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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

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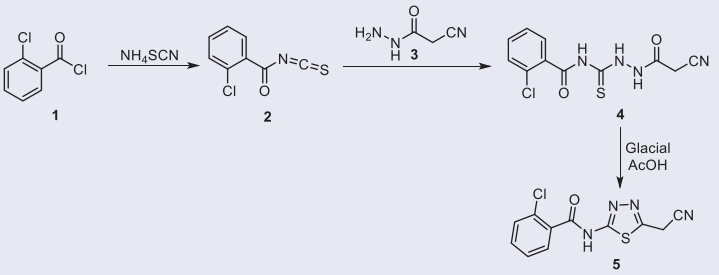
ABSTRACT

The current work is devoted to the synthesis of 2-chloro-*N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide **5** by an efficient synthetic methodology. The authors decided to exploit the reactivity of cyanomethylene functionality to construct new heterocycles hybrid with 1,3,4-thiadiazole moiety. These compounds have been structurally characterized with the aid of elemental analysis and spectroscopic techniques such as IR, ^{1}H and ^{13}C NMR and mass spectra. The synthesized compounds were evaluated for the insecticidal activity against cotton leaf worm (*spodoptera littoralis*). Among of them, compounds **7**, **10**, **12** and **17** showed much higher insecticidal activity. In particular, compound **12** exhibited the highest insecticidal activity.

GRAPHICAL ABSTRACT



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Aryl isothiocyanate; cyanoacetohydrazide; cyanomethylene moiety; insecticidal activity; 1,3,4-thiadiazole

Introduction

Nowadays, 1,3,4-thiadiazole is one of the essential motifs in agricultural, pharmaceutical, and environmental aspects because of their diverse biological activities, probably by virtue of the –N=C–S– group.[1,2] For examples, the 2,5-disubstituted-1,3,4-thiadiazoles[3,4] possess a broad spectrum of biological activities including antimicrobial,[5–10] antifungal,[11–14] antibacterial,[15,16] insecticidal,[17–21] acaricidal,[21] herbicidal,[22]

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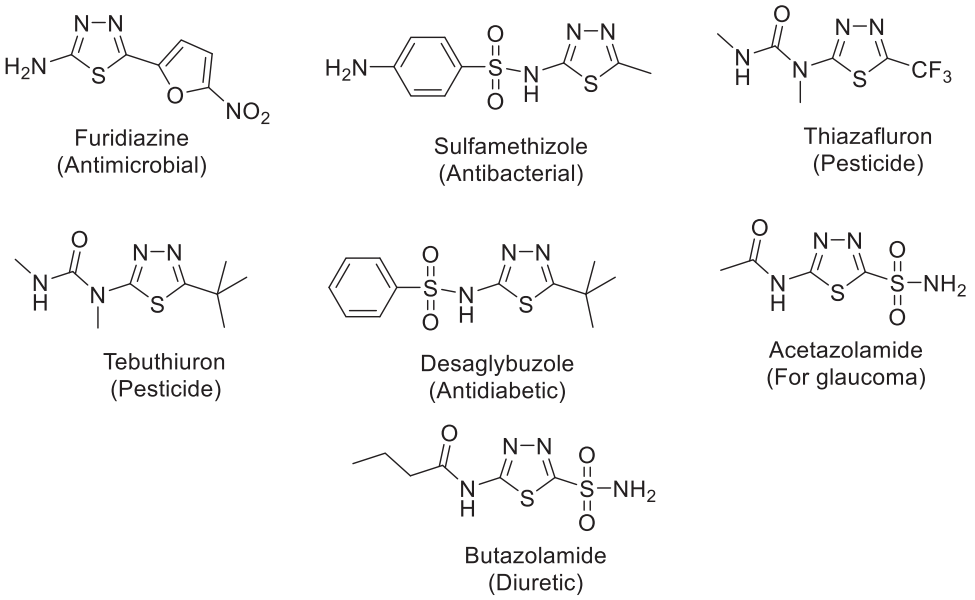


Figure 1. Commercially available 1,3,4-thiadiazol moiety in variant aspects.

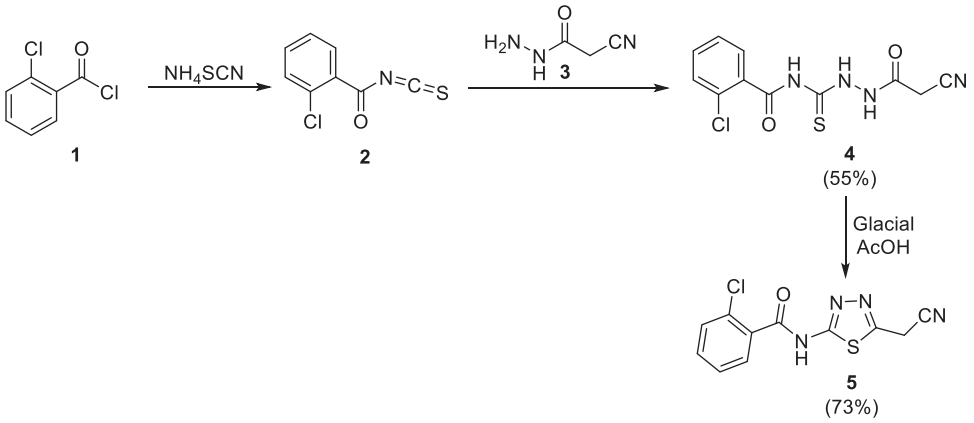
anticancer,[23–27] antioxidant,[28,29] antiviral,[30] analgesic,[31] anti-inflammatory,[32] antituberculosis,[33,34] anticonvulsant,[35,36] antidiabetic,[37] antidepressant,[38,39] anxiolytic,[39] antipsychotic,[40] antihypertensive,[41] antihistamine,[42] anti-hepatitis B viral,[43] antiproliferative[44] and antiparkinson.[45]

Commercially, 1,3,4-thiadiazole moiety participates in numerous fields such as Furidiazine (antimicrobial), Sulfamethizole (antibacterial), Thiazafluron (pesticide), Tebuthiuron (pesticide), Desaglybuzole (antidiabetic), Acetazolamide (for glaucoma), and Butazolamide (diuretic) as exemplified in Figure 1. According to their importance, this endowed us enormous impetus to study the insecticidal activity of the newly synthesized 1,3,4-thiadiazole derivatives.

The rational use of agrochemicals plays a pivotal role in agricultural production by effectively controlling plant diseases.[46–48] Unfortunately, due to the rapidly developing resistance of insects to pesticides[46] and their negative impacts on the environment,[18] the application of traditional pesticides is greatly limited.[18,47] Therefore, the discovery of new leading structures with ideal properties and environmentally friendly agrochemicals remains an arduous challenge in pesticide chemistry.[49,50]

To the best of our knowledge,[51–54] the 1,3,4-thiadiazole moiety has been synthesized using variant methods as described in the literatures.[3,4,55,56] Herein, the formation of 1,3,4-thiadiazole moiety was performed by combination of aryl isothiocyanate with cyanoacetohydrazide, followed by cyclization in glacial acetic acid.[3]

On the other hand, the requisite cyanomethylene unit possesses two neighboring reactive sites, one of them, the methylene group which act as a nucleophilic site in the presence of a base, and the other is the cyano group which act as an electrophilic site. Noteworthy, it plays a vital role as a key material in building another heterocyclic moiety beside 1,3,4-thiadiazole ring to study the insecticidal activity against cotton leaf



Scheme 1. The strategy pathway to synthesize 2-chloro-*N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**5**).

worm (*spodoptera littoralis*) for the newly compounds. By considering the facts aforementioned, 2-chloro-*N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide **5** was utilized as available precursor for performance novel 1,3,4-thiadiazole derivatives have bright prospects.

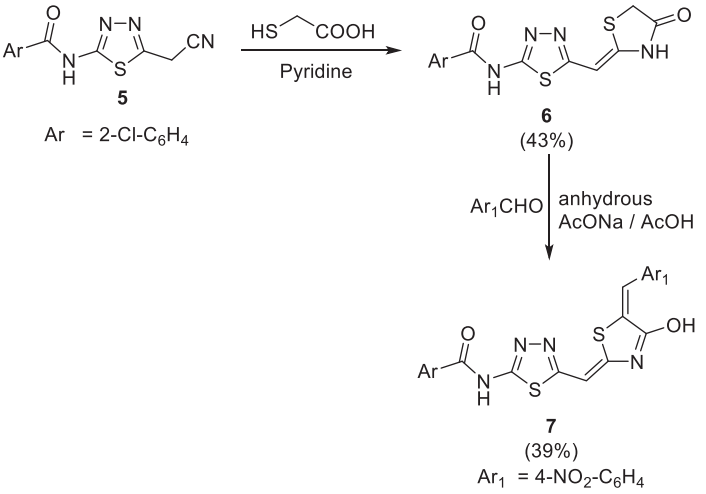
Results and discussion

Chemistry

The synthetic strategy was implemented for the synthesis of hitherto undocumented title compound as exemplified in Scheme 1. Stirring of 2-chlorobenzoyl chloride **1** with ammonium thiocyanate in dry acetonitrile afforded the 2-chlorobenzoyl isothiocyanate **2**, *in situ* cyanoacetohydrazide **3** was added on the later under stirring at ambient temperature, followed by refluxing of the engendered 2-chloro-*N*-(2-(2-cyanoacetyl)hydrazine-1-carbonothioyl)benzamide **(4)** in glacial acetic acid to afford 1,3,4-thiadiazole derivative **5** (Scheme 1).

The IR spectrum of compound **4** exhibited absorption bands for υ_{NH} at 3375 and 3217 cm^{-1}, $\upsilon_{C\equiv N}$ at 2257 cm^{-1}, $\upsilon_{C=O}$ at 1700 cm^{-1} and $\upsilon_{C=S}$ at 1244 cm^{-1}. Moreover, the ^{1}H NMR spectrum manifested the presence of three singlet peaks at 12.24, 12.11 and 11.21 ppm exchangeable with D_2O compatible with three NH protons, a multiplet peak at 7.60-7.41 ppm compatible with four aromatic protons and a singlet peak at 3.85 ppm compatible with CH_2 protons. Furthermore, the ^{13}C NMR spectrum showed three peaks at 178.0, 167.6 and 167.1 ppm corresponding to the carbons of C=S and two C=O groups, respectively.

On the other hand, the chemical structure of **5** was unequivocally elaborated by spectroscopic data and elemental analysis. For example, the ^{1}H NMR of compound **5** revealed only one singlet characteristic peak exchangeable with D_2O at 13.26 ppm corresponding to one NH proton and a singlet peak at $\delta = 4.61$ ppm corresponding to the methylene protons. Also, the ^{13}C NMR spectrum of compound **5** fits with the foreseeable structure.



Scheme 2. Synthetic pathway of compounds **6** and **7**.

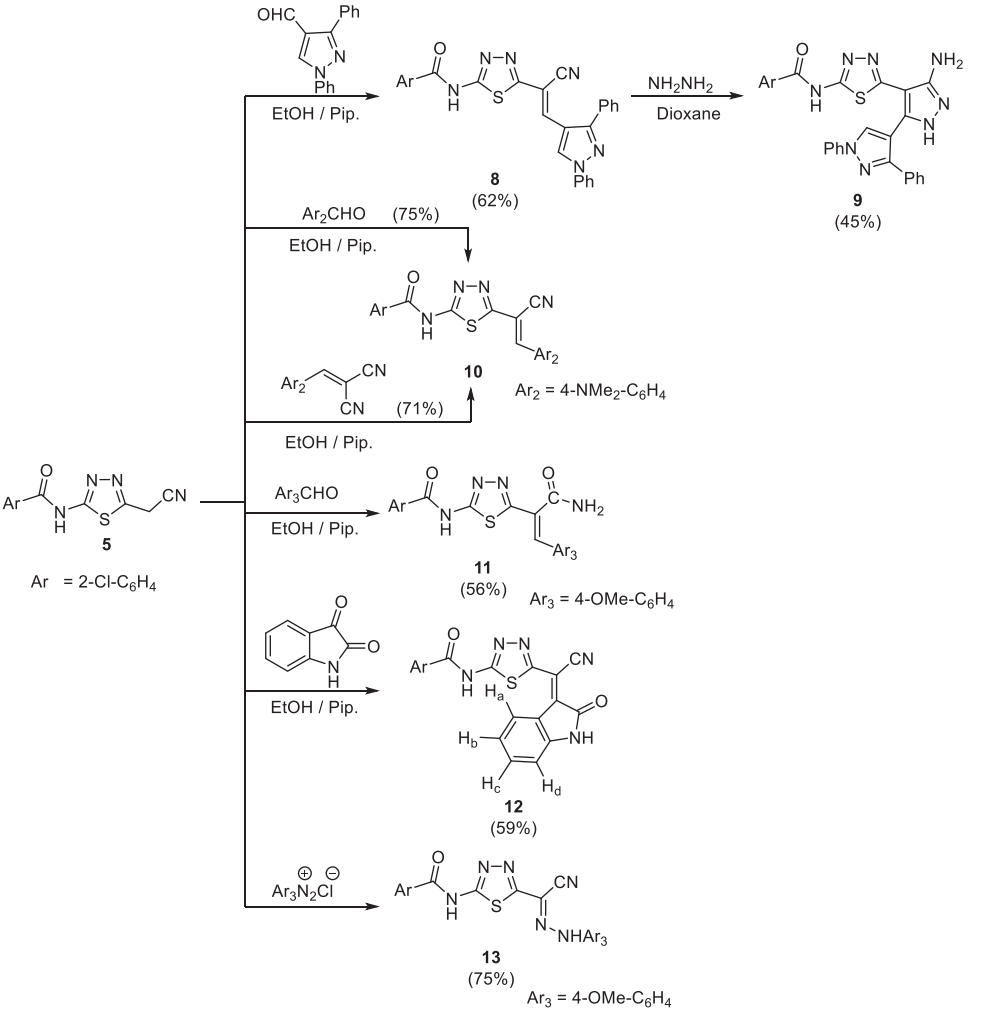
The reactivity of cyanomethylene moiety of compound **5** encouraged us to a robust approach for the synthesis of diverse novel heterocyclic compounds. Therefore, heterocyclization of **5** with thioglycolic acid in dry pyridine afforded the thiazolidinone derivative **6** (Scheme 2), which proved the reactivity of cyano group. The IR spectrum of **6** displayed a band at 1723 cm^{-1} corresponding to $C{=}O_{(thiazolidinone)}$ and lacked the stretching band for C≡N group. Furthermore, in DMSO-d_6 solution, the ^1H NMR spectrum of **6** unambiguously ascertained the chemical structure of it by the showing of two singlet peaks at 13.02 and 11.43 ppm corresponding to two NH protons exchangeable with D_2O and two singlet peaks at 6.36 and 3.94 ppm corresponding to olefinic and methylene protons, respectively. Moreover, the ^{13}C NMR spectrum of **6** manifested peaks at 173.7, 146.7 and 34.2 ppm compatible with the three carbons of thiazolidinone ring (C=O, CN(S), CH_2) and a peak at 90.0 compatible with the olefinic carbon.

The reactivity of the methylene group of the thiazolidinone ring of compound **6** was examined, through the reaction with *p*-nitrobenzaldehyde in the presence of anhydrous sodium acetate as a basic catalyst in glacial acetic acid, which afforded the condensed product **7** (Scheme 2). The mass spectrum of compound **7** showed M^+=485 (64.27%) corresponding to molecular formula $C_{20}H_{12}ClN_5O_4S_2$.

On the other hand, the reactivity of active methylene of the parent compound **5** was estimated with various electrophilic reagents, namely aromatic aldehyde, heterocyclic aldehyde, heterocyclic ketone, diazonium salt, arylidene malononitrile, phenyl isothiocyanate and carbon disulfide.

Practically, refluxing ethanolic mixture of compound **5** with heterocyclic aldehyde, namely 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde including drops of piperidine as a basic catalyst yielded the foreseeable condensed pyrazole derivative **8** as the sole product (Scheme 3). The IR spectrum of compound **8** exhibited a band at 2222 cm^{-1} characteristic for the conjugated nitrile group. Additionally, the ^1H NMR spectrum exhibited two singlet characteristic peaks at 9.22 and 7.95 ppm for C_5-$H_{(pyrazole)}$ and olefinic proton.

Hydrazinolysis of compound **8** with hydrazine monohydrate in boiling dioxane afforded 3,4′-bipyrazole derivative **9** (Scheme 3). The chemical structure of **9** was



Scheme 3. Synthetic pathway of compounds **8**–**13**.

elaborated by variant spectroscopic data and elemental analysis. The ^{1}H-NMR spectrum of compound **9** indicated the presence of extra signals and protons, as two singlet peaks at 9.12 and 8.68 ppm compatible with C_5-$H_{pyrazole}$ and a multiplet peak at 8.01–7.38 ppm compatible with twenty four aromatic protons beside two broad singlet peaks at 4.60 and 3.33 ppm (exchangeable with D_2O) corresponding to NH_2 protons, which indicated the presence of compound **9** in two atropisomers **9 A** and **9B**, because of the rotation of 1,3-diphenyl pyrazole ring around another pyrazole moiety about pivot bond was hindered[57] (Fig. 2).

Smoothly, reaction of **5** with either 4-(dimethylamino)benzaldehyde or 2-(4-(dimethylamino)benzylidene)malononitrile in ethanolic solution containing a catalytic amount of piperidine achieved the same condensed product **10** in an excellent yield as orange crystals

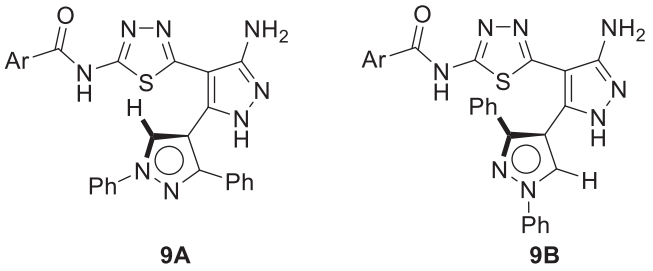


Figure 2. The atropisomers of compound **9**.

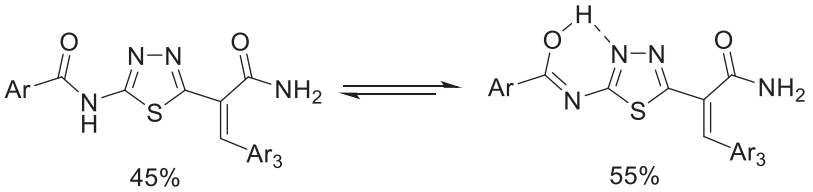


Figure 3. The lactam-lactim tautomers of compound **11**.

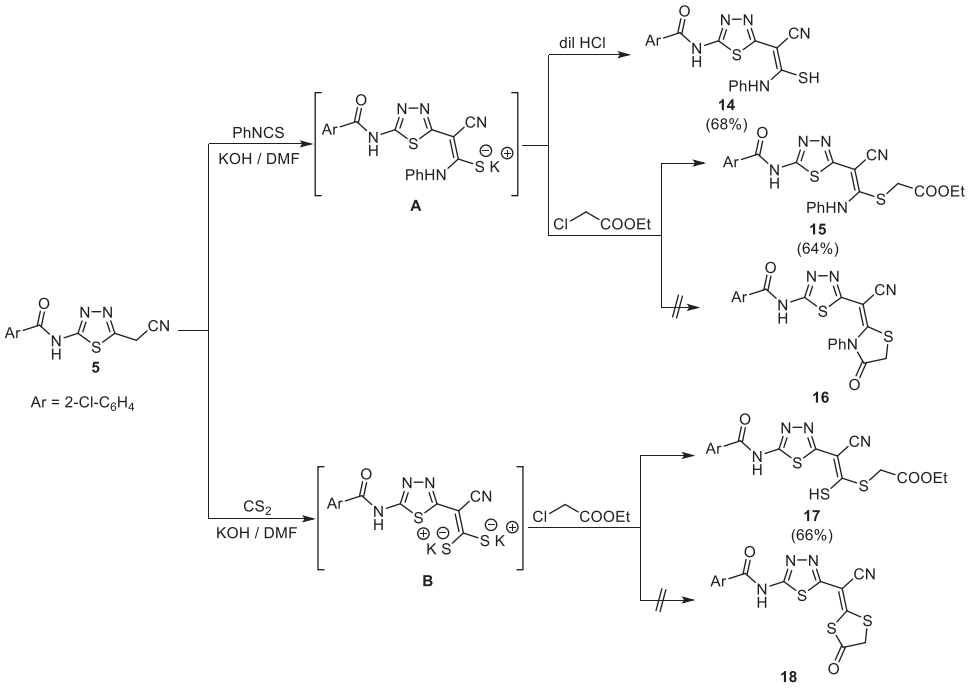
(Scheme 3). The chemical structure of **10** was ascertained on the fundaments of spectral and elemental data.

On the other hand, refluxing a mixture of compound **5**, *p*-anisaldehyde and drops of piperidine in ethanol afforded the condensed product **11** after partially hydrolyzed of the cyano group into the corresponding amide (Scheme 3). The ^{1}H NMR spectrum of compound **11** in DMSO-d_6 solution emerged the existence of it in lactam-lactim tautomers[57,58] in the ratio 45:55. The higher proportion of the lactim tautomer is due to the formation of intramolecular chelation H-bond in six membered ring as depicted in Figure 3.

The indolinone moiety **12** was emanated from the condensation of isatin with compound **5** at the active methylene group in ethanolic solution containing few drops of piperidine (Scheme 3). As a confirming of the proposed structure of **12**, the IR spectrum showed bands at 2223 and 1711 cm^{-1} corresponding to C≡N and $C{=}O_{(indolinone)}$ groups, respectively. Moreover, the ^{1}H NMR of compound **12** exhibited two singlet peaks at 13.50 and 11.27 ppm compatible with deshielded two NH protons, beside extra four protons in aromatic region characteristic to indolinone moiety.

The 2-carbohydrazonoyl cyanide **13** was commenced by stirring a mixture of compound **5**, *p*-anisidine diazonium chloride and anhydrous sodium acetate under cooling system in ethanol (Scheme 3). The IR of compound **13** manifested stretching absorption bands for υ_{NH} at 3245 and 3135 cm^{-1}, $\upsilon_{C\equiv N}$ at 2202 cm^{-1} and $\upsilon_{C=O}$ at 1692 cm^{-1}. Additionally, the ^{13}C NMR spectrum of **13** revealed peak at 55.7 ppm corresponding to the carbon of OMe group.

At ambient temperature, reaction of compound **5** with phenyl isothiocyanate in dimethyl formamide (DMF) containing KOH gave the intermediate **A**, *in situ* firstly acidification of the intermediate **A** with dil HCl awarded **14** as brown precipitate (Scheme 4). Secondly treatment of the intermediate **A** with ethyl chloroacetate afforded the uncyclized product **15** instead of the expected 1,3-thiazolidin-4-one moiety[59] **16**



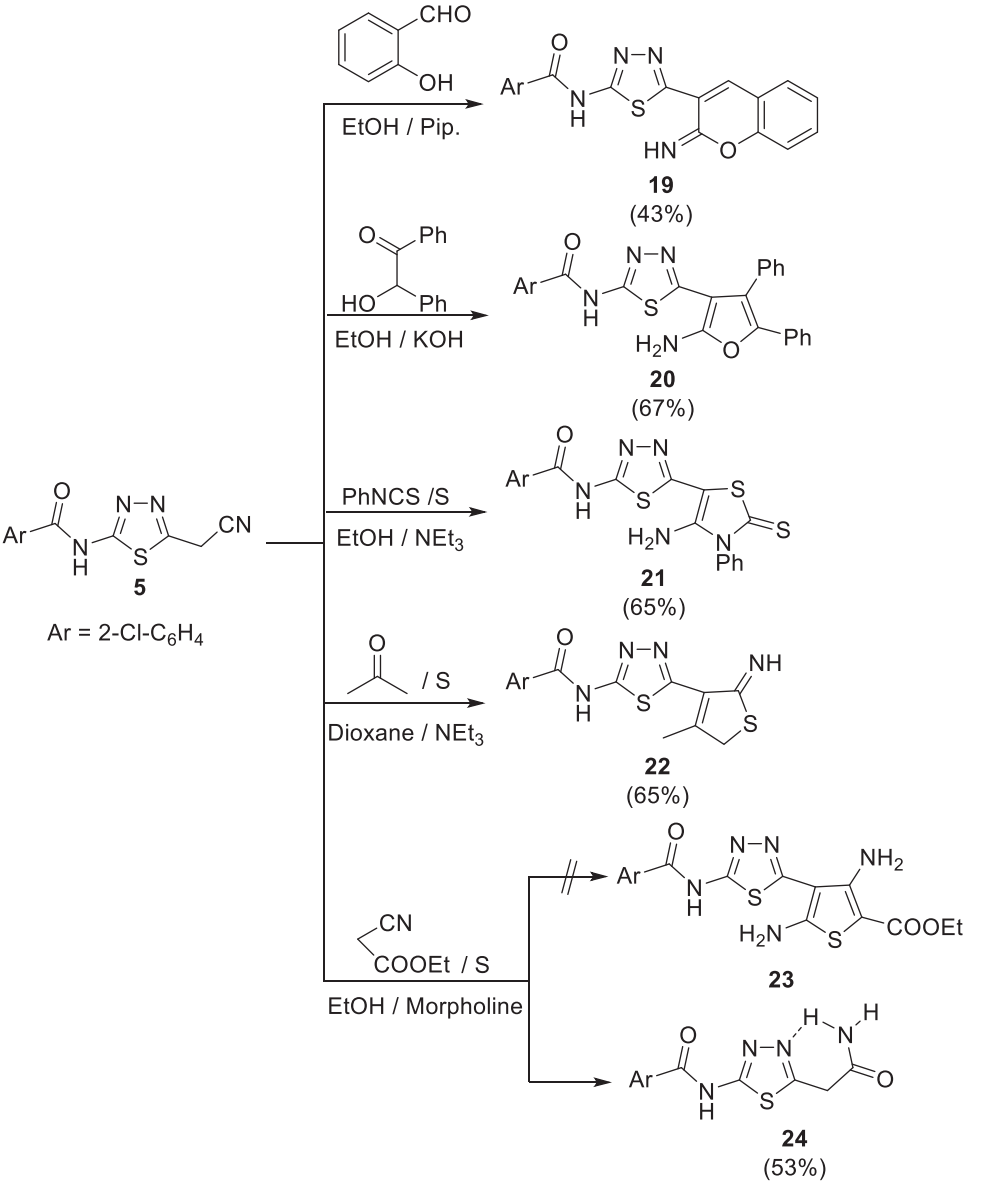
Scheme 4. Synthetic pathway of compounds **14**–**17**.

(Scheme 4), it was explained by the appearance of a broad peak which disappeared with D_2O corresponding to two NH protons at 13.20 ppm in the ^{1}H NMR spectrum beside the appearance of a quartet and a triplet signals at 4.19 and 1.21 ppm compatible with the ethyl protons of the ester group.

Similarly, the uncyclized product **17** was obtained instead of the 1,3-dithiolan-4-one moiety[60] **18** when the intermediate **B** was treated with ethyl chloroacetate, whereas, the intermediate **B** was obtained by stirring the target compound **5** with carbon disulfide in dimethyl formamide (DMF) containing KOH at ambient temperature (Scheme 4).

The proclivity of both cyano and methylene groups was investigated toward reagents having electrophilic and nucleophilic centers, for example, refluxing compound **5** with salicylaldehyde in the presence of few drops of piperidine as a base in ethanolic solution to give iminocoumarin derivative **19** (Scheme 5).[61] The structure **19** was supported by spectral data, whereas its IR spectrum lacked the absorption band of cyano group and its ^{1}H NMR spectrum exhibited the appearance of deshielded two NH protons at $\delta = 13.10$ and 9.05 ppm and a singlet peak at $\delta = 8.60$ ppm corresponding to C_4-$H_{(iminocoumarin)}$ beside the absence of a singlet peak of the methylene group.

Reaction of compound **5** with benzoin in ethanolic KOH was fluently done to afford the furan moiety **20** (Scheme 5). As well, affording of *N*-(5-(4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)-1,3,4-thiadiazol-2-yl)-2-chlorobenzamide **21** was emanated from refluxing a mixture of compound **5**, phenyl isothiocyanate and elemental sulfur in absolute ethanol under basic condition (triethyl amine) (Scheme 5). The foreseeable structure of **21** was ambiguously proven via inspection of the IR spectrum, which



Scheme 5. Synthetic pathway of compounds **19**–**24**.

exhibited the absorption band for $\upsilon_{C=S}$ at 1238 cm^{-1} and the absence of C≡N group. Additionally, the ^{1}H NMR spectrum conspicuously manifested a singlet peak at 6.60 ppm exchangeable with D_2O corresponding to NH_2 protons. Moreover, the ^{13}C NMR of **21** revealed a peak at 185.9 ppm compatible with the carbon of the thione group.

Treatment of a mixture of compound **5**, acetone and elemental sulfur in dioxane as a solvent containing triethyl amine as a base gave thiophen-2(5*H*)-imine moiety **22** (Scheme 5). The expected structure **22** was explicated by the disappearance of cyano group from the IR spectrum and the existence of two singlet peaks at 2.92 and 2.06 ppm corresponding to CH_2 and CH_3 groups, respectively. At the same time, the

Table 1. Insecticidal activity of arylidiene containing thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis*).

	Concentration in ppm								
Compounds	250	500	750	1000	1250	1500	LC_{50}	Toxicity index	Slope
7	39.16	56.69	66.57	72.98	77.48	80.83	384.26	85.45	1.474
8	32.51	54.92	67.77	75.83	81.23	85.05	431.02	76.18	1.917
10	36.81	58.24	70.08	77.42	82.33	85.80	383.78	85.56	1.810
11	25.51	46.95	60.40	69.33	75.57	80.11	547.79	59.94	1.933
12	41.16	63.48	75.07	81.92	86.32	89.33	328.34	100	1.886

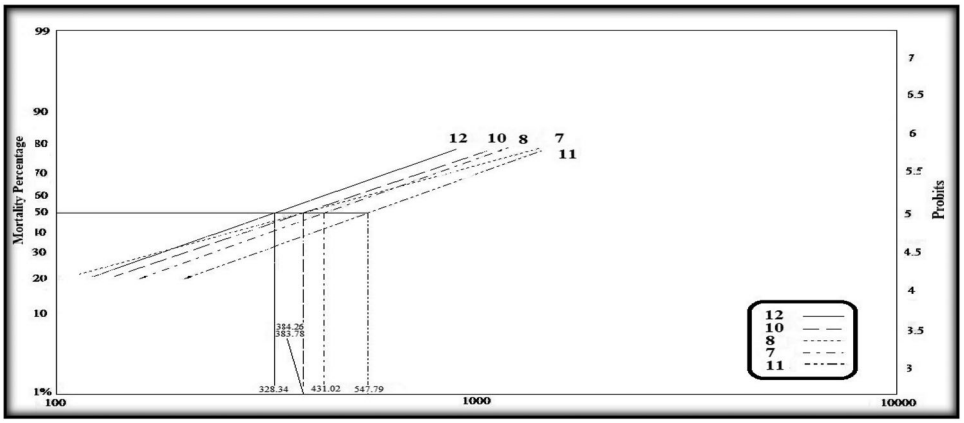


Figure 4. The Ldp line of the synthesized thiadiazole arylidiene derivatives.

mass spectrum recorded the molecular ion peak at $m/z = 350$ (22.71%) which is in keeping with its molecular formula $C_{14}H_{11}ClN_4OS_2$.

Unfortunately, refluxing of compound **5** with ethyl cyanoacetate and elemental sulfur in ethanol containing morpholine as a base furnished the corresponding amide derivative **24** instead of the prospective thiophene derivative[62] **23** (Scheme 5). On the basis of spectroscopic analyses, the formation of compound **23** was excluded, because of the absorption band of C = O of ester group does not exist in the IR spectrum, as well, the quartet and triplet peaks of ethyl group of ester were lacked in the ^{1}H NMR spectrum. Whereas the IR spectrum showed absorption bands at 3330 and 3140 cm^{-1} corresponding to υ_{NH2} and at 1687 cm^{-1} corresponding to $\upsilon_{C=O(amide)}$ with the absence of cyano group. Moreover, the ^{1}H NMR spectrum manifested a singlet peak at 3.96 ppm attributable to CH_2 protons and two singlet peaks exchangeable with D_2O at 7.76 and 7.25 ppm corresponding to NH_2 protons of amide, one of them more deshielded than the other because one proton became more deshielded due to it makes intramolecular H-bonding chelated in six-membered ring with the nitrogen atom of 1,3,4-thiadiazole ring. As well, the ^{13}C NMR spectrum of **24** is keeping with its chemical structure.

Insecticidal activity

The insecticidal activity of arylidene thiadiazole analogues against cotton leaf worm (*spodoptera littoralis*) was listed in Table 1 and the Ldp curves were shown by Figure 4. As it is clear from these data, we first showed that, as the treatment concentration

Table 2. Insecticidal activity of Sulfur containing thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis*).

	Concentration in ppm								
Compounds	250	500	750	1000	1250	1500	LC_{50}	Toxicity index	Slope
14	32.33	53.00	63.74	71.35	76.67	80.58	465.60	77.19	1.698
15	32.71	56.94	70.50	78.74	84.08	87.72	411.64	87.31	2.068
17	37.90	61.03	73.37	80.73	85.48	88.72	359.41	100.00	1.954

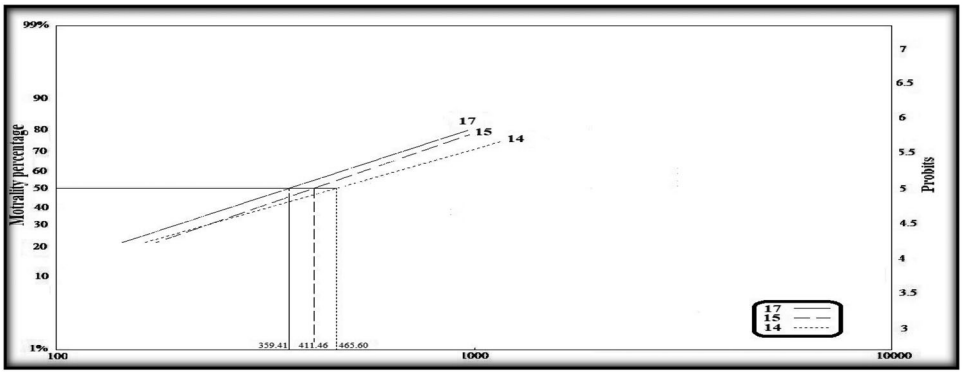


Figure 5. The Ldp line of the synthesized sulfur containing thiadiazole derivatives.

increase the insecticidal potency of the tested thiadizole derivatives also increase. It is also evident that, arylidene thiadiazole **12** was the most effective compound against target pest where this derivative recorded LC_{50} of 328.34 ppm. While compound **11** was the least effective compound and its LC_{50} was 547.79 ppm. We can now proceed analogously to the other compounds where they arranged as **10**, **7** and **8** with LC_{50} values 383.78, 384.26 and 431.02 ppm respectively. Concerning on the toxicity index values (Table 1), it is quite clear that the toxicity of **12** against (*spodoptera littoralis*) was 1.17-fold more toxic than both **10** and **7** and 1.3- and 1.6-fold more toxic than **8** and **11**, respectively.

Table 2 and Figure 5 plots the mortality percent versus the concentration of the treatment sulfur containing thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis).* The data revealed that the mortality percent is directly proportional to the treatment concentration of sulfur thiadiazole derivatives. From these data, it can be also concluded that, compound **17** was the most potent derivative among these categories of prepared thiadiazole derivatives where its LC_{50} was 359.41 ppm followed by compound **15** and finally **14** where their LC_{50} were 411.64 and 465.60 ppm on consequence. On the other hand, toxicity index of **17** was 1.15- and 1.3-fold more toxic than both **15** and **14** consecutively.

Data tabulated in Table 3 and depicted by Figure 6 illustrated the relation between mortality percent of the tested benzamide derivatives of the thiadiazole and its treatment concentration against cotton leaf worm (*spodoptera littoralis*). These data indicated that, there is a direct relationship between the treatment concentration of the benzamide thiadiazole derivatives and the mortality percent caused by these compounds. As shown in Table 3 and Figure 6, the mortality percent of this group of compounds are so close

Table 3. Insecticidal activity of some benzamide thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis*).

	Concentration in ppm								
Compounds	250	500	750	1000	1250	1500	LC_{50}	Toxicity index	Slope
4	30.00	36.67	53.33	60.00	66.67	76.67	647.08	81.40	1.584
5	26.67	40.00	56.67	63.33	70.00	82.00	605.85	86.93	1.863
13	22.53	42.97	56.38	65.55	72.11	76.98	618.50	85.16	1.918
21	26.54	48.26	61.69	70.51	76.64	81.07	526.69	100.00	1.937
24	26.00	44.00	58.00	65.00	78.00	91.00	553.99	95.07	2.225

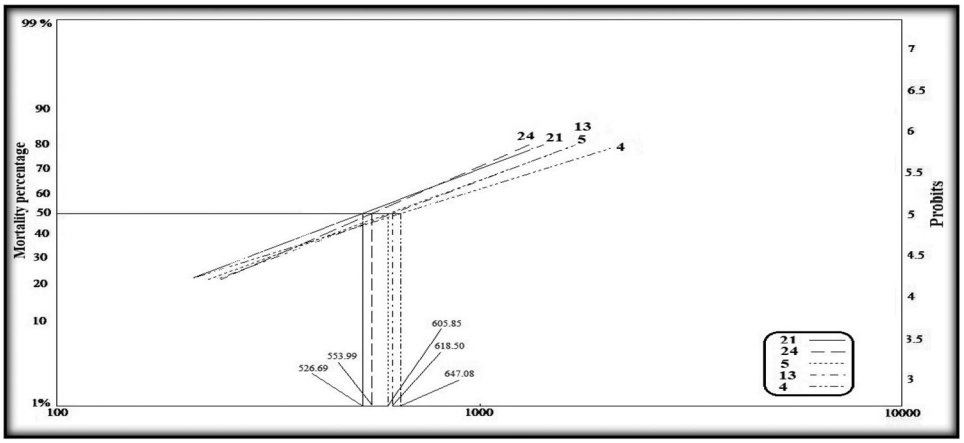


Figure 6. The Ldp line of the some synthesized benzamide thiadiazole derivatives.

Table 4. Insecticidal activity of some benzamide thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis*).

	Concentration in ppm								
Compounds	250	500	750	1000	1250	1500	LC_{50}	Toxicity index	Slope
6	11.55	27.73	40.68	50.65	58.38	64.48	981.70	73.00	2.017
9	14.46	32.90	46.75	56.93	64.55	70.39	821.94	87.18	2.050
19	14.00	31.51	44.77	56.64	62.14	67.97	873.56	82.03	1.989
20	11.44	28.25	41.76	52.10	60.06	66.28	943.60	75.94	2.087
22	17.56	37.51	51.61	61.60	68.88	74.34	716.60	100.00	2.039

to each other where the difference in LC_{50} values of the most effective compound **21** which recorded LC_{50} of 526.69 ppm and the least potent one **4** which recorded LC_{50} of 647.08 ppm is only 120.39 ppm. The other derivatives are arranged as follow **24**, **5** and **13** their LC_{50} were 553.99, 605.85 and 618.50 consecutively. From the toxicity index data, it was clear that **21** was more toxic by 1.07- to 1.3-fold than the other derivatives **24**, **5**, **13** and **4** respectively.

Table 4 and Figure 7 exhibited the insecticidal activity of the other benzamide thiadiazole derivatives against cotton leaf worm (*spodoptera littoralis)*. It is clear that, these compounds are the least potent than other benzamide derivatives and among the overall tested thiadiazole componds. Among these compounds the most functional derivative

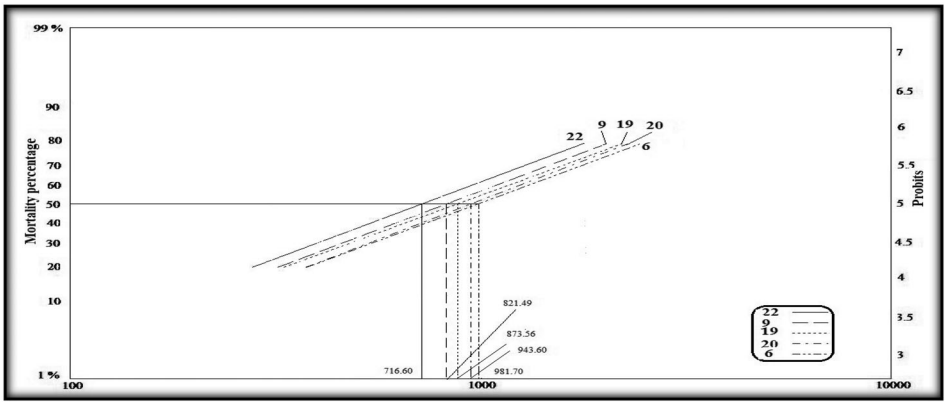


Figure 7. The Ldp line of the some synthesized benzamide thiadiazole derivatives.

was **22** where its LC_{50} was 716.60 ppm while the less influential one all over the overall experiment were **6** and **20** where their LC_{50} were 981.7 and 943.6 ppm, respectively. The rest of the tested compounds were **9** and **19** their LC_{50} were 821.94 and 873.56, respectively. Taking in consideration the toxicity index data, it was evident that compound **22** was 1.14- and 1.22-fold more toxic than **9** and **19**, while it was 1.34- and 1.37-fold more toxic than **20** and **6,** respectively.

In this study, the mortality percentage of eighteen tested thiadiazole derivatives **4** and **5**-**24** against cotton leaf worm (*spodoptera littoralis*) imply that the insecticidal activity of tested thiadiazole depends mainly on the substituent present on C-2 of thiadiazole moiety where the activity increases when substituents are group carrying electron withdrawing functional group as CN, C = O, *p*-NO_2 phenyl group, it is clear that as these groups become in direct attachment to the thiadiazole the insecticidal activity of the compound increase as in **12**, **17**, **15**, **24** and **10** as examples. Also, it was found that, the insecticidal activity decreased as the substituent on C-2 of thiadiazole is an electron rich group as *p*-metoxyphenyl, aminofuran, dihydrothiophene, iminochromone, thiazolidene and subimidazole moieties as in **11**, **20**, **22**, **19**, **6** and **9**.

Generally, the insecticidal potency of the thiadiazole results from its interference with the RNA in the processes of protein synthesis affected by the substituent position on thiadiazole ring, as the electron withdrawing of the substituents group, the bioactivity of the synthesized product also increases.[63] Finally, the bioactivity increases as the number of electron deficient groups increase and vice versa.

Conclusion

In summary, a novel of variant heterocyclic compounds incorporating 1,3,4-thiadiazole moiety were synthesized and characterized efficiently. Eighteen compounds were evaluated for their insecticidal activity against cotton leaf worm (*spodoptera littoralis*). The results of this evaluation imply that compounds **7**, **10**, **12** and **17** showed promising insecticidal activity. In particular, compound **12** emerged the most potent insecticidal activity.

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

Experimental

The melting points were measured by utilizing Mel-Temp II melting point apparatus and are uncorrected. IR spectra were recorded on Nicolet iS10 FT-IR spectrometer (Thermo Scientific, Waltham, USA) by using the KBr wafer technique in the region ($400-4000\,cm^{-1}$). The ^{1}H-NMR (at 400 MHz) and ^{13}C-NMR (at 100 MHz) spectra were implemented at chemical warfare labs, Cairo, Egypt, with a Varian Gemini spectrometer (International Equipment Trading Ltd., Mundelein, Illinois, USA) by using tetramethylsilane (TMS) as a reference in DMSO-d_6 as a solvent. CHN elemental analysis was performed on Perkin-Elmer 2400 CHN elemental analyzer (PerkinElmer, Inc., Waltham, USA at Faculty of Science, Cairo University, Egypt). The mass spectrum was performed on Shimadzu GC-MS QP1000EX apparatus (Shimadzu, Kyoto, Japan) at Faculty of Science, El-Azhar University, Cairo, Egypt. All reactions were monitored by thin layer chromatography (TLC) (Kieselgel 60 F_{254}, Merck, Darmstadt, Germany) and spots were visualized under UV lamp (Thomas Scientific, Swedesboro, New Jersey, USA) (254 nm). The insecticidal activity assays were carried out at Central Agricultural Pesticide Lab., Pesticide Formulations Department, Agricultural research Center, Giza, Egypt.

2-Chloro-N-(2-(2-cyanoacetyl)hydrazine-1-carbonothioyl)benzamide 4

A mixture of 2-chlorobenzoyl chloride **1** (1.75 ml, 0.1 mol) and ammonium thiocyanate (1.14 g, 0.15 mol) in 10 ml of acetonitrile was stirred at room temperature for 30 min, follow filtration, then cyanoacetohydrazid **3** (0.99 g, 0.1 mol) was added to the filtrate and 5 ml of acetonitrile was added, and the mixture was stirred at room temperature for 4 h. The solid formed was filtrated, dried and then recrystallized from ethanol to give **4** as white crystals; m.p.:193–195 °C, yield: 55%. Anal. Calcd. for $C_{11}H_9ClN_4O_2S$ (296.73): C, 44.53; H, 3.06; Cl, 11.95; N, 18.88; S, 10.80. Found: C, 44.39; H, 2.97; Cl, 11.91; N, 18.91; S, 10.79. FTIR (KBr, ν/cm^{-1}): 3375, 3217 (NH), 2953, 2915 (C–$H_{aliph.}$), 2257 (C≡N), 1700 (C=O), 1244 (C=S). MS *m/z* (%): 296 ($M^{\cdot+}$; 26.65). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.24 (*s*, 1H, NH, exchangeable with D_2O), 12.11 (*s*, 1H, NH, exchangeable with D_2O), 11.21 (*s*, 1H, NH, exchangeable with D_2O), 7.60–7.41 (*m*, 4H, Ar-H), 3.85 (*s*, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ (ppm): 178.0, 167.6, 167.1, 134.4, 132.6, 131.9, 130.3, 129.7, 128.0, 127.5, 25.0.

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

Compound **4** (2.96 g, 0.01 mol) was refluxed in glacial acetic acid (30 ml) for 4 h, the reaction mixture was poured onto ice cold water. The precipitated solid was filtered off, dried and then recrystallized from toluene to give **5** as white crystals; m.p.: 253–255 °C, yield: 73%. Anal. Calc. for $C_{11}H_7ClN_4OS$ (278.71): C, 47.40; H, 2.53; Cl, 12.72; N, 20.10; S, 11.50. Found: C, 47.34; H, 2.49; Cl, 12.76; N, 20.01; S, 11.43. FTIR (KBr, ν/cm^{-1}):

3160 (NH), 2942, 2915 (C–$H_{aliph.}$), 2255 (C≡N) 1667 (C = O). MS *m/z* (%): 279 ($M^{\cdot+}$+1;1.43). ^{1}H-NMR (DMSO-d_6) δ (ppm): 13.26 (*s*, 1H, NH, exchangeable with D_2O), 7.69–7.67 (d, 1H, Ar-H, J = 7.3 Hz), 7.59–7.48 (*m*, 3H, Ar-H), 4.61 (*s*, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ (ppm): 160.0, 154.9, 149.0, 134.0, 132.7, 130.7, 130.3, 130.0, 127.7, 116.9, 18.8.

Insecticidal activity

Materials and methods

Cotton leaf worm strain

Susceptible strain of *S. littoralis* was mass reared in the laboratory under the higrothermic conditions of 25 ± 2 °C and 75 ± 5% R.H. as described by El-Defrawi (1964) away from any chemical pressure. The larvae were fed on castor oil-bean leaves (*Ricinus communis L.*) and kept in 1-litre glass jars covered with muslin which fixed tightly by a rubber band. The number of larvae per jar was differed according to the developing instar. After pupation, the resulting pupae were sexed and grouped in groups of 12 pupae at a sex ratio of 2♀: 1♂ and then placed in the glass jar. After the emergence of the moths, they were supplied with a piece of cotton moistened with 10% sugar solution and paper strips to act as sites for egg deposition. The deposited egg masses were daily collected and left till hatching. The newly hatched larvae were transferred to clean jar and supplied with fresh leaves.[64,65]

Chemical used

The newly synthesized thiadiazole heterocyclic compounds.

Bioassay technique

The leaf-dipping bioassay method was used to determine the median lethal concentration (LC_{50}) values. A stock solution of each chemical was freshly prepared. Subsequent water dilutions were made to get series of concentrations of 250,500, 750, 1000, 1250 and 1500 ppm of the tested compounds. Castor-bean leaves were dipped for 30 seconds in each concentration then left for one hour to dry. The treated leaves were offered to newly molted 4th instar larvae of susceptible strain. Mortality percentages were recorded after 24 hrs and corrected according to Abbott (1925).[66] To estimate the LC_{50} values, the data were analyzed using an adopted computer program based on a standard implementation of the probit analysis recommended by Finney (1971). [67] The toxicity index calculated according to Yun-Pei Sun equation.[68]

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

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References

[1] Luo, Y. P.; Yang, G. F. Discovery of a New Insecticide Lead by Optimizing a Target-Diverse Scaffold: Tetrazolinone Derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 1716–1724. DOI: 10.1016/j.bmc.2006.12.002.

[2] Hiroshi, K.; Rokuro, S.; Isao, H.; Takuo, O. Herbicidal Activity of 1,3,4-Thiadiazole Derivatives. *J. Agric. Food Chem.* **1970**, *18*, 60–65.

[3] 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.

[4] 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.

[5] Farghaly, T. A.; Abdallah, M. A.; Aziz, M. R. A. Synthesis and Antimicrobial Activity of Some New 1,3,4-thiadiazole Derivatives. *Molecules.* **2012**, *17*, 14625–14636. DOI: 10.3390/molecules171214625.

[6] El-Gohary, N. S.; Shaaban, M. I. Synthesis, Antimicrobial, Antiquorum-Sensing, Antitumor and Cytotoxic Activities of New Series of Fused [1,3,4]Thiadiazoles. *Eur. J. Med. Chem.* **2013**, *63*, 185–195. DOI: 10.1016/j.ejmech.2013.02.010.

[7] Sah, P.; Bidawat, P.; Seth, M.; Gharu, C. P. Synthesis and Biological Significances of 1,3,4-Thiadiazolines and Related Heterocyclic Compounds. *Arabian. J. Chem.* **2014**, *7*, 181–187. DOI: 10.1016/j.arabjc.2010.10.023.

[8] Gür, M.; Şener, N.; Muğlu, H.; Çavuş, M. S.; Özkan, O. E.; Kandemirli, F.; Şener, İ. Şener, I. New 1,3,4-Thiadiazole Compounds Including Pyrazine Moiety: Synthesis, Structural Properties and Antimicrobial Features. *J. Mol. Struct.* **2017**, *1139*, 111–118. DOI: 10.1016/j.molstruc.2017.03.019.

[9] Gür, M.; Şener, N.; Kaştaş, Ç. A.; Özkan, O. E.; Muğlu, H.; Elmaswari, M. A. M. Synthesis and Characterization of Some New Heteroaromatic Compounds Having Chirality Adjacent to a 1,3,4-Thiadiazole Moiety and Their Antimicrobial Activities. *J. Heterocyclic. Chem.* **2017**, *54*, 3578–3590. DOI: 10.1002/jhet.2984.

[10] Sekhar, M. M.; Nagarjuna, U.; Padmavathi, V.; Padmaja, A.; Reddy, N. V.; Vijaya, T. Synthesis and Antimicrobial Activity of Pyrimidinyl 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Triazoles. *Eur. J. Med. Chem.* **2018**, *145*, 1–10. DOI: 10.1016/j.ejmech.2017.12.067.

[11] Chen, C. J.; Song, B. A.; Yang, S.; Xu, G. F.; Bhadury, P. S.; Jin, L. H.; Hu, D. Y.; Li, Q. Z.; Liu, F.; Xue, W.; et al. Synthesis and Antifungal Activities of 5-(3,4,5-Trimethoxyphenyl)-2-Sulfonyl-1,3,4-Thiadiazole and 5-(3,4,5-Trimethoxyphenyl)-2-Sulfonyl-1,3,4-Oxadiazole Derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 3981–3989. DOI: 10.1016/j.bmc.2007.04.014.

[12] Zuo, X.; Mi, N.; Fan, Z. J.; Zheng, Q. X.; Zhang, H. K.; Wang, H.; Yang, Z. K. Synthesis of 4-Methyl-1,2,3-Thiadiazole Derivatives via Ugi Reaction and Their Biological Activities. *J. Agric. Food Chem.* **2010**, *58*, 2755–2762. DOI: 10.1021/jf902863z.

[13] Zoumpoulakis, P.; Camoutsis, C.; Pairas, G.; Soković, M.; Glamočlija, J.; Potamitis, C.; Pitsas, A. Synthesis of Novel Sulfonamide-1,2,4-Triazoles, 1,3,4-Thiadiazoles and 1,3,4-Oxadiazoles, as Potential Antibacterial and Antifungal Agents. Biological Evaluation and Conformational Analysis Studies. *Bioorg. Med. Chem.* **2012**, *20*, 1569–1583. DOI: 10.1016/j.bmc.2011.12.031.

[14] Zhang, L.-J.; Yang, M.-Y.; Sun, Z.-H.; Tan, C.-X.; Weng, J.-Q.; Wu, H.-K.; Liu, X.-H. Synthesis and Antifungal Activity of 1,3,4-Thiadiazole Derivatives Containing Pyridine Group. *Lddd.* **2014**, *11*, 1107–1111. DOI: 10.2174/15701808116661406102127 31.

[15] 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.

[16] 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.

[17] Yu, P.; Hu, J.; Zhou, T. Y.; Wang, P.; Xu, Y. H. Synthesis, Insecticidal Evaluation of Novel 1,3,4-Thiadiazole Chrysanthemamide Derivatives Formed by EDCI/HOBt Condensation. *J. Chem. Res. (S).* **2011**, *35*, 703–706. DOI: 10.3184/174751911X13230201951890.

[18] Wan, R.; Zhang, J. Q.; Han, F.; Wang, P.; Yu, P.; He, Q. Synthesis and Insecticidal Activities of Novel 1,3,4-Thiadiazole 5-Fluorouracil Acetamides Derivatives: An RNA Interference Insecticide. *Nucleosides Nucleotides Nucleic Acids.* **2011**, *30*, 280–292. DOI: 10.1080/15257770.2011.580811.

[19] 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.

[20] 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. *RSC Adv.* **2017**, *7*, 39773–39785. DOI: 10.1039/C7RA06087D.

[21] 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.

[22] 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.

[23] 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.

[24] 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.

[25] 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.

[26] 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.

[27] 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.

[28] Sunil, D.; Isloor, A. M.; Shetty, P.; Satyamoorthy, K.; Prasad, A. S. B. 6-[3-(4-Fluorophenyl)-1H-Pyrazol-4-yl]-3-[(2-Naphthyloxy)Methyl][1,2,4]Triazolo[3,4-b][1,3,4]Thiadiazole as a Potent Antioxidant and an Anticancer Agent Induces Growth Inhibition Followed by Apoptosis in HepG2 Cells. *Arabian. J. Chem.* **2010**, *3*, 211–217. DOI: 10.1016/j.arabjc.2010.06.002.

[29] Gür, M.; Muğlu, H.; Çavuş, M. S.; Güder, A.; Sayıner, H. S.; Kandemirli, F. Synthesis, Characterization, Quantum Chemical Calculations and Evaluation of Antioxidant Properties of 1,3,4-Thiadiazole Derivatives Including 2- and 3-Methoxycinnamic Acids. *J. Mol. Struct.* **2017**, *1134*, 40–50. DOI: 10.1016/j.molstruc.2016.12.041.

[30] Chen, Z.; Xu, W.; Liu, K.; Yang, S.; Fan, H.; Bhadury, P. S.; Hu, D.-Y.; Zhang, Y. Synthesis and Antiviral Activity of 5-(4-chlorophenyl)-1,3,4-thiadiazole sulfonamides. *Molecules.* **2010**, *15*, 9046–9056. DOI: 10.3390/molecules15129046.

[31] Ragab, F. A.; Heiba, H. I.; El-Gazzar, M. G.; Abou-Seri, S. M.; El-Sabbagh, W. A.; El-Hazek, R. M. Anti-Inflammatory, Analgesic and COX-2 Inhibitory Activity of Novel Thiadiazoles in Irradiated Rats. *J. Photochem. Photobiol. B. Biol.* **2017**, *166*, 285–300. DOI: 10.1016/j.jphotobiol.2016.12.007.

[32] 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. DOI: 10.1016/j.ejmech.2010.08.007.

[33] Alegaon, S. G.; Alagawadi, K. R.; Sonkusare, P. V.; Chaudhary, S. M.; Dadwe, D. H.; Shah, A. S. Novel Imidazo[2,1-*b*][1,3,4]Thiadiazole Carrying Rhodanine-3-Acetic Acid as Potential Antitubercular Agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1917–1921. DOI: 10.1016/j.bmcl.2012.01.052.

[34] Bhatia, R.; Sharma, A.; Kaundal, A. A. Review on 1, 3, 4-Thiadiazole Derivatives. *Indian J. Pharm. Sci. Res.* **2014**, *4*, 165–172.

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

[36] Luszczki, J. J.; Karpińska, M.; Matysiak, J.; Niewiadomy, A. Characterization and Preliminary Anticonvulsant Assessment of Some 1,3,4-Thiadiazole Derivatives. *Pharmacol. Rep.* **2015**, *67*, 588–592. DOI: 10.1016/j.pharep.2014.12.008.

[37] Pattan, S. R.; Kekare, P.; Dighe, N. S.; Nirmal, S. A.; Musmade, D. S.; Parjane, S. K.; Daithankar, A. V. Synthesis and Biological Evaluation of Some 1,3,4-Thiadiazoles. *J. Chem. Pharm. Res.* **2009**, *1*, 191–198.

[38] Yusuf, M.; Khan, R. A.; Ahmed, B. Syntheses and anti-Depressant Activity of 5-Amino-1,3,4-Thiadiazole-2-Thiol Imines and Thiobenzyl Derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 8029–8034. DOI: 10.1016/j.bmc.2008.07.056.

[39] Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. Synthesis of 2-Amino-5-Sulfanyl-1,3,4-Thiadiazole Derivatives and Evaluation of Their Antidepressant and Anxiolytic Activity. *J. Med. Chem.* **2001**, *44*, 931–936. DOI: 10.1021/jm001027w.

[40] Kaur, H.; Kumar, S.; Vishwakarma, P.; Sharma, M.; Saxena, K. K.; Kumar, A. Synthesis and Antipsychotic and Anticonvulsant Activity of Some New Substituted Oxa/Thiadiazolylazetidinonyl/Thiazolidinonylcarbazoles. *Eur. J. Med. Chem.* **2010**, *45*, 2777–2783. DOI: 10.1016/j.ejmech.2010.02.060.

[41] Hasui, T.; Matsunaga, N.; Ora, T.; Ohyabu, N.; Nishigaki, N.; Imura, Y.; Igata, Y.; Matsui, H.; Motoyaji, T.; Tanaka, T.; et al. Identification of Benzoxazin-3-One Derivatives as Novel, Potent, and Selective Nonsteroidal Mineralocorticoid Receptor Antagonists. *J. Med. Chem.* **2011**, *54*, 8616–8631. DOI: 10.1021/jm2011645.

[42] Gupta, J. K.; Yadav, R. K.; Dudhe, R.; Sharma, P. K. Recent Advancements in the Synthesis and Pharmacological Evaluation of Substituted 1,3,4-Thiadiazole Derivatives. *Int. J. Pharmtech. Res.* **2010**, *2*, 1493–1507.

[43] Balaji, K.; Bhatt, P.; Mallika, D.; Jha, A. Design, Synthesis and Antimicrobial Evaluation of Some Mannich Base Derivative of 2(2-Substituted)-5-Aminothiadiazoles. *Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 145–149.

[44] Yadagiri, B.; Gurrala, S.; Bantu, R.; Nagarapu, L.; Polepalli, S.; Srujana, G.; Jain, N. Synthesis and Evaluation of Benzosuberone Embedded with 1,3,4-Oxadiazole, 1,3,4-Thiadiazole and 1,2,4-Triazole Moieties as New Potential anti Proliferative Agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2220–2224. DOI: 10.1016/j.bmcl.2015.03.032.

[45] Gomha, S. M.; Kheder, N. A.; Abdelhamid, A. O.; Mabkhot, Y. N. One Pot Single Step Synthesis and Biological Evaluation of Some Novel Bis(1,3,4-Thiadiazole) Derivatives as Potential Cytotoxic Agents. *Molecules.* **2016**, *21*, 1532–1839. DOI: 10.3390/molecules21111532.

[46] Zhong, X.; Wang, X.; Chen, L.; Ruan, X.; Li, Q.; Zhang, J.; Chen, Z.; Xue, W. Synthesis and Biological Activity of Myricetin Derivatives Containing 1,3,4-Thiadiazole Scaffold. *Chem. Cent. J.* **2017**, *11*, 106DOI: 10.1186/s13065-017-0336-7.

[47] Xu, W. M.; Han, F. F.; He, M.; Hu, D. Y.; He, J.; Yang, S.; Song, B. A. Inhibition of Tobacco Bacterial Wilt with Sulfone Derivatives Containing an 1,3,4-oxadiazole moiety. *J. Agric. Food Chem.* **2012**, *60*, 1036–1041. DOI: 10.1021/jf203772d.

[48] Wang, P. Y.; Zhou, L.; Zhou, J.; Wu, Z. B.; Xue, W.; Song, B. A.; Yang, S. Synthesis and Antibacterial Activity of Pyridinium-Tailored 2,5-Substituted-1,3,4oxadiazole Thioether/Sulfoxide/Sulfone Derivatives. *Bioorgan. Med. Chem. Lett* **2016**, *26*, 1214–1217. DOI: 10.1016/j.bmcl.2016.01.029.

[49] Wang, X.; Li, P.; Li, Z.; Yin, J.; He, M.; Xue, W.; Chen, Z.; Song, B. Synthesis and Bioactivity Evaluation of Novel Arylimines Containing a 3-Aminoethyl-2[(*ρ*-Trifluoromethoxy)Anilino]-4(3H)-Quinazolinone Moiety. *J. Agric. Food. Chem.* **2013**, *61*, 9575–9582. DOI: 10.1021/jf403193q.

[50] Chen, M. H.; Wang, X. B.; Tang, B. C.; Zhang, X. Synthesis and Antibacterial Evaluation of Novel Schiff Base Derivatives Containing 4(3H)-Quinazolinone Moiety. *Chem. Pap.* **2016**, *70*, 1521–1528.

[51] Abu El-Azm, F. S. M.; El-Shahawi, M. M.; Elgubbi, A. S.; Madkour, H. M. F. Design, Synthesis, anti-Proliferative Activity, and Molecular Docking Studies of Novel Benzo[*f*]Chromene, Chromeno [2,3-d]Pyrimidines and Chromenotriazolo[1,5-c]Pyrimidines. *Synth. Commun.* **2020**, *50*, 669–683. DOI: 10.1080/00397911.2019.1710850.

[52] Khlosy, T. A.; Salem, M. S.; Ali, A. T.; Madkour, H. M. F. Synthesis and Cytotoxic Activity against Human Tumor Cells of Heterocyclic Systems Derived from 2-Thioxo-1,2-Dihydro-4*H*-3,1-Benzothazin-4-One. *J. Heterocyclic Chem.* **2020**, *57*, 60–68. DOI: 10.1002/jhet.3745.

[53] Salem, M. S.; Hussein, R. A.; El-Sayed, W. M. Substitution at Phenyl Rings of Chalcone and Schiff Base Moieties Accounts for Their Antiproliferative Activity. *Anticancer Agents Med. Chem.* **2019**, *19*, 620–626. DOI: 10.2174/1871520619666190225122338.

[54] Madkour, H. M. F.; El-Hashash, M. A. E. M.; Salem, M. S.; Mahmoud, A.-S. O. A. Synthesis, Antileishmanial and Cytotoxicity Activities of Fused and Nonfused Tetrahydroquinoline Derivatives. *Res. Chem. Intermed.* **2018**, *44*, 3349–3364. DOI: 10.1007/s11164-018-3311-6.

[55] 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.

[56] 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.

[57] Ali, Y. M.; Ismail, M. F.; Abu El-Azm, F. S. M.; Marzouk, M. I. Design, Synthesis and Pharmacological Assay of Novel Compounds Based on Pyridazine Moiety as Potential Antitumor Agents. *J. Heterocyclic Chem.* **2019**, *56*, 2580–2591. DOI: 10.1002/jhet.3662.

[58] Ismail, M. F.; Elsayed, G. A. Dodecanoyl Isothiocyanate and *N*'-(2-Cyanoacetyl)Dodecanehydrazide as Precursors for the Synthesis of Different Heterocyclic Compounds with Interesting Antioxidant and Antitumor Activity. *Synth. Commun.* **2018**, *48*, 892–905. DOI: 10.1080/00397911.2018.1428345.

[59] Mahmoud, M. R.; El-Ziaty, A. K.; Abu El-Azm, F. S. M.; Ismail, M. F.; Shiba, S. A. Utility of cyano-N-(2-Oxo-1,2-Dihydroindol-3-Ylidene)Acetohydrazide in the Synthesis of Novel Heterocycles. *J. Chem. Res.* **2013**, *37*, 80–85. DOI: 10.3184/174751912X13567100793191.

[60] Ismail, M. F.; El-Sayed, A. A. Synthesis and in-Vitro Antioxidant and Antitumor Evaluation of Novel Pyrazole-Based Heterocycles. *J. Iran. Chem. Soc.* **2019**, *16*, 921–937. DOI: 10.1007/s13738-018-1566-x.

[61] Hamed, N. A.; Marzouk, M. I.; Ismail, M. F.; Hekal, M. H. *N*'-(1-([1,1'-Biphenyl]-4-yl)Ethylidene)-2-Cyanoacetohydrazide as Scaffold for the Synthesis of Diverse Heterocyclic Compounds as Prospective Antitumor and Antimicrobial Activities. *Synth. Commun.* **2019**, *49*, 1–3029. DOI: 10.1080/00397911.2019.1655578.

[62] Salman, A. S.; Mahmoud, N. A.; Abdel-Aziem, A.; Mohamed, M. A.; Elsisi, D. M. Synthesis, Reactions and Antimicrobial Activity of Some New 3-Substituted Indole Derivatives. *IJOC*. **2015**, *05*, 81–99. DOI: 10.4236/ijoc.2015.52010.

[63] 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. DOI: 10.21608/jes.2017.20047.

[64] Ali, H. A.; Kordy, A. M.; Khaled, A. E.; Hassan, N. A.; Abdelsalam, N. R. Efficiency of Using Some New Insecticides against Cotton Leaf Worm (Spodopteralittoralis) Based on Biochemical and Molecular Markers. *Alexandria Sci. Exchange. J.* **2015**, *36*, 303–313.

[65] Eldefrawi, M. E.; Toppozada, A. T.; Salama, A.; ElKishen, S. A. Toxicological Studies on the Egyptian Cotton Leaf Worm, Prodenia Litura FII. Reversion of Toxaphene Resistance in the Egyptian Cotton Leafworm. *J. Econ. Entomol.* **1964**, *57*, 593–595. DOI: 10.1093/jee/57.4.593.

[66] 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.

[67] Finney, D. J. *Probit Analysis*. 3rd ed.; Cambridge University Press: Cambridge, England, 1971.

[68] Sun, Y.-P.; Hyman, J.; Denver, C. Toxicity Index-An Improved Method of Comparing the Relative Toxicity of Insecticides. *J. Econ. Entomol* **1950**, *43*, 45–53. DOI: 10.1093/jee/43.1.45.