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Design, synthesis and insecticidal activities of dihydropyridine-fused neonicotinoids compounds with trifluoromethyl group

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Abstract A series of novel neonicotinoids containing a dihydro-pyridine ring and a trifluoromethyl group were designed and synthesized by multicomponent reactions of 6-Cl-PMNI, triethoxymethane and 4,4,4-trifluoro-3-oxobutaneanilides (9) under solvent-free and catalyst-free conditions. The trifluoromethyl group plays an important role as an electron-withdrawing group in enhancing the reaction activity of compound 9. The target compounds were characterized by ^{1}H NMR, IR and elemental analysis. Bioassays indicated that most of the synthesized compounds exhibited moderate insecticidal activities against *Aphis craccivora*.

Keywords *cis*-Neonicotinoid · Dihydro-pyridine · Trifluoromethyl group · Insecticidal activity

Introduction

Neonicotinoids are natural product-derived pesticides and the most important new class of insecticides in the last two decades, and have a large impact on worldwide insecticide use [1, 2]. Neonicotinoids include Imidacloprid, Acetamiprid, Clothianidin, Dinotefuran, Nitenpyram, Thiacloprid, and Thiamethoxam [3, 4]. Neonicotinoids act selectively on the insect central nervous system (CNS) as agonists of the postsynaptic nicotinic acetylcholine receptors (nAChRs) [5]. The

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greatest attributes of neonicotinoids are their novel mode of action, low mammalian toxicity, broad insecticidal spectrum, and good systemic properties [6, 7]. They are now registered globally in more than 120 countries and extensively used in seed treatment and soil treatment, or directly applied to plant foliage for crop protection [8].

However, it remains essential to continually explore novel neonicotinoid candidates because significant increases in resistance and cross-resistance have been observed in various insect species after frequent field applications. Nitromethylene analogue 6-Cl-PMNI {2-chloro-5-[(2-(nitromethylene)imidazolidin-1-yl) methyl]pyridine, 1} exhibits remarkably higher receptor binding activity [9, 10] compared with Imidacloprid; however, its use has been limited owing to its photoinstability [11] and weak hydrophobicity [12]. In recent years, a large amount of modification of the structures has been invested in the development of 6-Cl-PMNI. These modification strategies include the *cis*-neonicotinoids family by introducing a ring into the lead compound to fix the nitro moiety in the *cis* position [13]. It is well established that *trans*/*cis* isomers may differ significantly in biological activity, toxicity, and metabolic properties in medicinal chemistry. Dicyclic neonicotinoid analogue 3 containing a tetrahydro-pyrimidine ring was discovered by Bayer, in which the nitro group is in *cis* to the chloropyridinylmethyl moiety, and also showing high biological activity [14]. Li et al. developed a series of systematic studies on moderating the neonicotinoids with fused tetrahydropyridine 4 [15] and dihydropyrrole 5 [16], which exhibited satisfactory insecticidal activity, and LC_{50} value of 5 was tenfold higher than imidacloprid against the cowpea aphid, *Aphis craccivora*.

On the other hand, the trifluoromethyl group is a very important substituent in medicinal chemistry, due to its unique stereoelectronic properties, and usually increases the lipophilicity of a molecule [17]. In order to find the diversity of nitromethylene neonicotinoids with *cis* nitro configuration, we have designed a novel neonicotinoids family by introducing a dihydro-pyridine ring and trifluoromethyl group into the lead compound to fix the nitro moiety in the *cis* position (6 in Fig. 1). We expected that the new structure could not only overcome its photoinstability but also improve hydrophobicity by the trifluoromethyl group. This paper describes the synthesis and biological activities of a number of nitromethylene derivatives containing dihydro-pyridine and the trifluoromethyl group.

Experimental

All starting materials and reagents were commercially available and used without further purification otherwise stated. Melting points were obtained with a digital melting point WRS-1B (Shen Guang Instrument, Shanghai, China) and were uncorrected. ^{1}HNMR spectra were recorded on a Bruker Avaace III (400 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Elemental analyses were determined on a Yanaco MT-3CHN elemental analyzer. IR spectra were recorded on a PE Spectrum with dried KBr as the adjuvant. Analytical thin-

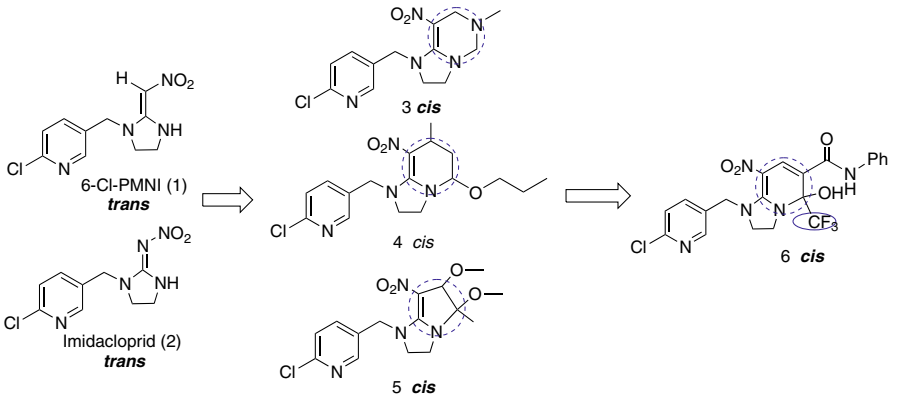


Fig. 1 Strategy to synthesis dihydro-pyridine-fused neonicotinoids with a trifluoromethyl group

layer chromatography (TLC) was carried out on precoated plates (silica gel GF254), and spots were visualized with ultraviolet (UV) light.

The activities of insecticidal compounds against *A. craccivora* were tested by the leaf-dip method. All bioassays were performed on representative test organisms reared in the laboratory. All compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted with distilled water containing Triton X-100 (0.1 mg/L) to obtain series concentrations of 500 and 100 mg/L and others for bioassays. For comparative purposes, imidacloprid was tested under the same conditions.

Horsebean plant leaves with 40–60 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg/L) for 5 s, and the excess dilution was sucked out with filter paper; the burgeons were placed in the conditioned room (25 ± 1 °C, 50 % RH). Water containing Triton X-100 (0.1 mg/L) was used as control. The mortality rates were evaluated 24 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis.

Synthetic procedures

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. The raw materials nine were synthesized according to the literature [18].

General synthetic procedure **6a–s**

6-Cl-PMNI (2.5 mmol), triethoxymethane (3 mmol) and 4,4,4-trifluoro-3- oxobutaneanilides (3 mmol) were placed into a 25 mL round-bottom flask and the mixture was refluxed. The resulting solution was stirred for 1–3 h, and the reaction progress was monitored by TLC. On completion of the reaction, the mixture was cooled to room temperature, and then a small amount of dichloromethane was added to

dissolve the mixture. The residue was purified by silica gel column chromatography to give the pure products.

Data for ***6a***

Yield, 85 %, Yellow solid; mp, 184–185 °C; ^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 8.34 (d, 1H, J = 1.6 Hz, Py–H), 8.11 (s, 1H), 7.80 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz, Py–H), 7.54 (s, 1H, Py–H), 7.53 (s, 1H, Ph–H), 7.35 (m, 3H, Ph–H), 7.17 (t, 1H, J = 7.2 Hz, Ph–H), 5.09 (d, 1H, J = 15.2 Hz, Py–CH_2), 4.42 (d, 1H, J = 15.2 Hz, Py–CH_2), 4.21–3.63 (m, 4H, N–CH_2–CH_2–N); IR (KBr) σ(cm^{-1}) : 3,270, 3,195, 3,133, 3,073, 2,893, 1,643, 1,545, 1,451, 1,347, 1,267, 1,177, 955, 755; Anal. Calcd for $C_{21}H_{17}ClF_3N_5O_4$: C, 50.87; H, 3.46; N, 14.12. Found: C, 50.97; H, 3.57; N, 14.23.

6b

Yield, 88 %, Yellow solid; mp, 148–149 °C; ^{1}H NMR ($CDCl_3$): δ 8.50 (s, 1H), 8.33 (d, 1H, J = 1.6 Hz, Py–H), 8.09 (s, 1H), 7.78 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz, Py–H), 7.39 (d, 2H, J = 8.4 Hz, Ph–H), 7.35 (d, 1H, J = 8.0 Hz, Ph–H), 7.13 (m, 2H, Ph–H), 5.08 (d, 1H, J = 15.2 Hz, Py–CH_2–), 4.41 (d, 1H, J = 15.2 Hz, Py–CH_2–), 4.16-3.62 (m, 4H, N–CH_2–CH_2–N), 2.32 (s, 3H, –CH_3); IR(KBr) σ (cm^{-1}): 3,281, 3,079, 2,905, 1,645, 1,547, 1,449, 1,253, 1,175, 815; Anal. Calcd for $C_{22}H_{19}ClF_3N_5O_4$: C, 51.82; H, 3.76; N, 11.18. Found: C, 51.94; H, 3.70; N, 11.23.

6c

Yield, 68 %, Yellow solid; mp, 164–165 °C; ^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1H), 8.34 (d, 1H, J = 1.6 Hz, Py–H), 8.08 (s, 1H), 7.79 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.0 Hz, Py–H), 7.44 (m, 2H, Ph–H), 7.38 (d, 1H, J = 8.8 Hz, Py–H), 6.86 (d, 2H, J = 8.8 Hz, Ph–H), 5.08 (d, 1H, J = 15.2 Hz, Py–CH_2–), 4.40 (d, 1H, J = 15.2 Hz, Py–CH_2–), 4.16–3.61 (m, 4H, N–CH_2–CH_2–N), 3.84 (s, 3H, –OCH_3); IR (KBr) σ(cm^{-1}): 3,285, 3,015, 2,979, 2,911, 1,647, 1,555, 1,457, 1,263, 1,173, 951, 779; Anal. Calcd for $C_{22}H_{19}ClF_3N_5O_5$: C, 50.25; H, 3.64; N, 13.32. Found: C, 50.43; H, 3.51; N, 13.23.

6d

Yield, 72 %, Yellow solid; mp, 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.34 (d, 1 H, J = 2.0 Hz, Py–H), 8.09 (s, 1H), 7.80 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, Py–H), 7.42 (d, 2H, J = 8.4 Hz, Ph–H), 7.36 (d, 1H, J = 8.4 Hz, Py–H), 7.16 (d, 2H, J = 8.4 Hz, Ph–H), 5.10 (d, 1 H, J = 15.2 Hz, Py–CH_2), 4.41 (d, 1 H, J = 15.6 Hz, Py–CH_2), 4.17–3.49 (m, 4H, N–CH_2–CH_2–N), 2.63 (m, 2H, Ph–CH_2), 1.23 (m, 3H, CH_3); IR (KBr) σ(cm^{-1}): 3,280, 3,062, 2,968, 2,826, 1,636, 1,566, 1,266, 1,176, 952, 828; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.97; H, 4.16; N, 13.57.

6e

Yield, 70 %, Yellow solid; mp, 176–177 °C; ^{1}H NMR ($CDCl_3$): δ 8.35 (d, 1H, $J = 2.4$ Hz, Py–H), 8.32 (s, 1H), 8.09 (s, 1H), 7.79 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, Py–H), 7.51 (m, 2H, Ph–H), 7.39 (d, 1H, $J = 8.4$ Hz, Py–H), 7.26 (m, 2H, Ph–H), 5.12 (d, 1H, $J = 15.2$ Hz, Py–CH_2–), 4.46 (d, 1H, $J = 15.6$ Hz, Py–CH_2–), 4.17–3.63 (m, 4H, –N–CH_2–CH_2–N–); IR(KBr) σ(cm^{-1}): 3,259, 3,199, 3,125, 3,061, 2,909, 1,641, 1,573, 1,539, 1,495, 1,251, 1,175, 955, 825; Anal. Calcd for $C_{21}H_{16}Cl_2F_3N_5O_4$: C, 47.56; H, 3.04; N, 13.21. Found: C, 47.73; H, 3.16; N, 13.37.

6f

Yield, 65 %, Yellow solid; mp, 149–150 °C; ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H), 8.38 (d, 1H, $J = 2.0$ Hz, Py–H), 8.24 (s, 1H, Py-H), 7.85 (dd, 1 H, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, Py–H), 7.48 (m, 1H, Ph–H), 7.14(m, 2H, Ph–H), 4.87 (d, 1H, $J = 16.0$ Hz, Py–CH_2), 4.64 (d, 1H, $J = 16.4$ Hz, Py–CH_2), 4.04–3.84 (m, 4H, N–CH_2–CH_2–N), 2.54 (t, 2H, $J = 7.6$ Hz), 1.52 (m, 2H, CH_2), 1.27 (m, 2H, CH_2), 0.89 (t, 3H, $J = 7.2$ Hz, CH_3); IR (KBr) σ (cm^{-1}): 3,291, 3,061, 2,921, 2,861, 1,633, 1,561, 1,353, 1,237, 1,169, 829; Anal. Calcd for $C_{25}H_{25}ClF_3N_5O_4$: C, 54.40; H, 4.57; N, 12.69. Found: C, 54.72; H, 4.34; N, 12.76.

6g

Yield, 86 %, Yellow solid; mp, 192–193 °C; ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H), 8.35 (d, 1H, $J = 2.0$ Hz, Py–H), 8.09 (s, 1H), 7.80 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 8.2$ Hz, Py–H), 7.51 (m, 2H, Ph–H), 7.37 (d, 1 H, $J = 8.4$ Hz, Py–H), 7.05 (m, 2H, Ph–H), 5.09 (d, 1H, $J = 15.6$ Hz, Py–CH_2), 4.43 (d, 1H, $J = 15.2$ Hz, Py–CH_2), (m, 4H, N–CH_2–CH_2–N); IR (KBr) σ(cm^{-1}): 3,263, 3,212, 3,057, 2,903, 1,637, 1,555, 1,513, 1,347, 1,245, 1,175, 959, 831; Anal. Calcd for $C_{21}H_{16}ClF_4N_5O_4$: C, 49.09; H, 3.14; N, 13.63. Found: C, 49.21; H, 3.98; N, 13.79.

6h

Yield, 73 %, Yellow solid; mp, 190–191 °C; ^{1}H NMR ($CDCl_3$): δ 10.18 (s, 1H), 9.82 (s, 1H), 8.38 (d, 1H, $J = 2.4$ Hz, Py–H), 8.23 (s, 1H), 7.85 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, Py–H), 7.54 (d, 1H, $J = 8.4$ Hz, Py–H), 7.49 (d, 2H, $J = 8.8$ Hz, Ph–H), 6.91 (m, 2H, Ph–H), 4.87 (d, 1H, $J = 16.4$ Hz, Py–CH_2–), 4.63 (d, 1H, $J = 16.0$ Hz, Py–CH_2–), 4.08–3.80 (m, 6H, N–CH_2–CH_2–N and –O–CH_2–), 1.31 (t, 3H, $J = 7.2$ Hz –CH_3). IR (KBr) σ (cm^{-1}) : 3,445, 3,275, 3,065, 2,979, 2,919, 1,629, 1,573, 1,505, 1,353, 1,237, 1,169, 837; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_5$: C, 51.17; H, 3.92; N, 12.97. Found: C, 51.37; H, 3.86; N, 13.05.

6i

Yield, 69 %, Yellow solid; mp, 202–203 °C; ^{1}H NMR ($CDCl_3$): δ 9.99 (s, 1H), 8.39 (s, 1H), 8.30 (s, 1H, Py–H), 7.86 (d, 1H, $J = 8.4$ Hz, Py–H), 7.84 (d, 1H,

J = 8.4 Hz, Py–H), 7.10 (s, 3H, Ph–H), 4.88 (d, 1H, J = 16.0 Hz, Py–CH_2), 4.56 (d, 1H, J = 16.4 Hz, Py–CH_2), 4.03-3.57 (m, 4H, N–CH_2–CH_2–N), 2.13 (s, 6H, CH_3); IR (KBr) σ (cm^{-1}): 3,295, 3,029, 2,975, 2,913, 1,647, 1,557, 1,469, 1,333, 1,267, 1,185, 959, 775; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.92; H, 3.93; N, 13.56.

6j

Yield, 73 %, Yellow solid; mp, 147–148 °C; ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H), 9.77 (s, 1H), 8.38 (d, 1H, J = 2.4 Hz, Py–H), 8.26 (s, 1H), 7.85 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, Py–H), 7.55 (d, 1H, J = 8.4 Hz, Py–H), 7.24 (s, 2H, Ph–H), 6.76 (s, 1H, Ph–H), 4.87 (d, 1H, J = 16.0 Hz, Py–CH_2–), 4.64 (d, 1H, J = 16.0 Hz, Py–CH_2–), 4.07–3.81 (m, 4H, –N–CH_2–CH_2–N–), 2.25 (s, 6H, –CH_3); IR (KBr) σ (cm^{-1}): 3,433, 3,316, 3,087, 2,919, 2,777, 1,677, 1,575, 1,517, 1,303, 1,217, 1,191, 951, 827; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.89; H, 4.01; N, 13.46.

6k

Yield, 78 %, Yellow solid; mp, 135–136 °C; ^{1}H NMR (DMSO–d_6): δ 8.83 (s, 1H), 8.41 (s, 1H), 8.38 (d, 1H, J = 2.4 Hz, Py–H), 8.17(s, 1H), 8.06 (m, 1H), 7.80 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, Py–H), 7.37 (d, 1H, J = 8.0 Hz, Py–H), 7.08 (m, 3H, Ph–H), 5.08 (d, 1H, J = 15.6 Hz, Py–CH_2–), 4.42 (d, 1H, J = 15.6 Hz, Py–CH_2–), 4.22–3.62 (m, 4H, N–CH_2–CH_2–N); IR (KBr) σ (cm^{-1}): 3,661, 3,361, 3,055, 2,893, 1,649, 1,533, 1,453, 1,313, 1,257, 1,179, 753; Anal. Calcd for $C_{21}H_{16}ClF_4N_5O_4$: C, 49.09; H, 3.14; N, 13.63. Found: C, 49.33; H, 3.04; N, 13.56.

6l

Yield, 68 %, Yellow solid; mp, 163–164 °C; ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 8.37 (d, 1H, J = 2.0 Hz, Py-H), 8.19 (d, 1H, J = 6.8 Hz, Ph-H), 8.10 (s, 1H), 7.85 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, Py-H), 7.40 (d, 1H, J = 8 Hz, Py-H), 7.11 (t, 1H, J = 8 Hz, Ph-H), 6.97 (t, 1H, J = 7.8 Hz, Ph-H), 6.90 (d, 1H, J = 8 Hz, Ph-H), 5.13 (d, 1H, J = 15.2 Hz, Py-CH_2-), 4.43 (d, 1H, J = 15.6 Hz, Py-CH_2-), 4.21-3.63 (m, 4H, -N-CH_2-CH_2-N-). IR (KBr) σ (cm^{-1}): 3,363, 3,099, 2,955, 2,835, 1,641, 1,551, 1,457, 1,223, 1,183, 1,019, 949, 755; Anal. Calcd for $C_{21}H_{16}Cl_2F_3N_5O_4$: C, 47.56; H, 3.04; N, 13.21. Found: C, 47.76; H, 3.11; N, 13.38.

6m

Yield, 73 %, Yellow solid; mp, 146–147 °C; ^{1}H NMR($CDCl_3$): δ 8.44 (s, 1H), 8.36 (d, 1H, J = 2.0 Hz, Py–H), 8.20 (dd, 1H, J_1 = 1.2 Hz, J_2 = 8.0 Hz, Py–H), 8.09 (s, 1H), 7.84 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.4 Hz, Py–H), 7.39 (d, 1H, J = 8.4 Hz, Ph–H), 7.11 (m, 1H, Ph–H), 6.97 (m, 2H, Ph–H), 5.10 (d, 1H, J = 15.6 Hz, Py–CH_2–), 4.42 (d, 1H, J = 15.2 Hz, Py–CH_2–), 4.19–3.62 (m, 4H, N–CH_2–CH_2–N), 3.96 (s, 3H, –OCH_3); IR (KBr) σ (cm^{-1}): 3,353, 3,079, 2,929, 2,843, 1,635, 1,547,

1,461, 1,325, 1,229, 1,189, 1,177, 1,109, 1,019, 951, 755; Anal. Calcd for $C_{22}H_{19}ClF_3N_5O_5$: C, 50.25; H, 3.64; N, 13.32. Found: C, 50.46; H, 3.57; N, 13.23.

6n

Yield, 77 %, Yellow solid; mp, 178–179 °C; ^{1}H NMR(DMSO–d_6): δ 9.99 (s, 1H), 9.79 (s, 1H), 8.34 (m, 3H), 7.82 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, Py–H), 7.55 (d, 1H, $J = 8.0$ Hz, Py–H), 6.93 (m, 1H, Ph–H), 4.89 (d, 1H, $J = 16.0$ Hz, Py–CH_2–), 4.72 (d, 1H, $J = 16.4$ Hz, Py–CH_2–), 4.12–3.86 (m, 6H, N–CH_2–CH_2–N and –O–CH_2–), 1.36 (t, 1H, J = 6.8 Hz, –CH_3); IR (KBr) σ (cm^{-1}): 3,446, 3,352, 3,066, 2,988, 2,930, 1,658, 1,534, 1,452, 1,348, 1,238, 1,194, 968, 750; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_5$: C, 51.17; H, 3.92; N, 12.97. Found: C, 51.26; H, 4.09; N, 13.23.

6o

Yield, 70 %, Yellow solid; mp, 183–184 °C; ^{1}H NMR (DMSO–d_6): δ 8.35 (d, 1H, $J = 2.0$ Hz, Py–H), 8.25 (s, 1H), 8.14 (s, 1H), 7.81 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.0$ Hz, Py–H), 7.36 (d, 1H, $J = 8.4$ Hz, Py–H), 7.27 (m, 2H, Ph–H), 7.07 (m, 2H, Ph–H), 5.06 (d, 1H, $J = 15.6$ Hz, Py–CH_2–), 4.42 (d, 1H, $J = 15.6$ Hz, Py–CH_2–), 4.20–3.62 (m, 4H, N–CH_2–CH_2–N), 2.27 (m, 3H, –CH_3), 2.10 (s, 3H, –CH_3). IR (KBr) σ (cm^{-1}): 3,383, 3,245, 3,069, 2,933, 1,645, 1,567, 1,451, 1,345, 1,255, 1,169, 949, 779; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.68; H, 4.14; N, 13.55.

6p

Yield, 73 %, Yellow solid; mp, 128–129 °C; ^{1}H NMR ($CDCl_3$): δ, 8.37 (d, 1H, $J = 2.4$ Hz, Py–H), 8.11 (s, 1H), 7.98 (s, 1H), 7.84 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, Py–H), 7.39 (d, 1H, $J = 8.4$ Hz, Py–H), 7.34 (d, 1H, $J = 7.6$ Hz, Py–H), 7.01 (d, 2H, $J = 8.4$ Hz, Ph–H), 5.08 (d, 1H, $J = 15.6$ Hz, Py–CH_2), 4.45 (d, 1H, $J = 15.6$ Hz, Py–CH_2), 4.18– 3.89 (m, 4H, N–CH_2–CH_2–N), 2.31 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). IR (KBr) σ (cm^{-1}): 3,400, 3,242, 2,952, 1,652, 1,560, 1,530, 1,458, 1,266, 1,174, 820, 742, 646; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.93; H, 3.93; N, 13.45.

6q

Yield, 65 %, Yellow solid; mp, 182–183 °C; ^{1}H NMR ($CDCl_3$): δ 10.06 (s, 1H), 9.82 (s, 1H), 8.39 (d, 1H, $J = 2.4$ Hz, Py–H), 8.38 (s, 1H), 7.85 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 8.4$ Hz, Py–H), 7.59 (s, 1H, Ph–H), 7.57 (d, 1H, $J = 8.0$ Hz, Py–H), 7.10 (d, 1H, $J = 3.6$ Hz, Ph–H), 6.90 (d, 1H, $J = 7.2$ Hz, Ph–H), 4.89 (d, 1H, $J = 16$ Hz, Py–CH_2–), 4.66 (d, 1H, $J = 16.0$ Hz, Py–CH_2–), 4.08–3.81 (m, 4H, –N–CH_2–CH_2–N–), 2.26 (s, 3H, –CH_3), 2.15 (s, 3H, –CH_3). IR (KBr) σ (cm^{-1}) : 3,241, 3,083, 3,013, 2,943, 2,921, 2,857, 1,651, 1,567, 1,343, 1,275, 1,177, 1,001, 807; Anal. Calcd for $C_{23}H_{21}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.89; H, 4.23; N, 13.49.

6r

Yield, 80 %, Yellow solid; mp, 185–186 °C; ^{1}H NMR ($CDCl_3$): δ 9.98 (s, 1H), 9.94 (s, 1H), 8.41 (d, 1H, J = 2.0 Hz, Py–H), 8.31 (s, 1H), 7.89 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.2 Hz, Py–H), 7.56 (d, 1H, J = 8.4 Hz, Py–H), 6.91 (s, 2H, Ph–H), 4.89 (d, 1H, J = 16.0 Hz, Py–CH_2), 4.57 (d, 1H, J = 16.4 Hz, Py–CH_2), 4.06–3.81 (m, 4H, N–CH_2–CH_2–N), 2.11 (s, 3H, CH_3), 2.10 (s, 6H, CH_3). IR (KBr) σ (cm^{-1}) : 3,211, 2,977, 2,917, 2,871, 1,645, 1,563, 1,507, 1,337, 1,247, 1,173, 1,011, 955, 735; Anal. Calcd for $C_{24}H_{23}ClF_3N_5O_4$: C, 52.73; H, 4.04; N, 13.37. Found: C, 52.86; H, 4.11; N, 13.48.

6s

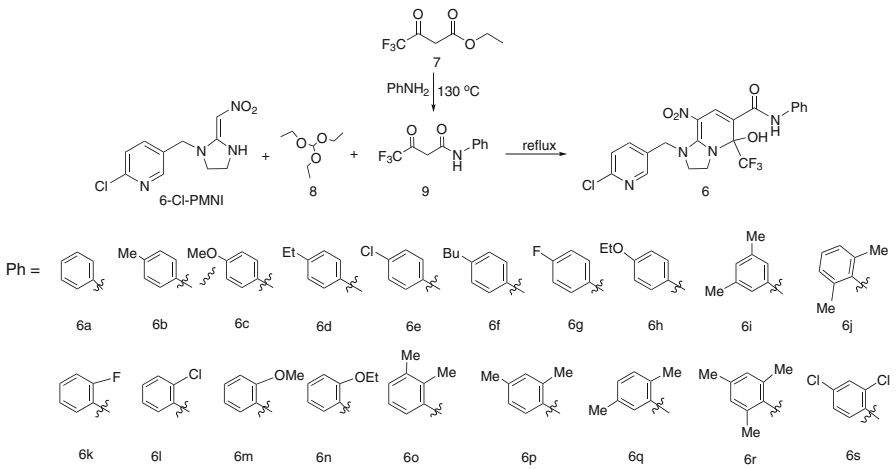
Yield, 85 %, Yellow solid; mp, 146–147 °C; ^{1}H NMR (DMSO–d_6): δ 10.10 (s, 1H), 9.96 (s, 1H), 8.37 (m, 3H), 7.83 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, Py–H), 7.71 (d, 1H, J = 2.4 Hz, Ph–H), 7.55 (d, 1H, J = 8.0 Hz, Py–H), 7.45 (dd, 1H, J_1 = 2.8 Hz, J_2 = 9.2 Hz, Ph–H), 4.89 (d, 1H, J = 16.0 Hz, Py–CH_2–), 4.70 (d, 1H, J = 16.4 Hz, Py–CH_2–), 4.12–3.86 (m, 4H, N–CH_2–CH_2–N). IR (KBr) σ (cm^{-1}): 3,453, 3,329, 3,085, 2,925, 2,845, 1,677, 1,577, 1,427, 1,465, 1,303, 1,215, 1,183, 827. Anal. Calcd for $C_{21}H_{15}Cl_3F_3N_5O_4$: C, 44.66; H, 2.68; N, 12.40. Found: C, 44.59; H, 2.77; N, 12.56.

Results and discussion

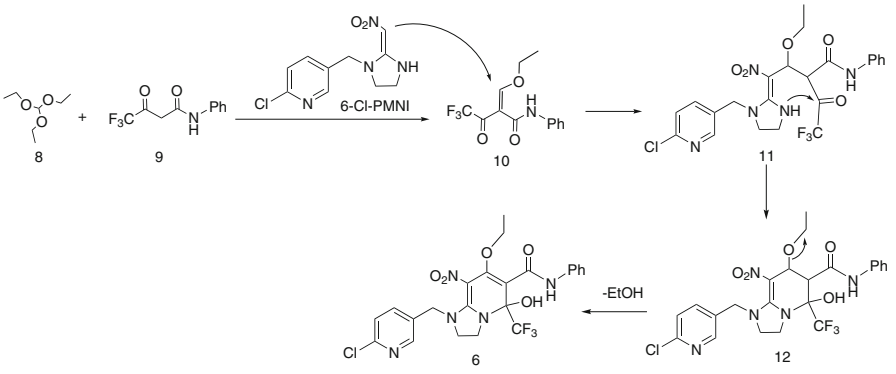
Synthesis

Starting from ethyl 4,4,4-trifluoro-3-oxobutanoate (7), condensates with anilines afforded the corresponding intermediate 4,4,4-trifluoro-3-oxobutaneanilides (9) according to reported methods [16]. The title compounds (6) were prepared in 65–88 % yield by reacting 6-Cl-PMNI, triethoxymethane and 4,4,4-trifluoro-3-oxobutaneanilides (9) in one-pot, under solvent-free and catalyst-free conditions. Trifluoromethyl group plays an important role as an electron-withdrawing group in enhancing the reaction activity of compound 9. If the trifluoromethyl group was replaced by a methyl group, the expected compound was not found in the reaction process. This method offered several advantages, such as short reaction time, relatively good yield and simple post-processing. The synthetic route is illustrated in Scheme 1, and their structures were confirmed by ^{1}H NMR, IR and elemental analyses.

The plausible mechanism was presumed in Scheme 2. The assembly of 6 can be explained via the initial Michael addition of 10 to the ylidenic bond in 1, leading to the formation of an acyclic intermediate 11, which cyclized into the intermediate 12 via nucleophilic attack of an NH group on a carbonyl carbon. Then, intermediate 12 removed the ethanol to give the final product 6. The formation of 10 is via the condensation reaction of triethoxymethane 8 and appropriate 4,4,4-trifluoro-3-oxobutaneanilides 9.



Scheme 1 General synthetic route for title compounds **6**



Scheme 2 Presumed mechanism for the multicomponent reaction

To verify the structure of the product dihydro-pyridine, 6 was selected as a representative compound and characterized by X-ray crystallography as shown in Fig. 2.

Insecticidal activities

Insecticidal activities of compounds 6 against *Aphis craccivora* are shown in Table 1. In general, most of the compounds showed moderate insecticidal activity at 500 mg/L. The insecticidal activities of compounds **6f**, **6j**, and **6k** displayed >90 % at 500 mg/L, and showed >50 % at 100 mg/L. The insecticidal activity of compounds **6i**, **6l**, **6m**, **6n**, **6o**, and **6p** were over 70 % at 500 mg/L.

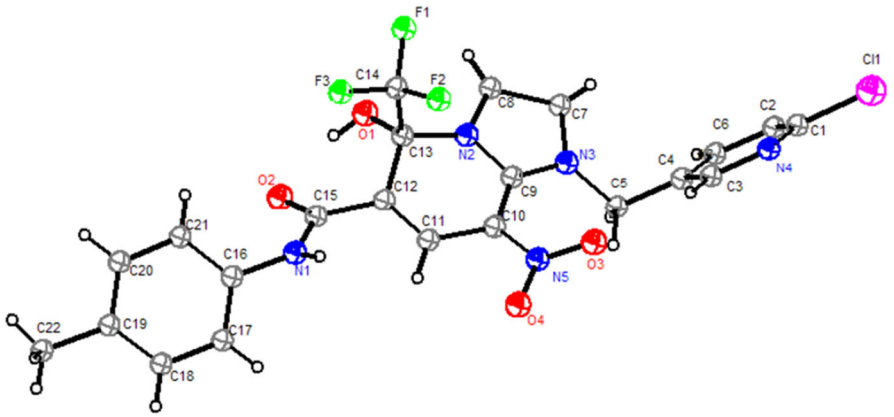


Fig. 2 Crystal structures of compound **6b**

Table 1 Insecticidal activity results of the synthetic compounds **6a–s**

Compounds	–Ph	Mortality (%)	
		500 mg/L^{-1}	100 mg/L^{-1}
6a	Aniline	15	nt[a]
6b	4-CH_3-aniline	35	nt
6c	4-OCH_3-aniline	32	nt
6d	4-Et-aniline	41	nt
6e	4-Cl-aniline	10	nt
6f	4-Bu-aniline	93	56
6g	4-F-aniline	18	nt
6h	4-OEt-aniline	32	nt
6i	2,6-Dimethylaniline	88	20
6j	3,5-Dimethylaniline	92	62
6k	2-F-Aniline	91	51
6l	2-Cl-Aniline	76	nt
6m	2-OCH_3-Aniline	79	nt
6n	2-OEt-Aniline	65	nt
6o	2,3-Dimethylaniline	83	26
6p	2,4-Dimethylaniline	70	nt
6q	2,5-Dimethylaniline	33	nt
6r	2,4,6-Trimethylaniline	45	nt
6s	2,4-Dichloroaniline	56	nt

[a] Not tested

Conclusions

To summarize, we have achieved the one-pot, three-component synthesis of a highly functional dihydro-pyridine ring and containing a trifluoromethyl group under solvent-free and catalyst-free conditions. The trifluoromethyl group plays an important role as an electron-withdrawing group in enhancing the reaction activity of compound 9. Bioassays indicated that most of the synthesized compounds exhibited moderate insecticidal activities against *A. craccivora*.

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