Synthesis, Crystal Structure, and Insecticidal Activity of (*Z*)-Nitenpyram Derivatives with Optical Activity

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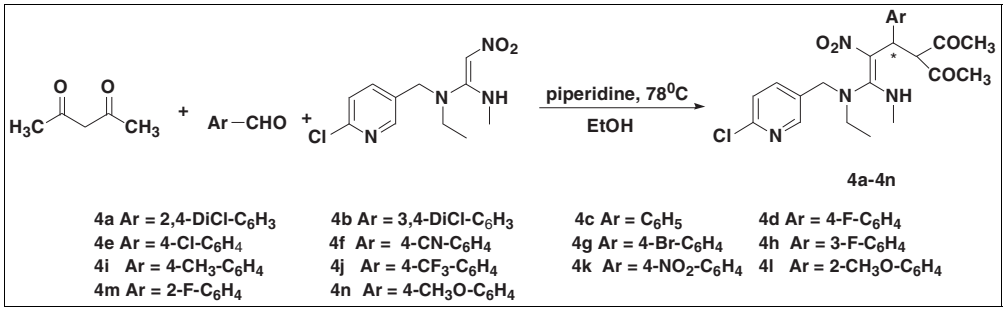

Fourteen novel nitenpyram derivatives (*Z*)-4-substituted-3-acetyl-6-methylamino −6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-5-nitno-2-oxa-5-hexene **4a–4n** were synthesized, and their structures were confirmed by ^{1}H NMR, IR, and elemental analysis. The stereostructure of **4h** was determined by the single-crystal X-ray analysis. The preliminary bioassay tests showed that most of the title compounds exhibited good insecticide activities against *Nilaparvata lugens* as well as *Aphis medicaginis* at 500 mg/L, whereas compound **4h** afforded the best activity, with 100% mortality against *A. medicaginis* at 100 mg/L.

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INTRODUCTION

Recently, neonicotinoid insecticides have gained worldwide attention for being the fastest growing class of insecticides in modern crop protection, with widespread use against most of the sucking and certain chewing pests. Because imidacloprid [1] was first introduced to the market in 1991, many new neonicotinoid insecticides are now on the market with their own prominence. As the second of the chloronicotinyl subclass, nitenpyram [2], which was brought to the market in 1995, was characterized with a somewhat lower toxicity against the mammals than imidacloprid [3]. However, during the past decades, frequent field applications have inevitably led to insect resistance to the major class of neonicotinoid insecticides [4–6]. Besides, the situation of bee pesticide poisoning had become worse [7]. Hence, the development of novel neonicotinoids with both good insecticidal activities and less resistance is highly desirable.

It is well known that the structure optimization of commercial neonicotinoids is one of the resistance management tactics [4,5,8]. The electron-withdrawing group of -NO_2 in neonicotinoids plays an important role in their activities [9], and according to X-ray analysis and ^{1}H NMR measurements at ambient temperature, the -NO_2 group in all commercialized neonicotinoids is in (*E*)-configuration. However, some neonicotinoid analogues with (*Z*)-configuration have been described to possess high insecticidal activity [8,10], and it was speculated that neonicotinoids in the (*Z*)-configuration might bind to the receptor in a different way.

Lightened by the aforementioned views, in our previous work [11–13] (Fig. 1), we have focused on designing novel cis-configuration nitenpyram analogues by forming a tetrahydropyrimidine ring, and these analogues exhibited good insecticide activities against *Nilaparvata lugens*. To search for more neonicotinoid compounds with novel structural features and broad insecticidal spectrum, on the basis of the aforementioned reports, using nitenpyram **1** as the leading compound, we synthesized a series of novel nitenpyram derivatives **4a–4n** possessing a chiral center adjacent to the aryl group (Ar) by introducing bulky substituent-fixed (*Z*)-configuration (Scheme 1). To confirm the structure with precise three-dimensional information, the single-crystal structure of compound **4h** was determined by X-ray diffraction (Fig. 2). Compared with the (*E*)-configuration of the structure of nitenpyram [14], compound **4h** obviously adopts a (*Z*)-configuration. The preliminary insecticidal activity tests indicated that most of title compounds **4a–4n** exhibited good activities against *N. lugens* as well as *Aphis medicaginis* at 500 mg/L.

RESULTS AND DISCUSSION

Synthesis of compounds. Target compounds **4a–4n** were prepared in multicomponent reactions, by treating compounds nitenpyram **1** with acetylacetone **2** and appropriate aromatic aldehydes **3a–3n** in ethanol at 78°C (Scheme 1). In addition, the products were purified by chromatography on silica gel by using ethyl acetate: petroleum ether (1:1) as eluent.

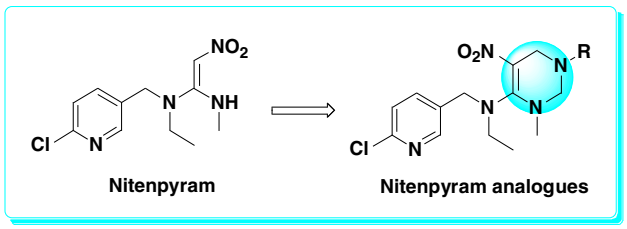
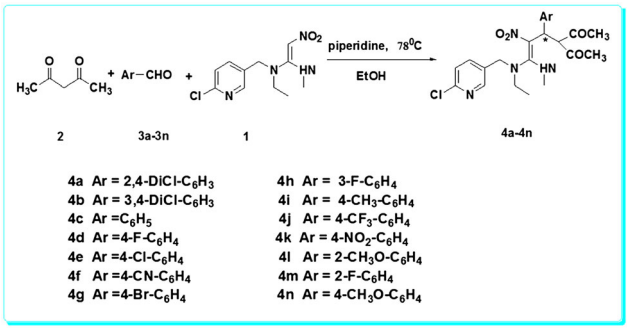


Figure 1. Nitenpyram analogues with tetrahydropyrimidine fixed cis-configuration in our group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 1. Structures and synthesis of **4a–4n**.



Insecticidal activity. Compounds **4a–4n** were tested for insecticidal activities against *N. lugens* as well as *A. medicaginis* at different concentrations. As indicated in Table 1, compounds **4a–4n** exhibited good insecticidal activities against *N. lugens* as well as *A. medicaginis* at 500 mg/L. Among these compounds, **4e**, **4f**, and **4h** had 100% mortality against *A. medicaginis* at 500 mg/L, especially compound **4h**, which afforded the best *in vitro* activity and had 100% mortality against *A. medicaginis* at 100 mg/L.

For the effect of monosubstituent at the phenyl group, it is observed that an electron-withdrawing group showed better potency compared with that of an electron-donating group from the data in Table 1, for example, 4-NO_2 (**4k**) > H (**4c**) > 2-CH_3O (**4l**), 4-CH_3O (**4n**) > 4-CH_3 (**4i**), whereas disubstituents (e.g., **4a** and **4b**) on the benzene ring are unfavorable to activities. Further studies of the insecticidal activity test at various dosages and structure–activity relationships are on the way.

X-ray crystal structure of 4h discussion. The molecular view of **4h** with atomic numbering scheme and packing diagram is shown in Figures 2 and 3.

As expected, the structure of compound **4h** adopts a (*Z*)-configuration obviously (Fig. 2). Interestingly, because of the transfer of lone-pair electrons on the amine (N(2), N(3)) to C(9)═C(13), the C(9)-N(3) and C(9)-N(2) bonds (1.412(2) and 1.341(2) Å) are remarkably shorter than the C-N single bond (1.50 Å) but close to C═N (1.33 Å) [15].

In the crystal structure, a five-membered ring (C(14), H(14), N(3), C(9), and C(13)), a six-membered ring (C(15), H(15B), O(2), N(4), C(13), and C(14)), and a seven-membered ring (C(6), H(6A), O(1), N(4), C(13) C(9), and N(2)) are established by intramolecular hydrogen bonds of C(14)-H(14)···N(3), C(15)-H(15B)···O(2), and C(6)-H(6A)···O(1), respectively. Intermolecular hydrogen bonds are found between adjacent molecules, forming a three-dimensional interaction network, which may help stabilize the crystal structure.

EXPERIMENTAL

All chemical reagents and solvents were purchased and used as received without further purification. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Bruker AVANCE 400 MHz with TMS as an internal standard. Elemental analyses were performed with a Perkin-Elmer 2400 instrument, and melting points were determined by an RK1 microscopic melting apparatus. IR spectra were obtained from KBr disks in the range of 4000–400 cm^{-1} on a Nicolet 5DX FTIR spectrophotometer.

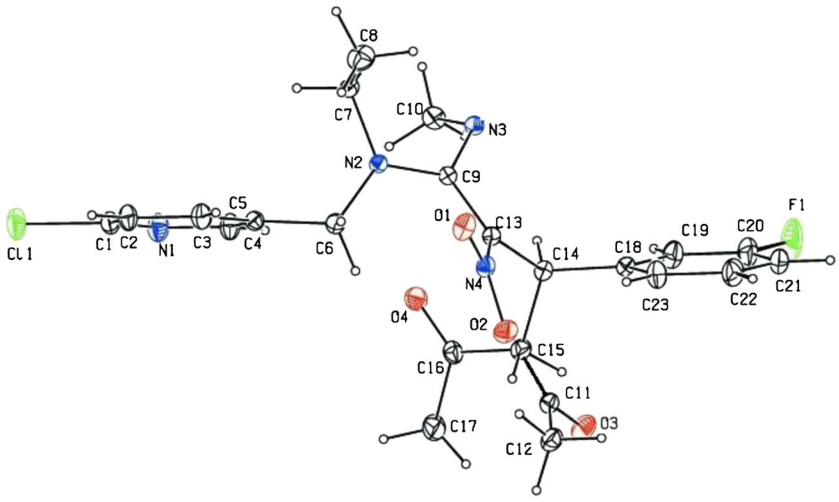


Figure 2. Molecular structure of compound **4h**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Insecticidal activities of target compounds **4a–4n** against *Nilaparvata lugens* as well as *Aphis medicaginis*.

		Mortality (%) at different concentrations (mg/L)					
		Nilaparvata lugens			*Aphis medicaginis*		
Compound	Ar	500	100	20	500	100	20
4a	2,4-diCl-C_6H_3	70	65	40	70	70	40
4b	3,4-diCl-C_6H_3	75	75	50	70	65	25
4c	C_6H_5	75	65	20	80	70	nt
4d	4-F-C_6H_4	85	80	nt	95	85	60
4e	4-Cl-C_6H_4	90	80	50	100	85	50
4f	4-CN-C_6H_4	85	70	40	100	80	65
4g	4-Br-C_6H_4	80	70	20	90	70	55
4h	3-F-C_6H_4	95	80	40	100	100	75
4i	4-CH_3-C_6H_4	70	65	55	70	60	50
4j	4-CF_3-C_6H_4	90	80	nt	95	70	60
4k	4-NO_2-C_6H_4	90	80	20	90	80	60
4l	2-CH_3O-C_6H_4	75	70	10	70	50	30
4m	2-F-C_6H_4	90	70	60	80	70	45
4n	4-CH_3O-C_6H_4	70	60	10	70	60	nt
Nitenpyram		100	100	100	100	100	100

nt, not tested.

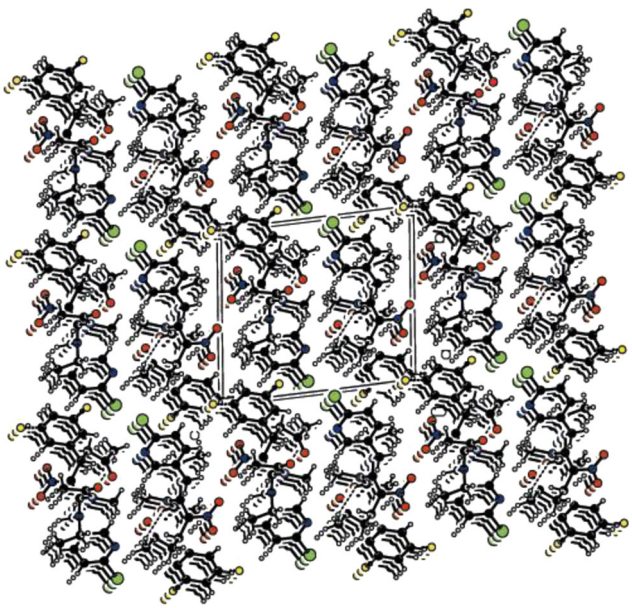


Figure 3. Packing diagram of compound **4h**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

General synthetic procedure for synthesis of 4a–4n. A mixture of nitenpyram **1** (10 mmol), acetylacetone **2** (15 mmol), appropriate aromatic aldehydes **3a–3n** (15 mmol), and piperidine (catalytic amount) in ethanol (30 mL) was heated to 78°C and stirred for 6 h at the same temperature. The reaction mixture was concentrated under reduced pressure and treated with 20 mL of water. Then, the solution was extracted three times with ethyl acetate, and the combined extracts were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure, and crude product was subjected to flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether to afford pure products.

The analytical data for compounds **4a–4n** were summarized as follows.

(+)-(5Z)-4-(2,4-Dichlorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4a). Yield: 82%, yellow crystal, mp 152–153°C; $[\alpha]_D^{25}$ +6.752 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2890, 2846, 3384, 1660, 1638, 1325, 1435, 1480, 1480, 950 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.42 (d, *J* = 31.9 Hz, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 13.4, 7.9 Hz, 2H), 7.22–7.16 (m, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 4.17 (d, *J* = 17.6 Hz, 1H), 3.96 (dd, *J* = 18.3, 9.9 Hz, 1H), 3.82 (d, *J* = 15.1 Hz, 1H), 3.21 (s, 3H), 3.05 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.79 (d, *J* = 4.7 Hz, 1H), 2.25 (s, 1H), 2.14 (s, 3H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{25}Cl_3N_4O_4$: C, 52.34; H, 4.77; N, 10.61. Found: C, 52.35; H, 4.78; N, 10.62.

(+)-(5Z)-4-(3,4-Dichlorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4b). Yield: 76%, yellow solid, mp 163–164°C; $[\alpha]_D^{25}$ +8.772 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2968, 2910, 3220, 1660; 1335, 1545, 1500, 1458, 980 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.40 (d, *J* = 32.8 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 13.4, 7.9 Hz, 2H), 7.22–7.16 (m, 1H), 4.23 (d, *J* = 14.6 Hz, 1H), 4.21 (d, *J* = 17.6 Hz, 1H), 3.96 (dd, *J* = 18.3, 9.9 Hz, 1H), 3.80 (d, *J* = 17.1 Hz, 1H), 3.21 (s, 3H), 3.05 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.77 (d, *J* = 4.7 Hz, 1H), 2.25 (s, 1H), 2.12 (s, 3H), 1.58 (d, *J* =7.1 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{25}Cl_3N_4O_4$: C, 52.34; H, 4.77; N, 10.61. Found: C, 52.34; H, 4.76; N, 10.63.

(+)-(5Z)-4-(1-Phenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4c). Yield: 79%, yellow solid, mp 132–134°C; $[\alpha]_D^{25}$ +10.961 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2928, 2890, 3500, 1680, 1652, 1380, 1530, 1400, 1458, 980 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (d, *J* = 2.1 Hz, 1H), 7.83 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.16 (dd, *J* = 18.4, 8.3 Hz, 5H), 4.24 (d, *J* = 14.7 Hz, 1H), 4.11 (d, *J* = 7.4 Hz, 1H), 3.97 (dd, *J* = 10.9,

4.0 Hz, 1H), 3.78 (d, J = 14.6 Hz, 1H), 3.29 (s, 3H), 3.06 (dd, J = 14.3, 7.2 Hz, 1H), 2.89 (d, J = 5.9 Hz, 1H), 2.26 (s, 1H), 2.12 (s, 3H), 1.62 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{27}ClN_4O_4$: C, 60.19; H, 5.93; N, 12.21. Found: C, 60.18; H, 5.94; N, 12.20.

(+)-(5Z)-4-(4-Fluorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4d). Yield: 79%, yellow solid, mp 114–116°C; $[\alpha]_D^{25}$ +4.877 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2938, 2856, 3228, 1660, 1638, 1342, 1545, 1490, 1480, 950 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.46 (d, J = 1.8 Hz, 1H), 8.33 (d, J = 1.7 Hz, 1H), 7.83 (dd, J = 8.2, 2.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.30–7.27 (m, 1H), 7.01–6.94 (m, 2H), 4.27 (d, J = 14.7 Hz, 1H), 4.12 (dd, J = 18.6, 10.8 Hz,1H), 3.98 (dd, J = 10.9, 3.9 Hz, 1H), 3.78 (d, J = 14.7 Hz, 1H), 3.32 (s, 3H), 3.09 (dd, J = 14.3, 7.1 Hz, 1H), 2.88–2.84 (m, 1H), 2.26 (s, 1H), 2.12 (s, 3H), 1.65 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}ClFN_4O_4$: C, 57.92; H, 5.49; N, 11.75. Found: C, 57.91; H, 5.50; N, 11.76.

(+)-(5Z)-4-(4-Chlorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4e). Yield: 88%, yellow crystal, mp 152–153°C; $[\alpha]_D^{25}$ +15.426 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2890, 2846, 3384, 1660, 1638, 1325, 1435, 1480, 1480, 950 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (s, 2H), 7.82 (d, J = 7.0 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.23 (s, 4H), 4.26 (d, J = 14.6 Hz, 1H), 4.09 (dd, J = 18.8, 11.4 Hz, 1H), 3.95 (dd, J = 10.8, 3.5 Hz, 1H), 3.76 (d, J = 14.7 Hz, 1H), 3.30 (s, 3H), 3.08 (dt, J = 14.6, 8.0 Hz, 1H), 2.85 (d, J = 4.3 Hz,1H), 2.25 (s, 1H), 2.11 (s, 3H), 1.65 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}Cl_2N_2O_4$: C, 59.36; H, 5.63; N, 6.02. Found: C, 59.38; H, 5.61; N, 6.03.

(+)-(5Z)-4-(4-Cyanophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4f). Yield: 84%, yellow solid, mp 175–176°C; $[\alpha]_D^{25}$ + 18.973 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2898, 2886, 3320, 1680, 1668, 1355, 1460, 1480, 1284, 972 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.47 (s, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.43 (d, J = 7.5 Hz,4H), 7.33 (d, J = 7.9 Hz, 1H), 4.29 (d, J = 15.1 Hz, 2H), 4.02 (d, J = 11.1 Hz, 1H), 3.77 (d, J = 14.6 Hz, 1H), 3.33 (s, 3H), 3.11 (dd, J = 12.9, 8.6 Hz, 1H), 2.89 (d, J = 7.9 Hz, 1H), 2.25 (s, 1H), 2.13 (s, 3H), 1.65 (s, 3H), 1.17 (d, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{24}H_{26}ClN_5O_4$: C, 59.56; H, 5.42; N, 14.47. Found: C, 59.55; H, 5.44; N, 14.46.

***(+)-(5Z)*-4-(4-Bromophenyl)-3-acetyl-6-methylamino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-5-nitno-2-oxa-5-hexene (4g).** Yield: 78%, yellow solid, mp 159–161°C; $[\alpha]_D^{25}$ +14.158 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2968, 2686, 3480, 1690, 1598, 1390, 1485, 1370, 1484, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (d, J = 1.7 Hz, 1H), 7.82 (dd, J = 8.2, 2.3 Hz, 1H), 7.42 (s, 1H), 7.39 (d, J = 5.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.26 (d, J = 14.7 Hz, 1H), 4.12 (d, J = 10.6 Hz, 1H), 3.94 (dd, J = 10.8, 3.8 Hz, 1H), 3.76 (d, J = 14.6 Hz, 1H), 3.30 (s, 3H), 3.13–3.04 (m, 1H), 2.80 (d, J = 4.1 Hz, 1H), 2.11 (s, 3H), 2.25 (s, 1H), 1.66 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}BrClN_4O_4$: C, 51.36; H, 4.87; N, 10.42. Found: C, 51.34; H, 4.88; N, 10.43.

(+)-(5Z)-4-(3-Fluorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4h). Yield: 80%, yellow crystal, mp 130–131°C; $[\alpha]_D^{25}$ +17.841 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2945, 2785, 3320, 1710, 1658, 1378, 1465, 1390, 1324, 1238 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.47 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 8.2, 2.4 Hz,1H), 7.42 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 10.2 Hz, 1H), 7.01–6.91 (m, 3H), 4.27 (d, J = 14.7 Hz, 1H), 4.12 (d, J = 7.7 Hz,1H), 4.00 (dd, J = 10.8, 3.8 Hz, 1H), 3.78 (d, J = 14.8 Hz, 1H), 3.31 (s, 3H), 3.09 (dd, J = 14.4, 7.2 Hz, 1H), 2.89 (d, J = 3.9 Hz, 1H), 2.26 (s, 1H), 2.13 (s, 3H), 1.67 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}ClFN_4O_4$: C, 57.92; H, 5.49; N, 11.75. Found: C, 57.94; H, 5.50; N, 11.73.

(+)-(5Z)-4-(4-Methylphenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4i). Yield: 75%, yellow solid, mp 122–123°C; $[\alpha]_D^{25}$ +21.627 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2962, 2682, 3390, 1710, 1658, 1378, 1465, 1540, 1454, 1136 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.44 (d, J = 1.8 Hz,1H), 7.82 (dd, J = 8.2, 2.4 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.11 (dd, J = 25.9, 7.7 Hz, 2H), 7.08 (d, J = 7.4 Hz, 2H), 4.23 (d, J = 14.7 Hz, 1H), 4.11 (d, J = 7.1 Hz, 1H), 3.96 (dd, J = 10.8, 4.1 Hz, 1H), 3.77 (d, J = 14.7 Hz, 1H), 3.28 (s, 3H), 3.06 (dd, J = 14.2, 7.3 Hz, 1H), 2.86 (d, J = 4.3 Hz,1H), 2.29 (s, 3H), 2.23 (s, 1H), 2.11 (s, 3H), 1.63 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H); *Anal*. Calcd for $C_{24}H_{29}ClN_4O_4$: C, 60.95; H, 6.18; N, 11.85. Found: C, 60.92; H, 6.19; N, 11.84.

(+)-(5Z)-4-(4-Trifluorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4j). Yield: 77%, yellow solid, mp 180–181°C; $[\alpha]_D^{25}$ +5.695 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2892, 2882, 3295, 1728, 1658, 1378, 1465, 1470, 1394, 1236 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.47 (d, J = 1.3 Hz, 1H), 7.83 (dd, J = 8.2, 2.4 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 1H), 4.28 (d, J = 14.7 Hz, 1H), 4.17–4.10 (m, 1H), 4.05 (dd, J = 10.6, 3.5 Hz, 1H), 3.77 (d, J = 15.3 Hz, 1H), 3.33 (s, 3H), 3.10 (dd, J = 14.0, 6.8 Hz, 1H), 2.91–2.85 (m, 1H), 2.25 (s, 1H), 2.13 (s, 3H), 1.64 (s, 3H), 1.22–1.16 (m, 3H); *Anal*. Calcd for $C_{24}H_{26}ClF_3N_4O_4$: C, 54.70; H, 4.97; N, 10.63. Found: C, 54.69; H, 4.98; N, 10.64.

(+)-(5Z)-4-(4-Nitrophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4k). Yield: 68%, yellow solid, mp 178–180°C; $[\alpha]_D^{25}$ +11.574 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2991, 2798, 3328, 1756, 1598, 1365, 1585, 1570, 1394, 1236 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.40 (d, J = 52.9 Hz, 1H), 8.19–8.09 (m, 2H), 7.82 (d, J = 8.2 Hz,1H), 7.49 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 4.31 (d, J = 14.9 Hz, 1H), 4.16 (d, J = 12.9 Hz, 1H), 4.10 (s, 1H), 3.78 (d, J = 14.6 Hz, 1H), 3.34 (s, 3H), 3.12 (dd, J = 14.3, 7.0 Hz, 1H), 2.90 (d, J = 5.4 Hz, 1H), 2.26 (s, 1H), 2.14 (s, 3H), 1.66 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}ClN_5O_6$: C, 54.82; H, 5.20; N, 13.93. Found: C, 54.81; H, 5.22; N, 13.94.

(+)-(5Z)-4-(2-Methoxylphenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4l). Yield: 82%, yellow solid, mp 112–113°C; $[\alpha]_D^{25}$ +19.674 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2987, 2795, 3187, 1739, 1468, 1348, 1565, 1580, 1420, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.43 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 8.1, 2.2 Hz, 1H), 7.44 (dd, J = 7.6, 1.1 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.24–7.17 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 4.21 (d, J = 14.7 Hz, 1H), 4.11 (d, J = 7.1 Hz, 1H), 3.96 (dd, J = 18.3, 10.8 Hz, 1H), 3.82 (d, J = 11.8 Hz, 1H), 3.75 (s, 3H), 3.20 (s, 3H), 3.02 (dd, J = 14.2, 7.2 Hz, 1H), 2.82 (d, J = 4.6 Hz, 1H), 2.26 (s, 1H),2.12 (s, 3H), 1.53 (s, 4H), 1.13 (t, J = 7.1 Hz, 3H); *Anal*. Calcd for $C_{24}H_{29}ClN_4O_5$: C, 58.95; H, 5.98; N, 11.47. Found: C, 58.97; H, 5.97; N, 11.49.

(+)-(5Z)-4-(2-Fluorophenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4m). Yield: 80%, yellow solid, mp 134–135°C; $[\alpha]_D^{25}$ +3.241 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2968, 2686, 3480,

1690, 1598, 1390, 1485, 1370, 1484, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.2, 2.4 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.17–7.10 (m, 4H), 4.23 (d, J = 14.7 Hz, 1H), 4.11 (d, J = 7.4 Hz, 1H), 3.97 (dd, J = 10.9,4.1 Hz, 1H), 3.77 (d, J = 14.7 Hz, 1H), 3.29 (s, 3H), 3.06 (dd, J = 14.3, 7.3 Hz, 1H), 2.88 (d, J = 4.5 Hz, 1H), 2.26 (s, 1H), 2.12 (s, 3H), 1.62 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{23}H_{26}ClFN_4O_4$: C, 57.92; H, 5.49; N, 11.75. Found: C, 57.94; H, 5.50; N, 11.76.

(+)-(5Z)-4-(4-Methoxylphenyl)-3-acetyl-6-methylamino-6-[N-(6-chloro-3-pyridinylmethyl)-N-ethyl]amino-5-nitno-2-oxa-5-hexene (4n). Yield: 88%, yellow solid, mp 129–130°C; $[\alpha]_D^{25}$ + 21.135 (*c* 1.00, C_2H_5OH); IR (KBr) ν: 2980, 2789, 3167, 1730, 1458, 1340, 1560, 1600, 1470, 1330 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (d, J = 2.2 Hz, 1H), 7.83 (dd, J = 8.2, 2.5 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 6.81 (dd, J = 8.9, 2.6 Hz, 2H), 4.24 (d, J = 14.7 Hz, 1H), 4.10 (d, J = 7.5 Hz, 1H), 3.94 (dd, J = 10.9, 4.1 Hz, 1H), 3.78–3.75 (m, 4H), 3.30 (s, 3H), 3.07 (dd, J = 14.3, 7.1 Hz, 1H), 2.85 (d, J = 4.4 Hz, 1H), 2.26 (s, 1H), 2.11 (s, 3H), 1.65 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); *Anal*. Calcd for $C_{24}H_{29}ClN_4O_5$: C, 58.95; H, 5.98; N, 11.46. Found: C, 58.97; H, 5.97; N, 11.47.

Insecticidal activity assay. The insecticidal activities of compounds **4a–4n** were measured against *A. medicaginis* according to the standard test [16] with a slight modification. The test analogues were dissolved in DMF and serially diluted with water containing Triton X-80 (0.1 mg/L) to obtain the required concentrations. The insects were reared at 25°(±1)°C, and groups of 10 were transferred to glass Petri dishes and sprayed with the aforementioned solutions by using a Potter sprayer. Assessments were made after 72 h by the number and size of live insects relative to that in the negative control, and evaluations are based on a percentage scale of 0–100, in which 100 the total kill and 0 no activity. The mortality rates were subjected to probit analysis. The reference compounds were nitenpyram, whereas water containing Triton X-80 (0.1 mg/L) was used as a negative control. All experiments were carried out in three replicates according to statistical requirements, and the results were shown in Table 1.

X-ray crystallography. The yellow crystal of compound **4h** having approximate dimensions of 0.20 × 0.10 × 0.10 mm^3 was mounted on a glass fiber in a random orientation. The data were collected by a Bruker Smart Apex CCD diffractometer with a graphite-monochromated MoKα radiation (λ = 0.71073 Å) by using a φ–ω scan mode in the range of 2.23° ≤ θ ≤ 24.75° at 298(2) K. Empirical absorption correction was applied. A total of 12,094 reflections including 4416 unique ones [R(int) = 0.0351] were measured. The intensity data were corrected for Lp factors and empirical absorption. The structure was solved by direct methods and expanded by using Fourier difference techniques with SHELXS-97 [17] program package. All the nonhydrogen atoms were refined anisotropically, and hydrogen atoms were located at their idealized positions. The final R = 0.0549, wR = 0.1603 ($w = 1/[s^2(Fo^2) + (0.0964P)^2 + 0.0770P]$, where $P = (Fo^2 + 2Fc^2)/3$), S = 1.111, $(\Delta/\sigma)max$ = 0.000, $(\Delta\rho)max$ = 0.458, and $(\Delta\rho)min$ = −0.428 e/Å^3. The structural plots were drawn with SHELXTL-97 software package. The details of the data collection and refinement parameters are given in Table 2. Other details of the structure have been deposited with the Cambridge Crystallographic Data Centre No. CCDC 835027.

Table 2

Crystal data and structure refinement parameters for $C_{23}H_{26}ClFN_4O_4$ (**4h**).

	4h
Empirical formula	$C_{23}H_{26}ClFN_4O_4$
Formula weight	476.93
Temperature (K)	298 (2)
Wavelength (Å)	0.71073
Crystal system, space group	Triclinic, P-1
a, b, c (Å)	7.9732 (8), 12.2451 (12), 12.9624 (13)
α, β, γ (°)	94.231, 97.266, 107.781
Volume (Å^3)	1186.9 (2)
Z	2
Density (calcd) (Mg/m^3)	1.334
Absorption coefficient (mm^{-1})	0.205
F(000)	500
Crystal size (mm^3)	0.20 × 0.10 × 0.10
Index ranges	$-9 \le h \le 9$, $-14 \le k \le 14$, $-15 \le l \le 15$
Flections collected/unigue	12094/4416 [R(int) = 0.0351]
Refinement method	Full-matrix least squares on F^2
Completeness to theta (%)	99.7
Data/restraints/parameters	4416/2/312
Goodness-of-fit on F^2	1.111
Final R indices [I > 2sigma(I)]	R1 = 0.0549, wR2 = 0.1603
R indices (all data)	R1 = 0.0689, wR2 = 0.1698
Largest diff peak and hole (Å^{-3})	0.458 and −0.428

CONCLUSION

In summary, a novel series of optical active (*Z*)-nitenpyram derivatives **4a–4n** possessing a chiral center adjacent to the aryl group (Ar) by introducing bulky group into nitenpyram was synthesized, and the (*Z*)-configuration was confirmed by X-ray diffraction. The structures of title compounds were characterized by IR, ^1H NMR, and elementary analysis. Bioassay against *N. lugens* and *A. medicagini*s at 500 mg/L shows that compounds **4a–4h** exhibit good insecticide activities, especially compound **4h**, which afforded the best activity, with 100% mortality against *Aphis medicagini*s at 100 mg/L.

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