Synthesis and antimicrobial evaluation of new 1,3,4 – Thiadiazole Derivatives

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Abstract

The amino thiadiazole [I] on treatment with aromatic aldehydes yielded Schiff bases [II_{a-c}] , which cyclized to thiazolidinone [III_{a-c}] derivatives by reaction with thioglycolic acid .Reaction of carbon disulfide and methyl iodide with [I] gavedithiomethyl[IV] which on treatment with o-phenylenediamine gave the condensed N-Imidazolythiadiazolylamine [V] , However , reaction of [I] with phenylisocyanate and phenylisothiocyanate afforded the carbamideand carbothiamide derivatives[$VI.VII]_{a-c}$.

The structure of these compounds was characterized from their melting point , FTIR spectroscopy and elementalanalysis .

Kew words : antimicrobial 1,3,4–Thiadiazole, thiazolidinone , imidazoly , thiadiazolylamine .

Introduction

The recent literature is enriched with progressive findings about the synthesis and pharmacological activity of fused heterocycles. Heterocycles bearing atriazole or 1,3,4 – thiadiazole moiety are reported to show biological properties such as antibacterial [1-2] antiaggregatory agent [3] , antiviral [4] , antiinflammatory activities [5-6] , anticonvulsant [7] , and antihypertensive [8] . 1,3,4 – thiadiazoles exhibit broad spectrum of biological activities , possibly due to the presence of toxophoric N-C-S moiety [9] . They found applications as antibacterial , antitumor , antiinflammatory agents , pesticides , herbicides , dyes , lubricants and analytical reagents [10] .

Experimental

All melting points, were determined by using " Electro thermal melting point apparatus mettle and are uncorrected . FTIR spectrophotometer (8300) , by using KBr disc , C.H.N-Elemental Analysis (Elmer 240 B – perken) .

• **Starting material :** 2- amino – 5 – mercapto – 1,3,4 – thiadiazole [I] was prepared from thiosemicarbazide and carbondisulfide as previously described by [11] .

• **Schiff Bases [II_{a-c}] :** A mixture of [I] (0.01 mol) and aromatic aldehydes (0.01mol) was dissolved in ethanol containing few drops Et3N, and heated under reflux for 4hr. After cooling the precipitated solid was collected by filtration and crystaillazed [12] from ethanol , see scheme 1

• **N – Benzylidene – 5 – mercapto – 1,3,4 – thiadiazole -2- amine [II_a] .**

• **N – (4- chlorobenzylidene) 5 – mercapto -1,3,4 –thiadiazole – 2 – amino [II_b] .**

• **N – (4- methoxybenzylidene) -5- mercapto – 1,3,4 – thiadiazole -2- amine [II_c]** : see physical properties in table 1.

• **3- [5- mercapto – 1,3,4 – thiadiazole – 2 – yl) – 2- aryl thiazolidin – 4 – one [III_{a-c}] [13]** : A mixture of individual derivative [II_a-II_c] (0.01 mol) and thioglycolicacid (0.01mol) was refluxed in absolute ethanol (30 ml) for 4hr .After cooling the reaction mixture , the precipitated solid was filtered off and crystallized from ethanol .

• **3 - [5- mercapto – 1,3,4 – thiadiazole -2- yl] -2- phenyl thiazolidin -4- one [III_a] .**

• **3 - [5- mercapto – 1,3,4 – thiadiazole -2- yl] -2- (4-chlorophenyl) thiazolidin -5- one [III_b] .**

• **3 - [5- mercapto – 1,3,4 – thiadiazole -2- yl] -2- (4- methoxy phenyl) thiazolidin -5- one [III_c]** . see physical properties in (table 1, 2) .

• **N – Di (methyl thio) methylene [5- thio methyl -1,3,4 – thiadiazole – 2 – yl] – amino [IV] :** To stirred cold solution of [I] (0.05 mol) in DMF (25ml), 20 M- NaOH (5 ml) , carbondisulfide (8 ml) , and methyl iodide (0.1 mol) were added and the stirring was continued for additional 4hr . The mixture was poured into cold water and the formed solid was crystallized from benzene . see physical properties in (table 1,2) .

• **N – [5- thio methyl – 1,3,4 – thiadiazole -2- yl] – 1H – benzo [d] imidazole – 2 – yl – amine [V] :** A mixture of [IV] (0.04 mol) and o- phenylenediamine(0.04 mol) in DMF (30 ml) was refluxed for 8hr . After cooling the formed solid crystallized from ethanol . see physical properties in (table 1, 2) .

• **1 - [5- mercapto – 1,3,4 – thiadiazole – 2 – yl] – 3 – phenyl urea [VI_a] :** A mixture of [I] (0.01 mol) and phenylisocyanate (0.01mol) was refluxed in ethanol (30 ml) for 8hr . The separated solid was filtered off and crystallized from benzene , see physical properties in table 1.

• **1- [5- mercapto -1,3,4 – thiadiazole -2- yl] -3- phenyl thio urea [VI_b]** [14] : A mixture of [I] (0.01mol) and phenylisothiocyanate (0.01mol) was refluxed in ethanol (30ml) for 8hr.

The separated solid was filtered off and crystallized from benzene , see physical properties in (table 1, 2) .

• 1 – [5-mercapto – 1,3,4 – thiadiazole -2- yl] -3- phenyl dihydropyrimidne–2,4,6– trione [VII_a] .

A mixture of [VI_a] (0.01mol) and malonic acid (0.01mol) was refluxed in acetyl chloride (30 ml) for 3hr . After cooling the obtained solid was filtered off and crystallized from benzene. see physical properties in (table 1 , 2) .

• 3- [5- mercapto – 1,3,4 – thiadiazole – 2-yl] -1- phenyl -2- thioxodihydropyrimidine -4 , 6 – dione [VII_b] .

A mixture of [VI_b] (0.01mol) and malonic acide (0.01mol) was refluxed in acetyl chloride (30 ml) for 3hr . After cooling the obtained solid was filtered off and crystallized from benzene.

Discussion

The reaction of 2- Amino -5- mercapto – 1,3,4 – thiadiazole [I] with aromatic aldehydes in refluxing ethanol afforded schiffbases [II_{a-c}] , the IR spectra of Schiff bases showed the stretching bands at (1670 – 1675) cm^{-1} for (C = N) groups and disappeared at (3450 – 3300 cm^{-1}) , (3290 – 3250 cm^{-1}) due to (NH_2) . Schiff bases which on condensation with thioglycolic acid yielded 3- [5- mercapto – 1,3,4 – thiadiazole -2- yl] -2- aryl thiazolidin – 4- ones [III $_{a-c}$] (scheme 1) in the first route the thiadiazole [I] reacted with disulfide and methyliodide in the presesnce of concentrated aqueous sodium hydroxide leading to the formation of N- di (methyl thio) methylene [5- thiomethyl – 1,3,4 – thiadiazole -2- yl] – amine [IV],the IR spectra showed the stretching bands at (1620) $cm^{-1}$for (C = N) group and (1415cm^{-1}) due to (CH_3- S) then the compound [IV] on treatment with nucleophilic reagent such as o-phenylenediamine afforded N- [5- thio methyl – 1,3,4 – thiadiazole -2- yl] -1 H- benzo [d] imidazole -2- yl –amine [V] the IR spectrum showed the following characteristic absorption bands (3340 -3350 cm^{-1}) (NH) , (1615 – cm^{-1}) (C = N).

Finally in the second one [VI_a] [VI_b] was obtained by direct refluxing of [I] with phenyl isocyanate in ethanolic solution . Similarly [I] was converted to 1- [5- mercapto -1,3,4 – thiadiazole -2-yl] -3- phenyl thiourea [VI_b] by the reaction with phenylisothiocyanate . The IR spectra of these compounds revealed the absence of the stretching bands of (NH_2) groups and appearance of stretching of (N –H amide) at (3200 – 3300cm^{-1}) for compound [VI_a] and at (3247-3217 cm^{-1}) for compound [VI_b] , and also showed the appearance of two stretching bands at (1670 cm^{-1}) due to (C = O) amide and (1625 cm^{-1}) due to (C = N) group for compound [VI_a] and at (1240 cm^{-1}) due to (C = S) and (1658 cm^{-1}) due to (C = N) group for compound [VI_b].

The urea derivatives [VI_a] and thio urea derivatives [VI_b] on reaction malonic acid in the presence of acetyl chloride under went intermolecular cyclization and yielded 1- [5- mercapto – 1,3,4 – thiadiazole -2-yl] -3- phenyl dihydro pyrimidine – 2,4,6 – trione [VII_a] and 3- [5- mercapto -1,3,4 – thiadiazole -2- yl] 1- phenyl – 2- thioxodihydropyrimidine – 4,6- dione [VII_b] .

The IR spectra which showed stretching bands at (1670 – 1680 cm^{-1}) of (C = O amide) (1610 – 1620 cm^{-1}) of (C = N) and (3116 , 3031 cm^{-1}) of (C – H aromatic) of the benzene ring for compound [VII_a] , compound [VII_b] gave diagnostic IR stretching bands at (1255 cm^{-1}) of (C = S), (1600 -1610) of (C=N) and (3110,3025 cm^{-1}) of (C-H) aromatic of the benzene ring .

Antimicrobial Activites

The antimicrobial activites of the synthesized compounds were determined in vitro using hole plate and filter paper disc method [15] .

Different species of gram-positive and gram-negative bacteria in addition to some fungal plant pathogens were used (see table 3).

The considered compounds were dissolved in 10% acetone , different concentrations have been chosen (125 , 250 , 500 Mg cm^{-3}) .

Agar plates were surface inoculated uniformly from fresh broth culture of microorganisms . The discs were incubated at 28C^{o} to 24hr , the formed inhibition Zones were measured in mm.

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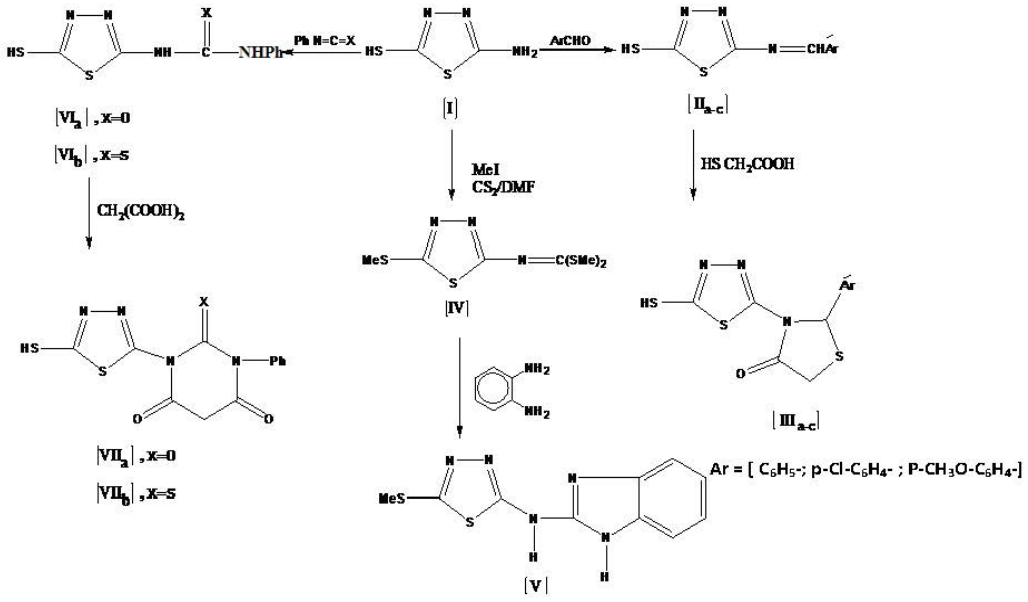
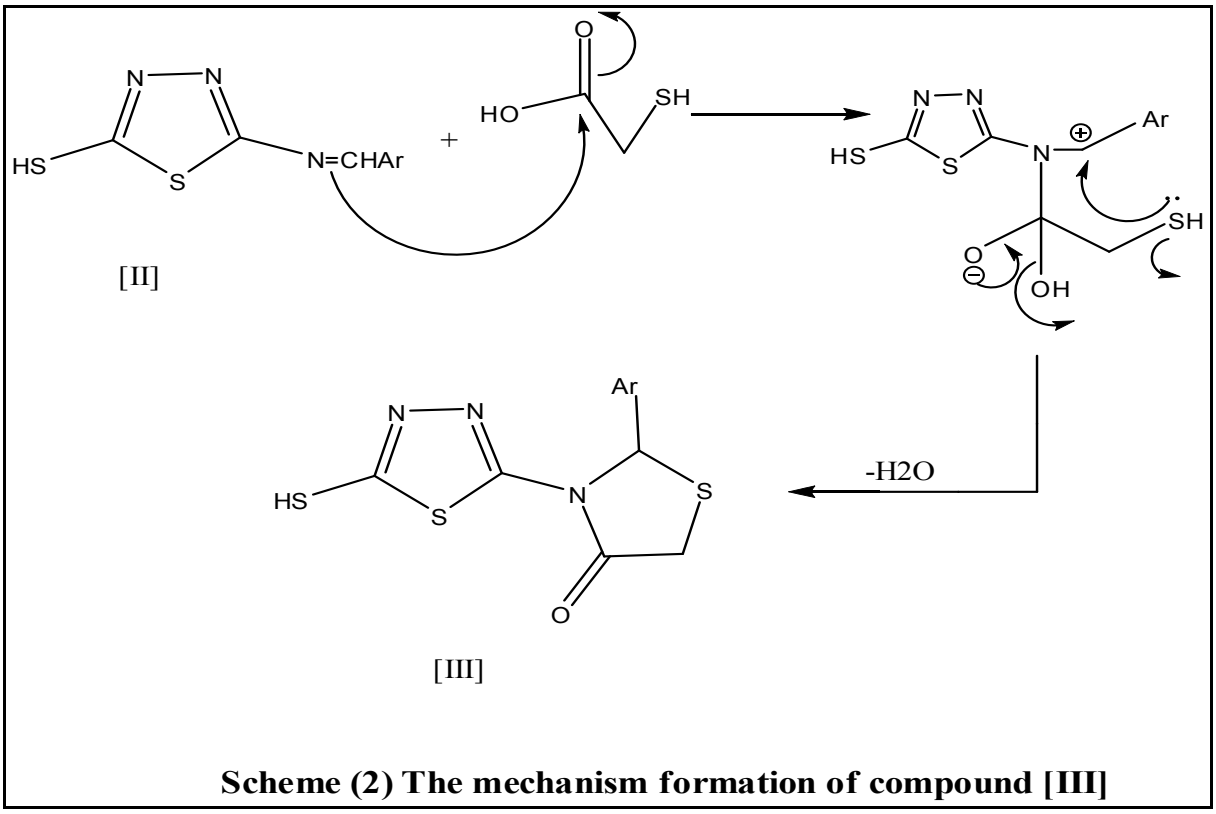
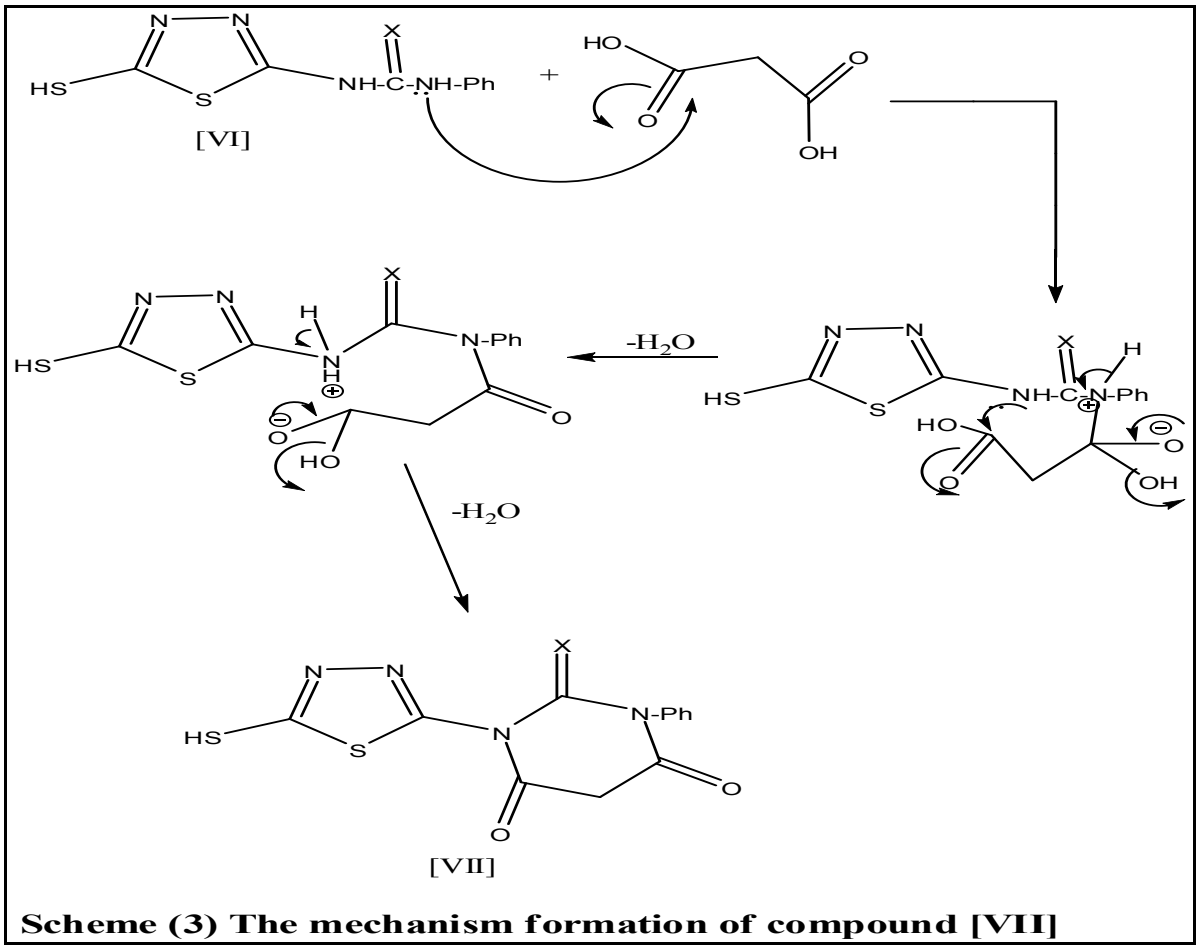


(Scheme 1)



Scheme (2) The mechanism formation of compound [III]



Scheme (3) The mechanism formation of compound [VII]

Table (1): Physical properties of prepared compounds

Com. No .	Formula	M.W.	Elemental Analysis %					
			Calc. %			found%		
			C	H	N	C	H	N
II_a	$C_9H_7N_3S_2$	221	48.88	3.16	19.00	48.75	3.10	18.85
II_b	$C_9H_6CLN_3S_2$	255.5	42.27	2.34	16.43	42.15	2.31	16.33
II_c	$C_{10}H_9N_3OS_2$	251	47.80	3.58	16.73	47.61	3.45	16.66
III_a	$C_{11}H_{10}N_3OS_3$	296	44.59	3.37	14.18	44.50	3.30	14.11
III_b	$C_{11}H_9CLN_3O_3S$	330.5	39.93	2.72	12.70	39.85	2.60	12.55
III_c	$C_{12}H_{12}N_3O_2S_3$	326	36.80	3.68	12.88	36.68	3.61	12.71
IV	$C_6H_9N_3S_4$	251	28.68	3.58	16.73	28.52	3.41	16.66
V	$C_{10}H_9N_5S_2$	263	45.62	3.42	26.61	45.53	3.40	26.55
VI_a	$C_9H_8N_4S_2O$	252	42.85	3.17	22.22	42.77	3.11	22.15
VI_b	$C_9H_8N_4S_3$	268	40.29	2.98	20.89	40.12	2.82	20.81
VII_a	$C_{12}H_8N_4O_3S_2$	320	45.10	2.50	17.50	45.02	2.44	17.47
VII_b	$C_{12}H_8N_4O_2S_3$	336	42.85	2.38	16.66	42.79	2.29	16.58

Table (2): Physical properties of prepared compounds

Com. No .	Colour	m.p. c^{o}	Yield %	Infrared data(V max Cm^{-1})
II_a	Pale yellow	170-172	65	(C=N)1670;(C=S)1310;(C-H arom)3000–3100
II_b	Yellow	185-187	62	(C=N)1670;(C=S)1325;(C-H arom)3020-3100
II_c	Yellow	157-159	66	(C=N)1645;(C=S)1290;(C-H arom)3000–3080
III_a	Brown	130-132	63	(C=N)1650;(C=S)1315;(C = O) 1680
III_b	Reddish–yellow	144-146	50	(C = N) 1665 ; (C = S) 1315 ; (C = O) 1675
III_c	Reddish–yellow	151-153	56	(C = N) 1645 ; (C = S) 1305 ; (C = O) 1670
IV	Pale–yellow	177-179	62	(C=N)1620;(CH_3–S)1415;(C–H alph)2920–2980
V	Brown	230-232	55	(C = N) 1615 ;(CH_3–S)1415;(N–H)3340– 3350
VI_a	Brown	191-193	45	(C = N) 1625;(C=O) 1670 ; (N–H) 3200 – 3300
VI_b	Reddish yellow	188-190	59	(C = N) 1658;(C=S) 1240 ; (N–H) 3247 – 3217
VII_a	Brown	210-212	71	(C = N) 1620;(C=O) 1680 ; (C=S) 1265
VII_b	Brown	220-222	63	(C = N)1610 ; (C=S) 1255

Table(3): Response of various microorganisms to synthesized Denivatives in vitro

Compound	Bacillus cereus		Escherichacoli		Aspergillusniger		Peniciliumnotatum	
	A	(MIC)	A	(MIC)	A	(MIC)	A	(MIC)
II_a	++	125	+	250	++	125	+	250
II_b	++	250	++	250	++	250	++	125
II_c	++	125	+	250	+	250	+	250
IV_a	++	250	++	250	+	250	++	250
IV_b	+	250	+	250	+	250	+	125
IV_c	+	250	+	250	+	250	+	250
VI	++	125	++	250	+++	125	++	125
VII	+	250	+	250	+	250	+	250
$VIII_a$	++	125	+	250	++	125	+	250
$VIII_b$	+	250	++	250	+	125	+	125
IV	+++	125	++	250	++	125	+++	250
V	++	125	++	250	+++	125	++	125

A : antimicrobial activity of tested compounds ; the width of the zone of inhibition indicates the potency of antimicrobial activity , no antimicrobial activity , + weak activity width diameter equal to 0.5-0.7cm , ++ moderate activity with the diameter zone equal to 1.0-1.2cm .
+++ marked activity with the diameter zone equal to 1.6-1.8cm.
MIC : minimum inhibition concentration / (Mg cm^{-3}) .

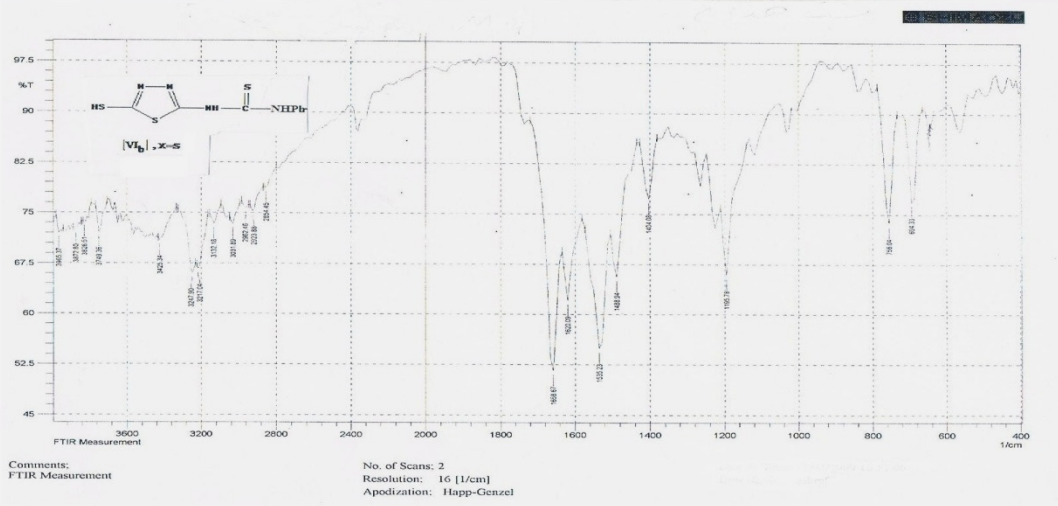


Fig . (1) : (Compound VI b)

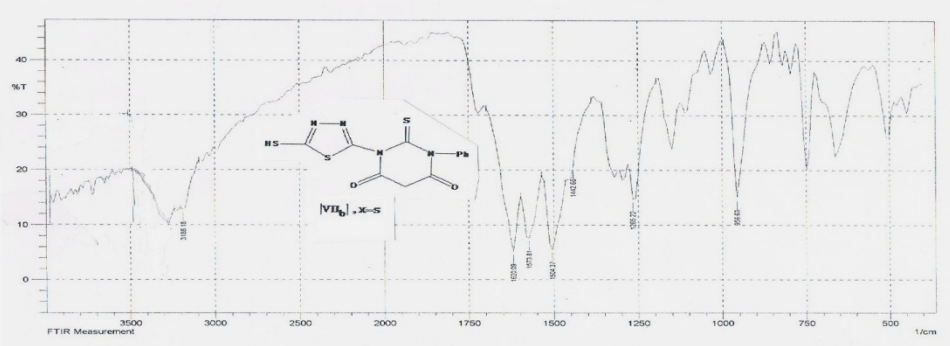


Fig . (2) : (compound VII b)

تحضير وتقييم الفعالية البايلوجية لمشتقات جديدة من مركبات 1,3,4 ثاياديازول

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الخلاصة

تم في هذا البحث معاملة المركب امينوثاياديازول[I] مع الالديهايدات الاروماتية للحصول على قواعد شف ، بعدها غلقت للحصول على مشتقات تحوي على حلقات الثايازوليدايون من خلال مفاعلتها مع الحامض –ثايوكلايكولك .

ثم فوعل المركب [I] مع كاربون ثنائي الكبريت ويوديد المثيل للحصول على مركب ثنائي مثيل ثايو الذي تم معاملته مع الاورثوفنيلين ثنائي الامين ،حيث اعطى الناتج N - اميدازو ثايازوليل امين .

فيما بعد حضرت سلسلة اخرى من مفاعلة المركب [I] مع فنيل ايزوسيانيت أو مع فنيل ايزوثايوسيانيت للحصول على المشتقات كارباميدوكارباثاياميد على التوالي ، شخصت هذه المركبات من خلال درجات الانصهار وتقنية FTIR وتحليل العناصر .

الكلمات المفتاحية : الدراسة البايلوجية لمركبات 1 ، 3 ، 4 – ثايودايازول ، ثايوزوليدون ، اميدوزول ثايوزويل امين .