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cis-Nitenpyram Analogues Containing 1,4-Dihydropyridine: Synthesis, Insecticidal Activities, and Molecular Docking Studies

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A novel series of *cis*-nitenpyram analogues (**2a**—**2p**) were designed and prepared by introducing the 1,4-dihydropyridine, with their *cis*-configuration confirmed by X-ray diffraction. Preliminary bioassays showed that most compounds exhibited good insecticidal activities at 20 mg/L against *Aphis medicagini*, and analogues **2a** and **2d** afforded the best activity, and both of them had 100% mortality at 4 mg/L. In addition, molecular docking studies were also performed to model the ligand-receptor complexes, and the results explained the structure-activity relationships observed *in vitro*, which may provide some useful information for future design of new insecticides.

Keywords *cis*-nitenpyram analogue, 1,4-dihydropyridine, synthesis, insecticidal acvitity, molecular docking

Introduction

In the past decades, neonicotinoid insecticides have gained worldwide attention for being the fastest growing class of insecticides in modern crop protection, with widespread use against most of sucking and certain chewing pests. As potent agonists, they act selectively on the insect nicotinic acetylcholine receptors (nAChRs).[1] The greatest attributes of the neonicotinoids include their novel mode of action, low mammalian toxicity, broad insecticidal spectrum, and good systemic properties.[2] Since imidacloprid[3] (IMI) was first introduced to the market in 1991, many new neonicotinoid insecticides (NNSs) are now on the market with their own prominence. As the second of the chloronicotinyl subclass, nitenpyram,[4] which was brought to market in 1995, was characterized with much lower toxicity against the mammals than imidacloprid.[5] Besides, nitenpyram also had higher selectivity[6-8] and better systemic properties[9,10] against mammals, birds, aquatic life than insects, due to the differential binding affinities with the nAChR of their neurosystem.[11]

As a popular saying goes, "everything has two sides". On one hand, now the agricultural industry is benefiting more and more from NNSs. On the other hand, a serious potential problem facing all insecticides is the development of resistance. Although NNSs have a new mode of insecticidal action, frequent applications of structural analogues of neonicotinoids have led to the acquisition of resistance and cross-resistance in a range of species.[12-15] Besides, the situation of bee pesticide poisoning had become worse,[16] some of the NNSs, such as imidacloprid has been banned or restricted in some European and American countries, because of its killing effect on bees and other pollinators. Hence, the development of novel neonicotinoids with both good insecticidal activities and less resistance is highly desirable.

According to the literature, changing the configuration of commercial neonicotinoids' pharmacophore is one of the effective resistance-management tactics.[17,18] The nitro groups in all commercialized neonicotinoids have a *trans* configuration, on which three proposals formodes of action are based.[19] However, In the late 1980s, Bayer and Nihon Tokushu Noyaku Seizo Co. reported that several *cis*-configuration neonicotinoids showed high insecticidal activity,[17,18] which implied that neonicotinoids in the *cis*-configuration might bind to the receptor in a different way,[7,20] and their insecticidal activities may benefit from it. In addition, considering the pharmacophore moieties, these commercialized neonicotinoids can be divided into two groups: the open-chain compounds and the 5- or 6-membered compounds (Scheme 1), which makes them different in their molecular characteristics. Until recently, most of the structural optimization of NNSs are based on cyclic neonicotinoid insecticides, such as imidacloprid. However, few studies have been focused on the structural modification of acyclic NNSs, such as nitenpyram.

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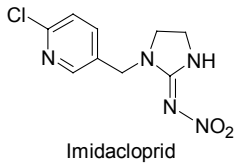
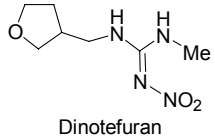
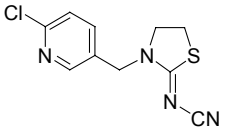
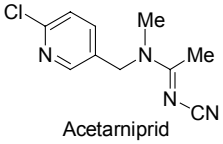
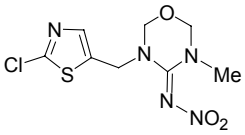
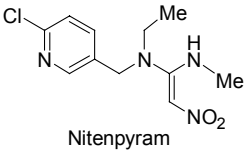
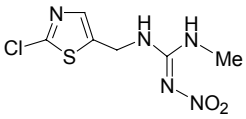
Scheme 1 Seven commercial neonicotinoid insecticides

5- and 6-membered compounds (Cyclic NNSs)	Open-chain compounds (Acyclic NNSs)
 Imidacloprid **1**	 Dinotefuran **4**
 Thiacloprid **2**	 Acetarniprid **5**
 Thiamethoxam **3**	 Nitenpyram **6**
	 Clothianidin **7**

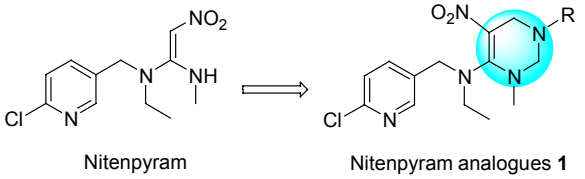


Figure 1 Nitenpyram analogues with tetrahydropyrimidine fixed *cis* configuration in our group.

In our previous work,[21-23] we have focused our attention on designing novel neonicotinoids, in which the nitenpyam structure was reserved and the different substituents R were introduced into the lead compound through forming a 1,2,3,6-tetrahydropyrimidine ring to fix the nitro group in the *cis* position (Figure 1). Correspondingly, a series of *cis*-configuration nitenpyram analogues **1** (Figure 1) were synthesized by introducing 1,2,3,6-tetrahydropyrimidine, these compounds exhibited good insecticide activities against *Nilaparvata lugens*. However, the insecticidal spectra of these compouds are narrow. In order to search for lead compouds of neonicotinoid insecticides with novel structural features, high activity, less resistance and broad insecticidal spectra, based on the above mentioned reports, we developed a new design strategy by introducing a 1,4-dihydropyridine ring into nitenpyram fixing the nitro group in *cis*-configuration (Figure 2, confirmed by X-ray diffraction). In order to enhance the hydrogen bond interactions, NH_2, $COOCH_3$, $COOCH_2CH_3$ and CN were introduced to the 2-position and 3-position of this ring. A new series of nitenpyram analogues (**2a**—**2p**) described herein were synthesized by multicomponet reaction (MCRs) and tested. Preliminary bioassay against *Aphis medicagini* showed that all these compounds exhibited excellent insecticide activities, and their structure-activity relationships were discussed. To further investigate their binding interactions, molecular docking simulations were carried out. As expected, active analogues exhibited significant hydrogen bonding interactions with the nAChR target. The docking results explained the structure-activity relationships observed *in vitro*, and shed a light on the novel insecticidal mechanism of these new analogues, which may provide some useful information for future design of new insecticides.

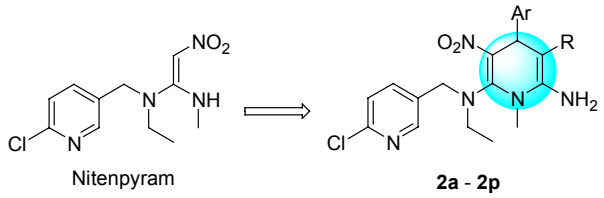


Figure 2 The target compounds based on nitenpyram (**2a**—**2p**).

Experimental

Materials and physical measurements

Unless otherwise noted, reagents and solvents were of analytical reagent grade or were chemically pure and used as received without further purification. Melting points were measured using an uncorrected RK^{-1} microscopic melting point apparatus. ^1H NMR spectrum ($CDCl_3$) was recorded on a Bruker AVANCE-400 MHz with TMS as an internal standard. Coupling constants (*J* values) are in Hertz. 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.

Synthesis of target compounds 2a—2p (exemplified by 2a)

A mixture of methyl cyanoacetate (12 mmol), benzaldehyde (12 mmol), piperidine (0.1 mmol), and nitenpyram (10 mmol) in anhydrous alcohol (20 mL) was heated to 60—75 ℃ 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

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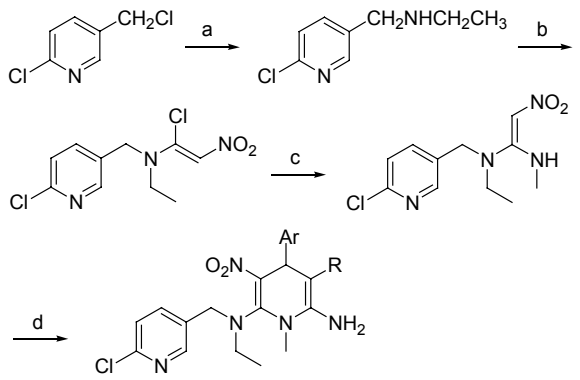
Scheme 2 Synthesis of nitenpyram analogues with 1,4-dihydropyridine ring (**2a**—**2p**).



2a Ar = Ph, R = $COOCH_3$; **2b** Ar = Ph, R = $COOCH_2CH_3$

2c Ar = Ph, R = CN; **2d** Ar = 4-Cl-C_6H_4, R = $COOCH_3$

2e Ar = 4-Cl-C_6H_4, R = $COOCH_2CH_3$; **2f** Ar = 4-Cl-C_6H_4, R = CN

2g Ar = 4-NO_2-C_6H_4, R = $COOCH_3$; **2h** Ar = 4-NO_2-C_6H_4, R = CN

2i Ar = 4-F-C_6H_4, R = $COOCH_2CH_3$; **2j** Ar = 4-F-C_6H_4, R = CN

2k Ar = 4-OCH_3-C_6H_4, R = $COOCH_3$; **2l** Ar = 4-OCH_3-C_6H_4, R = CN

2m Ar = 2-Cl-C_6H_4, R = $COOCH_3$; **2n** Ar = 3-Cl-C_6H_4, R = $COOCH_3$

2o Ar = 4-$CH(CH_3)_2$-C_6H_4, R = CN; **2P** Ar = 4-CF_3-C_6H_4, R = CN

Reagents and conditions: (a) Ethanamine (42%). (b) 1,1,1-Trichloro-2-nitroethane/$CHCl_3$, 2—7 ℃ (65%). (c) Methanamine, 3—7 ℃ (58%). (d) substituted aromatic aldehydes, cyano compounds, piperidine/anhydrous alcohol, 60—75 ℃ (65.5%—86.0%)

phase was evaporated under reduced pressure, and crude product was subjected to flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (3∶1) to afford pure products **2a**.

The syntheses of **2a**—**2p** were carried out by the similar method. The analytical data for the compounds **2a**—**2p** were summarized as follows:

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-3-methoxycarbonyl-4-phenyl-5-nitro-1,4–dihydropyridine (2a)** Yellow crystals, yield 75.1%, m.p. 217—218 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.21 (d, J=15.2 Hz, Py-H, 1H), 7.30—7.02 (m, Ph-H, 4H), 7.10 (d, J=8.0 Hz, Py-H, 1H), 6.80 (d, J=7.6 Hz, Py-H, 1H), 6.32 (s, NH_2, 2H), 5.67 (d, J=17.1 Hz, CH, 1H), 4.40 (d, J=14.8 Hz, NCH_2CH_3, 1H), 4.18 (d, J=14.9 Hz, NCH_2CH_3, 1H), 3.58 (s, $COOCH_3$, 3H), 3.30 (s, 1H), 3.21 (s, NCH_3, 3H), 3.13—3.08 (m, 1H), 1.33 (t, J=6.8 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2923 (CH_3), 3335, 3202 (NH_2), 1502—1416 (NO_2), 1646, 1615, 1592 (benzene) cm^{-1}. Anal. calcd for $C_{22}H_{24}ClN_5O_4$: C 57.70, H 5.28, N 15.29; found C 57.78, H 5.26, N 15.25. ESI-MS (M+H) *m*/*z*: 458.15.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-ethoxycarbonyl-1-methyl-5-nitro-4-phenyl-1,4-dihydropyridine (2b)** Yellow crystals, yield 81.23%, m.p. 167—168 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.08 (s, Py-H, 1H), 7.82 (s, Py-H, 1H), 7.19—7.18 (m, Ph-H, 3H), 7.05 (s, Ph-H, 2H), 6.98 (s, Py-H, 1H), 6.19 (s, NH_2, 2H), 5.49 (s, CH, 1H), 4.32 (d, J=14.6 Hz, NCH_2CH_3, 1H), 4.16—4.10 (m, $COOCH_2CH_3$, 2H), 4.06 (d, J=14.8 Hz, NCH_2CH_3, 1H), 3.27—3.19 (m, 1H), 3.16 (s, NCH_3, 3H), 3.10 (dt, J=13.9, 7.0 Hz, 1H), 1.31 (t, J=7.0 Hz, $COOCH_2CH_3$, 3H), 1.23 (t, J=7.0 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3327, 3200 (NH_2), 2984, 2935, 2870 (C=O), 1343 (NO_2), 1308 ($\nu_{as,C-O-C}$), 1235 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{23}H_{26}ClN_5O_4$: C 58.53, H 5.55, N 14.84; found C 58.64, H 5.53, N 14.81. ESI-MS (M+H) *m*/*z*: 472.17.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-1-methyl-5-nitro-4-phenyl-1,4-dihydropyridine (2c)** Yellow crystals, yield 86.0%, m.p. 100—102 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.08 (d, J=12.4 Hz, Py-H, 1H), 7.34 (d, J=8.9 Hz, Py-H, 1H), 7.24 (s, PhH, 3H), 7.08 (d, J=7.8 Hz, Py-H, 1H), 7.05—6.95 (m, PhH, 2H), 5.06 (s, CH, 1H), 4.79 (s, NH_2, 2H), 4.33 (d, J=14.8 Hz, 1H), 4.06 (d, J=14.6 Hz, 1H), 3.35—3.20 (m, 1H), 3.17 (s, NCH_3, 3H), 3.10 (dd, J=13.8, 7.3Hz, 1H), 1.33—1.21 (m, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2974 (CH_3) 3327, 3197 (NH_2), 2184 (CN), 1457, 1409 (NO_2), 1648, 1614, 1557 (benzene) cm^{-1}. Anal. calcd for $C_{21}H_{21}ClN_6O_2$: C 59.36, H 4.98, N 19.78; found C 59.28, H 4.97, N 19.74. ESI-MS (M+H) *m*/*z*: 425.14.

***cis*-2-Amino-4-(4-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-3-methoxycarbonyl-5-nitro-1,4-dihydropyridine (2d)** Yellow crystals, yield 83.2%, m.p. 227—228 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.20 (d, J=16.8 Hz, Py-H, 1H), 7.19—7.09 (m, Ph-H, 4H), 7.04 (d, J=7.9 Hz, Py-H, 1H), 6.98 (d, J=7.0 Hz, Py-H, 1H), 6.22 (s, NH_2, 2H), 5.73 (d, J=17.1 Hz, CH, 1H), 4.38 (d, J=14.8 Hz, NCH_2CH_3, 1H), 4.12 (d, J=14.9 Hz, NCH_2CH_3, 1H), 3.65 (s, $COOCH_3$, 3H), 3.28 (s, 1H), 3.20 (s, NCH_3, 3H), 3.10—3.06 (m, 1H), 1.33 (t, J=6.8 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3364, 3278 (NH_2), 2981, 2945, 2876 (C=O), 1342 (NO_2), 1309 ($\nu_{as,C-O-C}$), 1235 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{22}H_{23}Cl_2N_5O_4$: C 53.67, H 4.71, N 14.22; found C 53.56, H 4.72, N 14.24. ESI-MS (M+H) *m*/*z*: 492.11.

***cis*-2-Amino-4-(2-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-ethoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (2e)** Yellow crystals, yield 65.5%, m.p. 174—175 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.19 (s, Py-H, 1H), 7.81 (s, Py-H, 1H), 7.27 (s, Py-H, 1H), 7.22 (d, J=6.0 Hz, Ph-H, 1H), 7.14—7.06 (m, Ph-H, 2H), 7.04 (t, J=8.2 Hz, Ph-H, 1H), 6.24 (s, NH_2, 2H), 5.68 (s, CH, 1H), 4.37 (d, J=14.5 Hz, NCH_2CH_3, 1H), 4.14—4.08 (m, $COOCH_2CH_3$, 2H), 4.07—4.03 (m, NCH_2CH_3, 1H), 3.23 (s, NCH_3, 3H), 3.20 (d, J=7.3 Hz, 1H), 3.11 (dd, J=13.7, 6.9 Hz, 1H), 1.32 (dd, J=13.3, 6.2 Hz, $COOCH_2CH_3$, 3H), 1.21 (t, J=7.1 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3384, 3298 (NH_2), 3065, 2981, 2933 (C=O), 1337 (NO_2), 1294 ($\nu_{as,C-O-C}$), 1267 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{23}H_{25}Cl_2N_5O_4$: C 54.55, H 4.98, N 13.83; found C 54.65, H 4.96, N 13.87. ESI-MS (M+H) *m*/*z*: 506.13.

***cis*-2-Amino-4-(4-chlorophenyl)-6-[*N*-(6-chloro-3-**

pyridinylmethyl)-*N*-ethyl]amino-3-cyano-1-methyl-5-nitro-1,4-dihydropyridine (2f) Yellow crystals, yield 85.5%, m.p. 102—104 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.30 (s, Py-H, 1H), 8.09 (s, Py-H, 1H), 7.78 (s, Py-H, 1H), 7.21 (d, J=7.3 Hz, PhH, 1H), 7.10 (d, J=6.8 Hz, PhH, 1H), 7.01 (d, J=7.8 Hz, PhH, 1H), 6.94 (d, J=7.5 Hz, PhH, 1H), 5.01 (s, CH, 1H), 4.51 (s, NH_2, 2H), 4.33 (d, J=14.2 Hz, 1H), 4.10 (dd, J=16.9, 10.8 Hz, 1H), 3.25—3.16 (m, 1H), 3.16 (s, NCH_3, 3H), 3.14—3.08 (m, 1H), 1.35—1.20 (m, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2927 (CH_3), 3447, 3319, 3196 (NH_2), 2184 (CN), 1485—1413 (NO_2), 1648, 1608, 1557 (benzene) cm^{-1}. Anal. calcd for $C_{21}H_{20}Cl_2N_6O_2$: C 54.91, H 4.39, N 18.30; found C 55.01, H 4.38, N 18.24. ESI-MS (M+H) *m*/*z*: 459.10.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-methoxycarbonyl-1-methyl-5-nitro-4-(4-nitrophenyl)-1,4 -dihydropyridine (2g)** Yellow crystals, yield 78.1%, m.p. 194—195 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.13 (d, J=8.1 Hz, Py-H, 1H), 8.06 (d, J=8.3 Hz, Ph-H, 2H), 7.42 (d, J=8.0 Hz, Py-H, 1H), 7.17 (d, J=12.5 Hz, Ph-H, 2H), 6.95 (d, J=8.1 Hz, Py-H, 1H), 6.34 (br, NH_2, 2H), 5.48 (s, CH, 1H), 4.35 (d, J=14.6 Hz, NCH_2CH_3, 1H), 3.57 (s, $COOCH_3$, 3H), 4.09 (dd, J=12.3, 5.3 Hz, NCH_2CH_3, 1H), 3.38 (dd, J=13.7, 6.7 Hz, 1H), 3.30 (s, NCH_3, 3H), 3.23—3.16 (m, 1H), 1.19 (t, J=7.1 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3385, 3297 (NH_2), 3083, 2980, 2935 (C=O), 1349 (NO_2), 1300 ($\nu_{as,C-O-C}$), 1237 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{22}H_{23}ClN_6O_6$: C 52.54, H 4.61, N 16.71; found C 52.64, H 4.60, N 16.74. ESI-MS (M+H) *m*/*z*: 503.14.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-1-methyl-5-nitro-4-(4-nitrophenyl)-1,4-dihydropyridine (2h)** Yellow crystals, yield 83.1%, m.p. 133—135 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.11 (s, Py-H, 1H), 7.78 (s, Py-H, 1H), 7.38 (d, J=7.5 Hz, Py-H, PhH, 2H), 7.16—6.86 (m, Ph-H, 3H), 5.01 (s, CH, 1H), 4.60 (s, NH_2, 2H), 4.35 (d, J=13.6 Hz, 1H), 4.09 (d, J=14.1 Hz, 1H), 3.27 (d, J=7.2 Hz, 1H), 3.20 (s, NCH_3, 3H), 3.08 (d, J=5.0 Hz, 1H), 1.29 (t, J=10.7 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2930 (CH_3), 3333, 3203 (NH_2), 2186 (CN), 1347 (NO_2), 1647, 1611, 1518 (benzene) cm^{-1}. Anal. calcd for $C_{21}H_{20}ClN_7O_4$: C 53.68, H 4.29, N 20.87; found C 53.84, H 4.30, N 20.89. ESI-MS (M+H) *m*/*z*: 470.13.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-ethoxycarbonyl-4-(4-fluorophenyl)-1-methyl--5-nitro-1,4-dihydropyridine (2i)** Yellow crystals, yield 81.2%, m.p. 189—191 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.12 (s, Py-H, 1H), 7.80 (s, Py-H, 1H), 7.36 (s, Py-H, 1H), 7.33 (d, J=8.1 Hz, Ph-H, 1H), 7.10 (d, J=6.4 Hz, Ph-H, 1H), 7.03 (d, J=8.1 Hz, Ph-H, 1H), 6.93 (d, J=6.4 Hz, Ph-H, 1H), 6.06 (br, NH_2, 2H), 5.41 (s, CH, 1H), 4.34 (d, J=14.6 Hz, NCH_2CH_3, 1H), 4.16—4.12 (m, $COOCH_2CH_3$, 2H), 4.09 (d, J=14.9 Hz, NCH_2CH_3, 1H), 3.30 (dd, J=13.8, 7.0 Hz, 1H), 3.20 (s, NCH_3, 3H), 3.16 (dd, J=14.0, 7.1 Hz, 1H), 1.33 (t, J=7.0 Hz, $COOCH_2CH_3$, 3H), 1.21 (t, J = 7.1 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3399, 3291 (NH_2), 2976, 2929, (C=O), 1358 (NO_2), 1305 ($\nu_{as,C-O-C}$), 1275 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{23}H_{25}ClFN_5O_4$: C 56.39, H 5.14, N 14.29; found C 55.56, H 5.15, N 14.26. ESI-MS (M+H) *m*/*z*: 490.16.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-4-(4-fluorophenyl)-1-methyl-5-nitro-1,4-dihydropyridine (2j)** Yellow crystals, yield 80.5%, m.p. 202—203 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.20 (s, Py-H, 1H), 8.12 (s, Py-H, 1H), 7.25 (s, Py-H, 1H), 7.21—6.51 (m, Ph-H, 5H), 5.10 (s, CH, 1H), 4.70 (s, NH_2, 2H), 4.32 (d, J=14.3 Hz, 1H), 4.11 (d, J=14.8 Hz, 1H), 3.35—3.21 (m, 1H), 3.19 (s, NCH_3, 3H), 3.14 (d, J=6.5 Hz, 1H), 1.35—1.24 (m, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2937 (CH_3), 3467, 3326, 3198 (NH_2), 2183 (CN), 1504—1343 (NO_2), 1653, 1603, 1558 (benzene) cm^{-1}. Anal. calcd for $C_{21}H_{20}ClFN_6O_2$: C 56.95, H 4.55, N 18.98; found C 57.12, H 4.53, N 19.03. ESI-MS (M+H) *m*/*z*: 443.13.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-methoxycarbonyl-4-(4-methoxylphenyl)-1-methyl-5-nitro-1,4-dihydropyridine (2k)** Yellow crystals, yield 78.5%, m.p. 201—202 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.19 (s, Py-H, 1H), 7.81 (s, Py-H, 1H), 7.27 (s, Py-H, 1H), 7.22 (d, J=8.0 Hz, Ph-H, 2H), 7.03 (d, J=8.0 Hz, Ph-H, 2H), 6.24 (s, NH_2, 2H), 5.68 (s, CH, 1H), 4.36 (d, J=14.5 Hz, 1H,), 4.07—4.03 (m, 1H), 3.80 (s, OCH_3, 3H), 3.65 (s, $COOCH_3$, 3H), 3.23 (s, NCH_3, 3H), 3.19 (d, J=7.3 Hz, 1H), 3.11 (dd, J=13.7, 6.9 Hz, 1H), 1.21 (t, J=7.1 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2963 (CH_3), 3323, 3211 (NH_2), 1477, 1413 (NO_2), 1652, 1612, 1577 (benzene). Anal. calcd for $C_{23}H_{26}ClN_5O_5$: C 56.62, H 5.37, N 14.35; found C 56.78, H 5.36, N 14.37. ESI-MS (M+H) *m*/*z*: 488.16.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-4-(4-methoxylphenyl)-1-methyl-5-nitro-1,4-dihydropyridine (2l)** Yellow crystals, yield 80.5%, m.p. 173—175 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.30 (s, Py-H, 1H), 8.11 (s, Py-H, 1H), 7.80 (s, Py-H, 1H), 7.12 (d, J=6.4 Hz, Ph-H, 1H), 7.01 (d, J=7.2 Hz, Ph-H, 1H), 6.93 (d, J=7.5 Hz, Ph-H, 1H), 6.77 (d, J=8.0 Hz, Ph-H, 1H), 4.98 (s, CH, 1H), 4.45 (d, J=22.7 Hz, NH_2, 2H), 4.33 (d, J=14.3 Hz, 1H), 4.07 (d, J=14.3 Hz, 1H), 3.80 (s, OCH_3, 3H), 3.30—3.21 (m, 1H), 3.18 (s, NCH_3, 3H), 3.15—3.06 (m, 1H), 1.29 (dd, J=17.0, 9.9 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2928 (CH_3), 3412, 3330 (NH_2), 2184 (CN), 1507, 1417 (NO_2), 1653, 1608, 1559 (benzene) cm^{-1}. Anal. calcd for $C_{22}H_{23}ClN_6O_3$: C 58.09, H 5.01, N 18.47; found C 58.26, H 5.02, N 18.43. ESI-MS (M+H) *m*/*z*: 455.15.

***cis*-2-Amino-4-(2-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-methoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (2m)** Yellow crystals, yield 83.2%, m.p. 227—228 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.20 (d, J=16.8 Hz, Py-H, 1H), 7.19—7.09 (m, Ph-H, 4H), 7.04 (d, J=7.9 Hz, Py-H, 1H), 6.98 (d, J=7.0 Hz, Py-H, 1H), 6.22 (s, NH_2, 2H), 5.73 (d, J=17.1 Hz, CH, 1H), 4.38 (d, J=14.8 Hz, NCH_2CH_3, 1H), 4.12 (d, J=14.9 Hz, NCH_2CH_3, 1H), 3.65 (s, $COOCH_3$,

3H), 3.28 (s, 1H), 3.20 (s, NCH_3, 3H), 3.10—3.06 (m, 1H), 1.33 (t, J=6.8 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3364, 3278 (NH_2), 2981, 2945, 2876 (C=O), 1342 (NO_2), 1309 ($\nu_{as,C-O-C}$), 1235 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{21}H_{20}Cl_2N_6O_2$: C 54.91, H 4.39, N 18.30; found C 55.01, H 4.40, N 18.26. ESI-MS (M+H) *m*/*z*: 459.10.

***cis*-2-Amino-4-(4-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-methoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (2n)** Yellow crystals, yield 81.2%, m.p. 197—198 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.13 (d, J=8.1 Hz, Py-H, 1H), 7.80 (s, Py-H, 1H), 7.34—7.27 (m, Py-H, Ph-H, 2H), 7.16 (d, J=5.6 Hz, Ph-H, 1H), 7.05 (d, J=8.0 Hz, Ph-H, 1H), 6.91 (d, J=7.0 Hz, Ph-H, 1H), 6.27 (br, NH_2, 2H), 5.43 (d, J=12.0 Hz, CH, 1H), 4.35 (d, J=14.5 Hz, 1H), 4.10 (d, J=14.8 Hz, 1H), 3.67 (s, $COOCH_3$, 3H), 3.30—3.27 (m, 1H), 3.23 (s, NCH_3, 3H), 3.18 (dt, J=13.7, 6.9 Hz, 1H), 1.32 (t, J=7.1 Hz, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 3364, 3278 (NH_2), 2981, 2945, 2876 (C=O), 1342 (NO_2), 1309 ($\nu_{as,C-O-C}$), 1235 ($\nu_{a,C-O-C}$) cm^{-1}. Anal. calcd for $C_{22}H_{23}Cl_2N_5O_4$: C 53.67, H 4.71, N 14.22; found C 53.77, H 4.69, N 14.26. ESI-MS (M+H) *m*/*z*: 492.10.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-4-(4-isopropylphenyl)-1-methyl-5-nitro-1,4-dihydropyridine (2o)** Yellow crystals, yield 82.1%, m.p. 117—118 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.15 (s, Py-H, 1H), 7.35 (s, Py-H, 1H), 7.11 (d, J=6.6 Hz, Ph-H, 3H), 7.04 (d, J=7.4 Hz, Py-H, 1H), 6.94 (d, J=7.5 Hz, Ph-H, 1H), 5.03 (s, 1H, CH), 4.50 (d, J=18.2 Hz, NH_2, 2H), 4.35 (d, J=13.8 Hz, 1H), 4.03 (d, J=14.6 Hz, 1H), 3.20 (s, 1H), 3.14 (s, NCH_3, 3H), 3.09—2.97 (m, 1H), 2.93—2.82 [m, $CH(CH_3)_2$, 1H], 1.32—1.25 (m, NCH_2CH_3, 3H), 1.23 [d, J=6.6 Hz, $CH(CH_3)_2$, 6H]; IR (KBr) ν_{max}: 2960 (CH_3), 3329, 3194 (NH_2) , 2185 (CN), 1461, 1411 (NO_2), 1648, 1612, 1554 (benzene) cm^{-1}. Anal. calcd for $C_{23}H_{27}ClN_6O_3$: C 61.73, H 5.83, N 18.00; found C 61.85, H 5.81, N 18.05. ESI-MS (M+H) *m*/*z*: 467.19.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-1-methyl-5-nitro-4-(4-triflourophenyl)-1,4-dihydropyridine (2p)** Yellow crystals, yield 82.1%, m.p. 117—118 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.30 (s, Py-H, 1H), 8.09 (s, Py-H, 1H), 7.78 (s, Py-H, 1H), 7.21 (d, J=7.3 Hz, Ph-H, 1H), 7.10 (d, J=6.8 Hz, Ph-H, 1H), 7.01 (d, J=7.8 Hz, Ph-H, 1H), 6.94 (d, J=7.5 Hz, Ph-H, 1H), 5.01 (s, CH, 1H), 4.51 (s, NH_2, 2H), 4.33 (d, J=14.2 Hz, 1H), 4.10 (dd, J=16.9, 10.8 Hz, 1H), 3.25—3.18 (m, 1H), 3.16 (s, NCH_3, 3H), 3.14—3.03 (m, 1H), 1.35—1.20 (m, NCH_2CH_3, 3H); IR (KBr) ν_{max}: 2927 (CH_3), 3447, 3319, 3196 (NH_2), 2184 (CN), 1485—1413 (NO_2), 1648, 1608, 1557 (benzene) cm^{-1}. Anal. calcd for $C_{22}H_{20}ClF_3N_6O_2$: C 53.61, H 4.09, N 17.05; found C 53.71, H 4.10, N 17.08. ESI-MS (M+H) *m*/*z*: 493.13.

Crystal growth and X-ray data for crystal structure of 2o

Yellow crystal of compound **2o** with approximate dimensions of 0.20 mm×0.20 mm×0.20 mm, which is suitable for singlecrystal X-ray diffraction, was obtained by slowly evaporating a solution of **2o** in mixed acetone and petroleum at 25 ℃. The crystal was mounted on a glass fiber for data collection on a Bruker Smart Apex CCD diffractometer equipped with a graphite-monochromatic Mo Kα radiation (λ=0.71073 Å). The ψ-ω scan mode in the range of $1.84° \leqslant \theta \leqslant 25.00°$ at 298 K was used. A total of 14933 reflections were collected with 4485 unique ones (R_{int} 0.0280), of which 4485 with $I>2\sigma(I)$ were considered as observed and used in the subsequent refinements. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all nonhydrogen atoms.

Crystal data for **2o**: space group $P2_1/c$ with a=11.1272(10) Å, b=13.4939(13) Å, c=17.1732(16) Å, V=2560.0(4) $Å^3$, D_c=1.212 Mg/m^3, $F(000)$=984, μ=0.180 mm^{-1}, Z=4. The final refinement gave S=1.137, R=0.0816 and $w=1/[\sigma^2(F_o^2)+(0.0996P)^2]+1.1836P$, where $P=(F_o^2+2F_c^2)/3$. The crystal was analyzed with SHELXTL-97 software package and the structural plots were drawn with Otrep. Crystall ographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 823444. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax:+44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Result and Discussion

Synthesis

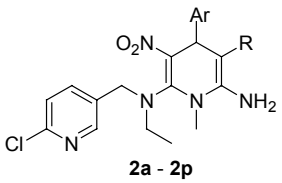
To prepare the title analogues with 1,4-dihydropyridine ring fixing the nitro group in *cis*-configuration, an efficient synthesis approach is developed as depicted in Scheme 2. The target compounds (**2a**—**2p**) were prepared via Knoevenagel reaction, Michael addition and nucleophilic addition by means of MCRs (multicomponent reactions). The MCRs included three components: nitenpyram, substituted aromatic aldehydes and cyano compounds. This new series of *cis*-nitenpyram analogues (**2a**—**2p**) were synthesized in good yields under microwave irradiation.

Evaluation of insecticidal activities

The insecticidal activities of these *cis*-nitenpyram analogues were evaluated against *Aphis medicagini*. As depicted in Table 1 (**2a**—**2p**), most of our designed compounds exhibited good insecticidal activities against *Aphis medicagini*, having >80% mortality at 100 mg/L. Among these analogues, **2a** and **2d** afforded the best *in vitro* activity, with 100% mortality at 4 mg/L, and their LC_{50} values were close to nitenpyram's LC_{50} value. When different substituents R and Ar were introduced to the 3-position and 4-position of the 1,4-dihydropyridine ring, their insecticidal activities varied greatly. As for the substituent R, their insecticidal activities in-

creased in the order cyano group (**2c**)＜ethyl ester group (**2b**)＜methyl ester group (**2a**), while the Ar group is the same (Ph). In addition, as the substituent Ar is concerned, this series of compounds demonstrated good activities with either electron-withdrawing or electron-donating groups. Moreover, the substituent position on the phenyl groups also caused changes in the insecticidal activities, and their inhibitory potency decreased in the order 4-position (**2d**)＞2-position (**2m**)＞3-position (**2n**), which may be related to their different affinities to the nAChR target, such as the number of hydrogen bondings.

Table 1 Insecticidal activities of nitenpyram analogues **2a**—**2p** against *Aphis medicagini*



2a - 2p

Compd.	Ar	R	Mortality (%) at different concentrations (mg/L) 500	100	20	4
2a	Ph	$COOCH_3$	100	100	100	90
2b	Ph	$COOCH_2CH_3$	100	90	80	70
2c	Ph	CN	100	80	70	65
2d	4-Cl-C_6H_4	$COOCH_3$	100	100	100	100
2e	2-Cl-C_6H_4	$COOCH_2CH_3$	100	100	50	40
2f	4-Cl-C_6H_4	CN	100	90	40	30
2g	4-NO_2-C_6H_4	$COOCH_3$	95	90	60	30
2h	4-NO_2-C_6H_4	CN	90	50	40	20
2i	4-F-C_6H_4	$COOCH_2CH_3$	100	100	100	20
2j	4-F-C_6H_4	CN	90	50	30	n.t.
2k	4-OCH_3-C_6H_4	$COOCH_3$	100	100	80	50
2l	4-OCH_3-C_6H_4	CN	80	60	50	15
2m	2-Cl-C_6H_4	$COOCH_3$	100	100	100	55
2n	3-Cl-C_6H_4	$COOCH_3$	100	90	80	40
2o	4-$CH(CH_3)_2$-C_6H_4	CN	100	90	70	25
2p	4-CF_3-C_6H_4	CN	95	50	30	n.t.
Nitenpyram			100	100	100	100

n.t.＝not tested.

Single-crystal structure of compound 2o

To confirm the *cis*-configuration with precise three-dimensional information, the single-crystal structure of compound **2o** was investigated and determined by X-ray diffraction analysis (CCDC Number: 823444). As compared with the *trans* configuration of nitro in the crystal structure of nitenpyram,[24] the nitro group in **2o** is obviously in the *cis* configuration as anticipated. In addition, the 1,4-dihydropyridine ring of the compound **2o** adopts a skew boat conformation (Figure 3). Interestingly, the bond lengths of C—C on the 1,4-dihydropyridine are obviously shorter than the pure C—C single bond (1.54 Å),[25] such as C(16)—C(12), C(12)—C(11), C(11)—C(15) and C(12)—C(13) being 1.520(7) Å, 1.521(4) Å, 1.406(4) Å and 1.507(4) Å, respectively. Similarly, the bond lengths of C—N on the 1,4-dihydropyridine are obviously shorter than the pure C—N single bond (1.47 Å),[25] such as C(10)—N(4), C(9)—N(3), and C(13)—N(6), their lengths are 1.341(4), 1.377(3), and 1.371(4) Å, respectively. On the contrary, the bond lengths [1.355(4) Å, 1.402(4) Å, respectively] of the C(11)＝C(10) and C(13)＝C(9) are longer than the pure C＝C bond (1.34 Å).[25] The bond lengths of C(15)≡N(5) is 1.135(4) Å, a bit shorter than pure C≡N bond (1.15 Å).[25] Based on these data, we can presume that there is a homo conjugation effect on the 1,4-dihydropyridine ring in the compound **2o**. As all the modes of action were put forward based on *trans*-configuration, this unique *cis*-configuration may confer some new properties onto the compounds.

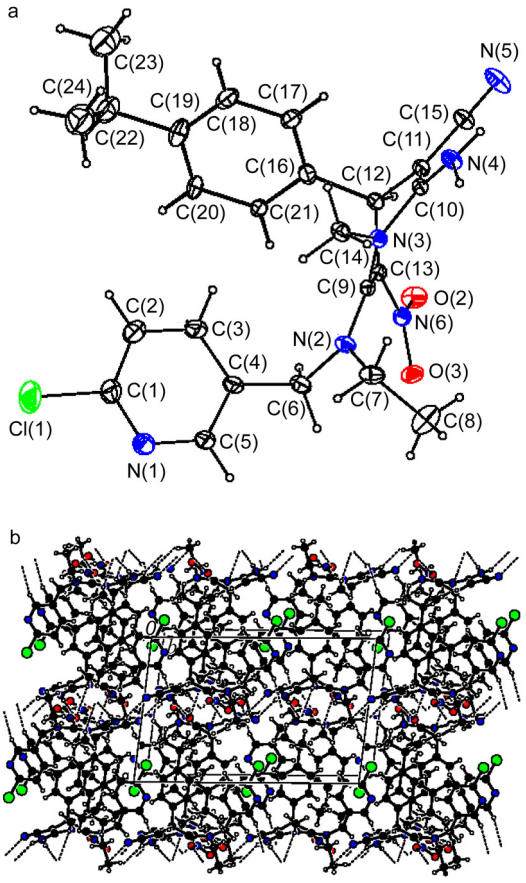


Figure 3 Molecular structure of compound **2o** (Number CCDC 823444) with atom-labeling and packing diagram.

Molecular docking study

To further explore the structural features for better activities, models of these new inhibitors-receptor complexes were investigated by docking studies with AutoDock version 4.0.[26] Since the amino acids form-

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ing the active sites are both structurally and functionally consistent in the diverse nAChRs and AchBPs, and none of the insect nAChRs has been published until now, the crystal structure of a *Lymnaea stagnalis*-AChBP (*Ls*-AChBP) co-crystallized with imidacloprid (PDB ID: 2zju)[27] was used as the template of receptor. The docking was carried out through the graphical user interface AUTODOCKTOOLS (ADT 1.4.6). The only modification was the number of docking runs that was set to 300 (previously 100) for more 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 significant hydrogen bonding interactions with the nAChR target. As expected, the most potent compound **2d** is nicely accommodated within the subunit interfacial binding pocket between the two faces of adjacent subunits (Figure 4 a, b). Its binding conformation exhibited two important hydrogen bonds between its nitro and H—O of Tyr192 (Figure 4b), and the O30 of its ester group hydrogen-bonds the H—O of Tyr185, while its chloropyridine interacts primarily with the side chain of Glu190, and its chlorophenyl also hydrogen-bonds the side chain of Gln55. Moreover, **2d** also showed the important additional H bonding interactions with Trp143 at the interface of two adjacent nAChR subunits (Figure 4c). In addition, due to the novel structure of compound **2d**, all these interactions above may greatly enhance the binding affinity of inhibitor **2d**, and account for its high inhibitory potency. Hence, the observations herein have also explained the structure-activity relationships observed *in vitro*.

Furthermore, most of the other active analogues (**2a**, **2j**) shared a similar binding mode with **2d**, and many of them exhibited more than four hydrogen bonds with different amino acids of the active pocket between the nAChR subunits (unpublished result), which is consistent with their high insecticidal activities. Since these amino acids (Gln55, Trp 143, Tyr185, Glu190, and Tyr192) of the active site residues were different from the ones that interacted with nitenpyram, the above results suggested a novel mechanism of their insecticidal effects. Thereby, compared with nitenpyram, the newly introduced substituents of the designed analogues presumably played important roles in ligand recognition and binding interactions, which may enhance their activities and contribute to the selectivity as well. Based on these, further inhibitory tests on special insect nAChR target(s) and advanced insecticide design are underway.

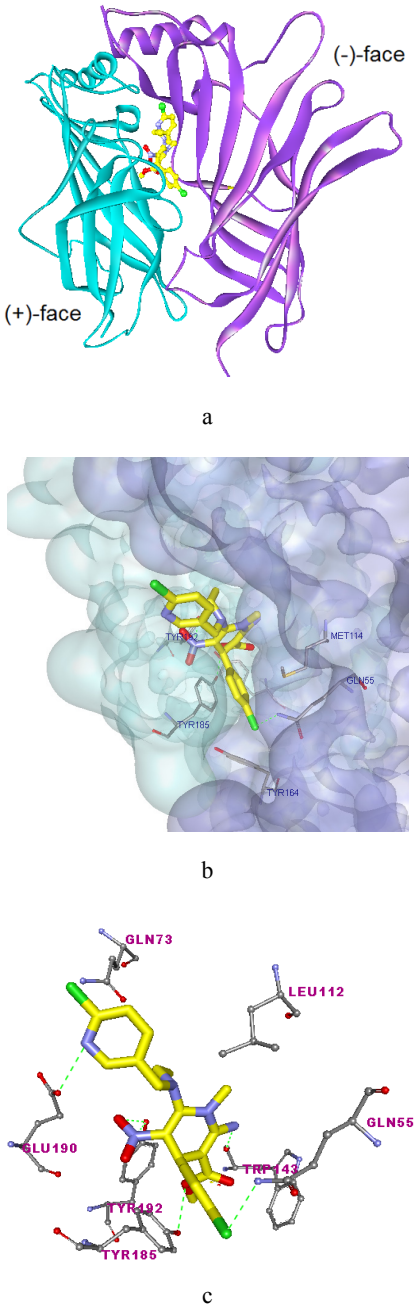

Figure 4 Modeling of the docking results of compounds **2d** in the extracellular domain of insect nAChR. (a) **2d** nestled in the interfacial agonist-binding pocket between the (+)-face (primary, cyan) and (−)-face (complementary, purple) subunits of the *Ls*-AChBP (PDB ID: 2zju), as a structural surrogate of the insect nAChR. The second structure of the protein is represented as solid ribbon; (b) nAChR-**2d** binding site interactions (zoomed-in), and the corresponding subunits which are also colored cyan and purple, respectively; (c) The hydrogen-bonding between **2d** and the active site residues of nAChR.

Conclusions

In this paper, in order to search for lead compounds of neonicotinoid insecticides with novel structural features, high activity, less resistance and broad insecticidal spectra, a new series of *cis*-nitenpyram analogues (**2a**—**2p**) were designed and synthesized by introducing the 1,4-dihydropyridine ring. All the target compounds presented good insecticidal activity against *Aphis medicagini* at 100 mg/L. Among these analogues, **2a** and **2d** afforded the best activity, and had 100% mortality at 4 mg/L. The most active analogue was **2d** with LC_{50} values of 0.136 mg/L, although less than nitenpyram. The

single *cis*-configuration of compound **2o** was confirmed by X-ray diffraction, and a homo conjugation effect on the 1,4-dihydropyridine ring was discovered. In addition, molecular docking investigation was also carried out to model the ligand-receptor complexes and analyze their interactions for improved activity. The docking results revealed a unique binding mode other than nitenpyram, and the docking scores were in good agreement with their high insecticidal potential, which also explained the structure-activity relationships observed *in vitro*. Further researches are underway to verify their molecular nAChR target and evaluate the inhibitory activities against resistant insect species. The study herein has shed a light on the mechanism of action of these new *cis*-configuration neonicotinoid analogues, and may facilitate receptor structure-guided design of novel insecticides with less resistance and better selectivity.

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