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Synthesis and insecticidal activity of diacylhydrazine derivatives containing a 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole scaffold

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Abstract

Background: The diacylhydrazine derivatives have attracted considerable attention in recently years due to their simple structure, low toxicity, and high insecticidal selectivity. As well as 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole is an important scaffold in many insecticidal molecules. In an effort to discover new molecules with good insecticidal activity, a series of diacylhydrazine derivatives containing a 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole scaffold was synthesized and bio-assayed.

Results: Bioassays demonstrated that some of the title compounds exhibited favorable insecticidal activities against *Helicoverpa armigera* and *Plutella xylostella*. The insecticidal activity of compounds **10g**, **10h**, and **10w** against *H. armigera* were 70.8, 87.5, and 79.2%, respectively. Compounds **10c**, **10e**, **10g**, **10h**, **10i**, **10j** and **10w** showed good larvicidal activity against *P. xylostella*. In particular, the LC_{50} values of compounds **10g**, **10h**, and **10w** were 27.49, 23.67, and 28.90 mg L^{-1}, respectively.

Conclusions: A series of diacylhydrazine derivatives containing a 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole scaffold was synthesized and bio-assayed. The results of insecticidal tests revealed that the synthesized diacylhydrazine derivatives possessed weak to good insecticidal activities against *H. armigera* and *P. xylostella*. Compounds **10g**, **10h**, and **10x** showed much higher insecticidal activity than tebufenozide, and exhibited considerable prospects for further optimization. Primary structure–activity relationship revealed that phenyl, 4-fluoro phenyl and four fluoro-phenyl showed positive influence on their insecticidal activities, and introduction of a heterocyclic ring (pyridine and pyrazole) showed negative impacts on their insecticidal effects.

Keywords: Diacylhydrazine, 3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole, Synthesis and insecticidal activity

Background

Diacylhydrazines are important of nonsteroidal ecdysone agonists inducing agent against lepidopteron, which show excellent insecticidal activity by inducing precocious molting. The earliest insecticidal diacylhydrazine was developed by Rohm and Haas Company and named RH-5849, which was also investigated for their mode of action [1, 2]. Tebufenozide, the first commercialized diacylhydrazine as a specific insecticide for lepidopteron, was applied widely in many countries [3]. And then, several diacylhydrazine insecticides such as halofenozide, methoxyfenozide, chromafenozide, and JS-118 (Fig. 1), were also commercialized gradually [4–7]. Recently, diacylhydrazine derivatives have attracted considerable attention due to their simple structure, low toxicity, and

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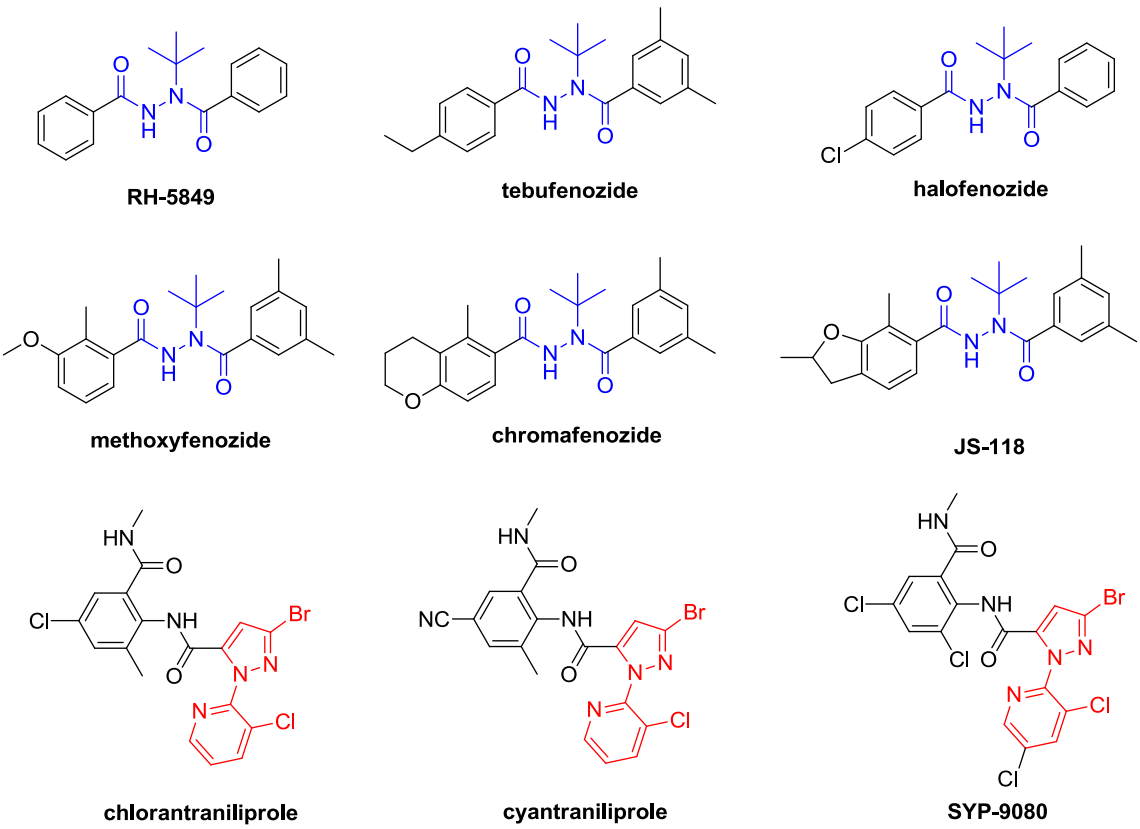


Fig. 1 The structures of commercial insecticides containing the substructures of diacylhydrazine and 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole

high insecticidal selectivity, and a large number of insecticidal molecules were discovered [8–23].

3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole is an important scaffold and appear in several commercial insecticides structures, such as chlorantraniliprole [24], cyantraniliprole [25], and SYP-9080 (Fig. 1) [26]. In recent years, a large number of insecticidal molecules containing a 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole were reported [27–30]. Among which, some diacylhydrazines containing 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole scaffold were also reported [11, 31], such as *N*-(2-(2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbonyl)-2-(*tert*-butyl) hydrazinecarbonyl)-5-chloro-3-methylphenyl) acetamide show 100% larvicidal activity against *Mythimna separate* at 100 mg L^{-1}. And in our previous works [15, 32–35], a series of diacylhydrazine derivatives containing 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole was also been confirmed to show good insecticidal activities.

Encouraged by descriptions above and as a continuation of insecticidal molecules with 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole, we herein sought to retain the substructure of 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole and *tert*-butyl diacylhydrazine, and introducing different substituted aryls (Fig. 2). A series of novel diacylhydrazine derivatives was designed and synthesized. Structures of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HR-MS. Results of bioassays indicated that most synthesized compounds exhibit good insecticidal activities against *P. xylostella*. In particular, the compounds **10g**, **10h**, and **10x** exhibited excellent insecticidal activities, with LC_{50} values of 27.49, 23.67, and 28.90 mg L^{-1}, respectively. These compounds showed slightly higher insecticidal activity than commercial tebufenozide (LC_{50} = 37.77 mg L^{-1}).

Results and discussion

Chemistry

The synthesis of the 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbohydrazide derivatives are depicted in Scheme 1. Firstly, the key intermediate 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**5**) was obtained in good yield via reactions of hydrazinolysis, cyclization, bromination, oxydehydrogenation, and acidolysis by employing 2,3-dichloropyridine (**1**), hydrazine hydrate and diethyl maleate as starting materials [24, 33, 34]. Then compound **5** was allowed to further react with thionyl chloride under reflux to afford

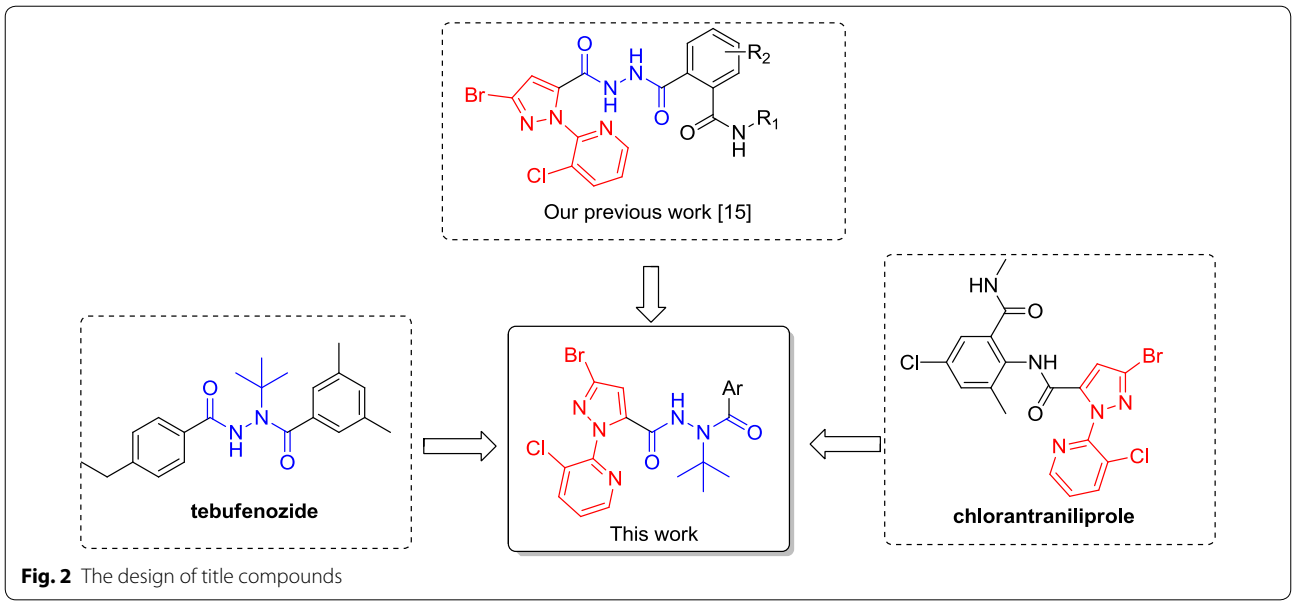
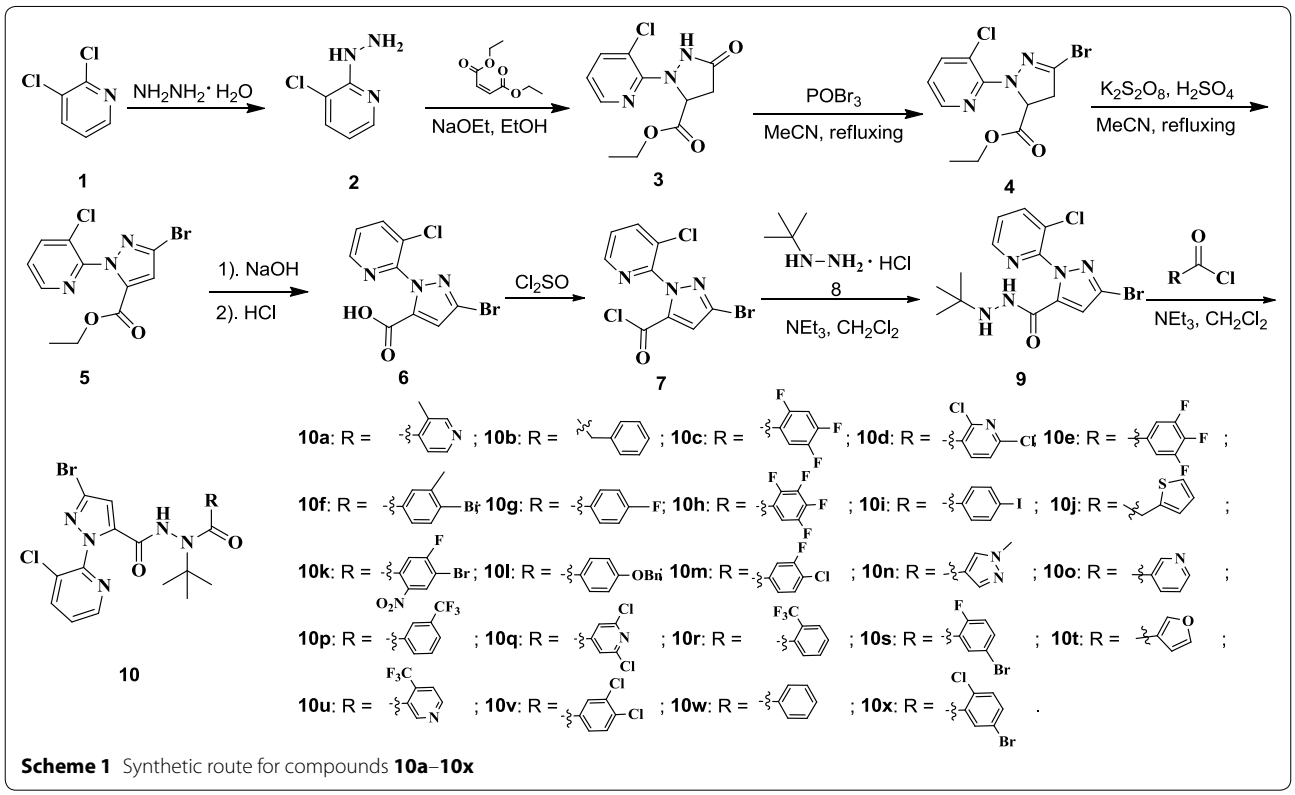


Fig. 2 The design of title compounds



Scheme 1 Synthetic route for compounds **10a**–**10x**

3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbonyl chloride (**7**) [35]. Subsequent treatment of intermediate **7**, with *tert*-butyl hydrazine hydrochloride (**8**) in the presence of triethylamine in trichloromethane at ambient temperature afforded 3-bromo-*N*′-(*tert*-butyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbohydrazide (**9**) in 80% yield. Finally, the title compounds (**10a**–**10x**) were conveniently obtained in an >70% yield by treating of

intermediate **9** with the corresponding acyl chloride in the presence of triethylamine in acetone or acetonitrile.

Structures of the title compounds (**10a–10x**) were established on basis of their spectroscopic data. In the ^{1}H NMR spectra, the N–H proton appeared as a broad singlet near δ 11.10 ppm. The proton at position 5 of pyridine appeared as a doublet of doublets near δ 8.45 due to the coupling coefficients from the protons at 3 and 4 positions of the pyridine ring; the coupling constants were $^{3}J = 4.7$ Hz and $^{4}J = 1.5$ Hz respectively. As well as the protons at positions 3 and 4 showed as doublet of doublets near δ 8.2 and 7.7 ppm, respectively, because of the coupling coefficients from both 5 positions and the each other from 4 and 3 positions of the pyridine ring, respectively. 4-pyrazole-H exhibited a singlet near δ 6.90 ppm. The rest of the aromatic protons appeared range from 7.0 to 8.0 ppm, the nine protons $(-CH_3)_3$ appeared as a singlet near δ 1.45 ppm; In ^{13}C NMR spectra for the fluorine contained compounds, the carbons were split into multiplet due to the coupling coefficients from "F", take compound **10m** as example, the carbon near "F" resonance frequency is near δ_C 158.27 ppm as a doublet and with the coupling constant ($^{1}J_{C\text{-}F}$) was 249.5 Hz; and the carbons at ortho-position of F were also split into doublets with coupling constant ($^{2}J_{C\text{-}F}$) ranged from 18.1 Hz to 21.4 Hz. The properties, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HR-MS data of the synthesized compounds **10a** to **10x** are summarized in more detail in the "Experimental section".

Insecticidal activity

The insecticidal activities of the synthesized compounds against both *Helicoverpa armigera* and *Plutella xylostella* were evaluated using procedures reported previously [17, 33–36] and summarized in Tables 1 and 2, respectively. Commercial tebufenozide, chlorantraniliprole, and chlorpyrifos were used as positive controls.

The results listed in Table 1 indicated that the synthesized compounds displayed weak to good larvicidal activity against *Helicoverpa armigera* at the test concentration. For example, the larvicidal activity of compounds **10c** to **10j**, **10l**, **10o–10q**, **10v**, and **10w** showed >50% mortality on *H. armigera* at 500 mg L^{-1}, and the larvicidal activity of **10g**, **10h**, and **10w** were 70.8, 87.5, and 79.2%, respectively, whereas the concentration was 100 mg L^{-1}, the mortalities of *H. armigera* for compounds **10h** and **10w** were still >50%.

As shown in Table 2, the synthesized compounds shown larvicidal activity against *Plutella xylostella*, with mortality range from 6.7 to 100%. And it can be seen that most of the synthesized compounds show over 60% activity at 500 mg L^{-1}, and compounds **10e**, **10g** to **10j** and **10w** displayed >90% activities. In particular, compounds **10g**, **10h** and **10w** showed good larvicidal activity, both **10h** and **10w** showed 100% activities against *Plutella xylostella* at 200 mg L^{-1}, and the activity of compound **10g** was up to 96.7%. When the concentration was 50 mg L^{-1}, the activities of compounds **10g**, **10h** and **10w** were 66.7, 76.7 and 70% at 50 mg L^{-1}, respectively, whereas these three compounds showed moderate activity at 25 mg L^{-1}.

The median lethal concentrations (LC_{50}) of compounds **10c**, **10e**, **10g**, **10h**, **10i**, **10j** and **10w** were further determined. For comparison, the LC_{50} value of tebufenozide (a commonly used insecticide) were also evaluated. The results are given in Table 3. The LC_{50} values of compounds **10e**, **10g**, **10h**, **10j** and **10w** were less than 100 mg L^{-1} (Table 3). In particular, the compounds **10g**, **10h**, and **10w** exhibited excellent insecticidal activities, with LC_{50} values of 27.49, 23.67, and 28.90 mg L^{-1},

Table 1 Larvicidal activity of compounds 10a–10s against *Helicoverpa armigera*

Compounds	Larvicidal activity (%) at different concentrations (mg L^{-1})				
	500	200	100	50	25
10a	45.8	22.2	0.0	/	/
10b	16.7	0.0	/	/	/
10c	62.5	44.4	21.4	6.7	/
10d	58.3	38.9	14.3	/	/
10e	62.5	44.4	21.4	/	/
10f	58.3	38.9	14.3	/	/
10g	70.8	55.6	35.7	/	/
10h	87.5	77.8	64.3	43.3	16.7
10i	54.2	33.3	7.1	/	/
10j	66.7	40.0	28.6	13.3	/
10k	33.3	5.6	0.0	/	/
10l	58.3	38.9	14.3	/	/
10m	37.5	11.1	0.0	/	/
10n	41.7	16.7	0.0	/	/
10o	63.3	46.7	26.7	6.7	/
10p	54.2	33.3	7.1	/	/
10q	58.3	38.9	14.3	/	/
10r	30.0	0.0	/	/	/
10s	41.7	16.7	0.0	/	/
10t	33.3	5.6	0.0	/	/
10u	0.0	/	/	/	/
10v	54.2	33.3	7.0	/	/
10w	79.2	60.0	53.3	23.3	6.7
10x	41.7	16.7	0.0	/	/
Tebufenozide	100	93.3	70.0	50	40.0
Chlorpyrifos	100	100	100	90	83
Chlorantraniliprole	100	100	100	100	100

Table 2 Larvicidal activity of compounds (10a–10s) against *Plutella xylostella*

Compounds	Larvicidal activity (%) at different concentrations (mg L^{-1})				
	500	200	100	50	25
10a	70.0	46.7	21	/	/
10b	33.3	16.7	0.0	/	/
10c	86.7	56.7	30.0	16.7	/
10d	76.7	53.3	23.6	/	/
10e	90.0	73.3	53.3	36.7	16.7
10f	66.7	53.5	30.2	/	/
10g	100	96.7	80.0	66.7	50.0
10h	100	100	93.3	76.7	53.3
10i	90.0	63.3	43.3	33.3	16.7
10j	96.7	83.3	53.3	36.7	23.3
10k	56.7	23.3	3.3	/	/
10l	73.3	53.3	16.7	6.7	/
10m	63.3	33.3	16.7	/	/
10n	56.7	33.3	13.1	/	/
10o	80.0	63.3	33.7	16.7	/
10p	76.7	53.3	13.0	/	/
10q	73.3	49.0	20.0	/	/
10e	43.3	23.3	13.3	/	/
10s	66.7	33.3	16.7	/	/
10t	43.3	23.3	6.7	/	/
10u	6.7	0.0	/	/	/
10v	80.0	66.7	23.3	/	/
10w	100	100	86.7	70.0	46.7
10x	66.7	33.3	13.3	/	/
Tebufenozide	100	96.7	80.0	56.7	26.7
Chlorpyrifos	100	100	100	90	83
Chlorantraniliprole	100	100	100	100	100

Table 3 LC_{50} values for insecticidal activity against *Plutella xylostella*

Comp.	y = a + bx	r	LC_{50} (mg L^{-1})
10c	Y = 0.632181 + 1.993794x	0.99	155.13
10e	Y = 1.699094 + 1.701997x	0.99	86.98
10g	Y = 2.248458 + 1.91187x	0.97	27.49
10h	Y = 1.687545 + 2.410609x	0.99	23.67
10i	Y = 1.661246 + 1.658921x	0.98	102.95
10j	Y = 1.699094 + 1.701997x	0.99	69.07
10w	Y = 1.85713 + 2.15129x	0.99	28.90
Tebufenozide	Y = 1.429139 + 2.2641 x	0.99	37.77

respectively. These compounds showed slightly higher insecticidal activity than commercial tebufenozide (LC_{50} = 37.77 mg L^{-1}). As revealed by data in Tables 1 and 2, the insecticidal activity of the title compound was effected by R group. When R was a benzene ring (**10w**), the compound showed excellent insecticidal activity (compare with tebufenozide), and the activity could be slightly enhanced by introduction of a fluorine at 4 position of benzene (compound **10g**) or four fluorines on benzene (**10h**). However, the activity decreased when benzene was substituted by tri-fluorine at 3, 4, 5 positions, as well as decreased by introducing other substituents, such as nitro, 2-trifluoromethyl, 3-trifluoromethyl, 3,4-di-chloro, and 4-iodine. In addition, when R was a heterocyclic ring (i.e., pyridine, pyrazole, furan), the corresponding compounds showed much weaker activities than the compounds with a benzene ring. Moreover, a compound containing the benzyl show no larvicidal activity. But interestingly, a compound containing the 2-thiophen-2-yl (**10j**) was found to show good insecticidal activity.

Experimental section

Materials and instruments

All aromatic acids were purchased from Accela ChemBio Co., Ltd (Shanghai, China). Melting points were determined using a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and left uncorrected. The NMR spectra was recorded on a AVANCE III HD 400M NMR (Bruker corporation, Switzerland) or JEOL ECX 500 NMR spectrometer (JEOL Ltd., Japan) operating at room temperature using DMSO as solvent. HR-MS was recorded on an Orbitrap LC–MS instrument (Q-Exative, Thermo Scientific™, American). The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF254. All reagents were of analytical grade or chemically pure. All anhydrous solvents were dried and purified according to standard techniques just before use.

Synthetic procedures

General procedure for intermediates (2–6)

Intermediates **2**–**6** were prepared by following the known procedures, [24, 33, 34] and the acyl chloride (**7**) was synthesized according to reported method [35]. The detailed synthetic procedures and physical properties for these intermediates can be found in Additional file 1.

Synthesis of intermediate (9)

To a well-stirred suspension of *tert*-butyl hydrazine hydrochloride **8** in dichloromethane, two equivalents of triethylamine was added, the resulted mixture was stirred at room temperature for 10 min, then the solution of acyl chloride **7** in dichloromethane was then added dropwise. After stirring and refluxing for 2 h, dichloromethane was removed in vacuo. The mixture was washed with saturated sodium bicarbonate solution. The solution was

filtered to obtain a crude product, which was recrystallized with ethanol to obtain the 3-bromo-*N′*-(*tert*-butyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbohydrazide (**9**). Brown solid, yield, 80%, ^{1}H NMR (500 MHz, DMSO-D6) δ 10.08 (brs, 1H, N–H), 8.47 (d, J = 4.6 Hz, 1H, pyridine-H), 8.15 (d, J = 8.0 Hz, 1H, pyridine-H), 7.58 (dd, J = 8.0, 4.7 Hz, 1H, pyridine-H), 7.25 (s, 1H, pyrazole-H), 4.78 (brs, 1H, N–H), 0.96 (s, 9H, 3 CH_3).

General procedure for the preparation of title compounds (10a–10y)

Different fresh acyl chloride (1 mmol) were added to a well-stirred solution of **9** (1 mmol) in chloroform (5 mL) in present of triethylamine. The resulting mixture was stirred for 50 min at ambient temperature to afford a white solid, and then filtered and recrystallized from ethanol in good yield.

N′-(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl)-3-methylisonicotinohydrazide (10a)

White solid. M.p: 286–287 °C; yield: 78%; ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H, N–H), 8.50 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.44 (s, 1H, pyridine-H), 8.35 (d, ^3J = 4.9 Hz, 1H, Ar–H), 8.23 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 6.97 (s, 1H, pyrazole-H), 6.69 (s, 1H, pyridine-H), 2.17 (s, 3H, $-CH_3$), 1.45 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 170.00, 157.50, 151.54, 147.99, 147.70, 147.02, 144.56, 140.09, 137.31, 128.01, 127.45, 127.25, 119.22, 110.78, 61.57, 27.66, 15.68. HR-MS (ESI$^+$) m/z Calcd for $C_{20}H_{20}BrClN_6O_2$ $[M + H]^+$ 491.05978; found 491.05980.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(2-phenylacetyl)-1H-pyrazole-5-carbohydrazide (10b)

White solid, M.p: 211–213 °C; yield: 83%; ^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H, N–H), 8.49 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.27 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.68 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.31 (s, 1H, benzene-H), 7.30–7.19 (m, 3H, benzene-H), 7.12–7.07 (m, 2H, benzene-H), 4.04 (s, 2H, $-CH_2-$), 1.33 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 172.28, 157.85, 150.97, 147.72, 140.25, 137.77, 135.92, 129.97, 128.59, 127.96, 127.42, 126.82, 123.46, 111.46, 61.06, 40.94, 27.87. HR-MS (ESI$^+$) m/z Calcd for $C_{21}H_{21}BrClN_5O_2$ $[M + H]^+$ 490.06399; found 490.06392.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(2,4,5-trifluorobenzoyl)-1H-pyrazole-5-carbohydrazide (10c)

White solid, M.p: 226–227 °C; yield: 85%; ^{1}H NMR (400 MHz, DMSO) δ 11.18 (s, 1H, N–H), 8.45 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.65–7.59 (m, 1H, benzene-H), 7.20 (td, ^3J = 9.4 Hz, ^4J = 6.3 Hz, 1H, benzene-H), 7.03 (s, 1H, pyrazole-H), 1.42 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −116.38, −132.12; ^{13}C NMR (100 MHz, DMSO) δ 165.61, 163.14 (d, J = 229.6 Hz), 157.08, 153.64 (d, J = 243.2 Hz), 148.14, 147.62, 139.98, 136.94, 128.10, 127.49, 127.36, 122.50 (dd, J = 20.0, 4.3 Hz), 111.11, 116.74 (dd, J = 20.8, 5.8 Hz), 106.83 (dd, J = 28.6, 21.8 Hz) 61.97, 27.66; HR-MS (ESI$^+$) m/z Calcd for $C_{20}H_{16}BrClF_3N_5O_2$ $[M + H]^+$ 530.02008; found 530.02012.

N′-(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl)-2,6-dichloronicotinohydrazide (10d)

White solid. M.p: 223–224 °C; yield: 65%; ^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H, N–H), 8.50 (d, ^3J = 3.5 Hz, 1H, pyridine-H), 8.21 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 7.68 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.56 (s, 1H, pyridine-H), 7.55 (s, 1H, pyridine-H), 6.99 (s, 1H, pyrazole-H), 1.44 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 166.76, 166.00, 165.37, 149.28, 148.40, 148.00, 147.98, 147.73, 140.17, 140.14, 139.45, 136.93, 136.91, 127.96, 127.53, 127.37, 123.72, 111.42, 62.07, 27.51; HR-MS (ESI$^+$) m/z Calcd for $C_{19}H_{16}BrCl_3N_6O_2$, $[M + H]^+$ 544.96565; found 544.96531; $[M + Na]^+$ 566.94759; found 566.94752.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(3,4,5-trifluorobenzoyl)-1H-pyrazole-5-carbohydrazide (10e)

White solid. M.p: 260–262; yield: 73%; ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H, N–H), 8.42 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.18 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.66 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.31–7.23 (m, 2H, benzene-H), 7.05 (s, 1H, pyrazole-H), 1.41 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −116.37, −132.12, −142.79; ^{13}C NMR (100 MHz, DMSO) δ 168.68, 156.82 (d, J = 245 Hz), 151.24 (d, J = 9.7 Hz) 148.08 (d, J = 245 Hz), 147.55, 139.95, 137.11, 128.11, 127.50, 127.46, 112.58, 112.36, 111.01, 100.00, 61.78, 27.61; HR-MS (ESI$^+$) m/z Calcd for $C_{20}H_{16}BrClF_3N_5O_2$, $[M + H]^+$ 530.02008; found 530.02013; $[M + Na]^+$ 552.00202, found 552.00243.

3-Bromo-N′-(4-bromo-3-methylbenzoyl)-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10f)

White solid. M.p: 262–263 °C; yield: 72%; ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H, N–H), 8.53–8.44 (m, 1H, Ar–H), 8.27–8.15 (m, 1H, Ar–H), 7.67 (dd, ^3J = 12.2 Hz, ^4J = 7.3 Hz, 1H, pyridine-H), 7.52–7.41 (m, 1H, Ar–H), 7.33 (s, 1H, Ar–H), 6.98 (s, 1H, pyrazole-H),

6.70 (d, ^3J = 16.0 Hz, 1H, Ar–H), 2.17 (s, 3H, CH_3), 1.44 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 171.28, 157.32, 147.98, 147.63, 140.04, 137.60, 133.14, 128.19, 127.96, 127.41, 127.20, 121.90, 110.79, 61.30, 27.76, 18.63; HR-MS (ESI$^+$) *m/z* Calcd for $C_{21}H_{20}Br_2ClN_5O_2$, $[M + H]^+$ 567.97450; found 567.97471.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(4-fluorobenzoyl)-1H-pyrazole-5-carbohydrazide (10g)

White solid, M.p: 256–257 °C; yield: 82%; ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H, N–H), 8.45 (dd, ^3J = 4.7 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 8.17 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 7.63 (dd, ^3J = 8.1 Hz,^4J = 4.7 Hz, 1H, pyridine-H), 7.46–7.37 (m, 2H, benzene-H), 7.19 (t, ^3J = 8.9 Hz, 2H, benzene-H), 6.90 (s, 1H, pyrazole-H), 1.41 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −110.71; ^{13}C NMR (100 MHz, DMSO) δ 170.98, 164.36, (d, $^1J_{C\text{-}F}$ = 246.7 Hz), 156.79, 148.08, 147.62, 139.95, 137.58, 133.68, 129.89, 129.81, 127.92, 127.33, 115.24 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 110.67, 61.31, 27.81; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{18}BrClFN_5O_2$, $[M + H]^+$ 494.03892, found 494.03852.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(2,3,4,5-tetrafluorobenzoyl)-1H-pyrazole-5-carbohydrazide (10h)

White solid, M.p: 185–187 °C; yield: 69%; ^{1}H NMR (400 MHz, DMSO) δ 11.24 (s, 1H, N–H), 8.44 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.20 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1H, pyridine-H), 7.68 (dd, ^3J = 8.1, ^4J = 4.7 Hz, 1H, pyridine-H), 7.19–7.11 (m, 1H, benzene-H), 7.09 (s, 1H, pyrazole-H), 1.43 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −138.96, −141.16, −154.38, −155.29; ^{13}C NMR (126 MHz, DMSO-D6) δ 164.54, 157.29, 148.20, 147.65, 147.47–147.17, 145.68–144.33, 143.11–142.51, 141.91–140.72, 140.05, 139.83–139.15, 136.84, 128.23, 127.61, 127.50, 110.55 (d, *J* = 20.3 Hz), 62.35, 27.65; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{15}BrClF_4N_5O_2$, $[M + H]^+$ 548.01065, found 548.01032.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(4-iodobenzoyl)-1H-pyrazole-5-carbohydrazide (10i)

White solid. M.p: 268–269 °C; yield: 76%; ^{1}H NMR (400 MHz, DMSO) δ 11.05 (s, 1H, N–H), 8.44 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.16 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.73 (d, ^3J = 8.4 Hz, 2H, benzene-H), 7.63 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.15 (d, ^3J = 8.4 Hz, 2H, benzene-H), 6.90 (s, 1H, pyrazole-H), 1.41 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 171.22, 156.79, 148.06, 147.60, 139.96, 137.53, 136.98, 136.73, 129.23, 127.94, 127.34, 110.75, 97.17, 61.39, 27.77; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{18}BrClIN_5O_2$, $[M + H]^+$ 601.94498, found 601.94452.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(2-(thiophen-2-yl)acetyl)-1H-pyrazole-5-carbohydrazide (10j)

White solid, M.p: 219–220 °C; yield: 72%; ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H, N–H), 8.50 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.27 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.39 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1H), 7.35 (s, 1H, pyrazole-H), 6.95 (dd, ^3J = 5.1 Hz, ^4J = 3.4 Hz, 1H), 6.83 (dd, ^3J = 3.4 Hz, ^4J = 1.0 Hz, 1H), 3.95 (d, ^3J = 17.3 Hz, 1H), 3.54 (dd, ^3J = 17.0, ^4J = 0.7 Hz, 1H), 1.34 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 171.06, 157.86, 148.30, 147.73, 140.27, 137.69, 136.94, 127.92, 127.62, 127.43, 127.07, 126.88, 125.73, 111.55, 61.25, 35.27, 27.79; HR-MS (ESI$^+$) *m/z* Calcd for $C_{19}H_{19}BrClN_5O_2S$, $[M + H]^+$ 496.02041, found 496.02063.

3-Bromo-N′-(4-bromo-5-fluoro-2-nitrobenzoyl)-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10k)

White solid. M.p: 126–127 °C yield: 68%; ^{1}H NMR (400 MHz, DMSO) δ 11.05 (s, 1H, N–H), 8.62 (d, ^3J = 5.9 Hz, 1H, benzene-H), 8.47 (d, ^3J = 4.5 Hz, 1H, pyridine-H), 8.20 (d, ^3J = 8.0 Hz, 1H, pyridine-H), 7.70 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.13 (d, ^3J = 8.0 Hz, 1H, benzene-H), 7.07 (s, 1H, pyrazole-H), 1.45 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −96.90; ^{13}C NMR (100 MHz, DMSO) δ 166.32, 162.91, 160.36, 157.54, 148.23, 147.67, 140.43, 140.00, 136.55, 135.52, 135.43, 130.60, 128.27, 127.58, 127.31, 115.64, 115.38, 111.63, 109.91, 109.68, 100.00, 61.87, 27.25; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{16}Br_2ClFN_6O_4$, $[M + H]^+$ 616.93451, found 616.93433; $[M + Na]^+$ 638.91464, found 638.91453.

N′-(4-(Benzyloxy)benzoyl)-3-bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10l)

White solid. M.p: 236–238 °C yield: 68%; ^{1}H NMR (400 MHz, DMSO) δ 10.99 (s, 1H, N–H), 8.43 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.15 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.62 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.46–7.31 (m, 7H, benzene-H), 7.00–6.93 (m, 2H, benzene-H), 6.91 (s, 1H, pyrazole-H), 5.12 (s, 2H, $-CH_2-$), 1.41 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 171.50, 159.95, 156.79, 148.13, 147.60, 139.93, 137.84, 137.21, 129.49, 129.44, 128.90, 128.38, 128.23, 127.89, 127.30, 127.27, 114.21, 110.61, 69.72, 61.11, 27.91; HR-MS (ESI$^+$) *m/z* Calcd for $C_{27}H_{25}BrClN_5O_3$, $[M + H]^+$ 582.09021, found 582.09052.

3-Bromo-N′-(tert-butyl)-N′-(4-chloro-3-fluorobenzoyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10m)

White solid. M.p: 269–270 °C; yield: 72%; ^{1}H NMR (400 MHz, DMSO) δ 11.12 (s, 1H, N–H), 8.44 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.16 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.64 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.57 (dd, ^3J = 7.2 Hz, ^4J = 1.9 Hz, 1H, benzene-H), 7.49–7.33 (m, 2H, benzene-H), 6.98 (s, 1H, pyrazole-H), 1.42 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −113.90;^{13}C NMR (100 MHz, DMSO) δ 169.60, 158.27 (d, $J_{C\text{-}F}$ = 249.5 Hz), 157.03, 156.69, 148.04, 147.62, 139.92, 137.36, 134.80, 134.76, 129.79, 128.49, 128.41, 127.99, 127.39, 119.40 (d, $J_{C\text{-}F}$ = 18.1 Hz), 119.31, 116.94 (d, $J_{C\text{-}F}$ = 21.4 Hz), 116.83, 110.81, 61.55, 40.60, 40.39, 40.19, 39.98, 39.77, 39.56, 39.35, 27.72; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{17}BrCl_2FN_5O_2$, $[M + H]^+$ 527.9995, found 528.0013; $[M + H]^+$ 549.98189, found 549.98161.

N′-(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl)-1-methyl-1H-pyrazole-3-carbohydrazide (10n)

White solid. M.p: 234–235 °C yield: 74%; ^{1}H NMR (400 MHz, DMSO) δ 11.17 (s, 1H, N–H), 8.46 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.64 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.37 (d, ^3J = 2.0 Hz, 1H, pyrazole-H), 7.07 (s, 1H, pyrazole-H), 6.44 (d, ^3J = 2.0 Hz, 1H, pyrazole-H), 3.69 (s, 3H), 1.42 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 164.05, 157.45, 148.12, 147.63, 139.98, 137.51, 137.27, 136.68, 127.92, 127.43, 127.29, 110.96, 106.38, 61.66, 38.07, 27.74; HR-MS (ESI$^+$) *m/z* Calcd for $C_{18}H_{19}BrClN_7O_2$, $[M + H]^+$ 480.05449, found 480.05432.

N′-(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl) nicotinohydrazide (10o)

White solid. M.p: 203–205 °C; yield: 81%; ^{1}H NMR (400 MHz, DMSO) δ 11.19 (s, 1H, N–H), 8.63–8.50 (m, 2H, pyridine-H), 8.47–8.39 (m, 1H, pyridine-H), 8.21–8.11 (m, 1H, pyridine-H), 7.74 (d, ^3J = 7.9 Hz, 1H, pyridine-H), 7.63 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.40 (dd, ^3J = 7.5 Hz, ^4J = 5.1 Hz, 1H, pyridine-H), 6.92 (s, 1H, pyrazole-H), 1.44 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 170.02, 156.86, 150.96, 147.99, 147.82, 147.65, 139.98, 137.33, 134.79, 133.04, 127.85, 127.34, 127.30, 123.45, 110.81, 61.56, 27.76; HR-MS (ESI$^+$) *m/z* Calcd for $C_{19}H_{18}BrClN_6O_2$, $[M + H]^+$ 477.04359, found 477.04385; $[M + Na]^+$ 499.02554, found 499.02576.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(3-(trifluoromethyl)benzoyl)-1H-pyrazole-5-carbohydrazide (10p)

White solid. M.p: 274–276 °C; yield: 67%; ^{1}H NMR (400 MHz, DMSO) δ 11.15 (s, 1H, N–H), 8.43 (dd, ^3J = 4.7 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 8.13 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 7.81–7.72 (m, 2H, benzene-H), 7.68–7.56 (m, 3H, benzene-H), 6.87 (s, 1H, pyrazole-H), 1.44 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −61.02; ^{13}C NMR (100 MHz, DMSO) δ 170.37, 156.69, 148.03, 147.62, 139.88, 138.10, 137.31, 131.42, 129.57, δ 128.88 (q, $J_{C\text{-}F}$ = 32.0 Hz), 128.40, 127.94, 127.34, 127.02 (q, $J_{C\text{-}F}$ = 7.6 Hz), 125.75, 124.40 (q, $J_{C\text{-}F}$ = 272.5 Hz),123.90 (q, $J_{C\text{-}F}$ = 7.6 Hz), 123.04, 110.68, 61.53, 27.73; HR-MS (ESI$^+$) *m/z* Calcd for $C_{21}H_{18}BrClF_3N_5O_2$, $[M + H]^+$ 544.03573, found 544.03551.

N′-(3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl)-2,6-dichloroisonicotinohydrazide (10q)

White solid. M.p: 235–236 °C; yield: 65%; ^{1}H NMR (400 MHz, DMSO) δ 11.15 (s, 1H, N–H), 8.46 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.18 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.42 (s, 2H, pyridine-H), 7.07 (s, 1H, pyrazole-H), 1.42 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 167.14, 156.91, 150.64, 149.55, 148.02, 147.74, 139.95, 136.82, 128.10, 127.50, 121.20, 111.26, 62.20, 27.50; HR-MS (ESI$^+$) *m/z* Calcd for $C_{19}H_{16}BrCl_3N_6O_2$, $[M + H]^+$ 544.96565, found 544.96541.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(2-(trifluoromethyl)benzoyl)-1H-pyrazole-5-carbohydrazide (10r)

White solid. M.p: 260–262 °C; yield: 74%; ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H, N–H), 8.52 (s, 1H, pyridine-H), 8.23 (s, 1H, pyridine-H), 7.80–7.65 (m, 2H, benzene-H + pyridine-H), 7.57 (d, ^3J = 6.6 Hz, 2H, benzene-H), 7.13 (s, 1H, pyrazole-H), 6.66 (s, 1H, benzene-H), 1.44 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 170.37, 156.69, 148.03, 147.62, 139.88, 138.10, 137.31, 131.42, 129.57, δ 128.88 (q, $J_{C\text{-}F}$ = 32.0 Hz), 128.40, 127.94, 127.34, 127.02 (q, $J_{C\text{-}F}$ = 7.6 Hz), 125.75, 124.40 (q, $J_{C\text{-}F}$ = 272.5 Hz),123.90 (q, $J_{C\text{-}F}$ = 7.6 Hz), 123.04, 110.68, 61.53, 27.73; HR-MS (ESI$^+$) *m/z* Calcd for $C_{21}H_{18}BrClF_3N_5O_2$, $[M + H]^+$ 544.03573, found 544.03557.

3-Bromo-N′-(5-bromo-2-fluorobenzoyl)-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10s)

White solid. M.p: 223–224 °C yield: 72%; ^{1}H NMR (400 MHz, DMSO) δ 11.14 (s, 1H, N–H), 8.47 (dd,

^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.65 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.62 (dd, ^3J = 9.4 Hz, ^4J = 1.8 Hz, 1H, Ar–H), 7.38 (dd, ^3J = 8.2 Hz, ^4J = 1.8 Hz, 1H, Ar–H), 7.11 (t, ^3J = 7.8 Hz, 1H, Ar–H), 6.92 (s, 1H, pyrazole-H), 1.42 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 166.85, 157.95 (d, $J_{C\text{-}F}$ = 251.7 Hz) 157.14, 148.06, 147.64, 140.01, 137.21, 130.03 127.97, 127.78, 127.42, 127.31, 125.14 (d, $J_{C\text{-}F}$ = 17.4 Hz), 123.17 (d, $J_{C\text{-}F}$ = 9.4 Hz), 119.41 (d, $J_{C\text{-}F}$ = 25.0 Hz) 111.01, 61.80, 27.69; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{17}Br_2ClFN_5O_2$, $[M + H]^+$ 571.94943, found 571.94928, $[M + Na]^+$ 593.93138, found 593.93181.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(furan-3-carbonyl)-1H-pyrazole-5-carbohydrazide (10t)

White solid. M.p: 221–223 °C yield: 73%; ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H, N–H), 8.45 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.96 (dd, ^3J = 1.5 Hz, ^4J = 0.8 Hz, 1H, furan-H), 7.67–7.65 (m, 1H, Furan-H), 7.63 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.31 (s, 1H, pyrazole-H), 6.65 (dd, ^3J = 1.9 Hz, ^4J = 0.8 Hz, 1H, furan-H), 1.39 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 164.93, 157.48, 148.39, 147.62, 145.52, 143.52, 139.97, 137.53, 128.06, 127.61, 127.36, 122.44, 110.99, 61.47, 27.92; HR-MS (ESI$^+$) *m/z* Calcd for $C_{18}H_{17}BrClN_5O_3$, $[M + H]^+$ 466.02761, found 466.02732, $[M + Na]^+$ 488.00955, found 488.00913.

N′-(3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbonyl)-N-(tert-butyl)-4-(trifluoromethyl)nicotinohydrazide (10u)

White solid. M.p: 187–189 °C; yield: 70%; ^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H, N–H), 8.84 (d, ^3J = 5.1 Hz, 1H, pyridine-H), 8.50 (s, 1H, pyridine-H), 8.21 (d, ^3J = 7.7 Hz, 1H, pyridine-H), 7.80 (d, ^3J = 5.1 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 7.9 Hz, ^3J = 4.7 Hz, 1H, pyridine-H), 6.84 (s, 1H, pyrazole-H), 1.45 (s, 9H, $3CH_3$); ^{19}F NMR (471 MHz, DMSO-D6) δ −60.17; ^{13}C NMR (100 MHz, DMSO) δ 170.83, 167.31, 151.50, 147.93, 147.76, 140.13, 137.06, 129.88, 127.87, 127.38, 127.28, 120.75, 111.24, 62.12, 27.34; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{17}BrClF_3N_6O_2$, $[M + H]^+$ 545.03098, found 545.03062.

3-Bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-N′-(3,4-dichlorobenzoyl)-1H-pyrazole-5-carbohydrazide (10v)

White solid. M.p: 228–225 °C; yield: 71%; ^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1H, N–H), 8.36 (dd, J = 4.7, 1.5 Hz, 1H, pyridine-H), 8.08 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.58 (dd, ^3J = 3.4 Hz, ^4J = 1.3 Hz, 1H, Ar–H), 7.56 (dd, ^3J = 3.2 Hz, ^4J = 1.4 Hz, 1H, Ar–H), 7.51 (d, ^4J = 2.0 Hz, 1H, Ar–H), 7.29 (d, ^4J = 1.1 Hz, 1H, Ar–H), 7.26 (dd, ^3J = 8.3, ^4J = 2.0 Hz, 1H, Ar–H), 6.91 (s, 1H, pyrazole-H), 1.34 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 169.54, 156.69, 148.02, 147.61, 139.92, 137.56, 137.30, 132.93, 131.05, 130.64, 129.32, 128.13, 128.00, 127.55, 127.40, 127.12, 110.86, 61.63, 27.69; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{17}BrCl_3N_5O_2$, $[M + H]^+$ 543.97040, found 543.97081, $[M + Na]^+$ 565.95234, found 565.95271.

N′-Benzoyl-3-bromo-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10w)

White solid. M.p: 269–270 °C; yield: 78%; ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H, N–H), 8.45 (dd, ^3J = 4.7 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 8.17 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, pyridine-H), 7.63 (dd, ^3J = 8.1, ^4J = 4.7 Hz, 1H, pyridine-H), 7.42–7.34 (m, 5H, benzene-H), 6.79 (s, 1H, pyrazole-H), 1.43 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO) δ 181.36, 172.00, 156.91, 148.08, 147.62, 139.98, 137.72, 137.38, 130.11, 128.13, 127.90, 127.29, 127.21, 127.12, 110.58, 61.17, 27.83; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{19}BrClN_5O_2$, $[M + H]^+$ 476.04834, found 476.04871, $[M + Na]^+$ 498.03029, found 498.03072.

3-Bromo-N′-(2-bromo-5-chlorobenzoyl)-N′-(tert-butyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbohydrazide (10x)

White solid. M.p: 208–210 °C; yield: 72%; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H, N–H), 8.52 (d, ^3J = 3.9 Hz, 1H, benzene-H), 8.21 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, pyridine-H), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 4.7 Hz, 1H, pyridine-H), 7.56 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H, pyridine-H), 7.42 (d, ^3J = 8.5 Hz, 1H, benzene-H), 6.90 (s, 1H, pyrazole-H), 1.45 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, DMSO) δ 167.44, 157.30, 148.15, 147.75, 140.01, 137.04, 133.41, 131.50, 129.59, 128.21, 127.40, 127.22, 119.95, 111.11, 56.51, 27.56; HR-MS (ESI$^+$) *m/z* Calcd for $C_{20}H_{17}Br_2Cl_2N_5O_2$, $[M + H]^+$ 587.91988, found 587.91951.

Biological assay

All bioassays were conducted on test organisms reared in the lab and repeated at 25 ± 1 °C according to statistical requirements. Mortalities were corrected using Abbott's formula [37]. Evaluations were based on a percentage scale (0 = no activity and 100 = complete eradication), at intervals of 5%.

Insecticidal activity against H. armigera

The insecticidal activities of some of the synthesised compounds and avermectins against *Helicoverpa armigera* were evaluated by the diet-incorporated method [33]. A quantity of 3 mL of prepared solutions containing the compounds was added to the forage (27 g), subsequently

diluted to different concentrations and then placed in a 24-pore plate. One larva was placed in each of the wells on the plate. Mortalities were determined after 72–96 h.

Insecticidal activity against P. xylostella

The insecticidal activities of compounds **10a**–**10y** against third instar larvae of *P. xylostella* were evaluated according to a previously reported procedure [33–35]. Fresh cabbage discs (diameter: 2 cm) were dipped into the prepared solutions containing compounds **10a**–**10y** for 10 s, air-dried, and then placed in a Petri dish (diameter: 9 cm) lined with filter paper. Then, ten third instar larvae of *P. xylostella* were carefully transferred to the Petri dish. Each assay was conducted in triplicate. Mortality was calculated 72 h after treatment. The control groups were treated with distilled water containing TW-80 (0.1 mL/L). Commercial insecticides (i.e., chlorantraniliprole, chlorpyrifos, and avermectins) were tested and compared under the same conditions.

Conclusions

Twenty-four novel 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbohydrazide derivatives (**10a**–**10x**) were designed and synthesized based on combinating the sub-structures of chlorantraniliprole and diacylhydrazines. These compounds were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, HR-MS. A preliminary evaluation of the insecticidal activities of the synthesized compounds was conducted. Most compounds exhibited good insecticidal activity against *Helicoverpa armigera* and *P. xylostella*. In particular, the LC_{50} values of compounds **10e**, **10g**, **10h**, **10j** and **10x** were 86.98, 27.49, 23.67, 69.07, and 28.90 mg L^{-1}, respectively. Notably, compounds **10g**, **10h**, and **10x** showed much higher insecticidal activity than that of tebufenozide (LC_{50} = 37.77 mg L^{-1}). Preliminary SAR analysis indicated that phenyl, 4-fluoro phenyl and four fluorophenyl had positive influence on the insecticidal activity of synthesized compounds, and introduction of a heterocyclic ring (pyridine and pyrazole) could decrease their insecticidal effects. Further structural modification and biological evaluation to explore the full potential of this kind of 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbohydrazide derivatives are currently underway.

Additional file

Additional file 1. All the copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR for the title compounds were presented in Additional information.

Authors' contributions

The current study is an outcome of constructive discussion with JW. YYW, FZX, ALD and ZQL carry out their synthesis and characterization experiments; GY, JS and CHL performed the insecticidal activities; JHX and FHW carried out the ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectral analyses; FZX carried out the HR-MS. JW was also involved in the drafting of the manuscript and revising the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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