

## Synthesis and Biological testing of new 1,3- oxazepine derivatives of pharmaceutical interest

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### Abstract

Some derivatives of 1,3 oxazepine – Schiff bases have been synthesized by the reaction of some aromatic aldehydes with N-phenyl azo aniline to synthesis of the compounds ,2-(*p*-phenyl azo)-1,4-phenylene aniline(1-6) ,and these compounds (1-6) were reacted with phthalic anhydride to obtain derivatives of 1,3- oxazepine. The chemical structures of the products were characterized by (IR ,and <sup>1</sup>H NMR) and biological activity for some of these compounds were studied against three kinds of bacteria.

تحضير ودراسة الفعالية البيولوجية لبعض مشتقات 3,1- اوكسازيبين الجديدة ذات الاهمية الصيدلانية

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مفتاح الكلمات: تخليق , قواعد شف , 3,1- اوكسازيبين, فحص الفعالية البيولوجية

### الخلاصة:

تم تحضير بعض مشتقات مركبات 3,1- اوكسازيبين – قواعد شيف من تفاعل بعض الالديهيدات الأروماتية المعوضة مع N-phenyl azoaniline لاننتاج مركبات (1-6) 2-(*p*-phenyl azo)-1,4-phenyleneamine وتم مفاعلة هذه المركبات مع انهدريد فتاليك للحصول على مشتقات 3,1- اوكسازيبين (1-6) وتم تشخيص هذه المركبات بواسطة اطياف الاشعة تحت الحمراء ( FT-IR ) والرنين النووي المغناطيسي (<sup>1</sup>H NMR). كما تم دراسة الفعالية البيولوجية لنماذج منها ضد ثلاثة انواع من البكتريا.

### Introduction

Azo compounds of Schiff bases<sup>(1)</sup> and their derivatives<sup>(2)</sup> have been used in medicinal and industrial applied as in visual process reactions<sup>(3)</sup> which include enzymatic transamination reaction<sup>(4)</sup> and other reaction as acceleration by vit.B<sup>(5)</sup>. Azo compounds composed of two neighborhood nitrogen atoms connected with double-bond(-N=N-) The starting materials of azo compound preparation is the diazonium salts, which are more important in the synthesis of different pure organic compounds<sup>(6) (7)</sup>. The oxazepine are unsaturated compounds of 7-membered heterocyclic ring which contains five carbon atoms and 2-non hetero atoms (oxygen and nitrogen). For 7-members<sup>(8) (9)</sup>, which interest the researcher to discover different ways for 7-members heterocyclic double-bound synthesis<sup>(10)</sup>. The reaction between (-C=N-) for Schiff bases with phthalic anhydride produce different new compounds<sup>(11)</sup>, which are used in drugs and other medicinal pharmaceutical uses<sup>(12)</sup>, for example in treatment of cancer diseases<sup>(13)</sup> and psychotic depression<sup>(14) (15)</sup>, schezofrenia<sup>(16)</sup>, for example (dibenzoxazepine, amoxapine) and they have inhibitor action to presynaptic reuptake of Norepinephrine and serotonin also blocked the response of dopamine receptors to dopamine<sup>(17)</sup>. Some compounds which contains two cyclic 1,3-oxazepine-7-4-dione are prepared by reaction of Schiff base with phthalic anhydride compounds<sup>(18) (19) (20)</sup>. The interesting biological

activities attracted our attention to the chemistry of nitrogen, oxygen heterocyclic. Some of the prepared compounds were screened for their in vitro antimicrobial activity against different strains of bacteria (E.coli, kilpsillia , pseudomonas).

## Experimental

### Instruments

Melting points were determined by using (Electro thermal) Melting point apparatus-Gallenkamp -,and remain uncorrected.

The ( FT-IR) spectra were recorded on a shimadzu infrared spectrophotometer in KBr discs( $\delta\text{cm}^{-1}$ )

Melting points, crystallization solvents of percentage yields are listed in a tables (1,2,3,4,5).

$^1\text{H}$  NMR Spectra (DMSO- $d_6$ ) were recorded on Bruker 500 MHZ-Avance instrument university of Jordan, faculty of science, Department of chemistry.

### Materials

Some of the chemicals used directly while others were purified to obtain the highest purity. Oxazepine derivatives with azo compounds are prepared from diazonium salts <sup>(21)</sup> which are important for synthesis of a many pure organic compounds.

#### 1) Preparation of derivatives of N-phenylazoaniline (Schiff bases) (1-4)

A mixture of aromatic aldehyde (0.01mol) and the compound N-phenyl azoaniline (0.01mol). dissolved in (25 mL) of absolute ethanol ,were refluxed (75  $^{\circ}\text{C}$ ) with continuous stirring ,after cooling to room temperature, the precipitate filtered and recrystallized from ethanol, the end of the reaction checked by TLC. physical properties for N-phenylazoaniline derivatives are listed in table (1)

#### 2) Preparation of derivatives of 2-(p-nitro phenyl azo)1,4-phenylenediamine (Shiff bases)

A mixture of aromatic aldehyde (0.002mol) and the compound 2-(p-nitrophenyle azo)-1,4-phenylene diamine was dissolved in excess of absolute ethanol with a drops of glacial acetic acid. The mixture was refluxed (75 $^{\circ}\text{C}$ ) with continuous stirring for 3hr, cooling to room temperature; gelatinic precipitate was formed, recrystallized from absolute ethanol. physical properties are listed in table (2).

#### 3) Preparation of derivatives of 4,4-Bis(amino phenylazo)bis-phenyl(Azo Schiff bases)(compound-6)

A mixture of aromatic aldehyde (0.02mol) and 4,4-Bis(amino phenyl azo)-bis phenyl (0.01mol) was mixed in a beaker (50ml),using glass rode until the colour of the mixture is changed, the mixture is moisted with some water ,then heating quietly for 10 minute. The mixture is cooled at room temperature. The precipitate is washed by petroleum ether and then washed several times by ethanol. physical properties are listed in table (3).

#### 4) Preparation of derivatives of 3-(p-nitro phenylazo)-6-hydroxy benzaldehyde (Azo Schiff bases) (compound-7)

A mixture of substituted amine (2-amino phenyl-4-nitro aniline) (0.01mol) and 3-(*p*-nitro phenyl azo)-6-hydroxy benzaldehyd (0.02mol) in ( 25 ml) of absolute ethanol, refluxed (75C<sup>o</sup>) with stirring for 4hr. cooling to room temperature, the precipitate is filtered, washed with cold ethanol, then recrystallized from absolute ethanol. The physical properties are listed in table(4).

### 5) Preparation 1,3 -oxazepine derivatives of Azo Schifft bases(1-7) compounds

A mixture of (0.01mol) Schiff bases which was synthesized before and (0.01mol) of phthalic anhydride for the compounds (1,2,3,4) and (0.02mol) for the compounds (5,6,7,8) in (50mL) of absolute ethanol was refluxed (75C<sup>o</sup>) with stirring for 3hr. Cooling at room temperature, then the precipitate, formed is filtered off and recrystallized from absolute ethanol. The physical properties are listed in table (5).

### Biological testing

Antimicrobial activity of the compounds (9, 10,11,14) was examined by agar diffusion method<sup>(20)</sup>, using three different species i.e (E-coli. Kilpsillia, Pseudomonas). The zone of inhibition was measuring in mm<sup>(21)</sup>. The diameter zone of inhibition was measured in mm and are represented by (±), (++) , ( + + + ) depending upon the diameter ,the antimicrobial screening data are recorded in table(6). The results indicated that all the assayed compounds have activity against the tested organism, but with different effects of sensitivity. Using two antibiotic (Amoxicillin ,Gentamycin) to compare between the different species activity used (E.coli , Kilpsillia ,Pseudomonas).

### Results and discussions

#### a. FT.IR .Spectral

In this search we take single lines to prepare the outline compounds, where the last compounds is synthesized from (Schiff base); which cyclized to produce compounds contain more than one seven membered rings called (oxazepine comp). This compounds are (8,9,10,11,12,13,14), spectral data showed the bands of functional groups in the above compounds ;we take the chart №(9) as a sample for this compounds. The band at (1512 cm<sup>-1</sup>) is for azo group (-N=N-). the band at (1139 cm<sup>-1</sup>) is for ether group (-C-O-C). The bands at (1618 cm<sup>-1</sup>) is for group (-C=C-) of aromatic rings .The bands at (2869-3078cm<sup>-1</sup>) for aliphatic and aromatic (-C-H) groups .The broad bands at (1681cm<sup>-1</sup>) for Lactam (-C<sup>=O</sup>-N-) group finally the weak bands at (1776cm<sup>-1</sup>) for Lacton (-C<sup>=O</sup>-O-) group<sup>(22)</sup>.

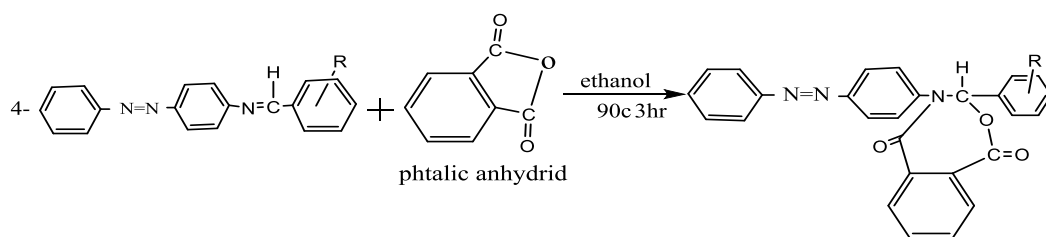
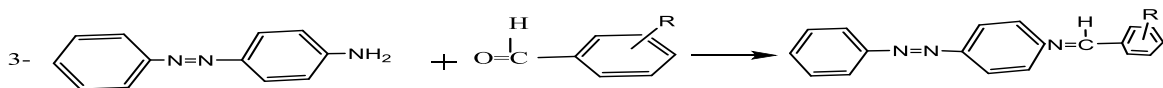
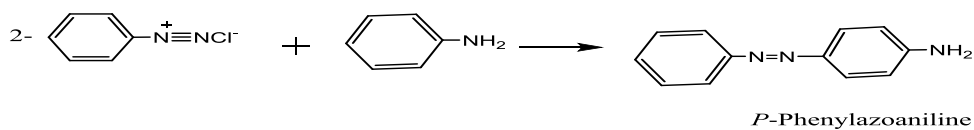
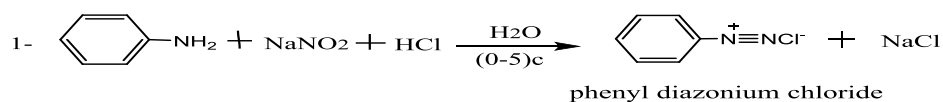
#### b. <sup>1</sup>HNMR, spectral

The NMR .data spectral for the synthesized compounds (8,9,10,11,12,13,14).we take the chart for the compound №(13) as a sample for these compounds .The observed double bands at (δ=2.5 ppm) for the protons of the Methyl groups (  $\text{---N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$  ).

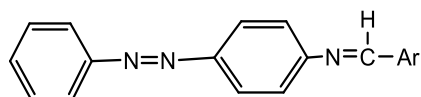
The band at (δ=3.2ppm) is for the proton for benzal (  $\text{---} \overset{\text{I}}{\text{C}} \text{---} \overset{\text{I}}{\text{N}} \text{---}$  ), the ether band at (δ=7.8ppm) for the protons of phenyl rings.

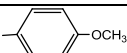
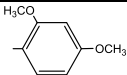
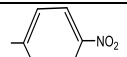
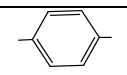
The bands at (δ=8.2-8.5ppm) for the Lactam benzene ring (ph-N-C<sup>=O</sup>-). The bands at (δ=7.4ppm) for protons of Ph-N- group.

**The scheme below show the pathway synthesis of azo compounds of oxazepine derivatives in our research .**

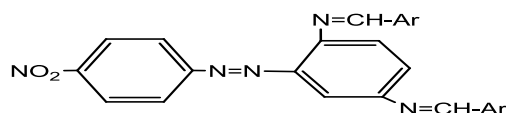


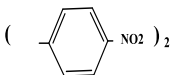
Table(1): the physical properties of schiffs bases compounds(1-4)



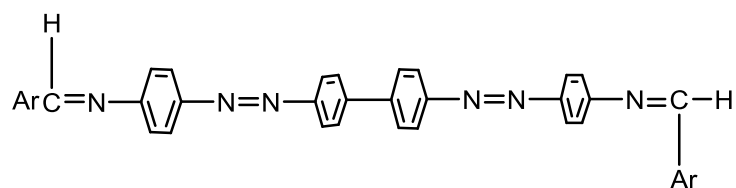
Comp. No	Ar	Molecular formula	Colour	M.P	yield	T r f	Crystallized solvent
1-		C <sub>20</sub> H <sub>17</sub> N <sub>3</sub> O	Brown	136-138	85	5	Ethanol
2-		C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>	yellow	122-124	92	1	Ethanol
3-		C <sub>19</sub> H <sub>13</sub> N <sub>4</sub> O <sub>4</sub>	orange	178-179	61	2	Ethanol
4-		C <sub>19</sub> HN <sub>3</sub>	Dark brown	136-138	95	3	Ethanol

Table(2) : the physical properties of shifts base compound (5)



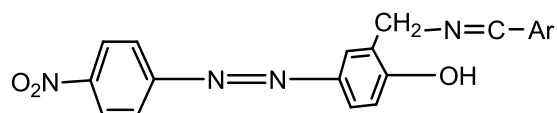
Comp. No	Ar	Molecular formula	Colour	M.P	yield	T r f	Crystallized solvent
5		C <sub>29</sub> H <sub>24</sub> N <sub>5</sub> O <sub>3</sub>	Dark brown	Decomp. 188	62	3	Ethanol

**Table (3): the physical properties of schiffs base compound (6)**



Comp. No	Ar	Molecular formula	Colour	M.P	yield	T r f	Crystalized solvent
6-		C <sub>42</sub> H <sub>36</sub> N <sub>8</sub>	brown	decompose 275	65	3	Ethanol

**Table (4): the physical properties of schiffs base compound(7)**



Comp. No	Ar	Molecular formula	Colour	M.P	yield	T r f	Crystalized solvent
7		C <sub>25</sub> H <sub>18</sub> N <sub>6</sub> O <sub>3</sub>	orange	Decomp 295	85	2	Ethanol

**Table (5): the physical properties of 1,3- oxazepine derivatives of azo schiffs base compounds (8-14)**

Comp. No	Molecular formula	Colour	M.P	yield	Crystalized solvent
8	C <sub>28</sub> H <sub>21</sub> N <sub>3</sub> O <sub>4</sub>	Red	222-224	66	Ethanol
9	C <sub>29</sub> H <sub>23</sub> N <sub>3</sub> O <sub>5</sub>	Light brown	218-220	64	Ethanol
10	C <sub>27</sub> H <sub>18</sub> N <sub>4</sub> O <sub>5</sub>	Light orange	139-140	67	Ethanol
11	C <sub>27</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	brown	185-187	69	Ethanol
12	C <sub>48</sub> H <sub>26</sub> N <sub>8</sub> O <sub>6</sub>	Deep Red	190-192	60	Ethanol
13	C <sub>50</sub> H <sub>42</sub> N <sub>8</sub> O <sub>6</sub>	Light black	120-123	53	Ethanol
14	C <sub>42</sub> H <sub>25</sub> N <sub>7</sub> O <sub>12</sub>	Pale yellow	~320 decom	56	Ethanol

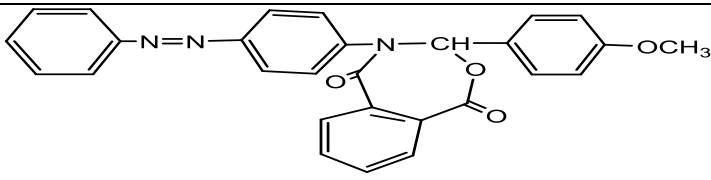
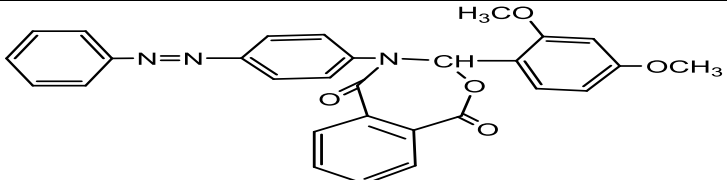
**Table (6) Biological testing for some prepared compounds**

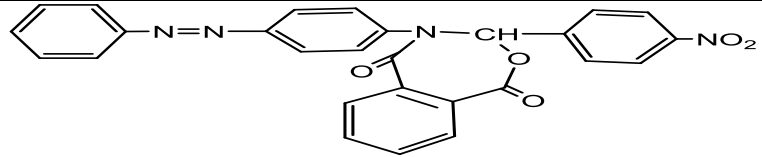
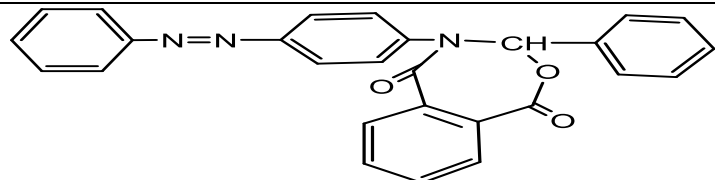
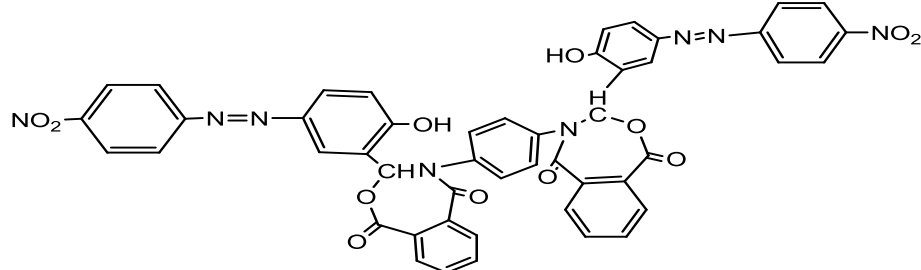
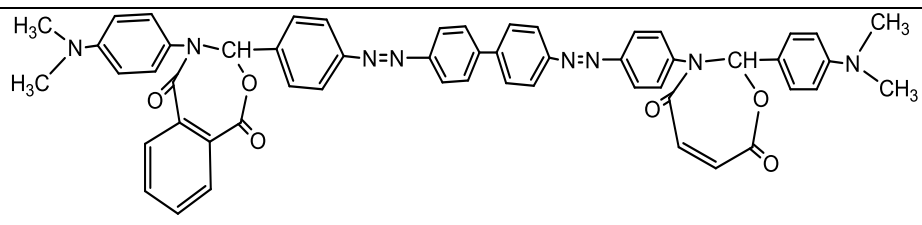
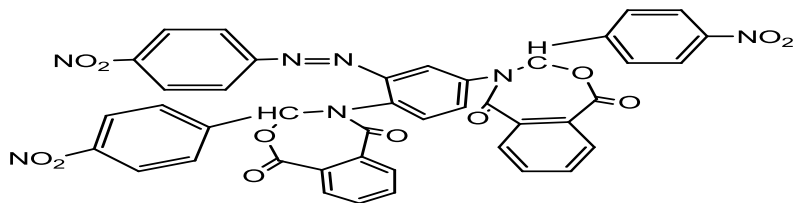
Sample . №	Concentration Mg/MI	E-Coli	Kilpsillia	pseudomonas
9	0.1	++	++	±
	0.05	++	±	±
10	0.1	±	++	++
	0.5	±	±	±
11	0.1	++	++	++
	0.05	++	±	±
14	0.1	±	±	±
	0.05	±	±	±
Amoxicillin	0.1	+++	+++	+++
	0.05	+++	+++	+++
Gentaycin	0.1	+++	+++	+++
	0.05	+++	+++	+++

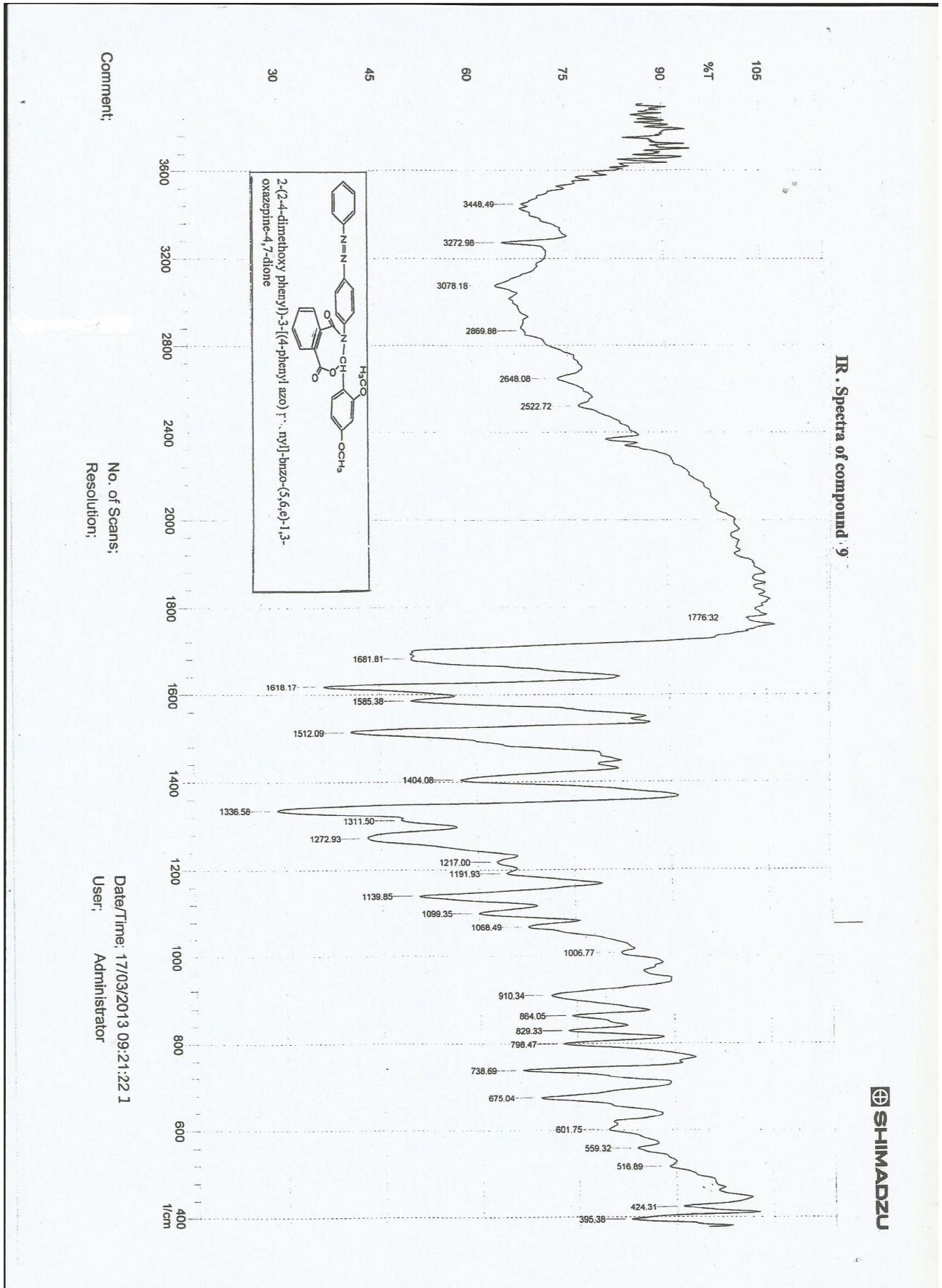
**Key The symbols(±) =1-7mm,(++)=8-12mm,(+++)=13-23mm**

Prepared compounds

المركبات المحضرة

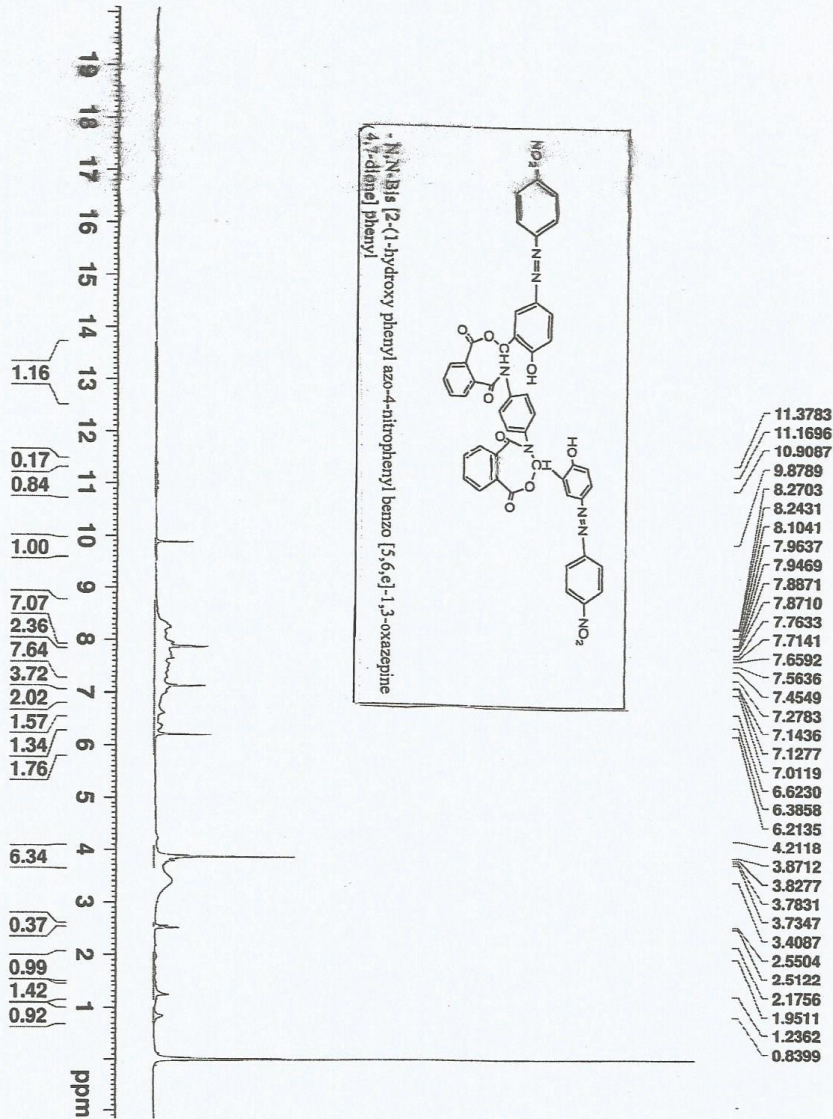
Comp. №	Structure and name
8	 <p>2-(4-Methoxy phenyl)-3-[(4-phenylazo) phenyl]-benzo-(5,6)-1,3-oxazepine-4,7-dione</p>
9	 <p>2-(2,4-dimethoxy phenyl)-3-[(4-phenyl azo) phenyl]-bnzo-(5,6)-1,3-oxazepine-4,7-dione</p>

10	 <p>2-(4-nitro phenyl)-3-[(4-phenylazo) phenyl]-benzo-(5,6)-1,3-oxazepine-4,7-dione</p>
11	 <p>2-( phenyl)-3-[(4-phenylazo) phenyl]-benzo-(5,6)-1,3-oxazepine-4,7-dione</p>
12	 <p>- N,N-Bis [2-2-hydroxy -4- (4-nitrophenylazo) phenyl benzo [5,6]-1,3-oxazepine 4,7-dione] benzene</p>
13	 <p>2,2-Bis(4-dimethyl amino)-2,2-Bis(amino phenyl azo)-Bis phenyl -Bis[1,3-oxazepin-4,7-dione]</p>
14	 <p>2,2-Bis(4-nitro phenyl)-2-(4-nitro phenyl azo)-2,3-dihydro-benzo[5,6]-1,3-oxazepine-4,7-dione benzene.</p>





<sup>1</sup>H NMR Spectra of compound 13



The University of Jordan  
Faculty of Science  
Department of Chemistry  
Instrument Model:  
Bruker 500 MHz-Avance III



nmr500@ju.edu.jo

Current Data Parameters  
NAME 1may13Jara1  
EXNO 681  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20130528  
Time 14.15  
SOLVENT DMSO  
TE 298.3 K  
INSTRUM spect  
PULPROG zg30  
ROBHD 5 mm PABBO BB/  
TD 19998  
NS 64  
DS 0  
SMH 10638.298 Hz  
FIDRES 0.531968 Hz  
AQ 0.3399560 sec  
RG 79.19  
DM 47.000 usec  
DE 6.50 usec  
DI 1.00000000 sec  
TD0 1

CHANNEL f1  
NUC1 1H  
PI 11.40 usec  
PLW1 17.37800026 W  
SFO1 500.1347367 MHz  
F2 - Processing Parameters

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