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Studying the toxicity and structure-activity relationships of some synthesized polyfunctionalized pyrimidine compounds as potential insecticides

Ali M. Drar[a], Shaban A. A. Abdel-Raheem[b*], Amr H. Moustafa[c,d] and Bahgat R. M. Hussein[c]

[a]*Plant Protection Research Institute, Agriculture Research Center, Dokki, Giza, Egypt*
[b]*Soils, Water, and Environment Research Institute, Agricultural Research Center, Giza, Egypt*
[c]*Department of Chemistry, Faculty of Science, Sohag University, Sohag, 82524, Egypt*
[d]*Faculty of Science, King Salman International University, Ras sudr, Sinai 46612, Egypt*

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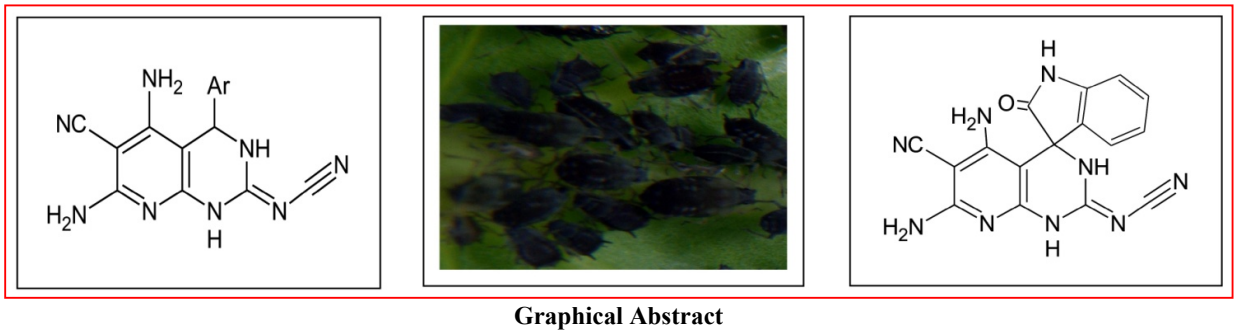
This work includes the synthesis of ten heterocyclic compounds (**3a-i** and **4**) containing pyrimidine moiety incorporated in their structures. Structure characterizations of these compounds were performed by using elemental and spectroscopic analyses. Their toxicity as potential insecticidal agents against the adults and nymphs of cowpea Aphid, *Aphis craccivora* Koch was evaluated. The results of this toxicological activity test revealed that a reasonable number of these compounds possess excellent toxicological activity against cowpea aphids such as compounds (**3d**), (**3c**), and (**3b**) with LC_{50} values 0.0125, 0.0134, and 0.0383 ppm, respectively. The toxicological activities of the rest of the tested compounds ranged from good to moderate against the same insects.



Graphical Abstract

1. Introduction

Heterocyclic compounds have a vital role in our biological system. They are an integral part of many pharmacologically active molecules, natural products and nucleic acids.[1-15] The base pair of DNA & RNA (guanine, cytosine, adenine and thymine) are also made up of heterocyclic compounds like purine, pyrimidine etc. Also, chemistry of *N*-containing compounds, especially pyrimidine compounds, has been developed intensely during the last decades which could be attributed to the discovery of compounds with several activities in this series.[16-18] Pyrimidine derivatives, which play an

* Corresponding author.
E-mail address drshaban202025@gmail.com (S. A. A. Abdel-Raheem)

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important role in synthesis of various active molecules, have various therapeutic applications in medicinal chemistry. One anticipated reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA & RNA.[19] Number of chemical compounds consisting of pyrimidine as core nucleus were synthesized and evaluated for anticancer,[20] antimicrobial and anti-inflammatory agents,[21] antihyperglycemic,[22] analgesic,[23] antibacterial and antifungal,[24] anti-HIV,[25] antitubercular,[26] and herbicidal activities.[27] Due to the wide range of pyrimidine bioactivites, scientists have attracted towards developing new pyrimidine molecules.

Plant insect diseases have posed serious threats to crops in the world and caused a severe loss throughout the world.[28] Nowadays, some of the available traditional fungicides and insecticides, such as Kresoxim-methyl, Pyrimethanil, Chlorantraniliprole, etc., are widely used to prevent plant harmful fungal and insect diseases. However, prolonged use of traditional pesticides can not only lead to drug resistance, but also have a harmful influence on the safety of the plants and the environment. Therefore, the development of novel and promising fungicides and insecticides is still an urgent task.

Cowpea is mainly cultivated for local consumption, either at green shell or at mature stage for dry seeds. Aphids are the most important insect pests of different crops all over the world.[29] On the other hand, faba bean and cowpea plants are of the most important crops in Egypt. The cowpea aphid, *A. craccivora*, is considered one of the most injurious pests infesting these plantation and other leguminous species by sucking the plant sap.[30-31] Pesticides and their residues often have direct effect on aphids, including mortality, decreased longevity and reduced fecundity.

It was reported that pyrimidines were used before in the agricultural field since, new 1,3,4-thiadiazole and 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives were synthesized *via* reactions with variant electrophilic reagents under solvent-free conditions and were evaluated for the insecticidal activity against cotton leaf worm (*Spodoptera littoralis*).[32] So, to develop effective pesticidal agents, the objective of this study was to evaluate the effect of some compounds having pyrimidine moiety incorporated in their structures as potential insecticides against the adults and nymphs of cowpea Aphid, *Aphis craccivora* Koch.

2. Results and Discussion

2.1 Chemistry

As following of our studies in preparation and toxicity evaluation of new bioactive agents, herein ten N-containing compounds, namely, (*E*)-*N*-(5,7-diamino-6-cyano-4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3a**), (*E*)-*N*-(5,7-diamino-4-(4-chlorophenyl)-6-cyano-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3b**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(2,4-dichlorophenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3c**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(4-fluorophenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3d**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(*o*-tolyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3e**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(4-methoxyphenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3f**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(naphthalen-1-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3g**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(naphthalen-2-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3h**), (*E*)-*N*-(5,7-diamino-6-cyano-4-(thiophen-2-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3i**), (*E*)-*N*-(5',7'-diamino-6'-cyano-2-oxo-1'*H*-spiro[indoline-3,4'-pyrido[2,3-*d*]pyrimidin]-2'(3'*H*)-ylidene)cyanamide (**4**) have been prepared in pure state according to literature procedure,[33] since the series of pyrimidine compounds (**3a-i**) was prepared *via* the one-pot four-component reaction of cyanoguanidine with aromatic aldehydes and malononitrile with molar ratio (1:1:2) using sodium methoxide as catalyst (**Fig. 1**). In this method, the formation of the compounds (**3a-i**) was achieved in one-pot through three steps: (i) at first, malononitrile was stirred at room temperature in 3M sodium methoxide for 30 min, (ii), aromatic aldehyde was added to the reaction mixture and further stirred at room temperature for 30 min in 0.5M sodium methoxide, (iii), the reaction was refluxed for 10 hrs after addition of cyanoguanidine **2**. Compound (**4**) was produced *via* one-pot multicomponent reactions of cyanoguanidine **2**, isatin and malononitrile.[33] The synthetic method of these compounds is shown in **Fig. 1**.

Spectral characterization and elemental analyses were used to prove and clarify the structures of all the prepared compounds. Elemental analysis results were in accordance with the values calculated before. Spectral characterization data of the prepared compounds were in a good agreement with their suggested structures. The IR spectrum of **3b** showed characteristic absorption bands at 2172, 2198 cm^{-1} for two C≡N groups, 2945 cm^{-1} for the aliphatic C-H, 3023 cm^{-1} for the aromatic C-H and 3190, 3342, 3417 cm^{-1} for NH_2 and NH groups. Its ^1H NMR spectrum showed the presence of three singlet signals at δ 6.33, 6.43 and 10.26 ppm characteristic of two NH_2 and NH-1 groups, respectively; also it exhibited two doublet signals at δ 5.66, 5.67 and 9.12, 9.13 ppm due to CH-4 and NH-3 groups, respectively; and two doublet signals at δ 7.29, 7.31 and 7.41, 7.43 ppm for aromatic *p*-phenylene protons. The ^{13}C NMR spectrum of **3b** showed eight signals at δ 128.9, 129.0, 133.0, 141.6, 150.0, 154.3, 156.5, 161.0 ppm, which are assigned to aromatic and olefinic carbons; one signal at δ116.9 ppm due to two nitrile groups; while C-4, C-2 and C-6 are characterized by signals at δ 50.4, 70.6 and 88.5 ppm, respectively.

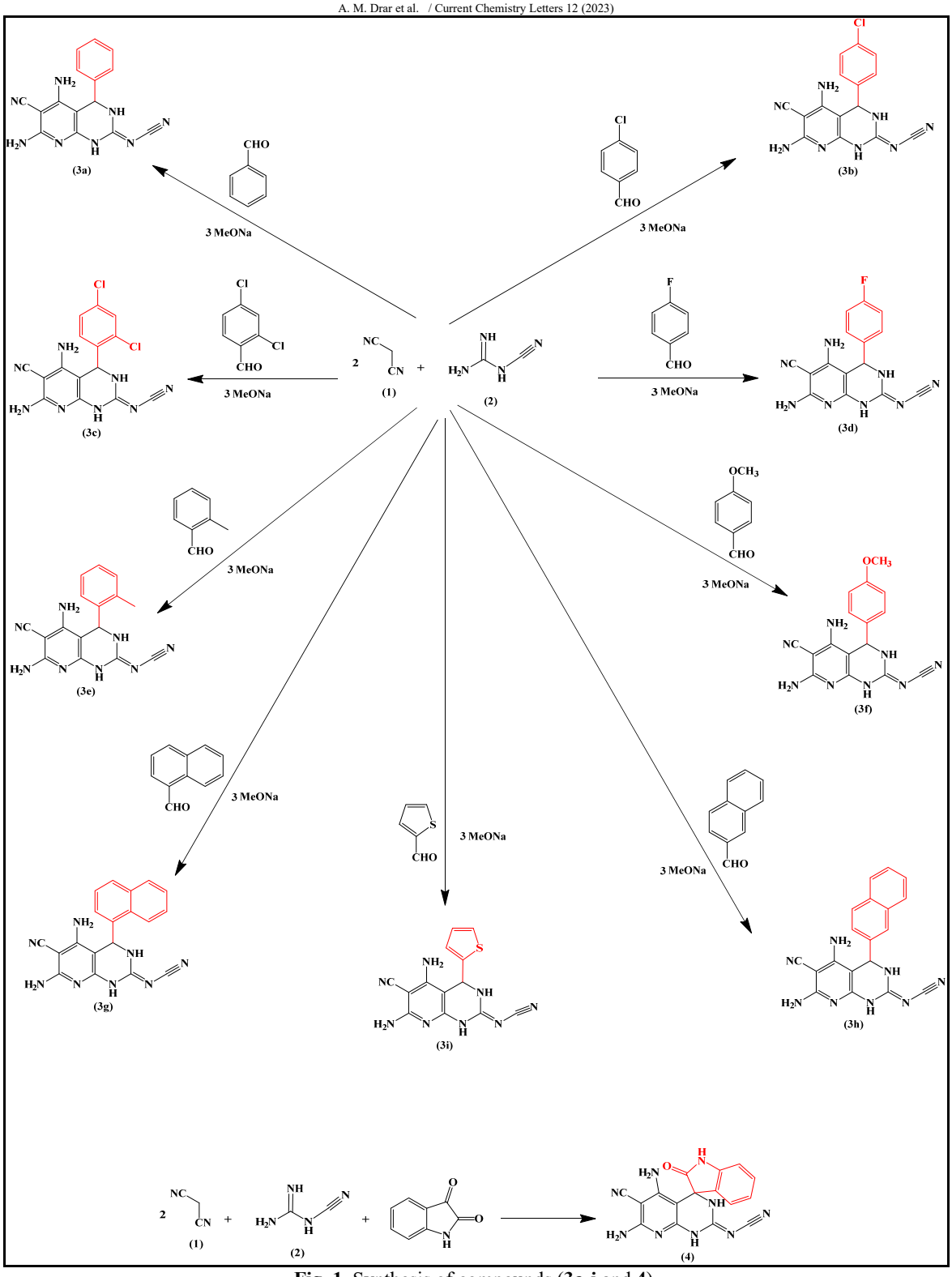

Fig. 1. Synthesis of compounds (**3a-i** and **4**).

2.2 Insecticidal activity

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

2.2.1. Toxicological activity test for the cowpea aphid adults

Compounds (**3a-i** and **4**) were tested for their toxicological activity against the adults of the collected aphids and the results are illustrated in **Table 1** and **Fig. 2**. After 24 h of testing, toxicological activity data showed that the tested compounds exhibited strong to weak biological activity against adults of cowpea aphid and the LC_{50} values ranged from

0.31 to 32.75 ppm. From the LC_{50} values, it was found that the insecticidal activity of compounds (**3d**) is the highest the insecticidal activity against adults of cowpea aphid, *Aphis craccivora* Koch because the LC_{50} value of compounds (**3d**) was 0.31 ppm, whilst the LC_{50} value of compounds (**3g**) was 32.75 ppm and hence the insecticidal activity of this compound is considered the lowest the insecticidal activity. The toxicological activity of compounds **3a**, **3b**, **3c**, **3e**, **3f**, **3h**, **3i**, and **4** ranged from good to moderate and their LC_{50} values were 5.37, 3.27, 3.03, 18.57, 1.096, 28.01, 5.30, and 13.59 ppm, respectively.

2.2.2 Insecticidal activity test for the cowpea aphid nymphs

Compounds (**3a-i** and **4**) were tested for their toxicological activity against the nymphs of the collected aphids and the results are illustrated in **Table 1** and **Fig. 2**. The results showed that after 24 h, compounds (**3a-i** and **4**) showed a strong to weak toxicological activity and the LC_{50} values ranged from 0.0125 to 12.39 ppm. From the LC_{50} values, it was found that the toxicological activity of compounds (**3d**) is the highest activity against nymphs of cowpea aphid, *Aphis craccivora* Koch because the LC_{50} value of compounds (**3d**) was 0.0125 ppm, whilst the LC_{50} value of compounds (**3g**) was 12.39 ppm and hence the insecticidal activity of this compound is considered the lowest the insecticidal activity against nymphs of cowpea aphid, *Aphis craccivora* Koch. The toxicological activity of the rest of the selected ten compounds (**3a**, **3b**, **3c**, **3e**, **3f**, **3h**, **3i**, and **4)** ranged from high to low and LC_{50} values of these compounds were 0.8703, 0.0383, 0.0134, 0.4583, 0.1195, 6.3267, 2.39, and 3.464 ppm.

Table 1. Toxicological activity of compounds (**3a-i** and **4**) 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	0.4909±0.3012	5.37	0.058	0.4213±0.2499	0.8703	0.014
3b	0.4351±0.2625	3.27	0.095	0.2357±0.2454	0.0383	0.326
3c	0.1450±0.2905	3.03	0.102	0.1006±0.1570	0.0134	0.933
3d	0.0726±0.2322	0.31	1	0.0855±0.1631	0.0125	1
3e	0.4492±0.2788	18.57	0.017	0.1329±0.1543	0.4583	0.027
3f	0.4521±0.2463	1.096	0.283	0.3738±0.2496	0.1195	0.105
3g	0.4782±0.2622	32.75	0.009	0.3201±0.1452	12.39	0.001
3h	0.6086±0.2328	28.01	0.011	0.2324±0.1418	6.3267	0.002
3i	0.5424±0.2570	5.30	0.058	0.6165±0.2723	2.39	0.005
4	0.3520±0.2950	13.59	0.023	0.5343±0.2419	3.464	0.004

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

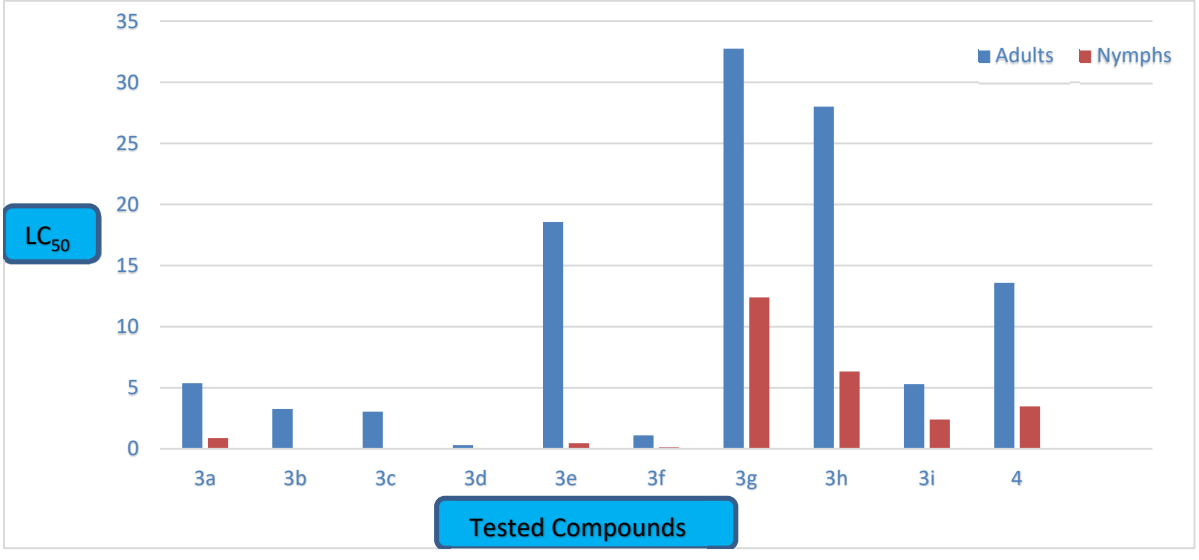

Fig. 2. Toxicological activity of compounds (**3a-i** and **4**) against the adults and nymphs of cowpea aphid, *A. craccivora*, after 24 h of treatment.

3. Structure-Action Relationships

As a continuation of this study and according to the toxicity values presented in **Table 1** and **Fig. 2**, the structure-activity relationships (SAR) were reported here. It is shown that the compound (*E*)-*N*-(5,7-diamino-6-cyano-4-(4-fluorophenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-ylidene)cyanamide (**3d**) is more active against cowpea aphid than the other

pyrimidine synthesized derivatives, and this high activity associated with this compound may be due to the presence of fluorophenyl moiety attached to its structure. Also, the high activity associated with compounds (**3b**) and (**3c**) may be due to the presence of the chlorophenyl and dichlorophenyl moieties, respectively in their structures. Also, toxicity of compound (**3f**) is higher than that of compound (**3a**) and compound (**3e**), this may be due to the presence of methoxyphenyl moiety in compound (**3f**) and the absence of this group in compounds (**3a**) and compound (**3e**) which may cause the insecticidal activity. The presence of thiophenyl group may reflect better activity than the indoline group and this is shown in compounds (**3i**) and (**4**).

4. Materials and methods

*4.1. Instrumentation and Chemical*s

All commercially available reagents were purchased from Aldrich, Merck and Fluka and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) using precoated plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light (254 nm/365 nm) for visualization. Melting points were detected with a Kofler melting points apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra for all 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). 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. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

Compounds **(3a-i** and **4)** were obtained according to the literature procedure.[33] 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 procedures for the synthesis of compounds **3a-i** and **4**:*

Malononitrile (0.02 mol, 1.32 g) was stirred at room temperature for 30 min in 10 mL sodium methoxide 3M (0.69 g sodium metal in 10 mL methanol). Onto the mixture, an aromatic aldehyde, thiophene-2-aldehyde and/or isatin (0.01 mol) in 50 mL methanol was added and stirred for 30 min, then cyanoguanidine **2** (0.01 mol, 0.84 g) was added to the reaction mixture. The resulting mixture was refluxed for about 10 hr. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The formed precipitate was collected, filtered, washed several times with distilled water, dried and recrystallized from ethanol.

*4.2.1. (E)-N-(5,7-diamino-4-(4-chlorophenyl)-6-cyano-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-ylidene)cyanamide (**3b**):*
Yield (82%); yellow solid; m.p. > 310 °C. IR (ATR) n_{max}3417, 3342, 3190, 3023, 2945, 2198, 2172, 1613 cm^{-1}. ^{1}HNMR δ 10.26 (s, 1H, NH^{1}), 9.13, 9.12 (d,,J = 3.2 Hz, 1H, NH^{3}), 7.43, 7.41 (d, J= 8.4 Hz, 2H, CH$_{arom.}$), 7.31, 7.29 (d, J = 8.4 Hz, 2H, CH$_{arom.}$), 6.43 (s, 2H, NH$_2$), 6.33 (s, 2H, NH$_2$), 5.67, 5.66 (d, J = 4.0 Hz, 1H, CH^{4}). ^{13}C NMR δ 161.0, 156.5, 154.3, 150.0, 141.6, 133.0, 129.0, 128.9, 116.9 (2CN), 88.5, 70.6, 50.4. Anal. Calcd. for $C_{15}H_{11}ClN_8$ (338.75): C, 53.18; H, 3.27; N, 33.08. Found: C, 52.92; H, 3.24; N, 33.15.

*4.2.2. (E)-N-(5,7-diamino-6-cyano-4-(thiophen-2-yl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-ylidene)cyanamide (**3i**):*

Yield (84%); brown solid; m.p.: 300-302 °C. IR (ATR) n_{max} 3448, 3322, 3157, 3113, 3023, 2916, 2196, 2179, 1635 cm^{-1}. ^{1}HNMR δ 10.32 (s, 1H, NH^{1}), 9.24, 9.23 (d, J = 3.2 Hz, 1H, NH^{3}), 7.40, 7.39 (d, J = 4.8 Hz, 1H, CH$_{arom.}$), 7.06, 7.06 (d, J = 2.7 Hz, 1H, CH$_{arom.}$), 6.97-6.95 (t, J = 4.1 Hz, 1H, CH$_{arom.}$), 6.54 (s, 2H, NH$_2$), 6.35 (br. s., 2H, NH$_2$), 5.97, 5.96 (d, J = 3.7 Hz, 1H, CH^{4}). ^{13}C NMR δ 161.0, 156.6, 154.2, 149.7, 147.0, 127.1, 125.9, 125.7, 116.8 (2CN), 89.8, 70.7, 47.1. Anal. Calcd. for $C_{13}H_{10}N_8S$ (310.33): C, 50.31; H, 3.25; N, 36.11. Found: C, 50.25; H, 3.12; N, 36.06.

*4.2.3. (E)-N-(5',7'-diamino-6'-cyano-2-oxo-1'H-spiro[indoline-3,4'-pyrido[2,3-d]pyrimidin]-2'(3'H)-ylidene)cyanamide (**4**):*
Yield (73%); brown solid; m.p.: > 310 °C. IR (ATR) n_{max} 3440, 3368, 3334, 3291, 3220, 3062, 2191 (br.), 1748, 1639 cm^{-1}. ^{1}HNMR δ 12.38 (br. s, 1H, NH$^{1'}$), 10.53 (s, 1H, NH^{1}), 9.88 (s, 1H, NH^{3}), 7.31-7.26 (m, 1H, CH$_{arom.}$), 7.11, 7.09 (d, J = 8.0 Hz, 1H, CH$_{arom.}$), 7.02-6.97 (m, 2H, CH$_{arom.}$), 6.37 (s, 2H, NH$_2$), 5.33 (s, 2H, NH$_2$). ^{13}C NMR δ 176.1, 160.6, 156.9, 152.3, 137.2, 130.3, 125.8, 125.2, 122.2, 117.9, 117.1, 116.1, 115.3, 83.7, 70.0, 66.1. Anal. Calcd. for $C_{16}H_{11}N_9O$ (345.31): C, 55.65; H, 3.21; N, 36.51. Found: C, 55.57; H, 3.13; N, 36.46.

4.3. Laboratory bioassay

Toxicological activity of the title compounds was estimated by leaf dip bioassay method.[34] Reported here the results of laboratory screening to find out the concentrations of the target compounds which are demanded to kill 50% (LC_{50}) of cowpea aphids. Six concentrations of solution of each prepared compound plus 0.1% Triton X-100 as a surfactant were

used. 20 nymphs and 20 adult insects, nearly the same size, were dipped for ten seconds in every concentration three times. Cowpea aphids which were treated were permitted to dry at room temperature for about 0.5 hr. Control batches of used aphids were also utilized. After the treated batches of insects had dried, they were moved to Petri dishes (9 centimeters diameter) and remained for 24 hr at 22 ± 2 °C, 60 ± 5% relative humidity and photoperiod of 12:12 (light/ dark). The aphid mortality was screened after 24 hours of testing by using a binocular microscope. The aphid that was unable to coordinate forward movement was considered dead. Toxicological activity test of each compound was repeated two times and the obtained data were corrected by Abbott's formula.[35] Median lethal concentrations (LC_{50}) and slope values of the ten synthesized compounds were computed by using a computerized Probit regression analysis program and expressed in parts per million (ppm).[36] Hence, this work confirms that different heterocyclic compounds can be used as an important bioactive agents and this is also shown by several research papers reported before.[37-73]

5. Conclusion

A chain of *N*-containing compounds with a cyano group attached to their structures and are analogues to neonicotinoid insecticides were chemically synthesized by the one-pot four-component reaction, using available starting materials; cyanoguanidine, aromatic aldehydes and malononitrile as 1:1:2 molar ratio in the presence of sodium methoxide as catalyst. The toxicological activity of the synthesized compounds was evaluated against the adults and nymphs of cowpea Aphid, *Aphis craccivora* Koch. The results of this test demonstrated that some of the synthesized target compounds have a great toxicological activity such as compounds (**3d**), (**3c**), and (**3b**) with LC_{50} values 0.0125, 0.0134, and 0.0383 ppm, respectively. Compound (**3d**) was the most toxic compound against the adults and nymphs of cowpea aphids. The presence of different functional groups in the structures of the synthesized compounds revealed a great spectrum of the toxicological activities, and this is shown in the resulted LC_{50} values of the ten compounds, since it is interesting to note that the insecticidal activities of the tested compounds against the nymphs of cowpea aphid after 24 h of treatment obey the following smooth order: (**3d**) > (**3c**) > (**3b**) > (**3f**) > (**3e**) > (**3a**) > (**3i**) > (**4**) > (**3h**) > (**3g**). This variation in the toxicological activities of all tested compounds proves that many pyrimidine derivatives can be used in the agricultural fields as promising insecticidal agents.

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