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Synthesis, Characterization and Biological Activates Studies of some New Derivatives From 2-aminoo-5-mercapto-1, 3, 4-thiadiazole

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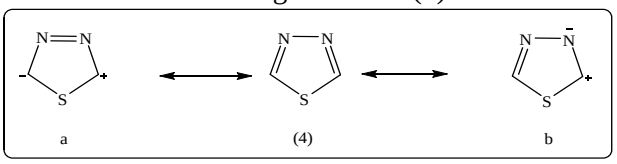
Abstract:

In this work, thiadiazole derivatives were prepared by taking advantage of active sites in (2-amino-5-mercapto-1, 3, 4-thiadiazole) as a starting material base. The main heterocyclic compounds (1, 3, 4-thiadiazole, oxazole) etc, 2-amino-5-mercapto-1,3,4-thiadiazole compound (1) was prepared by cyclic closure of thiosemicarbazide compound with anhydrous sodium carbonate and carbon disulfide. Oxidation of (1) via hydrogen peroxide, to have (2) which was treated with chloro acetyl chloride to get (3). Preparation of thiazole ring (4) was from reacting of (3) with thiourea. Synthesis of diazonium salts (5) from compound (4) using sodium nitrite and HCl. Compound (5) reacted with different ester compounds to prepare a new azo compounds (6–8).Compound (3) reacts with viruses secondary amine to prepare compound (9–11). Full characterization of the synthesized compounds was done by using spectroscopic analysis such as FT-IR, ^{1}H-NMR and C.H.N.S. technique.

Keywords: 1,3,4-thiadiazole, diazonium salt, thiosemicarbazide, heterocyclic.

Introduction:

1, 3, 4-thiadiazole is a polar symmetric molecule displaying pseudo aromatic nature. Some vital canonical forms of 1, 3, 4- thiadiazole are written underneath, of which 4 with dienic performance is the extreme contributing structure. (1).



In the nature, they occur in four isomeric structures. 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole, 1,3,4- thiadiazole.(2) 1,3,4-Thiadiazole was first defined in 1882 by Fischer and further advanced by Busch and his coworkers.(3) Many studies exposed that many thiadiazoles have resulted in many possible medications and are known to display a broad range of pharmacological properties. The specific pharmacological activities including Antitumor (4) Antiviral, Antibacterial, Amoebicidal, Anti-inflammatory, Antitubercular, Antipyretic, Anticancer, Antischistosomal (5) Herbicidal, Insecticidal, Pesticidal and Hypoglycemic.(2).

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The origin of azo chemistry date from the initial generation of diazonium succinamic acid from asparagine by (Piria) in 1849. (Caro.Griess) in 1861 – 1862, he prepared the first azo coupling product in compound.(6) Azo compound is an aliphatic, aromatic, or heterocyclic compound in which a –N2 group is attached to a carbon atom. This group can be present such as (diazo compounds in the narrowest sense), It can carry a positive charge (diazonium salts), or the nitrogen atom in the β-position can carry a substituent (diazo compounds in the wide-ranging). Compounds containing the RN_2X— group are named by adding the suffix "diazonium" to the name of the parent compound RX, followed by the name of X (e.g., benzenediazonium chloride), whereas compounds having the N_2 group in the neutral form attached to a carbon atom are named by adding the prefix "diazo" to the name of the parent compound (e.g., diazomethane)(7).

Azo compounds one of the major kinds of scientifically. Created organic compounds are strong in drug and make-ups (8). Of all kinds of dyestuffs, azo dyes have achieved the varied collection of practice because differences in chemical structures are willingly possible and

methods of application are usually not multifaceted (9)

Azo dye compounds have a lot of applications in industry and photodynamic therapy as well as photosensitive species in photographic or electro photographic systems and are dominant organic photoconductive materials. (10)

Materials and Methods:

All chemicals were supplied from different corporations such as Thomas baker, Merck, BDH, GCC and Scharlau and used without further purification. Melting points are determined on an electro thermal melting point apparatus (Stuart Germany), and they are uncorrected. Completion of reaction and purity of all compounds are checked on aluminum coated TLC plates 60 F245 (E. Merck) using Methanol and Ethanol as the mobile phase and imagined under iodine vapor. Determinations of infrared spectra were done and recorded as a KBr disks in the range of (400 -4000 cm^{-1}) using FTIR Shimadzu (Japan).The proton ^{1}H-NMR spectra were verified for the synthesized compounds using Bruker DMX-500 spectrophotometer (500 MHZ, solvent DMSO-d6). Likewise, elemental analysis (C.H.N.S) was approved for compounds (3), (8) and (11).

Synthesis Methods:

Synthesis of 2-amino-5-mercapto-1, 3, 4-thiadiazole compound (1) (11)

Thiosemicarbazide (0.05 mole, 4.56 gm) has been dissolved in 15 ml of absolute ethanol in 50 ml round bottom flask, then (0.005 mole, 2.84 gm) of anhydrous sodium carbonate added (after drying for 30 minute in 40 C°) with continues stirring, (12 ml) of CS2 added and the mixture refluxed in sand bath at temperature 50 C° for 1 hour then increase the temperature to (120 – 130) C° for 7 hours, the mixture cooled at room temperature, the precipitate filtered and washed by hot distilled water, then (drop by drop) of Concentrated HCl added to the filtered until precipitate shown, the precipitate washed by cold dist. water to remove acid presence.

To indicate the presence of the acid, a solution of $AgNO_3$ (0.01N) can be used the clarity of the filtered mean that the acid has been removed. The precipitate purified by recrystallization from distilled Water then dried.

Synthesis of 5,5'-disulfanediylbis(1,3,4-thiadiazol-2-amine) compound (2) (12)

Compound (1) (0.03 mole, 3.99 gm) was added to absolute Ethanol (20 ml) in (50 ml) beaker, then few drops hydrogen peroxide (50%) to the mixture with continuous stirring for 3 hours at room temperature. The precipitate filtered and wash with distil Water and dried overnight, recrystallization with ethanol/water (1:2) and the product dried overnight. Collected as yellow powder.

Synthesis of N, N'-(5,5'-disulfanediylbis(1,3,4-thiadiazole-5,2-diyl))bis(2-chloroacetamide) compound (3) (13)

In beaker, added (20 ml) Pyridine to (0.012 mole, 3 gm) of compound (2) in ice bath (0 - 3) C°, after 15 min. drops of Chloro acetyl chloride gradually added with magnetic stirring for 4 hours. The mixture was poured in iced water and the solid precipitate separated by filtration and dried, recrystallized from ethanol.

Synthesis of N5, N5'-(5,5'-disulfanediylbis(1,3,4-thiadiazole-5,2-diyl))dithiazole-2,5-diamine compound (4) (14)

Compound (3) (0.008 mole, 0.3 gm) with thiourea, (0.003 mole, 0.2 gm) fused for 1 hour at (160) C°, then cooled at room temperature, washed several times by distil water, the precipitate filtered and recrystallized from absolute ethanol.

Synthesis of Diazonium salt (5) (15)

Compounds (6, 7) (0.0003 mole, 0.1 gm) were dissolved in a suitable volume of (2.5 ml Conc. HCl in 3 ml H_2O) and cooled in an iced bath, the temperature maintained at (0 – 5) C°, another aqueous solution prepared from (0.0018 mole, 0.12 gm $NaNO_2$ in 3 ml H_2O) added drop by drop with stirring to the mixture in an iced bath until precipitate appearance. The salt was filtered, dried and recrystallized from DMF.

Synthesis of azo compounds (6 – 8) (16)

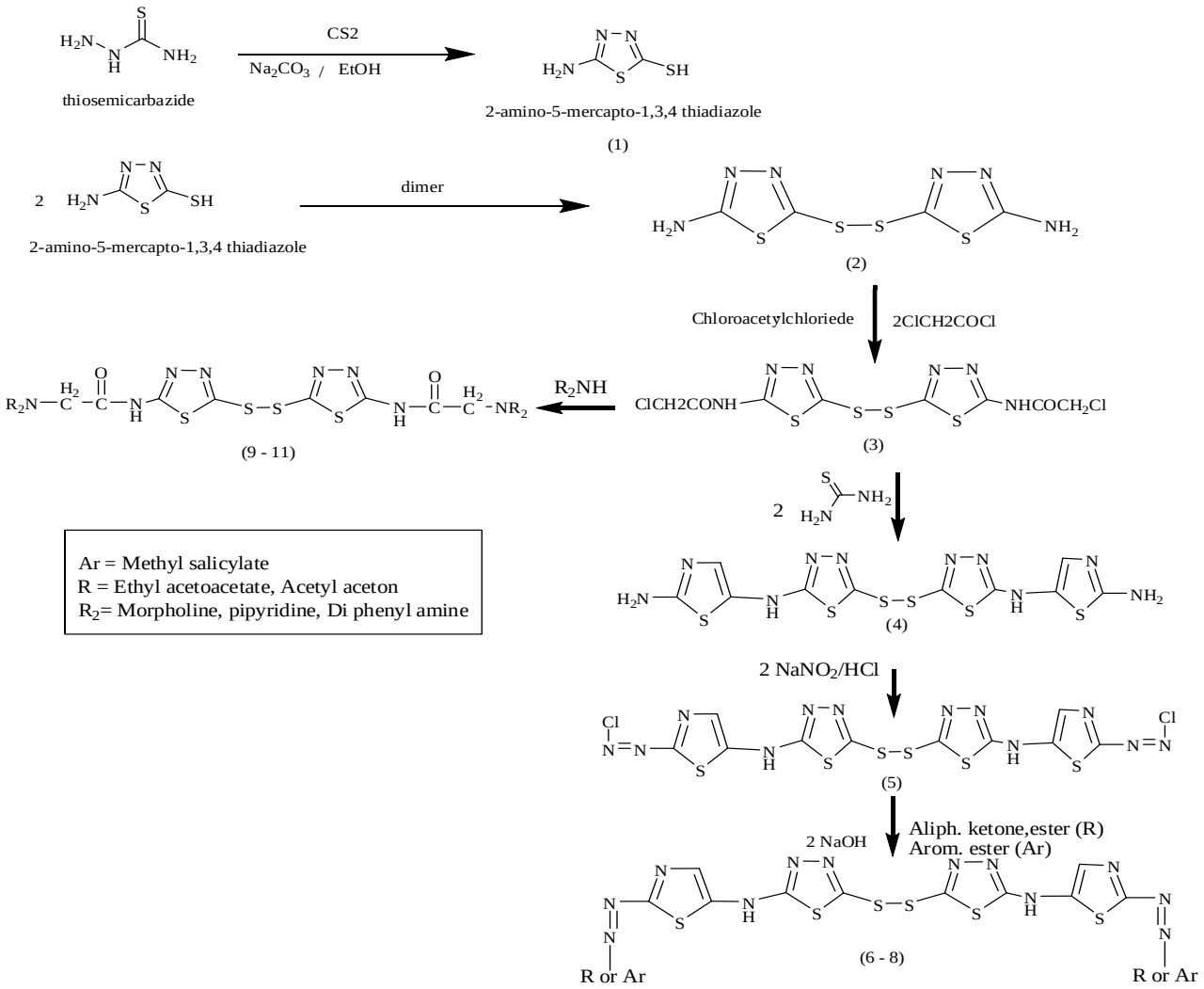
Different esters (0.002 mole, 0.2 gm) were dissolved in (20 ml) absolute ethanol and added to the mixture (0.08 gm) NaOH with stirring about 10 Min. then (0.001 mole, 0. 4 gm) of compound (4) added to the mixture, refluxed for (7 – 10) hours. The product obtained filtered, dried and recrystallized from absolute ethanol.

Synthesis of Compounds (9 – 11) (17)

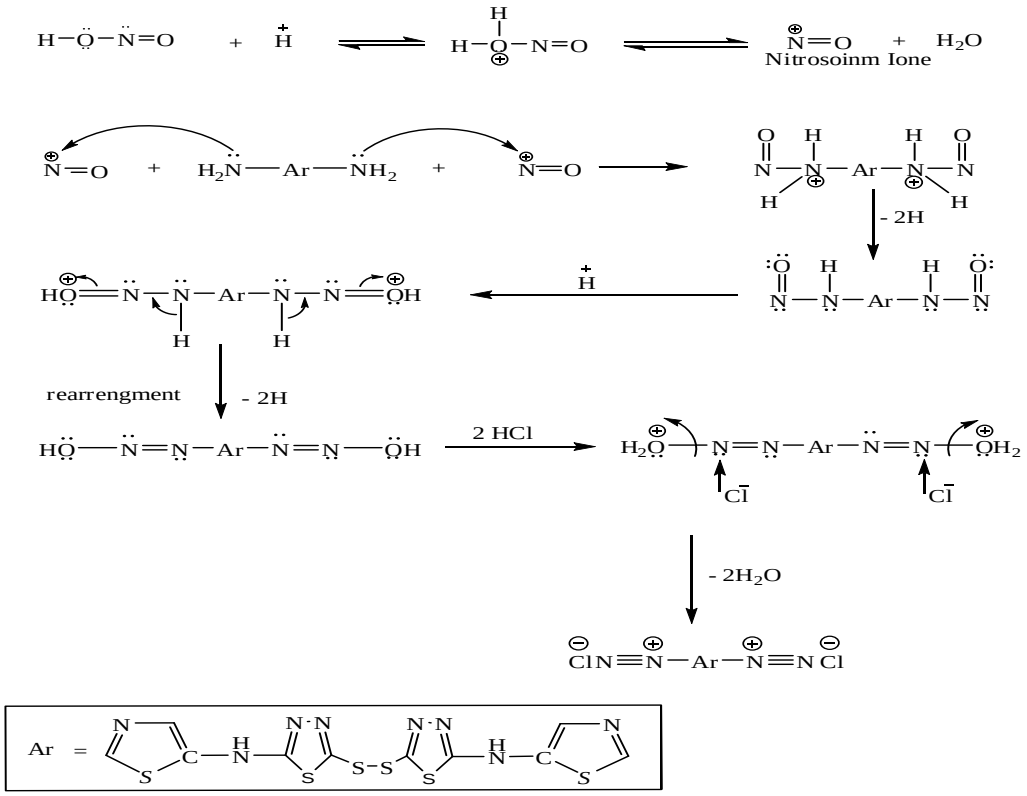
Compound (3) (0.0005 mole, 0.23 gm), dissolved in (20 ml) of ethanol, (0.001 mole, 1 ml) of different secondary amine added to the mixture. Then reflexed for 5 – 7 hours at (140 – 160) C°, lifted to cool at room temperature, filtered the precipitate and recrystallized from absolute ethanol.

Results and Discussion:

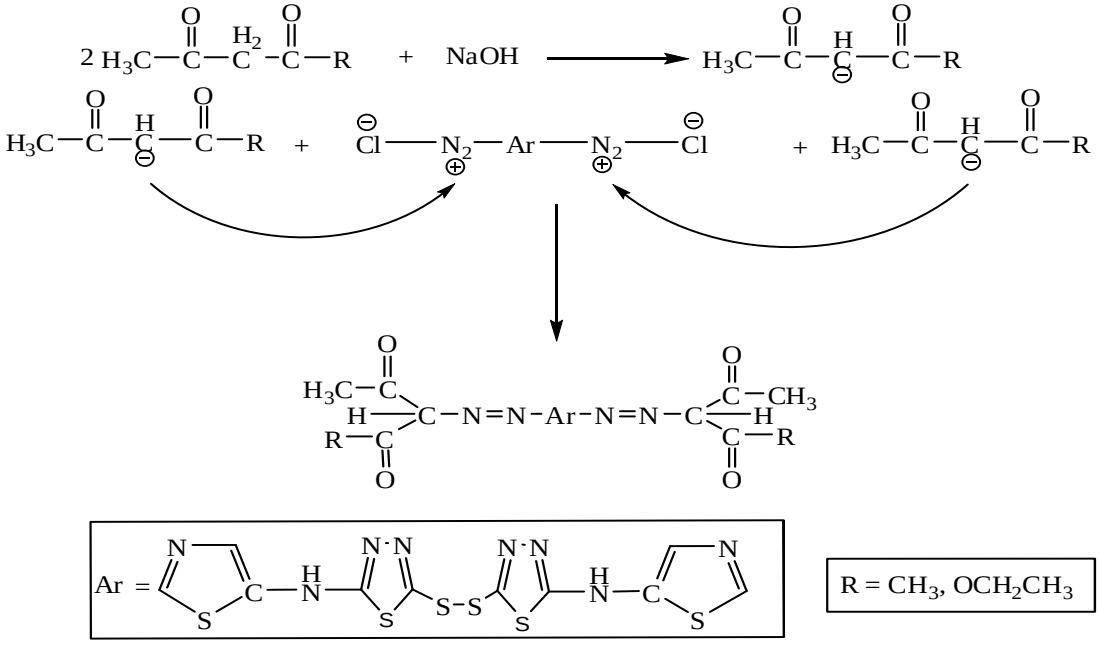
The general reaction was brief in Scheme (1)



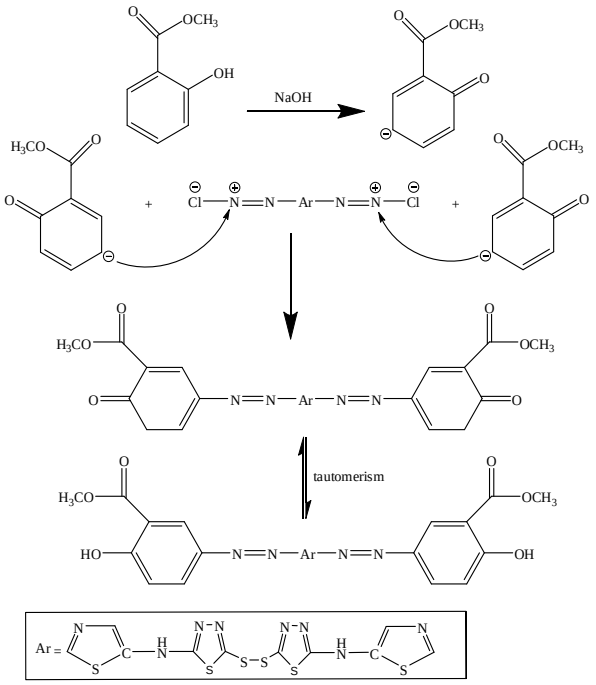
Compound (1) was prepared by the reacting of thiosemicarbazide with carbon disulphide in the presence of anhydrous Sodium carbonate in ethanol followed by concentrated hydrochloric acid (18). Oxidation of compound (1) through hydrogen peroxide H_2O_2 (percent 30%) gives disulfide compound (2). (19) Compound (3) was prepared from reacting of compound (2) with chloroacetyl chloride (1:2) in the presence of dry pyridine. Mechanism includes nucleophilic aggression on the positive carbon atom in chloroacetyl chloride by the lone pair on the amine group in the compound (2), flowed via liberate of two HCl molecules. Compound (4) has been prepared from fusing compound (3) with thiourea (1:2). The reaction occurred as a result of adding nucleophile to the carbonyl group in compound (3), then elimination of the H_2O molecule. Compound (5) was obtained through the reaction of compound (4) with sodium nitrite ($NaNO_2$) in the presence of diluted hydrochloric acid and cooled the mixture in saline water bath at temperature of (0 – 5) C° to maintain the non- dismantlement of the product and increase melting of nitrous acid and reduce of nitrous gas. Diazonium salt possesses electrophilic properties that are able to band with compound containing groups (-NH2, -OH, -OR). This reaction was increased by presence of sedimentary groups on the heterogeneous ring in the diazonium salt as it draws the electron towards it. The electrolyte increases on the two nitrogen atoms in the diazonium salt.(20)
The suggested mechanism steps are shown in Scheme (2)



Compounds (6, 7 and 8) were prepared from reaction compound (5) with acetyl acetone, ethyl acetoacetate and methyl salicylate in ethanol in the presence basic medium. The mechanism steps of compounds (6, 7) are shown in Scheme (3). (21)



The suggested mechanism of compound (8) is shown in Scheme (4) (22)



Compounds (9 – 11) were prepared from the mix of compound (3) with different secondary amines in the presence absolute ethanol were refluxed (5 – 7) hours.

The suggested mechanism for these reactions involve nucleophilic substation reaction, starting with attack of the amine group in the secondary amine (as a result of the presence electronic pair on the nitrogen atom) on carbon atom of CH_2 followed by lose 2 HCl molecules. As showed in Scheme (5) (23)

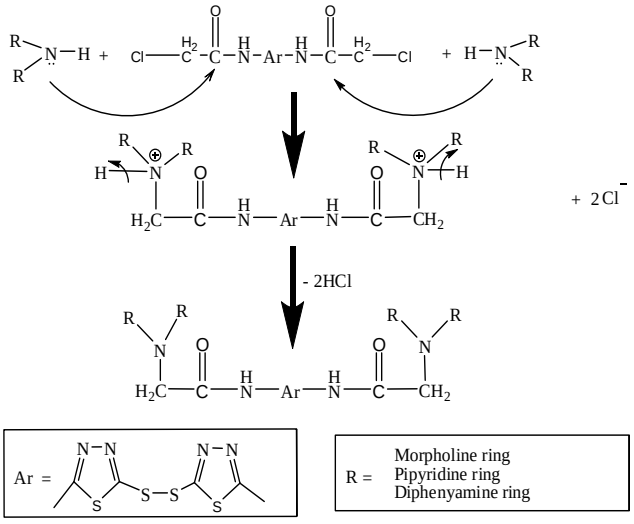


Table 1. Physical properties of the compounds (1 – 11)

Comp	Molecules formula	M.Wt	Yield%	Color	M.P/ C°
(1)	$C_2H_3N_3S_2$	133.20	50	Whiteish yellow	228 – 230
(2)	$C_4H_4N_6S_4$	264.37	90	Yellow	200 – 202
(3)	$C_8H_6C_{l2}N_6O_2S_4$	417.34	88	Yellow – tan	180 – 182
(4)	$C_{10}H_8N_{10}S_6$	460.63	88	Orange	213 – 215
(5)	$C_{10}H_4N_{12}S_6Cl_2$	555.52	80	Reddish brown	212 – 214
(6)	$C_{22}H_{22}N_{12}O_6S_6$	742.88	73	Dark red	Oily
(7)	$C_{20}H_{18}N_{12}O_4S_6$	682.82	83	Black	98 – 100
(8)	$C_{26}H_{18}N_{12}O_6S_6$	786.89	93	Dark red	220 – 222
(9)	$C_{16}H_{22}N_8O_4S_4$	518.66	50	Light Yellow	210 – 212
(10)	$C_{18}H_{26}N_8O_2S_4$	514.71	50	Yellow	196 – 198
(11)	$C_{32}H_{26}N_8O_2S_4$	682.86	53	Grey	198 – 200

Table 2. FT-IR Spectral data of compounds (1 – 11) in cm^{-1}

Comp	υ(NH_2)	υ(N-H)	υ(C=N)	υ(C-N)	υ(N-N)	Others
1	3367-3263	3178	———	1315	1531	υ(SH) 2615, υ(C=S) 1165, υ(C-S) 648
2	3309-3250	———	1635	———	1453	υ(NH_2)bending 1508, υ(S-S) 474, υ(C-S-C) 682
3	———	3259	1635	1319	1496	υ(C-H)aliph. 2935-2920, υ(C=O) amide 1670, υ(C-Cl) 748, υ(NH)bend. 1554, υ(S-S) 435
4	3398-3275	3174	1639	1330	1562	υ(C-H)arom. 3086, υ(C=C)1535
5	———	3275	1624	1338	1469	υ(C-H)arom. 3035, υ(C=C)1554, υ(N=N) 1554
6	———	3275	1651	1319	———	υ(N=N) 1558, υ(C-H)arom. 3059, υ(C-H)aliph. 2981, 2939, υ(C=O) keto 1716, υ(C=O) ester1732, υ(C=C) 1442
7	———	3288	1651	1327	1512	υ(C-H)aliph. 2951, υ(C-H)arom. 3059, υ(C=O) keto 1701, υ(N=N) 1562
8	———	3246	1674	1300	1465	υ(C-H)aliph. 2985, υ(C-H)arom. 3059, υ(O-H) 3405, υ(C=O) ester 1716, υ(N=N) 1585, υ(C-O) 1215
9	———	3267	1639	1388	———	υ(C-H)aliph. 2954, υ(C-H) arom. 3070, υ(C=O) amide. 1670, υ(C=C).1504
10	———	3267	1620	1388	———	υ(C-H)aliph. 2954. υ(C-H)arom. 3074, υ(C=O) amide. 1643, υ(C=C) 1496
11	———	3271	1635	1388	———	υ(C-H)aliph. 2954. υ(C-H)arom. 3070, υ(C=O) amide. 1635, υ(C=C) 1496

Table 3. ^{1}H-NMR data and their interpretation for the synthesized compounds

Compound (3)			
(ppm)	***No. of H***	***Multiplicity***	***Interpretation***
7.7	2H	Singlet	Protons of the NH-C=O
3.3	4H	Singlet	Protons of the CH_2-Cl
Compound (8)			
(ppm)	***No. of H***	***Multiplicity***	***Interpretation***
11	2H	Singlet	Protons of OH
7.1 – 7.6	6H	Multiplied	Protons of Ar-H
6.5 – 6.6	2H	Singlet	Protons of thiazole ring
5.7 – 5.8	2H	Singlet	Protons of NH
2.1 – 2.3	6H	Triplet	Protons of CH_3
Compound (11)			
(ppm)	***No. of H***	***Multiplicity***	***Interpretation***
7.7	20H	Singlet	Protons of Ar-H
7.1	2H	Singlet	Proton of amide group
3.34	4H	Singlet	Protons of CH_2

Table 4. Elemental microanalysis data (%) of the synthesized compounds (C.H.N.S.)

Compound (3) ($C_8H_6C_{l2}N_6O_2S_4$)			**Compound (8) ($C_{26}H_{18}N_{12}O_6S_6$)**			**Compound (11) ($C_{32}H_{26}N_8O_2S_4$)**		
Element	***Calculated***	***Founded***	***Element***	***Calculated***	***Founded***	***Element***	***Calculated***	***Founded***
C	23.00	23.02	C	41.30	39.64	C	58.01	56.23
H	1.43	1.34	H	2.71	2.28	H	3.83	3.80
N	20.12	23.47	N	20.58	21.34	N	16.22	16.4
S	30.6	33.69	S	23.46	24.39	S	19.12	18.74

Table 5. Biological activity for some synthesized compounds.

Inhibition zone (mm.)				
Gram negative			**Gram positive**	**Fungi (yeast)**
No. inhibition zone	**Compound No.1000 ppm**	**E.coli**	**Staphylococcus aureus**	**Candida albicans**
1	3	13	Nil	15
2	9	13	Nil	16
Control	0	0	0	0

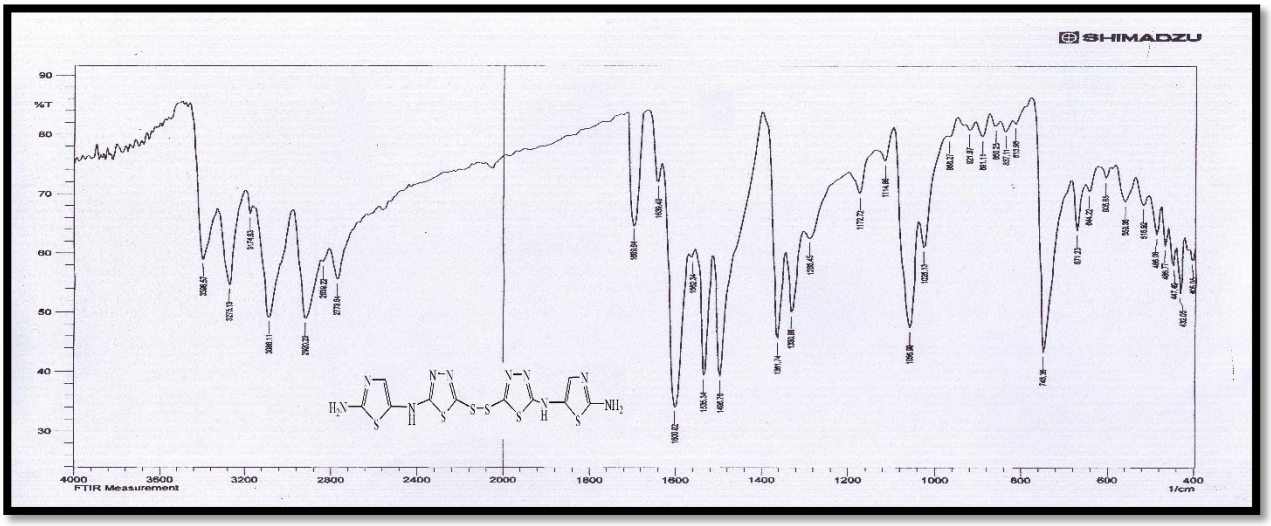


Figure 1. FT-IR spectrum of compound 4

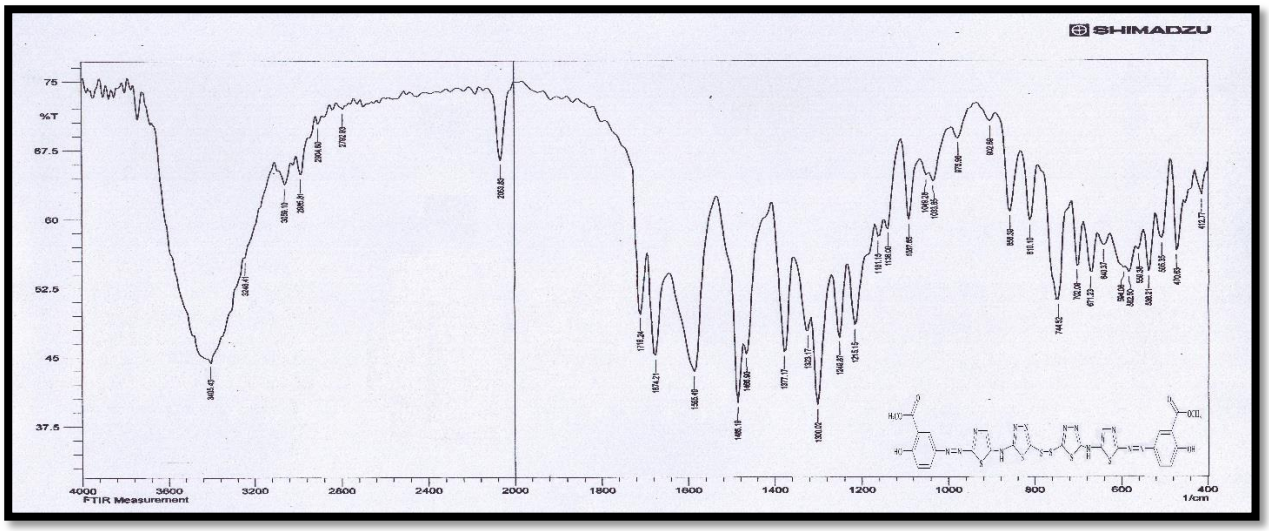


Figure 2. FT-IR Spectrum of compound 8

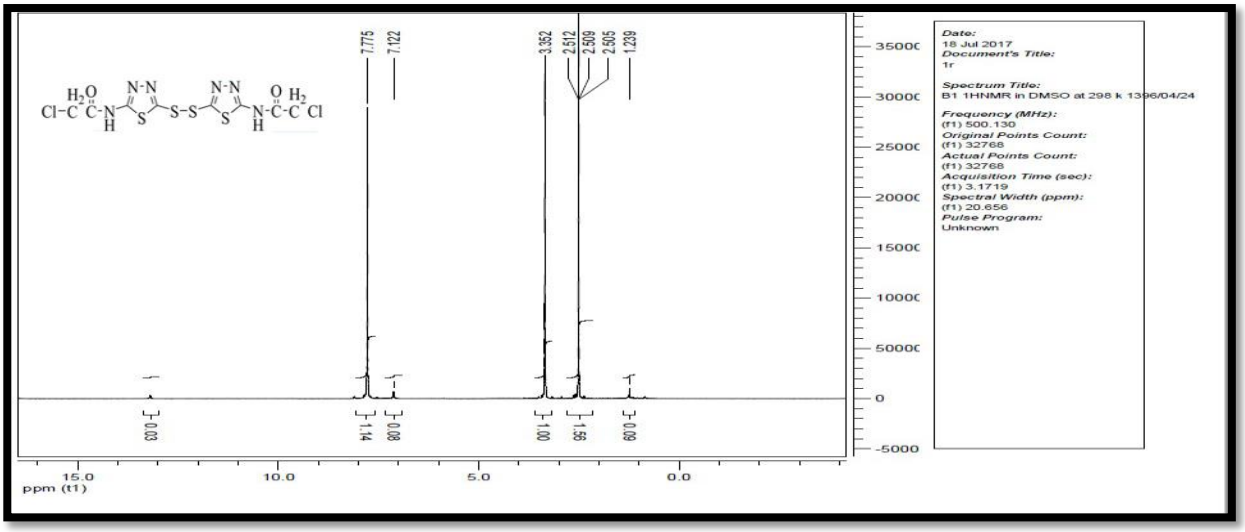


Figure 3. ^{1}H-NMR Spectrum of compound 3

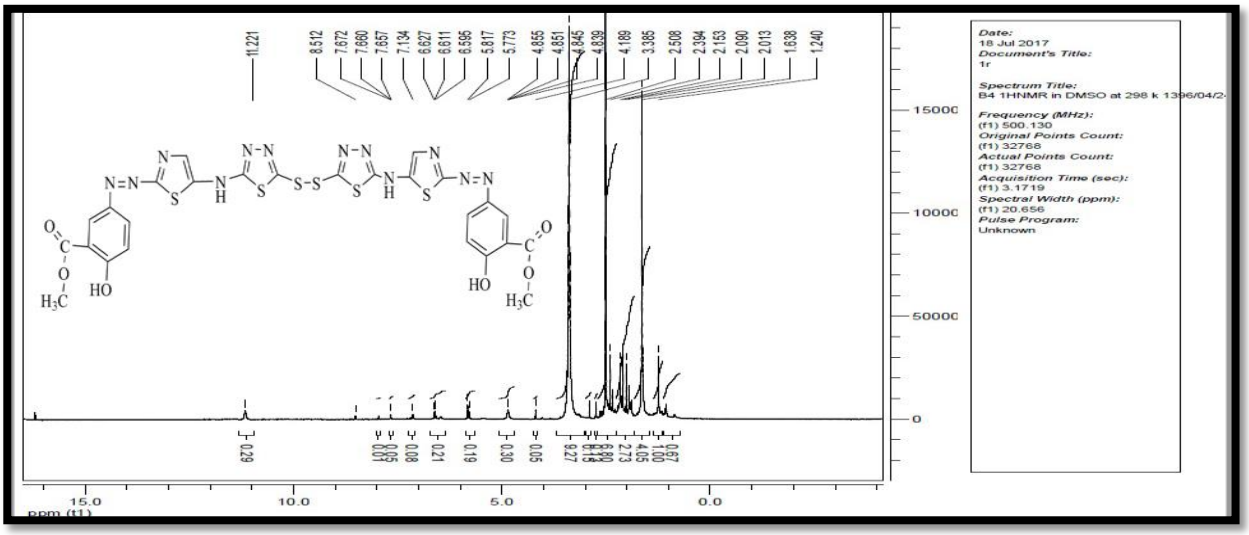


Figure 4. ^{1}H-NMR spectrum of compound 8

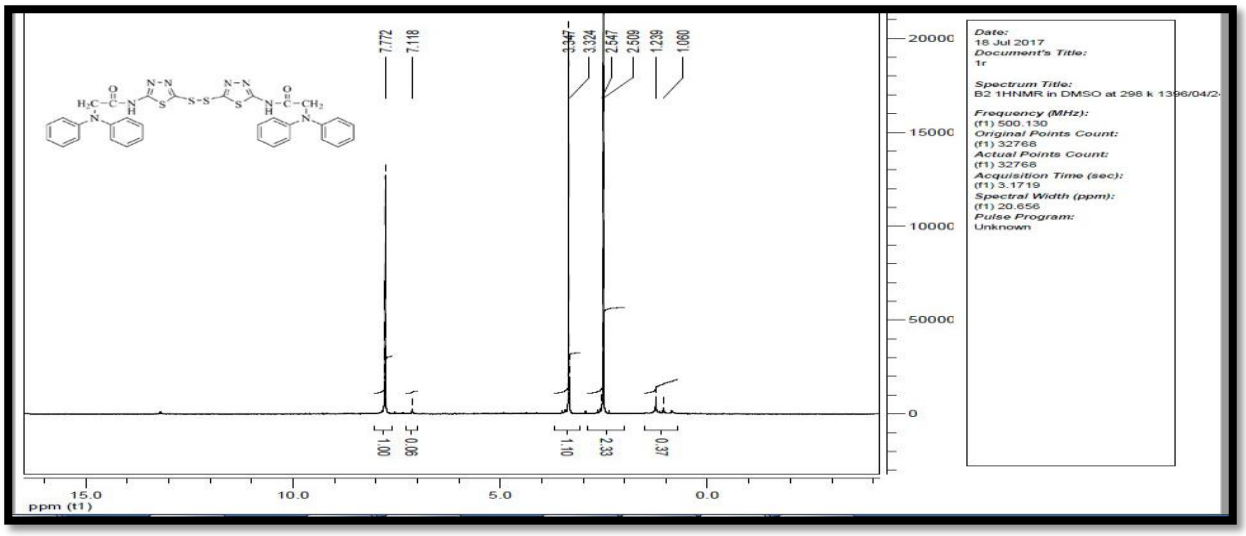


Figure 5. ^{1}H-NMR spectrum of compound 11

Conclusion:

During the preparation of the new derivatives from the basic compound (2-amino-5-mercapto-1,3,4-thiadiazole), was noticed a high stability of new synthesized hetero cyclic compounds and fused rings have a very biological activity, analytical and spectral data (FT-IR,^{1}H-NMR,C.H.N.S) proved the proposed structures.

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تحضير،تشخيص ودراسة الفعالية البايولوجية لمشتقات جديدة للمركب 2-امينو-5-مركبتو-4,3,1-ثادايازول

شذى فاضل الزبيدي[1] **زينب هيثم كاظم[2]**
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[1، 2، 3، 4] قسم الكيمياء، كلية العلوم للبنات، جامعة بغداد، بغداد، العراق.

الخلاصة:

في هذا البحث، تم تحضير مشتقات الثاديازول من خلال الاستفادة من المواقع الفعالة في المركب (2-امينو-5-ميركبتو-4,3,1-ثاديزول). من المركبات الحلقية الغير متجانسة الرئيسية هي (4,3,1-ثاديزول،اوكسازول ... الخ). المركب (1) يحضر من خلال الغلق الحلقي للمركب الثايوسيميكاربازايد مع كاربونات الصوديوم اللامائية وغاز ثنائي كبريتيد الكاربون. ثم اكسدة المركب (1) بواسطة بيروكسبد الهيدروجين نحصل على مركب (2) والذي يعامل مع كلورواسيتايل كلورايد لنحصل على المركب (3). وتحضر حلقة الثادايازول المركب (4) من خلال تفاعل المركب (3) مع الثايوريا . وتخلق املاح الدايازونيوم المركب (5) من تفاعل المركب (4) مع نتريت الصوديوم بوجود حامض الهيدروكلوريك، ولتحضير مركبات الازو الجديدة المركبات (6 – 8) من تفاعل المركب (5) مع مركبات استرية مختلفة. ومن تفاعل المركب (3) مع امينات ثانوية مختلفة ونحصل على المركبات (9 – 11). جميع المركبات شخصت بواسطة تحاليل طيفية (طيف الاشعة التحت الحمراء ، طيف الرنين النووي المغناطيسي وقياس التحليل الكمي الدقيق للعناصر).

الكلمات المفتاحية : 4,3,1-ثادايازول، املاح الدايازونيوم، الثايوسيميكاربازايد، مركبات حلقية