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Synthesis , Chalcone and Study of the Biological Activity for Different Heterocyclic Compounds from the Chalcone Derivative.

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الخلاصة :

تضمنت هذه الدراسة تحضير وتشخيص مركب chalicon المحضر من تفاعل terephthalaldehyde مع 4-bromoasetopheone وعدد من المركبات الحلقية غير المتجانسة منه بتفاعل مع كل من (Thiourea)، (urea), (2,4-dinitrophenyl hydrazine) و المركبات التي تم تحضيرها هي (1,2-diamine benzene) (Pyrazole ، Oxazine ، Thiazine ، diazepine). تم تشخيص المركبات المحضرة جميعها بواسطة طيف الاشعة تحت الحمراء (FT-IR) وطيف الرنين النووي المغناطيسي للبروتون ^{1}H.NMR بعدها تم دراسة الفعالية الحيوية لهذه المركبات و تأثيرها على نوعين من البكتريا (*staphylococcus, Escherichia coli*) .

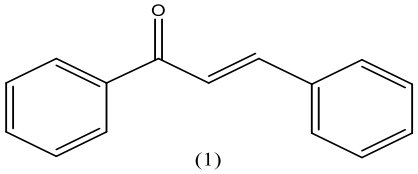
ABSETRACT :

This study included preparation and characterization of the chalicon compound that which prepared from reaction terephthalaldehyde with 4-bromoasetopheone and also prepared a number of heterocyclic compounds from the chalicon derivative with (Thiourea), (urea), (2,4-dinitrophenyl hydrazine),(1,2-diamine-benzene) these dreivatives are (Thiazine, Oxazine, Pyrazole, diazepine). All the prepared compounds were diagnosed by means of the FT-IR spectra and the proton ^{1}H.NMR spectra. Then the bio-activity of these compounds and their effect on two types of bacteria (staphylococcus, Escherichia coli) were studied some compounds were identified that have a strong inhibitory effect.

Key words: Chalcone , Thiazine, Oxazine, Pyrazole, diazepine

INTRODUCTION

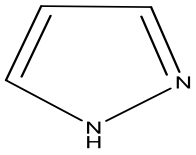
Aromatic ketones (α-unsaturated carbonyl compounds, β-form the main classes of Flavonoids flavonoids [(1)]. Formed by condensation of Aryl ketone with Aromatic aldehyde, in the presence of a base in a polar solvent [(2)]. Addition of reaction by aldol and Claisen condensation [(3)] General Schmidt [(4)] Claisen - Schimdt condensation Chalcons are prepared by two aromatic rings by three aliphatic carbon atoms [(5)] , connecting you to the general formula Structuer (1) : -



(1)

chalcones are unique compounds associated with many biological activities. The compounds whose structural component is chalcon possesses various biological and pharmacological activity as anti-inflammatory, anti-microbial, analgesic, anti-tumor, anti-malarial, anti-viral, anti-oxidant and anti-cancer [(6)].

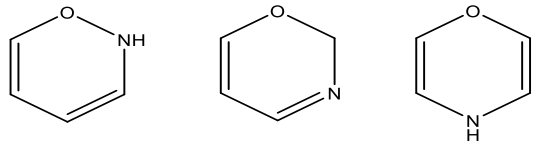
Pyrazole are pentagonal heterocyclic compound consisting of three carbon atoms and two nitrogen atoms at the position 1 and 2 (1,2-diazole or 1, 4-diazo) possessing the molecular formula ($C_3H_4N_2$) and also called (cyclopentadiene) , and it has the structural formula as shown in Formul Structueres (2) as follows: -



pyrazole
(2)

Azoles-1,2 derivatives containing pyrazole, isoxazole and isothiazole occupied a distinct place in the preparation and synthesis of new bioactive compounds that carry out remarkable pharmaceutical activities such as drugs where their activity was examined against three types of human cancer cells, namely breast cancer (MCF-7). Non-small cell lung cancer (NCI-H460) and central nervous system cancer (SF-268) were found to have significantly higher inhibitory effects against these three types of cancer cells [(7)]. And agricultural chemicals. As a result there was an increasing interest among chemists in myo-medicinal formulation in developing methods of rapid synthesis to these heterocyclics reported in the literature up to 2012 [(8)]

Oxazine are Hexagonal polyunsaturated heterocyclic compounds possessing one oxygen atom and one nitrogen atom [(9)] there are three isomers of oxazine (1,3-Oxazine) (1,2-Oxazine), 1,4-Oxazine)) depending on the location of the oxygen and nitrogen atom. And on the site of the binary [(10)] in the composition as shown in Structueres (3) as follows: -

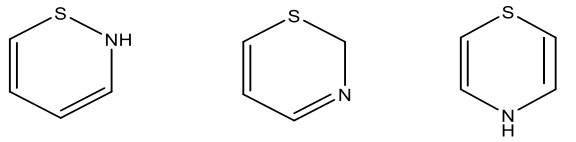


1,2-Oxazine 1,3-Oxazine 1,4-Oxazine

(3)

The worlds Holy and Cope were the first to attend the aromatic oxazines in 1944 in the Mannich reaction [(11)]. Most of these compounds are 1,2-Oxazine and 1,4-Oxazine, and the most important of them are morpholine or tetrahydro1-, 4-oxazine (a colorless, miscible liquid. In water) [(12)] 1,3-Oxazine is also the item that has received more attention because it forms an important layer for pharmacological activities, as well as natural and non-natural products such as antitumor, antimicrobial, anti-HIV, and anti-malarial agents that have therapeutic potential for the treatment of Parkinson's disease [(13)]. As well as the presence of oxygen, nitrogen and double bonds in its composition, it possesses a wide range of important biological properties [(14)] such as analgesic and anti-inflammatory, anti-leukemia [(15)] and anti-malaria, antipyretic, anti-rheumatic [(16)], antispasmodic, antioxidant and bacteriostatic [(17).]

Thiazine are Hexagonal heterocyclic compounds contain one sulfur atom, one nitrogen atom and four carbon atoms and there are several isomers of thiazines depending on the position of the nitrogen and sulfur atoms on the ring [(18)] . As shown in Structueres (4) the following: -

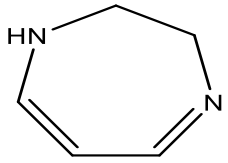


1,2-Thiazine 1,3-Thiazine 1,4-Thiazine

(4)

Thiazines are used as intermediate compounds in the preparation of many different organic derivatives [(19)]. The 1,3-Thiazine derivative possesses an NCS component that is used in the fields of medicinal and pharmaceutical chemistry, as it has recorded a number of vital activities as anti-fungal, anti-cellulitis, anti-bacterial, anti-inflammatory, sedative, hypnotic and immunosuppressive agent in addition to that it has been used in digestive disorders. Or prevention of diabetes and antioxidants [(20)]. 1,3-Thiazine is the most important form of Cephalosprins [(21)].

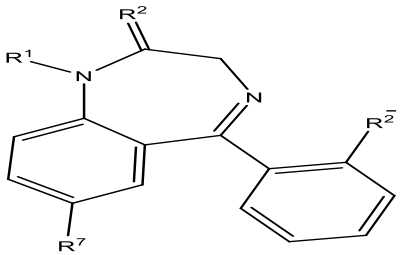
1,4-diazepine is one of the seven unsaturated heterocyclic compounds. It contains two nitrogen atoms that are in site (1) and site (4) in addition to the presence of five carbon atoms [(22)]. Which has the following Structuere (5): -



diazepine

(5)

1,4-diazapines are used in the health field, as they were used as antipsychotics, anxiolytics, worms, anticonvulsants, antibacterial and anti-fungi, as well as anticancer and compounds derived from it, such as benzodiazepines, more widely around the world where they were discovered by chance as studies have shown that their chemical composition has a pharmacological property Structuere (6):-

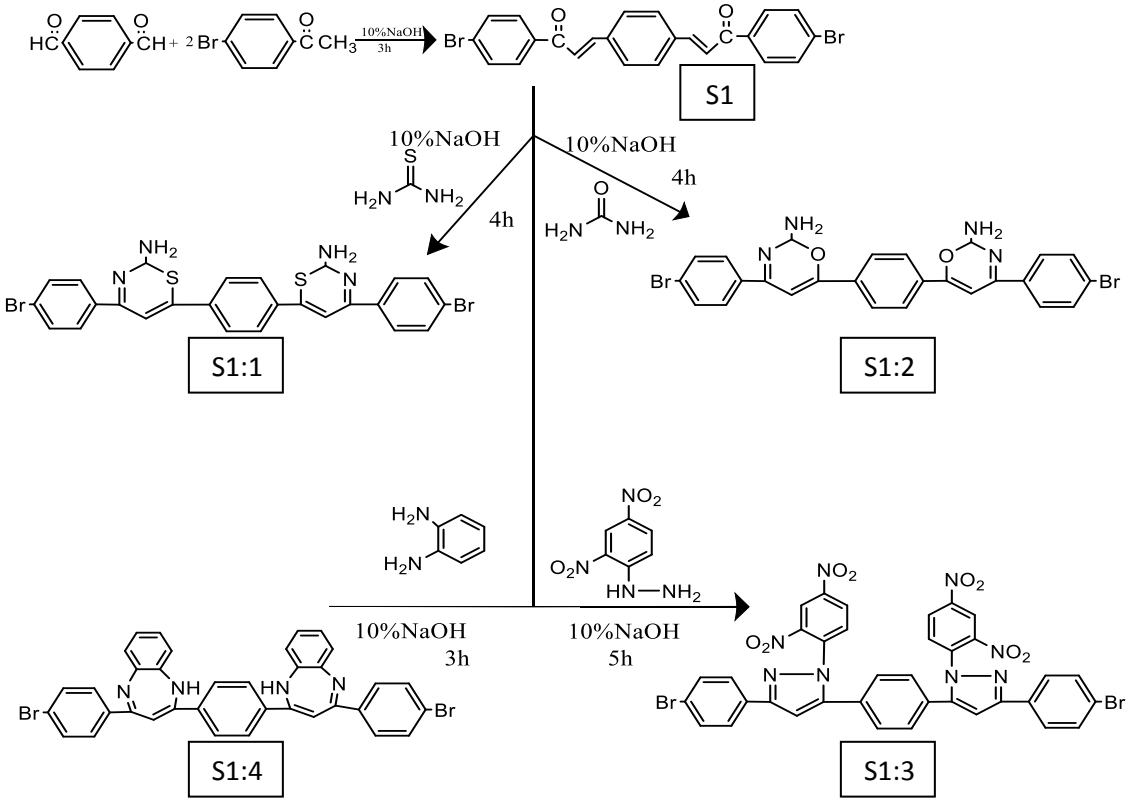


(6)

PRACTICAL PART

First step: preparation of chalcone S1 by treating (terephthalaldehyde) with (4-bromoacetopheone).

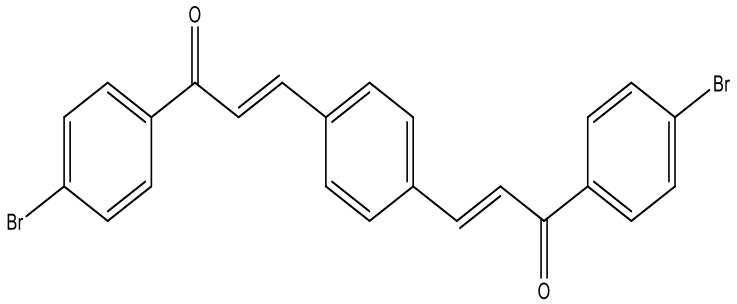
Second step: Preparing the heterocyclic hexocyclic compound of the thiazine derivative (S1: 1) by treating the chalcone (S1) compound with theorem.
Third step: Preparing (S1: 2) exocyclic compound for the derivative (Oxazine) by treating chalicon (S1) with urea.
Fourth step: Preparation of (S1: 3) heterocyclic cyclic compound by treating the chalcone compound prepared in the first step (S1) with (2,4-dinitrophenyl) hydrazine.
Fifth step: Preparation of (S1: 4) heterocyclic heterocyclic compound by treating the chalcone compound prepared in the first step (S1) with (1,2-diamine-benzene).
The path can be illustrated in the following chart



Synthesis of (1,4-phenylene)bis(1-(4-bromophenyl)prop-2-en-1-one)

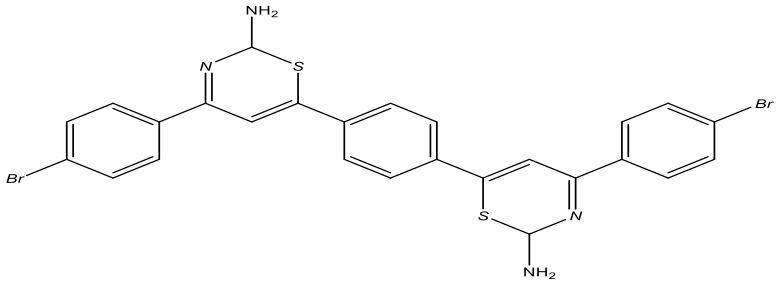
Dissolve (3.98 g, 0.02mole) of (4-bromoacetophenone) in (40mL) of Absolute Ethanol with continuous stirring on a Hot plate magnetic stirr for a period of (30min) at laboratory temperature, then add (1.34g, 0.01mole)of (1,4-dicarbaldehyde-benzene) (10mL)From a solution of sodium hydroxide at a concentration of 10%, then it was added and slowly for the solution prepared from the first step with continuous stirring on a magnetic stirring device at room temperature for a period of (5hr).

The reaction was followed by the (TLC) technique using (2mL Ethanol: 3mL benzene), then the reaction mixture was neutralized with dilute (HCl) acid, the sediment was filtered and washed after the sedimentation process was completed with cold distilled water several times, then it was dried and re-crystallized using Absolute Ethanol. The physical properties are listed in Table No (1).



Synthesis of 6,6'-(1,4-phenylene)bis(4-(4-bromophenyl)-2H-1,3-thiazin-2-amine

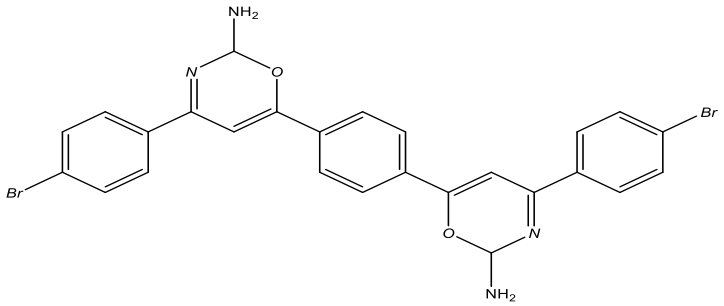
Dissolve (0.496g, 0.001mol) of compound (S1) previously prepared in (20mL of Absolute Ethanol) with continuous stirring on Hot plate magnetic stirr until melting, after which (0.152 g, 0.002mol) of thiourea were added to the prepared chalcone solution (S1) slowly with stirring Then ،



(5mL) of sodium hydroxide solution was added at a concentration of (10%) while the reaction mixture remained on the magnetic stirring device for(3hr). Then I added (20 mL) of cold distilled water and then returned the reaction flask on the magnetic stirring device again for one hour The reaction was followed by the (TLC) technique using (1 mL Ethanol: 4ml dry benzene), and then the reaction mixture was cooled to (5) C˚ for a period of (24hr), the sediment formed was filtered and then dried and re-crystallized using absolute ethanol. The physical properties are listed in the table No (1).

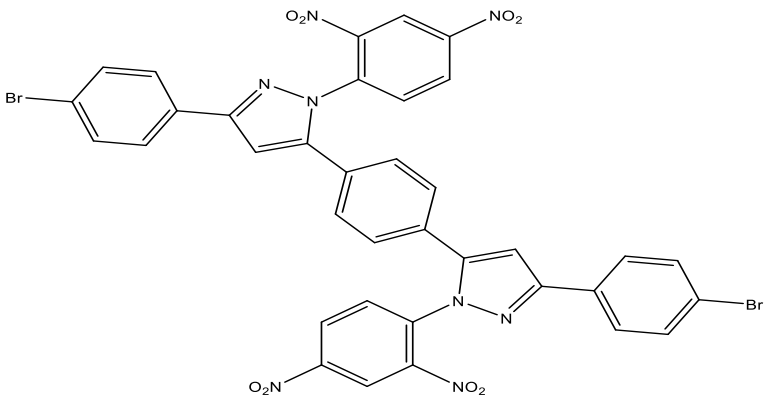
Synthesis of 6,6'-(1,4-phenylene)bis(4-(4-bromophenyl)-2H-1,3-oxazin-2-amine)

Dissolve (0.496g, 0.001mol) of compound S1 previously prepared in (20mL of Absolute Ethanol) with continuous stirring on a Hot plate magnetic stirr until melting, after which (0.12 g, 0.002mol) of urea was added to the prepared chalcone solution (S1) slowly with stirring Then, (5mL) of sodium hydroxide solution was added at a concentration of (10%) while the reaction mixture remained on the magnetic stirring device for 3h. Then I added (20 mL) of cold distilled water and then returned the reaction flask on the magnetic stirring device again for one hour Then the reaction was followed by the (TLC) technique using (1 mL Ethanol: 4mL dry benzene), and then the reaction mixture was cooled to (5) C˚ for a period of (24hr). The sediment formed was filtered and then dried and recrystallized using absolute ethanol. The physical properties are listed in the table No. (1).



Synthesis of 1,4-bis(3-(4-bromophenyl)-1-(2,4-dinitrophenyl)-1H-pyrazol-5-yl)benzene

Dissolve (0.496g, 0.001mol) of compound(S1) previously prepared in (20mL of Absolute Ethanol) with continuous stirring on a Hot plate magnetic stirr until melting, after which(0.198g , 0.002mol) (2,4-dinitrophenyl)hydrazine was added to the prepared chalcone solution (S1) slowly with stirring Then, (5mL) of sodium hydroxide solution was added at a concentration of (10%) while the reaction mixture remained on the magnetic stirring device for 3hr. Then I added (20 mL) of cold distilled water and then returned the reaction flask on the magnetic stirring device again for one hour Then the reaction was followed by the (TLC) technique using (1 mLEthanol: 4mLdry benzene), and then the reaction mixture was cooled to (5) C˚ for a period of (24hr). The sediment formed was filtered and then dried and recrystallized using absolute ethanol. The physical properties are listed in the table NO.(1).



Synthesis of 1,4-bis(4-(4-bromophenyl)-1H-benzo[b][1,4]diazepin-2-yl)benzene

Dissolve (0.496g, 0.001mol) of compound S1 previously prepared in (20mL of Absolute Ethanol) with continuous stirring on Hot plate magnetic stirr until melting, after which (0.108g, 0.002mol) of (1,2-diamine-benzene) was added to the prepared chalcone solution (S1) slowly with stirring Then, 5ml of sodium hydroxide solution was added at a concentration of (10%) while the reaction mixture remained on the magnetic stir device for 3hr. Then I added (20 mL) of cold distilled water and then returned the reaction flask on the magnetic stirring device again for one hoer The reaction was followed by the (TLC) technique using (2 mL Ethanol: 3mL dry benzene), and then the reaction mixture was cooled to (5) C˚ for a period of (24hr), the sediment formed was filtered and then dried and re-crystallized using absolute ethanol. The physical properties are listed in the table NO.(1).

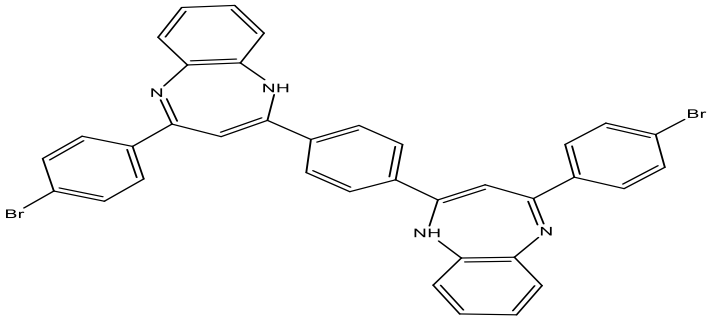


TABLE 1.the physical properties of compounds

No	M.f.	M.wt	mp (^{0}C)	Colors	Rf	Yield%	Time
S1	$C_{24}H_{16}O_2Br_2$	496.19	285-290	yellow	0.6	80	5hr
S1-1	$C_{26}H_{20}N_4S_2Br_2$	612.41	250-255 (decompose)	yellow	0.7	85	4hr
S1-2	$C_{26}H_{20}O_2N_4Br_2$	580.278	210-213	yellow	0.6	70	4hr
S1-3	$C_{36}H_{20}O_8N_8Br_2$	852.41	190-193	Dark Walnut	0.7	72	6hr
S1-4	$C_{36}H_{22}N_4Br_2$	670.40	180-184	walnut	0.6	75	5hr

Discussion the result of preparation Culture dishes for Biological Tests

Here the biological activity of chalcon and Heterocyclic compounds from with solutions of (1×10^{-3}M) and(5×10^{-3}M) by using (EtOH) solvent and studying its effect on two types of bacteria which are positive for *Staph .Aureus* for gramdye and negative for the *Escherichia Coli* gramdye. The amount of inhibition of the chalcon and Heterocyclic prepared compound (Zone of inhibition) in the ruler and the table 2 below shows that the vital amount of inhibition See Table 2.

TABLE 2. Illustrates the biological effectiveness of the compounds

(-) no inhibition , (+) 5-10 mm, (++) 15-20 mm

Compounds	*Staph .Aureus* 1×10^{-3}mol	*E. Coli* 1×10^{-3}mol	*Staph .Aureus* 5×10^{-3}mol	*E. Coli* 5×10^{-3}mol
S1	+	+	++	+
S1-1	++	-	++	-
S1-2	++	-	+	+
S1-3	+	-	+	+
S1-4	+	+	++	+

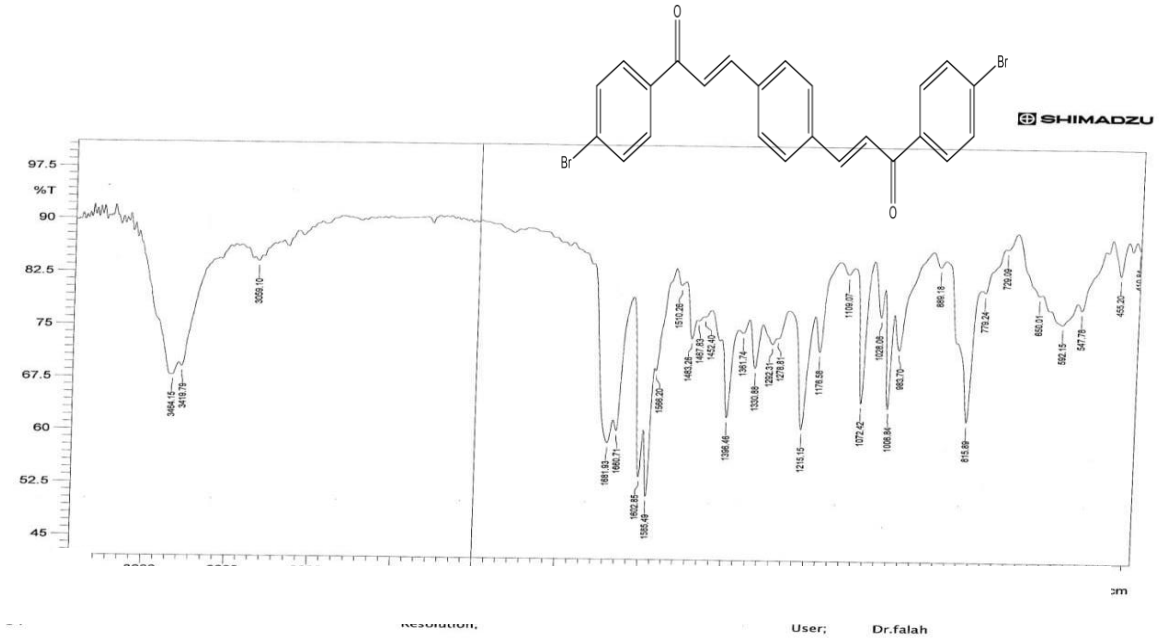


FIGURE 1. FT-IR spectrum for comp (S1)

Identification (S1) ,The FT-IR spectrum(cm^{-1}) **Figure 1**. Show bands at, (C = C $_{Alphtic}$ = 1585), (C=C $_{Aromatic}$ = 1602) , (C=O = 1681), (C-H $_{Alphtic}$ = 2940) and (C-H $_{Aromatic}$ = 3059).

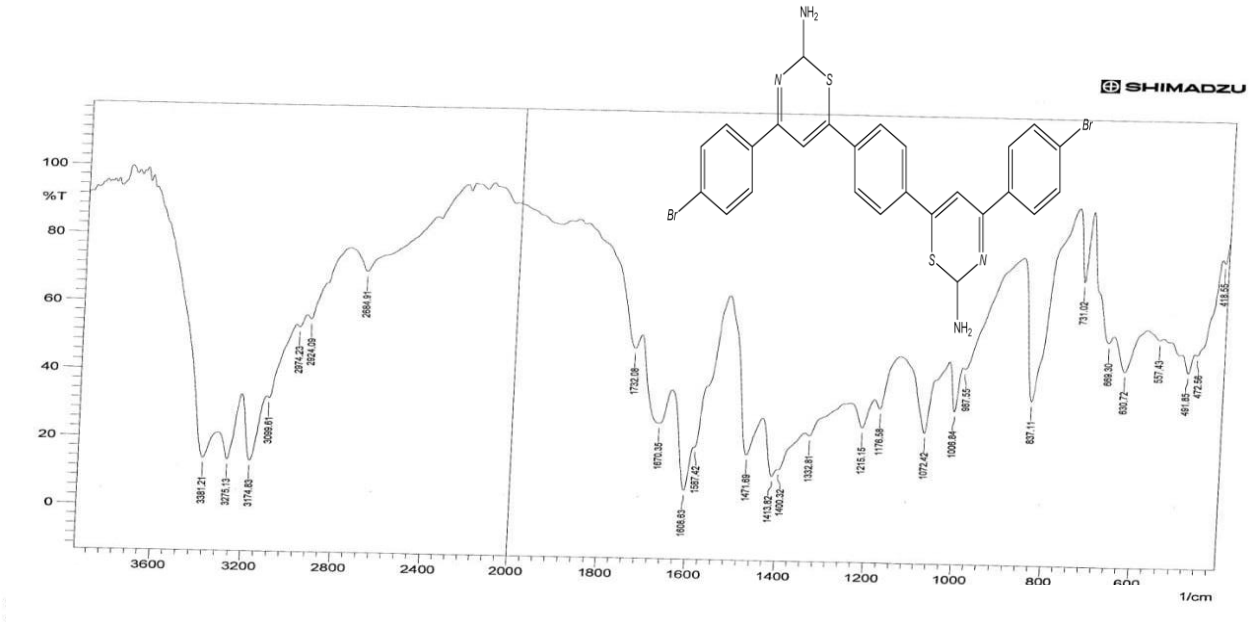


FIGURE 2. FT-IR spectrum for comp (S1:1)

Identification (S1:1) ,The **FT-IR** spectrum(cm^{-1}) **Figure 2**. Show bands at, (C=N = 1670) , (C = $C_{Alphtic}$ = 1587), (C-NH_2 =3381 & 3275) ,(C=$C_{Aromatic}$ = 1608),(C-H $_{Alphtic}$ = 2974) and (C-H $_{Aromatic}$ = 3099).

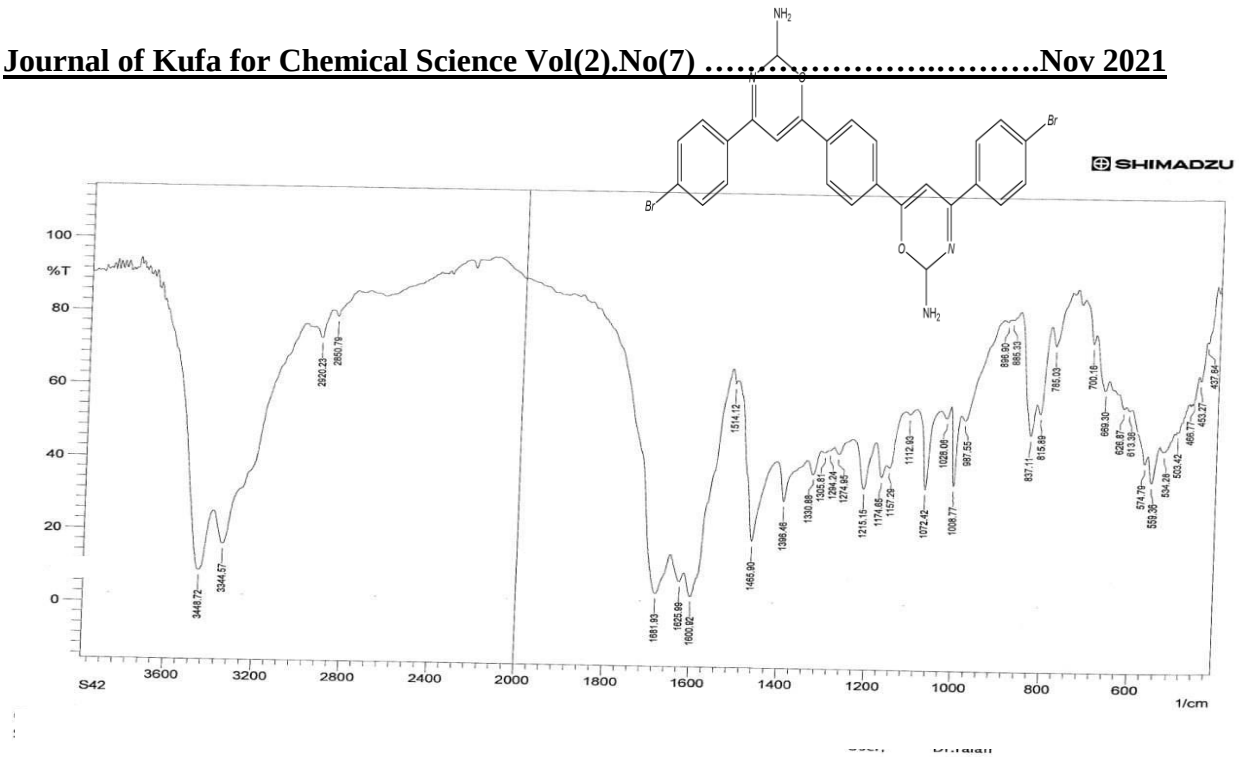


FIGURE 3. FT-IR spectrum for comp (S1:2)

Identification (S1:2) ,The **FT-IR** spectrum(cm^{-1}) **Figure 3**. Show bands at,(C=N = 1681),(C-S-C = 1267) ,(C=C $_{Aromatic}$ = 1600), and (C-NH_2 =3448 & 3344).

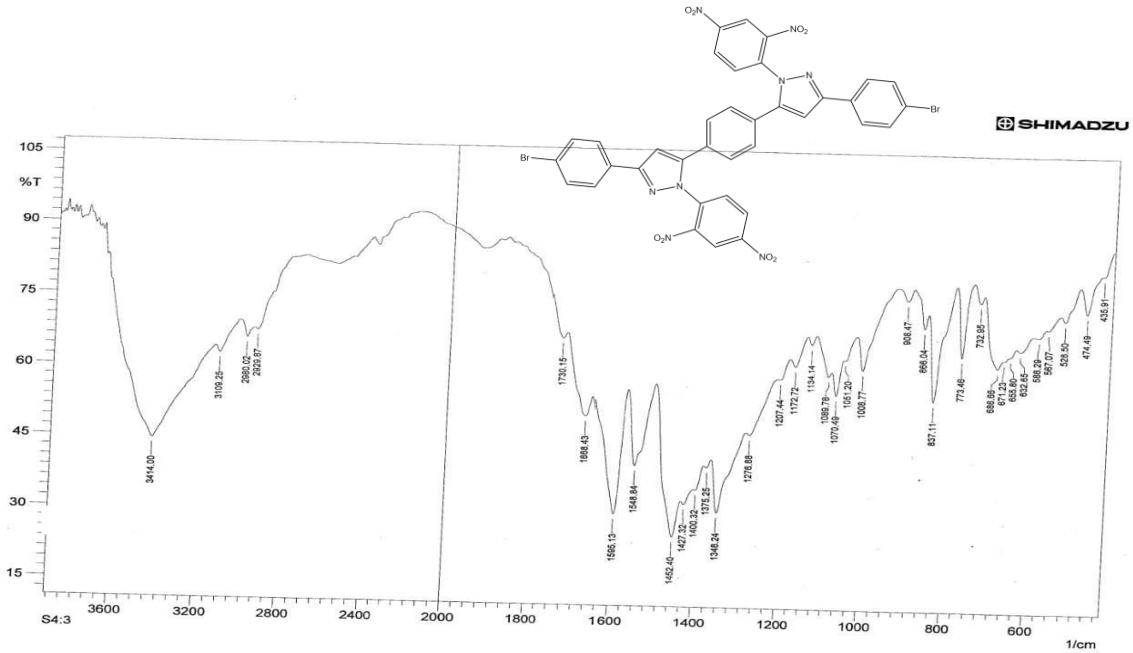


FIGURE 4. FT-IR spectrum for comp (S1:3)

Identification (S1:3) ,The **FT-IR** spectrum(cm^{-1}) **Figure 4**. Show bands at, (C-N = 1172) , (C=C $_{Aromatic}$ = 1595) , (C-NO_2 =1348) , (C=O = 1681) , (C=N =1668) (C-H $_{Alphtic}$=2980) and (C-H $_{Aromatic}$ = 3010).

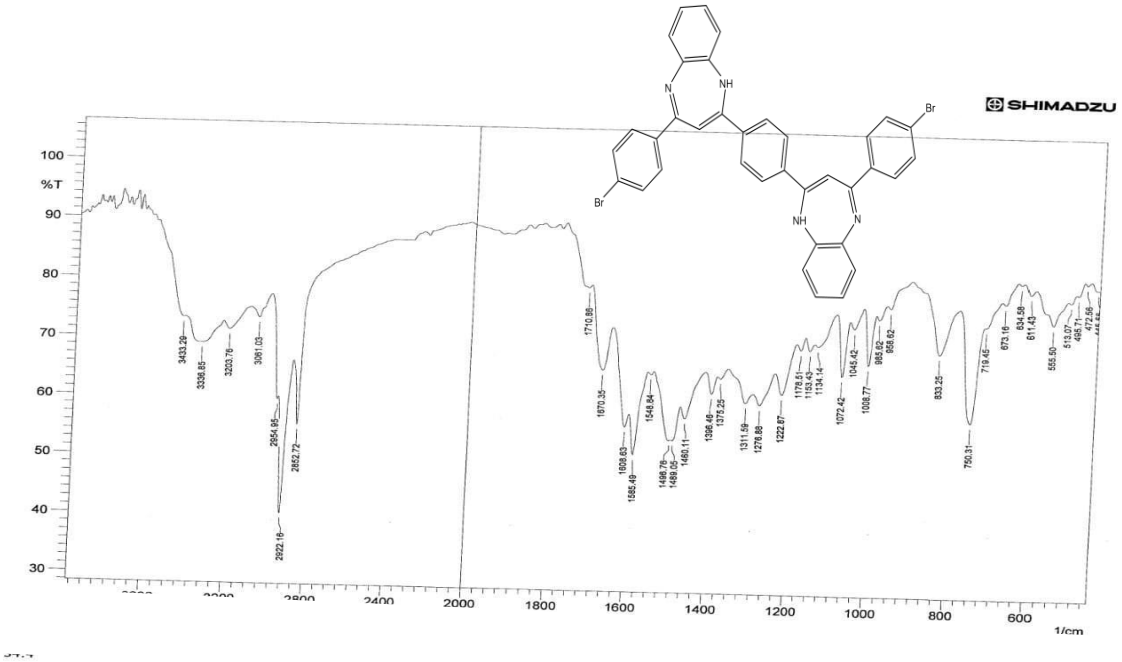


FIGURE 5. FT-IR spectrum for comp (S1:4)

Identification (S1:4) ,The **FT-IR** spectrum(cm^{-1}) **Figure 5**. Show bands at (C-N = 1222) (N-H=3433), (C=N = 1670) , (C=C $_{Aromatic}$ = 1585) and (C-H $_{Aromatic}$ = 3061).

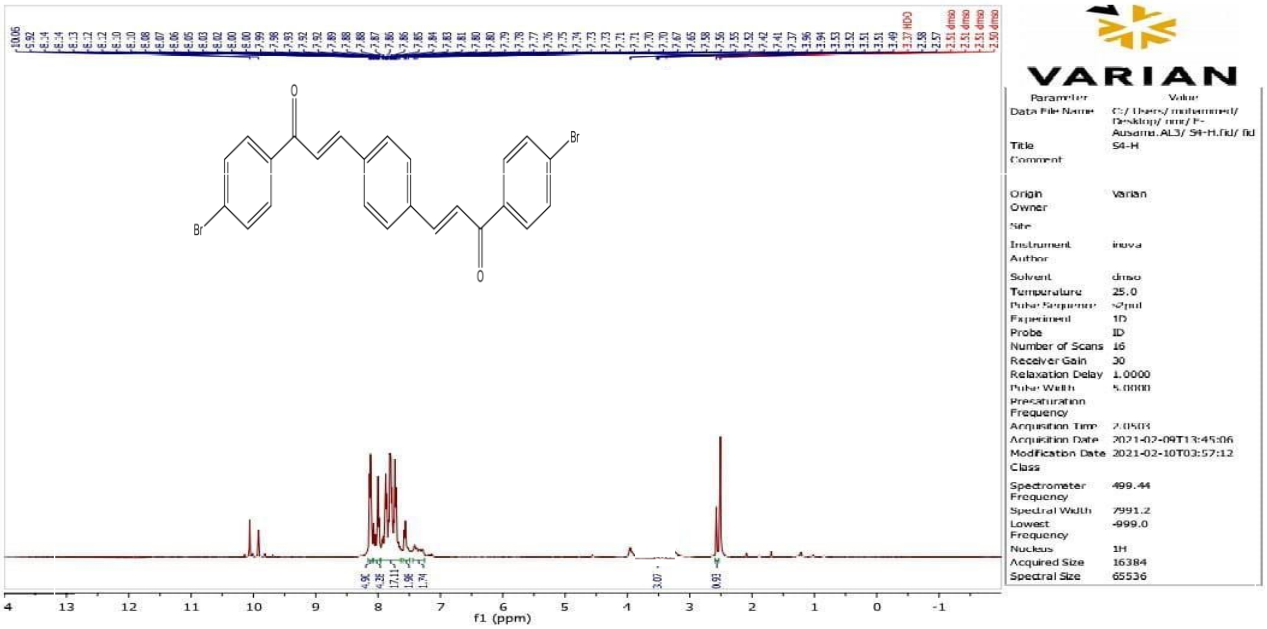


FIGURE 6. 1H-NMR spectrum of comp (S1)

The 1H-NMR proton magnetic resonance spectrum of the compound (S1) **Figure 6**. Showed the following signals: (DMSO = 2.51ppm) (C-H aliphatic = doublet signals at 7.55, 8.05ppm) and (C-H aromatic = multiple signals at 7.35,8.6 ppm)

Objective of the research

Due to the interest of studying many researchers in the preparation of chalcones and heterocyclic compounds, as well as the importance of these compounds in the medical, pharmaceutical and industrial fields mentioned above in the literature, in this topic, different classes of organic compounds have been prepared, including: -

1. chalcon compounds.
2. Pyrazole heterocyclic compounds.
3. Hexagonal hexocyclic compounds (1,3-oxazine) and (1,3-thiazine).

Seven-heterocyclic compounds (1,4-diazepine

Conclusion:

1. The prepared compounds possess high melting points and have relatively carbonization degrees. This indicates that they are stable compounds with a high molecular weight.
2. Demonstrates the biological effect of the prepared derivatives and their potential use in the medical field through their clear effect on inhibiting the growth of many types of bacteria, such as Streptococcus and (taphylococcus aureus), a type of Gram positive bacteria, and Escherichia coli, a type of stain-negative bacteria. Cram (Gram Negative Bacteria).
3. The variation of the time periods of the prepared compounds, and this mainly depends on the effect of the drawing groups and the driving groups present in the interaction mediums and the amine derivatives.

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