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cis-Configuration: A New Tactic/Rationale for Neonicotinoid Molecular Design

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ABSTRACT: Resistance development and limited lepidopteran activities call for the discovery of "super-neonicotinoids" solving these problems. Compounds with the *cis*-configuration offer an opportunity for further optimization. Fixing the nitro group in the *cis*-configuration provided a new approach for neonicotinoid molecular design. Introductions of the heterocycle or a bulky group are two synthesis concepts to fix the *cis*-configuration of the nitro group. The design, synthesis, bioactivity, and preliminary modes of action of five types of *cis*-neonicotinoids are reviewed. *cis*- and *trans*-Neonicotinoids have some differences in bioactivities and modes of action. This study focused, especially, on the reaction diversities of nitromethylene analogues of imidacloprid with various aldehydes.

KEYWORDS: neonicotinoids, *cis*-configuration, insecticide, selectivity

INTRODUCTION

Natural and synthetic insecticides are key components of today's integrated pest management (IPM) best practices.[1,2] Since their introduction in the 1980s, neonicotinoids have been established as the insecticides of choice for agricultural, animal health, and public health usages. Imidacloprid,[3] for example, is the top-selling insecticide today. It contains the core substructure of nicotine and nitromethylene[4] (Figure 1). Neonicotinoids act selectively on the insect central nervous system (CNS) as agonists of the postsynaptic nicotinic acetylcholine receptors (nAChRs).[5−7] The greatest attributes of the neonicotinoids are their novel mode of action, low mammalian toxicity, broad insecticidal spectrum, and good systemic properties.[8,9] These properties along with their favorable environmental footprint enable the neonicotinoids to replace the more toxic and nonselective organophosphorus, pyrethroid, and carbamate insecticides. Although 30 years have been passed since their invention, the discovery of novel neonicotinoid molecules,[10−15] further exploration for modes of action,[5,16,17] and receptor structure guided neonicotinoid design continue to be active areas of intense research today.[13,14]

Most of the reported neonicotinoids consist of four primary structural features: (1) an aromatic heterocycle, (2) a flexible linkage, (3) a hydroheterocyle or guanidine/amidine, and (4) an electron-withdrawing functional group (Scheme 1).[9,18] Detailed structure−activity relationship studies on these four segments revealed that the most common electron-withdrawing segements are C═N—NO_2, C═C—NO_2, and C═N—CN. Due to the existence of the C═C or C═N double bond, neonicotinoids can exist as an isomer in which the nitro or cyano group is located away from the aromatic heterocycle (*trans*) or as an isomer in which the nitro or cyano group is pointed in the same direction as the aromatic heterocycle (*cis*). Crystallographic analysis of imidacloprid showed that the pyridine moiety and the nitro group are oriented in the opposite direction, that is, *trans* configuration, relative to the chloropyridinylmethyl moiety.[19] Quantum chemistry calculations confirmed that the *trans*-configuration was more stable than the *cis*-isomer in both the gaseous and aqueous phases (0.000005% of the *cis*-isomer in gas phase and 0.0012% of the *cis*-isomer in aqueous phase).[20] All modes of action were put forward on the basis of the *trans*-configuration.[16,20,21] Furthermore, high-resolution crystallographic structure analysis of AChBP−neonicotinoid complexes[5,17] affirmed that imidacloprid (clothianidin or thiacloprid) bound with the receptor in the *trans*-configuration. However, there is very little information on the biological properties and binding model of the *cis*-neonicotinoids. In the late 1980s, Bayer and Nihon Tokushu Noyaku Seizo Co. reported that several *cis*-configuration neonicotinoids, **4**−**8** (Figure 2), showed high insecticidal activity.[22,23] Casida's group reported that the high affinity of **4** with *Drosophila* nAChRs was comparable to that of the *trans*-neonicotinoids,[24] but there is no follow-up research in this lead area.

It is well established that *trans*/*cis* isomers may differ significantly in biological activity, toxicity, and metabolic properties in medicinal chemistry. Due to the importance of electron-withdrawing moieties (C═N—NO_2, C═C—NO_2, and C═N—CN) in the activity spectrum and binding properties,[19,20] it is necessary to reemphasize the importance of addressing *trans*/*cis* chemistry in neonicotinoid development. This *cis*/*trans* isomeric selectivity has been an ongoing research interest of our laboratory

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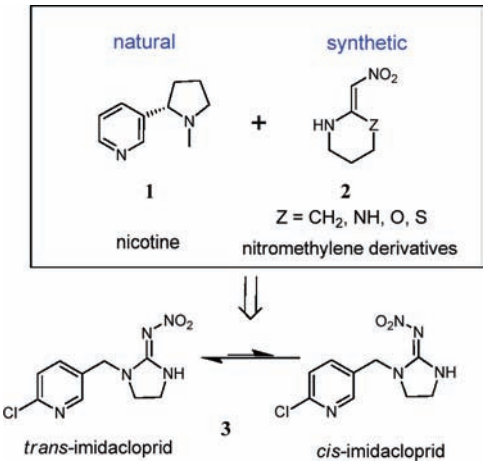
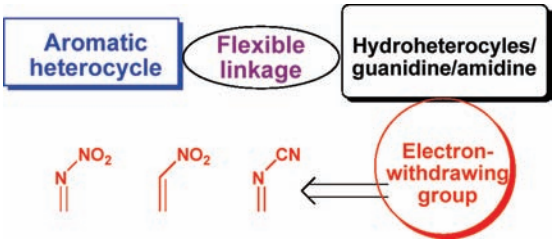


Figure 1. Imidacloprid, a combination of the natural nicotine and synthetic nitromethylene substructure.

Scheme 1. General Structure of Neonicotinoids and Structural Feature of Electron-Withdrawing Group



over the past several years. We conducted extensive research to explore the chemical and biological properties of the *cis*-neonicotinoids. The rationale for fixing the direction of the nitro or cyano group involved the use of fused heterocycles or bulky groups.

We provide in this paper our findings on the synthesis and biological activity of the *cis*-neonicotinoids. A perspective of future research trends and research needs in this area is also presented.

NEONICOTINOIDS WITH TETRAHYDROPYRIMIDINE FIXED *CIS*-CONFIGURATION

As mentioned above, Bayer CropSciences reported the first synthesis of *cis*-neonicotinoid **4** in 1988 using tetrahydropyrimidine to fix the *cis*-configuration. However, no further development of this series of compounds was reported. The molecular design principle for our initial foray into this area was on the basis of "me-too" methodology. Because of the saturation of the C═N double bond in imidacloprid, it was impossible to introduce another functional group/substructure to fix the *cis*/*trans* configuration. Compound **9** (the tetrahydropyrimidinyl nitromethylene analogue of imidacloprid)[25] had an unsaturated C═C double bond; thus, further chemical modification was possible (Figure 3). Our first approach was to improve the hydrophobicity; a saturated cyclopentane ring was introduced to the tetrahydropyrimidine to generate compound **10**. Compound **10** (calculated log *P* = 2.71) had a higher log *P* value than **9**

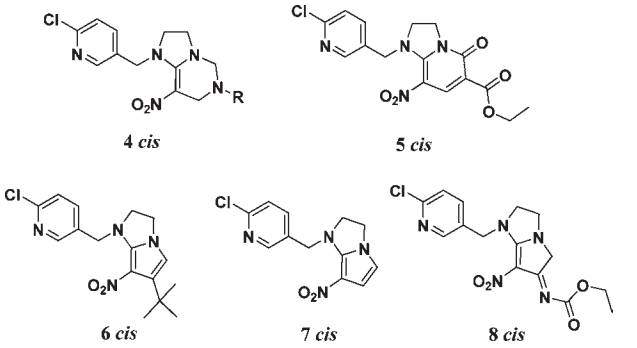


Figure 2. Neonicotinoids with *cis*-configuration discovered by Bayer and Nihon Nohyaku.

(calculated log *P* = 1.70). Our second approach was to introduce a tetrahydropyrimidine heterocyclic moiety to yield compound **11** with a *cis*-configuration. Unfortunately, compound **11** showed only moderate activity (30−80% mortality at 500 mg L^{-1}) against cowpea aphids (*Aphis craccivora*).[26] No further follow-up with this compound series was carried out.

Our next approach was to prepare a series of compounds **13** using the nitromethylene intermediate **12**. A series of compounds were obtained in which the common pyridine was replaced with a unique dioxolane ring; however, this approach did not improve the biological activity (0−60% mortality at 500 mg L^{-1}).[27]

NEONICOTINOIDS WITH TETRAHYDROPYRIDINE FIXED *CIS*-CONFIGURATION

To improve the poor biological activity of the compound **13** series, we explored 6-Cl-PMNI (**14**), a nitromethylene neonicotinoid discovered before imidacloprid, as the lead compound (Figure 4). 6-Cl-PMNI analogues exhibited higher insecticidal activities and receptor binding affinity[28] than imidacloprid; however, its lack of photostability[29] and weak hydrophobicity[30] limited its utility as a crop protection product. Tokumitsu reported that 2-(nitromethylene)imidazolidine reacted with α,β-unsaturated aldehydes using concentrated HCl or glacial acetic acid as catalyst, yielding hexahydroimidazo[1,2-α]pyridine derivatives. Using this approach, we examined this cyclization reaction to determine if we could fix the C═C—NO_2 moiety of 6-Cl-PMNI to the desired *cis*-configuration. This approach led to the discovery of compounds **15** with tetrahydropyridine fixed *cis*-configuration.[18] Some of these *cis*-compounds showed good insecticidal activity (>90% mortality at 500 mg L^{-1}) against cowpea aphids (*A. craccivora*). To explore the influence of alkyl substituents on the activity, various alkyl substituents were introduced into the 5-, 6-, and 7-positions of hexahydroimidazo-[1,2-α]pyridine scaffold of compounds **15**. Some of the compound **16** analogues showed not only high activity against cowpea aphids (LC_{50} = 0.0965−0.2645 mmol L^{-1}; imidacloprid LC_{50} = 0.031 mmol L^{-1}) but also activity (up to 3−5-fold that of imidacloprid) against imidacloprid-resistant brown planthopper (*Nilaparvata lugens*) (LC_{50} = 0.0173−0.0252 mmol L^{-1}; imidacloprid LC_{50} = 0.0774 mmol L^{-1}).[31] This is a welcome observation because alternative compounds are needed to combat the potential resistance problem of the current commercialized neonicotinoids.[32−39] Compound **17** (R^1 = methyl, R^2 = R^3 = H, R^4 = *n*-propyl) has the highest insecticidal activity, and it is

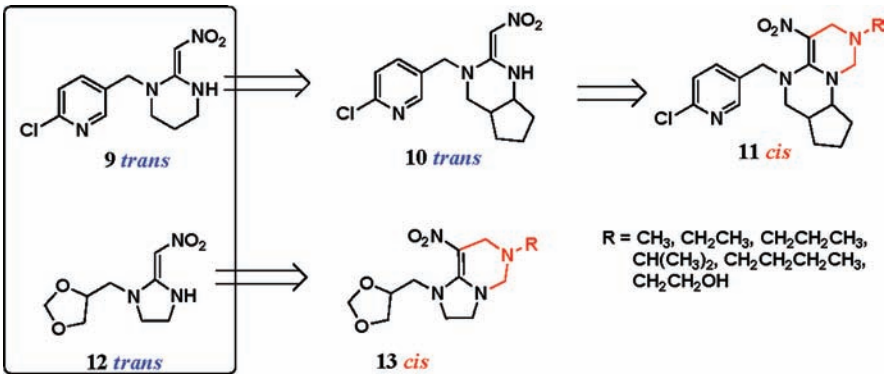


Figure 3. Neonicotinoids with tetrahydropyrimidine fixed *cis*-configuration.

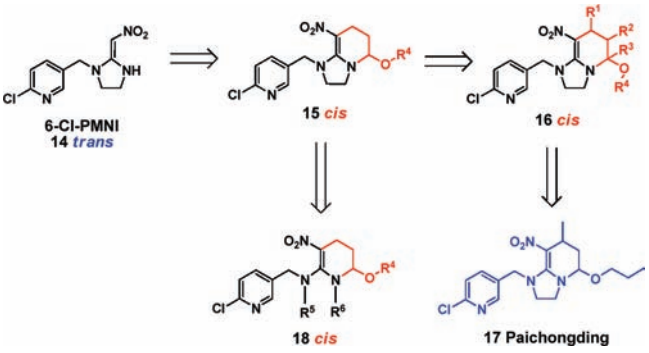


Figure 4. Neonicotinoids with tetrahydropyridine fixed *cis*-configuration.

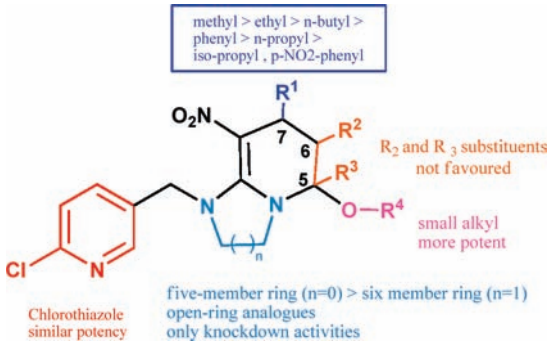


Figure 5. Structure−activity relationships of neonicotinoids with tetrahydropyridine fixed *cis*-configuration.

commercialized in China under the trade name "Paichongding". A series of open-ring analogues **18** was also synthesized, and a unique knock-down property against cowpea aphids was observed.

Structure−activity relationships (SAR) are summarized in Figure 5. Chlorothiazole analogues maintained high insecticidal activity because the 2-chloro-5-thiazole unit is an effective bioisosteric replacement for the 2-chloro-5-pyridine. For the effects of R^4, modification with a longer alkyl group showed decreasing insecticidal activity. Changing the five-membered imidazolidine to a six-membered hexahydropyrimidine attenuated the activity. Introducing a methyl or ethyl at the 7-position increased the insecticidal activity, whereas other substituents decreased the activity. When the alkyl substitutents attached at the 7-position were compared, the insecticidal activity against cowpea aphids decreased in the order methyl > ethyl > *n*-butyl > phenyl > *n*-propyl > isopropyl, *p*-NO_2-phenyl. Modifications at the 5- or 6-position or at both the 6- and 7-positions with methyl or ethyl diminished the activity. The optimal condition of **15** was the addition of a methyl group to the 7-position, showing increased insecticidal activity against cowpea aphid and imidacloprid-resistant brown planthopper with no apparent cross-resistance.

The unique structural property and insecticidal activity of *cis*-neonicotinoids make it interesting to investigate their mode of action. Primarily studies revealed that **17** and imidacloprid interact differently with nAChRs of brown planthopper (*N. lugens*). Two imidacloprid binding sites were found in *N. lugens*: high-affinity and low-affinity binding sites. Compound **17** preferentially interacts at the high-affinity imidacloprid binding site, whereas it interacted weakly at the lower affinity imidacloprid binding site.[40]

NEONICOTINOIDS WITH BULKY GROUP FIXED *CIS*-CONFIGURATION

Another configuration-modulating approach is to utilize steric or electronic constraints to hinder the interconversion and force the nitro group into the *cis*-configuration. Reaction of five-membered cyclic aromatic aldehydes with 6-Cl-PMNI, catalyzed by concentrated hydrochloric acid, yielded compounds **19** with bulky aromatic heterocycles adjacent to the nitro group (Figure 6). The *cis*-configuration of these compounds was confirmed by heteronuclear chemical shift correlation experiments (HMBC and NOESY).[41]

Most of these compound **19** analogues showed excellent insecticidal activity comparable to that of imidacloprid against cowpea aphid, *Nephotettix bipunctatus* (Fabricius), small brown rice planthopper (*Laodelphasx striatellus*), and armyworm (*Pseudaletia separate* Walker).[41] In general, compounds **19** showed good activity against not only homopteran insects but also lepidopteran species. One good example is compound **20**, which is up to 30-fold more active than imidacloprid against imidacloprid-resistant brown planthopper (LC_{50} = 0.7312 ng/pest; imidacloprid LC_{50} = 22.1614 ng/pest).

NEONICOTINOIDS WITH HIGHLY CONGESTED TETRAHYDROPYRIDINE FIXED *CIS*-CONFIGURATION CONSTRUCTED BY DIELS−ALDER REACTIONS

Compounds **19** described above were synthesized as the corresponding hydrochloric acid salts. However, we have to convert them into the neutral form prior to field evaluation.

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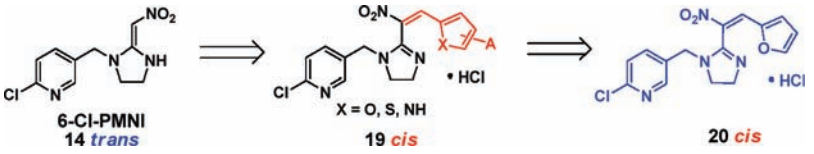

Figure 6. Neonicotinoids with bulky group fixed *cis*-configuration.

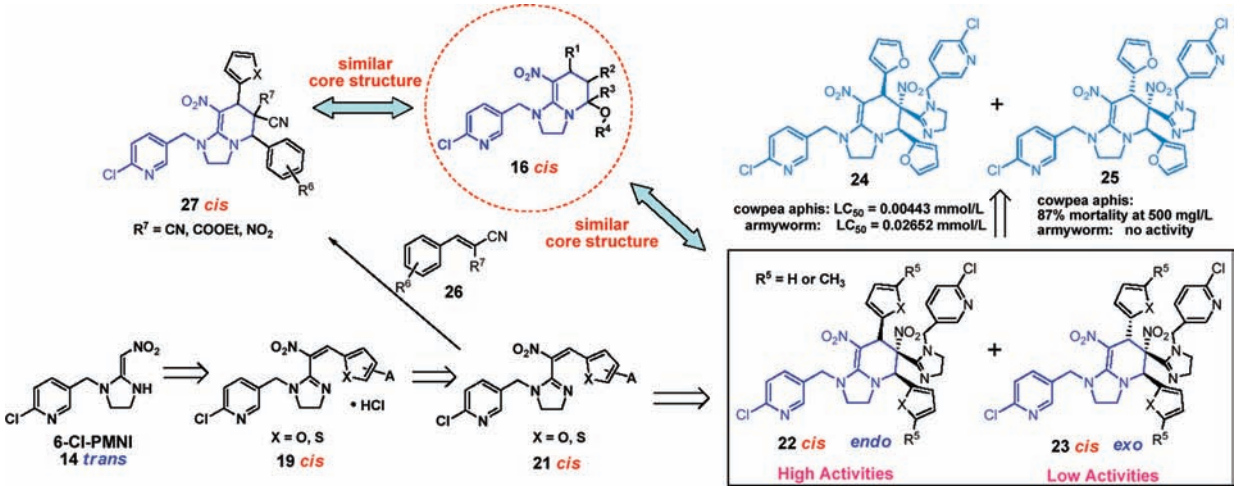

Figure 7. Neonicotinoids with highly congested tetrahydropyridine fixed *cis*-configuration constructed by Diels−Alder reactions.

However, compounds **21** were unstable and underwent self-Diels−Alder reaction to yield two new hexahydroimidazo[1,2-α]pyridine isomers, **22** and **23**.[42] Compounds **22** and **23** can be considered as neonicotinoids with the tetrahydropyridine moiety fixed at the *cis*-configuration (Figure 7).

Compound **22** and **23** isomers provided a new and unexplored scaffold as novel neonicotinoids. They can be prepared through self-aza-Diels−Alder reactions using compounds **21** as starting materials though a convenient, one-pot procedure with 6-Cl-PMNI.[42] Preliminary bioassay data showed the *endo*-derivatives **22** were active against cowpea aphids and armyworm, whereas the *exo*-derivatives **23** showed only limited activity. For example, the LC_{50} values of compound **24** against cowpea aphids and armyworm were 0.00443 and 0.03652 mmol L^{-1}, respectively, whereas **25** produced 87% mortality at 500 mg L^{-1}. The difference in biological activity between the *endo*- and *exo*-conformations indicated that molecular conformation was an important factor in the biological properties of the neonicotinoids. Compound **24** is about 10-fold more active than imidacloprid against imidacloprid-resistant brown planthopper (LC_{50} = 0.00376 mmol L^{-1}; imidacloprid LC_{50} = 0.03882 mmol L^{-1}).[42]

On the basis of the above observations, it is evident that the C═C—C═N moiety in compounds **21** could serve as both the diene and dienophile in the Diels−Alder (DA) reaction. DA reactions of **21** might be another way to construct neonicotinoids with tetrahydropyridine fixed *cis*-configuration. Consequently, we extended the DA reactions of **21** as dienes with other dienophiles with a view to derivatize **21**. However, no reaction occurred when other electron-deficient dienophiles, such as methyl acrylate, acrylonitrile, and 1,1-dichloro-2-nitroethene, were investigated as dienophile. Finally, reactions with dienophiles **26** were feasible, and a series of compounds **27** were synthesized. Many of the reaction products showed good activity against cowpea aphids and armyworm at 500 mg L^{-1}.[43]

■ OXABRIDGED *CIS*-NEONICOTINOIDS CONSTRUCTED BY DIALDEHYDES

The discovery of oxabridged *cis*-neonicotinoids was serendipitous. 6-Cl-PMNI can be considered a cyclic β-nitroenamine, which contains two nucleophilic centers (C and NH). When 6-Cl-PMNI reacted with α,β-unsaturated aldehydes or other five-membered aromatic aldehydes described above, two types of neonicotinoids were obtained. We are especially interested in investigating the behavior of dialdehydes when reacted with 6-Cl-PMNI. Unexpectedly, when succinaldehyde and glutaraldehyde were reacted with 6-Cl-PMNI, peculiar oxabridged *cis*-neonicotinoids **28** and **29** were formed (Figure 8). Compound **28** exhibited higher activity than imidacloprid against cowpea aphids (LC_{50} = 0.00471 mmol L^{-1}) and armyworm (LC_{50} = 0.03873 mmol L^{-1}). Furthermore, its activity (LC_{50} = 0.49 ng/pest) was 50-fold higher than that of imidacloprid (LC_{50} = 22.16 ng/pest) against resistant brown planthopper. Compound **29** had lower activity against cowpea aphids (87% mortality at 500 mg L^{-1}) and brown planthopper (LC_{50} = 0.0742 ng/pest) and was nonactive against armyworm.[44] The directions of oxabridges in these two compounds were opposite when we examined the crystal structures of **28** and **29**. Small differences in structural configuration can lead to large differences in the overall activity. Preliminary study showed that compound **28** might act on nAChRs as an antagonist. Most neonicotinoids are partial or full agonists of native and recombinant nAChRs; only some bis-neonicotinoids had been reported to be antagonists of nAChRs expressed by ganglion neurons of the American cockroach,

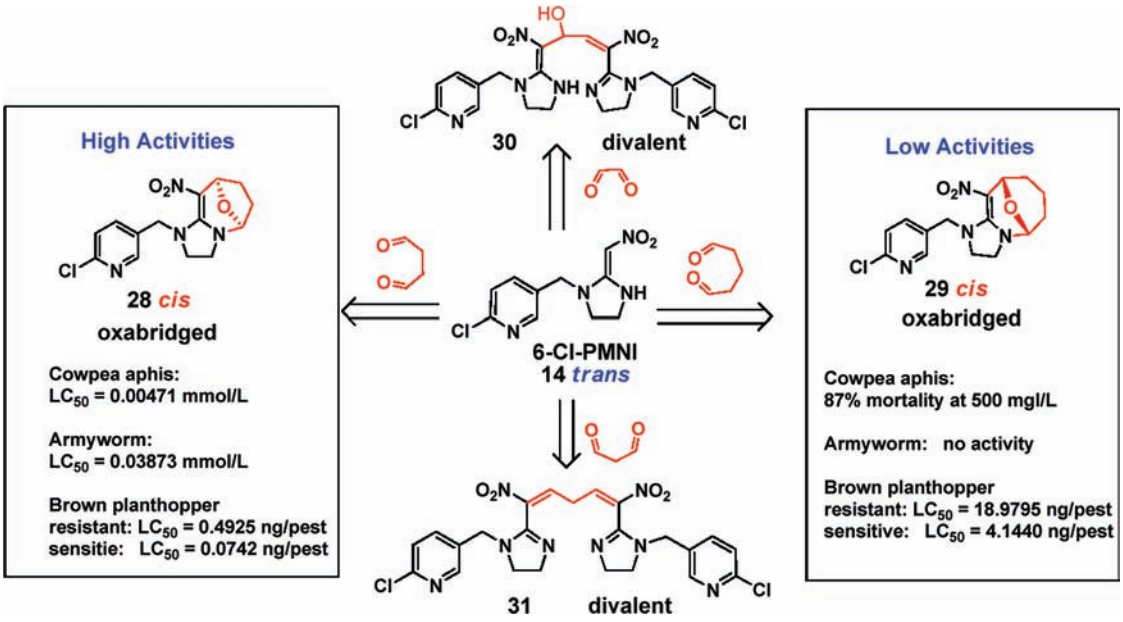

Figure 8. Oxabridged and divalent neonicotinoids constructed by dialdehydes.

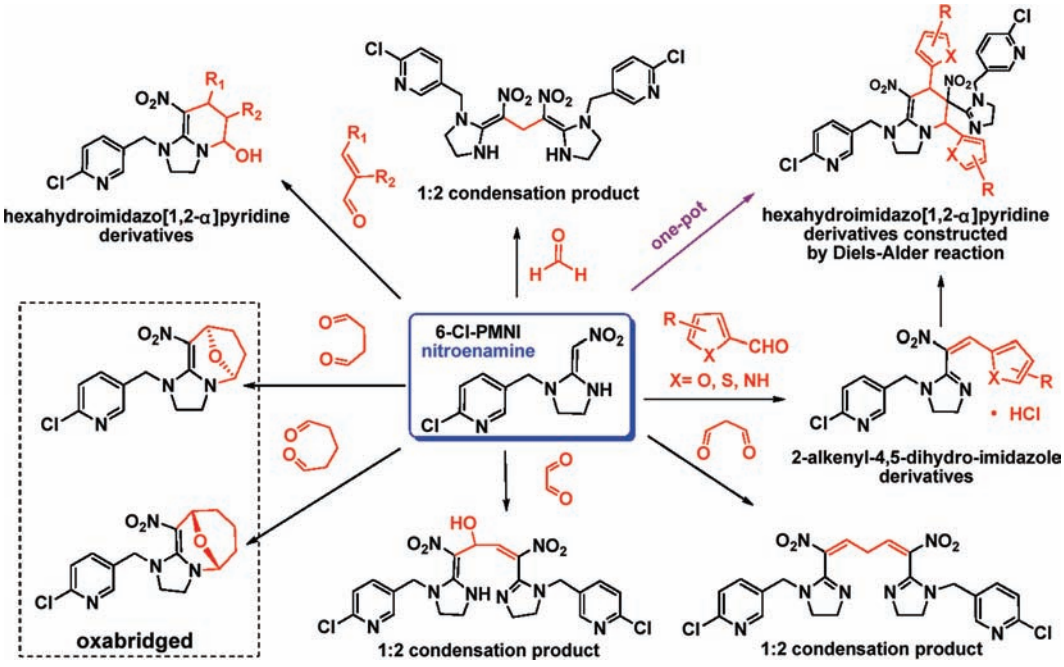

Figure 9. Reaction diversity of 6-Cl-PMNI with aldehydes.

Periplaneta americana.[45] It is important to point out that reactions of oxalaldehyde and malonaldehyde with 6-Cl-PMNI yielded two divalent neonicotinoids, compounds **30** and **31**.[44]

■ REACTION DIVERSITY OF 6-Cl-PMNI WITH ALDEHYDES: APPLICATION TO THE DERIVATION OF β-NITROENAMINES

6-Cl-PMNI reacts readily with different aldehyde reactants; 6-Cl-PMNI can be classified as a cyclic β-nitroenamine, which attracted considerable attention as a versatile intermediate in organic synthesis.[46−48] The biological spectra of β-nitroenamines are not limited to neonicotinoid insecticides but also include use as antiulcerative drugs.[49,50] Recent research has revealed that the two electron-donating amino groups and fixed C−N bonds in the five-membered ring make C in C═C a potential nucleophilic center, whereas the N in imidazolidine acted as another nucleophilic center.[51]

With regard to the cyclic nitroenamine 6-Cl-PMNI compound series, reaction with different aldehyde reactants led to vast product diversity. Reaction of 6-Cl-PMNI with formaldehyde, α,β-unsaturated aldehydes, five-membered aromatic aldehydes,

and dialdehydes yielded hexahydroimidazo[1,2-α]pyridine derivatives, 2-alkenyl-4,5-dihydroimidazole derivatives, and 1:2 condensation products or oxabridged heterocyclic compounds, respectively (Figure 9). Highly congested analogues such as hexahydroimidazo[1,2-α]pyridine derivatives can be synthesized by a simple one-pot DA reaction between 6-Cl-PMNI and the various five-membered aromatic aldehydes (Figure 9). This synthetic route could be easily adapted to prepare nitroenamines as well as other functional or structural analogues.

CONCLUSION

cis- and *trans*-configurations are common phenomena in organic chemistry, but they have uncommon implications when employed in neonicotinoids; *cis*-neonicotinoids emerged and expanded molecular alphabets in neonicotinoid libraries, and this new class of compounds has achieved proof of concept in bioassays. The systematic design and synthesis of an extensive series of *cis*-neonicotinoids was performed to explore subtle relationships between structures using fundamental chemistry principles. *cis*-Neonicotinoids exhibited excellent activities against a broad spectrum of insects; some *cis*-neonicotinoids were shown to have high activity against imidacloprid-resistant insects and had different binding models compared with imidacloprid. Although strategies for the intentional design and synthesis of *cis*-neonicotinoid molecules are emerging, research on *cis*-neonicotinoids is still in its infancy. It is an attractive area for further lead optimization effort. Whether the bioactivities can be maintained and whether metabolic profiles can be altered in field application for some compounds still need further study. Additional research on binding model and the differences between *cis*- and *trans*-compounds is necessary to broaden our understanding on the interaction with nAChRs of these *cis*-neonicotinoids. Obtaining high-resolution crystal structures of nAChRs *cis*-neonicotinoid complexes will continue to be a challenging research area to elucidate the actual interaction situation. The continued success of the neonicotinoids will depend on whether we can minimize their resistance development potential in sensitive species, high bee toxicity,[52] and low lepidopteran activities. We hope our enthusiasm and persistent dedication will make some contribution to this area.

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