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Some oxoimidazolidine and cyanoguanidine compounds: Toxicological efficacy and structure-activity relationships studies

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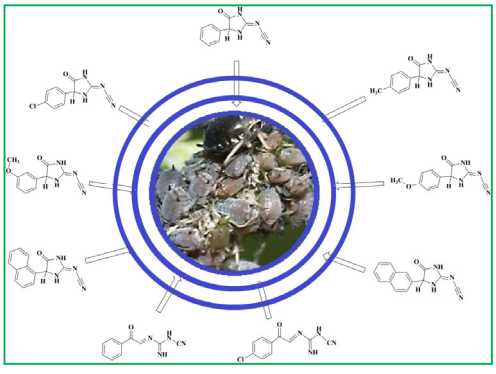
A B S T R A C T

This manuscript reports the preparation and toxicological efficacy testing of nine oxoimidazolidine and cyanoguanidine compounds (**3a, 3b, 3c, 3d, 3e, 3f**, **3g 4a,** and **4b**) against cowpea aphid, *Aphis craccivora* Koch. Bioefficacy data revealed that the tested compounds exhibited a range of toxicological activities against these insects, with compound **3b** being the most toxic and compound **4a** being the least effective. The LC_{50} value of compound **3b** was 1.72 ppm for adults and 0.02 ppm against nymphs of the cowpea aphid, while the LC_{50} value of compound **4a** was 72.51 ppm for adults and 18.02 ppm against nymphs. The manuscript also presents the structure-activity relationships of these compounds. These results provide valuable insights into the development of effective pest control agents for the management of such insects.



Graphical Abstract

1. Introduction

Oxoimidazolidine and cyanoguanidine compounds represent two classes of organic chemicals that have been the subject of extensive research due to their various bioactive properties in different fields such as pharmaceuticals, agrochemicals, and materials science, in addition to the applications of the other organic compounds.[1-20] These compounds have demonstrated significant biological activities, making them attractive targets for the development of novel therapeutic agents and pesticides.One such application is in the control of agricultural pests, such as the cowpea aphid, Aphis craccivora Koch, a major pest affecting important legume crops worldwide.Oxoimidazolidines are a class of heterocyclic compounds

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containing a five-membered ring with two non-adjacent nitrogen atoms, an oxygen atom, and a carbonyl group. These compounds have attracted considerable attention due to their broad spectrum of biological activities, including antiviral, antitubercular,and antifungal properties.[21-22]

In recent years, research has focused on developing novel synthetic strategies for the preparation of oxoimidazolidine derivatives and exploring their potential applications in drug discovery and development.[23] Cyanoguanidines are organic compounds featuring a guanidine moiety with a cyano group attached to one of the nitrogen atoms. These compounds have been widely studied for their pharmacological properties, such as anti-inflammatory and antihypertensive activities.[24-25] Cyanoguanidines also serve as key intermediates in the synthesis of many bioactive compounds and have been utilized in the development of novel pesticides and herbicides.[26]

Plant insect diseases have posed serious risks to crops in the world and caused a severe loss throughout the world.[27] The cowpea aphid, scientifically known as *Aphis craccivora* Koch, is a small insect that feeds on the sap of plants in the legume family, including cowpeas, soybeans, and alfalfa. This pest is known for its destructive impact on crops, as it can cause significant yield lossesby directly feeding on plant sap and transmitting plant viruses and reduce the quality of the affected plants.[28-29] The cowpea aphid is found in many parts of the world, and is considered a major agricultural pest in many regions.Despite its small size, this insect can reproduce rapidly and infest crops in large numbers, making it a significant threat to food security and agricultural sustainability.Understanding the biology, behavior, and ecology of the cowpea aphid is essential for developing effective strategies to manage this pest and minimize its impact on crop production. Current management strategies for *A. craccivora* include the use of synthetic insecticides and biological control agents. However, issues such as resistance development and environmental concerns have necessitated the search for new bioactive compounds acting as possible insecticides.Given the potential biological activities of oxoimidazolidine and cyanoguanidine compounds, further research exploring their prospective as new agents for the control of *Aphis craccivora* Koch is performed here in this work.

2. Results and Discussion

2.1 Chemistry

Herein, the desired compounds (**3a, 3b, 3c, 3d, 3e, 3f** and **3g**) have been prepared in pure state according to literature procedure,[17] *via* the reaction of cyanoguanidine (**1**) with different reagents, namely, 2,2-dihydroxy-1-phenylethan-1-one (**2a**); 1-(4-chlorophenyl)-2,2-dihydroxyethan-1-one (**2b**); 2,2-dihydroxy-1-(4-methylphenyl)ethan-1-one (**2c**); 2,2-dihydroxy-1-(3-methoxyphenyl)ethan-1-one (**2d**); 2,2-dihydroxy-1-(4-methoxyphenyl)ethan-1-one (**2e**); 2,2-dihydroxy-1-(naphthalen-1-yl)ethan-1-one (**2f**); 2,2-dihydroxy-1-(naphthalen-2-yl)ethan-1-one (**2g**), respectively, in ethanol in presence of sodium ethoxide as the best basic catalyst, which was successfully chosen by studying the optimizing various reaction parameters such as: the basic catalyst used, the reaction temperature the suitable solvent, and the cyanoguanidine equivalent amount (**Fig. 1**).[17]

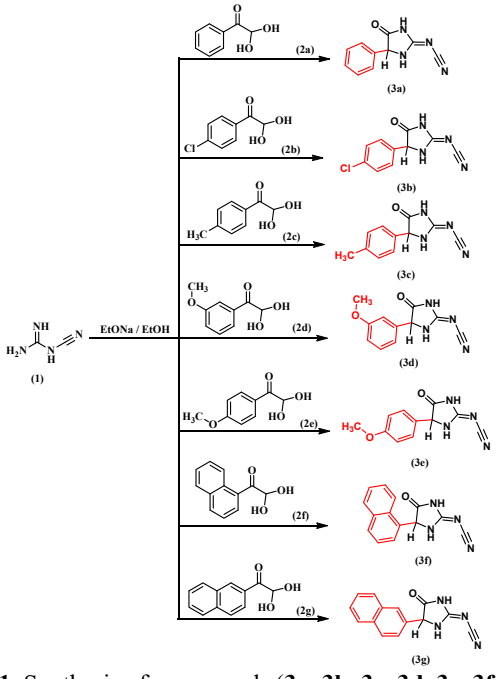


Fig. 1. Synthesis of compounds (**3a, 3b, 3c, 3d, 3e, 3f**, **3g**).

Whereas, cyanoguanidine compounds **4a** and **4b** can be obtained in good yield (55%) according to literature procedure,[17] when refluxing of the cyanoguanidine (**1**) with Arylglyoxals, namely, 2,2-dihydroxy-1-phenylethan-1-one (**2a**) and 1-(4-chlorophenyl)-2,2-dihydroxyethan-1-one (**2b**) in presence of triethylamine as basic catalyst in methanol. The target products **4a** and **4b** insoluble in hot ethanol thus, it can be separated *via* crystallization of the precipitate form ethanol, which was contaminated with soluble imidazolidines **3a** and **3b** (in low yield 29%) (**Fig. 2**).

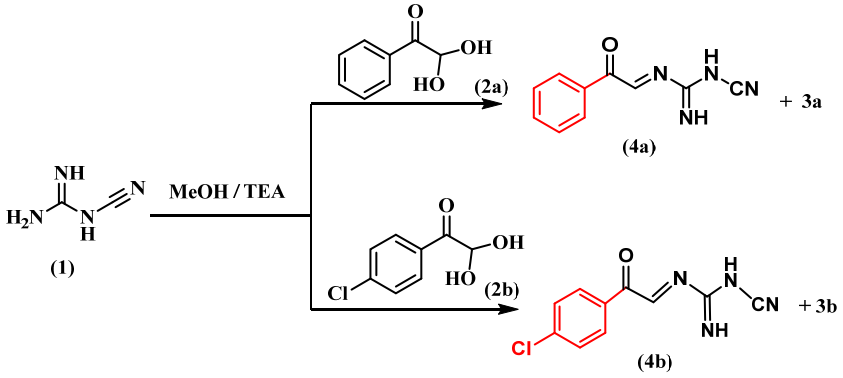


Fig. 2. Synthesis of compounds (**4a** and **4b**).

The chemical structures of the synthesized compounds **3a-g**, **4a** and **4b** were confirmed by their spectralanalyses,[17] the IR spectrum of **4b** given as an example showed absorption bands at 3156 and 3169 cm^{-1} corresponding to two NH groups, 3043 due to CH aromatic 2211 cm^{-1} for cyano group, 1689 cm^{-1} given to carbonyl group and 1632 for C=N group. Its ^1H NMR spectrum showed the presence of two singlets at δ10.62 and 12.54 ppm characteristic for two NH protons, and five multiplet signals at δ7.38-7.45 ppm due to the *para*-phenylene and CH olefinic protons. Its ^{13}C NMR spectrum exhibited five signals at δ72.54, 128.09, 130.01, 130.26 and 134.92 ppm given to aromatic and olefinic carbons, while carbons of cyano, imino and carbonyl groups are characterized by signals at δ 114.88, 160.56 and 171.62 ppm, respectively.

2.2 Toxicological efficacy

All the title compounds have been screened for toxicological efficacy as described below:

2.2.1. Toxicological activity test for the cowpea aphid adults

The toxicological efficacy of a series of compounds **(3a, 3b, 3c, 3d, 3e, 3f**, **3g 4a,** and **4b)** was assessed against the adults of cowpea aphids, and the results are presented in **Table 1** and **Fig. 3**. Following a 24-hour exposure, the tested compounds exhibited varying degrees of biological activity as potential insecticides against the aphids, with LC_{50} values spanning 1.72 to 72.51 ppm. From the LC_{50} values, it is notable to mention that compound **(3b)** was found to have the highest insecticidal activity against adults of cowpea aphid, *Aphis craccivora* Koch, with an LC_{50} value of 1.72 ppm. In contrast, compound **(4a)** had the lowest insecticidal activity, with an LC_{50} value of 72.51 ppm. Compounds **(3a**, **3c**, **3d**, **3e**, **3f**, **3g**, and **4b)** exhibited moderate to good toxicological activity against adults of cowpea aphid and their LC_{50} values were 26.97, 19.17, 10.58, 5.17, 42.52, 29.65, and 2.55 ppm, respectively.

2.2.2 Insecticidal activity test for the cowpea aphid nymphs

The toxicological efficacy of compounds **(3a, 3b, 3c, 3d, 3e, 3f, 3g 4a, and 4b)** against the nymphs of collected aphids was evaluated and the results are presented in **Table 1** and **Fig. 3**. The study revealed that the aforementioned compounds exhibited varying degrees of toxicity, with LC_{50} values ranging from 0.02 to 18.02 ppm after 24 hours. Compound **(3b)** was found to be the most effective in terms of toxicological activity against cowpea aphid nymphs, with LC_{50} value of 0.02 ppm, while compound **(4a)** exhibited the lowest insecticidal activity against nymphs of cowpea aphid, *Aphis craccivora* Koch, with LC_{50} value of 18.02 ppm. The remaining compounds **(3a**, **3c**, **3d**, **3e**, **3f**, **3g**, and **4b)** demonstrated moderate to high toxicological activity, with LC_{50} values of2.98, 3.90, 1.63, 0.93, 15.83, 5.24, and 0.06 ppm, respectively. So, these results provide valuable insights into the potential of these compounds as insecticides against cowpea aphids.

Table 1. Toxicological activity of compounds (**3a, 3b, 3c, 3d, 3e, 3f**, **3g 4a,** and **4b**) against the adults and nymphs of cowpea aphid, *A. craccivora*, after 24 hr of treatments.

	Adults of cowpea aphid			Nymphs of cowpea aphid		
Comp.	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**	**Slope ± SE**	**LC_{50} (ppm)**	**Toxic ratio**
3a	0.0559±0.5232	26.97	0.064	0.1696±0.4200	2.98	0.007
3b	0.9783±0.6779	1.72	1	0.3616±0.6504	0.02	1
3c	0.4498±0.7376	19.17	0.089	0.4722±0.5232	3.90	0.005
3d	0.1874±0.6307	10.58	0.163	0.6265±0.5901	1.63	0.012
3e	0.6235±0.9815	5.17	0.333	0.4652±0.8774	0.93	0.022
3f	0.8904±0.7795	42.52	0.040	0.5383±0.5164	15.83	0.001
3g	0.9593±0.4875	29.65	0.058	0.9905±0.4390	5.24	0.003
4a	0.6021±0.5720	72.51	0.024	0.4932±0.4654	18.02	0.001
4b	0.2438±0.8418	2.55	0.675	0.4624±0.5027	0.06	0.333

Notes: Toxic ratio is calculated as the LC_{50} value of compound **(3b)** for baseline toxicity / the compounds' LC_{50} value.

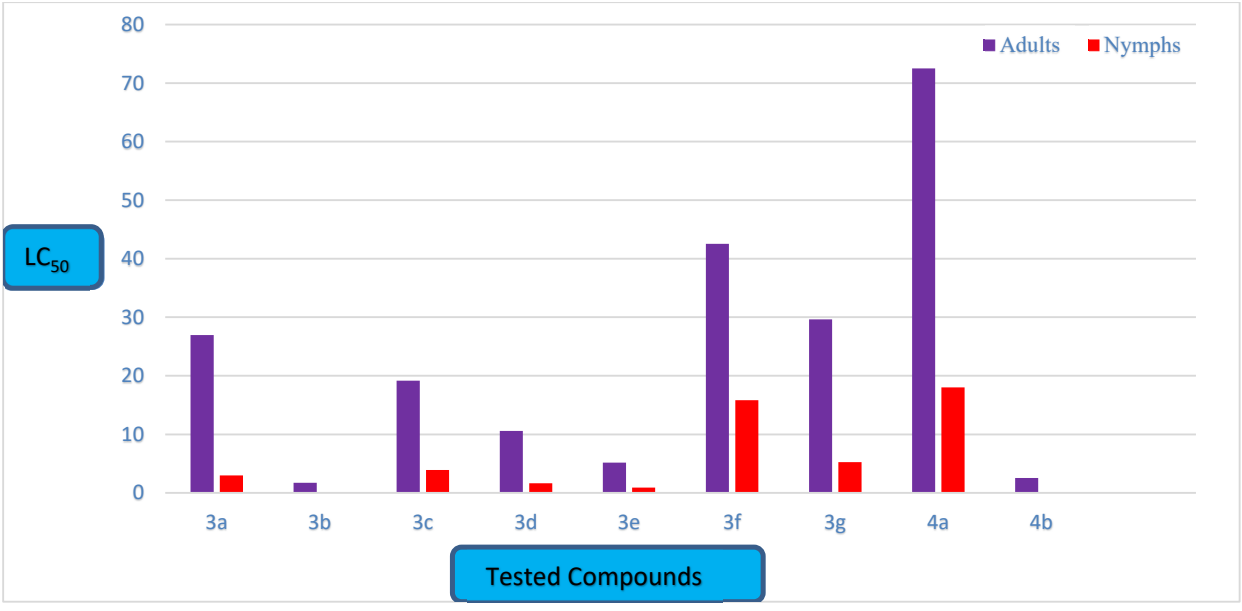


Fig. 3. Toxicological activity of compounds (**3a, 3b, 3c, 3d, 3e, 3f**, **3g 4a,** and **4b**) against the adults and nymphs of cowpea aphid, *A. craccivora*, after 24 h of treatment.

3. Structure-Action Relationships

In this study, the structure-activity relationships (SAR) were reported based on the toxicity values presented in **Table 1** and **Fig. 3**. Among the synthesized compounds, the compound [5-(4-chlorophenyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3b)** was found to exhibit superior activity against cowpea aphid, potentially attributed to the presence of fluorophenyl and imidazole moieties in its structure. These structural features may have contributed to its heightened efficacy, as compared to the other compounds studied. Also, the high activity associated with compounds (**3e**) and (**4b**) may be due to the presence of the p-methoxyphenyl and chlorophenyl moieties, respectively in their structures. The toxicity analysis revealed that compound **(3d)** exhibited greater toxicity than compounds **(3c)** and **(3g)**, possibly due to the presence of a methoxyphenyl moiety in **(3d)** and its absence in **(3c)** and **(3g)**. This structural disparity may have contributed to the observed differences in insecticidal activity among the compounds. The presence of imidazole moiety may reflect better activity than the compounds containing other groups and this is shown in compounds (**3a,b**) and (**4a,b**).

4. Materials and methods

4.1. Instrumentation and Chemicals

All commercially available reagents were purchased from Merck, Aldrich and Fluka and were used without further purification. Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer and are given as cm^{-1} using the attenuated total reflection (ATR) method. ^{1}H NMR and ^{13}C NMR spectra for all the prepared compounds were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. For ^{1}H-NMR, chemical shifts (δ) were given in parts per million (ppm) with reference to tetramethylsilane (TMS) as an internal standard (δ=0); coupling constants (J) were given in hertz (Hz) and data are reported as follows: chemical shift, integration, multiplicity (s= singlet, d= doublet, m=

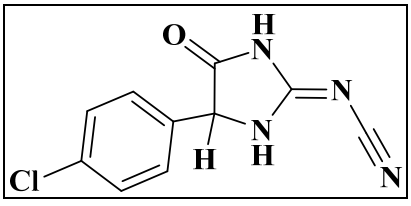
multiplet). For ^{13}C-NMR, TMS (δ=0) or DMSO (δ=39.51) was used as internal standard and spectra were obtained with complete proton decoupling.

Compounds (**3a-g**, **4a,** and **4b**) were obtained according to the literature procedure.[17] The batches of cowpea aphid, *A. craccivora* insects were gathered from faba bean, *Vicia faba* L.*,* fields of agricultural research center, Sohag branch. Toxicity of the ten target compounds was screened against the collected aphids.

4.2.General procedure for the synthesis of 2-cyanoiminoimidazolidines (3a-g):

A mixture of the selected reagents (**2a-g**) (3 mmol) and cyanoguanidine (0.63 g, 7.5 mmol) in 30 mL sodium ethoxide (0.14 g sodium metal in 30 mL ethanol) was refluxed for 1.5 hrs. After completion of the reaction (monitored with TLC), the reaction mixture was cooled to room temperature, poured into ice-cold distilled water and neutralized to pH ~ 4 with dilute hydrochloric acid. The formed precipitate was collected, filtered, washed several times with distilled water, dried and recrystallized from ethanol.

4.2.1. [5-(4-Chlorophenyl)-4-oxoimidazolidin-2-ylidene]cyanamide(3b):

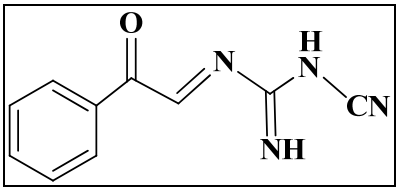


Yield 82%;white solid; m.p.: 232-234°C. IR (ATR) ν_{max}3128 (N-H), 3068 (C-H aromatic), 2930, 2793(C-H aliphatic), 2199 (C≡N), 1771 (C=O), 1646 (C=N) cm^{-1}. ^{1}HNMR(400MHz,DMSO-d_6)δ5.42 (s, 1H, $CH_{imidazolidine}$), 7.37, 7.39 (d, J = 8.4 Hz,2H, $CH_{arom.}$), 7.48, 7.50 (d, J = 8.4 Hz, 2H, $CH_{arom.}$), 10.00 (s, 1H, NH), 11.95 (br. s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ62.4, 115.8 (C≡N), 129.2, 129.3, 133.8, 133.9, 162.9, 174.0 (C=O).

4.3. General procedure for the synthesis of cyanoguanidine (4a and 4b):

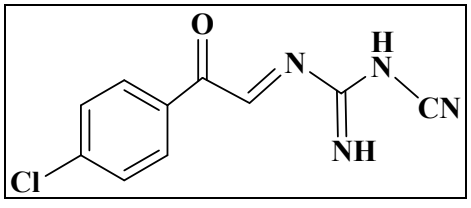
A mixture of the selected reagents (**2a** and **2b**) (3 mmol), cyanoguanidine (0.63 g, 7.5 mmol) in 30 mL methanol and TEA (0.6 g, 6 mmol) was refluxed for 2 hrs. After completion of the reaction (monitored with TLC), the reaction mixture was concentrated, cooled to room temperature and the formed precipitate was collected, filtered, washed with dilute hydrochloric acid, washed several times with distilled water, dried and recrystallized from ethanol to give the insoluble target products **4a** and **4b**beside the solubleimidazolidines**3a** and **3b**.

4.3.1. 1-Cyano-3-(2-oxo-2-phenylethylidene)guanidine(4a):



Yield 55%;white solid; m.p.: >300°C. IR (ATR) ν_{max}3162, 3186(2N-H), 3053(C-H aromatic, 2204(C≡N), 1696(C=O), 1627(C=N) cm^{-1}.^{1}HNMR(400MHz,DMSO-d_6)δ7.34-748(m,5H, $CH_{arom.}$), 7.72 (s, 1H, CH), 10.59(s, 1H, NH), 12.39(br. s, 1H, NH).

4.3.2. 1-[2-(4-Chlorophenyl)-2-oxoethylidene]-3-cyanoguanidine(4b):



Yield 55%;white solid; m.p.: >300°C. IR (ATR) ν_{max}3156, 3169 (2N-H), 3043 (C-H aromatic, 2211 (C≡N), 1689 (C=O), 1632 (C=N) cm^{-1}.^{1}HNMR(400MHz,DMSO-d_6)δ7.38-7.45 (m,5H, $CH_{arom.}$), 10.62 (s, 1H, NH), 12.54 (br. s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ72.54, 114.88 (C≡N), 128.09, 130.01, 130.26, 134.92, 160.56 (C=NH), 171.62 (C=O).

4.3. Laboratory bioassay

The study evaluated the toxicity of the title compounds using leaf dip bioassay method.[30] The laboratory screening results are presented here, revealing the concentrations of the target compounds required to kill 50% (LC_{50}) of cowpea aphids. For each prepared compound, 6 different solution concentrations were created, each containing 0.1% Triton X-100 as a surfactant. Insects, consisting of 20 nymphs and 20 adults of similar size, were dipped into each concentration of the solution three times for duration of ten seconds. After treatment, the cowpea aphids were allowed to air dry for approximately half an hour at room temperature. Control groups of untreated aphids were also included in the experiment. Once the treated insects had dried, they were transferred to Petri dishes with a diameter of 9 centimeters and left for 24 hours in an environment with a temperature of 22 ± 2 °C, relative humidity of 60 ± 5%, and a 12-hour light/dark photoperiod. After 24 hours, the aphid mortality rate was examined using a binocular microscope. Any aphids that were unable to move forward in a coordinated manner were considered deceased. Each compound underwent two rounds of toxicological activity testing, and the resulting data was adjusted using Abbott's formula.[31] The computerized Probit regression analysis program was used to calculate the median lethal concentrations (LC_{50}) and slope values for each of the synthesized compounds, which were then expressed in parts per million (ppm).[32] This work adds to the existing body of scientific knowledge that supports the use of heterocyclic compounds as important bioactive agents in different fields and this is shown by a lot of scientific papers reported before.[33-79]

5. Conclusion

Nine heterocyclic compounds of oxoimidazolidine and cyanoguanidine compounds (**3a, 3b, 3c, 3d, 3e, 3f**, **3g 4a,** and **4b**), namely, (4-oxo-5-phenylimidazolidin-2-ylidene)cyanamide **(3a)**, [5-(4-chlorophenyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3b)**, [5-(4-methylphenyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3c)**, [5-(3-methoxyphenyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3d)**, [5-(4-methoxyphenyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3e)**, [5-(1-naphthyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3f)**, [5-(2-naphthyl)-4-oxoimidazolidin-2-ylidene]cyanamide **(3g)**, 1-cyano-3-(2-oxo-2-phenylethylidene)guanidine **(4a)**, 1-[2-(4-chlorophenyl)-2-oxoethylidene]-3-cyanoguanidine **(4b)** have been prepared in pure state according to literature procedure,[17] by reaction of cyanoguanidine (**1**) with different reagents and under different conditions. After that, these compounds were tested for their biological activity as promising insecticides against the adults and nymphs of cowpea Aphid, *Aphis craccivora* Koch. The findings of this study revealed that certain synthesized compounds, such as **(3b)**, **(3e)**, and **(3a)**, exhibited substantial toxicological activity, with respective LC_{50} values of 1.72, 5.17, and 2.55 ppm, respectively. Among the synthesized compounds, **(3b)** demonstrated the highest toxicity against both adults and nymphs of cowpea aphids, while compound **(4a)** exhibited the lowest toxicity against the same insects. The inclusion of various functional groups in the structure of the compounds resulted in a wide range of toxicological activities, as evidenced by the diverse LC_{50} values obtained from the insecticidal activity test of the prepared compounds.

Author Contributions

Bahgat R. M. Hussein & Amr H. Moustafa: designed the study, synthesized the chemical compounds, paper preparation, and wrote original draft. Shaban A. A. Abdel-Raheem & Ali M. Drar: performed and written the toxicological efficacy part, adjusting the paper linguistically and spelling, and adjusting the paper according to the style of the journal.

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