Microwave-Assisted Synthesis of Five and Seven-Membered Heterocycles and Study Their Biological Activity

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Abstract

In this study, we synthesized one azo compound (S19) and then condensat this compound with a carbonyl compound to give a Schiff base (S20) as the key step. The next step Schiff base reacted with some Amino acids and Anhydrides by cycloaddition reaction to give five-membered (S22, S23) and seven-membered (S21, S24) heterocyclic compounds. The chemical Structure for of the synthesized compounds were confirmed by using spectroscopic techniques (IR and NMR). In addition, tested their biological activity against *Staphylococcus Aureus* and *Escherichia Coli* displayed good activity.

Key words: azo, imidazolidine, oxazepine, *Staphylococcus Aureus, Escherichia Coli*, Azomethine

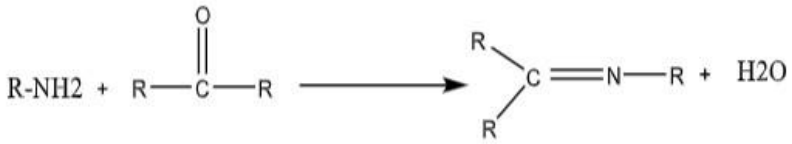
Introduction

Heterocyclic compounds are those compounds that have a ring structure that contains at least one atom different [1] from carbon atoms such as (P, S, N, O) and arranged according to the most common, but may contain other atoms that are widely known as Phosphorous, Arsenic and Antimony and Silicon, Boron and Bismuth [2] , heterocyclic compounds are of very importance in industrial application and medicinal chemistry [3] and are also present in most natural products, where we find that some types of sugars and their derivatives are biologically effective as in vitamins [4] and to her pharmacological bio-efficacy for many diseases such as cancer, memory loss, depression, pain and fungal infection [5-7] .

Azo compounds they the oldest and largest class in the manufacture of organic dyes with multiple applications in various fields, such as studying biomedicine and dyeing textile fibers [8-9], as well as antibacterial and antibacterial. For malaria [10] and as reagents in analytical chemistry [11]. Azo compounds containing the functional

group azo (-N=N-) [12] were discovered and named by Greiss for his discovery of the aromatic diazonium salts [13] .

Schiff bases are organic compounds formed from the union of the nitrogen of the primary amine with the carbonyl group in ketones or aldehydes to form the azomethine group [14], Which was how first attended by the German scientist (HugoSchiff) Equation (1). The Schiff bases containing aryl substitutes are considered to be faster and more stable than that containing alkylation substitutes [15], and the Schiff bases have importance in medicinal and pharmaceutical chemistry with many biological applications as anti-cancer [16], antiviral [17], and anti-bacterial [18].



Ir ıd with the molecular formula ($C_3H_8N_2$) [19]. The imidaolidine ring important because it is the building blocks for the formation of bioactive compounds [20]. And some of its derivatives are anti-fungal, anti-cancer, and anti-viral [21]. prepared from the cyclo addition reactions [22]. Oxazepine has applications where it has shown anti-cancer, anti-bacterial and anti-fungal activity [24], as well as pharmaceutical applications as anti-inflammatory, in addition to its entry into the antibiotic industry [24].

Experimental

Chemicals, Biologicals and Instrumentation

From Merck, Sigma, BDH, Difco, Santacruze, Flow labs, and GCC, all supplies were purchased. We used Silica gel precoated aluminum sheets from Merck for thin layer chromatography (TLC) to calculate R_f and To follow the progress of the reaction.of the reaction. Using melting point equipment from Cole-Parmer Ltd. in the UK, the melting points were ascertained in open capillary. On Shimadzu, Japan, a Fourier Transform Infrared Spectrophotometer was captured. For ^{1}H and ^{13}C NMR, deuterated DMSO was utilized as the solvent with a Bruker Avance 400 MHz NMR spectrometer.

The Methods

Preparation of azo compound S19

1-(4-((4-amino-2-nitrophenyl)diazenyl)phenyl)ethan-1-one

The azo compound (S19) was prepared by dissolving (1 g, 0.007 mole) of 4-aminoacetophyton in a mixture consisting of (3ml) of concentrated (HCl) and (20mL) of distilled water, and the mixture was cooled in an ice bath at (0 -5 C°). Then a solution consisting (0.483 g, 0.007 mole) of ($NaNO_2$) sodium nitrite was added to it, dissolved in (10mL) of cold distilled water, drop by drop with continuous stirring, and left the formed solution for a period of (20 min) to settle to complete the process Nitrogenation, then the solution of diazonium formed dropwise with continuous stirring was added to a solution consisting of (1 g, 0.007mole) of 3-nitroaniline in a mixture of (20 mL) Ethanol Absolute and (10 mL) of sodium hydroxide solution (NaOH 10%). It was observed that the solution had a dark brown color at (pH = 7), and the formed solution was left for 24hrs, then the precipitate was filtered after completing the sedimentation process, and then it was washed with distilled water several times. recrystallized from absolute ethanol.

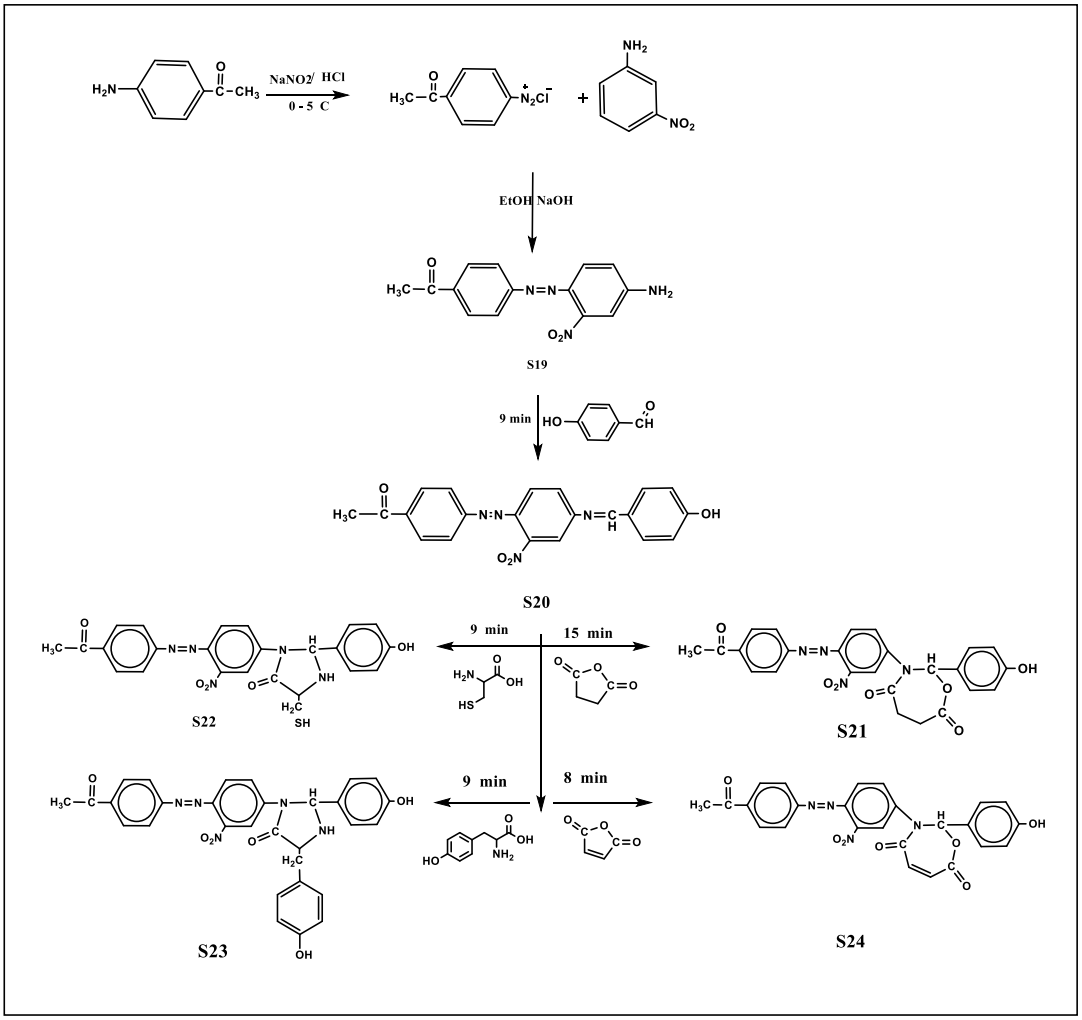
Preparation of Schiff base compound S20

[1-(4-((4-((4-hydroxybenzylidene)amino)-2 nitrophenyl) diazenyl) phenyl)ethan-1-one]

space using microwave irradiation, crush (1.136 g, 0.004mole) of the prepared azo (S19) with (0.488 g, 0.004mole) of 4-hydroxybenzaldehyde well, dissolve the mixture with absolute ethanol and add 3 drops of glacial acetic acid. Then enter the microwave at (120 watts) for (9 min), and follow up the reaction by using chromatography TLC with (3 ml benzene: 2 ml EtOH abs) as solvent and then recrystallization of the product

Preparation of S21, S22, S23, S24 from Schiff base compound (S20)

Space Equivalent moles (1:1 mole) of S20 with succinic anhydride, cysteine, tyrosine, maleic anhydride to prepare S21, S22, S23, and S24 respectively in (5ml) of dry benzene and then put it in the microwave at (120 W) for (8-15 minutes) TLC (3 ml benzene: 2 ml EtOH abs) was used to check the reaction completion Solid product obtained was crystallized from absolute ethanol.



Scheme (1) Synthesis of compounds (S19- S24)

Results and discussion

(FT-IR) Spectrum.For the Azo (S19) appearance of the stretching band of the (NH_2) group at the frequency (3300) cm^{-1}, the appearance of the absorption band at the frequency (3095) cm^{-1} is due to the stretching of the aromatic (C-H) band, and the appearance of the absorption band at the frequency (3007) cm^{-1} belongs to the stretching of the bond (C-H) aliphatic, the appearance of an absorption band at frequency (1664)cm^{-1} belonging to the ketogenic (C=O) group, with the appearance of an absorption band at frequency (1435)cm^{-1} belonging to the azo group (N=N), as well as The appearance of two absorption bands for the (NO_2) group, it appeared at the first two frequencies, an asymmetric frequency in the region (1523)cm^{-1} and the symmetrical frequency in the (1352)cm^{-1} region.

(FT-IR)Spectrum.For the Schiff base(S20) appearance of the (OH) group at a frequency of (3383)cm^{-1}, and the appearance of an absorption band at a frequency of (3169)cm^{-1}, back to the stretching of the aromatic (C-H) bond, and the appearance of

an absorption band at a frequency of (2974)cm^{-1} that goes back to Stretching of the aliphatic (C-H) bond, the appearance of the carbonyl absorption band at the frequency (1670)cm^{-1} belongs to the (C=O) ketogenic group, and the appearance of the absorption band at the frequency cm-1 (1595)cm^{-1} belonging to the (C=N) azomethine group, with a band Absorption at the frequency (1452)cm^{-1} goes back to the bond of the azo group (N=N), and two absorption bands of the group (NO_2) appeared at the first two frequencies, an asymmetric frequency in the region (1517)cm^{-1} and the symmetrical frequency in the region (1354)cm^{-1}.

(FT-IR) Spectrum .For the compound (S21) appearance of the (C-N) band in region (1217) cm-1, the spectrum of the (NO_2) group showed two absorption bands, one of which is asymmetric at the frequency (1517) cm-1 and the other is symmetric at the frequency (1350) cm^{-1} , appearance of the absorption band (N=N) At the frequency (1446) cm-1, as well as the appearance of Lactame (C=O) the absorption band at the frequency (1591)cm^{-1}, appearance of the absorption band (C=O) for lactone in (1680)cm^{-1} the region of the oxazepine ring , appearance of the absorption band for the (OH) group at a frequency of (3174) cm^{-1} , appearance of the aliphatic absorption band (C-H) at a frequency of (2968) cm^{-1} .

(FT-IR)Spectrum. For the compound (S22) appearance of an absorption band at frequency (3300) cm^{-1} is due to the (NH) band stretching, and the appearance of an absorption band at frequency (3188)cm^{-1} belongs to the (OH) group, as well as the appearance of an absorption band at frequency (2833)cm^{-1} due to stretching the insistence (C-H) aliphatic, where we notice the disappearance of the absorption band of the group (C=N) and the appearance of the carbonyl absorption band at the frequency (1668)cm^{-1} belonging to the imidazole ring, and also the appearance of the absorption band of the group (C=C) at the frequency (1589)cm^{-1} , With the appearance of two absorption bands of the (NO_2) group, one of them is asymmetric at the frequency (1517)cm^{-1} and the other is identical at the frequency (1338)cm^{-1} ,and also the appearance of an absorption band at the frequency (1452) cm^{-1} belongs to the azo group (N=N), and the frequency in the (1222) cm^{-1} region is due to the (C-N) stretching absorption band, and the SH group's absorption band appeared at the (2623) cm^{-1} frequency.

1H-NMR Spectrum for (S22)

The spectrum showed a single signal at ppm (1.5) belonging to the group (CH_3), as well as the appearance of a single signal at (1.9)ppm belonging to the group (CH_2), and also the appearance of a single signal at (3.9)ppm belonging to (CH) belonging to the ring. And the appearance of a binary signal at (7.6)ppm that belongs to the (NH) group, and the appearance of poly-aromatic signals at (7.71, 7.81)ppm , as well as the appearance of a single signal at (3.0)ppm that belongs to the group (C-N) belonging to

the ring, the appearance of a signal at (9.4)ppm belonging to the group (SH). The sign at (9.9)ppm goes back to the (OH) group. The sign of the solvent appears at (2.5)ppm

(^{13}C-NMR)Spectrum. For (S22)

appearance of a signal at (183)ppm belongs to the carbon of the (C=O) acetyl group. Also, the appearance of a single signal at (173)ppm belongs to the carbon of the amide (C=O) group. A signal appeared at (160)ppm belonging to the (OH) group carbon. Multiple signals appeared at (132-111)ppm related to the carbon of the aromatic rings, a single signal appeared at (37)ppm belonging to the (CH_2) group carbon, the appearance of a signal Alone at (19)ppm belongs to the carbon of group (CH_3). As for the sign of the solvent, the sign appeared at (40)ppm

(FT-IR)Spectrum. For the compound (S23) appearance of an absorption band (OH) at frequency (3211)cm^{-1}, the appearance of an absorption band at frequency (3180) cm^{-1} is due to the (NH) band stretching, and the appearance of an absorption band at frequency (2875)cm^{-1} is due to the stretching of the band (C-H) aliphatic and the appearance of the absorption band of the aldehyde (CH) group at the frequency (2827)cm^{-1}, where we notice the disappearance of the absorption band of the group (C=N) and the appearance of the absorption band of the carbonyl (C=O) at the frequency (1668) cm^{-1} of the imidazole ring, with the appearance of two absorption bands for the (NO_2) group at two frequencies, an asymmetric frequency in (1514)cm^{-1} and an identical frequency in (1334) cm^{-1}, as well as the appearance of an absorption band at a frequency of (1452)cm^{-1} due to the group bond Azo (N=N), and the frequency in the region (1222)cm^{-1} is due to the absorption band stretching the (C-N) band.

(FT-IR) Spectrum . For the compound (S24) appearance of the (C-N) band in region (1220) cm-1, the spectrum of the (NO_2) group showed two absorption bands, one of which is asymmetric at the frequency (1514) cm-1 and the other is symmetric at the frequency (1359) cm^{-1} , appearance of the (N=N) absorption band in the (1446) cm^{-1} , the appearance of Lactame (C=O) the absorption band at the frequency (1595)cm^{-1}, appearance of the absorption band (C=O) for lactone in (1674)cm^{-1} the region of the oxazepine ring , appearance of the (C-H) aromatic in the (3174) cm^{-1} , appearance of the (C-H) absorption band aliphatic (2927) cm^{-1} and appearance of the (OH) phenolic absorption band in the (3410) cm^{-1}.

1H-NMR Spectrum for (S24)

The appearance of a single signal at ppm (1.9) belongs to the group (CH_3), and a binary signal to the group (HC=CH) at ppm (6.57,6.58), as well as the appearance of a triple signal of the group (CH) at ppm (7.00,7.03), as the spectrum showed Multiple aromatic signals at ppm (7.60, 7.64), and the appearance of a single signal at ppm

(11.4) belongs to the (OH) group, while the signal of the solvent appeared at ppm (2.50).

Table(1) : physical propereties for synthesis compounds (S19-S24)

Compound	Moleculer	M. wt	M.P°C	Rf	Color	Yeild
S19	$C_{14}H_{12}N_4O_3$	284.27	120 C°		Dark Brouwn	72.35%
S20	$C_{21}H_{16}N_4O_4$	388.38	94-98C°	0.9	Brouwn	75.28%
S21	$C_{25}H_{20}N_4O_7$	488.45	75-80C°	0.7	Brouwn	84.66%
S22	$C_{24}H_{21}N_5O_5S$	491.52	95 C°	0.6	Brouwn	90.91%
S23	$C_{30}H_{25}N_5O_6$	551.55	85-90C°	0.8	DarkOrange	89.88%
S24	$C_{25}H_{18}N_4O_7$	486.43	92 C°	0.8	Brouwn	76.73%

Biological tests

The biological activity of some azo derivatives Schiff base derivatives (S21, S22, S23) that were dissolved by DMSO solvent, and study of the effect on two types of bacteria *Escherichia coil* G- and *Staphylococcus aureus* G+ the inhibition zone measured by a ruler as in the table (2) :

Table (2) : The biological activity of the compounds

compounds	**Anti-Bacterial Activity**	
	StaphylococcusAureus Mm	*EscherichiaColi* mm
S21	13	13
S22	12	13
S23	12	11

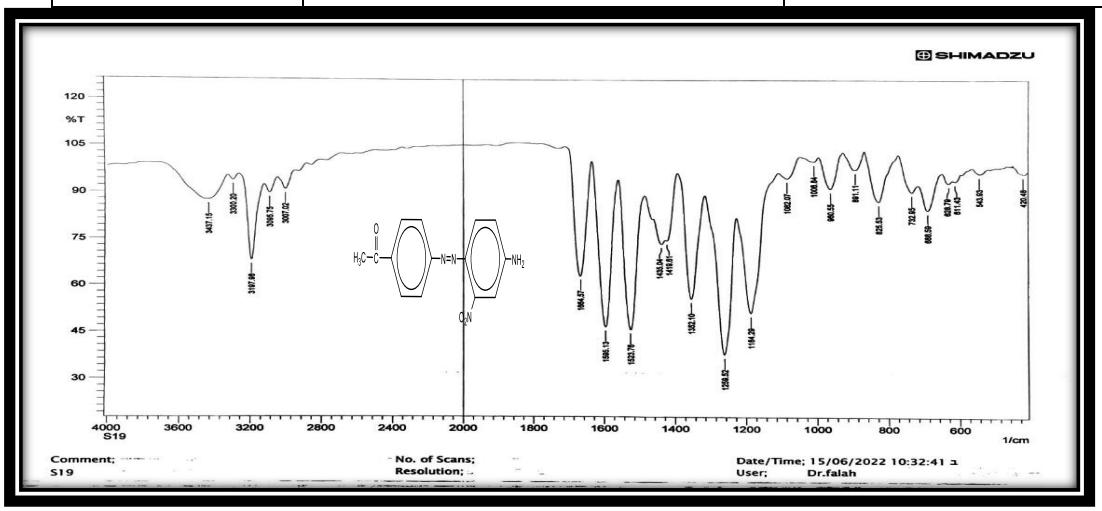


Figure 1 ;FTIR Spectrum for Compound S19

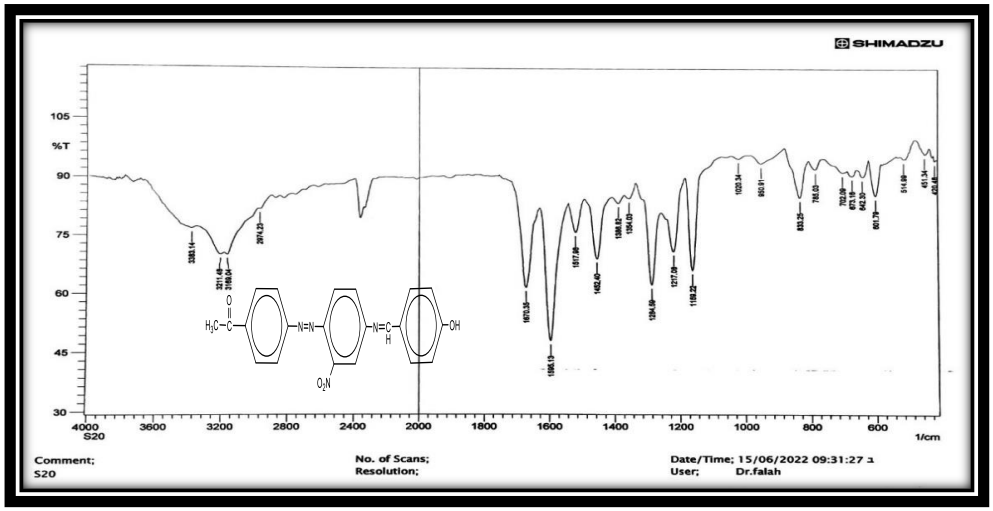


Figure 2 ;FTIR Spectrum for Compound S20

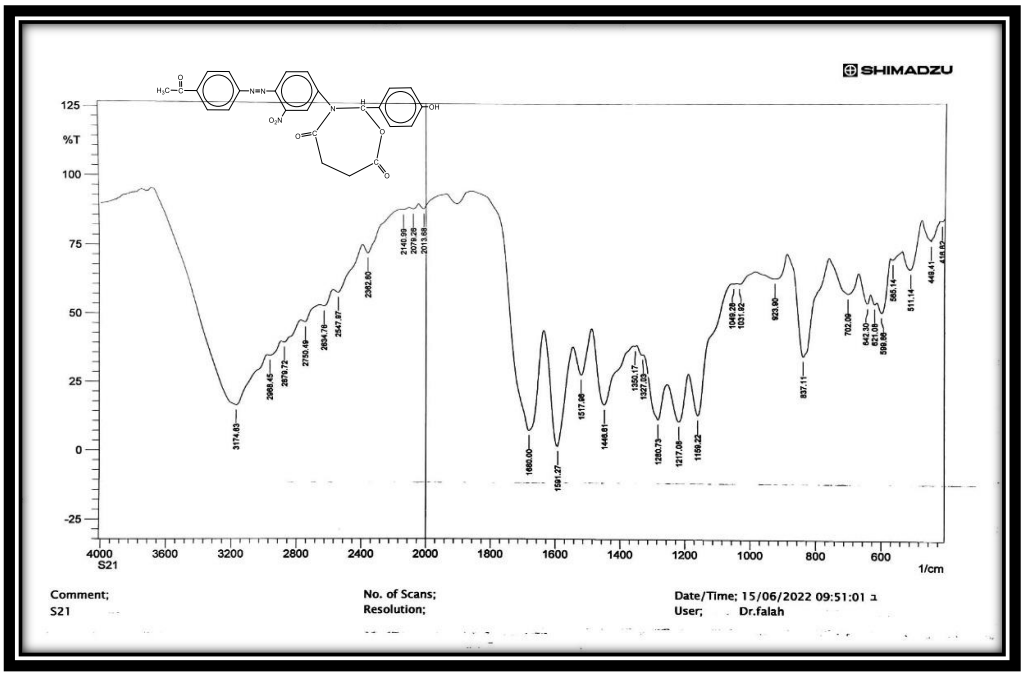


Figure 3 ;FTIR Spectrum for Compound S21

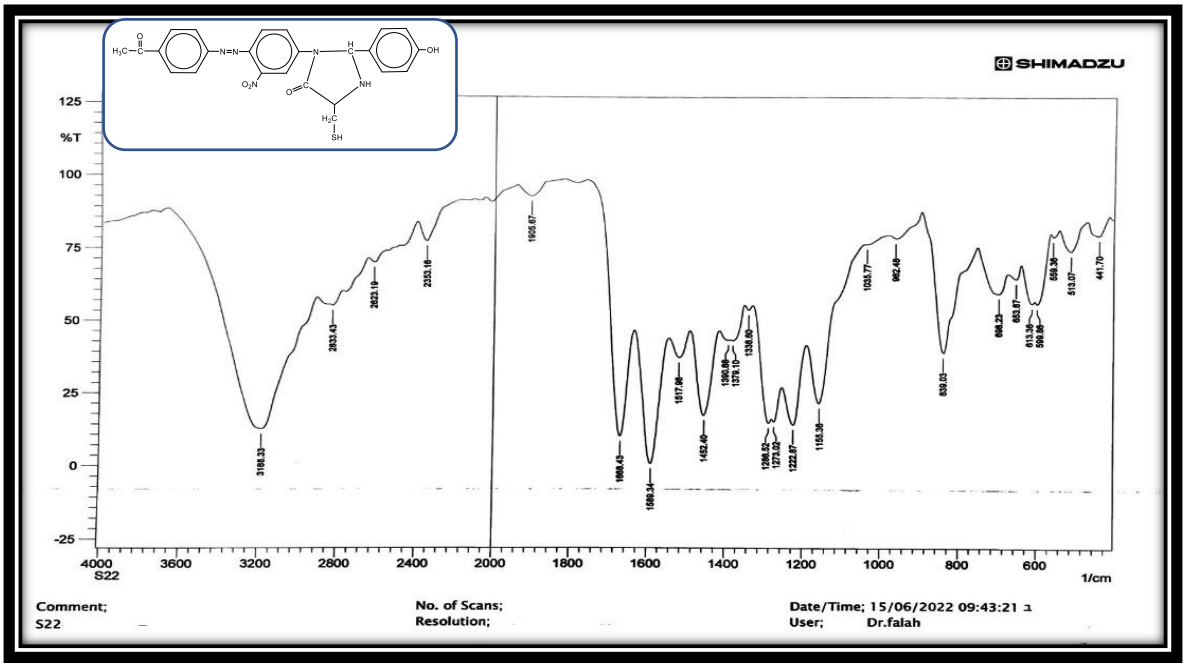


Figure 4 ;FTIR Spectrum for Compound S22

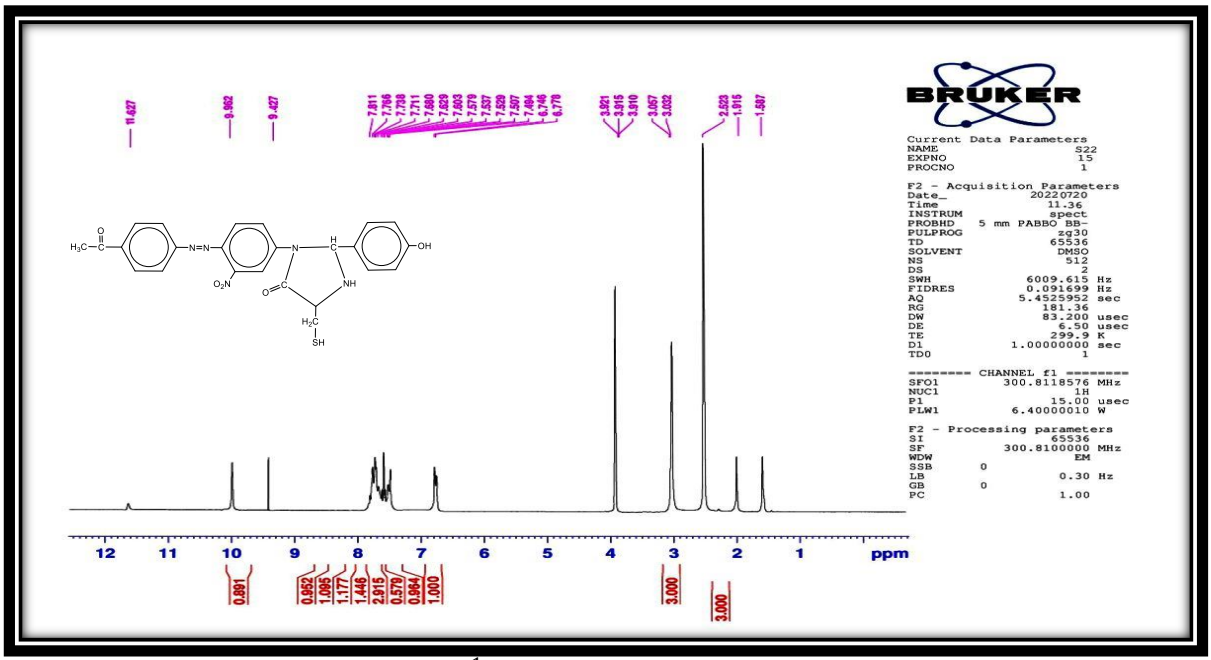


Figure 5 ; ^{1}HNMR Spectrum for Compound S22

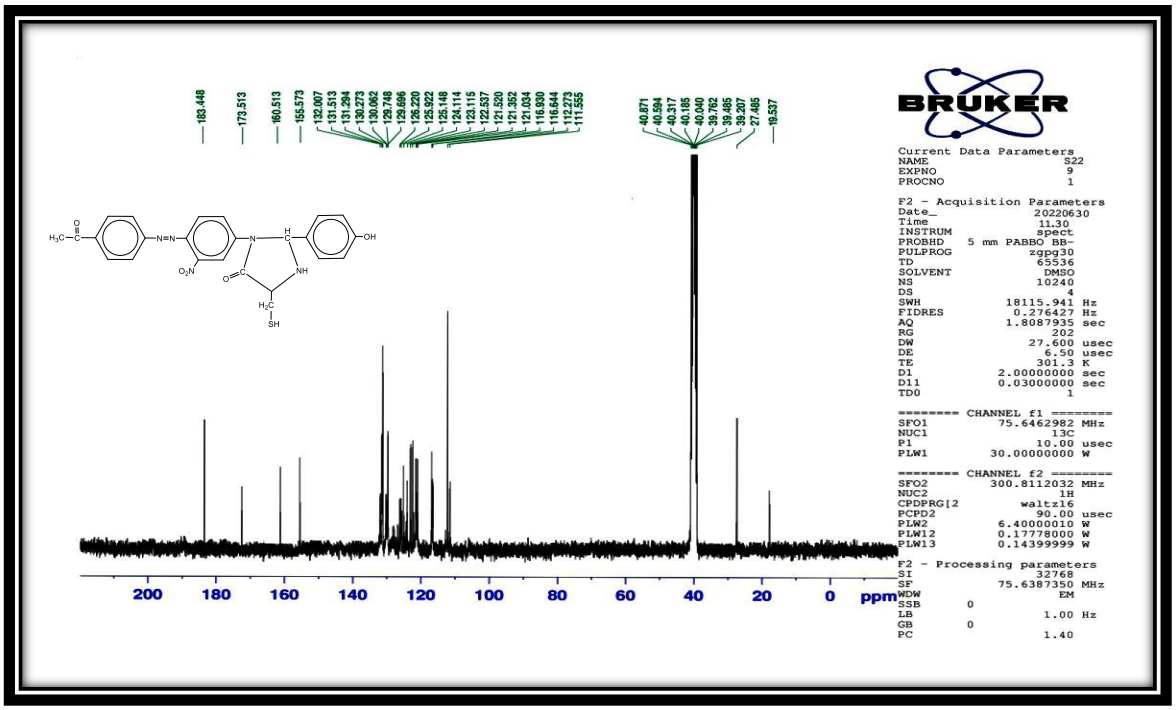


Figure 6 ; ^{13}C-NMR Spectrum for Compound S22

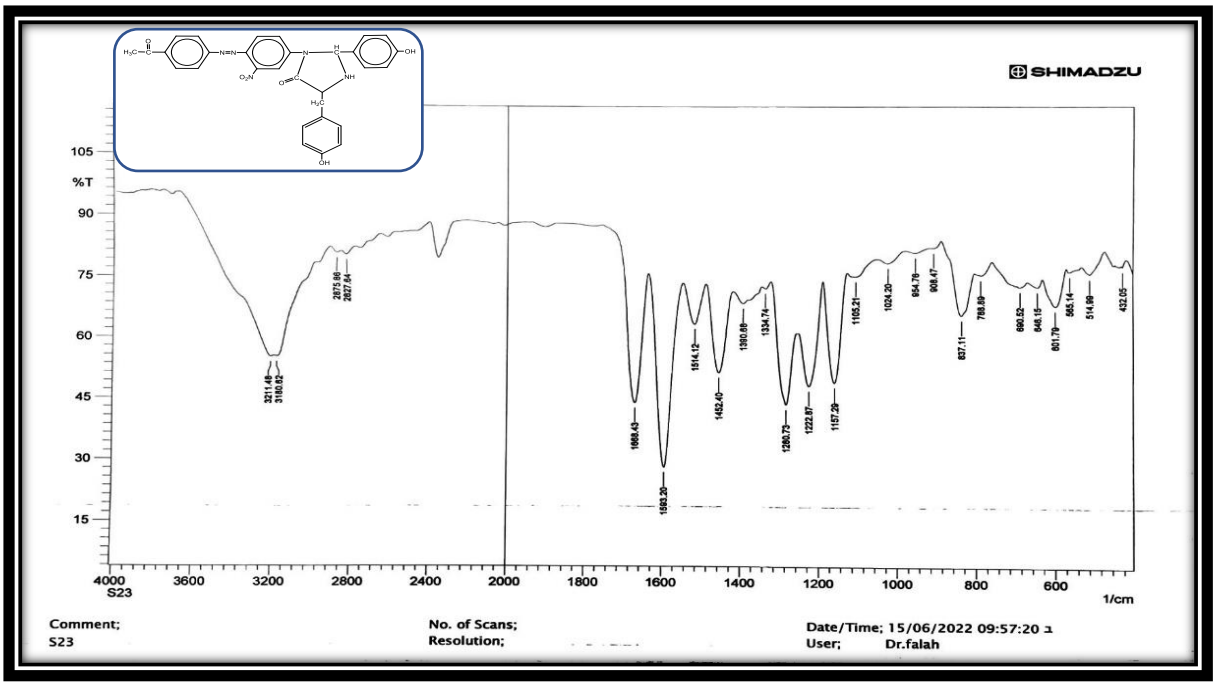


Figure 7 ;FTIR Spectrum for Compound S23

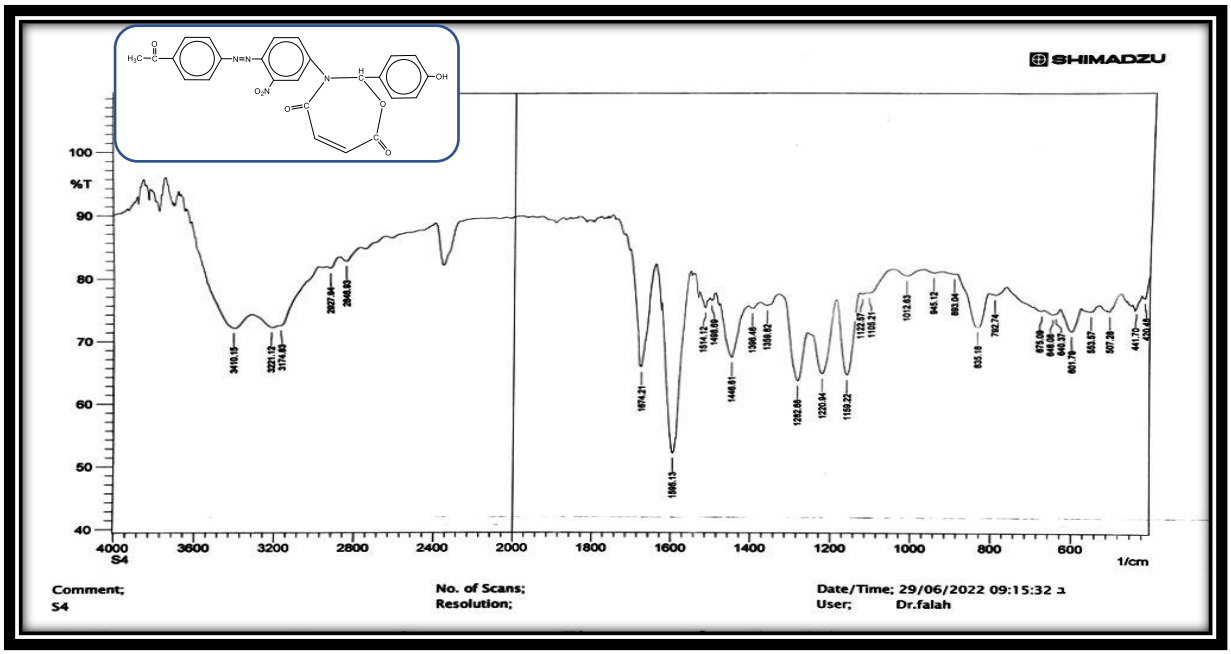


Figure 8 ;FTIR Spectrum for Compound S24

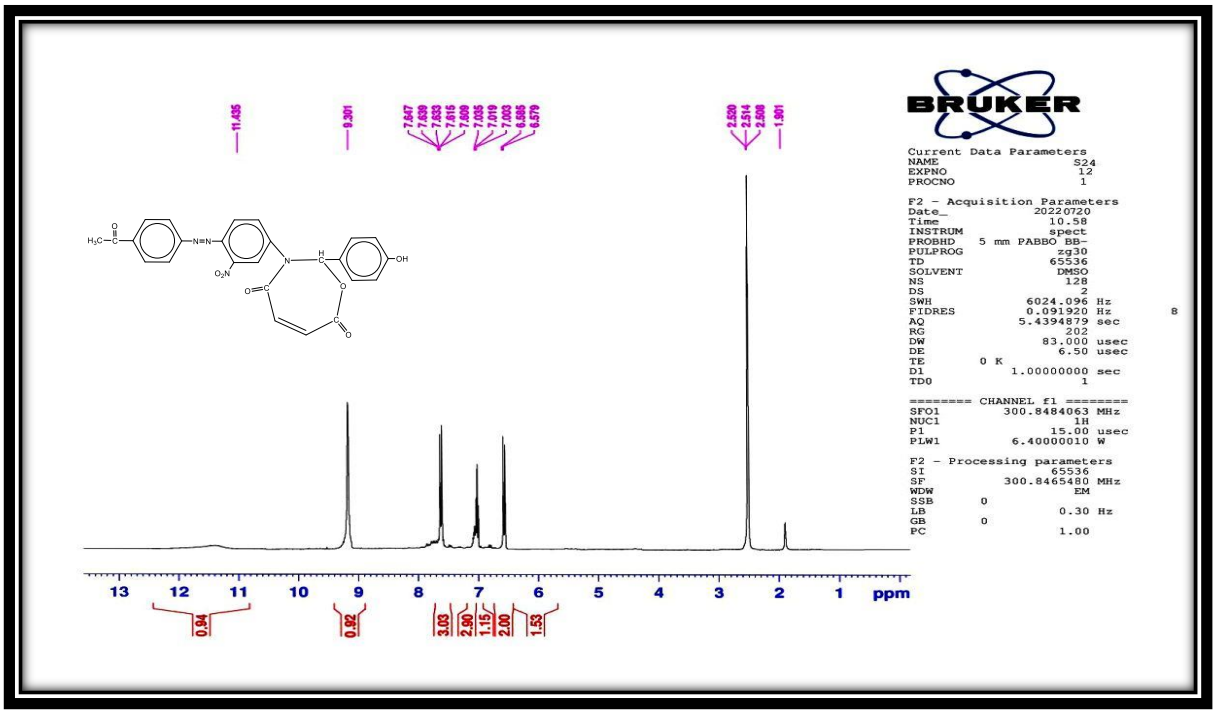


Figure 9 ; ^{1}HNMR Spectrum for Compound S24

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