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Synthesis and Characterization of Heterocyclic Derivatives Containing Five membraned rings from 2-mercapto-5-methyl-oxadiazole

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Abstruct

The present work included the synthesis of some new Schiff base derivatives of hydrazine hydrate coupled with ethyl-5-phenyl-2-(1,3,4-oxadiazole thiol) acetate, ***this role*** reacted with mercapto-acetic acid to synthesize five-membered ring heterocyclic compound derivatives. The yields of all synthesized compounds were good. All compounds were confirmed by their melting point, FT-IR spectra, and ^{1}HNMR spectra for some of them.

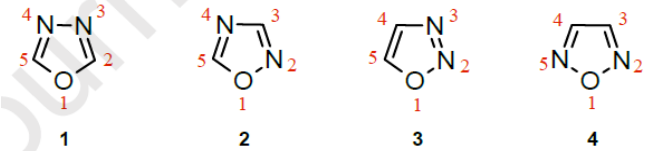
Keyword: Schiff bases,mercapto-acetic acid, Oxadiazole, hydrazine

الخلاصه :

تضمن البحث تخليق قواعد شيف جديده من الهيدرازيد المحضر بواسطة تفاعل(اثيل – 5 فنيل 1، 3، 4 اوكسادايازول ثايول) اسيتيت مع الهيدرازين المائي ، وهذا بدوره يتفاعل مع مركبتو حامض الخليك لتخليق مشتقات حلقيه خماسيه شخصت جميع المركبات المحضرة بواسطة درجات الانصهار وأطياف الأشعة تحت الحمراء وطيف الرنين النووي المغناطيسي لبعض منها.

1. Introduction

Oxadiazoles are a monocyclic ring system with multiple applications. Although the 1,3,4-oxadiazole ring system was known in 1880, the proper study of its chemistry, structure, physicalproperties, and application of various derivatives began only in 1950 [1] ,N-containing heterocycles, especially five-membered rings, are of great interest as they are found in natural products [2] and used frequently in medicinal chemistry. There are three known isomers:1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole. Amongst oxadiazole isomers, 1,3,4-oxadiazole derivatives are known to be the most stable [3].



1 2 3 4

Literature studies have revealed that the 1,3,4-oxadiazole moiety possesses a broad spectrum of biological activity, including anti-fungal [4], anti-inflammatory [5], analgesic [6], antiviral [7], antibacterial [8], anti-HBV activity [9], anti-Alzheimer activity [10], anticancer [11]. Thiazolidinones are five-member ring heterocyclic compounds that contain sulfur and nitrogen atoms. These compounds are not aromatic [12].Thiazolidinones have been demonstrated to exhibit antibacterial, antifungal, antiviral, antituberculostatic, anti-HIV, antihistamini, anticancer, anticonvulsant, and anti-inflammatory properties [13,14].

2. Experimental

2.1 General

The used chemicals were obtained from Sigma Aldrich. Melting points were recorded by Gallen-Kamp MFB-600 melting point apparatus. The FT-IR spectra were recorded on an FT-IR-8400S-Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 400MHZ spectrophotometer (Germany), deuterated solvents (DMSO-d_6) were used for sample preparation, and tetramethylsilane TMS was used as an internal standard.

2.2. Synthesis of phenyl hydrazide S1

A mixture of phenyl acetate (4 mL, 0.03 mol) and excess hydrazine hydrate (2 mL, 0.04 mol) in 25 mL of ethanol, the mixture was refluxed for 10 hrs. The resulting product was recrystallized from ethanol [15]. Physical properties of the compound, yield: 95 (%), M.P: 112 ^{o}C, white crystalline solid.

2.3. Synthesis of 5-phenyl-2-mercapto (1,3,4-oxadiazole) S2

A mixture of phenyl hydrazide (1 g, 0.007 mol) and an excess of carbon disulfide (2.5 mL) in absolute ethanol (25 mL) with an alkaline medium (potassium hydroxide 0.4 gm), The reaction was refluxed for 8 hrs. After checking the finish, all the H_2S gas stopped by lead acetate was added drops of HCl 10% for neutralization of the base (the precipitate was filtered off and washed with water to afford the desired compounds (potassium chlorides salt) [16].

2.4. synthesis of ethyl-5-phenyl-2-(1,3,4-0xadiazole thiol)acetate S3

Compound **S2** (2 gm, 0.0011 mol) was dissolved in absolute acetone (30 mL) and potassium carbonate (1.6 gm,0.0011Lmol). Ethyl chloroacetete (2.57 mL,0.0011 mol) was added

drop wise. The reaction was refluxed for 8hrs, after which the precipitate was filtered and washed with cold water. The excess solvent was evaporated [17].

2.5. Synthesis of 5-phenyl-2-(1,3,4-0xadiazole thiol)acetohydrazide S4

Compound **S3** (5 gm, 0.018 mol) was dissolved in absolute ethanol (75 mL) and an excess of hydrazine hydrate (99 %, 14.7 ml) was added to the mixture gradually. The reaction was stirred for 24 hr then poured into ice cold water, filtered, dried, and recrystallized from ethanol to give a white crystalline [18].

2.6. General procedure for the synthesis of Schiff bases from 5-phenyl-2-(1,3,4-0xadiazole thiol) acetohydrazide S5-S13

A mixture of compound **S4** (0.5 gm,0.002 mmol) and different aromatic aldehydes (0.002 mol) in absolute ethanol (30 mL)and a few drops of glacial acetic acid was refluxed for 6 hrs. After that, the mixture was cooled down and the precipitated product was filtrated, washed with cold water, dried, and recrystallized from ethanol [19].

2.7. Synthesis of 4-thiazolidinone derivatives S14-S22

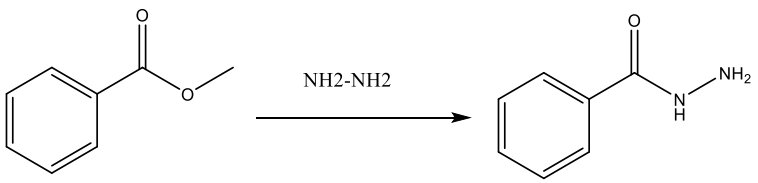
A mixture of Schiff bases **S5-S13** (0.001mol) and excess of thioglycolic acid (0.002 mol) in ethanol was refluxed for 18-20 hrs. The solvent was evaporated and the residue was neutralized with 5% sodium bicarbonate solution to remove excess of thioglycolic acid. The formed precipitate was filtered, washed several times with distilled water and recrystallized from ethanol[20].

3 Results and discussion

This work includes synthesis of new heterocyclic ring derivatives

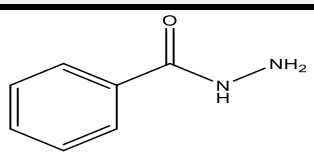
(3-1) – Synthesis of Benzohydrazide (S1)

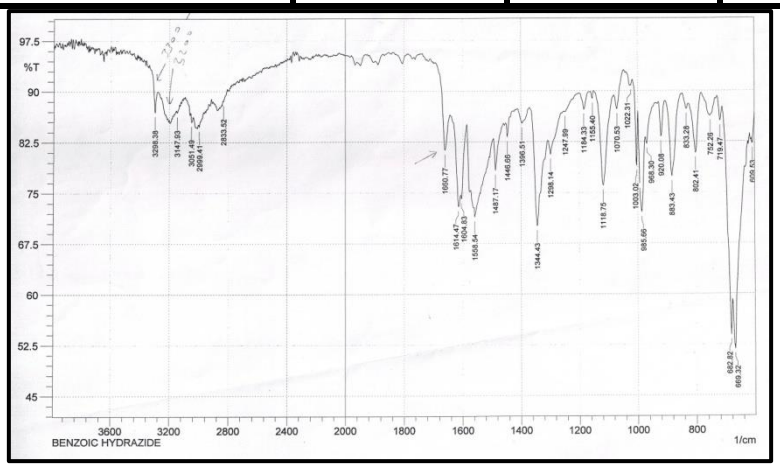
Benzohydrazide (S1) was prepared by treatment of methyl benzoate with hydrazine hydrate in ethanol as shown in Equation (3.1)



Equation (3.1)

Table (3-1): FTIR spectral data (cm^{-1}) of compound [S1]

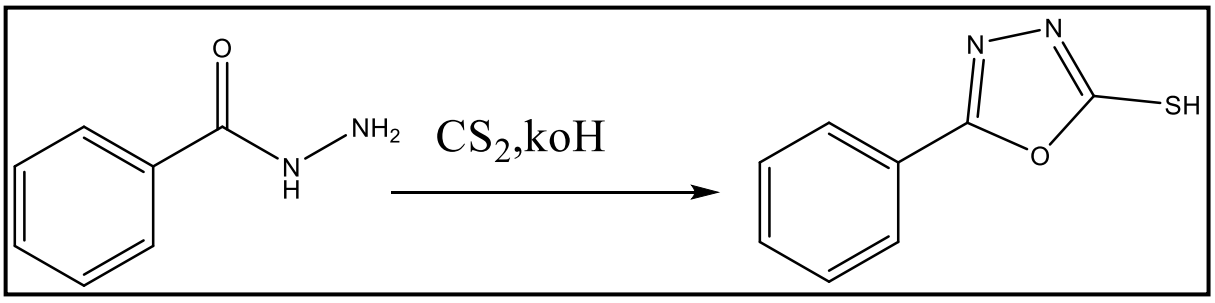
Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}		
		(C=O) amide	(NH)	Other bands
S1		1660	3147	NH2Asym 3298, Sym 3200



FTIR spectrum of compound S1

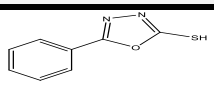
(3-2) – 5-phenyl-1,3,4-oxadiazole-2-thiol (S2)

Benzohydrazide (S1) reacted with carbon disulfide in alkali medium that used to prepare the compound [S2] as shown in Equation (3.2).

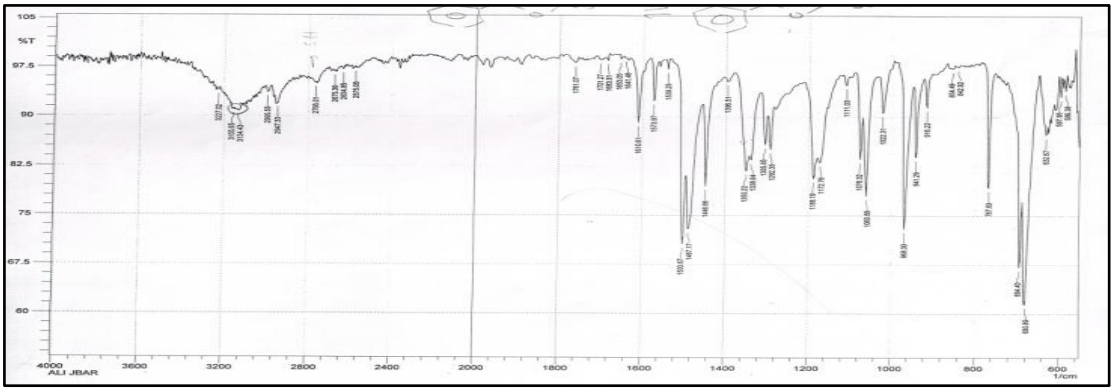


Equation (3.2).

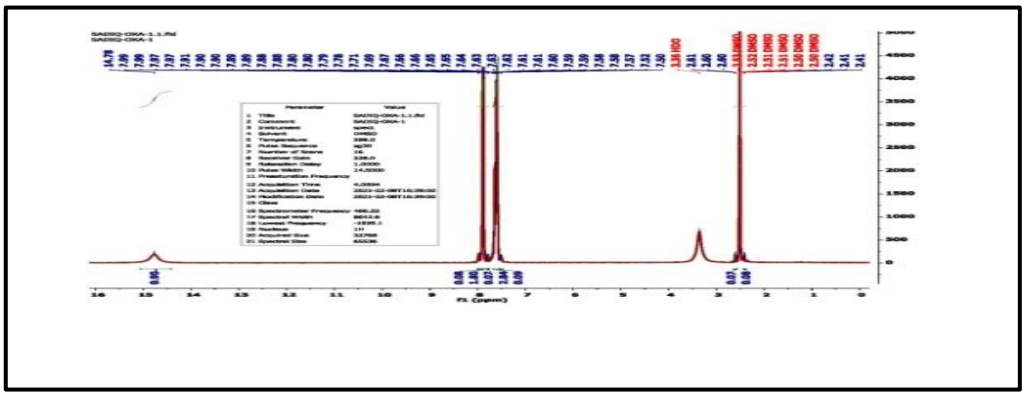
Table (3-1): FTIR spectral data (cm^{-1}) of compounds [S2]

Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}		
		(C=N)	(-SH)	Other bands
S2		1610	2755	

[-^{1}HNMR spectrum of compound [S2] showed a singlet signal at δ= (14.7) ppm due to (-SH) proton and signals at δ= (7.5-7.9) ppm due to (CH aromatic ring), Figure (3.2).



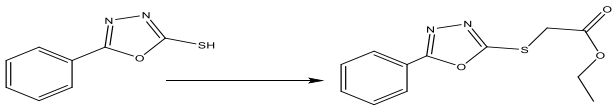
FTIR spectrum of compound S2



^{1}HNMR of compound S2

(3.3)- ethyl 2-((5-phenyl-1,3,4-oxadiazole-2-yl)thio)acetate.(S3)

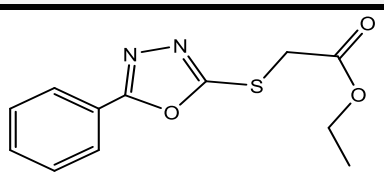
5-phenyl-1,3,4-oxadiazole-2-thiol (S2) reacted with ethyl chloro acetate in alkali medium that used to prepare the compound [S3] as shown in Equation (3.3).

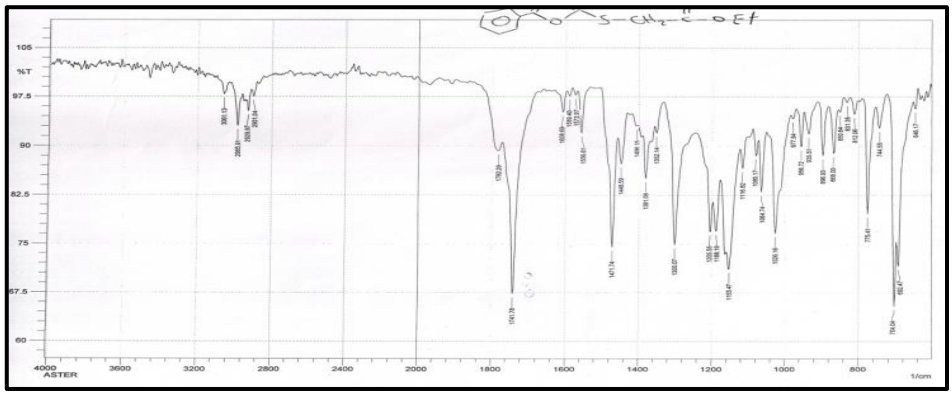


Equation (3.3)

FT-IR spectral data of compound (S3) showed the appearance of characteristic(1741) cm-1 belong to (C=O) of ester group ,(2931)cm-1belong to (C-H) aliphatic and disappearance of the absorption band at (2755) cm^{-1} (S-H)

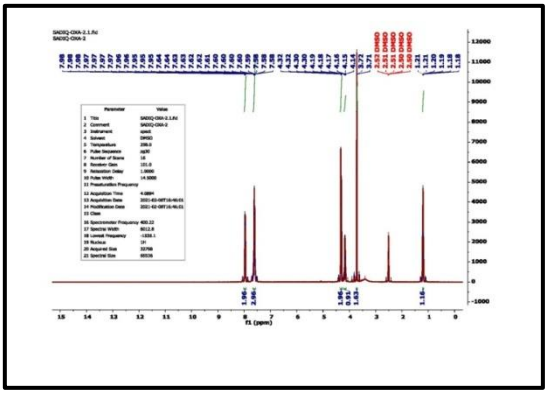
Table (3-1): FTIR spectral data (cm^{-1}) of compound [S3]

	Comp. structure	FT-IR spectral data, cm^{-1}		
		(C=O) ester	(C=N)	Other bands
S3		1741	1608	2931 (C-H) aliph



FTIR spectrum of compound S3

^{1}HNMR spectrum of compound [S3] showed a triplet signal at δ= (1.18) ppm due to (-CH_3)protons, quartet signal at δ= (4.1) ppm due to (-O-CH_2) protons, signal at δ= (3.7) ppm due to (S-CH_2-C=O) protons, signals at (7.5-7.9) ppm due to (CH aromatic ring) protons

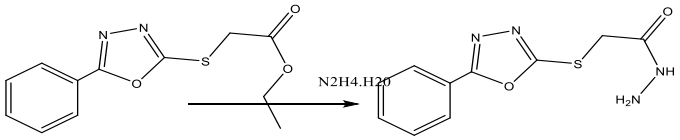


^{1}HNMR of compound S3

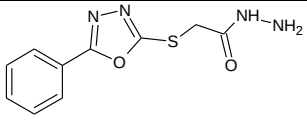
(3-4)- 2-((5-phenyl-1,3,4-oxadiazole-2-yl)thio)acetohydrazide (S4)

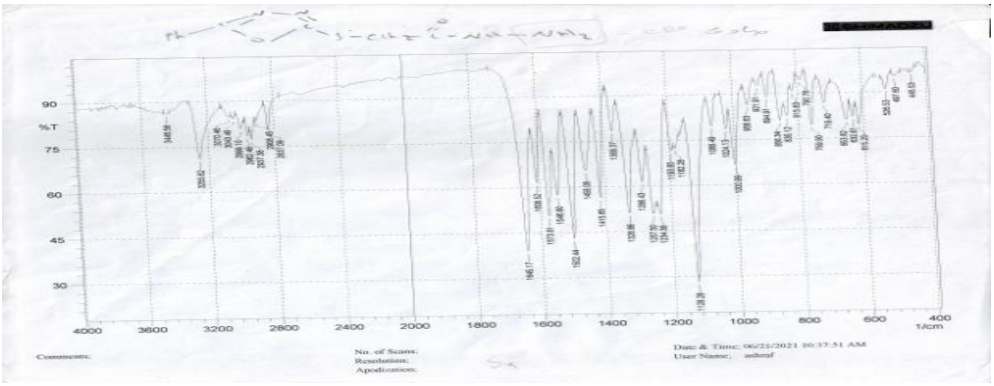
This part involved conversion of the prepared ester [S3] to the corresponding acetohydrazide [S4]

FT-IR spectra data of compound (S4) showed the appearance of the characteristic absorption band at (3446-3255) cm-1belong to v (NH2) asym. sym., characteristic absorption band at (1645) cm^{-1} v (C=O) due to amid carbonyl group and disappearance of the absorption band (1741) cm^{-1} v (C=O)due to ester carbonyl group



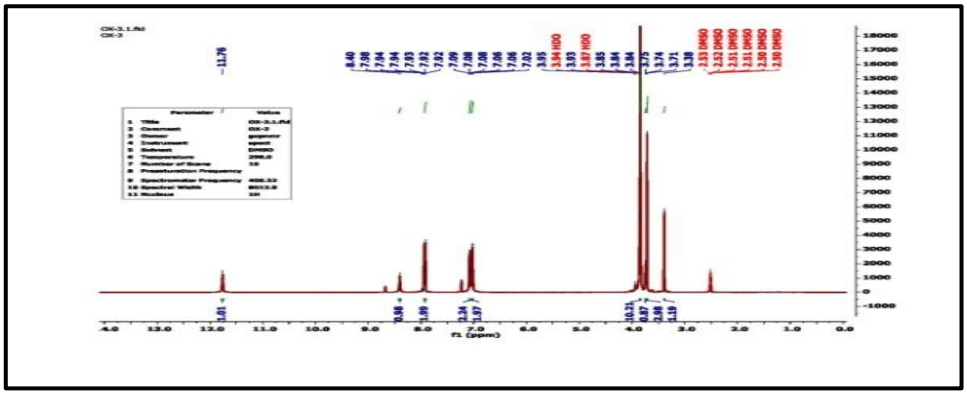
Equation (3.4)

Comp. no.	Comp.	FT-IR spectral data, cm^{-1}		
		(C=O) amide	(NH, NH_2)	Other bands
S4		1645	Asym3446 Sym 3255	(CH2) alph 2999



spectrum of compound S4

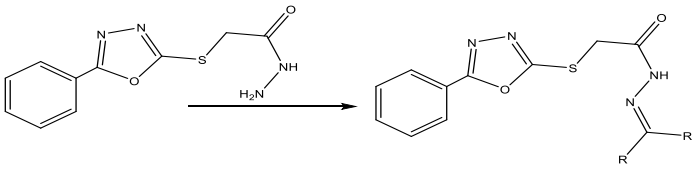
^{1}HNMR spectrum of compound [S4] showed singlet signal at δ= (3.7) ppm due to(-NH_2), signals at δ= (3.38) ppm due to (S-CH_2-C=O) protons, signals atδ= (7.1-7.9) ppm due to (CH aromatic ring) protons, and singlet signal atδ= (11.7) ppm due to (-NH) proton



^{1}HNMR of compound S4

(3-5) -New Schiff bases derivatives from 2-((5-phenyl-1,3,4-oxadiazole-2-yl)thio)acetohydrazide [S5-S13].

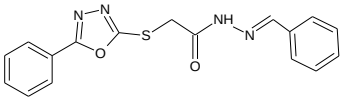
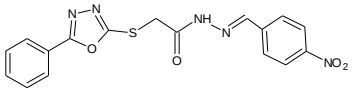
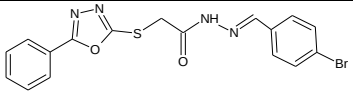
The titled compounds were synthesized from the reaction between compound [S4] and appropriate aldehydes in absolute ethanol in the presence of glacial acetic acid, as shown in Equation (3.5).

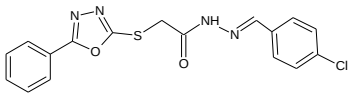
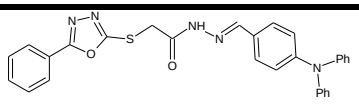
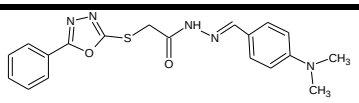
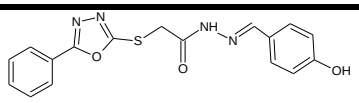
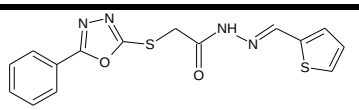


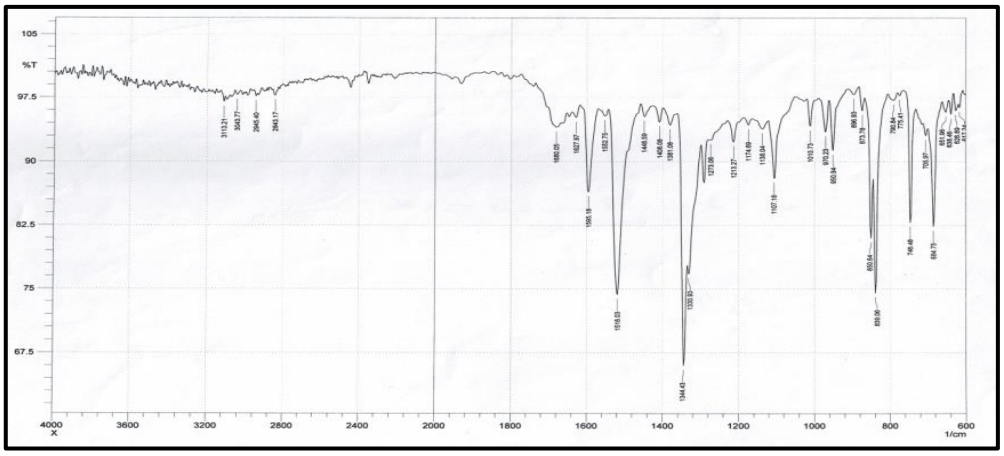
Equation (3.5)

FT-IR spectrum data of compounds (S5-S13) showed appearance of characteristic absorption bands at (3047-3180) cm^{-1}belong to v (N-H) ,characteristic absorption band at (1658-1672) Cm^{-1} v (C=O)due to carbonyl of amid group, (1602-1627) Cm^{-1} belong to (C=N) and disappearance of the absorption bands (3217,3120) Cm^{-1} belong to v (NH2) asym.,sym. All details of FTIR spectral data of compounds (S5-S13) are listed in Table (3-2)

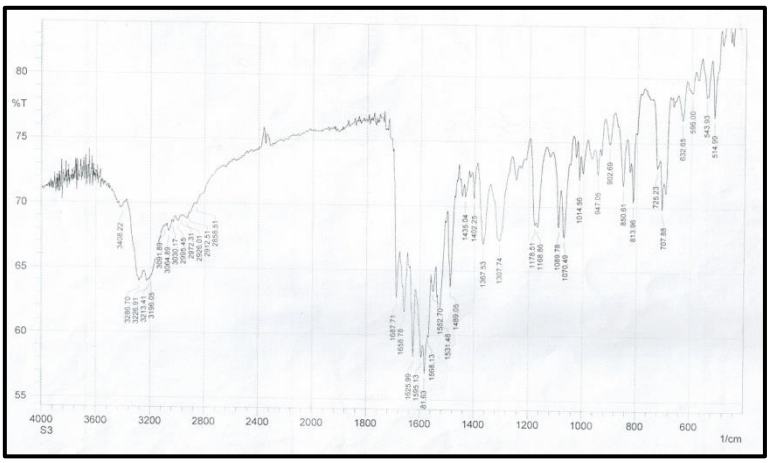
Table (3-2): FTIR spectral data (cm^{-1}) of compounds [S5-S13]

Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}						
		(N-H)	(C-H) Ali.	(C-H) Aro	(C=O)	(C=N)	(C=C)	Other Bands
S5		**3238**	**2931**	**3028**	1668	1627	**1579**	
S6		3113	**2945**	**3043**	1680	1627	**1518**	NO_2Asym (1595) Sym. (1344)
S7		**3062**	**2941**	**3001**	**1660**	**1627**	**1568**	

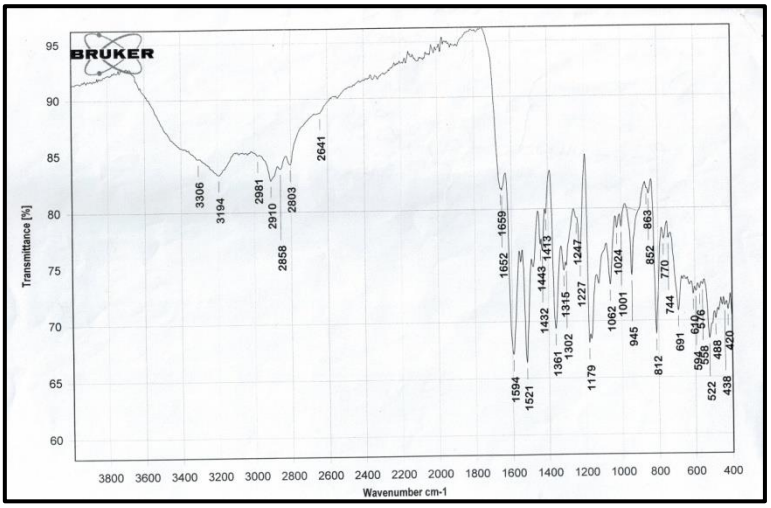
S8		**3213**	**2995**	**3064**	**1658**	**1625**	**1595**	**C-cl 632**
S10		**3194**	**2910**		**1659**	**1652**	**1521**	
S11		**3113**	**2989**	**3030**	**1660**	**1629**	**1550**	
S12		**3273**	**2806**	**3062**	**1660**	**1606**	**1514**	
S13		**3141**	**2967**	**3004**	**1652**	**1621**	**1522**	



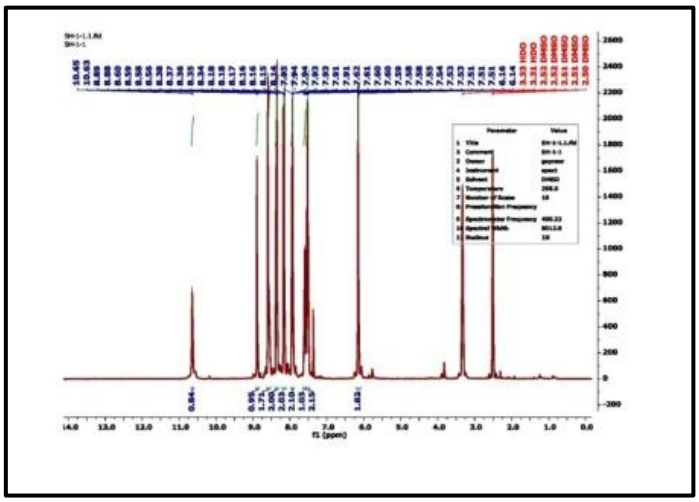
FTIR spectrum of compound S6



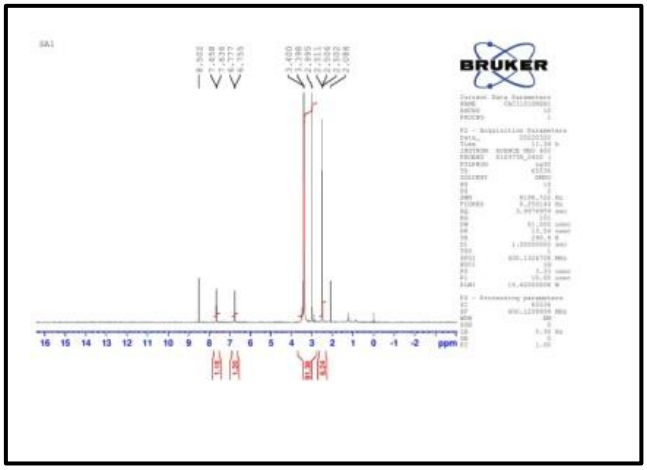
FTIR spectrum of compound S8



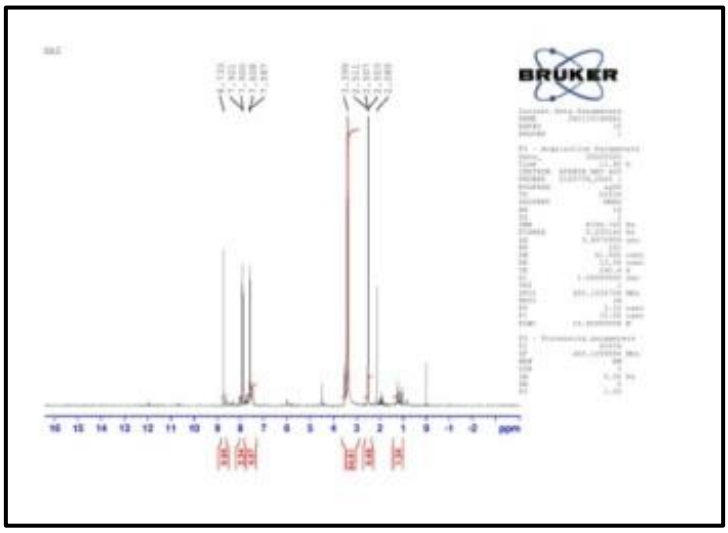
FTIR spectrum of compound S10



^{1}HNMR of compound S6



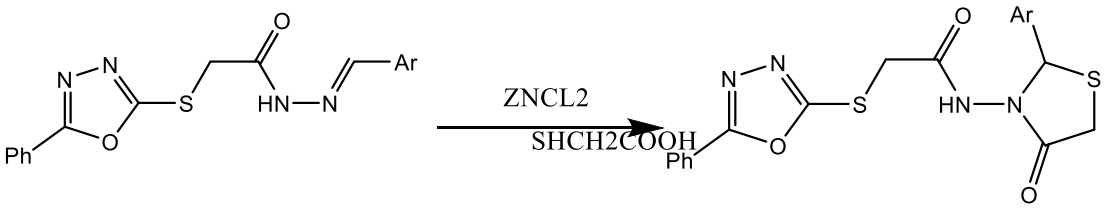
^{1}HNMR of compound S8



^{1}HNMR of compound S10

(3-6)- 4-thiazolidinone derivatives [S14-S22].

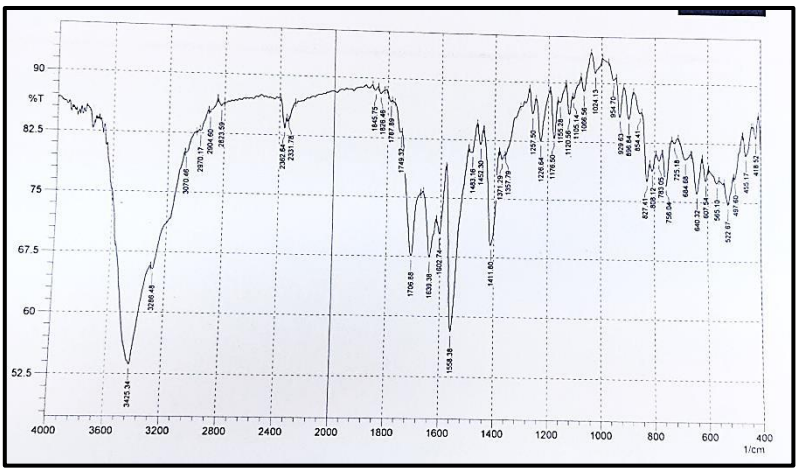
The 4-thiazolidinone derivatives [S14-S22] were synthesized by refluxing equimolar amounts from the imine derivatives with thioglycolic acid and $ZnCl_2$ ascatalyst in ethanol as shown in Equation (3-6).



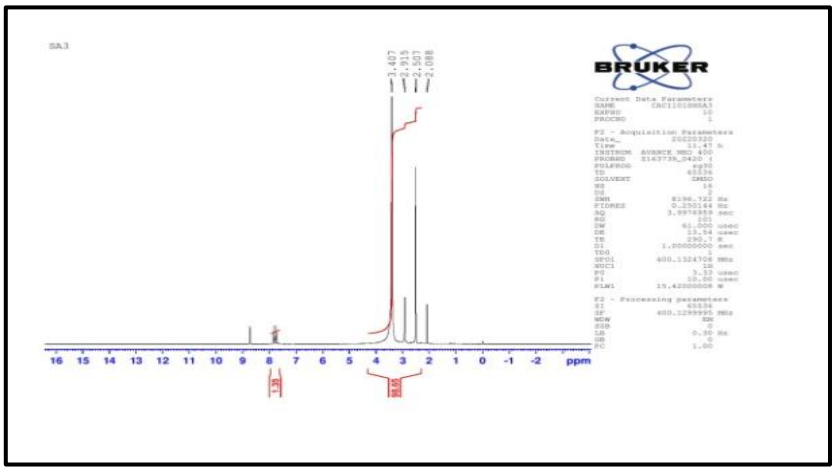
Equation (3-6).

FTIR spectrum data of compounds [S14-S22] Figure (3-1) showed appearance of stretching band of carbonyl amide group at (1603-1676) stretching band of carbonyl group at (1695- 1726) cm^{-1} due to thiazolidinone ring, stretching band of the (C=C) group for aromatic ring at (1556-1587)cm^{-1} and disappearance stretching band of (C=N). All details of FTIR spectral data of compounds [S14-S22] are listed in Table (3-6).

^{1}HNMR spectrum of compound [S16] showed signal atδ= (2.9) ppm due to (S-CH_2-C=O) protons, signal atδ= (3,4)ppm due to (-CH_2-S ring)protons, signals atδ= (7.6- 7.8)ppm due to(CH aromatic ring)protons and singlet signal at (8.7)ppm due to(N-H), Figure(3.24).

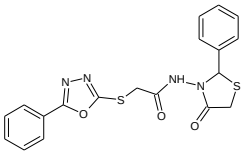
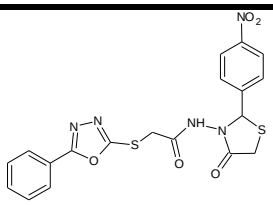
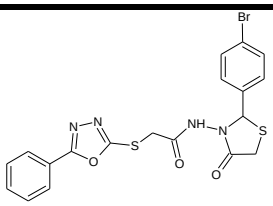
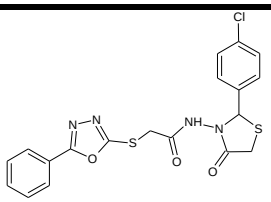
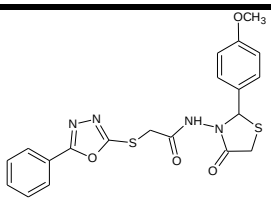
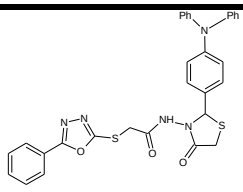


FTIR spectrum of compound S16



^{1}HNMR of compound S16

Table (3-6): FTIR spectral data (cm^{-1}) of compounds [S14-S22]

Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}						
		(N-H)	(C-H) Ali	(C-H) Aro	(C=O) lactame	(C=O) amide	(C=C)	Other Bands
S14		**3170**	2952	**3056**	**1708**	**1676**	**1558**	
S15		**3286**	**2962**	**3056**	**1706**	**1620**	**1562**	
S16		**3266**	**2970**	**3070**	**1706**	**1639**	**1558**	
S17		**3152**	**2943**	**3084**	**1726**	**1623**	**1587**	**C-cl 628**
S18		**3172**	**2906**	**3058**	**1706**	**1641**	**1560**	(C-O-C)
S19		**3292**	**2975**	**3184**	**1701**	**1639**	**1556**	

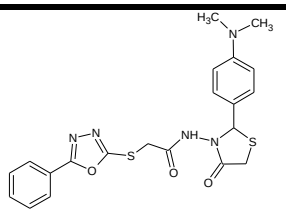
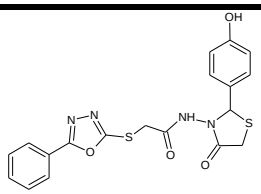
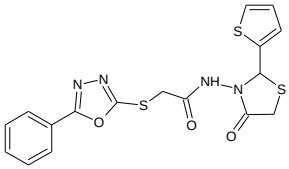
S20		**3290**	**2980**	**3200**	**1695**	**1603**	**1582**	
S21		**3226**	**2974**	**3039**	**1772**	**1697**	**1568**	
S22		**3274**	**2981**	**3213**	**1780**	**1683**	**1562**	

Table (3-1): Physical properties of compounds(S1 – S22)

1S	C7H8ON2	136	112	white	95
S2	C8H6N2OS	178	215	Pale yellow	75
S3	C12H12N2O3S	264	70	yellow	86
S4	C10H10O2N4S	250	160	white	52
S5	C17H13O4N5S	383	247	yellow	90
S6	C17H14O2N4S	338	90	Grey	65
S7	C31H24 O3N5S2	508	140	Orange	99
S8	C17H13O2N4SCl	372	160	White	65
S9	C17H13O2N4Br	417	190	Pale yellow	70
S10	C18H16O3N4S	368	170	brown	50
S11	C19 H19O2N5S	381	210	Yellow	60
S12	C17 H14O3N4S	354	210	Brown	55

S13	C15H12O2N4S2	336	235	Yellow	55
S14	$C_{19}H_{14}O_3N_4S_2$	105	410	Light yellow	77
S15	$C_{19}H_{13}O_5N_5S_2$	260	455	Yellow	60
S16	$C_{19}H_{13}O_3N_4S_2Br$	290	489	Off white	70
S17	$C_{19}H_{13}O_3N_4S_2Cl$	270	444	Light yellow	65
S18	$C_{20}H_{16}O_4N_4S_2$	180	440	White	65
S19	$C_{31}H_{24}O_3N_5S_2$	168	578	Orange	55
S20	$C_{21}H_{19}O_3N_5S_2$	290	453	white	75
S21	$C_{19}H_{14}O_4N_4S_2$	185	426	white	55
S22	$C_{17}H_{12}O_4N_4S_3$	235	408	white	60

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