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Article

One-Pot, Four-Component Reaction for the Design, Synthesis, and SAR Studies of Novel Pyridines for Insecticidal Bioefficacy Screening against Cowpea Aphid (*Aphis craccivora*)

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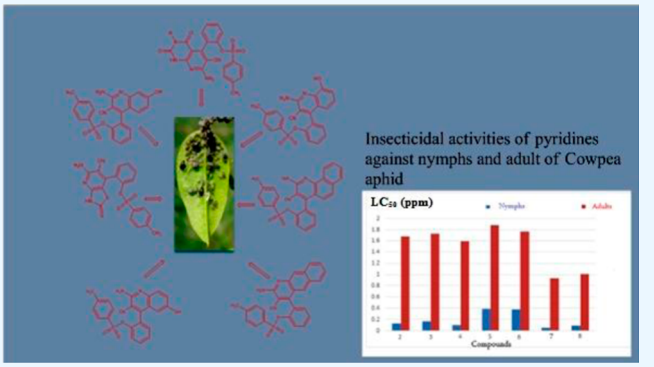
ABSTRACT: In this paper, novel pyridines **2**−**8** were designed and synthesized via the one-pot, four-component reaction of 2-formylphenyl 4-tolylsulfonate with malononitrile, ammonium acetate, and phenols or 2-thioxo-1,3-thiazolidin-4-one or 6-aminopyrimidine-2,4(1*H*,3*H*)-dione under microwave irradiation in an aqueous solution of water and ethanol (1:1 ratio). The structures of new pyridines **2**−**8** were elucidated by elemental and spectral analyses such as IR, ^{1}H NMR, and ^{13}CNMR. This application has many advantages, such as having easy workup, eco-friendliness, reaction time being short (6−13 min), high production (94−98%), inexpensiveness, and avoiding the use of harmful solvents. Moreover, all compounds have been investigated as insecticidal agents against cowpea aphid (*Aphis craccivora*) insects, and the toxicity effect was studied, followed by the structure−activity relationship. From the LC_{50} values, it has been found that compounds 7 and 8 were excellent and promising insecticidal agents, with LC_{50} values of 0.05 and 0.09 ppm against nymphs and 0.93 and 1.01 ppm against adults of cowpea aphid. Furthermore, the obtained results indicated that compounds 2−8 can be applied as insecticidal agents for the control of cowpea aphids and to protect agricultural crops from this destructive pest, which effects crop production and causes major economic damage.



1. INTRODUCTION

It is known that pyridine derivatives are important compounds in organic synthesis due to their various applications in agricultural, biological, and medical fields as antioxidants, anti-inflammatory agents, antibiotics, antivirals, anti-Alzheimer, anticancer, and analgesic drugs, and insecticides (Figure 1).[1−8] In the agriculture field, pyridine derivatives are important due to their wide spread application as insecticides.[9−11] In modern agriculture, pesticides are widely used to protect crops from insect pests and ensure food security. Some crops, such as legumes, suffer from the attack of various types of aphids. The cowpea aphid, scientifically known as *Aphis craccivora* Koch, is a small insect that feeds on the sap of leguminous plants, such as cowpea, alfalfa, and soybeans,[12−14] which can cause significant production losses by feeding on plant sap that transmits plant viruses.[15−19] Many traditional insecticides for controlling aphids have become less effective due to pest resistance.[20] This fact makes scientists look for the preparation of new insecticides with different structures to overcome resistance problems; new insecticides may have a powerful effect on getting rid of these harmful insects. Recently, scientists have tended to replace traditional with modern methods in the synthesis of organic compounds, such as applying microwave irradiation, which has many advances such as inexpensive, eco-friendly, cheap, avoiding the use of harmful solvents, reducing the time of preparation from hours to minutes, and achieving a higher yield compared with traditional methods.[21−23]

For these reasons, we had to develop new pyridine derivatives using the microwave technique, hoping that these compounds would be less hazardous to mammals, safer for the environment, and powerful in controlling destructive pests. Many pyridine derivatives are used as pesticides. So, these synthesized derivatives were tested for their toxicity and efficacy toward *A. craccivora* in laboratory settings. The bioassay results of these compounds encourage further experiments. Field on various agricultural crops.

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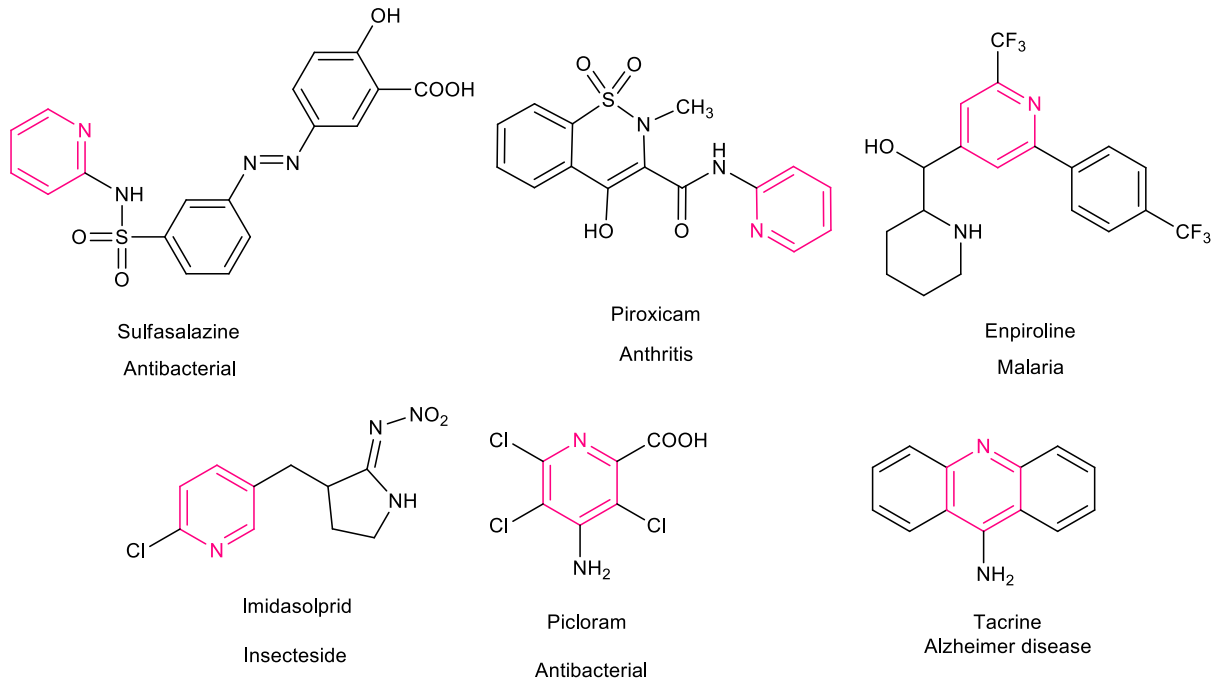

Figure 1. Examples of insecticides and drugs containing pyridine nuclei.

2. RESULTS AND DISSECTION

2.1. Chemistry. In this paper, we designed a one-pot, four-component reaction of 2-formylphenyl 4-methylbenzenesulfonate (**1**), malononitrile, ammonium acetate, and phenol derivatives, such as catechol, resorcinol, hydroquinone, 1-naphthol, and 2-naphthol or with 2-thioxo-1,3-thiazolidin-4-one or 6-aminopyrimidine-2,4(1*H*,3*H*)-dione under microwave irradiation in an aqueous solution of water and ethanol (1:1 ratio), affording pyridine derivatives **2**−**8** (Scheme 1). The reaction was monitored by thin-layer chromatography (TLC) until the reaction was completed. In this strategy, the application of the microwave technique for the synthesis of pyridine derivatives **2**−**8** has many advantages, such as having an easy workup, being eco-friendly, reducing reaction time from hours to minutes (6−13 min), obtaining high-quality and pure products 94−98%, being inexpensive, being more safe, and avoiding toxic solvents. The optimized yield is shown in Table 1.

The structures of new compounds **2**−**8** were elucidated by elemental and spectral analyses, such as IR, ^{1}H NMR, and ^{13}CNMR. Their IR spectra showed the disappearance of the aldehydic carbonyl group in the starting material and the appearance of new absorption bands from 3412−3369 cm^{-1} for OH groups; 3310−3114 cm^{-1} due to the NH_2 and NH groups, and the cyano groups in the range 2216−2225 cm^{-1}, in addition to the amidic carbonyl group at 1652 cm^{-1} in compound **8**. ^{1}H NMR spectra showed, in addition to the expected aromatic protons signals, new singlet signals at 12.26, 10.05, and 10.18 ppm due to OH groups in compounds **2**−**4**, respectively, and NH and NH_2 groups with the aromatic proton signals (disappeared with D_2O). Furthermore, their ^{13}CNMR spectra showed a signal at 187.87 ppm171.64 and 170.84 ppm due to C═S and two C═O groups in compounds **7** and **8**, respectively.

To synthesize pyridines, we investigated the solvent ratio via treatment of compound **1**, malononitrile, ammonium acetate, and catechol under microwave irradiation in different ratios of water and ethanol (3:1, 2:1, and 1:1), respectively. It was found that the best yield was obtained (96%) when the solvent ratio was 1:1, as shown in Table 2.

2.2. Insecticidal Bioefficacy Screening. All toxicological data of aphid's mortality were analyzed with probit analysis via a statistics (LDP-line) package to calculate the LC_{50} values, and all data are represented in Tables 2, 3 and Figures 2, 3, including LC_{50} values, toxic ratio, and slope. The laboratory bioassay experiments were done on cowpea aphids to estimate the insecticidal activities of seven target synthesized pyridine derivatives as insecticidal agents against a sensitive strain of nymphs and adults of the cowpea aphid pest. The newly synthesized compounds after 1 day of treatment showed high to moderate insecticidal activity, with LC_{50} values ranging from 0.05 to 0.39 ppm toward nymphs and from 0.93 to 1.88 ppm toward adults. Compounds **7** and **8** showed high insecticidal activity; they are more efficient than other synthesized compounds to control the cowpea aphid pest. All detailed bioassay results shown below:

2.2.1. Toxicological Activity against Nymphs of A. craccivora after 24 h of Treatment. Bioassay results for seven synthesized derivatives are recorded in Table 3, including LC_{50} values, slope, and toxic ratio; all these parameters showed that all tested compounds have insecticidal activity toward nymphs of *A. craccivora*, with LC_{50} values starting from **0.05** to **0.39** ppm, after 24 h of treatment. In particular, the LC_{50} values of compounds 2, 3, 4, 5, 6, 7, and 8 were 0.13, 0.17, 0.10, 0.39, 0.38, 0.05, and 0.09 ppm, respectively. Among all tested synthesized derivatives, compounds **7** and **8** showed the highest insecticidal activity with LC_{50} values of **0.05** and **0.09** ppm, respectively.

2.2.2. Toxicological Activity against Adults of A. craccivora after 24 h of Treatment. Bioassay results for seven synthesized derivatives against adults are recorded in Table 4, including LC_{50} values, the slope, and the toxic ratio; all these parameters showed the insecticidal activities of compounds **2**−**8** against insect *A. craccivora* after 24 h of

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Scheme 1. Synthesis of Pyridines 2−8 under Microwave Irradiation

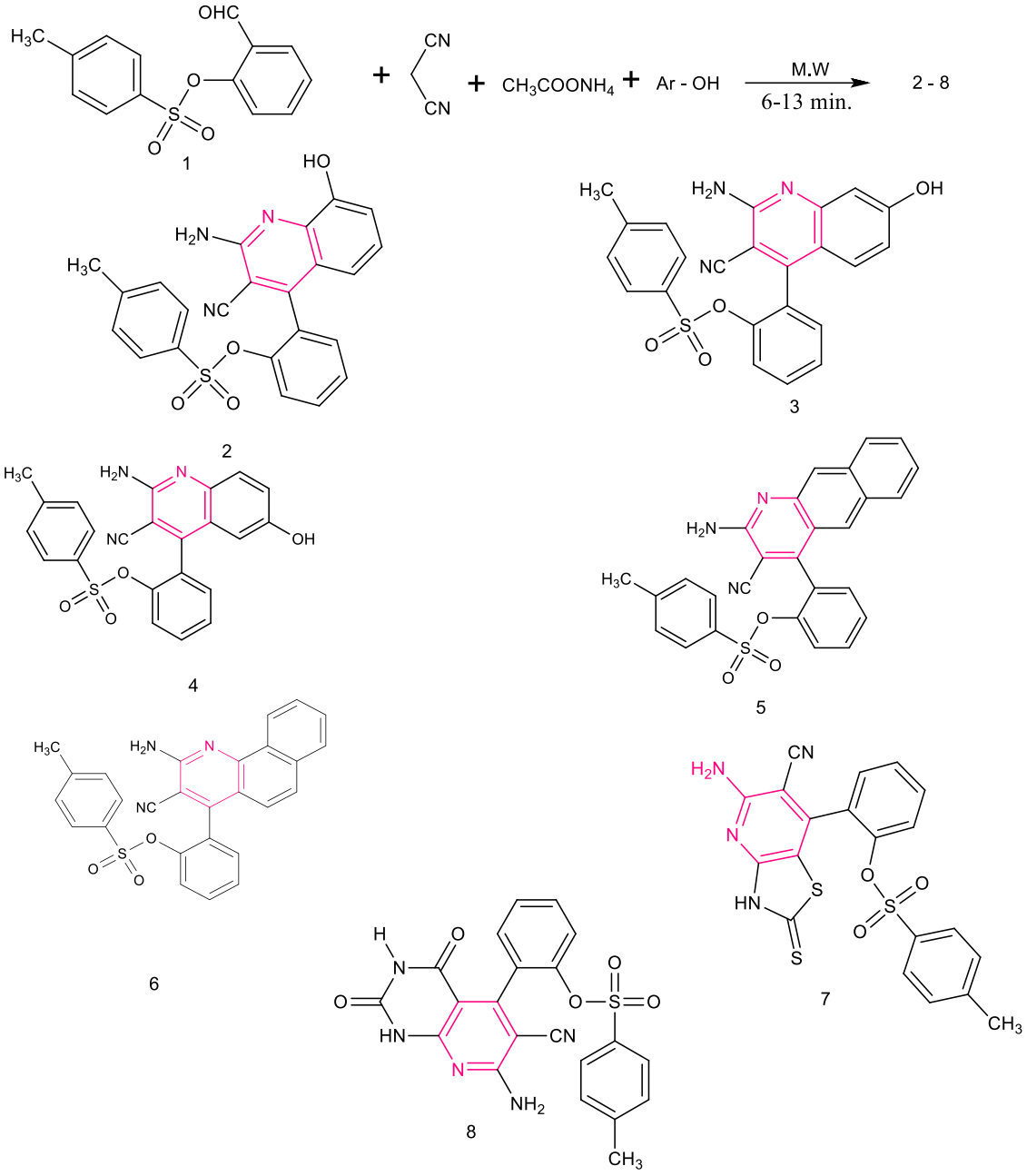

Table 1. Synthesis of Pyridines 2−8 under Microwave Irradiation

Comp	yield (%)	time (min.)
2	96	8
3	95	6
4	**98**	13
5	94	6
6	96	13
7	94	10
8	97	9

Table 2. Effect of the Solvent Ratio for the Synthesis of Compound 2

(H_2O/EtOH)	yield %	time/min
3:1	26	15
2:1	74	15
1:1	96	8

treatment. All compounds have insecticidal activity against the adults of *A. craccivora*, with LC_{50} values ranging from 0.93 to 1.88 ppm. Compounds 7 and **8** showed the highest insecticidal activity, with LC_{50} values of 0.93 and 1.01, respectively. In particular, LC_{50} values of compounds **2−8** are 1.86, 1.73, 1.59, 1.88, 1.77, 0.93, and 1.01 ppm, respectively.

The data mentioned in Tables 3 and 4 and Figures 2 and 3 explain the differences between nymphs and adults of cowpea aphids toward synthesized compounds. Bioassay results obtained show that nymphs are more sensitive toward pyridine derivatives than adults; pyridine derivatives can control

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Table 3. Compounds Activity as Insecticidal Agents against Nymphs of *A. craccivora* Insects after 24 h of Treatment

	nymphs of *A. craccivora*		
comp	LC_{50} (ppm)	toxic ratio	slope
2	0.13	0.38	0.4446 ± 0.2767
3	0.17	0.29	0.4018 ± 0.2865
4	0.10	0.5	0.4516 ± 0.2831
5	0.39	0.12	0.4718 ± 0.2928
6	0.38	0.13	0.4602 ± 0.2926
7	**0.05**	**1**	**0.3318 ± 0.2752**
8	0.09	0.55	0.3710 ± 0.2859

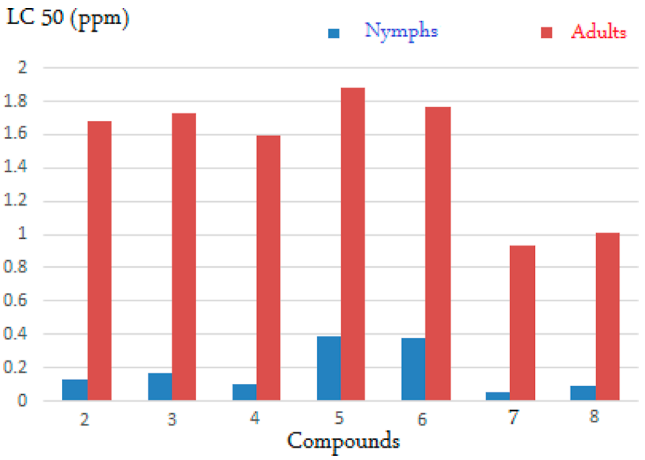

Figure 2. Comparison between the activity of the compounds against adults and nymphs of *A. craccivora* after 24 h of treatment.

nymphs at small concentrations and need more concentrations to effect adults of cowpea aphids.

3. STRUCTURE–ACTIVITY RELATIONSHIPS

From the results recorded in Tables 2 and 3 and Figures 2 and 3, it is clear that all synthesized compounds showed high toxicological activity toward cowpea aphids; the toxicity of synthesized chemical compounds depends on their chemical structures, the main moiety structure, and the substituted groups attached to them. The toxicological activities of seven synthesized pyridines may be due to the presence of the pyridine and benzenesulfonate moiety, which is the main component in all synthesized pyridines. Bioassay experiments are carried out on nymphs and adults of *A. craccivora* insects, which indicate that the adults of *A. craccivora* are more resistant to these compounds than nymphs. Therefore, adults of *A. craccivora* insects need higher concentrations of these compounds; also, experiments indicate that compounds **7** and **8** possess the highest activity in this series compared to other synthesized pyridines. This may be due to rings attached to compounds **7** and **8** being more efficacious. Compound **7** is chemically formed from pyridine and benzenesulfonate, as well as all other compounds, in addition to the thiazole ring attached to pyridine, which leads to increased insecticidal activity. In addition, compound **8** has a pyrimidine ring attached to the pyridine ring; the presence of these rings leads to increased insecticidal activity compared to other compounds. Compound **2** has an OH group attached to the quinoline ring at position no. 8, while the hydroxyl group in compound **3** is attached to the quinoline ring at position no. 6. A change in the hydroxyl group position attached to these compounds causes a change in their toxicological efficacy. Synthesized pyridines **2**–**8** have a pyridine ring and different chemical groups in their chemical structures, leading to an increase in their insecticidal activities. From previous toxicity data for these synthesized compounds, we note that their toxicological activities depend on the pyridine ring.

3.1. Insect Collection and Rearing. *A. craccivora* insect is a great destructive pest which attacks many agricultural crops in Egypt. Batches of *A. craccivora* insects were collected from pest's laboratory (PPRI), Agricultural Research Center.

3.2. Laboratory Bioassay. All seven synthesized pyridines were tested on the cowpea aphid insect to illustrate their insecticidal activities by using the leaf-dipping method under laboratory conditions[17−19] by dissolving pyridine derivatives in acetone, and the addition of a volume of water to prepare the desired solution concentration and 0.1% Tween-80 as a surfactant was used (only acetone, water, and 0.1% Tween-80 used as a control). Nearly the same-sized 20 nymphs and 20 adults of *A. craccivora* were dipped for 10 s in every concentration of each derivative (repeat three times). The tested insects were left to dry at room temperature for about half an hour. These toxicological tests were carried out at 5% relative humidity and at a temperature of 25 °C. After the used pests had dried, they were transferred to glass jars containing water. By a binocular microscope, the aphid mortality was taken after 24 h of treatment. The aphids that were unable to move were considered dead. All toxicity data of synthesized pyridines were analyzed by using Abbott's formula.[21] The evaluation of toxicological activity depends on LC_{50} values, which were estimated by probit analysis.[22,23]

4. EXPERIMENTAL SECTION

4.1. Chemistry. All melting points were recorded on a Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker at 400 and 100 MHz using TMS as an internal reference and DMSO-d_6 as the solvent. The elemental analyses were carried out on a PerkinElmer 240C Microanalyzer. Microwave irradiations were carried out in a Kenstar OM9925E MW oven (2450 MHz, 800 W) at 140 °C. All compounds were checked for their purity on TLC plates.

*4.1.1. General Procedure for the Synthesis of Compounds **2**–**8**.* An equimolar amount (0.001 mol) of *o*-formylphenyl-4-tolylsulfonate (**1**), malononitrile, ammonium acetate, and phenol derivatives, namely, catechol, resorcinol, hydroquinone, 1-naphthol, and 2-naphthol or with 2-thioxo-1,3-thiazolidin-4-one or 6-aminopyrimidine-2,4(1*H*,3*H*)-dione, was dissolved in an aqueous solution of water and ethanol (1:1 ratio); then, the reaction mixture was irradiated in an MW oven for the appropriate time, as recorded in Table 1. After cooling to room temperature, the precipitates were washed with cold water several times and recrystallized with ethanol.

*4.1.1.1. 2-(2-Amino-3-cyano-8-hydroxyquinolin-4-yl)-phenyl 4-Methylbenzenesulfonate (**2**).* Mp 212 °C; IR: 3412 (OH), 3287−3167 (NH_2, NH), 3082 (CH_{arom}), 2914 (CH_{aliph}), 2219 (CN) cm^{-1}; ^{1}H NMR: δ 12.26 (OH), 7.99−7.32 (m, 13H CH_{arom} + NH_2), 2.35 (s, 3H, $-\underline{CH_3}$ tosyl); ^{13}C NMR; 146.21, 133.67, 133.16, 131.76, 131.54, 130.85, 130.68, 128.69, 128.57, 128.40, 123.33, 122.40, 121.96, 22.50; Anal. Calcd for $C_{23}H_{17}N_3O_4S$ (431.46) C (64.03%); H (3.97%); N (9.74%); S (7.43%). Found C (63.96%); H (4.04%); N (9.69%); S (7.23%).

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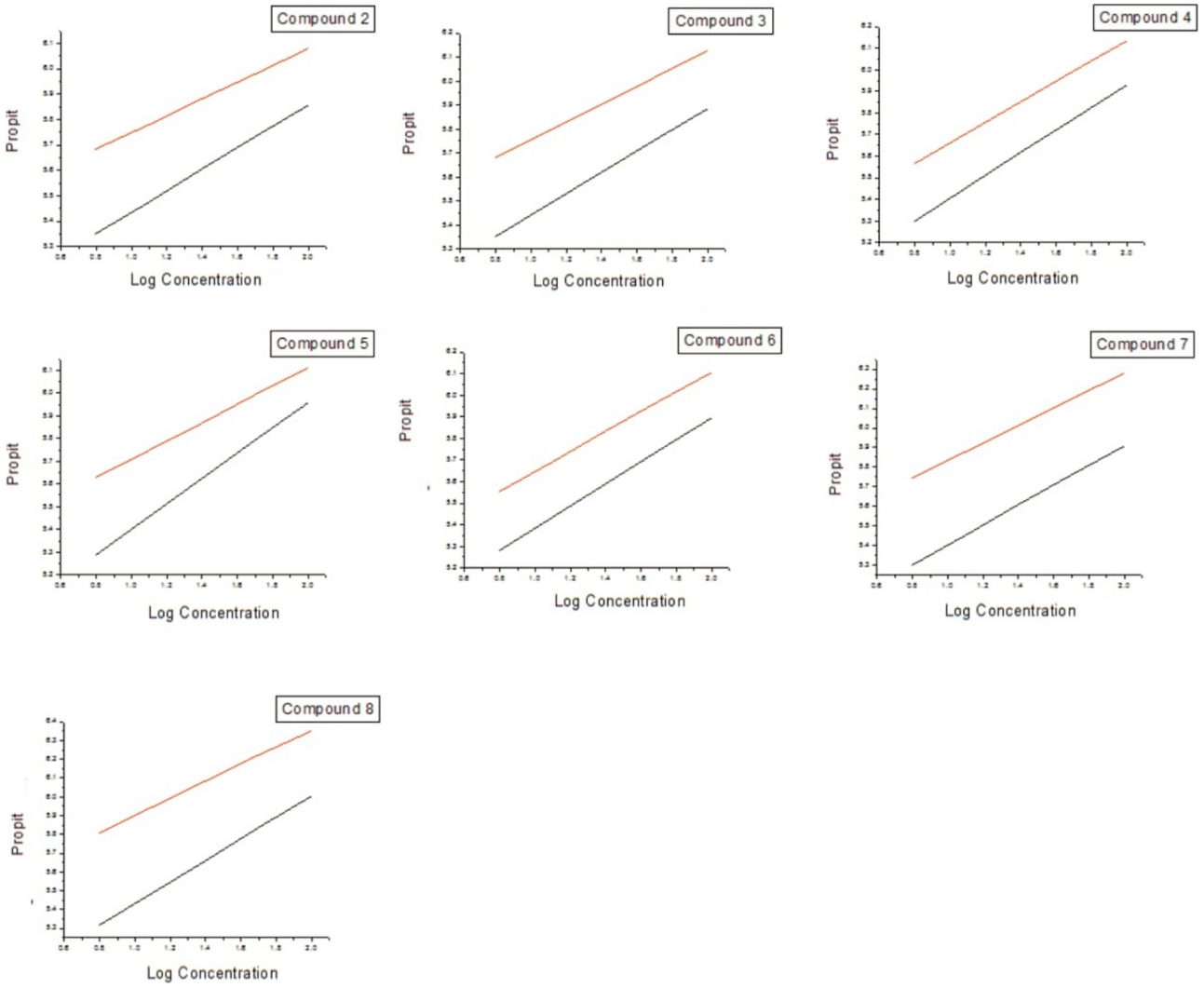

Figure 3. Insecticidal activities of compounds **2-8** against nymphs (red line) and adults (black line) of cowpea aphid after 24 h of treatment.

Table 4. Compounds Activity as Insecticidal Agents against Adults of *A. craccivora* Insects after 24 h of Treatment

	adults of *A. craccivora*		
comp	LC_{50} (ppm)	toxic ratio	slope
2	1.68	0.55	0.5249 ± 0.264
3	1.73	0.53	0.5696 ± 0.2760
4	1.59	0.58	0.5066 ± 0.2915
5	1.88	0.49	0.5546 ± 0.2771
6	1.77	0.52	0.5116 ± 0.2945
7	**0.93**	**1**	**0.4232 ± 0.2704**
8	1.01	0.92	0.4447 ± 0.2673

*4.1.1.2. 2-(2-Amino-3-cyano-7-hydroxyquinolin-4-yl)-phenyl 4-Methylbenzenesulfonate (**3**).* Mp 221 °C; IR: 3369 (OH), 3314−3209 (NH_2, NH), 3094 (CH_{arom}), 2954 (CH_{aliph}), 2220 (CN) cm^{-1}; ^1H NMR: δ 10.05 (OH), 8.03−7.21 (m, 13H CH_{arom} + NH_2), 2.45 (s, 3H, −$\underline{CH_3}$ tosyl); ^{13}C NMR; 152.50, 150.15, 147.66, 146.42, 143.37, 133.84, 132.77, 131.70, 130.61, 129.85, 129.82, 129.41, 128.59, 124.72, 122.37, 115.65, 21.04; Anal. Calcd for $C_{23}H_{17}N_3O_4S$ (431.46) C (64.03%); H (3.97%); N (9.74%); S (7.43%). Found C (63.86%); H (4.11%); N (9.76%); S (7.32%).

*4.1.1.3. 2-(2-Amino-3-cyano-6-hydroxyquinolin-4-yl)-phenyl 4-Methylbenzenesulfonate (**4**).* Mp 218 °C; IR: 3385 (OH), 3298−3140 (NH_2, NH), **2224** (CN) cm^{-1}; ^1H NMR: δ 10.18 (OH), 7.70−6.96 (m, 13H CH_{arom} + NH_2), 2.49 (s, 3H, −$\underline{CH_3}$ tosyl); ^{13}C NMR: δ 137.91, 137.05, 133.12, 131.85, 131.47, 131.35, 130.39, 130.17, 129.60, 129.50, 129.33, 129.16, 128.82, 128.19, 127.55, 127.23, 126.54, 126.35, 116.01, 21.58 Anal. Calcd for $C_{23}H_{17}N_3O_4S$ (431.46) C (64.03%); H (3.97%); N (9.74%); S (7.43%). Found C (64.14%); H (3.99%); N (9.62%); S (7.43%).

*4.1.1.4. 2-(2-Amino-3-cyano-6-hydroxyquinolin-4-yl)1-naphthyl 4-Methylbenzenesulfonate (**5**).* Mp 287 °C; IR (KBr, cm^{-1}): **3268−3114** (NH_2, NH), **2225** (CN); ^1H NMR: δ 7.92−7.24 (m, 16H, CH_{arom} + NH_2), 2.37 (s, 3H, −$\underline{CH_3}$ tosyl); ^{13}C NMR: δ 146.05, 145.00, 141.02, 137.54, 133.57, 133.41, 129.92, 129.33, 128.51, 126.03, 125.06, 123.80, 122.81, 120.74, 19.42; Anal. Calcd for $C_{27}H_{19}N_3O_3S$ (465.52) C (69.66%); H (4.11%); N (9.03%); S (6.89%). Found C (69.58%); H (4.19%); N (8.97%); S (6.94%).

*4.1.1.5. 2-(2-Amino-3-cyano-6-hydroxyquinolin-4-yl)2-naphthyl 4-Methylbenzenesulfonate (**6**).* Mp 295 °C; IR (KBr, cm^{-1}): **3324−3214** (NH_2, NH), **2216** (CN); ^1H NMR: δ 7.52−6.90 (m, 16H, CH_{arom} + NH_2), 2.45 (s, 3H, −$\underline{CH_3}$ tosyl); ^{13}C NMR: δ 151.53, 150.52, 146.72, 145.28, 135.16,

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134.47, 132.72, 132.18, 131.46, 131.00, 130.78, 129.87, 129.33, 127.60, 125.35, 123.10, 122.80, 117.65, 21.38 Anal. Calcd for $C_{27}H_{19}N_3O_3S$ (465.52) C (69.66%); H (4.11%); N (9.03%); S (6.89%). Found C (69.54%); H (4.25%); N (9.08%); S (6.97%).

*4.1.1.6. 4-(7-Amino-6-cyano-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl)phenyl 4-Methylbenzenesulfonate (**7**).* Mp 234−236 °C; IR: 3219−3155 (NH_2 + NH), 3079 (CH_{arom}), 2914 (CH_{aliph}), 2218 (CN), 1652 (C═O) cm^{-1}; ^1H NMR; δ 11.09 (s, 1H, NH), 7.89−6.94 (m, 10H, CH_{arom} + NH_2), 2.43 (s, 3H, $-\underline{CH_{3\ tosyl}}$); ^{13}C NMR: δ 187.87 (C═S), 138.40, 135.38, 134.08, 131.98, 131.97, 129.22, 127.67, 127.56, 127.42, 127.41, 124.06, 30.04; Anal. Calcd for $C_{20}H_{14}N_4O_3S_3$ (454.54) C (52.85%); H (3.10%); N (12.33%); S (21.16%). Found C (52.93%); H (3.02%); N (12.41%); S (21.32%).

*4.1.1.7. 2-(7-Amino-6-cyano-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-5-yl)phenyl 4-Methylbenzenesulfonate (**8**).* Mp 254−255 °C; IR: 3310−3207 (NH_2+NH), 3054 (CH_{arom}), 2946 (CH_{aliph}), 2222 (CN), 1648 (C═O) cm^{-1}; ^1H NMR: δ10.00 (NH), 7.95−7.27 (m, 11H, CH_{arom} + NH_2+NH), 2.43 (s, 3H, $-\underline{CH_{3\ tosyl}}$) ^{13}C NMR: δ 171.64, 170.84 (C═O), 146.83, 146,04, 141.70, 131.99, 130.57, 128.82, 127.84, 126.27, 124.99, 124.47, 122.65, 22.31 Anal. Calcd for $C_{21}H_{15}N_5O_5S$ (449.43) C (56.12%); H (3.36%); N (15.58%); S (7.13%). Found C (56.12%); H (3.36%); N (15.58%); S (7.13%).

5. CONCLUSIONS

In conclusion, we have successfully developed an efficient and quick method for the design of pyridine derivatives via a one-pot, four-component reaction using microwave irradiation as a green application. Overall, products were designed, synthesized, and evaluated for their insecticidal activities against cowpea aphids *A. craccivora* in an attempt to discover new insecticides; toxicity experiments indicate that synthesized pyridines have promising toxicological activities. Compounds **7** and **8** showed the most effectiveness against *A. craccivora* insects, with LC_{50} values of 0.05 and 0.09 ppm against nymphs, respectively, and LC_{50} values of 0.93 and 1.01 ppm against adults, respectively. These bioassay results confirm that the novel products have biological importance for insects, with excellent advances such as rapid death of pests and inexpensive materials. These synthesized pyridine derivatives control both nymphs and adults of cowpea aphids under laboratory conditions. Therefore, we nominate these compounds for further biological tests, especially under field conditions.

■ ASSOCIATED CONTENT

Data Availability Statement

The data that support the findings of this article are available in the Supporting Information of this article.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02055.

Synthesis of pyridines, IR spectra, ^1H NMR spectra, ^{13}CNMR spectra, and elemental analysis (PDF)

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Notes

The authors declare no competing financial interest.

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