Synthesis and study the biological activity of some new heterocyclic compounds.

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Abstract:

This work involves synthesis of different types of heterocyclic compounds. These compounds including oxadiazole rings and its derivatives. These compounds containing thioester linkage by reacting the oxadiazoles with different acid chlorides. The prepared compounds were characterized by FT-IR,H-NMR- MASS and UV/vis spectroscopy.

Key words: Hetrocyclic compounds,oxadiazole,Schiff base,Thiadiazole.

تحضير ودراسه الفعاليه الحيويه لبعض المركبات الغير متجانسه الحلقه الجديده.

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الكلمة المفتاحيه :المركبات الغير متجانسه الحلقة ,الاوكساديزول,قواعد شف ,ثاياديازول

الملخص :

يتضمن هذا البحث تحضير انواع مختلفه من مشتقات الغير متجانسه الحلقه .تتضمن هذه المركبات حلقات الاوكسادايزول ومشتقاته .وتحتوي هذه المركبات على روابط ثايو استريه من مفاعله الاوكسادايزول مع هاليدات الحوامض المختلفه .شخصت المركبات المحضره بواسطه اطياف الاشعه تحت الحمراء وطيف الرنين النووي المغناطيسي وطيف مقياس الكتله والاشعه الفوق البنفسجيه.

Introduction:

Heterocyclic compounds have been synthesized mainly because of their wide range of biological activities[1-4]. It plays an important role in medicinal chemistry. oxadiazoles are five – membered ring compounds with three hetero atoms one oxygen atom and two nitrogen atoms[5]. A number of 2,5-disubstituted -1,3,4-oxadiazole are prepare under microwave irradiation through the reaction of variable hydrazides with different carboxylic acids in the presence of phosphorous oxychloride[6].

The method provides an excellent approach for the safe, rapid, and simple synthesis of medically important 2,5-disubstituted 1,3,4-oxadiazole. It has reported that heterocycles such as oxadiazoles are themselves important chemotherapeutic agents and exhibit antitubercular , bacteriostatic , hypoglycemic, antiviral, antifungal, antithyroid, carcinostatic and strong herbicidal activities when properly substituted in 2 and 5 positions[7-10]. As well as thiadiazole derivatives having antifungal and antibacterial effects [11-12] , and in continuation of the works on the synthesis of biologically active heterocycles. Here we synthesized some new compounds having 1,3,4-oxadiazole derivatives and 1,3,4- thiadiazole derivatives moiety in order to obtain new biologically active compounds.

Experimental part:

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and they were uncorrected.

2- Infrared spectra are recorded using Fourier Transform infrared *SHIMADZU* (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Chemistry Department, Baghdad University and using Fourier Transform infrared *SHIMADZU* (8400) (F.T.IR) infrared spectrophotometer, KBr disc was performed by Al-Mustansryia Univrsity.

3- Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram Silg, and the plates were developed with iodine vapour.

4- UV/vis spectra were recorded on Foruier Transform Varian spectrometer in Bahgdad University college of Education Ibn-Al-Haitham of pure science .

5-^{1}H-NMR spectra were recorded on Foruier Transform Varian spectrometer, operating at 300 MHz with tetramethylsilane as internal standard in DMSO-d6; Measurements were made at Chemistry Department, in Iran.

6- EuroEA Elemental Analyzer (C.H.N.S.) was carried out with:

EuroEA 3000 were made at Chemistry Department, College of Education Ibn-Al-Haitham, University of Baghdad / Baghdad- Iraq.

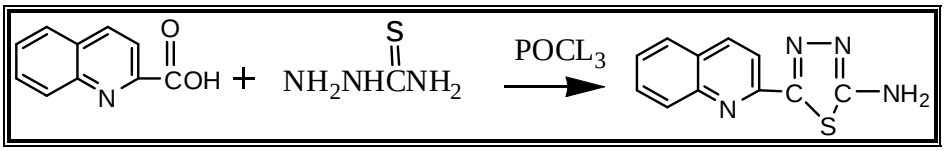
7- Biology activity was studied at Biology department, Baghdad University.

8-MASS Spectroscopy GC/Ms Mnstansyria University .

These measurements were recorded by using GC/Ms –Qp 2010 Ulta shimadzu 24 in Mnstansyria University .

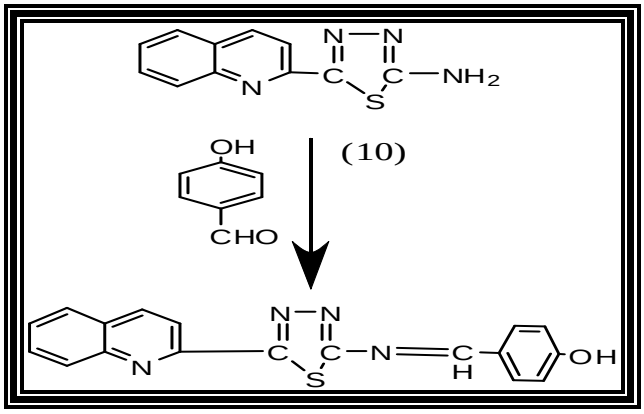
Preparation methods:

1 -Synthesis of 2-amino-5-(quinoline-2-yl)-1,3,4-thiadiazole [9][(13)]:



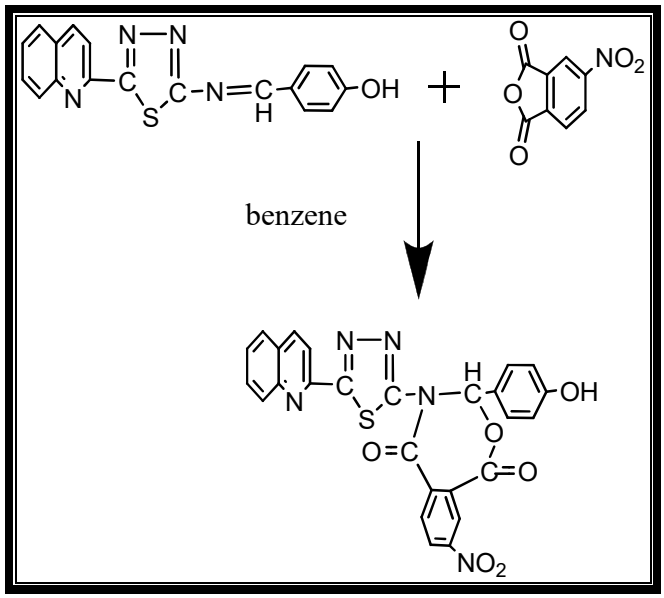
Quinaldic acid(3.0gm,0.02mol) with (1.7gm,0.2mol) thiosemecarbazide in $POCl_3$ (10ml) ,(98%) and refluxed for 3hs., after cooling water was added and refluxed for 1h. Cooling after that and neutralizing the mixture with sodium hydroxide, lead to separate a solid which was filtered , washed with water and recrystallized to give final product,m.p. is (177-180^{0}C),while the yield is (80%).

2- Synthesis of 4-((5-(quinolin-2-yl)-1,3,4-thiadiazol-2-ylimino)methyl)phenol [10][14].



2-amino-5-(quinoline-2-yl)-1,3,4-thiadiazole [9], (2.0gm, 0.009mol)with *p*-hydroxy benzaldehyde (1.2gm, 0.009mol) in absolute ethanol and 3 drops of glacial acetic acid after that refluxed for 3h., the precipitate was dried after filtered off and recrystallized from ethanol to give final yellow product m.p. (164-166 ^{o}C), yield (73%).

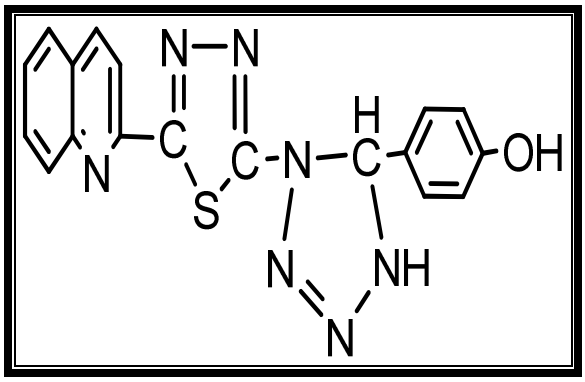
3– synthesis of 2N[*p*- hydroxyphenyl],3-[2-amino-5-quinoline-2-yl-1,3,4-thiadiazole]-2,3-dihydro-[1,3-oxazepine-[3-nitrobenzen ,maleic,benzene]-4,7-dione [12,16,17][15].



Schiff base (0.01gm,0.16mol) with (0.16mol) of 3-nitro phthalic anhydride ,or phthalic or maleic anhydride dissolved in dry benzene and refluxed for 5h., after that the solid was filtered

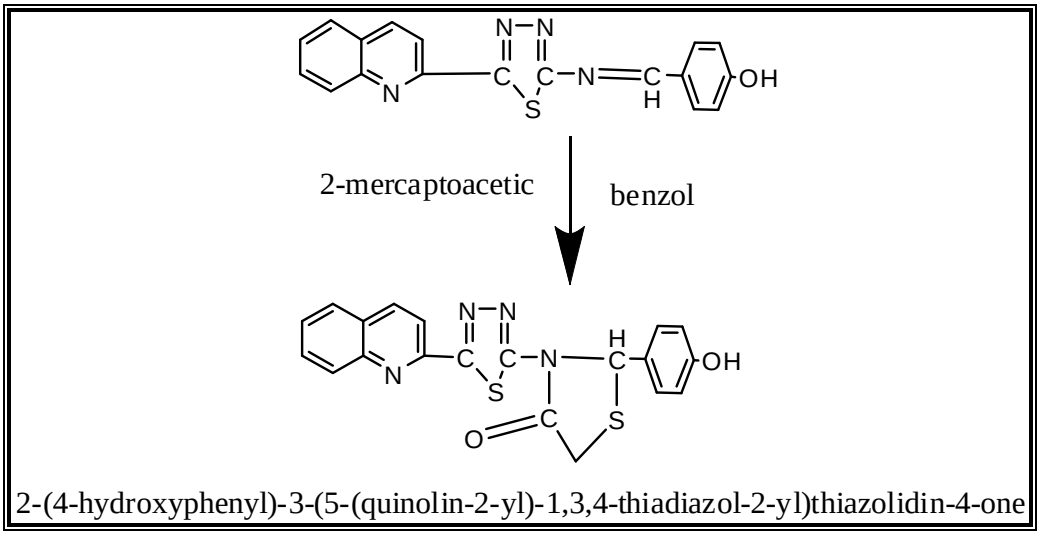
washed with water and recrystallized to give final product, m.p.for [12] is (162-164^{0}C),for [16] is> 263^{0}C ,for [17] is (192-194) ^{0}C while the yield is (about 60-80 %).

4 - Synthesis of 2N-[5-(*p*-hydroxy phenyl)-tetrazolo-1-yl]-2-amino-5-(quinoline-2-yl)-1,3,4-thiadiazole [14][(16)].



Schiffe base[11],(0.5 gm, 0.0016mol)with (0.1gm, 0.0016mol) of sodium azide in tetrahydro furan and refluxed for 3h. Cooled after that and water was added then filtered off and recrystallized from ethanol m.p. (236>^{o}C), yield (73%).

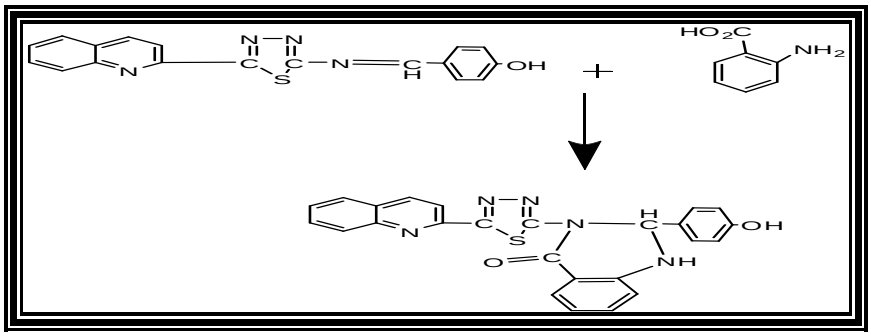
5 -Synthesis of 2-(4-hydroxy phenyl)-3-(5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one [14][(17)]:-



2-(4-hydroxyphenyl)-3-(5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one

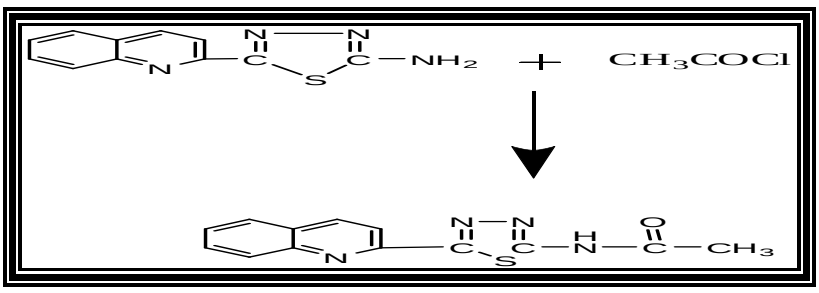
Schiffe base (0.2gm,0.00065 mol) with(0.1 gm,0.00065 mol) of 2-mercapto acetic acid dissolved in benzene and refluxed for7h., cooled in crushed ice and neutralizing the mixture with aqueous potassium carbonate solution, lead to separate a solid which was filtered , washed with water and recrystallized to give final product, m.p. is (174-180^{0}C),while the yield is (80%).

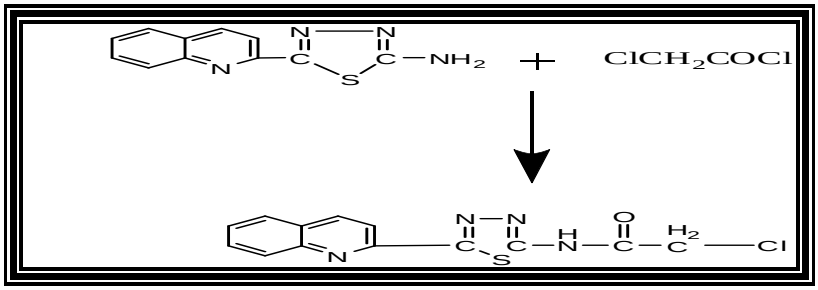
6- Synthesis of 3-(4-hydroxyphenyl)-2-(5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroiso quinoline-1,4-dione:-[15][(18)].



Schiff base (0.15gm, 0.00014mol) with(0.1gm,0.00014 mol) of anthranilic acid in benzene and refluxed for 5h., the formed solid was filtered,washed with ethanol and recrystallized to give final product, m.p. is (210-214^{0}C),while the yield is (80%).

7- Synthesis 2-quinoline-5-(quinoline-2-yl)-1,3,4-thiadiazole- acetamide or chloro acetamide [18,19][(19)].



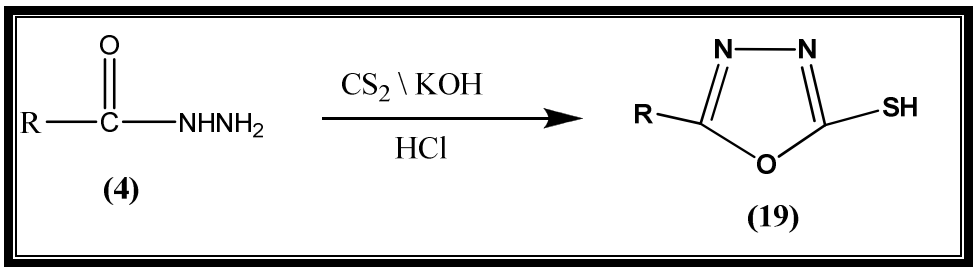


2-amino-5-(quinoline-2-yl)-1,3,4-thiadiazole [9],(0.1gm ,0.00049mol) dissolved in pyridine (10ml) with cooling and added (0.00049 mol) of acetyl chloride or chloro acetyl chloride drop by drop after stirring for 3h., poured in crushed ice with diluted HCl, filtered off , washed with distilled water and recrystallized from ethanol m.p. for [18] (218-220C), for [19] is 118-120 ^{0}C yield~ (73%).

8- General procedure for preparation of Acid chlorides: Acetyl chloride, chloro acetyl chloride, 2-chloro-benzoyl chloride, 4-chloro benzoyl chloride and benzoyl chloride[(20)].

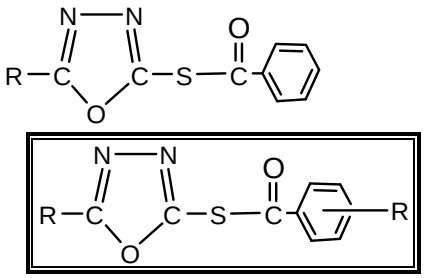
The acid chlorides were synthesized as described in previously literature [(20)].

9- Synthesis of 5-(quinolin-2-yl)-1,3,4-oxadiazole-2-thiol[20][(21)].



Hydrazide compound [4],(0.1gm ,mol) dissolved in ethanol (10ml) with cooling and added (1.0gm, mol) of NaOH and (gm, mol) of CS_2(carbon disulfide) after refluxing for 3h., the solvent was evaporated and dissolved in distilled water ,neutralized with diluted HCl, filtered off , washed with distilled water and recrystallized from ethanol .

10- Synthesis of 2N[*p*- hydroxyphenyl] ,3-[2-amino-5-quinoline-2-yl-1,3,4-oxadiazole]-2,3-dihydro-[1,3-oxazepine-[maleic]-4,7-dione [21-25][0].



R=2-chloro,4-chloro,H

5-(quinolin-2-yl)-1,3,4-oxadiazole-2-thiol[20], (0.1gm ,mol) dissolved in pyridine (10ml) with cooling and added (1.0gm, mol) of [acetyl chloride or chloro acetyl chloride,2-chloro benzoyl chloride, *p*-chloro benzoyl chloride and benzoyl chloride] drop by drop after stirring for 3h., poured in crushed ice with diluted HCl, filtered off , washed with distilled water and recrystallized from ethanol .

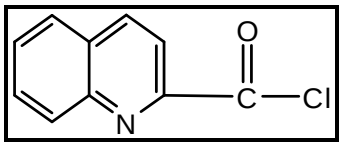
Table (2-1): Some physical properties of the prepared compounds.

Comp. No.	*Molecular Formula*	*Molecular Weight (g/mole)*	*Yield (%)*	*M.P (ºC)*	*Colour*	*RF*
4	$C_{10}H_9N_3O$	187.20	85	153-155	Pale yellow	-
5	$C_{18}H_{10}N_4O_5$	362.30	85	225-227	Green	0.91
6	$C_{14}H_{11}N_3O_3$	269.26	75	109-111	Yellow	0.90
7	$C18H11N_3O_3$	317.30	70	225-227	Yellow	0.81
8	$C12H_9N3O2$	227.22	77	139-141	Pale yellow	0.85
9	$C11H_8N4S$	228.27	72	(164-166	Brown	0.89
10	$C20H_{18}N4OS$	362.45	73	160-162	Brown	0.93
11	$C_{26}H_{15}N_5O_5S$	509.49	80	169-172	Yellow	0.94
12	$C_{19}H_{17}N_7O$ S	391.45	73	236-240	Yellow	0.91
13	$C_{20}H_{14}N_4O_2$ S	406.48	80	177-180	Green	0.83
14	$C_{25}H_{17}N_5O_2S$	451.50	80	211-214	Black	0.86
15	$C_{22}H_{14}N_4O_3S$	414.44	85	236-238	Yellow	0.73
16	$C_{26}H_{16}N_4O_3S$	464.50	80	189-192	White	0.88
17	$C_{13}H_{10}N_4$ OS	270.31	85	118-120	Black	0.89
18	$C_{13}H_9Cl$ N_4 OS	304.75	80	117-120	Black	0.93

19	$C_{11}H_7N_3OS$	229.26	80	268-270	Orange	0.91
20	$C_{18}H_{11}N_3O_2S$	333.36	85	101-104	White	0.89
21	$C_{18}H_{10}ClN_3O_2S$	367.81	82	78-80	Green	0.91
22	$C_{13}H_9N_3O_2S$	271.29	88	129-131	Orange	0.93
23	$C_{18}H_{10}ClN_3O_2S$	367.81	84	159-162	Yellow	0.89

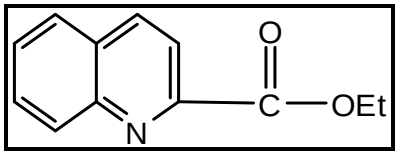
Results and Discussion:

1 Characterization of quinoline -2 acyl chloride [2].



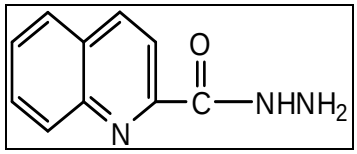
This compound was prepared by the reaction of Quinaldic Acid with thionyl chloride. The FT-IR spectrum of this compound exhibited band at 1630cm^{-1} due to (C=O) carbonyl of acid chloride and at 1530,1470 cm^{-1} attributed to (C=C) of aromatic group besides the disappearance of band of (OH) group of carboxylic acid[22].

2- Characterization of quinoline 2-yl - ethyl acetate [3].

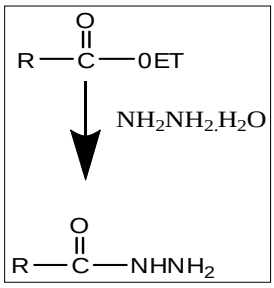


This compound was prepared from the reaction of acid chloride [2] with absolute ethanol as intermediate compound for preparing anothor compounds. The ester compound was characterized as usual by FT-IR spectrum which revealed the following bands: at 1735 cm^{-1}that due to stretching band of (CO) carbonyl of ester group, and at 2960,2845cm^{-1}due to stretching band of (CH_2) group.

3- Characterizationof (quinolin-2-yl) acid hydrazide [4]:-

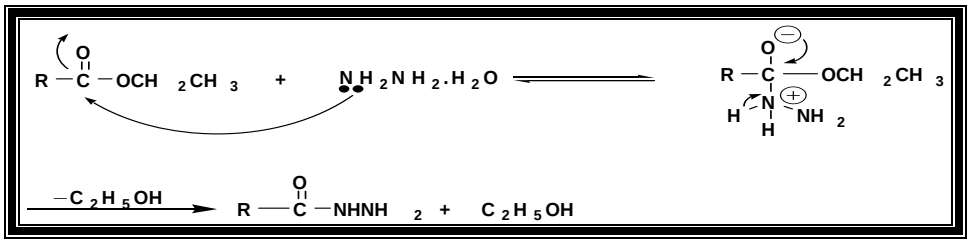


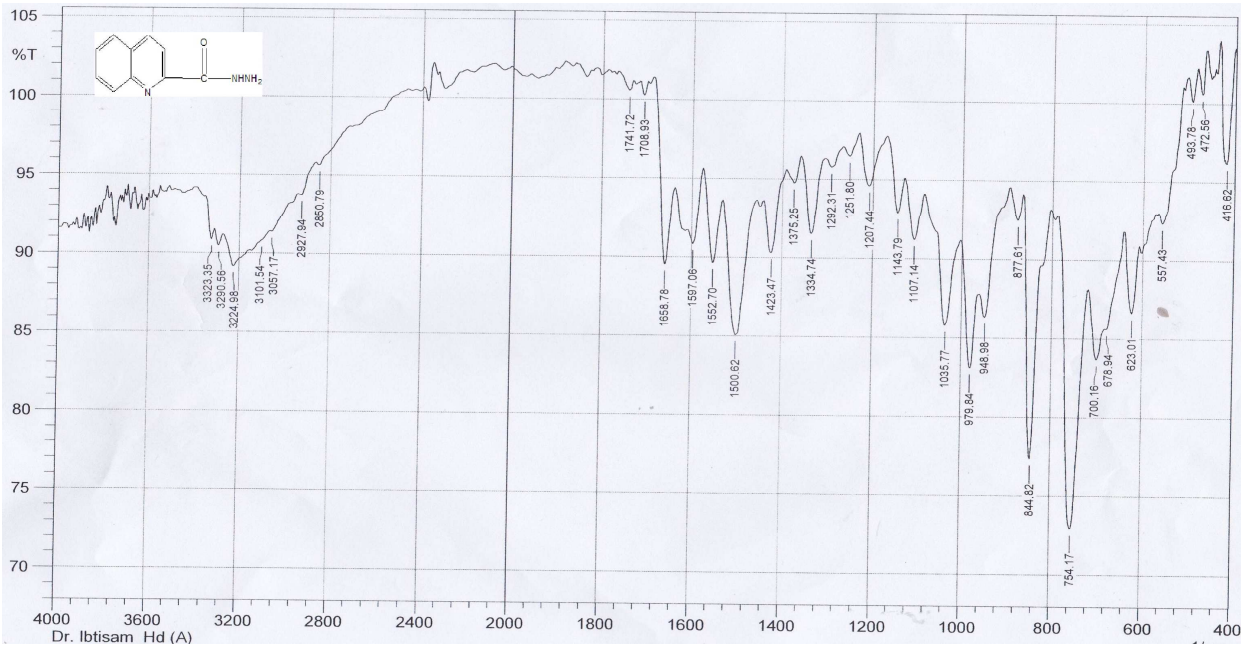
The acid hydrazide was synthesized by reaction of ester [3] with hydrazine hydrate in absolute ethanol. The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide, it is a tetrahedral nucleophilic substitution reaction .



The FT-IR spectrum for the hydrazide compound ,Fig [1], showed the appearance of the characteristic absorption bands in the region (3323-3224, 3101) cm^{-1} due to the asymmetric and symmetric stretching vibration of the (-NH-NH_2) group, the F.T.IR for this compound also showed the disappearance of absorption bands at (1735) cm^{-1}due to the stretching vibration of carbonyl group of ester while a new band appeared at 1643 cm^{-1} due to stretching vibration of amide group and (-CH) aliphatic at (2960), Fig(2) shows the ^{1}H-NMR spectrum of this compound. ^{1} H-NMR spectrum of compound [4] showed signal at (δ=4.6) belong to(NH) amide protons, signals at (7.6-8.5-)ppm belong to aromatic protons

The mechanism of the reaction is shown below:

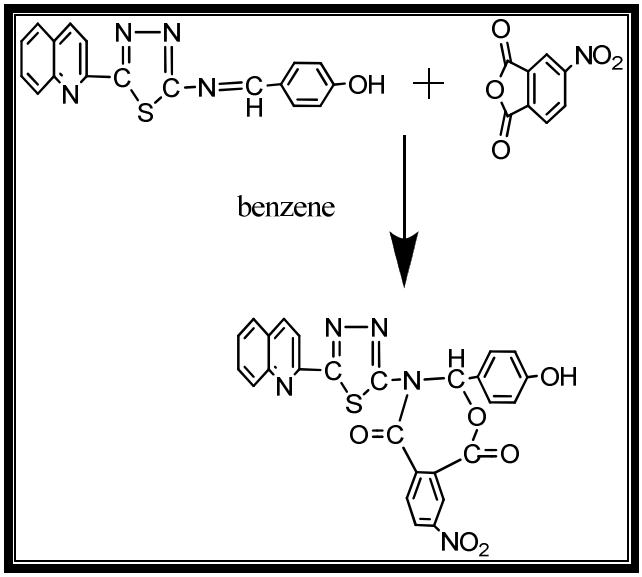




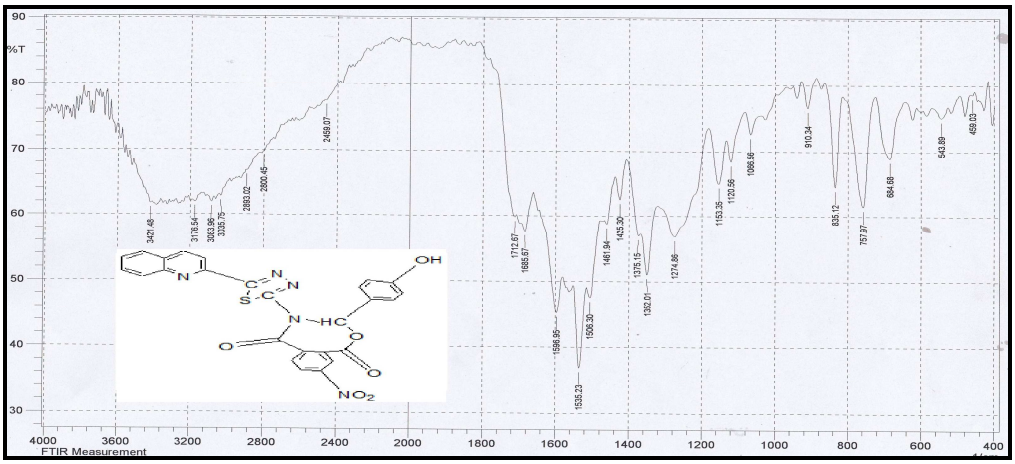
Fig(1): FT-IR spectrum of quinoline acid hydrazide [4].

4- Synthesis and characterizationof 2N[p- hydroxyphenyl],3-[2-amino-5-quinoline-2-yl-1,3,4-thiadiazole]-2,3-dihydro-[1,3-oxazepine-[3-nitro phthaleic anhydride ,maleic, anhydride]-4,7-dione [12,16,17].

Compound [11] was synthesized from the reaction of compound[10] with 3-Nitro phthaleic anhydride in benzene. The compound was characterized by its melting point and F.T.IR spectrum and checked by T.LC .



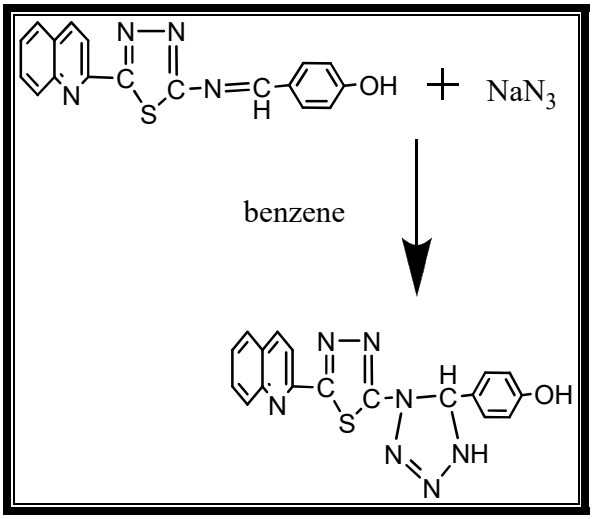
The F.T.IR spectrum of compound [12] was confirmed from the appearance of carbonyl group band at (1685cm^{-1}) and C-H aliphatic band at (2893cm^{-1}) and bands at (1283and 1072cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band and Nitro groups(1535cm^{-1}) Figure (3) shows the F.T.IR spectrum of compound [12].



Fig(3) : FT-IR spectrum of compound [12].

5- Synthesis and characterization of 2N-[5-(*p*-hydroxy phenyl)-tetrazolo-1-yl]-2-amino-5-(quinoline-2-yl)-1,3,4-thiadiazole [13].

Compound [12] was synthesized from the reaction of compound [10] with sodium azide in THF. The compound was characterized by its melting point and F.T.IR Uv/vis spectrum.

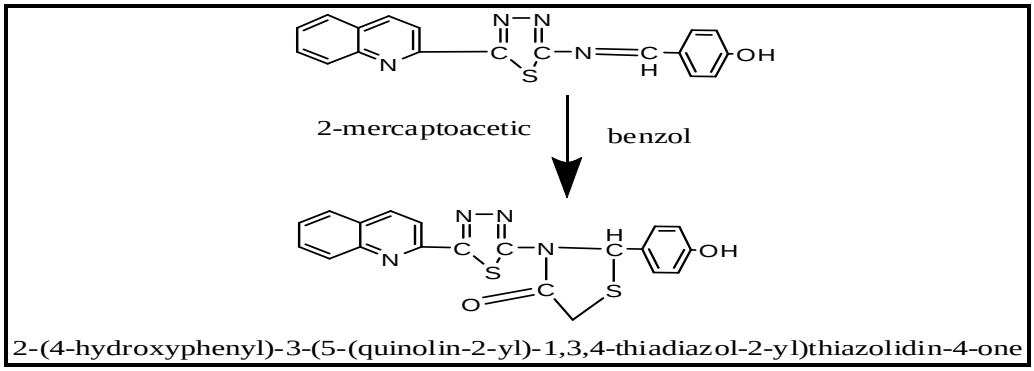


The FT-IR spectrum of compound [13] was confirmed from the appearance of N-H band at (3107cm^{1}) and (1022cm^{-1}) and OH group(3259cm^{1})and C-N stretch (aryl) belong to the

asymmetric and symmetric (C-O-C) band(1417 cm^{-1}). The UV/vis spectrum, gave absorption bands at different wave lengths (295, 319) nm for the. resulted amino thiadiazole, due to(n-π*),and (π- π*) transitions .

6 - Synthesis and characterization of 2-(4-hydroxyphenyl)-3-(5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one [14]:-

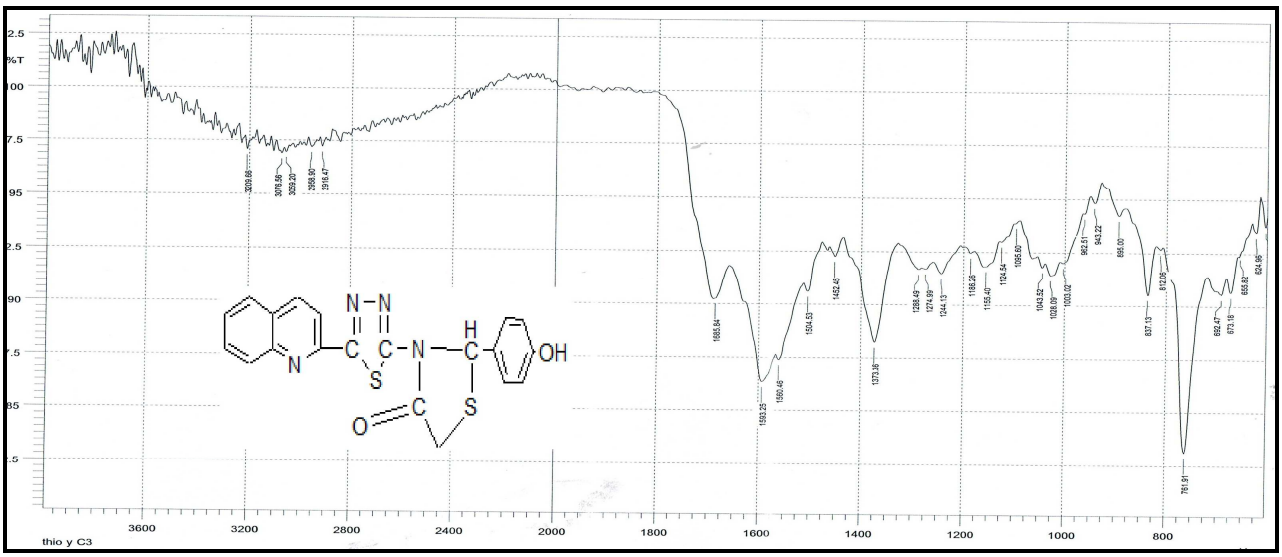
Compound [14] was synthesized from the reaction of compound [11] with 2-mercaptoacetic acid in dry benzene. The compound was characterized by its melting point and F.T.IR ,H-NMR spectra.



Scheme (1): reagents and reaction of Schiff with mercapto acetic acid.

The F.T.IR spectrum of compound [14] was confirmed from the appearance of carbonyl group band at (1685cm^{-1}) and OH group(3209cm^{1}) and C-H aliphatic band at (2958cm^{-1}) and (1022cm^{-1}) and C-N stretch (aryl) (1417cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (5) shows the F.T.IR spectrum of compound [14].

H-NMR spectrum of this compound exhibited the peak at 3-4.3)ppm due to CH_2 and (CH) ring protons and at 7.5-8.3) ppm due to aromatic protons, fig.(6).



Fig(5): FT-IR spectrum of compound [14].

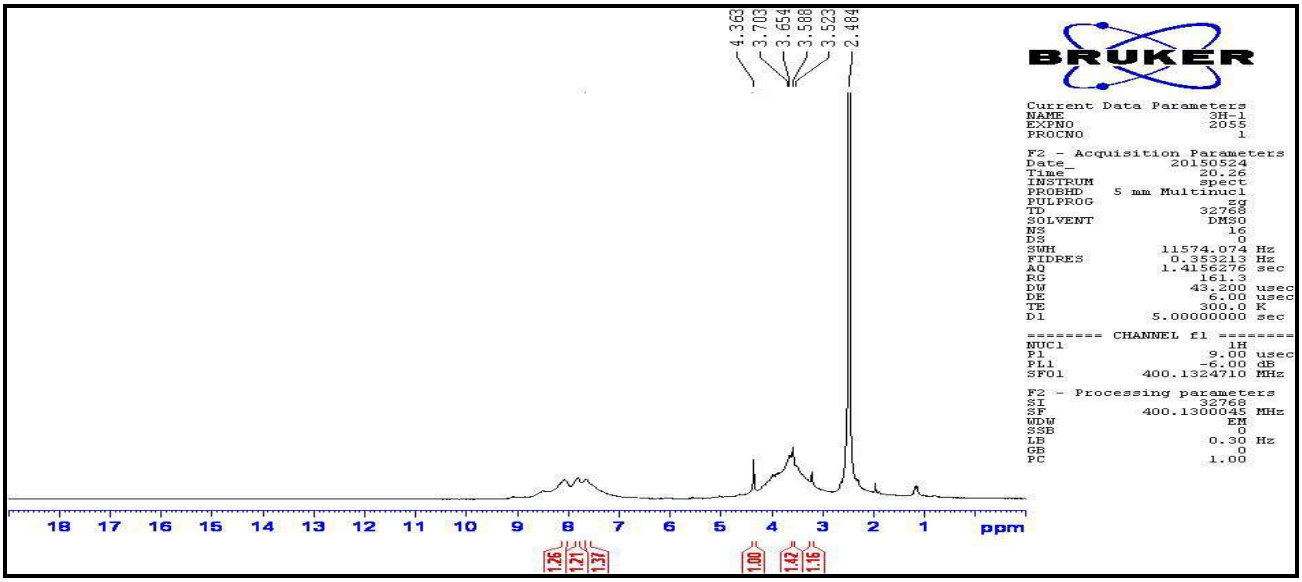
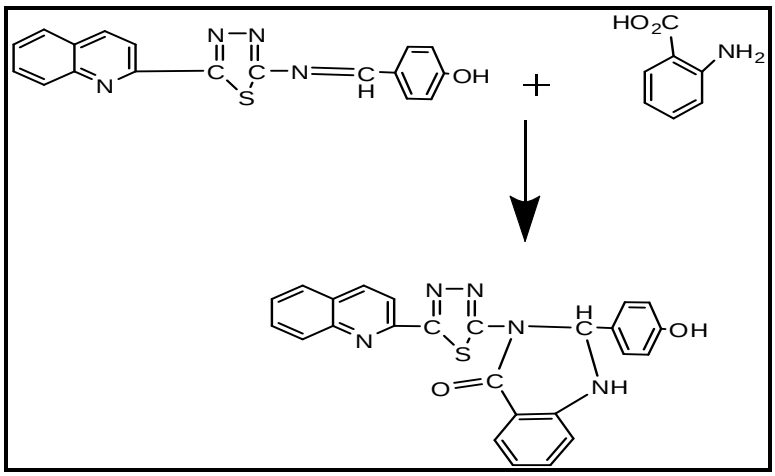


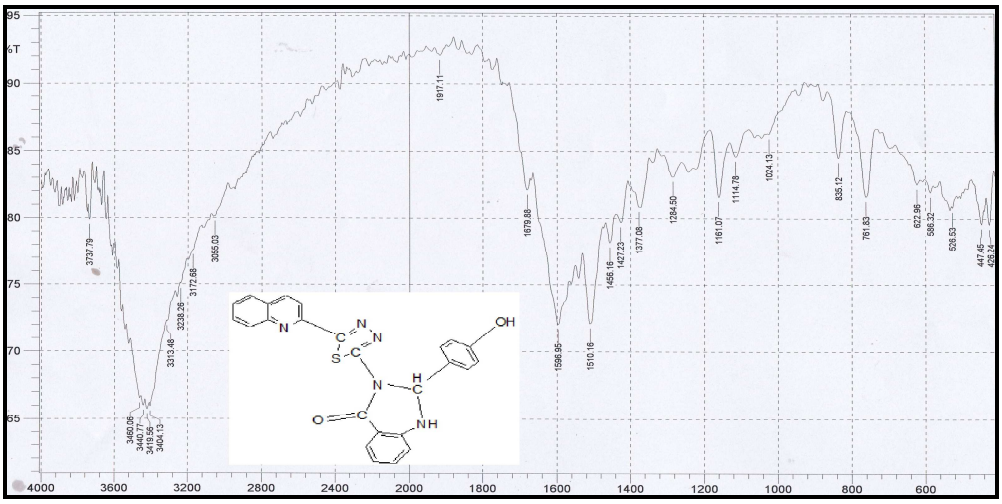
Fig.(6): ^{1}H-NMR spectrum of compound [14].

7- Synthesis and caharacterization of 3-(4-hydroxyphenyl)-2-(5-(quinolin-2-yl)-1,3,4-thiadiazol-2-yl)-2,3-dihydroisoquinoline-1,4-dione:-

Compound [15] was synthesized from the reaction of compound [11] with 2-aminobenzoic acid in dry benzene. The compound was characterized by its melting point and F.T.IR spectrum.

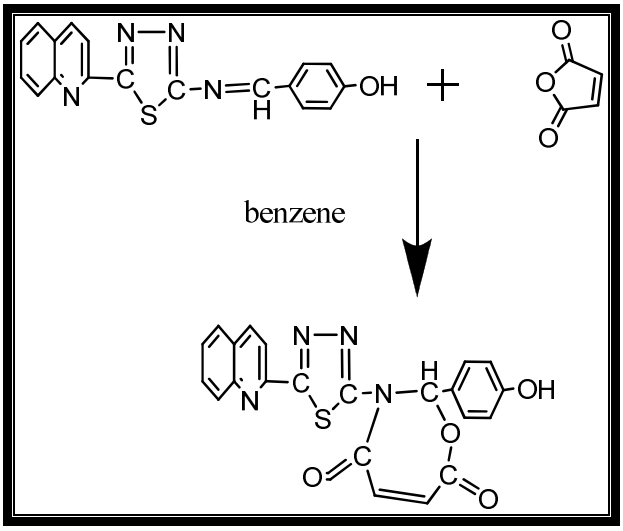


The F.T.IR spectrum of compound [15] was confirmed from the appearance of carbonyl group band at (1679cm^{-1}) and OH group(3440cm^{1}) N-H band at (3127cm^{1}) and (1022cm^{-1}) and C-N stretch (aryl) (1417cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (7) shows the F.T.IR spectrum of compound [15].



Fig(7): FT-IR spectrum of compound [15].

8- Synthesis and characterizationof 2N[*p*- hydroxyphenyl] ,3-[2-amino-5-quinoline-2-yl-1,3,4-thiadiazole]-2,3-dihydro-[1,3-oxazepine-[maleic]-4,7-dione [16].



Compound [16] was synthesized from the reaction of compound [11] with maleic anhydride in dry benzene. The compound was characterized by its melting point and F.T.IR spectrum.

The F.T.IR spectrum of compound [16] was confirmed from the appearance of carbonyl group band at (1649cm^{-1}) and OH group(3483cm^{1}) N-H band at (3377cm^{1}) and C-H aliphatic band at (2923cm^{-1}) and (1064cm^{-1}) and C-N stretch (aryl) (1427cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (8) shows the F.T.IR spectrum of compound [16].

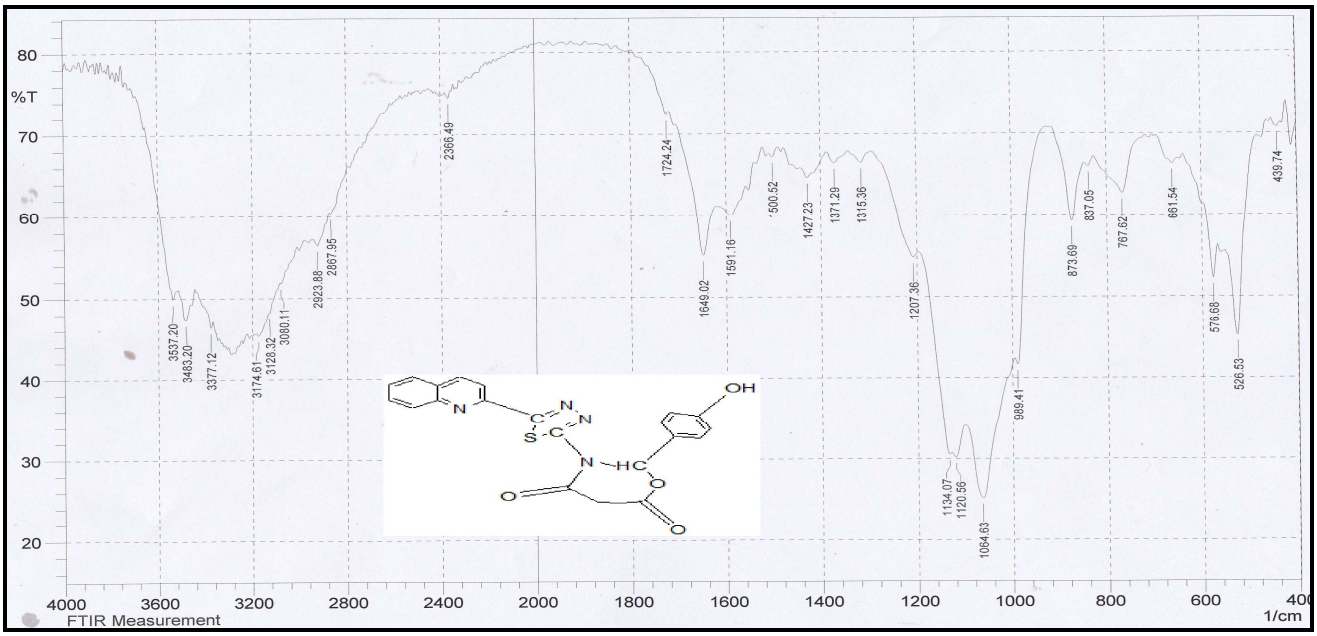
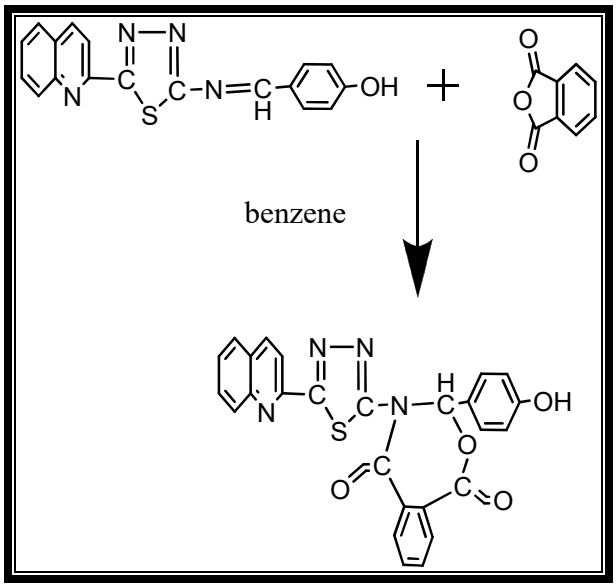


Fig.(8): FT-IR spectrum of compound [16].

9- Synthesis and characterizationof 2N[*p*- hydroxyphenyl] ,3-[2-amino-5-quinoline-2-yl-1,3,4-thiadiazole]-2,3-dihydro-[1,3-oxazepine-[benzne]-4,7-dione [16].

Compound [16] was synthesized from the reaction of compound [10] with phthalic anhydride in dry benzene. The compound was characterized by its melting point and F.T.IR spectrum.



The F.T.IR spectrum of compound [16] was confirmed from the appearance of carbonyl group band at (1680cm^{-1}) and (CH) aliphatic group(2955cm^{1}) , O-H band at (3300 cm^{1}) and C-N stretch (aryl) (1400 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (9) shows the F.T.IR spectrum of compound [17].

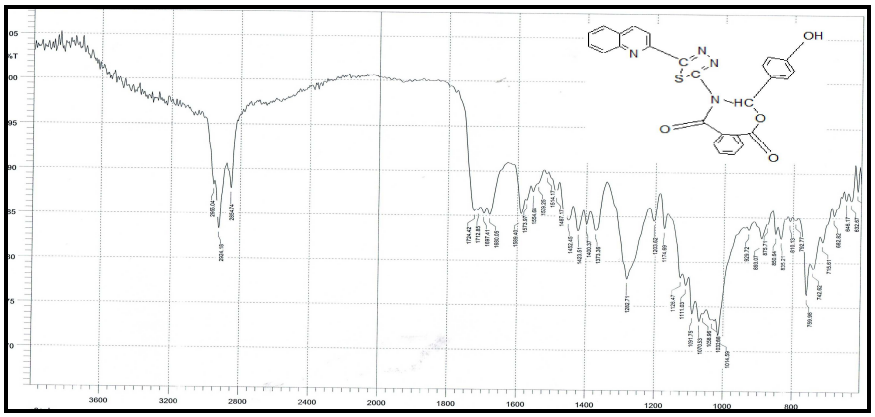
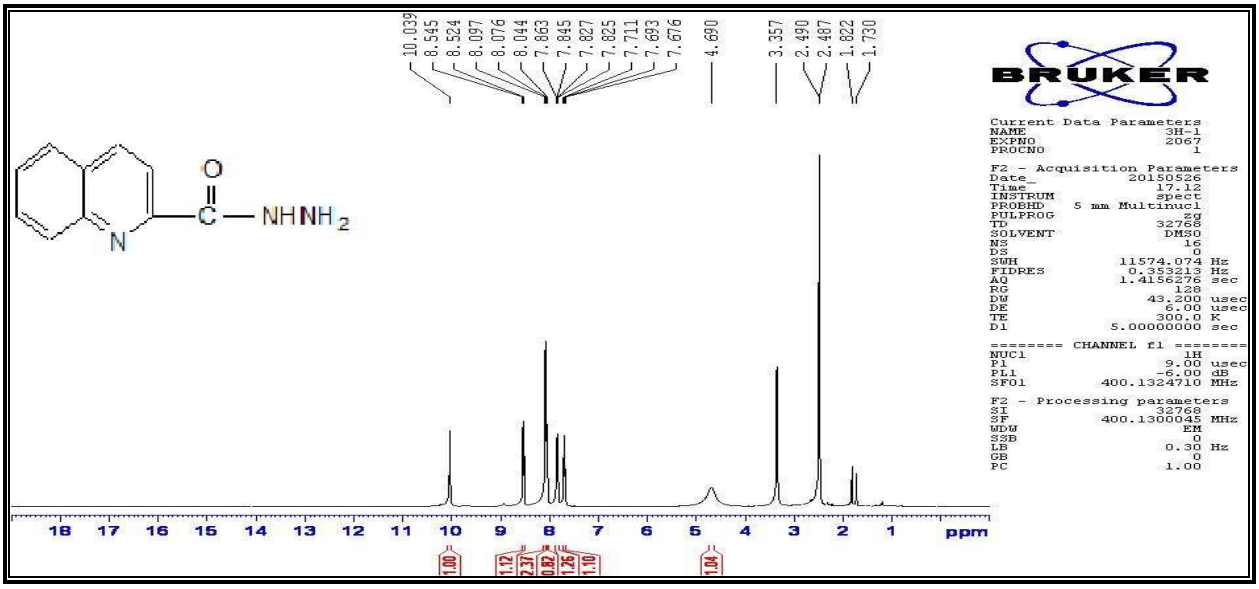


Fig.(9): FT-IR spectrum of compound [17].



Fig(10): ^{1}H-NMR spectrum of Quinoline acid hydrazide [4].

Comp. NO	Molecular Formula	found				Calculated			
		C%	H%	N%	S%	C%	H%	N%	S%
4	$C_{10}H_9N_2O$	64.9	5.2	23.2		64.1	4.8	22.4	
13	$C_{19}H_{12}N_4S_2O_2$	58.7	3.11	14.8	16.54	58.1	3.06	14.2	16.32

Fig.(11): C.H.N.S. Analysis of compound [4.13].

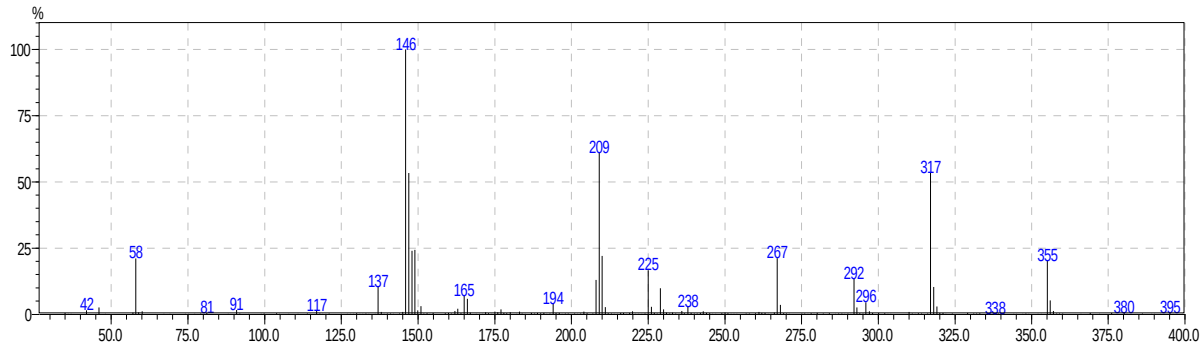


Fig.(12): Mass spectrum of compound [7].

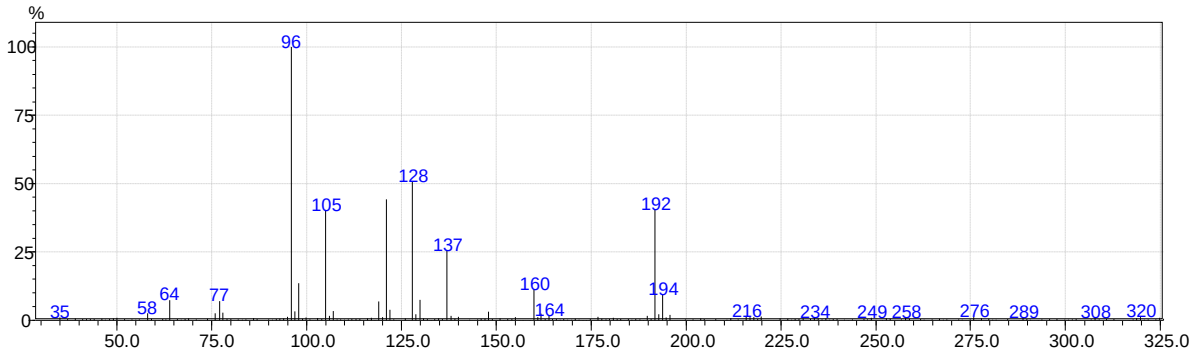


Fig.(13): Mass spectrum of compound [21].

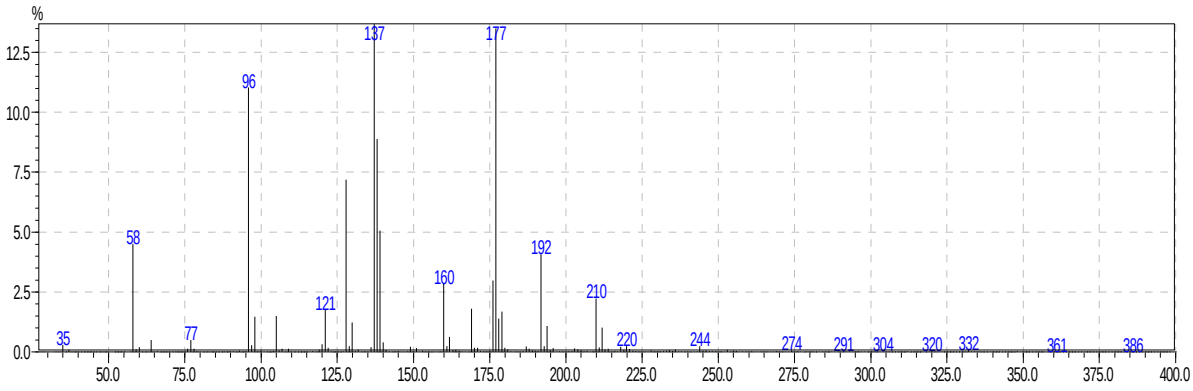


Fig.(14): Mass spectrum of compound [24].

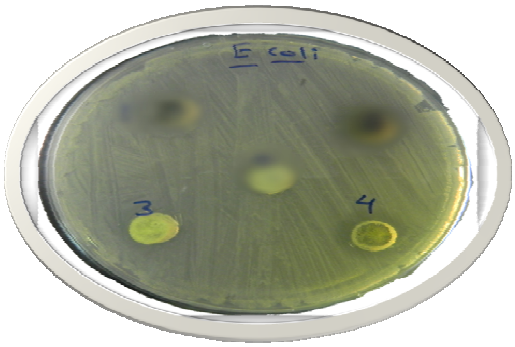


Figure (12): The effect of compound (3 and 4) on E.coli.

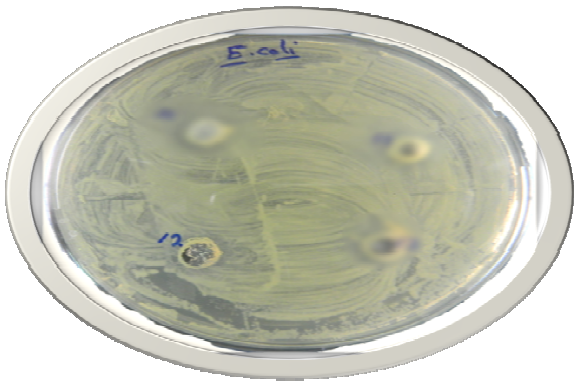


Figure (13): The effect of compound (12) on E.coli.

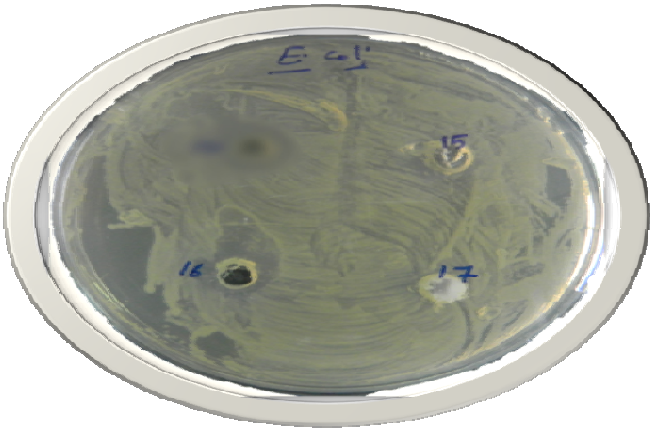


Figure (14): The effect of compound (15, 16, and 17) on E.coli.

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