



Original Article

Synthesis and biological activity of 2-((3-Cyano-4,6-distyrylpyridin-2-yl) thio) acetamide and its cyclized form

Shaban A. A. Abdel-Raheem ^{a*}, Adel M. Kamal El-Dean ^b, Reda Hassanien ^c, Mohamed E. A. El-Sayed ^a and Aly A. Abd-Ella ^{d*}

^a Soil, Water, and Environment Research Institute, Agriculture Research Center, Giza, Egypt

^b Chemistry Department, Faculty of Science, Assiut University, 71516 Assiut, Egypt

^c Chemistry Department, Faculty of Science, New Valley University, El-Kharja, 72511, Egypt

^d Plant Protection Department, Faculty of Agriculture, Assiut University, 71526 Assiut, Egypt

ARTICLE INFOR

Article history:

Received 06 November 2020

Revised 15 December 2020

Accepted 19 December 2020

Keywords:

Synthesis;
Insecticidal activity;
Acetamidiprid;
Cowpea aphid;
Characterization.

ABSTRACT

In this paper, 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2) and its cyclized form, 3-amino-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (3), were prepared and their structure characterizations were performed by the means of elemental and spectroscopic analyses. Their biological activity as insecticides against cowpea aphid *Aphis craccivora* Koch using acetamidiprid insecticide as a reference was studied. The bioassay results for compounds (2) and (3) against nymphs of cowpea aphid showed that the LC₅₀ values were 0.192 and 0.841 ppm, respectively, after 24 h of treatment but the LC₅₀ values were 0.041 and 0.095 ppm, respectively, after 48 h of treatment. Furthermore, the bioassay results for compounds (2) and (3) showed that the LC₅₀ values were 1.233 and 2.949 ppm, respectively, after 24 h of treatment and the LC₅₀ values were 0.142 and 0.270 ppm, respectively, after 48 h of treatment against adults of cowpea aphid. Given these observations, it has been found that there is a remarkable relationship between the biological activity and the structure of the used compounds.

© 2020 Faculty of Natural Sciences and Life, University of Echahid Hamma Lakhdar. All rights reserved

1. Introduction

The chemistry of heterocyclic compounds is widely known and pyridine ring system is widely distributed in nature, especially in plant kingdom [1, 2, 3]. Also, different pharmacological and biological activities of many pyridine derivatives, as a part of the heterocyclic compounds, were reported [4, 5, 6, 7]. It was found that some neonicotinoids have a pyridine ring in their structure and at present the use of neonicotinoids insecticides is increased in the field of crop protection as a result of their low mammalian toxicity, protecting a great range of crops, a novel mode of action specific for (nAChRs) and their high efficacy with lack cross-resistance to other insecticides [8, 9, 10, 11, 12, 13, 14].

Exposure to imidacloprid as a neonicotinoid insecticide was monitored recently. The results of this monitoring showed that genotoxic effect, DNA damage, oxidative stress, and clastogenic effect can exist after long-term exposure of rabbits to that insecticide [15, 16, 17, 18]. Hence, there was a need to find organic compounds that are similar to neonicotinoids compounds hoping to be with higher insecticidal activity and being safer and to achieve this purpose, two organic compounds were synthesized and screened for their biological activity as insecticides against cowpea aphid, *Aphis craccivora* Koch (Homoptera: Aphididae) in the presence of acetamidiprid insecticide as a reference.

* Corresponding authors *Shaban A. A. Abdel-Raheem*

E-mail addresses: drshaban202025@gmail.com

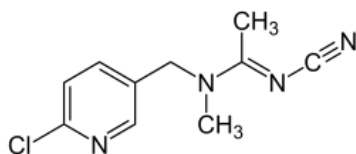


Fig 1. Structure of acetamiprid insecticide.

2. Materials and Methods

2.1. Instrumentation and Chemicals

Melting points were determined by using a Fisher-Johns apparatus for the synthesized compounds. Infrared (IR) spectra were determined by a Pye-Unicam SP3-100 spectrophotometer using the KBr disk technique. Elemental analyses (C, H, N, and S) were determined by a Vario EL C, H, N, S analyzer. DEPT 135, ^1H NMR and ^{13}C NMR spectra measurements were accomplished via a Bruker 400 MHz spectrometer in the presence of tetramethylsilane (TMS) as an internal reference. δ (ppm) is the unit of chemical shifts and thin-layer chromatography (TLC) was used for the purity check of the synthesized compounds. Compound **1** was prepared according to the reported method [6] and the acetamiprid insecticide was purchased from Sigma-Aldrich (France). The field strain of cowpea aphids was gathered from faba bean, *Vicia faba* L., fields of the experimental farm of Assiut University. Compounds **2** and **3** and acetamiprid were tested against the collected cowpea aphids, *A. craccivora*.

2.2 Synthetic procedure for 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (2).

A mixture of compound (**1**) (2 g, 0.006 mol), chloroacetamide (0.006 mol), and fused sodium acetate (0.6 g, 0.007 mol) in ethanol (25 mL) was heated under reflux for 30 min. The formed precipitate was collected and recrystallized from ethanol-dioxane mixture (1:2) as pale yellow crystals of compound **2**. Yield: 90%. m. p. 165–166°C. IR (v) (KBr) cm^{-1} : 3364, 3192 (NH_2), 2922, 2850 (C-H aliphatic), 2207 ($\text{C}\equiv\text{N}$), 1655 ($\text{C}=\text{O}$), 1634 ($\text{C}=\text{N}$). ^1H NMR (DMSO- d_6 , 400 MHz): 7.10–8.03 (m, 17H, 2CH=CH, NH_2 and Ar-H), 4.03 (s, 2H, CH_2). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 169.42, 161.87, 157.33, 149.08, 138.61, 137.31, 136.35, 129.38, 127.38, 126.75, 122.13, 121.91, 115.44, 114.56, 101.89, 34.49. DEPT 135 (DMSO- d_6 , 100 MHz): δ 138.61 (CH), 137.31 (CH), 136.35 (CH), 129.38 (CH), 127.38 (CH), 126.75 (CH), 122.13 (CH), 121.90 (CH), 114.55 (CH), 34.49 (CH_2). Elemental Analysis Calculated for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{OS}$ (%): C, 72.52; H, 4.82; N, 10.57; S, 8.07. Found (%): C, 72.56; H, 4.81; N, 10.55; S, 8.08.

2.3 Synthetic procedure for 3-amino-4,6-distyrylthieno[2,3-b]pyridine-2-carboxamide (3).

Compound (**2**) (1.99 g, 0.005 mol) was suspended in sodium ethoxide solution (0.5 g of sodium in 31 mL of absolute ethanol) and heated for 5 min under reflux. The formed product after cooling was collected and recrystallized from ethanol-dioxane mixture (1:2) as yellow crystals of compound **3**. Yield: 92%. m. p. 207–208°C. IR (v) (KBr) cm^{-1} : 3455, 3308, 3152 (2NH_2), 2917, 2849 (C-H aliphatic), 1636 ($\text{C}=\text{O}$). ^1H NMR (DMSO- d_6 , 400 MHz): 6.81–8.05 (m, 19H, 2CH=CH, 2 NH_2 and Ar-H). ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 167.50, 159.77, 155.51, 148.12, 137.11, 136.97, 136.42, 136.11, 129.33, 129.25, 128.05, 127.69, 123.78, 122.59, 121.64, 117.29. DEPT 135 (DMSO- d_6 , 100 MHz): δ 137.11 (CH), 136.97 (CH), 136.42 (CH), 128.05 (CH), 127.69 (CH), 123.78 (CH), 122.59 (CH), 121.64 (CH), 117.29 (CH). Elemental Analysis Calculated for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{OS}$ (%): C, 72.52; H, 4.82; N, 10.57; S, 8.07. Found (%): C, 72.54; H, 4.85; N, 10.56; S, 8.03.

2.4 Laboratory bioassay

The biological activity as insecticides for compounds **2** and **3** was tested via the leaf dip bioassay method [19]. The results of laboratory tests are reported here to obtain the concentration of these chemical compounds that is required to kill 50% (LC_{50}) of cowpea aphids. Six concentrations of compounds **2** and **3** plus 0.1% Triton X-100 as a surfactant were used. A total of 20 adults and 20 nymphs, approximately of the same size, were dipped for 10 s in each concentration 3 times. The treated aphids were allowed to dry at room temperature for about 0.5 h. Control batches of aphids were similarly dipped in a solution of distilled water plus 0.1% Triton X-100. After drying of the treated batches of aphids, they were transferred to Petri dishes (9 cm diameter) and held for 24 and 48 h at 22 + 2 °C, 60 + 5% relative humidity, and photoperiod of 12:12 (light/dark). Aphid mortality was recorded 24 and 48 h after treatment by using a binocular microscope. The aphid that unable of coordinated forward movement was considered dead. Biological activity test of compounds **2** and **3** as insecticides was repeated twice and the results were corrected using Abbott's formula [20]. Median lethal concentrations (LC_{50}) and slope values of title compounds were determined by the Probit regression analysis program and expressed in parts per million (ppm) [21].

3. Results and Discussion

3.1 Chemistry

As a result of the biological activity of the compounds containing pyridine moiety, compounds **2** and **3** were synthesized here. Starting from compound (**1**) "3-cyano-

4,6-distyrylpyridin-2(1*H*)-thione" which was prepared according to the reported method [6], compound **1** was reacted with chloroacetamide to afford 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (**2**). The chemical structure of compound **2** was confirmed by spectral and elemental analysis. Compound **2** underwent cyclization upon heating in ethanolic sodium ethoxide solution to give the corresponding cyclized form 3-amino-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (**3**). Spectroscopic data and elemental analysis of compound **3** was in agreement with its proposed structure.

IR spectrum of compound **2** showed absorption bands at 3364, 3192, 2207 and 1655 cm^{-1} characteristics for (NH_2), ($\text{C}\equiv\text{N}$) and ($\text{C}=\text{O}$) groups respectively. The absorption band of ($\text{C}\equiv\text{N}$) of compound **2** was disappeared when cyclized to give the thienopyridine **3** and was replaced by 3455 and 3308 cm^{-1} for NH_2 . ^1H NMR spectrum ($\text{DMSO-}d_6$, 400 MHz) of compound **2** showed singlet signal at 4.03 for (CH_2) group. The signal of (CH_2) group of compound **2** in the ^1H NMR spectrum was disappeared when cyclized to give compound **3**. DEPT 135 ($\text{DMSO-}d_6$, 100 MHz) spectrum of compound **2** showed characteristic signal at 34.49 for the (CH_2) group. The signal of (CH_2) group of compound **2** in the DEPT 135 spectrum was disappeared when cyclized to give compound **3**.

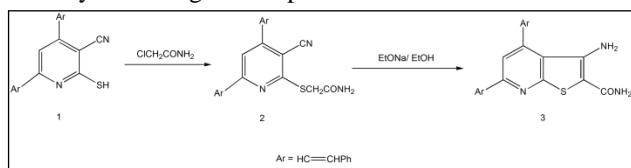


Fig 2. Synthesis of compounds **2** and **3**.

3.2 Biological activity of compounds **2** and **3**.

3.2.1 Biological activity test for the cowpea aphid nymphs.

Compounds **2** and **3** were tested for their insecticidal activity against the nymphs of the collected aphids and the results are presented in Table 1. After 24 h of the test,

Table 1. Insecticidal activity of acetamiprid and compounds **2** and **3** against the cowpea aphid nymphs after 24 and 48 h of treatment.

Compound	24 h after treatment			48 h after treatment		
	Slope \pm SE	LC ₅₀ (ppm)	Toxic ratio	Slope \pm SE	LC ₅₀ (ppm)	Toxic ratio
Acetamiprid	0.34 \pm 0.02	0.045	1	0.42 \pm 0.03	0.006	1
2	0.38 \pm 0.03	0.192	0.234	0.43 \pm 0.03	0.041	0.146
3	0.36 \pm 0.02	0.841	0.054	0.41 \pm 0.02	0.095	0.063

Notes: toxic ratio is defined as the ratio of acetamiprid's LC₅₀ value for baseline toxicity and the compound's LC₅₀ value.

Table 2. Insecticidal activity of acetamiprid and compounds **2** and **3** against the cowpea aphid adults after 24 and 48 h of treatment.

Compound	24 h after treatment			48 h after treatment		
	Slope \pm SE	LC ₅₀ (ppm)	Toxic ratio	Slope \pm SE	LC ₅₀ (ppm)	Toxic ratio
Acetamiprid	0.24 \pm 0.02	0.225	1	0.32 \pm 0.03	0.023	1
2	0.36 \pm 0.02	1.233	0.182	0.35 \pm 0.03	0.142	0.162
3	0.36 \pm 0.03	2.949	0.076	0.40 \pm 0.03	0.270	0.085

Notes: toxic ratio is defined as the ratio of acetamiprid's LC₅₀ value for baseline toxicity and the compound's LC₅₀ value.

biological activity data showed that compounds **2** and **3** exhibited high to low insecticidal activity against nymphs of cowpea aphid and the LC₅₀ values were 0.192 and 0.841 ppm, respectively, whereas the LC₅₀ value of acetamiprid was 0.045 ppm. After 48 h of test, it is found that the insecticidal activity of compounds **2** and **3** against nymphs of cowpea aphid ranged from strong to weak and LC₅₀ values were 0.041 and 0.095 ppm, respectively, whilst the LC₅₀ value of acetamiprid 0.006 ppm. These results indicate that compounds **2** and **3** have good biological activity compared with the biological activity of acetamiprid insecticide.

3.2.2 Biological activity test for the adults of cowpea aphid

Compounds **2** and **3** were tested for their insecticidal activity against the nymphs of the collected aphids and the results are presented in Table 2. The data showed that after 24 h of test, compounds **2** and **3** had strong to weak activity and LC₅₀ values were 1.233 and 2.949 ppm, respectively, whilst the LC₅₀ value of acetamiprid was 0.225 ppm. After 48 h of biological activity test as insecticides, the insecticidal activity of compounds **2** and **3** varied from high to low and LC₅₀ values were 0.142 and 0.270 ppm, respectively, against cowpea aphid adults, whilst 0.023 ppm was the LC₅₀ value of acetamiprid.

3.2.3 Structure-action relationship

From the structure of the tested compounds **2** and **3**, it appears that the compound 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide (**2**) is more active than the compound 3-amino-4,6-distyrylthieno[2,3-*b*]pyridine-2-carboxamide (**3**) against the cowpea aphids, which may be due to the presence of the opened form structure in compound **2** and the presence of cyano group, but compound **3** was found in the cyclized form and cyano group is absent in its structure.

4. Conclusion

Compounds **2** and **3**, which are considered neonicotinoid analogs, were prepared and biological activity as

insecticides against cowpea aphid, *Aphis craccivora* Koch was estimated. The results of this biological activity test proved that heterocyclic compounds containing pyridine part in their structure are of great importance in the agricultural field.

References

- Al-Taifi EA, Abdel-Raheem ShAA, Bakhite EA. Some reactions of 3-cyano-4-(*p*-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione; Synthesis of new tetrahydroquinolines and tetrahydrothieno[2,3-*b*]quinolines. Assiut University Journal of Chemistry (AUJC). 2016, 45: 24-32.
- Kamal El-Dean AM, Abd-Ella AA, Hassanien R, El-Sayed MEA, Zaki RM, Abdel-Raheem ShAA. Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents. Toxicology Reports. 2019, 6: 100-104.
- Bakhite EA, Abd-Ella AA, El-Sayed MEA, Abdel-Raheem ShAA. Pyridine derivatives as insecticides. Part 1: Synthesis and toxicity of some pyridine derivatives against Cowpea Aphid, *Aphis craccivora* Koch (Homoptera: Aphididae). Journal of Agricultural and Food Chemistry. 2014, 62(41): 9982–9986.
- Bakhite EA, Abd-Ella AA, El-Sayed MEA, Abdel-Raheem ShAA. Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their Insecticidal Activity. Journal of Saudi Chemical Society. 2017, 21(1): 95–104.
- Abdel-Raheem ShAA, Kamal El-Dean AM, Hassanien R, El-Sayed MEA, Abd-Ella AA. Synthesis and characterization of some distyryl-derivatives for agricultural uses. European Chemical Bulletin. 2021, 10(1): 35-38.
- Altaf AA, Shahzad A, Gul Z, Rasool N, Badshah A, Lal B, Khan EA. Review on the Medicinal Importance of Pyridine Derivatives. Journal of Drug Design and Medicinal Chemistry. 2015, 1: 1-11.
- Kamal El-Dean AM, Abd-Ella AA, Hassanien R, El-Sayed MEA, Abdel-Raheem ShAA. Design, Synthesis, Characterization, and Insecticidal Bioefficacy Screening of Some New Pyridine Derivatives. ACS Omega. 2019, 4: 8406-8412.
- Zhang N, Tomizawa M, Casida JE. α -Nitro Ketone as an Electrophile and Nucleophile: Synthesis of 3-Substituted 2-Nitromethylenetetrahydrothiophene and tetrahydrofuran as *Drosophila* Nicotinic Receptor Probes. The Journal of Organic Chemistry. 2004, 69: 876-881.
- Shimomura M, Yokota M, Ihara M, Akamatsu M, Sattelle DB, Matsuda K. Role in the Selectivity of Neonicotinoids of Insect-Specific Basic Residues in Loop D of the Nicotinic Acetylcholine Receptor Agonist Binding Site. Molecular Pharmacology. 2006, 70: 1255–1263.
- Tomizawa M, Casida JE. Selective toxicity of neonicotinoids attributable to specificity of insect and mammalian nicotinic receptors. Annual Review of Entomology. 2003, 48: 339–364.
- Tomizawa M, Talley T, Maltby D, Durkin KA, Medzihradsky KF, Burlingame AL, Taylor P, Casida JE. Mapping the elusive neonicotinoid binding site. Proceedings of the National Academy of Sciences of the United States of America. 2007, 104: 9075–9080.
- Kagabu S, Ishihara R, Nishimura K, Naruse Y. Insecticidal and neuroblocking potencies of variants of the imidazolidine moiety of imidacloprid-related neonicotinoids and the relationship to partition coefficient and charge density on the pharmacophore. Journal of Agricultural and Food Chemistry. 2007, 55: 812–818.
- Yang ZB, Hu DY, Zeng S, Song BA. Novel hydrazone derivatives containing pyridine amide moiety: Design, synthesis, and insecticidal activity. Bioorganic & Medicinal Chemistry Letters. 2016, 26: 1161-1164.
- Tian Z, Shao X, Li Z, Qian X, Huang Q. Synthesis, insecticidal activity and QSAR of novel nitromethylene neonicotinoids with tetrahydropyridine fixed cis configuration and exo-ring ether modification. Journal of Agricultural and Food Chemistry. 2007, 55: 2288–2292.
- Stivaktakis PD, Kavvalakis MP, Tzatzarakis MN, Alegakis AK, Panagiotakis MN, Fragkiadaki P, Vakonaki E, Ozcagli E, Hayes WA, Rakitskii VN, Tsatsakis AM. Long-term exposure of rabbits to imidacloprid as quantified in blood induces genotoxic effect. Chemosphere. 2016, 149: 108-113.
- Vardavas AI, Ozcagli E, Fragkiadaki P, Stivaktakis PD, Tzatzarakis MN, Kaloudis K, Tsardi M, Datseri G, Tsiaoussis J, Tsitsimpikou C, Carvalho F, Tsatsakis AM. DNA damage after long-term exposure of rabbits to Imidacloprid and sodium tungstate. Toxicology Letters. 2016, 258S: S247- S248.
- Vardavas AI, Ozcagli E, Fragkiadaki P, Stivaktakis PD, Tzatzarakis MN, Alegakis AK, Vasilakia F, Kaloudisa K, Tsiaoussis J, Kouretas D, Tsitsimpikou Ch, Carvalhof F, Tsatsakis AM. The metabolism of imidacloprid by aldehyde oxidase contributes to its clastogenic effect in New Zealand rabbits. Mutation Research - Genetic Toxicology and Environmental Mutagenesis. 2018, 829–830: 26–32.
- Stivaktakis P, Kavvalakis M, Goutzourelas N, Stagos D, Tzatzarakis M, Kyriakakis M, Rezaee R, Kouretas D, Hayes W,

- Tsatsakis A. Evaluation of oxidative stress in long-term exposed rabbits to subtoxic levels of imidacloprid. *Toxicology Letters*. 2014, 229S, No. S228.
19. O'Brien PJ, Abdel-Aal YA, Ottea JA, Graves JB. Relationship of insecticide resistance to carboxylesterases in *Aphis gossypii* (Homoptera: Aphididae) from Midsouth cotton. *Journal of Economic Entomology*. 1992, 85: 651–657.
 20. Abbott WS. A method of computing the effectiveness of an insecticide. *Journal of Economic Entomology*. 1925, 18: 265–267.
 21. Finney (Ed.) DJ. *Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve*. Cambridge University Press, Cambridge, U. K. 1952.

Recommended Citation

Shaban A. A. Abdel-Raheem, Adel M. Kamal El-Dean, Reda Hassanien, Mohamed E. A. El-Sayed, Aly A. Abd-Ella. Synthesis and biological activity of 2-((3-Cyano-4,6-distyrylpyridin-2-yl)thio)acetamide and its cyclized form. *Algerian Journal of Biosciences*. 2020, 01;02:046-050.

DOI : <http://dx.doi.org/10.5281/zenodo.4393610>



This work is licensed under a [Creative Commons Attribution-NonCommercial 4.0 International License](https://creativecommons.org/licenses/by-nc/4.0/)