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Synthesis of Some New Thiadiazole/Thiadiazine derivatives as potent Biologically Active Compounds

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Abstract: Due to the significant pharmacological and industrial value of 1,3,4-thiadiazole and 1,3,4-thiadiazine, they are continuing to be of considerable interest to many researchers, therefore it is expected that the number of publications in the synthetic field much outweighs those in all other fields. In this work, we aimed to prepare, characterize, and investigate some unprecedented hybrid compounds comprising carboxamide and 1,3,4-thiadiazole in addition to 1,3,4-thiadiazine motifs synthesized from thioxoacetamide derivatives. Here, thioxoacetamide derivatives are used as building blocks in the preparation process of these compounds. Moreover, the reaction of thioxoacetamide was examined with some reagents having electrophilic centers such as ethyl chloroformate, phenyl isothiocyanate, triethylorthoformate, malononitrile and diethyl-2- (bis(methylthio)methylene) malonate, to give five-membered heterocyclic rings, also reacted with ethyl chloroacetate, and chloroacetonitrile and the resulting products are six-membered heterocyclic rings. The synthesized compounds were characterized and investigated their validity by full spectral analysis. According to previous studies, these compounds are expected to have high biological activity in various antidotes.

Keywords: Carboxamide, thioxoacetamide, thiadiazole, thiadiazine, thiohydrazides

1. Introduction

The physicochemical characteristics of the nitrogen and sulfur heterocyclic systems are relevant to the development of novel medications, making them particularly intriguing **[1,2]**. Recently, the biological activities of heterocyclic rings, such as thiadiazole, triazoles, indoles, pyrones, morpholines, pyridines, and pyrazoles, have been reviewed widely **[3-6]**. Many of the derivatives of those substances comprising 1,3,4-thiadiazines and 1,3,4-thiadiazoles are utilized to treat hypertensive as well as cardiotonic drugs **[7,8]**. In addition to that they can be used to treat tumors and acquired immune deficiency syndrome (AIDS)" **[9]**. 1,3,4-Thiadiazoles have a variety of pharmacological effects, including anti-bacterial **[10]**, anti-malarial, anti-microbial, antioxidant **[11]**, anticonvulsant **[12]**, anti-parasitic **[13]**, anti-tuberculosis **[14]**, anti-leishmanial **[15]**, anti-inflammatory **[16]** and anti-cancer effects **[17]**. Also, 4-thiazolidinones exhibit distinct biological activities such as anti-inflammatory **[18]**, anti-microbial **[19]**, anti-diabetic **[20]**, anti-tuberculosis **[21],** and anti-cancer **[22].** The well-known 1,3,4 thiadiazole-containing commercial drugs are Acetazolamide and Methazolamide (Diuretics, carbonic anhydrase inhibitors), Megazol (Antiprotozoal, protein, and DNA synthesis inhibitor), Sulphamethizole (Antimicrobial, dihydropteroate synthase inhibitor), Cefazolin and Cefazedone (antibiotics, cell wall synthesis inhibitors), are shown in Fig. 1.

Thiadiazine derivatives have a strong affinity for matrix metalloproteinase (MMP9) I, II and have an inhibitory effect on several cancer cell lines and against several matrix metalloproteinases (MMPs) **[23–26]** (*see* **Fig. 2**). Enzymes called MMPs play a significant role in tumor invasion and metastasis and are overexpressed in lung cancer **[27]**.

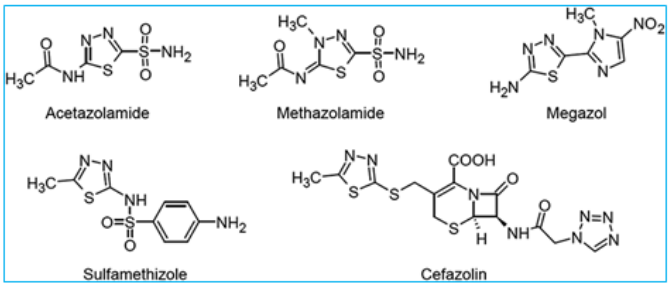


Fig.1. Several medications with a 1,3,4-thiadiazole core are available.

Various 1,2,4-triazolo[3,4-b] alternatives are also available. 1,3,4-Thiadiazines and Schiff's bases have been associated with an extensive variety of pharmacological actions, including plant growth regulation, analgesic, anthelmintic, antifungal antitubercular, antiviral, and anticancer **[28-32]**.

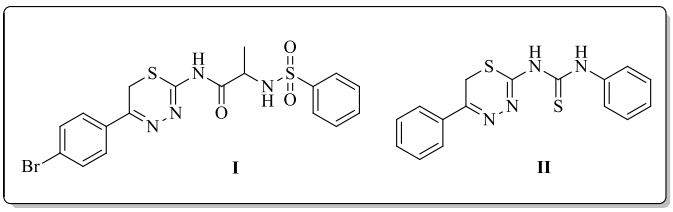
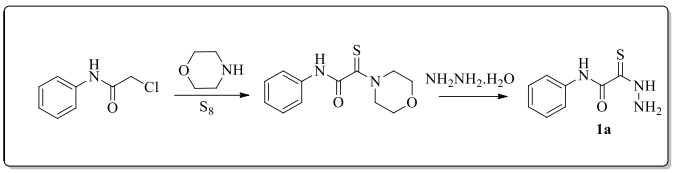


Fig.2. Two examples of drugs possessing 1,3,4-Thiadiazine.

Thioxoacetamide fragments are present in natural products **[33].** Currently, thioxoacetamides are under intensive research as biologically active compounds **[34,35]**. Of particular interest is the use of thioxoacetamides as complex structures **[36].** However, despite the high synthetic potential, these

compounds had been studied little before our work [37], mostly due to the lack of practical procedures for their synthesis.

In furtherance of our investigation into the usage of organic compound byproducts of *S*-functionalization in the preparation of *S, N*-heterocyclic substances [38-41], In the present work we used the reported method for synthesis of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)** by reaction of 2-chloro-*N*-phenyl acetamide with morpholine and sulfur, followed by reaction with hydrazine [42-44] and used it as a building block nucleus in further preparations, especially some novel 1,3,4-thiadiazoles and 1,3,4-thiadiazines linked to *N*-phenyl carboxamide chain, in a smooth way, short period and high yield which expected to show high biological activity. Eq.1.



Equation 1: synthesis of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**

2. Materials and methods

Thin layer chromatography (TLC) was utilized to monitor some reactions (compounds **2**, **6,** and **10**) using precolated silica gel plates G/UV-254 and its thickness is 0.25 mm (Merck 60F254). For visibility, we used UV light (254 nm/365 nm). To record all melting points the uncorrected Kofeler instrument was used. On an FT-IR spectrophotometer, KBr pellets were used to analyze IR spectra. At Sohag University, ^{1}H NMR and ^{13}C NMR (DMSO-d_6) spectra were operated at 400 MHz furthermore 100 MHz, respectively. For ^{1}H NMR data, the following information is provided: chemical shift, multiplicity (singlet, doublet, triplet, and multiplet), and integration. For Chemical shifts (δ) were given in parts per million (ppm) concerning tetramethylsilane (TMS) as an internal standard (= 0 ppm). We used DMSO (= 39.51 ppm) or TMS (= 0 ppm) as internal standards for ^{13}C NMR. For elemental analyses, a Perkin-Elmer CHN analyzer model was performed.

5-Oxo-N-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (2):

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide, 1.3 mmol (0.14g) of ethyl chloroformate, and triethylamine (0.5 mL) in ethanol (10 mL) was heated under reflux for 4 hrs (monitored with TLC). The solid formed was purified from ethanol.

Pale white crystals, yield 87% (0.20g), mp. 180-182 ºC FT-IR (ATR) λ max: (3413, 3315), (2NH), 1714 (C=O$_{cyclic}$), 1676 (-C=O$_{amidic}$); ^{1}H NMR: δ 11.42 (s, H, NH$_{cyclic}$, exchangeable by D$_2$O), 10.01 (s, 2H, NH$_2$, exchangeable by D$_2$O) 7.88- 7.68 (m, 5H, ArH), ppm; ^{13}C NMR: δ 176.33 (-C=O$_{cyclic}$), 161.75 (-C=O$_{amidic}$), 154.88(-C=N), 136.52, 129.27, 124.28, 122.64 ppm Arom. Anal. Calcd. for $C_9H_7N_3O_2S$ (221.24): C, 48.86; H, 3.13; N, 18.99; S, 14.49% Found: C, 48.82; H, 3.19; N, 18.95; S, 14.51%.

***N*-Phenyl-5-(phenylamino)-1,3,4-thiadiazole-2-carboxamide (3):**

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, 1 mmol (0.14g) of phenyl isothiocyanate, and 3 mmol (0.17g) potassium hydroxide 15 mL of dioxane was heated under reflux for 6 hrs. The solid product formed was purified from ethanol.

White crystals, yield 88% (0.26g), mp. 172-174 ºC FT-IR (ATR) λ max: (3344, 3269) (2NH), 1680 (-C=O$_{amidic}$); ^{1}H NMR: δ 10.80 (s, H, NH$_{amidic}$, exchangeable by D$_2$O), 8.67 (s, H, NH$_{phenylamino}$, exchangeable by D$_2$O), 7.84 -7.08 (m, 10H, ArH); ^{13}C NMR: δ 163.70 (C=O), 158.10 (-C=N), 155.31(-C=N), 137.22, 135.85, 130.28, 128.32, 124.87, 124.28, 122.64, 121.72 ppm Arom. Anal. Calcd. For $C_{15}H_{12}N_4OS$ (296.35): C, 60.79; H, 4.08; N, 18.91; S, 10.82% Found: C, 60.83; H, 4.02; N, 18.95; S, 10.81%.

***N*-Phenyl-1,3,4-thiadiazole-2-carboxamide (4):**

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, 5 mL triethylorthoformate, and triethylamine (0.5 mL) was heated under reflux for 4 hrs. The mixture was cooled, then the collected product was purified from ethanol.

White crystals, yield 75% (0.16g), mp. 175-177 ºC FT-IR (ATR) λ max: (3230) (NH), 1680 (-C=O$_{amidic}$); ^{1}H NMR: δ 10.74 (s, H, NH$_{amidic}$, exchangeable by D$_2$O), 10.22 (s, H, NH, exchangeable by D$_2$O), 8.96 (s, 1H, -CH=N) 7.86- 7.13 ppm (m, 5H, ArH); ^{13}C NMR: δ 160.153 (-C=O), 156.46 (-C=N), 153.20 (-CH=N), 137.22, 131.86, 127.75, 124.87 ppm Arom. Anal. Calcd. for $C_9H_7N_3OS$ (205.03): C, 52.67; H, 3.44; N, 20.47; S, 15.62% Found: C, 52.69; H, 3.42; N, 20.44; S, 15.61%.

5-(Cyanomethyl)-N-phenyl-1,3,4-thiadiazole-2-carboxamide (5):

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, 1 mmol (0.07g) of malononitrile, and 2 mmol (0.28g) potassium carbonate in 10 mL of DMF was heated under reflux for 5 hrs. The cooled mixture was poured into crushed ice (20 mL) and the formed precipitate formed was purified from ethanol.

White crystals, yield 84% (0.21g), mp. 207-209 ºC FT-IR (ATR) λ max: (3319) (NH), 2205 (-CN) 1669 (-C=O$_{amidic}$); ^{1}H NMR: δ 10.04 (s, H, NH$_{amidic}$, exchangeable by D$_2$O), 7.79-7.15 (m, 5H, ArH), 3.86 ppm (s, 2H, CH$_2$) ; ^{13}C NMR: δ 167.19 (-C=O), 160.53 (C=N), 156.65 (-C=N), 136.52, 129.10, 126.81, 122.64 Arom, 114.49 (-CN), 20.20 ppm (-CH$_2$). Anal. Calcd. For $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.94; S,13.13% Found: C, 54.11; H, 3.29; N, 22.93; S, 13.10%.

***N*^{2}, *N*^{5}-Diphenyl-1,3,4-thiadiazole-2,5-dicarboxamide (6):**

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, with/without diethyl-2-(bis(methylthio)methylene) malonate and 3 drops triethylamine in 10 mL ethanol was heated under reflux for 2 hrs (monitored with TLC). Filtration was used to collect the produced product, which was then purified using ethanol.

White crystals, yield 89% (0.29g), mp. 156-158 ºC FT-IR (ATR) λ max: (3237) (NH), 1679 (-C=O_{amidic}); ^{1}H NMR: δ 11.22 (s, H, NH, exchangeable by D_2O), 7.88- 7.19 (m, 5 H, ArH) ppm; ^{13}C NMR: δ 169.69 (-C=O), 156.23 (-C=N), 137.93, 129.26, 125.24, 121.57 ppm Arom. Anal. Calcd. for $C_{16}H_{12}N_4O_2S$ (324.36): C, 59.25; H, 3.73; N, 17.27; S, 9.89% Found: 59.29; H, 3.75; N, 17.24; S, 9.75%.

5-Oxo-N-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamide (8):

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, 1.2 mmol (0.15g) of ethyl chloroacetate, and triethylamine (0.5 mL) in ethanol (10 mL) was refluxed for 4 hrs. The solid formed was purified from ethanol.

White crystals, yield 77% (0.18g), mp. 193-195 ºC FT-IR (ATR) λ max: (3345, 3312) (2NH), 1678 (C=O_{cyclic}), 1659 (-C=O_{amidic}); ^{1}H NMR: δ 11.80 (s, H, NH_{cyclic}, exchangeable by D_2O), 10.22 (s, 2H, NH_2, exchangeable by D_2O) 7.72- 7.11 (m, 5H, ArH), 3.58 ppm (s, 2H, CH_2); ^{13}C NMR: δ 160.14 (-C=O), 160.07 (-C=O), 141.27 (-C=N), 138.15, 129.17, 124.77, 121.03 Arom, 24.65 ppm (CH_2). Dept-135: δ 129.16,124.78,121.04 Arom, 29.36, 14.57 ppm. Anal. Calcd. for $C_{10}H_9N_3O_2S$ (235.26): C, 51.05; H, 3.86; N, 17.86; S, 13.63% Found: C, 51.11; H, 3.82; N, 17.82; S, 13.60%.

6-(4-Chlorobenzylidene)-5-oxo-N-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamides (9a-c):

A mixture of 1 mmol (0.24g) of 5-oxo-*N*-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamide **(8)**, 1 mmol of benzaldehyde derivatives (20 mL acetic acid) and ammonium acetate (20 mmol) was heated under reflux for 10 hrs. The solid formed was purified from ethanol.

6-Benzylidene-5-oxo-N-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamide (9a):

White crystals, yield 78% (0.26g), mp. 228-220 ºC FT-IR (ATR) λ max: (3413, 3325) (2NH), 1713 (-C=O_{cyclic}), 1667 (-C=O_{amidic}); ^{1}H NMR: δ 11.66 (s, H, NH_{amidic}, exchangeable by D_2O), 10.17 (s, H, $NH_{hydrazide}$, exchangeable by D_2O), 7.82-7.10 (m, 9H, ArH); ^{13}C NMR: δ 161.04 (-C=O), 158.33 (-C=O), 152.76 (C=N), 141.29, 137.24, 133.77, 128.30, 126.13, 123.88, 123.55, 120.27, 120.04, 116.79 ppm Arom. Anal. Calcd. for $C_{17}H_{13}N_3O_2S$ (323.37): C, 63.14; H, 4.05; N, 12.99; S, 9.92% Found: C, 63.19; H, 4.02; N, 12.96; S, 9.90%.

6-(4-Chlorobenzylidene)-5-oxo-N-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamide (9b):

White crystals, yield 90% (0.32g), mp. 237-239 ºC FT-IR (ATR) λ max: (3374, 3267) (2NH), 1726 (C=O_{cyclic}), 1690 (-C=O_{amidic}); ^{1}H NMR: δ 11.71 (s, H, NH_{amidic}, exchangeable by D_2O), 10.15 (s, H, $NH_{hydrazide}$, exchangeable by D_2O), 7.80-7.12 (m, 10H, ArH); ^{13}C NMR: δ 160.07 (C=O), 159.28 (-C=O), 153.79 (-C=N), 141.24, 138.21, 131.89, 129.38, 129.12, 124.94, 124.71, 121.21, 121.06, 117.53 ppm Arom. Anal. Calcd. for $C_{17}H_{12}ClN_3O_2S$ (357.03): C, 57.06; H, 3.38; Cl, 9.91; N, 11.74; S, 8.96% Found: C, 57.08; H, 3.42; Cl, 9.89; N, 11.73; S, 8.91%.

6-(4-Nitrobenzylidene)-5-oxo-N-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine-2-carboxamide (9c):

White crystals, yield 72% (0.27g), mp. 237-239 ºC FT-IR (ATR) λ max: (3426, 3349) (2NH), 1729 (-C=O_{cyclic}), 1682 (-C=O_{amidic}), 1346,1535 (-NO_2); ^{1}H NMR: δ 11.71 (s, H, NH_{amidic}, exchangeable by D_2O), 10.15 (s, H, $NH_{hydrazide}$, exchangeable by D_2O), 7.80- 7.12 (m, 10H, ArH); ^{13}C NMR: δ 160.07 (-C=O), 159.28 (-C=O), 153.79 (-C=N), 141.24, 138.21, 131.89, 129.38, 129.12, 124.94, 124.71, 121.21, 121.06, 117.53 ppm Arom. Anal. Calcd. for $C_{17}H_{12}N_4O_4S$ (368.37): C, 55.43; H, 3.28; Cl, 9.91; N, 15.21; S, 8.70% Found: C, 55.48; H, 3.30; Cl, 9.90; N, 15.17; S, 8.68%.

5-Amino-N-phenyl-6H-1,3,4-thiadiazine-2-carboxamide (10):

A mixture of 1 mmol (0.20g) of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)**, 1 mmol (0.08g) of chloroacetonitrile, and 3 mmol (0.41g) potassium carbonate in ethanol (20 mL) was heated under reflux for 6 hrs (monitored with TLC). After cooling, the recrystallization was done with 20 mL ethanol.

White crystals, yield 80% (0.19g), mp. 256-258 ºC FT-IR (ATR) λ max: (3327, 3286, 3224) (NH_2, 2NH), 1657 (-C=O_{amidic}); ^{1}H NMR: δ 10.78 (s, H, NH_{amidic}, exchangeable by D_2O), 7.96- 7.65 (m, 5H, ArH), 6.99 (s, 2H, NH_2, exchangeable by D_2O), 4.49 ppm (s, 2H, CH_2) ; ^{13}C NMR: δ 163.34 (C=S), 160.82 (C=O), 157.31, 136.93, 130.92, 126.81, 123.97, 30.94 ppm Arom. Anal. Calcd. for $C_{10}H_{10}N_4OS$ (234.28): C, 51.27; H, 4.30; N, 23.91; S, 13.69% Found: C, 51.23; H, 4.33; N, 23.91; S, 13.66%.

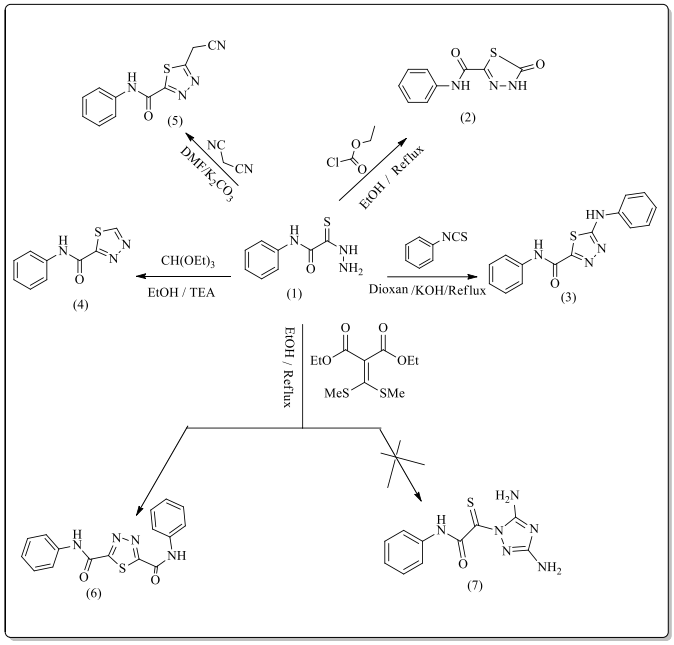
3. Results and Discussion:

It is important to note that, by published procedures, several oxamic acid thiohydrazide derivatives were produced from chloroacetanilides in explant yields by treating them with sulfur and morpholine before adding hydrazine [42, 43]. Herein, we are interested in introducing the synthesis of 2-hydrazinyl-*N*-phenyl-2-thioxoacetamide **(1)** [44] as a starting material for the preparation of 1,3,4-thiadiazole Furthermore 1,3,4-thiadiazine moieties linked to the carboxamide chains.

The reaction of thioxoacetamides **1** with some reagent namly ethyl chloroformate, phenyl isothiocyanate, triethylorthoformate, malononitrile, and diethyl-(bis(methylthio)methylene) malonate in deferent condition (see **Scheme 1**) to give novel 1,3,4 thiadiazole compounds **2,3,4,5** and **6**, respectively. The chemical structures of recently synthesized compounds were proved by their spectral (IR, ^{1}H, ^{13}C NMR), as well as elemental analysis, (see **Experimental part)**. TheIR spectrum of compound **2** explained the disappearance of theNH_2 group of compound **1** and the appearance of a new band at 1714 cm^{-1} which belongs to the-C=O_{cyclic} group. While its ^{1}H NMR showed a new signal at 11.42 ppm for the$NH_{hydrazide}$ group, whichdisappeared by D_2O, at the same time the peak for theamino group disappeared. In ^{13}C NMR showed a new signal at 176.33 ppm which return to the–C=O group of the formed 1,3,4 thiadiazole rings.

Spectrum data of compounds **3, 4, and5** confirmed the expected structure where IR spectrum showed disappearance of NH_2 group of compound **1**; ^{1}HNMR spectrum showed the appearance of new signals of NH group at 8.67 ppm for compound **3**, the $CH_{thiadiazole}$ group arose at 8.96 ppm for compound **4**, the CH_2 group appeared at 3.86 ppm for compound **5**; ^{13}C NMR spectrum agreed with expected structure.

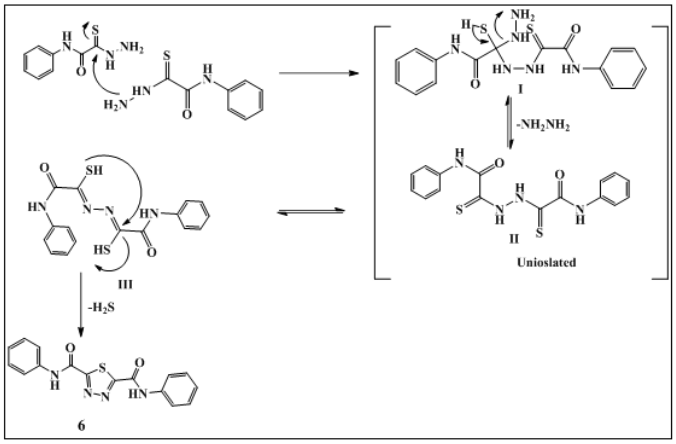
When compound **1** reacted with/without diethyl 2-diethyl (bis(methylthio)methylene)malonate and 3 drops triethylamine in ethanol, it give a new and unexpected ***N*^{2},*N*^{5}**-diphenyl-1,3,4-thiadiazole-2,5-dicarboxamide **(6)** instead of the expected product of the expected product 2-(3,5-diamino-1H-1,2,4-triazol-1-yl)-*N*-phenyl-2-thioxoacetamide **(7).**



Scheme 1. Preparation of 1,3,4-thiadiazole deravatives.

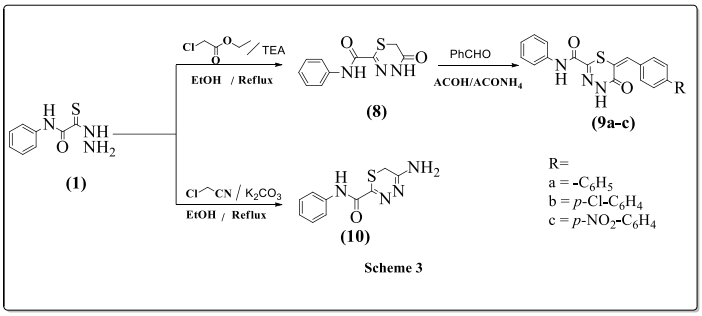
The illustrated reaction mechanism for the formation of thiadiazole **6** was supposed, via nucleophilic addition of terminal amino group at thione carbon of another molecule to form intermediate **I**, followed by elimination of hydrazine to afford unisolated intermediate 2,2'-(hydrazine-1,2-diyl) bis(*N*-phenyl-2-thioxoacetamide) **II**, which exists in tautomeric form **III**. The later intermediate undergoes intramolecular cyclization through nucleophilic attack of sulfur lone pair at C=N giving the target thiadiazole **6** with elimination of hydrogen sulfide, **Scheme 2**. Here, Compound **6** confirmed by their spectral, IR illustrated the disappearance of theNH_2 group, while its ^{1}HNMR showed only anew singlet signal at 11.22 ppm for theNH_{amidic} group, disappeared by D_2O and aromatic group at 7.88-7.19 ppm. In ^{13}C NMR illustrated a new signal at 156.23 ppm which returns to the(-C=N) group of the formed structure.

Nevertheless, compound **1** reacted with active halo compounds namely, ethyl chloroacetate and chloroacetonitrile in abasic medium giving the corresponding structures **8** and **10 (**see **scheme 3)**. The structures of the newly obtained compounds were characterized by their elemental and spectral data. The IR spectra of compound **8** exhibited the presence of abroad band: at 3345-3312 cm^{-1} corresponding to two NH groups, and a new band at 1678 cm^{-1} belongs to the C=O group of the formed 1,3,4 thiadiazole ring. The Proton-NMR spectrum, for example, of compound **8** illustrated the presence of a singlet band at 3.58 ppm characterized by the -CH_2 group. Its ^{13}CMR revealed the following signals: 160.14 and 160.07 ppm which return the two –C=O groups of the structure, also it appeared a new signal at 24.65 ppm (-CH_2). Finally, DEPT–135 proves the presence of –CH_2– (24.65 ppm) in the methylene group where it showed a negative phase. When structure **8** reacted with aldehyde derivatives, it afforded a new ligand **(9a-c),** that we hoped to form good complexes. The IR spectra of compounds **(9a-c)** exhibited the presence of anew band at 1713, 1726, and1729 cm^{-1} belonging to the C=O group of the formed 1,3,4 thiadiazine ring, respectively. The Proton -NMR spectrum, for example, of compound **9a** revealed the absence of a single band at 3.58 ppm characterized to CH_2 group. Its ^{13}CMR revealed the following signals: 160.07 and 159.28 which return the two carbonyl groups of the structure, also it appeared a new signal at 117.53 ppm (CH).



Scheme 2. The illustrated mechanism for the formation of thiadiazole **6**

In addition, the structure of compound **10** appear a new peak at 3327, 3286, and3224 which correspond NH_2 and NH groups in theIR spectrum, while its Proton NMR showed a new signal at 6.99 ppm which belongs to the amino group and at 4.49 ppm indicated to the methylene group, in ^{13}C NMR show a new signal at 30.94 ppm refer to -CH_2 group.



Scheme 3. Preparation of 1,3,4-thiadiazine derivatives.

4. Conclusion

Thioxoacetamide fragments are very important in the preparation of 1,3,4-thiadiazole as well as 1,3,4-thiadiazine as potent biologically active compounds. Where, thioxoacetamide reacts with several chemicals that have electrophilic centers, including ethyl chloroformate, malononitrile, triethlorthoformate, phenylisothiocyanate and diethyl-2-(bis(methylthio)methylene) malonate to afford new 1,3,4-thiadiazole derivatives. Additionally, it reacts with ethyl chloroacetate to afford compound **8**, which reacted with some aldehydes to afford new ligands derived from 1,3,4-thiadiazine derivatives.

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