Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

# Design, synthesis and insecticidal activity of new 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-a]pyrimidine derivatives under solvent-free conditions

Mahmoud F. Ismail, Hassan M. F. Madkour, Marwa S. Salem, Ali M. M. Mohamed & Aly Fahmy Aly

**To cite this article:** Mahmoud F. Ismail, Hassan M. F. Madkour, Marwa S. Salem, Ali M. M. Mohamed & Aly Fahmy Aly (2021): Design, synthesis and insecticidal activity of new 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-a]pyrimidine derivatives under solvent-free conditions, Synthetic Communications, DOI: 10.1080/00397911.2021.1945106

**To link to this article:** https://doi.org/10.1080/00397911.2021.1945106

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2021.1945106

Taylor & Francis
Taylor & Francis Group



# Design, synthesis and insecticidal activity of new 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-a]pyrimidine derivatives under solvent-free conditions

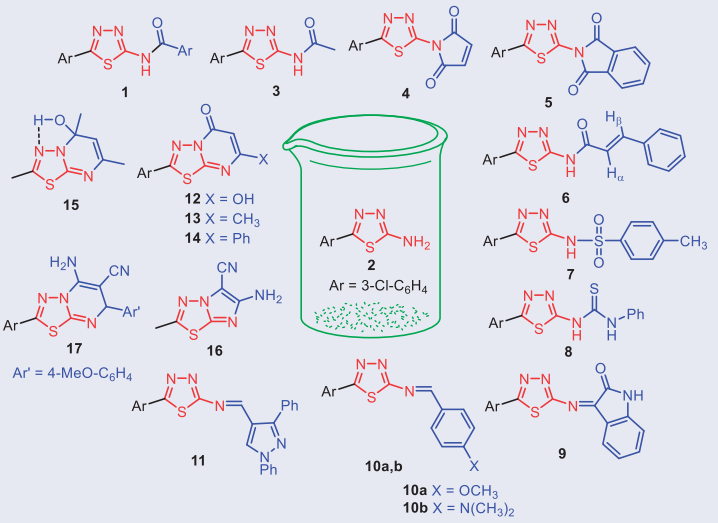
Mahmoud F. Ismail[a], Hassan M. F. Madkour[a], Marwa S. Salem[a], Ali M. M. Mohamed[a], and Aly Fahmy Aly[b]

[a]Department of Chemistry, Faculty of Science, Ain Shams University, Cairo, Egypt Abbassia; [b]Central Agricultural Pesticide Lab., Pesticide Formulations Department, Agricultural research Center, Giza, Egypt Dokky

## ABSTRACT

5-(3-Chlorophenyl)-1,3,4-thiadiazol-2-amine **2** was synthesized and employed to synthesize new 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives *via* reactions with variant electrophilic reagents under solvent-free conditions. The chemical structures of these novel compounds were elucidated scrupulously by aiding elemental data and spectroscopic techniques. The synthesized compounds were evaluated for the insecticidal activity against cotton leaf worm (*Spodoptera littoralis*). It was realized that the insecticidal activity of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives emerged remarkable results comparable with 1,3,4-thiadiazole derivatives against cotton leafworm (*Spodoptera littoralis*).

## GRAPHICAL ABSTRACT




## ARTICLE HISTORY

Received 23 April 2021

## KEYWORDS

1,3,4-Thiadiazole; 1,3,4-thiadiazolo[3,2-a]pyrimidine; thiosemicarbazide; *m*-chlorobenzoic acid; insecticidal activity

**CONTACT** Mahmoud F. Ismail fawzy2010@sci.asu.edu.eg Department of Chemistry, Faculty of Science, Ain Shams University, Cairo, Egypt Abbassia.

Supplemental data for this article can be accessed on the publisher's website

## Introduction

The cotton leafworm *(Spodoptera littoralis)* (Boisd.) is a polyphagous insect that feeds on leaves and is distributed worldwide. This insect is one of the major cotton pests that cause serious harm to many important vegetables and field crops. The pest's larvae can feed on about 90 economically important plant species belonging to 40 families.[1–3]

There is a need for various insecticides with various modes of action, so scientists are searching for alternative materials that are effective against this disease, safe for humans, ecologically friendly, and consistent with targeted pest management (IPM) practices.

During the past years, substituted 1,3,4-thiadiazole derivatives have received significant attention and have been increasingly investigated due to their broad spectrum of biological activities.[4–11] Such ring system reported to possess antiviral,[12] antibacterial,[13,14] anti-inflammatory[15] anticancer,[16–21] anticonvulsant,[22] anti-depressant,[23] COX-2 inhibitors,[24] insecticidal,[4,25–28] herbicidal[29] and acaricidal[28] activities. Commercially, 1,3,4-thiadiazole motif is available in variant aspects such as Thiazafluron and Tebuthiuron (pesticides).

It is worth noting that the applications of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine skeleton have been prevalent in a wide range of areas, including antitumor,[30–32] antiviral agents,[33] antibacterial and antifungal,[34,35] agrochemicals and herbicides.[36,37]

The literature survey revealed that the 1,3,4-thiadiazole moiety has been synthesized using variant methods.[25,26,38–41] In this regard, we utilized a methodology that depending on the reaction of an acid with thiosemicarbazide in the presence of phosphorus oxychloride.[25]

By taking a closer look at the chemical structure of 2-amino-1,3,4-thiadiazole derivative, it is evident that it possesses two neighboring nucleophilic sites as shown in Figure 1, subsequently, we turned our attention to exploit the nucleophilicity of the two nitrogen atoms of its compound to attack different electrophilic sites to construct novel 1,3,4-thiadiazole and fused-thiadiazole compounds in order to evaluate their insecticidal activity against cotton leafworm (*Spodoptera littoralis*) for the newly thiadiazole compounds.

## Results and discussion

### *Chemistry*

In the first efforts to obtain 5-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine **2**, **the** reaction of *m*-chlorobenzoic acid with thiosemicarbazide in the ratio (1:1) in the presence of $POCl_3$, compound **1** was obtained instead of the desired product **2**[42] practically. Structurally, the unexpected product **1** was elucidated by spectroscopic analyses such as IR, $^1$H NMR and mass spectra. Meanwhile, the requisite target compound **2** was smoothly obtained in outstanding yield (85%) by the same methodology but with changing the ratio between *m*-chlorobenzoic acid and thiosemicarbazide into (1:2). This

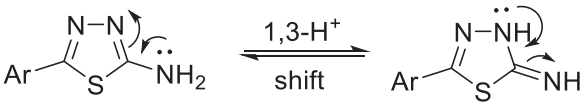
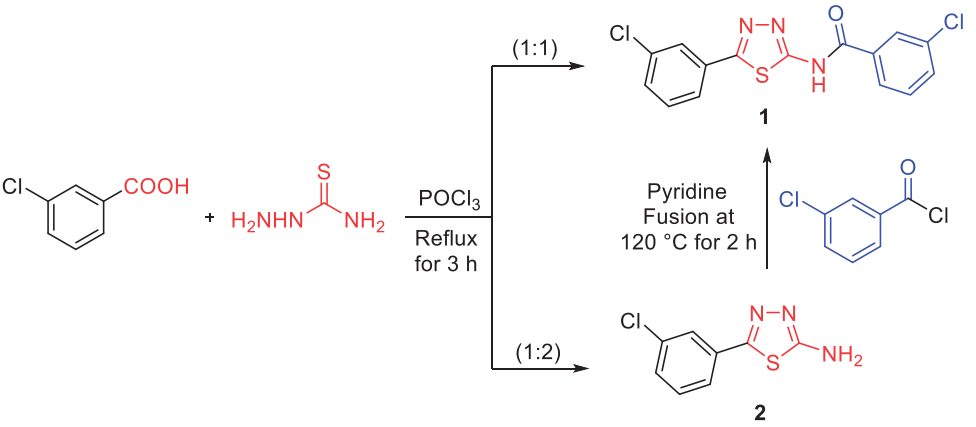



Figure 1. Tautmerism of 2-amino-1,3,4-thiadiazole derivative.




**Scheme 1.** Synthesis of 1,3,4-thiadiazole derivatives **1** and **2**.

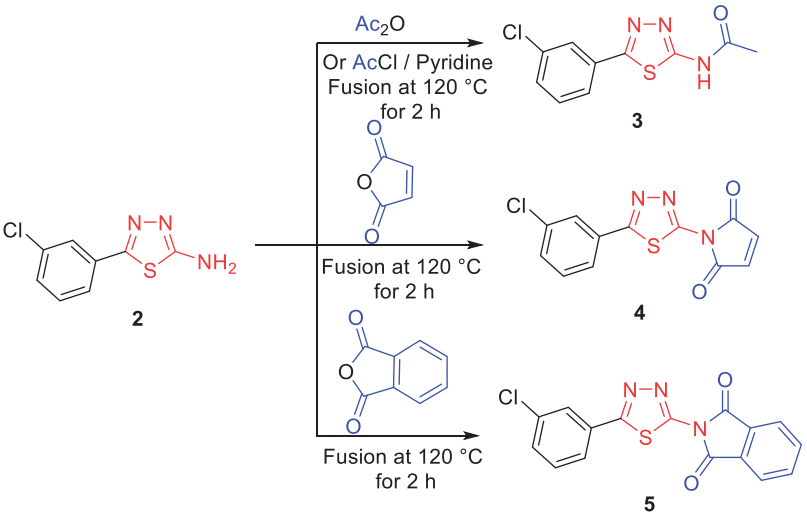
problem may be explained on the basis of consumption of a part of thiosemicarbazide by HCl, that evolved upon conversion of the acid to its acid chloride. So that, the formation of compound **2** needs an extra quantity of thiosemicarbazide. (Scheme 1).

As a prove of the chemical structure of compounds **1** and **2**, the IR spectrum of compound **1** exhibited the presence of the stretching absorption band at 1673 $cm^{-1}$ compatible with $\upsilon_{C=O}$ of the amide group. Moreover, the $^{1}H$ NMR spectrum revealed the presence of a singlet peak (exchangeable with $D_2O$) at 13.31 ppm corresponding to one NH proton, and six peaks compatible with the aromatic protons as two singlet peaks at 8.17 and 8.01 ppm and three doublet peaks at 8.06, 7.92 and 7.72 ppm corresponding to five protons and one multiplet peak at 7.61–7.53 ppm corresponding to the remaining three protons. Furthermore, the $^{13}C$ NMR spectrum exhibited a peak at 163.2 ppm compatible with the amide carbonyl carbon. On the other hand, the IR spectrum of compound **2** displayed absorption bands at 3383 and 3299 $cm^{-1}$ compatible with $NH_2$ group. Furthermore, the $^{1}H$ NMR spectrum of compound **2** manifested a singlet peak at 7.79 ppm, two doublet peaks at 7.89 and 7.07 ppm corresponding to three aromatic protons and a multiplet peak at 7.56–7.47 ppm corresponding to one aromatic proton beside two protons exchangeable with $D_2O$ corresponding to $NH_2$ protons. At the same time, the $^{13}C$ NMR spectrum of compound **2** is in keeping with the proposed chemical structure.

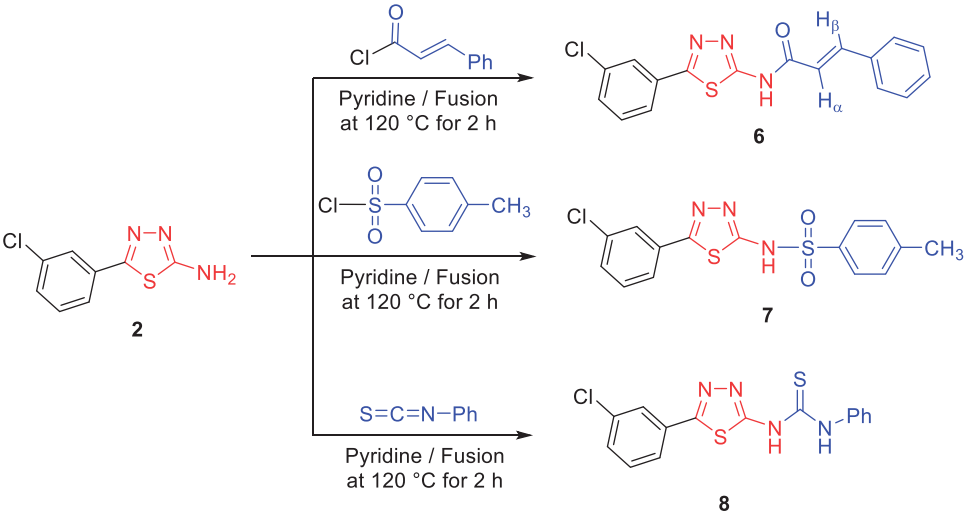
Further proof for the chemical structure of compound **1** was practically implemented by synthesis of an authentic sample, through a reaction of compound **2** with *m*-chlorobenzoyl chloride in the presence of pyridine. (Scheme 1)

Practically, we exploited the nucleophilic centers of compound **2** to synthesize a new 1,3,4-thiadiazole and fused-thiadiazole derivatives under solvent-free conditions, to diminution utilizing the toxic solvent to preserve on the environment. At the same time, we avoided using an eco-friendly solvent such as ethanol especially in this current stage, because it is now very important in the medical field and sterilization after the world was infected with the coronavirus disease (COVID-19).

Fusion of compound **2** with freshly distilled acetic anhydride and/or acetyl chloride in the presence of pyridine afforded the monoacetyl derivative **3** (Scheme 2). This structure was supported by the appearance of an absorption band at 1694 $cm^{-1}$ ($\upsilon_{C=O}$) in the IR spectrum. Moreover, the $^{1}H$ NMR spectrum indicated the presence of a singlet




**Scheme 2.** Synthetic Pathway of compounds **3**–**5**.




**Scheme 3.** Synthetic Pathway of compounds **6**–**8**.

peak exchangeable with $D_2O$ at 12.66 ppm compatible with NH proton and another singlet peak at 2.21 ppm compatible with $CH_3$ protons. The $^{13}C$ NMR spectrum also elucidated the chemical structure of compound **3** by the appearance of two peaks at 160.1 and 22.3 ppm corresponding to the acetyl carbons.

Fusion of compound **2** with maleic anhydride in sand bath gave *N*-maleimide moiety **4** (Scheme 2). Similarly, and under the same conditions, the *N*-phthalimido moiety **5** was emanated from the reaction of compound **2** with phthalic anhydride. The chemical structures of compounds **4** and **5** are in keeping with their spectroscopic and elemental analyses.

The reaction of 2-aminothiadiazole derivative **2** with cinnamoyl chloride in the presence of pyridine as a base-catalyzed furnished *N*-cinnamoyl derivative **6** (Scheme 3).

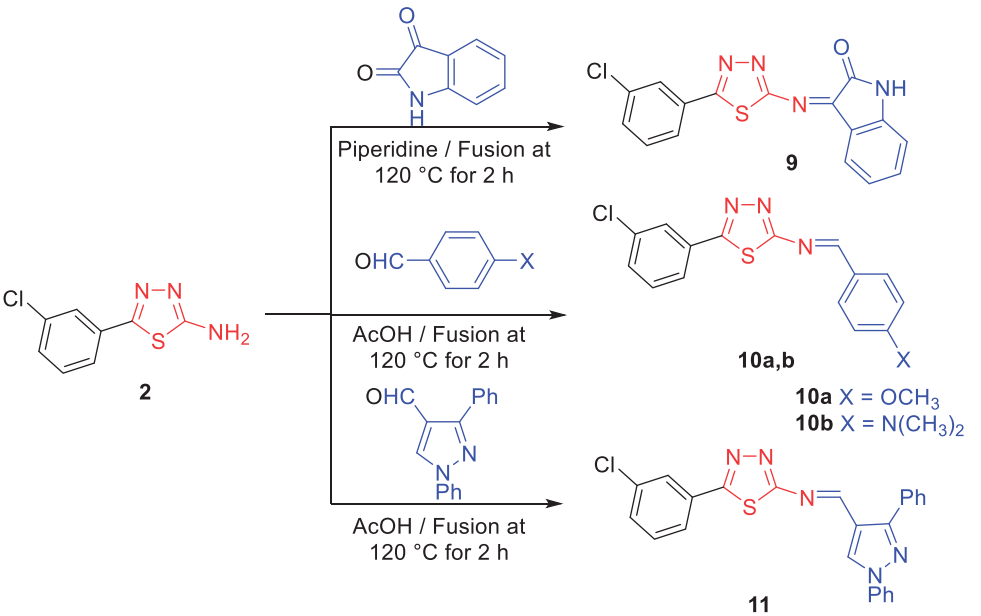
The $^{1}$H-NMR spectrum of compound **6** clearly underscores the foreseeable structure for it, where it displayed a broad singlet peak at 13.02 ppm fit with one NH proton, and two doublet peaks at 7.81 and 7.00 ppm with $J = 15.6$ Hz, both peaks fit with the two olefinic trans protons ($H_\beta$ and $H_\alpha$), respectively. Moreover, the $^{13}$C NMR spectrum clarified this structure.

In like manner, *p*-toluenesulfonamide derivative **7** was commenced by fusion of compound **2** with *p*-toluenesulphonyl chloride (Scheme 3). This structure was clearly supported by elemental analysis besides spectral data. The IR spectrum of compound **7** emerged in the presence of two bands at 1332 and 1205 cm$^{-1}$ corresponding to the $SO_2$ functional group. At the same time, the $^{1}$H NMR spectrum also emerged two singlet peaks at 13.21 and 2.28 ppm matching with NH and $CH_3$ protons, respectively, besides two additional doublet peaks in the aromatic region at 7.47 and 7.10 ppm corresponding to aryl protons of *p*-tolyl moiety. Also, $^{13}$C NMR spectrum of compound **7** revealed a peak at 20.8 ppm corresponding to methyl carbon.

After reaction of compound **2** with different electrophilic centers such as C=O and O=S=O, now we estimate the nucleophilicity of compound **2** with other electrophilic centers as C=S, namely phenyl isothiocyanate under the solvent-free condition to afford phenyl thiourea derivative **8** (Scheme 3).

The insertion of 3-iminoindolin-2-one moiety with compound **2** to give compound **9** was performed by fusion of compound **2** with isatin in the presence of drops of piperidine (Scheme 4). The IR spectrum of compound **9** unequivocally ascertained its structure by the appearance of the absorption band at 1712 cm$^{-1}$ characteristic for C=O of indolinone moiety.

The reaction of compound **2** with variant aryl aldehydes, namely 4-methoxybenzaldehyde and 4-(dimethylamino)benzaldehyde afforded Schiff bases **10a,b**, respectively. Both



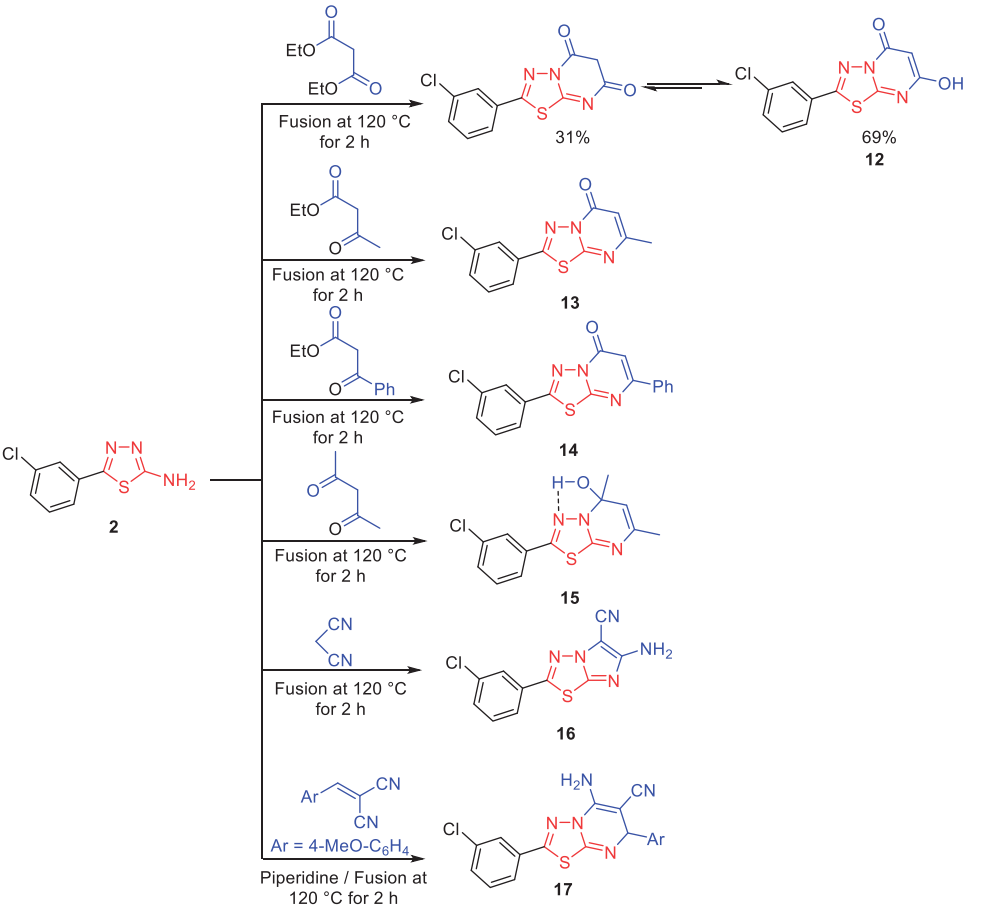

**Scheme 4.** Synthetic Pathway of compounds **9**–**11**.

Schiff bases were elucidated by the appearance of a singlet peak in $^1$H NMR spectra at 8.94 and 8.77 ppm corresponding to azo-methine protons.

Similarly, reaction of compound **2** with heteroaryl aldehyde exemplified by 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde afforded *N*-(5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)methanimine **(11)**. Also, this Schiff base unambiguously was determined by manifesting two singlet peaks in $^1$H NMR spectrum at 9.42, 8.91 ppm corresponding to $C_5$–$H_{(pyrazole)}$ and azo-methine protons, respectively.

Among our endeavors in this work, reaction of 2-aminothiadiazole derivative **2** with active methylene-containing reagents, for example, diethyl malonate, ethyl acetoacetate, ethyl benzoyl acetate, acetylacetone, malononitrile and arylidene malononitrile, to construct various fused-thiadiazole derivatives as shown in Scheme 5.

At this interesting point, the fusion of 2-aminothiadiazole derivative **2** with diethyl malonate afforded thiadiazolo[3,2-*a*]pyrimidinone derivative **12** (Scheme 5). The IR spectrum of compound **12** showed characteristic bands at 3425 and 1673 cm$^{-1}$ compatible with OH and C=O functionalities, respectively. Moreover, the $^1$H NMR spectrum of compound **12** in DMSO-$d_6$ solution manifested the presence of two singlet peaks at 12.99 (exchangeable with $D_2O$) and 3.91 ppm corresponding to OH proton for the enol tautomer and $CH_2$ protons for the keto tautomer. This means that it undergoes enol-




**Scheme 5.** Synthetic Pathway of compounds **12–17**.

keto isomerization (prototropy) and it is comprising of a diasteromeric mixture of enol-keto tautomers (prototopic tautomers) in the ratio (69:31) as depicted in scheme 5.

The reaction of 2-aminothiadiazole derivative **2** with ethyl acetoacetate gave 7-methyl thiadiazolo[3,2-*a*]pyrimidinone **13** in an excellent yield (81%). The structure of **13** was interpreted depending on variant spectroscopic data and elemental analysis. For example, the $^{1}$H NMR spectrum revealed two singlet peaks at 6.47 and 2.63 ppm corresponding to $C_6$–$H_{(thiadiazolopyrimidinone)}$ and methyl protons, respectively.

Similarly, 2-(3-chlorophenyl)-7-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **(14)** was commenced by fusion of 2-aminothiadiazole derivative **2** with ethyl benzoylacetate in a sand bath.

The reaction of compound **2** with *β*-diketone, namely acetylacetone awarded thiadiazolopyrimidine derivative **15** as the sole product (Scheme 5). The predictable structure of **15** was confirmed *via* the IR spectrum which exhibited the stretching absorption band at 3387 cm$^{-1}$ compatible with the OH group. Moreover, the $^{1}$H NMR spectrum of compound **15** manifested three singlet peaks at 6.88, 2.42 and 1.90 ppm compatible with $C_6$–$H_{(thiadiazolopyrimidinone)}$ and two methyl protons, respectively, and the hydroxyl proton appeared as a broad peak at a higher deshielded chemical shift due to the formation of intramolecular chelation H-bonding in the five-membered ring as shown in scheme 5. Moreover, the $^{13}$C NMR spectrum exhibited peaks at 93.1, 25.4 and 23.2 ppm compatible with the saturated ($Sp^3$) C–OH and two methyl carbons, respectively.

Noteworthy, the suggested mechanistic pathways for the formation of compounds **12**–**15** are illustrated with efficiency as shown in scheme 6.

In case of fusion of compound **2** with malononitrile absolutely gave 6-amino-2-(3-chlorophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile **(16)**. The IR spectrum displayed an absorption band at 2206 cm$^{-1}$ corresponding to the conjugated cyano group. Furthermore, the $^{1}$H NMR spectrum showed a peak at 6.24 ppm (exchangeable with $D_2O$) which is in keeping with $NH_2$ protons.

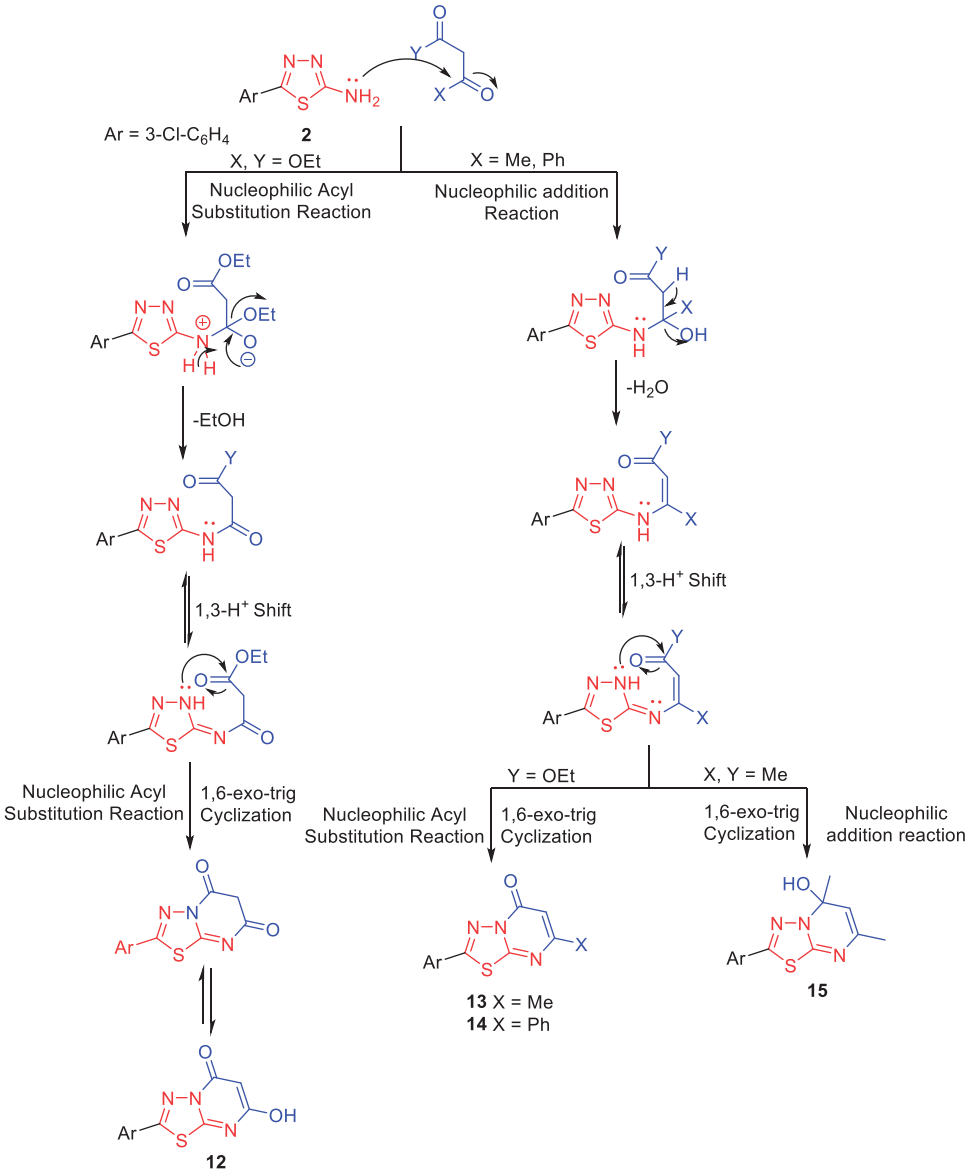
Ultimately, the reaction of compound **2** with 2-(4-methoxybenzylidene)malononitrile furnished thiadiazolopyrimidine derivative **17**.

## Insecticidal activity

### *Results and discussion*

In a continuation of our previous studies on searching about bioactive compounds bearing 1,3,4-thiadiazole moiety,[25,26] we report here on the insecticidal activity of some 1,3,4-thiadiazole derivatives.

The data presented in Table 1 and illustrated by Figure 2 showed the insecticidal activity of the synthesized thiadiazolyl amine and imine derivatives. From this result, we concluded that the Schiff base derivative **11** was the most potent compound against cotton leafworm *(Spodoptera littoralis)* where its $LC_{50}$ was (556.94 *μ*g/mL) and the least potent compound was the Schiff base derivative **10a** which recorded $LC_{50}$ of (735.97 *μ*g/mL). the other two derivatives are arranged in the following order **2** and **10b** where their $LC_{50}$ were 576.71 and 605.47 *μ*g/mL, respectively. $LC_{50}$ of a compound under investigation is calculated from Ldp curves in which the response percentages and the concentration of compounds in ppm are represented in the vertical and horizontal axes, respectively.




**Scheme 6.** The suggested mechanistic Pathways to compounds **12–15**.

**Table 1.** The insecticidal activity of newly synthesized thiadiazolyl amine and imine derivatives.

| | Concentration in ppm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | 250 | 500 | 750 | 1000 | 1250 | $LC_{50}$ | $LC_{90}$ | Toxicity index | Slope |
| **2** | 26.73 | 45.78 | 57.74 | 65.87 | 71.73 | 576.71 | 3235.37 | 23.809 | 1.711 |
| **10a** | 29.84 | 42.49 | 50.37 | 55.97 | 60.24 | 735.97 | 10064.51 | 18.654 | 1.128 |
| **10b** | 34.35 | 46.53 | 53.87 | 59.01 | 62.90 | 605.47 | 10178.47 | 22.652 | 1.046 |
| **11** | 28.90 | 47.02 | 58.19 | 65.78 | 71.27 | 556.94 | 3526.81 | 24.654 | 1.599 |

On considering the toxicity lines slope, we noticed that the slope decreases in the following order 1.711, 1.599, 1.128 and 1.046 for thiadiazoles **2, 11, 10a** and **10b**, respectively. This order revealed that the homologous response of treated strain of cotton

leafworm *(Spodoptera littoralis)* showed variation in its response toward the tested compounds to be in the following order **2** > **11** > **10a** > **10b**.

The tabulated data in Table 2 and exhibited by Figure 3 represented the insecticidal activity of the newly synthesized 1,3,4-thiadiazolo[3,2-*a*]pyrimidine and imidazo[2,1-b][1,3,4]thiadiazole derivatives against cotton leafworm *(Spodoptera littoralis)*. From this table, we showed that this class of compounds is the most potent derivatives among all the tested compounds, where they recorded the least values of $LC_{50}$. Also, we deduced that the thiadiazolopyrimidine derivatives **14** and **17** were the most potent synthesized compounds all over the tested compounds, where their $LC_{50}$ were 137.28 and 144.34 $\mu$g/mL, respectively. Table 2 also showed that imidazothiadiazole derivative **16** has more insecticidal activity than the other thiadiazolopyrimidine derivative **15** and the recorded $LC_{50}$ of both was 147.37 and 185.92 $\mu$g/mL on the sequence.

In contrast to the previous results and according to the slope value of the toxicity lines we concluded that the response of cotton leafworm *(Spodoptera littoralis)* was in the following order **16** > **17** > **15** > **14** where the slopes were 2.708. 2.509. 1.621 and 0.980, respectively.

The result tabulated in Table 3 and exhibited by Figure 4 represented the insecticidal activity of the newly synthesized thiadiazolyl amide derivatives against cotton leafworm *(Spodoptera littoralis)*. From the results, we obtained that thiadiazolyl cinnamamide derivative **6** has more potential activity than both thiadiazolyl acetamide **3** and thiadiazolyl benzamide **1** since the recorded $LC_{50}$ were 361.51, 520.50 and 548.11 $\mu$g/mL, respectively.

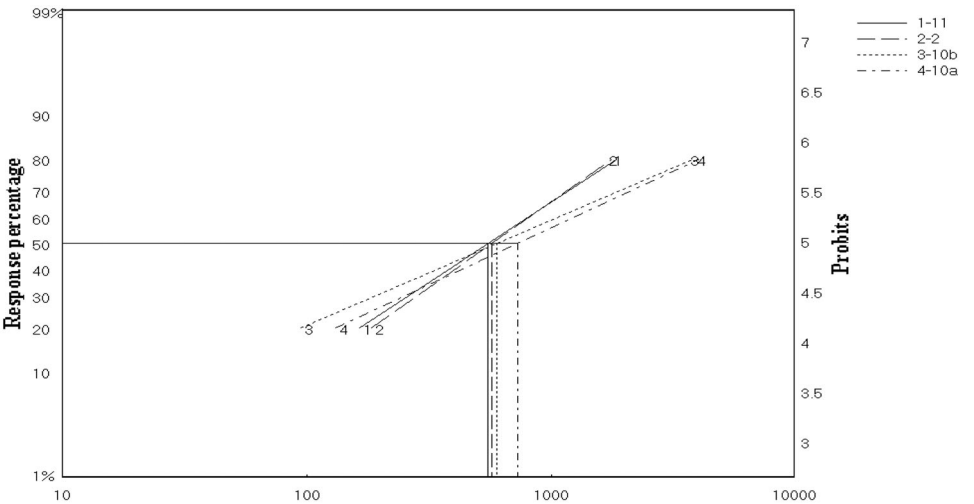



**Figure 2.** Ldp line of the newly synthesized thiadiazolyl amine and imine derivatives.

**Table 2.** The insecticidal activity of newly synthesized synthesized thiadiazolopyrimidine and carbonitrile derivatives.

| Compound | Concentration in ppm | | | | | $LC_{50}$ | $LC_{90}$ | Toxicity index | Slope |
|---|---|---|---|---|---|---|---|---|---|
| | 250 | 500 | 750 | 1000 | 1250 | | | | |
| **14** | 60.07 | 70.89 | 76.50 | 80.12 | 82.64 | 137.28 | 2789.06 | 100.00 | 0.980 |
| **15** | 58.26 | 75.69 | 83.69 | 88.18 | 91.01 | 185.92 | 1148.16 | 73.90 | 1.621 |
| **16** | 73.16 | 92.39 | 97.17 | 98.71 | 99.40 | 147.37 | 439.67 | 93.09 | 2.708 |
| **17** | 72.47 | 91.15 | 96.31 | 98.18 | 99.05 | 144.34 | 469.39 | 95.33 | 2.502 |

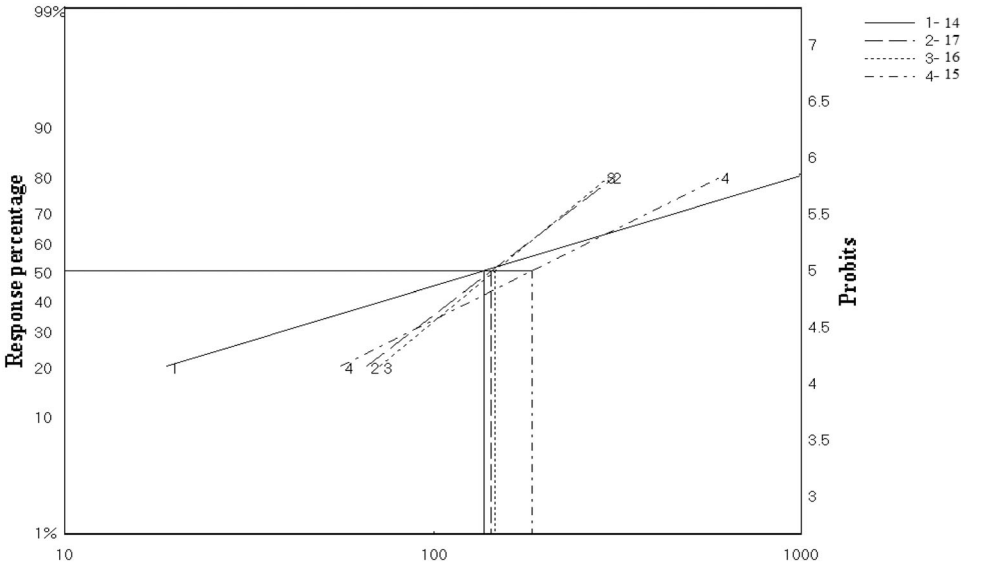



**Figure 3.** Ldp line of the newly synthesized thiadiazolopyrimidine and imidazothiadiazole derivatives.

**Table 3.** The insecticidal activity of newly synthesized thiadiazolyl amide derivatives.

| | Concentration in ppm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | 250 | 500 | 750 | 1000 | 1250 | $LC_{50}$ | $LC_{90}$ | Toxicity index | Slope |
| **1** | 31.25 | 47.73 | 57.74 | 64.59 | 69.61 | 548.11 | 4292.61 | 25.049 | 1.434 |
| **3** | 28.73 | 48.78 | 61.02 | 69.14 | 74.88 | 520.50 | 2776.58 | 26.281 | 1.763 |
| **6** | 43.98 | 55.29 | 61.78 | 66.18 | 69.47 | 361.51 | 8206.58 | 37.976 | 0.945 |

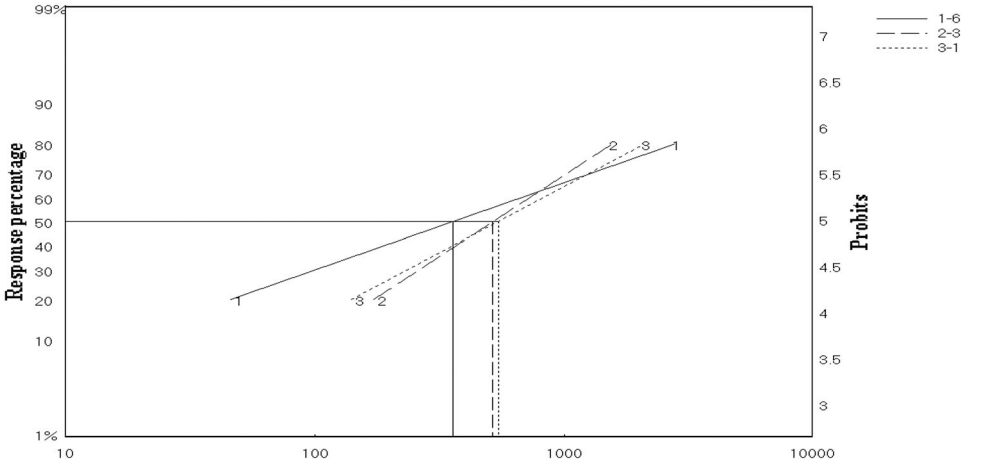



**Figure 4.** Ldp line of the newly synthesized thiadiazolyl amide derivatives.

The strain homogeneity has a great effect on the insecticidal activity results, this fact could be clear on studying the slope values of the toxicity which declared that, the treated strain of cotton leafworm *(Spodoptera littoralis)* showed a high response toward thiadiazolyl acetamide **3** followed by thiadiazolyl benzamide **1** and finally thiadiazolyl cinnamamide **6** as shown from the slope values 1.763, 1.434 and 0.945 on a sequence.

On concerning the data presented in Table 4 and illustrated by Figure 5 which represented the insecticidal activity of the newly synthesized thiadiazole derivatives containing pyrrolone moiety against cotton leafworm *(Spodoptera littoralis)*. We showed that as the concentration of the tested compound increases the mortality percent increases. Also, we deduced that compound **5** was the most active compound against the treated pest, where it recorded $LC_{50}$ of 275.47 $\mu$g/mL followed by compounds **9** and **4**, where they recorded $LC_{50}$ values of 332.78 and 410.14 $\mu$g/mL, respectively.

The slope of the toxicity revealed the overall response of the treated pest against the tested thiadiazole derivatives where it showed the homologous response in the order **4** > **9** > **5**, where the slopes were 2.398, 1.667 and 1.084 on rank order.

Table 5 and Figure 6 exhibited the insecticidal activity of thiadiazole derivatives containing (=S) against cotton leaf worms *(Spodoptera littoralis)*. This data showed that *p*-toluene sulfonamide derivative **7** was more potent than phenyl thiourea derivative **8** as given from the $LC_{50}$ values 466.72 and 513.68 $\mu$g/mL, respectively.

On the other hand, the order of homologous response is somewhat different to be compound **8** > **7** as a result of the slope values which are 1.666 and 1.158 on the sequence.

**Table 4.** The insecticidal activity of newly synthesized thiadiazole derivatives containing pyrrolone moiety.

| | Concentration in ppm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | 250 | 500 | 750 | 1000 | 1250 | $LC_{50}$ | $LC_{90}$ | Toxicity index | Slope |
| **4** | 30.30 | 58.18 | 73.52 | 82.33 | 87.71 | 410.14 | 1403.8 | 33.471 | 2.398 |
| **5** | 48.18 | 60.07 | 68.14 | 72.82 | 76.18 | 275.47 | 4187.14 | 48.951 | 1.084 |
| **9** | 41.80 | 61.59 | 72.18 | 78.71 | 83.09 | 332.78 | 1955.16 | 41.263 | 1.667 |

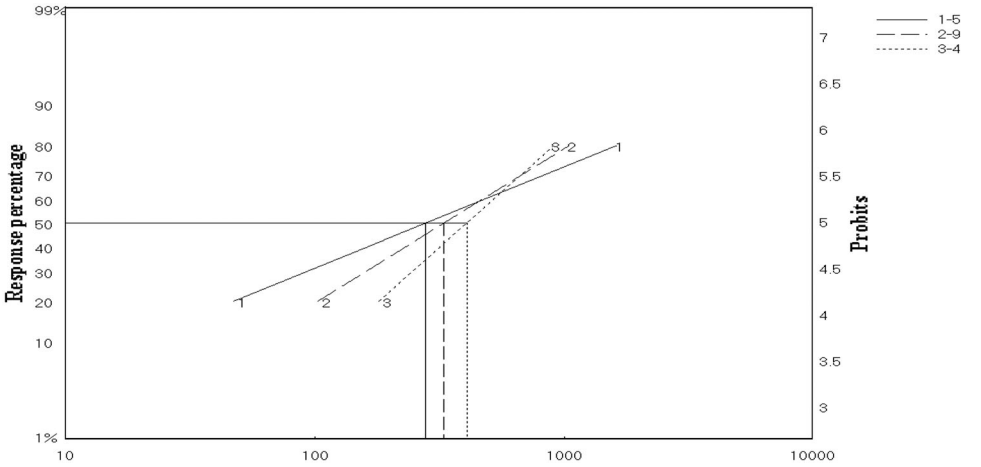



**Figure 5.** Ldp line of the newly synthesized thiadiazole derivatives containing pyrrolone moiety.

**Table 5.** The insecticidal activity of newly synthesized thiadiazole derivatives containing (=S).

| | Concentration in ppm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | 250 | 500 | 750 | 1000 | 1250 | $LC_{50}$ | $LC_{90}$ | Toxicity index | Slope |
| **7** | 37.68 | 51.38 | 59.43 | 64.93 | 69.01 | 466.72 | 5963.92 | 29.422 | 1.158 |
| **8** | 30.12 | 49.22 | 60.79 | 68.51 | 74.01 | 513.68 | 3020.12 | 26.728 | 1.666 |

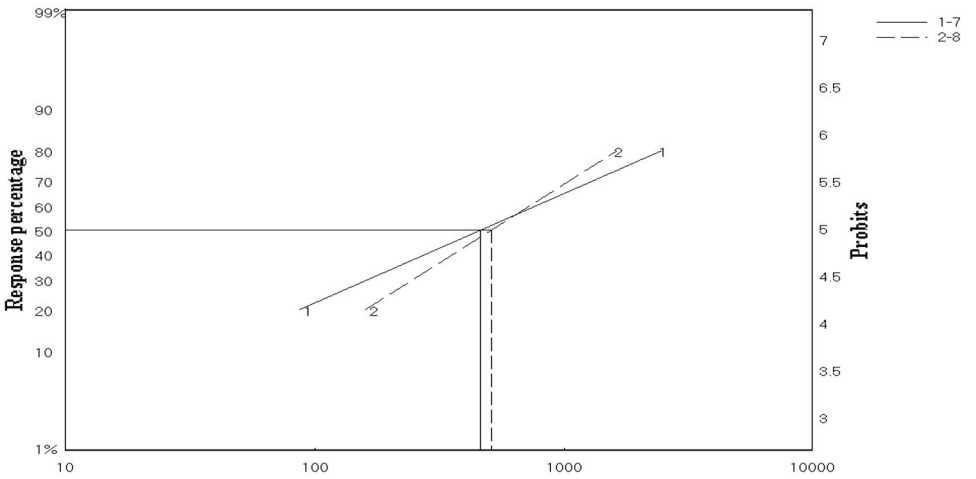



**Figure 6.** Ldp line of the newly synthesized thiadiazole derivatives containing (=S).

On studying the results of the toxicity index, we declared that the thiadiazolopyrimidine and imidazothiadiazole possess the highest insecticidal activity toward cotton leafworm *(Spodoptera)* followed by thiadiazole derivatives containing pyrrolone moiety and the least insecticidal activity showed with thiadiazolyl amine and imine derivatives. The order of the insecticidal activity for synthesized thiadiazole derivatives with respect to toxicity index was as follows **14 > 17 > 16 > 15 > 5 > 9 > 6 > 4 > 7 > 8 > 3 > 1 > 11 > 2 > 10b > 10a.** This order may be attributed to the presence of substituent or ring system as thiadiazolopyrimidine, imidazothiadiazole and pyrrolone rings, carbonyl group (C=O) and cyano group (CN) which act to stabilize the strong aromaticity of the ring, which also provides great in vivo stability to this five-membered ring system and low toxicity for higher vertebrates, including human beings which also, potentiates the = N–C–S moiety of the thiadiazole ring where It is supposed that 1,3,4-thiadiazole derivatives exhibit various biological activities due to the presence of this = N–C–S moiety.[43–46]

## Conclusion

In conclusion, various mixed-heterocyclic compounds incorporating 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives were synthesized under solvent-free conditions. The synthesized compounds were evaluated for their insecticidal activity against cotton leaf worms (*Spodoptera littoralis*). The results indicated that 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives displayed remarkable results more than 1,3,4-thiadiazole derivatives against cotton leafworm (*Spodoptera littoralis*).

Full experimental details and spectroscopic data for all synthesized compounds could be found *via* the "Supplementary Content" section of this article's webpage.

## Experimental

All reactions were followed by thin-layer chromatography (TLC) (Kieselgel 60 $F_{254}$, Merck, Darmstadt, Germany) and under UV lamp (Thomas Scientific, Swedesboro,

New Jersey, USA) (254 nm) spots were seen. The melting points of the newly synthesized compounds were measured by Mel-Temp II melting point apparatus and are uncorrected. IR spectra were recorded in KBr disk on Nicolet iS10 FT-IR spectrometer (Thermo Scientific, Waltham, USA). The $^{1}$H-NMR (at 300 MHz) and $^{13}$C-NMR (at 75 MHz) spectra were implemented on a Varian Gemini spectrometer (International Equipment Trading Ltd., Mundelein, Illinois, USA) in DMSO-$d_6$ as a solvent by using tetramethylsilane (TMS) as a reference at Faculty of Science, Cairo University, Giza, Egypt. Elemental analysis was performed on Perkin-Elmer 2400 CHN elemental analyzer (PerkinElmer, Inc., Waltham, USA). The mass spectrum was performed on Shimadzu GC-MS QP1000EX apparatus (Shimadzu, Kyoto, Japan) at the Faculty of Science, El-Azhar University, Cairo, Egypt. Evaluation of the insecticidal activity was implemented at Central Agricultural Pesticide Lab., Pesticide Formulations Department, Agricultural Research Center, Giza, Egypt.

### 3-Chloro-N-(5-(3-chlorophenyl)-1,3,4-thiadiazol-2-yl)benzamide 1

#### Method a

A mixture of *m*-chlorobenzoic acid (1.56 g, 0.01 mol) and phosphorus oxychloride (15 ml) was refluxed for 15 min, then thiosemicarbazide (0.91 g, 0.01 mol) was added, afterward the reflux was persistent for 3 h, then the reaction mixture was cooled and 5 ml of water was added drop by drop and then the reflux was persistent for 45 min. After cooling, the reaction mixture was poured onto cooled water containing pieces of ice, then the mixture was neutralized by NaOH (40%) solution. The deposited solid was filtered off and washed well with water, dried and recrystallized from ethanol to give **1**, yield: 65%.

#### Method B

A mixture of 2-aminothiadiazole derivative **2** (2.11 g, 0.01 mol) and *m*-chlorobenzoyl chloride (1.28 ml) in pyridine (0.5 ml) was fused in the sand bath at 120 °C for 2 h. After cooling, the product was collected, dried and recrystallized from dioxane to give **1**, yield: 68%.

**1**: As yellow crystals; m.p.:248–250 °C. Anal. Calcd. for $C_{15}H_9Cl_2N_3OS$ (350.22): C, 51.44; H, 2.59; N, 12.00; S, 9.15. Found: C, 51.41; H, 2.55; N, 12.11; S, 9.12. FTIR (KBr, $\nu$/cm$^{-1}$): 3133 (NH), 1673 (C=O). MS *m/z* (%): 349 ($M^{\cdot+}$; 11.18). $^{1}$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 13.31 (s, 1H, NH, exchangeable with $D_2O$), 8.17 (s, 1H, Ar–H), 8.06 (d, 1H, Ar–H, $J = 8.0$ Hz), 8.01 (s, 1H, Ar–H), 7.92 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.72 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.61–7.53 (m, 3H, Ar–H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 169.1, 163.2, 154.7, 134.1, 133.8, 132.9, 132.4, 131.9, 131.3, 131.0, 129.2, 127.8, 126.3, 125.4, 125.0.

5-(3-Chlorophenyl)-1,3,4-thiadiazol-2-amine 2[42]. A mixture of *m*-chlorobenzoic acid (1.56 g, 0.01 mol) and phosphorus oxychloride (15 ml) was refluxed for 15 min, then thiosemicarbazide (1.8 g, 0.02 mol) was added, afterward, the reflux was persistent for 3 h, then the reaction mixture was cooled and 8 ml of water was added drop by drop and then the reflux was persistent for 3 h. After cooling, the reaction mixture was poured onto cooled water containing pieces of ice, then the mixture was neutralized by NaOH (40%) solution.

The deposited solid was filtered off and washed well with water, dried and recrystallized from ethanol to give **2** as yellow crystals; m.p.:175–177 °C (Lit. m.p.: 212v214 °C)[42], yield: 85%. Anal. Calcd. for $C_8H_6ClN_3S$ (211.67): C, 45.40; H, 2.86; N, 19.85; S, 15.15. Found: C, 45.38; H, 2.83; N, 19.89; S, 15.22. FTIR (KBr, $\nu$/cm$^{-1}$): 3383, 3299 ($NH_2$), 1664 (C = N), 1618 (C = C). MS *m/z* (%): 211.34 ($M^{\cdot+}$;18.70). $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 7.89 (d, 1H, Ar–H, $J$ = 6.6 Hz), 7.79 (s, 1H, Ar–H), 7.07 (d, 1H, Ar–H, $J$ = 6.9 Hz), 7.56–7.47 (m, 3H, ((1H, Ar–H) + (2H, $NH_2$, exchangeable with $D_2O$)). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 169.0, 154.7, 133.7, 132.8, 130.9, 129.1, 125.4, 125.0.

## Insecticidal activity

### Materials and methods

#### Susceptible strain insect

In the current research, the cotton leafworm strain was taken from field colonies and reared in the central laboratory for agricultural pesticides. This strain was collected from the province of Sharkia. The strain was held at 25 ± 2 °C and 65 ± 5 percent relative humidity away from any chemical pressure under laboratory conditions.

#### Chemical used

The newly synthesized 1,3,4-thiadiazole and fused thiadiazole derivatives.

#### Method of bioassay technique

The effects on 4 instar larvae of cotton leafworm *(Spodoptera littoralis)* of the synthesized thiadiazole derivatives were determined to simulate the actual treatments under field conditions using the leaf dipping technique.[47] A stock solution of each chemical was freshly prepared. Subsequent water dilution was made to achieve serial concentrations of 250, 500, 750, 1000 and 1250 ppm. Fresh castor bean leaves were dipped in each concentration for ten seconds then left to dry. The treated leaves were transferred to petri-dishes and ten larvae were placed in each one then it was covered. Leaf disks immersed in distilled water as control treatment. On drying, the leaf disks were placed in individual Petri dishes (9-cm diameter). Each treatment (concentration) was replicated 3 times, including water solvent control. Ten of the 4$^{th}$ instar larvae were placed on each leaf disk (replication), and thus the total number of tested larvae per concentration was 30. Mortalities were recorded 24 h after insecticide treatment. Mortality data were corrected using Abbott's formula[48] and subjected to statistical analysis by the method of Finney.[49] The $LC_{50}$ and toxicity index were also estimated. Noteworthy, the toxicity index calculated according to the Yun-Pei Sun equation.[50]

$$\text{Toxicity index} = LC_{50}\text{of most potent compound}/LC_{50}\text{of tested compound} \times 100$$

## ORCID

Mahmoud F. Ismail http://orcid.org/0000-0002-9243-6236
Marwa S. Salem http://orcid.org/0000-0001-7237-6451

## References


[1] Magd El-Din, M.; El-Gengaihi, S. E. Joint Action of Some Botanical Extracts against the Egyptian Cotton Leafworm, *Spodoptera littoralis* (Boisd.) (Lepidoptera: Noctuidae). *Egypt. J. Biol. P. Cont.* **2000**, *10*, 51–56.

[2] El-Khawas, M. A. M.; Abd El-Gawad, H. A. S. The Efficiency of Two Plant Extracts (Fenugreek and Lupine) and Commercial Biofungicide (Biofly) on the Cotton Leafworm, *Spodoptera littoralis* (Boisd.) (Lepidoptera: Noctuidae) Larvae as a New Approach of Control. *J. Egypt. Ger. Soc. Zool.* **2002**, *37*, 39–57.

[3] Shonouda, M. L.; Osman, S. L. New Botanical Derivatives, Used in Medicinal Reparations, Showing Bioactive Action on Insect Pests.1 – Toxicological Effect on the Development of *Spodoptera littoralis* (Boisduval) (Lepidoptera: Noctuidae). *J. Egypt. Ger. Soc. Zool.* **2000**, *31*, 227–234.

[4] Hu, Y.; Li, C.-Y.; Wang, X.-M.; Yang, Y.-H.; Zhu, H.-L. 1,3,4-Thiadiazole: synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry. *Chem. Rev.* **2014**, *114*, 5572–5610. DOI: 10.1021/cr400131u.

[5] Gomha, S. M.; Muhammad, Z. A.; Al-Hussain, S. A.; Zaki, M. E. A.; Abdel-Aziz, H. M. Synthesis, Characterization, and Antimicrobial Evaluation of Some New 1,4-Dihydropyridine Hybrid with 1,3,4-Thiadiazole. *Polycycl. Aromat. Compd.* **2020**. DOI: 10.1080/10406638.2020.1804410.

[6] Rashdan, H. R. M.; Abdelmonsef, A. H.; Shehadi, I. A.; Gomha, S. M.; Soliman, A. M. M.; Mahmoud, H. K. Synthesis, Molecular Docking Screening and anti-Proliferative Potency Evaluation of Some New Imidazo[2,1-*b*]Thiazole Linked Thiadiazole Conjugates. *Molecules.* **2020**, *25*, 4997. DOI: 10.3390/molecules25214997.

[7] El-Enany, W. A. M. A.; Gomha, S. M.; El-Ziaty, A. K.; Hussein, W.; Abdulla, M. M.; Hassan, S. A.; Sallam, H. A.; Ali, R. S. Synthesis and Molecular Docking of Some New Bis-Thiadiazoles as anti-Hypertensive α-Blocking Agents. *Synth. Commun.* **2020**, *50*, 85–96. DOI: 10.1080/00397911.2019.1683207.

[8] Gomha, S. M.; Edress, M. M.; Muhammad, Z. A.; Gaber, H. M.; Amin, M. M.; Matar, I. K. Synthesis under Microwave Irradiation and Molecular Docking of Some Novel Bioactive Thiadiazoles. *MRMC.* **2019**, *19*, 437–447. DOI: 10.2174/1389557518666180329122317.

[9] Gomha, S. M.; Abdelrazek, F. M.; Abdelrahman, A. H.; Metz, P. Synthesis of Some New Pyridine-Based Heterocyclic Compounds with Anticipated Antitumor Activity. *J. Heterocyclic Chem.* **2018**, *55*, 1729–1737. DOI: 10.1002/jhet.3210.

[10] Gomha, S. M.; Abdelhamid, A. O.; Kandil, O. M.; Kandeel, S. M.; Abdelrehem, N. A. Synthesis and Molecular Docking of Some Novel Thiazoles and Thiadiazoles Incorporating Pyranochromene Moiety as Potent Anticancer Agents. *Mini. Rev. Med. Chem.* **2018**, *18*, 1670–1682. DOI: 10.2174/1389557518666180424113819.

[11] Gomha, S. M.; Edrees, M. M.; Muhammad, Z. A.; El-Reedy, A. A. 5-(Thiophen-2-yl)-1,3,4-Thiadiazole Derivatives: synthesis, Molecular Docking and In Vitro Cytotoxicity Evaluation as Potential Anticancer Agents. *DDDT.* **2018**, *12*, 1511–1523. DOI: 10.2147/DDDT.S165276.

[12] Gan, X.; Hu, D.; Chen, Z.; Wang, Y.; Song, B. Synthesis and Antiviral Evaluation of Novel 1,3,4-Oxadiazole/Thiadiazole-Chalcone Conjugates. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4298–4301. DOI: 10.1016/j.bmcl.2017.08.038.

[13] Othman, A. A.; Kihel, M.; Amara, S. 1,3,4-Oxadiazole, 1,3,4-Thiadiazole and 1,2,4-Triazole Derivatives as Potential Antibacterial Agents. *Arab. J. Chem.* **2019**, *12*, 1660–1675. DOI: 10.1016/j.arabjc.2014.09.003.

[14] Li, P.; Shi, L.; Gao, M.-N.; Yang, X.; Xue, W.; Jin, L.-H.; Hu, D.-Y.; Song, B.-A. Antibacterial Activities against Rice Bacterial Leaf Blight and Tomato Bacterial Wilt of 2-Mercapto-5-Substituted-1,3,4-Oxadiazole/Thiadiazole Derivatives. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 481–484. DOI: 10.1016/j.bmcl.2014.12.038.

[15] Kadi, A. A.; Al-Abdullah, E. S.; Shehata, I. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. Synthesis, Antimicrobial and anti-Inflammatory Activities of Novel 5-(1-Adamantyl)-1,3,4-Thiadiazole Derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 5006–5011. 45DOI: 10.1016/j.ejmech.2010.08.007.

[16] Juszczak, M.; Matysiak, J.; Szeliga, M.; Pożarowski, P.; Niewiadomy, A.; Albrecht, J.; Rzeski, W. 2-amino-1,3,4-Thiadiazole Derivative (FABT) Inhibits the Extracellular Signal-Regulated Kinase Pathway and Induces Cell Cycle Arrest in Human Non-Small Lung Carcinoma Cells. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5466–5469. DOI: 10.1016/j.bmcl.2012.07.036.

[17] Aliabadi, A.; Eghbalian, E.; Kiani, A. Synthesis and Evaluation of the Cytotoxicity of a Series of 1,3,4-Thiadiazole Based Compounds as Anticancer Agents. *Iran. J. Basic Med. Sci.* **2013**, *16*, 1133–1138.

[18] Mohammadi-Farani, A.; Heidarian, N.; Aliabadi, A. N-(5-Mercapto-1,3,4-Thiadiazol-2-yl)-2-Phenylacetamide Derivatives: Synthesis and In-Vitro Cytotoxicity Evaluation as Potential Anticancer Agents. *Iran. J. Pharm. Res.* **2014**, *13*, 487–492.

[19] Polkam, N.; Rayam, P.; Anireddy, J. S.; Yennam, S.; Anantaraju, H. S.; Dharmarajan, S.; Perumal, Y.; Kotapalli, S. S.; Ummanni, R.; Balasubramanian, S. Synthesis, In Vitro Anticancer and Antimycobacterial Evaluation of New 5-(2,5-Dimethoxyphenyl)-1,3,4-Thiadiazole-2-Amino Derivatives. Bioorg. *Med. Chem. Lett.* **2015**, *25*, 1398–1402. DOI: 10.1016/j.bmcl.2015.02.052.

[20] Dawood, K. M.; Gomha, S. M. Synthesis and Anticancer Activity of 1,3,4-Thiadiazole Derivatives Having 1,3,4-Oxadiazole Moiety. *J. Heterocyclic Chem.* **2015**, *52*, 1400–1405. DOI: 10.1002/jhet.2250.

[21] Raj, V.; Rai, A.; Saha, S. Human Cancer Cell Line Based Approach of 1,3,4-Thiadiazole and Its Fused Ring: A Comprehensive Review. *Anticancer Agents Med. Chem.* **2017**, *17*, 500–523. DOI: 10.2174/1871520616666161013150151.

[22] Raj, V.; Rai, A.; Singh, M.; Kumar, R.; Kumar, A.; Kumar, V. Recent Update on 1,3,4-Thiadiazole Derivatives: As Anticonvulsant Agents. *EC Pharm. Sci.* **2015**, *2*, 202–229.

[23] Can, N. Ö.; Can, Ö. D.; Osmaniye, D.; Demir, Ö. Ü. Synthesis of Some Novel Thiadiazole Derivative Compounds and Screening Their Antidepressant-like Activities. *Molecules* **2018**, *23*, 716. DOI: 10.3390/molecules23040716.

[24] Alegaon, S. G.; Hirpara, M. B.; Alagawadi, K. R.; Hullatti, K. K.; Kashniyal, K. Synthesis of Novel Pyrazole–Thiadiazole Hybrid as Potential Potent and Selective Cyclooxygenase-2 (COX-2) Inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5324–5329. DOI: 10.1016/j.bmcl.2014.08.062.

[25] Madkour, H. M. F.; Azab, M. E.; Aly, A. F.; Khamees, M. S. M. Novel Heterocycles Based on 1,3,4-Thiadiazole Scaffold as Insecticides. *J. Environ. Sci.* **2017**, 40, 19–44.

[26] Mohamed, A. M. M.; Ismail, M. F.; Madkour, H. M. F.; Aly, A. F.; Salem, M. S. Straightforward Synthesis of 2-chloro-*N*-(5-(Cyanomethyl)-1,3,4-Thiadiazol-2-yl)Benzamide as a Precursor for Synthesis of Novel Heterocyclic Compounds with Insecticidal Activity. *Synth. Commun.* **2020**, *50*, 3424–3442. DOI: 10.1080/00397911.2020.1802652.

[27] Fadda, A. A.; El Salam, M. A.; Tawfik, E. H.; Anwar, E. M.; Etman, H. A. Synthesis and Insecticidal Assessment of Some Innovative Heterocycles Incorporating a Thiadiazole Moiety against the Cotton Leafworm, *Spodoptera littoralis*. *RSC Adv.* **2017**, *7*, 39773–39785. DOI: 10.1039/C7RA06087D.

[28] Dai, H.; Li, G.; Chen, J.; Shi, Y.; Ge, S.; Fan, C.; He, H. Synthesis and Biological Activities of Novel 1,3,4-thiadiazole-containing pyrazole oxime derivatives. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3818–3821. DOI: 10.1016/j.bmcl.2016.04.094.

[29] Li, Z. S.; Wang, W. M.; Lu, W.; Niu, C. W.; Li, Y. H.; Li, Z. M.; Wang, J. G. Synthesis and Biological Evaluation of Nonsymmetrical Aromatic Disulfides as Novel Inhibitors of Acetohydroxyacid Synthase. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3723–3727. DOI: 10.1016/j.bmcl.2013.05.013.

[30] Abdel Rahman, D. E.; Mohamed, K. O. *Der Pharma Chemica* **2014**, *6*, 323–335.

[31] Taher, A. T.; Georgey, H. H.; El-Subbagh, H. I. Novel 1,3,4-heterodiazole Analogues: Synthesis and In-Vitro Antitumor Activity. *Eur. J. Med. Chem.* **2012**, *47*, 445–451. DOI: 10.1016/j.ejmech.2011.11.013.

[32] El-Sayed, N. S.; El-Bendary, E. R.; El-Ashry, S. M.; El-Kerdawy, M. M. Synthesis and Antitumor Activity of New Sulfonamide Derivatives of Thiadiazolo [3,2-a] Pyrimidines. *Eur. J. Med. Chem.* **2011**, *46*, 3714–3720. DOI: 10.1016/j.ejmech.2011.05.037.

[33] Hossion, A. M. L.; Islam, R.; Kandahary, R. K.; Nagamatsu, T. Synthesis and Chemoselective N- and O-Alkylation of Thiadiazolopyrimidine Nucleosides and Uridines. *Synthesis.* **2009**, *2009*, 2689–2696. DOI: 10.1055/s-0029-1216882.

[34] Saeed, S.; Rashid, N.; Jones, P. G.; Tahir, A. J. Synthesis and Pharmacological Properties of N-Substituted-N′-(4,6-Dimethylpyrimidin-2-yl)-Thiourea Derivatives and Related Fused Heterocyclic Compounds. *J. Heterocyclic Chem.* **2011**, *48*, 74–82. DOI: 10.1002/jhet.510.

[35] Coburn, R. A.; Glennon, R. A.; Chmielewicz, Z. F. Mesoionic Purinone Analogs. 7. In Vitro Antibacterial Activity of Mesoionic 1,3,4-Thiadiazolo[3,2-a] Pyrimidine-5,7-Diones. *J. Med. Chem.* **1974**, *17*, 1025–1027. DOI: 10.1021/jm00255a029.

[36] Wang, M. R.; Jiang, L.; Zhou, S. F.; Zhang, Z. Y.; Ji, Z. C. Ultrasound-Assisted Synthesis and Preliminary Bioactivity of Novel 2H-1,2,4-Thiadiazolo[2,3-a]Pyrimidine Derivatives Containing Fluorine. *Chin. Chem. Lett.* **2012**, *23*, 561–564. DOI: 10.1016/j.cclet.2012.03.005.

[37] Duan, L. P.; Zhao, Q. F.; Zhang, H. B. Novel 2H-[1,2,4]thiadiazolo[2,3-a]pyrimidine derivatives bearing chiral S(-)-2-(4-chlorophenyl)-3-methylbutyric acid moiety: Design, synthesis and herbicidal activity. *Arab. J. Chem.* 2010, *3*(4), 225–228.

[38] Mahmoud, M. R.; Shiba, S. A.; El-Ziaty, A. K.; Abu El-Azm, F. S. M.; Ismail, M. F. Synthesis and Reactions of Novel 2,5-Disubstituted 1,3,4-Thiadiazoles. *Synth. Commun.* **2014**, *44*, 1094–1102. DOI: 10.1080/00397911.2013.846381.

[39] Mahmoud, M. R.; Ismail, M. F. Recent Developments in Chemistry of 1,3,4-Thiadiazoles. *JAC.* **2014**, *10*, 2812–2842. DOI: 10.24297/jac.v10i6.5507.

[40] Zarei, M. One-Pot Synthesis of 1,3,4-Thiadiazoles Using Vilsmeier Reagent as a Versatile Cyclodehydration Agent. *Tetrahedron* **2017**, *73*, 1867–1872. DOI: 10.1016/j.tet.2017.02.042.

[41] Shahcheragh, S. M.; Habibi, A.; Khosravi, S. Straightforward Synthesis of Novel Substituted 1,3,4-Thiadiazole Derivatives in Choline Chloride-Based Deep Eutectic Solvent. *Tetrahedron Lett.* **2017**, *58*, 855–859. DOI: 10.1016/j.tetlet.2017.01.057.

[42] Guan, P.; Wang, L.; Hou, X.; Wan, Y.; Xu, W.; Tang, W.; Fang, H. Fang H. Improved Antiproliferative Activity of 1,3,4-Thiadiazole-Containing Histone Deacetylase (HDAC) Inhibitors by Introduction of the Heteroaromatic Surface Recognition Motif. *Bioorg. Med. Chem.* **2014**, *22*, 5766–5775. DOI: 10.1016/j.bmc.2014.09.039.

[43] Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. New Bis-Aminomercaptotriazoles and Bis-Triazolothiadiazoles as Possible Anticancer Agents. *Eur. J. Med. Chem.* **2002**, *37*, 511–517. DOI: 10.1016/s0223-5234(02)01358-2.

[44] Yousif, E.; Majeed, A.; Al-Sammarrae, K.; Salih, N.; Salimon, J.; Abdullah, B. Metal Complexes of Schiff Base: Preparation, Characterization and Antibacterial Activity. *Arab. J. Chem.* **2017**, *10*, S1639–S1644. DOI: 10.1016/j.arabjc.2013.06.006.

[45] Li, Y.; Geng, J.; Liu, Y.; Yu, S.; Zhao, G. Thiadiazole – A Promising Structure in Medicinal Chemistry. *Chem. Med. Chem.* **2013**, *8*, 27–41. DOI: 10.1002/cmdc.201200355.

[46] Wermuth, C. G.; Aldous, D.; Raboisson, P.; Rognan, D. *The Practice of Medicinal Chemistry*, 4th ed.; Academic Press, Elsevier: London, 2015; p 196.

[47] Ahmed, M. Observed Potentiation between Pyrethroid and Organophosphorus Insecticides for the Management of *Spodoptera litura* (Lepidoptera: Noctuidae). *Crop Prot.* **2009**, *28*, 264–268. DOI: 10.1016/j.cropro.2008.11.001.

[48] Abbott, W. S. A Method of Computing the Effectiveness of an Insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267. DOI: 10.1093/jee/18.2.265a.

[49] Finney, D. J. Statistical Methods in Biological Assay. *Probit Analysis*, 3rd ed.; Cambridge Univ. Press: London, 1952; p 333.

[50] Sun, Y.-P.; Hyman, J. Co., Denver, Colo. *J. Econ. Entomol.* **1950**, *43*, 45–53. DOI: 10.1093/jee/43.1.45.