Synthesis of Imidacloprid Analogues from Novel Chloronicotinaldehydes

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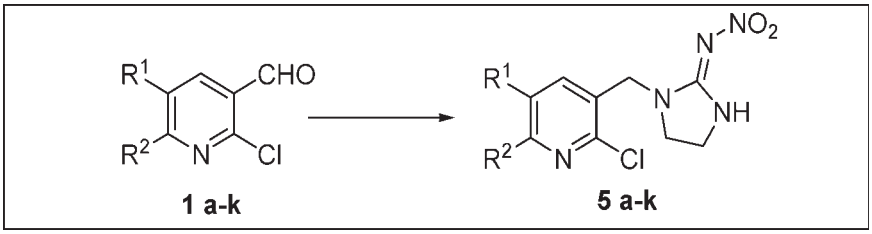

A serious of imidacloprid analogues have been synthesized from novel chloronicotinaldehydes. The chloronicotinaldehydes are the important synthons obtained from Vilsmeier reaction of various enamides. Thus synthesized imidacloprid analogues are new heterocyclic compounds obtained in very good yields.

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INTRODUCTION

Neonicotinoids [1] are used worldwide for controlling insects because of their low mammalian toxicity, potency, and broad insecticidal and systemic properties. Imidacloprid (Fig. 1) is a new systemic insecticide for crop protection [2], and it is the first chloronicotinyl nonnatural insecticide, which consists of 2-(*N*-nitroimino)imidazolidine coupled with (6-chloropyridin-3-yl)methyl (CPM) residue [3]. It belongs to chloronicotinyl subclass of nicotinoids, which are a novel and distinct chemical class of insecticides with remarkable chemical and biological properties. It has a novel mode of action—binding to the nicotinergic acetylcholine receptor in the postsynaptic region of the insect nerve. Because of the importance of neonicotinoids, several imidacloprid analogues has been synthesized and reported in the literature [4].

Synthesis of large number of new heterocyclic molecules and their bioevaluation in agrochemical and pharmaceutical areas is the worldwide current interest. Discovery of new insecticides is an ongoing process and challenging area for organic chemists. Because of our continuous interest on synthesis of bioactive heterocyclic molecules [5a–g], we report the synthesis of novel imidacloprid derivatives from the substituted chloronicotinaldehydes in very good yields.

RESULTS AND DISCUSSION

The imidacloprid analogues reported in this article are synthesized from substituted chloronicotinaldehydes by Vilsmeier reaction of various enamide substrates according to our earlier reported method [5a]. Thus, prepared chloronicotinaldehydes were an important synthons used for various organic transformations such as synthesis of 2-chloro-5-methylpyridine-3-carbaldehydeimines (Schiff bases) [5b], Baylis-Hillman adducts [5e], reactions with cyclic enones [5c], and conversion of Baylis-Hillman adducts to synthesis of biologically important quinolines [5d]. As mentioned in the Scheme 1, the carboxaldehydes (**1a–k**) were subjected for reduction using sodium borohydride in methanol to give corresponding alcohols (**2a–k**). Under these reaction conditions, all the aldehydes (**1a–k**) were smoothly converted to alcohols (**2a–k**) without disturbing other functional groups present in the compounds. These alcohols (**2a–k**) were then converted to corresponding chlorides (**3a–k**) by using thionyl chloride, with catalytic amounts of dimethylformamide (DMF) as chlorinating agent in heptane solvent. The DMF used in catalytic amounts enhances the rate of reaction, subsequently, the reaction proceeds efficiently because of the formation of a complex between thionyl chloride and DMF, which actually acts as chlorinating agent.

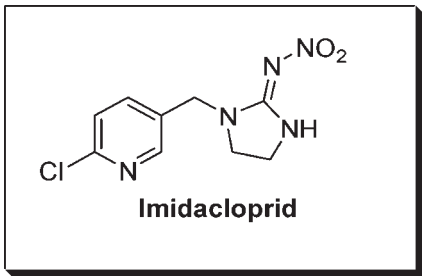


Figure 1. Imidacloprid.

The formed chlorides (**3a–k**) were allowed to react with nitroimino imidazole moiety (**4**) in acetonitrile using potassium carbonate and CsCl (5 mol%) under reflux conditions to give corresponding imidacloprid analogues (**5a–k**, Scheme 2) in very good yields. Thus prepared imidacloprid analogues (**5a–k**) are new compounds and are characterized by spectral data.

The 2-nitroiminoimidazole (**4**) is synthesized from ethylenediamine and nitroguanidine in the presence of hydrochloric acid as per our reported procedure [6]. In conclusion, the imidacloprid analogues have been synthesized from chloronicotinaldehydes in very good yields. Thus prepared new heterocyclic compounds are well characterized by spectral data. To achieve these target molecules, the important synthons such as chloronicotinaldehydes and nitraminoimidazolidine were used to complete the imidacloprid analogues.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian, Gemini 200 and Avance 300 MHz spectrometer in $CDCl_3$ with TMS as internal standard. Infrared (IR) spectra were recorded on Nicollet 740 FT spectrometer. EI-MS obtained on 7070H spectrometer operating at 70 eV using a direct inlet system. Melting points were determined in open glass capillary tubes on a Metler FP 51 melting point apparatus and are uncorrected. The CHN analyses were recorded on Vario EL analyzer. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); spots were visualized under UV light. Merck silica gel (60–120; 100–200 mesh) was used for chromatography.

General procedure for the synthesis of 2-chloro-5/6-substituted pyridyl methanol (2a–k). Methyl 6-chloro-5-formyl-2-pyridinecarboxylate (**1j**; 200 mg, 0.0012 mol) was dissolved in methanol solvent, and sodium borohydride (15 mg, 0.00039 moles) was added slowly at 0°C over a period of 15 min. The reaction was monitored by TLC, and after completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution, solvent was removed under reduced pressure, and the residue was extracted with dichloromethane and obtained methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (**2j**) on column chromatography. All the alcohols were synthesized by using the similar procedure.

(2-Chloro-5-methyl-3-pyridyl)methanol (2a). Yield: 92%, solid; mp: 59–61°C. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.73 (s, 2H, -CH_2OH), 7.66 (s, 1H, heteroaromatic), 8.07 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 157 (90) (M^+), 142 (23), 130 (9), 122 (100), 106 (20), 99 (4), 92 (57), 78 (10), 65 (25), 51 (8), 39 (14), 31 (3). UV: λ_{max} = 268 nm in acetonitrile. IR (KBr): ν = 3325, 2969, 2932, 2874, 1568, 1432, 1399, 1355, 1164, 1083, 1044, 904, 731 cm^{-1}. Anal. Calcd for C_7H_8ClNO: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.39; H, 5.19; N, 8.72.

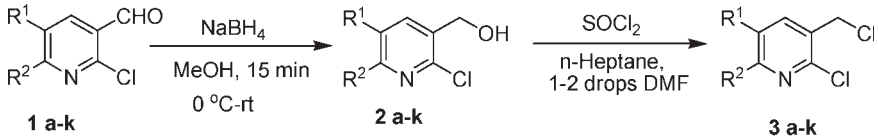
(2-Chloro-5-ethyl-3-pyridyl)methanol (2b). Yield: 91%, solid; mp: 62–64°C. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_3), 2.65 (q, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 171 (50) (M^+), 174 (40), 154 (100), 140 (5), 91 (20), 77 (15). UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3330, 2960, 2935, 2870, 1575, 1340, 1160, 1090, 1040, 906, 735 cm^{-1}. Anal. Calcd for $C_8H_{10}ClNO$: C, 55.99; H, 5.87; N, 8.18. Found: C, 56.02; H, 5.84; N, 8.21.

(2-Chloro-5-propyl-3-pyridyl)methanol (2c). Yield: 90%, solid; mp: 64–65°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 185.

(2-Chloro-5-isopropyl-3-pyridyl)methanol (2d). Yield: 90%, solid; mp: 70–72°C. ^{1}H NMR ($CDCl_3$): δ 1.2–1.4 (m, 6H, $2CH_3$), 3.20 (m, 1H, CH), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 185.

(2-Chloro-5-pentyl-3-pyridyl)methanol (2e). Yield: 87%, solid; mp: 58–60°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3),

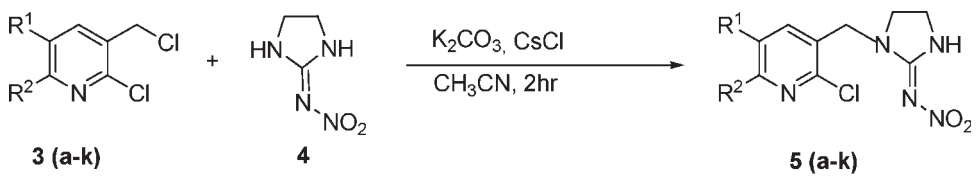
Scheme 1



1 a-k **2 a-k** **3 a-k**

1a = **2a** = **3a**: R^1 = Me; R^2 = H
1b = **2b** = **3b**: R^1 = Et; R^2 = H
1c = **2c** = **3c** : R^1 = n-Pr; R^2 = H
1d = 2d = 3d: R^1 = i-Pr; R^2 = H
1e = **2e** = **3e**: R^1 = n-Pent; R^2 = H
1f = **2f** = **3f**: R^1 = Ph; R^2 =H
1g = **2g** = **3g**: R^1 = *p*-(OCH_3)Ph; R^2 = H
1h = **2h** = **3h**: R^1 = Me; R^2 = Ph
1i = **2i** = **3i**: R^1 = CO_2Et; R^2 = Ph
1j = **2j** = **3j**: R^1 = H; R^2 = CO_2Me
1k = **2k** = **3k**: R^1 = CH_3; R^2 = CO_2Me

Scheme 2



3 (a-k) **4** **5 (a-k)**

3a = **5a:** R^1 = Me; R^2 = H
3b = **5b:** R^1 = Et; R^2 = H
3c = **5c:** R^1 = n-Pr; R^2 = H
3d = **5d:** R^1 = i-Pr; R^2 = H
3e = **5e:** R^1 = n-Pentyl; R^2 = H
3f = **5f:** R^1 =Ph; R^2 = H
3g = **5g:** R^1 = *p*-(OCH_3)Ph; R^2 = H
3h = **5h:** R^1 = Me; R^2 = Ph
3i = **5i:** R^1 = COOEt; R^2 = Ph
3j = **5j:** R^1 = H; R^2 = COOMe
3k = **5k:** R^1 = Me; R^2 = COOMe

1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 4.75 (s, 2H, CH_2OH), 7.73 (s, 1H, heteroaromatic), 8.09 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 213.

(2-Chloro-5-phenyl-3-pyridyl)methanol (2f). Yield: 90%, solid; mp: 89–91°C. ^{1}H NMR ($CDCl_3$): δ 4.85 (s, 2H, -CH_2OH), 7.46 (m, 3H, aromatic), 7.59 (m, 2H, aromatic), 8.08 (m, 1H, heteroaromatic), 8.55 (m, 1H, heteroaromatic). EI-MS (*m*/*z*): 219 (100) (M^+), 184 (45), 166 (5), 154 (38), 140 (5), 127 (24), 115 (9), 102 (8), 77 (10). UV: λ_{max} = 254 nm in acetonitrile. IR (KBr): ν = 3420, 2240, 1665, 1520, 1370, 1037, 1030, 760 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.75; H, 4.56; N, 6.39. Found: C, 65.66; H, 4.62; N, 6.36.

[2-Chloro-5-(4-methoxyphenyl)-3-pyridyl]methanol (2g). Yield: 94%, solid; mp: 63–64°C. ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 3H, OCH_3), 4.62 (s, 2H, CH_2OH), 6.93 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 8.07 (s, 1H, heteroaromatic), 8.34 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 249 (M^+) (100), 206 (13), 179 (25), 162 (60), 137 (70), 105(55), 66 (100), 43 (80). UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3423, 2253, 2127, 1653, 1516, 1433, 1378, 1027, 764 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.65; H, 4.82; N, 5.62. Found: C, 62.61; H, 4.84; N, 5.71.

(2-Chloro-5-methyl-6-phenyl-3-pyridyl)methanol (2h). Yield: 96%, solid; mp: 78–80°C, ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.71 (s, 2H, CH_2OH), 7.35–7.45 (m, 5H), 7.69 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 233 (42) (M^+), 232 (100), 196 (5), 167 (10), 115 (6), 77 (4). UV: λ_{max} = 284 nm acetonitrile. IR (KBr): ν = 3384, 3059, 2924, 2856, 1591, 1550, 1415, 1054, 701 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.95; H, 5.18; N, 5.99. Found: C, 66.91; H, 5.22; N, 6.01.

Ethyl-6-chloro-5-(hydroxymethyl)-2-phenylnicotinate (2i). Yield: 90%, light yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.80 (s, 2H, CH_2OH), 7.42 (m, 3H), 7.60 (m, 2H), 8.76 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 291 (15) (M^+), 262 (100), 246 (37), 218 (6), 190 (6), 127 (7). UV: λ_{max} = 252 nm acetonitrile. IR (KBr): ν = 3443, 3269, 2985, 2922, 2853, 1732, 1540, 1431, 1305, 1221, 1134, 1016, 701 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.85; H, 4.84; N, 4.80. Found: C, 61.80; H, 4.89; N, 4.82.

Methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (2j). Yield: 92%, solid; mp: 68–70°C. ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2OH), 8.07 (s, 2H, heteroaromatic). EI-MS (*m*/*z*): 201 (3) (M^+), 171 (20), 143 (100), 112 (19), 78 (11), 51 (4). UV: λ_{max} = 276 nm. IR (KBr): ν = 3416, 2923, 2853, 1730, 1310, 1258, 1046, 778 cm^{-1}. Anal. Calcd for $C_8H_8ClNO_3$: C, 47.76; H, 4.00; N, 6.95. Found: C, 47.69; H, 4.11; N, 6.99.

Methyl-6-chloro-5-(hydroxymethyl)-3-methyl-2-pyridinecarboxylate (2k). Yield: 91%, Solid; mp: 86–88°C. ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2OH), 7.78 (s, 2H, heteroaromatic). EI-MS (*m*/*z*): 215 (M^+) (55), 200 (5), 183 (100), 157 (70), 137 (11), 126 (20), 92 (17), 65 (11), 51 (3), 39 (6). UV: λ_{max} = 282 nm. IR (KBr): ν = 3468, 1705, 1440, 1406, 1327, 1243, 1120, 1063, 722 cm^{-1}. Anal. Calcd for $C_9H_{10}ClNO_3$: C, 50.23; H, 4.67; N, 6.50. Found: C, 50.14; H, 4.68; N, 6.46.

General procedure for the synthesis of 2-chloro-3-chloromethyl-5/6-substituted pyridines (3a–k). Methyl-6-chloro-5-(hydroxymethyl)-2-pyridinecarboxylate (**2j**) (200 mg, 0.0009 moles) was dissolved in heptane (50 mL) and added one drop of DMF. The reaction mixture was heated to 60–65°C. Thionyl chloride (150 mg; 0.00135 mol) was added dropwise to the hot reaction mixture. After completion of the addition, the temperature was raised to 80°C and maintained for 2 h. Progress of the reaction was monitored by TLC. The organic solvent was removed under reduced pressure, and obtained crude methyl-6-chloro-5-(chloromethyl)-2-pyridinecarboxylate (**3j**) was recrystallized in hexane.

2-Chloro-3-(chloromethyl)-5-methylpyridine (3a). Yield: 88%, solid; mp: 55–58°C. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.62 (s, 2H, -CH_2Cl), 7.65 (s, 1H, heteroaromatic), 8.17 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 175 (40) (M^+), 140 (100), 104 (12), 77 (23), 51 (9), 39 (5). UV: λ_{max} = 258 nm in acetonitrile. IR (KBr): ν = 2971, 2934, 2874, 1563, 1429, 1407, 1076, 908, 758 cm^{-1}. Anal. Calcd for $C_7H_7Cl_2N$: C, 48.02; H, 4.01; N, 8.00. Found: C, 48.09; H, 4.08; N, 7.99.

2-Chloro-3-(chloromethyl)-5-ethylpyridine (3b). Yield: 94%, solid; mp: 63–64°C. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 4.75 (s, 2H, CH_2Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 189 (23) (M^+), 174 (13), 154 (100), 91 (5), 77 (4), 51 (3). UV: λ_{max} = 266 nm in acetonitrile. IR (KBr): ν = 2990, 2960, 1560, 1420, 1417, 1070, 900, 750 cm^{-1}. Anal. Calcd for $C_8H_9Cl_2N$: C, 50.79; H, 4.77; N, 7.40. Found: C, 50.71; H, 4.82; N, 7.38.

2-Chloro-3-(chloromethyl)-5-propylpyridine (3c). Yield: 88%, solid; mp: 65–66°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 217.

2-Chloro-3-(chloromethyl)-5-isopropylpyridine (3d). Yield: 89%, solid; mp: 66–68°C. ^{1}H NMR ($CDCl_3$): δ 1.2–1.4 (m, 6H, $2CH_3$), 3.20 (m, 1H, CH), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 217.

2-Chloro-3-(chloromethyl)-5-pentylpyridine (3e). Yield: 88%, solid; mp: 70–72°C. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3), 1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 4.75 (s, 2H, CH_2-Cl), 7.65 (s, 1H, heteroaromatic), 8.18 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 231.

2-Chloro-3-(chloromethyl)-5-phenylpyridine (3f). Yield: 91%, solid; mp: 78–80°C. ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 2H, CH_2), 7.44–7.58 (m, 5H), 8.06 (s, 1H, heteroaromatic), 8.58 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 237 (82) (M^+), 202 (100), 166 (18), 139 (17), 115 (11), 101 (6), 69 (5). UV: λ_{max} = 256 nm in acetonitrile. IR (KBr): ν = 2970, 2910, 2880, 1420, 1240, 1170, 1060, 1020 cm^{-1}. Anal. Calcd for $C_{12}H_9$ Cl_2 N: C, 60.75; H, 3.79; N, 5.90. Found: C, 60.77; H, 3.72; N, 5.88.

2-Chloro-3-(chloromethyl)-5-(4-methoxyphenyl)pyridine (3g). Yield: 91%, solid; mp: 79–80°C. ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 4.77 (s, 2H, -CH_2Cl), 6.97 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 7.98 (s, 1H, heteroaromatic), 8.50 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 267 (100) (M^+), 252 (15), 232 (45), 189 (6), 154 (6), 127 (12), UV: λ_{max} = 276 nm in acetonitrile. IR (KBr): ν = 2957, 2925, 2854, 1735, 1606, 1426, 1249, 1182, 1082, 1027, 832, 753 cm^{-1}. Anal. Calcd for $C_{13}H_{11}$ Cl_2 NO: C, 58.43; H, 4.13; N, 5.24. Found: C, 58.33; H, 4.22; N, 5.21.

2-Chloro-3-(chloromethyl)-5-methyl-6-phenylpyridine (3h). Yield: 88%, solid; mp: 78–82°C. ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 4.70 (s, 2H, -CH_2Cl), 7.28–7.38 (m, 5H), 7.73 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 251 (44) (M^+), 250 (100), 216 (39), 180 (11), 153 (13), 140 (4), 128 (5), 115 (5), 89 (5), 76 (10), 63 (4), 51 (5). UV: λ_{max} = 288 nm in acetonitrile. IR (KBr): ν = 2967, 2927, 1588, 1543, 1443, 1412, 1383, 1185, 1067, 984, 735, 702 cm^{-1}. Anal. Calcd for $C_{13}H_{11}$ Cl_2N: C, 62.16; H, 4.40; N, 5.57. Found: C, 60.81; H, 4.42; N, 5.61.

Ethyl-6-chloro-5-(chloromethyl)-2-phenylnicotinate (3i). Yield: 91%, light yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 4.74 (s, 2H, -CH_2Cl), 7.46 (m, 3H, aromatic), 8.76 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 309 (18) (M^+), 280 (100), 264(34), 245 (11), 229 (7), 202 (6), 166 (14), 139 (17), 105 (7). UV: λ_{max} = 256 nm in acetonitrile. IR (KBr): ν = 2925, 2853, 1724, 1573, 1531, 1440, 1237, 1129, 757 cm^{-1}. Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.28; H, 4.22; N, 4.52. Found: C, 58.21; H, 4.28; N, 4.61.

Methyl-6-chloro-5-(chloromethyl)-2-pyridinecarboxylate (3j). Yield: 93% solid; mp: 78–80°C. ^{1}H NMR ($CDCl_3$): δ 4.04 (s, 3H, OCH_3), 4.76 (s, 2H, -CH_2Cl), 8.08 (q, 2H). EI-MS (*m*/*z*): 219 (4) (M^+), 189 (20), 161 (100), 124 (15), 90 (11), 63 (10). UV: λ_{max} = 258 nm in acetonitrile. IR (KBr): ν = 2925, 2854, 1728, 1562, 1450, 1369, 1137, 744 cm^{-1}. Anal. Calcd for C_8H_7 Cl_2NO_2: C, 43.84; H, 3.20; N, 6.39. Found: C, 37.21; H, 2.69; N, 7.21.

Methyl-6-chloro-5-(chloromethyl)-3-methyl-2-pyridinecar-boxylate (3k). Yield: 90%, solid; mp: 75–77°C. ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2Cl), 7.80 (s, 1H, heteroaromatic). EI-MS (*m*/*z*): 234 (43) (M^+), 218 (5), 201(100), 175 (64), 138 (46), 102 (20), 77 (15), 51 (9). UV: λ_{max} = 286 nm in acetonitrile. IR (KBr): ν = 2915, 2850, 1729, 1560, 1455, 1360, 1130, 740 cm^{-1}. Anal. Calcd for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.84; N, 5.98. Found: C, 46.18; H, 3.92; N, 5.92.

General procedure for the synthesis of (substituted pyridyl)-methyl]tetrahydro-1*H*-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5a–k). A mixture of pyridine substituted methyl chloride (**3**; 0.5 g, 0.002 moles), 2-nitraimino imidazole (0.67 g, 0.005 mol), K_2CO_3 (0.33 g, 0.002 mol), and CsCl (5 mol %) in CH_3CN (10 mL) was refluxed for 2.5 h. After completion of the reaction, acetonitrile was removed. The solid crude was washed with water. The solid when recrystallized by methanol gave the title compounds in good yield.

2-{1-[(2-Chloro-5-methyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5a). Yield: 82%, solid; mp: 193–195°C. ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.62 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, NH, 1H). UV: λ_{max} = 272 nm in acetonitrile. EI-MS (*m*/*z*): 269; IR (KBr): ν = 3792, 3307, 2922, 2861, 1584, 1546, 1439, 1286, 1240, 1148, 1053, 724, 679, 642 cm^{-1}. Anal. Calcd for $C_{10}H_{12}Cl$ N_5O_2: C, 44.61; H, 4.48; N, 26.06. Found: C, 44.64; H, 4.51; N, 26.12.

2-{1-[(2-Chloro-5-ethyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5b). Yield: 81%, solid; mp: 197–199°C. ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, NH, 1H). EI-MS (*m*/*z*): 283; IR (KBr): ν = 3790, 3300, 2855, 1580, 1540, 1280, 1240, 1050, 724, cm^{-1}. Anal. Calcd for $C_{11}H_{14}ClN_5O_2$: C, 46.56; H, 4.97; N, 24.68. Found: C, 46.59; H, 4.99; N, 24.70.

2-{1-[(2-Chloro-5-propyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5c). Yield: 82%, solid; mp: 196–198°C. ^{1}H NMR (DMSO-d_6): δ 0.9 (t, 3H, CH_3), 1.7 (m, 2H, CH_2), 2.64 (t, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.64 (s, 1H, heteroaromatic), 8.22 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 297.

2-{1-[(2-Chloro-5-isopropyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5d). Yield: 84%, solid; mp: 190–192°C. ^{1}H NMR (DMSO-d_6): δ 1.2–1.4 (m, 6H, $2CH_3$), 3.20 (m, 1H, CH), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.64 (s, 2H, -CH_2N-), 7.60 (s, 1H, heteroaromatic), 8.21 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 297.

2-{1-[(2-Chloro-5-pentyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5e). Yield: 86%, solid; mp: 198–201°C. ^{1}H NMR (DMSO-d_6): δ 0.9 (t, 3H, CH_3), 1.38 (m, 4H, $2CH_2$), 1.70 (q, 2H, CH_2), 2.7 (t, 2H, CH_2), 3.5–3.8 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -CH_2N-), 7.62 (s, 1H, heteroaromatic), 8.20 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 325.

2-{1-[(2-Chloro-5-phenyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden}-1-oxo-1-hydraziniumolate (5f). Yield: 80%, solid; mp: 248–250°C. ^{1}H NMR (DMSO-d_6): δ 3.60–3.80 (m, 4H, -CH_2-CH_2-), 4.62 (s, 2H, -CH_2N-), 7.50 (m, 3H, aromatic), 7.75 (d, 2H, aromatic), 8.05 (s, 1H, heteroaromatic), 8.68 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). EI-MS (*m*/*z*): 331; UV: λ_{max} = 262 nm in acetonitrile. IR (KBr): ν = 3253, 3065, 2879, 1580, 1542, 1438, 1284, 1240, 1145, 1050, 953, 759, 687 cm−^{1}. Anal. Calcd for $C_{15}H_{14}ClN_5O_2$: C, 54.30; H, 4.25; N, 21.11. Found: C, 55.41; H, 4.32; N, 21.21.

2-(1-{[2-Chloro-5-(4-methoxyphenyl)-3-pyridyl]methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5g). Yield: 81%, solid; mp: 159–160°C. ^{1}H NMR (DMSO-d_6): δ 3.60–3.80 (m, 4H, -CH_2-CH_2-), 3.84 (s, 3H, OCH_3), 4.62 (s, 2H, -CH_2N-), 6.97 (d, 2H, aromatic), 7.49 (d, 2H, aromatic), 8.05 (s, 1H, heteroaromatic), 8.68 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). IR (KBr): ν = 3416, 2923, 2853, 1572, 1540, 1436, 1282, 1237 cm^{-1}. EI-MS (*m*/*z*): 361; Anal. Calcd for $C_{16}H_{16}Cl\ N_5O_3$: C, 53.11; H, 4.45; N, 19.39. Found: C, 53.21; H, 4.29; N, 19.35.

2-{1-[(2-Chloro-5-methyl-6-phenyl-3-pyridyl)methyl]-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5h). Yield: 89%, solid; mp: 168–170°C. ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.60–3.78 (m, 4H, -CH_2-CH_2-), 4.58 (s, 2H, -CH_2N-), 7.40–7.60 (m, 5H, aromatic), 7.78 (s, 1H, heteroaromatic), 9.05 (s, 1H, NH). UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3331, 2925, 2854, 1554, 1433, 1292, 1261, 1228, 1126, 1044, 982, 701 cm^{-1}. EI-MS (*m*/*z*): 345; Anal. Calcd for $C_{16}H_{16}Cl\ N_5O_2$: C, 55.57; H, 4.66; N, 20.25. Found: C, 55.61; H, 4.77; N, 20.21.

2-(1-{[2-Chloro-5-(ethoxycarbonyl)-6-phenyl-3-pyridyl]-methyl}tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5i). Yield: 88%, solid; mp: 133–135°C. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, CH_3), 3.62 (m, 2H,CH_2), 3.80 (m, 2H, CH_2), 4.22 (q, 2H, CH_2), 4.78 (s, 2H, -CH_2N-), 7.42 (m, 3H, aromatic), 7.60 (m, 2H, aromatic), 8.28 (s, 1H, NH), 8.72 (s, 1H, heteroaromatic). UV: λ_{max} = 270 nm in acetonitrile. EI-MS (*m*/*z*): 403; IR (KBr): ν = 3255, 2899, 1734, 1570, 1525, 1441, 1402, 1259, 1230, 1114, 1049, 1008, 951, 777, 695, 622 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClN_5O_4$: C, 53.53; H, 4.49; N, 17.34. Found: C, 53.61; H, 4.52; N, 17.41.

2-(1-{[2-Chloro-6-(methoxycarbonyl)-3-pyridyl]methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5j). Yield: 86%, solid; mp: 169–170°C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.69 (q, 2H, CH_2), 3.82 (q, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.66 (s, 2H, -CH_2N-), 7.88 (d, 1H, heteroaromatic), 8.03 (d, 1H, heteroaromatic), 8.16 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 41.63, 44.62, 45.32, 52.10, 115.53, 124.80, 136.27, 149.57, 151.48, 161.55, 168.28. EI-MS (*m*/*z*): (M^+ + 23) 336. UV: λ_{max} = 272 nm. IR (KBr): ν = 3341, 2924, 1713, 1574, 1445, 1322, 1264, 1055, 786 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClN_5O_4$: C, 42.11; H, 3.85; N, 22.32. Found: C, 42.18; H, 3.98; N, 22.33.

2-(1-{[2-Chloro-6-(methoxycarbonyl)-5-methyl-3-pyridyl]-methyl}-tetrahydro-1H-2-imidazolyliden)-1-oxo-1-hydraziniumolate (5k). Yield: 80%, solid; mp: 175–177°C. ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.6–3.7 (q, 2H, CH_2), 3.8–3.9 (q, 2H, CH_2), 3.98 (s, 3H, OCH_3), 4.72 (s, 2H, -CH_2N), 7.72 (s, 1H, heteroaromatic), 8.24 (s, 1H, NH). EI-MS (*m*/*z*): (M^++ 23) 350. UV: λ_{max} = 272 nm in acetonitrile. IR (KBr): ν = 3412, 2921, 2852, 1712, 1579, 1441, 1320, 1293, 1240, 1120, 1045 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClN_5O_4$: C, 43.97; H, 4.30; N, 21.36. Found: C, 43.99; H, 4.32; N, 21.41.

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REFERENCES AND NOTES

[1] (a) Samaritoni, J. G.; Demeter, D. A.; Gifford, J. M.; Watson, G. B.; Kempe, M. S.; Bruce, T. J. J. Agri Food Chem 2003, 51, 3035; (b) Tian, Z.; Jiang, Z.; Li, Z.; Song, G.; Huang, Q. J Agri Food Chem 2007, 55, 143.

[2] Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K.; Kagabu, S. Biosci Biotechnol Biochem 1992, 56, 364.

[3] Jeschke, P.; Moriya, K.; Lantzsch, R.; Seifert, H.; Linder, W.; Jelish, K.; Gohrt, A.; Beck, M. E.; Etzel, W. Pflanzenschutz-Nachrichten Bayer. 2001, 54, 147.

[4] (a) Novak, L.; Hornyanszky, G.; Kiraly, I.; Rohaly, J.; Kolonits, P.; Szantay, C. Heterocycles 2001, 55, 45; (b) Brackmann, F.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; De Meijere, A. Eur J Org Chem 2005, 3, 600; (c) Latli, B.; D'Amour, K.; Casida, J. E. J Med Chem 1999, 42, 2227; (d) Zhang, N.; Tomizawa, M.; Casida, J. E. J Med Chem 2002, 45, 2832; (e) Kagabu, S.; Maienfisch, P.; Zhang, A.; Granda-Minones, J.; Haettenschwiler, J.; Kayser, H.; Maetzke, T.; Casida, J. E. J Med Chem 2000, 43, 5003; (f) Zhang, N.; Tomizawa, M.; Casida, J. E. J Org Chem 2004, 69, 876; (g) Kagabu, S. Synth Commun 2006, 36, 1235.

[5] (a) Gangadasu, B.; Narender, P.; Kumar, S. B.; Ravinder, M.; Anada Rao, B.; Ramesh, Ch.; China Raju, B.; Jayathirtha Rao, V. Tetrahedron 2006, 62, 8398; (b) Gangadasu, B., China Raju, B.; Jayathirtha Rao, J. Heterocyclic Commun 2002, 8, 243; (c) Narender, P.; Gangadasu, B.; Ravinder, M.; Jayathirtha Rao, V. Tetrahedron 2006, 62, 954; (d) Narender, P.; Srinivas, U.; Ravinder, M.; Ramesh, Ch.; Anand Rao, B.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Jayathirtha Rao, J. Bioorg Med Chem 2006, 14, 4600; (e) Narender, P.; Srinivas, U.; Gangadasu, B.; Jayathirtha Rao, V. Bioorg Med Chem Lett 2005, 15, 5378; (f) Narender, P.; Gangadasu, B.; Ramesh, Ch.; China Raju, B.; Jayathirtha Rao, V. Synth Commun 2004, 34, 1097; (g) Srinivas, K.; Srinivas, U.; Kishore, K. H.; Jayathirtha Rao, V.; Bhanuprakash, K.; Murthy, U. S. N. Bioorg Med Chem Lett 2005, 15, 1121.

[6] China Raju, B.; Jayathirtha Rao, V. Indian J Chem 2002, 41B, 2180.