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SYNTHESIS AND INSECTICIDAL ACTIVITIES OF TETRAHYDROIMIDAZO[1,2-a]PYRIDINONES: FURTHER EXPLORATION ON *CIS*-NEONICOTINOIDS

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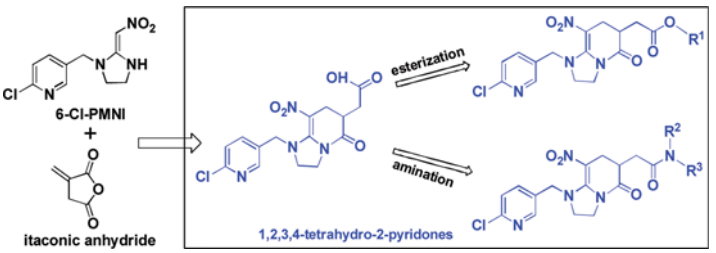
GRAPHICAL ABSTRACT



Abstract cis-*Neonicotinoid, in which the nitro and cyano pharmacophore point to the same position relative to the heteroaromatic moiety, is a further extension of the neonicotinoid library. While seeking new* cis-*neonicotinoid candidates, a series of tetrahydroimidazo[1,2-a]pyridinone derivatives were synthesized by reactions of nitromethylene analogs with itaconic anhydride. All the compounds were confirmed by* ^{1}H *NMR,* ^{13}C *NMR, and high-resolution mass spectroscopy. The target compounds had excellent insecticidal activities against cowpea aphids (*Aphis craccivora*) and brown planthopper (*Nilaparvata lugens*). Against armyworm, most of the compounds showed moderate activities. Interestingly, compound* ***12p*** *was active against* Tetranychus cinnabarinus. *The synthesized compounds displayed good insecticidal activities against different insect species, which might provide useful guidance for further design of* cis-*neonicotinoid candidates.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Activities; insecticide; neonicotinoids

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INTRODUCTION

The largest group of insecticides used worldwide today is the neonicotinoids.[1,2] They act selectively on insect central nervous system as agonists of the postsynaptic nicotinic acetylcholine receptors (nAChRs).[3] Although many years have passed since their invention, research relating to neonicotinoids is still an active area. These studies focus mainly on discovery of novel neonicotinoid molecules to conquer resistance and high bee toxicity,[4] elucidation of modes of action,[5,3a,6] resistance monitoring and management,[7] metabolism[8], and receptor structure-guided neonicotinoid design.[4b,4c,9] Sulfoxaflor, developed by Dow AgroSciences as a new chemotype of neonicotinoid, is a good representative.[10] Sulfoxaflor exhibits high potency and lacks cross-resistance, which could be used as an alternative tool in controlling sap-feeding insect pests.[11,12]

Nitromethylene neonicotinoid 2-chloro-5-((2-(nitromethylene)imidazolidin-1-yl)methyl)pyridine (6-Cl-PMNI) is not only an insecticidal compound but also an attractive scaffold for further transformations.[13] Lots of chemical derivatizations focusing on 6-Cl-PMNI have been performed in our group to construct *cis*-neonicotinoids, and two of them, paichongding and cycloxaprid (Fig. 1), have been commercialized in China.[14]

In the effort to develop neonicotinoids with *cis*-configuration, reactions of 6-Cl-PMNI with various aldehydes were investigated systematically. Different types of aldehydes exhibited different reaction behaviors toward 6-Cl-PMNI. Reaction of 6-Cl-PMNI with formaldehyde, α,β-unsaturated aldehydes, five-membered aromatic aldehydes, and succinaldehyde afforded 1:2 condensation product,[13] hexahydroimidazo [1,2-α]pyridine derivatives,[15] 2-alkenyl-4,5-dihydro-imidazole derivatives,[16] and oxabridged compound,[17] respectively (Fig. 2). The encouraging results inspired us to further explore reaction diversity of 6-Cl-PMNI for constructing novel *cis*-neonicotinoids.

Itaconic anhydride **5** is an important chemical intermediate with multiple reactive sites and could react with heterocyclic ketene animals **6** (Fig. 3).[18] Enlightened by this observation, we examined the reaction behavior of 6-Cl-PMNI with itaconic anhydride with a view to search for novel *cis*-neonicotinoid derivatives (Fig. 2). Herein, we present the results of our findings on insecticidal tetrahydroimidazo[1,2-a]pyridinone derivatives.

RESULTS AND DISCUSSION

Synthesis

The synthetic route of the target compounds is depicted in Scheme 1. From precursor 2-chloro-5-chloromethylpridine, the desired β-nitroenamines 6-Cl-PMNI

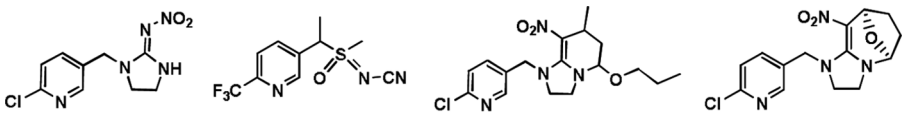


Figure 1. Commercialized neonicotinoids imidacloprid, sulfoxaflor, paichongding, and cycloxaprid.

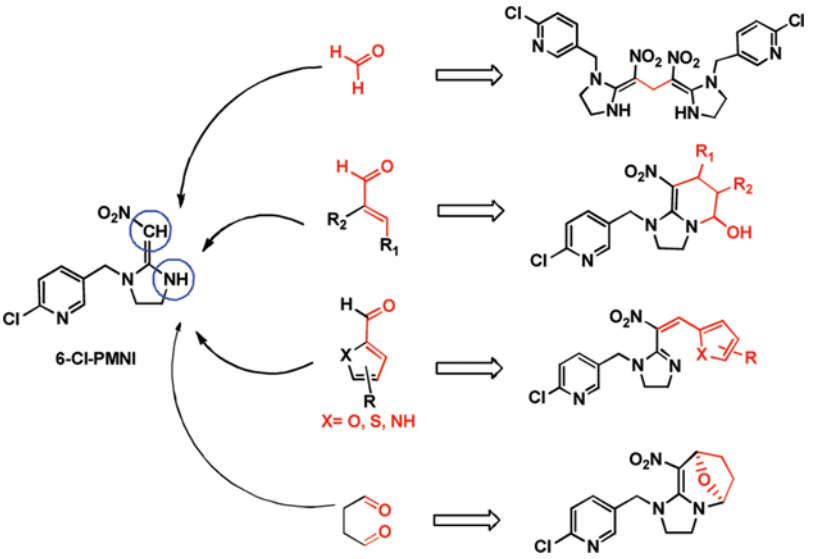


Figure 2. Reaction diversity of 6-Cl-PMNI towards various aldehydes. (Figure is provided in color online.)

was readily synthesized according to the conventional method.[19] It can be categorized as a cyclic β-nitroenamine with two reactive nucleophilic sites (the C in C=C and the N in imidazolidine), which were proven to be efficient partners in aza-annulation reactions. 6-Cl-PMNI manifests itself as a common enamine in electrophilic reactions in spite of the presence of the strongly electron-withdrawing nitro group, and reactions of nitroenamines with a variety of electrophiles (such as such as sulfurisocyanatidic chloride, thiocyanogen, phenyl isocyanate, benzoyl isothiocyanate, and acrylate) have been well studied.[20]

6-Cl-PMNI could react smoothly with itaconic anhydride in acetonitrile at refluxing temperature, and compound **10** precipitated from the reaction mixture with good purity as expected. After filtration, compound **10** was obtained as a pale yellow powder and was used directly for further reaction without purification. Reactions of

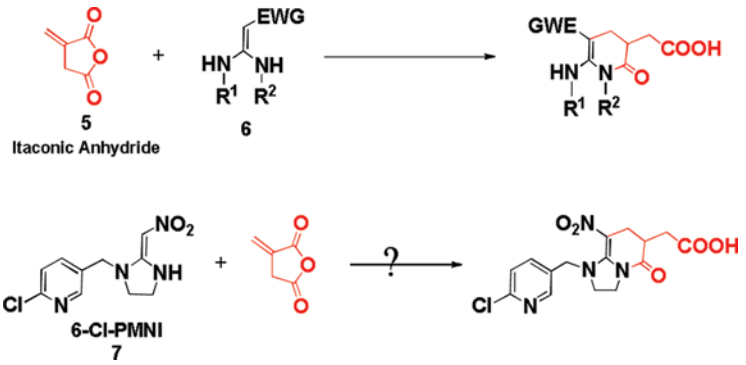
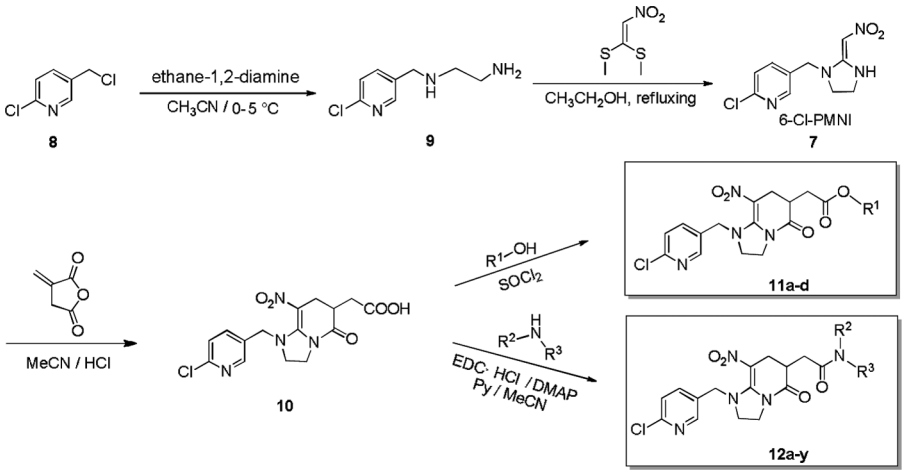


Figure 3. Design of novel tetrahydroimidazo[1,2-a]pyridinones. (Figure is provided in color online.)



Scheme 1. Synthetic route of tetrahydroimidazo[1,2-a]pyridinones.

10 with various alcohols could proceed readily catalyzed by thionyl chloride furnishing the corresponding esters **11a–d** in moderate yields. Amination of **10** with various amines in acetonitrile catalyzed by ethylene dichloride (EDC), dimethylaminopyride (DMAP), and pyridine afforded amides **12a–y** in good yields. The solubility of acid **10** is very poor, which makes it take a long time for the reaction to complete. Various solvent (such as dichloromethane, THF, acetonitrile, and acetone) had been screened. No reactions were detected in dichloromethane, THF, acetonitrile, or acetone, due to the poor solubility of **10** in these solvents, while the pyridine and acetonitrile mixture had good solubility to **10** and was selected as the reaction solvent. The reaction temperature must be controlled below 40 °C, for many by-products would form and the yield was rather poor (<10%) at higher temperature. The electron-withdrawing substituents and bulky groups of benzene in amine would decrease the yield of amination; for example, the 2-iodoaniline could not react with **10** at room temperature, and the reaction temperature should be raised to 80 °C.

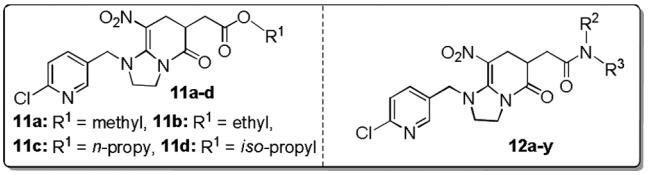
Activity

To evaluate the overall insecticidal activities of tetrahydroimidazo[1,2–a] pyridinones, four representative insects from three different orders (Lepidoptera, Hemiptera, and Acarina) were selected as the test pests. Table 1 lists the results against these four insects. Cycloxaprid, a *cis*-neonicotinoids with the greatest activities discovered in our group, was selected as a comparison. Meanwhile, nitenpyram and emamectin were also tested under the same conditions.

Insecticidal Activities Against Cowpea Aphids (*Aphis craccivora*)

Acid **10** and the esters **11a–d** were initially tested, but all these compounds demonstrated poor activity. Subsequently, amides **12a–y** were obtained with improvement of activity. All the amide analogs showed moderate insecticidal activity with the exception of **12o**. Compound **12o** gave the best activity with 40% mortality

Table 1. Insecticidal activities of compounds **10, 11a–d**, and **18a–y** against cowpea aphids (*Aphis craccivora*), *Tetranychus cinnabarinus*, armyworm (*Pseudaletia separate Walker*), and brown planthopper (*Nilaparvata lugens*)



Compound	Yield (%)	R^2	R^3	Concentration (mg L^{-1})	Mortality (%) *Aphis craccivora*	*Tetranychus cinnabarinus*	*Pseudaletia separate Walker*	*Nilaparvata lugens*
10	79	–	–	500	20	–	0	–
11a	47	–	–	500	28	–	0	–
11b	32	–	–	500	17	–	0	–
11c	44	–	–	500	47	–	0	–
11d	52	–	–	500	18	–	0	–
12a	63	Ethyl	Ethyl	500	100	0	30	100
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12b	47	R^2 and R^3 taken together formed -CH_2 CH_2 CH_2 CH_2-		500	0	0	50	100
				100	–	–	0	60
				20	–	–	0	0
				4	–	–	0	0
12c	68	H	*n*-Butyl	500	0	0	50	100
				100	–	–	0	70
				20	–	–	0	0
				4	–	–	0	0
12d	88	H	Phenyl	500	0	0	90	100
				100	0	–	0	100
				20	0	–	0	80
				4	0	–	0	0
12e	80	H	4-Fluorophenyl	500	0	0	90	100
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12f	36	H	2-Methyl-4-(perfluoropropa-n-2-yl)phenyl	500	0	0	100	100
				100	0	–	0	40
				20	0	–	0	0
				4	0	–	0	0
12g	28	H	2,3-Difluorophenyl	500	100	0	100	100
				100	0	–	0	85
				20	0	–	0	0
				4	0	–	0	0
12h	25	H	2,4,5-Trifluorophenyl	500	0	0	90	100
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12i	37	H	3-Chloro-4-fluorophenyl	500	100	0	100	100
				100	0	–	0	0
				20	0	–	0	0
				4	0	–	0	0
12j	21	H	4-Nitrophenyl	500	0	0	90	100

(*Continued*)

Table 1. Continued

Compound	Yield (%)	R^2	R^3	Concentration (mg L^{-1})	Mortality (%)			
					Aphis craccivora	*Tetranychus cinnabarinus*	*Pseudaletia separate Walker*	*Nilaparvata lugens*
				100	0	–	0	0
				20	0	–	0	0
				4	0	–	0	0
12k	55	H	p-Tolyl	500	100	0	20	100
				100	0	–	0	100
				20	0	–	0	95
				4	0	–	0	0
12l	58	H	2,6-Dimethylphenyl	500	0	0	0	100
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12m	51	H	Thiazol-2-yl	500	0	0	100	0
				100	0	–	0	0
				20	0	–	0	0
				4	0	–	0	0
12n	60	H	Pyridin-2-yl	500	100	0	0	95
				100	30	–	0	0
				20	0	–	0	0
				4	0	–	0	0
12o	70	H	4-Methylpyridin-2-yl	500	100	0	100	95
				100	100	–	30	0
				20	70	–	0	0
				4	40	–	0	0
12p	77	H	Pyridin-3-yl	500	0	95	95	100
				100	0	0	0	20
				20	0	0	0	0
				4	0	0	0	0
12q	51	H	6-Chloropyridin-3-yl	500	0	0	100	0
				100	0	–	0	0
				20	0	–	0	0
				4	0	–	0	0
12r	90	H	Benzyl	500	100	0	0	100
				100	80	0	0	70
				20	0	0	0	0
				4	0	0	0	0
12s	35	H	4-Trifluoromethyl-benzyl	500	100	0	100	100
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12t	66	H	3,4-Difluorobenzyl	500	100	0	100	100
				100	60	–	0	95
				20	0	–	0	30
				4	0	–	0	0
12u	56	H	2,5-Difluorobenzyl	500	100	0	30	100
				100	0	–	0	100
				20	0	–	0	70
				4	0	–	0	0
12v	56	H	3-Chloro-4-fluorobenzyl	500	100	0	0	100
				100	0	–	0	100
				20	0	–	0	85
				4	0	–	0	0
12w	54	H	2,3,6-Trifluorobenzyl	500	100	0	100	100

(*Continued*)

Table 1. Continued

Compound	Yield (%)	R^2	R^3	Concentration (mg L^{-1})	Mortality (%) *Aphis craccivora*	*Tetranychus cinnabarinus*	*Pseudaletia separate Walker*	*Nilaparvata lugens*
				100	0	–	0	100
				20	0	–	0	0
				4	0	–	0	0
12x	90	H	3-Trifluoromethyl-benzyl	500	100	0	70	100
				100	0	–	0	100
				20	0	–	0	30
				4	0	–	0	0
12y	60	H	4-Methoxybenzyl	500	100	0	50	100
				100	0	–	0	100
				20	0	–	0	95
				4	0	–	0	0
Cycloxaprid				4	100	–	30	100
				1	100	–	10	90
Nitenpyram				4	100	100	–	100
Emamectin benzoate				4	–	–	100	–

at the dosage of 4 mg L^{-1}. From the existing results, it had some difficulties in acquiring precise structure–activity relationship. The influence of substituent's electronic property, position, or number was also not easy to determine. Monofluorinated **12e** showed no activities, all difluorinated substituted compounds **12g, 12t,** and **12u** exhibited certain activity irrespective of fluorine's positions, and trifluorinated compounds manifested poor (**12w**) or no (**12h**) activity. Compound **12n** with pyridine-2-yl had good activity, whereas **12p** with pyridine-3-yl was totally devoid of activity. All the compounds showed less activity than cycloxaprid and nitenpyram, which could not meet the requirements for commercialized development.

Insecticidal Activities Against *Tetranychus cinnabarinus* and Armyworm (*Pseudaletia separate Walker*)

As anticipated, no activities were found in synthesized compounds against *Tetranychus cinnabarinus* except compound **12p** with 95% mortality at 500 mg L^{-1}, which was consistent with the fact that all the commercialized neonicotinoids showed no or poor activity against *Tetranychus cinnabarinus*. Against armyworm, most of the target compounds exhibited 20% to 100% mortality at 500 mg L^{-1}, whereas the ester compounds **11a–d** and amide analogs **12 l** and **12v** were completely inactive. When tested at the dosage lower than 100 mg L^{-1}, all the candidates lose the activity, which made it difficult to find the influence factor on bioactivity tendency.

Insecticidal Activities Against Brown Planthopper (*Nilaparvata lugens*)

Although **12m** and **12q** were ineffective, the rest of the amide analogs were endowed with high activity against brown planthopper. At the dosage of 20 mg L^{-1},

compounds **12d, 12k, 12t, 12u, 12v, 12x,** and **12y** still exhibited good activity. Interestingly, compound **12o** had excellent activity against cowpea aphids but very poor activity against brown planthopper. In comparison with cycloxaprid, nitenpyram and imidacloprid, the activities of the target compounds were not high enough, and they need further structural modification to improve activity.

CONCLUSION

Tetrahydroimidazo[1,2–a]pyridinones expanded the molecular libraries of *cis*-neonicotinoid. These tetrahydroimidazo[1,2–a]pyridinone derivatives could easily be synthesized by nitromethylene analogs of imidacloprid and itaconic anhydride. Against hemiptera insects, brown planthopper, and cowpea aphids, the synthesized compounds exhibited excellent insecticidal activity, whereas the activities against *Tetranychus cinnabarinus* and armyworm were not desirable enough. This type of compounds could be used as the lead compounds for further structural optimization.

EXPERIMENTAL

Chemical Synthesis

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. Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 (400-MHz) spectrometer with dimethylsulfoxide (DMSO-d_6) as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra (HRMS) 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.

General synthetic procedure for compound 10. A mixture of compound 6-Cl-PMNI (10 mmol), itaconic anhydride (10 mmol), and acetonitrile was refluxed until the reaction was completed and the product was precipitated. The precipitate was filtered, washed with acetonitrile, and dried to give the corresponding product.

General synthetic procedure for compounds 11a–d. A mixture of compound **10** (1.5 mmol) and corresponding alcohol (12 ml) was stirred at room temperature for 10 min, then $SOCl_2$ was dropped into it, and the reaction liquid was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the organic solvent was extracted thoroughly with CH_2Cl_2, washed with water, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 4:1) to afford target products **11a–d.**

General synthetic procedure for compounds 12a–y. A mixture of compound **10** (1.5 mmol), corresponding anime (2.25 mmol), EDC · HCl (1.8 mmol),

DMAP (0.15 mmol), and pyridine (10 ml) was stirred at room temperature for 10 min. Then, acetonitrile (20 ml) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (v/v 10:1) to afford target products **12a–y.**

Biological Assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at $25 \pm 1\,^{\circ}C$ according to statistical requirements. All compounds with a purity of more than 98% 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, $125.0\,mg\,L^{-1}$ and others for bioassays.

Experimental details, characterization of the target compounds, and bioassay methods are available online as the Supplemental Information.

ACKNOWLEDGMENTS

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