Discovery of broflanilide, a novel insecticide

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(Received December 23, 2018; Accepted February 3, 2019)

Broflanilide (1), discovered by Mitsui Chemicals Agro, Inc., has a unique chemical structure characterized as a meta-diamide and exhibits high activity against various pests, including Lepidopteran, Coleopteran, and Thysanopteran pests. Because broflanilide has a novel mode of action, the Insecticide Resistance Action Committee (IRAC) categorized it as a member of a new group: Group 30. The meta-diamide structure was generated via drastic structural modification of a lead compound, flubendiamide (2), and the subsequent structural optimization of meta-diamides on each of its three benzene rings led to the discovery of broflanilide. In the present study, the details of the generation of meta-diamides from the lead compound and the structural optimization of meta-diamides are described. © Pesticide Science Society of Japan

Keywords: Meta-diamide, broflanilide, MIE-1209FL, insecticide, Lepidopteran pests.

Electronic supplementary material: The online version of this article contains supplementary material (Supplemental Table S1), which is available at http://www.jstage.jst.go.jp/browse/jpestics/

Introduction

The emergence of insects showing resistance to various insecticides is a serious problem worldwide, and new insecticides with a novel mode of action are always needed in agriculture. After our research and development of neonicotinoids, which exhibit excellent activity against Hemipteran pests, had been completed, we planned to discover a novel insecticide that is effective against Lepidopteran pests, which are as serious a problem in agriculture as Hemipteran pests. Flubendiamide (2; Fig. 1), discovered and developed by Nihon Nohyaku Co. Ltd.,11 has been tested in several official trials in Japan since 2000 under the code number NNI-0001. Flubendiamide had a unique structure that had not been found in any other agrochemicals, and it exhibited high insecticidal activity against various Lepidopteran pests. We began our drug discovery research in 2002, setting flubendiamide as the lead compound. As a result of lead generation from flubendiamide, we discovered that compounds with meta-diamide structures exhibit high activity against Lepidopteran pests23 and that they exhibit insecticidal symptoms different from those exhibited by flubendiamide. The change in the mode of action predicted from insecticidal symptoms encouraged us to conduct the optimization of meta-diamides, leading to the identification of broflanilide (1; Fig. 1), N-[2-bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-(N-methylbenzamido)benzamide, which

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Published online #M## #D##, 2019
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Fig. 1. Chemical structure of broflanilide and flubendiamide.
exhibits extremely high activity against not only Lepidopteran pests but also Thysanopteran and Coleopteran pests.\textsuperscript{3,4)}

The suspension concentrate formulation containing 5\% broflanilide has been tested in official trials in Japan since 2008 under the code number MIE-1209FL, and it has been confirmed that MIE-1209FL is highly applicable for protecting leaf vegetables and fruit vegetables from various Lepidopteran and Coleopteran pests. Furthermore, studies have reported the action of broflanilide on the insect ionotropin $\gamma$-aminobutyric acid (GABA) receptor.\textsuperscript{5–7)} As a result of our drastic structural modification, broflanilide's mode of action was shown to be different from that of flubendiamide, which is classified as a member of Group 28 (mode of action: ryanodine receptor modulators; chemical class: diamides) by the IRAC’s classification.\textsuperscript{8)} In 2017, the IRAC classified broflanilide as a member of a new group, Group 30 (mode of action: Group 30 GABA-gated chloride channel allosteric modulator; chemical class: \textit{Meta}-diamides & Isoxazolines).\textsuperscript{8)} Broflanilide, with its new mode of action, is expected to exhibit high activity against Lepidopteran pests, which have developed resistance to diamide and other insecticides.

In the present report, we describe the details of the discovery, synthesis, structure–activity relationships, and some insecticidal properties of broflanilide and its derivatives.

### Materials and Methods

#### 1. Preparation of compounds

Melting points were uncorrected. Chemical structures were confirmed by $^1$H-NMR spectroscopy using a JEOL JNM-A400 FT-NMR system at 400 MHz with tetramethylsilane as the internal standard.

#### 1.1. Synthesis

The synthetic pathway of broflanilide and its derivatives is shown in Fig. 2. $N$-[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-phenyl]-3-nitrobenzamide derivatives (5) were obtained by reacting 3-nitrobenzoyl chloride derivatives (4) derived from commercially available 3-nitrobenzoic acid derivatives with corresponding 4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)anilines (3).\textsuperscript{2–4,9) Derivatives of 2-fluoro-$N$-[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)phenyl]-3-nitrobenzamide (6) were obtained by reacting the corresponding 2-chloro compounds (5) with potassium fluoride. We obtained 3-amino-$N$-[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)phenyl]benzamides (7) by reacting the corresponding nitro compound (5 or 6) with stannous chloride under acidic conditions.

\textit{Meta}-diamide derivatives (8) that do not have $N$-methyl groups in their structures were synthesized by reacting the corresponding anilines (7) with the corresponding acid chlorides in the presence of pyridine as a base. \textit{Meta}-diamide derivatives (10) that do have $N$-methyl groups in their structure were syn-

![Fig. 2. Synthetic pathway of broflanilide and its derivatives.](image-url)
thesized by reacting the corresponding N-methyl anilines (9) obtained by the N-methylation of anilines (7) with the corresponding acid chlorides (8) in the presence of pyridine as a base.

2-Fluoro-N-[(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-methyl-2-(trifluoromethyl)phenyl]-3-(benzamido)benzamide (11) and 2-fluoro-N-[(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(difluoromethyl)phenyl]-3-(benzamido)benzamide (12) were synthesized from compound 8 via trifluoromethylation using difluoro(fluorosulfonyl)acetic acid methyl ester.

As a representative example, the procedures used to synthesize broflanilide (1) are described in the following sections.

1.2. N-[2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-chloro-3-nitrobenzamide (5; X=Br, Y=CF₃, R=2-Cl)

2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)aniline (6; 3.6 g, 8.8 mmol) was added to anhydrous THF (20 mL), and the mixture was cooled to −70°C. Subsequently, 2.0 M lithium diisopropylamide in hexane (4.85 mL, 9.7 mmol) was added dropwise to the mixture at −70°C under nitrogen. The 2-chloro-3-nitrobenzyl chloride (4; 2.34 g, 10.6 mmol) prepared from 2-chloro-3-nitrobenzoic acid and thionyl chloride was dissolved in anhydrous THF (5 mL), and the resulting mixture was added dropwise to the above cooled mixture at −70°C. The reaction mixture was stirred at −70°C for 30 min and then at room temperature for 30 min, and it was poured into an aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the obtained residue was purified using silica gel chromatography (eluent=hexane:ethyl acetate, 10:1) to yield a white solid (5) (1.76 g, 34% yield). ¹H-NMR (CDCl₃) δ ppm: 7.61 (1H, t, J=7.8 Hz), 7.67 (1H, s), 7.93–7.97 (3H, m), 8.18 (1H, d, J=14.6 Hz).

1.3. N-[2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-nitrobenzamide (6; X=Br, Y=CF₃)

Potassium fluoride (spray-dried product; 2.4 g, 41 mmol) was added under nitrogen to a solution of N-[2-bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-chloro-3-nitrobenzamide (5; 4.9 g, 8.3 mmol) in anhydrous DMF (50 mL), and the mixture was stirred at 130°C for 10 hr. Liquid separation was conducted by adding ethyl acetate, hexane, and water to the reaction mixture. The organic layer was washed with water and saturated brine, followed by drying over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified using silica gel chromatography (eluent=hexane:ethyl acetate, 10:1) to yield a white solid (6) (0.94 g, 20% yield). ¹H-NMR (CDCl₃) δ ppm: 7.33 (1H, t, J=7.3 Hz), 7.93 (1H, d, J=14.1 Hz), 8.17–8.18 (2H, m), 8.28–8.32 (1H, m), 8.44–8.48 (1H, m).

1.4. 3-Amino-N-[2-bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluorobenzamide (7; X=Br, Y=CF₃, R=2-F)

N-[2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-nitrobenzamide (6; 0.94 g, 1.6 mmol) and anhydrous stannous chloride (0.96 g, 5.1 mmol) were added to ethanol (10 mL), followed by the addition of concentrated hydrochloric acid (1.02 mL) to the mixture. The mixture was stirred at 60°C for 4 hr and poured into water. The resulting mixture was adjusted to pH 10 by adding aqueous sodium hydroxide solution, and the precipitated insolubles were removed by filtration using Celite. The filtrate on Celite was washed and extracted with ethyl acetate, and the organic layer was washed with a 20% aqueous sodium hydroxide solution and saturated brine, then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified using silica gel chromatography (eluent=hexane:ethyl acetate, 4:1) to yield a white solid (7) (0.88 g, 99% yield). ¹H-NMR (CDCl₃) δ ppm: 3.93 (2H, brs), 6.99–7.04 (1H, m), 7.11 (1H, t, J=7.8 Hz), 7.47–7.49 (1H, m), 7.91 (1H, s), 8.14 (1H, s), 8.28 (1H, d, J=14.6 Hz).

1.5. N-[2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-(methylamino)benzamide (9; X=Br, Y=CF₃, R=2-F)

3-Amino-N-[2-bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluorobenzamide (7; 0.93 g, 1.7 mmol) was added to concentrated sulfuric acid (5 mL), followed by the dropwise addition of 37% aqueous formaldehyde solution (10 mL) to the mixture at 40°C. The reaction mixture was stirred for 30 min and poured into ice water, and the resulting mixture was adjusted to pH 10 using a solution of aqueous sodium hydroxide. The mixture was extracted with ethyl acetate, and the organic layer was washed with a 20% aqueous sodium hydroxide solution and saturated brine, then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified using silica gel chromatography (eluent=hexane:ethyl acetate, 8:1) to yield a white solid (9) (0.69 g, 72% yield). ¹H-NMR (CDCl₃) δ ppm: 2.94 (3H, s), 4.14 (1H, brs), 6.86–6.93 (1H, m), 7.18 (1H, t, J=7.8 Hz), 7.37–7.41 (1H, m), 7.90 (1H, s), 8.13 (1H, s), 8.27 (1H, d, J=14.6 Hz).

1.6. N-[2-Bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-(N-methylbenzamido)benzamide (10; X=Br, Y=CF₃, R=2-F, Q=Ph-Broflanilide (I))

Benzyol chloride (0.46 g, 3.3 mmol) was added to a solution of N-[2-bromo-4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-(methylamino)benzamide (9; 1.54 g, 2.75 mmol) and pyridine (0.33 g, 4.2 mmol) in THF (5 mL), and the mixture was stirred for 60°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1 M hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution, and saturated brine, then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified using silica gel column chromatography (eluent=hexane:ethyl acetate, 8:1). The obtained solid was washed with isopropyl ether to yield a white
solid (1) (1.45 g, 79% yield). $^1$H-NMR (CDCl$_3$) δ ppm: 3.50 (3H, s), 6.99–7.33 (6H, m), 7.43–7.45 (1H, m), 7.90 (1H, s), 7.97–8.06 (2H, m), 8.13 (1H, s). m.p. : 154.0–155.5°C.

1.7. Other derivatives
The other derivatives were synthesized using similar methods, and commercially available reagents and solvents were used. $^1$H-NMR spectrum data of the other derivatives are described in the Supplemental material (Table S1).

2. Biological assay
2.1. Insects
We used laboratory strains of Spodoptera litura, Plutella xylostella, Helicoverpa armigera, Adoxophyes honnai, and Frankliniella occidentalis maintained at the Agrochemicals Research Center, Mitsui Chemicals Agro Inc. (Mobara, Chiba, Japan), and a field strain of Phyllotreta striolata collected from Ibaraki Prefecture in 2008.

2.2. Insecticidal toxicity assay against S. litura and P. xylostella
The synthesized compounds were dissolved in acetone and the resulting solutions were diluted with a 0.1% solution of New Gramin™ (10% polyoxyethylene nonylphenyl ether, 10% polyoxyethylene dodecyl ether, and 12% calcium lignin sulfonate; Mitsui Chemicals Agro, Inc.) to yield predetermined concentrations. New Gramin™ was used to spread compound solutions uniformly over the test materials. The final concentration of acetone was 20% and the total volume of compound solutions was 15 mL.

The compound solutions were poured into plastic dishes (ϕ 8 cm, depth 4 cm), and cabbage (Brassica oleracea L.) leaf segments (5×5 cm$^2$) were cut out and submerged in these solutions, then air-dried at room temperature. Each treated leaf segment was inoculated with five second-instar larvae of S. litura or five third-instar larvae of P. xylostella and placed in a plastic dish (ϕ 8 cm, depth 4 cm) and kept at 25°C under light/dark (16 hr/8 hr) conditions. Each treatment was replicated at least twice. Mortality was assessed after 3 days. A mixture containing acetone and New Gramin™ but lacking added insecticidal compounds was used as a control, which had no effect on mortality.

2.3. Insecticidal toxicity assay against H. armigera
An insecticidal toxicity assay against H. armigera was performed as described in Section 2.2 with the following modifications: Cabbage (B. oleracea L.) leaf segments (ϕ 3 cm) were cut out and submerged in these compound solutions, then air-dried at room temperature. Five treated leaf segments were each inoculated with one third-instar larva of H. armigera and placed individually in wells of a six-well plastic tray.

2.4. Insecticidal toxicity assay against A. honnai
An insecticidal toxicity assay against A. honnai was performed as described in Section 2.2 with the following modifications: Pieces of a thinly sliced artificial diet (Insecta LFS; Nosan Corporation) were submerged in these compound solutions, then air-dried at room temperature. The pieces of artificial diet were inoculated with five third-instar larvae of A. honnai.

2.5. Insecticidal toxicity assay against F. occidentalis
An insecticidal toxicity assay against F. occidentalis was performed as described in Section 2.2 with the following modifications: Green bean (Phaseolus vulgaris) leaf segments (ϕ 4 cm) were cut out and submerged in these compound solutions, then air-dried at room temperature. Each treated leaf segment was inoculated with ten second-instar nymphs of F. occidentalis and placed in a plastic dish (ϕ 5 cm, depth 3 cm) containing 1.5% agar.

2.6. Insecticidal toxicity assay against P. striolata
An insecticidal toxicity assay against P. striolata was performed as described in Section 2.2 with the following modifications: Synthesized compound solutions were poured into plastic dishes (ϕ 12 cm, depth 9 cm). The roots of radish (Raphanus sativus) seedlings were wrapped in wet cotton and their leaves were air-dried at room temperature after being dipped in these synthesized compound solutions. Each treated seedling was inoculated with five adult P. striolata beetles and placed in a plastic dish (ϕ 12 cm, depth 9 cm).

2.7. Translaminar activity against P. xylostella in cabbage leaves
The synthesized compounds were dissolved in dimethyl sulfoxide and the resulting solutions were diluted with a solution containing 0.01% Gramin™ S (15% polyoxyethylene nonylphenyl ether, 4% polyalkyl methacrylate sodium sulfonate, and 5% polyoxyethylene fatty acid ester; Mitsui Chemicals Agro, Inc.), 0.01% Newcol 710 (polyoxyethylene polycyclic phenyl ether; Nippon Nyukazai Co., Ltd.), and 0.01% of a 20% polyvinyl alcohol solution to yield 25 ppm of each compound solution. The final concentration of dimethyl sulfoxide was 0.0025%, and the total volume of compound solutions was 2 mL. The compound solutions were sprayed onto the upper side of cabbage (B. oleracea L.) leaves, then air-dried at room temperature. The leaves were cut into segments (5×5 cm$^2$), and each leaf segment was sanded using a plastic slide with a hole (ϕ 3 cm) on the untreated surface and a plastic slide without a hole on the treated surface. The untreated leaf surfaces were inoculated with five second-instar larvae of P. xylostella through the hole of the plastic slide and kept at 25°C under light/dark (16 hr/8 hr) conditions. Each treatment was replicated four times. Mortality was assessed after 3 days.

2.8. S. litura injection assay
The synthesized compounds were dissolved in dimethyl sulfoxide to yield 1,000 or 10,000 ppm compound solutions. Fifth-instar larvae of S. litura were injected with 0.25 µL of the compound solutions on the lateral side of the abdomen using a micro syringe. The treated insects were placed in a plastic dish (ϕ 8 cm, depth 4 cm) and kept at 25°C under light/dark (16 hr/8 hr) conditions. Insecticidal symptoms of treated insects were observed over a 24 hr period. Injection of dimethyl sulfoxide without added compounds showed no insecticidal symptoms.
Results and Discussion

1. Lead generation

1.1. Modification to yield meta-substituent compounds

We were interested in a Lepidopteran insecticide, flubendiamide (2), which has unique structures that had not previously been found in agrochemicals, such as an ortho-phthalidic diamide structure and a heptafluoroisopropyl group.

Because we thought the heptafluoroisopropyl group of flubendiamide played an important role in the high activity exhibited against Lepidopteran pests, we left the N-(heptafluoroisopropyl)phenyl carbamoyl group unchanged. In contrast, to drastically change the structure of flubendiamide, various compounds that had a carboxamide group or a carbamate group at the meta position of the heptafluoroisopropyl phenyl carbamoyl group were synthesized, and their insecticidal activities against Lepidopteran pests were evaluated (Table 1; compounds 13–16). As shown in Table 1, each benzene ring is named “A” or “B” as a matter of convenience. Compound 13, with an N-isopropyl amide group, and compound 14, with an isobutyramide group, exhibited no insecticidal activity against S. litura or P. xylostella. However, compound 15, with an isopropyl carbamate group, exhibited very weak activity against P. xylostella, and compound 16, with a trichloroethyl carbamate group, exhibited very weak activity against both S. litura and P. xylostella. We focused on the carbamates of compounds 15 and 16, which showed weak activity against Lepidopteran pests, and continued our drug-discovery research.

1.2. Introduction of methyl groups to phenyl rings

It is known that the introduction of a substituent to the ortho position of the amide moiety often affects the biological activity of the compound as a result of a large conformational change.10–12 We introduced a methyl group to the ortho position of the amide moiety in the A or B ring of compound 16, anticipating the improvement of its insecticidal activity (Table 1; compounds 17–21). Following the introduction of a methyl group to the A ring, compounds 17 and 18 exhibited no insecticidal activity against S. litura or P. xylostella, and compound 19 exhibited the same level of activity as compound 16. In contrast, compound 20, with substituent dimethyl groups at the B ring, exhibited 100-fold higher activity against S. litura and 10-fold higher activity against P. xylostella than did compound 16. The enhancement of insecticidal activity following the introduction of a methyl group to the B ring was also observed in compound 21, which exhibited more than 100-fold higher activity against S. litura than did compound 15. Furthermore, compounds 20 and 21 showed different insecticidal symptoms than did flubendiamide (Fig. 3).

1.3. Modification of carbamate and generation of meta-diamides

Since compounds 20 and 21 exhibited moderate activity (LC<sub>90</sub> 10–100 ppm) against Lepidopteran pests as compared with flubendiamide (LC<sub>90</sub> 0.1–1 ppm), we replaced the carbamate bond with other covalent bonds (Table 1; compounds 22–27).

Fig. 3. Symptoms of fifth-instar larvae of Spodoptera litura treated via chemical injections. (a) Flubendiamide at 0.25 ng, 3 hr after application: immobility, body contractions, and vomiting. (b) Compound 20 at 2.5 ng, 3 hr after application: vigorous excitation and vomiting (compound 21 showed the same insecticidal symptoms as compound 20). (c) Compound 25 at 2.5 ng, 3 hr after application: vigorous excitation and vomiting. (d) Control (DMSO only)

A urea derivative of compound 22 and compound 23 with a reverse-carbamate of compound 15 exhibited no activity. Regarding the amide bond, an isobutyramide derivative of compound 24 exhibited no activity. In contrast, a benzamide derivative of compound 25 exhibited 10 ppm activity against both S. litura and P. xylostella. Compounds 26 and 27, which were reverse-amide analogs of compounds 24 and 25, respectively, exhibited no activity.

Because compound 25, which had a meta-diamide structure, exhibited 10-fold higher activity against P. xylostella than did compound 20 and exhibited the same level of activity against two species of Lepidopteran pests, it was expected to have higher activity against various Lepidopteran pests following further structural modifications. Furthermore, compound 25 showed the same insecticidal symptoms as compound 20, which had insecticidal symptoms different from flubendiamide (Fig. 3), thus encouraging further study.

2. Lead optimization

We set compound 25 as a second lead compound and conducted structural optimization on each of its phenyl rings. As shown in Table 2, each benzene ring is named “A,” “B,” or “C” as a matter of convenience.

2.1. A ring

Introducing a fluorine atom to an active compound at the ap-
Table 1. Insecticidal activity of N-[4-heptfluoroisopropyl-2-(methyl)phenyl]-3-(substituted)benzamides

| Compound No. | R         | X   | Y   | EC_{70} (mg ai./L) |
|--------------|-----------|-----|-----|------------------|
|              |           |     |     | S. litura       | P. xylostella |
| 13           | —         | —   | H   | >1000            | >1000        |
| 14           | —         | —   | H   | >1000            | >1000        |
| 15           | —         | —   | H   | >1000            | 1000         |
| 16           | —         | 2-Me| H   | >1000            | >1000        |
| 17           | —         | 4-Me| H   | >1000            | >1000        |
| 18           | —         | 6-Me| H   | 1000             | 1000         |
| 19           | —         | —   | Me  | 10               | 100–1000     |
| 20           | —         | —   | Me  | 10               | 100–1000     |
| 21           | —         | —   | Me  | >1000            | >1000        |
| 22           | —         | —   | Me  | >1000            | >1000        |
| 23           | —         | —   | Me  | >1000            | >1000        |
| 24           | —         | —   | Me  | >1000            | >1000        |
| 25           | —         | —   | Me  | 1000             | >1000        |
| 26           | —         | —   | Me  | 1000             | >1000        |
| 27           | —         | —   | Me  | >1000            | >1000        |
| 2 (Flubendiamide) | —       | —   | 1   | 0.1–1           |

2 (Flubendiamide)
appropriate position will likely enhance the biological activity of the compound.\(^{13}\) Therefore, compounds with a fluorine atom at various positions of the A ring of compound 25 were synthesized, and their insecticidal activities were investigated (Table 2; compounds 28–30).

Compound 30, with a fluorine atom at the 6-position of the A ring, exhibited lower activity than did compound 25, and a 4-fluoro derivative of compound 29 exhibited the same level of activity as did compound 25. In contrast, a 2-fluoro derivative of compound 28 exhibited 10-fold higher activity against both *S. litura* and *P. xylostella* than did compound 25. As the 2-position of the A ring appeared to play a major role in enhancing the insecticidal activity, other substituents were introduced to the 2-position of the A ring of compound 25 (Table 2; compounds 31, 32). A 2-methoxy derivative of compound 31 exhibited only weak activity, and a 2-chloro derivative of compound 32 exhibited no activity. Therefore, compound 28, with a fluorine atom at the 2-position of the A ring, was set as a new lead compound for the following structural optimization.

### 2.2. B ring

We converted compound 28 into compounds with various substituents at the B ring. In this report, only the insecticidal activities of compounds with promising substituents (trifluoromethyl groups or bromine atoms at both *ortho* positions of the amino moiety of the B ring) are listed in Table 2 (compounds 11, 12, 33, and 34). The results of other analogs will be described in a subsequent paper.\(^{14}\) Compound 11, with a trifluoromethyl group and a methyl group at the *ortho* positions to the B ring, exhibited higher activity against *P. xylostella* than did compound 28; compounds 33, 34, and 12, with trifluoromethyl groups or bromine atoms at the two *ortho* positions, exhibited 10-fold higher activity against both *S. litura* and *P. xylostella* than did compound 28. To rank the insecticidal activities of compounds 33, 34, and 12 against Lepidopteran pests, their insecticidal activities against *H. armigera*, which causes serious problems in agriculture worldwide, were also evaluated. Of these three compounds, compound 34, with a bromine atom and a trifluoromethyl group, was the most active compound against *H. armigera*. Therefore, the structural optimization of the C ring in the next section was performed by setting a bromine atom and a trifluoromethyl group at the *ortho* positions of the amino moiety at the B ring.

### 2.3. C ring

We synthesized compounds that had various substituents at the C ring, and many of these compounds exhibited high insecticidal activity against *S. litura* or *P. xylostella*.\(^{14}\) Only those compounds exhibiting the same activity against both *S. litura* and *P. xylostella*, which had a cyano group or a fluorine atom at the 2- or 3-position of the C ring, and their insecticidal activities against Lepidopteran pests are listed in this paper (Table 3; compounds 35–38). The insecticidal activities of compounds 34–38 against *A. honmai*, which belongs to Lepidoptera, and *F. occidentalis*, which belongs to Thysanoptera, were also evaluated to rank the insecticidal activities of these compounds against

### Table 2. Insecticidal activity of 3-benzamido-N-2,6-disubstituted-4-(heptafluoroisopropyl)-phenyl]benzamides

| Compound No. | R   | X     | Y     | EC\(_{50}\) (mg ai./L) |
|--------------|-----|-------|-------|-----------------------|
|              |     |       |       | *S. litura* | *P. xylostella* | *H. armigera* |
| 25 | —   | Me    | Me    | 10 | 10 | ND |
| 26 | 2-F | Me    | Me    | 1  | 1  | ND |
| 29 | 4-F | Me    | Me    | 1–10 | 10 | ND |
| 30 | 6-F | Me    | Me    | 100–1000 | 100–1000 | ND |
| 31 | 2-OMe | Me | Me    | 1000 | 1000 | ND |
| 32 | 2-Cl | Me    | Me    | >1000 | >1000 | ND |
| 11 | 2-F | Me    | CF\(_3\) | 1  | 0.1–1 | ND |
| 33 | 2-F | Br    | Br    | 0.1 | 0.1  | 1 |
| 34 | 2-F | Br    | CF\(_3\) | 0.1 | 0.1  | 0.1 |
| 12 | 2-F | CF\(_3\) | CF\(_3\) | 0.1 | 0.1 | 1 |
| 2 (Flubendiamide) |     |       |       | 1  | 0.1–1 | ND |

ND: No data
various kinds of insects. Judging from the insecticidal activity against four insects, compound 34, which had no substituent at the C ring, had the most superior characteristics among these compounds.

2.4. A–C connection
To confirm the substituent effect on the amide bond, N-methyl derivatives at the A–C connection (compounds 34–38) were synthesized, and their insecticidal activities against various pests were evaluated (Table 3; compounds 1, 39–42).

All N-methyl compounds exhibited similar activity against S. litura, P. xylostella, A. honmai, and F. occidentalis when converted to their corresponding N-hydrogen compounds. Judging from the insecticidal activity against these pests, compound 1 (broflanilide), which had no substituent on the C ring, and compound 41, which had a fluorine atom at the 3-position of the C ring, showed promise as insecticidal compounds. Furthermore, to rank the insecticidal activities of these two compounds, we evaluated their insecticidal activities against P. striolata, which belongs to the order Coleoptera. Compound 1 exhibited higher activity against P. striolata than did compound 41. These results indicated that the non-substituted compound at the C ring exhibited the highest activity against various insects, similar to N-hydrogen compounds.

Next, we investigated the translaminar effect of compounds 1 and 34. Solutions of each compound (25 ppm) were sprayed on the upper side of a leaf, and insecticidal activity against P. xylostella on the underside of the leaf was evaluated. Compound 1 showed a 100% mortality rate in this test, whereas compound 34 showed only a 75% mortality rate. This result suggested that compound 1, with an N-methyl group, had more stable insecticidal activity in the field than did compound 34. It is known that introducing a methyl group to an active compound often improves its physical properties, such as water solubility, because the introduced methyl group inhibits the intermolecular interaction (e.g., hydrogen bonds and dipole interactions) in its crystal state and reduces its crystal lattice energy. Furthermore, N-methylation of peptide bonds sometimes improves bioavailability, probably due to the improvement of passive membrane permeability and metabolic stability. Thus, the physical properties and bioavailability of compound 1 were considered to be improved by this methyl-group effect.

Finally, compound 1 (broflanilide) was selected as the developed compound, considering various factors, such as insecticidal activity against various Lepidopteran pests and other pests and stability in the field.

Conclusion
We used flubendiamide as a lead compound and explored various chemical modifications to discover a new insecticide for Lepidopteran pests. First, the insecticidal activity against Lepidopteran pests was evaluated with the various compounds that had a carbonyl amino moiety at the meta position of the N-(4-heptafluoroisopropyl)phenyl carbamoyl group, and we found that the compounds with alkyl carbamate groups exhibited very weak activity against Lepidopteran pests. Second, the compound that had two substituents at the ortho position of the amino

| Compound No. | R   | X    | S. litura | P. xylostella | A. honmai | F. occidentalis | P. striolata |
|--------------|-----|------|-----------|---------------|-----------|----------------|-------------|
| 34           | H   | —    | 0.1       | 0.1           | 1         | ≦10            | ND          |
| 35           | H   | 4-F  | 0.1       | 0.1           | 1–10      | 10             | ND          |
| 36           | H   | 4-CN | 0.1       | 0.1           | 100       | >100           | ND          |
| 37           | H   | 3-F  | 0.1       | 0.1           | ≦1        | 10–100         | ND          |
| 38           | H   | 3-CN | 0.1       | 0.1           | 1         | >100           | ND          |
| 1 (Broflanilide) | Me | —    | 0.1       | 0.1           | 0.1–1     | 10             | 0.1         |
| 39           | Me  | 4-F  | 0.1       | 0.1           | >10       | 10             | 1           |
| 40           | Me  | 4-CN | 0.1       | 0.1           | 10–100    | >100           | ≦1          |
| 41           | Me  | 3-F  | 0.1       | 0.1           | 1         | 10             | 1–10        |
| 42           | Me  | 3-CN | 0.1       | 0.1           | 1         | >100           | 1–10        |

ND: No data
group on the heptafluoroisopropyl phenyl group showed dramatically increased activity against Lepidopteran pests. Third, changing the alkyl carbamate group to a benzamide group led to meta-diamide compounds, which exhibited high activity against both *S. littura* and *P. xylostella*. Finally, structural optimization of the meta-diamides on each of their three benzene rings, and finding an improvement in physical properties following the introduction of a methyl group to the amide bond, led to the discovery of broflanilide.

Broflanilide, which is scheduled to be launched onto the market in 2020, is expected to make a contribution to world agriculture due to its high insecticidal activity and new mode of action.

**Acknowledgements**

The authors would like to thank all members of people who were involved in the research and development of broflanilide.

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