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SYNTHESIS AND INSECTICIDAL EVALUATION OF NOVEL CYANOPYRIDINE DERIVATIVES AGAINST *APHIS GOSSYPII*

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ABSTRACT. Another important factor driving the development of new therapeutic and insecticidal agents is the rapid emergence of resistance to conventional pesticides and antibiotics. One promising strategy for addressing this challenge is the exploration of new chemical scaffolds with diverse modes of action. In this study, a series of pyridine derivatives was synthesized efficiently using ultrasound-assisted technology as an alternative to conventional synthetic methods. The compounds were prepared through a simple four-component reaction involving substituted aromatic benzaldehydes, aryl acetyl compounds, sodium alkoxides, and malononitrile. All synthesized derivatives exhibited insecticidal activity against both nymphal and adult stages of the cotton aphid, *Aphis gossypii*. These pyridine derivatives were designed as structural analogs of neonicotinoid insecticides, and their toxicity toward *A. gossypii* was evaluated under laboratory conditions. Among the tested compounds, **if** and **ic** demonstrated the highest insecticidal potency, with LC_{50} values of 0.102 and 0.108 mg/L, respectively. The findings highlight the potential of these pyridine-based compounds as promising candidates for the discovery and development of novel insecticidal agents. Furthermore, the effects of compounds **ib, ic**, and **if** were investigated at sublethal concentrations below their respective LC_{50} values to assess their additional biological effects on the tested aphid populations.

KEY WORDS: Insecticidal activity, Cotton aphid, Pyridine, Neonicotinoids, *Aphis gossypii*

INTRODUCTION

Over 45% of the annual food output is lost due to insect invasion; therefore, operative pest management consuming a diversity of pesticides is necessary to combat pests and boost crop productivity [1]. *Aphis gossypii* Glover (Hemiptera: Aphididae), a polyphagous sap-sucking aphid pest of cotton worldwide, is a major issue because of the honeydew contamination of the open boll lint [1, 2]. Its prominence as a cotton pest has improved throughout the cotton-growing regions of the world [4]. *A. gossypii* is regarded as one of the most dangerous pests in the Middle East, and its damage also has an impact on cottonseed output and fiber quality, in addition to the spread of viral illnesses [5]. The most popular method used by farmers to get rid of many other arthropod pests, including cotton aphids, is chemical treatment [6]. Certain widely used insecticides have the potential to exacerbate an aphid outbreak by eliminating aphid predator species and enabling a sharp rise in population. Populations of this pest are now resistant to a number of insecticide classes as a result of years of heavy pesticide application [7, 8]. Due to insect pests like aphids becoming more resistant to the most common insecticides, selective insecticides (like neonicotinoids) have replaced organophosphates and methyl carbamates in the market in recent years [9-12]. A wide variety of commercially significant sucking insect pests, including aphids, whiteflies, thrips, leafhoppers, and others, can be effectively controlled as seed and foliar treatments with acetamiprid, imidacloprid, thiamethoxam, and dinotefuran, a novel class of nicotinoid insecticides that work by binding to nicotinoid acetylcholine receptors (Figure 1) [13-15].

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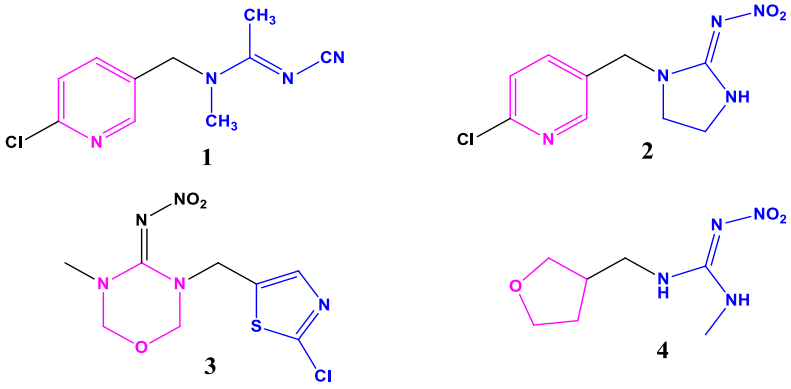


Figure 1. Chemical structure of acetamiprid (**1**), imidacloprid (**2**), thiamethoxam (**3**), and dinotefuran (**4**).

Because of their special qualities, neonicotinoid counterparts, and numerous uses, pyridine compounds are among the most prominent of them [16-19]. Pyridine derivatives are frequently found in the structures of numerous bioactive compounds in medical chemistry, such as antioxidant, anti-inflammatory, and anticancer medicines. Pyridine compounds are also being studied for their potential as insecticidal agents in agriculture, which goes beyond their use in medicine [20-22]. One of the most pressing issues facing humanity is crop damage brought on by dangerous pests. Significant losses in crop productivity result from the persistent use of traditional pesticides, which frequently leads to the creation of more resistant insect species [23]. Research has shown that pyridine compounds are quite effective against agricultural pests [24]. The ability of pyridine's structure to affect pests' biological systems allows it to prevent the growth of a variety of insect pests, including scale insects and aphids, which helps lower agricultural losses [25]. It is a viable choice for creating an efficient insecticide because of its efficacy [26, 27]. Furthermore, research has shown that the effects of pyridine extend to enhancing plant growth by improving nutrient absorption, as some pyridine compounds act as growth promoters, which may increase agricultural yields [28]. Because of their low toxicity, pyridine compounds provide a safer and more sustainable option in light of growing concerns about the use of conventional chemical insecticides and their detrimental effects on the environment. The potential of these substances to create efficient and eco-friendly pesticides is still being investigated in recent studies.

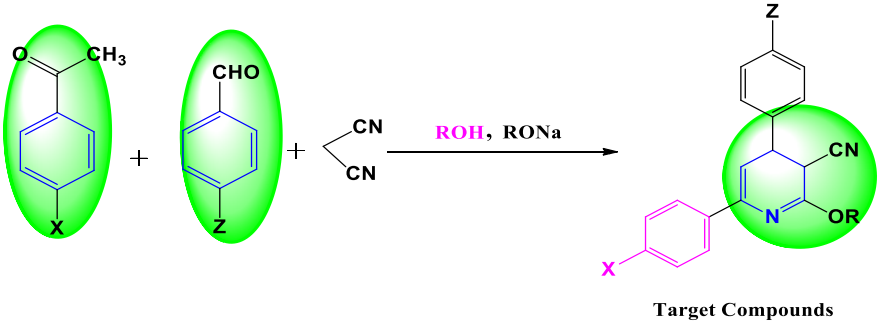


Figure 2. Designing strategy and structure optimization of insecticidal substances.

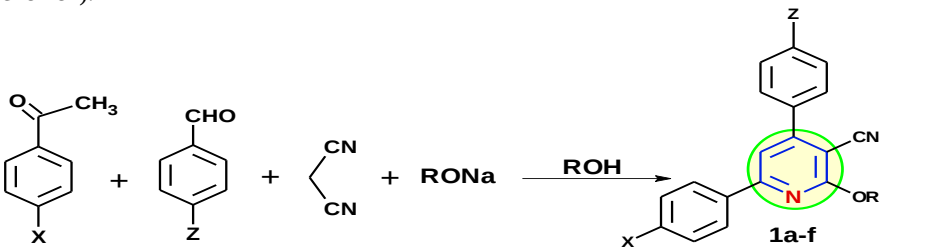
This study intends to synthesize different pyridine compounds and assess their insecticidal efficacy against both nymphs and adults of the cotton aphid, *A. gossypii*, in light of the

aforementioned evidence and our ongoing efforts to study pyridine compounds and other bioactive materials (Figure 2). The goal is to identify effective pesticides that not only exhibit durable activity against major agricultural pests but also prioritize environmental safety.

RESULT AND DISCUSSION

Synthesis

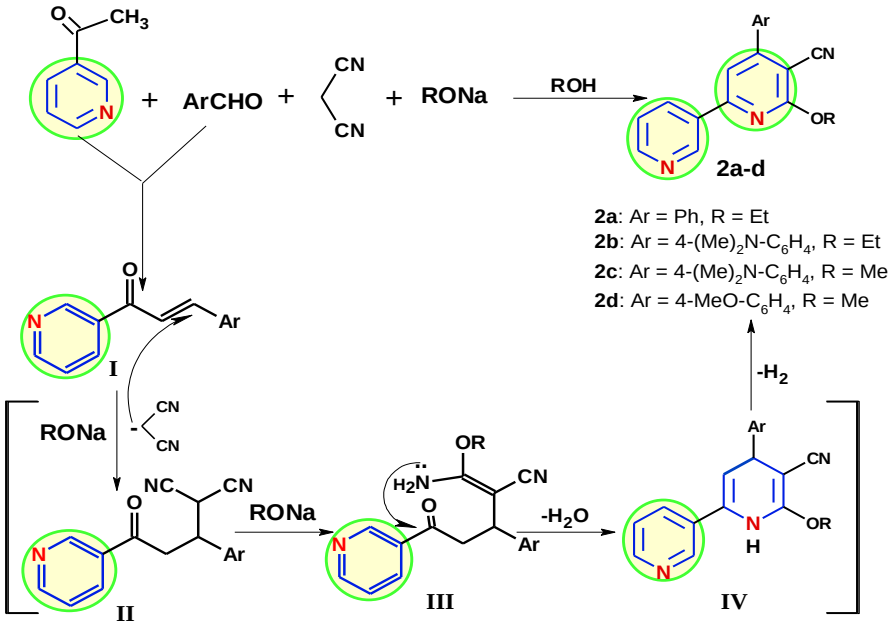
The four-component reaction involving acetyl aryl compounds, Ar-CHO, cyanoacetonitrile, and R-ONa in methyl alcohol and/or sodium ethoxide in methyl alcohol at 60 °C under ultrasonic irradiation produced the prepared compounds (**1a-b**) using straightforward and effective methods (Scheme1).



1a: X = MeO, Z = H, R = Me
1b: X = Cl, Z = H, R = Me
1c: X = Cl, Z = $(Me)_2N$, R = Me
1d: X = Cl, Z = MeO, R = Me
1e: X = MeO, Z = H, R = Et
1f: X = Cl, Z = H, R = Et
1g: X = Cl, Z = $(Me)_2N$, R = Et
1h: X = Cl, Z = MeO, R = Et
1i: X = MeO, Z = MeO, R = Et
1j: X = MeO, Z = Cl, R = Et

Scheme 1. Synthesis of compounds **1a-j**.

Given these findings, it was noteworthy to use the same techniques for the preparation of heterocyclic substances that have two pyridine rings in the hopes of obtaining these compounds with applications for increased biological activity. Therefore, by reacting aromatic aldehydes, 3-acetylpyridine, cyano acetonitrile, and RO-Na under the same reaction conditions, the analogous processes were expanded to make 4-phenyl-cyanopyridines (**2a-d**) (Scheme 2).



Scheme 2. Designing of materials **2a-d**.

The cyano acetonitrile anion was added at α, β-unsaturated carbonyl to form intermediate II, which reacted with RO- to form adduct III. The adduct III cyclized via intramolecular cyclizing to produce IV, which was then dehydrogenated to produce the alkoxypyridines-3-carbonitrile **2a-d** (Scheme 2). This was the assumed reaction mechanism for the yielding of the materials **2a-d**. The infrared, NMR spectrum analysis, and melting temperatures of compounds **1a-j** and **2a-d** were used to determine their chemical structures. For instance, 6-ethoxy-4-phenyl-2,3'-bipyridine-5-carbonitrile (**2a**)'s infrared spectrum lacks any C=O-specific absorption peaks. Cyano band characteristic was seen at 2224 cm^{-1}. Its ^{1}H-NMR spectra demonstration four peaks at 9.370, 8.630, 8.520, and 7.090 ppm, which are suggestive of a pyridine nucleus. Additionally, it has a multiplied signal at 7.930 that is attributed to 2H aromatic and 1H of the pyridine ring, and the aromatic protons exhibit additional multiplied signals at 7.57-7.09 ppm. The ^{13}C-NMR spectra of **2a** show that, in addition to aryl carbons at δ 164.520, 155.790, 152.8, 150.33, 148.50, 136.52, 134.75, 134.45, 134.27, 130.99, 129.41, and 124.

Insecticidal bio-efficacy screening

According to Table 1, the concentration that eliminates the half of the aphid population is a more useful point statistically for comparison. Aphid mortality data were evaluated expending probity analysis utilizing some statistical software (LDP-line) to determine the LC_{50} values and "95" educible limits of upper and lower confidence limits, standard error, slope, chi-square, and correlation coefficient.

Table 1. Insecticidal efficiency of substances **1a-j**, **2a-d**, and acetamiprid towards *A. gossypii* (nymphs & adults) after one day of management.

	Nymphs				Adults			
Comps.	LC_{50} (mg/L)	Slope	χ^2	Toxic ratio	LC_{50} (mg/L)	Slope	χ^2	Toxic ratio*
1a	0.742	0.458 ± 0265	0.987	0.074	1.437	0.570 ± 0.267	0.410	0.193
1b	0.153	0.336 ± 0.288	0.592	0.359	0.511	0.402 ± 0267	0.431	0.565
1c	0.108	0.381 ± 0.282	0.841	0.509	0.457	0.496± 0.267	0.177	0.193
1d	0.137	0.345 ± 0.271	1.030	0.401	0.498	0.401 ± 0.281	0.161	0.580
1e	0.612	0.436 ± 0.276	0.151	0.089	1.319	0.523 ± 0.269	0.951	0.219
1f	0.102	0.386 ± 0.284	0.375	0.539	0.434	0.451 ± 0.271	0.122	0.665
1g	0.119	0.356 ± 0.275	0.594	0.462	0.512	0.411 ± 0.283	0.322	0.561
1h	0.175	0.431 ± 0.286	0.357	0.324	0.678	0.490 ± 0.265	0.463	0.426
1i	0.716	0.481 ± 0.276	0.287	0.076	1.414	0.582 ± 0.270	0.057	0.204
1j	0.568	0.473 ± 0.267	0.589	0.096	1.121	0.554 ± 0.2**71**	0.276	0.257
2a	0.543	0.431 ± 0.268	0.274	0.101	1.102	0.551 ± 0.271	0.667	0.262
2b	0.266	0.473 ± 0.287	0.268	0.206	0.841	0.483 ± 0.276	0.811	0.343
2c	0.604	0.479 ± 0.273	0.784	0.091	1.394	0.580 ± 0.283	0.303	0.207
2d	0.952	0.412 ± 0.269	0.311	0.057	1.498	0.545 ± 0.277	0.376	0.192
R. I**	0.055	0.380 ± 0.282	0.411	1	0.289	0.386 ± 0.283	0.389	1

**R.I. = Reference insecticide acetamiprid.

*The Toxicity Ratio is determined by dividing the baseline toxicity of acetamiprid by the LC_{50} value of the compound.

According to Table 1, and Figure 3, all eleven tested analogs have a moderate or weak toxicological conclusion on cotton aphids (nymphs), with LC_{50} values ranging from 0.102 to 0.952 mg/L after 24 hours of treatment. Some of these analogs have toxicological effectiveness that is comparable to that of a reference acetamiprid (LC_{50} = 0.055 mg/L). Compounds **1a-j, 2a-d**, and acetamiprid, in particular, had LC_{50} values of 0.742, 0.153, 0.108, 0.137, 0.612, 0.102, 0.119, 0.175, 0.716, 0.568, 0.543, 0.266, 0.604, and 0.952 mg/L. Pyridine compounds **1f** and **1c** have the highest insecticidal effectiveness of all the substances studied, with LC_{50} values of 0.102 and 0.108 mg/L, respectively.

The insecticidal properties of compounds **1a-J,** and **2a-d** against adult's insect of cotton aphid after 1 day of treatment possesses moderate to feeble toxicological effectiveness towards the cotton aphid (adults) with LC_{50} values varied beginning 0.434 into 1.498 mg/L after 1 day of treatment, and only one of them possesses toxicological activity in closely with that of acetamiprid reference (LC_{50} = 0.289 mg/L). In particular: LC_{50} values of compounds **1a-j, 2a-d,** and acetamiprid are 1.437, 0.511, 0.457, 0.498, 1.319, 0.434, 0.512, 0.678, 1.414, 1.121, 1.102, 0.841, 1.394, 1.498, and 0.289 mg/L respectively. Among all tested compounds, pyridine derivatives **1f** and **1c** possesses the uppermost toxicological effectiveness with LC_{50} value of 0.434 and 0.457 mg/L, respectively. In comparison with other tested compounds, substance **1f** presented the highest toxicity and is more closely in effectiveness to a reference insecticide.

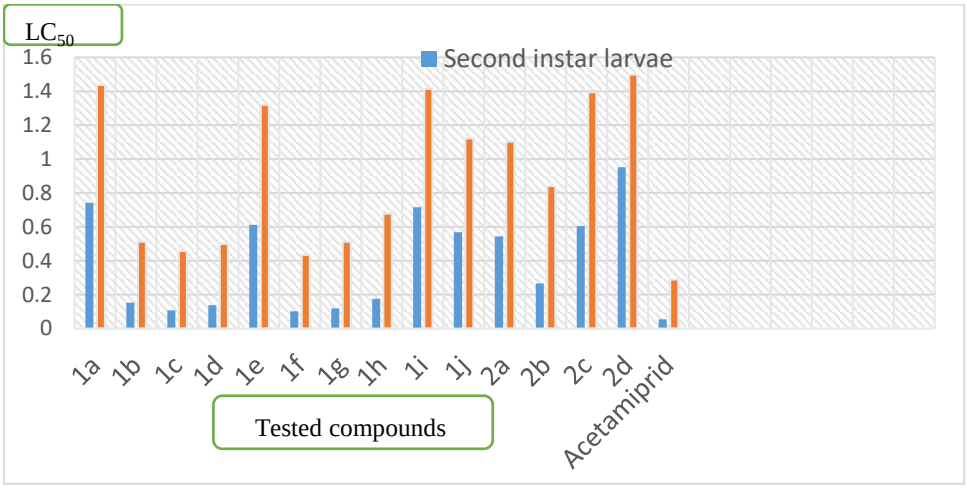


Figure 3. Insecticidal effectiveness of selective pyridine derivatives synthesized substances **1a-j, 2a-d** and acetamiprid as reference insecticide against the nymphs and adult of *A. gossypii* after one day of treatment.

Sub lethal concentrations studies

The many sublethal impacts of pesticides on both persons and insect communities are ascertained through the use of biological parameters [29]. Five sublethal concentrations of compound **1b** on *A. gossypii* were found to have concentration response bioassay values of 0.306, 0.612, 1.224, 2.44, and 4.896 mg/L, respectively; control aphids showed no mortality 24 hours after treatment (Table 2). Our findings showed that the duration of nymphal instars, generation time, and adult longevity of *A. gossypii* nymphs exposed to sublethal quantities of compound **1b** had discernible impacts. With the exception of concentration C5, the duration of the nymphal instars was considerably longer than the control. However, compared to the control, adult longevity was considerably lower. With an average of 5.82 days, the first concentration (C1) recorded the shortest developmental time. Ultimately, it was evident how exposure to the five concentrations of compound **1b** affected the generation time, and there were notable variations between the concentrations and control as well as between the various concentrations and one another. When nymphs were exposed to C1, the longest generation time was noted. On the other hand, control had the shortest generating time.

Table 2. The length of nymphal instars, adult longevity, and generation of *A. gossypii* treated to five sublethal concentrations of the control and target chemical **1b**.

Comp. No.	Treatment	Development time (d)					
		First instar	Second instar	Third instar	Fourth instar	Longevity	Generation
1b	C1	1.26±0.11^{a}	1.65±0.08^{a}	2.09±0. 12^{a}	2.18±0.16^{a}	5.82±0.04^{c}	8.90±0.20^{a}
	C2	1.26±0.11^{a}	1.65±0.12^{a}	2.09±0.12^{a}	2.08±0.14^{b}	5.80±0.04^{c}	8.91±0.19^{a}
	C3	1.25±0.09^{b}	1.63±0.12^{b}	2.09±0.12^{a}	2.04±0.12^{c}	5.94±0.03^{b}	7.99±0.12^{b}
	C4	1.25±0.08^{b}	1.33±0.10^{b}	1.68±0.10^{b}	2.03±0.11^{c}	5.94±0.03^{b}	7.65±0.12^{c}
	C5	1.25±0.08^{b}	1.23±0.10^{b}	1.58±0.10^{b}	2.02±0.10^{c}	6.91±0.02^{b}	6.60±0.10^{d}
Control		1.21±0.04^{c}	1.12±0.08^{c}	1.50±0.08^{c}	1.90±0.10^{d}	6.50±0.02^{a}	6.15±0.07^{e}

Five sublethal concentrations of compound **1c** on *A. gossypii* nymphs were found to have concentration response bioassay values of 0.216, 0.432, 0.864, 1.728, and 3.450 mg/L, respectively; control aphids showed no mortality 24 hours after treatment (Table 3). The nymphal instars were considerably impacted by the exposure to the five concentrations of compound **1c**, according to the findings in Table 3. Exposure to C1 and C2 resulted in the longest durations for the first and second nymphal instars, with average numbers of 1.33±0.11 and 1.33±0.11 and 1.89±0.08 and 1.89±0.12, respectively. When exposed to C2, the third nymphal instar had the longest longevity, with an average of 1.99±0.12. The fourth nymphal instar, on the other hand, lasted the longest when exposed to C1, averaging 2.48±0.16. Conversely, the control group had the shortest duration for each of the four nymphal instars. Exposure to various concentrations had an impact on adult longevity, resulting in a reduction in longevity when compared to the control (Table 3). Nymphs exposed to C1 had the lowest adult longevity, with an average of 5.01±0.04. The control group's adult longevity was recorded at 6.52±0.02 days. In contrast to longevity, the generation time rose with increasing pesticide doses. The nymphs that were exposed to C1 had the longest generation period, averaging 8.15±0.20 days. The control group's insect generation time was 6.15±0.076 days.

Table 3. *A. gossypii* treated to five sublethal concentrations of target compound **1c** and control were measured for nymphal instar duration, adult longevity, and generation.

Compd. No.	Treatment	Development time (d)					
		First instar	Second instar	Third instar	Fourth instar	Longevity	Generation
1c	C1	1.33 ± 0.11^{a}	1.89 ± 0.08^{a}	1.90 ± 0.12^{a}	2.48 ± 0.16^{a}	5.01 ± 0.04^{f}	8.15 ± 0.20^{a}
	C2	1.33 ± 0.11^{a}	1.89 ± 0.12^{a}	1.99 ± 0.12^{a}	2.30 ± 0.14^{b}	5.34 ± 0.03^{e}	7.31 ± 0.19^{b}
	C3	1.20 ± 0.09^{b}	1.62 ± 0.12^{b}	1.58 ± 0.12^{b}	2.41 ± 0.12^{c}	5.50 ± 0.03^{d}	7.39 ± 0.12^{c}
	C4	1.20 ± 0.08^{c}	1.63 ± 0.10^{b}	1.63 ± 0.10^{c}	2.09 ± 0.11^{c}	5.94 ± 0.02^{c}	6.40 ± 0.12^{d}
	C5	1.20 ± 0.08^{c}	1.34 ± 0.08^{c}	1.62 ± 0.10^{c}	1.92 ± 0.10^{d}	6.09 ± 0.03^{b}	6.26 ± 0.12^{d}
Control		1.20 ± 0.04^{d}	1.10 ± 0.08^{d}	1.52 ± 0.09^{d}	1.90 ± 0.10^{d}	6.52 ± 0.02^{a}	6.15 ± 0.08^{e}

Five sublethal concentrations of compound **1f** on *A. gossypii* nymphs were found to have concentration response bioassay values of 0.244, 0.488, 0.846, 1.687 and 3.374 mg/L, respectively, while control aphids showed no mortality 24 hours after treatment. The nymphal instars were considerably impacted by the exposure to the five concentrations of compound **1f**, according to data in Table 4. When exposed to C1, the first, second, third, and fourth nymphal instars had the longest lengths, averaging 1.25 ± 0.11, 1.99 ± 0.09, 2.10 ± 0.12, and 2.68 ± 0.16 days, respectively. Conversely, the control group had the shortest duration times for the first, second, third, and fourth nymphal instars, with average values of 1.19 ± 0.04, 1.10 ± 0.08, 1.49 ± 0.09, and 1.90 ± 0.10 days. Exposure to the various concentrations had an impact on adult longevity, which decreased when compared to the control. Nymphs exposed to C1 had the lowest average adult longevity (4.98 ± 0.10). The control group's adult longevity was 6.50 ± 0.02 days. In contrast to longevity, the generation time rose with increasing pesticide doses. The nymphs that were exposed to C1 had the longest generation period, averaging 8.42 ± 0.20 days. The control group's insect generation time was 6.16 ± 0.076 days.

Table 4. The length of the nymphal instars, adult longevity, and generation of *A. gossypii* subjected to five sublethal concentrations of target compound **1f** and control.

Compd. No.	Treatment	Development time (d)					
		First instar	Second instar	Third instar	Fourth instar	Longevity	Generation
1f	C1	1.25 ± 0.11^{a}	1.99 ± 0.09^{a}	2.10 ± 0.12^{a}	2.68 ± 0.16^{a}	4.98 ± 0.10^{d}	8.42 ± 0.20^{a}
	C2	1.24 ± 0.11^{a}	1.93 ± 0.12^{a}	2.08 ± 0.12^{a}	2.48 ± 0.14^{b}	5.50 ± 0.02^{c}	7.96 ± 0.19^{b}
	C3	1.23 ± 0.09^{b}	1.93 ± 0.12^{a}	1.99 ± 0.12^{b}	2.40 ± 0.12^{c}	5.42 ± 0.02^{c}	7.38 ± 0.13^{c}
	C4	1.23 ± 0.08^{b}	1.53 ± 0.10^{b}	1.94 ± 0.10^{c}	2.38 ± 0.11^{c}	5.99 ± 0.03^{b}	7.04 ± 0.13^{c}
	C5	1.22 ± 0.08^{b}	1.34 ± 0.10^{b}	1.90 ± 0.10^{d}	2.33 ± 0.10^{d}	6.09 ± 0.03^{b}	6.63 ± 0.12^{d}
Control		1.190 ± 0.04^{c}	1.10 ± 0.08^{c}	1.49 ± 0.09^{e}	1.90 ± 0.10^{e}	6.50 ± 0.02^{a}	6.16 ± 0.08^{e}

MATERIALS AND METHODS

Fisher-John mechanical equipment was used to check the prepared products' m.p. Using the KBr disc method, the infrared spectrum was obtained. Consuming a Bruker 400 MHz spectrometer, the NMR spectra was measured using Si $(CH_3)_4$ (TMS) as a source of insight and creativity. Mass spectra of the Jeol JMS-400 were fully utilized. A Power Sonic 410 device (DAIHAN LABTECH Co., LTD, KOERA) was used to perform ultrasonication. 20 V, A.C. 60 Hz, ultrasonic Watts 500W/2A, serial number 2017120708, was the electric supply. Each of the synthetic compounds was produced using a separate technique.

*General procedure for the preparation of functionalized pyridines **1a–j** and **2a-d***

An equimolar mixture (0.01) of acetophenone derivatives and aromatic aldehydes was added to sodium alkoxide solution (0.011 mol of sodium in 30 mL of absolute methanol and/or ethanol, respectively), and stirred for 10 min at room temperature. Then malononitrile (0.01 mol) was added, and the reaction mixture was irradiated with an ultrasonic generator in a water bath at 50 ^{o}C for 1–3 hrs. Irradiation was continued until completion of the reaction (TLC monitoring); the reaction mixture was allowed to cool to room temperature and poured into 100 mL of water. Then, the solid precipitate was collected by filtration, washed several times with water, dried, and recrystallized from a suitable solvent.

*2-methoxy-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile (**1a**.* Yield 79%; mp.181-183 °C (reported 180 °C); IR: 2948, 2851 (CH-aliph), 2218 (CN); ^{1}H-NMR: δ 8.245(s, 2H, arom), 7.730 (s,3H, 2Harom + 1Hpyridine), 7.586 (s, 3H, arom),7.077(s, 2H, arom), 4.134 (s, 1H, OCH_3), 3.844(s, 3H, OCH_3); ^{13}C-NMR: δ 164.794, 162.017, 157.684, 156.662, 136.534, 130.372, 129.623, 129.243, 128.980, 115.861, 114.824, 113.244, 91.731, 55.898, 54.824; Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; Found: C, 76.00; H, 5.15; N, 8.80.

*6-(4-chlorophenyl)-2-methoxy-4-phenylpyridine-3-carbonitrile (**1b**).* Yield 82%; mp.181-182 °C; IR: 2988,2946 (CH-aliph), 2225 (CN); ^{1}H-NMR: δ 8.312(d, J = 6.9 Hz, 2H, arom),7.864(s,1H, 1Hpyridine), 7.756(s, 2H, arom), 7.601(s, 5H, arom), 4.154(s, 3H, OCH_3); ^{13}C-NMR: δ 164.829, 157.060, 156.544, 136.253, 136.066, 130.549, 129.729, 129.390, 129.284, 129.056, 115.599, 114.352, 93.245, 55.046; Anal. Calcd. for $C_{19}H_{13}ClN_2O$: C, 71.14; H, 4.08; N, 8.73; Found: C, 71.17; H, 4.18; N, 8.70.

*6-(4-chlorophenyl)-4-[4-(dimethylamino)phenyl]-2-methoxypyridine-3-carbonitrile (**1c**).* Yield 78%; mp. 286-287 °C; IR: 2994, 2946 (CH-aliph), 2214 (CN); ^{1}H-NMR: δ 8.285(s, 2H, arom), 7.767 (s,1H, 1Hpyridine), 7.683(s, 2H, arom),7.597(s, 2H, arom), 6.860(s,2H, arom), 4.118(s, 3H,

OCH_3), 3.017(s, 6H, $N(CH_3)_2$); Anal. Calcd. for $C_{21}H_{18}ClN_3O$: C, 69.32; H, 4.99; N, 11.55; Found: C, 69.39; H, 4.88; N, 11.47.

6-(4-chlorophenyl)-2-methoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile ***(1d)***. Yield 82%; mp.238-239 °C; IR: 2981, 2945 (CH-aliph), 2221(CN); ^{1}H-NMR: δ 8. 306(d, J = 6 Hz, 2H, arom) 7.818 (s,1H, 1Hpyridine), 7.748 (d, J = 6.2 Hz, 2H, arom), 7. 605(d, J = 5.9 Hz, 2H, arom), 7.149(d, J = 6.3 Hz, 2H, arom), 4.140(s, 3H, OCH_3), 3.865(s, 3H, OCH_3); ^{13}C-NMR: δ 161.439, 156.621, 156.318, 136.158, 135.967, 130.689, 129.691, 129.366, 128.340, 114.845, 114.093, 92.732, 55.949, 54.977; Anal. Calcd. for $C_{20}H_{15}ClN_2O_2$: C, 68.48; H, 4.31; N, 7.99; Found: C, 68.51; H, 4.19; N, 8.01.

2-ethoxy-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile ***(1e)***. Yield 77%; mp. 180-181°C; IR: 2983, 2947, 2898 (CH-aliph), 2216(CN); ^{1}H-NMR: δ 8.214(s, 2H, arom), 7.716(s, 3H, 2Harom+1Hpyridine), 7.582(s, 3H, arom), 7.070(s, 2H, arom) 4.618(q, J = 6.9 Hz, 2H, CH_2), 3.840(s, 3H, OCH_3), 1.445(t, J= 7 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.454, 161.984, 157.679, 156.679, 136.608, 130.333, 129.694, 129.557, 129.227, 128.968, 115.864, 114.827, 113.079, 91.795, 63.423, 55.890, 14.806; Anal. Calcd. for $C_{20}H_{15}N_2O_2$: C, 80.26; H, 5.01; N, 9.36; Found: C, 80.38; H, 5.24; N, 9.49.

6-(4-chlorophenyl)-2-ethoxy-4-phenylpyridine-3-carbonitrile ***(1f)***. Yield 75%; mp. 150-152 °C; IR: 2984, 2973 (CH-aliph), 2220(CN); ^{1}H-NMR: δ 8.269(s, 2H, arom), 7.791(s, 1H, 1Hpyridine), 7.741(s, 2H, arom), 7.591(m, 5H, arom), 4.456(q, J= 3.9, 2H, CH_2), 1.456(t, J = 3.9 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.471, 157.043, 156.521, 136.315, 136.037, 130.498, 129.652, 129.372, 129.256, 129.037, 115.589, 114.150, 93.282, 63.669, 14.768.; Anal. Calcd. for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37; Found: C, 71.66; H, 4.39; N, 8.29.

6-(4-chlorophenyl)-4-[4-(dimethylamino)phenyl]-2-ethoxypyridine-3-carbonitrile ***(1g)***. Yield 73%; mp. 211-212 °C; IR: 2972, 2919, 2848 (CH-aliph), 2216 (CN); ^{1}H-NMR: δ 8.240(s, 2H, arom), 7.725(m, 5H, 4Harom+1Hpyridine), 6.847(s, 2H, arom), 4.604(q, J = 7.7 Hz, 2H, OCH_2), 3.010(s, 6H, $N(CH_3)_2$), 1.436(t, J= 7.8 Hz, 3H, CH_3); Anal. Calcd. for $C_{22}H_{20}ClN_3O$: C, 69.93; H, 5.33; N, 11.12; Found: C, 69.90; H, 5.28; N, 11.11.

6-(4-chlorophenyl)-2-ethoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile ***(1h)***. Yield 68%; mp.162-163 °C; IR: 2955, 2848 (CH-aliph), 2217 (CN); ^{1}H-NMR: δ 8.302(d, J = 8.6 Hz, 2H, arom), 7.820(s, 1H, 1Hpyridine), 7.757(d, 2H, J = 8.7 Hz, arom), 7.615(d, 2H, J = 8.5 Hz, arom), 7.156(d, J = 8.5 Hz, 2H, arom) 4.634(q, J = 6.9 Hz, 2H, CH_2), 3.865(s, 3H, OCH_3), 1.448(t, J= 7 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.611, 161.406, 156.626, 156.312, 136.203, 135.923, 130.660, 129.625, 129.359, 128.413, 115.896, 114.823, 113.900, 92.791, 63.575, 55.937, 14.785; Anal. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68; Found: C, 69.19; H, 4.81; N, 7.61.

2-ethoxy-4,6-bis(4-methoxyphenyl)pyridine-3-carbonitrile ***(1i)***. Yield 65%; mp.186-167°C; IR: 2950, 2835 (CH-aliph), 2218(CN); ^{1}H-NMR: δ 8.198(s, 2H, arom), 7.699(m, 3H, 2Harom+1Hpyridine), 7.098(m, 2H, arom), 4.596(q, J = 6.3 Hz, 2H, CH_2), 3.845(s, 6H, $2OCH_3$), 1.422(t, J= 6.6 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.574, 161.905, 161.263, 157.455, 156.237, 130.547, 129.802, 129.491, 128.705, 116.157, 114.784, 112.807, 91.363, 63.324, 55.890, 14.814; Anal. Calcd. for $C_{22}H_{20}N_2O_3$ (360): C, 73.32; H, 5.59; N, 7.77; Found: C, 73.31; H, 5.42; N, 7.64.

4-(4-chlorophenyl)-2-ethoxy-6-(4-methoxyphenyl)pyridine-3-carbonitrile ***(1j)***. Yield 69%; mp. 230-231 °C; IR: 2939, 2840 (CH-aliph), 2218 (CN); ^{1}H-NMR: δ 8.165(s, 2H, arom), 7.715 (m, 2H, arom), 7.640 (m, 3H, 2Harom+1Hpyridine), 7.041 (s, 2H, arom), 4.567 (q, J = 6.3 Hz, 2H,

CH_2), 3.825 (s, 3H, OCH_3), 1.414 (t, J= 6.2 Hz, 3H, CH_3); ^{13}C-NMR: δ 164.387, 162.012, 157.773, 155.240, 135.415, 135.315, 130.842, 129.539, 129.242, 115.707, 114.775, 112.911, 91.654, 63.457, 55.855, 4.760; Anal. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68; Found: C, 79.21; H, 4.73; N, 7.69.

*6-ethoxy-4-phenyl-2,3'-bipyridine-5-carbonitrile (**2a**).* Yield, 80%; mp 232-233 °C; IR: 2918, 2848 (CH-aliph), 2222 (CN); 1H-NMR: δ 9.371(s, 1H, 1Hpyridine), 8.637 (d, J= 4.6Hz, 1Hpyridine), 8.521 (m, 1H, pyridine nucleus), 7.929(m, 3H, 2Harom +1Hpyridine), 7.574-7.515 (m, 3H, arom), 7.089(s, 1H, pyridine nucleus), 4.505 (q, J= 7.1 Hz, 2H, CH_2), 1.407 (t, J= 6.9 Hz, 3H, CH3); ^{13}C-NMR: δ 164.522, 155.788, 152.797, 150.700, 150.331, 148.502, 136.517, 134.750, 134.454, 134.274, 130.993, 129.413, 124.048, 111.933, 107.622, 61.963, 14.970.; Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94; Found: C, 75.81; H, 5.07; N, 13.90.

*4-[4-(dimethylamino)phenyl]-6-ethoxy-2,3'-bipyridine-5-carbonitrile (**2b**).* Yield, 83%; mp 262-263 °C; IR: 2986, 2900, 2812 (CH-aliph), 2218(CN); ^{1}H-NMR: δ 9.375(s, 1Hpyridine), 8.681 (s, 1Hpyridine), 8.529 (d, J= 7.9 Hz, 1Hpyridine), 7.784 (s, 1Hpyridine), 7.685(d, J= 8.6 Hz, 2Harom), 7.537 (d, J = 8.5Hz, 1Hpyridine), 6.854(d, J= 8.9 Hz, 2H, arom), 4.621(q, J= 5.2Hz, 2H, CH_2), 3.018 (s, 6H, $N(CH_3)_2$), 1.444 (t, J= 5.3 Hz, 3H, CH_3); Anal. Calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27; Found: C, 73.31; H, 5.80; N, 16.19.

*4-[4-(dimethylamino)phenyl]-6-methoxy-2,3'-bipyridine-5-carbonitrile (**2c**).* Yield 79%; mp 263-264 °C; IR: 2946, 2856 (CH-aliph), 2215 (CN); ^{1}H-NMR: δ 9.402 (s, 1Hpyridine), 8.694(s, 1Hpyridine), 8.564 (d, J= 7.7Hz, 1Hpyridine), 7.808 (s, 1Hpyridine), 7.694 (d, J= 8.3Hz, 2H, arom), 7.549 (s, 1Hpyridine), 6.861 (d, J= 8.0 Hz, 2H, arom), 4.145 (s, 3H, OCH_3), 3.023(s, 6H, $N(CH_3)_2$); Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96; Found: C, 72.83; H, 5.50; N, 17.00.

*6-methoxy-4-(4-methoxyphenyl)-2,3'-bipyridine-5-carbonitrile (**2d**).* Yield 82%; mp 241-142 °C; IR: 2953, 2845 (CH-aliph), 2220 (CN); ^{1}H-NMR: δ 9.429 (s, 1Hpyridine), 8.709 (s, 1Hpyridine), 8.604 (d, J= 7.6Hz, 1Hpyridine), 7.884 (s, 1Hpyridine), 7.767 (d, J= 8.1Hz, 2H, arom), 7.569 (s, 1Hpyridine), 7.168 (d, J= 6 Hz, 2H, arom), 4.177 (s, 3H, OCH_3), 3.877 (s, 3H, OCH_3); ^{13}C-NMR: δ 165.092, 161.494, 156.693, 155.447, 151.552, 149.102, 135.266, 132.914, 130.749, 128.246, 124.246, 115.823, 114.871, 114.475, 93.150, 55.962, 55.100; Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24; Found: C, 72.07; H, 4.70; N, 13.22.

Insect collection and rearing

The insect laboratory in Bisha, Saudi Arabia generously provided the sensitive clone of cotton aphid, *A. gossypii*, 87-212B, which was initially acquired from untreated weed hosts. Every aphid used in the studies was regularly raised on cotton plants in the lab using the caging method at 27 ± 2°C, 65 ± 5% relative humidity, and a photoperiod of 16:8 hours (light: dark).

Laboratory bioassay

Using the leaf dipping bioassay method, the insecticidal qualities of the above compounds were assessed against the cotton aphids [30]. Five concentrations of each target chemical were created by diluting the commercial formulation for pyridine-based materials and acetamiprid as the active ingredients based on ppm. In this experiment, cotton leaves are submerged for ten seconds in each of the previously prepared component concentrations and then allowed to dry for thirty minutes [31]. For every strain under investigation, medicated leaves are used to create adults and nymphs, which are then kept in glass containers covered with gauze for an entire day [32]. As an untreated

control, leaves are merely dipped in distilled water and triton-80. The preserved leaves were then removed and replaced with fresh, untreated leaves for a day. 3 duplicates of 50 nymphs and adults each were analyzed for each concentration. For every insecticide under test, a toxicity experiment was conducted twice, and the results were modified using Abbott's formula (1925) [33].

Corrected mortality percentage = (1- No. in T after treatment / No. in C after treatment) X 100

Where: T = Mortality percentage in treatment, C = Mortality percentage in control. According to Finney (1970), the corrected death rate for each of the previously developed compounds is calculated statistically [34]. The relevant concentration test lines (LDP lines, Ehab Bakr Editor of LdP Line) were evaluated using this rate [35]. The Costat program was used to determine the likelihood level of comparison for the differences between parameter averages ($P < 0.05$), and all biochemical features were analyzed using SPSS 13.0 software [36]. The bioassay was conducted in transparent 6 cm plastic Petri plates using the newborn *A. gossypii* nymphs. Five concentrations of the pyridine derivatives **1b**, **1c**, and **1f** were used, together with 0.1% Tween 80 as the surfactant. Agar was made by combining one percent weight-for-weight agar powder. Before adding the agar to the Petri dishes, it was cooled for 10 minutes. The cotton leaves were sliced with a metal tube to create the leaf disk. Each disk was affixed to the medium's surface. A small, damp brush was used to gently manipulate each aphid, causing it to move on the leaf disc. Next, we carefully lifted the aphid once more using a small brush and set it on the newly attached cotton leaf [37]. To keep the aphid in its typical feeding behavior, we turned each Petri dish upside down. *A. gossypii* nymphs in their first instar were employed in a dose-response bioassay using the leaf dip technique at five different concentrations. Before being placed on paper to dry, each leaf disc was individually immersed in each solution for ten seconds. The control leaf disc was submerged in a solution of 0.05% Tween-80 and distilled water. The first instar nymphs were then placed on the air-dried leaf discs, which were affixed to the agar medium with the top side facing down. After a day of exposure, we computed the death rate. If the nymphs were found standing on their heads or still after being prodded with a small piece of brush, it was believed that they were dead [38]. The Chi technique was used to assess and compute the life history data of *A. gossypii* cohorts exposed to sublethal concentrations of the three target chemicals and control [39, 40].

CONCLUSION

The creation of novel pyridine compounds that function as insecticides was deemed beneficial in this research. By using a computerized regression analysis tool to determine the toxicity values in Table 1 and Figure 3, the LC50 and slope values of the target compounds were calculated and expressed in ppm. Acetamiprid was used as a reference pesticide to compare the insecticidal activity of materials **1a-j** and **2a-d** against cotton aphids in contrast to the adult and nymph insects. This section established the structure-action link. Compared to all the other derivative pyridines, component 1f is more active in opposing cotton aphid adults and nymphs. The presence of cyano groups, phenyl moieties, and chlorophenyl moieties in component **1f**'s structure may be the reason for its high efficacy. The findings of this work support additional research on these intriguing substances and the use of their toxicological effectiveness to create novel chemical pesticides that combat sucking pests.

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Declaration of competing interests

The authors declare that they have no known competing financial interests in this paper.

Supporting data

IR spectra, ^{1}H-NMR spectra, ^{13}C-NMR spectra, and elemental analysis of pyridine derivatives.

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