Thi-Qar Medical Journal (TQMJ): Vol. (28), No. (2), 2024
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218 ISSN (Online): 3006-4791

Synthesis and Evaluation of the Biological Activity of Heterocyclic Derivatives Containing the 1,3,4-Thiadiazole Ring

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Abstract: In this article: A series of new heterocyclic molecules with five and six members were prepared from 1,3,4-thiadiazole derivative with a terminal primary amine group and was used to synthesize a Schiff base (6) by interaction with 5-chloro salicylaldehyde and using ethanol as a solvent. After that, it was able to prepare numerous chemical compounds utilizing the Schiff base. Which contains a C=N group with (2-aminobenzoic acid, 2-mercaptobenzoic acid, valine, alanine, and sodium azide) to prepare hydroqinazoline (6a), thiazinone derivative (6b), and imidazolidine derivatives, (6c,6d). TLC follows these reactions and Melting points for derivatives were measured. These compounds were determined by ^{13}C-NMR, ^{1}H-NMR, and FT-IR spectra, along with studying the biological activity of the prepared derivatives.

Keywords: Tetrazole 1,3,4thiadiazole, Shef base

1. Introduction:

Heterocyclic compounds are organic compounds that contain (at least) one atom different from carbon. The most common heterocyclic atoms are nitrogen, oxygen, and sulfur, but they can also contain other well-known atoms such as phosphorus, arsenic, antimony, and silicon. [1-2]. The compounds are considered Heterocyclics are of wide importance in the bio-industrial aspect because they are present in most natural products; as we find that some types of sugars and their derivatives contain within their composition penta- or hexagonal heterocyclic rings that contain oxygen [3-4].

1,3,4thiadiazole is a heterocyclic compound consisting of five atoms containing one sulfur atom and two nitrogen atoms. It is highly valued due to its activity against microbes. Much research has shown that compounds containing 1,3,4thiadiazole represent a promising group of compounds for inclusion. In the fields of antibacterial treatment[5-6].

Schiff bases are a class of organic compounds that carry the functional group of imine or azomethine. Schiff bases played an influential role in the development of chemistry[7-8]. These compounds have great importance in many fields, as Schiff bases are considered the starting material for preparing a large number of heterocyclic compounds [9]. Studies have also shown that

they are It has distinctive and many biological activities, including antibacterial and antifungal properties [10].

2-Materials and Methods: Melting points were recorded using a Gallen-Kamp MFB-600 melting point meter. "(FTIR) spectra (400-4000 cm-1) in KBr slices were recorded using a SHIMADZU FTIR-8400S Fourier Transform." ^{13}C-NMR and ^{1}HNMR were recorded with (DMSO-d6) at (500 MHz) using a Varian Agilent USA. The measurements were performed at the Department of Chemistry, University of Basra, Basra.

Synthesis of compound (1)[11]**:** A mixture of (0.01 mol) 4-dimethylaminobenzoic acid and (0.01 mol) thiosemicarbazide in (5 mL) POCL 3 was refluxed for 3 hours and excess POCL 3 was removed. The remaining material was dissolved in distilled water (25 ml), then heated for 4 hours, filtered, and neutralized. The precipitate was then filtered with KOH, dried, and recrystallized from ethanol.

Synthesis of compound (6)[12]: Preparation of Schiff base involved the reaction compound (1) (1g, 0.004 mol) with (0.004 mol) of 5-chloro salicylaldehyde These components were added to (30 ml) of CH_3CH_2OH, followed by 3 dropwise of glacial acetic acid, and evaporation at 70°C for 20 hours. The mixture is then allowed to settle to room temperature so that the methanol-crystallized sediments can be separated again.

Synthesis of compound (6a)[13]**:** A mixture of compounds (6) (0.003 mol) was reacted with 3ml of (DMF) and a solution of 2-amino benzoic acid (0.003 mol) in dioxan. For 20 hours, this mixture was cooked in a water bath the reaction process was followed by the TLC technique.

Synthesis of compound (6b)[14]**:** A stirring of compounds (6) (0.003 mol) in 20 ml of dry benzene and 3 ml of (DMF) was used to dissolve (0.003 mol) of 2-mercapto benzoic acid. TLC was used to check on the reaction purity and track progress after (5 drops) of (Tri ethyl amine) and the mixture was refluxed at (36 h), filtering extracting drying, and recrystallizing with pure ethanol.

Synthesis of compound (6c-6d)[15]**:** A mixture of (0.003 mol) of Schiff bases (6) with tetrahydrofuran (THF) 22 ml and Valine, Alanine (0.003 mol) was heated in a water bath. A temperature of (55 °C) (TLC) was used to verify the reaction's completion.

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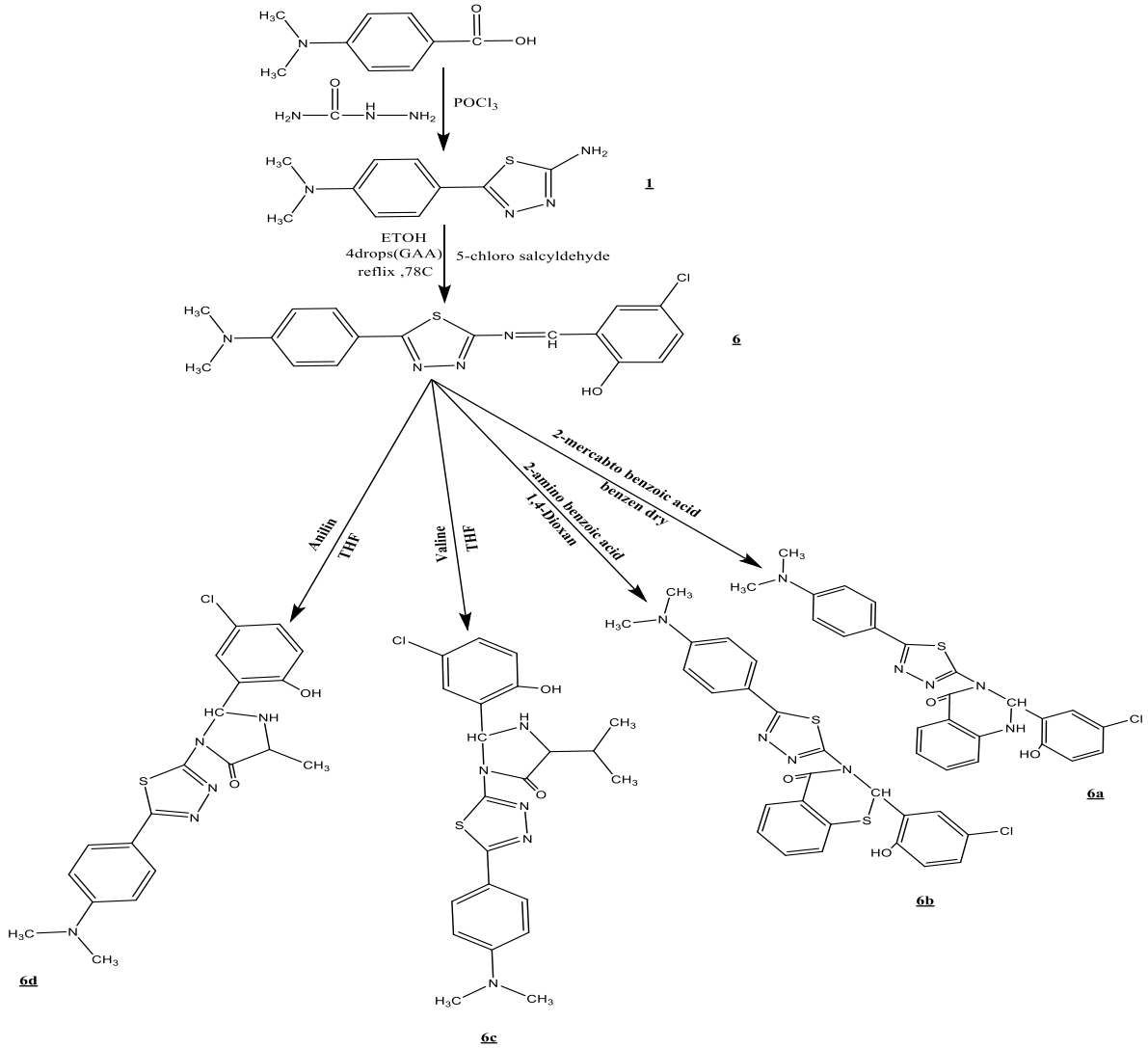

Schem (1) prepares some heterocyclic derivatives.

3. Results and Discussion

Characterizations of compound (1): 5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-amine
The spectra exhibited the fundamental vibration modes **IR: (KBr) (ν cm^{-1})** NH_2 (3371-3278), C-H aromatic (3109), -C-H aliphatic stretching (2939), -C=N in thiadiazole (1604), -C=C aromatic stretching (1571-1435 ¨) **. ^{1}H-NMR: δppm** (400 MHz, $DMSOd_6$), δ=9.32 [s, 2H, NH_2], δ=6.69-7.75 ppm [m, 4H, CH aromatic], δ=2.96 [s, 6H, $2CH_3$]. ^{13}CNMR: δ ppm (400 MHz, DMSO-d_6) δ= 168-167.6. [C=N thiadiazole ring], δ= 157.5 [C-NH_2], δ= 111.9-131.3 [C=C aromatic].

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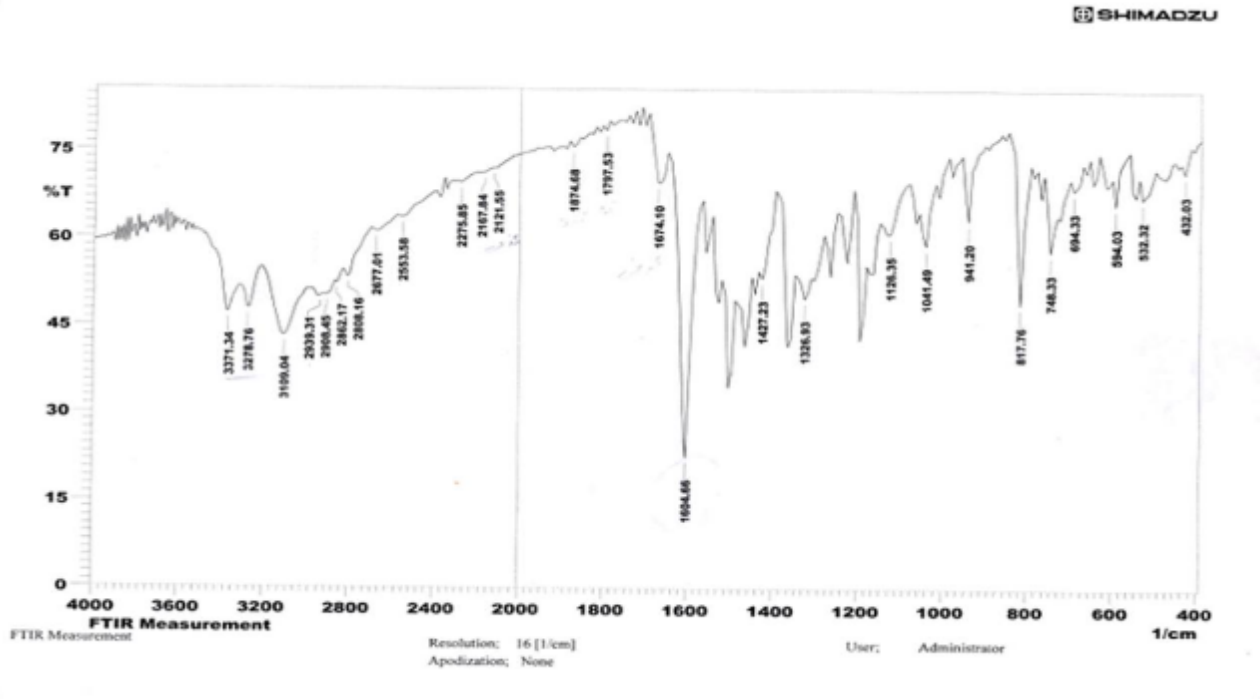

Figure (1) FTIR Spectrum of compound (1)

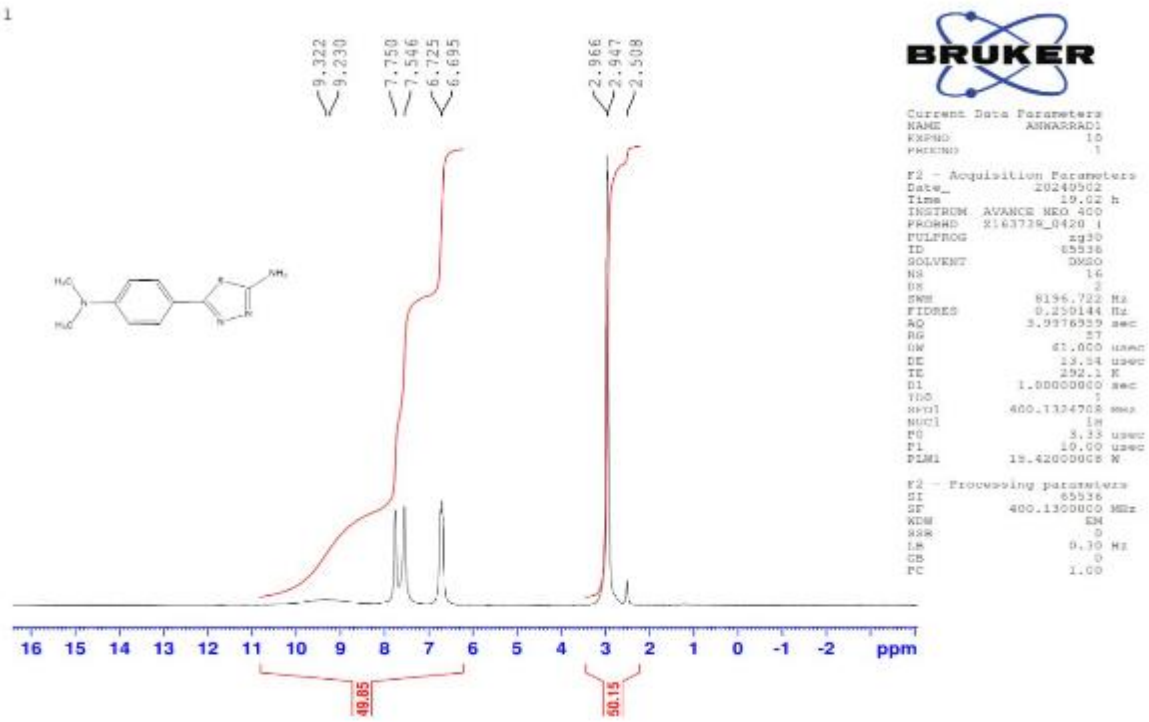

Figure (2) ^{1}H-NMR spectrum of compound (1)

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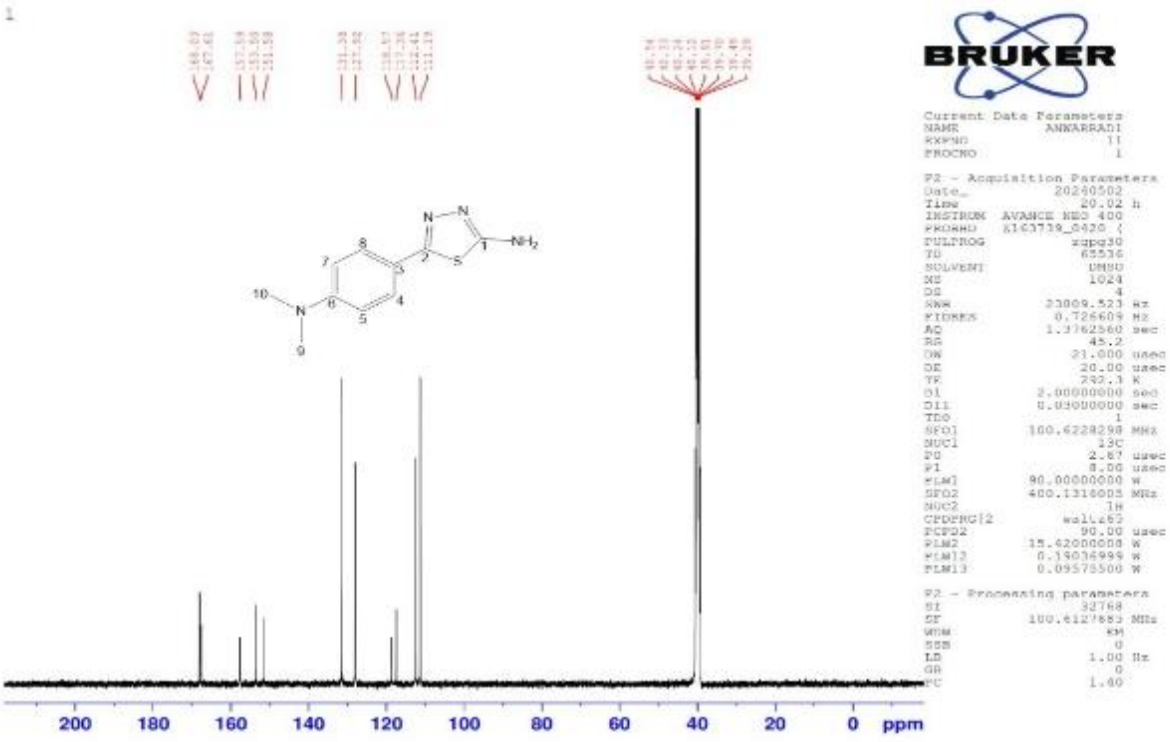

Figure (3): ^{13}C-NMR spectrum of compound (1)

Characterizations of compound (6): 4-chloro-2-(((5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol

^{1}H-NMR: δppm (400.MHz, DMSOd_6), δ= 8.97 ppm [s, 1H , OH] , δ=6.70-7.76 [m, H, CH-aromatic], δ=3.16 [s, 6H ,2CH_3]. ^{13}CNMR: δ ppm (400 MHz, DMSO-d6) δ= 157.14 [CH=N], 153.58 [CH=N] in thiadizol ring, δ= 152.30[C-OH], δ= 111.39-131.46 [C=C aromatic], δ= 29.44 [2CH_3],

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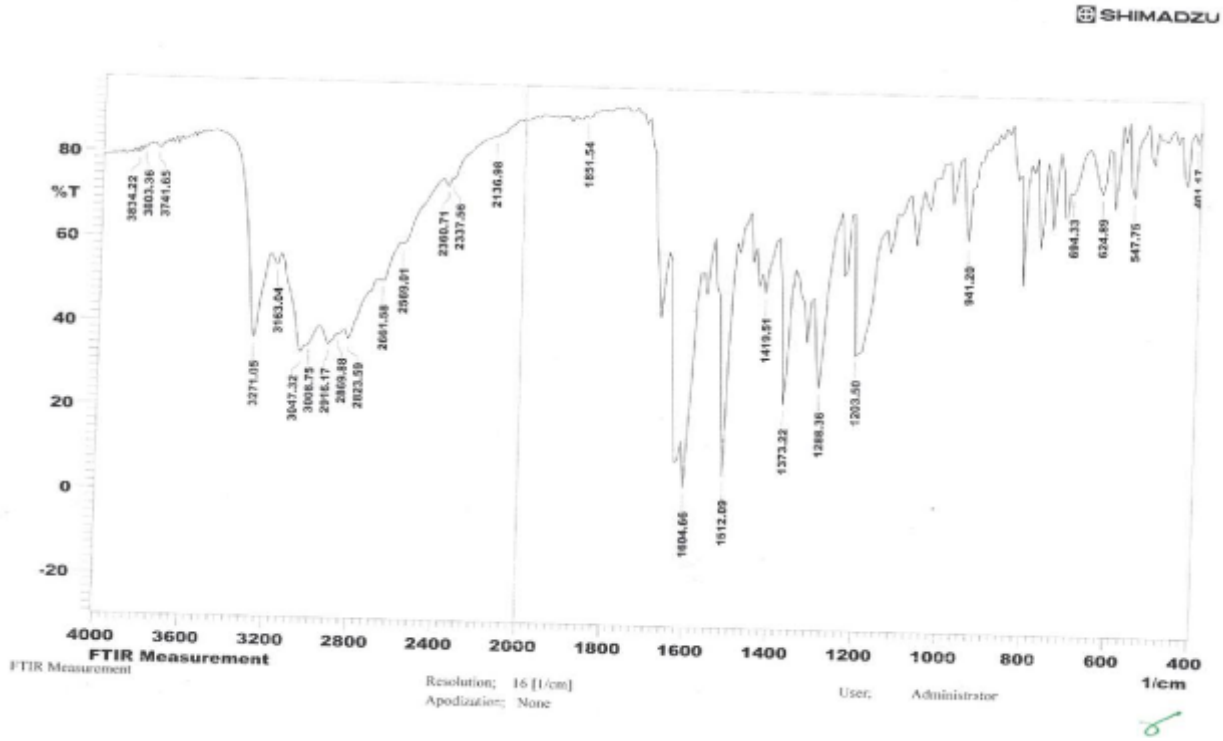

Figure (4) FTIR Spectrum of compound (6)

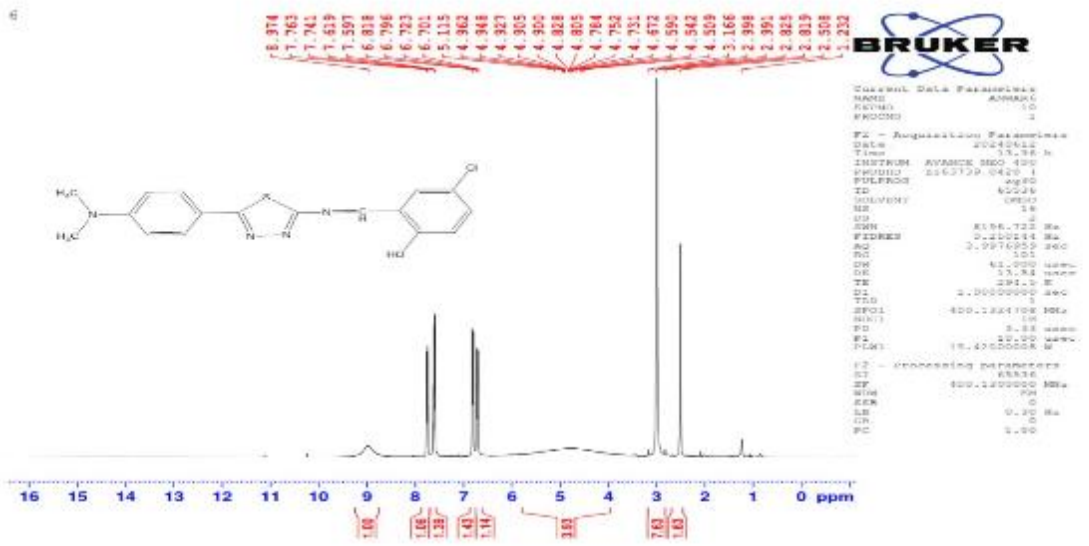

Figure (5) ^{1}HNMR spectrum of compound (6)

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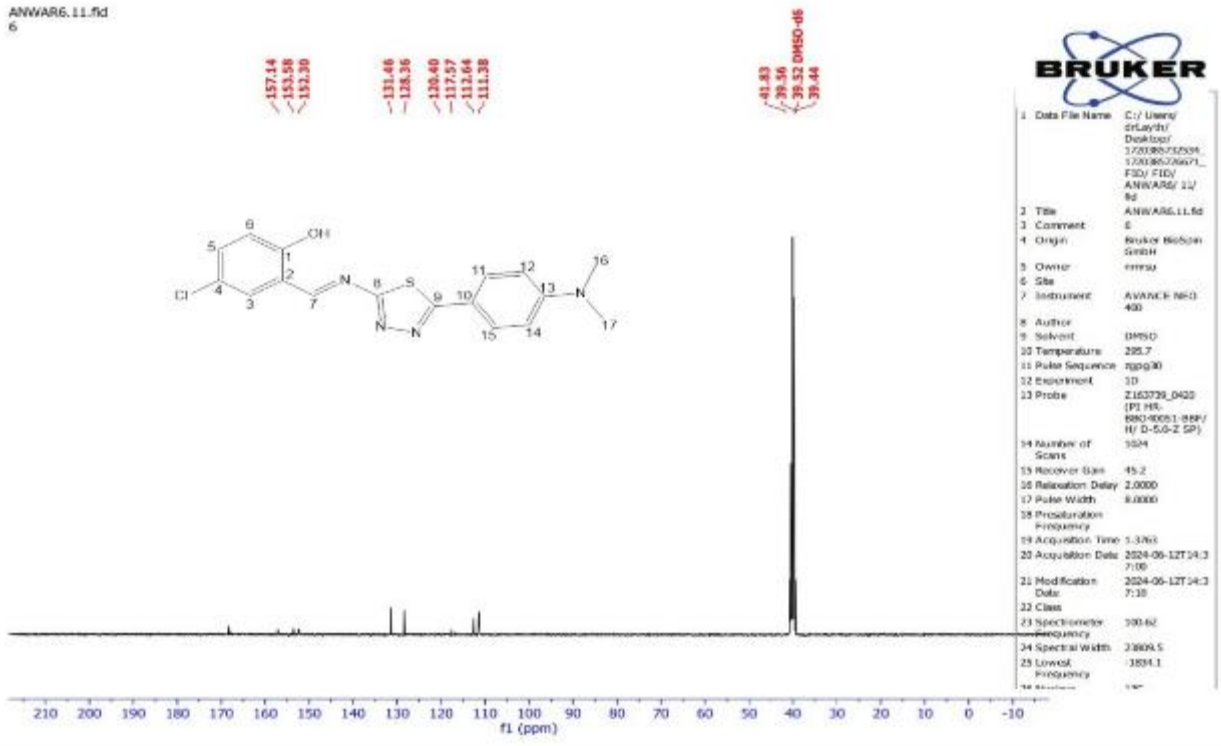

Figure (6) ^{13}C-NMR spectrum of compound (6)

Characterizations of compound (6a)

2-(5-chloro-2-hydroxyphenyl)-3-(5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroquinazolin-4(1H)-one

^{1}H NMR : δ ppm(DMSO-d^{6} 400MHz), δ=8.97 [s, 1H , OH], δ=6.47-7.16 [m CH- aromatic], δ=2.95 [s, 6H ,2CH_3].^{13}C-NMR: δppm (400 MHz, DMSO-d6) δ= 170.10 [C=O lactam],δ= 168.02[$CH-N$], δ= 153.56[C-OH], δ= 110.12-140.21 [C=C aromatic], δ= 29.63 [2CH_3], δ= 63.29 [C-Cl].

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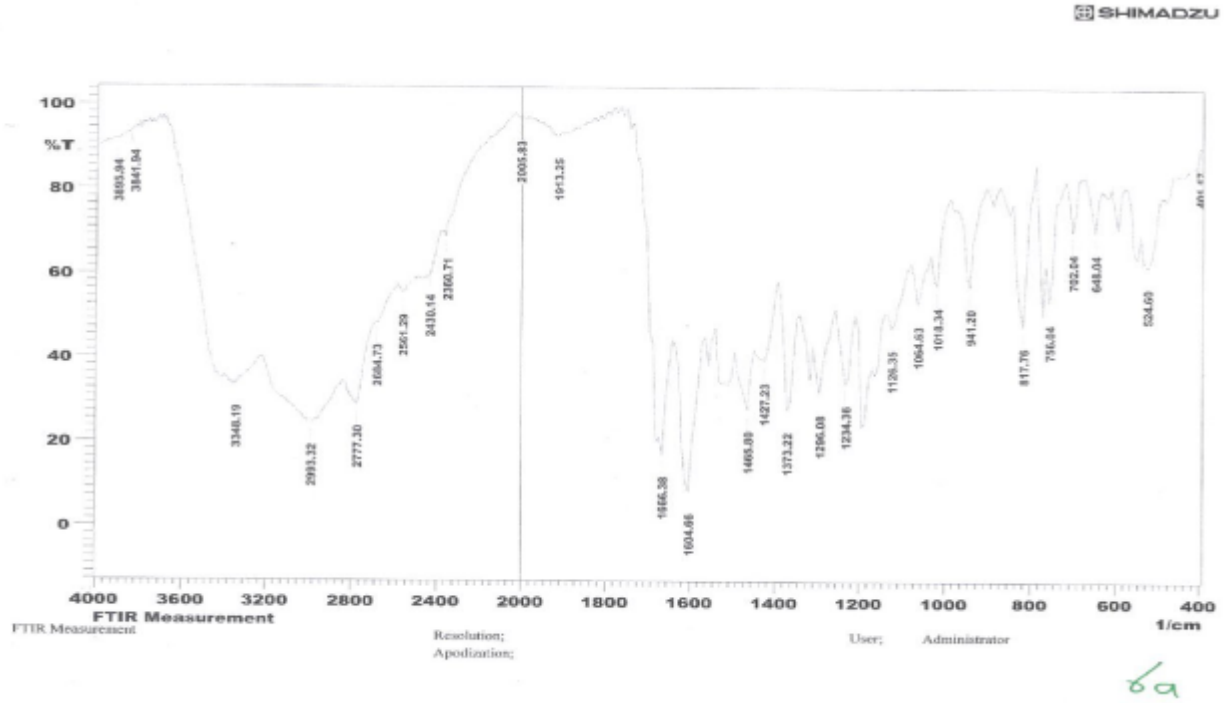

Figure (7) FTIR Spectrum of compound (6a)

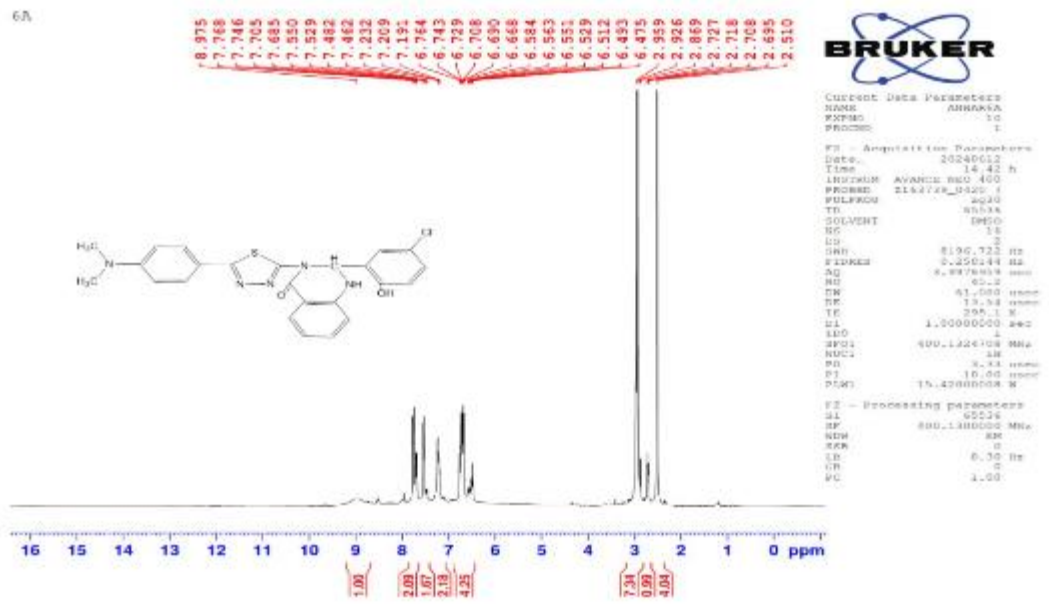

Figure (8) ^{1}H-NMR spectrum of compound (6a)

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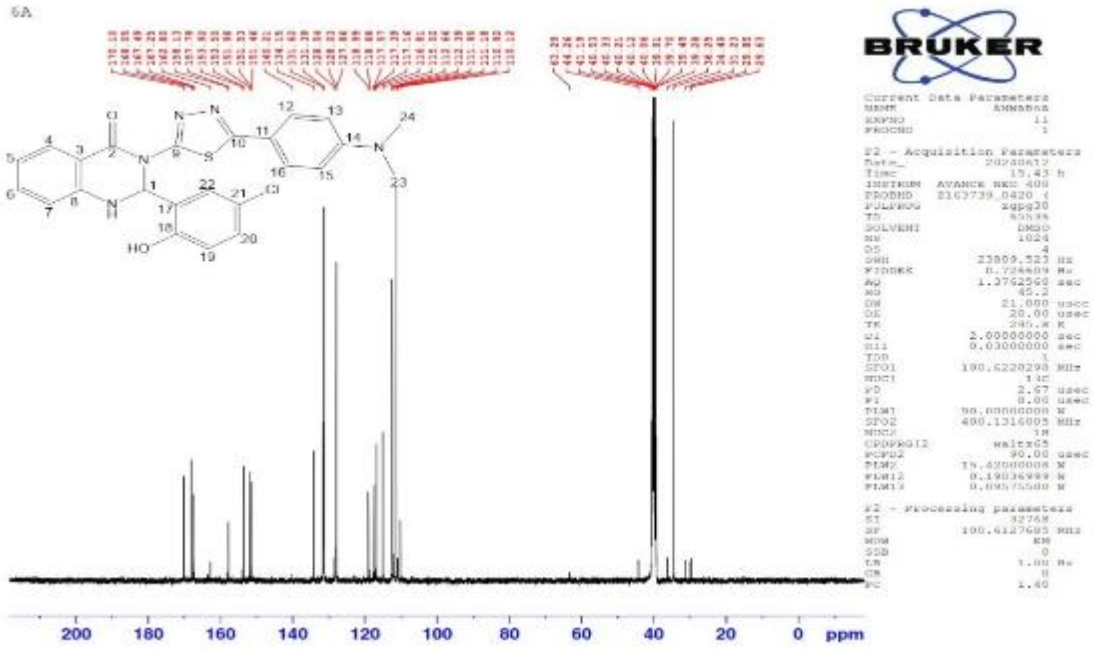

Figure (9) ^{13}C-NMR spectrum of compound (6a)

Characterizations of compound (6b): 2-(5-chloro-2-hydroxyphenyl)-3-(5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-yl)-2,3-dihydro-4H-benzo[e][1,3]thiazin-4-one ^{1}H-NMR: δppm (DMSO-d^{6} and 400MHz), δ= 8.029 [s, 1H , OH], δ= 8.010 [s, 1H , NH],δ=6.68-7.98 [m, CH- aromatic], δ=2.95 [s, 6H ,2CH_3]. ^{13}C-NMR: δ ppm (400 MHz, DMSO-d6): δ= 168.37 [C=O lactam], δ= 167.42[$CH-N$], δ= 153. [C-OH], δ= 111.21-139.33 [C=C aromatic], δ= 39.34 [2CH3], δ= 45.78 [C-Cl].

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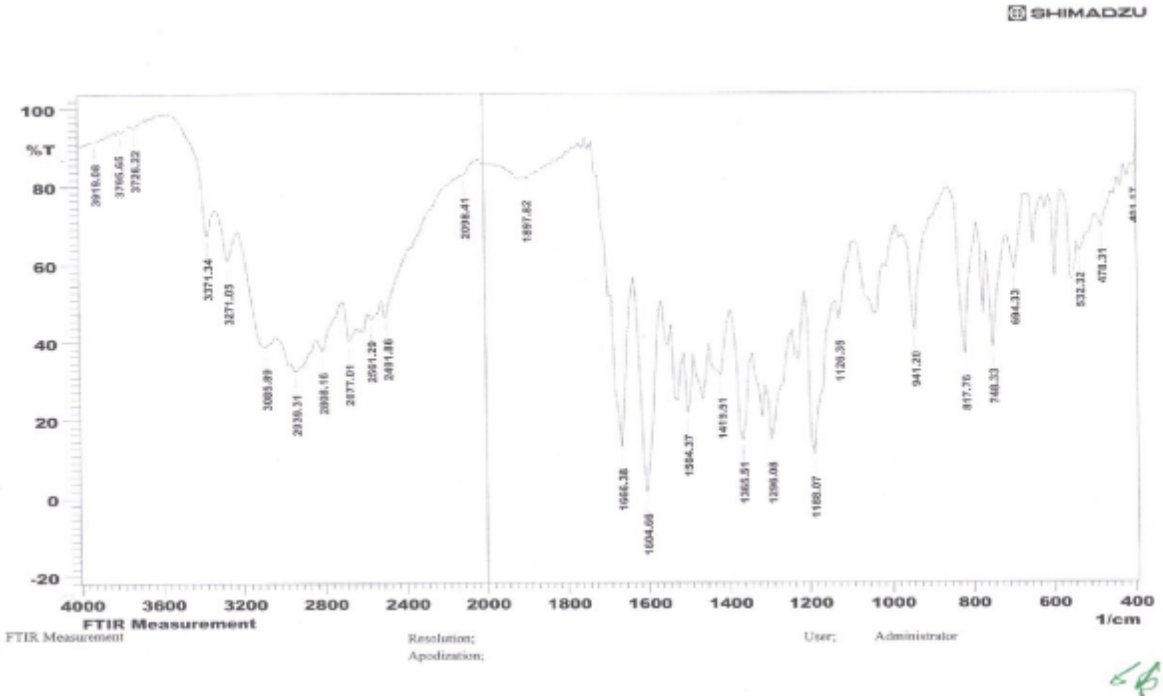

Figure (10) FTIR Spectrum of compound (6b)

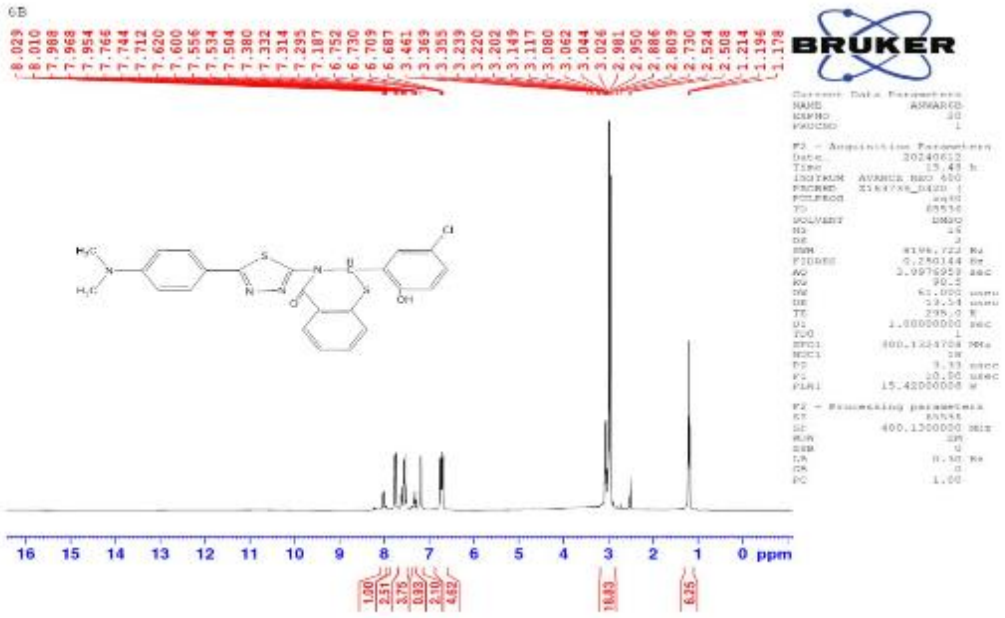

Figure (11) ^{1}H-NMR spectrum of compound (6b)

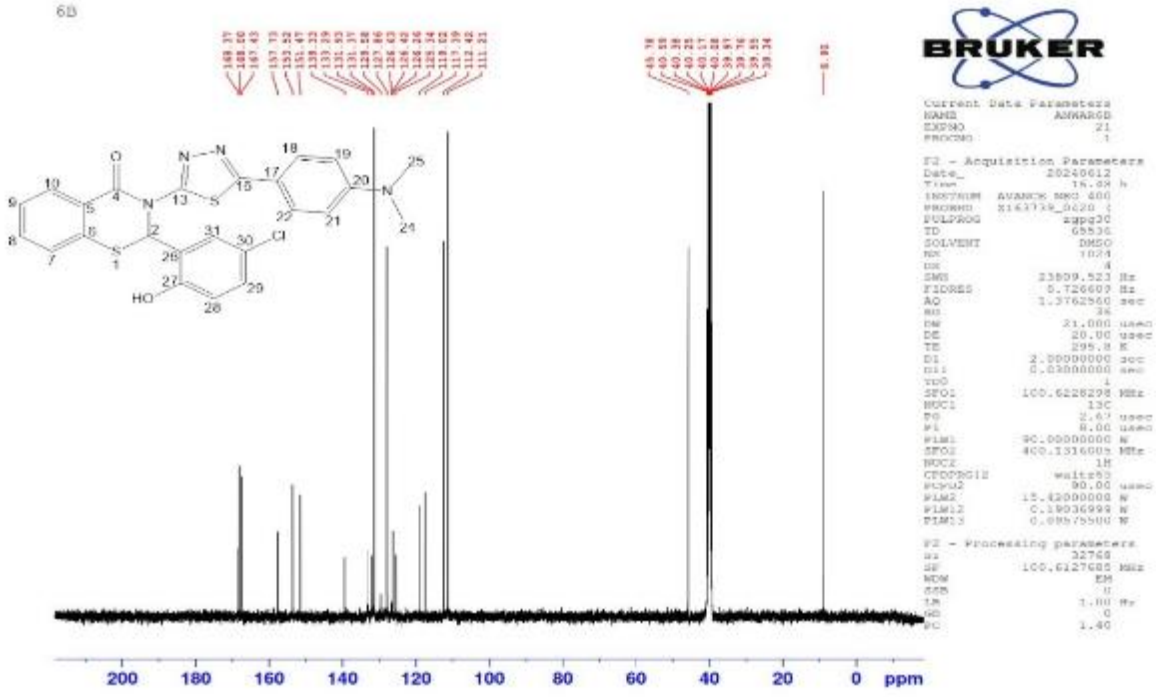

Figure (12) ^{13}C-NMR spectrum of compound (6b)

Characterizations of compound (6c)

2-(5-chloro-2-hydroxyphenyl)-3-(5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-yl)-5-isopropylimidazolidin-4-one

^{1}H-NMR : δ ppm(DMSO-d^{6} and 400MHz), δ= 8.37 [s, 1H , OH], δ= 8.341 [s, 1H , NH],δ=6.68-7.94 [m, CH- aromatic], δ=2.195 [s, 6H ,2CH_3]in five ring, δ=2.95 [s, 6H ,2CH_3] . ^{13}C-NMR: δ ppm (400 MHz, DMSO-d6): δ= 168.37 [C=O lactam], δ= 167.42[$CH-N$], δ= 153. [C-OH], δ= 111.21-139.33 [C=C aromatic], δ= 39.34 [2CH3], δ= 45.78 [C-Cl].

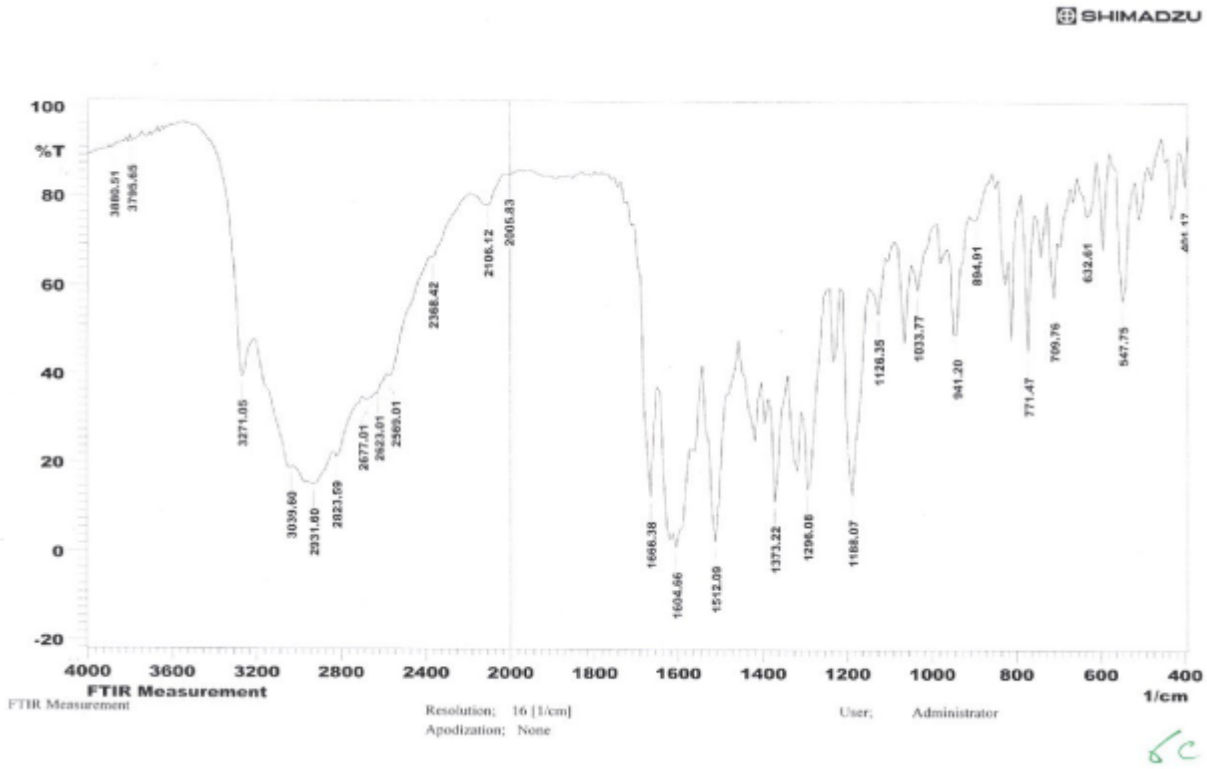

Figure (13) FTIR Spectrum of compound (6c)

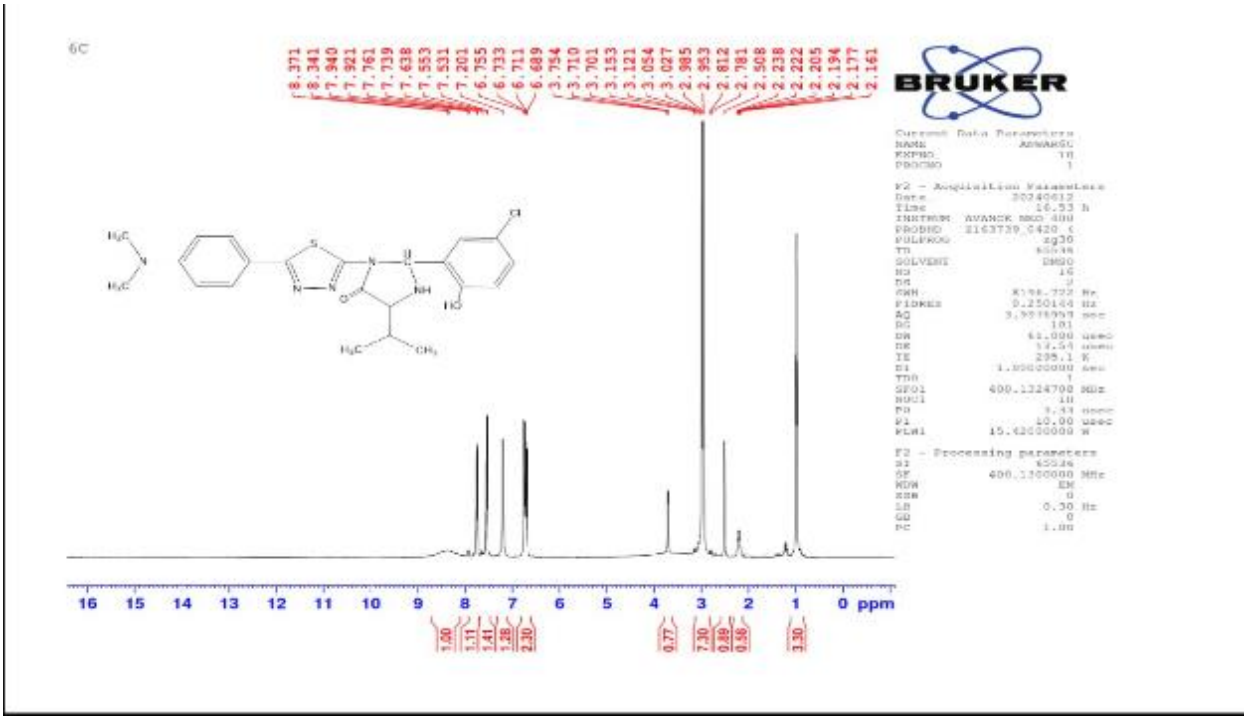

Figure (14) ^{1}H-NMR spectrum of compound (6c)

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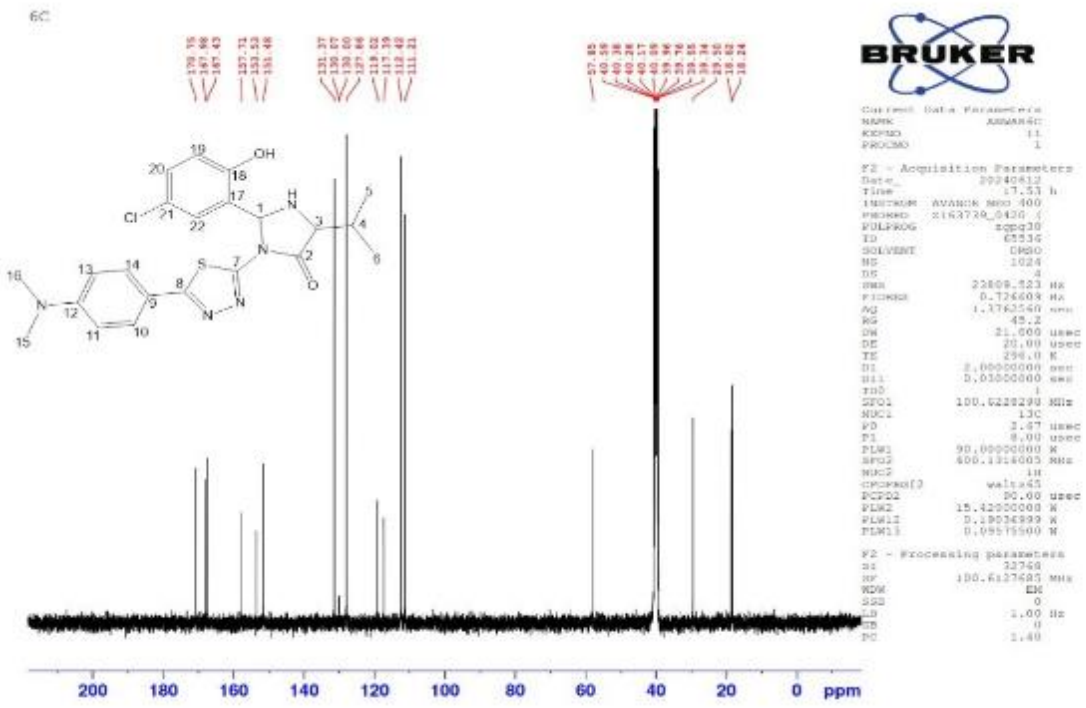

Figure (15) ^{13}C-NMR spectrum of compound (6c)

Characterizations of compound (6d)

2-(5-chloro-2-hydroxyphenyl)-3-(5-(4-(dimethylamino)phenyl)-1,3,4-thiadiazol-2-yl)-5-methylimidazolidin-4-one

^{1}H-NMR: δ ppm (DMSO-d^{6} and 400MHz): δ=8.039 [s, 1H, OH], δ=8.02 [s,1H , NH], δ=6.69-7.76 [m, CH- aromatic], δ=2.89 [s, 3H ,2CH_3], δ=3.078 [s, 3H , CH_3]. ^{13}C-NMR: δ ppm (400 MHz, DMSO-d6): δ= 170.77 [C=O lactam], δ= 168.12 [CH-N], δ= 153.54 [C- OH], δ= 111.22-139.38. [C=C aromatic], δ= 18.58, 8.88 [CH_2, CH_3 in five ring].

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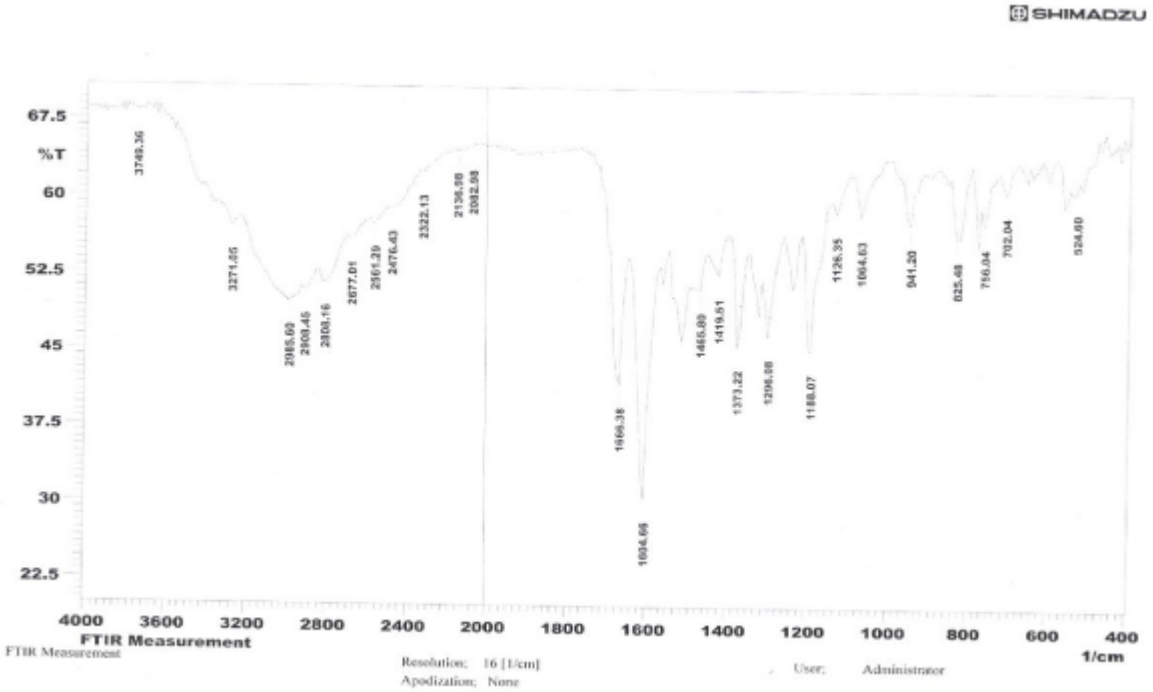

Figure (16) FTIR Spectrum of compound (6d)

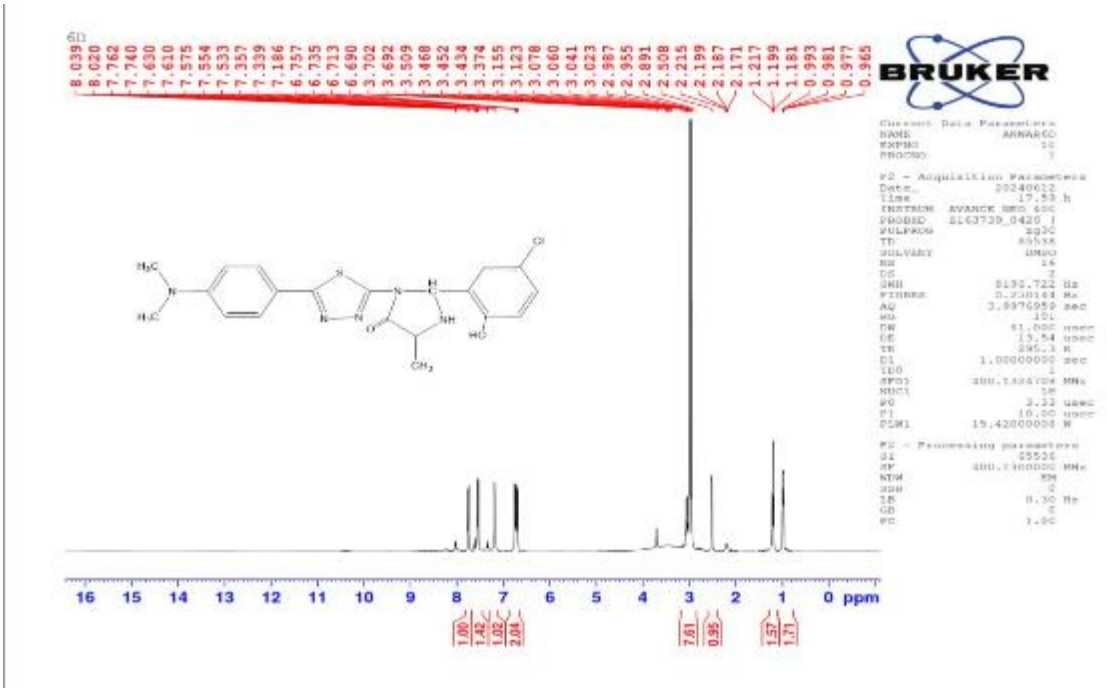

Figure (17) ^{1}H-NMR spectrum of compound (6d)

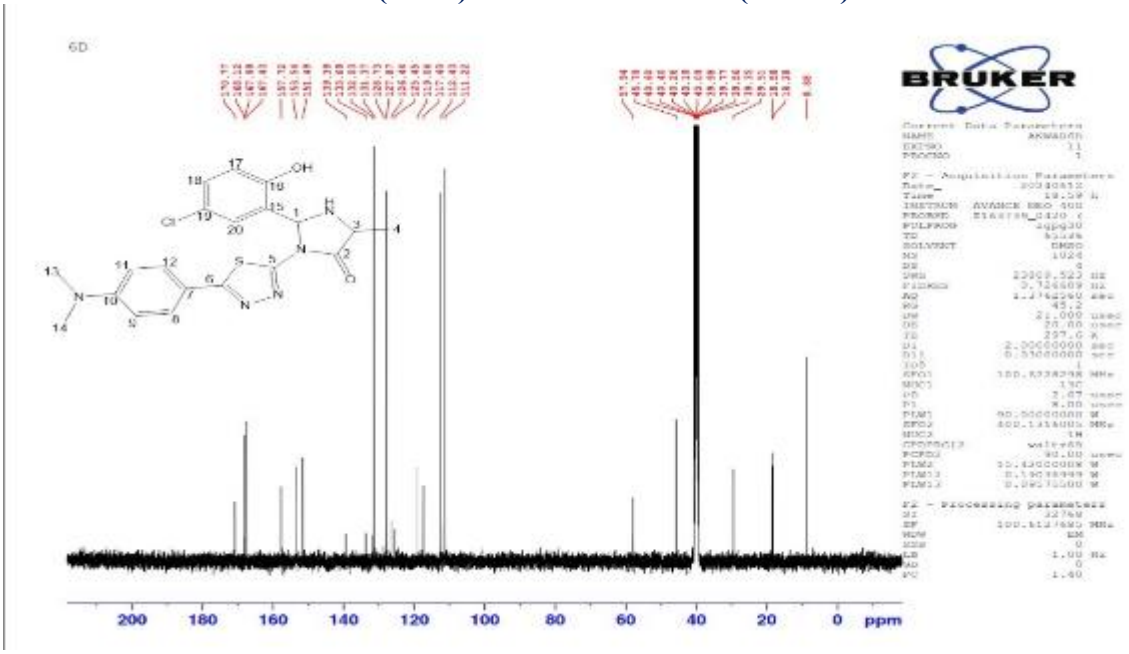

Figure (18) ^{13}C-NMR spectrum of compound (6d)

Table (1) Physical properties of compounds

Comp No	Molecular Formula	M. Wt. G\Mol)(	Yield%	Mp (°c)	Color	Rf
1	$C_{10}h_{12}sn_4$	220	80	240	Yellow	0.89
6	$C_{17}h_{15}son_4$ Cl	358	70	243	Purple	0.86
6a	$C_{24}h_{20}n_5so_2$ Cl	465	90	250	Black	0.95
6b	$C_{24}h_{19}n_4s_2o_2$ Cl	494	92	270	rick Red	0.90
6c	$C_{21}h_{28}n_5s$ O_2 Cl	449	85	272	Brown	0.82
6d	$C_{20}h_{25}n_5s$ O_2 Cl	434	73	266	Grey	0.87

Antibacterial activity : In this study, it was found that the prepared compounds significantly reduce the antibacterial effectiveness against *Staphylococcus aureus and E. coli* bacteria, and the compounds that have good activity are (6a, 6b).

In this work, a series of 1,3,4-thiadiazole derivatives were prepared due to their biological properties and wide pharmaceutical uses. Through 1,3,4-thiadiazole, a series of new heterocyclic molecules (6-6C) were prepared. The prepared compounds were characterized and their functional groups were determined through different characterization tools such as 13C-NMR, 1H-NMR, and FT-IR. The prepared compounds were proven against two types of bacteria, Staphylococcus aureus and Escherichia coli. It was proven that compounds (6A, and 6B) have good activity against E. coli and S. aureus, while compound 6C showed greater activity against E. coli.

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Table (2) shows the inhibition range of each of the complexes against some bacteria

NO	Compound	Corresponding			
		E. Coli		*S. Aureus*	
		Ppm 500		Ppm 500	
1	Amox	+	5	+	6
2	6	-	2	-	2
3	6a	++	20	++	15
4	6b	++	13	++	13
5	6c	++	13	+	10
6	6d	+	10	+	5

"+= (5-10)mm =slightly active, ++= (11-20)mm moderately +++ = More than 20, good active"

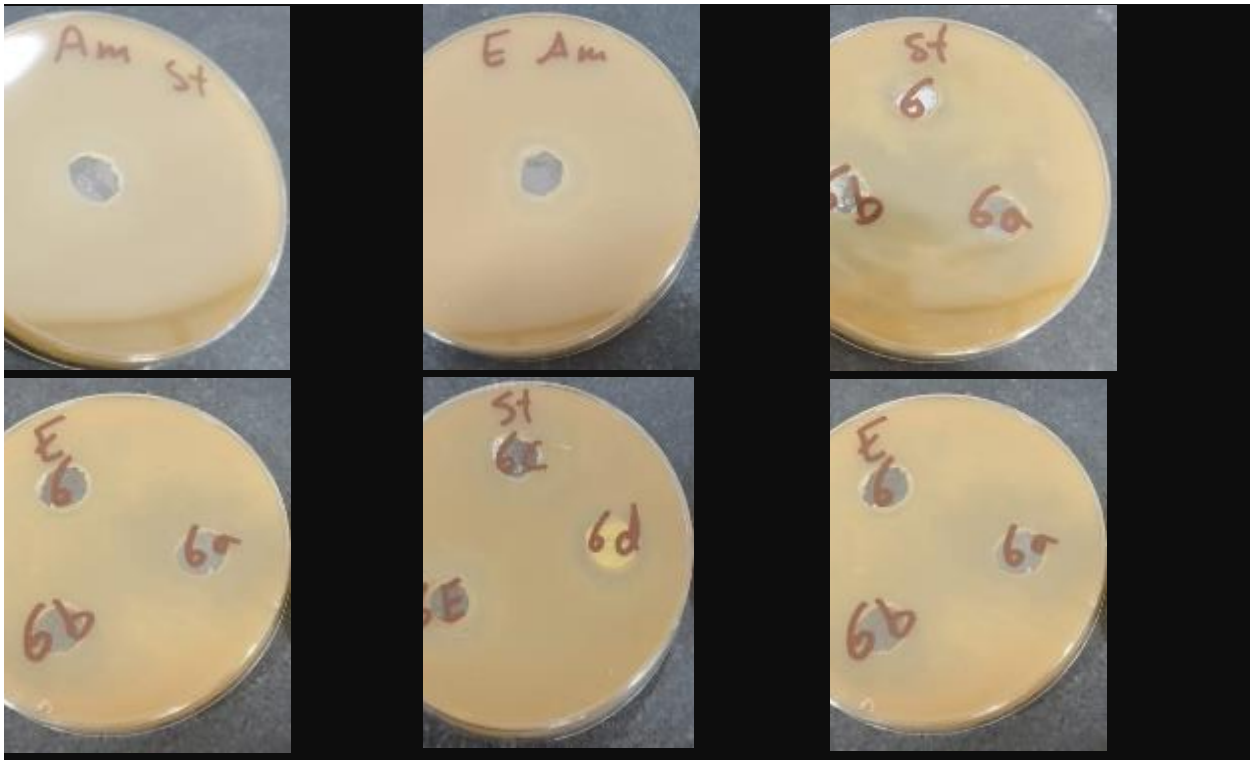

Figure (35) Biological activity of compound-prepared *E. Coli* and *S. Aureus*

Discussion: The results obtained from the study of the compounds prepared from 1,3,4-thiadiazole derivatives indicate their clear activity against two types of bacteria: *Staphylococcus aureus* and *Escherichia coli*. Compounds 6a and 6b showed remarkable antibacterial activity against both species, indicating that these compounds have promising properties in the pharmaceutical field, especially in combating various bacterial infections. This activity enhances the possibility of developing these compounds as future antibiotics.

Conclusion: In this work, a series of 1,3,4-thiadiazole derivatives were prepared due to their biological properties and wide pharmaceutical uses. From 1,3,4-thiadiazole, compound (6) was prepared as a Schiff base, and then a series of new heterocyclic molecules (6a, 6b, 6c, 6d) were prepared. The prepared compounds were characterized and their functional groups were determined by different characterization tools such as ^{13}C-NMR, ^{1}H-NMR, and FT-IR. The prepared compounds were tested against two types of bacteria and the compounds showed good activity against *Staphylococcus aureus* and *Escherichia coli*. Compounds (6a, and 6b) had good activity against *Escherichia coli* and *Staphylococcus aureus*, while compound (6c) showed greater activity against *Escherichia coli*. In conclusion, the results of the preliminary activity of this class of compounds may have the potential for designing future molecules with modifications on the substituents.

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