Current Chemistry Letters 12 (2023) 599–606

Contents lists available atGrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

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*

Mohamed S. A. El-Gaby[a*], Modather F. Hussein[b,c], Faraghally A. Faraghally[c], Ali M. Drar[d] and Mohamed A. Gad[d]

[a]*Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo 11884, Egypt*
[b]*Chemistry department, Collage of Science, Jouf University, P.O. Box 2014, Sakaka, Aljouf, Saudi Arabia*
[c]*Chemistry Department, Faculty of Science, Al-Azhar University, Assiut 71524, Egypt*
[d]*Plant Protection Research Institute, Agriculture Research Center, 12112 Giza, Egypt*

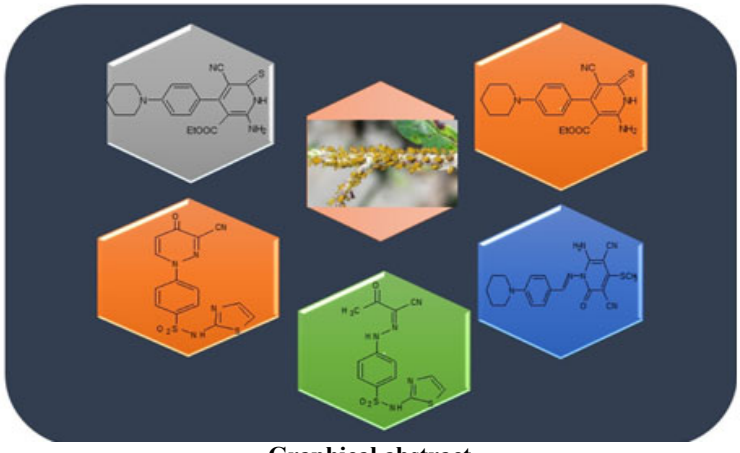
C H R O N I C L E

Article history:
Received December 20, 2022
Received in revised form
January 28, 2023
Accepted February 18, 2023
Available online
February 18, 2023

Keywords:
Dihydropyridine
Pyradazin-4-one
Hydrazone
Sulfonamide
Insecticidal activity
Aphis nerii

A B S T R A C T

In our work we study the toxic effects of the prepared pyridine and pyradazine derivatives. Five compounds have been synthesized in pure state as reported procedures, and their toxicity as potential insecticidal agents against adult and nymphs of *Aphis nerii* were screened. The toxicity data in adults, exhibited that compound **6a** is more toxic than other synthesized compounds, which LC_{50} was1.04 ppm while, in nymph compound **4a** is more toxic than other synthesized compounds, which LC_{50} was 0.02 ppm. The other screened compounds showed weak to strong toxicological activity. The structure-activity relationships (SAR) for these compounds were also discussed.



Graphical abstract

* Corresponding author.
E-mail address samy_adjey@yahoo.com (M. S. A. El-Gaby)

doi: 10.5267/j.ccl.2023.2.003

1. Introduction

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.[1] 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*.[2] 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.[3] Pyridines and heterocyclic annulated pyridazines have been investigated intensively for their applications in agriculture, and in particular for their biological activity for use as potential drugs.[4] The trend of insecticide development is changing from organophosphorus, carbamate, and synthetic pyrethroids to nicotinic and diamide insecticides.[5] During the past decade, compounds possessing a variety of novel modes of action have also been launched or are under development. Neonicotinoids are utilized throughout the world, accounting for more than one-fourth of the global insecticide market.[6-8] Currently, novel nicotinic compounds flupyradifurone (FPF), triflumezopyrim (TFM), and dicloromezotiaz, arbitrarily classified here as new generation, are introduced into the market (**Fig. 1**).[9-11]

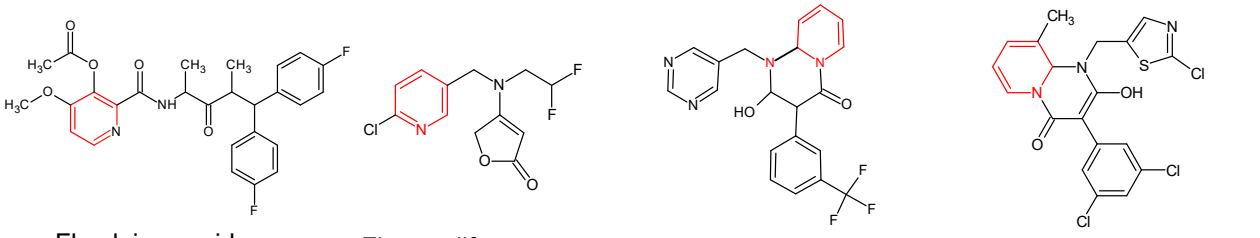


Fig.1. Chemical structure of some nicotine insecticide

Meiji Seika Pharma discovered a novel chemotype insecticide flupyrimin (FLP), providing important biological properties featuring outstanding insecticidal potency to the resistant rice pests as well as superior safety toward beneficial organisms, including pollinators.[9] Flupyradifurone and flupyrimin, exhibiting extremely low honeybee toxicity, have been developed and subjected to practical use. Florylpicoxamid controls a wide range of pathogens including *Septoria* spp., powdery mildew, *Botrytis* spp., Anthracnose, *Alternaria*, scab, *Monilinia*, and others. Florylpicoxamid is a neopicolinamide fungicide under development and presumed to be a QiI, having the same mode of action as fenpicoxamid.[12] The pyridine derivatives neonicotinoid analogues were designed and used as insecticides against cowpea aphid (*Aphis craccivora*).[13] Hydrazones are also used as plant growth regulators[14], insecticides[15], and pesticides (substituted nalidixic acid based hydrazones).[16] Recently a novel series of 1,3-di- and 1,3,5-trisubstituted 1,6-dihydro-6-iminopyridazines (DIPs) was designed and evaluated their antagonistic effects against common cutworm and housefly RDLRs.[17] The results indicate that several compounds exhibit excellent antagonism against both RDLRs, with micromolar IC_{50} values from 2.2 to 24.8 μM. Moreover, most 1,3-disubstituted DIPs showed moderate larvicidal activity against common cutworms at 100 mg kg^{-1}. However, the effect on the in *vivo* or in *vitro* activities by introducing aromatic groups at the 5-position of the pyridazine ring remains to be clarified by more structural modifications. This work is a summary of our preliminary research on the fully selective synthesis of nitro-functionalized nicotine analogs. Although the considered reactions may theoretically proceed giving four regio- and stereoisomeric cycloadducts, a single isomeric product has been obtained.[18] Cyclization of thioacrylamide with malononitrile and ethyl cyanoacetate in ethanolic solution containing a catalytic amount of triethylamine afforded the pyridine derivatives. The polyfunctionally substituted 1,2-Dihydropyridine was obtained in good yield by cyclization of cyanoacetic acid with ketene dithioacetal**.** diazotiazation of sulfonamide followed by coupling with 3-aminocrotonitrile in ethanol at room temperature in the presence of sodium acetate afforded hydrazon-3-oxobutanenitrile.1,4-dihydropyradazin-4-one was obtained by intramolecular cyclization of hydrazon-3-oxobutanenitrile with dimethylformamide-dimethylacetal (DMF-DMA) under refluxing in dry *m*-xylene.[19-22] The principal goal of the work is to explore the insecticidal activity of these compounds. As continuation of our earlier work on pyridazine derivatives and related compounds, in this article we report the synthesis and insecticidal activities and results of our toxicity studies.

2. Materials and methods

2.1. Chemicals

The target compounds 6-Amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile **1,** 2-amino-3-ethoxycarbonyl-6-thioxo-1,6-dihydro-pyridine-5-carbonitrile **2**[17]**,** 1,2-Dihydropyridine **6**[23]**,** hydrazon-3-oxobutanenitrile **9a,b**[24] and 3-cyano-1,4-dihydro-1-[4-*N*-(2-thiazolyl sulfamoyl)]-phenyl]pyradazin-4-one **10**[25] were synthesized according to our previously reported methods. The aphids of *Aphis nerii* insects were gathered from experimental farm fields of Agricultural research center, Sohag branch during 2022 season.

2.2. Laboratory Bioassay

Toxicity of the target compounds was screened by leaf dip bioassay method.[25-36] Results of laboratory screening to find out the concentrations of the target compounds which are demanded to kill 50% (LC_{50}) of *Aphis nerii* were declared here. Five concentrations of each prepared compound plus 0.1% tween-80 as a surfactant were utilized. Five concentrations of each synthesized compound are prepared by dissolving each compound (pure state) in acetone and water plus 0.1% tween-80 as a surfactant were utilized. A number of nymphs and adults of insects, nearly the same size, (nearly 20 nymphs and 20 adults of insects, which nearly have the same size), were immersed for ten seconds in every concentration with replicate three times. Insects which were treated were permitted to dry at room temperature for about one hour. Control batches of used insects (immersed only in solution of acetone, water and tween-80) were also utilized. After the treated batches of insects had dried, they were moved to Petri dishes (9 cm diameter) and remained for 24 h at 22 ± 2 °C, 60 ± 5% relative humidity and photoperiod of 12:12 (light/ dark). With a binocular microscope the aphid mortality was counted after 24 h of test. The aphid that was unable to coordinate forward movement was considered dead. The insecticidal activity test of each compound was repeated three times and the obtained data were corrected by Abbott's formula.[37] By using a computerized Probit regression analysis program, median lethal concentrations (LC_{50}) and slope values of target compounds were computed and reported as parts per million (ppm).[38]

Table 1. Insecticidal activity of compounds **2**, **3**, **6**, **9a** and **10** against the adult and nymph of *Aphis nerii* after 24 h of treatment

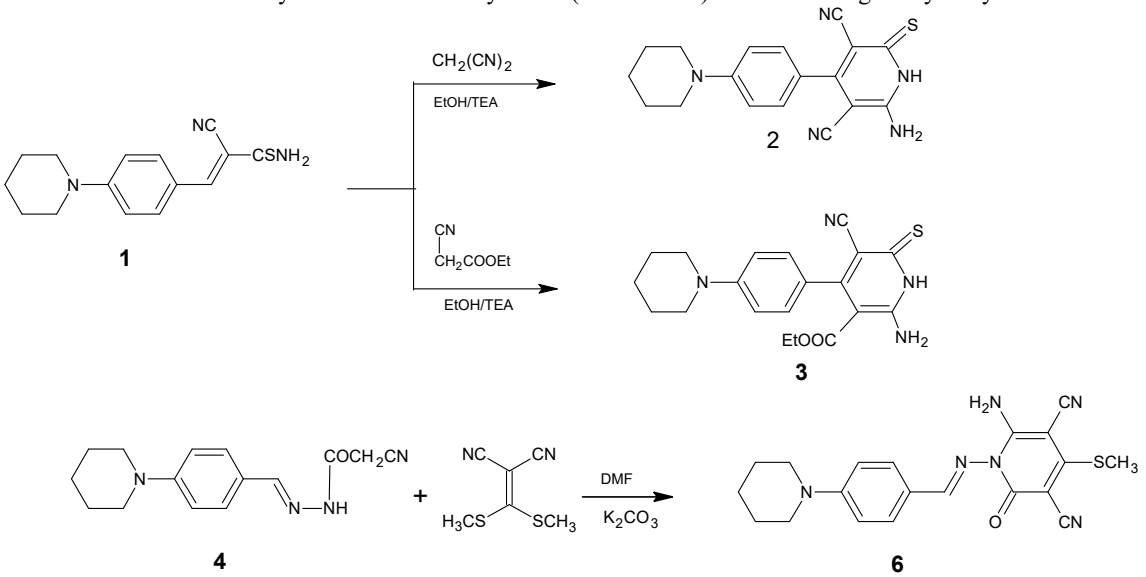
	Adults of *Aphis nerii*			Nymphs of *Aphis nerii*		
Comp.	LC_{50}	Toxicity Index [a]	Slope	LC_{50}	Toxicity Index	Slope
2	52.45	50.43	0.6081 ± 0.2064	1.70	58.0	0.2283±0.2546
3	15.22	14.63	0.2197 ± 0.1593	0.02	1.00	0.0476±0.1876
6	1.04	1.00	0.1362 ± 0.2157	0.59	29.5	0.1449 ± 0.2710
9a	37.89	36.43	0.3566 ± 0.2764	13.30	665	0.3507 ± 0.2000
10	15.00	14.43	0.6694 ± 0.2565	5.26	263	0.3505 ± 0.1948

[a] Notes: toxicity index is calculated as most LC_{50} value for baseline toxicity/the compounds' LC50 value X 100.

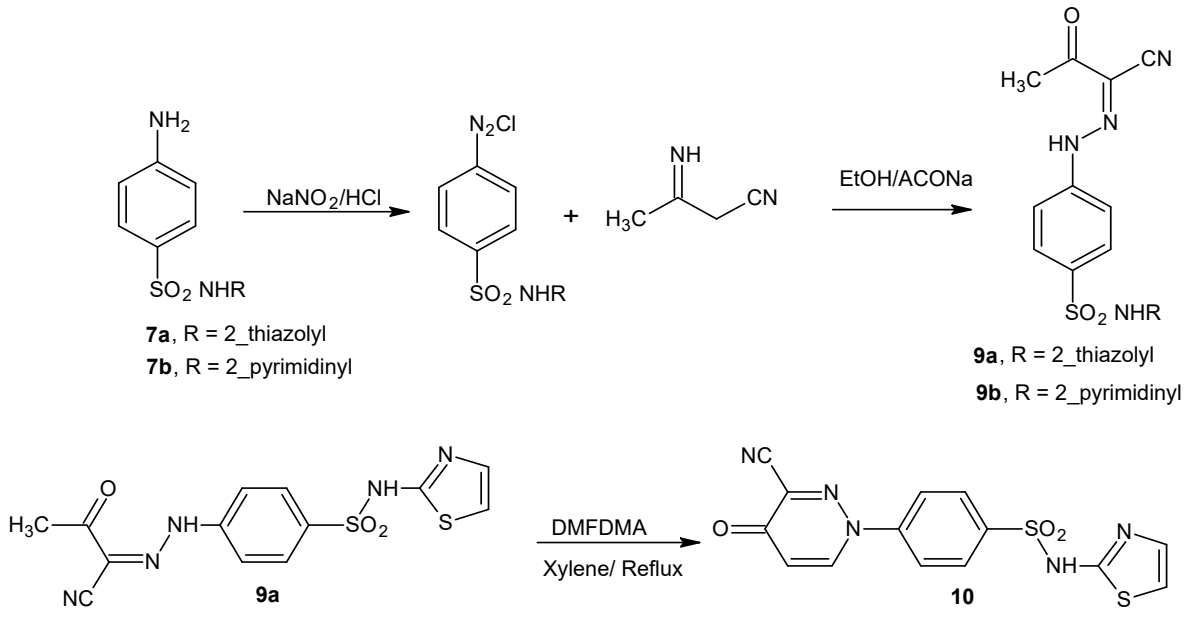
3. Results and discussion

3.1. Chemistry

The synthetic route of the target compounds is summarized in (Schemes 1 and 2). Cyclization of 2-cyano-3-[4-(piperidin-1-yl) phenyl]thioacrylamide **1** with malononitrile and ethyl cyanoacetate in ethanolic solution containing a catalytic amount of triethylamine afforded the 6-Amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile **2** and 2-amino-3-ethoxycarbonyl-6-thioxo-1,6-dihydro-pyridine-5-carbonitrile **3** derivatives, respectively. The polyfunctionally substituted 1,2-Dihydropyridine **6** was obtained in good yield by cyclization of cyanoacetic acid [4-(morpholin-4-yl)benzylidenyl]hydrazide **4** with ketene dithioacetal**.** Diazotiazation of sulfonamide (**7a, b**) followed by coupling with 3-aminocrotonitrile in ethanol at room temperature in the presence of sodium acetate afforded hydrazon-3-oxobutanenitrile (**9a, b)**. The 3-cyano-1,4-dihydropyradazin-4-one **10** was obtained by intramolecular cyclization of hydrazon-3-oxobutanenitrile **9a** with dimethylformamide-dimethylacetal (DMF-DMA) under refluxing in dry *m*-xylene.



Scheme 1: Synthesis of 6-amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile **2**, 2-amino-3-ethoxycarbonyl-6-thio-1,6-dihydropyridino-5-carbnitrile **3** and 6-amino-4-methyl sulfonyl-2-oxo-1,2-dihydropyridino-3,5-dicarbonitrile **6.**



Scheme 2: Synthesis of hydrazon-3-oxobutanenitriles (**9a, b**) and 3-cyano-1,4-pyridazin-4-one (**10**).

3.2. Insecticidal bio-efficacy screening

All the target compounds have been screened for insecticidal activity as described below:

3.2.1. Toxicological activity test for the adults of Aphis nerii:

The toxicity results as shown in Table 1 the target compounds are varied in toxicological activity after 24 h of the test with LC_{50} values varying from 52.45 to 1.04 ppm. Compounds **2, 3, 6, 9a** and **10** gave a high toxicity with LC_{50} values of 52.45, 15.22, 1.04, 37.89 and 15.00 ppm, respectively. Compound **6** revealed the highest toxicity of insecticide compared to the other target compounds.

2.2.2. Toxicological activity test for the nymphs of Aphis nerii,

Our target compounds were screened for their toxicity as insecticides and this is illustrated below. As shown in Table 1 the five synthesized compounds exhibited strong to weak toxicological activity against the nymphs of *Aphis nerii* because a number of them were as active as or more than other after 24 h of the test with LC_{50} values of compounds **2, 3, 6, 9a** and **10** were1.70, 0.02, 0.59, 13.30 and 5.026 ppm, respectively. From the results in above, the toxicity of compound **3** against the nymphs of *Aphis nerii* was about twofold that of other synthesized compounds after 24 h of the test because LC_{50} value of compound **3** was 0.02 ppm.

4. Structure-action relationship

As a continuation of this work, the structure-activity relationships (SAR) were reported here according to the toxicity values in **Table 1,** and **Fig. 2** and **Fig. 3** as well. All compounds exhibited higher insecticidal activity towards nymphs *of Aphis nerii* than that of adults of *Aphis nerii* after 24 h of treatment. The preliminary SAR analysis indicated that compounds **6** and **3** showed the highest toxicological activity against adults and nymphs of *Aphis nerii,* this may be due to each one of them having a pyridine nucleus. Compound **6** was the strongest insecticides against adults, this heights in activity may be due to the presence of two cyano groups, S-metyl moiety, pyridine ring in addition to piperidine ring, respectively in their structure. In addition to the toxicity of compound **3** possessing the strongest activity against nymphs, may be due to the presence of cyano group, pyridine ring and to piperidine ring in their structure. However, compound **2** also possesses pyridine-2-thion with the substituent groups NH_2 and two CN groups without ester groups, we think that the second cyano groups may cancel the effect of cyano groups or decrease it. So, compound **2** has weaker activity than other **3** or **6**.

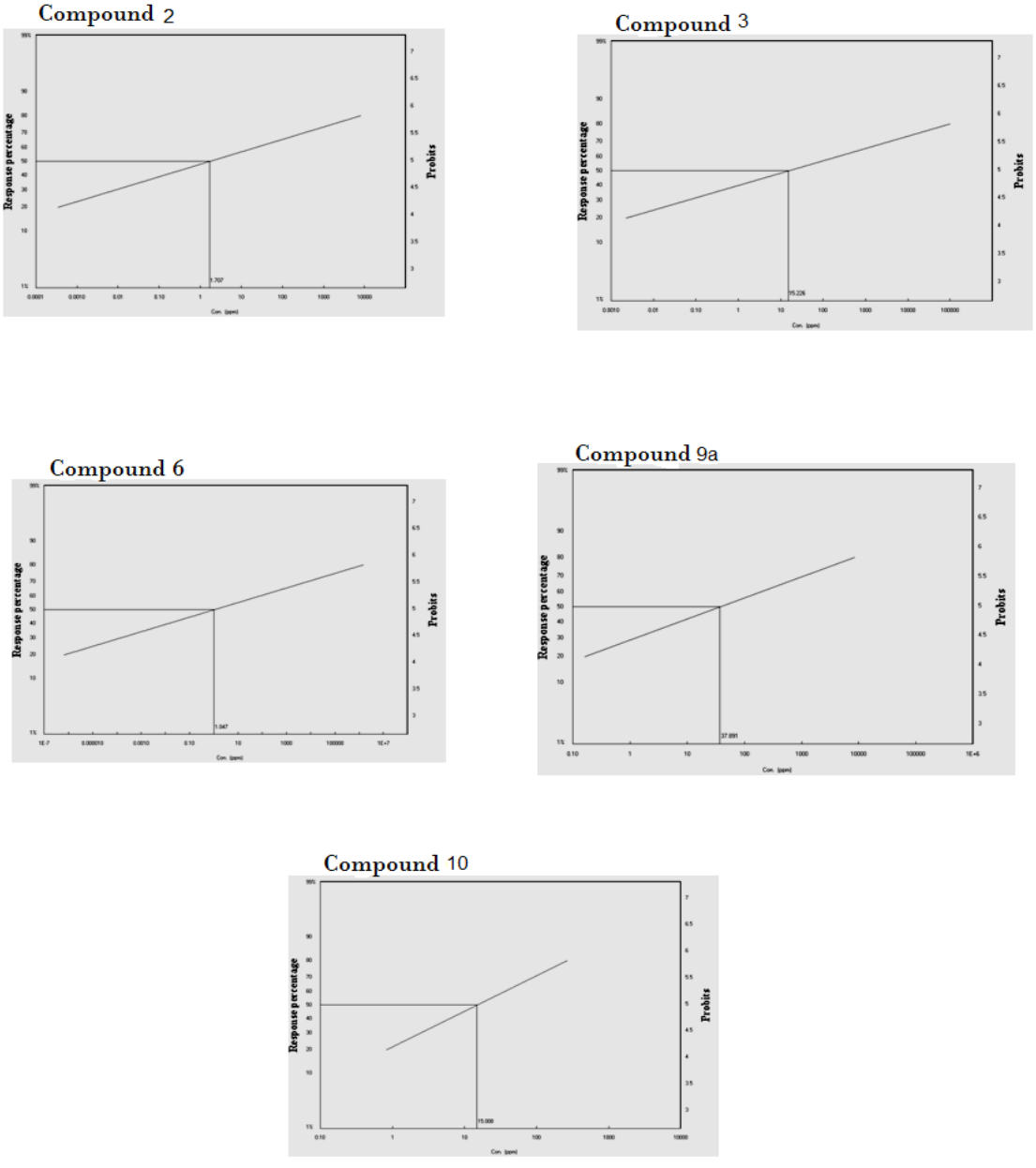


Fig. 2. insecticidal activity of compounds **2, 3, 6, 9a** and **10** against adults of *Aphis nerii.*

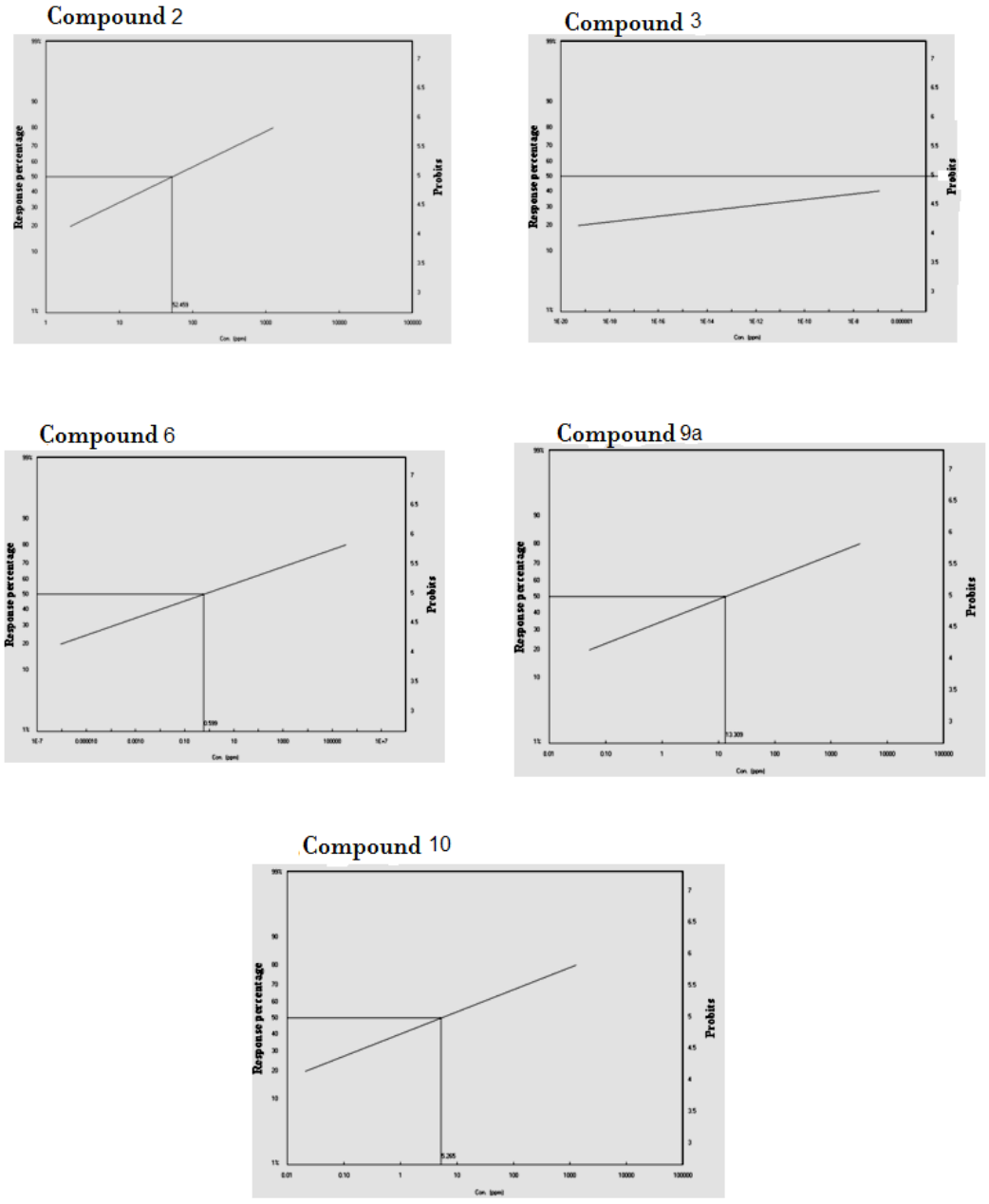


Fig. 3. insecticidal activity of compounds **2, 3, 6, 9a** and **10** against nymphs of *Aphis nerii*

5. Experimental

General Synthetic Procedure for 6-Amino-4-[4-(piperidin-1-yl)phenyl]-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (2) and 2-amino-4-[4-(piperidin-1-yl)phenyl]-3-ethoxycarbonyl-6-thioxo-1,6-dihydro-pyridine-5-carbonitrile (3): As starting substancea mixture of thioacrylamide **1** (0.01 mmol) and active methylene compound (0.01 mmol) and in ethanol (30 ml), a few drops of triethylamine was added. The reaction mixture was heated under reflux for 1 h. A crystalline solid was obtained on cooling. Synthesis of 6-Amino-4-methylsulfanyl-2-oxo-1-[(4-(piperidin-1-yl)benzylidenyl)amino]-1,2-dihydro- pyridine-3,5-dicarbonitrile (6): To a solution of hydrazone **7** (0.01 mmol) in dimethylformamide (8 mL), potassium carbonate anhydrous (1 gm) and ketene dithioacetal **5** (0.01 mmol) was added. The reaction mixture was heated under reflux until the evolution of methyl mercaptan had stopped. After cooling, the reaction mixture was poured into cold water (100 mL) and acidified with HCl. The resulting solid product was collected by filtration, washed with water to obtain the 1,2-dihydropyridine 6.[25]

General Synthetic Procedure for hydrazon-3-oxobutanenitrile (**9a, 9b):** Sulfonamide (0.01 mmol) was dissolved in a mixture of concentrated HCl (5 ml) and water (5 ml) and cooled to 0 ^{0}C in an ice bath. A cold aqueous solution of sodium nitrite (0.01 mmol) was then added. The diazonium salt obtained was filtered into a cooled mixture of sodium acetate (2 g) and 3-aminocrotonitrile (0.01 mmol) in ethanol (20 ml)**.** The resulting solid product was washed with water washed with water to obtain the hydrazon-3-oxobutanenitrile.[26]

General Synthetic Procedure for synthesis of 3-cyano-1,4-dihydro-1-[4-*N*-(2-thiazolyl salfamoyl)phenyl]pyradazin-4-ones 10: To a solution of hydrazone **4b** (0.01 mmol) in dry *m*-xylene (20 ml), dimethylformamide-dimethylacetal (DMF-DMA) (0.01 mmol) was added. The reaction mixture was heated under reflux for 1 h. The solvent was removed by evaporation under reduced pressure and the remainder was left to cool. The solid product so formed was collected by filtration, washed with petroleum ether (bp 40-60 ^{0}C).[26]

6. Conclusion

A series early stage aphicidally active hydrazone dihydropyridine and pyradazine derivatives were chemically prepared. The toxicity of these compounds was estimated against adult and nymphs of *Aphis nerii* and showed that a number of the prepared compounds possess good toxicological activities as insecticides. Especially, compound **6** had the best insecticidal activity against adults of *Aphis nerii* than the other synthesized derivatives which LC_{50} was 1.04 ppm. Compound **3** had the best insecticidal activity against nymphs of *Aphis nerii* than the other synthesized derivatives which LC_{50} was 0.02 ppm. The activity concerning compound **6** may be due to the existence of the S-methyl, tow cyano group,pyridine and piperidine ring attached to molecular structure. These results are hopeful and valuable for additional work on the improvement of new and other potent pesticides. Our research demonstrated that the hydrazone dihydropyridine and pyradazine derivatives could effectively control against adult and nymphs of *Aphis nerii*.

References

(1) Blackman R. L. and Eastop V. F. (**2000**) Aphids on the World's Crops: an Identification and Information Guide. Wiley, New York.
(2) Essig E. O. (**1958**) Insects and Mites of Western North America. MacMillan Publishers, New York.
(3) Hall R. W. and Ehler L. E. (**1980)** Population ecology of Aphis nerii on oleander. *Environmental Entomology* 9, 338-344.
(4) Meanwell N. A. and Seiler S. M. (**1990**) *Drugs Future*, 15, 369.
(1) Umetsu N. and Shirai Y. (**2020**) Development of novel pesticides in the 21st century, *J. Pestic. Sci.* 45 (2) 54–74.
(5) Tomizawa, M. and Casida, J. E. (**2009**) Molecular recognition of neonicotinoid insecticides: the determinants of life or death. *Acc. Chem. Res*. 42, 260−269.
(6) Tomizawa, M. (**2013**) Chemical biology of the nicotinic insecticide receptor. *Adv. Insect Physiol.* 44, 63−99.
(7) Casida, J. E. and Durkin, K. A. (**2013**) Neuroactive insecticides: targets, selectivity, resistance, and secondary effects. *Annu. Rev. Entomol*., 58, 99−117.
(8) Nauen R., Jeschke P., Velten R., Beck M. E., EbbinghausKintscher U., Thielert W.,Wölfel K., Haas M., Kunz K. and Raupach, G. (**2015**) Flupyradifurone: a brief profile of a new butenolide insecticide. *Pest Manage. Sci.*, 71, 850−862.
(9) Cordova D., Benner E. A., Schroeder M. E., Holyoke C. W., Zhang W., Pahutski T. F., Leighty R. M., Vincent, D. R. and Hamm, J. C. (2**016**) Mode of action of triflumezopyrim: a novel mesoionic insecticide which inhibits the nicotinic acetylcholine receptor. *Insect Biochem. Mol. Biol*. 74, 32−41.
(10) Pahutski T. F. (**2012**) Mesoionic pyrido[1,2-a]pyrimidine pesticides. PCT Int. Appl. WO 2012092115 A1.
(11) Zhang W., Holyoke C. W., Jr.; Barry J., Cordova D., Leighty R. M., Tong M.-H. T., Hughes K. A., Lahm G. P., Pahutski T. F., Xu M., Briddell T. A., McCann S. F., Henry Y. T.and Chen Y. (**2017**) Mesoionic pyrido[1,2a]pyrimidinones: Discovery of dicloromezotiaz as a lepidoptera insecticide acting on the nicotinic acetylcholine receptors*. Bioorg. Med. Chem. Lett*. 27, 911−917
(12) Kagabu, S.; Mitomi, M.; Kitsuda, S.; Horikoshi, R.; Nomura, M. and Onozaki, Y. (**2013**) *Pest control agent*. US 9073866B2.
(13) AbdelhamidA. A., Aref S. A., Ahmed N. A., Elsaghier A. M. M, Abd El Latif F. M., Al-Ghamdi S. N., and Gad M. A. (**2023**) Design, Synthesis, and Toxicological Activities of Novel Insect Growth Regulators as Insecticidal Agents against *Spodoptera littoralis* (Boisd). *ACS Omega.* 8 (1) 709-717.
(14) El-Dean A. M. K., Abd-Ella A. A., Hassanien R., El-Sayed M. E., and Abdel-Raheem S. A. A. (**2019**) Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New Pyridine Derivatives.*ACS Omega.* 4 (2019) 8406–8412.
(15) Hedrich L. W., Patel N. R., and Kirkpatrick J. L. (**1982**) Heterocyclic-Substituted Hydrazides and Hydrazones as Plant Growth Regulators. US patent US4, 319, 026A.
(16) Wang Y., Yu X., Zhi X., Xiao X., Yang C., and Xu H. (**2014**) Synthesis and insecticidal activity of novel hydrazone compounds derived from a naturally occurring lignan podophyllotoxin against Mythimnaseparata (Walker). *Bioorganic & Medicinal Chemistry Letters.* 24 (12) 2621–4.

(18) Kula K., Łapczuk A., Sadowski M., Kras J., Zawadzińska K., Demchuk O. M., Gaurav G. K., Wróblewska A., Jasiński R. (**2022**) On the Question of the Formation of Nitro-Functionalized 2,4-Pyrazole Analogs on the Basis of Nitrylimine Molecular Systems and 3,3,3-Trichloro-1-Nitroprop-1-Ene. *Molecules.* 27(23), 8409-8424.
(19) Fryźlewicz A., Olszewska A., Zawadzińska K., Woliński P., Kula K., Kącka-Zych A,, Łapczuk-Krygier A. and Jasiński R. (**2022**) On the Mechanism of the Synthesis of Nitrofunctionalised Δ^2-Pyrazolines via [3+2] Cycloaddition Reactions between α-EWG-Activated Nitroethenes and Nitrylimine TAC Systems. *Organics*. 3 (1) 59-76.
(20) Kula K., Kącka-Zych A., Łapczuk-Krygier A., Wzorek Z., Nowak A. K. and Jasiński R. (**2021**) Experimental and Theoretical Mechanistic Study on the Thermal Decomposition of 3,3-diphenyl-4-(trichloromethyl)-5-nitropyrazoline. *Molecules.* 26 (5) 1364-1389.
(21) Fryźlewicz A., Łapczuk-Krygier A., Kula K., Demchuk O. M., Dresler E. and Jasiński R. (**2021**) Regio- and stereoselective synthesis of nitrofunctionalized 1,2-oxazolidine analogs of nicotine *Chem. Heterocycl. Compd.*, 56 (1) 120-122.
(22) Kula K., Joanna Dobosz J., Jasinski R., Kacka-Zych A., Łapczuk-Krygier A., Mirosław B., and Demchuk O. M. (**2020**) [3+2] Cycloaddition of diaryldiazomethanes with (E)-3,3,3-trichloro-1-nitroprop-1-ene: An experimental, theoretical and structural study. *J. Mol. Struct*. 1203 (2020) 127473-12783.
(23) Aggarwal N., Kumar R., Srivastva C., Dureja P., and Khurana J. M. (**2010**) Synthesis of Nalidixic Acid Based Hydrazones as Novel Pesticides. *J Agric Food Chem*.58 (5) 3056–61.
(24) Liu G., Zhou C., Zhang Z., Wang C., Luo X., Ju X., Zhao C. and Ozoe Y.(**2022**) Novel insecticidal 1,6-dihydro-6-iminopyridazine derivatives as competitive antagonists of insect RDL GABA receptors. *Pest Manag Sci*. 78, 2872–2882.
(25) El-Gaby M. S. A. (**2004)** Syntheses of Hitherto Unknown Thiazole, Ylidene and Pyridinethione Derivatives Having a Piperidin-1-yl Moiety and Their Use as Antimicrobial Agents , *J. the Chinese Chemical Society*, 51, 125-134.
(26) El-Gaby M. S. A. (**2003)** Synthesis and antimicrobial evaluation of some newly 4-sulfamoyl phenylhydrazone,azopyrazole,azopyrazolo[1,5-a]pyrimidine, dihydro pyradazine and pyradazin-4-one, *Al-Azhar Bull. Sci.,* 14, 417-428.
(27) Abdelhamid A. A., Elsaghier A. M. M., Aref S. A., Gad M. A., Ahmed N. A., and Abdel-Raheem Sh. A. A. (**2021**) Preparation and biological activity evaluation of some benzoylthiourea and benzoylurea compounds. *Curr. Chem. Lett.*, 10 (4) 371-376.
(28) Gad M. A., Aref S. A., Abdelhamid A. A., Elwassimy M. M., and Abdel-Raheem Sh. A. A. (**2021**) Biologically active organic compounds as insect growth regulators (IGRs): introduction, mode of action, and some synthetic methods. *Curr. Chem. Lett.*, 10 (4) 393-412.
(29) Abdelhamid A. A., Elwassimy M. M., Aref S. A., and Gad M. A. (**2019**) Chemical design and bioefficacy screening of new insect growth regulators as potential insecticidal agents against Spodoptera littoralis (Boisd.). *Biotechnology Reports*, 24 (2019) 394-401.
(30) Abdelhamid A. A, Salama K. S. M., Elsayed A. M., Gad M. A., and El-Remaily M. A. A. A. (**2022**) Synthesis and Toxicological effect of some new pyrrole derivatives as prospective insecticidal agents against the cotton leafworm, spodoptera littoralis (Boisduval). *ACS Omega*, 7 (2022) 3990-4000.
(31) El-Gaby M. S. A., Ammar Y. A., Drar A. M., Gad M. A. (**2022**) Insecticidal bioefficacy screening of some chalcone and acetophenone hydrazone derivatives on *Spodopetra Frugiperda* (Lepidoptera: Noctuidae). *Curr. Chem. Lett.*, 11 (4) 263-268.
(32) Jasinski J. P., Akkurt M., Mohamed Sh. K., Gad M. A. and Albayati M. R. (**2015**) Crystal structure of N-(propan-2-yl-carbamothioyl)benzamide. *Acta Cryst*., 71 (1) 56-57.
(33) Bakhite E. A., Marae I. S., Gad M. A., Mohamed Sh. K., Mague J. T., and Abuelhassan S. (**2022**) 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.* 70 (31) 9637–9644.
(34) Ali M. A., Salah H., Gad M. A., Youssef M. A. M, and Elkanzi N. A. A. (**2022**) Design, Synthesis, and SAR Studies of Some Novel Chalcone Derivatives for Potential Insecticidal Bioefficacy Screening on *Spodoptera frugiperda* (Lepidoptera: Noctuidae). *ACS Omega.* 7 (44) 40091-40097.
(35) Khodairy A.,Mansour, Erian. S., Elhady, Omar M., Drar, A. M. (**2021**) Novel N-cyanoguanidyl derivatives: Synthesis and studying their toxicological activity against *Spodoptera littoralis* and schizaphisgraminum. *Curr. Chem. Lett*. 10 (4) 363 – 370.
(36) Khodairy A., Mansour, Erian. S., Elhady, Omar M., Drar, A. M. (**2021**) Synthesis of Neonicotinoid analogues and study their toxicological aspects on *Spodoptera littoralis* and *Schizaphis graminum. Int. J Pest Manag*., Accepted Manuscript (DOI: 10.1080/09670874.2021.1943048)..
(37) Abbott W. S. (1925) A method of computing the effectiveness of an insecticide. *J. Econ. Entomol*., 18 (2) 265-267.
(38) Finny D. J. (**1952**) Probit analysis: A statistical treatment of the sigmoid response curve, 2nd Ed, Cambridge Univ. Press, Cambridge, U. K.