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Synthesis, Physicochemical Properties, and Biological Activities of 4-(*S*-Methyl-*N*-(2,2,2-Trifluoroacetyl)Sulfilimidoyl) Anthranilic Diamide

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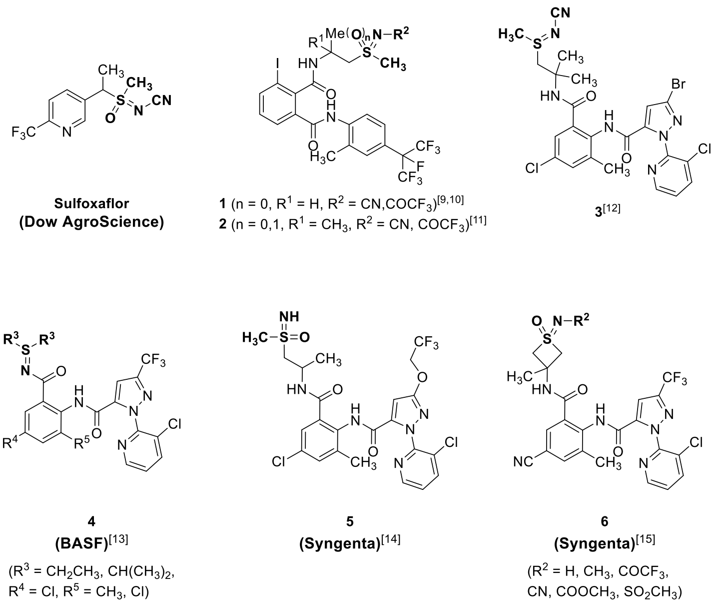
Academic Editors: Paula Sério Branco, Filipa Siopa and Wim Dehaen
Received: 19 July 2019; Accepted: 19 September 2019; Published: 23 September 2019

Abstract: Novel anthranilic diamides with sulfilimidoyl and sulfoximidoyl functionalities were successfully prepared. Among newly-prepared organosulfur compounds, 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylthio)phenyl)-1*H*-pyrazole-5-carboxamide and (*S*,*E*)-3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-4-(S-methyl-*N*-(2,2,2-trifluoroacetyl)sulfinimidoyl)-6-(methylcarbamoyl)phenyl)-1*H*-pyrazole-5-carboxamide showed good levels of efficacy and a strong correlation between insecticidal activities and physical properties, respectively. In particular, available data indicated that the *N*-trifluoroacetyl sulfilimine moiety could be an appealing structural scaffold for the discovery of a new crop-protecting agent.

Keywords: anthranilic diamide; sulfilimine; sulfoximine; insecticide

1. Introduction

After the discovery of sulfoxaflor by Dow AgroScience [1–3], compounds with sulfoximine moiety have received remarkable attention in crop protection. Consequently, a large number of studies have examined the chemistry and mode of action of sulfoxaflor and sulfoximine insecticides [4–8]. As shown in Figure 1, the interest in the sulfoximine moiety has led to the discovery of highly-active sulfilimine-containing insecticides **1**–**4** [9–13]. For patent applications, researchers at BASF prepared sulfilimine-based anthranilic diamides **4** and reported that it is highly active in insects which are resistant to ryanodine modulator insecticide [13]. Furthermore, various sulfoximine-containing anthranilamides **6** have been reported by researchers at Syngenta (Figure 1) [14,15]. In addition to crop-protection applications, many research groups reported that sulfoximine could be a bioisostere of sulfones and sulfonamides with enhanced absorption, distribution, metabolism, and excretion (ADME) properties. These suggests that introducing a sulfur–nitrogen bond could be a promising approach for the discovery of new biologically-active molecules [16–22]. For the preparation of sulfilimine- and sulfoximine-based compounds, synthetic methods and strategies have been widely investigated by many research groups [23–27]. In particular, Bolm et al. reported facile and practical synthetic approaches [28], which are applied in this study.



Sulfoxaflor
(Dow AgroScience)

1 (n = 0, R^1 = H, R^2 = CN,$COCF_3$)[9,10]
2 (n = 0,1, R^1 = CH_3, R^2 = CN, $COCF_3$)[11]

3[12]

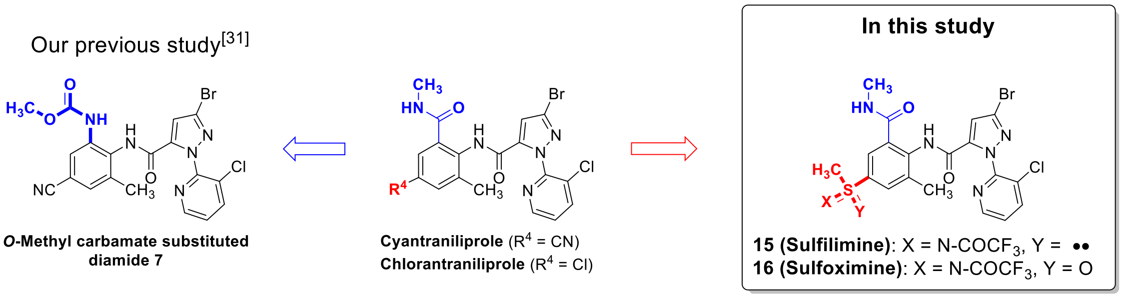
4
(BASF)[13]
(R^3 = CH_2CH_3, $CH(CH_3)_2$,
R^4 = Cl, R^5 = CH_3, Cl)

5
(Syngenta)[14]

6
(Syngenta)[15]
(R^2 = H, CH_3, $COCF_3$,
CN, $COOCH_3$, SO_2CH_3)

Figure 1. Examples of alkyl sulfilimine- and sulfoximine-substituted insecticides [1–15].

Based on previous research and interest in sulfilimine and sulfoximine functionalities, we began to identify these groups for the development of novel insecticides. Because alkyl sulfilimine- and sulfoximine-substituted diamides have so far been reported in the literature (Figure 1), a more focused exploration in our studies was sulfilimine and sulfoximine moieties directly substituted to the 4-position on the anthranilamide ring (Figure 2). We hypothesized that better insecticidal activity could be obtained by these small, lipophilic, electron-withdrawing substituents [1,29,30].



Our previous study[31]

***O*-Methyl carbamate substituted diamide 7**

Cyantraniliprole (R^4 = CN)
Chlorantraniliprole (R^4 = Cl)

In this study

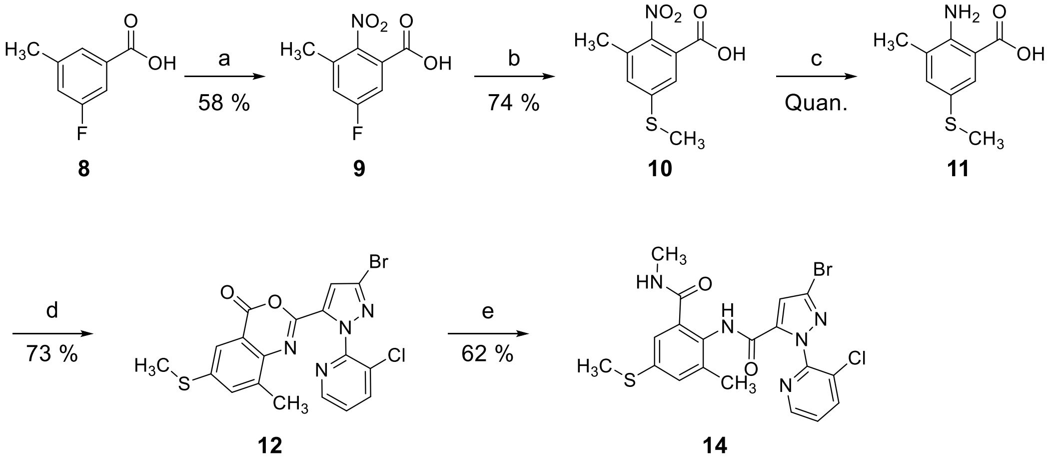
15 (Sulfilimine): X = N-$COCF_3$, Y = ••
16 (Sulfoximine): X = N-$COCF_3$, Y = O

Figure 2. Previously-developed anthranilic diamide [31] and newly-designed insecticides in this study.

2. Results

In our previous study on a novel anthranilic diamide insecticide **7**, we showed that the replacement of *N*-methylcarbamoyl with *O*-methyl carbamate had a beneficial effect, resulting in high insecticidal activity and low toxicity (Figure 2) [31]. Encouraged by these results, we have initially investigated the synthesis of the sulfilimine- and sulfoximine-based diamide **15**, **16** derivatives (Figure 2).

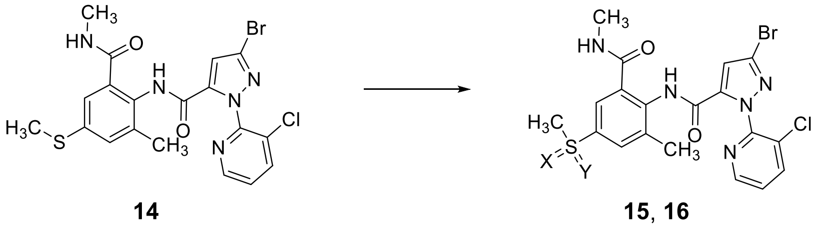
As shown in Scheme 1, the targeted compound **14** was successfully prepared using commercially-available 3-fluoro-5-methylbenzoic acid **8**. Regio-selective nitration of **8** provided 2-nitrobenzoic acid **9** in good yield [29,32]. The nitrated product **9** was readily converted to thiomethylated aniline **11** by reaction sequence previously used [31,33,34]. Then, 2-amino-3-methyl-5-(methylthio)benzoic acid **11** was coupled with 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid **13** [12,14,33,34] to give the desired benzoxazinone **12** in good yield [13]. After ring opening reaction of **12** with methylamine [12,14,29,30,34], 4-methylthio anthranilamide **14** was readily obtained.



Scheme 1. Reagents and conditions: (a) KNO_3, H_2SO_4, RT, 1 h; (b) aqueous NaSMe (21 wt%), 150 °C, 18 h; (c) $Na_2S_2O_4$, THF/H_2O (3:2), 60 °C, 0.5 h; (d) 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid **13**, $MeSO_2Cl$, pyridine, CH_3CN, RT, 13 h; (e) CH_3NH_2 (2.0 M in THF), THF, 60 °C, 5 h.

Next, the sulfur imination and oxidation of diamides **14** was explored (Table 1). Rhodium-catalyzed imination of secondary amide-bearing sulfide **14** and sulfoxide **15b** also provided the desired sulfilimine **15a** and sulfoximine **16a**, respectively (entries 1 and 2, Table 1) [28]. It is worth noting that this metal-catalyzed imination of sulfide **14** led to a mixture of sulfilimine **15a** and sulfoxide **15b** (entry 1, Table 1). For the 4-sulfone group, an oxidation method using MonoPeroxyPhthalate hexahydrate (MMPP·6H_2O) easily provided the desired compound **16b** (entry 3, Table 1).

Table 1. Synthesis of aryl organosulfur analogs of diamide insecticides



Entry	Reaction Conditions [a]	Substrates	Products			Yield (%) [b]
		Compd	Compd	X	Y	
1	Imination	**14**	**15a**	N-$COCF_3$	●●	29
			15b	O	●●	22
2	Imination	**15b**	**16a**	N-$COCF_3$	O	43
3	Oxidation	**14**	**16b**	O	O	93

[a] Imination: H_2NCOCF_3, $PhI(OAc)_2$, MgO, $Rh_2(OAc)_2$, CH_2Cl_2, 0 °C, 0.5 h; oxidation: MonoPeroxyPhthalate hexahydrate (MMPP·6H_2O), MeOH/CH_2Cl_2 (1:5), RT, overnight, [b] after column chromatography; Compd: compound; ●●: 1 lone pair on sulfur.

For the practical test, newly-prepared compounds **14–16** were evaluated for their insecticidal activities against the third instar larvae of *Spodoptera litura* according to the reported leaf-dip method [35].

In addition to sulfilimine **15a** and sulfoximine **16a**, all other synthetic compounds, that is, sulfide **14**, sulfoxide **15b**, and sulfone **16b**, were also tested for their larvicidal activities (Table 2). Among them, sulfide **14** and *N*-trifluoroacetyl sulfilimine **15a** showed good activities with high inhibition of feeding behaviors (eating area—**14** and **15a**: 5–10%, ref.: 0–5%, Table 2) (for images, please see the Supplementary Materials). Highly sensitive and functional group specific insecticidal activities were observed.

Table 2. Insecticidal activities of sulfide- and *N*-trifluoroacetyl sulfilimine-based diamide **14** and **15a** against the third instar larvae of Spodoptera litura.

Entry	Diamides		Against the Third Instar Larvae of *S. litura* [a]		
	Compd	**Functionality**	**Larvicidal Activity (%) at Time (h)**		**Eating Area (%)**
			72 h	**96 h**	**96 h**
1	**14**	sulfide	46.7	73.3	5–10
2	**15a**	*N*-trifluoroacetyl sulfilimine	46.7	53.3	5–10
3	**15b**	sulfoxide	0	0	>30
4	**16a**	*N*-trifluoroacetyl sulfoximine	0	0	>30
5	**16b**	sulfone	0	0	>30

[a] Concentration of **14** and **15a** was 50 ppm.

Because we believed that the physicochemical properties of newly-prepared diamides play important roles in their insecticidal activities [14,36], the studies were extended to investigate the bioavailability of organosulfur-based crop-protecting agents **14**, **15a**, **15b**, **16a**, and **16b** in terms of plant systemic properties [14] and membrane permeability [36]. As references, their properties of chlorantraniliprole and cyantraniliprole were also measured. Equilibrium solubility, log P, and parallel artificial membrane permeability assay (PAMPA) values are reported in Figure 3 [37].

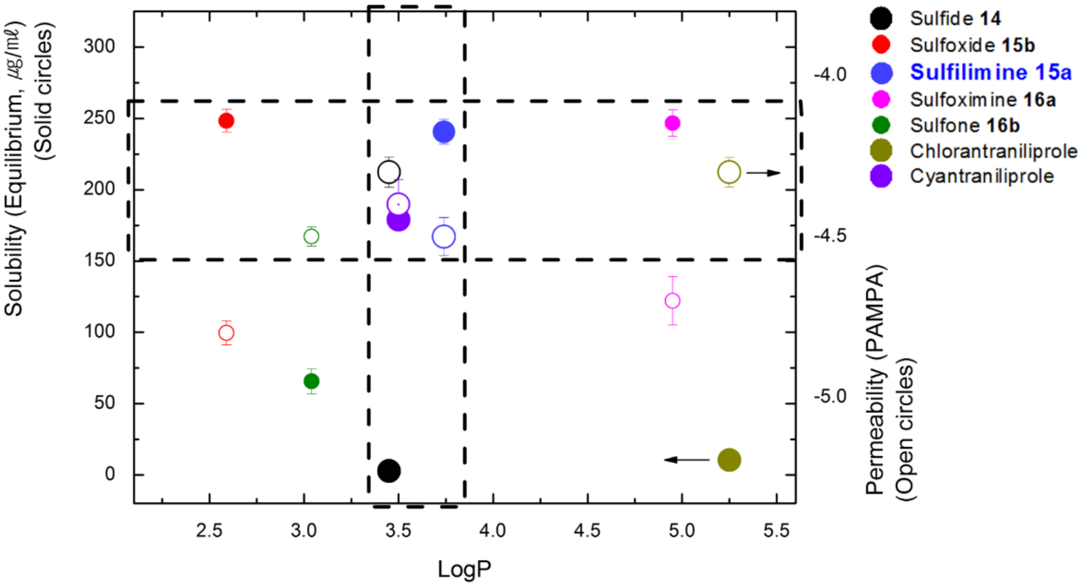


Figure 3. Physical properties of organosulfur-substituted anthranilic diamides **14**–**16** [38–40]: Open and solid circles represent permeability (parallel artificial permeability assay, PAMPA) and solubility (equilibrium), respectively; horizontal dash box describes similar permeability (PAMPA) with chlorantraniliprole (dark yellow) and cyantraniliprole (violet); vertical dash box represents similar log P with cyantraniliprole (violet).

Although poor water solubility was observed, sulfide **14** displayed relatively low log P and high permeability value (black circle, Figure 3). According to the solubility and log P data, sulfoxide **15b** is believed to have hydrophilic properties (red circle, Figure 3) [41]. In the case of *N*-trifluoroacetyl sulfilimine **15a** and sulfoximine **16a**, it seems that sulfilimine **15a** is more bioavailable than sulfoximine **16a**, especially considering its log P value (blue circle vs pink circle, Figure 3). In physicochemical property tests on organosulfur-based anthranilic diamides, it has been proven that similar values (log P and permeability) of sulfide **14** and *N*-trifluoroacetyl sulfilimine **15a** to cyantraniliprole have resulted in promising insecticidal activities. It is worth noting that sulfilimine **15a** has highly competitive water solubility and permeability to cyantraniliprole, which should aid in plant uptake and translocation [29].

3. Material and Methods

General Information

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates precoated with a 0.2 mm thickness of silica gel. The TLC plates were visualized by shortwave (254 nm), potassium permanganate, or ceric ammonium molybdate stain. Flash chromatography was carried out with Kieselgel 60 (230−400 mesh) silica gel. Melting points: Barnstead/Electrothermal 9300, measurements were performed in open glass capillaries. NMR spectra: Bruker AV 300MHz (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz), AV 500MHz (^{1}H-NMR: 500 NHz, ^{13}C-NMR: 125 MHz), AV2 500MHz (^{19}F-NMR: 470 MHz), the spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as internal standard and are reported in ppm. ^{1}H-NMR data are reported as: (s = singlet, d = doublet, t = triplet, q = quartet, br = broad singlet, qui = quintet, oct = octet, m = multiplet; coupling constant(s) in Hz; integration, proton assignment). High resolution mass spectra (HRMS): JEOL JMS-700. All solvents were purified using a column filter solvent purification system before use unless otherwise indicated. Reagents were purchased and used without further purification.

5-Fluoro-3-methyl-2-nitrobenzoic Acid (**9**)

To a solution of 3-fluoro-5-methylbenzoic acid (**8**, 100 mg, 0.6488 mmol) in H_2SO_4 (0.8 mL) was added potassium nitrate (72.16 mg, 0.7137 mmol) at 0 °C. After stirring at room temperature for 1 h, the resulting solid was washed with H_2O to give 5-fluoro-3-methyl-2-nitrobenzoic acid (**9**, 75.3 mg, 58%) as a white solid. Analytical data: lit [33].

3-Methyl-5-(methylthio)-2-nitrobenzoic Acid (**10**)

To a solution of 5-fluoro-3-methyl-2-nitrobenzoic acid (**9**, 387.2 mg, 1.95 mmol) was added an aqueous sodium thiomethoxide (21%, 6.5 mL, 19.5 mmol) at 0 °C. After stirring at 150 °C for 18 h, the reaction mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting solid was washed with H_2O to give 3-methyl-5-(methylthio)-2-nitrobenzoic acid (**10**, 325.5 mg, 74%). mp. 178 °C; ^{1}H-NMR (300 MHz, DMSO) δ 7.54 (s, 1H), 7.41 (s, 1H), 2.54 (s, 3H), 2.23 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ 165.4, 147.2, 141.5, 130.2, 129.4, 128.8, 124.4, 16.5, 14.3.

2-Amino-3-methyl-5-(methylthio)benzoic acid (**11**)

To a solution of 3-methyl-5-(methylthio)-2-nitrobenzoic acid (**17**, 42.9 mg, 0.1888 mmol) in THF (3 mL) was added sodium hydrosulfite (75%, 219 mg, 0.9440 mmol) in H_2O (2 mL) at 0 °C. After stirring at 60 °C for 0.5 h, the reaction mixture was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting solid was washed with H_2O to give 2-amino-3-methyl-5-(methylthio)benzoic acid (**11**, quantitative). mp. 172 °C; ^{1}H-NMR (300 MHz, DMSO) δ 7.60 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 3.34 (br, 2H), 2.36 (s, 3H), 2.10 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ 169.4, 148.6, 135.9, 129.8, 124.5, 120.4, 109.7, 17.9, 17.3.

2-(3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-8-methyl-6-(methylthio)-4*H*-benzo[*d*][1,3]oxazin-4-one (**12**)

To a solution of 3-bromo-1-(pyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**13**, 432.5 mg, 1.4298 mmol) in dried acetonitrile (1 mL) was added pyridine (0.23 mL, 2.8596 mmol) and methanesulfonyl chloride (0.16 mL, 2.1447 mmol) at 0 °C. After stirring at 0 °C for 30 min, a solution of 2-amino-3-methyl-5-(methylthio)benzoic acid (**11**, 282.67 mg, 1.4298 mmol) in dried acetonitrile and pyridine (0.35 mL, 4.2894 mmol) were added at 0 °C. After stirring at room temperature for 13 h, the reaction mixture was extracted with EtOAc (200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting crude residue was purified by column chromatography on silica gel (EtOAc/*n*-Hexane, 1:1) to give 2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-8-methyl-6-(methylthio)-4*H*-benzo[*d*][1,3]oxazin-

4-one (**12**, 481.4 mg, 73%). ^{1}H-NMR (300 MHz, DMSO) δ 8.62 (dd, *J* = 1.4 Hz, *J* = 4.7 Hz, 1H), 8.34 (dd, *J* = 1.4 Hz, *J* = 8.1 Hz, 1H), 7.76 (dd, *J* = 4.7 Hz, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.47 (s, 1H), 2.54 (s, 3H), 1.71 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ 157.7, 148.6, 147.7, 145.5, 140.5, 140.3, 139.9, 136.3, 135.8, 134.3, 128.5, 127.9, 127.3, 120.5, 117.8, 112.5, 15.8, 14.3.

3-Bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylthio)phenyl)-1*H*-pyrazole-5-carboxamide (**14**)

To a solution of 2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-8-methyl-6-(methylthio)-4*H*-benzo[*d*][1,3]oxazin-4-one (**12**, 400 mg, 0.8626 mmol) in THF (1.5 mL) was added methylamine solution (2.0 M in THF, 1.4 mL, 2.8465 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 h, the mixture was extracted with EtOAc (200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylthio)phenyl)-1*H*-pyrazole-5-carboxamide (**14**, 263.4 mg, 62%). mp. 247 °C; LC/MS: R_t = 2.82 mins, *m/z* (ES-) = 494 (M + H for $C_{19}H_{17}BrClN_5O_2S$); IR (KBr): ν 1654, 1633, 1540, 1535, 1459, 1344, 1311, 1024, 958, 878, 861, 801, 794, 761 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.45 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 7.05 (s, 2H), 6.26 (s, 1H), 2.92 (d, *J* = 3.1 Hz, 3H), 2.43 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ 167.0, 155.5, 148.3, 147.0, 139.5, 139.1, 136.8, 136.6, 134.6, 129.3, 128.6, 127.7, 126.7, 126.5, 122.5, 110.4, 26.0, 17.7, 14.5; HRMS (EI) calcd for $C_{19}H_{17}BrClN_5O_3S$ 494.9975, found 494.9949.

3-Bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-4-(S-methyl-*N*-(2,2,2-trifluoroacetyl)sulfinimidoyl)-6-(methylcarbamoyl)phenyl)-1*H*-pyrazole-5-carboxamide (**15a**) and 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylsulfinyl)phenyl)-1*H*-pyrazole-5-carboxamide (**15b**)

To a solution of 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylthio) phenyl)-1*H*-pyrazole-5-carboxamide (**14**, 50 mg, 0.1014 mmol) in dried CH_2Cl_2 (1 mL) was added trifluoroacetamide (22.92 mg, 0.2028 mmol), magnesium oxide (16.35 mg, 0.4056 mmol), Rhodium(II) acetate (2.2 mg, 0.005 mmol), and iodobenzene diacetate (49 mg, 0.1521 mmol) at 0 °C. After stirring at room temperature for 13 h, the reaction mixture was extracted with CH_2Cl_2 (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The resulting crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-4-(S-methyl-*N*-(2,2,2-trifluoroacetyl)sulfinimidoyl)-6-(methylcarbamoyl)phenyl)-1*H*-pyrazole-5-carboxamide (**15a**, 17.9 mg, 29%) and 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylsulfinyl)phenyl)-1*H*-pyrazole-5-carboxamide (**15b**, 11.3 mg, 22%). **15a:** mp. 199–200 °C; IR (KBr): ν 1635, 1535, 1465, 1413, 1354, 1302, 1266, 1183, 1145, 962, 801 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.43 (d, *J* = 4.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 7.37 (dd, *J* = 4.7 Hz, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 6.93 (d, *J* = 4.7 Hz, 1H), 2.94 (d, *J* = 4.7 Hz, 3H), 2.86 (s, 3H), 2.24 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.0, 164.6 (q, CF_3CO, *J* = 33.4 Hz), 155.4, 148.2, 147.0, 139.2, 139.1, 138.2, 136.6, 135.5, 131.2, 130.3, 127.7, 126.8, 126.5, 124.6, 116.8 (q, CF_3, *J* = 289.8 Hz), 110.8, 32.8, 26.0, 17.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -73.28 ppm; HRMS (EI) calcd for $C_{21}H_{17}BrClF_3N_6O_3S$ 603.9907, found 603.9898. **15b:** mp. 155 °C; IR (KBr): ν 1654, 1636, 1533, 1459, 1355, 1344, 1297, 1241, 1041, 1024, 959, 797 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.46 (dd, *J* = 1.5 Hz, *J* = 4.7 Hz, 1H), 7.85 (dd, *J* = 1.5 Hz, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.38 (dd, *J* = 4.7 Hz, *J* = 8.0 Hz, 2H), 7.09 (s, 1H), 6.70 (d, *J* = 4.7 Hz, 1H), 2.97 (d, *J* = 4.8 Hz, 3H), 2.67 (s, 3H), 2.27 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.3, 155.7, 149.0, 146.9, 143.0, 139.0, 138.9, 137.7, 136.8, 130.2, 129.0, 128.3, 128.3, 125.8, 119.6, 111.0, 44.0, 26.9, 19.6; HRMS (EI) calcd for $C_{19}H_{17}BrClN_5O_3S$ 508.9924, found 508.9893.

3-Bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-4-(S-methyl-*N*-(2,2,2-trifluoroacetyl)sulfonimidoyl) -6-(methylcarbamoyl)phenyl)-1*H*-pyrazole-5-carboxamide (**16a**)

To a solution of 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylsulfinyl)phenyl)-1*H*-pyrazole-5-carboxamide (**15b**, 30 mg, 0.0587 mmol) in dried CH_2Cl_2 (1 mL) was added trifluoroacetamide (13.28 mg, 0.1175 mmol), magnesium oxide (9.46 mg, 0.2348 mmol), Rhodium(II) acetate (1.3 mg, 0.003 mmol), and iodobenzene diacetate (28.36 mg, 0.0881 mmol) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was extracted with CH_2Cl_2 (×2). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-4-(S-methyl-*N*-(2,2,2-trifluoroacetyl)sulfonimidoyl)-6-(methylcarbamoyl)phenyl)-1*H*-pyrazole-5-carboxamide (**16a**, 15.7 mg, 43%). mp. 213.3 °C; IR (KBr): ν 1678, 1640, 1545, 1468, 1411, 1367, 1315, 1239, 1177, 1151, 1111, 994, 963, 838 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.46 (dd, *J* = 1.5 Hz, *J* = 4.7 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.87 (dd, *J* = 1.5 Hz, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.39 (dd, *J* = 4.7 Hz, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 6.50 (s, 1H), 3.41 (s, 3H), 3.01 (d, *J* = 4.9 Hz, 3H), 2.32 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.5, 164.1 (CF_3CO), 155.5, 148.8, 146.9, 140.5, 139.1, 138.8, 138.4, 133.4, 131.4, 130.1, 129.1, 128.4, 125.9, 123.5, 115.8 (q, CF_3, *J* = 288.5 Hz), 111.3, 44.2, 27.1, 19.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.90 (s); HRMS (EI) calcd for $C_{21}H_{17}BrClF_3N_6O_4S$ 619.9856, found 619.9852.

3-Bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylsulfonyl)phenyl)-1*H*-pyrazole-5-carboxamide (**16b**)

To a solution of 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylthio) phenyl)-1*H*-pyrazole-5-carboxamide (**14**, 30 mg, 0.0609 mmol) in MeOH/CH_2Cl_2 (1:5, 1 mL) was added magnesium bis(monoperoxyphthalate) hexahydrate (80%, 75.25 mg, 0.1217 mmol) at 0 °C. After stirring at room temperature for 18 h, the reaction mixture was extracted with EtOAc (×2). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting crude residue was purified by column chromatography on silica gel (EtOAc/*n*-Hexane, 3:1) to give 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(2-methyl-6-(methylcarbamoyl)-4-(methylsulfonyl)phenyl)-1*H*-pyrazole-5-carboxamide (**16b**, 29.9 mg, 93%). mp. 122 °C; IR (KBr): ν 1662, 1543, 1464, 1411, 1342, 1307, 1141, 962, 796, 764 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO) δ 10.54 (br, 1H), 8.50 (dd, *J* = 1.3 Hz, *J* = 4.7 Hz, 1H), 8.17 (dd, *J* = 1.3 Hz, *J* = 8.1 Hz, 1H), 7.91 (s, 1H), 7.82 (s, 1H), 7.61 (dd, *J* = 4.7 Hz, *J* = 8.1 Hz, 1H), 7.41 (s, 1H), 3.22 (s, 3H), 2.69 (d, *J* = 4.5 Hz, 3H), 2.26 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ 166.2, 155.5, 148.3, 147.2, 139.4, 139.2, 138.5, 137.8, 137.4, 134.6, 130.1, 127.9, 126.9, 126.7, 124.5, 110.9, 43.5, 26.2, 18.1; HRMS (EI) calcd for $C_{19}H_{17}BrClN_5O_4S$ 524.9873, found 524.9844.

4. Conclusions

In summary, novel anthranilic diamides, in which organosulfur groups were substituted at the 4-position on the phenyl ring, were prepared and tested for their insecticidal activities and physical properties. For preparation of the target molecules, we expanded reported sulfur imination procedures [28] to amide groups containing sulfide **14**. Our results concerning the relationship between insecticidal activities and physical properties showed that a better bioavailability profile (relatively low log P and high permeability) results in efficacy of sulfide **14** and sulfilimine **15a** (Table 2 and Figure 3). Due to its higher water solubility, *N*-trifluoroacetyl sulfilimine **15a** could be considered the most promising candidate for discovery of a new diamide insecticide. Notably, these studies have demonstrated that changing the substituents on sulfur atoms could lead to compounds with the desired physicochemical property profiles. Among organosulfur groups, *N*-trifluoroacetyl sulfilimine motif brings about desired properties such as solubility, lipophilicity, and permeability.

Supplementary Materials: The following are available online at http://www.mdpi.com/1420-3049/24/19/3451/s1, Figure S1: ^{1}H, ^{13}C, and ^{19}F NMR of compounds **9**–**16**, Figure S2: pH-metric log P of compounds **14**–**16**, Table S1: Larvicidal activity depend on time, Table S2: Picture of eating area.

Author Contributions: Methodology, H.J.L., W.H.L. and S.J.P.; investigation, H.J.L. and S.J.P.; analysis: H.J.L., W.H.L. and S.J.P.; writing—original draft preparation, S.J.P.; writing—review and editing, H.J.L. and S.J.P.

Funding: This work was fully supported by KRICT/ Kyung Nong Co. Ltd. co-research project (TS171-09R, TS181-10R, TS191-06R, and KK1932-30). This research was funded by Ministry of Trade, Industry and Energy, Republic of Korea, grant number 10052734 and 10077494.

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

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Sample Availability: Not available.