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Full Paper

Novel Anthranilic Diamide Insecticides: Design, Synthesis, and Insecticidal Evaluation

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Three series of new anthranilic diamide derivatives containing sulfide, *N*-cyanomethylsulfilimine, and *N*-cyanomethylsulfoximine groups were designed and synthesized by coupling the active substructures of anthranilic diamides and sulfoxaflor. The structures of the synthesized compounds were confirmed by infrared spectroscopy, ^{1}H and ^{13}C NMR, and elemental analysis. Several unique structural characteristics were revealed via the crystal structure analysis of compound *N*-(2-(2-methyl-2-(methylthio)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide **16e**. Bioassay results indicated that most of the synthesized compounds showed superior insecticidal activities against *Mythimna separata* and *Plutella xylostella* when compared with the positive control cyantraniliprole. In particular, *N*-(2-(2-methyl-2-(*N*-cyanomethylsulfideimino)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide **17e** showed excellent insecticidal activity against *Mythimna separata*, with a mortality rate of 100 % at a concentration of 1 μg mL^{-1}. These results indicated that sulfide, *N*-cyanomethylsulfilimine, and *N*-cyanomethylsulfoximine moieties, as important active substructures, could improve or maintain the activity of the anthranilic diamide and promote novel pesticide development.

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Introduction

Ryanodine receptors (RyRs) comprise a class of intracellular calcium release channels in various excitable tissues and cells such as muscles and neurons.[1,2] These receptors are the major cellular mediators of calcium ion release from the sarcoplasmic and endoplasmic reticulum,[2,3] an essential step in muscle excitation–contraction coupling (ECC).[2–5] Diamide insecticides have emerged as one of the most promising new compound classes in insecticide chemistry owing to their excellent insecticidal efficacy and high levels of mammalian safety.[6] Cyantraniliprole,[7] chlorantraniliprole,[8] and flubendiamide,[9] the first three insecticides developed from this class, demonstrate exceptional broad-spectrum activity against *Lepidoptera*.[6,10] Flubendiamide is a phthalic diamide, whereas chlorantraniliprole and cyantraniliprole (Fig. 1) belong to the anthranilic diamide structural class. Although structurally distinct, both classes of compounds exhibit insecticidal properties via activation of the ryanodine receptors, leading to uncontrolled calcium release originally stored in the muscle, thus preventing further muscle contraction, and ultimately leading to death.[6,11–13] The exceptional levels of mammalian safety are attributed to a strong selectivity for insects over mammalian receptors.[6]

Sulfoxaflor (Fig. 1) is the first product from a novel class of insect control agents based on the sulfoximine scaffold[14,15] developed by Dow AgroSciences. It exhibits broad-spectrum control of many sap-feeding insect pests including aphids, whiteflies, hoppers, and insects of the genus *Lygus*.[14] Furthermore, sulfoxaflor is notable for its efficacy against sap-feeding insect pests that are resistant to currently available insecticides.[16,17] The insecticidal mechanism of sulfoxaflor is reliant on the agonistic action towards the insect nicotinic acetylcholine receptor (nAChR).[18–21] The effects of sulfoxaflor on the insects include excitatory symptoms, such as tremors, followed by paralysis and mortality, thereby suggesting that the molecule acts on the insect nervous system.[19]

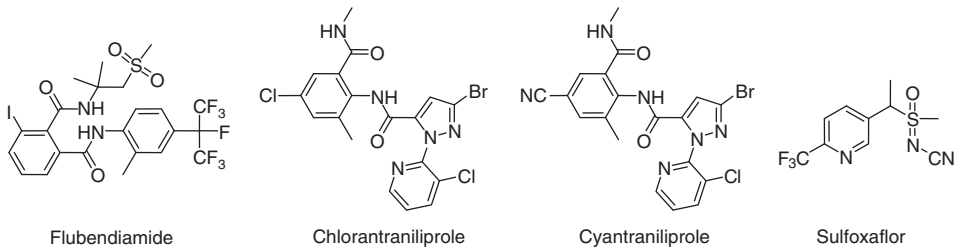
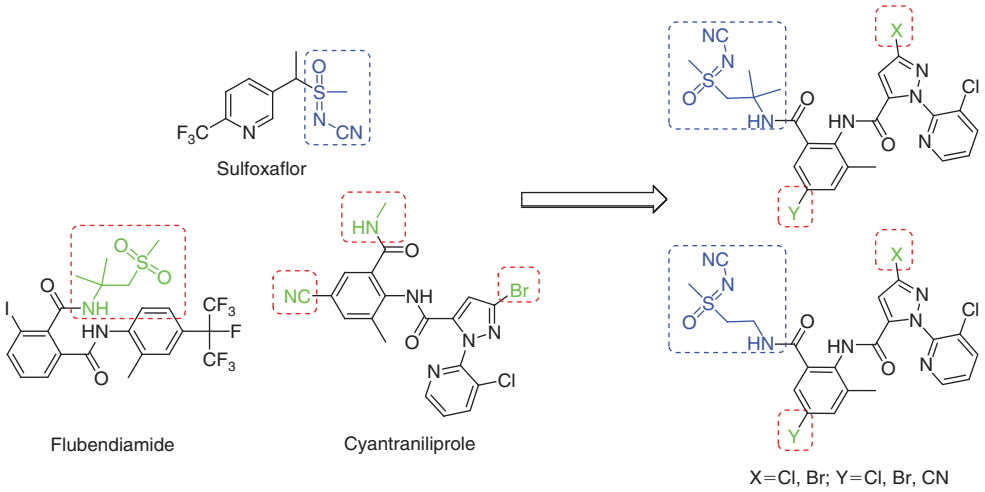


Fig. 1. Structures of diamide insecticides and sulfoxaflor.



Scheme 1. Design strategy of target molecules.

Recent studies have reported that the sulfoximine structure can improve the insecticidal activities of anthranilic diamides. The consistently high activity of sulfoximines is thought to be due to their high water solubility and relatively low logP, leading to systemicity (or compound uptake) in the plant and good distribution in the soil.[22] In this study, active substructures consisting of sulfide, *N*-cyanomethylsulfilimine, and *N*-cyanomethylsulfoximine groups were introduced into the anthranilic diamide to obtain highly active compounds with improved absorption profiles (Scheme 1). A convenient, effective, and rapid synthetic route towards the synthesis of intermediates **8a**–**f** and target compounds **16a**–**e**, **17a**–**e**, **18a**–**e**, **19a**–**f**, **20a**–**f**, and **21a**–**e** was designed and carried out according to the schemes in Tables 1 and 2, respectively.

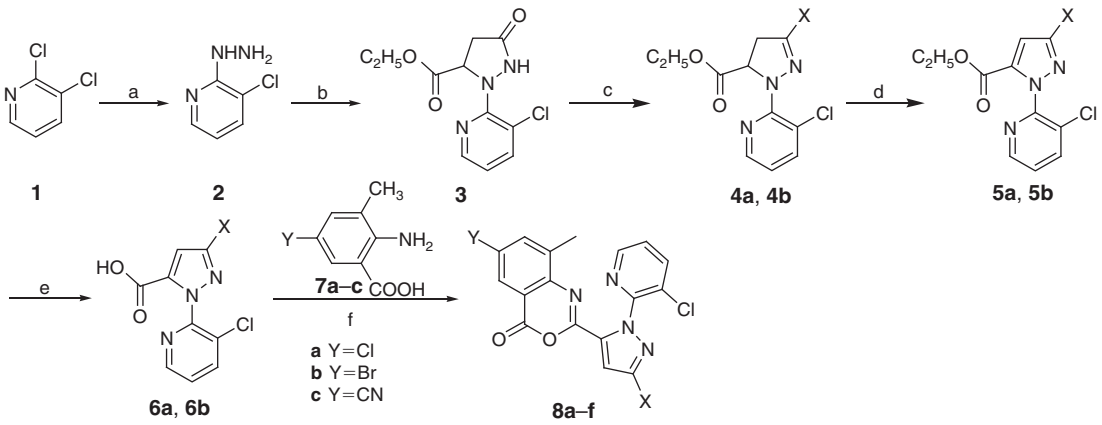
Results and Discussion

Chemistry

The corresponding substituted pyrazine intermediates **8a**–**f** were synthesized from the starting materials 2,3-dichloropyridine and diethyl maleate. *(3-Chloropyridin-2-yl)hydrazine* (**2**) was synthesized by refluxing 2,3-dichloropyridine (**1**) and 80 % hydrazine hydrate in ethanol. *1-(3-Chloropyridin-2-yl)-3-pyrazolidinone-5-carboxylate* (**3**) was prepared by reaction between compound **2** and diethyl maleate in the presence of an appropriate amount of sodium ethoxide. Intermediate **3** was converted into the corresponding *ethyl 1-(3-chloropyridin-2-yl)-3-halo-4,5-dihydro-1*H*-pyrazole-5-carboxylates* (**4a** and **4b**) by refluxing with phosphorus oxychloride or phosphorus oxybromide in acetonitrile. Compounds **4a** and **4b** were converted into the corresponding *ethyl 1-(3-chloropyridin-2-yl)-3-halo-1*H*-pyrazole-5-carboxylates* (**5a** and **5b**) by oxidation with potassium persulfate in concentrated sulfuric acid (volume fraction 98 %). *1-(3-Chloropyridin-2-yl)-3-halo-1*H*-pyrazole-5-carboxylic acids* (**6a** and **6b**) were synthesized by hydrolysis of the corresponding esters **5a** and **5b** with sodium hydroxide in methanol. Intermediates *2-amino-5-chloro (or bromo)-3-methylbenzoic acids* (**7a** and **7b**) were obtained by reaction between 2-amino-3-methylbenzoic acid and *N*-chlorosuccinimide (or *N*-bromosuccinimide) in *N*,*N*-dimethylformamide (DMF); *2-amino-5-iodo-3-methylbenzoic acid* was prepared in the same manner. *2-Amino-5-cyano-3-methylbenzoic acid* (**7c**) was synthesized by heating 2-amino-5-iodo-3-methylbenzoic acid and copper(I) cyanide to 140°C in *N*,*N*-dimethylformamide (DMF). The pyrazine intermediates **8a**–**f** were synthesized according to the reported literature.[7] First, to a solution of methanesulfonyl chloride in acetonitrile was added dropwise a mixture of compounds **6a** and **6b** and pyridine in acetonitrile at 0–5°C. Then, substituted benzoic acid **7a**–**c** and pyridine, followed by methanesulfonyl chloride were added. The two types of substituted amines (**11** and **15**) were prepared according to the reactions in Scheme 2. *2-Methyl-1-(methylthio)propan-2-amine* (**11**) was synthesized from the raw material *2-amino-2-methylpropan-1-ol* (**9**) as reported in literature.[23] First, compound **9** was converted into the corresponding sulfonic acid ammonium salt **10** by refluxing with 98 % H_2SO_4 in toluene/water (v/v 60 : 1). Then, amine **11** was synthesized by heating compound **10** with 10 % NaOH solution, 20 % $NaSCH_3$ solution at 80°C in toluene. *2-(Methylthio)ethanamine hydrochloride* (**15**) was obtained through the reactions of protection of amino group with $(Boc)_2O$, substitution of chloro with methylthio group, and deprotection of amino group with HCl gas from the starting material 2-chloroethanamine (**12**), as reported in literature.[24] Amine **12** was converted into compound **13** by protecting its amino group

Table 1. Synthesis of intermediates 8a–f

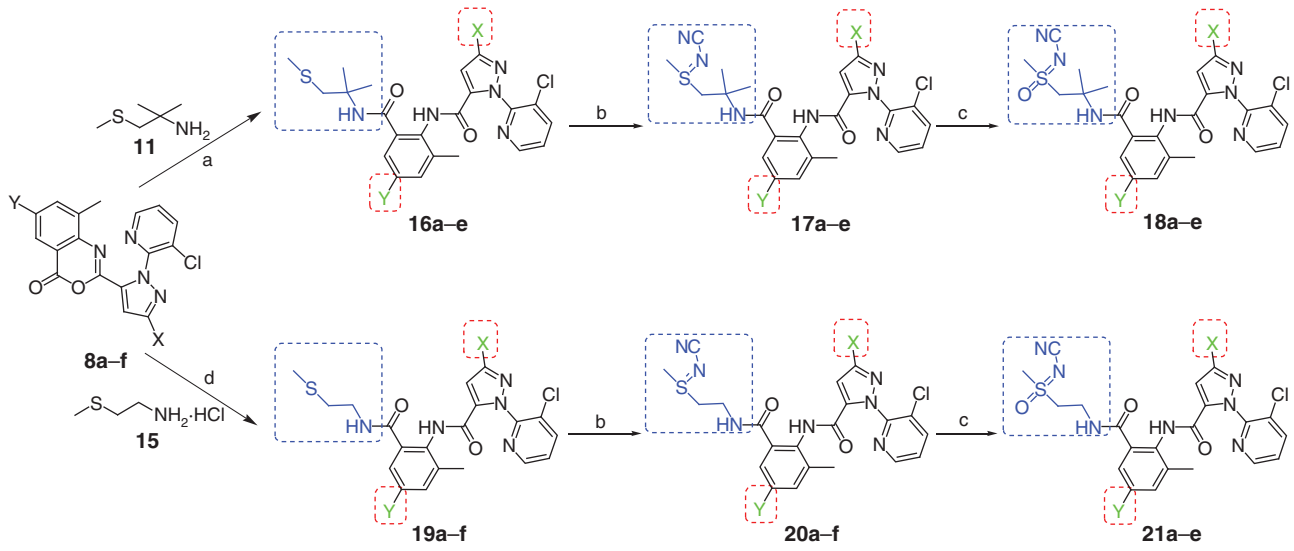
Reagents and conditions: (a) 80 % $NH_2NH_2 \cdot H_2O$, C_2H_5OH, reflux, 24 h, yield 94 %; (b) (i) diethylmaleate, Na/C_2H_5OH, reflux, 30 min, (ii) acetic acid, 40°C, yield 46 %; (c) $POCl_3$ or $POBr_3$, CH_3CN, reflux, 3 h; (d) $K_2S_2O_8$, 98 % H_2SO_4, CH_3CN, reflux, 6 h; (e) NaOH, CH_3OH, room temperature (RT), 12 h; (f) CH_3SO_2Cl, pyridine, CH_3CN, RT, 6 h



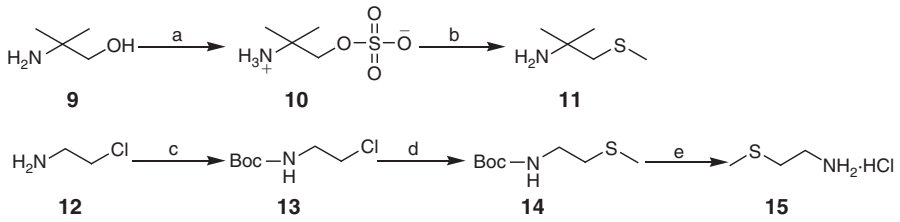
Intermediates	X	Y	Yield [%]	Intermediates	X	Y	Yield [%]
4a	Cl	–	98	**8a**	Cl	Cl	85
5a	Cl	–	72	**8b**	Cl	Br	77
6a	Cl	–	74	**8c**	Cl	CN	67
4b	Br	–	95	**8d**	Br	Br	84
5b	Br	–	74	**8e**	Br	Cl	92
6b	Br	–	81	**8f**	Br	CN	70

Table 2. Synthesis of target compounds 16a–e, 17a–e, 18a–e, 19a–f, 20a–f, and 21a–e

Reagents and conditions: (a) tetrahydrofuran (THF), 60°C, 8 h; (b) $NCNH_2$, (diacetoxyiodo)benzene ($PhI(AcO)_2$), THF, 0°C, 10 h; (c) 3-chloroperoxybenzoic acid (mCPBA), K_2CO_3, CH_3OH/H_2O, 0°C, 8 h; (d) triethylamine (Et_3N), THF, RT, 6 h



Products	X	Y	Yield [%]	Products	X	Y	Yield [%]	Products	X	Y	Yield [%]
16a	Cl	Cl	56	**18b**	Cl	Br	83	**20a**	Cl	Cl	90
16b	Cl	Br	42	**18c**	Cl	CN	71	**20b**	Cl	Br	59
16d	Br	Br	50	**18d**	Br	Br	56	**20c**	Cl	CN	89
16e	Br	Cl	46	**18e**	Br	Cl	57	**20e**	Br	Cl	45
17a	Cl	Cl	92	**19a**	Cl	Cl	91	**20f**	Br	CN	49
17b	Cl	Br	77	**19b**	Cl	Br	81	**21a**	Cl	Cl	68
17c	Cl	CN	63	**19c**	Cl	CN	51	**21b**	Cl	Br	60
17d	Br	Br	69	**19d**	Br	Br	57	**21c**	Cl	CN	52
17e	Br	Cl	62	**19e**	Br	Cl	65	**21d**	Br	Br	47
18a	Cl	Cl	51	**19f**	Br	CN	55	**21e**	Br	Cl	55



Scheme 2. Synthesis of amine intermediates **11** and **15**. Reagents and conditions: (a) 98 % H_2SO_4, toluene/water (v/v 60 : 1), reflux, 20 h, yield 89 %; (b) 10 % NaOH solution, 20 % $NaSCH_3$ solution, toluene, 80°C, 8 h, yield 78 %; (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, RT, 24 h, yield 92 %; (d) KI (catalytic amount), tetrabutylammonium bromide (catalytic amount), 20 % $NaSCH_3$ solution, CH_3CN, reflux, 24 h, yield 86 %; (e) HCl (gas), ethyl ether, 4 h, 0°C, yield 85 %.

with $(Boc)_2O$ in dichloromethane. Then, compound **14** was obtained via substitution of the chloride atom with methylthio group in the presence of catalytic amounts of potassium iodide and tetrabutylammonium bromide in acetonitrile. Intermediate **15** was synthesized by Boc-deprotection of compound **14** with HCl gas in ethyl ether. The synthetic route towards the target compounds is summarised in Table 2. Subsequently, a total of 30 target molecules were smoothly synthesized by reaction between substituted pyrazine intermediates **8a**–**f** and two types of substituted amines (**11** and **15**). Products **16a**–**e** and **19a**–**f** were obtained by nucleophilic reactions between amine **11** or **15** and pyrazine compounds **8a**–**f** in tetrahydrofuran. Owing to the stronger nucleophilic activity of amine **15**, the reactions were carried out at room temperature for amine **15**, and under reflux for amine **11**. Molecules **17a**–**e** and **20a**–**f** were prepared through oxidation reactions of compounds **16a**–**e** and **19a**–**f** with (diacetoxyiodo)benzene, cyanamide in tetradydrofuran. Compounds **17a**–**e** and **20a**–**f** were converted into target products **18a**–**e** and **21a**–**e** by oxidation with 3-chloroperoxybenzoic acid, potassium carbonate in methanol/water. All target compounds were purified by chromatography on silica gel using petroleum ether/ethyl acetate as eluent. The synthesized compounds were identified and characterised by infrared spectroscopy (IR), ^{1}H NMR, ^{13}C NMR, elemental analysis (EA), and (for select compounds) high-resolution mass spectrometry (HRMS).

Crystal Structure Analysis

Several molecular characteristics were revealed upon crystal structure analysis of compound **16e** (Fig. 2; CCDC no. 965590). The torsion angles of N(3)–N(2)–C(5)–C(4) and C(8)–N(2)–C(5)–N(1) were −98.2(3)° and −109.9(3)°, respectively, indicating that the pyridine and pyrazole rings were non-planar, adopting an approximately perpendicular conformation. The torsion angles of N(2)–C(8)–C(9)–O(1) and C(10)–C(15)–C(17)–O(2) were 13.8(4)° and 46.8(4)°, respectively, indicating that the pyrazole ring and amide group, as well as the benzene ring and the other amide group, were non-planar. The torsion angles of C(7)–C(8)–C(9)–N(4) and C(9)–N(4)–C(10)–C(15) were 18.4(5)° and 105.5(3)°, respectively, indicating that the pyrazole and benzene rings were non-planar. The angles of C(6)–C(7)–H(7), C(8)–C(7)–H(7), and C(8)–C(7)–C(6) were 128.2°, 128.2°, and 103.5(3)°, respectively, and the sum of these angles was 360°, indicating the sp^2 hybridisation state of the C(7) atom. As expected, the C–N amide bonds possessed some double bond character.[25] The bond lengths of C(9)–N(4) and C(17)–N(5) were 1.351(4) Å and 1.344(4) Å, respectively, and were much shorter than the normal C–N bond length (1.47 Å),[26] but slightly greater than C=N (1.33 Å).[25,26] From the data, the sum of C(9)–N(4)–C(10), C(9)–N(4)–H(4), and

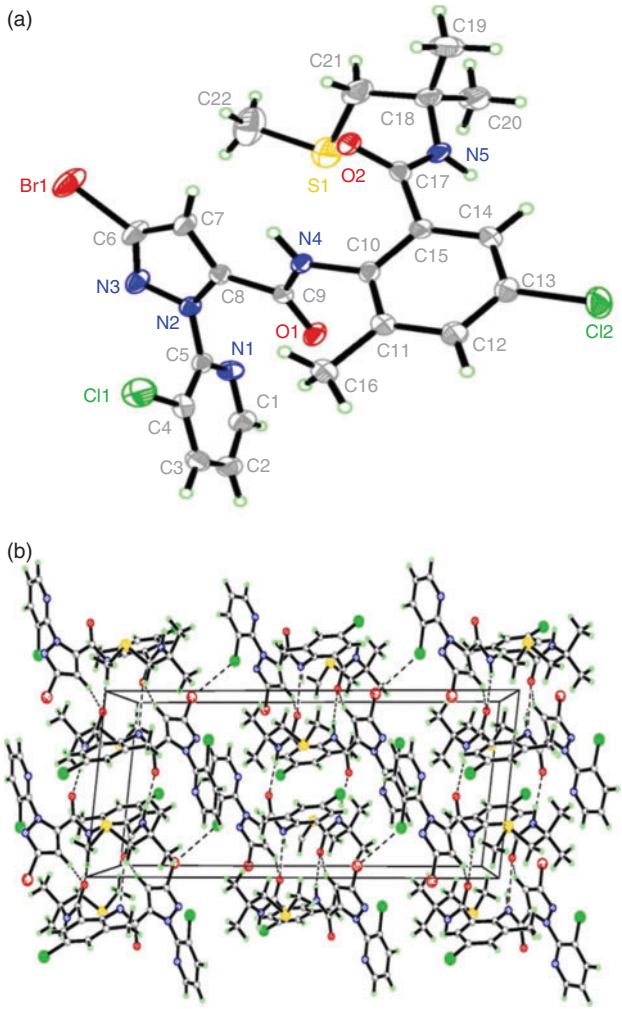


Fig. 2. Single crystal structure of compound **16e**: (a) molecular structure and (b) crystal packing.

C(10)–N(4)–H(4) angles was 359.3°, indicating the sp^2 hybridisation state of the N(4) atom. Similarly, the N(5) atom also adopted an sp^2 hybridisation state. As noted, one intermolecular hydrogen bond, N(4)–H(4)···O(2), and two intermolecular weak interactions at C(7)–H(7)···O(2) and N(5)–H(5)···O(1) linked the adjacent molecules to form a one-dimensional chain structure (Fig. 2). These chains intersected into a two-dimensional framework by the intermolecular weak interactions at Cl(1)···Br(1) and C(3)–H(3)···N(1). Additionally, weak π–π interactions occurred among the benzene, pyridine, and pyrazole

Table 3. Insecticidal activities of the target compounds
–: not detected (activities for **19c**, **19f**, **20a**–**c**, and **21c** were not detected at concentrations of 1 and 0.1 μg mL^{-1})

Compound	Substituent groups		Mortality [%]			
	X	Y	*M. separata*			*P. xylostella*
			5 μg mL^{-1}	1 μg mL^{-1}	0.1 μg mL^{-1}	10 μg mL^{-1}
16a	Cl	Cl	100	20	0	100
16b	Cl	Br	100	50	0	86
16d	Br	Br	100	0	0	86
16e	Br	Cl	100	70	0	100
19a	Cl	Cl	100	20	0	100
19b	Cl	Br	100	0	0	100
19c	Cl	CN	40	–	–	86
19d	Br	Br	100	0	0	100
19e	Br	Cl	100	50	0	100
19f	Br	CN	20	–	–	100
17a	Cl	Cl	100	0	0	86
17b	Cl	Br	100	0	0	86
17c	Cl	CN	100	70	0	100
17d	Br	Br	100	40	0	100
17e	Br	Cl	100	100	0	86
20a	Cl	Cl	40	–	–	100
20b	Cl	Br	60	–	–	100
20c	Cl	CN	60	–	–	100
20e	Br	Cl	100	0	0	86
20f	Br	CN	100	0	0	100
18a	Cl	Cl	100	0	0	71
18b	Cl	Br	100	0	0	57
18c	Cl	CN	80	0	0	100
18d	Br	Br	100	0	0	86
18e	Br	Cl	100	0	0	71
21a	Cl	Cl	70	0	0	100
21b	Cl	Br	100	20	0	71
21c	Cl	CN	20	–	–	100
21d	Br	Br	100	0	0	86
21e	Br	Cl	100	0	0	86
cyantraniliprole	–	–	100	100	0	100

rings of the adjacent molecules, and strengthened the stability of the 2D networks.

Biological Activities Against Mythimna separata *and* Plutella xylostella

The insecticidal activities of the target compounds, with cyantraniliprole as a positive control, against *Mythimna separata* (*M. separata*) at 5 μg mL^{-1} and *Plutella xylostella* (*P. xylostella*) at 10 μg mL^{-1} are shown in Table 3. The literature reports that *P. xylostella* is more sensitive to anthranilic diamides than *M. separata*.[27] Our experimental studies revealed that the amount of food taken by *P. xylostella* is less than that of *M. separata*, hence, the insecticidal activity against *M. separata* at 5 μg mL^{-1} was chosen for subsequent experiments for comparison with compounds that display good results against *P. xylostella* at 10 μg mL^{-1}. The compounds displaying insecticidal activities against *M. separata* over 70 % were further tested at concentrations of 1 μg mL^{-1} and 0.1 μg mL^{-1} for a fair comparison of the activity of the target compounds with that of cyantraniliprole. The results of gradient concentration screening are shown in Table 3. As can be seen from the table, compounds **16a**, **16b**, **16d**–**e**, **19a**, **19b**, **19d**, **19e**, **17a**–**e**, **20e**, **20f**, **18a**, **18b**, **18d**–**e**, **21b**, **21d**, and **21e** displayed good insecticidal activity against *M. separata* at 5 μg mL^{-1}, with a mortality rate of 100 %. Furthermore, **17e** showed an excellent insecticidal activity against *M. separata* at 1 μg mL^{-1}, with a mortality of 100 %. The synthetic compounds also demonstrated good insecticidal activity against *P. xylostella* at 10 μg mL^{-1}, with mortality rates over 80 % (Table 3). From the data, the insecticidal activity of compounds containing sulfide and *N*-cyanosulfilimine moieties was higher than that of compounds containing *N*-cyanosulfoximine. This result is probably due to the greater polarity of *N*-cyanosulfoximine, thereby exhibiting greater insect repulsion when compared with the other two kinds of compounds studied. Moreover, in a given category, compounds with a cyano group instead of a chloride or bromide group in the anthraniloyl moiety commonly had very low insecticidal activities. For example, the mortality against *M. separata* at a concentration of 5 μg mL^{-1} was 100 % for compounds **18a**, **18b**, **18d**, **18e**, **19a**, **19b**, **19d**, **19e**, **21b**, **21d**, and **21e**, but the corresponding insecticidal activities of **18c**, **19c**, **19f**, and **21c** were 80, 40, 20, and 20 % respectively. This result is significant for pesticide development. Furthermore, the insecticidal activities of compounds containing the 2-methylpropylcarbamoyl group in the anthraniloyl moiety were higher than those containing the ethylcarbamoyl group. For example, in a given category, the mortality rates against *M. separata* at a concentration of 1 μg mL^{-1} of compounds **16a**, **16b**, **16e**, **17c**, **17d**, and **17e** were 20, 50, 70, 70, 40, and 100 %, respectively, but the

corresponding insecticidal activities of compounds **19a**, **19b**, **19d**, **19e**, **20e**, and **20f** were only 20, 0, 0, 50, 0, and 0 %, respectively. From the above results, it is concluded that either a chloride or a bromide group, a sulfide or *N*-cyanosulfilimine, and a 2-methylpropylcarbamoyl group in the anthraniloyl moiety will enhance the insecticidal activity. However, the mortality rate against *M. separata* at 0.1 μg mL^{-1} of all target compounds and positive control cyantraniliprole was 0 %. This result indicates that a concentration of 0.1 μg mL^{-1} is below the required minimum effective concentration of target compounds against *M. separata*.

Conclusion

In conclusion, three important anthranilic diamide structural classes were designed and synthesized via incorporation of sulfide, *N*-cyanomethylsulfilimine, or *N*-cyanomethylsulfoximine moiety into the lead structure. The structures of the novel synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR, and EA, and the insecticidal activities of the compounds against *Mythimna separata* and *Plutella xylostella* were tested. Bioassay results indicated that most of the synthesized compounds possessed good insecticidal activities against *M. separata* at 5 μg mL^{-1} and *P. xylostella* at 10 μg mL^{-1} when compared with the positive control cyantraniliprole. However, no compounds exhibited higher activities than that of cyantraniliprole against *M. separata* when concentrations were reduced to 1 μg mL^{-1}, with the exception of compound **17e**, which showed an excellent insecticidal activity against *M. separata*, with a mortality rate of 100 %. Furthermore, none of the compounds tested (including the control) exhibited insecticidal activity against *M. separata* on further concentration reduction to 0.1 μg mL^{-1}.

Experimental

General

Melting points of all compounds were determined on an X-4 binocular microscope (Gongyi Tech. Instrument Co., Henan, China), and the temperatures were not corrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained at 400 MHz using a Bruker AV-400 spectrometer; chemical-shift values (δ) were reported as parts per million (ppm) with tetramethylsilane as the internal standard. Elemental analyses were determined on a Yanaca CHN Corder MT-3 recorder. Infrared (IR) spectra were recorded on a Bruker Vector 22 Fourier transform infrared (FTIR) spectrometer using KBr pellets. Mass spectra were recorded using a high-resolution mass spectrometer (HRMS) (Varian 7.0T FTMS). All solvents and liquid reagents were of analytical grade and were dried and distilled before use. Column chromatography purification was carried out using silica gel (200–300 mesh).

General Procedure for the Synthesis of Acids *6a* and *6b*

Compound **2** was synthesized by heating 2,3-dichloropyridine **1** and 80 % hydrazine hydrate to reflux in ethanol. Intermediates **3**, **4a**, and **4b**, and esters **5a** and **5b** were designed and prepared as previously reported.[28] Acid **6a** was also synthesized as previously reported.[28] To a 250-mL flask containing compound **5a** (15.07 g, 0.05 mol) and methanol (90 mL) was added dropwise a mixture of sodium hydroxide (2.53 g, 0.06 mol) in methanol (30 mL). The reaction was stirred for 6 h at room temperature, and reaction progress was monitored by thin layer chromatography (TLC). Following completion of the reaction, the reaction mixture was concentrated using a rotary evaporator to remove methanol. The residue was dissolved in water (60 mL) and then washed with diethyl ether (3 × 30 mL). The water layer was acidified to pH 2. The resulting precipitate was filtered off, washed with water, and dried to give **6a** as a pale yellow solid (10.13 g, 81 %). Compound **6b** was synthesized in a similar manner.

General Procedure for the Synthesis of Substituted Benzoic Acids *7a–c*

2-Amino-5-chloro-3-methylbenzoic acid **7a** was synthesized according to a literature procedure.[29] To a solution of 2-amino-3-methylbenzoic acid (4.00 g, 26.5 mmol) in *N*,*N*-dimethylformamide (30 mL) was added *N*-chlorosuccinimide (3.72 g, 27.8 mmol), and the reaction mixture was heated at 75°C (oil bath temperature) overnight, and reaction progress was monitored by TLC. After reaction completion, the reaction mixture was cooled to room temperature and slowly poured into ice water (100 mL) to precipitate a light grey solid. The solid was filtered, washed with water, and dried to give **7a** (4.47 g, 91 %). Compounds **7b** and *2-amino-5-iodo-3-methylbenzoic acid* were synthesized in the same manner.

2-Amino-5-cyano-3-methylbenzoic acid **7c** was prepared according to a literature procedure.[29] A mixture of 2-amino-5-iodo-3-methylbenzoic acid (15.00 g, 54.1 mmol) and copper(I) cyanide (7.27 g, 81.2 mmol) was heated to 140–145°C in *N*,*N*-dimethylformamide (150 mL) for 20 h, and reaction progress was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, and most of the *N*,*N*-dimethylformamide was removed by concentration on a rotary evaporator. The residue was poured into ice water (150 mL), followed by immersion in ethylenediamine (20 mL). The mixture was stirred vigorously to dissolve most of the solid, and the residual solid was recovered by filtration. Then, concentrated hydrochloric acid was added to the filtrate to adjust the pH to 4 to precipitate a light grey solid. The solid was filtered, washed with water, dried, and purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 3 : 1) as eluent to give **7c** (4.48 g, 47 %).

2-Amino-5-chloro-3-methylbenzoic Acid 7a

Light grey solid (91 % yield), mp 198–199°C. δ_H (400 MHz, [D6]DMSO) 7.55 (s, 1H, Ph-H), 7.22 (s, 1H, Ph-H), 2.10 (s, 3H, CH_3).

2-Amino-5-bromo-3-methylbenzoic Acid 7b

Light grey solid (88 % yield), mp 215–217°C (lit.[30] 218–220°C). δ_H (400 MHz, [D6]DMSO) 7.68 (s, 1H, Ph-H), 7.30 (s, 1H, Ph-H), 2.08 (s, 3H, CH_3).

2-Amino-5-cyano-3-methylbenzoic Acid 7c

Light grey solid (47 % yield), mp 184–186°C. δ_H (400 MHz, [D6]DMSO) 7.96 (s, 1H, Ph-H), 7.49 (s, 1H, Ph-H), 7.40 (br, 1H), 2.12 (s, 3H, CH_3).

General Procedure for the Synthesis of Intermediates *8a–f*

6-Chloro-2-(3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-8-methyl-4H-benzo[d][1,3]oxazin-4-one **8a** was synthesized according to a literature procedure.[7] To a solution of methanesulfonyl chloride (3.50 g, 30.5 mmol) in acetonitrile (20 mL) was added dropwise a mixture of 1-(3-chloropyridin-2-yl)-3-chloro-1*H*-pyrazole-5-carboxylic acid (5.25 g, 20.3 mmol) and

pyridine (3.21 g, 40.6 mmol) in acetonitrile (20 mL) at 0–5°C. The reaction temperature was maintained at ~0°C throughout the addition. After stirring for 15 min, 2-amino-5-chloro-3-methylbenzoic acid (3.78 g, 20.3 mmol) was added and stirring was continued for an additional 10 min. A solution of pyridine (4.82 g, 61.0 mmol) in acetonitrile (20 mL) was then added dropwise, and the reaction mixture was stirred for 30 min, followed by the addition of methanesulfonyl chloride (4.66 g, 40.7 mmol). The reaction mixture was stirred for 15 min at 0°C and then warmed to room temperature and stirred overnight, and reaction progress was monitored by TLC. After reaction completion, water (~100 mL) was added, and extraction followed with ethyl acetate (3 × 50 mL). The combined organic phases were washed with water (1 × 20 mL), followed by brine (1 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 3 : 1) as eluent to give **8a** (7.02 g, 85 %). Compounds **8b**–**f** were synthesized using the same procedure.

6-Chloro-2-(3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-8-methyl-4H-benzo[d][1,3]oxazin-4-one ***8a***

Yellow solid (85 % yield), mp 189–191°C. δ_H (400 MHz, [D6]DMSO) 8.63 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 8.35 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.85 (d, J 1.6, 1H, Ar-H), 7.77 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.74 (d, J 1.6, 1H, Ar-H), 7.47 (s, 1H, pyrazole-H), 1.70 (s, 3H, CH_3).

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

Yellow solid (77 % yield), mp 194–196°C. δ_H (400 MHz, $CDCl_3$) 8.55 (dd, J_1 4.4, J_2 1.2, 1H, pyridine-H), 8.11 (d, J 2.0, 1H, Ar-H), 7.97 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.64 (d, J 1.6, 1H, Ar-H), 7.50 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.16 (s, 1H, pyrazole-H), 1.79 (s, 3H, CH_3).

6-Cyano-2-(3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-8-methyl-4H-benzo[d][1,3]oxazin-4-one ***8c***

Yellow solid (67 % yield), mp 222–224°C. δ_H (400 MHz, [D6]DMSO) 8.63 (d, J 4.8, 1H, pyridine-H), 8.35–8.36 (m, 2H, pyridine-H, Ar-H), 8.08 (s, 1H, Ar-H), 7.77 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.55 (s, 1H, pyrazole-H), 1.71 (s, 3H, CH_3).

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

Yellow solid (84 % yield), mp 204–205°C. δ_H (400 MHz, $CDCl_3$) 8.56 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 8.13 (d, J 2.0, 1H, Ar-H), 7.97 (dd, J_1 8.0, J_2 1.6, 1H, pyridine-H), 7.65 (d, J 1.6, 1H, Ar-H), 7.50 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.25 (s, 1H, pyrazole-H), 1.80 (s, 3H, CH_3).

6-Chloro-2-(3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-8-methyl-4H-benzo[d][1,3]oxazin-4-one ***8e***

Yellow solid (92 % yield), mp 192–193°C. δ_H (400 MHz, [D6]DMSO) 8.63 (dd, J_1 4.5, J_2 1.2, 1H, pyridine-H), 8.35 (dd, J_1 8.1, J_2 1.2, 1H, pyridine-H), 7.88 (d, J 2.0, 1H, Ar-H), 7.74–7.79 (m, 2H, pyridine-H, Ar-H), 7.52 (s, 1H, pyrazole-H), 1.71 (s, 3H, CH_3).

6-Cyano-2-(3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-8-methyl-4H-benzo[d][1,3]oxazin-4-one ***8f***

Yellow solid (70 % yield), mp 233–235°C. δ_H (400 MHz, [D6]DMSO) 8.63 (d, J 4.8, 1H, pyridine-H), 8.36–8.37 (m, 2H, pyridine-H, Ar-H), 8.08 (s, 1H, Ar-H), 7.76 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.55 (s, 1H, pyrazole-H), 1.70 (s, 3H, CH_3).

General Procedure for the Synthesis of Target Compounds ***16a–e***

N-(2-(2-Methyl-2-(methylthio)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide **16a** was synthesized according to a literature procedure.[7] To a 250-mL flask was added a solution of compound **8a** (7.02 g, 17.2 mmol) and 2-methyl-1-(methylthio)propan-2-amine (6.16 g, 51.6 mmol) in tetrahydrofuran (70 mL). The mixture was heated to 60°C and stirred for 8 h, and reaction progress was monitored by TLC. After completion, the solvent was removed and the residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 3 : 1) as eluent to give **16a** (5.08 g, 56 %). Compounds **16b**–**e** were synthesized in the same manner.

N-(2-(2-Methyl-2-(methylthio)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***16a***

Transparent granules (56 % yield), mp 187–189°C. ν_{max}(KBr)/cm^{-1} 3262, 3064, 2976, 2908, 2358, 1641, 1541, 1462, 1368, 1312, 1247, 1198, 1135, 1030, 971, 877, 809, 758, 658. δ_H (400 MHz, [D6]DMSO) 10.20 (s, 1H, NH), 8.49 (dd, J_1 4.4, J_2 1.2, 1H, pyridine-H), 8.18 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.84 (s, 1H, NH), 7.62 (dd, J_1 8.0, J_2 4.4, 1H, pyridine-H), 7.46 (d, J 2.0, 1H, Ar-H), 7.35 (d, J 0.8, 1H, Ar-H), 7.28 (s, 1H, pyrazole-H), 2.93 (s, 2H, CH_2), 2.16 (s, 3H, Ar-CH_3), 2.03 (s, 3H, SCH_3), 1.27 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.7, 156.8, 149.6, 148.2, 140.7, 140.4, 140.2, 139.9, 138.4, 132.2, 132.0, 129.1, 127.8, 126.8, 108.4, 55.7, 44.8, 27.2, 18.8, 18.1. Anal. Calc. for $C_{22}H_{22}Cl_3N_5O_2S$: C 50.15, H 4.21, N 13.29. Found: C 50.06, H 4.33, N 13.02.

N-(2-(2-Methyl-2-(methylthio)propylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***16b***

White granules (42 % yield), mp 195–197°C. ν_{max}(KBr)/cm^{-1} 3366, 3143, 3066, 2979, 2922, 2358, 1645, 1540, 1460, 1370, 1304, 1197, 1149, 1026, 974, 866, 807, 759, 661. δ_H (400 MHz, $CDCl_3$) 10.15 (s, 1H, NH), 8.44 (dd, J_1 4.8, J_2 1.6, 1H, pyridine-H), 7.84 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.37 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.36 (s, 1H, Ar-H), 7.24 (s, 2H, Ar-H, pyrazole-H), 6.24 (s, 1H, NH), 2.95 (s, 2H, CH_2), 2.11 (s, 3H, Ar-CH_3), 2.09 (s, 3H, SCH_3), 1.40 (s, 6H, CH_3). δ_C (400 MHz, $CDCl_3$) 167.7, 157.2, 149.3, 146.8, 141.6, 139.1, 138.8, 138.3, 135.9, 135.0, 130.7, 129.2, 127.2, 125.7, 120.8, 107.9, 55.7, 45.1, 26.4, 18.3, 17.6. Anal. Calc. for $C_{22}H_{22}BrCl_2N_5O_2S$: C 46.25, H 3.88, N 12.26. Found: C 46.43, H 3.98, N 12.18.

N-*(2-(2-Methyl-2-(methylthio)propylcarbamoyl)-4-bromo-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***16d***

White granules (50 % yield), mp 213–215°C. ν_{max}(KBr)/cm^{-1} 3258, 3062, 2975, 2906, 2357, 1641, 1541, 1461, 1353, 1246, 1193, 1132, 1031, 959, 866, 811, 763, 655. δ_H (400 MHz, [D6]DMSO) 10.19 (s, 1H, NH), 8.50 (d, *J* 4.4, 1H, pyridine-H), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.87 (br, 1H, NH), 7.62 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.60 (s, 1H, Ar-H), 7.42 (s, 2H, Ar-H, pyrazole-H), 2.94 (s, 2H, CH_2), 2.17 (s, 3H, Ar-CH_3), 2.04 (s, 3H, SCH_3), 1.28 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 165.4, 155.4, 148.4, 147.0, 139.2, 139.1, 139.0, 137.4, 133.8, 131.4, 128.4, 127.9, 126.7, 126.6, 119.4, 110.6, 54.5, 43.6, 26.0, 17.5, 16.9. Anal. Calc. for $C_{22}H_{22}Br_2ClN_5O_2S$: C 42.91, H 3.60, N 11.37. Found: C 42.68, H 3.85, N 11.08.

N-*(2-(2-Methyl-2-(methylthio)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***16e***

Pale yellow solid (46 % yield), mp 185–186°C. ν_{max}(KBr)/cm^{-1} 3127, 3066, 2972, 2921, 2356, 1669, 1536, 1466, 1365, 1299, 1137, 1032, 957, 873, 808, 750. δ_H (400 MHz, $CDCl_3$) 10.16 (s, 1H, NH), 8.43 (dd, J_1 4.8, J_2 1.6, 1H, pyridine-H), 7.82 (dd, J_1 8.0, J_2 1.6, 1H, pyridine-H), 7.47 (s, 1H, NH), 7.35 (dd, J_1 8.0, J_2 4.4, 1H, pyridine-H), 7.06 (d, *J* 2.0, 1H, Ar-H), 7.02 (d, *J* 2.0, 1H, Ar-H), 6.26 (s, 1H, pyrazole-H), 2.93 (s, 2H, CH_2), 2.09 (s, 3H, Ar-CH_3), 2.05 (s, 3H, SCH_3), 1.38 (s, 6H, CH_3). δ_C (400 MHz, $CDCl_3$) 168.0, 157.3, 149.3, 146.8, 138.9, 138.8, 138.4, 136.1, 132.8, 131.9, 129.9, 129.1, 128.1, 125.7, 124.4, 111.4, 55.7, 45.1, 26.4, 18.2, 17.6. Anal. Calc. for $C_{22}H_{22}BrCl_2N_5O_2S$: C 46.25, H 3.88, N 12.26. Found: C 46.13, H 3.95, N 12.17.

General Procedure for the Synthesis of Target Compounds ***19a–f***

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* **19a** was synthesized according to a literature procedure.[7] To a solution of compound **8a** (4.89 g, 12.0 mmol) in tetrahydrofuran (40 mL) was added 2-(methylthio)ethanamine hydrochloride (3.06 g, 24.0 mmol). The mixture was stirred for 10 min at 0–5°C, followed by dropwise addition of triethylamine (3.64 g, 36.0 mmol). The reaction was then warmed to room temperature and stirred for 6 h, and reaction progress was monitored by TLC. After completion, the mixture was filtered and the filtrate was concentrated. The crude material was purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 3 : 1) as eluent to give **19a** (5.45 g, 91 %). Compounds **19b**–**f** were synthesized similarly.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***19a***

White granules (91 % yield), mp 147–149°C. ν_{max}(KBr)/cm^{-1} 3263, 3068, 2980, 2920, 2359, 1650, 1534, 1465, 1367, 1303, 1196, 1138, 1032, 974, 877, 806, 757. δ_H (400 MHz, [D6]DMSO) 10.22 (s, 1H, NH), 8.49 (s, 2H, pyridine-H, NH), 8.17 (d, *J* 8.0, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.0, 1H, pyridine-H), 7.49 (s, 1H, Ar-H), 7.35 (s, 2H, Ar-H, pyrazole-H), 3.32 (q, *J* 6.4, 2H, CH_2), 2.52 (t, *J* 6.0, 2H, CH_2), 2.18 (s, 3H, Ar-CH_3), 2.06 (s, 3H, SCH_3). δ_C (400 MHz, [D6]DMSO) 165.7, 155.6, 148.4, 147.0, 139.6, 139.2, 138.7, 135.8, 131.6, 131.6, 131.2, 130.8, 127.9, 126.6, 125.4, 107.3, 38.3, 32.4, 17.6, 14.5. Anal. Calc. for $C_{20}H_{18}Cl_3N_5O_2S$: C 48.16, H 3.64, N 14.04. Found: C 48.06, H 3.92, N 13.86.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***19b***

White powder (81 % yield), mp 107–108°C. ν_{max}(KBr)/cm^{-1} 3249, 3066, 2978, 2918, 2358, 1656, 1533, 1462, 1365, 1301, 1190, 1137, 1032, 973, 863, 803, 757, 659. δ_H (400 MHz, $CDCl_3$) 10.07 (s, 1H, NH), 8.44 (dd, J_1 4.4, J_2 1.2, 1H, pyridine-H), 7.84 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.36 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.29 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.13 (s, 1H, pyrazole-H), 6.76 (s, 1H, NH), 3.54 (q, *J* 6.4, 2H, CH_2), 2.64 (t, *J* 6.4, 2H, CH_2), 2.11 (s, 3H, Ar-CH_3), 2.09 (s, 3H, SCH_3). δ_C (400 MHz, $CDCl_3$) 168.0, 156.7, 149.2, 146.8, 141.7, 138.9, 138.5, 138.4, 135.6, 133.3, 131.6, 129.0, 127.5, 125.7, 120.2, 107.8, 38.2, 33.3, 18.5, 15.0. Anal. Calc. for $C_{20}H_{18}BrCl_2N_5O_2S$: C 44.22, H 3.34, N 12.89. Found: C 44.57, H 3.52, N 12.74.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-cyano-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***19c***

White granules (51 % yield), mp 200–202°C. ν_{max}(KBr)/cm^{-1} 3376, 3272, 3049, 2983, 2928, 2358, 2228, 1643, 1524, 1459, 1364, 1304, 1146, 1041, 972, 893, 808, 762. δ_H (400 MHz, [D6]DMSO) 10.52 (s, 1H, NH), 8.56 (s, 1H, NH), 8.50 (dd, J_1 4.4, J_2 0.8, 1H, pyridine-H), 8.18 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.90 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.62 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.39 (s, 1H, pyrazole-H), 3.33 (q, *J* 6.8, 2H, CH_2), 2.52 (t, *J* 6.8, 2H, CH_2), 2.24 (s, 3H, Ar-CH_3), 2.06 (s, 3H, SCH_3). δ_C (400 MHz, [D6]DMSO) 165.4, 155.4, 148.3, 147.1, 139.6, 139.2, 138.8, 137.7, 137.1, 135.3, 134.8, 129.6, 127.9, 126.7, 118.0, 109.2, 107.6, 38.4, 32.3, 17.7, 14.5. Anal. Calc. for $C_{21}H_{18}Cl_2N_6O_2S$: C 51.54, H 3.71, N 17.17. Found: C 51.33, H 3.91, N 17.07.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-bromo-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***19d***

Pale yellow solid (57 % yield), mp 216–218°C. ν_{max}(KBr)/cm^{-1} 3222, 3066, 2969, 2922, 2358, 1664, 1533, 1459, 1354, 1300, 1131, 1034, 959, 865, 805, 753. δ_H (400 MHz,$CDCl_3$) 10.06 (s, 1H, NH), 8.43 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 7.82 (d, *J* 8.0, 1H, pyridine-H), 7.34 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.26 (s, 1H, Ar-H), 7.22 (s, 2H, Ar-H, pyrazole-H), 6.94 (s, 1H, NH), 3.52 (q, *J* 6.4, 2H, CH_2), 2.62 (t, *J* 6.4, 2H, CH_2), 2.10 (s, 3H, Ar-CH_3), 2.04 (s, 3H, SCH_3). δ_C (400 MHz, $CDCl_3$) 167.0, 155.6, 148.1, 145.8, 137.8, 137.5, 137.3, 134.3, 132.7, 130.3, 127.9, 127.2, 126.6, 124.7, 119.2, 110.2, 37.3, 32.2, 17.3, 14.0. Anal. Calc. for $C_{20}H_{18}Br_2ClN_5O_2S$: C 40.87, H 3.09, N 11.92. Found: C 40.65, H 3.49, N 11.79.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H-*pyrazole-5-carboxamide* ***19e***

Pale yellow solid (65 % yield), mp 160–162°C. ν_{max}(KBr)/cm^{-1} 3253, 3064, 2977, 2917, 2357, 1655, 1533, 1462, 1353, 1301, 1193, 1132, 1031, 960, 875, 805, 756. δ_H (400 MHz, $CDCl_3$) 10.08 (s, 1H, NH), 8.47 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 7.86 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.38 (dd, J_1 8.0, J_2 4.8,

1H, pyridine-H), 7.22 (s, 2H, Ar-H, pyrazole-H), 7.16 (s, 1H, Ar-H), 6.62 (s, 1H, NH), 3.59 (q, *J* 6.4, 2H, CH_2), 2.68 (t, *J* 6.4, 2H, CH_2), 2.16 (s, 3H, Ar-CH_3), 2.12 (s, 3H, SCH_3). δ_C (400 MHz, $CDCl_3$) 167.9, 156.3, 149.0, 146.9, 138.9, 138.8, 138.5, 133.0, 132.2, 131.6, 129.0, 128.2, 125.7, 124.5, 111.0, 38.1, 33.4, 18.8, 15.0. Anal. Calc. for $C_{20}H_{18}BrCl_2N_5O_2S$: C 44.22, H 3.34, N 12.89. Found: C 44.13, H 3.59, N 12.75.

N-*(2-(2-(Methylthio)ethylcarbamoyl)-4-cyano-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***19f***

Pale yellow solid (55 % yield), mp 216–218°C. ν_{max}(KBr)/cm^{-1} 3380, 3277, 3049, 2980, 2925, 2358, 2228, 1684, 1640, 1524, 1458, 1349, 1302, 1144, 1041, 959, 893, 808, 762. δ_H (400 MHz, $CDCl_3$) 10.52 (s, 1H, NH), 8.46 (dd, J_1 6.0, J_2 2.0, 1H, pyridine-H), 7.87 (dd, J_1 10.4, J_2 2.0, 1H, pyridine-H), 7.63 (s, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.40 (dd, J_1 10.8, J_2 6.4, 1H, pyridine-H), 7.04 (s, 1H, pyrazole-H), 6.63 (s, 1H, NH), 3.64 (q, *J* 8.0, 2H, CH_2), 2.74 (t, *J* 8.0, 2H, CH_2), 2.25 (s, 3H, Ar-CH_3), 2.13 (s, 3H, SCH_3). Anal. Calc. for $C_{21}H_{18}BrClN_6O_2S$: C 47.25, H 3.40, N 15.74. Found: C 47.54, H 3.79, N 15.53.

General Procedure for the Synthesis of Target Compounds ***17a–e*** *and* ***20a–f***

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino)propylcarbamyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* **17a** was synthesized as previously described.[31] A solution of compound **16a** (3.71 g, 7.04 mmol) and cyanamide (0.59 g, 14.1 mmol) in tetrahydrofuran (30 mL) was stirred for 10 min at 0–5°C, followed by addition of (diacetoxyiodo)benzene (2.49 g, 7.74 mmol). Stirring was continued at 0–5°C and the reaction progress was monitored by TLC. After completion, the solvent was removed and the residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 1 : 1) as eluent to give **17a** (3.09 g, 92 %). Compounds **17b–e** and **20a–f** were synthesized similarly.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino) propylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***17a***

White granules (92 % yield), mp 111–112°C. ν_{max}(KBr)/cm^{-1} 3261, 3058, 2982, 2926, 2358, 2147, 1671, 1537, 1463, 1370, 1308, 1248, 1158, 1033, 972, 881, 811, 764. δ_H (400 MHz, [D6]DMSO) 10.20 (s, 1H, NH), 8.51 (dd, J_1 4.8, J_2 1.6, 1H, pyridine-H), 8.40 (s, 1H, NH), 8.18 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.4, 1H, pyridine-H), 7.48 (d, *J* 2.0, 1H, Ar-H), 7.38 (d, *J* 2.0, 1H, Ar-H), 7.35 (s, 1H, pyrazole-H), 3.66 (d, *J* 13.6, 1H, H_A-CH_2), 3.49 (d, *J* 13.6, 1H, H_B-CH_2), 2.75 (s, 3H, $n = SCH_3$), 2.18 (s, 3H, Ar-CH_3), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). δ_C (400 MHz, [d6]DMSO) 166.1, 155.6, 148.5, 147.1, 139.6, 139.2, 139.0, 138.6, 136.3, 131.1, 130.8, 127.9, 126.6, 125.8, 120.4, 107.2, 57.8, 52.2, 33.3, 26.9, 26.6, 17.6. HRMS (MALDI) 588.0519, 589.0556, 590.0488, 591.0525, 592.0458, 593.0493 ($[M + Na]^+$). Anal. Calc. for $C_{23}H_{22}Cl_3N_7O_2S$: C 48.73, H 3.91, N 17.30. Found: C 48.60, H 4.25, N 17.22.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino) propylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***17b***

White powder (77 % yield), mp 193–195°C. ν_{max}(KBr)/cm^{-1} 3248, 2999, 2921, 2356, 2138, 1669, 1533, 1464, 1371, 1301, 1247, 10742, 1030, 977, 864, 810, 760, 673. δ_H (400 MHz, [D6]DMSO) 10.21 (s, 1H, NH), 8.52 (d, *J* 4.0, 1H, pyridine-H), 8.40 (s, 1H, NH), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.61–7.65 (m, 2H, pyridine-H, Ar-H), 7.50 (s, 1H, Ar-H), 7.36 (s, 1H, pyrazole-H), 3.67 (d, *J* 13.6, 1H, H_A-CH_2), 3.50 (d, *J* 13.6, 1H, H_B-CH_2), 2.76 (s, 3H, $n = SCH_3$), 2.19 (s, 3H, Ar-CH_3), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.0, 155.5, 148.4, 147.1, 139.6, 139.2, 139.0, 138.9, 136.6, 134.0, 131.5, 128.6, 127.9, 126.6, 120.4, 119.4, 107.2, 57.7, 52.2, 33.3, 26.9, 26.6, 17.5. Anal. Calc. for $C_{23}H_{22}BrCl_2N_7O_2S$: C 45.19, H 3.63, N 16.04. Found: C 45.31, H 3.84, N 15.69.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino) propylcarbamoyl)-4-cyano-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***17c***

White granules (63 % yield), mp 237–239°C. ν_{max}(KBr)/cm^{-1} 3247, 3127, 3060, 2979, 2915, 2357, 2226, 2154, 1682, 1535, 1464, 1374, 1305, 1218, 1155, 1030, 972, 888, 819, 762, 668. δ_H (400 MHz, [D6]DMSO) 10.44 (s, 1H, NH), 8.52 (d, *J* 4.8, 1H, pyridine-H), 8.48 (s, 1H, NH), 8.19 (d, *J* 8.0, 1H, pyridine-H), 7.91 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H), 7.63 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.38 (s, 1H, pyrazole-H), 3.64 (d, *J* 13.6, 1H, H_A-CH_2), 3.52 (d, *J* 13.6, 1H, H_B-CH_2), 2.77 (s, 3H, $n = SCH_3$), 2.25 (s, 3H, Ar-CH_3), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). δ_C (400 MHz, [D6]DMSO) 165.8, 155.4, 148.3, 147.2, 139.6, 139.3, 138.8, 137.6, 136.8, 135.2, 135.1, 130.2, 127.9, 126.7, 120.5, 118.0, 109.2, 107.5, 57.7, 52.2, 33.4, 26.9, 26.6, 17.6. Anal. Calc. for $C_{24}H_{22}Cl_2N_8O_2S$: C 51.71, H 3.98, N 20.10. Found: C 51.77, H 4.16, N 19.98.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino) propylcarbamoyl)-4-bromo-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***17d***

White granules (69 % yield), mp 175–176°C. ν_{max}(KBr)/cm^{-1} 3276, 3210, 2976, 2865, 2358, 2147, 1672, 1529, 1464, 1353, 1301, 1255, 1159, 1063, 962, 864, 814, 767, 672. δ_H (400 MHz, [D6]DMSO) 10.10 (s, 1H, NH), 8.51 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 8.42 (s, 1H, NH), 8.17 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.60–7.63 (m, 2H, pyridine-H, Ar-H), 7.49 (s, 1H, Ar-H), 7.41 (s, 1H, pyrazole-H), 3.66 (d, *J* 13.6, 1H, H_A-CH_2), 3.49 (d, *J* 13.6, 1H, H_B-CH_2), 2.75 (s, 3H, $n = SCH_3$), 2.18 (s, 3H, Ar-CH_3), 1.37 (s, 3H, CH_3), 1.35 (s, 1H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.0, 155.4, 148.4, 147.1, 139.2, 139.2, 138.8, 136.6, 134.0, 131.6, 128.6, 127.9, 126.8, 126.6, 120.4, 119.3, 110.6, 57.8, 52.2, 33.3, 27.0, 26.6, 17.5. Anal. Calc. for $C_{23}H_{22}Br_2ClN_7O_2S$: C 42.12, H 3.38, N 14.95. Found: C 42.05, H 3.58, N 14.85.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfideimino) propylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***17e***

White solid (62 % yield), mp 128–130°C. ν_{max}(KBr)/cm^{-1} 3251, 3058, 2980, 2924, 2358, 2147, 1674, 1536.27, 1462, 1355, 1304, 1246, 1153, 1029, 960, 879, 809, 761. δ_H (400 MHz, [D6]DMSO) 10.20 (s, 1H, NH), 8.51 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 8.40 (s, 1H, NH), 8.18 (dd, J_1 8.4, J_2 1.2, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.4, 1H, pyridine-H), 7.48 (d, *J* 2.0, 1H, Ar-H), 7.41 (s, 1H, pyrazole-H), 7.38 (d, *J* 2.4, 1H, Ar-H), 3.65 (d, *J* 13.6, 1H, H_A-CH_2), 3.49 (d, *J* 13.6, 1H, H_B-CH_2), 2.75 (s, 3H,

$n = SCH_3$), 2.18 (s, 3H, Ar-CH_3), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.2, 155.5, 148.4, 147.1, 139.2, 139.1, 138.6, 136.4, 131.1, 130.9, 127.9, 126.8, 126.6, 125.8, 120.4, 110.6, 57.7, 52.2, 33.3, 27.0, 26.6, 17.6. Anal. Calc. for $C_{23}H_{22}BrCl_2N_7O_2S$: C 45.19, H 3.63, N 16.04. Found: C 44.97, H 3.81, N 15.88.

N-*(2-(2-(*N*-Cyanomethylsulfideimino)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***20a***

White granules (90 % yield), mp 198–200°C. ν_{max}(KBr)/cm^{-1} 3217, 3067, 2986, 2357, 2151, 1647, 1539, 1465, 1370, 1308, 1162, 1038, 972, 880, 808, 763, 690. δ_H (400 MHz, [D6]DMSO) 10.32 (s, 1H, NH), 8.78 (s, 1H, NH), 8.53 (d, *J* 4.0, 1H, pyridine-H), 8.19 (d, *J* 7.6, 1H, pyridine-H), 7.62 (dd, J_1 7.2, J_2 4.4, 1H, pyridine-H), 7.52 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.36 (s, 1H, pyrazole-H), 3.51–3.57 (m, 2H, CH_2), 3.19–3.32 (m, 2H, CH_2), 2.82 (s, 3H, $n = SCH_3$), 2.19 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 166.1, 155.7, 148.4, 147.1, 139.7, 139.3, 139.1, 138.8, 135.3, 131.5, 131.3, 131.0, 127.9, 126.6, 125.5, 120.4, 107.4, 48.8, 33.3, 32.3, 17.6. Anal. Calc. for $C_{21}H_{18}Cl_3N_7O_2S$: C 46.81, H 3.37, N 18.20. Found: C 46.71, H 3.45, N 18.12.

N-*(2-(2-(*N*-Cyanomethylsulfideimino)ethylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***20b***

White granules (59 % yield), mp 184–186°C. ν_{max}(KBr)/cm^{-1} 3201, 3067, 2992, 2358, 2153, 1671, 1532, 1464, 1367, 1304, 1186, 1140, 1036, 866, 807, 754. δ_H (400 MHz, [D6]DMSO) 10.28 (s, 1H, NH), 8.62 (s, 1H, NH), 8.51 (d, *J* 4.0, 1H, pyridine-H), 8.18 (d, *J* 7.6, 1H, pyridine-H), 7.63 (s, 2H, pyridine-H, Ar-H), 7.49 (s, 1H, Ar-H), 7.36 (s, 1H, pyrazole-H), 3.45–3.55 (m, 2H, CH_2), 2.78–2.99 (m, 2H, CH_2), 2.54 (s, 3H, $n = SCH_3$), 2.18 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 165.7, 155.6, 148.4, 147.1, 139.5, 139.2, 139.1, 139.0, 135.9, 134.2, 132.8, 131.8, 128.2, 127.9, 126.6, 119.3, 107.3, 52.6, 38.0, 33.1, 17.5. Anal. Calc. for $C_{21}H_{18}BrCl_2N_7O_2S$: C 43.24, H 3.11, N 16.81. Found: C 43.37, H 3.45, N 16.72.

N-*(2-(2-(*N*-Cyanomethylsulfideimino)ethylcarbamoyl)-4-cyano-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***20c***

Yellow powder (89 % yield), mp 202–203°C. ν_{max}(KBr)/cm^{-1} 3148, 3074, 2974, 2358, 2230, 2151, 1671, 1536, 1467, 1369, 1307, 1161, 1035, 972, 895, 811, 765. δ_H (400 MHz, [D6]DMSO) 10.57 (s, 1H, NH), 8.92 (s, 1H, NH), 8.52 (s, 1H, pyridine-H), 8.18 (s, 1H, pyridine-H), 7.84–7.90 (m, 2H, pyridine-H, Ar-H), 7.62 (s, 1H, Ar-H), 7.34 (s, 1H, pyrazole-H), 3.50–3.57 (m, 2H, CH_2), 3.20–3.25 (m, 2H, CH_2), 2.82 (s, 3H, $n = SCH_3$), 2.23 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 165.8, 155.6, 148.4, 147.1, 147.1, 139.6, 139.3, 139.2, 137.6, 135.4, 129.8, 129.7, 127.9, 126.7, 120.4, 118.1, 107.5, 48.8, 33.4, 32.2, 17.7. Anal. Calc. for $C_{22}H_{18}Cl_2N_8O_2S$: C 49.91, H 3.43, N 21.17. Found: C 49.76, H 3.59, N 21.12.

N-*(2-(2-(*N*-Cyanomethylsulfideimino)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***20e***

White solid (45 % yield), mp 206–208°C. ν_{max}(KBr)/cm^{-1} 3224, 3065, 2992, 2358, 2150, 1671, 1536, 1464, 1355, 1304, 1164, 1034, 962, 878, 806, 763. δ_H (400 MHz, [D6]DMSO) 10.27 (s, 1H, NH), 8.75–8.78 (m, 1H, NH), 8.52 (d, *J* 4.0, 1H, pyridine-H), 8.18 (d, *J* 7.6, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.50 (s, 1H, Ar-H), 7.39–7.41 (m, 2H, Ar-H, pyrazole-H), 3.45–3.60 (m, 2H, CH_2), 3.18–3.28 (m, 2H, CH_2), 2.81 (s, 3H, $n = SCH_3$), 2.18 (s, 3H, Ar-CH_3). Anal. Calc. for $C_{21}H_{18}BrCl_2N_7O_2S$: C 43.24, H 3.11, N 16.81. Found: C 43.01, H 3.49, N 16.71.

N-*(2-(2-(*N*-Cyanomethylsulfideimino)ethylcarbamoyl)-4-cyano-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***20f***

White solid (49 % yield), mp 245–247°C. ν_{max}(KBr)/cm^{-1} 3224, 3074, 2976, 2359, 2229 2152, 1681, 1533, 1466, 1353, 1301, 1161, 1036, 962, 895, 811, 768. δ_H (400 MHz, [D6]DMSO) 9.07 (s, 1H, NH), 8.52 (d, *J* 3.6, 1H, pyridine-H), 8.18 (d, *J* 6.8, 1H, pyridine-H), 7.88 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.62 (dd, J_1 4.8, J_2 8.0, 1H, pyridine-H), 7.39 (s, 1H, pyrazole-H), 3.50–3.59 (m, 2H, CH_2), 3.17–3.26 (m, 2H, CH_2), 2.81 (s, 3H, $n = SCH_3$), 2.22 (s, 3H, Ar-CH_3). HRMS (MALDI) 595.0035, 596.0082, 597.0010, 598.0055, 599.0004, 600.0049 ($[M + Na]^+$). Anal. Calc. for $C_{22}H_{18}BrClN_8O_2S$: C 46.05, H 3.16, N 19.53. Found: C 45.79, H 3.69, N 19.31.

General Procedure for the Synthesis of Target Compounds ***18a–e*** *and* ***21c–e***

N-*(2-(2-Methyl-2-(N-cyanomethylsulfoximino)propylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* **18a** was synthesized according to a literature procedure.[31] To a solution of 3-chloroperoxybenzoic acid (1.78 g, 10.3 mmol) in methanol (20 mL) was added dropwise a mixture of potassium carbonate (2.14 g, 15.5 mmol) and water (20 mL) at 0°C. The reaction was stirred for 20 min at 0°C, followed by addition of a solution of compound **17a** (2.92 g, 5.15 mmol) in methanol (20 mL). The reaction mixture was stirred at 0°C, and the progress was monitored by TLC. After completion, the methanol was removed and the residue was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with water (1 × 20 mL), followed by brine (1 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by chromatography on silica gel using petroleum ether/ethyl acetate (v/v 1 : 1) as eluent to give **18a** (1.53 g, 51 %). Compounds **18b–e** and **21b–e** were synthesized in a similar manner.

N-*(2-(2-Methyl-2-(*N*-cyanomethylsulfoximino) propylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide* ***18a***

White powder (51 % yield), mp 142–144°C. ν_{max}(KBr)/cm^{-1} 3279, 3065, 2986, 2924, 2359, 2195, 1675, 1536, 1463, 1366, 1308, 1246, 1194, 1035, 974, 879, 814, 762. δ_H (400 MHz, [D6]DMSO) 10.20 (s, 1H, NH), 8.49 (dd, J_1 4.8, J_2 1.2, 1H, pyridine-H), 8.29 (s, 1H, NH), 8.17 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.48 (d, *J* 1.6, 1H, Ar-H), 7.36 (d, *J* 2.0, 1H, Ar-H), 7.33 (s, 1H, pyrazole-H), 4.20 (s, 2H, CH_2), 3.45 (s, 3H, N(O)=SCH_3), 2.18 (s, 3H, Ar-CH_3), 1.42 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.0, 155.5, 148.4, 147.0, 139.6, 139.2, 138.9, 138.6, 136.5, 131.1, 131.0, 130.9, 127.9, 126.6, 125.8, 112.4, 107.2, 58.9, 52.3, 42.7, 26.9, 26.8, 17.5. HRMS (MALDI) 604.0460, 605.0500, 606.0435, 607.0467, 608.0423, 609.0453, 610.0395, 611.0432 ($[M + Na]^+$).

N-(2-(2-Methyl-2-(N-cyanomethylsulfoximino) propylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***18b***

White granules (83 % yield), mp 125–127°C. ν_{max}(KBr)/cm^{-1} 3277, 3063, 2988, 2924, 2358, 2196, 1672, 1533, 1466, 1371, 1305, 1249, 1197, 1030, 976, 868, 813, 759. δ_H (400 MHz, [D6] DMSO) 10.20 (s, 1H, NH), 8.50 (d, *J* 4.4, 1H, pyridine-H), 8.31 (s, 1H, NH), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.62–7.64 (m, 2H, pyridine-H, Ar-H), 7.50 (s, 1H, Ar-H), 7.34 (s, 1H, pyrazole-H), 4.22 (s, 2H, CH_2), 3.47 (s, 3H, N(O)=SCH_3), 2.19 (s, 3H, Ar-CH_3), 1.44 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.4, 156.1, 149.0, 147.6, 140.1, 139.7, 139.5, 139.3, 137.2, 134.5, 132.0, 129.1, 128.4, 127.2, 119.8, 112.9, 107.7, 59.4, 52.8, 43.2, 27.4, 27.3, 18.0. Anal. Calc. for $C_{23}H_{22}BrCl_2N_7O_3S$: C 44.03, H 3.53, N 15.63. Found: C 43.88, H 3.87, N 15.56.

N-(2-(2-Methyl-2-(N-cyanomethylsulfoximino) propylcarbamoyl)-4-cyano-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***18c***

Colourless granules (71 % yield), mp 135–137°C. ν_{max}(KBr)/cm^{-1} 3284, 3064, 2994, 2890, 2354, 2194, 2056, 1996, 1686, 1534, 1468, 1370, 1253, 1150, 1035, 978, 884, 813, 758. δ_H (400 MHz, [D6]DMSO) 10.44 (s, 1H, NH), 8.51 (d, *J* 4.4, 1H, pyridine-H), 8.42 (s, 1H, NH), 8.19 (d, *J* 8.0, 1H, pyridine-H), 7.91 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.63 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.38 (s, 1H, pyrazole-H), 4.22 (s, 2H, CH_2), 3.48 (s, 3H, N(O)=SCH_3), 2.26 (s, 3H, Ar-CH_3), 1.44 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.9, 156.6, 149.5, 148.3, 140.8, 140.5, 139.9, 138.8, 138.0, 136.5, 136.3, 131.3, 129.1, 127.9, 119.3, 113.6, 110.4, 108.7, 60.2, 53.5, 43.9, 28.1, 28.0, 18.8. HRMS (MALDI) 595.0804, 596.0848, 597.0783, 598.0828, 599.0790, 600.0830 ([M + Na]$^+$). Anal. Calc. for $C_{24}H_{22}Cl_2N_8O_3S$: C 50.27, H 3.87, N 19.54. Found: C 50.13, H 4.02, N 19.44.

N-(2-(2-Methyl-2-(N-cyanomethylsulfoximino) propylcarbamoyl)-4-bromo-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***18d***

White powder (56 % yield), mp 136–138°C. ν_{max}(KBr)/cm^{-1} 3272, 3063, 2989, 2923, 2365, 2196, 1669, 1533, 1465, 1353, 1302, 1248, 1196, 1029, 966, 867, 813, 758. δ_H (400 MHz, [D6] DMSO) 10.18 (s, 1H, NH), 8.50 (d, *J* 4.4, 1H, pyridine-H), 8.31 (s, 1H, NH), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.62–7.64 (m, 2H, pyridine-H, Ar-H), 7.50 (s, 1H, Ar-H), 7.40 (s, 1H, pyrazole-H), 4.22 (s, 2H, CH_2), 3.47 (s, 3H, N(O)=SCH_3), 2.19 (s, 3H, Ar-CH_3), 1.43 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.0, 155.4, 148.4, 147.1, 139.2, 139.1, 138.8, 136.7, 134.0, 131.5, 128.6, 127.9, 126.8, 126.6, 119.3, 112.4, 110.6, 58.9, 52.3, 42.7, 26.9, 26.8, 17.5. Anal. Calc. for $C_{23}H_{22}Br_2ClN_7O_3S$: C 41.12, H 3.30, N 14.59. Found: C 40.94, H 3.62, N 14.29.

N-(2-(2-Methyl-2-(N-cyanomethylsulfoximino) propylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***18e***

White solid (57 % yield), mp 131–132°C. ν_{max}(KBr)/cm^{-1} 3283, 3065, 2987, 2926, 2358, 2196, 1673, 1534, 1464, 1353, 1303, 1249, 1197, 1135, 1029, 965, 878, 812, 757. δ_H (400 MHz, [D6]DMSO) 10.29 (s, 1H, NH), 8.50 (d, *J* 4.0, 1H, pyridine-H), 8.37 (s, 1H, NH), 8.19 (d, *J* 8.0, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.0, 1H, pyridine-H), 7.48 (s, 1H, Ar-H), 7.39 (s, 2H, Ar-H, pyrazole-H), 4.22 (s, 2H, CH_2), 3.47 (s, 3H, N(O)=SCH_3), 2.19 (s, 3H, Ar-CH_3), 1.44 (s, 6H, CH_3). δ_C (400 MHz, [D6]DMSO) 166.1, 162.4, 155.5, 148.5, 147.0, 139.2, 138.4, 131.0, 127.9, 126.8, 126.6, 125.8, 112.4, 110.5, 58.9, 52.2, 42.6, 26.9, 26.8, 17.6. HRMS (MALDI) 647.9930, 649.0066, 649.9937, 651.0013, 651.9921, 653.0014 ([M + Na]$^+$). Anal. Calc. for $C_{23}H_{22}BrCl_2N_7O_3S$: C 44.03, H 3.53, N 15.63. Found: C 43.88, H 3.69, N 15.58.

N-(2-(2-(N-Cyanomethylsulfoximino)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***21a***

White granules (68 % yield), mp 112–114°C. ν_{max}(KBr)/cm^{-1} 3272, 3068, 3006, 2925, 2363, 2197, 1670, 1534, 1466, 1370, 1304, 1252, 1198, 1134, 1032, 974, 878, 812, 758. δ_H (400 MHz, [D6]DMSO) 10.29 (s, 1H, NH), 8.75 (s, 1H, NH), 8.51 (d, *J* 4.4, 1H, pyridine-H), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.62 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.53 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 7.36 (s, 1H, pyrazole-H), 3.72–3.80 (m, 2H, CH_2), 3.63–3.64 (m, 2H, CH_2), 3.49 and 3.00 (s, 3H, N(O)=SCH_3), 2.20 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 166.1, 155.7, 148.4, 147.1, 139.6, 139.3, 139.1, 138.6, 135.1, 131.6, 131.4, 130.8, 127.9, 126.6, 125.5, 112.4, 107.3, 52.9, 40.6, 33.0, 17.6. HRMS (MALDI) 576.0149, 577.0191, 578.0119, 579.0157, 580.0088, 581.0127 ([M + Na]$^+$). Anal. Calc. for $C_{21}H_{18}Cl_3N_7O_3S$: C 45.46, H 3.27, N 17.67. Found: C 45.28, H 3.52, N 17.52.

N-(2-(2-(N-Cyanomethylsulfoximino)ethylcarbamoyl)-4-bromo-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***21b***

White powder (60 % yield), mp 123–125°C. ν_{max}(KBr)/cm^{-1} 3276, 3068, 3007, 2927, 2358, 2197, 1674, 1533, 1466, 1369, 1303, 1253, 1196, 1133, 1032, 972, 864, 810, 759. δ_H (400 MHz, [D6]DMSO) 10.30 (s, 1H, NH), 8.76 (br, 1H, NH), 8.52 (s, 1H, pyridine-H), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.65 (s, 2H, pyridine-H, Ar-H), 7.55 (s, 1H, Ar-H), 7.36 (s, 1H, pyrazole-H), 3.76–3.77 (m, 1H, H_A-CH_2), 3.64–3.65 (m, 1H, H_B-CH_2), 3.55–3.56 (m, 1H, H_C-CH_2), 3.50 and 3.00 (s, 3H, N(O)=SCH_3), 3.24–3.26 (m, 1H, H_D-CH_2), 2.20 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 166.2, 156.1, 149.0, 147.6, 140.1, 139.8, 139.6, 139.3, 135.0, 134.9, 132.4, 128.8, 128.4, 127.1, 119.7, 112.9, 107.8, 53.4, 53.3, 41.1, 33.7, 33.5, 18.0. Anal. Calc. for $C_{21}H_{18}BrCl_2N_7O_3S$: C 42.09, H 3.03, N 16.36. Found: C 41.97, H 3.28, N 16.28.

N-(2-(2-(N-Cyanomethylsulfoximino)ethylcarbamoyl)-4-cyano-6-methylphenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***21c***

White granules (52 % yield), mp 200–202°C. ν_{max}(KBr)/cm^{-1} 3273, 3072, 2987, 2930, 2358, 2199, 1648, 1535, 1465, 1368, 1304, 1263, 1136, 1076, 1034, 970, 894, 811, 760. δ_H (400 MHz, [D6]DMSO) 10.53 (s, 1H, NH), 8.79 (br, 1H, NH), 8.51 (d, *J* 4.0, 1H, pyridine-H), 8.18 (d, *J* 8.0, 1H, pyridine-H), 7.93 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H), 7.62 (dd, J_1 7.6, J_2 4.8, 1H, pyridine-H), 7.38 (s, 1H, pyrazole-H), 3.73–3.80 (m, 1H, H_A-CH_2), 3.62–3.65 (m, 1H, H_B-CH_2), 3.53–3.56 (m, 1H, H_C-CH_2), 3.48 and 2.99 (s, 3H, N(O)=SCH_3), 3.23–3.26 (m, 1H, H_D-CH_2), 2.26 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 165.8, 155.6, 148.3, 147.2, 139.7, 139.3, 138.8, 137.6, 137.0,

135.6, 135.5, 129.8, 127.9, 126.7, 118.0, 112.4, 109.2, 107.6, 52.9, 52.8, 40.6, 33.3, 33.0, 17.6. HRMS (MALDI) 567.0493, 568.0533, 569.0464, 570.0505, 571.0436, 572.0461 ($[M+Na]^+$). Anal. Calc. for $C_{22}H_{18}Cl_2N_8O_3S$: C 48.45, H 3.33, N 20.55. Found: C 48.19, H 3.52, N 20.37.

N-(2-(2-(N-Cyanomethylsulfoximino)ethylcarbamoyl)-4-bromo-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***21d***

White solid (47 % yield), mp 206–208°C. ν_{max}(KBr)/cm^{-1} 3226, 3068, 3008, 2925, 2355, 1660, 1540, 1461, 1300, 1195, 1133, 1035, 961, 865, 800, 757. δ_H (400 MHz, [D6]DMSO) 10.50 (s, 1H, NH), 8.84 (dd, J_1 4.4, J_2 2.4, 1H, pyridine-H), 8.51 (s, 1H, NH), 8.18 (d, J 7.2, 1H, pyridine-H), 7.93 (d, J 0.8, 1H, Ar-H), 7.81 (d, J 0.8, 1H, Ar-H), 7.62 (dd, J_1 6.4, J_2 4.8, 1H, pyridine-H), 7.42 (s, 1H, pyrazole-H), 3.74–3.77 (m, 1H, H_A-CH_2), 3.62–3.64 (m, 1H, H_B-CH_2), 3.53–3.54 (m, 1H, H_C-CH_2), 3.48 and 2.98 (s, 3H, N(O)=SCH_3), 3.23–3.25 (m, 1H, H_D-CH_2), 2.25 (s, 3H, Ar-CH_3). δ_C (400 MHz, [D6]DMSO) 165.8, 155.5, 148.4, 147.1, 139.2, 138.9, 135.6, 134.4, 131.8, 128.3, 127.8, 126.8, 126.6, 119.3, 110.6, 52.7, 40.5, 33.2, 17.5. Anal. Calc. for $C_{21}H_{18}Br_2ClN_7O_3S$: C 39.18, H 2.82, N 15.23. Found: C 38.99, H 3.11, N 15.15.

N-(2-(2-(N-Cyanomethylsulfoximino)ethylcarbamoyl)-4-chloro-6-methylphenyl)-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide ***21e***

White solid (55 % yield), mp 142–144°C. ν_{max}(KBr)/cm^{-1} 3267, 3068, 3007, 2924, 2357, 2197, 1672, 1533, 1466, 1354, 1302, 1251, 1197, 1132, 1033, 965, 877, 811, 757. δ_H (400 MHz, $CDCl_3$) 9.61 (s, 1H, NH), 8.45 (dd, J_1 4.8, J_2 1.6, 1H, pyridine-H), 7.88 (dd, J_1 8.0, J_2 1.2, 1H, pyridine-H), 7.40 (dd, J_1 8.0, J_2 4.8, 1H, pyridine-H), 7.31 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.09 (s, 1H, pyrazole-H), 3.89–3.93 (m, 2H, CH_2), 3.60–3.64 (m, 2H, CH_2), 3.28 (s, 3H, N(O)=SCH_3), 2.19 (s, 3H, Ar-CH_3). HRMS (MALDI) 619.9640, 620.9679, 621.9609, 622.9645, 623.9592, 624.9626, 625.9574, 626.9619 ($[M+Na]^+$). Anal. Calc. for $C_{21}H_{18}BrCl_2N_7O_3S$: C 42.09, H 3.03, N 16.36. Found: C 41.91, H 3.41, N 16.26.

X-ray Diffraction Analysis

A crystal of the target compound **16e** was extracted in ethyl acetate and petroleum ether. A colourless crystal of **16e** with dimensions of 0.20 × 0.18 × 0.12 mm was selected and mounted on a glass fibre for X-ray diffraction analysis. All measurements were made on a Rigaku Saturn 724 CCD diffractometre $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The data were collected at a temperature of 113(2) K to a maximum θ value of 27.88°. The molecular formula is $C_{22}H_{22}BrCl_2N_5O_2S$ and the formula weight is 571.32. The crystal is a monoclinic system, space group $P2(1)/c$, with unit cell parameters: $a = 9.498(2)$ Å, $b = 11.107(2)$ Å, $c = 23.921(5)$ Å, $V = 2504.9(9)$ Å^3, $Z = 4$, density (calculated) = 1.515 g cm^{-3}, and linear absorption coefficient 1.967 mm^{-1}. In total, 25834 integrated reflections were collected, reducing to a dataset of 5981 unique with $R_{int} = 0.0566$, and completeness of data (to $\theta = 27.88°$) of 99.9 %. Data were collected and processed using *CrystalClear* (Rigaku). An empirical absorption correction was applied using *CrystalClear* (Rigaku). The structure was resolved by direct methods with the *SHELXL-97* program.[32] Refinements were done by the full-matrix least-squares on F^2 with *SHELXL-97*. All the non-H atoms were refined anisotropically by full-matrix least-squares to give the final $r = 0.0558$ and $wR = 0.1287$, $w = 1/(\sigma^2(F_0^2) + (0.0653P)^2 + 0.0000P)$, where $P = (F_0^2 + 2F_c^2)/3$ with $(\Delta/\sigma)_{max} = 0.999$ and $S = 1.067$ using the *SHELXL* program. The hydrogen atoms were located from a difference Fourier map and refined isotropically. The corrections for absorption is multi-scan, $T_{min} = 0.6944$, $T_{max} = 0.7982$.

Insecticidal Activity Screening

Mythimna separata *Screening*

The activity of the target compounds against *M. separata* was tested using the leaf-disk method.[33,34] Fresh corn leaves were dipped for 10 s in the test acetone solution (5 μg mL^{-1}), which was diluted with 200 μg mL^{-1} of mother solution containing 3.0 mg of target compound and 15 mL acetone. After air-drying to evaporate the acetone and water, the treated leaves were cut into small pieces and placed in petri dishes with a 10-cm diameter. Thirty individual *M. separata* were transferred to each petri dish. The petri dishes were finally secured with rubber bands and placed in a standard cultivation room at 25°C for 72 h with 80 % humidity. The percentage mortality was evaluated according to the corresponding blank controls, whereby cyantraniliprole was used as a positive control and water as a negative control. Each experiment was performed in triplicate. Target compound concentrations of 1 μg mL^{-1} and 0.1 μg mL^{-1} were tested in the same manner. The insects displaying no reaction when touched by a brush pen were regarded as dead.

Plutella xylostella *Screening*

The insecticidal activity of the synthesized compounds against *P. xylostella* was tested using the leaf-dip method.[35–38] Fresh cabbage discs (7 cm × 2 cm) were dipped in the test water solutions (10 μg mL^{-1}) for 10 s. The test water solutions were diluted with 200 μg mL^{-1} of mother solution containing target compounds (2.0 mg), DMF (0.5 mL), and water with 9.5 mL Tween 80 (0.2 %). After drying in air, the discs were placed individually in glass tubes (length 10 cm). Ten larvae of second-instar *P. xylostella* were carefully transferred to the glass tubes, which were then kept in a chamber at 20 ± 1°C and relative humidity of 60 %. Cyantraniliprole was used as a positive control, and each experiment was performed in triplicate. Mortality levels were determined after 72 h. Leaves treated with water served as a negative control. The insects displaying no reaction when touched by a brush pen were regarded as dead.

Supplementary Material

The Supplementary Material contains crystal data for compound **16e** and characterisation data of all target compounds, including IR, ^{1}H and ^{13}C NMR, and HRMS. It is available on the Journal's website.

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References

[1] M. Fill, J. A. Copello, *Physiol. Rev.* **2002**, *82*, 893.
[2] L. Zhu, X. W. Zhong, S. R. Wayne Chen, N. Banavali, Z. Liu, *J. Biol. Chem.* **2013**, *288*, 903. doi:10.1074/JBC.M112.429670
[3] S. L. Hamilton, *Cell Calcium* **2005**, *38*, 253. doi:10.1016/J.CECA.2005.06.037
[4] L. Kimlicka, F. Petegem, *Sci. China C Life Sci.* **2011**, *54*, 712. doi:10.1007/S11427-011-4198-2

[5] A. F. Dulhunty, *Clin. Exp. Pharmacol. Physiol.* **2006**, *33*, 763. doi:10.1111/J.1440-1681.2006.04441.X
[6] G. P. Lahm, D. Cordova, J. D. Barry, *Bioorg. Med. Chem.* **2009**, *17*, 4127. doi:10.1016/J.BMC.2009.01.018
[7] K. A. Hughes, G. P. Lahm, T. P. Selby, T. M. Stevenson, *W. O. Patent 2004067528 A1* **2004**.
[8] G. P. Lahm, T. P. Selby, T. M. Stevenson, *W. O. Patent 2003015519 A1* **2003**.
[9] M. S. Tohnishi, H. K. Nakao, E. H. Kohno, T. T. Nishida, T. I. Furuya, T. K. Shimizu, A. H. Seo, K. K. Sakata, S. K. Fujioka, H. I. Kanno, *E. P. Patent 1006107* **2010**.
[10] B. S. Chai, X. M. He, J. F. Wang, Z. N. Li, C. L. Liu, *Agrochemicals* **2010**, *49*, 167. [In Chinese]
[11] S. Tiwari, L. L. Stelinski, *Pest Manag. Sci.* **2013**, *69*, 1066. doi:10.1002/PS.3468
[12] L. A. Teixeira, J. T. Andaloro, *Pestic. Biochem. Physiol.* **2013**, *106*, 76. doi:10.1016/J.PESTBP.2013.01.010
[13] D. B. Sattelle, D. Cordova, T. R. Cheek, *Invert. Neurosci.* **2008**, *8*, 107. doi:10.1007/S10158-008-0076-4
[14] Y. M. Zhu, X. P. Huang, R. Rogers, M. R. Loso, G. Whiteker, J. Daeuble, B. Nugent, In *Proceedings of the 242nd ACS National Meeting & Exposition*, Denver, CO, USA, 28 August–1 September 2011. **2011**; ORGN-326 (American Chemical Society, Washington, D. C.).
[15] C. Longhurst, J. M. Babcock, I. Denholm, K. Gorman, J. D. Thomas, T. C. Sparks, *Pest Manag. Sci.* **2013**, *69*, 809. doi:10.1002/PS.3439
[16] T. C. Sparks, M. R. Loso, G. B. Watson, J. M. Babcock, V. J. Kramer, Y. M. Zhu, B. M. Nugent, J. D. Thomas, in *Modern Crop Protection Compounds*, 2nd edn (Eds W. Kraemer, U. Schirmer, P. Jeschke) **2012**, Vol. 3, pp. 1226–1237 (VCH Verlagsgesellschaft: Weinheim).
[17] J. M. Babcock, C. B. Gerwick, J. X. Huang, M. R. Loso, G. Nakamura, S. P. Nolting, R. B. Rogers, T. C. Sparks, J. Thomas, G. B. Watson, *Pest Manag. Sci.* **2011**, *67*, 328. doi:10.1002/PS.2069
[18] R. J. Rasoulpour, J. Reza, R. G. Ellis-Hutchings, C. Terry, N. S. Millar, C. L. Zablotny, A. Gibb, V. Marshall, T. Collins, E. W. Carney, R. Billington, *Toxicol. Sci.* **2012**, *127*, 522. doi:10.1093/TOXSCI/KFS118
[19] Y. M. Zhu, M. R. Loso, G. B. Watson, T. C. Sparks, R. B. Rogers, J. X. Huang, B. C. Gerwick, J. M. Babcock, D. Kelley, V. B. Hegde, B. M. Nugent, J. M. Renga, *J. Agric. Food Chem.* **2011**, *59*, 2950. doi:10.1021/JF102765X
[20] T. C. Sparks, G. B. Watson, M. R. Michael, C. X. Geng, J. M. Babcock, J. D. Thomas, *Pestic. Biochem. Physiol.* **2013**, *107*, 1. doi:10.1016/J.PESTBP.2013.05.014
[21] P. Cutler, R. Slater, A. J. F. Edmunds, P. Maienfisch, R. G. Hall, F. G. P. Earley, T. Pitterna, S. Pal, V. L. Paul, J. Goodchild, *Pest Manag. Sci.* **2013**, *69*, 607. doi:10.1002/PS.3413
[22] C. Gnamm, A. Jeanguenat, A. C. Dutton, C. Grimm, D. P. Kloer, A. J. Crossthwaite, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3800. doi:10.1016/J.BMCL.2012.03.106
[23] H. Blaschke, S. Pazenok, *W. O. Patent 2007022901 A1* **2007**.
[24] J. H. Choi, M. H. Kim, S. H. Kim, C. H. Park, B. Y. Joe, K. Chun, B. K. Oh, D. Ryu, R. Won, J. S. Park, K. H. Kim, H. C. Lee, *W. O. Patent 2009061131 A2* **2009**.
[25] Z. J. Ye, L. N. Shi, X. S. Shao, X. Y. Xu, Z. P. Xu, Z. Li, *J. Agric. Food Chem.* **2013**, *61*, 312. doi:10.1021/JF3044132
[26] F. F. Jian, H. L. Xiao, P. S. Zhao, *Chinese J. Struct. Chem.* **2004**, *23*, 486.
[27] J. F. Zhang, J. Y. Xu, B. L. Wang, Y. X. Li, L. X. Xiong, Y. Q. Li, Y. Ma, Z. M. Li, *J. Agric. Food Chem.* **2012**, *60*, 7565. doi:10.1021/JF302446C
[28] K. A. Hughes, G. P. Lahm, T. P. Selby, *W. O. Patent 2004046129 A2* **2004**.
[29] G. P. Lahm, T. P. Selby, *W. O. Patent 2005118552 A2* **2005**.
[30] P. J. Montoya-Pelaez, Y.-S. Uh, C. Lata, M. P. Thompson, R. P. Lemieux, C. M. Crudden, *J. Org. Chem.* **2006**, *71*, 5921. doi:10.1021/JO060553D
[31] M. R. Loso, B. M. Nugent, R. B. Rogers, Y. M. Zhu, J. M. Renga, V. B. Hegde, J. J. Demark, *W. O. Patent 2007095229 A2* **2007**.
[32] *SHELXTL ver. 5.0* (Ed G. M. Sheldrick) **2001** (University of Göttingen: Göttingen, Germany).
[33] H. Xu, J. L. Zhang, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5177. doi:10.1016/J.BMCL.2011.07.075
[34] J. Cui, M. L. Li, M. S. Yuan, *J. Pestic. Sci.* **2012**, *37*, 95. doi:10.1584/JPESTICS.G11-47
[35] G. Goudar, A. R. Alagawadi, *J. Biopestic.* **2012**, *5*, 208.
[36] Q. Feng, Z. L. Liu, L. X. Xiong, M. Z. Wang, Y. Q. Li, Z. M. Li, *J. Agric. Food Chem.* **2010**, *58*, 12327. doi:10.1021/JF102842R.
[37] J. Wu, B. A. Song, D. Y. Hu, M. Yue, S. Yang, *Pest Manag. Sci.* **2012**, *68*, 801. doi:10.1002/PS.2329
[38] C. P. Moraes, L. A. Foerster, *Cienc. Rural* **2012**, *42*, 1335. doi:10.1590/S0103-84782012000800001