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Synthesis, insecticidal activities, and structure–activity relationships of 1,3,4-oxadiazole-ring-containing pyridylpyrazole-4-carboxamides as novel insecticides of the anthranilic diamide family

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Abstract

The preparation of novel anthranilic diamide derivatives is extremely important for agricultural pest control. In this study, pyridylpyrazole-4-carboxamides containing a 1,3,4-oxadiazole ring were designed and synthesized via the dehydration of aromatic hydrazine derivatives and formanilides in the presence of an alkali. The insecticidal activities of these new compounds against the diamondback moth (*Plutella xylostella*) were evaluated. N-(4-chloro-2-methyl-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide (**8h6**) showed 67%, 50%, 34%, 20%, and 17% activity at concentrations of 100, 50, 10, 5, and 1 μg ml^{-1}, respectively. Density functional theory calculations showed that the introduction of the 1,3,4-oxadiazole ring significantly changed the electron distributions in both the highest occupied and lowest unoccupied molecular orbitals, resulting in these compounds having much larger energy gaps than the well-known insecticide chlorantraniliprole, which may account for their lower activity. The results of this study demonstrate that anthranilic diamides substituted with a 1,3,4-oxadiazole ring are effective insecticides that can be used for pest management.

1 | INTRODUCTION

Selective synthetic insecticides with high activity and low toxicity to mammals play an important role in eradicating pests and reducing disease transmission to ensure the safety of food supplies, meet global food demands, and reduce environmental residues [1]. Anthranilic diamides are one of the safest classes of insecticides and offer high effectivity, low mammalian toxicity [2], and a new mode of action involving ryanodine receptor (RyR) activation [3]. In the past decade, the pioneering work of DuPont has led to highly effective anthranilic diamides [4], including chlorantraniliprole and cyantraniliprole (Figure 1) [5]. These efficient insecticides are widely applicable to crops and can control *Lepidoptera*, *Hemiptera*, and *Coleoptera* pests [6]. Binding of these compounds to RyR, which is a calcium channel, induces the unregulated release of calcium stores and interferes with muscle contraction [4–7] by altering the conductance of the channel [4], leading to lethargy, paralysis, and death [3]. The general chemical structure of an anthranilic diamide consists of a substituted benzene ring (**A**), an *N*-pyridylpyrazole amide group (**B**), and an aliphatic amide moiety (**C**) (Figure 2). Most previous studies have investigated substitution at either **A** [5,8–10] or **B** [11–16]. In particular, the methyl group on the benzene ring has been substituted to produce a series of pyridine, pyrazole, formyl, and acetyl derivatives that exhibit insecticidal activities [1,17]. The carboxamide substituent in **B** has been shifted from the 5-position to 4-position

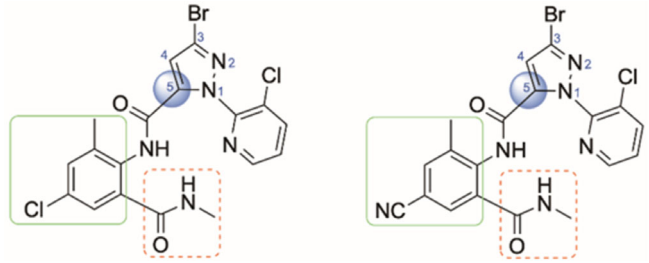


FIGURE 1 Structures of chlorantraniliprole and cyantraniliprole

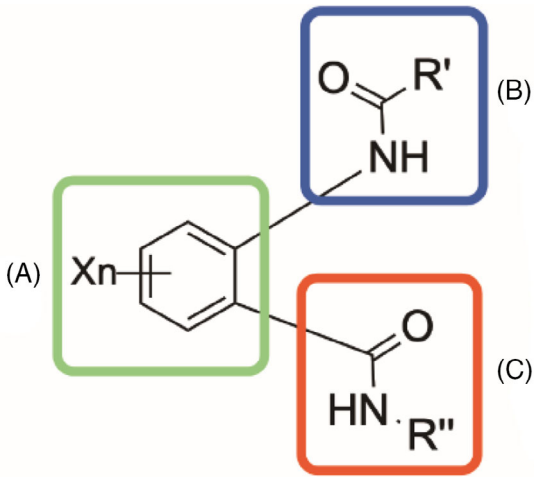


FIGURE 2 General structure of anthranilic diamides. R′: Substituted or nonsubstituted pyridylpyrazolyl, R″: Substituted oxadiazole ring, Xn: Cl

of the pyrazole ring to obtain pyridylpyrazole-4-carboxamides [1,6]. Such *N*-pyridylpyrazole derivatives have been screened for antitumor properties [17] and demonstrate potent antimicrobial activity [18–20]. The cyclization of the aliphatic amide moiety **C** yields heterocycles such as 1,3,4-oxadiazole derivatives [6,21] by dehydrating the two amide groups of the aliphatic amide moiety in **C** [1,2,6]. These derivatives show significantly higher insecticidal activity than other heterocyclic derivatives. Structural modification with heterocyclic oxadiazole rings, especially five-membered regioisomeric 1,2,4- and 1,3,4-oxadiazoles, imparts potent biological properties and increases anticancer activity [22].

DuPont has reported that R′ in **B** has a strong effect on insecticidal activity [4], with high activity observed for R′ = substituted or unsubstituted N,S heterocycles such as pyridine, pyrazole, oxazole, triazole, and thiazole, and pyridylpyrazolyl, which exhibits maximal activity. The structure–activity relationships (SARs) for anthranilic compounds with R′ = pyridyl or pyrazolyl show that the activity increases for 3-substituted pyrazole groups in the order of $OCH_3 < OCHF_2 < OCH_2CF_3$, Cl < Br═$CF_3$

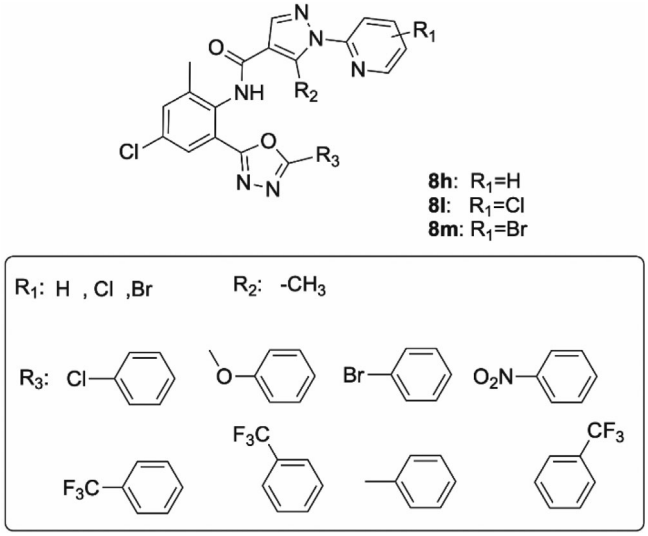


FIGURE 3 General structure of target molecules

[23]. The bromine substituent at the 3-position of pyrazole can be substituted for an methylazide group with no significant loss of activity [15,24]. Furthermore, when the pyridine group was replaced with a nitro-substituted phenyl group, excellent insecticidal activities were observed against the diamondback moth (*Plutella xylostella*) and armyworm at low concentrations [24].

Finally, **C** can be modified by derivatization of the amide at R″, and the insertion of a carbonyl group forms a structure similar to a carbonyl amide group [25]. The insecticidal activity of such modified compounds is dependent on R″. Exchanging the amide unit for a hydrazone bridge resulted in good activity against *P. xylostella*. Several pyridylpyrazole-5-carboxamides containing a 1,3,4-oxadiazole ring and differing from previously synthesized pyridylpyrazole-4-carboxamides have been reported [21]. Investigations of the SARs of compounds with R″ = 1,3,4-oxadiazole indicated that with a 2-substituted phenyl group at R″, the activity increases in the order of *meta-* < *ortho-* < *para*-substituted compounds. The activity of the ortho- and meta-substituted target compounds (Figure 3) decreased in the order of H > Cl > Br, whereas that of the *para*-substituted compound decreased in the order of $NO_2 > OCF_3 > Br > CH_3 > CF_3 >$ Cl when R_1 = H (**8h** compounds) (Figure 3). When R_3 = Ph-NO_2 and Ph-Br, the activity was affected by the R_1 substituent in the order of H > Br > Cl. This behavior indicated that the electronegativity of the substituent on the phenyl ring has a significant effect on R_3 in the 1,3,4-oxadiazole ring, which in turn affects the activity. Considering previous studies [6] and bioisosterism [26], **C** of anthranilic diamides containing a potential 1,3,4-oxadiazole ring (Figure 3) can be synthesized by facile routes that are widely used in the

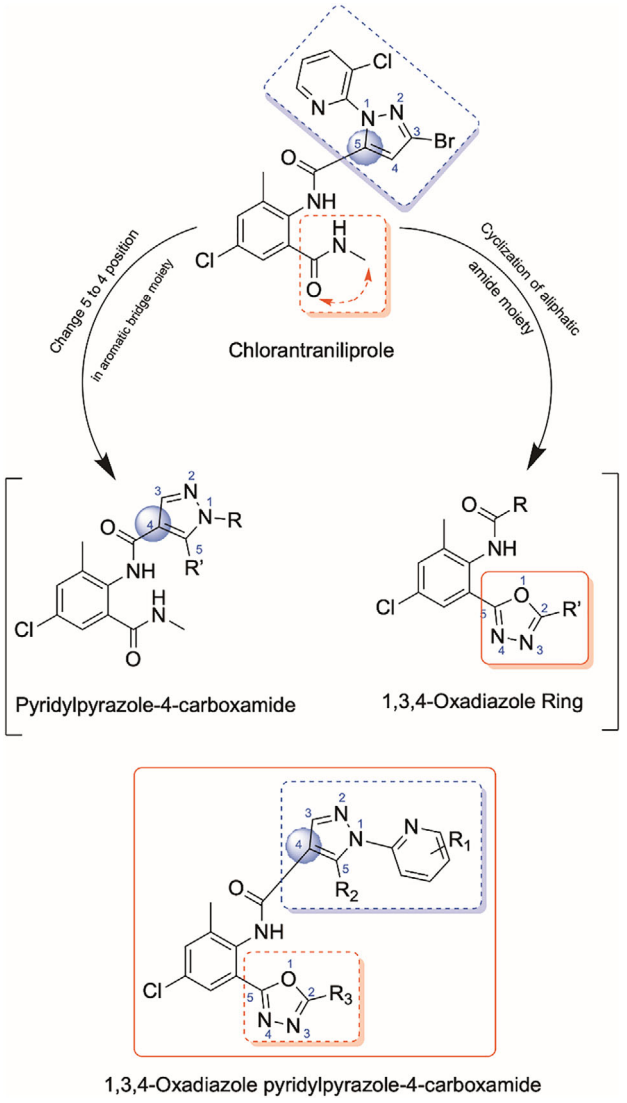
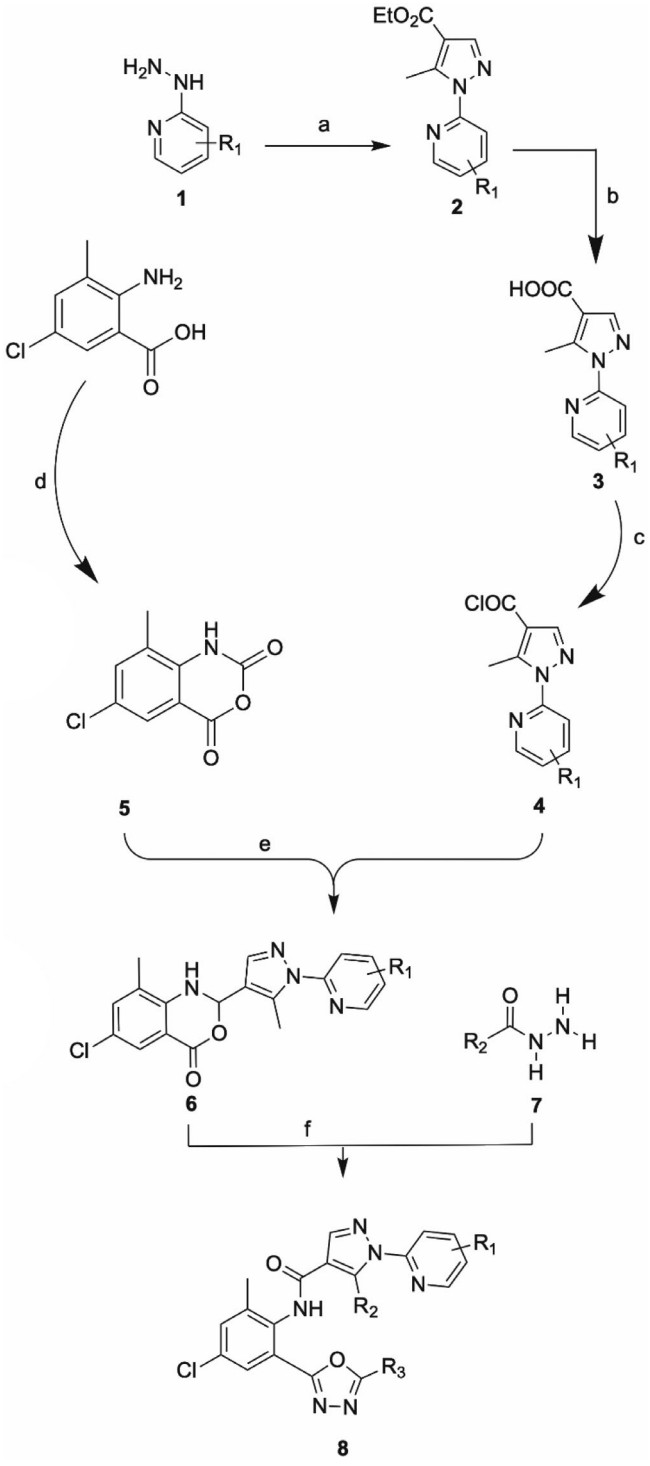


FIGURE 4 Design strategy for target compounds



SCHEME 1 General synthetic route for compounds **8h1–8**, **8l1–8**, and **8m1–8.** Reagents and conditions: (a) (i) ethyl 2-(ethoxymethylene) acetoacetate, ethanol, 80°C, and (ii) ethyl acetate; (b) (i) NaOH, 50–55°C, 0.5 h, and (ii) DCM, HCl; (c) DMF, oxalyl chloride, 20 min; (d) (i) 1,4-dioxane, ethyl chloroformate, reflux 6 h, and (ii) acetyl chloride, 50–55°C, 10 h; (e) pyridine, 80°C, reflux; (f) (i) NaOH, DMF, 25°C, 6–12 h, (ii) DIPEA, TsCl, 12 h, and (iii) saturated sodium bicarbonate

preparation of pesticides and drug molecules [21,22,27–29]. Thus, novel anthranilic diamide derivatives containing both pyridylpyrazole-4-carboxamide and 1,3,4-oxadiazole functionalities (Figure 3) were designed via structure-based bioisosterism (Figure 4). Because 1,3,4-oxadiazole is a viable bioisostere of the aliphatic amide, we considered it to be an excellent candidate for lead optimization that might enhance insecticidal activity and provide an understanding of the binding of 1,3,4-oxadiazole anthranilic diamides to RyR.

2 | RESULTS AND DISCUSSION

2.1 | Synthesis

We aimed to synthesize pyridylpyrazole-4-carboxamides containing a 1,3,4-oxadiazole ring as novel anthranilic diamide insecticides for agricultural pest control because the 1,3,4-oxadiazole ring is a bioisostere of fatty acid amides. The key step in the synthesis of compounds **8h1–8**, **8l1–8**, and **8m1–8** was the reaction of intermediate

6 [1,6] with intermediate **7** in the presence of NaOH at 25°C (Scheme 1) with the subsequent addition of N,N-diisopropylethylamine (DIPEA) and *p*-toluene sulfonylchloride (TsCl). Intermediate **6** was synthesized by hydrolysis of substituted pyrazole-4-carboxylate **2** to the corresponding carboxylic acid **3**. **3** was then converted to the acid chloride **4** by oxalyl chloride in the presence of an *N*,*N*-dimethylformamide (DMF) catalyst. Finally, **4** was coupled with **5** in pyridine–CH_3CN to give **6**.

2.2 | Structure

The structures of all the synthesized compounds were confirmed by ^1H nuclear magnetic resonance (NMR) spectroscopy, ^{13}C NMR spectroscopy, mass spectrometry (MS), and elemental analysis. The single peak in each ^1H NMR spectrum at 9.99–9.75 ppm was assigned to the aromatic amide hydrogen (O═C—NH—). Further, the peak at 8.25 ppm was assigned to the pyridine ring (s, 1H, and pyridine-H), and the protons of the aromatic phenyl ring were observed at 7.03–8.42 ppm. The peak at 2.94–3.89 ppm (s, 3H, pyrazole-CH_3) was assigned to the hydrogen at the 5-position of the pyrazole ring. The peak at 2.42–2.44 ppm (s, 3H, Ar—CH_3) was identified as the hydrogen at the 2-position of the benzene ring. The peak at 3.89 ppm (s, 3H, Ar—CH_3O), corresponded to the hydrogen at the 4-position of the phenyl ring. The disappearance of the peaks corresponding to the aromatic amide protons illustrated the successful amide cyclization in the target compounds (Table 1).

TABLE 1 The substitutions of target compounds

Compound	R_1	R_2	R_3	Yield %
8h1	H	CH_3	2-(CF_3)Ph	71
8h2	H	CH_3	3-(CF_3)Ph	68
8h3	H	CH_3	4-BrPh	72
8h4	H	CH_3	4-(CF_3)Ph	75
8h5	H	CH_3	4-ClPh	75
8h6	H	CH_3	4-(NO_2)Ph	56
8h7	H	CH_3	4-(CH_3O)Ph	82
8h8	H	CH_3	4-CH_3Ph	86
8l1	2-Cl	CH_3	2-(CF_3)Ph	55
8l2	2-Cl	CH_3	3-(CF_3)Ph	49
8l3	2-Cl	CH_3	4-BrPh	55
8l4	2-Cl	CH_3	4-(CF_3)Ph	58
8l5	2-Cl	CH_3	4-CH_3Ph	67
8l6	2-Cl	CH_3	4-ClPh	60
8l7	2-Cl	CH_3	4-(NO_2)Ph	47
8l8	2-Cl	CH_3	4-(CH_3O)Ph	65
8m1	2-Br	CH_3	2-(CF_3)Ph	52
8m2	2-Br	CH_3	3-(CF_3)Ph	57
8m3	2-Br	CH_3	4-BrPh	65
8m4	2-Br	CH_3	4-(CF_3)Ph	59
8m5	2-Br	CH_3	4-CH_3Ph	78
8m6	2-Br	CH_3	4-ClPh	68
8m7	2-Br	CH_3	4-(NO_2)Ph	49
8m8	2-Br	CH_3	4-(CH_3O)Ph	73

2.3 | Biological activities and SARs

The in vivo larvicidal activities of compounds **8h1–8**, **8l1–8**, and **8m1–8** against *P. xylostella* were evaluated using a previously described dipping method [30–32]. The toxicity and mortality results are listed in Tables 2 and 3, respectively. Chlorantraniliprole was used as a control.

The lethal concentration (LC_{50}) of the control agent chlorantraniliprole against *P. xylostella* larvae treated for 96 h was 0.27 μg ml^{-1} (Table 2). According to the survey data, the calculated death rate of each treatment was adjusted using the DPS data processing system, and the LC_{50}, LC_{90}, standard error (b), equivalence, and 95% confidence limit of the LC_{50} were calculated.

In comparison, the activities of compounds **8h1–8** were lower (Table 2), with the highest toxicity observed in **8h6** (LC_{50} = 39.17 μg ml^{-1}).

Most of the compounds showed moderate to good insecticidal activity against *P. xylostella* (Table 3). Compounds **8h6**, **8l5**, and **8h1** exhibited the best performance with activities of 67%, 60%, and 57%, respectively, at 100 μg ml^{-1}. At 10 μg ml^{-1}, most of compounds **8h1–8** still displayed good activity, whereas compounds **8l1–8** and **8m1–8** exhibited activities of 0.00%–10%. Compound

TABLE 2 LC_{50} values and LC_{90} values of compounds **8h1–8h8** and chlorantraniliprole against *P. xylostella*

Compound	LC_{50}/μg ml^{-1} (96 h)	LC_{90}/μg ml^{-1} (96 h)
8h1	198.09	6079.85
8h2	71.29	267.53
8h3	155.14	43,199.00
8h4	1295.18	2,759,325.00
8h5	74.15	279.64
8h6	39.17	2578.04
8h7	77.31	224,076.10
8h8	297.23	557,104.04
Chlo*	0.27	1.08

Abbreviation: chlo*, chlorantraniliprole.

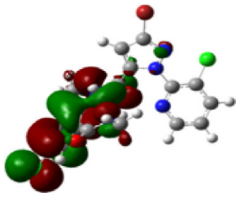
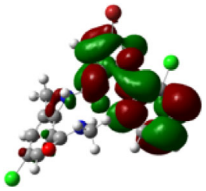
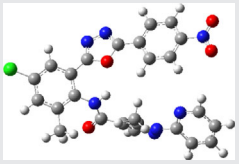
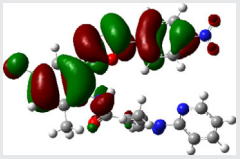
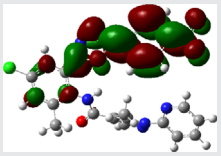
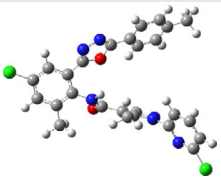
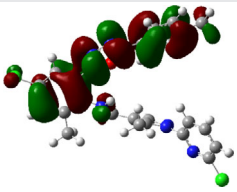
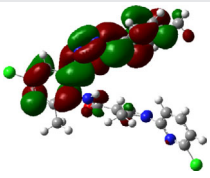
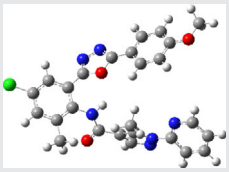
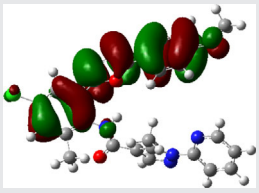
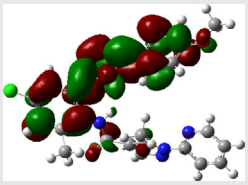
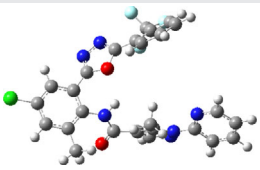
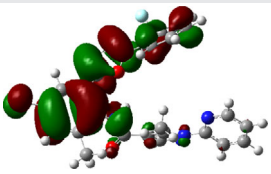
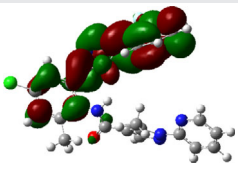
TABLE 3 Larvicidal activity against *P. xylostella* and physiochemical properties of compounds **8h1–8, 8l1–8, 8m1–8**, and chlorantraniliprole

Compound	log *P*	Conc./ μg ml^{-1}	Mortality/%		
			24 h	48 h	96 h
8h1	2.199	100	7	14	57
		50	4	10	17
		10	0	4	14
		5	0	0	7
		1	0	0	4
		0	—	—	—
8h2	2.199	100	14	30	40
		50	4	7	34
		10	0	0	14
		5	0	4	4
		1	0	0	0
		0	—	—	—
8h3	2.179	100	0	30	47
		50	0	17	40
		10	0	7	27
		5	0	7	20
		1	0	7	14
		0	—	—	—
8h4	2.199	100	4	20	37
		50	0	7	27
		10	0	7	24
		5	0	4	14
		1	0	4	14
		0	—	—	—
8h5	2.029	100	10	10	50
		50	4	7	20
		10	0	0	14
		5	0	0	4
		1	0	0	0
		0	—	—	—
8h6	1.059	100	0	54	67
		50	0	44	50
		10	0	20	34
		5	0	7	20
		1	0	7	17
		0	—	—	—
8h7	1.235	100	7	24	54
		50	7	10	44
		10	4	4	40
		5	0	4	34
		1	0	4	24
		0	—	—	—
8h8	1.815	100	7	17	44
		50	4	14	37
		10	0	14	30
		5	0	7	24
		1	0	4	17
		0	—	—	—
Ck		0	—	—	—
chlo*	2.364	100	—	100	100
		10	—	60	100
		1	—	60	90

Note: The logarithm of the partition coefficient (log *P*) was estimated using [*n*-octanol/water] [33].

8h7 exhibited 24% larvicidal activity against *P. xylostella* at the lowest concentration of 1 μg ml^{-1}, which indicated that *N*-pyridylpyrazole (R_1 = H, R_2 = CH_3) induced greater mortality than the compounds with bromine or chlorine substituents on the pyridinyl group. This effect may be due to *N*-pyridylpyrazole being more hydrophobic than the halogenated *N*-pyridylpyrazole groups. At 10 μg ml^{-1}, compounds **8l5** (R_1 = H, R_2 = CH_3, R_3 = 4-[CH_3]Ph, and log *P* = 2.528), **8h3** (R_1 = Cl, R_2 = CH_3, R_3 = 4-BrPh, and log *P* = 2.179), **8h8** (R_1 = H, R_2 = CH_3, R_3 = 4-(CH_3)Ph, and log *P* = 1.815), and **8h7** (R_1 = H, R_2 = CH_3, R_3 = 4-(CH_3O)Ph, and log *P* = 1.235) exhibited larvicidal activities of 10%, 27%, 30%, and 40%, respectively, against *P. xylostella*. This trend showed that the electron-withdrawing nature of substituent R_3 was correlated to the insecticidal activity [2]. This relationship is explicitly explained by the log *P* value [33], with the most suitable value being similar to that of chlorantraniliprole. This trend can also be used to predict drug absorption behavior [34]. The SARs of all the compounds were influenced by the substituents on *N*-pyridylpyrazole (R_1) and the 1,3,4-oxadiazole ring (R_3) (Figure 4). The position and type of substituent at R″ had different effects on activity. For example, the activity increased in the order of *meta-* < *ortho-* < *para*-substitution. Furthermore, at the *ortho-* and *meta*-positions, an activity order of H > Cl > Br was observed, whereas the *para*-substituted compounds exhibited activity in the order of NO_2 > OCF_3 > Br > CH_3 > CF_3 > Cl when R_1 = H (**8h** compounds). When R_3 = Ph-NO_2 and Ph-Br, the activity depended on the R_1 substituent in the order of H > Br > Cl. These trends indicate that the electronegativity of the substituent plays an important role in

TABLE 4 Frontier orbital maps of **8h6**, **8l5**, **8h7**, **8h1**, and chlorantraniliprole (green: Positive molecular orbitals; red: Negative molecular orbitals)

Compound	Molecular structure	HOMO	LUMO
Chlo*			
8h6			
8l5			
8h7			
8h1			

Abbreviations: chlo*, chlorantraniliprole; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital.

determining the activity of anthranilic diamides containing a 1,3,4-oxadiazole ring. Thus, the cyclization of the aliphatic amide into a 1,3,4-oxadiazole gave novel pyridylpyrazole-4-carboxamides (Figure 4) that were significantly different from the chlorantraniliprole lead compound and exhibited high insecticidal activities.

2.4 | General procedures for biological assay

The biological assays of **8** against *P. xylostella* were evaluated by the previously described dipping method [31]. The target compound (20 mg) was dissolved in acetone, and Tween solution was prepared into a 2000-ppm mother liquor. The mother liquor was diluted with 0.05% of Tween solution to achieve the required concentration. Every treatment was repeated in triplicate, and a blank sample was used as a control. A freshly prepared amaranth leaf disc was immersed into the liquid for 10 seconds, removed, and allowed to dry. Three leaf discs were placed in separate Petri dishes, one per dish, together with seven third instar *P. xylostella* larvae per dish, and the dishes were sealed. The number of dead insects was affirmed after 1, 2, and 3 days, and statistical analysis was completed. Mortality was determined as 100% × (number of pest deaths/total number of pests), with results listed in Table 3. Chlorantraniliprole was used as a control.

2.5 | Theoretical calculations

The structures of **8h6**, **8l5**, **8h7**, and **8h1** were selected for theoretical study, as they were the most active insecticides. These molecules were constructed using the ChemDraw module and then preliminarily optimized using the MOPAC procedure with the default settings in

TABLE 5 LUMO and HOMO energies and HOMO−LUMO (H−L) energy gaps of **8h6, 8l5, 8h7, 8h1**, and chlorantraniliprole

Compound	HOMO/eV	LUMO/eV	H–L gap/eV
8h6	−0.31739	0.01440	0.33179
8l5	−0.29810	0.05352	0.35162
8h7	−0.29041	0.06122	0.35163
8h1	−0.31527	0.04733	0.3626
Chlo*	−0.06847	0.05924	0.00923

Note: 1 Hartree = $4.35974417 \times 10^{-18}$ J = 27.2113845 eV.
Abbreviation: chlo*, chlorantraniliprole.

the Chem3D module of the ChemOffice software. Subsequently, the structures were optimized at the rHF/6-31G* [35–41] level within Gaussian 03 [42] software. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies and the corresponding maps were obtained using the GaussView software. The frontier orbital energies were calculated at the same level of theory. The optimized structures and energies of the frontier orbitals (HOMO and LUMO) are provided in Tables 4 and 5. The HOMO and LUMO energies represent the capability of a compound to donate and accept an electron, respectively [43,44]. Accordingly, these energies are the most important factors affecting bioactivity in several chemical and pharmacological processes [45], and thus provide useful information on the biological mode of action. The HOMO of chlorantraniliprole (Table 4) was mainly located on the benzene ring, chlorine atom, and amide moiety, whereas the LUMO was mainly located on the bromine atom, nitrogen of the heterocyclic ring, and chlorine atom, with a HOMO–LUMO energy gap of 0.00923 Ha. For both, the HOMO and LUMO of **8h1** were mainly located on the aromatic ring, and the HOMO–LUMO energy gap was 0.3626 Ha. Compounds **8h7** and **8l5** had similar electron distributions, featuring HOMO–LUMO energy gaps of 0.35163 and 0.35162 Ha, respectively. The HOMO energies of these four compounds decreased in the following order: **8h7** > **8l5** > **8h1** > **8h6**, whereas the LUMO energies decreased in the following order: **8h6** > **8h1** > **8l5** > **8h7**. The HOMO–LUMO energy differences therefore increased in the following order: **8h6** < **8l5** < **8h7** < **8h1**. Previous data suggest that chlorantraniliprole is chemically active because it is easily excited. Evidently, the number and position of NO_2, CH_3, and OCH_3 groups affect the distribution of both the HOMO and LUMO [46]. Moreover, the substitution of NO_2, CH_3, and OCH_3 groups at the *para*-phenyl position with a 1,3,4-oxadiazole ring significantly changed the distribution of both the HOMO and LUMO of **8h6**, **8l5**, and **8h7**. The CF_3 group at the *ortho*-phenyl position in **8h1** also affected the HOMO–LUMO distribution. The most important parameter affecting the activity of these compounds was the HOMO-LUMO energy gap; compounds displaying higher insecticidal activity invariably had a smaller HOMO-LUMO energy gap.

3 | CONCLUSIONS

Novel anthranilic diamides were prepared by cyclizing the aliphatic amide moiety to form a 1,3,4-oxadiazole ring and moving the aromatic acyl moiety from the 5-position to the 4-position. The activity of the synthesized compounds against the diamondback moth *P. xylostella* and the corresponding SARs were examined in detail. Preliminary bioassays indicated that the title compounds exhibited moderate to good larvicidal activities. In particular, *N*-(4-chloro-2-methyl-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h6**) displayed activities of 67%, 50%, 34%, 20%, and 17% at concentrations of 100, 50, 10, 5, and 1 μg ml^{-1}, respectively. The substituents of the synthesized compounds had a pronounced effect on the distributions of both the HOMO and LUMO. Among the compounds with 1,3,4-oxadiazole substituents, the HOMO and LUMO were mainly distributed on the 1-chlorobenzene groups, 1,3,4-oxadiazole ring, and benzene ring near the nitro group. The HOMO of compound **8h6** was delocalized over the entire molecule except for the *p*-nitrobenzene ring, whereas the LUMO was mainly located on the *p*-nitrobenzene ring. The synthesized compounds containing pyridylpyrazole-4-carboxamide and 1,3,4-oxadiazole functionalities differ significantly from the lead chlorantraniliprole but nonetheless show significant potential as insecticides.

4 | MATERIALS AND METHODS

All reagents were purchased from commercial suppliers including Aladdin, Energy Chemical and Sinopharm Chemical Reagent Co., Ltd. China, and used without further purification, whereas all solvents were distilled before use. Analytical thin-layer chromatography (TLC) was performed on silica gel GF254. Silica gel (200–300 mesh) was used for flash column chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-100 spectrometer at 100 MHz or a Bruker AV-400 spectrometer at 400 MHz using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent 1100 Series LC/MSD Trap SL system. The synthetic procedures and detailed characterization data for intermediates **2–6** and different derivatives of

compound **8** can be found in the electronic supporting information (ESI).

4.1 | General procedure for the synthesis of 2

A mixture of 2-hydrazinylpyridine (0.10 mol) and ethyl 2-(ethoxymethylene)acetoacetate (0.10 mol) in ethanol (50 ml) was stirred at 80°C for 1 h. The solution was concentrated and then diluted with ethyl acetate. After washing with brine, the layers were separated and the organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford **2**.

4.2 | General procedure for the synthesis of 3

NaOH (3 N, 8.7 ml, 26.0 mmol) was slowly added to an ethanolic solution of **2** (12.0 mol) at 50–55°C over 0.5 h. The reaction was monitored by TLC (6 ml of ethyl acetate with one drop of acetic acid, $R_f = 0.68$). The solvent was removed by distillation and the residue was dissolved in water (30 ml). The aqueous solution was washed with dichloromethane (DCM) (3 × 30 ml) and acidified with dilute HCl to pH 2.5–3.0. After filtering the obtained mixture, the filter cake was washed with water (20 ml) and dried in air to obtain compound **3**, which was directly used to synthesize **4** without further purification.

4.2.1 | 5-Methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxylic acid

White solid, yield 81.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.61 (s, 1H, COOH), 8.55 (m, 1H, pyridine-H), 8.04 (m, 2H, pyridine-H), 7.81 (m, 1H, pyrazole-H), 7.46 (m, 1H, pyridine-H), 2.80 (s, 3H, pyrazole-CH_3). MS *m/z*: calcd. for $C_{10}H_9N_3O_2$ ($[M-H]^-$) 202.2, found 202.1.

4.3 | General procedure for the synthesis of 4

To a solution of **3** (33.0 mmol) and DMF (1 ml) in dichloromethane (150 ml), oxalyl chloride (6.30 g, 49.0 mmol) was added dropwise over 20 min at 25°C. The reaction mixture was stirred at reflux overnight. Subsequently, the solvent was evaporated to obtain crude **4**, which was directly used to synthesize **6**.

4.4 | General procedure for the synthesis of 5

A suspension of 2-amino-5-chloro-3-methylbenzoic acid (7.46 g, 0.040 mol) in 1,4-dioxane (45 ml) was heated to reflux, treated with ethyl chloroformate (20.7 g, 0.19 mol), refluxed for a further 6 h, and then cooled to 50°C. Acetyl chloride (200 ml, 0.26 mol) was then added and the reaction mixture was maintained at 50–55°C for 10 h. After cooling to 25°C, the precipitate was filtered, rinsed with toluene, and dried to obtain **5** as a white powder.

4.5 | General procedure for the synthesis of 6

Compound **4** (5.00 g, 24.0 mol) was added to a solution of **5** (35.0 mmol) and pyridine (150 ml) in acetonitrile (400 ml) at 80°C over 20 min. After the addition was completed, the reaction mixture was stirred, refluxed overnight, and concentrated to afford the crude product, which was purified by silica gel column chromatography (hexanes/EtOAc = 4/1, v/v).

4.5.1 | 6-Chloro-8-methyl-2-(5-methyl-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one

White solid, yield 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (m, 1H, pyridine-H), 8.28 (s, 1H, Ar—H), 8.03 (m, 1H, pyridine-H), 7.90 (m, 2H, pyridine-H), 7.61 (m, 1H, Ar—H), 7.34 (m, 1H, pyrazole-H), 3.12 (s, 3H, pyrazole-CH_3), 2.59 (s, 3H, Ar—CH_3). MS *m/z*: calcd. for $C_{18}H_{13}ClN_4O_2$ ($[M + H]^+$) 353.7, found 353.2.

4.6 | General procedure for the synthesis of 8

Compound **6** (1 g, 2.84 mmol), **7** (0.49 g, 3.27 mmol), and sodium hydroxide (0.23 g, 5.68 mmol) were added in sequence to DMF (70 ml). The reaction mixture was stirred at 25°C for 6–12 h and a colorless, transparent solution was obtained. After adding DIPEA (1.47 g, 11.36 mmol) and TsCl (2.17 g, 11.36 mmol), the solution was stirred at 25°C for 12 h. The reaction was monitored by TLC. When reaction was completed, the reaction mixture was filtered to remove a small amount of unreacted **6** and saturated sodium bicarbonate solution was added to the filtrate. The obtained white precipitate was filtered and the filter cake was

purified by column chromatography (MeOH/DCM = 300/1, v/v) to obtain **8** as a white solid (0.6 g, yield 44%).

4.6.1 | *N*-(4-Chloro-2-methyl-6-(5-(2-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl) phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h1**)

White solid, yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O═C—NH—), 8.52 (s, 1H, pyridine-H), 8.26 (s, 1H, Ar—H), 8.14–8.12 (m, 1H, Ar—H), 7.92–7.72 (m, 6H, Ar—H), 7.49 (s, 1H, Ar—H), 7.32–7.29 (m, 1H, pyridine-H), 2.97 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.07, 162.46, 161.83, 147.84, 144.69, 140.22, 138.63, 138.60, 134.42, 134.37, 132.32, 132.03, 131.85, 131.41, 127.35, 127.30, 127.24, 127.18, 125.44, 122.51, 118.07, 117.94, 19.76, 13.08; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{18}N_6O_2F_3Cl$ ($[M + Na]^+$) 561.1030, found 561.1036.

4.6.2 | *N*-(4-Chloro-2-methyl-6-(5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl) phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h2**)

White solid, yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.38 (s, 1H, Ar—H), 8.32 (d, J = 8 Hz, 1H, Ar—H), 8.25 (s, 1H, Ar—H), 7.92–7.83 (m, 4H, Ar—H), 7.70 (t, J = 8 Hz, 1H, pyridine-H), 7.51 (d, J = 4 Hz, 1H, Ar—H), 7.33–7.25 (m, 1H, pyridine-H), 2.95 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.39, 162.96, 161.81, 152.84, 147.84, 144.69, 140.10, 138.82, 138.63, 134.44, 134.36, 131.39, 130.16, 129.98, 128.78, 125.36, 124.04, 123.98, 123.95, 122.54, 118.13, 117.93, 116.61, 19.77, 13.07; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{18}N_6O_2F_3Cl$ ($[M + H]^+$) 539.1210, found 539.1216.

4.6.3 | *N*-(2-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-4-chloro-6-methylphenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h3**)

White solid, yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.25 (s, 1H, Ar—H), 7.99–7.84 (m, 5H, Ar—H), 7.70–7.67 (m, 2H, Ar—H), 7.48 (s, 1H, Ar—H), 7.33–7.29 (m, 1H, pyridine-H), 2.94 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.45, 163.08, 161.81, 152.84, 147.85, 144.67, 140.14, 138.73, 138.62, 134.27, 132.62, 131.30, 128.45, 127.09, 125.27, 122.54, 122.04, 118.24, 117.93, 116.65, 19.77, 13.07; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{18}N_6O_2ClBr$ ($[M + H]^+$) 549.0441, found 549.0443.

4.6.4 | *N*-(4-Chloro-2-methyl-6-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl) phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h4**)

White solid, yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.24 (d, J = 8 Hz, 3H, Ar—H), 7.89–7.80 (m, 5H, Ar—H), 7.50 (s, 1H, Ar—H), 7.32–7.29 (m, 1H, pyridine-H), 2.95 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.47, 162.97, 161.82, 152.84, 147.85, 144.71, 140.09, 138.89, 138.61, 134.43, 134.36, 131.41, 127.42, 126.42, 126.30, 126.26, 126.22, 125.38, 122.54, 118.24, 117.91, 116.61, 19.72, 13.04; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{18}N_6O_2F_3Cl$ ($[M + Na]^+$) 561.1030, found 561.1028.

4.6.5 | *N*-(4-Chloro-2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h5**)

White solid, yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.25 (s, 1H, Ar—H), 8.05 (d, J = 8.0 Hz, 2H, Ar—H), 7.91–7.84 (m, 3H, Ar—H), 7.52–7.48 (m, 3H, Ar—H), 7.32–7.29 (m, 1H, pyridine-H), 2.94 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.35, 163.05, 161.82, 152.83, 147.85, 144.67, 140.14, 138.73, 138.62, 134.27, 134.24, 131.30, 129.65, 128.34, 125.27, 122.54, 121.60, 118.26, 117.93, 116.65, 19.76, 13.07; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{18}N_6O_2Cl_2$ ($[M + H]^+$) 505.0947, found 505.0952.

4.6.6 | *N*-(4-Chloro-2-methyl-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h6**)

White solid, yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (s, 1H, O═C—NH—), 8.52 (s, 1H, pyridine-H), 8.42–8.22 (m, 5H, Ar—H), 7.91–7.78 (m, 3H, Ar—H), 7.51 (s, 1H, Ar—H), 7.33–7.26 (m, 1H, Ar—H), 2.94 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 163.86, 162.43, 161.83, 149.85, 147.89, 144.75, 140.04, 139.05, 138.65, 134.65, 134.40, 131.56, 128.66, 128.47, 128.03, 125.49, 124.53, 122.61, 118.18, 117.93, 19.70, 13.04; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{18}N_7O_4Cl$ ($[M + Na]^+$) 538.1006, found 538.1016.

4.6.7 | *N*-(4-Chloro-2-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h7**)

White solid, yield 82%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.25 (s, 1H, Ar—H), 8.05 (d, J = 8.0 Hz, 2H, Ar—H), 7.91–7.85 (m, 3H, Ar—H), 7.46 (s, 1H, Ar—H), 7.32–7.28 (m, 1H, pyridine-H), 7.03 (d, J = 8 Hz, 2H, Ar—H), 3.89 (s, 3H, Ar—CH_3O), 2.95 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.11, 162.77, 162.47, 161.87, 147.81, 144.62, 140.24, 138.58, 138.52, 134.19, 133.89, 131.16, 128.93, 125.12, 122.46, 118.46, 117.95, 115.58, 114.68, 55.52, 19.78, 13.07; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{21}N_6O_3Cl$ ($[M + H]^+$) 501.1442, found 501.1443.

4.6.8 | *N*-(4-Chloro-2-methyl-6-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1-(pyridin-2-yl)-1*H*-pyrazole-4-carboxamide (**8h8**)

White solid, yield 86%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.99 (s, 1H, O═C—NH—), 8.52 (d, J = 4 Hz, 1H, pyridine-H), 8.25 (s, 1H, Ar—H), 8.00 (d, J = 8.0 Hz, 2H, Ar—H), 7.91–7.84 (m, 3H, Ar—H), 7.47 (s, 1H, Ar—H), 7.35–7.29 (m, 3H, Ar—H), 2.95 (s, 3H, pyrazole-CH_3), 2.43 (t, J = 4 Hz, 6H, Ar—CH_3); ^{13}C NMR δ: 164.29, 162.69, 161.84, 147.82, 144.62, 142.96, 140.23, 138.59, 138.53, 134.25, 134.00, 131.17, 129.94, 127.06, 125.18, 122.49, 120.34, 118.37, 117.95, 21.72, 19.80, 13.07; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{21}N_6O_2Cl$ ($[M + H]^+$) 485.1493, found 485.1498.

4.6.9 | *N*-(4-Chloro-2-methyl-6-(5-(2-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l1**)

White solid, yield 55%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O═C—NH—), 8.25 (s, 1H, Ar—H), 8.14–8.12 (m, 1H, Ar—H), 7.93–7.81 (m, 4H, Ar—H), 7.75–7.73 (m, 2H, Ar—H), 7.50 (d, J = 4 Hz, 1H, Ar—H), 7.33–7.31 (m, 1H, Ar—H), 3.01 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.06, 162.47, 161.59, 152.41, 149.10, 145.18, 140.88, 140.60, 138.60, 134.45, 134.24, 132.32, 132.05, 131.84, 131.50, 127.36, 127.31, 127.25, 127.20, 125.45, 122.54, 118.02, 117.23, 115.51, 19.76, 13.26; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3Cl_2$ ($[M-H]^-$) 571.0644, found 571.0662.

4.6.10 | *N*-(4-Chloro-2-methyl-6-(5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l2**)

White solid, yield 49%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.86 (s, 1H, O═C—NH—), 8.38 (s, 1H, Ar—H), 8.32 (d, J = 8 Hz, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 7.90–7.81 (m, 4H, Ar—H), 7.70 (t, J = 8 Hz, 1H, Ar—H), 7.51 (d, J = 4 Hz, 1H, Ar—H), 7.33–7.31 (m, 1H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.39, 162.98, 161.57, 152.39, 149.10, 145.19, 140.89, 140.49, 138.81, 134.47, 134.27, 131.49, 130.16, 129.98, 128.84, 128.81, 128.77, 128.73, 125.37, 124.03, 124.00, 123.96, 122.56, 118.12, 117.14, 115.49, 19.75, 13.25; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3Cl_2$ ($[M-H]^-$) 571.0644, found 571.0671.

4.6.11 | *N*-(2-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-4-chloro-6-methylphenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l3**)

White solid, yield 55%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O═C—NH—), 8.24 (s, 1H, Ar—H), 7.99 (d, J = 4 Hz, 2H, Ar—H), 7.85 (s, 3H, Ar—H), 7.69 (d, J = 8 Hz, 2H, Ar—H), 7.49 (s, 1H, Ar—H), 7.32 (s, 1H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.48, 163.08, 161.58, 152.39, 149.11, 145.17, 140.89, 140.53, 138.73, 134.30, 134.20, 132.63, 131.40, 128.46, 128.25, 127.13, 125.27, 122.56, 122.03, 118.21, 117.18, 115.49, 19.75, 13.24; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_6O_2Cl_2Br$ ($[M-H]^-$) 580.9895, found 580.9896.

4.6.12 | *N*-(4-Chloro-2-methyl-6-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l4**)

White solid, yield 58%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H, O═C—NH—), 8.25 (d, J = 8 Hz, 3H, ArH), 7.88–7.80 (m, 5H, Ar—H), 7.51 (d, J = 4 Hz, 1H, Ar—H),

7.32 (d, J = 8 Hz, 1H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.46, 162.99, 161.57, 152.37, 149.12, 145.21, 140.90, 140.50, 138.85, 134.49, 134.28, 131.48, 127.44, 126.37, 126.32, 126.29, 126.25, 125.37, 122.58, 118.14, 117.13, 115.49, 19.75, 13.24; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3Cl_2$ ([M-H]$^-$) 571.0644, found 571.0660.

4.6.13 | *N*-(4-Chloro-2-methyl-6-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l5**)

White solid, yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H, O=C—NH—), 8.25 (s, 1H, Ar—H), 8.00 (d, J = 8 Hz, 2H, Ar—H), 7.87–7.81 (m, 3H, Ar—H), 7.47 (s, 1H, Ar—H), 7.35–7.30 (m, 3H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.44 (d, J = 8 Hz, 6H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.31, 162.67, 161.60, 152.42, 149.08, 145.11, 143.00, 140.86, 140.61, 138.52, 134.13, 134.02, 131.27, 129.94, 127.06, 125.19, 122.50, 120.31, 118.37, 117.27, 115.50, 21.72, 19.78, 13.25; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{20}N_6O_2Cl_2$ ([M-H]$^-$) 517.0947, found 517.0954.

4.6.14 | *N*-(4-Chloro-2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l6**)

White solid, yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O=C—NH—), 8.24 (s, 1H, Ar—H), 8.06 (d, J = 8 Hz, 2H, Ar—H), 7.85–7.81 (m, 3H, Ar—H), 7.54–7.49 (m, 3H, Ar—H), 7.32 (d, J = 8 Hz, 1H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.37, 163.06, 161.57, 152.39, 149.11, 145.17, 140.88, 140.54, 138.72, 138.68, 134.28, 134.20, 131.39, 129.67, 128.35, 125.26, 122.55, 121.59, 118.21, 117.18, 115.49, 19.76, 13.24; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_6O_2Cl_3$ ([M-H]$^-$) 537.0400, found 537.0407.

4.6.15 | *N*-(4-Chloro-2-methyl-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l7**)

White solid, yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.78 (s, 1H, O=C—NH—), 8.42–8.24 (m, 5H, Ar—H), 7.89–7.82 (m, 3H, Ar—H), 7.52 (s, 1H, Ar—H), 7.34–7.31 (m, 1H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.87, 162.43, 161.55, 152.37, 149.89, 149.16, 145.25, 140.92, 140.44, 139.01, 134.71, 134.37, 131.61, 128.63, 128.04, 125.46, 124.55, 122.62, 118.04, 117.08, 115.49, 19.73, 13.24; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_7O_4Cl_2$ ([M-H]$^-$) 548.0641, found 548.0649.

4.6.16 | *N*-(4-Chloro-2-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-1-(6-chloropyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8l8**)

White solid, yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.99 (s, 1H, O=C—NH—), 8.24 (s, 1H, Ar—H), 8.06 (d, J = 12 Hz, 2H, Ar—H), 7.87–7.81 (m, 3H, Ar—H), 7.47 (s, 1H, Ar—H), 7.32–7.30 (m, 1H, Ar—H), 7.04 (d, J = 12 Hz, 2H, Ar—H), 3.89 (s, 3H, pyrazole-CH_3), 3.00 (s, 3H), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.12, 162.79, 162.46, 161.61, 152.43, 149.08, 145.11, 140.86, 140.62, 138.48, 134.08, 133.93, 131.24, 128.93, 125.12, 122.49, 118.40, 117.29, 115.50, 114.69, 55.53, 19.78, 13.25; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{20}N_6O_3Cl_2$ ([M-H]$^-$) 533.0896, found 533.0901.

4.6.17 | 1-(4-Bromopyridin-2-yl)-*N*-(4-chloro-2-methyl-6-(5-(2-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m1**)

White solid, yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O=C—NH—), 8.25 (s, 1H, Ar—H), 8.14–8.12 (m, 1H, Ar—H), 7.93–7.71 (m, 6H, Ar—H), 7.50–7.46 (m, 2H, Ar—H), 3.00 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.06, 162.47, 161.58, 152.48, 145.20, 140.62, 140.59, 139.17, 138.60, 134.46, 134.24, 132.33, 132.06, 131.84, 131.51, 127.31, 127.26, 126.36, 125.45, 118.03, 117.26, 115.79, 19.75, 13.19; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3ClBr$ ([M-H]$^-$) 615.0159, found 615.0170.

4.6.18 | 1-(4-Bromopyridin-2-yl)-*N*-(4-chloro-2-methyl-6-(5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m2**)

White solid, yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H, O=C—NH—), 8.39 (s, 1H, Ar—H), 8.32 (d, J = 8 Hz, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 7.90–7.84 (m, 3H, Ar—H),

7.75–7.69 (m, 2H, Ar—H), 7.51–7.46 (m, 2H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.39, 162.99, 161.56, 152.46, 145.20, 140.60, 140.50, 139.17, 138.81, 134.48, 134.27, 131.49, 130.16, 129.98, 126.38, 125.37, 124.03, 123.96, 118.11, 117.17, 115.78, 19.75, 13.18; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3ClBr$ ([M-H]$^-$) 615.0159, found 615.0167.

4.6.19 | *N*-(2-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-4-chloro-6-methylphenyl)-1-(6-bromopyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m3**)

White solid, yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O=C—NH—), 8.24 (s, 1H, Ar—H), 8.00–7.68 (m, 7H, Ar—H), 7.49 (s, 2H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.48, 163.08, 161.57, 152.45, 145.19, 140.59, 140.55, 139.18, 138.73, 134.30, 134.19, 132.64, 131.41, 128.46, 127.14, 126.38, 125.28, 122.02, 118.21, 117.21, 115.78, 19.75, 13.17; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_6O_2ClBr_2$ ([M-H]$^-$) 624.9390, found 624.9396.

4.6.20 | 1-(6-Bromopyridin-2-yl)-*N*-(4-chloro-2-methyl-6-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m4**)

White solid, yield 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H, O=C—NH—), 8.25 (d, J = 8 Hz, 3H, Ar—H), 7.90–7.71 (m, 5H, Ar—H), 7.51–7.46 (m, 2H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.46, 162.98, 161.55, 152.45, 145.22, 140.60, 140.51, 139.19, 138.85, 134.49, 134.28, 131.48, 127.45, 126.40, 126.37, 126.33, 126.29, 125.37, 118.13, 117.16, 115.77, 19.75, 13.18; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{17}N_6O_2F_3ClBr$ ([M-H]$^-$) 615.0159, found 615.0161.

4.6.21 | 1-(6-Bromopyridin-2-yl)-*N*-(4-chloro-2-methyl-6-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m5**)

White solid, yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H, O=C—NH—), 8.24 (s, 1H, Ar—H), 8.00 (d, J = 8 Hz, 2H, Ar—H), 7.88 (s, 2H, Ar—H), 7.73 (t, J = 4 Hz, 1H, pyridine-H), 7.48 (s, 2H, Ar—H), 7.34 (d, J = 8 Hz, 2H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.44 (d, J = 8 Hz, 6H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.32, 162.68, 161.60, 152.49, 145.13, 143.01, 140.63, 140.57, 139.15, 138.53, 134.13, 134.04, 131.29, 129.95, 127.07, 126.33, 125.20, 120.31, 118.37, 117.30, 115.79, 21.72, 19.77, 13.18; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{20}N_6O_2ClBr$ ([M + Na]$^+$) 585.0417, found 585.0423.

4.6.22 | 1-(6-Bromopyridin-2-yl)-*N*-(4-chloro-2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m6**)

White solid, yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H, O=C—NH—), 8.23 (s, 1H, Ar—H), 8.06 (d, J = 8 Hz, 2H, Ar—H), 7.90–7.86 (m, 2H, Ar—H), 7.73 (t, J = 8 Hz, 1H, pyridine-H), 7.54–7.46 (m, 4H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.43 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.39, 163.07, 161.57, 152.49, 145.19, 140.58, 140.56, 139.18, 138.73, 138.70, 134.30, 134.22, 131.41, 129.68, 128.36, 126.37, 125.27, 121.61, 118.22, 117.23, 115.78, 19.76, 13.17; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_6O_2Cl_2Br$ ([M-H]$^-$) 580.9895, found 580.9889.

4.6.23 | 1-(6-Bromopyridin-2-yl)-*N*-(4-chloro-2-methyl-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m7**)

White solid, yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (s, 1H, O=C—NH—), 8.42–8.24 (m, 5H, Ar—H), 7.89 (s, 2H, Ar—H), 7.76–7.72 (m, 1H, Ar—H), 7.53–7.47 (m, 2H, Ar—H), 2.99 (s, 3H, pyrazole-CH_3), 2.44 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.85, 162.42, 161.53, 149.87, 145.26, 140.63, 140.45, 139.21, 138.99, 134.71, 134.35, 131.60, 128.85, 128.62, 128.04, 126.45, 125.45, 124.55, 118.02, 117.09, 115.77, 77.33, 77.01, 76.69, 19.73, 13.17; HR-MS (ESI) *m/z*: Calcd for $C_{25}H_{17}N_7O_4ClBr$ ([M-H]$^-$) 592.0136, found 592.0143.

4.6.24 | 1-(6-Bromopyridin-2-yl)-*N*-(4-chloro-2-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methylphenyl)-5-methyl-1*H*-pyrazole-4-carboxamide (**8m8**)

White solid, yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.99 (s, 1H, O=C—NH—), 8.24 (s, 1H, Ar—H), 8.06 (d, J = 12 Hz, 2H, Ar—H), 7.90–7.86 (m, 2H, Ar—H), 7.72 (t, J = 8 Hz, 1H, pyridine-H), 7.47–7.46 (m, 2H, Ar—H), 7.04 (d, J = 12 Hz, 2H, Ar—H), 3.89 (s, 3H, pyrazole-CH_3), 2.99 (s, 3H), 2.42 (s, 3H, Ar—CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.12, 162.79, 162.45, 161.60, 152.49, 145.12, 140.64, 140.57, 139.14, 138.49, 134.06, 133.93, 131.25, 128.93, 126.32, 125.12, 118.41, 117.31, 115.78, 115.52, 114.69, 55.53, 19.78, 13.18; HR-MS (ESI) *m/z*: Calcd for $C_{26}H_{20}N_6O_3ClBr$ ([M-H]$^-$) 577.0391, found 577.0395.

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DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

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