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Design, Synthesis and Insecticidal Activity of Novel *meta*-Diamide Compounds Containing Methoxy Group

Limei Liang, [a] ***Minghui Wu,*** [b] ***Pengmian Huang*,*** [a] ***and Jiyong Liu*,*** [b]

[a]*School of Chemistry and Chemical Engineering, Changsha University of Science and Technology, Changsha 410114, China*

[b]*CAC Nantong Chemical Co. Ltd., Nantong 226407, China*

This work is based on the precursor compound cyproflanilide and designs a series of methoxy containing *meta*-diamine compounds. By replacing the fluorine atom on the phenyl ring in cyproflanilide with methoxy group, 17 derivatives (**12a-12q**) were obtained with yields ranging from 46 to 92%, which were characterized by high-resolution mass spectrometry, and nuclear magnetic resonance (^{1}H and ^{13}C) spectroscopy and infrared. The insecticidal activities were evaluated against the *Plutella xylostella* and *Spodoptera frugiperda*. Compound *N*-(3-((2-bromopropane-4-(perfluoropropan-2-yl))-6-(trifluoromethyl)phenyl)methoxyphenyl)-*N*-(cyclopropylmethyl)-6-fluoronicotinamide (**12q**) showed significant insecticidal activity against the *Plutella xylostella* with a mortality rate of 97.67% at a concentration of 1 mg L^{-1}. It also exhibited moderate activity against the *Spodoptera frugiperda* at a concentration of 0.1 mg L^{-1}, which can be used as a template for structure modification to obtain higher insecticidal activity.

Keywords: methoxy group, *meta*-diamide compounds, insecticidal activity, structure-activity relationship

Introduction

Synthetic pesticides have been widely used to prevent pest infestations and greatly increased crop productivity since the emergence of modern agriculture. However, with the advancement of pesticide technologies and the increased focus on health and environmental protection, high insecticidal activity is no longer the sole criterion used to evaluate pesticide quality.[1,2] Rather, it has become crucial to evaluate their safety and compatibility with the environment and human health. Organic farming, utilizing fewer synthetic pesticides and emphasizing eco-friendly farming practices, is popular to control pests. Today, low toxicity is also an important standard for pesticides. Thus, high insecticidal activity and low mammalian toxicity of insecticides are crucial for controlling the spread of pests and meeting the global food safety and reducing environmental pollution.[3,4] It is true that the use of pesticides will inevitably add pest resistance,[5,6] which creates a need for new insecticides with novel mechanisms of action.

Diamide insecticides with low mammalian toxicity and less cross resistance against other existing insecticides have shown great activity against lepidopteron pests and attracted worldwide attention.[7-9] The reported diamide insecticides include flubendiamide (**1**; Figure 1), chlorantraniliprole (**2**; Figure 1), cyantraniliprole (**3**; Figure 1), tetrachlorantraniliprole (**4**; Figure 1) and cyclaniliprole (**5**; Figure 1).[10-15] These insecticides mainly act on the insect's fish nicotine receptor (RyR), continuously dredge the Ca^{2+} ion channel and infect insects.[16-20] However, due to the unreasonable use of pesticides, some lepidopteran pests have increased resistance to existing diamide insecticides, such as the *Plutellidae Plutella* and *Spodoptera exigua*.[21-24] Broflanilide (**6**; Figure 1) is a new and charming type of diamide insecticide developed. The structure of broflanilide contains a *meta*-positioned diamide group, which is the primary difference between it and traditional diamide insecticides. It acts on insect γ-aminobutyric acid (GABA) receptors and has been classified as a new group (group 30) by the Insecticide Resistance Action Committee (IRAC).[25-27] In 2019, it was reported a new insecticide, cyproflanilide (**7**; Figure 1), which demonstrated better effect against *Diamondback moth* and *Chilo suppressalis* than broflanilide.[28]

Recent studies had highlighted that most phenyl methoxy compounds exhibit good biological activities.

*e-mail: huangpengmian@126.com; jiyong_liu@cacch.com
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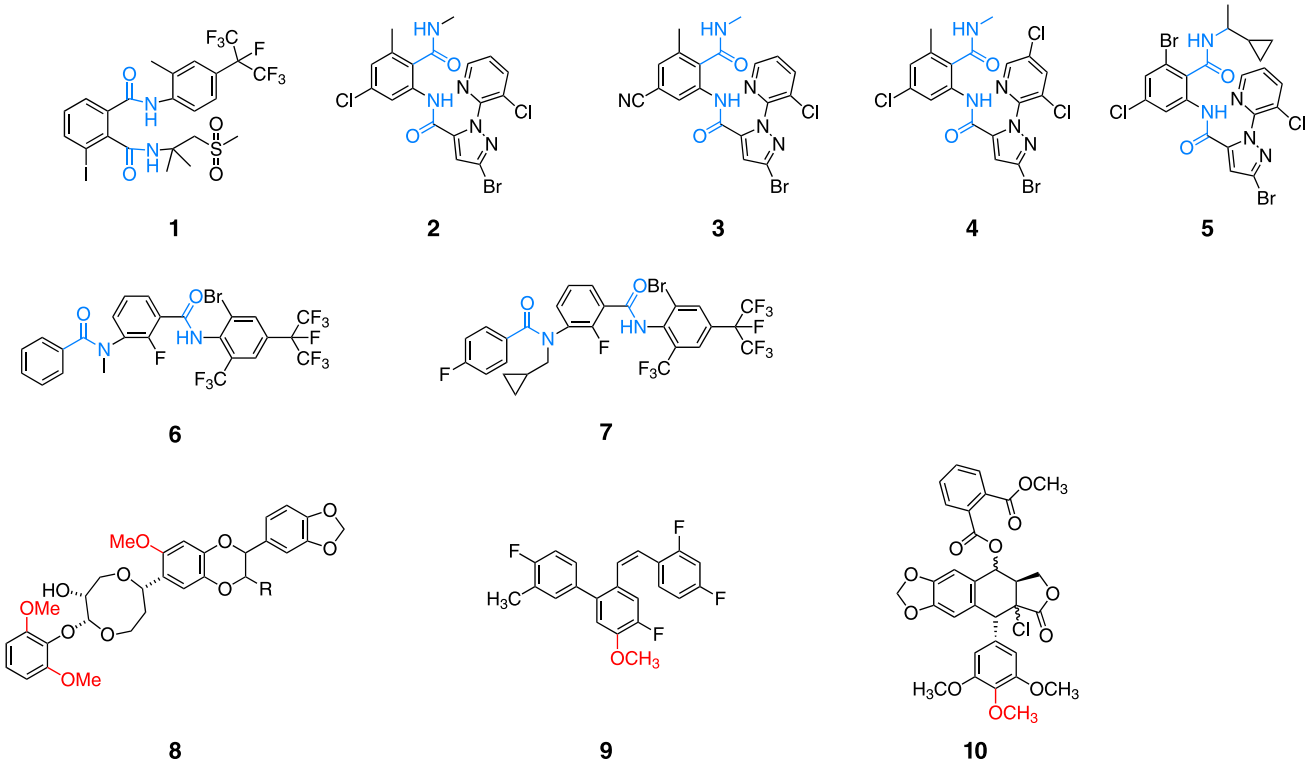


Figure 1. Structure of some insecticides containing diamines and methoxy groups.

For instance, Satoshi *et al.*[29] modified the methoxymethyl group of the 6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-1,4benzodioxan-7-yl with several alkyl groups (**8**; Figure1). The assay results indicated that the oxygen atom of the methoxymethyl group had a certain influence on its biological activity. Horty *et al.*[30] prepared a series of (*E*/*Z*)-2-arylstilbenes, and the assays results indicated that the (*Z*)-4-fluoro-3-methyl-2-(2,4-difluorostyryl)-4-fluoro-5-methoxy-1,1'-bipheny (**9**; Figure1) compound exhibit good activity in several pests, including *Spodoptera exigua*, *Trichoplusia ni*, *Helicoverpa zea*, *Plutella xylostella*, and *Pseudoplusia includens*. Xu *et al.*[31] synthesized a series of monomethyl phthalate derivatives of podophyllotoxin (**10**; Figure 1), all the assays tested showed that the synthesized derivatives had good insecticidal activity. Structure activity relationship (SAR) indicated that the 4-methoxy group was an important structural property of podophyllotoxins for good insecticidal activity.

Inspired by the aforementioned view, we aimed to synthesize insecticides with high insecticidal activity against *Plutella xylostella* and *Spodoptera frugiperda* by replacing the fluorine atom on the benzene ring in the middle of cyproflanilide with a methoxy group and modifying the Q substituent (Figure 2).

In the present study, a series of novel methoxy-containing *meta*-diamine compounds were synthesized based on the new mechanism of cyproflanilide and the extensive biological activity of methoxybenzene derivatives. The bioactivity of these compounds against *Plutella xylostella* and *Spodoptera frugiperda* was evaluated, and their structure-activity relationship was also discussed.

Experimental

General information

All reagents and solvents used in the work were purchased from Macklin (Shanghai, China) and Aladdin

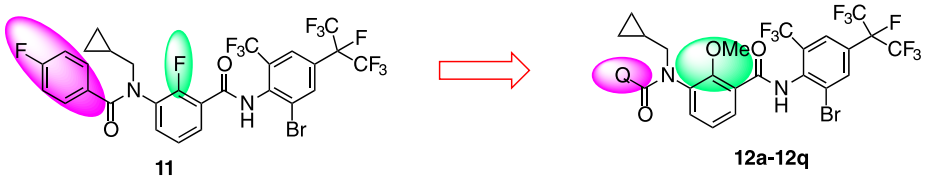


Figure 2. Design strategy of the target compounds.

(Shanghai, China). The thin-layer chromatography (TLC) analyses were performed on 0.25 mm silica gel plates (GF254) and visualized with a ZF-20D ultraviolet. Flash column chromatographic separations were carried out on silica gel (200**-**300 mesh) using ethyl acetate and hexane as eluents.^{1}H and ^{13}C nuclear magnetic resonance (NMR) were recorded at 400 and 101 MHz, respectively, using Bruker AV400 (Bruker Co., Switzerland) with tetramethylsilane as the internal standard in deuterated dimethyl sulfoxide (DMSO-d_6) solution. The chemical shift (δ) is given in 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. Infrared (IR) spectra in the range of 4000-500 cm^{-1} were obtained using a Bruker INVENIO infrared spectrometer (Bruker Co., Germany). The melting points were measured using Hai Neng mp430 (Shanghai, China) video melting point apparatus. Mass spectra were obtained with an Agilent 1100 LC-MSD-Trap mass spectrometer (Agilent, CA, USA) equipped with standard electrospray ionization (ESI) apparatus.

Synthesis

Synthesis of intermediates **15-18**

The intermediates **15**, **17**, **18** were synthesized according to the literature procedure.[32]

Synthesis of *N*-(2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)-2-fluoro-3-nitrobenzamide (**15**)

2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) aniline (10.03 g, 24.60 mmol) was combined with 2-fluoro-3-nitrobenzoyl chloride (5.0 g, 24.60 mmol), 4-dimethylaminopyridine (DMAP) (0.60 g, 4.92 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (6.36 g, 49.2 mmol) in a 50 mL three-necked flask with a magnetic stir bar. The reaction mixture was stirred magnetically at 120 °C for 7 h. After the reaction end, the pH was adjusted to 8 using 10% aqueous NaOH. The mixture was then extracted with ethyl acetate, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (10:1 v v^{-1}) as an eluent. The compound **15** was obtained as a dark brown oil in a 46% yield (6.16 g, 10.73 mmol).

Synthesis of *N*-(2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)-2-methoxy-3-nitrobenzamide (**16**)

Methanol (70 mL) and compound **15** (6.6 g, 11.48 mmol) were added to a 250 mL three-necked flask with magnetic stirrer. Then, sodium methoxide (0.86 g, 17.22 mmol) and K_2CO_3 (7.94 g, 57.4 mmol) were added to the solution in turn. After the reaction continued for 3 h at 80 °C, the reaction solution was extracted with water and ethyl acetate. The extract solution was removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (5:1 v v^{-1}) as eluent. The compound **16** was obtained as a yellow solid in 87% yield (5.86 g, 10 mmol). The structure of compound **16** is confirmed by the data present below.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 7.53 (t, *J* 7.9 Hz, 1H), 7.94 (dd, *J* 7.7, 1.7 Hz, 1H), 7.98 (s, 1H), 8.15-8.12 (m, 1H), 8.45 (s, 1H), 10.88 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 64.1, 118.4 (d, *J* 27.3 Hz), 121.2 (d, *J* 27.9 Hz), 122.5 (dd, *J* 297 Hz), 122.8, 124.7, 126.3 (d, *J* 21.6 Hz), 127.3, 128.8, 130.7, 131.0, 131.3, 131.6, 133.8, 134.2 (d, *J* 10.6 Hz), 138.6, 144.2, 150.4, 164.3; HRMS (ESI) *m/z*, calcd. for $C_{18}H_9BrF_{10}N_2O_4$ $[M + H]^+$: 585.9586, found: 585.9569.

Synthesis of 3-amino-*N*-(2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)-2-methoxybenzamide (**17**)

To a 250 mL round bottom flask, compound **16** (5.86 g, 10 mmol), ethanol (60 mL), stannous chloride (9.0 g, 86.54 mmol) and concentrated hydrochloric acid (2 mL) were added sequentially. The reaction mixture was stirred magnetically for 3 h at 110 °C. TLC analysis confirmed the completion of the reaction. The solvent was removed under reduced pressure. Solution of water and ethyl acetate were added to the residue, adjusted to pH 10 by 10% aqueous NaOH. Then, the organic phase was concentrated. The residue was purified by silica gel column chromatography using hexane-ethyl acetate (3:1 v v^{-1}) as eluent. The compound **17** was obtained as a yellow solid in 59% yield (3.26 g, 5.86 mmol). The structure of compound **17** is confirmed by the data present below.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 5.23 (s, 2H), 6.98-6.88 (m, 3H), 7.95 (s, 1H), 8.39 (s, 1H), 10.30 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 60.3, 116.4, 118.3, 118.6, 120.7, 121.3 (d, *J* 27.6 Hz), 122.1 (dd, *J* 267 Hz), 122.5, 124.3, 125.8 (d, *J* 21.4 Hz), 127.6, 129.0 (d, *J* 1.7 Hz), 130.9 (dd, *J* 4.0, 0.0 Hz), 133.9 (d, *J* 10.1 Hz), 139.8, 142.2, 144.1, 165.5; HRMS (ESI) *m/z*, calcd. for $C_{18}H_{11}BrF_{10}N_2O_2$ $[M + H]^+$: 555.9844, found: 555.9823.

Synthesis of *N*-(2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)-3-((cyclopropylmethyl)amino)-2-methoxybenzamide (**18**)

Compound **17** (2.0 g, 5.59 mmol), 1,2-dichloroethane 45 mL, trifluoroacetic acid (2.43 g, 21.31 mmol) and cyclopropyl formaldehyde (0.024 g, 3.33 mmol) were added to 250 mL three-neck flask. The reaction mixture

was magnetic stirred for 1 h at room temperature. Sodium triacetoxyborohydride (2.27 g, 10.71 mmol) was slowly added and stirred for 3 h at room temperature. After the reaction completion the solution was adjusted to pH 8 by saturated sodium carbonate solution, extract with the solution of dichloromethane and water. After organic phase was concentrated the residue was purified by silica gel column chromatography using hexane-ethyl acetate (5:1 v v^{-1}) as eluent. The compound **18** was obtained as a yellow solid in 70% yield (2.26 g, 3.70 mmol). The structure of compound **18** is supported by the data present below.

IR (KBr) ν / cm^{-1} 3357, 3308, 1674, 1598, 1584, 1480, 1451, 1423, 1341, 1321, 1304, 1276, 1238, 1202, 1165, 1146, 1120,1084, 1005, 985, 890, 845, 760, 748, 726, 706, 685, 430; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.27-0.21 (m, 2H), 0.46 (dd, *J* 8.0, 5.6 Hz, 2H), 1.12 (t, *J* 7.9 Hz, 1H), 3.04 (d, *J* 6.1 Hz, 2H), 3.78 (s, 3H), 5.40 (s, 1H), 6.90 (dd, *J* 18.0, 7.9 Hz, 2H), 7.07 (t, *J* 7.9 Hz, 1H), 7.96 (s, 1H), 8.41 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.3, 10.6, 47.0, 60.9, 113.5, 115.6, 118.4 (d, *J* 27.4 Hz), 121.3 (d, *J* 27.4 Hz), 122 (dd, *J* 272.5 Hz), 122.6, 123.4, 124.6, 125.8 (d, *J* 21.4 Hz), 127.5, 129.0 (d, *J* 1.5 Hz), 130.6 (d, *J* 31.4 Hz), 131.2 (d, *J* 30.0 Hz), 134.0 (d, *J* 9.9 Hz), 139.7, 142.2, 144.4, 165.7; HRMS (ESI) *m/z*, calcd. for $C_{22}H_{17}BrF_{10}N_2O_2$ $[M + H]^+$: 610.0314, found: 610.0284.

Synthesis of compounds **12a-12q**

Intermediate **18** (0.24 g, 0.39 mmol), tetrahydrofuran (4 mL), pyridine (0.5 mL) and benzoyl chloride (66 mg, 0.47 mmol) were added to a 50 mL single mouth bottle in turn. The solution was stirred at 80 °C for 4-5 h. After reaction completion, solution was neutralized to acid state with dilute hydrochloric acid, then extracted with water and ethyl acetate. After the organic phase was concentrated, the residue was purified by silica gel column chromatography using hexane-ethyl acetate (5:1 v v^{-1}) as eluent to obtain compound **12a**.

The compounds **12b-12q** were synthesized using similar method of compound **12a**. The structure of compounds **12b-12q** were confirmed by the data present below.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(*N*-(cyclopropylmethyl)benzamido)-2-methoxybenzamide (**12a**)

Yield 85%; white solid; mp 113.7-115.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.15 (d, *J* 26.8 Hz, 2H), 0.43 (s, 2H), 1.07 (brs, 1H), 3.84 (s, 3H), 4.11 (s, 2H), 7.26 (d, *J* 42.2 Hz, 5H), 7.55 (d, *J* 35.4 Hz, 3H), 7.94 (s, 1H), 8.40 (s, 1H), 10.49 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.6, 4.6, 10.3, 29.8, 31.9, 53.4, 62.2, 118.8 (d, *J* 27.4 Hz), 121.0, 121.5, 121.8, 122.8 (dd, *J* 291.2 Hz), 123.1, 123.7 (d, *J* 8.3 Hz), 124.4, 124.7, 126.5 (d, *J* 21.5 Hz), 128.1, 128.3 (d, *J* 3.3 Hz), 129.4 (d, *J* 15.1 Hz), 130.0, 131.2 (d, *J* 32.3 Hz), 131.7, 133.7 (d, *J* 4.0 Hz), 134.5 (d, *J* 10.3 Hz), 136.9 (d, *J* 36.8 Hz), 139.5, 154.0 (dd, *J* 7.1, 3.1 Hz), 165.4, 170.4; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{21}BrF_{10}N_2O_3$ $[M + H]^+$: 714.0576, found: 714.0549.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(*N*-(cyclopropylmethyl)-4-fluorobenzamido)-2-methoxybenzamide (**12b**)

Yield 89%; white solid; mp 142-143.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.16 (s, 2H), 0.44 (s, 2H), 1.09 (s, 1H), 3.53-3.36 (m, 1H), 3.82 (s, 3H), 4.03 (q, *J* 7.1 Hz, 1H), 7.04 (s, 2H), 7.24 (s, 1H), 7.37 (s, 2H), 7.60 (dd, *J* 14.3, 7.3 Hz, 2H), 7.94 (s, 1H), 8.40 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.7, 4.5, 10.3, 53.7, 62.2, 114.8 (d, *J* 18.0 Hz), 118.7 (d, *J* 27.8 Hz), 120.8, 121.6 (d, *J* 28.2 Hz), 122.2 (dd, *J* 262.5 Hz), 123.5, 123.8, 126.3, 126.4, 126.6, 128.9, 129.5, 130.8, 131.1, 131.4, 132.9 (d, *J* 3.1 Hz), 134.2 (d, *J* 10.7 Hz), 137.2, 139.3, 153.8, 159.0 (d, *J* 261 Hz), 161.6, 164.1, 165.0, 169.5; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{20}BrF_{11}N_2O_3$ $[M + H]^+$: 732.0482, found: 732.0442.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(4-chloro-*N*- (cyclopropylmethyl)benzamido)-2-methoxybenzamide (**12c**)

Yield 86%; white solid; mp 119-121.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.17 (s, 2H), 0.45 (s, 2H), 1.09 (s, 1H), 3.51-3.37 (m, 1H), 3.82 (s, 3H), 4.10-4.00 (m, 1H), 7.36-7.18 (m, 5H), 7.61 (t, *J* 8.2 Hz, 2H), 7.94 (s, 1H), 8.40 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.2, 4.1, 9.8, 53.2, 59.6, 61.8, 118.3 (d, *J* 27.9 Hz), 120.4, 121.1 (d, *J* 27.3 Hz), 121.7 (dd, *J* 270.8 Hz), 122.5, 123.1, 123.4, 126.1 (d, *J* 21.4 Hz), 127.4, 128.4, 129.2, 129.6, 130.4, 130.7, 131.0, 132.5, 133.7 (d, *J* 10.0 Hz), 134.3, 134.9, 136.6, 138.8, 153.4, 164.4, 169.0; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{20}BrClF_{11}N_2O_3$ $[M + H]^+$: 748.0186, found: 748.0072.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(4-bromo-*N*-(cyclopropylmethyl)benzamido)-2-methoxybenzamide (**12d**)

Yield 68%; white solid; mp 83.4-84.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.18 (s, 2H), 0.45 (s, 2H), 1.09 (s, 1H), 3.49-3.37 (m, 1H), 3.82 (s, 3H), 4.10-3.99 (m, 1H), 7.25 (s, 3H), 7.46-7.35 (m, 2H), 7.68-7.55 (m, 2H), 7.94 (s, 1H), 8.40 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 2.9, 3.8, 9.5, 52.8, 61.6, 118.6 (d, *J* 26.6 Hz),

120.8, 121.5 (d, *J* 28.1 Hz), 122.1 (d, *J* 270.8 Hz), 123.2, 123.5 (d, *J* 7.7 Hz), 123.6,123.8, 126.2, 126.3 (d, *J* 21.5 Hz), 127.9 (d, *J* 4.2 Hz), 129.0, 129.4, 130.2, 130.8, 131.2, 133.0, 134.3 (d, *J* 10.5 Hz), 135.8, 136.8, 139.3, 153.7, 164.9, 169.4; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{20}Br_2F_{10}N_2O_3$ $[M + H]^+$: 791.9681, found: 791.9642.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(*N*-(cyclopropylmethyl)-4-(trifluoromethyl) benzamido)-2-methoxybenzamide (**12e**)

Yield 46%; white solid; mp 73.5-74.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.21 (s, 2H), 0.48 (s, 2H), 1.14 (s, 1H), 3.50 (dd, *J* 12.8, 7.1 Hz, 1H), 3.84 (s, 3H), 4.05 (dq, *J* 14.2, 6.9 Hz, 1H), 7.26 (t, *J* 7.4 Hz, 1H), 7.74-7.46 (m, 6H), 7.92 (s, 1H), 8.39 (s, 1H), 10.28 (d, *J* 68.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 1.9, 2.6, 8.4, 51.7, 60.5, 116.8 (d, *J* 28.3Hz), 118.8 (d, *J* 5.1 Hz), 119.6 (d, *J* 27.4 Hz), 121.0 (d, *J* 21.3 Hz), 121.6, 122.2 (d, *J* 11.3 Hz), 122.9, 122.6 (d, *J* 281 Hz), 123.5 (d, *J* 18.5 Hz), 124.4 (d, *J* 21.7 Hz), 126.4 (dd, *J* 12.3, 5.5 Hz), 127.1 (d, *J* 19.7 Hz), 127.7 (dd, *J* 7.7, 2.2 Hz), 128.0 (d, *J* 5.2 Hz), 129.0 (d, *J* 3.5 Hz), 130.1 (d, *J* 16.2 Hz), 131.0 (d, *J* 4.3 Hz), 131.4 (d, *J* 4.8 Hz), 132.4 (d, *J* 9.8 Hz), 134.9, 136.5 (d, *J* 2.1 Hz), 137.5, 138.8, 151.8, 167.4; HRMS (ESI) *m/z*, calcd. for $C_{30}H_{20}BrF_{13}N_2O_3$ $[M + H]^+$: 782.0450, found: 782.0411.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(4-cyano-*N*-(cyclopropylmethyl)benzamido)-2-methoxybenzamide (**12f**)

Yield 55%; white solid; mp 79.7-81.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.21 (s, 2H), 0.48 (s, 2H), 1.12 (s, 1H), 3.50 (m, 1H), 3.82 (s, 3H), 4.09-3.97 (m, 1H), 7.26 (t, *J* 7.5 Hz, 1H), 7.45 (d, *J* 7.8 Hz, 2H), 7.61 (d, *J* 7.2 Hz, 1H), 7.68 (d, *J* 7.7 Hz, 3H), 7.94 (s, 1H), 8.40 (s, 1H), 10.32 (d, *J* 38.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.7, 4.4, 10.1, 53.5, 62.4, 112.1, 115.3, 118.5, 120.7, 121.3 (d, *J* 3.3 Hz), 121.4, 121.5 (d, *J* 1.3 Hz), 121.6 (d, *J* 2.3 Hz), 123.0 (d, *J* 297.9 Hz), 123.5, 124.0, 126.3 (d, *J* 21.6 Hz), 128.8, 129.0, 129.4, 130.2, 131.5 (d, *J* 57.0 Hz), 132.8 (d, *J* 22.6 Hz), 134.3 (d, *J* 10.0 Hz), 136.4, 139.2, 141.1, 153.6, 166.3, 169.0; HRMS (ESI) *m/z*, calcd. for $C_{30}H_{20}BrF_{10}N_3O_3$ $[M + H]^+$: 739.0528, found: 739.0588.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(*N*-(cyclopropylmethyl)-3-fluorobenzamido)-2-methoxybenzamide (**12g**)

Yield 89%; yellow solid; mp 91.6-93.4 °C; IR (KBr) ν / cm^{-1} 3081, 1718, 1686, 1654, 1589, 1474, 1442, 1442, 1426, 1376, 1304, 1278, 1232, 1196, 1171, 1005, 985, 891, 795, 747, 728; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.19 (s, 2H), 0.47 (s, 2H), 1.10 (s, 1H), 3.54-3.44 (m, 1H), 3.82 (s, 3H), 4.03-3.95 (m, 1H), 7.08 (s, 1H), 7.44-7.19 (m, 2H), 7.74–7.52 (m, 2H), 7.85-7.78 (m, 1H), 7.94 (s, 1H), 8.40 (s, 1H), 10.34 (s, 1H), 10.38 (d, *J* 28.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.3, 4.0, 9.7, 53.3, 61.9, 116.4, 117.7 (d, *J* 17.9 Hz), 118.2 (d, *J* 17.2 Hz), 120.3, 121.0 (d, *J* 28.0 Hz), 122.0 (d, *J* 283.9 Hz), 122.5, 123.0, 123.5, 124.8, 125.8, 126.0, 126.7 (dd, *J* 7.7, 3.4 Hz), 128.5, 128.6, 132.1, 133.6, 133.8 (d, *J* 9.6 Hz), 138.9, 147.8 (d, *J* 13.1 Hz), 150.3 (d, *J* 13.1 Hz), 150.7 (d, *J* 248.0 Hz), 151.0 (d, *J* 12.5 Hz), 153.2, 153.6 (d, *J* 12.7 Hz), 165.3, 167.8; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{20}BrF_{11}N_2O_3$ $[M + H]^+$: 732.0482, found 733.0315.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)-2-fluorobenzamide (**12h**)

Yield 79%; white solid; mp 70.2-73.5 °C; IR (KBr) ν / cm^{-1} 3308, 3083, 1690, 1654, 1614, 1582, 1490, 1454, 1426, 1382, 1306, 1279, 1229, 1204, 1169,1144, 1081, 1005, 985, 891, 757, 728, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25-0.12 (m, 2H), 0.47 (q, *J* 5.4 Hz, 2H), 1.17-1.04 (m, 1H), 3.90 (m, 4H), 4.12 (dd, *J* 14.0, 6.8 Hz, 1H), 7.04 (t, *J* 8.1 Hz, 2H), 7.16 (t, *J* 7.8 Hz, 1H), 7.35-7.24 (m, 1H), 7.40 (q, *J* 7.6 Hz, 1H), 7.52 (d, *J* 7.8 Hz, 1H), 7.59 (d, *J* 9.2 Hz, 1H), 7.94 (s, 1H), 8.39 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 2.7, 3.9, 9.5, 52.0, 61.5, 114.9 (d, *J* 21.1 Hz), 116.5 (d, *J* 22.2 Hz), 118.0 (d, *J* 28.9 Hz), 118.9 (d, *J* 10.2 Hz), 119.1 (d, *J* 259.6), 120.8 (d, *J* 28.8 Hz), 122.5, 123.4, 124.0 (d, *J* 3.8 Hz), 124.6 (d, *J* 16.8 Hz), 125.7 (d, *J* 21.5 Hz), 127.0, 128.5 (d, *J* 14.6 Hz), 128.9, 129.2, 130.2, 130.6, 130.8 (d, *J* 8.1 Hz), 131.5, 132.3, 133.7 (d, *J* 10.4 Hz), 134.0, 134.3 (d, *J* 8.9 Hz), 134.8, 138.8 (d, *J* 25.3 Hz), 153.6, 154.0, 156.1, 158.5, 159.0 (d, *J* 250 Hz), 159.5, 162.0, 164.7 (d, *J* 3.0 Hz), 165.6 (d, *J* 31.7 Hz); HRMS (ESI) *m/z*, calcd. for $C_{29}H_{20}BrF_{11}N_2O_3$ $[M + H]^+$: 732.0482, found: 733.0315.

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)-3-(*N*-(cyclopropylmethyl)-3-(trifluoromethyl) benzamido)-2-methoxybenzamide (**12i**)

Yield 73%; white solid; mp 61.5-62.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20 (s, 2H), 0.47 (s, 2H), 1.12 (s, 1H), 3.45 (dd, *J* 12.3, 6.7 Hz, 1H), 3.84 (s, 3H), 4.06 (d, *J* 16.5 Hz, 1H), 7.24 (s, 1H), 7.50-7.38 (m, 1H), 7.62 (m, 5H), 7.93 (s, 1H), 8.39 (s, 1H), 10.36 (d, *J* 42.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 2.5, 3.6, 9.4, 51.8, 61.4, 118.0 (d, *J* 29.7 Hz), 119.3, 119.8, 120.2, 120.8 (d, *J* 28.4 Hz), 122.5, 122.7, 122.9 (d, *J* 3.8 Hz), 123.6,124.7 (d, *J* 257 Hz), 125.1 (dt, *J* 7.9, 4.5 Hz), 125.7 (d, *J* 3.9 Hz), 125.8, 128.4 (d, *J* 8.1 Hz), 128.6, 128.7 (d, *J* 5.5 Hz), 128.9, 129.0-128.9 (m), 129.2, 129.7, 131.5, 132.8, 133.3 (d,

J 6.0 Hz), 133.7 (d, *J* 8.9 Hz), 135.1, 135.4, 136.1, 136.6 (d, *J* 19.1 Hz), 138.7, 153.2, 164.7, 165.6, 169.2, 171.9; HRMS (ESI) *m/z*, calcd. for $C_{30}H_{20}BrF_{13}N_2O_3$ $[M + H]^+$: 782.0450, found: 782.0410.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)-2,6-difluorobenzamide (**12j**)

Yield 78%; brown solid; mp 135-137 °C; IR (KBr) *v* / cm^{-1} 3009, 1695, 1663, 1626, 1590, 1478, 1420, 1308, 1275, 1236, 1204, 1169, 1131, 1020, 985, 920, 891, 804, 770, 728, 594; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.26-0.15 (m, 2H), 0.48 (d, *J* 12.3 Hz, 2H), 1.14-1.03 (m, 1H), 3.42 (s, 1H), 3.89 (d, *J* 10.6 Hz, 4H), 4.12-4.00 (m, 1H), 7.27-7.03 (m, 3H), 7.62 (t, *J* 6.5 Hz, 2H), 7.94 (s, 1H), 8.40 (s, 1H); 10.49 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 2.8, 3.9, 9.5, 52.1, 54.6, 110.7 (d, *J* 18.5 Hz), 111.4, 112.3-111.5 (m), 113.6 (d, *J* 24.4 Hz), 114.3 (t, *J* 22.4 Hz), 118.0 (d, *J* 28.7 Hz), 120.9 (d, *J* 29.5 Hz), 122.1 (d, *J* 297Hz), 122.4, 123.0 (d, *J* 9.7 Hz), 125.6, 125.9, 128.5 (d, *J* 14.4 Hz), 129.1, 129.5, 130.3 (d, *J* 12.6 Hz), 131.3 (t, *J* 10.0 Hz), 132.1-131.6 (m), 132.6 (t, *J* 10.4 Hz), 133.7, 138.7 (d, *J* 24.8 Hz), 153.9, 157.7 (d, *J* 7.1 Hz), 160.2 (d, *J* 6.9 Hz), 160.9 (d, *J* 21.4 Hz), 161.8 (d, *J* 265.5Hz), 164.5, 164.7; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{19}BrF_{12}N_2O_3$ $[M + H]^+$: 750.0387, found: 750.0039.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl) carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)-2,4,5-trifluorobenzamide (**12k**)

Yield 50%; white solid; mp 116.7-117.5 °C; IR (KBr) *v* / cm^{-1} 3325, 3078, 1654, 1629, 1582, 1517, 1490, 1448, 1426, 1381, 1321, 1304, 1279, 1231, 1203, 1170, 1146, 1081, 1005, 985, 891, 852, 811, 761, 750, 728, 701; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.22 (s, 2H), 0.58-0.44 (m, 2H), 1.10 (d, *J* 7.2 Hz, 1H), 3.51 (m, 1H), 3.87 (m, 3H), 4.03-3.96 (m, 1H), 7.27 (t, *J* 7.8 Hz, 1H), 7.51-7.33 (m, 2H), 7.71-7.57 (m, 2H), 7.94 (s, 1H), 8.40 (s, 1H), 10.38 (d, *J* 50.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.9, 4.3, 10.4, 54.4, 61.5, 106.3 (dd, *J* 28.7, 21.5 Hz), 108.1 (dd, *J* 29.2, 21.4 Hz), 116.8 (dt, *J* 12.3, 4.2 Hz), 118.3-117.7 (m), 118.8 (d, *J* 27.6 Hz), 120.1 (d, *J* 20.3 Hz), 121.9 (d, *J* 27.9 Hz), 122.2 (d, *J* 18.3 Hz), 123.1, 123.7, 123.9, 124.3 (d, *J* 283.7 Hz), 126.6 (d, *J* 21.4 Hz), 129.3 (d, *J* 13.8 Hz), 129.8, 134.5 (d, *J* 10.7 Hz), 135.7, 139.6 (d, *J* 24.9 Hz), 144.6 (d, *J* 13.0 Hz), 145.0 (dd, *J* 12.7, 3.7 Hz), 147.0, 147.1 (d, *J* 3.8 Hz), 147.5-147.3 (m), 148.8 (d, *J* 13.1 Hz), 151.6-151.0 (m), 152.4 (d, *J* 11.1 Hz), 153.9 (d, *J* 26.5 Hz), 154.9 (d, *J* 9.4 Hz), 156.4 (d, *J* 13.1 Hz), 158.1 (d, *J* 236 Hz), 159.0 (d, *J* 12.9 Hz), 163.8, 165.5, 170.8; HRMS (ESI) *m/z*, calcd. for $C_{29}H_{18}BrF_{13}N_2O_3$ $[M + H]^+$: 768.0293, found: 769.0130.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)-2-fluoroisonicotinamide (**12l**)

Yield 65%; yellow solid; mp 67.8-68.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20 (s, 2H), 0.53–0.44 (m, 2H), 1.10 (s, 1H), 3.47 (dd, *J* 12.9, 7.3 Hz, 1H), 3.85 (s, 3H), 4.09-3.99 (m, 1H), 7.07 (s, 1H), 7.18 (d, *J* 4.7 Hz, 1H), 7.27 (t, *J* 7.9 Hz, 1H), 7.64 (d, *J* 7.2 Hz, 1H), 7.71 (d, *J* 7.6 Hz, 1H), 7.94 (s, 1H), 8.09 (d, *J* 5.0 Hz, 1H), 8.40 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.4, 4.2, 9.8, 53.1, 62.2, 108.0 (d, *J* 39.3 Hz), 109.3 (d, *J* 39.2 Hz), 118.4 (d, *J* 26.1 Hz), 120.5, 121.3, 121.8 (d, *J* 261.1 Hz), 123.0 (d, *J* 47.5 Hz), 123.6, 126.1 (d, *J* 21.4 Hz), 128.8, 129.7, 131.0, 132.7, 134.1 (d, *J* 9.6 Hz), 135.3, 139.0, 147.4 (d, *J* 14.5 Hz), 148.9 (d, *J* 15.0 Hz), 149.8 (d, *J* 7.4 Hz), 153.6, 161.3, 163.6, 164.1 (d, *J* 235.5Hz), 164.8, 167.0; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{19}BrF_{11}N_3O_3$ $[M + H]^+$: 733.0434, found: 733.0399.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)isonicotinamide (**12m**)

Yield 78%; white solid; mp 154.2-155.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.18 (s, 2H), 0.47 (d, *J* 7.4 Hz, 2H), 1.09 (s, 1H), 3.41 (dd, *J* 12.9 Hz, 7.4 Hz, 1H), 3.85 (s, 3H), 4.07 (dd, *J* 14.0, 6.9 Hz, 1H), 7.23 (dd, *J* 12.9, 6.0 Hz, 3H), 7.63 (s, 2H), 7.94 (s, 1H), 8.40 (s, 1H), 8.44 (d, *J* 4.9 Hz, 2H), 10.48 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.9, 4.8, 10.4, 53.6, 62.6, 118.9, 119.1 (d, *J* 4.9 Hz), 121.2, 121.7 (d, *J* 5.7 Hz), 122.4, 123.0 (d, *J* 257.5 Hz), 123.4, 124.0 (d, *J* 14.9 Hz), 126.7 (d, *J* 21.5 Hz), 129.5, 130.2, 131.4 (d, *J* 30.3 Hz), 133.6, 134.7 (d, *J* 10.8 Hz), 136.3, 138.7, 139.6, 144.4, 149.9, 151.3, 154.3, 165.4, 166.8, 168.8; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{20}BrF_{10}N_3O_3$ $[M + H]^+$: 715.0528, found: 715.0489.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl) phenyl)carbamoyl)-2-methoxyphenyl)-2-chloro-*N*-(cyclopropylmethyl)isonicotinamide (**12n**)

Yield 64%; white solid; mp 121-123.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20 (s, 2H), 0.54-0.43 (m, 2H), 1.09 (s, 1H), 3.51-3.41 (m, 1H), 3.85 (s, 3H), 4.01 (dd, *J* 12.9, 6.8 Hz, 1H), 7.23 (d, *J* 4.6 Hz, 1H), 7.27 (t, *J* 7.9 Hz, 1H), 7.40 (s, 1H), 7.64 (d, *J* 6.9 Hz, 1H), 7.72 (d, *J* 7.7 Hz, 1H), 7.94 (s, 1H), 8.26 (d, *J* 5.0 Hz, 1H), 8.40 (s, 1H), 10.49 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.6, 9.1, 52.5, 61.6, 117.8 (d, *J* 26.9 Hz), 119.9, 120.4 (d, *J* 10.1 Hz), 120.7, 121.6 (d, *J* 270.0 Hz), 121.9 (d, *J* 35.3 Hz), 122.6, 122.9 (d, *J* 10.8 Hz), 123.6, 125.6, 127.2, 129.1, 130.2 (d, *J* 29.7 Hz), 132.1, 133.4 (d, *J* 9.9 Hz), 134.7, 138.4, 141.3, 146.8, 149.0, 150.5, 153.0, 164.1 (d, *J* 23.9 Hz), 166.2;

HRMS (ESI) *m/z*, calcd. for $C_{28}H_{19}BrClF_{10}N_3O_3$ $[M + H]^+$: 749.0139, found: 749.0101.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)nicotinamide (**12o**)

Yield 79%; white solid; mp 139.4-140.6 °C; IR (KBr) *v* / cm^{-1} 3369, 1685, 1663, 1588, 1487, 1455, 1425, 1396, 1377, 1345, 1304,1277, 1233, 1204, 1163, 1133, 1080, 1024, 983, 890, 767, 728, 708, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.18 (s, 2H), 0.46 (s, 2H), 1.10 (s, 1H), 3.46 (d, *J* 20.6 Hz, 1H), 3.83 (s, 3H), 4.04 (dd, *J* 12.8, 5.1 Hz, 1H), 7.26 (d, *J* 6.4 Hz, 2H), 7.66 (td, *J* 17.8, 14.5, 7.2 Hz, 3H), 7.94 (s, 1H), 8.39 (s, 1H), 8.45 (s, 2H), 10.48 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 2.7, 3.5, 9.23, 55.9, 61.3, 117.8 (d, *J* 27.3 Hz), 119.9, 120.6 (d, *J* 27.9 Hz), 122.4-122.0 (m), 123.0 (t, *J* 27.3 Hz), 124.0 (d, *J* 263.8 Hz), 125.5 (d, *J* 21.6 Hz), 127.3, 128.5 (d, *J* 44.9 Hz), 130.2 (d, *J* 30.1 Hz), 131.6, 132.1, 133.5 (d, *J* 11.1 Hz), 134.9, 135.6, 136.3, 138.4, 147.7, 149.6 (d, *J* 10.4 Hz), 152.8 (d, *J* 9.2 Hz), 164.2, 165.7, 167.5, 171.4; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{20}BrF_{10}N_3O_3$ $[M + H]^+$: 715.0528, found: 716.0363.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-6-chloro-*N*-(cyclopropylmethyl)nicotinamide (**12p**)

Yield 81%; white solid; mp 165.8-166.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20 (s, 2H), 0.47 (d, *J* 6.9 Hz, 2H), 1.12-1.02 (m, 1H), 3.55 (dd, *J* 12.9, 7.2 Hz, 1H), 3.81 (s, 3H), 3.97 (dd, *J* 14.2, 7.1 Hz, 1H), 7.30 (t, *J* 7.8 Hz, 1H), 7.38 (d, *J* 8.2 Hz, 1H), 7.66 (t, *J* 8.2 Hz, 1H), 7.74 (t, *J* 9.1 Hz, 2H), 7.93 (s, 1H), 8.25 (s, 1H), 8.39 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.9, 9.7, 54.7, 62.0, 118.3, 120.3, 121.0 (d, *J* 27.5 Hz), 121.8 (d, *J* 268.8 Hz), 122.5, 123.2, 123.7, 124.3, 125.8, 126.0 (d, *J* 10.3 Hz), 128.6, 129.3 (d, *J* 30.1 Hz), 130.6 (d, *J* 30.4 Hz), 132.0, 133.8 (d, *J* 10.5 Hz), 136.0, 138.8, 140.2, 148.4, 150.5 (d, *J* 18.0 Hz), 152.8, 153.8, 164.3, 165.2, 166.9; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{19}BrClF_{10}N_3O_3$ $[M + H]^+$: 749.0139, found: 749.0098.

N-(3-((2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)carbamoyl)-2-methoxyphenyl)-*N*-(cyclopropylmethyl)-6-fluoronicotinamide (**12q**)

Yield 92%; white solid; mp 162.5-164.0 °C; IR (KBr) *v* / cm^{-1} 3373, 1686, 1663, 1594, 1487, 1456, 1426, 1401, 1375, 1346, 1305, 1276, 1232, 1205, 1164, 1128, 1081, 1024, 1003, 983, 891, 838,770, 727, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20 (s, 2H), 0.47 (d, *J* 6.2 Hz, 2H), 1.11 (s, 1H), 3.55 (dd, *J* 12.8, 7.1 Hz, 1H), 3.81 (s, 3H), 3.98 (dd, *J* 14.1, 7.0 Hz, 1H), 7.05 (d, *J* 7.4 Hz, 1H), 7.34-7.26 (m, 1H), 7.68 (dd, *J* 33.4, 7.2 Hz, 2H), 7.92 (d, *J* 12.5 Hz, 2H), 8.10 (s, 1H), 8.39 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 3.2, 3.7, 9.5, 53.0, 61.7, 108.4 (d, *J* 35.0 Hz), 109.4 (d, *J* 37.8 Hz),120.1, 121.1 (d, *J* 273.0 Hz), 122.4, 122.8, 123.5, 125.6, 128.4, 128.8, 130.4 (d, *J* 4.3 Hz), 131.8 (d, *J* 5.1 Hz), 133.6 (d, *J* 10.1 Hz), 136.0, 138.6, 141.4 (d, *J* 6.7 Hz), 142.8 (d, *J* 9.6 Hz), 146.6 (d, *J* 16.3 Hz), 149.2 (d, *J* 16.9 Hz), 152.7, 164.2 (d, *J* 248 Hz), 164.8, 166.7; HRMS (ESI) *m/z*, calcd. for $C_{28}H_{19}BrF_{11}N_3O_3$ $[M + H]^+$: 733.0434, found: 733.0401.

Biological assay

The tested insects *Plutella xylostella* and *Spodoptera frugiperda* were 3rd instar larvae supported by Shanghai International Trading Co., Ltd. They were continuously fed indoors during the experiment. The leaf-dip method[32] was used to test the insecticidal activity of the target compounds against *Plutella xylostella* and *Spodoptera frugiperda*. Commercially available cyproflanilide was used as a positive control. To prepare the target compound, 10 mg was dissolved in 1 mL of *N*,*N*-dimethylformamide (DMF) to make a 10000 mg L^{-1} mother liquor. The required concentration solution for testing was obtained by diluting the mother liquor with 0.05% warm water.

The experiment was conducted as follows: the leaf plates were immersed in the solution for 10 s and dried in Petri dishes. Four plates were placed in each dish with filter paper to moisturize. 10 3rd instar *Plutella xylostella* larvae were placed in each Petri dish, and the experiment was repeated 3 times. The Petri dishes were placed in a light incubator at 25 °C for 14 h. The number of *Plutella xylostella* larvae deaths was recorded after 1, 2, and 3 days, and the lethality rate was calculated. Lethality rate were corrected using Abbott's formula. The testing method for *Spodoptera frugiperda* was the same as that for *Plutella xylostella*.

Overall, the study aimed to evaluate the insecticidal activity of the target compounds on *Plutella xylostella* and *Spodoptera frugiperda* using the leaf-dip method. Commercially available cyproflanilide was used as the positive control, and the target compounds were tested in various concentrations. The experiments were conducted using the third instar larvae, and lethality rate were calculated over a 3-day period. The study results could offer significant information on the potential of the target compounds as insecticides.

Results and Discussion

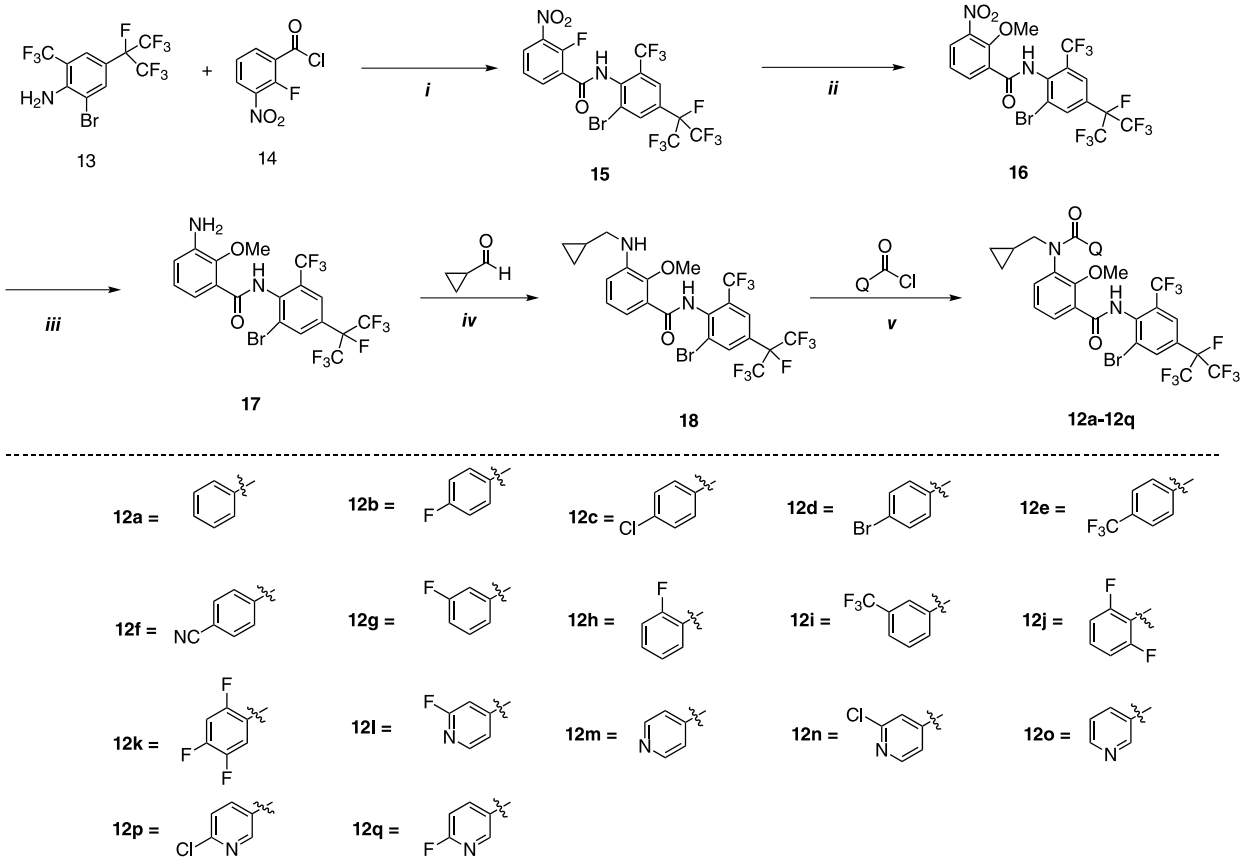
The target compounds **12a-12q** were prepared in

five steps according to the synthesis route shown in Scheme 1. In the first step, 2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)aniline was reacted with 2-fluoro-3-nitrobenzoyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to prepare intermediates **15** with yield 46%.[33] In the second step, compound **15** was reacted with sodium methanol to prepare compound **16** with 87% yield. In the third step, compound **16** was involved in the reduction of nitro group by $SnCl_2{\cdot}2H_2O$ to obtain intermediate **17**,[33] which then reacted with cyclopropanecarbaldehyde to produce intermediate **18**.[33] In the last step, in order to evaluate the effect of methoxy-substituted Q group on the biological activity of the compounds, 17 new compounds were synthesized by amide condensation reaction with yields ranging from 46 to 92%.

After being synthesized and characterized, the biological activities of compounds **12a**-**12q** were tested, and the results are presented in Table 1. The insecticidal activity of cyproflanilide was evaluated under the same conditions.

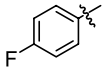
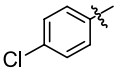
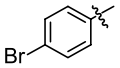
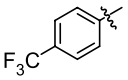
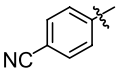
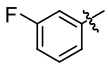
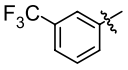
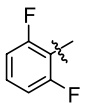
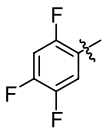
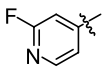
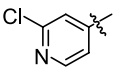
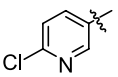
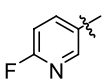
Insecticidal activities against *Plutella xylostella*

The biological activity test results showed that compounds **12a** and **12b** exhibited certain insecticidal activity, with lethality rates of 83.33 and 63.33%, respectively, at a concentration of 1 mg L^{-1}. The effect of different substituents at the *para*-position of the phenyl ring on insecticidal activity was compared. When the *para*-position of the phenyl ring was substituted with halogen atoms Cl or Br, corresponding compounds **12c** and **12d** behaved no biological activity and the lethality rate was 0.00% at a concentration of 1 mg L^{-1}. Studies[34,35] have found that bulky and polarizable halogen atoms can occupy available pockets and interact with the binding site of biological targets through halogen bonding. Therefore, the lack of insecticidal activity in compounds **12c** and **12d** may be due to the large size and steric hindrance of the Cl and Br atoms. Based on the lethality rates results, the activity order of introducing halogen atoms on the phenyl ring is **12b** (*para*-F) > **12c** (*para*-Cl) and **12d** (*para*-Br). This is contrary to the results of da Silva *et al.*,[35,36] who showed good biological activity when polarizable halogen



Scheme 1. General synthetic procedure for target compounds **12a-12q**. (*i*) *N*,*N*-Diisopropylethylamine (DIPIA), DMAP, 120 °C, (yield 46%); (*ii*) NaOMe, K_2CO_3, 80 °C, (yield 87%); (*iii*) EtOH, $SnCl_2{\cdot}2H_2O$, HCl, 110 °C, (yield 59%); (*iv*) cyclopropanecarbaldehyde, 35 °C, (yield 70%); (*v*) pyridine, tetrahydrofuran (THF), 80 °C, (yield 46-92%).

Table 1. The insecticidal activities of compounds **12a-12q**

Compound	Q	3-Day mortality / %			
		Plutella xylostella			*Spodoptera frugiperda*
		1 mg L^{-1}	0.1 mg L^{-1}	0.01 mg L^{-1}	0.1 mg L^{-1}
12a		83.33	3.33	3.33	8.33
12b		63.33	6.67	0.00	4.17
12c		0.00	3.33	0.00	0.00
12d		0.00	12.33	0.00	0.00
12e		0.00	0.00	0.00	8.33
12f		33.33	6.67	3.33	25.00
12g		43.33	3.33	0.00	12.50
12h		3.33	6.67	0.00	4.17
12i		6.67	3.33	0.00	16.67
12j		3.33	6.67	0.00	4.17
12k		0.00	0.00	0.00	0.00
12l		73.33	3.33	0.00	4.17
12m		10.00	3.33	3.33	4.17
12n		26.67	0.00	0.00	4.17
12o		30.00	3.33	0.00	0.00
12p		33.33	0.00	0.00	20.83
12q		96.67	12.33	0.00	58.33
Cyproflanilide	—	100.00	80.00	20.00	100.00

substituents were introduced at the *para*-position of the phenyl ring. When CF_3 and CN groups were introduced at the *para*-position of the phenyl ring, corresponding compounds **12e** had no biological activity, with lethality rates of 0.00 and 33.33%, respectively, at a concentration of 1 mg L^{-1}. Based on the results of *para*-substitution on the phenyl ring, moderate insecticidal activity was observed when the *para*-position was substituted with an F atom. In order to investigate the effect of introducing a fluorine atom on the insecticidal activity, we introduced fluorine atoms at the *meta*- and *para*-positions of the phenyl ring, corresponding to compounds **12g** (43.33%, 1 mg L^{-1}) and **12h** (3.33%, 1 mg L^{-1}), respectively. However, from the lethality rates results, there was no improvement in insecticidal activity. Increasing the number of fluorine substitutions on the phenyl ring, compounds **12j** (3.33%, 1 mg L^{-1}) and **12k** (0.00%, 1 mg L^{-1}) had almost no insecticidal activity. This may be due to the increased number of fluorine atoms substituted on the benzene ring leads to excessive steric hindrance, which may reduce the insecticidal activity. In our previous work,[37] changing the position of the fluorine atom substitution on the phenyl ring and increasing the number of fluorine substitutions also led to a reduction of insecticidal activity of the compounds.

When the Q substituent was a pyridine ring, compounds **12m** and **12o** had low insecticidal activity with lethality rates of 10.00 and 30.00%, respectively, at a concentration of 1 mg L^{-1}. When Cl atoms were introduced at the 2-position of pyridine-4-yl and 6-position of pyridine-3-yl, compounds **12n** (26.67%, 1 mg L^{-1}) and **12p** (33.33%, 1 mg L^{-1}) had low insecticidal activity. However, when F atoms were introduced at the 2-position of pyridine-4-yl and 6-position of pyridine-3-yl, surprisingly, compounds **12l** and **12q** had lethality rates of 73.33 and 96.67%, respectively, at a concentration of 1 mg L^{-1}. Especially compound **12q** had a lethality rate close to that of cyproflanilide (100%) against *Plutella xylostella* larvae. It shows that the introduction of *para*-fluorine can improve the insecticidal activity because it may resonate with the aromatic ring and modification of electron-withdrawing group.[38] Since fluorine atom is a good hydrogen bond receptor with ideal hydrophilicity and metabolic stability of C–F bond,[30,39-42] the introduction of fluorine atom may increase the affinity of parent compounds to insect receptors.

Insecticidal activities against *Spodoptera frugiperda*

The insecticidal activity of compounds **12a**-**12q** against *Spodoptera frugiperda* showed similarly structure-activity relationship as *Plutella xylostella*. It is further proved that the introduction of fluorine atoms is beneficial to the improvement of the insecticidal activity of the target compounds.

Conclusions

Overall, this study successfully synthesized a series of *meta*-diamine compounds containing methoxy group and conducted corresponding biological activity tests. Among them, compound **12q** showed good insecticidal activity and promising application value. This result provides valuable idea to design novel insecticides with excellent activity.

Supplementary Information

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

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References

1. Talekar, N. S.; Shelton, A. M.; *Annu. Rev. Entomol.* **1993**, *38*, 275. [Crossref]
2. Wang, B. L.; Zhu, H. W.; Ma, Y.; Xiong, L. X.; Li, Y. Q.; Zhao, Y.; Zhang, J. F.; Chen, Y. W.; Zhou, S.; Li, Z. M.; *J. Agric. Food Chem.* **2013**, *61*, 5483. [Crossref]
3. Chen, K.; Liu, Q.; Ni, J. P.; Zhu, H. J.; Li, Y. F.; Wang, Q.; *Pest Manage. Sci.* **2015**, *71*, 1503. [Crossref]
4. Khallaf, A.; Wang, P.; Zhuo, S.; Zhu, H. J.; Liu, H.; *J. Heterocycl. Chem.* **2021**, *58*, 2189. [Crossref]
5. Heckel, D. G.; *Science* **2012**, *337*, 1612. [Crossref]
6. Liu, Y. H.; Chung, Y. C.; Xiong, Y.; *Appl. Environ. Microbiol.* **2001**, *67*, 3746. [Crossref]
7. Brugger, K. E.; Cole, P. G.; Newman, I. C.; Parker, N.; Scholz, B.; Suvagia, P.; Walker, G.; Hammond, T. G.; *Pest Manage. Sci.* **2010**, *66*, 1075. [Crossref]
8. Chen, R. J.; Wang, J. J.; Han, L.; Gu, Y. C.; Xu, Z. P.; Cheng, J. G.; Shao, X. S.; Xu, X. Y.; Li, Z. J.; *J. Heterocycl. Chem.* **2021**, *58*, 1429. [Crossref]
9. Koppenhöfer, A. M.; Fuzy, E. M.; *Biol. Control.* **2008**, *45*, 93. [Crossref]

10. Zhu, B. C.; Xing, J. H.; Xu, T. M.; Zheng, Z. W.; Chen, J.; Peng, W. L.; Xu, Y. H.; Kong, X. L.; Wei, Y. C.; Dong, D. Z.; Yuan, J.; Wei, W.; *WO pat. 2012034472*, **2012**.
11. Chen, X. P.; Liu, A. P.; Guan, S. F.; Xu, W. W.; Ren, Y. G.; Liu, X. P.; *World Pestic.* **2021**, *43*, 12. [Crossref]
12. Sakai, M. T.; Kawachinagano, H. N.; Habikino, E. K.; Tondabayashi, T. N.; Izumisano, T. F.; Kawachinagano, T. S.; Hashimoto, A. S.; Kawachinagano, K. S.; Kawachinagano, S. F.; Ibaraki, H. K.; *US pat. 6603044*, **2003**.
13. Sakai-shi, T. M.; Kawachinagano-shi, N. H.; Habikino-shi, K. E.; Tondabaya shi-shi, N. T.; Izumisano-shi, F. T.; Kawachinagano-shi, S. T.; Hashimoto-shi, S. A.; Kawachinagano-shi, S. K.; Kawachinagano-shi Osaka, F. S.; Ibaraki-shi, K. H.; *EP pat. 1006107*, **2000**.
14. YuanZheng, X. F.; ZhongWei, Y. M.; KeYe, R. S.; XiTian, L. S.; Gu, G. J.; QingShui, S. M.; LaiWei, M.; BanTian, H. Z.; *CN pat. 99122802.2*, **2000**.
15. Zhu, B. C.; Xing, J. H.; Xu, T. M.; Zheng, Z. W.; Chen, J.; Peng, W. L.; Xu, Y. H.; Kong, X. L.; Wei, Y. C.; Dong, D. Z.; Yuan, J.; Wei, W.; *CN pat. 101935291*, **2011**.
16. Kato, K.; Kiyonaka, S.; Sawaguchi, Y.; Tohnishi, M.; Masaki, T.; Yasokawa, N.; Mizuno, Y.; Morioue, K.; Hamachi, I.; Takeshima, H.; Mori, Y.; *Biochemistry* **2009**, *48*, 10342. [Crossref]
17. Samurkas, A.; Fan, X. N.; Ma, D.; Sundarraj, R.; Lin, L. Y.; Yao, L.; Ma, R. F.; Jiang, H.; Cao, P.; Gao, Q. Z.; Yuchi, Z. G.; *J. Agric. Food Chem.* **2020**, *68*, 4528. [Crossref]
18. Xu, T.; Yuchi, Z.; *BMC Biol*. **2019**, *17*, 1. [Crossref]
19. Yin, C.; Bi, Y. Y.; Han, L. J.; Fan, Z. J.; Song, S. Y.; Qin, F. Y.; *World Pestic*. **2021**, *43*, 15. [Crossref]
20. Zhou, Y. Y.; Ma, D.; Lin, L. Y.; You, M. S.; Yuchi, Z. G.; You, S. J.; *J. Agric. Food Chem*. **2020**, *68*, 1731. [Crossref]
21. Lai, T. C.; Li, J.; Su, J. Y.; *Pestic. Biochem. Physiol*. **2011**, *101*, 198. [Crossref]
22. Silva, J. E.; Assis, C. P. O.; Ribeiro, L. M. S.; Siqueira, H. A. A.; *J. Econ. Entomol*. **2016**, *109*, 2190. [Crossref]
23. Wang, X. L.; Wu, Y. D.; *J. Econ. Entomol*. **2012**, *105*, 1019. [Crossref]
24. Zhang, Y.; Li, Y. X.; Li, H.; Shang, J. F.; Li, Z. M.; Wang, B. L.; *Chin. Chem. Lett*. **2022**, *33*, 501. [Crossref]
25. Katsuta, H.; Nomura, M.; Wakita, T.; Daido, H.; Kobayashi, Y.; Kawahara, A.; Banba, S.; *J. Pestic. Sci.* **2019**, *44*, 120. [Crossref]
26. Nakao, T.; Banba, S.; Hirase, K.; *J. Pestic. Biochem. Phys.* **2015**, *120*, 101. [Crossref]
27. Zhou, C. C.; Ji, Y. F.; Ren, L. P.; Shao, X. S.; *J. Photochem. Photobiol. Sci*. **2020**, *19*, 854. [Crossref]
28. Lv, L.; Liu, J. Y.; Xiang, J. C.; Ma, W. J.; Zhou, L. Q.; Hou, S.; Ni, Y. P.; Li, Z. C.; *CN pat. 109497062A*, **2019**.
29. Satoshi, Y.; Yoshikawa, H.; Kawamura, F.; Itaya, M.; Taniguchi, H.; *Biosci., Biotechnol., Biochem*. **1992**, *56*, 1995. [Crossref]
30. Horty, L. G.; Daeuble, J. F.; Castetter, S.; Olson, M. B.; Wessels, F. J.; Wang, N. X.; *Pest Manage. Sci*. **2019**, *75*, 3015. [Crossref]
31. Xu, H.; He, X. Q.; *Bioorg. Med. Chem. Lett*. **2010**, *20*, 4503. [Crossref]
32. Zhang, J. F.; Xu, J. Y.; Wang, B. L.; Li, Y. X.; Xiong, L. X.; Li, Y. Q.; Ma, Y.; Li, Z. M.; *J. Agric. Food Chem.* **2012**, *60*, 7565. [Crossref]
33. Lv, L.; Xiang, J. C.; Ma, W. J.; Zhou, L. Q.; Hou, S.; Ni, J. P.; Li, Z. C.; *CN pat*. *109497062B*, **2019**.
34. Hernandes, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; Azevedo Jr., W. F. D.; Leite, A. L.; *Curr. Drug Targets* **2010**, *11*, 303. [Crossref]
35. da Silva, J. B. P.; Navarro, D. M. A. F.; da Silva, A. G.; Santos, G. K. N.; Dutra, K. A.; Moreira, D. R.; Ramos, M. N.; Espíndola, J. W. P.; de Oliveira, A. D. T.; Brondani, D. J.; Leite, A. C. L.; Hernandes, M. Z.; Pereira, V. R. A.; da Rocha, L. F.; de Castro, M. C. A. B.; de Oliverira, B. C.; Lan, Q.; Merz Jr., K. M.; *Eur. J. Med. Chem*. **2015**, *100*, 162. [Crossref]
36. da Silva, A. G.; Navarro, D. M. A. F.; Santos, G. K. N.; de Aguiar, J. C. R. O. F.; França, K. A.; Tébéka, I. R. M.; Anjos, J. V.; Solva, J. B. P.; Kanis, L. A.; Srivastava, R. M.; Neves Filho, R. A. W.; Ramos, M. N.; *J. Braz. Chem. Soc*. **2023**, *34*, 333. [Crossref]
37. Huang, P. M.; Wu, M. H.; Lv, L.; Zhou, L. Q.; Liu, X. W.; Liu, J. Y.; *Tetrahedron Lett*. **2022**, 153743. [Crossref]
38. Neves Filho, R. A. W.; da Silva, C. A.; da Silva, C. S. B.; Brustein, V. P.; Navarro, D. M. A. F.; dos Santos, F. A. B.; Alves, L. C.; dos Santos Cavalcanti, M. G.; Srivastava, R. M.; Carneiro-Da-Cunha, M. D. G.; *Chem. Pharm. Bull*. **2009**, *57*, 819. [Crossref]
39. Wu, C.-C.; Wang, B.-L.; Liu, J.-B.; Wei, W.; Li, Y. X.; Liu, Y.; Chen, M. G.; Xiong, L.-X.; Yang, N.; Li, Z.-M.; *Chin. Chem. Lett*. **2017**, *28*, 1248. [Crossref]
40. Mori, T.; Ujihara, K.; Matsumoto, O.; Yanagi, K.; Matsuo, N.; *J. Fluorine Chem*. **2007**, *128*, 1174. [Crossref]
41. Llark, D. A.; Lahm, G. P.; Smith, B. K.; Barry, J. D.; Clagg, D. G.; *Bioorg. Med. Chem*. **2008**, *16*, 3163. [Crossref]
42. Lima, Â. M. A.; de Paula, W. T.; Leite, I. C. H. L.; Gazolla, P. A. R.; de Abreu, L. M.; Fonseca, V. R.; Romão, W.; Lacerda Jr., V.; de Queiroz, V. T.; Teixeira, R. R.; Costa, A. V.; *J. Braz. Chem. Soc*. **2022**, *33*, 1200. [Crossref]

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