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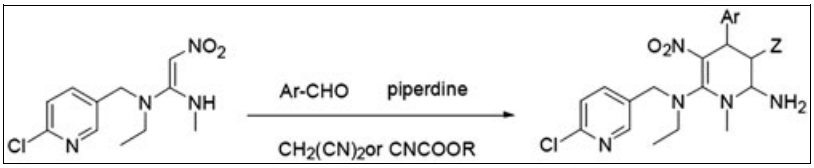


By means of multicomponent reactions, *via* Michael addition, nucleophilic addition, using nitenpyram, substituted aromatic aldehydes, and cyanoacetate compounds or propanedinitrile, a new series of *cis*-configuration nitenpyram analogs (**1a-1k**) were synthesized by introducing the 1,4-dihydropyridine scaffold pharmacophore, as shown in Scheme 1. The structures of all compounds were confirmed by IR, $^{1}$HNMR, $^{13}$C NMR, and elemental analysis. The preliminary bioassay showed that most of the target compounds exhibited good mortality against *Aphis craccivora* at 500 mg/L.

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## INTRODUCTION

Neonicotinoid insecticides (NNs), 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 [1,2].

The NNs exhibit a novel mode of action because they are agonists of the nicotinic acetylcholinereceptor (nAChR), leading to paralysis and death of pest organisms [3]. This selectivity of neonicotinoids to insect nAChR is attributed to the pharmacophore group, such as nitromethylene ( C $NO_2$) in nitenpyram because they have a much higher affinity for insects as compared to vertebrate nAChRs, and the loss of the nitro group can completely reverse the selective toxicity of neonicotinoids for insects over vertebrates [4]. The nitro groups in all commercialized neonicotinoids have a *trans* configuration, on which three proposals formodes of action are based [5]. However, there is very little information on the biological properties and binding model of the *cis*-neonicotinoids.

Nowadays, a well-recognized potential problem facing all insecticides is the insects' acquisition of resistance [6,7], during the past decade, significant increases in resistance and cross-resistance were observed in a range of species after frequent applications of NNSs [8], such as nitenpyram [9].

Hence, research in the design and screening for novel neonicotinoid leading compounds with less resistance is a high priority [10]. In the late 1980s, Bayer and Nihon Tokushu Noyaku Seizo. reported that several *cis*-configuration neonicotinoids [11,12], showed high insecticidal activity. Li and coworkers introductions of the heterocycle or a bulky group are two synthesis concepts to fix the *cis*-configuration of the nitro group, which show excellent insectidal activities [13,14]. It is well established that *trans*/*cis* isomers may differ significantly in biological activity, toxicity, and metabolic properties and medicinal chemistry. Fixing the nitro group in the *cis*-configuration provided a new approach for neonicotinoid molecular design. This *cis*/*trans* isomeric selectivity has been an ongoing research interest for our laboratory over the past years.

To discover novel neonicotinoid leading compounds, based on these reports, by means of Michael addition, nucleophilic addition, using nitenpyram, substituted aromatic aldehydes, and cyanoacetate compounds or propanedinitrile, fixing the nitro group in the *cis*-configuration, a new series of *cis*-configuration nitenpyram analogues (**1a-1k**) were designed and synthesized. The structures of all title compounds were confirmed by IR, $^{1}$H NMR, and elemental analysis. The result of preliminary biological activity test showed that a majority of compounds exhibited good insecticidal activity against *Aphis craccivora*.

## RESULTS AND DISCUSSION

**Synthesis of compounds.** The title compounds **1a**–1**k** were synthesized by the method outlined in Scheme 1. By means of MCRs (multicomponent reactions), the nitenpyram, substituted aromatic aldehydes and cyanoacetate compounds or propanedinitrile *via* Knoevenagel reaction, Michael addition, nucleophilic addition form 1,4-dihydropyridine scaffold, fixing the nitro group in the *cis*-configuration.

**Insecticidal activity.** The insecticidal activities of the title compounds **1a–1k** were screened against *Aphis craccivora* using the standard testing method [15] with a slight modification. Results of the *in vitro* insecticidal

**Scheme 1**

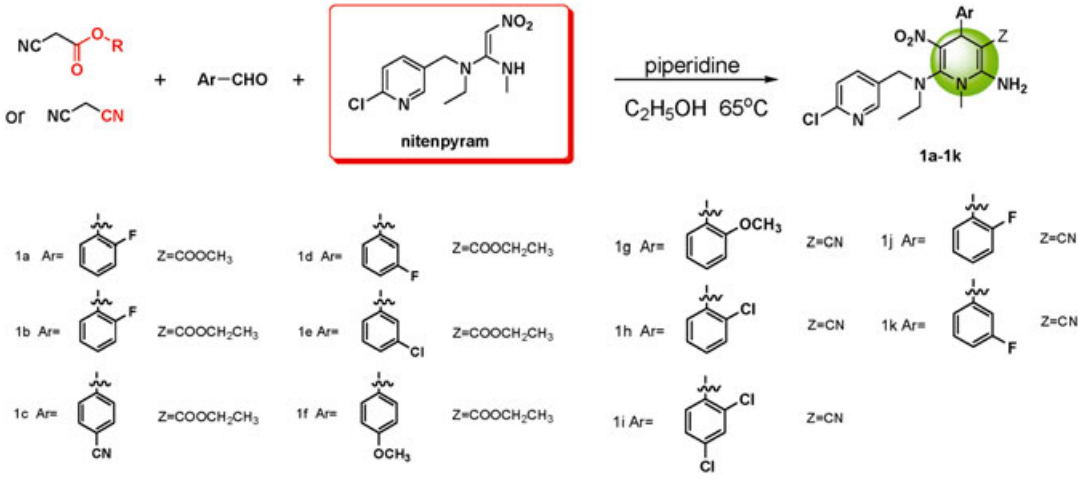


**Table 1**

The insectcidal activities of target compounds in 500(mg/L).

| | | | Mortality (%) at 500 (mg/L) |
|---|---|---|---|
| Compound | Ar | Z | 500 |
| **1a** | 2 F $C_6H_4$ | $COOCH_3$ | 90 |
| **1b** | 2 F $C_6H_4$ | $COOCH_2CH_3$ | 85 |
| **1c** | 4 CN $C_6H_4$ | $COOCH_2CH_3$ | 85 |
| **1d** | 3 F $C_6H_4$ | $COOCH_2CH_3$ | 80 |
| **1e** | 3 Cl $C_6H_4$ | $COOCH_2CH_3$ | 70 |
| **1f** | 4 $OCH_3$ $C_6H_4$ | $COOCH_2CH_3$ | 75 |
| **1g** | 2 $OCH_3$ $C_6H_4$ | CN | 65 |
| **1h** | 2 Cl $C_6H_4$ | CN | 80 |
| **1i** | 2,4 diCl $C_6H_4$ | CN | 80 |
| **1j** | 2 F $C_6H_4$ | CN | 70 |
| **1k** | 3 F $C_6H_4$ | CN | 80 |
| Nitenpyram | | | 100 |

activities of compounds **1a-1k** were summarized in Table 1. As indicated in Table 1, most of our synthesized compounds showed good insecticidal activities against *Aphis craccivora* at 500 mg/L. Among these analogs, 1a afforded the best *in vitro* activity, and had 90% mortality at 500 mg/L. When *Z* are different subsitutents in the 1,4-dihydropyridine scaffold, their insecticidal activities vary wildly, their insecticidal activities increased in the order cyano group(**1c,1d**) < ethyl ester group (**1b,1e**) < methyl ester group (**1a**), respectively. As for the effect of substituents at the benzene, it was observed that compounds demonstrated better activities with electron-withdrawing than electron-donating groups, not only in compound (**1a-1f**), but also in compound (**1f-1k**). In addition, the substituent positions on the benzene also causes changes in different insecticidal activities, 2-position(**1d**) > 3-position(**1b**), which may be related to their relatively strong affinities with their target. And in conclusion, the substituent Z show more influence than substituent phenyl groups in insecticidal activity, such as compound **(1a,1b)** > **(1g,1h)**.

## CONCLUSION

In summary, we have been synthesized 11 unreported *cis*-Nitenpyram analogs with 1,4-dihydropyridine scaffold **(1a-1k)**, and their structures were characterized by $^1$H NMR, IR, and elemental analysis. Bioassay against *Aphis craccivora* shows that the compounds **(1a-1k)** exhibit a certain insecticide activities at 500 mg/L.

## EXPERIMENTAL

Thin-layer chromatography was carried out on silica gel 60 $F_{254}$ plates Merck KGaA. $^1$H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using $CDCl_3$ as solvents and tetramethylsilane as internal standard. Melting points were determined by an RK1 microscopic melting apparatus uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 instrument. IR spectra were obtained on a Nicolet 5DX FTIR spectrophotometer in the region 4000–400 $cm^{-1}$ using KBr discs. Reagents and solvents were of analytical reagent grade or were chemically pure and used as received without further purification

**General synthetic procedure for synthesis of 1a-1k.** 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°C for 5 min in a microwave reactor and stirred for 30 min at the 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 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 **1a**. Compounds **1b-1k** were synthesized with the same method.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-4-(2-fluorophenyl)-1-methyl-3-methoxycarbonyl -5-nitro-1,4-dihydropyridine (1a).** Yield: 51.1%; yellow solid. m.p.: 159–161°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2923 ($CH_3$), 3335, 3202 ($NH_2$), 1502–1416($NO_2$),1646,1615,1592(benzene); $^1H$ NMR (400MHz, $CDCl_3$): δ 8.12 (s, 1H, Py H), 7.83 (d,1H, J = 7.5 Hz, Py H), 7.35(s, 1H, Py H), 7.19–7.15 (m, 2H, Ph H), 7.07–6.99 (m, 2H, Ph H), 6.21 (br, 2H, $NH_2$), 5.29 (s, 1H, CH), 4.32 (d, *J* = 4 Hz,1H), 4.02 (d, J = 16 Hz, 1H), 3.8 (s, 3H, $OCH_3$), 3.21 (s, 3H, $NCH_2CH_3$), 3.19–3.13 (m, 1H), 3.11–3.04 (m, 1H), 1.22–1.20 (t, *J* = 8 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 13.9, 25.5, 29.9, 42.4, 50.8, 51.1, 82.2, 91.1, 114.5, 115.5, 122.2, 123.5, 131.3, 132.1, 138.7, 144.2, 145.3, 148.8, 151.3, 163.1, 166.8, 169.4. Anal. Calcd for $C_{22}H_{23}ClFN_5O_4$:C,55.52; H, 4.87; N, 14.72. Found: C, 55.54; H, 4.92; N, 14.73.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl-*N*-ethyl] amino-3-ethoxycarbonyl-4-(2-fluorophenyl)-1-methyl -5-nitro-1,4-dihydropyridine (1b).** Yield: 57.3%; yellow solid. m.p.: 169–171°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2956 ($CH_3$), 3322, 3196($NH_2$), 1501–1415($NO_2$), 1647, 1615, 1590(benzene); $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H, Py H), 7.84 (s, 1H, Py H), 7.33 (d, *J* = 7.8 Hz, 1H, Py H), 7.19–7.12 (m, 1H, Ph H), 7.04–6.98 (dd, *J* = 15.6, 7.8 Hz, 2H, Ph H), 6.88 (dd, *J* = 11.5, 8.4 Hz, 1H, Ph H), 6.18 (br, 2H, $NH_2$), 5.36 (s, 1H, CH), 4.35 (d, *J* = 14.5 Hz, 1H), 4.10–4.05 (m, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.02 (d, *J* = 14.5 Hz, 1H), 3.27 (s, 3H, $NCH_2CH_3$), 3.23–3.21 (m, 1H), 3.14–3.05 (m, 1H), 1.33–1.29 (*t*, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.23–1.20 (*t*, *J* = 7.2 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 13.7, 25.1, 29.4, 42.4, 50.9, 51.5, 61.9, 83.1, 91.6, 115.1, 114.9, 122.3, 122.9, 131.3, 132.1, 138.7, 144.3, 145.7, 148.2, 151.7, 163.4, 167.2, 168.5. Anal. Calcd for $C_{23}H_{25}ClFN_5O_4$:C, 56.39; H, 5.14; N, 14.29. Found: C, 56.41; H, 5.16; N, 14.32.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-4-(4-cyanophenyl)-3-ethoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (1c).** Yield: 56.7 %; yellow solid. m.p: 205-207 °C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2954($CH_3$), 3325, 3194 ($NH_2$), 1501–1415($NO_2$), 1649, 1613, 1585(benzene) $^1H$ NMR(400 MHz, $CDCl_3$) δ 8.31 (s, 1H, Py H), 8.07 (s, 1H, Py H), 7.36 (s, 1H, Py H), 7.47 (d, *J* = 8.0 Hz, 2H, Ph H), 7.09 (d, *J* =8.0 Hz, 2H, Ph H), 6.26 (br, 2H, $NH_2$), 5.42 (s, 1H, CH), 4.32 (d, *J* = 14.6 Hz, 1H), 4.15–4.11 (m, 2H, $COOCH_2CH_3$), 4.08–4.05 (m, 1H), 3.32–3.28 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.25 (s, 3H, $NCH_2CH_3$), 3.18–3.13 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H, $COOCH_2CH_3$), 1.16 (t, *J* = 7.1 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 25.9, 27.9, 30.3, 45.7, 51.5, 53.6, 85.4, 91.6, 114.6, 116.3, 117.1, 119.2, 124.7, 126.2, 132.5, 134.5, 139.2, 145.4, 146.4, 149.1, 152.5, 164.4, 167.2, 169.4. Anal. Calcd for $C_{24}H_{25}ClN_6O_4$: C, 58.01; H, 5.07; N, 16.91. Found: C, 58.03; H, 5.09; N, 16.89.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-3-ethoxycarbonyl-4-(3-fluorophenyl)-1-methyl-5-nitro-1,4-dihydropyridine (1d).** Yield: 82.1%; yellow solid. m.p: 184–186°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2967(CH3), 3322, 3201 ($NH_2$), 1485–1421($NO_2$), 1644, 1621, 1577(benzene) $^1H$ NMR (CDCl3, 400 MHz) 8.24 (d, 1H, *J* = 7.8 Hz, Py H), 7.83 (s, 1H, Py H), 7.36 (d, 1H, *J* = 8.1 Hz, Py H), 7.23–6.96 (m, 4H, Ph H), 6.18 (br, 2H, $NH_2$), 5.36 (s, 1H, CH), 4.35 (d, *J* = 14.5 Hz, 1H), 4.10–4.05 (m, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.02 (d, *J* = 14.5 Hz, 1H), 3.27 (s, 3H, $NCH_2CH_3$), 3.23–3.21 (m, 1H), 3.14–3.05 (m, 1H), 1.33–1.29 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.21–1.20 (t, *J* = 7.2 Hz, 3H, $NCH_2CH_3$) $^{13}C$ NMR (400 MHz, $CDCl_3$) 13.9, 24.6, 29.1, 44.5, 51.9, 52.3, 62.8, 84.5, 92.3, 117.7, 115.4, 123.1, 125.3, 132.7, 133.5, 136.3, 145.3, 146.3, 148.3, 151.7, 163.1, 167.5, 167.9. Anal. Calcd for $C_{23}H_{25}ClFN_5O_4$: C, 56.39; H, 5.14; N, 14.29. Found: C, 56.37; H, 5.17; N, 14.33.

***cis*-2-Amino-4-(3-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-ethoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (1e).** Yield: 66.2%; yellow solid. m.p.: 147–149°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2919($CH_3$), 3329, 3195 ($NH_2$), 1465, 1413($NO_2$), 1652, 1612, 1562(benzene) $^1H$ NMR ($CDCl_3$, 400MHz) δ 8.10 (s, 1H, Py H), 7.82 (d, 1H, *J* = 8.0 Hz, Py H), 7.31(s, 1H, Py H), 7.19–7.18 (m, 3H, Ph H), 6.98 (d, *J* = 8.0 Hz, 1H, Py H), 6.19–6.02 (2H, br, $NH_2$), 5.49 (s, 1H, CH), 4.32 (d, *J* = 14.6 Hz, 1H), 4.16–4.09 (m, 2H, $COOCH_2CH_3$), 4.06 (d, *J* = 14.8 Hz, 1H), 3.27–3.20 (m,1H), 3.16 (s, 3H, $NCH_3$), 3.09 (m, 1H), 1.31 (t, *J* = 7.0 Hz, 3H, $OCH_2CH_3$), 1.23 (t, *J* = 7.0 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$)14.9, 25.2, 28.7, 43.9, 51.6, 52.7, 61.1, 81.3, 91.6, 118.7, 114.1, 125.6, 126.1, 132.7, 133.5, 136.5, 145.1, 145.5, 146.1, 151.6, 163.1, 167.5, 167.6. Anal. Calcd for $C_{23}H_{25}Cl_2N_5O_4$: C, 54.55; H, 4.98; N, 13.83. Found: C, 54.57; H, 5.02; N, 13.85.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-3-ethoxycarbonyl-4-(4-methoxylphenyl)-1-methyl-5-nitro-1,4-dihydropyridine (1f).** Yield: 71.6%; yellow solid. m.p.: 166–168°C. IR (KBr $cm^{-1}$): $\nu_{max}$ 2963($CH_3$), 3323, 3211 ($NH_2$), 1477, 1413($NO_2$), 1652, 1612, 1577 (benzene) $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.19 (s, 1H, Py H), 7.81 (s, 1H, Py H), 7.27 (s, 1H, Py H), 7.22 (d, *J* = 8.0 Hz, 2H, Ph H), 7.03 (d, *J* = 8.0 Hz, 2H, Ph H), 6.24 (s, 2H, $NH_2$), 5.68 (s, 1H, CH), 4.36 (d, *J* = 14.5 Hz, 1H), 4.14–4.09 (m, 2H, $COOCH_2CH_3$), 4.07–4.033 (m, 1H), 3.80 (s, 3H, $OCH_3$), 3.23 (s, 3H, $NCH_3$), 3.19 (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, 3H, $COOCH_2CH_3$), 1.21 (t, *J* = 7.1 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$)15.9, 24.7, 27.3, 44.9, 52.6, 53.3, 53.6, 62.1, 85.2, 92.6, 117.8, 114.4, 125.6, 125.1, 132.7, 132.5, 136.1, 142.9, 144.6, 147.1, 151.6, 163.8, 167.9, 167.4. Anal. Calcd for $C_{24}H_{28}ClN_5O_5$: C, 57.43; H, 5.62; N, 13.95. Found: C, 57.46; H, 5.65; N, 13.91.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-3-cyano-1-methyl -4-(2-methoxylphenyl)-5-nitro-1,4-dihydropyridine (1g).** Yield: 58.3%; yellow solid. m.p: 175–177°C; IR (KBr, $cm^{-1}$): $\nu_{max}$ 2934($CH_3$), 3332, 3201 ($NH_2$), 2185(CN), 1460, 1410($NO_2$), 1648, 1610, 1556 (benzene) $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, 1H, Py H), 7.84 (s, 1H, Py H), 7.37(s, 1H, Py H), 7.20–7.17 (m, 2H, Ph H), 6.93–6.77 (m, 2H, Ph H), 5.30 (s, 1H, CH), 4.44 (s, 1H), 4.32 (s, 2H, $NH_2$), 4.14 (dd, *J* = 14.3, 7.2 Hz, 1H), 3.91 (s, 3H, $OCH_3$), 3.31–3.18 (m, 4H), 3.10–3.05 (m, 1H), 1.28 (dd, *J* = 13.5, 6.4 Hz, 3H, $NCH_2CH_3$) $^{13}C$ NMR (400 MHz, $CDCl_3$) 18.7, 24.6, 29.6, 44.6, 53.7, 53.9, 54.6, 87.8, 94.7, 117.3, 115.8, 123.2, 126.6, 133.8, 133.4, 135.7, 142.9, 144.6, 147.1, 151.6, 167.9, 167.2. Anal. Calcd for $C_{22}H_{23}ClN_6O_3$: C, 58.09; H, 5.10; N, 18.47. Found: C, 58.12; H, 5.12; N, 18.51.

***cis*-2-Amino-4-(2-chlorophenyl)-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl]amino-3-cyano-1-methyl-5-nitro-1,4-dihydropyridine (1h).** Yield: 44.6%; yellow solid. m.p: 144–146°C. IR (KBr $cm^{-1}$): $\nu_{max}$ 2989 (CH3), 3333, 3224 ($NH_2$), 2188(CN), 1489, 1423($NO_2$), 1658, 1625, 1588 (benzene) $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, *J* = 7.9, 1H,

Py H), 7.84 (dd, *J* = 14.1, 6.9, 1H, Py H), 7.37 (d, *J* = 7.5, 1H, Py H), 7.23–7.18 (m, 2H, Ph H), 6.91–6.81 (m, 2H, Ph H), 5.29 (s, 1H, CH), 4.42 (s, 1H), 4.32 (s, 2H, $NH_2$), 4.12 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.30–3.19 (m, 1H), 3.12 (s, 3H, $NCH_3$), 3.11–3.04 (m,1H), 1.29 (t, *J* = 8.5 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 19.4, 25.2, 28.1, 45.7, 54.9, 55.6, 88.8, 92.1, 113.6, 118.6, 123.2, 126.6, 133.2, 133.7, 135.1, 142.6, 144.2, 147.3, 151.5, 167.7, 167.9. Anal. Calcd for $C_{21}H_{20}Cl_2N_6O_2$: C, 54.91; H, 4.39; N, 18.30. Found: C, 54.95; H, 4.36; N, 18.32.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-4-(2,4-dichlorophenyl)-3-ethoxycarbonyl-1-methyl-5-nitro-1,4-dihydropyridine (1i).** Yield: 77.2%; yellow solid. m.p: 136–138°C. IR (KBr $cm^{-1}$): $\nu_{max}$ 2975($CH_3$), 3328, 3199 ($NH_2$), 1410 ($NO_2$), 1656, 1614, 1557 (benzene). $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H, Py H), 7.78 (s, 1H, Py H), 7.35 (s, 1H, Py H), 7.14 (d, *J* = 14.2 Hz, 2H, Ph H), 6.63 (s, 1H, Ph H), 5.32 (d, *J* =13.2 Hz, 1H, CH), 4.57 (s, 2H, $NH_2$), 4.42 (d, *J* = 13.2 Hz, 1H), 4.13 (m, 2H, $COOCH_2CH_3$) 4.12–4.04 (m, 1H), 3.30–3.25 (m, 4H), 3.14 (d, *J* = 2Hz, 1H), 1.32–1.27 (m, 3H, $COOCH_2CH_3$), 1.14–1.12 (t, *J* = 7.2 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 19.4, 25.2, 28.1, 45.7, 54.9, 55.2, 88.9, 91.6, 112.4, 116.2, 124.8, 125.1, 134.6, 135.2, 137.5, 143.6, 145.4, 147.6, 151.2, 168.9, 171.2. Anal. Calcd for $C_{21}H_{19}Cl_3N_6O_2$: C, 51.08; H, 3.88; N, 17.02. Found: C, 51.11; H, 3.87; N, 17.03.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-3-cyano-4-(2-fluorophenyl) 1-methyl-5-nitro-1,4-dihydropyridine (1j).** Yield: 72.4%; yellow solid. m.p: 184–186°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2973($CH_3$), 3331, 3199 ($NH_2$), 2186(CN), 1507–1411 ($NO_2$), 1648, 1613, 1608 (benzene); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 19.0 Hz, 1H, Py H), 7.80 (s, 1H, Py H), 7.31 (d, *J* = 7.2 Hz, 1H, Py H), 7.12–6.87 (m, 5H, Ph H), 4.97 (s, 1H, CH), 4.37(d, *J* =15.8 Hz, 1H), 4.01 (d, *J* = 14.7 Hz, 2H, $NH_2$), 3.45–3.28 (m, 1H), 3.25(s, 3H, $NCH_3$), 3.11 (dd, *J* = 13.6, 6.6 Hz, 1H), 1.29 (dd, *J* = 20.1, 7.0 Hz, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 19.5, 25.7, 27.5, 45.2, 53.6, 56.1, 88.9, 91.6, 112.4, 116.2, 124.8, 125.1, 134.6, 135.2, 137.4, 143.7, 144.5, 148.2, 152.7, 169.1, 174.5. Anal. Calcd for $C_{21}H_{20}ClFN_6O_2$: C, 56.95; H, 4.55; N, 18.98. Found: C, 56.92; H, 4.51; N, 18.99.

***cis*-2-Amino-6-[*N*-(6-chloro-3-pyridinylmethyl)-*N*-ethyl] amino-3-cyano-4-(3-fluorophenyl) 1-methyl -5-nitro-1,4-dihydropyridine (1k).** Yield: 79.7%; yellow solid. m.p.: 173–175°C; IR (KBr $cm^{-1}$): $\nu_{max}$ 2981($CH_3$), 3322, 3203 ($NH_2$), 2186(CN), 1486, 1412($NO_2$), 1653, 1607, 1589(benzene) $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.31 (s, 1H, Pyridine), 8.07 (s, 1H, Pyridine), 7.36 (s, 1H, Pyridine), 7.23–6.99 (m, 5H, Ph H), 5.06 (s, 1H, CH), 4.69 (br, 2H, $NH_2$), 4.35 (d, *J* = 14.3 Hz, 1H), 4.09 (d, *J* = 14.8 Hz, 1H), 3.36–3.24 (m, 1H), 3.21 (s, 3H, $NCH_3$), 3.16 (d, *J* = 6.5 Hz, 1H), 1.36–1.27 (m, 3H, $NCH_2CH_3$). $^{13}C$ NMR (400 MHz, $CDCl_3$) 21.7, 24.2, 26.4, 48.4, 54.8, 59.8, 88.9, 91.6, 112.4, 112.5, 125.2, 126.8, 135.3, 136.8, 136.6, 144.8, 145.5, 149.9, 151.2, 169.6, 172.1. Anal. Calcd for $C_{21}H_{20}ClFN_6O_2$: C, 56.95; H, 4.55; N, 18.98. Found: C, 56.97; H, 4.56; N, 18.93.

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