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Design, Synthesis and Biological Activities of Novel *meta*-Diamide Compounds Containing 1,2,4-Oxadiazole Group

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To discover new bisamide compounds with insecticidal and fungicidal activities, 19 novel cyproflanilide derivatives containing 1,2,4-oxadiazole group were designed and synthesized according to the principle of biologically active factor splicing. Preliminary biological assay data indicated that the majority of target compounds demonstrated significant insecticidal activity against Lepidopteran pests. Meanwhile, compounds **5p** and **5q** showed 97.22 and 100% lethality against *Tetranychus cinnabarinus* at 400 mg L^{-1}, which were better than cyproflanilide (41.11% at 400 mg L^{-1}). In addition, it is exciting that we have achieved our initial goals as some of the target compounds exhibited both insecticidal and fungicidal activities. For instance, compounds **5b** and **5c** showed 59.26 and 74.07% fungicidal activities against *Cucumber downy mildew* at 400 mg L^{-1}, as well as 100% insecticidal activity against *Plutella xylostella* and armyworm at 100 mg L^{-1}. Compound **5h** showed 100% insecticidal activity against armyworm at 10 mg L^{-1}, and also displayed 66.67% fungicidal activity against *Cucumber downy mildew* at 400 mg L^{-1}. The inhibition rate of compounds **5l** and **5s** against *Cucumber downy mildew* reached 88.89 and 96.30% at 400 mg L^{-1}. This work showed the effectively fungicidal application of 1,2,4-oxadiazole group in bisamide compounds and provides insights for optimal structural design.

Keywords: 1,2,4-oxadiazole group, insecticidal activity, fungicidal activity, *meta*-diamide compounds, structure-activity relationship

Introduction

Pesticides play a particularly important role in the modern agriculture.[1-3] However, long-term widespread and irrational use of pesticides brought increasing resistance and environment damage.[4] Therefore, it is essential to discover new pesticides with novel structures and insecticidal mechanism.[5]

Diamide insecticides, especially *meta*-diamide (structures labeled in red in Figure 1) compounds represented by broflanilide (**3**; Figure 1), because of their novel insecticidal mechanism and excellent efficacy, have become a research hotspot in recent years.[6-10] Based on broflanilide, many *meta*-diamide insecticides were invented such as cyproflanilide (**4**; Figure 1).[11-13] They all have broad-spectrum, highly-efficiency and no cross-resistance with traditional diamide insecticides such as flubendiamide (**1**; Figure 1) and chlorantraniliprole (**2**; Figure 1).[14,15] In particular, they both showed excellent insecticidal activity against Lepidoptera pests and can become a valuable tool in insecticide resistance management (IRM). However, the fungicidal activities of these compounds are rarely reported.

1,2,4-Oxadiazole group as a member of the five-membered heterocyclic rings, due to their antidiabetes,[16] antitumor,[17-19] insecticidal,[20-25] fungicidal,[26] bactericidal,[27,28] herbicidal,[29] and other activities have attracted more and more attention in the medicine and pesticide field. Many 1,2,4-oxadiazole derivatives have been developed and commercialized, such as oxolamine, pleconaril and tioxazafen (Figure 2). Especially, flufenoxadiazam has a unique histone deacetylase (HDACs) sterilization mechanism and no cross-resistance with other fungicides.[30] It is an ideal choice for the development of new fungicides.

Inspired by the view above, to add the development of new *meta*-diamide compounds with fungicidal activities

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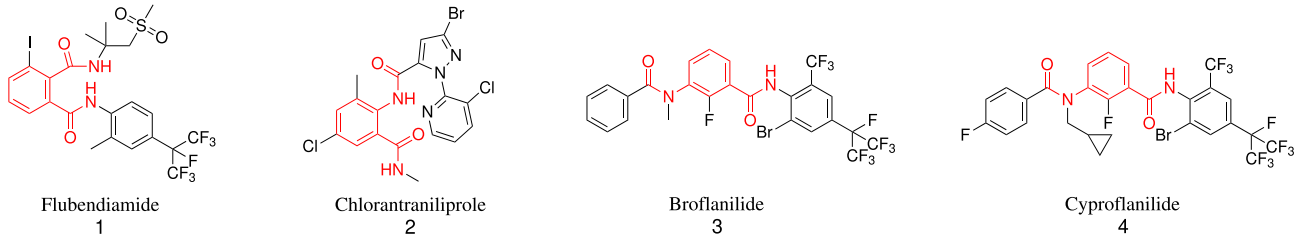


Figure 1. Chemical structures of diamide insecticides.

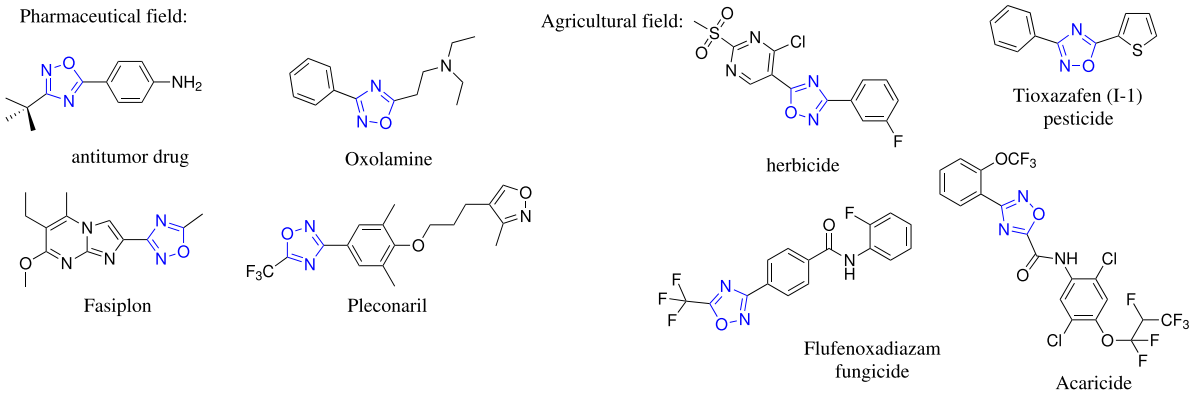


Figure 2. 1,2,4-Oxadiazole derivatives with different biological activities.

and continue our previous works,[31-33] this study introduced 1,2,4-oxadiazole group into the structure of cyproflanilide and discussed the effect of different substituted anilines on activity. A series of novel *meta*-diamide compounds with 1,2,4-oxadiazole group were designed and synthesized (Figure 3). Their bioactivities against *Plutella xylostella*, armyworm, *Tetranychus cinnabarinus* and *Cucumber downy mildew* were also tested accordingly and the preliminary structure-activity relationships were discussed. The present work provides some basis and direction for subsequent studies.

Experimental

Materials and methods

All reagents and solvents used in the work were purchased from Shanghai Macklin Biochemical Technology Co., Ltd (Shanghai, China), Bide Pharmatech Ltd (Shanghai, China) and Shanghai Aladdin Biochemical Technology Co., Ltd (Shanghai, China). All solvents and liquid reagents were dried by standard methods in advance and distilled before use. ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR were recorded at 400 and

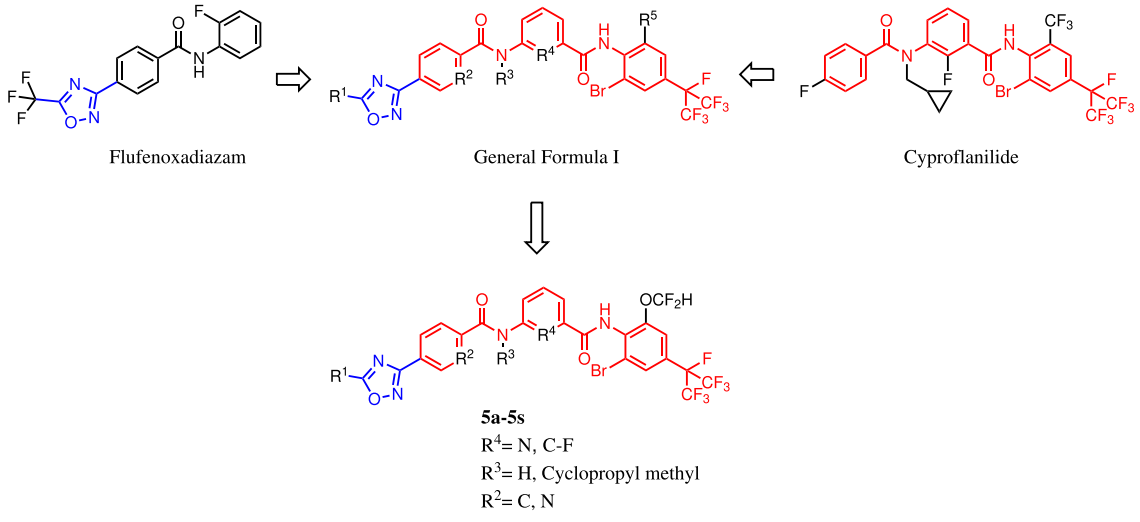


Figure 3. Design strategy of the target compounds.

100 MHz, respectively, using a Bruker AV400 spectrometer (Bruker Co., Fallanden, Switzerland) in dimethyl sulfoxide (DMSO-d_6) solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts *per* million (ppm). The multiplicity is indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quarlet), dd (double of doublets), td (doublet of triplets), m (multiplet). All coupling constants (*J* values) were given in Hz. Mass spectra were obtained with an Agilent 1100 LC-MSD-Trap mass spectrometer (California, USA) equipped with standard electrospray ionization (ESI) apparatus. The thin-layer chromatography (TLC) analyses were performed on 0.25 mm silica gel plates (GF254) and visualized with a ZF-20D ultraviolet (Shanghai, China). Flash column chromatographic separations were carried out on silica gel (200-300 mesh) using ethyl acetate and hexane as eluents and Agela Technologies AS-204P which was purchased from Tianjin Bonna-Agela Technologies Co., Ltd (Tianjin, China), flow rate 30 mL min^{-1}. The melting points were measured using Hanon instruments MP430 video melting point apparatus which was purchased from Hanon Group (Jinan, China), temperature range: 40-200 °C. Each reaction was stirred in a ZNCL-TS-HT17 (100 mL) intelligent magnetic stirrer which was purchased from Aibote Henan Science and Technology Development Co., Ltd (Zhengzhou, China).

Synthesis

2-(Difluoromethoxy)-4-(perfluoropropan-2-yl) aniline was used as the starting material.. The target compounds **5a-5s** were obtained in 23 to 97% yields through multi-step reactions. The structures of the target compounds were identified by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry (HRMS). The details for all the target compounds **5a-5s** were listed below. The synthetic route is outlined in Scheme 1.

General synthesis procedure for intermediates **6-12**

The intermediates **6-11** were synthesized according to the literature procedure.[34]

General synthesis procedure for intermediate **12**

To the solution of intermediate **11** (2.04 g, 2.81 mmol) in ethanol absolute (21 mL) it was added triethylamine (0.64 g, 6.32 mmol) and hydroxylamine hydrochloride (0.29 g, 4.21 mmol) in turn, the reaction mixture was stirred at 90 °C for 4 h. After the reaction was completed, the reaction solution was quenched with water and extracted with ethyl acetate. The combined organic phases were dried with sodium sulfate, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography to obtain intermediate **12**. The eluent was hexane:ethyl acetate = 1.5:1.

The synthesis procedure of intermediate **14** was the same as that of **12**. The structure of intermediates **12** and **14** were confirmed by ^{1}H NMR and HRMS, and detailed information was summarized in the Supplementary Information (SI) section.

General synthesis procedure for compounds **5a-5s**

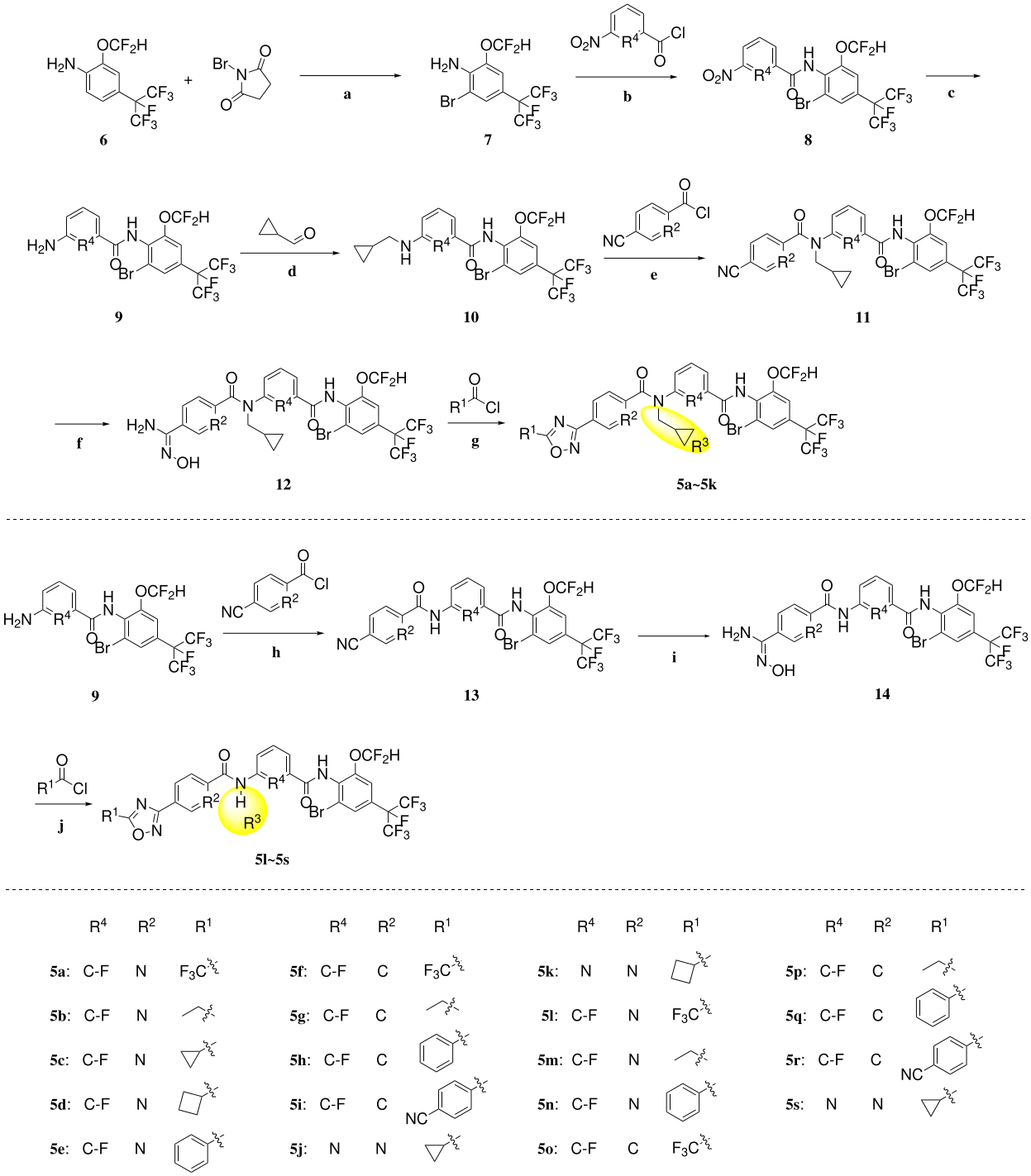
The general synthesis procedure for compound **5i** was: to the solution of intermediate **12** (0.30 g, 0.40 mmol, 1.0 eq) in *N*,*N*-dimethylformamide (4 mL), it was added triethylamine (0.16 g, 1.58 mmol, 4.0 eq) and 4-cyanobenzoylchloride (0.078 g, 0.47 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for 1 h and heated to reflux for 4 h. After completion of the reaction, the reaction mixture was adjusted by aqueous solution of saturated sodium bicarbonate to pH = 8 and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography to obtain compound **5i**. The eluent was hexane:ethyl acetate = 1:1.

The synthesis procedure of compounds **5a-5h**, **5j-5s** was the same as that of **5i**.

Insecticidal assay

All biological assays were performed on test organisms reared in a greenhouse. The bioassay was replicated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected by applying Abbott's formula.[35] Error of the experiments was 5%. The insecticidal activity of compounds **5a-5s** against *Plutella xylostella* and armyworm were tested according to the leaf-dip method using the reported procedure.[36] The insecticidal activity of some title compounds against *Tetranychus cinnabarinus* was tested according to the reported immersion method.[37] For comparative purposes, the cyproflanilide was tested as positive control under the same conditions.

The insecticidal activities test of *meta*-diamide compounds: *Plutella xylostella*, armyworm and *Tetranychus cinnabarinus* were provided by Shanghai International Trading Co., Ltd. for indoor continuous feeding of 3rd instar larvae. The target substance (10 mg) was weighed, dissolved with dimethylformamide (DMF) (1 mL) to prepare 10000 mg L^{-1} mother liquor, then diluted with 0.05% warm water to prepare the required concentration of solution.



	R4	R2	R1		R4	R2	R1		R4	R2	R1		R4	R2	R1
5a:	C-F	N	F_3C	**5f**:	C-F	C	F_3C	**5k**:	N	N		**5p**:	C-F	C	
5b:	C-F	N		**5g**:	C-F	C		**5l**:	C-F	N	F_3C	**5q**:	C-F	C	
5c:	C-F	N		**5h**:	C-F	C		**5m**:	C-F	N		**5r**:	C-F	C	NC
5d:	C-F	N		**5i**:	C-F	C	NC	**5n**:	C-F	N		**5s**:	N	N	
5e:	C-F	N		**5j**:	N	N		**5o**:	C-F	C	F_3C				

Scheme 1. General synthetic procedure for target compounds **5a-5s**. (a) Dimethylformamide (DMF), 60 °C, 2 h, (yield 68%); (b) KI, acetonitrile, 90 °C, 4 h, (yield 69-81%); (c) Fe, NH_4Cl, EtOH, H_2O, 95 °C, 2 h, (yield 87-96%); (d) $NaBH(AcO)_3$, AcOH, DCE, RT, 4 h, (yield 65-77%); (e) pyridine, toluene, 120 °C 4 h, (yield 72-90%); (f) $NH_2OH{\cdot}Cl$, Et_3N, EtOH, 90 °C, 2 h, (yield 53-87%); (g) DMF, Et_3N, 100 °C, 4 h, (yield 23-97%); (h) pyridine, toluene, 120 °C, 4 h (yield 86%); (i) $NH_2OH{\cdot}Cl$, Et_3N, EtOH, 90 °C, 2 h, (yield 44-68%); (j) DMF, Et_3N, 100 °C, 4 h, (yield 23-97%).

Insecticidal activity of *Plutella xylostella* and armyworm were tested. The activity was tested by leaf soaking dish feeding method. The leaf plate was immersed in the solution for 10 s, dried in the Petri dish, 4 plates for each dish. Then, filter paper was placed in the Petri dish to moisturize. The test insects of 10 *Plutella xylostella* were connected to each dish and repeated 3 times. They were placed in the light incubator (temperature: 25 °C, light: 14 h). The number of dead moths of *Plutella xylostella* were investigated for 1, 2 and 3 days after treatment, and the mortality was calculated. The test method of armyworm was the same as that of *Plutella xylostella*.

Insecticidal activity of *Tetranychus cinnabarinus* was tested. The activity test was carried out by immersion method. The leaves with nymphs were immersed in the drug solution for 10 s and inserted into a penicillin bottle filled with clean water, sealed, dried, and covered with a transparent plastic cup. 15-30 *Tetranychus cinnabarinus* were placed on each leaf, and the experiment was repeated 3 times. During drug soaking, the same drug was carried out successively from low concentration to high concentration with blank control and solvent control. After treatment, it was placed in the observation in an indoor room (temperature: 19-26 °C, humidity: 35-65%, light: 14 h).

The insecticidal test results of compounds **5a-5s** against *Plutella xylostella*, armyworm and *Tetranychus cinnabarinus* were listed in Table 1.

Fungicidal assay

Each of the test compounds (4 mg) was first dissolved in 5 mL of acetone/methanol (1:1, v v^{-1}) and then 5 mL of water containing 0.1% Tween 80 was added to generate a 10 mL stock solution of concentration 400 mg L^{-1}. Serial test solutions were prepared by diluting the above solution (testing range 3.13-400 mg L^{-1}).

Evaluations of fungicidal activity of the synthesized compounds against *Cucumber downy mildew* were performed as follows: cucumber seeds (*Cucumis sativus* L.) were grown to the one-leaf and one-heart stage and then the test solution was sprayed on the host plant with a homemade sprayer. After 24 h, the leaf of the host plant was inoculated with sporangium suspension of fungus *Pseudoperonospora cubensis* cultured by Shenyang Sinochem Agrochemicals R&D Co., Ltd. (Shenyang, China) at a concentration of 5×10^5 spores mL^{-1} using a PS289 Procon Boy WA double-action 0.3 mm airbrush (GSI, Tokyo, Japan). The cucumber plants were stored in a humidity chamber (24 ± 1 °C, relative humidity (RH) > 95%, dark) and then transferred into a greenhouse (18-30 °C, RH > 50-60%) for 24 h after infection. Three replicates were carried out. The activity of each compound was estimated by visual inspection after 7 days, and screening results were reported in the range from 0% (no control) to 100% (complete control). The inhibitory activity (%) was estimated as [(viability of the blank control – viability of the treatment)/ viability of the blank control] × 100. The fungicidal test results of compounds **5a-5s** against *Cucumber downy mildew* were also listed in Table 1.

Compounds **8**-**11**

The yield data of intermediates **8-11** were listed by the data present below.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-2-fluoro-3-nitrobenzamide (**8a**)

Yield 81%; yellow solid; purity 96.33%.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-6-nitropicolinamide (**8b**)

Yield 69%; yellow solid; purity 95.00%.

3-Amino-*N*-(2-bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-2-fluorobenzamide (**9a**)

Yield 96%; brown liquid; purity 98.36%.

6-Amino-*N*-(2-bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)picolinamide (**9b**)

Yield 87%; brown liquid; purity 92.50%.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-3-((cyclopropylmethyl)amino)-2-fluorobenzamide (**10a**)

Yield 65%; brown liquid; purity 92.77%.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-6-((cyclopropylmethyl)amino)picolinamide(**10b**)

Yield 77%; brown liquid; purity 95.45%.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-cyano-*N*-(cyclopropylmethyl)picolinamide (**11a**)

Yield 90%; yellow solid; purity 96.29%.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-3-(4-cyano-*N*-(cyclopropylmethyl)benzamido)-2-fluorobenzamide (**11b**)

Yield 86%; yellow solid; purity 94.43%.

N-(6-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)pyridin-2-yl)-5-cyano-*N*-(cyclopropylmethyl)picolinamide (**11c**)

Yield 72%; yellow solid; purity 97.25%.

Compounds **5a**-**5s**

The structure of compounds **5a-5s** were confirmed by the data present below.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl) picolinamide (**5a**)

Yield 87%; yellow green solid; mp 121.6-122.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.85 (s,

1H), 8.48-8.43 (m, 1H), 7.89 (d, *J* 7.6 Hz, 2H), 7.59-7.52 (m, 3H), 7.31 (t, *J* 72.0 Hz, 1H), 7.24 (t, *J* 8.0 Hz, 1H), 3.93 (dd, *J* 14.0, 6.7 Hz, 1H), 3.63 (dd, *J* 13.6, 7.0 Hz, 1H), 1.08 (s, 1H), 0.46 (d, *J* 7.6 Hz, 2H), 0.22-0.15 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.40, 166.70, 165.61, 162.60, 156.80, 146.73, 136.43, 133.99, 132.78, 131.29, 129.56, 126.76, 126.69, 126.56, 126.35, 126.10, 124.87, 124.60, 124.04, 123.89, 121.94, 121.85, 116.76, 116.40, 116.29, 114.82, 53.42, 9.87, 4.17, 3.60; HRMS (ESI) *m/z*, calcd. for $C_{30}H_{17}BrF_{13}N_5O_4$ $[M + H]^+$: 838.0256, found: 838.0153.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)picolinamide (**5b**)

Yield 51%; yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.78 (d, *J* 10.8 Hz, 1H), 8.36 (d, *J* 8.4 Hz, 1H), 7.89 (s, 1H), 7.84 (d, *J* 8.0 Hz, 1H), 7.56-7.51 (m, 3H), 7.31 (t, *J* 72.0 Hz, 1H), 7.24 (t, *J* 7.6 Hz, 1H), 4.03 (q, *J* 7.2 Hz, 1H), 3.91 (dd, *J* 14.0, 7.2 Hz, 1H), 3.00 (d, *J* 7.6 Hz, 2H), 1.30 (d, *J* 6.4 Hz, 3H), 1.17 (t, *J* 7.2 Hz, 1H), 0.45 (d, *J* 7.6 Hz, 2H), 0.18 (d, *J* 4.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.37, 167.57, 165.67, 155.91, 149.29, 146.36, 135.83, 133.89, 132.81, 131.47, 129.41, 126.69, 126.55, 126.33, 126.09, 124.83, 124.49, 123.99, 123.45, 119.36, 116.76, 116.45, 53.43, 31.63, 30.31, 29.53, 20.08, 10.84, 9.90, 4.15, 3.62; HRMS (ESI) *m/z*, calcd. for $C_{31}H_{22}BrF_{10}N_5O_4$ $[M + H]^+$: 798.0695, found: 798.0603.

N-3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-*N*-(cyclopropylmethyl) picolinamide (**5c**)

Yield 24%; yellow liquid; mp none; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.75-8.71 (m, 1H), 8.32 (dd, *J* 8.0, 1.8 Hz, 1H), 7.90 (s, 1H), 7.83 (d, *J* 8.0 Hz, 1H), 7.57-7.51 (m, 3H), 7.31 (t, *J* 72.0 Hz, 1H), 7.24 (t, *J* 7.6 Hz, 1H), 3.91 (dd, *J* 14.0, 7.2 Hz, 1H), 3.63 (dd, *J* 13.6, 7.6 Hz, 1H), 2.40 (s, 1H), 1.23 (s, 2H), 1.17 (s, 2H), 0.99 (t, *J* 7.2 Hz, 1H), 0.45 (d, *J* 7.2 Hz, 2H), 0.18 (d, *J* 4.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.99, 167.55, 165.67, 162.60, 155.87, 149.31, 146.35, 135.81, 133.89, 132.81, 131.51, 129.41, 126.67, 126.56, 126.34, 126.06, 124.81, 124.45, 123.42, 119.35, 116.76, 116.45, 116.34, 114.16, 55.40, 53.46, 29.53, 10.75, 9.89, 7.71, 4.13, 3.60; HRMS (ESI) *m/z*, calcd. for $C_{32}H_{22}BrF_{10}N_5O_4$ $[M + H]^+$: 810.0695, found: 810.0601.

N-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-*N*-(cyclopropylmethyl)picolinamide (**5d**)

Yield 82%; yellow solid; mp 59.8-60.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.80-8.76 (m, 1H), 8.38 (d, *J* 1.6 Hz, 1H), 8.36 (d, *J* 2.0 Hz, 1H), 7.89 (s, 1H), 7.84 (d, *J* 8.4 Hz, 1H), 7.54 (d, *J* 11.2 Hz, 3H), 7.31 (t, *J* 72.0 Hz, 1H), 3.69-3.55 (m, 2H), 3.00 (d, *J* 0.8 Hz, 1H), 2.10 (s, 2H), 1.87 (s, 2H), 1.79 (s, 2H), 1.07 (s, 1H), 0.45 (d, *J* 6.8 Hz, 2H), 0.18 (d, *J* 4.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.37, 167.56, 165.70, 155.89, 149.31, 146.38, 135.85, 133.89, 132.81, 131.63, 129.41, 126.67, 126.54, 126.06, 124.85, 124.47, 123.48, 116.75, 116.44, 116.32, 55.41, 53.44, 31.62, 30.99, 30.30, 29.53, 27.03, 24.99, 18.77, 9.90, 4.14, 3.62; HRMS (ESI) *m/z,* calcd. for $C_{32}H_{24}BrF_{10}N_5O_4$ $[M + H]^+$: 824.0852, found: 824.0765.

N-3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)carbamoyl)-2-fluorophenyl)-*N*-(cyclopropylmethyl)-5-(5-phenyl-1,2,4-oxadiazol-3-yl)picolinamide (**5e**)

Yield 97%; yellow solid; mp 139.2-140.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.88 (s, 1H), 8.49-8.47 (m, 1H), 8.47-8.44 (m, 1H), 8.18 (d, *J* 7.6 Hz, 3H), 7.90 (d, *J* 5.2 Hz, 3H), 7.66 (s, 2H), 7.52 (s, 2H), 7.31 (t, *J* 72.0 Hz, 1H), 3.97-3.90 (m, 2H), 1.29 (s, 1H), 0.46 (d, *J* 7.2 Hz, 2H), 0.20-0.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.39, 167.55, 166.46, 156.07, 149.32, 146.53, 136.00, 134.14, 133.92, 132.81, 130.12, 129.44, 128.86, 128.53, 126.69, 126.53, 126.33, 126.06, 124.88, 124.56, 123.89, 123.53, 123.34, 116.77, 116.38, 60.25, 55.41, 53.49, 31.62, 30.30, 29.53, 14.57, 9.90, 4.16, 3.62; HRMS (ESI) *m/z*, calcd. for $C_{35}H_{22}BrF_{10}N_5O_4$ $[M + H]^+$: 846.0695, found: 846.0599.

N-2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-3-(*N*-(cyclopropylmethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)-2-fluorobenzamide (**5f**)

Yield 84%; white solid; mp 152.5-152.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.02-7.83 (m, 3H), 7.77-7.60 (m, 2H), 7.53 (s, 4H), 7.31 (t, *J* 72.0 Hz, 1H), 3.75 (d, *J* 37.2 Hz, 2H), 1.10 - 1.01 (m, 1H), 0.44 (d, *J* 7.2 Hz, 2H), 0.19-0.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.55, 168.29, 166.45, 165.40, 156.57, 149.30, 140.08, 134.21, 132.75, 130.86, 129.81, 129.00, 128.17, 127.50, 126.68, 126.59, 126.38, 126.07, 125.84, 125.32, 124.29, 119.34, 117.57, 116.74, 116.43, 114.85, 114.15, 53.44, 9.89, 3.99, 3.64; HRMS (ESI) *m/z*, calcd. for $C_{31}H_{18}BrClF_{13}N_4O_4$ $[M + H]^+$: 837.0304, found: 837.0191.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-3-(*N*-(cyclopropylmethyl)-4-(5-ethyl-1,2,4-oxadiazol-3-yl)benzamido)-2-fluorobenzamide (**5g**)

Yield 73%; white solid; mp 149.8-150.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.87 (d, *J* 21.2 Hz,

3H), 7.66 (s, 2H), 7.49 (d, *J* 26.8 Hz, 4H), 7.34-7.28 (t, *J* 72.0 Hz, 1H), 3.73 (d, *J* 37.6 Hz, 2H), 3.02-2.93 (m, 2H), 1.29 (s, 3H), 1.04 (s, 1H), 0.48-0.36 (m, 2H), 0.21-0.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.96, 167.33, 149.25, 139.00, 134.11, 132.80, 132.77, 129.68, 129.31, 128.78, 127.78, 127.02, 126.57, 126.36, 126.07, 125.28, 124.31, 124.18, 123.10, 121.65, 119.33, 119.09, 117.35, 116.74, 116.45, 53.46, 29.53, 20.06, 10.90, 9.89, 4.00, 3.67; HRMS (ESI) *m/z*, calcd. for $C_{32}H_{23}BrF_{10}N_4O_4$ $[M + H]^+$: 797.0743, found: 797.0651.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-3-(*N*-(cyclopropylmethyl)-4-(5-phenyl-1,2,4-oxadiazol-3-yl)benzamido)-2-fluorobenzamide (**5h**)

Yield 46%; yellow solid; mp 64.9-65.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.17 (d, *J* 7.6 Hz, 2H), 7.92 (d, *J* 22.8 Hz, 3H), 7.70 (dt, *J* 32.0, 7.4 Hz, 5H), 7.52 (s, 4H), 7.31 (t, *J* 72.0 Hz, 1H), 3.75 (d, *J* 38.8 Hz, 2H), 1.06 (s, 1H), 0.44 (d, *J* 7.2 Hz, 2H), 0.15 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.09, 169.71, 168.13, 149.25, 139.22, 134.15, 133.97, 132.77, 130.09, 129.79, 129.71, 128.86, 128.75, 128.44, 127.60, 127.38, 127.19, 126.69, 126.57, 126.35, 126.06, 125.27, 124.22, 123.74, 121.65, 119.35, 116.75, 114.15, 107.71, 53.47, 29.54, 9.92, 4.00, 3.66; HRMS (ESI) *m/z*, calcd. for $C_{36}H_{23}BrF_{10}N_4O_4$ $[M + H]^+$: 845.0743, found: 845.0651.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl) phenyl)-3-(4-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(cyclopropylmethyl)benzamido)-2-fluorobenzamide (**5i**)

Yield 58%; white solid; mp 164.1-165.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.32 (d, *J* 8.0 Hz, 2H), 8.13 (d, *J* 8.4 Hz, 2H), 8.08 (d, *J* 8.4 Hz, 1H), 7.98 (d, *J* 8.4 Hz, 2H), 7.89 (s, 1H), 7.72-7.66 (m, 1H), 7.52 (s, 4H), 7.31 (t, *J* 72.0 Hz, 1H), 3.75 (d, *J* 40.0 Hz, 2H), 1.06 (s, 1H), 0.44 (d, *J* 7.2 Hz, 2H), 0.19-0.08 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.77, 172.83, 169.68, 168.35, 166.57, 149.26, 139.39, 135.33, 133.98, 133.18, 132.75, 130.43, 129.73, 129.18, 128.90, 127.59, 127.26, 126.70, 126.57, 126.36, 126.06, 125.31, 124.34, 121.65, 119.35, 118.70, 118.42, 116.75, 116.44, 116.32, 115.96, 115.59, 114.15, 53.45, 9.93, 3.99, 3.68; HRMS (ESI) *m/z*, calcd. for $C_{37}H_{22}BrF_{10}N_5O_4$ $[M + H]^+$: 870.0695, found: 870.0610.

N-(6-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)pyridin-2-yl)-5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-*N*-(cyclopropylmethyl)picolinamide (**5j**)

Yield 37%; yellow solid; mp 146.5-147.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.74 - 8.69 (m, 1H), 8.38 (dd, *J* 8.2, 2.1 Hz, 1H), 8.00 (d, *J* 8.2 Hz, 1H), 7.94 (t, *J* 7.8 Hz, 1H), 7.89 (s, 1H), 7.86-7.83 (m, 1H), 7.51 (d, *J* 8.9 Hz, 2H),7.26(t, *J* 72.0 Hz ,1H), 4.11 (d, *J* 7.0 Hz, 2H), 2.43-2.38 (m, 1H), 1.31 - 1.28 (m, 2H), 1.18 (d, *J* 4.4 Hz, 2H), 1.15 (d, *J* 7.0 Hz, 1H), 0.43 - 0.38 (m, 2H), 0.21 (d, *J* 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.96, 168.54, 168.07, 165.74, 162.58, 156.17, 155.04, 149.36, 147.31, 146.25, 140.29, 136.19, 133.07, 126.19, 125.42, 124.35, 123.67, 120.16, 116.71, 60.24, 55.40, 52.09, 31.61, 30.39, 29.51, 21.23, 14.56, 10.75, 10.63, 7.70, 4.04; HRMS (ESI) *m/z*, calcd. for $C_{31}H_{22}BrF_9N_6O_4$ $[M + H]^+$: 793.0742, found: 793.0394.

N-(6-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)pyridin-2-yl)-5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-*N*-(cyclopropylmethyl)picolinamide (**5k**)

Yield 23%; yellow solid; mp 110.5-111.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.80-8.73 (m, 1H), 8.43 (dd, *J* 8.0, 2.0 Hz, 1H), 8.02 (d, *J* 8.0 Hz, 1H), 7.95 (t, *J* 7.6 Hz, 1H), 7.90-7.87 (m, 1H), 7.85 (d, *J* 7.2 Hz, 1H), 7.55-7.48 (m, 2H), 7.26 (t, *J* 72.0 Hz, 1H), 4.11 (d, *J* 6.8 Hz, 2H), 2.45 - 2.37 (m, 3H), 2.09 (td, *J* 8.8, 2.0 Hz, 1H), 1.98 (t, *J* 9.6 Hz, 1H), 1.31 (d, *J* 15.2 Hz, 3H), 0.41 (dd, *J* 6.8, 2.4 Hz, 2H), 0.22 (d, *J* 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.33, 172.51, 170.80, 168.56, 165.79, 162.58, 156.22, 155.06, 149.34, 147.34, 146.30, 140.27, 136.20, 133.09, 126.41, 125.43, 124.35, 123.75, 120.15, 116.72, 116.23, 114.13, 60.23, 55.38, 52.10, 31.02, 27.05, 24.98, 18.78, 14.53, 10.63, 4.03; HRMS (ESI) *m/z*, calcd. for $C_{32}H_{24}BrF_9N_6O_4$ $[M + H]^+$: 807.0899, found: 807.0808.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)picolinamide (**5l**)

Yield 76%; yellow liquid; mp none; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 10.53 (s, 1H), 9.39 (dd, *J* 2.0, 0.8 Hz, 1H), 8.75 (dd, *J* 8.4, 2.0 Hz, 1H), 8.44-8.39 (m, 1H), 8.25-8.18 (m, 1H), 7.95-7.91 (m, 1H), 7.59-7.53 (m, 2H), 7.44 (t, *J* 8.0 Hz, 1H), 7.39 (t, *J* 72.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.84, 165.81, 162.99, 162.10, 153.41, 152.16, 150.89, 149.29, 147.58, 137.90, 132.83, 127.43, 126.73, 126.33, 126.10, 125.04, 124.41, 124.05, 123.64, 121.96, 121.70, 119.40, 116.81, 116.29, 114.84, 114.21; HRMS (ESI) *m/z*, calcd. for $C_{26}H_{11}BrF_{13}N_5O_4$ $[M + H]^+$: 783.9787, found: 783.9632.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)picolinamide (**5m**)

Yield 63%; yellow solid; mp 135.9-136.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 10.53 (s, 1H), 9.31

(s, 1H), 8.65 (dd, *J* 8.2 2.0 Hz, 1H), 8.37 (d, *J* 8.2 Hz, 1H), 8.21 (t, *J* 7.2 Hz, 1H), 7.93 (s, 1H), 7.55 (d, *J* 6.8 Hz, 2H), 7.43 (t, *J* 8.0 Hz, 1H), 7.39 (t, *J* 72.0 Hz, 1H), 3.08 (q, *J* 7.6 Hz, 2H), 1.38 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.16, 163.01, 162.38, 154.53, 153.22, 150.63, 149.28, 147.24, 137.15, 132.85, 131.29, 127.11, 126.77, 126.54, 126.32, 126.09, 125.05, 124.13, 123.99, 122.66, 121.69, 119.40, 116.81, 116.41, 114.21, 26.23, 9.59; HRMS (ESI) *m/z*, calcd. for $C_{27}H_{16}BrF_{10}N_5O_4$ $[M + H]^+$: 744.0226, found: 744.0117.

N-(3-((2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)carbamoyl)-2-fluorophenyl)-5-(5-phenyl-1,2,4-oxadiazol-3-yl)picolinamide (**5n**)

Yield 23%; white solid; mp 140.8-141.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 10.54 (s, 1H), 9.41 (dd, *J* 2.0, 0.8 Hz, 1H), 8.74 (dd, *J* 8.4, 2.0 Hz, 1H), 8.41 (dd, *J* 8.4, 0.8 Hz, 1H), 8.27-8.20 (m, 3H), 7.95-7.91 (m, 1H), 7.80-7.75 (m, 1H), 7.73-7.67 (m, 2H), 7.56 (d, *J* 6.4 Hz, 2H), 7.44 (t, *J* 8.0 Hz, 1H), 7.39 (t, *J* 72.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.59, 178.81, 176.56, 172.11, 166.52, 163.02, 162.17, 153.23, 151.44, 149.34, 147.36, 142.92, 137.41, 134.21, 132.84, 130.15, 129.08, 128.56, 127.15, 126.79, 126.70, 126.55, 126.10, 125.04, 124.78, 124.13, 124.00, 123.49, 116.81, 116.41, 114.21; HRMS (ESI) *m/z*, calcd. for $C_{31}H_{16}BrF_{10}N_5O_4$ $[M + H]^+$: 792.0226, found: 792.0137.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-2-fluoro-3-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzamido)benzamide (**5o**)

Yield 98%; white solid; mp 146.3-147.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59-10.45 (m, 2H), 8.28-8.17 (m, 4H), 7.94-7.80 (m, 2H), 7.56 (s, 2H), 7.42 (d, *J* 8.0 Hz, 1H), 7.38 (t, *J* 72.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.43, 165.29, 163.18, 154.81, 152.28, 149.31, 137.66, 132.86, 130.40, 129.54, 128.09, 127.91, 127.13, 126.88, 126.70, 126.53, 126.32, 126.13, 124.76, 124.49, 121.95, 119.41, 117.63, 116.81, 116.27, 114.92, 114.22; HRMS (ESI) *m/z*, calcd. for $C_{27}H_{12}BrF_{13}N_4O_4$ $[M + H]^+$: 782.9834, found: 782.9876.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-3-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)benzamido)-2-fluorobenzamide (**5p**)

Yield 52%; white solid; mp 162.3-163.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* 5.2 Hz, 2H), 8.18 (s, 4H), 7.94 - 7.90 (m, 1H), 7.88-7.82 (m, 1H), 7.56 (s, 2H), 7.41 (t, *J* 8.0 Hz, 1H), 7.38 (t, *J* 72.0 Hz, 1H), 3.05 (q, *J* 7.6 Hz, 2H), 1.37 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.14, 167.47, 165.45, 163.19, 154.82, 152.29, 149.34, 136.69, 132.87, 130.42, 129.87, 129.29, 127.60, 127.06, 126.97, 126.85, 126.69, 126.53, 126.31, 126.14, 124.74, 119.41, 116.81, 116.39, 116.28, 114.22, 20.15, 10.93; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{17}BrF_{10}N_4O_4$ $[M + H]^+$: 743.0273, found: 743.0168.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-2-fluoro-3-(4-(5-phenyl-1,2,4-oxadiazol-3-yl)benzamido)benzamide (**5q**)

Yield 71%; yellow solid; mp 196.1-197.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55-10.51 (m, 2H), 8.28 (d, *J* 8.8 Hz, 2H), 8.24 (s, 3H), 8.22 (d, *J* 1.6 Hz, 2H), 7.89-7.83 (m, 1H), 7.79-7.74 (m, 1H), 7.69 (dd, *J* 8.0, 6.8 Hz, 2H), 7.60 (d, *J* 6.0 Hz, 1H), 7.56 (s, 1H), 7.45-7.41 (m, 1H), 7.39 (t, *J* 72.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.27, 168.25, 165.44, 163.20, 154.83, 152.30, 149.35, 146.12, 136.88, 134.02, 132.88, 131.94, 130.44, 130.13, 129.68, 129.34, 128.87, 128.51, 127.77, 127.09, 126.97, 126.53, 126.31, 126.14, 124.75, 124.34, 123.78, 121.96, 119.42, 116.82, 116.38, 116.29; HRMS (ESI) *m/z*, calcd. for $C_{32}H_{17}BrF_{10}N_4O_4$ $[M + H]^+$: 791.0273, found: 791.0173.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-3-(4-(5-(4-cyanophenyl)-1,2,4-oxadiazol-3-yl)benzamido)-2-fluorobenzamide (**5r**)

Yield 23%; white solid; mp > 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (d, *J* 6.8 Hz, 2H), 8.41-8.37 (m, 2H), 8.29 (d, *J* 8.4 Hz, 2H), 8.23 (d, *J* 8.8 Hz, 2H), 8.19-8.14 (m, 2H), 7.94 - 7.91 (m, 1H), 7.89-7.83 (m, 1H), 7.63-7.58 (m, 1H), 7.57-7.55 (m, 1H), 7.42 (t, *J* 8.0 Hz, 1H), 7.38 (t, *J* 72.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.94, 168.47, 165.39, 163.19, 154.82, 152.29, 149.34, 137.02, 134.00, 132.87, 130.43, 129.38, 129.25, 127.80, 127.62, 127.08, 126.95, 126.82, 126.68, 126.60, 126.53, 126.32, 126.14, 124.76, 124.47, 124.33, 119.41, 118.44, 116.82, 116.38, 116.27, 115.98, 114.22; HRMS (ESI) *m/z*, calcd. for $C_{33}H_{16}BrF_{10}N_5O_4$ $[M + H]^+$: 816.0226, found: 816.0143.

N-(2-Bromo-6-(difluoromethoxy)-4-(perfluoropropan-2-yl)phenyl)-6-(5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)picolinamido)picolinamide (**5s**)

Yield 24%; white solid; mp 108.9-109.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 10.70 (s, 1H), 9.02 (d, *J* 1.2 Hz, 1H), 8.60 (d, *J* 8.4 Hz, 1H), 8.42 (dd, *J* 8.0, 2.0 Hz, 1H), 8.35 (d, *J* 8.4 Hz, 1H), 8.18 (t, *J* 8.0 Hz, 1H), 7.93 (s, 1H), 7.56 (d, *J* 2.0 Hz, 1H), 7.37 (t, *J* 72.0 Hz, 1H), 7.18 (s, 1H), 2.51 (d, *J* 1.6 Hz, 1H), 1.17 (t, *J* 7.2 Hz, 1H), 1.11 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.15, 165.68, 162.96, 162.20, 150.82, 150.20, 149.43, 147.79, 147.09, 141.22, 137.48, 133.23, 126.51, 126.44,

126.31, 126.23, 123.66, 119.34, 119.15, 117.34, 116.74, 116.10, 60.27, 21.25, 14.57, 10.86, 7.83; HRMS (ESI) *m/z*, calcd. for $C_{27}H_{16}BrF_9N_6O_4$ $[M + H]^+$: 739.0273, found: 739.0169.

Results and Discussion

The biological activities of the target compounds **5a-5s** against *Plutella xylostella*, armyworm, *Tetranychus cinnabarinus* and *Cucumber downy mildew* are presented in Table 1. Most of the title compounds demonstrated significant insecticidal activity against Lepidoptera pests at 100 mg L^{-1}. Especially, compound **5i** showed a mortality rate of 96.67% against armyworm when the concentration was reduced to 1 mg L^{-1}, which was very close to cyproflanilide (100% at 1 mg L^{-1}). Meanwhile, for the insecticidal activities of *Tetranychus cinnabarinus*, compounds **5p** and **5q** exhibited 97.22 and 100% lethal rate at 400 mg L^{-1}, respectively, which was superior to cyproflanilide (44.11% at 400 mg L^{-1}).

In addition, some of the target compounds exhibited both insecticidal and fungicidal activities. For example, compounds **5b** and **5c** showed 59.26 and 74.07% fungicidal activities against *Cucumber downy mildew* at 400 mg L^{-1}, as well as 100% insecticidal activity against *Plutella xylostella* and armyworm at 100 mg L^{-1}. Compound **5h** showed 100% insecticidal activity against armyworm at 10 mg L^{-1}, and also displayed 66.67% fungicidal activity against *Cucumber downy mildew* at 400 mg L^{-1}. At the same tested concentration, the inhibition rate of compounds **5l** and **5s** against *Cucumber downy mildew* reached 88.89 and 96.30%, respectively. The results of this study were in line with our expectations. It was shown that the incorporation of 1,2,4-oxadiazole group in *meta*-diamide compounds can improve their effectiveness in fungicide applications.

From Table 1, it is evident that the phenyl and 2-fluorophenyl substitutions were more effective than pyridyl for the R^4 part substitution. For instance, compounds **5c** and **5d** exhibited better activities against *Plutella xylostella* and armyworm at 100 mg L^{-1} compared to compounds **5j** and **5k**. The title compounds **5f**, **5g**, **5a**, **5b** also showed the same structure-activity relationship against armyworm. Furthermore, when part R^3 was replaced with a hydrogen atom, it showed no detectable activities against *Plutella xylostella* and armyworm at 10 mg L^{-1} by comparing with compounds **5n**, **5r** and **5e**, **5i**.

Table 1. Biological activity of title compounds **5a-5s**

Compound	3-day mortality / %								
	Plutella xylostella			Armyworm			*Tetranychus cinnabarinus*	*Cucumber downy mildew*	
	100 mg L^{-1}	10 mg L^{-1}	1 mg L^{-1}	100 mg L^{-1}	10 mg L^{-1}	1 mg L^{-1}	400 mg L^{-1}	400 mg L^{-1}	100 mg L^{-1}
5a	0	0	0	60	0	0	0	66.67	0
5b	100	0	0	100	0	0	0	59.26	0
5c	100	0	0	100	0	0	0	74.07	0
5d	100	0	0	100	100	16.67	0	0	0
5e	100	90	0	100	100	16.67	0	0	0
5f	76.67	0	0	100	90	0	0	22.22	0
5g	100	100	0	100	100	0	62.5	0	0
5h	43.33	0	0	100	100	0	0	66.67	0
5i	100	100	0	100	100	96.67	62.5	0	0
5j	100	96.67	10	0	0	0	0	0	0
5k	0	0	0	0	0	0	0	0	37.04
5l	0	0	0	0	0	0	0	88.89	37.04
5m	23.33	0	0	86.67	66.67	23.33	0	0	0
5n	0	0	0	100	0	0	0	0	0
5o	100	0	0	100	0	0	0	0	0
5p	100	0	0	100	0	0	97.22	0	0
5q	100	0	0	100	0	0	100	0	0
5r	0	0	0	100	0	0	0	0	0
5s	0	0	0	0	0	0	0	96.30	44.44
Cyproflanilide	100	100	100	100	100	100	41.11	–	–

–: untested.

Simultaneously, when the substituent R^1 of 1,2,4-oxadiazole was phenyl, it had a crucial effect on insecticidal activity. Especially, the *para*-position in phenyl was CN, that is more beneficial to maintenance of the insecticidal activity. For example, when R^4 was C–F, R^3 was H, and R^2 was N, the insecticidal activities of corresponding compounds **5l**, **5m** and **5n** against armyworm at 100 mg L^{-1} were 0, 86.67 and 100%, respectively, showing the sequence **5n > 5m > 5l**. The title compounds **5o**, **5p**, **5q** also showed the same structure-activity relationship against *Tetranychus cinnabarinus*. At the same time, comparing the insecticidal activities of **5a-5s** against armyworm at 1 mg L^{-1}, compound **5i** showed the highest lethality. Additionally, the R^1 group of the compounds with fungicidal activity were trifluoromethyl and cyclopropyl, regardless of variation in the three groups R^4, R^3 and R^2, which provides valuable reference for future research on novel fungicides.

Conclusions

In summary, 19 new *meta*-diamide compounds containing 1,2,4-oxadiazole group were designed, synthesized and evaluated their biological activities against *Plutella xylostella*, armyworm, *Tetranychus cinnabarinus* and *Cucumber downy mildew*. Preliminary biological assay data indicated that the majority of them demonstrated significant insecticidal activity against Lepidopteran pests. Compounds **5p** and **5q** showed better insecticidal activity than cyproflanilide against *Tetranychus cinnabarinus* at 400 mg L^{-1}. Meanwhile, compounds **5a**, **5b**, **5c**, **5f** and **5h** exhibited both insecticidal and fungicidal activities. In particular, compounds **5l** and **5s** showed 88.89 and 96.30% fungicidal activities against *Cucumber downy mildew* at 400 mg L^{-1}. In addition, the structure-activity relationship of these compounds was discussed in detail, which indicated 1,2,4-oxadiazole group was introduced into *meta*-diamide structure could be a lead for the discovery of novel fungicides.

Supplementary Information

Supplementary data (NMR and high-resolution mass spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

Ting Yang and Minghui Wu performed most of the experiments and analyzed the data; JunCheng Xiang performed most of the bio-activity tests; Pengmian Huang, Ting Yang, and Jiyong Liu wrote the manuscript. All authors approved the final version of the manuscript.

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