

Novel *N*-cyanoguanidyl derivatives: Synthesis and studying their toxicological activity against *Spodoptera littoralis* and *Schizaphisgraminum*

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ABSTRACT

Reaction of *N*-cyanoguanidine with acid chlorides and aroyl isothiocyanates gave the respective; *N*-(*N*-cyanocarbamimidoyl)aryl-2-carboxamides **1-5** and *N*-[(*N*-cyanocarbamimidoyl)carbamothioyl]benzamides **6-10**, which have a Neonictinoid insecticide's active group moiety (=N-CN). They have more toxicological activity against wheat Aphid (*Schizaphisgraminum*) than *Spodoptera littoralis*.

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1. Introduction

Aphids are one of the major constraints of wheat production, by sucking the plant's cell sap, aphids reduce the wheat yield either directly (35-40%) or indirectly (20-80%) by transmitting fungal and viral diseases.¹

Egyptian cotton leafworm (*S. littoralis*) (Boisduval, 1833) is a member of the cutworm family (Noctuidae) and is one of the major economic pests of cotton in Egypt that causes considerable damage to many other vegetables and crops.^{2,3}

In the beginning of 1990s, a new Neonicotinoid group (e.g., imidacloprid, acetamiprid, thiacloprid, dinotefuran, thiamethoxam, and clothianidin) (**Fig. 1**) known as insecticides.^{4,5}

Neonicotinoids have become the fastest-growing insecticide class since the commercialization of pyrethroids, carbamate and organophosphates (OP) insecticides.⁶ They exhibit physicochemical properties, rendering them more useful over other classes of insecticides⁷. They having a wide range of application techniques (e.g., foliar, seed treatment, soil drench and stem applications) and easy in controlling biting and sucking insects (i.e., leaf miners, beetle, whiteflies, trips and lepidopteran species).⁷

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The structural fragment $C=N-C\equiv N$ group in cyanoiminodihydropyrimidines was synthesized via the reaction of cyanoguanidine with dimethyl cyanoimidodithiocarbonate, diphenyl cyanoimidocarbonate, acrylic acids, dicarbonyl compounds, malononitrile and aromatic aldehydes, chalcone or bis(methylthio)methylene malononitrile with amines.⁸⁻¹⁴

The important of synthetic organic compounds as effective biological activities in different fields was previously reported.¹⁵⁻²⁵ Also, it was found that, cyanoguanidine is the suitable reagent to prepare compounds containing cyanoimino or cynoguanidyl moiety.¹¹⁻¹⁴ Thus, here in this work, we aimed to react cyanoguanidine with different acid chlorides and/or isothiocyanates to afford new neonicotinoids analogues.

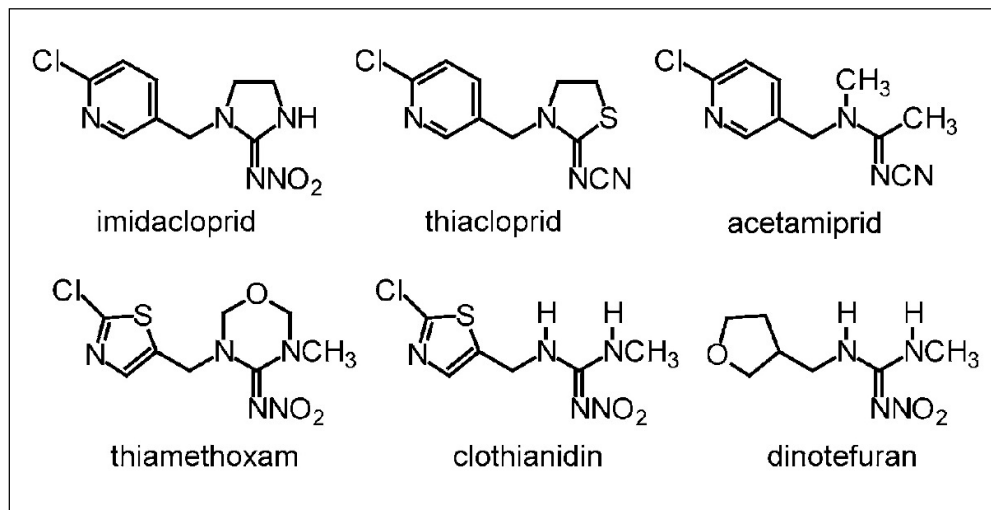


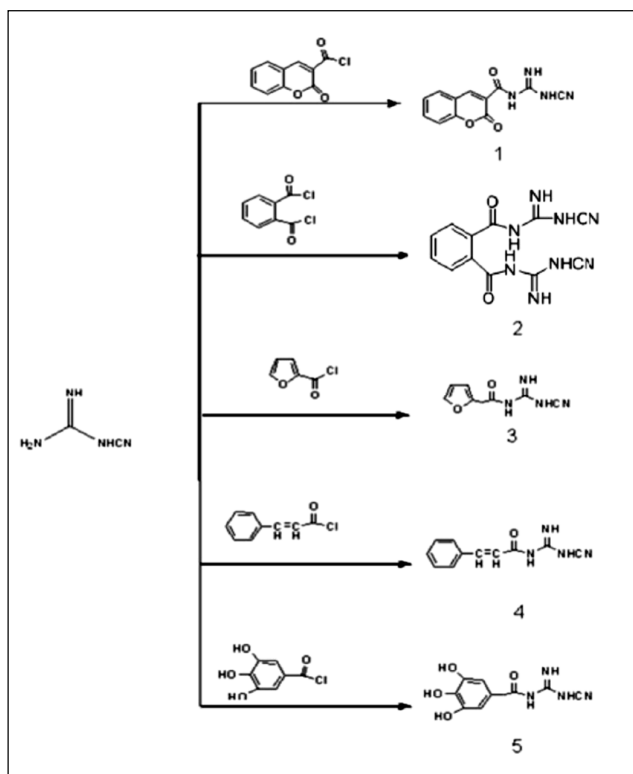
Fig. 1. Group of neonicotinoid insecticides.

2. Results and Discussion

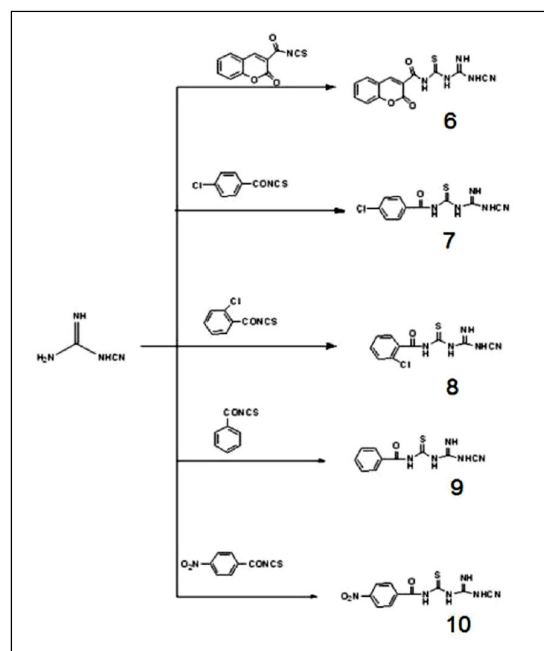
2.1 Chemistry

Treatment of cyanoguanidine with chromene-3-oyl chloride, phthaloyl dichloride, furyl chloride, 3-phenylprop-2-enoyl chloride and 3,4,5-trihydroxybenzoyl chloride in dry acetone and drops of pyridine afforded; N-(N-cyanocarbamimidoyl)-2-oxo-2H-chromene-3-carboxamide (**1**), N,N'-bis(N-cyanocarbamimidoyl)benzene-1,2-dicarboxamide (**2**), N-(N-cyanocarbamimidoyl) furan-2-carboxamide (**3**), N-(N-cyanocarbamimidoyl)-3-phenylprop-2-enamide (**4**) and N-(N-cyanocarbamimidoyl)-3,4,5-trihydroxybenzamide (**5**), respectively (**Scheme 1**). Their IR spectra showed the following absorption bands corresponding to 3329 – 3100 (NH), 3059 (CH_{arom}) and 2195 (CN). 1H -NMR spectrum of compound **1** (δ ppm) showed the following signals: 7.93-7.40 (m, 5H, CH_{arom}) and 3.85 (s, 3H, $NH_{\text{exch.}}$). Its ^{13}C NMR spectrum showed new signals corresponding to C=O group 159, (C=N) 158, (CN) 116 and other aromatic C-H carbons (cf. experimental).

Cyanoguanidine was reacted with chromene-3-oylisothiocyanate,²⁶ 4-chlorobenzoylisothiocyanate, 2-chlorobenzoylisothiocyanate, benzoylisothiocyanate and 4-nitrobenzoylisothiocyanate²⁷ to yield; N-[(N-cyanocarbamimidoyl)carbamothioyl]-2-oxo-2H-chromene-3-carboxamide (**6**), 4-chloro-N-[(N-cyanocarbamimidoyl)carbamothioyl]benzamide (**7**), 2-chloro-N-[(N-cyanocarbamimidoyl)carbamothioyl]benzamide (**8**), N-[(N-cyanocarbamimidoyl)carbamothioyl]benzamide (**9**) and N-[(N-cyanocarbamimidoyl)carbamothioyl]-4-nitrobenzamide (**10**) (**Scheme 2**). Their IR spectra showed the following absorption bands corresponding to 3344 - 3100 (N-H), 3089 (CH_{arom}), 2173 (CN). 1H -NMR spectrum of compound **6** (δ ppm) showed the following signals: 12.06 (s, 1H, N-H $_{\text{exch.}}$), 8.02-7.47 (m, 5H, CH_{arom}), 4.1 (s, 3H, N-H $_{\text{exch.}}$).



Scheme 1. Synthesis of compounds 1-5.



Scheme 2. Synthesis of compounds 6-10.

2.2 Toxicity test

2.2.1 Wheat Aphid (*Schizaphisgraminum*)

Toxicity test for the Wingless *Schizaphisgraminum*, revealed compound **6** is the most effective, giving LC_{50} value (**0.81 ppm.**), while, compounds **1 – 3** and **7- 10** showed the LC_{50} values (**6.7, 16.99, 9.04, 3.47, 2.79, 13.89** and **3.19 ppm.**), respectively (**Table 1**).

Table 1. Toxicity effect of compounds **1-3** and **6-10** against Wingless *Schizaphisgraminum*

Compd	LC_{25} (ppm)	LC_{50} (ppm)	Toxicity index	Slop
1	0.03	6.70	8.27	0.2876 +/- 0.1899
2	1.14	16.99	20.97	0.5766 +/- 0.7440
3	0.52	9.04	11.16	0.5443 +/- 0.5988
6	0.01	0.81	1	0.3729 +/- 0.1202
7	0.04	3.47	4.28	0.3625 +/- 0.2242
8	0.02	2.79	3.44	0.3105 +/- 0.1282
9	1.16	13.89	17.14	0.6256 +/- 0.7750
10	0.04	3.19	3.93	0.2332 +/- 0.6885

2.2.2 *S.littoralis*.

Toxicity test for the 4th instar larvae of the cotton leaf worm *S. littoralis* (Boisd.), revealed compound **6** is the most effective compound, giving LC_{50} value (153.42 ppm.), while, compounds **1 – 3** and **7 – 10** showed the LC_{50} values (633.31, 333.53, 363.55, 284.75, 451.73, 413.21 and 269.46 ppm.), respectively (**Table 2**).

Table 2. Toxicity of compounds **1-3** and **6-10** against 4th instar of *S. littoralis*

<i>Comp</i>	<i>LC25(ppm)</i>	<i>LC50 (ppm)</i>	<i>Toxicity index</i>	<i>Slop</i>
1	16.02	633.31	4.12	0.4224 +/- 0.3435
2	93.92	333.53	2.17	1.2196 +/- 0.433
3	83.92	363.55	2.36	1.0592 +/- 0.474
6	11.84	153.42	1	0.6063 +/- 0.1905
7	5.78	284.75	1.85	0.3986 +/- 0.2444
8	5.02	451.73	2.94	0.3449 +/- 0.1998
9	158.69	413.21	2.69	1.6229 +/- 0.4864
10	96.56	269.46	1.75	1.5713 +/- 0.4934

It was shown that, compound **6** is the most effective with LC₅₀ (**0.81**) on Aphids (*Schizaphisgraminum*) and LC₅₀ (**153.42**) on *S. littoralis*, beside that all compounds are most effective against Aphids (*Schizaphisgraminum*) more than *s. littoralis* that mean these compounds more efficient on sucking pest (**Tables 1,2**).

3. Experimental

3.1 Materials and methods

Melting points are uncorrected and were determined by Kofeler melting point apparatus. IR (cm⁻¹) spectra were listed (KBr disc) on a Shimadzu DR-8001 spectrophotometer. ¹HNMR and ¹³CNMR (DMSO-*d*₆) spectra were listed at 400 and 100 MHz on a Varian Gemini NMR spectrometer, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference. Elemental analyses were carried out on a Perkin-Elmer 240°C Micro analyzer.

3.2 Synthesis of Compounds 1-5.

General Procedure: A mixture of cyanoguanidine (0.84 g, 0.01mol) and an appropriate acid chloride (0.01 mol): chromene-3-oyl chloride (2 g), phthloyl dichloride (2 g), furyl chloride (1 g), 3-phenylprop-2-enoyl chloride (1.6 g) or 3,4,5-trihydroxybenzoyl chloride (1.1 g) in acetone (30 ml) and drops of pyridine was refluxed for 2-3 hrs.(TLC).The reaction mixture was evaporated, the obtained precipitate was collected, treated with water, filtered of, dried and crystallization from ethanol (**Scheme 1**).

3.2.1 *N-(N-Cyanocarbamimidoyl)-2-oxo-2H-chromene-3-carboxamide (1)*.

White solid (81% yield), mp. 247-250 °C; IR (ν, cm⁻¹): 3322 (N-H), 3059 (CH_{arom}), 2195 (CN), 1739 (C=O_{coumarin}), 1664 (C=O). ¹H NMR (δ, ppm): 8.77 (s, 1H, CH_{coumarin}), 7.93-7.40 (m, 4H, CH_{arom}), 3.85 (s, 3H, NH_{exch.}). ¹³C NMR: 165 (C=O), 159 (C=O), 158 (C=N), 149(C-O), other aromatic C-H carbons at 134, 130, 125, 118 and 116(CN),^s. Anal. *Data.* for C₁₂H₈N₄O₃ (256.21) Calcd/Found: C:56.20/56.35, H: 3.12/3.22 and N:24.97/24.77%.

3.2.2 *N,N'-Bis(N-cyanocarbamimidoyl)benzene-1,2-dicarboxamide (2)*.

White solid (73% yield), mp. 168-172 °C.; IR (ν-, cm⁻¹): 3396 (N-H), 3381 (N-H), 3087.31(CH_{arom}), 2208(CN), 1637(C=O). ¹H NMR (δ ppm): 6.53 (s, 4H, CH_{arom}), 4.31 (s, 2H, N-H_{exch}), 3.45 (s, 4H, N-H_{exch}), Anal. *Data.* For C₁₂H₁₀N₈O₂ (298.26) Calcd/Found: C:48.28/48.69, H: 3.35/3.18 and N:23.46/23.15.%.

3.2.3 *N*-(*N*-Cyanocarbamimidoyl)furan-2-carboxamide (3).

Brown solid (76% yield), mp. 184 °C.; IR (v-, cm⁻¹): 3322 (N-H), 3056(CH_{arom}), 2194(CN), 1638(C=O). ¹H NMR (δ ppm): 10.12 (s, 1H, N-H_{exch}), 8.21 (m, 3H, CH_{arom}), 7.19-7.14(m, 2H, NH_{exch}). Anal. Data For C₇H₆N₄O₂ (178.14) Calcd/Found: C: 47.15/47.63, H: 3.36/3.18 and N:31.43/31.11 %.

3.2.4 *N*-(*N*-Cyanocarbamimidoyl)-3-phenylprop-2-enamide (4).

Yellow solid (87% yield), mp. 196-198°C.; IR (v-, cm⁻¹): 3234 - 3104 (N-H), 3071(CH_{arom}), 2214(CN), 1646(C=O). ¹H NMR (δ ppm): 7.1-7.33(m, 5H, CH_{arom}), 6.40 (s, 1H, CH), 6.36 (s, 1H, CH), 3.42 (s, 3H, N-H_{exch}), Anal. Data For C₁₁H₁₀N₄O (214.2) Calcd/Found: C: 61.62/61.65, H: 4.66/4.48, and N:26.11/26.41 %

3.2.5 *N*-(*N*-Cyanocarbamimidoyl)-3,4,5-trihydroxybenzamide (5).

Browne solid (77% yield), mp. 194 °C.; IR (v-, cm⁻¹): 3218 (N-H), 3028(CH_{arom}), 2279(CN), 1664(C=O). ¹H NMR (δ ppm): 7.24 -7.15(s, 2H, CH_{arom}), 5.82 (s, 3H, OH_{exch}), 3.84 (s, 3H, N-H_{exch}), Anal. Data For C₉H₈N₄O₄ (236.18) Calcd/Found: C: 45.72/75.91, H: 3.38/3.11 and N:23.71/23.44 %.

3.3 Synthesis of Compounds 6-10.

General Procedure: A mixture of cyanoguanidine (1.2 g, 0.014 mol) and selected isothiocyanate reagent (0.01 mol): chromene-3-oyl isothiocyanate (2.3 g), benzoyl isothiocyanate (1.6 g), 4-chlorobenzoylisothiocyanate (1.9 g), 2-chloro-benzoylisothiocyanate (1.9 g) or 4-nitrobenzoylisothiocyanate (2 g) in acetone (30 ml) and drops of pyridine was refluxed for 2 hrs. (TLC). The formed precipitate was filtrated while hot, washed with water, dried and crystallized from ethanol (**Scheme 2**).

3.3.1 *N*-[(*N*-Cyanocarbamimidoyl)carbamoithioyl]-2-oxo-2*H*-chromene-3-carboxamide (6).

White solid (89% yield), mp. 226-228 °C.; IR (v-, cm⁻¹): 3328 (N-H), 3059 (CH_{arom}), 2195(CN), 1739 (C=O_{coumarin}), 1652 (C=O). ¹H NMR (δ ppm): 12.06 (s, 1H, N-H_{exch}) 8.87 (s, 1H, CH_{coumarin}), 8.02-7.46 (m, 4H, CH_{arom}), 4.1(s, 3H, N-H_{exch}). Anal. Data For C₁₃H₉N₅O₃S (315.30) Calcd/Found: C:49.47/49.19, H: 2.85/2.96, N:22.20/22.47, S: 10.14/11.02%.

3.3.2 4-Chloro-*N*-[(*N*-cyanocarbamimidoyl)carbamoithioyl]benzamide (7).

White solid (91% yield), mp.176-178 °C.; IR (v-, cm⁻¹): 3344 (N-H), 3011(CH_{arom}), 2173(CN), 1679 (C=O). ¹H NMR (δ ppm): 11.25 (s, 1H, N-H_{exch}), 7.96-7.04 (m, 4H, CH_{arom}), 3.86 (m, 3H, N-H_{exch}). Anal. Data For C₁₀H₈ClN₅OS (281.72) Calcd/Found: C:42.59/42.39, H: 2.83/2.98, N:24.84/24.77, S: 11.35/10.14%

3.3.3 2-Chloro-*N*-[(*N*-cyanocarbamimidoyl)carbamoithioyl]benzamide (8).

White solid (88% yield), mp. 228-232 °C.; IR (v-, cm⁻¹): 3326 (N-H), 3089 (CH_{arom}), 2202(CN), 1631(C=O). ¹H NMR (δ ppm): 7.62-7.29 (m, 6H, CH_{arom} + 2H, N-H_{exch}), 6.39 (s, 1H, N-H_{exch}), 3.47 (s, 1H, N-H_{exch}). Anal. Data For C₁₀H₈ClN₅OS (281.72) Calcd/Found: C:42.59/42.39, H: 2.83/2.98, N:24.84/24.77, S: 11.35/10.14%.

3.3.4 *N*-[(*N*-Cyanocarbamimidoyl)carbamoithioyl]benzamide (9).

White solid (78% yield), mp. 180-184 °C.; IR (v-, cm⁻¹): 3368 (N-H), 3325 (N-H), 3061 (CH_{arom}), 2125(CN), 1628(C=O). ¹H NMR (δ ppm): 10.25 (s, 1H, N-H_{exch}), 8.15(s, H, N-H_{exch}), 7.26-7.06 (m, 5H, CH_{arom}), 6.62 (s, 2H, N-H_{exch}). Anal. Data For C₁₀H₉N₅OS (247.27) Calcd/Found: C:48.52/48.91, H: 3.63/3.44, N:28.30/28.67, S: 12.94/13.24%.

3.3.5N-[(N-Cyanocarbamidoyl)carbamothioyl]-4-nitrobenzamide (10).

Brown crystal (86% yield), mp. 190-192 °C.; IR (ν -, cm^{-1}): 3346 (N-H), 3047 (CH_{arom}), 2235(CN), 1643(C=O). ^1H NMR (δ ppm): 9.62 (s, 1H, N-H_{exch}), 8.43-8.17 (m, 4H, CH_{arom}), 3.92(s, 3H, N-H_{exch}). Anal. Data For $\text{C}_{10}\text{H}_8\text{N}_6\text{O}_3\text{S}$ (292.27) Calcd/Found: C:41.05/41.35, H: 2.73/2.15 and N:28.74/28.46, S: 10.94/11.8%.

3.4. Laboratory bioassay wheat aphid (*Schizaphisgraminum*).

Toxicity of the title compounds was screened by leaf dip bioassay method,²⁸ results of laboratory screening to find out the concentrations of the target compounds which are demanded to kill 50% (LC_{50}) of Wheat aphids were declared here. Six concentrations of solution of each prepared compound were utilized. Wingless insects were immersed for ten seconds in every concentration three times. Insects which were treated were permitted to dry at RT for about 0.5 h. Control (Water+acetone) batches of used insects were also utilized. After the treated batches of insects had dried, they were moved to Petri dishes (9 cm diameter) and remained for 24 h at 22 ± 2 °C, $60 \pm 5\%$ relative humidity and photoperiod of 12:12 (light/ dark). With a binocular microscope the aphid mortality was counted after 24 h of test. The aphid that was unable to coordinate forward movement was considered dead. The insecticidal activity test of each compound was repeated two times and the obtained data were corrected by Abbott's formula.²⁹ By using a computerized Probit regression analysis program, median lethal concentrations (LC_{50}) and slope values of target compounds were computed and reported as parts per million (ppm).³⁰

3.5. laboratory bioassay(*S. littoralis*).

A series of concentrations (acetone) for each compound were prepared as the active ingredients based on ppm by diluting with water. Castor-bean leaves were dipped (Leaf-dipping technique corresponding to that described by Tabashnik.³¹ For 30 seconds in each concentration then left to dry for one hour. The 4th instars larvae tested were confined with treated leaves in glass jars covered with muslin for 24 hrs. Treated leaves were then removed and fresh untreated leaves provided. Three replicates (each of 20 larvae) were tested for each concentration. The average mortality percentage was corrected using Abbott's formula.²⁹ The corrected mortality percentage of each compound was statistically computed according to Finney, (1971). From which the corresponding concentration probit lines (ld-p lines) were estimated in addition to determining 50 and 90% mortalities, slope values of tested compounds were also estimated.

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