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Insecticidal efficacy and structure activity relationship study of some synthesized cyano-benzylidene and bisbenzylidene derivatives against *Aphis nerii*

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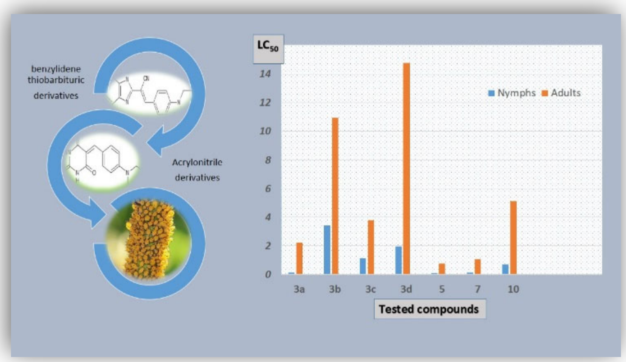
In this study, seven cyano-benzylidene and bisbenzylidene derivatives were designed and synthesized. All synthesized compounds were evaluated to determine their insecticidal activities as potential insecticides against nymphs and adults of *Aphis nerii*. These efforts led to the discovery of compounds **3a-d, 5, 7** and **10** with potent insecticidal activity (LC_{50} range from 0.0141 to 3.4351ppm). Compound **5** exhibited the highest insecticidal potency with 0.0141ppm. In addition, it indicated that compound **3b** is less toxic than benzylidene and other precursors. Therefore, our results suggest that compound **5** has strong potential as a candidate component for developing a novel eco-friendly insecticide for control Aphids.



Graphical Abstract

1. Introduction

Modern agrochemicals play a vital role in safeguarding and improving the production, quality, and quantity of food, feed, fiber, and fuel. With the current offerings on insecticides, herbicides, fungicides and biotechnology products together with considerable investments in research and development the global agribusiness industry contributes to growing public

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expectations for adequate supply of high-quality food and agricultural sustainability.[1,2] Cyano-containing derivatives[3-5] are a kind of important organic compounds due to their wide existence in pesticides, dyes, medicines, materials, and so on.[6,7] Pesticides containing nitrile groups have been reported and reveal excellent antimicrobial activities, **Fig.1**.

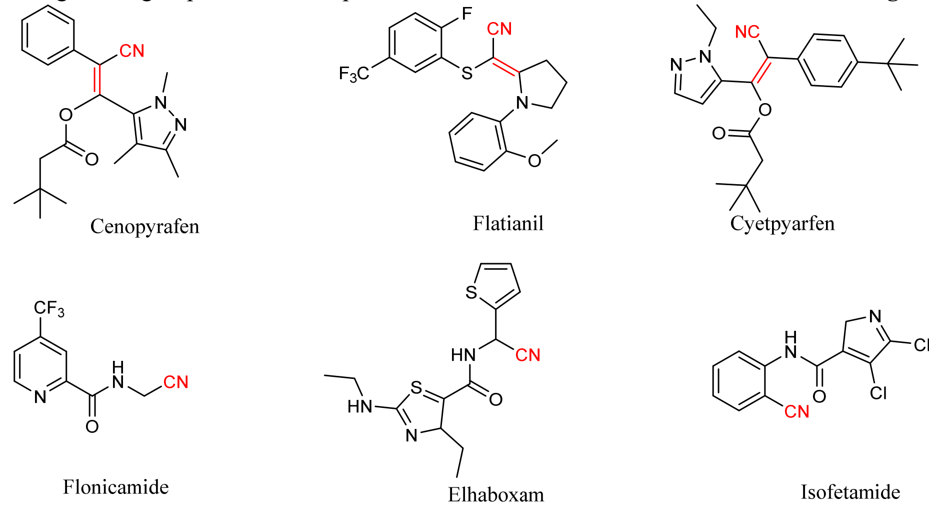


Fig. 1. Marketed pesticides containing cyano groups

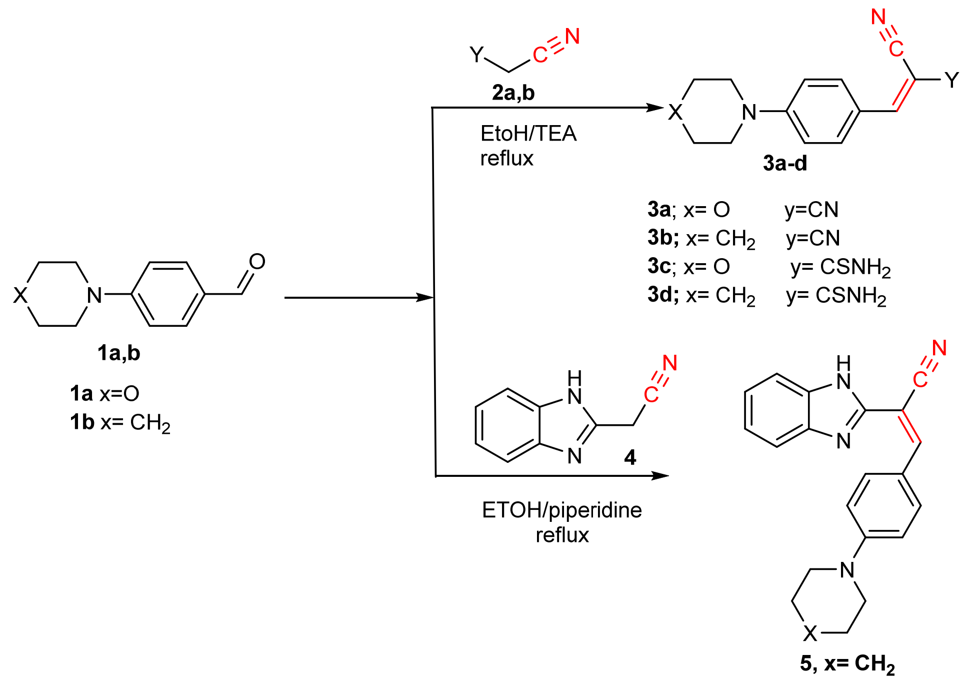
One of the best known acrylonitrile derivatives is cyenopyrafen which integrates the advantages of pyrazole compounds and acrylonitrile compounds and possesses high safety level on beneficial insects and high acaricidal activity.[8] Cyenopyrafen displays excellent bioactive to controlling spider mites (*Tetranychus, Oligonychus, and Panonychus*) during all life stages, although some *Tetranchus urticae* strains might prossess cross-resistance.[9] Flutianil is chemically characterized as a cyanomethylene thiazolidine. It exhibits therapeutic and preventive effects against powdery mildew at a low dosage.[10] Cyetpyrafen is presumed to be an inhibitor of the mitochondrial electron transport chain complex II based on the similarity in chemical structure to cyenopyrafen.[11] Flonicamide can control aphids without cross resistance from other agents.[12,13] Meanwhile, ethaboxam is employed to control grape downy mildew and potato late blight.[14] Isofetamid has a good bactericidal effect on grapevine gray mold.[15] The oleander aphid, *Aphis nerii* Boyer de Fonscolombe, sometimes called the milkweed aphid, is a common pest of several important ornamental plants in the family's Apocynaceae and Asclepiadaceae.[16] This bright yellow aphid with black appendages is commonly found in Egypt feeding on oleander, *Nerium oleander*, milkweeds, such as butterfly weed, *Asclepias tuberosa*, and scarlet milkweed, *Asclepias curassavica*.[17] The oleander aphid ingests sap from the phloem of its host plant. The damage caused by aphid colonies is mainly aesthetic due to the large amounts of sticky honeydew produced by the colony members and the resulting black sooty mold that grows on the honeydew. In addition, the growing terminals can be deformed. Of more concern to nursery managers is the potential for stunted plant growth due to repeated heavy infestation throughout the year.[18]

2. Results and discussion

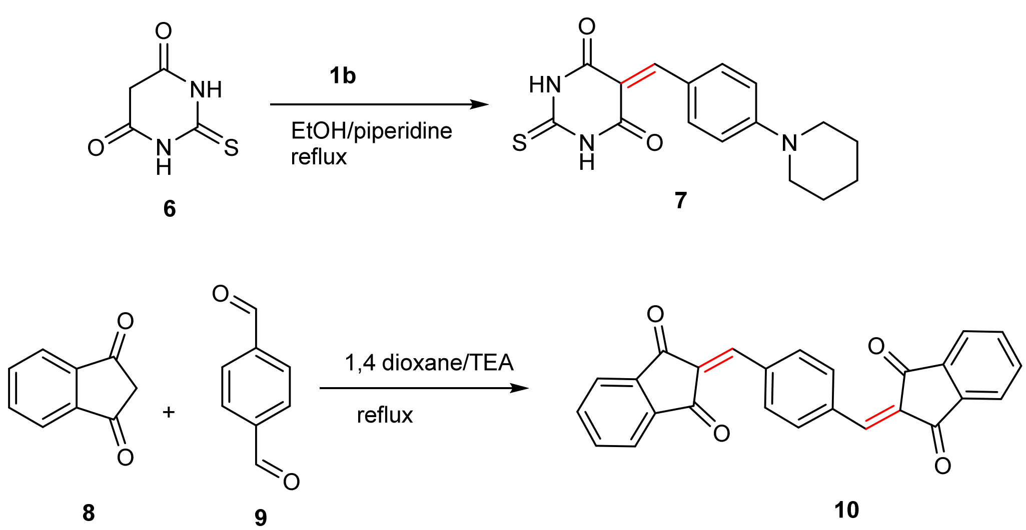
2.1. Chemistry

One of the most well-known chemical reactions for the carbon-carbon double bond formation in organic chemistry is the Knoevenagel condensation that occurs between carbonyl compounds and an activated methylene compound.[19] Due to the Knoevenagel condensation, the α,β-unsaturated compound is formed, which is one of the essential intermediates in producing dyes, herbicides, carbohydrates, pharmaceuticals, chemicals, and pesticides.[20,21] The target benzylidines **3a-d** , **5** and **7** were prepared *via* Knoevenagel condensation between benzaldehydes **1a,b** and active methylene compounds according to our previously reported methods[22] are depicted in (Schemes 1 and 2). Substituted benzylidene malanonitile **3a,b** were obtained by treatment of benzaldehydes **1a,b** with malononitrile **2a** at room temperature in ethanol in the presence of triethylamine. Also, condensation of benzaldehydes **1a,b** with cyanothioacetamide **2b** at room temperature afforded the thioacrylamides **3c,d.** The acrylonitrile **5** was obtained by treatment of benzaldehyde **1b** with benzimidazol-2-ylacetonitrile **4.**[22]

Refluxing of thiobarbituric acid **6 with** benzaldehyde **1b** in 1,4-dioxane in the presence of piperidine yielded benzylidene thiobarbituric derivative **7** as shown in Scheme 2. Our study was extended to synthesize bis-benzylidene from aromatic active methylene. The 2,2'-(1,4-phenylenebis (methanylylidene)) bis (1*H*-indene-1,3(2*H*)-dione) **10** was achieved by Knoevenagel condensation reaction of terephthalaldehyde **9** with indan-1,3-dione **8.** The chemical structure of compound **8** was established by its elemental analysis and spectral data. Its infrared spectrum showed the characteristic absorption bands at 1724 and 1691cm^{-1} for the two carbonyl groups (C=O stretching), and 1605 cm^{-1} for the C=C stretching vibrations. Also, the ^{1}HNMR spectrum of compound **10** showed the presence of two doublets at δ 7.10, 7.40 ppm for the AB-system and a multiplet at δ 7.60-7.61 ppm for the bis-indanyl moiety. The most downfield signal appeared at δ 7.82 ppm which was assigned to the benzylidene protons.



Scheme 1. Synthesis of benzylidene malanonitile **3a,b,** thioacrylamide **3c,d and** acrylonitrile **5** derivatives



Scheme 2. synthesis of benzylidene - thiobarbituric **7** and bis-benzylidene **10** derivatives

2.2. Experimental

General synthetic procedure for 2-[4-(morpholin-4-yl)-benzylidenyl]malono nitrile **3a,** 2-[4-(Piperidin-1-yl)benzylidenyl] malononitriles **3b,**2-cyano-3-[4-(morpholin-4-yl)phenyl]thio-acrylamide **3c,**and 2-cyano-3-[4-(piperidin-1-yl)phenyl]thioacrylamide **3d.** To a mixture of aldehyde **1** (0.01 mmol) and active methylene compound **2** (0.01 mmol) in ethanol (50 mL), a few drops of triethylamine was added. The reaction mixture was stirred at room temperature for 15 min. The resulting solid product was collected by filtration and recrystallized to give **3a-d.** General synthetic procedure for 2-(1H-benzimidazol-2-yl)-3-[4-(piperidin-1-yl)phenyl] acrylonitrile **5** and 5-[4-(piperidin-1-yl)benzylidenyl]-2-thioxo-dihydropyrimidine-4,6-dione **7.** A mixture of aromatic aldehyde (0.01 mmol) and active methylene compound (0.01 mmol) and piperidine (0.1 mmol) in ethanol (20 mL) was heated under reflux for 1 h. The solid product which was produced on heating was collected and recrystallized from the proper solvent. Synthesis of 2,2'-(1,4-phenylenebis(methanylylidene))bis(1H-indene-1,3(2H)-di one) **10.** A mixture of terephthalaldehyde **9 (**0.01 mmol) and 1,3-indan-dione **8** (0.01 mmol) and piperidine (0.1 mmol) in 1,4-dioxane (20 mL) was heated under reflux for 30 min. The solid product which was produced on heating was collected and recrystallized from the proper solvent. This compound was obtained as yellow crystals from 1,4-dioxane ; yield 88% ; m.p. 300 °C. IR: 3089 (CH-arom), 2217 (CN), 1724, 1605 (C=C). ^{1}H NMR (DMSO-d_6, ppm) δ: 7.10,7.40 (2d,4H,AB-system),7.60 (m,4H,Ar-H),and 7.82 (s,2H, benzylidene - H). .Anal. Calcd. for $C_{26}H_{14}O_4$; C,89.21; H, 3.59. Found: C, 89.20; H, 3.60.

3. Laboratory Bioassay

The insecticidal activity of all the cyano-benzylidene and bisbenzylidene derivatives was measured via leaf dip bioassay methods.[22-3] the strain of *A. nerii* was collected from the Agricultural Research Center, Shadawel, Sohag branch during season 202/2023. Tests sought to determine the required concentrations to kill 50% (LC_{50}) of the nymphs and adults of *A. nerii* insects. In this search, five concentrations of each cyano-benzylidene and bisbenzylidene derivatives and 0.1% tween 80 as surfactant were used. Nearly the same size 50 nymphs and 50 adults of *A. nerii* insects were dipping for 10 second in every concentration of synthesized target compounds three times. Tested Insects were left to dray at room temperature for about half hour also insects were dunked in distilled water and tween 80 only used as control. Applications are carried out at 5% relative humidity, and at a temperature of 25 °C. After the used insect had dried, they were transferred to glass jars containing dechlorinated water. With a new binocular microscope the aphid mortality was taken after 24 hrs after test. The aphid that unable to move was considered dead.

The data of aphid's mortality were analyzed using probit analysis via a statistics (LDP-line) package to calculate the LC values with 95% educible limits of lower and upper confidence limit, slope, standard error, chi-square, and correlation coefficient. The insecticide bio-activity of the test every synthesized compounds were repeated three times and the given data were corrected by Abbott's formula.[٣7] the measurements mortality relapse line were measurably dissected by probit analysis.[38]

Table 1. Insecticidal activity of compounds **3a-d, 5, 7** and **10** against the nymphs and adult of *A. nerii* after 24 h of treatment.

	Nymphs of *A. nerii*			Adult of *A. nerii*		
Comp.	LC_{50} (ppm)	Slope	Toxic ratio	LC_{50} (ppm)	slope	Toxic ratio
3a	0.1361	0.3107 ± 0.2363	0.1029	2.2303	0.4943 ± 0.2740	0.3340
3b	3.4351	0.7033 ± 0.3251	0.0040	10.937	0.8000 ± 0.2790	0.0681
3c	1.1321	0.2425 ± 0.2821	0.0123	3.7961	0.362 3± 0.3320	0.1965
3d	1.9703	0.3610 ± 0.2518	0.0071	14.768	0.7297 ± 0.3644	0.0504
5	0.0141	0.2034 ± 0.2273	1	0.7459	0.6263 ± 0.2768	1
7	0.0210	0.0780 ± 0.2217	0.6661	1.0513	0.1487 ± 0.3331	0.7088
10	0.7148	0.0973 ± 0.2390	0.0196	5.1125	0.5083 ± 0.2809	0.1457

Note: Toxicity ratio is calculated as LC_{50} value for baseline toxicity / compounds LC_{50} value.

4. Insecticidal bio-efficacy screening:

All the target synthesized compounds have been screened for insecticidal bio-efficacy as explained as following:

4.1. Toxicological activity test for nymphs of A. nerii after 24 h of treatment.

The results of the insecticidal activity for the prepared compounds exhibited excellent mortality against nymph and adult of lab strains of *A nerii*, the result of compound **3a-d, 5, 7** and **10** were tested against *A. nerii* as seen in Table 1. After 24 hrs of treatment which LC_{50} values vary from 0.0141 to 4.0347 for example LC_{50} value of compounds **3a-d, 5, 7** and **10** were 0.1361, 3.4351, 1.1321, 1.9703, 0.0141, 0.0210 and 0.7148 ppm respectively. For this result, the toxicity of compound **5** and **7** against nymphs of *A. nerii* were the most toxicity than the other prepared compounds after 24 h of the test.

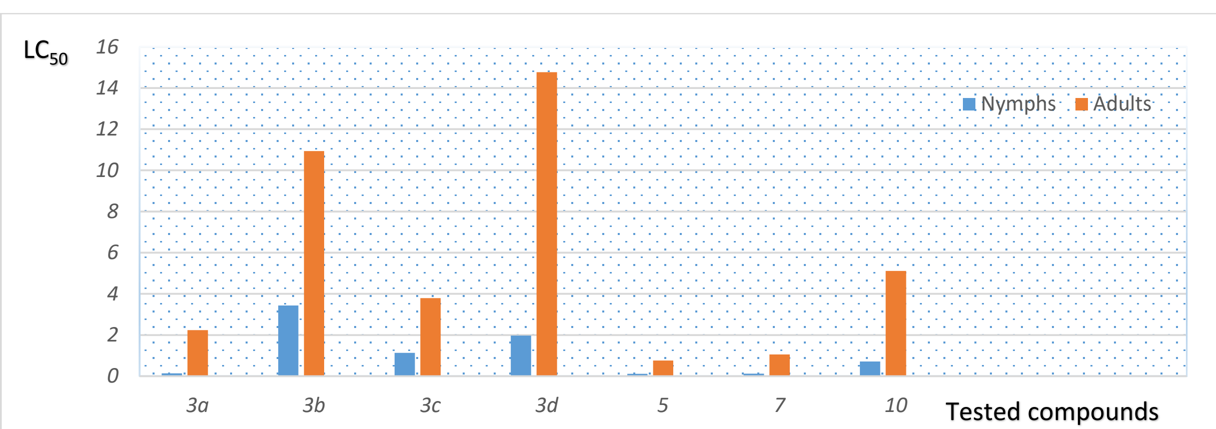


Fig. 2. Insecticidal activity of selective synthesized compounds **3a-d, 5, 7** and **10** against the nymphs and adult of *A. nerii* after 24 h of treatment.

4.2. Toxicological activity test for adults of A. nerii after 24 h of treatment.

On studding result of toxicity index as seen in Table 1 that compound were tested against *A. nerii* distributed from low to high insecticidal activity against the adults of *A.nerii.* The insecticidal activity of compound **5** and **7** were most effected after 24 h of the test because LC_{50} value of compound **5** is 0.7459 ppm and compound **7** was 1.0513 ppm. The other LC_{50} value of compounds **3a-d, 5, 7** and **10** were 2.2303, 10.937, 3.7961, 14.768 and 5.1125 ppm, respectively.

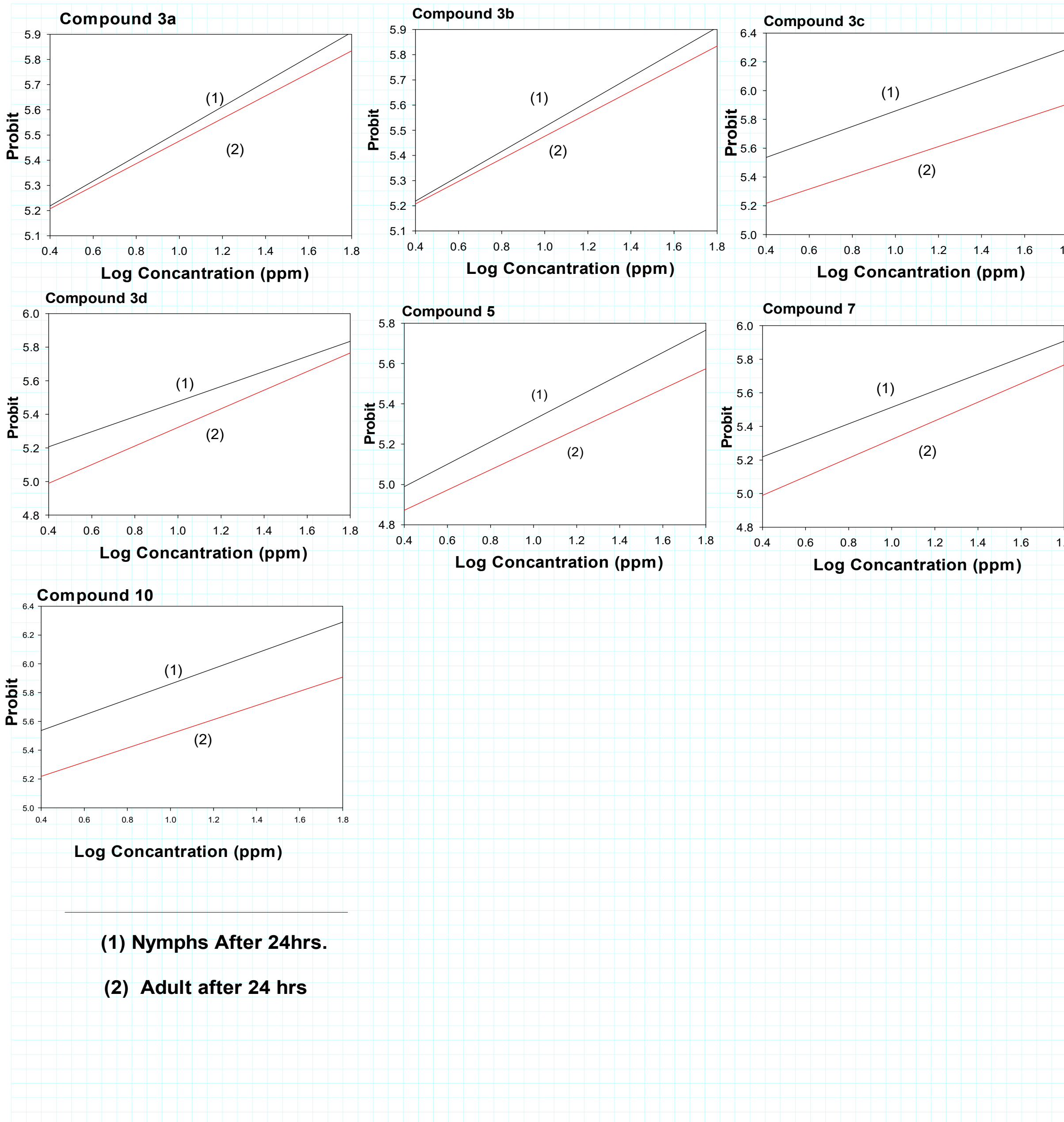


Fig. 3. Insecticidal activity of selective synthesized compounds **3a-d, 5, 7** and **10** against the nymphs and adult of *A. nerii* after 24 h of treatment.

5. Structure-action relationship

In our worka series of cyano-benzylidene and bisbenzylidene derivatives prepared, which possess excellent insecticidal activity toward nymphs and adult of *A. nerii* after 24 h of treatment**.** SAR studying was introduced here according to the toxicity value in the Table 1 and **Fig. 2** and **3.** The order of the insecticidal activity for the synthesized pyrimidine derivatives with the toxicity index was **5 > 7 > 3a > 10 > 3c > 3b > 3b** this order may be attributed to the presence of cyano group in addition to phenyl ring attached to the chemical structure. It is shown that the compound **5** was more activity than other compounds against nymphs and adults of *A. nerii*. The high activity associated with compound **5** may be due to the presence of phenyl nucleus and piperidine moiety in their structure. Also, toxicity of compounds **7** is higher than that of **3a** analog, this may be due to the presence of cyano group, piperidine, and benzylidene moieties, respectively in their structure.

6. Conclusion

A series of cyano-benzylidene and bisbenzylidene derivatives were chemically prepared. The toxicity of these synthesized compounds was estimated as insecticides against adult and nymphs of *A. nerii*. Especially, compound **5** had the best insecticidal activity against nymphs and adult of *A. nerii* than the other synthesized derivatives which LC_{50} was 0.0141 ppm. Compound **7** had the best insecticidal activity against nymphs and adults of *A. nerii* than the other synthesized derivatives which LC_{50} was 0.0210 ppm. The activity concerning compound **5** may be due to the existence of phenyl nucleus and piperidine moiety attached to molecular structure. These results are hopeful and valuable for additional work on the improvement of new and other potent pesticides.

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