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# Design, synthesis and insecticidal activity of novel analogues of flubendiamide containing alkoxyhexafluoroisopropyl groups†

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Flubendiamide has received considerable attention in the agriculture field due to its novel mode of action and excellent insecticidal activity. However, the high cost and toxicity to aquatic invertebrates associated with flubendiamide limit its agronomic utility. On the basis of the structure of the lead compound, flubendiamide, we designed and synthesized a series of novel analogues of flubendiamide bearing a alkoxyhexafluoroisopropyl moiety using 2-methyl-4-(2-alkoxyhexafluoroisopropyl) anilines as the key intermediates. Their insecticidal activities against the oriental armyworm (*Mythimna separata* Walker) were evaluated. The results indicated that most of the target compounds exhibited high insecticidal activities. Specifically, compound **8h** showed the best insecticidal activity against the armyworm and its insecticidal activity reached 70% at 0.156 mg L<sup>-1</sup>. The LC<sub>50</sub> value of compound **8h** (0.0512 mg L<sup>-1</sup>) is nearly the same as the corresponding commercial product flubendiamide (0.0412 mg L<sup>-1</sup>). Furthermore, the acute toxicity test showed that the 48 h LC<sub>50</sub> values of compound **8h** and flubendiamide against *Daphnia magna* Straus were 0.0066 and 0.0021 mg L<sup>-1</sup>, respectively. The toxicity of compound **8h** is obviously lower than flubendiamide.

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## Introduction

Flubendiamide, a new generation of synthetic insecticide, has attracted continuing interest in recent years because of its unique insecticide mode of action, high activity against a broad spectrum of lepidopterous insects and low acute toxicity to mammals.<sup>1,2</sup> It directly activates the insect ryanodine receptors (RyRs), which causes permanent muscle contraction, paralysis and eventually results in the death of the insect.<sup>3,4</sup> Since the first commercial Ca<sup>2+</sup> channel modulator, flubendiamide, was launched in 2007 by Nihon Nohyaku and Bayer CropScience, there have been many reports on the synthesis and bioassay of flubendiamide.<sup>5–7</sup>

Flubendiamide often serves as an ideal lead compound for developing a new and selective ryanodine receptor activator.<sup>8,9</sup> Generally, the structure of flubendiamide is composed of three parts as shown in Fig. 1: (A) the phthaloyl moiety, (B) the aliphatic amine moiety and (C) the aromatic amine moiety.<sup>10–12</sup> Therefore, extensive efforts have been focused on the modification of these three moieties and a variety of structurally

diverse novel flubendiamide analogues have been discovered.<sup>13–16</sup> It has been demonstrated that the heptafluoroisopropyl group in the aromatic amine moiety (part C) is essential for high insecticidal activity and remarkably broadens the insecticidal spectrum.<sup>17</sup> However, the use of expensive starting material (heptafluoroisopropyl iodide) and the poor stability and operational inconvenience of this reagent greatly restrict the widespread applications of flubendiamide in crop protection.<sup>18</sup> The high cost of heptafluoroisopropyl iodide likely drives researchers to search other alternative polyfluorinated substrates. For example, in 2010, Zhu *et al.* synthesized a series of phthalic acid diamides bearing the CF<sub>3</sub> group at *meta* position on the aniline ring.<sup>19</sup> In 2014, the group of Zheng-ming Li modified the structure of flubendiamide by replacing heptafluoroisopropyl group with different fluorinated functionalities in the aromatic amine moiety.<sup>20</sup> Some of these novel flubendiamide derivatives exhibited high insecticidal activities. Tohnishi *et al.* indicated that incorporation of fluoroalkoxy group at the 4-position of the aromatic amine moiety could improve insecticidal activity.<sup>21</sup> In addition, like heptafluoroisopropyl group, the hexafluorocarbonyl moiety (–C(CF<sub>3</sub>)<sub>2</sub>OH) is also an attractive pharmacophore that is often included in medicines or bioactive compounds (*e.g.* Fig. 1, compound **I**).<sup>22–25</sup>

Inspired by the structure of flubendiamide and compound **I**, in 2012, we synthesized a series of novel analogues of flubendiamide containing a hexafluoro-2-hydroxypropan-2-yl

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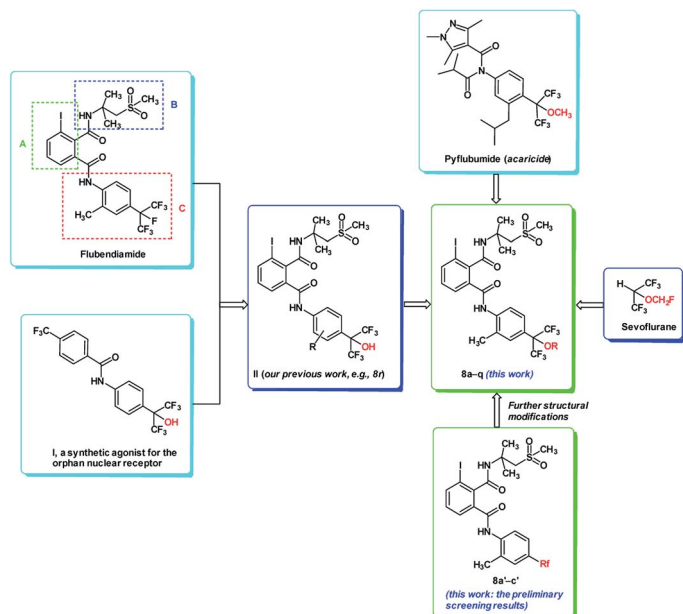


Fig. 1 Design strategy for novel flubendiamide derivatives containing alkoxyhexafluoroisopropyl group **8a–q**.

moiety (Fig. 1, compound **II**).<sup>26</sup> Compound **II** has some significant advantages over its leading compound, flubendiamide, due to the use of cheap, stable and commercially available starting material,  $\text{CF}_3\text{COCF}_3 \cdot \text{H}_2\text{O}$ . However, compound **II** such as **8r** ( $\text{R} = 2\text{-CH}_3$ ) (Fig. 1) exhibited worse activity than flubendiamide. Therefore, the requirements to develop novel analogues of flubendiamide with low cost, low aquatic species toxicity and excellent insecticidal activity are highly desirable. In our initial experiments, three polyfluorinated groups (Rf) were introduced into the aromatic amine moiety of flubendiamide to replace heptafluoroisopropyl group (Fig. 1, **8a'–c'**). Preliminary results indicated that analogue of flubendiamide bearing fluoroalkoxy group **8c'** possessed high insecticidal activity, implying that the introduction of fluoroalkoxy group might be favorable for retaining insecticidal activity. In addition, pyflubumide is a novel acaricide with remarkable activity against spider mites. The structural feature of pyflubumide is that it contains a methoxy-substituted hexafluoroisopropyl group on the aromatic amine moiety (Fig. 1, pyflubumide).<sup>27</sup> Another bioactive compound bearing 2-fluoroalkoxyhexafluoroisopropyl group is Sevoflurane, a widely used inhalational anesthetic agent (Fig. 1, Sevoflurane).<sup>28</sup>

In 2016, Cruciani *et al.* replaced the *tert*-butyl group of bosentan with heptafluoroisopropyl, hexafluoro-2-hydroxyprop-2-yl and hexafluoro-2-methoxyprop-2-yl group, respectively (Fig. 2a).<sup>29</sup> These fluorinated analogues of bosentan exhibited an improved metabolic stability towards certain specific cytochromes. More recently, after carefully analysis of three X-ray crystal structures of polyfluorinated isopropyl benzenes (Fig. 2b, compounds **X1**, **X2** and **X3**), Maienfisch *et al.* found that the dihedral angles of **X1** ( $\text{C}=\text{C}/\text{C}-\text{F}$ ), **X2** ( $\text{C}=\text{C}/\text{C}-\text{OH}$ ), and **X3** ( $\text{C}=\text{C}/\text{C}-\text{OCH}_3$ ) were slightly different. The subtle differences in

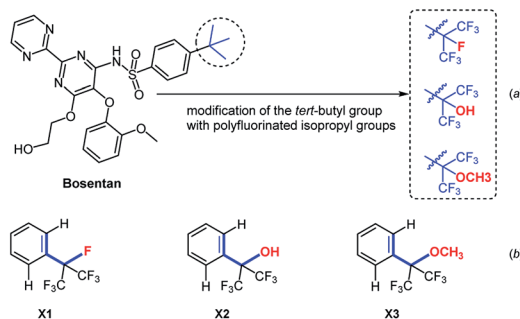


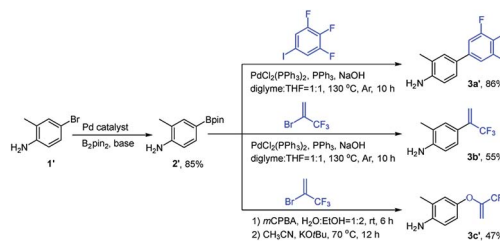
Fig. 2 (a) Modification of the *tert*-butyl group of Bosentan with the polyfluorinated isopropyl groups. (b) The dihedral angles of different polyfluorinated isopropyl benzenes.

the conformation of polyfluorinated substituents on the benzene ring were observed.<sup>30</sup>

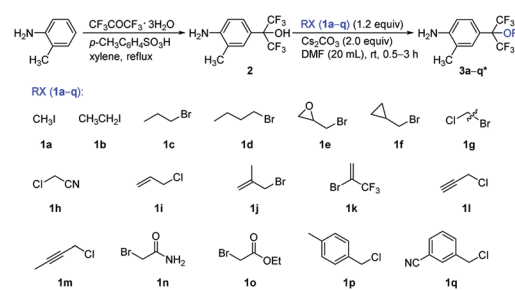
On the basis of the above consideration and preliminary results of bioassay, we envisioned that the introduction of hexafluoro-2-alkoxyprop-2-yl group to the aromatic amine moiety of flubendiamide might retain or improve the activity of parent compound. In this paper, we designed and synthesized a series of novel analogues of flubendiamide bearing alkoxyhexafluoroisopropyl moiety (Fig. 1, **8a–q**). Their insecticidal activities of the target compounds against oriental armyworm and the acute toxicity of **8h** against *Daphnia magna* Straus were also evaluated.

## Results and discussion

The synthetic routes of the intermediates **2'**, **3a'–c'** and **3a–q** and compounds **8a'–c'** and **8a–q** are outlined in Schemes 1–4,



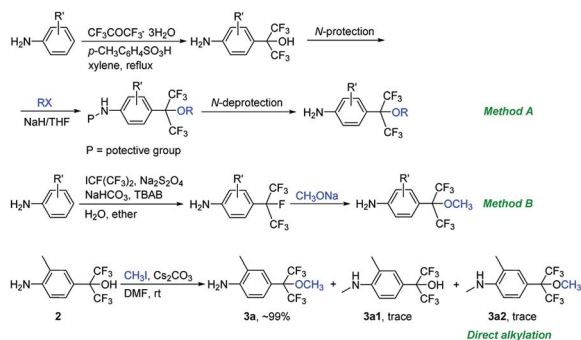
Scheme 1 Synthesis of fluorine-containing anilines **3a'–c'**.



\* The yields of compounds **3a–q** ranged from 77% to 99%. For details of yields, see ESI†

Scheme 2 Synthesis of novel anilines containing hexafluoro-2-alkoxyprop-2-yl group **3a–q**.





**Scheme 3** Two reported and our methods for the synthesis of 4-(hexafluoro-2-alkoxypropan-2-yl)anilines.

respectively. These intermediates and title compounds were readily synthesized according to the reported methods.<sup>26,31–33</sup> In some case, slight modifications of these reaction conditions were necessary in order to obtain satisfying yields (see ESI† for details).

The highly efficient synthesis of the key intermediates **3a–q** was one of the key steps in the total synthesis of these novel analogues of flubendiamide (Scheme 2). A survey of the literature revealed that only a few methods were used to synthesize the analogues of intermediates **3a–q** (Scheme 3, methods A and B).<sup>34–36</sup> However, these methods suffer from the use of expensive starting material (heptafluoroisopropyl iodide) and/or the lengthy protection and deprotection of amido group.

To access the above-mentioned intermediates in a convenient and efficient manner, we tried to alkylate intermediates **2** with various alkyl halides (RX) directly. However, the chemoselective alkylation of intermediates **2** remains a challenge due to the presence of two possible highly reactive sites (NH<sub>2</sub> and OH groups),<sup>37</sup> which leads to the formation of different products (Scheme 3, **3a**, **3a1** and **3a2**, RX=CH<sub>3</sub>I). After careful screening of bases, solvents, and reaction temperatures, we found that the chemoselective alkylation of hydroxyl group in intermediate **2** could proceed smoothly in the presence of 1.2 equiv. of CH<sub>3</sub>I and 1.5 equiv. of Cs<sub>2</sub>CO<sub>3</sub> using DMF as the solvent at 25 °C for 0.5 h and afforded the desired *O*-alkylated product **3a** in excellent yields. Only trace amounts of *N*-alkylated product **3a1** and double alkylated product **3a2** were detected. Subsequently, compound **2** was alkylated with a variety of alkyl halides RX under the optimized experimental conditions to afford *O*-alkylated products **3a–q** in high yields and high purity

**Table 2** Insecticidal activities against oriental armyworm of compounds **8a–r** and flubendiamide (**Flu**)<sup>a</sup>

| Compds     | Insecticidal activity (%) at different concentration (mg L <sup>-1</sup> ) |     |     |     |     |      |       |       |
|------------|--|-----|-----|-----|-----|------|-------|-------|
|            | 100  | 50  | 10  | 5   | 2.5 | 1.25 | 0.625 | 0.156 |
| <b>8a</b>  | 100  | 100 | 100 | 80  | 67  | 57   | 50    | 0     |
| <b>8b</b>  | 100  | 100 | 100 | 87  | 77  | 73   | 40    | 0     |
| <b>8c</b>  | 70   | 57  | 40  | 0   |     |      |       |       |
| <b>8d</b>  | 20   |     |     |     |     |      |       |       |
| <b>8e</b>  | 73   | 60  | 50  | 10  |     |      |       |       |
| <b>8f</b>  | 100  | 100 | 100 | 90  | 87  | 83   | 73    | 40    |
| <b>8g</b>  | 100  | 100 | 90  | 83  | 80  | 77   | 70    | 23    |
| <b>8h</b>  | 100  | 100 | 100 | 100 | 90  | 87   | 85    | 70    |
| <b>8i</b>  | 100  | 100 | 100 | 97  | 90  | 83   | 80    | 60    |
| <b>8j</b>  | 100  | 100 | 70  | 50  | 13  |      |       |       |
| <b>8k</b>  | 100  | 100 | 100 | 90  | 90  | 87   | 83    | 60    |
| <b>8l</b>  | 100  | 100 | 100 | 90  | 90  | 87   | 60    | 17    |
| <b>8m</b>  | 100  | 100 | 87  | 83  | 80  | 77   | 73    | 30    |
| <b>8n</b>  | 100  | 90  | 67  | 47  | 20  |      |       |       |
| <b>8o</b>  | 10   |     |     |     |     |      |       |       |
| <b>8p</b>  | 10   |     |     |     |     |      |       |       |
| <b>8q</b>  | 30   |     |     |     |     |      |       |       |
| <b>8r</b>  | 100  | 100 | 100 | 80  | 80  | 67   | 30    | 0     |
| <b>Flu</b> | 100  | 100 | 100 | 97  | 93  | 90   | 85    | 70    |

<sup>a</sup> Note that blank cells mean not tested.

(Scheme 2). Some crude *O*-alkylation products **3a–q** could be used for the next step without additional purification (see ESI† for details). The structures of **3a**, **3a1** and **3a2** were determined by the <sup>1</sup>H NMR spectra and GC-MS, or <sup>1</sup>H NMR spectra of their corresponding pure compounds reported in the literature.<sup>34–36</sup>

The insecticidal activities of compounds **8a'–c'**, **8a–r** and flubendiamide (as a control) against oriental armyworm were listed in Tables 1 and 2.

As shown in Table 1, analogues of flubendiamide having fluoroalkoxy group **8c'** showed higher activity than other compounds (**8a'** and **8b'**). These preliminary bioassay results suggested that the incorporation of fluoroalkoxy group into the aromatic amine moiety (part C) could provide useful clue for further structural optimization for the discovery of novel analogues of flubendiamide.

Subsequently, seventeen novel analogues of flubendiamide containing alkoxyhexafluoroisopropyl group **8a–q** were designed and synthesized. Their bioassay results of seventeen novel analogues of flubendiamide containing alkoxyhexafluoroisopropyl group **8a–q** and **8r** are summarized in Table 2. Most of the alkoxyhexafluoroisopropyl-containing compounds displayed good to excellent larvicidal activities. The bioactivities of compounds **8a–q** were significantly affected by the electronic nature and the steric properties of the alkyl group (R) attached to the oxygen atom. Generally, the larvicidal activities decreased with an increase in the size of the substituent R in the C(CF<sub>3</sub>)<sub>2</sub>OR moiety. The steric bulk of substituents was detrimental for activity (for example, **8a** versus **8p** and **8q**). The target compounds bearing short-chain alkyl group such as methyl (**8a**) showed better larvicidal activities than that of compound bearing long-chain alkyl group (**8c** and **8d**). It was observed that

**Table 1** Insecticidal activities against oriental armyworm of compounds **8a'–c'** and flubendiamide (**Flu**)

| Compds     | Insecticidal activity (%) at concentration (mg L <sup>-1</sup> ) |     |     |    |
|------------|--|-----|-----|----|
|            | 400  | 200 | 100 | 10 |
| <b>8a'</b> | 47   | 7   | 3   | 0  |
| <b>8b'</b> | 100  | 90  | 20  | 0  |
| <b>8c'</b> | 100  | 100 | 70  | 43 |
| <b>Flu</b> | 100  | 100 | 100 | 97 |



Table 3 LC<sub>50</sub> values of compounds **8a–c**, **8e–n**, **8r** and flubendiamide (**Flu**) at 72 h against oriental armyworm

| Compds     | Regression equation     | LC <sub>50</sub> (mg L <sup>-1</sup> ) | 95% confidence interval of LC <sub>50</sub> (mg L <sup>-1</sup> ) | <i>r</i> |
|------------|-------------------------|--|---|----------|
| <b>8a</b>  | $y = 0.91177x + 5.1361$ | 0.7092                                 | 0.4376–1.1492   | 0.9839   |
| <b>8b</b>  | $y = 1.4626x + 5.1970$  | 0.7334                                 | 0.5419–0.9925   | 0.9457   |
| <b>8c</b>  | $y = 0.7456x + 3.9798$  | 23.3582                                | 14.2972–38.1618   | 0.9864   |
| <b>8e</b>  | $y = 0.5605x + 4.4081$  | 11.3793                                | 4.5377–28.5361  | 0.9475   |
| <b>8f</b>  | $y = 1.0690x + 5.7120$  | 0.2158                                 | 0.1426–0.3265   | 0.9752   |
| <b>8g</b>  | $y = 1.7053x + 5.7005$  | 0.3884                                 | 0.3126–0.4825   | 0.9804   |
| <b>8h</b>  | $y = 1.0188x + 6.3151$  | 0.0512                                 | 0.0168–0.1560   | 0.9760   |
| <b>8i</b>  | $y = 0.9241x + 5.9809$  | 0.0868                                 | 0.0428–0.1760   | 0.9743   |
| <b>8j</b>  | $y = 2.667x + 2.9565$   | 5.8372                                 | 5.1008–6.6797   | 0.9785   |
| <b>8k</b>  | $y = 0.8938x + 6.0201$  | 0.0722                                 | 0.0315–0.1657   | 0.9802   |
| <b>8l</b>  | $y = 1.9854x + 5.6844$  | 0.4521                                 | 0.3770–0.5423   | 0.9839   |
| <b>8m</b>  | $y = 1.1781x + 5.5729$  | 0.3264                                 | 0.2357–0.4520   | 0.9392   |
| <b>8n</b>  | $y = 1.604x + 3.7044$   | 6.4223                                 | 5.2645–7.8353   | 0.9832   |
| <b>8r</b>  | $y = 2.2959x + 5.0371$  | 0.9635                                 | 0.8172–1.1359   | 0.9729   |
| <b>Flu</b> | $y = 0.8931x + 6.2370$  | 0.0412                                 | 0.0146–0.1160   | 0.9996   |

Table 4 Insecticidal activities of compound **8h** and chlorantraniliprole (**CAP**) against four insects<sup>a</sup>

| Concentration<br>(mg L <sup>-1</sup> ) | Insecticidal activity (%) at different concentration (mg L <sup>-1</sup> ) |            |               |            |                   |            |                  |            |
|--|--|------------|---------------|------------|-------------------|------------|------------------|------------|
|  | Oriental armyworm  |            | Tea geometrid |            | Cabbage butterfly |            | Diamondback moth |            |
|  | <b>8h</b>  | <b>CAP</b> | <b>8h</b>     | <b>CAP</b> | <b>8h</b>         | <b>CAP</b> | <b>8h</b>        | <b>CAP</b> |
| 100                                    | 100  | 100        | 100           | 100        | 100               | 100        | 87               | 100        |
| 20                                     | 100  | 100        | 90            | 90         | 90                | 90         | 60               | 90         |
| 4                                      | 100  | 100        | 50            | 60         | 50                | 70         | 50               | 70         |
| 0.8                                    | 90   | 100        | 30            | 30         | 30                | 60         | 40               | 50         |
| 0.16                                   | 70   | 80         | 0             | 0          |                   |            | 0                | 0          |

<sup>a</sup> Note that blank cells mean not tested.

the introduction of appropriate small substituents with terminal halide atoms or unsaturated groups into the (2-hydroxyhexafluoroisopropyl) aniline moiety often had a positive effect on insecticidal activity. For example, compound **8g** (R=CH<sub>2</sub>Cl) and compound **8h** (R=CH<sub>2</sub>CN) exhibited 23% and 70% larvicidal activity against oriental armyworm at 0.156 mg L<sup>-1</sup>, respectively. Especially, compound **8h** showed nearly the same larvicidal activity as flubendiamide on armyworm. Furthermore, compound **8i** (R=CH<sub>2</sub>CH=CH<sub>2</sub>), compound **8j** (R=CH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>), compound **8k** (R=CF<sub>3</sub>C=CH<sub>2</sub>), compound **8l** (R=CH<sub>2</sub>C≡CH) and compound **8m** (R=CH<sub>2</sub>C≡CH) also had good insecticidal activities due to the presence of unsaturated carbon-carbon bonds in alkyl group. Interestingly, replacement of a cyclopropylmethyl group (**8f**) by an oxiran-2-ylmethyl group (**8e**) or an acetamide group (**8n**) by an acetate group (**8o**) resulted in a remarkable decrease in activity. These two compounds (**8e** and **8o**) exhibited weak insecticidal activities against oriental armyworm at a test concentration of 5 mg L<sup>-1</sup> (10% or 47%, respectively). Delightfully, the insecticidal activities of compounds **8f–i** and **8k–m** exhibited apparently higher larvicidal activities than compound **8r**, previously reported by our group (Scheme 1), suggesting that the introduction of alkyl group into the (2-hydroxyhexafluoroisopropyl)

aniline moiety might have a beneficial effect on the insecticidal activity of the title compounds.

Furthermore, the LC<sub>50</sub> values of compounds **8a–c**, **8e–n**, **8r** as well as flubendiamide against oriental armyworm were calculated and summarized in Table 3. Compounds **8d** and **8o–q** were excluded from the regression analysis because these compounds did not give acceptable LC<sub>50</sub> values. As shown in Table 3, compounds **8f**, **8i** and **8k** exhibited excellent insecticidal activity against armyworm, with the LC<sub>50</sub> values of 0.2158, 0.0868, and 0.0722 mg L<sup>-1</sup>, respectively. In particular, the LC<sub>50</sub> value of compound **8h** was 0.0512 mg L<sup>-1</sup>, which was near that of flubendiamide (0.0412 mg L<sup>-1</sup>).

Table 5 Acute toxicity of compound **8h** and flubendiamide (**Flu**) to *Daphnia magna*

| Compds     | Acute toxicity (%) at different concentration (mg L <sup>-1</sup> ) |        |         |         |         |         |         |
|------------|---|--------|---------|---------|---------|---------|---------|
|            | 0.175   | 0.0875 | 0.04375 | 0.02188 | 0.01092 | 0.00546 | 0.00273 |
| <b>8h</b>  | 97  | 95     | 79      | 66      | 61      | 44      | 39      |
| <b>Flu</b> | 97  | 95     | 81      | 76      | 70      | 67      | 58      |

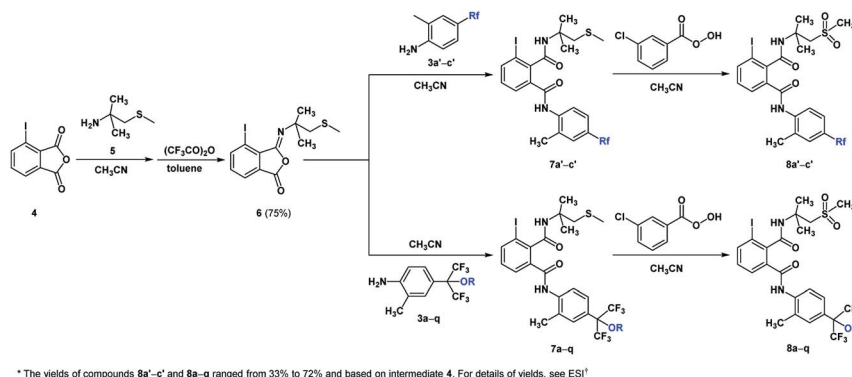




Table 6 LC<sub>50</sub> and LC<sub>90</sub> values of compound **8h** and flubendiamide (Flu) against *Daphnia magna*

| Compds     | Toxicity equation      | LC <sub>50</sub> <sup>a</sup> (mg L <sup>-1</sup> ) | LC <sub>90</sub> <sup>a</sup> (mg L <sup>-1</sup> ) | r <sup>b</sup> |
|------------|------------------------|---|---|----------------|
| <b>8h</b>  | $y = 1.1899x + 7.5975$ | 0.0066 (0.0035–0.0099)                              | 0.0784 (0.0512–0.1495)                              | 0.97           |
| <b>Flu</b> | $y = 0.8523x + 7.2910$ | 0.0021 (0.0004–0.0046)                              | 0.0654 (0.0369–0.1765)                              | 0.96           |

<sup>a</sup> Values are given with 95% confidence intervals. <sup>b</sup> Correlation coefficient.

Scheme 4 The synthesis of new flubendiamide derivatives **8a'–c'** and **8a–q**.

To get a better understanding of the insecticidal activity of synthesized compounds, the best bioactive compound **8h** and commercial insecticide chlorantraniliprole (CAP) were selected to further evaluate the activities against oriental armyworm, tea geometrid, cabbage butterfly and diamondback moths (Table 4). The results of the preliminary bioassays indicated that compound **8h** displayed good to high insecticidal activities against these four insects. The larvicidal activity of compound **8h** was comparable to that of chlorantraniliprole.

Recently, it was reported that flubendiamide was restricted or banned in certain countries due to its toxicity to aquatic invertebrates.<sup>38,39</sup> Consequently, the acute toxicity tests of compound **8h** and flubendiamide to *Daphnia magna* were carried out. *Daphnia magna* were exposed to different concentrations of compound **8h** and flubendiamide after 48 h. The LC<sub>50</sub> values of compound **8h** and flubendiamide against *Daphnia magna* were 0.0066 and 0.0021 mg L<sup>-1</sup>, respectively (Tables 5 and 6). The toxicity of compound **8h** is lower than that of flubendiamide. It implied that the replacement of secondary C–F bond in flubendiamide by C–OR moiety might lead to a decrease in the acute toxicity for *Daphnia magna*, whereas this modification in the aromatic amine moiety could retain or improve insecticidal activity.

## Conclusions

In summary, we designed and synthesized a variety of structurally diverse analogues of flubendiamide containing alkoxylhexafluoroisopropyl group. The key intermediates, 2-methyl-4-(2-alkoxyhexafluoroisopropyl) anilines (**3a–q**), were synthesized in good to excellent yields by the straightforward

chemoselective alkylation of 2-methyl-4-hexafluoroisopropyl aniline. The bioassay results indicated that some compounds displayed high insecticidal activities against oriental armyworm (*Mythimna separata* Walker) in comparison with flubendiamide. Particularly, the insecticidal activity of compound **8h** against armyworm was as high as 70% at 0.156 mg L<sup>-1</sup>, the same as that of control flubendiamide (0.156 mg L<sup>-1</sup>, 70%). The LC<sub>50</sub> values of **8h** and flubendiamide were 0.0512 and 0.0412 mg L<sup>-1</sup>, respectively. Furthermore, compound **8h** also exhibited strong insecticidal activities against tea geometrid, cabbage butterfly and diamondback moths, which is comparable to commercial chlorantraniliprole. In addition, the acute toxicity test showed that the 48 h LC<sub>50</sub> value of compound **8h** against *Daphnia magna* Straus was 0.0066 mg L<sup>-1</sup>, whereas the LC<sub>50</sub> value of flubendiamide was 0.0021 mg L<sup>-1</sup>. The modification resulted in an obvious decrease in toxicity. The preliminary structure–activity relationship of the title compounds revealed that the introduction of small, electron-poor substituent or unsaturated group into the (2-hydroxyhexafluoroisopropyl) aniline moiety may be favorable for retaining high insecticidal activity. The findings obtained in these studies provided useful guidance for the design of novel analogues of flubendiamide bearing poly-fluorinated group. Further modification of flubendiamide and field trials of compound **8h** are currently underway.

## Experimental

### General information

All reagents were of analytic grade and obtained from commercial suppliers and used without further purification. Reactions were monitored by GC–MS or thin-layer



chromatography (TLC) on silica gel 60 GF<sub>254</sub> with ultraviolet detection. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as the internal standard. CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> were used as NMR solvent. The <sup>19</sup>F NMR spectra were recorded on a Bruker AM-400 spectrometer (376 MHz) using CF<sub>3</sub>CO<sub>2</sub>H as external standard. Gas chromatography-mass spectra (GC-MS) were recorded on HP 5973 MSD with 6890 GC. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument.

### Procedures for the synthesis of compounds in Scheme 4

Intermediates **4**, **5** and **6** were prepared according to the literature procedures with some modification.<sup>26,33</sup> General procedure for the synthesis of target compounds **8a'–c'** and **8a–q**. To a solution of **6** (1.87 g, 5 mmol) in acetonitrile (25 mL) was added substituted anilines **3a'–c'** or **3a–q** (5.5 mmol) and trifluoroacetic acid (28.5 g, 0.25 mmol). The mixture was then stirred for 3 h. The progress of the reaction was monitored by TLC. When the reaction was complete, without further purification, the intermediate **7a'–c'** or **7a–q** (5 mmol) was allowed to react with the solution of *m*-chloroperoxybenzoic acid (1.90 g, 11 mmol) in acetonitrile (25 mL). The solution was stirred for another 3 h at room temperature until the reaction was complete. Then the solution was concentrated under reduced pressure and the residue was dissolved in dichloromethane (10 mL). The organic layer was washed by water and dried over anhydrous MgSO<sub>4</sub>. The CH<sub>2</sub>Cl<sub>2</sub> was removed under reduced pressure, and the residue was purified by silica gel column chromatograph (eluent: petroleum ether (60–90 °C)/ethyl acetate = 3/2, v/v) to afford compounds **8a'–c'** and **8a–q**. The physical characteristics, yields, <sup>1</sup>H NMR, <sup>13</sup>CNMR, <sup>19</sup>F NMR and HRMS (ESI) data of the target compounds can be found in ESI.†

### Biological assays

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula. Evaluations are based on a percentage scale of 0–100 in which 0 = no activity and 100 = total kill.

Larvicidal activity against oriental armyworm (*Mythimna separata* Walker). The larvicidal activity of compounds **8a'–c'** and **8a–r** (**8r**, Fig. 1, R = 2-CH<sub>3</sub>) against oriental armyworm was tested according to the leaf-dip method using the literature procedures.<sup>40,41</sup> In leaf-dip bioassay, leaf disks (about 5 cm) were cut from fresh corn leaves and dipped in insecticide solutions for 5 s, and then air-dried on filter paper. Leaf disks dipped in water were used as controls. After drying, the treated leaf disks were placed on a bed of agar in a small Petri dish (7 cm in diameter). Each dried treated leaf disk was infested with 10 third-instar oriental armyworm larvae. Percentage mortalities were assessed 3 days later. Each treatment was performed three times. To compare their activities, the commercial

flubendiamide was tested under the same conditions. The larvicidal activities of **8a'–c'**, **8a–r** and flubendiamide against oriental armyworm are listed in Tables 1 and 2. In addition, the LC<sub>50</sub> values of compounds **8a–c**, **8e–n**, **8r** and flubendiamide (**Flu**) against oriental armyworm as shown in Table 3.

Larvicidal activity against armyworm and other three insects. The larvicidal activity of the typical compound **8h** and chlorantraniliprole against oriental armyworm (*Mythimna separata* Walker), tea geometrid (*Ectropis oblique hypulina* Wehrli), cabbage butterfly (*Pieris rapae* L.) and diamondback moths (*Plutella xylostella* Linnaeus) were evaluated according to the leaf-dip method using the literature procedures (Table 4).<sup>13,41–43</sup> The acute toxicity test of compound **8h** and flubendiamide to *Daphnia magna* Straus were also performed according the reported method with some modifications.<sup>44–46</sup> The results were summarized in Tables 5 and 6.

### Conflicts of interest

There are no conflicts to declare.

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### Notes and references

- H. Hamaguchi and T. Hirooka, in *Modern Crop Protection Compounds*, ed. W. Krämer and U. Schirmer, Wiley-VCH Verlag, Weinheim, Germany, 2nd edn, 2007, vol. 3, p. 1121.
- P. L. George, C. Daniel and D. B. James, *Bioorg. Med. Chem.*, 2009, **17**, 4127.
- K. Kato, S. Kiyonaka, Y. Sawaguchi, M. Tohnishi, H. Takeshima and Y. Mori, *Biochemistry*, 2009, **48**, 10342.
- S. Z. Qi and J. E. Casida, *Pestic. Biochem. Physiol.*, 2013, **107**, 321.
- U. Ebbinghaus-Kintscher, P. Lümmer, K. Raming, T. Masaki and N. Yasokawa, *Pflanzenschutz-Nachr. Bayer*, 2007, **60**, 117.
- K. Tsubata, M. Tohnishi, H. Kodama and A. Seo, *Pflanzenschutz-Nachr. Bayer*, 2007, **60**, 105.
- M. L. Feng, Y. F. Li, H. J. Zhu, J. P. Ni, B. B. Xi and L. Zhao, *Pest Manage. Sci.*, 2012, **68**, 986.
- Y. T. Xie, S. Zhou, Y. X. Li, M. Chen, B. Wang, L. Xiong, N. Yang and Z. M. Li, *Chin. J. Chem.*, 2018, **36**, 129.
- Y. B. Chen, Y. X. Xiao, X. S. Shao, X. Y. Xu and Z. Li, *Chin. J. Chem.*, 2014, **32**, 592.
- S. Zhou, T. Yan, S. Zhou, X. W. Hua, L. X. Xiong and Z. M. Li, *Chin. J. Chem.*, 2014, **32**, 567.
- S. Zhou, Z. H. Jia, L. X. Xiong, T. Yan and Z. M. Li, *J. Agric. Food Chem.*, 2014, **62**, 6269.
- H. Hamaguchi and T. Hirooka, in *Modern Crop Protection Compounds*, ed. W. Krämer, U. Schirmer, P. Jeschke and M. Witschel, Wiley, Weinheim, Germany, 2nd edn, 2012; vol. 3, p. 1396.



- 13 M. Liu, Y. Wang, Y. L. Cui, S. Z. Liu and C. H. Rui, *J. Agric. Food Chem.*, 2010, **58**, 6858.
- 14 C. Gnam, A. Jeanguenat, A. C. Dutton, C. Grimm, D. P. Kloer and A. J. Crossthwaite, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3800.
- 15 S. Zhou, X. Meng, R. Jin, Y. Ma, Y. Zhao and Z. M. Li, *Mol. Diversity*, 2017, **21**, 915.
- 16 S. Zhou, Y. C. Gu, M. Liu, B. L. Wang, L. X. Xiong, N. Yang and Z. M. Li, *J. Agric. Food Chem.*, 2014, **62**, 11054.
- 17 M. Tohnishi, T. Nishimatsu, K. Motoba, T. Hirooka and A. Seo, *J. Pestic. Sci.*, 2010, **35**, 490.
- 18 M. Onishi, A. Yoshiura, E. Kohno and K. Tsubata, EP 1006102 B1, 2000.
- 19 M. L. Feng, Y. F. Li, H. J. Zhu, L. Zhao, B. B. Xi and J. P. Ni, *J. Agric. Food Chem.*, 2010, **58**, 10999.
- 20 Y. W. Chen, Y. X. Li, L. Pan, J. B. Liu, N. Yang, H. B. Song and Z. M. Li, *Bioorg. Med. Chem.*, 2014, **22**, 6366.
- 21 T. Masaki, N. Yasokawa, S. Fujioka, M. Tohnishi and T. Hirooka, *J. Pestic. Sci.*, 2009, **34**, 37.
- 22 Y. J. Wang, N. Kumar, P. Nuhant, M. D. Cameron and P. R. Griffin, *ACS Chem. Biol.*, 2010, **5**, 1029.
- 23 L. Li, J. W. Liu, L. S. Zhu, S. Cutler, H. Hasegawa, B. Shan and J. C. Medina, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1638.
- 24 R. Narlawar, K. Baumann, C. Czech and B. Schmidt, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5428.
- 25 L. T. Kong, J. Wang, X. C. Fu, Y. Zhong, T. Luo and J. H. Liu, *Carbon*, 2010, **48**, 1262.
- 26 M. X. Wu, W. W. Zhao, G. Y. Jin, Q. C. Huang and S. Cao, *Chin. J. Chem.*, 2012, **30**, 1310.
- 27 T. Furuya, K. Machiya, S. Fujioka, M. Nakano and I. K. nagaki, *J. Pestic. Sci.*, 2017, **42**, 132.
- 28 K. Ramakrishna, C. Behme, R. M. Schure and C. Bieniarz, *Org. Process Res. Dev.*, 2000, **4**, 581.
- 29 S. Lepri, L. Goracci, A. Valeri and G. Cruciani, *Eur. J. Med. Chem.*, 2016, **121**, 658.
- 30 M. E. Qacemi, S. Rendine, P. Maienfisch, G. Haufe and F. R. Leroux, Recent applications of fluorine in crop protection—new discoveries originating from the unique heptafluoroisopropyl group, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier Academic Press, 2019, ch. 17, pp. 607–629, DOI: 10.1016/B978-0-12-812733-9.00017-9.
- 31 B. H. Lipshutz, R. Moser and K. R. Voigtritter, *Isr. J. Chem.*, 2010, **50**, 691.
- 32 R. Masciadri, M. Kamer and N. Nock, *Eur. J. Org. Chem.*, 2003, 4286.
- 33 M. Tohnishi, H. Nakao, T. Furuya, T. Hirooka and T. Nishimatsu, *J. Pestic. Sci.*, 2005, **30**, 354.
- 34 R. Bakthavatchalam, WO 2010138879 A1, 2010.
- 35 S. M. Masoud, A. K. Mailyan, V. Dorcet, T. Roisnel, P. H. Dixneuf, C. Bruneau and S. N. Osipov, *Organometallics*, 2015, **34**, 2305.
- 36 T. Furuya, A. Suwa, M. Nakano, S. Fujioka, N. Yasokawa and K. Machiya, *J. Pestic. Sci.*, 2015, **40**, 38.
- 37 B. Grimm, C. Risko, J. D. Azoulay, J. Brédas and G. C. Bazan, *Chem. Sci.*, 2013, **4**, 1807.
- 38 B. Erickson, *Chem. Eng. News*, 2016, **94**(10), 18.
- 39 Bee, *Chem. Eng. News*, 2016, **94**(7), 20.
- 40 S. C. Chen, Y. Zhang, Y. X. Liu and Q. M. Wang, *J. Agric. Food Chem.*, 2019, **67**, 13544.
- 41 J. Zhang, X. H. Tang, I. Ishaaya, S. Cao, J. J. Wu, J. L. Yu, H. Li and X. H. Qian, *J. Agric. Food Chem.*, 2010, **58**, 2736.
- 42 C. J. Cui, Y. Q. Yang, T. Y. Zhao, H. M. Cai, X. C. Wan and R. Y. Hou, *Molecules*, 2019, **24**, 4518.
- 43 E. E. Mansour, G. Zhang, F. Y. Mi, Y. M. Wang and A. Kargbo, *Pestic. Biochem. Physiol.*, 2012, **102**, 237.
- 44 F. Cui, T. Chai, L. Qian and C. J. Wang, *Chemosphere*, 2017, **169**, 107.
- 45 Y. H. Liu, R. X. Guo, S. K. Tang, F. Y. Zhu, Z. Y. Yan and J. Q. Chen, *Chemosphere*, 2018, **195**, 542.
- 46 V. Lavtizar, R. Helmus, S. A. E. Kools, D. Dolenc, S. L. Waaijers and M. H. S. Kraak, *Environ. Sci. Technol.*, 2015, **49**, 3922.

