Synthesis ,Characterization and Antioxidant Activity of Schiff base derivatives from [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin)]

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Abstract

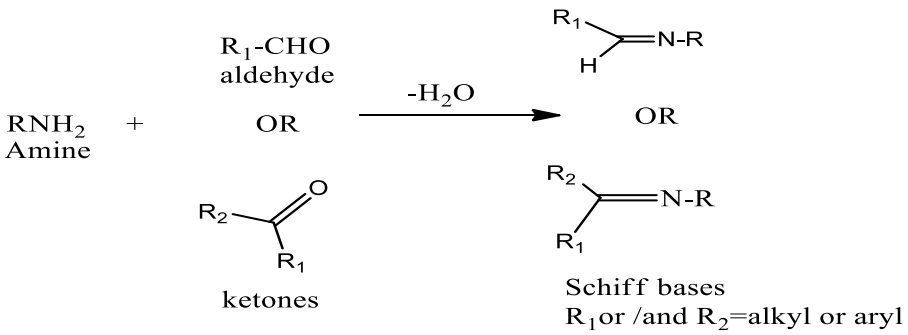
Two Hetreterocyclic compounds prepared from condensation reaction of Bis chalcone([3,3(1,4-phenylene)bis(1(4-aminophenyl)prop-2-en-1-one]with thiourea and urea By condensing a novel six-member heterocyclic (pyrimidene ring) with the suitable aromatic, new substituted azomethines of (*o, m, and p*) hydroxy benzaldehyde with heterocyclic substituents were created. By using NMR and FTIR spectroscopy, the novel heterocyclic compounds and these derivatives of schiff bases were identified.

A DPPH free radical scavenging assay was performed on the synthesized compounds, and the heterocyclic substituted thiol group and its Schiff base derivative demonstrated remarkable antioxidant activity.

Keywords: Schiff bases, pyrimidine, chalcone and, antioxidant

1. Introduction

German scientist Hugo Schiff (1864–1915) is mentioned. He found some bases and gave them the name Schiff bases [(1)]. Under particular circumstances, a primary amine reacts with carbonyl (aldehydes or ketones) to produce schiff bases. The major function is imine or azomethine (-C=N-) group because the general structure is $R_1R_2C=NR$ (R= H).[(2)]



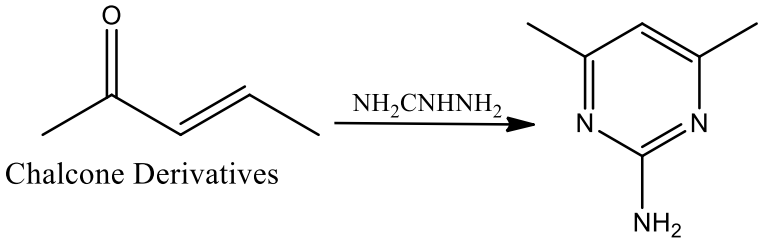
Scheme 1: General formation of Schiff bases

A variety of pharmacological and biological actions, including antibacterial, cytotoxic, antifungal, antimalarial, anticonvulsant, antioxidant, and anti-inflammatory properties, were demonstrated by Schiff bases, particularly those associated with heterocyclic moiety (3, 4).

Heterocyclic compound is the class of cyclic organic compounds those having at least one heteroatom (i.e. atom other than carbon) in the cyclic ring system. The most common heteroatoms are nitrogen (N), oxygen (O) and sulphur (S).Chalcones are thought to be one of the most beneficial sources of heterocyclic compounds. Due to their extensive biological activity, these compounds and their derivatives are regarded as some of the top medicinal chemistry molecules(5).

Chalcone undergoes a cyclization reaction under specific conditions to produce these heterocyclic rings with five, six, and seven members

pyrimidine ring example for Six membered unsaturated aromatic heterocyclic conmpound, scheme (2)(2) It was once believed that pyrimidines (also known as "m-diazine") were the byproducts of nitric acid's oxidation of uric acid. Pyrimidin ring containing two nitrogen atoms at positions 1 and 3 of the six-membered rings.(6)



Scheme (2)general synthesis pyrimidine from chalcone

2. Experimental:-

A- Materials: - Merck (Germany), Fluka (Germany), and Sigma Aldrich (UK) Chemicals Co. provided all the chemicals, which were all utilized exactly as they were given.

B- Instrumentation: The Department of Chemistry, College of Science, University of Basrah, calculated melting points in open capillary tubes using an electro thermal digital melting point instrument (England.

The University of Basra Polymer Research Center employed the Fourier Transform Infrared Spectrophotometer (FT-IR), which was made in Japan, to measure the IR spectra of heterocyclic compound.

The NMR spectrometer for thiopyrimidine derivative was obtained using a Bruker 400MHz, model Advance Ultrasheild equipment in the diluted solvent DMSO (Switzerland). Tetra methyl silane (TMS) was measured in the chemistry lab of the Education College of Basra in its conventional form.

3. Synthesis procedures:-

3.1. Procedure for the Preparation of Bis-chalcone[3,3(1,4-phenylene)bis(1(4-aminophenyl)prop-2-en-1-one].(compound no.1)

4-aminoacetophenone (0.015 mol, 2.013884 g) with an aromatic amine (0.00750 mol, 1.005975 g) Terphthaldehyde was mixed in 15 ml of ethanol $_{(7)}$, and after 20 minutes of stirring, 10 ml of an aqueous sodium hydroxide solution (60%) was added dropwise while the mixture was still being stirred.

At room temperature, the mixture was stirred for 24 hours. The required product $_{(8)}$, having a melting point of 140-142^{o}C and a yield of 65%, was then obtained by diluting it with 100ml of ice-cold, distilled water, leaving it for 15 minutes, filtering, washing thoroughly in cold water to remove NaOH, and monitoring with PH papers. It was then dried in the air and recrystallized from the ethanol.

3.2 Procedure for the Preparation of[6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-thiol)] (compound no2)

The literature provided a description of how to make pyrimidin [6]. In our study, it was prepared in a different way than the method mentioned in that study.

Bis-Chalcone (0.004 mol) was refluxed with Thiourea (0.009 mol) in toluene solvent (20 ml) and a catalytic a small amount of glacial acetic acid at 80^{O}C for 24h. The reaction was monitored by TLC using (Chloroform : Methanol) (9.5 ml + 0.5ml).

After the reaction was finished, the precipitate was filtered, dried, and recrystallized with toluene to produce the desired product, which had a melting point of 150–152^{o}C and a yield of 60%, dark brown powder.

3.3 synthesis of [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-ol)] (compound no.3)

The method for synthesizing pyrimidine was published in the literature[9]. In contrast to the procedure described in that article, it was made differently in our investigation.

Bis-Chalcone (0.004 mol) and urea (0.0010 mol) were refluxed in toluene (20 ml) for 24 hours at 80^{o}C with catalytic addition of a little amount of glacial acetic acid after 15 minutes. TLC and (Chloroform: Methanol) (9.5 ml + 0.5 ml) were employed to monitor the reaction.

After the reaction is finished, In order to produce the desired product with the specified melting point (260^{o}C decomposition) and yield (64%) was produced, an oily substance was generated, which was removed from the solvent and washed with ethanol. Crystals were then formed, which were separated, dried, and cleaned by ethanol.

3.4 Synthesis Schiff bases derivative from heterocyclic compounds and (o,m and p) hydroxy benzaldehydes

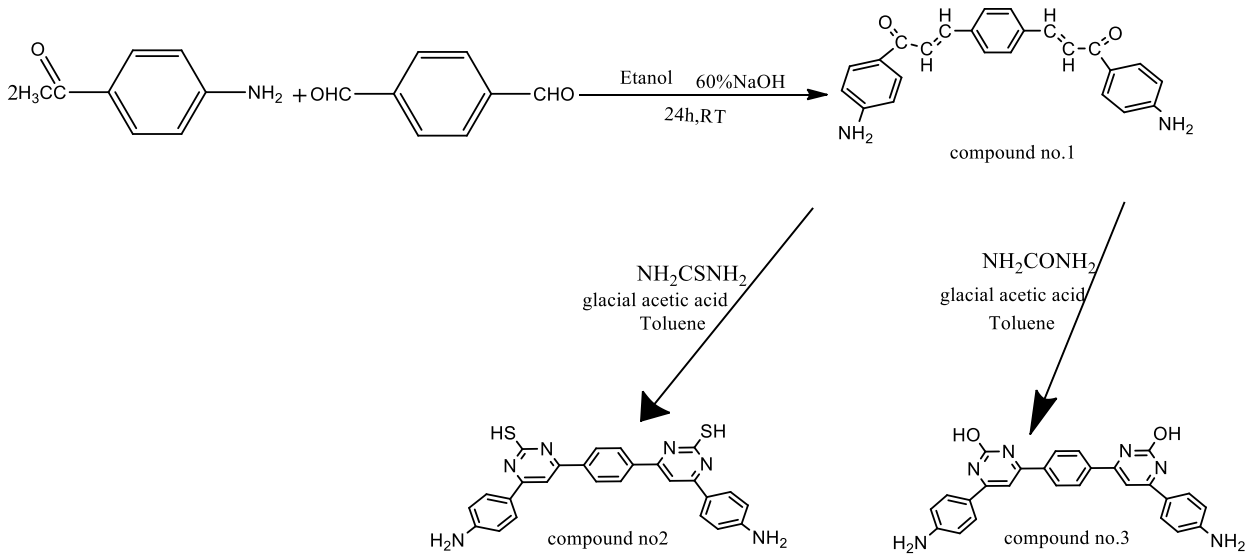
Schiff base was prepared as mentioned in the literature [10]. In our research Schiff base compounds were synthesized by the reflux condensation reaction of (*o,p,m*)-hydroxybenzaldehyde compounds (0.003mole) along with (0.001mole) diamine heterocyclic compounds(Scheme 3) using 15ml absolute ethanol as solvent in addition of a small amount of p-toluene sulphonic acid as catalyst. The

reaction was carried out at 70-80^{o}C temperature with continuous stirring for about 15 hours into a 100 ml of round bottom flask with monitoring by thin layer chromatography TLC(9.5 ml Chloroform : 0.5ml Methanol).

oily or powder were obtained after (48) hours dried at room temperature. Diethylether was used for washing and product was recrystallized with ethanol and dried at room temperature.

4. Results and discussion

The synthesis heterocyclic derivative from Bis-chalcones and their was carried out in accordance with Scheme (3), and Table (1)contains physical information on these compounds. The initial chalcone, [3,3(1,4-phenylene) bis(1(4-aminophenyl)prop-2-en-1-one], was created using the Claisen-Schmidt reaction of 4-aminoacetophenone with Terphthaldehyde in ethanol in the presence of aqueous sodium hydroxide at room temperature. In acid medium at 80 ^{O}C, the Bis-chalcone and Thiourea (or urea) were allowed to react for 24 hours to obtain pyrimidine rings, these compounds are shown in scheme (3)



Scheme (3) synthesis Bis-chalcone and primidine derivatives its

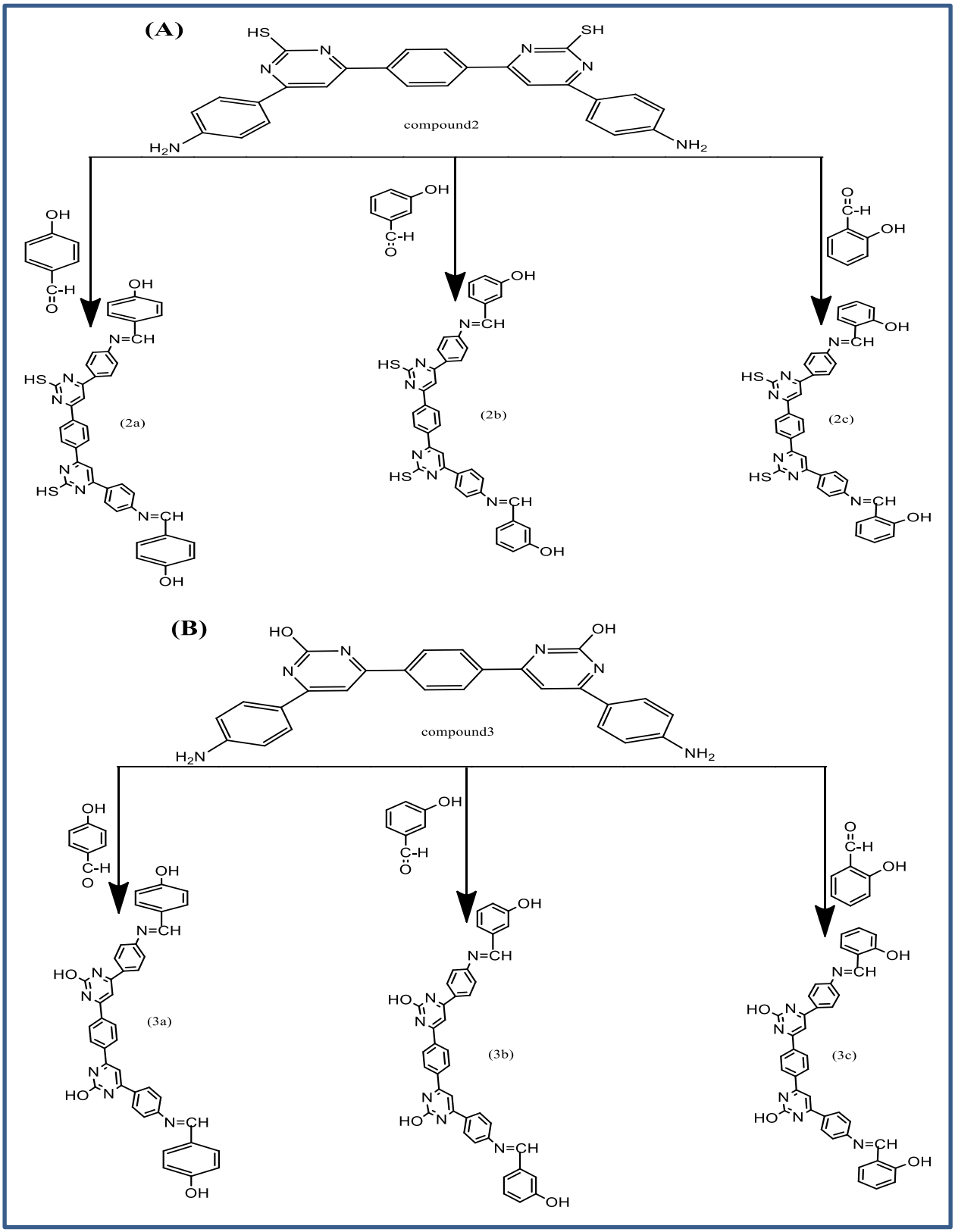
The prepared compounds are characterized by FTIR and ^{1}H NMR spectroscopy (11-13). The characteristic FTIR adsorption band of heterocyclic compounds showed the disappearance of two absorption bands of the CH=CH and C=O groups in

(1700-1770)$cm^{-1}$and 1600cm^{-1} respectively in the chalcone. Shown in Figures (1and 2)

FTIR [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-thiol)](compound2)and [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-ol)](compound3) appearance of new absorption bands for C=C hetro ring stretching in 1570$cm^{-1}$and 1516cm^{-1} respectively. SH and C-S stretching for compound (2) around 2640 cm^{-1} and 729.9cm^{-1}, respectively. The compound (3) appearance new stretching band for (OH) in 3205cm^{-1}.The FTIR spectral data of these compounds are shown in Table (2).

TetraMethylSilane (TMS) was used as an internal standard in the ^{1}H NMR analysis of heterocyclic compounds (2and 3) in DMSO, [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-thiol)](compound2) which revealed the following signals: A doublet signal in the region of 7.89 ppm could be attributed to two protons of the pyrimidine ring, a sharp singlet signal at 6.07 ppm due to the four proton of the two amine groups, and a singlat signal in the region of 6.62 ppm for two protons of the (SH) groups substituted in heterocyclic, where [6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-ol)](compound3) appeared doublet signal in 7.56 ppm to two protons of the pyrimidine ring, a singlet signal at 6.06 ppm to the four proton of the two amine groups, and a singlet signal in the region of 8.78 ppm for two protons of the (OH) groups substituted in heterocyclic Table(3) displays the ^{1}HNMR spectral information for these substances.

Schiff base compounds were synthesized by condensation reaction of hydroxyl benzaldehyde drevitives (0.001mole) along with (0.003mole) diamine heterocyclic compounds at 70-80^{o}C temperature in acid medium. The physical properties of these compounds in the table (4) and the synthetic route to the compounds is outlined in Scheme (4)**.**



Scheme (4)(A,B)Schiff base compound derivative from heterocyclic compounds in scheme(2-2).

The synthesized Schiff base compounds' FTIR spectra, which are depicted in Figures (3) to (8), revealed the elimination of the amine band for heterocyclic compounds in the range of (3100-3300) cm^{-1} and the carbonyl band for aldehyde compounds in the region of (1700-1770) cm^{-1}. The stretching frequency of the azomethine group in the range (1600 -1690) cm^{-1} caused a new unique medium to strong intensity band to form in the spectrums.

The FTIR spectra of all the prepared compounds showed a wide and distinct band in the region (3000-3500) cm^{-1} due to the hydroxide groups. Table (5) displays the results for these chemicals' absorption bands

The singlet signal at position (6.07ppm), which is a member of the amine group of heterocycles, vanished from the 1H NMR spectra of Schiff bases generated in Figures (11–16). This shows how aldehyde compounds' amine group and carbonyl group interact.

It was also found the emergence of a new signal belonging to the azomethine group within the range δ (9.67-8.17)ppm. The spectra also showed a singlet signal due to the hydroxyl groups within the range δ (10.26-8.76)ppm. As well as found multiplet signal to aromatic rings located between δ (7 -8.5) as shown in the table below(6)

It was also found that all derivatives gave a doublet signal within the range δ (5-8) ppm due to the proton of the heterocyclic ring.

Table (1) Physical properties o f synthesized compounds (in scheme 3)

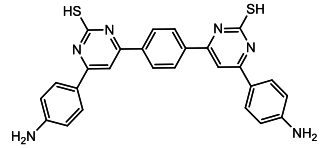
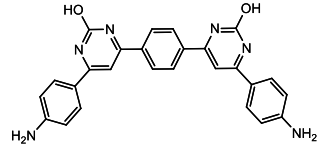
Comp. No.	Nomenclature	Molcular formula	M.Wt. g.mol^{-}	m.p.^{o}C	Rf	Yield%	Color	Structure
2	6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-thiol)	$C_{26}H_{20}N_6S_2$	480.12	150-152	0.59	60%	Dark brown	
3	6,6'-(1,4-phenylene)bis(4-(4-aminophenyl) pyrimidin-2-ol)	$C_{26}H_{20}N_6O_2$	448.48	260(d)	0.68	64%	Brown	

Table (2): The FT- IR data of the synthesized heterocyclic compounds

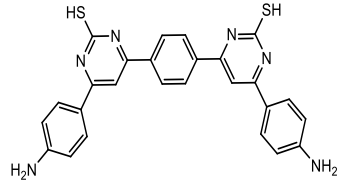
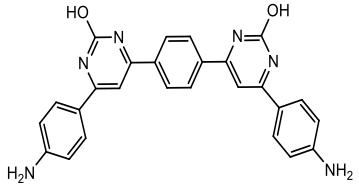
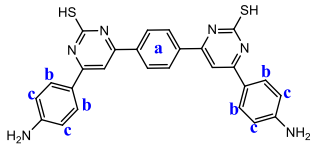
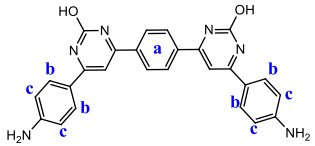
Comp.no.	Structure	(NH_2) stretching	C-N stretching	C=C Ar. Stretching	C-H Ar. stretching	C=C hetro. Stretching	Others
2.3		3383.5(w)	1168.65(s)	1597.73(s)	3177.15(w)	1570(m)	SH stretching=2640(W) C-S stretching= 729.9(m)
2.4		3353.6 (b)	1178.29(m)	1592.91(s)	3090(w)	1516(s)	OH stretching=3205(W)
S=strong , b=broad , m=medium , w=weak							

Table (3): The chemical shifts values of the synthesized heterocyclic compounds

Comp.no.	structure	a (4H)	b (4H)	c (4H)	CH ring (2H)	NH_2 (4H)	Other
2		7.68-7.6 (m)	7.58-7.5 (m)	6.81-6.66 (m)	7.89(d) J=8Hz	6.07(s)	(2H)SH=6.62(s)
3		8.12-7.82 (m)	7.75-7.63 (m)	6.96-6.57 (m)	7.56(d) J=8Hz	6.06(s)	(2H) OH=8.78(s)
Where : m= multiplet, d=doublet , s=singlet , J= coupling constant							

Table(4) The physical properties for the Schiff bases are derived from hetrocyclic compounds(scheme4)

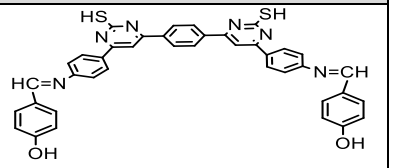
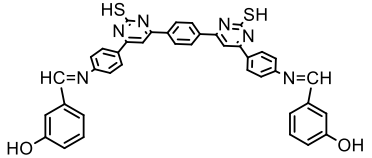
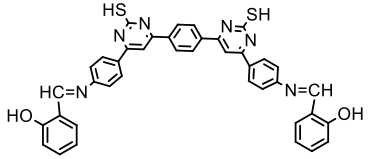
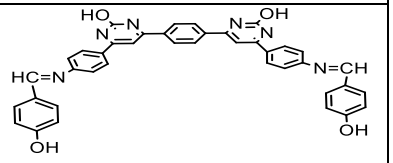
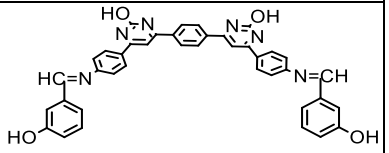
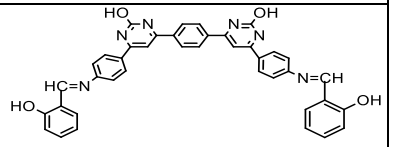
Com. No.	Nomenclature	Molecular formula	M.wt. g.mol^{-}	m.p.^{o}C	R_f	Yield %	color	Structure
2a	4,4'-((((6,6'-(1,4-phenylene)bis(2-mercaptopyrimidine-6,4-diyl))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol	$C_{40}H_{28}N_6O_2S_2$	688.82	160-162	0.56	25%	Red	
2b	3,3'-((((6,6'-(1,4-phenylene)bis(2-mercaptopyrimidine-6,4-diyl))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol	$C_{40}H_{28}N_6O_2S_2$	688.17	120-122	0.63	14%	Brown	
2c	2,2'-((((6,6'-(1,4-phenylene)bis(2-mercaptopyrimidine-6,4-diyl))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol	$C_{40}H_{28}N_6O_2S_2$	688.82	150-153	0.7	63%	Brown	
3a	6,6'-(1,4-phenylene)bis(4-(4-((4-hydroxybenzylidene)amino)phenyl)pyrimidin-2-ol)	$C_{40}H_{28}N_6O_4$	656.69	240(d)	0.6	56%	Orange	
3b	6,6'-(1,4-phenylene)bis(4-(4-((3-hydroxybenzylidene)amino)phenyl)pyrimidin-2-ol)	$C_{40}H_{28}N_6O_4$	656.69	220-222 (d)	0.78	29%	Orange	
3c	6,6'-(1,4-phenylene)bis(4-(4-((2-hydroxybenzylidene)amino)phenyl)pyrimidin-2-ol)	$C_{40}H_{28}N_6O_4$	656.69	281-283 (d)	0.58	43%	Orange	

Table (5): The FT- IR data of the synthesized Schiff Bases compounds

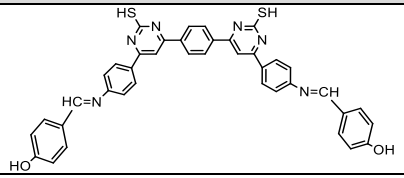
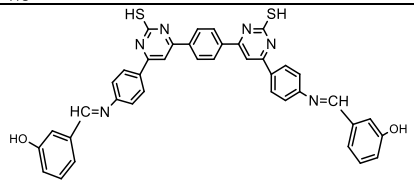
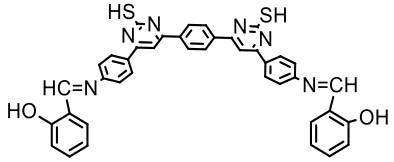
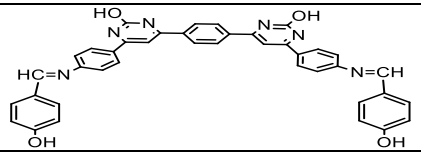
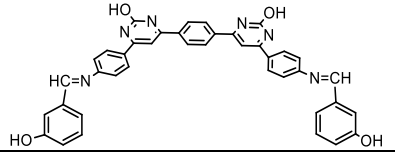
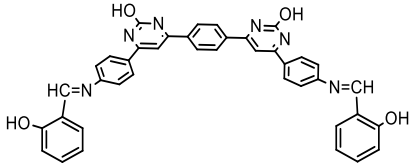
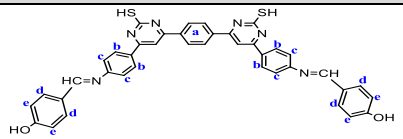
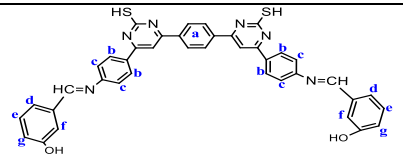
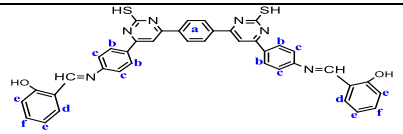
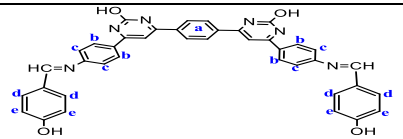
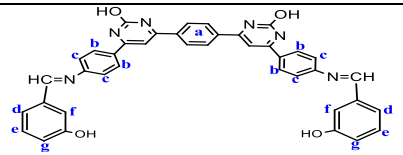
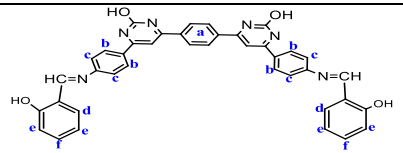
comp. no.	Structure	(C=N) stretching	C-N stretching	C=C Ar. stretching	C-H Ar. stretching	C=C hetro. stretching	(OH) stretching	Others Stretching
2a		1630(m)	1169 (s)	1597.7 (s)	3205 (w)	1545.6 (m)	3328.5 (s)	SH=2917.7(m)
2b		1685.1(m)	1172.7 (s)	1593.6 (s)	3193.8 (w)	1523 (m)	3318.0 (b)	SH=2925.9 (W)
2c		1610.8(m)	1176.2 (s)	1594.7 (s)	3179.7 (w)	1570 (m)	3322.9 (b)	SH=2923.0(w)
3a		1655(m) 1675(m)	1177.3 (s)	1590.9 (s)	3010 (w)	1521 (s)	3407(b)	OH connect with hetro.ring =3340
3b		1673.8(m)	1177.9 (s)	1589.1 (s)	3110.6 (w)	1515 (s)	3346.7(b)	OH connect with hetro.ring .=3196.7(b)
3c		1674.2(m)	1176.58 (s)	1587.4 (s)	3099.6 (w)	1516.1 (s)	3468.1(b)	OH connect with hetro.ring =3290.5(b)
S=strong , b=broad , m=medium , w=weak								

Table (6): The chemical shifts values of the synthesized Schiff bases compounds.

comp. no.	Structure	a (4H)	b (4H)	c (4H)	d	e	CHring (2H)	CH=N (2H)	OH	other
2a		7.65(d) J=8Hz	7.56-7.61(m)	6.73(d) J=4Hz	7.75-7.78 (m) (4H)	6.9(d) (4H) J=8Hz	7.88(d) J=4Hz	9.67 (s)	9.79 (s)	SH (2H)=6.59(s)
2b		7.47(d) J=8Hz	7.41(d) J=8Hz	7.36(d) J=8Hz	7.24 (s) (2H)	7.12(d) (2H) J=8Hz	8.20 (s)	9.26 (s)	9.91 (s)	SH(2H)=6.49(s) f(2H)=6.19(d) J=8Hz g(2H)=6.61(s)
2c		7.88(d) J=8Hz	7.68-7.65 (m)	7.46 (s)	7.11(d) (2H) J=8Hz	7.01-6.94 (m) (2H)	8.14 (s)	9.67 (s)	10.26 (s)	SH(2H)=6.59(s) f(2H)=7.55(d) J=16Hz
3a		7.9(d) J=8Hz	7.61(d) J=8Hz	7.12(d) J=8Hz	7.48(d) (4H) J=8Hz	6.85(d) (4H) J=12Hz	7.98 (s)	8.17(d) J=12Hz	8.76 (S)	OH connected with hetro ring(2H) =9.09(S)
3b		7.71 (s)	7.62(d) J=12Hz	7.54 (s)	7.49(d) (2H) J=4Hz	7.12(d) (2H) J=8Hz	8.11 (s)	8.22(d) J=8Hz	9.28 (s)	OH connected with hetro ring (2H) =9.91(S) f(2H)=6.9(d) J=8Hz
3c		7.71 (s)	7.63(d) J=8Hz	7.12(d) J=8Hz	7.49(d) (2H) J=8Hz	6.03(s) (2H)	8.12 (s)	8.22 (s)	-	OH connected with hetro ring (2H) =9.21(s) f(2H)=6.9(d) J=8Hz
Where : m= multiplet, d=doublet , s=singlet , J= coupling constant										

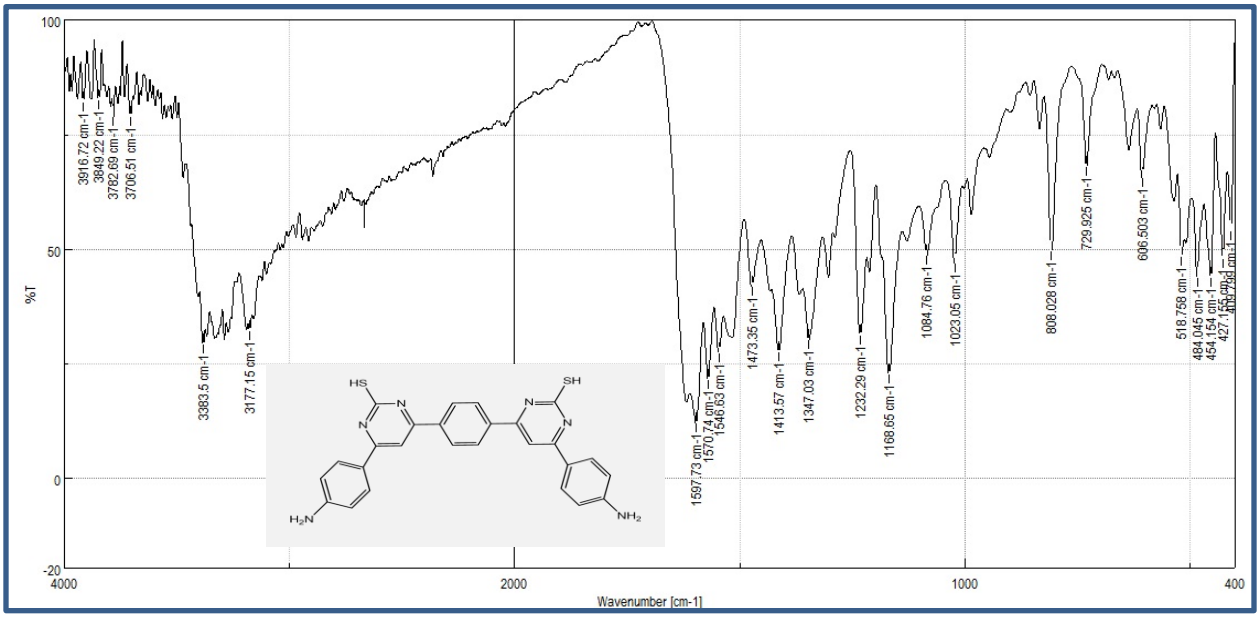


Figure (1): The FT-IR Spectrum of the compound (2)

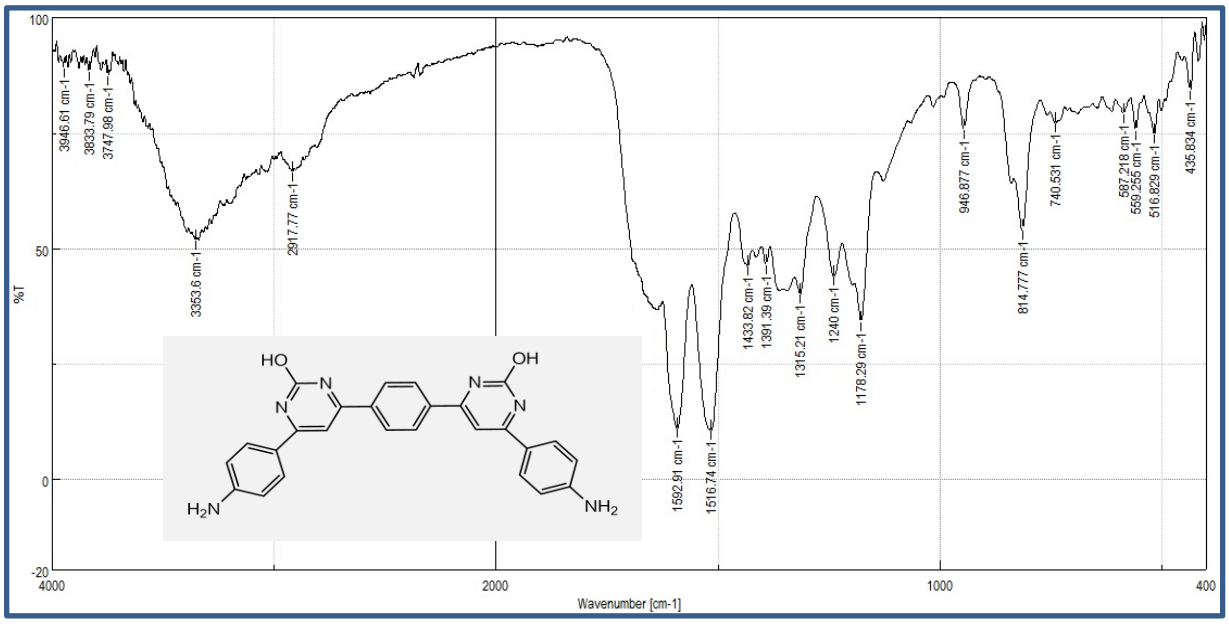


Figure (2): The FT-IR Spectrum of the compound (3)

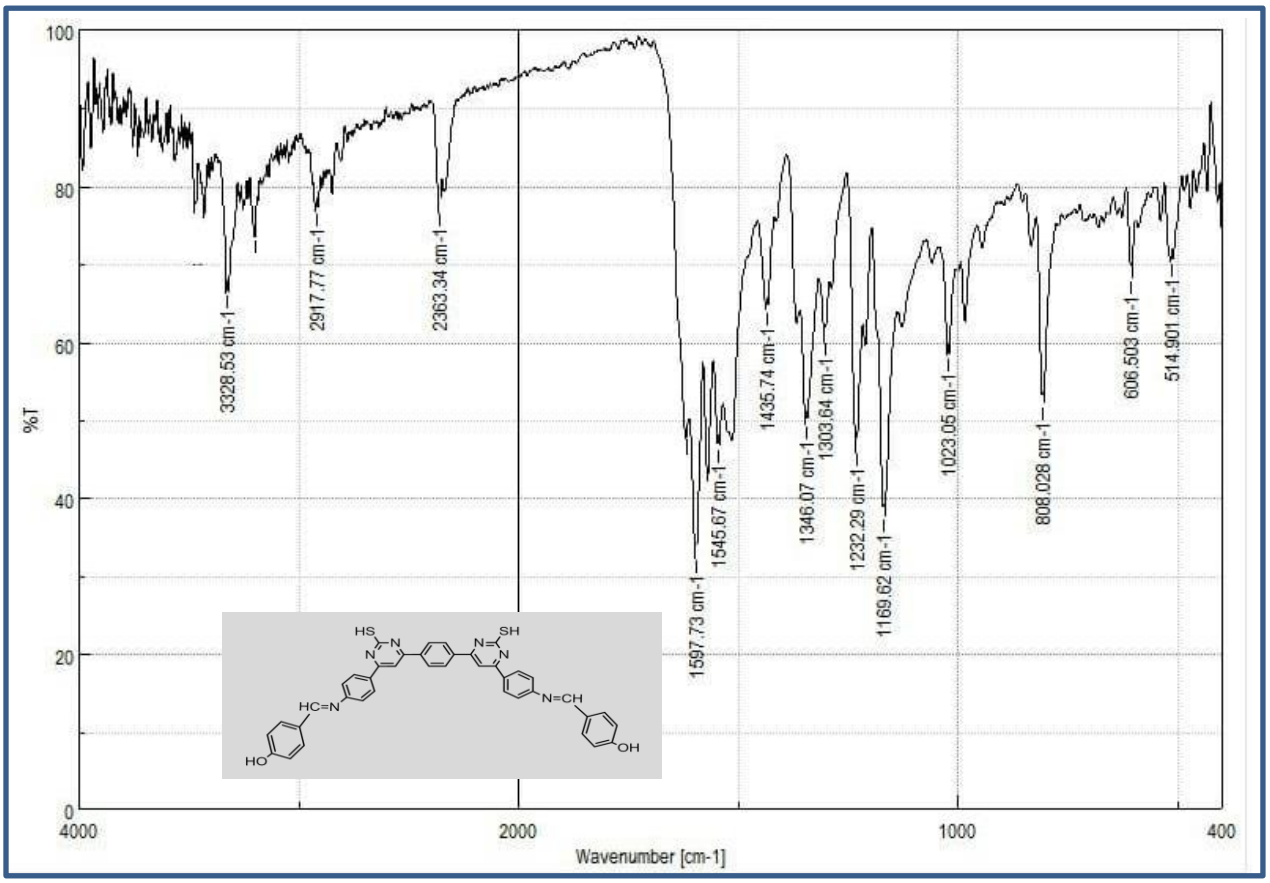


Figure (3): The FT-IR Spectrum of the compound (2a)

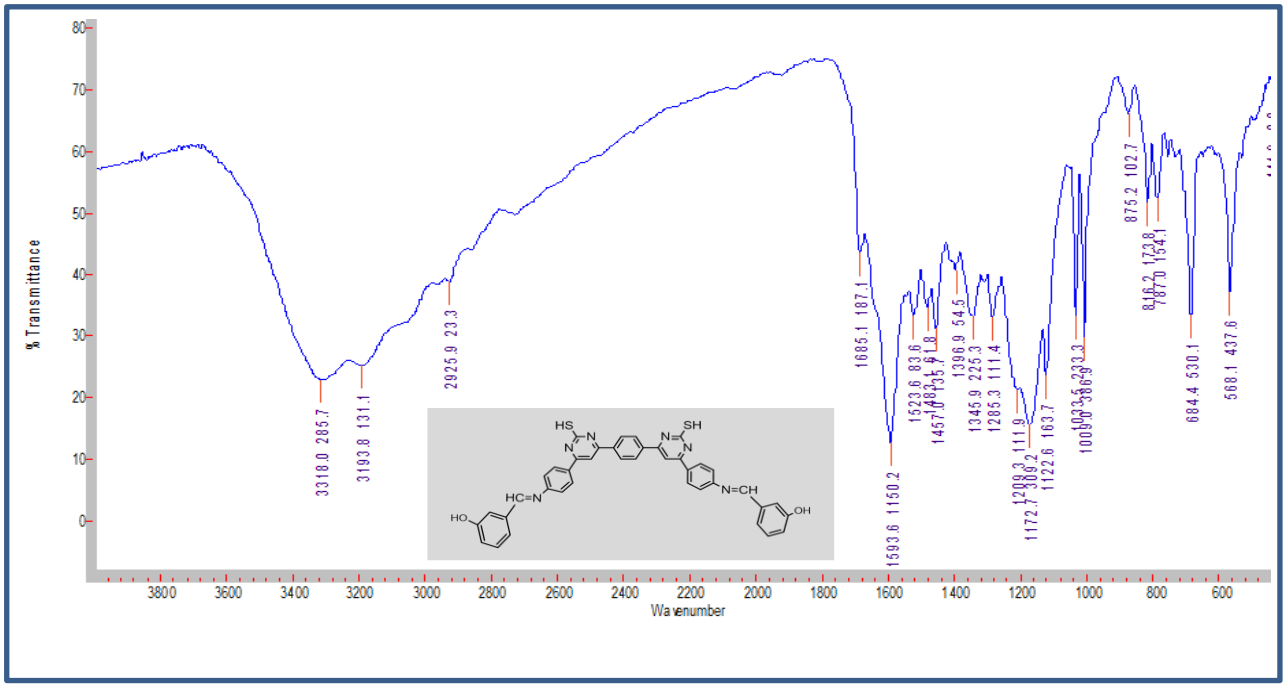


Figure (4): The FT-IR Spectrum of the compound (2b)

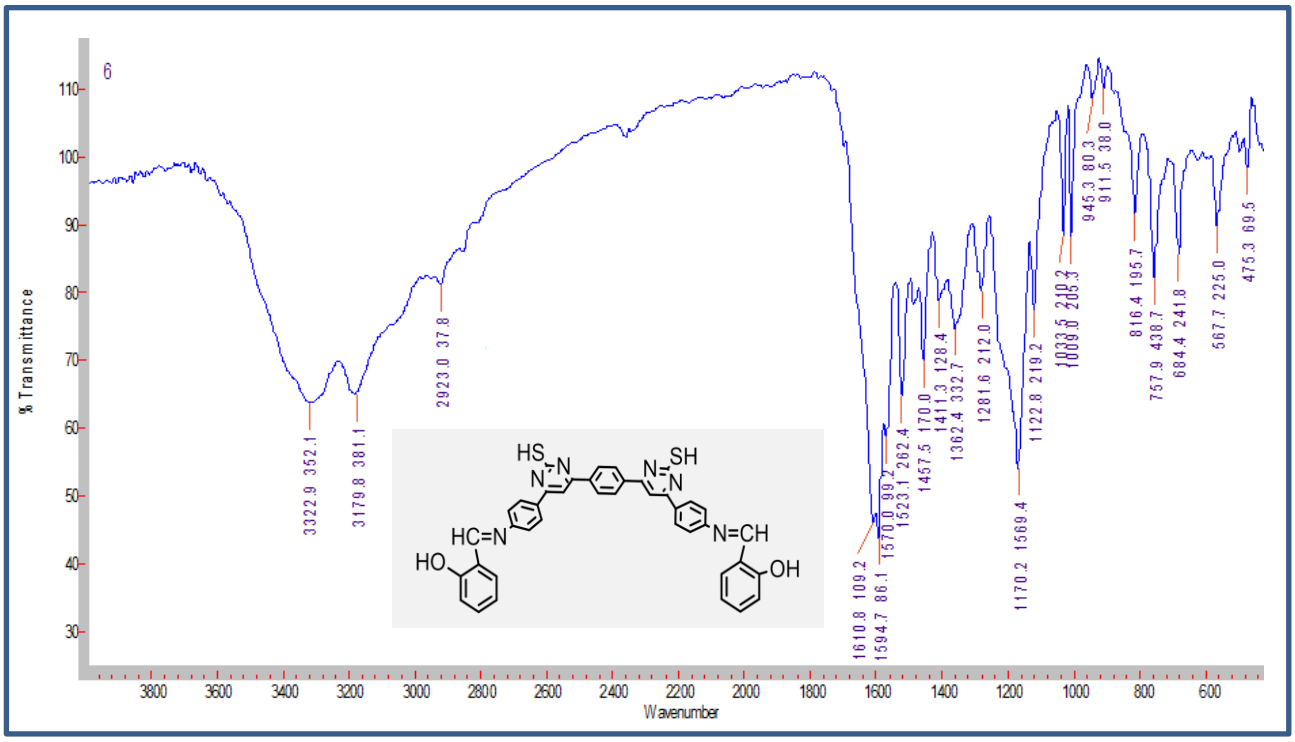


Figure (5): The FT-IR Spectrum of the compound (2c)

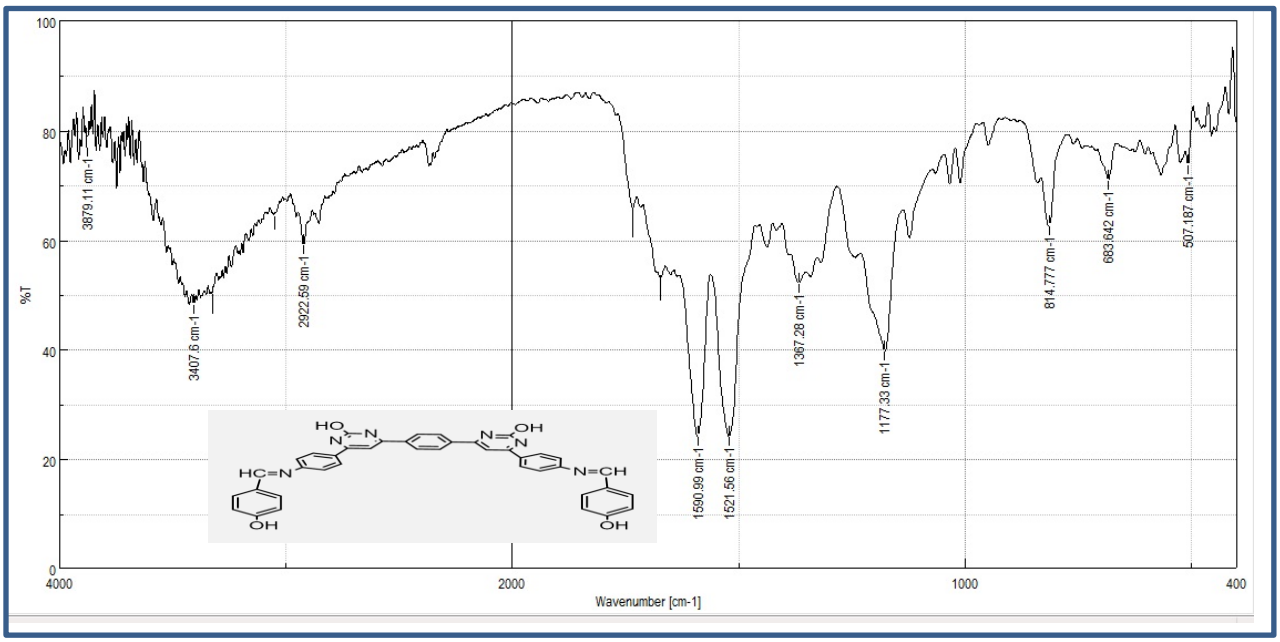


Figure (6): The FT-IR Spectrum of the compound (3a)

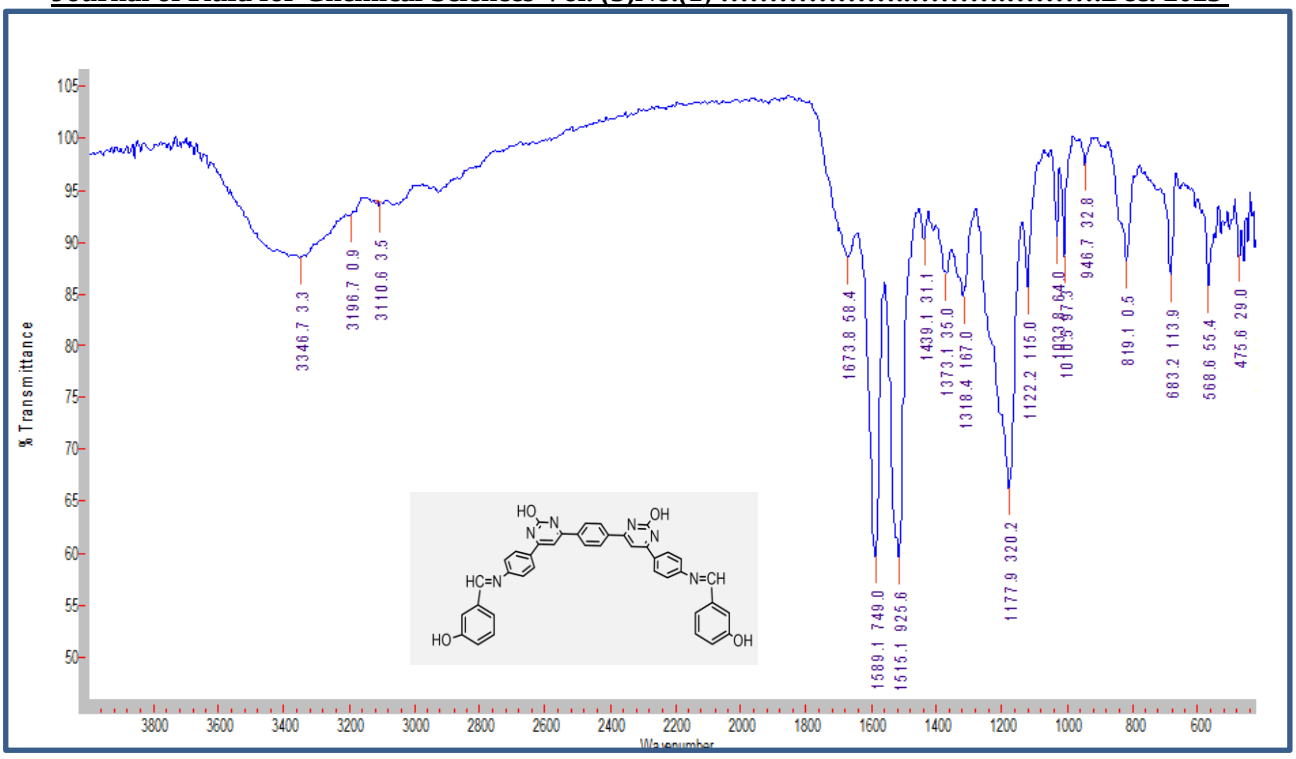


Figure (7): The FT-IR Spectrum of the compound (3b)

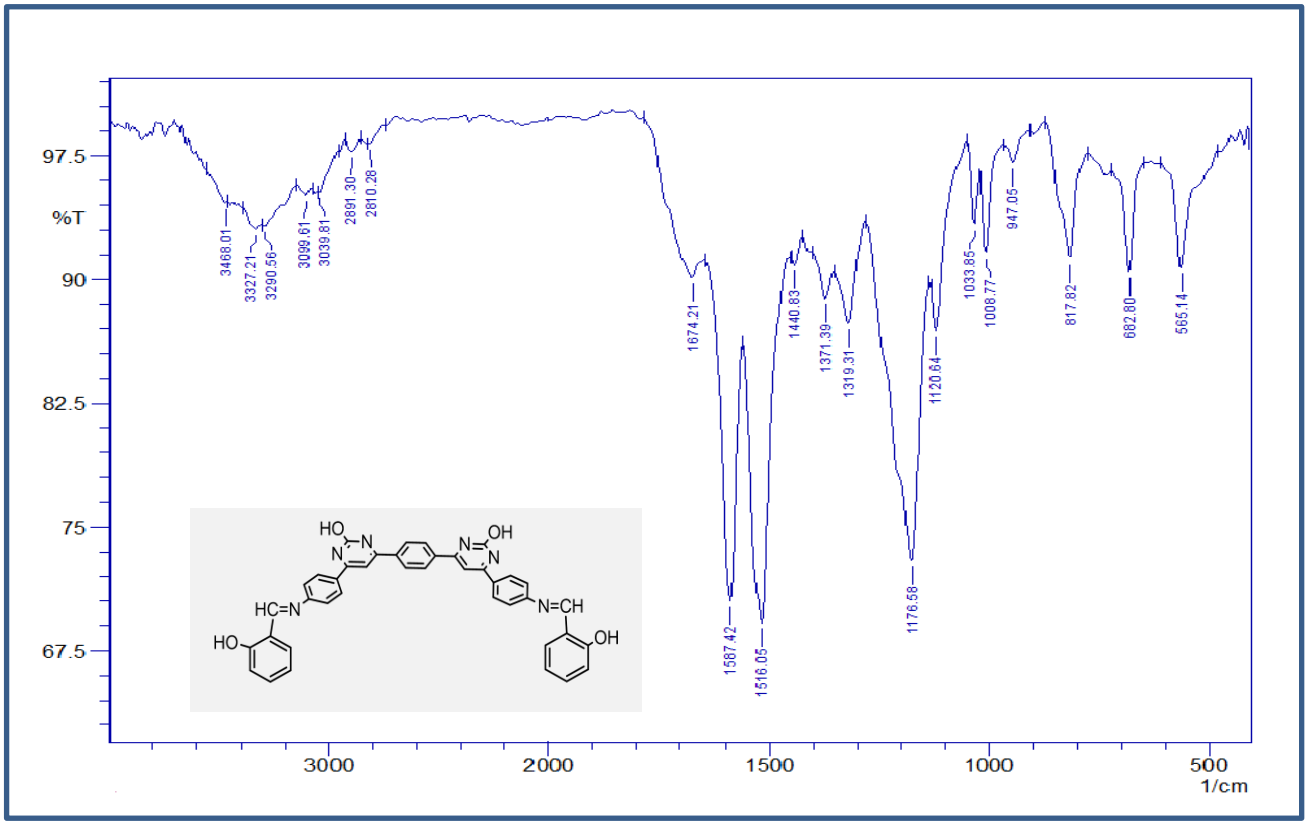


Figure (8): The FT-IR Spectrum of the compound (3c)

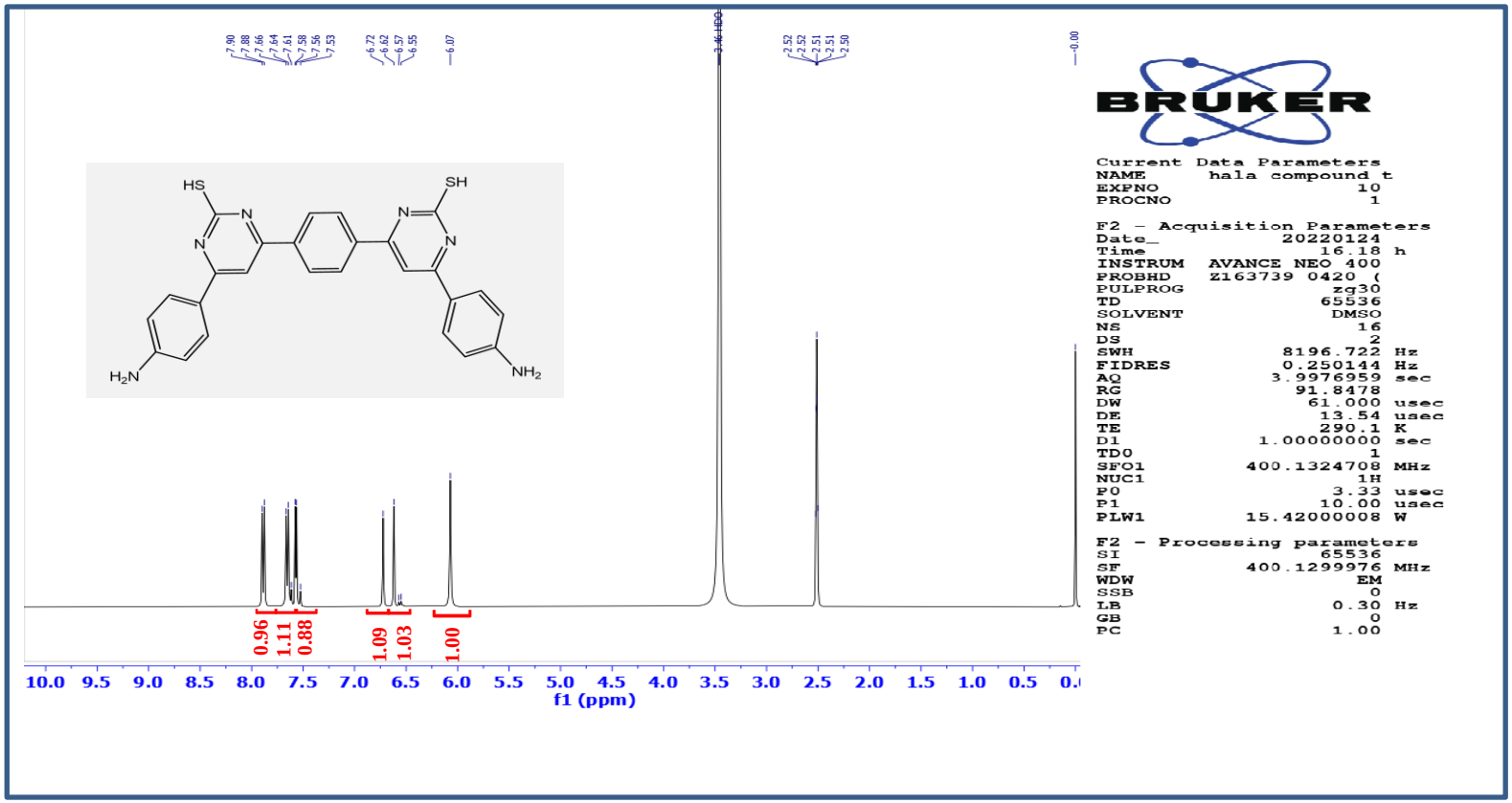


Figure (9): H^1-NMR of compound(2)

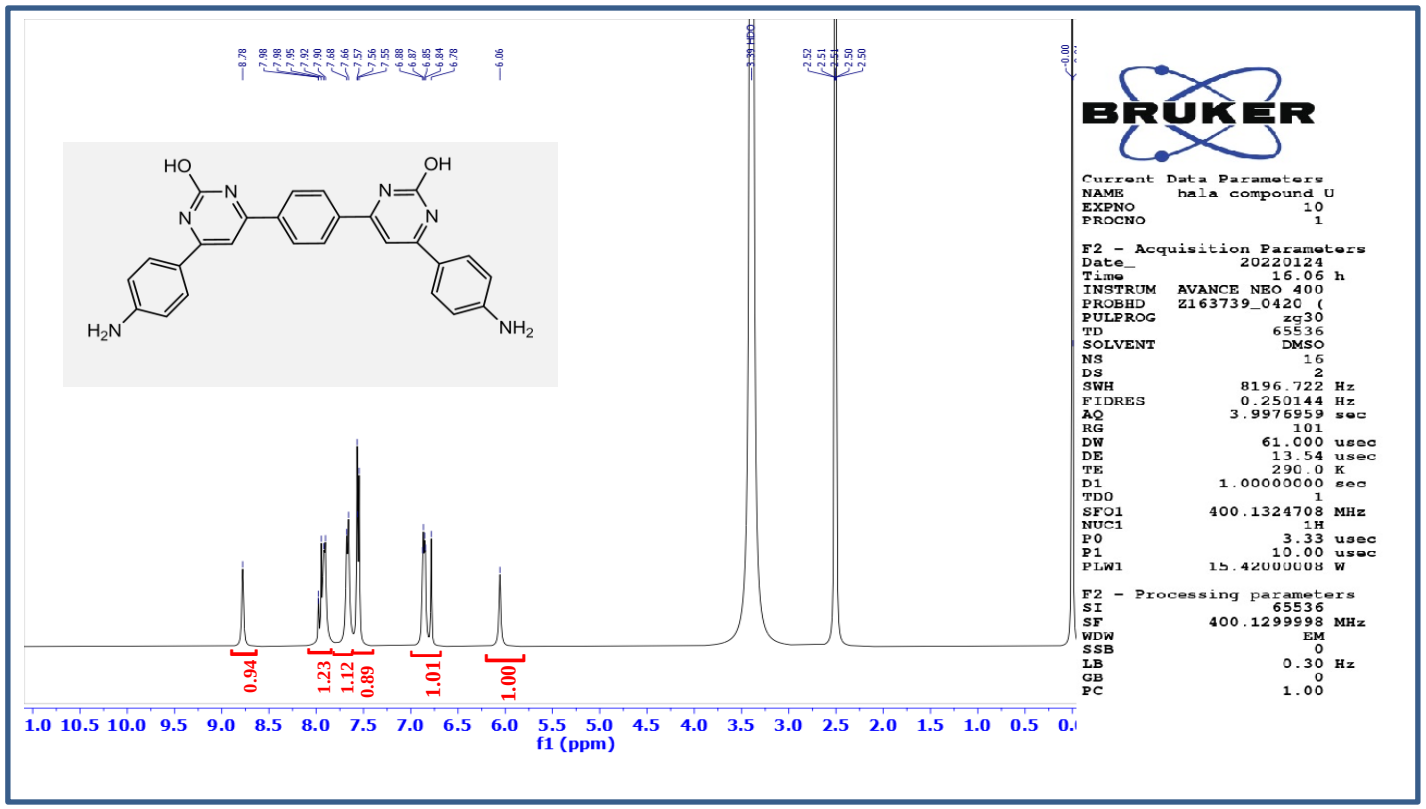


Figure (10): H^1-NMR of compound (3)

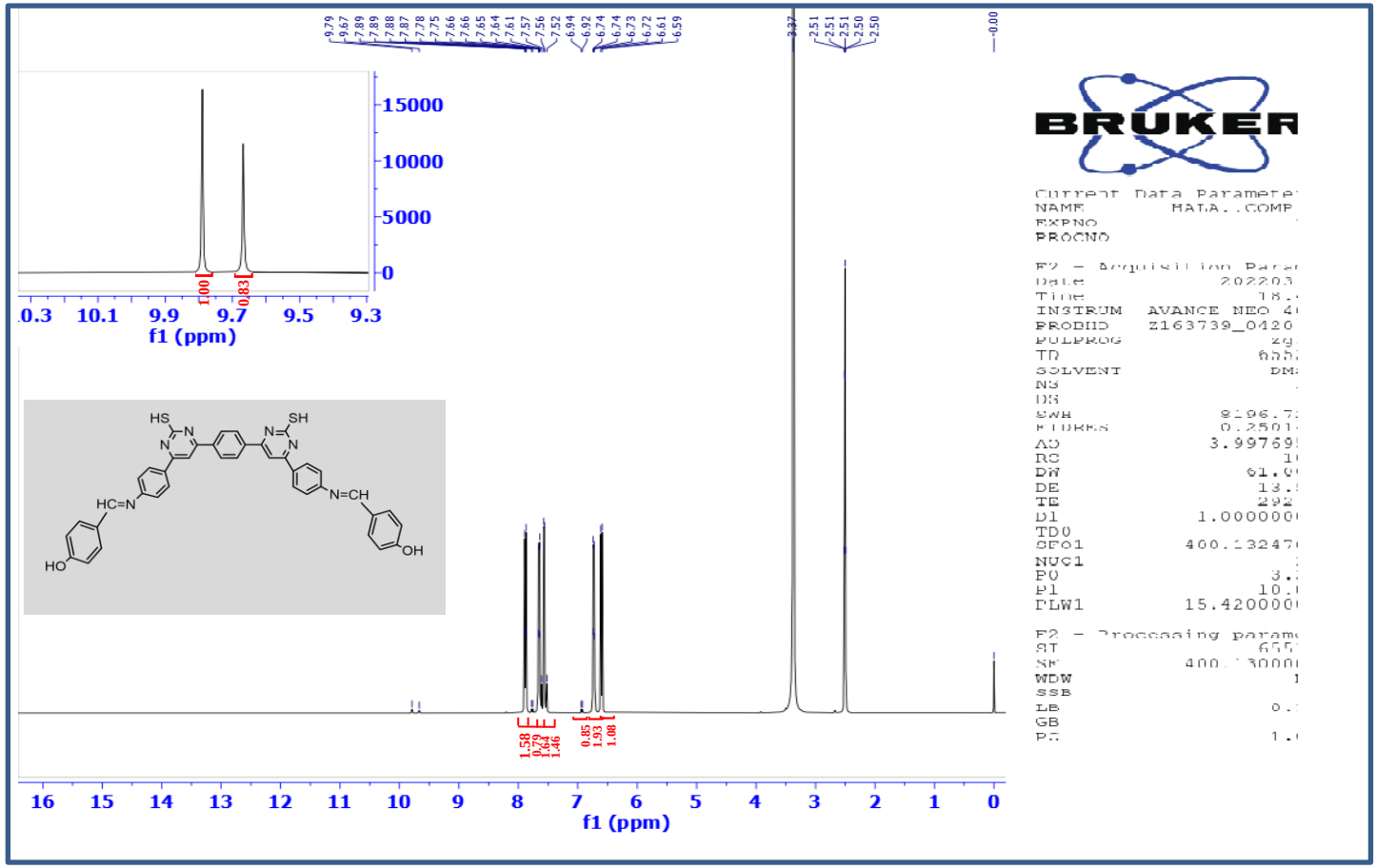


Figure (11): H^1-NMR of compound (2a)

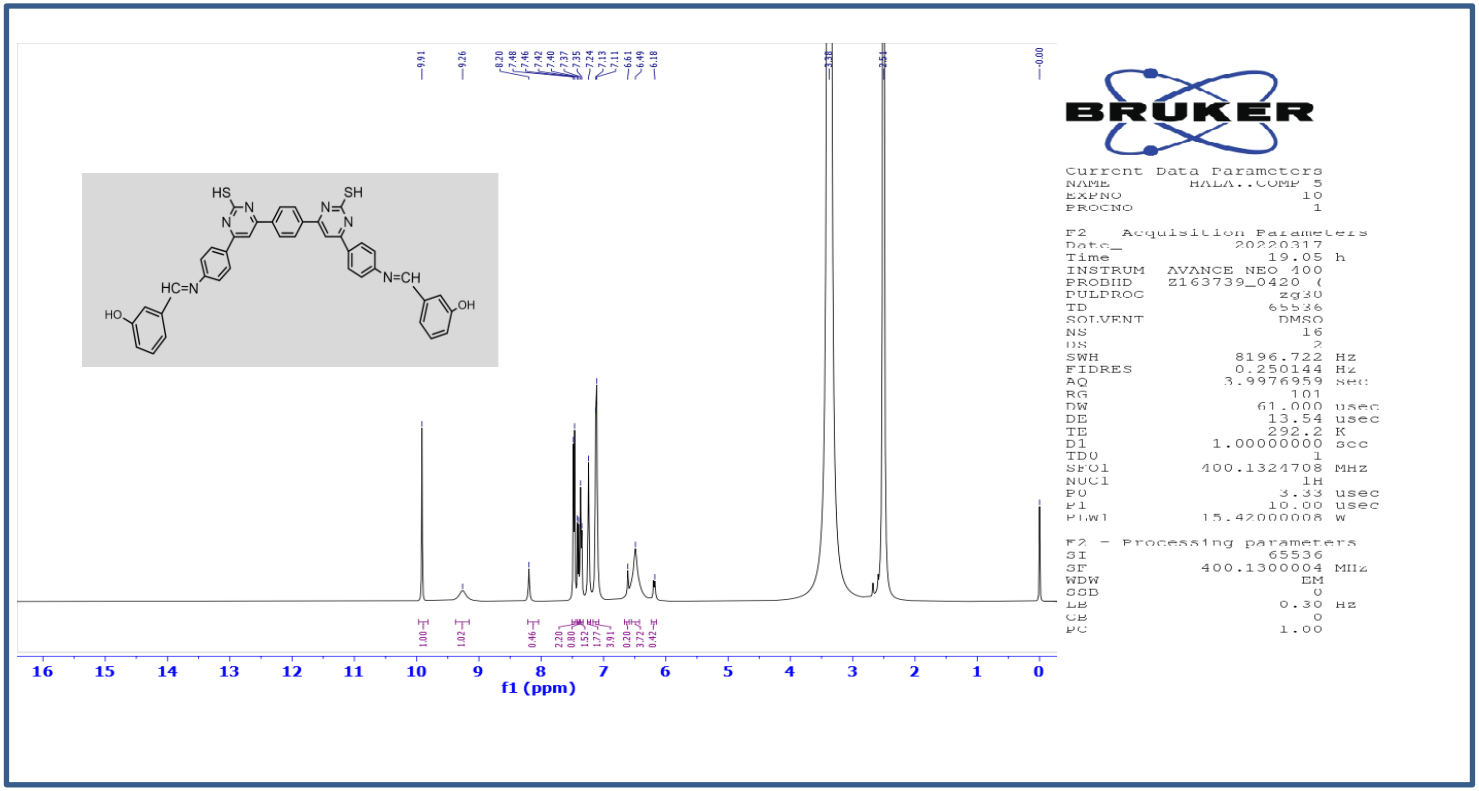


Figure (12): H^1-NMR of compound (2b)

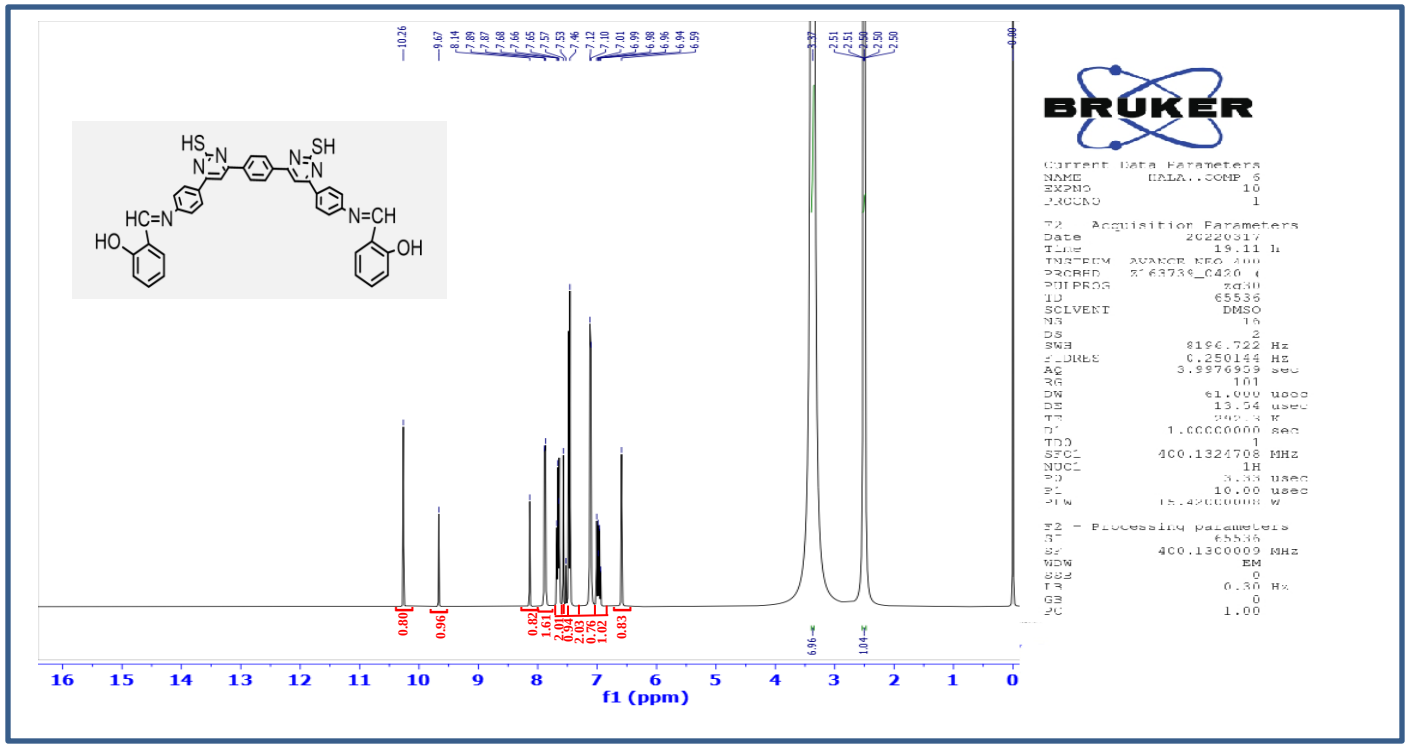


Figure (13): H^1-NMR of compound (2c)

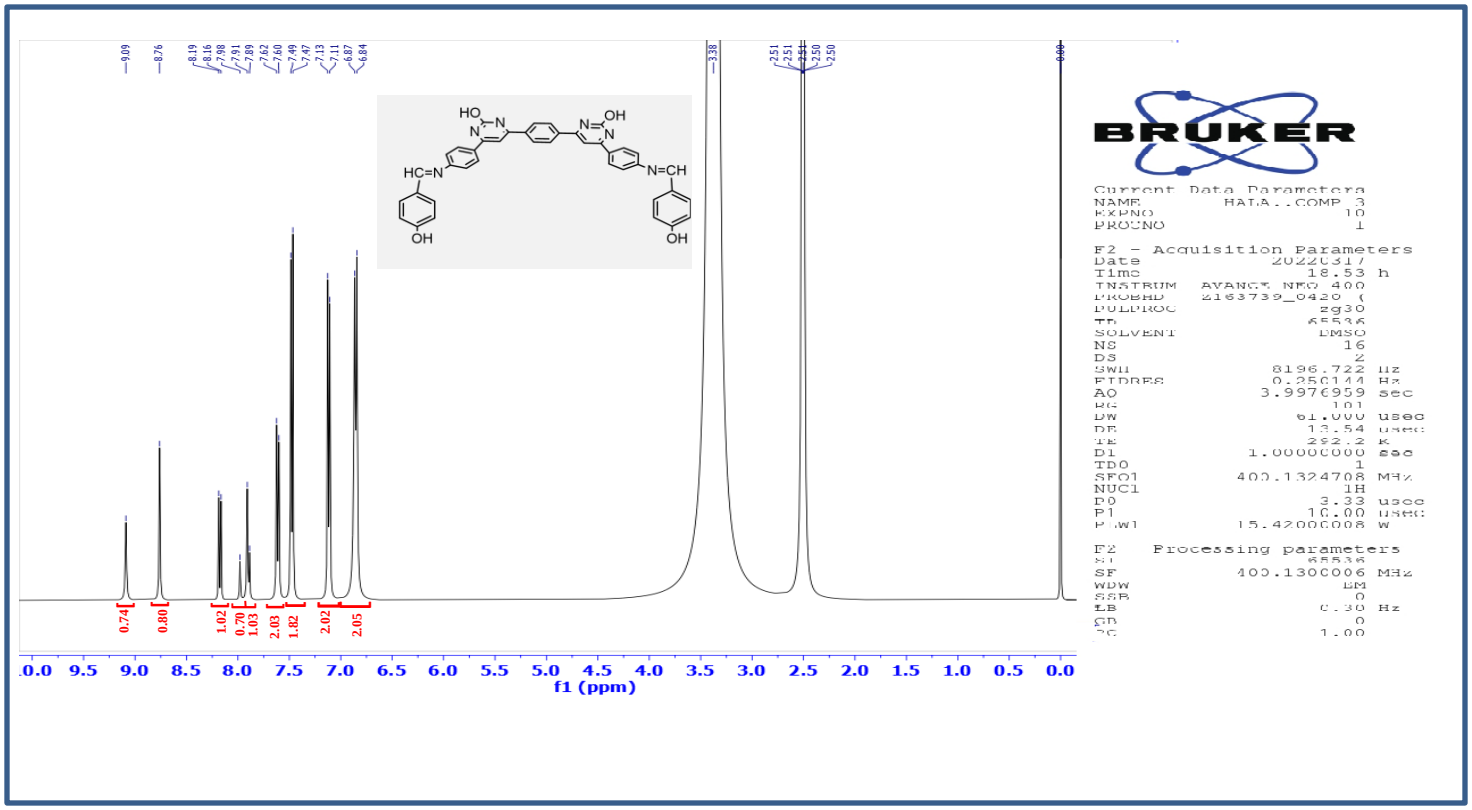


Figure (14): H^1-NMR of compound (3a)

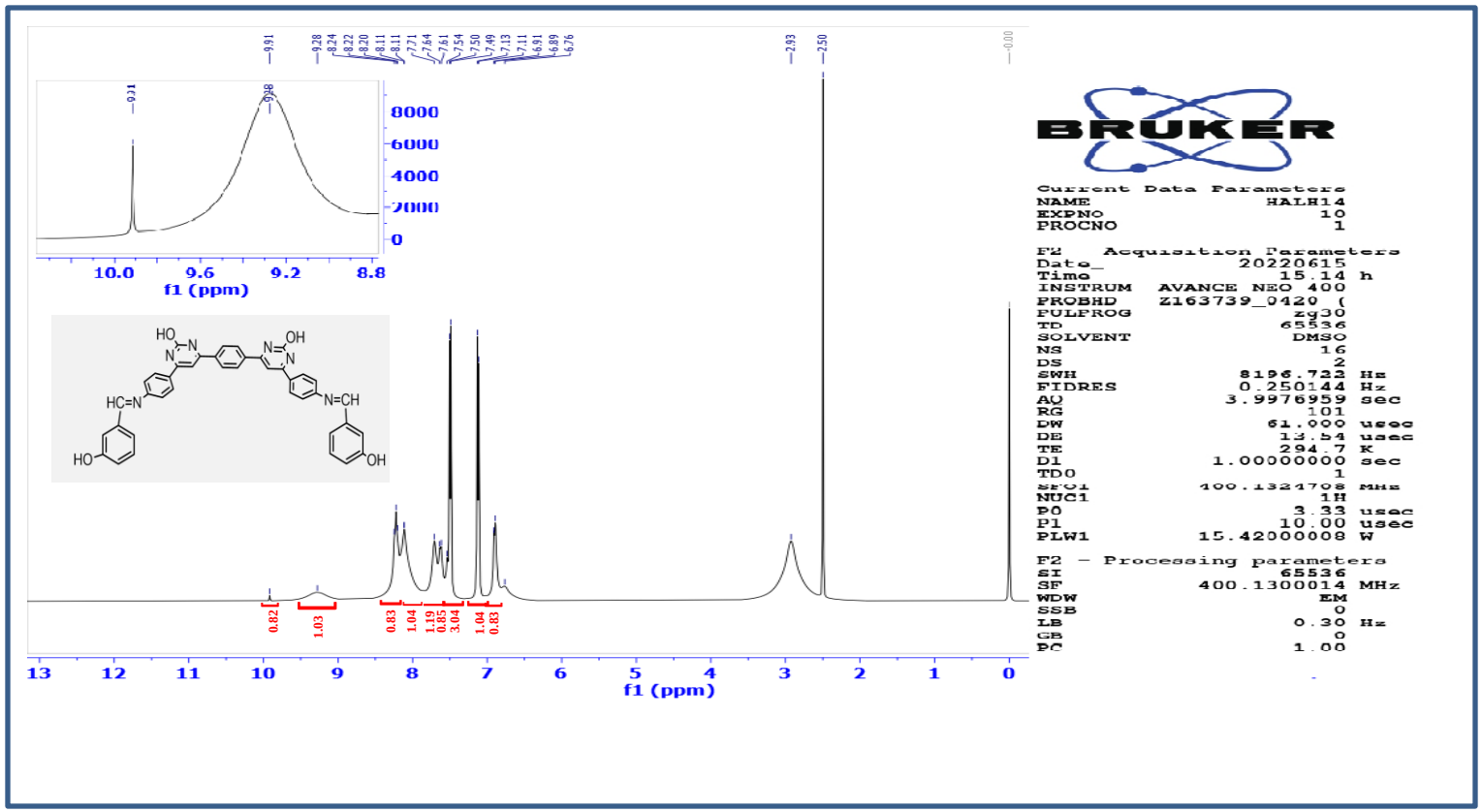


Figure (15): H^1-NMR of compound (3b)

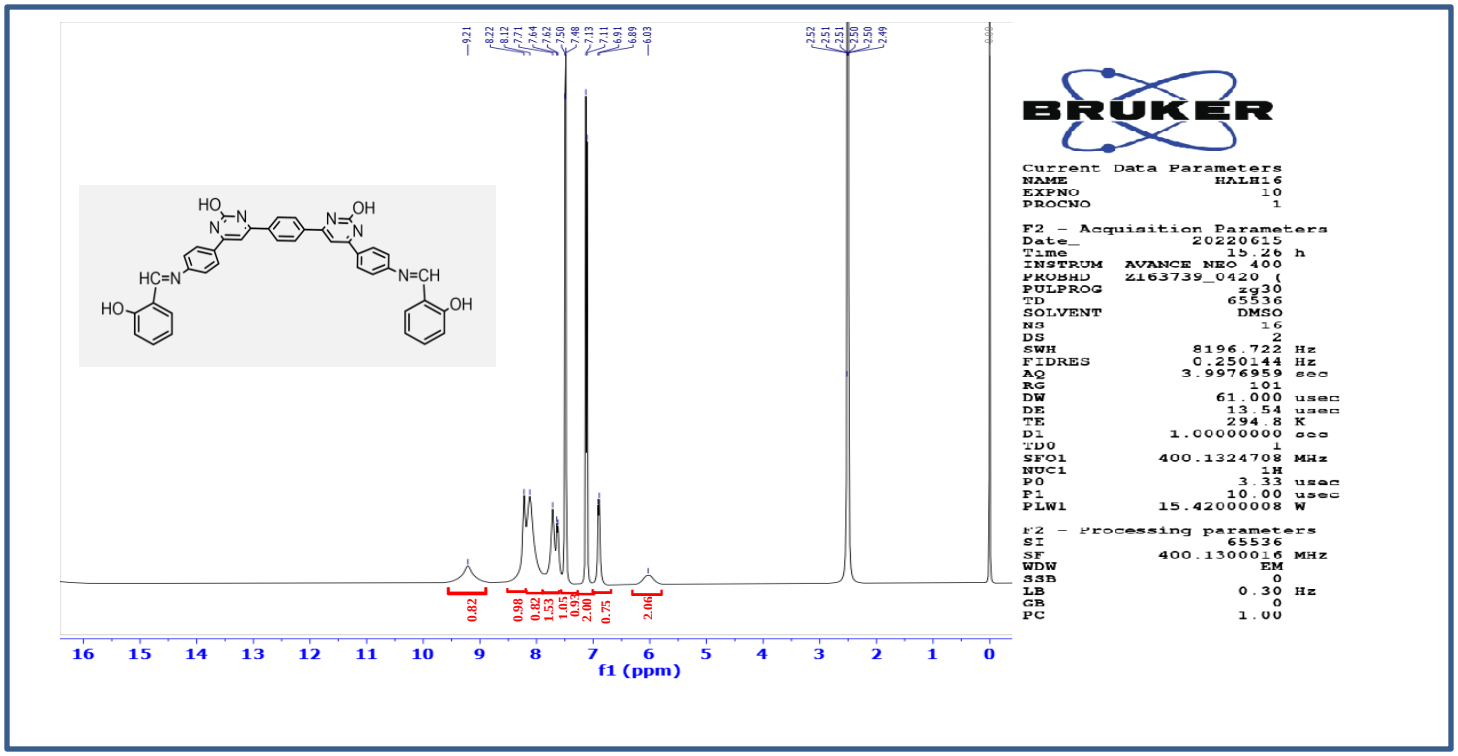
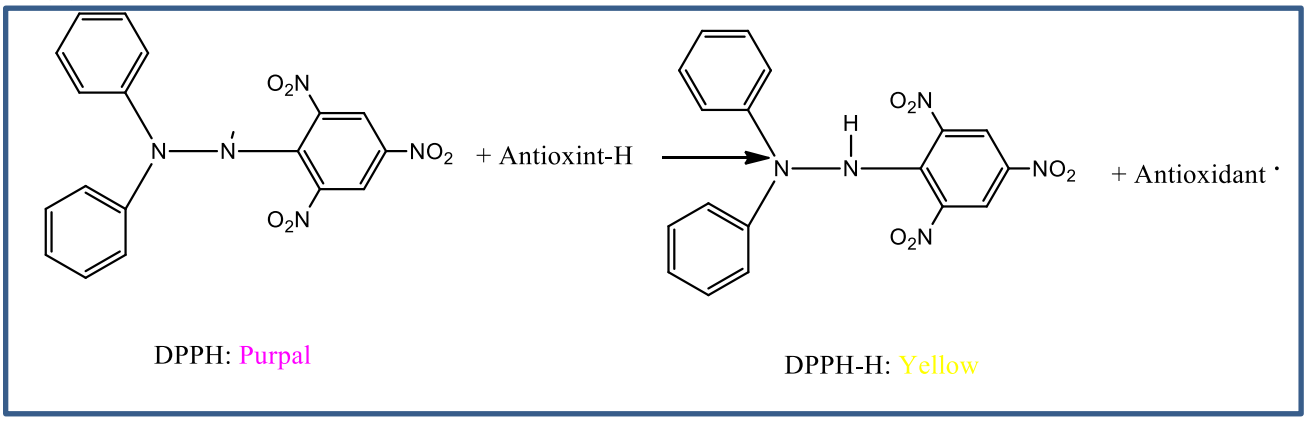


Figure (16): H^1-NMR of compound (3c)

5. Antioxidant activity

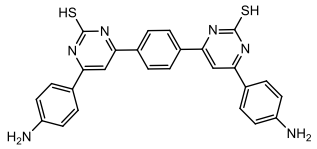
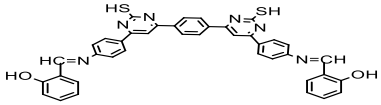
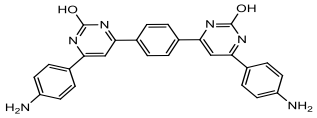
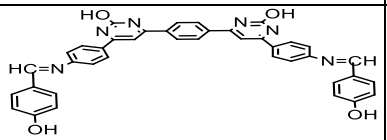
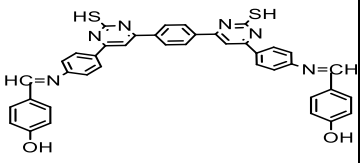
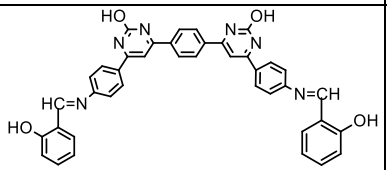
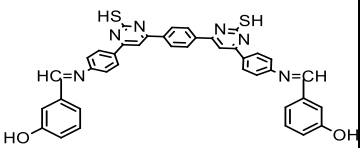
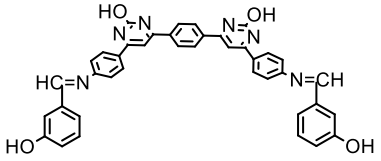
The DPPH assay is carried out under the assumption that an antioxidant reduces (decolorizes) DPPH free radicals by acting as a hydrogen donor. Scheme (One technique to gauge a substance's antioxidant strength is to assess its ability to scavenge DPPH, which can be done by observing a decrease in the maximum DPPH absorption at 570 nm (14). The compound (2) and Schiff bases derivative it's appeared antioxidant activity compare with the compound (3) and its derivative. The antioxidant activity of the created heterocyclic compounds was shown in table (7)



Scheme (5) principal of the antioxidant DPPH assay

The table (8-11) displayed the %RSA and IC50 for compounds that were antioxidant actives, with the IC50 values calculated from formulae on charts of the curves in the figures (17-20)

Table (7): DPPH ASSY for the prepared compounds

Comp.	DPPH assay	Comp.	DPPH assay
	+		+
	-		-
	+		-
	+		-

Table(8) : calculation of %Radical Scavenger Activity and IC50 from DPPH Assay for the compound (2)

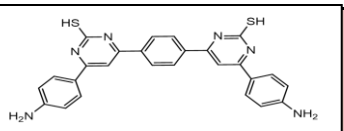
	**Absorbance Measurement Data**			
Concentration (mg/ml)	**Blank (DMSO)**	**Sample**	**%RSA**	**IC50**
500	0.618	0.308	50.162	6936.44
250	0.875	0.522	40.343	3334.14
125	0.887	0.597	32.694	1532.98
62.5	0.729	0.598	17.970	632.41
31.25	0.774	0.576	25.581	182.12
15.6	0.797	0.637	20.075	-43.39
8	1.091	0.957	12.282	-152.90

Table (9): calculation of %Radical Scavenger Activity and IC50 from DPPH Assay for the compound (2a)

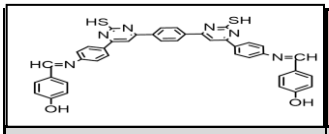
	**Absorbance Measurement Data**			
Concentration(mg/ml)	**Blank (DMSO)**	**Sample**	**%RSA**	**IC50**
500	0.618	0.169	72.654	3609.731
250	0.875	0.297	66.057	1739.873
125	0.887	0.361	59.301	804.944
62.5	0.729	0.63	13.580	337.479
31.25	0.774	0.688	11.111	103.747
15.6	0.797	0.671	15.809	-13.306
8	1.091	0.918	15.857	-70.150

Table (10) calculation of %Radical Scavenger Activity and IC50 from DPPH Assay for the compound (2b)

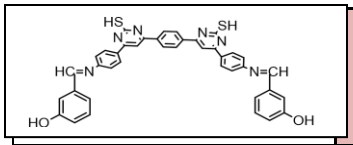
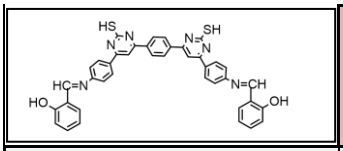
	**Absorbance Measurement Data**			
Concentration(mg/ml)	**Blank (DMSO)**	**Sample**	**%RSA**	**IC50**
500	0.618	0.168	72.816	568.599
250	0.875	0.269	69.257	259.957
125	0.887	0.367	58.625	105.636
62.5	0.729	0.359	50.754	28.475
31.25	0.774	0.504	34.884	-10.105
15.6	0.797	0.512	35.759	-29.426
8	1.091	0.716	34.372	-38.809

Table (11) calculation of %Radical Scavenger Activity and IC50 from DPPH Assay for the compound (2c)

	**Absorbance Measurement Data**			
Concentration(mg/ml)	**Blank (DMSO)**	**Sample**	**%RSA**	**IC50**
500	0.618	0.157	74.595	4027.937
250	0.875	0.244	72.114	1896.650
125	0.887	0.319	64.036	831.006
62.5	0.729	0.509	30.178	298.184
31.25	0.774	0.612	20.930	31.773
15.6	0.797	0.623	21.832	-101.645
8	1.091	0.814	25.390	-166.436

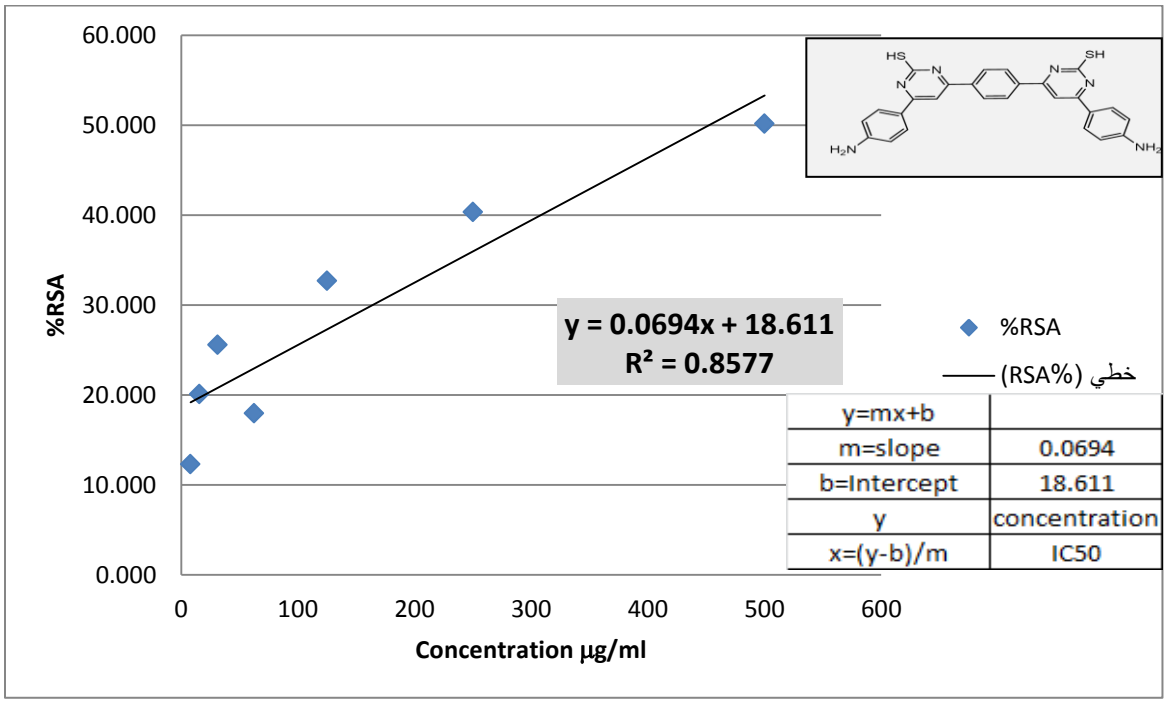


Figure (17) DPPH Assay for the compound (2)

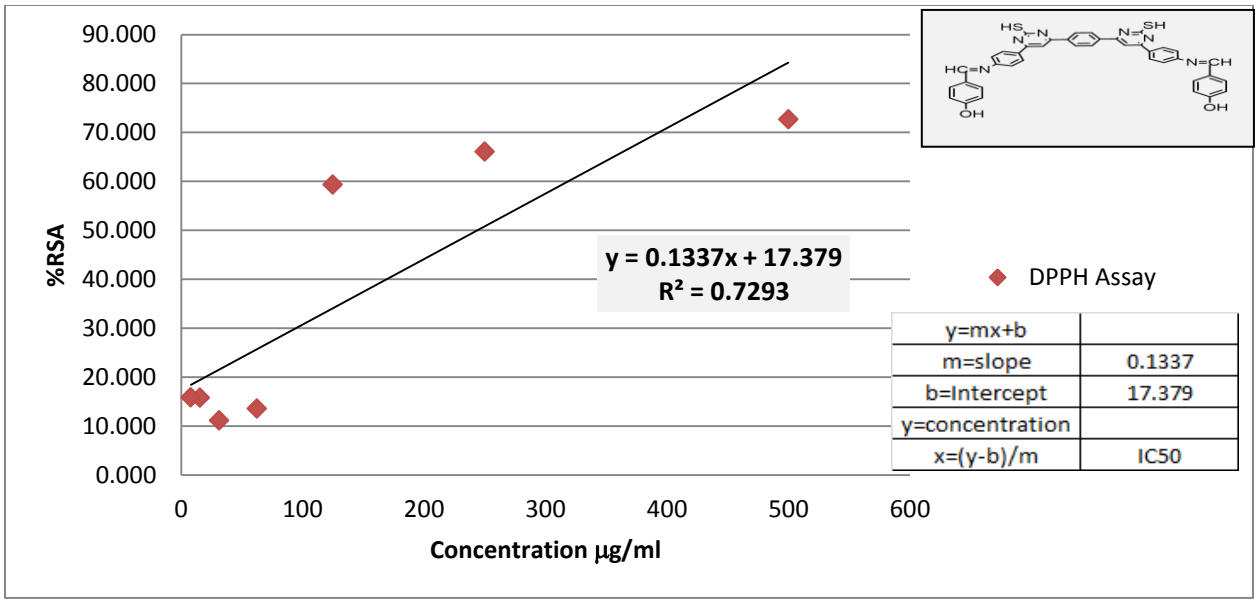


Figure (18) DPPH Assay for the compound (2a)

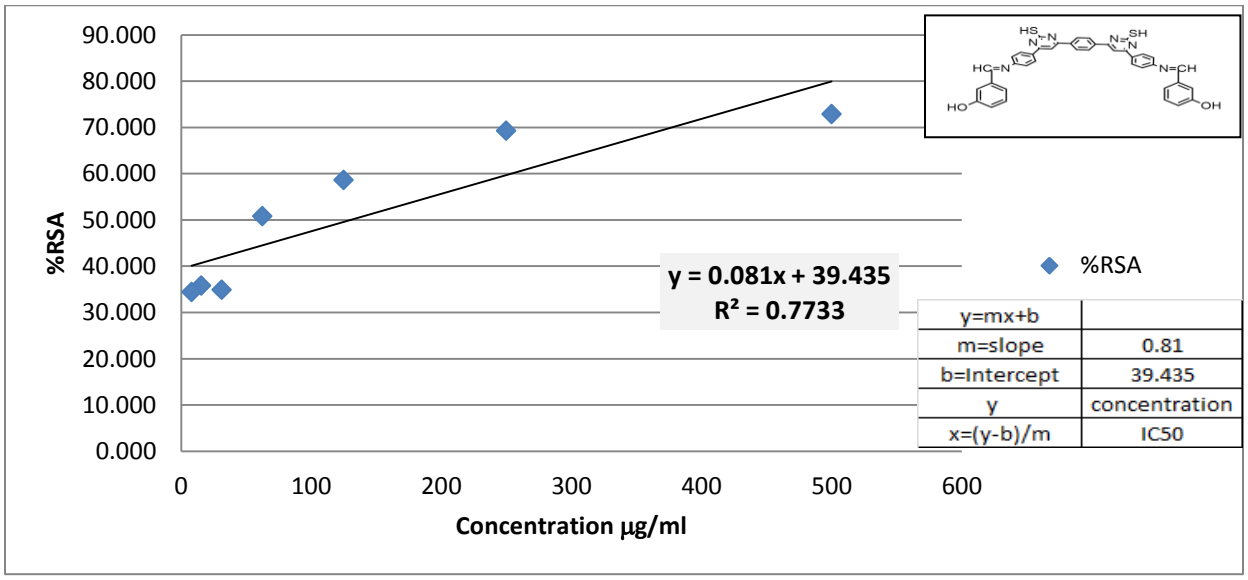


Figure (19) DPPH Assay for the compound (2b)

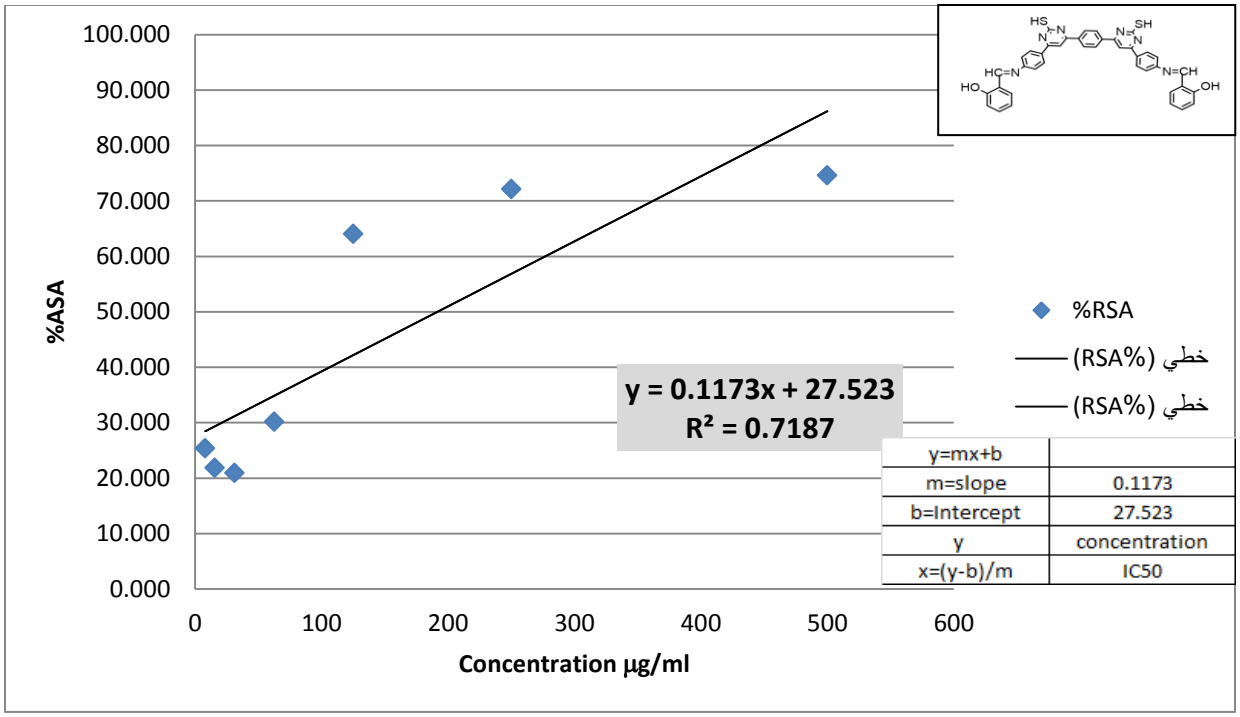


Figure (20) DPPH Assay for the compound (2c)

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