Overview of the Status and Global Strategy for Neonicotinoids[†]

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ABSTRACT: In recent years, neonicotinoid insecticides have been the fastest growing class of insecticides in modern crop protection, with widespread use against a broad spectrum of sucking and certain chewing pests. As potent agonists, they act selectively on insect nicotinic acetylcholine receptors (nAChRs), their molecular target site. The discovery of neonicotinoids can be considered as a milestone in insecticide research and greatly facilitates the understanding of functional properties of the insect nAChRs. In this context, the crystal structure of the acetylcholine-binding proteins provides the theoretical foundation for designing homology models of the corresponding receptor ligand binding domains within the nAChRs, a useful basis for virtual screening of chemical libraries and rational design of novel insecticides acting on these practically relevant channels. Because of the relatively low risk for nontarget organisms and the environment, the high target specificity of neonicotinoid insecticides, and their versatility in application methods, this important class has to be maintained globally for integrated pest management strategies and insect resistance management programs. Innovative concepts for life-cycle management, jointly with the introduction of generic products, have made neonicotinoids the most important chemical class for the insecticide market.

KEYWORDS: neonicotinoid insecticides, agonist, acetylcholine receptor, acetylcholine-binding protein, application methods, resistance management, homology model

INTRODUCTION

One of the insecticide molecular target sites of growing importance (total market share in 2007 for agricultural use: 24%) is the nicotinic acetylcholine receptor (nAChR), which plays a central role in the mediation of fast excitatory synaptic transmission in the insect central nervous system (CNS). Despite the application of the alkaloid (S)-nicotine as a natural insecticide (aqueous tobacco extract) for a long time, the nAChR has been an underexploited biochemical target for agrochemisty, with an estimated total insecticide world market share of around 1.5% in 1987. Because of its high mammalian toxicity and relatively low level of insecticidal activity, no major class could be established through taking (S)-nicotine as lead structure. However, the nAChR has become an important target site in modern crop protection with the discovery and commercialization of three classes of insecticides:[1] (i) the very small group of so-called nereistoxin analogues (4-N,N-dimethylamino-1,2-dithiolane) such as the bis(thiocarbamate) proinsecticides cartap, bensultap, and thiocyclam; (ii) from the lead structure nithiazine (2-nitromethylenetetrahydro-1,3-thiazine), resulting neonicotinoid insecticides such as five-membered ring systems (imidacloprid, thiacloprid) and six-membered ring systems (thiamethoxam) as well as noncyclic structures (nitenpyram, acetamiprid, clothianidin, dinotefuran); (iii) the spinosyns as a family of fermentation-derived insecticidal macrocyclic lactones, such as the bioinsecticides spinosad and the semisynthetic member spinetoram[2] [because of their different binding sites in comparison to neonicotinoids, spinosyns have a different mode of action (MoA) classification by the Insecticide Resistance Action Committee (IRAC; an expert committee of CropLife): nAChR allosteric activators, group 5].

The success story of neonicotinoid insecticides started in 1991 with the launch of the forerunner, imidacloprid, by Bayer CropScience, which has been the world's largest selling insecticide for many years.[3]

STATUS OF NEONICOTINOID INSECTICIDES

Today, neonicotinoids are the most important chemical class of insecticides introduced to the global market since the synthetic pyrethroids. Neonicotinoids are registered globally in more than 120 countries, and they are among the most effective insecticides for control of sucking insect pests such as aphids, whiteflies, leaf- and planthoppers, thrips, some micro-Lepidoptera, and a number of coleopteran pests. The outstanding development of neonicotinoid insecticides for modern crop protection, consumer/professional products, and animal health markets between 1990 and today reflects the enormous importance of this chemical class.[4]

Market Environment. The unique success of neonicotinoid insecticides is reflected in their turnover figures in 1990 as compared with 2008. In 1990, before the launch of the first neonicotinoid insecticide, imidacloprid, the agrochemical market (total volume of €7.942 billion) was dominated by organophosphates (OPs) (43%), pyrethroids (18%), and carbamates (16%).[5] In 2008, neonicotinoids had gained a 24% share of a slightly decreased total market of €6.330 billion, mainly at the expense of OPs (13.6%) and carbamates (10.8%) (see Figure 1) (see ref 6 and internal data from Bayer CropScience).
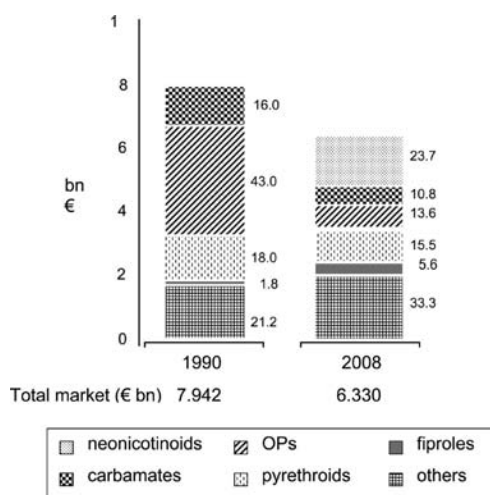
Figure 1. Development of insecticide classes in modern crop protection, 1990−2008, expressed as percentage of total.
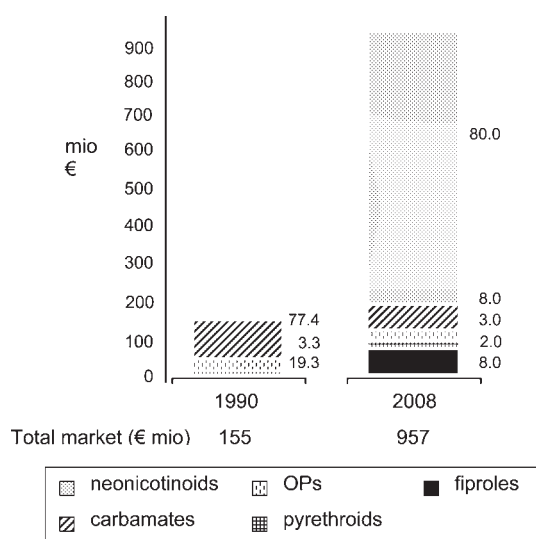

Figure 2. Development of insecticide classes in seed treatment, 1990−2008, expressed as percentage of total.

On the other hand, the turnover figures for seed treatment are very impressive. A so-called niche market of €155 million for insecticidal seed treatment in 1990 was dominated by carbamates (77.4%). It has been developed to a €957 million market, with a share for neonicotinoid insecticides of 80% in 2008 (Figure 2).

Structural Diversity. Seven neonicotinoid insecticides are currently on the market: three cyclic compounds, that is, neonicotinoids with five-membered ring systems such as imidacloprid[7,8] and thiacloprid[9] (Bayer CropScience) and the six-membered neonicotinoid thiamethoxam (Syngenta),[10] and four noncyclic compounds, that is, nitenpyram (Sumitomo Chemical Takeda Agro Co.),[11] acetamiprid (Nippon Soda),[12] clothianidin (Sumitomo Chemical Takeda Agro Co./Bayer CropScience),[13] and dinotefuran (Mitsui Chemicals).[14] Considering their pharmacophore moieties [−N—C(E)=X—Y], neonicotinoid insecticides can be classified as N-nitroguanidines (imidacloprid, thiamethoxam, clothianidin, and dinotefuran), nitromethylenes (nitenpyram), and N-cyanoamidines (acetamiprid
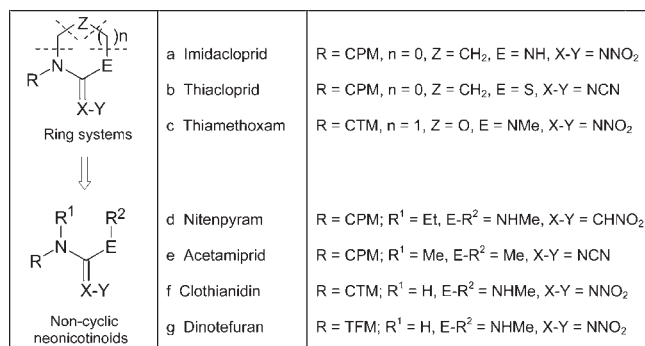

Figure 3. Commercial neonicotinoid insecticides: ring systems (a−c) versus noncyclic neonicotinoids (d−g).

and thiacloprid).[15] The overall chemical structure for both ring systems and noncyclic commercial neonicotinoids consists of different segments (Figure 3):[16,17] (i) for five- and six-membered ring systems the bridging fragment $[-CH_2—Z—(CH_2)_n—$ ($n =$ 0; Z = CH_2; and n = 1; Z = O, NMe] and for noncyclic neonicotinoids the separate substituents (R^1, R^2); (ii) the hetarylmethyl or heterocyclylmethyl group R [R = 6-chloro-pyrid-3-ylmethyl (CPM), 2-chloro-1,3-thiazol-5-ylmethyl (CTM), and (±)-6-tetrahydrofur-3-ylmethyl (TFM)]; (iii) the functional group [=X—Y] (e.g., [=N—NO$_2$], [=N—CN] and [=CH—NO$_2$]) as part of the different pharmacophore types [−N—C(E)=X—Y].

In comparison to the corresponding ring systems (imidacloprid, thiacloprid, and thiamethoxam), the noncyclic neonicotinoids show similar broad insecticidal activity by forming a so-called quasi-cyclic conformation when binding to the insect nAChRs.[18] Therefore, the four commercial noncyclic neonicotinoids (nitenpyram, acetamiprid, clothianidin, and dinotefuran) can be regarded as examples, if retrosynthetic considerations are carried out.[19] Figure 4 shows the superposition of van der Waals volumes of ring systems (A) and noncyclic neonicotinoids (B).

On the other hand, the partial ring cleavage of the six-membered ring system thiamethoxam into the noncyclic clothianidin (Figure 4; transformation of c into f) in insect and plant tissues has recently been demonstrated and discussed.[20,21]

During the past years, expansion of neonicotinoid insecticides has been driven by growth of established products such as imidacloprid as well as newer entrants such as thiamethoxam and clothianidin. Imidacloprid currently accounts for approximately 41.5% of the whole neonicotinoid market (in 2009: U.S. $2632 million). At U.S. $1091 million imidacloprid is the largest selling insecticide in the world; its sales value growth is also being affected by generic material. Thiamethoxam is now the second biggest neonicotinoid (in 2009: U.S. $627 million) in terms of sales, and clothianidin has grown rapidly to U.S. $439 million. In 2009 the sales of other neonicotinoids such as acetamiprid (U.S. $276 million), thiacloprid (U.S. $112 million), dinotefuran (U.S. $79 million), and nitenpyram (U.S. $8 million) are estimated to have grown as well.

In total, N-nitroguanidines are the most prominent subclass; they account for around 85% of the neonicotinoid insecticide market (in 2009: U.S. $2236 million).

Physicochemical Properties. The physicochemical properties of the five- and six-membered ring systems and noncyclic neonicotinoids played an important role in their successful
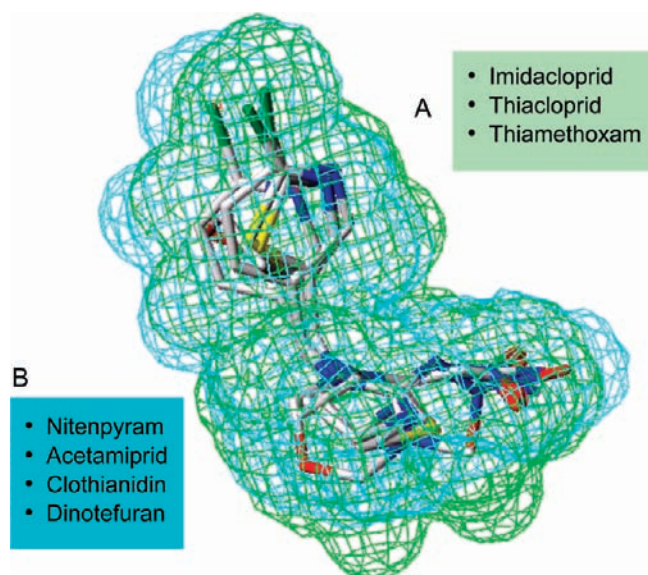
Figure 4. Superposition of van der Waals volumes of neonicotinoid insecticides in their minimum energy conformations: (A) ring systems (imidacloprid, thiacloprid, and thiamethoxam); (B) noncyclic compounds (nitenpyram, acetamiprid, clothianidin, and dinotefuran).

development as modern insecticides.[16] In this context photostability is a significant factor in field performance of all neonicotinoid insecticides. As already described,[22−24] the energy gap for the different functional groups [=X—Y] from the ground state to the excited singlet state increases in the order [=CH—NO$_2$] < [=N—NO$_2$] < [=N—CN]. For technical application methods for neonicotinoids in the field, such as for soil drench, seed treatment, or foliar application, their uptake, good translaminar, and acropetal distribution in plants is crucial for their insecticidal activity against numerous sucking pests. Therefore, not only the bioisosteric fragments [CPM vs CTM substituents or pharmacophor moieties][16] but also the whole molecular shape, including the resulting water solubility, has to be considered.[19] Neonicotinoid insecticides are so-called "*push—pull olefins*", forming conjugated electron-donating and electron-accepting groups.[23] In comparison with other nonpolar insecticide classes, the polar, nonvolatile neonicotinoids have greater water solubilities (e.g., in the case of nitenpyram: 840 g/L at pH 7) and lower log P_{OW} values (e.g., dinotefuran: −0.644 at 25 °C) (Table 1).

From these observations, the following conclusions can be drawn:

(a) Generally, noncyclic neonicotinoids are less lipophilic than the corresponding five- and six-membered ring systems.

(b) Water solubility is influenced by the functional group [=X—Y] within the pharmacophore moiety [—N—(C(E))=X—Y] and increases in the order [=N—NO$_2$] < [=N—CN] < [=CH—NO$_2$].

(c) With regard to E, the lipophilicity increases in the order NH < O < C < S.[25]

According to Briggs et al.,[26] somewhat more lipophilic neonicotinoid insecticides should be favorable for seed treatment application, because their root uptake and translocation are more effective than in the case of more hydrophilic compounds. Because of the higher lipophilicity, thiacloprid and clothianidin show the best root uptake,[26] whereas nitenpyram and dinotefuran are more xylem mobile than the other neonicotinoids.[3,4]

Mode of Action Classification. In contrast to the naturally occurring (*S*)-nicotine (IRAC MoA classification: *n*AChR agonsists, group 4B), all neonicotinoids act selectively on the insect CNS as agonists of the postsynaptic *n*AChRs, their molecular target site.[1,4] As a result of the efficient MoA, there is no cross-resistance to conventional long-established insecticide classes, such as chlorinated hydrocarbons, OPs, carbamates, pyrethroids, and several other chemical classes of insecticides used to control insect pests on major crops.[27,28] Since the introduction of imidacloprid in 1991, all neonicotinoids have been classified in the same MoA class (*n*AChR agonsists, group 4A) by IRAC.

Spectrum of Efficacy. The biological activity and agricultural uses of neonicotinoid insecticides are enormous, and numerous overviews, articles, and book chapters have been published over the past decade.[3−5,16,19,29] Due to their unique physicochemical properties (see previous section), neonicotinoids can be used in a variety of crops. Besides a high intrinsic acute and residual activity against sucking insects and some chewing species, a high efficacy against aphids, whiteflies, leafhoppers and planthoppers, and the Colorado potato beetle, neonicotinoids show an excellent acropetal translocation in plants as well.

These agricultural uses include aphids (e.g., *Aphis gossypii, Myzus persicae, Phorodon humilii, Rhopalosiphum padi*) on vegetables, sugar beet, cotton, pome fruit, cereals, and tobacco; leafhoppers and planthoppers (e.g., *Nephotettix cincticeps, Nilaparvata lugens*); beetles on potatoes (e.g., *Leptinotarsa decemlineata*); water weevil on rice (*Lissorhoptrus oryzophilus*); whiteflies (e.g., *Bemisia tabaci, Trialeurodes vaporarium*) and thrips (e.g., *Thrips tabaci*) on vegetables, cotton, and citrus; micro-Lepidoptera (e.g., *Cydia pomonella, Phyllocnistis citrella*) on pome fruit and citrus; and wireworms (*Agriotes* spp.) on sugar beet and corn.[3,5]

In addition to crop protection, applications of neonicotinoid insecticides in nonagricultural fields has also expanded in recent years,[16] such as household sectors, lawn, and garden (summarized as professional use) for controlling termites (e.g., *Reticulotermes* spp.) (cf. imidacloprid: Merit)[30] and turf pests such as white grubs and cockroaches (e.g., *Blattella germanica*). New bait gel formulations containing imidacloprid such as Maxforce Prime (Bayer EnvironmentalSciences), for the control of cockroaches, and thiamethoxam, such as Optigard (Syngenta), for broad-spectrum control of ants, are now on the market.

On the other hand, neonicotinoid insecticides can be used as ectoparasiticides for controlling cat and dog fleas (e.g., *Ctenocephalides felis, Ctenocephalides canis*) (cf. imidacloprid, Advantage; nitenpyram, Capstar),[31,32] lice (e.g., *Linognathus setosus, Trichodectus canis*), and flies (e.g., *Musca domestica*) in animal health as well.[33]

Recently, several new neonicotinoid insecticide combinations with other active ingredients from different substance classes were launched such as AdvantageMulti (or Advocate; Bayer Animal Health) as spot-on formulation of the imidacloprid and the macrolactone moxidectin, which shows efficacy against ear mites (*Otodectes cynotis*) and fleas (*C. felis*).[34] K9 Advantix (Bayer Animal Health) as spot-on topical solution of imidacloprid and the pyrethroid permethrin for dogs, which work synergistically against the most common and important external parasites such as the long star tick, *Amblyomma americanum*.[35] Finally, Vectra 3D (Summit VetPharm) is a new topical spot-on ectoparasiticide containing a combination of dinotefuran, permethrin, and pyriproxyfen against *A. americanum* and the Gulf Coast tick *A. maculatum* on dogs.[36]

2899

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Table 1. Selection of Physicochemical Properties of Neonicotinoid Insecticides

neonicotinoid insecticide	color and physical state	melting point (°C)	density (g mL^{-1} at 20 °C)	solubility in water (g L^{-1} at 20 °C)	log P_{OW} (at 25 °C)
ring systems					
imidacloprid	colorless crystals	144	1.54	0.61	0.57[a]
thiacloprid	yellow crystalline powder	136	1.46	0.185	1.26[b]
thiamethoxam	slightly creamy crystalline powder	139.1	1.57	4.1	−0.13
noncyclic compounds					
nitenpyram	pale yellow crystals	83−84	1.40[c]	840[d]	−0.64
acetamiprid	colorless	98.9	1.330	4.20[e]	0.8
clothianidin	clear colorless solid powder	176.8	1.61	0.327	0.7
dinotefuran	white crystalline solid	94.6−101.5	1.33	54.3 ± 1.3	0.644

[a] At 22 °C. [b] At 20 °C. [c] At 26 °C. [d] At pH 7. [e] At 25 °C.

Neonicotinoids for Plant Virus Vector Control. Due to its plant systemic properties, neonicotinoid insecticides such as imidacloprid, thiamethoxam, and clothianidin also control important vectors of plant virus diseases, thereby suppressing the secondary spread of viruses in various crops.[5] For imidacloprid this control has been discovered during its early development supported by antifeedant effects of sublethal dosages of imidacloprid concentrations on *B. tabaci*[37] and was later observed, for example, for the persistent barley yellow dwarf virus (BYDV) transmitted by *R. padi* and *Sitobion avenae*.[38] Applied as a pellet of 90 g of ai unit^{-1}, beet mild yellow virus (BMYV) was effectively controlled in sugar beet seed, as demonstrated in field trials conducted in the United Kingdom between 1989 and 1991.[39,40] Outstanding crop protection was achieved with seed treatment or foliar applications in cereals against aphids and BYDV,[41−43] in tobacco against thrips and tomato spotted wilt virus (TSWV),[44] in tomato against whiteflies and tomato yellow leaf curl virus (TYLCV), and in citrus against glassy-winged sharpshooters as vector for the bacterium *Xylella fastidiosa* to mention just a few.[5]

Versatile Application Methods for Neonicotinoids. The neonicotinoid insecticides have a high degree of versatility, not seen to the same extent in other chemical classes. Most neonicotinoids can be used as foliar sprays, seed treatments (see next section), and via soil application. Today approximately 60% of all neonicotinoid applications are soil/seed treatments, and most spray applications are especially targeted against pests attacking crops such as cereals, corn, rice, vegetables, sugar beet, potatoes, cotton, and others.[5,29]

However, the increasing success of neonicotinoid insecticides also relies on versatile application methods such as irrigation water in drip or drench systems for vegetables or in floating box systems for tobacco seedlings (e.g., Confidor S), which offer long-lasting control of aphids and whiteflies.[45] Seedling box application in rice gives excellent control of rice pests such as hopper species and rice water weevil.[46,47] Soil drenching in permanent crops protects young citrus trees against citrus leafminer (*P. citrella*).[48,49]

Applications to the base of the trunk result in efficient control of *Eriosoma lanigerum* (Hausmann) in apple trees. In addition, drench and drip applications are well suited for the control of *Perileucoptera coffeella* (Guérin-Méneville) in coffee and *Planococcus* sp. and other mealy bug species in grapevines. Soil injection to protect emerging vegetable seedlings against soil-inhabiting and sucking pests is common practice in the United States. On the other hand, banana weevil and thrips are controlled via trunk and bud injection.[5]
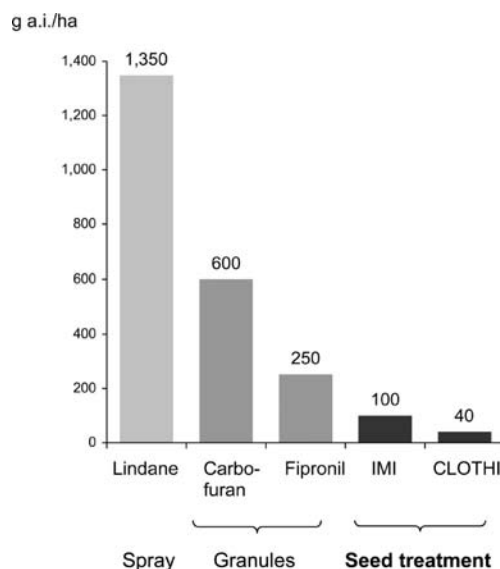

Figure 5. Development in the application methods for crop protection products in maize; applied grams of active ingredient (ai) per hectare in maize. IMI, imidacloprid; CLOTHI, clothianidin (adapted from ref 53).

An important aspect is the excellent fit of neonicotinoid insecticides for integrated pest management (IPM) systems. Depending on the application method and timing, nontarget organisms are not affected by neonicotinoids. Safety for beneficials and pollinators has especially been optimized by selectivity in space.[50] Application into the soil by different methods allows the transport of the compound to the pest within the plant without harming beneficial organisms.[51] On the other hand, selectivity in time allows, for example, foliar application against starting pest populations when beneficial arthropods are still absent.[5]

Seed Treatment with Neonicotinoids. Due to the development of seed treatment application with neonicotinoid insecticides, new opportunities have been opened up in modern crop protection.[52] Besides seed dressing, also film coating, pelleting, and multilayer coating allow an environmentally safe and perfect protection of young plants against insect attack.[5] With this method, application of the active ingredient is virtually independent of the weather and can be applied directly at the site of action. The application amount (g of ai ha^{-1}) used per unit area is thereby reduced remarkably, as shown for neonicotinoids in corn (Figure 5, spray > granules > seed treatment).[53]

2900

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Today, the plant systemic neonicotinoids imidacloprid, thiamethoxam, and clothianidin are widely used for seed treatment in different crops such as cotton, corn, cereals, sugar beet, oilseed rape, and others. Table 2 demontrates the spectrum of activity of clothianidin seed treatment (Poncho) for the control of early and midseason corn pests in the United States against a broad range of soil-inhabitating, root-, stem-, and leaf-feeding pests from different orders such as Coleoptera, Lepidoptera, Diptera, Homoptera, Hemiptera, and Hymenoptera.[54]

As a corn seed treatment, clothianidin (Poncho) protects young plants against the entire early-season pest complex (soil and leaf pests) and especially wireworms, *Agriotes* spp., and cicadas in many crops. Furthermore, chlothianidin is very effective against different species of *Diabrotica* (term is corn rootworm) such as the western (*D. virgifera virgifera*), northern (*D. barberi*), southern (*D. undecimpunctata howardi*), and Mexican (*D. virgifera zeae*) corn root worms. Larvae feed on primary and secondary corn roots. Excessive loss of root tissues from larval feeding can cause an instability of the corn plants that results in lodging. Massive lodging reduces the harvest efficiency and, therefore, causes severe losses in yields. Feeding damage on roots will also reduce water and nutrient uptake, root and plant growth, and ultimately yield, especially under favorable dry soil conditions.

Profiles of Neonicotinoid Insecticides. Key crops for neonicotinoid insecticides are vegetables, pome and stone fruits, citrus, rice, cotton, corn, potato, sugar beet, oilseed rape, and soybean, among many others. Table 3 describes the seven commercial neonicotinoid insecticides according to their additional biological profile and common application technique.[5]

The number of crop uses are indicated (e.g., foliar and soil applications in potato are defined as two crop uses). In addition to the common neonicotinoid spectrum, each product has its specific target pest spectrum, mentioned in Table 3 under additional pest spectrum. The commercial products also differ considerably with respect to soil and seed treatment uses, as soil stability is limited for some of them such as nitenpyram, acetamiprid, and dinotefuran, respectively. Uses are classified as follows: +++, broad; ++, good; +, limited; −, not relevant.[5]

Today, the first neonicotinoid imidacloprid has gained registration for over 140 crop uses in more than 120 countries under the main trade names Confidor and Admire for foliar use and Gaucho for seed treatment. Besides the development of nitenpyram (Capstar, Takeda/Syngenta) as a fast-acting, adult flea control product in cats and dogs for animal health, its uses for control of sucking insects in rice, fruit, tea, vegetables, and field crops in Japan have been marketed under the trade name Bestguard. Acetamiprid has been marketed, for example, under the trade name Mospilan and is registered for cotton, vegetables (Assail), potato, orchards for codling moth control, vines, citrus, tea, and ornamentals (ChipcoTristar). In addition, acetamiprid is also of interest for the control of termites and household pests. Thiamethoxam is marketed as Actara for foliar application, as Platinum for soil application, and as Cruiser for seed treatment uses. Today, thiamethoxam is registered for 115 crop uses in at least 65 countries on a wide range of crops such as vegetables, potatoes, rice, cotton, fruit, tobacco, and cereals, respectively. Its pest spectrum includes all major sucking insects, as well as some chewing and soil-living pests. Thiacloprid was launched under the trade name Calypso and is active against sucking and chewing pests on crops such as fruit, cotton, vegetables, oilseed rape, cereals, potato, rice, and ornamentals. Besides aphids, various species of beetles, lepidopteran leafminers, and *C. pomonella* (L.) are controlled. It has a favorable beneficial profile and is bee safe.[55] Therefore, thiacloprid can also be applied on flowering crops.[56] Clothianidin covers a broad pest spectrum, which

Table 2. Spectrum of Activity of Clothianidin Seed Treatment for the Control of Early- and Mid-Season Corn Pests in the United States[a]

insect order		insect species
Coleoptera	corn rootworm	*Diabrotica* spp.
	wireworm	*Melanotus* spp., *Agriotes* spp.
	flea beetle	*Chaetocnema pulicania* (Mersheimer)
	grape colaspis	*Colaspis brunnea* (F.)
	beet leaf weevil	*Tanymecus* spp.
	white grub	*Lachnosterna implicate*
	Japanese beetle	*Popillia japonica* (Newman)
Lepidoptera	black cutworm	*Agrotis ypsilon*
Diptera	seedcorn maggot	*Delia platura* (Meigen)
	frit fly	*Oscinella frit* (L.)
Homoptera	corn leaf aphid	*Rhopalosiphum maidis* (Fitch)
	leafhopper	*Empoasca* spp.
	leafhopper	*Macrosteles* spp.
	leafhopper	*Zyginida* spp.
Hemiptera	chinch bug	*Blissus leucopterus* (Say)
	stink bug	*Nezara viridula* (L.)
Hymenoptera	imported fire ant	*Solenopsis* spp.

[a] Modified after ref 54.

Table 3. Biological Profiles of Commercial Neonicotinoid Insecticides[a]

neonicotinoid insecticide	no. of crop uses	additional pest spectrum	foliar uses	soil uses	seed treatment
imidacloprid	140	thrips, mealybugs, leafminers, termites	++(+)	+++	++(+)
nitenpyram	12	−	++	+	−
acetamiprid	60	codling moth, diamondback moth	+++	+	−
thiamethoxam	115	mealybugs, plant bugs, leafminers, termites	+++	+++	++
thiacloprid	50	codling moth, pollen beetle	+++	+	+
clothianidin	40	wooly aphid, oriental fruit moth, corn rootworm	++(+)	++	+++
dinotefuran	35	soft scales, thrips, mealybugs	+++	++	−

[a] Modified after ref 5. Uses are defined as follows: +++, broad; ++, good; +, limited; −, not relevant.

2901

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resulted in applications as insecticide for seed treatment (Poncho), for soil (Dantotsu), and for foliar use (Dantop). The pest spectrum includes Coleoptera, Diptera, Hemiptera, and some Lepidoptera. The product can be applied on different crops such as rice, cereals, corn, oilseed rape, fruit, potatoes, sugar beets, and vegetables. Dinotefuran launched under the trade name Starkle and is marketed in the United States as Safari in ornamentals and as Venom in fruit, cotton, potatoes, and vegetables.

■ GLOBAL STRATEGY FOR NEONICOTINOID INSECTICIDES

Further success of neonicotinoid insecticides within the next few years in modern crop protection for insect control will be influenced by growth of the established neonicotinoid members owing to their benefit in replacing older substance classes such as OPs and carbamates worldwide. In the future, competition in the field of generic products will increase considerably and will lead to price erosion, which will open new opportunities in low-price markets as well. In addition, there is a tangible threat of resistance development, especially in major markets where loss of neonicotinoids would have severe negative consequences to insect and disease control. Therefore, a global strategy for neonicotinoid insecticides will be focused on an efficient resistance management according to the IRAC guidelines. Combined with an active life-cycle management such as new formulation concepts, innovative developments on new product combinations, and the search for additional unique selling points and target-site investigations by using modern techniques, neonicotinoids will be the most important chemical class within the next few years in modern crop protection for insect control. This also includes aspects on risk assessment and food safety as required for proper product positioning and registration legislation.[16]

Generic Products. Today, sales value growth of neonicotinoid insecticides is increasingly being affected by generic products. As first member, imidacloprid became generic (off-patent) in many countries in 2006, since when it has been used in an even broader scale. However, this will definitely facilitate the development of resistance to neonicotinoid insecticides, because it has been shown that in many cases the neonicotinoid class is affected as a whole once resistance to imidacloprid develops (see next section).[28] In addition, patent protection on nitenpyram, thiacloprid, acetamiprid, and clothianidin is starting to expire as well (Table 4), which has resulted recently in generic manufacture and increasing price erosion.

Generic versions of expired neonicotinoid insecticides are already manufactured and established in numerous markets such as India and China.

Resistance Management. In 1996 the first guidelines on resistance management for neonicotinoids (e.g., chloronicotinyl insecticides) were proposed by Elbert et al.[57] (updated in 2005) based on the experience with imidacloprid. Recently, current *IRAC Guidelines for Resistance Management of Neonicotinoids* are designed by the Neonicotinoid Working Group of IRAC for all *n*AChR agonists (group 4B) as version 1.3.[58]

After 18 years of use, several of the insect pests that are a core target for neonicotinoids have been shown to possess a high potential for resistance development such as whiteflies *B. tabaci* (Gennadius) and *T. vaporariorum* (Westwood),[59] the brown planthopper *N. lugens* (Stål),[28,60] the Colorado potato beetle

Table 4. Patent Protection of Neonicotinoid Insecticides

neonicotinoid insecticide	patent protection	
	priority year	expired
imidacloprid	1985	2005
nitenpyram	1986	2006
thiacloprid	1987	2007
acetamiprid	1988	2008
clothianidin	1989	2009
thiamethoxam	1992	2012
dinotefuran	1993	2013

L. decemlineata (Say),[28] and a few others such as the mango leafhopper *Idioscopus clypealis* (Lethierry).[5]

Therefore, guidelines for correct use of neonicotinoid insecticides and resistance management are described in 12 important points as follows (http://www.irac-online.org/):

(1) Always use products at recommended label rates and spray intervals.

(2) Rotation of products acts against rapid selection of resistant populations.

(3) Use suitable rotation partners for neonicotinoids.

(4) Use neonicotinoids against different pests in the same crop.

(5) Do not control a multigeneration pest exclusively with neonicotinoids.

(6) Plan the use of neonicotinoids in such a way that they complement the efficacy of the prevalent beneficial organisms.

(7) Never use neonicotinoids for follow-up treatments where resistance has already reduced their effectiveness.

(8) Use nonspecific products to help prevent the development of resistance.

(9) Good agricultural practices should be applied alongside physical and biological pest control methods.

(10) Practice crop–pest management.

(11) Integrate escape crops into the cropping system.

(12) Monitor problematic pest populations to detect first shifts in sensitivity.

Because resistance development is difficult to predict with certainty, care should be taken to consider these guidelines whenever group 4 products including the neonicotinoids (group 4B) are utilized for crop protection.

New Formulation Concept for Neonicotinoids. The distribution of systemic neonicotinoids largely depends on conditions during and after application. Often, even when good delivery to the plant surface is ensured after spray application of the active ingredient, there are limitations for maximum systemic performance if its foliar penetration is low. Bayer CropScience has developed the new formulation technology O-TEQ (oil dispersion, OD) for foliar application of both neonicotinoids imidacloprid (Confidor) and thiacloprid (Calypso).[61−66] The O-TEQ formulations facilitate leaf penetration, particularly under suboptimal conditions for foliar uptake. Systemicity and rain fastness of neonicotinoids reach a level not achievable up to now. In comparison with conventional SC formulation retention (e.g., thiacloprid SC 480), leaf coverage and spreading of the spray deposit on the barley leaf surface are improved remarkably as shown for Biscaya O-TEQ 240 (Figure 6).

Generally, the O-TEQ formulation provides minimized runoff and a better retention on the plant in the event of rainfall. Once
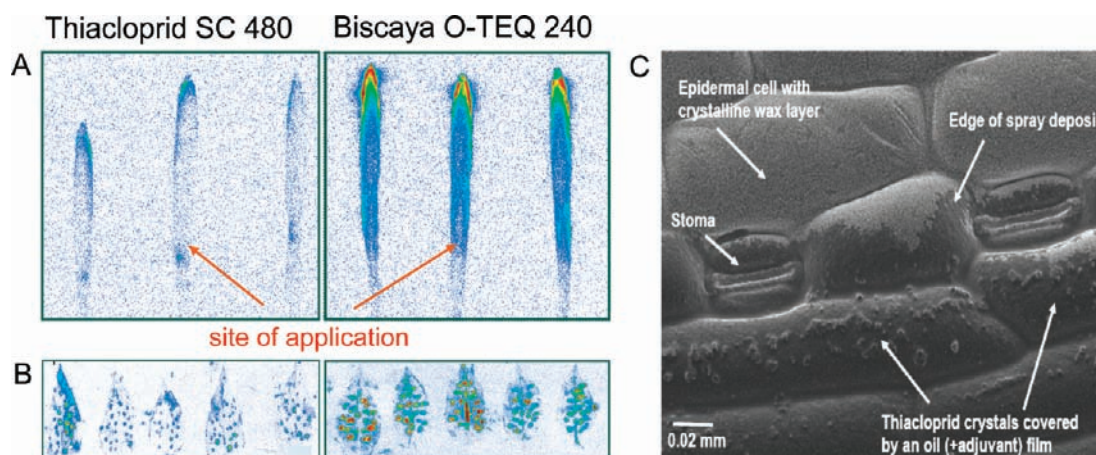
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Figure 6. Comparison of the thiacloprid formulations SC 480 and O-TEQ 240: (A) translocation of thiacloprid in barley leaves 48 h after foliar application, 0.2 g of ai/L; (B) presence of thiacloprid after 10 min of rain within 3 h (5 × 2 mm) (adapted from ref 63); (C) spray deposit of thiacloprid OD on barley leaf (electron micrograph) (adapted from ref 62).

on the leaf, the neonicotinoid shows a smooth spreading of the oil after the evaporation of the spray water, resulting in optimal coverage and distribution. Subsequently, the active ingredient penetrates through the leaf cuticle and is translocated into the leaf tissue.[64,65]

Combinations as Replacements of WHO Class I Insecticides. Novel combinations of imidacloprid with pyrethroids have been developed by Bayer CropScience with the aim of broadening the spectrum of neonicotinoid insecticides and to substitute WHO Class I products from older chemical classes as shown below:

(a) Muralla (imidacloprid and cyfluthrin) is a regional solution for Central America and Chile for vegetables and rice.

(b) Confidor S (imidacloprid and cyfluthrin) is a formulation for the control of tobacco pests in South America.

(c) Leverage is a well-established brand in the United States for broad-spectrum pest control in cotton.

(d) Connect (imidacloprid and β-cyfluthrin) is active against stinkbugs and other pests in soybean.

(e) Solomon and Thunder (imidacloprid and β-cyfluthrin) are cost-competitive solutions for African and Asian markets.

(f) Confidor Energy (imidacloprid and deltamethrin) is used in Europe for broad-spectrum insect control in vegetables, potato, tobacco, sugar beet, and cereals.

Foliar Sprays To Reduce Yield Losses by Drought Stress. Plant growth and yield are greatly influenced by environmental stress to which crops are continuously exposed.[66] Stress can be (a) biotic, imposed by insect pests, weeds, and pathogens, or (b) abiotic, arising from an excess or deficit in the physical or chemical environment such as cold, heat, salt, ozone, oxygen deficiency, or drought.

Field results indicate that multiple foliar spay applications of imidacloprid improved health and increased plant growth even in situations without insect infestations. Imidacloprid treatment led to considerable reduction of yield losses by drought stress compared to other neonicotinoids, as established in a pepper field in Georgia.[66] Water-deficit field studies confirmed the potential of Trimax (optimized imidacloprid formulation) to moderate water stress in plants with an average lint yield increase in cotton of 10%.[66]

The response of Trimax-treated barley to pure abiotic stress stimuli was investigated in detail to elucidate the underlying physicochemical and biochemical mechanisms. In this case, a significant leaf-area growth improvement following imidacloprid soil application could be shown after short-term drought stress. Plants from these trials were analyzed at different elapsed time intervals using DNA microarrays (barley chip consisting of 400,000 expressed sequence tags with information on 22,840 barley genes), a tool for profiling gene expression in plants. After imidacloprid treatment, results from the DNA microarray experiments show two different plant reactions to drought stress: (c) the expression level of drought-stress marker genes in barley is significantly delayed, suggesting a mitigation of drought stress; (d) photosynthesis-related genes are simultaneously expressed at a higher level (energy production is ongoing), whereas in untreated plants photosynthesis declines more rapidly; and (e) in contrast to nontreated plants, numerous pathogenesis-related proteins were found to be overexpressed, explaining field observations of synergistic fungicidal and bactericidal effects.[66]

In addition to its insecticidal activity, a stress shield MoA of imidacloprid supports plants in overcoming the effects of abiotic and biotic stresses. As a trigger of these effects of imidacloprid, its major metabolite 6-chloronicotinic acid (6-CNA) is discussed as a systemic plant inducer, which possibly causes physiological changes in the plant, resulting in stress protection.

Neonicotinoids are a unique chemical class for sucking insect pest control owing to their (i) broad spectrum of efficacy, (ii) selective activity as agonists on insect nAChRs, (iii) exhibition of long-lasting residual effects, (iv) control of insects resistant to conventional insecticides, (v) high systemicity and excellent plant virus vector control, and (vi) versatile application methods, especially in seed treatment and soil application.

Quantitative Structure—Activity Relations (QSARs) for Neonicotinoids. In 2000, Okazawa et al.[67] described a set of 25 ring systems and noncyclic neonicotinoids used in a comparative molecular field approach (CoMFA) study of the binding affinity to house fly *M. domestica* nAChR. Neonicotinoid structures and their partial charges were taken from AM1 calculations. All compounds were superimposed by root-mean-square (rms) fit of four key atoms (N atoms of pyridine and imidazolidine rings an adjacent two C atoms) to the reference conformation of imidacloprid, derived from its X-ray structure.

Recently, a slightly different superimposition rule together with optimized DFT/COSMO structures was discussed by Beck and Schindler[68] using WAVE-3D, a new 3D-QSAR method and a

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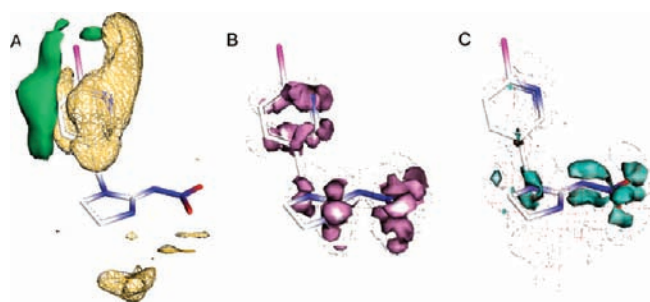dx.doi.org/10.1021/jf101303g |*J. Agric. Food Chem.* 2011, 59, 2897–2908

Figure 7. Variance-weighted model coefficients for the neonicotinoids, superimposed to imidacloprid. Positive contributions, that is, those increasing activity, are shown as solid isosurfaces and negative contributions as mesh: (A) electron density, ρ; (B) LUMO density; (C) Fukui function f (adapted from ref 68).

Figure 8. Isosurfaces of the Fukui functions for preferred sites of oxidative metabolic attack (red arrows) on (A) imidacloprid and (B) thiamethoxam. Three levels of isosurfaces are displayed, 0.005 (green, opaque), 0.001 (yellow, transparent), and 0.0005 (white, transparent). Electron densities were obtained numerically after geometry optimization at RI-DFT[75] level of theory, using the Becke–Perdew combination of functionals,[76] and Ahlrichs basis sets of triple-ζ quality (TZVP) at all atomic centers (adapted from ref 77). Solvation effects were accounted for by a continuum model, COSMO (adapted from ref 78), assuming a value of 80.2 for the dielectric constant of water. The Fukui function was calculated by finite differences.

helpful tool for better understanding the active conformations and metabolism of neonicotinoid insecticides as well as for prediction of structural optimization of nAChR ligands.

Instead of the two carbon atoms used in the publication from Okazawa et al.,[67] the N atom of the acceptor Y ($Y = NO_2$ or CN) within the functional group [=X—Y] was a favorable third point for the alignment fit, which could be confirmed by the smooth distribution of high similarities in the Carbo similarity matrix with respect to the electron density ρ.[68] It was found that one of the best CoMFA-like three-dimensional QSAR models (3D-QSARs) in Wavelet Space (WAVE 3D) for neonicotinoids uses the electron density ρ (and its square, ρ^2), the LUMO density, and the Fukui function, f^-, for attack by an electrophile. A Fukui function is a three-dimensional function calculated quantum chemically from electron density differences between the neutral molecule and its radical cation or anion, respectively. It exhibits maxima in regions of space, where a molecule prefers to be attacked by a nucleophile/electrophile or radical. However, one has to keep in mind that the Fukui function as a molecular property describes the response of the total electron density to the addition or removal of an electron. Any enzyme-specific effects are not accounted for within the Fukui framework.[69]

Visual inspection of LUMO, LUMO+1, and Fukui function f^- of neonicotinoids such as imidacloprid shows that both frontier orbitals contribute significantly to the Fukui function f (Figure 7).

This explains why LUMO and the Fukui function f^- behave like different descriptors in this model, which is well reflected in the variance-weighted model coefficients.

Local Reactivity Discriptors for Understanding Neonicotinoid Metabolism. The metabolism of neonicotinoids such as imidacloprid is strongly influenced by the method of application.[70] Whereas in foliar application most of the residues on the leaf surface display unchanged parent compound, most of the imidacloprid administered to plants by soil application or seed treatment is metabolized more or less completely,[71] depending on plant species and time.[72] According to the metabolic pathway of imidacloprid in cotton whitefly $B.$ $tabaci$,[73] it is known that hydroxylation of the imidazolidine five-membered ring leads in general to mono- and bishydroxylated metabolites.

In this context, the Fukui function f^- was used successfully.[74] In the case of selected neonicotinoids such as imidacloprid or thiamethoxam it can be shown that local maxima of the electrophilic Fukui function relate to preferred sites of oxidative metabolic attack.
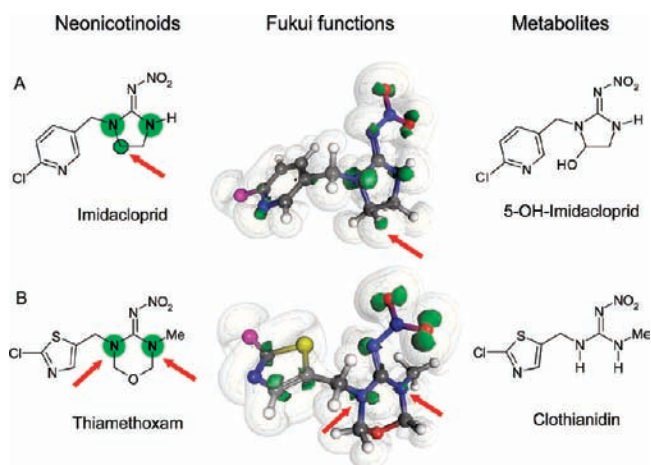
Visual inspection of the maxima of the electrophilic Fukui function of imidacloprid shows that the 5-position of the five-membered imidazolidine ring system corresponds to the major site of electrophilic, oxidative metabolic attack as displayed by the level of isosurface (color coded in green) (Figure 8A).[75–78]

This fact may serve as a useful hint as to why imidacloprid is metabolized in the 4- and/or 5-position, forming the monohydroxylated metabolites such as 5-hydroxy-imidacloprid.

On the other hand, the electrophilic Fukui functions of thiamethoxam show maxima at experimentally observed sites of metabolism for the six-membered ring system (color coded in green) (Figure 8B). The Fukui functions are focused at the 3,5-positions of the core heterocyclic perhydro-1,3,5-oxadiazine ring system, which could correspond to the major site of metabolic attack. This result may serve also as a hint that thiamethoxam is metabolized in the 5- and/or 3,5-position of the six-membered ring system, forming N-desmethylthiamethoxam and/or the noncyclic clothianidin In Vivo in insects and plant tissues.[20,21]

AChBP as Suitable and Functional Surrogates of the Insect nAChRs. The important work of recent years on binding studies of neonicotinoid insecticides with the insect nAChR is recognized by the inclusion of the crystal structures of two soluble homopentameric acetylcholine binding proteins (AChBPs).

In 2001 the crystal structure of the first soluble homopentameric AChBP was resolved.[79,80] This AChBP subtype is secreted by glia cells of a mollusk, the freshwater snail $Lymnaea$ $stagnalis$ L. (L-AChBP). Some years later a second AChBP subtype (A-AChBP), isolated from the saltwater mollusk $Aplysia$ $californica$, was characterized. A-AChBP shares only 33% amino acid identity with L-AChBP, but it possesses all of the functional residues identified in L-AChBP.[81,82] Whereas A-AChBP has a similar high sensitivity for both electronegative neonicotinoid insecticides and cationic nicotinoids such as (S)-nicotine, L-AChBP
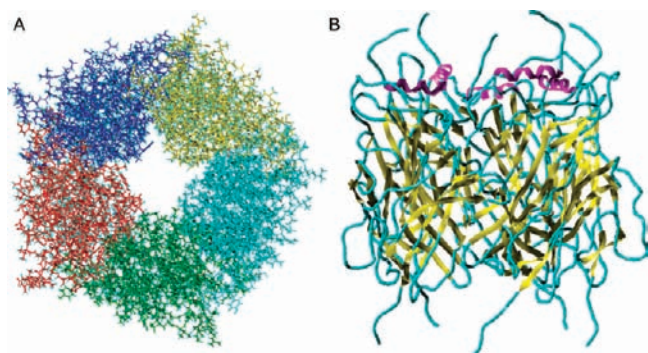
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Figure 9. Insect *n*AChR homology model based on the X-ray of the homopentameric *Lymnea stagnalis* AChBP (adapted from ref 87) and *n*AChR subunit Mpα3 from peach−potato aphid (*M. persicae*) (adapted from ref 90): (A) top view; (B) side view of the insect *n*AChR homology model.

demonstrates lower neonicotinoid and higher nicotinoid sensitivities.[83,84] In 2005 Unwin described[85] a refined 4 Å resolution electron microscopy structure of the heteropentameric vertebrate muscle type $(\alpha1)_2\beta\gamma\delta$ *n*AChR showing considerable structural similarity to the L-AChBP ligand-binding domain (LBD).

High-resolution crystal structures of A-AChBP with imidacloprid and thiacloprid as well as L-AChBP with imidacloprid and clothianidin were published.[86,87] In this context some findings are important. Characteristic of several agonists such as imidacloprid and thiacloprid, loop C largely envelopes the ligand, positioning aromatic side chains to interact optimally with conjugated and hydrophobic regions of the neonicotinoid insecticides, which is consistent with results of solution-based photoaffinity labelings.[86] On the other hand, cocrystallization of L-AChBP with imidacloprid and clothianidin suggested that the guanidine moiety in both stacks with Tyr 185, whereas the *N*-nitro group of imidacloprid but not of clothianidin makes a H bond with Gln 55. The H bond of NH at position 1 with the backbone carbonyl group of Trp 143 offers for clothianidin an explanation for the diverse actions of neonicotinoids on insect *n*AChRs.[87] Because of this similarity, L-AChBP is now considered as a structural and functional surrogate for the extracellular LBD of insect *n*AChRs.[86]

Insect *n*AChR Homology Model Based on *Lymnea stagnalis* AChBP. The crystal structures of the AChBPs from different snail species show a conserved architectural fold that has been recognized as a template to construct homology models for the ligand-binding domains of mammalian neurotransmitter receptors.[79,82,88,89]

For structure-based drug discovery procedures to identify novel and selective neonicotinoid ligands of the insect *n*AChRs a homology model based on the homopentameric L-AChBP (already cocrystallized as receptor−ligand complex with imidacloprid and clothianidin, see ref 87) and the *n*AChR subunit Mpα3 from the peach−potato aphid (*M. persicae*) could be of interest. Huang et al.[90] reported the isolation of three α-subunit genes (Mpα3−5) with overall amino acid sequence identities between 43 and 76% to characterized *n*AChR subunits. Heterologous coexpression of the *M. persicae* α-subunits, such as Mpα3 cDNA, with the rat β2 in *Drosophila* S2 cells indicates their pharmacological diversity and resulted for the Mpα3 subunit in high-affinity binding of [³H]imidacloprid.[90]

A homology modeling procedure can be broken down into several major steps. Necessary prerequisites for a successful approach are the known amino acid sequence of the protein to be constructed and at least one experimental X-ray structure of a homologous protein, which will serve as a template for the homology model. In the case of neonicotinoids, one approach would be to start with genes that are known to be reactive to, for example, imidacloprid. As an example, using the Mpα3 sequence from *M. persicae* *n*AChR[90] for which no three-dimensional structure is available, a sequence comparison revealed a high similarity to L-AChBP, for which the X-ray structure exists.[87] This was therefore selected as template. After having transformed one monomer of the homopentameric L-AChBP into a *M. persicae* *n*AChR monomer, the overall structure of the of L-AChBP pentamer was used to construct a *M. persicae* *n*AChR pentamer (Figure 9).

This structural model is further refined by geometry optimizations and molecular dynamics calculations.

Finally, the insect *n*AChR homology model based on L-AChBP can be used for in silico docking simulations or virtual screening of chemical libraries[91] to identify new insecticidally active *n*AChR ligands on the basis of receptor-bound structures in discovery projects, providing an important complementary approach to empirical screening in modern crop protection.

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2908

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