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Original Article

Synthesis and Structure-Activity Relationships of Dinotefuran Derivatives: Modification in the Nitroguanidine Part

Takeo WAKITA,* Katsutoshi KINOSHITA, Naoko YASUI, Eiichi YAMADA, Nobuyuki KAWAHARA and Kenji KODAKA

Functional Chemicals Laboratory, Mitsui Chemicals, Inc., 1144 Togo Mobara, Chiba 297–0017, Japan

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Dinotefuran ((*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine) is a new neonicotinoid which has a characteristic (±)-tetrahydro-3-furylmethyl moiety instead of the pyridine-like moiety of other neonicotinoids. A series of dinotefuran derivatives were synthesized and tested against hemiptera. SAR (structure-activity relationships) of the nitroguanidine part of dinotefuran are summarized as follows: (1) the mono-methyl group as a *N*-substituent gave the best activity for the acyclic nitroimino and nitromethylene compounds, (2) the acyclic compounds showed the same activity as the cyclic compounds against *Nephotettix cincticeps* and were superior to them against *Laodelphax striatellus*, (3) *N*-acylation of this series scarcely changed the level of activity. On the basis of these results, we selected dinotefuran for development. © Pesticide Science Society of Japan

Keywords: dinotefuran, neonicotinoids, (±)-tetrahydro-3-furylmethyl, structure-activity relationships (SAR).

INTRODUCTION

Insecticides which have a structure and mechanism similar to nicotine are called neonicotinoids.[1] Neonicotinoids are highly insecticidal, are systemic in plants, and now account for over 10% of the insecticide market.

Every neonicotinoid has two sites, a cationic site and a hydrogen acceptor site, for binding to nicotinic acetylcholine receptors. In regard to the hydrogen acceptor site, a chloropyridine or a chlorothiazole ring had been considered to be indispensable for neonicotinoids because of their structural similarity to the pyridine part of nicotine. Six neonicotinoids, which have the pyridine-like moiety, have been commercialized and many SARs for these neonicotinoids have been reported (Fig. 1).[2–4]

We started our research in 1992 to look for a novel neonicotinoid. It resulted in dinotefuran which has a (±)-tetrahydro-3-furylmethy moiety as the hydrogen acceptor site and the nitroguanidine moiety as the cationic site.[5–8] In this research, hundreds of related compounds were synthesized and the SARs for two moieties were obtained. Since publication of our research on dinotefuran, much related research has been reported, but many of the studies were about residue analysis,[9,10] metabolism[11–13] and mode of action,[14–16] and there are not enough reports about the SAR of dinotefuran.[5,15,17] In this paper we describe the preparation of four types of (±)-tetrahydro-3-furylmethy derivatives and the SAR for the nitroguanidine part of dinotefuran.

* To whom correspondence should be addressed.
E-mail: takeo.wakita@mitsui-chem.co.jp

MATERIALS AND METHODS

1. *Instrumental Analysis*

Melting points were obtained on a Mettler FP62 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA400 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-7300 spectrometer. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Spots were detected under UV light or with iodine.

2. *Synthesis*

Four types of (±)-tetrahydro-3-furylmethyl compounds were synthesized according to the following four methods, as shown in Fig. 2. Acyclic nitromethylene compounds (**iv**) were prepared by substitution of nitroethylenes (**iii**) with amines (Method A). Acyclic nitroimino compounds (**vii**) were prepared by substitution of nitroisothioureas (**vi**) with amines followed by acylation or alkylation (Method B), or acylation of *S*-methyl-*N*-nitroisothiourea (**viii**) followed by substitution with amines (**i**) (Method C). Cyclic nitroimino and nitromethylene compounds (**xi** and **xii**) were prepared by condensation of diamines from (**x**) with (**ii**) or with *S*-methyl-*N*-nitro-*N'*-phthaloylisothiourea (**v**) (Method D). The (tetra-

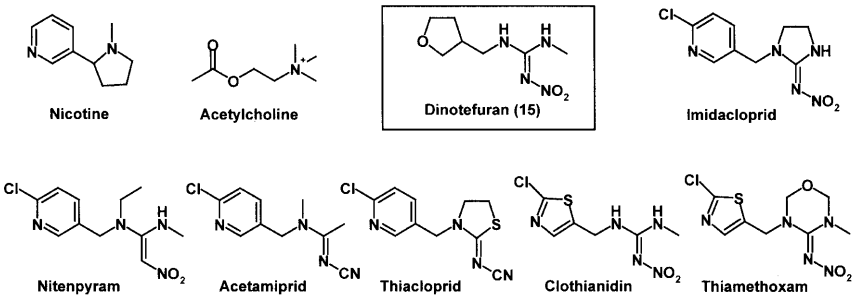


Fig. 1. Neonicotinoids and their lead compounds, Nicotine and Acetylcholine.

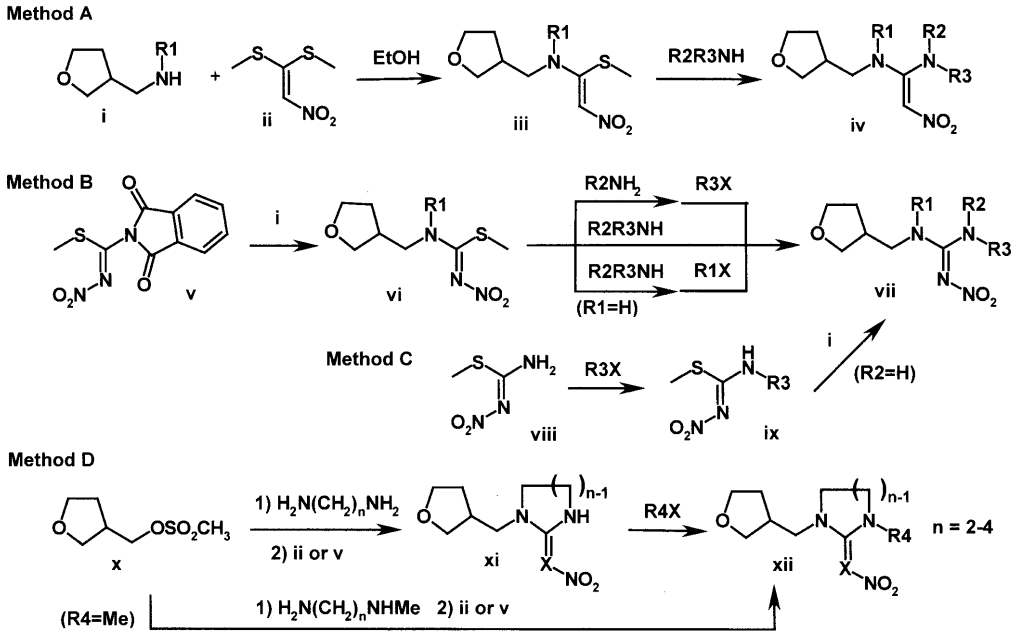


Fig. 2. Synthesis of tetrahydro-3-furylmethyl compounds, **iv**–**xi** and **xii**.

hydro-3-furyl)methyl derivatives (**i** and **x**[5]) and the isothiourea derivatives (**v**[18] and **viii**[19]) were prepared according to established procedures. Typical synthetic procedures are described as follows.

*2.1. Typical synthetic procedures for the acyclic nitromethylene compounds (**iv**) (Method A)*

*2.1.1. 1-Methylamino-2-nitro-1-{(tetrahydro-3-furyl)methylamino}ethylene (**5**)*

A solution of 3-(aminomethyl)tetrahydrofuran (**i**, 0.70 g, 6.9 mmol) and 1,1-bis(methylthio)-2-nitroethylene (**ii**, 1.25 g, 7.56 mmol) in acetonitrile (15 ml) was stirred at 70°C for 5 hr. The mixture was concentrated to dryness under reduced pressure. The resulting material was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1) to give 1.10 g (73%) of 1-methylthio-2-nitro-1-{(tetrahydro-3-furyl)methylamino}-ethylene (**1**, **iii**) as a yellow solid, mp 85–86°C. ^{1}H NMR δ ($CDCl_3$): 1.62–1.74 (1H, m), 2.09–2.20 (1H, m), 2.45 (3H, s), 2.63 (1H, septet, J=6.6 Hz), 3.39 (1H, dd, J=6.6 Hz, J=13.9 Hz), 3.49 (1H, dd, J=6.6 Hz, J=13.9 Hz), 3.61 (1H, dd, J=5.1 Hz, J=8.8 Hz), 3.73–3.88 (2H, m), 3.95 (1H, dt, J=5.1 Hz, J=8.8 Hz), 6.58 (1H, s), 10.6 (1H, br). IR (KBr) cm^{-1}: 3149, 1574.

A solution of **1** (0.40 g, 1.8 mmol) and 40% $MeNH_2$ (in MeOH, 0.60 g, 10 mmol) in MeOH (10 ml) was stirred at room temperature for 2 hr. The mixture was concentrated to dryness under reduced pressure. The resulting material was purified by silica gel column chromatography (EtOAc : MeOH = 9 : 1) to give 0.30 g (81%) of 1-methylamino-2-nitro-1-{(tetrahydro-3-furyl)methylamino}ethylene (**5**, **iv**) as a white solid, mp 140–141°C. ^{1}H NMR δ (DMSO): 1.51–1.63 (1H, m), 1.94–2.05 (1H, m), 2.50 (1H, br), 2.72 (3H, br), 3.09–3.28 (2H, m), 3.43 (1H, br), 3.59–3.81 (3H, m), 6.47 (1H, s), 7.26 (1H, br), 10.1 (1H, br). IR (KBr) cm^{-1}: 3186, 1637.

*2.1.2. 1-Methylthio-2-nitro-1-{N-methyl-(tetrahydro-3-furyl)methylamino}ethylene (**2**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.53–1.65 (1H, m), 2.02–2.11 (1H, m), 2.45 (3H, s), 2.64–2.74 (1H, m), 3.13 (3H, s), 3.50 (1H, dd, J=5.1 Hz, J=8.1 Hz), 3.62 (2H, dd, J=2.2 Hz, J=8.1 Hz), 3.72–3.91 (3H, m), 6.73 (1H, s). IR (neat) cm^{-1}: 1548, 1266.

*2.1.3. 1-Ethylamino-2-nitro-1-{(tetrahydro-3-furyl)methylamino}ethylene (**6**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.21–1.41 (3H, m), 1.65–1.82 (1H, m), 2.05–2.20 (1H, m), 2.55–2.71 (1H, m), 3.02–3.34 (3H, m), 3.55–4.01 (4H, m), 6.58 (1H, s), 10.5 (1H, br). IR (neat) cm^{-1}: 3274, 1615.

*2.1.4. 2-Nitro-1-propylamino-1-{(tetrahydro-3-furyl)-methylamino}ethylene (**7**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.00 (3H, br), 1.65–1.74 (3H, m), 2.10–2.30 (1H, m), 2.55–2.69 (1H, m), 3.05–3.25 (4H, m), 3.55–4.05 (4H, m), 6.57 (1H, s), 10.5 (1H, br). IR (neat) cm^{-1}: 3274, 1616.

*2.1.5. 2-Nitro-1-propargyl-1-{(tetrahydro-3-furyl)methylamino}ethylene (**8**)*

Mp 135–136°C. ^{1}H NMR δ ($CDCl_3$): 1.60–1.72 (1H, m), 2.05–2.21 (1H, m), 2.54–2.70 (1H, m), 2.65 (1H, s), 3.22 (2H, s), 3.52–4.20 (6H, m), 6.66 (1H, s), 7.41 (1H, s), 10.4 (1H, br). IR (KBr) cm^{-1}: 3221, 1577.

*2.1.6. 1-Methylamino-2-nitro-1-{N-methyl-(tetrahydro-3-furyl)methylamino}ethylene (**9**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.48–1.58 (1H, m), 2.01–2.12 (1H, m), 2.61–2.70 (1H, m), 2.93 (3H, s), 3.01 (3H, d, J=5.1 Hz), 3.20 (2H, dd, J=1.5 Hz, J=8.8 Hz), 3.48 (1H, dd, J=5.1 Hz, J=8.8 Hz), 3.71–3.82 (2H, m), 3.89 (1H, dt, J=5.1 Hz, J=8.8 Hz), 6.53 (1H, s), 9.73 (1H, br). IR (neat) cm^{-1}: 3420, 1616.

*2.1.7. 1-Methylamino-2-nitro-1-{N-ethyl-(tetrahydro-3-furyl)methylamino}ethylene (**10**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.20 (3H, t, J=7.3 Hz), 1.47–1.62 (1H, m), 1.97–2.10 (1H, m), 2.54–2.67 (1H, m), 3.01 (3H, d, J=5.1 Hz), 3.05–3.17 (2H, m), 3.25 (2H, q, J=7.3 Hz), 3.49 (1H, dd, J=5.1 Hz, J=8.1 Hz), 3.69–3.79 (2H, m), 3.89 (1H, dt, J=5.1 Hz, J=7.3 Hz), 6.55 (1H, s), 9.89 (1H, br). IR (neat) cm^{-1}: 3422, 1602.

*2.1.8. 1-Methylamino-2-nitro-1-{N-propyl-(tetrahydro-3-furyl)methylamino}ethylene (**11**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 0.91 (3H, t, J=7.3 Hz), 1.47–1.66 (3H, m), 1.97–2.07 (1H, m), 2.63 (1H, septet, J=6.6 Hz), 3.00 (3H, d, J=5.1 Hz), 3.11–3.18 (4H, m), 3.48 (1H, dd, J=5.1 Hz, J=8.1 Hz), 3.69–3.84 (2H, m), 3.88 (1H, dt, J=5.1 Hz, J=8.8 Hz), 6.55 (1H, s), 9.88 (1H, br). IR (neat) cm^{-1}: 3258, 1593.

*2.1.9. 1-Dimethylamino-2-nitro-1-{(tetrahydro-3-furyl)methylamino}ethylene (**12**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.57–1.69 (1H, m), 2.11–2.29 (1H, m), 2.51–2.68 (1H, m), 2.94 (6H, s), 3.19–3.35 (2H, m), 3.54–3.59 (1H, m), 3.70–3.95 (3H, m), 6.51 (1H, s), 9.63 (1H, br). IR (neat) cm^{-1}: 3260, 1615.

*2.1.10. 1-Dimethylamino-2-nitro-1-{N-methyl-(tetrahydro-3-furyl)methylamino}ethylene (**13**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.42–1.57 (1H, m), 2.00–2.12 (1H, m), 2.59–2.71 (1H, m), 2.95 (6H, s), 2.96 (3H, s), 3.17–3.25 (2H, m), 3.42 (1H, dd, J=5.1 Hz, J=8.8 Hz), 3.68–3.87 (3H, m), 6.34 (1H, s). IR (neat) cm^{-1}: 1524, 1256.

*2.2. Typical synthetic procedures for the acyclic nitroimino compounds (**vii**) (Method B)*

*2.2.1. 1,3-Diacetyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**23**)*

To a solution of *S*-methyl-*N*-nitro-*N'*-phthaloylisothiourea (**v**, 3.00 g, 11.3 mmol) in dichloromethane (20 ml) in an ice-cold bath, 3-(aminomethyl)tetrahydrofuran (**i**, 1.14 g, 11.3 mmol) in dichloromethane (10 ml) was added dropwise. The mixture was stirred at room temperature for 3 hr. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure. The obtained material was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1) to give 2.10 g (85%) of *S*-methyl-*N*-nitro-*N'*-{(tetrahydro-3-furyl)methyl}isothiourea (**3**, **vi**) as a white solid, mp 69–71°C. ^{1}H NMR δ ($CDCl_3$): 1.61–1.78 (1H, m), 2.09–2.27 (1H, m), 2.53 (3H, s), 2.54–2.72 (1H, m), 3.37–3.52 (2H, m), 3.55–4.02 (4H, m), 10.2 (1H, br). IR (KBr) cm^{-1}: 3354, 1562.

A solution of **3** (1.50 g, 6.85 mmol) and 40% $MeNH_2$ (in MeOH, 1.00 g, 12.9 mmol) in MeOH (10 ml) was stirred at room temperature for 1 hr. The mixture was concentrated to dryness under reduced pressure and the solid was washed with ether (15 ml), and then dried to give 1.25 g (90%) of 1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**15**, **vii**, dinotefuran) as a white solid, mp 94.5–101.5°C. ^{1}H NMR δ ($CDCl_3$): 1.62–1.74 (1H, m), 2.09–2.22 (1H, m), 2.59–2.79 (1H, m), 2.96 (3H, d. J=5.1 Hz), 3.35 (2H, t, J=5.1 Hz), 3.66–3.80 (3H, m), 3.92–4.08 (1H, m). IR (KBr) cm^{-1}: 3303, 1619, 1239.

To a stirred mixture of 60% NaH (0.40 g, 10 mmol) in acetonitrile (10 ml) at room temperature, **15** (0.80 g, 4.0 mmol) was added. The mixture was stirred for 30 min, then acetyl chloride (0.89 g, 11.3 mmol) in DMF (5 ml) was added dropwise at 0°C. After stirring at room temperature for 1 hr, the solid was filtered off and the filtrate was concentrated under reduced pressure. The resulting material was purified by silica gel column chromatography (hexane : EtOAc = 1 : 1) to give 0.86 g (75%) of 1,3-diacetyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**23**, **vii**) as a oil. ^{1}H NMR δ ($CDCl_3$): 1.52–1.68 (1H, m), 2.02–2.14 (1H, m), 2.20 (3H, s), 2.40 (3H, s), 2.62–2.78 (1H, m), 3.16 (3H, s), 3.48–3.95 (6H, m). IR (neat) cm^{-1}: 1706, 1558.

*2.2.2. S-Methyl-N-methyl-N'-nitro-N-{(tetrahydro-3-furyl)methyl}isothiourea (**4**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.58–1.71 (1H, m), 2.01–2.14 (1H, m), 2.55 (3H, s), 2.62–2.74 (1H, m), 3.24 (3H, s), 3.52–3.63 (2H, m), 3.70–3.85 (3H, m), 3.94 (1H, dt, J=5.1 Hz, J=8.8 Hz). IR (neat) cm^{-1}: 1735, 1451.

*2.2.3. 2-Nitro-1-(tetrahydro-3-furylmethyl)guanidine (**14**)*

Mp 119–123°C. ^{1}H NMR δ ($CDCl_3$): 1.60–1.65 (1H, m), 2.00–2.15 (1H, m), 2.49–2.64 (1H, m), 3.26 (2H, t, J=6.6 Hz), 3.48–3.62 (1H, m), 3.68–3.95 (3H, m), 7.80 (2H, br), 8.17 (1H, s). IR (KBr) cm^{-1}: 3321, 1592.

*2.2.4. 1-Ethyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**16**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.26 (3H, t, J=7.3 Hz), 1.59–1.71 (1H, m), 2.02–2.18 (1H, m), 2.49–2.66 (1H, m), 3.21–3.38 (4H, m), 3.59–3.94 (4H, m). IR (neat) cm^{-1}: 3289, 1614.

*2.2.5. 1-Benzyl-2-nitro-3-(tetrahydro-3-furylmethyl)-guanidine (**17**)*

Mp 108–116°C. ^{1}H NMR δ ($CDCl_3$): 1.40–1.55 (1H, m), 1.85–2.00 (1H, m), 2.40–2.57 (1H, m), 3.27 (2H, d, J=5.9 Hz), 3.38–3.86 (4H, m), 4.49 (2H, d, J=5.1 Hz), 7.27–7.45 (5H, m). IR (KBr) cm^{-1}: 3330, 1636.

*2.2.6. 1,3-Dimethyl-2-nitro-3-(tetrahydro-3-furylmethyl)-guanidine (**18**)*

Mp 93–96°C. ^{1}H NMR δ (DMSO): 1.45–1.57 (1H, m), 1.83–1.96 (1H, m), 2.45–2.57 (1H, m), 2.72 (3H, d, J=5.1 Hz), 2.98 (3H, s), 3.30–3.47 (3H, m), 3.58–3.73 (3H, m), 8.18 (1H, br). IR (KBr) cm^{-1}: 3218, 1632.

*2.2.7. 1-Ethyl-3-methyl-2-nitro-1-(tetrahydro-3-furylmethyl)guanidine (**19**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.25 (3H, t, J=7.3 Hz), 1.58–1.69 (1H, m), 2.03–2.14 (1H, m), 2.58–2.71 (1H, m), 2.98 (3H, d, J=5.1 Hz), 3.22 (1H, dd, J=9.5 Hz, J=14.7 Hz), 3.39 (1H, dd, J=7.3 Hz, J=14.7 Hz), 3.47 (2H, q, J=7.3 Hz), 3.62–3.71 (2H, m), 3.81 (1H, dt, J=5.9 Hz, J=8.8 Hz), 3.98 (1H, dt, J=5.9 Hz, J=8.8 Hz), 6.79 (1H, br). IR (neat) cm^{-1}: 3281, 1623.

*2.2.8. 1,1-Dimethyl-2-nitro-3-(tetrahydro-3-furylmethyl)-guanidine (**20**)*

Mp 127–129°C. ^{1}H NMR δ ($CDCl_3$): 1.55–1.68 (1H, m), 2.06–2.23 (1H, m), 2.48–2.60 (1H, m), 3.10 (6H, s), 3.29–3.50 (2H, m), 3.58–3.82 (3H, m), 3.85–4.00 (1H, m), 6.77 (1H, br). IR (KBr) cm^{-1}: 3274, 1637.

*2.2.9. 1-Ethyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**21**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.25 (3H, t, J=7.3 Hz), 1.58–1.70 (1H, m), 2.04–2.17 (1H, m), 2.55–2.66 (1H, m), 3.04 (3H, s), 3.30–3.47 (2H, m), 3.64–3.85 (3H, m), 3.95 (1H, dt, J=5.1 Hz, J=8.1 Hz), 6.56 (1H, br).

*2.2.10. 1,1,3-Trimethyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**22**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.50–1.62 (1H, m), 1.95–2.10 (1H, m), 2.56–2.69 (1H, m), 2.96 (6H, s), 2.99 (3H, s), 3.26–3.40 (2H, m), 3.47 (1H, dd, J=5.1 Hz, J=8.8 Hz), 3.70–4.02 (3H, m). IR (neat) cm^{-1}: 1734, 1439.

*2.2.11. 1,3-Diacetyl-1-ethyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**24**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.20–1.40 (3H, m), 1.51–1.68 (1H, m), 2.00–2.35 (4H, m), 2.41 (3H, s), 2.65–2.84 (1H, m), 3.25–4.00 (8H, m). IR (neat) cm^{-1}: 1705, 1560.

*2.2.12. 1,3-Dibenzoyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**25**)*

Mp 133–135°C. ^{1}H NMR δ ($CDCl_3$): 1.60–1.75 (1H, m), 1.87–2.01 (1H, m), 2.51 (3H, s), 2.57–2.70 (1H, m), 3.03–3.12 (1H, m), 3.19–3.27 (1H, m), 3.37–3.54 (1H, m), 3.64–3.90 (3H, m), 7.43–7.75 (10H, m). IR (KBr) cm^{-1}: 1698, 1545.

*2.2.13. 1,3-Bis(methoxycarbony)l-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**26**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.52–1.69 (1H, m), 2.07–2.19 (1H, m), 2.65–2.80 (1H, m), 3.10–3.36 (4H, br), 3.47–3.62 (2H, br), 3.81 (3H, s), 3.84 (3H, s), 3.71–3.94 (3H, m). IR (neat) cm^{-1}: 1743, 1542.

*2.2.14. 1,3-Dibenzyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**27**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.46–1.57 (1H, m), 1.98–2.11 (1H, m), 2.61–2.75 (1H, m), 2.79 (3H, s), 3.12–3.29 (2H, m), 3.44–3.49 (1H, m), 3.66–3.87 (3H, m), 4.41 (2H, d, J=2.9 Hz), 4.48 (2H, s), 7.19–7.43 (10H, m). IR (neat) cm^{-1}: 1714, 1540.

*2.2.15. 1-Acetyl-3-methoxycarbonyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**28**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.61–1.80(1H, m), 2.08–2.25 (1H, m), 2.15 (3H, s), 2.70–2.89 (1H, m), 3.08 (3H, s), 3.51–4.00 (6H, m), 3.89 (3H, s). IR (neat) cm^{-1}: 1749, 1705, 1564.

*2.2.16. 1-Benzoyl-3-methoxycarbonyl-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**29**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.43–1.58 (1H, m), 1.83–2.01 (1H, m), 2.44–2.60 (1H, m), 3.06–3.24 (2H, m), 3.25–3.39 (1H, m), 3.36 (3H, s), 3.64–3.86 (3H, m), 3.76 (3H, s), 7.43–7.66 (5H, m). IR (neat) cm^{-1}: 1748, 1697, 1558.

*2.3. Typical synthetic procedures for the acyclic nitroimino compounds (**vii**) (Method C)*

*2.3.1. 1-Benzoyl-2-nitro-3-(tetrahydro-3-furylmethyl)-guanidine (**31**)*

To a solution of *S*-methyl-*N*-nitroisothiourea (**viii**, 1.20 g, 8.89 mmol) in pyridine (4 ml) in an ice-cold bath, benzoylchloride (1.45 g, 10.3 mmol) was added dropwise. The mixture was stirred at room temperature for 2 hr. The mixture was poured into water (30 ml) and extracted with EtOAc (30 ml×2). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 2.10 g (99%) of *S*-methyl-*N*-benzoyl-*N'*-nitroisothiourea (**ix**) as a white solid, mp: 107–112°C. ^{1}H NMR δ (acetone-d_6): 2.51 (3H, s), 7.45–7.76 (5H, m). IR (KBr) cm^{-1}: 3275, 1703, 1635.

A solution of **ix** (0.80 g, 3.3 mmol) and 3-(aminomethyl)tetrahydrofuran (**i**, 0.50 g, 5.0 mmol) in acetonitrile (10 ml) was stirred at room temperature for 1 hr. The mixture was concentrated to dryness under reduced pressure. The resulting material was purified by silica gel column chromatography (hexane : EtOAc=1 : 1) to give 0.30 g (31%) of 1-benzoyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**31**, **vii**) as an oil, ^{1}H NMR δ ($CDCl_3$): 1.64–1.76 (1H, m), 2.12–2.23 (1H, m), 2.60–2.75 (1H, m), 3.54 (2H, dd, J=5.9 Hz, J=7.3 Hz), 3.63 (1H,dd, J=4.4 Hz, J=8.8 Hz), 3.74–3.99 (3H, m), 7.55–7.60 (2H, m), 7.68–7.73 (1H, m), 7.93–7.96 (2H, m), 9.81 (1H, br). IR (neat) cm^{-1}: 3271, 1695, 1581.

*2.3.2. 1-Acetyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (**30**)*

Mp 96–98°C. ^{1}H NMR δ ($CDCl_3$): 1.60–1.70 (1H, m), 2.04–2.18 (1H, m), 2.32 (3H, s), 2.56–2.67 (1H, m), 3.45 (2H, dd, J=5.9 Hz, J=7.3 Hz), 3.57 (1H, dd, J=5.9 Hz, J=7.3 Hz), 3.71–3.94 (3H, m), 9.51 (1H, br.). IR (KBr) cm^{-1}: 3266, 1707, 1621.

*2.3.3. N-Methoxycarbonyl-N′-nitro-N″-(tetrahydro-3-furylmethyl)guanidine (**32**)*

Mp 68–77°C. ^{1}H NMR δ ($CDCl_3$): 1.54–1.71 (1H, m), 2.06–2.19 (1H, m), 2.57–2.69 (1H, m), 3.44–3.49 (2H, m), 3.57–3.61 (1H, m), 3.72–3.97 (3H, m), 3.89 (3H, s), 8.76 (1H, br). IR (KBr) cm^{-1}: 3293, 1743, 1580.

*2.4. Typical synthetic procedures for cyclic nitroimino and nitromethylene compounds (**xi** and **xii**) (Method D)*

*2.4.1. 1-Acetyl-2-nitroimino-3-{(tetrahydro-3-furyl)-methyl}hexahydropyrimidine (**41**)*

A mixture of 3-(methylsulfonyloxymethyl)tetrahydrofuran (**x**, 2.61 g, 14.5 mmol), 1,3-diaminopropane (10 ml), potassium carbonate (4.01 g, 28.9 mmol) and sodium iodide (0.10 g) in acetonitrile (80 ml) was stirred at 70°C for 4 hr. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure to give crude *N*-(tetrahydro-3-furyl)methyl-1,3-diaminopropane (2.90 g).

A solution of *S*-methyl-*N*-nitro-*N′*-phthaloylisothiourea (**v**, 4.90 g, 18.5 mmol) and crude *N*-(tetrahydro-3-furyl)methyl-1,3-diaminopropane (2.90 g) in EtOH (20 ml) was refluxed for 3 hr. EtOAc (20 ml) was added and the resulting solid was filtered off. The mixture was concentrated to dryness under reduced pressure. The resulting material was purified by silica gel column chromatography (acetone : EtOAc = 1 : 2) to give 2.02 g (61% from **x**) of 2-nitroimino-1-{(tetrahydro-3-furyl)methyl}hexahydropyrimidine (**37**, **xi**) as a colorless solid, mp 88–91°C. ^{1}H NMR δ ($CDCl_3$): 1.56–1.72 (1H, m), 1.96–2.12 (3H, m), 2.67–2.82 (1H, m), 3.32–3.57 (5H, m), 3.62–3.95 (5H, m), 9.79 (1H, br). IR (KBr) cm^{-1}: 3256, 1593.

To a stirred mixture of 60% NaH (0.20 g, 5.0 mmol) in acetonitrile (20 ml) at room temperature, **37** (1.00 g, 4.39 mmol) was added. The mixture was stirred for 30 min, then acetyl chloride (0.39 g, 11.3 mmol) in acetonitrile (5 ml) was added at 0°C. After stirring at room temperature for 1 hr, the solid was filtered off and the filtrate was concentrated under reduced pressure. The resulting material was purified by silica gel column chromatography (chloroform : MeOH = 20 : 1) to give 0.82 g (69%) of 1-acetyl-2-nitroimino-3-{(tetrahydro-3-furyl)methyl}hexahydropyrimidine (**41**, **xii**) as an oil. ^{1}H NMR δ ($CDCl_3$): 1.59–1.77 (1H, m), 1.99–2.28 (3H, m), 2.32 (3H, s), 2.63–2.85 (1H, m), 3.41–3.62 (4H, m), 3.67–3.98 (6H, m). IR (neat) cm^{-1}: 1706, 1569.

*2.4.2. 2-Nitromethylene-1-{(tetrahydro-3-furyl)methyl}-imidazolidine (**33**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.44–1.62 (1H, m), 2.01–2.10 (1H, m), 2.46–2.58 (1H, m), 3.26–3.96 (10H, m), 6.57 (1H, s), 10.6 (1H, br). IR (neat) cm^{-1}: 1568.

*2.4.3. 2-Nitromethylene-1-{(tetrahydro-3-furyl)methyl}-hexahydropyrimidine (**34**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.51–1.68 (1H, m), 2.00–2.18 (3H, m), 2.58–2.72 (1H, m), 3.13 (1H, dd, J=7.3 Hz, J=14.1 Hz), 3.27 (1H, dd, J=7.3 Hz, J=14.1 Hz), 3.35–3.59 (5H, m), 3.70–3.82 (2H, m), 3.88–3.99 (1H, m), 6.66 (1H, s), 10.9 (1H, br). IR (neat) cm^{-1}: 1589.

*2.4.4. 2-Nitromethylene-1-(tetrahydro-3-furyl)methyl-1,3-diazacycloheptane (**35**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.52–1.68 (1H, m), 1.69–1.86 (4H, m), 2.02–2.19 (1H, m), 2.56–2.72 (1H, m), 3.10–3.58 (7H, m), 3.68–3.98 (3H, m), 6.56 (1H, s), 10.1 (1H, br). IR (neat) cm^{-1}: 3449, 1584.

*2.4.5. 2-Nitroimino-1-{(tetrahydro-3-furyl)methyl}imidazolidine (**36**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.58–1.71 (1H, m), 1.99–2.09 (1H, m), 2.60 (1H, septet, J=7.3 Hz), 3.33 (1H, dd, J=7.3 Hz, J=14.0 Hz), 3.51 (1H, dd, J=5.9 Hz, J=8.8 Hz), 3.62–3.94 (7H, m), 8.15 (1H, br). IR (neat) cm^{-1}: 3412, 1619.

*2.4.6. 2-Nitroimino-1-(tetrahydro-3-furyl)methyl-1,3-diazacycloheptane (**38**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.57–1.75 (1H, m), 1.79–1.90 (4H, m), 1.99–2.14 (1H, m), 2.60–2.80 (1H, m), 3.30–3.62 (7H, m), 3.68–3.95 (3H, m), 9.33 (1H, br). IR (neat) cm^{-1}: 3586, 1671, 1560.

*2.4.7. 1-Methyl-2-nitromethylene-3-{(tetrahydro-3-furyl)-methyl}hexahydropyrimidine (**39**)*

Oil. ^{1}H NMR δ($CDCl_3$): 1.58–1.74 (1H, m), 1.95–2.25 (3H, m), 2.47–2.65 (1H, m), 3.22 (3H, s), 3.30–3.99 (10H, m), 6.36 (1H, s). IR (neat) cm^{-1}: 1593.

*2.4.8. 3-Methyl-2-nitroimino-1-{(tetrahydro-3-furyl)-methyl}hexahydropyrimidine (**40**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.58–1.74 (1H, m), 1.96–2.21 (3H, m), 2.52–2.71 (1H, m), 3.12 (3H, s), 3.38 (1H, dd, J=8.1 Hz, J=13.9 Hz), 3.50 (4H, t, J=5.9 Hz), 3.45–3.93 (3H, m). IR (neat) cm^{-1}: 1612.

*2.4.9. 1-Acetyl-2-nitroimino-3-{(tetrahydro-3-furyl)-methyl}hexahydropyrimidine (**41**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.59–1.77 (1H, m), 1.99–2.28 (3H, m), 2.32 (3H, s), 2.68–2.85 (1H, m), 3.41–3.62 (4H, m), 3.67–3.98 (6H, m). IR (neat) cm^{-1}: 1706, 1569.

*2.4.10. 1-Benzoyl-2-nitroimino-3-{(tetrahydro-3-furyl)methyl}hexahydropyrimidine (**42**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.57–1.73 (1H, m), 1.98–2.15 (1H, m), 2.23–2.38 (2H, m), 2.65–2.83 (1H, m), 3.41–3.99 (10H, m), 7.42–7.55 (5H, m). IR (neat) cm^{-1}: 1689, 1563.

3. Biological Tests

3.1. Insects

Biological tests were conducted against the small brown planthopper, *Laodelphax striatellus* Fallen and the green rice leafhopper, *Nephotettix cincticeps*.

All tests were replicated twice and done at 25(±2)°C, at 65(±5)% RH and under a 16 : 8 hr light : dark photoperiod.

3.2. Contact/feeding activity in L. striatellus and N. cincticeps

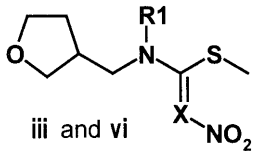
A bundle of rice seedlings (about third-leaf stage) was sprayed with water+acetone (4+1 by volume) containing the test compound at a concentration of 1, 10, 100 or 1000 ppm. After drying, the treated seedlings were covered with a metal gauze cylinder, and 10 one- to three-day-old male adults of *L. striatellus* or *N. cincticeps* were released into the cylinder. Mortality was checked 3 days later.

Insecticidal activity was graded as follows: 0: LC_{70} >1000 ppm, 1: 1000–100 ppm, 2: 100–10 ppm, 3: 10–1 ppm, 4: 1–0.1 ppm.

RESULTS AND DISCUSSION

Insecticidal activities of the precursors (**1–4**), the acyclic nitromethylene compounds (**5–13**), the acyclic nitroimino compounds (**14–32**) and the cyclic nitroimino and nitromethylene compounds (**33–42**) are shown in Tables 1–4. The SARs of the four types, except for inactive precursors, are described below.

Table 1. Insecticidal activities of precursor **iii** and **vi**



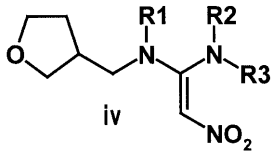
iii and vi

No.	R1	X	LS	NC
1	H	CH	0	0
2	Me	CH	0	0
3	H	N	2	2
4	Me	N	0	0

LS: *Laodelphax striatellus*

NC: *Nephotettix cincticeps*

Table 2. Insecticidal activities of acyclic nitromethylene compounds **iv**

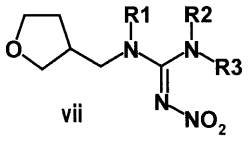


iv

No.	R1	R2	R3	LS	NC
5	H	H	Me	4	4
6	H	H	Et	2	2
7	H	H	Pr	1	1
8	H	H	propargyl	0	0
9	Me	H	Me	3	3
10	Et	H	Me	3	2
11	Pr	H	Me	2	2
12	H	Me	Me	4	3
13	Me	Me	Me	3	2

Abbreviations, see Table 1.

Table 3. Insecticidal activities of acyclic nitroimino compounds **vii**

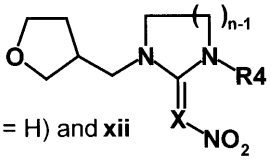


vii

No.	R1	R2	R3	LS	NC
14	H	H	H	0	1
15	H	H	Me	4	4
16	H	H	Et	1	2
17	H	H	Bzl	0	0
18	Me	H	Me	3	3
19	Et	H	Me	2	2
20	H	Me	Me	3	4
21	H	Et	Me	2	2
22	Me	Me	Me	2	2
23	Ac	Ac	Me	4	4
24	Ac	Ac	Et	2	2
25	Bz	Bz	Me	3	4
26	COOMe	COOMe	Me	3	4
27	Bzl	Bzl	Me	2	2
28	COOMe	Ac	Me	3	4
29	COOMe	Bz	Me	3	4
30	H	H	Ac	0	0
31	H	H	Bz	0	0
32	H	H	COOMe	0	2

Bzl: benzyl, Bz: benzoyl. Other abbreviations, see Table 1.

Table 4. Insecticidal activities of cyclic nitroimino compounds **xi** and **xii**



xi (R4 = H) and xii

No.	X	n	R4	LS	NC
33	CH	2	H	2	4
34	CH	3	H	3	4
35	CH	4	H	2	3
36	N	2	H	2	3
37	N	3	H	3	4
38	N	4	H	1	2
39	CH	3	Me	2	2
40	N	3	Me	1	2
41	N	3	Ac	2	4
42	N	3	Bz	2	4

Abbreviations, see Table 1.

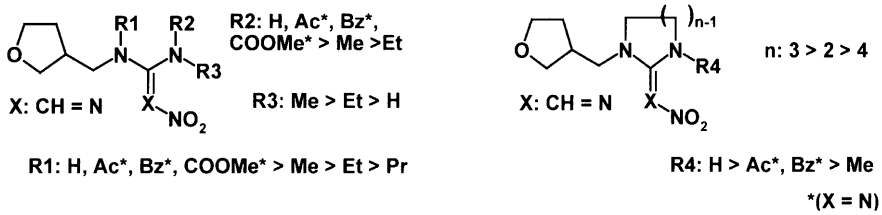


Fig. 3. Structure-activity relationships of the acyclic and cyclic compounds.

*1. Insecticidal Activities of Acyclic Nitromethylene Compounds (**iv**)*

Table 2 shows the effects of *N*-substituents on the nitroethylene moiety. The mono-methyl compound (R3=methyl, **5**) showed the highest level of activity among these compounds and the activity was reduced as the size of the *N*-substituents increased (see **5**–**7** and **9**–**11**). Another methylation of the guanidine reduced the activity (**5**, **9**, **12** and **13**).

*2. Insecticidal Activities of Acyclic Nitroimino Compounds (**vii**)*

Table 3 shows the effects of *N*-substituents on the nitroguanidine moiety of the acyclic nitroimino compounds (**14**–**32**). These compounds can be divided into three derivatives: alkyl derivatives (**14**–**22**), their double-protected derivatives (**23**–**29**) and single-protected derivatives (**30**–**32**).

The SARs for the alkyl derivatives (**14**–**22**) and the acyclic nitromethylene derivatives (**5**–**13**) are almost the same. The mono-methyl compound (R3=methyl, **15**) showed the highest level of activity of the acyclic nitroimino compounds, and the activity was reduced as the number of substituents and the size of R1, R2 and R3 increased.

The double-protected derivatives (**23**–**29**), except for **27**, were as effective as the unsubstituted compounds (**15**, **16**), respectively, against *N. cincticeps*, but they were slightly inferior to **15** and **16** against *L. striatellus*. The activity of the di-benzyl compound (**27**) was 100-fold lower than **15** against both insects.

The single-protected derivatives (**30**–**32**), which have no *N*-alkyl substituent, were significantly less active against both insects.

*3. Insecticidal Activities of Cyclic Nitroimino and Nitromethylene Compounds (**xi** and **xii**)*

Table 4 shows the effects of the *N*-substituent of the cyclic nitroimino and nitromethylene compounds (**33**–**42**). Both types showed the same trend of activity, so these compounds can be divided into three derivatives of the R4-substituent: hydrogen derivatives (**33**–**38**), methyl derivatives (**39** and **40**) and acyl derivatives (**41** and **42**).

Six-membered ring compounds (**34**, **37**) showed the highest levels of activity among five- to seven-membered ring compounds. These cyclic compounds displayed the same activity level as the acyclic compounds (**5**, **15**) against *N. cincticeps*, but were 10-fold less active against *L. striatellus*.

The methyl derivatives (**39** and **40**) showed 10- to 100-fold less activity than the other cyclic derivatives.

The acyl derivatives (**41** and **42**) have the same levels of activity as the unsubstituted compound (**37**) against against *N. cincticeps*, but were 10-fold less active against *L. striatellus*.

*4. Similarities of Activities between Acyclic Nitroimino and Nitromethylene Compounds (**iv** and **vii**)*

The acyclic nitroimino compounds (**14**–**22**) and the acyclic nitromethylene compounds (**5**–**13**) are similar in SAR and activity level. Both derivatives have the same clear trend for decreased activity with increasing size of the *N*-alkyl substituents. The mono-methyl compounds (**15**) and (**5**), which showed the highest levels of activity among these compounds, had the same activity level. Removal of the methyl substituent on the guanidine of **15** strongly reduced the activity (see **14**). These results indicate that the mono-methyl group as the *N*-substituent gave the best activity for the acyclic nitroimino and nitromethylene compounds.

*5. Similarities and Differences of Activities between Acyclic and Cyclic Nitroimino Compounds (**vii**, **xi** and **xii**)*

The acyclic nitroimino compounds (**14**–**32**) and the cyclic nitroimino compounds (**37** and **40**–**42**) also showed similar trends in activity and SAR. But against *L. striatellus*, the cyclic compounds were less active than the acyclic compounds. As for tri-substituted compounds, acyclic tri-methyl compound (**22**) showed the same activity level as cyclic *N*-methyl compound (**40**).

*6. Similarities of Activities between Acylated and Non-protected Nitroimino Compounds (**vii**, **xi** and **xii**)*

The non-protected acyclic compounds (**14**–**22**) and cyclic nitroimino compound (**37**) showed almost the same activity as their acyl and/or carbamate compounds (**23**–**26**, **28**, **29** and **30**–**32**), respectively. This suggests that these compounds would show activity after cleavage of acyl and carbamate groups by metabolism in the insect body and/or in plants. This correlation does not apply to di-benzyl substitutions (**27**). The activity is about 100-fold lower than that of **15** probably because of the difficulty of metabolic debenzylation.

*7. Selection of Dinotefuran (**15**) for Development Compound*

The SAR for the acyclic and cyclic compounds against *L.*

striatellus and *N. cincticeps* are summarized in Fig. 3. The acyclic nitromethylene compound (**5**), the acyclic nitroimino compound (**15**), its acylated compounds (**25**, **26**, **28** and **29**) and the cyclic compounds (**34**, **37**) showed the highest levels of insecticidal activity. The acylated compounds were nearly as active as the other compounds, but none of them significantly excelled, and all of them would be more expensive to prepare commercially. We chose four compounds (**5**, **15**, **34** and **37**) as candidates and, based on further considerations of activity, safety, residual control properties and production costs, selected the acyclic nitroimino compound (**15**, dinotefuran) for development.

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