Research and development of a novel insecticide, flonicamid

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Flonicamid, a novel class insecticide possessing a unique chemical structure, was discovered in 1992, developed by Ishihara Sangyo Kaisha, Ltd., and registered in Japan in 2006 under the trade name of Ulala DF. This compound is very active against a wide range of aphid species and also is effective against some other species of sucking insects. It rapidly inhibits the feeding behavior of aphids and provides long-lasting control. Flonicamid shows no cross-resistance to conventional insecticides and exhibits excellent systemic and translaminar activity. It has no negative impact on beneficial insects and mites. Furthermore, it has a favorable toxicological, environmental and ecotoxicological profile. These characteristics make flonicamid well suited for resistant management strategies and integrated pest-management programs. © Pesticide Science Society of Japan

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Introduction

While conducting research on trifluoromethylpyridine derivatives, we discovered that some (trifluoromethyl)nicotinamides were effective in controlling aphids. Out of a variety of analogues, N-cyanomethyl-4-(trifluoromethyl)nicotinamide (flonicamid) was selected as a candidate for commercial development based on its insecticidal activity and its environmental profile. This novel insecticide is registered in forty-one countries including in the Americas, Asia, Europe and Africa as of Jan. 31, 2014, as an insecticide mainly used in a foliar treatment for potatoes, cereals, cotton, pome fruits, stone fruits and vegetables. This paper describes, in brief, the discovery, chemistry, synthesis, structure–activity relationships, biological properties and toxicological profiles.

Discovery and Synthesis

We have been interested in the syntheses and biological characteristics of trifluoromethyl-substituted pyridine (CF₃-pyridine) derivatives. In a series of our studies, we discovered a number of unique agrochemicals such as fluaizifop-butyl, flazasulfuron, chlorfluazuron and fluazinam. All of these compounds have trifluoromethyl groups substituted at the β-position and the pyridine ring is bonded to the hetero atom (O, S, N) at the 2-position.

In the project to find novel and biologically active compounds, we focused on CF₃-pyridine derivatives, where the CF₃ group is substituted except at the β-position of the pyridine ring. Consequently, we discovered an interesting compound 1, N-(2-pyridylmethyl)-4-(trifluoromethyl)nicotinamide. Although this compound 1 did not show remarkable biological activity for Spodoptera littoralis or Tetranichus urticae, a moderate insecticidal effect for Myzus persicae was detected. Interestingly, it also had a good systemic effect. From these results, we chose the compound 1 as the lead, and then a significant number of derivatives were synthesized for the biological evaluation.

In this optimization step, a key starting material of 4-(trifluoromethyl)nicotinic acid was synthesized from known 2,6-dihydroxy-4-(trifluoromethyl)nicotinonitrile, which was obtained through the reaction of 2-cyanoacetamide with ethyl 4,4,4-trifluoroacetooacetate. Amide derivatives were prepared from a corresponding amine and an acid chloride which was obtained by the reaction with thionyl chloride.

We tested a variety of derivatives, in which the nicotinyloyl moiety and the N-pyridylmethyl moiety were transformed from 1. In the course of our research, we found that the trifluoromethyl group at the 4-position of nicotinoyl moiety was essential for the insecticidal effect, and N-alkylamide compounds showed a very good insecticidal effect for aphid species.
Through the evaluation of the various N-alkylamide derivatives, N-cyanomethyl-4-(trifluoromethyl)nicotinamide was selected for a development stage.

**Physicochemical Properties**

Common name: flonicamid  
Trade name: Ulala™, Teppeki™, Mainman™, Carbine™, Turbine™, Beleaf™, Aria™  
Code number: IKI-220  
CAS registry No.: 158062-67-0  
Chemical name (IUPAC): N-cyanomethyl-4-(trifluoromethyl)-nicotinamide  
Molecular formula: C₉H₆F₃N₃O  
Molecular weight: 229.16  
Appearance: White crystalline powder, odourless  
Solubility in water: 5.2 g/L at 20°C  
Melting point: 157.5°C  
Partition coefficient: Log P_{ow} = 0.3 at 29.8°C

**Biological Properties**

Flonicamid is a highly selective insecticide. Although it does not control coleopteran, lepidopteran, or dipteran insects and mites, it is effective against both nymph and adult stages of aphids. At the recommended doses under field conditions (50–100 g a.i./ha or 2.5–10 g a.i./100 L), this compound shows very good efficacy for controlling a broad range of aphid species and some other species of sucking insects such as the greenhouse whitefly (Trialeurodes vaporariorum), yellow tea thrips (Scirtothrips dorsalis), Indian cotton leafhopper (Amrasca biguttula), tea green leafhopper (Empoasca onukii), tarnished plant bug (Lygus lineolaris), potato psyllid (Bactericera cockerelli) and brown rice planthopper (Nilaparvata lugens). On the other hand, flonicamid does not show negative impact to a wide range of beneficial arthropods such as predatory mites, parasitic wasps, predatory insects and pollinators. Within 0.5 hr after treatment this compound inhibits the feeding behavior of aphids without noticeable poisoning symptoms such as convulsions or knockdown. The precise mechanism of action of flonicamid is under investigation, but it is clearly different from any conventional one. Actually flonicamid exhibits no response against the existing insecticide targets such as acetylcholine esterase, the sodium channel and the nicotinic acetylcholine receptor. Leaf dip assays in the laboratory show that flonicamid is highly effective against every 15 field clones of Aphis gossypii and showed no cross-resistance to conventional insecticides such as organophosphates, carbamates or pyrethroids. Flonicamid shows a long-lasting efficacy, and it controls aphids for three to four weeks at 50 ppm. It possesses excellent translaminar and systemic activity through xylem vessels.

**Toxicological and Ecotoxicological Profile**

Acute oral LD₅₀, Rat male: 884 mg a.i./kg  
Rat female: 1768 mg a.i./kg  
Acute dermal LD₅₀, Rat: >5000 mg a.i./kg  
Acute inhalation LD₅₀, Rat: >4900 mg a.i./m³  
Eye irritation, Rabbit: slight-irritant  
Skin irritation, Rabbit: Non-irritant  
Skin sensitization, Guinea pig: Non-sensitizing  
Carp LC₅₀ (96 hr): >100 mg a.i./L  
Daphnia magna EC₅₀ (48 hr): >100 mg a.i./L  
Algal growth inhibition E₅₀ (0–72 hr): >96.7 mg/L