

As. 121.296

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No. 12-113709- -00008-0000

Fecha: 2013-10-24 16:49:35 Dep. 2020 DIR NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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Señor

**DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E.

S.

D.

REF: Expediente No. **12 113.709**– solicitud de patente de invención a favor de **EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY**. Título **COMPUESTOS DIVALENTES Y HETEROCÍCLICOS UNIDOS POR PIENTE OXA RELACIONADOS CON NICOTINA Y MÉTODOS DE PREPARACIÓN DE LOS MISMOS**.

RESPUESTA A EXAMEN DE FONDO

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito dar respuesta al oficio número 13465 relacionado con la patentabilidad de la presente invención y notificado por fijación en lista el 30 de Julio de 2013.

Atentamente nos permitimos remitir a su Despacho un nuevo pliego reivindicatorio compuesto por ocho (8) reivindicaciones, las cuales se encuentran sustentadas de manera apropiada en el capítulo descriptivo y no exceden en ningún momento el alcance de la materia inicialmente divulgada.

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A este respecto, nos permitimos mencionar que se eliminaron las reivindicaciones 8 y 11-18 en concordancia con el comentario del señor Examinador, debido a que éstas hacían referencia a los usos de la composición reivindicada, lo cual no es patentable.

Asimismo, la reivindicación 1 fue restringida de modo tal que ahora se definen de manera específica cada uno de los posibles radicales de la molécula de acuerdo a los ejemplos incluidos en el capítulo descriptivo. En este sentido, nos permitimos resaltar que los radicales R_3 y R_4 ahora son definidos como sigue:

" R_3 y R_4 forman en conjunto $-CH_2-CH_2-$, o $-CH_2-CH_2-CH_2-$."

De acuerdo con lo anterior, nos permitimos mencionar que, a pesar de que en los compuestos preparados y ensayados en el ejemplo descrito en el capítulo descriptivo contienen el grupo $-CH_2-CH_2-$ en ambos radicales, la invención también admite la inclusión del grupo $-CH_2-CH_2-CH_2-$ en concordancia con lo divulgado en el capítulo descriptivo, partiendo de que el grupo $-CH_2-CH_2-CH_2-$ exhibe propiedades químicas similares al grupo $-CH_2-CH_2-$.

Novedad y Nivel inventivo

A este respecto nos permitimos mencionar que el examen de novedad y nivel inventivo llevado a cabo por el señor Examinador no es válido, ya que el citado documento D1 no fue publicado el 12 de Noviembre de 2009, sino el **11 de Diciembre de 2009**, siendo esta última fecha posterior a la fecha de prioridad de la presente solicitud (**9 de Diciembre de 2009**). Seguramente la confusión se presentó en la fecha indicada en el artículo que es 12/11/2009, sin embargo dicha fecha está en el formato Mes/Día/Año.

Como respaldo, adjuntamos a la presente respuesta el soporte documental pertinente en donde se observa claramente que la fecha de publicación es **DICIEMBRE 11 DE 2009**, con lo cual aspiramos sea reconsiderada la objeción que afecta al presente pliego reivindicatorio.

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Por todo lo anterior, solicitamos el retiro de las objeciones de la presente solicitud y la concesión del privilegio solicitado, ya que en opinión del solicitante cumple con todos los requisitos establecidos en la Decisión 486.



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.S.J.

C.C. 80.410.337 de Usaquén

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Discovery of Imidacloprid and Further Developments from Strategic Molecular Designs Abstract

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DOI: 10.1021/jf101824y

Section: **Agrochemical Bioregulators** PDF w/ Links [1044K] Full Text HTML

Discovery of Imidacloprid and Further Developments from Strategic Molecular Designs ... Table 9 shows the insecticidal activity by injection of selected **divalent** imidacloprid derivatives against American cockroaches. ... The binding mode as

for which such alkylene-tethered divalent molecules act agonistically or antagonistically will be another interesting question. ...

1. 1,2-Dichloroethane
 2. 1,1-Dichloroethane
 3. 1,2-Dibromoethane
 4. 1,1-Dibromoethane
 5. 1,2-Dichloropropane
 6. 1,1-Dichloropropane
 7. 1,2-Dibromopropane
 8. 1,1-Dibromopropane
 9. 1,2-Dichlorobutane
 10. 1,1-Dichlorobutane
 11. 1,2-Dibromobutane
 12. 1,1-Dibromobutane
 13. 1,2-Dichloropentane
 14. 1,1-Dichloropentane
 15. 1,2-Dibromopentane
 16. 1,1-Dibromopentane
 17. 1,2-Dichlorohexane
 18. 1,1-Dichlorohexane
 19. 1,2-Dibromohexane
 20. 1,1-Dibromohexane
 21. 1,2-Dichloroheptane
 22. 1,1-Dichloroheptane
 23. 1,2-Dibromoheptane
 24. 1,1-Dibromoheptane
 25. 1,2-Dichlorooctane
 26. 1,1-Dichlorooctane
 27. 1,2-Dibromooctane
 28. 1,1-Dibromooctane
 29. 1,2-Dichlorononane
 30. 1,1-Dichlorononane
 31. 1,2-Dibromononane
 32. 1,1-Dibromononane
 33. 1,2-Dichlorodecane
 34. 1,1-Dichlorodecane
 35. 1,2-Dibromodecane
 36. 1,1-Dibromodecane
 37. 1,2-Dichloroundecane
 38. 1,1-Dichloroundecane
 39. 1,2-Dibromoundecane
 40. 1,1-Dibromoundecane
 41. 1,2-Dichlorododecane
 42. 1,1-Dichlorododecane
 43. 1,2-Dibromododecane
 44. 1,1-Dibromododecane
 45. 1,2-Dichlorotridecane
 46. 1,1-Dichlorotridecane
 47. 1,2-Dibromotridecane
 48. 1,1-Dibromotridecane
 49. 1,2-Dichlorotetradecane
 50. 1,1-Dichlorotetradecane
 51. 1,2-Dibromotetradecane
 52. 1,1-Dibromotetradecane
 53. 1,2-Dichloropentadecane
 54.

Figure 1 of 12

Controlled Release of Isoproturon, Imidacloprid, and Cyromazine from Alginate–Bentonite-Activated Carbon Formulations Abstract

F. J. Garrido-Herrera, E. González-Pradas, and M. Fernández-Pérez PDF [126K]
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Publication Date (Web): December 8, 2006 (Article)
DOI: 10.1021/jf062084m

ACS Section: Agrochemical Bioregulators Add to ACS ChemWorx

Controlled Release of Isoproturon, Imidacloprid, and Cyromazine from Alginate-Bentonite-Activated Carbon Formulations ... The prepared CRFs were based on the swelling properties of the alginate in the presence of divalent

based on the gelling properties of the alginate in the presence of divalent cations. ...

name	age	height	weight	gender	hair_color	eye_color	skin_color	hair_length	hair_type
John	30	180	75	male	brown	blue	white	short	straight

Figure 1 of 7

[Divalent and Oxabridged Neonicotinoids Constructed by](#) [Abstract | Supporting Info](#)

Dialdehydes and Nitromethylene Analogues of Imidacloprid: Design, Synthesis, Crystal Structure, and Insecticidal

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J. Agric. Food Chem., **2010**, *58* (5), pp 2696-2702

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☐ **Divalent and Oxabridged Neonicotinoids Constructed by Dialdehydes and Nitromethylene Analogues of Imidacloprid: Design, Synthesis, Crystal Structure, and Insecticidal Activities**

Xusheng Shao, Hua Fu, Xiaoyong Xu, Xinglei Xu, Zewen Liu, Zhong Li and Xuhong Qian

J. Agric. Food Chem., 2010, 58 (5), pp 2696 - 2702

Publication Date (Web): December 11, 2009 (Article)

DOI: 10.1021/jf902531y

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Section: Agrochemical Bioregulators

Divalent and Oxabridged Neonicotinoids Constructed by Dialdehydes and Nitromethylene Analogues of Imidacloprid: Design, Synthesis, Crystal Structure,

Divalent and Oxabridged Neonicotinoids Constructed by Dialdehydes and Nitromethylene Analogues of Imidacloprid: Design, Synthesis, Crystal Structure, and Insecticidal Activities[†]

XUSHENG SHAO,[§] HUA FU,[‡] XIAOYONG XU,^{*,§} XINGLEI XU,[§] ZEWEN LIU,[#] ZHONG LI,^{*,§}
AND XUHONG QIAN[§]

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A series of divalent and oxabridged neonicotinoids were synthesized by reactions of nitromethylene analogues of imidacloprid and dialdehydes, and their structures were confirmed by ¹H NMR, ¹³C NMR, high-resolution mass spectroscopy, and X-ray diffraction analysis. The bioassays indicated that some of them were endowed with excellent insecticidal activities against cowpea aphid (*Aphis craccivora*), armyworm (*Pseudaletia separata* Walker), and brown planthopper (*Nilaparvata lugens*). Divalent neonicotinoid **6** and oxabridged **8a** had higher activities than imidacloprid against cowpea aphids and armyworm; furthermore, the activity of **8a** was 40.4-fold higher than that of imidacloprid against imidacloprid-resistant brown planthopper.

KEYWORDS: Neonicotinoids; dialdehydes; imidacloprid; insecticide; oxabridge

INTRODUCTION

The past decades have witnessed the great power and versatile ability of neonicotinoids as a novel class of insecticides (1, 2), which account for 18% of world insecticide sales with a turnover of \$1.7 billion in 2006 (3). By virtue of novel modes of action (targeting insect nicotinic acetylcholine receptors (nAChRs)) (4–6), low mammalian toxicity, broad insecticidal spectra, and good systemic properties (7, 8), neonicotinoids are increasingly used in crop protection and animal health care against a broad spectrum of sucking and biting insects. Since their inception about 30 years ago, the development of neonicotinoids with novel structures and higher insecticidal activities has provoked continuing interest; for example, divalent neonicotinoids (9, 10), proinsecticides of imidacloprid (11), neonicotinoids with extended N-substituted-imine (12), neonicotinoid substituents forming a water bridge (13), and crown-capped imidacloprid (14) have consecutively appeared in the literature in recent years. Furthermore, the discoveries of high-resolution crystal structures of AChBP–neonicotinoid complexes have promoted the receptor structure guided neonicotinoid design (4, 12, 13, 15). Despite the tremendous amount of effort invested in the development of neonicotinoids, it is still essential to explore novel neonicotinoid candidates, because significant increases in resistance have been

observed in a range of species after frequent field applications (16–23).

The rationale for our molecular design involved the use of fused heterocycles or bulky groups to fix the direction of the nitro group, which was one of the most important groups in neonicotinoids. Fortunately, our foray into this arena met with encouraging insecticidal activities, and some novel neonicotinoids with high activities happened to be discovered (24–28). In our previous studies, it was found that 6-Cl-PMNI (1) could react with various α,β -unsaturated aldehydes to give high-insecticidal compounds **2** with tetrahydropyridine fixed *cis*-configuration (26, 27), and it could also react with five-membered aromatic aldehydes to give compounds **3** with bulky groups fixed in the direction of the nitro group, which showed higher insecticidal activities than imidacloprid (28). It is noteworthy that toward α,β -unsaturated aldehydes and five-membered aromatic aldehydes, C1 or N1 in 6-Cl-PMNI acted as nucleophilic centers.

Inspired by the promising results described above, we next turned our attentions to reactions of dialdehydes with 6-Cl-PMNI with a view to incorporate dialdehydes to 6-Cl-PMNI and search for high insecticidal neonicotinoids. Fortunately, different fates of dialdehydes upon reacting with 6-Cl-PMNI were observed due to the two electrophilic aldehyde groups in dialdehydes. Herein, for the sake of comparison and extending our studies, we report the synthesis and insecticidal activities of divalent and oxabridged neonicotinoids constructed by dialdehydes and nitromethylene analogues of imidacloprid.

[†]Part of the ECUST-Qian Pesticide Cluster.

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MATERIALS AND METHODS

Instruments. Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with CDCl_3 or $\text{DMSO}-d_6$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. X-ray diffraction was performed with a Bruker Smart 1000.

Synthesis. The general synthetic methods for compounds **4**, **5**, **6**, **8a–d**, and **9a–d** are depicted in Schemes 2–5. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. All reactions were carried out under a protective atmosphere of drying nitrogen or utilizing a calcium chloride tube.

4-(1-((6-Chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-1-(1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-ylidene)-1,4-dinitrobut-3-en-2-ol (4). A mixture of compound **1** (2.54 g, 10 mmol), 40% oxalaldehyde aqueous solution (4 mL, 30 mmol), and acetonitrile (50 mL) was stirred at room temperature. After it was stirred for about 1 h, concentrated hydrochloric acid (0.20 mL) was added to the reaction mixture. The progress of the reaction was monitored by TLC. After completion, the solvent was removed under reduced pressure. The obtained residue was added to methanol (20 mL), and then the product was precipitated. The precipitate was filtered, washed with dichloromethane, and dried to give the corresponding product as a white solid: yield, 58%; mp, 164.6–165.3 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 9.01 (s, 1H), 8.41 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.80–7.86 (m, 2H), 7.51–7.54 (m, 2H), 6.50 (d, J = 7.2 Hz, 1H), 5.34 (d, J = 15.2 Hz, 1H), 5.18 (d, J = 15.2 Hz, 1H), 4.84 (dd, J_1 = 2.4 Hz, J_2 = 7.2 Hz, 1H), 4.77 (d, J = 16.8 Hz, 1H), 4.67 (d, J = 16.8 Hz, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.86–3.95 (m, 2H), 3.61–3.80 (m, 5H), 3.40–3.47 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 162.7, 158.7, 148.3, 148.2, 148.0, 147.7, 138.1, 137.7, 130.9, 130.2, 123.1, 123.0, 102.5, 101.4, 81.4, 53.8, 52.6, 49.4, 48.8, 46.4, 41.2, 41.0. HRMS (ES+) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{35}\text{Cl}_2$ (M + H) $^+$, 549.1168; found, 549.1178; calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{35}\text{Cl}^{37}\text{Cl}$ (M + H) $^+$, 551.1139; found, 551.1152; calcd for $\text{C}_{22}\text{H}_{23}\text{N}_8\text{O}_5^{37}\text{Cl}_2$ (M + H) $^+$, 553.1109; found, 553.1108.

2-Chloro-5-((2-(4-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-1,4-dinitrobut-3-enylidene)imidazolidin-1-yl)methyl)pyridine (5). To a mixture of compound **4** (1.1 g, 2 mmol), methanol (10 mL), and dichloromethane (30 mL) was added three drops of concentrated hydrochloric acid. The resulting mixture was refluxed for 10 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products as a brown solid: yield, 20%; mp, 170.2–170.6 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 8.38–8.39 (m, 2H), 7.81–7.86 (m, 2H), 7.50–7.55 (m, 2H), 5.37 (d, J = 15.4 Hz, 1H), 5.14 (d, J = 15.4 Hz, 1H), 4.69 (s, 2H), 4.62 (d, J = 2.2 Hz, 1H), 3.83–4.01 (m, 3H), 3.67–3.82 (m, 5H), 3.50–3.58 (m, 1H), 3.20 (s, 3H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 164.0, 161.1, 150.0, 149.9, 149.6, 149.3, 139.7, 139.3, 132.4, 132.0, 124.7, 124.6, 104.0, 102.3, 90.8, 55.4, 55.1, 54.4, 52.9, 50.8, 48.1, 45.5, 42.7. HRMS (ES+) calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{35}\text{Cl}_2\text{Na}$ (M + Na) $^+$, 585.1144; found, 585.1113; calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{35}\text{Cl}^{37}\text{ClNa}$ (M + Na) $^+$, 587.1115; found, 587.1104; calcd for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_5^{37}\text{Cl}_2\text{Na}$ (M + Na) $^+$, 589.1085; found, 589.1110.

2-Chloro-5-((2-(5-(1-((6-chloropyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)-1,5-dinitropenta-1,4-dienyl)-4,5-dihydroimidazol-1-yl)methyl)pyridine (6). Malonaldehyde was prepared according to the previously reported procedure (29). 1,1,3,3-Tetramethoxypropane (2.2 g, 13 mmol) was stirred with 5.0 mL of 2.0 M HCl for 1.5 h. Then compound **1** (2.54 g, 10 mmol) was added followed by 30 mL of acetonitrile, and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the pH value of the filtrate was adjusted to 7–8 by triethylamine, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 2:1) to afford the desired

product as a brown solid: yield, 39%; mp, 136.5–137.8 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.34 (d, J = 2.4 Hz, 2H), 7.82 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.96 (t, J = 2.8 Hz, 2H), 4.81 (d, J = 15.8 Hz, 2H), 4.44 (d, J = 15.8 Hz, 2H), 3.92–3.97 (m, 4H), 3.65–3.72 (m, 2H), 3.49–3.56 (m, 2H), 1.92–1.93 (m, 2H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.3, 147.9, 147.8, 138.0, 130.9, 122.7, 104.8, 502, 48.9, 48.5, 48.5, 28.1. HRMS (ES+) calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{35}\text{Cl}_2$ (M + H) $^+$, 545.1219; found, 545.1201; calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{35}\text{Cl}^{37}\text{Cl}$ (M + H) $^+$, 547.1190; found, 547.1178; calcd for $\text{C}_{23}\text{H}_{23}\text{N}_8\text{O}_4^{37}\text{Cl}_2$ (M + H) $^+$, 549.1160; found, 549.1181.

General Synthetic Procedure for 8a–d. Succinaldehyde was prepared according to the previously reported procedure (30). A mixture of 2,5-diethoxytetrahydrofuran (2 g, 12.5 mmol) and HCl aqueous solution (0.1 M, 10 mL) was heated to 90 °C for 1 h and then cooled to room temperature. Acetonitrile (40 mL), compound **1** or **7a–c** (10 mmol), and anhydrous Na_2SO_4 (3 g) were successively added, and the obtained mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the mixture was filtered to remove Na_2SO_4 , and then the pH value of the filtrate was adjusted to 7–8 by triethylamine and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products **8a–d**.

Data for 8a: yield, 53%; mp, 149.0–150.0 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.35 (d, J = 2.4 Hz, 1H), 7.81 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 5.36–5.39 (s, 2H), 5.00 (d, J = 15.6 Hz, 1H), 4.68 (d, J = 15.6 Hz, 1H), 3.57–3.73 (m, 4H), 1.94–2.04 (m, 4H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.6, 149.7, 149.6, 139.7, 132.6, 124.5, 109.6, 87.0, 75.1, 51.2, 50.3, 46.6, 31.9, 31.7; HRMS (ES+) calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3^{35}\text{Cl}$ (M + H) $^+$, 323.0911; found, 323.0912; calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3^{37}\text{Cl}$ (M + H) $^+$, 325.0811; found, 325.0895; calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_3^{35}\text{ClNa}$ (M + Na) $^+$, 345.0730; found, 345.0722; calcd for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{O}_3^{37}\text{ClNa}$ (M + Na) $^+$, 347.0701; found, 347.0692.

Data for 8b: yield, 56%; mp, 136.5–138.0 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.47 (s, 1H), 5.61 (d, J = 5.2 Hz, 1H), 5.28 (d, J = 15.4 Hz, 1H), 5.16 (d, J = 5.00 Hz, 1H), 4.70 (d, J = 15.4 Hz, 1H), 3.66–3.82 (m, 3H), 3.54–3.61 (m, 1H), 2.22–2.29 (m, 1H), 2.12–2.21 (m, 2H), 1.99–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 154.6, 154.3, 140.6, 135.1, 110.4, 87.4, 75.4, 49.6, 47.9, 46.5, 31.8, 31.8. HRMS (ES+) calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3\text{S}^{35}\text{Cl}$ (M + H) $^+$, 329.0475; found, 329.0475; calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_3\text{S}^{37}\text{Cl}$ (M + H) $^+$, 331.0446; found, 331.0461.

Data for 8c: yield, 58%; mp, 149.0–149.8 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.28–7.39 (m, 5H), 5.66 (d, J = 4.3 Hz, 1H), 5.14 (d, J = 4.5 Hz, 1H), 4.92–5.01 (m, 2H), 3.57–3.74 (m, 3H), 3.47–3.53 (m, 1H), 2.30–2.34 (m, 1H), 2.13–2.22 (m, 2H), 2.00–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.5, 135.9, 128.9, 128.2, 128.1, 87.7, 75.6, 54.4, 48.9, 47.2, 31.8, 31.6. HRMS (ES+) calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3$ (M + H) $^+$, 287.1270; found, 287.1272.

Data for 8d: yield, 38%; mp, 140.0–140.9 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 7.27–7.34 (m, 4H), 5.63 (d, J = 5.4 Hz, 1H), 5.14 (d, J = 5.2 Hz, 1H), 5.04 (d, J = 15.1 Hz, 1H), 4.78 (d, J = 15.1 Hz, 1H), 3.62–3.73 (m, 3H), 3.45–3.51 (m, 1H), 2.26–2.31 (m, 1H), 2.11–2.21 (m, 2H), 1.98–2.07 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 155.3, 134.4, 133.9, 129.6, 129.0, 110.2, 87.6, 75.5, 53.9, 49.2, 47.0, 31.8, 31.7. HRMS (ES+) calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3^{35}\text{Cl}$ (M + H) $^+$, 322.0958; found, 322.0972; calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3^{37}\text{Cl}$ (M + H) $^+$, 324.0929; found, 324.0938.

General Synthetic Procedure for 9a–d. A mixture of compound **1** or **7a–c** (10 mmol), 25% glutaraldehyde aqueous solution (4 mL), and acetonitrile (50 mL) was stirred at room temperature. After it had been stirred for about 30 min, concentrated hydrochloric acid (0.20 mL) was added to the reaction mixture. The progress of the reaction was monitored by TLC. After completion, the pH value of the filtrate was adjusted to 7–8 by triethylamine, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 3:1) to afford the desired products **9a–d**.

Data for 9a: yield, 76%; mp, 174.7–175.4 °C; ^1H NMR (400 Mz, $\text{DMSO}-d_6$) δ 8.38 (dd, J_1 = 0.6 Hz, J_2 = 2.4 Hz, 1H), 7.84 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.52 (dd, J_1 = 0.6 Hz, J_2 = 8.4 Hz, 1H), 5.12 (s, 1H), 5.04–5.05 (m, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.71 (d, J = 15.6 Hz, 1H), 3.62–3.74 (m, 4H), 1.66–1.81 (m, 4H), 1.51–1.55 (m, 1H), 1.32–1.44 (m, 1H); ^{13}C NMR (100 Mz, $\text{DMSO}-d_6$) δ 156.6, 149.7, 149.6, 139.7, 132.9, 124.5, 105.8, 81.7, 68.9, 51.7, 50.0, 46.3, 28.8, 27.2, 14.8. HRMS (EI+)

calcd for $C_{15}H_{17}N_4O_3^{35}Cl$ (M^+), 336.0989; found, 336.0988; calcd for $C_{15}H_{17}N_4O_3^{37}Cl$ (M^+), 338.0960; found, 338.0968.

Data for 9b: yield, 62%; mp, 159.1–160.5 °C; ^1H NMR (400 Mz, DMSO- d_6) δ 7.48 (s, 1H), 5.30 (d, J = 3.2 Hz, 1H), 5.24 (d, J = 15.4 Hz, 1H), 4.98 (s, 1H), 4.78 (d, J = 15.4 Hz, 1H), 3.76–3.87 (m, 1H), 3.60–3.71 (m, 3H), 2.12 (d, J = 14.0 Hz, 1H), 1.82–1.96 (m, 2H), 1.64–1.77 (m, 2H), 1.48–1.60 (m, 1H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 155.7, 154.1, 140.5, 135.6, 107.0, 82.7, 69.4, 49.4, 48.3, 46.2, 29.4, 26.5, 14.9. HRMS (EI+) calcd for $C_{15}H_{17}N_4O_3^{35}Cl$ (M^+), 342.0553; found, 342.0548; calcd for $C_{15}H_{17}N_4O_3^{37}Cl$ (M^+), 344.0524; found, 344.0564.

Data for 9c: yield, 77%; mp, 180.5–181.2 °C; ^1H NMR (400 Mz, DMSO- d_6) δ 7.29–7.37 (m, 5H), 5.33 (d, J = 3.1 Hz, 1H), 5.02 (d, J = 15.0 Hz, 1H), 4.95 (s, 1H), 4.85 (d, J = 15.0 Hz, 1H), 3.68–3.75 (m, 1H), 3.48–3.64 (m, 3H), 2.14 (d, J = 13.1 Hz, 1H), 1.81–1.93 (m, 2H), 1.51–1.70 (m, 3H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 156.6, 136.4, 128.8, 128.3, 128.0, 106.7, 83.0, 69.7, 54.8, 48.6, 46.7, 29.5, 26.5, 15.0. HRMS (EI+) calcd for $C_{16}H_{19}N_3O_3$ (M^+), 301.1426; found, 301.1429.

Data for 9d: yield, 70%; mp, 156.9–158.3 °C; ^1H NMR (400 Mz, DMSO- d_6) δ 7.29–7.34 (m, 4H), 5.33 (d, J = 4.0 Hz, 1H), 5.05 (d, J = 15.1 Hz, 1H), 4.96 (s, 1H), 4.75 (d, J = 15.1 Hz, 1H), 3.66–3.73 (m, 1H), 3.55–3.60 (m, 3H), 2.14 (d, J = 13.6 Hz, 1H), 1.82–1.95 (m, 2H), 1.51–1.71 (m, 3H); ^{13}C NMR (100 Mz, DMSO- d_6) δ 156.5, 134.9, 133.8, 129.7, 129.0, 106.8, 83.0, 69.6, 54.4, 48.9, 46.6, 29.6, 26.5, 15.0. HRMS (EI+) calcd for $C_{16}H_{18}N_3O_3^{35}Cl$ (M^+), 335.1037; found, 335.1044; calcd for $C_{16}H_{18}N_3O_3^{37}Cl$ (M^+), 337.1007; found, 337.1036.

X-ray Diffraction. Compound **8a** was recrystallized by slow evaporation from dichloromethane to afford a suitable single crystal. Colorless blocks of **8a** (0.421 mm $\times$ 0.369 mm $\times$ 0.327) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo K α radiation (λ = 0.71073 Å); θ_{max} = 25.50; 7954 measured reflections; 2958 independent reflections (R_{int} = 0.0985). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.7954 and T_{max} = 1.0000). The structure was solved by direct methods with SHELXS-97 (31). All other calculations were performed with Bruker SAINT System and Bruker SMART programs (32). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0903P)^2 + 0.0000P]$ gave final values of R = 0.0744, ωR = 0.1670, and GOF (F) = 0.977 for 213 variables and 2958 contributing reflections. Maximum shift/error = 0.000(3) and max/min residual electron density = 0.510/–0.522 e Å $^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Compound **9a** was recrystallized by slow evaporation from dichloromethane to afford a suitable single crystal. Colorless blocks of **9a** (0.468 mm $\times$ 0.391 mm $\times$ 0.229) were mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo K α radiation (λ = 0.71073 Å); θ_{max} = 27.00; 8730 measured reflections; 3254 independent reflections (R_{int} = 0.0649). Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.84981 and T_{max} = 1.0000). The structure was solved by direct methods with SHELXS-97. All other calculations were performed with Bruker SAINT System and Bruker SMART programs. Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.0585P)^2 + 0.1852P]$ gave final values of R = 0.0482, ωR = 0.1193, and GOF (F) = 1.032 for 208 variables and 3254 contributing reflections. Maximum shift/error = 0.000(3) and max/min residual electron density = 0.280/–0.215 e Å $^{-3}$. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 $\pm$ 1 °C according to statistical requirements. All compounds were dissolved in *N,N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L $^{-1}$) to obtain series concentrations of 500.0, 250.0, and 125.0 mg L $^{-1}$ and others for bioassays. For comparative purposes, imidacloprid was tested under the same conditions.

Insecticidal Test for Cowpea Aphid (*Aphis craccivora*). The activities of insecticidal compounds against cowpea aphid were tested by leaf-dip method according to our previously reported procedure (25, 26). Horsebean plant leaves with 40–60 apterous adults were dipped in diluted

solutions of the chemicals containing Triton X-100 (0.1 mg L $^{-1}$) for 5 s, and the excess dilution was sucked out with filter paper; burgeons were placed in a conditioned room (25 $\pm$ 1 °C, 50% RH). Water containing Triton X-100 (0.1 mg L $^{-1}$) 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 as before.

Insecticidal Test for Armyworm (*Pseudaletia separata* Walker).

The activities of insecticidal compounds against armyworm were tested using previously reported procedures (33, 34). The insecticidal activity against armyworm was tested by foliar application. Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compound solution and exposed to dry. The dishes were infested with 10 second-instar larvae and placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subjected to probit analysis as before.

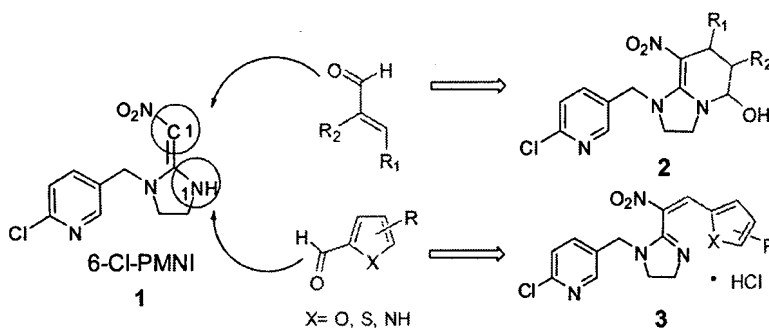
Insecticidal Test for Brown Planthopper (*Nilaparvata lugens*).

The bioassay against brown planthopper followed the microtopical application technique reported by Nagata (35). Macropterous adult females (2–3 days old, unmated) were used as test animals. Insecticidal compounds were diluted to a series of concentrations with acetone. Under carbon dioxide anesthesia, a droplet (0.08 μ L) of insecticide solution was applied topically to the prothorax notum of test hoppers with a hand microapplicator (Burkard Manufacturing Co. Ltd., Rickmansworth, U.K.). About 30 insects were treated at each concentration, and every treatment was repeated three times. The controls used acetone instead of insecticide solution. The treated insects were reared on seedlings cultured soilless in the rearing box (20 $\times$ 20 $\times$ 10 cm) at 25 $\pm$ 1 °C and 16/8 h light/dark. The results were checked after 48 h. LD $_{50}$ values were determined on the basis of standard probit analysis.

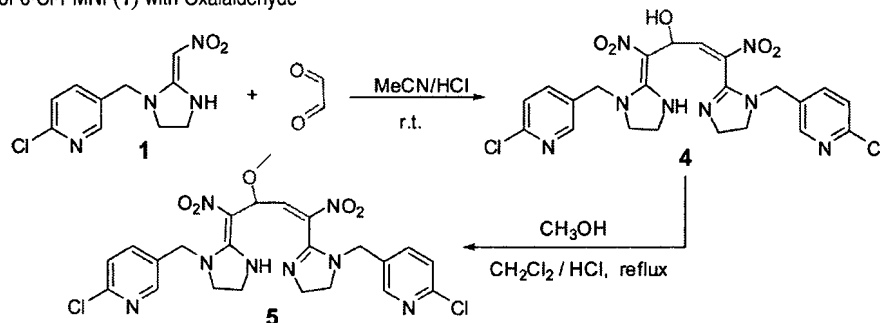
RESULTS AND DISCUSSION

Synthesis. Compounds **1** and **7a–c** were prepared according to the literature (36). **1** and **7a–c** were cyclic β -nitroenamines, which consist of push–pull ethylene systems with a donor (amine) at one end and an acceptor (nitro) at the other end of the ethylene. These nitroenamines manifest themselves as common enamines in electrophilic reactions and could react with a variety of electrophiles, with electrophilic attack proceeding at either or both of two nucleophilic centers (C1 and N1 in Scheme 1) (36–40). Shiokawa et al. made tremendous efforts on the chemical derivatizations of cyclic nitroenamine units by attack of the electrophile (such as sulfurizocyanatidic chloride, thiocyanogen, phenyl isocyanate, benzoyl isothiocyanate, and acrylate), and some neonicotinoid derivatives with desirable activities were found (40). Dialdehydes bearing two electrophilic centers are good electrophiles, which could readily react with cyclic β -nitroenamine. The synthetic procedures for the title compounds are depicted in Schemes 2–5.

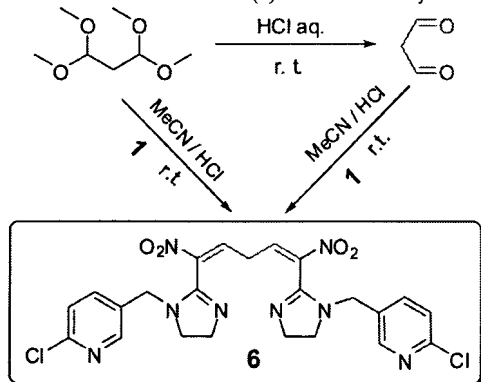
Initially, the reaction of compound **1** with oxalaldehyde in acetonitrile catalyzed by concentrated hydrochloric acid at room temperature was investigated; the reaction proceeded smoothly, and a white powder was precipitated from the reaction mixture (Scheme 2). Analysis of the isolated precipitate by NMR showed the formation of 1:2 condensation compound **4**. HRMS lent further support for formation of divalent compound **4**. ^1H NMR spectra of compound **4** showed the signal of NH at 9.01 ppm, which agreed with the one in compound **1** (8.90 ppm). Complete disappearance of the OH signal at 3.98 ppm on deuteration showed the existence of a hydroxyl group in **4**. To further confirm the structure of **4**, the etherization of **4** by methanol was carried out in refluxing dichloromethane catalyzed by concentrated HCl, and compound **5** was formed as expected. When malonaldehyde was subjected to reaction with **1** according to the aforementioned reaction conditions, a novel type of divalent neonicotinoid **6** was generated. Different from compound **4**, no hydroxyl group was

Scheme 1. Reactions of 6-Cl-PMNI (1) with α,β -Unsaturated Aldehydes and Five-Membered Aromatic Aldehydes

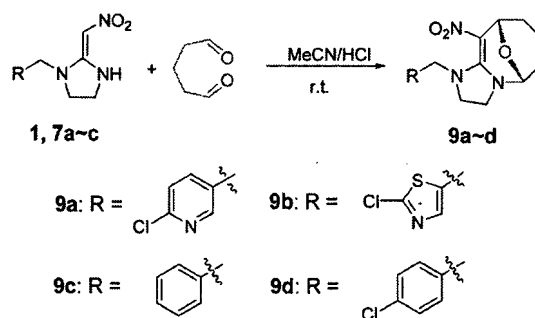
Scheme 2. Reactions of 6-Cl-PMNI (1) with Oxalaldehyde



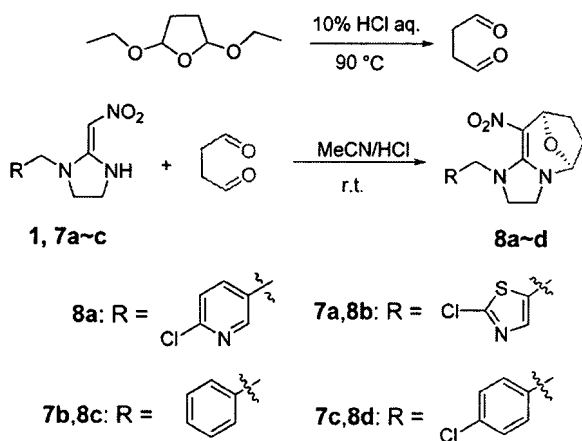
Scheme 3. Reactions of 6-Cl-PMNI (1) with Malonaldehyde



Scheme 5. Reactions of 6-Cl-PMNI (1) with Glutaraldehyde



Scheme 4. Reactions of 6-Cl-PMNI (1) with Succinaldehyde



retained in compound 6. The latter observation revealed that reaction of 1 with 1,1,3,3-tetramethoxypropane in acetonitrile catalyzed by concentrated hydrochloric acid at room temperature

could also proceed to afford 6 (Scheme 3), which provided one-pot operation for the procurement of compound 6. Previously, Kagabu also reported some divalent neonicotinoids, in which two imidacloprid molecules were coupled between two nitrogen atoms on the imidazoline (9), whereas linking two carbon atoms as described here could be another way to construct novel divalent neonicotinoids.

Subsequently, we embarked on reaction of 1 with succinaldehyde. Commercially available 2,5-diethoxytetrahydrofuran was stirred in 0.1 M HCl at 90 °C, affording succinaldehyde, and this mixture was used immediately without further purification. Upon treatment of 1 with succinaldehyde in the presence of hydrochloric acid in acetonitrile at room temperature, a white powder was obtained after column chromatography. The product was found to be a peculiar oxabridged compound 8a rather than a divalent compound on the basis of its spectral and analytical data. Reaction of glutaraldehyde with 1 was accomplished under identical conditions, affording the oxabridged compound 9a in 76% yield. Oxabridged compounds 8b–d and 9b–d, analogues of 8a and 9a, respectively, were easily obtained under similar conditions.

Crystal Structure Analysis. The oxabridged structure of compounds 8a and 9a was unambiguously confirmed by X-ray crystallographic diffraction analysis (Figures 1 and 2), which

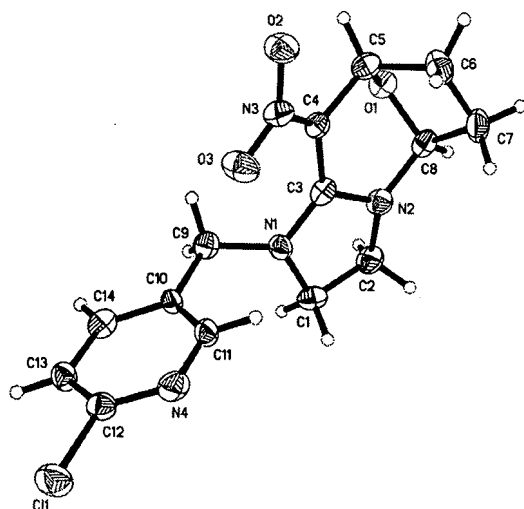


Figure 1. ORTEP drawing of **8a** with the atom-labeling scheme. Ellipsoids are drawn at the 30% probability level.

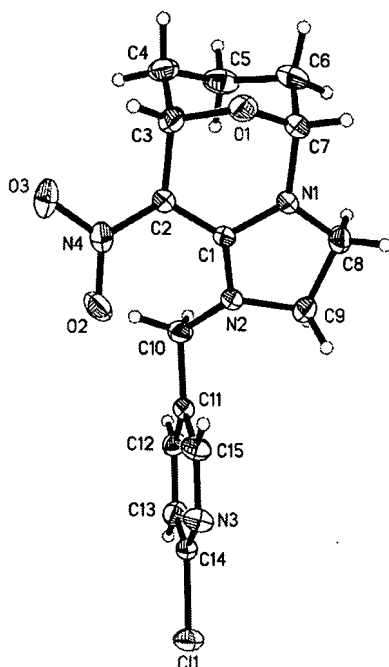


Figure 2. ORTEP drawing of **9a** with the atom-labeling scheme. Ellipsoids are drawn at the 30% probability level.

successfully provided the most convincing evidence for their proposed molecular structures. Although most key bond angles and distances are comparable for compounds **8a** and **9a**, rather surprisingly, the torsion angles of the chains containing oxygen are considerably different. When the torsion angle of **8a** was positive, the corresponding one of **9a** was negative and vice versa. For **8a**, the nitrogen atom in the pyridine ring and the oxygen atom pointed in opposite directions, whereas these two atoms in **9a** were oriented in the same direction.

Insecticidal Activities. Table 1 shows the insecticidal activities of the title compounds against cowpea aphid and armyworm. Divalent compound **4** showed moderate insecticidal activity against cowpea aphid at 500 mg L⁻¹ and high activity against armyworm with an LC₅₀ value of 0.19271 mmol L⁻¹. The etherified product **5** also had high insecticidal activity against cowpea aphid. Divalent compound **6** not only exhibited higher

Table 1. Insecticidal Activities of Compounds **4**, **5**, **6**, **8a–d**, and **9a–d** and Imidacloprid against Cowpea Aphid (*Aphis craccivora*) and Armyworm (*Pseudaletia separata* Walker)

compd	<i>Aphis craccivora</i>		<i>Pseudaletia separata</i> Walker	
	mortality (%, 500 mg L ⁻¹)	LC ₅₀ (mmol L ⁻¹)	mortality (%, 500 mg L ⁻¹)	LC ₅₀ (mmol L ⁻¹)
4	78.1	nt ^a	100	0.19471
5	97.7	nt	100	nt
6	100	0.00951	100	0.02798
8a	100	0.00471	100	0.03873
8b	100	0.00883	100	0.04956
8c	13.6	nt	0	nt
8d	95.7	nt	0	nt
9a	87.3	nt	0	nt
9b	98.2	nt	0	nt
9c	55.6	nt	0	nt
9d	38.9	nt	0	nt
imidacloprid	100	0.03502	100	0.12549
6-Cl-PMNI	100	0.00512	100	0.07087

^a Not tested.

Table 2. Insecticidal Activities of Compounds **8a** and **9a** and Imidacloprid against Imidacloprid-Resistant Brown Planthopper (*Nilaparvata lugens*)

strain	compd	$y = a + bx$	LC ₅₀ (ng/pest)	toxic ratio ^a
sensitive	8a	$y = 7.3127 + 2.0474x$	0.0742 ± 0.0106	1.77
	9a	$y = 3.9543 + 1.6936x$	4.1440 ± 0.6136	0.32
	imidacloprid	$y = 7.1823 + 2.4778x$	0.1316 ± 0.0154	1.00
resistant	8a	$y = 5.4068 + 1.3225x$	0.4925 ± 0.0811	50.00
	9a	$y = 3.1320 + 1.4613x$	18.9795 ± 2.3501	1.17
	imidacloprid	$y = 2.5873 + 1.7930x$	22.1614 ± 3.7522	1.00

^a Toxic ratio is defined as the ratio of the imidacloprid's LC₅₀ value for baseline toxicity and the compounds' LC₅₀ value.

activity than imidacloprid against cowpea aphid, but also had excellent activity against armyworm, which indicated that linkage of the two molecules in this way could maintain the insecticidal activities.

Oxabridged compound **8a** constructed by succinaldehyde demonstrated remarkable activities, which were higher than that of imidacloprid, against cowpea aphid (LC₅₀ = 0.00471 mmol L⁻¹) and armyworm (LC₅₀ = 0.03873 mmol L⁻¹). Intriguingly, the insecticidal activity of compound **8a** against imidacloprid-resistant brown planthopper was 50-fold higher than that of imidacloprid based on the value of LC₅₀, and **9a** also exhibited higher activity than imidacloprid (Table 2). The higher insecticidal activity of **8a** than imidacloprid might be attributed to the improved hydrophobicity. Replacement of 2-chloro-5-pyridine in **8a** with 2-chloro-5-thiazole to generate analogue **8b** maintained high insecticidal activity, which was consistent with the fact that the 2-chloro-5-thiazole unit has been proved to be an effective bioisosteric replacement for the 2-chloro-5-pyridine. Benzyl analogue **8c** and 4-chlorobenzyl counterpart **8d** showed low insecticidal activities as anticipated. Unexpectedly, compound **9a** constructed by glutaraldehyde had moderate activity against cowpea aphid but was inactive against armyworm. Analogues **9c** and **9d** also exhibited weak activities against cowpea aphid but no activity against armyworm. The volume or conformation of substituent at the N3-atom on the imidazoline had an influence on activities (*1*, *7*, *10*, *41*), and the difference of ring size and conformation between **8a** and **9a** could possibly account in part for the higher potency of **8a** than of **9a**.

In conclusion, a series of divalent and oxabridged neonicotinoids were designed and synthesized by incorporating dialdehydes to nitromethylene analogues of imidacloprid. The bioassays showed that some of the compounds exhibited excellent insecticidal activities against cowpea aphid and armyworm. Further bioassay demonstrated that compound **8a** displayed a 50-fold higher activity against imidacloprid-resistant brown planthopper than imidacloprid. Oxabridged **8a** constructed by succinaldehyde had better activities than **9a** constructed by glutaraldehyde. Studies on the modes of action of **8a** and further field trials and structural modifications of compound **8a** are underway.

Supporting Information Available: CIF data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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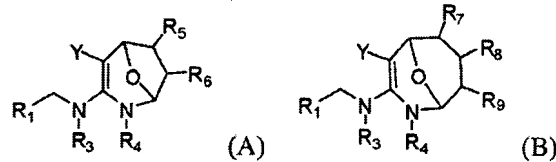
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Received for review July 21, 2009. Revised manuscript received November 4, 2009. Accepted November 19, 2009. This work was financially supported by the National Basic Research Program of China (973 Program, 2010CB126100), the National High Technology Research and Development Program of China (863 Program, 2006AA10A201), the National Science Foundation China Program Grant (20872034), and the Program for New Century Excellent Talents in University (NCET070284). This work was also partly supported by the Shanghai Foundation of Science and Technology (08391911600, 0XD1401300, 073919107), the grant “Application of Nuclear Techniques in Agriculture” from the Chinese Ministry of Agriculture (Grant 200803034), and the Shanghai Leading Academic Discipline Project, Project B507.111 Project B07023.

13

REIVINDICACIONES

1. Un compuesto heterocíclico unido por puente oxa relacionado a nicotina, en donde dicho compuesto corresponde a cualquier compuesto que se selecciona del grupo que consiste en compuestos con la estructura ilustrada por la Fórmula (A), o un isómero óptico o sal agroquímicamente aceptable del mismo, y compuestos con la estructura ilustrada por la Fórmula (B), o un isómero óptico o sal agroquímicamente aceptable del mismo:



caracterizado porque:

R₁ es un heterociclo de cinco o seis miembros que contiene nitrógeno, oxígeno y/o azufre; un heterociclo de cinco o seis miembros que contiene nitrógeno, oxígeno o azufre halogenado; o un fenilo sustituido o no sustituido, en donde el sustituyente es halógeno;

R₃ y R₄ forman en conjunto -CH₂-CH₂-, o -CH₂-CH₂-CH₂-;

R₅, R₆, R₇, R₈, y R₉ son hidrógeno; y

Y es nitro.

2. El compuesto de la reivindicación 1, caracterizado porque el compuesto se selecciona del grupo que comprende los siguientes compuestos:

9-((6-cloropirid-3-il)metil)-4-nitro-8-oxa-10,11-dihidroimidazo-[2,3-a]-biciclo-[3,2,1]-oct-3-eno;

9-((2-clorotiazol-5-il)metil)-4-nitro-8-oxa-10,11-dihidroimidazo-[2,3-a]-biciclo-[3,2,1]-oct-3-eno;

9-benzil-4-nitro-8-oxa-10,11-dihidroimidazo-[2,3-a]-biciclo-[3,2,1]-oct-3-eno;

9-(4-cloro-bencil)-4-nitro-8-oxa-10,11-dihidroimidazo-[2,3-a]-biciclo-[3,2,1]-oct-3-eno;

9-((tetrahydrofurano-3-il)metil)-4-nitro-8-oxa-10,11-dihidroimidazo-[2,3-a]-biciclo-[3,2,1]-oct-3-eno;

10-((6-cloropirid-3-il)metil)-4-nitro-9-oxa-11,12-dihidroimidazo-[2,3-a]-biciclo-[3,3,1]-non-3-eno;

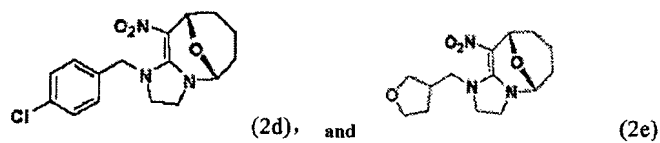
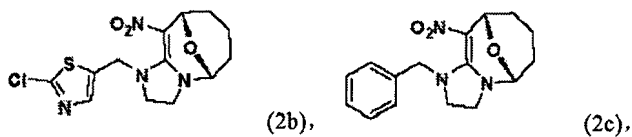
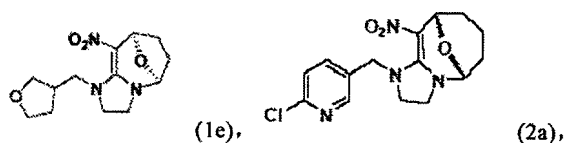
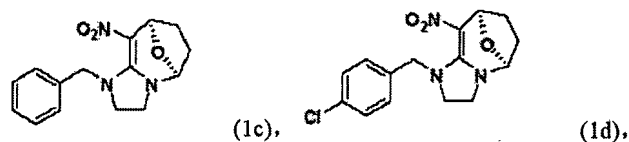
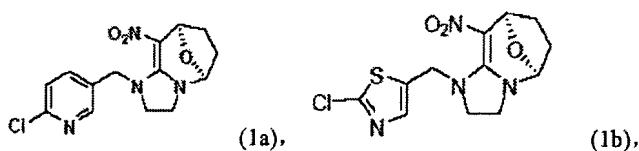
10-((2-clorotiazol-5-il)metil)-4-nitro-9-oxa-11,12-dihidroimidazo-[2,3-a]-biciclo-[3,3,1]-non-3-eno;

10-bencil-4-nitro-9-oxa-11,12-dihidroimidazo-[2,3-a]-biciclo-[3,3,1]-non-3-eno;

10-(4-clorobencil)-4-nitro-9-oxa-11,12-dihidroimidazo-[2,3-a]-biciclo-[3,3,1]-non-3-eno; y

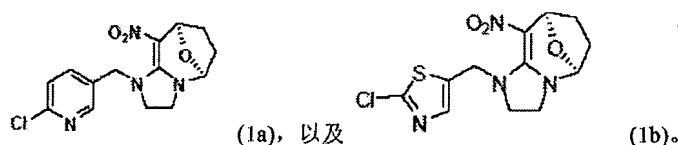
10-((tetrahidrofuran-3-il)metil)-4-nitro-9-oxa-11,12-dihidroimidazo-[2,3-a]-biciclo-[3,3,1]-non-3-eno.

3. El compuesto heterocíclico unido por puente oxa relacionado a nicotina o a un isómero óptico o una sal agroquímicamente aceptada del mismo de la reivindicación 1, caracterizado porque el componente heterocíclico unido por puente oxa relacionado a nicotina se selecciona del siguiente grupo:



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4. El compuesto heterocíclico unido por puente oxa relacionado a nicotina, o un isómero óptico o sal agroquímicamente aceptable del mismo de la reivindicación 1, caracterizado porque el compuesto heterocíclico unido por puente oxa relacionado a nicotina se selecciona del siguiente grupo:



5. Compuesto heterocíclico unido por puente oxa relacionado a nicotina, o un isómero óptico o sal agroquímicamente aceptable del mismo de la reivindicación 4, caracterizado porque la actividad de los compuestos heterocíclicos unidos puente oxa relacionados a nicotina (1a) y (1b) contra saltamontes marrones de planta resistentes a imidacloprida, y moscas blancas del tabaco, es 2 a 30 veces aquella de imidacloprida.

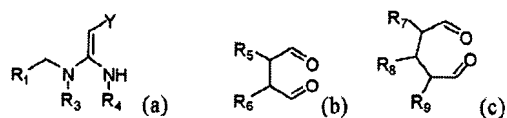
6. Una composición agroquímica caracterizada porque comprende:

(a) 0,001 a 99.99 % en peso del compuesto heterocíclico unido por puente oxa relacionado a nicotina de cualquiera de las reivindicaciones 1 a 5, un isómero óptico o sal agroquímicamente aceptable del mismo, o una combinación de los mismos; y

(b) un portador y/o excipiente agroquímicamente aceptable.

7. Método para preparar el compuesto heterocíclico unido por puente oxa relacionado a nicotina, o un isómero óptico o sal agroquímicamente aceptable del mismo de cualquiera de las reivindicaciones 1 a 5, método que comprende el paso de:

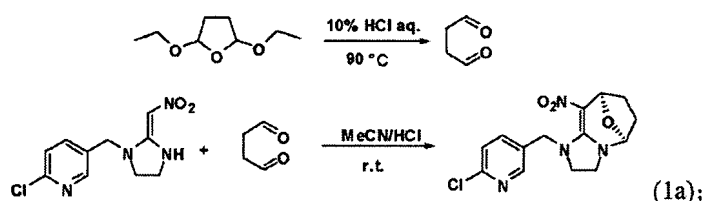
preparar los compuestos de las Fórmulas (A) y (B) reactando del compuesto de la Fórmula (a) con el compuesto de la Fórmula (b) o (c) temperatura ambiente en la presencia de una cantidad catalítica de ácido,



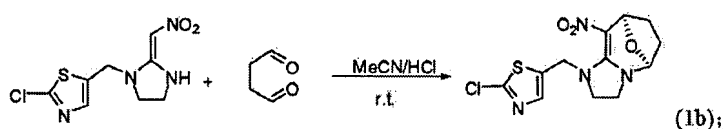
caracterizado porque R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉ e Y son como se definen en la reivindicación 1.

8. Método de la reivindicación 7, caracterizado porque el método comprende los pasos de:

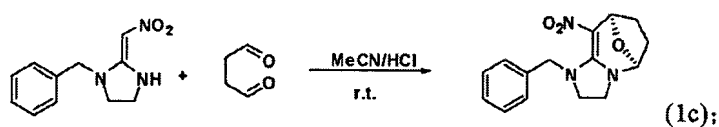
obtener el compuesto de la Fórmula (1a) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



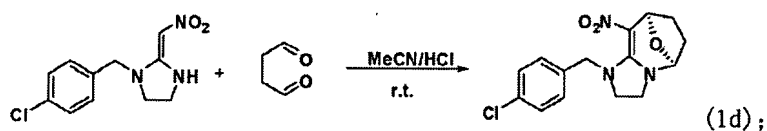
obtener el compuesto de la Fórmula (1b) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



obtener el compuesto de la Fórmula (1c) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



obtener el compuesto de la Fórmula (1d) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;

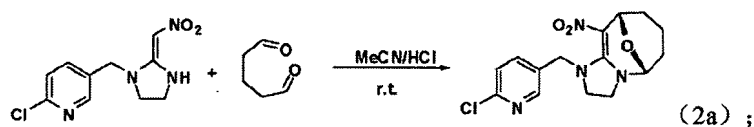


obtener el compuesto de la Fórmula (1e) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;

A



obtener el compuesto de la Fórmula (2a) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



obtener el compuesto de la Fórmula (2b) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



obtener el compuesto de la Fórmula (2c) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



obtener el compuesto de la Fórmula (2d) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;



y obtener el compuesto de la Fórmula (3b) llevando a cabo la siguiente reacción por 2 a 24 horas en acetonitrilo a temperatura ambiente en la presencia de una cantidad catalítica de ácido;

