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# Nitromethylene Neonicotinoids Analogues with Tetrahydropyrimidine Fixed *cis*-Configuration: Synthesis, Insecticidal Activities, and Molecular Docking Studies

Chuanwen Sun,*,† Dingrong Yang,† Jiahua Xing,‡ Haifeng Wang,† Jia Jin,† and Jun Zhu†

†College of Life and Environment Sciences, Shanghai Normal University, Shanghai 200234, China, and ‡Bioassay department, Branch of National Pesticide R&D South Center, Hangzhou 310023, China

Two series of new nitromethylene neonicotinoid analogues (**2a**−**2h** and **3a**−**3h**) were designed and prepared, with the *cis*-configuration confirmed by X-ray diffraction. Preliminary bioassays showed that most analogues exhibited excellent insecticidal activities at 500 mg/L, and analogues with optical activity (**2c**−**2g**) were highly potent at 100 mg/L, while compound **2d** had >90% mortality at 20 mg/L, which suggested that it could be used as a lead for future insecticides development. Modeling the ligand−receptor complexes by molecular docking study explained the structure−activity relationships observed in vitro and revealed an intriguing molecular binding mode at the active site of the nAChR model, thereby possibly providing some useful information for future receptor structure-based designs of novel insecticidal compounds.

**KEYWORDS: *cis*-Configuration; neonicotinoid; tetrahydropyrimidine; L-α-amino acid methyl ester; substituent benzoyl hydrazine; X-ray diffraction; insecticidal activities; molecular docking**

## INTRODUCTION

Neonicotinoid insecticides (NNSs), which act agonistically on the insect nicotinic acetylcholine receptors (nAChRs), are gaining widespread use as a way to control pests, because of their high potency, low mammalian toxicity, and broad insecticidal spectra (*1*). The first successful member of this family was imidacloprid (**1a**) in 1991 (**Figure 1**) (*2*). As the second of the chloronicotinyl subclass, nitenpyram (**1b**) from Takada Chemical Industries (*3*) was brought to market in 1995 and was characterized with a much lower toxicity against mammals than imidacloprid (*4*). However, a recent potential problem facing all insecticides is the development of resistance. Although NNSs have a new mode of action, frequent applications of structural analogues of neonicotinoids have led to the acquisition of resistance and cross-resistance in a range of species (*5*−*8*). Especially, resistant species increased in potency during the late 1990s, with more recently collected strains of this whitefly exhibiting more than 100-fold resistance to imidacloprid and comparable levels of resistance to thiamethoxam and acetamiprid (*9*, *10*). Hence, development of noval neonicotinoids with good insecticidal activities and less resistance is highly desirable.

As well-known, the electron-withdrawing group of $NO_2$ in neonicotinoids plays an important role in their insecticidal activities. The nitro groups in all commercialized neonicotinoids have a trans configuration, on which three proposals for modes of action are based (*11*). More recently, Li and his co-workers reported the synthesis of novel neonicotinoid analogues **1c** (**Figure 1**) and introduced a tetrahydropyridine ring to fix the nitro moiety in the cis position, resulting in high biological activity, which implies that neonicotinoids in the cis configuration might bind to the receptor in a different way (*12*, *13*).

Motivated by the aforementioned findings, we developed a new design strategy, conceiving that replacement of the tetrahydropyridine ring with tetrahydropyrimidine (**Scheme 1**) and introduction of active ingredients L-α-amino acid methyl esters or substituent benzoyl hydrazines might result in good biological activities. To confirm the cis configuration with precise three-dimensional information, the single-crystal structure of **2b** was further determined by X-ray diffraction (**Figure 2**). As compared with the trans configuration of **1b** (*14*), analogue **2b** obviously adopted the cis configuration. Furthermore, the present research is devoted to the fast microwave-assisted synthesis of tetrahydropyrimidine derivatives. As compared with conventional conditions, controlled microwave irradiation has proven to be a powerful tool to speed up reactions with good yields (*15*). In addition, a preliminary bioassay against *Nilaparvata legen* showed that all test compounds exhibited good insecticide activities at 500 mg/L, and compound **2d** had the highest activity at 20 mg/L, which implied further possibilities for lead compound development. Their structure−activity relationships (SARs) were also discussed.

To further explore the structural requirement for activity improvement and better selectivity, these compounds were studied for their binding activity into nAChR by molecular docking simulations, which revealed an intriguing molecular recognition and binding mode of these analogues at the nAChR structural model, thereby prompting necessary features for the future design of improved NNS pesticides.

*To whom correspondence should be addressed. E-mail: willin112@163.com.

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## 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 DMSO-$d_6$ as the solvent and tetramethylsilane as the internal standard. The IR spectra were obtained from KBr discs in the range 4000 to 400 cm$^{-1}$ on a Nicolet 5DXFT-IR spectrophotometer. Combustion analyses for elemental composition were made with 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. Optical rotations were determined on a Jasco P-1020 polarimeter.

**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 Procedure for the Synthesis of Target Compounds 2a−2h.** A mixture of compound **1b** (2.75 g, 9.8 mmol), L-α-amino acid methyl ester hydrochlorides (11.9 mmol), $Et_3N$ (1.7 mL), and formaldehyde (1.91 mL, 37%) in ethanol (20 mL) was heated to 60−75 °C for 5 min in a microwave reactor and stirred for 30 min at the 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 $MgSO_4$. 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.

**General Procedure for the Synthesis of Target Compounds 3a−3h.** To a mixture of compound **1b** (2.65 g, 9.8 mmol), substituent benzoyl hydrazine (11.95 mmol) and formaldehyde (1.96 mL, 37%) were added to ethanol (20 mL) in a microwave reactor. The resulting mixture was heated to 70−75 °C for 3 min with the temperature maintained for 30 min. After completion of the reaction, the mixture was cooled to room temperature and filtered to give the solid products **3a−3h**, which were washed with ethanol and dried in air. Tetrahydropyrimidine derivatives **3a−3h** were obtained in high purity (>98% by $^1$H NMR) and did not require further purification.

*s-(+)-2-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl] Propanoic Acid Methyl Ester* (***2a***). Yield, 76.2%; orange oil. $^1$H NMR (DMSO-$d_6$): δ 8.31 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.71 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.1 Hz, 1H, Py-H), 7.31 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.50 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.19 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.78−3.81 (m, 4H), 3.73 (s, 3H, $COOCH_3$), 3.60 (q, $J$ = 2.8 Hz, 1H, NCHCO), 3.25−3.26 (m, 1H), 2.97 (s, 3H, $NCH_3$),

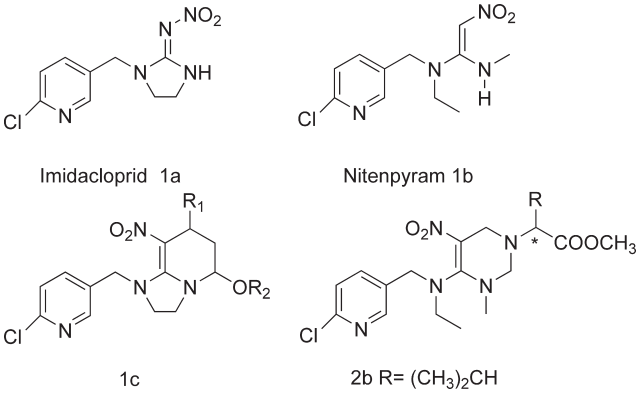



**Figure 1.** Chemical structures of **2b**.

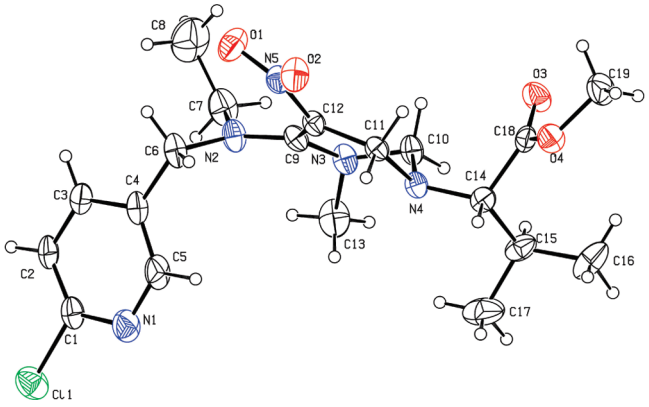
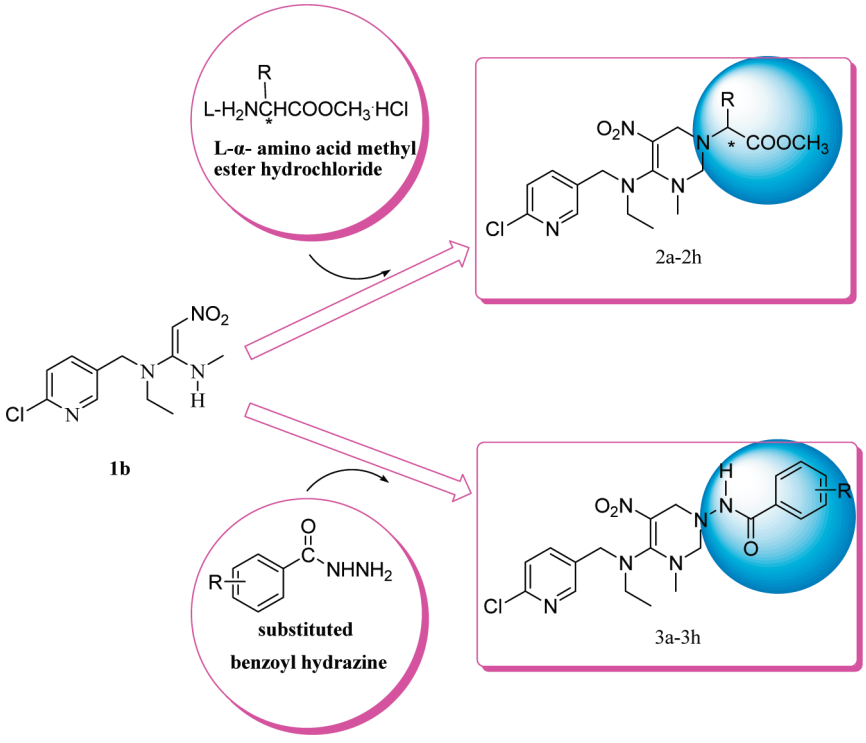
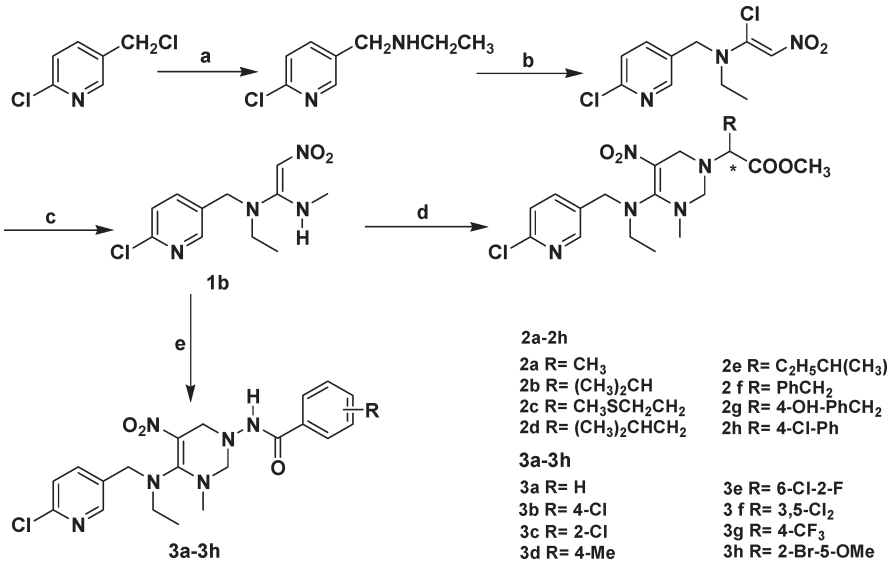


**Figure 2.** Molecular structure of compound **2b**.

**Scheme 1**



**Scheme 2.** [a]




[a] Reagents and conditions: (a) Ethanamine (42%). (b) 1,1,1-Trichloro-2-nitroethane/$CHCl_3$, 2−7 °C (65%). (c) Methanamine, 3−7 °C (58%). (d) L-α-Amino acid methyl ester hydrochloride, HCHO, $Et_3N$/EtOH (71−77%). (e) Substituent benzoyl hydrazine, HCHO/EtOH (65−73%).

2.88−2.92 (m, 1H), 1.39 (d, 3H, $J$ = 6.8 Hz, $CHCH_3$), 1.14 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, $cm^{-1}$): 2937, 2874, 1734, 1550, 1303, 1251. Anal. calcd for $C_{17}H_{24}ClN_5O_4$: C, 51.32; H, 6.08; N, 17.60. Found: C, 51.38; H, 6.14; N, 17.69. $[\alpha]_D^{25}$ = +21.833° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*3-methylbutanoic Acid Methyl Ester* (***2b***). Yield, 77.4%; mp 114−116 °C. $^1$H NMR (DMSO-$d_6$): δ 8.30 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.72 (dd, $J_1$ = 3.1 Hz, $J_2$ = 8.3 Hz, 1H, Py-H), 7.32 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.52 (d, $J$ = 16.2, 1H, Py-$CH_2$), 4.20 (d, $J$ = 16.2 Hz, 1H, Py-$CH_2$), 3.78−3.82 (m, 4H), 3.62 (s, 3H, $COOCH_3$), 3.52 (d, $J$ = 2.4 Hz, 1H, NCHCO), 3.13−3.18 (m, 1H), 2.98 (s, 3H, $NCH_3$), 2.88−2.91 (m, 1H), 1.80−1.83 [m, 1H, $CH(CH_3)_2$], 1.12 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$), 0.93 (d, $J$ = 5.6 Hz, 3H, $CHCH_3$), 0.88 (d, $J$ = 5.6 Hz, 3H, $CHCH_3$). IR (KBr, $cm^{-1}$): 2954, 2869, 1732, 1552, 1301, 1251. Anal. calcd for $C_{19}H_{28}ClN_5O_4$: C, 53.58; H, 6.63; N, 16.44, Found: C, 53.51; H, 6.68; N, 16.49. $[\alpha]_D^{25}$ = +10.783° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*4-methylthiobutanoic Acid Methyl Ester* (***2c***). Yield, 75.3%; yellow oil. $^1$H NMR (DMSO-$d_6$): δ 8.30 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.74 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.32 (d, $J$ = 8.2 Hz, 1H, Py-H), 4.52 (d, $J$ = 16.4, 1H, Py-$CH_2$), 4.18 (d, $J$ = 16.4 Hz, 1H, Py-$CH_2$), 3.76−3.83 (m, 4H), 3.74 (s, 3H, $COOCH_3$), 3.58 (t, $J$ = 2.4 Hz, 1H, NCHCO), 3.22−3.25 (m, 1H), 2.95 (s, 3H, $NCH_3$), 2.86−2.91 (m, 1H), 2.05 (s, 3H, $SCH_3$), 1.82 (d, $J$ = 8.0 Hz, 2H, $CH_2SCH_3$), 1.14 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, $cm^{-1}$): 2948, 2862, 1732, 1552, 1301, 1252. Anal. calcd for $C_{19}H_{28}ClN_5O_4S$: C, 49.83; H, 6.16; N, 15.29. Found: C, 49.78; H, 6.11; N, 15.35. $[\alpha]_D^{25}$ = +16.562° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*4-methylpentanoic Acid Methyl Ester* (***2d***). Yield, 78.2%; yellow oil. $^1$H NMR (DMSO-$d_6$): δ 8.32 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.73 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.1 Hz, 1H, Py-H), 7.31 (d, $J$ = 8.2 Hz, 1H, Py-H), 4.51 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 4.19 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.72−3.81 (m, 4H), 3.65 (s, 3H, $COOCH_3$), 3.63 (t, $J$ = 3.2 Hz, 1H, NCHCO), 3.04−3.07(m, 1H), 2.96 (s, 3H, $NCH_3$), 2.93−2.95 (m, 1H), 1.60−1.64 [m, 1H, $CH(CH_3)_2$], 1.56−1.62 (m, 2H, $CHCH_2$), 1.06 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$), 0.96 (d, $J$ = 5.6 Hz, 3H, $CHCH_3$), 0.91 (d, $J$ = 5.6 Hz, 3H, $CHCH_3$). IR (KBr, $cm^{-1}$): 2964, 2875, 1731, 1553, 1300, 1249. Anal. calcd for $C_{20}H_{30}ClN_5O_4$: C, 54.60; H, 6.87; N, 15.92, Found: C, 54.69; H, 6.82; N, 15.97. $[\alpha]_D^{25}$ = +31.733° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*3-methylpentanoic Acid Methyl Ester* (***2e***). Yield, 77.6%; yellow oil. $^1$H NMR (DMSO-$d_6$): δ 8.31 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.72 (dd, $J_1$ = 3.1 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.33 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.52 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 4.20 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.71−3.82 (m, 4H), 3.64 (s, 3H, $COOCH_3$), 3.64 (d, $J$ = 2.4 Hz, 1H, NCHCO), 3.04−3.07 (m, 1H), 2.97 (s, 3H, $NCH_3$), 2.93−2.95 (m, 1H), 1.90−1.94 (m, 1H), 1.36 (q, $J$ = 5.8 Hz, 2H, $CH_2CH_3$), 1.05 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$), 0.94 (d, $J$ = 5.6 Hz, 3H, $CHCH_3$), 0.92 (t, $J$ = 5.6 Hz, 3H, $CH_2CH_3$). IR (KBr, $cm^{-1}$): 2964, 2875, 1731, 1553, 1300, 1249. Anal. calcd for $C_{20}H_{30}ClN_5O_4$: C, 54.60; H, 6.87; N, 15.92. Found: C, 54.68; H, 6.80; N, 15.96. $[\alpha]_D^{25}$ = +34.653° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*3-phenylpropanoic Acid Methyl Ester* (***2f***). Yield, 73.5%; orange oil. $^1$H NMR (DMSO-$d_6$): δ 8.30 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.72 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 7.16−7.24 (m, 5H, Ph-H), 4.53 (d, $J$ = 16.4, 1H, Py-$CH_2$), 4.52 (d, 2H, $J$ = 16 Hz, Ph−$CH_2$), 4.20 (d, $J$ = 16.4 Hz, 1H, Py-$CH_2$), 3.80−3.85 (m, 4H), 3.66 (s, 3H, $COOCH_3$), 3.46 (t, $J$ = 8.0 Hz, 1H, NCHCO), 3.10−3.17 (m, 1H), 2.95 (s, 3H, $NCH_3$), 2.84−2.92 (m, 1H), 1.13 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, $cm^{-1}$): 2949, 2872, 1732, 1552, 1301, 1252. Anal. calcd for $C_{23}H_{28}ClN_5O_4$: C, 58.29; H, 5.95; N, 14.78. Found: C, 58.25; H, 5.99; N, 14.70. $[\alpha]_D^{25}$ = +13.562° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*3-(4-hydroxyphenyl) Propanoic Acid Methyl Ester* (***2g***). Yield, 71.2%; mp 89−91 °C. $^1$H NMR (DMSO-$d_6$): δ 9.20 (dd, $J_1$ = 2.0 Hz, $J_2$ = 6.0 Hz, 1H, Ph−OH), 8.30 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.72 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 6.63−7.02 (m, 4H, Ph-H), 4.53 (d, $J$ = 16.4, 1H, Py-$CH_2$), 4.20 (d, $J$ = 16.4 Hz, 1H, Py-$CH_2$), 3.80−3.85 (m, 4H), 3.66 (s, 3H, $COOCH_3$), 3.46 (t, $J$ = 8.0 Hz, 1H, NCHCO), 3.10−3.17 (m, 1H), 2.96−3.15 (m, 2H, Ph−$CH_2$), 2.95 (s, 3H, $NCH_3$), 2.84−2.92 (m, 1H), 1.13 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, $cm^{-1}$): 3549, 2949, 2872, 1732, 1552, 1301. Anal. calcd for $C_{23}H_{28}ClN_5O_5$: C, 56.38; H, 5.76; N, 14.29. Found: C, 56.31; H, 5.71; N, 14.34. $[\alpha]_D^{25}$ = +24.522° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*s*-(+)-*2*-[(*4Z*)-*4*-[[(*6-Chloro-3-pyridinyl*)*methyl*]*ethylamino*]-*3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl*]-*3-(4-chlorophenyl) Ethanoic Acid Methyl Ester* (***2h***). Yield, 72.1%; mp 153−155 °C. $^1$H NMR (DMSO-$d_6$): δ 8.32 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.74 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.0 Hz, 1H, Py-H), 7.39−7.46 (m, 4H, Ph-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.54 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.21 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.79−3.83 (m, 4H), 3.64 (s, 3H, $COOCH_3$), 3.46 (dd, $J$ = 3.6 Hz, J = 3.6 Hz, 1H, NCHCO), 3.11−3.19 (m, 1H), 2.96 (s, 3H, $NCH_3$), 2.86−2.90 (m, 1H), 1.12 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, $cm^{-1}$): 2963, 2872, 1731, 1556, 1301, 1251. Anal. calcd for $C_{22}H_{25}Cl_2N_5O_4$: C, 53.45; H, 5.10; N, 14.17. Found: C, 53.49; H, 5.18; N, 14.22. $[\alpha]_D^{25}$ = +26.541° ($C$ = 0.01 g/mL $CH_3COCH_3$).

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]*benzamide* (***3a***). Yield, 72.5%; mp 235−237 °C. $^1$H NMR (DMSO-$d_6$), $\delta$ 9.97 (s, 1H, NNHCO), 8.36 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.78 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.0 Hz, 1H, Py-H), 7.47−7.57 (m, 5H, Ph-H), 7.36 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.54 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.21 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.79−3.83 (m, 4H), 3.10−3.17 (m, 1H), 2.95 (s, 3H, $NCH_3$), 2.84−2.92 (m, 1H), 1.13 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3252, 3077, 1682, 1541, 1311, 752. Anal. calcd for $C_{20}H_{23}ClN_6O_3$: C, 55.75; H, 5.38; N, 19.50. Found: C, 55.67; H, 5.31; N, 19.58.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*4*-*chlorobenzamide* (***3b***). Yield, 70.2%; mp 221−222 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.95 (s, 1H, NNHCO), 8.34 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.76 (dd, $J_1$ = 3.4 Hz, $J_2$ = 8.4 Hz, 1H, Py-H), 7.55−7.82 (m, $J$ = 8.0 Hz, $J$ = 8.0 Hz, 4H, Ph-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.53 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.23 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.80−3.85 (m, 4H), 3.12−3.18 (m, 1H), 2.97 (s, 3H, $NCH_3$), 2.81−2.91 (m, 1H), 1.10 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3254, 3078, 1680, 1540, 1310, 810. Anal. calcd for $C_{20}H_{22}Cl_2N_6O_3$: C, 51.62; H, 4.77; N, 18.06. Found: C, 51.71; H, 4.78; N, 18.14.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*2*-*chlorobenzamide* (***3c***). Yield, 68.9%; mp 208−210 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.94 (s, 1H, NNHCO), 8.32 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.75 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.0 Hz, 1H, Py-H), 7.50−7.80 (m, 4H, Ph-H), 7.32 (d, $J$ = 8.2 Hz, 1H, Py-H), 4.51 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.21 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.82−3.87 (m, 4H), 3.10−3.16 (m, 1H), 2.95 (s, 3H, $NCH_3$), 2.80−2.92 (m, 1H), 1.12 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3253, 3080, 1679, 1541, 1309, 749. Anal. calcd for $C_{20}H_{22}Cl_2N_6O_3$: C, 51.62; H, 4.77; N, 18.06. Found: C, 51.69; H, 4.71; N, 18.11.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*4*-*methylbenzamide* (***3d***). Yield, 72.8%; mp 219−220 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.93 (s, 1H, NNHCO), 8.31 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.76 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.42−7.64 (m, $J$ = 8.2 Hz, $J$ = 8.2 Hz, 4H, Ph-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.53 (d, $J$ = 16.2, 1H, Py-$CH_2$), 4.23 (d, $J$ = 16.2 Hz, 1H, Py-$CH_2$), 3.82−3.85 (m, 4H), 3.13−3.17 (m, 1H), 2.97 (s, 3H, $NCH_3$), 2.81−2.94 (m, 1H), 2.36 (s, 3H, Ph−$CH_3$), 1.15 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3251, 3080, 1682, 1541, 1308, 805. Anal. calcd for $C_{21}H_{25}ClN_6O_3$: C, 56.69; H, 5.66; N, 18.89. Found: C, 56.75; H, 5.73; N, 18.95.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*6*-*chloro*-*2*-*fluorobenzamide* (***3e***). Yield, 70.5%; mp 213-215 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.92 (s, 1H, NNHCO), 8.35 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.78 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.4 Hz, 1H, Py-H), 7.60−7.76 (m, 3H, Ph-H), 7.33 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.53 (d, $J$ = 16.4, 1H, Py-$CH_2$), 4.23 (d, $J$ = 16.4 Hz, 1H, Py-$CH_2$), 3.85−3.89 (m, 4H), 3.12−3.18 (m, 1H), 2.92 (s, 3H, $NCH_3$), 2.83−2.94 (m, 1H), 1.14 (t, $J$ = 7.0 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3256, 3079, 1683, 1542, 1310, 808. Anal. calcd for $C_{20}H_{21}Cl_2FN_6O_3$: C, 49.70; H, 4.38; N, 17.39. Found: C, 49.78; H, 4.30; N, 17.32.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*3,5*-*dichlorobenzamide* (***3f***). Yield, 71.3%; mp 209−211 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.93 (s, 1H, NNHCO), 8.33 (d, $J$ = 2.0 Hz, 1H, Py-H), 7.76 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.58−7.73 (m, 3H, Ph-H), 7.34 (d, $J$ = 8.0 Hz, 1H, Py-H), 4.52 (d, $J$ = 16.2, 1H, Py-$CH_2$), 4.22 (d, $J$ = 16.2 Hz, 1H, Py-$CH_2$), 3.81−3.87 (m, 4H), 3.11−3.17 (m, 1H), 2.93 (s, 3H, $NCH_3$), 2.81−2.92 (m, 1H), 1.16 (t, $J$ = 7.0 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3257, 3083, 1684, 2544, 1308, 823, 703. Anal. calcd for $C_{20}H_{21}Cl_3N_6O_3$: C, 48.06; H, 4.24; N, 16.82. Found: C, 48.12; H, 4.32; N, 16.88.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*4*-*trifluoromethylbenzamide* (***3g***). Yield, 65.4%; mp 206−208 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.92 (s, 1H, NNHCO), 8.32 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.74 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.2 Hz, 1H, Py-H), 7.68−7.75 (m, $J$ = 8.0 Hz, $J$ = 8.0 Hz, 4H, Ph-H), 7.32 (d, $J$ = 8.2 Hz, 1H, Py-H), 4.51 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.21 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.80−3.86 (m, 4H), 3.14−3.16 (m, 1H), 2.93 (s, 3H, $NCH_3$), 2.80−2.95 (m, 1H), 1.13 (t, $J$ = 7.0 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3258, 3081, 1682, 1543, 1310, 810. Anal. calcd for $C_{21}H_{22}ClF_3N_6O_3$: C, 50.56; H, 4.44; N, 16.85. Found: C, 50.51; H, 4.49; N, 16.78.

*N*-[(*4Z*)-*4*-[[(*6*-*Chloro*-*3*-*pyridinyl*)*methyl*]*ethylamino*]-*3*-*methyl*-*5*-*nitro*-*1,2,3,6*-*tetrahydropyrimidin*-*1*-*yl*]-*2*-*bromo*-*5*-*methoxybenzamide* (***3h***). Yield, 72.6%; mp 206−208 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 9.94 (s, 1H, NNHCO), 8.32 (d, $J$ = 2.4 Hz, 1H, Py-H), 7.75 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.0 Hz, 1H, Py-H), 7.50−7.74 (m, 3H, Ph-H), 7.32 (d, $J$ = 8.2 Hz, 1H, Py-H), 4.51 (d, $J$ = 16.0, 1H, Py-$CH_2$), 4.21 (d, $J$ = 16.0 Hz, 1H, Py-$CH_2$), 3.83−3.87 (m, 4H), 3.80 (s, 3H, $OCH_3$), 3.10−3.16 (m, 1H), 2.95 (s, 3H, $NCH_3$), 2.80−2.92 (m, 1H), 1.12 (t, $J$ = 7.2 Hz, 3H, $NCH_2CH_3$). IR (KBr, cm$^{-1}$): 3254, 3082, 1685, 1543, 1309, 1260, 754. Anal. calcd for $C_{21}H_{24}BrClN_6O_4$: C, 46.72; H, 4.48; N, 15.57. Found: C, 46.78; H, 4.43; N, 15.52.

**X-ray Crystallography.** The yellow crystal of the title compound **2b** (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 Ka radiation ($k$ = 0.71073 Å), using an $\varphi$-$\omega$ scan mode in the range of $2.47 \le \theta \le 26.49°$ 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 (*16*). All of the nonhydrogen atoms were refined anisotropically, and hydrogen atoms were located at their idealized positions. The final $R$ = 0.0746, $wR$ = 0.1586 $\{w = 1/[\sigma^2(F_o^2) + (0.0749P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$, $S$ = 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 SHELXTL-97 software package. Other details of the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC740000.

**Biology Assay.** The bioassay was measured according to the standard test (*17*) with a slight modification, and all analogues were tested against *N. legen* to evaluate their insecticidal activities. The compounds were dissolved in dimethyl formamide (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 according to statistical requirements. The insects were reared at 25 (±1) °C, 60 (±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 (*18*). All results are shown in **Table 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.

**Experimental Protocol of Docking Study.** The high nAChR inhibitory activity of compound **2d** was chosen to understand the ligand−protein interactions in detail, and AutoDock 4.0 (*19*) was used to carry out the molecular modeling study. Because the amino acids forming the active pockets are both structurally and functionally consistent in the diverse nAChRs and AchBPs, the crystal structure of the *Lymnaea stagnalis* AchBP (*Ls*-AChBP) complexed with imidacloprid (protein data bank code: 2zju) (*20*) was used as the template to construct the models. The receptor was prepared for docking by the addition of hydrogen atoms and the removal of cocrystallized molecules. The putative active binding site was characterized by selecting all residues within a 12 Å radius of the original binding substrate in the X-ray structure. Each ligand was iteratively minimized and assigned the Gasteiger−Hückel charges.

The studied compounds were flexibly docked automatically in the active site of nAChR. The AMBER force field was used to calculate a three-dimensional grid of interaction energies for the target nAChR by AutoGrid (Component of the AutoDock 4.0 program), and these grids were precomputed to store the electrostatic and van der Waals values. Default values were used for all docking parameters with 20 independent docking runs for each ligand. Intermolecular energy, torsional free energy, and intermolecular hydrogen bonds were included to evaluate their binding free energy. Cluster analysis was performed on the docked results using a root-mean-square deviation (rmsd) tolerance of 0.75 Å. For each cluster, the conformation with the lowest binding energy in the binding site was chosen for further analysis and comparison. Accelrys DS visualizer 2.5 [Accelrys Inc., San Diego, CA (2009)] was used for molecular modeling to determine their binding orientations and interactions.

**Table 1.** Yields of the Title Compounds under Conventional Conditions and Microwave Irradiation

| | | yield | |
|---|---|---|---|
| entry | R | conventional condition | microwave irradiation |
| **2a** | $CH_3$ | 68.3 | 76.2 |
| **2b** | $(CH_3)_2CH$ | 69.8 | 77.4 |
| **2c** | $CH_3SCH_2CH_2$ | 70.9 | 75.3 |
| **2d** | $(CH_3)_2CHCH_2$ | 68.5 | 78.2 |
| **2e** | $C_2H_5CH(CH_3)$ | 70.3 | 77.6 |
| **2f** | $C_6H_5CH_2$ | 67.4 | 73.5 |
| **2g** | $4\text{-}OHC_6H_4CH_2$ | 67.2 | 72.1 |
| **2h** | $4\text{-}ClC_6H_4$ | 68.3 | 72.5 |
| **3a** | H | 65.4 | 72.5 |
| **3b** | 4-Cl | 63.5 | 70.2 |
| **3c** | 2-Cl | 61.6 | 68.9 |
| **3d** | $4\text{-}CH_3$ | 63.8 | 72.8 |
| **3e** | 6-Cl-2-F | 62.7 | 70.5 |
| **3f** | $3,4\text{-}Cl_2$ | 64.5 | 71.3 |
| **3g** | $4\text{-}F_3C$ | 58.7 | 65.4 |
| **3h** | H | 64.1 | 72.6 |

**Table 2.** Insecticidal Activities of Nitromethylene Analogues against *N. legen*

| | | mortality (%) at different concentrations (mg/L) | | |
|---|---|---|---|---|
| compd | R | 500 | 100 | 20 |
| **2a** | $CH_3$ | 84 | 63 | 31 |
| **2b** | $(CH_3)_2CH$ | 95 | 67 | 42 |
| **2c** | $CH_3SCH_2CH_2$ | 100 | 91 | 73 |
| **2d** | $(CH_3)_2CHCH_2$ [b] | 100 | 100 | 100 |
| **2e** | $C_2H_5CH(CH_3)$ | 100 | 94 | 91 |
| **2f** | $C_6H_5CH_2$ | 100 | 85 | 41 |
| **2g** | $4\text{-}OHC_6H_4CH_2$ | 100 | 93 | 87 |
| **2h** | $4\text{-}ClC_6H_4$ | 62 | 26 | NT[a] |
| **3a** | H | 95 | 31 | NT |
| **3b** | 4-Cl | 100 | 52 | 37 |
| **3c** | 2-Cl | 100 | 56 | 32 |
| **3d** | $4\text{-}CH_3$ | 93 | 38 | NT |
| **3e** | 6-Cl-2-F | 100 | 67 | 51 |
| **3f** | $3,4\text{-}Cl_2$ | 100 | 65 | 53 |
| **3g** | $4\text{-}F_3C$ | 100 | 69 | 56 |
| **3h** | 2-Br-5-OMe | 95 | 54 | 28 |
| **1b** | nitenpyram [c] | 100 | 100 | 100 |

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

## RESULTS AND DISCUSSION

**Synthesis.** L-α-Amino acid and substituent benzoic acid were converted to the intermediates of L-α-amino acid methyl ester hydrochloride and substituent benzoyl hydrazine according to the procedures given in the literature (*21*, *22*), respectively. Starting from 2-chloro-5-chloromethylpridine, a set of (*E*)-*N*-(6-chloro-3-pyridylmethyl)-*N*-ethyl-1-chloro-2-nitroethylene-1-amine and **1b** were prepared based on the procedures in the literature (*23*, *24*). The further reaction of **1b** with L-α-amino acid methyl ester hydrochloride or substituent benzoyl hydrazine could proceed readily under microwave irradiation (**Scheme 2**), which was a highly efficient way, as compared to those obtained under conventional conditions by refluxing of the starting materials in ethanol for 6 h. Furthermore, the yields of **2a**−**2h** and **3a**−**3h** were higher than those obtained under conventional conditions (**Table 1**), and the purity of the compounds was also satisfactory.

**Crystal Structure Analysis.** The structure of compound **2b** 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 **2b** adopts a sofa conformation (**Figure 2**), five atoms of C(9)−N(3)−C(10)−C(11), and C(12) defines a plane with the biggest deviation from the plane being 0.602 Å for N(4) atom. Interestingly, because of the transfer of the lone pair electrons on the amines to the C(9)−C(12) double bond, the C(9)−N(3) bond length (1.369 Å) is remarkably shorter than the pure C−N single bond (1.47 Å) but close to C=N (1.33 Å) (*25*). The delocalization of the electrons extends as far as the electron-withdrawing group ($-NO_2$), forming a coplanar olefin−amine π-electron network. As compared with the trans configuration of nitro in the crystal structure of nitenpyram, the nitro group in **2b** is obviously in the cis configuration as anticipated.

**SAR.** Most of our designed analogues exhibited good insecticide activities against *N. legen* (**Table 2**) and had >95% mortality at 500 mg/L. Among these compounds, **2d** afforded the best in vitro inhibitory activity and had 100% mortality 20 mg/L. When different substituents (R) were introduced to the α-position of the carboxylic ester (**2a**−**2h**), their insecticidal activities increased in the order *p*-Cl-phenyl (**2h**) < methyl (**2a**) < isopropyl (**2b**) < benzyl (**2f**) < MeS-ethyl (**2c**) < *p*-OH-benzyl (**2g**) < sec-butyl (**2e**) < isobutyl (**2d**). In addition, analogue **2h** with R = 4-chlorophenyl exhibited about 10-fold less potency than compounds (**2e** and **2d**) with a relatively long and flexible alkyl group. These observations clearly suggest that the potency of these derivatives (**2a**−**2h**) depends significantly upon the length and flexibility of the substituent R.

The *N*-(substituent)-benzoyl amide tetrahydropyrimidine derivatives (**3a**−**3h**) also exhibited excellent insecticidal activities against *N. legen* at 500 mg/L. However, as compared with **2a**−**2h**, the activities of some of them (**3a** and **3d**) decreased remarkably when the dose was reduced to 100 mg/L, which may be related to their relatively weak affinities with their target. Interestingly, the introduction of F element into the substituent R showed increasing tendency in biological activity. Because compound **2d** displayed insecticidal potency that is comparable to nitenpyram ($LC_{50}$ = 0.129 mg/L), further insecticidal activity assay was carried out for compound **2d**. It was found that the $LC_{50}$ value of **2d** against *N. legen* is 0. 216 mg/L, which implies further possibilities for lead compound development.

**Molecular Docking Study.** To further explore the structural requirement for better activities, binding site interactions of these new compounds were simulated with *Ls*-AChBP based on its crystal structure cocomplexed with bound imidacloprid. As expected, compound **2d** attained the highest score and fitted the best in the interfacial binding pocket between the two faces of adjacent nAChR subunits (**Figure 3a**), with its backbone and chains nicely nestled. The binding conformation of **2d** in this docking simulation revealed an intriguing molecular binding mode at the active site of nAChR, with a very low docked energy. As illustrated in **Figure 3b**, analogue **2d** exhibits two hydrogen bonds via its nitro O(22) and O(23) with the backbone and side chain O of Glu190, respectively, and the O(24) of its ester moiety interacts with the side chain O of Gln55, while its chloropyridine N hydrogen bonds the GLN73 backbone. These active site amino acids are different from the ones that interact with the bound imidacloprid in the cocrystallized nAChR complex, which might suggest a novel mechanism of the insecticidal effect by these new compounds.

Furthermore, most of the other active analogues (**2c**, **2e**, and **2g**) shared a quite similar nice binding mode with **2d**. However, consistent with the SARs observed in vitro, the binding interactions of analogues with low inhibitory potency were not satisfactory, so did their docking scores. Little formation of hydrogen bonds and hydrophilic or hydrophobic contact could be found in their best binding conformations, such as the

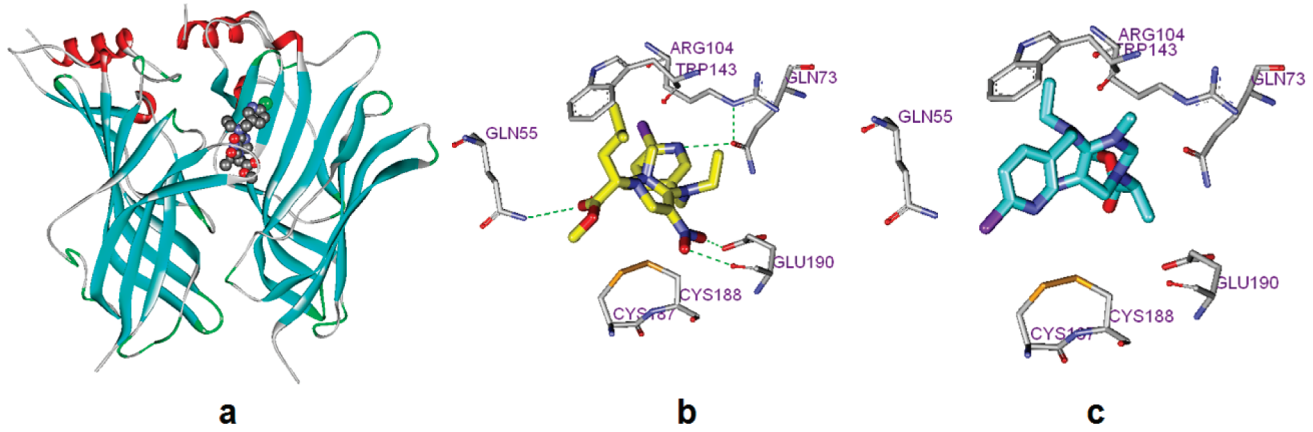



**Figure 3.** Binding site interactions of analogue **2d** with the extracellular domain of nAChR (protein data bank code: 2zju). (**a**) Compound **2d** is bound into the subunit interfacial binding pocket between two faces of adjacent subunits. For clarity, only two of five subunits are extracted and shown from the pentameric nAChR structure, and the corresponding interfacial binding pocket of interest is displayed. (**b**) Zoomed-in view of the interactions between compound **2d** and amino acids from the active site of the receptor. (**c**) The predicted binding mode of compound **2a** with relatively low activity.

predicted binding mode of compound **2a** (**Figure 3c**). Thus, our docking results coincided well with the experimental activities. Thereby, the binding model proposed here may provide an alternative way close to the actual binding features of these new series of neonicotinoids analogues, which may provide some useful information for future receptor structure-guided design of novel insecticides.

In summary, we have designed and synthesized two series of novel tetrahydropyrimidine nitromethylene analogues, bearing a nitro group in the cis position and optical activity *N*-(α-substituted)-methyl acetate or *N*-(substituent)-benzoyl amide, all tested compounds presented good insecticidal activity, and some of them showed high insecticide potency at 20 mg/L. SARs clearly indicated that the length and flexibility of the substituent group at the α-position had major impacts on the biological activities of the designed analogues (**2a**−**2h**). In addition, a molecular docking investigation was also carried out by docking the test compounds into the active site of nAChR. The docking simulation demonstrated that **2d** was nicely accommodated by nAChR, which is in good agreement with its high insecticidal activity and the SAR analyze mentioned above and reveals a unique mode that these neonicotinoids bind to nAChR. Thus, analysis of these binding modes in insect's nAChRs will help to improve the understanding of their mechanism of action and facilitate receptor structure-guided design of novel insecticidal compounds with less resistance and better selectivity.

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## LITERATURE CITED

(1) Yu, H. B.; Qin, Z. F.; Dai, H.; Zhang, X.; Qin, X.; Wang, T. T.; Fang, J. X. Synthesis and insecticidal activity of *N*-substituted(1,3-thiazole)alkyl sulfoximine derivatives. *J. Agric. Food Chem.* **2008**, *56*, 11356–11360.

(2) Elbert, A.; Overbeck, H.; Iwaya, K.; Tsuboi, S. Imidacloprid, a novel systemic nitromethylene analogue insecticide for crop protection. *Proc. Brighton Crop Prot. Conf.-Pests Dis.* **1990**, *1*, 21–28.

(3) Minamida, I.; Iwanaga, K.; Tabuchi, T. Synthesis and insecticidal activity of acyclic nitroethene compounds obtaining a heteroarylethylamino group. *J. Pestic. Sci.* **1993**, *18*, 41–48.

(4) Kashiwada, Y. Bestguard (nitenpyram, TI-304)-A new systemic insecticide. *Agrochem. Jpn.* **1996**, *68*, 18–19.

(5) Elbert, A.; Nauen, R. Resistance of bemisia tabaci (Homoptera: Aleyrodidae) to insecticides in southern Spain with special reference to neonicotinoids. *Pest Manage. Sci.* **2000**, *56*, 60–64.

(6) Ninsin, K. D. Acetamiprid resistance and cross-resistance in the diamondback moth, plutella xylostella. *Pest Manage. Sci.* **2004**, *60*, 839–841.

(7) Sanchez, D. M.; Hollingworth, R. M.; Grafius, E. J.; Moyer, D. D. Resistance and cross-resistance to neonicotinoid insecticides and spinosad in the Colorado potato beetle, leptinotarsa decemlineata (Say) (Coleoptera: Chrysomelidae). *Pest Manage. Sci.* **2006**, *62*, 30–37.

(8) Gorman, K. G.; Devine, G.; Bennison, J.; Coussons, P.; Punchard, N.; Denholm, I. Report of resistance to the neonicotinoid insecticide imidacloprid in trialeurodes vaporariorum (Hemiptera: Aleyrodidae). *Pest Manage. Sci.* **2007**, *63*, 555–558.

(9) Rauch, N.; Nauen, R. Identification of biochemical markers linked to neonicotinoid cross resistance in *Bemisia tabaci* (Hemiptera: Aleyrodidae). *Arch. Insect Biochem. Physiol.* **2003**, *54*, 165–176.

(10) Nauen, R.; Denholm, I. Resistance of insect pests to neonicotinoid insecticides: Current status and future prospects. *Arch. Insect Biochem. Physiol.* **2005**, *58*, 200–215.

(11) Tomizawa, M.; Zhang, N. J.; Durkin, K. A.; Olmstead, M. M.; Casida, J. E. The eonicotinoid electronegative pharmacophore plays the crucial role in the high affinity and selectivity for the drosophila nicotinic receptor: An anomaly for the nicotinoid cation-π interaction model. *Biochemistry* **2003**, *42*, 7819–7827.

(12) Tian, Z. Z.; Shao, X. S.; Li, Z.; Qian, X. H.; Huang, Q. C. Synthesis, insecticidal activity, and QSAR of novel nitromethylene neonicotinoids with tetrahydropyridine fixed cis configuration and exo-ring ether modification. *J. Agric. Food Chem.* **2007**, *55*, 2288–2292.

(13) Shao, X. S.; Zhang, W. W.; Peng, Y. Q.; Li, Z.; Tian, Z. Z.; Qian, X. H. cis-Nitromethylene neonicotinoids as new nicotinic family: Synthesis, structural diversity, and insecticidal evaluation of hexahydroimidazo[1,2-α]pyridine. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6513–6516.

(14) Xu, L. Z.; Yang, Z.; Yi, X.; An, G. W. (*E*)-*N*-(6-Chloro-3-pyridylmethyl)-*N*-ethyl-*N*′-methyl-2-nitroethylene-1,1-diamine. *Acta Crystallogr.* **2008**, *E64*, o1074.

(15) Knellarkpls, J.; Woerweibo, D.; Erdolen, C. Tetrahydropyrimidine derivatives. WO 973287, 1997.

(16) Kou, H. Z.; Gao, S.; Sun, B. W.; Zhang, J. Metamagnetism of the first cyano-bridged two-dimensional brick-wall-like 4f-3d array. *Chem. Mater.* **2001**, *13*, 1431–1433.

(17) Zhao, P. L.; Wang, F.; Zhang, Z. M. Synthesis, fungicidal, and insecticidal activities of β-methoxyacrylate-containing *N*-acetyl pyrazoline derivatives. *J. Agric. Food Chem.* **2008**, *56*, 10767–10773.

(18) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1995**, *18*, 265–267.

(19) Huey, R.; Morris, G. M.; Olson, A. J. A semiempirical free energy force field with charge-based desolvation. *J. Comput. Chem.* **2007**, *28*, 1145–1152.
(20) Ihara, M.; Okajima, T.; Yamashita, A. Crystal structures of *Lymnaea stagnalis* AChBP in complex with neonicotinoid insecticides imidacloprid and clothianidin. *Invertebr. Neurosci.* **2008**, *8*, 71–81.
(21) Lu, X. Q.; Zhao, G. Q.; Song, X.; Xie, J. M. A novel method of synthesis of polar amino acid methyl ester hydrochlorides. *Chemical World* **2007**, *48*, 357–359.
(22) Chen, W. J.; Liao, D. H. Synthesis of o-chlorobenzoyl hydrazine. *Chemical World* **2006**, *47*, 285–286.
(23) Wang, D. S. The synthesis methods of nitenpyram. *Pesticide* **2002**, *41*, 43–44.
(24) Isao, M.; Koichi, I.; Tetsuo, O. α-Unsaturated amines, their production and use. EP 0302389A2, 1989.
(25) Kagabu, S.; Matsuno, H. Chloronicotinyl insecticides. 8. Crystal and molecular structures of imidacloprid and analogous compounds. *J. Agric. Food Chem.* **1997**, *45*, 276–281.

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