Synthesis and bioactivities of novel neonicotinoids dioxolane compounds

Zhongzhen Tian, Zhong Li*, Qingchun Huang, Xiaoyong Xu, Tao Yu, Yingli Wu and Xuhong Qian*

Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai 200237, China

As candidates for the screening of neonicotinoid insecticides, nine novel compounds were designed and synthesised *via* Mannich reaction of (1,3-dioxolane-4-yl)methyl-2-(nitromethylene) imidazoline with corresponding primary amines and formaldehyde. Preliminary bioassays indicated that most of these compounds had moderate insecticidal activities against *pea aphids*.

Keywords: neonicotinoid, dioxolane, synthesis, bioactivities

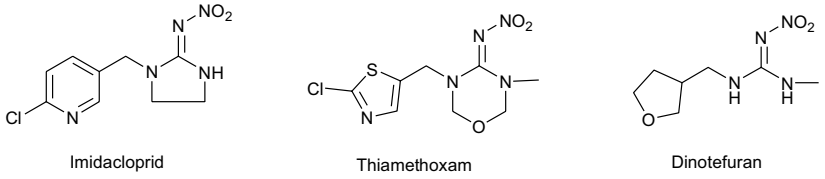
Since the debut of Imidacloprid® in the 1990 s,[1] neonicotinoid insecticides have become rapidly the important chemical class of insecticides. Neonicotinoid insecticides are characterised by persistent effects, broad spectra, good systemic properties and low toxicity to mammals and aquatic life.[2,3] Hence, the development of neonicotinoid insecticides has been a promising area in the innovation of new pesticides.[4,5]

Investigations in this search involved the modification of the heterocyclic substructures. On the one hand, based on the pyridine ring in Imidacloprid®, a variety of alternative scaffolds have been found to be practicable, for example thiazole ring in Thiamethoxam® and tetrahydrofuran ring in Dinotefuran® (Scheme 1).[6,7] On the other hand, as indicated by previous studies, the nitrogen atom in pyridine and thiazole ring, and the oxygen atom in tetrahydrofuran ring played very important role in their bioactivities.[8] So it implied that the introduction of heteroatom into the heterocycle will remarkably influence the activities of target compounds. Herein we report our results in the design and synthesis of a serial of new pesticide-like compounds with dioxolane ring. In these compounds, the tetrahydrofuran ring in Dinotofuran® was replaced by a dioxolane ring. Their structures were characterised by IR, ^{1}H NMR and HRMS. Preliminary bioassays indicated that most of the new compounds had moderate insecticidal activities against *pea aphids*.

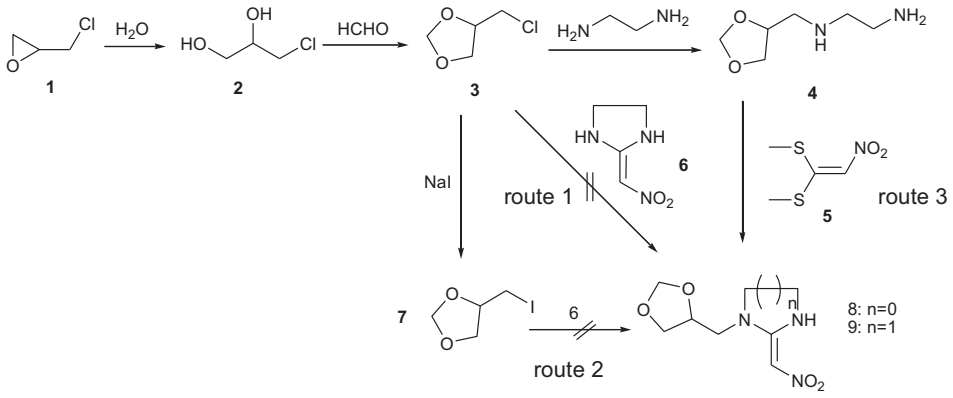
Initially, the 3-chloropropane-1,2-diol **2** was prepared by heating epoxychloropropane **1** with water in the presence of *p*-TsOH (Scheme 2), which reacted subsequently with paraformaldehyde, water and concentrated sulfuric acid to obtain **3** in 71% overall yield.

We had attempted to prepare 1-[(1,3-dioxolane-4-yl)methyl]-2-(nitromethylene)imidazoline **8** by the reaction of 4-(chloromethyl)-1,3-dioxolane **3** with 2-(nitromethylene) imidazolidine **6** under strongly basic conditions (NaH); however, the desired **8** could not be obtained through route 1. Thus, a more reactive intermediate, 4-(iodomethyl)-1,3-dioxolane **7**, was employed in our investigation. Unfortunately, it also led to negative results in route **2**.

Finally, the route 3 was chosen and gave satisfactory yields of desired products. Compound **3** reacted with ethylenediamine to afford *N*′-(1,3-dioxolane-4-yl)methyl-1,2-ethanediamine **4**. 1,1-bis(thiomethyl)-2-nitroethylene **5** was prepared from nitromethane, carbon disulfide and iodomethane in 70% yield followed a literature procedure.[11] The key intermediate **8** was thus obtained by refluxing **4** and **5**. The desired products (**10a–f**) were obtained by stirring compound **8** with primary amine and formaldehyde in THF. Similarly, compound **9** was synthesised by the method described above. The structures of all of the products were confirmed by ^{1}H NMR, HRMS and IR.

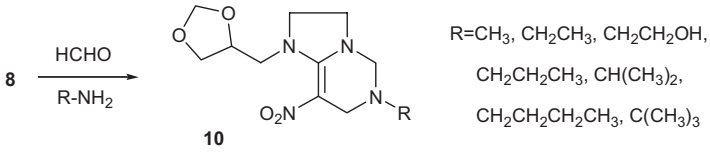


Scheme 1



Scheme 2

* Correspondent. E-mail: xhqian@ecust.edu.cn



Scheme 3

Table 1 Insecticidal activities for new compounds **8**, **9** and **10a–g**

Compound no.	–R	Concentration (mg/l)	Mortality (%) against *Pea aphids*
8	–	500	56.9
9	–	500	55.6
10a	$-CH_3$	500	35.5
10b	$-CH_2CH_3$	500	44.3
10c	$-CH_2CH_2OH$	500	8.2
10d	$-CH_2CH_2CH_3$	500	0
10e	$-CH(CH_3)_2$	500	54.2
10f	$-CH_2CH_2CH_2CH_3$	500	15.1
10g	$-C(CH_3)_3$	500	44.6

The insecticidal activities of the title compounds **8**, **9** and **10a–g** were tested and the results were listed in Table 1. The preliminary bioassays showed that some of the title compounds exhibited only moderate activities against pea aphids (*Aphis Laburni* Kaltenbach, a pest of pea) in 500 mg/l compared with that of imidacloprid. The LC_{50} of imidacloprid is 10 mg/l according to our experimental result.

Experimental

Melting points (m.p.) were obtained with Büchi Melting Point B540 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. IR spectra were measured on a Nicolet FT-IR-20SX instrument in potassium bromide (KBr) disk Mass spectra were recorded under electro-spray-impact conditions using a LCT KC317 instrument. All chemicals or reagents were purchased from standard commercial supplies.

3-chloropropane-1,2-diol (**2**): A mixture of epoxychloropropane (0.26 mol, 20 ml) in water (20 ml), and toluene-*p*-sulfonic acid (0.1 g) was added. The mixture was heated under reflux for 6 h, and water and epoxychloropropane were removed by distillation under reduced pressure. The residue was distilled and 26 g of the colourless liquid was obtained (91%). b.p. 114–116°C (16 mmHg) (lit. ref.[9] b.p. 119–122°C (18 mmHg)).

4-(chloromethyl)-1,3-dioxolane (**3**): A solution of Paraformaldehyde (16.7 g, 0.18 mol) in water (13 ml), concentrated H_2SO_4 (2.38 ml) was added. The mixture was heated with stirring and the distillate (often heterogeneous) was collected until the still head temperature reached 100°C. The distillate, which contains cyclic formal and water, was saturated with K_2CO_3, the organic phase separated, and the aqueous layer extracted with diethyl ether (*ca* two 2-ml portions for a 1-mol scale reaction). The combined organic phases were dried (K_2CO_3), the diethyl ether removed by distillation, and the residue was distilled. Yield 78%. b.p. 146–148°C (760 mmHg) (lit. ref.[10]. b.p. 146–147°C (745 mmHg)).GC-MS *m/z* (%): 122 (M^+, 63), 73 (100), 57 (18).

N'-(1,3-dioxolane-4-yl)methyl-1,2-ethanediamine (**4**): A solution of compound 3 (6.13 g, 50 mmol), ethylenediamine (3.01 g, 50 mmol) and K_2CO_3 (6.91 g, 50 mmol) in 60 ml ethanol was heated under reflux for 40 h, then cooled to room temperature and added to 100 ml water. The solution was extracted three times with dichloromethane. The extract was dried (Na_2SO_4) and concentrated to give 4.2 g as an oil. The residue was used for further operations without purification.

1,1-bis(thiomethyl)-2-nitroethylene (**5**): To a solution of 40 g (0.65 mol) of nitromethane in EtOH (100 ml) was added 60 ml (1 mol) of carbon disulfide. A solution of KOH (80 g, 1.42 mol) in EtOH (400 ml) was added dropwise to the reaction mixture at 308K. Stirring was continued for 30 min at room temperature. The red precipitate was filtered and washed with EtOH and Et_2O. The crude product (87.2 g, yield 62%) was used without purification. This salt (42 g, 0.2 mol) was dissolved in DMF (200 ml), 65.8 g (0.46 mol) of iodomethane was added dropwise. The reaction mixture was stirred at room temperature for 1 h, and then water (1.2 l) was added, and the formed precipitate was collected by filtration, washed with H_2O, and dried under reduced pressure. Yield: 72%. m.p. 125.2–126.1°C (lit. ref.[11]. m.p. 126°C). GC–MS *m/z* (%): 165 (M^+, 31), 148 (17), 104 (66), 86 (100), 72 (93), 57 (20).

1-[(1,3-dioxolan-4-yl)methyl]-2-(nitromethylene)imidazoline (**8**): A solution of 4.2 g of compound 4 and 4.7 g (29 mmol) of compound 5 in 50 ml ethanol was heated under reflux for 8 h, then cooled to room temperature. The mixture was evaporated under reduced pressure. The resulting oil was purified by flash chromatography (dichloromethane-methanol, 95: 5). A pale yellow solid was obtained. Yield: 64%. m.p. 129.9–131.5°C; ^{1}H NMR ($CDCl_3$) δ: 3.19–3.23 (m, 1H), 3.34 (d, 1H, J = 14.7 Hz), 3.62 (m, 1H), 3.78–3.81 (m, 3H), 3.87 (d, 1H, J = 8.9 Hz), 3.98–4.01 (m, 1H), 4.26 (br s, 1H), 4.85 (s, 1H, OCH_2O), 5.09 (s, 1H, OCH_2O), 6.56 (s, 1H, $CHNO_2$), 8.71 (br s, 1H, NH). IR (KBr, cm^{-1}): 3153, 3032, 2870, 1576, 1257, 1033; MS *m/z* (%): 215 ([M^+], 6), 185 (18), 142 (24), 108 (100), 96 (30), 56 (83); HRMS: calcd. for $C_8H_{13}N_3O_4$ (M^+) 215.0906; found 215.0930.

1-[(1,3-dioxolan-4-yl)methyl]-2-(nitromethylene)hexahydropyrimidine (**9**): Following the above method, 0.71 g sight yellow solid was obtained. Yield: 62%. m.p. 134.4–135.1°C; ^{1}H NMR ($CDCl_3$) δ: 2.03–2.08 (m, 2H, C–CH_2–C), 3.15–3.20 (m, 1H), 3.43–3.50 (m, 4H), 3.57–3.60 (m, 1H), 3.62–3.67 (m, 1H), 3.97–4.00 (m, 1H), 4.29–4.34 (m, 1H), 4.84 (s, 1H, OCH_2O), 5.09 (s, 1H, OCH_2O), 6.46 (s, 1H, $CHNO_2$), 10.82 (br s, 1H, NH). HRMS: calcd. for $C_9H_{16}N_3O_4$ (MH^+) 230.1141; found: 230.1178.

1-[(1,3-dioxolane-4-yl)methyl]-6-alkyl-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-f]pyrimidine (**10a–f**)

10a: To a solution of compound 6 (0.67 g, 3.0 mmol) in THF (20 ml) was added a solution of formaldehyde (0.48 g, 6.6 mmol, 37% solution in water) and methylamine (0.37 g, 3.0 mmol, 25% solution in water). The resulting mixture was stirred overnight, concentrated in vacuum, and purified by vacuum column chromatography on a silica gel to give 0.52 g of the desired product as sight yellow solid. Yield: 66%. m.p. 91.4–92.1°C. ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 3.31–3.35 (m, 1H), 3.62–3.69 (m, 3H), 3.74–3.83 (m, 3H), 3.89–3.94 (m, 2H), 4.04–4.12 (m, 3H), 4.51–4.55 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.05 (s, 1H, OCH_2O). IR (KBr, cm^{-1}): 2871, 1569, 1423, 1366, 1078; HRMS: calcd. for $C_{11}H_{19}N_4O_4$ (MH^+) 271.1406; found: 271.1397.

10b: Following the above method and using 0.13 g ethylamine (3 mmol), 0.71 g sight yellow solid was obtained. Yield: 83%. m.p. 95.5–96.4°C. ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, 3H, J = 7.2 Hz, CH_3), 2.62 (q, 2H, J = 7.2 Hz, CH_2CH_3), 3.29–3.33 (m, 1H), 3.62–3.68 (m, 3H), 3.72–3.89 (m, 3H), 3.93–4.01 (m, 2H), 4.03–4.11 (m, 3H), 4.51–4.55 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.05 (s, 1H, OCH_2O). HRMS: calcd. for $C_{12}H_{21}N_4O_4$ (MH^+) 285.1563; found: 285.1569.

10c: Following the above method and using 0.18 g ethanolamine (3 mmol), 0.81 g pale yellow liquid was obtained. Yield: 90%. ^{1}H NMR ($CDCl_3$) δ: 2.74 (t, 2H, J = 5.0 Hz), 3.35–3.39 (m, 1H), 3.61–3.63 (t, 1H), 3.71–3.73 (m, 4H), 3.75–3.85 (m, 3H), 4.02–4.07 (m, 3H), 4.11–4.17 (q, 2H), 4.49–4.50 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.04 (s, 1H, OCH_2O). HRMS: calcd. for $C_{12}H_{21}N_4O_5$ (MH^+) 301.1512; found: 301.1522.

10d: Following the above method and using 0.18 g propylamine (3 mmol), 0.68 g yellow liquid was obtained. Yield: 76%. ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.4 Hz, CH_3), 1.53–1.58 (m, 2H, CH_2), 2.50 (t, 2H, J = 7.5 Hz, CH_2), 3.31–3.35 (m, 1H), 3.61–3.68 (m, 3H), 3.75–3.84 (m, 3H), 3.97–4.10 (m, 5H), 4.52–4.53 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.04 (s, 1H, OCH_2O). HRMS: calcd. for $C_{13}H_{23}N_4O_4$ (MH^+) 299.1719; found: 299.1670.

10e: Following the above method and using 0.18 g isopropyl amine (3 mmol), 0.69 g sight yellow solid was obtained. Yield: 78%. ^{1}H NMR ($CDCl_3$) δ: 1.14 (d, 6H, J = 6.5 Hz, CH_3), 2.90–2.95 (m, 1H, $CH(CH_3)_2$), 3.26–3.31 (m, 1H), 3.61–3.74 (m, 4H), 3.79–3.82 (m, 1H), 3.89–3.95 (m, 2H), 4.00–4.10 (m, 4H), 4.52–4.55

(m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.04 (s, 1H, OCH_2O). HRMS: calcd. for $C_{13}H_{23}N_4O_4$ (MH^+) 299.1719; found: 299.1701.

10f: Following the above method and using 0.22 g *n*-butylamine (3 mmol), 0.64 g yellow liquid was obtained. Yield: 68%. ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, J = 7.4 Hz, CH_3), 1.33–1.37 (m, 2H, CH_2), 1.49–1.53 (m, 2H, CH_2), 2.51–2.54 (t, 2H, J = 7.5 Hz, CH_2), 3.30–3.35 (m, 1H), 3.62–3.67 (m, 3H), 3.73–3.87 (m, 3H), 3.94–4.00 (m, 2H), 4.03–4.11 (m, 3H), 4.50–4.54 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.04 (s, 1H, OCH_2O). HRMS: calcd. for $C_{14}H_{25}N_4O_4$ (MH^+) 313.1876; found: 313.1885.

10g: Following the above method and using 0.22 g *tert*-butyl amine (3 mmol), 0.58 g pale yellow liquid was obtained. Yield: 62%. ^{1}H NMR ($CDCl_3$) δ: 1.18 (s, 9H, CH_3), 3.25–3.29 (m, 1H), 3.62–3.74 (m, 4H), 3.75–3.79 (m, 1H), 3.86–3.93 (m, 2H), 4.00–4.10 (m, 4H), 4.52–4.57 (m, 1H, OCH), 4.86 (s, 1H, OCH_2O), 5.05 (s, 1H, OCH_2O). HRMS: calcd. for $C_{14}H_{25}N_4O_4$ (MH^+) 313.1876; found: 313.1865.

This work was financial supported by National Key Project for Basic Research (2003CB114405), National Natural Science Foundation of China. The authors also thank to the partly support from Shanghai Education Committee and Shanghai Foundation of Science and Technology.

Received 15 April 2006; accepted 5 July 2006
Paper 06/3905

References

1 K. Shiokawa, S. Tsuboi, S. Kagabu and K. Moriya, *Eur. Patent*., EP192 060, 1986.
2 I. Yamamoto, G. Yabuta, M. Tomizawa, T. Saito, T. Miyamoto and S. Kagabu, *Nippon. Noyaku. Gakkaishi*., 1995, **20**, 33.
3 D. Bai, S. Lummis, W. Leicht, H. Breer and D. Sattelle, *Pestic. Sci*., 1991, **33**, 197.
4 I. Aoki, T. Tabuchi and I. Minamida, *Eur. Patent*., EP381130, 1990.
5 M. Matsuda and H. Takahashi, *Agrochem. Jpn*., 1996, **68**, 20.
6 K. Moriie, J. Ootsu, Y. Hatsutori, A. Watanabe and A. Ito, *Jpn. Patent*., JP7224062, 1995.
7 K. Kodaka, K. Kinoshita, T. Wakita, S. Shiraishi, K. Ohnuma, E. Yamada, Y, Naoko, M. Nakaya, H. Matsuno, N. Kawahara and K. Ebiharai, *Eur. Patent*., EP649845, 1995.
8 M. Tomizawa, N. Zhang, K.A. Durkin, M.M. Olmstead and J.E. Casida, *Biochemistry*., 2003, **42**, 7819.
9 M. Moghadam, S. Tangestaninejad, V. Mirkhanib and R. Shaibania, *Tetrahedron*., 2004, **60**, 6105.
10 W.F. Bailey and A.D. Rivera, *J. Org. Chem*., 1984, **49**, 4958.
11 J.M. Contreras, Y.M. Rival, S. Chayer, J.J. Bourguignon and C.G. Wermuth, *J. Med. Chem*., 1999, **42**, 730.