Synthesis and Characterization of Some New Derivatives of Heterocyclic Compounds and its Polymers with study their Biological Activity

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Abstract:

Three series of heterocyclic compounds were synthesized derived from 2-amino-5-styryl-1,3,4-thiadiazole[1]. The first series includes the Shiff bases(II) prepared from the reaction between 2-amino 5-styryl-1,3,4-thiadiazole(I) with different substituted benzaldehydes in presence of glacial acetic acid and absolute ethanol. Then these derivatives have transformed to its polymers(III) by using dibenzoylperoxide as initiator. The third series was prepared from the reaction of the Shiff bases and 2,3-dimethyl maleic anhydride to give oxazepine compounds(IV). The reactions was followed by TLC.,and then these identified by FTIR, UV./Vis., (^{1}H-NMR,^{13}C-NMR for some of them) spectra and melting points. The biologically activity for some of the prepared compounds-was--studied----against *Staphylocaccus Sal. Typhi , Ps. Arugenosa and Escherichia Coli.*

Introduction :

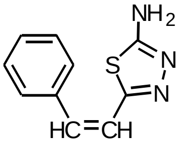
2-amino-1,3,4-thiadiazole constitute an important class of compounds having a wide spectra of biological activity. A great number of variously substituted 1,3,4-thiadiazole derivatives have been synthesized and tested for their fungicidal**(1-2)**, nematocidal**(3)**, antibacterial**(4)** and anti-inflammatory activities**(5)**, besides the industrial applications**(6)**. Most of the substitution reactions have been carried out of (2) and (5) position of the thiadiazole ring. The synthesis of these heterocycles has received considerable attention in recent years**(7-8)**. Khosrow et. al.**(9)** have synthesized some new substituted 1,3,4-thiadiazole and their derivatives through the intermolecular cyclization of 1,4-disubstitution thiosemicarhazides. The 5-amino 1,3,4-thiadiazole enalogues were also reported to be active against vaccinia**(10)** substituted 1,3,4-thiadiazole with aryl mercurium chloride have been synthesized under microwave irradiation in dry media**(11)**. In view of these observations, synthesis of series of derivatives of amino thiadiazole with its polymers have been synthesized.

Experimental Part:

Materials:

Chemicals employed were of analytical reagent and used without further purification. Melting points were determined by using an "Electrothermal" melting apparatus IR spectra were recorded on a SHIMADZU Infrared spectrophotometer Fourier transform FTIR-8400S in the 4000-200 cm^{-1}range using KBr disc. The reactive process was monitered by TLC until the starting material nearly disappeared. All reactions were followed by TLC (benzene/methanol) (2:1). NMR Ultra Shield 300 MHz, Bruker 2003, Switzerland. UV./Vis.spectra:Ultraviolet visible spectrophotometer company HITACHI U2000 spectrophotometer.

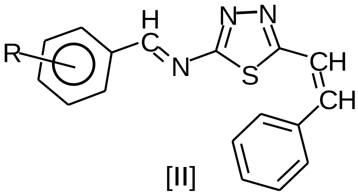
1-Preparation of 2-amino 5-styryl -1,3,4-thiadiazole [I]:



[I]

A mixture of (0.01mole)of cis-cinnamic acid and (0.01mole) of thiosemicarbazide in (10ml)of $POCl_3$ was refluxed for 4hrs.The excess of $POCl_3$ was removed and the residue dissolved in distilled water (50ml) and heated for 1hr. Then, the resulting product cooled, filtered and the filtrate was neutralized with KOH. The precipitate was filtered, dried and re-crystallized from ethanol.

2-Preparation of Schiff bases [II]:



[II]

R=H, p-OH, p-Cl ,p-N $(CH_3)_2$, p-NO_2 ,p-CH_3 , m-NO_2 , 3,4 Di- OH.

The hot ethanol solution of 2-amino 5- styryl-1,3,4-thiadiazole (0.01mole) mixed with a solution of the corresponding substituted benzaldehyde (0.01mole) in (10 ml) of absolute ethanol with some drops of glacial acetic acid. The mixture was refluxed for 30 minutes. The product was separated by filtration, The physical properties of these compounds are listed in Table (1).

Table (1): Physical properties of the prepared compounds (II).

Comp. No.	R	Molecular formula	Molecular weight	M.P.^{0} C	Yield %
IIa	H	$C_{17}H_{13}N_3$ S	291	160	75
IIb	*p*-OH	$C_{17}H_{13}N_3OS$	307	220	70
IIc	*p*-Cl	$C_{17}H_{12}N_3SCl$	325	>250	75
IId	*p*-NO$_2$	$C_{17}H_{12}N_4O_2S$	336	100	80
IIe	*m*-NO$_2$	$C_{17}H_{12}N_4O_2S$	336	140	85
IIf	2,4-diOH	$C_{17}H_{13}N_3O_2S$	323	220dec	85
IIg	*p*-Br	$C_{17}H_{12}N_3SBr$	370	220	80
IIh	*p*N(CH$_3$)$_2$	$C_{19}H_{18}N_4S$	317	180	90
IIi	*p*-Me	$C_{18}H_{15}N_3S$	305	140	75

3-The polymerization (III):

The polymerization of these monomers was carried out in THF by using AIBN or dibenzoyl peroxide as initiator. A solution of the monomer (0.5gm) in THF (15ml) and (6mg) of initiator were mixed in a flask. The mixture was refluxed in water bath. After 24hrs., the contents of the flask were poured into a large amount of methanol/water to precipitate the polymer, See Table(2).

Table (2): Physical properties of the prepared polymers (III).

Comp.No.	R	M.P.^{0}C
IIIa	H	100
IIIb	*p* -Br	110
IIIc	*p*-NO$_2$	120
IIId	*p*-N(CH$_3$)$_2$	>250
IIIe	*p*-OH	150
IIIf	2,4-di OH	122
IIIg	*p*- Me	220 dec.

4-Preparation of 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-aryl-2,3-dihydro-1,3-oxazepine-4,7-dione (IV).

2-N-Arylidene imino (III) added 2,3-di methyl maleic anhydride to give 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-arylidene--2,3-di hydro -1,3-oxazepine-4,7-diones (IV). These compounds were identified by their melting points and IR spectra. See Table (3).

Table (3): Physical properties of the compounds (IV).

Comp. No.	R	Molecular formula	Molecular weight	M.P.^{0}C	Yield %
IVa	H	$C_{23}H_{19}N_3O_3S$	417	220	70
IVb	*p* -OH	$C_{23}H_{19}N_3O_4S$	433	85	65
IVc	*p*-Br	$C_{23}H_{18}N_3O_3SBr$	496	205	75
IVd	*p*-N(CH$_3$)$_2$	$C_{25}H_{24}N_4O_3S$	460	210	70
IVe	*p*-Me	$C_{24}H_{21}N_3O_3S$	431	200	70
IVf	2,3diOH	$C_{23}H_{18}N_4O_5S$	462	180	75

Results and discussion:

Thiadiazole derivatives were prepared by the direct reaction between the corresponding cinnamic acid and dry powder of thiosemicarbazide in presence of phosphorus oxychloride to give compound I.

The IR spectrum of compound I Fig.(1),exhibited significant two bands in the region 3110-3250cm^{-1}, which could be attributed to a symmetric stretching vibration of NH$_2$ group(12) besides this, a band at about 1612 cm^{-1}, due to cyclic C=N, stretching is also observed.

The Shiff bases compounds were synthesized from 2-amino 5-styryl-1,3,4-thiadiazole with different substituted benzaldehydes in presence of glacial acetic acid. The synthesis of these compounds was carried out according to the steps outlined in scheme 1, and the physical properties are given in Table (1).

The reaction was followed by disappearance of NH$_2$ absorption band at 3500cm^{-1} and appearance of C=N absorption band in the IR spectra of the products Table(4). ^{1}H-NMR spectrum Fig.(2a) of compound (IIh) showed a signals at δ 3.0(6H-singlet), δ 6.7 (1H-doublet) , δ7.6 (2H-doublet) and δ9.3(5H-singlet).

In the ^{13}C-NMR spectrum Fig(2b), the appearance of the two carbons of di-methyl rings at 40ppm. The signals at 145 and 190 ppm attributed to the benzene rings. The thiadiazole carbon atoms appeared at 125 and the signal at 111ppm due to carbon of azomethine group. The signal at 132ppm may attributed to the carbon of styrene ring.

Table (4): Infra-red and Uv./Vis. spectral data for compounds (II).

Comp. No.	R	ν C=C Ar.	ν =C-H Ar.	ν C=N	ν C-H Aliph.	C-N	N-N	C-S	UV,λmax (nm),DMSO
IIa	H	1590,1461	3080	1610	2900	1390	1102	650	250
IIb	*p*-OH	1585,1473	3100	1600	2890	1400	1177	681	270
IIc	*p*-Cl	1589,1482	3090	1600	2980	1385	1180	677	260,370
IId	*p*-NO$_2$	1560,1466	3100	1600	2900	1400	1178	645	280,320
IIe	*m*-NO$_2$	1590,1501	3100	1620	2890	1395	1166	684	250,340
IIf	2,4-diOH	1580,1455	3090	1630	2890	1387	1165	668	240,350
IIg	*p*-Br	1580,1494	3100	1620	2890	1400	1170	680	250,370
IIh	*p*-N(CH$_3$)$_2$	1590,1488	3080	1630	2900	1378	1132	671	260,370
IIi	*p*-Me	1590,1467	3100	1620	2900	1388	1169	653	280,370

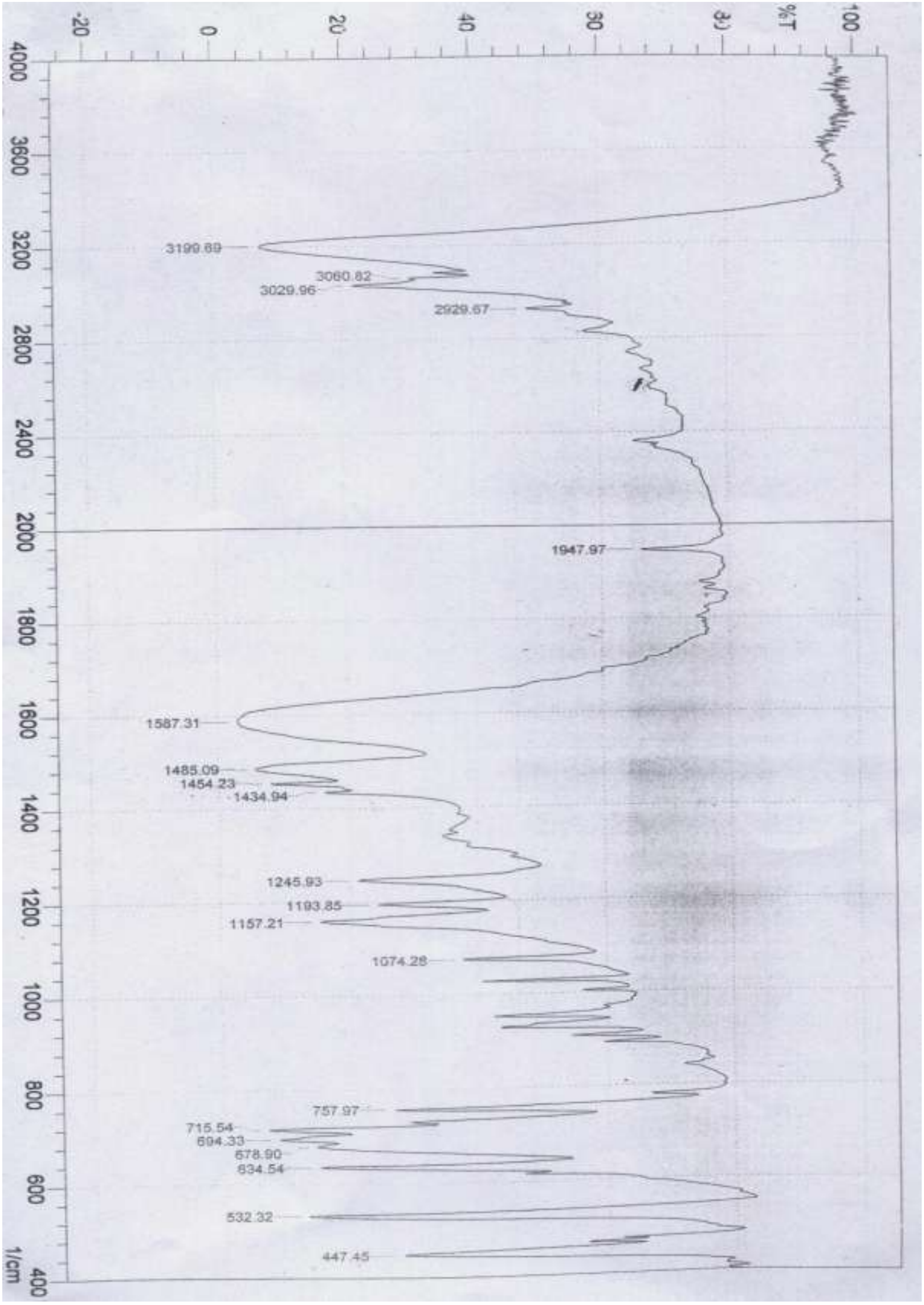
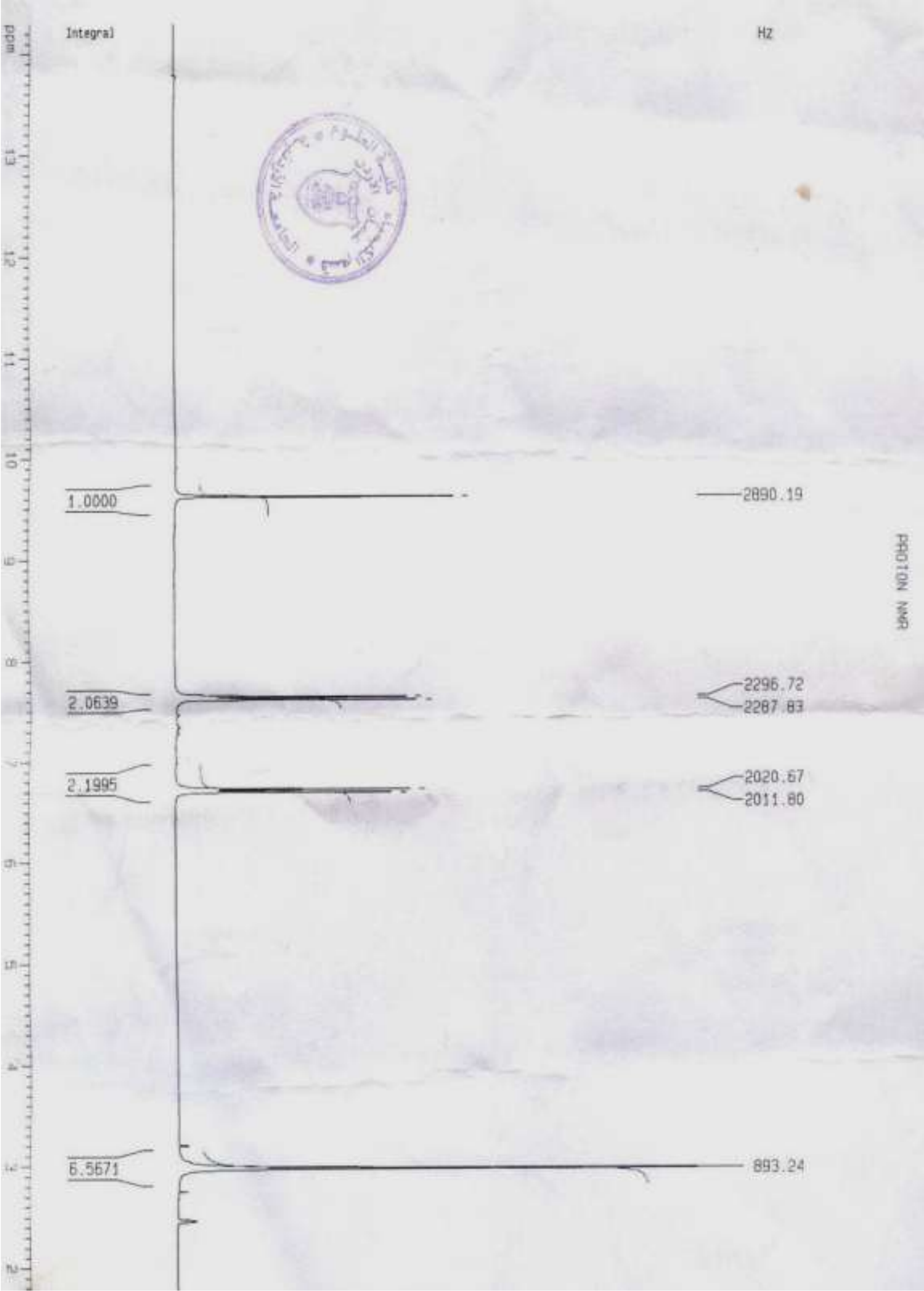
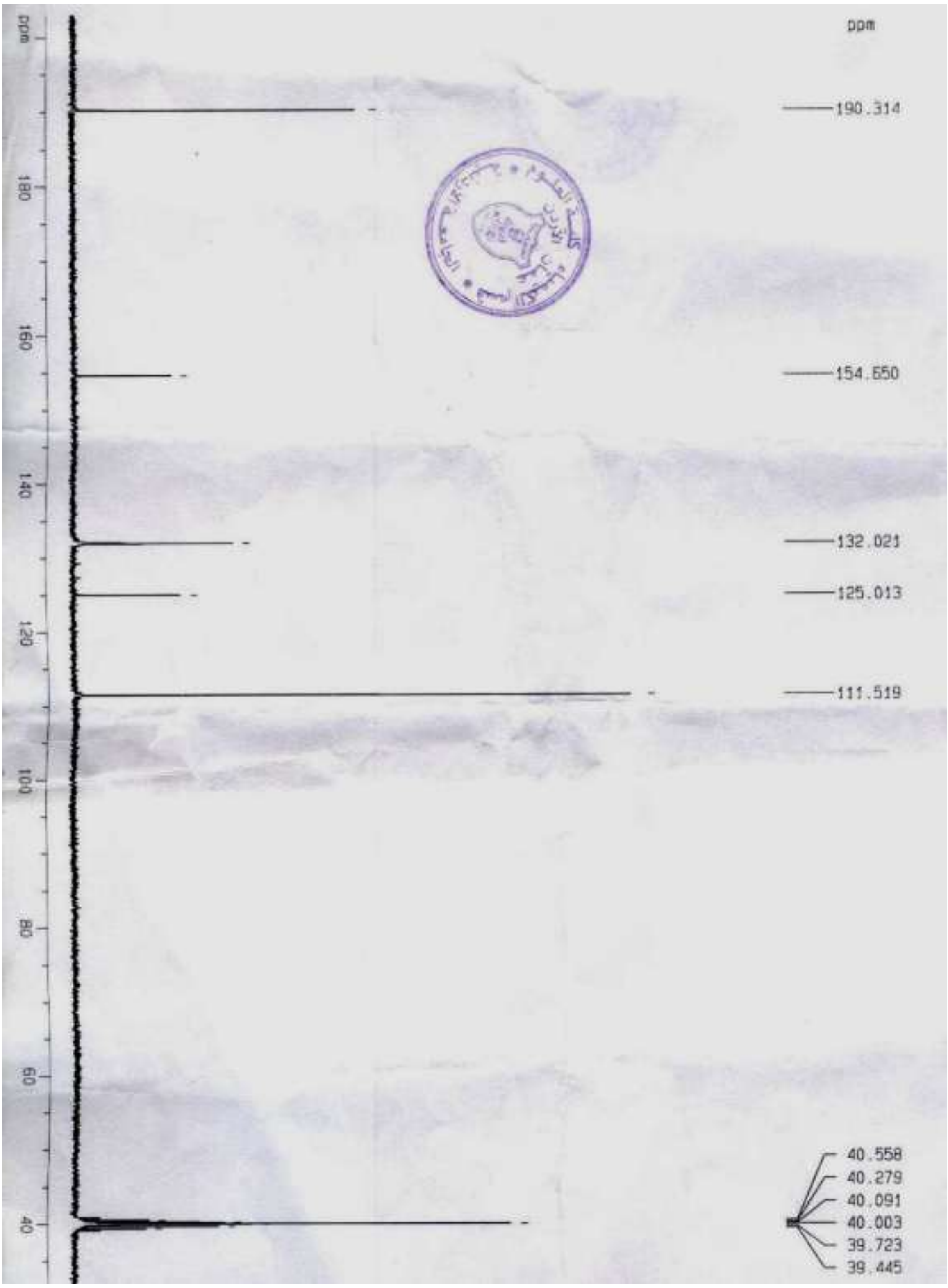


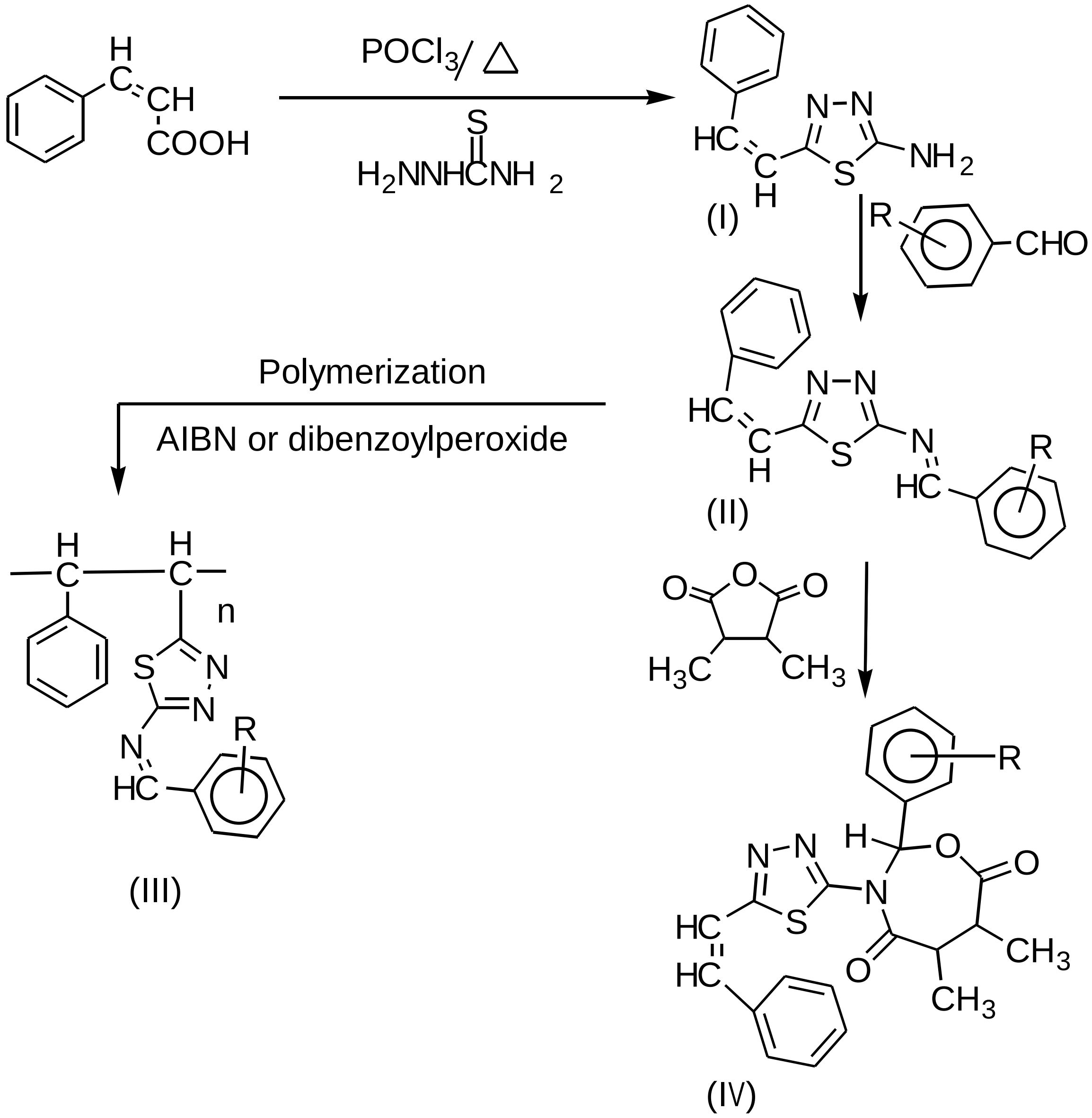
Fig (1): The IR spectrum of compound (I).



Fig(2a): The^1 H-NMR spectrum of compound (IIh).



Fig(2b): The ^{13}C-NMR spectrum of compound(IIh).



R=H, p-OH, p-Cl ,p-N $(CH_3)_2$, p-NO_2 ,p-CH_3 , m-NO_2 , 3,4 Di- OH.

Scheme (1): The synthetic routs of the prepared compounds.

2- The polymers :

These polymers were prepared according to Kapzuk's method$^{(13)}$. The polymerization of the monomers (II) was carried out in tetrahydrofuran (THF) with dibenzoyl peroxide as initiator.

The structures of the obtained polymers were confirmed from their melting points, IR, Uv./Vis. spectra and the viscosity were measured.

The IR spectra for these polymers, showed the disappearance of the absorption band of 1600-1610 cm^{-1} assigned to the double bond (C=C) in the monomer, it also showed the characteristic band of the monomer.

The absorption band at 1620 cm^{-1}which is typical to the azomethine group of Schiff bases, it also showed the absorption bands which characteristic to(C=C) aromatic and at 600-800 cm^{-1}that belongs to the para-substitution of benzene ring.

The Uv./Vis. spectra of these compounds are shown in Table (5). It showed the absorption band at 260 nm and 362-400 nm which attributed to the (C=O) and(C=C) groups respectively, that represents the n-π and π- π* vibration.

All these polymers were soluble in all common organic solvents, such as dimethyl formamide (DMF), dimethyl sulphoxide(DMSO), chloroform ($CHCl_3$), and THF.

The viscosity measurments of synthesized polymers of this study were determined by using viscometer (type Ubbelohod viscometer) was placed in water bath, the temperature was controlled by using a thermostat(Table 6).

Table (5): IR,Uv./Vis. spectral data for the prepared polmers (III).

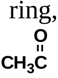
Comp.No.	ν.C=N	ν.C=C Ar.	ν. C-H Aliph.	=C-H Ar.	UV,λmax (nm), DMSO	others
IIIa	1620	1590,1468	2900	3100	286	-
IIIb	1625	1586,1481	2890	3090	260,274,362	C-Br(860)
IIIc	1630	1590,1493	2900	3095	279	C-NO_2(1540)
IIId	1620	1580,1461	2890	3090	266	-
IIIe	1630	1589,1489	2900	3100	280	-
IIIf	1625	1590,1464	2900	3095	274	-
IIIg	1630	1585,1500	2900	3100	285	-

Table (6): Viscosity measurments of the prepared polymers .

Polymer No.	$_{rel.}\eta$ $\eta_{rel} = t/t_0$	$_{inh}\eta$. $= \ln \eta_{rel} /C$	η_{spc}	$_{red}\eta$	$[\eta]$ $=(1/2C)(\eta_{spc} + \ln \eta_{rel})$(14)
IIIa	1.3	3.4	0.4	4.0	0.3
IIIb	1.3	2.7	0.3	3.1	0.2
IIIc	1.42	3.5	0.4	4.2	0.3
IIId	1.4	3.4	0.40	4.0	0.37
IIIe	1.25	2.2	0.2	2.0	0.22
IIIf	1.28	2.3	0.28	2.3	0.24

Synthesis of 3-[2-imino-1,3,4-thiadiazole-5-yl]-2-aryl-2,3-dihydro-1,3-oxazepine-4,7-dione IV.

The reaction of Schiff bases with maleic anhydride is a sort of cycloaddition reaction. Cycloadditon is a ring formation that results from the addition of π bonds to either δ or π bonds with formation of new δ bonds. This class of reaction and its reverse encompasses a large number of individual types(12).

Huisgen(15) has formulated a useful classification of diverse cycloadditions in terms of the new σ bonds, the ring size of the product, and the number of atoms in the components taking part in the cycloaddition. This cycloaddition is classified as 5+2→7, implying a 5-atom component plus 2 atom component leading to 7-membered heterocyclic ring, but the mechanism involves addition of one σ bond  $CH_3\overset{\overset{O}{\|}}{C}$ to one π bond (N=C) to give 4-membered cyclic transition state which opens into maleic anhydride (5-membered ring) to give 7-membered ring .

It is obvious that N-aryl-1,3,4-thiadiazole contains both a (C=C) function and an azomethine function (C=N) and either one or both are able to react with maleic anhydride. The reaction, actually, involves interaction between the Homo orbital of maleic anhydride with Lumo orbital of (C=C) or (C=N), since the oxygen has higher electronegativity than nitrogen, the energy gab between its Lumo orbital and the Homo orbital of maleic anhydride is larger than it is between the Lumo orbital of azomethine and the Homo orbital of maleic anhydride. Energetically, the interaction between the Homo orbital of maleic anhydride and the Lumo orbital of azomethine is more favorable.

Incidently, even in the absence of (C=N) no interaction between the Homo orbital of maleic anhydride and the Lumo orbital of (C=C) is observed for the same reason.

It is obvious that the two absorption bands at (1740-1780)$cm^{-1}$and at (1800-1850)cm^{-1}in the IR spectrum of pure maleic anhydride(12) have disappeared when the anhydride became part of the 7-membered heterocyclic ring. The (C=O) group of the title compounds absorbs at (1700-1750)cm^{-1}(oxazepine) and (C-O), (O=C-O-) at (1000-1300)cm^{-1}. This confirms the assigned 7-membered heterocyclic ring structure.

Biological activity:

In this work, the anti-microbial test was performed according to agar well diffusion method(16). The prepared compounds were tested against four pathogenic microorganism, *staphylococcus Aurus , E. Coli , Sal. Typh and Ps. aerugenosa*. In the solidified media (Nutrient agar), suitable spaced apart holes were made (6mm in diameter) these holes were filled with (0.1ml) of prepared compounds concentration that dissolve in DMSO (Dimethyl sulphoxide) after spread the bacteria on agar. these plates were incubated at 37 ^{0}C for 24 hour, the zone of inhibition of bacteria growth around the hole was observed and measured in mm and are represented by (-), (±), (+), and (++) depending upon the diameter and clarity as in Table (7).

The preliminary screening results reveal that the compounds contained (NO_2), compound [IIe] exhibit the highest antibacterial activity against while the other compounds showed either low or no activity against both or all organisms.

Table (7): Antibacterial activity of the prepared Shiff bases (II).

Comp. No.	Staphaureus	E.Coli	Sal. Typhi	Ps.aerugenosa
IIa	+	+	+	_
IIb	_	±	±	_
IIc	_	+ +	_	±
IId	+	+	+	+
IIe	_	+ +	_	+ +
IIf	+ +	+	_	±
IIg	±	+	±	±
IIh	+	±	±	_

Key to symbols:(-) =No inhibition, (±)=6- 9mm, (+) =10-14mm, (++) =15-22mm.

References :

1-Xia-Juan,Lu-Hua.Lai,Gui-Yu-Jin, and Zu-Xrng Zhang, J.Agric. Food chem. 50,3757-3760 (2002).

2-Kidwai M. and Bhushan K.R., *Chem.Papers 53(2) 114-117 (1999).*

3- Li Z., Wang XC. and Da YX., *Synth. Commun. 30(21):3971-3983(2000).*

4-Shaukath Akhanum,Sheena Shashikanth and Belagurs sudha, *Science Asia La, 383-392 (2003).*

5-EL-Emam A.A, Moustafa M.A, Bayomia S.M. ,and EL-Ashmawy M. B.,Journal of the Chinese Chemical Society ,36,353-356 (1989).

6-Robert B.Faltermeier *,Studies in Conservation 44,121-128 (1998).*

7-Hausoug chen ,Zhenginging Li, and Yufeng Han *,J.Agric Food Chem. 48, 5312-5315 (2000).*

8-Shankath A Khanun, Sheena ,Shashlkanth and Belagur S Sudha *,Science Asia, 29, 383-392 (2003).*

9-Khosrow Zamani, Klalil Faghihi, Reza Sangi M., and Javad Zolgharnein , *Turk J Chem ,27,119-125 (2003).*

10- Sadler PW, J. Org. Chem., 26, 1315-16 (1961).

11-a) Volna,F., Odlerova, Z., and Lacova, M., Cesk. Epidemiol., *Mikrobiol., Imunol. 22, 223 (1973);* b) Nayak, N. C., *Acta Sci. Ind. Chem. 9, 128 (1983*).

12- Silverstein R. M. ,Bassel c. c., and Morrill T. C.,"Spectrometric Identification of Organic Compounds " *Academic Press, New York (1981).*

13- G. Hazupoβ, E.π. Yepkeβa, and B.A. Kapzuk, *Vysokomol. Soedin., Ser, B, 14,,764(1972).*

14- O.F.Solomon and I.Z. Ciuta, *J. Appl. Sci., 6,683(1962).*

15- R. Huisgen, *Angew. Chem. Internat. Edit. ,7,321,(1968).*

16- M.U. Rahman, and S. Gul., Antibacterial activity of hydrodistilled essential oil of Psammogeton canescens N.O.Umbelliferae. *Biotechnol.1(1):55-60.*

تحضير وتشخيص بعض المشتقات الجديدة غير المتجانسة الحلقة وبوليمراتها مع دراسة تاثيراتها البايولوجية.

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الملخص:

تم في هذا البحث تحضير عدد من مشتقات المركب ٢-امينو-٥-ستايريل ١، ٣، ٤-ثايادايزول الجديدة . حيث تم تحضير ٢-امينو-٥-ستايريل ١، ٣، ٤-ثايادايزول من حامض السناميك ، $POCl_3$ وثايوسيميكاربازايد ثم تمت مفاعلة هذه المادة مع مختلف الالديهايدات الاروماتية لتكوين قواعد شف (II) ومن ثم مفاعلة قواعد شف مع ٢، ٣-ثنائي ماليك انهدرايد لتكوين مشتقات اوكسازيين (IV) ،وكذلك تمت بلمرة قواعد شف باستعمال ثنائي بنزوايل بيروكسيد كبادىء لعملية البلمرة وباستخدام THF كمذيب لتكوين البوليمرات (III) وتمت دراسة تاثير هذه المركبات على بعض انواع البكتريا المقاومة لدراسة تاثيراتها البايولوجية.

وقد شخصت المركبات المحضرة باستخدام اطياف الاشعة تحت الحمراء،طيف الاشعة فوق البنفسجية ، (طيف ^{1}H NMR ، ^{13}C NMR للبعض منها)وكذلك قياس درجات الانصهار.