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Synthesis, Insecticidal Activity, and Structure−Activity Relationship of Trifluoromethyl-Containing Phthalic Acid Diamide Structures

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Phthalic acid diamides have received considerable interest in agricultural chemistry due to a novel action mode, extremely high activity against a broad spectrum of lepidopterous insects, low acute toxicity to mammals, and environmentally benign characteristics. A series of phthalic acid diamides (**4I**−**4IV**) with the CF_3 group at meta position on the aniline ring were synthesized. Their structures were characterized by ^{1}H NMR and ^{13}C NMR (or elemental analysis). The structure of N^2-[1,1-dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[3-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide (**4If**) was determined by X-ray diffraction crystallography. Their insecticidal activities against *Plutella xylostella* were evaluated. The results show that some of the title compounds exhibit excellent larvicidal activities against *P. xylostella*, and improvement in larvicidal activity requires a reasonable combination of substituents in the parent structure, which provides some hints for further investigation on structure modification.

KEYWORDS: Phthalic acid diamides; insecticidal; structure−activity relationships

INTRODUCTION

Modern crop production cannot develop without chemical means for pest control, which are referred to as pesticides. Insecticides are quite necessary pesticides, which ensure successful protection from plant insects (*1*). On the other hand, as a result of overyear application of the same insecticide or insecticides of the same mode of action, insects become resistant to these chemicals; therefore, the discovery of insecticides with novel mechanisms of action is an important aspect of effective management of insects (*2*). The ryanodine receptor (RyR) represents a new biochemical target for pest management, and shows great promise in integrated and resistance strategies for pest management (*3*, *4*).

RyRs are a distinct class of ligand-gated calcium channels controlling the release of calcium from intracellular stores (*5*). The name is derived from ryanodine, a toxic natural alkaloid present in *Ryania speciosa* which is best known for its defining role in the characterization and purification of an important class of ion channels and for its use as a natural insect control chemical (*4*, *6*). Ryanodine itself has long been utilized as an insecticide, but its mammalian toxicity has precluded its continued use (*6*).

Recently, there has been renewed interest in this field because of the synthetic chemistry of phthalic acid diamides, which are potent activators of insect RyRs and can be used as a new structural class of highly potent insecticides especially against lepidopteran insects (*7*). Phthalic acid diamides have yielded the important commercial product flubendiamide (**Figure 1**)—the first artificially synthesized insecticide targeting RyRs—which was discovered by Nihon Nohyaku and jointly developed with Bayer (*2*).

Since the first commercial phthalic acid diamide, flubendiamide, was discovered in 1998, a series of phthalic acid diamide derivatives have been investigated in recent years (*8*−*15*). The chemical structure of potent phthalic acid diamides is characterized by three parts as shown **Figure 2**: (A) the phthaloyl moiety, (B) the aliphatic amide moiety and (C) the aromatic amide moiety (*16*). Previous researchers have focused mainly on the substitutions at both the aniline ring and the aliphatic side chain (*8*−*15*). The introduction of a fluorine or polyfluorine atoms into organic molecules has become more mainstream, especially in the pharmaceutical and pesticide industries (*17*). The CF_3 group sometimes greatly modifies the biological activity of molecules due to its intrinsic properties, such as relatively small size, electronegativity, high thermal stability, and increased lipophilicity (*18*). Luckily, when the CF_3 group was introduced into the aniline ring, we found that compound **4Ia** with 3-CF_3 group on the aniline ring showed good insecticidal activity against lepidopterous larvae at the concentration of 100 μg mL^{-1}. The results prompted us to explore the further improvement of its insecticidal activity by structural modifications. Enlightened by all of the descriptions above, we herein report a family of trifluoromethyl-containing phthalic acid diamide structures based on general structure **2** as shown **Figure 3**, which are obtained easily

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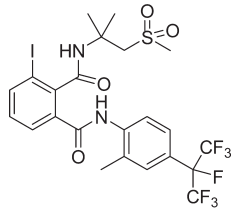
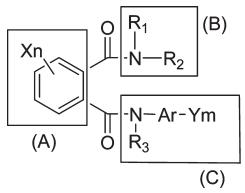


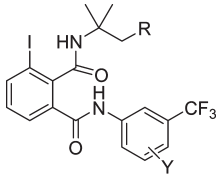
flubendiamide

Figure 1. The chemical structure of flubendiamide.



General structure 1

Figure 2. General formula of phthalic acid diamides.



General structure 2

Figure 3. General structure of the compounds discussed in the text.

and some of them exhibit good insecticidal activities against lepidopterous larvae. Although some of them (compounds **4Ib**, **4Ic** and **4IVb**) have been reported alone on synthesis and insecticidal properties by Nihon Nohyaku (*8*, *9*), the structure−activity relationships of these compounds are, for the first time, reported in this work. Currently, we report the preparation, crystal structure and insecticidal activities of a series of compounds **4I**−**4IV** and discuss their structure−activity relationships.

MATERIALS AND METHODS

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification while all solvents were redistilled before use. Melting points (mp) were taken on an X-4 microscope electrothermal apparatus (Taike China) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer at 500 MHz or a Bruker AV-300 spectrometer at 300 MHz using $CDCl_3$ or DMSO-d_6 as the solvent, with tetramethylsilane as internal standard. The elemental analyses were performed with a Vario EL III elemental analyzer. Compounds 3-iodophthalic anhydride **1** (*19*−*21*), 2-methoxy-5-(trifluoromethyl) aniline **i** (*21*−*23*), 4-methoxy-5-(trifluoromethyl) aniline **e** (*21*−*23*), 1,1-dimethyl-2-(methylthio) ethylamine **I** (*24*), 1,1-dimethyl-2-methoxyethylamine **II** (*25*, *26*), and phthalic acid diamides **4I**−**4IV** (*2*, *27*, *28*) were synthesized according to the methods reported in the literature with some modification, and the detailed procedure and characterization data for intermediates **1**, **e**, **i**, **I** and **II** can be found in the Supporting Information.

General Procedure for the Synthesis of Compounds 2I−2III. A mixture of aliphatic amine (**I**−**III**) (20 mmol) and triethylamine (20 mmol) in dichloromethane (50 mL) was slowly added to a solution of 3-iodophthalic anhydride (20 mmol) in dichloromethane (60 mL) at room temperature. The reaction mixture was stirred for 16 h, poured into water (50 mL), and acidified with dilute hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 15 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was washed with a mixed solution of ether and hexane.

Data for N-(1,1-Dimethyl-3-methylthioethyl)-3-iodophthalamic Acid ***2I***. Yield: 75%; mp 134−135 °C (lit. (*2*): 125−128 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (s, 6H, CH_3-C-CH_3), 2.12 (s, 3H, CH_2-S-CH_3), 2.99 (s, 2H, CH_2-S-CH_3), 7.19 (t, J = 7.9 Hz, 1H, 5-ArH), 7.86 (dd, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H, 4-ArH), 7.91 (s, 1H, O=C−NH−C−CH_3), 8.03 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H, 6-ArH), 13.09 (s, 1H, COOH).

Data for N-(1,1-Dimethyl-3-methoxyethyl)-3-iodophthalamic Acid ***2II***. Yield: 70%; mp 125−126 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (s, 6H, CH_3-C-CH_3), 3.28 (s, 3H, CH_2-O-CH_3), 3.48 (s, 2H, CH_2-O-CH_3), 7.18 (t, 1H, J = 7.9 Hz, 5-ArH), 7.72 (s, 1H, O=C−NH−C−CH_3), 7.86 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1H, 4-ArH), 8.02 (dd, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H, 6-ArH), 13.06 (s, 1H, COOH).

Data for N-tert-Butyl-3-iodophthalamic Acid ***2III***. Yield: 77%; mp 165−168 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 (s, 9H, $C(CH_3)_3$), 7.18 (t, 1H, J = 7.8 Hz, 5-ArH), 7.77 (s, 1H, O=C−NH−C−CH_3), 7.85 (dd, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H, 4-ArH), 8.02 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H, 6-ArH), 13.11 (s, 1H, COOH).

General Procedure for the Synthesis of Compounds 3I−3III. A slurry of 2.5 mmol of phthalamic acid (**2I**−**2III**) in 30 mL of dichloromethane was cooled with an ice bath while 2.6 g (2.5 mmol) of triethylamine was added dropwise with stirring. The solution was stirred and cooled to < 5 °C followed by dropwise addition of 2.9 g (2.5 mmol) of methylsulfonyl chloride at a rate so as to maintain the temperature below 10 °C. The reaction mixture was stirred under ice bath. The progress of the reaction was followed by TLC (petroleum ether/ethyl acetate = 3:1). The reaction solution was used in the subsequent reaction without workup.

General Procedure for the Synthesis of the Title Compounds 4I−4III. To the above reaction solution of **3I**−**3III** (2.5 mmol) in dichloromethane was added aromatic amine (**a**−**j**) (2.5 mmol). The reaction mixture was stirred an additional hour under ice bath and then allowed to warm to room temperature or reflux temperature. The progress of the reaction was followed by TLC (petroleum ether/ethyl acetate = 3:1). The reaction solution was washed with dilute hydrochloric acid, water, an aqueous sodium carbonate solution and water respectively and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1).

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ia***. Yield: 89%; mp 134−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 6H, CH_3-C-CH_3), 2.08 (s, 3H, CH_3-S-CH_2), 2.91 (s, 2H, CH_3-S-CH_2), 6.11 (s, 1H, O=C−NH−C−CH_3), 7.16 (t, J = 7.8 Hz, 1H, 5-ArH), 7.24−7.27 (m, 2H, N^1-4,5-ArH), 7.60 (d, J = 7.7 Hz, 1H, 4-ArH), 7.74−7.78 (m, 2H, 6-ArH, N^1-6-ArH), 7.89 (s, 1H, N^1-2-ArH), 9.77 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{20}F_3IN_2O_2S$: C, 44.79; H, 3.76; N, 5.22. Found: C, 44.63; H, 3.93; N, 5.19.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[4-chloro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ib***. Yield: 86%; mp 170−174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 6H, CH_3-C-CH_3), 2.15 (s, 3H, CH_3-S-CH_2), 2.89 (s, 2H, CH_3-S-CH_2), 6.03 (s, 1H, O=C−NH−C−CH_3), 7.20 (t, J = 7.9 Hz, 1H, 5-ArH), 7.33 (d, J = 8.6 Hz, 1H, N^1-5-ArH), 7.66 (d, J = 6.8 Hz, 1H, 4-ArH), 7.78 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1H, N^1-6-ArH), 7.82 (d, 1H, J = 7.0 Hz, 6-ArH), 7.89 (d, J = 2.5 Hz, 1H, N^1-2-ArH), 9.64 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{19}ClF_3IN_2O_2S$: C, 42.08; H, 3.36; N, 4.91. Found: C, 41.99; H, 3.37; N, 4.92.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[4-fluoro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ic***. Yield: 86%; mp 184−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 6H, CH_3-C-CH_3), 2.10 (s, 3H, CH_3-S-CH_2), 2.92 (s, 2H, CH_3-S-CH_2), 6.07 (s, 1H, O=C−NH−C−CH_3), 6.98 (t, J = 10.59 Hz, 1H, N^1-5-ArH), 7.17 (t, J = 7.8 Hz, 1H, 5-ArH), 7.56 (dd, J_1 = 7.68 Hz, J_2 = 0.9 Hz, 1H, 4-ArH), 7.71−7.82 (m, 3H, 6-ArH, N^1-6-ArH, N^1-2-ArH), 9.64 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{19}F_4IN_2O_2S$: C, 43.33; H, 3.45; N, 5.05. Found: C, 43.19; H, 3.64; N, 4.90.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[4-cyano-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Id***. Yield: 87%; mp

202−205 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.30 (s, 6H, CH_3−C−CH_3), 2.00 (s, 3H, CH_3−S−CH_2), 2.85 (s, 2H, CH_3−S−CH_2), 7.20 (t, J = 7.8 Hz, 1H, 5-ArH), 7.65 (dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 8.02−8.03 (m, 2H, 6-ArH, O═C−N*H*−C−CH_3), 8.09 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H, N^1-5-ArH), 8.15 (d, J = 8.6 Hz, 1H, N^1-6-ArH), 8.35 (d, J = 1.8 Hz, 1H, N^1-2-ArH), 10.84 (s, 1H, O═C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 17.22, 25.31, 44.30, 54.88, 95.18, 101.90, 110.72, 115.62, 116.84, 122.35, 126.95, 129.92, 135.29, 136.27, 136.48, 140.96, 141.63, 143.46, 166.22, 166.96.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[4-methoxy-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ie***. Yield: 81%; mp 164−167 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 6H, CH_3−C−CH_3), 2.02 (s, 3H, CH_3−S−CH_2), 2.86 (s, 2H, CH_3−S−CH_2), 3.87 (s, 3H, CH_3OAr), 7.23 (t, 1H, J = 7.8, 5-ArH), 7.28 (d, 1H, J = 9.0, N^1-5-ArH), 7.59 (d, 1H, J = 7.5, 4-ArH), 7.85 (dd, 1H, J_1 = 9.0, J_2 = 2.0, N^1-6-ArH), 7.95 (s, 1H, O═C−N*H*−C−CH_3), 7.98 (d, 1H, J = 8.0, 6-ArH), 8.02 (d, 1H, J = 2.5, N^1-2-ArH), 10.13 (s, 1H, O═C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 17.25, 25.26, 44.33, 54.83, 56.21, 95.01, 113.30, 116.41, 116.65, 117.97, 124.90, 126.88, 129.87, 131.79, 136.19, 140.36, 141.41, 152.95, 165.17, 167.12.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[3-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4If***. Yield: 85%; mp 184−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 6H, CH_3−C−CH_3), 2.10 (s, 3H, CH_3−S−CH_2), 2.91 (s, 2H, CH_3−S−CH_2), 6.06 (s, 1H, O═C−N*H*−C−CH_3), 6.95 (d, J = 7.3 Hz, 1H, N^1-4-ArH), 7.21 (t, J = 7.8 Hz, 1H, 5-ArH), 7.54 (s, 1H, N^1-6-ArH), 7.65 (d, J = 7.8 Hz, 1H, 4-ArH), 7.74−7.82 (m, 2H, 6-ArH, N^1-2-ArH), 10.18 (s, 1H, O═C−NH−Ar). Anal. Calcd for $C_{20}H_{19}F_4IN_2O_2S$: C, 43.33; H, 3.45; N, 5.05. Found: C, 43.16; H, 3.69; N, 4.87.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[3,5-(ditrifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ig***. Yield: 86%; mp 232−235 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 (s, 6H, CH_3−C−CH_3), 2.08 (s, 3H, CH_3−S−CH_2), 2.86 (s, 2H, CH_3−S−CH_2), 7.27 (t, J = 7.8 Hz, 1H, 5-ArH), 7.66 (dd, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 7.82 (s, 1H, N^1-4-ArH), 8.01−8.03 (t, 2H, 6-ArH, O═C−N*H*−C−CH_3), 8.36 (s, 2H, N^1-2,6-ArH), 10.73 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 17.18, 25.32, 44.30, 54.86, 95.25, 119.26, 121.34, 124.95, 126.85, 129.94, 130.46, 130.92, 135.42, 140.76, 140.88, 166.08, 167.04.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[3-methoxy-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ih***. Yield: 89%; mp 200−204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (s, 6H, CH_3−C−CH_3), 2.00 (s, 3H, CH_3−S−CH_2), 2.85 (s, 2H, CH_3−S−CH_2), 3.82 (s, 3H, CH_3OAr), 6.98 (s, 1H, N^1-4-ArH), 7.24 (t, J = 7.8 Hz, 1H, 5-ArH), 7.53 (s, 1H, N^1-6-ArH), 7.60 (d, J = 7.3 Hz, 1H, 4-ArH), 7.69 (s, 1H, N^1-2-ArH), 8.03−7.98 (t, 2H, 6-ArH, O═C−N*H*−C−CH_3), 10.33 (1H, s, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 17.26, 25.26, 44.31, 54.86, 55.58, 95.07, 105.33, 107.37, 108.19, 108.70, 126.87, 129.93, 130.18, 136.01, 140.55, 140.87, 141.47, 160.39, 165.71, 167.06.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[2-methoxy-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ii***. Yield: 83%; mp 150−154 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 6H, CH_3−C−CH_3), 1.92 (s, 3H, CH_3−S−CH_2), 2.80 (s, 2H, CH_3−S−CH_2), 3.92 (s, 3H, CH_3OAr), 7.24−7.28 (m, 2H, 5-ArIH, N^1-3-ArH), 7.48 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H, N^1-4-ArH), 7.62 (d, J = 7.7 Hz, 1H, 4-ArIH), 8.01 (d, J = 7.6 Hz, 1H, 6-ArIH), 8.25 (s, 1H, O═C−N*H*−C−CH_3), 8.58 (d, J = 1.0 Hz, 1H, N^1-6-ArH), 9.34 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 17.11, 25.18, 44.15, 54.85, 56.24, 94.80, 111.36, 116.60, 120.55, 120.98, 121.60, 127.47, 127.85, 130.10, 135.54, 140.72, 140.88, 151.50, 165.47, 167.52.

Data for N^2-[1,1-Dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-[2-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4Ij***. Yield: 89%; mp 213-215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (s, 6H, CH_3−C−CH_3), 1.97 (s, 3H, CH_3−S−CH_2), 2.86 (s, 2H, CH_3−S−CH_2), 7.25 (t, J = 7.8 Hz, 1H, 5-ArH), 7.65−7.52 (m, 3H, N^1-3-ArH, N^1-4-ArH, 4-ArH), 8.01 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H, 6-ArH), 8.09 (s, 1H, O═C−N*H*−C−CH_3), 8.46 (dd, 1H, N^1-6-Ar), 10.06 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 17.18, 25.25, 44.22, 54.86, 94.98, 116.66, 116.94, 120.13, 122.62, 126.97, 127.13, 127.28, 129.99, 135.25, 140.79, 141.23, 156.78, 165.90, 167.30.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIa***. Yield: 87%; mp 113−116 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22 (s, 6H, $C(CH_3)_2$), 3.15 (s, 3H, CH_2−O−CH_3), 3.32 (s, 2H, CH_2−O−CH_3), 7.24 (t, J = 7.8 Hz, 1H, 5-ArH), 7.44 (d, J = 7.8 Hz, 1H, N^1-4-ArH), 7.58−7.61 (m, 2H, N^1-5-ArH, 4-ArH), 7.78 (s, 1H, O═C−N*H*−C−CH_3), 7.85 (d, J = 8.4 Hz, 1H, N^1-6-ArH), 7.99 (dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.16 (s, 1H, N^1-2-ArH), 10.34 (s, 1H, O═C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 23.40, 53.85, 58.35, 77.79, 94.90, 115.51, 119.88, 122.96, 125.11, 126.87, 129.23, 129.48, 129.88, 136.02, 139.61, 140.45, 141.49, 165.73, 167.03.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[4-chloro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIb***. Yield: 85%; mp 183−186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23 (s, 6H, CH_3−C−CH_3), 3.16 (s, 3H, CH_3−O−CH_2), 3.33 (s, 2H, CH_3−O−CH_2), 7.24 (t, J = 7.8 Hz, 1H, 5-ArH), 7.61 (d, J = 7.6 Hz, 1H, 4-ArH), 7.71 (d, J = 8.8 Hz, 1H, N^1-5-ArH), 7.79 (s, 1H, O═C−N*H*−C−CH_3), 7.86 (d, J = 8.7 Hz, 1H, N^1-6-ArH), 8.00 (dd, J_1 = 7.9 Hz, J_2 = 0.8 Hz, 1H, 6-ArH), 8.26 (d, 1H, J = 2.3 Hz, N^1-2-ArH), 10.47 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 23.43, 53.87, 58.37, 77.80, 95.01, 118.13, 120.84, 124.22, 126.87, 129.89, 132.09, 132.79, 135.75, 137.15, 138.35, 140.62, 141.61, 165.80, 167.03.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[4-cyano-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IId***. Yield: 83%; mp 216−218 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23 (s, 6H, $C(CH_3)_2$), 3.16 (s, 3H, CH_2−O−CH_3), 3.34 (s, 2H, CH_2−O−CH_3), 7.26 (t, 1H, J = 7.8 Hz, 5-ArH), 7.64 (dd, J_1 = 7.7 Hz, J_2 = 1.1 Hz, 1H, 4-ArH), 7.84 (s, 1H, O═C−N*H*−C−CH_3), 8.02 (dd, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H, 6-ArH), 8.08 (dd, J_1 = 8.6 Hz, J_2 = 1.9 Hz, 1H, N^1-5-ArH), 8.10 (d, J = 8.6 Hz, 1H, N^1-6-ArH), 8.34 (d, J = 1.9 Hz, 1H, N^1-2-ArH), 10.84 (s, 1H, O═C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 23.42, 53.90, 58.37, 77.74, 95.08, 101.93, 115.62, 116.79, 122.33, 126.91, 129.90, 131.49, 131.74, 135.29, 136.49, 140.92, 141.73, 143.42, 166.28, 166.94.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[4-methoxy-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIe***. Yield: 83%; mp 169−172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.24 (s, 6H, $C(CH_3)_2$), 3.17 (s, 3H, CH_2−O−CH_3), 3.34 (s, 2H, CH_2−O−CH_3), 3.87 (s, 3H, CH_3OAr), 7.26 (t, J = 7.8 Hz, 1H, 5-ArH), 7.28 (d, J = 9.0 Hz, 1H, N^1-5-ArH), 7.58 (t, J = 6.8 Hz, 1H, 4-ArH), 7.77 (s, 1H, O═C−N*H*−C−CH_3), 7.84 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H, N^1-6-ArH), 7.97 (dd, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H, 6-ArH), 8.02 (d, J = 2.4 Hz, 1H, N^1-2-ArH), 10.12 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 23.45, 53.85, 56.22, 58.41, 77.86, 94.96, 113.31, 116.32, 116.72, 117.96, 124.88, 126.88, 129.86, 131.80, 136.18, 140.33, 141.51, 152.97, 165.22, 167.13.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[3-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIf***. Yield: 87%; mp 162−167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 6H, $C(CH_3)_2$), 3.17 (s, 3H, CH_2−O−CH_3), 3.34 (s, 2H, CH_2−O−CH_3), 7.25 (t, J = 7.8 Hz, 1H, 5-ArH), 7.39 (d, J = 8.5 Hz, 1H, N^1-4-ArH), 7.61 (dd, J_1 = 7.2 Hz, J_2 = 0.9 Hz, 1H, 4-ArH), 7.81−7.84 (d, 2H, N^1-2,6-ArH), 7.91 (s, 1H, O═C−N*H*−C−CH_3), 8.00 (dd, J_1 = 7.4 Hz, J_2 = 0.9 Hz, 1H, 6-ArH), 10.58 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 23.41, 53.89, 58.36, 77.79, 95.06, 107.13, 107.42, 109.52, 109.87, 111.89, 126.84, 129.90, 135.61, 140.72, 141.63, 141.64, 163.59, 165.96, 167.00.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[3,5-(ditrifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIg***. Yield: 89%; mp 179−183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 6H, $C(CH_3)_2$), 3.14 (s, 3H, CH_2−O−CH_3), 3.33 (s, 2H, CH_2−O−CH_3), 7.26 (t, J = 7.8 Hz, 1H, 5-ArH), 7.65 (d, J = 7.4 Hz, 1H, 4-ArH), 7.81−7.84 (d, 2H, O═C−N*H*−C−CH_3, N^1-4-ArH), 8.02 (d, J = 7.8 Hz, 1H, 6-ArH), 8.35 (s, 2H, N^1-2,6-ArH), 10.71 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 23.41, 53.87, 58.29, 77.73, 95.13, 116.42, 119.25, 124.27, 126.81, 129.92, 132.51, 135.41, 140.73, 140.83, 141.74, 166.14, 167.03.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[2-methoxy-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIi***. Yield: 80%; mp 154−156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19 (s, 6H, $C(CH_3)_2$), 3.06 (s, 3H, CH_2−O−CH_3), 3.28 (s, 2H, CH_2−O−CH_3), 3.92 (3H, s, CH_3OAr), 7.22−7.28 (m, 2H, 5-ArH, N^1-3-ArH), 7.48 (d, J = 8.5 Hz, 1H, N^1-4-ArH), 7.61 (d, J = 7.7 Hz, 1H, 4-ArH), 8.00 (d, J = 7.9 Hz, 1H, 6-ArH), 8.12 (s, 1H, O═C−N*H*−C−CH_3), 8.58 (s, 1H, N^1-6-ArH), 9.37 (s, 1H, O═C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 23.29, 53.89, 56.22, 58.29, 77.58, 94.71, 111.36, 116.53, 120.55, 120.98, 121.56, 127.42, 127.86, 130.03, 135.50, 140.68, 141.07, 151.53, 165.53, 167.55.

Data for N^2-[1,1-Dimethyl-2-(methoxy)ethyl]-3-iodo-N^1-[2-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIj***. Yield: 88%; mp 193−196 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.24 (s, 6H, $C(CH_3)_2$), 3.11 (s, 3H, CH_2-O-CH_3), 3.33 (s, 2H, CH_2-O-CH_3), 7.25 (t, J = 7.8 Hz, 1H, 5-ArH), 7.63−7.54 (m, 3H, 4-ArH, N^1-3,4-ArH), 7.90 (s, 1H, O=C−NH−C−CH_3), 8.01 (dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.47 (d, J = 5.4 Hz, 1H, N^1-6-ArH), 10.04 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 23.31, 53.88, 58.32, 77.68, 94.79, 116.67, 116.84, 119.98, 122.51, 126.97, 127.08, 127.17, 130.94, 135.26, 140.69, 141.0733, 156.05, 165.96, 167.23.

Data for N^2-tert-Butyl-3-iodo-N^1-[3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIIa***. Yield: 89%; mp 225−228 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.25 (s, 9H, $C(CH_3)_3$), 7.24 (t, J = 7.8 Hz, 1H, 5-ArH), 7.44 (d, J = 7.5 Hz, 1H, N^1-4-ArH), 7.57−7.61 (m, 2H, 4-ArH, N^1-5-ArH), 7.88−7.86 (d, 2H, N^1-6-ArH, O=C−NH−C−CH_3), 7.99 (d, J = 8.0 Hz, J = 0.5 Hz, 1H, 6-ArH), 8.14 (s, 1H, N^1-2-ArH), 10.35 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 28.07, 50.87, 95.02, 115.50, 119.86, 122.93, 126.92, 129.25, 129.50, 129.78, 129.89, 135.96, 139.62, 140.44, 141.78, 165.77, 166.85.

Data for N^2-tert-Butyl-3-iodo-N^1-[4-chloro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIIb***. Yield: 85%; mp 266−268 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 9H, $C(CH_3)_3$), 7.24 (t, J = 7.8 Hz, 1H, 5-ArH), 7.61 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 7.71 (d, J = 8.5 Hz, 1H, N^1-5-ArH), 7.89 (s, 1H, O=C−NH−C−CH_3), 7.93 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H, N^1-6-ArH), 7.99 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.23 (d, J = 2.5 Hz, 1H, N^1-2-ArH), 10.48 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 28.09, 50.86, 95.09, 118.11, 121.54, 124.19, 126.54, 126.78, 126.89, 129.76, 132.09, 135.67, 138.33, 140.59, 141.89, 165.81, 166.81.

Data for N^2-tert-Butyl-3-iodo-N^1-[4-methoxy-3-(trifluoromethyl)-phenyl]-1,2-benzenedicarboxamide ***4IIIe***. Yield: 82%; mp 243−245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 9H, $C(CH_3)_3$), 3.87 (s, 3H, CH_3OAr), 7.22 (t, J = 7.8, 1H, 5-ArH), 7.27 (d, J = 8.5, 1H, N^1-5-ArH), 7.58 (d, J = 7.5 Hz, 1H, 4-ArH), 7.83−7.85 (t, 2H, N^1-6-ArH, O=C−NH−C−CH_3), 7.97 (d, J = 8.0 Hz, 1H, 6-ArH), 8.00 (d, J = 2.5 Hz, 1H, N^1-2-ArH), 10.11 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 28.10, 50.85, 56.18, 95.02, 113.29, 117.97, 122.37, 124.54, 124.86, 126.90, 129.73, 131.75, 136.10, 140.29, 141.76, 152.92, 165.23, 166.91.

Data for N^2-tert-Butyl-3-iodo-N^1-[3-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIIf***. Yield: 88%; mp 232−234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 5.68 (s, 1H, O=C−NH−C−CH_3), 6.92 (d, J = 6.0 Hz, 1H, N^1-2-ArH), 7.18 (t, J = 4.7 Hz, 1H, 5-ArH), 7.54 (s, 1H, N^1-6-ArH), 7.59 (d, J = 4.6 Hz, 1H, 4-ArH), 7.73−7.77 (m, 1H, 6-ArH, N^1-4-ArH), 10.12 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{19}H_{17}F_4IN_2O_2$: C, 44.90; H, 3.37; N, 5.51. Found: C, 45.02; H, 3.48; N, 5.49.

Data for N^2-tert-Butyl-3-iodo-N^1-[3-methoxy-5-(trifluoromethyl)-phenyl]-1,2-benzenedicarboxamide ***4IIIh***. Yield: 88%; mp 227−230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (s, 9H, $C(CH_3)_3$), 3.82 (s, 3H, CH_3OAr), 6.98 (s, 1H, N^1-4-ArH), 7.23 (t, J = 7.8 Hz, 1H, 5-ArH), 7.52 (s, 1H, O=C−NH−C−CH_3), 7.59 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 7.67 (s, 1H, N^1-6-ArH), 7.88 (s, 1H, N^1-2-ArH), 7.99 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 10.32 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 28.09, 50.88, 55.57, 95.09, 105.27, 108.15, 108.66, 126.90, 129.79, 130.18, 130.60, 135.92, 140.49, 140.84, 141.83, 152.92, 165.23, 166.91.

Data for N^2-tert-Butyl-3-iodo-N^1-[2-methoxy-5-(trifluoromethyl)-phenyl]-1,2-benzenedicarboxamide ***4IIIi***. Yield: 84%; mp 209−212 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.21 (s, 9H, $C(CH_3)_3$), 3.92 (s, 3H, CH_3OAr), 7.23−7.27 (m, 1H, 5-ArH, N^1-5-ArH), 7.48 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H, N^1-4-ArH), 7.62 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 8.01 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.18 (s, 1H, O=C−NH−C−CH_3), 8.57 (d, J = 2.0 Hz, 1H, N^1-2-ArH), 9.32 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 27.86, 50.92, 56.18, 94.77, 111.33, 116.41, 120.63, 120.83, 121.58, 127.56, 127.76, 129.95, 135.30, 140.71, 141.27, 151.45, 165.47, 167.33.

Data for N^2-tert-Butyl-3-iodo-N^1-[2-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IIIj***. Yield: 83%; mp 228−230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.26 (s, 9H, $C(CH_3)_3$), 7.23 (t, J = 7.8 Hz, 1H, 5-ArH), 7.53−7.64 (m, 3H, 4-ArH, N^1-4,5-ArH), 8.00−8.01 (m, 2H, O=C−NH−C−CH_3, 6-ArH), 8.43 (d, J = 5.0 Hz, 1H, N^1-2-ArH), 10.03 (s, 1H, O=C−NH−Ar); ^{13}C NMR (500 MHz, DMSO-d_6) δ 27.95, 50.90, 94.91, 116.72, 116.89, 120.10, 122.63, 126.89, 126.99, 127.30, 129.82, 135.10, 140.73, 141.62, 156.13, 165.93, 167.09.

General Procedure for the Synthesis of Target Compounds 4IV. To a solution of **4I** (0.3 mmol) in dichloromethane (10 mL) was added *m*-chloroperoxybenzoic acid (MCPBA) (0.66 mmol). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate = 1:1). After the disappearance of compound **4I**, the mixture was poured into water. The product was extracted with chloroform. The organic layer was washed with an aqueous sodium hydrosulfite solution and an aqueous sodium carbonate solution respectively, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1:1).

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVa***. Yield: 89%; mp 119−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 6H, CH_3-C-CH_3), 2.88 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.62 (s, 2H, $CH_3-S(O)_2-CH_2$), 6.37 (s, 1H, O=C−NH−C−CH_3), 7.19 (t, J = 7.8 Hz, 1H, 5-ArH), 7.24−7.31 (m, 2H, N^1-4,5-ArH), 7.53 (d, J = 7.6 Hz, 1H, 4-ArH), 7.73−7.81 (m, 3H, 6-ArH, N^1-2,6-ArH), 9.66 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{20}F_3IN_2O_4S$: C, 42.27; H, 3.55; N, 4.93. Found: C, 42.10; H, 3.71; N, 4.90.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[4-chloro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVb***. Yield: 90%; mp 116−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (s, 6H, CH_3-C-CH_3), 2.96 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.89 (s, 2H, $CH_3-S(O)_2-CH_2$), 6.40 (s, 1H, O=C−NH−C−CH_3), 7.20 (t, J = 7.8 Hz, 1H, 5-ArIH), 7.26 (d, J = 8.6 Hz, 1H, N^1-5-ArH), 7.52 (d, J = 7.7 Hz, 1H, 4-ArH), 7.76−7.72 (m, 3H, 6-ArH, N^1-2,6-ArH), 9.93 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{19}ClF_3IN_2O_4S$: C, 39.85; H, 3.18; N, 4.65. Found: C, 39.72; H, 3.25; N, 4.52.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[4-fluoro-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVc***. Yield: 88%; mp 215−218 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 6H, CH_3-C-CH_3), 2.98 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.69 (2 s, H, $CH_3-S(O)_2-CH_2$), 7.26 (t, J = 7.8 Hz, 1H, 5-ArH), 7.47 (t, J = 10.0 Hz, 1H, N^1-5-ArH), 7.66 (d, J = 7.6 Hz, 1H, 4-ArH), 7.95 (t, 1H, N^1-2-ArH), 8.00 (d, J = 7.8 Hz, 1H, 6-ArH), 8.17 (d, J = 4.4 Hz, 1H, N^1-6-ArH), 8.30 (s, 1H, O=C−NH−C−CH_3), 10.50 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{19}F_4IN_2O_4S$: C, 40.97; H, 3.27; N, 4.78. Found: C, 40.82; H, 3.43; N, 4.81.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[4-cyano-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVd***. Yield: 87%; mp 185−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6H, CH_3-C-CH_3), 2.92 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.56 (s, 2H, $CH_3-S(O)_2-CH_2$), 6.54 (s, 1H, O=C−NH−C−CH_3), 7.22−7.28 (t, 1H, 5-ArH), 7.60−7.68 (m, 2H, 4-ArH, N^1-5-ArH), 7.83 (d, J = 8.2 Hz, 1H, N^1-6-ArH), 7.93−7.95 (d, 2H, N^1-2-ArH, 6-ArH), 9.99 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{21}H_{19}F_3IN_3O_4S$: C, 42.51; H, 3.23; N, 7.08. Found: C, 42.33; H, 3.43; N, 7.22.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[4-methoxy-3-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVe***. Yield: 85%; mp 118−121 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52 (s, 6H, CH_3-C-CH_3), 2.98 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.64 (s, 2H, $CH_3-S(O)_2-CH_2$), 3.87 (s, 3H, CH_3OAr), 7.24−7.29 (m, 2H, N^1-5-ArH, 5-ArH), 7.66 (d, J = 7.6 Hz, 1H, 4-ArH), 7.88 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H, N^1-6-ArH), 8.00 (dd, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H, 6-ArH), 8.02 (d, J = 2.3 Hz, 1H, N^1-2-ArH), 8.28 (s, 1H, O=C−NH−C−CH_3), 10.25 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{21}H_{22}F_3IN_2O_5S$: C, 42.15; H, 3.71; N, 4.68. Found: C, 41.91; H, 3.77; N, 4.64.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[3-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVf***. Yield: 88%; mp 215−217 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 6H, CH_3-C-CH_3), 3.00 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.65 (s, 2H, $CH_3-S(O)_2-CH_2$), 6.41 (s, 1H, O=C−NH−C−CH_3), 6.87 (d, J = 8.1 Hz, 1H, N^1-4-ArH), 7.21 (t, J = 7.8 Hz, 1H, 5-ArH), 7.50 (d, J = 7.7 Hz, 1H, 4-ArH), 7.52 (s, 1H, N^1-2-ArH), 7.58 (d, J = 10.7 Hz, 1H, N^1-6-ArH),

7.70 (d, J = 7.9 Hz, 1H, 6-ArH), 10.18 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{20}H_{19}F_4IN_2O_4S$: C, 40.97; H, 3.27; N, 4.78. Found: C, 41.02; H, 3.47; N, 4.69.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[3,5-(ditrifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVg***. Yield: 90%; mp 225−228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H, CH_3-C-CH_3), 3.04 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.64 (s, 2H, $CH_3-S(O)_2-CH_2$), 6.49 (s, 1H, O=C−NH−C−CH_3), 7.23 (t, J = 7.9 Hz, 1H, 5-ArH), 7.37 (s, 1H, N^1-4-ArH), 7.49 (dd, J_1 = 7.3 Hz, J_2 = 1.0 Hz, 1H, 4-ArH), 7.68 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 7.99 (s, 2H, N^1-2,6-ArH), 10.62 (s, 1H, O=C−NH−Ar). Anal. Calcd for $C_{21}H_{19}F_6IN_2O_4S$: C, 39.64; H, 3.01; N, 4.40. Found: C, 39.61; H, 3.23; N, 4.27.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[3-methoxy-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVh***. Yield: 87%; mp 198−200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 6H, CH_3-C-CH_3), 2.99 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.82 (s, 2H, $CH_3-S(O)_2-CH_2$), 4.06 (s, 3H, CH_3OAr), 6.99 (s, 1H, N^1-4-ArH), 7.27 (t, J = 7.7 Hz, 1H, 5-ArH), 7.58 (s, 1H, N^1-6-ArH), 7.67 (d, J = 7.6 Hz, 1H, 4-ArH), 7.71 (1 s, H, N^1-2-ArH), 8.02 (d, J = 7.9 Hz, 1H, 6-ArH), 8.33 (s, 1H, O=C−NH−C−CH_3), 10.46 (s, 1H, O=C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 26.04, 43.08, 52.36, 55.58, 60.84, 95.28, 105.54, 108.21, 108.72, 127.00, 130.07, 130.21, 130.63, 135.90, 140.78, 140.87, 141.36, 159.93, 165.68, 167.39.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-methoxy-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVi***. Yield: 89%; mp 138−142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.47 (s, 6H, CH_3-C-CH_3), 2.87 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.59 (s, 2H, $CH_3-S(O)_2-CH_2$), 3.93 (s, 3H, CH_3OAr), 7.29−7.25 (m, 2H, 5-ArH, N^1-3-ArH), 7.50 (dd, J_1 = 8.6 Hz, J_2 = 1.7 Hz, 1H, N^1-4-ArH), 7.66 (d, J = 7.5 Hz, 1H, 4-ArH), 8.02 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.49 (s, 1H, O=C−NH−C−CH_3), 8.53 (s, 1H, N^1-6-ArH), 9.39 (s, 1H, O=C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 25.84, 43.09, 52.35, 56.25, 60.50, 94.94, 111.52, 117.00, 120.68, 120.93, 121.83, 127.44, 127.64, 130.28, 135.62, 140.57, 140.81, 151.74, 165.43, 167.62.

Data for N^2-[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-[2-fluoro-5-(trifluoromethyl)phenyl]-1,2-benzenedicarboxamide ***4IVj***. Yield: 85%; mp 191−194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (s, 6H, CH_3-C-CH_3), 2.96 (s, 3H, $CH_3-S(O)_2-CH_2$), 3.66 (s, 2H, $CH_3-S(O)_2-CH_2$), 7.27 (t, J = 7.8 Hz, 1H, 5-ArH), 7.53−7.62 (m, 2H, N^1-4,5-ArH), 7.70 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1H, 4-ArH), 8.03 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, 6-ArH), 8.37−8.32 (m, 2H, N^1-2-ArH, O=C−NH−C−CH_3), 10.21 (s, 1H, O=C−NH−Ar); ^{13}C NMR (300 MHz, DMSO-d_6) δ 25.95, 43.15, 52.36, 60.64, 95.24, 116.83, 117.11, 121.04, 123.08, 126.72, 126.89, 127.40, 130.11, 135.17, 140.97, 141.13, 157.37, 165.76, 167.47.

X-ray Diffraction. The crystal of compound **4If** (0.28 × 0.22 × 0.20 mm) was obtained by slow evaporation from a solution of methanol. All measurements were made with a Bruker SMART Apex CCD area detector under graphite monochromatized Mo Kα (λ = 0.71073 Å) radiation at 291 K. The structure was solved by direct methods and refined on F^2 using all data by full-matrix least-squares procedures with SHELXL-97 (*29*).

Evaluation of Insecticidal Activities. The larvicidal activities of the title compounds (**4I**−**4IV**) against *Plutella xylostella* were evaluated according to the literature procedures (*2*). The insecticidal activity against *P. xylostella* was tested by the dipping method. Cabbage leaf disks (8 cm in diameter) were dipped into a test solution for 10 s and air-dried on filter paper. The treated diet was released into the Petri dish, and seven third-instar *P. xylostella* were released into the Petri dish. The *P. xylostella* affected by this treatment were assessed for 3 days after the treatment.

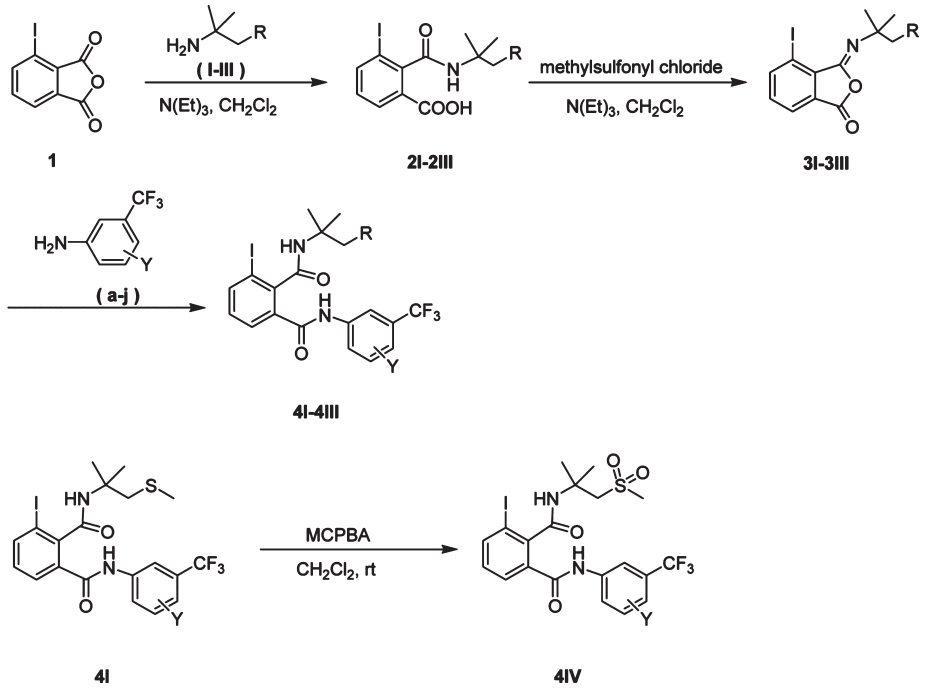
P. xylostella with abnormal symptoms such as body contraction, feeding cessation, or paralysis were included in the number of dead (*2*). The results are listed in **Table 1**, in which the mortality percentage was expressed as the mean of values obtained in three independent experiments. Flubendiamide, the lead compound, was used as a control.

Table 1. Structures and Larvicidal Activities against *P. xylostella* of Compounds **4I**−**4IV**

				mortality (%)	
compd	R	Y	concn (μg mL^{-1})	2 d	3 d
4Ia	SCH_3	H	100	100	
			10	90	100
4Ib	SCH_3	4-Cl	100	100	
			10	100	
4Ic	SCH_3	4-F	100	100	
			10	100	
4Id	SCH_3	4-CN	100	100	
			10	6	42
4Ie	SCH_3	4-OMe	100	5	50
4If	SCH_3	3-F	100	90	100
			10	43	100
4Ig	SCH_3	3-CF_3	100	71	85
4Ih	SCH_3	3-OMe	100	0	5
4Ii	SCH_3	2-OMe	100	5	5
4Ij	SCH_3	2-F	100	41	65
4IIa	OCH_3	H	100	60	100
			10	0	13
4IIb	OCH_3	4-Cl	100	5	52
4IId	OCH_3	4-CN	100	0	0
4IIe	OCH_3	4-OMe	100	0	0
4IIf	OCH_3	3-F	100	10	19
4IIg	OCH_3	3-CF_3	100	0	0
4IIi	OCH_3	2-OMe	100	0	0
4IIj	OCH_3	2-F	100	6	12
4IIIa	H	H	100	100	
			10	50	100
4IIIb	H	4-Cl	100	85	100
			10	20	70
4IIIe	H	4-OMe	100	0	5
4IIIf	H	3-F	100	14	76
4IIIh	H	3-OMe	100	10	10
4IIIi	H	2-OMe	100	0	0
4IIIj	H	2-F	100	57	62
4IVa	$S(O)_2CH_3$	H	100	100	
			10	95	100
4IVb	$S(O)_2CH_3$	4-Cl	100	100	
			10	100	
4IVc	$S(O)_2CH_3$	4-F	100	100	
			10	100	
4IVd	$S(O)_2CH_3$	4-CN	100	57	100
			10	0	50
4IVe	$S(O)_2CH_3$	4-OMe	100	0	0
4IVf	$S(O)_2CH_3$	3-F	100	100	
			10	57	91
4IVg	$S(O)_2CH_3$	3-CF_3	100	40	90
4IVh	$S(O)_2CH_3$	3-OMe	100	0	0
4IVi	$S(O)_2CH_3$	2-OMe	100	0	0
4IVj	$S(O)_2CH_3$	2-F	100	43	67
flubendiamide			100	100	
			10	67	100

RESULTS AND DISCUSSION

Synthesis. The reaction sequence employed for the synthesis of the title compounds is shown in **Figure 4**. Compounds **2I**−**2III** were prepared in high yields by the reaction of 3-iodophthalic anhydride (**1**) with various aliphatic amines (**I**, **II**, **III**) in the dichloromethane using triethylamine as the acid acceptor. In these reactions, a minor precipitate was observed when complete formation of product had occurred. The precipitate was attributed to 3-iodophthalic acid arising from the presence of traces of water. In the presence of methylsulfonyl chloride, compounds **2I**−**2III** first generated corresponding *N*-substituted isoimides **3I**−**3III** at 0−5 °C and subsequently reacted with various aromatic amines (compounds **a**−**i**) to give the title compounds **4I**−**4III** at room temperature in good yields. Unexpectedly, 2-fluoro-5-(trifluoromethyl)aniline (**j**) did not react with intermediates **3I**−**3III** to provide the corresponding compounds unless the reaction mixture was refluxing, while 2,5-bis(trifluoromethyl) aniline is still not able to react with intermediates **3I**−**3III** to form the



I: R = SCH_3 II: R = OCH_3 III: R = H IV: R = SO_2CH_3

a: Y = H b: Y = 4-Cl c: Y = 4-F d: Y = 4-CN

e: Y = 4-OMe f: Y =3-F g: Y = 3-CF_3 h: Y = 3-OMe

i: Y = 2-OMe j: Y = 2-F

Figure 4. General synthetic route for the title compounds **4I**−**4IV**.

corresponding compounds even under reflux conditions, which might be due to the low nucleophilic reactivities and large steric effect of these compounds.

Structure. The structures of all synthesized compounds were confirmed by ^{1}H NMR. As a result of the difference of shielding effect between S, O and $-S(O)_2$, for compounds **4I**, **4II** and **4IV**, the chemical shift of the CH_2 in the aliphatic side chain appears at δ 2.85−2.92, δ 3.28−3.34 and δ 3.56−3.89 respectively and the CH_3 group attached to the heteroatom in the aliphatic side chain appears at δ 1.97−2.15, δ 3.06−3.17, and δ 2.87−3.04 respectively. A signal peak appearing at the lowest field of 9.64−10.84 in the ^{1}H NMR showed that the target compounds have aromatic amide hydrogen. The chemical shift of −CO−NH−C− in aliphatic amide moiety is influenced by the solvent. It appears at δ 5.68−6.54 and δ 7.52−8.33 with $CDCl_3$ and DMSO-d_6 as solvent, respectively. In addition, the results of X-ray single-crystal diffraction of **4If** further validated the structure of the title compounds because we could not ensure the relative position of iodine atom, aliphatic amide and aromatic amide, which gave limited information in the ^{1}H NMR spectra. The results demonstrate that compound **4If** has the desired structure. In the crystal structure of compound **4If**, intramolecular N−H···S, N−H···O, C−H···S and C−H···O and intermolecular N−H···O and C−H···F hydrogen bonds link the molecules to form a three-dimensional network (**Figure 5** and **Figure 6**), in which they may be effective in the stabilization of the structure.

Biological Activities and Structure−Activity Relationships. For the convenience of structure−activity relationship analysis, according to the type substitution aliphatic amide moiety, R of compounds **4I**, **4II**, **4III** and **4IV** were substituted by $-SCH_3$, $-OCH_3$, H and $-SO_2CH_3$ respectively. The results of in vivo larvicidal activities of these compounds (**4I**−**4IV**) against *P. xylostella* are listed in **Table 1**. These compounds were tested at the concentration of 100 and 10 μg mL^{-1}. Although it seems difficult to construct an obvious structure−activity relationship from the data shown in **Table 1**, we can conclude clearly that $-SCH_3$ (**4I**) substitutions were most active followed by H (**4III**) and $-OCH_3$ (**4II**), and the last series were almost inactive. See the

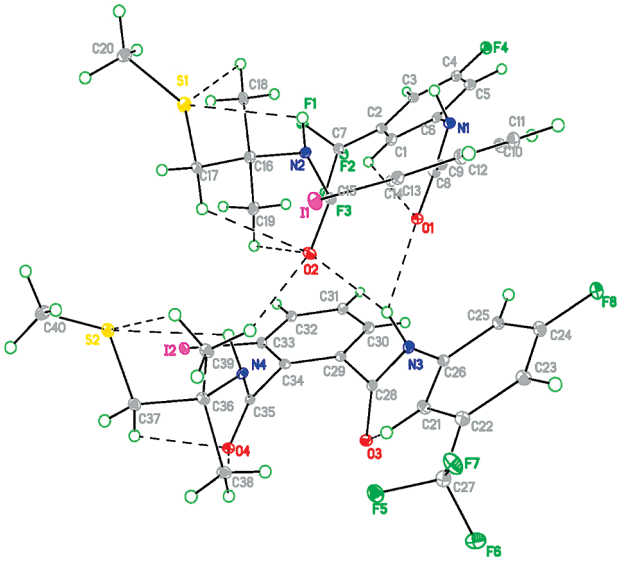


Figure 5. X-ray structure of compound **4If**.

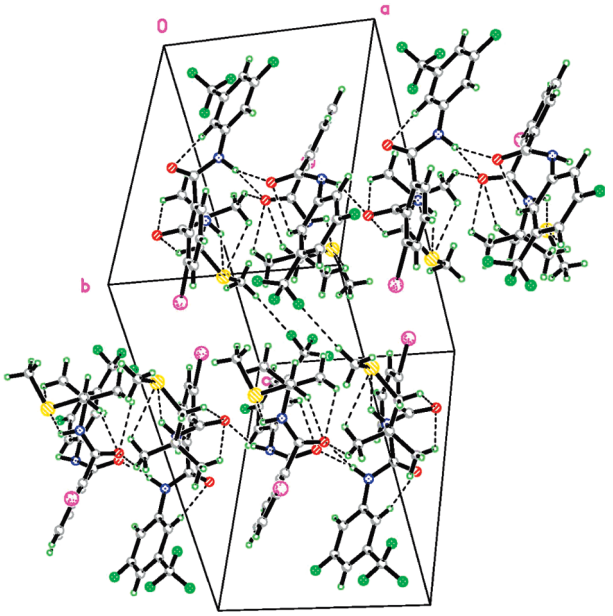


Figure 6. Packing diagram in a unit cell of compound **4If**.

comparison of compounds **4Ia** vs **4IIIa** (Y = 4-H), **4Ib** vs **4IIIb** (Y = 4-Cl), **4Ie** vs **4IIIe** (Y = 4-OMe), **4If** vs **4IIIf** (Y = 3-F), and **4Ij** vs **4IIIj** (Y = 2-F). Compounds **4II** did not show larvicidal activity against *P. xylostella* at the concentration of 100 μg mL^{-1} except **4IIa**. However, at the concentration of 10 μg mL^{-1}, **4IIa** did not exhibit any larvicidal activity against *P. xylostella*. For $-SO_2CH_3$ (**4IV**) substitutions, their larvicidal activities against *P. xylostella* were nearly equal to those of their corresponding $-SCH_3$ (**4I**) substitutions, as seen in the comparison compounds **4Ia** vs **4IVa** (Y = H), **4Ib** vs **4IVb** (Y = 4-Cl), **4Ic** vs **4IVc** (Y = 4-F), **4Id** vs **4IVd** (Y = 4-CN), **4Ig** vs **4IVg** (Y = 3-CF_3), **4Ih** vs **4IVh** (Y = 3-OMe), **4Ii** vs **4IVi** (Y = 2-OMe), and **4Ij** vs **4IVj** (Y = 2-F). However, compounds **4If**, **4IVf** (Y = 4-F), **4Ie** and **4IVe** (Y = 4-OMe) are four exceptions: compound **4If** (100%) displayed higher insecticidal activity than compound **4IVf** (91%) at 10 μg mL^{-1}, and compound **4Ie** showed 50% insecticidal activity at 100 μg mL^{-1}, while compound **4IVe** did not exhibit any insecticidal activity at the same concentration. These observations show that the differences in insecticidal activity are due to variations in combination of aliphatic amide and aromatic amide moieties.

To examine the electronic effect of substituent Y on the aniline ring, the electron-donating substituent $-OCH_3$ and electron-withdrawing substituents Cl, F, CN, $-CF_3$ were introduced. Compounds with electron-withdrawing substituents displayed higher larvicidal activities against *P. xylostella* than compounds with electron-donating substituents, as seen in the comparison of the compounds **4Ib** (Y = 4-Cl), **4Ic** (Y = 4-F), **4Id** (Y = 4-CN) and **4Ie** (Y = 4-OCH_3) of the series with Y at 4-position on the aniline ring, **4If** (Y = 3-F), **4Ig** (Y = 3-CF_3) and **4Ih** (Y = 3-OCH_3) of the series with Y at 3-position on the aniline ring, and **4Ij** (Y = 2-F) and **4Ii** (Y = 2-OCH_3) of the series with Y at 2-position on the aniline ring. These observations revealed that substitution patterns on the aniline ring have an important influence on the larvicidal activity. Compounds with electron-withdrawing substituents showed excellent larvicidal activities against *P. xylostella,* while compounds with electron-donating substituents did not display any larvicidal activity.

According to the relative position of $-CF_3$ and the substituents Y on the aniline ring, compounds **4Ia**, **4IIa**, **4IIIa** and **4IVa**; **4Ib**−**4Id**, **4IIIb** and **4IVb**−**4IVd**; **4If**, **4Ig**, **4IIIf** and **4IVf**−**4IVg**; and **4Ij**, **4IIIj** and **4IVj** were defined as nonderivatives, ortho-derivatives, meta-derivatives, and para-derivatives, respectively. The sequence of larvicidal activity *P. xylostella* is ortho-derivatives > meta-derivatives > para-derivatives, irrespective of difference in substituent R in the aliphatic amide moiety. For example, within the series of R = $-SCH_3$ derivatives, ortho-derivative **4Ic** (Y = 4-F) displayed a much higher larvicidal activity against *P. xylostella* than the corresponding meta-derivative **4If** (Y = 3-F), while the para-derivative **4Ij** (Y = 2-F) showed the lowest larvicidal activity. Similar speculation could apply to the compounds **4III** (R = H) or the compounds **4IV** (R = $-SO_2CH_3$). However, the relationships between the larvicidal activities of ortho-derivatives, meta-derivatives, para-derivatives and the corresponding nonderivatives were related to the difference in substituent R in the aliphatic amide moiety. For compounds **4I** (R = $-SCH_3$) and **4IV** (R = $-SO_2CH_3$), in most cases, ortho-derivatives showed increased activity in comparison with that observed for the corresponding nonderivatives against the larvae of *P. xylostella*, for example, compounds **4Ib** (Y = 4-Cl), **4Ic** (Y = 4-F), **4IVb** (Y = 4-Cl), **4IVc** (Y = 4-F) and **4Ia** (Y = H). However, compounds **4Ib** and **4IVd** (Y = 4-CN) exhibited lower larvicidal activities against *P. xylostella* than the corresponding nonderivative **4IVa** (Y = H) at the concentration of 10 μg mL^{-1}. Meta-derivatives and para-derivatives showed reduced activity in comparison with that observed for the corresponding nonderivatives against the larvae of *P. xylostella*, for example, compounds **4If** (Y = 3-F), **4Ig** (Y = 3-CF_3), **4Ij** (Y = 2-F), **4IVf** (Y = 3-F), **4IVg** (Y = 3-CF_3), **4IVj** (Y = 2-F) and **4Ia** (Y = H). For compounds **4III** (R = H), the effect of introducing another group into the aniline ring is to reduce activity irrespective of difference in positions (compare ortho-derivative **4IIIb** (Y = 4-Cl), meta-derivative **4IIIf** (Y = 3-F), para-derivative **4IIIj** (Y = 2-F) and corresponding nonderivative **4IIIa** (Y = H)).

Table 2. Insecticidal Activities against *P. xylostella* of Compounds **4Ib**, **4Ic**, **4IVb** and **4IVc**

	concn (μg mL^{-1})				
	5	1	0.5	0.1	LC_{50} (μg mL^{-1})
4Ib	100	62	57	0	0.42
4Ic	100	33	0	0	
4IVb	100	52	29	4.8	0.98
4IVc	100	29	5	0	
flubendiamide	100	95	90	20	0.15

In addition, as shown in **Table 1**, **4Ib**, **4Ic**, **4IVb** and **4IVc** were the most active compounds. All of their larvicidal activities against *P. xylostella* at 10 μg mL^{-1} were 100% after two days, while the larvicidal activity of the commercial product flubendiamide was 66.67% at the same concentration after two days. These results indicated that compounds **4Ib**, **4Ic**, **4IVb** and **4IVc** displayed comparable larvicidal activity with flubendiamide against *P. xylostella* at 10 μg mL^{-1}. Therefore, we carried out further insecticidal activity assay for compounds **4Ib**, **4Ic**, **4IVb** and **4IVc**, and flubendiamide was used as a control to make a judgment on the larvicidal potency of these compounds. As shown in **Table 2**, it was found that the LC_{50} value of compound **4Ib** against *P. xylostella* was 0.42 μg mL^{-1}, while that of the commercial control flubendiamide was 0.15 μg mL^{-1}.

In summary, a series of phthalic acid diamides were synthesized, and their larvicidal activities against *P. xylostella* were evaluated. The preliminary bioassays indicate that some of the phthalic acid diamides exhibit excellent insecticidal activities against *P. xylostella*. Structure−activity relationship study reveals that the improvement of insecticidal activity requires a reasonable combination of both aliphatic amide and aromatic

amide moieties, and the type and position of substituent Y on the aniline ring are critical.

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Supporting Information Available: Preparation of compounds **1**, **e**, **i**, **I**, and **II**. This material is available free of charge via the Internet at http://pubs.acs.org.

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