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**NOVEL NITENPYRAM ANALOGUES WITH
TETRAHYDOPYRIDONE-FIXED CIS-CONFIGURATION: SYNTHESIS,
INSECTICIDAL ACTIVITIES, AND MOLECULAR DOCKING STUDIES**

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Abstract – To make further researches on the diversity of nitenpyram analogues with a *cis*-nitromethylene configuration, a series of *cis*-nitenpyram analogues (**3a-q**) with tetrahydropyridone-fixed *cis*-configuration were designed and synthesized. Preliminary bioassays showed that most of the designed nitenpyram analogues exhibited good insecticidal activity at 100 mg/L against *Nilaparvata lugens* and *Myzus persicae*, while analogues **3n** afforded the best *in vitro* activity. Modeling the ligand-receptor complexes by molecular docking study revealed the analogues **3** with various substituents on phenyl show their different binding affinities to the insect nAChR, which also explained the structure-activity relationships observed *in vitro*.

INTRODUCTION

Nowadays, neonicotinoids insecticides (NNSs) are the most important chemical class of insecticides introduced to the global market since the synthetic pyrethroids.¹ Interacting with the insect nicotinic acetylcholine receptors (nAChRs),²⁻⁴ NNSs have a higher affinity for the insect receptor than for the mammalian and are relatively safe toward mammals and aquatic life.⁵⁻⁸ Although NNSs are fruitful in modern agricultural pest management and environmental protection, it is still essential to explore novel

neonicotinoid candidates, because insecticide resistance and cross-resistance have been observed in a range of species after frequent field applications.⁹⁻¹⁶

According to the chemical structures of neonicotinoids developed in the past several decades, the nitro group play an important role in the activities of neonicotinoids and nitromethylene segments are in *trans*-configuration in commercialized neonicotinoids.¹⁷ In the recent years, a number of neonicotinoid analogues with *cis*-configuration have been reported and shown high insecticidal activities and gained valuable results in resistance management.¹⁷⁻¹⁹ But most of these *cis*-configuration neonicotinoid analogues are designed on cyclic neonicotinoid insecticides, such as imidacloprid, few studies have been focused on the structural modification of acyclic NNSs, such as nitenpyram and acetamiprid. Encouraged by this, we have designed and synthesized *cis*-nitenpyram analogues **2** by using a tetrahydropyrimidine ring to fix the the direction of nitro group of nitenpyram (**Figure 1**) in previous studies.²⁰⁻²³ Preliminary bioassays indicated that most of nitenpyram analogues **2** showed good insecticidal activities against *Nilaparvata lugens*. However, we found that analogues **2** have similar skeleton— tetrahydropyrimidine ring, this is not satisfactory in the research of the diversity of nitenpyram analogues. Therefore, to find the diverse skeleton of nitenpyram analogues with a *cis* nitromethylene configuration, our interest is to design novel nitenpyram analogues by introducing a new heterocycle ring into the nitenpyram.

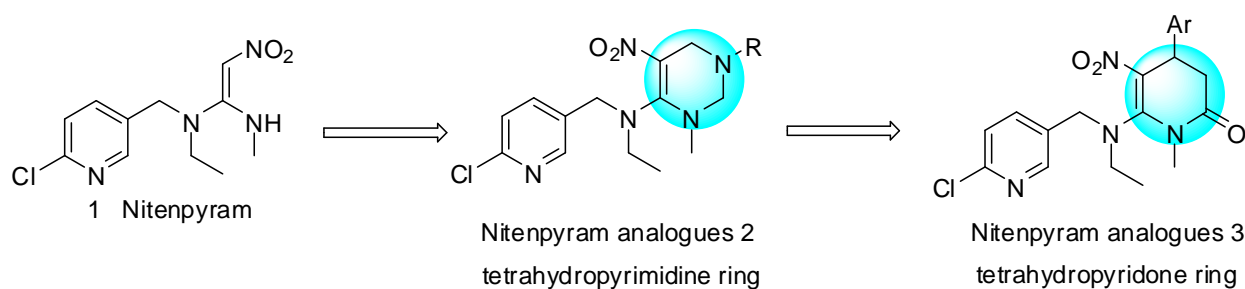


Figure 1. The design of the diversity *cis*-Nitenpyram analogues in our group

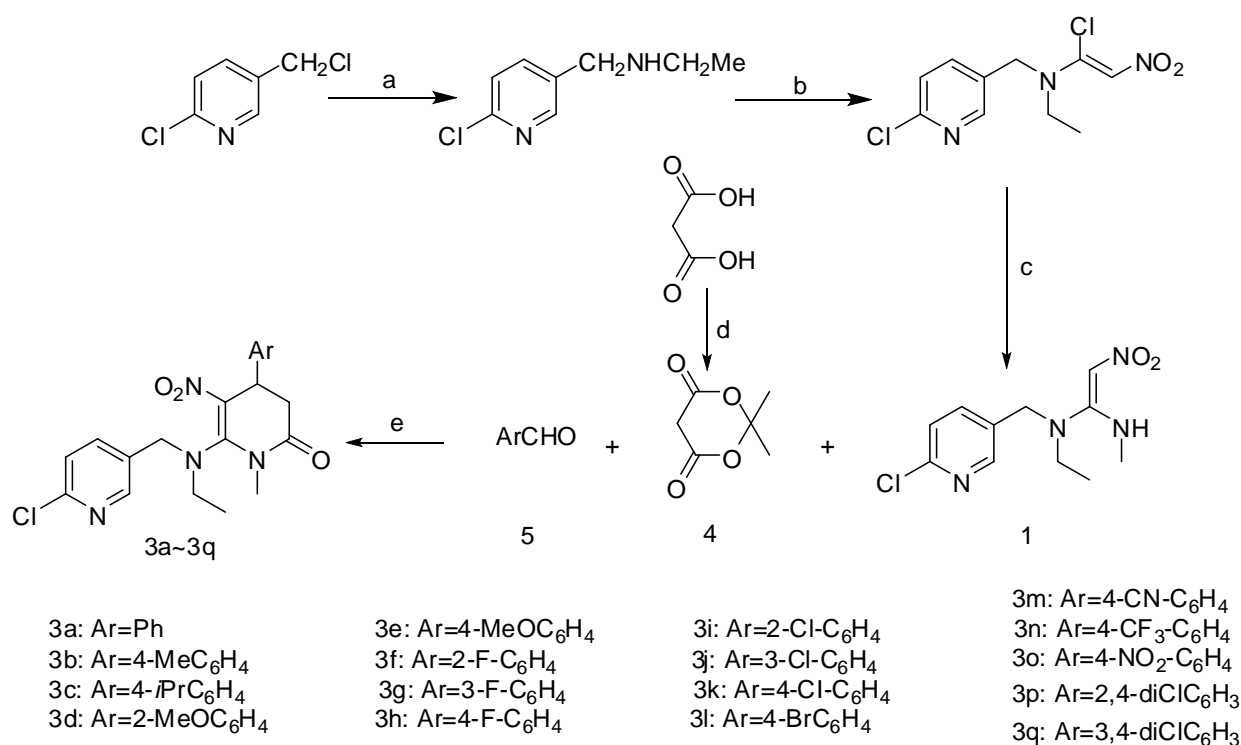
The applications of Meldrum's acid to the synthesis of heterocyclic compounds in recent years are reviewed. All these heterocyclic compounds are related to pyranoid, pyridine, furan rings, tetrahydropyridone rings and so on.²⁴⁻²⁸ Motivated by this, we using nitenpyram **1**, aromatic aldehyde and Meldrum's acid as starting materials through a rapid microwave (MW)-promoted method (Scheme 1) to obtain new *cis*-nitenpyram analogues **3** by introducing a tetrahydropyridone ring into the nitenpyram

(Figure 1). The preliminary insecticidal activities of the target compounds were tested, most of the designed nitenpyram analogues (**3a-3q**) showed good insecticide activities against *Myzus persicae*, *Aphis medicaginis* and *Nilaparvata lugens*. To further investigate their binding interactions, molecular docking simulations were carried out by docking the nitenpyram analogues **3** into the active site of nAChR.

RESULTS AND DISCUSSION

1. Chemistry

The nitenpyram analogues bearing a tetrahydropyridone ring (**3a-q**) were synthesized as shown in **Scheme 1**. Nitenpyram **1** and Meldrum's acid **4** were prepared as described in the literatures,²⁹⁻³⁰ respectively. Three-component microwave-assisted reaction of nitenpyram, aromatic aldehyde and Meldrum's acid in ethanol gave good yields (59-89%).

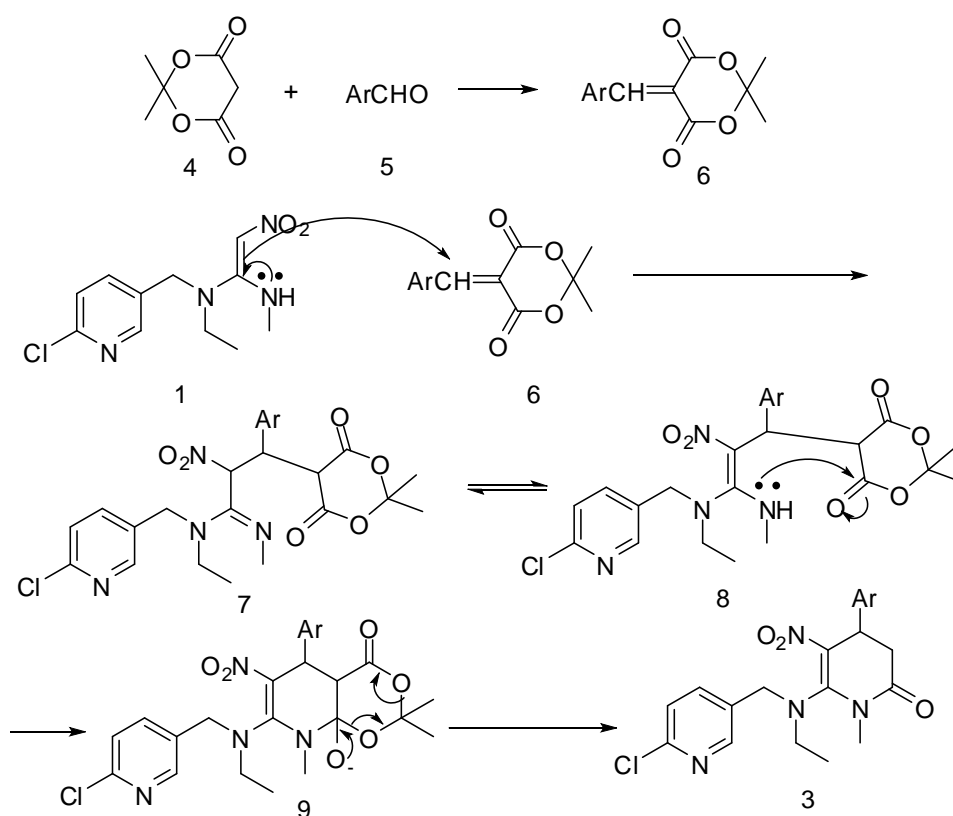


Reagents and conditions: (a) ethanamine (42%); (b) 1,1,1-trichloro-2-nitroethane/CHCl₃ 2-7 °C (65%); (c) methanamine 3-7 °C (58%); (d) acetone, H₂SO₄, Ac₂O, 60 °C (78%); (e) piperidine, EtOH, MW, 65 °C, (59-89%).

Scheme 1. General Synthetic Route for the Target Compounds

Possible mechanism for the formation of the nitenpyram analogues is described in **Scheme 2**. The assembly of **7** can be explained via the initial Michael addition of enamine double bond in **1** to **6**, leading

to the formation of an acyclic intermediate **8**, which cyclized into the intermediate **9** via nucleophilic attack of an NH group on a carbonyl carbon, then one molecule of acetone and carbon dioxide are split off and finally the tetrahydropyridine ring can be closed.²⁷ It is an efficient and promising method to construct the tetrahydropyridone skeleton.



Scheme 2. Possible mechanism for the formation of the target compounds.

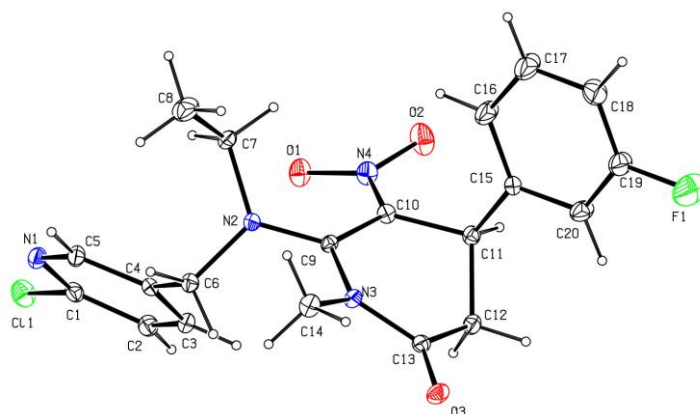


Figure 2. Molecular structure of compound **3g** (Number CCDC 825017) with atom-labeling.

2. Crystal Structure Analysis

The structure of compounds **3g** was unambiguously confirmed by X-ray crystallographic diffraction analysis. As compared with the *trans* configuration of nitromethylene in the crystal structure of nitenpyram,³¹ **3g** is obviously in the *cis* configuration as anticipated. From **Figure 2**, the tetrahydropyridone ring adopts a skew boat conformation and a N2/C9/C10/N4 dihedral angle of -20.2 (5)°. In the tetrahydropyridone moiety, C(13)–C(12), C(11)–C(10) and C(12)–C(11) bond lengths (1.484(4) Å, 1.501(4) Å and 1.533(4) Å) are slightly shorter than normal (1.54 Å). The C(13)–N(3), C(9)–N(3), and C(10)–N(4) bond lengths (1.390 Å(4), 1.405Å(3), and 1.412 Å(4), respectively) are slightly shorter than normal (1.47 Å), while the C(9)=C(10) bond length (1.371(4) Å) is slightly longer than normal (1.34 Å). Besides, the dihedral angle between the mean planes of the benzene and pyridine rings is 80.7 (3)°.

3. Structure activity relationship

The insecticidal activities against *Nilaparvata lugens*, *Myzus persicae* and *Aphis medicaginis* of the title compounds were investigated using nitenpyram as a control, and the results are presented in **Table 1**. Most of our designed analogues showed better insecticide activities against *Myzus persicae*, *Nilaparvata lugens* and *Aphis medicaginis* (**Table 1**). Among these analogues, **3n** afforded the best in vitro inhibitory activities and had 100% mortality at 20 mg/L against *Myzus persicae* and *Nilaparvata lugens*, the LC₅₀ values of **3n** against *Myzus persicae* and *Nilaparvata lugens* are 0.191 mg/L and 0.219 mg/L, respectively, that is very close to nitenpyram. In general, the analogues with different substituents on benzene ring exhibited equivalent activities at high dose (500 mg/L). However, the insecticidal activities showed significant differences when the doses were reduced to 100 and 20 mg/L.

As depicted in **Table 1**, against *Nilaparvata lugens*, compound **3a** with no substitution on the phenyl group presented moderate insecticidal activity at 100 and 20 mg/L. Introducing electron-donating substituents on benzene ring were unfavorable to activities, most of these compounds (**3b-e**) exhibited unpleasing insecticidal effectiveness. For the effect of electron-withdrawing groups, introducing halogen atoms such as single fluoro, chloro atom on benzene ring did not contribute to activity improvement of the corresponding compounds, insecticidal activities of compounds (**3f-k**) were little more than those with electron-donating substituents on benzene ring (**3b-e**). Interestingly, bring bromo atom in the benzene ring

(3l) resulted in greatly increased insecticidal activity, whereas double chloro atoms on benzene ring (3p, 3q) also significantly increased activities. Among electron-withdrawing groups on benzene ring, trifluoromethyl (3n) was most prominent group in increasing activity. For *Myzus persicae* and *Aphis medicaginis*, all these *cis*-nitenpyram analogues have the similar structure activity relationship. Considering the discussion above, we found that insecticidal potencies of our designed nitenpyram analogues could be increased by the introduction of bromo, trifluoromethyl and dichloride substituents on benzene rings.

Table 1. Insecticidal Activities of Nitenpyram Analogues **3** against *Nilaparvata lugens*, *Myzus persicae* and *Aphis medicaginis*.

Compd.	Ar	Mortality (%) at different concentrations (mg/L)								
		<i>Nilaparvata lugens</i>			<i>Myzus persicae</i>			<i>Aphis medicaginis</i>		
		500	100	20	500	100	20	500	100	20
3a	Ph	100	100	80	100	68	41	100	80	65
3b	4-MeC ₆ H ₄	100	60	20	93	52	38	100	30	NT ^a
3c	4- <i>i</i> PrC ₆ H ₄	100	100	60	90	85	48	100	70	NT
3d	2-MeOC ₆ H ₄	80	NT	NT	100	62	25	80	NT	NT
3e	4-MeOC ₆ H ₄	100	80	20	100	85	20	100	68	10
3f	2-F-C ₆ H ₄	80	NT	NT	83	20	NT	65	NT	NT
3g	3-F-C ₆ H ₄	100	80	60	100	95	68	80	60	NT
3h	4-F-C ₆ H ₄	100	100	40	85	52	38	100	80	20
3i	2-Cl-C ₆ H ₄	100	80	50	80	58	28	80	30	NT
3j	3-Cl-C ₆ H ₄	100	50	NT	92	76	55	80	60	NT
3k	4-Cl-C ₆ H ₄	80	NT	NT	82	36	NT	80	40	10
3l	4-Br-C ₆ H ₄	100	100	100	100	100	74	100	75	10
3m	4-CN-C ₆ H ₄	80	40	10	100	85	0	80	0	NT
3n	4-CF ₃ -C ₆ H ₄	100	100	100 ^b	100	100	100 ^c	100	70	20
3o	4-NO ₂ -C ₆ H ₄	80	40	20	100	80	0	100	0	NT
3p	2,4-diClC ₆ H ₃	100	100	100	100	100	80	100	90	30
3q	3,4-diClC ₆ H ₃	100	100	80	95	80	62	80	80	20
	Nitenpyram ^{d,e}	100	100	100 ^d	100	100	100 ^e	100	100	100

^aNT, not tested. ^bLC₅₀ = 0.219 mg/L. ^cLC₅₀ = 0.191 mg/L. ^dLC₅₀ = 0.129 mg/L. ^eLC₅₀ = 0.136 mg/L.

4. Molecular docking study

To further explore the structural features for better activities, models of these new compounds-receptor complexes were investigated by docking studies with CDOCKER.²⁰⁻²² Since the amino acids forming 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) co-crystallized with imidacloprid (PDB ID: 2zju)³² was used as the template of receptor. The docking study was performed by using the program CDOCK (Discovery Studio 3.1).

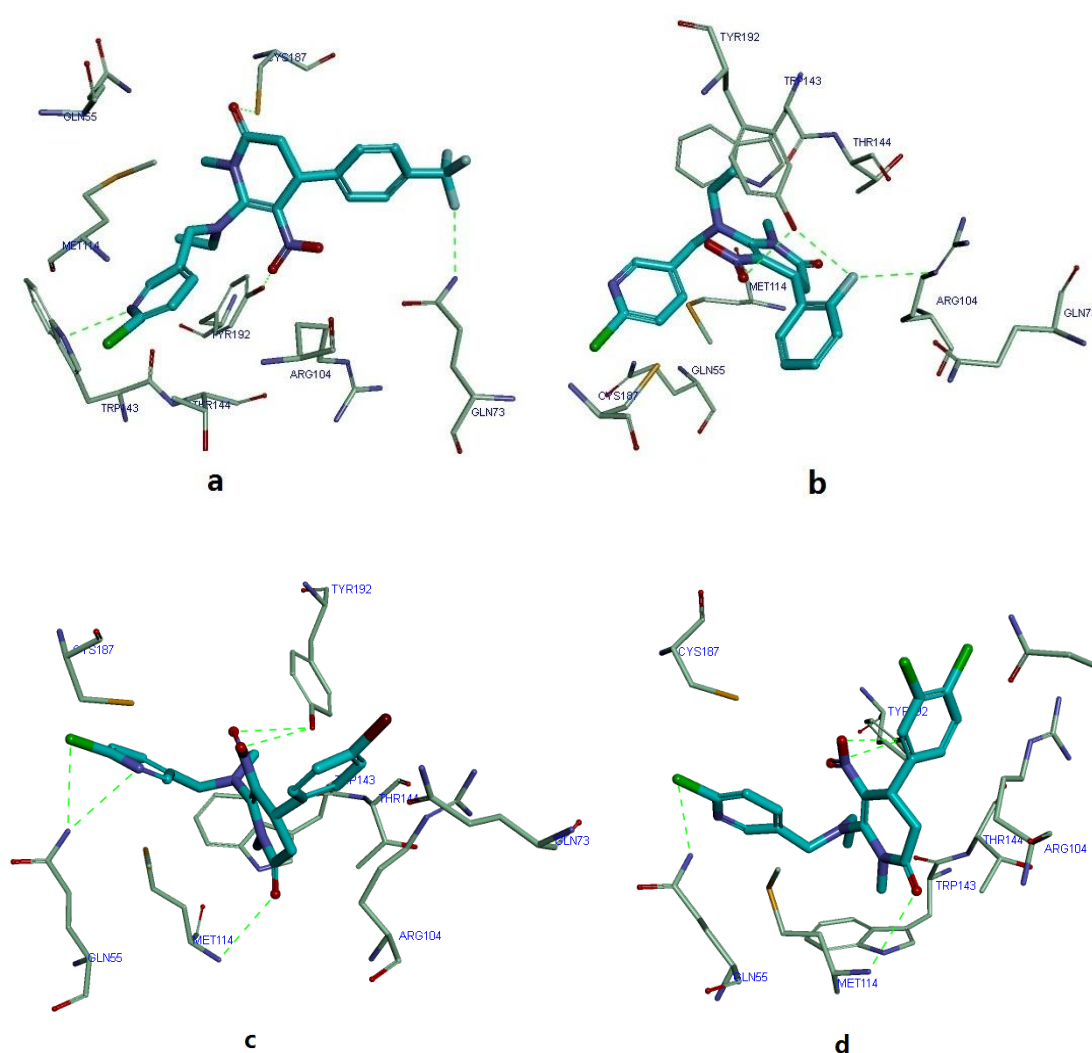


Figure 3. Binding site interactions of analogue **3n**, **3g**, **3l**, **3q** with the extracellular domain of nAChR (protein data bank code: 2zju). (a) Zoomed-in view of the interactions between compound **3n** and amino acids from the active site of the receptor. (b) Zoomed-in view of the interactions between compound **3g** and amino acids from the active site of the receptor. (c) Zoomed-in view of the interactions between compound **3l** and amino acids from the active site of the receptor. (d) Zoomed-in view of the interactions between compound **3q** and amino acids from the active site of the receptor.

As a result, all active analogues exhibited significant hydrogen-bonding interactions with the nAChR target. As illustrated in **Figure (3a)**, chloropyridine N of **3n** exhibits a hydrogen bond with NH of Trp143 backbone on loop B, while the nitro O(32) interact with OH of Tyr192 on loop C, which suggest that chloropyridine N and nitro O play a key role in recognizing and interacting with the binding site. In addition, its binding conformation exhibits another two important hydrogen bonds: O(24) of its carbonyl interacts with SH of Cys187, and F(27) interacts with the side chain NH of Gln55. These observations have also explained why the analogue **3n** attained the highest score.

Furthermore, most of the other active analogues shared a quite similar binding mode with analogue **3n** 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 carbonyl O(24) of analogues **3** can form hydrogen bond within the same hydrogen bond distance, such as the binding mode of analogue **3g (Figure 3(b))**, O(24) of its carbonyl cannot interact with amino acid residues from the Ls-AChBP.

Moreover, we found that analogues offered high experimental activities when carbonyl can exhibit hydrogen-bond with different amino acids residues (**Figure 3(a, c, d)**). These observations have also explained the structure-activity relationships observed in vitro. Thereby, the newly introduced substituents of the designed analogues presumably played important roles in ligand recognition and binding interactions, which may further enhance their activities and contribute to the selectivity as well. Based on these, further target inhibitory tests and advanced insecticide design are underway.

CONCLUSION

In conclusion, a series of *cis*-nitenpyram analogues (**3a-q**) with tetrahydropyridone fixed *cis*-configuration were designed and synthesized. Preliminary bioassays showed that most of the designed nitenpyram analogues exhibited good insecticidal activity at 100 mg/L while the analogues **3n** afforded the best in vitro activity. The docking results revealed that analogues **3** with various substituents on phenyl show their different binding affinities to the insect nAChR, which explained the SARs observed in vitro. Moreover, carbonyl O(24) of some analogues can exhibit hydrogen-bond with amino acid residues of receptor, which play a crucial role for their high insecticidal activities. The study herein has shed a light on the mechanism of action of these *cis*-nitenpyram analogues (**3a-q**) containing tetrahydropyridone,

further researches on much more test objects and structural modification of nitenpyram are underway.

EXPERIMENTAL

Melting points were measured using an uncorrected RK-1 microscopic melting-point apparatus. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance-400 at 400 and 100 MHz, respectively. ^1H NMR and ^{13}C NMR spectra were recorded with $\text{DMSO}-d_6$ or CDCl_3 as an internal standard, coupling constants (J) were recorded in Hz. The IR spectra were obtained from KBr discs in the range $4000\text{-}400\text{cm}^{-1}$ on a Nicolet 5DXFT-IR spectrophotometer. Mass spectra were in general recorded on an AMD 402/3 or a HP 5989A mass selective detector. Combustion analyses for elemental composition were made with a Perkin-Elmer 2400 instrument. All microwave experiments were performed using YL8023B1 microwave reactor possessing a single-mode microwave cavity producing controlled irradiation at 2.45GHz. 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 Compounds 3a-3q

A solution of aromatic aldehyde (15 mmol), Meldrum's acid (15 mmol) and Nitenpyram 1 (10 mmol) in EtOH (30 mL), piperidine (0.1 mmol) used as catalyst was added dropwise. The mixture solution heated to $65\text{ }^\circ\text{C}$ for 30 min in a microwave reactor and cooled to room temperature. The reaction mixture was concentrated under reduced pressure and treated with 20 mL of water. Then, the solution was extracted three times with CH_2Cl_2 , 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 EtOAc /petroleum ether (1:1) to afford pure products.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-phenyl-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3a): yield 67%; a yellow solid; mp $163\text{-}164\text{ }^\circ\text{C}$; IR (KBr, cm^{-1}) 2981, 2934, 1703, 1584, 1273, 1207, 1099; ^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H, Py-H), 7.40 (s, 1H, Py-H), 7.19-7.28 (m, 4H, Py-H and benzene-H), 6.99 (s, 2H, benzene-H), 4.68 (t, $J = 3.8$ Hz, 1H, benzene-CH), 4.39 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 4.18 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 3.13-3.15 (m, 2H), 3.09 (d, $J = 4.0$ Hz, 2H), 3.04 (s, 3H, N- CH_3), 1.29 (t, $J = 6.9$ Hz, 3H, N CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 151.7, 149.8, 146.2, 140.3, 139.2, 131.4, 128.4, 127.9, 125.7, 123.5, 98.8, 53.5, 40.8, 35.9, 29.4, 27.1, 13.8; MS (ESI) m/z : 401 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_3$; C, 59.92; H, 5.28; N, 13.98. Found: C, 59.90; H, 5.25; N, 13.95.

6-[*N*-(6-Chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-4-(4-methylphenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3b): yield 62%; a yellow solid; mp 192-193 °C; IR (KBr, cm^{-1}) 2993, 2970, 1706, 1572, 1438, 1276, 1098; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H, Py-H), 7.32 (s, 1H, Py-H), 7.13 (s, 1H, Py-H), 6.79-6.99 (m, 4H, benzene-H), 4.56 (s, 1H, benzene-CH), 4.32 (d, $J = 14.6$ Hz, 1H), 4.11 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 3.06-3.15 (m, 2H), 2.97-3.00 (m, 5H), 2.24 (s, 3H), 1.22 (t, $J = 6.6$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 173.2, 155.2, 149.2, 144.3, 139.2, 135.1, 133.4, 130.2, 129.1, 127.8, 125.3, 96.8, 52.7, 40.1, 36.1, 29.1, 27.0, 20.9, 12.9; MS (ESI) m/z : 415 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{ClN}_4\text{O}_3$; C, 60.79; H, 5.59; N, 13.50. Found: C, 60.78; H, 5.60; N, 13.57.

6-[*N*-(6-Chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-4-(4-isopropylphenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3c): yield 72%; a yellow solid; mp 164-165 °C; IR (KBr, cm^{-1}) 2992, 2980, 1704, 1578, 1431, 1273, 1090; ^1H NMR (400 MHz, CDCl_3) δ 8.20 (s, 1H, Py-H), 7.35 (s, 1H, Py-H), 7.12-7.15 (m, 1H, Py-H), 7.02-7.04 (m, 2H, benzene-H), 6.79 (s, 2H, benzene-H), 4.56 (t, $J = 3.5$ Hz, 1H, benzene-CH), 4.33 (d, $J = 14.6$ Hz, 1H, Py-CH), 4.13 (d, $J = 14.6$ Hz, 1H, Py-CH), 3.06-3.08 (m, 2H), 2.99 (s, 2H), 2.98 (s, 3H), 2.76-2.83 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.23 (t, $J = 7.0$ Hz, 3H, NCH_2CH_3), 1.16 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 151.9, 147.2, 146.1, 145.4, 140.1, 137.4, 131.8, 127.6, 126.2, 123.8, 97.4, 53.5, 40.1, 35.1, 31.7, 28.2, 27.0, 24.4, 13.5; MS (ESI) m/z : 443 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{ClN}_4\text{O}_3$; C, 62.37; H, 6.14; N, 12.65. Found: C, 62.35; H, 6.10; N, 12.66.

6-[*N*-(6-Chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-4-(2-methoxyphenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3d): yield 78%; a yellow solid; mp 182-183 °C; IR (KBr, cm^{-1}) 2990, 2968, 1708, 1580, 1430, 1281, 1089; ^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H, Py-H), 7.53 (s, 1H, Py-H), 7.27-7.29 (m, 1H, Py-H), 7.20-7.22 (m, 1H, benzene-H), 6.74-6.87 (m, 2H, benzene-H), 6.35 (s, 1H, benzene-H), 4.84 (s, 1H, benzene-CH), 4.45 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 4.23 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 3.82 (s, 3H), 3.16-3.19 (m, 2H), 3.11 (s, 3H, OCH_3), 2.94-3.05 (m, 2H), 1.34 (t, $J = 7.2$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 159.8, 151.9, 149.1, 146.9, 138.8, 130.5, 128.9, 126.7, 125.8, 123.5, 120.7, 114.3, 98.9, 56.1, 53.9, 40.2, 35.8, 27.0, 19.5, 14.0; MS (ESI) m/z : 431 ($[\text{M}+\text{H}]^+$). Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{ClN}_4\text{O}_4$; C, 58.54; H, 5.38; N, 13.00. Found: C, 58.50; H, 5.36; N, 13.06.

6-[*N*-(6-Chloro-3-pyridinylmethyl)-*N*-ethyl]amino-1-methyl-4-(4-methoxyphenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3e): yield 69%; a yellow solid; mp 176-177 °C; IR (KBr, cm^{-1}) 2971, 2931, 1703, 1584, 1445, 1209, 1095; ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H, Py-H), 7.20-7.42 (m, 2H,

Py-H), 6.76-6.86 (m, 4H, benzene-H), 4.60 (s, 1H, benzene-CH), 4.39 (d, $J = 14.6$ Hz, 1H, Py-CH₂), 4.19 (d, $J = 14.6$ Hz, 1H, Py-CH₂), 3.79 (s, 3H, OCH₃), 3.10-3.14 (m, 2H), 3.05 (s, 5H), 1.29 (t, $J = 6.4$ Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 161.4, 151.6, 148.1, 146.1, 138.2, 132.5, 130.8, 125.7, 120.9, 114.0, 97.9, 56.0, 53.4, 40.6, 35.2, 29.0, 26.8, 14.1; MS (EI) m/z : 431 ([M+H]⁺). Anal. Calcd for C₂₁H₂₃ClN₄O₄; C, 58.54; H, 5.38; N, 13.00. Found: C, 58.58; H, 5.34; N, 13.02.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(2-fluorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3f): yield 81%; yellow solid; mp 136-138 °C; IR (KBr, cm⁻¹) 2992, 2970, 1706, 1572, 1436, 1279, 1091; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H, Py-H), 7.45 (s, 1H, Py-H), 7.18-7.26 (m, 3H, Py-H and benzene-H), 7.10 (s, 1H, benzene-H), 6.84 (s, 1H, benzene-H), 4.66-4.67 (m, 1H, benzene-CH), 4.41 (d, $J = 14.7$ Hz, 1H, Py-H), 4.16 (d, $J = 14.7$ Hz, 1H, Py-H), 3.13-3.14 (m, 2H), 3.02-3.11 (m, 5H), 1.30 (t, $J = 7.5$ Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 160.7, 151.8, 149.9, 148.2, 140.1, 130.8, 128.4, 127.9, 127.0, 124.0, 123.8, 115.4, 98.1, 53.1, 40.9, 35.1, 27.7, 18.6, 13.3; MS (ESI) m/z : 419 ([M+H]⁺). Anal. Calcd for C₂₀H₂₀ClFN₄O₃; C, 57.35; H, 4.81; N, 13.38. Found: C, 57.33; H, 4.80; N, 13.36.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(3-fluorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3g): yield 80%, a yellow solid; mp 146-148 °C; IR (KBr, cm⁻¹) 2992, 2970, 1711, 1534, 1436, 1256, 1091; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H, Py-H), 7.42 (s, 1H, Py-H), 7.22-7.24 (m, 2H, Py-H and benzene-H), 6.92-6.97 (m, 1H, benzene-H), 6.76-6.78 (m, 2H, benzene-H), 4.68 (s, 1H, benzene-CH), 4.40 (d, $J = 14.7$ Hz, 1H, Py-CH₂), 4.18 (d, $J = 14.7$ Hz, 1H, Py-CH₂), 3.08-3.14 (m, 4H), 3.06 (s, 3H), 1.30 (t, $J = 7.0$ Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 162.0, 151.5, 149.9, 146.5, 141.8, 138.4, 131.8, 130.0, 124.2, 123.5, 114.9, 112.7, 98.0, 53.5, 40.5, 35.9, 28.7, 27.5, 13.2; MS (ESI) m/z : 419 ([M+H]⁺). Anal. Calcd for C₂₀H₂₀ClFN₄O₃; C, 57.35; H, 4.81; N, 13.38. Found: C, 57.31; H, 4.80; N, 13.35.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-fluorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3h): yield 84%; a yellow solid; mp 168-170 °C; IR (KBr, cm⁻¹) 2994, 2973, 1702, 1578, 1432, 1274, 1090; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H, Py-H), 7.32-7.40 (s, 1H, Py-H), 7.13-7.20 (m, 1H, Py-H), 6.80-6.88 (m, 4H, benzene-H), 4.56 (s, 1H, benzene-CH), 4.32 (d, $J = 14.7$ Hz, 1H, Py-CH₂), 4.12 (d, $J = 14.7$ Hz, 1H, Py-CH₂), 3.08 (s, 2H), 2.99-3.07 (m, 5H), 1.22 (t, $J = 6.9$ Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 159.3, 150.9, 148.9, 146.8, 139.2, 135.8, 131.5, 129.5, 123.5, 115.4, 98.5, 53.8, 40.9, 35.2, 29.8, 27.0, 13.4; MS (ESI) m/z : 419 ([M+H]⁺). Anal. Calcd for

C₂₀H₂₀ClFN₄O₃; C, 57.35; H, 4.81; N, 13.38. Found: C, 57.38; H, 4.80; N, 13.37.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(2-chlorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3i): yield 71%, a yellow solid; mp 188-189 °C; IR (KBr, cm⁻¹) 2993, 2971, 1706, 1576, 1436, 1274, 1091; ¹H NMR (400MHz, CDCl₃) δ 8.38 (s, 1H, Py-H), 7.54 (s, 1H, Py-H), 7.39 (d, *J* = 7.9 Hz, 1H, Py-H), 7.28 (d, *J* = 8.1 Hz, 1H, benzene-H), 7.19 (t, *J* = 7.7 Hz, 1H, benzene-H), 7.05 (t, *J* = 7.5 Hz, 1H, benzene-H), 6.25 (s, 1H, benzene-H), 4.92-4.94 (m, 1H, benzene-CH), 4.46 (d, *J* = 14.6 Hz, 1H, Py-CH₂), 4.27 (d, *J* = 14.6 Hz, 1H, Py-CH₂), 3.20-3.22 (m, 2H), 3.15 (s, 3H), 2.98-3.12 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 152.1, 149.9, 146.1, 140.6, 139.1, 133.1, 131.2, 129.3, 128.8, 127.1, 126.5, 123.8, 98.1, 53.9, 40.1, 35.6, 27.5, 20.4, 13.2; MS (ESI) *m/z*: 435 ([M+H]⁺). Anal. Calcd for C₂₀H₂₀Cl₂N₄O₃; C, 55.18; H, 4.63; N, 12.87. Found: C, 55.12; H, 4.64; N, 12.88.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(3-chlorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3j): yield 59%; a yellow solid; mp 56-57 °C; IR (KBr, cm⁻¹) 2991, 2971, 1706, 1580, 1440, 1200, 1085; ¹H NMR (400MHz, CDCl₃) δ 8.25 (s, 1H, Py-H), 7.45 (s, 1H, Py-H), 7.18-7.26 (m, 3H, Py-H and benzene), 7.10 (s, 1H, benzene-H), 6.84 (s, 1H, benzene-H), 4.66-4.67 (m, 1H, benzene-CH), 4.41 (d, *J* = 14.7 Hz, 1H, Py-CH₂), 4.16 (d, *J* = 14.7 Hz, 1H, Py-CH₂), 3.13-3.14 (m, 2H), 3.02-3.11 (m, 5H), 1.30 (t, *J* = 7.5 Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 152.3, 148.4, 145.8, 141.6, 139.2, 133.7, 131.8, 129.9, 128.4, 126.5, 126.0, 121.2, 98.2, 53.9, 40.5, 35.8, 28.9, 27.5, 13.0; MS (ESI) *m/z*: 435 ([M+H]⁺). Anal. Calcd for C₂₀H₂₀Cl₂N₄O₃; C, 55.18; H, 4.63; N, 12.87. Found: C, 55.17; H, 4.67; N, 12.88.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-chlorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3k): yield 75%; a yellow solid; mp 180-182 °C; IR (KBr, cm⁻¹) 2991, 2970, 1708, 1577, 1436, 1274, 1095; ¹H NMR (400MHz, CDCl₃) δ 8.15 (s, 1H, Py-H), 7.31 (s, 1H, Py-H), 7.15-7.20 (m, 3H, Py-H and benzene-H), 6.85 (s, 2H, benzene-H), 4.57 (s, 1H, benzene-CH), 4.32 (d, *J* = 14.7 Hz, 1H, Py-CH₂), 4.12 (d, *J* = 14.7 Hz, 1H, Py-CH₂), 3.05-3.08 (m, 2H), 2.96-3.00 (m, 5H), 1.22 (t, *J* = 6.2 Hz, 3H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 150.8, 148.6, 145.8, 140.2, 138.3, 130.8, 131.0, 129.4, 128.8, 123.9, 98.6, 53.2, 40.0, 35.2, 29.2, 27.8, 14.3; MS (ESI) *m/z*: 435 ([M+H]⁺). Anal. Calcd for C₂₀H₂₀Cl₂N₄O₃; C, 55.18; H, 4.63; N, 12.87. Found: C, 55.16; H, 4.60; N, 12.87.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-bromophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3l): yield 87%; a yellow solid; mp 205-206 °C; IR (KBr, cm⁻¹) 2991, 2970, 1704,

1579, 1436, 1273, 1095; ^1H NMR (400MHz, CDCl_3) δ 8.25 (s, 1H, Py-H), 7.45 (s, 1H, Py-H), 7.18-7.26 (m, 3H, Py-H and benzene-H), 7.10 (s, 1H, benzene-H), 6.84 (s, 1H, benzene-H), 4.66-4.67 (m, 1H, benzene-CH), 4.41 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 4.16 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 3.13-3.14 (m, 2H), 3.02-3.11 (m, 5H), 1.30 (t, $J = 7.5$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 152.6, 150.2, 149.4, 146.1, 140.3, 132.2, 131.4, 130.5, 123.8, 120.5, 98.0, 53.5, 40.1, 35.7, 29.2, 27.9, 13.0; MS (ESI) m/z : 479 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{BrClN}_4\text{O}_3$; C, 50.07; H, 4.20; N, 11.68. Found: C, 50.06; H, 4.20; N, 11.67.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-cyanophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one(3m): yield 71%; a yellow solid; mp 96-98 °C; IR (KBr, cm^{-1}) 2995, 2978, 1702, 1578, 1438, 1211, 1065; ^1H NMR (400MHz, CDCl_3) δ 8.18 (s, 1H, Py-H), 7.35-7.56 (m, 3H, Py-H and benzene-H), 7.07-7.19 (m, 3H, benzene-H), 4.70 (s, 1H, benzene-CH), 4.37 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 4.23 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 3.16-3.20 (m, 2H), 3.09-3.12 (m, 5H), 1.31 (t, $J = 6.5$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 170.2, 151.8, 149.8, 145.4, 144.3, 140.2, 131.4, 129.4, 128.6, 125.7, 116.5, 109.8, 99.1, 53.5, 40.8, 36.2, 28.8, 28.2, 14.3; MS (ESI) m/z : 426 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{ClN}_5\text{O}_3$; C, 59.23; H, 4.73; N, 16.44. Found: C, 59.26; H, 4.72; N, 16.45.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-trifluoromethylphenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3n): yield 86 %; a yellow solid; mp 152-153 °C; IR (KBr, cm^{-1}) 2992, 2970, 1706, 1572, 1436, 1279, 1091; ^1H NMR (400MHz, CDCl_3) δ 8.45 (s, 1H, Py-H), 7.75 (s, 1H, Py-H), 7.51-7.54 (m, 2H, Py-H and benzene-H), 7.35-7.39 (s, 1H, benzene-H), 7.08-7.20 (m, 2H, benzene-H), 4.72 (s, 1H, benzene-CH), 4.40 (d, $J = 14.8$ Hz, 1H, Py- CH_2), 4.22 (d, $J = 14.8$ Hz, 1H, Py- CH_2), 3.11-3.12 (m, 2H), 3.06-3.07 (m, 5H), 1.26 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 150.2, 148.3, 146.1, 143.5, 139.1, 131.8, 128.4, 127.9, 125.2, 122.8, 119.3, 98.1, 53.4, 40.6, 35.8, 29.8, 27.5, 13.9; MS (ESI) m/z : 469 ($[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{ClF}_3\text{N}_4\text{O}_3$; C, 53.30; H, 4.30; N, 11.95. Found: C, 53.35; H, 4.31; N, 11.98.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(4-nitrophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3o): yield 89%; a yellow solid; mp 200-201 °C; IR (KBr, cm^{-1}) 2990, 2975, 1702, 1578, 1432, 1274, 1092; ^1H NMR (400MHz, CDCl_3) δ 8.19 (s, 1H, Py-H), 8.13 (s, 1H, Py-H), 8.11 (s, 1H, Py-H), 7.39 (s, 1H, benzene-H), 7.17-7.19 (m, 3H, benzene-H), 4.75 (s, 1H, benzene-CH), 4.41 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 4.23 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 3.13-3.20 (m, 4H), 3.10 (s, 3H), 1.31 (t, $J = 7.2$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 151.8, 149.9, 146.8, 146.2, 145.6, 139.2,

131.2, 128.4, 123.7, 123.1, 98.2, 53.6, 40.9, 35.8, 29.2, 27.8, 13.2; MS (ESI) m/z : 446 ($[M+H]^+$). Anal. Calcd for $C_{20}H_{20}ClN_5O_5$; C, 53.88; H, 4.52; N, 15.71. Found: C, 53.85; H, 4.55; N, 15.77.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(2,4-dichlorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3p): yield 76%; a yellow solid; mp 178-180 °C; IR (KBr, cm^{-1}) 2998, 2973, 1702, 1578, 1432, 1270, 1092; 1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, Py-H), 7.51 (s, 1H, Py-H), 7.41 (s, 1H, Py-H), 7.03-7.30 (m, 2H, benzene-H), 6.07-6.09 (s, 1H, benzene-H), 4.85 (s, 1H, benzene-CH), 4.46 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 4.28 (d, $J = 14.6$ Hz, 1H, Py- CH_2), 3.21-3.28 (m, 2H), 3.16 (s, 3H), 3.08 (d, $J = 16.7$ Hz, 1H), 2.97 (d, $J = 16.7$ Hz, 1H), 1.35 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 152.1, 149.2, 145.2, 139.2, 138.7, 134.6, 132.4, 131.1, 130.7, 129.2, 126.9, 121.6, 100.4, 54.8, 41.2, 35.6, 26.5, 20.3, 13.2; MS (ESI) m/z : 469 ($[M+H]^+$). Anal. Calcd for $C_{20}H_{19}Cl_3N_4O_3$; C, 51.14; H, 4.08; N, 11.93. Found: C, 51.15; H, 4.10; N, 11.96.

6-[N-(6-Chloro-3-pyridinylmethyl)-N-ethyl]amino-1-methyl-4-(3,4-dichlorophenyl)-5-nitro-1,2,3,4-tetrahydropyridin-2-one (3q): yield 83%; a yellow solid; mp 157-158 °C; IR (KBr, cm^{-1}) 2994, 2973, 1702, 1578, 1432, 1274, 1090; 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, Py-H), 7.36 (s, 1H, Py-H), 7.27 (d, $J = 8.3$ Hz, 1H, Py-H), 7.14-7.20 (m, 2H, benzene-H), 6.73 (s, 1H, benzene-H), 4.56-4.58 (m, 1H, benzene-CH), 4.34 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 4.09 (d, $J = 14.7$ Hz, 1H, Py- CH_2), 3.05-3.07 (m, 2H), 2.98-3.02 (m, 5H), 1.23 (t, $J = 7.2$ Hz, 3H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 153.9, 149.2, 145.8, 139.7, 138.0, 133.5, 132.4, 131.6, 130.2, 129.7, 127.4, 122.6, 99.3, 53.5, 42.2, 35.3, 28.9, 26.4, 13.2; MS (ESI) m/z : 469 ($[M+H]^+$). Anal. Calcd for $C_{20}H_{19}Cl_3N_4O_3$; C, 51.14; H, 4.08; N, 11.93. Found: C, 51.13; H, 4.11; N, 11.96.

X-Ray Crystallography

A yellow crystal of compound **3g** was recrystallized by slow evaporation from a mixed solution of EtOAc/petroleum ether (v:v = 1:5), with dimensions of 0.16 mm x 0.12 mm x 0.10 mm was mounted on a glass fiber for data collection which was made on a BRUKER SMART APEX 1000 CCD diffractometer equipped with a graphite-monochromatic $MoK\alpha$ radiation ($\lambda = 0.71073$ Å) by using a ϕ - ω scan mode in the range of $1.82 \leq \theta \leq 25.50^\circ$ ($-10 \leq h \leq 13$, $-23 \leq k \leq 23$, $-10 \leq l \leq 10$) at 298(2) K. A total of 10184 reflections were collected with 3672 unique ones ($R_{int} = 0.0565$), of which 2051 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. The intensity data were corrected for Lp factors and empirical absorption. The final $R = 0.0594$, $wR = 0.1275$ ($w = 1/[\sigma^2(F_o^2) + (0.0621P)^2 + 0.000P]$, where $P = (F_o^2 + 2F_c^2)/3$), $S = 1.000$, $(\Delta/\sigma)_{max} = 0.001$, $(\Delta\rho)_{max} = 0.351$ and $(\Delta\rho)_{min} = -0.266$ $e/\text{\AA}^3$. The

structural graphics was drawn with SHELXTL-97 software package. Other details of the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC 825017.

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REFERENCES

1. P. Jeschke, R. Nauen, M. Schindler, and A. Elbert, *J. Agric. Food Chem.*, 2011, **59**, 2897.
2. M. Tomizawa and J. E. Casida, *Annu. Rev. Pharmacol. Toxicol.*, 2005, **45**, 247.
3. K. Matsuda, M. Shimomura, M. Ihara, M. Akamatsu, and D. B. Sattelle, *Biosci. Biotechnol. Biochem.*, 2005, **69**, 1442.
4. I. Ohno, M. Tomizawa, K. A. Durkin, Y. Naruse, J. E. Casida, and S. Kagabu, *Chem. Res. Toxicol.*, 2009, **22**, 476.
5. D. Bai, S. C. R. Lummis, W. Leicht, H. Breer, and D. B. Sattelle, *Pest. Manage. Sci.*, 1991, **33**, 197.
6. M. Liu and J. E. Casida, *Pestic. Biochem. Physiol.*, 1993, **46**, 40.
7. K. Nishimura, Y. Kanda, A. Okazawa, and T. Ueno, *Pestic. Biochem. Physiol.*, 1994, **50**, 51.
8. K. Mori, T. Okumoto, N. Kawahara, and Y. Ozoe, *Pest. Manage. Sci.*, 2001, **58**, 190.
9. R. Nauen and I. Denholm, *Insect. Biochem. Physiol.*, 2005, **58**, 200.
10. R. Nauen and A. Elbert, *Pest. Manag. Sci.*, 2000, **56**, 60.
11. M. Reyes, P. Franck, P. J. Charmillot, C. Ioriatti, J. Olivares, E. Pasqualini, and B. Sauphanor, *Pest. Manag. Sci.*, 2007, **63**, 890.
12. Z. W. Liu, Z. J. Han, Y. C. Wang, L. C. Zhang, H. W. Zhang, and C. Liu, *Pest. Manag. Sci.*, 2003, **59**, 1355.

13. K. D. Ninsin, [Pest. Manag. Sci., 2004, 60, 839.](#)
14. D. M. Sanchez, R. M. Hollingworth, E. J. Grafius, and D. D. Moyer, [Pest. Manag. Sci., 2006, 62, 30.](#)
15. K. Gorman, G. Devine, J. Bennison, P. Coussons, N. Punchard, and L. Denholm, [Pest. Manag. Sci., 2007, 63, 555.](#)
16. M. Kristensen and J. B. Jespersen, [Pest. Manag. Sci., 2008, 64, 126.](#)
17. X. S. Shao, W. W. Zhang, Y. Q. Peng, Z. Li, Z. Z. Tian, and X. H. Qian, [Bioorg. Med. Chem. Lett., 2008, 18, 6513.](#)
18. X. S. Shao, Z. Li, X. H. Qian, and X. Y. Xu, [J. Agric. Food Chem., 2009, 57, 951.](#)
19. X. S. Shao, H. Fu, X. Y. Xu, X. L. Xu, Z. W. Liu, Z. Li, and X. H. Qian, [J. Agric. Food Chem., 2010, 58, 2696.](#)
20. C. W. Sun, D. R. Yang, J. H. Xing, H. F. Wang, J. Jin, and J. Zhu, [J. Agric. Food Chem., 2010, 58, 3415.](#)
21. C. W. Sun, X. Xu, Y. H. Xu, D. L. Yang, T. Fang, and T. Y. Liu, [J. Agric. Food Chem., 2011, 59, 4828.](#)
22. C. W. Sun, J. Jin, D. R. Yang, J. H. Xing, H. F. Wang, and J. Zhu, [Bioorg. Med. Chem. Lett., 2010, 20, 3301.](#)
23. X. B. Ma, A. Q. Yin, and S. J. Xue, *J. Shanghai Normal University (Natural science)*, 2011, **40**, 41.
24. A. S. Ivanov, [Chem. Soc. Rev., 2008, 37, 789.](#)
25. A. M. Dumas and E. Fillion, [Acc. Chem. Res., 2010, 43, 440.](#)
26. J. Quiroga, A. Hormaza, and B. Insuasty, [J. Heterocycl. Chem., 1997, 34, 521.](#)
27. S. J. Tu, S. L. Zhu, Z. Shao, X. Zou, S. J. Ji, and Y. Zhong, *Chin. J. Org. Chem.*, 2005, **25**, 987.
28. Z. G. Han, C. B. Miao, F. Shi, N. Ma, G. Zhang, and S. J. Tu, [J. Comb. Chem., 2010, 12, 16.](#)
29. S. Y. Lu, X. S. Shao, Z. Li, Z. P. Xu, S. S. Zhao, Y. L. Wu, and X. Y. Xu, [J. Agric. Food Chem., 2012, 60, 322.](#)
30. A. C. Shaikh and C. P. Chen, [Bioorg. Med. Chem. Lett., 2010, 20, 3664.](#)
31. L. Z. Xu, Z. Yang, X. Yi, and G. W. An, [Acta. Cryst., 2008, E64, o1074.](#)
32. M. Ihara, T. Okajima, and A. Yamashita, [Invertebr. Neurosci., 2008, 8, 71.](#)