



Preparation, Identification and study Antibacterial Activity of Some new 2,3- Dihydroquinazolin-4 (1H)-one Derivatives

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DOI: <http://dx.doi.org/10.25130/tjps.23.2018.149>

ARTICLE INFO.

Article history:

-Received: 2 / 1 / 2018

-Accepted: 25 / 1 / 2018

-Available online: / / 2018

Keywords: Azo dye, Schiff bases, 2,3-dihydroquinazolin-4(1H)-one.

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Abstract

In this study some new compounds have been prepared including the reaction of diazonium salt of 1,4-phenylenediamine with 2-mercaptobenzaldehyde at (0-5)⁰C[F₁]. Then Schiff bases [F₂-F₆] were then synthesized through the reaction of compound [F₁] with substituted aniline in absolute ethanol, and Schiff bases were converted into 2,3 - dihydroquinazolin - 4(1H) - one derivatives [F₇-F₁₁] by the reaction with 2-amino benzoic acid in ethanol. The prepared compounds were characterized by color and melting point, FT-IR, UV-Vis spectral analysis. Some of the prepared compounds were identified by ¹H-NMR spectra and C.H.N analysis. The antibacterial activities were studied against different kinds of bacteria, in addition, the stability of prepared dyes which proved to be of high stability and bright colors was studied, in addition the conformation of prepared compounds at the lower energy level were studied.

Introduction

Azo dyes contain at least one Nitrogen-Nitrogen double bond (N=N); however, many different structures are possible[1]. Mono azo dyes have only (N=N) double bond, while diazo and triazo dyes contain two and three (N=N) double bonds, respectively. The azo groups are generally connected to benzene and naphthalene rings, but can also be attached to aromatic heterocyclic such as chloroquine [2].

Schiff bases are one of the most prevalent and important mixed donor systems in the field of coordination chemistry. The first preparation of imines was reported in the 19th century by Schiff (1864), which were prepared by condensing primary amines with an aldehyde or ketone under specific conditions. Because of the relative easiness of preparation, flexibility and special properties of C=N group, Schiff bases are considered as an excellent chelating agents. Schiff bases and its metal complexes have found to exhibit biological activities[3-8].

Quinazolinones are among the most important classes of heterocyclic compounds, which possess versatile types of biological activities such as; anticancer [9,10], anti-tubercular [11], antibacterial [12], antifungal, anti-HIV activities[13].

Experimental

Materials: All chemicals have been used as supplied by (Merch, Fluka, BDH and Aldrich).

Devices used: The melting points were determined by Electrothermal Melting Apparatus 9300 in open capillary tubes that were uncorrected. Thin layer chromatography (TLC) was used for monitoring the reaction and to check purity. The FT-IR spectra were recorded using FT-IR 8400S Shimadzu spectrophotometer Scale (4000-400)cm⁻¹. The UV-Vis. spectra was measured in ethanol using Shimadzu 800UV in rang (200-400) nm. H¹-NMR Spectra was recorded on Varian operating at 400 MHz instrument using DMSO-d₆ as a solvent. Quantitative analysis of the spectrophotometer elements determined using C.H.N analysis.

Preparation methods:

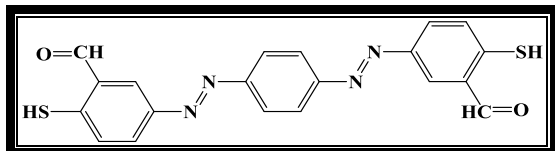
1-Preparation of Azo dye[14] [F₁] :

Azo dye was prepared using two main steps:

Step 1/ Preparation of diazonium salt: (0.02 mol, 2.16 gm) of 1,4- phenylene diamine was dissolved in (25 ml) of acidic solution (1HCl+2H₂O) at a temperature of (0-5) ⁰C with continuous stirring, then a solution of sodium nitrite was added.

Step 2/ Coupling reaction: (0.04 mol, 5.52 gm) of 2-mercapto benzaldehyde was dissolved in (35 ml) of Pyridine, then cooled to (0-5) ⁰C in ice bath. This

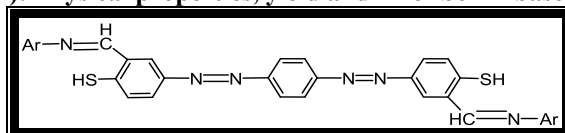
solution was then slowly added to the cooled diazonium salt solution (step1) to yield azo compound. The product was then filtered, dried and recrystallized in absolute ethanol. M.F.(C₂₀H₁₄N₄O₂S₂), Yield (69%), Color(red), R. f.(0.73)M.P. (220-222°C).



2-Preparation of Schiff bases[15] [F₂ - F₆]:

(0.01 mol, 5.5 gm) of the prepared azo dye [F₁] was dissolved in (50 ml) of absolute ethanol. After complete dissolving, (0.02 mol) of substituted aniline was added. After adding (4drops) of glacial acetic acid, the mixture was then refluxed for (4-6) hrs., and cooled to room temperature, filtered, dried and recrystallized in absolute ethanol. Physical properties, yield and R_f are given in Table (1).

Table (1): Physical properties, yield and R_f of Schiff bases [F₂-F₆].



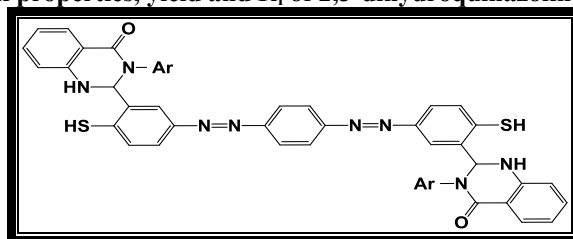
Comp. No.	Ar	Molecular Formula/ M. Wt.	Color	M.P (C ⁰)	T. Ref. (hr.)	Yield (%)	R _f
F ₂		C ₃₂ H ₂₄ N ₆ S ₂ 556.71	Dark red	190-192	5	80	0.81
F ₃		C ₃₂ H ₂₂ I ₂ N ₆ S ₂ 808.50	Deep brown	160-162	5	65	0.55
F ₄		C ₃₂ H ₂₂ Cl ₂ N ₆ S ₂ 625.59	Brown	199-201	4	72	0.89
F ₅		C ₃₂ H ₂₄ N ₆ O ₂ S ₂ 588.70	Orange	240-242	6	69	0.84
F ₆		C ₃₂ H ₂₂ Br ₂ N ₆ S ₂ 714.50	Deep brown	185-187	4	76	0.60

3-Preparation of 2,3-dihydroquinazolin- 4(1H)-one[15][F₇ - F₁₁]:

(0.004 mol, 0.55 gm) of 2-amino benzoic acid mixed with (0.002 mol) of the prepared Schiff's bases [F₂-F₆] in (50 ml) ethanol and (4ml) of triethylamine, and refluxed for (4-7 hr.). The solvent evaporated and

then treated with 10% sodium bicarbonate, and the formed precipitate was collected and recrystallized from mixture of (benzene – petroleum ether). Physical properties, yield and R_f are given in Table (2).

Table (2): Physical properties, yield and R_f of 2,3-dihydroquinazolin-4(1H)-one [F₇-F₁₁].



Comp No.	Ar	Molecular Formula M.Wt.	Color	M.P (C ⁰)	T. Ref. (hr.)	Yield (%)	R _f
F ₇		C ₄₈ H ₃₈ N ₈ O ₂ S ₂ 822.26	Orange	162-164	4	84	0.92
F ₈		C ₄₈ H ₃₆ I ₂ N ₈ O ₂ S ₂ 1074.80	Light red	158-160	5	62	0.74
F ₉		C ₄₈ H ₃₆ Cl ₂ N ₈ O ₂ S ₂ 891.89	Brown	182-184	6	67	0.82
F ₁₀		C ₄₈ H ₃₈ N ₈ O ₂ S ₂ 855.00	Dark brown	244-246	7	50	0.45
F ₁₁		C ₄₈ H ₃₆ Br ₂ N ₈ O ₂ S ₂ 980.80	Deep brown	192-194	6	77	0.63

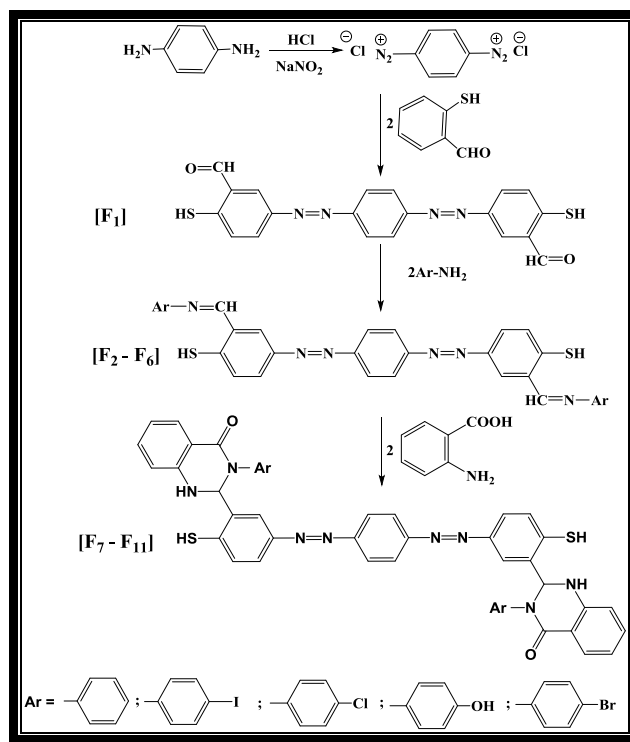
Dyeing processes[16]

Dyeing was done for cotton and wool by dissolving prepared compounds [F₁-F₁₁] in ethanol, then the cotton and wool were dried at (50°C) for one hour. Washing was done with distilled water, and dried again, washed with sodium hypochlorite (NaOCl) and

then dried. The stability of prepared pigments and the dyes proved high stability and bright colors.

Results and Discussion

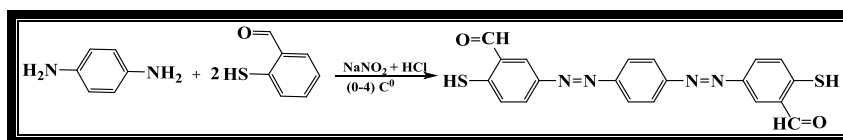
In this research many compounds were prepared including azo, Schiff bases and 2,3-dihydroquinazolin-4(1H)-one, as in the following Scheme:



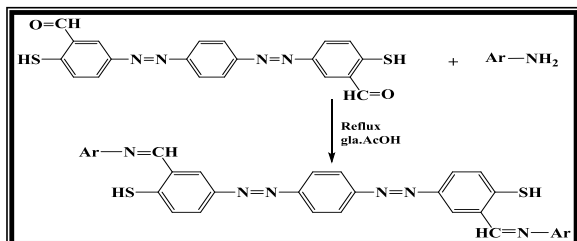
Scheme: Represents preparation compound [F₁-F₁₁]

Azo dye[F₁] was prepared by the reaction diazonium salt of 1,4-phenylenediamine with 2-mercapto benzaldehyde at (0-5) °C.

U.V-Vis. and FT-IR Spectrum of azo dye are given in table (3), fig. (1), C.H.N analysis is given in table (6). ¹H-NMR spectrum of compound [F₁] is given in fig. (4).



The Schiff bases [F₂-F₆] were prepared by the reaction of compound [F₁] with substituted aniline in absolute ethanol. The prepared compounds were characterized by FT-IR, ¹H-NMR, UV-Vis. Spectra, and C.H.N analysis

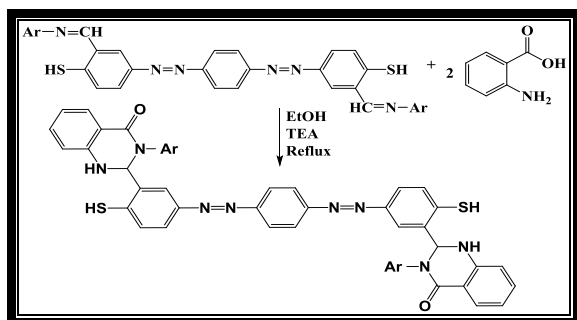


The UV spectra showed the transitions $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ which have confirmed the presence of the un-bonded electrons pair on Nitrogen, Sulphur atoms and aromatic system (double bond).

The FT-IR spectrum for Schiff bases showed the disappearance of two bands due to amino group, beside new bands which appear at (1649-1676) cm^{-1} attributed to the azomethine (C=N) more than the appearance of band at (1473- 1541) cm^{-1} , and (1513-1587) cm^{-1} due to (C=C) aromatic, and at (2560-2590) cm^{-1} attributed to (SH). In addition, a band at (3040-3091) cm^{-1} attributed to (C-H) aromatic, as shown in fig (2). U.V and FT-IR Spectrum were given in table (3). The heat of formation for prepared compounds [F₁-F₆] were given in table (7). The steric conformation of compound [F₁-F₆] were studied in lower energy level using Chem office (2015) see fig (12-17).

2,3-Dihydroquinazolin-4(1H)-one derivatives [F₇-F₁₁] were prepared from the reaction of 2-aminobenzoic acid with Schiff bases [F₂-F₆] in ethanol.

The UV-Vis. spectra showed the transitions $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ which have confirmed the presence of the un-bonded electrons pair on Nitrogen, Sulphur, Oxygen atoms and aromatic system (double bond).



The FT-IR spectrum showed a bands at (3278-3357) cm^{-1} due to (N-H), and at (1652-1693) cm^{-1} due to (C=O) for imide compounds, respectively. Besides other bands at (1503-1564) cm^{-1} and at (1568-1598) cm^{-1} due to (C=C) aromatic ring, and at (3065-3084) cm^{-1} for aromatic (C-H), beside which appear bands at (2546-2652) cm^{-1} due to (S-H) and at (2925-2968) cm^{-1} due to (C-H) aliphatic and band at (1112-1190) cm^{-1} due to (C-N). U.V. and FT-IR spectrum were given in table (4). $^1\text{H-NMR}$ spectrum of compound [F₉] was given in table (5) and Fig. (5). The heat of formation for prepared compounds [F₇-F₁₁] were given in table (7). The steric conformation of compound [F₇-F₁₁] were studied in lower energy level using Chem office (2015) see fig (18-22).

Table (3): FT-IR and UV/Vis data of the azo dye and Schiff bases derivatives [F₁-F₆]

Comp. No.	Ar	λ_1 max λ_2 max	IR (KBr) cm^{-1}					
			$\nu(\text{C}=\text{N})$	$\nu(\text{CH})$ arom.	ν (S-H)	ν (C=C)	ν (N=N)	other
F ₁	-----	280 344	-----	3032	2552	1587 1513	1453	(C=O) 1720 $\nu(\text{CH})$ alde. 2811,2740
F ₂		261 393	1660	3070	2576	1526 1569	1442	----
F ₃		277 396	1676	3050	2590	1480 1530	1463	$\nu(\text{C-I})$ 575
F ₄		227 354	1662	3040	2580	1473 1596	1438	$\nu(\text{C-Cl})$ 1000
F ₅		236 320	1668	3082	2582	1587 1513	1455	ν (C-OH) 3320
F ₆		232 375	1647	3083	2560	1473 1582	1475	$\nu(\text{C-Br})$ 560

Table (4): FT-IR and UV/Vis data of the 2,3-dihydroquinazolin-4(1H)-one derivatives[F₇-F₁₁]

Comp. No.	Ar	λ_1 max λ_2 max	IR (KBr) cm^{-1}					
			$\nu(\text{C}=\text{O})$	$\nu(\text{C-H})$ Arom. Aliph.	ν (NH) ν (S-H)	ν (C=C)	ν (N=N)	Others
F ₇		236 375	1676	3065 2932	3290 2550	1540 1568	1455	-----
F ₈		238 373	1673	3084 2937	3286 2546	1564 1585	1483	$\nu(\text{C-I})$ 600
F ₉		227 264	1660	3064 2925	3292 2567	1530 1587	1456	$\nu(\text{C-Cl})$ 1040
F ₁₀		263 376	1658	3102 2928	3357 2652	1598 1503	1453	ν (OH) 3417
F ₁₁		236 386	1693	3082 2937	3278 2558	1552 1580	1489	$\nu(\text{C-Br})$ 540

Table (5): $^1\text{H-NMR}$ spectra of 2,3-dihydroquinazolin-4(1H)-one derivatives[F₁, F₉]

Comp. No.	Data ppm
F ₁	2.58 (DMSO- d_6 solvent), 4.41 (s, 2H, SH), 7.62-8.12(14H, CH, aroma.)10.92 (s,2H, CHO aldehyde).
F ₉	2.52 (DMSO- d_6 solvent), 4.24 (s,2H,SH), 6.24(s,2H,CH alipha.) 6.48(s,2H,NH) , 6.65-7.35(26H, CH aroma.)

Table (6): Elemental analysis of compounds [F₁, F₂, F₅, F₁₀, F₁₁].

Comp. No.	Molecular Formula	Found					Calculated				
		C%	H%	N%	O%	S%	C%	H%	N%	O%	S%
F ₁	C ₂₀ H ₁₄ N ₄ O ₂ S ₂	58.80	3.40	13.71	8.39	15.70	59.01	3.47	13.78	7.87	15.77
F ₂	C ₃₂ H ₂₄ N ₆ S ₂	69.10	4.30	15.14	-----	11.46	69.04	4.35	15.10	-----	11.52
F ₅	C ₃₂ H ₂₄ N ₆ O ₂ S ₂	65.21	4.07	14.22	5.40	10.87	65.29	4.11	14.28	5.41	10.91
F ₁₀	C ₄₆ H ₃₄ N ₈ O ₂ S ₂	66.79	4.19	13.12	7.10	7.68	66.81	4.14	13.55	7.74	7.75
F ₁₁	C ₄₆ H ₃₄ Br ₂ N ₈ O ₄ S ₂	57.90	3.35	11.71	-----	6.85	57.99	3.39	11.79	-----	6.73

Table (7): Heat of formation of prepared compounds [F₁-F₁₁].

Comp. No.	Heat of Formation KJ/ mole	Comp. No.	Heat of Formation KJ/mol
F ₁	196.35	F ₇	834.93
F ₂	757.33	F ₈	967.73
F ₃	888.10	F ₉	484.93
F ₄	702.91	F ₁₀	480.31
F ₅	402.70	F ₁₁	864.65
F ₆	787.05		

Dyeing process: The resulting new dyes were highly colored and proven, as these dyes have thermal stability in which temperatures exceeded 100 °C, It was characterized by bright colors and showed clear consistency when washed with distilled water and dried, and then washed with sodium hypochlorite (NaOCl). This is due to the length of the double bonds sequence resulted from the large structural formulas of the prepared compounds, as shown in fig. (6,7).

Antibacterial activity

The effect of the prepared compounds on the growth of bacteria, namely: 1- *Escherichia coli* 2- *Klebsiella Pneumonia* 3- *Staphylococcus aureus* 4- *Staphylococcus epidermidis*.

Antibacterial activity of the prepared compounds were studied and the results showed that some of the prepared compounds possess good antibacterial activity [17]. The results were shown in table (8), see Fig. (8-11).

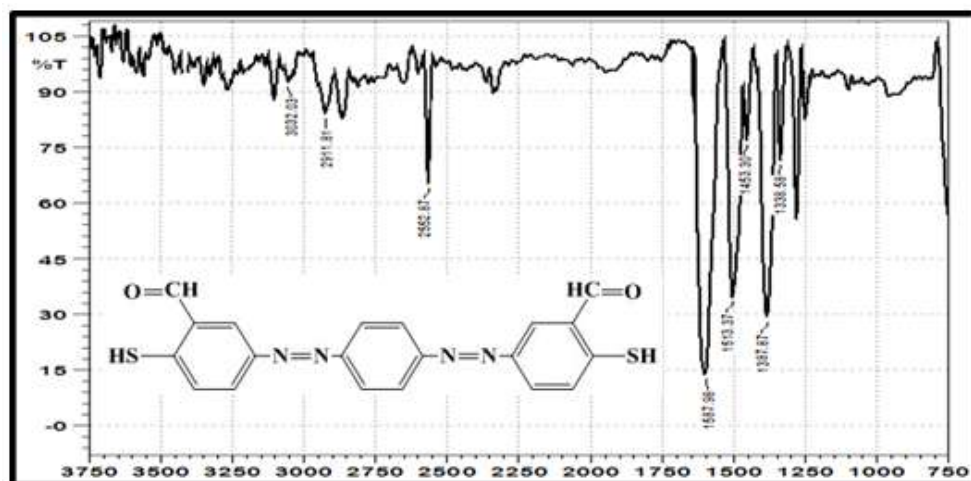
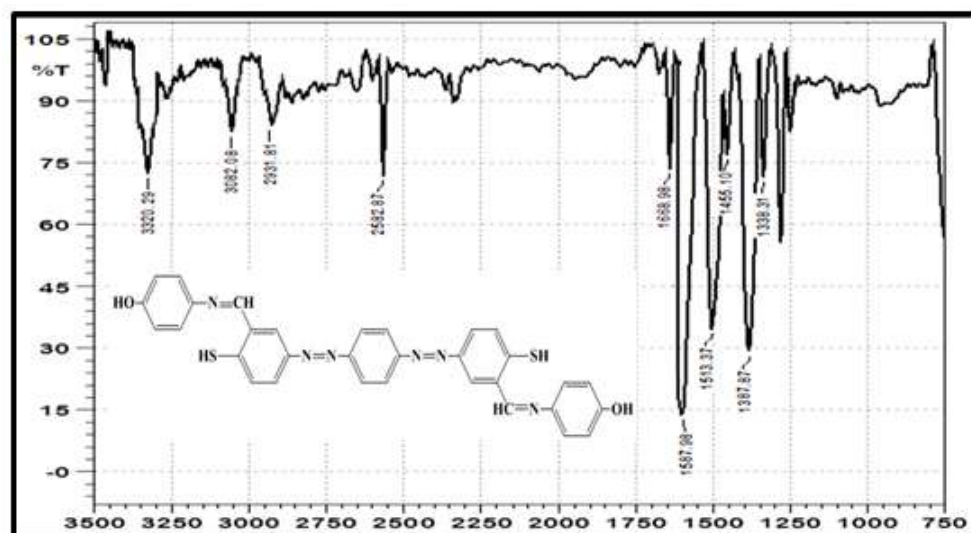
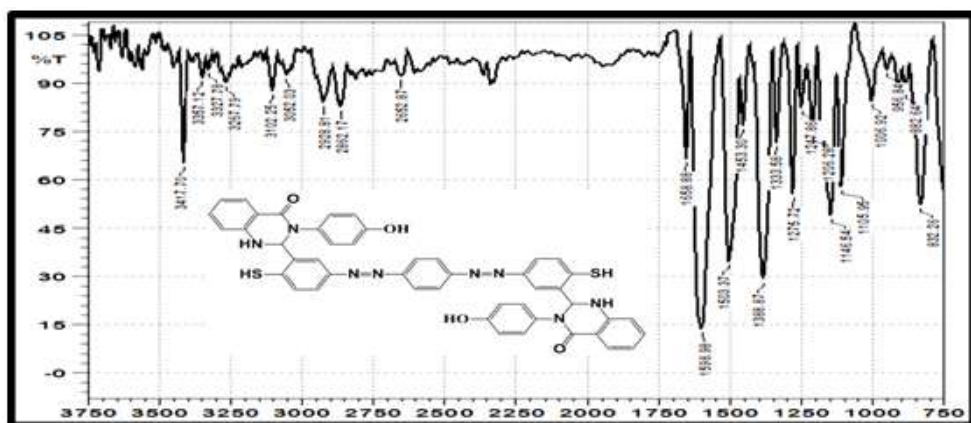
Table (8): Antibacterial activity of the prepared compounds[F₁-F₁₁].

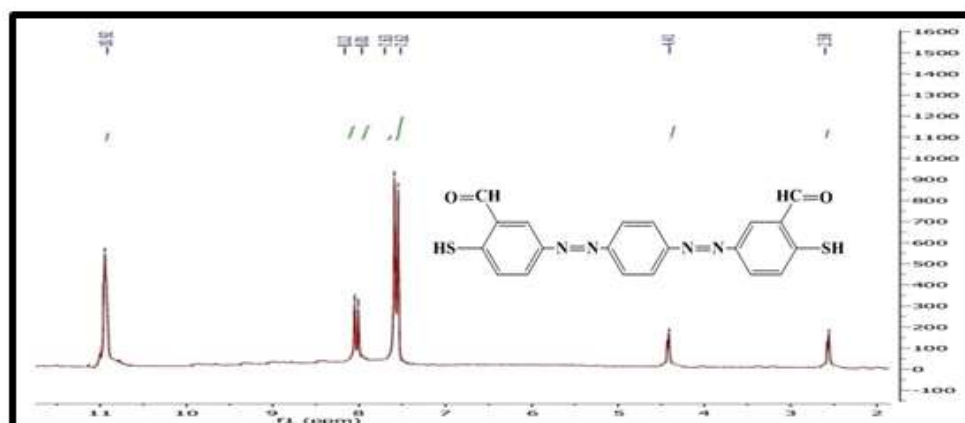
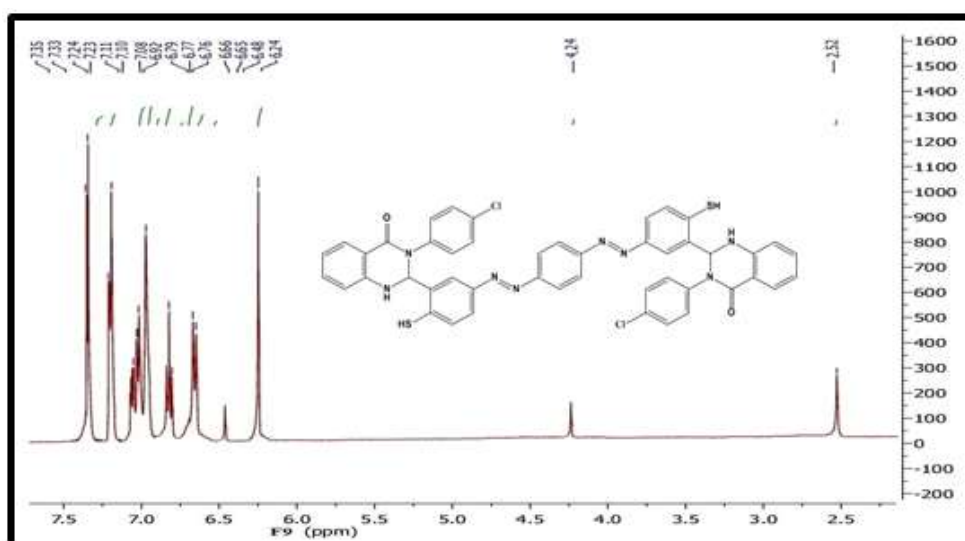
Comp. No.	Conc. mg/ml	<i>E.Coil</i>	<i>K.Pneumonia</i>	<i>S. Aureus</i>	<i>S. Epidermidis</i>
F ₁	25	-	-	+	-
	50	-	+	+	+
	100	-	++	++	+++
F ₂	25	+	-	+	-
	50	++	+	+	+
	100	++	+	+++	++
F ₃	25	+	-	++	+
	50	+	+	++	++
	100	+	++	+++	++
F ₄	25	+	-	+	++
	50	++	+	+++	++
	100	++	++	+++	+++
F ₅	25	-	+	+	-
	50	+	++	+	+
	100	++	++	+++	+
F ₆	25	-	-	-	-
	50	+	+	++	++
	100	++	+	++	++
F ₇	25	-	+	-	-
	50	+	++	++	++
	100	++	+++	+++	+++
F ₈	25	-	+	-	+
	50	++	++	++	++
	100	++	+++	+++	+++
F ₉	25	++	-	+	-
	50	++	++	++	++
	100	+++	++	+++	+++
F ₁₀	25	-	+	-	+
	50	++	++	+	++
	100	++	+++	++	+++
F ₁₁	25	-	+	=	+
	50	+	++	++	++
	100	++	+++	++	+++

(-) = No inhibition (+) = Inhibition zone (1-2) cm (++) = Inhibition zone (2-4) cm (+++) = Inhibition zone (4-5) cm

Table (9): Antibacterial efficacy of control treatments (antibiotics) in the growth of a number of negative and positive bacteria (diameter of the inhibition circuit measured by cm).

Comp. No.	Name	<i>E. Coil</i>	<i>K. Pneumonia</i>	<i>S. Aureus</i>	<i>S. Epidermidis</i>
1	Amoxicillin	2.6	2.5	3.3	2.8
2	Ampicillin	3.5	2.6	2.4	2.1
3	Blank disk	0	0	0	0

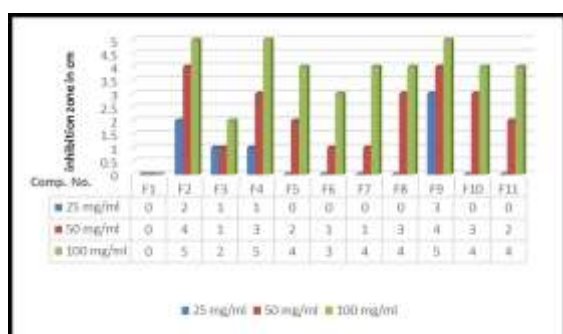
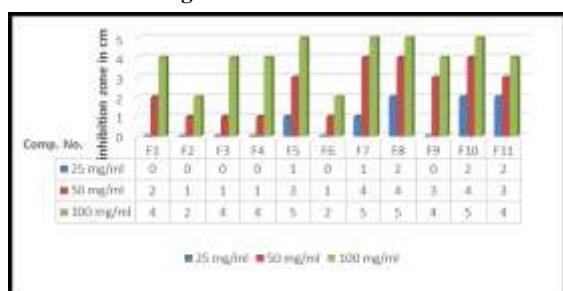
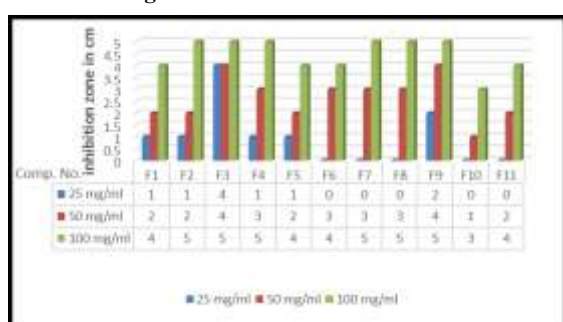
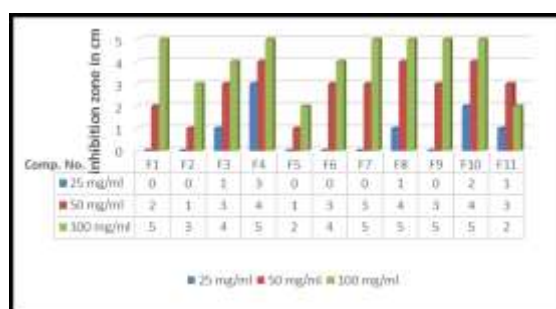
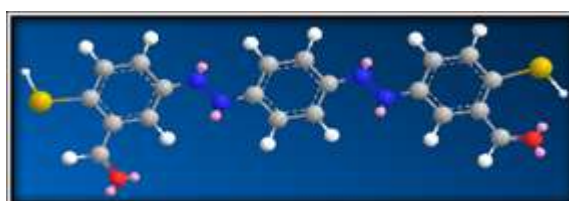
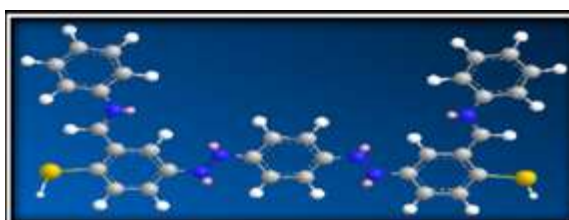
Fig (1): FT-IR spectrum of compound [F₁].Fig (2): FT-IR spectrum of compound [F₅].Fig (3): FT-IR spectrum of compound [F₁₀].

Fig (4): ¹H-NMR spectrum of compound [F₁].Fig (5): ¹H-NMR spectrum of compound [F₉].

Comp. No.	Cotton after dyeing	After washing with H ₂ O	After washing with NaOCl
F ₁			
F ₂			
F ₃			
F ₄			
F ₅			

Fig. (6): Cotton dyeing pictures of compound [F₁-F₅]

Comp. No.	Wool after dye	After washing with H ₂ O	After washing with NaOCl
F ₆			
F ₇			
F ₈			
F ₉			
F ₁₀			

Fig. (7): Wool dyeing pictures of compound [F₆-F₁₀].Fig (8):Antibacterial activity of compounds[F₁-F₁₁] against *E. Coli* bacteriaFig (9):Antibacterial activity of compounds[F₁-F₁₁] against *K. Pneumonia* bacteriaFig (10):Antibacterial activity of compounds[F₁-F₁₁] against *S. Aureus* bacteriaFig (11):Antibacterial activity of compounds[F₁-F₁₁] against *S. Epidermidis* bacteriaFig. (12):Minimize energy conformation of compound [F₁].Fig. (13):Minimize energy conformation of compound [F₂].

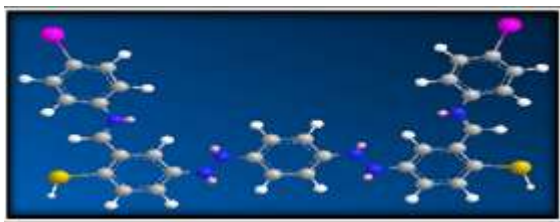


Fig. (14):Minimize energy conformation of compound [F₃].

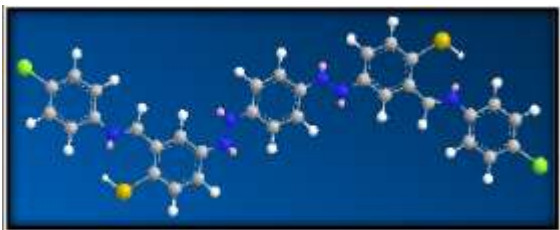


Fig. (15):Minimize energy conformation of compound [F₄].

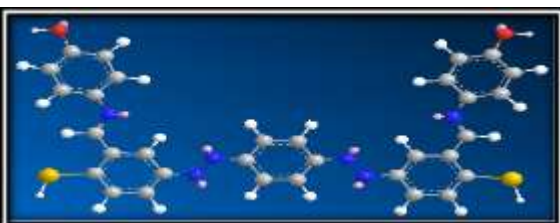


Fig. (16):Minimize energy conformation of compound [F₅].



Fig. (17):Minimize energy conformation of compound [F₆].

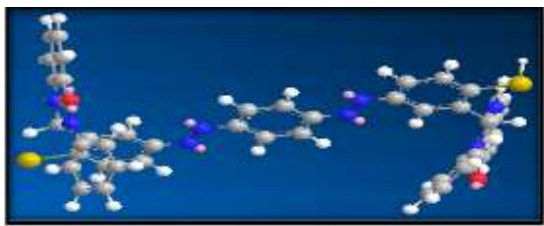


Fig. (18):Minimize energy conformation of compound [F₇].



Fig. (19):Minimize energy conformation of compound [F₈].

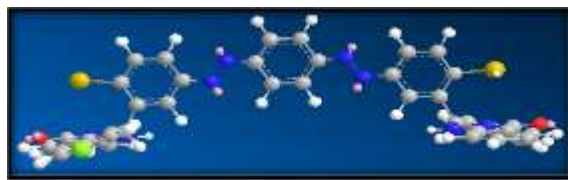


Fig. (20):Minimize energy conformation of compound [F₉].

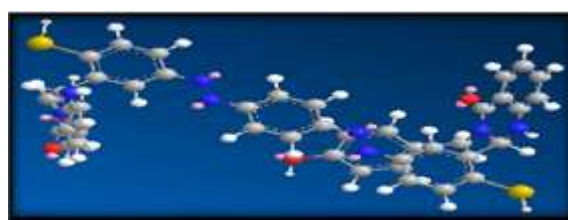


Fig. (21):Minimize energy conformation of compound [F₁₀].

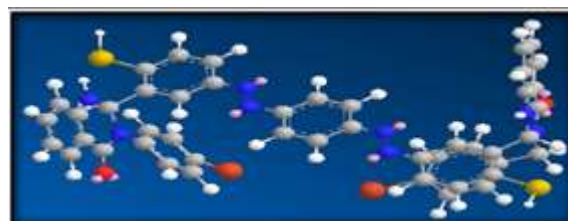


Fig. (22):Minimize energy conformation of compound [F₁₁].

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تحضير وتشخيص ودراسة الفعالية المضادة للبكتيريا لبعض مشتقات 3,2 - ثنائي

هايدروكوينازولين-4 (H1) - اون الجديدة

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الملخص

تم في هذا البحث تحضير بعض المركبات الجديدة لصبغة الازو من خلال تفاعل ملح الديازونيوم لمركب 4,1- فنلين ثنائي امين مع 2- مركبتو بنزالديهايد عند درجة حرارة (0-5) مئوية [F₁]. كما حضرت بعض مشتقات قواعد شيف الجديدة [F₆-F₂] من خلال تفاعل مركب [F₁] مع معوضات الأثلين بالايثانول المطلق ثم حولت قواعد شيف الى مشتقات 3,2- ثنائي هايدروكوينازولين-4 (H1) -اون [F₁₁-F₇] المقابلة من خلال تفاعلها مع مركب 2- امينو حامض البنزويك. شخّصت المركبات المحضرة بالطرق الطيفية من طيف الاشعة فوق البنفسجية (UV) والاشعة تحت الحمراء (FT-IR) وطيف الرنين النووي المغناطيسي للبروتون (¹H-NMR) والتحليل الدقيق للعناصر (C.H.N). كما تم تقييم الفعالية المضادة للبكتيريا لبعض المركبات المحضرة على أربع أنواع مختلفة من البكتيريا الموجبة والسالبة لصبغة كرام، اضافة الى ذلك تم دراسة ثباتية الاصباغ المحضرة على القطن والصوف والتي اثبتت انها ذات ثباتية جيدة واللوان زاهية. كما تم دراسة الهياكل الفراغية للمركبات المحضرة في المستوى الطاقى الأدنى.