# Synthesis of Some New 1,3,4-Thiadiazole Derivatives and studying their Biological Activities

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## Abstract

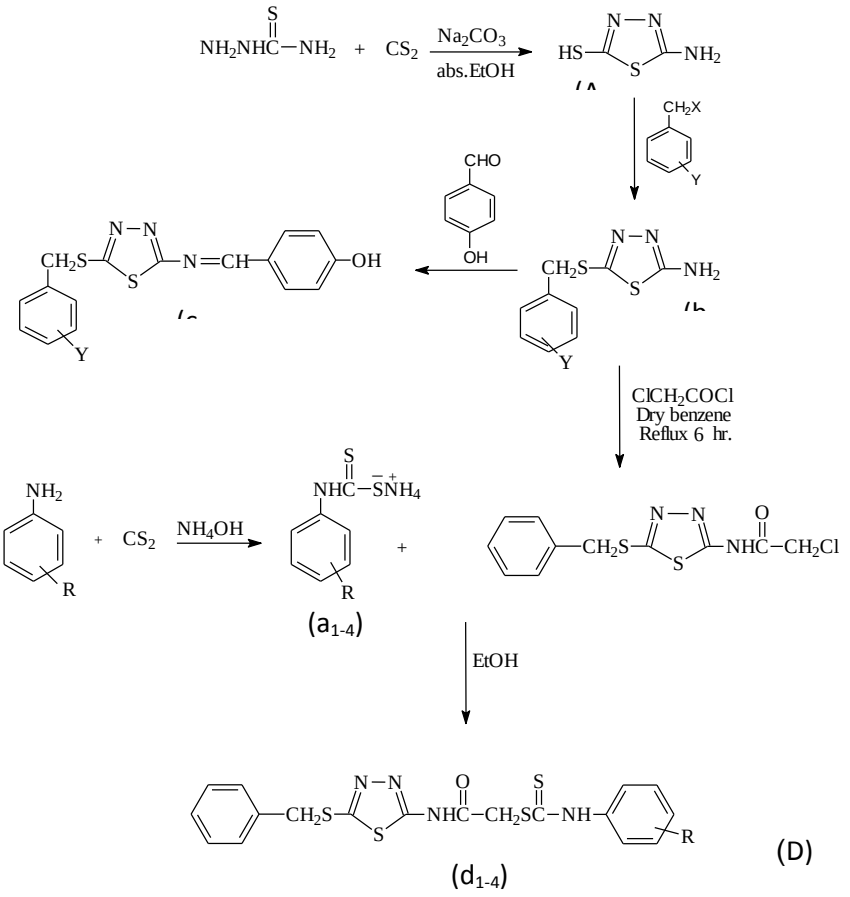
2-amino-1,3,4-thiadiazole-5-thiol have been prepared by heating thiosemicarbazide with carbon disulphide and anhydrous sodium carbonate in absolute ethanol. This product was treated with substituted benzyl halides, then treated with chloro acetyl chloride in dry benzene to yield 5-substituted benzyl thio-2-chloroacetamido-1,3,4- thiadiazole. Several new [5-substituted benzyl thio(2-thiadiazolyl)-carbamoyl] methyl dithio carbanilates have been prepared by condensing the ammonium salt of aryl dithiocarbamic acid with 5- substituted benzyl thio-2-chloroacetamido-1,3,4-thiadiazoles in dry acetone. 2-amino-5-substituted benzyl thio-1,3,4-thiodiazole was prepared by heating 2-amino-5-substituted benzyl thio-1,3,4-thiadiazole with substituted benzyl halide. Treatment with p-hydroxybenzaldehyd gave the corresponding Shiff bases. The synthesized compounds have been characterized on the basis of IR spectral analysis and the results were compatible with their assigned structures. The synthesized compounds ($b_2$,$b_3$,$c_4$,$d_1$,$d_3$) were tested against five types of bacteria *(Staphylococcus aureusBacillussubtilis, Klebsiella pneumonia, Proteus vulgaris, Escherichia coli,*),the compounds ($b_3$,$d_3$) showed expected biological activity.

**Keywords:** Dithiocarbamate, 1,3,4- thiadiazole**.**

## Introduction

The therapeutic effect of compound containing 1,3,4-thiadiazole ring have been well studied for number of pathological states including antibacterial, antimycotic, antituberculer, anti - Parkinson cancer drug, anti-inflammatory and anticonvulsant[1-7]. Moreover, synthesis of thiadiazole and dithiocarbamate had attracted widespread attention due to their diverse applications as antifungal, agricultural insecticidal, anti-depressing agent and anti-psychotic agent[8– 11]. 1,3,4-thadiazoles have also used as multi-functional ligands [12 , 13]

According to above mentioned facts, it was planned to synthesize the title compounds, scheme (1), with the hope that the incorporation of the above moiety with imine and thiol groups may enhanced the biological activity.




X= Cl , Br
R=Y= H , p-Br, p-$NO_2$ , o-Cl

**Scheme (1)**

## Experimental

Melting points were determined on Electro thermal Apparatus and uncorrected. The IR absorption spectra were recorded on FT−IR model 84005 Shimadzu Japan. Infrared spectrophotometer as KBr disk.

### Synthesis of 2-amino-1,3,4-thiadiazole-5-thiol [4, 15].(A)

To thiosemicarbazide (3.6 gm , 0.02 mole) suspended in ethanol (15 ml) were added anhydrous sodium carbonate (2.12 gm , 0.02 mole) and carbon disulphide (3 ml), The mixture was warmed with stirring under reflux for(1 hr),then heated on the steam bath for (4 hrs). The solvent was largely removed, the residue was dissolved in ice-water and acidified with concentrated hydrochloric acid to give 92 % of the product m.p.233 °C.

### Synthesis of Ammonium salt of aryl dithiocarbamic acid [17, 18].($a_{1-4}$)

Ammonium salt of aryl dithiocarbamic acid was prepared by stirring mixture of the substituted aniline (0.01 mole) in carbon disulphide (3 ml) and ammonia solution (5ml) in ice-bath until crystalline precipitate of the required product was obtained. The product was recrystallized from benzene. The physical properties of the synthesized compounds were given in Table (1).

### Synthesis of 5-(substituted benzyl thio) -2-amino 1,3,4-thiadazole [1,19].($b_{1-4}$)

To a solution of 5-mercapto-2-amino-1,3,4-thiadiazole (0.003 mole) in absolute ethanol (30 ml), (1.12 gm) of potassium hydroxide and (0.03mole) substituted benzyl halides were added, the mixture was refluxed for (2 hr). After cooling precipitate was collected by filtration, dried and recrystallized from acetic acid. The physical properties of the synthesized compounds were given in Table (2).

### Synthesis of 2 – N - (p-hydroxybenzylidino) 5-substituted benzyl thio 1,3,4-thiadazole [20].($c_{1-4}$)

A suspension of p-hydroxybenzaldehyde (0.01mole) in EtOH (50 ml) and 5-substituted benzyl thio-2-amino-1,3,4-thiadazole (0.01mole), two drops of glacial acetic acid was heated under reflux for (2 hrs). The product was collected after cooling and recrystallized from ethanol. The physical properties of the synthesized compounds were given in Table (3).

### Synthesis of substituted benzyl thio 2-(chloroacetamido)-1,3,4-thiadiazole [10,16] (D)

Freshly distilled chloro acetyl chloride (2.5ml) dissolved in dry benzene (100 ml) was gradually added to a mixture of (0.033 mole) 2-amino-1,3,4-thiadiazole-5-thiol in dry Benzene (30 ml). The reaction mixture was refluxed on a water bath for (2 hrs). Benzene was distilled off and the residue was washed with 5% sodium bicarbonate solution and finally washed with distilled water. It was dried and recrystallized from ethanol to give 85 %. of red powder decomposes 264 °C.IR spectrum is showed in figure (2).

### Synthesis of [(5-benzyl thio-1,3,4-thiadiazol-2-yl)carbamoyl]methyl dithiocarbanilates.[17,18] ($d_{1-4}$)

A mixture of (0.01 mole) ammonium salt of aryl dithiocarbamic acid and 5-mercapto-2-chloro acetamido-1,3,4-thiadiazole (0.01mole) in dry acetone was stirred for (1/2 hr) at room temperature then heated under reflux (1.5 hr), excess acetone was distilled off and the reaction product was washed thoroughly with distilled water and dried. The product was crystallized from ethanol. The physical properties of the synthesized compounds were given in Table (4).

### Micro-Organisms Tested

The following strains of bacteria were used:

- *Staphylococcus aureus*
- *Bacillus subtilis*
- *Klebsiella pneumonia*
- *Proteus vulgaris*
- *Escherichia coli*

They were obtained from department of Biology/College of Education/Mosul University.

### Antibacterial assay:

Leven et al. (1997) [21] method that depended on Vandepitte et al. (1991) [22] method was followed to perform this test.

Nutrient agar was incubated by using single colony of the five types of bacteria a foresaid singly then the media was incubated at (37 °C) for (24 hrs). The microbial suspension was diluted by normal saline solution by comparison with standard test tube (Macferland No.1). It contained $10^8$ cell/$cm^3$ from the microbial suspension. Then it was spread on agar media surface by using glass spreader, the dishes were incubated for (30 min) until the absorption has been completed. Then, the dishes were prepared from filter paper (Whatman No.1) diameter (6mm), and saturated by different concentrations of isolated material from plant under test. The disks were fixed by sterilized tong and incubated at (37 °C) for (24 hrs) and finally the inhibiting regions were measured and compared with standard antibiotics control samples [23].

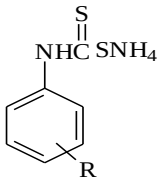


**Table (1): Physical and spectral data of compounds (a1-4)**

| Comp. No. $a_{1-4}$ | R | m.p °C | Yield (%) | IR □ $cm^{-1}$, KBr / Type of vibration (stretching) | | |
|---|---|---|---|---|---|---|
| | | | | C=S | -NH | CH-Ar |
| $a_1$ | H | 65-67 | 80 | 1346 | 3350 | 3180 |
| $a_2$ | p-Br | 108-110 | 70 | 1300 | 3300 | 3100 |
| $a_3$ | p-Cl | 68-71 | 70 | 1320 | 3250 | 3030 |
| $a_4$ | m-$NO_2$ | 102-104 | 85 | 1330 | 3200 | 3025 |

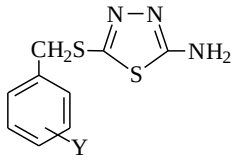


**Table (2): Physical and spectral data of compounds ($b_{1-4}$)**

| Comp No $b_{1-4}$ | Y | m.p °C | Yield (%) | IR □ $cm^{-1}$, KBr / Type of vibration (stretching) | | | |
|---|---|---|---|---|---|---|---|
| | | | | C-S-C | C=N | CH- Ar | N-H |
| $b_1$ | H | 86-90 | 70 | 1096 | 1630 | 3100 | 3500 |
| $b_2$ | p-Br | 153-156 | 60 | 1090 | 1630 | 3100 | 3450 |
| $b_3$ | o-Cl | 110 d | 70 | 1084 | 1640 | 3180 | 3400 |
| $b_4$ | p-$NO_2$ | 230-233 | 45 | 1075 | 1645 | 3100 | 3440 |

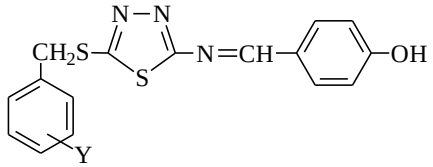


**Table (3): Physical and spectral data of compounds ($c_{1-4}$)**

| Comp. No $c_{1-4}$ | Y | m.p °C | Yield (%) | IR □ $cm^{-1}$, KBr / Type of vibration (stretching) | | |
|---|---|---|---|---|---|---|
| | | | | C-S-C | C=N | CH-Ar |
| $c_1$ | H | 200d | 40 | ١٥٦5 | ١٥٩٧ | 31٤٢ |
| $c_2$ | p-Br | 168-171 | 40 | 1088 | 1640 | 3020 |
| $c_3$ | o-Cl | 149-153 | 60 | 1095 | 1635 | 3030 |
| $c_4$ | p-$NO_2$ | 270 d | 50 | 1092 | 1645 | 3100 |

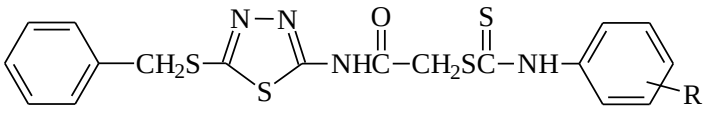


**Table (4): Physical and spectral data of compounds ($d_{1-4}$)**

| Comp. No. $d_{1-4}$ | R | m.p °C | Yield (%) | IR □ $cm^{-1}$, KBr / Type of vibration (stretching) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | C=S | C=O | -NH | C=N | CH- Ar |
| $d_1$ | H | 140-143 | 75 | 1340 | 1730 | 3300 | 1630 | 3100 |
| $d_2$ | p-Br | 248-250 | 45 | 1300 | 1710 | 3350 | 1635 | 3020 |
| $d_3$ | p-Cl | 263-265 | 50 | 1330 | 1700 | 3200 | 1640 | 3100 |
| $d_4$ | p-$NO_2$ | 238-240 | 65 | 1331 | 1689 | 3275 | 1645 | 3180 |

## Results and Discussion

2-amino-1,3,4-thiadiazole-5-thiol was synthesized by cyclization of thiosemicarbazide with carbon disulfide in presence of absolute ethanol and sodium carbonate in reflux temperature. The FT-IR spectrum of 2-amino-5-mercapto-1,3,4-thiadiazole showed bands at(3386–3270 $cm^{-1}$) due to stretching of (N-H) group, and other one appeared at (3105 $cm^{-1}$), band at (1595 $cm^{-1}$) for C=N group , band at (1095 $cm^{-1}$) attributed to (C-S-C), this band is a good evidence for thiadiazole formulation with appearance of a weak band at (2542 $cm^{-1}$) due to (S-H) group, band at (1346 $cm^{-1}$) of thion group (C=S) appeared respectively. 5-substituted benzyl thio-2-amino-1,3,4-thiadazole($b_{1-4}$) were synthesized from the reaction of 2-amino-5-mercapto-1,3,4- thiadiazole and substituted benzyl halides. The structures of the synthesized compounds were conformed by their melting-point and IR-spectra. Characteristic absorption bands were shown in Table (2). The reaction of these compounds ($b_{1-4}$) with p-hydroxybenzaldehyde gave the corresponding shiff bases ($c_{1-4}$). The formation of these condensed products was conformed by measuring their melting-points. The IR characterization data were given in figure (1) and table (3).The compound [(5-benzyl thio-2-thiadiazolyl) carbamoyl] Methyl dithiocarbanilates were synthesized through the reaction of 2-chloro[5-mrcapto-2-chloro acetamidoamino-1,3,4-thiadiazole] with ammonium salt of aryl dithiocarbamic acid in the presence of acetone (scheme 1).The structures of the synthesized compounds were conformed by their melting-point and IR-spectroscopy. Characteristic absorption bands were shown in figure (3) and Table (4). It was worth to say here that the synthesized compounds were showed their biological activity toward *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumonia*, *Proteus vulgaris* and *Escherichia coli*. The results were illustrated in Table (5).

**Table (5): Inhibiting activity of synthesized compounds comparison with antibiotics (inhabiting diameter mm)**

| Comp. No. | | Conc. (mg/ml) | Staphylococcus aureus | Bacillus subtilis | Klebsiella pneumonia | Proteus vulgaris | Escherichia coli |
|---|---|---|---|---|---|---|---|
| $b_2$ | | 10 | 14 | 16 | - | - | - |
| | | 1 | 6 | 8 | - | - | - |
| | | 0.1 | - | - | - | - | - |
| | | 0.01 | - | - | - | - | - |
| $b_3$ | | 10 | 12 | 14 | 10 | 12 | 10 |
| | | 1 | 6 | 6 | - | 6 | - |
| | | 0.1 | - | - | - | - | - |
| | | 0.01 | - | - | - | - | - |
| $c_4$ | | 10 | 13 | 12 | 10 | 11 | 10 |
| | | 1 | 7 | 6 | - | - | - |
| | | 0.1 | - | - | - | - | - |
| | | 0.01 | - | - | - | - | - |
| $d_1$ | | 10 | - | - | - | - | - |
| | | 1 | - | - | - | - | - |
| | | 0.1 | - | - | - | - | - |
| | | 0.01 | - | - | - | - | - |
| $d_3$ | | 10 | 20 | 22 | 18 | 24 | 19 |
| | | 1 | 8 | 10 | 9 | 12 | 8 |
| | | 0.1 | 6 | 8 | - | 7 | - |
| | | 0.01 | - | - | - | - | - |
| Chloramphenicol (30 mg/disc) | Control | | 15 | 12 | 18 | 13 | 18 |
| Gentamycin (10 mg/disc) | | | 15 | 15 | 13 | 12 | 13 |

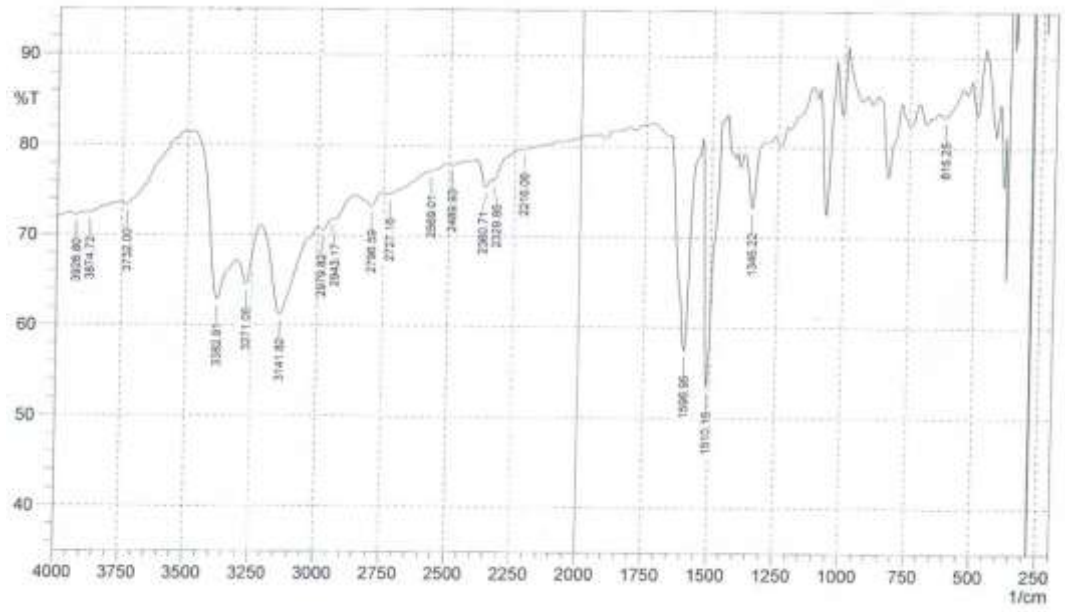



**Figure (1) : shows IR spectrum of compound $C_1$**

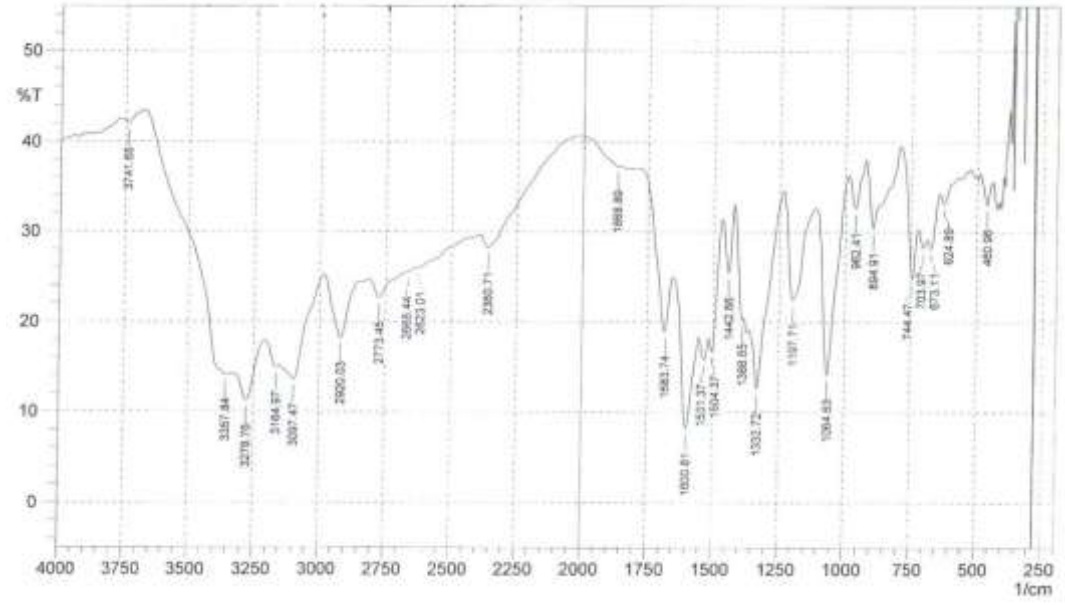



**Figure (2) : shows IR spectrum of compound D**

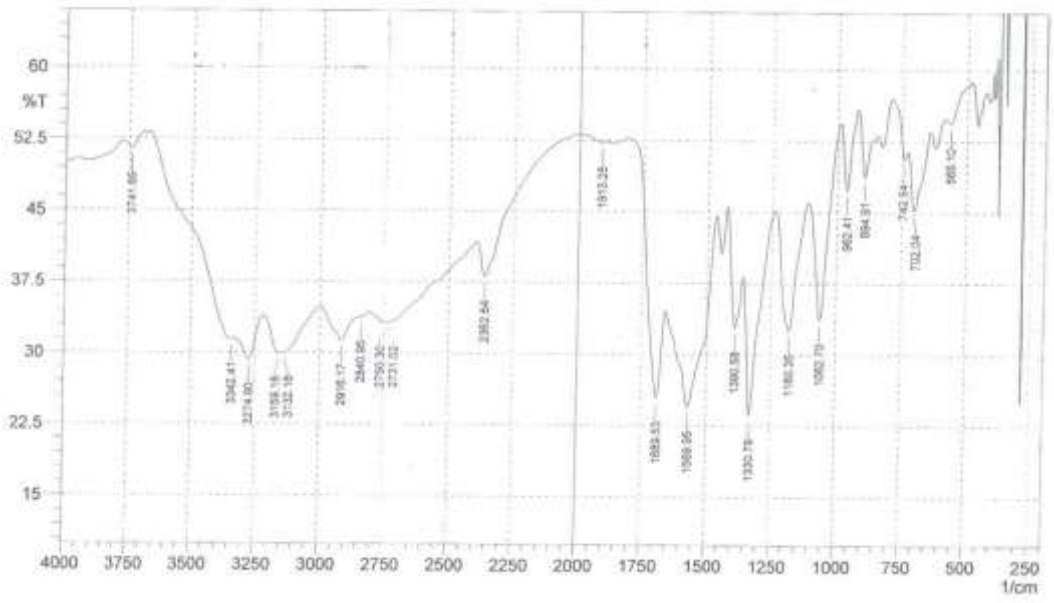



**Figure (3) : shows IR spectrum of compound $d_4$**

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# تحضير بعض مشتقات ٤،٣،١ – ثايادايازول الجديدة ودراسة فعاليتها البايولوجية

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( تاريخ الاستلام:١٢ / ٣ / ٢٠٠٨ ، تاريخ القبول: ٢٥ / ١٠ / ٢٠٠٩ )

**الملخص**

حضر المركب٢–امينو ٥– مركبتو ٤،٣،١ – ثايادايازول من خلال تفاعل الثايو سيميكاربازيد مع ثنائي كبريتيد الكاربون وكاربونات الصوديم اللامائية في الايثانول المطلق. تفاعل ٢–امينو٥– بنزايل ثايو–٤،٣،١ – ثايادايازول مع معوضات هاليدات الاريل ثم يتفاعل الناتج مع كلورو كلورايد الاستيل في البنزين الجاف ليعطي الناتج ٢– كلورو[ ٥– بنزايل ثايو–٤،٣،١ – ثايادايازولايل] اسيتامايد. كذلك حضرت مشتقات[٥– بنزايل ثايو –٢–امينو( ٤،٣،١ – ثايادايازولايل) كاربامويل] مثيل داي ثايوكاربانيليت من تفاعل ٢– كلورو [٥– بنزايل ثايو–٤،٣،١ – ثايادايازولايل] اسيتامايد مع املاح الامونيوم لحامض ثنائي ثايوكارباميك الاريلية .معوضات ٥– بنزايل ثايو ٤،٣،١ – ثايادايازول تفاعلت مع بارا هيدروكسي بنزالديهايد لتعطي قواعد شف المقابلة. شخصت المركبات المحضرة بالطرق الطيفية والفيزياوية المتاحة. اختبرت فعالية المركبات ($b_2,b_3,c_4,d_1,d_3$) تجاه البكتريا *Staphylococcus aureus* ، *Bacillus subtilis* ، *Klebsiella pneumonia*، *Proteus vulgaris* ، *Escherichia coli* فاظهر المركبان ($b_3$،$d_3$) فعالية بايولوجية متوقعة.

**الكلمات المفتاحية:** داي ثايوكارباميت ، ٤،٣،١– ثايادايازول.