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ORIGINAL RESEARCH ARTICLE

Synthesis, Characterisation and Application of New Amino Acid Proline Derivatives

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ABSTRACT

Five carrier drugs derived from proline were synthesised from proline 1 through an identical synthetic pathway: N-(carboxymethyl proline)-Ampicillin (A1), N-(carboxymethyl proline)-4-Amino antipyrine (A2), N-(carboxymethyl proline)-Cephalexin (A3), N-(carboxymethyl proline)-Ciprofloxacin (A4), and N-(carboxymethyl proline)-Sulfadiazine (A5). All intermediates and final products were identified using IR and 1H-NMR techniques. The antibacterial efficacy was assessed using the paper disc diffusion method. A strategy aimed at Gram-negative (Escherichia coli) and Gram-positive (Staphylococcus aureus) bacteria revealed that specific synthesised compounds demonstrated potential effectiveness against the evaluated pathogens compared to the commercially available antibiotic (Ampicillin). Molecular docking simulations were conducted for all synthesised compounds against DNA gyrase of Staphylococcus aureus and E. coli; the results indicated that the screened compounds possess potential activity for inhibiting DNA gyrase.

Keywords: Proline derivatives; Cephalexin; Sulfadiazine; 4-Amino antipyrine

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1. Introduction

Proline and its substituted derivatives are found in nature [1] and synthetic bioactive substances [2]. Over the past three decades, there has been a notable increase in publications regarding the chemistry and biology of numerous products where substituted prolines are essential components of the target molecules. Non-proteinogenic prolines have gained prominence as vital intermediates due to their role in synthesizing conformationally rigid bioactive peptides, angiotensin-converting enzyme inhibitors, and pharmacological probes [3,4]. Proline and its derivatives are commonly utilised as asymmetric catalysts in organic reactions, such as CBS reductions, proline-catalysed aldol reactions, and Minnich reactions. Additionally, L-proline functions as an osmo-protectant and is therefore employed in various pharmacological and biotechnological applications [5,6,7]. In the last decade, the role of (S)-proline and its derivatives as catalysts has advanced organocatalysis into a significant and dynamic field in organic chemistry [8]. It is well-established that enantiopure (S)-proline, [9] Compound A (R = H), and its derivatives are highly regarded substances widely employed in asymmetric synthesis and organocatalysis [10]. The pursuit offer asymmetric catalysts that yield high outputs and enantioselectivities persists as an ongoing effort for organic chemists. A notable field explored in recent years is asymmetric organocatalysis, which is particularly beneficial due to its exclusion of metals, which are typically expensive and harmful.

Proline is recognised as a versatile organocatalyst [11]. Conversely, Carbohydrates represent a crucial category of fundamental elements for the synthesis of diverse N-heterocycles and have practical applications in agrochemicals and pharmaceuticals. Proline is acknowledged as an anti-stress compound in specific plants, known to accumulate in response to environmental stressors such as cold temperatures, salinity, and air pollution. Research has shown that the administration of abscisic acid (ABA) leads to increased proline concentrations in plants [12,13,14]. Proline plays a critical role in the synthesis of collagen and cartilage, contributing to the flexibility of muscles and joints while helping to alleviate sagging and wrinkling associated with ultra violet (UV) exposure and the natural aging of the skin. It aids in preventing arteriosclerosis by facilitating the discharge of fat accumulation from the arterial walls into the bloodstream, thereby reducing the size of obstructions to the heart and adjacent veins. Consequently, proline mitigates the pressure generated by these obstructions, thereby reducing the risk of cardiovascular disease. L-Proline acts as an osmo-protectant and is therefore utilised in numerous medicinal and biotechnological applications [15]. Pauling and Rath contend that sufficient Vitamin C consumption notably enhances cardiovascular health , as it aids in collagen production, which is vital for maintaining arterial health, alongside the amino acids L-lysine and L-proline that facilitate the effective use of cholesterol in relation cardiovascular well-being [16]. Proline and its chimeras demonstrate unique dynamic and structural roles in protein folding due to their ability to stabilise peptide secondary structures, including β-turns and polyproline helices. Furthermore, proline derivatives and peptides have been widely utilised as catalysts in stereoselective chemical synthesis [17,18]. In this regard, 3- and 4-hydroxyprolines (3-Hyp, 4-Hyp) are significant due to their distinctive catalytic capabilities and ability to be converted into more complex molecules through hydroxy group modification. The O-alkylation and O-acylation processes yield catalytically active proline ethers and esters, respectively, along with precursors for the synthesis of pyrrolidinyl PNA [19-22], proline-containing polymers [23], dendrimers [24], silica-grafted prolines [25], and O-glycosylated-Hype [26], the latter of which are significant structural constituents of various plant glycoproteins [27]. Chiral carboxylic acids are essential natural products, medicines, or crucial precursors for the synthesis of many compounds with biological and pharmacological effects. The investigation of chiral recognition of carboxylic acids by synthetic receptors is essential for synthesising, isolating, and analysing enantiomerically pure carboxylic acids and clarifying the interaction processes of these acids with biological systems. Consequently, various chiral shift reagents, including chiral amines [28], are introduced. We demonstrate the synthesis of proline L-based receptors and their capacity to recognise carboxylic acids, amines, amino acids, and amino acid derivatives. We employed antibacterial activity and molecular docking to evaluate their biological activities [29].

2. Experimental section

Materials

All components, chemicals, and reagents were provided by the trading suppliers Sigma and Merck and were used upon receipt: L-Proline, chloroacetic acid, ampicillin, Cephalexin, Ciprofloxacin, sulfadiazine, and 4-aminoantipyrine (99%). Solvents, such as pure methanol (MeOH), dimethyl sulfoxide (DMSO), triethylamine (Et_3N), and thionyl chloride ($SOCl_2$), were used as provided by Aldrich.

2.1. Instrumentatio

The instruments used in this investigation comprised an electronic balance, a UV-vis spectrophotometer, an oven, a magnetic stirrer, and Fourier-transform infrared (FTIR) spectroscopy, which was conducted for the title compounds on the Shimadzu spectrophotometer from 4000 to 400 cm^{-1} at 25 °C using KBr plates. ^1H-NMR spectra were recorded in DMSO-d6 on a Bruker (500 MHz) spectrophotometer at the College of Science, University of Basra, Iraq. Melting points were determined using glass capillaries.

2.2. Procedure

2.2.1. Preparation of N-(carboxymethyl proline) (A) – (Scheme 1)

A total of 5 g (0.044 mol) of proline was dissolved in 25 ml of methanol, followed by the direct addition of 0.5 g of triethylamine (TEA). Subsequently, 7.5 g (0.044 mol) of chloroacetic acid was slowly added to the reaction mixture, which was then incubated at 70 °C for 12 hours. The reaction was neutralised with chloroform solution. The chloroform was reduced using a rotary evaporator and the resulting precipitate was slowly formed at 5 °C to 10 °C using acetone. The precipitate was air-dried to obtain a white powder, with the melting point of the compound recorded at 261 °C [30]. IR(KBr): (υ cm^{-1}) 2522–2997s (CH_2) **proline ring,** 2997 CH_2, 1651s (C = O), 3329–3400s OH **carboxylic group**[1] ; H-NMR (500 MHz, DMSO-d6) ppm: 1.19–1.26 (m, CH_2 from pyrrolidine); 2.5, (s, CH2) from N-CH2; 3.9 (CH) alpha –C-COOH from methane;10.786, 9.05 (2s, OH) **carboxylic acid**. The diagram illustrates the process of preparing the compound N-(carboxymethyl proline) (A) **(Scheme 4).**

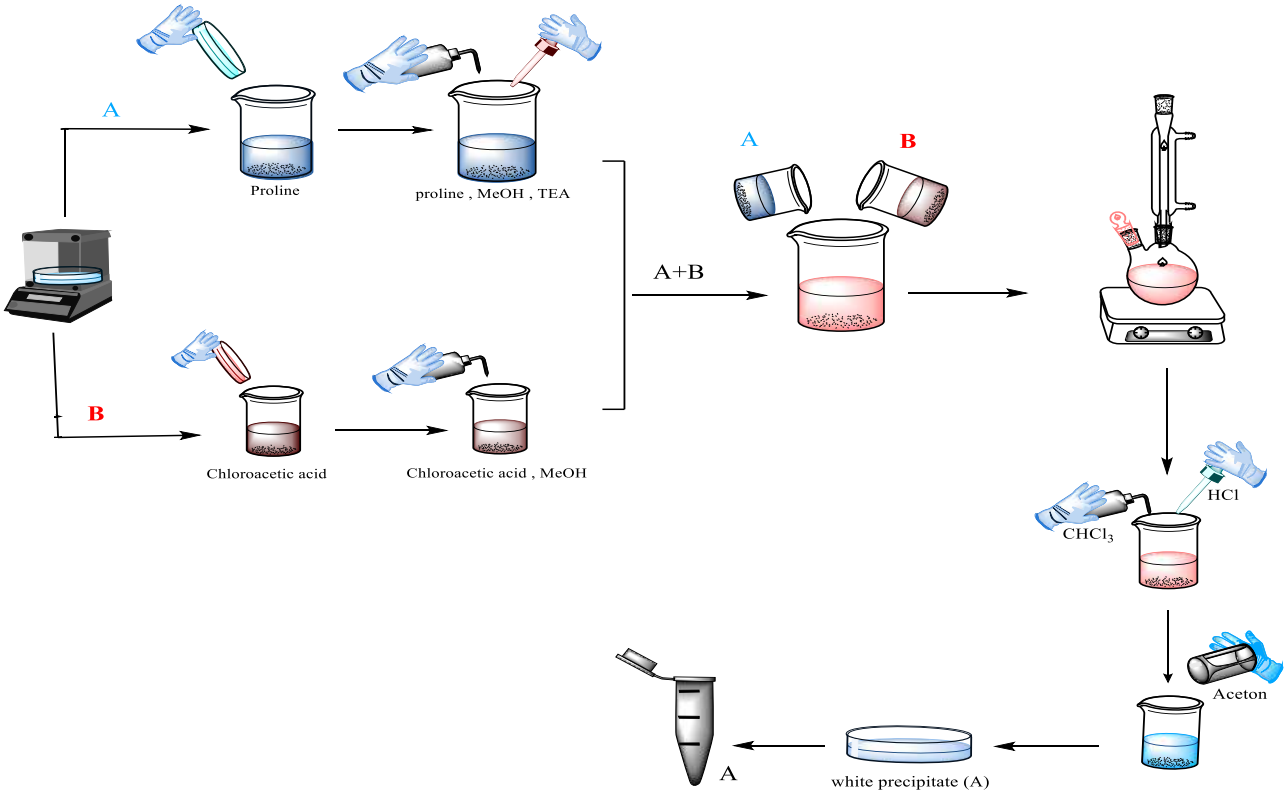


Figure 1. General synthesis of compounds (A)

2.2.2. Preparation of N-(carboxymethyl proline)-Ampicillin (A1) – (Scheme 3).

The proline derivative (A1) was prepared by reacting carboxymethyl proline (A) (0.5 gm, 0.0028mol) dissolved in 10 to 15 ml of dichloromethane (DCM) with three to five drops of thionyl chloride ($SOCl_2$), which converts the carboxyl group in compound (A) to an acyl group **(Scheme 2).** Subsequently, 1 g (0.00259 mol) of ampicillin was added along with 3 ml to 5 ml of methanol (MeOH), and the mixture was refluxed for two to three hours at a temperature of 45 °C to 65 °C. At the end of the reaction, the mixture was cooled, the solvent was discarded, and a white precipitate was obtained, with a melting point of 265 °C to 270 °C recorded. Yield: (86%). IR (KBr): (υ cm^{-1}) 2837–2895 s (CH_2) **proline ring, 2985 CH_2,** 3028 CH from the aromatic ring; 1518, 1610 s (C = C) phenyl group; 1697 s (C = O), 3192–3321s OH **carboxylic group;** 3419 s NH amide. ^{1}H-NMR (500 MHz, DMSO-*d6*) ppm: 1.29–2.19 (m, CH_2 from pyrrolidine); 2.507 (s, CH_2) from N-CH2; 3.575 (CH) alpha-C-COOH from methane; 4.33–4.66 H from alpha propionate; 10.6, 9.027 (2s, OH) **carboxylic acid; 8.97** (NH amide); 6.777–8.75 (CH from benzene ring).

2.2.3. Preparation of N-(carboxymethyl proline)-4-Amino antipyrine (A2)

Compound A2 was prepared by reacting carboxymethyl proline (A) (0.5 gm, 0.0028mol) dissolved in dichloromethane (DCM) (10–15 ml) with of thionyl chloride ($SOCl_2$) (3–5 drops), which converts the carboxyl group in compound (A) to an acyl group (**Scheme 2)**. Following that, 1 g (0.0049 mol) of 4-Amino antipyrine and 3 ml of methanol (MeOH) were added to the mixture, which was then refluxing for six hours at a temperature of 50 °C to 65 °C. The mixture was cooled, the solvent was discarded, and a red precipitate was obtained, with a melting point of 288 °C to 295 °C recorded. Yield: (88%). IR (KBr): (υ cm^{-1}) 2623–2742 s (CH_2) $_{\text{proline ring, 2927 CH}_2\text{, 3062}}$ CH from the aromatic ring; 1531, 1620 s (C = C) phenyl group; 1649 s (C = O), 3425 s NH amide. ^{1}H-NMR (500 MHz, DMSO-*d6*) ppm: 1.883–2.226 (m, CH_2 from pyrrolidine); 2.507 (s, CH2) from N-CH_2; 10.46 (NH amide), 7.330–8.839 (CH from benzene ring).

2.2.4. Preparation of N-(carboxymethyl proline)-cephalexin (A3).

The proline derivative A3 was prepared by reacting carboxymethyl proline (A) (0.5 g, 0.0028 mol (dissolved in dichloromethane (DCM) (10–15 ml) with of thionyl chloride ($SOCl_2$) (3–5 drops), which converts the carboxyl group in compound (A) to an acyl group (**Scheme 2)**. Subsequently, 1 gram – 0.0028 mol of cephalexin and 3 ml to 5 ml of methanol (MeOH) was added, and the mixture was refluxed for three hours at a temperature of 50 °C to 65 °C. The mixture was cooled, the solvent was discarded, and a brown precipitate was obtained, with a melting point of 275 °C to 280 °C recorded. Yield: (84%). IR (KBr): (υ cm^{-1}) 2625–2668s (CH_2) $_{\text{proline ring, 2981 CH}_2\text{,}}$ 3167 CH from the aromatic ring; 1552, 1643 s (C = C) phenyl group; 1695 s (C = O), 3197s OH $_{\text{carboxylic group;}}$ 3404 s NH amide. ^{1}H-NMR (500 MHz, DMSO-*d6*) ppm: 0.889–2.244 (m, CH_2 from pyrrolidine); 2.507 (s, CH2) from N-CH_2; 3.609 (CH) alpha-C-COOH from methane; 4.019–4.19 H from alpha propionate; 10.709 (2s, OH) $_{\text{carboxylic acid; 8.870}}$ (NH amide); 7.399–8.250 (CH from benzene ring).

2.2.5. Preparation of N-(carboxymethyl proline) - Ciprofloxacin (A4).

The derivative A4 was prepared by reacting carboxymethyl proline (A) (0.5 g, 0.0028 mol) dissolved in dichloromethane (DCM) (10–15 ml) with three to five drops of thionyl chloride ($SOCl_2$), which converts the carboxyl group in compound (A) to an acyl group. After that, 1 g (0.0030 mol) of ciprofloxacin, 3 ml of methanol, and 2 ml of tetrahydrofuran (THF) were added to the mixture, which was then refluxed for two hours at a temperature of 50 °C to 75 °C. The mixture was cooled, the solvent was discarded, and a red precipitate was obtained, with a melting point of 283 °C to 288 °C recorded. Yield: (88%). IR (KBr): (υ cm^{-1}) 2613–2875s (CH_2) $_{\text{proline ring, 2951 CH}_2\text{,}}$ 3024 CH from the aromatic ring; 1506, 1625 s (C = C) phenyl group; 1735 s (C = O), 3361s OH $_{\text{carboxylic group;}}$ 3437 s NH amide. ^{1}H-NMR (500 MHz, DMSO-*d6*) ppm: 1.1–2.6 (m, CH_2 from pyrrolidine); 2.5, 3.7 (s, CH_2) from N-CH2CH2-N; 3.515 (CH) alpha-C-COOH from methane; 3.724–4.25 H from N-cyclopropane; 15.055 (s, OH) $_{\text{carboxylic acid; 10.36}}$ (NH amide); 7.6–8.6 (CH from benzene ring).

2.2.6. Preparation of N-(carboxymethyl proline)-Sulfadiazine (A5)

The derivative A5 was prepared by reacting carboxymethyl proline (A) (0.5 g, 0.0028 mol) dissolved in dichloromethane (DCM) (10–15 ml) with three to five drops of thionyl chloride ($SOCl_2$), which converts the carboxyl group in compound (A) to an acyl group. After that, 1 g (0.004 mol) of sulfadiazine and 3 ml to 5 ml of methanol (MeOH) were added to the mixture, which was then refluxed for four hours at a temperature of 45 °C to 65 °C. The mixture was cooled, the solvent was discarded, and a green precipitate with a melting point of 225 °C to 228 °C recorded. Yield: (90%). IR (KBr): (υ cm^{-1}) 2642–2877 s (CH_2) $_{\text{proline ring, 2943 CH}_2\text{,}}$ 3030 CH from the aromatic ring; 1525, 1608 s (C = C) phenyl group; 1732 s (C = O), 3441 s NH amide. ^{1}H-NMR (500 MHz, DMSO-*d6*) ppm: 1.155–1.191 (m, CH_2 from pyrrolidine); 3.01 (s, CH_2) from N-CH2-; 10. 3 (NH amide); 7.005–8.494 (CH from benzene ring).

The diagram below illustrates a simulation of the experiment and the methodology employed. It depicts the reaction of compound N-(carboxymethyl proline) (A) with amino drugs (Drug–NH_2–Ampicillin, Cephalexin, Ciprofloxacin, Sulfadiazine, 4-Amino antipyrine) in the presence of suitable solvents (dichloromethane and methanol) at a temperature of 70 °C to 75 °C for two hours **(Scheme 5).** The resulting pharmaceutical compounds are represented in the diagram (Table 3).

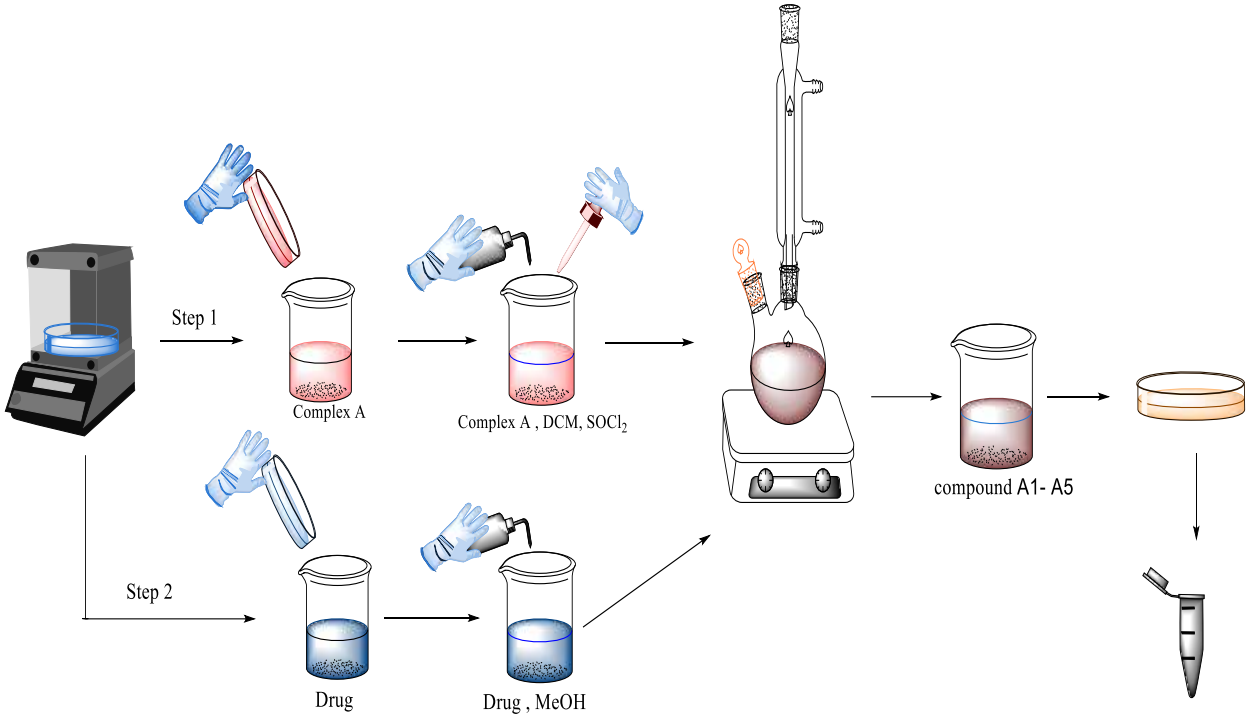


Figure 2. General synthesis of compounds (A1-A5)

3. Molecular docking simulation

After assessing the antibacterial activity of the compounds A1-A5, these compounds were subjected to molecular docking simulation to investigate their mechanism of action. Molecular docking using Autodock vina was performed for Compound A1-A5 against the potential two targets: DNA gyrase of *Staphylococcus aureus* (pdb code:5cph) and *E-coli* (pdb code: 1ei1). AutoDockTools (ADT) version 1.5.6, was used to prepare the proteins, where unwanted molecules such water, small molecules and salts were removed, then Gasteiger charges and polar hydrogen bonds were added, finally the prepared protein was saved in PDBQT format. The structures of compounds A1-A5 were drawn using ChemDraw Ultra 12.0 software. The 3D sketched structures were converted to PDBQT format using Open Babel v. 2.0. Docking simulations was performed employing AutoDock Vina version 1.1.2, while Discovery Studio Visualizer (version 4.5) was used to visualize the protein-ligand complexes, all the parameters was set as default . Table (6) illustrates the molecular docking process of the prepared compounds.

Table 1. It explains the molecular bonding process of the prepared compounds.

Figure 2: Ligand-protein interaction of compound A1 with 1ei1

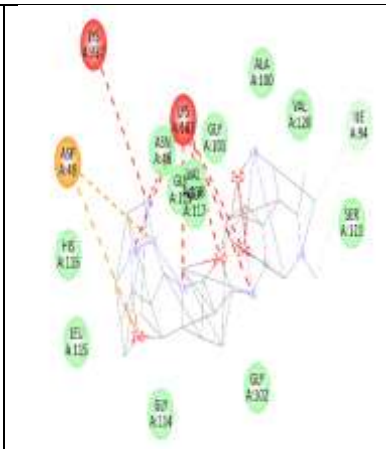


Figure 3: Ligand-protein interaction of compound A2 with 1ei1

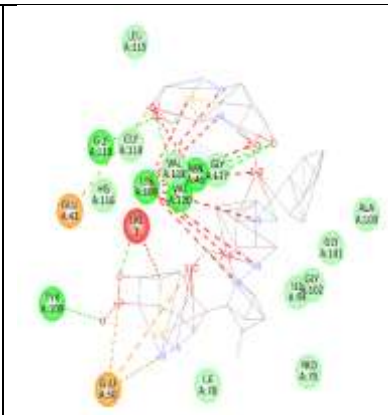


Figure 4: Ligand-protein interaction of compound A3 with 1ei1

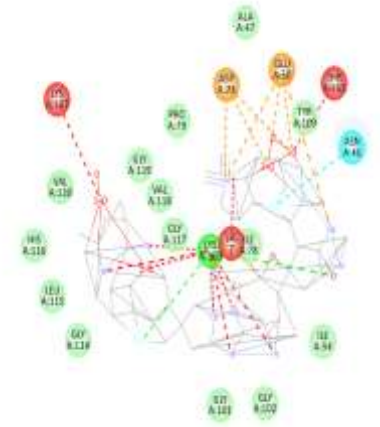


Figure 5: Ligand-protein interaction of compound A4 with 1ei1

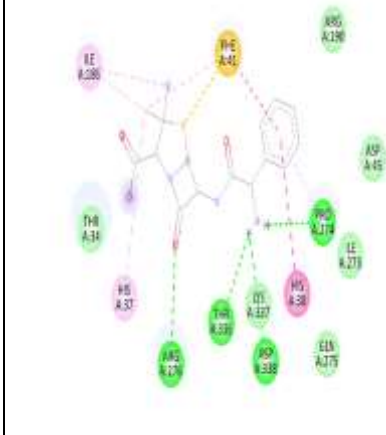


Figure 6: Ligand-protein interaction of the standard with 1ei1

4. Results and discussion

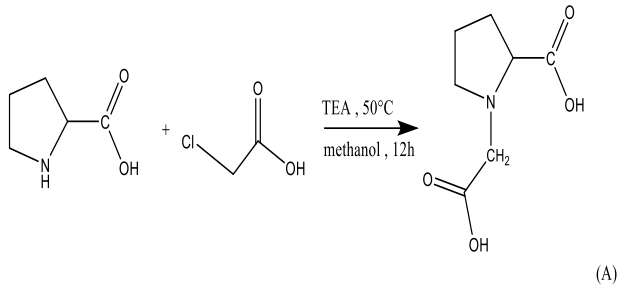
Compound A was prepared by reacting proline with chloroacetic acid. The progress of the reaction was monitored by TLC, resulting in a 70% yield, as illustrated in the following equation **(Scheme 1).**

The prepared compounds were characterised by infrared (IR) spectroscopy, where the band of the NH amine group (3420 cm^{-1}) disappeared. The compound was described in the ^{1}H-NMR spectrum, where the appearance of a peak at 1.2 ppm indicated the presence of CH_2, and a peak at 10 ppm indicated the presence of a hydrogen proton of the carboxylic acid. TEA accelerated the reaction, making the reaction environment basic and thereby deprotonating the carboxyl group, thus avoiding zwitter ions. This also increased the attack ability of NH on the amino acid proline towards the chloroacetic acid compound.

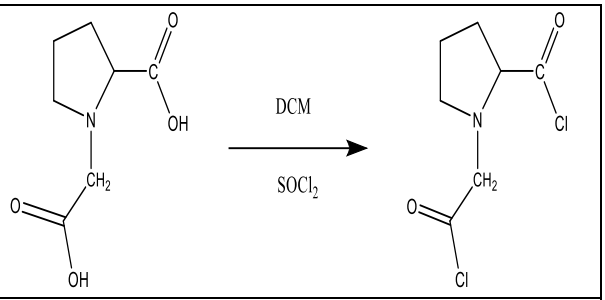
In the reaction, thionyl chloride ($SOCl_2$) was used to convert the hydroxyl group of compound A to an acyl group, which was then exploited in the reaction with several drugs via amide formation, as represented in the following scheme, which illustrates the conversion of the carboxyl group to the acyl group **(Scheme 2).**

After converting the carboxyl group to an acyl group, this new acyl group was reacted with ampicillin, a drug containing an active group (NH_2), to form compound A1. The reaction between the NH_2 group of the drug and the acyl group (COCl) of the modified amino acid was performed under mild conditions. Moreover, 4-Amino antipyrine, cephalexin, ciprofloxacin, and Sulfadiazine reacted with the proline derivative (A) in the same manner as ampicillin was prepared and identified by FT-IR and ^{1}H-NMR spectroscopic methods (**Scheme 3).**

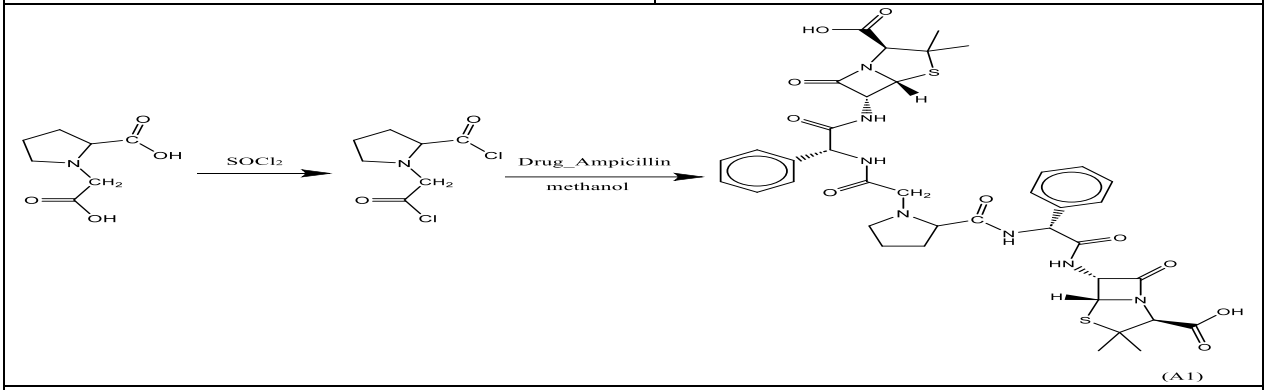
Table 2. Structure of the Drugs that Reacted with Proline Derivatives



Scheme 1. Synthesis of N- (carboxymethyl proline) (A)



Scheme 2. Shows the addition of thionyl chloride to the compound N- (carboxymethyl proline

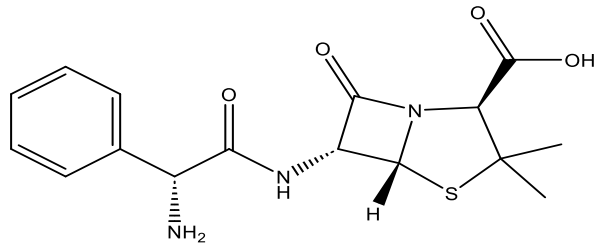
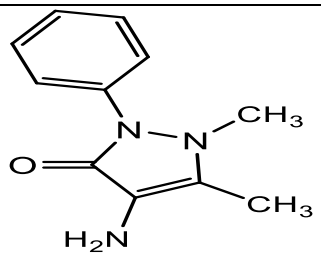
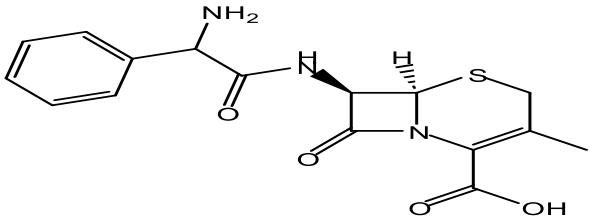
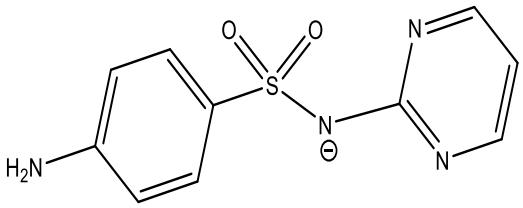
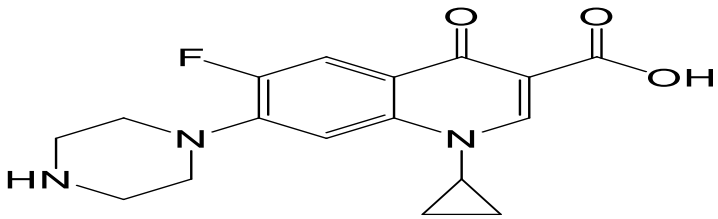


Scheme 3. Reaction N- (carboxymethyl proline) with Ampicillin -Drug

Compounds A1 to A5 were characterised by IR spectroscopy and ^{1}H-NMR, where the band of the amine group disappeared at 3405 cm^{-1}. A new band appeared at 3315 cm^{-1}, belonging to NH of the amide, while the carboxyl group band also disappeared at 3350 cm^{-1}, and a new band appeared at 1690 cm^{-1}, belonging to (C = O) of the amide. The compounds were further identified by $^{1H\text{-}NMR,}$ which appeared at $^{1H\text{-}NMR}$ (500 MHz, DMSO-*d6*), ppm: 1.29–2.19 (m, CH_2 from pyrrolidine); 2.507 (s, CH2) from N-CH_2; 3.575 (CH) alpha-C-COOH from methane; 4.33–4.66 H from alpha propionate; 10.6, 9.027 (2s, OH) **carboxylic acid; 8.97** (NH amide); 6.777–8.75 (CH from benzene ring).

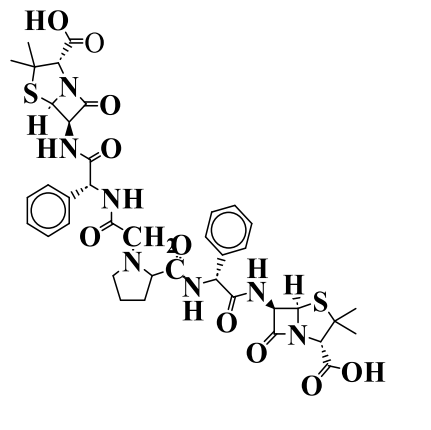
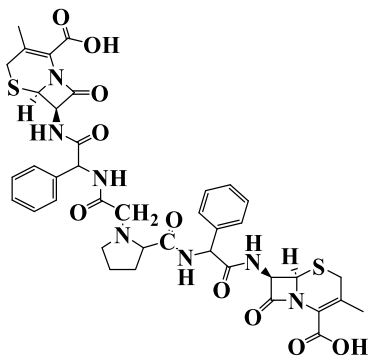
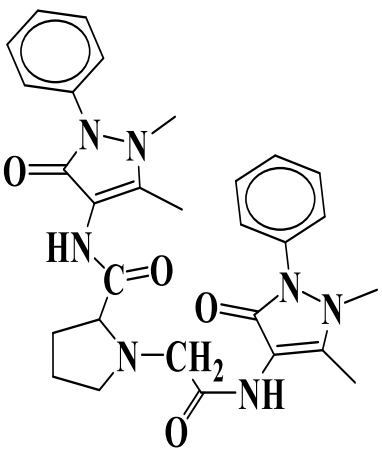
The physical properties of the compounds were measured, and the melting points ranged from 265 °C to 270 °C, indicating that the compounds were thermally stable. TLC also characterised the resulting compounds. The drugs, such as 4-amino antipyrine, cephalexin, sulfadiazine, and ciprofloxacin, reacted with N-(carboxymethyl proline) (A) in the same manner as ampicillin was prepared and identified by spectroscopic methods. The structural formula of the aforementioned drugs is illustrated below.

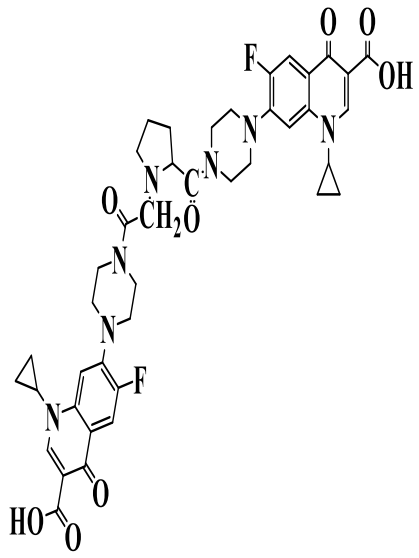
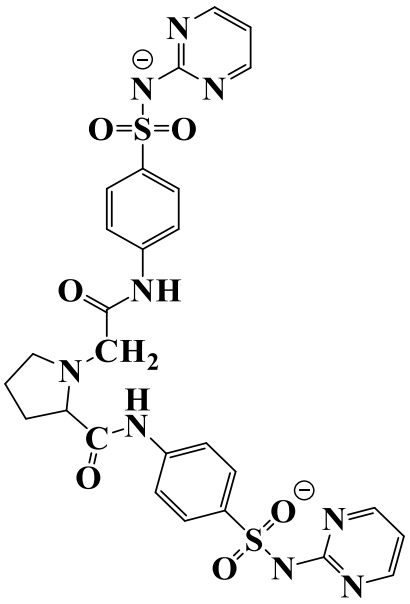
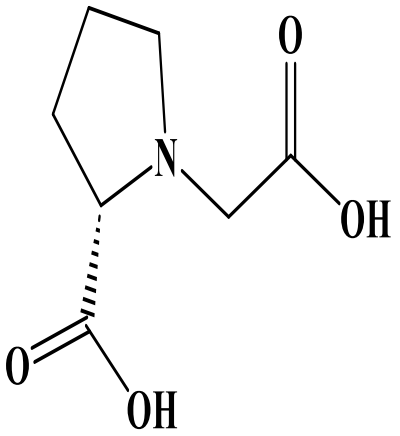
Table 3. Structure of the Drugs that Reacted with Proline Derivatives

	
Ampicillin	4- Amino antipyrine
	
cephalexin	Sulfadiazine
	
Ciprofloxacin	

All the drugs mentioned in Table 2 were reacted with N-(carboxymethyl proline) derivatives, where the (NH_2) group present in the drug reacted with the acyl group present in the proline derivative to form the amide. IR spectroscopy confirmed their identities by the disappearance of the amine group at 3400–3320 cm^{-1} and the appearance of the new amide group at 1610–1630 cm^{-1}, attributed to the carbonyl group. The table below shows the structure of the prepared pharmaceutical compounds

Table 4. Structure (scheme) of the Pharmaceutical Compounds Resulting From the Reaction of Compound N-(carboxymethyl proline) (A) with Amino Drugs

Compound (A) interacted with the drug ampicillin.	Compound (A) interacted with the drug cephalexin	Compound (A) interacted with the drug 4-Amino antipyrine
		
Compound (A) interacted with the drug ciprofloxacin	Compound (A) interacted with the drug sulfadiazine	Compound (A)

Antibacterial Activity of Proline Derivatives

The antibacterial activity was carried out using Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*). Table 2 presents the results obtained for these compounds, which exhibited good antibacterial activity for all of the tested compounds compared to the available antibiotic ampicillin.

Figure 3. Antibacterial Activity of the Prepared Compounds

Table 5. Antibacterial Activity of the Prepared Proline Derivatives

Compound No.	**Inhibition Zone (mm)**	
	Staphylococcus aureus	***E.coli***
A1	14	15
A2	24	10
A3	19	21
A4	23	35
A5	23	21
ampicillin (Standard)	12	10

The compounds we prepared exhibit higher antibacterial activity against *E. coli* and *Staphylococcus* aureus than the ampicillin antibiotic drug.

To obtain deeper insights into the antibacterial mechanism of our synthesised compounds (A1–A5), we employed molecular docking simulations as a computational approach to predict the binding affinity and interaction modes between the compounds and a potential bacterial target protein. Molecular docking serves as a valuable tool in drug discovery studies, as it enables the understanding of how small molecules interact with the active sites of biological macromolecules. Through simulations, we can better understand the potential biological targets of our compounds and rationalise their obtained *in vitro* antibacterial activity. Based on the broad-spectrum antibacterial effects exhibited by our compounds, which demonstrated significant inhibition zones against both *Staphylococcus aureus* and *Escherichia coli*, we selected DNA Gyrase subunit B (GyrB) as the primary molecular target for docking studies. DNA gyrase, a type II topoisomerase, plays a vital role in bacterial DNA replication, transcription, and repair. It is composed of two subunits (GyrA and GyrB), with the GyrB subunit responsible for ATP hydrolysis, an essential step in the supercoiling process of bacterial DNA. DNA gyrase is highly conserved and essential in both Gram-positive and Gram-negative bacteria, making it an ideal target for our study. Additionally, it is well-established as a target for several classes of antibiotics, including fluoroquinolones, which supports its relevance in antibacterial drug development. By focusing on GyrB, we aimed to explore whether our compounds have the potential to inhibit this critical enzymatic function and thus contribute to bacterial growth inhibition. The docking results (Table 3) revealed that all screened compounds (A1–A5) have good binding affinity towards DNA gyrase of both bacteria compared to the standard drug (ampicillin). The results obtained from molecular docking simulations illustrate the mechanism of action of these compounds.

Table 6. Molecular Docking Results of Compounds A1–A5 Against DNA Gyrase of Staphylococcus aureus (PDB code: 5cph) and E. coli (PDB code: 1ei1)

Compound	*Molecular docking score (kcal/mol)*	
	Staphylococcus aureus	***E-coli***
A1	-14.9	-15.8
A2	-13.4	-14.2
A3	-13.2	-15.5
A4	-15.6	-18.2
A5	-12.9	-14.2
Ampicillin (standard)	-6.8	-7.8

5. Conclusion

The prepared compounds exhibit high antibacterial activity against *E. coli* and *Staphylococcus aureus* compared to the antibiotic ampicillin. Proline derivatives incorporated with drug molecules are expected to exhibit strong antibacterial activity due to their unique chemical structure, which combines features of both amino acids and antibiotics. Based on to the predicted mechanism of action, the synthesised compounds may be further optimised to yield more active and less toxic new molecules. After assessing the antibacterial activity of the compounds A1-A5, these compounds were subjected to molecular docking simulation to investigate their mechanism of action. Molecular docking using Autodock vina was performed for Compound A1-A5 against the potential two targets: DNA gyrase of *Staphylococcus aureus* (pdb code:5cph) and *E-coli* (pdb code: 1ei1). AutoDockTools (ADT) version 1.5.6, was used to prepare the proteins

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Conflict of interest

The authors declare no conflict of interest

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