Synthesis of new distyrylpyridine analogues bearing amide substructure as effective insecticidal agents

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\textbf{ABSTRACT}

In examining for unique insecticidal agents, two derivatives namely, 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)-N-(4-nitrophenyl)acetamide (2) and 3-amino-N-(4-nitrophenyl)-4,6-distyrylthieno[2,3-b]pyridine-2-carboxamide (3) were synthesized from distyrylpyridine-2-thione (1). The new compounds were structurally clarified by spectral and elemental analysis data. The insecticidal activity of these compounds were carried out against cowpea aphid, \textit{Aphis craccivora} Koch. It is demonstrated that the compounds 2 and 3 have noteworthy insecticidal activity against nymphs of cowpea aphid with LC\textsubscript{50} values of 0.025-0.027 ppm and 0.005-0.006 ppm after 24 h and 48 h of treatment, respectively. Also, the compounds 2 and 3 have noteworthy insecticidal activity against adults of cowpea aphid with LC\textsubscript{50} values of 0.112-0.129 ppm and 0.014-0.015 ppm after 24 h and 48 h of treatment, respectively, that were comparable to that of the control acetamiprid.

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\textbf{Keywords:}
Nitro group
Amide bond
Cowpea aphid
Pyridine

1. Introduction

Insecticides play a forceful role in harvest protection and foodstuff security and expansively advance human life.\textsuperscript{1,2} On the other hand, with overuse and immoral uses of pesticides, not only has the struggle with insects become gradually stronger, but rigorously contaminated the environment, too. The occurrence of pest resistance has significantly reduced the efficiency of pesticides, therefore, studies on new pesticide agents were continuing with active levels.\textsuperscript{3,4}

Heterocyclic compounds have widespread diversity of application in the pharmaceutical and agrochemical manufacturers. It is informed that nearly 70% of the commercial structures of pesticides in the previous 20 years enclose at least individual heterocyclic system.\textsuperscript{5} Consequently, the improvement of heterocyclic structure to control pests is a research content that researchers are concerned in.\textsuperscript{3} Pyridine as one category of azaheterocyclics, is extensively used in the field of agrochemicals and further physiological activities.\textsuperscript{6-8}

Besides, amide groups could surely make hydrogen bonds with the forceful portions of the known enzymes and administer the object organisms. Furthermore, introducing the amide structure was valuable for the biodegradation of pesticides. Consequently, amide structures were fervently studied.\textsuperscript{9,10}

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Based on the above-mentioned facts and as part from our attentions to the synthesis of bioactive agents, the aim of the present study have been focused to the synthesis of novel distyrylpyridine analogues through amide linker between distyrylpyridin-2-thione as pharmacophore and 4-nitrobenzene.

2. Results and Discussion

2.1 Chemistry

For the synthesis of the distyrylpyridine derivatives 2 and 3, the procedure was offered in Fig. 1. The essential 3-cyano-4,6-distyrylpyridine-2(1H)-thione (1) was prepared according to the literature manner. Overall, treatment of distyrylpyridine-2-thione 1 with 2-chloro-N-(4-nitrophenyl)acetamide in ethanol and an excess of anhydrous sodium acetate afforded the corresponding S-alkylated derivative 2. Compound 2 was subjected to intramolecular cyclization through Thorpe-Ziegler reaction in the presence of catalytic quantity of sodium ethoxide for 5 min under reflux yielded the distyrylthienopyridine analogue 3. The synthesized compounds gave suitable analyses for the suggested structures, which were clarified according to their spectral data.

IR spectrum of compound 2 showed absorption bands at 3253 (NH), 2213 (C≡N) and 1674 cm⁻¹ (C=O). The absorption band of (C≡N) of compound 2 was disappeared when cyclised to give the thienopyridine 3 and was replaced by NH₂ at 3461 and 3407 cm⁻¹. ¹H NMR spectrum (DMSO-d₆, 400 MHz) of compound 2 showed singlet signals for (NH) at 10.14 ppm and (CH₂) at 4.25 ppm. The signal of (CH₂) group of compound 2 in the ¹H NMR spectrum disappeared when cyclised to give compound 3. It is further clarified by a signal at 35.67 ppm for (CH₂) group in DEPT 135 spectrum which disappeared when cyclised to give compound 3.

Fig. 1. Synthesis of compounds 2 and 3

2.2 Insecticidal activity of compounds 2 and 3.

2.2.1 Insecticidal activity test for the cowpea aphid nymphs.

Compounds 2 and 3 were verified for their insecticidal activity against the nymphs of the collected aphids and the results are presented in Table 1. After 24 h of testing, the results revealed that the LC₅₀ of compounds 2 and 3 was extended from 0.025 and 0.027 ppm, respectively. So, these compounds have strong to weak activity, while 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 good to moderate and LC₅₀ values were 0.005 and 0.006 ppm, respectively, whilst the LC₅₀ value of acetamiprid 0.006 ppm. Above outcomes indicate that the studied compounds have excellent insecticidal activity which is more than or equivalent to acetamiprid and this is observable from the LC₅₀ values after 24 and 48 h of examination.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>24 h after treatment</th>
<th>48 h after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope ± SE</td>
<td>LC₅₀ (ppm)</td>
</tr>
<tr>
<td>Acetamiprid</td>
<td>0.34±0.02</td>
<td>0.045</td>
</tr>
<tr>
<td>2</td>
<td>0.38±0.03</td>
<td>0.025</td>
</tr>
<tr>
<td>3</td>
<td>0.39±0.03</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Notes: toxic ratio is defined as the ratio of acetamiprid’s LC₅₀ value for baseline toxicity and the compound’s LC₅₀ value.
2.2.2 Insecticidal activity test for the cowpea aphid adults

Compounds 2 and 3 were verified for their insecticidal activity against the adults of the gathered aphids and the results are in Table 2. After 24 h of testing, the results showed that the LC50 of compounds 2 and 3 was ranged from 0.112 and 0.129 ppm, respectively. So, these compounds have strong to weak activity, whilst the LC50 value of acetamiprid was 0.225 ppm. After 48 h of test, the insecticidal activity of compounds 2 and 3 varied from high to low and LC50 values were 0.014 and 0.015 ppm, respectively, while the LC50 value of acetamiprid was 0.023 ppm. Above outcomes indicate that the insecticidal activity of the studied compounds against adults of cowpea aphid was more than that of acetamiprid after 24 and 48 h of treatment.

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

<table>
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<td>0.112</td>
</tr>
<tr>
<td>3</td>
<td>0.38±0.03</td>
<td>0.129</td>
</tr>
</tbody>
</table>

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

2.2.3 Structure-action relationship

According to the general configuration of the studied compounds 2 and 3, it seems that the corresponding S-alkylated derivative 2 is more potent than the thienopyridine analogy 3 against the cowpea aphids. The high activity related with compound 2 may be owing to the presence of the opened structure in compound 2 and the existence of cyano group, while compound 3 was produced in the cyclic structure and cyano group is lacking in its structure.

3. Conclusion

Two derivatives of novel distyrylpyridine analogues bearing a amide substructure namely, 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)-N-(4-nitrophenyl)acetamide (2) and 3-amino-N-(4-nitrophenyl)-4,6-distyryl thieno[2,3-b]pyridine-2-carboxamide (3) were synthesized and their insecticidal activity were estimated. Bioassay results indicated that the target compounds have promising activity against cowpea aphid compared with that of acetamiprid insecticide and this emphasizes the importance of pyridine compounds as lead molecules for further applications.

4. Experimental

4.1 Materials and methods

Melting points were uncorrected and taken in a Fisher-Johns apparatus. Elemental analyses were determined with a Vario EL C, H, N, S analyzer. Infrared (IR) spectra were determined by a Pye-Unicam SP3-100 spectrophotometer using the KBr disk technique. DEPT 135, 1H NMR and 13C NMR spectra were accomplished with a Bruker 400 MHz spectrometer with tetramethylsilane (TMS) as an internal reference, δ (ppm) is the unit of chemical shifts. Thin-layer chromatography (TLC) technique was carried out for the purity check of the synthesized compounds. The essential distyrylpyridin-2-thione 1 was prepared according to the literature procedure, and the acetamiprid insecticide was purchased from Sigma-Aldrich (France). Insecticidal activity of synthesized compounds was achieved against cowpea aphid, Aphis craccivora Koch (Homoptera: Aphididae) in the presence of acetamiprid insecticide as a reference.

4.2 Synthetic procedure for 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)-N-(4-nitrophenyl)acetamide (2).

Equimolar quantities (0.006 mol) of compound 1 and 2-chloro-N-(4-nitrophenyl)acetamide were mixed in ethanol (25 mL) comprising anhydrous sodium acetate (0.6 g, 0.007 mol) and refluxed for 30 min. The formed precipitate was collected and recrystallized from ethanol-dioxane mixture (1:2) as yellow crystals of compound 2. Yield 84%; m. p. 236–237°C. IR (ν (KBr) Cm-1): 3253 (NH), 3058 (C-H aromatic), 2927 (C-H aliphatic), 2213 (C≡N), 1674 (C=O), 1634 (C=N). 1H NMR (DMSO-d6, 400 MHz): δ 10.14 (s, 1H, NH), 6.92-7.78 (m, 19H, 2CH=CH and Ar-H), 4.25 (s, 2H, CH2). 13C NMR (DMSO-d6, 100 MHz): δ 166.42, 162.38, 157.64, 149.71, 144.50, 143.51, 135.98, 135.49, 132.77, 130.33, 129.60, 129.21, 128.10, 127.88, 126.91, 122.05, 115.58, 114.70, 101.81, 35.67. DEPT 135 (DMSO-d6, 100 MHz): δ 135.50 (CH), 132.77 (CH),
elemental analysis calculated for C_{30}H_{22}N_{4}O_{3}S (%): C, 69.48; H, 4.28; N, 10.80; S, 6.18. Found (%): C, 69.51; H, 4.27; N, 10.78; S, 6.19.

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

A suspension of 2 (0.005 mol) in sodium ethoxide solution (0.5 g of Na in 31 mL of abs. ethanol) was gradually heated for 5 min under reflux. The formed product after cooling was collected and recrystallized from ethanol-dioxane mixture (1:2) as orange crystals of compound 3. Yield 90%; m. p. 281-282°C. IR (v) (KBr) cm⁻¹: 3461, 3407, 3324 (NH₂, NH), 3024 (C-H aromatic), 1647 (C=O), 1633 (C=N). ¹H NMR (DMSO-d₆, 400 MHz): δ 10.03 (s, 1H, NH), 7.10-8.25 (m, 21H, 2CH=CH, NH₂ and Ar-H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 162.11, 157.09, 153.68, 147.25, 143.17, 141.35, 136.81, 135.22, 133.96, 133.14, 129.38, 129.16, 128.79, 127.98, 127.80, 127.52, 126.31, 124.19, 122.05, 114.70 (CH), 127.66, 35.67 (CH₂). DEPT 135 δ 133.96 (CH), 133.14 (CH), 128.79 (CH), 127.98 (CH), 127.80 (CH), 127.52 (CH), 126.57 (CH), 124.19 (CH), 122.05 (CH), 117.67 (CH). Elemental Analysis Calculated for C_{30}H_{22}N_{4}O_{3}S (%): C, 69.48; H, 4.28; N, 10.80; S, 6.18. Found (%): C, 69.51; H, 4.27; N, 10.78; S, 6.19.

4.4 Laboratory bioassay

The insecticidal activity for the compounds 2 and 3 was tested via leaf dip bioassay method. The concentration of these chemical compounds that is required to kill 50% (LC₅₀) of cowpea aphids was reported here. In this testing, six concentrations of compounds 2 and 3 plus 0.1% Triton X-100 as a surfactant were used and a total of 20 adults and 20 nymphs, nearly of the identical size, were dipped for 10 s, in test solutions three times. The tested aphids were allowed to dry out naturally for about 0.5 h. Control batches of aphids were similarly soaked in a solution of distilled water comprising 0.1% Triton X-100. Then, after dehydrating of the treated batches of cowpea aphids, they were located in 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). Mortalities were recorded 24 and 48 h after treatment by using a binocular microscope. The aphid, unable to coordinate forward movement, was considered dead. Each experiment of compounds 2 and 3 was carried out duplicate and the outcomes were adjusted using Abbott’s formula. Median lethal concentrations (LC₅₀) and slope values of the tested compounds were evaluated using the Probit regression analysis program and stated in parts per million (ppm).

References


