The discovery of thiamethoxam: a second-generation neonicotinoid†

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Abstract: Neonicotinoids represent a novel and distinct chemical class of insecticides with remarkable chemical and biological properties. In 1985, a research programme was started in this field, in which novel nitroimino heterocycles were designed, prepared and assayed for insecticidal activity. The methodology for the synthesis of 2-nitroimino-hexahydro-1,3,5-triazines, 4-nitroimino-1,3,5-oxadiazinanes and 4-nitroimino-1,3,5-thiadiazinanes is outlined. Bioassays demonstrated that 3-(6-chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-oxadiazinane exhibited better insecticidal activity than the corresponding 2-nitroimino-hexahydro-1,3,5-triazine and 4-nitroimino-1,3,5-thiadiazinane. In most tests, this compound was equally or only slightly less active than imidacloprid. A series of structural modifications on this lead structure revealed that replacement of the 6-chloro-3-pyridyl group by a 2-chloro-5-thiazolyl moiety resulted in a strong increase of activity against chewing insects, whereas the introduction of a methyl group as pharmacophore substituent increased activity against sucking pests. The combination of these two favourable modifications led to thiamethoxam (CGA 293 343).

Thiamethoxam is the first commercially available second-generation neonicotinoid and belongs to the thianicotinyl sub-class. It is marketed under the trademarks Actara® for foliar and soil treatment and Cruiser® for seed treatment. The compound has broad-spectrum insecticidal activity and offers excellent control of a wide variety of commercially important pests in many crops. Low use rates, flexible application methods, excellent efficacy and the favourable safety profile make this new insecticide well-suited for modern integrated pest management programmes in many cropping systems.

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Keywords: insecticides; neonicotinoids; thiamethoxam; discovery; synthesis; 2-nitroimino-hexahydro-1,3,5-triazines; 4-nitroimino-1,3,5-oxadiazinanes; 4-nitroimino-1,3,5-thiadiazinanes; insecticidal activity; structure-activity relationships

1 INTRODUCTION

Neonicotinoids[1] represent a novel and distinct chemical class of insecticides with remarkable chemical and biological properties.[2] Researchers at Shell described in 1972 for the first time the insecticidal properties of some simple nitromethylene heterocycles (Fig 1, **1**).[3,4] Their work resulted in the discovery of nithiazine (**2**),[5] a compound which has never been commercialised as a crop-protection agent. This compound, however, has served as a neonicotinoid lead structure. Thirteen years later, with the synthesis of imidacloprid (**3**), Nihon Tokushu Nohyaku (now Nihon Bayer) achieved an important breakthrough in this chemistry. By introducing a 6-chloropyridin-3-ylmethyl group as a substituent of the nitromethylene heterocycle, the insecticidal activity against green rice leafhoppers could be enhanced by a factor of more than 100.[6] First patent applications covering this new invention were published in 1985,[7] and this triggered extensive research activities within several other companies. Ciba (since 1996 Novartis), Takeda, Nippon Soda, Agro Kanesho, Mitsui Chemicals and others immediately entered this promising research area. Shortly after the launch of imidacloprid in 1991, nitenpyram (**4**)[8] (Takeda, 1995) and acetamiprid (**5**)[9] (Nippon Soda, 1996) were brought to the market. Each of these three products has a 6-chloropyrid-3-ylmethyl moiety as a heterocyclic group. This is a common structural feature of first-generation neonicotinoids.[10]

In 1998, Novartis launched thiamethoxam (**6**),[10–12] a novel neonicotinoid with a unique structure and outstanding insecticidal activity. Three other products, thiacloprid (**7**)[13] (Bayer), clothianidin (**8**)[14–16] (Takeda, Bayer) and dinotefuran (**9**)[17] (Mitsui Chemicals), are currently under development and are expected to enter the marketplace in due course.

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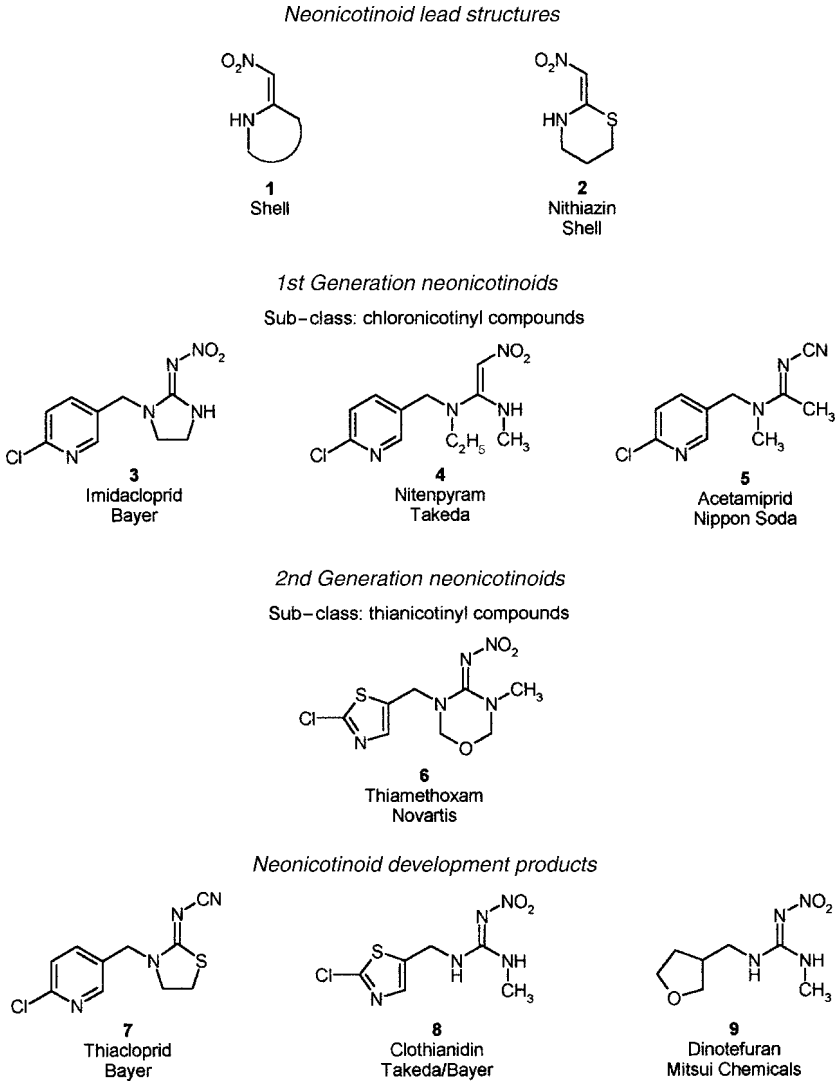


Figure 1. Neonicotinoid lead, commercial and development compounds.

Since the market introduction of imidacloprid, the neonicotinoids have been the fastest growing chemical class of insecticide. This tremendous success can be explained by their unique chemical and biological properties, such as broad-spectrum insecticidal activity, low application rates, excellent uptake and translocation in plants, new mode of action and favourable safety profile.

Ciba started a research programme on neonicotinoids in 1985. Our efforts resulted in the synthesis of acyclic nitroenamines, acyclic cyanoguanidines, acyclic nitroguanidines, 3-heterocyclylmethyl-2-nitromethylene-pyrrolidines, isoxazoles and novel nitroimino heterocycles such as 4-nitroimino-1,3,5-oxadiazinanes.[10] Among these chemistries, 4-nitroimino-1,3,5-oxadiazinane derivatives were found to possess the most interesting chemical and biological properties. Thiamethoxam (**6**) was identified as the best representative of this novel class of compound and selected for world-wide development. Belonging to the sub-class of thianicotinyl compounds,[10] it represents the first example of second-generation neonicotinoids. The present communication reports the discovery of this compound, which is marketed under the trade names Actara® for foliar and soil treatment, and Cruiser® for seed treatment.

2 MATERIALS AND METHODS

2.1 Chemical synthesis

Imidacloprid (**3**),[7] nitenpyram (**4**),[18] acetamiprid (**5**),[19] *S*-methyl-*N*-nitroisothiourea (**10**),[20] compound **24**,[21] 6-chloropyridin-3-ylmethylamine,[18] 6-chloropyridin-3-ylmethyl chloride,[22] 2-chlorothiazol-5-ylmethyl chloride[23] and 2-chlorothiazol-5-ylmethylamine[18] were prepared according to literature procedures. The synthetic pathways used to prepare the new nitroimino-heterocycles are discussed in detail in Section 3.2 and the syntheses of the 4-nitroimino-1,3,5-oxadiazinanes in Section 3.3.

Representative procedures are given below; the yields were not optimised. All spectra were consistent with the assigned structures, and all compounds were >98% purity based on TLC and [^{1}H]NMR spectra.

2.1.1 N-*(6-chloropyridin-3-ylmethyl)*-N′-*nitroguanidine (**11a**)*

A mixture of *S*-methyl-*N*-nitroisothiourea (**10**; 3.0 g, 22.2 mmol) and 6-chloropyridin-3-ylmethylamine (3.17 g, 22.2 mmol) in ethanol (25 ml) was heated at 80 °C for 3 h. On cooling to room temperature, *N*-(6-chloropyridin-3-ylmethyl)-*N′*-nitroguanidine (**11a**) crystallised out of the reaction mixture as a white solid. Yield 4.26 g, 84%, mp 198–200 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.97 (bs, 1H), 8.38 (d, J = 2 Hz, 1H), 8.08 (bs, 2H), 7.79 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.55 (d, J = 7 Hz, 1H), 4.44 (bd, J = 3 Hz, 2H). Calculated for $C_7H_8ClN_5O_2$: C, 36.61; H, 3.51; Cl, 15.44; N, 30.50. Found: C, 36.9; H, 3.7; Cl, 15.4; N, 30.5.

*2.1.2 1-(6-chloropyridin-3-ylmethyl)-5-methyl-2-nitroimino-hexahydro-1,3,5-triazine (**12**)*

A mixture of **11a** (2.59 g, 11.3 mmol), 37% aqueous formaldehyde solution (1.75 ml, 22.6 mmol), 40% aqueous methylamine solution (1.0 ml, 11.3 mmol) and ethanol (10 ml) was heated to 50 °C for 4 h. The solution was then evaporated to dryness under reduced pressure, and the solid residue recrystallised from ethanol + ethyl acetate to afford **12** as a white solid, yield 2.78 g, 86%, mp 157–159 °C. [^{1}H]NMR (250 MHz, $CDCl_3$): 9.64 (bs, 1H), 8.32 (d, J = 2 Hz, 1H), 7.82 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.36 (d, J = 7 Hz, 1H), 4.65 (s, 2H), 4.38 (bs, 2H), 4.26 (s, 2H), 2.47 (s, 3H). Calculated for $C_{10}H_{13}ClN_6O_2$: C, 42.19; H, 4.60; Cl, 12.45; N, 29.52. Found: C, 42.2; H, 4.7; Cl, 12.1; N, 29.2.

*2.1.3 (6-Chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-oxadiazinane (**13a**)*

2.1.3.1 Method A. A mixture of **11a** (3.0 g, 13.1 mmol), 37% aqueous formaldehyde solution (10 ml) and formic acid (10 ml) was heated to 80 °C for 18 h. After cooling to 0 °C, aqueous sodium hydroxide solution (300 g litre^{-1}, approximately 30 ml) was added to adjust the solution to pH 8. The resulting mixture was then extracted with dichloromethane. The organic layer was separated, washed with brine, dried with anhydrous sodium sulfate and evaporated. The solid residue was recrystallised from ethyl acetate + ether to afford **13a** as a white solid, yield 2.09 g, 59%, mp 166–168 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 9.81 (bs, 1H), 8.37 (d, J = 2 Hz, 1H), 7.81 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.53 (d, J = 7 Hz, 1H), 5.02 (s, 2H), 4.95 (d, J = 2 Hz, 2H), 4.60 (s, 2H). Calculated for $C_9H_{10}ClN_5O_3$: C, 39.79; H, 3.71; Cl, 13.05; N, 25.78. Found: C, 39.71; H, 3.74; Cl, 12.92; N, 25.74.

2.1.3.2 Method B. A mixture of 4-nitroimino-1,3,5-oxadiazinane (**17a**; 2.5 g, 17 mmol), 6-chloropyridin-3-ylmethyl chloride (2.8 g, 17 mmol) and potassium carbonate (5.6 g, 40 mmol) in *N*,*N*-dimethylformamide (DMF; 20 ml) was stirred at 30 °C for 18 h. The reaction mixture was filtered through Celite, the filtrate concentrated under vacuum, and the residue purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to yield **13a**, yield 1.1 g, 24%. 3,5-Bis(6-chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-oxadiazinane (**19**) was isolated as a by-product, yield 0.5 g, 11%, mp 190–192 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.48 (d, J = 2 Hz, 2H), 7.82 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 7.57 (d, J = 7 Hz, 2H), 5.12 (s, 4H), 4.60 (s, 4H).

*2.1.4 3-(6-Chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-thiadiazinane (**14**)*

2.1.4.1 Method A. To a mixture of **11a** (10.0 g, 46.6 mmol) and 37% aqueous formaldehyde solution (8.7 ml) in nitromethane (130 ml) was added concentrated hydrochloric acid (43.5 ml) and then, over a 10 min period, sodium sulfide nonahydrate (10.4 g, 43.3 mmol). The mixture was heated at reflux temperature for 5 h and then concentrated under vacuum. The residue was purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to yield **14** as a white solid, yield 0.10 g, 0.8%, mp 161–163 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 10.21 (s, 1H), 8.38 (d, J = 2 Hz, 1H), 7.81 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.55 (d, J = 7 Hz, 1H), 4.79 (s, 2H), 4.75 (s, 2H), 4.63 (s, 2H). Calculated for $C_9H_{10}ClN_5O_2S$: C, 37.57; H, 3.50; Cl, 12.32; N, 24.34; S, 11.14. Found: C, 37.52; H, 3.56; Cl, 12.15; N, 24.49; S, 11.32.

2.1.4.2 Method B. A mixture of 4-nitroimino-1,3,5-thiadiazinane (**18**; 27.0 g, 166 mmol), 6-chloropyridin-3-ylmethyl chloride (27.0 g, 166 mmol) and potassium carbonate (55.0 g, 399 mmol) in DMF (200 ml) was stirred at room temperature for 24 h. After filtration, the filtrate was concentrated under vacuum and the residue was purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to give **14**, yield 11.2 g, 23%. 3,5-Bis(6-chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-thiadiazinane (**20**) was isolated as a by-product, yield 13.0 g, 19%, mp 181–182 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.41 (d, J = 2 Hz, 2H), 7.85 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 7.58 (d, J = 7 Hz, 2H), 4.81 (s, 4H), 4.77 (s, 4H).

2.1.5 N-*Methyl*-N′-*nitroguanidine (**15b**)*

A mixture of **10** (83.0 g, 0.614 mol) and an 8.0 M solution of methylamine in ethanol (91.0 ml, 0.737 mol) in ethanol (230 ml) was stirred for 1 h at room temperature and then for 3 h at 80 °C. On cooling to 0 °C, **15b** crystallised out of the reaction mixture as a white solid, yield 70.0 g, 97%, mp 160–162 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.60 (bs, 1H), 7.85 (bs, 2H), 2.78 (d, J = 3 Hz, 3H). Calculated for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44. Found: C, 20.37; H, 5.17; N, 47.17.

*2.1.6 5-Methyl-2-nitroimino-hexahydro-1,3,5-triazine (**16**)*

A mixture of nitroguanidine (**15a**; 26.0 g, 0.25 mol), 37% aqueous formaldehyde solution (38.0 ml, 0.50 mol), an 8.03 M solution of methylamine in ethanol (31.1 ml, 0.25 mol) and ethanol (100 ml) was heated to 50 °C for 3 h. On cooling to 0 °C, **16** crystallised out as a white solid, yield 28.3 g, 71%, mp 173–175 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.72 (bs, 2H), 4.19 (s, 4H), 2.41 (s, 3H). Calculated for $C_4H_9N_5O_2$: C, 30.19; H, 5.70; N, 44.00. Found: C, 30.20; H, 5.88; N, 43.92.

*2.1.7 4-Nitroimino-1,3,5-oxadiazinane (**17a**)*

A mixture of nitroguanidine (**15a**; 5.0 g, 38.4 mmol), 37% aqueous formaldehyde solution (40 ml) and formic acid (40 ml) was heated to 80 °C for 16 h. After cooling to 0 °C, aqueous sodium hydroxide solution (300 g litre^{-1}, approximately 90 ml) was added to adjust the solution to pH 8. The resulting mixture was then extracted with dichloromethane. The organic layer was separated, washed with brine, dried with anhydrous sodium sulfate and evaporated. The solid residue was recrystallised from ethyl acetate to afford **17a** as a white solid, yield 2.90 g, 52%, mp >250 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 9.17 (bs, 2H), 4.88 (s, 4H). Calculated for $C_3H_6N_4O_3$: C, 24.66; H, 4.14; N, 38.35. Found: C, 24.7; H, 4.1; N, 38.3.

*2.1.8 3-Methyl-4-nitroimino-1,3,5-oxadiazinane (**17b**)*

A mixture of *N*-methyl-*N′*-nitroguanidine (**15b**; 4.0 g, 33.9 mmol), 37% aqueous formaldehyde solution (25 ml) and formic acid (25 ml) was heated to 80 °C for 15 h. After cooling to 0 °C, aqueous sodium hydroxide solution (300 g litre^{-1}, approximately 60 ml) was added to adjust the solution to pH 8. The resulting mixture was then extracted with dichloromethane. The organic layer was separated, washed with brine, dried with anhydrous sodium sulfate, and evaporated. The solid residue was recrystallised from ethyl acetate + diethyl ether to afford **17b** as a white solid, yield 3.84 g, 71%, mp 140–142 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 9.64 (bs, 1H), 4.90 (bs, 4H), 2.87 (s, 3H). Calculated for $C_4H_8N_4O_3$: C, 30.00; H, 5.04; N, 34.99. Found: C, 30.09; H, 4.94; N, 34.89.

*2.1.9 4-Nitroimino-1,3,5-thiadiazinane (**18**)*

To a mixture of nitroguanidine (**15a**; 41.6 g, 0.40 mol), and 37% aqueous formaldehyde solution (80 ml) in nitromethane (120 ml) was added concentrated hydrochloric acid (88 ml) and then, over a 30-min period, sodium sulfide nonahydrate (96 g, 0.40 mol). The mixture was heated at reflux temperature for 5 h, then filtered and concentrated under vacuum to give **18** as a white solid, 53.0 g, 41%, mp 222–223 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 9.46 (bs, 2H), 4.51 (d, J = 3 Hz, 4H). Calculated for $C_3H_6N_4O_2S$: C, 22.22; H, 3.73; N, 34.55; S, 19.77. Found: C, 22.27; H, 3.71; N, 34.62; S, 19.37.

*2.1.10 3-(6-Chloropyridin-3-ylmethyl)-5-methyl-4-nitroimino-1,3,5-oxadiazinane (**21a**)*

2.1.10.1 Method A. A mixture of 3-methyl-4-nitroimino-1,3,5-oxadiazinane (**17b**; 1.44 g, 9.0 mmol), 6-chloropyridin-3-ylmethyl chloride (2.20 g, 13.5 mmol) and potassium carbonate (3.73 g, 27.0 mmol) in DMF (20 ml) was stirred at 50 °C for 5 h. The reaction mixture was then filtered through Celite, and the resulting solution concentrated under vacuum. The residue was purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to give **21a** as a white solid, yield 1.93 g, 75%, mp 129–130 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 8.34 (d, J = 2 Hz, 1H), 7.77 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.55 (d, J = 7 Hz, 1H), 5.07 (s, 2H), 5.02 (s, 2H), 4.66 (s, 2H), 2.88 (s, 3H). Calculated for $C_{10}H_{12}ClN_5O_3$: C, 42.04; H, 4.23; Cl, 12.41; N, 24.51. Found: C, 42.2; H, 4.2; Cl, 12.3; N, 24.5.

2.1.10.2 Method B. A mixture of 3-(6-chloropyridin-3-ylmethyl)-4-nitroimino-1,3,5-oxadiazinane (**13a**; 1.50 g, 5.5 mmol), methyl iodide (1.18 g, 8.3 mmol) and potassium carbonate (1.91 g, 13.8 mmol) in DMF (20 ml) was stirred at 40 °C for 3 h. The reaction mixture was then filtered through Celite and the resulting solution concentrated under vacuum. The residue was purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to give **21a** as a white solid, yield 1.0 g, 63%.

*2.1.11 3-(2-Chlorothiazol-5-ylmethyl)-5-methyl-4-nitroimino-1,3,5-oxadiazinane (thiamethoxam; **6**)*

2.1.11.1 Method A. A mixture of 3-methyl-4-nitroimino-1,3,5-oxadiazinane (**17b**; 8.30 g, 52.0 mmol), 2-chlorothiazol-5-ylmethyl chloride (11.0 g, 65 mmol) and potassium carbonate (17.3 g, 125 mmol) in DMF (50 ml) was stirred at 50 °C for 16 h. The reaction mixture was then filtered through Celite and the resulting solution concentrated under vacuum. The residue was purified by chromatography on silica gel using dichloromethane + methanol (19 + 1 by volume) as eluent to give 6 as a white solid, yield 10.7 g, 71%, mp 140–141 °C. [^{1}H]NMR (250 MHz, d_6-DMSO): 7.64 (s, 1H), 5.07 (s, 2H), 4.98 (s, 2H), 4.77 (s, 2H), 2.87 (s, 3H). Calculated for $C_8H_{10}ClN_5O_3S$: C, 32.94; H, 3.46; Cl, 12.15; N, 24.01; S, 10.99. Found: C, 33.02; H, 3.44; Cl, 12.21; N, 24.08; S, 10.98.

2.1.11.2 Method B. A mixture of 3-(2-chlorothiazol-5-ylmethyl)-4-nitroimino-1,3,5-oxadiazinane (**13b**; 1.50 g, 5.4 mmol), methyl iodide (1.15 g, 8.1 mmol) and potassium carbonate (1.87 g, 13.5 mmol) in DMF (20 ml) was stirred at 40 °C for 3 h. The reaction mixture was then filtered through Celite and the resulting solution concentrated under vacuum. The residue was purified by chromatography on silica gel

using THF + hexane (4 + 1 by volume) as eluent to give **6**, yield 1.22 g, 77%.

2.2 Biological assays

Each compound was formulated as a standard 50 g litre^{-1} (5% w/v) EC which was then diluted with water containing a wetting agent to give AI concentrations of 200, 50, 12, 3, 0.8, 0.2 and 0.05 mg litre^{-1} for determinations of LC_{80} values. Compounds were evaluated in up to eight standard tests (primary screening assays in Sections 2.2.1 to 2.2.8) for initial activity. Selected compounds were tested for residual activity (secondary screening assays in Sections 2.2.9 to 2.2.12).

2.2.1 Aphis craccivora*: contact/feeding activity*
Pea seedlings, infested with an *Aphis craccivora* Koch (black bean aphid) population of mixed ages, were treated with the test solutions in a spray chamber and checked for mortality 6 days after treatment.

2.2.2 Aphis craccivora*: systemic activity*
Pea seedlings, infested with an *A craccivora* population of mixed ages, were placed directly in the test solutions. Mortality was assessed 6 days after introduction.

2.2.3 Myzus persicae*: contact/feeding activity*
Pea seedlings, infested with a *Myzus persicae*-Sulz (green peach aphid) population of mixed ages, were treated with the test solutions in a spray chamber and assessed for mortality 6 days after treatment.

2.2.4 Myzus persicae*: systemic activity*
Pea seedlings, infested with an *M persicae* population of mixed ages, were placed directly in the test solutions and mortality was assessed 6 days after introduction.

2.2.5 Nilaparvata lugens*: contact/feeding activity*
Rice seedlings were treated with the test solutions in a spray chamber. After drying, they were infested with 10–20 N_3 nymphs of *Nilaparvata lugens* (Staol) (brown plant hopper). Six to 12 days after treatment, samples were checked for mortality, growth regulation, and effects on F_1 generation.

2.2.6 Spodoptera littoralis*: contact/feeding activity*
Cotton leaf discs were placed on agar in Petri dishes and sprayed with the test solutions in a spray chamber. After drying, the leaf discs were infested with 20–25 1st-instar (L_1) larvae of *Spodoptera littoralis* (Boisch) (cotton leaf worm). The samples were checked for mortality, repellent effect, feeding behaviour, and growth regulation 1 and 4 days after treatment.

2.2.7 Spodoptera littoralis*: systemic activity*
Seedlings of maize *Zea mays* L were placed directly in the test solutions. Six days after introduction, the leaves were cut and transferred into Petri dishes with moist filter paper and infested with 12–15 L_1 larvae of *S littoralis*. The samples were checked for mortality, repellent effect, feeding behaviour, and growth regulation 4 days later.

2.2.8 Diabrotica balteata*: contact/feeding activity*
Maize seedlings were placed on filter paper in plastic cups, and 3 ml of the test solution was pipetted onto them. In addition, seedlings were treated in a spray chamber and infested with 12–15 2nd-instar (L_2) larvae of *Diabrotica balteata* Lec (banded cucumber beetle). The samples were checked for mortality and growth regulation 6 days after treatment.

2.2.9 Diabrotica balteata*: contact/feeding activity, soil persistence*
The test solutions were well mixed into a standard field soil. Thirty days after treatment, five maize seedlings and 10 L_2 larvae of *D balteata* were added into the soil. The samples were checked for mortality and growth regulation 10 days after infestation.

2.2.10 Myzus persicae*: systemic activity, soil persistence*
Potted pepper plants (in standard field soil) were treated with the test solutions by drench application. Twenty-eight days after treatment, plants were infested with a mixed *M persicae* population. Mortality was assessed 2 and 7 days after infestation.

2.2.11 Nilaparvata lugens*: contact/feeding activity, foliar persistence*
Rice seedlings were treated with the test solutions in a spray chamber. After four days, they were infested with 10–20 N_3 nymphs of *N lugens*. Samples were checked for mortality and growth regulation 6 days after treatment.

2.2.12 Nilaparvata lugens*: systemic activity, persistence in water/soil*
The test solutions were introduced into the water in a paddy system in which potted rice seedlings were grown. Twenty-eight days after treatment, the seedlings were infested with 10–20 N_3 nymphs of *N lugens*. Six days after treatment, samples were checked for mortality and growth regulation.

3 RESULTS AND DISCUSSION

3.1 Design of novel neonicotinoids

The extremely high insecticidal activity of neonicotinoids, such as imidacloprid (**3**) and its six-ring analogue **24** (Fig 2), described in a patent application of Nihon Bayer in 1985[7] encouraged us to investigate some novel structural modifications. From our own work and from published data, we concluded that the best insecticidal activity would be obtained with a nitroamidine moiety as pharmacophore and a 6-chloro-3-pyridyl moiety as heterocyclic group. However, little was known on the influence of the nitroimino heterocycle on the biological activity. We therefore selected compounds **12, 13a** and **14**, posses-

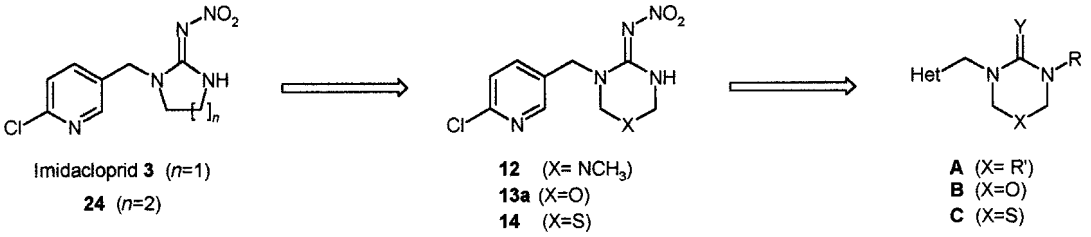


Figure 2. Design of novel neonicotinoids.

sing an additional heteroatom in the nitroimino heterocycle, as our initial target compounds. An additional heteroatom may be capable of polar interactions with nicotinic acetylcholine receptors, leading to stronger binding and consequently to improved insecticidal activity. Moreover, such heteroatoms may also have a strong influence on pharmaco-kinetic behaviour (transport and metabolism), possibly resulting in improved bioavailability.[24]

Any of our initial target compounds found to possess interesting insecticidal activity were seen as having three structural elements for further chemical exploration: the heterocyclic group (**Het**), the pharmacophore (N–C(=Y)–N) and the pharmacophore substituent **R**. On the basis of this design, we planned to prepare hexahydro-1,3,5-triazines **A**, oxadiazinanes **B** and thiadiazinanes **C**, respectively, in our optimisation programme (Fig 2).

3.2 Synthesis of the initial target compounds 12, 13a and 14

At the start of our research, no practical methods for the preparation of the novel nitroimino heterocycles, such as the 2-nitroimino-hexahydro-1,3,5-triazine **12**, the 4-nitroimino-1,3,5-oxadiazinane **13a** and the 4-nitroimino-1,3,5-thiadiazinane **14** were available. We first concentrated our efforts towards the synthesis of the 2-nitroimino-hexahydro-1,3,5-triazine **12**. After some experimentation, we found a two-step procedure which proved to be widely applicable and which produced 2-nitroimino-hexahydro-1,3,5-triazines in excellent yields starting from *S*-methyl-*N*-nitrothiourea (**10**).[25,26] Thus, treatment of **10** with 6-chloropyridin-3-ylmethylamine at 80 °C in ethanol for 3 h afforded the monosubstituted nitroguanidine **11a**, which could then be converted in a Mannich type cyclisation reaction with 1 equivalent of methylamine and 2 equivalents of formaldehyde to the nitroimino-hexahydro-1,3,5-triazine **12** (Fig 3). Compound **12** could also be prepared from nitroguanidine via the unsubstituted nitroimino-hexahydro-1,3,5-triazine **16**. However, the yield was low due to insufficient selectivity in the alkylation reaction.

This first representative (compound **12**) of nitroimino-hexahydro-1,3,5-triazines was synthesised in January 1990 and subjected to our primary greenhouse screening. In response to the promising biological results obtained, we started a broad optimisation programme on the lead compound **12** which resulted in the preparation of a series of 4-nitroimino-hexahydro-1,3,5-triazines **A**. In October 1990 we filed a patent application for these compounds.[25] We did not

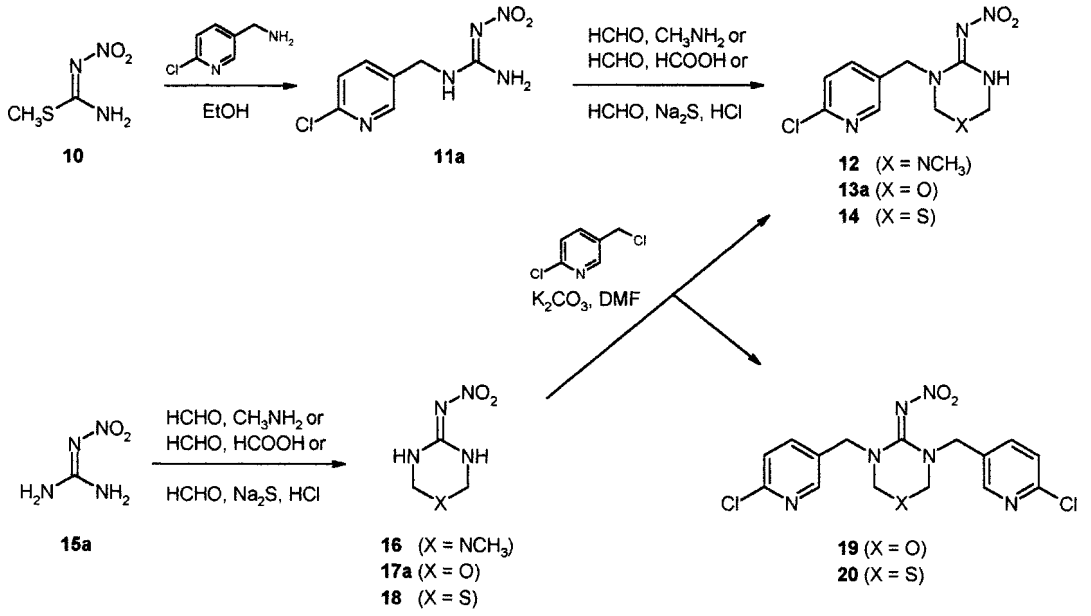


Figure 3. Methods for the preparation of novel nitroimino heterocycles.

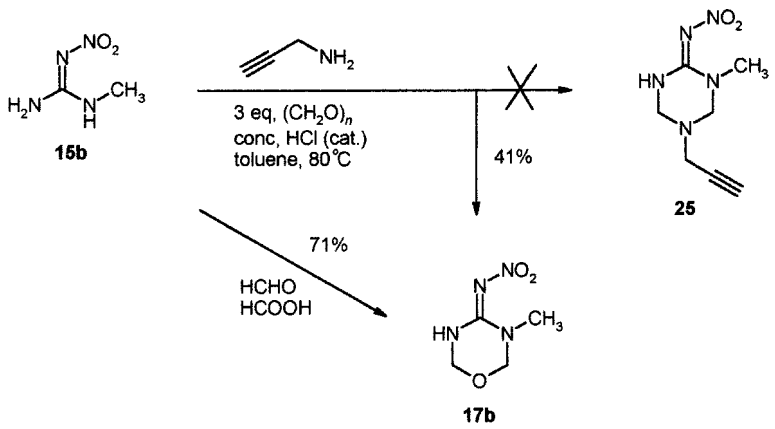


Figure 4. First syntheses of 3-methyl-4-nitroimino-1,3,5-oxadiazinane (**17b**).

know at that time, but must have feared due to the considerable competition in this field, that our competitors had already been pursuing the same idea and had themselves submitted patent applications for nitroimino-hexahydro-1,3,5-triazines.[27–29]

We therefore now focused our attention towards the synthesis of 4-nitroimino-1,3,5-oxadiazinanes. However, all our initial attempts failed. A literature search performed in 1990 revealed only one publication on 4-nitroimino-1,3,5-oxadiazinanes.[30] This paper contained a two-step synthesis of 4-nitroimino-1,3,5-oxadiazinane (**17a**) from nitroguanidine, but neither the experimental procedures nor the yields were given. Following the suggested route, we were not able to produce pure oxadiazinane **17a**. Also, a method for the preparation of 3-methyl-4-cyanoimino-1,3,5-oxadiazinane from *N*-methyl-nitroguanidine (**15b**), which was published in 1989 by Shiba *et al*,[31] could not be applied successfully for the synthesis of 4-nitroimino-1,3,5-oxadiazinane.

Our first success towards the synthesis of 4-nitroimino-1,3,5-oxadiazinanes was based on serendipity. Previously, we had converted monosubstituted nitroguanidines **11** or **15** to the corresponding 2-nitroimino-hexahydro-1,3,5-triazines **A** (Y = N–NO_2) in high yields with formaldehyde or paraformaldehyde and more than 40 different amines.[25] In none of these reactions was the formation of a 4-nitroimino-1,3,5-oxadiazinane as a side-product observed. However, when we treated **15b** with 1 equivalent of propargylamine and three equivalents of paraformaldehyde in the presence of a catalytic amount of concentrated hydrochloric acid, the expected product **25** was not formed; instead 3-methyl-4-nitroimino-1,3,5-oxadiazinane (**17b**) could be isolated as the only product in 41% yield (Fig 4). After some experimentation, we discovered an improved method for the preparation of **17b**. Thus, heating of **15b** in a 1:1 mixture of aqueous formaldehyde solution and formic acid for several hours to 80 °C afforded the nitroimino-1,3,5-oxadiazinane **17b** in 71% yield.

This novel method was applied to the nitroguanidine **11a** and enabled the synthesis of our target compound **13a** in 59% yield (Fig 3). Alternatively, **13a** could be prepared in two steps from nitroguanidine (**15a**) via 4-nitroimino-1,3,5-oxadiazinane (**17a**). Compound **17a** was obtained in 52% yield from nitroguanidine (**15a**) by our novel Mannich type cyclisation method, and subsequent alkylation with 6-chloropyridin-3-ylmethyl chloride gave compound **13a** in 24% yield. The dialkylated oxadiazinane **19** was isolated in 11% yield as a by-product.

From the good insecticidal activity shown by compound **13a** in the primary greenhouse screening tests we were confident of the high biological potential of 4-nitroimino-1,3,5-oxadiazinanes and we started an extensive optimisation programme (see Section 3.3). In 1992 we filed a first patent application for insecticidal 4-nitroimino-1,3,5-oxadiazinanes.[32] This patent application included thiamethoxam (**6**) and many other oxadiazinanes **B** with good insecticidal activity. Subsequently, other companies have performed further chemical work on neonicotinoids of the oxadiazinane sub-class, which has resulted so far in two patent applications.[33,34]

Parallel with our optimisation programme on oxadiazinanes **B** we started to work on 4-nitroimino-1,3,5-thiadiazinanes. The synthesis of our first target compound **14** was achieved as shown in Fig 3. Treatment of **11a** with formaldehyde and sodium sulfide in the presence of concentrated hydrochloric acid afforded compound **14** in only very low yield. Alternatively, the thiadiazinane **14** could be obtained in two steps from **15a** via the cyclic intermediate **18**. Best yields for the Mannich type cyclisation reaction **15a** → **18** were obtained if the reaction conditions described by Moriie *et al*[33] were applied. Alkylation of **18** with 6-chloropyridin-3-ylmethyl chloride gave the target compound **14** in 23% yield and, as a by-product, the dialkylated thiadiazinane **20** in 19% yield. The first patent application[33] on the synthesis of 4-nitroimino-1,3,5-thiadiazinanes was filed in February 1994 by one of our competitors in this field and was, together with the limited biological activity of compound **14**, the reason why we stopped our research on this subclass.

3.3 Optimisation of the oxadiazinane lead structure 13a

In the course of our optimisation program on the

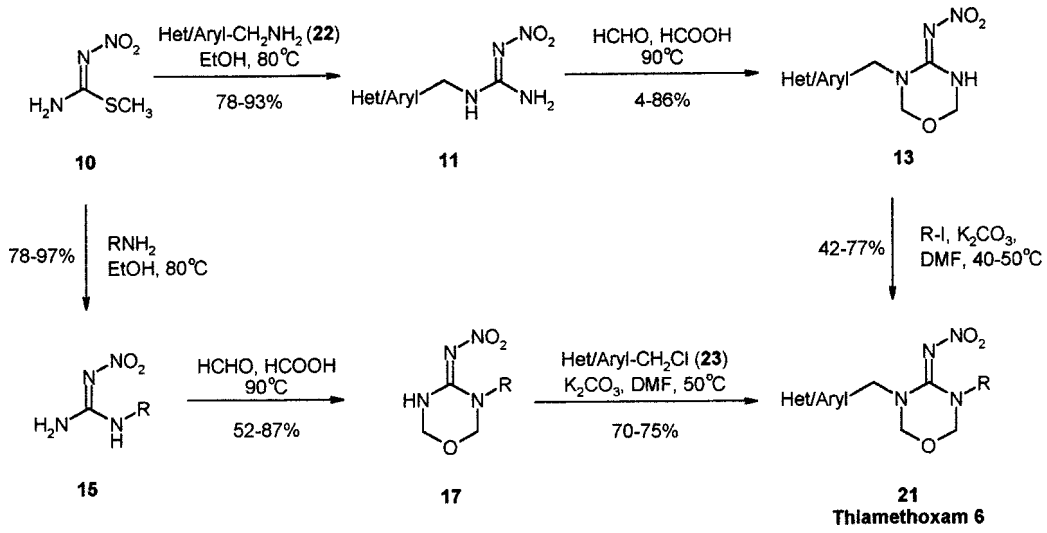
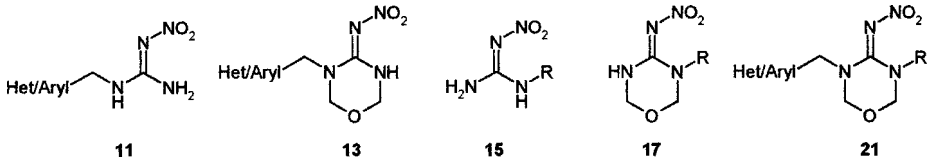


Figure 5. Syntheses of novel 4-nitroimino-1,3,5-oxadiazinanes.

oxadiazinane lead structure **13a** we developed a broadly applicable method for the preparation of the novel 3-heterocyclylmethyl-5-alkyl-4-nitroimino-1,3,5-oxadiazinanes **21** which allowed the introduction of the heterocyclylmethyl or arylmethyl group either from a heterocyclylmethyl or arylmethylamine **22** or a heterocyclylmethyl or arylmethyl chloride **23** (Fig 5; Table 1).[35] Thus, treatment of *S*-methyl-*N*-nitroisothiourea (**10**) with amines **22** afforded *N*-monosubstituted-*N′*-nitroguanidines **11**, which could be converted to 3-monosubtituted-4-nitroimino-1,3,5-oxadiazinane **13** using a 1:1 mixture of formal-

Table 1. Structure and chemical data of compounds **11, 13, 15, 17, 21** and **6**



Compound	*Het/Aryl*	*R*	*mp [°C]*	*Yield (%)*	*Starting material*
11a	Cl–Py[a]	—	198–200	84	**10**
11b	Cl–Th[b]	—	167–169	83	**10**
11c	Py[c]	—	203–205	78	**10**
11d	Cl–Ph[d]	—	194–195	93	**10**
13a	Cl–Py	—	166–168	59/24	**11a/17a**
13b	Cl–Th	—	167	4	**11b**
13c	Py	—	177	7 (20)	**11c**
13d	Cl–Ph	—	140–141	86	**11d**
15a	—	H			
15b	—	CH_3	160–162	97	**10**
15c	—	CH_2CH_3	146–148	87	**10**
15d	—	$(CH_2)_2CH_3$	98–99	78	**10**
17a	—	H	>250	52	**15a**
17b	—	CH_3	140–142	71	**15b**
17c	—	CH_2CH_3	96–97	87	**15c**
17d	—	$(CH_2)_2CH_3$	79–80	85	**15d**
21a	Cl–Py	CH_3	129–130	63/75	**13a/17b**
21b	Cl–Py	CH_2CH_3	115–117	52	**13a**
21c	Cl–Py	$(CH_2)_2CH_3$	81–83	42/70	**13a/17d**
6	Cl–Th	CH_3	140–141	77/71	**13b/17b**

[a] 6-Chloropyridin-3-yl.
[b] 2-Chlorothiazol-5-yl.
[c] Pyridin-3-yl.
[d] 4-Chlorophenyl.

dehyde and formic acid. Alkylation with an alkyl halide gave the 4-nitroimino-1,3,5-oxadiazinane **21** in good yields. Alternatively, compounds **21** could be prepared from *N*-alkyl-*N′*-nitroguanidines **15**, which were obtained from **10** and an alkylamine *via* the 3-alkyl-4-nitroimino-1,3,5-oxadiazinanes **17**. All oxadiazinane ring formation reactions (**11** → **13**; **15** → **17**) were performed with a 1:1 mixture of formaldehyde and formic acid at 80 °C. Best yields for the alkylation reactions (**13** → **21**; **17** → **21**) were obtained using 2.5 equivalents of potassium carbonate as a base and *N,N*-dimethylformamide as solvent. In general, the route via the oxadiazinanes **17** gave better overall yields than the route via compounds **13**. This is mainly due to the fact that some of the heterocyclic groups, such as 2-chloro-5-thiazolyl (compound **11b**) and 3-pyridyl (compound **11c**) were found to undergo side-reactions under the conditions used to achieve the oxadiazinane ring formation.

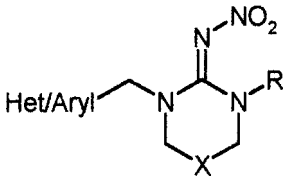
This methodology was also applied to the synthesis of thiamethoxam (**6**), which was obtained in three steps from *S*-methyl-*N*-nitroisothiourea (**10**) via the oxadiazinane **17b** in an overall yield of 49%. Furthermore, other methods for the preparation of thiamethoxam have been developed. These results have already been published by Goebel *et al.* [23]

3.4 Insecticidal activity of novel nitroimino heterocycles

The effects of the novel nitroimino heterocycles were evaluated in our primary screening against *A craccivora, M persicae, N lugens, S littoralis* and *D balteata* in eight different test systems and the results are shown in Table 2. The initial target compounds **12, 13a**, and **14** were found to be effective against all five insect species and to possess contact/feeding as well as systemic activity. Among these compounds, the oxadiazinane **13a** is clearly the most active compound. Compared with our standards, imidacloprid (**3**) and its 6-ring analogue **24, 13a** looked very promising; in most tests **13a** was equally or only slightly less active than the standards.

In the course of our optimisation programme on the oxadiazinane lead structure **13a** we prepared the analogues **13b–13d, 19** and **21a–21c**. Removal of the chlorine atom (compound **13c**) in **13a** and replacement of the 6-chloro-3-pyridyl moiety by a 4-chlorophenyl group (compound **13d**) strongly reduced the insecticidal activity. However, the substitution of the 6-chloro-3-pyridyl moiety by a 2-chloro-5-thiazolyl group (compound **13b**) resulted in a strong increase of the activity against chewing insects (*S littoralis* and *D balteata*) and was found to be the most successful modification of the heterocyclic group **Het**. The introduction of a pharmacophore substituent **R** gave variable results. Whereas an ethyl (compound **21b**), *n*-propyl (compound **21c**) or 6-chloropyridin-3ylmethyl group (compound **19**) undoubtedly had a negative influence on efficacy, especially against chewing insects, a methyl group (compound **21a**) increased

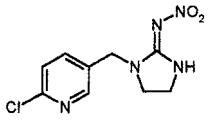
Table 2. Biological data of novel nitroimino-heterocycles (including thiamethoxam **6**) in comparison with the standards imidacloprid **3** and **22**



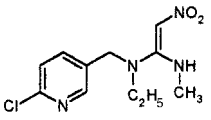
				LC_{80} (mg AI litre^{-1})							
				Ac[a]	*Ac*	*Mp*[b]	*Mp*	*Nl*[c]	*Sl*[d]	*Sl*	*Db*[c]
Compound	*Het/Aryl*	*R*	*X*	*cf*[f]	*sy*[g]	*cf*	*sy*	*cf*	*cf*	*sy*	*cf*
12	Cl–Py[h]	H	N–CH_3	>200	3	12	3	50	50	>12	200
13a	Cl–Py	H	O	50	0.8	0.8	0.05	50	12	>12	3
13b	Cl–Th[i]	H	O	200	12	200	3	>200	3	3	0.8
13c	Py[j]	H	O	>100	nt[m]	nt	nt	>100	>100	nt	>100
13d	Cl–Ph[k]	H	O	>100	nt	nt	>12	>100	>100	nt	>100
14	Cl–Py	H	S	200	12	12	0.8	50	200	>12	12
19	Cl–Py	Cl–Py–CH_2	O	>200	>12	>200	3	>200	>200	>12	>200
21a	Cl–Py	CH_3	O	12	0.2	3	0.2	12	50	>12	50
21b	Cl–Py	CH_2CH_3	O	200	3	12	0.8	200	>200	>12	>200
21c	Cl–Py	$(CH_2)_2CH_3$	O	>200	12	3	0.2	>200	>200	>12	200
6	Cl–Th	CH_3	O	12	0.8	3	0.2	0.8	3	0.8	0.8
24	Cl–Py	H	CH_2	12	0.2	3	0.2	3	0.8	3	3
3	Cl–Py	H	—	12	0.2	0.8	0.05	3	3	3	0.8

Test insects: [a] *Aphis craccivora*, [b] *Myzus persicae*, [c] *Nilaparvata lugens*, [d] *Spodoptera littoralis*, [e] *Diabrotica balteata.*
Type of activity: [f] feeding/contact activity, [g] systemic activity.
[h] 6-Chloropyridin-3-yl, [i] 2-Chlorothiazol-5-yl, [j] Pyridin-3-yl, [k] 4-Chloro-phenyl.
[m] Not tested.

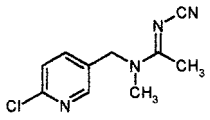
Table 3. Residual activity of thiamethoxam **6** and commercial neonicotinoids **3**, **4** and **5**



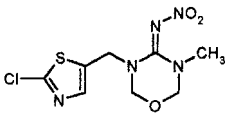
3
Imidacloprid



4
Nitenpyram



5
Acetamiprid



6
Thiamethoxam

	LC_{80} [mg AI litre^{-1}]			
	Db[a]	*Mp*[b]	*Nl*[c]	*Nl*
	cf[d]	*sy*[e]	*cf*	*sy*
Compound	*30 DAT*[f]	*28 DAT*	*4 DAT*	*21 DAT*
3	3	0.8	25	0.05
4	nt[g]	3	12	0.2
5	12	>12	>100	3
6	0.8	0.8	3	0.05

Test insects: [a] *Diabrotica balteata*, [b] *Myzus persicae*, [c] *Nilaparvata lugens*.
Type of activity: [d] Contact/feeding activity, [e] Systemic activity.
[f] Days after treatment.
[g] Not tested.

the insecticidal activity against sucking pests, such as *A craccivora* and *N lugens*.

The combination of the two most favourable modifications, the replacement of the 6-chloro-3-pyridyl moiety by a 2-chloro-5-thiazolyl group and the introduction of a methyl group as pharmacophore substituent, finally led to thiamethoxam (**6**). This compound showed strongly improved contact/feeding and systemic activity against all chewing and most of the sucking insects. It was clearly the most active compound in the 4-nitroimino-1,3,5-oxadiazinane series and its overall performance in our primary screening was comparable to that of the standards imidacloprid and compound **24**.

Thiamethoxam was further evaluated in our secondary screening for residual activity. Against *D balteata, M persicae N lugens*, thiamethoxam showed outstanding residual effects, which clearly surpassed those of the commercial neonicotinoids imidacloprid (**3**), nitenpyram (**4**) and acetamiprid **5**) (Table 3).

3.5 Field performance of thiamethoxam

Novartis has carried out extensive field trials over several years on key target pests, and thiamethoxam has proven to be an outstanding product. After foliar or soil application or as a seed treatment, it provides excellent control of a broad range of commercially important pests, such as aphids, whiteflies, thrips, rice hoppers, Colorado potato beetle, flea beetles, wireworms and leaf miners, as well as some Lepidopterous species.[10]

Low use rates, flexible application methods and excellent efficacy combined with a long-lasting residual effect are exceptional characteristics of thiamethoxam. In general, control of most insect pests is superior or equivalent to all currently registered insecticides. In many situations an outstanding level of control is obtained at even low rates of application, compared with the best products such as imidacloprid and acetamiprid.

3.6 Thiamethoxam, the first second-generation neonicotinoid

Thiamethoxam was first synthesised in 1991. In many laboratory and field tests it was identified as the best compound prepared during our research programme on neonicotinoids and was subsequently selected for development. It is a unique molecule. Its chemical structure differs remarkably from that of other neonicotinoid commercial and development compounds in that it possesses a novel 1,3,5-oxadiazinane ring, which is substituted at the 5-position by a methyl group, and is the first commercially available neonicotinoid having a 2-chloro-5-thiazolyl heterocycle. This unique combination of structural features is responsible for its outstanding insecticidal activity eg the methyl group at the 5-position enhances the activity against sucking insects whereas the 2-chloro-5-thiazolyl heterocycle is essential for improved efficacy against chewing pests.

Thiamethoxam is the first representative of second-generation neonicotinoids and belongs to the thianicotinyl sub-class.[10] It was first introduced to the market in 1998. To date, registrations have been granted in 52 countries, mainly in Latin America, Eastern Europe and Asia. Registration submissions were also made to the USA and Canadian authorities in late 1998, and in Europe and Japan in early 1999, and approvals are expected to be received in late 2000 or 2001.

4 CONCLUSIONS

We have demonstrated that novel variations of the

nitroimino heterocycle of imidacloprid lead to highly active insecticidal compounds such as the nitroimino-hexahydro-1,3,5-triazine **12**, the nitroimino-1,3,5-thiadiazine **14** and especially the nitroimino-1,3,5-oxadiazinane **13a**. Novel methodology for the preparation of these compounds and derivatives of **13a** has been developed. The synthesis and testing of a large number of chemically modified nitroimino-1,3,5-oxadiazinanes has led to a structure-activity profile for this novel type of compound. Based on biological activity and the best overall laboratory and field performance, thiamethoxam (CGA 293 343) has been selected as the preferred compound.

Thiamethoxam represents the first commercially available second-generation neonicotinoid and belongs to the thianicotinyl sub-class. It is marketed under the trademarks Actara® for foliar and soil treatment and Cruiser® for seed treatment. The compound has broad-spectrum insecticidal activity and offers excellent control of a wide variety of commercially important pests in many crops. Control of most insect pests with thiamethoxam is superior or equivalent to that of currently registered neonicotinoid insecticides. The compound exhibits contact, stomach and systemic activity. Its good stability and excellent systemic characteristics make thiamethoxam appropriate for foliar, granular and seed treatment application. The long-lasting residual effect is a special benefit of this compound. Low use rates, flexible application methods, excellent efficacy and the favourable safety profile make this new insecticide well-suited for modern integrated pest management programmes in many cropping systems.

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