



**SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS DERIVED FROM BIS (5-AMINO-1,3,4-THIADIAZOLE- 2-YL) DISULFIDE**

<sup>1</sup>Redha I. H. AL-Bayati, <sup>2\*</sup>Sajida Munadi Th. AL-Suraify, <sup>3</sup>Raad M. Al-Saedi

<sup>1</sup>Department of Chemistry, College of Sciences, AL Mustansiriya University.

<sup>2</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, Misan University.

<sup>3</sup>Department of Clinical Biochemistry, College of Medicine, Misan University.

\*Correspondence for Author: Dr. Sajida Munadi Th. AL-Suraify

Department of Pharmaceutical Chemistry, College of Pharmacy, Misan University.

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**ABSTRACT**

In present study, 14 compounds derived from 2-amino-5-mercapto-1,3,4-thiadiazole were synthesized, The first route included oxidation above compound by hydrogen peroxide to disulfide ( or dithio ) compound (1). The reaction of compound (1) with sodium nitrite in concentration hydrochloric acid organized diazonium salt (2) which interrelate with o-hydroxy aceto phenone and salicylic aldehyde to produce azo derivatives (3,4), respectively . Adsorbing of carbonyl groups of azo derivatives (3,4) with p-methyl aniline donating schiff bases (5,10). Then, when the last cyclized with mercapto acetic acid generate thiazolidine-4-one derivatives (9,12). While adsorbing of compounds (3,4) with o-bromo benzaldehyde and DHA by claisen-schirnidt condensation formed chalcones (6,11) respectively. Cyclization of chalcones with malononitrile in attendance of piperidine gave compounds (8,14) . eventually, oxazine derivatives (7,13) were produced by reaction of chalcones with urea. All synthesized compounds were describing by employ some spectroscopic assay such as UV, FTIR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR.

**KEYWORDS:** disulfide compounds, chalcone derivatives, schiff bases, azo compounds.

**INTRODUCTION**

1,3,4-thiadiazole are important because of their multiple skills biological act which declare a broad multifarious of biological actions such as CNS depressants, hypoglycemic, antimicrobial, anticancer and antioxidant activity. Thiadiazoles carrying mercapto and amino substituents can exists in many tautomeric forms and considered as useful intermediates in organic synthesis<sup>[1]</sup>. Azo compounds are highly important, it widely used substances in the textile, paper, colouring agents for foods and cosmetics industries. Furthermore, azo compounds were reported to show a variety of biological activities including antibacterial, antifungal, antiviral and anti-inflammatory activities<sup>[2]</sup>. chalcones are made by Claisen-Schmidt condensation, Which includes cross aldol. Condensation of fit aldehyde and ketones by base catalyzed or acid catalyzed followed by dehydration chalone<sup>[3]</sup>. The existence of reactive  $\alpha$ - $\beta$ -unsaturated keto function in chalcones is found to be responsible for their antimicrobial action, which may be changed depending on the sort and position of substituent on aromatic ring<sup>[4]</sup>.

However, chalcones are important intermediates for the made of number of heterocyclic system, for example oxazine rings can produce from reaction of chalcones with malononitrile in alkaline medium. oxazine hetero cycles have special caring because they constitute an important

class of natural and non natural products and show useful biological activities<sup>[5]</sup>. Schiff bases are characterized by (-N=C) imine group which imports in elucidating the mechanism of transamination and transamination reaction in biological system. Schiff bases are active against a wide range of organism for example; *Candida albicans*, *Echerichia coli*, *Staphylococcus aureus* and *Plasmopora viticola*<sup>[6]</sup>.

**MATERIALS AND METHODS**

Melting point were designed on Gallen – Kamp (MFB-600) melting point device and are uncorrected. The IR spectra of the compounds were recorded on Shimadzu FT-IR 3800 spectrometer as KBr disk .The U.V spectra were performed on Cintra-5-Gbes scientific equipment. The <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra (solvent DMSO) were recorded on Bruker 300 MHz spectrophotometer using TMS as internal standard in chemistry department-AL-Byat university\ Jordan.

**General procedure for the synthesis of compounds  
Synthesis of compound(1)<sup>[7]</sup>**

In a 100-mL, round-bottomed flask equipped with a magnetic stirrer are placed (0.01 mol.,1.33g) of 2-amino-5-mercapto-1,3,4- thiadiazole in 50 ml ethanol. The admixture is stirred and cooled an ice bath and 30mL of 30% aqueous hydrogen peroxide is added drop wise over

a period of 15 min through as well as funnel. After accomplishment of the addition, the ice bath is eliminate and the reaction mixture is admitted to stir at room temperature for 24 hrs. The solids are aggregated on a Buchner funnel and dried and recrystallized from chloroform.

#### Synthesis of compounds (2,3,4)<sup>[8]</sup>

Compound (1) (0.01 mol., 2.64 g) was dissolved in (15 mL) of concentrated hydrochloric acid and (15 mL) of distilled water contained in a small beaker. The mixture was cold at (0°C) in an ice bath. Then a solution of sodium nitrite (1.656 g, 0.024 mol.) dissolved in (20 mL) of distilled water was added dropwise to the mixture with stirring, the temperature of the ice bath was controlled between (0-5°C). A solution of (2-hydroxy acetophenone, 2-Hydroxybenzaldehyde) (0.02 mol.) dissolved in (20 mL) of (10%) sodium hydroxide solution in (150 mL) beaker was prepared and cold to (5°C) by immersion in an ice bath. (2-Hydroxybenzaldehyde, 2-hydroxy acetophenone) solution was then stirred vigorously, then the diazonium salt solution was added very slowly to the (2-Hydroxybenzaldehyde, 2-hydroxy acetophenone solution), a red colour, dark red crystals soon separated (compounds 3,4) respectively. When all the diazonium salt solution was added, the mixture was admitted to stand in an ice bath for 30 min, with accidental stirring. The solution was filtered, cleaning well with distilled water, recrystallized from ethanol and dried upon filter paper.

#### Synthesis of compounds (5,10)<sup>[9]</sup>

To a blending of compounds (3,4) (0.01 mol.) and *p*-methyl aniline (0.02 mol., 2.14 g) in a 50 ml round bottomed flask, add 25 ml Ethanol, a few drops of 20% KOH solution were added and the reaction mixture was refluxed for 18-20 hrs. The reaction mixture was retained a side for cooling and then pouring in to crushed ice with active stirring. The solution of reaction admixture was acidified with 10% HCl to eliminate unreacted amines. Then the manufacturing was recrystallized from fit solvent.

#### Synthesis of compounds (9, 12)<sup>[10]</sup>

Assortment (0.01 mol.) of (5, 10) and Mercapto acetic acid (0.02 mol., 1.6 g) in DMF (25 mL including a nip of anhydrous ZnCl<sub>2</sub>) was refluxed for 8 hrs. The reaction mixture was then cooled and pouring into ice-cold water. The output solid was filtered, washed with water a few times, after that recrystallized from ethyl acetate.

#### Synthesis of compounds (6, 11)<sup>[11]</sup>

A mixture of compounds (3,4) (0.005 mol.) and *o*-bromo benzaldehyde, dehydroacetic acid (0.01 mol.) consecutively was refluxed in ethanol (10 mL) and then an aqueous solution of potassium hydroxide (50%, 7.5 mL) was added to it. The admixture was retained for 24 hrs. and it was acidified with 1:1 HCl and H<sub>2</sub>O. Then it was filtered under vacuum and the solid was cleaned

with water, then crystallized from chloroform. The physical and spectral data of the chalcones were declare in Table (1,2).

#### Synthesis of compounds (7, 13)<sup>[12]</sup>

A mixture of chalcones (6,11) (0.01 mol.) and urea (0.02 mol., 1.2 g) were dissolved in ethanol sodium hydroxide solution (10 mL) was stirred for 3 hrs., then it was poured into 250 mL of cold water with ongoing stirring for 1 hr., after that leaving overnight. The sediment formed was filtered, washed and recrystallized from ethanol. The physical and spectral data of the compounds were display in Table (1,2).

#### Synthesis of compounds (8, 14)<sup>[13]</sup>

A mixture of chalcones (6, 11) (0.01 mol.) and malononitrile (0.02 mol., 1.32 g) in absolute ethanol containing few drops of piperidine as a catalyst was refluxed for 8 hrs. the resulting manufacture filtered off, dried and recrystallized from ethanol 50%. The physical and spectral data of the compounds were declare in Table (1, 2).

## RESULTS AND DISCUSSION

Disulfide compound (1) can be make by the action of hydrogen peroxide, compound (1) was distinguished by UV, FT-IR and <sup>1</sup>HNMR spectra. U.V spectra gave two absorption bands at (230, 295) nm due to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  respectively. FTIR spectrum displayed absorption band at 480 cm<sup>-1</sup> due to (S-S) of disulfide and another two bands at (3300, 3450) cm<sup>-1</sup> due to NH<sub>2</sub> group, also another bands are recorded in table (2). <sup>1</sup>HNMR spectrum donated the following data in ppm: 4 (S, 4H, 2NH<sub>2</sub>).

When compound (1) allowed to react with sodium nitrite in hydrochloric acid was formed corresponding diazonium salt, which was directly converted to the coupling derivatives (3, 4) via the reaction with *o*-hydroxy aceto phenone and salicylaldehyde respectively, U.V spectrum of (3, 4) gave two bands at (225, 210) nm responsible for  $\pi \rightarrow \pi^*$  and another at (270, 255) due to  $n \rightarrow \pi^*$  transition respectively. FTIR of derivatives (3, 4) were conformed by appearance of stretching vibration of (N=N) at (1410, 1400) cm<sup>-1</sup>, also presence a band at (1695, 1705) cm<sup>-1</sup> due to carbonyl of ketone and aldehyde of (3, 4) respectively. <sup>1</sup>HNMR and <sup>13</sup>C-NMR data are listed in table (2). Carbonyl groups of azo derivatives (3, 4) were condensed with amino group of *p*-Tolylamine to produce azo schiff bases derivatives (5, 10). FT-IR spectrum of (5, 10) gave new band at (1630, 1637) cm<sup>-1</sup> attributed to stretching vibration of azo methane groups. Also disappearance bands of carbonyl group of ketone and aldehyde at (1695, 1705) cm<sup>-1</sup> is a good evidence for successful this reaction. Beside that, <sup>1</sup>HNMR of compound (5) gave the following data in ppm: 2.4 (6H, S, 2CH<sub>3</sub>-ph), 1 (6H, S, 2CH<sub>3</sub>-C=N), (6.8-8) aromatic protons. while derivative (10) showed the following signals: 8.5 (2H, S, 2CH=N), 5 (2H, S, 2Ar-OH), 2.5 (6H, S, 2Ar-CH<sub>3</sub> (6.8 - 7.5) aromatic

protons. From  $^{13}\text{C}$ -NMR spectrum of (5) observed the following data : 165 , 116 , 121 , 118 , 130 , 132 , 158 , 164 , 20 , 21 , 13 , 136.

Each one of schiff bases derivatives (5, 10) was reacted with mercapto acetic acid to give thiazoldine-4-one derivatives (9, 12), Its U.V spectra gave two absorption bands at (231, 215) nm and at (315, 320) nm due to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions respectively. In addition, FT-IR spectrum new band at (1755, 1760)  $\text{cm}^{-1}$  due to carbonyl group of thiazoldine ring and another bands at (713, 725)  $\text{cm}^{-1}$  due to stretching vibration of (C-S) of ring which indicate formation of derivatives (9, 12). Another spectral data listed in table (2).

On the other side, condensation of compounds (3 , 4) with O-bromo benzaldehyde and DHA in presence of aqueous solution of potassium hydroxide was formed chalone (6 , 11) respectively . U.V spectra gave two absorption bands at (223, 240) nm due to  $\pi \rightarrow \pi^*$  transitions and at (348, 335) nm due to  $n \rightarrow \pi^*$  transitions for derivatives (6, 11) respectively. Beside that, FT-IR spectra of these compounds showed new bands at (1585, 1655)  $\text{cm}^{-1}$  and (1592, 1650)  $\text{cm}^{-1}$  due to (C=C C=O) which indicate formation of chalone (6 , 11) respectively . Table (2) showed another spectral data of these chalone.

When the resulting chalone (6, 11) cyclized with urea in ethanolic sodium hydroxide solution, then gave oxazine

derivatives (7, 13). U.V spectra of (7, 13) gave two transitions at the following wave length (239, 211), (310, 328) nm due to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  respectively. Beside that, FT-IR spectra of (7, 13) showed new bands at (3250, 3280), (3433 , 3420)  $\text{cm}^{-1}$  responsible for stretching vibration of  $\text{NH}_2$  groups . Also another bands at (1620, 1625)  $\text{cm}^{-1}$  due to (C=N) of oxazine ring derivatives (7, 13) respectively.  $^1\text{H}$ NMR signals of (7, 13) and  $^{13}\text{C}$ -NMR of (13) are listed in table (2).

Ultimately chalone (6, 11) were reacted with malono nitrile to give derivatives (8 , 14) , Its U.V spectra gave bands at (230 , 247) nm and (295 , 303) nm responsible for  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions respectively . FT-IR spectra showed disappearance absorption bands at (1655, 1650)  $\text{cm}^{-1}$  due to stretching vibration of carbonyl groups for chalone , while appeared absorption bands at (2205 , 2217)  $\text{cm}^{-1}$  due to CN groups and another at (3220 , 3250) , (3370 , 3392)  $\text{cm}^{-1}$  referred to stretching vibration of  $\text{NH}_2$  groups for derivatives (8,14) respectively.

Interestingly,  $^1\text{H}$ NMR of compound (8) gave the following data in ppm : 4.8 (2H,d,2CH=C-O of pyran ring), 3.9 (2H, d, 2 CH-C-CN of pyran ring), 5 (2H, S, 2Ar-OH), (6.8-7.5) aromatic protons, 2.1 (4H, S, 2NH<sub>2</sub>).  $^1\text{H}$ NMR of derivative (14) and  $^{13}\text{C}$ -NMR of (8) data are listed in table (2).

**Table (1): physical properties of synthesized compounds**

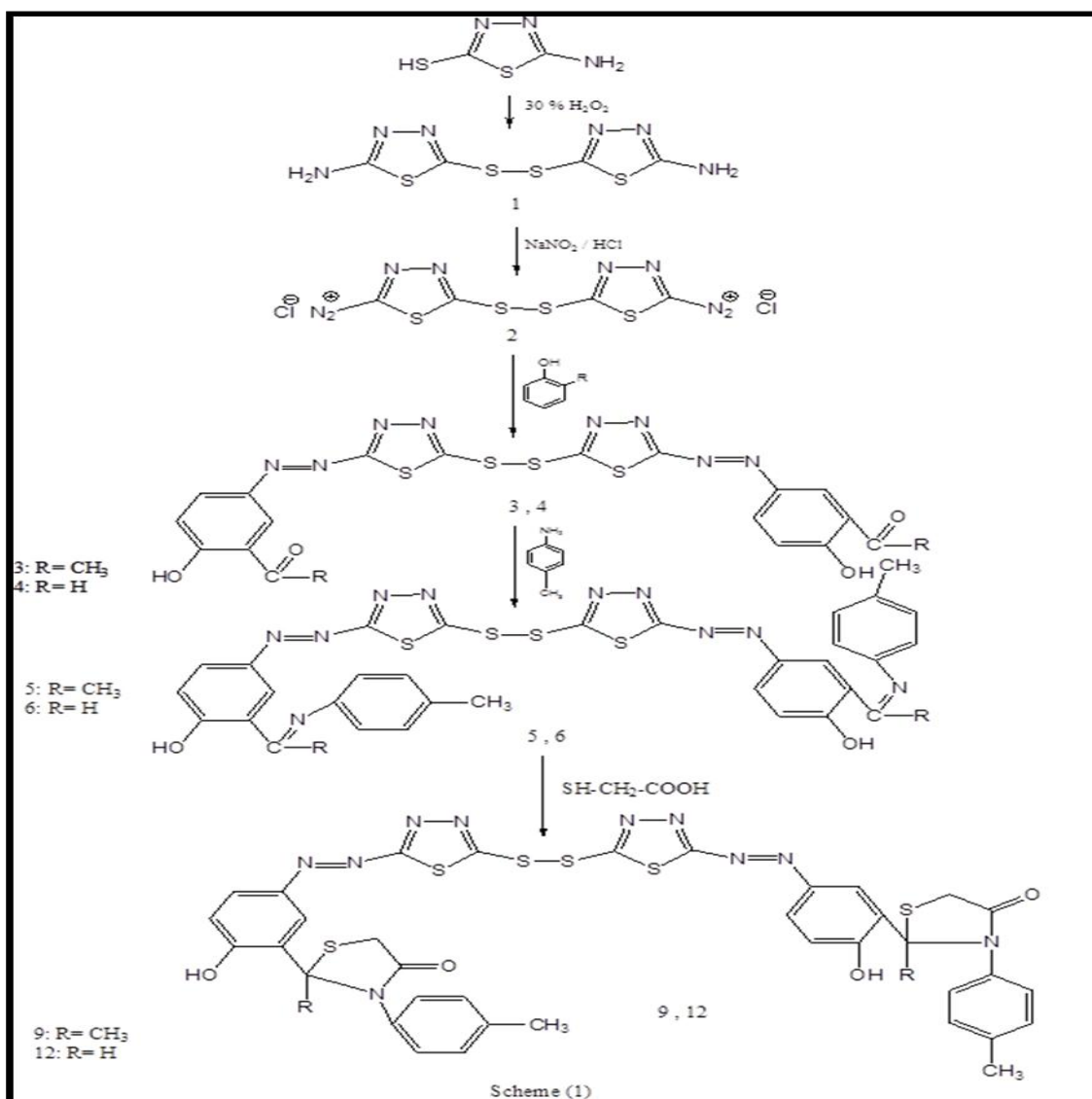
Comp. NO.	m.p. °C	Yield %	Color	Recrys. Solvent
1	264-266	70	Dark yellow	Chloroform
3	213-215	80	Red	Ethanol
4	221-223	88	Dark Red	Ethanol
5	282-284	95	Yellow	Ethanol 50%
6	159-161	81	Red	Chloroform
7	273-275	50	Off-white	Ethanol
8	202-204	79	pale yellow	Ethanol 50%
9	188-200	60	Yellow	Ethyl acetate
10	290-292	97	Dark yellow	Ethanol 50%
11	173-175	85	Red	Chloroform
12	227-229	73	pale yellow	Ethyl acetate
13	217-219	60	yellow	Ethanol
14	277-279	55	White	Ethanol 50%

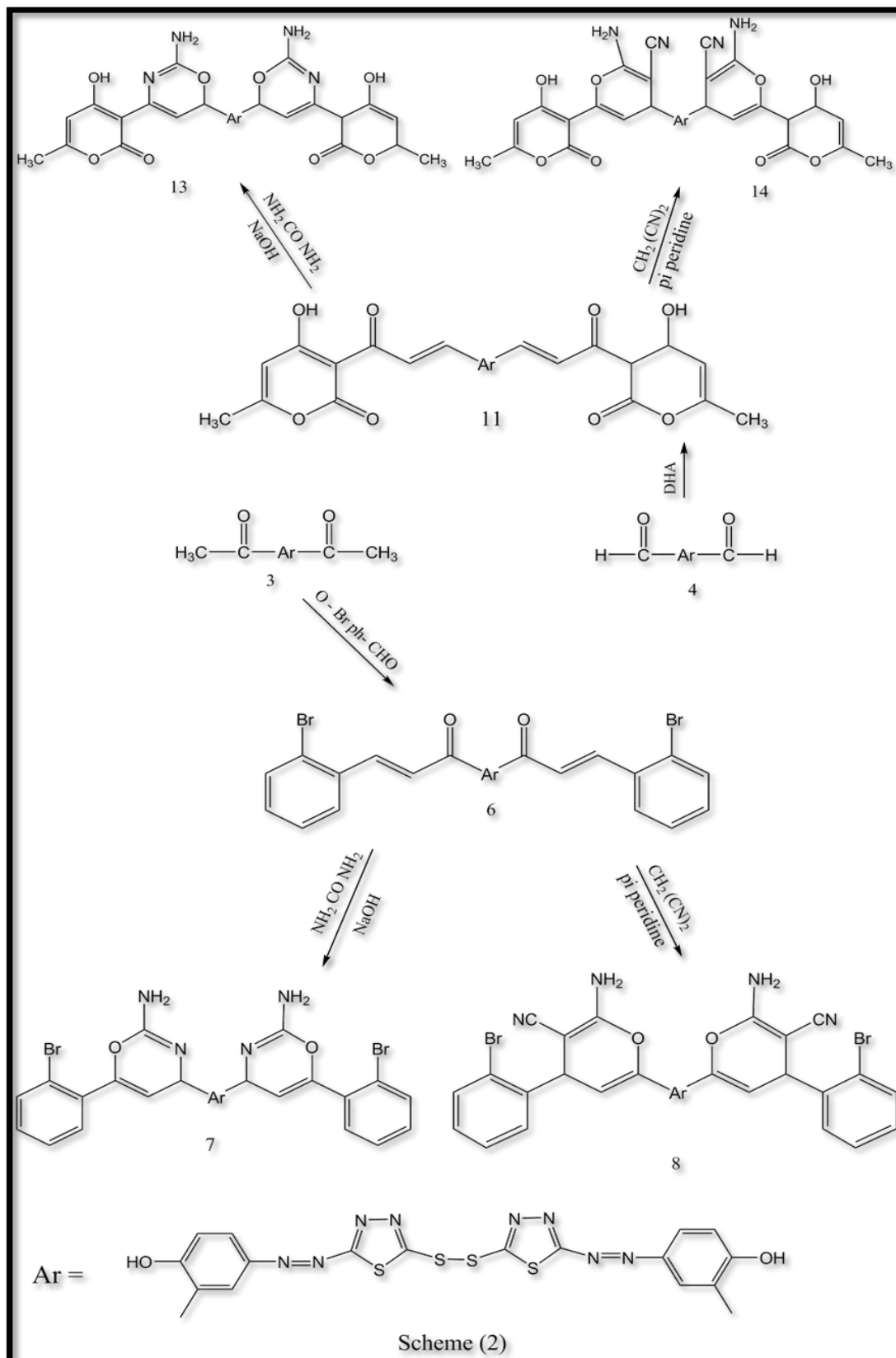
**Table (2): Spectral data of synthesized compounds**

Comp. NO.	U.V	FT-IR	$^1\text{H}$ -NMR	$^{13}\text{C}$ -NMR
	$\lambda$ max nm			
1	230 295	1615 , 1628 for C=N of thiazazole ring 3300 , 3450 for $\text{NH}_2$ , 480 for (S-S)	4 (S , 4H , 2NH <sub>2</sub> )	
3	225 270	1410 for derivatives (3 , 4)3085 for CH aromatic 1695 for (C=O) of ketone, 2960	2.6 (6H , S , O=C-CH <sub>3</sub> ) 5.2 (2H , S , 2OH)	116 , 121 , 130 , 134 ,

		for CH alpha, 3600 for phenolic OH	(6.8-8) ( Aromatic protons)	125 , 196 , 23
4	210 255	1400 for N=N 3097 for CH aromatic 1705 for (C=O) of aldehyde 2730 for CH of aldehyde 3610 for phenolic OH	(6.9-7.8) (Aromatic protons), 5.6 (2H, S, 2OH ) 10 (2H, S, 2CH of aldehyde).	116 , 124 , 122 , 131 , 160 , 190
5	233 275	1630 for azomethine group 1605 , 1617 for C=N of thiadiazole ring , 1412 for N=N	(6.8-8) ( Aromatic protons) 1(6H , S, 2CH <sub>3</sub> -C=N) 2.4 (6H , S , 2CH <sub>3</sub> -ph) 5 (2H , S , 2Ar-OH)	165 , 116 , 121 , 118 , 130 , 132 , 158 , 164 , 20 , 21 , 13 , 136
6	223 348	1585 , 1655 (C=C , C=O) of chalone 1550 (C=C) arom.	(6.8-7.9) ( Aromatic protons), 5.5 (2H , S , 2OH ) ,7.9 (2H , S , COCH=CH) 8.25 (2H , S , COCH=CH), 2.4 (6H , S , 2CH <sub>3</sub> -ph	116 , 122 , 124 , 131 , 136 , 159 , 123 , 120 , 129 , 142 , 127 , 138
7	239 310	3250 , 3433 for NH <sub>2</sub> , 1620 for C=N 700 for C-Br , 3610 for phenolic OH	2.2 (4H , S, 2NH <sub>2</sub> ) 5.2 (2H , d , 2CH-O of ring , 6.5 (2H , d , 2CH=C-N of ring (6.8-7.5) ( Aromatic protons), 5 (2H , S , 2OH phenolic )	
8	230 295	2205 for CN group , 3220 , 3370 for NH <sub>2</sub> , 1220 for (C-O)	4.8 (2H , d, 2 CH=C-O of pyran ring) 3.9 (2H , d , 2 CHC-CN of pyran ring ) , 5 (2H , S , 2Ar- OH ) (6.8-7.5) ( Aromatic protons), 2.1 (4H , S, 2NH <sub>2</sub> )	145 , 129 , 116 , 122 , 155 , 153 , 176 , 57 , 21 , 96 , 127 , 141 , 131
9	231 315	1755 for cyclic C=O of thiazoldine-4-one ring , 7013 for (C-S) 2953 for CH <sub>2</sub> -S	4.5 (4H , S , 2CH <sub>2</sub> of thiazoldine-4-one ring 1.9 (6H , S , 2CH <sub>3</sub> subst. on thiazoldine -4-one ring,(6.8-7.9) ( Aromatic protons) , 5 (2H , S , 2Ar- OH ) 2.4 (6H , S , 2CH <sub>3</sub> -ph)	
10	237 298	1637 for azo methine group 1600 , 1625 for C=N thiazol ring 1417 for N=N	8.5 (2H , S , 2CH=N) 5 (2H , S , 2Ar-OH) 2.5 (2H , ,2Ar- CH <sub>3</sub> ) (6.8-7.5) ( Aromatic protons)	
11	240 335	1592 , 1650 for (C=C , C=O) of chalone , 1560 (C=C) arom. 1718 for (C=O) of lactone	7.9 (2H , d, 2CH=CH-CO),6.8 (2H , d , 2CH=CH-CO),5 (2H , S , 2Ar- OH ) ,15 (2H , S , 2 OH of DHA ) 6.2 (2H , d , 2CH-O of DHA ) ,1.9(6H , S , 2CH <sub>3</sub> Subst. of DHA ) (6.8-7.5) ( Aromatic protons)	
12	215 320	1760 cyclic C=O of thiazoldine-4-one ring 725 for (C-S) , 2970 for CH <sub>2</sub> -S	5.9 (2H , S , 2CH of thiazoldine -4-one ring 4 (4H , S , 2CH <sub>2</sub> of thiazoldine -4-one ring 5 (2H , S , 2Ar- OH ) (6.6-7.5) ( Aromatic protons), 2.4 (6H , S , 2CH <sub>3</sub> -ph)	121 , 128 , 116 , 126 , 130 , 130 , 158 , 137 , 133 , 20 , 129 , 47 , 30 , 36 , 166
13	211	3280 , 3420 for NH <sub>2</sub>	2 (4H , S, 2NH <sub>2</sub> )	121 , 129 ,

	328	1625,1629 for C=N of thiadiazole ring , 3420 for OH of lactone ring .,1255 for C-N.	5 (2H , S , 2Ar- OH ) 6 (2H , d , 2CH=C-N of ring 4.5 (2H , d , 2CH-O of ring , 1.9 (6H , S , 2CH <sub>3</sub> of DHA) 6 (2H , d , 2CH of DHA) 15 (2H , S , 2OH of DHA)	116 , 123 , 155 , 142 , 117 , 55 , 161 , 166 , 99 , 102 , 144 , 22
14	247 303	2217 for CN group , 3250 , 3392 for NH <sub>2</sub> , 1225 for C-O	2 (4H , S , 2NH <sub>2</sub> ) 4 (2H , d , 2CH-C-CN of ring , 4.8 (2H , d , CH=C-O of ring , 6.2 (2H , d , CH of DHA) 1.9 (6H , S , 2CH <sub>3</sub> of DHA) 15 (2H , S , 2OH of DHA)	





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