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Design and Synthesis of Novel meta-Diamide Compounds Containing Sulfur Derivatives as Potential Pesticides

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Abstract

As a typical meta-Diamide (*m*-diamide) insecticide, Broflanilide is highly effective, exhibits low toxicity, and shows no cross resistance with traditional insecticides that act on the γ-aminobutyric acid (GABA) receptor. As a high halogen content potentially causes risks and was concerning to researchers, easily derivatized sulfur with diverse biological activities was introduced into leading compound based on the principles of the molecular drug design. Fifteen novel sulfur-containing *m*-amide derivatives, **A-F,** were synthesized through a series of experiments, and the structures were confirmed by melting point determinations, ^{1}H NMR, ^{13}C NMR and HRMS. The biochemical properties of the compounds were closely related to their structural characteristics. However, the insecticidal activities of the target compounds were lower than expected. Structure-activity relationship (SAR) results revealed that the compounds R_1 = CN exhibited better insecticidal activity (**D-3**, 46.67%; **E-3**, 50.00%; and **F-3**, 34.48%) than that of other compounds against *Plutella xylostella* (*P. xylostella*) at 500 mg·L^{-1}. These experiments provide a reference for related research on the synthesis and derivatization of sulfur-containing compounds.

Keywords: *m*-diamine, sulfur, design, synthesis, insecticidal activity

INTRODUCTION

Diamides, which are highly efficient, exhibit low toxicity and are environmentally friendly, currently occupy the largest share in the insecticide market and play a vital role in increasing the yield and quality of agricultural crops [1, 2]. Broflanilide (**Fig. 1**) is a typical *m*-diamide insecticide that acts on GABA receptors, which regulate the transmission of chloride ions into cells; as a result, pests vomit and become stimulated until death [3]. The difference between Broflanilide and noncompetitive antagonist GABA insecticides for mechanism cause it to have an excellent mortality rate against antagonistic pests. Broflanilide is a highly selective green insecticide because its sensitivity to GABA receptors is different in mammals and insects [4, 5]. In particular, the novel *m*-diamide structure is significantly different from that of traditional GABA receptor insecticides and can effectively alleviate cross-resistance to traditional insecticides [3, 6]. Therefore, structural modification of Broflanilide as the leading structure has been substantially explored. Among numerous research achievements, Cyproflanilide [7] (**Fig. 1**), discovered by the Tahoe Group, was the most successful new drug and can effectively control pests such as Lepidoptera and Coleoptera. The successful release of Cycloflunilide has greatly inspired researchers to develop novel pesticides with diamide structures. The halide contents of Broflanilide and Cycloflanilide were greater than 50%, which can be attributed to fluorine atoms, bromine atoms, trifluoromethyl groups, and heptafluoroisopropyl groups. The hydrophilicity and environmental friendliness of pesticides are associated with certain risks due to the high halogen content. Therefore, determining how to reduce the halogen content while ensuring its efficacy has become an important research direction for developing new pesticides with Broflanilide as the leading compound.

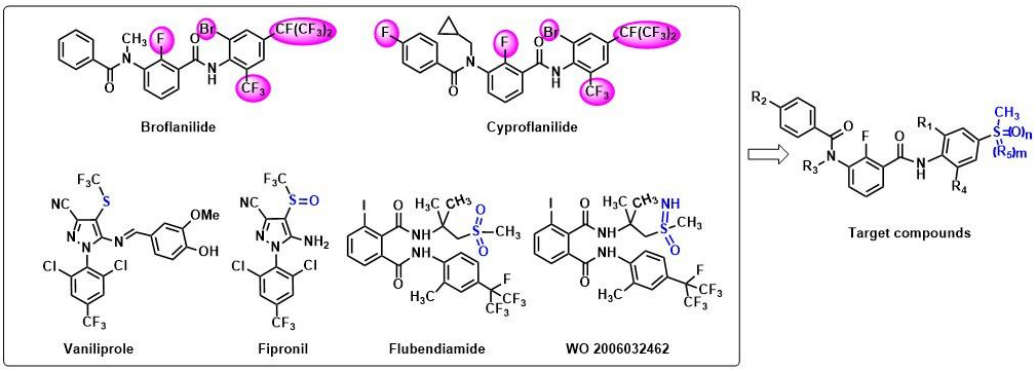


Fig. 1. The structures of several *m*-diamide and sulfur-containing insecticides and the designed target compounds in this paper

Currently, more than 30% of pesticides contain at least one sulfur atom because sulfur exhibits diverse biological activities and structural characteristics that are easily derivatized [8-10]; therefore, sulfurs have long been the focus of pesticide research. Sulfoxides, sulfones and sulfoximine are the four most recognized kinds of sulfurs and are the corresponding compounds (Vaniliprole, Fipronil, Flubendiamide, etc.) with excellent insecticidal activities. Recently, the Wu [11] group reported that the remaining compounds exhibited good insecticidal activity against *Nilaparvata lugens* (98.92%, 100 $mg \cdot L^{-1}$) when sulfurs were introduced into the leading compounds to replace the trifluoromethyl group. Therefore, developing new *m*-diamide compounds that contain sulfur derivatives as potential insecticides may be important for future pesticide research.

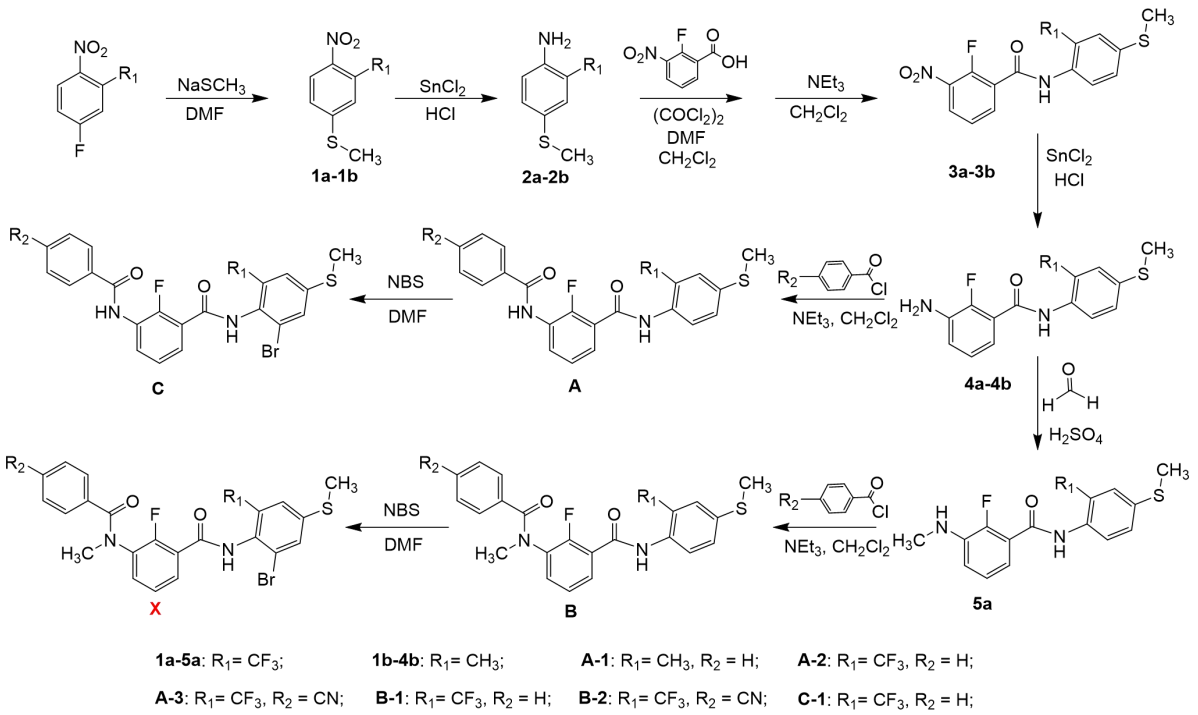
For the abovementioned reasons, sulfur derivative structures with extensive pharmacological activity were introduced into the lead compound to replace the high fluorine group, heptafluoroisopropyl, and maintain the basic nucleus structure of Broflanilide. By exploring the target synthesis route and biological activity, we analysed the SARs, which could provide a valuable reference for future research on sulfur-containing *m*-diamide compounds.

EXPERIMENTAL

Preparation of m-diamide Compounds Containing Thioether, Sulfoxide, Sulfone and Sulfoximine

In recent years, many studies have reported the preparation routes of *m*-diamide pesticides [12-14]. Zhang [15] used 2-fluoro-3-nitrobenzoic acid and 2-(trifluoromethyl)aniline as starting materials to successfully synthesize Broflanilide through linear chain reactions. These methods involve several advantages, as the raw materials are inexpensive, the reaction conditions are mild, the operation is simple and high yields are obtained. Therefore, the synthesis route for sulfur-containing *m*-diamide derivatives was designed as shown in **Scheme 1** based on the above methods. Intermediates **1-5** were successfully synthesized according to previously reported methods.

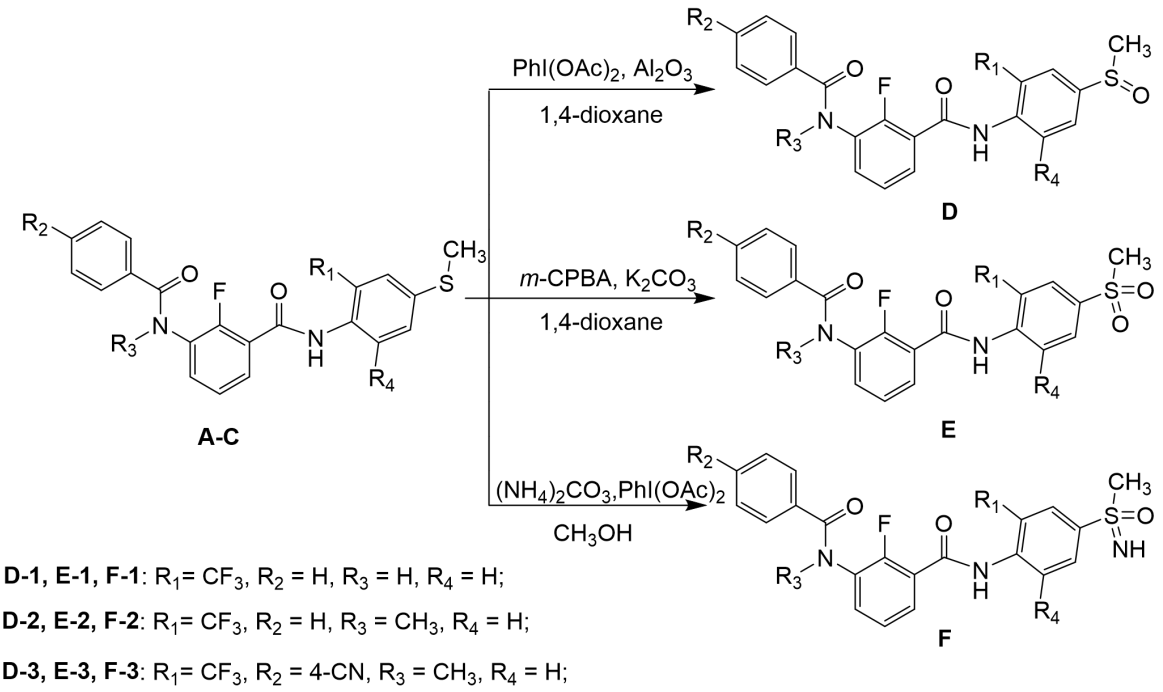
Scheme 1 Synthesis route for accessing novel *m*-diamide compounds that contain thioethers (**A-C**)



General procedure for the preparation of thioether-containing *m*-amide compounds **A** and **B** (**Scheme 1**): 27.30 mmol of *N*-(2-substituent group-4-(methylthio)phenyl), 2-fluoro-3-(substituent amino) benzamide (**4** or **5**) and 32.76 mmol of trimethylamine were dissolved in 50 mL of dichloromethane. The corresponding 4-substituted benzoyl chloride (27.30 mmol) was subsequently added dropwise to the reaction bottle at room temperature while stirring. Then, the mixture was slowly heated to reflux, after which the temperature was monitored by TLC until the reaction was complete [16]. The organic solvent was removed by vacuum distillation, extraction and drying, after which the target product was obtained by column chromatography purification.

General procedure for the preparation of thioether-containing *m*-amide compounds **C** (**Scheme 1**): compound **A** (0.62 mmol) and 0.68 mmol of *N*-bromosuccinimide (NBS) were added to 10 mL *of N*,*N*-dimethylformamide (DMF) and stirred for 6 h while refluxing. Upon completion of the reaction, 10 mL of water was added to the mixture, which was extracted and dried, after which the target product was obtained by column chromatography purification.

Scheme 2 The synthesis route for novel *m*-diamide compounds that contain sulfoxide (**D**), sulfone (**E**) and sulfoximine (**F**)



D-1, E-1, F-1: R_1= CF_3, R_2 = H, R_3 = H, R_4 = H;

D-2, E-2, F-2: R_1= CF_3, R_2 = H, R_3 = CH_3, R_4 = H;

D-3, E-3, F-3: R_1= CF_3, R_2 = 4-CN, R_3 = CH_3, R_4 = H;

General procedure for the preparation of sulfoxide-containing *m*-amide compounds **D** (**Scheme 2**): Thioether-containing *m*-diamide compound (1 mmol) was dissolved in 10 mL of 1,4-dioxane with 3 mmol of $PhI(OAc)_2$ and 1 mmol of Al_2O_3 and then warmed to reflux stirring for 6 h (monitored by TLC) [17]. After that, the mixture was concentrated, and the residue was dissolved in 20 mL of CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. The sulfoxide-containing compound **D** was afforded by further purification through column chromatography.

General procedure for the preparation of sulfone-containing *m*-amide compounds **E** (**Scheme 2**): Thioether-containing *m*-diamide compound (1 mmol) was dissolved in 10 mL of 1,4-dioxane supplemented with 3 mmol of *m*-CPBA and 1 mmol of K_2CO_3, warmed to reflux and maintained for approximately 6 h (monitored by TLC) [11]. After that, the mixture was concentrated, and the residue was dissolved in 20 mL of CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. The sulfoxide-containing compound **E** was afforded by further purification through column chromatography.

General procedure for the preparation of sulfoximine-containing *m*-amide compounds **F** (**Scheme 2**): Thioether-containing *m*-diamide compound (1 mmol) was dissolved in 10 mL of CH_3OH supplemented with 3 mmol $(NH_4)_2CO_3$ and 1.5 mmol of $PhI(OAc)_2$, after which the mixture was warmed to reflux and maintained for approximately 2 h (monitored by TLC) [18].

After that, the mixture was concentrated, and the residue was dissolved in 20 mL of CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. Sulfoximine-containing compound **F** was afforded by further purification through column chromatography.

Characterization of Novel m-diamide Compounds

Melting points were measured by an SGWX-4B melting point analyser and uncorrected. NMR spectra were recorded on a Bruker Avance NEO (400, 101 MHz) spectrometer using DMSO-*d6* (TMS as the 0 point internal standard) as the solvent. HRMS data were obtained on a Thermo Q Exactive Focus instrument with ESI ionization.

Procedure Larvicidal activity against P. xylostella

The larvicidal activities of the target compounds against *P. xylostella* larvae at 500 $mg \cdot L^{-1}$ were investigated (**Table 1**) through adding Broflanilide or a blank control without any medication; this procedure was performed in a greenhouse using the leaf soaking method [19]. The radish leaves were soaked in moderation solution containing the prepared test fluid for 10 seconds. The samples were subsequently placed in a plastic culture dish with filter paper and left to dry naturally in the shade. Each dish was infested with 10 second-instar diamondback moths and placed in an observation room at a temperature of 22 °C. The test results were observed after 48 hours. The insect was considered dead if it showed no response or could not crawl normally when it was touched lightly with a brush. This process was repeated three times for each sample.

Table 1. Insecticidal activity of target compounds against *P. xylostella* at a concentration of 500 $mg \cdot L^{-1}$.

Compd.	Larvicidal activity (%)	Compd.	Larvicidal activity (%)	Compd.	Larvicidal activity (%)
A-1	23.33	**D-1**	20.00	**F-1**	0
A-2	36.67	**D-2**	0	**F-2**	0
A-3	0	**D-3**	46.67	**F-3**	34.48
B-1	0	**E-1**	20.00	CK	0
B-2	23.33	**E-2**	20.00	Broflanilide	100
C-1	0	**E-3**	50.00		

RESULTS AND DISCUSSION

Characterization of the Physical Properties of the Target Compounds

3-Benzamido-2-fluoro-*N*-(2-methyl-4-(methylthio)phenyl)benzamide (A-1)

White solid (85%), m.p. 148-150 °C, ^{1}H NMR (400 MHz, DMSO) δ 10.24 (s, 1H, CO-NH), 9.87 (s, 1H, CO-NH), 8.00 (d, J = 8.5 Hz, 2H, Ph-H), 7.78 (t, J = 7.2 Hz, 1H, Ph-H), 7.63 (t, J = 7.2 Hz, 1H, Ph-H), 7.58-7.52 (m, 3H, Ph-H), 7.40 (d, J = 8.3 Hz, 1H, Ph-H), 7.34 (t, J = 7.8 Hz, 1H, Ph-H), 7.18 (s, 1H, Ph-H), 7.13 (d, J = 9.6 Hz, 1H, Ph-H), 2.48 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.1, 163.1, 154.5, 152.0, 135.7, 134.3, 134.2, 133.7, 132.4, 129.5, 129.0, 128.4, 128.3, 126.9, 126.8, 125.8, 124.5, 124.4, 18.3, 15.6. HRMS calcd for $C_{22}H_{19}FN_2O_2S$ $[M+H]^+$ 395.1230, found 395.1257.

3-Benzamido-2-fluoro-*N*-(4-(methylthio)-2-(trifluoromethyl)phenyl)benzamide (A-2)

White solid (82%), m.p. 159-160 °C. ^{1}H NMR (400 MHz, DMSO) δ10.25 (s, 1H, NH), 10.11 (s, 1H, NH), 8.02-7.98 (m, 2H, Ph-H), 7.79 (t, J = 7.5 Hz, 1H, Ph-H), 7.67-7.51 (m, 7H, Ph-H), 7.36 (t, J = 7.8 Hz, 1H, Ph-H), 2.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.1, 164.1, 154.7, 152.2, 138.8, 134.2, 132.5, 132.1, 131.7, 130.5, 130.1, 129.0, 128.3, 127.0, 126.8, 125.1, 124.9, 124.6, 123.6 (q, J = 273.7 Hz, CF_3), 15.1. HRMS calcd for $C_{22}H_{17}F_4N_2O_2S$ $[M+H]^+$ 449.0947, found 449.0944.

3-(4-Cyanobenzamido)-2-fluoro-*N*-(4-(methylthio)-2-(trifluoromethyl)phenyl)benzamide (A-3)

White solid (82%), m.p. 112-114 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.56 (s, 1H, NH), 10.15 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ph-H), 8.05 (d, J = 8.4 Hz, 2H, Ph-H), 7.81 (t, J = 7.0 Hz, 1H, Ph-H), 7.60-7.55 (m, 4H, Ph-H), 7.39 (d, J = 7.8 Hz, 1H, Ph-H), 2.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 168.7, 164.9, 144.6, 138.8, 138.3, 133.0, 131.9, 131.7, 130.6, 130.2, 130.0, 129.2, 127.1 (q, J = 30.3 Hz), 127.0 (q, J = 273.7 Hz, CF_3), 124.7, 123.6, 119.6, 118.8, 114.7, 111.8, 15.2. HRMS calcd for $C_{23}H_{15}F_4N_3O_2S$ $[M+H]^+$ 474.0899, found 474.0899.

2-Fluoro-3-(*N*-methylbenzamido)-*N*-(4-(methylthio)-2-(trifluoromethyl)phenyl)benzami--de (B-1)

White solid (80%), m.p. 118-120 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.06 (s, 1H, CO-NH), 7.62 (d, J = 6.6 Hz, 1H, Ph-H), 7.61-7.58 (m, 2H, Ph-H), 7.50-7.55 (m, 2H, Ph-H), 7.35-7.20 (m, 6H, Ph-H), 3.34 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 170.6, 163.5, 155.9, 153.5, 138.9, 135.9, 133.0, 131.8, 131.6, 130.5, 130.4, 129.4, 128.4,

128.1, 126.9, 126.8 (q, J = 29.3 Hz), 125.1 (q, J = 273.7 Hz, CF_3), 123.6 (d, J = 5.1 Hz), 122.3, 39.6, 15.1. HRMS calcd for $C_{23}H_{19}F_4N_2O_2S$ $[M+H]^+$ 463.1103, found 463.1105.

3-(4-Cyano-*N*-methylbenzamido)-2-fluoro-*N*-(4-(methylthio)-2-(trifluoromethyl)phenyl)--benzamildes (B-2)

White solid (80%), m.p. 140-142 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.03 (s, 1H, NH), 7.75 (s, 2H, Ph-H), 7.62-7.56 (m, 4H, Ph-H), 7.52-7.48 (m, 3H, Ph-H), 7.27 (s, 1H, Ph-H), 3.36 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 140.4, 138.9, 132.8, 132.5, 131.7, 131.6, 130.5, 129.8, 128.8, 127.08 (q, J = 29.3 Hz), 125.5, 125.4, 125.2 (q, J = 273.7 Hz, CF_3), 125.0, 123.60 (d, J = 5.1 Hz), 122.3, 118.6, 112.8, 40.6, 15.1. HRMS calcd for $C_{24}H_{18}F_4N_3O_2S$ $[M+H]^+$ 488.1056, found 488.1055

3-Benzamido-*N*-(2-bromo-4-(methylthio)-6-(trifluoromethyl)phenyl)-2-fluororobenzam--ide (C-1)

White solid (80%), m.p. 200-202 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.34 (s, 1H), 10.27 (s, 1H, NH), 8.09 (s, 1H, Ph-H), 8.07 (d, J = 8.3 Hz, 1H, Ph-H), 8.01 (d, J = 7.4 Hz, 2H, Ph-H), 7.88 (d, J = 8.3 Hz, 1H, Ph-H), 7.82 (t, J = 7.4 Hz, 1H, Ph-H), 7.60-7.53 (m, 3H, Ph-H), 7.38 (t, J = 7.8 Hz, 1H, Ph-H), 2.86 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.2, 164.1, 154.7, 152.2, 146.0, 137.6, 134.2, 132.5, 131.8, 130.3, 129.0, 128.3, 127.1, 126.9, 126.7 (q, J = 30.3 Hz), 124.9, 124.5 (q, J = 273.7 Hz, CF_3), 122.5 (d, J = 5.1 Hz), 122.2, 43.6. HRMS calcd for $C_{22}H_{16}BrF_4N_202S$ $[M+H]^+$ 527.0052, found 527.0055.

3-Benzamido-2-fluoro-*N*-(4-(methylsulfinyl)-2-(trifluoromethyl)phenyl)ben-zamildes (D-1)

White solid (52%), m.p. 223-225 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H, NH), 10.30 (s, 1H, NH), 8.09 (s, 1H, Ph-H), 8.07 (d, J = 9.7 Hz, 1H, Ph-H), 8.02–7.99 (m, 2H, Ph-H), 7.88 (d, J = 8.3 Hz, 1H, Ph-H), 7.81 (t, J = 7.1 Hz, 1H, Ph-H), 7.63 (d, J = 7.3 Hz, 1H, Ph-H), 7.56 (t, J = 7.5 Hz, 3H, Ph-H), 7.38 (d, J = 7.8 Hz, 1H, Ph-H), 2.86 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.2, 164.1, 146.0, 137.6, 134.5, 134.2, 132.5, 131.8, 130.3, 130.1, 129.1, 129.0, 128.3, 127.0, 126.9 (q, J = 273.7 Hz, CF_3), 126.5, 124.7, 124.6 (d, J = 5.1 Hz), 122.6, 43.6. HRMS calcd for $C_{22}H_{17}F_4N_2O_3S$ $[M+H]^+$ 465.0896, found 465.0891.

2-Fluoro-3-(*N*-methylbenzamido)-*N*-(4-(methylsulfinyl)-2-(trifluoromethyl)phenyl)benz--amide (D-2)

Yellow solid (48%), m.p. 82-84 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.60 (s, 1H, NH), 8.33 (s, 1H, Ph-H), 8.09 (s, 1H, Ph-H), 7.55 (s, 2H, Ph-H), 7.43-7.26 (m, 7H, Ph-H), 3.35 (s, 3H, N-CH_3), 2.90 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 170.6, 163.1, 156.0, 153.5,

136.0, 133.2, 133.0, 132.7, 132.6, 132.5, 130.4, 129.2, 128.4, 128.0, 125.1, 124.3, 121.9, 121.6, 120.6, 43.4, 40.3 HRMS calcd for $C_{23}H_{19}F_4N_2O_3S$ $[M+H]^+$ 479.1053, found 479.1052.

3-(4-Cyano-*N*-methylbenzamido)-2-fluoro-*N*-(4-(methylsulfinyl)-2-trifluoro-methyl) phenyl)benzamildes (D-3)

White solid (46%), m.p. 93-95 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.25 (s, 1H, NH), 8.09 (s, 1H, Ph-H), 8.06 (d, J = 8.4 Hz, 1H, Ph-H), 7.83 (d, J = 8.4 Hz, 1H, Ph-H), 7.78-7.70 (m, 2H, Ph-H), 7.66-7.58 (m, 2H, Ph-H), 7.49 (s, 2H, Ph-H), 7.32-7.26 (m, 1H, Ph-H), 3.37 (s, 3H, N-CH_3), 2.86 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 163.3, 146.2, 140.3, 137.4, 133.1, 132.6, 131.7, 129.9, 129.0, 128.8, 126.6, 126.5, 125.6, 124.8, 122.6 (d, J = 5.1 Hz), 122.1, 118.6, 112.9, 43.5, 39.3. HRMS calcd for $C_{24}H_{18}F_4N_3O_3S$ $[M+H]^+$ 504.1005, found 504.1003.

3-Benzamido-2-fluoro-*N*-(4-(methylsulfonyl)-2-(trifluoromethyl)phenyl)benzamide (E-1)

White solid (41%), m.p. 257-259 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H, NH), 10.29 (s, 1H, NH), 8.30 (d, J = 10.2 Hz, 1H, Ph-H), 8.27 (s, 1H, Ph-H), 8.03-7.98 (m, 3H, Ph-H), 7.82 (t, J = 7.5 Hz, 1H, Ph-H), 7.64–7.54 (m, 4H, Ph-H), 7.39 (t, J = 7.9 Hz, 1H, Ph-H), 3.37 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.2, 164.0, 154.8, 152.3, 140.2, 139.6, 134.2, 132.5, 132.4, 131.4, 131.0, 130.6, 129.0, 128.3, 127.0 (q, J = 273.7 Hz, CF_3), 126.3, 125.8 (q, J = 30.3 Hz), 124.7 (d, J = 3.9 Hz), 124.3, 43.7. HRMS calcd for $C_{22}H_{17}F_4N_2O_4S$ $[M+H]^+$ 481.0845, found 481.0848.

2-Fluoro-3-(*N*-methylbenzamido)-*N*-(4-(methylsulfonyl)-2-(trifluoromethyl)phenyl)benz--amide (E-2)

White solid (43%), m.p. 109-110 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, 1H, NH), 8.21–8.10 (m, 1H, Ph-H), 8.11-8.08 (m, 1H, Ph-H), 8.07-8.04 (m, 1H, Ph-H), 7.85 (d, J = 8.3 Hz, 1H, Ph-H), 7.65–7.55 (m, 3H, Ph-H), 7.35-7.29 (m, 4H, Ph-H), 3.35 (s, 3H, N-CH_3), 2.86 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 170.6, 166.6, 163.3, 156.0, 153.5, 139.6, 135.9, 133.6, 133.2, 132.5, 131.2, 130.4, 129.3, 128.0, 126.3 (q, J = 5.0 Hz), 125.8 (d, J = 31.3 Hz), 125.4, 124.5, 121.8, 43.7, 39.3. HRMS calcd for $C_{23}H_{19}F_4N_2O_4S$ $[M+H]^+$ 495.1002, found 495.1004.

3-(4-Cyano-*N*-methylbenzamido)-2-fluoro-*N*-(4-(methylsulfonyl)-2-(trifluoromethyl)phe--nyl)benzamide (E-3)

White solid (52%), m.p. 143-145 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H, NH), 8.29 (d, J = 8.4 Hz, 1H, Ph-H), 8.27 (s, 1H, Ph-H), 7.98 (d, J = 8.4 Hz, 1H, Ph-H), 7.76 (s, 2H, Ph-H), 7.69-7.62 (m, 2H, Ph-H), 7.49 (s, 2H, Ph-H), 7.31 (s, 1H, Ph-H), 3.37 (s, 6H, N-CH_3 + CH_3). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 166.5, 163.2, 140.3, 140.0, 139.8, 133.8, 133.1,

132.5, 131.4, 131.1, 130.0, 129.3, 128.8, 128.4, 126.3 (q, J = 5.0 Hz), 125.5, 118.6, 112.9, 43.7. HRMS calcd for $C_{24}H_{18}F_4N_3O_4S$ $[M+H]^+$ 520.0954, found 520.0956.

3-Benzamido-2-fluoro-*N*-(4-(S-methylsulfonimidoyl)-2-(trifluoromethyl)phenyl)benzam--ide (F-1)

White solid (39%), m.p. 236-237 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.41 (s, 1H, NH), 10.30 (s, 1H, NH), 8.32-8.26 (m, 2H, Ph-H), 8.01 (d, J = 7.1 Hz, 2H, Ph-H), 7.95 (d, J = 8.2 Hz, 1H, Ph-H), 7.84 (d, J = 6.2 Hz, 1H, Ph-H), 7.57 (d, J = 7.7 Hz, 4H, Ph-H), 7.39 (d, J = 7.9 Hz, 1H, Ph-H), 4.54 (s, 1H, S=NH), 3.19 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 166.1, 164.2, 154.8, 152.3, 134.2, 132.6, 132.5, 130.9, 130.2, 129.0, 128.3, 127.2, 127.0, 126.9, 126.3 (d, J = 5.0 Hz), 125.6, 124.6, 124.5, 122.2, 45.9. HRMS calcd for $C_{22}H_{18}F_4N_3O_3S$ $[M+H]^+$ 480.1005, found 480.1002.

2-Fluoro-3-(*N*-methylbenzamido)-*N*-(4-(S-methylsulfonimidoyl)-2-(trifluoromethyl)phe--nyl)benzamide (F-2)

White solid (42%), m.p. 77-79 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H, NH), 8.27 (d, J = 6.5 Hz, 2H, Ph-H), 7.91 (d, J = 8.9 Hz, 1H, Ph-H), 7.63–7.55 (m, 2H, Ph-H), 7.38-7.30 (m, 3H, Ph-H), 7.32-7.27 (m, 3H, Ph-H), 4.54 (s, 1H, S=NH), 3.35 (s, 3H, N-CH_3), 3.19 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 170.6, 163.4, 156.0, 153.5, 143.4, 139.0, 135.9, 133.3, 132.7, 131.2, 130.4, 129.6, 128.5, 128.0, 126.4 (q, J = 5.0 Hz), 125.7 (d, J = 30.3 Hz), 125.4 (d, J = 4.2 Hz), 124.6, 122.0, 45.8, 39.3. HRMS calcd for $C_{23}H_{20}F_4N_3O_3S$ $[M+H]^+$ 494.1162, found 494.1161.

3-(4-Cyano-*N*-methylbenzamido)-2-fluoro-*N*-(4-(S-methylsulfonimidoyl)-2-(trifluorome--thyl)phenyl)benzamide (F-3)

White solid (42%), m.p. 130-132 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H, NH), 8.26 (d, J = 7.7 Hz, 2H, Ph-H), 7.88 (d, J = 8.2 Hz, 1H, Ph-H), 7.76 (s, 2H, Ph-H), 7.68-7.60 (m, 2H, Ph-H), 7.52-7.46 (m, 2H, Ph-H), 7.30 (s, 1H, Ph-H), 4.54 (s, 1H, S=NH), 3.36 (s, 3H, N-CH_3), 3.18 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 164.2, 156.1, 153.7, 140.5, 132.5, 132.2, 130.4, 129.5, 128.8, 126.5, 126.3, 126.2, 125.2, 125.0, 125.1, 122.5, 118.6, 112.8, 46.1, 39.9. HRMS calcd for $C_{24}H_{18}F_4N_4O_3S$ $[M+H]^+$ 519.1114, found 519.1108.

The intermediates (**1~5**) can be efficiently prepared according to the methods shown in **Scheme 1**. Target compounds **A** and **B** were successfully synthesized by nucleophilic substitution in high yields (80%-85%). The procedures were slightly different when bromine atoms were introduced at the ortho position for amino acids (**A** and **B**). Compound **C** could be smoothly obtained by NBS under DMF reflux conditions for 6 h. However, the prospective structure of compound **B** failed to react under the same conditions; the methyl group on the

nitrogen atom in the amide bond was lost when the bromine atom was introduced into the benzene ring, as confirmed by nuclear magnetic resonance data analysis. Therefore, this novel synthesis route should be further explored. The sulfoxide-containing *m*-amide compound **D** **(**$PhI(OAc)_2$-Al_2O_3**)** and the sulfone-containing *m*-amide compound **E (***m*-CPBA-K_2CO_3) can be obtained by treating thioether-containing products **(A-C)** with 1,4-dioxane under different oxidant reflux conditions. A corresponding oxidation reaction with $(NH_4)_2CO_3$ as the nitrogen source and methanol as the solvent was necessary when sulfoximine-containing product **F** was synthesized. Due to the low solubility of the novel *m*-diamide compounds that contained sulfur oxide derivatives (**D**, **E** and **F**) resulted in overall low yields (39%-52%), there was a significant loss during their separation and purification.

The target *m*-diamide compounds **A-F** were identified by melting point, ^{1}H NMR, ^{13}C NMR and HRMS data. When R_1, R_2 and R_3 were identical, the melting points for the target compounds R_4 = Br were greater than R_4 = H due to the contribution of bromine atoms to the molecular weight (**C-1** (200-202 °C) > **A-2** (159-160 °C)). In addition, the substituents on nitrogen atoms in amide bonds had a significant impact on the melting point of compounds, which exhibited the contribution of R_3 = H to the melting point was significantly greater than R_3 = CH_3 (**A-2**(159-160 °C) > **B-1**(118-120 °C); **D-1**(223-226 °C) > **D-2**(82-84 °C) ; **E-1**(257-259 °C) > **E-2**(109-110 °C) ; **F-1**(236-237 °C) > **F-2**(77-79 °C)). Compared to R_3 = CH_3, this could occur because R_3 = H increased the perfection of the lattice for the corresponding target compound, resulting in a higher melting point. The melting points of sulfur in different oxidation states also decreased in the following sequence: sulfone-containing amides > sulfoxide-containing amides (**E-1** (257-259 °C) > **F-1** (223-225 °C); **E-2** (109-110 °C) > **F-2** (82-84 °C); and **E-3** (143-145 °C) > **F-3** (93-95 °C)). In the ^{1}H NMR spectra, the characteristic proton peak corresponding to the amide N-H bond appeared at δ 9.87-10.73 ppm for all the products, among which the signal for compound **A-1** was the only one lower than δ 10 ppm. Based on its chemical structure analysis, this difference might result from the electron donating properties of CH_3 adjacent to the amino group, which caused the group to migrate towards the lower field and higher position. When CH_3 was introduced to replace H of the amide bond, the N-CH_3 signal exhibited a chemical shift of 3.32-3.46 ppm. Notably, the different electronic effects of the –S–, –S(=O)– and –S(=O)$_2$– groups led to chemical shifts in $(O)_n$=S-$\underline{CH_3}$, which decreased in the following sequence: sulfone-containing compounds (δ 2.86-3.37 ppm) > sulfoxide-containing compounds (δ 2.56-2.92 ppm) > thioether-containing compounds (δ 2.48-2.86 ppm). Moreover, the typical proton chemical shift for the S=N$\underline{H}$ group of sulfoximine-containing compounds **F** appeared at δ 4.54 ppm.

The ^{13}C NMR spectra for the CF_3 group in some compounds were observed as quartets at δ 123.6-127.0 ppm (J = 273.7 Hz) owing to the coupling splitting of F. Meanwhile, the consistency between the theoretical and measured values of HRMS further confirmed the the target compound structure.

Bioactivities of the Target Compounds

The insecticidal activity data of target compounds **A-F** against *P. xylostella* at 500 $mg \cdot L^{-1}$ are listed in Table 1. The overall bioactivity test results revealed poor performance, as only some compounds exhibited larvicidal activity (20%-50%). Thus, using sulfur-containing derivatives to modify the heptafluoroisopropyl group in the leading compound Broflanilide was ineffective. However, we could reach some conclusions through the SAR data. Compounds bearing CF_3 (**A-2**, 36.67%) for R_1 exhibited a slightly greater lethality rate than H (**A-1**, 23.33%). In particular, R_2 = CN exhibited better insecticidal activity than that of the other compounds (**D-3**, 46.67%; **E-3**, 50.00%; and **F-3**, 34.48%). Therefore, if the R_2 position of the benzene ring is modified in future work, it might be desirable to introduce the synergistic effect of CN.

CONCLUSIONS

(1) Novel sulfur *m*-amide derivatives **A~F** were synthesized through a series of investigations by referencing and improving literature; the products were characterized by melting point, ^1H NMR, ^{13}C NMR and HRMS data. There was a clear correlation between the physical and chemical data and structural characteristics.

(2) Unfortunately, the insecticidal activities of the target compounds were worse than expected. Therefore, it was not feasible to obtain highly bioactive compounds by introducing active sulfur fragments to modify the heptafluoroisopropyl group in the leading compound as designed. Nevertheless, the results of this study provide useful information for the synthesis of novel sulfur-containing *m*-amides and novel compounds with good insecticidal activity.

SUPPLEMENTARY INFORMATION

The supporting information includes ^{1}H NMR, ^{13}C NMR and HRMS spectra of the target compounds.

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