ISSN Print: 2664-6781
ISSN Online: 2664-679X
Impact Factor: RJIF 5.32
IJACR 2023; 5(2): 28-41
www.chemistryjournals.net
Received: 15-07-2023
Accepted: 26-08-2023

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Synthesis and characterization of some new Sulfamethoxazole derivatives

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DOI: https://doi.org/10.33545/26646781.2023.v5.i2a.156

Abstract
Sulfamethoxazole (SMZ), a sulfonamide antibiotic that is widely used and frequently found in aquatic environments, has been chosen as a representative of this class of drugs. As an alternate group or as an alternative to another loop, the thiazolidenone ring has been incorporated into a broad variety of bioactive compounds, leading researchers to create several molecules that contain this component. Chalk chemistry also resulted in significant scientific readings all around the world. The construction and biodynamic processes of the Calcone have received the majority of attention in order to enable the development of several new heterogeneous cycles with suitable medicinal forms. Seven distinct aliphatic and aromatic molecules were employed in the successful development of synthetic processes to produce target compounds.

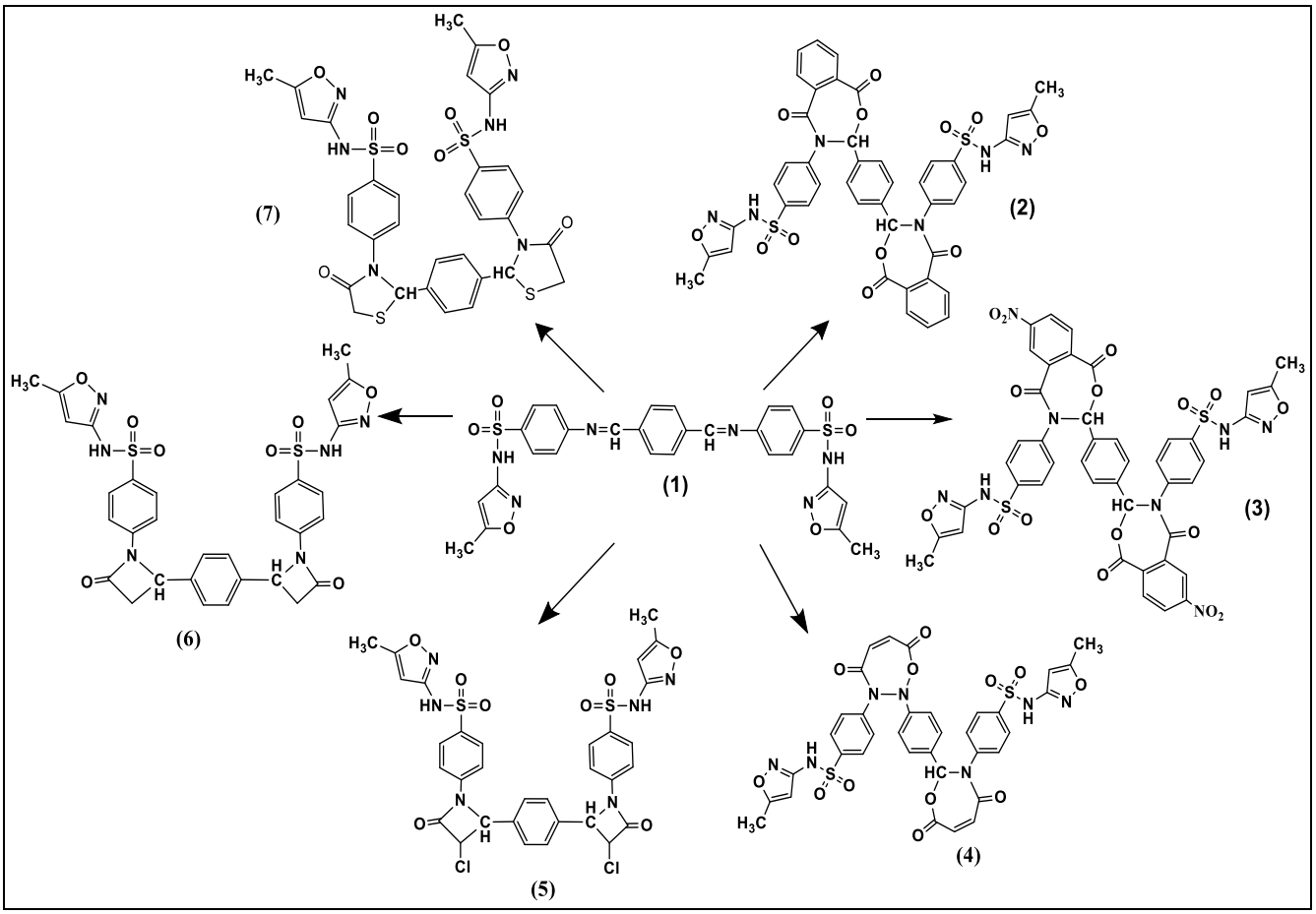
Keywords: Sulfamethoxazole, heterocyclic compounds, derivatives, antimicrobial

Introduction
The chemical name for sulfamethoxazole (SXZ), an antimicrobial sulfonamide, is 4. A chemical formula for amino-N-(5-methyl-3-isoxazolyl) benzene sulfonamide Powder with the molecular weight of 253.279 g/mole and the formula C10H11N3O3S. Practically without smell. The major type of sulfamethoxazole detected in urine is its derivative N4-acetyl, which is produced during metabolism [1]. A large variety of substances that are structural isotopes of aminobenzoic acid are included in the antibacterial sulphanilamide. By competitive inhibition of synthase dihydropetroate, an enzyme necessary for the manufacture of thymidine bacteria, bio Renate, and certain amino acids, they hinder the development of germs by blocking the integration of PAPA into folic acid [2]. Sulphanilamide is an antibacterial agent that works against both G + ve and G ve bacteria [3, 4]. After that, brontosyl usage started during the past 70 years, and sulphate medications have been widely utilized to treat a variety of microbiological infections [5]. Due to the emergence of resistance, it is currently mostly used in tandem with trimethoprim.
Co-trimoxazole, a mixture of sulfamethoxazole and trimethoprim, is used to treat a variety of bacterial infections, including those of the Reproductive tract, Urinary, And Middle ear.
Intestinal Infections and respiratory infections like bronchitis. Lung infections, aromatic, and no cardiosis are presently its principal applications. The most frequent adverse effects include digestive tract disorders "mostly nausea and vomiting" and skin Responses.
The outcomes of this medication formulation [6]. Throughout the 1950s and 1960s and up until 1990, research efforts were concentrated on finding naturally occurring antimicrobials, biochemical targets for antimicrobials, and enhancements to interesting elements discovered in nature [7]. Alternative antibacterial medications and fresh research approaches are more necessary now than they were twenty five years ago. Little success has been seen in the creation of novel antimicrobial agents, despite enormous attempts [8]. N1 - (5-methyl-3-isoxazolil) sulfanylamide is sulfamethoxazole. Pactrim pills (sulfamethoxazol and trimethoprim) should be used to prevent the growth of germs that are resistant to antibacterial treatments and to preserve the potency of these and other antibacterial medications. Bacterial cause [9].

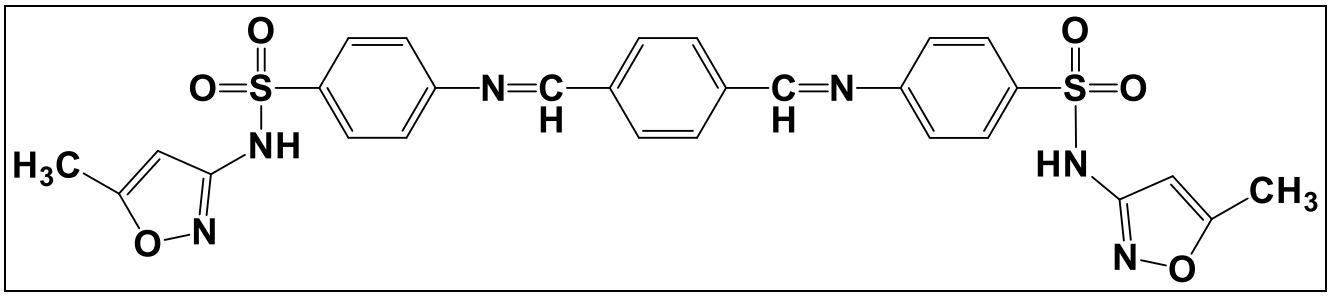
Experimental

1. Melting points were uncorrectedly recorded using a hot stage Gallen Kamp melting point equipment.
2. The Chemistry Department at Baghdad University and Ibn Sina conducted the Fourier Transform infrared SHIMADZU (F.T.IR) infrared spectrophotometer, KBr disc or thin film.
3. Using Fertigfollen precoated sheets of type Silica, thin layer chromatography (TLC) was performed, and the plates were produced using iodine vapors.
4. At Baghdad University, UV/vis spectra were captured using a Fourier Transform Varian spectrometer.
5. Tetramethylsilane was used as an internal standard in DMSO while 1H-NMR spectra were captured using a Foruier Transform Varian spectrometer running at 500 MHz. The measurements were performed at the Chemistry Department in Iran.
6. In the Iranian Chemical Department, analyzers (MASS) were created.
7. Activities at Baghdad University's biology department.
8. Pharmaceutical grade sulfamethoxazole powder was gifted by the State Corporation for Drug Industries and Medical Equipment Samara, Iraq, in pure form (99.99%). (SDI). Analytical-grade materials were utilized for all compounds and reagents.

Synthesis



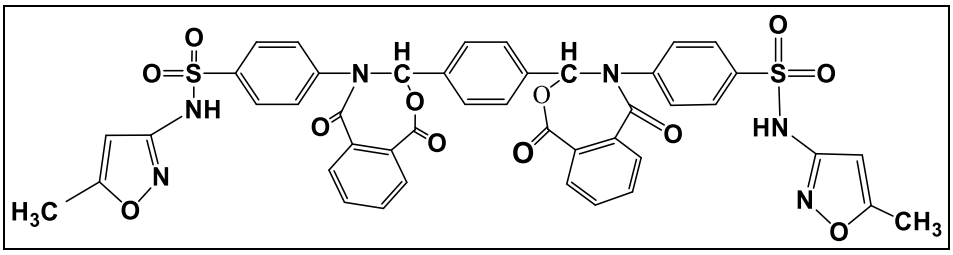
Schiff Base Synthesis Via Chemistry Creation of N- (isoxazol-3-yl) -4-((4-((N-(isoxazol-3-yl) sulfamoyl)benzylidene) amino)benzylidene) amino) benzenesulfonamide [10].



COMPOUND (A)

sulfamethoxazole (5gm),with terephthalaldehyde (3g) and (10ml) of absolut ethanol and add (5) drop of Acetic acid was mixed and refluxed for 6 hour, then coold and dried andre crystallzied from ethanol, yield 80%.

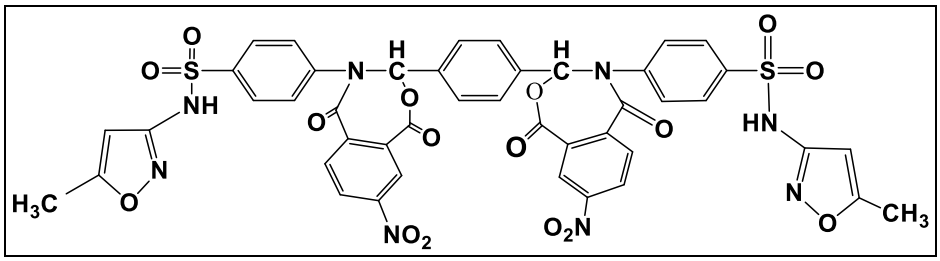
Synthesis of N-(5-methylisoxazol-3-yl)-4-(3-(4-(4-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepin-3-yl)phenyl)-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl)benzenesulfonamide [11].



COMPOUND (B)

Compound (1) (0.5gm) was mixed with phthalic anhydride (0.2gm) in bezene, the mixture was refluxed for 6 hours. The precipitate was filtered off, washed with water and recrystallized from ethanol to give final product, yield (70%).

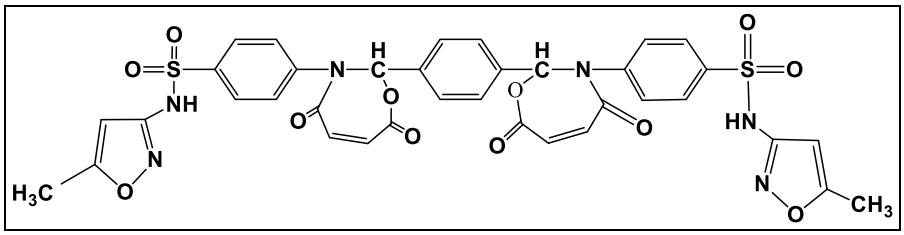
Synthesis of N-(5-methylisoxazol-3-yl)-4-(3-(4-(4-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-8-nitro-1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepin-3-yl)phenyl)-8-nitro-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl)benzenesulfonamide [12].



COMPOUND (C)

Compound (1) (0.5gm) with 3-nitrophthalic anhydride (0.3 gm) in benzene after refluxed 6h,then After being filtered out and dried, the precipitate was recrystallized, yielding an 85% yield.

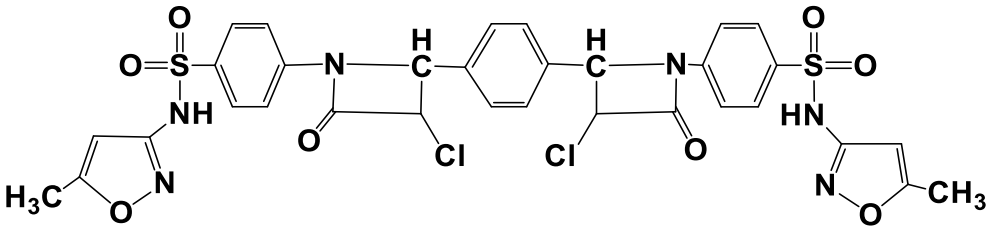
Synthesis of N-(5-methylisoxazol-3-yl)-4-(2-(4-(3-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4,7-dioxo-2,3,4,7-tetrahydro-1,3-oxazepin-2-yl)phenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)benzenesulfonamide [13].



COMPOUND (D)

Compound (1) (0.5gm) with Malice anhydride (0.13 gm) in benzene after refluxed 6h, Subsequently, after being filtered off and dried, the precipitate was recrystallized, yielding (85%)

Synthesis of 4-(3-chloro-2-(4-(3-chloro-1-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxoazetidin-2-yl)phenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide [14]:

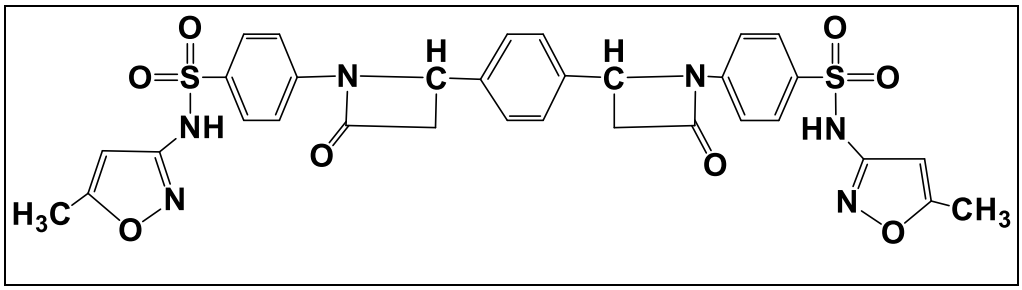


4-(3-chloro-2-(4-(3-chloro-1-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxoazetidin-2-yl)phenyl)-4-oxoazetidin-1-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide

COMPOUND (E)

Compound [1] with chloroacetyl chloride (1.3gm) in (5 mol) Benzen and add (7ml)try methyl amin and (5)drop of (DMF) to chloro acetyalchloried, The mixture was then refluxed for five hours. After adding five drops of HCL to cold water that has been cooled, the result was filtered off and recrystallized using ethanol, with an 85% yield. M.p. (165-175C).

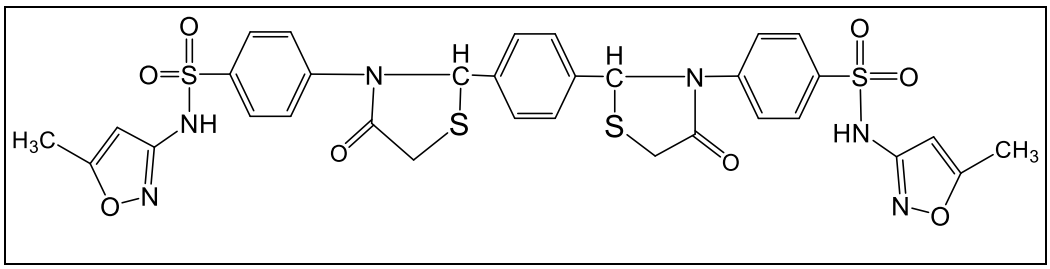
Synthesis of N-(5-methylisoxazol-3-yl)-4-(2-(4-(1-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxoazetidin-2-yl)phenyl)-4-oxoazetidin-1-yl)benzenesulfonamide [15].



COMPOUND (F)

Compound (1) 0,5gm was mixed 1gm glycrine in desolved (10ml) benzene and add (5) drop dimethyl formid ether the mixture was refluxed for 7h, after that add ethanol The precipitate from (ethanol-water) was filtered and recrystallized to provide the required product; the yield is (80.%) and the m.p. is (220>).

Synthesise of N-(5-methylisoxazol-3-yl)-4-(2-(4-(3-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-oxothiazolidin-2-yl)phenyl)-4-oxothiazolidin-3-yl)benzenesulfonamide [13].



COMPOUND (G)

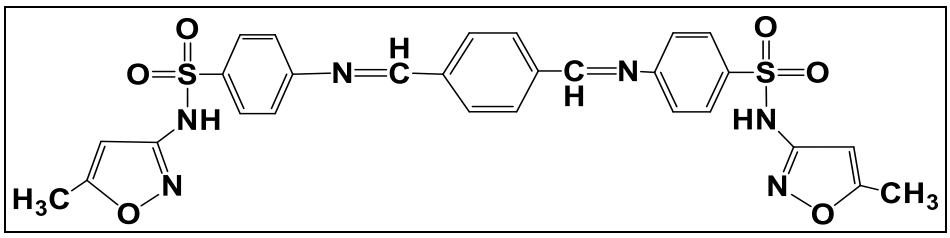
Compound (1) (0.5 gm, mol) with (1gm) thioglygolic acid desslove in (10ml) benzene after refluxed 7h, yield is (80.%) after being recrystallized from di ethyl ether and washed with water.

Table 2: Physical properties of the synthesized compounds.

Comp. No.	Molecular Formula	Molecular Weight (g/mole)	Yield (%)	M.P (ºC)	Colour	RF
1	$C_{28}H_{24}N_6O_6S_2$	604	85	230-223	yellow	0.92
2	$C_{44}H_{32}N_6O_{12}S_2$	900	85	260-270	Pale yellow	0.89
3	$C_{44}H_{32}N_8O_{16}S_2$	990	85	275-285	black	0.91
4	$C_{36}H_{28}N_6O_{12}S_2$	800	75	109-111	yellow Pale	0.90
5	$C_{32}H_{26}N_6O_8S_2CL_2$	755	70	165-170	black	0.81
6	$C_{30}H_{28}N_6O_8S_2$	688	77	220-235	yellow	0.85
7	$C_{28}H_{24}N_6O_8S_4$	752	90	250-260	yellow Pale	0.2

Results and Discussion

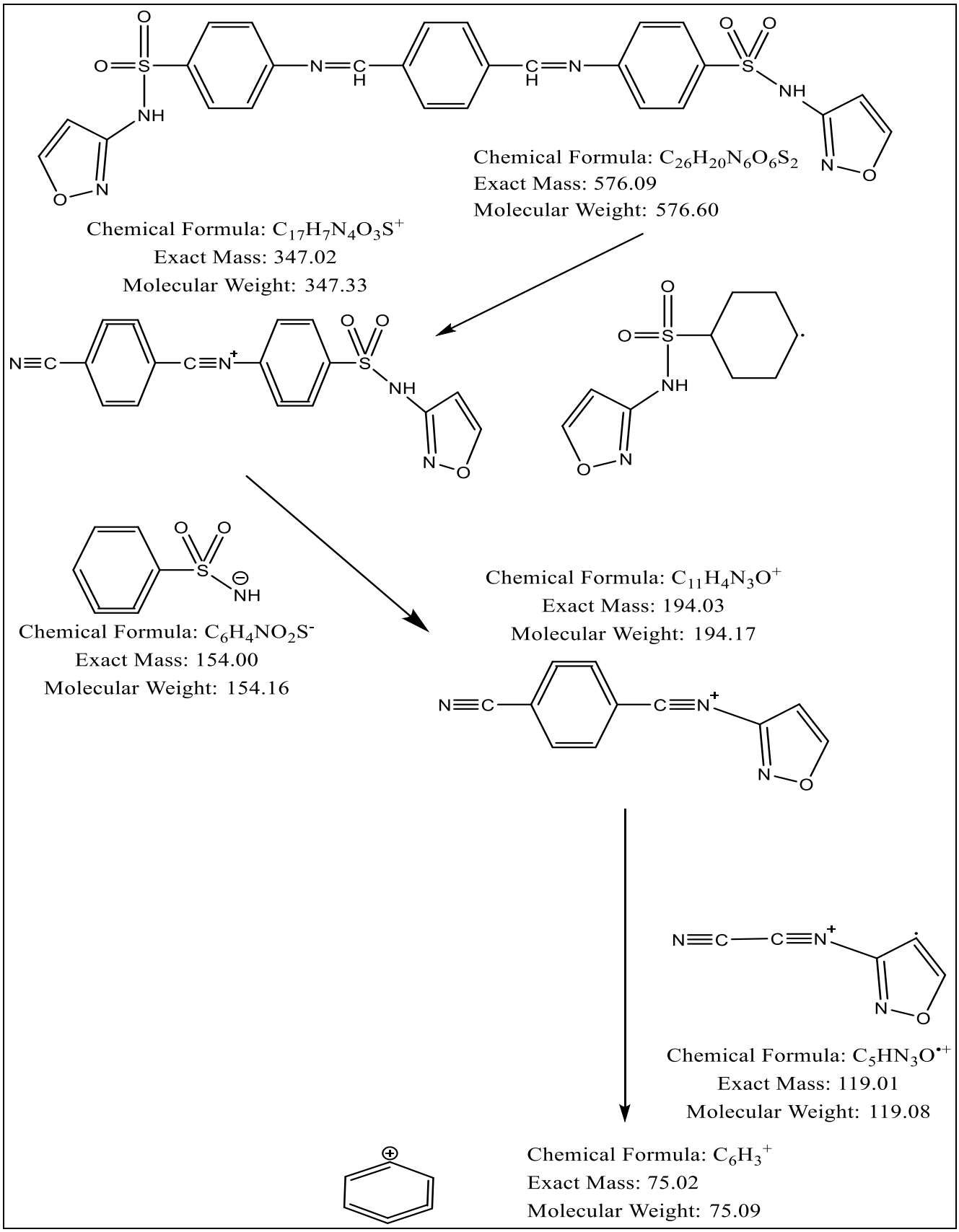
Characterization of N-(isoxazol-3-yl)-4-((4-((4-(N-(isoxazol-3-yl) sulfamoyl) benzylidene) amino)benzylidene)amino)benzenesulfonamide [10].



The F.T.IR spectra of compounds (1) demonstrated the vanishing of The N-H band at (3178cm-1), and carbonyl group at (1689 cm-1) compound, as well as sulfones asymmetric stretch (strong) occurs at (1354 -1182cm-1) and amines C=N, were all visible in the F.T.IR spectra of compounds (1). The NH2 band (3479 and 3414cm-1) of the beginning material [1] also disappeared (1689-1589 cm-1) Figure (1). (1).

The chemical (1)'s 1H-NMR spectra revealed the following peaks: 2.3 (6H) signals that might be attributed to (CH3)2 protons and 11.4 ppm signals from (N-H) proton. A peak emerged at 8.4 (2H), which might signal to a (N=CH) proton, and a multiplet signals between 6.1 and 6.9 that could be attributed to benzene rings protons. Figure (2).

Electrospray (+) mass spectra
Mass spectrometry (MS).
The positive electrospray mass spectrum of compound (1), and Figer (3), shows the father molecule of (s1f) at m/z = 576.09 amu (M^+) (39 %) for $C_{26}H_{20}N_6O_6S_2$. Peaks detected at m/z = 347.33 (7%), 194.17 (97%), 75.09 (19%) and 75.09 (19%) related to $[M-(C_9H_{13}N_2O_3S^{\bullet})]$,$[M-(C_9H_{13}N_2O_3S^{\bullet})+(C_6H_4NO_2S^-)]$, $[M-(C_9H_{13}N_2O_3S^{\bullet})+(C_6H_4NO_2S^-)+(C_5HN_3O^{\bullet+})]$, respectively. Scheme illustrates the task of the compound's ensuing discontinuity particles and their relative overflow (1).



Scheme (1): The fragmentation pattern and relative abundance of compound (1) fragments.

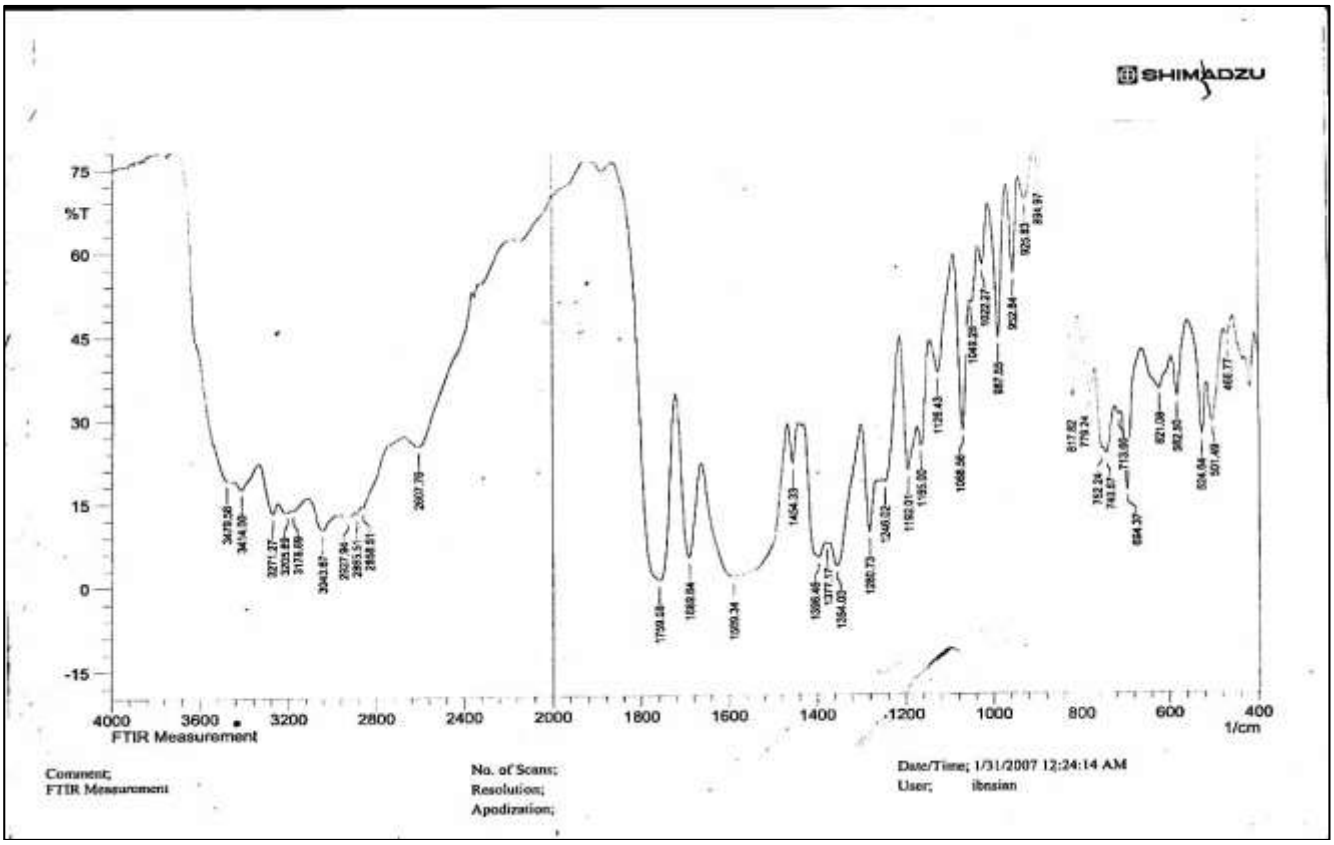


Fig 1: FT-IR spectrum of sulfamethxazol.

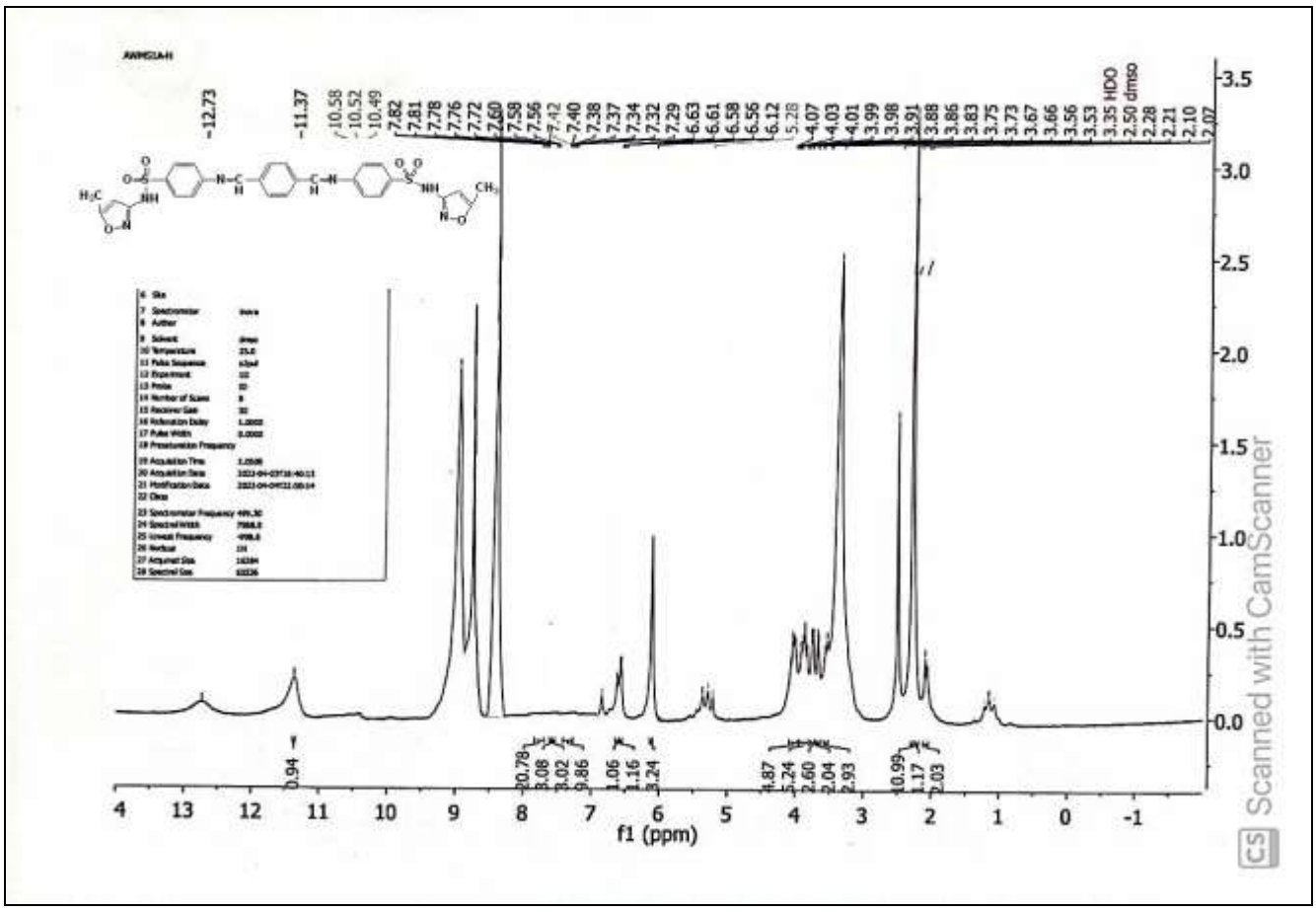


Fig 2: (H-NMR) spectrum of sulfamethxazol.

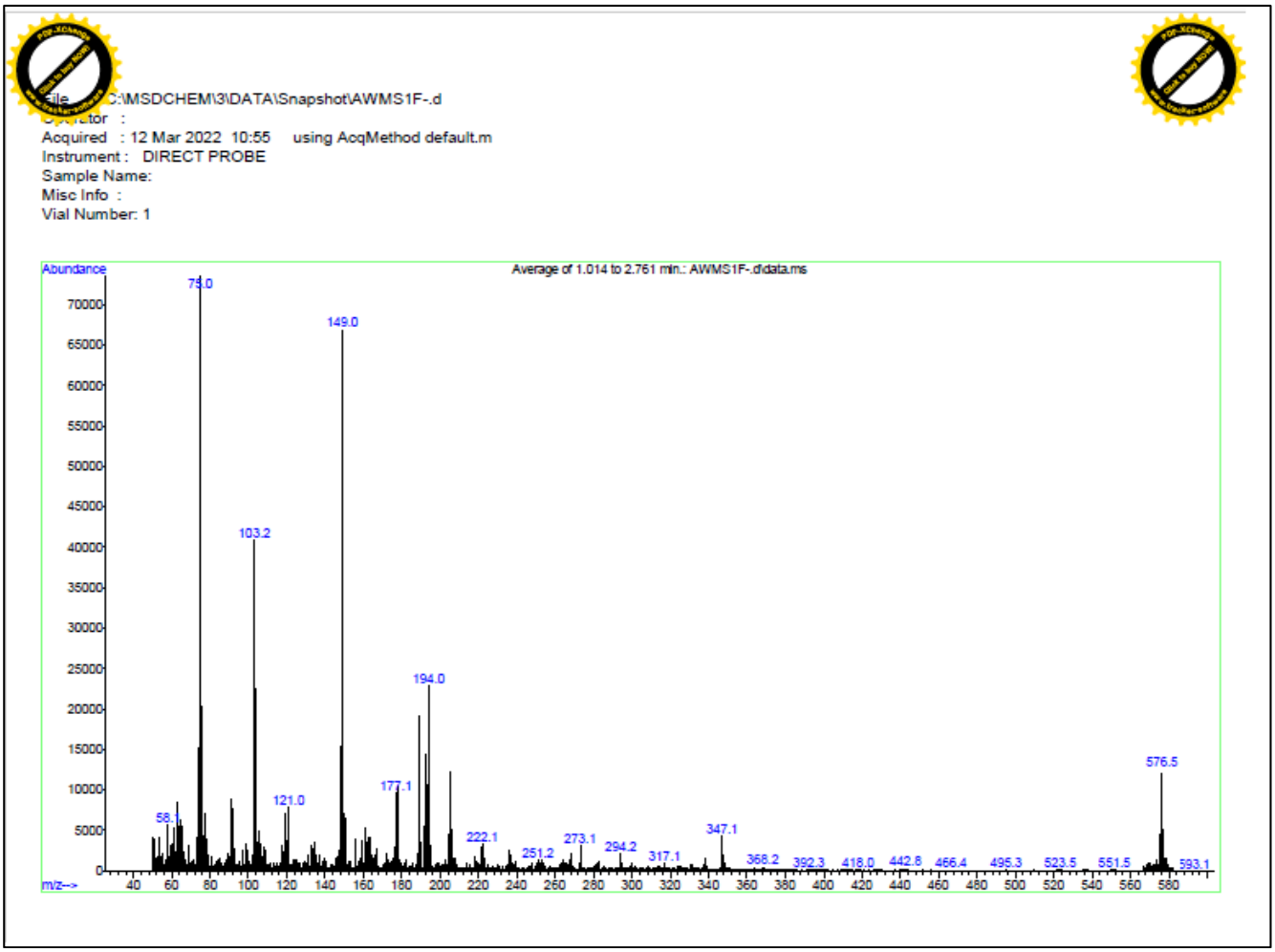
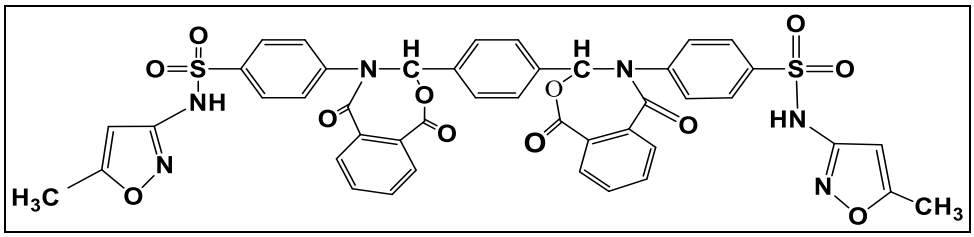


Fig 3: The electrospray (+) mass of sulfamethxazol.

Characterization of compound (B)



THE FTIR compound (2), figures (4) backed up the appearance of two bands due to carbonyl groups (lactones and lactam) at (1712m 1774) cm^{-1}, for the lactone. The lactam band appeared at (1618) cm^{-1}, and υ(N-H) Band at (3302 cm^{-1}), υ (C-H) aromatic Band at (3143) cm^{-1}, also band at of (1165, 1087) cm^{-1} belongs to asymmetric and symmetric υ (C-O-C) band, υ (C-H) aliphatic band at asymmetric and symmetric (2993,1845) cm^{-1}.

The ^{1}H-NMR compound (**2**) showed the following peaks: A signals at δ 2.4 [6H] that could be appointed to $(CH_3)_2$ protons, also showed a signal at δ 8.5 ppm (2H) that could be assigned to (NH), a signal at δ 7.2 ppm of (-O-CH-N) proton and many signals at δ (6 – 7) belong to the aromatic protons figures (5).

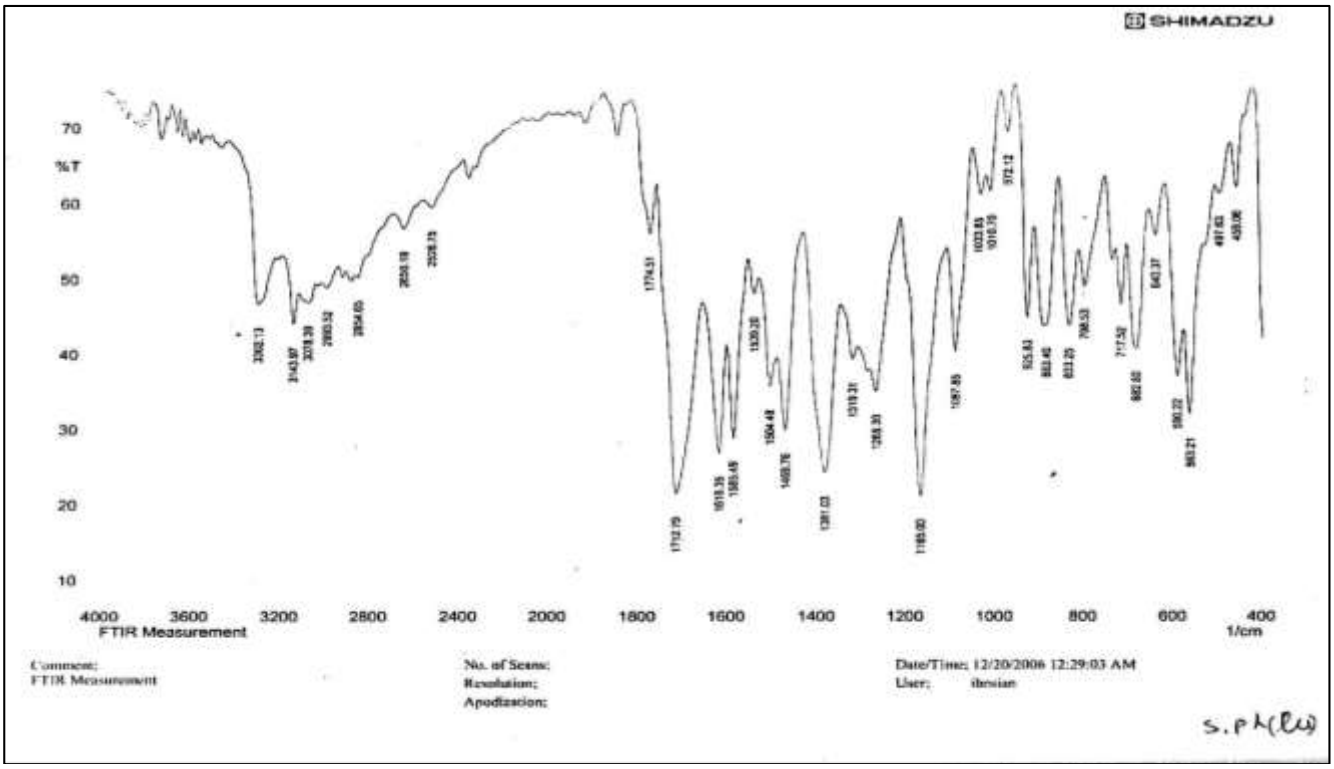


Fig 4: FT-IR of compound (2)

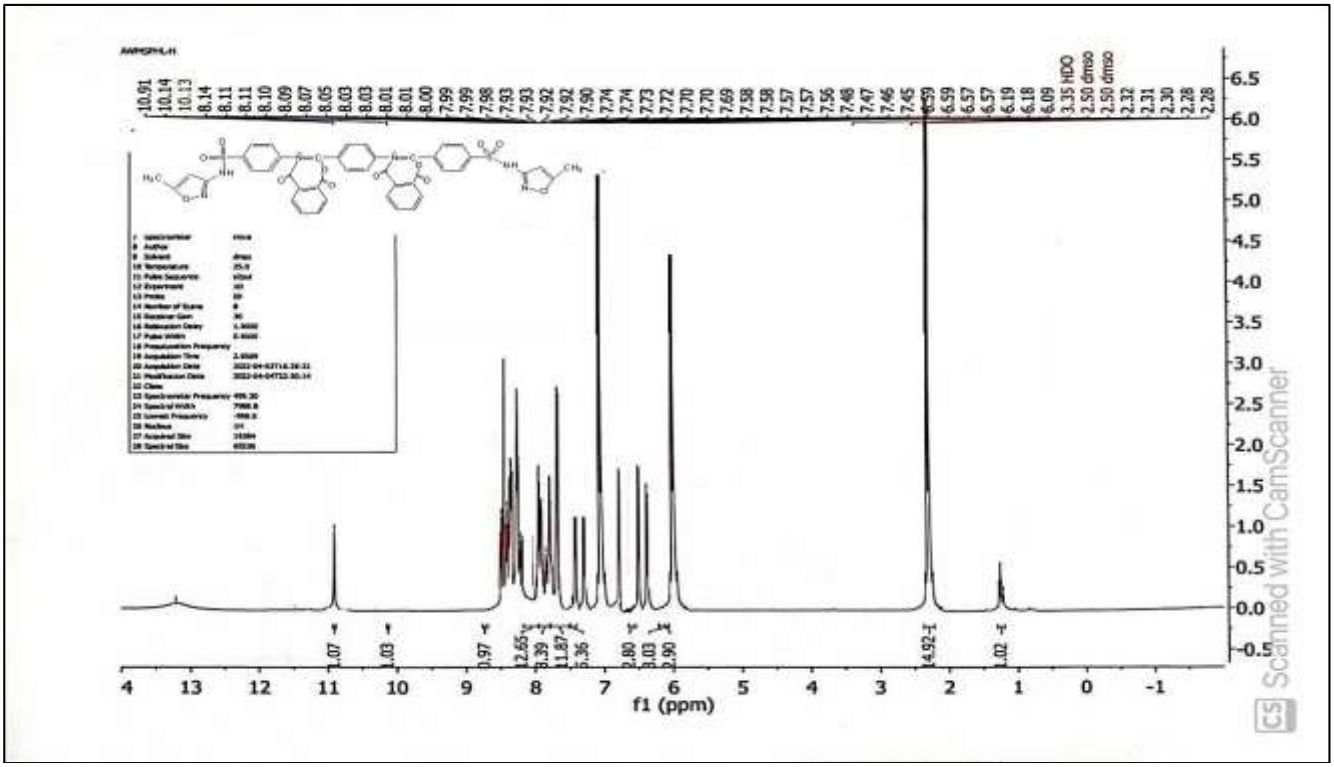
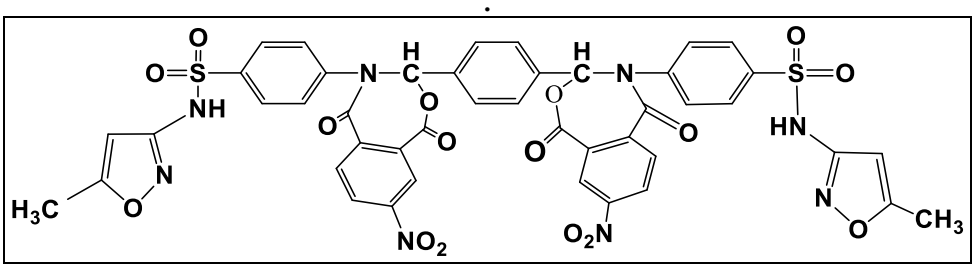


Fig 5: H-NMR of compound (2)

Characterization of COMPOUND (C)

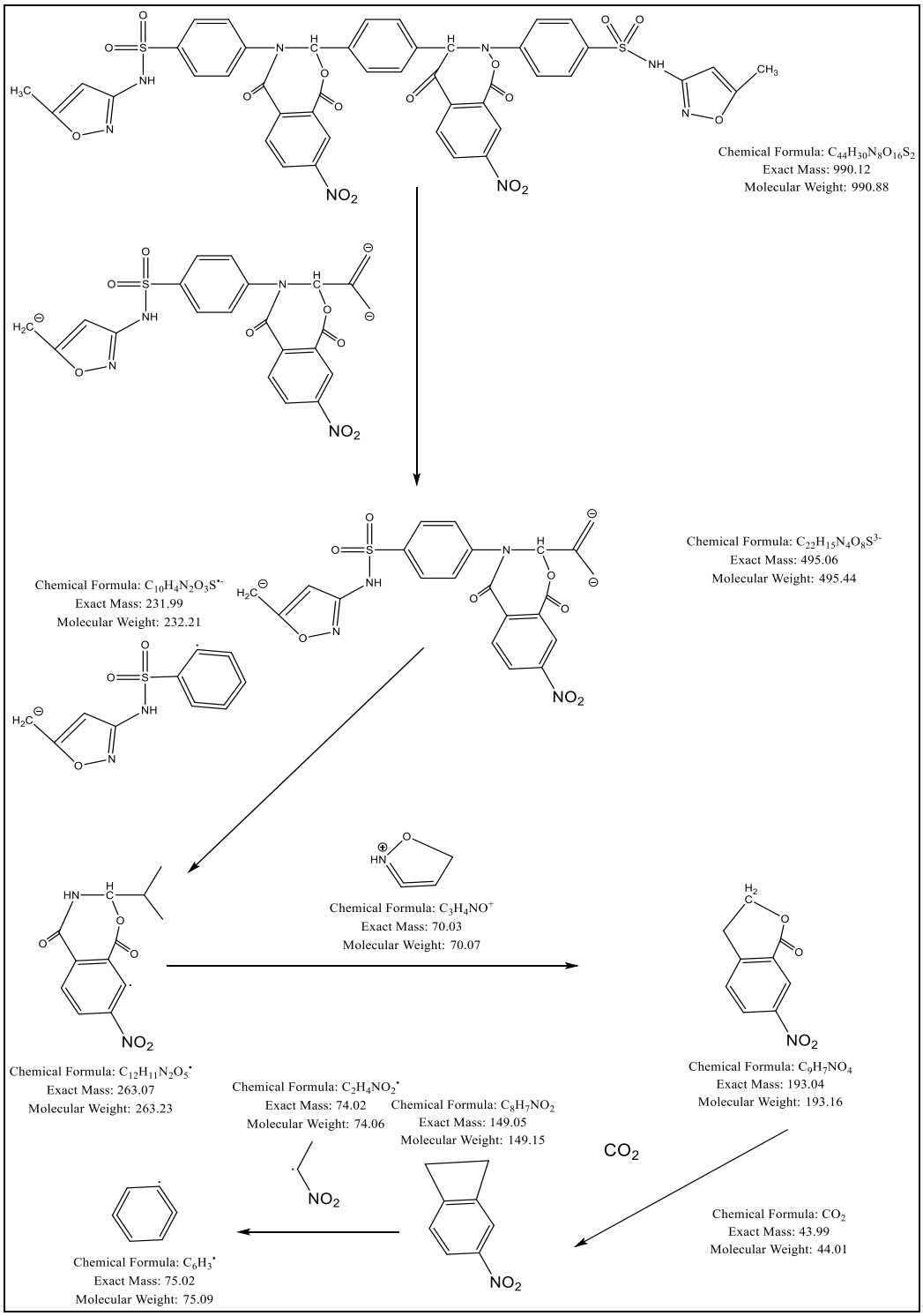


The FT-IR For the compound (3), figures (6) backed up the appearance of two bands due to carbonyl groups (lactones and lactam) at (1701, 1766) cm^{-1} for the lactone. The lactam Band show at (1616 cm^{-1}), and υ (C-H) aromat band at (3236) cm^{-1}, υ(C-H) aliph band at asymmetric and symmetric (3074, 1974) cm^{-1} also band in (1165, 1091) cm^{-1} belongs to asymmetric and symmetric υ(C-O-C) band and υ(N-H) band at (3414) cm^{-1}.

The H-NMR range of compound (3) showed the accompanying pinnacles: A signals δ 8.4 ppm (2H) that could be assigned to (NH), also showed a signal at δ 2.3 (6H) that could be assigned to $(CH_3)_2$, a signal δ 7.6 ppm due to (-O-CH-N) proton and many signals at δ (6 – 7) belong to the aromatic protons figures (7).

Mass in compounds [3]

The electrospray (+) mass spectrum in compound [3] Figer (8), shows the parent molecule of compound (3) at m/z = 495.6 amu (3%) $(M / 2)^+$ calculated for $C_{44}H_{30}N_8O_{16}S_2$ requires = 990.88. Peaks detected at m/z = 263.23 (22 %), 193.16 (13 %), 149.15 (40 %), and 75.09 (29 %), related to $[(M/2)-(C_{10}H_4N_2O_3S^{\bullet-})]$, $[(M/2)^+-(C_{10}H_4N_2O_3S^{\bullet-})(C_3H_4NO^+)]$, $[(M/2)^+-(C_{10}H_4N_2O_3S^{\bullet-})+(C_3H_4NO^+)+(CO_2)]$ and $[(M/2)^+-(C_{10}H_4N_2O_3S^{\bullet-})+(C_3H_4NO^+)+(CO_2)+(C_2H_4NO_2^{\bullet})]$, respectively. The task of the progressive fracture particles of the compound alongside their general overflow is displayed in Plan (2).



Scheme 2: The fragmentation of compounds [3].

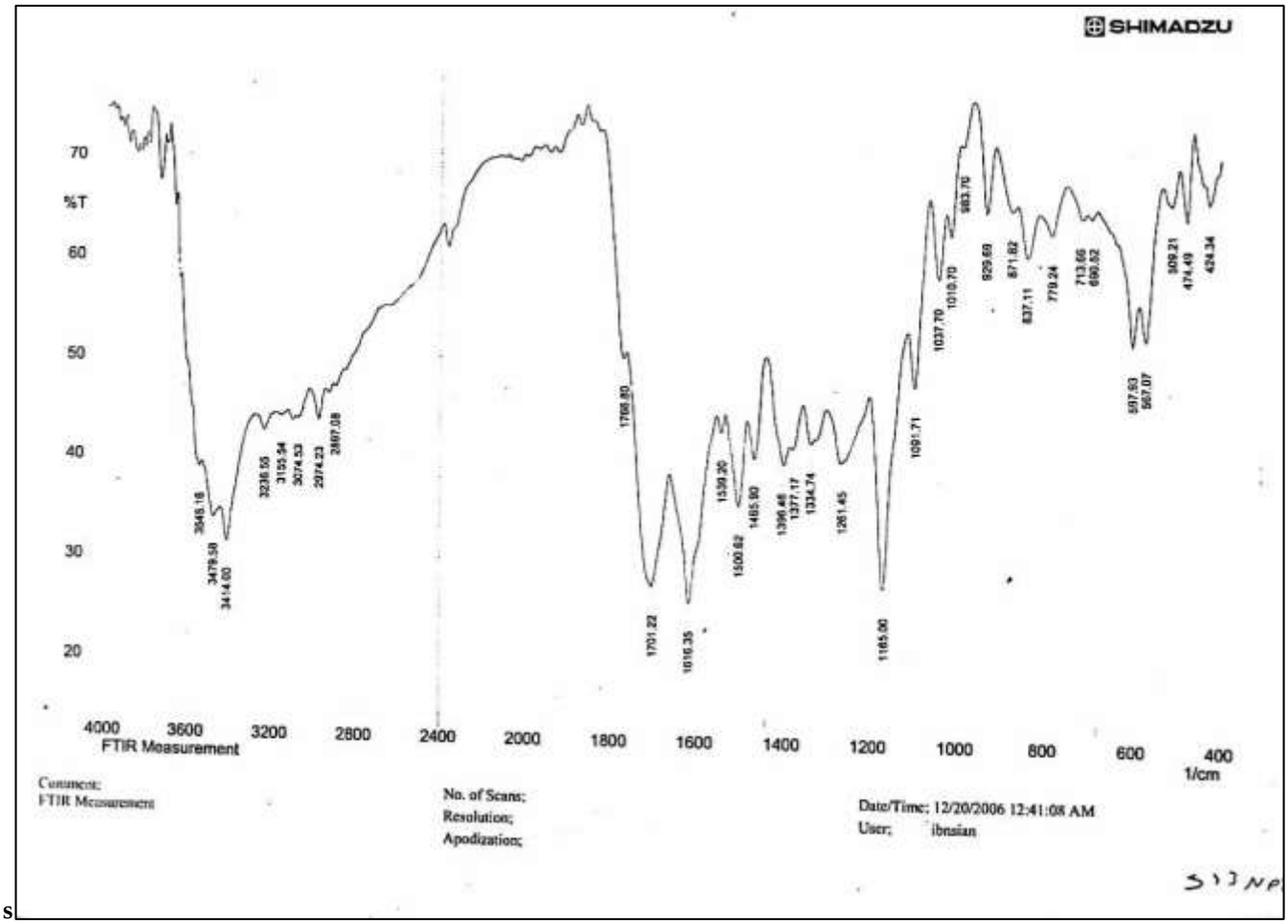


Fig 6: FT-IR in compound (3)

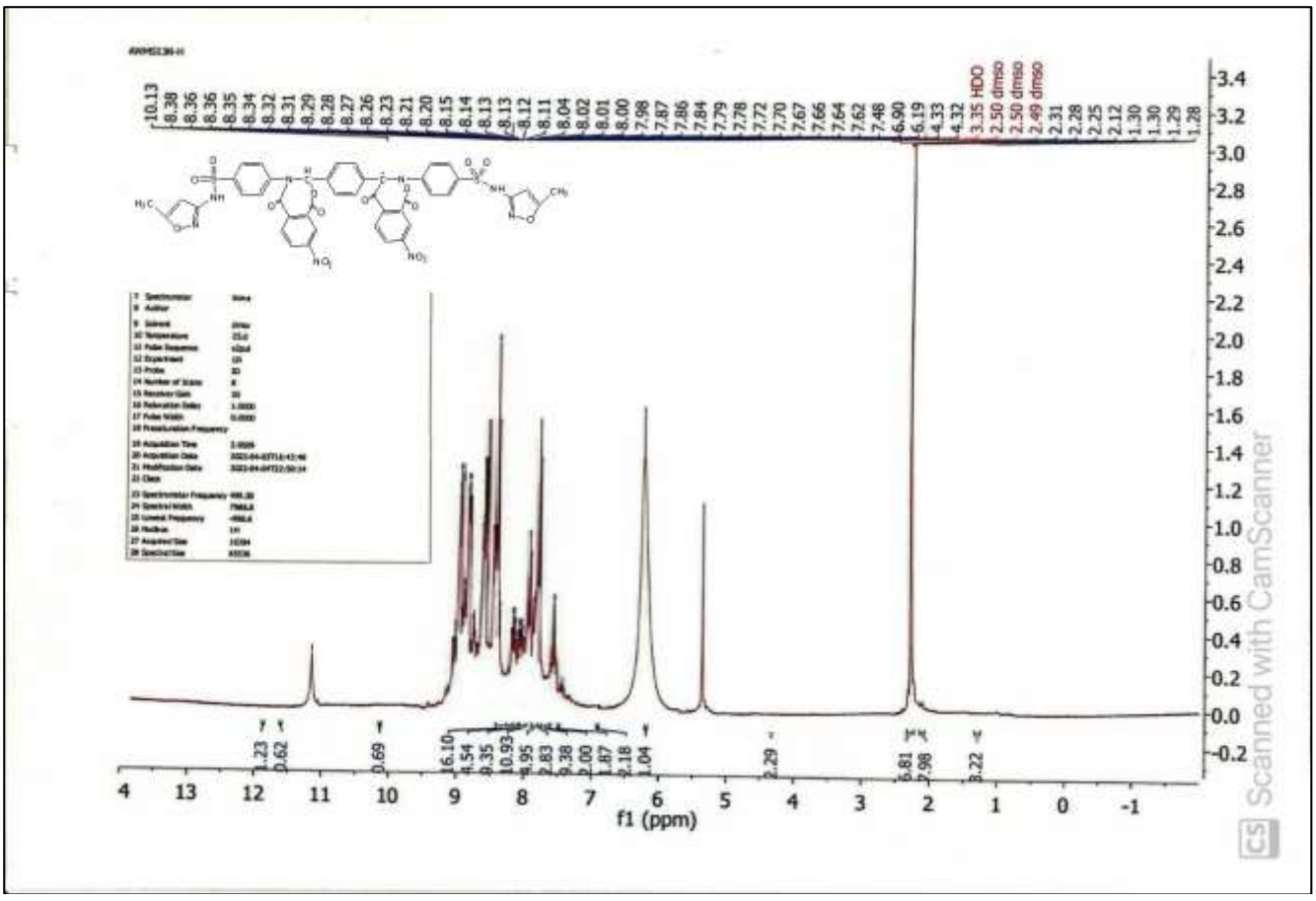


Fig 7: H-NMR of compound (3)

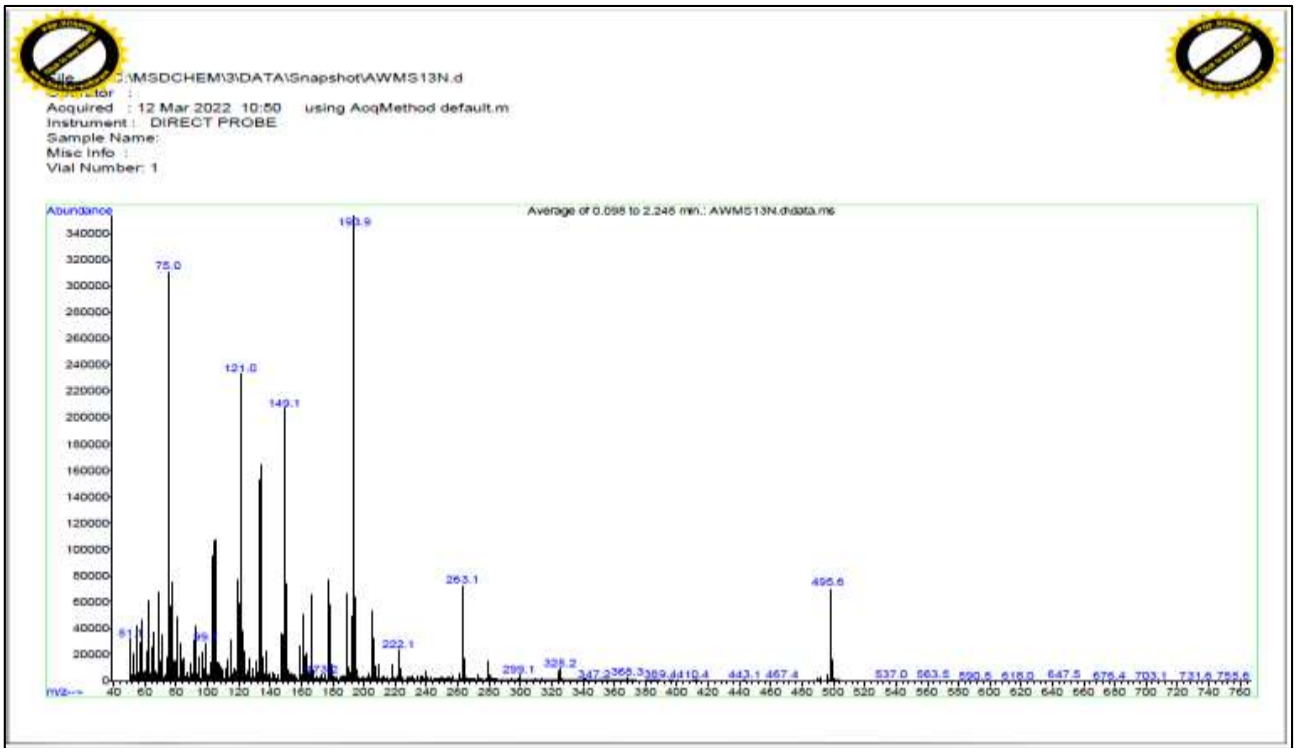
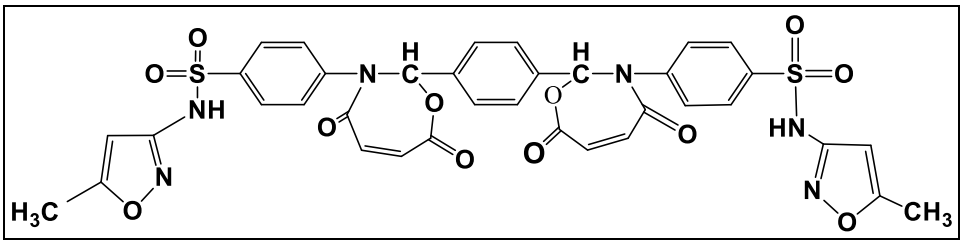


Fig 8: The electrospray (+) mass in compound (3)

Characterization of COMPOUND (D)

The FT_IR of Compound (4), confirmed the slow of (N-H) band in (3367 cm^{-1}), υ(C-H) aromatic band (3151) cm^{-1}, υ (C-H) aliphatic band at asymmetric and symmetric (3086-1993) cm^{-1} also two bands due to carbonyl groups (lactones and lactam) at (1720, 1616) cm^{-1} for the lactone figures (9).



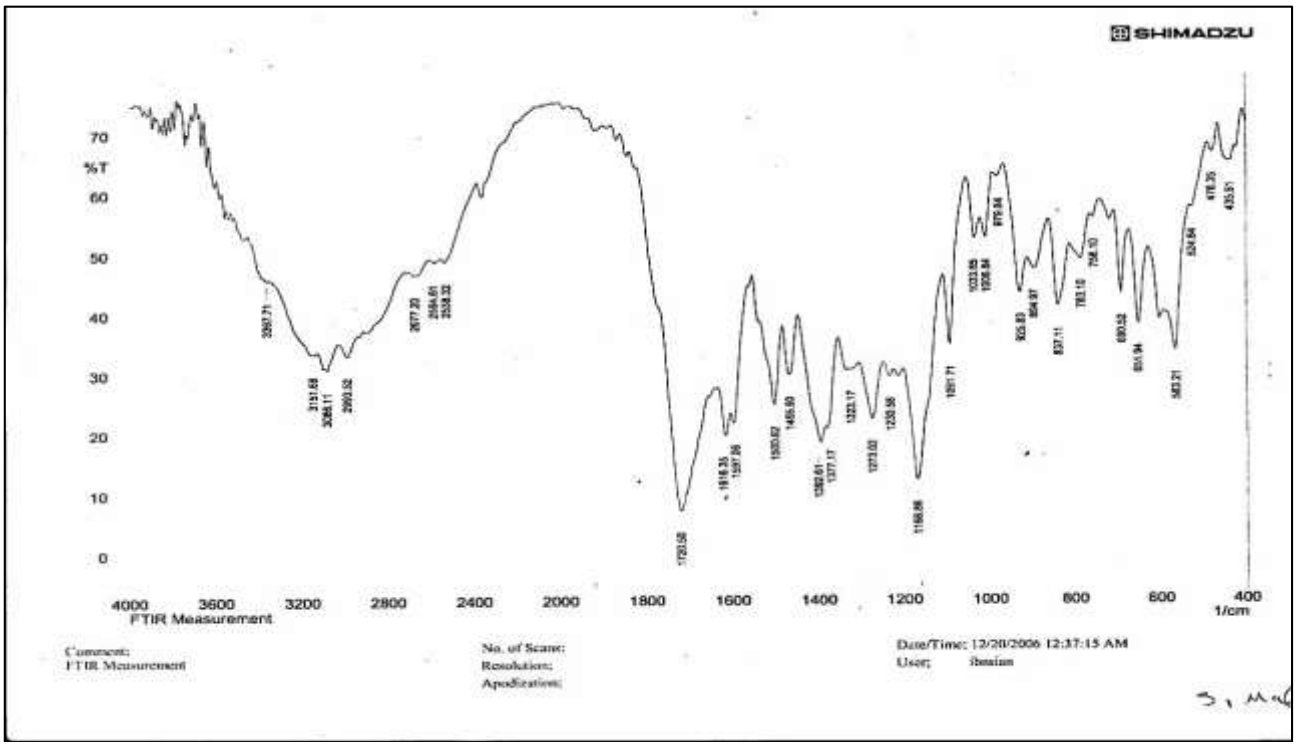
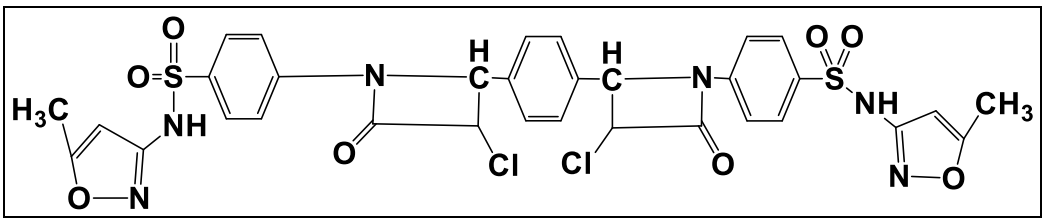


Fig 9: FT.IR of compounds (4)

Characterization of COMPOUND (E)



The [1]H-NMR of the compound (5) figures (10) showed the following peaks: A signals at δ 2.3 (6 Hours) This might be attributed to $(CH_3)_2$ proton, a signal at (δ 8.5) ppm (2H) that could be assigned to (NH), and many signals at δ (6 – 7) belong to the aromatic protons.

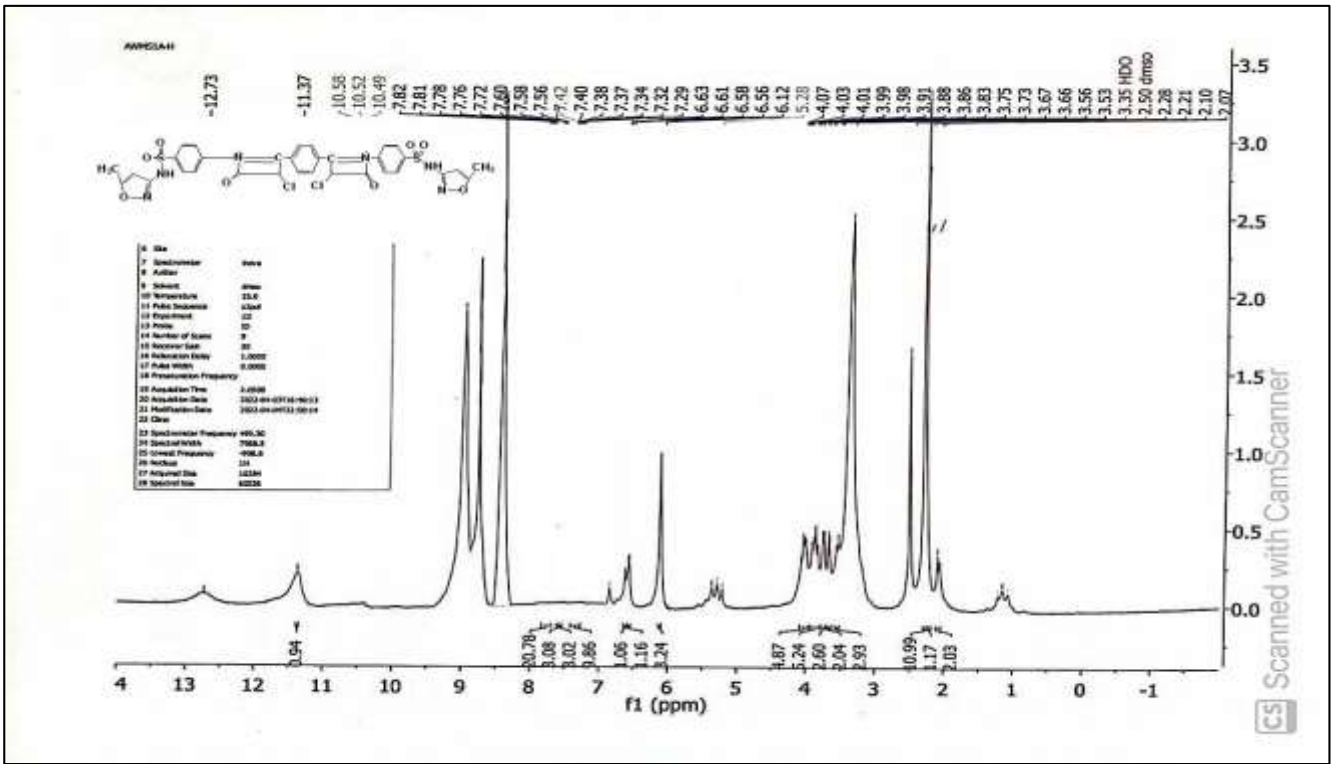
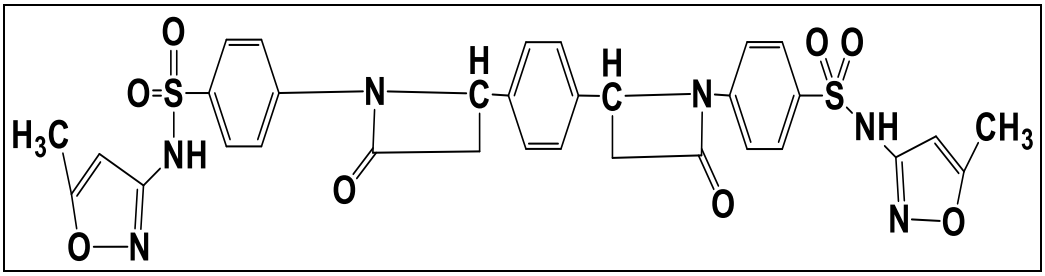


Fig 10: F.T.I.R spectrum of compound (5)

Characterization of COMPOUND (F)



The H_NMR of compound (6) showed that of the following peaks: many signals at δ(6 – 7) belong to the Aromatic proton. A signals at δ 8.2 ppm (2H) that could be assigned to (NH), also showed a signal at δ 2.2 (6HOUR) that may be assigned $(CH_3)_2$ proton and a signal at δ 7 (4H) ppm due to $(O{=}C\text{-}CH_2)_2$ proton figures [11].

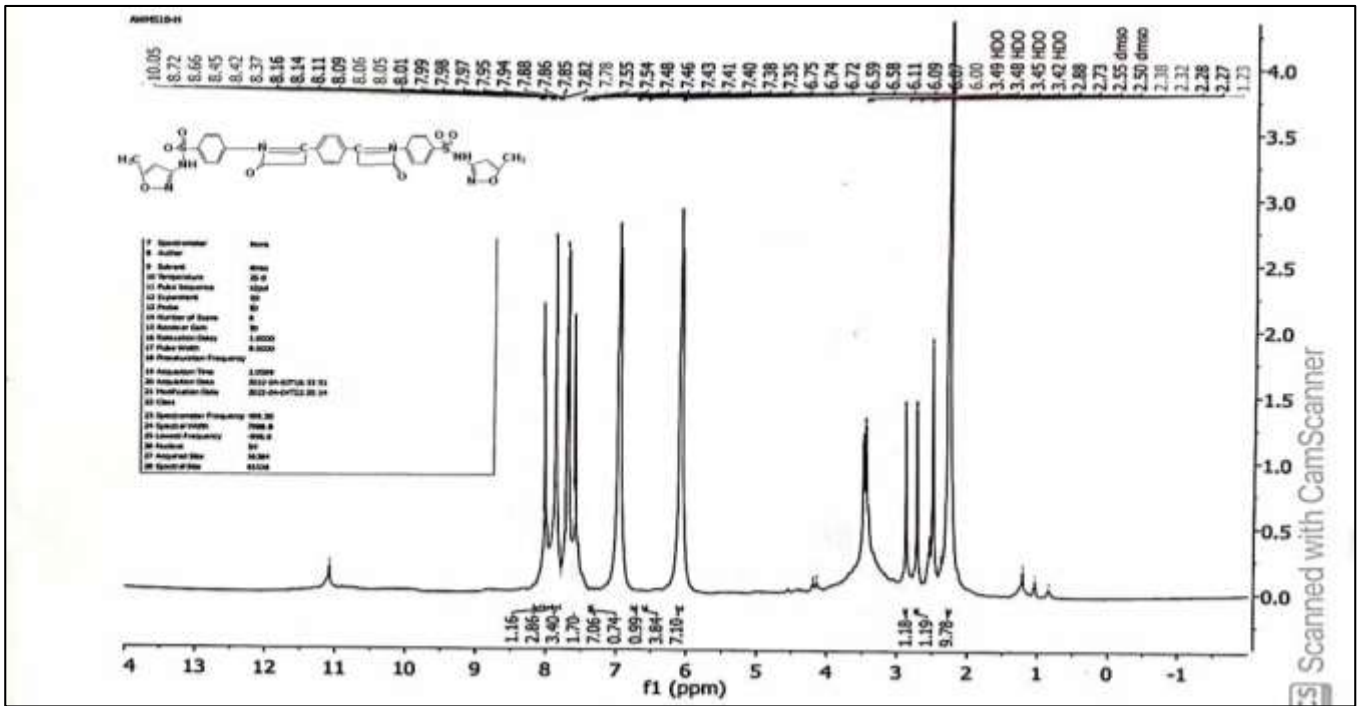


Fig 11: FT-IR spectrum of compound (6)

Discussion of biological activity

The biological activity of the compound was determined by measuring its diameter.

Vacant land (prohibited area) around the well.

1. Compounds [2, 3, 4, 7, 8, 10 and 11] have moderate efficacy against *E. coli*.
2. Compounds [2, 3, 7, 8, 10] have moderate efficacy against *Pseudomonas*.
3. Compounds [4 and 11] have little activity against *Pseudomonas* spp.
4. 4-Compound [3, 7, 10, 11] has high activity against *Staphylococcus*.
5. Compounds [2, 4, 8] are moderately effective against *Staphylococci*.

The results of the preliminary screening test are shown in Table (3)

Table 3: Antibacterial activities for some of the prepared compounds

Comp No	Sample No. (in image)	*E. coli* (G -)	*Pseudomonas* S (G -)	*Staphylococcus* (G+)
A	18	+ +	+ +	+ +
3	20	+ +	+ +	+ + +
4	22	+ +	+	+ + +
7	26	+ +	+ +	+ + +
8	27	+ +	+ +	+ +
10	26	+ +	+ +	+ + +
11	26	+ +	+ +	+ + +

Fig 12- 13: Effect of compounds A(18 = 4, 20 = 6), B(25 =12, 26 =6, 27 =7, 28=13) against *E. coli*.

Fig 14: Effect of compounds (18 = 4, 20 = 5) against *Pseudomonas* 1.

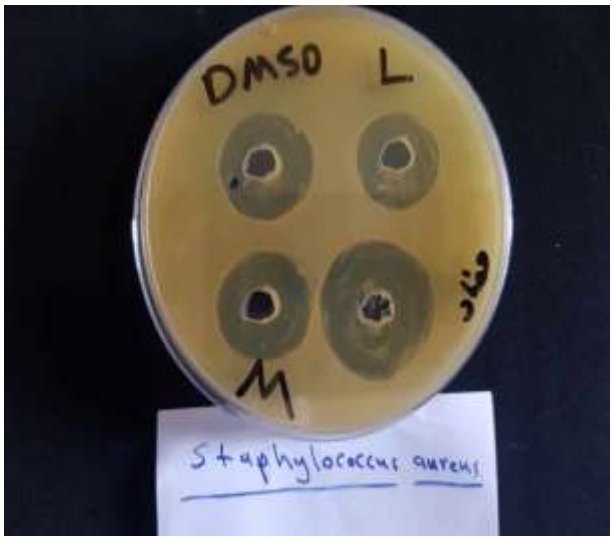


Fig 15: Effect of compounds A(18 =4, 20 = 5), B(25 =13, 26 = 9, 27 = 7, 28 = 12) against *Staphylococcus*.

Conclusion

1. Integration in vehicles has been achieved.
2. It is designed to set standards to reach the highest standards.
3. Our thinking on the organic movement showed that compounds (3-4-7) could be screened as antimicrobial specialists.

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