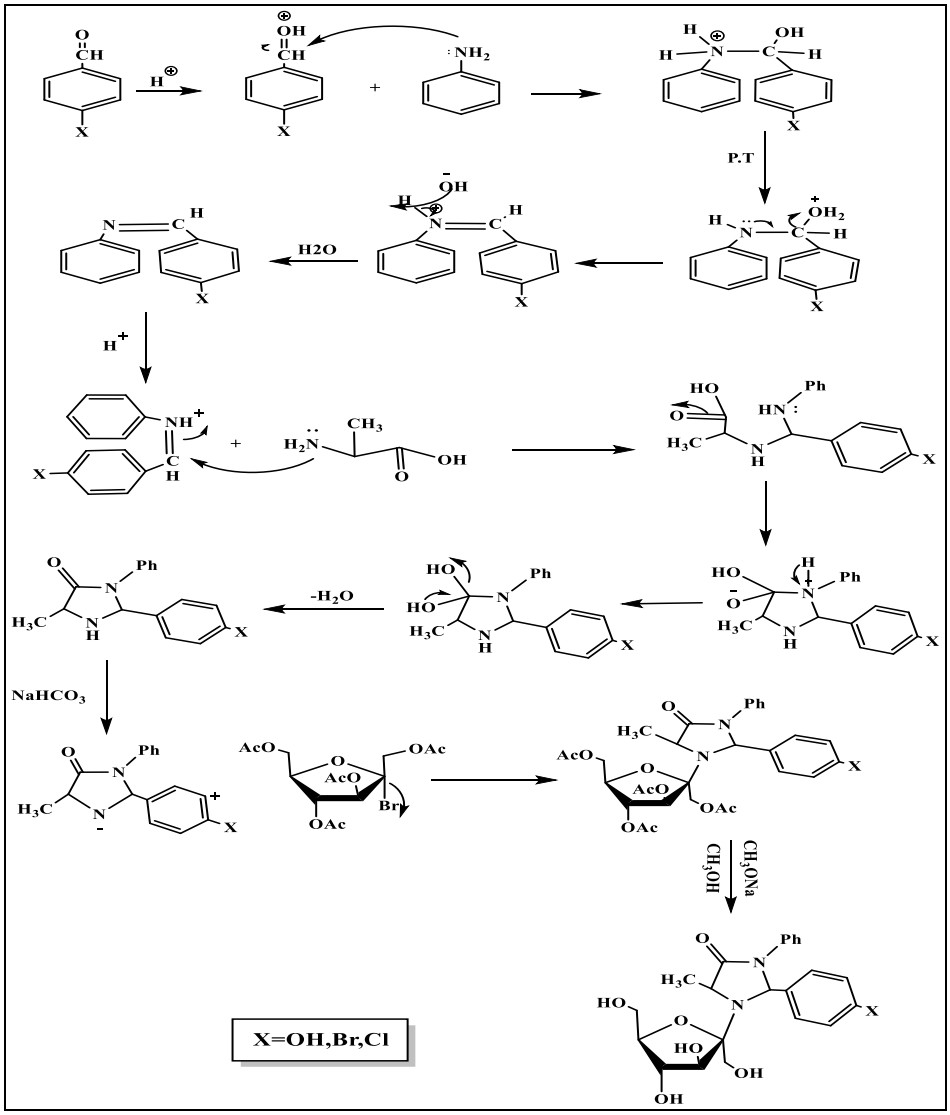
^{1}H NMR for Compound (12) (250 MHz, $CDCl_3$) δ (ppm):8.58 (s, 1H), 7.34 (m, 1H), 6.78 (m, 1H), 5.78 (s, 1H), 4.77 (m 1H), 4.39 (m, 2H), 4.13 (q, 1H), 3.54 (q, 12H), and 1.37 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 16.17, 58.78, 76.93, 98.38, 115.84, 125.19, 126.26, 129.70, 130.37, 134.41, 138.39, 157.86, and 173.71.

^{1}H NMR for Compound (13) (250 MHz, $CDCl_3$) δ (ppm): 7.53 (m, 1H), 7.23 (m, 1H), 5.78 (s, 1H), 4.39 (m, 1H), 4.32 (q,1H), 3.97 (m, 1H), 3.54 (q, 12H), and 1.37 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 13.66, 29.46, 65.52, 79.38, 84.16, 98.38, 125.19, 126.26, 139.70, 130.27, 134.94, 138.28,140.04 and 173.68.

^{1}H NMR for Compound (14) (250 MHz, $CDCl_3$) δ (ppm): 7.41 (m, 1H), 7.21 (m, 1H), 5.77 (s, 1H), 4.77 (m, 1H), 4.26 (q,1H), 3.98 (m, 1H), 3.56 (q, 12H), and 1.38 (d, 3H). ^{13}C NMR (250 MHz, CDCl3) δ (ppm): 16.17, 58.78, 68.89, 79.15, 89.23, 102.65, 124.41, 126.75, 130.93, 131.75, 132.81, 137.23,142.14 and 173.71.

3. Mechanistic Interpretation

According to the suggested mechanism (Scheme1), the synthetic pathway to the alanine-derived nucleoside analogues involves a multi-step process that includes imine production, cyclization, glycosylation, and ultimate deprotection.



Scheme 1: Suggested mechanisms of the synthetic route of targeted molecules.

Step 1: Schiff Base Formation

A substituted aromatic aldehyde (X = OH, Br, Cl) is first condensed with aniline by an acid, which then forms a Schiff base by the amine's nucleophilic assault on the protonated carbonyl group and dehydration. This imine intermediate is an essential building block for further ring formation.

Step 2: Alanine Cyclization

In the presence of L-alanine or a derivative of it, the Schiff base is electrophilically cyclized. By attacking the amino group nucleophilically, the amino acid aids in intramolecular cyclization, producing a fused heterocyclic indole-like structure. In this stage, the nucleobase moiety is mimicked by a stable amide-linked ring structure.

Step 3: Protected Fructose Nucleophilic Substitution

To produce the glycosyl bromide, HBr first activates the protected sugar, peracetylated *β-D*-fructofuranose, in acetic acid. Through an SN1/SN2-like route, the nucleophilic intermediate attacks the sugar's anomeric carbon in a basic medium ($NaHCO_3$), creating a new C–O glycosidic bond between the sugar and the heterocyclic core.

Step 4: Formation of the Final Product and Deacetylation

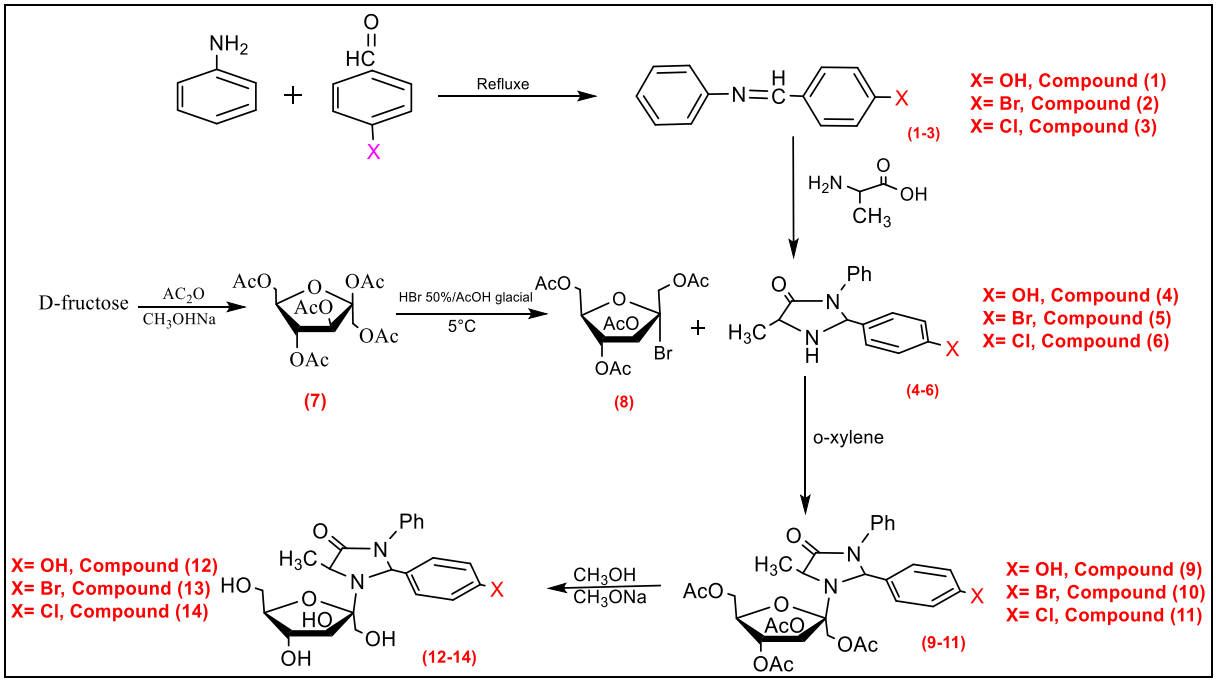
The final alanine-derived nucleoside analogue is obtained by mildly hydrolyzing the sugar, which removes the acetyl protecting groups and releases the free hydroxyl groups. By combining three essential pharmacophores a glycosyl unit, a heterocyclic core, and an amino acid fragment the resultant molecule closely resembles the structural makeup of natural nucleosides.

The crucial importance of Schiff base creation and Pictet-Spengler cyclization in creating nucleoside-like frameworks is highlighted by this process. Potential bioactivity is increased by adding alanine, while stability and synthetic accessibility are provided by glycosylation with a protected sugar. The finished compound shows promise as a nucleoside mimic for additional biological analysis.

4. Results and Discussions

4.1 Characterization of the Synthesized Compounds

This study investigates the synthesis of many nucleoside analogues derived from certain amino acids. The compounds were characterized using TLC, FT-IR, NMR, and melting point determination, as described in Chapter Two. The following technique was used to create the compounds using the experimental procedures outlined in Chapter Two:



Scheme 2: Synthetic route of the prepared.

By monitoring changes in physical characteristics like color, melting point, and thin-layer chromatography (TLC), the reaction's occurrence was verified. FT-IR spectroscopy was used to analyze Compounds 1, 2, and 3. The C=O stretching band at 1690 cm^{-1} in the reactant p-bromobenzaldehyde disappeared, whereas an absorption band at 1623 cm^{-1} corresponding to the stretching vibration of the C=N bond developed. The absorption band at 2881 cm^{-1} was caused by the stretching vibration of aliphatic C-H bonds, whereas the 3090 cm^{-1} band was caused by the stretching vibration of aromatic C-H bonds. The C-Br group exhibited a pronounced absorption band at 540 cm^{-1}. Absorption bands at 15 cm^{-1} were identified as aromatic C=C stretching vibrations. Every spectral data point was consistent with the references in the literature [25].

Compounds 4, 5, and 6 were examined by FT-IR spectroscopy as well. Two absorption bands were identified in the infrared spectrum: one for aromatic (C-H) stretching vibrations at 3028 cm^{-1} and one for aliphatic (-CH_2-) stretching vibrations at 2882 cm^{-1}. The aromatic C=C stretching vibrations were ascribed at 1581 cm^{-1}, whereas the N-H stretching was discovered at 3176 cm^{-1}. A notable absorption band that corresponded to the C=O formed at 1715 cm^{-1}. It was found that the C=N stretching vibration had eliminated the absorption band at 1620 cm^{-1}. At 536 cm^{-1}, the C-Br group that was joined to the benzene ring showed a clear absorption band. These results are consistent with previous research [26].

Characterization of the following substance was based on changes in its physical properties, such as color, melting points, and thin-layer chromatography. FT-IR spectroscopy was also employed to analyze Compound 7. The IR spectra indicated aliphatic (-CH_2-) stretching vibrations as the source of an absorption band at 2982 cm^{-1}, whereas the hydroxyl (-OH) group caused the absorption band to dissipate at 3409 cm^{-1}. The carbonyl (C=O) group showed a strong absorption band at 1740 cm^{-1}, whereas C-O stretching was represented by a band at 1216 cm^{-1}. An absorption band attributable to the ether (C-O-C) group was found at 1044 cm^{-1}. Every spectral data point was consistent with the references in the literature [27].

Compound 8 was characterized by changes in physical properties, such as color, melting points, and thin-layer chromatography (TLC). FT-IR spectroscopy was used to confirm Compound 8's structure. The aliphatic -CH_2- groups' stretching vibrations were represented as an absorption band at 2929 cm^{-1} in the infrared spectrum. A significant absorption band at 1733 cm^{-1} was found to be originating from the carbonyl (C=O) group, whereas a band at 1220 cm^{-1} was found to be originating from the C–O stretching vibration. Another absorption band at 1043 cm^{-1} indicated the existence of a C–O–C functional group, while a band at 603 cm^{-1} indicated the presence of a C–Br bond. Every spectral data point was consistent with the references in the literature [28].

Compound 9, 10, and 11 The structures have been verified using FT-IR spectroscopy. Infrared spectra show an absorption band at 2934 cm^{-1} for aliphatic -CH_2- groups and another at 3077 cm^{-1} for aromatic C-H stretching vibrations. An absorption band appeared at 1223 cm^{-1}, indicating C-O stretching. The absence of the N-H bond was proven by the disappearance of the absorption band at 3208 cm^{-1}, formerly attributed to N-H stretching. Aromatic C=C stretching vibrations caused a prominent band at 1583 cm^{-1}.Additionally, the emergence of a noticeable absorption band at 1720 cm^{-1} verified the presence of a carbonyl (C=O) group. The spectra also revealed an absorption band at 690 cm^{-1}, which is where the C–Cl bond attached to a benzene ring is located. All of the spectral data points were consistent with the literature's references [29].

In the infrared spectra, Compounds 12, 13, and 14 show an absorption band at 2986 cm^{-1} for aliphatic -CH_2- groups and a band at 3046 cm^{-1} for aromatic C-H groups. The absorption bands at 1215 cm^{-1} and 1538 cm^{-1} were used to identify C-O stretching and aromatic C=C stretching vibrations, respectively. At 1693 cm^{-1}, a distinct absorption band indicating the presence of a carbonyl (C=O) group developed. The 3200-3400 cm^{-1} range exhibited a significant absorption band, which is indicative of hydroxyl stretching. Every spectral data point was consistent with the references in the literature [30].

From the above results and discussions, it has been confirmed

that the synthesis of nucleoside analogous of alanine derivatives are possible based on the followed procedures and the utilized characterization methods.

5. Conclusions

In this work, new alanine-derived nucleoside analogues were synthesized in a multistep process that included Schiff base creation, cyclization, and glycosylation with protected fructose. This method allows the efficient creation of fused heterocyclic systems that resemble natural nucleosides. Comprehensive ^{1}H and ^{13}C NMR studies confirmed structural integrity. The incorporation of alanine enabled cyclization and provided potential bioactive sites, whereas sugar protection improved stability and synthetic accessibility. These findings demonstrate the applicability of amino acid-based approaches for producing various nucleoside analogues with potential antiviral or anticancer action, necessitating additional biological investigation and pharmacological improvement.

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