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Functionalized Pyridines: Synthesis and Toxicity Evaluation of Potential Insecticidal Agents against *Aphis craccivora*

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Cite This: *ACS Omega* 2023, 8, 29685−29692

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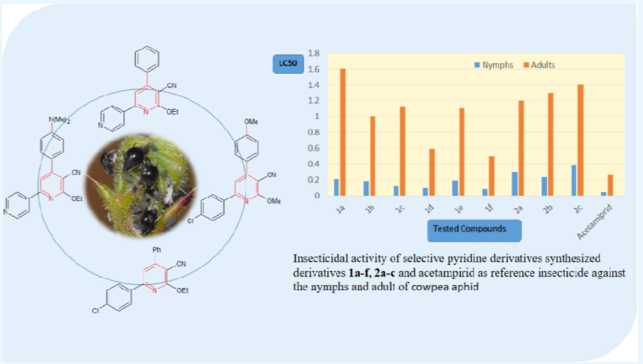
ABSTRACT: Using ultrasound technology instead of traditional methods, some pyridine derivatives were prepared by a simple procedure via a four-component reaction of different aromatic aldehydes, acetyl aryl, sodium alkoxide, and malononitrile, and additionally, all prepared compounds were monitored for insecticidal activities toward nymphs and adults of cowpea aphid. Though a lot of insecticides are discovered as a novelty on the other hand, neonicotinoid compounds are reflected as the most affected insecticides against aphids and many other pests. Thus, some of the pyridine derivatives were chemically prepared as analogues to a large group of insecticides called neonicotinoids. Under laboratory conditions, the toxicity of these components was measured toward adults and nymphs of *Aphis craccivora*. With respect to the LC_{50} values, components **1f**, **1d**, and **1c** have the utmost insecticidal bioactivity, with values of 0.080, 0.098, and 0.127 mg/L. This work covers the way to discover novel compounds for the prospective use as insecticidal representatives.



1. INTRODUCTION

More than 40% of the yearly food production is missing because of pest invasion, so an efficient pest management through employing a varied group of pesticides is a prerequisite for confronting pests and increasing crop production.[1] Due to the ability of pests for developing opposition to conventional insecticides, there is a continuing requirement for discovering and developing novel insecticides.[2] Pyridines exist widely in nature as vitamins, alkaloids, and coenzymes and own altered biological effects such as anti-microbial, antitumor, and antioxidant properties.[3−8] On the other hand, the pyridine ring seems to be the main framework of many neonicotinoid insecticides (Figure 1).[9,10] The great insecticidal effectiveness related to neonicotinoids has been demonstrated against numerous pests and homopteran insects, like aphids, which are one of the most dangerous pests that attack crops in Egypt, such as cotton, wheat, bean, maize, and others, causing huge damage to crops and a great economic loss; sucking plant sap and weakening it not only a reason to control aphids but the reason is aphids transmit viruses to plants; neonicotinoids were successful in controlling different types of aphids on different crop types.

However, many neonicotinoids have been banned in different countries around the world due to their toxicity to pollinators, especially honeybee. So, the search for new neonicotinoid analogues has become necessary, with the hope of finding a new one that has high toxicity against pests and is safer for honeybees. Also, their relative safety concerning aquatic life and mammals is well-known.[11] Using ultrasound technology in organic designing has acquired great attention in recent years, such as a green and valuable technique in particular organic production paralleled with a classical technique.[12−14] In view of the previously mentioned facts, the present work aims to prepare some pyridine derivatives by a simple procedure via a four-component reaction using ultrasound technology instead of traditional methods. Moreover, all prepared compounds will partition for insecticide effectiveness toward nymphs and adults of cowpea aphids.

2. MATERIALS AND TECHNIQUES

2.1. Chemistry. MP of the prepared products was analyzed using the Fisher−John mechanical apparatus. The infrared spectrum was measured by a KBr disc technique. The NMR spectrum was measured using a Bruker 400 MHz spectrometer by Si $(CH_3)_4$ (TMS) as a source of discernment and invention. Mass spectra were consummately measured using Jeol JMS-

Received: May 31, 2023
Accepted: July 21, 2023
Published: August 2, 2023

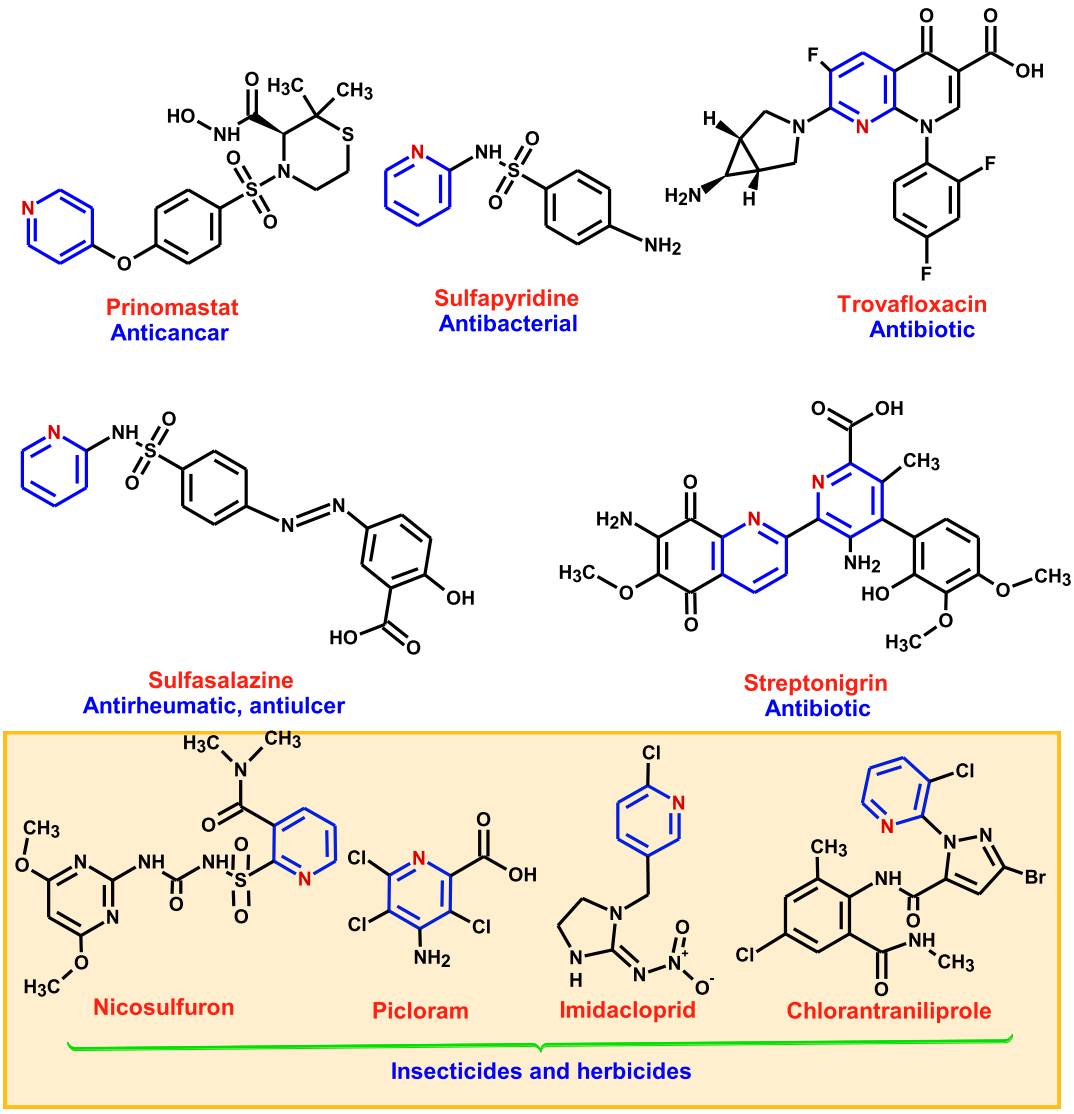


Figure 1. Some examples of drugs and insecticides containing pyridine scaffolds.

400. Ultrasonication was carried out in a Power sonic410 apparatus (DAIHAN LABTECH Co., LTD, KOERA). The electric supply was 20 V, AC 60 Hz; ultrasonic watts 500 W/2 A. serial no. 2016120709. All compounds **1a−j** and **2a−d** were synthesized by different methods.[15]

2.2. Insect Collection and Rearing. We found pyridine derivatives that were highly poisonous to both adults and nymphs of cowpea aphids. Cowpea aphid was collected from the insect laboratory, (PPRI), Agricultural Research Center and screened for insecticidal effectiveness of the objective products toward laboratory strain of adults and nymphs of cowpea aphid.

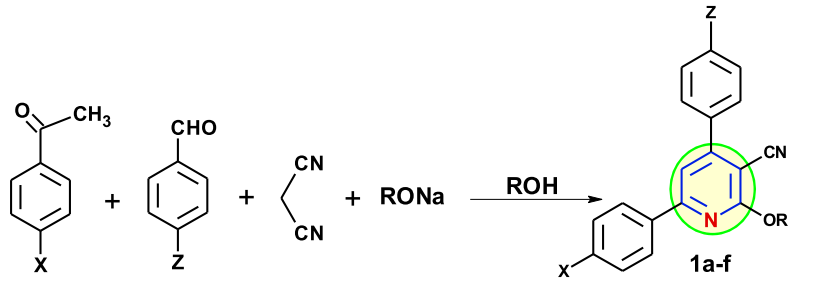
2.3. Laboratory Bioassay. The toxicological activities of target pyridine analogues were calculated using the leaf dipping technique under the same reported laboratory conditions.[16−35] Thus, we prepared five concentrations of all compounds dissolved in drops of dimethylformamide with the use of 0.1% Tween-80 as a surfactant. An identical size of 30 adults and also 30 nymphs of cowpea aphid insects were dipped for 10 s in each concentration of each compound "repeated three times". Target pests were kept at 25 °C to dry for approximately 1/2 h. In a control experiment, the insects were immersed in distilled water with "0.1% Tween-80". These procedures were carried out at 25 °C with "5%" relative humidity. The tested insects were transferred to glass jars containing water after they were dried. In addition, aphids were incapable to move and counted dead. Experimental results of all synthesized compounds were investigated by employing Abbott's formula.[36−38]

3. RESULTS AND DISCUSSION

3.1. Synthesis. The prepared products: 2-methoxy-6-(*p*-methoxyphenyl)-4-phenyl-3-cyanopyridine (**1a**), 6-(*p*-chlorophenyl)-2-methoxy-4-phenyl-3-cyanopyridine (**1b**), 6-(*p*-chlorophenyl)-4-[*p*-(dimethylamino)phenyl]-2-methoxy-3-cyanopyridine (**1c**), 6-(*p*-chlorophenyl)-2-methoxy-4-(*p*-methoxyphenyl)-3-cyanopyridine (**1d**), 2-ethoxy-6-(*p*-methoxyphenyl)-4-phenyl-3-cyanopyridine (**1e**), 6-(*p*-chlorophenyl)-2-ethoxy-4-phenyl-3-cyanopyridine (**1f**), 6-(*p*-chlorophenyl)-4-[*p*-(dimethylamino)phenyl]-2-ethoxy-3-cyanopyridine (**1g**), 6-(*p*-chlorophenyl)-2-ethoxy-4-(*p*-methoxyphenyl)-3-cyanopyridine (**1h**), 2-ethoxy-4,6-bis(*p*-methoxyphenyl)-3-cyanopyridine (**1i**), and 4-(*p*-chlorophenyl)-2-ethoxy-6-(*p*-methoxyphenyl)-3-cyanopyridine (**1j**) were synthesized by

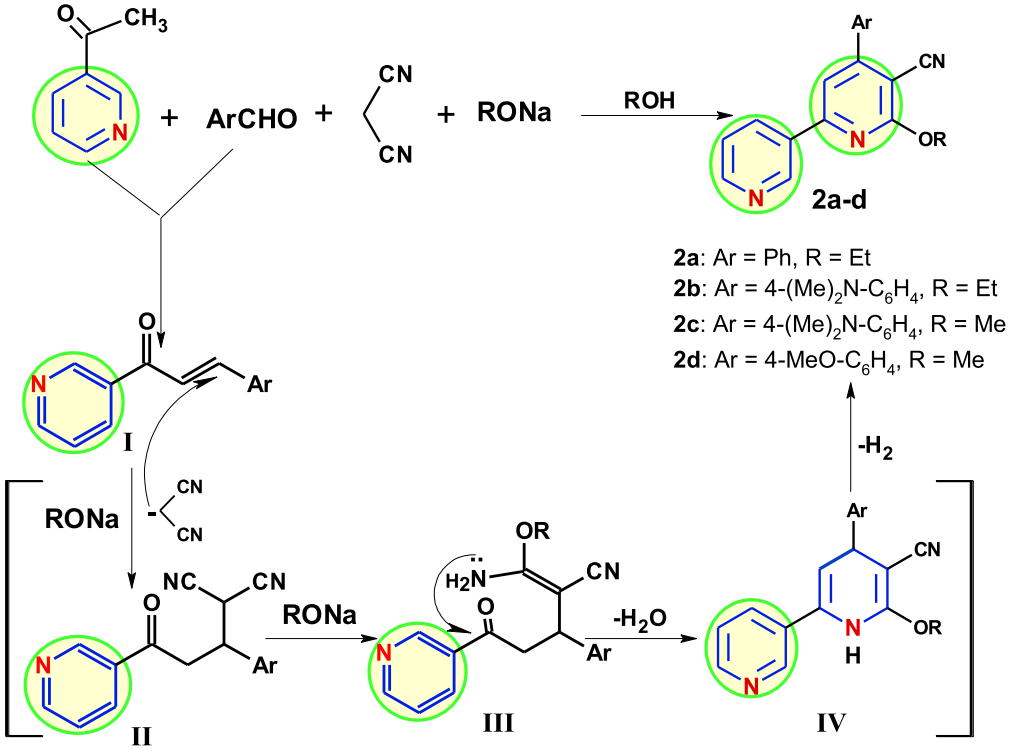
https://doi.org/10.1021/acsomega.3c03831
ACS Omega 2023, 8, 29685−29692

Scheme 1. Synthesis of Compounds 1a−j



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 2. Synthesis of Compounds 2a−d



2a: Ar = Ph, R = Et
2b: Ar = 4-$(Me)_2N$-C_6H_4, R = Et
2c: Ar = 4-$(Me)_2N$-C_6H_4, R = Me
2d: Ar = 4-MeO-C_6H_4, R = Me

simple and efficient procedures via a four-component reaction between acetyl aryl derivatives, aryl carbaldehydes, propanedinitrile, and sodium methoxide in methanol and/or sodium ethoxide in ethanol at 50 °C under ultrasound irradiation (Scheme 1).

In light of these data, it was worthy to employ the same methodologies for the synthesis of heterocyclic compounds, which contain two pyridine rings in the same compound, hoping to obtain these compounds with enhanced biological activity applications. Hence, the equivalent procedures were extended for the preparation of 4-phenyl-6-ethoxy-2,3′-bipyridine-5-cyanide (**2a**), 4-[*p*-(dimethylamino)phenyl]-2,3′-bipyridine-6-ethoxy-5-cyanide (**2b**), 4-[*p*-(dimethylamino)-phenyl]-6-methoxy-2,3′-bipyridine-5-cyanide (**2c**), and 4-(*p*-methoxyphenyl)-2,3′-bipyridine-6-methoxy-5-cyanide (**2d**) by the reaction of aryl carbaldehydes, 3-acetylpyridine, cyano acetonitrile, and RONa under the same reaction conditions (Scheme 2).

The reaction mechanism for the production of compounds **2a−d** was presumed through the formation of benzylideneacetophenone derivatives **I**, followed by the addition of the cyano acetonitrile anion at *α*, *β*-unsaturated carbonyl to generate intermediate **II** which reacted with RO^- for forming adduct **III**, the adduct **III** cyclized via intramolecular cyclizing to produce **IV**, and subsequent dehydrogenation of **IV** produce the alkoxypyridines-3-carbonitrile **2a−d** (Scheme 2). Chemical

https://doi.org/10.1021/acsomega.3c03831
ACS Omega 2023, 8, 29685−29692

structures of compounds **1a−j** and **2a−d** were determined using infrared spectroscopy, NMR spectral analysis, and melting points. For example, the IR spectrum of 6-ethoxy-4-phenyl-2,3′-bipyridine-5-cyanide (**2a**) does not have any absorption peak characteristic of =CO, while the band characteristic of CN was observed at 2223 cm^{-1}. Its ^1H NMR spectra show four peaks at 9.37, 8.63, 8.52, and 7.09 ppm characteristic of a pyridine nucleus. Also, it contains a multiplied signal at 7.93 attributed to 2H aromatic and 1H of the pyridine ring, and the aromatic protons show other multiplied signals at 7.57−7.09 ppm. ^{13}C NMR spectra of **2a** illustrate the peaks at δ 61.96 (exchangeable in dept-135) and 14.97 distinguishing ethoxide carbons besides aryl carbons at δ 164.52, 155.79, 152.80, 150.70., 150.33, 148.50, 136.52, 134.75, 134.45, 134.27, 130.99, 129.41, 124.05, 111.93, and 107.62.

*3.1.1. General Method of Designing Functionalized Pyridines **1a−j** & **2a−d**.* An equimolar of 0.01 mol acetophenone derivatives and aromatic aldehydes was mixed with RONa (0.011 moles Na in 30 mL of CH_3OH or CH_3CH_2OH, respectively) and stirred for 10 min at 25 °C. Then, cyanoacetonitrile (0.01 mol) was added, and the reaction mixture was allowed to irradiate through an ultrasonic generator at 60 °C for 1−3 h. Irradiation was continued until the completion of the reaction (thin-layer chromatography monitoring), and the reaction mixture was refrigerated to 25 °C and poured on 90 mL of H_2O. Then, the precipitated compounds were filtrated, washed many times with H_2O, and recrystallized from the appropriate solvents.

*3.1.1.1. 2-Methoxy-6-(4-methoxyphenyl)-4-phenyl-3-cyanopyridine (**1a**).* Yellow solid, Yield 79%; mp 181−183 °C (reported 181 °C); IR: 2948, 2851 (CH-aliphatic), 2218 (NC); ^1H NMR: δ 8.245 (s, 2H, aromatic), 7.730 (s, 3H, 2H, arom + 1H, pyridine), 7.586 (s, 3H, aromatic),7.077 (s, 2H, arom), 4.134 (s, 3H, OMe), 3.844 (s, 3H, OMe); ^{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, 5.16; N, 8.80.

*3.1.1.2. 6-(p-Chlorophenyl)-2-methoxy-4-phenyl-3-cyanopyridine (**1b**).* Brown crystal, Yield 82%; mp 181−182 °C; IR: 2988,2947 (CH-aliphatic), 2226 (NC); ^1H NMR: δ 8.312 (d, J = 6.9 Hz, 2H, aromatic), 7.864 (s, 1H, 1H, pyridine), 7.756 (s, 2H, aromatic), 7.601 (s, 5H, aromatic), 4.154 (s, 3H, OMe); ^{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.

*3.1.1.3. 6-(p-Chlorophenyl)-4-[p-(dimethylamino)phenyl]-2-methoxy-3-cyanopyridine (**1c**).* Brown crystal, Yield 78%; mp 286−287 °C; IR: 2214 (C≡N); ^1H NMR: Yield 78%; mp 286−287 °C; IR: 2995, 2944 (CH-aliphatic), 2214 (NC); ^1H NMR: δ 8.285 (s, 2H, aromatic), 7.767 (s, 1H, 1H, pyridine), 7.683 (s, 2H, aromatic),7.597 (s, 2H, aromatic), 6.860 (s, 2H, aromatic), 4.118 (s, 3H, OMe), 3.017 (s, 6H, $N(Me)_2$); Analysis Calculated/found $C_{21}H_{18}ClN_3O$: C, 69.32/69.39; H, 4.99/4.88; N, 11.55/11.47.

*3.1.1.4. 6-(p-Chlorophenyl)-2-methoxy-4-(p-methoxyphenyl)-3-cyanopyridine (**1d**).* Yellowish powder, Yield 82%; mp 238−239 °C; IR: 2982, 2946 (CH-aliphatic), 2221(NC); ^1H NMR: δ 8. 306 (d, J = 6 Hz, 2H, aromatic) 7.818 (s, 1H, 1H, pyridine), 7.748 (d, J = 6.2 Hz, 2H, aromatic), 7. 605 (d, J = 5.9 Hz, 2H, aromatic), 7.149 (d, J = 6.3 Hz, 2H, aromatic), 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 $C_{21}H_{18}ClN_3O$: C, 69.32; H, 4.99; N, 11.55, Found: C, 69.39; H, 4.88; N, 11.47.

*3.1.1.5. 2-Ethoxy-6-(4-methoxyphenyl)-4-phenyl-3-cyanopyridine (**1e**).* White powder, Yield 77%; mp 180−182 °C; IR: 2983, 2948, 2899 (CH-aliphatic), 2217(NC); ^1H NMR: δ 8.214 (s, 2H, aromatic), 7.716 (s, 3H, 2H, aromatic + 1H, pyridine), 7.582 (s, 3H, aromatic), 7.070 (s, 2H, aromatic) 4.618 (q, J = 6.9 Hz, 2H, CH_2), 3.840 (s, 3H, OMe), 1.445 (t, J = 7 Hz, 3H, Me); ^{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; Analysis Calculated/found $C_{20}H_{15}N_2O_2$: C, 80.26/80.38; H, 5.01/5.24; N, 9.36/9.49.

*3.1.1.6. 6-(4-Chlorophenyl)-2-ethoxy-4-phenyl-3-cyanopyridine (**1f**).* White powder, Yield 75%; mp 150−152 °C; IR: 2985, 2974 (CH-aliphatic), 2221(NC); ^1H NMR: δ 8.269 (s, 2H, aromatic), 7.791 (s, 1H, 1H, pyridine), 7.741 (s, 2H, aromatic), 7.591 (m, 5H, aromatic), 4.456(q, J = 3.9, 2H, CH_2), 1.456 (t, J = 3.9 Hz, 3H, Me); ^{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.; Analysis Calculated/found $C_{20}H_{15}ClN_2O$: C, 71.75/71.66; H, 4.52/4.39; N, 8.37/8.29.

*3.1.1.7. 6-(4-Chlorophenyl)-4-[p-(dimethylamino)phenyl]-2-ethoxy-3-cyanopyridine (**1g**).* White powder, Yield 73%; mp 211−212 °C; IR: 2972, 2919, 2849 (CH-aliphatic), 2217 (NC); ^1H NMR: δ 8.240 (s, 2H, aromatic), 7.725 (m, 5H, 4H, arom + 1H, pyridine), 6.847 (s, 2H, aromatic), 4.604 (q, J = 7.7 Hz, 2H, OCH_2), 3.010 (s, 6H, $N(Me)_2$), 1.436 (t, J = 7.8 Hz, 3H, Me); Analysis Calculated/found $C_{22}H_{20}ClN_3O$: C, 69.93/69.90; H, 5.33/5.23; N, 11.12/11.11.

*3.1.1.8. 6-(p-Chlorophenyl)-2-ethoxy-4-(p-methoxyphenyl)-3-cyanopyridine (**1h**).* Yellowish powder, Yielding compound 68%; mp 162−163 °C; IR: 2956, 2847 (CH-aliphatic), 2218 (NC); ^1H NMR: δ 8.302 (d, J = 8.6 Hz, 2H, aromatic), 7.820 (s, 1H, 1H, pyridine), 7.757 (d, 2H, J = 8.7 Hz, aromatic), 7.615 (d, 2H, J = 8.5 Hz, aromatic), 7.156 (d, J = 8.5 Hz, 2H, aromatic) 4.634 (q, J = 6.9 Hz, 2H, CH_2), 3.865 (s, 3H, OMe), 1.448 (t, J = 7 Hz, 3H, Me); ^{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; Analysis Calculated/found $C_{21}H_{17}ClN_2O_2$: C, 69.14/69.05; H, 4.70/4.62; N, 7.68/7.51.

*3.1.1.9. 2-Ethoxy-4,6-bis(p-methoxyphenyl)-3-cyanopyridine (**1i**).* Yellow powder, Yield 65%; mp 186−167 °C; IR: 2951, 2836 (CH-aliphatic), 2217(NC); ^1H NMR: δ 8.198 (s, 2H, aromatic), 7.699 (m, 3H, 2H, aromatic + 1H, pyridine), 7.098 (m, 2H, aromatic), 4.596 (q, J = 6.3 Hz, 2H, CH_2), 3.845 (s, 6H, 2OMe), 1.422 (t, J = 6.6 Hz, 3H, Me); ^{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; Analysis Calculated/found $C_{22}H_{20}N_2O_3$ (360): C, 73.32/73.21; H, 5.59/5.41; N, 7.77/7.71.

*3.1.1.10. 4-(p-Chlorophenyl)-2-ethoxy-6-(p-methoxyphenyl)-3-cyanopyridine (**1j**).* White powder, Yield 69%; mp 230−231 °C; IR: 2940, 2841 (CH-aliphatic), 2218 (NC); ^1H NMR: δ 8.165 (s, 2H, aromatic), 7.715 (m, 2H, aromatic), 7.640 (m, 3H, 2H, aromatic + 1H, pyridine), 7.041 (s, 2H,

https://doi.org/10.1021/acsomega.3c03831
ACS Omega 2023, 8, 29685−29692

Table 1. Insecticidal Effectiveness of Components 1a−f, 2a−c, and Acetamiprid as an Insecticide Reference toward Cowpea Aphid Insects (Nymphs and Adults) after 1 Day of Management

	nymphs			adults		
comp.	LC_{50} (mg/L)	slope	toxic ratio	LC_{50} (mg/L)	sSlope	toxic ratio
1a	0.207	0.394 ± 0.275	0.217	1.606	0.571 ± 0.267	0.166
1b	0.185	0.288 ± 0.265	0.243	1.002	0.527 ± 0.271	0.266
1c	0.127	0.396 ± 0.271	0.354	1.121	0.522 ± 0.267	0.238
1d	0.098	0.322 ± 0.267	0.459	0.593	0.492 ± 0.271	0.450
1e	0.189	0.319 ± 0.264	0.238	1.107	0.574 ± 0.273	0.241
1f	0.080	0.397 ± 0.265	0.562	0.498	0.461 ± 0.275	0.536
2a	0.304	0.419 ± 0.272	0.148	1.198	0.251 ± 0.269	0.222
2b	0.233	0.429 ± 0.274	0.193	1.302	0.557 ± 0.261	0.205
2c	0.388	0.416 ± 0.271	0.115	1.399	0.573 ± 0.270	0.190
acetamiprid	0.045	0.381 ± 0.283	1	0.267	0.387 ± 0.283	1

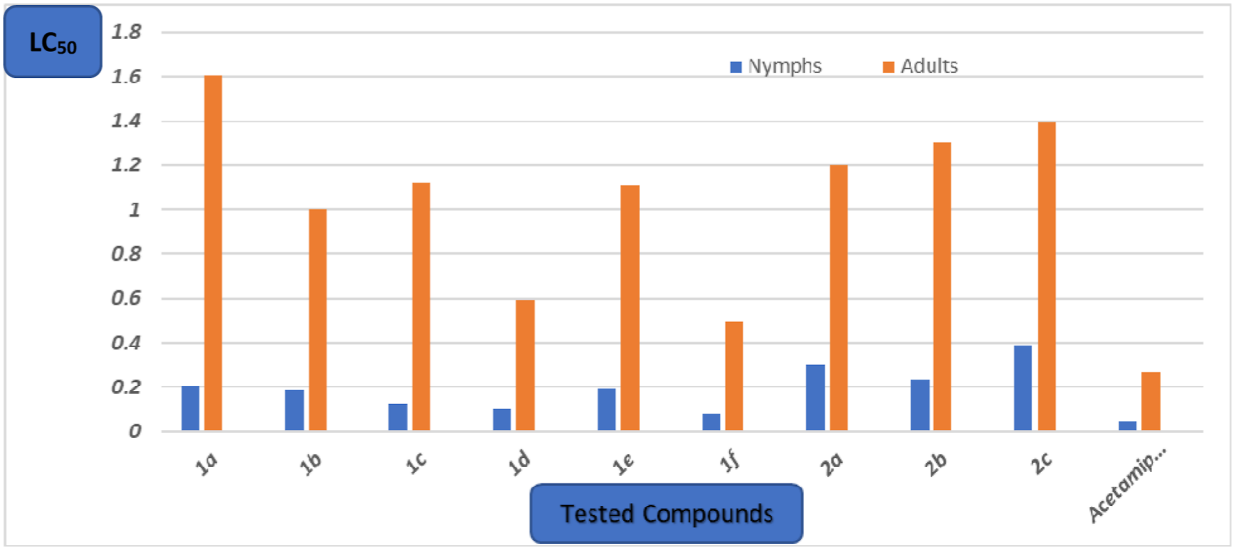


Figure 2. Insecticidal activity of selective pyridine synthesized derivatives **1a−f**, **2a−c**, and acetamiprid as reference insecticides on aphids.

aromatic), 4.567 (q, J = 6.3 Hz, 2H, CH_2), 3.825 (s, 3H, OMe), 1.414 (t, J = 6.2 Hz, 3H, Me),; ^{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; Analysis Calculated/found $C_{21}H_{17}ClN_2O_2$: C, 69.14/69.05; H, 4.70/4.59; N, 7.68/7.59.

*3.1.1.11. 5-Cyano-4-phenyl-6-Ethoxy-2,3′-bipyridine (**2a**).* White powder, Yield, 80%; mp 232−233 °C; IR: 2919, 2849 (CH-aliphatic), 2222 (NC); ^{1}H NMR: δ 9.371 (s, 1H, 1H, pyridine), 8.637(d, J = 4.6 Hz, 1H, pyridine), 8.521 (m, 1H, pyridine nucleus), 7.929 (m, 3H, 2H, arom + 1H, pyridine), 7.574−7.515 (m, 3H, aromatic), 7.089 (s, 1H, pyridine nucleus), 4.505 (q, J = 7.1 Hz, 2H, CH_2), 1.407 (t, J = 6.9 Hz, 3H, Me); ^{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.; Analysis Calculated/found $C_{19}H_{15}N_3O$: C, 75.73/75.79; H, 5.02/4.99; N, 13.94/13.87.

*3.1.1.12. 5-Cyano-4-[p-(dimethylamino)phenyl]- 2,3′-bipyridine-6-ethoxy-5-cyanide (**2b**).* White powder, Yield, 83%; mp 262−263 °C; IR: 2986, 2901, 2813 (CH-aliphatic), 2218(NC); ^{1}H NMR: δ 9.375(s, 1H, pyridine), 8.681(s, 1H, pyridine), 8.529(d, J = 7.9 Hz, 1H, pyridine), 7.784(s, 1H, pyridine), 7.685(d, J = 8.6 Hz, 2H, arom), 7.537(d, J = 8.5 Hz, 1H, pyridine), 6.854 (d, J = 8.9 Hz, 2H, arom), 4.621 (q, J = 5.2 Hz, 2H, CH_2), 3.018 (s, 6H, $N(Me)_2$),1.444 (t, J = 5.3 Hz, 3H, Me); Analysis Calculated/found $C_{21}H_{20}N_4O$: C, 73.23/73.18; H, 5.85/5.89; N, 16.27/16.25.

*3.1.1.13. 5-Cyano-4-[p-(dimethylamino)phenyl]-6-methoxy-2,3′-bipyridine (**2c**).* White crystal, Yield 80%; mp 264−265 °C; IR: 2947, 2858 (CH-aliphatic), 2216 (NC); ^{1}H NMR: δ 9.402(s, 1H, pyridine), 8.694(s, 1H, pyridine), 8.564(d, J = 7.7 Hz, 1H, pyridine), 7.808(s, 1H, pyridine), 7.694 (d, J = 8.3 Hz, 2H, aromatic), 7.549(s, 1H, pyridine), 6.861 (d, J = 8.0 Hz, 2H, aromatic), 4.145 (s, 3H, OMe), 3.023 (s, 6H, $N(CH_3)_2$); Analysis Calculated/found $C_{20}H_{18}N_4O$: C, 72.71/72.68; H, 5.49/5.41; N, 16.96/17.00.

*3.1.1.14. 5-Cyano-6-methoxy-4-(p-methoxyphenyl)-2,3′-bipyridine-5-cyanide (**2d**).* Yellowish powder, Yield 82%; mp 241−142 °C; IR: 2954, 2846 (CH-aliphatic), 2220 (NC); ^{1}H NMR: δ 9.429(s, 1Hpyridine), 8.709(s, 1H, pyridine), 8.604(d, J = 7.6 Hz, 1H, pyridine), 7.884(s, 1H, pyridine) 7.767 (d, J = 8.1 Hz, 2H, aromatic), 7.569(s, 1H, pyridine), 7.168 (d, J = 6 Hz, 2H, arom), 4.177 (s, 3H, OMe), 3.877 (s, 3H, OMe); ^{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; Analysis Calculated/found $C_{19}H_{15}N_3O_2$: C, 71.91/71.79; H, 4.76/4.68; N, 13.24/13.16.

https://doi.org/10.1021/acsomega.3c03831
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3.2. Insecticidal Bioefficacy Screening. The concentration which kills 50% of the aphid population is a more valuable point statistically, for comparative purposes, as shown in Table 1. In order to estimate the LC_{50} values and "95%" educible limits of upper and lower confidence, standard error, slope, chi-square, and correlation coefficient, the mortality data of aphids were analyzed using probity analysis through some statistics (LDP-line) software.

3.2.1. Toxicological Activity toward Nymphs of Cowpea Aphids after 1 Day of Treatment. From Table 1 and Figure 2, it can be seen that all tested 11 analogues exhibit a moderate or feeble toxicological effect toward cowpea aphids (nymphs) whose LC_{50} values varied from 0.080 to 0.385 mg/L after 24 h of treatment, and some of them possess toxicological activity in close to a reference acetamiprid. In particular, the LC_{50} values of compounds **1a−f**, **2a−c**, and acetamiprid are 0.207, 0.185, 0.127, 0.098, 0.189, 0.080, 0.304, 0.233, 0.385, and 0.045 mg/L, respectively; among all tested compounds, pyridine derivatives **1f** and **1d** possess the highest insecticidal activity with LC_{50} values of 0.080 and 0.098 mg/L, respectively.

3.2.2. Toxicological Activity toward Adults of Cowpea Aphids after 1 Day of Treatment. The insecticidal properties of compounds **1a** through **f**, **2a** through **c**, and acetamiprid against adult insects of cowpea aphids after 1 day of treatment possess moderate to feeble toxicological effectiveness toward the cowpea aphid (adults) with LC_{50} values varied from 0.498 to 1.606 mg/L after 1 day of treatment, and only one of them possesses toxicological activity in close to that of acetamiprid reference. In particular, the LC_{50} values of compounds **1a−f**, **2a−c**, and acetamiprid are 1.606, 1.002, 1.121, 0.593, 1.107, 0.498, 1.198, 1.302, 1.399, and 0.267 mg/L, respectively. Among all tested compounds, pyridine derivatives **1f** and **1d** possess the highest toxicological effectiveness with LC_{50} values of 0.498 and 0.593 mg/L, respectively. In comparison with other tested compounds, compound **1f** showed the highest toxicity and is close in activity to a reference insecticide.

3.3. Structure−Activity Relationship. It is evident from the results in Table 1 and Figure 2 that all components exhibited higher insecticidal activity due to the presence of pyridine rings, and their substituents attached to pyridine rings lead to a variety in toxicity; all analogues showed higher activity toward nymphs of cowpea aphids than the adults of cowpea aphids after 1 day of treatment; adults possess more resistance toward the target synthesized compounds than the nymphs' ones. Due to the inclusion of the 4-chlorophenyl group, two cyano groups, phenyl moiety, and an ethoxy group in its structure, compound **1f** has the highest activity in this series. Due to the inclusion of the 4-chlorophenyl group, cyano groups, and phenyl moiety in its structures, compound **1d** exhibits strong toxicological activity toward adults and nymphs of cowpea aphids. Additionally, compounds **1c** and **1b** of the tetrahydroisoquinoline family are more hazardous than the analogue **1e**, which may be because of the 4-chlorophenyl moiety in their structures. Compound **1a** may have insecticidal properties. The compounds **1a−f** demonstrate that the occurrence of the chlorophenyl group might reflect better effectiveness than the pyridine group. On considering the toxicity line and slope, we noticed that the slope increased in the following order **1f** > **1d** > **1c** > **1b** > **1e** > **1a**>**2b** > **2a** > **2c**. This order revealed the toxicity response of the tested cowpea aphid which showed variation in response toward the target insecticidal compounds.

4. CONCLUSIONS

In this article, it was worth designing new pyridine derivatives that act as an insecticide. Conferring to the poisonous value in Table 1 and Figure 2 through the employment of a computerized program of regression analysis, LC_{50} and slope values of the objective components were counted and described as ppm unit. The insecticidal activities of components **1a−f, 2a, b, 3, 4a, and b** in contradiction to the adults and nymph insects of aphids were compared with that of acetamiprid as a reference insecticide against cowpea aphid. In this section, the structure−activity relationship was established, in which component **3** is more active in contradiction to adults and nymphs of cowpea aphids than all the other derivative pyridines. The great effectiveness of component **3** may be owing to the presence of chlorophenyl moieties, two carbonitrile groups, and phenyl moieties in its configuration. This study's results encourage further testing of these promising compounds and the exploitation of their toxicological activity to produce new chemical insecticides against sucking pests.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03831.

IR spectra, ^{1}H NMR spectra, ^{13}C NMR spectra, and elemental analysis of pyridine derivatives (PDF)

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https://doi.org/10.1021/acsomega.3c03831
ACS Omega 2023, 8, 29685−29692

https://pubs.acs.org/10.1021/acsomega.3c03831

Notes

The authors declare no competing financial interest.
The raw/processed result produced in this work is existing upon request from the agreeing author.

■ ACKNOWLEDGMENTS

The authors acknowledge the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research at King Faisal University, Saudi Arabia, for their financial support under the annual funding track (**GRANT3, 533**).

■ REFERENCES

(1) Abhilash, P. C.; Singh, N. Pesticide use and application: an Indian scenario. *J. Hazard. Mater.* **2009**, *165*, 1−12.
(2) Wong, F.; Alegria, H. A.; Jantunen, L. M.; Bidleman, T. F.; Salvador-Figueroa, M.; Gold-Bouchot, G.; Ceja-Moreno, V.; Waliszewski, S. M.; Infanzon, R. Organochlorine pesticides in soils and air of southern Mexico: chemical profiles and potential for soil emissions. *Atmos. Environ.* **2008**, *42*, 7737−7745.
(3) Henry, G. D. De Novo Synthesis of Substituted Pyridines. *Tetrahedron* **2004**, *60*, 6043−6061.
(4) Ling, Y.; Hao, Z.-Y.; Liang, D.; Zhang, C. L.; Liu, Y. F.; Wang, Y. The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design. *Drug Des. Devel. Ther.* **2021**, *15*, 4289−4338.
(5) Altaf, A. A.; Shahzad, A.; Gul, Z.; Khan, S. A.; Badshah, A.; Tahir, M. N.; Zafar, Z. I.; Khan, E. Synthesis, Crystal Structure, and DFT Calculations of 1,3-Diisobutyl Thiourea. *J. Drug Des. Med. Chem.* **2015**, *2015*, 913435.
(6) Bakhite, E. A.; Abd-Ella, A. A.; El-Sayed, M. E. A.; Abdel-Raheem, S. A. Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their Insecticidal Activity. *J. Saudi Chem. Soc.* **2017**, *21*, 95−104.
(7) Amer, A. A. Synthesis of Some New Polyfunctionalized Pyridines. *J. Heterocyclic Chem.* **2018**, *55*, 297−301.
(8) Zaki, R. M.; Kamal El-Dean, A. M.; Mickey, J. A.; Marzouk, N. A.; Ahmed, R. H. Synthesis, reactions, and antioxidant activity of 3-(pyrrol-1-yl)-4,6-dimethyl selenolo[2,3-b]pyridine derivatives. *Synth. Commun.* **2017**, *47*, 2406−2416.
(9) Altaf, A. A.; Shahzad, A.; Gul, Z.; Khan, S. A.; Badshah, A.; Tahir, M. N.; Zafar, Z. I.; Khan, E. Synthesis, Crystal Structure, and DFT Calculations of 1,3-Diisobutyl Thiourea. *J. Drug Design & Med. Chem.* **2015**, *2015*, 913435.
(10) Guan, A.-Y.; Liu, C.-L.; Sun, X.-F.; Xie, Y.; Wang, M.-A. Discovery of pyridine-based agrochemicals by using Intermediate Derivatization Methods. *Bioorg. Med. Chem.* **2016**, *24*, 342−353.
(11) Simon-Delso, N.; Amaral-Rogers, V.; Belzunces, L. P.; Bonmatin, J. M.; Chagnon, M.; Downs, C.; Furlan, L.; Gibbons, D. W.; Giorio, C.; Girolami, V.; et al. Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites. *Environ. Sci. Pollut. Res.* **2015**, *22*, 5−34.
(12) Bretanha, L. C.; Teixeira, V. E.; Ritter, M.; Siqueira, G. M.; Cunico, W.; Pereira, C. M. P.; Freitag, R. A. Ultrasound-promoted synthesis of 3-trichloromethyl-5-alkyl(aryl)-1,2,4-oxadiazoles. *Ultrason. Sonochem.* **2011**, *18*, 704−707.
(13) Naeimi, H.; Didar, A. Efficient sonochemical green reaction of aldehyde, thiobarbituric acid and ammonium acetate using magnetically recyclable nanocatalyst in water. *Ultrason. Sonochem.* **2017**, *34*, 889−895.
(14) Xavier, D. M.; Goldani, B. S.; Seus, N.; Jacob, R. G.; Barcellos, T.; Paixão, M. W.; Luque, R.; Alves, D. Sonochemistry in organocatalytic enamine-azide[3+2]cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoylcarboxamides. *Ultrason. Sonochem.* **2017**, *34*, 107−114.
(15) Amer, A. A.; Abdelhamid, A. A. Microwave-assisted, One-pot Multicomponent Synthesis of Some New Cyanopyridines. *J. Heterocyclic Chem.* **2017**, *54*, 3126−3132.
(16) Abdelhamid, A. A.; Elsaghiera, A. M. M.; Aref, S. A.; Gad, M. A.; Ahmed, N. A.; Abdel-Raheem, S. A. A. Preparation and biological activity evaluation of some benzoylthiourea and benzoylurea compounds. *Curr. Chem. Lett.* **2021**, *10*, 371−376.
(17) Gad, M. A.; Aref, S. A.; Abdelhamid, A. A.; Elwassimy, M. M.; Abdel-Raheem, S. A. A. Biologically active organic compounds as insect growth regulators (IGRs): introduction, mode of action, and some synthetic methods. *Curr. Chem. Lett.* **2021**, *10*, 393−412.
(18) Abdelhamid, A. A.; Salama, K. S. M.; Elsayed, A. M.; Gad, M. A.; Ali Ali El-Remaily, M. A. E. A. Synthesis and Toxicological effect of some new pyrrole derivatives as prospective insecticidal agents against the cotton leafworm, spodoptera littoralis (Boisduval). *ACS Omega* **2022**, *7*, 3990−4000.
(19) El-Gaby, M. S. A.; Ammar, Y. A.; Drar, A. M.; Gad, M. A. Insecticidal bioefficacy screening of some chalcone and acetophenone hydrazone derivatives on Spodopetra Frugiperda (Lepidoptera: Noctuidae). *Curr. Chem. Lett.* **2022**, *11*, 263−268.
(20) Jasinski, J. P.; Akkurt, M.; Mohamed, S. K.; Gad, M. A.; Albayati, M. R. Crystal structure of N-(propan-2-yl-carbamothioyl)-benzamide. *Acta Crystallogr.* **2015**, *71*, 56−57.
(21) Bakhite, E. A.; Marae, I. S.; Gad, M. A.; Mohamed, S. K.; Mague, J. T.; Abuelhassan, S. Pyridine Derivatives as Insecticides. Part 3. Synthesis, Crystal Structure, and Toxicological Evaluation of Some New Partially Hydrogenated Isoquinolines against Aphis gossypii (Glover, 1887). *J. Agric. Food Chem.* **2022**, *70*, 9637−9644.
(22) Abdelhamid, A. A.; Aref, S. A.; Ahmed, N. A.; Elsaghier, A. M. M.; Abd El Latif, F. M.; Al-Ghamdi, S. N.; Gad, M. A. Design, Synthesis, and Toxicological Activities of Novel Insect Growth Regulators as Insecticidal Agents against Spodoptera littoralis (Boisd.). *ACS Omega* **2023**, *8*, 709−717.
(23) Ali, A. M.; Salah, H.; Gad, M. A.; Youssef, M. A. M.; Elkanzi, N. A. A. Design, Synthesis, and SAR Studies of Some Novel Chalcone Derivatives for Potential Insecticidal Bioefficacy Screening on Spodoptera frugiperda (Lepidoptera: Noctuidae). *ACS Omega* **2022**, *7*, 40091−40097.
(24) Khodairy, A.; Mansour, E. S.; Elhady, O. M.; Drar, A. M. Novel N-cyanoguanidyl derivatives: Synthesis and studying their toxicological activity against Spodoptera littoralis and schizaphisgraminum. *Curr. Chem. Lett.* **2021**, *10*, 363−370.
(25) Khodairy, A.; Mansour, E. S.; Elhady, O. M.; Drar, A. M. Synthesis of Neonicotinoid analogues and study their toxicological aspects on Spodoptera littoralis and Schizaphis graminum. *Int. J. Pest Manag.* **2021**, 1. Accepted Manuscript
(26) Elhady, O. M.; Mansour, E. S.; Elwassimy, M. M.; Zawam, S. A.; Drar, A. M.; Abdel-Raheem, S. A. A. Selective synthesis, characterization, and toxicological activity screening of some furan compounds as pesticidal agents. *Curr. Chem. Lett.* **2022**, *11*, 285−290.
(27) Abdel-Ghany, H.; El-Sayed, A. M.; Amer, A. A.; Ahmed, A. M. Synthesis of Novel Fused Heterocycles Based on 6-Amino-4-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile: Synthesis of New Heterocyclic Compounds. *J. Heterocycl. Chem.* **2016**, *53*, 2013−2019.
(28) Kamel, M. S.; Aboelez, M. O.; Elnagar, M. R.; Shokr, E. K.; Selim, H. M. R. M.; Abdel-Ghany, H. E.; Drar, A. M.; Belal, A.; El Hamd, M. A.; El-Remaily, M. A. E. A. A. A. Green Synthesis Design, Spectroscopic Characterizations, and Biological Activities of Novel Pyrrole Derivatives: An Application to Evaluate Their Toxic Effect on Cotton Aphids. *ChemistrySelect* **2022**, *7*, No. e202203191.
(29) Elhady, O. M.; Mansour, E. S.; Elwassimy, M. M.; Zawam, S. A.; Drar, A. M. Synthesis and characterization of some new tebufenozide analogues and study their toxicological effect against Spodoptera littoralis (Boisd.). *Curr. Chem. Lett.* **2022**, *11*, 63−68.
(30) Amer, A. A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2008**, *183*, 2330−2343.
(31) El-Gaby, M. S. A.; Hussein, M. F.; Faraghally, F. A.; Drar, A. M.; Gad, M. A. Insecticidal activity and structure activity relationship study of some synthesized hydrazone, dihydropyridine and 3-cyano-1,

4-dihydro-pyradazin-4-one derivatives against Aphis nerii. *Curr. Chem. Lett.* **2023**, *12*, 599−606.
(32) (a) Khlebnikov, A. .F.; Novikov, M. S.; Amer, A. A. *Russ. Chem. Bull.* **2004**, *5*, 1092−1101. (b) Amer, A. A. *J. Heterocyclic Chem.* **2018**, *55*, 297.
(33) Gad, M. A.; Alqurashi, E. A.; Alsenani, N. I.; Abd El Latif, F. M.; Aref, S. A.; Ahmed, N. A.; Abdelhamid, A. A.; El-Saghier, A. M. M. Insecticidal activity, and SAR studies of semicarbazide, thiosemicarbazide, urea and thiourea derivatives against Spodoptera littoralis (Boisd.). *J. Umm Al-Qura Univ. Appll. Sci.* **2023**, DOI: 10.1007/s43994-023-00037-6. Accepted Manuscript
(34) El-Gaby, M. S. A.; Bakry, M. M. S.; Hussein, M. F.; Faraghally, F. A.; Khalil, A. M.; Gad, M. A.; Drar, A. M. Insecticidal efficacy and structure-activity relationship study of some synthesized cyanobenzylidene and bisbenzylidene derivatives against Aphis nerii. *Curr. Chem. Lett.* **2023**, *12*, 529−536.
(35) Abdelhamid, A. A.; Elwassimy, M. M.; Aref, S. A.; Gad, M. A. Chemical design and bioefficacy screening of new insect growth regulators as potential insecticidal agents against Spodoptera littoralis (Boisd.). *Biotechnol. Rep.* **2019**, *24*, e00394−e00401.
(36) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265−267.
(37) Finny, D. J. *Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve*, 2nd ed.; Cambridge Univ. Press: Cambridge, U. K, 1952.
(38) Sun, Y. P. Toxicity index an improved method of comparing the relative toxicity of insecticides. *J. Econ. Entomol.* **1950**, *43*, 45−53.

https://doi.org/10.1021/acsomega.3c03831
ACS Omega 2023, 8, 29685−29692