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Design, Synthesis, and Insecticidal Activity of Novel Diacylhydrazine Derivatives Containing an Isoxazole Carboxamide or a Pyridine Carboxamide Moiety

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Abstract—In this study, two series of novel diacylhydrazine derivatives containing an isoxazole carboxamide or a pyridine carboxamide moiety have been synthesized and their structures confirmed by ^{1}H and ^{13}C NMR, and mass spectra. According to bioassay data LC_{50} values for the product 3-(2-chlorophenyl)-*N*-{2-[2-(2,6-difluorobenzoyl)-hydrazinecarbonyl]-4-fluorophenyl}-5-methylisoxazole-4-carboxamide (**5f**) against *Plutella xylostella* (*P. xylostella*) and *Empoasca vitis* (*E. vitis*) have been determined to be 1.67 and 1.29 mg/L, respectively, that were higher than those of spinosad, chlorpyrifos, beta cypermethrin, and azadirachtin.

Keywords: insecticidal activity, diacylhydrazine, isoxazole carboxamide, pyridine carboxamide

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INTRODUCTION

Over recent years, the damage to cruciferous plants such as cabbage, broccoli, broccoli, brussels sprouts, and radishes, and tea leaves caused by *P. xylostella* and *E. vitis*, respectively have become more and more serious and caused huge economic losses every year [1, 2]. The insecticides abuse has led to the resistance of *P. xylostella* and *E. vitis* to most of those [2–5]. Therefore, development of new insecticides for controlling *P. xylostella* and *E. vitis* is of considerable importance.

Diacylhydrazine derivatives have been used efficiently in synthesis of various new pesticides such as tebufenozide, halofenozide, methoxyfenozide, and chromafenozide [6–10]. Isoxazole carboxamide or pyridine carboxamide derivatives also demonstrated high efficiency in the synthesis of new pesticide characterized by broad activity [11–16]. Earlier our group had reported a series of isoxazole carboxamide or pyridine carboxamide derivatives (Fig. 1) with potent antiviral and insecticidal activities [13–16].

In this study, in search of "me-better" active molecules, we replaced the carboxamide or acylhydrazone by diacylhydrazine, as shown in Fig. 2, to design and synthesize two series of novel diacylhydrazine derivatives containing the isoxazole carboxamide or pyridine carboxamide moiety. To the best of our knowledge, it is the first report on diacylhydrazine derivatives containing an isoxazole carboxamide or a pyridine carboxamide moiety with potent insecticidal activities against *P. xylostella* and *E. vitis*.

RESULTS AND DISCUSSION

Intermediates **2**–**4** and **7**–**9** were prepared according to the previously reported methods [13–16] from 3-(2-chlorophenyl)-5-methylisoxazole-4-carbonyl chloride (**1**) and 5-bromonicotinoyl chloride (**6**) (Schemes 1 and 2). The compounds **5a**–**5f** and **10a**–**10i** were synthesized with yields of 70–90%, and their structures were confirmed by ^{1}H and ^{13}C NMR, and mass spectra.

The groups –CONH– and –CONHNHCO– were recorded in the ^{1}H NMR spectra of compounds **5a**–**5f**

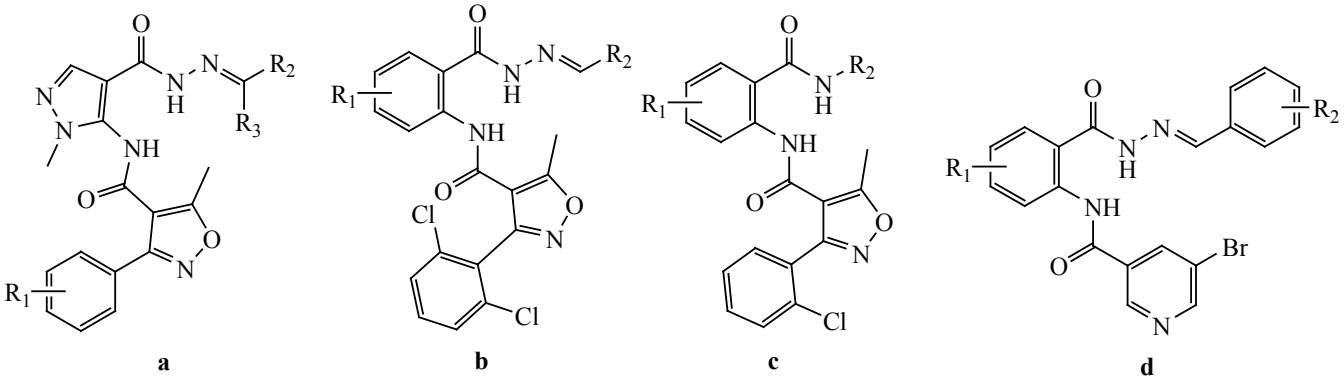


Fig. 1. Previously reported compounds with potent antiviral and insecticidal activity.

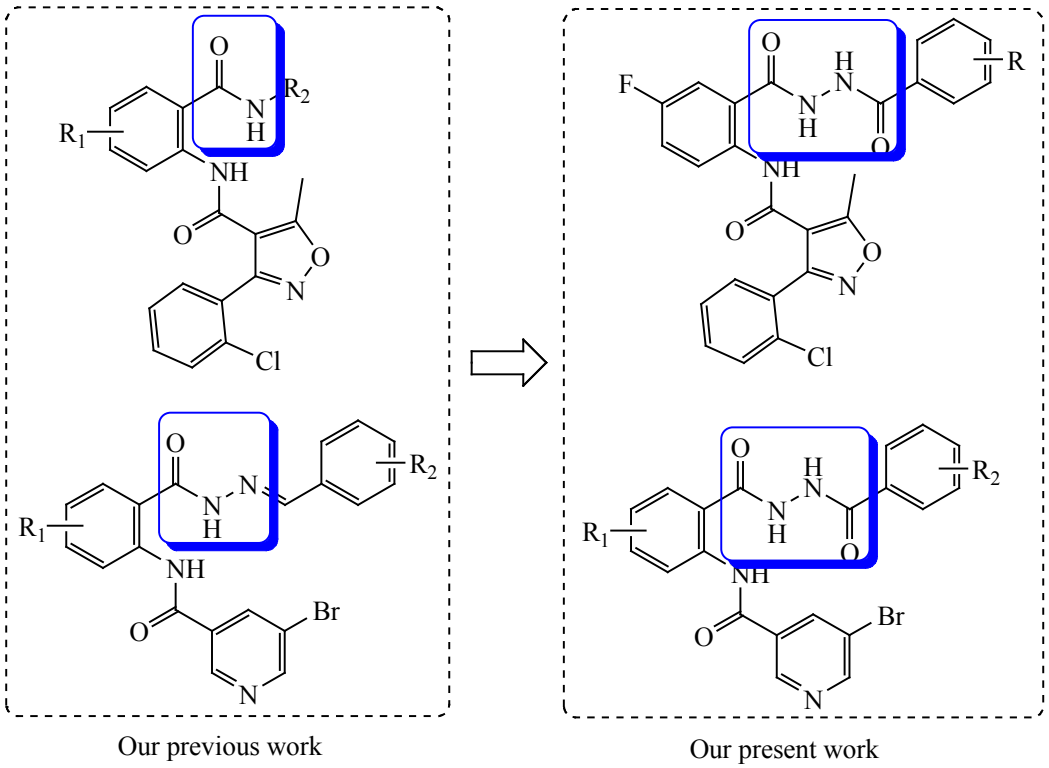
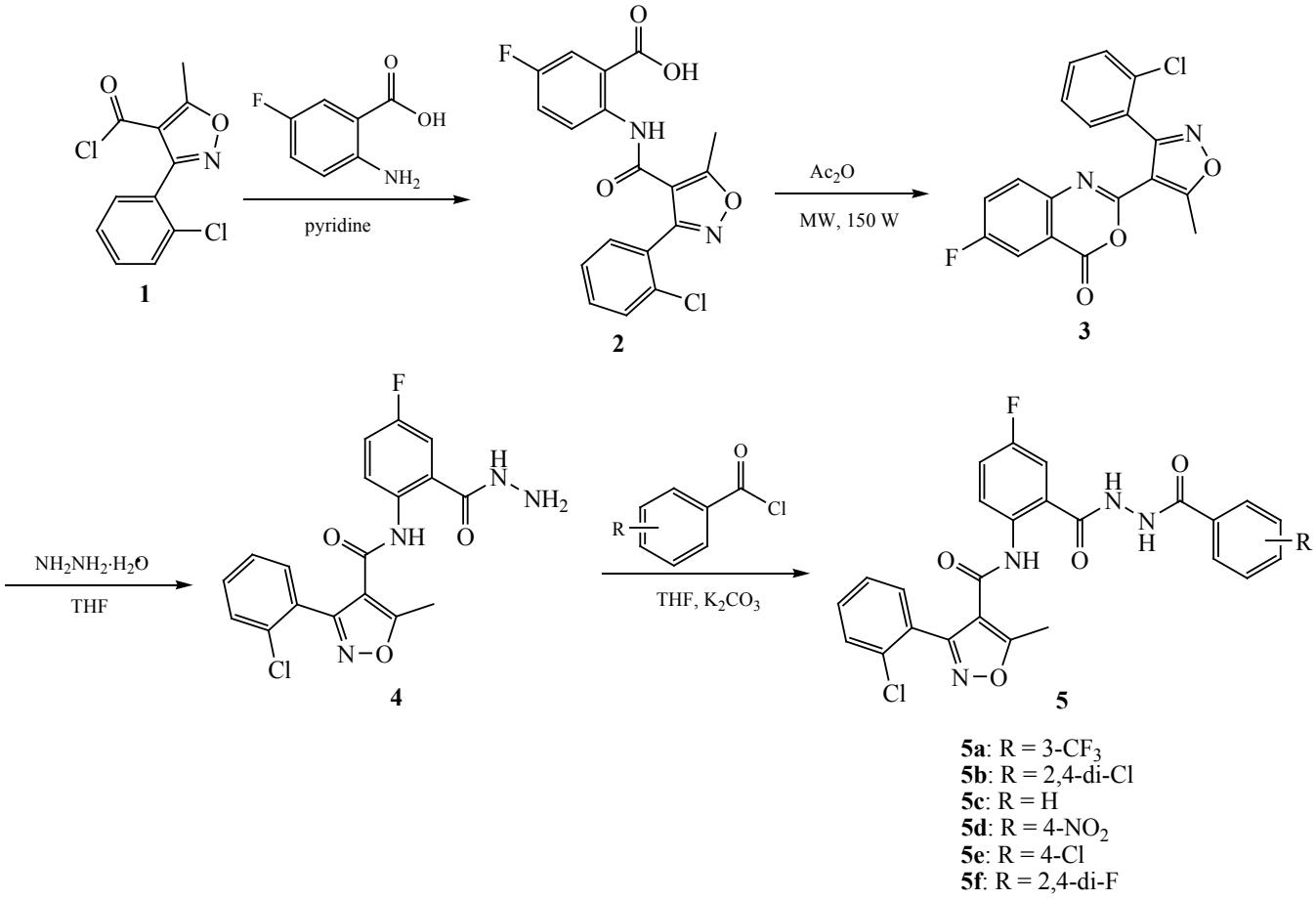


Fig. 2. Designed approach to the target compounds.

and **10a**–**10i** by signals in the range of 9.08–10.98 ppm. A singlet at 171.27–174.38 ppm and three singlets at 153.17–166.79 ppm in their ^{13}C NMR spectra indicated the presence of isoxazole ring and C=O, respectively.

Biological evaluation. The preliminary bioassay results listed in Table 1 showed that the target compounds **5a**, **5b**, **5e**, **5f**, **10g**, **10h**, and **10i** exhibited high insecticidal activity (100%) against *P. xylostella* and *E. vitis* at 500 mg/L after 72 h. The determined LC_{50} values of compounds **5a**–**5f** and **10a**–**10i** based on the preliminary bioassay (Table 2) indicated that the products exhibited moderate to good insecticidal activity against *P. xylostella* and *E. vitis*. The compound 3-(2-chlorophenyl)-*N*-{2-[2-(2,6-difluorobenzoyl)hydrazinecarbonyl]-4-fluorophenyl}-5-methylisoxazole-4-carboxamide (**5f**) exhibited the highest insecticidal activity against *P. xylostella* and *E. vitis* with LC_{50} values of 1.67 and

Scheme 1. Synthetic pathway to the target compounds **5a**–**5f**.



1.29 mg/L, respectively, that were superior to those of the standards. The results indicated that the series of diacylhydrazine derivatives containing an isoxazole carboxamide or pyridine carboxamide moiety could be used in development of potential agrochemicals for controlling *P. xylostella* and *E. vitis*.

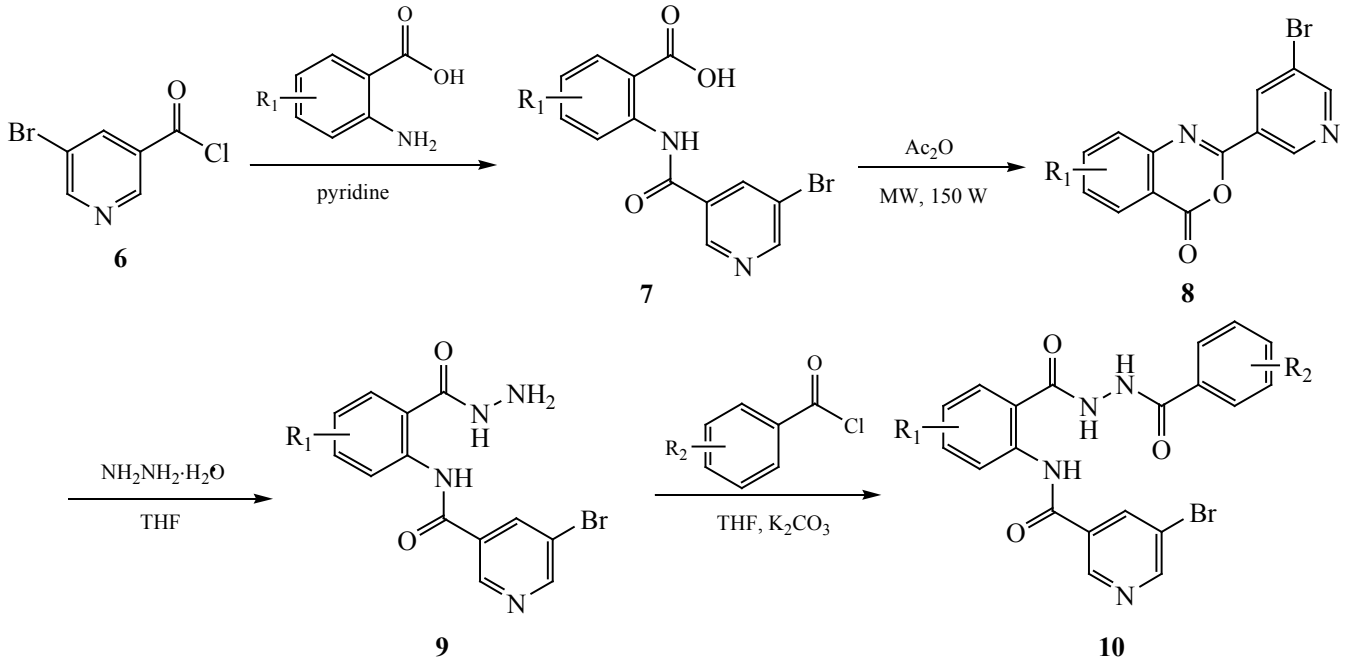
EXPERIMENTAL

The uncorrected melting points were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., Beijing, China). ^{1}H and ^{13}C NMR spectra were measured on a JEOL ECX 500 NMR (JEOL, Tokyo, Japan) spectrometer using DMSO-d_6 as a solvent. Elemental analysis was carried out on an Elemental Vario-III CHN analyzer (Elementar, Hanau, German). Mass spectra were measured on an Agilent mass spectrometer, model 5973, Agilent Technologies (Palo Alto, Canada). Microwave experiments were carried out in a 300 W CEM Discover Labmate Microwave Reactor (Matthews, NC, USA).

Preparation of intermediates 2–4 and 7–9. Intermediates **2**–**4** and **7**–**9** were prepared according to the previously reported methods [13–16]. As showed in Schemes 1 and 2, 3-(2-chlorophenyl)-5-methylisoxazole-4-carbonyl chloride **1** or 5-bromonicotinoyl chloride **6** (0.02 mol) was added dropwise to a solution of substituted 2-aminobenzoic acid (0.02 mol) in anhydrous pyridine (100 mL), and the reaction mixture was stirred for 2 h, then it was poured into a cool 5% HCl solution (200 mL). The residues were filtered, dried and crystallized from ethanol to give the corresponding intermediate **2** or **7**.

2-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxamido]-5-fluorobenzoic acid (**2**). White solid, yield 86%, mp 229–231°C. ^{1}H NMR spectrum, δ, ppm: 2.77 s (3H, CH_3), 7.34–7.67 m (7H, Ar-H), 8.45 s (1H, isoxazole-CONH), 11.56 s (1H, COOH).

Scheme 2. Synthetic approach to the target compounds **10a**–**10i.**



10a: R_1 = 3-CH_3, R_2 = 3-CF_3
10b: R_1 = 3-CH_3, R_2 = 2-Cl^{-4}-F
10c: R_1 = 3-CH_3, R_2 = 2,4-di-F
10d: R_1 = 3-CH_3, R_2 = 2-CF_3
10e: R_1 = 3-CH_3, R_2 = 2-CH_3
10f: R_1 = 3-CH_3, R_2 = 2-OCH_3
10g: R_1 = 5-Cl^{-3}-CH_3, R_2 = 3-CF_3
10h: R_1 = 5-Cl^{-3}-CH_3, R_2 = 2,4-di-F
10i: R_1 = 5-Cl^{-3}-CH_3, R_2 = 2,6-di-F

2-(5-Bromonicotinamido)-3-methylbenzoic acid (7). White solid, mp 269–271°C, yield 87%. ^{1}H NMR spectrum, δ, ppm: 2.89 s (3H, CH_3), 7.24–7.87 m (3H, Ar-H), 8.64 s (1H, pyridine-H), 8.78 s (1H, pyridine-H), 8.95 s (1H, pyridine-H), 9.06 s (1H, pyridine-CONH), 11.56 s (1H, Ar-COOH). An intermediate **2** or **7** (0.02 mmol) and acetic anhydride (150 mL) were added to a 250 mL round-bottom flask which was sealed and placed in a synthesizer irradiated at 145°C and 150 W for 10 min. Upon completion of the reaction, the residue was filtered off, washed with water, dried, and crystallized from anhydrous ethanol to give the corresponding compound **3** or **8**.

2-[3-(2-Chlorophenyl)-5-methylisoxazol-4-yl]-6-fluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (3). White solid, yield 90%, mp 148–149°C. ^{1}H NMR spectrum, δ, ppm: 2.91 s (3H, CH_3), 7.42–7.64 m (5H, Ar-H), 7.76–7.85 m (2H, Ar-H).

2-(5-Bromopyridin-3-yl)-8-methyl-4*H*-benzo[*d*]-[1,3]oxazin-4-one (8). White solid, mp 267–268°C, yield 93%. ^{1}H NMR spectrum, δ, ppm: 2.91 s (3H, CH_3), 7.38 d. d (1H, J = 2.25, 4.50 Hz, Ar-H), 7.52 t (1H, J = 14.30 Hz, Ar-H), 7.57 s (1H, Ar-H), 7.64 s (1H, pyridine-H), 7.93 d (1H, J = 8.60 Hz, pyridine-H), 8.04 s (1H, pyridine-H). To a solution of an intermediate **3** or **8** (0.02 mol) in THF (100 mL), 80% hydrazine hydrate (6 mL) was added, and the reaction mixture was reacted at room temperature for 2 h. Then the residue was filtered off, washed with water, anhydrous ethanol and crystallized from ethanol to give the corresponding intermediate **4** or **9**.

3-(2-Chlorophenyl)-*N*-[4-fluoro-2-(hydrazine-carbonyl)phenyl]-5-methylisoxazole-4-carboxamide (4). White solid, yield 91%, mp 186–188°C. ^{1}H NMR spectrum, δ, ppm: 2.77 s (3H, CH_3), 4.51 s (2H, NH_2), 7.35–7.60 m (6H, Ar-H), 8.35 q (1H, J = 14.30 Hz, Ar-H), 10.07 s (1H, Ar-CONH), 11.22 s (1H, isoxazole-CONH).

Table 1. Insecticidal activities of the target compounds **5a**–**5f** and **10a**–**i** against *P. xylostella* and *E. vitis* at 500 mg/L

Compound	Insecticidal activity, %	
	P. xylostella	*E. vitis*
5a	100.00 ± 1.59	100.00 ± 1.66
5b	100.00 ± 1.62	100.00 ± 1.58
5c	83.33 ± 1.05	83.33 ± 1.13
5d	66.67 ± 1.08	76.67 ± 1.15
5e	100.00 ± 1.01	100.00 ± 1.26
5f	100.00 ± 1.48	100.00 ± 1.61
10a	83.33 ± 1.26	90.00 ± 1.43
10b	70.00 ± 1.26	80.00 ± 1.38
10c	76.67 ± 1.31	83.33 ± 1.45
10d	80.00 ± 109	86.67 ± 1.16
10e	60.00 ± 1.17	63.33 ± 1.09
10f	50.00 ± 1.13	53.33 ± 1.06
10g	100.00 ± 1.76	100.00 ± 1.65
10h	100.00 ± 1.82	100.00 ± 1.86
10i	100.00 ± 1.68	100.00 ± 1.59
Chlorpyrifos	100.00 ± 1.46	100.00 ± 1.68
beta Cypermethrin	100.00 ± 1.42	100.00 ± 1.54
Spinosad	100.00 ± 1.36	100.00 ± 1.47
Azadirachtin	100.00 ± 1.29	100.00 ± 1.32

Table 2. The LC_{50} values of the products **5a**–**5f** and **10a**–**10i** against *P. xylostella* and *E. vitis*

Compound	LC_{50}, mg/L	
	P. xylostella	*E. vitis*
5a	1.75 ± 0.54	1.40 ± 0.43
5b	6.81 ± 0.97	5.39 ± 0.96
5c	41.65 ± 4.72	37.76 ± 4.25
5d	81.40 ± 5.69	65.62 ± 4.67
5e	2.52 ± 0.67	1.78 ± 0.65
5f	1.67 ± 0.55	1.29 ± 0.48
10a	44.42 ± 3.58	35.35 ± 3.67
10b	77.50 ± 6.76	61.94 ± 4.89
10c	59.18 ± 5.85	37.76 ± 3.21
10d	52.05 ± 5.32	52.79 ± 4.73
10e	132.50 ± 6.88	101.52 ± 6.87
10f	244.98 ± 6.97	210.41 ± 6.88
10g	2.26 ± 0.73	2.23 ± 0.69
10h	2.92 ± 0.87	2.53 ± 0.65
10i	3.86 ± 0.98	3.42 ± 0.74
Chlorpyrifos	7.71 ± 0.65	6.25 ± 0.72
beta Cypermethrin	12.77 ± 1.08	4.67 ± 0.52
Spinosad	4.88 ± 0.46	7.93 ± 0.74
Azadirachtin	10.22 ± 1.12	14.34 ± 1.21

5-Bromo-*N*-[2-(hydrazinecarbonyl)-3-methylphenyl]nicotinamide (9). White solid, mp 248–249°C, yield 94%. ^{1}H NMR spectrum, δ, ppm: 2.91 s (3H, CH_3), 4.87 s (2H, NH_2), 7.33 d. d (1H, J = 1.70), 2.85 Hz, Ar-H), 7.84 d (1H, J = 8.60 Hz, Ar-H), 8.45 t (1H, J = 4.55 Hz, Ar-H), 8.64 d (1H, J = 1.75 Hz, pyridine-H), 8.98 d (1H, J = 2.30 Hz, pyridine-H), 9.07 d (1H, J = 1.70 Hz, pyridine-H), 10.30 s (1H, Ar-CONH), 12.79 s (1H, pyridine-CONH).

Synthesis of compounds 5a–5f and 10a–10i. To the desired intermediate **4** or **9** (1 mmol), anhydrous THF (10 mL) and anhydrous potassium carbonate (1.5 mmol) were added. Then substituted benzoyl chloride (1 mmol) was added dropwise to the reaction mixture, and it was stirred for 4 h. Upon completion of the process, the mixture was poured into 50 mL of water, the residue was filtered off and recrystallized from anhydrous ethanol to give the corresponding compounds **5a**–**5f** and **10a**–**10i** as white solids.

3-(2-Chlorophenyl)-*N*-(4-fluoro-2-{2-[3-(trifluoromethyl)benzoyl]hydrazinecarbonyl}phenyl)-5-methylisoxazole-4-carboxamide (5a). mp 147–148°C, yield 85%. ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 7.22–7.26 m (2H, Ar-H), 7.44–7.64 m (8H, Ar-H), 8.25 q (1H, J = 14.30 Hz, Ar-H), 10.83 s (1H, Ar-CONH), 10.85 s (1H, Ar-CONH), 10.97 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 12.46, 112.08, 112.27, 113.12, 113.78, 115.06, 119.47, 122.22, 124.02, 127.33, 127.51, 129.70, 131.64, 131.74, 132.59, 132.71, 134.62, 156.52, 158.18, 158.44, 159.08, 160.04, 160.22, 165.81, 171.82. Found, %: C 55.95, H 3.42, N 10.26. $C_{26}H_{17}ClF_4N_4O_4$. Calculated, %: C 55.68, H 3.05, N 9.99. MS: *m/z*: 561.7 $[M + H]^+$.

3-(2-Chlorophenyl)-*N*-{2-[2-(2,4-dichlorobenzoyl)-hydrazinecarbonyl]-4-fluorophenyl}-5-methylisoxazole-4-carboxamide (5b). mp 265–267°C, yield 88%. ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 7.46–7.65 m (8H, Ar-H), 7.79 s (1H, Ar-H), 8.29 q (1H, J = 14.30 Hz, Ar-H), 10.62 s (1H, Ar-CONH), 10.90 s (1H, Ar-CONH), 10.94 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 13.00, 114.14, 115.29, 119.83, 122.37, 124.36, 127.69, 127.99, 128.10, 130.10, 130.19, 131.31, 132.17, 132.26, 133.04, 133.65, 135.18, 136.03, 156.91, 158.84, 159.54, 160.36, 165.29, 166.54, 171.55.

Found, %: C 53.67, H 2.83, N 10.25. $C_{25}H_{16}Cl_3FN_4O_4$. Calculated, %: C 53.45, H 2.87, N 9.97. MS: *m/z*: 562.7 $[M + H]^+$.

3-(2-Chlorophenyl)-*N*-[2-(2-benzoylhydrazinecarbonyl)-4-fluorophenyl]-5-methylisoxazole-4-carboxamide (5c). mp 153–155°C, yield 76%. ^{1}H NMR spectrum, δ, ppm: 2.71 s (3H, CH_3), 7.39–7.54 m (5H, Ar-H), 7.61–7.64 d. d (1H, *J*= 2.85, 5.70 Hz, Ar-H), 8.12 s (1H, Ar-H), 8.13 s (1H, Ar-H), 8.21–8.24 q (1H, *J* = 14.30 Hz, Ar-H), 8.37 s (2H, Ar-H), 8.39 s (1H, Ar-H), 10.78 s (1H, Ar-CONH), 10.87 s (1H, Ar-CONH), 10.96 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 13.81, 109.50, 113.83, 114.02, 118.45, 118.52, 125.43, 125.62, 127.74, 127.79, 128.33, 129.78, 129.84, 129.90, 131.88, 131.96, 132.18, 133.36, 143.26, 151.24, 157.81, 157.84, 160.26, 162.24, 174.38. Found, %: C 60.99, H 3.70, N 11.48. $C_{25}H_{18}ClFN_4O_4$. Calculated, %: C 60.92, H 3.68, N 11.37. MS: *m/z*: 493.8 $[M + H]^+$.

3-(2-Chlorophenyl)-*N*-{4-fluoro-2-[2-(4-nitrobenzoyl)hydrazinecarbonyl]phenyl}-5-methylisoxazole-4-carboxamide (5d). mp 266–268°C, yield 87%. ^{1}H NMR spectrum, δ, ppm: 2.74 s (3H, CH_3), 7.42–7.56 m (5H, Ar-H), 7.66 d. d (1H, *J* = 2.85, 5.70 Hz, Ar-H), 8.14 s (1H, Ar-H), 8.16 s (1H, Ar-H), 8.27 q (1H, *J* = 14.30 Hz, Ar-H), 8.39 s (1H, Ar-H), 8.41 s (1H, Ar-H), 10.81 s (1H, Ar-CONH), 10.90 s (1H, Ar-CONH), 10.98 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 12.94, 114.13, 115.25, 115.45, 119.81, 119.97, 122.71, 124.39, 127.68, 127.96, 129.62, 130.17, 132.14, 132.23, 133.03, 135.07, 138.28, 150.07, 156.98, 158.91, 159.60, 160.31, 164.74, 166.69, 171.52. Found, %: C 55.87, H 3.34, N 13.40. $C_{25}H_{17}ClFN_5O_6$. Calculated, %: C 55.82, H 3.19, N 13.02. MS: *m/z*: 538.8 $[M + H]^+$.

3-(2-Chlorophenyl)-*N*-{2-[2-(4-chlorobenzoyl)-hydrazinecarbonyl]-4-fluorophenyl}-5-methylisoxazole-4-carboxamide (5e). mp 255–257°C, yield 84%. ^{1}H NMR spectrum, δ, ppm: 2.73 s (3H, CH_3), 7.41–7.65 m (8H, Ar-H), 7.93 s (1H, Ar-H), 7.95 s (1H, Ar-H), 8.27 q (1H, *J* = 14.30 Hz, Ar-H), 10.73 s (1H, Ar-CONH), 10.80 s (1H, Ar-CONH), 10.82 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 12.93, 114.15, 115.38, 119.71, 119.90, 122.74, 124.39, 127.70, 127.95, 129.30, 129.99, 130.16, 131.40, 132.12, 132.22, 133.03, 135.08, 137.50, 156.95, 158.88, 159.58, 160.33, 165.26, 166.79, 171.46. Found, %: C 56.97, H 3.36, N 10.75. $C_{25}H_{17}Cl_2FN_4O_4$. Calculated, %: C 56.94, H 3.25, N 10.62. MS: *m/z*: 528.2 $[M + H]^+$.

3-(2-Chlorophenyl)-*N*-{2-[2-(2,6-difluorobenzoyl)-hydrazinecarbonyl]-4-fluorophenyl}-5-methylisoxazole-4-carboxamide (5f). mp 236–237°C, yield 87%. ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 7.27 t (2H, *J* = 15.45 Hz, Ar-H), 7.45–7.65 m (7H, Ar-H), 8.25 q (1H, *J* = 13.75 Hz, Ar-H), 10.84 s (1H, Ar-CONH), 10.86 s (1H, Ar-CONH), 10.97 s (1H, isoxazole-CONH). ^{13}C NMR spectrum, δ_C, ppm: 12.91, 112.53, 112.72, 113.57, 114.23, 115.52, 119.92, 122.67, 124.47, 127.78, 127.96, 130.15, 132.09, 132.19, 133.04, 133.16, 135.07, 156.97, 158.63, 158.90, 159.54, 160.49, 160.67, 166.26, 171.27. Found, %: C 56.87, H 3.42, N 10.58. $C_{25}H_{16}ClF_3N_4O_4$. Calculated, %: C 56.78, H 3.05, N 10.59. MS: *m/z*: 529.8 $[M + H]^+$.

5-Bromo-*N*-(2-methyl-6-{2-[3-(trifluoromethyl)-benzoyl]hydrazinecarbonyl}phenyl)nicotinamide (10a). mp 234–236°C, yield 82%. ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 7.44 t (1H, *J* = 15.50 Hz, Ar-H), 7.53–7.83 m (5H, Ar-H), 7.87 d. d (1H, *J* = 8.05 Hz, Ar-H), 8.59 s (1H, pyridine-H), 8.94 s (1H, pyridine-H), 8.95 s (1H, pyridine-H), 9.13 s (1H, Ar-CONH), 10.36 s (1H, Ar-CONH), 10.51 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.58, 120.55, 123.39, 124.56, 126.76, 127.34, 128.77, 129.84, 130.37, 132.06, 132.32, 133.02, 133.18, 134.19, 134.49, 137.14, 138.44, 147.96, 153.19, 163.21, 164.31, 166.77. Found, %: C 50.85, H 3.34, N 10.92. $C_{22}H_{16}BrF_3N_4O_3$. Calculated, %: C 50.69, H 3.09, N 10.75. MS: *m/z*: 528.2 $[M + H]^+$.

5-Bromo-*N*-{2-[2-(2-chloro-4-fluorobenzoyl)-hydrazinecarbonyl]-6-methylphenyl}nicotinamide (10b). mp 242–244°C, yield 75.4%. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 7.31–7.57 m (6H, Ar-H), 8.56 s (1H, pyridine-H), 8.90–8.94 m (2H, pyridine-H), 9.10 s (1H, Ar-CONH), 10.46 s (2H, pyridine-CONH, Ar-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.58, 114.82, 114.99, 115.09, 117.79, 117.98, 120.56, 126.89, 127.32, 131.73, 131.80, 132.29, 132.49, 132.57, 133.03, 137.15, 138.40, 148.00, 153.16, 161.93, 163.20, 166.66. Found, %: C 49.98, H 3.15, N 11.24. $C_{21}H_{15}BrClFN_4O_3$. Calculated, %: C 49.87, H 2.99, N 11.08. MS: *m/z*: 506.6 $[M + H]^+$.

5-Bromo-*N*-{2-[2-(2,4-difluorobenzoyl)hydrazinecarbonyl]-6-methylphenyl}nicotinamide (10c). mp 259–261°C, yield 77%. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 7.19–7.54 m (5H, Ar-H), 7.71 q (1H, *J* = 24.65 Hz, Ar-H), 8.53 t (1H, *J* = 4.00 Hz, pyridine-H), 8.91 d (1H, *J* = 2.30 Hz, pyridine-H), 9.07 d (1H, *J* = 1.70 Hz, pyridine-H), 10.20 s (1H, Ar-CONH), 10.35 s

(1H, Ar-CONH), 10.37 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.50, 105.12, 105.33, 105.54, 112.33, 120.56, 126.78, 127.44, 132.28, 132.39, 132.44, 133.01, 133.16, 134.35, 137.30, 138.36, 147.94, 153.21, 162.98, 163.23, 166.86. Found, %: C 51.73, H 3.45, N 11.59. $C_{21}H_{15}B_rF_2N_4O_3$. Calculated, %: C 51.55, H 3.09, N 11.45. MS: *m/z*: 490.1 $[M + H]^+$.

5-Bromo-*N*-(2-methyl-6-{2-[2-(trifluoromethyl)-benzoyl]hydrazinecarbonyl}phenyl)nicotinamide (10d). mp 253–255°C, yield 90%. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 7.36–7.78 m (6H, Ar-H), 7.82 d (1H, *J* = 8.05 Hz, Ar-H), 8.54 s (1H, pyridine-H), 8.89–8.95 m (2H, pyridine-H), 9.08 s (1H, Ar-CONH), 10.31 s (1H, Ar-CONH), 10.47 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.53, 116.20, 120.55, 122.94, 125.16, 126.89, 126.92, 127.14, 127.39, 129.72, 130.97, 132.28, 132.96, 133.11, 134.35, 134.61, 137.27, 138.37, 147.95, 153.17, 163.24, 166.88. Found, %: C 50.87, H 3.18, N 11.06. $C_{22}H_{16}BrF_3N_4O_3$. Calculated, %: C 50.69, H 3.09, N 10.75. MS: *m/z*: 522.2 $[M + H]^+$.

5-Bromo-*N*-{2-methyl-6-[2-(2-methylbenzoyl)-hydrazinecarbonyl]phenyl}nicotinamide (10e). mp 222–224°C, yield 72%. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.36 s (3H, CH_3), 7.10–7.44 m (7H, Ar-H), 7.59 d (1H, *J* = 8.05 Hz, pyridine-H), 8.56 s (1H, pyridine-H), 8.89 d (1H, *J* = 2.30 Hz, pyridine-H), 9.11 s (1H, Ar-CONH), 10.30 s (1H, Ar-CONH), 10.46 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.84, 19.90, 105.35, 106.46, 111.76, 114.85, 120.59, 126.03, 126.72, 127.82, 130.24, 131.05, 132.59, 132.71, 135.57, 136.46, 138.37, 148.00, 158.74, 162.58, 163.82, 166.35. Found, %: C 56.76, H 4.12, N 12.27. $C_{22}H_{19}B_rN_4O_3$. Calculated, %: C 56.54, H 4.10, N 11.99. MS: *m/z*: 468.3 $[M + H]^+$.

5-Bromo-*N*-{2-[2-(2-methoxybenzoyl)hydra-zinecarbonyl]-6-methylphenyl}nicotinamide (10f). mp 258–260°C, yield 70%. ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 3.88 s (3H, OCH_3), 7.08 t (1H, *J* = 14.85 Hz, Ar-H), 7.17 (d, 1H, *J* = 8.00 Hz, Ar-H), 7.39 t (1H, *J* = 15.50 Hz, Ar-H), 7.48–7.55 m (3H, Ar-H), 7.74 d (1H, *J* = 6.90 Hz, Ar-H), 8.54 s (1H, pyridine-H), 8.91 d (1H, *J* = 2.30 Hz, pyridine-H), 9.07 s (1H, pyridine-H), 10.01 s (1H, Ar-CONH), 10.21 s (1H, Ar-CONH), 10.44 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.57, 56.42, 112.63, 120.56, 121.06, 121.87, 126.76, 127.36, 131.05, 132.34, 132.77, 133.12, 133.38, 134.36, 137.24, 138.41, 147.94, 153.20, 157.57, 163.28, 164.72, 166.55. Found, %: C 54.82, H 4.06, N 11.66. $C_{22}H_{19}B_rN_4O_4$. Calculated, %: C 54.67, H 3.96, N 11.59. MS: *m/z*: 484.4 $[M + H]^+$.

5-Bromo-*N*-(4-chloro-2-methyl-6-{2-[3-(trifluoro-methyl)benzoyl]hydrazinecarbonyl}phenyl)nicotin-amide (10g). mp 216–218°C, yield 88%. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 7.20–7.71 m (6H, Ar-H), 8.52 t (1H, *J* = 4.60 Hz, pyridine-H), 8.92 d (1H, *J* = 2.25 Hz, pyridine-H), 9.06 d (1H, *J* = 2.30 Hz, pyridine-H), 10.25 s (1H, Ar-CONH), 10.44 s (1H, Ar-CONH), 10.50 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.72, 116.39, 120.74, 123.12, 125.35, 127.08, 127.11, 127.33, 127.58, 129.91, 131.16, 132.46, 133.15, 133.29, 134.53, 134.80, 137.46, 138.56, 148.13, 153.36, 163.42, 167.07. Found, %: C 47.95, H 2.78, N 10.31. $C_{22}H_{15}BrClF_3N_4O_3$. Calculated, %: C 47.55, H 2.72, N 10.08. MS: *m/z*: 556.6 $[M + H]^+$.

5-Bromo-*N*-{4-chloro-2-[2-(2,4-difluorobenzoyl)-hydrazinecarbonyl]-6-methylphenyl}nicotinamide (10h). mp 274–276°C, yield 85%. ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 7.23 t (1H, *J* = 16.60 Hz, Ar-H), 7.42 t (1H, *J* = 20.00 Hz, Ar-H), 7.54–7.71 m (3H, Ar-H), 8.52 t (1H, *J* = 4.55 Hz, pyridine-H), 8.92 d (1H, *J* = 2.30 Hz, pyridine-H), 9.06 d (1H, *J* = 2.30 Hz, pyridine-H), 10.25 s (1H, Ar-CONH), 10.43 s (1H, Ar-CONH), 10.50 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 18.26, 105.36, 105.57, 112.36, 112.53, 120.55, 126.44, 131.44, 132.00, 132.36, 132.48, 132.58, 133.51, 134.71, 138.38, 139.94, 147.96, 153.34, 163.01, 163.37, 165.55. Found, %: C 48.31, H 2.79, N 11.05. $C_{21}H_{14}B_rClF_2N_4O_3$. Calculated, %: C 48.16, H 2.69, N 10.70. MS: *m/z*: 524.6 $[M + H]^+$.

5-Bromo-*N*-{4-chloro-2-[2-(2,6-difluorobenzoyl)-hydrazinecarbonyl]-6-methylphenyl}nicotinamide (10i). mp 254–256°C, yield 80%. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 7.17–7.68 m (5H, Ar-H), 8.49 t (1H, *J* = 4.55 Hz, pyridine-H), 8.89 d (1H, *J* = 2.30 Hz, pyridine-H), 9.03 d (1H, *J* = 2.30 Hz, pyridine-H), 10.22 s (1H, Ar-CONH), 10.41 s (1H, Ar-CONH), 10.47 s (1H, pyridine-CONH). ^{13}C NMR spectrum, δ_C, ppm: 17.59, 104.69, 104.90, 111.69, 111.86, 119.88, 125.77, 130.77, 131.33, 131.69, 131.81, 131.91, 132.84, 134.04, 137.71, 139.27, 147.29, 152.67, 162.34, 162.70, 164.88. Found, %: C 48.24, H 2.88, N 10.83. $C_{21}H_{14}B_rClF_2N_4O_3$. Calculated, %: C 48.16, H 2.69, N 10.70. MS: *m/z*: 524.6 $[M + H]^+$.

Insecticidal activity. Insecticidal activity of the compounds **5a**–**5f** and **10a**–**10i** against *P. xylostella* and *E. vitis* was evaluated using the previously reported

methods with some modifications [17, 18]. Mortality rates were corrected using Abbott's formula based on the percentage scale (0 = no activity and 100% = complete eradication). The commercial insecticidal agents spinosad, chlorpyrifos, beta cypermethrin, and azadirachtin were used as positive controls, and water solvent was used as a blank control. All experiments were performed in triplicates.

Insecticidal activity against *P. xylostella.* Fresh cabbage discs (diameter 2 cm) were dipped into the prepared solutions containing the desired compound among **5a**–**5f** and **10a**–**10i** for 10 s, then dried in the air and placed in a petri dish (diameter 9 cm) lined with filter paper. Thirty second-instar larvae of *P. xylostella* were transferred to the petri dish, sealed with a fresh keeping film with some holes, and placed in a growth chamber (25 ± 1°C and 75%) with a light–dark period of 14 : 10 h.

Insecticidal activity against *E. vitis.* Fresh tea shoots (length 13 cm) dipped into the prepared solutions containing a compound **5a**–**5f** and **10a**–**10i** for 10 s were dried in the air, wrapped with wet cotton and parafilm, and packed in a test tube (3 × 20 cm). Thirty second-third-instar larvae of *E. vitis* were transferred into the tube. Finally, opening of the tube was wrapped with gauze and placed in the growth chamber (25 ± 1°C and 75%) with a light–dark period of 14 : 10 h.

CONCLUSIONS

In this study, two series of novel diacylhydrazine derivatives containing an isoxazole carboxamide or a pyridine carboxamide moiety have been designed and synthesized. The compound **5f** has been determined to be the most active against *P. xylostella* and *E. vitis*. This study provides the practical tool for the design and synthesis of novel promising insecticides for controlling *P. xylostella* and *E. vitis*.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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