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Synthesis and insecticidal assessment of some innovative heterocycles incorporating a thiadiazole moiety against the cotton leafworm, *Spodoptera littoralis*†

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New 2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (**1**) was utilized as a versatile precursor for the synthesis of various heterocycles, such as pyrrole, pyridine, coumarin, thiazole, pyrido[2′,3′:3,4]pyrazolo[5,1-*c*]triazine, triazolo[5,1-*c*]triazine, aminopyrazole, thiophene, 1,3-dithiolane, triazolo[1,5-*a*]pyrimidine and benzo[*d*]imidazole derivatives. The newly synthesized compounds were identified by IR, MS, ^{1}H NMR, ^{13}C NMR, DEPT, H–H COSY, HMBC, and HSQC. Representative compounds of the synthesized products were examined and estimated as insecticidal agents against the cotton leafworm, *Spodoptera littoralis*.

Introduction

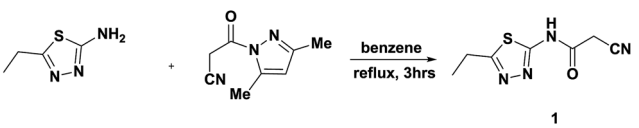
In recent years, the development of heterocyclic agrochemicals has become a main trend in research on pesticides because of their flexible structure, low mammalian toxicity, and high activity.[1] As an important class of heterocyclic compounds, 2,5-disubstituted 1,3,4-thiadiazoles are related with many types of biological properties, probably by virtue of the –N=C–S– group, including acaricidal,[1] insecticidal,[2] herbicidal,[3] antioxidant,[4] antibacterial,[5] antidepressant,[6] antidiabetic,[7] antifungal,[8] anticonvulsant[9] and anti-inflammatory effects.[10] In particular, many substituted 1,3,4-thiadiazole derivatives, including Schiff base derivatives, are of significant interest because they possess anticancer activities.[11] The thiadiazole moiety acts as a "hydrogen binding domain" and "two-electron donor system". Thiadiazoles are easily capable of crossing cellular membranes owing to their mesoionic nature and their better liposolubility, attributed to the presence of a sulfur atom. 1,3,4-Thiadiazoles are mesoionic systems,[12] *i.e.* they are polyheteroatomic systems and contain a five-membered heterocyclic ring associated with conjugated p and π electrons and discrete regions of positive and negative charges.

The synthetic approaches adopted to obtain the newly synthesized compounds depend on regioselective attack on the cyanoacetamido moiety of the precursor **1** by different reagents, which, in one or two steps, adds a highly functionalized substituent or heterocyclic ring to the molecule.[13] Cyanoacetamides are polyfunctional derivatives possessing both electrophilic and nucleophilic aspects. These chemical aspects have been used to build up diverse heterocycles with diverse ring sizes,[14–26] which have wide spectrums of biological activity.

Results and discussion

Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1–5. The new starting compound, 2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (**1**), was prepared in dry benzene by treatment of 2-amino-5-ethyl-1,3,4-thiadiazole with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile as the cyanoacetylation reagent according to the previously reported procedure[27] (Scheme 1). The structure **1** was elucidated according to its spectral data. The IR spectrum showed absorption bands at 3449 cm^{-1} for the NH function, stretching absorption bands at 2749–2955 cm^{-1} for CH aliphatic, a sharp band at 2260 cm^{-1} for the cyano group and a strong sharp band at 1702 cm^{-1} for the amidic carbonyl function. Its ^{1}H NMR spectrum (DMSO-d_6) indicated the existence of a triplet signal at δ_H 1.29 ppm due to protons of the



Scheme 1 Synthesis of starting compound **1**.

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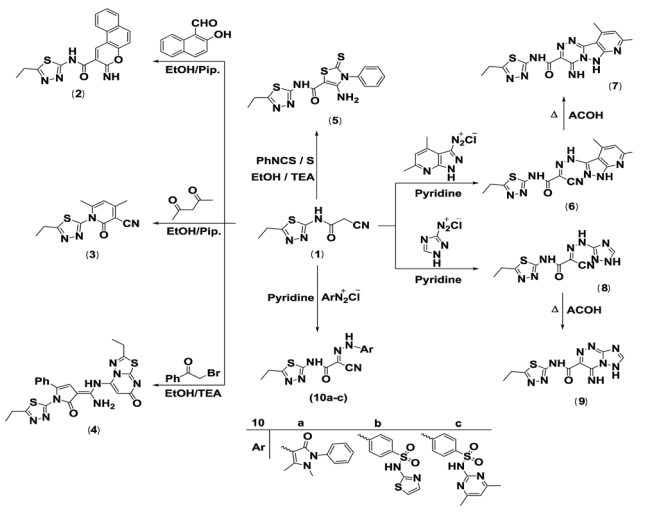
methyl group, a quartet signal at δ_H 3.01 ppm attributed to methylene protons and two singlet signals at δ_H 4.06 and δ_H 12.73 ppm ascribed to CH_2 protons and NH proton. Its ^{13}C NMR and DEPT spectra (DMSO-d_6) indicated the presence of a methyl carbon at δ_C 14.19 ppm and two methylene carbons at δ_C 23.16 and δ_C 26.49 ppm in addition to a cyano carbon at δ_C 115.57 ppm, two quaternary carbons at δ_C 158.44 and δ_C 162.69 ppm, and a carbonyl carbon at δ_C 166.49 ppm. The MS exhibited a molecular ion peak (M^+) at *m*/*z* 196 assigned to the molecular formula $C_7H_8N_4OS$.

Thus, cyclocondensation of compound **1** with 2-hydroxy-1-naphthaldehyde in hot ethanol containing piperidine as a basic catalyst furnished the coumarin derivative **2**. The reaction of **1** with 1,3-dicarbonyl compounds was studied for the purpose of establishment of pyridine derivatives with effective biological activities. Therefore, it reacted with acetylacetone to afford the pyridine derivative **3**. The previous product's structure was established according to its spectral data. The IR spectrum exhibited three absorption bands at 3447, 2221 and 1676 cm^{-1} due to OH, CN and CO function groups, respectively. The ^1H NMR spectrum indicated the appearance of three new singlets at δ_H 2.11, 2.42 and 6.56 ppm attributed to two methyl protons and the pyridinone H-5. In addition, its ^{13}C NMR spectrum indicated the presence of two new methyl carbons at δ_C 20.31 and δ_C 20.99 ppm and one aromatic carbon at δ_C 100.38 ppm. The structure of the pyridine derivative **3** was also established by 2D NMR, such as H–H COSY, HSQC and HMBC. The mass spectrum exhibited a molecular ion peak (M^+) at *m*/*z* 260, which agreed with the molecular formula $C_{12}H_{12}N_4OS$ (Scheme 2).

Recently, the reaction of α-halocarbonyl compounds with the cyanoacetamide moiety has been reported as a simple, new and effective synthetic route for the production of pyrrole derivatives.[28] Hence, it was fascinating to study the reaction of **1** with phenacyl bromide. Cyclocondensation of **1** with phenacyl bromide in hot ethanol containing a catalytic amount of triethylamine furnished the pyrrole derivative **4**. The proposed structure was in agreement with the analytical and spectral data. Therefore, the ^1H NMR spectrum of the yielded product exhibited three singlet signals at δ_H 7.02, 7.06 and 7.91 ppm corresponding to the pyrrolone proton H-4, pyrimidinone H-3 and NH proton, respectively, in addition to a broad singlet signal at δ_H 8.63 ppm due to NH_2 protons, two triplets at δ_H 1.26 and 1.41 ppm corresponding to two CH_3, two quartets at δ_H 2.95 and 3.19 ppm assignable to two CH_2, and a multiplet at δ_H 7.20–7.43 ppm assigned to aromatic protons. The IR spectrum revealed the presence of two CO groups stretching at 1666 and 1700 cm^{-1}, an NH_2 group at 3142 and 3331 cm^{-1} and an NH absorption band at 3408 cm^{-1}. The mass spectrum displayed a molecular ion peak at *m*/*z* 492 ascribed to the molecular formula $C_{22}H_{20}N_8O_2S_2$. Furthermore, Gewald reaction of compound **1** with both phenyl isothiocyanate and elemental sulfur in warm ethanol using triethylamine as a basic catalyst yielded the thiazole derivative **5**. The proposed structure was in agreement with the elemental analysis, IR and MS (Scheme 2).

Recently, diazotized heterocyclic amines have been reported as a perfect building block for the synthesis of bridged-head nitrogen heterocyclic systems.[29] Consequently, coupling of compound **1** with both 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-diazonium chloride and 1*H*-1,2,4-triazol-3-diazonium chloride[30] in pyridine at 0–5 °C furnished the corresponding hydrazono compounds **6** and **8**. When compounds **6** and **8** were heated under reflux in acetic acid, they cyclized to *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-imino-8,10-dimethyl-4,6-dihydropyrido[2′,3′:3,4]pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxamide (**7**) and *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-imino-4,6-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-3-carboxamide (**9**), respectively. The nucleophilic properties of the ring nitrogen enabled attack on the cyano group in order to synthesize compounds **7** and **9**. The IR spectrum of **7** exhibited three absorption bands at 3449, 3433, and 3406 cm^{-1} due to three NH groups besides one carbonyl absorption band at 1646 cm^{-1}. The ^1H NMR spectrum displayed two D_2O-exchangeable singlets at δ_H 12.33 and 12.82 ppm due to two NH protons, and additionally three singlets at δ_H 2.47, 2.79 and 6.98 ppm were characterized for two methyl protons of the pyridine ring and one aromatic proton of the pyridine ring, respectively. In addition, a triplet and a quartet were found at δ_H 1.31 and 3.02 ppm, characteristic of the side chain ethyl group. Its mass spectrum indicated a molecular ion peak at *m*/*z* 369 (M^+), which agreed with its molecular formula of $C_{15}H_{15}N_9OS$. Compound **9**'s structure was confirmed on the basis of spectral data. Its IR spectrum exhibited the lack of an absorption band attributed to the cyano function. Three NH absorption bands appeared at 3128, 3331 and 3440 cm^{-1}, while a strong absorption appeared at 1661 cm^{-1} for the amidic carbonyl group. The ^1H NMR spectrum (DMSO-d_6) indicated the absence of a singlet signal assignable to methylene protons, whereas a singlet signal was found at δ_H 8.58 ppm due to the aromatic proton of the triazole ring, as well as two singlets at δ_H 11.84 and 14.37 ppm characteristic of *N*HCO and =*N*H protons, while the side chain CH_2CH_3 protons appeared at δ_H 1.30 ppm as a triplet and at δ_H 3.02 ppm as a quartet. Moreover, the mass spectrum for the triazolo[5,1-*c*]triazine structure **9** displayed a molecular ion

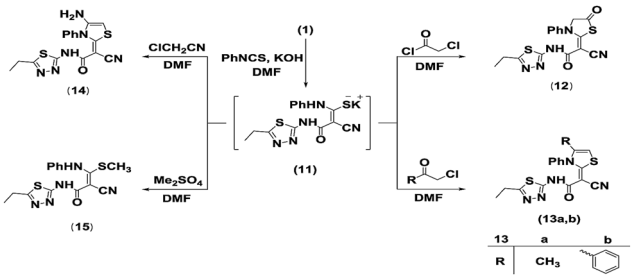


Scheme 2 Synthesis of coumarin, pyridine, pyrrole, thiazole, triazolo[5,1-*c*]triazine pyrido[2′,3′:3,4]pyrazolo[5,1-*c*]triazine and azo compound derivatives.

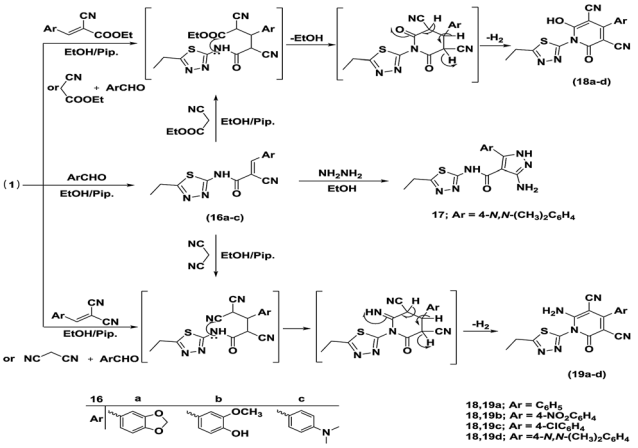
peak (M^+) at *m*/*z* 291 corresponding to the molecular formula $C_9H_9N_9OS$ (Scheme 2).

Due to its highly biological activity, next, the reactivity of the active methylene group existing in compound **1** towards various diazonium salts was also studied. Thus, diazocoupling reaction of compound **1** with antipyrine diazonium chloride, sulfathiazole diazonium chloride and sulfamethazine diazonium chloride in pyridine at 0–5 °C afforded the hydrazone derivatives **10a–c**. IR, ^{1}H NMR and MS results were in agreement with the proposed structures. Thus, the IR spectrum of **10b** exhibited an absorption band at 2231 cm^{-1} attributed to the cyano function, while absorption bands at 3130, 3226 and 3469 cm^{-1} were ascribed to three NH groups, in addition to a strong absorption band at 1665 cm^{-1} for the carbonyl group. Its ^{1}H NMR spectrum (DMSO-d_6) provided two olefinic protons, H-5 and H-4, of the thiazole ring, which appeared as doublets at δ_H 6.84 and 7.26 ppm that were coupled to each other with a coupling constant $J = 4$ Hz, while the aromatic protons appeared at δ_H 7.80 and 7.97 ppm as doublets in an AA′XX′ system, $J = 8$ Hz, in addition to three singlet signals at δ_H 12.37, 12.38 and 12.81 ppm ascribed to =N–NH, *N*HSO$_2$ and *N*HCO, respectively. Moreover, the methyl protons were appeared as triplet signals at δ_H 1.30 ppm, while the methylene protons appeared as quartet signal at δ_H 3.01 ppm. Moreover, the mass spectrum of compound **10b** displayed a molecular ion peak at *m*/*z* 462 ascribed to the molecular formula $C_{16}H_{14}N_8O_3S_3$ (Scheme 2).

The reactivity of the methylene group in the cyanoacetamide derivative **1** towards isothiocyanate was examined. Thus, treatment of **1** with phenyl isothiocyanate in DMF including potassium hydroxide at room temperature furnished the non-isolable thiocarbamoyl salt **11**, which underwent heterocyclization upon reaction with α-halocarbonyl compounds chloroacetyl chloride, chloroacetone and phenacyl chloride to give the corresponding thiazole derivatives **12**, **13a** and **13b**, respectively (Scheme 3). The structure of **12** was characterized by the appearance of a singlet signal equivalent to two protons at δ_H 4.02 ppm in the ^{1}H NMR spectrum, which represent the C5 protons of the thiazolidinone moiety. In addition, a multiplet signal equivalent to five protons at δ_H 7.38–7.52 ppm was ascribed to the aromatic protons. The IR spectrum revealed the presence of a new absorption band at 1747 cm^{-1} due to the carbonyl group at C4 of the thiazole ring. According to the MS of compound **12**, the *m*/*z* was 371 corresponding to its molecular formula $C_{16}H_{13}N_5O_2S_2$. The IR spectrum of **13a** exhibited stretching frequencies at 3486, 2184 and 1626 cm^{-1} for the NH, CN and CO frequencies, respectively. The ^{1}H NMR spectrum exhibited two singlet signals at δ_H 1.88 and 7.01 ppm due to the CH_3 and olefinic protons of the thiazole ring, a multiplet signal at δ_H 7.48–7.60 ppm related to aromatic protons, in addition to a triplet at δ_H 1.28 ppm and a quartet at δ_H 2.91 ppm assignable to the side chain ethyl group. The ^{13}C NMR spectrum was assigned by signals at δ_C 13.11 and 13.98 ppm for the two methyl carbons, a signal at δ_C 22.71 ppm due to the methylene carbon, a signal at δ_C 106.89 ppm related to the methine carbon, a signal at δ_C 115.16 ascribed to cyano carbon, and signals at δ_C 128.73–130.51 ppm assigned to aromatic carbons. The structure of the thiazole derivative **13a** was also established by DEPT ^{13}C



Scheme 3 Reaction of compound 1 with phenyl isothiocyanate.



Scheme 4 Synthesis of arylidene, aminopyrazole and 2-pyridone derivatives.

NMR and 2D NMR, such as H–H COSY, HSQC and HMBC. Its mass spectrum displayed a molecular ion peak (M^+) at *m*/*z* 369, which agreed with the molecular formula $C_{17}H_{15}N_5OS_2$. The IR spectrum of **13b** indicated an absorption band at 3446 cm^{-1} for the NH group, a sharp band at 2187 cm^{-1} for the cyano function and a strong sharp band at 1626 cm^{-1} for the carbonyl function. The ^{1}H NMR spectrum (DMSO-d_6) revealed the presence of two singlet signals at δ_H 7.19 and 14.49 ppm assignable to the olefinic proton of the thiazole ring and the NH proton, and a multiplet signal at δ_H 7.21–7.61 ppm assigned to aromatic protons, in addition of triplet and quartet signals at δ_H 1.30 and 2.96 ppm due to the ethyl group. The mass spectrum exhibited a molecular ion peak at *m*/*z* 431 attributed to the molecular formula $C_{22}H_{17}N_5OS_2$.

Moreover, the reaction of the intermediate **11** with chloroacetonitrile furnished (*E*)-2-(4-amino-3-phenylthiazol-2(3*H*)-ylidene)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (**14**). IR and MS results are compatible with the proposed structure (Scheme 3).

Treatment of the thiocarbamoyl salt intermediate **11** with dimethyl sulfate furnished the novel ketene *N*,*S*-acetal **15**. The structure of **15** was identified by spectral data. The IR spectrum displayed absorption bands at 3448, 3313 and 2227 cm^{-1} due to two NH groups and the nitrile function, respectively, in addition to a carbonyl absorption band at 1638 cm^{-1}. Its mass spectrum exhibited a molecular ion peak at *m*/*z* 345 (M^+), which agrees

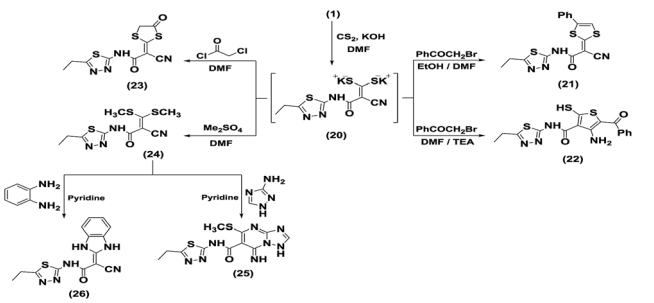
with its molecular formula $C_{15}H_{15}N_5OS_2$. Its ^{1}H NMR spectrum displayed three singlet signals at δ_H 2.85, 9.80 and 9.83 ppm assignable to SCH_3, *N*HPh and *N*HCO, respectively, a multiplet signal at δ_H 7.10–7.49 ppm related to the aromatic protons, and a triplet signal at δ_H 1.30 ppm and a quartet signal at δ_H 3.04 ppm corresponding to CH_2CH_3 protons. The ^{13}C NMR spectrum was identified by signals at δ_C 11.87 and 17.45 ppm characterized to the two methyl carbons, a signal at δ_C 24.38 ppm ascribed to the methylene carbon, a signal at δ_C 114.58 ppm assigned to the cyano carbon, signals at δ_C 123.6–128.41 ppm assigned to aromatic carbons, and a signal at δ_C 163.68 ppm attributed to the amidic carbonyl carbon atom. The structure of the ketene *N*,*S*-acetal **15** was also characterized by DEPT ^{13}C NMR and 2D NMR, such as H–H COSY, HSQC and HMBC (Scheme 3).

Next, the synthetic potency and applicability of cyanoacetamide derivative **1** were investigated to develop a facile and convenient route to some novel pyrazole and pyridine derivatives with an anticipated wide spectrum of bioresponses.[31,32] Thus, the Knoevenagel condensation of **1** with aromatic aldehydes, namely piperonal, vanilline, and 4-*N*,*N*-dimethylbenzaldehyde, in refluxing ethanol using piperidine as a basic catalyst afforded the corresponding arylidene derivatives **16a–c**. Treatment of **16c** with hydrazine hydrate in boiling ethanol yielded 3-amino-5-(4-(dimethylamino)phenyl)-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**17**). Michael addition of hydrazine hydrate to α,β-unsaturated nitrile **16c** led to the formation of compound **17** *via in situ* intramolecular 1,5-dipolar cyclization through the nucleophilic addition of the amino group to the cyano function to afford dihydropyrazole, which underwent auto oxidation to furnish the target pyrazole. The assignment of structures **16a–c** and **17** was supported by spectral data. The ^{1}H NMR (DMSO-d_6) spectra of structures **16a–c** exhibited, in general, a singlet signal at δ_H 8.082–8.353 ppm attributable to vinylic protons. Furthermore, the IR spectrum of compound **17** revealed the absence of a cyano function and instead, the appearance of a new absorption band at 3280 and 3152 cm^{-1} assigned to an NH_2 group.

One-pot reactions of the cyanoacetamide derivative **1** with ethyl cyanoacetate and different aromatic aldehydes, namely benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and 4-*N*,*N*-dimethylbenzaldehyde (1 : 1 : 1 molar ratio), in refluxing ethanol containing a catalytic amount of piperidine yielded the 2-pyridone derivatives **18a–d**, respectively. On the other hand, the 2-pyridone derivatives **18a–d**, were also acquired *via* reaction of cyanoacetamide **1** with arylidene ethyl cyanoacetate in hot ethanol under reflux containing piperidine as the catalyst. In addition, pyridin-2-ones **18d** and **19d** were also obtained *via* the reaction of the arylidene derivative **16c** with ethyl cyanoacetate and malononitrile, respectively, in ethanol in the presence of piperidine as the catalyst. Another route for the synthesis of 2-pyridone derivatives was the one-pot reaction of the cyanoacetamide derivative **1** with malononitrile and the same mentioned aromatic aldehydes (1 : 1 : 1 molar ratio) followed by refluxing in ethanol containing a few drops of piperidine to furnished **19a–d**. Moreover, when arylidene malononitrile was refluxed with the cyanoacetamide derivative **1** in ethanol in the presence of piperidine, it afforded 2-pyridone derivatives **19a–d**. The structures **18a–d** and **19a–d** were confirmed on the basis of spectral data.

Treatment of compound **1** with carbon disulfide in DMF, containing potassium hydroxide, at room temperature afforded the intermediate enaminonitrile **20**, which underwent heterocyclization upon treatment with α-halocarbonyl compounds, such as phenacyl bromide, chloroacetyl chloride, to give the corresponding ketene *S*,*S*-dithiolane derivatives or thiophene derivatives (Scheme 5). Thus, the *in situ* stirring reaction of the non-isolable intermediate **20** with phenacyl bromide or chloroacetyl chloride in the presence of a protic solvent such as ethanol afforded the 1,3-dithiolane derivatives **21** and **23**, respectively. On the other hand, when the intermediate enaminonitrile **20** was refluxed with phenacyl bromide in DMF only as an aprotic solvent and in the presence of a catalytic amount of triethylamine, a thiophene derivative **22** was obtained. The spectral data of the isolated products was in complete agreement with structures **21**, **22** and **23**. The IR spectrum of compound **22** indicated the lack of an absorption band assigned to a conjugated C≡N function and showed absorption bands at 3413, 3345, 3296, 2622, 1718 and 1645 cm^{-1} assignable to NH, NH_2, SH, PhCO, and amidic C=O functions, respectively. The ^{1}H NMR spectrum (DMSO-d_6) displayed a broad singlet signal at δ_H 8.35 ppm assignable to NH_2, and a multiplet signal in the δ_H 7.43–7.60 ppm region that is distinctive for aromatic protons, besides triplet and quartet signals at δ_H 1.31 and 2.95 ppm, respectively, corresponding to the side chain ethyl group. Its mass spectrum exhibited a molecular ion peak at *m*/*z* 390, corresponding to molecular formula $C_{16}H_{14}N_4O_2S_3$. The ^{13}C NMR spectrum was characterized by a signal at δ_C 12.37 ppm ascribed to the methyl carbons, a signal at δ_C 23.29 ppm ascribed to methylene carbon, a signal at δ_C 126.83–130.71 ppm attributed to aromatic carbons, and signals at δ_C 167.14 and 185.86 ppm corresponding to the two carbonyl carbon atoms. The structure of the thiophene derivative **22** was also characterized by DEPT ^{13}C NMR and 2D NMR, such as H–H COSY, HSQC and HMBC.

The ketene *S*,*S*-dithioacetal **24** was prepared by reaction of **1** with carbon disulfide in the presence of potassium hydroxide in DMF, followed by alkylation with dimethyl sulfate (Scheme 5). The structure of **24** was established on the basis of the spectral data (^{1}H NMR, ^{13}C NMR, DEPT ^{13}C NMR and 2D NMR, such as H–H COSY, HSQC and HMBC).



Scheme 5 Reaction of compound **1** with carbon disulfide.

Polarized cyanoketene *S*,*S*-acetals are utilized as a key intermediate for the synthesis of a wide-ranging variety of fused heterocycles. Thus, further reaction of **24** with 3-amino-1*H*-1,2,4-triazole in refluxing pyridine afforded triazolo[1,5-*a*] pyrimidine **25**. Compound **25** was also elucidated by the spectral data. Moreover, compound **24** was also used as a versatile starting material for the synthesis of fused heterocyclic compounds by treatment with bifunctional nucleophilic reagents. Thus, heating of **24** with *o*-phenylenediamine in pyridine afforded benzo[*d*]imidazole derivative **26**. The IR spectrum of **26** exhibited absorption bands at 3451, 3303, and 3130 cm^{-1} for three NH stretching modes, a band at 2219 cm^{-1} for the cyano function, and a strong absorption band for the amidic carbonyl group at 1679 cm^{-1}. The ^1H NMR spectrum revealed no signal for SCH_3 protons, while a multiplet signal at δ_H 7.47–7.64 ppm was assigned to aromatic protons, two singlet signals at δ_H 7.93 ppm and δ_H 8.35 ppm appeared for 2NH and *N*HCO protons, respectively, beside a triplet at δ_H 1.35 ppm attributed to CH_3 protons, and a quartet at δ_H 3.06 ppm assigned to CH_2 protons. Its mass spectrum exhibited a molecular ion peak at *m*/*z* 312, attributed to the molecular formula $C_{14}H_{12}N_6OS$ (Scheme 5).

Insecticidal activity

Toxicity test for the cotton leafworm, *Spodoptera littoralis*. The insecticidal activities of the newly synthesized tested compounds against the 2nd instar larvae of the cotton leafworm, *S. littoralis* (Boisd.), of the laboratory strain are shown in Table 1. The bioassay results revealed that all tested compounds possess strong to weak insecticidal activity after 7 days of treatment with median lethal concentration (LC_{50}) values that ranged from 627.94 to 64.12 ppm. The efficacy of the different tested compounds was measured by comparing the tested compounds (based on LC_{50} value) with the most effective compound (the lowest LC_{50} value) according to the toxicity index. Regarding the determined LC_{50} and LC_{90} values, 1,3,4-thiadiazole derivatives **10b**, **10c**, **7**, **10a** and **9** showed the most potent toxic effects with LC_{50} values of 64.12, 69.17, 75.51, 91.45 and 101.30 ppm, respectively, and toxicity indices of 100, 92.69, 84.91, 70.11 and 63.29%, respectively. It is interesting to note that the insecticidal activities of the tested compounds against the 2nd instar larvae of *S. littoralis* (Boisd.) after 7 days of treatment obey the following smooth order: **10b** > **10c** > **7** > **10a** > **9** > **5** > **18c** > **18b** > **17** > **19c** > **22** > **12** > **16a** > **4** > **19d** > **18d** > **25** > **18a** > **19b** > **13b** > **14** > **19a** > **26** > **3** > **2** > **16c** > **23** > **21** > **15** > **13a** > **24** > **1**.

Structure–activity relationship. The structure–activity relationship revealed that 1,3,4-thiadiazole derivatives **10b** and **10c** were the most potent toxic compounds and exhibited interesting biological activities, and thus emerged as potential leads for further development as insecticides candidates.[33] This may be due to the presence of a sulfonamide group in addition to a cyano group in their structures, beside the other common features of all compounds. Moreover, the results of the insecticidal activity clearly demonstrated that the presence of electron withdrawing groups/atoms is essential for enhancing insecticidal activity,[31] such as in the fused heterocyclic compounds **7**and **9**. Furthermore, compound **10a** possesses a toxic effect, which may be due to the presence of a pyrazolone moiety and a cyano group, thus suggesting that the compounds from the present series with electron withdrawing groups can serve as important gateways for the design and development of new insecticidal agents with potent activity and minimal toxicity.

Experimental

Instruments

All melting points were recorded using a Gallenkamp melting point apparatus in degrees centigrade and are uncorrected. The IR spectra (KBr) were determined on a Mattson 5000 FTIR spectrophotometer at the Faculty of Science, Mansoura University. NMR spectra (^1H, ^{13}C, DEPT, H–H COSY, HSQC and HMBC) were acquired using a Bruker WP 400 MHz, 500 MHz, 300 MHz and 125 MHz at the Faculty of Pharmacy, Beni-Suef University with DMSO-d_6 as the solvent, utilizing TMS as an internal standard reference, and chemical shifts are expressed as δ ppm. Mass spectra were measured using a Finnegan MAT 212 instrument at the Faculty of Science, Cairo University, and the Regional Center for Mycology & Biotechnology, Al-Azhar University. Elemental analyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University. TLC (silica gel, aluminium sheets 60 F_{254}, Merck) was carried out after all the reactions.

Synthesis of 2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (1)

A solution of 2-amino-5-ethyl-1,3,4-thiadiazole (5.16 g, 0.04 mol) in dry benzene (30 mL) was added to a solution of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (6.52 g, 0.04 mol) in the same solvent (15 mL) and the reaction mixture was refluxed for 3 h. After cooling, the solid precipitate was isolated by filtration and purified *via* recrystallization from ethanol to afford **1**. White crystals; mp 230–232 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3449 (NH), 2260 (CN), 1702 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.29 (t, 3H, CH_3), 3.01 (q, 2H, CH_2), 4.06 (s, 2H, CH_2), 12.73 (s, 1H, *N*HCO). ^{13}C NMR (400 MHz, DMSO-d_6): δ_C ppm 14.19, 23.16, 26.49, 115.57, 158.44, 162.7, 166.49. MS *m*/*z* (%): 197 (M^+ + 1, 83.33), 196 (M^+, 69.23), 181 (89.74), 155 (94.87), 139 (100), 110 (94.87), 71 (93.59), 61 (91.03). Anal. for $C_7H_8N_4OS$ (196.23): calcd: C, 42.85; H, 4.11; N, 28.55%; found: C, 42.92; H, 4.05; N, 28.43%.

Synthesis of *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-imino-3*H*-benzo[*f*]chromene-2-carboxamide (2)

To a solution of compound **1** (0.4 g, 0.002 mol) in absolute ethanol (25 mL) in the presence of piperidine (0.5 mL), 2-hydroxy-1-naphthaldehyde (0.35 g, 0.002 mol) was added. The reaction mixture was refluxed for 3 h and then left to cool. The formed precipitate was filtered off, purified by washing with ethanol, and then dried and recrystallized from ethanol to furnish **2**. Pale yellow crystals; mp 253–255 °C; yield 85%; IR (KBr) ν/cm^{-1}: 3435, 3322 (2NH), 1733 (CO). ^1H NMR (400 MHz,

Table 1 Insecticidal activity of the newly synthesized compounds against the 2nd instar larvae of the cotton leafworm, *S. littoralis* (Boisd.), after 7 days of treatment[a]

Tested compounds	LC_{50} (ppm) and confidence limits at 95%	LC_{90} (ppm) and confidence limits at 95%	Slope	Toxicity index % at LC_{50} value
10b	64.12, 47.12, 87.01	259.07, 163.95, 666.16	2.113 ± 0.417	100
10c	69.17, 53.80, 87.48	225.01, 164.53, 366.87	2.502 ± 0.351	92.69
7	75.51, 59.44, 95.05	235.22, 173.25 377.15	2.597 ± 0.355	84.91
10a	91.45, 67.78, 116.76	288.78, 210.83 493.24	2.566 ± 0.429	70.11
9	101.30, 76.88, 131.68	422.79, 295.71, 725.63	2.065 ± 0.267	63.29
5	115.48, 84.07, 150.36	454.49, 323.96, 774.83	2.154 ± 0.317	55.52
18c	235.41, 178.96, 309.27	993.61, 673.32, 1853.32	2.049 ± 0.288	27.23
18b	240.91, 181.73, 311.86	1279.72, 870.94, 2322.95	1.767 ± 0.231	26.61
17	262.31, 194.03, 334.36	973.84, 719.65, 1548.13	2.250 ± 0.319	24.44
19c	290.72, 215.83, 371.94	1114.06, 806.06, 1860.78	2.197 ± 0.322	22.05
22	294.26, 231.53, 369.04	1026.68, 762.93, 1571.35	2.362 ± 0.279	21.79
12	298.94, 224.51, 380.06	1098.63, 802.36, 1798.5	2.267 ± 0.326	21.44
16a	321.34, 242.23, 408.97	1206.54, 872.60, 2018.38	2.231 ± 0.323	19.95
4	334.04, 256.08, 416.27	1181.66, 904.50, 1731.51	2.336 ± 0.291	19.19
19d	344.93, 264.73, 439.91	1619.94, 1158.03, 2627.91	1.908 ± 0.222	18.58
18d	349.27, 268.69, 434.98	1221.88, 931.20, 1810.47	2.357 ± 0.298	18.35
25	375.58, 294.25, 470.43	1504.17, 1112.55, 2304.69	2.127 ± 0.241	17.07
18a	381.33, 296.33, 472.43	1310.07, 999.64, 1941.12	2.391 ± 0.302	16.81
19b	387.34, 294.35, 485.22	1494.55, 1129.37, 2243.94	2.186 ± 0.275	16.55
13b	389.93, 308.90, 482.03	1130.61, 855.53, 1745.80	2.772 ± 0.391	16.44
14	395.26, 300.87, 497.92	1584.55, 1162.05, 2541.15	2.125 ± 0.284	16.22
19a	428.20, 330.22, 531.29	1656.80, 1261.38, 2451.76	2.181 ± 0.266	14.97
26	448.32, 346.01, 556.57	1774.75, 1340.77, 2669.08	2.145 ± 0.264	14.30
3	476.84, 370.61, 601.48	2359.00, 1688.68, 3822.99	1.846 ± 0.211	13.44
2	481.22, 383.88, 582.89	1538.40, 1215.39, 2137.24	2.539 ± 0.295	13.32
16c	484.28, 377.30, 598.21	1877.49, 1418.89, 2829.16	2.178 ± 0.269	13.24
23	484.93, 378.15, 598.60	1868.67, 1414.22, 2808.55	2.188 ± 0.269	13.22
21	492.62, 381.52, 611.87	2020.45, 1503.41, 3137.98	2.091 ± 0.264	13.01
15	521.67, 412.29, 638.29	1889.44, 1445.06, 2792.62	2.293 ± 0.280	12.29
13a	550.83, 436.27, 682.24	1990.66, 1462.13, 3221.37	2.297 ± 0.309	11.64
24	564.99, 457.82, 683.14	1690.21, 1306.90, 2486.15	2.693 ± 0.347	11.34
1	627.94, 513.81, 747.33	1831.85, 1459.39, 2542.52	2.756 ± 0.333	10.21

[a] Toxicity index is defined as the ratio of the most effective compound's LC_{50} value to the other tested compound's LC_{50} value multiplied by 100.

DMSO-d_6): δ_H ppm 1.20 (t, 3H, CH_3), 2.80 (q, 2H, CH_2), 7.65–8.66 (m, 6H, Ar-H), 9.81 (s, 1H, CH=). ^{13}C NMR (400 MHz, DMSO-d_6): δ_C ppm 13.8, 23.11, 100.79, 112.33, 115.02, 116.75, 122.55, 126.86, 128.79, 129.07, 129.38, 129.98, 137.17, 149.6, 155.03, 157.20, 159.65, 168.08. Also H–H COSY, HSQC and HMBC proved the structure. MS *m*/*z* (%): 350 (M^+, 12.13), 288 (57.85), 274 (42.21), 194 (15.78), 182 (51.66), 169 (47.38), 152 (47.8), 120 (39.18), 97 (57.97), 71, (50.95), 64 (59.97), 51 (100). Anal. for $C_{18}H_{14}N_4O_2S$ (350.4): calcd: C, 61.70; H, 4.03; N, 15.99%; found: C, 61.55; H, 3.96; N, 16.05%.

Synthesis of 1-(5-ethyl-1,3,4-thiadiazol-2-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3)

An equimolar mixture of compound **1** (0.4 g, 0.002 mol) and acetylacetone (0.21 mL, 0.002 mol) in absolute ethanol (15 mL) containing three drops of piperidine was heated under reflux for 3 h. The reaction mixture was allowed to cool and the precipitate obtained was isolated by filtration and purified through recrystallization from ethanol to afford **3**. Colorless crystals; mp 175–177 °C; yield 89%; IR (KBr) ν/cm^{-1}: 3447 (OH), 2221 (CN), 1676 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.37 (t, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.19 (q, 2H, CH_2), 6.56 (s, 1H, pyridine H-5). ^{13}C NMR (400 MHz, DMSO-d_6): δ_C ppm 13.54, 20.31, 20.99, 23.76, 100.38, 110.02, 114.97, 151.26, 158.35, 160.08, 161.93, 176.27. The H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 261 (M^+ + 1, 12.78), 260 (M^+, 14.02), 205 (80.89), 178 (6.97), 147 (100), 119 (14.53), 104 (6.63), 77 (10), 51 (2.45). Anal. for $C_{12}H_{12}N_4OS$ (260.32): calcd: C, 55.37; H, 4.65; N, 21.52%; found: C, 55.25; H, 4.55; N, 21.38%.

Synthesis of (*E*)-5-((amino(1-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-pyrrol-3-ylidene)methyl)amino)-2-ethyl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-one (4)

Equimolar amounts of compound **1** (0.4 g, 0.002 mol) and phenacyl bromide (0.404 g, 0.002 mol) in absolute ethanol (25 mL) containing three drops of triethylamine was refluxed for 3 h. The solid product that formed was filtered off, purified and recrystallized from dry ethanol to furnish compound **4**. Pale yellow powder; mp > 300 °C; yield 80%; IR (KBr) ν/cm^{-1}: 3408 (NH), 3331, 3142 (NH_2), 1700, 1666 (2CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.26 (t, 3H, CH_3), 1.41 (t, 3H, CH_3), 2.95 (q,

2H, CH_2), 3.19 (q, 2H, CH_2), 7.02 (s, 1H, pyrimidine H-5), 7.06 (s, 1H, pyrrole H-4), 7.2–7.43 (m, 5H, Ar-H). MS *m*/*z* (%): 492 (M^+, 31.92), 368 (100), 313 (39.01), 299 (33.81), 262 (46.71), 239 (80.47), 186 (30.46), 179 (15.68), 123 (22.79). Anal. for $C_{22}H_{20}N_8O_2S_2$ (492.58): calcd: C, 53.64; H, 4.09; N, 22.75%; found: C, 53.55; H, 4.01; N, 22.80%.

Synthesis of 4-amino-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxamide (5)

To an ethanolic solution (25 mL) of compound **1** (0.4 g, 0.002 mol) containing three drops of triethylamine, elemental sulfur (0.064 g, 0.002 mol) and phenyl isothiocyanate (0.23 mL, 0.002 mol) were added. The reaction mixture was continuously stirred at 60 °C for 3 h, and then poured into a beaker containing a crushed ice/water mixture acidified by a few drops of hydrochloric acid. The solid precipitate that formed was isolated by filtration, dried, and recrystallized from a mixture of DMF and ethanol (3 : 1) to afford compound **5**. Brown powder; mp 248–250 °C; yield 75%; IR (KBr) ν/cm^{-1}: 3446 (NH), 3373, 3244 (NH_2), 1640 (C=O), 1232 (C=S). MS *m*/*z* (%): 364 (M^+ + 1, 3.51), 363 (M^+, 17.68), 330 (15.04), 298 (16.81), 266 (16.1), 235 (22.88), 208 (51), 136 (53.05), 135 (82.06), 129 (82.36), 93 (31.97), 77 (100), 74 (43.85), 60 (26.7). Anal. for $C_{14}H_{13}N_5OS_3$ (363.47): calcd: C, 46.26; H, 3.61; N, 19.27%; found: C, 46.22; H, 3.45; N, 19.21%.

General procedure for coupling reaction of 1 with different primary aromatic amine diazonium salts

To a cold (0–5 °C) solution of compound **1** (0.4 g, 0.002 mol) in pyridine (20 mL) was added the appropriate diazonium chloride [which was prepared by dissolving sodium nitrite (0.14 g, 0.002 mol) in cold water (3 mL) and adding to a cold solution of the appropriate aromatic amine (0.002 mol) containing an adequate amount of hydrochloric acid (1.5 mL) under continuous stirring conditions] portion-wise over a period of 25 min. The reaction mixture was kept overnight in the refrigerator, and then diluted with water. The formed solid that precipitated was filtered off, purified by washing in water, then dried and recrystallized from EtOH and DMF (2 : 1) to afford arylazo derivatives **6**, **8** and **10a–c**.

Synthesis of (*E*)-*N*-(4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-2-((5-ethyl-1,3,4-thiadiazol-2-yl)amino)-2-oxoacetohydrazonoyl cyanide (6)

Black powder; mp 280–282 °C; yield 85%; IR (KBr) ν/cm^{-1}: 3449 (NH), 2197 (CN), 1646 (CO). MS *m*/*z* (%): 371 (M^+ + 2, 5.96), 370 (M^+ + 1, 21.87), 369 (M^+, 100), 336 (16.7), 281 (25.17), 271 (16.77), 241 (18.99), 162 (33.41), 146 (36.88), 119 (28.06), 104 (16.43), 78 (33.58). Anal. for $C_{15}H_{15}N_9OS$ (369.41): calcd: C, 48.77; H, 4.09; N, 34.13%; found: C, 48.32; H, 4.01; N, 34.03%.

Synthesis of *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-imino-8,10-dimethyl-4,6-dihydropyrido[2′,3′:3,4]pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxamide (7)

A solution of **6** (0.74 g, 0.002 mol) in glacial acetic acid (25 mL) was refluxed for 3 h, and then allowed to cool. The formed precipitate was filtered off, purified by washing with ethanol and recrystallized from a mixture of EtOH–DMF (1 : 1) to furnish compound **7**. Reddish brown powder; mp > 300 °C; yield 93%; IR (KBr) ν/cm^{-1}: 3449, 3433, 3406 (3NH), 1646 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.31 (t, 3H, CH_3), 2.47 (s, 3H, CH_3-pyridine), 2.79 (s, 3H, CH_3-pyridine), 3.02 (q, 2H, CH_2), 6.98 (s, 1H, pyridine H-3), 12.33 (s, 1H, *N*HCO), 12.82 (s, 1H, =NH). Anal. for $C_{15}H_{15}N_9OS$ (369.41): calcd: C, 48.77; H, 4.09; N, 34.13%; found: C, 48.30; H, 3.98; N, 34.01%.

Synthesis of (*E*)-2-((5-ethyl-1,3,4-thiadiazol-2-yl)amino)-2-oxo-*N*-(1*H*-1,2,4-triazol-3-yl)acetohydrazonoyl cyanide (8)

Pale yellow crystals; mp 268–270 °C; yield 87%; IR (KBr) ν/cm^{-1}: 3440 (NH), 2217 (CN), 1661 (CO). MS *m*/*z* (%): 291 (M^+, 32.62), 279 (20.83), 258 (19.97), 214 (33.47), 201 (44.55), 185 (38.18), 161 (45), 156 (46.51), 143 (44.53), 129 (57.59), 116 (23.16), 100 (17.52), 78 (41.72), 69 (100), 60 (72.81). Anal. for $C_9H_9N_9OS$ (291.29): calcd: C, 37.11; H, 3.11; N, 43.28%; found: C, 37.05; H, 3.05; N, 43.18%.

Synthesis of *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-imino-4,6-dihydro-^{1,2,4}triazolo[5,1-*c*]^{1,2,4}triazine-3-carboxamide (9)

A solution of **8** (0.58 g, 0.002 mol) in glacial acetic acid (20 mL) was refluxed for 3 h, and then left to cool. The formed solid precipitate was filtered off, purified by washing with ethanol and recrystallized from a mixture of EtOH–DMF (1 : 1) to furnish compound **9**. Orange crystals; mp 290–292 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3440, 3331, 3128 (3NH), 1661 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 3.02 (q, 2H, CH_2), 8.58 (s, 1H, triazole H-3), 11.84 (s, 1H, *N*HCO), 14.37 (s, 1H, =NH). Anal. for $C_9H_9N_9OS$ (291.29): calcd: C, 37.11; H, 3.11; N, 43.28%; found: C, 37.00; H, 3.03; N, 43.12%.

Synthesis of (*E*)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-((5-ethyl-1,3,4-thiadiazol-2-yl)amino)-2-oxoacetohydrazonoyl cyanide (10a)

Deep yellow crystals; mp 218–220 °C; yield 92%; IR (KBr) ν/cm^{-1}: 3420, 3411 (2NH), 2220 (CN), 1736, 1658 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.31 (t, 3H, CH_3), 2.27 (s, 3H, CH_3-pyrazole), 3.02 (q, 2H, CH_2), 3.18 (s, 3H, *N*CH_3), 7.09 (m, 5H, Ar-H), 12.33 (s, 1H, NH), 12.82 (s, 1H, NH). MS *m*/*z* (%): 411 (M^+ + 1, 17.75), 410 (M^+, 2.21), 369 (3.31), 240 (9.15), 229 (10.51), 156 (7.79), 129 (10.99), 119 (30.09), 91 (32.82), 77 (50.67), 56 (100), 54 (27.07). Anal. for $C_{18}H_{18}N_8O_2S$ (410.46): calcd: C, 52.67; H, 4.42; N, 27.3%; found: C, 52.59; H, 4.39; N 27.18%.

Synthesis of (*E*)-2-((5-ethyl-1,3,4-thiadiazol-2-yl)amino)-2-oxo-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)acetohydrazonoyl cyanide (10b)

Orange crystals; mp 265–267 °C; yield 95%; IR (KBr) ν/cm^{-1}: 3469, 3226, 3165 (3NH), 2231 (CN), 1665 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 3.01 (q, 2H, CH_2), 6.84 (d, 1H, thiazole H-5, J = 4 Hz), 7.26 (d, 1H, thiazole H-4, J = 4 Hz), 7.81 (d, 2H, Ar-H, J = 8 Hz), 7.97 (d, 2H, Ar-H, J = 8 Hz), 12.37 (s, 1H, =N–NH), 12.38 (s, 1H, *N*HSO_2), 12.81 (s, 1H,

*N*HCO). MS *m*/*z* (%): 463 (M^+ + 1, 1.02), 462 (M^+, 4.16), 451 (2.96), 369 (9.5), 305 (7.88), 250 (10.7), 229 (4.14), 194 (6.01), 156 (17.25), 109 (21.87), 97 (49.14), 83 (51.29), 69 (100), 57 (99.58). Anal. for $C_{16}H_{14}N_8O_3S_3$ (462.52): calcd: C, 41.55; H, 3.05; N, 24.23%; found: C, 41.23; H, 2.95; N, 23.98%.

Synthesis of (*E*)-*N*-(4-(*N*-(4,6-dimethylpyrimidin-2-yl) sulfamoyl)phenyl)-2-((5-ethyl-1,3,4-thiadiazol-2-yl)amino)-2-oxoacetohydrazonoyl cyanide (10c)

Orange crystals; mp 208–210 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3588, 3527, 3231 (3NH), 2232 (CN), 1666 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.31 (t, 3H, CH_3), 2.27 (s, 6H, $2CH_3$-pyrimidine), 3.02 (q, 2H, CH_2), 6.77 (s, 1H, pyrimidine H-5), 7.98 (m, 4H, Ar-H), 12.33 (s, 1H, =N–NH), 12.79 (s, 1H, *N*HSO$_2$), 12.82 (s, 1H, *N*HCO). MS *m*/*z* (%): 485 (M^+, 1.79), 451 (1.5), 344 (5.88), 236 (4.42), 213 (41.28), 200 (6.19), 165 (15.29), 129 (19.51), 83 (45.29), 69 (46.63), 55 (61.02), 43 (100). Anal. for $C_{19}H_{19}N_9O_3S_2$ (485.54): calcd: C, 47.00; H, 3.94; N, 25.96%; found: C, 46.92; H, 3.90; N, 25.86%.

General procedure for the synthesis of thiazole derivatives 12, 13a, b and 14

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. The mixture was stirred for 30 min, and then phenyl isothiocyanate (0.23 mL, 0.002 mol) was added. Stirring the reaction was continued for 6 h. Then the appropriate α-halo compound [namely chloroacetyl chloride (0.16 mL, 0.002 mol), chloroacetone (0.16 mL, 0.002 mol), phenacyl chloride (0.31 g, 0.002 mol) and chloroacetonitrile (0.13 mL, 0.002 mol)] was added to the resulting mixture. The reaction mixture was stirred for an additional 3 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to furnish compounds **12**, **13a**, **b** and **14**, respectively.

Synthesis of (*E*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide (12)

Reddish brown crystals; mp 240–242 °C; yield 92%; IR (KBr) ν/cm^{-1}: 3461 (NH), 2211 (CN), 1747, 1656 (2CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.27 (t, 3H, CH_3), 2.91 (q, 2H, CH_2), 4.02 (s, 2H, CH_2-thiazolidinone), 7.38–7.52 (m, 5H, Ar-H), 14.4 (s, 1H, NH). MS *m*/*z* (%): 372 (M^+ + 1, 20.69), 371 (M^+, 13.43), 329 (2.37), 279 (9.19), 243 (76.54), 215 (100), 169 (12.92), 141 (17.58), 132 (43.76), 124 (26.47), 93 (16.59), 77 (80.99), 73 (12.68), 51 (12.48). Anal. for $C_{16}H_{13}N_5O_2S_2$ (371.43): calcd: C, 51.74; H, 3.53; N, 18.86%; found: C, 51.68; H, 3.48; N, 18.82%.

Synthesis of (*E*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetamide (13a)

Off white crystals; mp 265–267 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3486 (NH), 2184 (CN), 1626 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H ppm 1.28 (t, 3H, CH_3), 1.88 (s, 3H, CH_3-thiazole), 2.91 (q, 2H, CH_2), 7.01 (s, 1H, thiazole H-5), 7.48–7.6 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 13.11, 13.98, 22.71, 106.89, 115.16, 128.73, 129.42, 130.51, 136.25, 138.51, 166.51. DEPT ^{13}C NMR, H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 370 (M^+ + 1, 4.67), 369 (M^+, 26.96), 351 (6.59), 324 (19), 301 (8.47), 265 (18.23), 243 (100), 241 (54.49), 212 (37.02), 186 (35.26), 154 (21.6), 126 (39.35), 77 (45.46), 68 (64), 45 (64.59). Anal. for $C_{17}H_{15}N_5OS_2$ (369.46): calcd: C, 55.27; H, 4.09; N, 18.96%; found: C, 55.19; H, 4.05; N, 18.91%.

Synthesis of (*E*)-2-cyano-2-(3,4-diphenylthiazol-2(3*H*)-ylidene)-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (13b)

Beige powder; mp 245–247 °C; yield 93%; IR (KBr) ν/cm^{-1}: 3446 (NH), 2187 (CN), 1626 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 2.96 (q, 2H, CH_2), 7.19 (s, 1H, thiazole H-5), 7.21–7.61 (m, 10H, Ar-H), 14.49 (s, 1H, NH). MS *m*/*z* (%): 432 (M^+ + 1, 7.15), 431 (M^+, 8.76), 408 (10.59), 390 (10.12), 373 (14.88), 366 (40.31), 316 (22.04), 292 (22.45), 284 (12.94), 250 (37.24), 243 (47.44), 241 (27.25), 197 (24.51), 192 (32.43), 152 (50.08), 132 (33.16), 102 (40.44), 90 (43.04), 83 (64.41), 53 (64.15), 51 (100), 43 (57.47). Anal. for $C_{22}H_{17}N_5OS_2$ (431.53): calcd: C, 61.23; H, 3.97; N, 16.23%; found: C, 61.20; H, 3.93; N, 16.19%.

Synthesis of (*E*)-2-(4-amino-3-phenylthiazol-2(3*H*)-ylidene)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (14)

Deep green powder; mp 225–227 °C; yield 45%; IR (KBr) ν/cm^{-1}: 3415 (NH), 3209, 3154 (NH_2), 2186 (CN), 1644 (C=O). MS *m*/*z* (%): 371 (M^+ + 1, 2.43), 370 (M^+, 1.52), 359 (5.92), 330 (2.41), 297 (9.83), 271 (100), 225 (1.46), 174 (37.98), 129 (79.78), 77 (18.66), 60 (25.27), 51 (42.58). Anal. for $C_{16}H_{14}N_6OS_2$ (370.45): calcd: C, 51.88; H, 3.81; N, 22.69%; found: C, 51.85; H, 3.79; N, 22.67%.

Synthesis of (*E*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-(methylthio)-3-(phenylamino)acrylamide (15)

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. The mixture was stirred for 30 min, and then phenyl isothiocyanate (0.23 mL, 0.002 mol) was added. The reaction mixture was stirred for 6 h. Then dimethyl sulfate (0.19 mL, 0.002 mol) was added to the resulting mixture. Stirring continued for an additional 3 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to afford **15**. Colourless crystals; mp 270–272 °C; yield 70%; IR (KBr) ν/cm^{-1}: 3448, 3313 (2NH), 2227 (CN), 1638 (CO). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 2.85 (s, 3H, SCH_3), 3.04 (q, 2H, CH_2), 7.1–7.49 (m, 5H, Ar-H), 9.8 (s, 1H, *N*HPh), 9.83 (s, 1H, *N*HCO). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 11.87, 17.45, 24.38, 114.58, 123.6, 124.38, 128.41, 139.45, 157.02, 162.71, 163.68, 164.87, 179.58. DEPT ^{13}C NMR, H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 346 (M^+ + 1, 1.74), 345 (M^+, 3.78), 344 (9.39), 331 (9.35), 298 (23.07), 297 (100), 296 (45.5), 252 (93.69), 237 (9.73), 224 (7.7), 180 (12.87), 156 (12.72), 154 (17.42), 118 (5.91), 85 (16.87), 70 (12.05), 58 (4.37), 44 (10.43). Anal. for $C_{15}H_{15}N_5OS_2$ (345.44): calcd: C, 52.16; H, 4.38; N, 20.27%; found: C, 52.11; H, 4.32; N, 20.22%.

General procedure for the synthesis of arylidenes 16a–c

An equimolar mixture of cyanoacetamide **1** (0.4 g, 0.002 mol) and the appropriate aldehyde (namely piperonal, vanilline, and 4-*N*,*N*-dimethylbenzaldehyde) (0.002 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The obtained product was filtered off and recrystallized from EtOH to afford compounds **16a–c**.

Synthesis of (*E*)-3-(benzo[*d*][1,3] dioxol-5-yl)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acrylamide (16a)

Pale yellow crystals; mp 285–287 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3452 (NH), 2221 (CN), 1651 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 2.98 (q, 2H, CH_2), 4.1 (br s, 1H, NH), 6.2 (s, 2H, CH_2-dioxolane), 7.15 (d, 1H, Ar-H, J = 8 Hz), 7.57 (d, 1H, Ar-H, J = 8.4 Hz), 7.69 (s, 1H, Ar-H), 8.35 (s, 1H, vinylic-H). MS *m*/*z* (%): 329 (M^+ + 1, 23.55), 328 (M^+, 100), 327 (93.83), 299 (14.72), 268 (2.95), 207 (5.52), 200 (57.9), 170 (87.75), 142 (39.55), 114 (70.73), 87 (10.52), 73 (9.88), 63 (7.81). Anal. for $C_{15}H_{12}N_4O_3S$ (328.35): calcd: C, 54.87; H, 3.68; N, 17.06%; found: C, 54.85; H, 3.63; N, 16.95%.

Synthesis of (*E*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (16b)

Deep yellow crystals; mp 140–142 °C; yield 92%; IR (KBr) ν/cm^{-1}: 3454 (OH), 3350 (NH), 2211 (CN), 1709 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.26 (t, 3H, CH_3), 2.87 (q, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.89 (d, 1H, Ar-H, J = 8 Hz), 7.43 (d, 1H, Ar-H, J = 8.4 Hz), 7.72 (s, 1H, Ar-H), 8.08 (s, 1H, vinylic-H), 8.99 (s, 1H, OH), 9.02 (s, 1H, *N*HCO). MS *m*/*z* (%): 331 (M^+ + 1, 34.66), 330 (M^+, 100), 301 (5.1), 299 (2.73), 202 (25.53), 170 (36.67), 156 (13.85), 130 (10.67), 114 (11.17), 76 (3.28), 73 (4.35), 56 (1.54). Anal. for $C_{15}H_{14}N_4O_3S$ (330.36): calcd: C, 54.54; H, 4.27; N, 16.96%; found: C, 54.51; H, 4.23; N, 16.95%.

Synthesis of (*E*)-2-cyano-3-(4-(dimethylamino)phenyl)-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acrylamide (16c)

Orange crystals; mp 290–292 °C; yield 93%; IR (KBr) ν/cm^{-1}: 3455 (NH), 2214 (CN), 1651 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.30 (t, 3H, CH_3), 2.98 (q, 2H, CH_2), 3.09 (s, 6H, $N(CH_3)$ 2), 6.85 (d, 2H, Ar-H, J = 8.8 Hz), 7.93 (d, 2H, Ar-H, J = 8.8 Hz), 8.27 (s, 1H, vinylic-H), 12.85 (s, 1H, *N*HCO). MS *m*/*z* (%): 328 (M^+ + 1, 10.89), 327 (M^+, 46.31), 298 (1.56), 272 (3.04), 199 (100), 171 (33.82), 156 (8.7), 128 (2.69), 101 (1.36), 85 (0.94), 73 (2.5). Anal. for $C_{16}H_{17}N_5OS$ (327.40): calcd: C, 58.70; H, 5.23; N, 21.39%; found: C, 58.55; H, 5.21; N, 21.33%.

Synthesis of 3-amino-5-(4-(dimethylamino)phenyl)-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-4-carboxamide (17)

Equimolar amounts of arylidene derivative **16c** (0.654 g, 0.002 mol) and hydrazine hydrate (80%, 0.1 mL, 0.002 mol) in 20 mL of ethanol were heated under reflux for 3 h, then allowed to cool. The obtained solid precipitate was filtered off, purified by washing with ethanol, dried, and recrystallized from EtOH to furnish compound **17**. Yellow powder; mp 295–297 °C; yield 55%; IR (KBr) ν/cm^{-1}: 3411 (2NH), 3280, 3152 (NH_2), 1638 (C=O). MS *m*/*z* (%): 357 (M^+, 6.92), 341 (6.42), 310 (14.8), 309 (37.32), 294 (100), 278 (20.25), 266 (80.14), 251 (11.74), 214 (9.2), 199 (9.85), 174 (9.81), 159 (18.12), 157 (22.63), 147 (23.35), 130 (28.89), 118 (29.54), 104 (29.44), 96 (33.58), 77 (39.75), 70 (42.92), 55 (40.84). Anal. for $C_{16}H_{19}N_7OS$ (357.44): calcd: C, 53.77; H, 5.36; N, 27.43%; found: C, 53.72; H, 5.35; N, 27.39%.

General procedure for the synthesis of pyridin-2-ones 18a–d

Method A. Equimolar amounts of **1** (0.4 g, 0.002 mol) and the appropriate 2-(arylidene)-ethyl cyanoacetate [namely 2-(benzylidene)-ethyl cyanoactate, 2-(4-nitrobenzylidene)-ethyl cyanoactate, 2-(4-chlorobenzylidene)-ethyl cyanoactate, and 2-(4-*N*,*N*-dimethylbenzylidene)-ethyl cyanoactate] (0.002 mol) were placed in ethanol (25 mL) containing piperidine (0.5 mL), and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to cool. The solid product that was obtained was filtered off and recrystallized from ethanol.

Method B. A mixture of **1** (0.4 g, 0.002 mol), and the appropriate aldehyde (namely benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and 4-*N*,*N*-dimethylbenzaldehyde) (0.002 mol), piperidine (0.5 mL), and ethyl cyanoacetate (0.002 mol) in ethanol (25 mL) was refluxed for 3 h. The reaction mixture was allowed to cool. The precipitate that formed was isolated by filtration, dried and purified by recrystallization from EtOH.

Method C. A mixture of **16c** (0.33 g, 0.001 mol) and ethyl cyanoacetate (0.11 mL, 0.001 mol) in ethanol (20 mL) including piperidine (0.5 mL) was refluxed for 3 h. The obtained product was isolated by filtration and purified by recrystallization from ethanol to afford **18d**.

Synthesis of 1-(5-ethyl-1,3,4-thiadiazol-2-yl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (18a)

Yellow crystals; mp 290–292 °C; yield 65%; IR (KBr) ν/cm^{-1}: 3475 (OH), 2216 (2CN), 1694 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.25 (t, 3H, CH_3), 2.94 (q, 2H, CH_2), 7.21–7.41 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 11.96, 24.35, 44.17, 97.56, 101.15, 114.87, 117.8, 127.36, 127.51, 127.54, 138.21, 153.66, 158.87, 159.87, 160.28. MS *m*/*z* (%): 350 (M^+ + 1, 21.24), 349 (M^+, 80.58), 348 (100), 332 (8.96), 320 (5.88), 261 (2.92), 165 (5.7), 139 (3.44), 127 (3.16), 85 (3.88), 56 (4.57). Anal. for $C_{17}H_{11}N_5O_2S$ (349.37): calcd: C, 58.44; H, 3.17; N, 20.05%; found: C, 58.40; H, 3.14; N, 19.99%.

Synthesis of 1-(5-ethyl-1,3,4-thiadiazol-2-yl)-6-hydroxy-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (18b)

Deep brown powder; mp 250–252 °C; yield 85%; IR (KBr) ν/cm^{-1}: 3446 (OH), 2199 (2CN), 1670 (CO), 1522 (NO2). MS *m*/*z* (%): 394 (M^+, 5.01), 373 (5.45), 336 (5.59), 329 (28.08), 301 (16.62), 300 (62.34), 292 (1.40), 284 (23.61), 265 (32.96), 257 (34.87), 256 (100), 255 (25.28), 246 (19.31), 227 (5.23), 192 (4.91), 137 (6.49), 112 (14.78), 93 (17.79), 80 (23.63), 79 (20.13), 68 (12.58), 48 (9.77). Anal. for $C_{17}H_{10}N_6O_4S$ (394.37): calcd: C, 51.78; H, 2.56; N, 21.31%; found: C, 51.74; H, 2.52; N, 21.30%.

Synthesis of 4-(4-chlorophenyl)-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (18c)

Yellow powder; mp 265–267 °C; yield 82%; IR (KBr) ν/cm^{-1}: 3504 (OH), 2213 (2CN), 1692 (CO). MS *m*/*z* (%): 368 (M^+ − 15, 13.47), 366 (1.08), 353 (11.22), 328 (4.88), 313 (4.31), 297 (6.47), 265 (9.98), 236 (17.53), 229 (8.88), 159 (11.13), 137 (10.87), 123 (24.83), 109 (26.98), 97 (50.06), 84 (39.46), 71 (57.77), 69 (100), 57 (93.35), 43 (91.87). Anal. for $C_{17}H_{10}ClN_5O_2S$ (383.81): calcd: C, 53.2; H, 2.63; N, 18.25%; found: C, 53.15; H, 2.62; N, 18.19%.

Synthesis of 4-(4-(dimethylamino)phenyl)-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (18d)

Orange powder; mp 285–287 °C; yield 82%; IR (KBr) ν/cm^{-1}: 3445 (OH), 2209 (2CN), 1705 (CO). MS *m*/*z* (%): 392 (M^+, 3.00), 370 (3.08), 369 (5.40), 351 (4.94), 330 (3.73), 328 (5.18), 304 (20.99), 287 (8.14), 271 (31.05), 248 (16.77), 240 (100), 207 (45.35), 185 (23.2), 181 (48.16), 176 (11.13), 156 (62.39), 153 (31.52), 138 (20.18), 121 (18.63), 86 (82.77), 84 (51.31), 60 (45.65), 52 (49.38), 44 (98.88). Anal. for $C_{19}H_{16}N_6O_2S$ (392.44): calcd: C, 58.15; H, 4.11; N, 21.42%; found: C, 58.12; H, 4.08; N, 21.38%.

General procedure for the synthesis of pyridin-2-ones 19a–d

Method A. Equimolar amounts of **1** (0.4 g, 0.002 mol) and the appropriate 2-(arylidene)-malononitrile [namely 2-(benzylidene)-malononitrile, 2-(4-nitrobenzylidene)-malononitrile, 2-(4-chlorobenzylidene)-malononitrile, and 2-(4-*N*,*N*-dimethylbenzylidene)-malononitrile] (0.002 mol) were placed in ethanol (25 mL) containing piperidine (0.5 mL), and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to cool. The solid product that was obtained was filtered off and recrystallized from ethanol.

Method B. A mixture of **1** (0.4 g, 0.002 mol), and the appropriate aldehyde (namely benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and 4-*N*,*N*-dimethylbenzaldehyde) (0.002 mol), piperidine (0.5 mL), and malononitrile (0.002 mol) in ethanol (25 mL) was refluxed for 3 h. The reaction mixture was allowed to cool. The precipitate that formed was isolated by filtration, dried and purified by recrystallization from EtOH.

Method C. A mixture of **16c** (0.33 g, 0.001 mol) and malononitrile (0.07 g, 0.001 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was heated under reflux for 3 h. The obtained product was isolated by filtration and purified by recrystallization from ethanol to afford **19d**.

Synthesis of 6-amino-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (19a)

Yellow powder; mp 240–242 °C; yield 75%; IR (KBr) ν/cm^{-1}: 3444 (OH), 3343, 3208 (NH_2), 2212, 2163 (2CN), 1638 (CO). MS *m*/*z* (%): 348 (M^+, 1.38), 330 (7.03), 329 (11.78), 298 (2.47), 201 (2.9), 156 (13.48), 135 (26.66), 129 (33.61), 119 (16.51), 100 (8.53), 93 (23.43), 77 (100), 74 (75.38), 73 (43.98), 60 (82.11), 45 (72.42). Anal for $C_{17}H_{12}N_6OS$ (348.38): calcd: C, 58.61; H, 3.47; N, 24.12%; found: C, 58.57; H, 3.42; N, 24.05%.

Synthesis of 6-amino-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (19b)

Brown powder; mp 240–242 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3446 (OH), 3342, 3217 (NH_2), 2210 (2CN), 1636 (CO), 1521 (NO2). MS *m*/*z* (%): 394 (M^+ + 1, 1.96), 393 (M^+, 6.7), 363 (2.6), 346 (6.27), 338 (12.77), 311 (6.82), 282 (32.52), 265 (4.76), 236 (3.67), 184 (5.24), 175 (7.04), 156 (11.69), 136 (33.47), 129 (27.76), 106 (22.56), 90 (35.21), 89 (65.14), 84 (73.14), 78 (90.14), 69 (75.55), 56 (97.69), 43 (98.7), 41 (100). Anal. for $C_{17}H_{11}N_7O_3S$ (393.38): calcd: C, 51.91; H, 2.82; N, 24.92%; found: C, 51.88; H, 2.8; N, 24.89%.

Synthesis of 6-amino-4-(4-chlorophenyl)-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (19c)

Pale yellow crystals; mp 245–247 °C; yield 84%; IR (KBr) ν/cm^{-1}: 3445 (OH), 3338, 3197 (NH_2), 2211 (2CN), 1639 (CO). MS *m*/*z* (%): 383 (M^+ + 1, 98.26), 382 (M^+, 100), 381 (10.98), 366 (15.4), 356 (18.74), 337 (34.57), 320 (4.39), 295 (9.77), 294 (2.52), 270 (2.54), 255 (1.86), 199 (3.23), 190 (1.10), 161 (2.38), 138 (3.31), 125 (7.84), 113 (1.87), 86 (1.97), 84 (2.96), 73 (3.12), 56 (1.99). Anal. for $C_{17}H_{11}ClN_6OS$ (382.83): calcd: C, 53.34; H, 2.90; N, 21.95%; found: C, 53.32; H, 2.8; N, 21.89%.

Synthesis of 6-amino-4-(4-(dimethylamino)phenyl)-1-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (19d)

Orange crystals; mp 275–277 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3446 (OH), 3430, 3202 (NH_2), 2209 (2CN), 1705 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.29 (t, 3H, CH_3), 3.1 (s, 6H, $N(CH_3)2$), 4.27 (q, 2H, CH_2), 6.84 (d, 2H, Ar-H, J = 9.2 Hz), 7.96 (d, 2H, Ar-H, J = 8.8 Hz), 8.12 (s, 1H, NH). MS *m*/*z* (%): 392 (M^+ + 1, 5.29), 391 (M^+, 49.7), 387 (9.7), 368 (22.58), 326 (43.61), 288 (11.82), 272 (34.44), 247 (23.23), 246 (19.36), 228 (58.36), 211 (18.54), 206 (48.02), 198 (100), 196 (44.36), 169 (59.65), 155 (48.75), 140 (39.06), 131 (24.87), 113 (16.55), 105 (49.41), 99 (77.15), 94 (22.16), 77 (34.14), 52 (37.48), 50 (46.43). Anal. for $C_{19}H_{17}N_7OS$ (391.45): calcd: C, 58.30; H, 4.38; N, 25.05%; found: C, 58.10; H, 4.35; N, 25.02%.

Synthesis of (*Z*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-(4-phenyl-1,3-dithiol-2-ylidene)acetamide (21)

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. After stirring for 30 min, carbon disulfide (0.12 mL, 0.002 mol) was added. The reaction mixture was stirred for 12 h, and then phenacyl bromide (0.41 g, 0.002 mol) was added to the resulting mixture. Stirring was continued in the presence of ethanol for an additional 6 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to yield **21**. Pale yellow powder; mp 275–277 °C; yield 85%; IR (KBr) ν/cm^{-1}: 3421 (NH), 2204 (CN), 1647 (CO). MS *m*/*z* (%): 373 (M^+ + 1, 4.07), 372 (M^+, 8.73), 357 (14.78), 355 (44.95), 333 (21.48), 313 (16.82), 285 (11.9), 270 (88.53), 264 (14.2), 251 (9.09),

199 (7.67), 178 (13.55), 156 (15.94), 126 (11.2), 113 (32.26), 105 (89.81), 96 (57.73), 83 (62.68), 77 (100), 73 (78.59), 69 (40.34), 58 (61.95), 45 (69.49). Anal. for $C_{16}H_{14}N_4O_2S_3$ (372.48): calcd: C, 51.59; H, 3.25; N, 15.04%; found: C, 51.57; H, 3.21; N, 15.00%.

Synthesis of 4-amino-5-benzoyl-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-mercaptothiophene-3-carboxamide (22)

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. After stirring for 30 min, carbon disulfide (0.12 mL, 0.002 mol) was added. Stirring was continued for 12 h, and then phenacyl bromide (0.41 g, 0.002 mol) was added to the resulting mixture. The reaction mixture was refluxed in the presence of triethylamine (0.5 mL) for an additional 3 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to afford **22**. Green powder; mp 285–287 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3413 (NH), 3296 (NH_2), 2622 (SH), 1718, 1645 (2C=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H ppm 1.31 (t, 3H, CH_3), 2.95 (q, 2H, CH_2), 7.43–7.6 (m, 5H, Ar-H), 8.35 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 12.37, 23.29, 106.41, 122.18, 126.83, 128.29, 130.71, 140.48, 156.65, 159.56, 162.33, 167.14, 168.66, 185.86. DEPT ^{13}C NMR, H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 390 (M^+, 0.53), 357 (15.3), 356 (45.6), 355 (51.44), 339 (5.42), 300 (3.63), 292 (6.64), 286 (6.85), 249 (9.58), 234 (12.13), 201 (5.62), 172 (3.72), 158 (6.35), 146 (10.13), 129 (25.42), 105 (100), 93 (4.04), 86 (10.04), 77 (93.59), 74 (29.31), 70 (12.4), 51 (16.5). Anal. for $C_{16}H_{14}N_4O_2S_3$ (390.49): calcd: C, 49.21; H, 3.61; N, 14.35%; found: C, 49.16; H, 3.55; N, 14.22%.

Synthesis of (*E*)-2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-(4-oxo-1,3-dithiolan-2-ylidene)acetamide (23)

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. After stirring for 30 min, carbon disulfide (0.12 mL, 0.002 mol) was added. The reaction mixture was stirred for 12 h, and then chloroacetyl chloride (0.16 mL, 0.002 mol) was added dropwise to the resulting mixture. Stirring was continued for an additional 6 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to give **23**. Reddish brown powder; mp 190–192 °C; yield 45%; IR (KBr) ν/cm^{-1}: 3456 (NH), 2209 (CN), 1684, 1630 (2CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H ppm 1.29 (t, 3H, CH_3), 3.01 (q, 2H, CH_2), 4.07 (s, 2H, CH_2-dithiolane). MS *m*/*z* (%): 312 (M^+, 9.15), 289 (6.36), 288 (25.24), 270 (42.28), 270 (42.28), 238 (25.78), 217 (5.68), 207 (6.58), 191 (1.58), 180 (15.27), 160 (25.57), 146 (21.17), 129 (40.19), 110 (22.33), 86 (36.67), 76 (39.55), 64 (100), 60 (76.21), 59 (45.6), 54 (29.34), 45 (54.26). Anal. for $C_{10}H_8N_4O_2S_3$ (312.38): calcd: C, 38.45; H, 2.58; N, 17.94%; found: C, 38.41; H, 2.55; N, 17.90%.

Synthesis of 2-cyano-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-3,3-bis(methylthio)acrylamide (24)

To a stirred solution of KOH (0.11 g, 0.002 mol) in DMF (25 mL), compound **1** (0.4 g, 0.002 mol) was added. After stirring for 30 min, carbon disulfide (0.12 mL, 0.002 mol) was added. Stirring was continued for 12 h, and then dimethyl sulfate (0.38 mL, 0.004 mol) was added dropwise to the resulting mixture. Stirring was continued for an additional 6 h. Then, the reaction mixture was poured into a beaker containing a crushed ice/water mixture. The formed precipitate was filtered off, dried and purified by recrystallization from EtOH to furnish **24**. Pale yellow powder; mp 210–212 °C; yield 90%; IR (KBr) ν/cm^{-1}: 3445 (NH), 2188 (CN), 1642 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H ppm 1.39 (t, 3H, CH_3), 2.53 (s, 6H, 2SCH_3), 3.27 (q, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 11.94, 12.23, 16.71, 21.49, 90.76, 117.89, 157.24, 163.65, 165.91, 171.62. DEPT ^{13}C NMR, H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 300 (M^+, 1.67), 253 (3.91), 217 (0.80), 186 (5.96), 170 (39.01), 161 (5.11), 142 (6.59), 110 (23), 91 (34.23), 84 (22.77), 83 (100), 73 (28.82), 56 (21.85), 45 (33.82). Anal. for $C_{10}H_{12}N_4OS_3$ (300.42): calcd: C, 39.98; H, 4.03; N, 18.65%; found: C, 39.95; H, 4.00; N, 18.55%.

Synthesis of *N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-7-imino-5-(methylthio)-1,7-dihydro-^{1,2,4} triazolo[1,5-*a*]pyrimidine-6-carboxamide (25)

To a solution of compound **24** (0.4 g, 0.0013 mol) in pyridine (25 mL), 3-amino-1*H*-1,2,4-triazole (0.112 g, 0.0013 mol) was added. The reaction mixture was refluxed for 3 h, and then left to cool. The formed precipitate was isolated by filtration, then purified by recrystallization from EtOH to afford **25**. Deep yellow powder; mp 190–192 °C; yield 52%; IR (KBr) ν/cm^{-1}: 3464, 3433, 3409 (3NH), 1642 (CO). MS *m*/*z* (%): 336 (M^+, 11.45), 332 (24.08), 325 (32.54), 306 (14.82), 302 (64.48), 300 (37.42), 291 (29.25), 289 (8.13), 257 (12.77), 251 (22.55), 228 (43.51), 225 (21.62), 199 (23.43), 183 (24.76), 175 (54.19), 153 (30.74), 119 (54.27), 95 (49.89), 79 (32.62), 64 (100), 57 (27.07). Anal. for $C_{11}H_{12}N_8OS_2$ (336.4): calcd: C, 39.28; H, 3.6; N, 33.31%; found: C, 39.22; H, 3.45; N, 33.28%.

Synthesis of 2-cyano-2-(1,3-dihydro-2*H*-benzo[*d*]imidazol-2-ylidene)-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)acetamide (26)

To a solution of compound **24** (0.4 g, 0.0013 mol) in pyridine (20 mL), *o*-phenylenediamine (0.15 g, 0.0013 mol) was added. The reaction mixture was refluxed for 3 h, and then left to cool. The formed solid product was isolated by filtration, then purified by recrystallization from EtOH to afford **26**. Beige powder; mp 265–267 °C; yield 65%; IR (KBr) ν/cm^{-1}: 3451, 3303, 3130 (3NH), 2219 (CN), 1679 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H ppm 1.35 (t, 3H, CH_3), 3.07 (q, 2H, CH_2), 7.47–7.64 (m, 4H, Ar-H), 7.93 (s, 2H, 2NH), 8.35 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C ppm 13.85, 22.76, 97.26, 116.89, 123.87, 127.70, 132.21, 157.04, 162.61, 165.99, 175.77. DEPT ^{13}C NMR, H–H COSY, HSQC and HMBC results are in agreement with the proposed structure. MS *m*/*z* (%): 312 (M^+, 9.15), 294 (7.74), 272 (3.49), 257 (6.15), 251 (39.84), 232 (7.57), 205 (29.08), 135 (30.82), 112 (63.99), 107 (100), 93 (36.94), 87 (54.24), 68 (72.37), 44 (88.96). Anal. for $C_{14}H_{12}N_6OS$ (312.35): calcd: C, 53.83; H, 3.87; N, 26.91%; found: C, 53.81; H, 3.85; N, 26.88%.

Laboratory bioassay

Laboratory experiments were conducted to study the insecticidal activity of the newly synthesized tested compounds against the 2nd instar larvae of *S. littoralis*. The experiments were carried out using the leaf dip technique.[34] Six concentrations of each compound were formulated as emulsions in solvent, and 0.1% Triton X-100 was used as a surfactant. The emulsions were used immediately after preparation. For larvicidal action, fresh castor bean leaves were dipped in the tested concentrations for 10 seconds. The treated leaves were left in the shade to dry before being offered to the larvae. The larvae were allowed to feed on the treated leaves for 48 hours and then changed to untreated leaves. Three replicates of 10 larvae each were used for each concentration in addition to the control. Control (check) tests were carried out using the same technique. Castor bean leaves were dipped in a solution of 0.1% Triton X-100 and solvent at the same ratio used in the synthesized compound tests. Larval mortality counts were calculated at 1, 2, 3, 4, 5, 6 and 7 days after exposure period. Mortality was corrected according to Abbott's formula,[35] and then subjected to probit analysis. The toxicity lines (LC-p lines) were drawn on log concentration–probit paper and statistically analyzed according to Finney's method[36] to obtain the LC_{50} and LC_{90} values of different tested compounds in order to determine the most effective one. Slope values of the tested compounds were also estimated. In addition, the efficacy of the different compounds was measured by comparing the tested compounds with the most effective compound using the following equation: toxicity index = LC_{50} of the most effective compound/LC_{50} of the tested compound $\times$ 100, according to Sun.[37]

Conclusions

In the present work, a novel series of different heterocyclic compounds incorporating the thiadiazole moiety has been successfully synthesized and characterized. These compounds were evaluated for their insecticidal activities against the cotton leafworm, *S. littoralis*. Compounds **10b**, **10c** and **7** proved to be promising insecticidal agents since they clearly showed higher activities than the other tested compounds.

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Notes and references

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