Preliminary Communication

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Design and synthesis of heterocyclic enamine derivatives based on skeleton of neonicotinoids

Abstract: Novel heterocyclic enamine derivatives based on skeleton of neonicotinoids were designed and prepared by the substitution reaction between heterocyclic enamines with intermediates of neonicotinoids, which provides readily accessible neonicotinoid analogs for potential bioactivity assay.

Keywords: heterocyclic enamines; neonicotinoids; synthesis.

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The design and synthesis of novel neonicotinoids (Jepson et al., 2006; Kagabu et al., 2007) for crop protection and pet hygiene have received considerable attention in pesticide chemistry because neonicotinoids have taken the main share of the insecticidal market (in 2009, $2.632 billion USD) and have been used for insect control worldwide (Ohno et al., 2009; Jeschke et al., 2011).

Compared to organophosphorus, carbamate, and pyrethroid compounds, the lead compound imidacloprid as the fourth generation of insecticide has attracted great attention for searching novel neonicotinoid analogs. Many groups have reported the results on synthesis of imidacloprid derivatives and their potential modes of biological action (Wang et al., 2007; Shao et al., 2011). In this communication, we report a novel design and synthetic method for neonicotinoid derivatives through reactions of heterocyclic enamines with neonicotinoids intermediates (Figure 1).

The detailed synthesis routes are shown in Schemes 1 and 2. The squaric acid motif was introduced into neonicotinoid through bioisosteres replacement of nitro guanidine (Butera et al., 2000), and the target compounds **T1** and **T2** with chloropyridine and chlorothiazol fragment were designed and synthesized with high yields under mild condition. The heterocyclic enamines with an electron-withdrawing group such as pyridazinone, meldrum's acid and pyrazole substituted with a nitrile group were introduced into the skeleton of neonicotinoid (Samaritoni et al., 2003). New neonicotinoid derivates **T3–T6** were designed and synthesized by using these intermediate products. We are currently studying the potential bioactivity of the synthesized compounds.

Experimental section

Commercial reagents **1**, **3**, **4, 9–11** were used without further purification. Solvents were treated prior to use according to standard methods. Compounds **7** and **8** were prepared as previously reported (Moury, 1953; Cheikh et al., 1991). Melting points were taken on a micro-melting point apparatus made in Beijing and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (400 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr disks using a Nicolet FT-IR-20SX instrument. High resolution mass spectra were obtained on a MicroMass GCT CA 055 spectrometer. Analytical thin layer chromatography (TLC) was carried out on precoated plates (silica gel 60_{F254}), and spots were visualized with ultraviolet light.

3,4-Diethoxycyclobut-3-ene-1,2-dione (2) A mixture of squaric acid (1.25 g, 0.01 mol), ethanol (50 mL), and benzene (20 mL) was heated under reflux for 10 h, and then concentrated to afford crude compound **2** as an oil (Zhou et al., 2001) (yield 1.27 g, 75%); GC-MS: m/z 170 $[M]^+$, 142, 113, 85, 68, 58, 29.

***N*1-((6-Chloropyridin-3-yl)methyl)ethane-1,2-diamine (5)** A solution of ethane-1,2-diamine (6.06 g, 100 mmol) in acetonitrile (30 mL) was dropwise added over a period of 30 min to a solution of 2-chloro-5-(chloromethyl)pyridine (**3**) (3.24 g, 20 mmol) in 30 mL of acetonitrile. After 8 h of stirring, the solution was treated with 100 mL of water, and extracted with chloroform (3×30 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford compound **5** as a yellow liquid (Kagabu et al., 1992), which was directly used in the next step (yield 3.34 g, 90%); GC-MS: m/z 185 $[M]^+$, 155, 126, 99, 90.

***N*1-((2-Chlorothiazol-4-yl)methyl)ethane-1,2-diamine (6)** A mixture of ethane-1,2-diamine (6.25 mL, 75 mmol) and K_2CO_3 (2.07 g, 0.015 mol) was cooled to 0°C and dropwise added over a period of 30 min to a solution of 2-chloro-4-(chloromethyl)thiazole (**4**) (2.50 g, 15 mmol) in 30 mL of acetonitrile. After 8 h of stirring, the solution

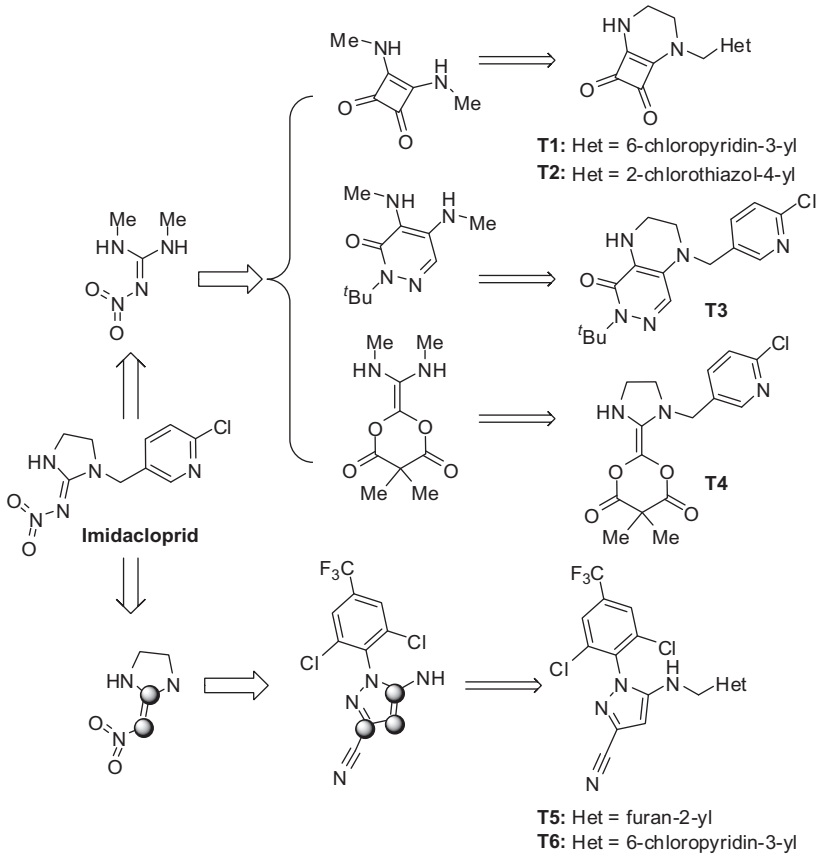


Figure 1 The designed target compounds **T1–T6**.

was treated with 100 mL of water, and the mixture was extracted with chloroform (3×30 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford compound **6** as a yellow liquid, which was directly used in the next step (yield 1.95 g, 68%); GC-MS: m/z 191 $[M]^+$, 155, 126, 73, 56.

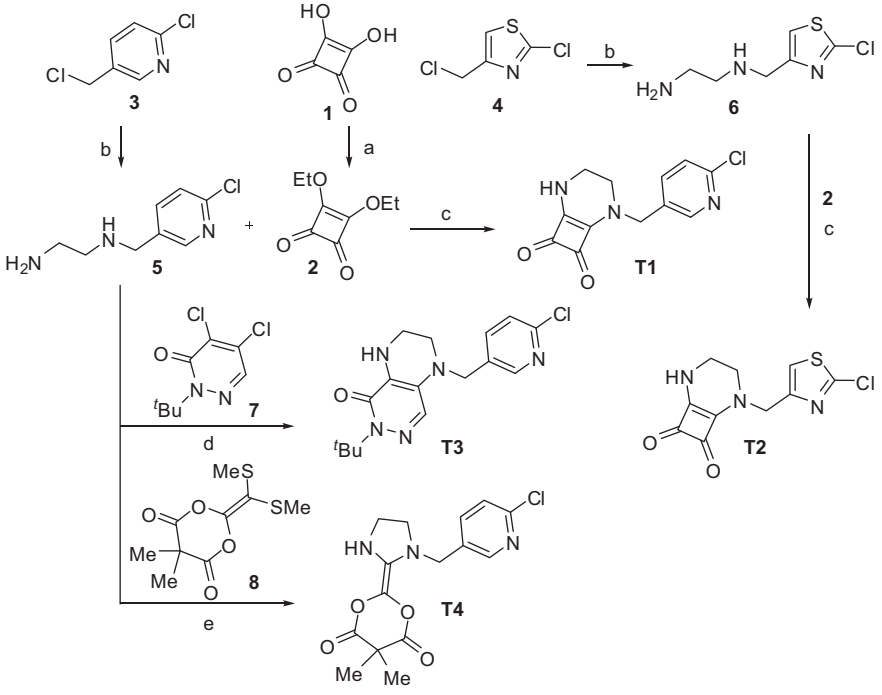
(*E*)-1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-5-(furan-2-ylmethyleneamino)-1*H*-pyrazole-3-carbonitrile (12) A solution of 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl-1*H*-pyrazole-3-carbonitrile (**9**) (3.20 g, 0.01 mol), furan-2-carbaldehyde (**10**) (1.44 g, 0.015 mol) and three drops of HCl was heated under reflux and the progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate, 8:1). The mixture was cooled to room temperature and the precipitate was collected, dried, and crystallized from ethanol to give pure product **12**; GC-MS: m/z 398 $[M]^+$, 379, 363, 213, 178, 106, 52.

(*E*)-5-((6-Chloropyridin-3-yl)methyleneamino)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (13) The procedure was similar to that described above for **12**; GC-MS: m/z 443 $[M]^+$, 424, 408, 372, 356, 281, 207, 178, 151, 124, 90, 63; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H, CH), 7.41 (d, *J* = 8 Hz, 1H, Pyridine-CH), 7.78 (s, 2H, ArH), 8.00 (dd, J_1 = 2 Hz, J_2 = 8 Hz 1H, Pyridine-CH), 8.70 (d, *J* = 2 Hz, 1H, Pyridine-CH), 8.72 (s, 1H, CH = N).

2-((6-Chloropyridin-3-yl)methyl)-2,5-diaza-bicyclo[4.2.0]oct-1(6)-ene-7,8-dione (T1) A solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (**2**) (0.17 g, 1 mmol) and *N*1-((6-chloropyridin-3-yl)methyl) ethane-1,2-diamine (**5**) (0.185 g, 1 mmol) in 20 mL of ethanol was heated under reflux for 6 h. The solution was concentrated and the residue was purified by silica gel chromatography to afford **T1** as a white solid (yield 0.16 g, 60%); mp 177.7–178.4°C; IR (KBr): ν 3200, 2940, 1784, 1665, 1053, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29 (t, *J* = 5 Hz, 2H, CH_2), 3.60 (t, *J* = 5 Hz, 2H, CH_2), 4.67 (s, 2H, CH_2), 6.98 (s, 1H, NH), 7.38 (d, *J* = 8 Hz, 1H, pyridine-H), 7.73 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H, pyridine-H), 8.36 (d, *J* = 3 Hz, 1H, pyridine-H); EIMS: m/z 263 $[M]^+$ (28), 234 (37), 219 (44), 206 (100), 172 (33), 126 (50), 98 (21), 90 (26), 72 (22), 63 (17), 56 (16), 53 (14); HRMS: Calcd for $C_{22}H_{14}N_5F_3Cl_2$ m/z 263.0462, found m/z 263.0455.

2-((2-Chlorothiazol-4-yl)methyl)-2,5-diaza-bicyclo[4.2.0]oct-1(6)-ene-7,8-dione (T2) A solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (**2**) (0.17 g, 1 mmol) and *N*1-((2-chlorothiazol-4-yl)methyl) ethane-1,2-diamine (**6**) (0.199 g, 1 mmol) in 20 mL of ethanol was heated under reflux for 6 h. The solution was concentrated and the residue was purified by silica gel chromatography to afford **T2** as a white solid (yield 0.18 g, 65%); mp 165.0–165.5°C; IR (KBr): ν 3200, 2940, 1784, 1665, 1053, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (t, *J* = 5 Hz, 2H, CH_2), 3.62 (t, *J* = 4 Hz, 2H, CH_2), 4.83 (s, 2H, CH_2), 7.02 (s, 1H, NH), 7.53 (s, 1H, thiazol-H); EIMS: m/z 269 $[M]^+$ (16), 234 (100), 206 (100), 172 (35), 178 (37), 152 (24), 131 (29), 80 (7), 70 (8), 56 (6); HRMS: Calcd for $C_{10}H_8N_3O_2SCl$ m/z 269.0026, found m/z 269.0026.

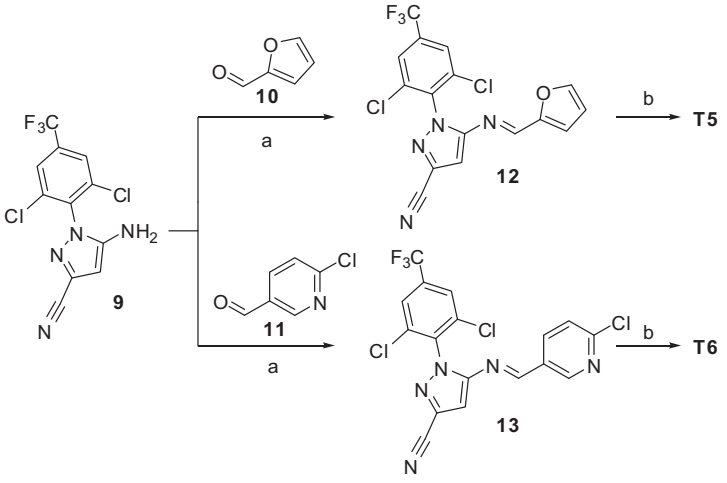
6-*tert*-Butyl-1-((6-chloropyridin-3-yl)methyl)-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazin-5(6*H*)-one (T3) A solution of



Scheme 1 Reagents and conditions: (a) C_2H_5OH, reflux; (b) $NH_2CH_2CH_2NH_2$, CH_3CN; (c) C_2H_5OH, reflux; (d) DMF/K_2CO_3, reflux; (e) C_2H_5OH, reflux.

2-*tert*-butyl-4,5-dichloropyridazin-3(2*H*)-one (7) (0.22 g, 1 mmol), *N*1-((6-chloropyridin-3-yl)methyl)ethane-1,2-diamine (**5**) (0.19 g, 1 mmol) and a catalytic amount of K_2CO_3 in 20 mL DMF was refluxed for 8 h. The solution was concentrated and the residue was purified by silica gel chromatography to afford **T3** as a white solid (yield 0.17 g, 52%); mp 112.5–112.9°C; IR (KBr): ν 3429, 3303, 2896, 1621, 1419, 1205, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, $C(CH_3)_3$), 2.96 (t, *J* = 5 Hz, 2H, CH_2), 3.40 (d, *J* = 5 Hz, 2H, CH_2), 3.85 (s, 2H, CH_2), 5.24 (s, 1H, NH), 7.32 (d, *J* = 8 Hz, 1H, pyridine-H), 7.53 (s, 1H, CH = N), 7.73 (d, *J* = 8 Hz, 1H, pyridine-H), 8.34 (d, *J* = 2 Hz, 1H, pyridine-H); EIMS: m/z 333 $[M]^+$ (5.01), 278 (6.88), 234 (7.01), 215 (28.82), 159 (100), 126 (41.11), 124 (3.82), 90 (3.37); HRMS: Calcd for $C_{16}H_{20}N_5OCl$: 333.1356. Found: 333.1435.

2-(1-((6-Chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-5,5-dimethyl-1,3-dioxane-4,6-dione (T4) A solution of 2-(bis (methylthio)methylene)-5,5-dimethyl-1,3-dioxane-4,6-dione (**8**) (0.25 g, 1 mmol), *N*1-((6-chloropyridin-3-yl)methyl)ethane-1,2-diamine (**5**) (0.19 g, 1 mmol) and a catalytic amount of K_2CO_3 in 20 mL of DMF was heated under reflux for 8 h. The solution was concentrated and the residue was purified by silica gel chromatography to afford **T4** as a white solid (yield 0.14 g, 42%), mp 213.3–214.3°C; IR (KBr): ν 3311, 2985, 1691, 1654, 1547, 1394, 1198, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 6H, $C(CH_3)_2$), 3.66 (t, *J* = 10 Hz, 2H, CH_2), 3.81 (d, *J* = 9 Hz, 2H, CH_2), 4.71 (s, 2H, CH_2), 7.36 (d, *J* = 8 Hz, 1H, pyridine-H), 7.88 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H, pyridine-H), 8.34 (d, *J* = 2 Hz, 1H, pyridine-H), 9.08 (s, 1H, NH); EIMS: m/z 337 $[M]^+$, 279 (72), 261 (100), 234 (21), 209 (38),



Scheme 2 Reagents and conditions: (a) C_2H_5OH, cat. HCl, reflux; (b) $NaBH_4$, C_2H_5OH, rt, 6 h.

167 (8), 153 (7), 126 (53), 99 (7), 58 (10), 55 (19), 43 (26); HRMS: Calcd for $C_{22}H_{14}N_5F_3Cl_2$ m/z 337.0829, found m/z 337.0829.

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-5-(furan-2-ylmethylamino)-1*H*-pyrazole-3-carbonitrile (T5) A solution of (*E*)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5-(furan-2-ylmethyleneamino)-1*H*-pyrazole-3-carbonitrile (**12**) (0.40 g, 1 mmol) in 10 mL of ethanol was treated with sodium borohydride (0.06 g, 1.5 mmol), and the mixture was stirred for 6 h at room temperature. The mixture was concentrated and the precipitate was collected, dried, and crystallized from ethanol to give pure product **T5** (yield 0.32 g, 82%), mp 151.7–152.4°C; IR (KBr): ν 3348, 2925, 2244, 1580, 1313, 1209, 882, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (t, 1H, *J* = 3 Hz, CH), 4.29 (d, *J* = 6 Hz, 2H, CH_2), 6.00 (s, 1H, CH), 6.26 (d, *J* = 3 Hz, 1H, CH), 6.34 (d, *J* = 3 Hz, 1H, CH), 7.37 (s, 1H, NH), 7.78 (s, 2H, ArH); EIMS: m/z 400 $[M]^+$ (9), 363 (5), 212 (5), 82 (6), 81 (100), 53 (7); HRMS: Calcd for $C_{22}H_{14}N_5F_3Cl_2$ m/z 400.0106, found m/z 400.0103.

5-((6-Chloropyridin-3-yl)methylamino)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (T6) A solution of (*E*)-5-((6-chloropyridin-3-yl)methyleneamino)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (**13**) (0.44 g, 1 mmol) in 10 mL of ethanol was treated with sodium borohydride (0.06 g, 1.5 mmol), and the mixture was stirred for 6 h at room temperature. The mixture was concentrated and the precipitate was collected, dried, and crystallized from ethanol to give pure product **T6** (yield 0.35 g, 80%), mp 229.1–229.6°C; IR (KBr): ν 3214, 2251, 1591, 1305, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 1H, NH), 4.35 (d, *J* = 6 Hz, 2H, CH_2), 5.88 (s, 1H, CH), 7.33 (d, *J* = 8 Hz, 1H, Pyridine-H), 7.60 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H, Pyridine-H), 7.79 (s, 2H, ArH), 8.34 (d, *J* = 2 Hz, 1H, Pyridine-H); EIMS: 445 m/z $[M]^+$ (43), 408 (4), 213 (9), 178 (2), 126 (100), 90 (9), 72 (4), 63 (2); HRMS: Calcd for $C_{22}H_{14}N_5F_3Cl_2$ m/z 444.9876, found m/z 444.9870.

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