Article

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Synthesis and Biological Activity Evaluation of Some New Heterocyclic Compounds Derived from Sulfamethoxazole Drug.

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Abstract. A sequence of five-membered molecules was developed from the drug sulfamethoxazole. The initial stage was the production of compound [S_1], which was generated by mixing terephthalaldehyde with cysteine to make a thiazolidine compound using a sublimation technique. The second stage was the production of compound [S_2] by the combining of sulfamethoxazole with the previously generated compound [S_1]. In the third stage, the compound [S_3] was produced by mixing compound [S_2] with thionyl chloride. The last step was the synthesis of imidazoline-based derivatives via the interaction of amino acids with 3. These were validated by evaluating the physical characteristics (melting point and Rf values, FT-IR spectra, ^{1}H-NMR and ^{13}C-NMR spectra). All of these derivatives were examined on various bacteria (E. coli and S. aureus). The efficiency of these derivatives is substantially better than that of the same quantity of sulfamethoxazole that is active, (S_2, S_6, S_7).

Keywords: Heterocyclic compounds, Sulfamethoxazole drug , Schiff bases, antibacterial

1. Introduction

Sulfamethoxazole is a chemical compound that is organic. It's a white or light yellow (1) powder that is odorless and slowly soluble in water, although it's quickly soluble in ethanol, acetone, and weak solutions of alkali metal hydroxides as well as inorganic acids. Sulfamethoxazole is reliant on sunshine, temperature, and potent oxidants (2,3). Schiff bases are generated from primary (aromatic) amines and include a ketone or aldehyde as their condensation product (-CR=N-). They are regarded to have a range of pharmacological effects, including the Azomethine group, which has been proved to be vital to biological action. For instance, Schiff bases, both natural and non-natural sources, have a promising impact on bacteria, tubers, and fungus, as well as an effect on parasitic worms and viruses, and an effect on antioxidants and cancer prevention (4,5). Heterocyclic compounds that include nitrogen coupled to a sulfonamide moiety have been the topic of substantial attention in the literature. Sulfonamides that have a wide variety of biological capabilities generated from the functional group of sulfonamides have impacted medicine substantially (6). Heterocyclic sulfonamides are exploited as inhibitors of carbon dioxide (7,8) and as agents against bacteria (9). Imidazolidinone is a cyclic structure that has two nitrogen atoms at the 1st and 3rd positions. The conclusion is a molecule with a saturated imidazole moiety that is not aromatic. These compounds are also referred to as methylene ethylenediamines and serve as secondary amines (10). Imidazolidinones and its derivatives have many pharmacological effects, including the stability of adenosine (11). Antispasmodic (12), antimicrobial, hypoglycemic orally (13), anti-inflammatory (14), and antiarrhythmic (15, 16). A range of novel imidazolidine-2,4-dione derivatives have been produced to be employed as fungicides and bactericides that are intended for use in clinical conditions (17). The potential of these chemicals to bind has been investigated with the objective of producing more effective and efficient antifungal and antibacterial therapies. The testing findings revealed that each compound had antibacterial capabilities, and some of the substances had a potential function in the treatment of bacterial disorders. The interaction between Schiff base compounds and amino acids resulted in the development of new molecules having imidazolidine characteristics (18).

2. MATERIAL AND METHODS:

Reagents and compounds were obtained as initially purchased from commercial suppliers without extra purification. The potency of the compounds and the degree to which they proceeded were examined using silica gel-G (Merck grade) thin layer chromatography that utilised a combination of ethanol and benzene as the mobile phase. The melting points of the components were obtained using a technique of open capillary that utilises a Stuart melting point meter (SMP30, UK). The quoted temperatures are not adjusted. The 1H and ^{13}C NMR spectra of the derivatives were obtained on a Bruker (Avance III, Bruker 400 MHz NMR spectrophotometer) using TMS as the internal standard. Values are presented in parts per million at the University of Toronto, Canada. Infrared (IR) spectra were acquired on a Shimadzu Prestige^{-21} spectrophotometer using potassium bromide (KBr pellets) and the results are reported in cm^{-1}.

2.1. Synthesis of Compound(S_1)(19) :

2-(4-formylphenyl)thiazolidine-4-carboxylic acid

Compound S1 was produced by dissolving 0.5 g (0.003 mol) of pinealdehyde and 0.36 g (0.003 mol) of cysteine in a combination of 15 mL of anhydrous ethanol and 5 mL of distilled water, this was followed by stirring for 24 hours. The reaction's completeness was then determined by TLC with 9:1 ratio of ethanol to chloroform. After the reaction was complete, a second round of recrystallization was undertaken using 20:6 alcohol + water. The combination was subsequently examined and recorded using infrared spectroscopy.

2.2 . Synthesis of Compound (S_2)(20) :

2-(4-(((4-(N-(5-methyl-4,5-dihydroisoxazolyl)sulfamoyl)phenyl)imino)methyl)phenyl)thiazolidine-4-carboxylic acid

The concentration of the sulfamethoxazole solution (1.0 g, 0.003 mol) was made up of 30 ml of anhydrous ethanol and (3) drops of glacial acetic acid were included under stirring. The mixture was dissolved using a magnetic stirrer at a temperature of 10 degrees Celsius for 10 minutes, then the first phase of the method was to add the thiazolidine S_1 (0.57 g, 0.003 mol) acquired in the first step. The mixture was heated to 85 degrees Celsius via reflux and engaged in 22 hours of reaction. The precipitate was then discarded and the remainder was furtherprocessed by means of crystallization using anhydrous alcohol.

2.3. Synthesis of Compound (S_3) (21) :

2-(4-(((4-(N-(5-methyl-4,5-dihydroisoxazol-3-yl)sulfamoyl)phenyl)imino)methyl)phenyl)thiazolidine-4-carbonyl chloride

The prepared thiazolidine (S_2) (0.5 g, 0.001 mol) was dissolved in 30 ml of anhydrous ethanol, then 0.11 g of thionyl chloride was added under constant stirring on a magnetic stirrer, and the reaction was monitored by TLC with ethanol: anhydrous benzene 1:4, then the product was cooled, filtered and re-crystallized from anhydrous ethanol.

2.4. Synthesis of imidazolinone(S_4,S_5,S_6,S_7) (22) :

2-(4-(1-(4-(N-(5-methyl-4,5-dihydroisoxazol-3-yl)sulfamoyl)phenyl)-5-oxoimidazolidin-2-yl)phenyl)thiazolidine-4-carboxylic acid (S4)

2-(4-(4-(4-hydroxyphenyl)-1-(4-(N-(5-methyl-4,5-dihydroisoxazol-3-yl)sulfamoyl)phenyl)-5-oxoimidazolin-2-yl)phenyl)thiazolidine-4-carboxylic acid (S5)

2-(4-(4-benzyl-1-(4-(N-(5-methyl-4,5-dihydroisoxazol-3-yl)sulfamoyl)phenyl)-5-oxoimidazolidin-2-yl)phenyl)thiazolidine-4-carboxylic acid (S5) 2-(4-(4-methyl-1-(4-(N-(5-methyl-4,5-dihydroisoxazol-3-yl)sulfamoyl)phenyl)-5-oxoimidazolidin-2-yl)phenyl)thiazolidine-4-carboxylic acid (S7)

Compound (S_3) (0.1 g, 0.0002 mol) was dissolved in 20 mL of anhydrous benzene, then glycine (0.02 g, 0.04 g, 0.033 g and 0.01 g, 0.0002 mol) were added successively, and the mixture was refluxed at 85 °C for 24 hours. The precipitate was collected and dried before being re-purposed in anhydrous alcohol. The procedure's reaction was monitored by TLC using a combination of 2:1 and 4:1 ratios of ethanol:anhydrous benzene.

3. Biological activity assay:

The antibacterial activity of the heterocyclic compounds was assessed against two bacteria species: Gram-positive Staphylococcus aureus and Gram-negative Klebsiella pneumoniae (25) in nutritional agar medium using the fine diffusion technique. The findings are given as the MIC (or

lowest inhibitory concentration) of the compounds, all of them were suspended in 100 ml of water-based solution in DMSO at varied concentrations, ranging from 1000 µg to 100 µg, Table 1.

Table 1.: The zones of inhibition of compounds and their breakdown products against various microorganisms (mm).

Nom	mater	Con	*Kleb. Pneum*	*staph. Usaureus*
1	**Con**	…..	0	0
2	**S1**	1000 µg/ml	12	0
		100 µg/ml	0	0
3	**S6**	1000 µg/ml	15	13
		100 µg/ml	0	0
4	**S7**	1000 µg/ml	15	14
		100 µg/ml	0	0
5	**S2**	1000 µg/ml	17	0
		100 µg/ml	0	0

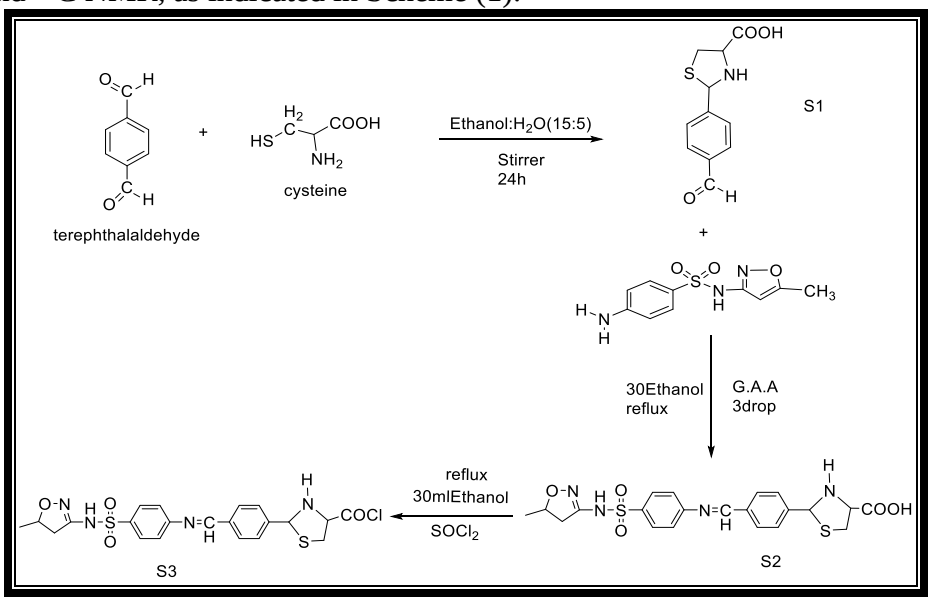
Table(2): The physical properties of imbued compounds.

No.	M.F	M.wt	m.p C^0	Color	R*f*	Yield %
S1	$C_{11}H_{11}NO_3S$	237.27	98-100	Orange	0.59	70
S2	$C_{21}H_{22}N_4O_5S_2$	474.55	139-140	White	0.82	81
S3	$C_{21}H_{21}ClN_4O_4S_2$	492.99	156-158	Yellow	0.47	87
S4	$C_{23}H_{25}N_5O_6S_2$	531.60	152-154	Dark brown	0.62	85
S5	$C_{29}H_{29}N_5O_7S_2$	623.70	166-168	brown	0.63	80

S6	$C_{30}H_{31}N_5O_6S_2$	621.73	160-162	Orange	0.60	86
S7	$C_{24}H_{27}N_5O_6S_2$	545.7	186-170	brown	0.67	91

4. Results &Discussion:

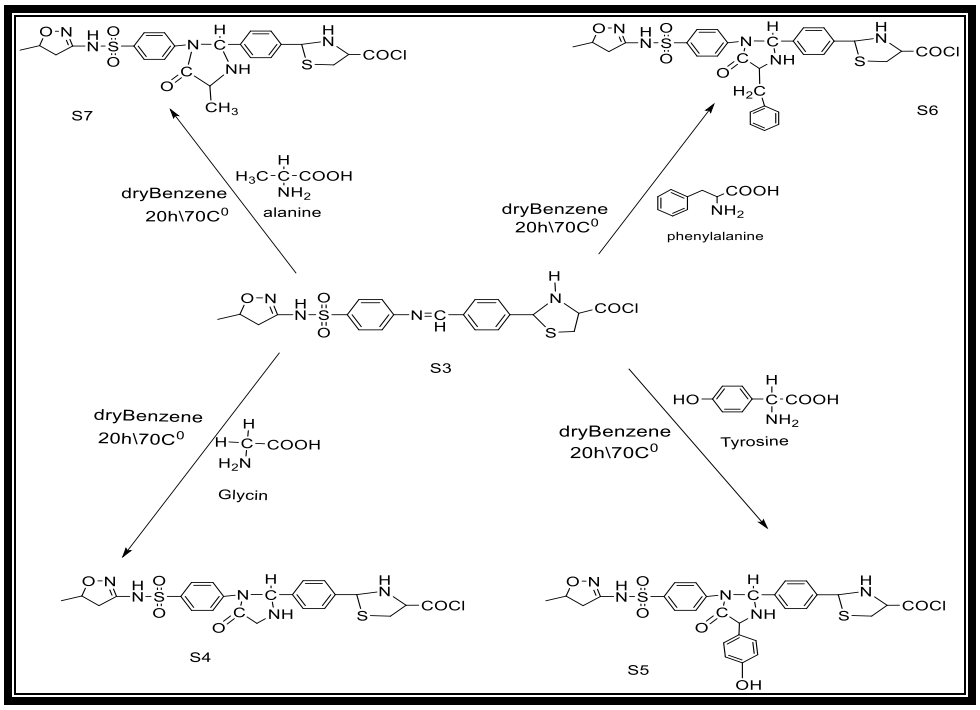
This inquiry discusses the technique and findings of additional derivatives' identification. These chemicals are formed from Schiff bases, which are major mediators with varied pharmacological and biological effects. The treatment of terephthalaldehyde with cysteine gave substance S_1, which was obtained by re-purification from alcohol. The treatment of compound S_1 with sulfamethoxazole and 3 drops of glacial acetic acid in anhydrous ethanol resulted in compound S_2, this was then mixed with thionyl chloride to make compound S_3. The reaction was monitored by TLC (benzene:ethanol) (2:3)) and the generated compounds were identified by melting point, FT-IR, ^1H and ^{13}C NMR, as indicated in Scheme (1):



Scheme(1): Synthesis of (S_1)and Schiff bases Compounds (S_1,S_2,S_3)

The chemical's composition was investigated by FT-IR spectroscopy, this indicated a band associated with NH at 3049 cm^{-1}, as well as a strong absorption band associated with OH in the carboxyl group at 3425 cm^{-1}. The aldehyde group at 1691 cm^{-1} and the hidden amine group at 3493 cm^{-1} in the original molecule were both assigned to the compound, this indicated extra bands. We then sought to combine (S_1) with (S_2) to form (S_3), which in turn produced many novel Schiff base compounds. Compounds (S_1, S_2) were detected using infrared spectroscopy. These compounds featured an intensive absorption band for ketones (S_2) at 1604 cm^{-1}, an inner ring band for C=N (1629 cm^{-1}), a hydroxyl band at 3469 cm^{-1}, a novel absorption band for imines (1610 cm^{-1}), and a strong absorption band for COCl compounds in compound S_3. Composition of chemicals (S_1, S_2) The composition of substances (S_1, S_2) was determined by 1H NMR spectra. The spectra of these compounds exhibited a single signal at (12.42, 12.24) ppm associated with the carboxyl protons, as well as multiple signals at (7.4-7.9) and (7.6-7.8) ppm for the aromatic protons of both compounds, a single signal at (1.6) ppm associated with the methyl protons of compound S_2, and a single signal at (9.3) ppm associated with the methyl protons of compound S_3. The amine segment of the five-membered isoxazole and thealdehyde

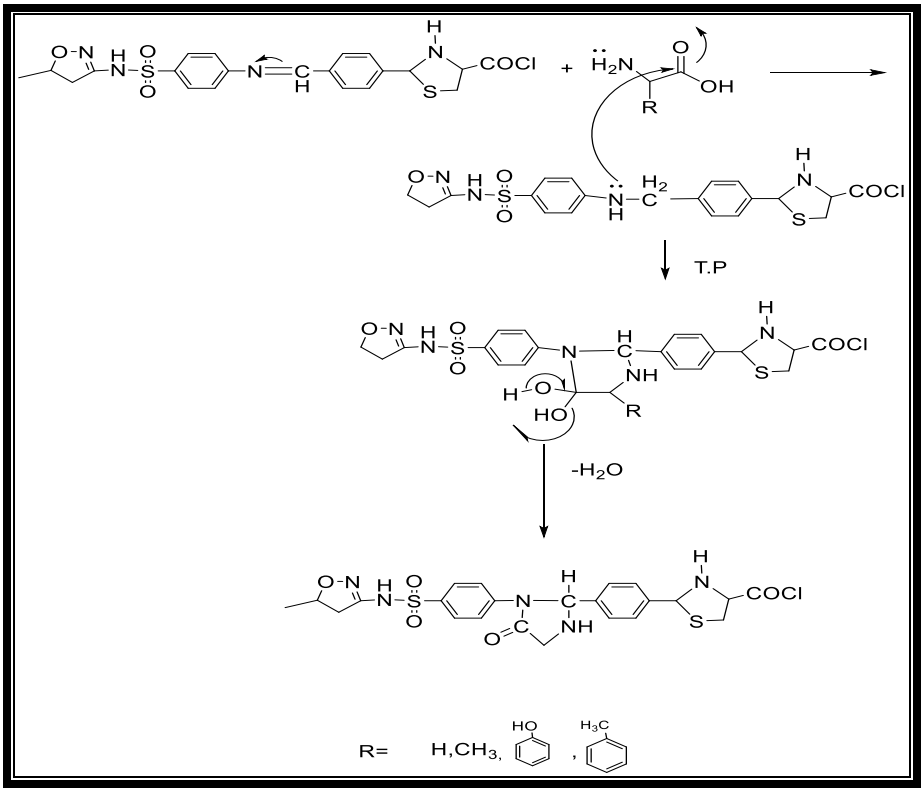
segment in compound S_1 form a single signal at (10.22). The ^{13}C NMR spectrum reveals a single signal for the carbon atom C=O of S_1 at (191.7) ppm, as well as a single signal for the carbon atom (CH_2-O) of the five membered ring of oxazole at (62) ppm and the methyl carbon atom of compound S_1 at (66) ppm (CH_2-N) and (24) ppm. In compound S_2, the hydroxyl signal is situated at (192.6) ppm, the imine signal is positioned at (174) ppm, the CH-N signal of the isoxazole group is located at (159) ppm, the Ar-C signal is located at (105-129) ppm, and the methyl signal is found at (24) ppm. This step includes the development of novel compounds having a five membered heterocyclic composition, Scheme (2).



Scheme(2): Synthesis of five membered rings Compounds

Compounds (S_3) and (S_4) were discovered by methods ofFT-IR analysis. For (S_3), a new strong band developed at 3469 cm^{-1} owing to the NH endocyclic group, a band appeared at 3041 cm^{-1} due to the NH endocyclic group, a band appeared at 1741 cm^{-1} due to the acyl chloride, and two similar and asymmetric bands appeared at 1388-1166 cm^{-1} due to the sulfonamide group. The S4 complex was identified using infrared spectroscopy. For (S_4), a new strong band appeared at 3381 cm^{-1} due to the NH endocyclic group, an NH peak appeared at 3116 cm^{-1}, a band appeared at 1722 cm^{-1} due to the acyl chloride, and two identical and asymmetric bands appeared at 1398-1149 cm^{-1} due to the sulfonamide group, while the amide group exhibited its band at 1682 cm^{-1}. For compound (S5), a new, strong band due to the OH group was observed at 3347 cm-1, an internal peak due to the NH group was observed at 3388 cm^{-1}, a band due to the Drug was observed at 3205 cm^{-1}, a band due to the Cl2 group was observed at 1724 cm^{-1}, two identical, but different bands due to the sulfonyl group were observed at 1373-1150 cm^{-1}, and a band of amide was located at 1688 cm^{-1}. The structures of these compounds were deduced by 1H-NMR analysis, a single signal of the carbonyl group of compound S_3 was observed at 10.5 ppm, a

signal of the secondary amine group was observed at 9.9 ppm, a signal of the amine group of the sulfone ring was observed at 8.7 ppm, and a signal of the imine group was observed at 3.9 ppm. For compound S4, a signal at 10.4 ppm was displayed owing to the carbonyl group, a signal at 9.8 ppm was exhibited for the secondary amine group, and a signal at 9.4 ppm was exhibited for the sulfonamide group. The spectra of these compounds were characterized by 1H NMR. The spectra of these molecules display a single signal connected with the protons atom C=O in the five membered ring of thiazole at 10.6 ppm, a single signal associated with the oxygen atom at 10.2 ppm, and a single signal linked with the imine group at 9.7 ppm. The spectra of these compounds were characterized using 13C NMR. The spectrum of this compound's spectrum is a single signal associated with the carbon atom C=O in the five membered ring of thiazole at 175.7 ppm, a single signal associated with the C= end of the cycle at 162.7 ppm, and a single signal associated with the imine group at 157.4 ppm. For chemical S4, the carbonyl group has a signal at 175.2 ppm, whereas the amide has a signal at 171.2 ppm and the methyl has a signal at 24.7 ppm. The spectrum of compound S5 reveals a single signal at 173.9 ppm associated with the carbon atom C=O in the five membered ring of the thiazole, a single signal at 154.2 ppm for the C=endocyclic group and a single signal at 161.9 ppm for the amide group. The methyl group exhibits a signal at 22.3 ppm.

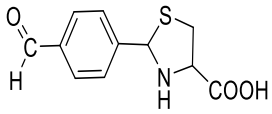
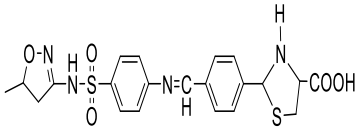
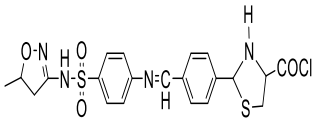


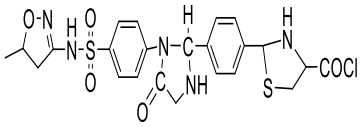
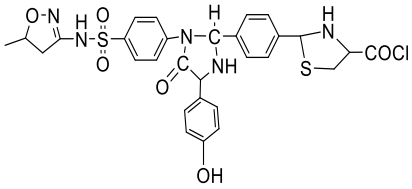
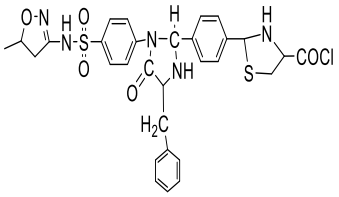
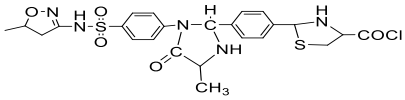
Scheme(3): Mechanism of cyclization of five- membered rings

Compounds (S_6, S_7) were detected byFT-IR spectroscopy and revealed new bands at (3400, 3398) cm^{-1} that matched to the NH groups (cyclic) of both compounds, moreover, the (C=N) band in compound (S3) was deleted from the spectrum. The NH groups (drugs) revealed new

bands at (3381, 3076) cm^{-1}, whereas the COCl groups of both compounds exhibited bands at (1716, 1740) cm^{-1}. Amide bands were identified in the bands at 1693 and 1688 cm^{-1}, whereas bands linked with C=N groups were observed at 1597 and 1602 cm^{-1}. Using 1H NMR spectroscopy, the compounds' structures were determined at the bands at (1388-1157 and 1311-1155 cm^{-1}, respectively). The single signal of the carbonyl group of compound S6 is situated at 10.1ppm, the signal of the secondary amine is placed at 9.9ppm, the signal of the amine is located at 9.4ppm, the signal of the imino group is located at 4.9ppm, and the signal of the N-CH is located at 9.9ppm. For chemical S_7, a signal is present at 10.7ppm owing to the carbonyl group, the secondary amine group displays a signal at 10.3ppm, and the Schiff base group exhibits a signal at 9.8ppm. The compounds' spectra are identified using 13C NMR. The spectra of these substances are distinctively defined by a signal at 162 ppm for the carbon atom of the amide group NHC=O in the thiazole ring, as well as a signal at 174 ppm for the COCl group. For compound S_7, the acyl chloride component has a signal at 173.2ppm, the carbon atom of the amide component NHC=O in the thiazole five-membered ring in the group has a signal at 160.1ppm, and the methyl component has a signal at 23.2ppm.

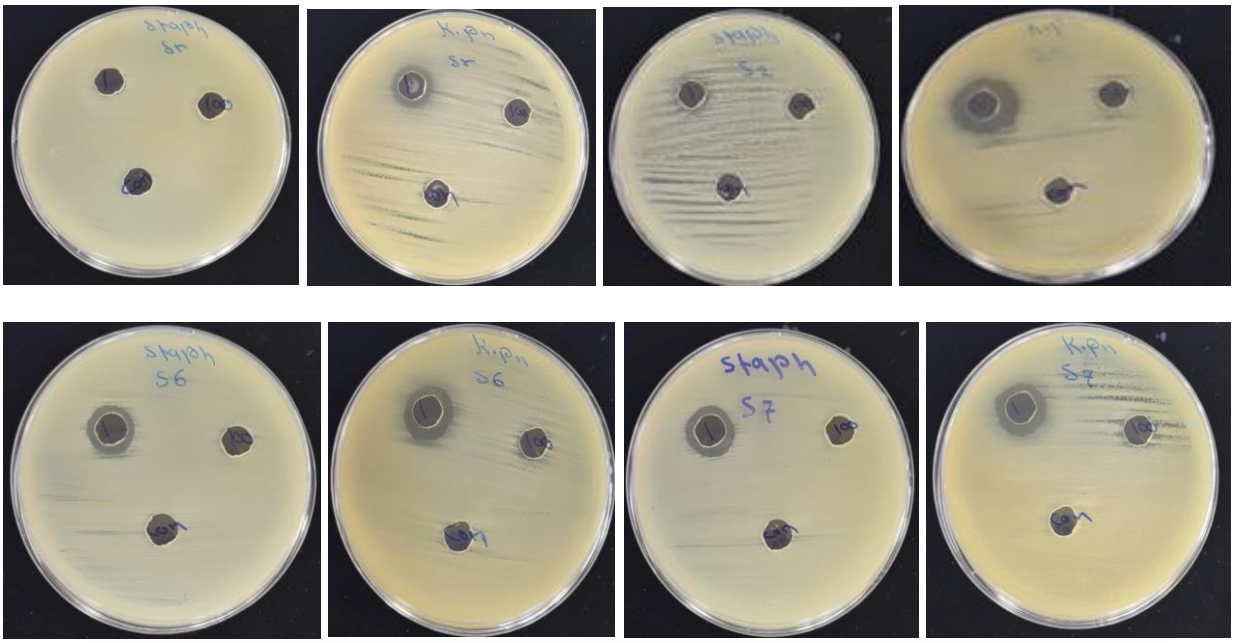
TABLE .3 ^{1}H-NMR and ^{13}C-NMR bands of compounds (S1-S7)

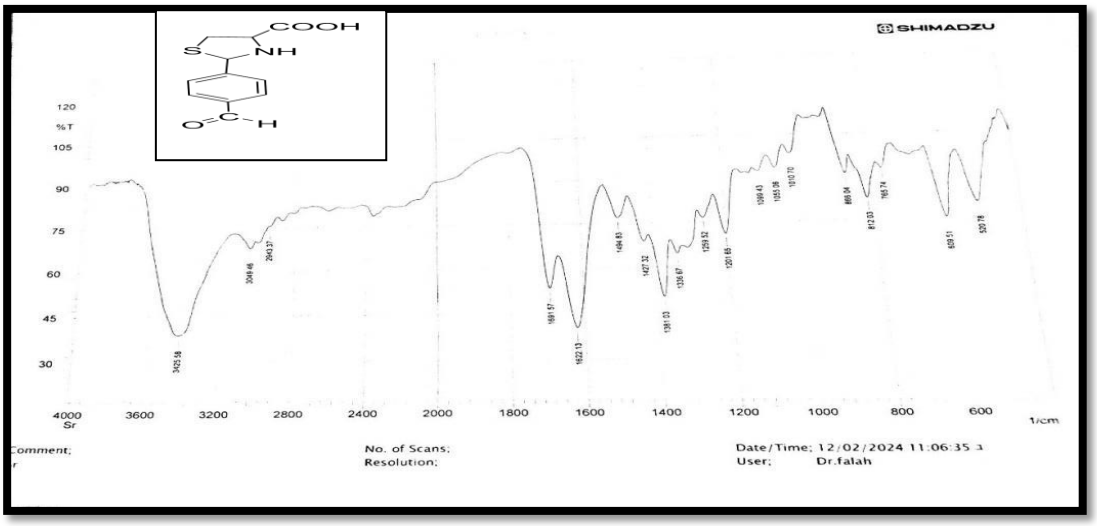
Comp. No .	Compound Structures	^{1}H-NMR Spectral data δppm	^{13}C-NMR Spectral data δppm
S1		3.10 (S,2H, CH_2) 3.95 (S,3H,NH-CH)five ring 6.10 (S,1H, CHS) 7.40-7.94(m,4H,Ar-H) 12.24(S,3H,OH) Carboxylic	24.75 (CH_2) 62.58(CH-S) five ring 116.63-131. 53 (m,C=C,Ar-C) 171.97(C-OH) Carboxylic 191.75(C=O) Carbonyl
S2		1.65(S,3H,CH_3) 2.21(S,2H,CH_2) Cyclo 3.11(S,1H,NH) 7.60-7.82(m,4H,Ar-H) 8.72(S,3H,C=N) Imime 9.90(S,1H, NH) Sulfonamide 9 (S,1H, NH) isoxazole 12.42(S,3H,OH) Carboxylic	24.18 (CH_3) 27.16(CH_2) 32.39(CH_2S) Cyclo 62.13(CH_2O) isoxazole 105.19-129.55 (m,C=C,Ar-C) 156.51 (CH_2N) isoxazole 174.68 (Imine) 192.61(COOH)
S3		1.68(S,3H,CH_3) 2.17(S,2H,CH_2)drug 3.18(S,3H,C=N) Imime 7.12-7.41(m,4H,Ar-H) 8.78(S,1H, NH) Sulfonamide 9.91 (S,1H, NH) isoxazole 9 (S,1H, C=O)	23.71 (CH_3) aliphatic 29.25 (CH_2) 63.71(CH-C-O) Ether Group 121.04-131.42 (m,C=C,Ar-C) 157.42 (C=N) Imime 162.70 (C=N)endocyclic 175.75(CO)

S4		1.58 (S,3H, CH_3)drug 2.41(S,2H,CH_2) Imine 3.94(3H,NCHS) 7.75-7.19(m,8H,Ar-H) 9.18(S,1H, NH) five ring 10.48 (S,1H, C=O)	24.17(CH_3) 32.39(CH_2) 63.22(C-ON) isoxazole 105.19-130.25 (m,C=C,Ar-C) 160.25 (C=N) Imine 171.25 (C-N)amide 175.26(C=O)
S5		1.85(S,3H,CH_3) 2.39(S,2H,CH_2) drug 5.29(S,3H, CHS) 7.14-7.92(m,8H,Ar-H) 9.73(S,1H, NH) five ring 10.28(S,1H,OH) 10.68(S,1H,C=O)	22.39(CH_3) 33.39(CH_2) 62.94(C-O) 67.14(CN) 74.94(C-S) 106.19 – 130.25 (m,C=C,Ar-C) 154.26(OH) 161.91(C=O)amide 162.28 (C=O)
S6		1.71(S,3H,CH_3)drug 2.41(S,2H,CH_2)Imine 3.94 (S,2H,OCH)five ring 4.95(S,2H,CHS) 7.60-7.80(m,8H,Ar-H) 9.40(S,1H, NH) 10.16(S,1H,C=O)	17.11 (CH_3) drug 27.11(CH_2) 52.41(NH-CO) 58.92(NH-CN) 116.62 – 131.22 (m,C=C,Ar-C) 162.64(C=O)amide 174.27(C=O)Carbonyl
S7		1.68 (S,3H, CH_3)drug 2.47(S,2H,CH_2)Imine 3(S,1H,CHN) 7.32-7.98(m,8H,Ar-H) 9.89(S,1H,C=N)amide 10.36(S,1H,NH)Sulf 10.76(S,1H,CO)	17.50 (CH_3) 31.48 (CH_2) 116.63 – 131.52 (m,C=C,Ar-C) 160.16 (C=O)amide 173.25(C=O)

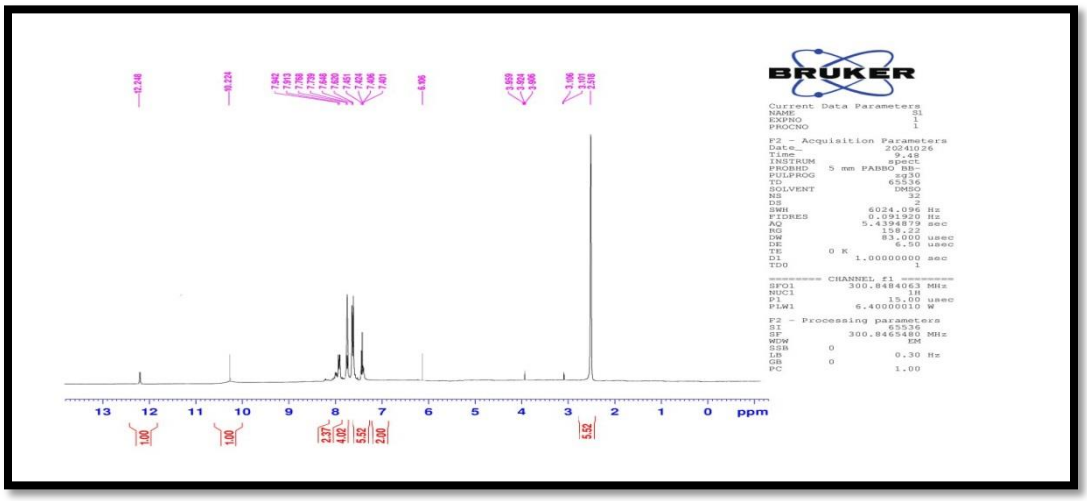
5. Biological activity

In the fight against infectious diseases, the identification of antibiotics against bacterial diseases is of special importance. The most significant findings are that the molecules (S_6) and (S_7) with a greater biological capacity have organic compounds with a sulfur atom as part of their composition. All of these substances demonstrated significant effectiveness at low concentrations. Additionally, the results demonstrated that none of these substances were as effective as sulfamethoxazole. Some compounds, including (S_1), (S_2), (S_6), and (S_7), have the potential to serve as targeted treatments for diseases caused by these bacteria, additional structural and pharmacological studies are necessary (Table 1)..

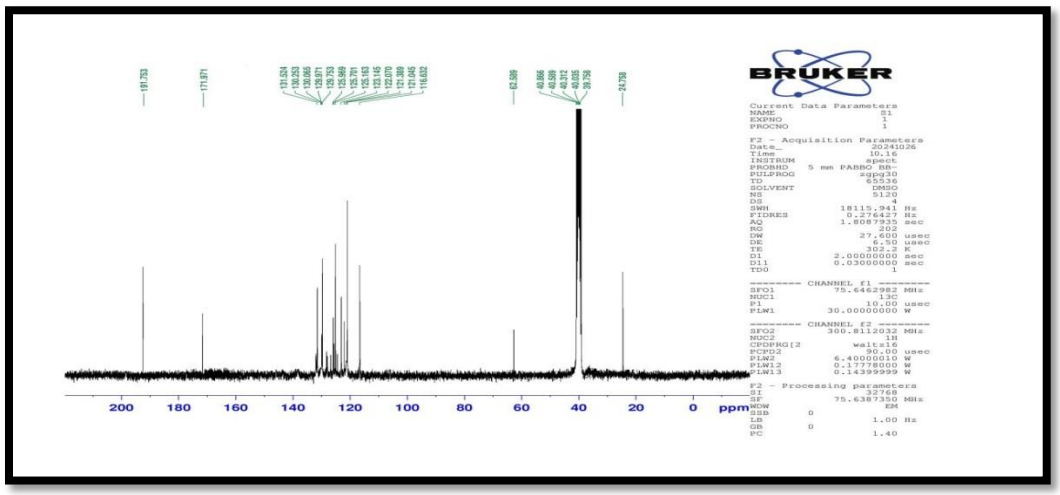




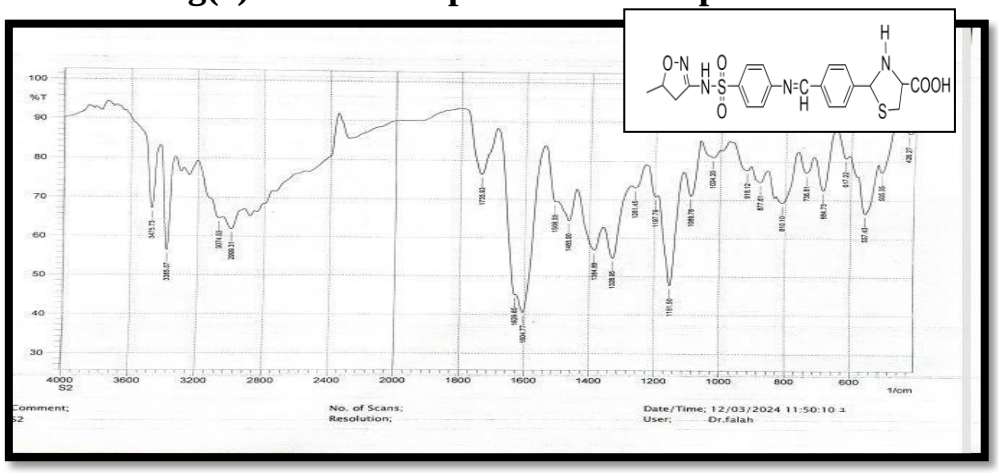
Fig(1): FT-IR spectrum of compound S1



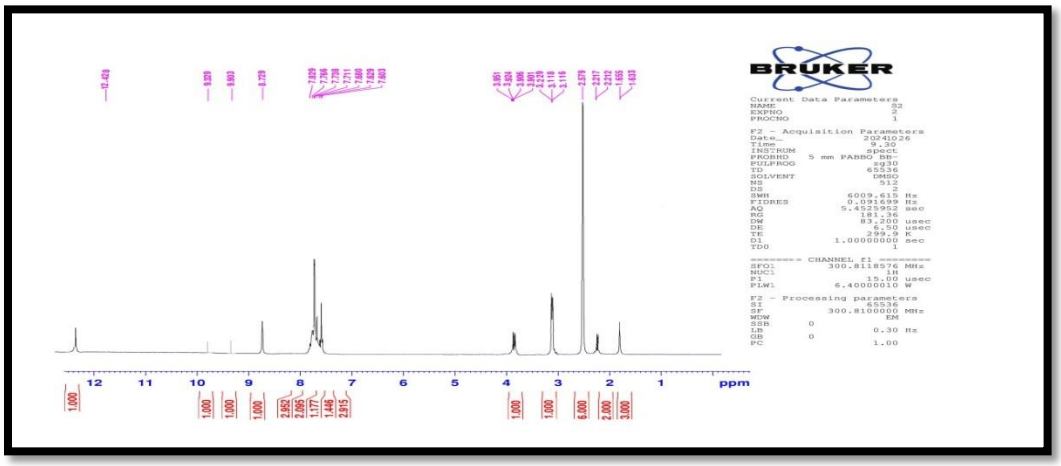
Fig(2): ^{1}H-NMR spectrum of compound S1



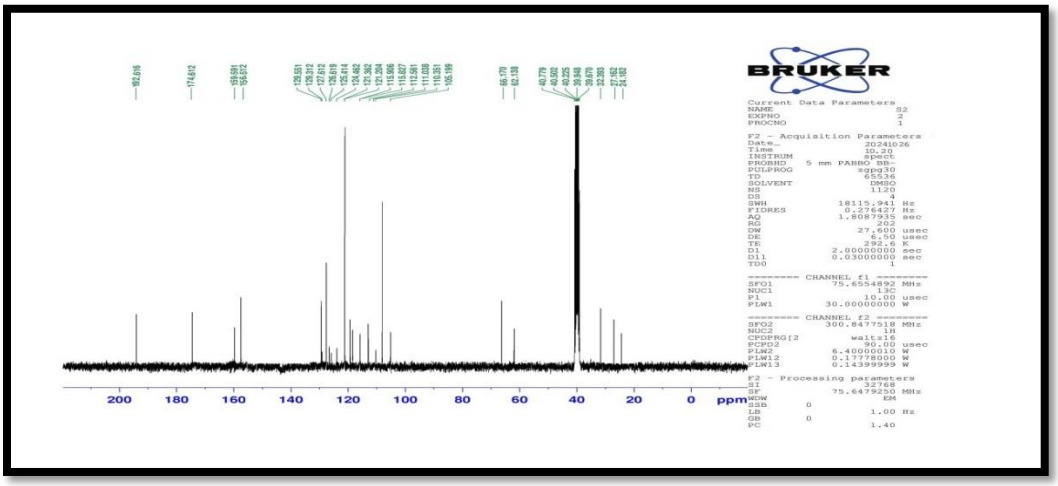
Fig(3): ^{13}C-NMR spectrum of compound S1



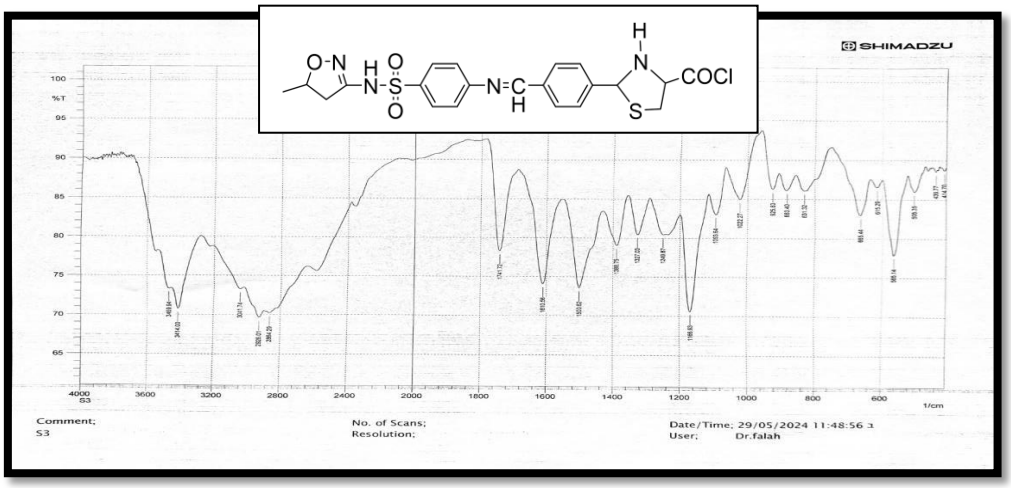
Fig(4): FT-IR spectrum of compound S2



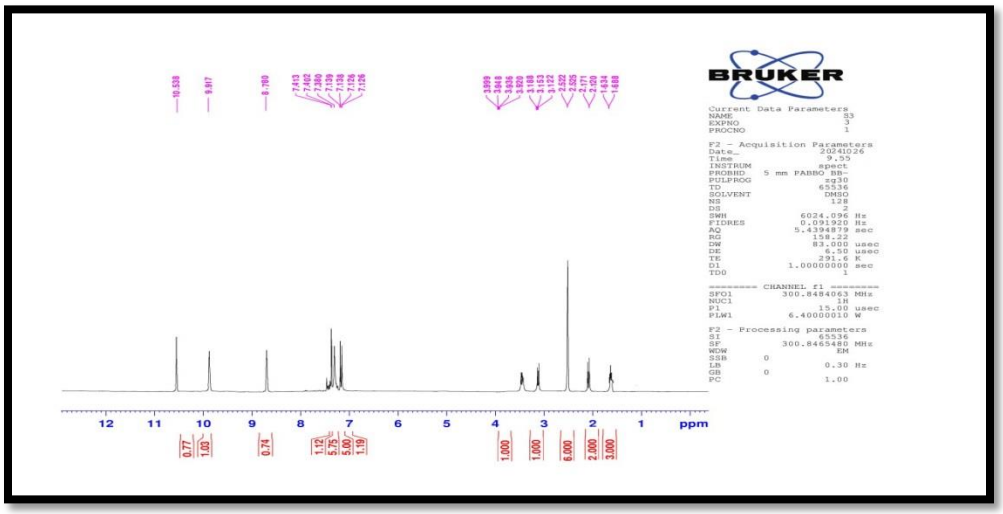
Fig(5): ^{1}H-NMR spectrum of compound S2



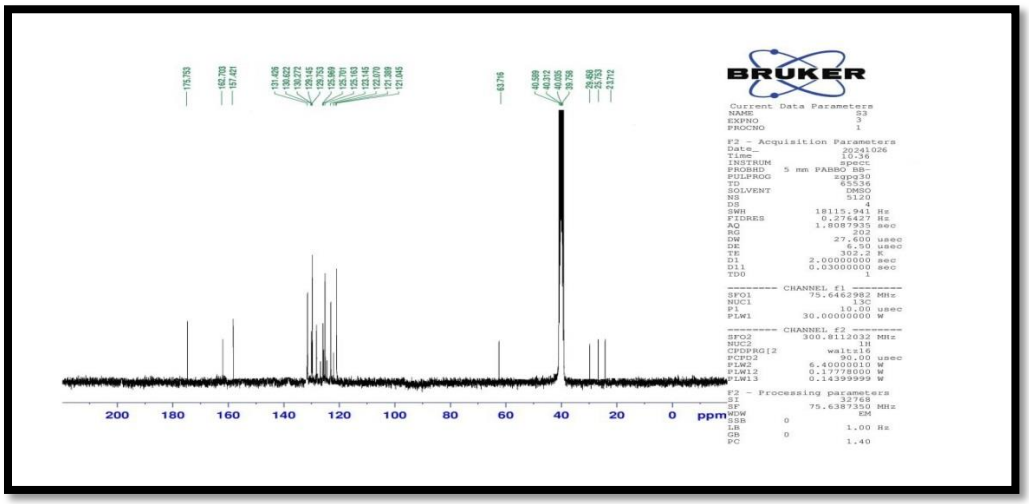
Fig(6): ^{13}C-NMR spectrum of compound S2



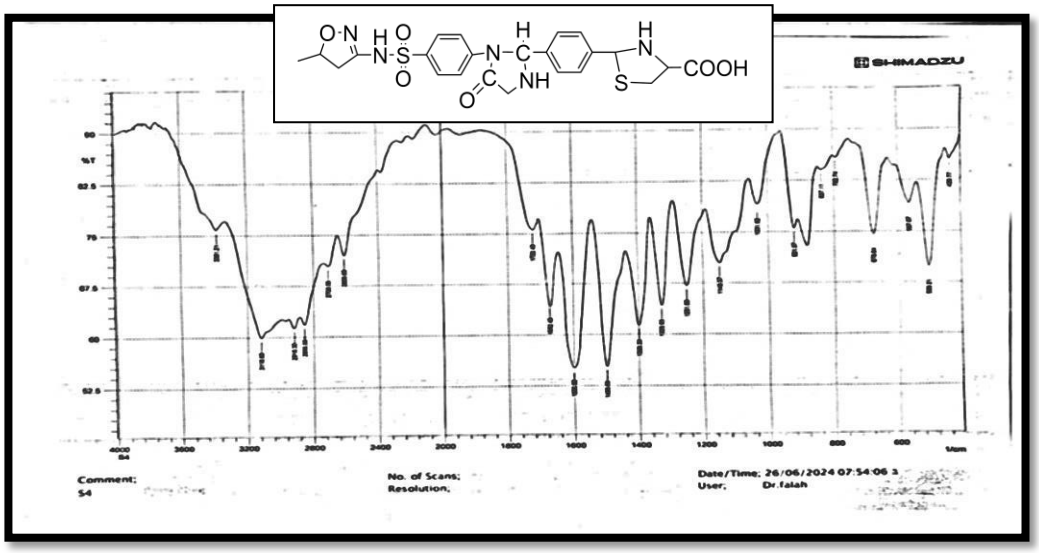
Fig(7): FT-IR spectrum of compound S3



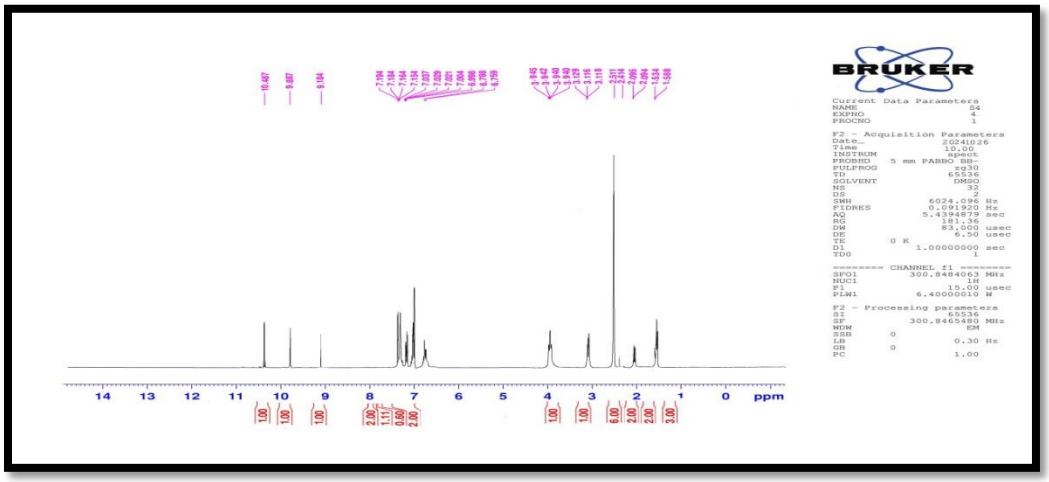
Fig(8): ^{1}H-NMR spectrum of compound S3



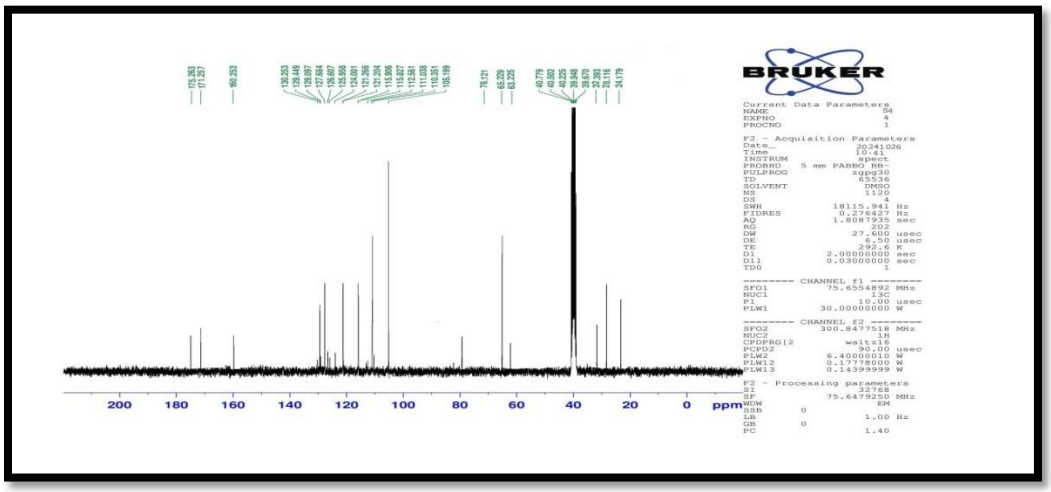
Fig(9): ^{13}C-NMR spectrum of compound S3



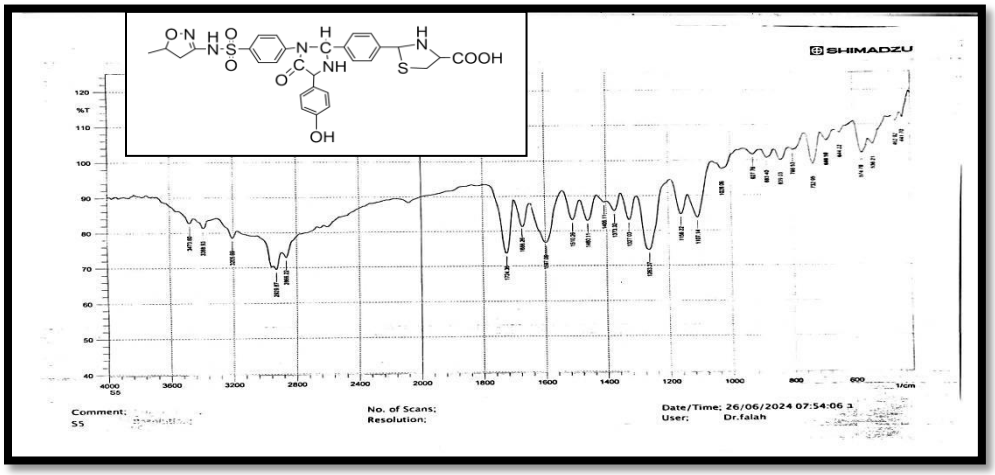
Fig(10): FT-IR spectrum of compound S4



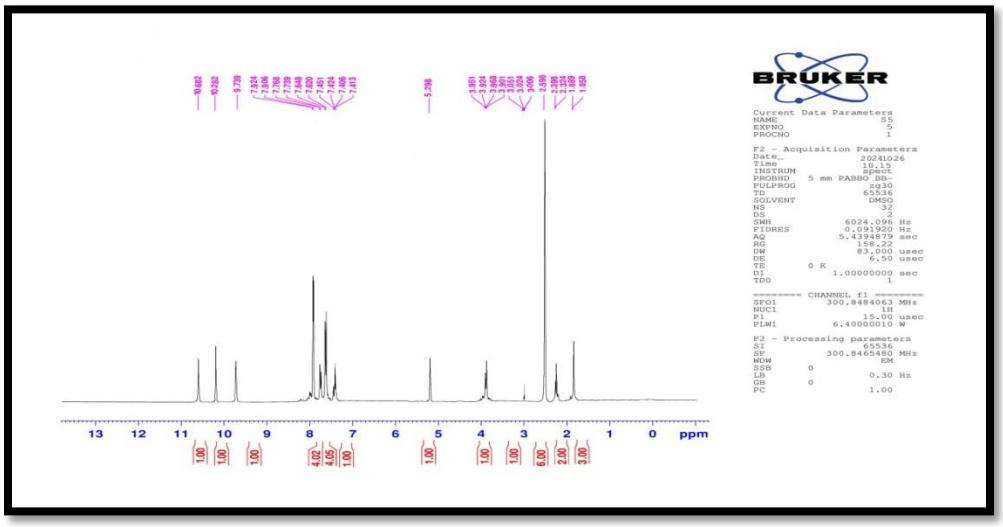
Fig(11): ^{1}H-NMR spectrum of compound S4



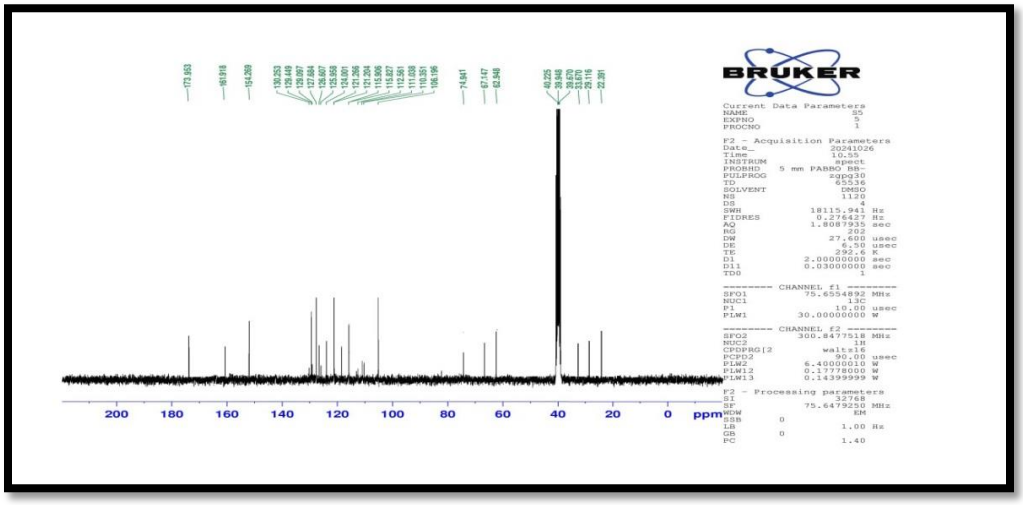
Fig(12): ^{13}C-NMR spectrum of compound S4



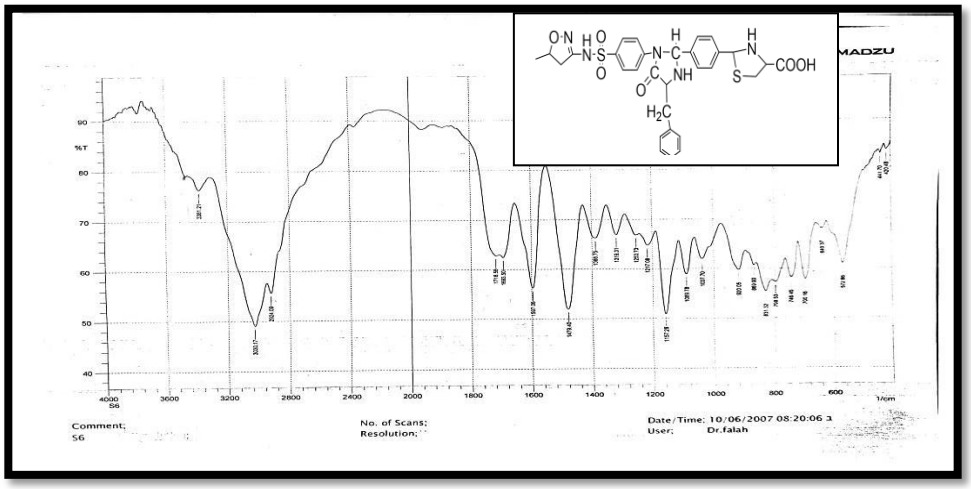
Fig(13): FT-IR spectrum of compound S5



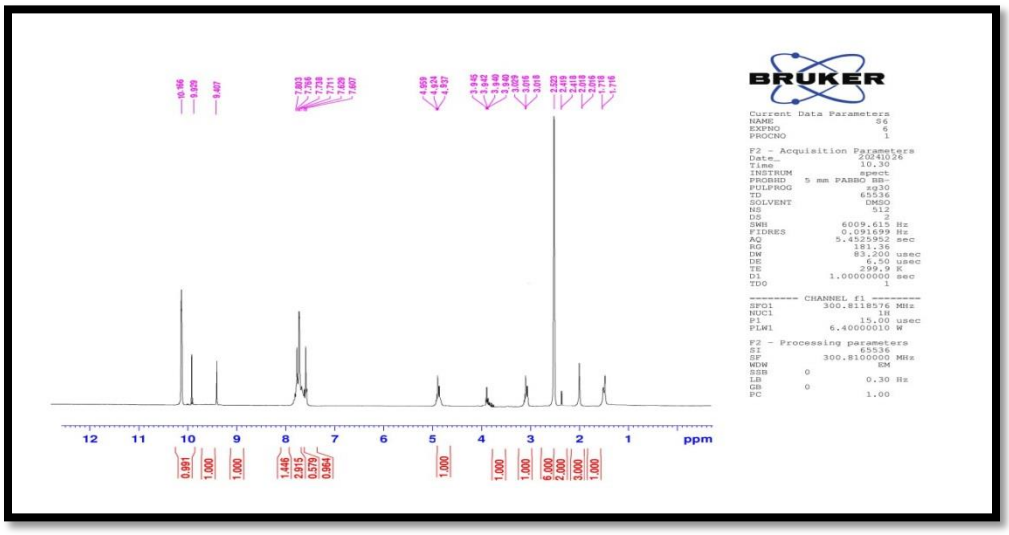
Fig(12): ^{1}H-NMR spectrum of compound S5



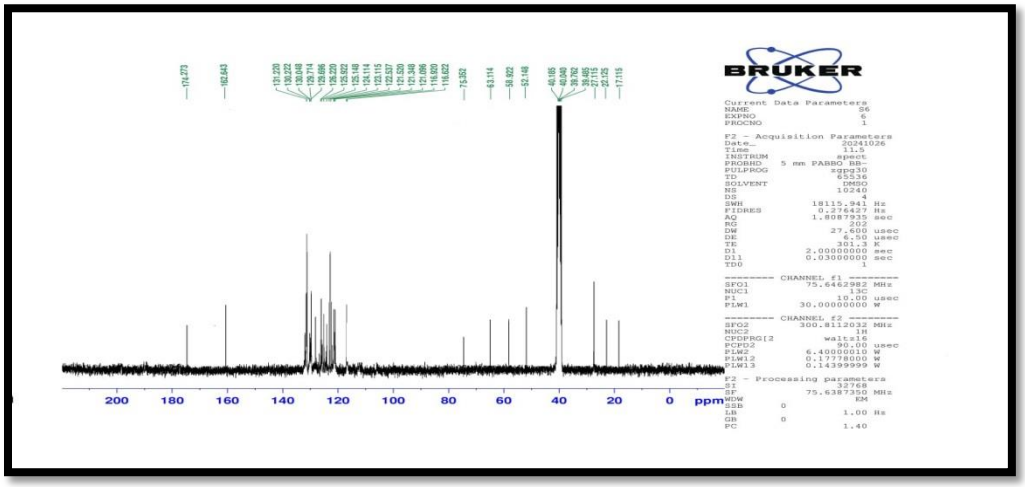
Fig(13): ^{13}C-NMR spectrum of compound S5



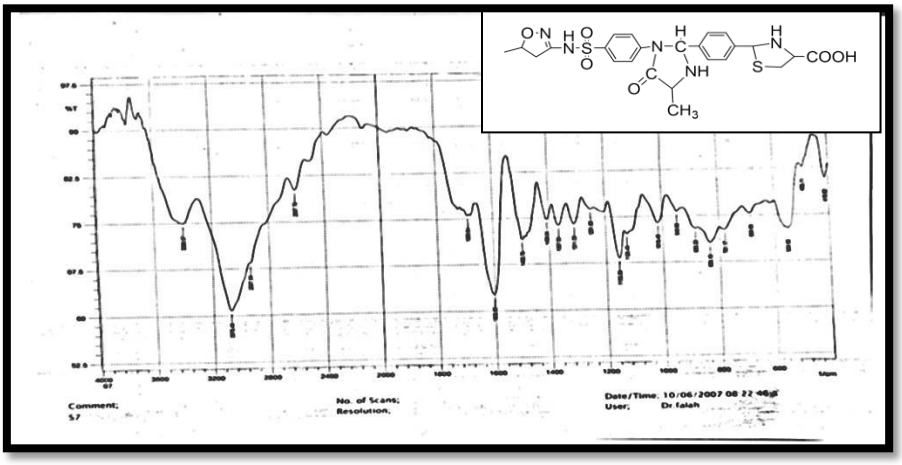
Fig(14): FT-IR spectrum of compound S6



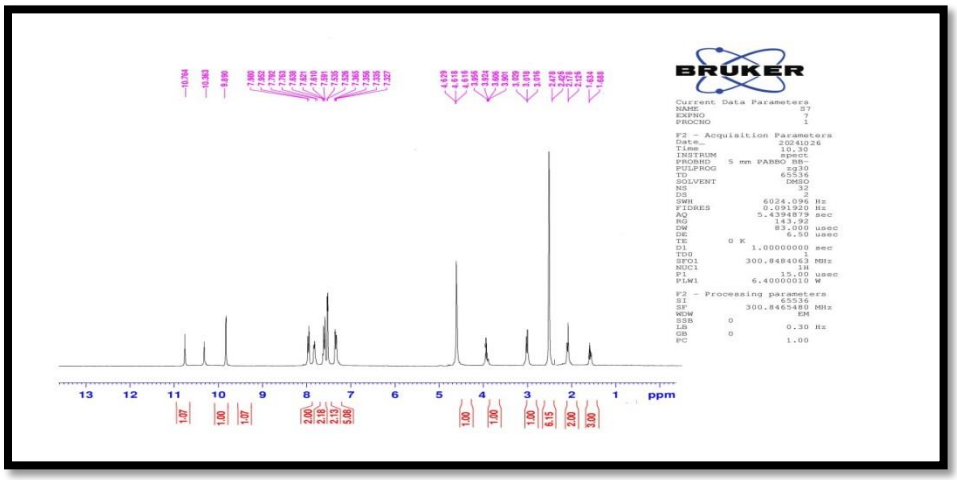
Fig(15): ^{1}H-NMR spectrum of compound S6



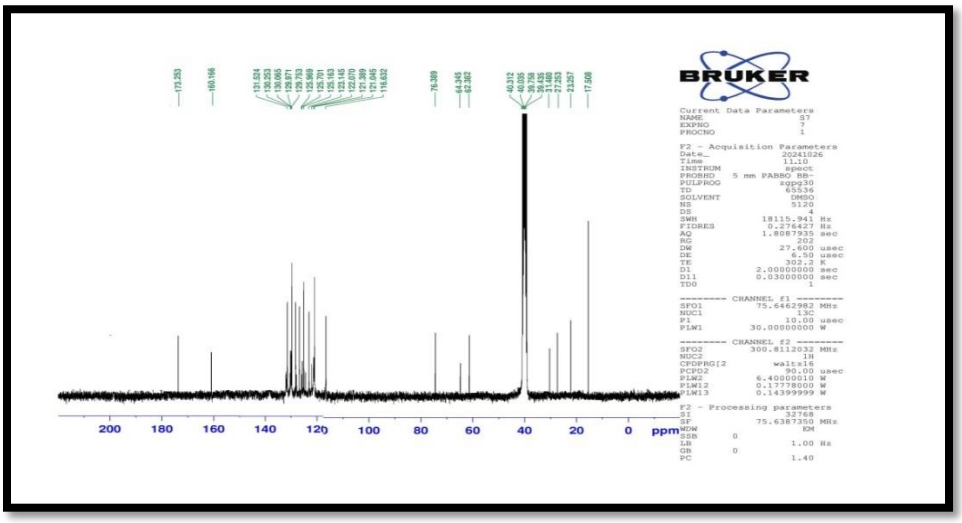
Fig(16): ^{13}C-NMR spectrum of compound S6



Fig(17): FT-IR spectrum of compound S7



Fig(18): ^{1}H-NMR spectrum of compound S7



Fig(19): ^{13}C-NMR spectrum of compound S7

6. Conclusion :

The desired molecules were successfully synthesised. FT-IR spectroscopy, ^{1}H-NMR, and ^{13}C-NMR spectroscopy were performed to validate the physical attributes and identify the target compounds. The antibacterial activities of the produced compounds were then evaluated using a range of bacterial strains that are Gram-positive or Gram-negative. For certain bacterial strains, the bulk of the chemicals generated showed a high degree of antibacterial activity, while, others exhibited no action at all..

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