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Development of a novel lepidopteran insect control agent, chromafenozide*

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Chromafenozide is a novel dibenzoylhydrazine insecticide that was developed in the collaborative research project between Nippon Kayaku Co., Ltd., and Sankyo Co., Ltd., and is categorized to be an insect hormone-ecdysone agonist. Two formulations of chromafenozide and one combination formulation with silafluofen are available in Japan under the trade names of MATRIC® FL, MATRIC® DL and MATRICJOKER® DL, respectively. Chromafenozide is found to be significantly potent against various lepidopterous insects, but at the same time almost non-toxic to non-lepidopterous species, including pollinators, predators and parasitoids. As chromafenozide has a low toxicity profile in mammals and non-target organisms described above, and has minimum impact on the environment, it would be an ideal agent for integrated pest management (IPM). © Pesticide Science Society of Japan

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Introduction

A novel lepidopteran insect control agent, chromafenozide, which is characterized by a methylchromane moiety in its dibenzoylhydrazine structure, is effective in controlling various lepidopterous pests (*i.e.* Tortricidae, Pyralidae, Noctuidae, *etc.*) on various crop plants at application rate ranging from 5 to 200 g active ingredient per hectare. Two formulations of chromafenozide and one combination formulation with silafluofen are available in Japan under the trade names of MATRIC® FL, MATRIC® DL and MATRICJOKER® DL, respectively. MATRIC® FL was registered in 1999 to be used with the following crops: rice, tea, apple, pear, cabbage, lettuce, strawberry, eggplant, tomato, sweet pepper, welsh onion, sugar beet and ornamental plants (*e.g.*, chrysanthemum and cherry tree). MATRIC® DL was also registered in 1999 to be used with rice and soybean crops. MATRICJOKER® DL was registered for soybean and rice in 2004, which controls lepidopteran insects and heteropteran bugs simultaneously.

This paper describes the chemical, physical, biological, and toxicological properties of chromafenozide and its environmental chemistry as well as its field performance and safety to non-target beneficial arthropods.

Discovery and Synthesis

20-Hydroxyecdysone (20-HE), one of the most active insect hormone-ecdysones, acts at every stage of the insect's growth to regulate molting and metamorphosis. As this hormone plays a crucial role in the insect's development systems, it is considered that its agonist or antagonist would be a new type of insecticide, which would act specifically on insects and therefore, exhibit a high level of mammalian safety. As the injection of an ecdysone agonist into lepidopterous larvae is thought to cause an immediate interruption of feeding, cessation of feeding by the larvae is also of great importance for plant protection.

We paid attention to Wing's scientific literatures, which reported that some dibenzoylhydrazines act as ecdysone agonists on a Drosophila cell line and intact insects and as a result, may cause premature molting to be initiated in larvae and stop their feeding. At the beginning of the collaborative research project by Nippon Kayaku Co., Ltd., and Sankyo Co., Ltd., a series of dibenzoylhydrazine derivatives were synthesized to clarify the essential structural feature of the lead compound required to exhibit insecticidal activity. Based on the simple hypothetical superimposition modeling of the dibenzoylhydrazines and 20-HE, various substituents on the bridge part of *tert*-butylhydrazine and the both side benzene rings of the dibenzoylhydrazine were introduced to its mole-

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cule and each part was optimized. The resulting product was chromafenozide.

Process Research and Development

Synthesis of chromafenozide consists of 1) synthesis of 5-methyl-6-chromanecarboxylic acid, 2) acylation of *tert*-butylhydrazine with 5-methyl-6-chromanecarbonyl chloride, and 3) acylation of the resulting hydrazide with 3,5-dimethylbenzoyl chloride. Elaboration of each part was performed to develop an economical and convenient procedure for an industrial production of chromafenozide.

Physical and Chemical Properties

Chemical name (IUPAC): 2′-*tert*-butyl-5-methyl-2′-(3,5-xyloyl)chromane-6-carbohydrazide
CAS registry number: 143807-66-3
ISO name: Chromafenozide
Trade name: Matric
Code number: ANS-118, CM-001
Molecular weight: 394.51
Molecular formula: $C_{24}H_{30}N_2O_3$
Physical state: Colorless crystals
Melting point: 186.4°C
Vapor pressure: $\leq 4\times10^{-9}$ Pa (25°C)
Partition coefficient: log P_{ow}=2.7 (22°C)
Solubility in water: 1.12 mg/L (20°C)

Formulation

Two formulations of chromafenozide and one combination formulation with silafluofen are available in Japan under the trade names of MATRIC® FL (5% chromafenozide flowable formulation), MATRIC® DL (0.3% chromafenozide dust formulation) and MATRICJOKER® DL (dust formulation with 0.2% chromafenozide and 0.5% silafluofen), respectively.

Safety Evaluation and Metabolism

Toxicity studies using laboratory animals revealed relatively low acute toxicity *via* any exposure route. Safety assessment with chronic toxicity, mutagenicity/carcinogenicity and developmental toxicity was carried out. No evidence of carcinogenicity or teratogenicity was observed in the experimental animals. Chromafenozide has large margins of safety to mammalian, avian and aquatic organisms and has no adverse effects toward non-target arthropods. These properties as well as the high specificity to target insect pests make chromafenozide a suitable tool for the integrated pest management (IPM).

The metabolism and degradation of chromafenozide in rats, plants, and aerobic and aquatic soils are studied along with its leaching properties in soils and photodegradation products. There were not found any environmentally toxic metabolites or degradation products.

Biological Properties

Chromafenozide shows toxic effects against larvae of various lepidopteran pests mainly via digestion and thus, has excellent efficacy on the crop protection from serious lepidopteran pest damages on vegetables, fruit trees, tea, rice, ornamental plants and other crops. Another remarkable biological property of this agent is that it shows almost same insecticidal activity on the every growth stage of lepidopteran larvae. Chromafenozide is non-toxic to a wide range of coleopteran, homopteran, orthopteran, hemipteran, dipteran and mite pests. The agent is relatively fast-acting, stopping the feeding of the treated insect within 10–12 hr after exposure to toxic doses of the agent and inducing the molting process. The ceasing of feeding by larvae stops the continuation of the damage before the death of the insect. A treated larva slips its head out of the old head capsule prematurely to attempt to molt. However, the larva does not complete the molting and survives, leaving the newly developed mouth part trapped inside the old head capsule. These symptoms exhibited in the chromafenozide-treated larvae are similar to those in larvae of abnormally high level of ecdysone.

Mode of Action

In order to evaluate the transcriptional activity and mode of action of chromafenozide, 1) a reporter gene assay and 2) an RT-PCR method for the detection of ecdysone-inducible mRNA were developed and the hormonal activity of chromafenozide was estimated. Similarly to one of potent ecdysone, ponasterone A, chromafenozide induced luciferase activity in a dose-dependent manner. These results showed that chromafenozide is capable of acting similarly to ponasterone A and inducing the transcription of the luciferase gene. Based on the results of the biological response in the intact insect and at the cellular level, as well as at the molecular level, chromafenozide can be duly characterized as an ecdysone agonist.

Field Efficacy

At a foliar application under field conditions, chromafenozide at 25–50 ppm has provided good efficacy against the common cutworm (*Spodoptera litura*), the beet armyworm (*Spodoptera exigua*), the cabbage armyworm (*Mamestra brassicae*), *Heliothis armigera*, the oriental tea tortrix (*Homona magnanima*), the smaller tea tortrix (*Adoxophyes honmai*), the tea leafroller (*Caloptilia theivora*), the mugwort looper (*Ascotis selenaria*), the apple tortrix (*Archips fuscocupreanus*) and the summer fruit tortrix (*Adoxophyes orana fasciata*). Likewise, at an application rate of nine grams per hectare, the agent has shown good efficacy against the common cutworm *S. litura* in soybean crops, and against the rice leafroller (*Cnaphalocrocis medinalis*) and the rice stem borer (*Chilo suppressalis*) in rice fields.

Conclusion

Chromafenozide is a promising insecticide with high efficacy and high level of safety against non-target organisms. The agent is suitable for IPM programs directed against lepidopteran pests.