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Original Article

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

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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 acetamiprid insecticide as a reference was studied. The bioassay results for compounds (2) and (3) against nymphs of cowpea aphid showed that the LC_{50} values were 0.192 and 0.841 ppm, respectively, after 24 h of treatment but the LC_{50} 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 LC_{50} values were 1.233 and 2.949 ppm, respectively, after 24 h of treatment and the LC_{50} 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.

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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 acetamiprid insecticide as a reference.

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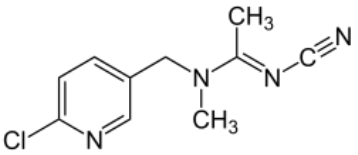

Fig 1. Structure of acetamiprid insecticide.

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, ^{1}H 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 (ν) (KBr) cm^{-1}: 3364, 3192 (NH_2), 2922, 2850 (C-H aliphatic), 2207 (C≡N), 1655 (C=O), 1634 (C=N). ^{1}H 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 $C_{24}H_{19}N_3OS$ (%): 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 (ν) (KBr) cm^{-1}: 3455, 3308, 3152 ($2NH_2$), 2917, 2849 (C-H aliphatic), 1636 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): 6.81-8.05 (m, 19H, 2CH=CH, $2NH_2$ 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 $C_{24}H_{19}N_3OS$ (%): 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), (C≡N) and (C=O) groups respectively. The absorption band of (C≡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 (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 (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**.

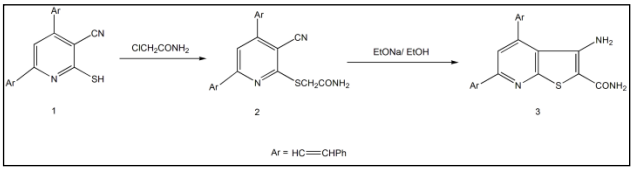

Fig 2. Synthesis of compounds **2** and **3**.

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, biological activity data showed that compounds **2** and **3** exhibited high to low insecticidal activity against nymphs of cowpea aphid and the LC_{50} values were 0.192 and 0.841 ppm, respectively, whereas the LC_{50} 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 LC_{50} values were 0.041 and 0.095 ppm, respectively, whilst the LC_{50} 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 LC_{50} values were 1.233 and 2.949 ppm, respectively, whilst the LC_{50} 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 LC_{50} values were 0.142 and 0.270 ppm, respectively, against cowpea aphid adults, whilst 0.023 ppm was the LC_{50} 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.

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

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

Notes: toxic ratio is defined as the ratio of acetamiprid's LC_{50} value for baseline toxicity and the compound's LC_{50} value.

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

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

Notes: toxic ratio is defined as the ratio of acetamiprid's LC_{50} value for baseline toxicity and the compound's LC_{50} value.

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.

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