Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.07.041

Synthesis, Characterization, and Study the Biological Activity of New Di-azetidinone Derivatives

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Submitted: 10 February 2023; Accepted: 17 March 2023; Published: 04 April 2023

ABSTRACT

A series of new β-lactam derivatives were synthesized in two steps: The first step involves the synthesis of Schiff base derivatives from Veronal (Barbital) which is used as a sleeping aid (hypnotic) from 1903 until the mid-1950s, the compound (L3A) is synthesized by loading two molecules of formaldehyde on macrocycles compound as an initial step with absolute ethanol as solvent to form Hemiaminal compound, the reaction occurred on the two secondary amine molecules), after that treated the reaction product (L3A) with p-Toluenesulfonyl chloride in anhydrous pyridine to produce compound (L3B). While the preparation of the compound (L3C) involves removing the sulfonate groups of two sites in the compound (L3B) by gradually adding sodium amide with water. Imine derivatives (L3C1, L3C2, L3C3, and L3C4) were synthesized by reaction of Barbital derivatives free amino groups and corresponding substituted benzaldehyde in the presence of glacial acetic acid.

The second step is done through added chloroacetyl chloride to the Schiff base derivatives very slowly to prevent the compound from turning into something like bitumen, this is followed by adding the trimethylamine base to remove the proton and complete the closing process and form a β-lactam ring of derivatives (L3C5, L3C6, L3C7, and L3C8). Finally, in vitro anticancer activity of (L3C7, and L3C8) derivatives were investigated using SK-OV-3: Human Ovarian Cancer Cell Lines compared with 5-floro uracil (5-FU), the results showed the ability of these compounds to inhibit the infected cells in different proportions, depending on the concentrations used.

Keywords: *β-lactam, Di-azetidinone, barbital, Schiff base, anticancer*

INTRODUCTION

Azetidinone is one of the most common heterocyclic rings found in many antibiotics (F.H. van der Steen et al., 2009) Indeed, the β-lactam amide group can undergo enzymatic hydrolysis, under the action of β-lactamases enzymes, thus providing compounds free of antibacterial activity (K. Busha, et al., 2018), β-lactam rings are an important organic compounds category of nitrogen-rich heterocyclic, showing the wide range of applications in various fields like drug development, organic synthesis, material science, and chemistry coordination (Y. Sik Park et al., 2020). Through non-covalent reactions, β-lactam can interact with many enzymes

and receptors in living organisms to demonstrate broad biological properties like anti-bacterial (V. Güner, et al., 2000, M. Peng et al.,2021, M. Babic, et al., 2006, I. Karaiskos, et al., 2022, Y. K. et al., 2013) anticancer (A. M. Malebari et al.,2017, D. Kuhn, et al., 2004, C. A. Hobson et al.,2020, J. L. Dong-Jun Fu, et al.,2020), antifungal (E. P. Luigino Troisi and C. Granito, 2010), anti-inflammatory (B. Mohan Sahoo and B. K. Banik, 2021, A. Gupta and A. K. Halve, 2015), antimalarial (A. Jarrahpour, et al., 2015), analgesic (S. S. Chhajed and C. D. Upasani, 2016) and anti-viral (J. W. Skiles and D. McNeil, 1990). On the other hand, synthesizing new barbiturates compounds containing β-Lactam rings could be of great interest in f modern life needs. Based on the fact that the barbiturates compounds have a high affinity, high solubility, and unharmful degradation in biological systems (M. Ali et al.,2020, J. Figueiredo et al., 2018, J. N. Suzana Apostolov1, et al., 2020, B. B. Sokmen, et al., 2013, W. Mohammed Najem, et al., 2022), so they are used mainly in pharmaceutical industries (D. Neumann, et al.,2004, J. T. Bojarski, et al.,1985, D. A. Cozanitis et al,. 2004, K A Savage and D Wielbo, et al., 2005)to increase the solubility of the proposed drug in aqueous media and reduce the toxicity.

EXPERIMENTAL

Materials and Methods

All chemicals were of the highest purity and supplied by Santa Cruz biotechnology, Sigma Aldrich, Fluka, and BDH Chemicals Companies. Measurements of the melting points were recorded by using electro thermal 9300, melting point engineering LTD-U.K. (T.L.C) Thin layer chromatography was performed on silica gel and spots were visualized by Iodine vapors. FT-IR spectra, Alpha-Broker (Germany) infrared spectrophotometer, and the values are expressed in cm-1, 1H-NMR & 13CNMR- spectra in (ppm) unit were operating in DMSO-d6 as solvent using (Bruker spectrometer 400MHz and 125 MHz respectively)-Tehran University /Iran. Mass spectra were recorded on the MS system, model 5975 quadrupole analyzer are performed at Tarbiat Modares University, Tehran-Iran.

Synthesis of b-Lactam compounds

Synthesis of (5-ethyl-1,3-bis(hydroxymethyl)-5-phenylpyrimidine-2,4,6(1H,3H, 5H)-trione (L3A)

A mixture of compound L3 (2.32 gm, 0.01 mol) and formaldehyde (1.5 ml, 0.025 mol) in ethanol 50 ml was stirred at 80 oC for 4 hours. The stirring continued and the progress was monitored using TLC, the solution was evaporated by rotary evaporation to give compound (L3A) pale brawn (yield 81%). (E. J. Almulla, et al.,2021)

FTIR data (cm-1): 3334 (υ O-H), 2941, 2960 (υ H-aliphatic), 1688, 1636 (υ C=O), 1143 (υ C-N). MS: [M+] calcd. for C14H16N2O5 : 292.1; found: 292.4.

NMR data :1HNMR (400 MHz, DMSO-d6): δ 1.02-1.28 (m, 5H, -CH2, -CH3), 5.15, 5.29 (dd, J = 8.2, 2.0 Hz, 4H, 2 N-CH2-O), δ 7.47-7.78 (m, 5H, of Ph.), δ 3.90 (s, 2H, of –OH). Besides, 13CNMR (125 MHz, CDCl3: δ 8.89 (CH3), 29.24 (CH2), 73.19, 70,32 (2 O-CH2-N), 62.22 (C of pyrimidine trione ring), 127.57, 127.81, 127.04, 128.25, 129.06, 129.60 (benzene ring). And 166.3, 192.9, 195.1 (3 C=O)

Synthesis of ((5-ethyl-2,4,6-trioxo-5-phenyldihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene) dibenzenesulfonate (L3B)

A solution of compound (L3A) (0.012 mol, 3.5 gm) was dissolved in pyridine (25 ml) in two necks round bottom flask and cool down to (5 oC) in an ice bath, on the other hand, p-toluenesulfonyl chloride (0.024 mol, 4.5 gm) in pyridine (15 ml) was added dropwise over 1 hour. The reaction was stirred for 7 hrs., after that the pyridine was evaporated and the residue was dissolved in chloroform and extracted with a dilute solution of hydrochloric acid (7%), then washed with H2O. The chloroform layer was separated and dry with MgSO4 to give compound (L3B) orange (yield 79 %). (I. Ling, et al., 2015).

FTIR data (cm-1): 3045 (υ H- Aromatic), 2980, 2942 (υ H-aliphatic), 1689, 1731 (υ C=O), 1168 (υ C-N). 1121-1390 (υas , υs (SO2). MS: [M+] calcd. for C26H24N2O9s2 : 601.0; found: 601.8

NMR data :1HNMR (400 MHz, DMSO-d6): δ 1.29 (t, J = 7.2 Hz, 3H, -CH3), δ 1.54 (q, 7.65 Hz,

2H, CH2), δ 2.12 (s, 6H, 2 CH3 of the tosyl group), 5.08-5.28 (dd, J = 8.2, 2.0 Hz, 4H, 2 N-CH2-O), δ 7.29-7.31(dt, J = 7.2, 5.5 Hz, 2H, of Ph.), δ 7.28-7.32 (dd, J = 7.2, 2.5 Hz, 2H, of Ph.), δ 7.54-8.31 (m, 8H, of the two tosyl rings). Besides, 13CNMR (125 MHz, CDCl3: δ 11.82 (CH3), 29.98 (CH2), 80.79, 70.19 (2 O-CH2-N), 65.22 (C of pyrimidine trione ring), 122.63, 125.97, 127.04, 127.19, 127.72, 128.31 (benzene ring NO. 1), 128.43, 129.35, 129.44, 129.74, 130.02, 132.50, 132.71, 133.37, 134.25, 135.18, 136.31, 147.92 (benzene ring NO. 2 and 3), 174.32, 192.92, 199.29 (3 C=O groups).

Synthesis of (1,3-bis(aminomethyl)-5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione (L3C)

A mixture of compound (L3B): (0.005 mol, 5.2gm) and (0.03 mol, 1.17 gm) of sodium amid were refluxed in 50 mL of 2:6 DMF and chloroform and 5 drops of H2O for 9 hours. After completion of the reaction (monitored by TLC (ethyl acetate-n-hexane, 2:1). Then mixture reaction was separated with 70 mL of diethyl ether two times, and the organic layer was washed several times with D.W. Subsequently, the separated organic phase was dried with (Na2SO4), and isolated by filtration. The diethyl ether was removed and then the product was dried and recrystallization from ethanol.

FTIR data (cm-1): 3056 (υ H- Aromatic), 2988 (υ H-aliphatic), 1689 (υ C=O), 1171 (υ N-C-N), 3409-3298 (υ (NH2). MS: [M+] calcd. for C14H18N4O3 : 291.3; found: 292.4

NMR data :1HNMR (400 MHz, DMSO-d6): δ 1.18(t, J = 7.2 Hz, 3H, -CH3), δ 2.50 (q, 7.65 Hz, 2H, CH2), 6.25, 6.38 (dd, J = 8.2, 2.0 Hz, 4H, 2 N-CH2-N), δ 7.41-7.54 (m, 5H, of Ph.), δ 3.19-3.59 (s, 4H, of –NH2). Besides, 13CNMR (125 MHz, CDCl3: δ 8.89 (CH3), 29.24 (CH2), , 73.19, 70,32 (2 N-CH2-N), 62.22 (C of pyrimidine trione ring), 127.57, 127.81, 127.04, 128.25, 129.06, 129.60 (benzene ring), 166.30, 192.92, 195.19 (3 C=O groups).

General Method for Synthesis of several Schiff bases (L3C1, L3C2, L3C3, and L3C4)

Several derivatives of aryl aldehyde (0.02 mol) were dissolved in a mixture of (20 mL absolute Ethanol and 3 drops of glacial acetic acid, then stirred for 30 min. Next, (0.01 mol) of compound L3C was added dropwise to the mixture and the stirring continued for additional hours (5-11 hrs.). The progress was monitored using TLC (ethanol-acetone, 3:1), the solution was evaporated by rotary evaporation to give compounds L3C1 yellow (yield 68%), L3C2 white brown (yield 71 %), L3C3 brown (yield 65 %) and L3C4 pale brown (yield 65%).(M. Szyma´nska et al.,2021)

FTIR data (cm-1) of compound L3C1: 1725 (υC=N), 2863, 2952, 2885(υ H-aliphatic), 3163, 3050 (υ H-aromatic) ,1675 (υ C=O).

FTIR data (cm-1) of compound L3C2: 1716 (υC=N), 2952, 2875(υ H-aliphatic), 3056, 3000 (υ H-aromatic), 1652 (υ C=O).

FTIR data (cm-1) of compound L3C3: 1732 (υC=N), 2982, 2849(υ H-aliphatic), 3092 (υ H-aromatic), 1638 (υ C=O).

FTIR data (cm-1) of compound L3C4: 1740 (υC=N), 2966, 2797(υ H-aliphatic), 3070 (υ H-aromatic), 1653 (υ C=O).

General Method for Synthesis of β-lactam derivatives (L3C5, L3C6, L3C7 and L3C8)

A solution of chloroacetyl chloride (2.22 gm, 0.02 mol) in dioxane (2 mL) was added dropwise to a solution of an imine (0.01 mol) and Et3N (0.011 mmol) in dry dioxane (10 mL) at temp.(50C) for 1hour, the reaction mixture was stirred for additional hours (12-15 hrs.) at 10 0C, then poured into crushed ice to dissolve The salt (Et3N+ HCl) tri ethyl amine hydrochloride. The mixture was extracted by using chloroform (CHCl3), then the solvent was evaporated and the yield was recrystallized from absolute ethanol to give compounds L3C5 dark brown (yield 69 %) m p: 205-207 ºC, L3C6 brown (yield 71%), m p: 199-201 ºC, L3C7 orange (yield 71%), m p: 198-200 ºC and L3C8 yellow (yield 75 %), m p: 205-207 ºC. The reaction was monitored by (T.L.C). (QI H-zhen,et al.,2011)

FTIR data (cm-1) of compound L3C5: 1744 (υC=O β-lactam), 2951, 2870(υ H-aliphatic), 3072, 3001 (υ H-aromatic), 1633 (υ C=O).

MS: [M+] calcd. for C36H36Cl4N4O3 : 774.1; found: 775.3

NMR data :1HNMR (400 MHz, DMSO-d6): δ 1.16 (t, J = 7.2 Hz, 3H, -CH3), δ 1.28 (q, 7.65 Hz, 2H, CH2), δ 2.83 (t, J = 8.2 Hz, 3H, -CH3), δ 3.25 (q, 7.65 Hz, 2H, CH2), 5.27, 5.42 (dd, J = 7.2, 2.0 Hz, 4H, 2 N-CH2-N), δ 6.39, 6.25 (s , 2H, CH of b-Lactam ring), δ 7.20-7.40 (m, 5H, of Ph.), δ 7.65 – 7.80 (dd, 4H, of benzene), δ 7.85 – 8.09 (dd, 4H, of benzene).

13CNMR (125 MHz, CDCl3): δ 11.88, 17.38, 24.28 (3 CH3), 29.91 (CH2), 59.99, 61.12 (2 CH2-O), 65.22, 70.19 (CH2-N b-lactam ring), 80.89, 82.22 (CH2-Cl), 91.92 (N-CH2-N), 122.71, 125.96, 127.75, 128.21, 128.45, 129.46 (benzene ring NO. 1), 130.04, 132.74, 134.29, 135.11, 136.32, 148.31, 154.92 (benzene ring NO. 2 and 3), 176.36, 184.52, 192.92, 207.99 (5 C=O groups).

FTIR data (cm-1) of compound L3C6: 1755 (υC=O β-lactam), 2941, 2740(υ H-aliphatic), 3078, 3165 (υ H-aromatic), 1693 (υ C=O).

FTIR data (cm-1) of compound L3C7: 1761 (υC=O β-lactam), 2961, 2808(υ H-aliphatic), 3082 (υ H-aromatic), 1684 (υ C=O).

FTIR data (cm-1) of compound L3C8: 1772 (υC=O β-lactam), 2940, 2843(υ H-aliphatic), 3022 (υ H-aromatic), 1615 (υ C=O).

Biological Activity Statistical analysis: Statistical analyses were performed using SPSS 21.0 for windows. Inc. Data were expressed as Mean ± SEM, Two-tailed T test unless otherwise stated by ANOVA test. In all tests, P <0.05 was considered statistically significant R 2 was calculated by Pearson Correlation Coefficient. The halve inhibitory concentration (IC50) of different composites was calculated by Graph Pad Prism 6. The anticancer activity of the synthesized derivative (L2) in vitro was determined against an Homo sapiens, human ,Colon cancer (Disease: Dukes' type B, colorectal adenocarcinoma) LS-174Tcell line using MTT reagents assay Compared to anticancer drugs which are Methotrexate(MTX)& Doxorubicin (DOX). The results were as follows

TABLE 1: The percentage of Inhibition and (IC50) for the derivative(L2)

(x) =Conc.of (L2) µg / ml	0.5	1	10	100	1000	2000	3000	4000	5000	10000
Log x	0	0	1	2	3	3.3	3.5	3.6	3.7	4
Inhibition %	42.8	51.3	53.8	51.6	54.9	60.8	61.7	69.2	81.8	90.6
IC50= 1386 µg / ml= 1. 386mg/ ml										

TABLE 2: The percentage of Inhibition and (IC50) for the Drugs MTX &DOX

	MTX					DOX				
Conc.ofMTX&DOX Drugs µg / ml(x)	0.5	1	10	50	100	0.5	1	10	50	100
Log (x)	0	0	1		2	0	0	1	1.698	2
Inhibition %	32.1	36.2	39.0	47.1	70.3	30.8	34.2	33.2	74.1	73.1
IC50	29.919 µg / ml= 0.03 mg/ ml					15.634 µg / ml=0.0156mg/ ml				

Antibacterial Activity

Monobactams and carbapenams are monocyclic 2-azetidinones, which are possessing biological activity onlyagainst Gram-negative bacteria (Accardo et al., 2014). However, the synthesized derivatives exhibited activity against both Gram-negative and Gram- positive bacteria. The biological activity of some Azetidinone derivatives was examined in this work against four types of bacteria Staphylococcus aureus, Bacillus are Gram + whilst Proteus mirabilis, Enterobacter are Gram- - compared with

antibiotic Amoxicillin (25µg) that did not give any inhibition against the four types of bacteria used. Two concentrations of each derivative were prepared (1000, 250ppm) and the results were shown in the table 6.

TABLE 3: Inhibition zones

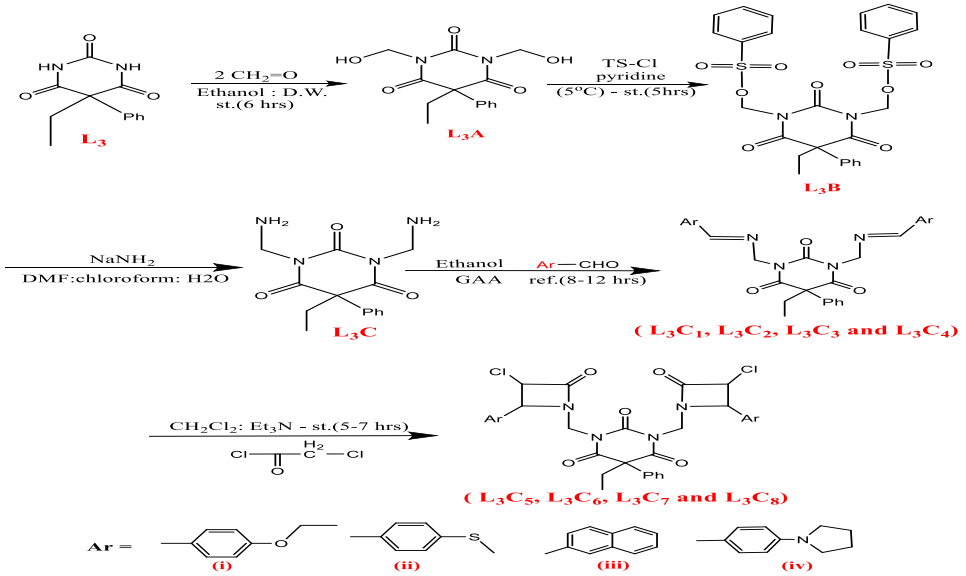
Conc. PP M / Comp.	*Staphylococcus aureus* (Gram +)		*Bacillus subtilis* (Gram +)		*Proteus mirabilis* (Gram -)		*Enterobacter* (Gram -)	
	1000	*250*	*1000*	*250*	*1000*	*250*	*1000*	*250*
L1	1mm	4mm	------	10mm	------	3mm	--------	10mm
L11	2mm	4mm	---	----	5mm	4mm	5mm	5mm
Amoxicillin25µg	Did not affect							

RESULTS AND DISCUSSION

In this study, we worked on the therapeutic compound (Barbital), which is used as a sleeping aid (hypnotic) from 1903 until the mid-1950s. We took advantage of the general structure of the compound to prepare several Barbital compounds that contain two heterogeneous nitrogen atoms loaded with two β-lactam rings, in addition to the presence of oxygen and Cl atoms in the general structure of all derivatives.

Synthesis of 1,3-bis(amino methyl) Barbital

The desired compounds (L3A, L3B, and L3C) were prepared in good to very good yields of 79–81% according to the procedure given in Scheme (1). The preparation of the compound (L3A) was achieved by loading two molecules of formaldehyde as an initial step on the barbital compound with absolute ethanol as a solvent for six hours to form a Hemiaminal compound (ß. Beltr,et al.,2015), the reaction occurred on the two secondary amine molecules to form compound (L3A). In the FT-IR spectrum, we observed the disappearance of a group of (υ N-H) group and showed new stretching vibration bands of (υ O-H) in the regions (3334) cm-1. The Mass spectrum of the compound (L3A) showed a peak at 292, representing the M+, while the peak at 293.4 was attributed to the M+1 for the isotopes 13C. The 1HNMR spectrum of compound L3A showed new signals in the ranges (δ 5.15, 5.29) for (2 O-CH2-N) ppm, and new signals appeared in the (3.90 ppm) for the protons of the OH group with the disappearance of (υ N-H) group. As shown in figure (1). Besides, the 13CNMR spectrum of compound L3A showed new carbon signals in (73.19, 70,32) refers to (2 O-CH2-N)) ppm. As shown in Figures (1,2).



SCHEME 1: Synthetic protocol for preparing β-lactam derivatives

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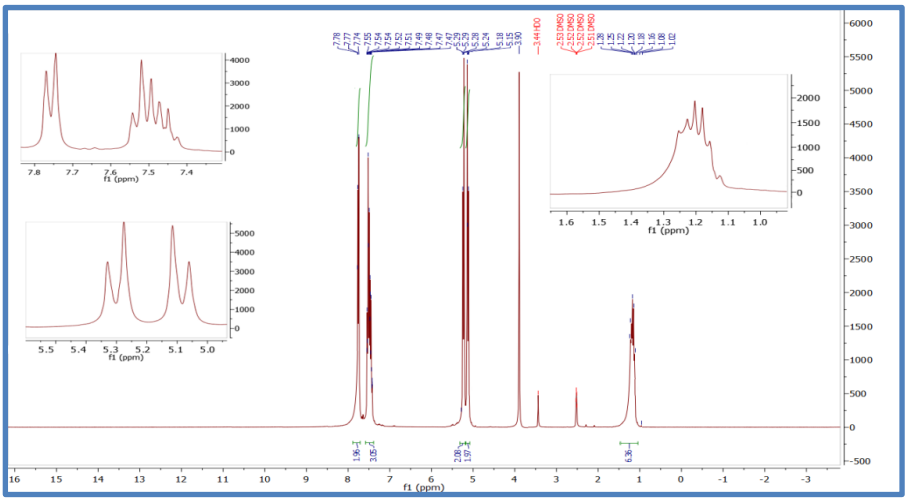

FIGURE 1: 1HNMR spectrum of compound L3A

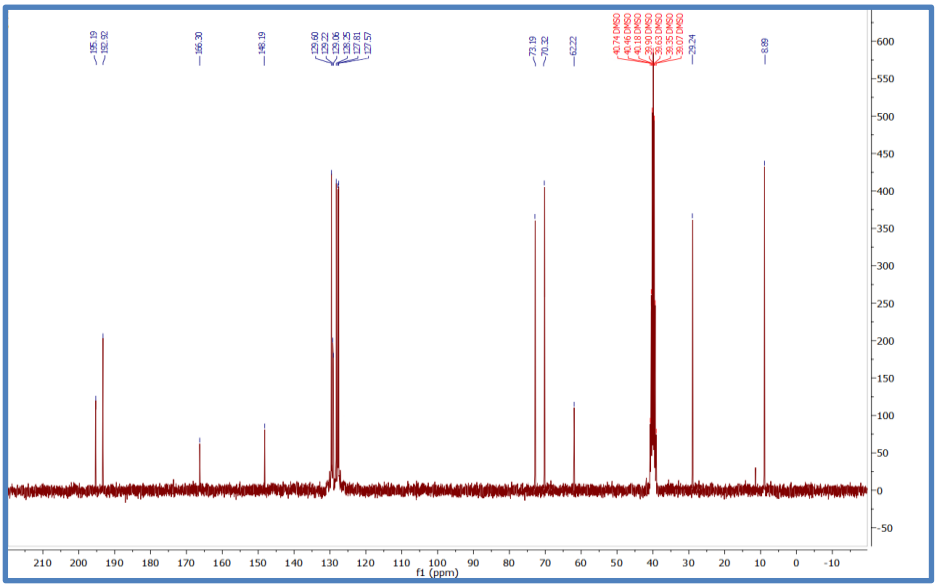

FIGURE 2: 13CNMR spectrum of compound L3A

On the other hand, compound (L3B) was achieved through the reaction between free hydroxyl groups of compound (L3A) and p-Toluenesulfonyl chloride in anhydrous pyridine under stirring.

In the FT-IR spectrum of compound (L3B), we observed the disappearance of a group of (υ O-H) group and showed new stretching vibration bands of (υ s,as SO2) in the regions (1121-1390) cm-1, The 1HNMR spectrum showed new signals in (δ 2.12 ppm) refers to (2 CH3) of sulfonate group and disappearance (OH group) of compound (L3A) and new signals appeared in the ranges (7.28-8.31 ppm) for the protons of benzene rings. Besides, the 13CNMR spectrum showed a new signal in (65.22) ppm for the methyl group (-CH3) of the sulfonate group, on the other hand, new signals appear in the range (127.72-147.92 ppm) referring to the carbon atom of the benzene rings. As shown in figures (3,4). While, the mass spectrum showed a peak at 601.8 which represented the M+, while the peak at 602.8 was attributed to the M+1 for the isotopes 13C.

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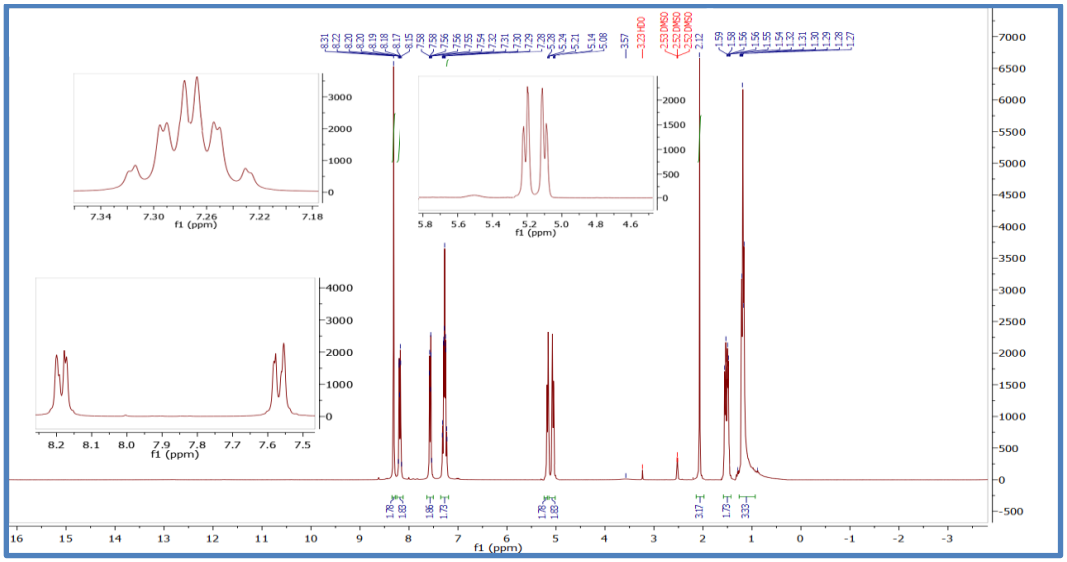

FIGURE 3: 1HNMR spectrum of compound L3B

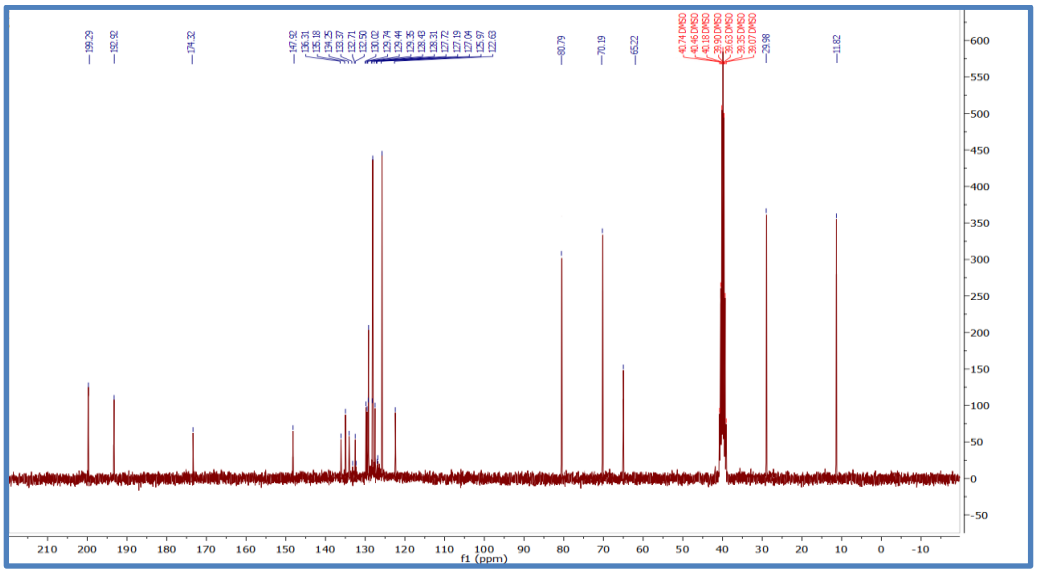

FIGURE 4: 13CNMR spectrum of compound L3B

While the preparation of compound (L3C) is considered one of the very difficult reactions to remove a sulfonate group of two sites in compound (L3A), sodium amide was added gradually to the reaction to ensure it was obtained. In the FT-IR spectrum of compound (L3C), we showed new stretching vibration bands of (-NH2) in the regions (3409-3298) cm-1, on the other hand, the disappearance of the sulfonate group of compound (L3B). The 1HNMR spectrum showed new signals appeared in the ranges (3.19-3.59) ppm for the protons of NH2, on the other hand, the disappearance of the sulfonate group of compound (L3B), Besides, the 13CNMR spectrum showed the disappearance of the sulfonate protons to compound (L3B) As shown in Figure (3-39). As shown in figures (5,6). The Mass spectrum of compound L3C showed a peak at 292.4 which represented the M+, while the peak at 293.4 was attributed to the M+1 for the isotopes 13C.

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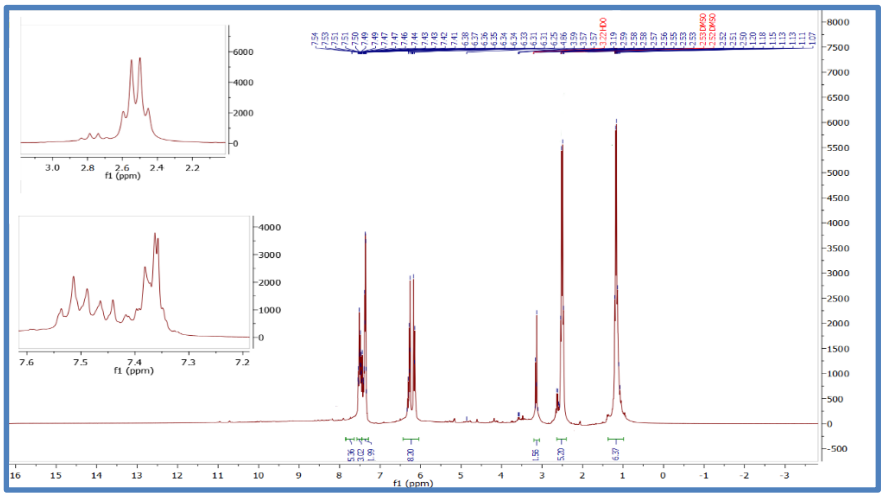

FIGURE 5: 1HNMR spectrum of compound L3C

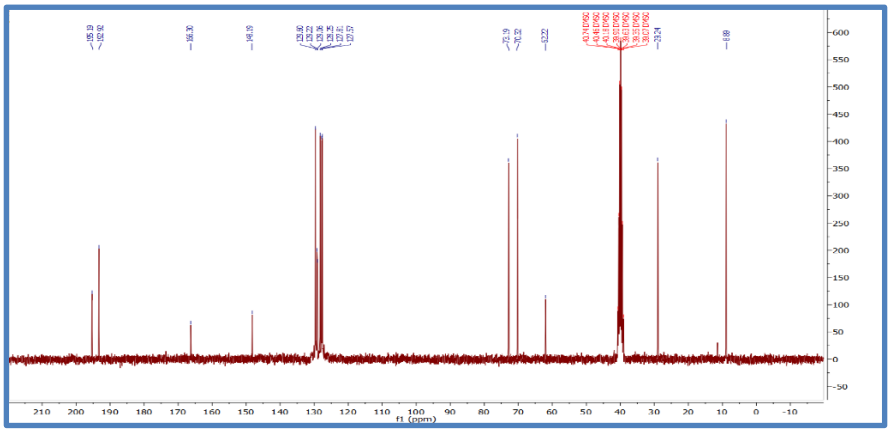

FIGURE 6: 13CNMR spectrum of compound L3C

Synthesis of Schiff base derivatives (L3C1, L3C2, L3C3, and L3C4)

The first step involves protonating the carbonyl group by reacting with glacial acetic acid to form a hydroxyl group, while the second step involves the amine group attacking from two sides of the aldehyde group and leaving a water molecule. Imine derivatives (L3C1, L3C2, L3C3, and L3C4) were synthesized by reaction of a barbital derivative with free amino groups and corresponding substituted benzaldehyde in the presence of glacial acetic acid. The FTIR spectrum showed the absence of the amines groups and showed new stretching vibration bands of (-N=CH) in the regions (1725, 1716, 1732, and 1740) cm-1 of all compounds respectively. (A.Aziz Abu-Yamin, et al., 2022)

Synthesis of β-Lactam compounds

This step is very difficult. Where chloroacetyl chloride is added to the Schiff base derivatives very slowly to prevent the compound from turning into something like bitumen, followed by adding the trimethylamine base to remove the proton and complete the closing process and form a β-lactam ring of derivatives (L3C5, L3C6, L3C7, and L3C8).

The FTIR spectrum of compounds (L3C5) showed the absence of the stretching vibration bands of (-N=CH) and showed a new stretching vibration band (C=O) of β-lactam in the region (1744) cm-1.). (M. Gil, et al.,2001) On the other hand, the 1HNMR spectrum showed new signals appeared in the ranges (6.39, 5.42 ppm) refers to for the protons (CH-N) of the b-Lactam ring, and signals in (δ 5.40, 5.25) ppm refer to (CO-CH-Cl)

of the β-lactam ring) and absence of the proton of the imine group (-N=CH). Besides, the 13CNMR spectrum showed new signals appear in (122.71-129.46 ppm) referring to two naphthalene rings and new signals appeared in the ranges (65.22, 70.19) ppm for the carbons (CH-N) of the b-Lactam ring, and signals in (δ 80.89 and 82.22) refer to (CO-CH-Cl) of the β-lactam ring. As shown in Figures (7,8). The Mass spectrum of compound L3C5 showed a peak at 775.3 which represented the M+, while the peak at 776.3 was attributed to the M+1 for the isotopes 13C.

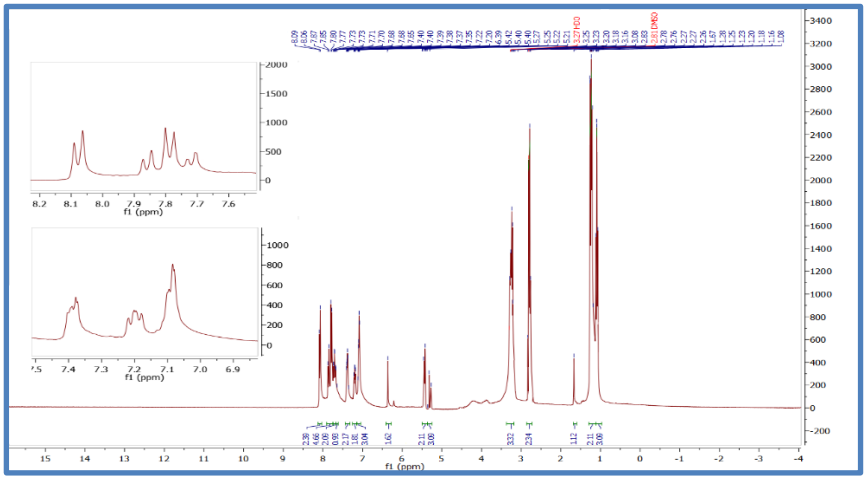

FIGURE 7: 1HNMR spectrum of compound L3C5

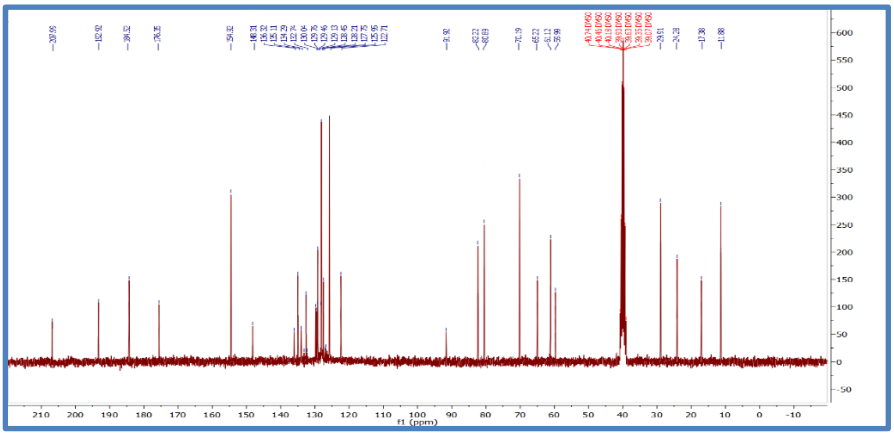

FIGURE 8: 13CNMR spectrum of compound L3C5

In the FT-IR spectrums of compound (L3C6, L3C7 and L3C8), we showed new stretching vibration bands of (C=O) of β-lactam in the regions (1755, 1761, 1775) cm-1 and disappearance of (υ N=CH) group.

CONCLUSIONS

In this study, we reported the possibilities to form different barbital derivatives containing β-lactam rings are high due to the manipulating of protecting groups based on different reactivities of secondary amino groups within the macrocycles compounds.

Selective removal of protecting groups are allowed the synthesis of a variety of β-lactam derivatives.

Different routes are used for the synthesis of Di-azetidinone Derivatives Based on Barbital Compound.

J Popul Ther Clin Pharmacol Vol 30(7):e349–e359; 04 April 2023.

These derivatives were found to be stable at room temperature due to their aromaticity.

Some of the β-Lactam derivatives are oily. These derivatives were confirmed from spectral data analysis; FTIR, 1H-NMR-13C-NMR and Mass.

REFERENCES

1. F.H. van der Steen and G.van koten, "Syntheses of 3-Amino-2-azetidinones: A Literature Survey," Tetrahedron, vol. 41, no. 36, pp. 7503–7524, 2009.
2. J. A. Joule and K. Mills, Heterocyclic Chemistry, Fifth Edit. A John Wiley & Sons, Ltd., Publication, pp. 588-592, 2010.
3. S. Alfei and A. Maria Schito, "β-Lactam Antibiotics and β-Lactamase Enzymes Inhibitors, Part 2: Our Limited Resources," pharmaceuticals, vol. 15, no. 476, 2022DOIoi: doi.org/10.3390/ph15040476.
4. K. Busha, "Past and Present Perspectives on b-Lactamases," Antimicrob. Agents Chemother., vol. 62, no. 10 e01076-18, 2018DOIoi: DOI : .org/10.1128/AAC.01076-18.
5. Y. Sik Park et al., "Structural Study of Metal Binding and Coordination in Ancient Metallo-β-Lactamase PNGM-1 Variants," Int. J. Mol. Sci., vol. 21, no. 14, 2020DOIoi: doi.org/10.3390/ijms21144926.
6. V. Güner, S. Yildirir, B. Özçelik, and U. Abbasoglu, "Synthesis and antimicrobial activity of 1,4-diaryl-2-azetidinones," Farmaco, vol. 55, no. 2. pp. 147–150, 2000DOIoi: 10.1016/S0014-827X(99)00126-3.
7. M. Peng et al., "In vitro Combined Inhibitory Activities of β- Lactam Antibiotics and Clavulanic Acid Against blaKPC-2-Positive Klebsiella pneumoniae," Infect. Drug Resist., vol. 14, pp. 361–368, 2021DOIoi: DOI: 10.2147/IDR.S292612.
8. M. Babic, A. M. Hujer, and R. A. Bonomo, "What's new in antibiotic resistance? Focus on beta-lactamases," Drug Resistance Updates, vol. 9, no. 3. pp. 142–156, 2006DOIoi: 10.1016/j.drup.2006.05.005.
9. Karaiskos, I. Galani, V. Papoutsaki, L. Galani, and H. Giamarellou, "Carbapenemase producing Klebsiella pneumoniae: implication on future therapeutic strategies," Expert Review of Anti-Infective Therapy, vol. 20, no. 1. pp. 53–69, 2022DOIoi: 10.1080/14787210.2021.1935237.
10. Y. K. and M. Y. Shinichiro Yamachika, Chika Sugihara, "Correlation between penicillin-binding protein 2 mutations and carbapenem resistance in Escherichia coli," J. Med. Microbiol., vol. 62, pp. 429–463, 2013DOIoi: DOI 10.1099/jmm.0.051631-0.
11. M. Malebari et al., "β-Lactam analogues of combretastatin A-4 prevent metabolic inactivation by glucuronidation in chemoresistant HT-29 colon cancer cells," European Journal of Medicinal Chemistry, vol. 130. pp. 261–285, 2017DOIoi: 10.1016/j.ejmech.2017.02.049.
12. D. Kuhn, C. Coates, K. Daniel, D. Chen, and Mohammad Bhuiyan, "Beta-lactams and their potential use as novel anticancer chemotherapeutics drugs," Front. Biosci., vol. 9, no. 4, pp. 2605–2617, 2004DOIoi: doi.org/10.2741/1420.
13. C. A. Hobson et al., "impact of anticancer chemotherapy on the extension of beta-lactamase spectrum: an example with Kpc- type carbapenemase activity towards ceftazidime-avibactam," Sci. Rep., vol. 10, p. 589, 2020DOIoi: doi.org/10.1038/s41598-020-57505-w.
14. J. L. Dong-Jun Fu, Y. F. Zhang, An-Qi Chang, "β-Lactams as promising anticancer agents: molecular hybrids, structure activity relationships and potential targets Dong-Jun," Eur. J. Med. Chem., vol. 201, no. 1, 2020DOIoi: doi.org/10.1016/j.ejmech.2020.112510.
15. E. P. Luigino Troisi and C. Granito, "Novel and Recent Synthesis and Applications of b-Lactams," Top Heterocycl Chem, vol. 22, pp. 101–209, 2010, doi: DOI 10.1007/7081_2009_12.
16. B. Mohan Sahoo and B. K. Banik, Therapeutic Potentials of β-Lactam : A Scaffold for New Drug Development. Synthetic Approaches to Nonaromatic Nitrogen Heterocycles- John Wiley & Sons Ltd, 2021.
17. Gupta and A. K. Halve, "Synthesis & Antifungal Screening of Novel Azetidin-2-ones," Open Chemistry Journal, vol. 2, no. 1. pp. 1–6, 2015DOIoi: 10.2174/1874842201502010001.
18. Jarrahpour, P. Shirvani, V. Sin,ou and C. Latour "Synthesis and biological evaluation of some new b-lactam-triazole hybrids," Med. Chem. Res., vol. 8, 2015DOIoi: DOI 10.1007/s00044-015-1474-x ORIGINAL.
19. S. S. Chhajed and C. D. Upasani, "Synthesis and in-silico molecular docking simulation of 3-chloro-4-substituted-1-(2- (1H-benzimidazol-2-yl)phenyl))-azetidin-2-ones as novel analgesic anti-inflammatory agent," Arab. J. Chem., vol. 9, no. 2, pp. 1779–1785, 2016DOIoi: doi.org/10.1016/j.arabjc.2012.04.038.
20. J. W. Skiles and D. McNeil, "Spiro indolinone beta-lactams, inhibitors of poliovirus and rhinovlrus 3C-proteinases," Tetrahedron Letters,

vol. 31, no. 50. pp. 7277–7280, 1990DOIoi: 10.1016/S0040-4039(00)88543-3.
21. M. Ali et al., "Enamine barbiturates and thiobarbiturates as a new class of bacterial urease inhibitors," Applied Sciences (Switzerland), vol. 10, no. 10. 2020DOIoi: 10.3390/app10103523.
22. J. Figueiredo et al., "Trisubstituted barbiturates and thiobarbiturates: Synthesis and biological evaluation as xanthine oxidase inhibitors, antioxidants, antibacterial and anti-proliferative agents," European Journal of Medicinal Chemistry, vol. 143. pp. 829–842, 2018DOIoi: 10.1016/j.ejmech.2017.11.070.
23. J. N. Suzana Apostolov1, Đ. Vaštag1, B. Matijević1and G. Mrđan, "Study Of The Biological Activity Descriptors Of The Barbituric Acid Derivatives," Contemp. Mater., Vol. 11, No. 2, 2020DOIOI: Doi 10.7251/Comen2002077a.
24. Jabbar Radhi, E. Hussein Zimam and A. J. Almulla "New Barbiturate Derivatives as Potent in vitro α-Glucosidase Inhibitors," Egypt. J. Chem., vol. 64, no. 1, pp. 117–123, 2021DOIoi: DOI: 10.21608/EJCHEM.2019.16210.1991.
25. B. Sokmen, S. Ugras, H. Y. Sarikaya, H. I. Ugras, and R. Yanardag, "Antibacterial, antiurease, and antioxidant activities of some arylidene barbiturates," Applied Biochemistry and Biotechnology, vol. 171, no. 8. pp. 2030–2039, 2013DOIoi: 10.1007/s12010-013-0486-6.
26. W. Mohammed Najem, M. Zuheir, Sami E. Al-Slami and A. Jabbar Radhi "Synthesis and Studying Antibacterial Activity of New Nitrogen Rich Polymers," Egypt. J. Chem., vol. 65, no. 2, pp. 29–33, 2022DOIoi: DOI: 10.21608/EJCHEM.2021 .34931.2727.
27. D. Neumann,The Design and Synthesis of Novel Barbiturates of Pharmaceutical Interest by, " "ScholarWorks @ UNO University of New Orleans Theses, pp 1-314, 2004.
28. J. T. Bojarski, J. L. Mokrosz, H. J. Bartoń, and M. H. Paluchowska, "Recent Progress in Barbituric Acid Chemistry," Advances in Heterocyclic Chemistry, vol. 38, no. C. pp. 229–297, 1985, doi: 10.1016/S0065-2725(08)60921-6.
29. D. A. Cozanitis et al, "One hundred years of barbiturates and their saint," Journal Of The Royal Society Of Medicine, vol. 97, pp. 594–597, 2004.
30. K A Savage and D Wielbo, "Pharmacology Of Legal And Illicit Drugs," Natl. Forensic Sci. Technol. Cent., pp. 435–446, 2005.
31. E. J. Almulla, A. J. Radhi and E. H. Zimam, "New Barbiturate Derivatives as Potent in vitro α-Glucosidase Inhibitors," Egypt. J. Chem., vol. 64, no. 1, pp. 117–123, 2021DOIoi: DOI: 10.21608/EJCHEM.2019.16210.1991.
32. Ling, R. Hashim, and K. J. Sabah, "Sugar thiacrown-ether appended calix[4]arene as a selective chemosensor for Fe2+ and Fe3+ ions," RSC Adv., vol. 5, no. 107, pp. 88038–88044, 2015DOIoi: 10.1039/c5ra15448k.
33. M. Szyma´nska et al., "Synthesis and Spectroscopic Investigations of Schiff Base Ligand and Its Bimetallic Ag(I) Complex as DNA and BSA Binders," Biomol. Artic., vol. 11, p. 1449, 2021DOIoi: doi.org/10.3390/biom11101449.
34. QI H-zhen, MO S-yan and XU Jia-xi, "Highly Stereoselective Synthesis of trans-3-Chloro-b-lactams from Imines and Mixed Chloroacetyl and Nitroacetyl Chlorides," CHEM. RES. CHINESE Univ., vol. 27, no. 6, p. 958—962 Highly, 2011DOIoi: DOI : 1005-9040(2011)-06-958-05.
35. ß. Beltr, B. Eleuterio ßlvarez, P. J. M. Mar and a.Requejo, "Direct Synthesis of Hemiaminal Ethers via aThree-Component Reaction," Adv.Synth. Catal., vol. 357, pp. 2821 –2826, 2015, doi: 10.1002/adsc .201500588.
36. A.Aziz Abu-Yamin , M. Siddiq Abduh , S. Ayesh Mohammed and N. Al-Gabri, " Synthesis, Characterization and Biological Activities of New Schiff Base Compound and Its Lanthanide Complexes" Pharmaceuticals 2022, 15, 454, doi.org/10.3390/ph15040454
37. M. Gil, J. L. Núñez, M. A. Palafox, and N. Iza, "FTIR study of five complex β-lactam molecules," Biopolymers - Biospectroscopy Section, vol. 62, no. 5. pp. 278–294, 2001, DOI: 10.1002/bip.1023.