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Synthesis, insecticidal activity, and structure–activity relationship (SAR) of anthranilic diamides analogs containing oxadiazole rings†

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A series of anthranilic diamides analogs (**3–11**, **16–24**) containing 1,2,4- or 1,3,4-oxadiazole rings were synthesized and characterized by ^{1}H NMR, MS and elemental analyses. The structure of 3-bromo-*N*-(2-(3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**18**, CCDC-924454) was determined by X-ray diffraction crystallography. The insecticidal activities against *Plutella xylostella* and *Spodoptera exigua* were evaluated. The results showed that most of title compounds displayed good larvicidal activities against *P. xylostella*, especially compound 3-bromo-*N*-(4-chloro-2-methyl-6-(5-(methylthio)-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**6**), which displayed 71.43% activity against *P. xylostella* at 0.4 μg mL^{-1} and 33.33% against *S. exigua* at 1 μg mL^{-1}. The structure–activity relationship showed that compounds decorated with a 1,3,4-oxadiazole were more potent than compounds decorated with a 1,2,4-oxadiazole, and different substituents attached to the oxadiazole ring also affected the insecticidal activity. This work provides some hints for further structure modification and the enhancement of insecticidal activity.

Introduction

With the increase of food demands, a safe and efficient way to protect large monocultures in modern agriculture is required.[1,2] The discovery of highly effective and selective pesticides is still one of the most crucial tools for preventing disease transmission and pest management. Luckily, a new pathway to anti-insect damage was found, which is the ryanodine receptor (RyR), a new biochemical target of non-voltage-gated calcium channels.[3] This target has been found to affect the uncontrolled release of calcium ions by locking channels in a partially opened state, which leads to a series of poisoning symptoms such as rapid feeding cessation, regurgitation, lethargy and contractile paralysis on lepidopteran larvae.[4–6] Since the first pyridine dicarboxamide chemical structure was found in 1993, the study of RyRs chemical analogs has attracted more and more interest in this field.[7–9]

Flubendiamide (Fig. 1) belongs to the first generation of phthalic amide chemical structures and was commercialized in 2007.[10] Chlorantraniliprole (Rynaxypyr™) and cyantraniliprole (Cyazypyr™) (Fig. 1) were developed as the second generation of commercialized anthranilic diamide structures later.[11,12] All of these showed higher activities and lower toxicities. Following this, a large number of structurally modified phthalic amides and anthranilic diamides have emerged during the past decade.[13,14] However, few literature reports showed the structure–insecticidal activity relationships of these compounds.[15] Generally, the chemical structure of

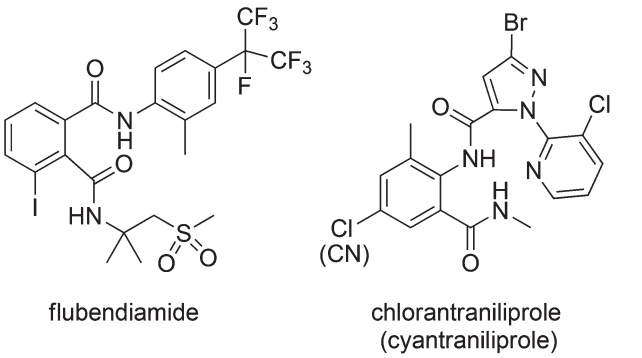

Fig. 1 The chemical structure of flubendiamide, chlorantraniliprole and cyantraniliprole.

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†Electronic supplementary information (ESI) available: General synthetic methods and schemes for intermediates **1a–1c** and amidoximes **M1–M7**, crystal and structure refinement data of compound **18**, and ^{1}H NMR spectra for all target compounds **3–24**. CCDC 924454. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40345a

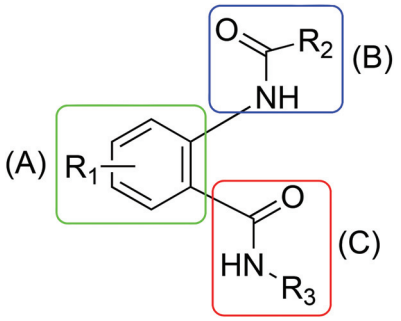


Fig. 2 General structure of anthranilic diamides.

anthranilic diamides could be characterized by three parts (Fig. 2): aromatic bridge moiety (A), *N*-pyridylpyrazole amide moiety (B) and aliphatic amide moiety (C).[13] The most successful example of modification of bridge moiety (A) is cyantraniliprole, which shows higher insecticidal activities than chlorantraniliprole.[12] For the *N*-pyridylpyrazole amide moiety (B), previous work indicated that it is a key pharmacophore in this kind of compounds and changing heterocycles or substituents would decrease the larvicidal activities.[16] As for aliphatic amide moiety (C), most modifications kept the carbonyl group and replaced the amide group with an ester group, a hydrazide group, *etc.*[17]

To prevent the problem of resistance and find more efficient pesticides, it is necessary to develop new structures of anthranilic diamides. Because oxadiazole rings contain N and O atoms, which qualified high biological activities and have been widely used in pesticide and medicine fields.[18,19] According to the bioisosteric relationship, the aliphatic amide part (C) of anthranilic diamides could be concealed in the oxadiazole ring (Fig. 3), which means that not only is the aliphatic amide part retained, but also that a high activity heterocycle is introduced into the *o*-heterocyclic phenylformamide structure. Taking all this into account, we successfully designed and synthesized a series of *o*-heterocyclic phenylformamide derivatives which contain 1,2,4-oxadiazole or 1,3,4-oxadiazole rings (Fig. 3). The single crystal structure of one target compound has been verified, which could stimulate a better understanding of the binding nature of these compounds, and help to explore new structures to enhance their biological activities. Furthermore, the larvicidal activities against *Plutella xylostella* (*P. xylostella*) and *Spodoptera exigua* (*S. exigua*) were tested accordingly, and their preliminary structure–activity relationships were also discussed.

Results and discussion

Synthesis

General synthetic routes for final compounds **3–11** and **16–24** are shown in Schemes 1 and 2. For the synthesis of compounds **3–9**, the key intermediates **2b** and **2c** were afforded by reaction of **1b** or **1c** reacted with 85% hydrazine hydrate. Following the ring-opening reaction, target compound **3** was obtained by reaction of **2b** with triphosgene at reflux, forming a 1,3,4-oxadiazole ring with hydroxyl group. Compounds **4** or **5** could be prepared *via* reaction of **2b** or **2c** with carbon bisulfide and afforded a 1,3,4-oxadiazole ring with a hydrosulfide group in high yield. In addition, reaction of compound **4** or **5** and an alkylating agent at room temperature (r.t.) afforded compounds **6–9**. In order to obtain directly alkyl substituted 1,3,4-oxadiazole rings, acethydrazide was allowed to react with **1a** or **1b**, which underwent ring-opening and dehydration reactions in one pot in *N*,*N*′-dimethyl formamide (DMF), and afforded compounds **10** and **11**.

The desired compounds **16–24** could be prepared by two routes. One is *via* a ring-opening reaction of compound **1b** or **1c** with different *N*-hydroxyamidines and a ring-closing reaction in two separate steps. The other one is direct reaction of **1b** or **1c** with substituted *N*-hydroxyamidines, using DMF as solvent, to afford the final products in one step. Following the literature method[20] (reaction at r.t., chloroform ($CHCl_3$) as solvent), the obtained products were not acid amide structure **25** (Scheme 2), but rather compounds **12–15** were separated. In principle, substituted *N*-hydroxyamidine has two reactive groups (–NH_2 and –OH), both of which could react with **1** and form either an ester or acid amide structure. After characterizing **12–15** by ^{1}H NMR (at 500 MHz in DMSO-d_6 δ 6.88–6.97 (s, 2H, NH_2)) and comparing them with substituted *N*-hydroxyamidine ^{1}H NMR (at 500 MHz in DMSO-d_6 δ 8.64–9.70 (s, 1H, OH), 5.32–6.01 (s, 2H, NH_2)), the products were identified as

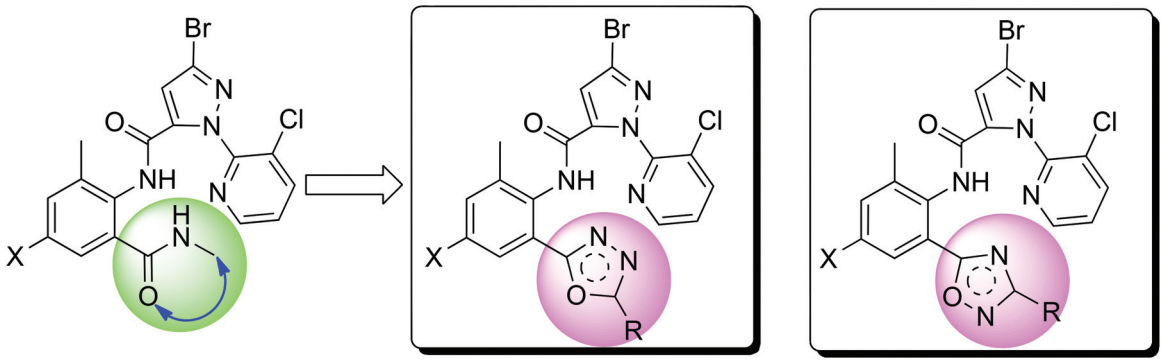
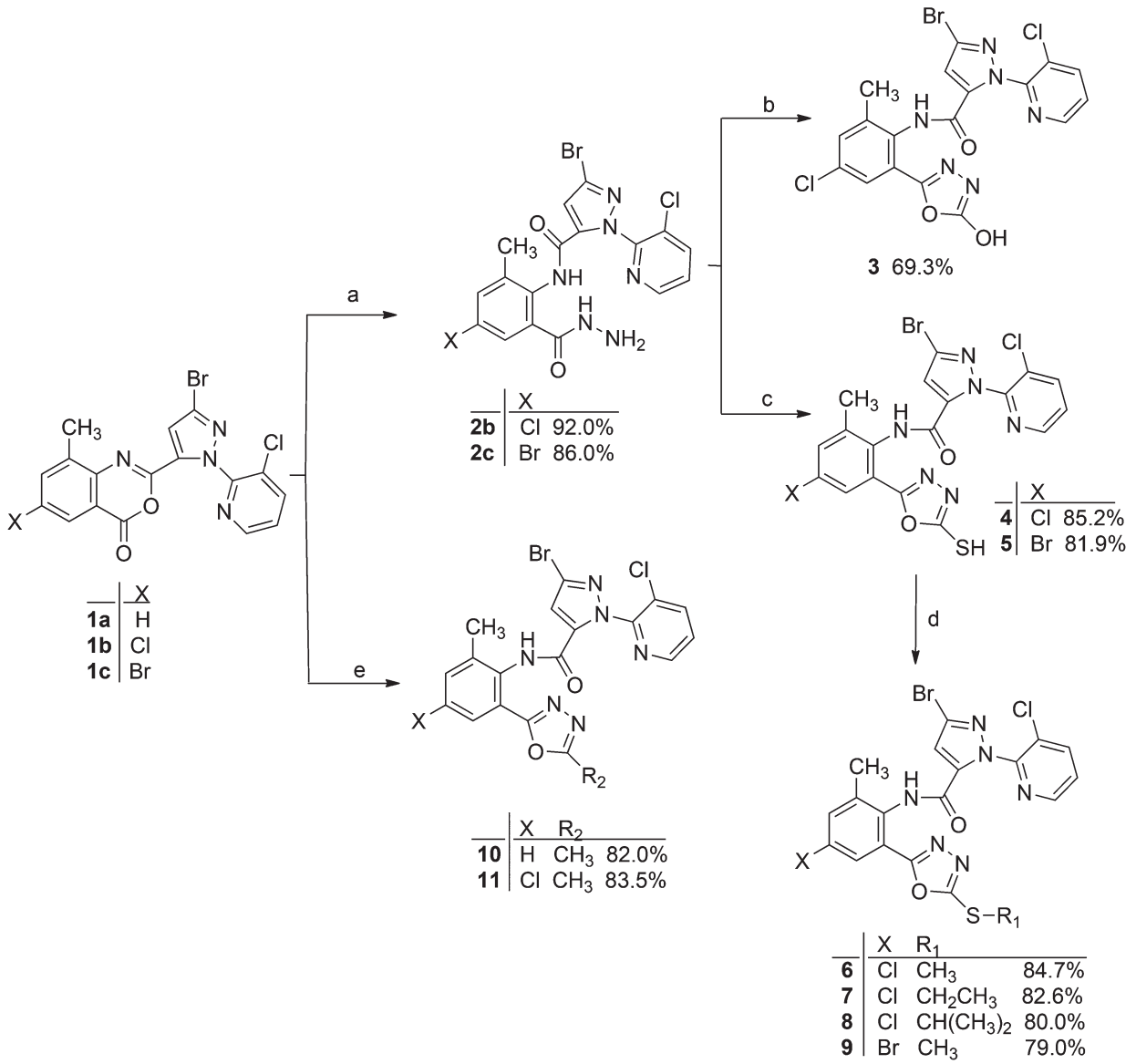


Fig. 3 Design strategy of the target compounds.

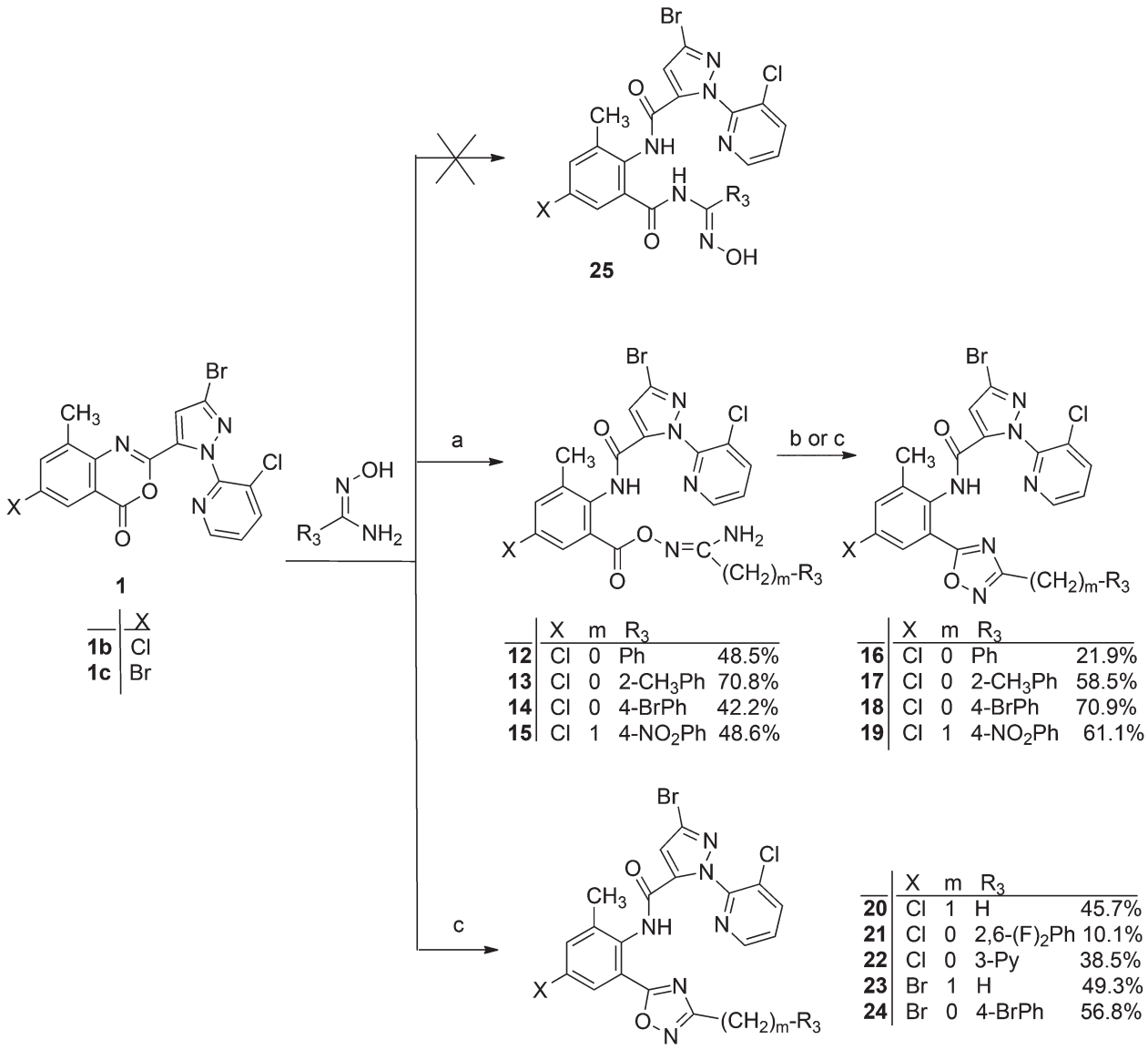


Scheme 1 General synthetic route of compounds **3–11**. Reagents and conditions: (a) 85% hydrazine hydrate, DMF, 30 min; (b) triphosgene, toluene, reflux, 4 h; (c) CS_2, KOH, EtOH, reflux, 8 h; (d) R_1I, NaOH, MeOH, r.t., 5 h; (e) acethydrazide, DMF, r.t., 12 h.

esters. When the temperature was increased to reflux, the desired products **16–24** containing a 1,2,4-oxadiazole ring were formed in low yield. After extending the reaction time from 30 h to 48 h, the conversion ratio was enhanced by about 5% and the total yield was about 50%, which indicated a low conversion ratio. However, when using DMF as solvent instead of $CHCl_3$, the reaction underwent a significant change and the 1,2,4-oxadiazole ring was formed in yields of up to 58–71%. When enhancing the reaction temperature and prolonging the reaction time, no obvious change in yields was observed. In addition, use of the one-pot method to make some compounds led to low yields, because most of starting materials did not react, although different conditions had been attempted. To optimize the reaction conditions, reaction of *N*-hydroxy-2-methyl benzimidamide or *N*-hydroxy-4-bromo benzimidamide with **1b** was selected as a model, and the yields are listed in Table 1.

Structure

The structures of all synthesized title compounds were confirmed by ^{1}H NMR, MS and elemental analysis. The single peak appearing at the lowest field of 10.64–9.95 ppm in the ^{1}H NMR can be assigned to the aromatic amide hydrogen (Ph-N*H*–C=O) of the target compounds. In addition, the crystal structure of **18** was determined by single crystal X-ray diffraction. It belongs to a triclinic system, $P\bar{1}$ space group with unit cell parameters: a = 9.2290 (18) Å, b = 11.1420 (2) Å, c = 12.5260 (3) Å, α = 76.53 (3)°, β = 80.97 (3)° and γ = 86.17 (3)°. The detailed crystallographic data for **18** can be found in the ESI (Table S1†).



Scheme 2 General synthetic route of compounds **12–24**. Reagents and conditions: (a) $CHCl_3$, r.t., 15 h; (b) DMF, 30 °C, 15 h; (c) DMF, 50 °C, 48 h.

Table 1 Optimized reaction conditions for preparation of compounds **13** or **17** and **14** or **18**

				Composition (%)	
R_3	Solvent	Time (h)	*T* (°C)	Ester	Oxadiazole
2-CH_3Ph	$CHCl_3$	15	30	70.8	5.0
		30	Reflux	38.1	19.8
		48	Reflux	27.5	24.5
	DMF	15	30	0	54.9
		15	50	0	55.5
		48	50	0	58.5
4-BrPh	$CHCl_3$	15	30	42.2	6.0
		30	Reflux	30.8	18.9
		48	Reflux	22.5	25.0
	DMF	15	30	0	66.1
		15	50	0	67.0
		48	50	0	70.9

The single crystal structure and packing diagram of **18** are shown in Fig. 4 and 5. The bridge benzene ring (C10 to C15) and the terminal benzene ring (C19 to C24) were connected with the 1,2,4-oxadiazole ring, which twisted 3.91° and 5.28° respectively and all three rings were located in almost the same plane. This is consistent with similar twist angles reported in the literature.[21] On the contrary, the pyrazole ring (C6/C7/C8/N1/N3) forms a dihedral angle of 68.99° with the bridge benzene ring (C10 to C15) and 85.39° with the terminal pyridine ring (C1/C2/C3/C4/N1/C6). It is obvious that the three rings exist in different planes which is in line with similar structures in the literature.[13] The intramolecular hydrogen bonds C–H···N, N–H···N and C–H···O resulted in the formation of two planar pseudo rings A (C16/H16A/N4/C10/C15) and B (C20/H20A/N5/C18/C19), and two non-planar pseudo

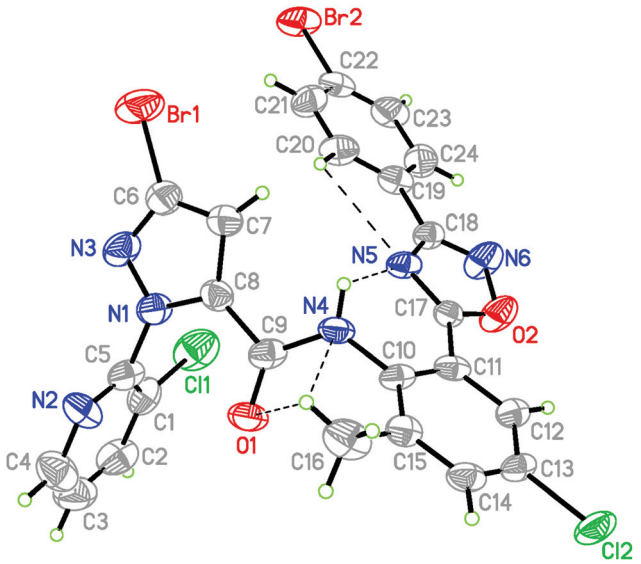


Fig. 4 A molecule structure of **18**.

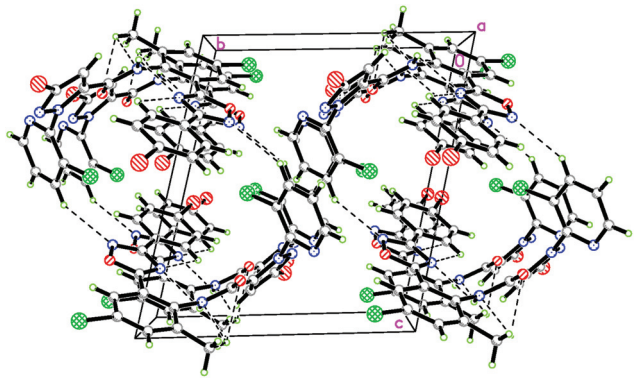


Fig. 5 A packing plot of **18** viewed along the crystallographic *a*-axis.

rings C (N4/H4A/N5/C17/C11/C10) and D (C16/H16A/O1/C9/N4/C10/C15). In the molecular packing of **18**, intermolecular C–H···N hydrogen bonds link the molecules stacked along the *a* axis. These crystallographic data could provide a basis for elucidating the effect on their biological activities.

Biological activities and structure–activity relationships

The results of *in vivo* larvicidal activities of all compounds against *P. xylostella* at concentrations of 100 μg mL^{-1} and 10 μg mL^{-1} were listed in Table 2. To understand which oxadiazole heterocycle shows better activity, compounds **3–11** for 1,3,4-oxadiazole and **16–24** for 1,2,4-oxadiazole were investigated. It is difficult to construct both heterocycles with the same substituent, but it's still shown that the compounds with a 1,3,4-oxadiazole attached presented a slightly higher larvicidal activity trend than compounds with a 1,2,4-oxadiazole attached. For instance, compounds **16–18**, **24** with a 1,2,4-oxadiazole attached showed no larvicidal activity at low concentration, while compounds **3–11** mostly showed a larvicidal activity at low concentration.

Table 2 Larvicidal activity against *P. xylostella* of compounds **3–24**

Compound	X	Ring (oxadiazole)	R	Concentration (μg mL^{-1})	Mortality 3 d (%)
3	Cl	1,3,4-	OH	100	90.48
				10	14.29
4	Cl	1,3,4-	SH	100	100.00
				10	57.14
5	Br	1,3,4-	SH	100	100.00
				10	42.86
6	Cl	1,3,4-	SCH_3	100	100.00
				10	100.00
				4	95.24
				1	80.95
				0.4	71.43
7	Cl	1,3,4-	SCH_2CH_3	100	100.00
				10	5.00
8	Cl	1,3,4-	$SCH(CH_3)_2$	100	100.00
				10	15.00
9	Br	1,3,4-	SCH_3	100	47.62
				10	4.55
10	H	1,3,4-	CH_3	100	20.00
				10	14.20
11	Cl	1,3,4-	CH_3	100	100.00
				10	100.00
				4	85.71
				1	45.45
12	Cl	—	Ph	100	68.18
				10	15.79
13	Cl	—	2-CH_3Ph	100	100.00
				10	61.90
14	Cl	—	4-BrPh	100	100.00
				10	19.05
15	Cl	—	CH_2(4-NO_2Ph)	100	100.00
				10	57.89
16	Cl	1,2,4-	Ph	100	95.24
				10	0.00
17	Cl	1,2,4-	2-CH_3Ph	100	95.24
				10	0.00
18	Cl	1,2,4-	4-BrPh	100	85.17
				10	0.00
19	Cl	1,2,4-	CH_2(4-NO_2Ph)	100	100.00
				10	47.62
20	Cl	1,2,4-	CH_3	100	100.00
				10	100.00
				4	61.90
				1	4.76
21	Cl	1,2,4-	2,6-$(F)_2$Ph	100	76.19
				10	0.00
22	Cl	1,2,4-	3-Py	100	100.00
				10	19.05
23	Br	1,2,4-	CH_3	100	100.00
				10	95.24
24	Br	1,2,4-	4-BrPh	100	57.89
				10	0.00
Chlorantraniliprole	—	—	—	100	100.00
				10	100.00
				4	100.00
				1	100.00
				0.4	68.89

In order to investigate structure–activity relationship of different groups linked to the 1,3,4-oxadiazole moiety and bridge benzene ring, compounds **3–11** were substituted with –OH, –SH, $-SCH_3$, $-SCH_2CH_3$, $-SCH(CH_3)_2$ or $-CH_3$ attached to the 1,3,4-oxadiazole ring and –H, –Cl, and –Br attached to the bridge benzene ring. Although it is hard to construct a clear structure–activity relationship from the data shown in Table 2, we can also conclude that the general trend in larvicidal

activity for the substituents on the 1,3,4-oxadiazole moiety was $-CH_3 \approx -SCH_3 > -SH > -OH \approx -SCH_2CH_3 \approx -SCH(CH_3)_2$. For example, compound **4** (–SH, 100%) displayed a higher insecticidal activity than compound **3** (–OH, 90%) at 100 μg mL^{-1}. Compounds **6** ($-SCH_3$) and **11** ($-CH_3$) exhibited a remarkable 100% mortality at 10 μg mL^{-1}, while compound **4** (–SH) has only 57.14% mortality at the same concentration. Compounds **3**, **7**, and **8** showed even lower insecticidal activities below 15% at 10 μg mL^{-1}. In addition, substituents on the bridge benzene ring showed a clear trend in larvicidal activity –Cl > –Br > –H. Compounds **9** (–Br) and **10** (–H) exhibited less than 50% activity at 100 μg mL^{-1} and 20% activity at 10 μg mL^{-1}, while compound **11** (–Cl) exhibited 100% activity at both 100 and 10 μg mL^{-1} dose. Compounds **4** (–Cl) and **5** (–Br) also showed the same trend at the same concentrations.

Compounds **16–24**, containing different groups such as $-CH_3$, $-CH_2Ph$, $-(2\text{-}CH_3)Ph$, *etc.*, were examined to investigate the influence of different substitutions on the 1,2,4-oxadiazole ring. According to the concept of aliphatic and aromatic substituents, the compounds **16–24** could are divided into two types. Compounds **20** and **23** belong to the aliphatic substituent type, and **16–19**, **21–22** and **24** belong to the aromatic substituent type, which showed a clear trend: compounds containing aliphatic substituents on the 1,2,4-oxadiazole ring are significantly more potent than aromatic substituted analogs. For example, compound **20** ($-CH_3$) showed insecticidal activity of 100% at 100 and 10 μg mL^{-1}, while compounds **16–18**, **21** and **24** showed no activities at 10 μg mL^{-1}. The decrease in activity at 10 μg mL^{-1} dose was displayed more clearly than for the 1,3,4-oxadiazole ring containing compounds. Two pairs of compounds **20** (–Cl, $-CH_3$) *vs.* **23** (–Br, $-CH_3$), and **18** (–Cl, –(4-Br)Ph) *vs.* **24** (–Br, –(4-Br)Ph) also confirmed that a Cl atom is favorable on the bridge benzene ring to enhance insecticidal activity compared to a Br or H atom.

Compounds **6**, **11** and **20** were the most active, displaying 100% larvicidal activities against *P. xylostella* at 10 μg mL^{-1}. The results indicate that these compounds displayed comparable larvicidal activities with reference product, *i.e.* chlorantraniliprole. Therefore, further insecticidal activity assays at lower concentration for **6**, **11** and **20** were performed. As shown in Table 2, it was found that compound **6** (1,3,4-oxadiazole, $-SCH_3$) still has 71.43% activity at 0.4 μg mL^{-1}, while chlorantraniliprole preserves 68.89% activity. Compounds **11** (1,3,4-oxadiazole, $-CH_3$) and **20** (1,2,4-oxadiazole, $-CH_3$) decreased to 45.45% and 4.76% activity, respectively. Furthermore, the broad insecticidal activity of compound **6** was investigated against *S. exigua*. The test results are shown in Table 3. Compound **6** displayed more than 30% insecticidal activity at 1 μg mL^{-1}, which showed a similar level to chlorantraniliprole. From the study of lower concentration and broad insecticidal activity, it is obvious that compound **6** with a 1,3,4-oxadiazole ring attached displayed a remarkable insecticidal activity against *P. xylostella* and *S. Exigua*, comparable with commercial product chlorantraniliprole.

Table 3 Insecticidal activities against *S. exigua* of compound **6**

	100[a]	40	10	4	1
6	83.33	77.78	66.67	38.89	33.33
Chlorantraniliprole	100.00	100.00	100.00	—	30.00

[a] The unit of concentration is μg mL^{-1}.

Materials and methods

Chemical synthesis

All solvents and reagents were obtained from commercial suppliers and used without further purification. Analytical thin layer chromatography was performed on silica gel GF254. Silica gel (100–200 mesh) was used for flash column chromatography. The melting points were measured on an X-4 microscope electrothermal apparatus (Taike China) and are uncorrected. The ^1H NMR spectra was recorded in $CDCl_3$ or DMSO-d_6 solvent on a Bruker AV 300, AV 500 or Varian 400 NMR spectrophotometer with TMS as the internal standard. Mass spectra were recorded with an Agilent 1100 Series LC/MSD Trap SL. Elemental analysis were performed on a Vario EL III elemental analysis instrument and the results were within 0.5% of the calculated value. X-ray intensity data were recorded on a Nonius CAD4 single crystal diffraction. The synthetic procedures and detailed characterization data of intermediates **1a–1c** and different amidoximes can be found in the ESI.†

General procedure for the synthesis of compounds 2b and 2c[16]

A mixture of **1b** or **1c** (44 mmol), 85% hydrazine monohydrate (120 mmol) and DMF (200 mL) was stirred at r.t. for 15 min. Then the mixture was poured into 800 mL H_2O to afford a white solid and filtered. The resulting filter cake was washed with 200 mL H_2O again and dissolved in ethyl acetate, dried over anhydrous magnesium sulfate, then concentrated under reduced pressure to obtain the corresponding product.

2-(((3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl)carbonyl)-amino)-3-methyl-5-chloro-benzoic acid hydrazide (2b). Yield 92.0%; mp 212–214 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, Ph-NH-C═O), 9.49 (s, 1H, N*H*NH_2), 8.45 (dd, J_1 = 4.7 Hz, J_2 = 1.5 Hz, 1H, Py-H), 8.12 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H, Py-H), 7.56 (dd, J_1 = 8.1 Hz, J_2 = 4.7 Hz, 1H, Py-H), 7.43 (d, J = 1.9 Hz, 1H, Ar-H), 7.34 (s, 1H, CHCBr), 7.26 (d, J = 2.3 Hz, 1H, Ar-H), 4.32 (s, 2H, NHNH_2), 2.10 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{17}H_{13}BrCl_2N_6O_2$ $(M + H)^+$ 483.0, $(M + H + 2)^+$ 485.0. Found $(M + H)^+$ 483.1, $(M + H + 2)^+$ 485.1.

2-(((3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl)carbonyl)-amino)-3-methyl-5-bromo-benzoic acid hydrazide (2c). Yield 86.0%; mp 215–218 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.29 (s, 1H, Ph-NH-C═O), 9.58 (s, 1H, N*H*NH_2), 8.46 (d, J = 4.1 Hz, 1H, Py-H), 8.03 (d, J = 8.4 Hz, 1H, Py-H), 8.11 (s, 1H, Ar-H), 7.50 (q, J = 8.1 Hz, 1H, Py-H), 7.45 (s, 1H, CHCBr), 7.36 (s, 1H, Ar-H), 4.28 (s, 2H, NHNH_2), 2.19 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{17}H_{13}BrCl_2N_6O_2$ $(M + H)^+$ 526.9, $(M + H + 2)^+$ 528.9. Found $(M + H)^+$ 526.9, $(M + H + 2)^+$ 528.9.

3-Bromo-*N*-(4-chloro-2-methyl-6-(5-hydroxy-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (3).[22] A mixture of compound **2b** (2.07 mmol) and triphosgene (2.68 mmol) in toluene (20 mL) was stirred and refluxed for about 4 h. After removing the solvent, the residue was poured into ice water slowly and stirred for 2 h, filtered, and the filter cake was washed to pH = 7. The residue was recrystallized with ether to afford a white solid. Yield 69.3%; mp 221–224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.56 (s, 1H, OH), 10.30 (s, 1H, Ph-NH-C═O), 8.44 (s, 1H, Py-H), 8.03 (s, 1H, Py-H), 7.36–7.69 (m, 3H, Ar-H, Py-H), 7.32 (s, 1H, CHCBr), 2.26 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{18}H_{11}BrCl_2N_6O_3$ $(M - H)^-$ 506.9, $(M - H + 2)^-$ 508.9. Found $(M - H)^-$ 507.0, $(M - H + 2)^-$ 509.0. Anal. calcd C 42.38, H 2.17, N 16.47, found C 41.90, H 2.50, N 16.07.

General procedure for the synthesis of compounds 4 and 5[23]

A mixture of **2b** or **2c** (2 mmol), potassium hydroxide (0.132 g, 2 mmol, 85%), carbon disulfide (0.52 g, 6.8 mmol) and ethanol (20 mL) was heated at reflux with stirring until the evolution of hydrogen sulfide ceased (about 8 h). Ethanol was distilled off under reduced pressure and the residue was dissolved in H_2O and then acidified with 10% aqueous hydrochloric acid solution. The resulting precipitate was extracted with ethyl acetate, washed with H_2O, dried and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel 100–200 mesh, hexane–ethyl acetate = 2 : 1, v/v) to afford the target compounds.

3-Bromo-*N*-(4-chloro-2-(5-mercapto-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (4). Yield 85.2%; mp 170–172 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.78 (s, 1H, SH), 10.46 (s, 1H, Ph-NH-C═O), 8.49 (dd, 1H, *J* = 4.7 Hz, Py-H), 8.16 (dd, 1H, *J* = 8.1 Hz, Py-H), 7.70 (d, 1H, *J* = 2.3 Hz, Ph-H), 7.68 (d, 1H, *J* = 2.3 Hz, Ph-H), 7.61 (q, 1H, *J* = 8.1 Hz, Py-H), 7.37 (s, 1H, CHCBr), 2.22 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{18}H_{11}BrCl_2N_6O_2S$ $(M - H)^-$ 522.9, $(M - H + 2)^-$ 524.9. Found $(M - H)^-$ 523.0, $(M - H + 2)^-$ 525.0. Anal. calcd C 41.09, H 2.11, N 15.97, found C 41.50, H 2.50, N 16.11.

3-Bromo-*N*-(4-bromo-2-(5-mercapto-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (5). Yield 81.9%; mp 245–248 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.80 (s, 1H, SH), 10.35 (s, 1H, Ph-NH-C═O), 8.45 (dd, 1H, *J* = 4.2 Hz, Py-H), 7.95 (dd, 1H, *J* = 8.0 Hz, Py-H), 7.86 (d, 1H, *J* = 7.8 Hz, Ph-H), 7.74 (d, 1H, *J* = 2.4 Hz, Ph-H), 7.54 (q, 1H, *J* = 8.0 Hz, Py-H), 7.11 (s, 1H, CHCBr), 2.26 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{18}H_{11}Br_2ClN_6O_2S$ $(M - H)^-$ 566.9, $(M - H + 2)^-$ 568.9. Found $(M - H)^-$ 567.0, $(M - H + 2)^-$ 569.0. Anal. calcd C 37.89, H 1.94, N 14.73, found C 37.60, H 2.38, N 14.55.

General procedure for the synthesis of compounds 6–9[24]

A mixture of compound **4** or **5** (1.16 mmol) in methanol (20 mL), sodium methoxide (0.096 g, 1.74 mmol, 98%) and alkyl iodides (1.39 mmol) was added and stirred at r.t. for about 5 h. After the solvent was removed, 100 mL H_2O was added, and then the residue was collected by filtration, washed with 50 mL H_2O and dried in vacuum to afford the desired products.

3-Bromo-*N*-(4-chloro-2-methyl-6-(5-(methylthio)-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (6). Yield 84.7%; mp 165–167 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H, Ph-NH-C═O), 8.47 (dd, 1H, *J* = 4.7 Hz, Py-H), 8.16 (dd, 1H, *J* = 8.1 Hz, Py-H), 7.81 (d, 1H, *J* = 2.4 Hz, Ph-H), 7.66 (d, 1H, *J* = 2.4 Hz, Ph-H), 7.60 (q, 1H, *J* = 8.1 Hz, Py-H), 7.37 (s, 1H, CHCBr), 2.23 (s, 3H, Ph-CH_3), 1.99 (s, 3H, SCH_3). MS *m*/*z* calcd for $C_{19}H_{13}BrCl_2N_6O_2S$ $(M + H)^+$ 538.9, $(M + H + 2)^+$ 540.9. Found $(M + H)^+$ 539.1, $(M + H + 2)^+$ 541.1. Anal. calcd C 42.24, H 2.43, N 15.56, found C 41.28, H 2.49, N 15.66.

3-Bromo-*N*-(4-chloro-2-methyl-6-(5-(ethylthio)-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (7). Yield 82.6%; mp 175–177 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H, ph-NH-C═O), 8.47 (dd, 1H, *J* = 4.7 Hz, Py-H), 8.15 (dd, 1H, *J* = 8.1 Hz, Py-H), 7.81 (d, 1H, *J* = 2.5 Hz, Ph-H), 7.66 (d, 1H, *J* = 2.5 Hz, Ph-H), 7.60 (q, 1H, *J* = 8.1 Hz, Py-H), 7.38 (s, 1H, CHCBr), 3.24 (q, *J* = 14.6 Hz, 2H, SCH_2CH_3), 2.23 (s, 3H, Ph-CH_3),1.37 (t, *J* = 7.3 Hz, 3H, SCH_2CH_3). MS *m*/*z* calcd for $C_{20}H_{15}BrCl_2N_6O_2S$ $(M + H)^+$ 553.0, $(M + H + 2)^+$ 555.0. Found $(M + H)^+$ 553.1, $(M + H + 2)^+$ 555.1. Anal. calcd C 43.34, H 2.73, N 15.16, found C 43.80, H 2.60, N 14.90.

3-Bromo-*N*-(4-chloro-2-methyl-6-(5-(isopropylthio)-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (8). Yield 80.0%; mp 230–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H, Ph-NH-C═O), 8.38 (d, 1H, *J* = 4.0 Hz, Py-H), 8.05 (d, 1H, *J* = 7.9 Hz,), 7.62–7.88 (m, 2H, Ar-H), 7.50–7.45 (m, 1H, Py-H), 7.21 (s, 1H, CHCBr), 3.80 (s, 1H, C*H*-$(CH_3)_2$), 2.44 (s, 3H, Ph-CH_3), 2.12 (s, 3H, $CH(CH_3)_2$), 1.28 (s, 3H, $CH(CH_3)_2$). MS *m*/*z* calcd for $C_{21}H_{17}BrCl_2N_6O_2S$ $(M + H)^+$ 567.0, $(M + H + 2)^+$ 569.0. Found $(M + H)^+$ 567.2, $(M + H + 2)^+$ 569.2. Anal. calcd C 44.38, H 3.02, N 14.79, found C 44.79, H 3.50, N 14.50.

3-Bromo-*N*-(4-bromo-2-methyl-6-(5-(methylthio)-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (9). Yield 79.0%; mp 193–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H, Ph-NH-C═O), 8.45 (d, 1H, *J* = 4.7 Hz, Py-H), 7.85 (m, 2H, Ph-H, Py-H), 7.52 (d, *J* = 6.0 Hz, 1H, Ph-H), 7.37 (m, 1H, Py-H), 7.19 (s, 1H, CHCBr), 2.81 (s, 3H, SCH_3), 2.26 (s, 3H, Ph-CH_3). MS *m*/*z* calcd for $C_{19}H_{13}BrCl_2N_6O_2S$ $(M + H)^+$ 582.9, $(M + H + 2)^+$ 584.9. Found $(M + H)^+$ 583.0, $(M + H + 2)^+$ 585.0. Anal. calcd C 39.03, H 2.24, N 14.37, found C 39.33, H 2.52, N 14.11.

General procedure for the synthesis of compounds 10–11

A mixture of **1a** or **1b** (4 mmol), acethydrazide (4.2 mmol) and DMF (20 mL) was stirred at r.t. for 12 h. Then the mixture was poured into 100 mL H_2O and filtered to afford a solid. The residue was washed with 50 mL H_2O and dried to afford the desired products.

3-Bromo-*N*-(2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (10). Yield

82.0%; mp 258–260 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.20 (s, 1H, Ph-NH-C═O), 8.56 (d, J = 4.2 Hz, 1H, Py-H), 7.95–8.06 (m, 2H, Ar-H, Py-H), 7.45–7.58 (m, 2H, Ar-H), 7.34–7.41 (m, 1H, Py-H), 7.25 (s, 1H, CHCBr), 1.83 (s, 3H, CH_3), 1.56 (s, 3H, ph-CH_3). MS m/z calcd for $C_{19}H_{14}BrClN_6O_2$ $(M + H)^+$ 473.0, $(M + H + 2)^+$ 475.0. Found $(M + H)^+$ 472.9, $(M + H + 2)^+$ 474.9. Anal. calcd C 48.17, H 2.98, N 17.74, found C 48.37, H 3.40, N 17.99.

3-Bromo-*N*-(4-chloro-2-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (11). Yield 83.5%; mp 202–204 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.23 (s, 1H, Ph-NH-C═O), 8.50 (d, J = 6.0 Hz, 1H, Py-H), 8.32 (d, J = 6.0 Hz, 1H, Py-H), 8.17 (s, 1H, Ar-H), 7.59 (q, J = 6.0 Hz, 1H, Py-H), 7.43 (s, 1H, Ar-H), 7.37 (s, 1H, CHCBr), 2.15 (s, 3H, CH_3), 1.89 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{19}H_{13}Br_2ClN_6O_2$ $(M + H)^+$ 507.0, $(M + H + 2)^+$ 509.0. Found $(M + H)^+$ 507.1, $(M + H + 2)^+$ 509.1. Anal. calcd C 44.91, H 2.58, N 13.95, found C 45.22, H 2.73, N 14.07.

General procedure for the synthesis of compounds 12–15[24]

A mixture of **1b** (1.1 mmol) and substituted *N*-hydroxyamidine (1.1 mmol) in chloroform (20 mL) was stirred at r.t. for 15 h. After the removal of solvent, petroleum ether (100 mL) was added to the residue, and the solid was filtered and collected. The crude product was purified by column chromatography (silica gel 100–200 mesh, hexane–ethyl acetate = 1 : 1, v/v) to afford the desired products.

3-Bromo-*N*-(2-((((amino(phenyl)methylene)amino)oxy)carbonyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (12). Yield 48.5%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H, Ph-NH-C═O), 8.48 (dd, J = 4.7 Hz, 1H, Py-H), 8.15 (d, J = 7.9 Hz, 1H, Py-H), 7.95 (d, J = 2.5 Hz, 1H, Ar-H), 7.72–7.74 (m, 2H, Ar-H), 7.64 (d, J = 2.4 Hz, 1H, Ar-H), 7.59 (q, J = 8.1 Hz, 1H, Py-H), 7.51–7.54 (m, 1H, Ar-H), 7.47 (t, J = 7.6 Hz, 1H, Ar-H), 7.34 (s, 1H, CHCBr), 7.37 (t, J = 3.2 Hz, 1H, Ar-H), 6.89 (s, 2H, NH_2), 2.20 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{17}BrCl_2N_6O_3$ $(M - H)^-$ 585.0, $(M - H + 2)^-$ 587.0. Found $(M - H)^-$ 585.0, $(M - H + 2)^-$ 587.0. Anal. calcd C 49.00, H 2.91, N 14.29, found C 49.21, H 3.05, N 14.40.

3-Bromo-*N*-(2-((((amino(2-tolyl)methylene)amino)oxy)carbonyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (13). Yield 70.8%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.34 (s, 1H, ph-NH-C═O), 8.48 (dd, J = 4.7 Hz, 1H, Py-H), 8.15 (dd, J = 8.1 Hz, 1H, Py-H), 7.91 (d, J = 2.4 Hz, 1H, Ar-H), 7.63 (d, J = 2.1 Hz, 1H, Ar-H), 7.60 (dd, J = 8.1 Hz, 1H, Py-H), 7.36–7.39 (m, 1H, Ar-H), 7.33 (s, 1H, CHCBr), 7.25–7.32 (m, 2H, Ar-H), 7.17–7.24 (m, 1H, Ar-H), 6.88 (s, 2H, NH_2), 2.34 (s, 3H, Ph-CH_3), 2.20 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{25}H_{19}BrCl_2N_6O_3$ $(M - H)^-$ 599.0, $(M - H + 2)^-$ 601.0. Found $(M - H)^-$ 598.9, $(M - H + 2)^-$ 600.9. Anal. calcd C 49.86, H 3.18, N 13.95, found C 50.04, H 3.60, N 13.60.

3-Bromo-*N*-(2-((((amino(4-bromophenyl)methylene)amino)oxy)carbonyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (14). Yield 42.2%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.36 (s, 1H, Ph-NH-C═O), 8.48 (dd, 1H, J = 4.7 Hz, Py-H), 8.15 (dd, 1H, J = 8.1 Hz, Py-H), 7.95 (d, 1H, J = 2.3 Hz, Ar-H), 7.69 (s, 4H, Ar-H), 7.64 (d, 1H, J = 2.1 Hz, Ar-H), 7.77 (q, 1H, J = 8.1 Hz, py-H), 7.34 (s, 1H, CHCBr), 6.97 (s, 2H, NH_2), 2.20 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{16}Br_2Cl_2N_6O_3$ $(M - H)^-$ 662.9, $(M - H + 2)^-$ 664.9. Found $(M - H)^-$ 662.8, $(M - H + 2)^-$ 664.8. Anal. calcd C 43.21, H 2.42, N 12.60, found C 43.33, H 2.69, N 12.27.

3-Bromo-*N*-(2-((((1-amino-2-(4-nitrophenyl)ethylidene)amino)oxy)carbonyl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (15). Yield 48.6%; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.29 (s, 1H, Ph-NH-C═O), 8.49 (dd, J = 4.7 Hz, 1H, Py-H), 8.19 (dd, J = 8.7 Hz, 2H, Ar-H), 8.15 (dd, J = 8.1 Hz, 1H, Py-H), 7.83 (d, J = 2.45 Hz, 1H, Ar-H), 7.58–7.62 (m, 4H, Ar-H, Py-H), 7.29 (s, 1H, CHCBr), 6.65 (s, 2H, NH_2), 3.58 (s, 2H, CH_2Ph), 2.18 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{25}H_{18}BrCl_2N_7O_5$ $(M - H)^-$ 676.9, $(M - H + 2)^-$ 678.9. Found $(M - H)^-$ 676.7, $(M - H + 2)^-$ 679.7. Anal. calcd C 46.39, H 2.80, N 15.15, found C 46.55, H 3.11, N 15.00.

General procedure for the synthesis of compounds 16–24

A mixture of **1b** or **1c** (1.1 mmol) and substituted *N*-hydroxyamidine (1.1 mmol) in DMF (20 mL) was stirred at 50 °C. After 48 h, the mixture was added to 100 mL H_2O, and the solid was filtered and collected. The residue was purified by column chromatography (silica gel 100–200 mesh, hexane–ethyl acetate = 1 : 1, v/v) to afford the target compounds.

3-Bromo-*N*-(2-(3-benzyl-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (16). Yield 21.9%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.47 (s, 1H, Ph-NH-C═O), 8.42 (dd, 1H, J = 4.7 Hz, Py-H), 8.13 (dd, 1H, J = 8.1 Hz, Py-H), 7.98–7.60 (m, 3H, Ar-H), 7.57 (q, 1H, J = 8.1 Hz, Py-H), 7.47–7.51 (m, 2H, Ar-H), 7.41 (s, 1H, CHCBr), 7.38 (d, 1H, J = 7.5 Hz, Ar-H), 7.29 (t, 1H, J = 7.6 Hz, Ar-H), 2.30 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{15}BrCl_2N_6O_2$ $(M - H)^-$ 581.0, $(M - H + 2)^-$ 583.0. Found $(M - H)^-$ 581.0, $(M - H + 2)^-$ 583.0. Anal. calcd C 50.55, H 2.65, N 14.74, found C 50.75, H 2.90, N 15.07.

3-Bromo-*N*-(2-(3-(2-tolyl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (17). Yield 58.5%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.58 (s, 1H, Ph-NH-C═O), 8.43 (dd, 1H, J = 4.7 Hz, Py-H), 8.11 (dd, 1H, J = 8.1 Hz, Py-H), 8.02 (d, 1H, J = 2.5 Hz, Ar-H), 7.89 (ds, 1H, J = 7.2 Hz, Ar-H), 7.78 (d, 1H, J = 2.4 Hz, Ar-H), 7.57 (q, 1H, J = 8.1 Hz, Py-H), 7.47–7.51 (m, 1H, Ar-H), 7.44 (s, 1H, CHCBr), 7.42 (d, 1H, J = 7.5 Hz, Ar-H), 7.33 (t. 1H, J = 7.6 Hz, Ar-H), 2.50 (s, 3H, Ph-CH_3), 2.29 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{25}H_{17}BrCl_2N_6O_2$ $(M - H)^-$ 581.0, $(M - H + 2)^-$ 583.0, Found $(M - H)^-$ 580.9, $(M - H + 2)^-$ 582.9. Anal. $(M + H_2O)$ calcd C 49.86, H 3.18, N 13.95, found C 50.35, H 14.39, N 13.47.

3-Bromo-*N*-(2-(3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (18). Yield 70.9%; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.59 (s, 1H, Ph-NH-C═O), 8.42 (dd, 1H, J = 4.7 Hz, Py-H), 8.11 (dd, J = 8.1 Hz, 1H, Py-H), 8.00 (d, J = 2.4 Hz, 1H, Ar-H), 7.94 (tt, J = 8.6 Hz, 2H, Ar-H), 7.76–7.79 (m, 3H, Ar-H), 7.57 (q, J = 8.1 Hz, 1H, Py-H), 7.43 (s, 1H, CHCBr), 2.29 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{14}Br_2Cl_2N_6O_2$ $(M - H)^-$ 644.9,

$(M - H + 2)^-$ 646.9. Found $(M - H)^-$ 644.9, $(M - H + 2)^-$ 646.9. Anal. calcd C 44.41, H 2.17, N 12.95, found C 44.55, H 2.39, N. 12.80.

3-Bromo-*N*-(2-(3-(4-nitrobenzyl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (19). Yield 61.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H, Ph-NH-C═O), 8.49 (dd, J = 4.7 Hz, 1H, Py-H), 8.19 (dd, J = 8.7 Hz, 2H, Ar-H), 8.15 (dd, J = 8.1 Hz, 1H, Py-H), 7.83 (d, J = 2.45 Hz, 1H, Ar-H), 7.56–7.64 (m, 4H, Ar-H, Py-H), 7.28 (s, 1H, CHCBr), 3.57 (s, 2H, CH_2Ph), 2.16 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{25}H_{16}BrCl_2N_7O_4$ $(M - H)^-$ 626.0, $(M - H + 2)^-$ 628.0. Found $(M - H)^-$ 625.9, $(M - H + 2)^-$ 627.9. Anal. calcd C 47.72, H 2.56, N 15.58, found C 47.80, H 2.59, N 15.30.

3-Bromo-*N*-(2-(3-methyl-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (20). Yield 45.7%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (s, 1H, ph-NH-C═O), 8.47 (dd, 1H, J = 4.7 Hz, Py-H), 8.17 (dd, 1H, J = 8.1 Hz, Py-H), 7.88 (d, 1H, J = 2.3 Hz, Ar-H), 7.75 (d, 1H, J = 2.5 Hz, Ar-H), 7.61 (q, 1H, J = 8.1 Hz, Py-H), 7.36 (s, 1H, CHCBr), 2.50 (s, 3H, CH_3), 2.26 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{19}H_{13}BrCl_2N_6O_2$ $(M - H)^-$ 505.0, $(M - H + 2)^-$ 507.0. Found $(M - H)^-$ 505.0, $(M - H + 2)^-$ 507.0. Anal. calcd C 44.91, H 2.58, N 16.54, found C 45.31, H 2.99, N 16.03.

3-Bromo-*N*-(2-(3-(2,6-difluorophenyl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (21). Yield 10.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (s, 1H, Ph-NH-C═O), 8.45 (dd, J = 4.7 Hz, 1H, Py-H), 8.13 (dd, J = 8.0 Hz, 1H, Py-H), 8.01 (d, J = 2.3 Hz, 1H, Ar-H), 7.71–7.83 (m, 3H, Ar-H), 7.59 (q, J = 8.0 Hz, 1H, Py-H), 7.44–7.45 (m, 1H, Ar-H), 7.37 (s, 1H, CHCBr), 7.01–7.07 (m, 1H, Ar-H), 2.29 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{13}BrCl_2F_2N_6O_2$ $(M + H)^+$ 605.0, $(M + H + 2)^+$ 607.0. Found $(M + H)^+$ 605.1, $(M + H + 2)^+$ 607.1. Anal. calcd C 47.55, H 2.16, N 13.86, found C 47.99, H 2.57, N 13.43.

3-Bromo-*N*-(2-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)-4-chloro-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (22). Yield 38.5%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H, Ph-NH-C═O), 9.16 (d, J = 1.6 Hz, 1H, Py-H), 8.80 (dd, J = 4.8 Hz, 1H, Py-H), 8.41 (dd, J = 4.7 Hz, 1H, Py-H), 8.34 (tt, J = 8.1 Hz, 1H, Py-H), 8.12 (dd, J = 8.1 Hz, 1H, Py-H), 8.02 (d, J = 2.2 Hz, 1H, Ar-H), 7.80 (d, J = 2.2 Hz, 1H, Ar-H), 7.60–7.63 (q, J = 8.1 Hz, 1H, Py-H), 7.58–7.56 (q, J = 8.1 Hz, 1H, Py-H), 7.44 (s, 1H, CHCBr), 2.30 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{23}H_{14}BrCl_2N_7O_2$ $(M - H)^-$ 568.0, $(M - H + 2)^-$ 570.0. Found $(M - H)^-$ 568.0, $(M - H + 2)^-$ 570.0. Anal. (M + hexane) calcd C 52.98, H 4.29, N 14.91, found C 53.23, H 4.70, N 14.67.

3-Bromo-*N*-(2-(3-methyl-1,2,4-oxadiazol-5-yl)-4-bromo-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (23). Yield 49.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H, Ph-NH-C═O), 8.46 (d, J = 4.4 Hz, 1H, Py-H), 8.09 (s, 1H, Py-H), 7.86 (d, J = 8.2 Hz, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 7.41 (m, 1H, Py-H), 7.11 (s, 1H, CHCBr), 2.53 (s, 3H, CH_3), 2.27 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{19}H_{13}Br_2ClN_6O_2$ $(M - H)^-$ 548.9, $(M - H + 2)^-$ 550.9. Found $(M - H)^-$ 548.7, $(M - H + 2)^-$ 550.7. Anal. calcd C 41.30, H 2.37, N 15.21, found C 41.55, H 2.50, N 15.11.

3-Bromo-*N*-(2-(3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)-4-bromo-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (24). Yield 56.8%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (s, 1H, Ph-NH-C═O), 8.43 (d, J = 3.4 Hz, 1H, Py-H), 8.09–8.17 (m, 2H, Ar-H, Py-H), 7.98–7.88 (m, 3H, Ar-H, Py-H), 7.59–7.55 (m, 1H, Ar-H), 7.43 (s, 1H, CHCBr), 2.20 (s, 3H, Ph-CH_3). MS m/z calcd for $C_{24}H_{14}Br_3ClN_6O_2$ $(M - H)^-$ 688.8, $(M - H + 2)^-$ 692.8. Found $(M - H)^-$ 688.7, $(M - H + 2)^-$ 692.7. Anal. (M + 1/2 hexane) calcd C 44.02, H 2.87, N 11.41, found C 44.45, H 3.10, N 11.30.

X-ray diffraction crystallography

A suitable single crystal of compound **18** was obtained by dissolving the compound in ethyl acetate and evaporating the solvent slowly at r.t. for about 10 d. The diffraction data were collected on a Nonius CAD4 single crystal diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å) by using a $\omega/2\theta$ scan mode at 296 K. The crystal structure was solved by the direct method and refined by the full-matrix least-squares procedure on F^2 using SHELXL-97 program.[25] All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were introduced at calculated positions.

Insecticidal activities assay

The larvicidal activities of the title compounds (**3–24**) against *Plutella xylostella* and *Spodoptera exigua* were evaluated by a dipping method according to the literature procedures.[1,26] Cabbage leaf disks (8 cm in diameter) were dipped into a test solution for 10 s and air-dried on filter paper. The treated diet was released into the petri dish, and twenty third-instar *P. xylostella* or *S. exigua* were released into the petri dish. *P. xylostella* and *S. exigua* with abnormal symptoms such as body contraction, feeding cessation or paralysis was included in the number of dead. The *P. xylostella* affected by this treatment were assessed for 3 d after the treatment. The *S. exigua* affected by this treatment were assessed for 5 d after the treatment. The mortality percentage was expressed as the mean of values obtained in three independent experiments. Chlorantraniliprole was used as a control.

Conclusions

In summary, by comparing two substituted heterocycle groups, a series of new anthranilic diamide analogs containing substituted 1,2,4- or 1,3,4-oxadiazole ring were designed and synthesized. The crystal structure of **18** was determined by single crystal X-ray diffraction analysis. Preliminary bioassays indicated that some of the compounds showed good larvicidal activities against *P. xylostella* at 100 μg mL^{-1} and 10 μg mL^{-1}. The structure–activity relationship (SAR) showed that substituted 1,3,4-oxadiazole compounds displayed higher insecticidal activity than substituted 1,2,4-oxadiazole compounds. The SAR also showed an enhanced activity trend of different substituents attached to the 1,3,4-oxadiazole: $-CH_3 \approx -SCH_3 > -SH > -OH \approx -SCH_2CH_3 \approx -SCH(CH_3)_2$. The activity trend for

different substituent on the bridge benzene ring is –Cl > –Br > –H. For the modified 1,2,4-oxadiazole target compounds, aliphatic substituted compounds showed higher insecticidal activity than those with aromatic substituents. Compared with chlorantraniliprole, compound **6** showed a similar insecticidal activity against *P. Xylostella* at 0.4 μg mL^{-1} and against *S. exigua* at 1 μg mL^{-1}. With the expectation of finding more new 1,3,4-oxadiazole containing anthranilic diamide analogs, further structural optimization and larvicidal activity tests are under way.

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References

1 M. Tohnishi, H. Nakao, T. Furuya, A. Seo, H. Kodama, K. Tsubata, S. Fujioka, H. Kodama, T. Hirooka and T. Nishimatsu, *J. Pestic. Sci.*, 2005, **30**, 354–360.
2 D. A. Clark, G. P. Lahm, B. K. Smith, J. D. Barry and D. G. Clagg, *Bioorg. Med. Chem.*, 2008, **16**, 3163–3170.
3 G. P. Lahm, D. Cordova and J. D. Barry, *Bioorg. Med. Chem.*, 2009, **17**, 4127–4133.
4 G. P. Lahm, B. J. Myers, T. P. Selby and T. M. Stevenson, *US Pat*, 6747047, 2004.
5 T. Caspar, D. Cordova, S. Gutteridge, J. J. Rauh, R. M. Smith, L. Wu and Y. Tao, *WO Pat*, 04027042, 2004.
6 G. Liu, X. Ju, J. Cheng and Z. Liu, *Chemosphere*, 2010, **78**, 300–306.
7 H. Nakao, H. Harayama, M. Yamaguchi, M. Tohnishi, M. Morimoto and S. Fujioka, *WO Pat*, 2002088074, 2002.
8 M. Tohnishi, H. Nakao, E. Kohno, T. Nishida, T. Furuya, T. Shimizu, A. Seo, K. Sakata, S. Fujioka and H. Kanno, *EP Pat*, 0919542, 1999.
9 M. Tohnishi, H. Nakao, T. Furuya, A. Seo, H. Kodama, K. Tsubata, S. Fujioka, H. Kodama, T. Hirooka and T. Nishimatsu, *J. Pestic. Sci.*, 2005, **30**, 354–360.
10 M. Tohnishi, H. Nakao, E. Kohno, T. Nishida, T. Furuya, T. Shimizu, A. Seo, K. Sakata, S. Fujioka and H. Kanno, *EP Pat*, 1006107, 2000.
11 G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark and D. Cordova, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4898–4906.
12 K. A. Hughes, G. P. Lahm, T. P. Selby and T. M. Stevenson, *WO Pat*, 2004067528, 2004.
13 W. Dong, J. Xu, L. Xiong, X. Liu and Z. Li, *Chin. J. Chem.*, 2009, **27**, 579–586.
14 J. Xu, W. Dong, L. Xiong, Y. Li and Z. Li, *Chin. J. Chem.*, 2009, **27**, 2007–2012.
15 M. Feng, Y. Li, H. Zhu, L. Zhao, B. Xi and J. Ni, *J. Agric. Food Chem.*, 2010, **58**, 10999–11006.
16 X. Zhang, H. He, H. Tan, N. Wang, X. Zeng and J. Ni, *CN Pat*, 101570535, 2009.
17 B. Li, D. Xiang, J. Yuan, H. Yang, H. Zhang and H. Yu, *CN Pat*, 101298451, 2008.
18 A. S. Aboraia, H. M. Abdel-Rahman, N. M. Mahfouz and M. A. Gendy, *Bioorg. Med. Chem.*, 2006, **14**, 1236–1246.
19 Z. Fan, Z. Shi, H. Zhang, X. Liu, L. Bao, L. Ma, X. Zuo, Q. Zheng and N. Mi, *J. Agric. Food Chem.*, 2009, **57**, 4279–4286.
20 M. Takahashi and A. Hiratsuka, *Heterocycles*, 1989, **29**, 975–978.
21 H. K. Fun, M. M. Rosli, S. Rai, A. M. Isloor and P. Shetty, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2010, **66**, o1196–o1197.
22 D. Zampieri, M. G. Mamolo, E. Laurini, M. Fermeglia, P. Posocco, S. Pricl, E. Banfi, G. Scialino and L. Vio, *Bioorg. Med. Chem.*, 2009, **17**, 4693–4707.
23 S. D. Joshi, H. M. Vagdevi, V. P. Vaidya and G. S. Gadaginamath, *Eur. J. Med. Chem.*, 2008, **43**, 1989–1996.
24 Y. Ho and W. Yao, *Dyes Pigm.*, 2009, **82**, 6–12.
25 G. M. Sheldrick, *SHELXL-97*, University of Göttingen, 1997.
26 J. R. Busivine, Recommended methods for measurement of pest resistance to pesticides, FAO Plant Production and Protection Paper 21, Rome, Italy, 1980.

