Synthesis and Characterization of some new heterocyclic derivatives from terphthaldehyde and study of their biological activity

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ABSTRACT:
In this study, some new heterocyclic compounds have been synthesized including the preparation of some chalcone from the reaction terphthadehyde with two moles of ketone derivative *p*-hydroxy acetophenone in a basic medium, After that . The stage includes the preparation of new heterocyclic compounds five-membered (pyrazole, Isoxazole) and six-membered (oxazine, thiazine). The prepared compounds were characterized by FT-IR,1H-NMR, and 13C-NMR techniqes, in addition to their melting points and TLC (Thin Layer Chromatography).Finally,the prepared compounds are tested against Gram-positive and Gram-negative bacteria to study their biological activity.

KEY WORDS: Terphthaldehyde, Chalcones , thiazine, oxazine, pyrazole and Isoxazole) , Antibacterial activity

1. INTRODUCTION:

Chalcones are aromatic ketones compounds that form one of the main classes of flavonoids[(1)]. They were named by Kostaneki and Tambor[(2)]. The reaction is called Aldol condensation and Claisen-Schimdt condensation [(3)]. Chalcones are linked to two aromatic rings by three aliphatic carbon atoms[(4)] They are compounds known as unsaturated carbonyl compounds that contain an active group (-CO-CH= CH-),which is responsible for the various biological activities in chalcone compounds. Chalcones are unique compounds associated with several vital activities. The compounds whose main structural part is chalcone have a variety of biological and pharmacological efficacy[(5)] as anti-Antifungal[(6)] , anti -microbial, anti-tumor, anti-malarial[(7)] and anti-viral.

As for is a heterocyclic five-ring compound consisting of three carbon atoms and two nitrogen atoms, as the site (1,2- diazole) was called pyrazole[8]. Pyrazole was synthesized by E. Buchner by heating pyrazole 3.4.5.-tricarboxylic acid[9]pyrazole has a wide range of applications[10] . Isoxazole is one of the five heterocyclic rings, including isoxazole containing two heterogeneous atoms, an oxygen atom, and a nitrogen atom, in addition to three carbon atoms. Bioactive drugs such as antibacterial[11], antimicrobial, antiviral, anticancer[12], anti-inflammatory[13], anticoagulant, antidiabetic[14] analgesic, anti-Alzheimer's[15]and insecticide .As for the six membered, they are heterocyclic compounds that contain two heterocyclic atoms of nitrogen and oxygen. As for the oxazines, they are classified according to the location of the heterocyclic nitrogen atom in the hexagonal ring into (1,2-oxazine[16], 1,3-oxazine[17], 1,4-oxazine)[18]containing two heterocyclic atoms nitrogen and sulfur called thiazines[19] are classified according to the position of the heterocyclic nitrogen atom in the hexagonal ring into (1,2-thiazine, 1,3-thiazine, 1,4- Thiazine)[20]

2. Experimental:

3. 2.1 Materials and Instruments

Reagents and reactants are used as obtained from commercial suppliers without further purification. The solvents were previously purified. The purity of the derivatives and the course of the reaction were monitored using Thin layer chromatography on silica gel G (Merck grade) with a mixture of ethanol and benzene as the mobile phase. Melting points were measured in open capillaries, with the help of a melting point (Stuart) apparatus (SMP30, England) pronounced in ï °C and uncorrected. The infrared (IR) spectra were recorded on a Shimadzu Prestige-21 spectrophotometer using potassium bromide (KBr pellets) and the values in cm^{-1}, 1 H NMR and 13 CNMR derivative spectra were recorded on a Bruker (Avance III, Bruker 300MHz NMR Spectrophotometer using TMS as an internal standard and values are expressed in ppm at University of Tehran – Iran

3.2 Preparations of chalcone

Synthesis of chalcone [21]

1,1'-(1,4-phenylene)bis(3-(4-hydroxyphenyl)prop-2-en-1-one) {Z}

Dissolve (1.088g ,0.008mole) of ketone derivative (*p*-hydroxy acetophenone) in(25mL) of absolute ethanol with continuous stirring until dissolution on the magnetic stirrer for a period of (30 min) at room temperature, then (5mL) of sodium hydroxide solution was added At a concentration of (10%), then (0.536g,0.004mole)

of terphthaldehyde was slowly added to the prepared solution through the first step with continuous stirring for (12hrs) on a magnetic stirrer at room temperature, and the course of the reaction was followed up by technical means. (TLC) using a solution of (Ethanol Absolute : dry benzene 2:4). Then the product was cooled, filtered, and recrystallized using ethanol absolute. The physical properties are listed in the **table1**

Synthesis of oxazine [22]

4,4'-(1,4-phenylenebis(2-amino-6H-1,3-oxazine-6,4-diyl))diphenol {**Z1**}

A mixture of chalcone (0.185g ,0.0005 moles) in 30ml of ethanol absolute was placed in a round bottom that (0.06g ,0.001mole) of urea was added with 5ml of %10 sodium hydroxide, the mixture was stirred at room temperature for 3 hours, then 20ml of cold water was added, the mixture was stirred for one hour and cooled in an ice- bath for two days. The reaction was followed by (TLC) using (2:4) (Ethanol: dry benzene) then the product was cooled, filtered, and recrystallized using ethanol absolute. The physical properties are listed in the **table1**

Synthesis of thaizine [22]

4,4'-(1,4-phenylenebis(2-amino-6H-1,3-thiazine-6,4-diyl))diphenol {***Z2***}

A mixture of chalcone (0.185g ,0.0005 mole) in 30ml of ethanol absolute was placed in a round bottom that (0.076g ,0.001mole) of thiouera was added with 5ml of %10 sodium hydroxide, the mixture was stirred at room temperature for 3 hours, then 20ml of cold water was added, the mixture was stirred for one hour and cooled in an ice- bath for two days. The reaction was followed by (TLC) using (2:4) (Ethanol: dry benzene) then the product was cooled, filtered and recrystallized using ethanol absolute. The physical properties are listed in the **table1**

Synthesis of isoxazole [23]

4,4'-(1,4-phenylenebis(isoxazole-3,5-diyl))diphenol {***Z3***}

A mixture of chalcone (0.185g, 0.0005 mol), hydroxylamine hydrochloride (0.069g, 0.001 mol) and sodium acetate (0.082g,0.001mole) in ethanol absolute (25 mL) was refluxed for 16 hours, then the reaction mixture was cooled. The precipitate obtained was filtered, washed and recrystallized from ethanol absolute. The physical properties are listed in the **table1**

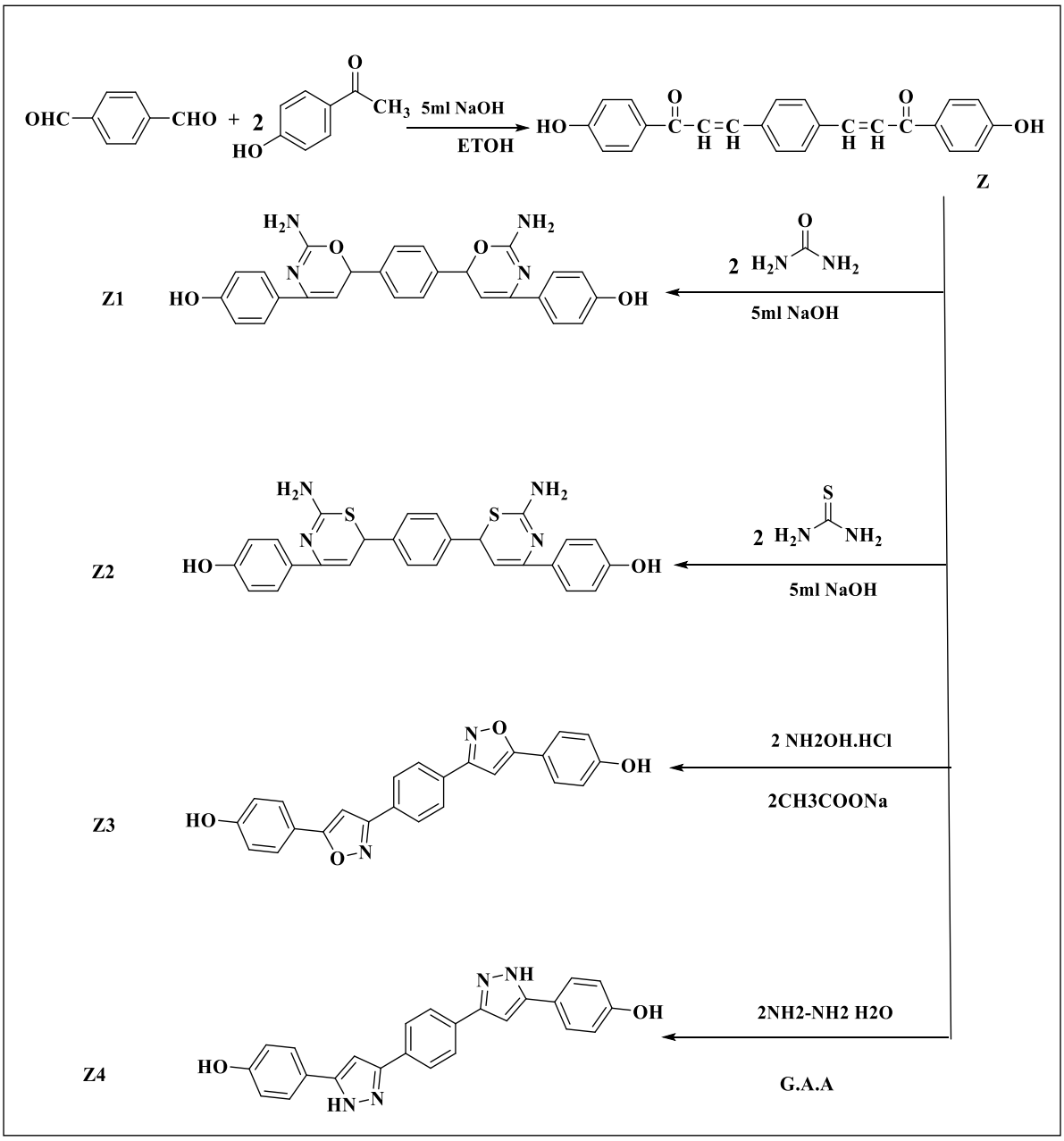
Synthesis of pyrazole

4,4'-(1,4-phenylenebis(1H-pyrazole-3,5-diyl))diphenol {***Z4***}

This five-chalcone derivative were previously prepared using (0,185g ,0.0005mol) of each with the addition of (0.05gm,0.001mol) of aqueous hydrazine (NH-NH H_2O) add 2-3drop G.A.A 30 ml of ethanol absolute, then the reaction mixture was ascended for a period of (20hr), the reaction was followed by (TLC) using (2:4) (Ethanol: dry benzene), then the product was cooled, filtered, and recrystallized using ethanol absolute. The physical properties are listed in the **table1**

Result and discussion:

The general synthetic method employed a synthesis procedure for the chalcone derivatives established on Claisen-Schmidt condensation terphthadehyde molecule with two moles of ketone derivative p-hydroxy acetophenone in a basic medium. In absolute ethanol, with 10% sodium hydroxide as a catalyst, New heterocyclic derivatives such as Oxazine, Thiazine, isoxazole and Pyrazole were synthesized by a reaction between chalcones with urea, thiourea, hydroxylamine hydrochloride and hydrazine hydrate, respectively **(Scheme 1)**. The structures of all the heterocyclic derivatives synthesized in this research were established based on FTIR and 1H-NMR and 13C-NMR spectral data.



Scheme(1): Synthesis of heterocylic compounds(five and six)membered rings from chalcone(Z)

1,1'-(1,4-phenylene)bis(3-(4-hydroxyphenyl)prop-2-en-1-one) {Z}

(FT-IR)Spectrum. As for the chalcone (Z) appearance band at 1674 Cm^{-1} (νC=O) appearance refers to the carbonyl from of chalcone, 3415 Cm^{-1} (ν OH)Hydroxyl ,3057 Cm^{-1} (ν CH) aromatic, 2905 Cm^{-1} (ν CH)aliphatic ,1593-1556 Cm^{-1} (ν C=C)Alkene group , 1510-1477 Cm^{-1} (ν C=C) aromatic. When we used the (1H-NMR) spectrum and [DMSO-*d6*] as a solvent, we created several singes for protons such as (CH=CH) to the chalcone ring at (6.99), 7.1-7.3 (Ar-H) protons of Benzene ring, 11.53 (OH) proton of phenol. When we used the (13C-NMR) spectrum and [DMSO-*d6*] as a solvent, we created several singes for carbon such as 121-131 (C-Ar) carbon of Benzene ring,153 (C-OH),163 (C=C) carbon of Alkene,186 (C=O) carbon of ketone

4,4'-(1,4-phenylenebis(2-amino-6H-1,3-oxazine-6,4-diyl))diphenol {Z1}

The chalcone (Z) condensation with urea affords oxazine derivative (Z1), FT-IR shows the disappearance of carbonyl chalcone and the appearance of NH_2 two bands symmetric and asymmetric 3346-3278 Cm^{-1} (νNH_2) primary amine ,3444 Cm^{-1} (ν OH)Hydroxyl ,3030 Cm^{-1} (ν CH) aromatic, 2905 Cm^{-1} (ν CH)aliphatic , 1658 Cm^{-1} (ν C=N) endocylic ,1618Cm^{-1} (ν C=C)Alkene group , 1587-1498 Cm^{-1} (ν C=C)aromatic. When 1H-NMR (DMSO-*d6*)of compound (Z1): 6.3(NH_2) protons amine group related of oxazine 7.4-7.9 (Ar-H) protons of Benzene ring, 11.54 (OH) proton of phenol.When 13C-NMR(DMSO-*d6*)of compound (Z1): 121-131 (C-Ar) carbon of Benzene ,87(C-O)endo cyclic oxazine ,153 (C-OH),161 (C=N) endo cyclic oxazine

4,4'-(1,4-phenylenebis(2-amino-6H-1,3-thiazine-6,4-diyl))diphenol {Z2}

The chalcone (Z) condensation with Thiourea affords thiazine derivative (Z2), FT-IR shows the disappearance of carbonyl chalcone and the appearance of NH_2 two bands symmetric and asymmetric 3180-3280 Cm^{-1} (νNH_2) primary amine, 3387 Cm^{-1} (νOH)Hydroxyl,3039 Cm^{-1} (ν CH) aromatic, 2910 Cm^{-1} (ν CH)aliphatic , 1651 Cm^{-1} (ν C=N)endocylic , 1612 Cm^{-1} (ν C=C)Alkene group , 1585-1454 Cm^{-1} (ν C=C)aromatic. When 1H-NMR (DMSO-*d6*)of compound (Z2): 6.3(NH_2) protons amine group related of thazine ,7.1-7.6 (Ar-H) protons of Benzene ring, 11.53 (OH) proton of phenol .When 13C-NMR (DMSO-*d6*)of compound (Z2): 121-131 (C-Ar) carbon of Benzene ,59 (C-S)endo cyclic thazine ,155 (C-OH),161 (C=N) endo cyclic thazine

4,4'-(1,4-phenylenebis(isoxazole-3,5-diyl))diphenol {Z3}

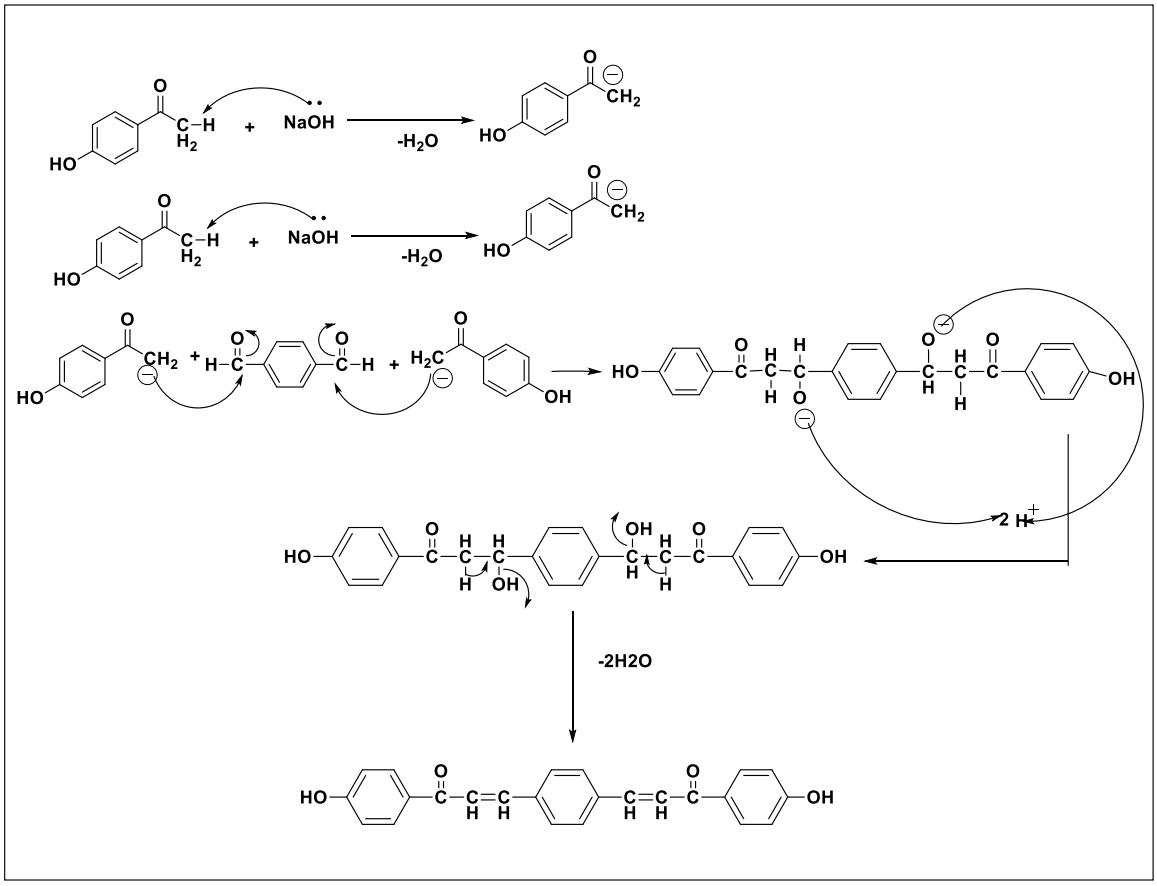
Spectra (FT-IR) ,3412 Cm^{-1} (ν OH)Hydroxyl ,3040 Cm^{-1} (ν CH) aromatic, 2925 Cm^{-1} (ν CH) aliphatic , 1647 Cm^{-1} (ν C=N) endocylic , 1604 Cm^{-1} (ν C=C)Alkene group , 1516 Cm^{-1} (ν C=C) aromatic. 1168 Cm^{-1} (ν C-O) . When 1H-NMR (DMSO-d6) of compound (Z3): 7.1-7.3 (Ar-H) protons of Benzene ring , 11.19 (OH) proton of phenol. When 13C-NMR (DMSO-d6)of compound (Z3): 112-142(C-Ar) carbon of Benzene ,156 (C-OH),162 (C=N) endo cyclic isoxazole

4,4'-(1,4-phenylenebis(1H-pyrazole-3,5-diyl))diphenol {Z4}

Spectra (FT-IR), 3425 Cm^{-1} (ν OH)Hydroxyl ,3354 Cm^{-1} (νNH)secondary amine ,3053 Cm^{-1} (ν CH) aromatic, 2933-2864 Cm^{-1} (ν CH)aliphatic , 1583 Cm^{-1} (ν C=N)endocylic ,1421 Cm^{-1} (ν C=C)

Table1: Physcical properties for compounds (Z-Z4)

No.	M.F	M.wt g/mol	M.p˚C	Color	R_f	Yield %
Z	$C_{24}H_{18}O_4$	370.40	209-211	orange	0.67	79%
Z1	$C_{26}H_{22}N_4O_4$	454.49	225-227	Yellow	0.71	64%
Z2	$C_{26}H_{22}N_4O_2S_2$	486.61	218-220	Yellow light	0.84	73%
Z3	$C_{24}H_{16}N_2O_4$	396.40	189-191	Brown	0.66	82%
Z4	$C_{24}H_{18}N_4O_2$	394.43	174-176	Yellow dark	0.75	69%



Scheme 2: : mechanism synthesis of chalcone derivative(Z)

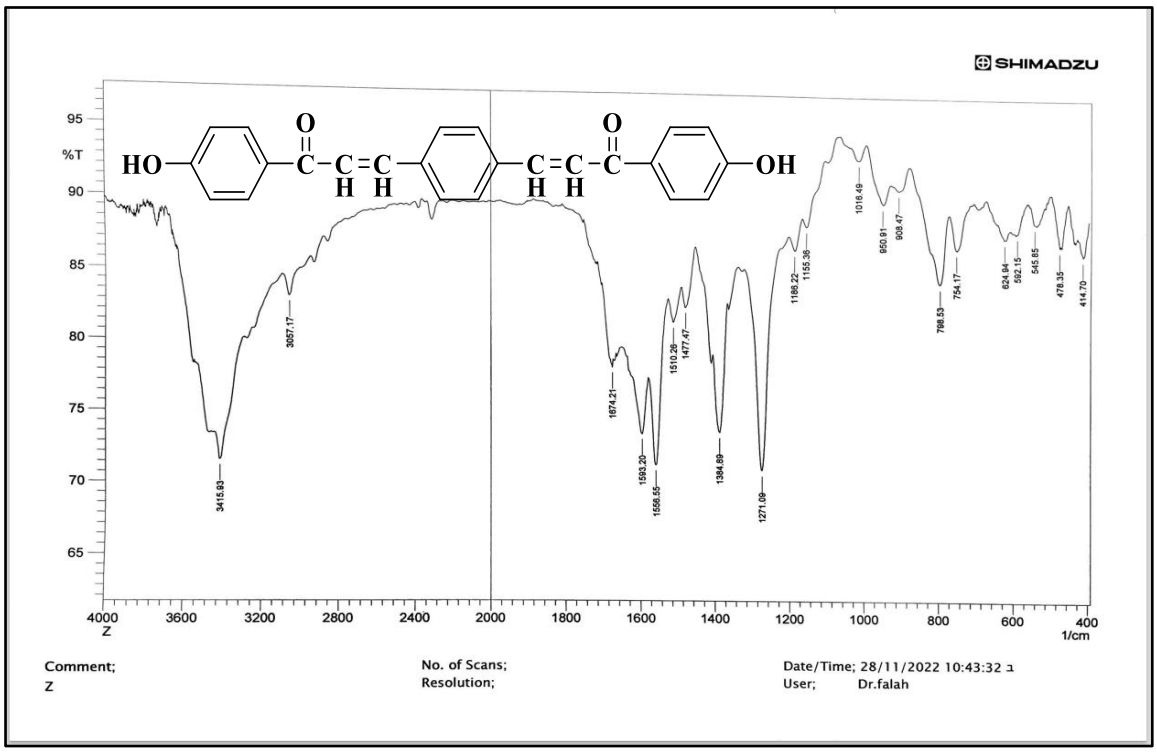


Figure (1):FT-IR spectrum for compound(Z)

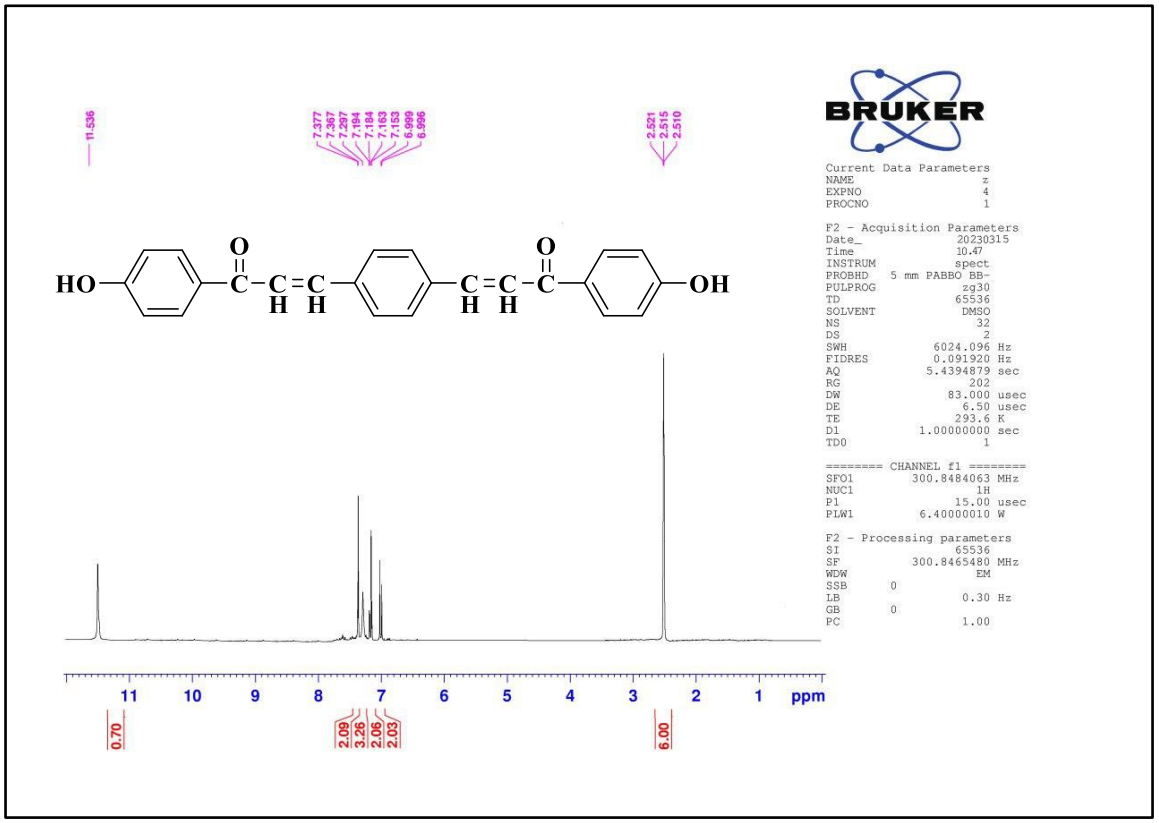


Figure (2):^{1}H-NMR spectrum for compound(Z)

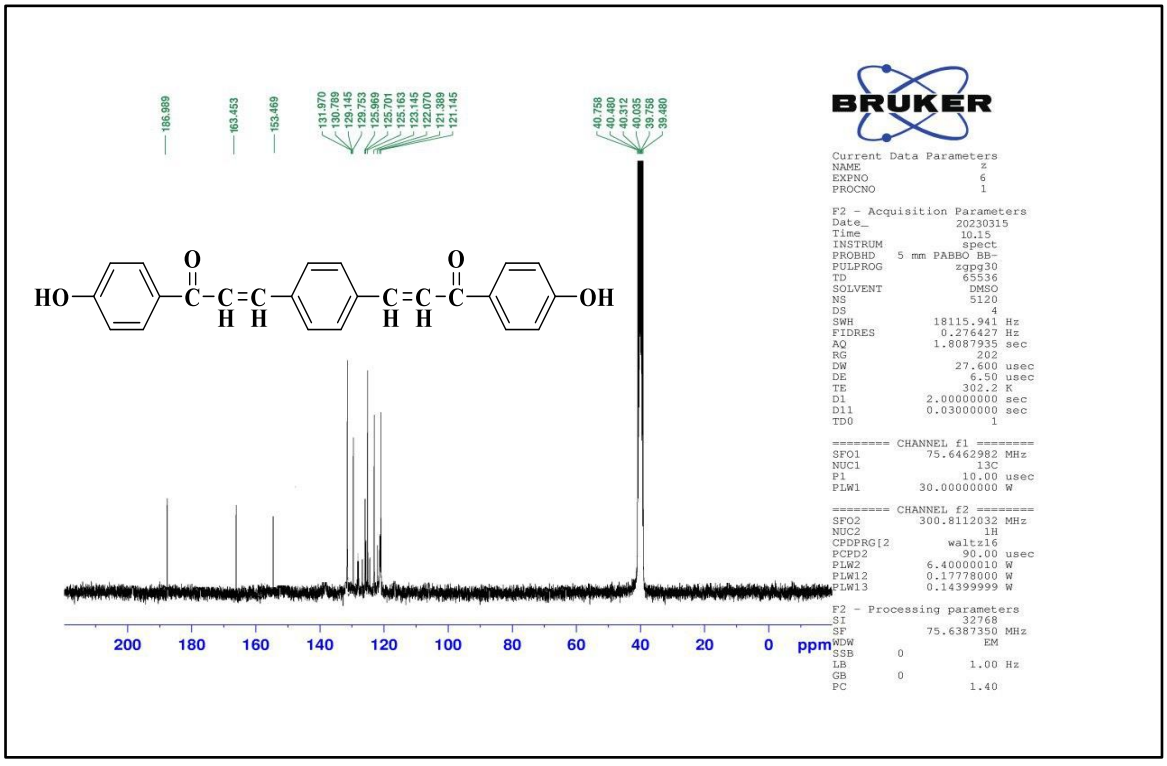


Figure (3):^{13}C-NMR spectrum for compound(Z)

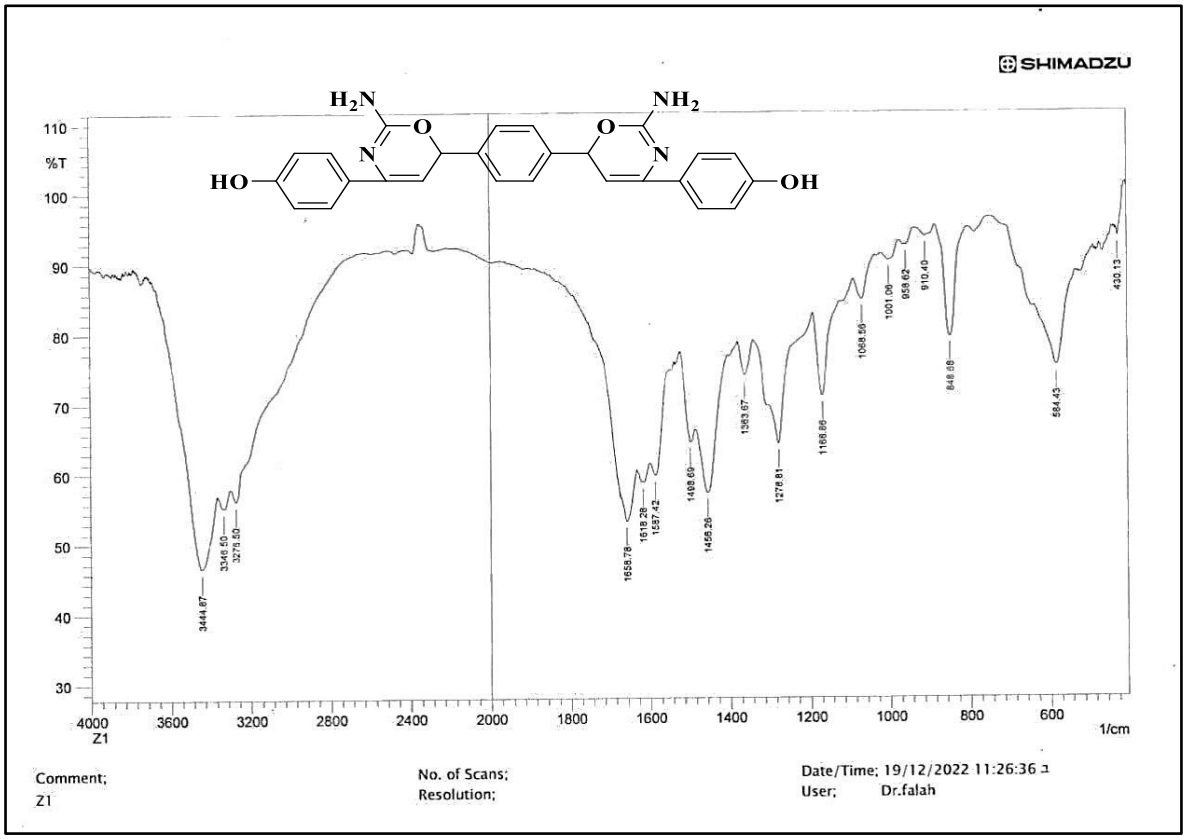


Figure (4): FT-IR spectrum for compound(Z1)

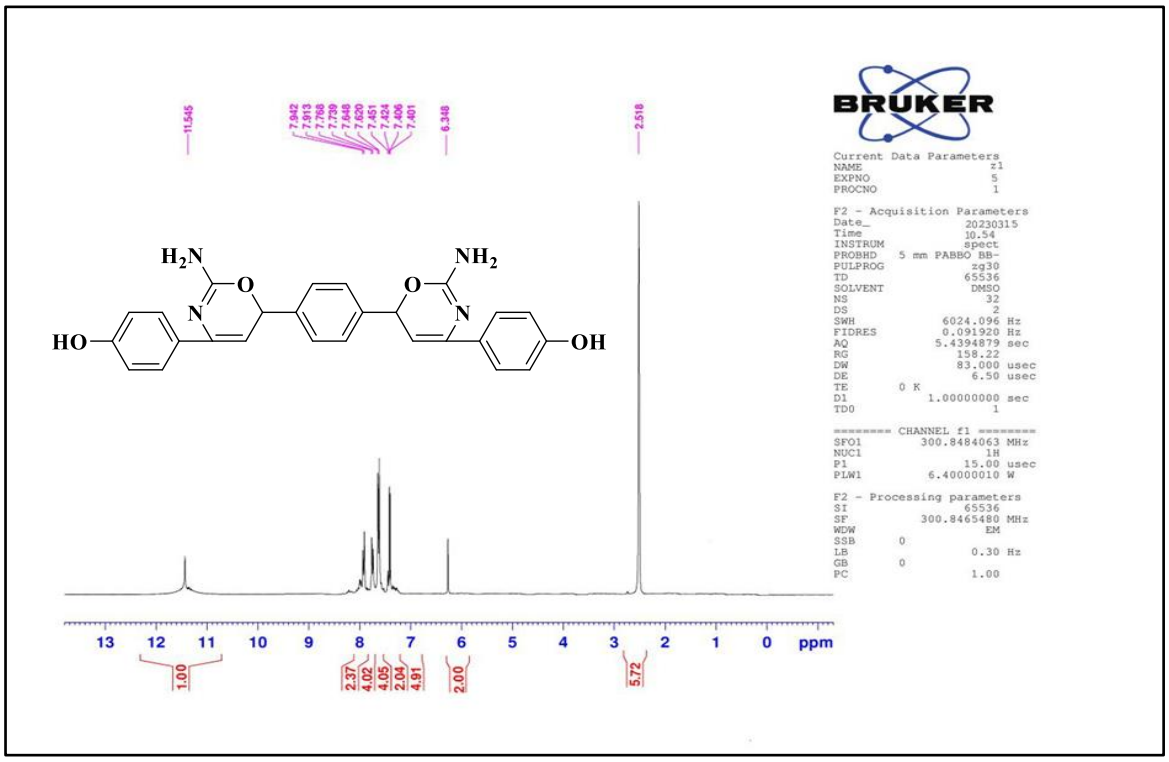


Figure (5):^{1}H-NMR spectrum for compound(Z1)

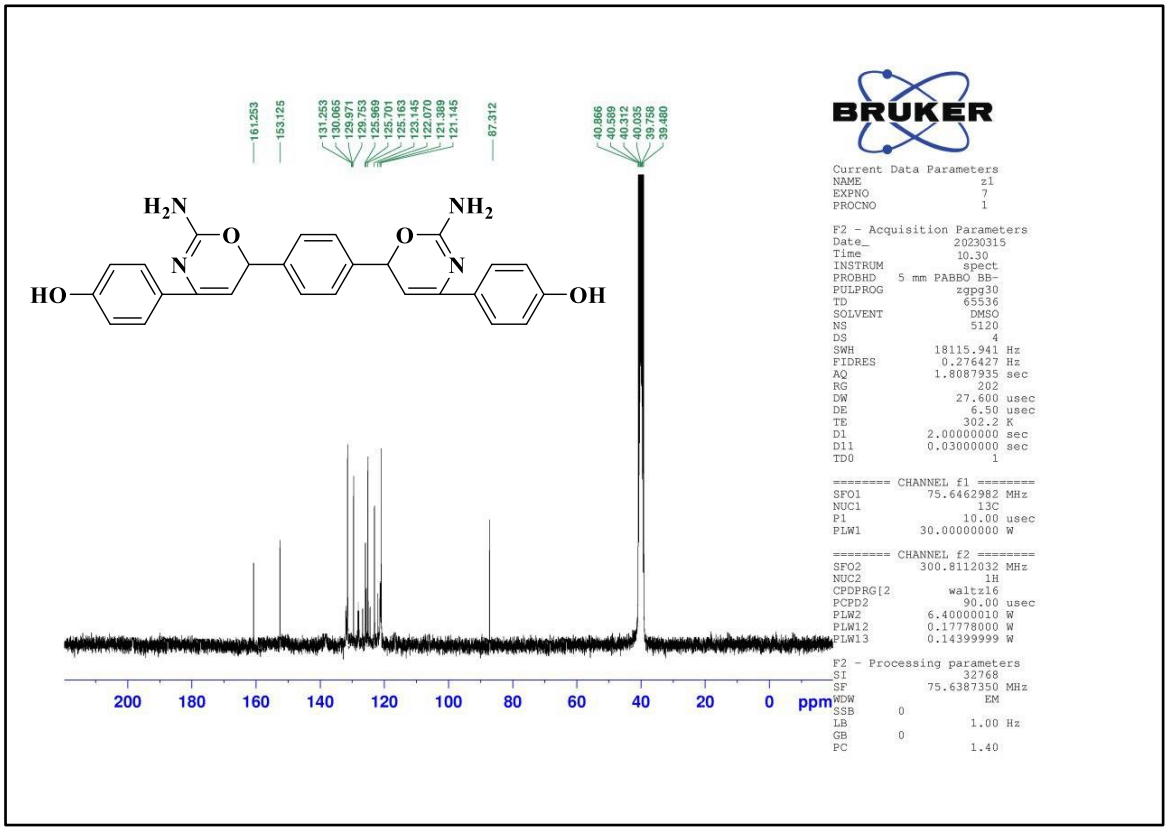


Figure (6):^{13}C-NMR spectrum for compound(Z1)

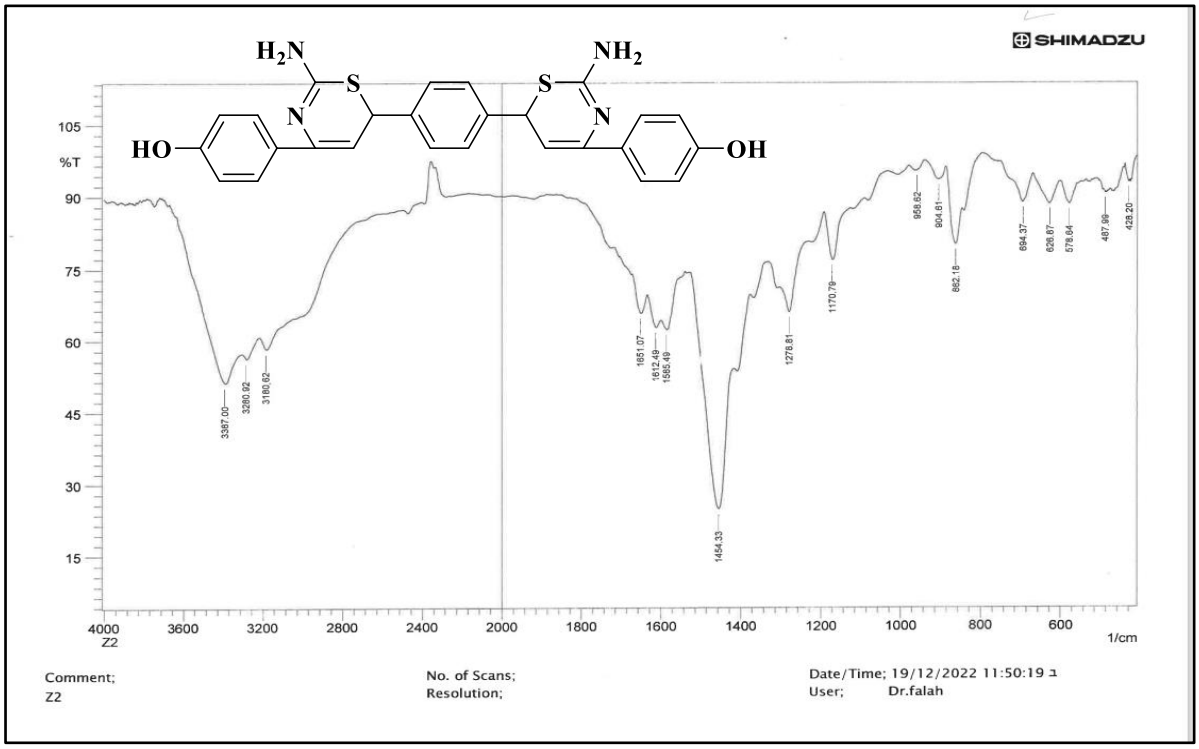


Figure (7):FT-IR spectrum for compound(Z2)

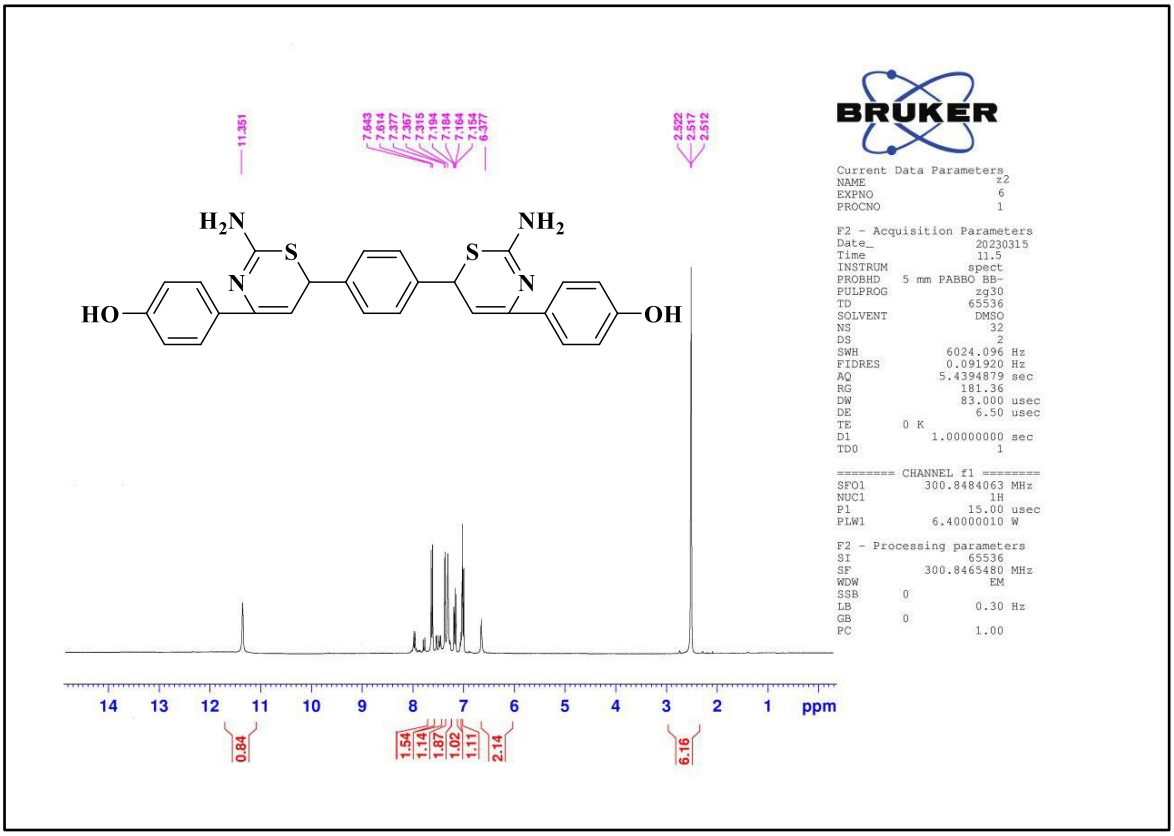


Figure (8):^{1}H-NMR spectrum for compound(Z2)

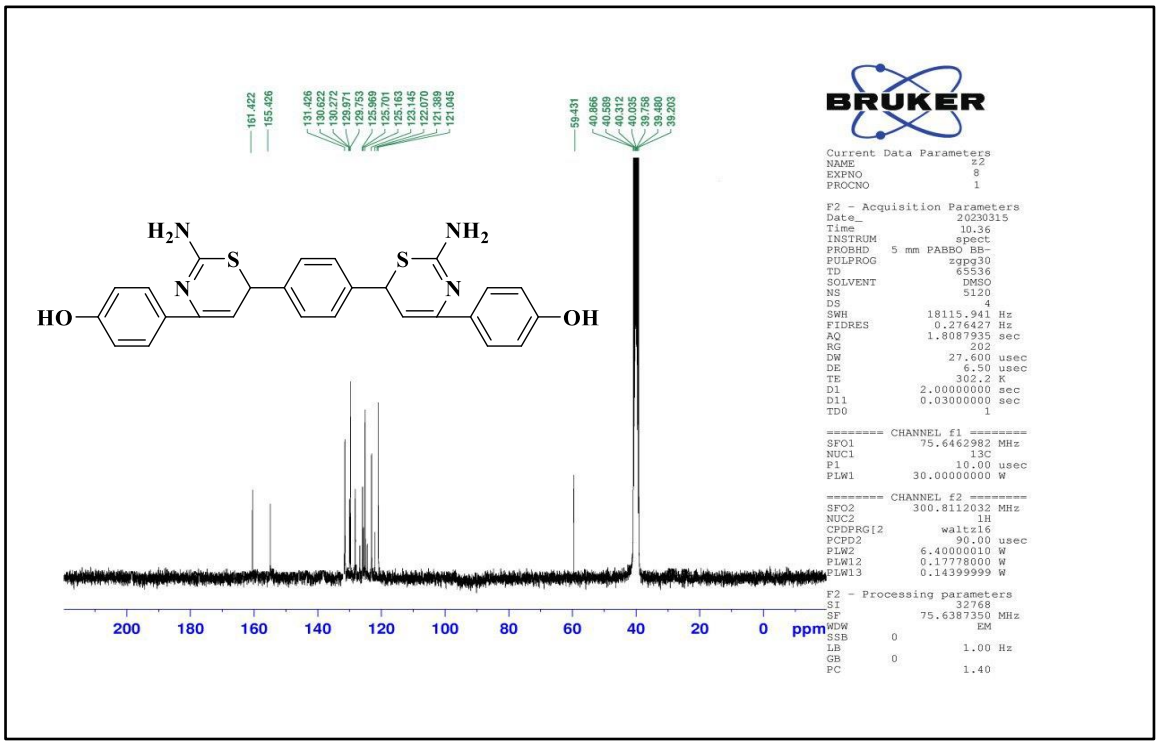


Figure (9):^{13}C-NMR spectrum for compound(Z2)

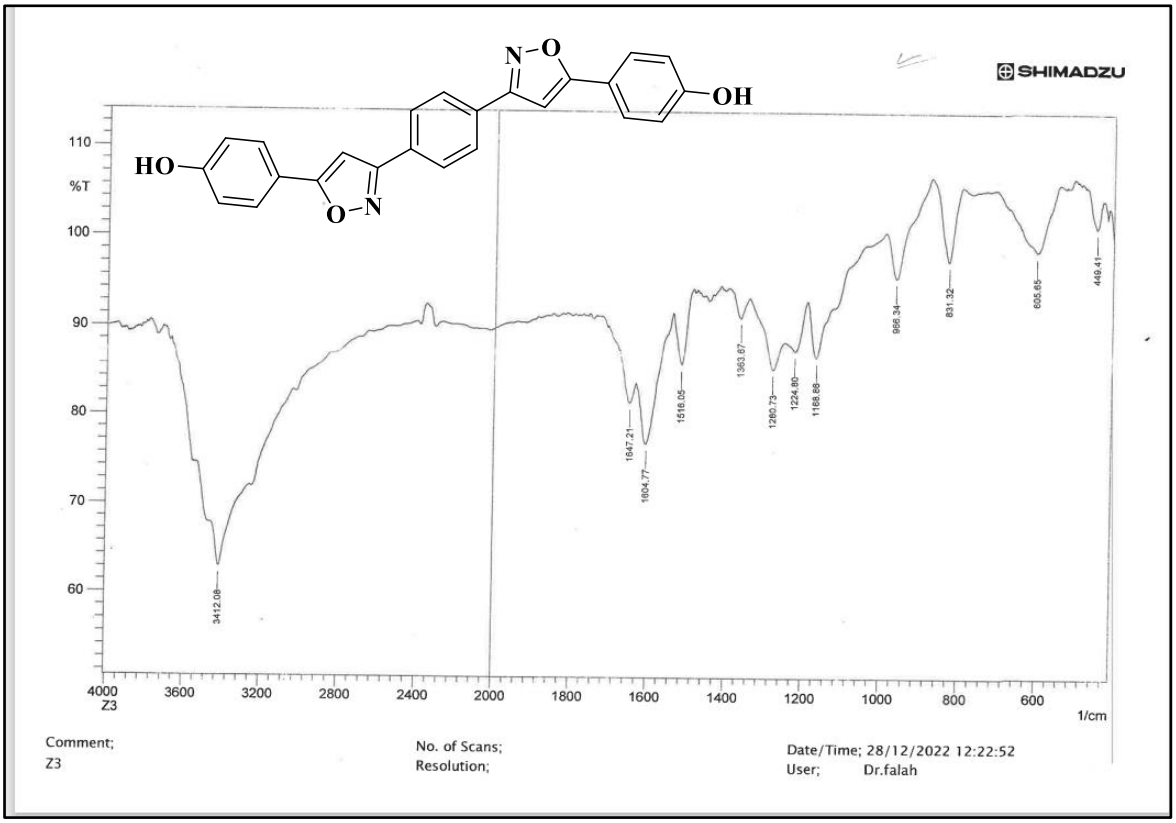


Figure (10):FT-IR spectrum for compound(Z3)

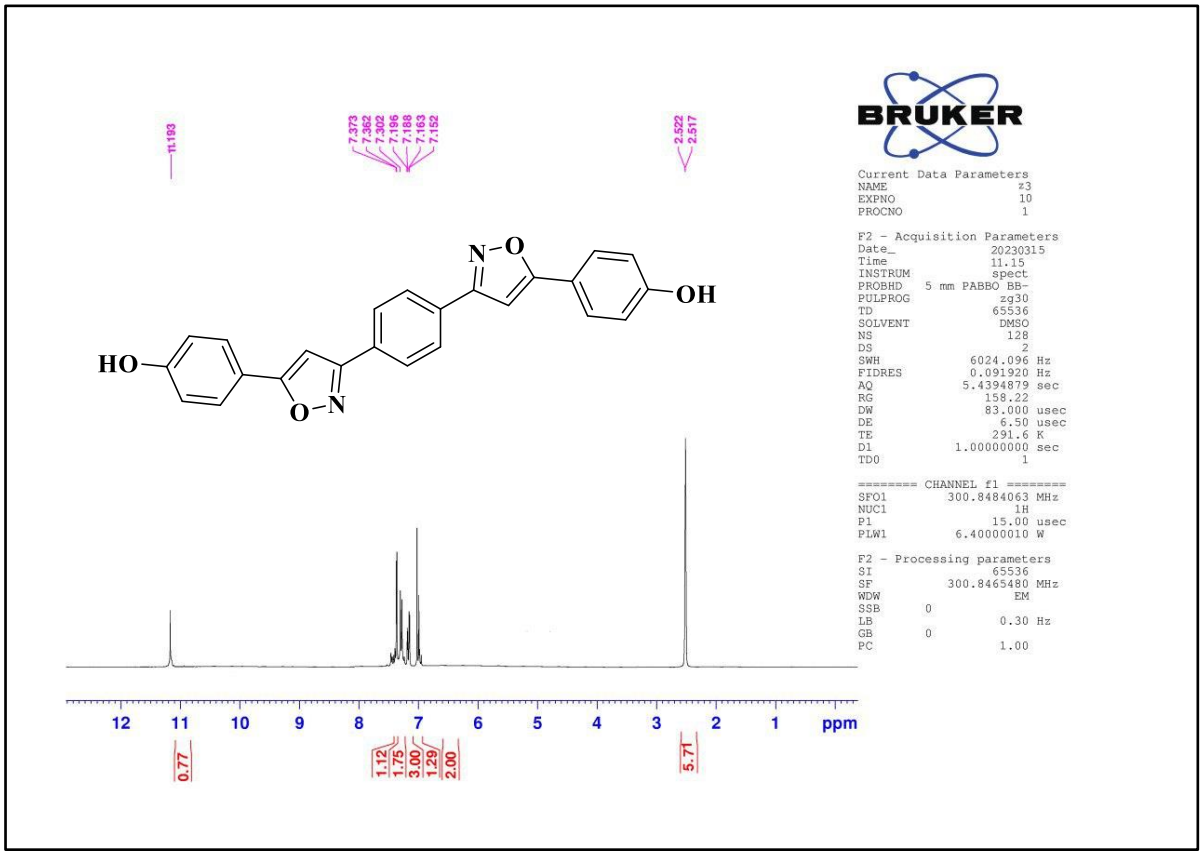


Figure (11):^{1}H-NMR spectrum for compound(Z3)

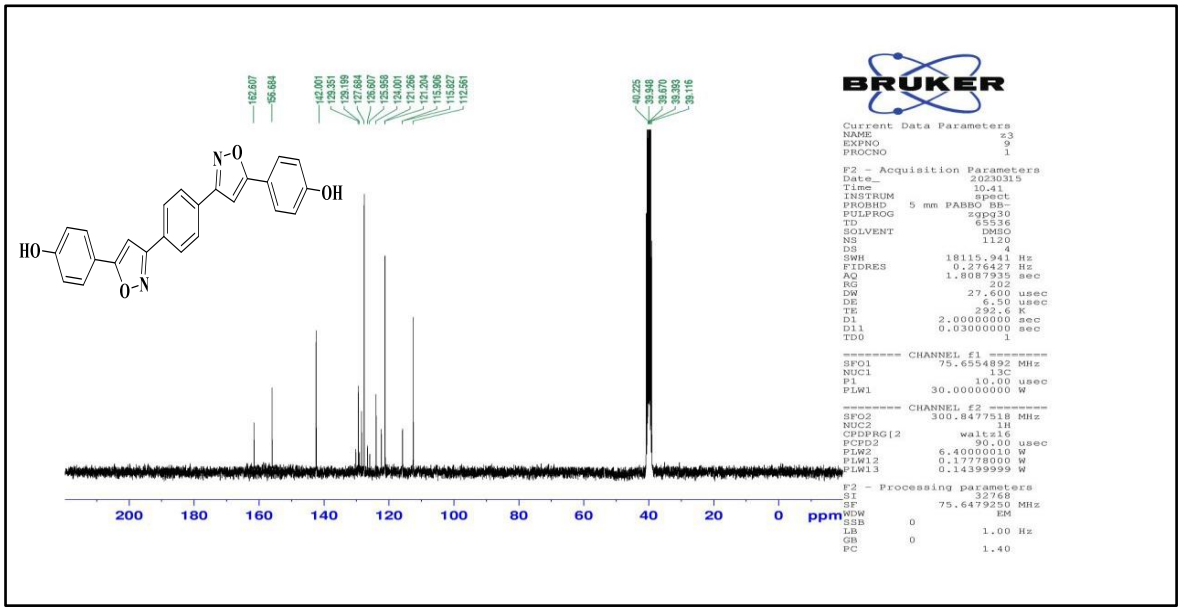


Figure (12):^{13}C-NMR spectrum for compound(Z3)

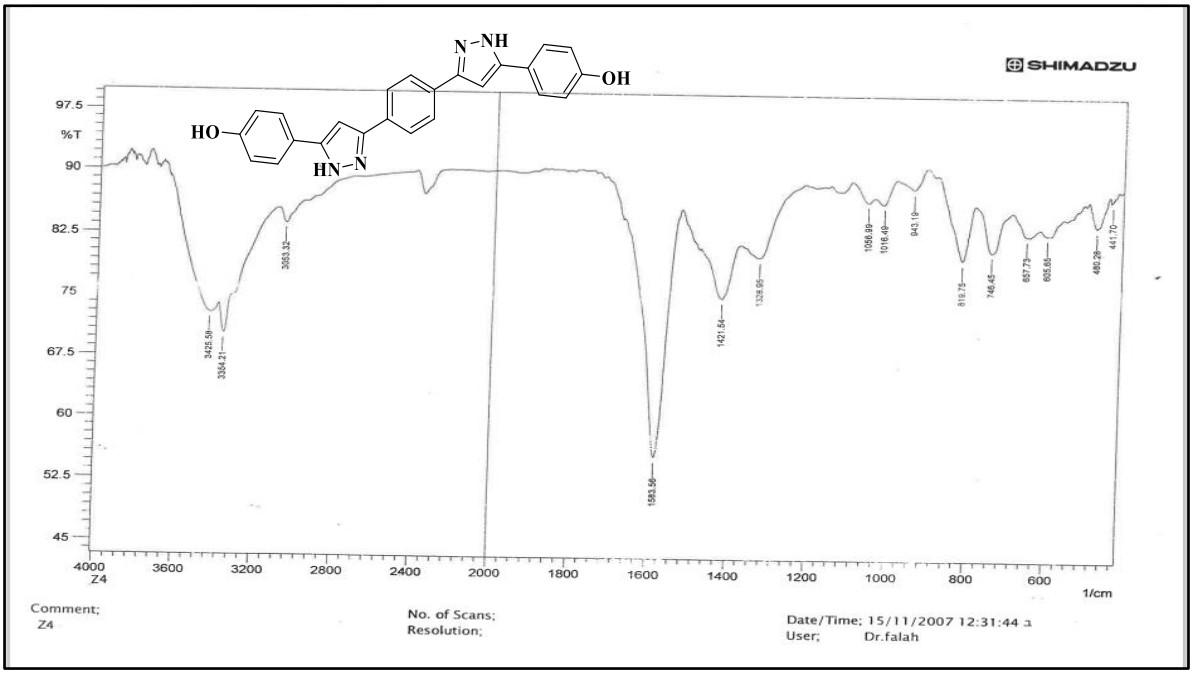


Figure (13):FT-IR spectrum for compound(Z

Biological activity[24]

Studies on microbes have found that many types of bacteria cause most of the infectious diseases of living organisms, which has sparked the interest of many researchers in developing antibiotics by preparing new derivatives that inhibit these types of bacteria . This method aims to study the biological activity of some new compounds of two types of isolated pathogenic bacteria, which are Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia Coli*). Under the same

conditions as the DMSO solvent, most of the compounds selected for the study of biological effects showed varying degrees of high and medium positive inhibition results. Some of the compounds had little or no effect on the growth of the bacteria selected for the study, due to differences in the binding groups and compounds used and as shown in Table (3- 3).

Table (3-3): The biological activity of the compounds

compounds	Anti-Bacterial Activity			
	Escherichia coil		*Staphylococcus aureus*	
	0.1mg/ml	1mg/ml	0.1mg/ml	1mg/ml
Z	12	16	10	11
Z1	11	15	11	12
Z2	0	0	13	15

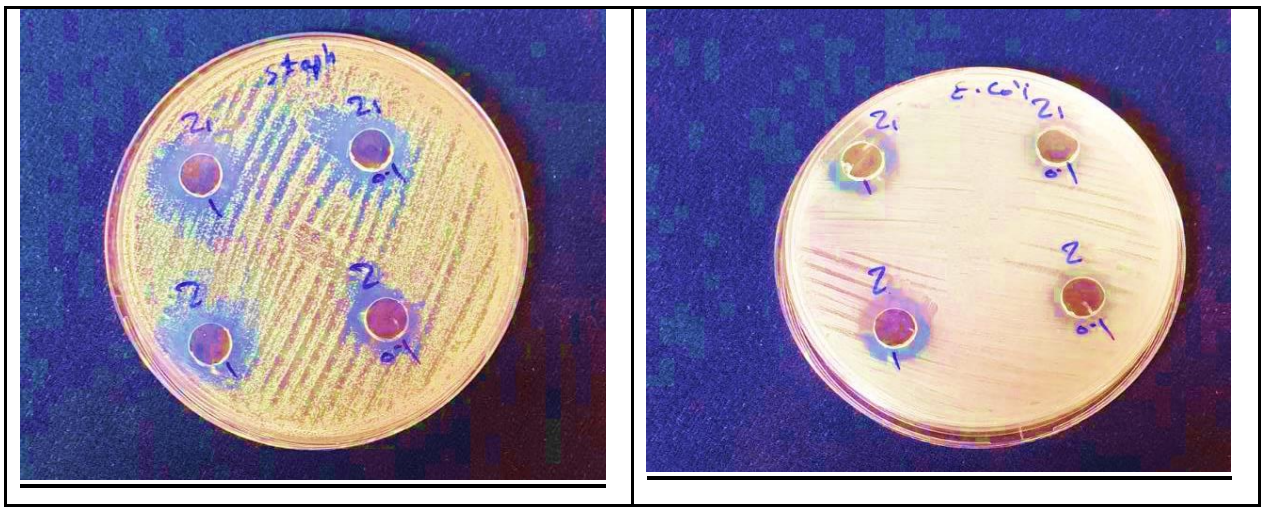


Figure (14): The Anti-Bacterial activity

Conclusion:

In conclusion, the synthesis method for the chalcone derivatives was established using two moles of the ketone derivative *p*-hydroxy acetophenone and terphthadehyde molecules by Claisen-Schmidt condensation in a basic medium. Chalcones were reacted with urea, thiourea, hydroxylamine hydrochloride and hydrazine hydrate to produce new heterocyclic derivatives including oxazine, thiazine, Isoxazole and pyrazole in ethanol absolute, with 10% sodium hydroxide as a catalyst. Based on FT-IR, 1H-NMR and 13C-NMR spectral data, the structures of all the heterocyclic derivatives synthesized in this study were established.

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