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Development of a novel fungicide, cyflufenamid*

Shinsuke SANO,** Isamu KASAHARA† and Homare YAMANAKA

Odawara Research Center, Nippon Soda Co., Ltd., 345 Takada, Odawara, Kanagawa 250–0216, Japan
† R & D Laboratory for High-Performance Materials, Nippon Soda Co., Ltd., 12–54 Goi-Minamikaigan, Ichihara, Chiba 290–0045, Japan

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Cyflufenamid is a novel and original fungicide discovered and developed by Nippon Soda Co., Ltd. The characteristic feature of its chemical structure is the benzamidoxime framework with 2,3-difluoro-6-(trifluoromethyl)phenyl and cyclopropylmethoxyimino groups. Cyflufenamid excellently controls powdery mildew of various crops by preventive or curative treatment, and shows long residual and vapor phase activity. The mode of action of cyflufenamid is considered different from that of other existing fungicides. It has favorable toxicological, ecotoxicological and environmental profiles. © Pesticide Science Society of Japan

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Introduction

Powdery mildew is one of the most serious crop diseases. Many fungicides have been developed and used for the control of powdery mildew. However, resistant strains of powdery mildew to some commercial fungicides have made disease control difficult. Cyflufenamid is a novel fungicide developed by Nippon Soda Co., Ltd. Cyflufenamid shows excellent control activities against powdery mildew of various plants and brown rot of stone fruits. It belongs to a new fungicide class, amidoximes. Its biological mode of action against pathogens is unique and differs from those of commercial fungicides. Cyflufenamid was first registrated in Japan in 2002. A mixture formulation of cyflufenamid with triflumizole was also developed to avoid the early appearance of resistant strains to the fungicide according to Nisso's resistance risk management strategies.

This paper describes the history of the discovery, synthesis, structure–activity relationships, biological activity, mode of action and safety of cyflufenamid.

Discovery and Synthesis

Since the 1960s, oxime ethers have been investigated in Nippon Soda to discover new pesticides, from which an acaricide and two herbicides have been launched onto the market. Under such a background, we studied the structural modification of metalaxyl which is a translocative fungicide, by introducing an oxime ether moiety in the molecule. Among a series of compounds, a benzamidoxime derivative was discovered as the lead compound showing fungitoxic activity. Structural optimization of the lead compound was performed in phenyl, oxime and amide moieties. Cyflufenamid was finally selected as the best compound on the basis of structure–activity profiles, physicochemical properties, field performance and safety. Cyflufenamid was synthesized by alkylation and acylation of benzamidoxime as the key intermediate. Construction of the 2,3-difluoro-6-(trifluoromethyl)phenyl moiety in cyflufenamid was the most challenging process in the synthesis. A method of *ortho* lithiation of benzotrifluoride was successfully applied to prepare the key intermediate.

Structure–Activity Relationships

In the phenyl moiety of the benzamidoxime, 2,6- or 2,3,6-substituted compounds showed potent activity against powdery mildew. Introduction of fluorine atoms into the phenyl group was also significant to give vapor phase activity to prevent plant disease. Cyflufenamid, having five fluorines in the phenyl group exhibited both translaminar and vapor phase activity to control powdery mildew effectively. For the oxime *O*-substituent, ethyl, propargyl and cyclopropylmethyl groups were more favorable than larger alkyl groups. The size and shape of the substituent were considerable to affect the activity. In the amide moiety, potent activity was exhibited by compounds having a phenylacetamide structure, in which 4-

* See Part II for the full Japanese article.

** To whom correspondence should be addressed.

methoxy, 4-methyl and unsubstituted phenyl were superior to other groups. The three-dimentional structure of cyflufenamid was predicted by quantum chemical calculations and NMR spectra, and confirmed by X-ray crystallography. The geometry of the C-N double bond in the oxime moiety was *Z*-form in crystals and predicted stable conformation.

Physical and Chemical Properties

Common name: cyflufenamid
Trade name: Pancho®
Experimental name: NF-149
CAS registry No.: 180409-60-3
Chemical name (IUPAC): (*Z*)-*N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide
Molecular formula: $C_{20}H_{17}F_5N_2O_2$
Molecular weight: 412.36
Appearance: white crystal
Melting point: 61.5–62.5°C
Solubility in water: 0.52 mg/l (20°C)
Vapor pressure: 3.54×10^{-5} Pa (20°C)
Partition coefficient: $\log P_{OW}=4.70$ (25°C)

Biological Properties

In the culture tests, some species of Ascomycetes and Deuteromycetes were sensitive to cyflufenamid. Especially, *Monilinia fructicola* were highly sensitive to cyflufenamid and were affected at the low concentration of 0.01 ppm. In pot tests, cyflufenamid showed excellent control activity against diseases caused by powdery mildew pathogens on various plants at 0.8 to 1.6 ppm. Fungicidal activity of cyflufenamid on cucumber powdery mildew was characterized by its excellent preventive, curative and long residual activity. It also has vapor phase activities in spite of its low vapor pressure. In field trials, a low dosage (25 ppm) of cyflufenamid showed excellent efficacy against powdery mildews of almost all plants caused by various pathogens in agricultural production.

Mode of Action

The mode of action of cyflufenamid is considered different from that of other existing fungicides. In the life cycle of *Brumeria graminis* f. sp. *tritici* causing wheat powdery mildew, although cyflufenamid did not affect infection behavior before appressorium formation on wheat leaves, the processes of haustorium formation, colony formation and suporulation were significantly inhibited. Cyflufenamid also affected germ tube elongation after spore germination of *M. fructicola*. After 24 hr, swelling at the tip point of germ tubes, and vacuolation and rupturing of germ tubes were observed. The results also suggest that the biochemical mode of action of cyflufenamid is different from those of commercial fungicides. We are now conducting experiments to clarify the action site of cyflufenamid.

Safety

Acute oral (rat, male/female) LD_{50}: >5000 mg/kg
Acute dermal (rat, male/female) LD_{50}: >2000 mg/kg
Acute inhalation (rat, male/female) LD_{50}: 4760 mg/m^3
Eye irritation (rabbit): very slightly irritating
Skin irritation (rabbit): non-irritating
Skin sensitization (guinea pig): non-sensitizing
Teratogenicity oral (rat, rabbit): negative
Mutagenicity (Ames test, chromosomal aberration and mouse micronucleus): negative