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Synthesis and Properties of Pentafluorosulfanyl Group (SF_5)-Containing Meta-Diamide Insecticides

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Academic Editors: György Szöllösi and Eva Frank
Received: 21 October 2020; Accepted: 23 November 2020; Published: 25 November 2020

Abstract: Herein, we describe novel pentafluorosulfanyl (SF_5) group-containing meta-diamide insecticides. For the facile preparation of the SF_5-based compounds **4a**–**d**, practical synthetic methods were applied. Among newly synthesized compounds, 3-benzamido-*N*-(2,6-dimethyl-4-(pentafluoro-λ^6-sulfanyl)phenyl)-2-fluorobenzamide **4d** showed (i) a high insecticidal activity, (ii) an excellent selectivity to insects, and (iii) good levels of water solubility and log P values. In this study, we demonstrated that the pentafluorosulfanyl moiety could serve as an attractive functionality for the discovery of a new scope of crop-protecting agents.

Keywords: meta-diamide; pentafluorosulfanyl; insecticide; GABARs

1. Introduction

The introduction of a fluorine atom into a biologically active compound can have a significant influence on its properties. One or more incorporated fluorine atoms can alter the electrostatic and hydrogen bonding parameters of the molecule as well as its physicochemical and pharmacokinetic properties [1,2]. Currently, fluorine-containing substituents, which are commonly encountered in commercial pharmaceuticals and agrochemicals, include fluoroaromatic, trifluoromethyl (CF_3), trifluoromethoxy (OCF_3), and trifluoromethlythio (SCF_3) functionalities [3,4]. Another fluorinated substituent that reflects the continuing development of a relatively new fluorinated building block with distinct properties could be the pentafluorosulfanyl (SF_5) group. The SF_5 group is often called the "super-trifluoromethyl group", and aryl sulfanyl pentafluorides display high thermal and chemical stability, electronegativity, and lipophilicity [5–7]. Due to its unique properties, the SF_5 group has widely been applied in drug discovery and crop protection research (Figure 1) [8–14], since the first organic pentafluorosulfanyl compound was described in 1950 [15].

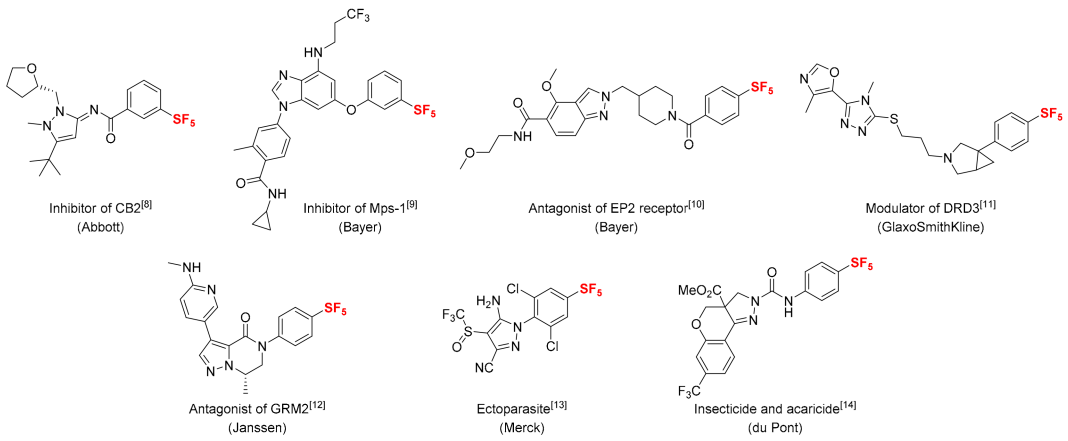


Figure 1. SF_5-containing biologically active compounds [8–14].

As a part of our ongoing efforts to discover new eco-friendly insecticides [16–18], we are particularly interested in small molecules containing the fluorine atom. One of the outstanding representatives of this category is broflanilide, which is known as an efficient broad-spectrum meta-diamide insecticide containing a high number of fluorine atoms [19,20]. Taking into account the suggested potential bioisosteric relationship between the SF_5 and CF_3 substituents [2,5], we proposed the novel design of the SF_5-containing meta-diamide insecticide **4d** (Figure 2). In order to examine the influence of SF_5 moiety on the properties of the meta-diamide **4d** (R^1 = H, R^2 and R^3 = CH_3) and investigate the significance of the effect caused by the replacement of the $CF(CF_3)_2$ group to SF_5 functionality, the known meta-diamide insecticide **BPB1** (R^1 = H, R^2 and R^3 = CH_3) was selected for this study (Figure 2). According to the previous studies on the development of meta-diamide-based insecticides, it was discovered that the insecticide **BPB3** (R^1 = CH_3) can be metabolized to its active form, **BPB1** (R^1 = H), which in its turn demonstrates insecticidal activity by acting on the target RDL GABARs gene subunit and inhibiting its expression [19,20].

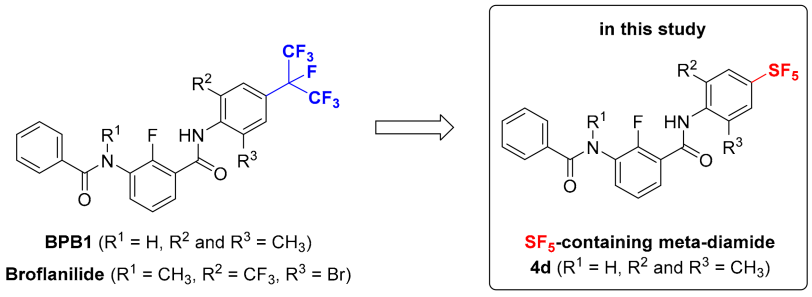
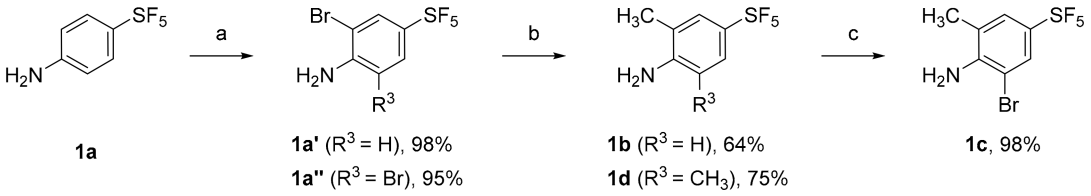


Figure 2. SF_5-containing meta-diamide insecticides in this study.

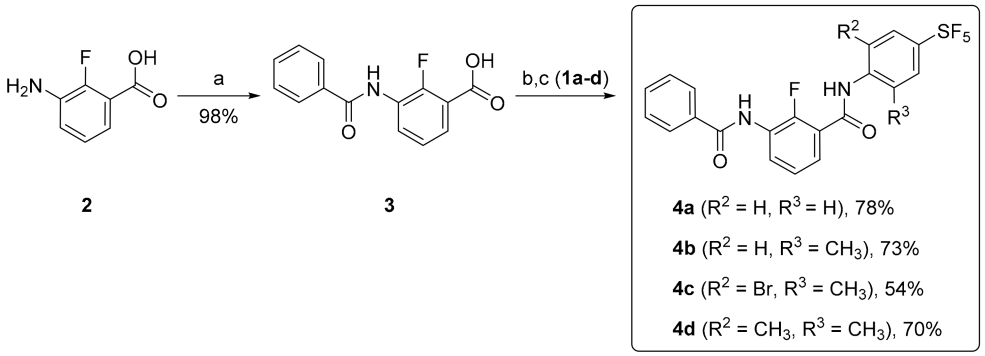
2. Results

The synthetic route shown in Scheme 1 was successfully applied for the preparation of the *para*-SF_5 substituted aniline derivatives, **1b**–**d**. The synthesis was initiated by the bromination of a commercially available aniline, **1a** using *N*-bromosuccinimide (NBS), which led to the formation of mono- and di-bromo anilines **1a′** and **1a″**, respectively. The molecules, **1a′** and **1a″** were subsequently methylated by the Pd-catalyzed cross-coupling to give the corresponding anilines, **1b** and **1d** in 64% and 75% yields, respectively. Finally, 2-methyl-aniline **1b** was further reacted with NBS in DMF to produce 2-methyl-6-bromo-aniline **1c** with excellent yield [21].



Scheme 1. Reagents and conditions: (a) for **1a′**: *N*-bromosuccinimide (1.1 eq), DMF, rt, 2 h; for **1a″**: NBS (2.5 eq), DMF, rt, 2 h; (b) from **1a′** to **1b**: $CH_3B(OH)_2$ (2.0 eq), $Pd(dppf)_2Cl_2$, Cs_2CO_3, 1,4-dioxane, reflux, 12 h; from **1a″** to **1d**: $CH_3B(OH)_2$ (4.0 eq), $Pd(dppf)_2Cl_2$, Cs_2CO_3, 1,4-dioxane, reflux, 12 h; (c) from **1b** to **1c**: *N*-bromosuccinimide (1.5 eq), DMF, rt, 2 h.

The target compounds with the incorporated SF_5 group were successfully prepared starting from 2-fluoro-3-nitrobenzoic acid, which is commercially available and can be readily converted into the corresponding aniline **2** [22]. Benzoylation of **2** provided 3-benzamido-2-fluorobenzoic acid **3** in excellent yield [23]. Then, SF_5-containing compounds **4a–d** were easily prepared by the condensation of benzoic acid **3** with 4-SF_5-anilines **1a–d** (Scheme 2) [24].

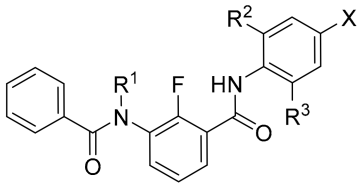


Scheme 2. Reagents and conditions: (a) Benzoyl chloride, NaOH, H_2O, rt, 6 h; (b) $SOCl_2$, reflux, 1 h; (c) 4-SF_5-anilines **1a–d**, $NaHCO_3$, Acetone/H_2O, reflux, 2 h.

The synthesized SF_5-containing derivatives **4a–d** were examined for their insecticidal activities at 10 ppm concentration against the 3rd instar larvae of *Plutella xylostella* using the leaf-dip method [16–18,25]. Among them, the compounds **4c** and **4d** showed excellent activities with high inhibition of feeding behaviors (entry 3 and 4, Table 1). Interestingly, 2,6-dimethyl-substituted compound **4d**, SF_5-containing meta-diamide **BPB1**, displayed an excellent potency with eating area—0~5%. According to the data in Table 1, it is reasonable to believe that the SF_5 group can be considered as an important part of the toxophore.

The target site specificities of newly prepared SF_5-based meta-diamide insecticide **4d** should differ in insect and mammalian GABA and glycine receptors. In this regard, the cell-based antagonist activities of the meta-diamide **4d** against the human $GABA_AR$ and glycine receptor (GlyR) A1 were investigated. According to the results obtained from previous studies, the mammalian $GABA_AR$ $\alpha1\beta3\gamma2$ and the human glycine receptor (GlyR) A1 were selected for this study [19,26,27]. As shown in Table 2, the estimated IC_{50} values of SF_5-containing meta-diamide **4d** and broflanilide against $GABA_AR$ and GlyR were more than 30 μM. This discovery implies that SF_5-containing meta-diamide **4d** has much higher selectivity toward targeted insects.

Table 1. Insecticidal activities of SF_5-containing meta-diamide insecticides **4a–d** against the 3rd instar larvae of *Plutella xylostella*.



4a–d

Entry	SF_5-Containing Meta-Diamide Insecticides					Against the 3rd Instar Larvae of *Plutella xylostella* at 10 ppm		
	Compound	R^1	R^2	R^3	X	Larvicidal Activity (%) at Time (h)		Eating Area (%)
						72 h	96 h	96 h
1	**4a**	H	H	H	SF_5	28	36	>30
2	**4b**	H	H	CH_3	SF_5	7	7	>30
3	**4c**	H	Br	CH_3	SF_5	90	90	5~10
4	**4d**	H	CH_3	CH_3	SF_5	83	87	0~5
5	Broflanilide	CH_3	Br	CF_3	$CF(CF_3)_2$	100	100	0~5

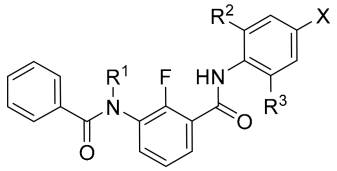
Table 2. Summary of the antagonist activities of SF_5-containing meta-diamide insecticide **4d** according to ion channel cell-based ionflux assays of wild-type $GABA_A$Rs and GlyRs.

Entry	Receptor	Estimated IC_{50} (μM)	
		SF_5-Containing Meta-Diamide 4d	Broflanilide
1	$GABA_AR$ α1β3γ2	>30	>30
2	GlyRA1	>30	>30

There are a number of studies for confirming the existence of the strong relationship between insecticidal activity and bioavailability of the potential insecticides [18,28]. In this context, SF_5-containing compound **4d**, which showed the highest potency, was further investigated in its physicochemical properties, including LogP and solubility. As a reference, properties of broflanilide were also measured. For lipophilicity, most commonly referred to as LogP [29], replacing the heptafluoroisopropyl group with the SF_5 moiety resulted in similar LogP values in broflanilide and the meta-diamide **4d** (entry 1, Table 3). In addition, both the molecules meta-diamide **4d** and broflanilide showed high levels of kinetic solubility [30].

Generally, the presence of fluoroaromatics and perfluoroalkanes increases the lipophilicity values of the molecules in comparison to the parental hydrocarbon bonds [31–35]. In addition to that, regarding its structural differences, the SF_5 group possesses superior properties over other available fluorine-containing functionalities. Taking into consideration that lipophilicity plays a key role in transport processes [36], this result could be an important finding to discover new functionalities for application in the development of crop protecting agents.

Table 3. Physical properties of SF_5-containing meta-diamide insecticide **4d**.



4d

Entry	Compound	R^1	R^2	R^3	X	LogP [a,b]	Solubility [c,d] (Kinetic)
1	**4d**	H	CH_3	CH_3	SF_5	4.68	313.3 ± 1.3 μM (153.0 ± 0.6 μg/mL)
2	Broflanilide	CH_3	CF_3	Br	$CF(CF_3)_2$	4.22	>500 μM (331.6 μg/mL)

[a] Using ACD/Labs T3 method (pH—metric); [b] for graphs, please see the supporting information; [c] Method for determination of kinetic solubility: nephelometry; [d] DMSO-stock solution 5% in water [18].

3. Material and Methods

3.1. General Information

Melting points: Barnstead/Electrothermal 9300—measurements were performed in open glass capillaries. NMR spectra: Bruker AV 300 MHz (Bruker corporation, Billerica, MA, USA)(^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz), AV 400 MHz (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz), AV 500 MHz (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 MHz), and AV2 500 MHz (^{19}F-NMR: 470 MHz); the spectra were recorded in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as the internal standard and are reported in ppm. 1H-NMR data are reported as follows: (s—singlet; d—doublet; t—triplet; q—quartet; dd—doublet of doublet; m—multiplet; coupling constant(s) J are given in Hz; integration, proton assignment). High-resolution mass spectra (HRMS): JEOL JMS-700.

2-Methyl-4-(pentafluorothio)aniline (**1b**) [37,38]. A mixture of 2-bromo-4-(pentafluorothio)aniline (500 mg, 3.223 mmol), methylboronic acid (2.0 eq., 6.446 mmol), Pd(dppf)Cl_2.DCM (0.1 eq., 0.322 mmol), and Cs_2CO_3 (3.0 eq., 9.669 mmol) in 1,4-dioxane (8.6 mL) was stirred at 105 °C for 5 h. The reaction mixture was diluted with EtOAc and washed with aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on a silica gel (hexane:EtOAc = 15:1) to give the desired product **1b** as a yellow solid (481 mg, 64%).

2-bromo-6-methyl-4-(pentafluorothio)aniline (**1c**). To a solution of 2-methyl-4-(pentafluorothio)aniline (350 mg, 1.5 mmol) in DMF (15 mL), NBS (1.03 eq., 1.545 mmol) was added. The reaction mixture was stirred at RT for 2 h, quenched with water, and extracted with EtOAc (10 mL). The organic layer was dried over $NaSO_4$, filtered, and concentrated. The residue was purified by column chromatography on a silica gel (hexane:EtOAc = 20:1) to give the desired product **1c** as a red solid (459 mg, 98%). mp 64~65 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 4.42 (s, 2H), 2.25 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.0, 144.7, 129.2, 127.9, 122.8, 107.8, 19.4; ^{19}F-NMR (470 MHz, $CDCl_3$) δ 86.46 (p, 1F, $J_{SF–SF4}$ = 150.3 Hz, SF), 64.90 (d, 4F, $J_{SF4–SF}$ = 150.2 Hz, SF_4); HRMS (EI) calcd. for $C_7H_7BrF_5NS$ 310.9403, found 310.9409 (see Supplementary Materials).

2,6-dimethyl-4-(pentafluorothio)aniline (**1d**). A mixture of 2-bromo-6-methyl-4-(pentafluorothio)aniline (200 mg, 0.64 mmol), methylboronic acid (2.0 eq., 1.28 mmol), Pd(dppf)Cl_2.DCM (0.1 eq., 0.064 mmol), and Cs_2CO_3 (3.0 eq., 1.92 mmol) in 1,4-dioxane (1.7 mL) was stirred at 105 °C for 5 h. The mixture was diluted in EtOAc, washed with aq. $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on a silica gel (hexane:EtOAc = 15:1) to give the desired product **1d** as a brown solid (119 mg, 75%). mp 205~206 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 2H), 3.90 (s, 2H), 2.20 (s, 6H); ^{13}C-NMR (100 MHz, CDCl3) δ 145.2, 144.1, 128.0, 126.5, 121.8, 120.7, 18.0;

^{19}F-NMR (470 MHz, $CDCl_3$) δ 87.32 (p, 1F, $J_{SF–SF4}$ = 149.9 Hz, SF), 64.88 (d, 4F, $J_{SF4–SF}$ = 149.8 Hz, SF_4); HRMS (EI) calcd. for $C_8H_{10}F_5NS$ 247.0454, found 247.0451 (see Supplementary Materials).

3-benzamido-2-fluorobenzoic acid (**3**). To 2-fluoro-3-nitro-benzoic acid (2 g, 10.8 mmol) in 44 mL of tetrahydrofuran, 20% palladium hydroxide on carbon (148 mg, 1.05 mmol) was added. The reaction was stirred under hydrogen for 2 h. The reaction mixture was filtered through a short pad of celite and the solution was evaporated (without a purification) to give the desired compound **3** as an ivory color solid (1.64 g, 98%). mp 257~258 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.32 (s, 1H), 10.22 (s, 1H), 8.02–7.95 (m, 2H), 7.86–7.79 (m, 1H), 7.76–7.69 (m, 1H), 7.66– 7.59 (m, 1H), 7.58–7.51 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 165.5, 164.8, 133.7, 131.9, 131.1, 128.5, 128.5, 128.3, 127.8, 126.9, 123.8, 123.8; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −119.6; HRMS (EI) calcd. for $C_{14}H_{10}FNO_3$ 259.0645, found 259.0638 (see Supplementary Materials).

*3.2. General Method for the Synthesis of **4a–d***

A mixture of 3-benzamido-2-fluorobenzoic acid **3** (50 mg, 0.193 mmol) and $SOCl_2$ (3.0 eq., 0.579 mmol) was refluxed for 2 h. The solution of aniline (0.9 eq., 0.174 mmol) and $NaHCO_3$ (2.7 eq., 0.52 mmol) in acetone/water (0.4 mL/0.04 mL) was added in the reaction mixture. The reaction mixture was refluxed for 1 h, quenched with water, and extracted with EtOAc (10 mL). The organic layer was dried over $NaSO_4$, filtered, and concentrated. The residue was purified by column chromatography on a silica gel (hexane:EtOAc = 10:1) to give the desired product.

3-Benzamido-2-fluoro-N-(4-(pentafluorothio)phenyl)benzamide (**4a**). This follows the general method. The residue was purified by column chromatography on a silica gel (Hexane:EtOAc = 10:1) to give the desired diamide **4a** as a white solid (55.3 mg, 78% yield). mp 193~194 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.63–8.57 (m, 1H), 8.44 (d, *J* = 12.4 Hz, 1H), 8.09 (s, 1H), 7.94–7.88 (m, 2H), 7.85–7.80 (m, 1H), 7.78 (s, 4H), 7.65–7.60 (m, 1H), 7.57–7.52 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 161.3, 140.2, 133.9, 132.6, 129.1, 127.2, 127.1,127.0, 126.8, 126.4, 126.3, 125.5, 125.4, 121.3, 121.2, 119.6; ^{19}F-NMR (470 MHz, $CDCl_3$) δ 84.83 (quin, 1F, $J_{SF–SF4}$, *J* = 150.3 Hz, SF), 63.41 (d, 4F, $J_{SF4–SF}$, *J* = 149.8 Hz, SF_4), −131.28–−131.40 (m, 1F); HRMS (EI) calcd. for $C_{20}H_{14}F_6N_2O_2S$ 460.0680, found 460.0680 (see Supplementary Materials).

3-benzamido-2-fluoro-N-(2-methyl-4-(pentafluorothio)phenyl)benzamide (**4b**). This follows the general method. The residue was purified by column chromatography on a silica gel (Hexane:EtOAc = 10:1) to give the desired diamide **4b** as a white solid (54.3 mg, 73% yield). mp 189~190 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.64–8.59 (m, 1H), 8.42–8.34 (m, 2H), 8.11 (s, 1H), 7.94–7.87 (m, 3H), 7.67 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.64–7.60 (m, 2H), 7.56–7.52 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 2.42 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 160.9, 152.2, 149.8, 138.6, 134.0, 132.6, 129.0, 127.9, 127.6, 127.1, 126.9, 126.8, 126.72, 126.70, 126.46, 126.44, 125.49, 125.46, 125.0, 121.3, 121.1, 121.0, 18.0; ^{19}F-NMR (470 MHz, $CDCl_3$) δ 85.10 (t, 1F, $J_{SF–SF4}$, *J* = 150.2 Hz, SF), 63.42 (d, 4F, $J_{SF4–SF}$, *J* = 149.9 Hz, SF_4), −132.30 (s, 1F); HRMS (EI) calcd. for $C_{21}H_{16}F_6N_2O_2S$ 474.0837, found 474.0837 (see Supplementary Materials).

3-benzamido-N-(2-bromo-6-methyl-4-(pentafluorothio)phenyl)-2-fluorobenzamide (**4c**). This follows the general method. The residue was purified by column chromatography on a silica gel (Hexane:EtOAc = 10:1) to give the desired diamide **4c** as a brown solid (51.2 mg, 54% yield). mp 209~210 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.69–8.63 (m, 1H), 8.17–8.07 (m, 2H), 7.94–7.89 (m, 3H), 7.89–7.83 (m, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.64–7.59 (m, 1H), 7.56–7.52 (m, 2H), 7.40–7.35 (m, 1H), 2.43 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 161.0, 152.4, 149.9, 138.9, 137.0, 134.0, 132.6, 129.1, 128.0, 127.6, 127.2, 127.1, 127.0, 126.5, 126.3, 125.4, 125.3, 121.4, 120.5, 120.4, 20.0; ^{19}F-NMR (470 MHz, $CDCl_3$) δ 82.97 (quin, 1F, $J_{SF–SF4}$, *J* = 150.5 Hz, SF), 63.35 (d, 4F, $J_{SF4–SF}$, *J* = 150.0 Hz, SF_4), −130.98 (s, 1F); HRMS (EI) calcd. for $C_{21}H_{15}BrF_6N_2O_2S$ 551.9942, found 551.9954 (see Supplementary Materials).

3-benzamido-N-(2,6-dimethyl-4-(pentafluorothio)phenyl)-2-fluorobenzamide (**4d**). This follows the general method. The residue was purified by column chromatography on a silica gel (Hexane:EtOAc = 10:1) to

give the desired diamide **4d** as a white solid (52.7 mg, 70% yield). mp 205~206 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.60 (t, *J* = 7.9 Hz, 1H), 8.13 (s, 1H), 7.93–7.90 (m, 2H), 7.85–7.80 (m, 2H), 7.64–7.59 (m, 1H), 7.56–7.51 (m, 4H), 7.36 (t, *J* = 8.0 Hz, 1H), 2.36 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 161.4, 161.3, 136.5, 136.4, 133.9, 132.5, 129.0, 127.1, 126.9, 126.8, 126.4, 126.4, 126.1, 126.15, 125.8, 125.8, 125.7, 125.3, 125.2, 18.9; ^{19}F-NMR (470 MHz, $CDCl_3$) δ 84.69 (quin, 1F, $J_{SF–SF4}$, *J* = 150.3, SF), 63.09 (d, 4F, $J_{SF4–SF}$, *J* = 149.7 Hz, SF_4), −131.55 (s, 1F); HRMS (EI) calcd. for $C_{22}H_{18}F_6N_2O_2S$ 488.0993, found 488.0988 (see Supplementary Materials).

4. Conclusions

In summary, starting from the known meta-diamide **BPB1** containing a heptafluoroisopropyl group and its isosteric replacement with pentafluorosulfanyl moiety (-SF_5) led to the meta-diamide insecticide **4d**, a compound with good potency, high selectivity toward insects, and a similar level of lipophilicity with broflanilide. For the preparation of SF_5-containing meta-diamide insecticides **4a–d**, an efficient synthetic route was established. This study has demonstrated that the pentafluorosulfanyl group (-SF_5) could be an appealing structural scaffold for the discovery of a new crop-protecting agent.

Supplementary Materials: The following are available online: 1H, 13C and 19F NMR spectroscopy of compound **1c**.; 1H, 13C and 19F NMR spectroscopy of compound **1d**.; 1H, 13C and 19F NMR spectroscopy of compound **3**.; 1H, 13C and 19F NMR spectroscopy of compound **4a**.; 1H, 13C and 19F NMR spectroscopy of compound **4b**.; 1H, 13C and 19F NMR spectroscopy of compound **4c**.; 1H, 13C and 19F NMR spectroscopy of compound **4d**.; Table S1 and S2: Larvicidal activity against Plutella xylostella (**4c** and **4d**); Figure S1: pH-metric Log P of compounds **4d** (KI-03066); Figure S2: pH-metric Log P of Broflanilide and Figure S3. Ion Channels assay of **4d** (KI-03066) and Broflanilide.

Author Contributions: Methodology, J.G.K., H.J.L. and S.J.P.; investigation, W.H.L., H.J.L. and S.J.P.; analysis, J.G.K., O.-Y.K., S.M.K., G.I., I.S.O., Y.L., W.H.L., H.J.L. and S.J.P.; writing—original draft preparation, H.J.L. and S.J.P.; writing—review and editing, O.-Y.K., S.M.K., G.I., I.S.O., Y.L., H.J.L. and S.J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This work was fully supported by KRICT/Kyung Nong Co. Ltd. co-research project (TS191-06R, TS201-18R, and SI2031-40). This research was funded by the Ministry of Trade, Industry and Energy, Republic of Korea, grant number 10077494. This research was also supported by the Bio and Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. 2019M3E5D506617712).

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are not available from the authors.