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Insecticidal activity against rice pest of oxazosulfyl, a novel sulfyl insecticide

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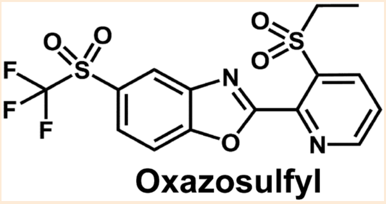

The development and commercialization of new chemical classes of insecticides are important for efficient crop protection, particularly for combatting insecticide resistance and providing sustainable agricultural production. This study reports on oxazosulfyl, a novel "sulfyl" class of insecticide, against a wide range of insect pests of rice. In the laboratory assay, oxazosulfyl showed insecticidal activity against all developmental stages of the brown planthopper *Nilaparvata lugens* (Stål). Phosphor imaging assays and soil drench bioassays demonstrated good systemic distribution in rice plants. Oxazosulfyl showed insecticidal activity against imidacloprid- and fipronil-resistant field populations of *N. lugens*, the white-backed planthopper *Sogatella furcifera* (Horváth), and the small brown planthopper *Laodelphax striatellus* (Fallén), as well as the respective susceptible strains. No cross-resistance was observed among oxazosulfyl, imidacloprid, and fipronil. Oxazosulfyl with a wide insecticidal spectrum is a potentially useful pest management tool for sustainable rice production.

Keywords: planthoppers, pest management, broad-spectrum, rice, systemic activity, resistance management.

Introduction

The global population is expected to reach 9.7 billion in 2050, and supplying food to this rapidly growing population is a global challenge.[1)] The discovery and development of new chemical pesticide classes are important for continuous and efficient food production.[2)] Recently, insecticide resistance has been reported for a wide range of insect pest species worldwide,[3)] with sustainable resistance management becoming increasingly important. A new chemical class of insecticides can be a powerful tool for managing insecticide resistance. Rice (*Oryza sativa* L.) is one of the most important crops worldwide, with rice production exceeding 470 million tons (milled basis).[4)] The warm and humid climate in South and Southeast Asia, in which rice is grown is propitious for the development of many insect pests.[5)] Planthoppers cause large economic losses in rice production. Many planthoppers, around harvest time, feed on phloem sap, causing rice wilting, called "hopper-burn".[6)] The brown planthopper (BPH), *Nilaparvata lugens* (Stål), often causes hopper-burn and transmits the ragged and grassy stunt viruses.[7–9)] In Asia, BPH has caused several outbreaks since the 1970s,[10)] causing an estimated rice production loss of over 300 million dollars annually.[11)] Other problematic planthoppers, the small brown planthopper (SBPH), *Laodelphax striatellus* (Fallén), and the white-backed planthopper (WBPH), *Sogatella furcifera* (Horváth), are vectors of the rice stripe and southern rice black-streaked dwarf viruses, respectively. These viral diseases cause high yield losses during rice production.[12,13)]

Synthetic insecticides have been used to control planthoppers for several decades, eventually leading to insect resistance.[10)] Since the 1990s, neonicotinoids and phenylpyrazoles, such as imidacloprid and fipronil, respectively, have been effective in controlling planthoppers. However, planthoppers have recently developed resistance to these insecticides in rice crops in Asia.[14–17)] Therefore, alternative insecticides are necessary to effectively control these resistant pests. Under these circumstances, Sumitomo Chemical Co., Ltd. initiated chemical screenings to discover novel molecules with broad-spectrum and adulticidal activity. Consequently, oxazosulfyl (2-[3-(ethylsulfonyl)-

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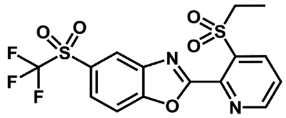
Common name:	Oxazosulfyl
Chemical name:	2-[3-(ethylsulfonyl)-2-pyridyl]-5-(trifluoromethyl-sulfonyl)-1,3-benzoxazole
CAS registration number:	1616678-32-0
Empirical formula:	$C_{15}H_{11}F_3N_2O_5S_2$
Molecular weight:	420.4 g/mol
Structural formula:	
Partition coefficient:	log P o/w = 2.69
Solubility in water:	15.6 mg/L
Melting point:	138.2 - 140.1 ° C

Fig. 1. Chemical structure and physicochemical properties of oxazosulfyl.

2-pyridyl]-5-(trifluoromethylsulfonyl)-1,3-benzoxazole) (Fig. 1), possessing insecticidal activity against rice pests belonging to Hemiptera, Lepidoptera, and Coleoptera was discovered.[18] The biological character of oxazosulfyl is poorly understood because it is the first molecule in the new sulfyl class of insecticides. Therefore, it is important to characterize oxazosulfyl for effective pest management in rice fields. Thus, this study introduces the biological profiles of oxazosulfyl, such as its insecticidal spectrum, systemic activity, and effectiveness to existing insecticide resistant pests.

Materials and methods

1. *Test insecticides*

Oxazosulfyl (>98.0%) and radiolabeled oxazosulfyl (benzoxazolyl-2-^{14}C, specific activity of 4.83 MBq/mg; purity 98.5%) were synthesized by the Health & Crop Sciences Research Laboratory of Sumitomo Chemical Co., Ltd. Imidacloprid (>98.0%), chlorantraniliprole (>98.0%), clothianidin (>98.0%), and fipronil (>98.0%) were purchased from FUJIFILM Wako Pure Chemical Corp., Japan.

For foliar spray and soil-drench bioassays, test insecticides were diluted in an organic solvent mixture (Acetone : Tween 20=95 : 5 v/v) to prepare a stock solution that was further diluted in deionized water. The test insecticides were diluted in acetone as the solvent carrier for the topical bioassay. At least five concentrations of the test solution (0.003–500 mg a.i./L) or acetone solution (0.0016–63 mg a.i./L) for all insecticides were prepared for each insecticidal bioassay. A surfactant (Shindain 0.05% v/v, Sumitomo Chemical Co., Ltd.) was added to the test solution for all foliar- and leaf-dipping bioassays. A surfactant with a water solution containing no insecticide was used as a blank for the foliar spray bioassays.

2. *Insects and plants*

Each insect was obtained from insecticide-susceptible strains maintained without insecticide pressure for over 10 years at the Health & Crop Sciences Research Laboratory, Sumitomo Chemical Co., Ltd. (except for rice water weevil (RWW) *Lissorhoptrus oryzophilus*, rice leaf beetle (RLB) *Oulema oryzae* (Kuwayama), and field populations of BPH, SBPH, and WBPH). In addition, colonies of planthoppers, rice green leafhopper (RGL), *Nephotettix cincticeps* (Uhler), rice leaf roller (RLR), *Cnaphalocrocis medinalis* (Guenée), rice stem borer (RSB), *Chilo suppressalis* (Walker) were reared on rice seedlings at 16 : 8 hr, L : D photoperiod, 25°C, and 60–70% relative humidity. Rice seedlings used for insect rearing and all bioassays were grown in culture soil in a greenhouse at 25°C and in a 12 : 12 hr, L : D photoperiod. Plants were watered daily. The treated insects were maintained in the laboratory (16 : 8 hr, L : D photoperiod, 25°C, and 60–70% relative humidity) during the bioassays. Insects that were abnormally dropped from plants or did not react to direct stimuli were regarded as intoxicated and included in calculating the median lethal concentration (LC_{50}) and median lethal dose (LD_{50}) values.

3. *Insecticidal spectrum*

3.1. *BPH, WBPH, SBPH, and RGL*

The test solution (10 mL) was sprayed onto five rice seedlings (two- to three-leaf stage) in plastic pots using a handheld sprayer. Then, each treated plant was placed in a glass test tube (⌀30×200 mm) with 10 third-instar BPH, WBPH, SBPH, and RGL nymphs. Each bioassay comprised one planthopper/leafhopper species; thus, four different bioassays were conducted. Each rice seedling was considered an experimental unit, and the assessment was performed 5 days following treatment.

3.2. *RLR and RSB*

The test solution (10 mL) was sprayed onto the five rice seedlings using a handheld sprayer. After drying, the rice leaf (with its sheath) was cut out from the treated seedlings and transferred to 70-mm-diameter filter paper containing 0.5 mL of deionized water in a plastic petri dish (⌀90×20 mm). Ten second-instar larvae of either RLR or RSB were released into the leaves. A bioassay was conducted with each pest species. Each rice seedling was considered an experimental unit, and the assessment was performed 5 days following treatment.

3.3. *RWW*

RWW adults were collected from rice fields in Sakuragawa, Ibaraki, Japan, and used in the experiment within 4 days of collection. Ten adults were anesthetized on ice, and acetone solution (1.0 μL) was applied to the ventral abdomen using a Burkard Auto Micro Applicator (Burkard Manufacturing Co., Ltd., Rickmansworth, UK). Treated insects were placed inside plastic Petri dishes (⌀90×20 mm) containing 70-mm-diameter filter paper (ADVANTEC TOYO KAISYA, LTD., Tokyo, Japan) at the bottom and 10 rice seedling leaves. The assessment was performed 5 days after treatment.

3.4. *RLB*

RLB adults were collected from rice fields in Yubari, Hokkaido, Japan, and used in the experiment within 4 days of collection. Five adult pairs (five females and five males) were anesthetized on ice, and acetone solution (0.5 μL) was applied to the notum using a PB600-1 repeating syringe dispenser (Hamilton Bonaduz AG, Bonaduz, Switzerland). Treated insects were placed in plastic Petri dishes (⌀90×20 mm) containing 70-mm-diameter filter paper at the bottom and 10 rice seedling leaves. The assessment was performed 10 days after treatment.

4. *Insecticidal activity against different developmental stages of BPH*

Three different developmental stages of BPH (first instar nymphs, short-winged male adults, and short-winged female adults) were tested using the same methodology described below. The test solution (10 mL) was sprayed onto the rice seedlings (two- to three-leaf stages) using a handheld sprayer. After drying, each plant was placed in a glass test tube (⌀30×200 mm), and 20 first-instar nymphs and 10 short-winged adults (males and females) were released into the test tubes. The assessment was performed 5 days after treatment.

5. *Cross-resistance assay*

Insects from natural field populations of BPH, WBPH, and SBPH were collected from rice fields in Satsumasendai, Kagoshima, Japan, in 2018 and maintained in the Health & Crop Sciences Research Laboratory of Sumitomo Chemical, Co., Ltd. (Hyogo, Japan) without any insecticide exposure. These field populations were maintained for 3–6 generations before the assay, using rice seedlings at 16 : 8 hr, L : D photoperiod, 25°C, and 60–70% relative humidity. The insecticidal spectra of oxazosulfyl, imidacloprid, and fipronil were evaluated using these field populations. Laboratory-maintained strains of BPH, WBPH, and SBPH kept in the Health & Crop Sciences Research Laboratory mentioned in Section 3.1. were used as susceptible (S) strains. The test methodology was the same as that described in Section 3.1. The resistance ratio (RR) for each insecticide was calculated using the following formula:

$$\mathrm{RR} = [\mathrm{LC}_{50}\text{value of field populations}]/[\mathrm{LC}_{50}\text{value of S-strains}]$$

6. *Soil drench assay*

Five rice seedlings (2.5- to 3-leaf stage) cultivated in plastic pots (⌀56×60 mm) were treated with the test solution (1 mL) and pipetted directly onto the soil surface. Ten short-winged adults (male : female = 5 : 5) of insecticide-susceptible strain and field populations (see section 5 in Materials and methods) BPH were released on the rice seedlings 3 days after treatment, and the seedlings were covered with transparent plastic cups (⌀50×200 mm). The assessment was performed 2 and 7 days after BPH release.

7. *Uptake of ^{14}C oxazosulfyl in rice plants*

The uptake of radiolabeled oxazosulfyl (^{14}C oxazosulfyl) was qualitatively studied by soil drench application. Radiolabeled ^{14}C oxazosulfyl dissolved in acetonitrile was used as a radiolabeled stock solution. A test solution (100 mg a.i./L) was prepared by mixing radiolabeled ^{14}C oxazosulfyl [9.4 μg] with a nonradiolabeled stock solution of oxazosulfyl. The test solution (1.0 mL) was applied to the soil surface of rice seedlings (2.5-leaf stage) cultivated in a plastic test tube (⌀30×115 mm). Three days after the treatment, the plants were removed from the test tube, the roots were rinsed off, and the roots were left to dry (30 min at 25°C). The plants were then placed on phosphor imaging plates (BAS-MS2040; FUJIFILM Corp., Tokyo, Japan) in cassettes (BAS 2040; FUJIFILM Corp.). The cassettes were stored in a shielded box for 16 hr. The phosphor imaging plates were scanned using a phosphor imaging analysis system (Typhoon FLA 7000; GE Healthcare, Illinois, US). The translocation of ^{14}C oxazosulfyl from the roots to the aerial parts of the plant was visualized in rice stems and true leaves using ImageQuant TL (GE Healthcare, Chicago, IL, US).

8. *Statistical analysis*

LC_{50} and LD_{50} values and their 95% confidence intervals were calculated using probit analysis. When necessary, the mortality values were corrected according to Abbott.[19)]

Results

1. *Insecticidal spectrum*

The LC_{50} and LD_{50} values of oxazosulfyl for each insect species are listed in Table 1.

The insecticidal activity of oxazosulfyl against hemipterans such as plant hoppers was comparable to that of imidacloprid and superior to that of chlorantraniliprole. In contrast, the insecticidal activity of oxazosulfyl against lepidopterans was superior to that of imidacloprid but inferior to that of chlorantraniliprole. The insecticidal activity of oxazosulfyl against RWW and RLB was comparable to those of clothianidin and imidacloprid, respectively.

2. *Insecticidal activity against different developmental stages of BPH*

The insecticidal activities of oxazosulfyl against different BPH developmental stages are presented in Table 2. Although insecticidal activity tended to decrease with BPH development, the LC_{50} values for oxazosulfyl against first- and third-instar nymphs and both female and male adults were not significantly different. These results indicate that oxazosulfyl is equally effective at all developmental stages of BPH.

3. *Cross-resistance assessment against field-collected planthoppers*

The BPH field population was highly resistant to imidacloprid (RR=568) and less susceptible to fipronil (RR=9.1) than to oxazosulfyl (RR=1.9) (Table 3). Similarly, the RR values of the WBPH and SBPH field populations to imidacloprid were 11 and 30, fipronil, 71 and 17, and oxazosulfyl, 0.8 and 0.4, respectively (Table 3). These results indicated a lack of high-level cross-resistance between imidacloprid, fipronil, and oxazosulfyl.

4. *Systemic activity*

The phosphor imaging assay evidently showed the uptake of ^{14}C oxazosulfyl from the root area and their translocation into the

Table 1. Insecticidal spectrum of oxazosulfyl against various insect pest species

Species	Stage (application)[a]	LC_{50}[b] or LD_{50}[c] (95% Cl)			
		Oxazosulfyl	Imidacloprid	Chlorantraniliprole	Clothianidin
Hemiptera					
Nilaparvata lugens	Nymph, 3rd, (f)	0.41 (0.32–0.51)	0.19 (0.14–0.24)	>500	—
Laodelphax striatellus	Nymph, 3rd, (f)	0.61 (0.48–0.79)	0.18 (0.13–0.24)	>500	—
Sogatella furcifera	Nymph, 3rd, (f)	0.82 (0.65–1.1)	0.17 (0.14–0.21)	>500	—
Nephotettix cincticeps	Nymph, 3rd, (f)	0.092 (0.071–0.12)	0.012 (0.005–0.018)	15 (13–20)	—
Lepidoptera					
Chilo suppressalis	Larva, 2nd (f)	0.20 (0.17–0.25)	28 (24–35)	0.076 (0.052–0.11)	—
Cnaphalocrocis medinalis	Larva, 2nd (f)	0.27 (0.21–0.35)	10 (7–17)	0.025 (0.019–0.031)	—
Coleoptela					
Lissorhoptrus oryzophilus	Adult, (t)	0.017 (0.011–0.026)	—	—	0.026 (0.012–0.053)
Oulema oryzae	Adult, (t)	0.0040 (0.0029–0.0057)	0.0043 (0.0029–0.0064)	—	—

[a] f: foliar spray, t: topical, [b] mg a.i./L, [c] μg a.i./insect.

aerial parts of the plant (Fig. 2A). The signal of ^{14}C oxazosulfyl was observed in the whole plant body 3 days after treatment. This result suggests apoplastic translocation of oxazosulfyl *via* the xylem. The soil drench assay of oxazosulfyl caused high BPH mortality in both insecticide-susceptible and field populations in rice plants 7 days after BPH release (Fig. 2B).

Discussion

Oxazosulfyl showed insecticidal activity against a wide range of rice insect pests, including Hemiptera, Lepidoptera, and Coleoptera, in our laboratory bioassays (Table 1). The insecticidal activity of oxazosulfyl against hemipteran pests was in the same range as that of imidacloprid and higher than that of chlorantraniliprole. Both insecticides are commonly used for rice production by nursery box treatment in Japan. In contrast, the insecticidal activity of oxazosulfyl against lepidopteran pests was superior to that of imidacloprid but lower than that of chlorantraniliprole. Although oxazosulfyl shows lower insecticidal activity against lepidopteran pests than chlorantraniliprole, its field performance is sufficient to control lepidopteran pests.[20] Furthermore, oxazosulfyl insecticidal activity is comparable to that of imidacloprid and clothianidin against coleopteran pests.[21–23] The insecticidal spectrum of oxazosulfyl makes it an ideal insecticide to protect rice plants since a wide variety of pests occur during rice growing season. Furthermore, oxazosulfyl has shown efficacy against various rice pests in the field test.[20]

Table 2. Insecticidal activity of oxazosulfyl against different developmental stages of *Nilaparvata lugens*

Stage	LC_{50}[a] (95% Cl)
Nymph, 1st instar	0.18 (0.16–0.21)
Nymph, 3rd instar[b]	0.41 (0.32–0.51)
Adult, female	0.48 (0.35–0.62)
Adult, male	0.59 (0.45–0.84)

[a] mg a.i./L, [b] data from Table 1.

We verified that oxazosulfyl is effective against all BPH developmental stages for the same dose range, from first-instar nymphs to adults (Table 2). Oxazosulfyl is suitable for controlling planthopper nymphs and adults because they feed on sap from the rice leaf sheath.

Since the mid-2000s, the resistance of planthoppers to imidacloprid and/or fipronil has become a serious problem in Asian rice fields. In Japan, SBPH has developed resistance to both imidacloprid and fipronil.[24] Several studies have reported that monooxygenase overexpression is associated with the main resistance factor to imidacloprid in BPH collected from China, Thailand, and Vietnam.[25,26] In the case of fipronil resistance in WBPH collected from China or Japan, both target-site insensitivity of γ-aminobutyric acid (GABA) receptor and enhanced metabolic activity have been reported.[27,28] In SBPH collected from China, the mechanism of imidacloprid resistance is suggested to involve monooxygenase overexpression.[29] However, neonicotinoid resistant field populations with nicotinic acetylcholine receptor mutations have not yet been reported. Although the main mechanisms of fipronil resistance in SBPH are reportedly target-site mutations of GABA receptor, there are no studies of enhancing metabolic activity as the main factor of fipronil resistance.[30,31]

No cross-resistance for oxazosulfyl was observed in any of the studies using field populations of the three planthopper species that were highly resistant to imidacloprid or fipronil, or both (Table 3). These results suggest that oxazosulfyl is not subject to the metabolic mechanisms involved in imidacloprid- and fipronil-resistant planthopper populations and support its usefulness as a new tool for insecticide resistant planthopper control. Furthermore, oxazosulfyl belongs to a new chemical class, making it an effective control material against rice pests that have developed resistance to several existing insecticides. Oxazosulfyl is classified into UN group in the classification of the Insecticide

Table 3. LC_{50} value and resistance ratio for oxazosulfyl, imidacloprid and fipronil against the susceptible strains and field populations of planthoppers

Insecticide	Species[a]	Strain/Population[b]	LC_{50}[c]	CI 95%	Slope	RR[d]
Oxazosulfyl[e]	BPH	S	0.41	0.32–0.51	2.4	—
		Kagoshima	0.78	0.61–0.97	2.4	1.9
	WBPH	S	0.82	0.65–1.06	2.3	—
		Kagoshima	0.69	0.55–0.87	2.2	0.8
	SBPH	S	0.61	0.48–0.79	2.1	—
		Kagoshima	0.23	0.16–0.30	1.7	0.4
Imidacloprid	BPH	S	0.19	0.14–0.24	1.8	—
		Kagoshima	106.29	79.49–143.90	1.5	568.4
	WBPH	S	0.17	0.14–0.21	2.2	—
		Kagoshima	1.85	1.45–2.33	2.4	10.9
	SBPH	S	0.18	0.13–0.24	2.5	—
		Kagoshima	5.32	3.03–9.18	0.9	30.2
Fipronil	BPH	S	0.26	0.21–0.32	2.6	—
		Kagoshima	2.37	1.87–2.98	2.2	9.1
	WBPH	S	0.17	0.13–0.21	2.3	—
		Kagoshima	12.06	9.28–15.53	2.0	71.0
	SBPH	S	0.23	0.18–0.28	2.5	—
		Kagoshima	3.72	2.24–6.10	1.0	16.5

[a] BPH; *N. lugens*, WBPH; *S. furcifera*, WBPH; *L. stnatellus*, [b] S; susceptible strains, Kagoshima; field populations collected from rice field in 2018, Kagoshima, [c] mg a.i./L, [d] RR (resistance ratio) = LC_{50} value of field strains/LC_{50} value of susceptible strains. [e] Data from Table 1.

Resistance Action Committee.[32] On the other hand, oxazosulfyl has been reported to act on the insect central nervous system,[33] and further detailed research is expected.

The systemic action of oxazosulfyl was confirmed using a phosphor imaging assay with radiolabeled oxazosulfyl in rice plants (Fig. 2A) and a soil drench assay against BPH (Fig. 2B). In the phosphor imaging assay, ^{14}C oxazosulfyl signals were detected in the whole plant 3 days after treatment (Fig. 2A), and

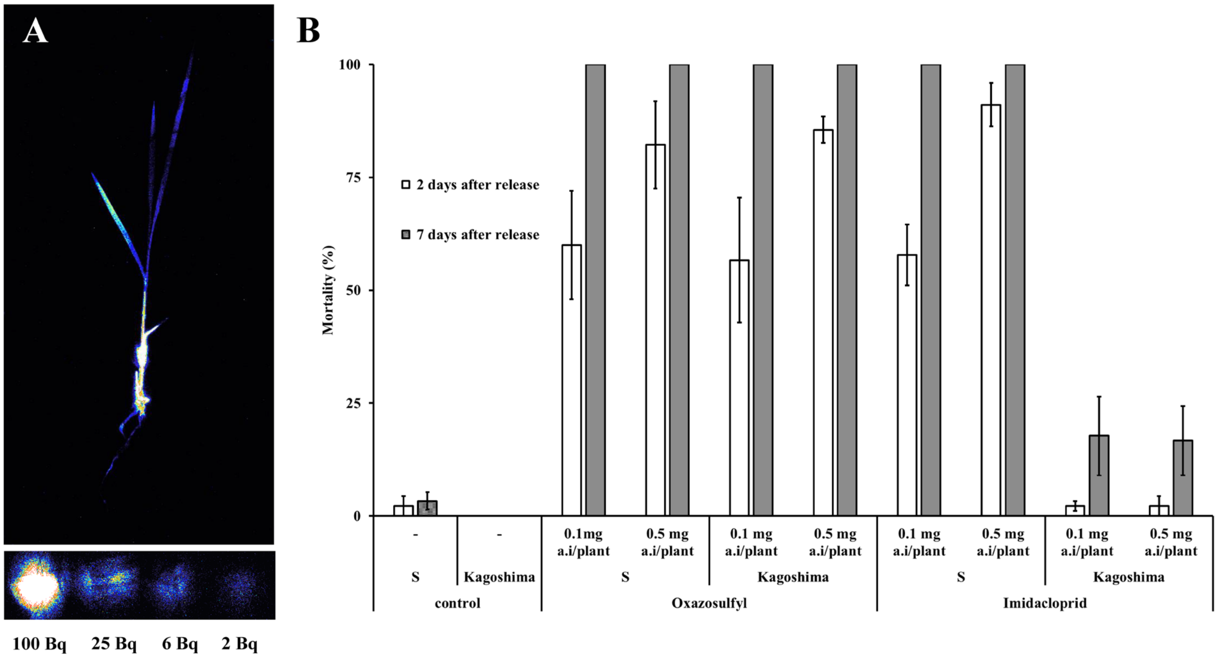


Fig. 2. Translocation of ^{14}C oxazosulfyl at different time intervals in rice plants *via* soil drench application and systemic activity of oxazosulfyl by soil drench application against adult *Nilaparvata lugens*. (A) 72 hr after application. (B) Mortality in 2 or 7 days after BPH release. S: Susceptible strains, Kagoshima; field populations collected from rice fields in Kagoshima, 2018. Data are presented as means ±SEs for three independent replicates.

signals were detected in the leaves and stem that pests prefer to attack. In the soil drench assay, oxazosulfyl caused high mortality against insecticide-susceptible strains and BPH field populations. Collectively, these results indicate the reasonable efficiency of oxazosulfyl as a soil-applied insecticide, as oxazosulfyl was translocated from rice roots to aerial parts, systematically protecting plants from the damage caused by insect pests.

Moreover, rice field trials conducted by the Japanese Plant Protection Association demonstrated the efficacy of oxazosulfyl using the nursery box treatment against planthoppers, which are developing resistance to commercialized insecticides and other rice-feeding pests such as *N. cincticeps, C. medinalis, L. oryzophilus*, and *O. oryzae* (data not shown).[34] Our results support the effectiveness of oxazosulfyl in rice production as a new tool for controlling a wide range of rice insect pests.

Conclusions

Oxazosulfyl was the first molecule in the sulfyl class of insecticides, originally discovered and developed by Sumitomo Chemical Co., Ltd. Oxazosulfyl has a broad insecticidal spectrum against a range of pests, including several rice pests, and has also been shown to be translocated in plant tissues. Oxazosulfyl is equally effective at all developmental stages of BPH. Also, no cross-resistance to existing insecticides was observed in field populations of three planthopper species. These features of oxazosulfyl are expected to be suitable for rice pest control. In 2021, oxazosulfyl was registered in Japan as a new pest management tool for rice production.

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Conflict of interest declaration

The authors declare no conflicts of interest associated with this manuscript.

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