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Additive effects on the improvement of insecticidal activity: Design, synthesis, and insecticidal activity of novel pymetrozine derivatives

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ABSTRACT

A series of new pymetrozine analogues containing both methyl on the imine carbon and phenoxy group at the pyridine ring were designed and synthesized. Their insecticidal activities against bean aphid (*Aphis craccivora*), mosquito larvae (*Culex pipiens pallens*), cotton bollworm (*Helicoverpa armigera*), corn borer (*Ostrinia nubilalis*) and oriental armyworm (*Mythimna separata*) were evaluated. The results of bioassays indicated that most of the target compounds showed good insecticidal activity against bean aphid; especially, **IIIf** (80%) and **IIIl** (80%) exhibited higher aphicidal activity than pymetrozine (30%) at 5 mg/kg, and the two compounds still showed 20% and 30% mortality at 2.5 mg/kg, respectively, whereas pymetrozine displayed no activity at the same concentration. These compounds exhibited a completely different structure–activity relationship to that of known pymetrozine derivatives, in which it is thought introducing alkyl group on the imine carbon could be detrimental to the activities. Our new result suggested that the methyl on the imine carbon and phenoxy group at the pyridine ring of phenoxy group may play additive effects on the improvement of aphicidal activity. Besides this, compound **IIIs**, containing an allyl at the *para* position of phenoxy group, exhibited excellent insecticidal activity against mosquito larvae, lepidoptera pests cotton bollworm, corn borer and oriental armyworm.

1. Introduction

Aphids, which have an extremely short life cycle, a high reproductive rate and an efficient dispersal strategy,[1] cause considerable damage to agriculture or horticulture either by feeding on the vascular system or transmission of plant viruses.[2] But to now, only a few natural enemies, such as parasitoids and predators, can reduce the aphid populations under field conditions.[3] There are also some synthetic aphicides, but many of them belong to carbamates, organophosphorus compounds, neonicotinoids, which hold a considerable risk of becoming ineffective due to the build-up of resistance.[4] To overcome this problem, there is an imperative need to research and develop aphicides with new mode of action.

Pymetrozine (Fig. 1), a pyridine azomethine compound discovered by Ciba-Geigy Corp (now Syngenta International AG) in 1989, represents a novel insecticide with a selective activity against aphids, whiteflies, and planthoppers.[5] It is a neuroactive insecticide affecting the nerve that controls the salivary pump of some sucking pests, causing irreversible cessation of feeding, followed by starvation and death. In the IRAC classification, it is classified as 9B (modulators of chordotonal organs) which is very close to flonicamid (classified as 9C).[6] This meant they had novel modes of action compared to other groups of insecticides and showed no cross-resistance with them.[7] Pymetrozine derivatives have attracted considerable attention for decades. Recently, the mode of action of the insecticides pymetrozine and pyrifluquinanzon were published. The two insecticides act selectively on a novel transient receptor potential (TRP) ion channel complex as the target protein. By activating this TRP ion channel complex, the insecticides overstimulate the stretch receptors, disturbing insect locomotion and feeding.[8] However, the structure of TRP ion channel complex is unknown. Thus, the modification of pymetrozine relies more on the analysis of known structure–activity relationships of pymetrozine derivatives. Previous research showed that the insecticidal activity was significantly decreased when the hydrogen atom of the imino group (CH=N) in pymetrozine was replaced by an alkyl group (compound **I**).[9] Therefore, most of the work thereafter focused on the modifications of triazine ring,[10–13] pyridine ring[14–18] and not the linkage part between them.

A substituted phenoxy group is a multifunctional substituent that can adjust the polarity, electronic effect, and steric effect of the molecules, so it is widely used in the field of pesticide and drug

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0968-0896/

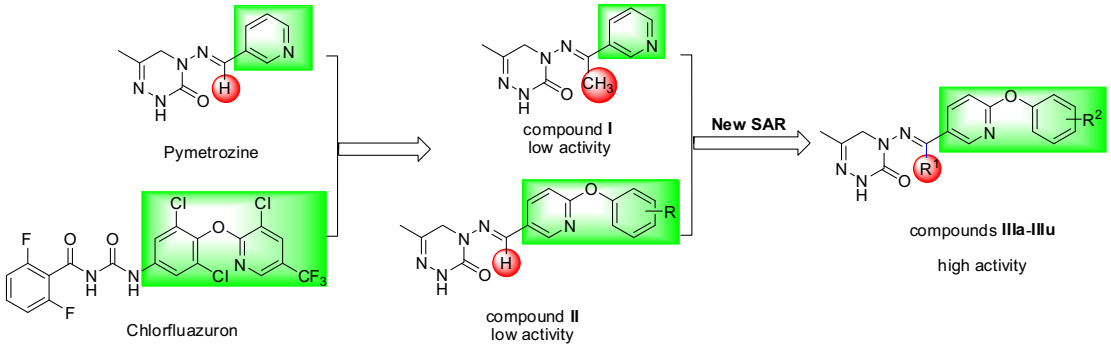


Figure 1. Design of target compounds.

molecular design. For example, chlorfluazuron discovered by Ishihara Sangyo Kaisha Ltd as an insect growth regulator contains a phenoxy group.[19] In our research we planed to introduce phenoxy group onto pymetrozine in order to increase its activity. However, when we introduced phenoxy group to the 4,5-dihydro-1,2,4-triazin-3(2*H*)-one derivatives (compound **II**), **II** did not exhibit good insecticidal activity against aphids. But pleasantly surprised, the aphicidal activity was significantly increased when the hydrogen atom on the imino group (CH═N) of compound **II** was replaced by a methyl group (compound **IIIa**) at the same time. This is a new structure–activity relationship which is different to that of pymetrozine derivatives. In the previous study it was thought that the introduction of alkyl to the imino group was detrimental to the biological activities.[9] We think it is probably the synergistic effect of the methyl and phenoxy group that increases the insecticidal activity. In order to investigate what combination could give better results, a series of pymetrozine analogues containing different substituents (R^1) at the linkage part and different substituents (R^2) on the phenoxy ring attached to the pyridine ring (compounds **IIIa**–**IIIu**) were designed and synthesized. The aphicidal activities of the target compounds against bean aphid (*Aphis craccivora*), as well as insecticidal activities against cotton bollworm (*Helicoverpa armigera*), corn borer (*Ostrinia nubilalis*), oriental armyworm (*Mythimna separata*) and mosquito (*Culex pipiens pallens*), were tested and discussed.

2. Results and discussion

2.1. Chemistry

The synthetic routes of the target compounds **I**, **II**, **IIIa**–**IIIu** are shown in Scheme 1. The key intermediate 4-amino-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**1**) was prepared according to the method in the literature.[18] Compound **1** was condensed with 1-(pyridin-3-yl)ethanone (**2**) to give the imine compound **I** using *p*-toluene sulfonic acid as catalyst. The intermediate aldehyde **4** was synthesized from 6-chloronicotinaldehyde (**3**) and phenol through Williamson ether synthesis in DMF, Cs_2CO_3 as a base, and CuCl as a catalyst.[20,21] Compound **1** reacted with aldehyde **4** giving compound **II**.

The compounds **6a**–**6d** were obtained by reacting phenol with various pyridyl ketones (**5a**–**5d**). In the initial process of preparing compound **6a**, when 1-(6-chloropyridin-3-yl)ethanone (**5a**) (1 equiv) was mixed with phenol (1 equiv) in DMF in the presence of Cs_2CO_3 and CuCl, we found that the reaction didn't occur even after the mixture was refluxed for 12 h. We assumed that the basicity of Cs_2CO_3 was insufficient for the reaction. Hence, we chose NaH as alkali and dimethylsulfoxide as solvent, and then the reaction was complete in 12 h and successfully afforded **6a**. Compounds **6b**–**6d** were synthesized using the same procedure as for **6a**. Similarly as described above, **6a**–**6u** were transformed to corresponding **IIIa**–**IIIu** by reacting with compound **1**.

The title compounds have all been characterized by melting point, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry (HRMS). All spectral data were consistent with the assigned structures. Since the NMR data indicated all compounds existed in single configuration, we assumed that the 1,2,4-triazin-3(2*H*)-one ring and phenoxypyridine ring have trans configuration.

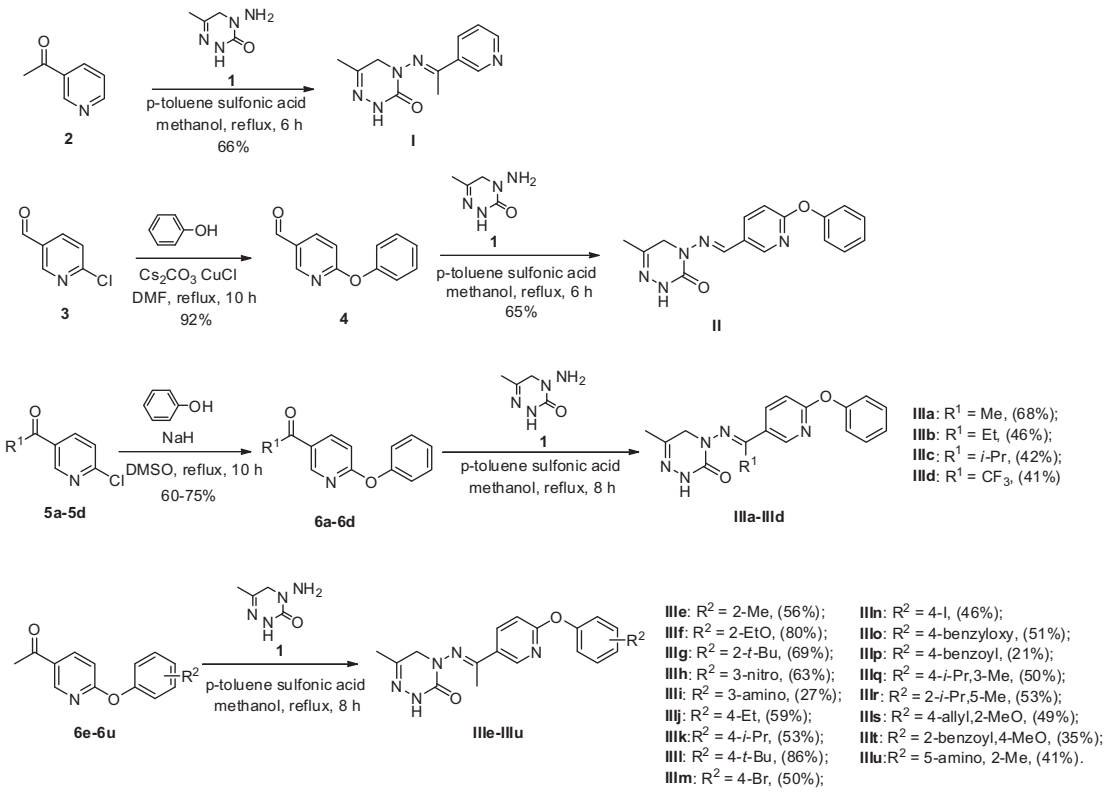
2.2. Biological evaluation

2.2.1. Foliar contact activity against bean aphid (*A. craccivora*)

The foliar contact activity against bean aphid of the synthesized compounds **I**, **II**, **IIIa**–**IIIu** are shown in Table 1 in comparison to pymetrozine. Compound **II**, with a phenoxy ring attached to the pyridine ring, exhibited much lower activity than pymetrozine; compound **I**, with a methyl at the imino group (CH═N), also exhibited much lower activity, which was consistent with the previously reported data.[9] But to our surprise, compared with **I** and **II**, the aphicidal activity of **IIIa** which is bearing a methyl on the imino group and a phenoxy group at the pyridine ring was significantly increased. Changing methyl to ethyl (**IIIb**), isopropyl (**IIIc**) or trifluoromethyl (**IIId**), the activity was slightly decreased in comparison with **IIIa**. Then, keeping the methyl at the imine group, different substituted-phenoxy group were introduced to the pyridine ring. Most of the compounds showed 100% activity at 100 mg/kg. Especially, **IIIf** (80%) and **IIIl** (80%) exhibited higher activities than pymetrozine (30%) at 5 mg/kg, and they still showed 20% and 30% mortality at 2.5 mg/kg, respectively, whereas pymetrozine showed no activity at the lower concentration. The result indicated that the additive effect of the methyl and phenoxy group play an important role in the aphicidal activity. In addition, the properties and positions of these substituents on the phenoxy ring have an important influence on the activities of these compounds. Compound **IIIl** (30% at 2.5 mg/kg), having a *tert*-butyl at the *para* position of benzene ring, exhibited much higher activity than compound **IIIg** (30% at 10 mg/kg), which has a *tert*-butyl at the *ortho* position of benzene ring.

2.2.2. Toxicity against mosquito larvae

The larvacidal activity against mosquito of the synthesized compounds **I**, **II**, **IIIa**–**IIIu** are shown in Tables 2 and 4 in comparison to pymetrozine. Most compounds exhibited excellent larvicidal activities against mosquito. In particular, the activities of compounds **IIIg**, **IIIl**, **IIIp**, **IIIq** and **IIIs** were much higher than the activity of pymetrozine, and compound **IIIs** exhibited the best larvicidal activity, which had 20% mortality even at 0.01 mg/kg. The position of the substituent on the benzene ring of the target



Scheme 1. General synthetic route for target compounds.

compounds was also important. For example, **IIIg** (containing a 2-*tert*-butyl) showed 40% mortality at 2 mg/kg but **IIII** (containing a 4-*tert*-butyl) showed 40% mortality at 0.5 mg/kg.

2.2.3. Insecticidal activity against lepidoptera pests

The insecticidal activity of the synthesized compounds **I**, **II**, **IIIa**–**IIIu** a against the larvae of lepidoptera pests cotton bollworm, corn borer and oriental armyworm are listed in Tables 3 and 4 in comparison to pymetrozine. Most of the compounds showed moderate insecticidal activity. But to our surprise, compound **IIIs**, containing an allyl group at the *para* position of the phenoxy group and a methoxy group in the *ortho*-position, exhibited remarkable insecticidal activity. For example, **IIIs** showed 100% mortality at 200 mg/kg against all three lepidoptera pests, whereas other compounds showed less than 100% mortality at 600 mg/kg. Even at 100 mg/kg, **IIIs** exhibited 30% mortality on cotton bollworm, 20% mortality on corn borer, and 60% mortality on oriental armyworm. The level of biological activity was much higher than that of pymetrozine (the mortality of cotton bollworm, corn borer and oriental armyworm were 20%, 35% and 50%, respectively, at 600 mg/kg).

3. Conclusion

In summary, a series of pymetrozine derivatives containing a methyl at the carbon of the C=N linker and a phenoxy on the pyridine were designed and synthesized. These compounds exhibited a completely different structure–activity relationship to previous derivatives of pymetrozine. The methyl and phenoxy group displayed additive effects on the improvement of aphicidal activity. The results of the bioassays indicated that most of the target compounds showed nearly the same level of aphicidal activity against bean aphid as pymetrozine, but **IIIf** and **IIII** exhibited higher activities than pymetrozine at the concentration of 5 and 2.5 mg/kg. Thus, compounds **IIIf** and **IIII** could be used as lead compounds for further research. Most of these compounds exhibited excellent larvicidal activities against bean aphid; compound **IIIs**, containing an allyl at the phenoxy group, also exhibited remarkable insecticidal activities against mosquito and lepidoptera pests (cotton bollworm, corn borer and oriental armyworm). Further studies on these compounds are in progress in our laboratory.

4. Experimental methods

4.1. Instrument

^{1}H NMR and ^{13}C NMR spectra were obtained at 400 MHz using a Bruker AV400 spectrometer in DMSO-d_6 or $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. HRMS data were obtained on an FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 binocular microscope melting point apparatus and are uncorrected.

4.2. Synthesis

4-Amino-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**1**) was prepared according to the method in the literature.[18]

4.2.1. Synthesis of (*E*)-6-methyl-4-(1-(pyridin-3-yl)-ethylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (I)

To a solution of **1** (0.51 g, 4.00 mmol) and 1-(pyridin-3-yl)ethanone (**2**) (0.48 g, 4.00 mmol) in methanol (50 mL) was added *p*-toluene sulfonic acid (0.14 g, 0.80 mmol), and then the mixture was refluxed for 6 h. The solution was cooled and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using petroleum ether (60–90 °C) and ethyl acetate (v/v = 4:1) as eluent to give compound **I** as a yellow solid (0.61 g, 66%); mp = 154–156 °C; ^{1}H NMR

Table 1
Foliar contact activities against bean aphid of compounds **I**, **II**, **IIIa–IIIu** and pymetrozine[a]

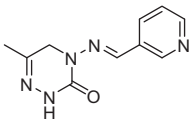
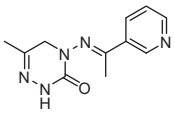
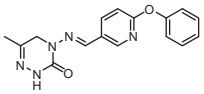
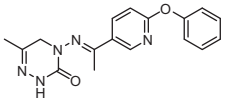
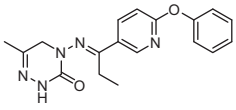
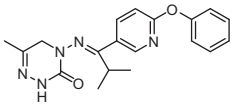
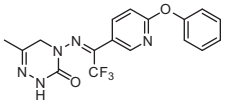
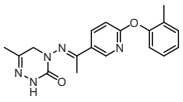
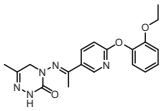
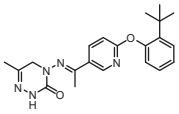
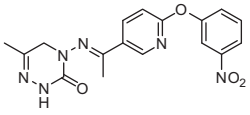
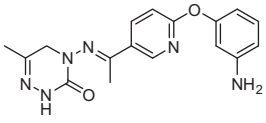
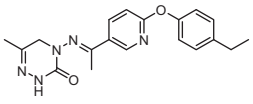
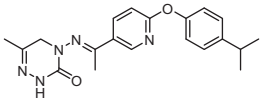
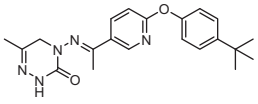
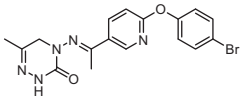
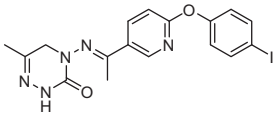
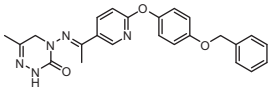
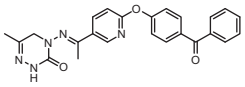
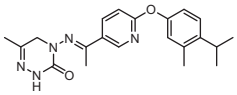
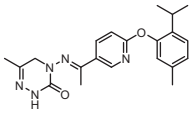
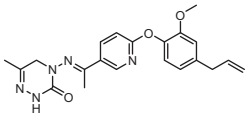
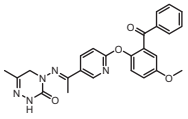
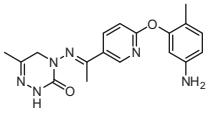
Compd	Structure	Mortality (%) at concn (mg/kg)				
		600	100	10	5	2.5
Pymetrozine		**100**	**100**	**90**	**30**	**0**
I		90	30	–	–	–
II		95	40	–	–	–
IIIa		100	95	50	–	–
IIIb		100	80	30	–	–
IIIc		100	70	20	–	–
IIId		100	70	20	–	–
IIIe		100	100	95	30	–
IIIf		**100**	**100**	**100**	**80**	**20**
IIIg		100	100	30	–	–
IIIh		100	100	30	–	–
IIIi		100	100	30	–	–
IIIj		100	100	90	20	–
IIIk		100	100	95	30	–
IIIl		**100**	**100**	**100**	**80**	**30**

Table 1 (*continued*)

Compd	Structure	Mortality (%) at concn (mg/kg)				
		600	100	10	5	2.5
IIIm		100	100	75	15	–
IIIn		100	100	20	–	–
IIIo		100	100	80	20	–
IIIp		100	90	30	–	–
IIIq		100	100	95	30	–
IIIr		100	95	80	20	–
IIIs		100	100	20	–	–
IIIt		100	100	30	–	–
IIIu		100	90	20	–	–

[a] "–" means activity is not tested. The data in bold are used to emphasize that these compounds showed good activity.

(400 MHz, DMSO-d_6): δ 10.02 (s, 1H, NH), 9.01 (s, 1H, Py-H), 8.67 (d, J = 3.6 Hz, 1H, Py-H), 8.21 (d, J = 8.0 Hz, 1H, Py-H), 7.47–7.50 (m, 1H, Py-H), 4.18 (s, 2H, CH_2), 2.22 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 151.3, 148.8, 147.9, 145.6, 134.4, 132.5, 123.6, 50.9, 20.2, 17.3. ESI-HRMS (m/z): Calcd for $C_{11}H_{14}N_5O$ $[M+H]^+$ 232.1193. Found 232.1198.

4.2.2. Synthesis of 6-phenoxynicotinaldehyde (4)

To a solution of 6-chloronicotinaldehyde (**3**) (0.28 g, 2 mmol) and phenol (0.19 g, 2 mmol) in DMF (30 mL) was added Cs_2CO_3 (0.78 g, 2.4 mmol) and CuCl (0.24 g, 2.4 mmol), then the mixture was refluxed for 10 h and then cooled to room temperature. The mixture was extracted with EtOAc, and the extract was washed successively with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by recrystallization using methanol to give compound **4** as a white solid (0.36 g, 92%); mp = 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H, CHO), 8.63 (s, 1H, Py-H), 8.19 (d, J = 8.4 Hz, 1H, Py-H), 7.46 (t, J = 7.6 Hz, 2H, Ar-H), 7.30 (d, J = 7.6 Hz, 1H, Ar-H), 7.17 (d, J = 7.6 Hz, 2H, Ar-H), 7.16 (d, J = 8.4 Hz, 1H, Py-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 167.3, 153.0, 152.8, 138.7, 129.9, 127.7, 125.8, 121.6, 112.1. ESI-HRMS (m/z): Calcd for $C_{12}H_{10}NO_2$ $[M+H]^+$ 200.0706. Found 200.0708.

4.2.3. Synthesis of (*E*)-6-methyl-4-((6-phenoxypyridin-3-yl)-methyleneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (II)

To a solution of **1** (0.51 g, 4.00 mmol) and 6-phenoxynicotinaldehyde (**4**) (0.80 g, 4.00 mmol) in methanol (50 mL) was added *p*-toluene sulfonic acid (0.14 g, 0.80 mmol), and then the mixture was refluxed for 6 h. The solution was cooled and then concentrated under reduced pressure. The crude product was purified by recrystallization using methanol to give compound **II** as a white solid (0.80 g, 65%); mp = 200–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 1H, NH), 8.37 (s, 1H, N=CH), 8.20 (d, J = 8.8 Hz, 1H, Py-H), 7.89 (s, 1H, Py-H), 7.44 (t, J = 7.6 Hz, 2H, Ar-H), 7.24 (t, J = 7.6 Hz, 1H, Ar-H), 7.17 (d, J = 7.6 Hz, 2H, Ar-H), 7.11 (d, J = 8.8 Hz, 1H, Py-H), 4.35 (s, 2H, CH_2), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 153.6, 147.3, 146.9, 144.0, 137.8, 136.8, 129.8, 126.7, 124.9, 121.4, 111.9, 47.7, 20.2. ESI-HRMS (m/z): Calcd for $C_{16}H_{16}N_5O_2$ $[M+H]^+$ 310.1299. Found 310.1300.

4.2.4. Synthesis of 6-phenoxynicotinaldehyde (6a)

To a stirred suspension of 0.12 g (3.00 mmol) of 60% sodium hydride in oil in DMSO (10 mL) at room temperature, was added phenol (0.19 g, 2 mmol) in DMSO (10 mL). After 30 min, 1-(6-chloropyridin-3-yl)ethanone (**5a**) (0.31 g, 2 mmol) in DMSO (10 mL) was added at room temperature. The reaction mixture

Table 2
Larvacidal activities against mosquito of compounds **I**, **II**, **IIIa–IIIu** and pymetrozine[a]

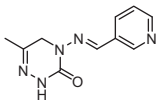
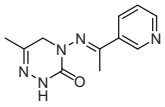
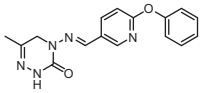
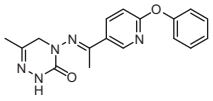
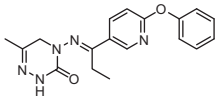
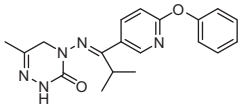
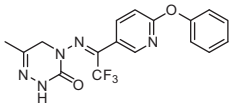
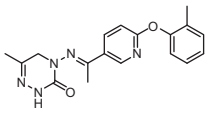
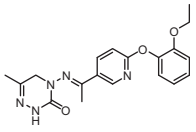
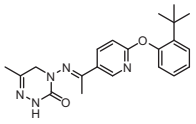
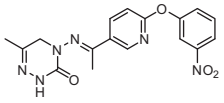
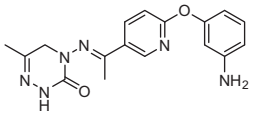
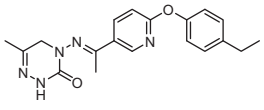
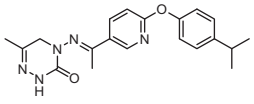
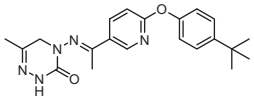
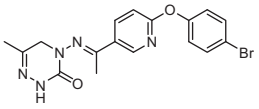
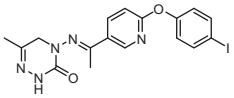
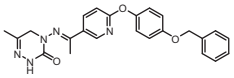
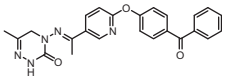
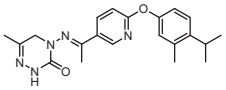
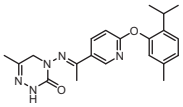
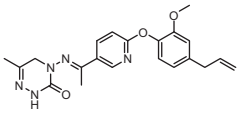
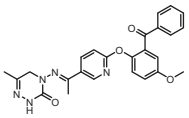
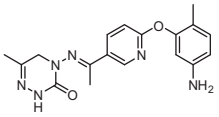
Compd	Structure	Mortality (%) at concn (mg/kg)				
		10	5	2	1	0.5
Pymetrozine		**100**	**40**	**0**	**–**	**–**
I		70	–	–	–	–
II		20	–	–	–	–
IIIa		45	–	–	–	–
IIIb		30	–	–	–	–
IIIc		70	–	–	–	–
IIId		100	20	–	–	–
IIIe		100	20	–	–	–
IIIf		50	–	–	–	–
IIIg		100	100	40	–	–
IIIh		100	10	–	–	–
IIIi		40	–	–	–	–
IIIj		100	20	–	–	–
IIIk		50	–	–	–	–
IIIl		**100**	**100**	**100**	**100**	**40**

Table 2 (*continued*)

Compd	Structure	Mortality (%) at concn (mg/kg)				
		10	5	2	1	0.5
IIIm		100	20	–	–	–
IIIn		100	40	–	–	–
IIIo		50	–	–	–	–
IIIp		100	100	60	–	–
IIIq		100	100	60	–	–
IIIr		100	20	–	–	–
IIIs		**100**	**100**	**100**	**100**	**100**
IIIt		100	20	–	–	–
IIIu		50	–	–	–	–

[a] "–" means activity is not tested. The data in bold are used to emphasize that these compounds showed good activity.

was refluxed for 12 h and then cooled to room temperature and quenched with ice water. The mixture was extracted with EtOAc, and the extract was washed successively with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography on silica gel using petroleum ether (60–90 °C) and ethyl acetate (v/v = 10:1) as eluent to give compound **6a** as a white solid (0.29 g, 68%); mp = 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H, Py-H), 8.27 (d, J = 8.8 Hz, 1H, Py-H), 7.45 (t, J = 7.6 Hz, 2H, Ar-H), 7.28 (t, J = 7.6 Hz, 1H, Ar-H), 7.16 (d, J = 7.6 Hz, 2H, Ar-H), 6.97 (d, J = 8.8 Hz, 1H, Py-H), 2.57 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 166.6, 153.4, 149.8, 139.4, 130.0, 128.4, 125.7, 121.7, 111.4, 26.6. ESI-HRMS (m/z): Calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0836. Found 214.0864.

Compounds **6b–6d** were synthesized using phenol and the compound **5b–5d** according to the same procedure as **6a**.

4.2.4.1. 1-(6-Phenoxypyridin-3-yl)propan-1-one (6b). This compound was obtained as a white solid in 74% yield; mp = 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H, Py-H), 8.27 (d, J = 8.8 Hz, 1H, Py-H), 7.44 (t, J = 7.6 Hz, 2H, Ar-H), 7.26 (t, J = 7.6 Hz, 1H, Ar-H), 7.16 (d, J = 7.6 Hz, 2H, Ar-H), 6.97 (d, J = 8.8 Hz, 1H, Py-H), 2.94 (q, J = 7.6 Hz, 2H, CH_2CH_3), 1.22 (t, J = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 166.4, 153.4, 149.3, 139.3, 129.9, 128.0, 125.6, 121.6, 111.4, 31.9, 8.17. ESI-HRMS (m/z): Calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1019. Found 228.1023.

4.2.4.2. 2-Methyl-1-(6-phenoxypyridin-3-yl)propan-1-one (6c). This compound was obtained as a white solid in 63% yield; mp = 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H, Py-H), 8.27 (d, J = 8.8 Hz, 1H, Py-H), 7.44 (t, J = 7.6 Hz, 2H, Ar-H), 7.26 (t, J = 7.6 Hz, 1H, Ar-H), 7.16 (d, J = 7.6 Hz, 2H, Ar-H), 6.97 (d, J = 8.8 Hz, 1H, Py-H), 3.40–3.47 (m, 1H, $CH(CH_3)_2$), 1.22 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 166.4, 153.4, 149.4, 139.8, 130.0, 125.6, 121.7, 115.5, 111.5, 35.8, 19.1. ESI-HRMS (m/z): Calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176. Found 242.1180.

4.2.4.3. 2,2,2-Trifluoro-1-(6-phenoxypyridin-3-yl)ethanone (6d). This compound was obtained as a yellow oil liquid in 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H, Py-H), 8.37 (d, J = 8.8 Hz, 1H, Py-H), 7.49 (t, J = 7.6 Hz, 2H, Ar-H), 7.33 (t, J = 7.6 Hz, 1H, Ar-H), 7.20 (d, J = 7.6 Hz, 2H, Ar-H), 7.10 (d, J = 8.8 Hz, 1H, Py-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (q, J = 37 Hz), 167.7, 152.8, 152.0 (q, J = 3.0 Hz), 140.8, 130.0, 126.1, 121.7, 121.5, 116.6 (q, J = 289 Hz), 112.1. ESI-HRMS (m/z): Calcd for $C_{13}H_9F_3NO_2$ $[M+H]^+$ 268.0580. Found 268.0580.

4.2.5. Synthesis of (*E*)-6-methyl-4-(1-(6-phenoxypyridin-3-yl)-ethylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIa)

To a solution of **1** (0.51 g, 4.00 mmol) and 1-(6-phenoxy-3-pyridyl)ethnone (**6a**) (0.85 g, 4.00 mmol) in methanol (80 mL) was added *p*-toluene sulfonic acid (0.14 g, 0.80 mmol), and then the

Table 3
Insecticidal activities against lepidoptera pest of compounds **I**, **II**, **IIIa–IIIu** and pymetrozine[a]

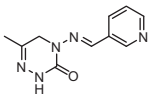
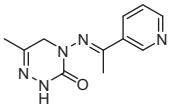
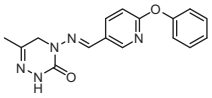
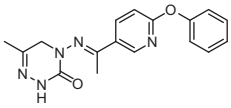
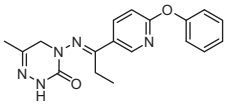
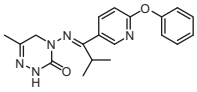
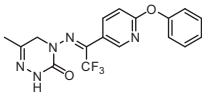
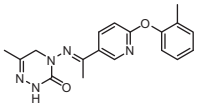
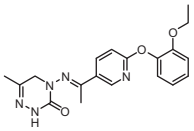
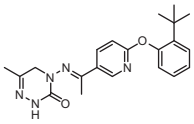
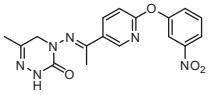
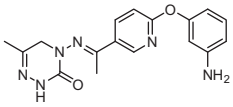
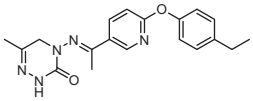
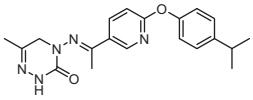
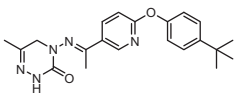
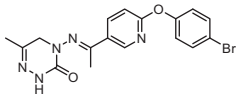
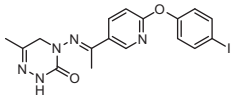
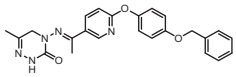
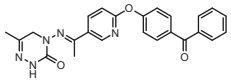
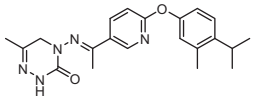
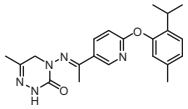
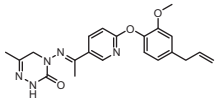
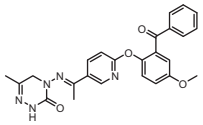
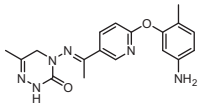
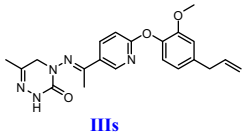
Compd	Structure	Mortality (%) at 600 mg/kg		
		Cotton bollworm	Corn borer	Oriental armyworm
Pymetrozine		**20**	**35**	**50**
I		25	55	50
II		35	50	65
IIIa		20	35	50
IIIb		70	75	40
IIIc		10	20	25
IIId		30	25	20
IIIe		40	35	60
IIIf		40	35	45
IIIg		20	15	20
IIIh		0	0	15
IIIi		0	0	5
IIIj		25	15	30
IIIk		5	0	5
IIIl		55	50	80

Table 3 (*continued*)

Compd	Structure	Mortality (%) at 600 mg/kg		
		Cotton bollworm	Corn borer	Oriental armyworm
IIIm		20	10	20
IIIn		55	50	65
IIIo		10	5	10
IIIp		15	5	10
IIIq		25	20	25
IIIr		0	0	5
IIIs		**100**	**100**	**100**
IIIt		20	20	25
IIIu		20	15	25

[a] The data in bold are used to emphasize that these compounds showed good activity.

Table 4
Larvacidal activities against mosquito and lepidoptera pests of compound **IIIs**[a]

Compd	Mortality (%)		Mortality (%) against lepidoptera pest			
	Concn (mg/kg)	Mosquito	Concn (mg/kg)	Cotton bollworm	Corn borer	Oriental armyworm
 **IIIs**	0.25	100	**200**	**100**	**100**	**100**
	0.1	100	100	30	20	60
	0.05	100				
	0.025	**100**				
	0.01	20				

[a] The data in bold are used to emphasize that the compound showed good activity at this concentration.

mixture was refluxed for 8 h. The solution was cooled and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using petroleum ether (60–90 °C) and ethyl acetate (v/v = 5:1) as eluent to give compound **IIIa** as a white solid (0.88 g, 68%); mp = 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H, NH), 8.27 (d, J = 8.8 Hz, 1H, Py-H), 7.75 (s, 1H, Py-H), 7.44 (t, J = 7.6 Hz, 2H, Ar-H), 7.25 (t, J = 7.6 Hz, 1H, Ar-H), 7.17 (d, J = 7.6 Hz, 2H, Ar-H), 6.94 (d, J = 8.8 Hz, 1H, Py-H), 4.21 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.4, 153.9, 149.0, 147.3, 145.7, 138.3, 129.9, 128.0, 125.2, 121.4, 111.2, 51.9, 20.6, 17.4. ESI-HRMS (m/z): Calcd for $C_{17}H_{18}N_5O_2$ $[M+H]^+$ 324.1455. Found 324.1459.

Compounds **IIIb**–**IIIu** were synthesized using compound **1** and the compounds **6b**–**6u** according to the same procedure as **IIIa**.

4.2.5.1. (*E*)-6-Methyl-4-(1-(6-phenoxypyridin-3-yl)propylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIb). This compound was obtained as a white solid in 46% yield; mp = 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H, NH), 8.19 (d, J = 8.8 Hz, 1H, Py-H), 7.75 (s, 1H, Py-H), 7.42 (t, J = 8.0 Hz, 2H, Ar-H), 7.23 (t, J = 7.6 Hz, 1H, Ar-H), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 6.93 (d, J = 8.8 Hz, 1H, Py-H), 4.13 (s, 2H, CH_2), 2.72 (q, J = 7.6 Hz, 2H, CH_2CH_3), 2.04 (s, 3H, CH_3), 1.12 (t, J = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 165.3, 153.8, 149.4, 147.6, 145.4, 139.0, 129.9, 126.6, 125.2, 121.5, 111.3, 51.8, 23.6, 20.7,

11.7. ESI-HRMS (*m*/*z*): Calcd for $C_{18}H_{20}N_5O_2$ $[M+H]^+$ 338.1612. Found 338.1611.

4.2.5.2. (*E*)-6-Methyl-4-(2-methyl-1-(6-phenoxypyridin-3-yl)propylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIc). This compound was obtained as a white solid in 42% yield; mp = 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H, NH), 7.65 (d, *J* = 8.4 Hz, 1H, Py-H), 7.46 (s, 1H, Py-H), 7.41 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.22 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.16 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.4 Hz, 1H, Py-H), 3.97 (s, 2H, CH_2), 2.89–2.99 (m, 1H, C*H*$(CH_3)_2$), 1.89 (s, 3H, CH_3), 1.19 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 163.8, 153.7, 148.4, 144.6, 144.4, 138.5, 129.9, 127.2, 125.2, 121.6, 110.9, 51.5, 37.2, 20.5, 20.1. ESI-HRMS (*m*/*z*): Calcd for $C_{19}H_{22}N_5O_2$ $[M+H]^+$ 352.1768. Found 352.1772.

4.2.5.3. (*Z*)-6-Methyl-4-(2,2,2-trifluoro-1-(6-phenoxypyridin-3-yl)ethylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIId). This compound was obtained as a white solid in 41% yield; mp = 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, NH), 8.13 (s, 1H, Py-H),7.82 (d, *J* = 8.0 Hz, 1H, Py-H), 7.45 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.28 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.19 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 1H, Py-H), 4.19 (s, 2H, CH_2), 2.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 153.2 (q, *J* = 33 Hz), 153.1, 146.8, 146.2, 146.0, 139.1, 129.8, 125.5, 121.6, 120.1 (q, *J* = 257 Hz), 111.5, 52.3, 20.5. ESI-HRMS (*m*/*z*): Calcd for $C_{17}H_{15}F_3N_5O_2$ $[M+H]^+$ 378.1172. Found 378.1181.

4.2.5.4. (*E*)-6-Methyl-4-(1-(6-(*o*-tolyloxy)pyridin-3-yl)ethylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIe). This compound was obtained as a white solid in 56% yield; mp = 166–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H, NH), 8.55 (s, 1H, Py-H), 8.31 (d, *J* = 8.8 Hz, 1H, Py-H), 7.34 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.27 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.19 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.13–7.07 (m, 2H, Py-H, Ar-H), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 164.8, 152.1, 149.3, 147.2, 145.9, 138.8, 131.7, 130.7, 128.1, 127.8, 125.8, 122.5, 110.8, 51.4, 20.6, 17.4, 16.4. ESI-HRMS (*m*/*z*): Calcd for $C_{18}H_{20}N_5O_2$ $[M+H]^+$ 338.1612. Found 338.1616.

4.2.5.5. (*E*)-4-(1-(6-(2-Ethoxyphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIf). This compound was obtained as a yellow solid in 80% yield; mp = 167–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.52 (s, 1H, Py-H), 8.27 (d, *J* = 8.8 Hz, 1H, Py-H), 7.12–7.23 (m, 3H, Ar-H), 6.96–7.04 (m, 2H, Py-H, Ar-H), 4.15 (s, 2H, CH_2), 3.96 (q, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_3$), 2.18 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.05 (t, *J* = 6.8 Hz, 3H, CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 164.5, 150.6, 148.8, 146.4, 145.3, 142.1, 137.9, 127.5, 126.2, 122.9, 120.9, 114.3, 110.0, 63.7, 50.9, 20.1, 16.9, 14.4. ESI-HRMS (*m*/*z*): Calcd for $C_{19}H_{22}N_5O_3$ $[M+H]^+$ 368.1717. Found 368.1722.

4.2.5.6. (*E*)-4-(1-(6-(2-*tert*-Butylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIg). This compound was obtained as a white solid in 69% yield; mp = 122–123 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.59 (s, 1H, Py-H), 8.30 (d, *J* = 8.8 Hz, 1H, Py-H), 7.43 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.25 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.18 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.07 (d, *J* = 8.8 Hz, 1H, Py-H), 6.99 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.31 (s, 9H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 164.6, 152.1, 148.8, 146.8, 145.4, 140.8, 138.3, 127.7, 127.2, 124.9, 123.5, 111.1, 50.9, 34.3, 30.1, 20.2, 16.9. ESI-HRMS (*m*/*z*): Calcd for $C_{21}H_{26}N_5O_2$ $[M+H]^+$ 380.2081. Found 380.2086.

4.2.5.7. (*E*)-6-Methyl-4-(1-(6-(3-nitrophenoxy)pyridin-3-yl)ethylideneamino)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIh). This compound was obtained as a white solid in 63% yield; mp = 171–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H, NH), 8.60 (s, 1H, Py-H), 8.38 (d, *J* = 8.8 Hz, 1H, Py-H), 8.12 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.06 (t, *J* = 2.0 Hz, 1H, Ar-H), 7.69–7.77 (m, 2H, Ar-H), 7.25 (d, *J* = 8.8 Hz, 1H, Py-H), 4.16 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 163.5, 153.8, 148.7, 148.6, 146.4, 145.4, 138.7, 131.0, 128.8, 128.4, 119.8, 116.5, 111.7, 50.9, 20.1, 17.1. ESI-HRMS (*m*/*z*): Calcd for $C_{17}H_{17}N_6O_4$ $[M+H]^+$ 369.1306. Found 369.1311.

4.2.5.8. (*E*)-4-(1-(6-(3-Aminophenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIi). This compound was obtained as a white solid in 27% yield; mp = 187–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.60 (s, 1H, Py-H), 8.27 (d, *J* = 8.8 Hz, 1H, Py-H), 7.04 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.96 (d, *J* = 8.8 Hz, 1H, Py-H), 6.42 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.29 (s, 1H, Ar-H), 6.24 (d, *J* = 7.2 Hz, 1H, Ar-H), 5.27 (s, 2H, NH_2), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 164.5, 154.4, 150.2, 148.6, 146.6, 145.2, 138.0, 129.7, 127.5, 110.6, 110.3, 107.6, 105.9, 50.7, 19.9, 16.8. ESI-HRMS (*m*/*z*): Calcd for $C_{17}H_{19}N_6O_2$ $[M+H]^+$ 339.1564. Found 339.1569.

4.2.5.9. (*E*)-4-(1-(6-(4-Ethylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIj). This compound was obtained as a white solid in 59% yield; mp = 131–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.56 (s, 1H, Py-H), 8.29 (d, *J* = 8.8 Hz, 1H, Py-H), 7.27 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.09–7.04 (m, 3H, Ar-H, Py-H), 4.15 (s, 2H, CH_2), 2.63 (q, *J* = 6.8 Hz, 2H, *CH*$_2$CH$_3$), 2.18 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.21 (t, *J* = 7.6 Hz, 3H, CH$_2$*CH*$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.6, 151.3, 148.8, 146.6, 145.4, 140.4, 138.3, 129.0, 127.8, 121.2, 110.9, 50.9, 27.6, 20.1, 17.0, 15.7. ESI-HRMS (*m*/*z*): Calcd for $C_{19}H_{22}N_5O_2$ $[M+H]^+$ 352.1768. Found 352.1772.

4.2.5.10. (*E*)-4-(1-(6-(4-Isopropylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIk). This compound was obtained as a white solid in 53% yield; mp = 128–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.57 (s, 1H, Py-H), 8.29 (d, *J* = 8.8 Hz, 1H, Py-H), 7.30 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.10–7.04 (m, 3H, Ar-H, Py-H), 4.15 (s, 2H, CH_2), 2.89–2.96 (m, 1H, *CH*$(CH_3)_2$), 2.18 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.22 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.6, 151.4, 148.8, 146.6, 145.4, 145.0, 138.3, 127.8, 127.5, 121.2, 110.9, 50.9, 32.9, 24.0, 20.1, 17.0. ESI-HRMS (*m*/*z*): Calcd for $C_{20}H_{24}N_5O_2$ $[M+H]^+$ 366.1925. Found 366.1930.

4.2.5.11. (*E*)-4-(1-(6-(4-*tert*-Butylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIl). This compound was obtained as a white solid in 86% yield; mp = 183–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.57 (s, 1H, Py-H), 8.30 (d, *J* = 8.8 Hz, 1H, Py-H), 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.11–7.04 (m, 3H, Ar-H, Py-H), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.31 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.6, 151.1, 148.8, 147.2, 146.6, 145.4, 138.3, 127.8, 126.5, 120.8, 110.9, 50.9, 34.2, 31.3, 20.1, 17.0. ESI-HRMS (*m*/*z*): Calcd for $C_{21}H_{26}N_5O_2$ $[M+H]^+$ 380.2081. Found 380.2089.

4.2.5.12. (*E*)-4-(1-(6-(4-Bromophenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIm). This compound was obtained as a white solid in 50% yield; mp = 204–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H, NH), 8.58 (s, 1H, Py-H), 8.32 (d, *J* = 8.8 Hz, 1H, Py-H), 7.62 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.19–7.13 (m, 3H, Ar-H, Py-H), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.94 (s, 3H,

CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 164.0, 152.8, 148.8, 146.5, 145.4, 138.5, 132.6, 128.3, 123.7, 117.0, 111.3, 50.9, 20.1, 17.0. ESI-HRMS (m/z): Calcd for $C_{17}H_{17}BrN_5O_2$ $[M+H]^+$ 402.0560. Found 402.0566.

4.2.5.13. (*E*)-4-(1-(6-(4-Iodophenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIn). This compound was obtained as a white solid in 46% yield; mp = 180–181 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.57 (s, 1H, Py-H), 8.31 (d, J = 8.8 Hz, 1H, Py-H), 7.77 (d, J = 7.6 Hz, 2H, Ar-H), 7.13 (d, J = 8.8 Hz, 1H, Py-H), 7.02 (d, J = 7.6 Hz, 2H, Ar-H), 4.15 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 163.9, 153.4, 148.7, 146.5, 145.3, 138.4, 128.3, 123.9, 111.3, 89.1, 50.9, 20.1, 17.0. ESI-HRMS (m/z): Calcd for $C_{17}H_{17}IN_5O_2$ $[M+H]^+$ 450.0421. Found 450.0416.

4.2.5.14. (*E*)-4-(1-(6-(4-(Benzyloxy)phenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIo). This compound was obtained as a white solid in 51% yield; mp = 149–150 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.55 (s, 1H, Py-H), 8.27 (d, J = 8.8 Hz, 1H, Py-H), 7.47 (d, J = 7.6 Hz, 2H, Ar-H), 7.41 (t, J = 8.8 Hz, 2H, Ar-H), 7.34 (t, J = 7.2 Hz, 1H, Py-H), 7.02–7.11 (m, 5H, Ar-H), 5.12 (s, 2H, OCH_2), 4.14 (s, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.8, 155.4, 148.8, 146.8, 146.6, 145.3, 138.2, 137.1, 128.4, 127.8, 127.7, 122.5, 115.6, 110.6, 69.6, 50.9, 20.1, 16.9. ESI-HRMS (m/z): Calcd for $C_{24}H_{24}N_5O_3$ $[M+H]^+$ 430.1874. Found 430.1881.

4.2.5.15. (*E*)-4-(1-(6-(4-Benzoylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIp). This compound was obtained as a yellow solid in 21% yield; mp = 173–174 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.64 (s, 1H, Py-H), 8.37 (d, J = 8.8 Hz, 1H, Py-H), 7.84 (d, J = 8.8 Hz, 2H, Ar-H), 7.76 (d, J = 7.2 Hz, 2H, Ar-H), 7.69 (t, J = 7.6 Hz, 1H, Ar-H), 7.58 (t, J = 7.6 Hz, 1H, Ar-H), 7.35 (d, J = 8.8 Hz, 2H, Ar-H), 7.23 (d, J = 8.8 Hz, 1H, Py-H), 4.16 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 166.7, 163.4, 157.3, 146.7, 145.4, 138.7, 137.2, 133.3, 132.5, 131.8, 129.5, 128.6, 120.9, 111.9, 50.9, 20.1, 17.1. ESI-HRMS (m/z): Calcd for $C_{24}H_{22}N_5O_3$ $[M+H]^+$ 428.1717. Found 428.1720.

4.2.5.16. (*E*)-4-(1-(6-(4-Isopropyl-3-methylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIq). This compound was obtained as a white solid in 50% yield; mp = 164–165 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.57 (s, 1H, Py-H), 8.28 (d, J = 8.8 Hz, 1H, Py-H), 7.28 (d, J = 8.0 Hz, 1H, Ar-H), 7.04 (d, J = 8.4 Hz, 1H, Ar-H), 6.98–6.91 (m, 2H, Ar-H, Py-H), 4.15 (s, 2H, CH_2), 3.07–3.13 (m, 1H, $CH(CH_3)_2$), 2.30 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.20 (d, J = 6.0 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.7, 150.9, 148.8, 146.7, 145.4, 143.0, 138.2, 136.4, 127.7, 125.8, 122.6, 118.9, 110.9, 50.9, 28.3, 23.2, 20.1, 18.9, 17.0. ESI-HRMS (m/z): Calcd for $C_{21}H_{26}N_5O_2$ $[M+H]^+$ 380.2081. Found 380.2087.

4.2.5.17. (*E*)-4-(1-(6-(2-Isopropyl-5-methylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIr). This compound was obtained as a yellow solid in 53% yield; mp = 165–166 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.56 (s, 1H, Py-H), 8.28 (d, J = 8.8 Hz, 1H, Py-H), 7.28 (d, J = 8.0 Hz, 1H, Ar-H), 7.06–7.01 (m, 2H, Ar-H, Py-H), 6.85 (s, 1H, Ar-H), 4.14 (s, 2H, CH_2), 2.90–2.97 (m, 1H, $CH(CH_3)_2$), 2.26 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.09 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 164.9, 150.3, 148.8, 146.7, 145.3, 138.3, 137.1, 136.4, 127.6, 126.7, 126.3, 122.6, 110.4, 50.9, 26.5, 22.9, 20.4, 20.1, 16.9. ESI-HRMS (m/z): Calcd for $C_{21}H_{26}N_5O_2$ $[M+H]^+$ 380.2081. Found 380.2087.

4.2.5.18. (*E*)-4-(1-(6-(4-Allyl-2-methoxyphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIs). This compound was obtained as a white solid in 49% yield; mp = 127–128 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H, NH), 8.51 (s, 1H, Py-H), 8.25 (d, J = 8.4 Hz, 1H, Py-H), 7.08 (d, J = 8.0 Hz, 1H, Ar-H), 7.00 (d, J = 8.4 Hz, 1H, Py-H), 6.97 (s, 1H, Ar-H), 6.81 (d, J = 8.0 Hz, 1H, Ar-H), 5.96–6.06 (m, 1H, =CH), 5.14 (d, J = 17.2 Hz, 1H, =CH), 5.08 (d, J = 10.0 Hz, 1H, =CH), 4.14 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.40 (d, J = 6.8 Hz, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 164.5, 151.2, 148.8, 146.5, 145.3, 139.8, 138.2, 138.0, 137.5, 127.4, 122.7, 120.5, 116.0, 113.2, 109.9, 55.6, 50.9, 20.1, 16.9. ESI-HRMS (m/z): Calcd for $C_{21}H_{24}N_5O_3$ $[M+H]^+$ 394.1874. Found 394.1880.

4.2.5.19. (*E*)-4-(1-(6-(2-Benzoyl-4-methoxyphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIt). This compound was obtained as a white solid in 35% yield; mp = 85–87 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H, NH), 8.42 (s, 1H, Py-H), 8.13 (d, J = 8.8 Hz, 1H, Py-H), 7.52–7.59 (m, 4H, Ar-H), 7.41 (t, J = 8.0 Hz, 2H, Ar-H), 6.98 (d, J = 8.8 Hz, 1H, Py-H), 6.91 (d, J = 2.4 Hz, 1H, Ar-H), 6.71 (d, J = 8.8 Hz, 1H, Ar-H), 4.12 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.4, 166.6, 163.7, 162.8, 152.7, 148.7, 146.0, 145.3, 138.1, 137.7, 132.7, 132.1, 129.1, 128.2, 127.9, 124.1, 111.0, 110.6, 108.6, 55.8, 50.9, 20.1, 16.9. ESI-HRMS (m/z): Calcd for $C_{25}H_{24}N_5O_4$ $[M+H]^+$ 458.1823. Found 458.1830.

4.2.5.20. (*E*)-4-(1-(6-(5-Amino-2-methylphenoxy)pyridin-3-yl)ethylideneamino)-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (IIIu). This compound was obtained as a white solid in 41% yield; mp = 84–85 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1H, NH), 8.57 (s, 1H, Py-H), 8.27 (d, J = 8.7 Hz, 1H, Py-H), 6.94 (t, J = 8.7 Hz, 2H, Ar-H, Py-H), 6.39 (d, J = 7.8 Hz, 1H, Ar-H), 6.26 (s, 1H, Ar-H), 5.04 (s, 2H, NH_2), 4.14 (s, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.88 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 164.6, 152.2, 148.8, 148.2, 146.8, 145.3, 138.2, 131.3, 127.3, 116.0, 111.3, 110.0, 107.1, 50.9, 20.1, 16.9, 15.0. ESI-HRMS (m/z): Calcd for $C_{18}H_{21}N_6O_2$ $[M+H]^+$ 353.1721. Found 353.1728.

4.3. Biological assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated in triplicate at 25 ± 1 °C. The error of the experiments was 5%. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[22] Evaluations were based on a percentage scale of 0–100, where 0 equals no activity and 100 equals total kill. As a standard pymetrozine was tested under the same conditions.

The foliar contact activity against bean aphid and the toxicity against mosquito larvae of compounds **I**, **II**, **IIIa**–**IIIu** and as a standard pymetrozine were evaluated according to reported procedures.[23]

The stomach toxicity against cotton bollworm, corn borer and oriental armyworm of compounds **I**, **II**, **IIIa**–**IIIu** and as a standard pymetrozine were evaluated according to reported procedures.[24]

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