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Synthesis, Insecticidal Activity, Crystal Structure, and Molecular Docking Studies of Nitenpyram Analogues with an ω-Hydroxyalkyl Ester Arm Anchored on the Tetrahydropyrimidine Ring

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Supporting Information

ABSTRACT: On the basis of the research of the proposed modes of action between neonicotinoids and insect nicotinic acetylcholine receptor (nAChR), a new series of nitenpyram analogues with an ω-hydroxyalkyl ester arm anchored on the tetrahydropyrimidine ring was designed and synthesized to further enhance the strength of the hydrogen-bonding action they display in binding with the nAChR. The structures of the target compounds were characterized by ^{1}H NMR, IR, and elemental analysis, and the *cis* configuration was confirmed by X-ray diffraction. Preliminary bioassays indicated that all of the nitenpyram analogues exhibited good insecticidal activity against *Nilaparvata lugens* and *Myzus persicae* at 100 mg/L, whereas analogues **4d** and **6a** afforded the best in vitro activity that had ≥95% mortality at 4 mg/L; the LC_{50} values of the analogues **4d** and **6a** were 0.170 and 0.154 mg/L, respectively. Structure−activity relationship (SAR) studies suggested that their insecticidal potency was also dual-controlled by the flexibility and size of the molecule. In addition, molecular docking simulations revealed that analogues **4d** and **6a** displayed stronger hydrogen-bonding action in binding with the nAChR, which explained the SARs observed in vitro and implied that the designed nitenpyram analogues are both practical and feasible.

KEYWORDS: *neonicotinoid insecticides, nitenpyram analogues, hydrogen-bonding action, ω-hydroxyalkyl ester, insecticidal activities, structure−activity relationships, molecular docking*

INTRODUCTION

Neonicotinoid insecticides (NNSs) selectively act on the insect nicotinic acetylcholine receptor (nAChR),[1−3] which represented a new generation of synthetic insecticides as they had some specific properties that allowed them to be the fastest growing synthetic insecticides on the market. Some of their properties are no cross-resistance to conventional long-established insecticide classes, a broad-spectrum insecticidal activity, low application rate, novel mode of action, and favorable safety profile.[4,5] Emerging as the fourth generation of pesticides replacing organophosphorus, carbamate, and pyrethroid compounds, neonicotinoids are increasingly used in crop protection and animal health care. However, a significant threat of resistance was observed after frequent applications of the NNSs. As a result, development of new neonicotinoids with novel structures and high insecticidal activities against resistance is an urgent requirement.[6−9] It is well-known that the structure optimization of commercial neonicotinoids is an effective resistance management tactic.[10−12]

In the development of neonicotinoid insecticides, there were three modes of action of neonicotinoids against nAChR, which were presumed successively by Yamamoto, Kagabu, and Casida.[13−15] The three modes of action demonstrated that the interactions between the neonicotinoid compounds and nAChR were not only due to the electrostatic interaction but also due to the hydrogen-bonding action. Therefore, the hydrogen-bonding action had an important effect on the insecticidal activities of neonicotinoid compounds.

A major emphasis in our previous study[16,17](Figure 1) involved the structure optimization of nitenpyram **1**; two series of nitenpyam analogues with different amino acid alkyl esters were synthesized, and the bioassays indicated that analogues **2** and **3** exhibited quite good insecticidal activities against *Nilaparvata lugens*. Considering the results of SARs and molecular docking simulations, we found that the higher insecticidal potency of compounds **2a** (R = ^{i}Bu), **3a** (R = ^{n}Pr, *n* = 2), and **3b** (R = ^{i}Pr, *n* = 2) (Figure 2) were controlled by the molecular flexibility and size. However, in the final analysis, we found that more hydrogen bonds were formed between the ester groups of compounds **2a**, **3a**, and **3b** and the relevant amino acid residues at the ligand binding pocket; therefore, compounds **2a**, **3a**, and **3b** had stronger hydrogen-bonding actions compared with their binding with the nAChR.

On the basis of the theory above, the core of our work of the neonicotinoid structural optimization or design is how to increase the strength of the hydrogen-bonding action of the neonicotinoid compounds in binding with the nAChR.

We suppose that the main method to control the strength of the hydrogen-bonding action is the introduction of an organic segment bearing the electronegative atom into the lead compounds. Therefore, to enhance the strength of the hydrogen-bonding action, on the basis of our previous work, starting from nitenpyram, various amino acid ω-hydroxyalkyl esters were introduced into the lead compounds (Scheme 1), and the other novel nitenpyram analogues **4**−**7** with an ω-

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Figure 1. Our previous studies of nitenpyam analogues with amino acid alkyl esters.

Figure 2. Structures of nitenpyram analogues **2a**, **3a**, and **3b**.

hydroxyalkyl ester arm anchored on the tetrahydropyrimidine ring were designed and synthesized. To confirm the structure of nitenpyram analogues **4**–**7** with precise three-dimensional information, the single-crystal structure of **4g** was further determined by X-ray diffraction (Figure 3). As expected, a preliminary bioassay against *Nilaparvata lugens* and *Myzus persicae* showed that nitenpyram analogues **4**–**7** exhibited good insecticidal activities at 100 mg/L, whereas analogues **4d** and **6a** afforded the best in vitro activity that had ≥95% mortality at 4 mg/L; the LC_{50} values of the analogues **4d** and **6a** were 0.170 and 0.154 mg/L, respectively. Their SAR studies in this paper suggested that their insecticidal potencies were also dual-controlled by the flexibility and size of the molecule. Moreover, in the rest of this paper, the molecular docking study was carried out to investigate the interaction between nAChR and nitenpyram analogues. The results of the molecular docking study showed that the higher insecticidal potency of analogues **4d** and **6a** exhibited stronger hydrogen bonding than the others. Therefore, the strength of the hydrogen-bonding action was the influential factor for the bioactivities of our designed nitenpyram analogues.

MATERIALS AND METHODS

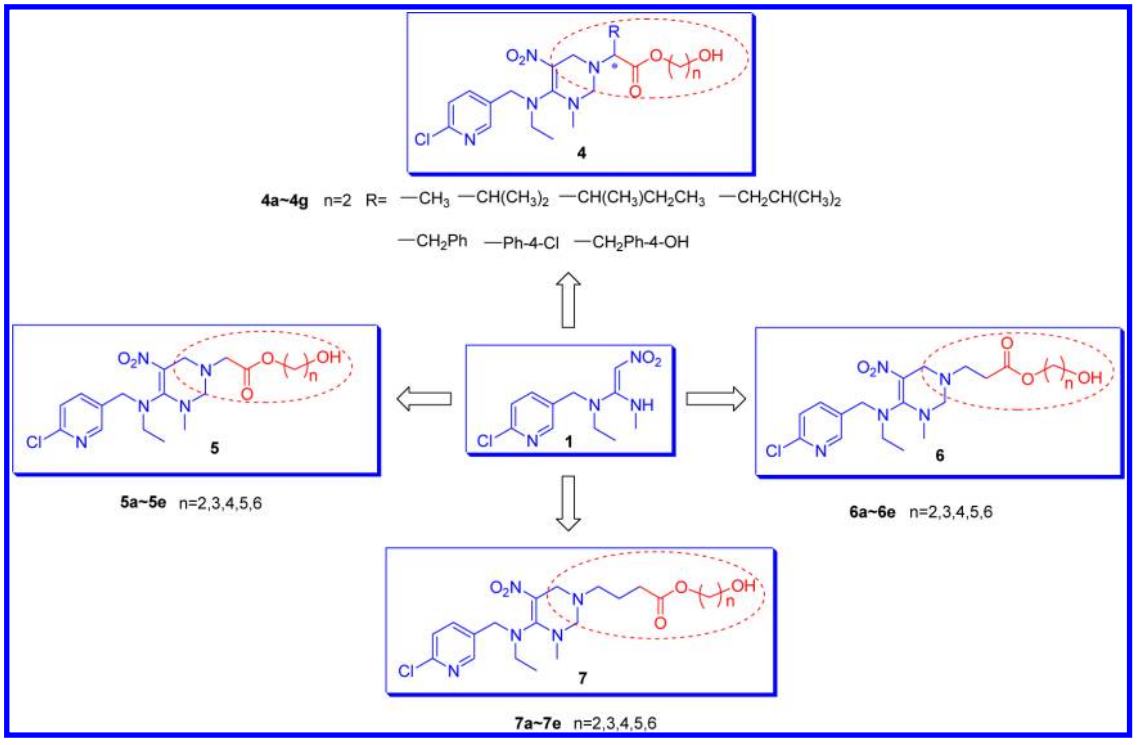
Instruments. Melting points were measured using an uncorrected RK-1 microscopic melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker AVANCE (400 MHz) spectrometer with chloroform ($CDCl_3$) as the solvent and tetramethylsilane as the internal standard. The IR spectra were obtained from KBr disks in the range of 4000–400 cm^{-1} on a Nicolet 5DXFT-IR spectrophotometer. Combustion analyses for elemental composition were conducted on a Perkin-Elmer 2400 instrument. All microwave experiments were performed using a YL8023B1 microwave reactor possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz.

Synthetic Procedures. Synthesis procedures for the title compounds are summarized in Scheme 2. Unless otherwise noted, reagents and solvents were of analytical reagent grade or were chemically pure and used as received without further purification.

General Synthetic Procedures for Target Compounds 4a–7e. Amino acids were converted to the intermediates of amino acid ω-hydroxyalkyl ester hydrochlorides according to the procedures given in the literature.[18] Starting from 2-chloro-5-chloromethylpyridine, a set of (*E*)-*N*-(6-chloro-3-pyridylmethyl)-*N*-ethyl-1-chloro-2-nitroethylene-1-amine and **1** was prepared according to the procedures in the literature.[19,20]

A mixture of compound **1** (2.71 g, 10.0 mmol), amino acid ω-hydroxyalkyl ester hydrochloride (12.0 mmol), Et_3N (1.7 mL), and formaldehyde (1.95 mL, 37%) in ethanol (20 mL) was heated to 65

Scheme 1. Structures of Novel Nitenpyram 4–7 with Different Amino Acid ω-Hydroxyalkyl Esters



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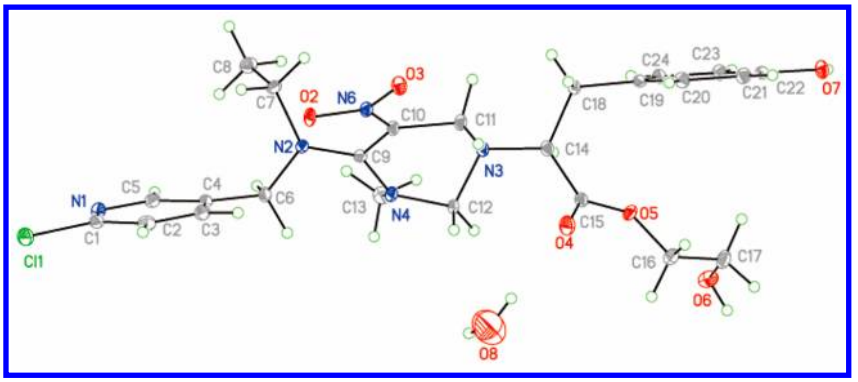
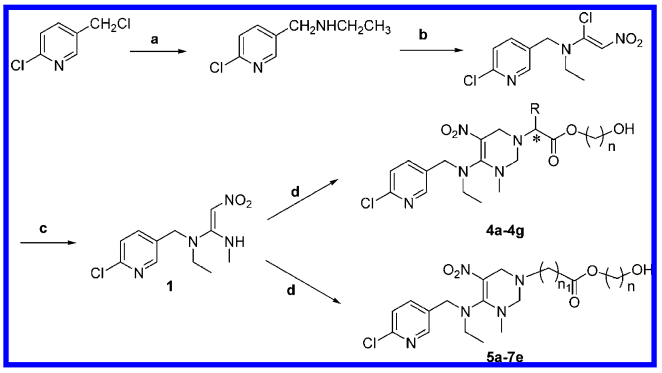


Figure 3. Crystal structures of compound **4g**.

Scheme 2. General Synthetic Route for the Target Compounds[a]



[a]Reagents and conditions: (a) ethanamine (41%); (b) 1,1,1-trichloro-2-nitroethane/$CHCl_3$, 2−7 °C (64%); (c) methanamine, 3−7 °C (56%); (d) amino acid ω-hydroxyalkyl ester hydrochloride, HCHO, Et_3N/EtOH (59−76%).

°C for 5 min in a microwave reactor and stirred for 20 min at that temperature. The reaction mixture was concentrated under reduced pressure and treated with 20 mL of water. Then, the solution was extracted three times with dichloromethane, and the combined extracts were dried over $MgSO_4$. The organic phase was evaporated under reduced pressure, and the residue was subjected to flash chromatography on silica gel, eluting with ethyl acetate/ethanol (15:1−20:1) to afford pure products.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**4a**):* yield 75%; yellow oil; $[\alpha]_D^{25}$ = +21.836° (*c* 0.01 g/mL, CH_3COCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32−8.31 (d, *J* = 2.0 Hz, 1H, Py-H), 7.77−7.68 (m, 1H, Py-H), 7.34−7.32(d, *J* = 8.2 Hz, 1H, Py-H), 4.56−4.51 (dd, *J* = 15.0, 6.4 Hz, 1H, Py-CH_2), 4.32−4.23 (m, 2H, $COOCH_2$), 4.21−4.16 (dd, *J* = 21.2, 6.1 Hz, 1H, Py-CH_2), 3.90−3.84 (m, 2H, CH_2OH), 3.84−3.68 (m, 4H), 3.67−3.60 (m, 1H, $CHCH_3$), 3.26 (m, 1H), 2.99−2.97 (d, *J* = 5.8 Hz, 3H, NCH_3), 2.95−2.86 (m, 1H), 2.04 (s, 1H, OH), 1.45−1.42 (dd, *J* = 7.1, 3.5 Hz, 3H, $CHCH_3$), 1.20−1.14 (q, *J* = 7.3 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2934, 2875, 1735, 1545, 1243. Anal. Calcd for $C_{18}H_{26}ClN_5O_5$: C%, 50.53; H%, 6.12; N%, 16.37. Found: C%, 50.48; H%, 6.15; N%, 16.38.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3-methyl butanate (**4b**):* yield 74%; yellow oil; $[\alpha]_D^{25}$ = +10.781° (*c* 0.01 g/mL, CH_3COCH_3); ^{1}H NMR($CDCl_3$, 400 MHz) δ 8.33−8.30 (d, *J* = 12.6 Hz, 1H, Py-H), 7.77−7.64 (dd, *J* = 7.9, 8.1 Hz, 1H, Py-H), 7.35−7.33 (d, *J* = 8.2 Hz, 1H, Py-H), 4.55−4.50 (dd, *J* = 14.8, 5.1 Hz, 1H, Py-CH_2), 4.33−4.26 (m, 2H, $COOCH_2$), 4.16−4.12 (dd, *J* = 40.5, 12.1 Hz, 1H, Py-CH_2), 3.87−3.84 (t, *J* = 4.6 Hz, 2H, CH_2OH), 3.82−3.67 (m, 4H), 3.31−3.24 (m, 1H), 3.12−3.08 (dd, *J* = 10.2, 4.9 Hz, 1H, NCHCO), 2.97−2.95 (d, *J* = 1.8 Hz, 3H, NCH_3), 2.94−2.87 (m, 1H), 2.15−2.08 (m, 1H), 2.05 (s, 1H, OH), 1.22−1.16 (q, *J* = 7.4 Hz, 3H, NCH_2CH_3), 1.10−1.06 (dd, *J* = 9.9, 6.7 Hz, 3H, $CHCH_3$), 0.96−0.95 (dd, *J* = 8.6, 6.1 Hz, 3H, $CHCH_3$); IR (KBr, cm^{-1}) ν 2938, 2871, 1738, 1542, 1243. Anal. Calcd for $C_{20}H_{30}ClN_5O_5$: C%, 52.69; H%, 6.63; N%, 15.36. Found: C%, 52.68; H%, 6.65; N%, 15.38.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3-methyl pentanate (**4c**):* yield 71%; yellow oil; $[\alpha]_D^{25}$ = +31.740° (*c* 0.01 g/mL, CH_3COCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33−8.30 (dd, *J* = 9.6, 1.8 Hz, 1H, Py-H), 7.74−7.64 (m, 1H, Py-H), 7.35−7.33 (d, *J* = 8.2 Hz, 1H, Py-H), 4.54−4.50 (dd, *J* = 15.0, 5.1 Hz, 1H, Py-CH_2), 4.41−4.36 (dd, *J* = 6.5, 4.6 Hz, 2H, $COOCH_2$), 4.26−4.14 (dd, *J* = 14.0, 10.8 Hz, 1H, Py-CH_2), 3.85−3.76 (m, 2H, CH_2OH), 3.74−3.61 (m, 4H), 3.35−3.27 (m, 1H), 3.25−3.22 (dd, *J* = 10.1, 2.6 Hz, 1H, NCHCO), 2.9−2.95 (d, *J* = 2.3 Hz, 3H, NCH_3), 2.94−2.88 (m, 1H), 2.06 (s, 1H, OH), 1.92 (m, 1H, $CHCH_3$), 1.72−1.64 (m, 2H, CH_2CH_3), 1.17−1.22 (q, *J* = 7.0 Hz, 3H, NCH_2CH_3), 1.00−0.93 (m, 6H); IR (KBr, cm^{-1}) ν 2933, 2875, 1732, 1546, 1245. Anal. Calcd for $C_{21}H_{32}ClN_5O_5$: C%, 53.67; H%, 6.86; N%, 14.90. Found: C%, 53.65; H%, 6.89; N%, 14.93.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-4-methyl pentanate (**4d**):* yield 71%; yellow oil; $[\alpha]_D^{25}$ = +31.743° (*c* 0.01 g/mL CH_3COCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34−8.31 (d, *J* = 11.3 Hz, 1H, Py-H), 7.76−7.68 (dd, *J* = 8.2, 7.1 Hz, 1H, Py-H), 7.35−7.33 (d, *J* = 8.0 Hz, 1H, Py-H), 4.55−4.52 (d, *J* = 15.3 Hz, 1H, Py-CH_2), 4.33−4.26 (dd, *J* = 12.0, 4.3 Hz, 1H, Py-CH_2), 4.24−4.18 (m, 2H, $COOCH_2$), 3.91−3.82 (t, *J* = 8.1 Hz, 2H, CH_2OH), 3.79−3.68 (m, 4H), 3.61−3.59 (t, *J* = 7.1 Hz, 1H, NCHCO), 3.32−3.26 (m, 1H), 2.95−2.94 (d, *J* = 3.4 Hz, 3H, NCH_3), 2.91−2.86 (m, 1H), 2.06 (s, 1H, OH), 1.75−1.67 (m, 2H), 1.66−1.61 (m, 1H, $CHCH_3$), 1.19 (dd, *J* = 12.9, 6.3 Hz, 3H, NCH_2CH_3), 1.00−0.95 (dd, *J* = 12.0, 5.9 Hz, 6H, $CH(CH_3)_2$); IR (KBr, cm^{-1}) ν 2933, 2875, 1732, 1546, 1245. Anal. Calcd for $C_{21}H_{32}ClN_5O_5$: C%, 53.67; H%, 6.86; N%, 14.90. Found: C %, 53.68; H%, 6.85; N%, 14.88.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3-phenyl propanate (**4e**):* yield 70%; yellow oil; $[R]_D^{25}$ = +13.562° (*c* 0.01 g/mL CH_3COCH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31−8.29 (d, *J* = 7.4 Hz, 1H, Py-H), 7.73−7.65 (m, 1H, Py-H), 7.35 (s, 1H, Py-H), 7.34−7.19 (m, 5H, Ph-H), 4.54−4.50 (d, *J* = 14.9 Hz, 1H, Py-CH_2), 4.22−4.18 (d, *J* = 14.7 Hz, 1H, Py-CH_2), 4.12−4.17 (dd, *J* = 8.4, 6.0 Hz, 2H, $COOCH_2$), 3.94−3.90 (m, 2H, CH_2OH), 3.84−3.74 (m, 4H), 3.69−3.62 (m, 1H, NCHCO), 3.30−3.21 (m, 1H), 3.13−3.11 (d, *J* = 7.7 Hz, 2H, CH_2-Ph), 2.96−2.88 (m, 1H), 2.83−2.81 (d, *J* = 6.9 Hz, 3H, NCH_3), 2.06 (s, 1H, OH), 1.20−1.15 (q, *J* = 7.0 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2931, 2874, 1738, 1546, 1244. Anal. Calcd for $C_{24}H_{30}ClN_5O_5$: C%, 57.20; H%, 6.00; N%, 13.90. Found: C %, 57.23; H%, 6.05; N%, 13.92.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-(4-chloro)phenyl acetate (**4f**):* yield 74%; yellow oil; $[R]_D^{25}$ = +26.541° (*c* 0.01 g/mLCH_3COCH_3); mp 95−103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33−8.31 (d, *J* = 7.8 Hz, 1H, Py-H), 7.75−7.66 (dd, *J* = 8.4

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Hz, 1H, Py-H), 7.43−7.37 (m, 3H, Ph-H), 7.36−7.34 (d, J = 8.0 Hz, 1H, Py-H), 7.28 (t, J = 1.7 Hz, 1H, Ph-H), 4.54−4.46 (dd, J = 12.1, 9.4 Hz, 1H, Py-CH_2), 4.35−4.32 (d, J = 10.3 Hz, 1H, Py-CH_2), 4.26−4.20 (m, 2H, $COOCH_2$), 3.85−3.82 (m, 2H, CH_2OH), 3.80−3.69 (m, 4H), 3.66−3.59 (m, 1H, NCHCO), 3.56−3.49 (dd, J = 16.1, 14.9 Hz, 2H,CH_2-Ph), 3.36−3.19 (m, 1H), 3.00−2.93 (dt, J = 14.4, 7.3 Hz, 1H), 2.90−2.86 (d, J = 16.5 Hz, 3H, NCH_3), 2.06 (s, 1H, OH), 1.23−1.17 (q, J = 7.5 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2939, 2877, 1733, 1545, 1249. Anal. Calcd for $C_{24}H_{29}C_{l2}N_5O_5$: C%, 53.54; H%, 5.43; N%, 13.01. Found: C%, 53.53; H%, 5.45; N%, 13.05.

*(+)-2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3-(4-hydroxyl) phenyl propanate(**4g**):* yield 72%; yellow solid; $[R]_D^{25}$ = +24.522° (c 0.01 g/mL CH_3COCH_3); mp 89−91 °C;^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30−8.24 (dd, J = 2.1 Hz, 1H, Py-H), 7.68 (m, 1H, Py-H), 7.37−7.28 (t, J = 4.8 Hz, 1H, Py-H), 7.28 (s, 1H, Ph-OH), 7.08−7.04 (t, J = 7.6 Hz, 2H, Ph-H), 6.83−6.80 (dd, J = 8.4, 3.2 Hz, 2H, Ph-H), 4.52−4.48 (dd, J = 13.5, 4.1 Hz, 1H, Py-CH_2), 4.22−4.18 (dd, J = 6.8, 2.3 Hz, 1H, Py-CH_2), 4.19−4.11 (m, 2H, $COOCH_2$), 3.99−3.85 (m, 2H, CH_2OH), 3.84−3.72 (m, 4H), 3.71−3.61 (m, 1H, NCHCO), 3.32−3.24 (dt, J = 14.2, 6.7 Hz, 1H), 3.07−3.00 (m, 2H,CH_2-Ph), 2.92−2.82 (m, 1H), 2.82−2.74 (d, J = 13.4 Hz, 3H, NCH_3), 2.05 (s, 1H, OH), 1.22−1.16 (q, J = 7.0 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2939, 2877, 1733, 1545, 1249. Anal. Calcd for $C_{24}H_{30}ClN_5O_6$: C%, 55.54; H%, 5.82; N%, 13.47. Found: C%, 55.50; H%, 5.85; N%, 13.45.

*2′-Hydroxyethyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] acetate (**5a**):* yield 68%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 2.4 Hz, 1H, Py-H), 7.73−7.71 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.54−4.51 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.32−4.27 (m, 2H, $COOCH_2$), 4.19−4.17 (d, J = 15.0 Hz, 1H, Py-CH_2), 3.91−3.84 (m, 2H, CH_2OH), 3.83−3.73 (m, 4H), 3.48 (s, 2H, $COCH_2N$), 3.30−3.23 (dt, J = 14.2, 7.1 Hz, 1H), 3.06 (s, 3H, NCH_3), 2.98−2.88 (m, 1H), 2.05 (s, 1H,OH), 1.20−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2933, 2875, 1735, 1541, 1249. Anal. Calcd for $C_{17}H_{24}ClN_5O_5$: C%, 49.34; H%, 5.85; N%, 16.92. Found: C%, 49.30; H%, 5.82; N%, 16.95.

*3′-Hydroxypropyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] acetate (**5b**):* yield 69%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33−8.32 (d, J = 2.3 Hz, 1H, Py-H), 7.74−7.71 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.54−4.51 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.33−4.30 (t, J = 6.2 Hz, 2H, $COOCH_2$), 4.20−4.16 (d, J = 15.0 Hz, 1H, Py-CH_2), 3.85−3.78 (m, 2H, CH_2OH), 3.76−3.69 (m, 4H), 3.45−3.44 (d, J = 1.4 Hz, 2H, $COCH_2N$), 3.27 (m, 1H), 3.05 (s, 3H, NCH_3), 2.98−2.88 (m, 1H), 2.04 (s, 1H, OH), 1.94−1.88 (m, 2H, CH_2CH_2OH), 1.20−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2933, 2875, 1735, 1541, 1249. Anal. Calcd for $C_{18}H_{26}ClN_5O_5$: C%, 50.53; H%, 6.12; N%, 16.37. Found: C%, 50.55; H%, 6.16; N%, 16.49.

*4′-Hydroxybutyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] acetate (**5c**):* yield 67%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H, Py-H), 7.73−7.71 (d, J = 8.2 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.55−4.51 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.22−4.18 (t, J = 6.4 Hz, 2H, $COOCH_2$), 4.17−4.10 (m, 1H, Py-CH_2), 3.83−3.79 (t, J = 8.6 Hz, 2H, CH_2OH), 3.79−3.67 (m, 4H), 3.43 (s, 2H, $COCH_2N$), 3.31−3.23 (m, 1H), 3.05 (s, 3H, NCH_3), 2.98−2.89 (m, 1H), 2.05 (s, 1H, OH), 1.81−1.74 (m, 2H), 1.69−1.60 (m, 2H), 1.20−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2938, 2871, 1733, 1541, 1249. Anal. Calcd for $C_{19}H_{28}ClN_5O_5$: C%, 51.64; H%, 6.39; N%, 15.85. Found: C%, 51.65; H%, 6.36; N%, 15.89.

*5′-Hydroxypentyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] acetate (**5d**):* yield 63%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, J = 2.3 Hz, 1H, Py-H), 7.74−7.71 (dd, J = 8.2, 2.4 Hz, 1H, Py-H), 7.36−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.55−4.51 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.19 (s, 1H, Py-CH_2), 4.18−4.16 (d, J = 6.5 Hz, 2H, $COOCH_2$), 3.86−3.70 (m, 4H), 3.69−3.66(t, J = 6.4 Hz, 2H, CH_2OH), 3.44 (s, 2H, $COCH_2N$), 3.32−3.23(m, 1H), 3.06 (s, 3H), 2.98−2.88 (m, 1H), 2.05 (s, 1H, OH), 1.75−1.68 (m, 2H), 1.65−1.58 (m, 2H), 1.47 (m, 2H), 1.21−1.19 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2934, 2871, 1733, 1549, 1249. Anal. Calcd for $C_{20}H_{30}ClN_5O_5$: C%, 52.69; H%, 6.63; N%, 15.36. Found: C%, 52.71; H%, 6.60; N%, 15.38.

*6′-Hydroxyhexyl-2-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] acetate (**5e**):* yield 59%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H, Py-H), 7.74−7.72 (d, J = 8.2 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.55−4.52 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.19−4.18 (d, J = 6.2 Hz, 1H, Py-CH_2), 4.16−4.15 (d, J = 6.5 Hz, 2H, $COOCH_2$), 3.83−3.69 (m, 4H), 3.67−3.64 (t, J = 6.5 Hz, 2H, CH_2OH), 3.44 (s, 2H, $COCH_2N$), 3.30−3.23 (m, 1H), 3.06 (s, 3H, NCH_3), 2.98−2.88 (m, 1H), 2.05 (s, 1H, OH), 1.70−1.67 (m, 2H), 1.61−1.58 (m, 2H), 1.42−1.41 (d, J = 3.1 Hz, 4H), 1.21−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2934, 2878, 1735, 1545, 1249. Anal. Calcd for $C_{21}H_{32}ClN_5O_5$: C%, 53.67; H%, 6.86; N%, 14.90. Found: C%, 53.71; H%, 6.89; N%, 14.92.

*2′-Hydroxyethyl-3-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**6a**):* yield 74%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, J = 2.5 Hz, 1H, Py-H), 7.70−7.67 (dd, J = 8.2, 2.4 Hz, 1H, Py-H), 7.33−7.30 (d, J = 8.2 Hz, 1H, Py-H), 4.52−4.48 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.39−4.35 (t, J = 5.6 Hz, 2H, $COOCH_2$), 4.19−4.15 (d, J = 15.0 Hz, 1H, Py-CH_2), 3.73−3.68 (m, 2H, CH_2OH), 3.65−3.62 (t, J = 5.9 Hz, 4H), 3.30−3.21 (m, 1H), 2.97 (s, 3H, NCH_3), 2.95−2.90 (m, 1H), 2.88−2.77 (m, 2H, $COCH_2CH_2$), 2.62−2.59 (t, J = 6.7 Hz, 2H, NCH_2CH_2), 2.03 (s, 1H, OH), 1.19−1.15 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2934, 2878, 1735, 1545, 1249. Anal. Calcd for $C_{18}H_{26}ClN_5O_5$: C%, 50.53; H%, 6.12; N%, 16.37. Found: C %, 50.53; H%, 6.18; N%, 16.35.

*3′-Hydroxypropyl-3-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**6b**):* yield 76%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 2.3 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.33−7.31(d, J = 8.1 Hz, 1H, Py-H), 4.51−4.47 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.33−4.28 (m, 1H, $COOCH_2$), 4.26−4.24 (m, 1H, $COOCH_2$), 4.21−4.17 (d, J = 14.8 Hz, 1H, Py-CH_2), 3.70−3.69 (t, J = 5.6 Hz, 2H, CH_2OH), 3.68−3.61 (m, 4H), 3.31−3.22 (m, 1H), 2.97 (s, 3H, NCH_3), 2.95−2.87 (dd, J = 14.1, 7.1 Hz, 1H), 2.86−2.76 (m, 2H, $COCH_2$), 2.59−2.55 (t, J = 6.7 Hz, 2H, NCH_2), 2.04 (s, 1H, OH), 1.92−1.86 (m, 2H, CH_2CH_2OH), 1.21−1.18 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2930, 2875, 1735, 1545, 1241. Anal. Calcd for $C_{19}H_{28}ClN_5O_5$: C%, 51.64; H%, 6.39; N%, 15.85. Found: C %, 51.65; H%, 6.36; N%, 15.89.

*4′-Hydroxybutyl-3-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**6c**):* yield 75%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 2.3 Hz, 1H, Py-H), 7.71−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.34−7.32 (d, J = 8.2 Hz, 1H, Py-H), 4.52−4.48 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.20−4.18 (d, J = 8.6 Hz, 1H, Py-CH_2), 4.17−4.12 (m, 2H, $COOCH_2$), 3.69−3.68 (d, J = 6.3 Hz, 2H, CH_2OH), 3.65−3.61 (m, 4H), 3.31−3.22 (m, 1H), 2.95 (s, 3H, NCH_3), 2.95−2.89 (dd, J = 14.3, 7.2 Hz, 1H), 2.86−2.84 (m, 2H, $COCH_2$), 2.58−2.54 (t, J = 6.8 Hz, 2H, NCH_2), 2.05(s,1H, OH), 1.80−1.71 (m, 2H), 1.67−1.60 (m, 2H), 1.21−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2930, 2875, 1735, 1545, 1241. Anal. Calcd for $C_{20}H_{30}ClN_5O_5$: C%, 52.69; H%, 6.63; N%, 15.36. Found: C%, 52.65; H%, 6.66; N%, 15.39.

*5′-Hydroxypentyl-3-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**6d**):* yield 64%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31−8.30 (d, J = 2.2 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.3 Hz, 1H, Py-H), 4.53−4.49 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.20−4.16 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.15−4.11 (t, J = 6.6 Hz, 2H, $COOCH_2$), 3.76−3.70 (m, 2H, CH_2OH), 3.68−3.63 (dd, J = 9.3, 5.8 Hz, 4H), 3.32−3.23 (m, 1H), 2.98 (s, 3H, NCH_3), 2.96−2.88 (m, 1H), 2.85−2.77 (m, 2H, $COCH_2$), 2.58−2.55 (t, J = 6.8 Hz, 2H, NCH_2), 2.05 (s, 1H, OH),1.72−1.67 (m, 2H), 1.64−1.57 (m, 2H), 1.51−1.42 (m, 2H), 1.21−1.18 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2933,

Table 1. Insecticidal Activities of Nitenpyram Analogues 4a−4g against *Myzus persicae* and *Nilaparvata lugens*

			mortality (%) at different concentrations					
			Myzus persicae			*Nilaparvata lugens*		
compd	*R*	*n*	100 mg/L	20 mg/L	4 mg/L	100 mg/L	20 mg/L	4 mg/L
4a	Me	2	100	40	NT[a]	95	45	NT
4b	^{i}Pr	2	100	58	NT	95	65	NT
4c	^{s}Bu	2	100	95	30	100	95	35
4d	^{i}Bu[b]	2	100	100	100	100	100	95
4e	benzyl	2	90	15	NT	80	20	NT
4f	4-Cl-ph	2	95	25	NT	95	25	NT
4g	4-OH-benzyl	2	85	10	NT	80	15	NT
2a						100	100	50[c]
nitenpyram[d]			100	100	100	100	100	100

[a]NT, not tested. [b]LC_{50} = 0.170 mg/L. [c]LC_{50} = 0.216 mg/L. [d]LC_{50} = 0.129 mg/L.

2877, 1735, 1545, 1246. Anal. Calcd for $C_{21}H_{32}ClN_5O_5$: C%, 53.67; H %, 6.86; N%, 14.90. Found: C%, 53.69; H%, 6.83; N%, 14.86.

*6′-Hydroxyhexyl-3-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] propanate (**6e**):* yield 62%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, J = 2.4 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.54−4.50 (d, J = 14.5 Hz, 1H, Py-CH_2), 4.20−4.16 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.14−4.10 (t, J = 6.6 Hz, 2H, $COOCH_2$), 3.76−3.71 (q, J = 7.0 Hz, 2H, CH_2OH), 3.67−3.64 (m, 4H), 3.32−3.23 (m, 1H), 2.99 (s, 3H, NCH_3), 2.97−2.87 (m, 1H), 2.86−2.77 (m, 2H, $COCH_2$), 2.58−2.55 (t, J = 6.8 Hz, 2H, NCH_2), 2.05 (s, 1H, OH), 1.68−1.65 (m, 2H), 1.60−1.57 (m, 2H), 1.42−1.40 (m, 4H), 1.21−1.18 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2933, 2877, 1735, 1545, 1246. Anal. Calcd for $C_{22}H_{34}ClN_5O_5$: C%, 54.60; H%, 7.08; N%, 14.47. Found: C%, 54.65; H%, 7.09; N% 14.43.

*2′-Hydroxyethyl-4-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] butanate (**7a**):* yield 69%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32−8.31 (d, J = 2.4 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.34−7.32 (d, J = 8.2 Hz, 1H, Py-H), 4.53−4.49 (d, J = 14.9 Hz, 1H, Py-CH_2), 4.36−4.34 (t, J = 6.2 Hz, 2H, $COOCH_2$), 4.21−4.17 (d, J = 15.0 Hz, 1H, Py-CH_2), 3.72−3.69 (t, J = 6.8 Hz, 2H, CH_2OH), 3.64−3.55 (m, 4H), 3.33−3.16 (m, 1H), 3.00 (s, 3H, NCH_3), 2.98−2.89 (m, 1H), 2.60−2.52 (m, 2H, $COCH_2CH_2$), 2.50−2.46 (t, J = 7.2 Hz, 2H, NCH_2), 2.05 (s, 1H, OH), 1.89 (m, 2H), 1.22−1.18 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2937, 2875, 1735, 1545, 1246. Anal. Calcd for $C_{19}H_{28}ClN_5O_5$: C%, 51.64; H%, 6.39; N%, 15.85. Found: C %, 51.63; H%, 6.38; N%, 15.87.

*3′-Hydroxypropyl-4-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] butanate (**7b**):* yield 73%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 2.2 Hz, 1H, Py-H), 7.71−7.68 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.33−7.31 (d, J = 8.2 Hz, 1H, Py-H), 4.50−4.47 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.23−4.20 (dd, J = 7.4, 4.2 Hz, 2H, $COOCH_2$), 4.17−4.16 (d, J = 5.3 Hz, 1H, Py-CH_2), 3.71−3.68 (t, J = 6.1 Hz, 2H, CH_2OH), 3.67−3.53 (m, 4H), 3.29−3.20 (m, 1H), 3.00 (s, 3H, NCH_3), 2.97−2.90 (dt, J = 14.1, 7.1 Hz, 1H), 2.56−2.44 (m, 2H, $COCH_2$), 2.42−2.38 (t, J = 7.1 Hz, 2H, NCH_2), 2.03 (s, 1H, OH), 1.90−1.87 (dd, J = 7.4, 4.9 Hz, 2H, CH_2CH_2OH), 1.85−1.80 (dd, J = 14.4, 7.1 Hz, 2H), 1.20−1.17 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2937, 2875, 1735, 1545, 1246. Anal. Calcd for $C_{20}H_{30}ClN_5O_5$: C%, 52.69; H%, 6.63; N%, 15.36. Found: C%, 52.65; H%, 6.66; N%, 15.39.

*4′-Hydroxybutyl-4-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] butanate(**7c**):* yield 70%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, J = 2.3 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.2 Hz, 1H, Py-H), 4.53−4.49 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.21−4.17 (d, J = 15.0 Hz, 2H, $COOCH_2$), 4.15−4.13 (dd, J = 6.8, 4.7 Hz, 1H, Py-CH_2), 3.71−3.67 (dd, J = 10.4, 6.4 Hz, 2H, CH_2OH), 3.66−3.55 (m, 4H), 3.32−3.23 (m, 1H), 3.00 (s, 3H, NCH_3), 2.98−2.91 (m, 1H), 2.56 − 2.46 (m, 2H, $COCH_2$), 2.43−2.40 (t, J = 7.2 Hz, 2H, NCH_2), 2.05 (s, 1H, OH), 1.91−1.84 (m, 2H), 1.78−1.75 (m, 2H), 1.67−1.60 (m, 2H), 1.22−1.18 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2937, 2872, 1735, 1547, 1242. Anal. Calcd for $C_{21}H_{32}ClN_5O_5$: C%, 53.67; H%, 6.86; N%, 14.90. Found: C %, 53.65; H%, 6.89; N%, 14.93.

*5′-Hydroxypentyl-4-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] butanate (**7d**):* yield 67%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 2.2 Hz, 1H, Py-H), 7.72−7.69 (dd, J = 8.2, 2.5 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.3 Hz, 1H, Py-H), 4.53−4.49 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.21−4.17 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.11−4.08 (t, J = 6.6 Hz, 2H, $COOCH_2$), 3.69−3.64 (t, J = 6.4 Hz, 2H, CH_2OH), 3.61−3.56 (m, 4H), 3.32−3.23 (m, 1H), 3.00 (s, 3H, NCH_3), 2.99−2.89 (m, 1H), 2.57−2.46 (m, 2H, $COCH_2$), 2.43−2.40 (t, J = 7.2 Hz, 2H, NCH_2), 2.05 (s, 1H, OH), 1.91−1.84 (m, 2H), 1.70−1.65 (dd, J = 14.8, 6.8 Hz, 2H), 1.63−1.57 (m, 2H), 1.50−1.42 (m, 2H), 1.22−1.18 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2933, 2872, 1735, 1541, 1247. Anal. Calcd for $C_{22}H_{34}ClN_5O_5$: C%, 54.60; H%, 7.08; N%, 14.47. Found: C%, 54.65; H%, 7.09; N%, 14.43.

*6′-Hydroxyhexyl-4-[4-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]-amino-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] butanate (**7e**):* yield 63%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H, Py-H), 7.71−7.69 (dd, J = 8.0, 2.1 Hz, 1H, Py-H), 7.35−7.33 (d, J = 8.3 Hz, 1H, Py-H), 4.54−4.49 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.21−4.17 (d, J = 15.0 Hz, 1H, Py-CH_2), 4.13−4.10 (t, J = 6.8 Hz, 2H, $COOCH_2$), 3.70−3.63 (t, J = 6.8 Hz, 2H, CH_2OH), 3.60−3.54 (m, 4H), 3.34−3.23 (m, 1H), 3.05 (s, 3H, NCH_3), 2.98−2.88 (m, 1H), 2.57−2.49 (m, 2H, $COCH_2$), 2.20−2.12 (m, 2H, NCH_2), 2.05 (s, 1H, OH), 1.90−1.84 (m, 2H), 1.69−1.64 (m, 2H), 1.61−1.58 (m, 2H), 1.44−1.39 (m, 4H), 1.22−1.18 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) ν 2939, 2872, 1737, 1543, 1247. Anal. Calcd for $C_{23}H_{36}ClN_5O_5$: C%, 55.47; H%, 7.29; N%, 14.06. Found: C%, 55.45; H%, 7.25; N%, 14.03.

X-ray Crystallography. The yellow crystal of the title compound **4g** (grown from a mixed solution of petroleum ether/ethyl acetate) was mounted on a glass fiber in a random orientation, with approximate dimensions of 0.20 mm × 0.13 mm × 0.10 mm. The data were collected by a Bruker Smart Apex CCD diffractometer with a graphite-monochromated Mo Kα radiation (k = 0.71073 Å), using a $\varphi-\omega$ scan mode in the range of 2.47° ≤ θ ≤ 26.49° at 298(2) K. Empirical absorption correction was applied, and a total of 13121 reflections including 4511 unique ones (R_{int} = 0.1048) were measured. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2 using the SHELXTL program package.[21] All of the non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located at their idealized positions. The final R = 0.0746 and wR = 0.1586 {$w = 1/[\sigma^2(F_o^2) + (0.0749P)^2 + 0.0000P]$, where $P = (F_o^2 + 2Fc^2)/3$, S = 1.097, $(\Delta/\sigma)_{max}$ = 0.004, $(\Delta\rho)_{max}$ = 0.385, and $(\Delta\rho)_{min}$ = −0.227 e/Å ^{3}}. The structural plots were drawn with the SHELXTL-97 software package. Other details of the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC740000 (see also the Supporting Information).

Table 2. Insecticidal Activities of Nitenpyram Analogues 5a−7e against *Myzus persicae* and *Nilaparvata lugens*

			mortality (%) at different concentrations					
			Myzus persicae			*Nilaparvata lugens*		
compd	n	n_1	100 mg/L	20 mg/L	4 mg/L	100 mg/L	20 mg/L	4 mg/L
5a	2	1	100	58	NT[a]	100	50	NT
5b	3	1	100	50	NT	100	45	NT
5c	4	1	100	33	NT	95	30	NT
5d	5	1	100	25	NT	90	23	NT
5e	6	1	95	10	NT	90	15	NT
6a	2	2	100	100	100	100	100	100[b]
6b	3	2	100	100	55	100	98	70
6c	4	2	100	83	NT	100	80	NT
6d	5	2	98	50	NT	100	40	NT
6e	6	2	95	33	NT	90	25	NT
7a	2	3	100	100	10	100	90	NT
7b	3	3	100	92	NT	100	80	NT
7c	4	3	95	70	NT	100	78	NT
7d	5	3	95	25	NT	98	15	NT
7e	6	3	88	10	NT	90	10	NT
3a						100	100	75[c]
3b						100	100	70[d]
nitenpyram			100	100	100[e]	100	100	100[e]

[a]NT, not tested. [b]LC_{50} = 0.154 mg/L. [c]LC_{50} = 0.194 mg/L. [d]LC_{50} = 0.162 mg/L. [e]LC_{50} = 0.129 mg/L.

Biology Assay. The bioassay was measured according to the standard test[22] with a slight modification, and all analogues were tested against *N. lugens* to evaluate their insecticidal activities. The compounds were dissolved in dimethylformamide (DMF) and serially diluted with water containing Triton X-80 (0.1 mg/L) to get the required test concentrations. All experiments were carried out in three replicates for the purpose of statistical requirements. The insects were reared at 25(±)1 °C, 25(±2)% relative humidity, and 12 h light photoperiod. Groups of 12 were transferred to glass Petri dishes and sprayed with the aforementioned solutions using a Potter sprayer. After they were air-dried, they were kept in a special room for normal cultivation. Assessments were made after 72 h by the number of killed and size of live insects relative to that in the negative control, and evaluations were based on a percentage scale of 0−100, in which 100 was total kill and 0 was no activity. The mortality rates were subjected to probit analysis.[23] All results are shown in Tables 1 and 2. The reference compound was nitenpyram, and water containing DMF (0.5 mg/L) and Triton X-80 (0.1 mg/L) was used as a negative control.

RESULTS AND DISCUSSION

Synthesis. The reaction of nitenpyam **1**, amino acid ω-hydroxyalkyl ester hydrochlorides, formaldehyde, and triethylamine could proceed readily in ethanol at 65 °C by Mannich reaction under microwave irradiation (Scheme 2), which was a highly efficient way that gave good yields (59−76%) and had easy post-treatments. The structures of the target compounds were well characterized by ^{1}H NMR, IR, and elemental analysis.

Crystal Structure Analysis. The structure of compound **4g** was confirmed on the basis of spectral data and finally by X-ray crystallographic data analysis. The crystal structure showed that the tetrahydropyrimidine cycle of the molecule **4g** adopts a sofa conformation (Figure 3). According to the single-crystal data, we found that five atoms of C(9)−N(4)−C(12)−C(11) and C(10) define a plane, with the biggest deviation from the plane being 0.9 Å for the N(3) atom. Also, because of the lone-pair electrons transferring on the N(2) and N(4) to C(9)═C(10), the C(9)—N(2) and C(9)—N(4) bond lengths are 1.35 and 1.36 Å, remarkably shorter than the typical C—N single bond (1.47 Å) but close to C═N (imine) (1.33 Å).[14] Due to the delocalization of the electrons, which extend to the strong electron-withdrawing group NO_2, a coplanar olefin−amine π-electron network is formed. In addition, the bond lengths of C(9)═C(10) and C(10)—N(6) are 1.42 and 1.37 Å, which are longer than the pure C═C(1.34 Å) and shorter than the typical C—N in C—NO_2 (1.49 Å). Besides, as compared with the *trans* configuration of nitro in the crystal structure of nitenpyram, the nitro group in **4g** is obviously in the *cis* configuration.

SARs. The insecticidal activities of the nitenpyam analogues **4**−**7** against *N. lugens* and *M. persicae* are listed in Tables 1 and 2. Most of them showed good insecticidal activities at 100 mg/L, and analogues **4d** and **6a** afforded the best in vitro inhibitory activities and had ≥95% mortality at 4 mg/L. The LC_{50} values of analogues **4d** and **6a** were 0.170 and 0.154 mg/L, respectively.

As for analogues **4a**−**4g**, based on the nitenpyram analogue **2**, they were derived from the chiral amino acid hydroxyethyl (n = 2) esters with different side chains R. As indicated in Table 1, all of the analogues **4a**−**4g** (n = 2) exhibited good activities at high dose (100 mg/L), but when the dose was reduced to 20 and 4 mg/L, analogue **4d**(R = ^{i}Bu, n = 2, LC_{50} = 0.170 mg/L) showed the best average insecticidal potency. Analogues **4a**−**4g** (n = 2) with different side chains R showed insecticidal activities increasing in the order **4g** (R = 4-OH-benzyl) < **4e** (R = benzyl) < **4f** (R = 4-Cl-ph) < **4a**(R = Me) < **4b** (R = ^{i}Pr) < **4c** (R = ^{s}Bu) < **4d** (R = ^{i}Bu). In addition, analogue **4d**(R = ^{i}Bu) exhibited about 10-fold more potency than analogue **4g** (R = 4-OH-benzyl), and also analogue **4a** (R = Me) exhibited about 3-fold more potency than analogue **4g** (R = 4-OH-benzyl). Therefore, these results clearly suggest that the insecticidal activities of analogues **4a**−**4g** were dual-controlled by the flexibility of side chain R and the size of the molecule.

Analogues **5a**−**7e** with a flexible hydroxyalkyl ester arm (n_1 = 1, 2, 3), based on the nitenpyram analogue **3**, were derived from three different length straight chain amino acid ω-hydroxyalkyl esters. As shown in Table 2, analogues **5a**−**7e**

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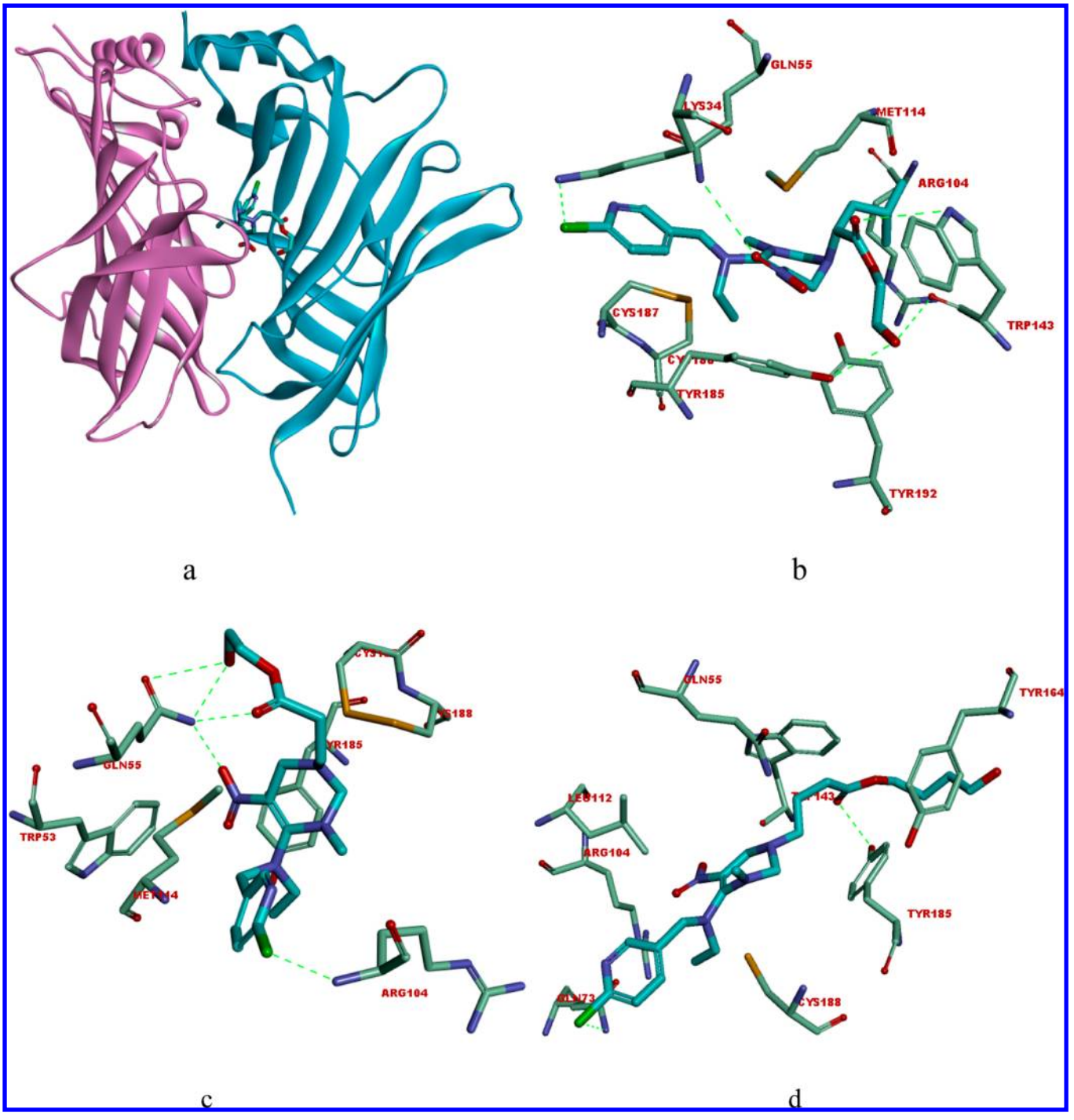

Figure 4. Binding site interactions of analogues **4d**, **6a**, and **7c** with the extracellular domain of nAChR (Protein Data Bank code 2zju). (a) Compound **6a** is bound into the subunit interfacial binding pocket between two faces of adjacent subunits. For clarity, only two of five subunits are extracted and shown from the pentameric nAChRs structure, and the corresponding interfacial binding pocket of interest is displayed. (b) Zoomed-in view of the interactions between compound **4d** and amino acids from the active site of the receptor. (c) Zoomed-in view of the interactions between compound **6a** and amino acids from the active site of the receptor. (d) The predicted binding mode of compound **7c** with relatively low activity. Key H-bonds are indicated by green dotted lines.

exhibited good activities at high dose (100 mg/L); however, the insecticidal activities showed significant differences when the doses were reduced to 20 and 4 mg/L. Clearly, analogues **6a**−**6e** (n_1 = 2) displayed better insecticidal potencies than analogues **5a**−**5e** (n_1 = 1) and analogues **7a**−**7e** (n_1 = 3). Furthermore, when various ω-hydroxyalkyl esters were introduced into the nitenpyram analogues, the flexibility of the molecule increased; the size also increased at the same time. Typical for analogues **6**, when the dose was reduced to 20 and 4 mg/L, analogues **6a** (n = 2, n_1 = 2, LC_{50} = 0.154 mg/L) showed higher insecticidal potency than **6b**−**6e** (n = 3, 4, 5, 6; n_1 = 2), and their insecticidal activities increased in the order **6e** (n = 6) < **6d** (n = 5) < **6c** (n = 4) < **6b** (n = 3) < **6a** (n = 2). Therefore, the analogues bearing the smaller ester groups had better insecticidal potency in the respective series. These differences clearly suggest that the insecticidal activities of analogues **5a**−

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7e were dual-controlled by the flexibility of the ester arm and the size of the molecule.

Considering the discussion above, we found the insecticidal potencies of our designed nitenpyram analogues in this paper were also dual-controlled by the flexibility and the size of the molecule. Only when a molecule can keep a good balance between flexibility and size will it have the best insecticidal activity, such as analogues **4d** and **6a**. Also, as compared with our previous analogues **2** and **3**, analogues **4d** and **6a** had a broader pesticidal spectrum, and the insecticidal activities were better than those of **2a** (LC_{50} = 0.216 mg/L), **3a** (LC_{50} = 0.194 mg/L), and **3b** (LC_{50} = 0.162 mg/L) when the doses were reduced to 4 mg/L. The LC_{50} values of analogues **4d** and **6a** are 0.170 and 0.154 mg/L, which is close to that of nitenpyram. These good results implied that the nitenpyram analogues designed in this paper are both practical and feasible.

Molecular Docking Study. To further explore the structural features for better activities, models of these new compound−receptor complexes were investigated by docking studies with CDOCK.[24] Because the amino acids formed at the active sites are both structurally and functionally consistent in the diverse nAChRs and AchBPs, the published crystal structure of a *Lymnaea stagnalis*−AChBP (Ls-AChBP) cocrystallized with imidacloprid (PDB ID: 2zju)[25] was used as the template of the receptor. The docking study was performed by using the program CDOCK (Discovery Studio 3.1); the only modification was the number of Top Hits, which was set to 30 (previously 10) for greater accuracy.

As a result, the scoring function of the docking program ranked the compounds in the same general order observed experimentally (data not shown), and all active analogues exhibited hydrogen-bonding interactions with the nAChR target. As illustrated in Figure 4, analogues **4d**, **6a**, and **7c** were chosen to understand the ligand protein interactions in detail, and analogues **4d** and **6a** had stronger hydrogen-bonding action in binding with the nAChR. Analogue **6a** exhibits two important hydrogen bonds via its nitro O(2) with NH of Gln155, respectively, and the Cl(1) of its chloropyridine interacts with NH of Arg104. Besides, its binding conformation exhibited three important hydrogen bonds: O(4) of the carbonyl and O(6) of the hydroxyl with NH of Gln155 and H of the hydroxyl with O of Gln155. These observations also explain why analogue **6a** attained the highest score.

Furthermore, most of the other active analogues shared a quite similar binding mode with analogue **6a**, and many of them exhibited more than two hydrogen bonds with different amino acids of the active pocket between the nAChR subunits. However, not all nitro O(2), carbonyl O(4), hydroxyl O(6), and hydroxyl H of analogues **4**−**7** can form hydrogen bonds within the same hydrogen bond distance, such as the binding mode of analogue **7c** (Figure 4d), nitro O(2), hydroxyl O(6), and the hydroxyl H cannot interact with amino acid residues from the Ls−AChBP.

Moreover, we found that analogues **4d** and **6a** offered the highest experimental activities when nitro O(2), carbonyl O(4), hydroxyl O(6), and the hydroxyl H can exhibit hydrogen bonds with different amino acid residues (Figure 4b,c). These observations also explain the structure−activity relationships observed in vitro. The newly introduced moiety of our designed analogues presumably played an important role in ligand recognition and binding interactions, which may further explain the strength of the hydrogen-bonding action as the influential factor for the bioactivities of our designed nitenpyram analogues. On these bases, further target inhibitory tests and advanced insecticide design are underway.

In conclusion, to further enhance the strength of the hydrogen-bonding action of the neonicotinoid compounds binding with the nAChR, a series of novel nitenpyram analogues **4**−**7** was synthesized by introducing different amino acid ω-hydroxyalkyl esters into nitenpyram. The target compounds were characterized by ^{1}H NMR, IR, and elemental analysis, and the *cis* configuration was confirmed by X-ray diffraction. All of the analogues exhibited good insecticidal activities at 100 mg/L against *N. lugens* and *M. persicae*, and analogues **4d** and **6a** afforded the best in vitro activity and had ≥95% mortality at 4 mg/L. The LC_{50} values of analogues **4d** and **6a** were 0.170 and 0.154 mg/L, respectively. SARs suggested that the insecticidal activities of our designed nitenpyram analogues were also dual-controlled by the flexibility and size of the molecule. In addition, molecular docking studies were also carried out to model the ligand−nAChR complexes. The docking results revealed that analogues **4**−**7** with various ω-hydroxyalkyl esters on the tetrahydropyrimidine ring showed different binding affinities to the insect nAChR, which explained the SARs observed in vitro. Moreover, carbonyl O(4) and hydroxyl H of analogue **4d** and carbonyl O(4), hydroxyl O(6), and hydroxyl H of analogue **6a** can exhibit hydrogen bonding with amino acid residues of the receptor. These differences suggested that analogues **4d** and **6a** exhibited stronger hydrogen bonding than the others, which had a crucial effect on their high insecticidal activities. Therefore, the docking study revealed that the strength of the hydrogen-bonding action was the influential factor for the bioactivities of our designed nitenpyram analogues, and further research on many more test objects of nitenpyram are underway.

■ ASSOCIATED CONTENT

Supporting Information

Crystal structure data of compound **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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