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Synthesis and Biochemical Investigation of (Thiazin, Oxadiazol, Thiadiazol)- Derivatives .

Zinah Hussien Ali
Assist. Lecture ,College of Pharmacy ,Department of Pharmaceutical Chemistry,Iraq.

Abstract
The study involved synthesis of six and five- membered rings from hetero cyclic compounds containing sulfur and nitrogen with oxygen atoms such as (thiazine, oxadiazol, thiadiazol)- derivatives., some of compounds were prepared from condensation reaction and other by chalcone .The synthesized compounds [1-10] were characterized by many methods {FT.IR- spectra, H.NMR- spectra, (C.H.N)- analysis} and tested for their potential antibacterial {Gram(+) positive and Gram(-) negative} and melting points .
Keywords: thiazine, chemical, oxygen .

Introduction

The oxadiazol, thiazine and thiadiazole nucleus are a useful structure for research and development of new pharmaceutical molecules ,it found in several natural and non- natural products., most of sulfur and nitrogene hetero cycles derivatives are marketed as anti-Psychotic drugs, antifungal, anti-thelmintic, antibacterial, anticancer, HIV- Inhibitors, anti- hypertensive, anti- allergic, anticonvulsant, anti-tubercular, anti- inflammatory activity, and some of derivatives have been found to possess some interesting bioactivities such as anti diabetic activity[1-4] .
These derivatives exhibit adverse biological activities possibly due the present of (N-C-S) moiety, which are very interesting compounds for their applications in pharmaceutical and analytical fields[5-7] .In addition ,these derivatives have been used for the preparation of structures in polymers .

Materials and Methods

Melting points were determined by electro thermal 9300, LTD, FT.IR- shimadzue 8300, KBr-disc, H.NMR- spectra in DMSO- solvent and (C.H.N)- analysis in Kashan University in Iran ., biological tests in bio- lab, biology department in college of education .

Synthesis of Compounds [1 - 3]:

According to procedures[8,9] ,a mixture of 2-amino imidazole (0.01mole) and chloro ethyl acetate (0.02mole) was reacted in presence of ethanol with potassium hydroxide under magnetic stirrer., then filtered and recrystallized to produce (84%) of compound [1], which (0.01mole) refluxed with (0.02mol) of thiosemicarbazide in presence of absolute ethanol for (3hrs), after filtered and recrystallized to yield (84%) of compound [2], which cyclized by addition ($POCl_3$) and refluxed in ethanol for (5hrs) to yield (82%) of compound [3] .

Synthesis of Compounds [4 , 5] :

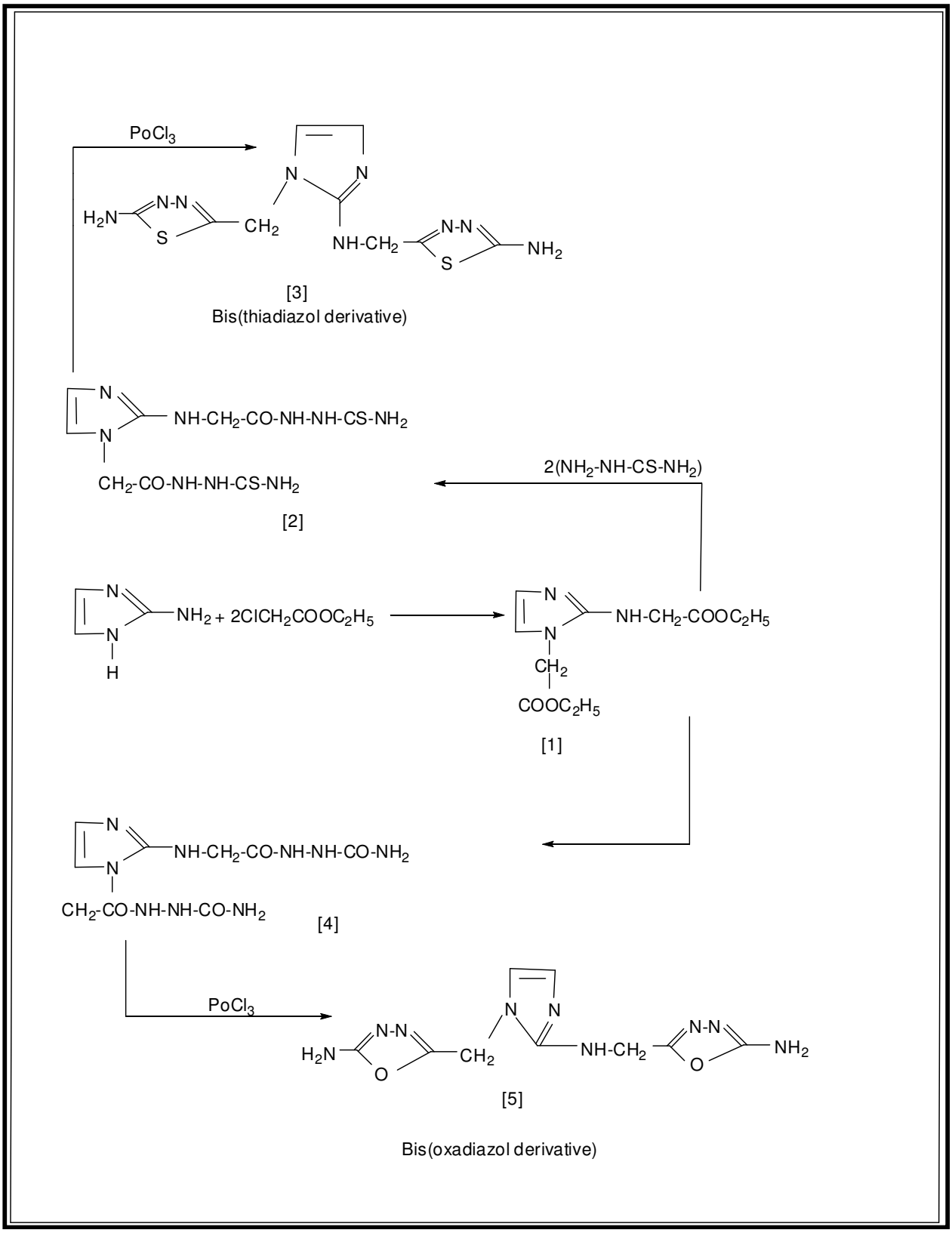
According to procedure[9] ., a mixture of compound [1] (0.01mol) and semicarbazide (0.02mole) was refluxed in present of absolute ethanol for (3hrs) ,then filtered and recrystallized to yield (86%) of compound [4]., which (0.01mole) cyclized in presence of $POCl_3$ with ethanol to produce (82%) of compound [5] .

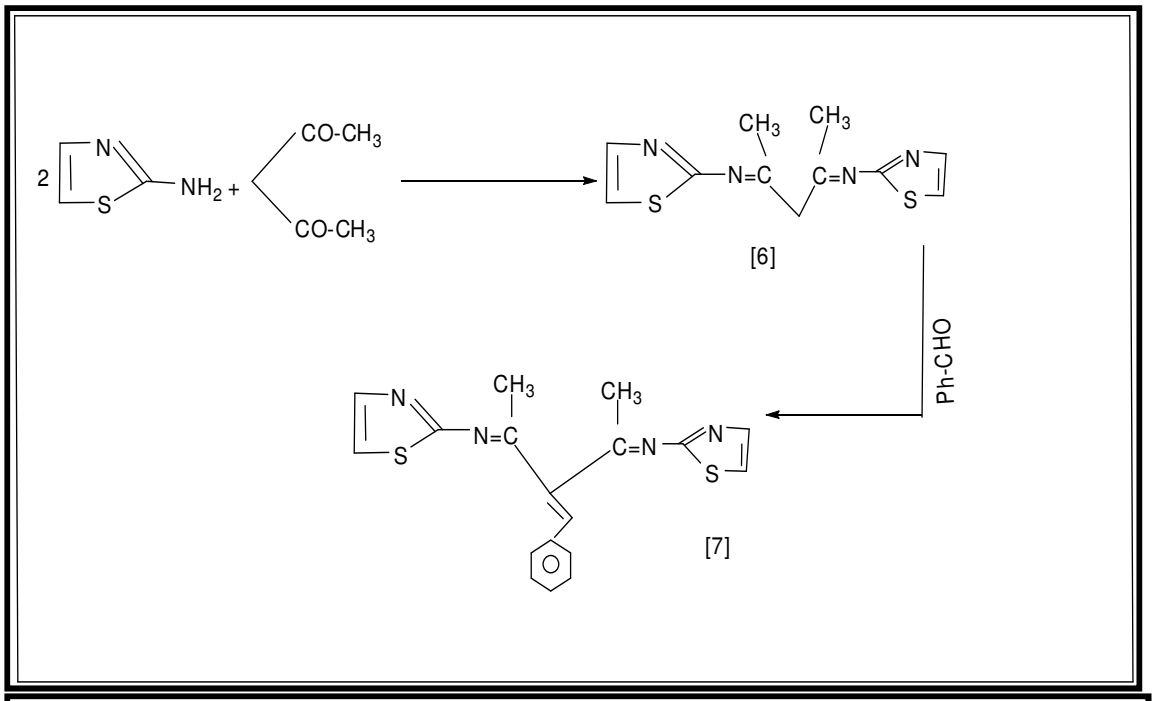
Synthesis of Compounds [6 , 7] :

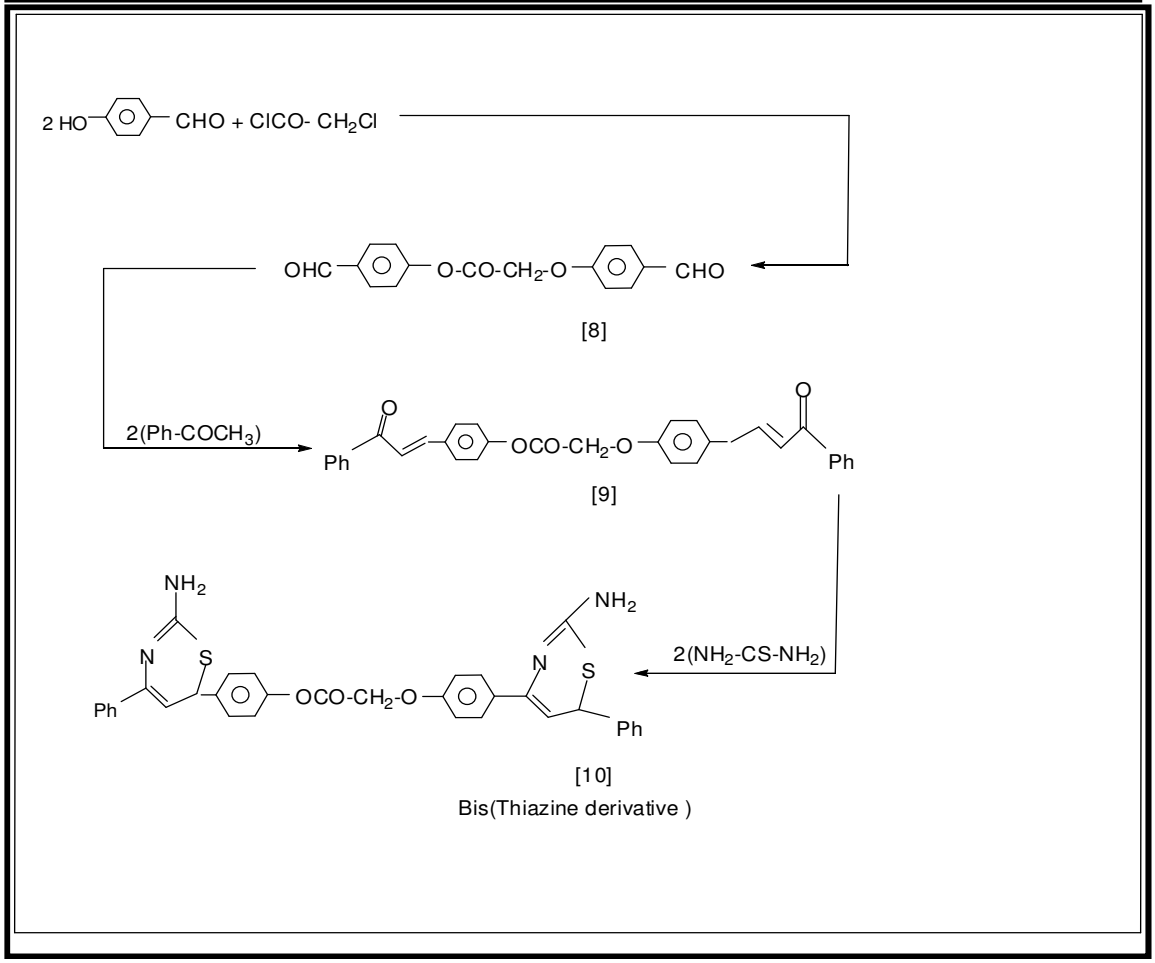
According to procedure[9] ., a mixture of (0.02 mol) of 2- amino thiazol and (0.01mol) acetyl aceton was refluxed in presence of absolute ethanol and drops of glacial acetic acid for (2hrs) ,then filtered and recrystallized with ethanol to yield (84%) of compound [6]., which (0.01mol) reacted at room temperature with (0.01mole) benzadehyde in presence of (10% NaOH) to yield (82%) of compound [7] .

Synthesis of Compounds [8 -10] :

According to procedure[9] ., a mixture of (0.02mol) P- hydroxyl benzaldehyde and (0.01mol) chloro acetyl chloride was reacted in presence of basic medium (KOH)., the solid filtered and dried , recrystallized to yield (82%) from compound [8]., which (0.01mol) reacted with (0.02mol) acetophenone at room temperature in presence of ethanol with (10% Na OH) to yield (84%) compound [9]., which (0.01mol) refluxed with (0.02mol) of thiourea in presence of ethanol with 5ml (HCl)., then filtered and dried , recrystallized to yield (84%) compound [10] .


PoCl3
[3]
Bis(thiadiazol derivative)
NH-CH2-CO-NH-NH-CS-NH2
CH2-CO-NH-NH-CS-NH2
[2]
2(NH2-NH-CS-NH2)
NH2 + 2ClCH2COOC2H5
NH-CH2-COOC2H5
COOC2H5
[1]
NH-CH2-CO-NH-NH-CO-NH2
CH2-CO-NH-NH-CO-NH2
[4]
PoCl3
[5]
Bis(oxadiazol derivative)





Results and Discussions

This study involved , synthesis of heterocyclic compounds (five and six) –membered rings such as thiadiazol and oxadiazol with thiazin rings ., these compounds [1-10] contain imidazole and thiazol in their structures which cause biological activity. All synthesized compounds [1-9] have been characterized by spectrophotometer

chemical methods [FT.IR , H.NMR, (C.H.N)- analysis] , melting points and physical properties with biological study :

The FT.IR- spectrum : showed an absorption band at 1722 cm^{-1} due to carbonyl of ester (-COO-) in compound [1], which disappeared and other bands appeared such as 1690 cm^{-1} for carbonyl of amide (CO-NH), bands at (3290 cm^{-1}, 3310 cm^{-1}) for amine group (NH_2) in compound [3] ,band at (1686)cm^{-1} for carbonyl of amide (CO-NH) in compound [4], bands at (1604, 1618)cm^{-1} for (C=N) end o cycle of oxadiazol rings and (3280, 3300) cm^{-1} for primary amine group (NH_2) in compound [5] . other bands at 1630 cm^{-1} for (C=N) and 782 cm^{-1} for (C-S) of thiazol ring in compound [6], band at 3102 cm^{-1} for (=CH) alkene in compound [7]., bands at {1710 cm^{-1} for carbonyl of aldehyde (CO-H), 1728 cm^{-1} for carbonyl of ester, 1230 cm^{-1} for (C-O-C) ether in compound [8]., bands at 1728 cm^{-1} for carbonyl of ester, 1687 cm^{-1} for carbonyl of chalcone , 1235 cm^{-1} for (C-O-C) ether, 3110 cm^{-1} for (CH=CH) alkene in compound [9], bands at (3280, 3300) cm^{-1} for primary amine group (-NH_2), 1725 cm^{-1} for carbonyl of ester, 3105 cm^{-1} for (=CH) alkene , 1235 cm^{-1} for (C-O-C) ether, 795 cm^{-1} for (C-S) in thiazine ring in compound [10]., and other bands[10-13] listed in table (1) .

Table (1): FT.IR-data (cm^{-1}) of Compounds [1-10]

Comp. No.	(C=N) endocycle	NH , NH_2	(-COO)	Other groups
[1]	1610	3190	1722	(CH)aliph **:** 2982
[2]	1608	3205	/	(CH) aliph **:** 2955**.,** (CO-NH) amide**:** 1690
[3]	1605**,** 1618	3290**,**3310	/	(CH) aliph**:** 2975
[4]	1610	3220	/	(CH) aliph**:** 2982**.,** (CO-NH) amide**:** 1686
[5]	1604**,** 1618	3280**,**3300	/	(CH) aliph**:** 2998
[6]	1612	/	/	(CH) aliph**:** 2981**.,** (C=N)**:** 1626 (C-S)**:** 782
[7]	1608	/	/	(CH)aliph**:** 2973**.,** (C=N)**:** 1630**.,** (=CH) alkene**:** 3102
[8]	/	/	1728	(CO-H) carbonyl of aldehyde: 1710., (C.O.C)ether: 1230., (CH)aliph: 2965., (CH) arom: 3080
[9]	/	/	1720	(CO-CH=CH) chalcone: 1687., (C-O-C)ether: 1235., (CH)aliph: 2990., (CH=CH): 3110
[10]	1614	3280**,**3300	1725	(=CH)alkene: 3105., (C-O-C)ether: 1242., (CH) aliph: 2982., (CH)arom: 3040., (C-S): 795

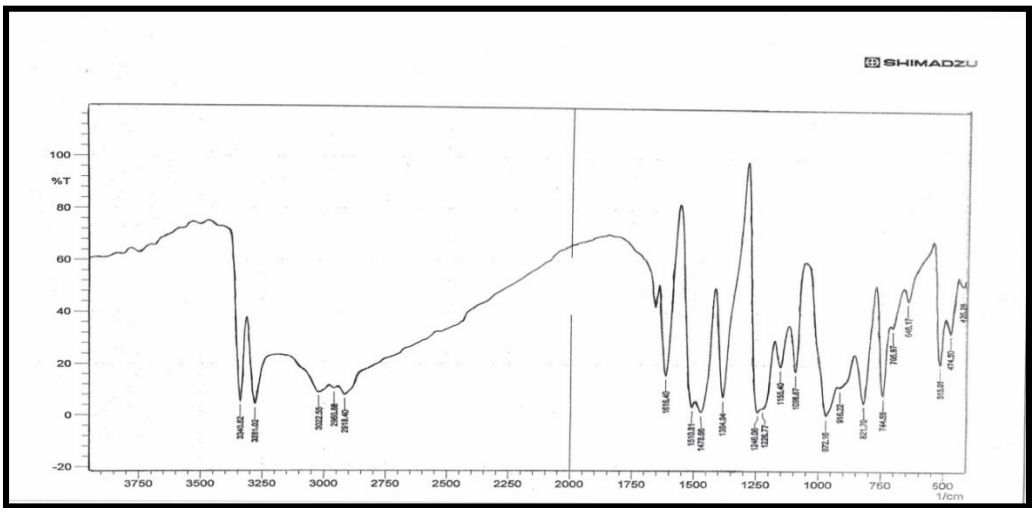


Fig (1) : FT.IR of Compound [2]

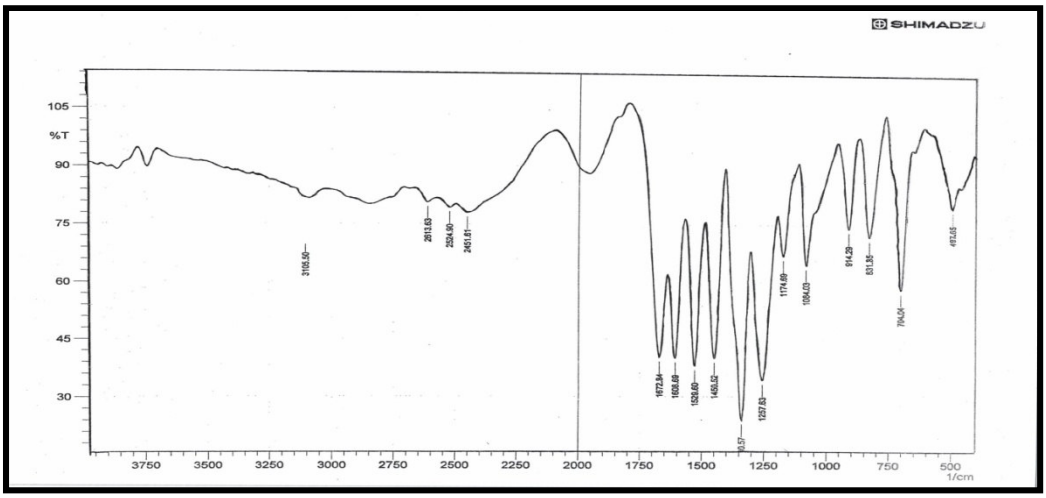


Fig (2) : FT.IR of Compound [6]

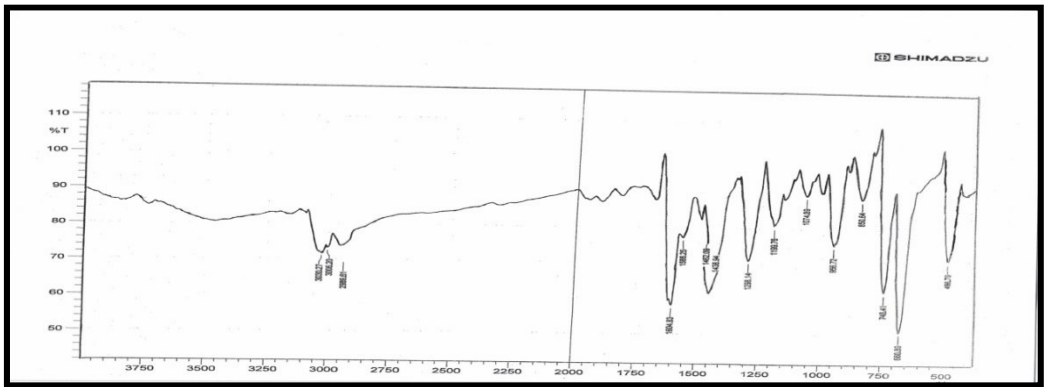


Fig (3) : FT.IR of Compound [7]

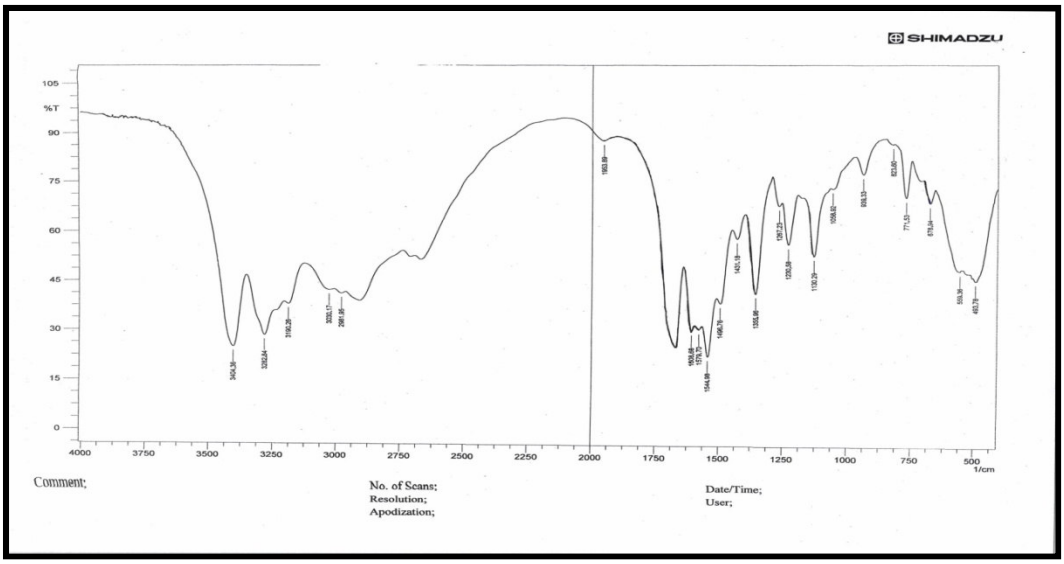


Fig (4) : FT.IR of Compound [10]

H.NMR- spectrum: showed signals at δ (3.8-4.30) for ($COOC_2H_5$) ethyl of ester in compound [1], which disappeared and other signals appeared at δ(5.0 **,** 5.25 **,** 5.34) for (NH_2 , NH) , δ 10.02 for (NH-CO) amide in compound [2], signals at δ(4.09, 5.20) for (NH_2 , NH) groups in compound [3] ,signals at δ(5.10, 5.25) for (NH) groups, signals at δ(10.04- 10.28) for amide groups (NH-CO) in compound [4] .,signals at δ(5.21**,** 5.03) for (NH, NH_2) amine groups in compound [5], signals at δ(7.93) for protons of thiazol ring in compound [6] .,signal at δ 6.04 for alkene (C=CH), signal at δ 7.10 for protons of phenyl group., signals at δ 3.98 for ester

($COOCH_2$-), signal at ƃ 11.82 for proton of aldehyde group (CO-H), signals at ƃ (6.9- 7.4) for protons of phenyl groups in compound [8]., signals at ƃ 3.86 for ester ($COOCH_2$-), signals at ƃ (6.52- 7.63) for protons of phenyl groups, signals at ƃ (5.72 , 5.85) for alkene (CH=CH) in compound [9], signals at ƃ 5.08 for (NH_2), signal at ƃ 3.94 for ester ($COOCH_2$-) ,signals at ƃ (6.76 - 7.54) for protons of phenyl groups., and other signals for functional groups[14-17] are listed in table (2) .

Table (2): ^{1}H.NMR - data (ƃ, ppm) of compounds [1-10]

Comp. No.	NH , NH_2	($COOCH_2$-) ester	(CH_2), (CH_3)	Other groups
[1]	5.02	(3.8- 4.30)	0.95, 1.15	Protons of imidazole ring **:** 7.8
[2]	5.0 , 5.25 , 5.34	/	1.0 , 1.15	Protons of imidazole ring : 7.86., (CO-NH) amide: 10.02
[3]	5.09, 5.20	/	0.98, 1.18	Protons of imidazole ring : 7.91
[4]	5.10 , 5.25	/	1.0 , 1.20	Protons of imidazole ring : 7.84., (CO-NH) amide and (CO-NH_2): (10.04-10.28)
[5]	5.21, 5.03	/	0.96, 1.13	Protons of imidazole ring : 7.81
[6]	/	/	1.04, 1.21	Protons of thiazol ring : 7.93
[7]	/	/	1.03	Protons of thiazol ring : 7.78., (C=CH): 6.04., Phenyl ring: 7.10 .
[8]	/	3.98	/	(HC=O) aldehyde: 11.82., Phenyl rings (6.9- 7.4)
[9]	/	3.86	/	Phenyl rings : 6.52- 7.63., (CH=CH) chalcone: 5.72, 5.85
[10]	5.08	3.94	/	Phenyl rings : 6.76- 7.54 .

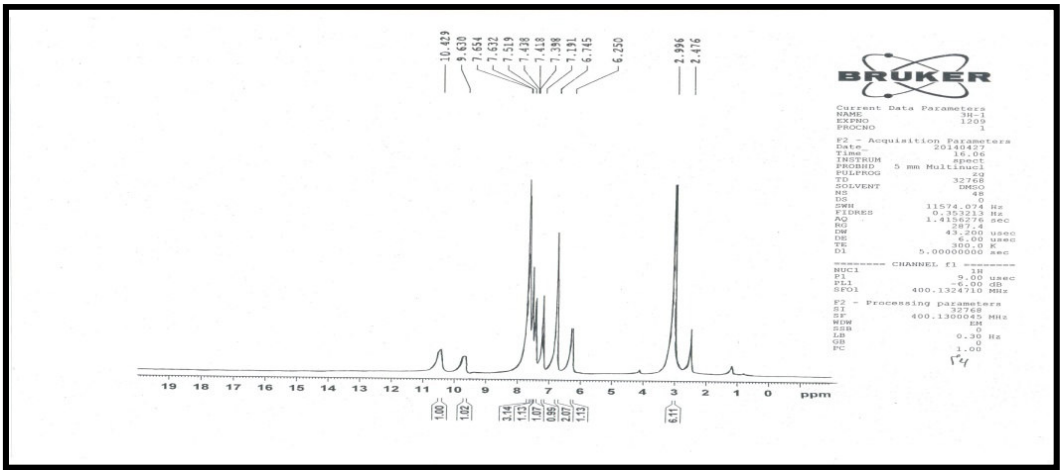


Fig (5) : H.NMR of Compound [8]

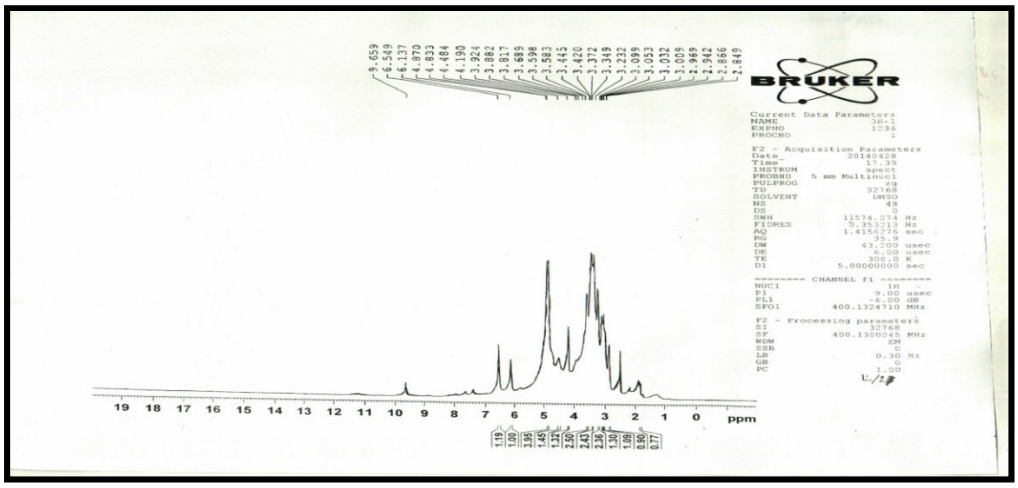


Fig (6) : H.NMR of Compound [9]

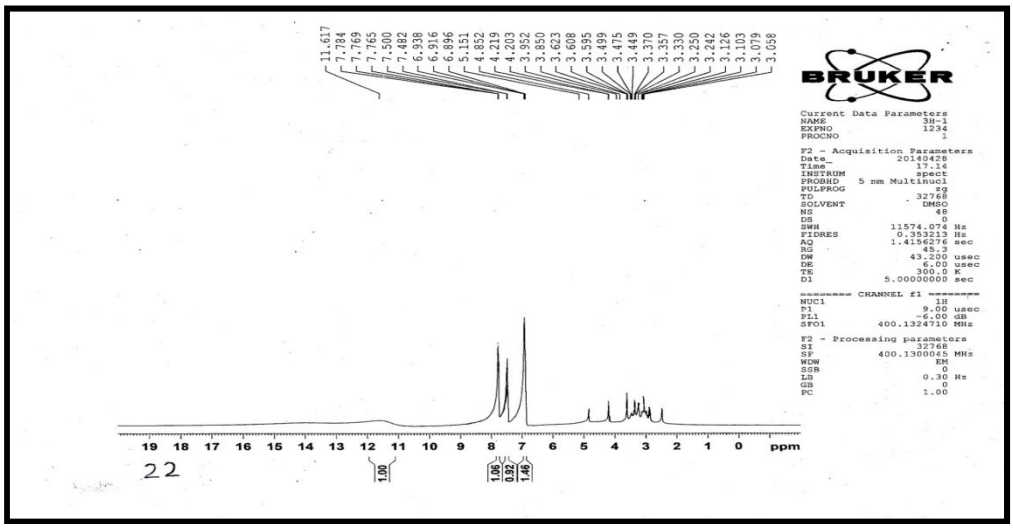


Fig (7) : H.NMR of Compound [10]

The (C.H.N)- analysis : the microanalytical of carbon, Hydrogene , Nitroge atoms ,melting points, solubility and other physical properties are listed in tables (3) and (4)

Table (3): Physical properties and (C.H.N)- analysis of compounds [1-10]

Comp. No.	M.F	M.P(C°)	Calc. /found		
			C%	H%	N%
[1]	$C_{11}H_{17}N_3O_4$	134	51.76 51.42	6.66 6.41	16.47 16.23
[2]	$C_9H_{15}N_9O_2S_2$	174	31.30 31.18	4.34 4.21	36.52 36.36
[3]	$C_9H_{11}N_9S_2$	208	34.95 34.74	3.55 3.33	40.77 40.59
[4]	$C_9H_{15}N_9O_4$	166	34.50 34.28	4.79 4.64	40.25 40.14
[5]	$C_9H_{11}N_9O_2$	200	38.98 38.77	3.97 3.80	45.48 45.25
[6]	$C_{11}H_{12}N_4S_2$	180	50.00 49.82	4.54 4.31	21.21 21.10
[7]	$C_{18}H_{16}N_4S_2$	190	61.36 61.19	4.54 4.30	15.90 15.72
[8]	$C_{16}H_{12}O_5$	182	67.60 67.39	4.22 4.09	/ /
[9]	$C_{32}H_{24}O_5$	220	78.68 78.40	4.91 4.68	/ /
[10]	$C_{34}H_{28}N_4O_3S_2$	232	67.54 67.31	4.63 4.38	9.27 9.12

Table (4): Analytical properties of compounds

Comp. No.	Color	Product %	Solubility in solvents (good solvents)
[1]	Yellow	84	Ethanol , DMSO
[2]	Yellow	84	Ethanol , DMSO
[3]	Yellow	82	Ethanol , DMSO
[4]	Pale yellow	86	Ethanol , DMSO
[5]	Yellowish orange	82	Ethanol , DMSO
[6]	Orange	84	Ethanol , DMSO
[7]	Yellowish Orange	82	Ethanol , DMSO
[8]	Yellow	82	Ethanol , DMSO
[9]	Yellowish Orange	84	Ethanol , DMSO
[10]	Orange	84	Ethanol , DMSO

Biological Study[8 , 9] :

Bacteria supplied from bio-Lab in college of Education .,antimicrobial activity was tested by the filtered paper disc diffusion method against gram (**+**) positive bacteria (*Staphylococcus aureus*) and gram (**-**) negative bacteria (*E-coli*) .,(0.1mol) of the bacterial suspensions was seeded on agar .To determine minimum inhibitory concentration (MIC) for each compounds [1-10] were performed with two replicates .

Generally, the results showed that the compounds [1-10] have good inhibitory effect against tested bacteria .

Table (5) showed the zone of inhibition of the compounds [1-10] in this study ranged (from 32 to 10) mm . from results , we noted the compounds [3, 5, 7, 10] have higher antibacterial activity against two type of bacteria (G+ and G-) due to their structures (consist of thiazole and imidazole rings with thiazine rings) consequently ,which it become more effective in precipitating proteins on bacteria

Table (5): Antibacterial Activity of Compounds [1-10]

Compounds	Diameter of zone (MM)	
	G+ : Staphylococcus aureus	***G- : E-coil***
Compound [1]	16	14
Compound [2]	22	16
Compound [3]	32	28
Compound [4]	18	12
Compound [5]	30	24
Compound [6]	24	16
Compound [7]	26	20
Compound [8]	14	10
Compound [9]	14	8
Compound [10]	28	20

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