*J. Pestic. Sci.* **50**(1), 14–17 (2025)
DOI: 10.1584/jpestics.J25-01

JOURNAL OF PESTICIDE SCIENCE

**Society Awards 2024**
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# Research and development of an insecticide, afidopyropen

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(Accepted November 13, 2024)

## Introduction

Afidopyropen (AFD, Fig. 1) is an insecticide with a meroterpenoid skeleton that was discovered in collaboration with the Kitasato Institute on pyripyropene (PP) derivatives. AFD has been registered in over 23 countries, including Australia, India, the U.S., Brazil, China, and Japan. Sefina DC, containing 4.9% AFD, has been marketed since 2023 in Japan to control aphids on wheat, potato, leafy vegetables, and pumpkin.

## Production of AFD

AFD can be produced by the selective acylation of tetraols obtained from the hydrolysis of PPs, including pyripyropene A, isolated from the microbial secondary metabolites of *Penicillium coprobium* (Fig. 2).

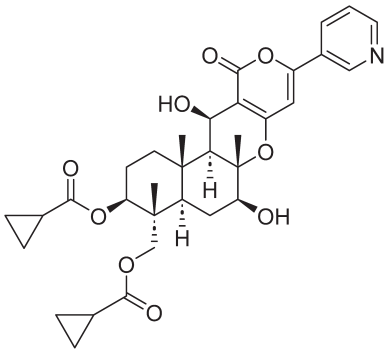


**Fig. 1.** Chemical structure of afidopyropen (AFD)

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Published online March 6, 2025



## Discovery study from microbial secondary metabolites

Many agrochemicals are derived from natural resources, and microbial secondary metabolites are particularly important. Sparks *et al.* reported that 134 active ingredients, occupying 17% of the active ingredients used in plant protection, are directly connected to natural substances, and approximately 35% originate from bacteria and filamentous fungi.[1)] Many naturally derived agrochemicals have a low environmental impact because they are often easily metabolized in the environment. Therefore, we believe that microbial secondary metabolites are effective resources for agrochemical research. For a long period, Meiji Seika Pharma Co., Ltd. (In 2022, the agrochemical division was merged into Mitsui Chemicals Agro, Inc., and in 2023, Mitsui Chemicals Crop & Life Solutions, Inc. was established, hereafter Mitsui) has been conducting agrochemical research of microbial secondary metabolites. Streptomycin fungicide and bialaphos herbicide were registered in 1963 and 1984, respectively. Furthermore, the insecticidal activity of the quinoline compound SF2420B has led to the discovery of tebufloquin fungicide and flometoquin insecticide. Thus, we accumulated knowledge on agrochemical discovery from microbial secondary metabolites and improved screening methods for natural resources, focusing on the physicochemical properties of active compounds that are suitable for controlling agricultural pests on crops. We discovered PP-A, the lead compound in AFD, as an insecticidal compound through our research on microbial secondary metabolites.[2)]

## AFD discovery from PP derivatives

Aphids treated with PP-A dropped from crops to the ground a few hours after spray application and wandered on the ground. All growing stages of aphids treated with PP-A exhibited similar symptoms, and abnormal behavior remained in the first instar larvae produced by treated adults. Such aphids finally died in a few days without settling on the leaves. PP-A also exhibited weak root systemicity and good translaminar activity from the leaf surface to the opposite side; however, PP-A did not show sufficient residual efficacy in field trials.[3)] PP-A is a potent in-

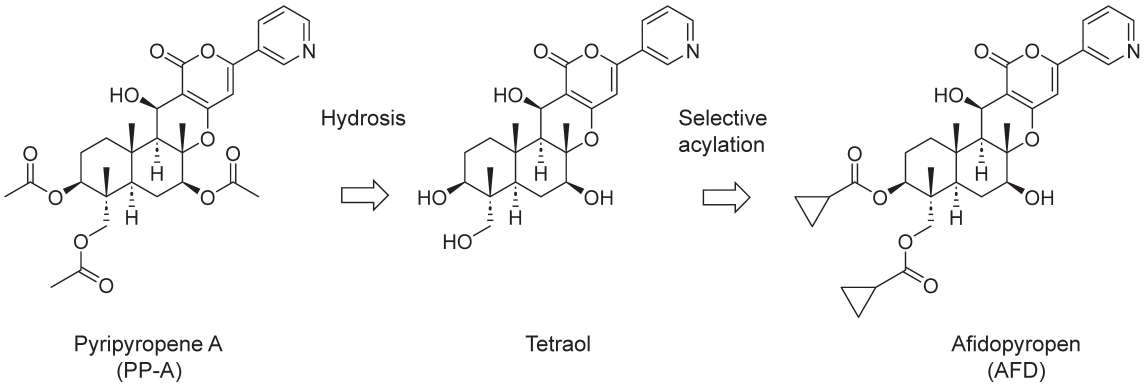
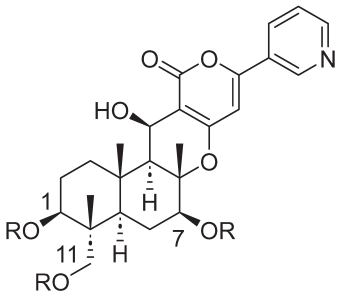



**Fig. 2.** Production method of AFD

hibitor of acyl-CoA: cholesterol acyltransferase, which is a target for hyperlipidemia drugs. PP-A was first isolated from *Aspergillus fumigatus* at the Kitasato Institute. In the derivative study at the Kitasato Institute, they synthesized several PP derivatives and accumulated synthetic know-how of PP derivatives.[4–12] To improve the efficacy of semi-synthesis from PP-A, we evaluated the insecticidal activity of the derivatives against green peach aphid, *Myzus persicae*. We found that the side chain structure at positions 1, 7, and 11 improved insecticidal activity and started a collaborative research with the Kitasato Institute. Initially, we conducted insecticidal evaluations using both foliar and insect spray methods against the first-instar larvae of the green peach aphid, and compound **4** was found to be 20-fold more active against the aphid (Fig. 3). Compound **4** showed high insecticidal activity; however, similar to PP-A, it did not exhibit sufficient field efficacy.[13]

In investigating strategies to improve field efficacy, we found that the root systemicity and translaminar activity considerably changed with the substituents at the 1, 7, and 11 positions and attempted to improve the insecticidal activity by considering systemic properties. Compounds with high lipophilicity tended to show high insecticidal activity in the green peach aphid test where the test compound was sprayed on both leaves and insects; the activity includes oral and dermal activity. Therefore, we selected compounds with strong oral activity by adding a foliar spray test against the cotton aphid, *Aphis gossypii*, where the test compound was sprayed only on leaves, and the compound with the strongest oral activity was selected. Consequently, AFD was selected as the agrochemical candidate with more than 80 times higher insecticidal activity against the green peach aphid ($LC_{50}$: 0.0068 ppm) than PP-A and good insecticidal activity against the cotton aphid ($LC_{50}$: 0.012 ppm). AFD also has good systemic activity, especially in monocotyledonous crops such as cereals. AFD exhibited superior efficacy to PP-A and Compound **4** and equivalent efficacy to existing insecticides for aphid control in field trials.[14,15] AFD had weak hydrophilicity and moderate log *P*, with a water solubility of 25.1 ppm and log *P* of 3.45. Compared to compound **4** (in the same order, 0.4 ppm and 4.8), the physicochemical properties tended to approach those of aphid and other sucking pest control agents such as neonicotinoid and organophosphate insecticides. Although the photostability of PP-A, compound **4**, and AFD to sunlight on Petri



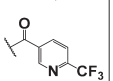

| Cpd. No. | R | $LC_{90}$ (ppm) | Cpd. No. | R | $LC_{90}$ (ppm) |
|---|---|---|---|---|---|
| PP-A |  | 0.56 | 6 |  | 18 |
| 1 | H | >100 | 7 |  | 88 |
| 2 |  | 0.66 | 8 |  | 16 |
| 3 |  | 1.3 | 9 |  | 18 |
| 4 |  | 0.026 | 10 |  | >100 |
| 5 |  | 0.030 | 11 |  | >100 |

**Fig. 3.** Insecticidal activity against the green peach aphid of derivatives modified at positions 1, 7, and 11.

**Table 1.** Insecticidal spectrum of AFD

| Scientific name | Efficacy |
|---|---|
| *Myzus persicae* | **** |
| *Aphis gossypii* | **** |
| *Aulacorthum solani* | **** |
| *Aphis spiraecola* | **** |
| *Rhopalosiphum padi* | **** |
| *Eriosoma lanigerum* | *** |
| *Trialeurodes vaporariorum* | *** |
| *Bemisia tabaci* | *** |
| *Pseudococcus comstocki* | *** |
| *Planococcus citri* | *** |
| *Empoasca onukii* | *** |
| *Diaphorina citri* | *** |

Field efficacy of AFD 10%WDG was evaluated in disclosed and non-disclosed trials by JPPA in foliar spray at 2000 times diluted solution. **** Equivalent or superior efficacy to commercial standards. *** Practical efficacy.

dishes did not improve, with a half-life of less than 1 day (not published), the improved field efficacy resulted from suitable physicochemical properties for sucking pest control.

## Field Efficacy of AFD

Field trials for AFD (code name: ME5343WDG; wettable dispersible granule, BAI-1603 DC; dispersible concentrate) were conducted by the Japan Plant Protection Association (JPPA) using a foliar spray on various crops, and its field efficacy against sucking pests on wheat, vegetables, fruit trees, and tea trees was demonstrated (Table 1). In Japan, Sefina DC, including 4.9% of the AFD, is registered as an insecticide for the control of aphids on wheat, potato, leafy vegetables, and pumpkin and has been registered for the control of aphids, whiteflies, leafhoppers, and scale insects overseas. AFD exhibited high efficacy against neonicotinoid-resistant populations of pests, as well as against susceptible populations, which are common control agents for sucking pests. In addition, AFD was an effective tool for suppressing disease infestation by the soybean dwarf disease virus transmitted by potato aphids.[16)]

## Mode of action

Aphids treated with AFD showed hyperactivity symptoms, and AFD suppressed the occurrence of nectar produced by aphids.[17)] AFD did not act on nicotinic acetylcholine receptors or acetylcholinesterase, which are the modes of action of existing controlling agents. The unique insecticidal symptoms implied a different mode of action from that of existing agents. Subsequently, BASF revealed that the target site of AFD is the TRPV (Transient Receptor Potential Vanilloid) channel, a type of TRP channel present in insects.[18)] The TRPV channel normally helps insects perceive gravity and external stimuli. AFD binds to the TRPV channel complex in chordotonal organs, disrupts channel gating, and inhibits normal signaling in sensory neurons. This causes abnormalities in aphid behavior and death. AFD is the only insecticide classified into group 9D of chordotonal organ TRPV channel modulators in the IRAC (Insecticide Resistance Action Committee) classification.[19)]

## Crop safety

Foliar spray with 2000, 4000 times diluted solutions of AFD 4.9% DC and 10% WDG did not cause phytotoxicity in cereals, vegetables, tea trees, fruit trees, or flowering plants in the field trials conducted by JPPA. This indicates that AFD products are safe for crops.

## Effects on non-target organisms

AFD has extremely low effects on aquatic organisms, honeybees, and natural enemies and is available in environments where natural enemies are used in greenhouses and when pollinator insects such as honeybees visit flowers. In addition to its low impact on non-target organisms, the application dose is also low, making AFD an eco-friendly agent with a low environmental impact.[15,16)]

## Conclusion

AFD is a novel insecticide that does not exhibit cross-resistance with existing insecticides. AFD has shown excellent efficacy in field trials worldwide, even when applied at low spray volumes, which is common worldwide. Furthermore, AFD can be used in combination with natural enemies to reduce environmental impact. Aphids have a short life cycle and easily develop resistance to existing insecticides; resistance to common insecticides has been reported in many cases.[20,21)] AFD products show a selective spectrum against sucking pests, such as aphids and whiteflies, and have a low impact on non-target organisms, making them safe agents for crop production. We believe that the AFD will contribute to sustainable crop production worldwide.

### Acknowledgements

In developing the AFD, BASF developed a formulation to enhance its efficacy, and its market penetration in Japan and other countries was promoted by BASF and BASF Japan. In addition, microbial production of PPs was greatly improved at Meiji Seika Pharma Co., Ltd. through microbial breeding technology, and a manufacturing platform was established with the support of the Production Technology Department of the Production Division. We would like to express our deep appreciation for the efforts of all related companies.

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