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Environmentally green synthesis and characterization of some novel bioactive pyrimidines with excellent bioefficacy and safety profile towards soil organisms

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ABSTRACT

The toxicity of a novel series of ten pyranothiazolopyrimidine derivatives (**1–9a,b**) against the insect *Aphis gossypii* (Glover, 1887) has been determined. In addition, the safety profile of two selected compounds **2,8** against earthworms was determined. Acetamiprid insecticide was utilized as a reference insecticide. Spectroscopic data and elemental analyses were used for verifying the structures of the synthesized compounds. Studying the toxicity of synthesized derivatives against the *Aphis gossypii* (Glover, 1887) revealed that compounds **2,8** were more active than the reference insecticide acetamiprid against *Aphis gossypii* (Glover, 1887), while the remaining compounds exhibited moderate to low activities. But, in detecting the safety profile against earthworms (*Aporrectodea caliginosa*) for compounds **2,8**, it was found that; compound **2** (LC_{50} = 32.7753–22.4079) and compound **8** (LC_{50} = 131.6081–101.0537) are less toxic and safer on earthworms than acetamiprid (LC_{50} = 0.1992–0.0086) after 5 and 10 days of test. Also, the chemical characteristics of the investigated soil holding the used earthworms diversified significantly before and after treatment with agrochemicals.

1. Introduction

In modern society, one of the major challenges is the global food supply, which must be taken into consideration. The loss in crop yields caused by the weeds, diseases of the plants, and pests would be up to 50%, and most of this ratio accounts for the pests [1]. Some insecticides such as pyrethroids, neonicotinoids, organophosphates, and other insecticides during the past decades performed a significant role in crop protection.

Pyrimidine moiety is abundant in heterocyclic derivatives with various biological uses, including antioxidant, insecticidal, antimicrobial, anti-inflammatory, anticancer, and antiviral, etc [2–7]. So, pyrimidine compounds attracted several chemists around the world to achieve the synthesis of different bioactive compounds. Insecticidal activity related to pyrimidine derivatives constitutes a part of the agricultural uses that are appearing nowadays [8].

Although neonicotinoid insecticides are the most utilized insecticides for the control of insects, some disadvantages of these compounds were reported [9–12]. Hence, there is a great demand for new organic compounds with a safety profile towards the environment and soil organisms such as earthworms. Since, before pesticide marketing authorization, risk assessments for pesticides should be conducted to reduce the environmental impact of pesticides and to provide scientific proof to stakeholders, several experiments are designed and included in

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these risk evaluations to determine the impact of pesticides on various water-based and terrestrial in nature organisms, such as earthworms [13–15].

Earthworms make up a significant amount of the soil's biological mass and perform crucial agroecological tasks that are essential to the health of agroecosystems. Earthworms have occasionally been utilized as bio-indicators to evaluate soil quality and the impact of farming practices and pollutants on the environment [16]. For example, earthworm mortality and/or reproduction are presently employed to evaluate the impact of pesticides in lab settings before marketing authorization. However, in cultivated fields, non-target creatures like earthworms are regularly exposed to various pesticide applications (such as insecticides, fungicides, and herbicides). Further research is necessary to investigate the effect of pesticides on these soil organisms, as they play a crucial role in soil functioning [16].

From these facts, this work comprises the synthesis of some novel compounds containing pyrimidine moiety, and their agricultural bioactivity was evaluated against *Aphis gossypii* (Glover, 1887). After that, two synthesized compounds were tested for their safety profile against earthworms.

2. Materials and methods

2.1. Instrumentation and chemicals

Using an APP Digital ST 15 melting point instrument, the melting points have been established and have not been corrected. Elemental analyses performed utilizing the Vario EL C, H, N, S Analyzer displayed a high degree of agreement with predicted values. The spectra of the FT-IR have been obtained employing a Pye-Unicam SP3–100 spectrophotometer throughout the KBr disc approach (v max in cm^{-1}). Using a Bruker 400 MHz spectrometer and tetramethylsilane (TMS) as the internal standard, ^{1}H-NMR, and ^{13}C-NMR spectra were recorded. The chemical shifts are represented in parts per million (ppm), whereas the coupling constant is stated in hertz (Hz). The purity of synthetic compounds was established *via* TLC. In our laboratory, we prepared the pyrimidine derivatives (**1–9a,b**), and the neonicotinoid insecticide *(E)*-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methylacetamidine (acetamiprid, greater than 98% purity) was gained from Sigma-Aldrich (France) [17]. The molecular formula of acetamiprid is $C_{10}H_{11}ClN_4$, its molecular weight is 222.68, and its chemical structure is shown in Fig. 1. This study utilized alluvial soil, a commonly found type of soil in Egypt, which was collected from multiple locations within the surface layer (0–30 cm) at the Research Farm located in Agriculture College, Abis, Alexandria, Egypt. The air-dry soil samples underwent a 2 mm mesh sieving process and were then subjected to analysis according to standard methods [15]. The physicochemical characteristics of the examined soil were generally as described in the following data: pH = 8.25; electrical conductivity (EC) = 1.32 ds/m at 25 °C; total carbonate = 7.87%; organic matter content = 4.49%, and clay loam texture of 24.2% clay, 12.2% silt, and 63.6% sand. As for the tested earthworms: the kinds of earthworms used in this study are widely distributed in Egypt (*Aporrectodea caliginosa*). The worms employed in the current research were obtained from fields surrounding the governorate of Alexandria and then reared in plastic containers containing soil. Before the beginning of the investigation, the worms were maintained in soil for a month at a temperature of 21 ± 2 °C. In this investigation, mature earthworms were used. No consideration is made for sexual differences because earthworms are hermaphrodites. To eliminate gut contents, the adults were withdrawn from the soil 24 h before their utilization and kept in Petri dishes on wet filter paper in the dark, at a temperature of 21 ± 2 °C [15]. This study was conducted between 15 May 2022 and 15 May 2023 at the Agricultural Research Center, Shandaweel Station in Sohag, Egypt (latitude: 26 26' N, longitude: 31o 68' E, and altitude: 70 m), Assiut University, Assiut, Egypt, and New Valley University, El-Kharja, Egypt. The derivatives (**1–9a,b**) and acetamiprid have been assessed for their efficacy towards adults and larvae of *Aphis gossypii* (Glover, 1887), while compounds **2,8** were investigated for their safety potential regarding earthworms.

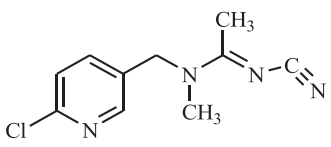


Fig. 1. Chemical structure of acetamiprid insecticide.

2.2. 2,7-Dioxo-4,9-diphenyl-3,4-dihydro-2H,7H-pyrano[2',3':4,5] thiazolo[3,2-a] pyrimidine-3,8-dicarbonitrile (1)

1.2 mL of piperidine was added to a mixture of compound **A** (1 g, 3.76 mmol) and ethyl 2-cyano-3-phenylacrylate **B** (1 g, 4.97 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 5 h. After cooling and filtration, the product that emerged was recrystallized from dioxane to generate orange crystals. Yield: 76%; m.p. 265–267 °C. FT-IR (ν) (KBr) cm^{-1}: 3036, 2978, 2120, 2107, 1658, and 1647. ^{1}H-NMR (DMSO-d_6): δ ppm: 7.62–7.61 (d, *J* = 7.8, 2 H, Ar-H), 7.43–7.34 (t, *J* = 7.9, 6 H, Ar-H), 7.32–7.30 (d, *J* = *8*, 2 H, Ar-H), 4.92 (d, *J* = 7.5, 1 H, CH), 3.73 (d, *J* = 7.3, 1 H, CH). ^{13}C-NMR (DMSO-d_6): δ ppm: 164.65, 159.76, 158.34, 153.62, 151.23, 138.98, 136.54, 132.22, 131.74, 129.65, 127.91, 126.88, 124.73, 123.76, 122.09, 94.34, 92.89, 50.46, 46.86. Anal. Calcd. For: $C_{23}H_{12}N_4O_3S$ (424.43): C, 65.09; H, 2.85; N, 13.20; S, 7.55%. Found: C, 65.05; H, 2.81; N, 13.25; S, 7.51%.

2.3. 2-Chloro-7-oxo-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidine-3,8-dicarbonitrile (2)

Compound **1** (10 g, 23.56 mmol) was combined with a sufficient quantity of phosphorus oxychloride (32 mL) and refluxed for 3 h in a water bath. The resulting mixture was cooled and then added to 200 g of ice-cold water, and then neutralized with a sodium carbonate solution. After stirring the reaction mixture for 1 h, a pale-yellow precipitate was obtained and collected through filtration. The precipitate was then washed with water several times, dried in the air, and recrystallized using ethanol: dioxane mixture (3:1), resulting in pale yellow crystals. Yield: 64%; m.p. 169–171 °C. FT-IR (ν) (KBr) cm^{-1}: 3028, 2994, 2123, 2108, 1665; ^{1}H-NMR (DMSO-d_6): δ ppm: 7.67–7.66 (d, *J* = 7.6, 2 H, Ar-H), 7.46–7.40 (t, *J* = 7.9, 3 H, Ar-H), 7.34–7.33 (d, *J* = *8*, 2 H, Ar-H), 7.27–7.24 (t, *J* = 7.5, 3 H, Ar-H), 4.97 (s, 1 H, CH), ^{13}C-NMR (DMSO-d_6): δ ppm: 163.76, 159.14, 156.78, 154.81, 151.16, 137.88, 136.64, 131.78, 131.51, 129.87, 127.34, 126.83, 124.98, 123.44, 122.17, 94.15, 92.76, 72.35, 46.76; Anal. Calcd. For: $C_{23}H_{11}ClN_4O_2S$ (442.88): C, 62.38; H, 2.50; Cl, 8.00; N, 12.65; S, 7.24%. Found: C, 62.42; H, 2.53; Cl, 8.05; N, 12.61; S, 7.20%.

2.4. 2-Mercapto-7-oxo-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo [3,2-a]pyrimidine-3,8-dicarbonitrile (3)

To obtain the desired product, a mixture of thiourea (15 mmol) and compound **2** (3 g, 6.77 mmol) in 100 mL of ethanol was heated under reflux for 5 h, followed by cooling. The yellow precipitate that formed was filtered and washed with ethanol. The produced thiouronium salt was subsequently dissolved in 50 mL of 10% NaOH and neutralized with diluted HCl. The impure product was collected by filtration, washing it several times with water, dried in the air, and recrystallized from acetic acid into pale yellow crystals, yielding the final product in 62%, m.p. 265–267 °C; FT-IR (ν) (KBr) cm^{-1}: 3032, 2987, 2120, 2104, 1665; ^{1}H-NMR (DMSO-d_6): δ ppm: 7.65–7.59 (d, *J* = 7.5, 2 H, Ar-H), 7.46–7.43 (t, *J* = 8.01, 3 H, Ar-H), 7.37–7.36 (d, *J* = *8*, 2 H, Ar-H), 7.28–7.26 (t, *J* = 7.7, 3 H, Ar-H), 5.21 (d, *J* = *8*, 1 H, CH), 4.77 (d, *J* = *8*, 1 H, CH), ^{13}C-NMR (DMSO-d_6): δ ppm: 163.78, 159.83, 156.65, 155.53, 151.34,

137.28, 136.64, 131.32, 131.50, 129.43, 127.27, 126.36, 124.88, 123.38, 122.72, 94.22, 92.32, 72.18, 46.45; Anal. Calcd. For: $C_{23}H_{12}N_4O_2S_2$ (440.50): C, 62.71; H, 2.75; N, 12.72; S, 14.56%. Found: C, 62.76; H, 2.71; N, 12.76; S, 14.59%.

2.5. Ethyl 2-((3,8-dicyano-7-oxo-4,9-diphenyl-4 H,7 H-pyrano [2',3':4,5]thiazolo[3,2-a]pyrimidin-2-yl)thio)acetate (4)

To synthesize the desired product, a combination of derivative **3** (2 g, 4.54 mmol), fused sodium acetate (0.75 g, 8.5 mmol), and ethyl chloroacetate reagent (2 mmol), in 20 mL of ethanol was refluxed for 3 h and then cooled. The solid product was separated by filtration, rinsed with water, desiccated, and recrystallized from a 1:1 ethanol-water solution to obtain the purified product in the form of pale orange crystals. Yield: 77%; m.p. 287–289 °C; IR (ν) (KBr) cm^{-1}: 3032, 2987, 2120, 2104,1728, 1665; ^{1}H-NMR (DMSO-d_6): δ 7.64–7.62 (d, J = 7.5, 2 H, Ar-H), 7.46–7.44 (t, J = 8.01, 3 H, Ar-H),7.42–7.37 (d, J = *8*, 2 H, Ar-H), 7.36–7.28 (t, J = 7.7, 3 H, Ar-H), 4.63 (s, 1 H, CH), 4.23 (q, J = *7.54*, 2 H, CH_2), 3.97 (s, 2 H, CH_2), 1.41 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 168.34, 167.45, 164.01, 153.88, 151.87, 141.16, 132.77, 131.26, 129.55, 127.68, 126.81, 124.24, 123.45, 122.76, 116.83, 114.62, 97.54, 95.42, 93.56, 63.67, 47.01, 38.41, 14.89; Anal. Calcd. For: $C_{27}H_{18}N_4O_4S_2$ (526.59): C, 61.58; H, 3.45; N, 10.64; S, 12.18%. Found: C, 61.54; H, 3.41; N, 10.69; S, 12.23%.

2.6. Ethyl 9-amino-3-cyano-2-oxo-4,10-diphenyl-2H,10H-thieno [3'',2'':5',6']pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidine-8-carboxylate (5)

To solution of derivative **4** (10 mmol) in absolute ethanol (20 mL) a few droplets of sodium ethoxide were added. The mixture was stirred at ambient temperature for 2 h. The precipitate was obtained and recrystallized from a 2:1 ethanol-water solution, yielding crystals of a delicate ivory color for the final product. Yield: 64%; m.p. 310–312 °C; FT-IR (ν) (KBr) cm^{-1}: 3475, 3353, 3042, 2916, 2104,1717, 1676; ^{1}H-NMR (DMSO-d_6): δ ppm: 7.64–7.63 (d, J = 7.6, 2 H, Ar-H), 7.47–7.43 (t, J = 8.03, 3 H, Ar-H), 7.37–7.36 (d, J = 8.01, 2 H, Ar-H), 7.28–7.27 (t, J = 7.7, 3 H, Ar-H), 6.54 (s, 2 H, NH_2), 4.60 (s, 1 H, CH), 4.26 (q, J = 7.54, 2 H, CH_2), 1.401 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 168.32, 167.43, 164.01, 153.85, 151.87, 141.21, 133.54, 132.77, 131.27, 129.53, 127.65, 126.80, 124.24, 122.75, 116.86, 97.54, 95.47, 93.53, 63.67, 47.16, 14.83; Anal. Calcd. For: $C_{27}H_{18}N_4O_4S_2$ (526.59): C, 61.58; H, 3.45; N, 10.64; S, 12.18%. Found: C, 61.54; H, 3.41; N, 10.69; S, 12.14%.

2.7. 9-Amino-3-cyano-2-oxo-4,10-diphenyl-2H,10H-thieno [3'',2'':5',6']pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidine-8-carbohydrazide (6)

Derivative **5** (1.00 g, 1.89 mmol) was combined with hydrazine hydrates 99.90% (0.15 mL, 5 mmol) and heated under solvent-free conditions for 30 min. In addition, 10 mL of ethanol was added and the reflux was contained for an additional 3 h to produce the desired product. The solid product that had formed during reflux was collected and recrystallized from dioxane, yielding crystals of a light brown. Yield: 60%; m.p. 356–358 °C; FT-IR (ν) (KBr) cm^{-1}: 3470, 3243, 3036, 2987,2107, 1688,1667; ^{1}H-NMR (DMSO-d_6): δ ppm: 8.78 (s, 1 H, NH), 7.63–7.62 (d, J = 7.5, 2 H, Ar-H), 7.48–7.43 (t, J = 8.15, 3 H, Ar-H),7.38–7.37 (d, J = 8.04, 2 H, Ar-H), 7.35–7.27 (t, J = 7.7, 3 H, Ar-H), 6.53 (s, 2 H, NH_2), 6.05 (s, 2 H, NH_2), 4.63 (s, 1 H, CH); ^{13}C-NMR (DMSO-d_6): δ ppm: 167.54, 166.33, 164.14, 153.77, 151.56, 141.34, 133.60, 132.78, 131.29, 129.56, 128.01, 126.93, 124.51, 122.72, 116.18, 109.12, 96.34, 95.57, 91.78, 47.34; Anal. Calcd. For: $C_{25}H_{16}N_6O_3S_2$ (512.56): C, 58.58; H, 3.15; N, 16.40; S, 12.51%. Found: C, 58.55; H, 3.12; N, 16.44; S, 12.55%.

2.8. 9-Amino-8-(3,5-dimethyl-1H-pyrazole-1-carbonyl)− 2-oxo-4,10-diphenyl-2H,10H-thieno[3'',2'':5',6']pyrano[2',3':4,5]thiazolo[3,2-a] pyrimidine-3-carbonitrile (7)

For producing the desired compound, aminocarbohydrazide compound **6** (0.39 g, 1.20 mmol) was gently fused with acetylacetone (3.00 mmol) under neat conditions for 20 min. Following the addition of 10 mL of absolute ethanol, the mixture was refluxed for an additional 3 h. The solid product that had formed throughout reflux was collected and purified by recrystallization from ethanol to yield yellow crystals as the final product. Yield: 58%; m.p. 378–379 °C; FT-IR (ν) (KBr) Cm^{-1}: 3347, 3277, 3049, 2902, 2110, 1683, 1649; ^{1}H-NMR (DMSO-d_6): δ ppm: 7.68–7.67 (d, J = 7.48, 2 H, Ar-H), 7.48–7.41 (t, J = 8.15, 3 H, Ar-H), 7.38–7.36 (d, J = 8.04, 2 H, Ar-H), 7.35–7.23 (t, J = 7.7, 3 H, Ar-H), 7.18 (s, 1 H, CH pyrazole), 6.58 (s, 2 H, NH_2), 4.64 (s, 1 H, CH), 2.33 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 167.79, 166.45, 161.56, 156.31, 149.88, 142.67, 134.22, 133.16, 131.63, 129.77, 128.18, 126.29, 125.01, 123.15, 121.71, 116.29, 109.46, 94.32, 92.67, 47.43, 17.45, 16.18; Anal. Calcd. For: $C_{30}H_{20}N_6O_3S_2$ (576.65): C, 62.49; H, 3.50; N, 14.57; S, 11.12%. Found: C, 62.45; H, 3.54; N, 14.55; S, 11.17%.

2.9. Ethyl 9-(2-chloroacetamido)− 3-cyano-2-oxo-4,10-diphenyl-2H,10H-thieno[3'',2'':5',6']pyrano[2',3':4,5]thiazolo[3,2-a] pyrimidine-8-carboxylate (8)

Derivative **5** (1.00 g, 1.89 mmol) was mixed with chloroacetyl chloride (3.50 mmol) in 10 mL dioxane then the mixture was heated at 60–70 °C for 4 h. After emptying the reaction mixture into an ice-water solution and neutralizing it with a diluted sodium carbonate solution, the reaction mixture is neutralized, the resulting solid product was collected, dried, and further purified by recrystallization from ethanol in the form of pale ivory crystals yielding 61%, m.p. 289–291 °C; FT-IR (ν) (KBr) cm^{-1}: 3339, 2918, 2114, 1716, 1687; ^{1}H-NMR (DMSO-d_6): δ ppm: 7.69 (s, 1 H, NH), 7.65–7.64 (d, J = 7.61, 2 H, Ar-H), 7.45–7.41 (t, J = 8.02, 3 H, Ar-H), 7.40–7.39 (d, J = 8.0, 2 H, Ar-H), 7.29–7.27 (t, J = 7.78, 3 H, Ar-H), 4.96 (s, 1 H, CH), 4.40 (s, 2 H, CH_2), 4.36 (q, 2 H, CH_2), 1.39 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 168.43, 164.55, 158.45, 154.11, 153.63, 152.45, 147.83, 143.16, 134.25, 133.71, 131.23, 129.16, 128.91, 126.37, 125.01, 123.65, 121.32, 116.45, 111.32, 95.17, 93.34, 67.43, 47.43, 35.45, 16.38; Anal. Calcd. For: $C_{29}H_{19}ClN_4O_5S_2$ (603.06): C, 57.76; H, 3.18; Cl, 5.88; N, 9.29; S, 10.63%. Found: C, 57.79; H, 3.14; Cl, 5.85; N, 9.33; S, 10.60%.

2.10. Ethyl3-cyano-2-oxo-4,10-diphenyl-9-(2-(phenylamino) acetamido)− 2H,10H-thieno[3'',2'':5',6']pyrano[2',3':4,5]thiazolo [3,2-a]pyrimidine-8-carboxylate (9a)

In a reaction vessel, (0.50 g, 0.83 mmol) of chloroacetyl amino derivative **8,** and (0.20 mL, 1.50 mmol) of aniline were suspended and refluxed under solvent-free conditions for 30 min. After that, 10 mL of absolute ethanol was added, and the reaction mixture was refluxed for an additional 3 h. The solid product, which had formed during reflux, was collected and subjected to recrystallization from dioxane to obtain the purified final product in the form of yellow crystals. Yield: 58%; m.p. 314–316 °C; FT-IR (ν) (KBr) cm^{-1}: 3226, 3177, 3054, 2948, 2109, 1718,1676, 1658; ^{1}H-NMR (DMSO-d_6): δ ppm: 8.02 (s, 1 H, NH), 7.65–7.61 (d, J = 7.61, 4 H, Ar-H), 7.48–7.44 (t, J = 8.02, 3 H, Ar-H), 7.40–7.37 (d, J = 8.0, 4 H, Ar-H), 6.67–6.63 (t, J = 7.78, 3 H, Ar-H), 7.11 (s, 1 H, NH), 4.87 (s, 1 H, CH), 4.43 (s, 2 H, CH_2), 4.38 (q, 2 H, CH_2), 1.41 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 168.35, 167.45, 166.55, 161.32, 157.42, 156.49, 154.35, 151.28, 147.67, 144.39, 136.53, 135.82, 134.54, 132.65, 129.76, 127.76, 126.67, 125.67, 124.78, 121.17, 119.47, 116.75, 112.56, 94.89, 92.83, 64.18, 59.76, 47.55, 16.18; Anal. Calcd. For: $C_{35}H_{25}N_5O_5S_2$ (659.74): C, 63.72; H, 3.82; N, 10.62; S, 9.72%. Found: C, 63.76; H, 3.84; N, 10.66; S, 9.75%.

2.11. Ethyl 9-(2-((4-chlorophenyl)amino)acetamido)− 3-cyano-2-oxo-4,10-diphenyl-2H,10H-thieno[3'',2'':5',6']pyrano[2',3':4,5]thiazolo [3,2-a]pyrimidine-8-carboxylate (9b)

In a reaction vessel, (0.50 g, 0.83 mmol) of derivative **8**, and (0.20 mL, 1.50 mmol) of *p*-chloro aniline were suspended and refluxed for 30 min under solvent-free conditions. After adding 10 mL of absolute ethanol, the reaction mixture was refluxed for an additional 3 h. The solid product, that formed throughout reflux, was gathered and purified by the recrystallization via dioxane, resulting in the production of yellow crystals that yielded the desired substance in 58%, m.p. 378–379 °C; IR (ν) (KBr) cm^{-1}: 3237, 3156, 3051, 2916, 2106, 1722, 1669, 1654; ^{1}H-NMR (DMSO-d_6): δ ppm: 8.40 (s, 1 H, NH), 7.47 (d, J = 7.61, 4 H, Ar-H), 7.45–7.44 (t, J = 8.02, 3 H, Ar-H), 7.27 (d, J = 8.0, 4 H, Ar-H), 6.63–6.51 (t, J = 7.78, 3 H, Ar-H), 6.53 (s, 1 H, NH), 4.74 (s, 1 H, CH), 4.36 (s, 2 H, CH_2), 4.13 (q, 2 H, CH_2), 1.39 (s, 3 H, CH_3); ^{13}C-NMR (DMSO-d_6): δ ppm: 168.76, 167.71, 166.45, 161.65, 157.83, 156.56, 154.63, 151.19, 147.81, 144.76, 136.62, 135.72, 134.01, 132.89, 129.34, 127.78, 126.61, 125.33, 124.45, 121.18, 119.77, 116.89, 112.12, 94.73, 92.06, 64.25, 59.76, 47.54, 16.45; Anal. Calcd. For: $C_{35}H_{24}ClN_5O_5S_2$ (694.18): C, 60.56; H, 3.48; Cl, 5.11; N, 10.09; S, 9.24%. Found: C, 60.53; H, 3.44; Cl, 5.15; N, 10.055; S, 9.21%.

2.12. Insect field strain

Aphis gossypii insects were collected from cotton farms in Sohag, Egypt, at the Agriculture Research Center, Shandaweel Station.

2.13. Laboratory bioassay

Using leaf immersion bioassay methods, the toxicological bioefficacy of all pyrimidine derivatives was determined[18]. This experiment aims to determine the concentrations required to exterminate 50% (LC_{50}) of the larvae and adults of *Aphis gossypii* (Glover, 1889) insects. To accomplish this, five concentrations of each pyrimidine derivative along with 0.1% Tween 80 as a surfactant were employed. 50 Nymphs and 50 adults, nearly of the same size, of *A. gossypii* insects were used, and 10-second immersions were performed three times in each concentration of the synthesized target compounds. The used Insects were allowed to air-dry for approximately 30 min at ambient temperature. The experiment also included a control group consisting of insects dipped only in distilled water and Tween 80. The applications are performed at a temperature of 25 °C and relative humidity of 5%. Once the treated insect batches were desiccated, they were transferred to Petri dishes with a 9 cm diameter and stored for 24 h at a temperature of 22 ± 2 °C and a relative humidity of 60 ± 5%. 24 h after treatment, the mortality of aphids was observed using a novel binocular microscope. Any aphid that exhibited no movement was categorized as dead. Each tested target compound's toxicological bioefficacy was repeated twice, and the resulting data were adjusted using Abbott's formula [19]. The probit regression analysis program was used to determine the measurements of the mortality relapse lines [20]. Sun equations were used to calculate the harmfulness index [21]. The acetamiprid as a neonicotinoid reference insecticide and the target synthesized compounds were tested against the collected *Aphis gossypii* insects, and compounds **2,8** were tested for safety profile against earthworms.

2.14. Statistical analysis

The data on mortality for *Aphis gossypii* was evaluated employing probit modeling within a statistics (LDP-line) program to calculate the values of the LC_{50} with 95% educible limitations of lower and upper credibility limits, standard error, slope, correlation coefficient, and chi-square.

3. Results and discussion

3.1. Synthesis

The synthetic process of the targets began by the reaction of 3,7-dioxo-5-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **A**, with ethyl 2-cyano-3-phenylacrylate **B** to give 2,7-dioxo-4,9-diphenyl-3,4-dihydro-2*H*,7*H*-pyrano[2',3':4,5]thiazolo[3,2-*a*]pyrimidine-3,8-dicarbonitrile derivative **1**. chlorination of compound **1** using $POCl_3$ produced chloropyranothiazolopyrimidinedicarbonitrile derivative **2**. Refluxing of compound **2** in ethanol in the presence of thiourea gave the corresponding mercaptodicarbonitrile derivative **3**. Reaction of 2-mercapto-7-oxo-4,9-diphenyl-4*H*,7*H*-pyrano[2',3':4,5]thiazolo[3,2-*a*]pyrimidine-3,8-dicarbonitrile **3** with ethyl chloroacetate under reflux in ethanol in the presence of fused sodium acetate to give the corresponding open amino ester derivative **4**, which was converted to a closed amino ester derivative **5** through the *Thorpe-Ziegler* reaction using ethanolic sodium ethoxide solution which is a vital starting material for the preparation of the rest of the target materials. (Scheme 1).

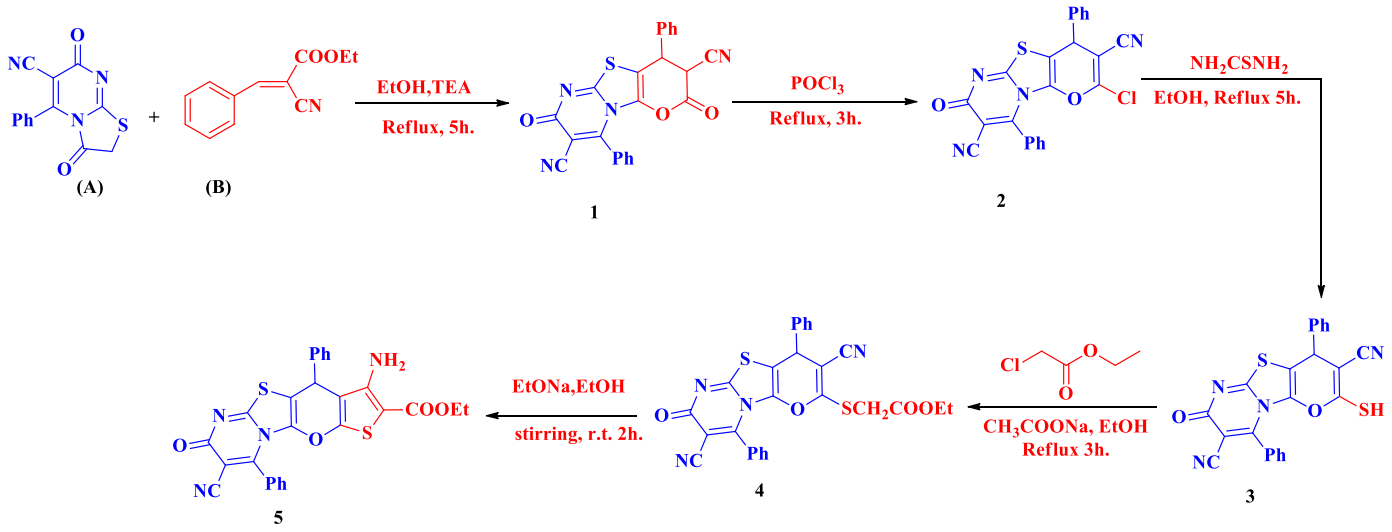
The corresponding amino thienopyranothiazolopyrimidinecarbohydrazide **6** was achieved by heating o-amino ester **5** together with hydrazine hydrate for 3 h in refluxing ethanol. In addition, the corresponding aminodimethylpyrazolyl derivative **7** was produced by condensing aminocarbohydrazide **6** with acetylacetone in refluxing ethanol. The chloroacetylamino derivative **8** was gained by chloroacetylation of the o-aminoester **5** with chloroacetylchloride in dioxane, which underwent nucleophilic substitution with aniline and *p*-chloroaniline and gave the corresponding phenylaminoacetamido derivatives **9a,b** (Scheme 2).

3.2. Characterization

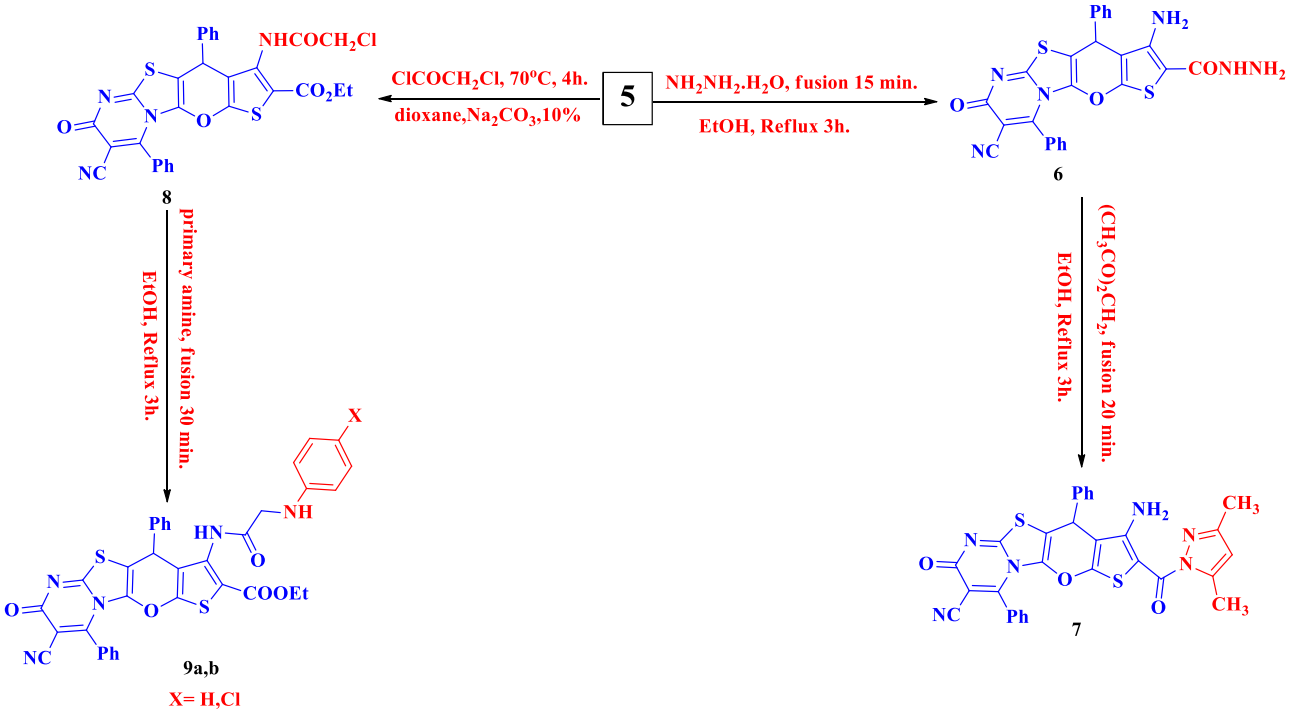
The structural formulas of all target compounds were confirmed on the basis of their spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C-NMR) and elemental analyses, and found to be reliable with their proposed structures.

The FT-IR spectrum of **2** exposed bands at 3036, 2978, 2120, 2107, 1658, and 1647 cm^{-1} characteristics of (CH aromatic), (CH aliphatic), (2 C≡N), and (2 C═O) groups. Compound **2** ^{1}H-NMR spectrum displayed two doublet signals at δ 4.92 and 3.73 ppm characteristic of 2CH groups. Besides, the ^{13}C-NMR spectrum exhibited the presence of signals at δ 164.65 and 159.76 ppm distinguishing C═O groups, respectively. Compound **4** FT-IR spectrum displayed two bands at 2120 and 2104 cm^{-1} for 2CN groups, with one of these bands disappearing upon *Thorpe-Ziegler* cyclization to yield compound **5** with absorption bands that were at 3475, 3353, 1717, and 1617 cm^{-1} for NH_2 and CO groups, respectively. ^{1}H-NMR spectrum of **5** displayed the appearance of a singlet signal at δ 6.54 ppm distinguished by NH_2 group and the disappearance of a signal at δ 3.97 ppm for the SCH_2 group which is present in compound **4**. ^{13}C-NMR spectrum of compound **4** exhibited the presence of a signal at δ 38.41 for CH_2 group which disappear upon cyclization to afford compound **5**.

FT-IR spectrum of derivative **6** demonstrated bands attributed to NH_2 and NH groups at 3470, 3243 cm^{-1}. ^{1}H-NMR spectrum demonstrated the vanishing of signals owing to the methyl and methylene groups of the ester in compound **5** and the appearance of singlet signals at δ 6.53, 6.05, and 8.78 ppm representative of NH_2 and NH groups, individually. The ^{13}C-NMR spectrum of the carbohydrazide compound **6** showed a signal at δ 164.14 ppm attributed to the CONH group. FT-IR spectrum of derivative **7** pointed the disappearance of characteristic absorption bands for NH and NH_2 groups in compound **6**. ^{1}H NMR of compound **7** revealed the appearance of singlet signals at δ 2.17 and 2.33 ppm for $2CH_3$ for the dimethylpyrazole and at δ 7.18 ppm for CH pyrazolyl. Also, ^{13}C-NMR of derivative 7 exhibited a signal at δ 17.45 and 16.18 ppm due to $2CH_3$ for the dimethylpyrazole and a signal at δ 109.46 ppm belonging to the CH pyrazole.



Scheme 1. Synthesis of the aminothienopyranothiazolopyrimidinecarboxylate **(5)**.



Scheme 2. Synthesis of the target derivatives **(6, 7, 8, 9a** and **9b)**.

Elemental and spectroscopic analyses established the structures of derivatives **8** and **9a,b**. FT-IR results of compound **8** revealed the appearance of bands at 3339 cm^{-1} for NH and at 1687 cm^{-1} for the CO amide group and the disappearance of bands at 3470, 3243 cm^{-1} characteristics of NH_2 group in the starting compound. ^1H NMR of derivative **8** revealed the presence of signals at δ 4.40 ppm for CH_2 and at δ 7.69 ppm for NH and the disappearance of the signal at δ 6.53 ppm attributed to the amino group in compound **5**. ^{13}C-NMR of derivative **8** affirmed a signal at δ 35.45 ppm attributed to CH_2 and signals at δ 158.45 and 164.55 ppm due to CO of amide and ester groups, respectively.

FT-IR spectrum of **9b** showed the appearance of bands at 3237 and 3156 cm^{-1} for 2NH group and at 1669 cm^{-1} for the CO amide group. ^1H-NMR of **9b** exhibited the appearance of signals at δ 6.53 and 8.40 ppm for 2NH (NH of aniline and CONH), respectively. Also, ^{13}C NMR of compound **9b** announced a signal at δ 59.76 ppm due to CH_2 and signals at δ 167.71, and 166.45 ppm due to CO of amide and ester groups, respectively.

3.3. Bioefficacy screening

(A) Insecticidal bioefficacy screening against *Aphis gossypii* (Glover, 1887).

The insecticidal bioefficacy of all synthesized target compounds was evaluated as described in the following:

3.3.1. Toxicological activity test for nymphs of Aphis gossypii

Compounds **1–9a,b** were screened against nymphs of *Aphis gossypii* for their toxicological activity, and the results are shown in Table 1 and Fig. 2. The results of the bioefficacy test conducted after 24 h of

Table 1
Insecticidal activity of acetamiprid and compounds (**1–9a,b**) against the nymphs and adults of *Aphis gossypii* after 24 h of Treatment.

Nymphs of Aphis				Adults of Aphis		
Compounds	**LC_{50} (ppm) (Confidence Limits)**	**Slope ± SE**	**Toxic ratio**	**LC_{50} (ppm) (Confidence Limits)**	**Slope ± SE**	**Toxic ratio**
Acetamiprid	0.045 (0.039–0.059)	0.340 ± 0.020	1	0.225 (0.182–0.403)	0.24 ± 0.02	1
1	0.123 (0.102–0.248)	0.392 ± 0.286	0.366	0.837 (0.530–1.236)	0.460 ± 0.259	0.269
2	0.039 (0.019–0.058)	0.374 ± 0.282	1.154	0.209 (0.092–0.462)	0.399 ± 0.286	1.077
3	0.117 (0.092–0.219)	0.391 ± 0.289	0.385	0.717 (0.655–0.862)	0.403 ± 0.283	0.314
4	0.055 (0.036–0.078)	0.380 ± 0.285	0.818	0.691 (0.466–0.882)	0.399 ± 0.281	0.326
5	0.173 (0.142–0.268)	0.393 ± 0.282	0.260	0.893 (0.674–1.037)	0.405 ± 0.285	0.252
6	0.647 (0.466–0.882)	0.400 ± 0.284	0.069	1.029 (0.975–1.907)	0.458 ± 0.275	0.219
7	0.402 (0.347–0.577)	0.396 ± 0.258	0.112	0.925 (0.832–1.84)	0.459 ± 0.280	0.243
8	0.044 (0.037–0.054)	0.389 ± 0.287	1.023	0.253 (0.193–0.462)	0.392 ± 0.281	0.889
9a	0.502 (0.405–0.610)	0.398 ± 0.024	0.089	1.018 (0.932–1.793)	0.456 ± 0.275	0.221
9b	0.249 (0.174–0.395)	0.386 ± 0.285	0.181	0.424 (0.379–0.594)	0.396 ± 0.290	0.531

Note: Toxic ratio is calculated as the LC_{50} value of acetamiprid for baseline toxicity / the LC_{50} value of the compound.

treatment demonstrated that the ten compounds mentioned earlier exhibited toxicological activity against the nymphs of *Aphis gossypii* with the degree of toxicity varying from high to low, and with LC_{50} values ranging from 0.039 to 0.647 ppm, whereas the LC_{50} value of acetamiprid was 0.045 ppm. In comparison to acetamiprid reference insecticide, two of the tested compounds (**2,8**) exhibited exceptional insecticidal activity against cowpea aphid larvae, as evidenced by their LC_{50} values of 0.039 and 0.044 ppm, respectively, whereas that of acetamiprid was 0.045 ppm. The other compounds (**1, 3, 4, 5, 6, 7, 9a,** and **9b** with LC_{50} values of 0.123, 0.117, 0.055, 0.173, 0.647, 0.402, 0.044, 0.502, and 0.249 ppm, respectively) exhibited moderate to low toxicological activities compared to acetamiprid. Based on these outcomes, it was concluded that the toxicity of compounds **2** and **8** against nymphs of *Aphis gossypii* was similar to that of acetamiprid, and compound **4** was close in activity to that of acetamiprid after 24 h of treatment.

3.3.2. Toxicological activity test for adults of Aphis gossypii

Compounds **1–9a,b** were screened against adults of *Aphis gossypii* for their toxicological activity, and the results are shown in Table 1 and Fig. 2. The toxicity test results revealed that, after 24 h of treatment, compounds **1–9a,b** exhibited varying degrees of toxicological activity against the adults of *Aphis gossypii*, ranging from high to low. The LC_{50} values of the tested compounds ranged from 0.209 to 1.029 ppm, whereas the LC_{50} value of acetamiprid was 0.225 ppm. Compound **2** was considered more active than acetamiprid because its LC_{50} value was 0.209 ppm, which is less than that of the acetamiprid reference insecticide. Compound **8** was close in activity to that of acetamiprid after 24 h of the test and its LC_{50} value is 0.253 ppm. The other compounds **1, 3, 4, 5, 6, 7, 9a** and **9b** exhibited moderate to low toxicological activities compared to that of acetamiprid, and their LC_{50} values were 0.837, 0.717, 0.691, 0.893, 1.029, 0.925, 1.018, and 0.424 ppm, respectively. So, from the above results, it was concluded that the toxicity of compounds **2, 8** was more than or close in activity to that of acetamiprid against the adults of *Aphis gossypii* after 24 h of treatment.

3.4. Structure-Activity Relationship (SAR)

As a continuation of this work, we have identified some novel pyrimidine derivatives with remarkable toxicological activity against larvae and adults of *Aphis gossypii* after 24 h of treatment. In this study, the structure-activity relationships were determined using the toxicity values in Table 1 and Fig. 2. According to their insecticidal activity against nymphs of *Aphis gossypii*, the order of the toxicological bioefficacy for the target-prepared pyrimidine compounds was **2 > 8 > 4 > 3 > 1 > 5 > 9b > 7 > 9a > 6**. The study demonstrated that among the synthesized pyrimidine derivatives, compound **2** exhibited greater activity against the nymphs and adults of *Aphis gossypii* than the others. The presence of two cyano groups and a chlorine atom in its chemical structure may account for the heightened activity observed in compound **2**. Also, the toxicity of pyrimidine derivatives **8** and **9b** is higher than that of compound **4** analog, according to the insecticidal activity against adults of aphis, and this is possibly due to the presence of chlorine atom attached to their chemical structures, and the absence of this moiety in compound **4**. Finally, the presence of a thiol group in the structure of compound **3**, which is lacking in compound **1**, could be the reason for the former's greater insecticidal activity compared to the latter.

(B) Screening the safety profile towards soil organisms (earthworms (*Aporrectodea caliginosa*)).

Compounds **2,8** and acetamiprid insecticide were screened for their bioefficacy towards soil organisms (earthworms (*Aporrectodea caliginosa*)) as the results explained in the following:

3.4.1. Toxicity of earthworms by a soil mixing test

In the soil mixing bioassay method, the earthworms were adapted in the laboratory using artificial soil. Following that, 100 g of artificial soil was put into plastic boxes (3.5 ×7.5 cm). The moisture content was set to 36% of the final weight. Using the tested soil, the boxes were treated with aqueous solutions of acetamiprid insecticide formulations (20% wettable powder (WP)) to obtain 0.001, 0.005, 0.01, 0.5, 1, 2.5, 5, 7.8125, 15.625, 31.25, 62.5, 125, 250 and 500 μg/g soil. These concentrations were prepared based on 100% purity of acetamiprid. Concentrations of 7.8125, 15.625, 31.25, 62.5, 125, 250, and 500 μg/g soil of compound **2** and compound **8** were used. Mature earthworms weighing between 0.65 and 0.75 g were chosen for the experiment. Four pre-washed and ventilated earthworms in their mature stage were then added to each box (three replicates for each concentration) then, covered with Parafilm, holed for aeration, and placed in an incubation chamber with a temperature of 21 ± 2ºC and a photoperiod of 12:12. Similar procedures were followed to create the control, except that only water was added to the soil. The moisture that was lost during the assessment was replenished based on the weight that was lost, and distilled water was used to replace the lost weight. The mortality rate was observed after 5 and 10 days, and the LdP line software was used to calculate the LC_{50} value of the employed agrochemicals[15].

The soil mixing test was used to gauge how harmful the agrochemicals under the test were to earthworms (*Aporrectodea caliginosa*). The soil mixing test is more accurate in simulating the natural environment of earthworms because the compounds are primarily absorbed by the stomach in this procedure. Therefore, when the pesticide toxicity to earthworms is evaluated, the soil mixing test is more useful [15,22]. When the exposure time was extended, the LC_{50} for agrochemical toxicity on earthworms using the soil mixing approach was increased. The LC_{50} was reduced from 0.1992 (0.6889–0.0530) to 0.0086 (0.0246–0.0031) for acetamiprid (reference insecticide), from 32.7753 (50.8695–21.0710) to 22.4079 (37.3440–13.3021) for compound **2** and from 131.6081 (175.7938–98.5212) to 101.0537 (147.1200–69.3789) for compound **8** at 5 and 10 days after treatment, respectively. More hazardous chemicals have lower LC_{50} values[22]. The toxicity of the

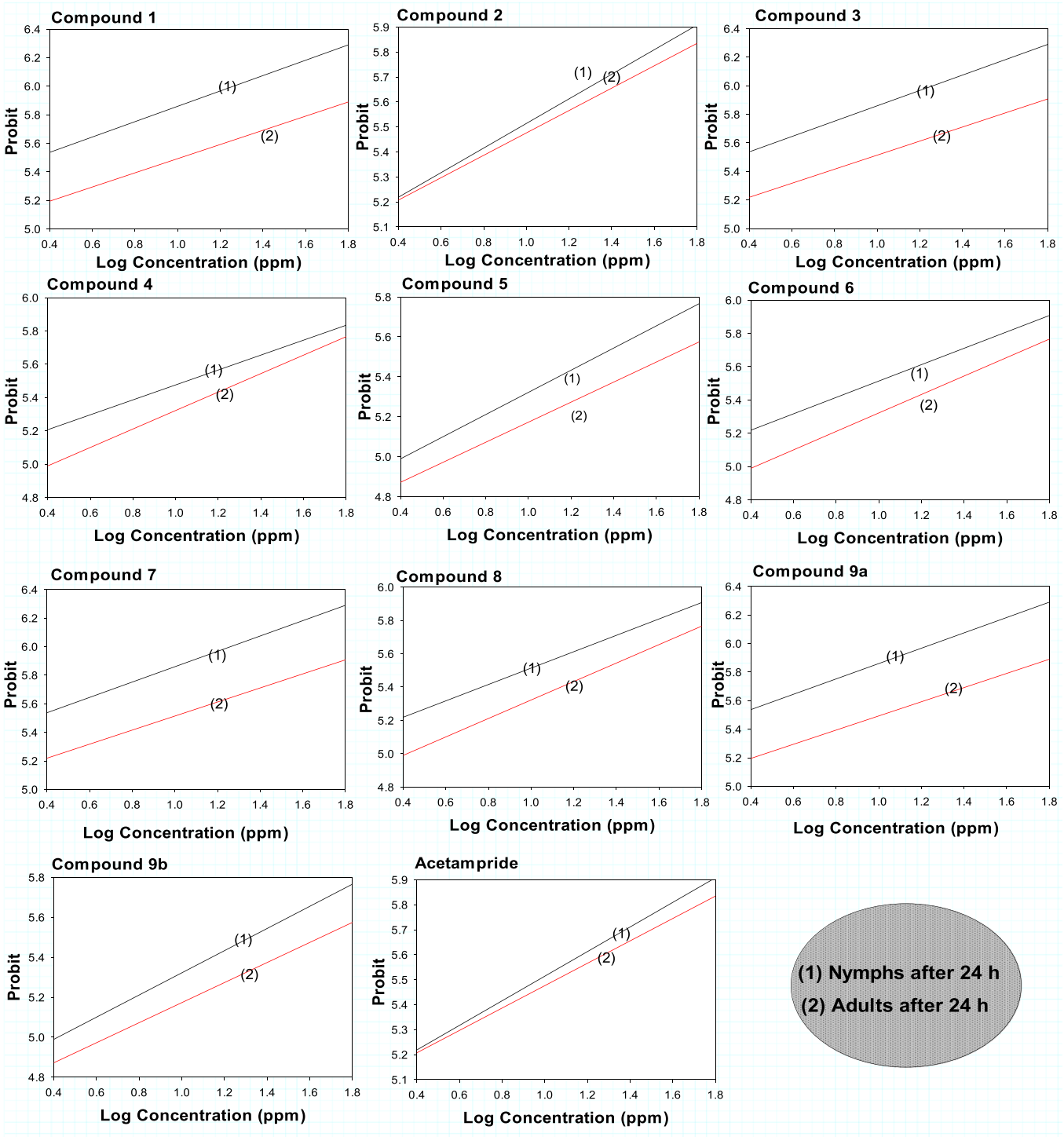


Fig. 2. Insecticidal activity of acetamiprid and compounds (**1–9a,b**) against the nymphs and adults of *Aphis gossypii* after 24 h of treatment.

tested agrochemicals was greater (lower LC_{50}) for acetamiprid at both time intervals than that of compound **2** and compound **8** as shown in Table 2. It is clear from these results that the prepared compounds **2** and **8** are less toxic and safer than acetamiprid on non-target organisms (earthworms).

3.5. The effect of the used agrochemicals (acetamiprid and compounds 2,8) on the chemical properties of soil

Soil chemical analysis was carried out before and after treatment with agricultural chemicals and it was presented in Table 3. A significant difference was observed between the soil before and after treatment with agrochemicals concerning chemical properties. The EC was increased significantly from (2.08–2.48 ds/m) by the treatment of the soil with agrochemicals (acetamiprid and compounds **2,8**) compared to untreated soil (1.32 ds/m). Before the treatment of soil, the pH was recorded to be (8.25) and this value is lower than the soil pH after treatment with acetamiprid (8.66), the soil pH after treatment with compound **2** (8.39), and the soil pH after treatment with compound **8** (8.65). The increase in pH may be due to the decomposition of agrochemicals by soil and earthworms [22–24]. The population growth of metabolically active bacteria, which causes the breakdown of

Table 2
Toxicity indices and parameters of acetamiprid and compounds (**2,8**) on earthworms by soil mixing test.

Compounds	Acetamiprid (reference)	Compound 2	Compound 8
Time	**5th day**		
LC_5	0.003	6.609	62.808
Upper/ Lpower	0.0240–0.0001	15.9991–2.6031	106.8947–36.7127
LC_{50}	0.199	32.775	131.608
Upper/ Lpower	0.6889–0.0530	50.8695–21.0710	175.7938–98.5212
LC_{95}	11.913	162.540	275.771
Upper/ Lpower	438.9238–1.8658	386.5489–71.3669	466.7872–163.7479
Slope	0.925723 ± 0.05679913	2.365353 ± 0.3173847	5.120052 ± 2.428761
Probability (P)	0.4492428	0.6869909	0.2205647
Chi Square	8.026797	2.265863	3.023128
Time	**10th day**		
LC_5	0.0004	3.506	30.123
Upper/ Lpower	0.0025–0.0001	11.2983–1.0000	62.3963–14.3141
LC_{50}	0.009	22.408	101.054
Upper/ Lpower	0.0246–0.0031	37.3440–13.3021	147.1200–69.3789
LC_{95}	0.229	143.197	184.543
Upper/ Lpower	2.7573–0.0250	387.8099–56.3423	690.3918–168.9582
Slope	1.154316 ± 0.1198987	2.041997 ± 0.2831968	3.129257 ± 0.6483456
Probability (P)	0.6422014	0.4947327	0.6820664
Chi Square	5.251666	3.390432	3.768127

Table 3
Chemical properties of the tested soils.

Chemical properties	Soil before treatment	Soil after treatment with acetamiprid	Soil after treatment with compound 2	Soil after treatment with compound 8
EC (ds/m) at 25C	1.32	2.13	2.48	2.08
Soil pH	8.25	8.66	8.39	8.65
Organic matter content (%)	4.49	2.55	3.62	6.10
Total carbonate (%)	7.87	9.91	3.89	8.48
Soluble cations conc. (meq/L):				
Ca^{++}	3.75	12.00	16.33	13.00
Mg^{++}	5.00	13.00	5.00	14.00
Na^{+}	9.41	13.04	19.57	14.13
K^{+}	0.50	0.77	0.82	0.74
Soluble anions conc. (meq/L):				
CO_3^{--}	1.60	6.00	4.00	3.00
HCO_3^{-}	2.60	7.50	17.00	2.50
Cl^{-}	8.50	12.60	17.10	8.10
SO_4^{--}	0.61	12.75	3.62	25.18

short-chain fatty acids and the precipitation of calcium carbonate and may have contributed to an increase in pH, is also supported by earthworms [23]. The organic matter content was also significantly different, 4.49% in the soil before treatment, 2.55% in the soil after treatment with acetamiprid, 3.62% in the soil after treatment with compound **2**, and 6.01% in the soil after treatment with compound **8**. Soluble cations (Ca^{++}, Mg^{++}, Na^{+}, K^{+}), and anions (CO_3^{--}, HCO_3^{-}, Cl^{-}, SO_4^{--}) concentrations were increased in soil after treatment with agrochemicals compared with untreated soil. The phosphate-solubilizing microorganisms are stimulated by the digestive enzymes of earthworms, which facilitates the release of phosphorus from vermicast[23].

4. Conclusion

The current focus of researchers is on developing pesticides that are safe for both humans and the environment. Pyrimidine compounds are a notable class of organic molecules that have shown a good activity as promising insecticides among many organic molecules that have exhibited insecticidal activity. So, a novel series of pyranothiazolopyrimidine derivatives (**1–9a,b**) have been designed and synthesized in pure state, and their insecticidal activity against *Aphis gossypii* (Glover, 1887) was investigated. Among the synthesized compounds, two compounds (**2,8**) exhibited a good insecticidal bioefficacy compared with that of acetamiprid reference insecticide. As a next step, the safety profile of compounds (**2,8**) was estimated against earthworms (*Aporrectodea caliginosa*) compared with the safety profile of acetamiprid insecticide. The results of the safety profile estimation revealed that compounds (**2,8**) are less toxic and safer on earthworms than acetamiprid after 5 and 10 days of test. The chemical properties of the used soil holding the earthworms varied significantly before and after treatment with compounds (**2,8**) and acetamiprid.

Supporting Information

Spectroscopic analyses of the compounds (PDF).

CRediT authorship contribution statement

Shaban A. A. Abdel-Raheem: Conceptualization, Writing – original draft, Visualization, Formal analysis, Methodology, Software, Data curation, Writing – review & editing, Validation, Investigation. **Mohamed R. Fouad**: Formal analysis, Methodology, Software, Data curation, Writing – review & editing, Validation, Investigation. **Mohamed A. Gad**: Formal analysis, Methodology, Software, Data curation, Writing – review & editing, Validation, Investigation. **Adel M. Kamal El-Dean**: Supervision, Conceptualization, Writing – original draft, Visualization, Formal analysis. **Mahmoud S. Tolba**: Conceptualization, Writing – original draft, Visualization, Formal analysis, Methodology, Software, Data curation, Investigation, Resources, Writing – review & editing, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2023.110839.

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