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Discovery of Imidacloprid and Further Developments from Strategic Molecular Designs

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ABSTRACT: The invention of imidacloprid, the most important neonicotinoid insecticide, was initiated by replacement of the framework of nithiazine with an imidazolidine ring. Through the finding of 1-(6-chloro-3-pyridylmethyl)-2-nitromethyleneimidazolidine, imidacloprid was invented. At the same time cyanoiminothiazolidinyl neonicotinoid thiacloprid was discovered. These products possess pronounced systemic properties and improved photostability in addition to supreme insecticidal ability. Crystal structure analysis led to the drug−receptor interaction model consisting of the guanidine (amidine) part conjugated to a powerful electron-withdrawing group bearing an H-bond accepting tip such as NO_2 or CN, and the chloronicotinyl group enhances the binding to the receptor. The QSAR study not only supports the key pharmacophore but also clarifies the crucial involvement of the phamacokinetic factors in the insecticidal activity. A concept for strategic and rational design led to the discovery of alkylene-tethered bis-imidacloprid derivatives with unexpected systemic insecticidal property and the unique binding mechanism revealing the second cavity in the neonicotinoid receptor.

KEYWORDS: imidacloprid, thiacloprid, neonicotinoid insecticides, pharmacophore, QSAR, Lipinski's rule, systemic property, bis-imidacloprid

INTRODUCTION

The discovery of imidacloprid (**1**) has been referred to as a milestone in the past three decades of insecticidal research.[1−4] The unprecedented high insecticidal potency and supreme systemic properties were immediately recognized and through the following additional finding of activity against strains resistant to the prevailing insecticides and low mammalian toxicity, imidacloprid soon took over the lead in the world insecticidal market and has been the frontrunner ever since. The new insecticide class called neonicotinoids (**1**−**7**, Figure 1) heralded by imidacloprid shares 20% of the current insecticide market. Discovery of a new compound leading to a new chemical class with a novel mode of action happens only once or twice in the time-span of one's career. This review describes how we encountered imidacloprid and our fundamental study of this new class as well as our trials of further development from the strategic point of view.

PATH TO THE DISCOVERY OF IMIDACLOPRID

We started the project by pursuing nithiazine (**8**) in 1979,[1,5,6] which Shell announced as a new insecticide in 1978.[7] Electrophysiological studies clarified that nithiazine acts on the nicotinic acetylcholine receptor (nAChR) in the same fashion as nicotine. It seemed to us there were no obvious structural similarities between the two compounds. There were several possible variations from nithiazine to explore, the tetrahydrothiazine ring, the N or S atom in the central ring, or the push−pull olefin part (Figure 2). The one we explored was the transformation of the perhydrothiazine framework to α,ω-diazacycloalkanes.

The screening test was done with the green rice leafhopper (*Nephotettix cincticeps*), one of the most important pests for rice culture. Table 1 shows the concentrations for 90% mortality, LC_{90}. The activity was dependent on the ring size, and the five-membered ring compound (**9**) showed the highest activity. As the ring size increases, the activity decreases, and the seven- and eight-membered ring compounds had a severe loss of activity. The acyclic compound (**13**) completely lost the activity. At the time we concluded that the active molecule must be a cyclic structure and preferably a plain ring such as a five-membered ring. This assumption may have facilitated our research, but it caused a strategic error in product development as discussed later.

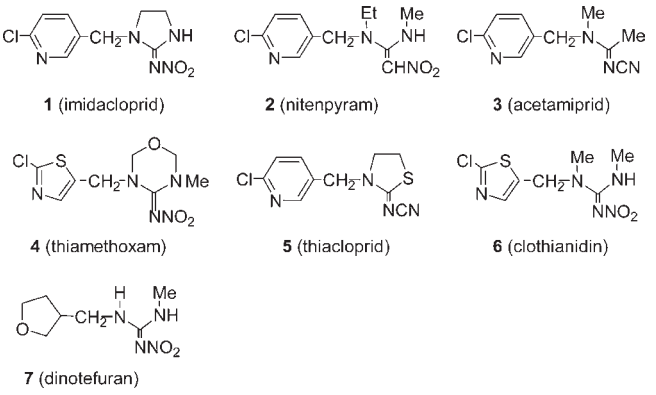

Figure 1. Commercial neonicotinoid insecticides.

Next we introduced various substituents to the five-membered ring and found that only the benzyl group enhanced the activity (Table 2). From this result, we first thought that the pharmacophore of this class may be the nitromethylene-imidazolidine itself

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and the activity would emerge when the benzyl group dissociated metabolically, noting the structure analogy to nithiazine.

However, when substituents were introduced to the benzylic benzene ring, the activity depended on the kind and position of the substituent, and the *p*-chloro and *m*-cyano derivatives (**21**, **25**) gave the best results (Table 3). The benzylic displacement is not likely affected so much by the kind and position of the substituent; therefore, we had to think that the active motif is not the nitromethylene-imidazolidine but the whole molecule

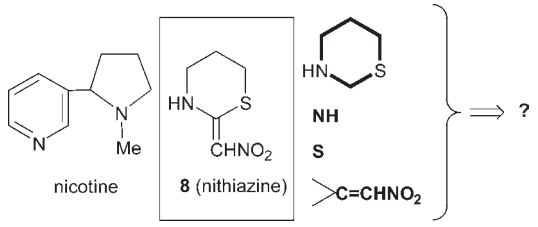
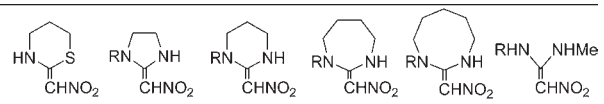


Figure 2. Nicotine and possible variants from nithiazine.

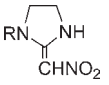
Table 1. Relationship between Ring Size and Insecticidal Activity (R = $CH_2C_6H_5$)[a]



	8 (nithiazine)	**9**	**10**	**11**	**12**	**13**
LC_{90}	40	200	>200	1000	1000	inactive

[a] Insecticidal activity was measured by exposing third-instar larvae of organophosphate- and carbamate-resistant strains mixed with the sensitive ones of the green rice leafhopper (*Nephotettix cincticeps*) to sprayed rice plants, and expressed by LC_{90}, the lowest concentration in ppm to kill >90% of the insects after 4 days.

Table 2. Relationship between Substituents and Insecticidal Activity in 2-Nitromethylene-imidazolidine[a]



	14	**15**	**16**	**17**	**9**	**18**
R	H	Me	cyclohexyl	Ph	$PhCH_2$	$PhCH_2CH_2$
LC_{90}	1000	1000	1000	1000	200	inactive

[a] See the footnote of Table 1.

containing the benzyl group with these substituents. This may have been a sign for the possible existence of active structures expanding from nithiazine, but we could not explore so far as this idea then, and above all the efficacies of our products were far short of that of nithiazine.

After two years, we took up nithiazine again in our work. This time we introduced heteroaromatic rings to the nitromethylene imidazolidine skeleton. After a few trials, we found that 3-pyridylmethyl (trivial name: nicotinyl) (**32**) and 4-pyridylmethyl derivatives (**33**) showed insecticidal activity superior to that of nithiazine. A similar enhancement was observed in other heteroaromatic rings with the nitrogen atom at the corresponding position (Table 4). At this stage we felt that we might be able to develop something in this class.

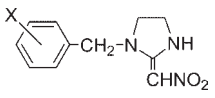
Soon after that, we found that a 6-chloro-3-pyridylmethyl group enhanced the activity extraordinarily. The LC_{90} of 6-chloro-3-pyridylmethyl-2-nitromethylene-imidazolidine (**41**) was 0.32 ppm (Table 5). This finding was the epoch-making event in our entire research road. We have keenly realized the miracle of nature whereby a molecule can change properties dramatically with the addition of only one atom. Around then we learned about the suspension of development of nithiazine.

We continued work on the structure−activity relationship study (SAR). For the functional group Y we had long believed that nitromethylene was the best. Actually, insufficient activity of derivatives with other functional groups (**52**−**56**) was along our prediction (Table 6). However, unexpectedly, the cyanoimine derivative (**57**) was highly insecticidal at 0.32 ppm, but other imino variants such as carbamate (**58**) or sulfonyl imine (**59**) were lower in activity. We continued working on the functional group variation and finally found the nitroimino derivative (**1**) with the highest activity. Thus, imidacloprid was born.

Imidacloprid was first prepared according to scheme 1 in Figure 3 on February 20, 1985. One week after that, the second candidate product in this class, thiacloprid (**5**), was prepared according to the given scheme. Bayer researchers devised the technical production for both compounds[8,9] and commercialized imidacloprid in 1991 and thiacloprid in 2000, and they have been used widely to control many kinds of harmful insects for major crops, vegetables, or parasites for pet animals.

When we look back, we are glad that we did not conclude that the nitromethylene derivative (**41**) was the best candidate but continued our work on the SAR for the functional group variations. Later, we figured out why nithiazine was canceled. It has a high photolability. Table 7 shows clearly the longer absorption wavelength of nitromethylene chromophores compared with nitroimines or cyanoimines and, consequently, essentially shorter half-lives under sun-lamp radiation.[10,11] This teaches us

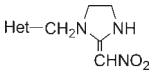
Table 3. Insecticidal Activity of *N*-(Substituted benzyl)-2-nitromethylene-imidazolidine[a]



	8[b]	**9**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
X		H	2-Cl	3-Cl	4-Cl	4-Me	4-MeO	$4\text{-}NO_2$	3-CN
LC_{90}									
green rice leafhopper	40	200	inactive	200	40	200	200	200	40
tobacco cutworm	<40				500				

[a] See the footnote of Table 1. [b] Nithiazine.

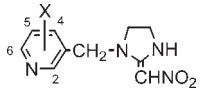
Table 4. Heteroarylmethylnitromethylene-imidazolidines and Insecticidal Activity[a]



Compound	26	27	28	29	30
Het:					
LC_{90}	200	200	200	200	500
Compound	31	32	33	34	
Het:					
LC_{90}	200	8	8	inactive	
Compound	35	36	37	38	39	40
Het:						
LC_{90}	40	8	8	8	40	200

[a] See the footnote of Table 1.

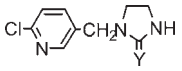
Table 5. Substituent Variations at the Pyridine Ring of 1-Nicotinyl-2-nitromethylene-imidazolidine[a]



	32	41	42	43	44	45	46	47	48	49	50	51
X	H	6-Cl	5-Cl	2-Cl	6-F	6-Br	6-Me	6-CF_3	6-CN	6-MeS	6-MeO	6-AcNH
LC_{90}	8	0.32	40	200	0.32	1.6	1.6	8	200	1000	200	1000

[a] See the footnote of Table 1.

Table 6. Variation of Functional Group on the Imidazolidine Ring[a]



	52	53	54	55	56	57	58	59	1 (imidacloprid)
Y	O	NH	CHCN	$CHCO_2Et$	$C(CN)_2$	NCN	NCO_2Et	NSO_2Me	NNO_2
LC_{90}	1000	1000	inactive	inactive	40	0.32	40	40	<0.32

[a] See the footnote of Table 1.

that stability under practical conditions is crucial for pesticide development.

Commercialization of a product cannot be realized only through the seeking work of synthetic chemists; it is first feasible through the cooperation of the overall sectors concerned. With regard to imidacloprid and thiacloprid, we should mention two critical contributions outside those of synthetic chemists. First, our biologists noticed the superb systemic property of nithiazine at the start of this project and built up the screening system targeting chewing hemipteran rice pests, instead of lepidopterans, which had been the target of nithiazine.[1] If we had focused on lepidopterans following Shell's approach, the discovery of imidacloprid may have been delayed; the compounds prepared at the earlier stages of this project were mostly low in activity against lepidopterans. The second noteworthy contribution to the exploration of the products worldwide is the devising of new formulations to make the most use of the pronounced physiological properties of imidacloprid, that is, the plant mobility and residual stability. Nursery box treatment is a case in point.[12] The active ingredient is mixed with the soil around the rice seedlings in a nursery box, and the treated soil with the seedlings is machine-planted to the rice field. This method has greatly reduced the labor for pest control and the pesticide load on the environment.

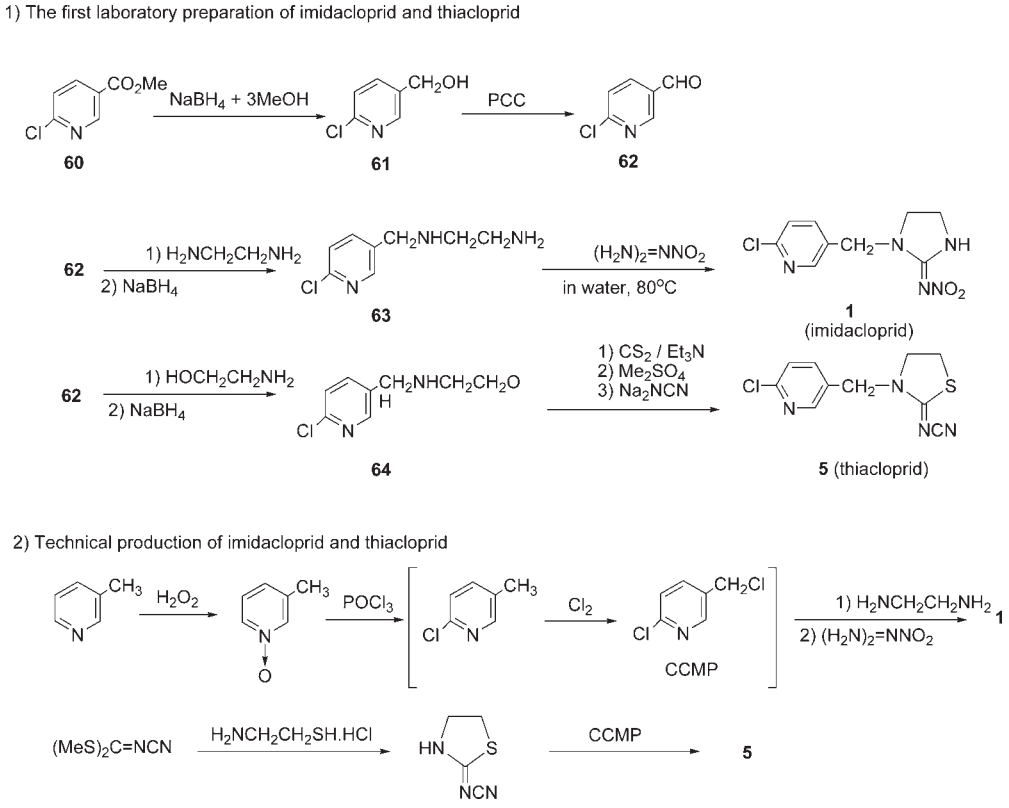
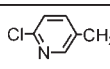
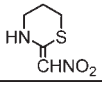


Figure 3. Schemes for the first laboratory preparation and technical production of imidacloprid and thiacloprid.

Table 7. Electronic Absorption of Chloronicotinyl Compounds in Water and Half-Life ($t_{1/2}$) by Photolysis[a]

Compound	R: 	Imax (nm) / log e (log e at 290 nm)	$t_{1/2}$ (hr)
1		269 / 4.17 (3.73)	3
65		269 / 3.61 (3.21)	3.5
41		323 / 4.09	1
66		313 / 4.17	2
67		357 / 4.23	<0.5
68		268 / 3.61 (< 0.01)	>24
8		348 / 4.07	0.5

[a] The $t_{1/2}$ data were obtained by irradiation of the compound in acetonitrile/water (8:2, v/v) solution by a 250 W sun lamp at 30 °C.

While we were heading for commercialization, other groups were not sleeping. Many researchers continually search the patents of rivals. We started with modifying the nithiazine and reached imidacloprid as shown in the development flow (Figure 4). In the early stage we assumed that the active molecule had to consist of a cyclic structure, preferably a five-membered ring, and conducted research in this direction.

However, this was a hasty conclusion. Later, we noted that the real key to the activity was not the ring size but the push−pull olefin substituted with a chloronicotinyl group. When we realized this and hurried to work on open-ring structures, other companies had already started research in acyclic molecules (Figure 5). Products **2**, **3**, **6**, **7**[13−16] can be looked at as the acyclic variants derived from our cyclic prototypes. The cyclic products of our competitors, thiamethoxam (**4**)[17] and AKD-1022 (**71**),[18] can be also viewed as following from acyclic clothianidin through a prodrug concept. As we see, all of our rivals' products are related with the acyclic modifications of our original cyclic products. The above competitors' strategy is our mere speculation based on the bioequivalency concept.[1] Needless to say, any significant products are created only through the serendipity and unbending effort of individual scientists. Now seven products, named neonicotinoids, are on market as one of the major classes with a new mode of action.

■ STUDY ON THE PHARMACOPHORE OF NEONICOTINOIDS

Binding Model Based on the Crystal Structure. Crystal structure analyses of several neonicotinoid molecules have been conducted and revealed the following structural features of imidacloprid (Figure 6).[19]

(1) The N1−C1 bond length on the imidazolidine ring, 1.34 Å, is remarkably shorter than the regular C−N (amine) (1.47 Å) but close to the C═N (imine) (1.33 Å) (**i**).

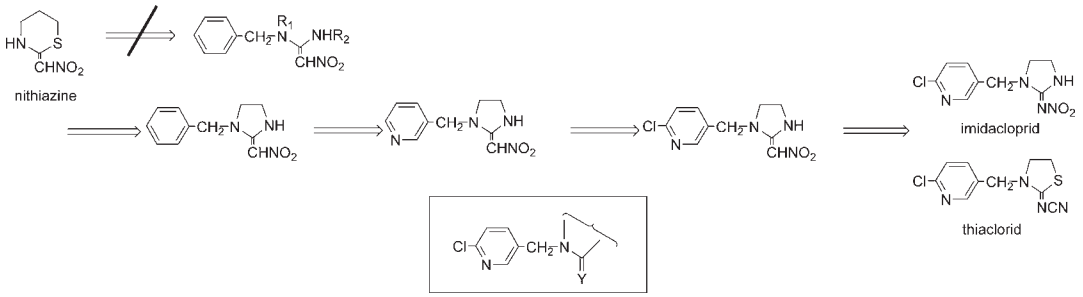


Figure 4. Development flow from nithiazine to imidacloprid and thiacloprid and the pharmacophore in block.

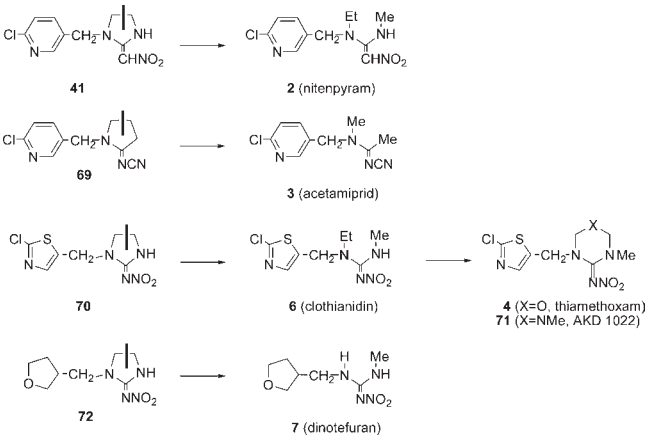


Figure 5. Conceptual derivatization from cyclic products to acyclic structures.

(2) The bond length of N−N in the $N-NO_2$, 1.23 Å, is shorter than the N−N in NH_2NO_2 (**i**).

(3) The C1−N3 bond length, 1.45 Å, is longer than the regular C═N (**ii**).

(4) The nitroimine part is coplanar to the imidazolidine ring plane (**ii**).

(5) The distance from N2 to O2 is 5.8 Å with the van der Waals surface (**iii**).

The crystal structure data suggest that the resonance structure of the key pharmacophore weighs over to the right structure, where the electrons shift from the imidazolidine nitrogen atoms to the nitro oxygen tips (Figure 7). The structures of other related neonicotinoid compounds had similar characteristics. It had been assumed that acetylcholine and nicotine interact with the nAChR by a Coulombic interaction between the ammonium nitrogen atom of each and the electron-rich region on the receptor and a hydrogen bond through the pyridine nitrogen or the oxygen atom. The distance between the two recognition sites on the nAChR is estimated to be 5.9 Å.[20] On the basis of the above crystal structure analyses in addition to the resemblance of mode of action to nicotine, we have proposed the binding model for neonicotinoids (Figure 8).

Imidacloprid is predicted to bind to the receptor in the following manner. First, because the partial positive guanidine atoms of sp^2 nature and the electron-deficient 2p orbital lobes extend vertically with respect to the imidazolidine plane, the guanidine part functions as a π-acid and approaches the anionic site on the receptor only from this vertical direction. Second, the nitro oxygen atom or the cyano nitrogen atom interacts with the receptor through a hydrogen bond. Third, the chloropyridyl nitrogen functions as an H-bond acceptor and the chlorine atom makes hydrophobic contacts, thereby consolidating the binding interaction with the receptor (Figure 9).

QSAR for the Key Pharmacophore. To estimate how the physicochemical parameters at the key pharmacophore are related to the insecticidal potencies, we carried out a QSAR study by injection to American cockroaches (*Periplaneta americana* L.). We used the Mulliken charge on the nitro oxygen atom or the cyano nitrogen atom as the electrostatic parameter (Figure 10) and obtained eq 1.

$$\log(1/\mathrm{BC}) = -3.103(\pm 4.992) - 20.160(\pm 11.824)(Q_{\mathrm{O2,N}}) + 1.647(\pm 0.426)(\log P) - 0.694(\pm 0.487)(\log P)^2 - 2.028(\pm 1.084)I_{\mathrm{NCN}} \quad (1)$$

$$n = 18,\ s = 0.260,\ r = 0.9221,\ F_{4,13} = 18.19$$

This equation reveals that the nerve blocking activity (BC) is actually proportional to the magnitudes of the Mulliken charge (Q), as the binding model predicts. The equation also reveals that the neuroblocking potency is related to the log P value of the molecule, and the optimal log P value was 1.2. This means that the biological activity is determined not only by the pharmacodynamic factors associated with the interactions involving the pharmacophore but also by the pharmacokinetic factors associated with the movement and distribution of molecules in the insect fluid. These factors relate to the whole molecule.[21,22]

TRIALS TO DEVISE NEW NEONICOTINOID INSECTICIDES

Okazawa and co-workers conducted a three-dimensional analysis of neonicotinoid and made a CoMFA map.[23] Such maps facilitate insight into the binding mode from the ligand side. The CoMFA map reveals that the area around the fifth and sixth positions on the pyridine ring should be sterically permissible. Actually, according to our QSAR study on the insecticidal activity of fifth-substituted imidacloprid derivatives (X = Cl, Y is varied in compound **73** in Figure 11) by injection under synergistic conditions, the potency was inversely proportional to the size of the substituent rather than the electronic properties as the potency ranks below.[24−27]

$$\mathrm{H} \geq \mathrm{F} \gg \mathrm{Me} > \mathrm{Cl} > \mathrm{OMe} > \mathrm{I} \gg \mathrm{CF_3} \sim \mathrm{N_3} > \mathrm{Ph} \gg \mathrm{CN}$$

$$\mathrm{H} \gg \mathrm{Me} > \mathrm{Et} \sim \mathrm{Ph} > \mathrm{n\text{-}Pr} \gg \mathrm{n\text{-}Bu}$$

It is noteworthy that the 5-F imidacloprid (**73a**: X = Cl, Y = F) showed highly insecticidal activity comparable with imidacloprid

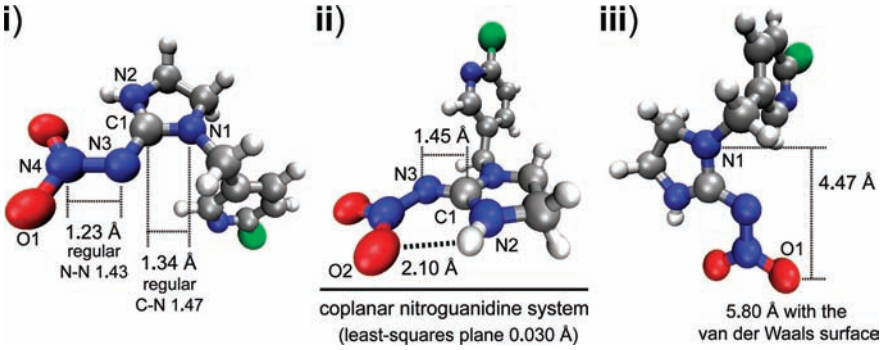


Figure 6. Molecular structures of imidacloprid and characterization of the bond lengths and interplane angles.

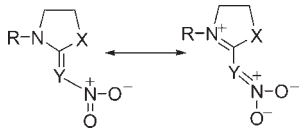


Figure 7. Resonance structures of nitro-neonicotinoid molecules.

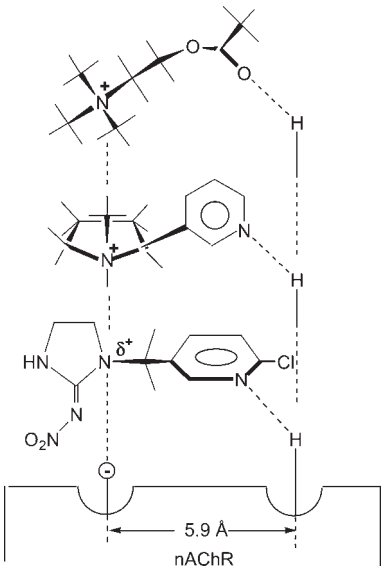


Figure 8. Binding model for acetylcholine, nicotine, and imidacloprid to nAChR.

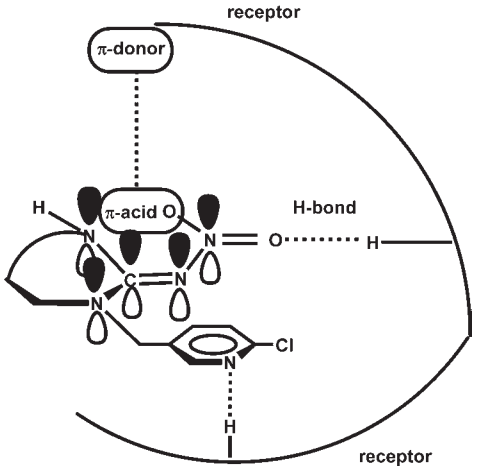


Figure 9. Binding model based on crystal structure.

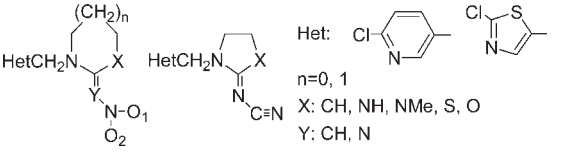


Figure 10. Molecular structures for calculation of the Mulliken charges.

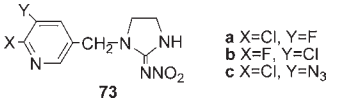


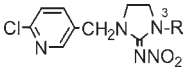
Figure 11. Substituent variants on the imidacloprid pyridine ring.

in the insecticidal test against brown rice planthopper (*Nilaparvata lugens* Stål) and green peach aphid (*Myzus persicae*). Interestingly, the inversely combined derivative (**73b**: X = F, Y = Cl) showed only modest activity.[27] Another noteworthy finding in the substitution study was that 5-azidoimidacloprid (**73c**: X = Cl, Y = N_3) had enormously high binding affinity with insect nAChR.[28,29] This compound and analogous azido derivatives have been used as photoaffinity probes to ultimately define the binding site interactions on the nAChRs.[30]

The CoMFA predicts that the area extending from the 3-N position is sterically restricted. Actually, all of the introduced alkyl groups lowered the insecticidal activity (Table 8).[31,32] Considering this, it appeared that the single alkylation at the N-atom would be hopeless. However, recently, we have found that the insecticidal activity is recreated surprisingly when the alkyl chain bears two pharmacophores, one at either end. Table 9 shows the insecticidal activity by injection of selected divalent imidacloprid derivatives against American cockroaches. Interestingly, the activity depended on the tether length, and the hexa-, hepta-, and nonamethylene bis-imidacloprid derivatives showed potencies comparable with that of imidacloprid;[33,34] the antagonistic phenomenon was observed using a patch clamp technique.[35] The binding strength with fruit fly (*Drosophila melanogaster*) brain nAChR was also dependent on the alkylene tether length, and the heptamethylene derivative showed the highest activity (Figure 12).[36]

The binding site interaction of heptamethylene compound with *Aplysia californica* AChBP on its structure cocrystallized

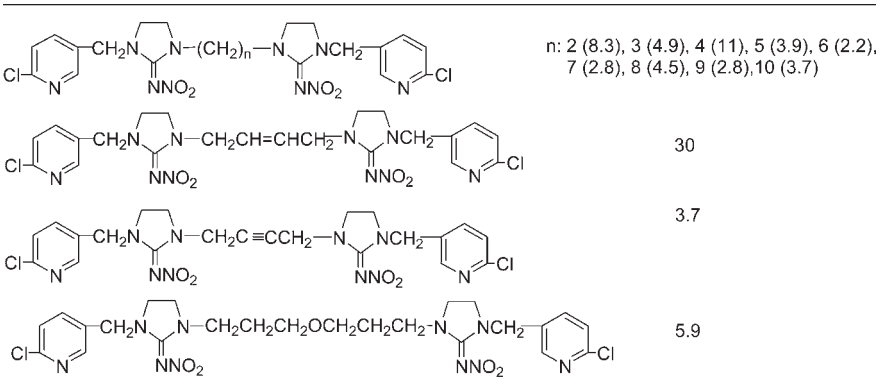
Table 8. Insecticidal Activity of 3N-Substituted Imidacloprid Derivatives[a]



	1	74	75	76	77	78	79	80	81	82
R	H	Me	Et	n-C_3H_7	$CH(CH_3)_2$	$CH_2CH{=}CH_2$	n-C_4H_9	n-C_5H_{11}	n-C_6H_{13}	6-chloronicotinyl
LC_{90}	<0.32	1.6	8	0.32	40	0.32	1.6	20	40	1.6

[a] See the footnote of Table 1.

Table 9. Insecticidal Activity by Injection of Alkylene-Tethered Bis-imidacloprid Derivatives to American Cockroach[a]



[a] Minimal lethal dose (nmol/insects).

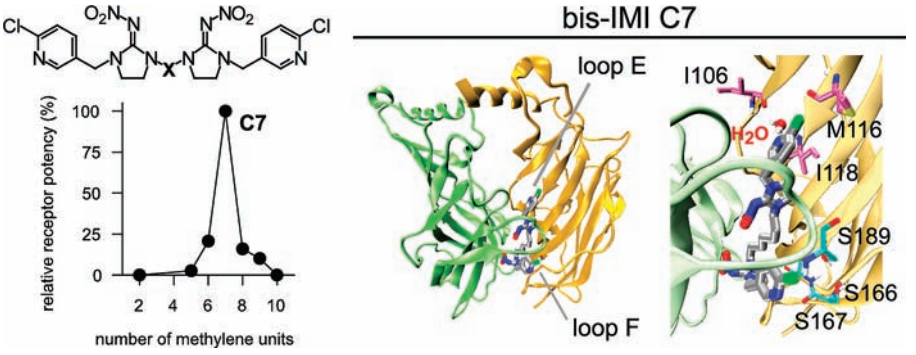


Figure 12. Bis-imidacloprid C7 analogue fits a nicotinic receptor model wherein the chloropyridine moieties contact loops E and F.

with bound imidacloprid was examined. The *Aplysia* AChBP serves as a suitable structural surrogate for the extracellular ligand-binding domain of the insect nAChRs.[30] The docking calculation revealed the existence of the possible cavity in loop F domain around heptamethylene length distant from the primary cavity in loop E for imidacloprid and other monovalent neonicotinoids. We propose that this cavity in loop F accommodates the second pharmacophore of heptamethylene bis-imidacloprid. Since the discovery of imidacloprid, it had been assumed that neonicotinoids bind to the receptor at one site, but the present experiment disclosed the existence of the second binding pocket for this class. It should be clarified whether the second cavity functions independently or in coordination with the primary one and suitable ligands for the second cavity have the same structures as those for the primary site. The binding mode as for which such alkylene-tethered divalent molecules act agonistically or antagonistically will be another interesting question. From the aspect of strategic molecular design the second site itself will be a target for new agents for insect nAChRs.

We next examined the biological responses of hexamethylene and heptamethylene derivatives under practical conditions. We were especially curious if these divalent compounds of such large molecular weights have systemic properties. Therefore, we conducted the insecticidal test in the way that the rice seedling roots were dipped in an aqueous solution of the ingredient and then brown planthoppers were released on the 3rd, 7th, and 14th days. Mortality was evaluated 24, 48, and 72 h after the infestation (Table 10).[37] It was shown that hexamethylene and heptamethylene derivatives suppressed the insects 72 h after the 3rd, 7th, and 14th infection days after infestation. In the experiment of soil treatment on cabbage the heptamethylene derivative controlled completely the green peach aphid. These two experiments indicate that the root uptake of the ingredients from the water solution or the soil and subsequent xylem translocation actually

Table 10. Systemic Insecticidal Test after Drench Application on Rice and Soil Treatment on Cabbage[a]

compound insect/host plant	time and mortality: 3 days[b] 24/48/72 h[c]	7 days[b] 24/48/72 h[c]	14 days[b] 24/48/72 h[c]
imidacloprid[d]			
brown planthopper/rice	47(±12)/80(±10)/100(±1)	89(±10)/100(±1)/100(±1)	95(±3)/100(±1)/100(±1)
IMI-$(CH_2)_6$-IMI[e]			
brown planthopper/rice	56(±12)/78(±20)/89(±9)	59(±10)/94(±5)/94(±5)	60(±18)/100(±0)/100(±0)
green peach aphid/cabbage	−/−/83(±8)	−/−/55(±10)	−/−/50(±10)
IMI-$(CH_2)_7$-IMI[f]			
brown planthopper/rice	13(±7)/40(±15)/100(±1)	83(±8) /100(±1)/100(±0)	100(±1)/100(±1)/100(±1)
green peach aphid/cabbage	−/−/100(±1)	−/−/100(±0)	−/−/100(±0)
control[g]			
brown planthopper/rice	−/−/0	−/−/0	−/−/0
green peach aphid/cabbage	10(±3)/14(±4)/14(±4)	5(±2)/5(±2)/10(±3)	0/15(±6)/ 0

[a] Results are expressed as mortality % (±SEM, $n = 3$). [b] Release time of insects after treatment of a 100 mg L^{-1} solution and green peach aphid, 3, 7, and 14 days for brown planthopper. [c] Assessment time after insect release. [d] Admire flowable formulation. [e] Hexamethylene 1,6-bis-imidacloprid. [f] Heptamethylene 1,7-bis-imidacloprid. [g] 0.4% Acetone + 0.4% ethanol + surfactants in water.

Table 11. Lipinski's Rule and Tice's Proposed Parameters for Insecticidal Candidates

molecule	molecular mass	(mlog P)[a]	H-bond donors	H-bond acceptor	rotatable bonds
Lipinski[b]	≤500	≤4.15	≤5	≤10	
Tice[c]	≥150, ≤500	≥0, ≤5.0	≤2	≥1, ≤8	≤12
imidacloprid[d]	256	1.88	1	6	3
IMI-$(CH_2)_7$-IIMI[a,e]	608	5.18	0	12	14

[a] Moriguchi log P.[40] [b] Data were extracted from ref 38. [c] Data were extracted from ref 39. [d] The values (mlog P) were calculated according to published procedures. The number of H-bond donors was obtained by counting the numbers of OH and NH bonds in each molecule. The H-bond acceptors are the sum of the numbers of nitrogen and oxygen atoms, as described by Lipinski et al.[38] except the nitrogen atom in the NO_2 in the present study. The number of rotatable bonds was the sum of the single bonds in the acyclic moieties except the N−O bonds in the NO_2 group as well as the C−H, C−Cl, and N−H bonds. [e] Heptamethylene 1,7-bis-imidacloprid.

occurred and the lethal doses were constantly provided over 14 days under these conditions.

Virtual screening methods have been recognized as a powerful tool to find promising lead compounds. Lipinski's rule is a standard protocol to extract drug-like molecules from vendor listings. This rule qualifies for orally bioavailable drugs several physicochemical parameters (Table 11). Tice has confirmed that Lipinski's rule for medicines can be in principle adapted for pesticides and has proposed modified rules for insecticides. Actually, imidacloprid matches this rule. On the other hand, bis-neonicotinoids obviously violate the rule. For example, the heptamethylene bis-imidacloprid derivative, which shows insecticidal potency comparable to that of imidacloprid, has a large molecular mass and mlog P value, and has large numbers of H-bond acceptors and rotatable bonds. Then how can we explain its potent biological behavior? Lipinski's rule and some other virtual screening methods will be useful tools to select promising molecules among the large numbers of randomly prepared compounds because these rules are based on the structural characteristics of the existing prototypes.[38,39] However, new types of insecticides such as bis-neonicotinoids have not been registered in the library, and therefore Lipinski's rule will not be able to explain their unique insecticidal properties.

Progress in genomics, molecular biology, and computer analysis allows us to draw a likely picture for drug−receptor interaction. The binding model will become more sophisticated as the number of input molecules increases and will delineate the molecular shape of suitable ligands. However, paradoxical as it may sound, such progress does not necessarily help product seekers because molecules specially designed to fit the model will have only the same pesticidal spectrum as earlier developed market products. The market will not need products with similar pesticidal features. There are two approaches for a product seeker to find potential effectors. One is to design a lead molecule based on the predicted models and optimize the lead by utilizing all of the knowledge of physicochemical parameters of existing molecules; this is called rational molecular design. Another one is to design a lead molecule that varies markedly from the prototype. This strategy focuses on the ambiguous points of the predicted model or deviates deliberately from the current pictures, which is so-called outlying molecular design. Taking either route, the decisive step to a new discovery for a market product will be made only through the creativity of individual scientists.

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