J. Pestic. Sci., **29**(4), 356–363 (2004)

Original Article

Synthesis and Structure-Activity Relationships of Dinotefuran Derivatives: Modification in the Tetrahydro-3-furylmethyl Part

Takeo WAKITA,* Katsutoshi KINOSHITA, Kenji KODAKA, Naoko YASUI, Atsuko NAOI and Sinichi BANBA

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

(Received May 19, 2004; Accepted July 9, 2004)

The (±)-tetrahydro-3-furylmethyl moiety, which is a characteristic part of the novel neonicotinoid dinotefuran, was found by research in which acetylcholine was selected as the lead compound. SAR (structure-activity relationships) for the tetrahydrofuran part indicated that the non-substituted moiety showed the highest level of activity, 4- and 5-substituted moieties showed intermediate levels, and 2- and 3-substituted moieties lost the activity. Conformational analysis of these compounds indicated that the substituents changed little the hypothetical active conformation of dinotefuran. Computational analysis proved that dinotefuran, a methoxypropyl compound and other neonicotinoids well overlapped, and dinotefuran adopts the active conformation more easily than the methoxypropyl compound. © Pesticide Science Society of Japan

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

INTRODUCTION

Neonicotinoid is a major chemical class of insecticide, whose sales have expanded because of its high level of activity and residual control properties. Seven neonicotinoids have been developed, and classified based on structural differences of a hydrogen acceptor site into three sub-classes: chloronicotinyl, thianicotinyl and furanicotinyl (Fig. 1).[1,2] The chloronicotinyl and thianicotinyl compounds have pyridine-like moieties, as is the case for the pyridine ring in nicotine (**1**), and the furanicotinyl compound dinotefuran (**2**) has a characteristic (±)-tetrahydro-3-furylmethyl moiety.[3]

The (±)-tetrahydro-3-furylmethyl moiety was detected by cyclization of the 3-methoxypropyl moiety which was led from acetylcholine (Fig. 2). These moieties and the pyridine ring are similar in the location of their oxygen and nitrogen atoms (Fig. 1), but the details have not been clarified. In this paper we report the SAR (structure-activity relationships) of substituted (tetrahydro-3-furyl)methy compounds and the molecular modeling of these derivatives, and discuss the relationship between tetrahydro-3-furan moieties and the pyridine-like moieties.

* 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. *Molecular Modeling*

All computations were performed using the molecular modeling software package SYBYL, version 6.9 (Tripos Associates, Inc., St. Louis, MO, USA). Energies were calculated with the Merck force field (MMFF94S)[4] and MMFF94 charges.[5] A dielectric permittivity of $\varepsilon_r = 1$ and a non-cutoff were used. In this computational analysis, the (*R*)-enantiomer of dinotefuran was used because there is no great difference in activity between (*R*) and (*S*) (data not shown).

To obtain conformational databases, each compound was subjected to a systematic search in which all rotatable bonds were allowed to vary in 30 steps (acyclic bonds) and 10 steps (ring closure bonds). The remaining structures were subsequently minimized with an electrostatic term until the rms (root-mean-square) gradient was less than 10^{-3} kcal mol^{-1} Å^{-1}. Structures that converged to the same

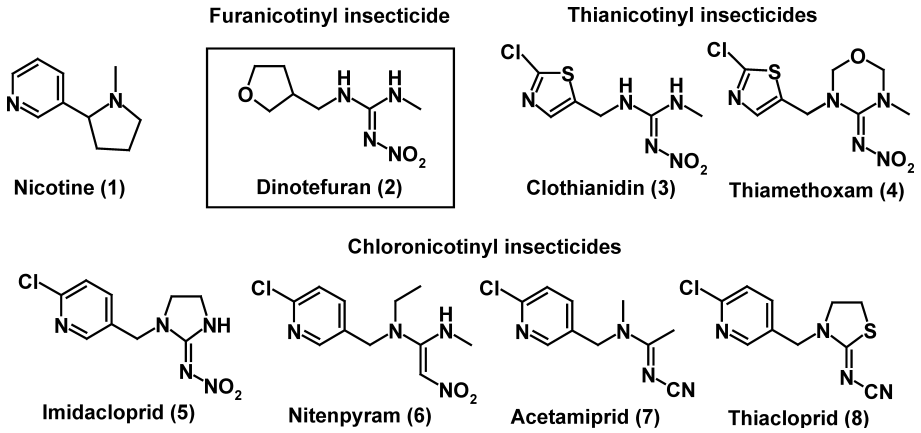


Fig. 1. Nicotine and Neonicotinoids.

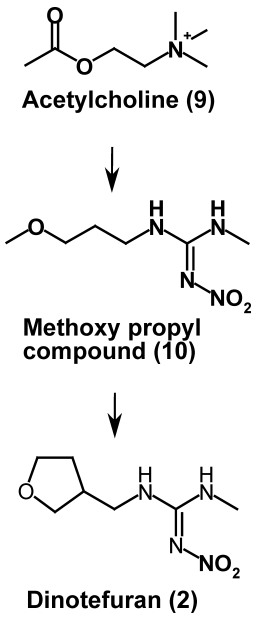


Fig. 2. Discovery of dinotefuran (**2**).

minimum were omitted on the basis of their energies and by an rms fitting procedure in which all non-hydrogen atoms were superimposed using 0.2 Å as a similarity cutoff. The remaining conformers were stored in conformational databases. Furthermore, the conformations of the nitroimino parts were filtered into one conformation (see Fig. 4), the rest being excluded from the databases.

To obtain pharmacophores among active compounds in a multiconformation structure database, we used the DISCO[6] (DIStance COmparison) program, an algorithm available in the Sybyl software. The first step of the DISCO search routine consists of identifying all potential pharmacophoric site points in each molecule. The site point assignments include aromatic and aliphatic ring centroids, functional groups with a hydrogen bond donor or acceptor potential, and external site points that represent receptor-associated hydrogen bond acceptors or donors. Secondly, the DISCO method was used to identify the most probable active conformations.

3. *Synthesis*

Four types of (±)-tetrahydro-3-furylmethyl compounds, acyclic nitroimino and nitromethylene (**xvi**), cyclic nitroimino and nitromethylene (**xvii**) with excellent insecticidal activities were synthesized according to the following methods (Fig. 3): 3- and 4-substituted derivatives (**iv** and **v**) were prepared by the reduction of triesters followed by cyclization[7] of triols (**iii**), which were obtained by the substitution of esters (**ii**) with malonates (**i**), followed by mesylation and amination. Four- and 5-substituted derivatives (**vii** and **viii**) were prepared by the same method as **iv** and **v** using **vi** instead of **ii**, and 5,5-dimethyl derivatives (**x** and **xi**) were prepared using **ix**. The 2-methyl derivative (**xiii**) was prepared by the reduction of oxime, which was synthesized from **xii**[8] and a 2-methoxy derivative (**xv**) was prepared by the reduction of amide which was synthesized from **xiv**.[9] Acyclic and cyclic (tetrahydro-3-furyl)methyl compounds (**xvi** and **xvii**) were synthesized according to published procedures,[3] using amines (**v**, **viii**, **xi**, **xiii** and **xv**) and mesylates (**iv**, **vii** and **x**). Typical procedures are described as follows.

3.1. Typical synthesis of acyclic nitroimino compounds (xvi)

3.1.1. 1-Methylthio-2-nitro-1-[{(4-ethyl)tetrahydro-3-furyl}methylamino]ethylene (26)

To a stirred solution of sodium (3.55 g, 154 mmol) in EtOH (100 ml) at room temperature, diethyl malonate (**i**, 24.6 g, 154 mmol) was added dropwise. The mixture was stirred at 70°C for 30 min, then ethyl 2-bromobutyrate (**ii**, 30.0 g, 154 mmol) was added dropwise at room temperature. After stirring at 70°C for 5 hr, water (100 ml) was added and extracted with EtOAc (100 ml×3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 44.2 g of crude ethyl 2-{bis(ethoxycarbonyl)methyl}butyrate as an oil, ^{1}H NMR δ ($CDCl_3$): 0.93 (3H, t, J=7.3 Hz), 1.22–1.31 (9H, m), 1.53–1.68 (2H, m), 3.08 (1H, ddd, J=4.4 Hz, J=8.0 Hz,

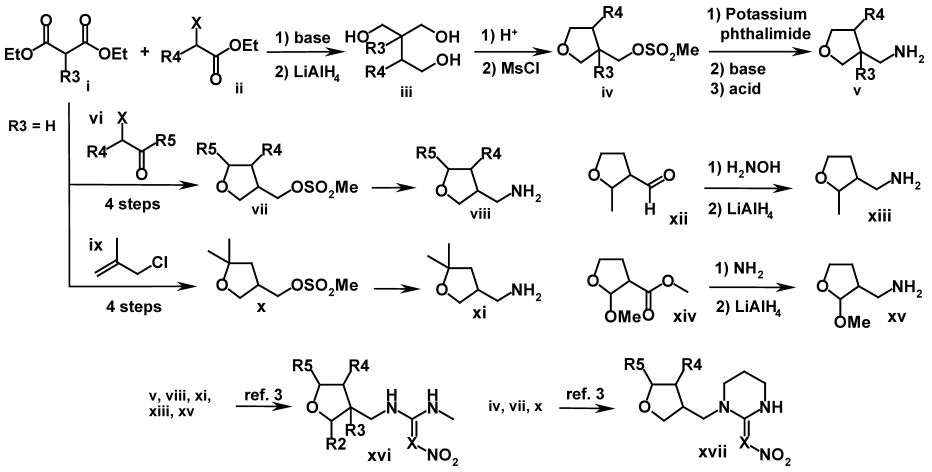


Fig. 3. Synthesis of substituted tetrahydro-3-furylmethyl derivatives **xvi** and **xvii**.

J=11.0 Hz), 3.75 (1H, d, *J*=11.0 Hz), 4.09–4.28 (6H, m).

To a stirred mixture of $LiAlH_4$ (12.0 g, 316 mmol) in THF (240 ml) in an ice-cold bath, crude ethyl 2-{bis(ethoxycarbonyl)methyl}butyrate (44.2 g) was added dropwise. The mixture was refluxed for 9 hr and cooled to room temperature. Water (12.0 g), 3 M NaOHaq. (12.0 g) and water (36.0 g) were added carefully in that order. The resulting solid was filtered off and washed with diethyl ether (200 ml). The combined filtrate was concentrated under reduced pressure to give crude 2-ethyl-3-hydroxymethyl-1,4-butanediol (**iii**, 19.5 g) as an oil.

A solution of crude 2-ethyl-3-hydroxymethyl-1,4-butanediol (19.5 g) and polyphosphoric acid (10 ml) was stirred at 100°C for 4 hr. Water (15 ml) was added and neutralized with potassium carbonate and extracted with diethyl ether (100 ml×2). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting material was purified by silica gel column chromatography (hexane : EtOAc=4 : 1–1 : 1) to give 14.5 g (73%, 3 steps) of 3-ethyl-4-(hydroxymethyl)tetrahydrofuran as an oil. ^{1}H NMR δ ($CDCl_3$): 0.93 (3H, t, *J*=7.3 Hz), 1.33–1.61 (2H, m), 1.77–1.86 (1H, m), 2.00–2.10 (1H, m), 3.39 (1H, dd, *J*=7.3 Hz, *J*=8.8 Hz), 3.56 (1H, dd, *J*=7.3 Hz, *J*=10.3 Hz), 3.67–3.73 (2H, m), 3.89 (1H, dd, *J*=7.3 Hz, *J*=8.8 Hz), 3.99 (1H, t, *J*=7.3 Hz).

To a stirred solution of 3-ethyl-4-(hydroxymethyl)tetrahydrofuran (11.5 g, 88.3 mmol) and methanesulfonylchloride (10.1 g, 88.5 mmol) in THF (80 ml) at room temperature, was added triethylamine (9.10 g, 89.9 mmol) and the mixture was further stirred for 6 hr. The mixture was quenched with water (50 ml) and extracted with EtOAc (70 ml×2). The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting material was purified by silica gel column chromatography (hexane : EtOAc=8 : 1–1 : 1) to give 7.60 g (41%) of 3-ethyl-4-(methylsulfonyloxymethyl)tetrahydrofuran as an oil.

A solution of 3-ethyl-4-(methylsulfonyloxymethyl)tetrahydrofuran (2.93 g, 14.1 mmol) and potassium phthalimide (2.70 g, 14.6 mmol) in DMF (15 ml) was stirred at 60°C for 7 hr. The mixture was quenched with water (50 ml) and extracted with EtOAc (100 ml). The organic layer was washed with water (50 ml×2), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, to give 3.00 g (82%) of *N*-[{(4-ethyl)tetrahydrofuran-3-yl}methyl]phthalimide as an oil.

A solution of *N*-[{(4-ethyl)tetrahydrofuran-3-yl}methyl]phthalimide (2.98 g, 11.5 mmol) and 25% NaOHaq. (2.0 g) in water (8 ml) was stirred at 70°C for 3 hr and the solution added to 10% HClaq. (8 ml) at 70°C and stirred for 4 hr. Toluene (15 ml) was added and stirred for 30 min at 70°C, then the water layer and solid were alkalified with 50% NaOHaq. The solution was extracted with chloroform (80 ml×3) dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, to give 1.05 g of crude 3-aminomethyl-4-ethyltetrahydrofuran as an oil.

A solution of crude 3-aminomethyl-4-ethyltetrahydrofuran (1.05 g) and 1,1-bis(methylthio)-2-nitroethylene (1.20 g, 7.26 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 1.27 g (45%, 2 steps) of 1-methylthio-2-nitro-1-[{(4-ethyl)tetrahydro-3-furyl}methylamino]ethylene as a yellow solid. ^{1}H NMR δ ($CDCl_3$): 0.94 (3H, t, *J*=7.3 Hz), 1.37–1.60 (2H, m), 1.81–1.92 (1H, m), 2.15–2.27 (1H, m), 2.45 (3H, s), 3.37–3.48 (3H, m), 3.63 (1H, dd, *J*=5.1 Hz, *J*=9.5 Hz), 3.89 (1H, dd, *J*=7.3 Hz, *J*=9.5 Hz), 4.05–4.16 (1H, m), 6.58 (1H, s), 10.6 (1H, br). IR (KBr) cm^{-1}: 3410, 1561.

A solution of 1-methylthio-2-nitro-1-[{(4-ethyl)tetrahydro-3-furyl}methylamino]ethylene (0.37 g, 1.5 mmol) in 40% $MeNH_2$ (in MeOH, 1.0 g) was stirred at room temperature for 1 hr. The mixture was purified by silica gel column chromatography (EtOAc : MeOH=5 : 1) to give 0.27 g (79%) of 1-methylamino-2-nitro-1-[(4-ethyl)tetrahydro-3-furyl}methylamino]ethylene (**26**) as a colorless solid, Mp 121–124°C. ^{1}H

NMR δ ($CDCl_3$): 0.94 (3H, t, J=7.3 Hz), 1.40–1.65 (2H, m), 1.82–1.92 (1H, br), 2.07–2.25 (1H, br), 2.82–2.95 (3H, br), 3.10–3.45 (4H, br), 3.70–3.85 (2H, br), 5.50–5.80 (1H, br), 6.58 (1H, s), 10.2–10.4 (1H, br). IR (KBr) cm^{-1}: 3256, 1566.

3.1.2. 1-Methyl-2-nitro-3-{(2-methyl)tetrahydro-3-furylmethyl}guanidine ***(14)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.26 (3H, d, J=6.6 Hz), 1.66–1.76 (2H, m), 2.09–2.27 (2H, m), 2.97 (3H, d, J=5.1 Hz), 3.35–3.39 (3H, m), 3.72–3.94 (3H, m). IR (neat) cm^{-1}: 3306, 1618.

3.1.3. 1-Methyl-2-nitro-3-{(2-methoxy)tetrahydro-3-furylmethyl}guanidine ***(15)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.60–1.75 (1H, m), 2.20–2.33 (1H, m), 2.42–2.57 (1H, m), 2.95–2.97 (3H, m), 3.28–3.40 (2H, m), 3.36 (2/3×3H, s), 3.39 (1/3×3H, s), 3.88–4.12 (2H, m), 4.81 (2/3×1H, d, J=2.2 Hz), 5.10 (1/3×1H, d, J=2.2 Hz).

3.1.4. 1-Methyl-2-nitro-3-{(3-methyl)tetrahydro-3-furylmethyl}guanidine ***(16)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.19 (3H, s), 1.78–1.92 (1H, m), 2.93 (3H, d, J=5.1 Hz), 3.15–3.40 (3H, m), 3.77–3.91 (2H, m), 4.04 (1H, dt, J=5.1 Hz, J=8.8 Hz). IR (neat) cm^{-1}: 3340, 1645.

3.1.5. 1-Methyl-2-nitro-3-{4-methyl)tetrahydro-3-furylmethyl}guanidine ***(17)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.05 (1/10×3H, d, J=6.6 Hz), 1.11 (9/10×3H, d, J=6.6 Hz), 1.86 (2H, br), 2.01–2.14 (2H, m), 2.95–2.98 (3H,m), 3.28–3.38 (3H, m), 3.67 (9/10×1H, dd, J=4.4 Hz, J=8.8 Hz), 3.74 (1/10×1H, dd, J=4.4 Hz, J=8.8 Hz), 3.90–4.07 (2H, t, m). IR (neat) cm^{-1}: 3304, 1618.

3.1.6. 1-Methyl-2-nitro-3-{(4-ethyl)tetrahydro-3-furylmethyl}guanidine ***(18)***

Oil. ^{1}H NMR δ ($CDCl_3$): 0.94 (3H, t, J=7.3 Hz), 1.38–1.59 (2H, m), 1.82–1.95 (1H, m), 2.15–2.27 (1H, m), 2.95 (3H, d, J=5.1 Hz), 3.30–3.43 (3H, m), 3.69 (1H, dd, J=3.7 Hz, J=9.5 Hz), 3.81 (1H, dd, J=6.6 Hz, J=9.5 Hz), 4.09 (3H, t, J=8.1 Hz). IR (neat) cm^{-1}: 3305, 1618.

3.1.7. 1-Methyl-2-nitro-3-{(3,4-dimethyl)tetrahydro-3-furylmethyl}guanidine ***(19)***

Oil. ^{1}H NMR δ ($CDCl_3$): 0.96–1.00 (3H, m), 1.02 (3/5×3H, s), 1.027 (2/5×3H, s), 2.04–2.22 (1H, m), 2.91–2.96 (3H, m), 3.05–3.21 (1H, m), 3.32–3.58 (3H, m), 4.71–4.90 (1H, m), 4.11–4.24 (1H, m). IR (neat) cm^{-1}: 3339, 1643.

3.1.8. 1-Methyl-2-nitro-3-{(5-methyl)tetrahydro-3-furylmethyl}guanidine ***(20)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.22 (1/2×3H, d, J=6.6 Hz), 1.29 (1/2×3H, d, J=6.6 Hz), 1.54–1.88 (2H, m), 2.05 (3H, s), 2.88–2.96 (2H, m), 3.33–4.20 (4H, m). IR (neat) cm^{-1}: 3313, 1619.

3.1.9. 1-Methyl-2-nitro-3-{(5-phenyl)tetrahydro-3-furylmethyl}guanidine ***(21)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.52–1.63 (1/2×1H, m), 1.99–2.22 (1/2×1H+1H, m), 2.51–2.61 (1/2×1H, m), 2.67–2.80 (1/2×1H, m), 2.84 (1/2×3H, d, J=5.1 Hz), 2.95 (1/2×3H, d, J=5.1 Hz), 3.41 (2H, d, J=5.1 Hz), 3.70–3.78 (1/2×1H, m), 3.86–4.01 (1H, m), 4.08–4.23 (1/2×1H, m), 4.84–4.89 (1/2×1H, m), 5.01–5.07 (1/2×1H, m), 7.23–7.36 (5H, m). IR (neat) cm^{-1}: 3301, 1617.

3.1.10. 1-Methyl-2-nitro-3-{(5,5-dimethyl)tetrahydro-3-furylmethyl}guanidine ***(22)***

Oil. ^{1}H NMR δ ($CDCl_3$): 1.22 (3H, s), 1.33 (3H, s), 1.43 (1H, dd, J=7.3 Hz, J=12.5 Hz), 2.01 (1H, dd, J=7.3 Hz, J=12.5 Hz), 2.68 (1H, septet, J=7.3 Hz), 2.97 (3H, d, J=4.4 Hz), 3.35 (1H, t, J=4.4 Hz), 3.62 (1H, dd, J=4.4 Hz, J=8.8 Hz), 3.95 (1H, dd, J=7.3 Hz, J=8.8 Hz). IR (neat) cm^{-1}: 3305, 1616.

3.1.11. 1-Methylamino-2-nitro-1-[{(2-methyl)tetrahydro-3-furyl}methylamino]ethylene ***(23)***

Mp 127–128°C. ^{1}H NMR δ ($CDCl_3$): 1.26–1.33 (3H, br), 1.64–1.76 (2H, br), 2.14–2.30 (2H, br), 2.88–2.96 (3H, br), 3.20–3.26 (2H, m), 3.71–3.98 (3H, m), 6.59 (1H, s), 10.3 (1H, br). IR (KBr) cm^{-1}: 3277, 1626.

3.1.12. 1-Methylamino-2-nitro-1-[{(2-methoxy)tetrahydro-3-furyl}methylamino]ethylene ***(24)***

Oil. ^{1}H NMR δ (DMSO): 1.45–1.60 (1H, br), 1.90–2.10 (1H, br), 2.70–2.80 (1H, br), 3.21 (3H, s), 3.34 (3H, s), 3.30–3.40 (2H, br), 3.75 (1H, q, J=8.1 Hz), 3.90 (1H, br), 4.83 (1H, br), 6.46 (1H, br), 7.25–7.73 (1H, br), 9.96–10.1 (1H, br).

3.1.13. 1-Methylamino-2-nitro-1-[{(4-methyl)tetrahydro-3-furyl}methylamino]ethylene ***(25)***

Mp 127–129°C. ^{1}H NMR δ ($CDCl_3$): 0.95 (1/10×3H, d, J=6.6 Hz), 1.00 (9/10×3H, d, J=6.6 Hz), 1.90–2.05 (2H, m), 2.65–2.85 (2H, br), 3.15–3.45 (4H, br), 3.75–3.90 (4H, m), 6.47 (1H, br), 10.1 (1H, br). IR (KBr) cm^{-1}: 3273, 1628.

3.1.14. 1-Methylamino-2-nitro-1-[{(5-methyl)tetrahydro-3-furyl}methylamino]ethylene ***(27)***

Mp 114–120°C. ^{1}H NMR δ (KBr): 1.12–1.30 (4H, m), 1.68–1.88 (1H, m), 2.19–2.29 (1H, m), 2.64 (1H, br), 2.87 (1/2×3H, d, J=5.1 Hz), 2.99 (1/2×3H, d, J=5.1 Hz), 3.20–3.45 (2H, br), 3.72–4.10 (3H, br), 6.60 (1H, s), 10.2 (1H, br).

3.1.15. 1-Methylamino-2-nitro-1-[{(5,5-dimethyl)tetrahydro-3-furyl}methylamino]ethylene ***(28)***

Mp 132–133°C. ^{1}H NMR δ ($CDCl_3$): 1.22 (3H, s), 1.33 (3H, s), 1.44–1.54 (1H, m), 2.02 (1H, dd, J=8.1 Hz, J=12.5 Hz), 2.69 (1H, septet, J=7.3 Hz), 2.87 (1/2×3H, 4, J=4.4 Hz), 3.00 (1/2×3H, d, J=4.4 Hz), 3.20–3.36 (2H, m), 3.56–3.62 (2H, m), 3.94–4.00 (2H, m), 6.32 (1/2×1H, br), 6.60 (1H, s), 6.61(1/2×1H, br), 10.3 (1H, br). IR (KBr) cm^{-1}: 3192, 1616.

3.1.16. 2-Nitromethylene-1-[{(4-methyl)tetrahydro-3-furyl}methyl]hexahydropyrimidine ***(29)***

Mp 94–97°C. ^{1}H NMR δ ($CDCl_3$): 1.01 (1/10×3H, d, J=6.6 Hz), 1.10 (9/10×3H, d, J=6.6 Hz), 1.62–2.10 (3H, m), 2.14–2.27 (1H, m), 3.09 (1H, dd, J=8.8 Hz, J=14.7 Hz), 3.30–3.48 (6H, m), 3.56 (1H, dd, J=5.9 Hz, J=8.8 Hz), 3.90 (1H, dd, J=6.6 Hz, J=8.8 Hz), 4.05 (1H, dd, J=7.3 Hz, J=8.8 Hz), 6.63 (1/10×1H, s), 6.65 (9/10×1H, s), 10.1 (1H, br). IR (KBr) cm^{-1}: 3490, 1585.

*3.1.17. 2-Nitromethylene-1-[{(4-ethyl)tetrahydro-3-furyl}methyl]hexahydropyrimidine (**30**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 0.93 (3H, t, J=7.3 Hz), 1.33–1.59 (2H, m), 1.71–1.82 (1H, m), 2.01–2.09 (2H, m), 2.21–2.32 (1H, m), 3.10 (1H, dd, J=8.8 Hz, J=14.7 Hz), 3.31 (1H, dd, J=6.6 Hz, J=14.7 Hz), 3.35–3.48 (4H, m), 3.56 (1H, dd, J=5.1 Hz, J=8.8 Hz), 3.72 (1H, q, J=7.3 Hz), 3.81 (1H, dd, J=7.3 Hz, J=8.8 Hz), 4.06 (1H, dd, J=7.3 Hz, J=8.8 Hz), 6.65 (1H, s), 9.75 (1H, br). IR (neat) cm^{-1}: 3428, 1589.

*3.1.18. 2-Nitromethylene-1-[{(5-methyl)tetrahydro-3-furyl}methyl]hexahydropyrimidine (**31**)*

Mp 92–93°C. ^{1}H NMR δ ($CDCl_3$): 1.23 (1/2×3H, d, J=6.6 Hz), 1.29 (1/2×3H, d, J=6.6 Hz), 1.60–1.81 (2H, m), 2.01–2.09 (2H, m), 2.63–2.76 (1H, m), 3.08–3.35 (2H, m), 3.40–3.48 (5H, m), 3.59–3.63 (1/3×1H, m), 3.76–3.82 (1/2×1H, m), 3.89–4.01 (1/2×1H, m), 4.09–4.21 (2/3×1H, m), 6.65 (1H, s), 10.3 (1H, br). IR (KBr) cm^{-1}: 3448. 1589.

*3.1.19. 2-Nitromethylene-1-[{(5,5-dimethyl)tetrahydro-3-furyl}methyl]hexahydropyrimidine (**32**)*

Mp 119–121°C. ^{1}H NMR δ ($CDCl_3$): 1.21 (3H, s), 1.32 (3H, s), 1.43 (1H, dd, J=8.1 Hz, J=12.4 Hz), 2.04 (1H, dd, J=8.1 Hz, J=12.5 Hz), 2.10 (2H, quintet, J=5.9 Hz), 2.73 (1H, septet, J=8.1 Hz), 3.21 (1H, dd, J=8.1 Hz, J=14.7 Hz), 3.32 (1H, dd, J=6.6 Hz, J=14.7 Hz), 3.42–3.48 (4H, m), 3.52 (1H, dd, J=6.6 Hz, J=8.8 Hz), 3.98 (1H, dd, J=7.3 Hz, J=8.8 Hz), 6.62 (1H, s), 9.88 (1H, br). IR (KBr) cm^{-1}: 1585, 1431.

*3.1.20. 2-Nitroimino-1-[{(4-methyl)tetrahydro-3-furyl}-methyl]hexahydropyrimidine (**33**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.01 (1/10×3H, d, J=6.6 Hz), 1.07 (9/10×3H, d, J=6.6 Hz), 1.67–2.10 (3H, m), 2.14–2.27 (1H, m), 3.31–3.53 (6H, m), 3.58 (1H, dd, J=6.6 Hz, J=8.8 Hz), 3.68 (1H, dd, J=6.6 Hz, J=13.7 Hz), 3.92 (1H, dd, J=7.3 Hz, J=8.8 Hz), 4.02 (1H, t, J=7.3 Hz), 9.78 (1H, br). IR (neat) cm^{-1}: 3276, 1735.

*3.1.21. 2-Nitroimino-1-[{(5-methyl)tetrahydro-3-furyl}-methyl]hexahydropyrimidine (**34**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.23 (1/2×3H, d, J=6.6 Hz), 1.27 (1/2×3H, d, J=6.6 Hz), 1.55–1.86 (2H, m), 2.01–2.15 (2H, m), 2.69–2.86 (1H, m), 3.32–3.50 (5H, m), 3.57–3.84 (2H, m), 3.92–4.00 (1H, m), 4.08–4.18 (1H, m), 9.78 (1H, br). IR (neat) cm^{-1}: 3275, 1592.

*3.1.22. 2-Nitroimino-1-[{(5,5-dimethyl)tetrahydro-3-furyl}methyl]hexahydropyrimidine (**35**)*

Oil. ^{1}H NMR δ ($CDCl_3$): 1.21 (3H, s), 1.31 (3H, s), 1.47 (1H, dd, J=8.8 Hz, J=12.5 Hz), 1.91 (1H, dd, J=8.8 Hz, J=12.5 Hz), 2.01–2.09 (2H, m), 2.71–2.88 (1H, m), 3.40–3.67 (7H, m), 3.94 (1H, dd, J=7.3 Hz, J=8.8 Hz), 9.78 (1H, br). IR (neat) cm^{-1}: 3285, 1592.

4. Biological Tests

4.1. 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 h light : dark photoperiod.

4.2. 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

1. Conformational Analysis of Dinotefuran (2), Clothianidin (3), Imidacloprid (5) and a 3-Methoxypropyl Compound (10)

When the 3-methoxypropyl moiety was cyclized to the (±)-(tetrahydro-3-furyl)methyl moiety, dinotefuran (**2**) exhibited more than a 100-fold higher level of activity than the 3-methoxypropyl compound (**10**) against *N. cincticeps*. We assumed that dinotefuran and other neonicotinoids have a common 3D-pharmacophore for binding to nicotinic acetylcholine receptors because of their structural similarity and mode of action,[10] and that it would be difficult for **10** to have the same conformation because of its weak activity. In order to test this hypothesis, a conformational analysis of neonicotinoids (dinotefuran (**2**), clothianidin (**3**), imidacloprid (**5**)) and the 3-methoxypropyl compound (**10**) was carried out.

First of all, we generated individual conformer databases according to the procedure described in the methods. The conformational databases were then entered into the DISCO program to perform the superimposition of the four compounds. The different superimposition models proposed by DISCO were grouped into three types that showed a good overlay of the compounds (Fig. 4). Superposition A, B and C shown in Fig. 2 correspond to the active conformation models proposed by Okazawa *et al.*[11,12] and Samaritoni *et al.*,[13] respectively. In all superposition models, the hypothetical receptor-associated hydrogen bond acceptor sites generated from the tetrahydro-3-furan, pyridine and thiazole rings are located in the same place. Thus, the oxygen atom in the tetrahydro-3-furan group of dinotefuran (**2**) can function as the hydrogen acceptor site in place of the nitrogen atoms in the pyridine or thiazole rings.

At the end of the conformational search, we obtained 16 and 78 energy-minimized conformers for dinotefuran (**2**) and compound **10** with energy ranges (the energy difference between the highest and the lowest energy conformer) of 4.5 and 8.1 kcal/mol, respectively. Three conformations out of 16 have the receptor-associated hydrogen bond acceptor within

2 Å from that of the active conformer when the imidazolidine parts are superposed onto superposition A. Twenty-four percent of all energy-minimized conformations took superposition A on the basis of the Boltzmann probability distribution at room temperature (300 kelvin). On the other hand, six conformations among 78 can take the conformation (superposition A) in **10**, but this was only 4.5%.

The straight-chain ether is so flexible that **10** has to lose

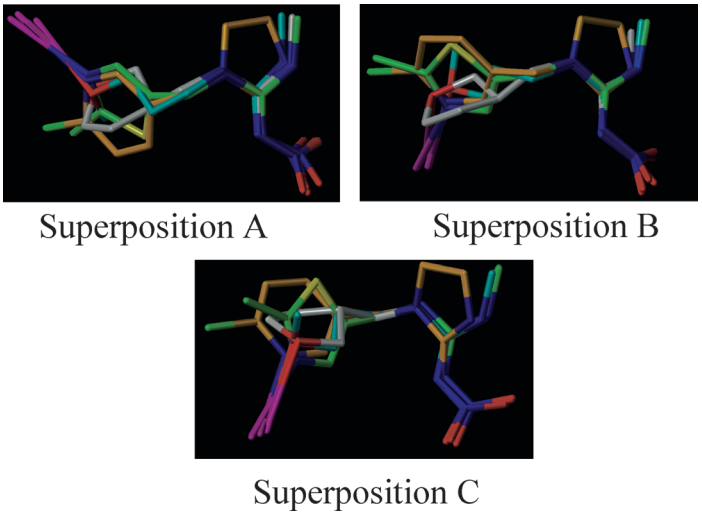


Fig. 4. Molecular superpositions of known neonicontinoids and the 3-methoxypropyl compound (**10**) using a hydrogen-devoid backbone-type representation. The carbons of dinotefuran (**2**), clothianidin (**3**), imidacloprid (**5**) and **10** are shown in white, green, orange and cyan, respectively. The oxygen, nitrogen and sulfar are shown in red, blue and yellow, respectively. The hydrogen acceptor site defined in DISCO is also shown in magenta. Hydrogen atoms are not shown.

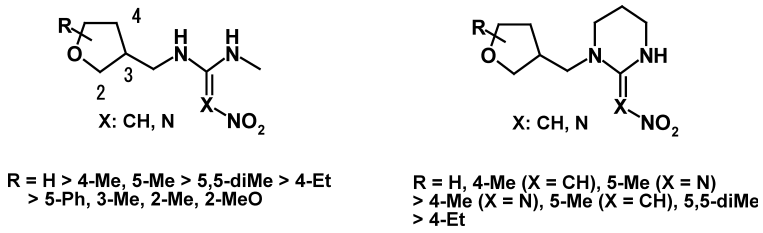


Fig. 5. SARs of the acyclic and cyclic compounds.

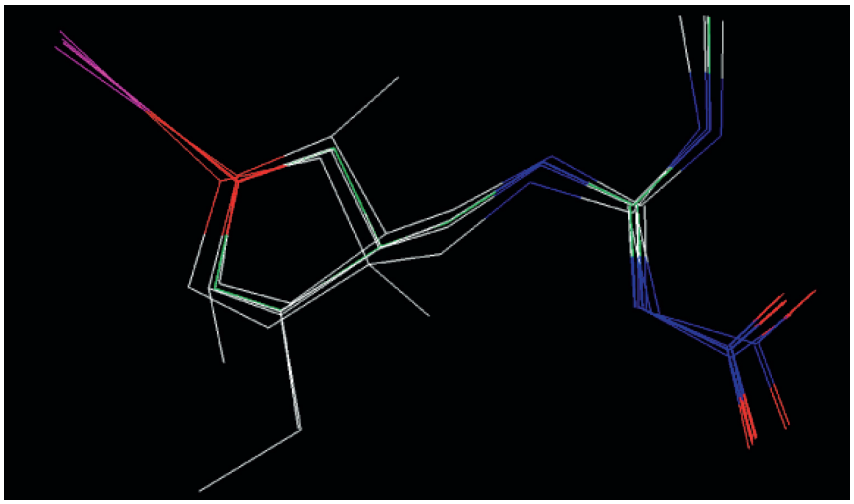


Fig. 6. Molecular superpositions of the acyclic nitroimino compounds with the Superposition A conformation. Carbon, oxygen and nitrogen are shown in white, red and blue, respectively. Hydrogen atoms are not shown. Dinotefuran is shown in green.

more entropy upon binding. On the other hand, cyclization of the ether group in dinotefuran (**2**) restricts the conformational degree of freedom and then reduces the entropy loss upon binding. We speculate that the reduced loss of conformational entropy of **2** upon binding (structural rigidity) contributes considerably to the activity as compared with **10**. However, **2** was over 100-fold more active than **10** (data not shown). These results suggest that the weak activity of **10** would be caused by the interaction with the receptor.

2. SAR for the Tetrahydro-3-furan Part of Dinotefuran

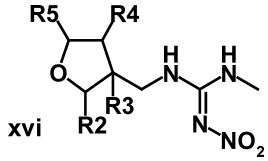
Four types of insecticidal activities; acyclic nitroimino compounds (**2** and **14**–**22**), acyclic nitromethylene compounds (**11** and **23**–**28**), cyclic nitroimino compounds (**13** and **33**–**35**) and cyclic nitromethylene compounds (**12** and **29**–**32**), are shown in Tables 1–3. In general, all four types have a similar SAR for the tetrahydro-3-furan part (Fig. 5). The 2- or 3-substitutions on tetrahydro-3-furan were detrimental to the activity, and the 4- and 5-substitutions reduced the activity to some extent but there is a size limitation. The details are as follows.

Unsubstituted compounds (**2** and **11**–**13**) showed the highest level of activity for each type. The 2-Me or 3-Me substituted compounds (**14**–**16**, **19** and **23**–**24**) lost activity. In regard to the 4- and/or 5-substituted compounds, various levels of activity were observed. As for acyclic nitroimino compounds, 4-Me and 5-Me substituted compounds (**17** and **20**) were 100-fold less active against *L. striatellus* and 10-fold less active against *N. cincticeps* than **2**. Increasing the size of the substituent from a methyl to ethyl, phenyl or dimethyl lowered the level of activity (**18**, **21** and **22**). Acyclic nitromethylene compounds showed the same SAR but the activity of cyclic compounds was not as weak as that of acyclic types. For example, the 4-Me-substituted nitromethylene compound (**29**) and the 5-Me-substituted nitroimino compound (**34**) showed the same level of activity as each unsubstituted compounds (**12** and **13**), and the other Me-substituted compounds did not exhibit a drop in activity of more than 10-fold (**31**–**33** and **35**) either.

3. Structural Analysis of Substituted (Tetrahydro-3-furyl)methyl Compounds

The conformational search was also performed with acyclic nitroimino compounds (Fig. 6; **14**, **16**–**18** and **20**). The substituent on the tetrahydrofuran ring, which has the trans con-

Table 1. Insecticidal activities of acyclic nitroimino compounds **xvi**



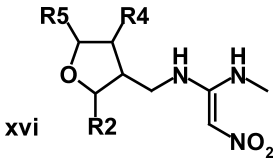
No.	R1–R5	LS	NC
2	H	4	4
14	2-Me[a]	0	0
15	2-MeO[b]	0	0
16	3-Me	0	0
17	4-Me[c]	2	3
18	4-Et[d]	0	1
19	3-Me, 4-Me[e]	0	0
20	5-Me[f]	2	3
21	5-phenyl[g]	0	0
22	5-Me, 5-Me	1	3

LS: *Laodelphax striatellus*.

NC: *Nephotettix cincticeps*.

[a–g] Diastereo mixtures (determined by ^{1}H NMR. [a] *trans*, [b] (2 : 1), [c] (9 : 1), [d] *trans*, [e] (3 : 2), [f] (1 : 1), [g] (1 : 1)).

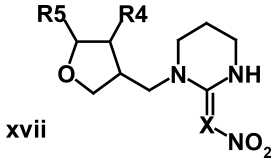
Table 2. Insecticidal activities of acyclic nitromethylene compounds **xvi**



No.	R2–R5	LS	NC
11	H	4	4
23	2-Me[a]	0	0
24	2-MeO[b]	0	0
25	4-Me[c]	3	3
26	4-Et[d]	0	1
27	5-Me[f]	2	3
28	5-Me, 5-Me	2	3

Abbreviations, see Table 1.

Table 3. Insecticidal activities of cyclic compounds **xvii**



No.	X	R4, R5	LS	NC
12	CH	H	3	4
29	CH	4-Me[c]	3	4
30	CH	4-Et[d]	1	0
31	CH	5-Me[f]	3	3
32	CH	5-Me, 5-Me	3	3
13	N	H	3	4
33	N	4-Me[c]	2	4
34	N	5-Me[f]	3	4
35	N	5-Me, 5-Me	2	3

Abbreviations, see Table 1.

figuration, was used. The conformational databases were then entered into the DISCO program to perform the superimposition of all compounds with dinotefuran, clothianidin and imidacloprid. All compounds could satisfy the conditions of superpositions A, B and C with the energy-minimized conformations. A typical example of superposition A is shown in Fig. 5. Their potential energies *in vacuo* are relatively low (within 3 kcal mol^{-1} from the lowest energy conformation). Thus, the weak activity of compounds **14** and **16** might be caused not by the difficulty in adopting the active conformation but by other factors, such as the interaction with the receptor and so on.

REFERENCES

1) I. Yamamoto: "Nicotinoid Insecticides and the Nicotinic Acetylcholine Receptor," ed. by I. Yamamoto and J. E. Casida, Springer, Tokyo, pp. 3–27, 1999.
2) T. Wakita, K. Konoshita, E. Yamada, N. Yasui, N. Kawahara, A Naoi, M. Nakaya, K. Ebihara, H, Matsuno and K. Kodaka: *Pest Manag. Sci.* **59**, 1016–1022 (2003).
3) T. Wakita, K. Kinoshita, N. Yasui, E. Yamada, N. Kawahara and K. Kodaka: *J. Pestic. Sci.* **29**, 348–355 (2004).
4) T. A. Halgren: *J. Comput. Chem.* **20**, 720–729 (1999).
5) T. A. Halgren: *J. Comput. Chem.* **17**, 520–552 (1996).
6) Y. C. Martin, M. G. Bures, E. A. Danaher, J. DeLazzer, I. Lico and P. A. Pavlick: *J. Comput. Aided Mol. Des.* **7**, 83–102 (1993).
7) T. Wakita, H. Matsuno and K. Kodaka (Mitsui Chemicals, Inc.): *Jpn. Kokai Tokkyo Koho* JP 8-291159 (1996) (in Japanese).
8) H. Suzuki, H. Yashima, T. Hirose, M. Takahashi, Y. Morooka and T. Ikawa: *Tetrahedron Lett.* **21**, 4927–4930 (1980).
9) F. Korte and H. Machleidt: *Chem. Ber.* **88**, 1684–1689 (1955).
10) T. Okumoto, K. Mori, N. Kawahara and Y. Ozoe: *Abstr. 25th Annu. Meeting Pestic. Sci. Soc. Jpn.*, p. 115 (2000) (in Japanese).
11) A. Okazawa, M. Akamatsu, A. Ohoka, H. Nishiwaki, W. Cho, Y. Nakagawa, K. Nishimura and T. Ueno: *Pestic. Sci.* **54**, 134–144 (1998).
12) A. Okazawa, M. Akamatsu, H. Nishiwaki, Y. Nakagawa, H. Miyagawa, K. Nishimura and T. Ueno: *Pest Manag. Sci.* **56**, 509–515 (2000).
13) J. Samaritoni, D. A. Demeter, J. M. Gifford, G. B. Watson, M. S. Kempe and T. J. Bruce: *J. Agric. Food Chem.* **51**, 3035–3042 (2003).