

Synthesis of novel thiazole and pyridine derivatives and evaluation of their insecticidal potency

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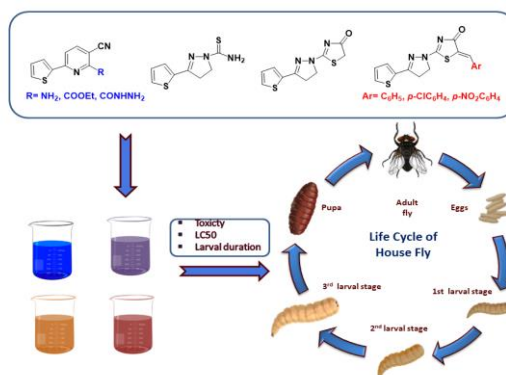
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Abstract

A novel series of 3-cyano-6-thienylpyridines and 3-thienyl-2-pyrazolines have been developed. The compounds were tested for their insecticidal efficacy against *Musca domestica* Linnaeus larvae. Selection of these pyridine and 2-pyrazoline-derived heterocycles was favoured due to their wide range of biological uses, making them safe for natural application. The studied compounds proved reasonable larvicidal effects and developmental arrest of *M. domestica*. This study indicated that such compounds can be utilized as insecticides in an efficient manner.



Keywords: Thiosemicarbazide, 2-pyrazolines, thiazol-4(5*H*)-one, thiophene, biological activity, insecticidal activity

Introduction

Musca domestica Linnaeus, commonly known as the house fly, carries numerous diseases, including diphtheria, typhoid, tuberculosis, dysentery, leprosy, cholera, anthrax, and intestinal parasites, which threaten public health.¹ *M. domestica* can transmit over 100 harmful pathogens, such as enteropathogenic microbes, enteroviruses and protozoan cysts to animals and humans.^{2,3} The house fly is a widely distributed species which makes up 98 percent of the flies that enter houses. It is considered to be one of the most unsanitary insect pests.⁴ *M. domestica* is challenging to control because it can easily adjust to various environmental conditions, has a high reproductive capacity, and overgrows. Regrettably, the resistance of house flies to commonly-used pesticides, such as organophosphates, insect growth regulators (IGR), and bacterial larvicides, is constantly growing. This resistance has become the main obstacle in managing vector-borne diseases.⁵ Direct contact with or immersion in housefly larvae can lead to the development of insects. Therefore, we are pursuing a traditional approach to the application of new pesticides using distinct chemical compounds to control the third larval stage of the housefly.

Heterocyclic chemistry is important in both chemical and natural systems.⁶ Pyridine and 2-pyrazoline-based heterocycles demonstrate a diverse array of biological activities, encompassing anti-cancer,⁷⁻⁹ antiviral,^{10, 11} antibacterial,¹²⁻¹⁴ and a pivotal role in pesticide production.^{15, 16}

Building upon the discoveries above and in line with previous endeavors,^{17, 18} we have chosen to create innovative insecticides containing pyridine or 2-pyrazoline rings to target the larval phase of the common housefly, *M. domestica* Linnaeus (Diptera: Muscidae). The aim of this study was to examine the impact of different compounds containing pyridine and 2-pyrazoline on the survival rates of third-instar larvae of *M. domestica*. Figure 1 displays the structures of various insecticides that are derived from pyridine, 2-pyrazoline, and thiophene, along with the compounds that are being investigated.

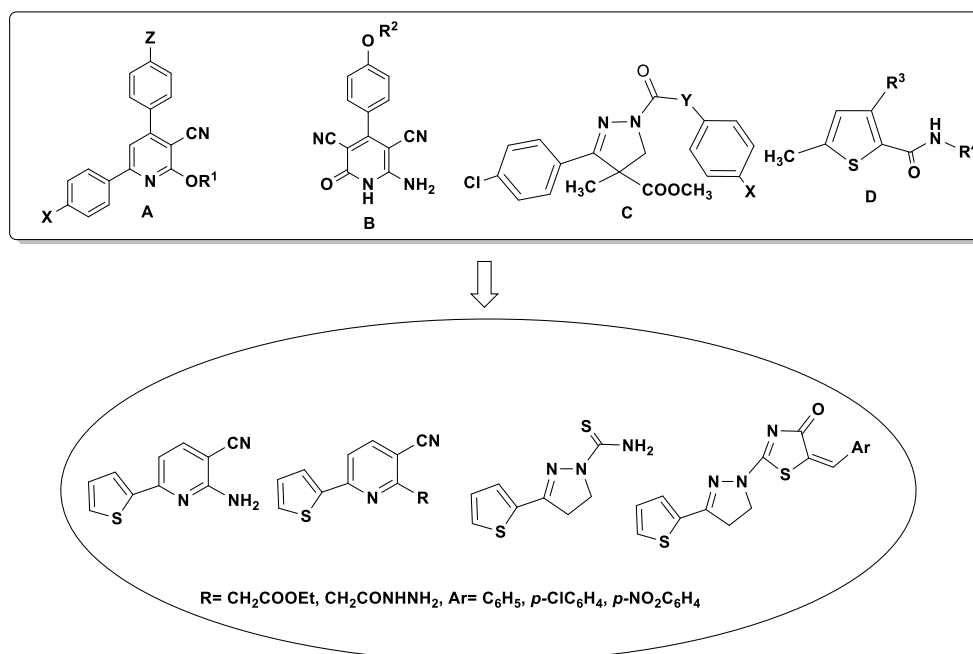


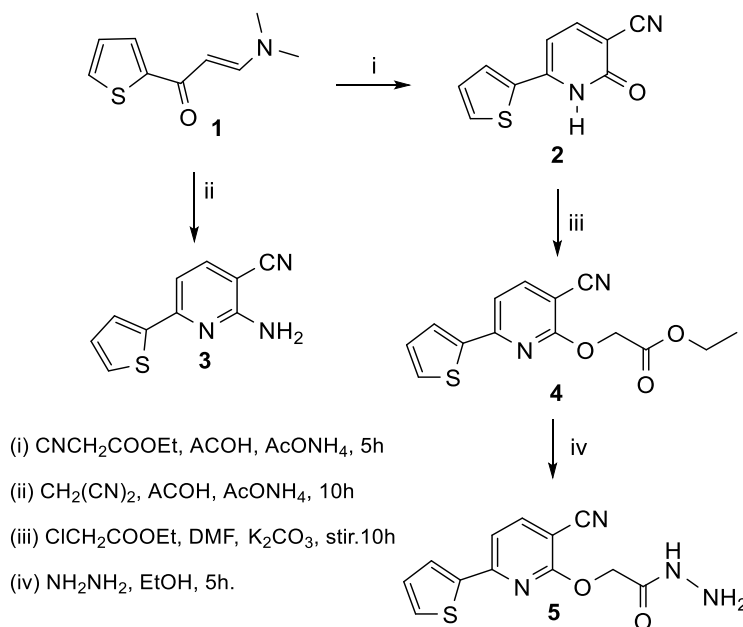
Figure 1. Structures of some reported insecticides based on pyridine derivatives (**A** and **B**), 2-pyrazoline **C**, and thiophene **D**, as well as the newly-synthesized compounds.

Results and Discussion

Chemistry

We report in this study the synthesis of several novel derivatives of pyridine and pyrazoline with thienyl nuclei. The synthesized compounds were tested in the laboratory for insecticidal activity against *Musca domestica* Linnaeus larvae. The crucial formation step, of β -enaminone **1**, was produced by reacting 2-acetylthiophene with dimethylformamide/dimethyl acetal in xylene. The intended compound **1** was treated with acidic hydrogen reagents that included ethyl cyanoacetate or malononitrile to get 2-oxypyridine-3-carbonitrile **2** and/or 2-aminopyridine-3-carbonitrile **3**. The product **2** was previously produced by the reaction of chalcone with cyanoacetamide¹⁹ (not part of this current work), and the structures **2** and **3** were validated using a variety of spectral and analytical methods. The Ft-IR spectrum of **2** indicated three strong peaks at ν 1675, 2217 and 3281 cm^{-1} , indicating the existence of C=O, CN, along with NH_2 groups, accordingly. The $^1\text{H-NMR}$ spectrum indicated an NH group signal at δ 12.58 ppm and the absence of the two methyl groups.

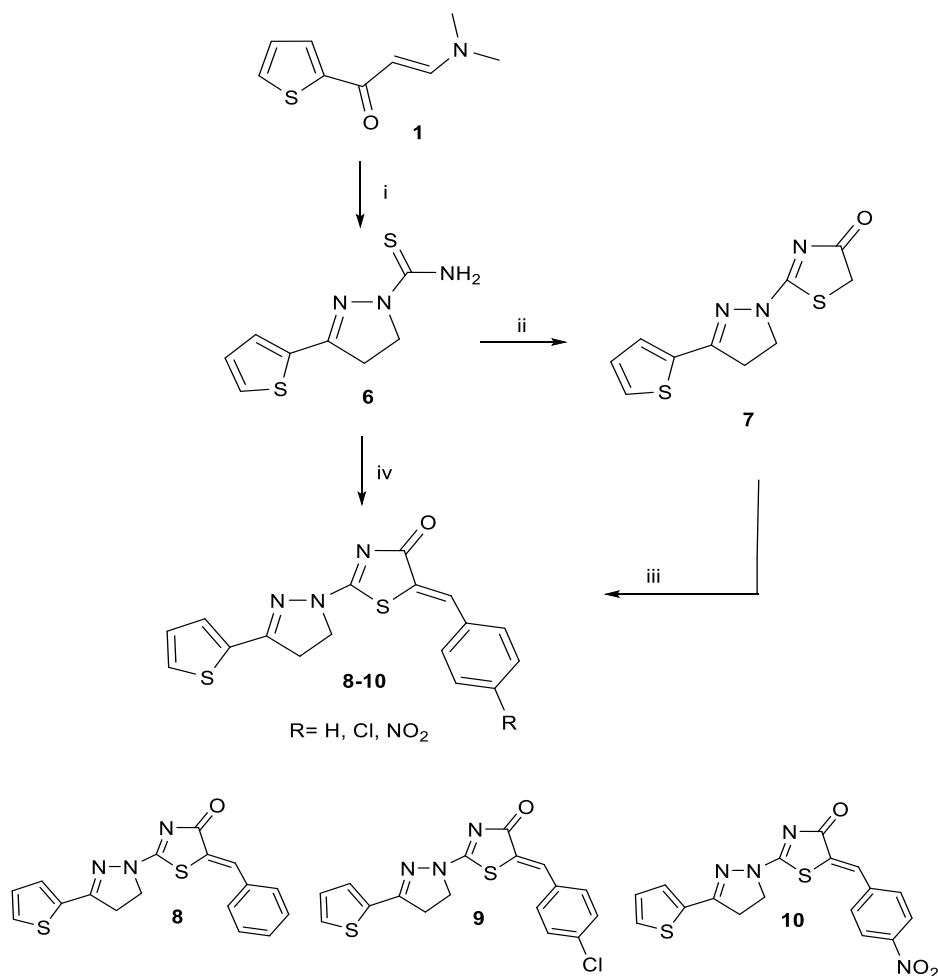
The compound 2-oxypyridine-3-carbonitrile **2** underwent a reaction with ethyl chloroacetate to produce the pyridine ester derivative **4**. Subsequently, boiling this derivative with hydrazine in ethanol resulted in the formation of the hydrazinocarbonyl analog **5** (Scheme 1). The spectral data confirmed the structures of compounds **4** and **5**. In contrast, while attempting to synthesize a 2-pyrazoline derivative, the β -enaminone **1** interacted with thiosemicarbazide, resulting in 1-thiocarbamoyl-3-(thien-2-yl)-2-pyrazoline **6**. The latter compound was earlier synthesized using a different approach (reaction of Mannich base with thiosemicarbazide).²⁰ The structure of **6** was investigated using elemental analysis and spectroscopic data, and was consistent with that previously produced.



Scheme 1. The pathway for the synthesis of pyridine analogues (**2-5**).

1-Thiocarbamoyl 2-pyrazoline **6**, used as a precursor to afford different thiazolones, was cyclized using chloroacetic acid, giving 2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4(5H)-one (**7**). The IR spectra of **7** indicated the elimination of the NH_2 peak and the detection of a signal at ν =1688 cm^{-1} attributed to the C=O group. The $^1\text{H-NMR}$ spectrum indicated a signal at δ 4.96 ppm from the two protons of the thiazolone ring; no amino-

group protons were present. Depending on the active methylene of the thiazolone ring, compound **7** was condensed with various aromatic aldehydes such as benzaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde to produce the arylidenes 5-benzylidene-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (**8**), 5-(*p*-chloro- benzylidene)-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (**9**), and 5-(*p*-nitrobenzylidene)-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (**10**), respectively (Scheme 2). The Ft-IR spectra of the arylidenes **8-10** indicated strong absorption bands of the functional groups, ranging from 1668-1710 cm^{-1} for the carbonyl groups, to an absorption band from 3009 to 3098 cm^{-1} owing to the C-H aromatic ring.



(i) $\text{NH}_2\text{NHCSNH}_2$, EtOH, NaOH, 8h; (ii) ClCH_2COOH , ACOH, AcONa, 8h;

(iii) Aromatic aldehydes, ACOH, AcONa, 6h; (iv) Aromatic aldehydes, ClCH_2COOH , ACOH, AcONa, 10h.

Scheme 2. Routes for the syntheses of 1-thiocarbamoyl 2-pyrazoline and thiazolone derivatives (**6-10**).

The molecular structures of compounds **8-10** were fully validated by ^1H -NMR and ^{13}C -NMR spectra, which proved the existence of new hydrogen and carbon signals, respectively, in the molecule. Compound **8** displayed the appearance of five aromatic protons with one proton of the thiophene ring and benzylidene proton at δ 7.60-8.22 ppm, as well as the loss of the two protons of the thiazolone rings. The carbons of the aromatic ring and $=\text{CH}-$ can be observed in ^{13}C -NMR. The Ft-IR spectrum of **9** showed bands at ν 3049 (Ar-H), and 1687 ($\text{C}=\text{O}$) cm^{-1} . The ^1H -NMR spectra verified the disappearance of the active methylene of the thiazolone ring. Similarly, the ^{13}C -NMR and ^1H -NMR spectra agreed with the proposed structure of **10**.

Compound **6** was refluxed with chloroacetic acid in an acetic acid solution containing benzaldehyde and fused sodium acetate, to confirm the chemical structure of the previously mentioned compound. The findings were in line with the molecular structures of arylidenes **8-10** (Scheme 2).

Insecticidal activity

The insecticidal activities of different doses of the compounds were studied against the third instar larvae of *M. domestica* L. in a controlled laboratory setting. The findings revealed that larval mortality increased with increasing compound concentrations. The lowest concentration of 100 ppm showed minor mortality effectiveness, with rates of 15.5%, 10.0%, 22.0%, 21.5%, 19.0%, 11.5%, 16.0%, 23.0%, 13.0%, and 11.0% for compounds **1-10**, respectively. At 700 ppm, compounds **8**, **5**, and **3** had the highest mortality rates, i.e., 94.0%, 94.0%, and 95.0%, respectively.

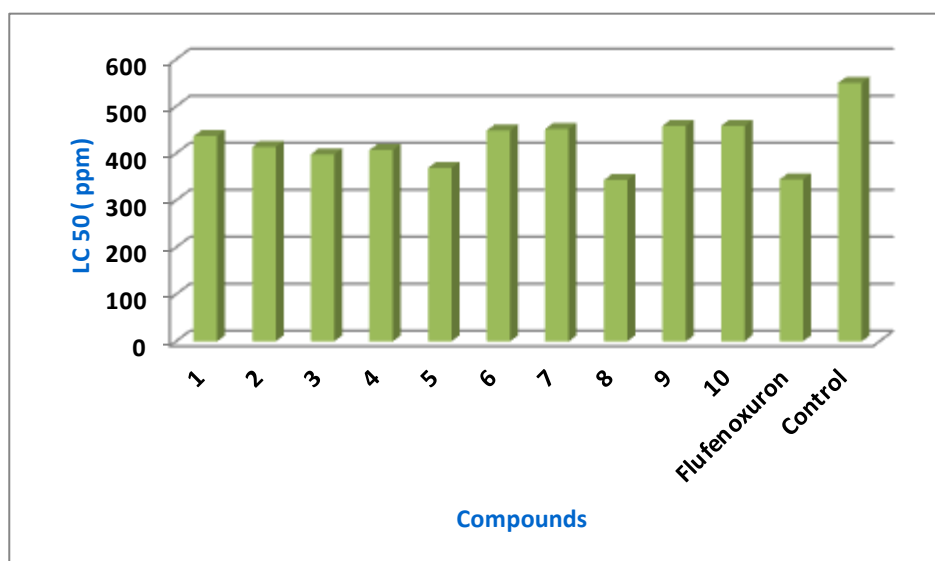


Figure 2. Larvicidal activity of the synthesized compounds **1-10** on *Musca domestica* third instar larvae 24 hours post-treatment.

Meanwhile, mortality rates reached 100% at the highest concentration employed (1000 ppm) for all compounds **1-10**, compared to 13%, 12%, and 14% for the control groups, and 29%, 100% and 100% for the groups treated with flufenoxuron. The probit-model analysis results in Figures 2 and 3 show that the highest toxicities, based on LC₅₀ values, were for compound **8** (343.0 ppm), compound **5** (369.1 ppm), compound **4** (407.1 ppm), and compound **3** (398.9 ppm). Compounds **6**, **7**, **9** and **10** had the lowest toxicities, with LC₅₀ values of 448.4, 452.1 ppm and 458.4 ppm, respectively, in comparison with 344.39 ppm for commercial flufenoxuron compound.

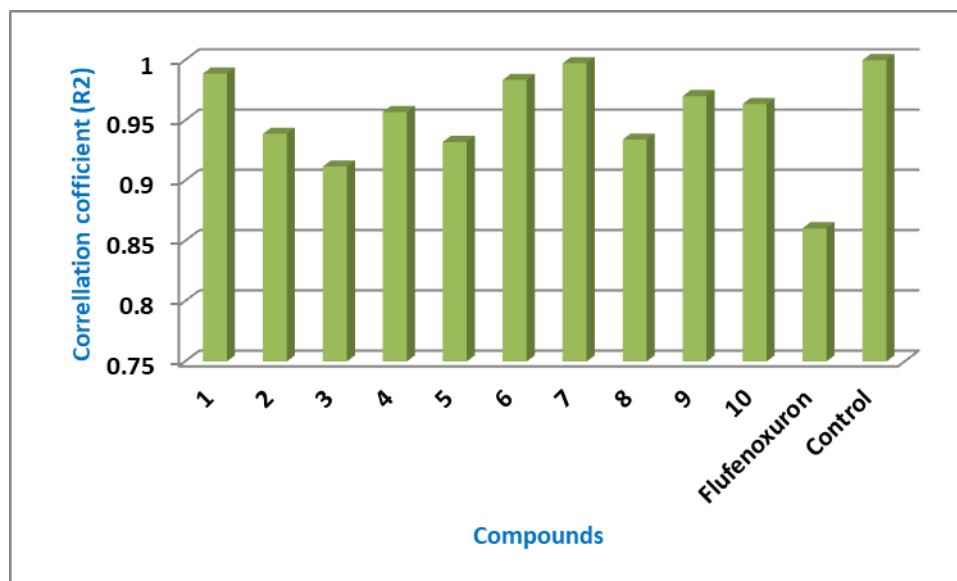


Figure 3. The correlation coefficients of *Musca domestica* third instar larvae exposed to the synthesized compounds **1-10** for 24 hours post-treatment.

Table 1 shows the impact of the tested compounds on the larval duration of the examined insect, *M. domestica* larvae. The study found that treating *M. domestica* larvae with the examined compounds resulted in a longer larval duration. The larval duration increased from 1.9 in controls to 3.1, 3.8, 2.4, 3.9, 3.1, 2.9, 3.2, 3.7, 3.5, and 3.9 days for all compounds at 400 ppm, respectively. In contrast, at 700 ppm concentrations, the larval lengths were 4.6, 5.0, 3.6, 5.1, 4.4, 3.7, 4.3, 4.8, 4.8, and 5.0 days for the same compounds, respectively, compared to 2.4 days for the control group. For the lowest concentration (100 ppm), larval duration values were similar to those of the untreated group. This demonstrates a clear toxic effect of the tested chemicals, particularly at high concentrations, on larval development. The rate of mortality was increasing in a dose-dependent manner. Additionally, there were slight fluctuations in the toxicity (as represented by LC₅₀) of these compounds against the larvae. *Hexafumuron* showed the most significant larval control pattern, with 100% larval mortality at 400 ppm, and the rate of mortality decreased with decreasing concentrations. Similar patterns were observed with lufenuron and *fufenoxuron*.

The current study suggested that the toxicities of the compounds tested also varied with changes in chemical structure although the fluctuations in toxicity were somewhat slight. Compounds **3**, **4**, **5**, **8** showed the highest toxicities while compounds **6**, **7**, **9** and **10** had the lowest. The current study clearly showed severe extension of larval period of *M. domestica* following treatments when compared to controls. These outcomes are a continuation of our earlier study which utilized newly synthesized compounds, identified as pyrazole-pyridine derivatives (PPD), which retarded the development of larvae to pupae, and the emergence of adults from the pupal stages, by approximately 20 percent and 17 percent, respectively.²¹ Control of medically-important insect pests became necessary because they are transmitting several pathogens responsible for infectious diseases. As a result, continuous research is being conducted to find novel, safe and cheap insecticides against the larvae and pupae of these insects. In general, the classical chemical-control method based on traditional insecticides was mainly achieved using carbamates, the organophosphates (OP), the pyrethroids (PYR), organochlorines (OC) and cyclodienes. Pyrazole rings combined with pyridine are heterocyclic organic compounds which are characterized by a broad spectrum of insecticide activities, safety to human environment, and lack of resistance by different insect taxa.²²⁻²⁴ The safety of many pyrazole and

pyridine derivatives is assured based on their broad spectrum of clinical applications,²² making them suitable for natural applications as promising tools in managing harmful insects.

Table 1. Efficacy of the synthesized compounds **1-10** on the larval duration period for *Musca domestica* third instars larvae 24 hours post-treatment

Compound No.	Conc. (ppm)/Mean larval period (days)± SD				*
	100 ppm	400 ppm	700 ppm	1000 ppm	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
1	1.9 ± 0.12	3.1 ± 0.16	4.6 ± 0.18	-	
2	2.5 ± 0.16	3.8 ± 0.18	5.0 ± 0.17	-	
3	1.5 ± 0.11	2.4 ± 0.15	3.6 ± 0.12	-	
4	1.9 ± 0.10	3.9 ± 0.19	5.1 ± 0.17	-	
5	1.7 ± 0.13	3.1 ± 0.16	4.4 ± 0.13	-	
6	1.4 ± 0.18	2.9 ± 0.13	3.7 ± 0.12	-	
7	1.7 ± 0.11	3.2 ± 0.12	4.3 ± 0.14	-	
8	1.6 ± 0.14	3.7 ± 0.19	4.8 ± 0.16	-	
9	1.7 ± 0.13	3.5 ± 0.15	4.8 ± 0.15	-	
10	2.0 ± 0.18	3.9 ± 0.19	5.0 ± 0.13	-	
Control	2.1 ± 0.18	1.9 ± 0.19	2.4 ± 0.13	2.0 ± 0.18	
Flufenoxurn	2.7 ± 0.15	4.2 ± 0.18	-	-	

Note: No. of tested larvae = 20; SD = standard deviation.

Conclusions

We have successfully synthesized a variety of heterocyclic compounds derived from the thiophene structure, resulting in 2-cyano-6-thienyl pyridines, a 3-thienyl-2-pyrazoline, and thiazol-4-one derivatives, which were subsequently evaluated for their insecticidal efficacy against the housefly larvae, *Musca domestica* Linnaeus. Our investigation found a positive correlation between the compounds and the growth of larval periods and larval mortality. Several compounds (**1**, **2**, **6**, **7**, **9**, and **10**) showed promising results, and several compounds, (**3**, **4**, **5**, and **8**) demonstrated strong larvicidal effectiveness against housefly larvae. The findings provide valuable insights into the potential of these compounds as sources for the development of insecticides and their potential integration into pest-management strategies. We recommend applying these compounds to combat housefly larvae, and, specifically, *Musca domestica* Linnaeus.

Experimental Section

General. The materials used in the current experiment were of analytical grade. The melting points that were not adjusted were estimated utilizing an APP Digital ST 15 melting-point instrument. A Shimadzu-408 infrared Spectrophotometer was used to record the FTIR spectra in cm^{-1} . NMR spectra were acquired using a Bruker Avance III 400 MHz spectrometer and are reported in parts per million (ppm). Chemical shifts were determined with TMS as an internal reference standard. Mass spectrometry was provided using a Varian MAT 312 instrument in EI mode (70 eV), Faculty of Science, Assiut University, Egypt. Chemical analysis of elements was carried out using a System GmbH Vario EL V2.3 1998 CHNS Mode.

6-(Thien-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2). Ethyl cyanoacetate (3 mmol) and 3-(dimethylamino)-1-(thiophen-2-yl)prop-2-en-1-one **1** (3 mmol) were mixed in EtOH (30 ml) with ammonium acetate (9 mmol) and refluxed at 100 °C for 5 h. Following the completion of the reaction, the product was separated and recrystallized with ethanol. Yield: (78%, yellow crystals), mp 286–288°C. IR (ν_{max}): 3281 (NH), 2217 (CN), 1675 (C=O) cm^{-1} ; ^1H -NMR (400 MHz, DMSO- d_6): δ 7.10–7.20 (m, 2H, thienyl-H), 7.35–7.37 (d, 1H, *J* 8 Hz, thienyl-H), 7.73–7.85 (m, 2H, pyridinone H), 12.58 (s, 1H, NH) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 110.0, 113.0, 117.0, 119.6 (CN), 122.4, 123.9, 127.4, 132.0, 136.8, 140.0 (C=O) ppm. EI-MS: *m/z* 202.0 (M^+ , 89%). Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{N}_2\text{OS}$ (202.23): C, 59.39; H, 2.99; N, 13.85; S, 15.85%. Found: C, 59.30; H, 2.91; N, 13.77; S, 15.75%.

2-Amino-6-(thien-2-yl) pyridine-3-carbonitrile (3). Malononitrile (0.32 g, 5 mmol) was dissolved in ethanol (20 ml) including β -enaminone **1** (0.91 g, 5 mmol) and ammonium acetate (1.16 g, 15 mmol). The solution was refluxed at 100 °C for 5 h. On cooling, the separated material was separated, dried, and recrystallized using ethanol. Yield: (72%, pale green crystals), mp 203–205°C. IR (ν_{max}): 3447, 3230 (NH_2), 2211 (CN) cm^{-1} ; ^1H -NMR (400 MHz, DMSO- d_6): δ 7.15–7.35 (m, 2H, thienyl-H), 7.51–7.61 (d, 1H, *J* 40 Hz, thienyl-H), 7.90–8.02 (m, 2H, pyridine-H), 12.11 (s, 2H, NH) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 108.1, 113.3, 114.5, 116.1, 119.0, (CN), 121.4, 124.8, 127.2, 134.5, 135.1 ppm. EI-MS: *m/z* 201.0 (M^+ , 48%). Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{S}$ (201.24): C, 59.68; H, 3.51; N, 20.88; S, 15.93%. Found: C, 59.60; H, 3.44; N, 20.80; S, 15.83%.

2-((Ethoxycarbonyl)methyloxy)-6-(2-thienyl) pyridine-3-carbonitrile (4). Pyridine analogue **2** (3 mmol) was added to ethyl chloroacetate (3 mmol) in DMF (10 ml) with anhydrous K_2CO_3 (2.25 g, 20 mmol). The resultant solution was stirred at room temperature for 10 h before being poured over crushed ice, forming a precipitate that was recrystallized using dioxane. Yield: (72%, pale yellow powder), mp 130–132°C. IR (ν_{max}): 2984 (Aliphatic-H), 2214 (CN), 1701 (C=O) cm^{-1} ; ^1H -NMR (400 MHz, DMSO- d_6): δ 1.20–1.28 (t, 3H, *J* 16 Hz, ethyl- CH_3), 4.24–4.36 (q, 2H, *J* 16 Hz, ethyl- CH_2), 4.91 (s, 2H, CH_2), 7.14–7.17 (m, 2H, thienyl-H), 7.19–7.20 (m, 1H, thienyl-H), 7.54–7.70 (m, 2H, pyridine-H) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 14.9 (CH_3), 47.4 (ethyl- CH_2), 62.7 (CH_2), 109.0, 116.0, 118.9 (CN), 123.5, 124.7, 128.8, 134.0, 136.1, 140.3, 146.89, 166.8 (CO) ppm. EI-MS: *m/z* 288.0 (M^+ , 86%). Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ (288.32): C, 58.32; H, 4.20; N, 9.72; S, 11.12%. Found: C, 58.25; H, 4.12; N, 9.65; S, 11.21%.

2-((Hydrazinocarbonyl)methyloxy)-6-(thien-2-yl) pyridine-3-carbonitrile (5). Hydrazine hydrate (0.98 ml, 2 mmol) and **4** (0.57 g, 2 mmol) were dissolved in ethanol (15 ml) and refluxed at 100 °C for 5 h. The solution was cooled, and the solid precipitate was removed, dried and recrystallized using ethanol. Yield: (70%, orange needles), mp 171–173°C. IR (ν_{max}): 3487 and 3271 (NH, NH_2), 2277 (CN), 1693 (CO) cm^{-1} ; ^1H -NMR (400 MHz, DMSO- d_6): δ 4.70 (s, 2H, CH_2), 5.36 (s, br., 2H, NH_2 , exchangeable), 7.20–7.31 (m, 2H, thienyl-H), 7.40–7.45 (m, 1H, thienyl-H), 7.61–7.91 (m, 2H, pyridine-H), 9.26 (s, 1H, NH exchangeable) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 60.4 (CH_2), 110.0, 113.1, 119.1, (CN), 121.9, 123.6, 129.3, 135.5, 136.8, 138.0, 141.9, 170.0 (C=O) ppm.

El.MS: m/z 274.1 (M^+ , 94%). Anal. Calcd. for $C_{12}H_{10}N_4O_2S$ (274.29): C, 52.55; H, 3.67; N, 20.43; S, 11.69%. Found: C, 52.48; H, 3.73; N, 20.34; S, 11.79%.

1-Thiocarbamoyl-3-(thien-2-yl)-2-pyrazoline (6). The mixture of β -enaminone **1** (3 mmol), thiosemicarbazide (3 mmol) in ethanol (15 ml) with sodium hydroxide (0.30 g) was refluxed at 100 °C for 8 h. After cooling, the solid product was filtered, washed with water, and recrystallized in ethanol. Yield: (77%, yellow crystals), mp 177-179 °C. IR (ν_{\max}): 3381 and 3181 (NH_2) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$): δ 3.20-3.30 (t, 2H, J 20 MHz, CH_2), 4.34-4.42 (t, 2H, J =20 MHz, CH_2); 6.50 (s, 2H, NH_2); 7.10-7.14 (dd, 1H, thienyl-H), 7.15-7.17 (dd, 1H, thienyl-H), 7.46-7.50 (dd, 1H, thienyl-H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$): δ 50.6 and 58.2 for (2 CH_2), 112.9, 121.6, 123.8, 135.9, 138.7, 179.6 (CS) ppm; El.MS: m/z 211.1 (M^+ , 83%). Anal. Calcd. for $C_8H_9N_3S_2$ (211.30): C, 45.47; H, 4.29; N, 19.89; S, 30.35%. Found: C, 45.55; H, 4.21; N, 19.79; S, 30.24%.

2-(3-(Thien-2-yl)-2-pyrazolin-1-yl)thiazol-4(5H)-one (7). 1-Thiocarbamoyl compound **6** (3 mmol) and chloroacetic acid (4 mmol), which included fused AcONa (0.28 g), were refluxed in acetic acid (20 ml) at 130 °C for 8 h. The reaction mixture was cooled and added to crushed ice. The resulting precipitate was collected, dried, and purified using dioxane. Yield: (77%, pale orange powder), mp 256-258 °C. IR (ν_{\max}): 3011 (Ar-H), 1688 ($C=O$) cm^{-1} ; 1H -NMR (400 MHz, $DMSO-d_6$): δ 3.29-3.37 (t, 2H, J 20 MHz, CH_2), 4.30-4.38 (t, 2H, J 20 MHz, CH_2); 4.92 (s, 2H, thiazolone- CH_2), 7.12-7.24 (m, 2H, thienyl-H), 7.28-7.60 (dd, 1H, thienyl-H) ppm; ^{13}C -NMR (100 MHz, $DMSO-d_6$): δ 51.6 and 57.2 for (2 CH_2), 60.1 (thiazole- CH_2), 112.7, 114.1, 121.9, 123.8, 126.3, 131.8, 170.8 ($C=O$) ppm; El.MS: m/z 251.1 (M^+ , 74%). Anal. Calcd. for $C_{10}H_9N_3OS_2$ (251.32): C, 47.79; H, 3.61; N, 16.72; S, 25.51%. Found: C, 47.71; H, 3.53; N, 16.65; S, 25.43%.

Thiazol-4(5H)-one condensation with aromatic aldehydes, syntheses of arylidenes (8-10). Chloroacetic acid (0.28 g, 3 mmol) was mixed in acetic acid (30 ml), then compound **6** (0.42 g, 3 mmol), aromatic aldehyde (3 mmol), and fused AcONa (0.30 g) were added and refluxed at 130 °C for 8 h. The resultant solution was cooled, poured over crushed ice, and the formed solid precipitate was collected, dried, and recrystallized using dioxane.

5-Benzylidene-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (8). Yield: (70%, reddish brown crystals), mp 160-162 °C. IR (ν_{\max}): 3009 (Ar-H), 1668 ($C=O$) cm^{-1} ; 1H -NMR (400 MHz, $DMSO-d_6$): δ 3.34-3.42 (t, 2H, J =20 MHz, CH_2), 4.42-4.50 (t, 2H, J 20 MHz, CH_2); 7.10-7.40 (m, 2H, thienyl-H), 7.60-8.00 (m, 7 H, 5 Ar-H, thienyl-H and =CH-) ppm; ^{13}C -NMR (100 MHz, $DMSO-d_6$): δ 51.2 and 56.9 for (2 CH_2), 111.9, 114.2, 120.9, 121.2, 123.9, 126.5, 132.8, 134.9, 138.5, 140.3, 145.4, 151.0, 176.0 ($C=O$) ppm. El.MS: m/z 339.30 (M^+ , 78%). Anal. Calcd. for $C_{17}H_{13}N_3OS_2$ (339.43): C, 60.16; H, 3.86; N, 12.38; S, 18.89%. Found: C, 60.08; H, 3.80; N, 12.29; S, 18.98%.

5-(*p*-Chlorobenzylidene)-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (9). Yield: (69%, orange crystals), mp 154-156 °C. IR (ν_{\max}): 3049 (Ar-H), 1687 ($C=O$) cm^{-1} ; 1H -NMR (400 MHz, $DMSO-d_6$): δ 3.31-3.39 (t, 2H, J 20 MHz, CH_2), 4.40-4.48 (t, 2H, J 20 MHz, CH_2); 7.14-7.41 (m, 2H, thienyl-H), 7.62-8.34 (m, 6H, 4 Ar-H, thienyl-H and =CH-) ppm; ^{13}C -NMR (100 MHz, $DMSO-d_6$): δ 50.2 and 54.2 for (2 CH_2), 110.8, 112.6, 122.8, 123.4, 125.3, 132.6, 135.0, 138.8, 141.3, 145.6, 148.2, 151.2, 154.4, 175.2 ($C=O$) ppm; El.MS: m/z 373.4 (M^+ , 100%), 375.3 ($M^+ + 2$, 32.8%). Anal. Calcd. for $C_{17}H_{12}N_3OS_2Cl$ (373.87): C, 54.61; H, 3.24; N, 11.24; S, 17.15; Cl, 9.48%. Found: C, 54.53; H, 3.15; N, 11.32; S, 17.05; Cl, 9.33 %.

5-(*p*-Nitrobenzylidene)-2-(3-(thien-2-yl)-2-pyrazolin-1-yl) thiazol-4-one (10). Yield: (80%, brown crystals), mp 181-183 °C. IR (ν_{\max}): 3098 (Ar-H), 1710 ($C=O$) cm^{-1} ; 1H -NMR (400 MHz, $DMSO-d_6$): δ 3.29-3.40 (t, 2H, J 20 MHz, CH_2), 4.39-4.47 (t, 2H, J 20 MHz, CH_2); 7.10-7.44 (m, 2H, thienyl-H), 7.60-8.32 (m, 6 H, 4 Ar-H, thienyl-H and =CH-) ppm; ^{13}C -NMR (100 MHz, $DMSO-d_6$): δ 51.0 and 54.4 for (2 CH_2), 111.5, 112.4, 121.8, 124.2, 125.4, 133.8, 136.2, 138.4, 140.9, 142.7, 152.6, 155.8, 177.0 ($C=O$) ppm; El.MS: m/z 384.0 (M^+ , 100%). Anal. Calcd. for $C_{17}H_{12}N_4O_3S_2$ (384.43): C, 53.11; H, 3.15; N, 14.57; S, 16.68%. Found: C, 53.03; H, 3.07; N, 14.50; S, 16.58%.

Insecticidal activity

Insect culture. The larvae were fed an artificial diet of wheat bran, milk, and powdered yeast (200:100:5 g)/200 ml of distilled water, as previously reported. ^[22] Third larval instars were used in toxicity and developmental assays. All assays were performed based on three independent replicates. To calculate mortalities, different concentrations of heterocycles (100, 400, 700 and 1000 ppm) were used to observe the effect on house fly larvae. ^[24] The third instar larvae were promptly placed in molded wells containing the medium having different concentrations of the synthesized compounds. Three separate replicates were normally used with every concentration using 20 larvae at each replicate. Mortality rates were determined for each treatment and control group on a daily basis. *Flufenoxuron* (Cascade 10% ECC-AS No.1014-63-69-8), *N*-[[4-[2-chloro-4-(trifluoromethyl) phenoxy]-2-fluorophenyl] carbamoyl]-2,6-difluoro benzamide, used as the standard control treatment, was kindly supplied by the Laboratory of Insecticides, Plant Protection Research Institute, Dokki, Giza, Egypt. The larval mortality was confirmed by their inability to respond to electrical stimulation. ^[25] In the untreated (negative) groups, only water was utilized, whereas in the untreated (positive) groups, the insecticide was dissolved in 3 ml of Tween 80 combined with dechlorinated water.

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Supplementary Material

Copies of FT-IR, ¹H, ¹³C NMR and mass spectra of new compounds and bar graph of mortality percentages of *Musca domestica* third instar larvae are provided in the Supplementary Material file associated with this manuscript.

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