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ORIGINAL ARTICLE

Pyridine derivatives as insecticides. Part 2: Synthesis of some piperidinium and morpholinium cyanopyridinethiolates and their insecticidal activity

Etify A. Bakhite [a,*], Aly A. Abd-Ella [b], Mohamed E.A. El-Sayed [c], Shaban A.A. Abdel-Raheem [c]

[a] *Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt*
[b] *Plant Protection Department, Faculty of Agriculture, Assiut University, Assiut 71526, Egypt*
[c] *Soil, Water and Environment Research Institute, Agriculture Research Center, Cairo, Egypt*

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Cowpea aphid;
Insecticides

Abstract The work included in this paper involves the synthesis of thirteen heterocyclic compounds, piperidinium and morpholinium 3-cyanopyridinethiolates **5–14**, **17**, **20** and **21** in our Lab. and their characterization using elemental and spectroscopic analyses. The insecticidal activities of these compounds against cowpea aphid, *Aphis craccivora* using acetamiprid insecticide as a reference were studied. The bioassay results showed that: (i) the insecticidal activities of compounds **13**, **14** and **20** against nymphs or adults of cowpea aphid are about 1.5-fold higher than that of acetamiprid after 48 h of treatment, (ii) the rest of the tested compounds (ten compounds) exhibit weak to strong toxicity against cowpea aphid and (iii) there is a remarkable relationship between the structure and activity of the tested compounds.

1. Introduction

In recent years, pyridine-containing neonicotinoids have been the fastest-growing and most important class for the insecticide market [1], with widespread use against a broad spectrum of sucking and certain chewing insects by acting selectivity on insect nicotinic acetylcholine receptors (*n*AChRs), their molecular target site [2–5]. Pyridine-containing neonicotinoids are reported to possess a relatively low risk for non-target organisms and the environment, high target specificity and versatile application methods [5]. The common molecular structural features of neonicotinoids consist of four sections: (i) aromatic heterocycle, (ii) flexible linkage, (iii) hydroheterocyle or guanidine/amidine and (iv) electron-withdrawing segment [6]. Encouraged by the above findings and as a continuation of our programme directed towards the synthesis of new pyridine-containing heterocycles with anticipated insecticidal activities [7], we undertook the synthesis of the title compounds, which contain the aforementioned main structural

* Corresponding author.
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features of neonicotinoids and studying their insecticidal activities against Cowpea aphid, *Aphis craccivora* hoping to get compounds with more potency, low insect resistance and no environmental pollution.

2. Experimental section

2.1. General

Melting points of all compounds were determined on Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N, and S) were conducted using a Vario EL C, H, N, S Analyzer. The IR spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer using KBr disc technique (ν_{max} in cm^{-1}). ^1H NMR Spectra were recorded on a Bruker 400 MHz spectrometer with chemical shifts given in δ (ppm) and coupling constant (J) given in Hz. using *TMS* as internal reference. Mass spectra were recorded on a Jeol JMS-600 mass spectrometer. The purity of the synthesized compounds was checked by TLC. Key intermediates **1a–d** [8], **2a,b** [9] and **3a,b** [10] were prepared in our laboratory according to the reported methods. Neonicotinoid insecticide, (*E*)-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methylacetamidine (acetamiprid, purity >98%) was purchased from Sigma–Aldrich chemicals (France). Field strain of cowpea aphids, *A. craccivora* were collected from faba bean, *Vicia faba,* fields of Assiut University Experimental Farm during 2014/2015 season.

Compounds **5**–**14**, **17**, **20** and **21** as well as acetamiprid were tested against nymphs and adults of cowpea aphids, *A. craccivora*.

2.2. Synthetic procedure for 3-cyano-5-ethoxycarbonyl-6-methyl-4-styrylpyridine-2(1H)-thione (2c)

To a mixture of β-styryl-α-thiocarbamoylacrylonitrile (**1c**) (2.14 g, 10 mmol) and ethyl acetoacetate (1.3 ml, 10 mmol) in ethanol (25 ml), a few drops of triethylamine were added. The resulting mixture was heated under reflux for 4 h and then acidified with drops of glacial acetic acid. The product that formed after cooling was collected by filtration and recrystallized from ethanol to give yellow crystals of **2c**. Yield: 53%. Melting point (mp): 260–262 °C. IR (ν) (KBr) cm^{-1}: 3200 (NH), 2220 (CN), 1730 (CO). ^1H NMR (CF_3CO_2D) δ: 7.35–7.60 (m, 7H, CH═CH and Ar—H), 4.30–4.52 (q, 2H, OCH_2), 2.63 (s, 3H, CH_3), 1.25–1.40 (t, 3H, CH_3). Elemental Analysis Calculated for $C_{18}H_{16}N_2O_2S$ (%): C, 66.65; H, 4.97; N, 8.64; S, 9.88. Found (%): C, 66.44; H, 4.77; N, 8.91; S, 10.15.

2.3. Synthetic procedure for 5-acetyl-3-cyano-6-methyl-4-(2′-thienyl)pyridine-2(1H)-thione (4)

To a mixture of β-(2′-thienyl)-α-thiocarbamoylacrylonitrile (**1d**) (2.09 g, 10 mmol) and acetylacetone (1.0 mL, 10 mmol) in ethanol (25 ml), a few drops of triethylamine were added. The resulting mixture was heated under reflux for 4 h and then acidified with a few drops of glacial acetic acid. The product that formed after cooling was collected by filtration and recrystallized from ethanol to give yellow crystals of **4**. Yield: 78%. mp: 273–275 °C. IR (ν) (KBr) cm^{-1}: 3200 (NH), 2220 (CN), 1700 (CO). ^1H NMR ($CDCl_3$) δ: 13.02 (s 1H, NH), 7.55 (s, 1H, CH thienyl), 7.26 (s, 1H, CH thienyl), 7.10 (s, 1H, CH thienyl), 2.41 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{14}H_{13}N_2OS_2$ (%): C, 58.11; H, 4.53; N, 9.68; S, 22.16. Found (%): C, 58.09; H, 4.43; N, 9.28; S, 22.00.

2.4. General procedure for the reaction of β-aryl-α-thiocarbamoylacrylonitrile (1a or 1b) with 5,5-dimethylcyclohexane-1,3-dione; formation of morpholinium salts 13 and 14

To a suspension of β-aryl-α-thiocarbamoylacrylonitrile (**1a** or **1b**) (10 mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1.4 g, 10 mmol) in ethanol (15 ml), 0.9 ml (10 mmol) of morpholine was added. The reaction mixture was heated under reflux for 6 h and then allowed to cool. The precipitated solid was filtered off and recrystallized from ethanol as yellow crystals of compounds **13** or **14**.

2.4.1. Morpholinium 3-cyano-7,7-dimethyl-4-(4′-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-2-thiolate (13)

Yield: 53%. mp: 208–210 °C. IR (ν) (KBr), cm^{-1}: 3440, 3279 (NH, N^+H_2), 2947 (C—H, aliphatic), 2173 (CN), 1619 (CO); ^1H NMR (DMSO-d_6) δ: 8.70 (br s, 2H, N^+H_2); 8.32 (s, 1H, NH), 7.01–7.03 (d, J = 8.0 Hz, 2H, Ar—H), 6.74–6.76 (d, J = 8.0 Hz, 2H, Ar—H), 4.20 (s, 1H, $C_{(4)}H$), 3.74–3.76 (t, J = 4.0 Hz, 4H, CH_2OCH_2), 3.69 (s, 3H, OCH_3), 3.08–3.10 (t, J = 4.0 Hz, 4H, $CH_2N^+CH_2$), 2.31 (s, 2H, CH_2 at C-8), 2.06–211 (d, J = 20.0 Hz 1H, $C_{(6)}H$), 1.89–1.93 (d, J = 16.0 Hz, 1H, $C_{(6)}H$), 0.98 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{23}H_{29}N_3O_3S$ (%): C, 64.61; H, 6.84; N, 9.83; S, 7.50: Found (%): C, 64.54; H, 6.61; N, 9.77; S, 7.19.

2.4.2. Morpholinium 4-(4′-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquino-line-2-thiolate (14)

Yield: 55%. mp: 207–209 °C. IR (ν) (KBr), cm^{-1}: 3420 (N^+H_2), 3278 (NH), 2948 (C—H, aliphatic), 2172 (CN), 1606 (CO); ^1H NMR (DMSO-d_6): 8.65 (br. s, 2H, N^+H_2); 8.42 (s, 1H, NH), 7.24–7.26 (d, J = 8.0 Hz, 2H, Ar—H), 7.10–7.12 (d, J = 8.0 Hz, 2H, Ar—H), 4.26 (s, 1H, $C_{(4)}H$), 3.75–3.77 (t, J = 4.0 Hz, 4H, CH_2OCH_2), 3.09–3.12 (t, J = 4.0 Hz, 4H, $CH_2N^+CH_2$), 2.32 (s, 2H, CH_2 at C-8), 2.08–2.11 (d, J = 12.0 Hz, 1H, $C_{(6)}H$), 1.90–1.94 (d, J = 16.0 Hz, 1H, $C_{(6)}H$), 0.98 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). Elemental Analysis Calculated for $C_{22}H_{26}ClN_3O_2S$ (%): C, 61.17; H, 6.07; N, 9.73; S, 7.42. Found (%): C, 61.25; H, 6.21; N, 9.52; S, 7.49.

2.5. Synthetic procedure for 4-(4′-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexa-hydroquinoline-2-thiol (15)

An aqueous solution of compound **14** (2.0 g) in 30 ml distilled water was acidified with diluted HCl (10 %). The solid product was collected by filtration and crystallized from ethanol to give compound **15** as fine white needles. Yield: 93%. mp: 271–272 °C. IR (ν) (KBr), cm^{-1}: 3220 (NH), 2239 (CN), 1622 (CO). ^1H NMR ($CDCl_3$): 11.83 (s, 1H, SH), 8.86 (s, 1H, NH), 6.87–6.89 (d, J = 8.0 Hz, 2H, Ar—H), 6.77–6.79 (d, J = 8.0 Hz, 2H, Ar—H), 4.19 (s, 1H, $C_{(4)}H$), 2.33 (s, 2H,

CH_2 at C-8), 2.17–2.19 (d, J = 8.0 Hz, 1H, $C_{(6)}H$), 2.06–2.08 (d, J = 8.0 Hz, 1H, $C_{(6)}H$), 1.01 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). EI-MS: m/z (fragment, %) = 344 (M^+, 100); 346 (M +2, 40). Elemental Analysis Calculated for $C_{18}H_{17}ClN_2OS$ (%): C, 62.69; H, 4.97; N, 8.12; S, 9.30. Found (%): C, 62.37; H, 4.84; N, 8.51; S, 9.49.

*2.6. Synthetic procedure for 4-(4′-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-quinoline-2(1H)-thione (**16**)*

A solution of compound **15** (1.5 g) in pyridine (20 ml) or DMSO (30 ml) was heated on a water bath for about 12 h and then left to cool. The formed product was recrystallized from ethanol as yellow crystals of compound **16**. Yield: 76–78%. mp: 298–300 °C. IR: 3200 (NH), 2226 (C≡N), 1680 (C═O). ^{1}H NMR ($CDCl_3$): δ 13.90 (s, 1H, NH), 7.38–7.40 (d, J = 8.0 Hz, 2H, Ar—H), 7.08–7.10 (d, J = 8.0 Hz, 2H, Ar—H), 2.75 (s, 2H, CH_2, C-8), 2.23 (s, 2H, CH_2, C-6), 0.95 (s, 6H, $2CH_3$). EI-MS: m/z (fragment, %) = 342 (M^+, 100); 344 (M + 2, 42). Elemental Analysis Calculated for $C_{18}H_{15}ClN_2OS$ (%): C, 63.06; H, 4.41; N, 8.17; S, 9.35. Found (%): C, 62.88; H, 4.16; N, 8.00; S, 9.43.

*2.7. Procedure for the ternary condensation of 4-anisaldehyde, cyanothioacetamide and cyclohexane-1,3-dione; formation of compounds **18** and **19***

To a mixture of 4-anisaldehyde (1.22 ml, 10 mmol), cyanothioacetamide (1.0 g, 10 mmol), cyclohexane-1,3-dione (1.12 g, 10 mmol) in ethanol (15 ml), 1.0 ml (10 mmol) of piperidine was added. The reaction mixture was stirred at room temperature for 2 h and left to stand overnight. The resulting precipitate was filtered off and recrystallized from ethanol as orange plates. This product was identified as *3-cyano-4-(4′-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2(1H)-thione* (*18*). Yield: (15%). mp: 305–307 °C. IR: 3414 (NH), 3091 (C—H aromatic), 2838 (C—H aliphatic), 2233 (C≡N), 1678 (C═O), 1605 (C═N). ^{1}H NMR (DMSO-d_6): δ 14.300 (s, 1H, NH), δ 7.145–7.180 (dd, J = 2.4 Hz, 2H, Ar—H), 7.951–7.987 (dd, J = 2.4 Hz, 1H, Ar—H), 3.816 (s, 3H, OCH_3), 3.013–3.032 (t, J = 4 Hz, 2H, CH_2 at C-8), δ 2.398–2.415 (t, J = 4 Hz, 2H, CH_2 at C-6), 1.993–2.035 (p, J = 4 Hz, 2H, CH_2 at C-7). Elemental Analysis Calculated for $C_{17}H_{14}N_2O_2S$ (%): C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found (%): C, 65.78; H, 4.41; N, 9.18; S, 10.30.

The mother liquor of the above crude product was acidified with hydrochloric acid (10%) to give a yellow precipitate which upon crystallization from aqueous ethanol was assigned as *3-cyano-4-(4′-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydro quinoline-2-thiol* (*19*). Yield: (45%). mp: 222–224 °C. IR (ν) (KBr), cm^{-1}: 3215 (NH), 2240 (CN), 1622 (CO). EI-MS: m/z (fragment, %) = 312 (M^+, 100%). Elemental Analysis Calculated for $C_{17}H_{16}N_2O_2S$ (%): C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found (%): C, 65.67; H, 4.89; N, 8.73; S, 10.55.

*2.8. General synthetic procedure for piperidinium/ morpholinium 3-cyanopyridine-2-thiolates **5–12**, **17** and **20***

A mixture of compound **2a–c, 3a,b, 4, 16** or **18** (10 mmol) and piperidine or morpholine (10 mmol) in ethanol (25 ml) was heated under reflux for 5 min. and then allowed to cool. The crystalline solid that formed was collected by filtration, air-dried and recrystallized from ethanol to give needle crystals of the thiolates **5–8, 9–11, 12, 17 and 20** respectively.

*2.8.1. Piperidinium 3-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylpyridine-2-thiolate (**5**)*

It is obtained using compound **2a** and piperidine in the above general procedure. Yield: 83%, mp: 209–211 °C. IR (ν) (KBr), cm^{-1}: 3430, 2510, 2390 (N^+H_2), 2967 (C—H, aliphatic), 2215 (C≡N), 1709 (C═O). ^{1}H NMR ($CDCl_3$): δ 6.86–7.19 (dd, J = 4 Hz, Ar—H), 6.49 (br. s, 2H, N^+H_2), 3.90–3.91 (q, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.16 (t, 4H, CH_2NCH_2), 2.37 (s, 3H, CH_3), 1.77 (p, 4H, $2CH_2$), 1.57 (p, 2H, CH_2), 0.85 (t, 3H, CH_3). Elemental analysis calculated for $C_{22}H_{27}N_3O_3S$ (%): C, 63.90; H, 6.58; N, 10.16; S, 7.75. Found (%): C, 63.87; H, 6.71; N, 10.00; S, 8.01.

*2.8.2. Morpholinium 3-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylpyridine-2-thiolate (**6**)*

It is obtained using compound **2a** and morpholine in the above general procedure. Yield: 83%. mp: 221–223 °C. IR (ν) (KBr), cm^{-1}: 3447, 2550, 2452 (N^+H_2), 2954 (C—H, aliphatic), 2217 (C≡N), 1713 (C═O). ^{1}H NMR ($CDCl_3$): δ 7.00–7.33 (m, 4 Hz, Ar—H), 4.80 (br. s, 2H, N^+H_2), 3.74–4.02 (m, 9H, $3OCH_2$ and OCH_3), 2.96 (s, 4H, $CH_2N^+CH_2$), 2.59 (s, 3H, CH_3 at C-6), 0.95 (t, 3H, CH_3). Elemental analysis calculated for $C_{21}H_{25}N_3O_4S$ (%): C, 60.70; H, 6.06; N, 10.11; S, 7.72. Found (%): C, 60.81; H, 6.08; N, 10.03; S, 7.51.

*2.8.3. Piperidinium 4-(4′-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-thiolate (**7**)*

It is obtained using compound **2b** and piperidine in the above general procedure. Yield: 83%, mp: 160–162 °C. IR (ν) (KBr), cm^{-1}: 3410, 2520, 2400 (N^+H_2), 2964 (C—H, aliphatic), 2217 (C≡N), 1713 (C═O). ^{1}H NMR ($CDCl_3$) δ: 7.35 (s, 2H, N^+H_2), 7.19–7.33 (m, 4H, Ar—H), 3.89–3.90 (q, 2H, OCH_2), 3.17 (t, 4H, CH_2NCH_2), 2.41 (s, 3H, CH_3), 1.79 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.19–1.25 (m, 2H, CH_2), 0.84 (t, 3H, CH_3). Elemental analysis calculated for $C_{21}H_{24}ClN_3O_2S$ (%): C, 60.35; H, 5.79; N, 10.05; S, 7.67. Found (%): C, 60.28; H, 5.68; N, 10.09; S, 7.33.

*2.8.4. Piperidinium 3-cyano-5-ethoxycarbonyl-6-methyl-4-styrylpyridine-2-thiolate (**8**)*

It is obtained using compound **2c** and piperidine in the above general procedure. Yield: 83%, mp: 241–243 °C. IR (ν) (KBr), cm^{-1}: 3430, 2507, 2410 (N^+H_2), 2947 (C—H, aliphatic), 2211 (C≡N), 1728 (C═O). ^{1}H NMR ($CDCl_3$) δ: 7.49 (m, 4H, CH═CH and Ar—H), 7.35–7.37 (m, 3H, Ar-H), 7.13 (s, 2H, N^+H_2) 4.30–4.32 (q, 2H, OCH_2), 3.26 (m, 4H, CH_2NCH_2), 2.43 (s, 3H, CH_3), 1.86 (m, 4H, $2CH_2$), 1.66 (m, 2H, CH_2), 1.28 (t, 3H, CH_3). Elemental analysis calculated for $C_{23}H_{27}N_3O_2S$ (%): C, 67.45; H, 6.65; N, 10.26; S, 7.83. Found (%): C, 67.39; H, 6.37; N, 10.00; S, 7.66.

*2.8.5. Piperidinium 3-cyano-5-ethoxycarbonyl-4-(4′-methoxyphenyl)-6-phenylpyridine-2-thiolate (**9**)*

It is obtained using compound **3a** and piperidine in the above general procedure. Yield: 83%. mp: 257–259 °C. IR (ν) (KBr), cm^{-1}: 3415, 2440, 2350 (N^+H_2), 2952 (C—H, aliphatic), 2213

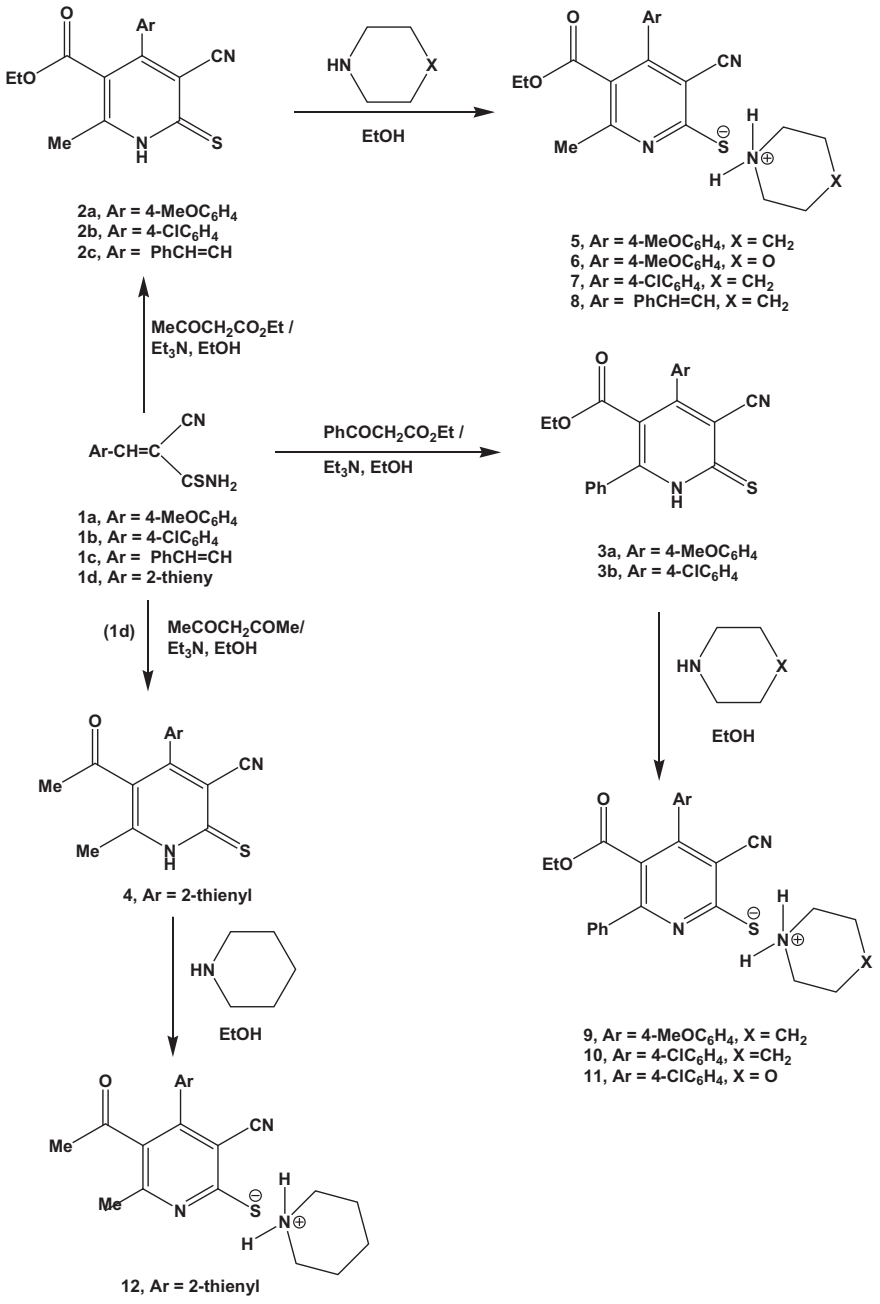
(C≡N), 1724 (C═O). ^{1}H NMR ($CDCl_3$) δ: 7.40 (br. s, 2H, Ar—H), 7.32 (br. s, 3H, Ar—H), 7.25–7.26 (d, 2H, Ar—H), 7.19 (br s, 2H, N^+H_2), 6.87–6.89 (d, 2H, Ar—H), 3.76 (s, 3H, OCH_3), 3.71–3.72 (q, 2H, OCH_2), 2.83 (t, 4H, CH_2NCH_2), 1.46 (p, 4H, $2CH_2$), 1.34 (p, 2H, CH_2), 0.70 (t, 3H, CH_3). Elemental analysis calculated for $C_{27}H_{29}N_3O_3S$ (%): C, 68.18; H, 6.15; N, 8.84; S, 6.74. Found (%): C, 68.22; H, 6.46; N, 8.69; S, 6.51.

*2.8.6. Piperidinium 4-(4′-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-phenylpyridine-2-thiolate (**10**)*

It is obtained using compound **3b** and piperidine in the above general procedure. Yield: 80%. mp: 219–221 °C. IR (ν) (KBr), cm^{-1}: 3420, 2480, 2400 (N^+H_2), 2952 (C—H, aliphatic), 2215 (C≡N), 1726 (C═O). ^{1}H NMR ($CDCl_3$): δ 7.20–7.33 (m, 11H, N^+H_2 and Ar—H), 3.70–3.71 (q, 2H, OCH_2), 2.86 (t, 4H, $CH_2N^+CH_2$), 1.35–1.37 (m, 4H, $2CH_2$), 1.18 (m, 2H, CH_2), 0.69 (t, 3H, CH_3). Elemental analysis calculated for $C_{26}H_{26}ClN_3O_2S$ (%): C, 65.06; H, 5.46; N, 8.75; S, 6.68. Found (%): C, 64.78; H, 5.22; N, 8.51; S, 6.92.

*2.8.7. Morpholinium 4-(4′-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-phenylpyridine-2-thiolate (**11**)*

It is obtained using compound **3b** and morpholine in the above general procedure. Yield: 88%. mp: 241–243 °C. IR (ν) (KBr), cm^{-1}: 3420, 2485, 2400 (N^+H_2), 2215 (C≡N), 1716 (C═O).

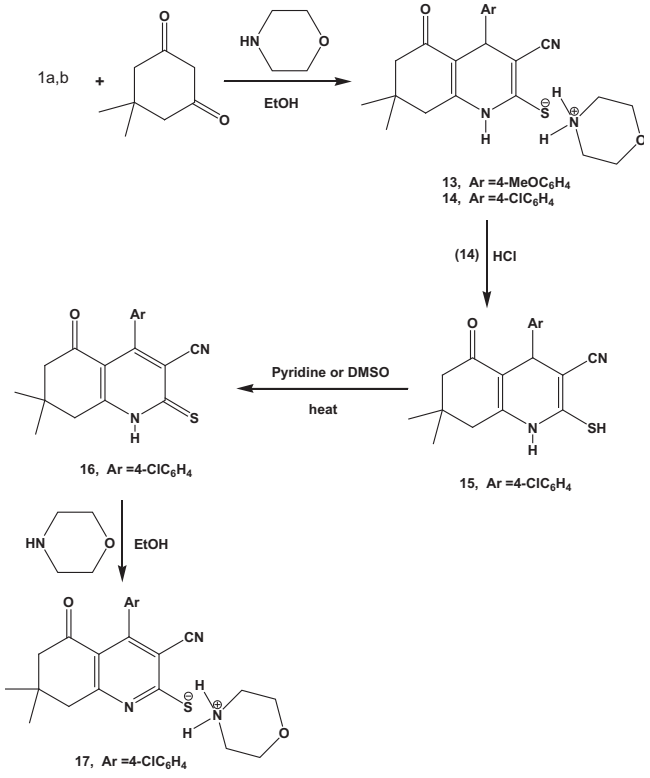


Scheme 1

^{1}H NMR ($CDCl_3$): δ 7.28–7.52 (m, 11H, N^+H_2 and Ar—H), 3.69–3.83 (m, 6H, OCH_2 and CH_2OCH_2), 3.06–3.07 (m, 4H, $CH_2N^+CH_2$), 0.81 (t, 3H, CH_3). Elemental analysis calculated for $C_{25}H_{24}ClN_3O_3S$ (%): C, 62.30; H, 5.02; N, 8.72; S, 6.65. Found (%): C, 62.71; H, 5.13; N, 8.80; S, 6.79.

*2.8.8. Piperidinium 5-acetyl-3-cyano-6-methyl-4-(2′-thienyl) pyridine-2-thiolate (**12**)*

It is obtained using compound **4** and piperidine in the above general procedure. Yield: 81%, mp: 121–123 °C. IR (ν) (KBr), cm^{-1}: 3399, 2521, 2433 (N^+H_2), 2979 (C—H, aliphatic), 2211 (C≡N), 1687 (C=O). ^{1}H NMR ($CDCl_3$) δ: 7.53 (s, 1H, CH thienyl), 7.22 (s, 1H, CH thienyl), 7.14 (s, 1H, CH thienyl), 4.87 (br. s, 2H, N^+H_2), 3.29 (t, 4H, $CH_2N^+CH_2$), 2.37 (s, 3H, CH_3), 1.89–1.92 (m, 7H, $2CH_2$ and CH_3), 1.68 (m, 2H, CH_2). Elemental analysis calculated for $C_{18}H_{21}N_3OS_2$ (%): C, 60.14; H, 5.89; N, 11.69; S, 17.84. Found (%): C, 60.45; H, 5.72; N, 11.27; S, 18.11.



Scheme 2

*2.8.9. Morpholinium 4-(4′-chlorophenyl)-3-Cyano-7,7-dime thyl-5-oxo-5,6,7,8-tetrahydroquinoline-2-thiolate (**17**)*

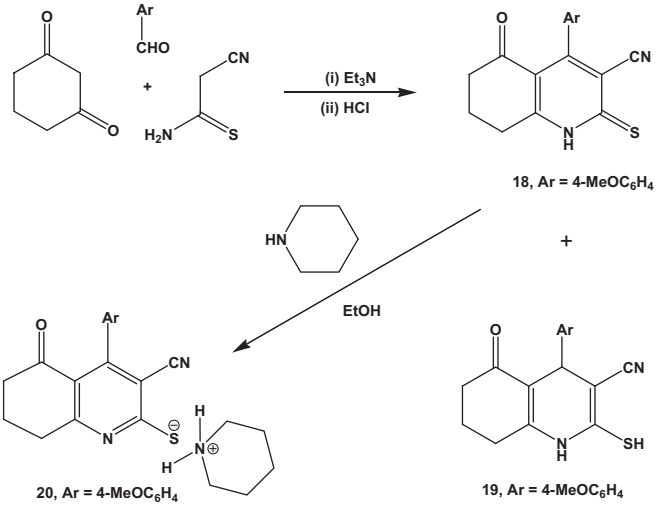
It is obtained using compound **16** and morpholine in the above general procedure. Yield: 81%. mp: 300–303 °C. IR (ν) (KBr), cm^{-1}: 3420 (NH), 2213 (C≡N), 1686 (C=O), 1593(C=N). ^{1}H NMR (DMSO-d_6): δ 8.10 (br. s, 2H, N^+H_2), 7.40–7.42 (d, J = 8.0 Hz, 2H, Ar—H), 7.11–7.13 (d, J = 8.0 Hz, 2H, Ar—H), 3.73 (s, 4H, CH_2OCH_2), 3.05 (s, 4H, $CH_2N^+CH_2$), 2.78 (s, 2H, CH_2, C-8), 2.26 (s, 2H, CH_2, C-6), 1.01 (s, 6H, $2CH_3$). Elemental analysis calculated for $C_{22}H_{24}ClN_3O_2S$ (%): C, 61.46; H, 5.63; N, 9.77; S, 7.46. Found (%): C, 61.78; H, 5.68; N, 9.69; S, 7.51.

*2.8.10. Piperidinium 3-cyano-4-(4′-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2-thiolate (**20**)*

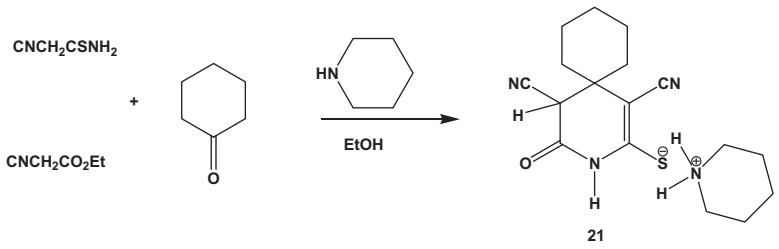
It is obtained using compound **18** and piperidine in the above general procedure. Yield: 89%. mp: 303–305 °C. IR (ν) (KBr), cm^{-1}: 3446, 2500, 2400 (N^+H_2), 2951(C—H, aliphatic), 2213 (C≡N), 1673 (C=O). ^{1}H NMR (DMSO-d_6): δ 8.20 (br. s, 2H, N^+H_2), 7.00–7.02 (d, J = 8.0 Hz, 2H, Ar—H), 6.88–6.90 (d, J = 8.0 Hz, 2H, Ar—H), 3.80 (s, 3H, OCH_3), 3.01–3.03 (t, J = 4.0 Hz, 4H, $CH_2N^+CH_2$), 2.81 (t, 2H, CH_2, C-8), 2.34 (t, 2H, CH_2, C-6), 1.94 (p, 2H, CH_2, C-7), a 1.50–1.65 (m, 6H, 3 CH_2 of piperidine ring). Elemental Analysis Calculated for $C_{22}H_{25}N_3O_2S$ (%): C, 66.81; H, 6.37; N, 10.62; S, 8.11. Found (%): C, 66.56; H, 6.12; N, 10.50; S, 8.09.

*2.9. Synthetic procedure for piperidinium 3,5-dicyano-4-cyclohexanespiro-5-oxo-1,2,3,4-tetrahydropyridine-2-thiolate (**21**)*

To a mixture of cyclohexanone (1.0 ml, 10 mmol), cyanothioacetamide (1.0 g, 10 mmol), ethyl cyanoacetate (1.06 ml,



Scheme 3



Scheme 4

Table 1 Insecticidal activity of acetamiprid, and compounds **5–14**, **17**, **20** and **21** against the nymphs of cowpea aphid, *A. craccivora*, after 24 and 48 h of Treatment.

24 h after treatment				48 h after treatment		
Compd.	Slope ± SE	LC_{50} (ppm)	Toxicity ratio	Slope ± SE	LC_{50} (ppm)	Toxicity ratio
Aceta-miprid	0.24 ± 0.02	0.023	1	0.36 ± 0.03	0.003	1
5	0.24 ± 0.03	0.203	0.113	0.28 ± 0.03	0.016	0.188
6	0.28 ± 0.02	0.077	0.298	0.32 ± 0.03	0.008	0.375
7	0.21 ± 0.02	1.221	0.019	0.28 ± 0.02	0.071	0.042
8	0.24 ± 0.02	0.465	0.046	0.25 ± 0.02	0.031	0.096
9	0.27 ± 0.03	0.121	0.190	0.29 ± 0.03	0.011	0.273
10	0.23 ± 0.02	0.493	0.047	0.27 ± 0.02	0.034	0.088
11	0.27 ± 0.02	0.099	0.232	0.28 ± 0.02	0.008	0.375
12	0.27 ± 0.02	0.071	0.324	0.28 ± 0.03	0.006	0.500
13	0.38 ± 0.03	0.041	0.561	0.52 ± 0.04	0.002	1.500
14	0.33 ± 0.02	0.045	0.511	0.45 ± 0.04	0.003	1.000
17	0.32 ± 0.03	0.059	0.390	0.43 ± 0.04	0.004	0.750
20	0.35 ± 0.03	0.036	0.639	0.49 ± 0.04	0.002	1.500
21	0.28 ± 0.03	0.126	0.183	0.31 ± 0.03	0.009	0.333

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

10 mmol) in ethanol (15 ml), 1.0 ml (10 mmol) of piperidine was added. The reaction mixture was stirred at room temperature for 2 h. The resulting precipitate was filtered off and recrystallized from ethanol as white needles of compound **21**. Yield: 70%. mp: 182–184 °C (literature value of 183–185 °C) [11]. IR (ν) (KBr) cm^{-1}: 3300, 2503, 2409 (NH, N^+H_2), 2931 (CH— aliphatic), 2255, 2181 (two C≡N), 1682 (C═O). ^1H NMR ($CDCl_3$): δ 8.62 (br. s, 1H, NH), 8.29 (br. s, 2H, N^+H_2), 3.66 (s, 1H, $C_{(5)}H$), 3.23 (t, 4H, $CH_2N^+CH_2$), 1.36–1.81 (m, 16H, $8CH_2$). Elemental Analysis Calculated for $C_{17}H_{24}N_4OS$ (%): C, 61.41; H, 7.28; N, 16.85; S, 9.64. Found (%): C, 61.12; H, 6.96; N, 16.49; S, 9.50 %.

2.10. Laboratory bioassay

The insecticidal activities of the title compounds against nymphs and adults of cowpea aphid were tested by leaf dip bioassay method [12]. Reported here are the results of laboratory tests to determine the concentration of these chemical compounds that is required to kill 50% (LC_{50}) of nymphs and adults with a modification in the toxicity tests. Six concentrations of aqueous solution of each compound plus 0.1% Triton X-100 as a surfactant were used. A total of 20 apterous adults and 20 nymphs, approximately of 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 the treated batches of aphids had dried, they were individually transferred to Petri dishes (9 cm diameter) and held for 24 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 with a binocular microscope. An aphid was considered dead if it was incapable of coordinated forward movement. The toxicity experiment of each compound was repeated twice and the results were corrected by Abbott's formula [13]. Median lethal concentrations (LC_{50}) and slope values of chemical compounds were determined by the Probit regression analysis programme and expressed in parts per million (ppm) [14].

3. Results and discussion

3.1. Chemistry

Our approach to the synthesis of the target compounds started from the famous reagent, cyanothioacetamide which upon condensation with some aldehydes yielded β-substituted-α-thio carbamoylacrylonitriles (**1a**–**d**) [8].

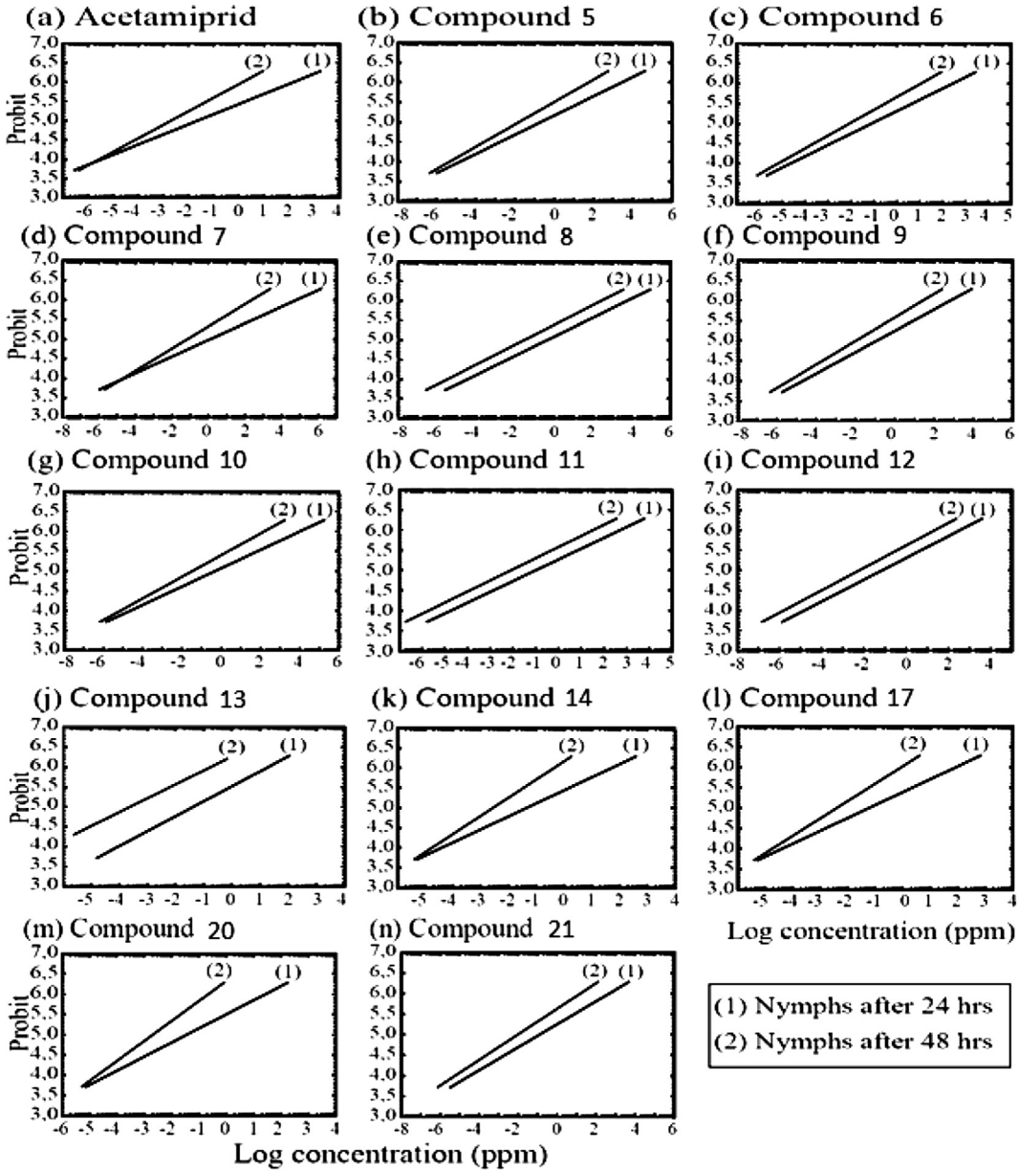


Figure 1 Insecticidal activities of acetamiprid, and compounds **5**–**14**, **17**, **20** and **21** against the nymphs of cowpea aphid, *A. craccivora*, after 24 and 48 h of treatment.

Treatment of **1a**–**c** with ethyl acetoacetate by refluxing in ethanol containing catalytic amount of triethylamine furnished 4-aryl or styryl-5-ethoxycarbonyl-3-cyano-6-methylpyridine-2-(1*H*)-thiones **2a**–**c**. Also, compounds **1a**,**b** were reacted with ethyl benzoylacetate to give the corresponding 6-phenyl analogues **3a**,**b**. In the same manner, reaction of **1d** with acetylacetone under the above conditions provided 5-acetyl-3-cyano-6-methyl-4-(2-thienyl)pyridine-2(1*H*)-thione (**4**) (Scheme 1). The acidic character of compounds **2a–c**, **3a**,**b** and **4** was tested via treatment with equimolar amount of piperidine or morpholine in boiling ethanol wherein the corresponding quaternary ammonium salts, piperidinium or morpholinium trisubstituted 3-cyanopyridine-2-thiolate derivatives **5**–**8**, **9**–**11** and **12** were isolated in good yields (Scheme 1).

The reaction of **1a** or **1b** with 5,5-dimethylcyclohexane-1,3-dione (dimedone) in the presence of equimolar amount of morpholine gave the corresponding morpholinium hexahydroquinoline-2-thiolate derivative **13** or **14**. The latter compound (**14**) was converted into the corresponding hexahydroquinoline-2-thiol **15** upon acidification with dilute HCl (10%). Dehydrogenation of compound 15 to give tetrahydroquinoline-2(1*H*)-thione **16** was achieved by heating in pyridine [15] or DMSO [16]. The interaction of thione **16** with morpholine in boiling ethanol resulted in the formation of the expected morpholinium salt **17** (Scheme 2).

Ternary condensation of cyanothioacetamide, 4-anisaldehyde and cyclohexane-1,3-dione in the presence of triethylamine produced a mixture of 3-cyano-4-(4′-methoxyphenyl)-

Table 2 Insecticidal activity of acetamiprid, and compounds **5–14**, **17**, **20** and **21** against the adults of cowpea aphid, *A. craccivora*, after 24 and 48 h of treatment.

24 h after treatment				48 h after treatment		
Compd.	Slope ± SE	LC_{50} (ppm)	Toxicity ratio	Slope ± SE	LC_{50} (ppm)	Toxicity ratio
Aceta- miprid	0.24 ± 0.03	0.078	1	0.28 ± 0.03	0.015	1
5	0.21 ± 0.03	4.791	0.016	0.24 ± 0.03	0.063	0.238
6	0.27 ± 0.03	0.988	0.079	0.29 ± 0.03	0.076	0.197
7	0.19 ± 0.02	23.541	0.003	0.22 ± 0.02	0.871	0.017
8	0.24 ± 0.03	1.330	0.059	0.24 ± 0.03	0.154	0.097
9	0.21 ± 0.03	0.121	0.645	0.25 ± 0.03	0.045	0.333
10	0.20 ± 0.03	13.032	0.006	0.21 ± 0.03	0.191	0.079
11	0.22 ± 0.03	0.483	0.161	0.24 ± 0.03	0.025	0.600
12	0.27 ± 0.03	0.624	0.125	0.26 ± 0.03	0.033	0.455
13	0.32 ± 0.03	0.173	0.451	0.35 ± 0.03	0.011	1.364
14	0.31 ± 0.03	0.174	0.448	0.34 ± 0.03	0.013	1.154
17	0.29 ± 0.03	0.255	0.306	0.30 ± 0.03	0.024	0.625
20	0.35 ± 0.03	0.160	0.488	0.38 ± 0.03	0.015	1.000
21	0.40 ± 0.04	0.575	0.136	0.28 ± 0.03	0.029	0.517

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

5-oxo-5,6,7,8-terahydroquinoline-2(1*H*)-thione (**18**) and 3-cyano-4-(4′-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexa-hydroquinoline-2-thiol (**19**). Heating compound **18** with piperidine in ethanol furnished piperidinium 3-cyano-4-(4′-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline-2(1*H*)-thiolate (**20**) (Scheme 3).

In contrast, ternary condensation of cyanothioacetamide with cyclohexanone and ethyl cyanoacetate in the presence of molar quantity of piperidine furnished the spiro compound **21** (Scheme 4).

The structure of all newly synthesized compounds were elucidated and confirmed on the basis of their elemental analyses and spectroscopic data. The results of elemental analyses were found to be in good agreement with the calculated values. The spectral data of all prepared compounds were in accordance with their proposed structures.

3.2. Insecticidal activity

3.2.1. Toxicity test for the cowpea aphid nymphs

Insecticidal activities of the tested compounds against the nymphs of cowpea aphid are given in Table 1 and Fig. 1. It is found that all compounds showed a high to low toxicity after a 24 h treatment with LC_{50} values that ranged from 0.036 to 1.221 ppm, whereas that of acetamiprid was 0.023 ppm. All compounds showed very strong to weak insecticidal activities against nymphs of cowpea aphid since some of them were as active as or more so than acetamiprid after 48 h of treatment. For example, the LC_{50} values of compounds **12**, **13**, **14**, **17** and **20** were 0.006, 0.002, 0.003, 0.004 and 0.002 ppm respectively, and that of acetamiprid was 0.003 ppm. It is interesting to note that the insecticidal activities of the tested compounds against the nymphs of cowpea aphid after both 24 h and 48 h of treatment obey the following smooth order: **20** > **13** > **14** (acetamiprid) > **17** > **12** > **6** > **11** > **9** (**21**) > **21** (**9**) > **5** > **10** (**8**) > **8** (**10**) > **7**.

3.2.2. Toxicity test for the cowpea aphid adults

Insecticidal activities of the tested compounds against the adults of cowpea aphid are shown in Table 2 and Fig. 2. The bioassay results revealed that all tested compounds possess strong to weak aphidicidal activity after a 24 h treatment with LC_{50} values that ranged from 23.541 to 0.121 ppm, whereas that of acetamiprid was 0.078 ppm. Compounds **9**, **13**, **14**, **17** and **20** showed the highest activity with LC_{50} values of 0.121, 0.173, 0.174, 0.255 and 0.160 ppm respectively. After a 48 h treatment, the insecticidal activity of the titled compounds against the adults of cowpea aphid had been strongly increased. Thus, compounds **13** and **14** showed higher activity than that of acetamiprid itself since their LC_{50} values became 0.011 and 0.013 ppm respectively, whilst that of acetamiprid is 0.015 ppm. Compound **20** exhibited the same toxicity index of acetamiprid. Compounds **9**, **11**, **12**, **17** and **21** showed good activity with LC_{50} values of 0.045, 0.025, 0.033, 0.024 and 0.029 ppm respectively.

3.2.3. Structure-action relationship

According to the general framework structure, it appeared that the tetrahydroquinolines **17**, **20** and hexahydroquinolines **13**, **14** are more active, against cowpea aphid, than pyridine moiety-containing compounds **5**–**12**. Both compounds **13** and **20** which possess the highest insecticidal activity contain 4-methoxyphenyl moiety and cyclohexene ring in their structure beside the other common features of all compounds. The insecticidal activity of hexahydroquinoline derivative **14** is more than that of tetrahydro analogue **17**, this may be due to the presence of extra two active sites at positions 1 and 4 in the structure of compound **14**. Compounds with 4-methoxyphenyl moiety such as **5**, **9** and **13** possess higher insecticidal activity than those containing 4-chlorophenyl one in their structure **7**, **11** and **14** respectively. This fact is consistent with that reported in our previous paper [7]. Pyridine derivatives with

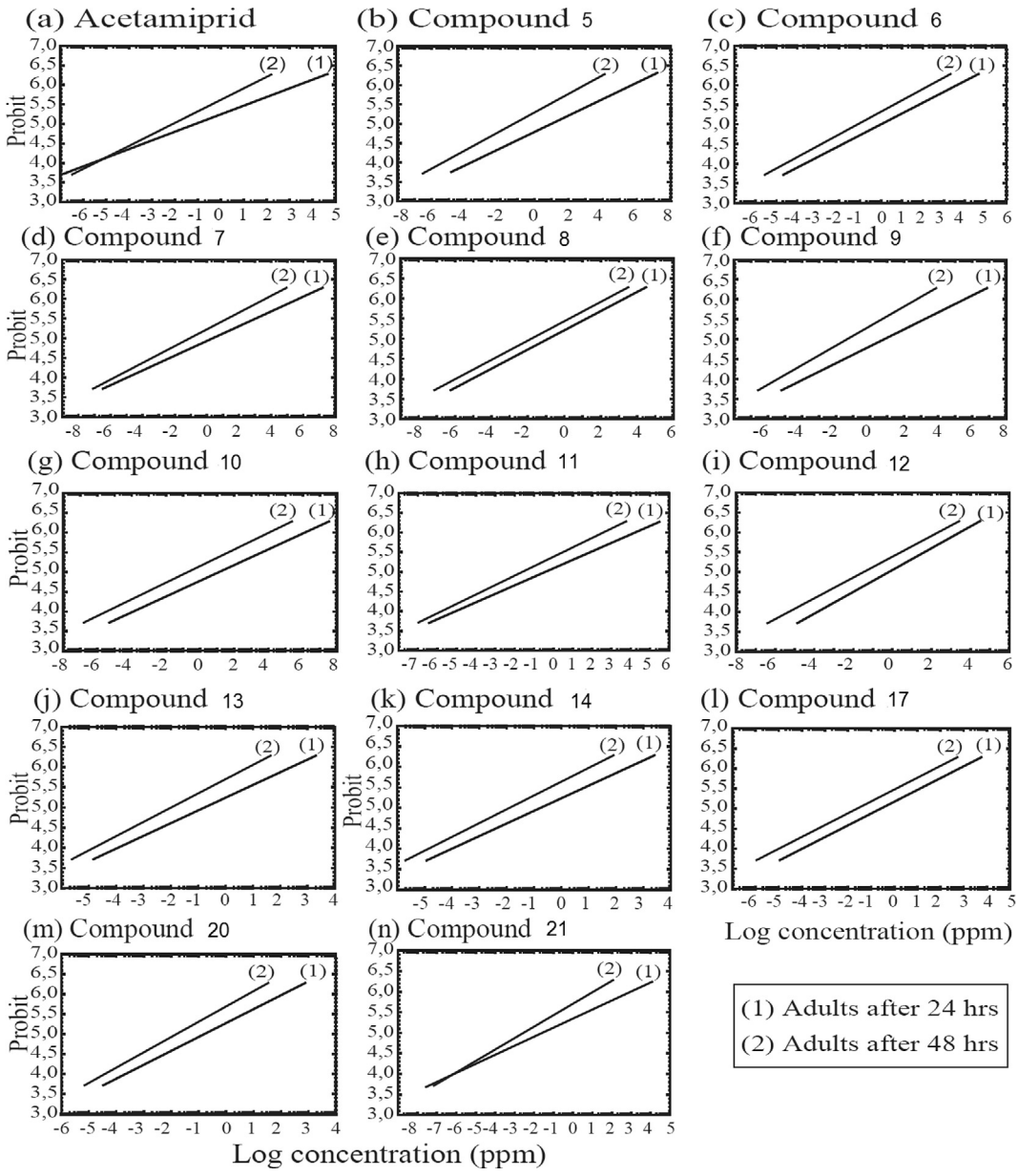


Figure 2 Insecticidal activities of acetamiprid, and compounds **5**–**14**, **17**, **20** and **21** against the adults of cowpea aphid, *A. craccivora*, after 24 and 48 h of treatment.

phenyl group at position 6 (**9** and **10**) are more active than the corresponding 6-methyl analogues (**5** and **7**). Finally, the insecticidal activity of morpholinium salts (**6** and **11**) is higher than that of the related piperidinium ones (**5** and **10**).

4. Conclusion

In the present work, we have successfully synthesized and characterized a new series of water-soluble compounds, piperidinium and morpholinium 3-cyanopyridinethiolates **5**–**14**, **17**, **20** and **21**. These compounds were screened for their insecticidal activities against cowpea aphids, *A. craccivora*. Compounds **13**, **14** and **20** proved to be promising insecticidal agents since they showed higher activities than those of acetamiprid insecticide itself.

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