Synthesis and Insecticidal Activities of 1,5-Disubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines

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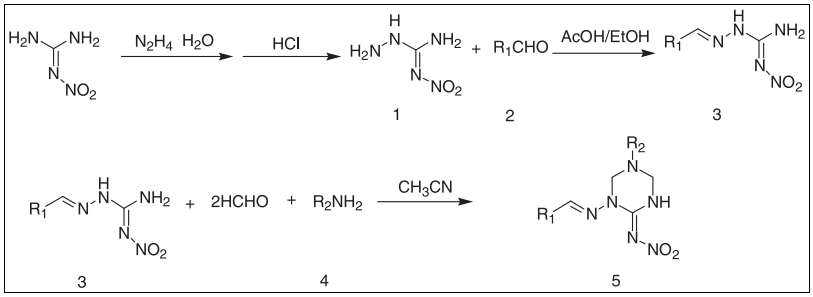

By extracting active moieties from typical insecticides and recombining to a same molecule, a series of novel title compounds were designed and synthesized as shown in Scheme 1. The structures of all compounds were confirmed by IR, ^{1}H NMR, MS, and elemental analysis. The preliminary bioassay showed that the partial target compounds gave 90% mortality against *Tetranychus cinnabarnus* at 500 mg/L.

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INTRODUCTION

Nitro hydrocarbylideneamino guanidine is of considerable pharmacological interest as a number of derivatives have shown outstanding insecticidal activities against *Myzus persicae* and *Aphis gossypii* [1].

Neonicotinoid insecticides represent the fastest-growing class of insecticides introduced to the market since the launch of pyrethroids. 6-Chloro-3-pyridylmethyl group and 2-tetrahydrofurfuryl group are structural segments of neonicotinoids [2–4].

Previous studies show that 1,5-disubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines have highly insecticidal activities. For example, 100% mortality was given against *Pseudaletia separate* Walker by 1-(2-chloro-5-thiazolylmethyl)-5-(3-pyridylmethyl)-1,3,5-hexahydrotriazine-2-*N*-nitroimine at 20 mg/L [5,6].

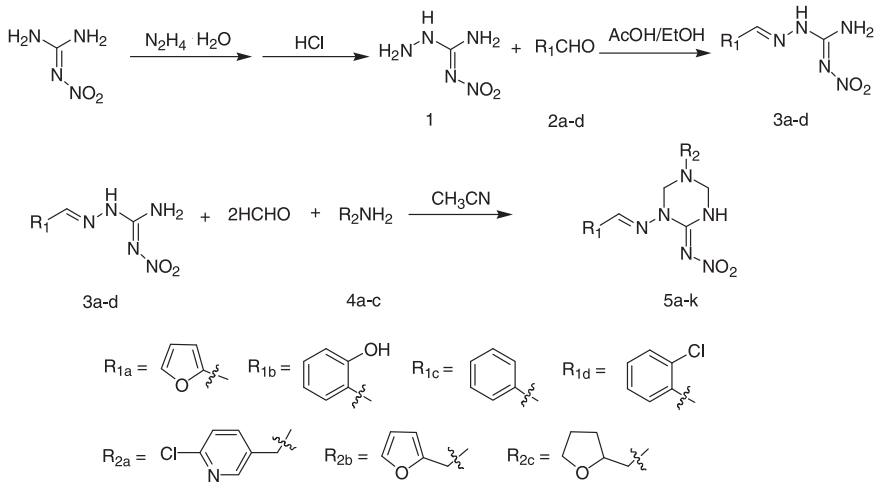
On the basis of above observations and obeying the principle of active-factor-addition, we synthesized a novel series of compounds for the purpose of obtaining the bioactive pesticide lead compounds *via* extracting active moieties from neonicotinoids and nitro hydrocarbylideneamino guanidine and recombining to a same molecule 1,5-disubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines by mannich reaction. The structures of all title compounds were confirmed by IR,^{1}H NMR, MS, and elemental analysis. The result of preliminary biological activity test showed that a majority of compounds had preferable insecticidal activity against *Tetranychus cinnabarnus*.

RESULTS AND DISCUSSION

Synthesis of compounds. The title compounds **5a–k** were synthesized by the method outlined in Scheme 1.

Insecticidal activity. The insecticidal activities of the title compounds **5a–k** were screened against *Tetranychus cinnabarnus* using the standard testing method [7] with a slight modification. Results of the *in vitro* insecticidal activities of compounds **5a–k** were summarized in Table 1. As indicated in Table 1, most of our synthesized compounds exhibited good insecticidal activities against *Tetranychus cinnabarnus* which had $>$ 70% mortality at 500 mg/L. Among them, the compounds **5a** and **5j** had the preferable insecticidal activity which gave $>$ 90% mortality against *Tetranychus cinnabarnus* at 500 mg/L. Other compounds' potential varied drastically, depending upon the types of the 1-position and 5-position substitution on 1,3,5-hexahydrotriazine. The introduction of 6-chloro-3-pyridyl methyl and 2-furyl methyl at the 5-position of 1,3,5-hexahydrotriazine showed preferable inhibitory activities. The appending 2-fururylamino at 1-position of 1,3,5-hexahydro-triazine also had conspicuous influence on their insecticide activities. In addition, the insecticidal activities of the synthesized compounds decreased in the order phenyl substituted with electron-withdrawing group $>$ phenyl $>$ phenyl substituted with electron-donating group introduced at 1-position. The observations herein corroborate our point of view that a heterocyclic methyl or phenyl with electron-withdrawing group introduced will increase the insecticidal activity of the compounds.

Scheme 1. Synthesis of title compounds **5a–k**.



EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates Merck KGaA. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using DMSO-d_6 as solvents and tetramethylsilane (TMS) as internal standard. The chemical shift (δ) values are expressed in parts per million (ppm) relative to tetramethylsilane as an internal standard: s = singlet, d = doublet, dd = double doublet, m = multiplet. Melting points were determined by an RK1 microscopic melting apparatus uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 instrument. IR spectra were obtained on a Nicolet 5DX FT-IR spectrophotometer in the region 4000–400 cm^{-1} using KBr discs. MS spectra were recorded on a Trace DSQ mass spectrograph.

The 2-chloro-5-(aminomethyl)pyridine was prepared according to the method from Ref.[[8]]. Unless otherwise noted, reagents and solvents were of analytical reagent grade or were chemically pure and used as received without further purification.

Nitroguanidine was converted to 1-amino-3 –nitroguanidine(**1**) in 35% yield as described in the literature [9].

General synthetic procedure for synthesis of 3a–d. Compound **1** (2.00 g, 0.017 mmol), glacial acetic acid (0.2 mL) were dissolved under heating in anhydrous ethanol (80 mL), which was added dropwise a solution of **2a** (1.79 g, 0.019 mmol) in anhydrous ethanol (5 mL). The reaction mixture was then heated at reflux for 2 h and cooled to room temperature. The product (**3a**) was separated out from the solution and then obtained by filtration. The product was washed three times with ethanol and dried at 50–60°C. Compound **3a** was given as brown power. Compounds **3b–d** were synthesized with the same method.

General synthetic procedure for synthesis of 5a–k. The mixture of 2-chloro-5-(aminomet-hyl)pyridine (1.45 g, 0.010 mol) and 37% formaldehyde (1.97 g, 0.024 mol) was gently stirred at room temperature for 0.5 h. A solution of **3a** (2.00 g, 0.010 mol) in acetonitrile (25 mL) was gently heated at 60°C till **3a** dissolved in acetonitrile, which was added previous mixture. Stirring was continued for 1h at 60°C. The reaction was

Table 1

Insecticidal activities of compounds **5a–k** against *Tetranychus cinnabarnus.*

			Concn (mg/L)[a]		
Compd	R_1	R_2	500	100	20
5a	2-furyl	6-Cl-Py-3-CH_2	+++++	+++	++
5b	2-furyl	2-furyl-CH_2	++++	+	–
5c	2-furyl	2-tetrahydrofuryl-CH_2	++++	++	–
5d	2-HO-C_6H_4	6-Cl-Py-3-CH_2	+++	+	n.t
5e	2-HO-C_6H_4	2-furyl-CH_2	++	–	n.t
5f	2-HO-C_6H_4	2-tetrahydrofuryl-CH_2	++	–	n.t
5g	C_6H_5	6-Cl-Py-3-CH_2	++++	++	+
5h	C_6H_5	2-furyl-CH_2	++++	++	–
5i	C_6H_5	2-tetrahydrofuryl-CH_2	+++	–	n.t
5j	2-Cl-C_6H_4	2-furyl-CH_2	+++++	+++	+
5k	2-Cl-C_6H_4	2-tetrahydrofuryl-CH_2	++++	++	–

[a]Rating system for the mortality percentage: ++++++, 100%; +++++, ≥ 90%; ++++, ≥ 80%; +++, ≥ 70%; ++, ≥ 60%; +, ≥ 50%; –, <50%; n.t means not tested.

monitored by TLC. The mixture was cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (v/v 1:2) to afford desired product **5a**. Compounds **5b–k** were synthesized with the same method.

1-(2-Furfurylideneamino)-5-(6-chloro-3-pyridylmethyl)-1,3,5-hexahydrotriazine-2-N-nitro-imine (5a). Yield: 63 %; m.p.: 153–155 °C; IR (KBr disc): 3134, 1646, 1630, 1100 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.718 (s, 1H, N H), 8.387–8.381 (d, J = 2.4 Hz, 1H, Pyri-H), 8.004 (s, 1H, CH N), 7.871–7.840 (m, 2H, Pyri-H), 7.541–7.521 (d, J = 8.0 Hz, 1H, Furan-H), 6.871–6.863 (d, J = 3.2 Hz, 1H, Furan-H) 6.642–6.650 (m, 1H, Furan-H) 4.867 (s, 2H, Py-CH_2), 4.350 (s, 2H, triazine), 3.951 (s, 2H, triazine). [M+H]$^+$: 364.2; Anal. Calc. for $C_{14}H_{14}ClN_7O_3$: C, 46.23; H, 3.88; N, 26.95.; Found C, 46.14; H, 3.97; N, 26.90.

1-(2-Furfurylideneamino)-5-(2-furfuryl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5b). Yield: 69 %; m.p.: 114–117°C; IR (KBr disc): 3130, 1641, 1633, 1100 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.835 (s, 1H, N H), 8.110 (s, 1H, CH N), 7.582–7.440 (m, 3H, Pyri-H), 6.916–6.908 (d, J = 3.2 Hz, 1H, Pyri-H), 6.543–6.502 (m, 2H, Py-H), 5.065–5.037 (d, J = 11.2 Hz, 2H, triazine), 4.807 (s, 2H, triazine), 4.026 (s, 2H, Furan-CH_2). [M+H]$^+$: 319.3; Anal. Calc. for $C_{13}H_{14}N_6O_4$: C, 49.06; H, 4.43; N, 26.40.; Found C, 49.14; H, 4.50; N, 26.81.

1-(2-Furfurylideneamino)-5-(2-tetrahydrofurfuryl)-1,3,5-hexahydrotriazine-2-N-nitro-imine (5c). Yield: 72 %; m.p.: 142–143°C; IR (KBr disc): 3129, 1649, 1629, 1115 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.820 (s, 1H, N H), 8.101 (s, 1H, CH N), 7.581 (s, 1H, Furan-H), 6.902 (s, 1H, Furan-H), 6.540–6.521 (m, 1H, Furan-H), 5.011–4.980 (d, J = 3.0 Hz, 1H, triazine), 4.818–4.790 (d, J = 3.0 Hz, 1H, triazine), 4.643–4.611 (d, J = 12.8 Hz, 1H, triazine), 4.503–4.471 (d, J = 12.8 Hz, 1H, triazine), 4.142–4.070 (m, 1H, THF-H), 3.877–3.771 (m, 2H, THF-CH_2), 2.958–2.848 (m, 2H, THF-H), 2.189 (d, J = 2.0 Hz, 1H, THF-H), 1.942–1.883 (m, 2H, THF-H), 1.296–1.256(m, 1H, THF-H). [M+H]$^+$: 324.1; Anal. Calc. for $C_{13}H_{18}N_6O_4$: C, 48.44; H, 5.63; N, 26.07.; Found C, 49.55; H, 4.69; N, 26.15.

1-(2-Hydroxybenzylideneamino)-5-(6-chloro-3-pyridylmethyl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5d). Yield: 59%; m.p.: 157–159°C; IR (KBr disc): 3150, 1639, 1630, 1100 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 11.326 (s, 1H, Ph-OH), 9.826 (s, 1H, N H), 8.414 (d, J = 2.4 Hz, 1H, Pyri-H), 8.266 (s, 1H, CH N), 7.891–7.864 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, Pyri-H), 7.460–7.436 (dd, J_1 = 2.4 Hz, J_2 = 8.2 Hz, 1H, Pyri-H) 7.329–7.286 (t, J_1 = 8.0 Hz, J_2 = 9.2 Hz, 1H, Ph-H), 6.937–6.905 (m, 2H, Ph-H), 4.984 (s, 2H, Py-CH_2), 4.389 (s, 2H, triazine), 3.996 (s, 2H, triazine).[M+H]$^+$: 390.4; Anal. Calc. for $C_{16}H_{16}ClN_7O_3$: C, 49.30; H, 4.14; N, 25.15.; Found C, 49.25; H, 4.17; N, 25.18.

1-(2-Hydroxybenzylideneamino)-5-(2-furfuryl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5e). Yield: 65%; m.p.: 163–166°C; IR (KBr disc): 3135, 1650, 1635, 1113 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 11.209 (s, 1H, Ph-OH), 9.779 (s, 1H, N H), 7.898 (s, 1H, CH N), 7.459 (d, J = 1.2 Hz, 1H, Ph-H), 7.355–7.311 (m, 1H, Ph-H), 7.195–7.172 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H, Furan-H), 6.916–6.876 (q, 1H, Furan-H), 4.841 (s, 2H, triazine), 4.530 (s, 2H, triazine), 4.039 (s, 2H, Furan-CH_2). [M+H]$^+$: 345.3; Anal. Calc. for $C_{15}H_{16}N_6O_4$: C, 52.32; H, 4.68; N, 24.41.; Found C, 52.28; H,4.72; N, 24.38.

1-(2-Hydroxybenzylideneamino)-5-(2-tetrahydrofurfuryl)-1,3,5-hexahydrotriazine-2-N-nit-roimine (5f). Yield: 66%; m.p.: 149–152°C; IR (KBr disc): 3129, 1648, 1629, 1115 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 11.318 (s, 1H, Ph-OH), 9.724 (s, 1H, N H), 7.875 (s, 1H, CH N), 7.315 (m, 1H, Ph-H), 7.178–7.158 (d, J = 8.0 Hz, 1H, Ph-H), 6.891–6.854 (t, J = 7.2 Hz, 1H, Ph-H), 5.142–5.112(d, J = 12.0, 1H, triazine), 4.853–4.824 (d, J = 12.0, 1H, triazine), 4.656–4.624(d, J = 12.8 Hz, 1H, triazine), 4.479–4.447 (d, J = 12.8 Hz, 1H, triazine), 4.147–4.078 (m, 1H, THF-H), 3.869–3.742 (m, 2H, THF-CH_2), 2.911–2.841 (m, 2H, THF-H), 2.065–2.006 (m, 1H, THF-H), 1.935–1.857 (m, 2H, THF-H), 1.598–1.527 (m, 1H, THF-H). [M+H]$^+$: 349.1; Anal. Calc. for $C_{15}H_{20}N_6O_4$: C, 51.72; H, 5.79; N, 24.12.; Found C, 51.68; H, 5.83; N, 24.16.

1-(Benzylideneamino)-5-(6-chloro-3-pyridylmethyl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5g). Yield: 55%; m.p.: 138–141°C; IR (KBr disc): 3120, 1649, 1625, 1128 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.678 (s, 1H, N H), 8.393 (s, 1H, Pyri-H), 8.108 (s, 1H, CH N), 7.876–7.849 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H, Pyri-H), 7.712–7.687 (m, 2H, Ph-H), 7.536 (d, J = 8.4 Hz, 1H, Pyri-H), 7.467–7.449 (m, 3H, Ph-H), 4.933 (s, 2H, Py-CH_2), 4.356 (s, 2H, triazine), 3.969 (s, 2H, triazine), 4.501 (s, 2H, triazine), 4.022 (s, 2H, Furan-CH_2), 4.818 (s, 2H, triazine). [M+H]$^+$: 374.2; Anal. Calc. for $C_{16}H_{16}ClN_7O_2$: C, 51.41; H, 4.31; N, 26.23.; Found C, 51.52; H, 4.29; N, 26.28.

1-(Benzylideneamino)-5-(2-furfuryl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5h). Yield: 63%; m.p.: 154–156°C; IR (KBr disc): 3109, 1652, 1640, 1128 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.859 (s, 1H, N H), 8.047 (s, 1H, CH N), 7.781–7.757 (q, 2H, Ph-H), 7.459–7.437 (m, 3H, Ph-H), 7.428–4.410 (m, 1H, Furan-H), 6.376–6.363 (q, 1H, Furan-H), 6.339–6.331 (d, J = 3.2 Hz, 1H, Furan-H), 4.818 (s, 2H, triazine), 4.501 (s, 2H, triazine), 4.022 (s, 2H, Furan-CH_2). Anal. Calc. for $C_{13}H_{14}N_6O_4$: C, 49.06; H, 4.43; N, 26.40.; Found C, 49.14; H, 4.50; N, 22.81. [M+H]$^+$: 330.2; Anal. Calc. for $C_{15}H_{16}N_6O_3$: C, 54.87; H, 4.91; N, 25.60.; Found C, 54.92; H, 4.85; N, 25.63.

1-(Benzylideneamino)-5-(2-tetrahydrofurfuryl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5i). Yield: 65%; m.p.: 113–114°C; IR (KBr disc): 3121, 1700, 1635, 1120 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.945 (s, 1H, N H), 8.339 (s, 1H, CH N), 8.162–8.160 (d, J = 8.0 Hz, 2H, Ph-H), 7.400–7.311 (m, 3H, Ph-H), 5.159–5.129(d, J = 12.0 Hz, 1H, triazine), 4.889–4.859 (d, J = 12.0 Hz, 1H, triazine), 4.674–4.641(d, J = 13.2 Hz, 1H, triazine), 4.513–4.481 (d, J = 13.2 Hz, 1H, triazine), 4.116 (d, J = 3.6 Hz, 1H, THF-H), 3.890–3.753 (m, 2H, THF-CH_2), 2.964–2.867 (m, 2H, THF-H), 2.086–2.003 (m, 1H, THF-H), 1.936–1.869 (m, 2H, THF-H), 1.597–1.501 (m, 1H, THF-H). [M+H]$^+$: 334.3; Anal. Calc. for $C_{15}H_{20}N_6O_3$: C, 54.21; H, 6.07; N, 25.29.; Found C, 54.25; H, 6.00; N, 25.23.

1-(2-Chloro-benzylideneamino)-5-(2-furfuryl)-1,3,5-hexahydrotriazine-2-N-nitroimine (5j). Yield: 52%; m.p.: 148–151°C; IR (KBr disc): 3170, 1658, 1640, 1130 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.968 (s, 1H, N H), 8.345 (s, 1H, CH N), 8.178–8.159 (d, J = 7.6 Hz, 1H, Ph-H), 7.460 (s, 1H, Furan-H), 7.392–7.341 (m, 3H, Ph-H), 6.382–6.374 (d, J = 3.2 Hz, 2H, Furan-H), 4.877 (s, 2H, triazine), 4.527 (s, 2H, triazine), 4.045 (s, 2H, Funan-CH_2). [M+H]$^+$: 363.1; Anal. Calc. for $C_{15}H_{15}N_6O_3$: C, 49.66; H, 4.17; N, 23.17.; Found C, 49.65; H, 4.12; N, 23.22.

1-(2-Chloro-benzylideneamino)-5-(2-tetrahydrofurfuryl)-1,3,5-hexahydrotriazine-2-N-nitr-oimine (5k). Yield: 57%; m.p.: 135–138°C; IR (KBr disc): 3142, 1692, 1640, 1100 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *c*9.863 (s, 1H, N H), 8.271 (s, 1H, CH N), 8.158–8.139 (d, J = 7.6 Hz, 1H, Ph-H), 7.412–7.310 (m, 3H, Ph-H), 5.159–5.129(d, J = 12.0 Hz, 1H, triazine), 4.889–4.859(d, J = 12.0 Hz, 1H, triazine),4.674–4.641(d,

J = 13.2 Hz, 1H, triazine), 4.513–4.481(d, *J* = 13.2 Hz, 1H, triazine), 4.125–4.116 (d, *J* = 3.6 Hz, 1H, THF-H), 3.873–3.735 (m, 2H, THF-CH_2), 2.964–2.850 (m, 2H, THF-H), 2.162–2.001 (m, 1H, THF-H), 1.935–1.859 (m, 2H, THF-H), 1.588–1.521 (m, 1H, THF-H). $[M+H]^+$: 367.3; Anal. Calc. for $C_{15}H_{19}ClN_6O_3$: C, 49.12; H, 5.22; N, 22.91.; Found C, 49.14; H, 5.18; N, 22.86.

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