Research Article

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Synthesis of novel *meta*-diamide compounds containing pyrazole moiety and their insecticidal evaluation

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Abstract: A novel series of *meta*-diamide compounds incorporating a pyrazole moiety (**2a**–**2v**) were designed and synthesized based on cyproflanilide. Their structures were validated through ^{1}H NMR, ^{13}C NMR, and HRMS analyses. These compounds were evaluated for their insecticidal activity against *Plutella xylostella, Mythimna separate, Tetranychus cinnabarinus*, and *Nilaparvata lugens*. Most of the title compounds exhibited good activity against *N. lugens* at 400 mg/L. Compound **2k** demonstrated potential for further optimization as an insecticidal lead, thereby extending the application of *meta*-diamide compounds in the field of sucking mouthparts.

Keywords: *meta*-diamide, pyrazole moiety, cyproflanilide, insecticidal activity, sucking mouthparts

1 Introduction

Meta-diamide insecticides, represented by broflanilide (**1**; Figure 1), are classified as group 30 insecticides [1–3]. Due to their novel mechanism of action, high efficiency, and lack of cross-resistance with traditional pesticides, *meta*-diamide insecticides have garnered considerable attention [4–6]. Based on broflanilide, numerous analogous *meta*-diamide compounds have been extensively modified and synthesized. For example, Lv et al. synthesized cyproflanilide (**2**; Figure 1) by replacing the methyl group of broflanilide with a cyclopropylmethyl group [7–9]. Furthermore, Zhang et al. synthesized compound **3** (Figure 1) by replacing the methyl group of broflanilide with a cyanomethyl ($CNCH_2$–) group [10]. Both compounds exhibited superior insecticidal activities compared to broflanilide.

The structural modification of *meta*-diamide insecticides primarily centers around four components: part A, part B, part C, and part D (**1**, Figure 1) [11–13]. In part A, the active groups are predominantly phenyl or pyridinyl moieties. In part B, alkyl chain substitutions, such as alkyl, alkoxy, and haloalkyl, are generally advantageous for insecticidal activity. Part C entails a substituted benzene with substituents including halogen, alkoxy, and cyano. Part D predominantly focuses on halogen atoms and alkyl groups. Moreover, the activity of *meta*-diamide insecticides has been mainly against chewing mouthpiece pests, such as lepidopteran pests. Conversely, their activity against sucking mouthparts, such as hemiptera, has been rarely reported.

Pyrazole groups, as a member of the five-membered heterocyclic rings, have garnered increasing attention in the pesticide domain due to their fungicidal, insecticidal, and herbicidal properties [14–18]. In the realm of insecticides, numerous pyrazole derivatives have been developed and commercialized, such as fipronil, fenpyroximate, tebufenpyrad, tolfenpyrad, chlorantraniliprole, cyantraniliprole, cyenopyrafen, and cyetpyrafen (Figure 2). Many of these compounds exhibit effective activity against sucking mouthpart [19–22] pests. For example, cyenopyrafen and cyetpyrafen demonstrate good efficacy in controlling spider mites.

To facilitate the development of novel *meta*-diamide compounds with a broader insecticidal spectrum and to build upon our previous research, this study regarded cyproflanilide as the lead compound. Pyrazole was introduced into the structure, and the effects of various substituted anilines on the activity were examined. A series of novel *meta*-diamide compounds incorporating 1-ethyl-3-methyl-1*H*-pyrazole-5-yl (easy synthesis and low cost)

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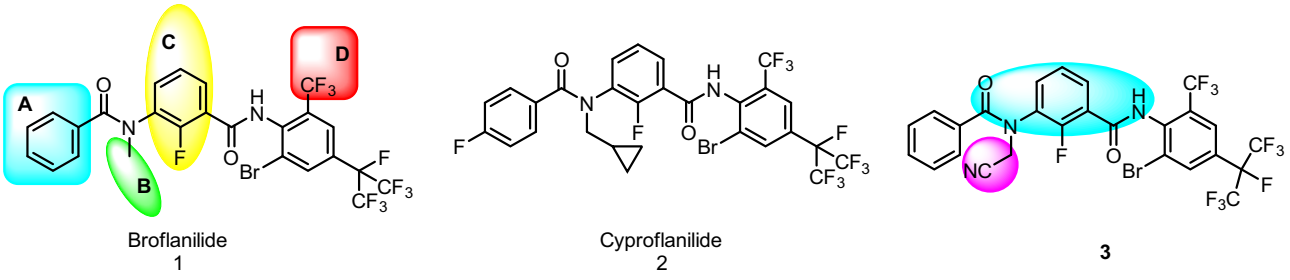


Figure 1: Representative *meta*-diamide compounds.

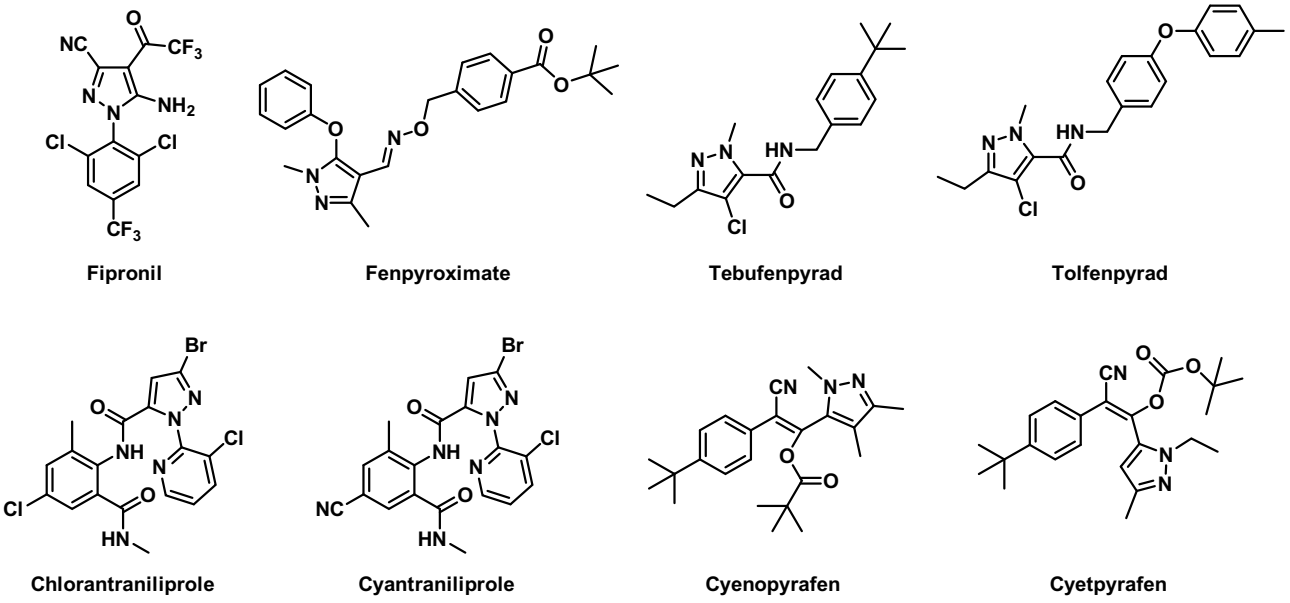


Figure 2: Representative insecticidal compounds.

were designed and synthesized (Figure 3). Their bioactivities against *Plutella xylostella*, *Mythimna separate*, *Tetranychus cinnabarinus*, and *Nilaparvata lugens* were subsequently evaluated. Notably, most of the title compounds exhibited notable activity against *N. lugens* at 400 mg/L, significantly surpassing cyproflanilide (0.00% at 400 mg/L). The preliminary structure–activity relationships (SARs) were also discussed. This study indicated that incorporating a pyrazole group could be useful for the application of *meta*-diamide compounds in the field of sucking mouthpart pests and provides guidance for subsequent research endeavors.

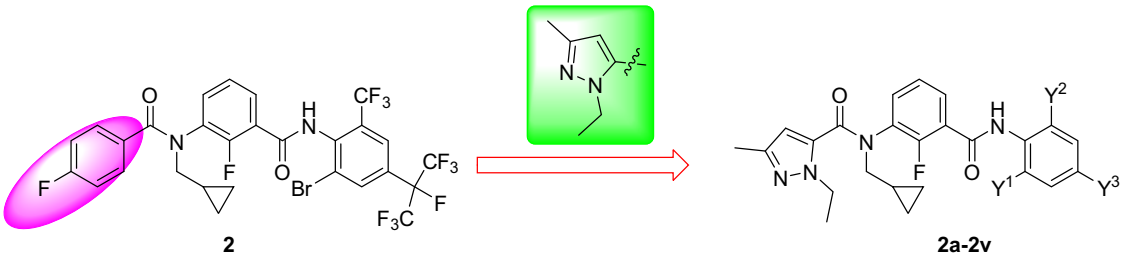


Figure 3: Design strategy employed for the target compounds.

2 Results and discussion

2.1 Synthesis

The synthesis route for compounds **2a**–**2v** is depicted in Scheme 1. Using methyl 3-amino-2-fluorobenzoate (**4**) as the starting material, we synthesized the key intermediate 3-(*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamido)-2-fluorobenzoic acid (**9**) through a series of reactions involving alkylation, amidation, and hydrolysis. Subsequently, intermediate **10** was subjected to further reaction with various anilines to obtain the final products **2a–2v**. All the target compounds were characterized and identified through ^{1}H NMR, ^{13}C NMR, and HRMS.

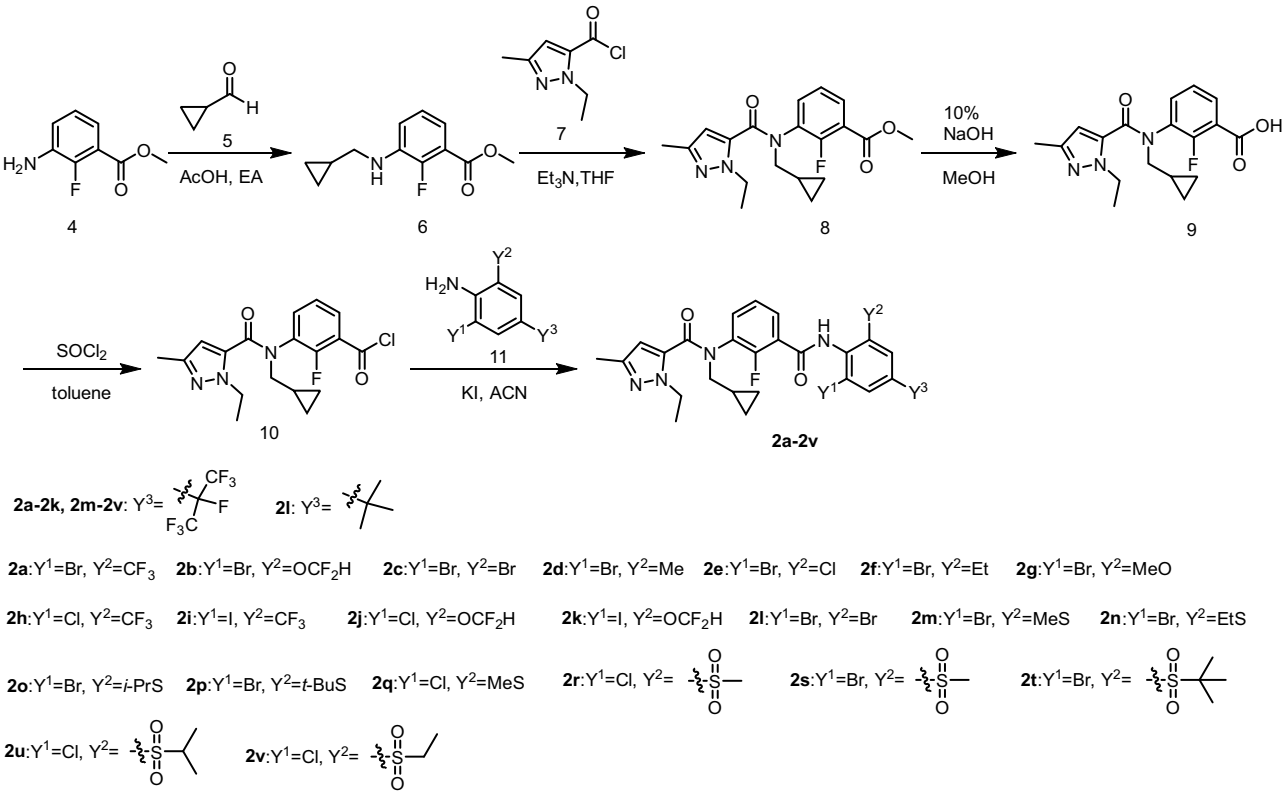
2.2 SAR

The insecticidal activity of the target compounds against *P. xylostella*, *M. separate*, *T. cinnabarinus*, and *N. lugens* was evaluated, with cyproflanilide serving as the control compound. The results are presented in Table 1.

For *P. xylostella* and *M. separate*, compounds **2a**–**2v** exhibited lower activities compared to cyproflanilide. The preliminary SAR analysis showed that the substituent groups Y^1, Y^2, and Y^3 on the aromatic ring exerted an important effect on the insecticidal activity of the target compounds. Regarding Y^1, especially the halogen substitution, I demonstrated superior activity compared to Cl and Br (compounds **2a**, **2h**, **2i** and **2b**, **2j**, **2k**). Regarding Y^2, trifluoromethyl and difluoromethoxy groups exhibited enhanced activity compared to other groups. Regarding Y^3, heptafluoroisopropyl proved beneficial in maintaining activity (compounds **2c** and **2l**).

For *T. cinnabarinus*, only compound **2k** exhibited a lethal rate of 91.72% at 100 mg/L, surpassing that of cyproflanilide (15.24% at 100 mg/L). Unfortunately, compound **2k** displayed no activity at 10 mg/L.

For *N. lugens*, most of the title compounds demonstrated good remarkable activity. For example, compounds **2a–2e**, **2h**–**2k**, **2n**, and **2r**–**2v** demonstrated lethality rates exceeding 90.00% at 400 mg/L, while cyproflanilide exhibited no activity at the same concentration. Moreover, compounds **2k**, **2t**, and **2v** maintained lethality rates of 98.41, 95.94, and 100% at 100 mg/L, respectively. In addition, altering the status of sulfur (sulfide or sulfoxide) influenced the activity. Based on the data of two groups (**2m**–**2v**), the activity of sulfoxide was higher than that of sulfide. For example, compounds **2m** and **2s** demonstrated mortality rates of 26.74 and 93.33% at 400 mg/L, respectively.



Scheme 1: Synthesis route for the target compounds **2a–2v**.

Table 1: Insecticidal activity of compounds **2a–2v** and **cyproflanilide**

Compound	Three-day mortality (%, mg/L)							
	P. xylostella		*M. separate*		*T. cinnabarinus*		*N. lugens*	
	1	**0.1**	**1**	**0.1**	**100**	**10**	**400**	**100**
2a	46.67	/	100	33.33	1.67	/	93.33	55.56
2b	3.33	/	86.67	20.00	61.17	/	100	83.43
2c	0.00	/	100	13.33	0.00	/	91.67	0.00
2d	3.33	/	86.67	0.00	0.00	/	93.33	0.00
2e	0.00	/	100	0.00	3.73	/	100	0.00
2f	0.00	/	36.67	/	5.41	/	67.53	/
2g	0.00	/	0.00	/	0.00	/	30.56	/
2h	40.00	/	93.33	3.33	0.00	/	100	26.63
2i	100	3.33	100	0.00	0.00	/	100	89.95
2j	6.67	/	46.67	/	2.08	/	100	46.85
2k	100	10.00	100	0.00	91.72	0.00	100	98.41
2l	0.00	/	0.00	/	1.75	/	15.53	/
2m	0.00	/	0.00	/	5.16	/	26.74	/
2n	0.00	/	0.00	/	0.00	/	94.12	46.67
2o	0.00	/	0.00	/	0.00	/	0.00	/
2p	0.00	/	0.00	/	0.00	/	0.00	/
2q	0.00	/	0.00	/	0.00	/	67.53	0.00
2r	0.00	/	3.33	/	0.00	/	91.67	78.41
2s	0.00	/	0.00	/	0.00	/	93.33	55.56
2t	0.00	/	0.00	/	0.00	/	100	95.94
2u	0.00	/	10.00	/	0.00	/	91.67	38.33
2v	10.00	/	20.00	/	0.00	/	100	100
Cyproflanilide	100	96.67	100	100	15.24	/	0.00	/
Nitenpyram	/	/	/	/	/	/	100	100

Note: "/" denotes untested.

Our results indicate that the introduction of pyrazole groups can expand the insecticidal spectrum of *meta*-diamide compounds to include hemiptera such as *N. lugens*. Specifically, compound **2k** not only exhibited 100% mortality at 1 mg/L against *P. xylostella* and *M. separate* but also displayed a 98.41% lethal rate at 100 mg/L against *N. lugens*. Compound **2k** presents promising potential as a lead for the discovery of novel insecticides. Furthermore, our results demonstrate that *meta*-diamide compounds hold potential for controlling sucking mouthpart pests. Further studies are currently ongoing in our laboratory.

3 Experimental section

3.1 Materials and methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were acquired using a Bruker AV400 spectrometer (Bruker Co., Switzerland) in either DMSO-d_6 or $CDCl_3$ solutions, with tetramethylsilane serving as the internal standard. Chemical shifts (δ) were reported in parts per million (ppm). Mass spectra were generated utilizing the Agilent 1100 LC-MSD-Trap Mass Spectrometer equipped with standard electrospray ionization (ESI) apparatus. Melting points (Mp) were determined using the MP450 melting-point apparatus (Shandong Nanon Instrument Ltd, CITY, China). Flash chromatography was performed using silica gel (200–300 mesh). The crude product was purified by column chromatography using ethyl acetate (EA) and petroleum ether (PE) as the eluent. All solvents and liquid reagents were dried using standard methods and distilled prior to usage.

3.2 Chemical synthesis

3.2.1 Methyl 3-((cyclopropylmethyl)amino)-2-fluorobenzoate (6)

In a 250 mL flask, Zn (5.80 g, 79.39 mmol) and AcOH (7.10 g, 132.32 mmol) were added to methyl 3-amino-2-fluorobenzoate (10.0 g, 66.16 mmol) in EA (100 mL), followed by the addition of compound **5** (4.14 g, 66.16 mmol). The temperature was increased to 60°C for 4 h. Thin-layer chromatography (TLC)

indicated the completion of the reaction. Subsequently, the solution was washed with a saturated sodium bicarbonate aqueous solution (100 mL), and the mixture was subjected to extraction using EA (200 mL). The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the obtained residue was purified via flash column chromatography using PE and EA as eluents, resulting in 9.68 g (yield: 73.35%) of the target compound in the form of yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.08–6.94 (m, 3H), 5.68 (s, 1H), 3.82 (s, 3H), 3.03–2.96 (m, 2H), 1.14–1.04 (m, 1H), 0.49–0.41 (m, 2H), 0.29–0.21 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 165.11, 165.08, 151.18, 148.67, 138.46, 138.34, 124.78, 124.74, 118.07, 118.00, 116.59, 116.18, 116.12, 52.56, 47.44, 10.89, 3.90. HRMS (ESI) *m*/*z*: Calcd. for $C_{12}H_{14}FNO_2$ $[M + H]^+$ 224.1008, found 224.1077.

3.2.2 Methyl 3-(*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamido)-2-fluorobenzoate (8)

N,*N*-diisopropylethylamine (3.73 g, 24.19 mmol) and compound **7** (3.83 g, 22.17 mmol) were added to a solution of compound **6** (4.50 g, 20.16 mmol) in anhydrous tetrahydrofuran (45 mL). Then, the mixture was stirred at 80°C for 6 h. TLC indicated the completion of the reaction. The reaction mixture was subjected to extraction using EA (100 mL) and H_2O (80 mL). The organic layer was subsequently washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the obtained residue was purified via flash column chromatography using PE and EA as eluents, resulting in 6.10 g (yield: 84.20%) of the target compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.85 (t, J = 6.7 Hz, 1H), 7.82–7.77 (m, 1H), 7.38 (t, J = 7.9 Hz, 1H), 5.44 (s, 1H), 4.22 (dd, J = 22.6, 7.8 Hz, 2H), 3.83 (s, 3H), 3.66 (d, J = 74.8 Hz, 2H), 1.93 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 0.94 (s, 1H), 0.37 (s, 2H), 0.00 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.84, 161.70, 158.51, 155.93, 145.63, 135.42, 135.36, 131.71, 125.38, 125.33, 119.51, 119.41, 107.34, 53.00, 45.62, 16.01, 13.38, 9.70, 3.61. HRMS (ESI) *m*/*z*: Calcd. for $C_{19}H_{22}FN_3O_3$ $[M + H]^+$ 360.1645, found 360.1709.

3.2.3 3-(*N*-(Cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamido)-2-fluorobenzoic acid (9)

Compound **8** (6.00 g, 16.70 mmol) was dissolved in methanol (60 mL). Subsequently, 10% sodium hydroxide aqueous solution (2.67 g, 66.80 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. TLC indicated the completion of the reaction. Upon removal of the solvent by distillation, the crude product was dissolved in H_2O (30 mL) and extracted using EA (50 mL). The pH of the aqueous phase was adjusted to 3 by adding 2 M hydrochloric acid, and then extraction was performed using EA (40 mL). The organic layer was subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to obtain 4.42 g (yield: 76.66%) of the target compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.39 (s, 1H), 7.85 (s, 1H), 7.77–7.71 (m, 1H), 7.34 (d, J = 15.7 Hz, 1H), 5.43 (s, 1H), 4.40–4.08 (m, 2H), 3.66 (d, J = 62.1 Hz, 2H), 1.93 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 0.96 (s, 1H), 0.38 (s, 2H), 0.05 (d, J = 43.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.84, 161.70, 158.51, 155.93, 145.63, 135.42, 135.36, 131.71, 125.38, 125.33, 119.51, 119.41, 107.34, 53.00, 45.62, 16.01, 13.38, 9.70, 3.61. HRMS (ESI) *m*/*z*: Calcd. for $C_{18}H_{20}FN_3O_3$ $[M + H]^+$ 345.1488, found 346.1550.

3.2.4 3-(*N*-(Cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamido)-2-fluorobenzoyl chloride (10)

Thionyl chloride (0.86 g, 7.24 mmol) was added to a solution of compound **9** (0.50 g, 1.45 mmol) in toluene (6 mL). Then, the mixture was heated and refluxed for 2 h. Following the removal of the solvent by distillation, crude product **10** in acetonitrile (3 mL) was utilized for the subsequent step without undergoing additional purification.

3.3 General chemical synthesis of compounds 2a–2v

To **11** (1.45 mmol), KI (0.12 g, 0.73 mmol) in acetonitrile (5 mL) was added **10**. The mixture was stirred at 80°C for 8 h. TLC indicated the completion of the reaction. Subsequently, the reaction mixture was diluted with H_2O (40 mL) and subjected to extraction using EA (60 mL). The organic layer was subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography, utilizing PE and EA as eluents to obtain the target compound.

3.3.1 *N*-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2a)

Compound **2a** was obtained as a yellow solid; yield: 37.32%; Mp: 134.5–135.5°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.64 (s, 1H), 8.43 (s, 1H), 7.96 (s, 1H), 7.75–7.63 (m, 2H), 7.42 (t, J = 7.6 Hz, 1H), 5.55 (s, 1H), 4.20 (s, 2H), 3.68 (s, 2H), 1.99

(s, 3H), 1.34 (d, J = 7.1 Hz, 3H), 1.01 (s, 1H), 0.43 (d, J = 7.6 Hz, 2H), 0.08 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.07, 161.93, 145.71, 139.20, 135.52, 134.62, 133.68, 131.66, 131.35, 129.69, 129.23, 126.93, 126.71, 125.44, 124.29, 123.66, 123.28, 120.93, 107.14, 45.51, 15.97, 13.45, 9.85, 3.72. HRMS (ESI) m/z: Calcd. for $C_{28}H_{22}BrF_{11}N_4O_2$ $[M + H]^+$ 735.0750, found 735.0810.

3.3.2 *N*-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2b)

Compound **2b** was obtained as a yellow solid; yield: 52.00%; Mp: 120.0–121.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.38 (s, 1H), 7.91 (s, 1H), 7.69 (t, J = 6.8 Hz, 2H), 7.55 (s, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 72.0 Hz, 1H), 5.55 (s, 1H), 4.20 (d, J = 12.3 Hz, 2H), 3.68 (d, J = 22.3 Hz, 2H), 1.99 (s, 4H), 1.33 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.42 (d, J = 7.7 Hz, 2H), 0.10 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.57, 161.85, 149.27, 135.50, 133.79, 132.72, 129.94, 126.56, 126.35, 126.08, 125.34, 124.40, 124.26, 119.34, 116.75, 116.36, 114.15, 60.22, 45.55, 21.21, 16.02, 14.53, 13.45, 9.84, 3.83. HRMS (ESI) m/z: Calcd. for $C_{28}H_{23}BrF_{10}N_4O_3$ $[M + H]^+$ 733.0793, found 733.0859.

3.3.3 *N*-(Cyclopropylmethyl)-*N*-(3-((2,6-dibromo-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2c)

Compound **2c** was obtained as a white solid; yield: 63.41%; Mp: 110.0–111.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H), 8.04 (s, 2H), 7.79–7.68 (m, 2H), 7.41 (t, J = 7.5 Hz, 1H), 5.55 (s, 1H), 4.20 (s, 3H), 3.74–3.60 (m, 2H), 1.97 (s, 3H), 1.33 (t, J = 7.2 Hz, 4H), 1.02 (s, 1H), 0.43 (d, J = 7.8 Hz, 2H), 0.11 (d, J = 18.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.19, 161.87, 154.35, 145.74, 139.93, 135.52, 133.70, 129.87, 129.54, 129.44, 127.31, 127.10, 126.33, 125.36, 124.36, 124.23, 121.62, 107.21, 45.56, 16.07, 13.51, 9.85, 3.81. HRMS (ESI) m/z: Calcd. for $C_{27}H_{22}Br_2F_8N_4O_2$ $[M + H]^+$ 747.2942, found 747.0029.

3.3.4 *N*-(3-((2-Bromo-6-methyl-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2d)

Compound **2d** was obtained as a white solid; yield: 70.41%; Mp: 143.0–144.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.25 (s, 1H), 7.80 (s, 1H), 7.69 (q, J = 6.9 Hz, 3H), 7.39 (t, J = 7.7 Hz, 1H), 5.56 (s, 1H), 4.32–4.12 (m, 2H), 3.77–3.61 (m, 2H), 2.36 (s, 3H), 1.97 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.02 (s, 1H), 0.43 (d, J = 7.7 Hz, 2H), 0.10 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.29, 161.88, 154.21, 145.68, 140.84, 139.07, 135.52, 133.39, 129.80, 127.43, 127.31, 127.10, 127.01, 125.80, 125.59, 125.40, 124.92, 124.79, 121.82, 118.96, 107.21, 53.34, 45.54, 19.06, 16.04, 13.49, 9.87, 3.84. HRMS (ESI) m/z: Calcd. for $C_{28}H_{25}BrF_8N_4O_2$ $[M + H]^+$ 681.1033, found 681.1094.

3.3.5 *N*-(3-((2-Bromo-6-chloro-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2e)

Compound **2e** was obtained as a white solid; yield: 48.41%; Mp: 111.0–112.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.59 (s, 1H), 8.06–7.91 (m, 2H), 7.72 (t, J = 6.9 Hz, 2H), 7.41 (t, J = 7.1 Hz, 1H), 5.55 (s, 1H), 4.21 (dd, J = 16.2, 7.2 Hz, 2H), 3.78–3.56 (m, 2H), 1.96 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H), 1.01 (s, 1H), 0.42 (d, J = 7.4 Hz, 2H), 0.11 (d, J = 19.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.30, 161.87, 154.34, 145.71, 138.46, 135.83, 135.50, 133.77, 129.92, 128.97, 128.87, 127.02, 126.80, 126.67, 126.51, 125.40, 124.29, 124.16, 121.59, 118.74, 107.20, 53.34, 45.56, 16.04, 13.49, 9.86, 3.69. HRMS (ESI) m/z: Calcd. for $C_{27}H_{22}BrClF_8N_4O_2$ $[M + H]^+$ 701.8402, found 701.0557.

3.3.6 *N*-(3-((2-Bromo-6-ethyl-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (2f)

Compound **2f** was obtained as a yellow solid; yield: 38.10%; Mp: 127.2–128.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.28 (s, 1H), 7.82 (s, 1H), 7.70 (t, J = 7.4 Hz, 2H), 7.64 (s, 1H), 7.40 (t, J = 7.7 Hz, 1H), 5.55 (s, 1H), 4.22 (dd, J = 17.7, 10.5 Hz, 2H), 3.70 (d, J = 6.6 Hz, 2H), 2.72 (d, J = 21.7 Hz, 2H), 1.98 (d, J = 9.7 Hz, 4H), 1.33 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 7.5 Hz, 3H), 1.02 (s, 1H), 0.43 (d, J = 7.6 Hz, 2H), 0.12 (d, J = 14.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.75, 161.91, 154.18, 146.55, 145.64, 138.57, 135.52, 133.26, 129.66, 127.47, 127.36, 126.21, 126.01, 125.78, 125.68, 125.53, 125.42, 125.02, 124.88, 107.19, 53.36, 45.53, 25.77, 16.01, 14.72, 13.48, 9.86, 3.75. HRMS (ESI) m/z: Calcd. for $C_{29}H_{27}BrF_8N_4O_2$ $[M + H]^+$ 695.4522, found 695.1247.

3.3.7 *N*-(3-((2-Bromo-6-methoxy-4-(perfluoropropan-2-yl) phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (2g)

Compound **2g** was obtained as a yellow solid; yield: 70.10%; Mp: 132.2–133.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.08 (s, 1H), 7.66 (t, J = 6.8 Hz, 2H), 7.43–7.31 (m, 2H), 7.23 (s, 1H), 5.54 (s, 1H), 4.36–4.15 (m, 2H), 3.90 (s, 3H), 3.68 (d, J = 56.5 Hz, 2H), 1.98 (d, J = 9.9 Hz, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.00 (s, 1H), 0.42 (d, J = 7.6 Hz, 2H), 0.11 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.84, 157.48, 154.27, 145.68, 135.50, 134.56, 133.58, 130.11, 127.87, 126.01, 125.80, 125.23, 124.80, 124.66, 121.78, 119.20, 118.26, 108.25, 108.14, 107.32, 57.23, 55.37, 45.57, 16.03, 13.47, 9.84, 3.93, 3.58. HRMS (ESI) m/z: Calcd. for $C_{28}H_{25}BrF_8N_4O_3$ $[M + H]^+$ 697.4242, found 697.1249.

3.3.8 *N*-(3-((2-Chloro-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2h)

Compound **2h** was obtained as a yellow solid; yield: 20.10%; Mp: 112.2–112.9°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.62 (s, 1H), 8.35 (s, 1H), 7.93 (s, 1H), 7.70 (dt, J = 16.6, 6.9 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 5.55 (s, 1H), 4.27–4.11 (m, 2H), 3.69 (d, J = 6.8 Hz, 2H), 1.97 (s, 3H), 1.32 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.42 (d, J = 7.4 Hz, 2H), 0.11 (d, J = 19.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.19, 161.92, 156.86, 154.33, 145.70, 138.11, 137.59, 135.49, 133.78, 131.72, 129.77, 126.84, 126.62, 125.48, 124.14, 123.72, 122.64, 120.99, 118.93, 107.19, 53.43, 45.50, 15.95, 13.43, 9.84, 3.72. HRMS (ESI) m/z: Calcd. for $C_{28}H_{22}ClF_{11}N_4O_2$ $[M + H]^+$ 691.9424, found 691.1318.

3.3.9 *N*-(Cyclopropylmethyl)-1-ethyl-*N*-(2-fluoro-3-((2-iodo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)carbamoyl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (2i)

Compound **2i** was obtained as a white solid; yield: 33.34%; Mp: 150.1–151.1°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.67 (s, 1H), 8.51 (s, 1H), 7.95 (s, 1H), 7.72 (t, J = 7.1 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 5.59 (s, 1H), 4.21 (dd, J = 16.0, 8.1 Hz, 2H), 3.69 (s, 2H), 1.97 (s, 5H), 1.02 (s, 1H), 0.43 (d, J = 7.2 Hz, 2H), 0.11 (d, J = 28.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.84, 161.94, 145.78, 142.46, 140.37, 135.56, 133.64, 130.25, 129.63, 126.69, 126.48, 125.37, 124.58, 124.45, 123.60, 120.88, 108.24, 107.13, 45.51, 16.00, 13.48, 9.85, 3.72. HRMS (ESI) m/z: Calcd. for $C_{28}H_{22}F_{11}IN_4O_2$ $[M + H]^+$ 783.0611, found 783.0667.

3.3.10 *N*-(3-((2-Chloro-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2j)

Compound **2j** was obtained as a yellow solid; yield: 41.11%; Mp: 116.1–117.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.40 (s, 1H), 7.82 (s, 1H), 7.68 (q, J = 6.8, 6.1 Hz, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.45–7.35 (m, 2H), 7.34 (t, J = 72.0, 1H), 5.54 (s, 1H), 4.28–4.12 (m, 2H), 3.68 (d, J = 30.2 Hz, 2H), 1.97 (s, 3H), 1.33 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.42 (d, J = 7.7 Hz, 2H), 0.10 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.63, 161.86, 156.86, 154.35, 149.33, 135.48, 133.84, 131.13, 129.99, 126.11, 125.89, 125.39, 124.34, 124.21, 123.82, 123.72, 119.32, 116.72, 115.80, 115.69, 114.13, 107.25, 53.34, 45.55, 16.00, 13.44, 9.84, 3.63. HRMS (ESI) m/z: Calcd. for $C_{28}H_{23}ClF_{10}N_4O_3$ $[M + H]^+$ 689.1299, found 689.1357.

3.3.11 *N*-(Cyclopropylmethyl)-*N*-(3-((2-(difluoromethoxy)-6-iodo-4-(perfluoropropan-2-yl)phenyl) carbamoyl)-2-fluorophenyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2k)

Compound **2k** was obtained as a yellow solid; yield: 54.00%; Mp: 166.0–167.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H), 8.02 (s, 1H), 7.69 (t, J = 6.9 Hz, 2H), 7.51 (d, J = 14.7 Hz, 1H), 7.43 (s, 1H), 7.31 (s, 1H), 7.34 t, J = 72.0, 1H), 5.57 (s, 1H), 4.29–4.11 (m, 2H), 3.67 (d, J = 6.9 Hz, 2H), 1.96 (s, 2H), 1.33 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.43 (d, J = 7.6 Hz, 2H), 0.11 (d, J = 14.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.87, 154.40, 148.24, 145.73, 135.91, 135.53, 133.73, 132.35, 129.86, 126.95, 126.74, 125.33, 124.59, 124.45, 121.66, 119.35, 116.76, 114.17, 107.17, 104.38, 45.56, 16.06, 14.53, 13.48, 9.82, 3.66. HRMS (ESI) m/z: Calcd. for $C_{28}H_{23}F_{10}IN_4O_3$ $[M + H]^+$ 781.0655, found 781.0711.

3.3.12 *N*-(Cyclopropylmethyl)-*N*-(3-((2,6-dibromo-4-(tert-butyl)phenyl)carbamoyl)-2-fluorophenyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2l)

Compound **2l** was obtained as a yellow solid; yield: 70.00%; Mp: 106.1–107.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.28 (s, 1H), 7.73–7.60 (m, 4H), 7.38 (t, J = 7.5 Hz, 1H), 5.55 (s, 1H), 4.21 (dd, J = 15.1, 7.2 Hz, 2H), 3.79–3.59 (m, 2H), 1.96 (s, 2H), 1.33 (t, J = 7.3 Hz, 13H), 1.01 (p, J = 6.6 Hz, 1H), 0.42 (d, J = 7.6 Hz, 2H), 0.11 (d, J = 12.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.42, 161.90, 156.79, 154.16, 145.69, 135.55, 133.31, 133.14, 129.80, 129.69, 125.21, 125.09, 124.95, 124.55, 107.23, 60.23, 53.35, 45.56, 35.22, 31.13, 21.24, 16.09,

14.56, 13.54, 9.87, 3.88. HRMS (ESI) *m*/*z*: Calcd. for $C_{28}H_{31}Br_2FN_4O_2$ $[M + H]^+$ 635.3884, found 635.1110.

3.3.13 *N*-(3-((2-Bromo-6-(methylthio)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2m)

Compound **2m** was obtained as a white solid; yield: 34.00%; Mp: 108.0–108.7°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H), 7.70 (dd, J = 12.1, 4.6 Hz, 3H), 7.46–7.32 (m, 2H), 5.55 (s, 1H), 4.31–4.13 (m, 2H), 3.77–3.61 (m, 2H), 3.48 (s, 2H), 1.98 (d, J = 11.4 Hz, 4H), 1.34 (d, J = 7.1 Hz, 3H), 1.01 (s, 1H), 0.48–0.38 (m, 2H), 0.12 (d, J = 19.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm): 162.33, 161.89, 156.84, 154.30, 145.70, 144.44, 136.35, 135.53, 133.53, 129.84, 126.69, 126.48, 125.58, 125.29, 125.12, 125.01, 124.71, 124.57, 120.58, 107.24, 55.38, 53.34, 45.56, 16.06, 14.65, 13.51, 9.86, 3.70. HRMS (ESI) *m*/*z*: Calcd. for $C_{28}H_{25}BrF_8N_4O_2S$ $[M + H]^+$ 713.0753, found 713.0816.

3.3.14 *N*-(3-((2-Bromo-6-(ethylthio)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2n)

Compound **2n** was obtained as a yellow solid; yield: 27.80%; Mp: 124.4–125.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.32 (s, 1H), 7.71 (dd, J = 15.8, 9.2 Hz, 3H), 7.47–7.35 (m, 2H), 5.55 (s, 1H), 4.21 (dd, J = 17.5, 7.0 Hz, 2H), 3.68 (d, J = 5.6 Hz, 2H), 3.04 (q, J = 7.3 Hz, 2H), 1.98 (d, J = 9.4 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 7.3 Hz, 3H), 1.01 (s, 1H), 0.43 (d, J = 7.5 Hz, 2H), 0.12 (d, J = 17.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.75, 161.91, 154.18, 146.55, 145.64, 138.57, 135.52, 133.26, 129.66, 127.36, 126.21, 126.01, 125.68, 125.53, 125.42, 125.02, 124.88, 121.81, 118.96, 107.19, 53.36, 45.53, 25.77, 16.01, 14.72, 14.53, 13.48, 9.86, 3.75. HRMS (ESI) *m*/*z*: Calcd. for $C_{29}H_{27}BrF_8N_4O_2S$ $[M + H]^+$ 727.0910, found 727.0971.

3.3.15 *N*-(3-((2-Bromo-6-(isopropylthio)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2o)

Compound **2o** was obtained as a yellow solid; yield: 41.11%; Mp: 150.4–151.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s, 1H), 7.79 (d, J = 10.1 Hz, 1H), 7.73–7.65 (m, 2H), 7.54 (s, 1H), 7.39 (s, 1H), 5.55 (s, 1H), 4.21 (dd, J = 13.6, 6.3 Hz, 2H), 3.64 (dd, J = 17.6, 11.0 Hz, 4H), 1.97 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H), 1.25 (d, J = 6.6 Hz, 6H), 1.01 (s, 1H), 0.43 (d, J = 7.6 Hz, 2H), 0.12 (d, J = 21.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 170.81, 162.26, 161.91, 154.38, 145.66, 135.56, 133.24, 133.18, 129.95, 126.46, 126.37, 125.57, 125.16, 124.40, 124.30, 122.08, 119.22, 118.97, 107.27, 107.21, 60.22, 45.54, 36.52, 22.53, 21.22, 16.08, 14.54, 13.52, 9.86, 3.71. HRMS (ESI) *m*/*z*: Calcd. for $C_{30}H_{29}BrF_8N_4O_2S$ $[M + H]^+$ 741.1066, found 741.1125.

3.3.16 *N*-(3-((2-Bromo-6-(tert-butylthio)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2p)

Compound **2p** was obtained as a yellow solid; yield: 63.33%; Mp: 125.1–126.1°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.62 (d, J = 12.0 Hz, 1H), 8.19–8.10 (m, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.83 (s, 1H), 7.56 (td, J = 7.6, 1.6 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 5.36 (s, 1H), 4.53–4.32 (m, 2H), 3.92 (s, 1H), 3.65 (s, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.21 (s, 9H), 1.10 (s, 1H), 0.51 (d, J = 7.2 Hz, 2H), 0.18 (d, J = 39.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.17, 161.82, 156.96, 154.42, 143.92, 136.21, 135.48, 133.83, 133.38, 130.88, 130.76, 129.81, 125.43, 125.21, 125.08, 125.00, 124.74, 124.62, 124.60, 122.02, 121.75, 118.89, 107.15, 48.57, 45.58, 31.08, 29.50, 16.07, 13.53, 9.85, 3.75. HRMS (ESI) *m*/*z*: Calcd. for $C_{31}H_{31}BrF_8N_4O_2S$ $[M + H]^+$ 755.1223, found 755.1281.

3.3.17 *N*-(3-((2-Chloro-6-(methylthio)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (2q)

Compound **2q** was obtained as a yellow solid; yield: 41.23%; Mp: 112.1–113.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.32 (s, 1H), 7.68 (d, J = 6.9 Hz, 2H), 7.61 (s, 1H), 7.46–7.33 (m, 2H), 5.56 (s, 1H), 4.21 (dd, J = 14.4, 7.4 Hz, 2H), 3.68 (d, J = 25.9 Hz, 2H), 2.52 (s, 3H), 1.96 (s, 3H), 1.33 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.42 (d, J = 7.6 Hz, 2H), 0.10 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.44, 154.29, 144.45, 135.52, 134.81, 133.60, 129.89, 126.45, 126.24, 125.35, 124.63, 124.49, 122.17, 119.93, 107.26, 53.32, 45.55, 16.04, 14.62, 13.49, 9.86, 3.87. HRMS (ESI) *m*/*z*: Calcd. for $C_{28}H_{25}ClF_8N_4O_2S$ $[M + H]^+$ 669.1259, found 669.1319.

3.3.18 *N*-(3-((2-Chloro-6-(methylsulfonyl)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (2r)

Compound **2r** was obtained as a yellow solid; yield: 33.33%; Mp: 133.1–133.7°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):

10.63 (s, 1H), 8.39 (s, 1H), 8.15 (s, 1H), 7.74 (t, J = 7.4 Hz, 2H), 7.43 (t, J = 7.8 Hz, 1H), 5.56 (s, 1H), 4.21 (dd, J = 16.5, 7.4 Hz, 2H), 3.75–3.62 (m, 2H), 2.52–2.48 (m, 4H), 1.97 (s, 4H), 1.33 (t, J = 7.2 Hz, 4H), 1.01 (s, 1H), 0.43 (d, J = 7.7 Hz, 2H), 0.11 (d, J = 21.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.27, 161.91, 156.98, 154.45, 145.74, 142.41, 138.04, 137.73, 135.52, 133.78, 132.52, 129.96, 126.67, 126.45, 125.63, 125.45, 123.96, 121.81, 118.94, 118.67, 107.18, 53.41, 45.54, 43.47, 16.04, 13.48, 9.86, 3.74. HRMS (ESI) m/z: Calcd. for $C_{28}H_{25}ClF_8N_4O_4S$ [M + H]$^+$ 701.1157, found 701.1214.

3.3.19 *N*-(3-((2-Bromo-6-(methylsulfonyl)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2s)

Compound **2s** was obtained as a yellow solid; yield: 54.12%; Mp: 127.1–127.7°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.65 (s, 1 H), 8.51–8.43 (m, 1 H), 8.19 (d, J = 1.6 Hz, 1 H), 7.74 (t, J = 7.4 Hz, 2 H), 7.43 (t, J = 7.7 Hz, 1 H), 5.56 (s, 1 H), 4.20 (dt, J = 13.9, 7.0 Hz, 2 H), 3.70 (d, J = 25.1 Hz, 2 H), 3.36 (s, 3 H), 1.97 (s, 3 H), 1.33 (t, J = 7.2 Hz, 4 H), 1.01 (s, 1 H), 0.43 (d, J = 7.9 Hz, 2 H), 0.11 (d, J = 29.0 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.20, 161.91, 154.46, 145.75, 142.42, 139.27, 135.54, 133.69, 129.92, 129.26, 126.88, 126.66, 126.15, 125.42, 124.22, 121.84, 118.71, 107.15, 53.37, 45.54, 43.46, 16.06, 13.50, 9.85, 3.75. HRMS (ESI) m/z: Calcd. for $C_{28}H_{25}BrF_8N_4O_4S$ [M + H]$^+$ 745.0652, found 745.0711.

3.3.20 *N*-(3-((2-Bromo-6-(tert-butylsulfonyl)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2t)

Compound **2t** was obtained as a white solid; yield: 29.33%; Mp: 143.21–143.8°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 8.51–8.48 (m, 1H), 8.03 (s, 1H), 7.91–7.88 (m, 1H), 7.84–7.78 (m, 1H), 7.46 (t, J = 7.8 Hz, 1H), 5.48 (s, 1H), 4.35–4.14 (m, 2H), 3.72 (d, J = 97.0 Hz, 2H), 1.97 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.20 (s, 9H), 0.99 (s, 1H), 0.42 (d, J = 7.5 Hz, 2H), 0.12 (d, J = 51.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 166.54, 140.72, 136.37, 136.34, 135.41, 133.81, 133.35, 133.21, 131.15, 129.55, 129.30, 128.56, 128.39, 125.55, 125.33, 62.51, 45.59, 31.61, 22.98, 16.04, 13.51, 9.84, 3.61. HRMS (ESI) m/z: Calcd. for $C_{31}H_{31}BrF_8N_4O_4S$ [M + H]$^+$ 787.1121, found 787.1183.

3.3.21 *N*-(3-((2-Bromo-6-(isopropylsulfonyl)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2u)

Compound **2u** was obtained as a yellow solid; yield: 63.33%; Mp: 101.2–102.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.65 (s, 1H), 8.53 (d, J = 1.9 Hz, 1H), 8.10 (s, 1H), 7.75 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 5.54 (s, 1H), 4.34–4.16 (m, 2H), 3.69 (d, J = 67.2 Hz, 4H), 1.97 (s, 3H), 1.33 (d, J = 7.2 Hz, 3H), 1.14 (d, J = 6.7 Hz, 6H), 1.00 (s, 1H), 0.42 (d, J = 7.4 Hz, 2H), 0.15 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.21, 161.80, 157.03, 154.52, 145.71, 139.86, 139.16, 135.95, 135.85, 135.45, 133.75, 129.91, 129.80, 127.47, 126.63, 126.42, 125.45, 123.97, 121.54, 118.69, 107.15, 54.25, 45.59, 16.04, 14.67, 13.49, 9.81, 3.71. HRMS (ESI) m/z: Calcd. for $C_{30}H_{29}BrF_8N_4O_4S$ [M + H]$^+$ 773.0965, found 773.1025.

3.3.22 *N*-(3-((2-Bromo-6-(ethylsulfonyl)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (2v)

Compound **2v** was obtained as a yellow solid; yield: 38.99%; Mp: 131.8–132.5°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.66 (s, 1H), 8.51 (s, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 5.55 (s, 1H), 4.21 (dd, J = 14.8, 7.5 Hz, 2H), 3.70 (d, J = 36.2 Hz, 2H), 3.43 (s, 2H), 1.97 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H), 1.07 (t, J = 7.3 Hz, 3H), 1.00 (s, 1H), 0.43 (d, J = 7.7 Hz, 2H), 0.11 (d, J = 27.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.22, 161.88, 145.76, 140.19, 139.64, 135.73, 135.51, 133.70, 131.14, 129.91, 129.63, 127.06, 126.76, 126.55, 125.45, 123.98, 107.08, 49.13, 45.56, 16.06, 13.50, 9.83, 7.17, 3.74. HRMS (ESI) m/z: Calcd. for $C_{29}H_{27}BrF_8N_4O_4S$ [M + H]$^+$ 759.0808, found 759.0863.

3.4 Insecticidal assay

According to statistical protocol, the bioassay was conducted three times at 25 ± 1°C. All compounds were dissolved in DMSO and further diluted with water containing Triton X-100 (0.1 mg/L) to obtain various concentrations for bioassays. Mortality rates were adjusted using Abbott's method and assessments were conducted based on the dead/alive status. Evaluations were based on a percentage

scale (0 indicating no activity and 100 indicating complete eradication). The experiments maintained a 5% error rate.

The insects *P. xylostella, M. separate, T. cinnabarinus*, and *N. lugens* evaluated in this study were provided by Green Tech Laboratory. The insecticidal activity of the title compounds against *T. cinnabarinus* was assessed using the immersion method [23]. Insecticidal activity against *P. xylostella* and *M. separate* was assessed using the leaf-dip method [24], while insecticidal activity against *N. lugens* was evaluated employing the rice seedling immersion method [25].

4 Conclusion

To expand the application of *meta*-diamide compounds in controlling sucking mouthpart pests, we synthesized 22 novel *meta*-diamide compounds containing a pyrazole group and validated them via ^{1}H NMR, ^{13}C NMR, and HRMS. Bioassay results indicated that most of the title compounds exhibit notable activity against *N. lugens* at 400 mg/L. Particularly, compound **2k** exhibits beneficial activity against all four insects tested. This underscores the utility of pyrazole groups in the application of *meta*-diamide compounds in the field of sucking mouthpart pests. Our study revealed that these molecules hold promise as lead molecules for the development of novel insecticidal agents.

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Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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