J. Pestic. Sci., **30**(2), 122–123 (2005)

Society Awards 2005

(on prominent achievement)

Development of a Novel Insecticide, Dinotefuran*

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(Accepted March 2, 2005)

Dinotefuran is a new neonicotinoid developed by Mitsui Chemicals and first registered in Japan in 2002 under the trade name of Starkle® and Albarin®. It has a characteristic tetrahydro-3-furylmethyl group instead of the aromatic heterocyclic ring that was previously considered indispensable for insecticidal activity of neonicotinoids. Dinotefuran was discovered by research using acetylcholine as the lead compound by way of a 3-methoxypropyl compound and its cyclization. It has excellent insecticidal properties and offers excellent control of a wide variety of pests in many kinds of crops. © Pesticide Science Society of Japan

Keywords: dinotefuran, neonicotinoid, acetylcholine.

INTRODUCTION

Neonicotinoids are a promising class of insecticides with excellent chemical and biological properties, such as wide spectrum, low application rate, and quick uptake and translocation in plants. These agents all have a pyridine ring or a thiazole ring considered indispensable to this chemical class because the action mechanism and structure are similar to those of nicotine. In 1992, we started researching a new neonicotinoid using acetylcholine as the lead compound, which acts on the same receptor as nicotine but does not have hetero rings. As a result of this approach, we found dinotefuran, which has a characteristic tetrahydro-3-furylmethyl group instead of the pyridine-like rings of other neonicotinoids.

This paper presents a short history of its discovery and characterization of dinotefuran.

DISCOVERY

A structural similarity between acetylcholine and neonicotinoids is the distance between the hydrogen acceptor site (HA site) and the cationic site, which is suitable for binding to nicotinic acetylcholine receptors (nAChRs). First, we modified the quarternary ammonium cation of acetylcholine into the (nitromethylene) imidazolidine which was expected to exhibit high insecticidal activity. As for the HA site, we assumed the optimal position of an oxygen atom, which is the binding point to nAChRs, to be at a length of two to three methylene chains from the nitrogen atom on the imidazolidine ring. We synthesized a series of compounds with straight carbon chains and evaluated their insecticidal activity. Although strong activity was not found in these compounds, we recognized two pieces of important information; 1) compounds with three methylene units showed higher activity than those with two methylene units, and 2) the ether form showed the highest activity among straight-chain compounds. From these results, we selected the 3-methoxypropyl compound as the next lead compound.

As a following step, we converted the straight chain ether compound to a cyclic ether compound in order to change the direction of the lone-pair electron of the oxygen atom and fix the location of the oxygen atom. We synthesized cyclic ether compounds and found a tetrahydro-3-furylmethy group, that showed more than 10 times the activity of the 3-methoxypropyl compound.

As the next step, the HA site was fixed to the tetrahydro-3-furylmethy group, and the cationic site was changed to other partial structures of the known neonicotinoids. Among these compounds, we chose the most active compound, dinotefuran, which has the tetrahydro-3-furylmethy group as the HA site and a nitroguanidine moiety as the cationic site.

STRUCTURE–ACTIVITY RELATIONSHIPS

The structure–activity relationships of dinotefuran analogues against *Nephotettix cincticeps* and *Laodelphax striatellus* are summarized as follows.

1) The non-substituted compound on the tetrahydro-3-furylmethy group exhibited the highest insecticidal activity. Introduction of a methyl group at the 4- or 5- position gave

* See Part II for the full Japanese article.

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intermediate activity and that at the 2- or 3- position reduced the activity significantly.

2) A methyl group on nitroguanidine was best for the activity among alkyl groups.

3) Acyl groups on the nitroguanidine were as effective as the unsubstituted compound.

PROPERTY

Dinotefuran exhibits a insecticidal activity against Hemiptera, Lepidoptera, Coleoptera, Diptera, Dictyoptera and Thysanoptera. Furthermore, it has very low phytotoxicity so that it can be utilized for many kinds of crops.

Dinotefuran is water-soluble and has excellent systemic and translaminar action in many plants. This property enables dinotefuran to be applied using various methods and various formulations.

The binding assay using insect nAChRs and the electrophysiological study showed that dinotefuran acted on nAChRs as an agonist. However, in the binding study, the affinity of dinotefuran against the binding site of other neonicotinoids was very low, suggesting that this compound acts on a different site than other neonicotinoids.

PHYSICAL AND CHEMICAL PROPERTIES

Common name: dinotefuran
Trade name: Starkle®, Albarin®
Experimental name: MTI-446
Chemical name: (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furyl-methyl)guanidine
Molecular formula: $C_7H_{14}N_4O_3$
Molecular weight: 202.21
Appearance: colorless crystal
Melting point: 107.5°C
Vapour pressure: $<1.7\times10^{-6}$ Pa (30°C)
Partition coefficient: log $P_{ow}=-0.549$ (25°C)
Solubility (water): 40 g/l (pH 7, 20°C)

SAFETY

The results of toxicological and ecotoxicological studies demonstrated that dinotefuran has a very low toxicity in mammals, birds and acuatic animals.

Toxicology

Acute oral (LD_{50})
rat male : 2804 mg/kg, female: 2000 mg/kg
mouse male : 2450 mg/kg, female: 2275 mg/kg
Acute dermal (LD_{50}) rat male/female: >2000 mg/kg
Skin sensitizing (guinea pig): non-sensitizing
Eye irritation (rabbit): slightly irritating
Teratogenicity oral (guinea pig, rabbit): negative
Carcinogenicity feed (rat, mouse): non-carcinogen
Genotoxicity (Ames test, Chromosomal aberration and Mouse micronucleus): negative

Ecotoxicology

Avian toxicity
Japanese quail (acute oral LD_{50}): >2000 mg/kg
Mallard duck (acute dietary LD_{50}): >1301 mg/kg
Aquatic toxicology
Carp (96 hr, LD_{50}): >100 ppm
Daphnia (48 hr, EC_{50}): >1000 ppm
Alga (72 hr, EC_{50}): >100 ppm