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cis-Nitromethylene neonicotinoids as new nicotinic family: Synthesis, structural diversity, and insecticidal evaluation of hexahydroimidazo[1,2-α]pyridine

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ABSTRACT

A series of neonicotinoids analogues of hexahydroimidazo[1,2-α]pyridine were modified at 5-, 6-, and 7-positions, and their insecticidal activities were evaluated. Introducing a methyl or ethyl at 7-position increased the insecticidal activities, while other substituents decreased activities. When alkyl substituents were introduced to 7-position, the insecticidal activities against Pea aphids decreased in the order methyl (**7a**) > ethyl (**7b**) > *n*-butyl (**7e**) > phenyl (**7f**) > *n*-propyl (**7c**) > *iso*-propyl (**7d**), *p*-NO_2-phenyl (**7g**). Modifications at 5-, 6- or both at 6- and 7-positions with methyl or ethyl were unfavorable to activities. Interestingly, introducing methyl to 7-position not only increased insecticidal activities against pea aphids, but also show higher insecticidal activities than imidacloprid against imidacloprid-resistant brown planthopper.

Nicotinic acetylcholine receptors (nAChRs) are major excitatory neurotransmitter receptors in both vertebrates and invertebrates.[1] Ligands for nAChRs are of considerable interest, due to their important physiological, pharmacological, medical, and insecticidal applications.[2,3] Insect nAChRs mediate fast synaptic transmission in the insect nervous system and are targets of a major group of insecticides, the neonicotinoids.[4] Neonicotinoids represented by imidacloprid[5] (**1**, Fig. 1) are the most important class of insecticides over the past three decades because of their potency, low mammalian toxicity, broad insecticidal spectra, and good systemic properties.[6,7] After imidacloprid, six insecticides of this class: acetamiprid,[8] nitenpyram,[9] thiamethoxam,[10,11] thiacloprid,[12] clothianidin,[13] and dinotefuran[14] were commercialized. The relatively low risk combined with their suitability for a range of application methods maintain neonicotinoids as major insecticides widely used against a broad spectrum of sucking and biting insects.[15]

A potential problem facing all insecticides is the development of resistance and its concomitant detrimental effect on agricultural productivity.[16] Although the new mode of action, frequent applications and structural similarity of neonicotinoids have led to the acquisition of resistance and cross-resistance in a range of species.[17–24] Especially, the brown planthopper, *Nilaparvata lugens*, a major rice pest in many parts of Asia, has developed strong resistance to imidacloprid.[17,20,25]

Discovering insecticides with novel structures or mode of actions is one of the effective resistance-management tactics. Hence, the development of new neonicotinoids with high insecticidal activities against resistance strains is highly desirable. As well known, the structural feature of $-NO_2$ in imidacloprid act important role in its activities. The $-NO_2$ in all commercialized neonicotinoids are in *trans*-configuration and three proposals for modes of action are based on *trans*-configuration.[26] However, some dicyclic neonicotinoids with *cis*-configuration also showed high insecticidal activities.[27,28] In previous study, we have found some potential neonicotinoids with *cis*-configuration, unfortunately, the activities of these compounds had no superiority over imidacloprid.[29–31] Interestingly, further bioassay on sensitive and resistance strains against imidacloprid of brown planthopper, *N. lugens*, showed that compounds **2** have higher activity against resistance strains, which implied the further structural modification might give valuable results in resistance management. Moreover, the previous results showed interesting effects of small alkyl substituents on final bioactivities. In order to explore the influence of alkyl

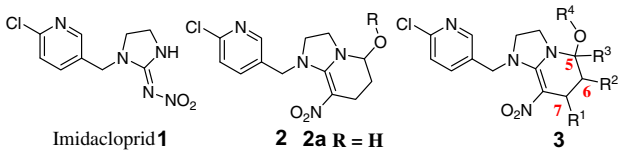

Figure 1. Neonicotinoids.

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substituents on the bioactivities, a series of nitromethylene neonicotinoids **3** were designed and synthesized by introducing various alkyl substituents at 5-, 6-, and 7-positions of hexahydroimidazo[1,2-α]pyridine scaffold of lead compounds **2**. Some of these candidates show higher activities against pea aphids, while four active compounds have higher activities against imidacloprid-resistant brown planthopper than imidacloprid.

The novel neonicotinoid derivatives described herein were synthesized as shown in Scheme 1. Starting from 2-chloro-5-chloromethylpridine **4**, *N*′-((5-chloropyridin-2-yl)-methyl)ethane-1,2-diamine **5** and intermediate **6** were obtained following the procedure reported previously.[32] Reaction of **6** with various α, β-unsaturated aldehydes or α, β-unsaturated ketones was catalyzed by concentrated HCl or glacial acetic acid in acetonitrile at 40–50 °C, affording desired compounds **7a–g**, **9**, **11a–b**, **12**, and **13**. The further reaction of **7a–g** or **9** with various alcohols could proceed readily in refluxing dichloromethane catalyzed by hydrochloric acid to give ethers **8a–y** or **10a–b**. The structures of the compounds were well characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and/or EA.

Ethers **8a–y** and **10a–b** were obtained in excellent yields. The yields of **7a–g**, **9**, **11a–b**, **12**, and **13** were relatively low and the reaction temperature should be controlled bellow 50 °C in order to inhibit the formation of hydroxyl-eliminated byproducts. α, β-unsaturated aldehydes bearing one substituent at 3-position could react smoothly with **6** under catalysis of glacial acetic acid, while α, β-unsaturated aldehydes bearing substituents at 2-positions (including cyclohex-1-enecarbaldehyde) react with **6** only in the presence of concentrated HCl, rather than AcOH. The reaction of **6** with α, β-unsaturated aldehydes bearing two substituents at 3-position could not proceed, which may be due to steric hindrance of two substituents.

In order to obtain precise three-dimensional structural information, compound **8a** was recrystallized by slow evaporation from mixed solvent of dichloromethane and acetone (V:V = 1:1) and its single-crystal structure was determined by X-ray crystallography as illustrated in Figure 2.[33] The tetrahydropyridine adopts a half-chair conformation. Owing to the transfer of the lone-pair electrons on the amines to C(1)–C(2) double bond, the C(1)–N(1) and C(1)–C(2) bond lengths, 1.332 and 1.335 Å, are remarkably shorter than the pure C–N single bond (1.47 Å) but close to C=N (1.33 Å).[34,35] The delocalization of the electrons extends as far as

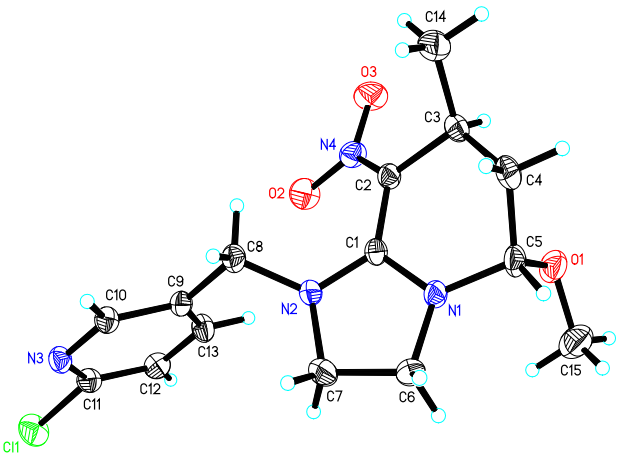
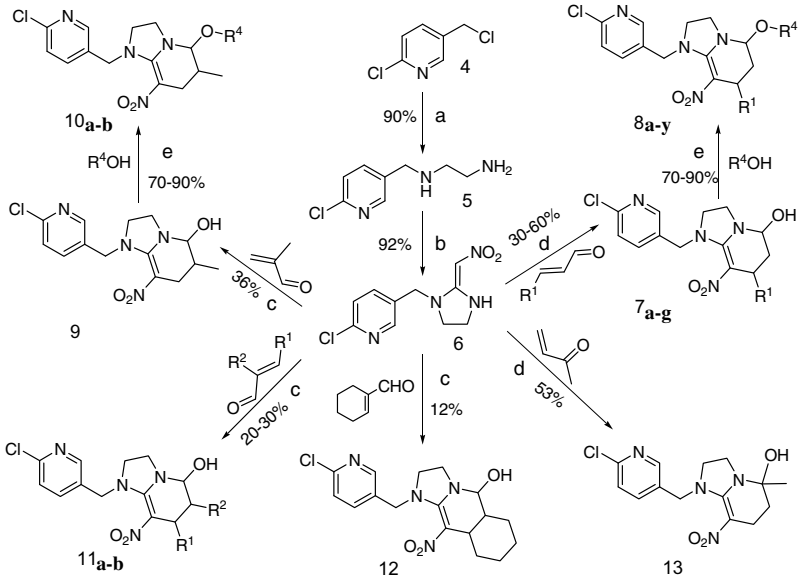


Figure 2. ORTEP view showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability for compound **8a**.

the electron-withdrawing group, $-NO_2$, forming a coplanar olefin-amine π-electron network. Furthermore, the bond lengths of C(1)=C(2) and C–NO_2 are 1.425 and 1.348 Å, which are longer than that of typical C=C (1.34 Å) and shorter than that of typical C–NO_2 (C–N in C–NO_2; 1.49 Å), respectively. Compared with the *trans*-configuration of nitro in the crystal structure of imidacloprid,[34] the nitro group in **8a** is obviously in *cis*-configuration as anticipated. As all the modes of action were put forward based on *trans*-configuration, this unique *cis*-configuration may confer some new properties onto the compounds.

The insecticidal activities of compounds **7a–g**, **8a–y**, **9**, **10a–b**, **11a–b**, **12** and **13**, and imidacloprid were screened against Pea aphids (*Aphis craccivora*) using the method described before.[30] Results were summarized in Table 1.

As indicated in Table 1, many of the compounds exhibited significant insecticidal activities against Pea aphids, although somewhat lower than that of imidacloprid (e.g., **7a**, **8c**, **8n**). The activities of the compounds in Table 1 varied drastically, depending upon the types and patterns of substitution on tetrahydropyridine. Introducing methyl or ethyl substituents at the 7-position of



Scheme 1. Reagents and conditions: (a) ethane-1,2-diamine, CH_3CN, 0–5 °C; (b) 1,1-bis(methylthio)-2-nitroethene, CH_3CH_2OH, refluxing; (c) CH_3CN, concd HCl., 40–50 °C; (d) CH_3CN, AcOH, 40–50 °C; (e) CH_2Cl_2, concd HCl, refluxing.

Table 1
Insecticidal activities of compounds **7a–g**, **8a–y**, **9**, **10a–b**, **11a–b**, **12**, **13**, and imidacloprid against Pea Aphids

Compound	R^1	R^2	R^3	R^4	Mortality (%) (500 mg/L)	LC_{50} (mg/L)
7a	Methyl	H	H	H	100	31.51
7b	Ethyl	H	H	H	100	61.01
7c	*n*-Propyl	H	H	H	25	n.t.
7d	*iso*-Propyl	H	H	H	0	n.t.
7e	*n*-Butyl	H	H	H	85	n.t.
7f	Phenyl	H	H	H	30	n.t.
7g	*p*-NO_2-Phenyl	H	H	H	0	n.t.
8a	Methyl	H	H	Methyl	100	50.00
8b	Methyl	H	H	Ethyl	100	65.43
8c	Methyl	H	H	*n*-Propyl	100	33.66
8d	Methyl	H	H	*iso*-Propyl	100	96.18
8e	Methyl	H	H	Chloroethyl	100	74.7
8f	Methyl	H	H	Allyl	100	n.t.[a]
8g	Methyl	H	H	*n*-Butyl	58.4	n.t.
8h	Methyl	H	H	*sec*-Butyl	0	n.t.
8i	Methyl	H	H	iso-Butyl	0	n.t.
8j	Methyl	H	H	Hydroxethyl	0	0
8k	Methyl	H	H	Cyclohexyl	0	n.t.
8l	Methyl	H	H	Benzyl	94	n.t.
8m	Ethyl	H	H	Methyl	90	n.t.
8n	Ethyl	H	H	Ethyl	100	48.86
8o	Ethyl	H	H	*n*-Propyl	100	86.42
8p	Ethyl	H	H	*iso*-Propyl	100	88.93
8q	*n*-Propyl	H	H	Methyl	89	n.t.
8r	*n*-Propyl	H	H	Ethyl	95	n.t.
8s	*n*-Propyl	H	H	*n*-Propyl	82	n.t.
8t	*n*-Propyl	H	H	*iso*-Propyl	79	n.t.
8u	*iso*-Propyl	H	H	Ethyl	72	n.t.
8v	Phenyl	H	H	Methyl	50	n.t.
8w	Phenyl	H	H	Ethyl	89	n.t.
8x	Phenyl	H	H	*n*-Propyl	45	n.t.
8y	Phenyl	H	H	*iso*-Propyl	0	n.t.
9	H	Methyl	H	H	70	n.t.
10a	H	Methyl	H	Methyl	73	n.t.
10b	H	Methyl	H	*iso*-Propyl	67	n.t.
11a	Methyl	Methyl	H	H	50	n.t.
11b	Ethyl	Methyl	H	H	0	n.t.
12					0	n.t.
13	H	H	Methyl	H	90	n.t.
7a[b]	H	H	H	H	100	58.30
Imidacloprid					100	7.90

[a] n.t., not tested.
[b] Compounds from our previous paper.

2a generated analogues **7a** and **7b** with increased (up to 2-fold) and similar insecticidal activities as **2a**, respectively. Meanwhile, introduction of other substituents was unfavorable to activities. Comparing the alkyl groups attached at the 7-position, the insecticidal activities of the corresponding analogues **7a–g** decreased in the order methyl (**7a**) > ethyl (**7b**) > *n*-butyl (**7e**) > phenyl (**7f**) > *n*-propyl (**7c**) > *iso*-propyl (**7d**), *p*-NO_2-phenyl (**7g**). For the effects of the R^4, the modification of compound **7a** with a longer alkyl group showed decreasing tendency in insecticidal activities. Compound **9**, **10a–b**, and **13**, bearing a methyl group at the 6- or 5-position of **2**, demonstrated lower activities than **2**. The compounds **11a**, **11b**, and **12** with two substituents or a six-member ring at both 6- and 7-position of **2a** have low or no activities.

Considering the bioassay results described above, compounds **7a**, **8c**, **8d** and **8m**, and imidacloprid were selected to further evaluate the activities against sensitive and imidacloprid-resistant brown planthopper (*N. lugens*) used the similar method employed for Pea aphids. The results were shown in Table 2. Although compounds **7a**, **8c**, **8d**, and **8m** showed lower insecticidal activities against sensitive brown planthopper than that of imidacloprid, they had higher (up to 2- to 3-fold) activities against imidacloprid-resistant strains. Brown planthopper exhibited certain cross-resistance to **8m**, but only slight cross-resistance to **7a**, **8c**, or **8d**.

In conclusion, a series of novel analogues of **2** with alkyl substituents at the 5-, 6-, and 7-positions were synthesized and their preliminary insecticidal activities were evaluated. Introduction of a methyl or ethyl substituent at the 7-position led to increased insecticidal activities against Pea aphids and brown planthopper (*N. lugens*). It was observed that alkyl substituents attached at 7-position give the insecticidal activities against Pea aphids in the order methyl (**7a**) > ethyl (**7b**) > *n*-butyl (**7e**) > phenyl (**7f**) > *n*-propyl (**7c**) > *iso*-propyl (**7d**), *p*-NO_2-phenyl (**7g**). Other alkyl substituents

Table 2
Insecticidal activities of compounds **7a**, **8c**, **8d**, **8m**, and imidacloprid against sensitive and imidacloprid-resistant strains of brown planthoppper (*Nilaparvata lugens*)

Strains	Compound	LC_{50}value (mg/L)	Index of relative toxicity
Sensitive strain	**7a**	20.72	145.2
	8c	7.35	7.5
	8d	5.57	51.5
	8m	1.07	39.1
	Imidacloprid	0.14	1.0
Resistant strain	**7a**	7.36	51.6
	8c	7.20	62.1
	8d	6.33	50.5
	8m	8.87	44.4
	Imidacloprid	19.73	138.3

at 5-, 6- or both at 6- and 7-positions were not desirable. The most beneficial alteration of the **2** was the addition of a methyl substituent to 7-position, which effected increased insecticidal activities against pea aphids, higher insecticidal activities against imidacloprid-resistant brown planthopper than imidacloprid and only slight cross-resistance to imidacloprid. The further structural modifications and studies on mode of actions are under investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.10.048.

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