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Natural Products in the Discovery of Agrochemicals

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Dedicated to John M. Clough

Abstract: Natural products have a long history of being used as, or serving as inspiration for, novel crop protection agents. Many of the discoveries in agrochemical research in the last decades have their origin in a wide range of natural products from a variety of sources. In light of the continuing need for new tools to address an ever-changing array of fungal, weed and insect pests, new agricultural practices and evolving regulatory requirements, the needs for new agrochemical tools remains as critical as ever. In that respect, nature continues to be an important source for novel chemical structures and biological mechanisms to be applied for the development of pest control agents. Here we review several of the natural products and their derivatives which contributed to shape crop protection research in past and present.

Keywords: Agrochemicals discovery · Biopesticides · Crop protection agents · Leads for new agrochemicals · Natural products

Natural products have a long history of use as pest management tools and have been intimately connected with agriculture from its beginning to its most recent developments. This review article aims to present some of the important natural products and their derivatives, past and recent, used as crop protection agents. A historical perspective is first given with the development of the pyrethroids, a landmark in its time for successful ligand-based design. Natural products are then discussed in the context of contemporary agrochemical research, and some of the molecules that contributed to shaping the field including those currently in late development are described. Owing to their ecological role in adaptation processes and defense mechanisms, several secondary metabolites from microbials and plants have found use as effective starting points from which new lead areas of chemistry have been derived. Phytochemicals applied in their semi-purified extract form are commercially used for the biological control of pests, as is the case for botanical insecticides. In that area, whereas plant secondary metabolites represent a historical sources of insect biocontrol agents, peptides from plants and other proteinaceous natural products may offer next generation solutions.

The chemical protection of crops probably began in the fertile crescent of Mesopotamia with the application of elemental sulfur introduced by the Sumerians in the earliest recorded instance of pest management to control insects and mites.[1] It is not possible to describe the exact moment when humans started using plants and their products to control insects and microorganisms, but it also has been historically associated with the onset of agriculture. Natural products such as ground tobacco, essential oils and lime, used against aphids, and ground pyrethrum flowers were some of the earliest pest control agents used.[2] If initially the use of natural product extracts was restricted to intuitive and naturalist procedures, the knowledge has spread and survived through different civilizations until the 19th and early 20th centuries, when the first scientific observations associated with empirical practices allowed the significant use of botanical extracts as pesticides.[3] In the same period, advances in chemistry allowed the identification and characterization of some plant secondary compounds and better defined plant extracts, such as derris (rotenone), pyrethrum or nicotine came into use. The era of synthetic agrochemicals really took off in the 1950s with the introduction of compounds such as dichlorodiphenyltrichloroethane (DDT) which earned the industrial chemist Paul Müller the Nobel Prize in Physiology or Medicine in 1948 for his discovery at J.R. Geigy AG of its highly efficient insecticidal properties, the carbamates for insect pest control, and 2,4-dichlorophenoxyacetic acid (2,4 D) for weed management. The arrival of synthetic pesticides revolutionized the control of agricultural pests. Soon after in the 1960s, chemistry research on natural products with pesticidal properties also started intensifying, in particular in insect control with the unforeseen problems of persistence and resistance encountered with DDT and the organochlorines.[4,5] The natural products brought bioinspiration to laboratories for the discovery of new weeds, plant pathogens, and insect pest control agents and played an important role in the advancement of crop protection research, uncovering new biology and mode of actions. An illustrative example, which inaugurated several approaches still in use in modern discovery and optimization of agrochemicals[6] has been the work done on the insecticidal pyrethroid esters.[7–10]

Pyrethroids for Control of Insect Pests

The insecticidal properties of *pyrethrum*, the powder obtained from ground flowers of *Chrysanthemum coccineum* and *Chrysanthemum cinerariaefolium*, have been known for centuries and efficiently applied for household use. In 1900, scientists in the viticulture research station of the canton of Vaud in Switzerland tested in one of the first recorded large field trials up to 80 different substances for their insecticidal activity against the European grape berry moth (*Eupoecilia ambiguella*). Alongside sulfur, copper, arsenates

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and soft soap, a large range of products isolated from plants including spices as well as pharmaceutically active ingredients were investigated. The best results were obtained with an aqueous solution of 1% of *pyrethrum* formulated with 3–5% of soft soap.[11] Due to the high cost of producing *pyrethrum*, its subsequent application on broad field crops proved to be unsustainable and eventually was limited only to certain highly valuable vineyards. Nevertheless, this field trial allowed recognition of the potential of this natural product for use as an effective insecticide for crop protection. These results and the increasing demand for *pyrethrum* attracted the attention of far-sighted chemists, initially in Japan where commercial production existed since the 1880s and later in Germany and Switzerland. In a landmark series of publications appearing in 1924, Staudinger and Ružička described the isolation of the odor- and colorless active ingredient through an ingenious procedure involving a self-developed bioassay-guided fractionation using the German cockroach (*Blattella germanica*) and disclosed the main structural features of two pyrethrin esters **1** and **2** (Fig. 1).[12,13] The full elucidation of the structures and the determination of configuration of the stereocenters took another 30 years enabled by advances in separation techniques and other new research methods (Fig. 1). The absolute stereochemistry was confirmed in the 1970s by X-ray crystallography.[14] *Pyrethrum* is composed of six main components, the pyrethrins, which can be divided into two subgroups: 'pyrethrins I', which are chrysanthemic esters (R = Me, Fig. 1); and 'pyrethrins II', which are pyrethric esters (R = MeO_2C, Fig. 1), with pyrethrin I (R = Me, R' = $CH{=}CH_2$) being the most biologically active molecule.

With full structural information in hand in the 1950s, the synthesis of potential analogues with improved insecticidal activity could be envisaged. Despite many similarities between drug and agrochemical discovery, the latter has unique characteristics due to the biodiversity of pests and the conditions of use. Because crop protection agents are used outdoors, photostability is an important property to be considered and in some cases is the key parameter to optimize. The limited stability of pyrethrins toward oxidation and photodegradation (Fig. 2) as well as their high cost of manufacturing impeded their use in crop protection but they otherwise possessed attractive features as an insecticide including high toxicity to the target pest, fast speed of kill, ease of application and a favorable human safety profile.

Hence pyrethrin I was used as starting point for the design of improved insecticides. The development of synthetic pyrethroids targeted both modified alcohol and carboxylic acid moieties. A brief historical perspective is given in Fig. 3.[7,8,14]

Early research by Laforge, a chemist at the bureau of entomology and plant quarantine of the U.S. Department of Agriculture, focused on the alcohol variation. The replacement of the complex cyclopentenolone *Z*-configured dienyl side chain by a simpler allyl brought the first improvements leading to allethrin (**3**), the first synthetic pyrethroid to be equipotent to pyrethrin I.[16] Sumitomo Chemical Ltd., who would become later a major player in the pyrethroid discovery process, developed on the basis of the work of LaForge a technical synthesis and brought to the market Allethrin as the first pyrethroid in 1954, followed later by S-bioallethrin (**4**), the isolated most active stereoisomer. Allethrin represented an important step as it proved it was possible to find potent synthetic analogues of the pyrethrins. The next structural modifications were initially very incremental but the weakly active piperonyl ester (**5**) from earlier work of Staudinger and Ružička provided a new avenue, pointing towards the potential of replacing the alcohol part by simpler and more economical achiral moieties. The use of aromatic alcohols as in furamethrin (**6**) provided the first potent pyrethroids in this new class and improved photostability. During the development of the technical synthesis of furamethrin, scientists at Sumitomo prepared compound **7** as a reference to study impurity profiles in the process and discovered that α-substitution with ethynyl significantly increased potency over furamethrin. This modification proved to be applicable to other pyrethroids. Further optimization led to the exchange of ethynyl with the more stable cyano substituent, which eventually would become an element of design applied in many pyrethroids. The later introduction of the 3-phenoxybenzyl alcohol or its cyanohydrin analog led to the discovery of even more stable and safer insecticides (compared to contemporary agrochemicals) such as ciphenothrin (**8**).[15] Modification of the chrysanthemic acid moiety also was needed because of its poor stability towards oxygen, heat and light. The two methyl groups in the isobutenyl, in particular the one in *trans*-(*E*) position, are sensitive to radical attack leading to rapid photodecomposition upon sun lamp irradiation in laboratory stability tests.[16] Hundreds of analogues with different substituents at the double-bond were synthesized and eventually the exchange of the methyl groups with halogen atoms proved

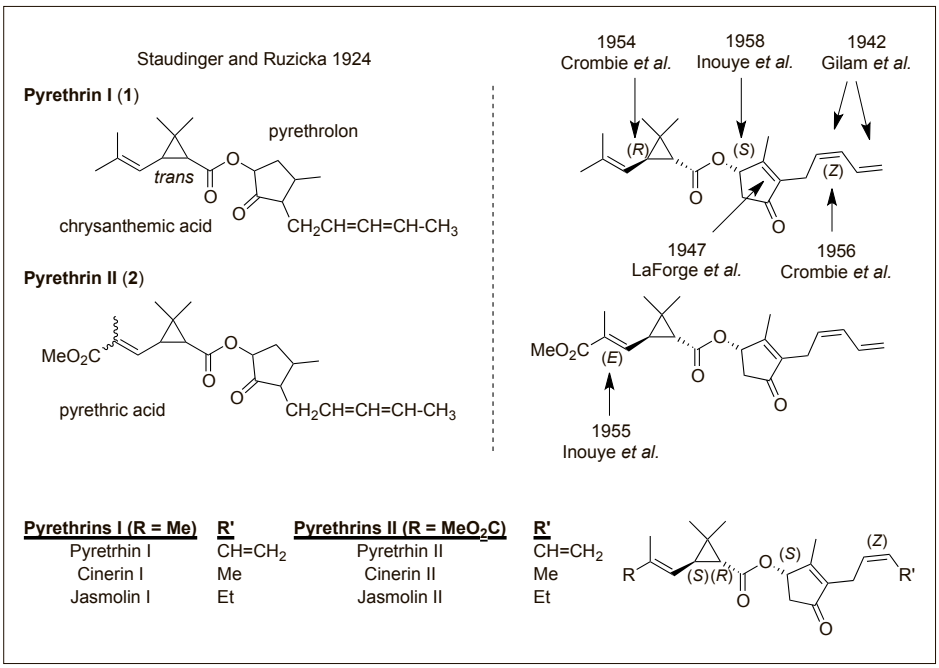


Fig. 1. The arduous structure elucidation of pyrethrin I and II.

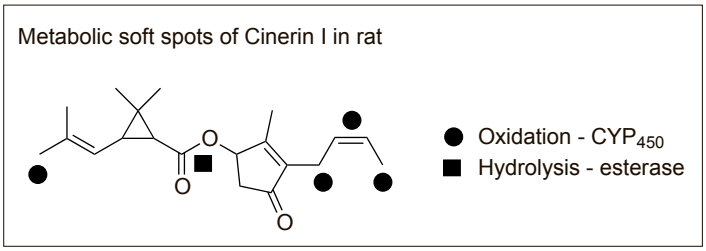


Fig. 2. Hydrolytic and oxidative liabilities of the pyrethrins.

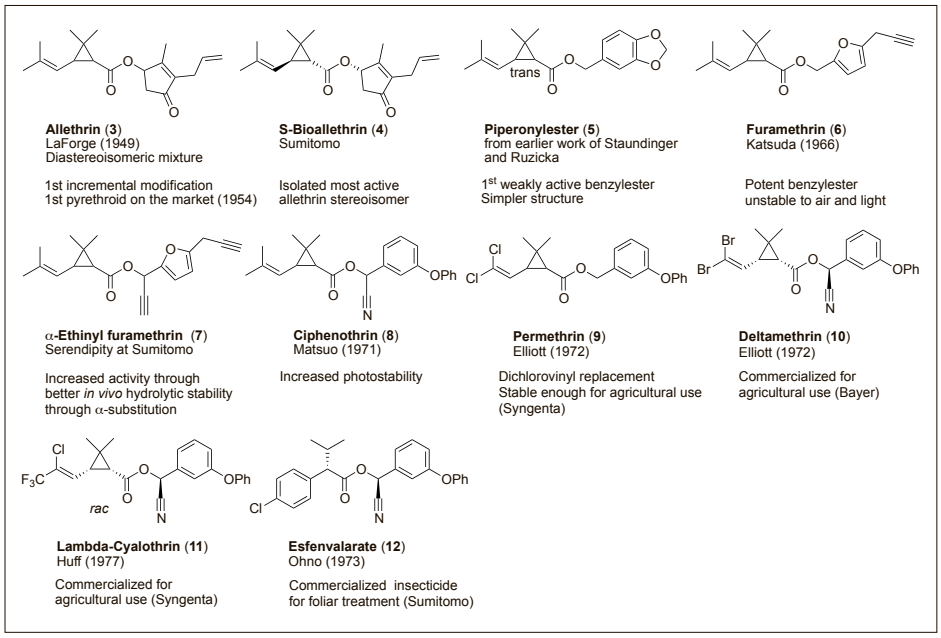


Fig. 3. The evolution of the pyrethroids and selected compounds commercialized for agricultural use.

to be the solution of choice.[17] Elliott and his team at the Rothamsted Experimental Station investigated this option with the best benzylic alcohols described in the previous paragraph and discovered new insecticides with unprecedented potency at the time. This research culminated with the discovery of permethrin (**9**) and deltamethrin (**10**) which were the first pyrethroids with sufficient stability toward oxidative or photodegradation to be suited for agricultural use.[18,19] A further refinement was the replacement of a chlorine atom of cypermethrin by a CF_3 group to give lambda-cyhalothrin (**11**).[20] Eventually, to simplify the pyrethroid scaffold further, scientists at Sumitomo, designed fenvalerate and its enantio-enriched form esfenvalerate (**12**), a synthetic pyrethroid that no longer contained a cyclopropyl carboxylic ester.

Pyrethroids proved to be broad spectrum insecticides effective against a broad range of foliar pests, including *Coleoptera* (beetles and weevils), *Diptera* (flies and mosquitoes), *Heteroptera* (bugs), *Homoptera* (aphids, whiteflies, and leafhoppers), *Lepidoptera* (moths and butterflies), *Thysanoptera* (thrips), and *Orthoptera* (cockroaches and grasshoppers). Pyrethroids exert their insecticidal action through an interaction with the insect voltage-gated sodium channels.[21] They preferentially bind and stabilize the open state of sodium channels, producing prolonged channel opening and conductance of sodium, which ultimately results in permanent axonal membrane depolarization, eventually paralysis and death of the insect.[22] Mammalian (rat) sodium channels are up to 1000-fold less sensitive than insect channels to pyrethroids.[23] Differential metabolism, *i.e.* preferential degradation of the insecticide in mammals by means of esterases and cytochrome P_{450}, also contributes to selective toxicity.[24]

Pyrethroid insecticides hence evolved in a now classical sequence of natural product research: activity observed in a natural extract, isolation and identification of the active compounds serving as template to generate optimized agrochemicals. The ligand-based design for the optimization of the pyrethrins, the importance of efficient synthesis to maintain cost of manufacturing of these chiral molecules in profitable range, smart exploitation of serendipities and, for natural products, collaboration between academic and industrial partners,[9] are still illustrative of many of the features in today's agrochemical discovery. Most importantly, the pyrethroids inaugurated the era of synthetically more complex, but toxicologically and environmentally more friendly molecules used in modern crop protection.

Natural Products in Agrochemical Research

For nearly three-quarters of a century, there has been a constant need for innovations in crop protection technology that helps to provide a sustainable food supply for an increasing global demand. The continued search for selective, safe and cost-effective new agrochemical classes is stimulated by a number of important factors: resistance development to existing crop protection products, new agricultural practices and technologies such as integrated pest management programs and seed treatment applications, the shifting of pest populations and the changing regulatory landscape, in particular with the requirements for improved environmental and toxicological profiles and the de-registration of older active ingredients.[6,25,26]

Typical for agrochemical research is the testing of compounds directly on agronomically relevant whole organisms, that is, the weed, fungus, or insect. Such methodology allows the generation of *in vivo* data on target species to control, very early in discovery. Scientists in crop protection research use a variety of chemical inputs from which new lead areas of chemistry are derived:[27,28] Designed libraries based on molecular target hypotheses,[29,30] competitor-inspired chemistry, library acquisition from universities or chemical vendors, project compounds and intermediates in other indications, collections exchanged with pharmaceutical companies and natural products.[31,32]

Utilizing natural products as a source of input for the discovery of new agrochemicals offers a number of advantages. Natural product chemotypes offer the ability to target underexplored areas of the biologically relevant chemical space[33,34] and their biological activity resulting from Darwinian selection increases the likelihood of discovering a structure that has utility as a pesticide or as a molecular scaffold for pesticide design. As such, natural product hits in screenings can reveal new molecular target sites generating new potential intervention points for pest control ultimately leading to novel modes of action, which is particularly valuable for resistance management. Natural products and their semi-synthetic derivatives can have lower environmental half-lives. Owing to their structural complexity, they also often show high target specificity and low toxicity towards non-target organisms and their shorter persistence offer opportunities for differential *in vivo* metabolism and exposure. Taken altogether, these features also provide an advantage for public and regulatory acceptance. However there are a number of problems and limitations associated with natural product-based discovery programs in agrochemical research, in particular with the screening of compounds on whole organisms.

The data generated from screenings driven by symptomology read-out on whole organisms is complex, multifactorial and is tainted with uncertainty due to the variability of the tests. This is especially challenging when a mode of action hypothesis is lacking and the *in vitro* biochemical assay or structural biology tools which help reduce complexity are not available. In addition, for a compound to give a reliable signal in a high-throughput screening on a whole organism, its affinity for the putative target protein generally has already to be at very high level, typically

nanomolar, meaning that confirmed hits from screening are very rare. On the other hand, the attrition rate is lower than in pharmaceutical research where the initial *in vitro* optimization may be hard or impossible to translate to the target. Because of the low initial hit rates, testing small collections of purified natural products plays against the odds. The natural products' physicochemical properties[35] can often be inadequate and their *in vivo* half-lives excessively short, which hides their true potential in a primary screening on whole organisms where absorption, distribution, metabolism, and excretion play a role. Prioritization of such hits is not easy, in particular when the activity is only moderate and could possibly just be due to general toxicity. Moreover, the bioassays used are also sensitive to pan-assay interference compounds (PAINS) or other promiscuous groups including some frequently found in natural products such as the catechols, quinones, Michael acceptors, 1,3-dioxolanyl and siderophores.[36,37] Screening of crude or semi-purified extracts, as done in bioassay-guided fractionation processes, brings additional complications due to frequent unwanted interferences between the screened materials and the bioassays.[38]

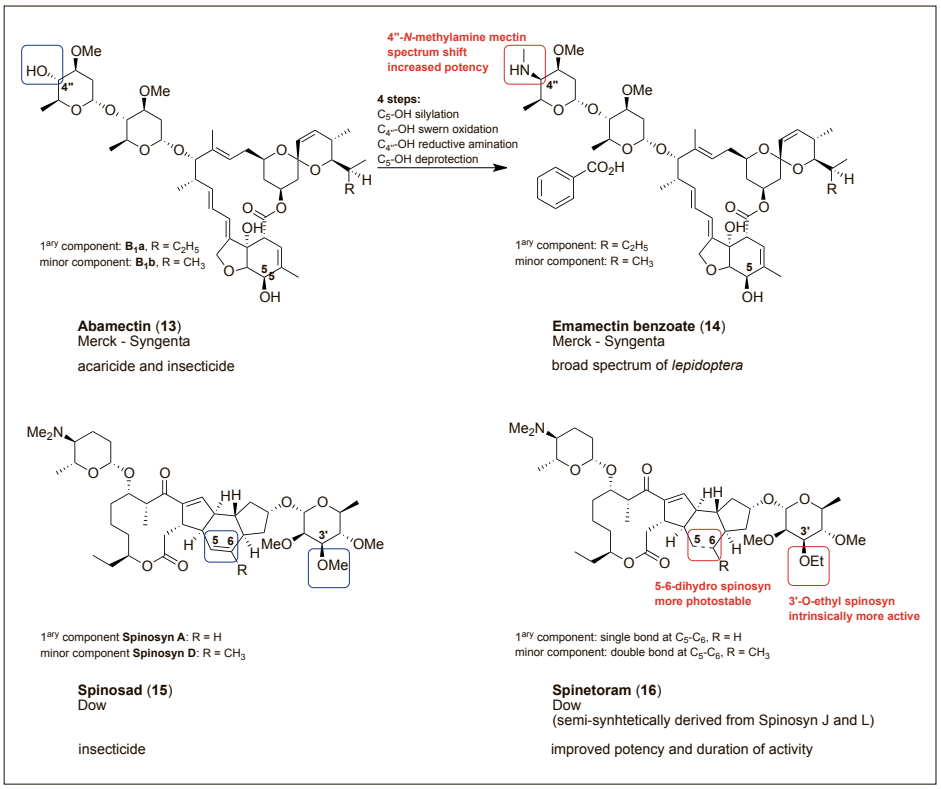
Nevertheless, natural product-directed discovery programs have over the years delivered a significant number of valuable starting points and some of the most important modes of action in agrochemicals. The output of such effort is threefold: the identification of new ingredients that become commercial crop protection chemicals without further transformation, active molecules that require some synthetic modification (semi-synthesis) and active molecules that inspire development of purely synthetic solutions (synthetic mimics).[32,39] Other valuable outputs include the possible discovery of a new target site of action leading to target-based screening efforts or the identification of a new structural motif that may inspire new classes of chemical structures. The identification of a molecule that has all of the required properties to be effective as an agrochemical product directly from the screening of natural products, as was the case for insecticidal spinosyns[40,41] and the mectins[42] is very infrequent. Rather, it is the identification of active molecules with intriguing activity profiles that can serve as a starting point for further optimization. This can either involve a few steps of modifications of the naturally occurring molecule, as exemplified by spinetoram,[43] emamectin benzoate and more recently afidopyropen[44] in insect control and fenpicoxamid[45] in plant pathogen control, or an overall reconfiguration of the core structure of the natural product, as in the case of the strobilurins.

The Mectins and the Spinosyns

Natural products isolated from microbial fermentation and their semi-synthetic derivatives have been most important to the development of new insect control agents. Abamectin (**13**, Scheme 1), a naturally occurring mixture of avermectins B_1a and B_1b (16-member ring macrolides), is effective against a large number of mite and lepidopteran pest insect species and acts *via* the γ-aminobutyric acid (GABA)/glutamate-gated chloride channels.[45] Spinosad (**15**), also a naturally occurring mixture (12-member ring macrolides; spinosyns A and D), is active against a wide range of lepidopteran, dipteran and thyasnopteran pests and functions as an allosteric nicotinic acetylcholine receptor (nAChR) agonist.[46] Abamectin and spinosad have been synthetically modified, leading to insecticides that have an altered spectrum, improved efficacy and/or improved duration of activity. For example, synthetic modification to the 4''-hydroxy group of abamectin to form 4''-*N*-methylamine yielded emamectin benzoate (**14**), which possesses greatly improved efficacy for lepidopteran species (spectrum of activity shift). Likewise, synthetic modifications (ethoxylation of the 3'-hydroxy on the rhamnose and reduction of the 5,6-double bond of spinosyn J) of a mixture of spinosyns J and L resulted in spinetoram (**16**), a semi-synthetic spinosyn insecticide with improved potency and extended residual activity.

The spinosyns and the mectins possess many of the features required nowadays for performance and product safety in particular with regards to environmental safety (Fig. 4). Starting in the 1970s, selectivity requirements initially were focused on mammalian versus pest selectivity, the desire being for products that were less toxic to mammals. The development of the pyrethroids saw the introduction of insecticides that possessed overall improved mammalian toxicological profiles on a per gram/Kg basis coupled with an increase in overall insecticidal activity. Gradually, with the implementation of integrated pest management programs[47] addressing the regulatory needs for an improved toxicological and environmental profile in insect control, emphasis also was put on better environmental safety, starting with less persistent molecules and subsequently moving to low toxicity towards non-target organisms and low mobility in soil. In this journey to modern agrochemicals, the mectins, spinosad and its semi-synthetic derivative spinetoram provided early examples of favorable mammalian and environmental safety profile coupled with excellent utility and efficacy.

These products are degraded rapidly in the environment after application though a combination of routes.[41,42] Photolysis on plant surfaces is fast, and the compounds bind tightly to soil, where they are rapidly degraded by soil microorganisms. No leaching or bioaccumulation occurs due to rather high lipophilicity, low to moder-



Scheme 1. Mectins and spinosyns natural products and their modified analogues.

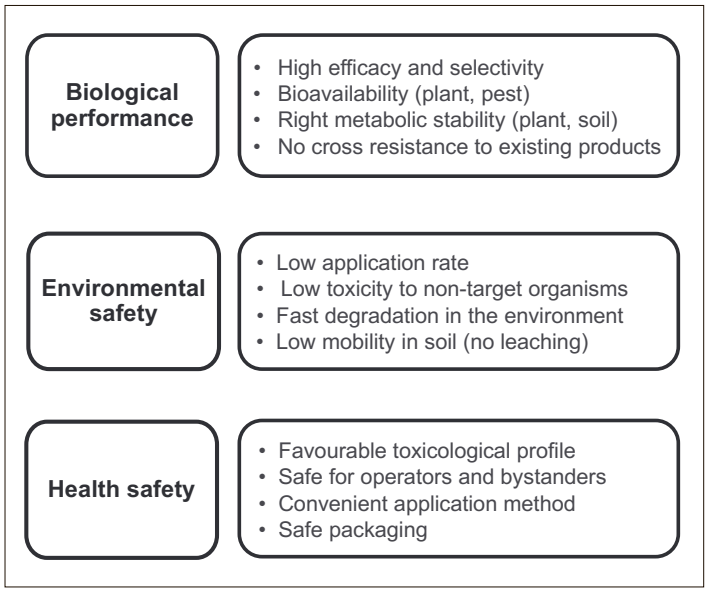


Fig. 4. Profile of a modern agrochemical.

ate water solubility and short persistence. Their impact on populations of beneficial predacious insects and mites is much lower than on target pests. This wide margin of safety is due to the rapid uptake into the foliage after application, combined with the fast degradation of surface residues under sunlight, which makes the compound less bioavailable to beneficials than to pests under field condition. The combination of insecticidal efficacy and safety profile of the spinosyns was recognized by the U.S. Presidential Green Chemistry Award in 1999 for spinosad and in 2008 for spinetoram. The application rates for the highly potent mectin insecticides and acaricides are in the range 10–30 g-a.i./ha (10 g/ha means that only one teaspoon of an active ingredient (a.i.) is required to protect the area of a soccer pitch) which constitutes a landmark in the dramatic reduction of use rates of crop protection considering that as recently as in the 1960s more than 1 kg of a crop protection chemical was typically applied per ha.

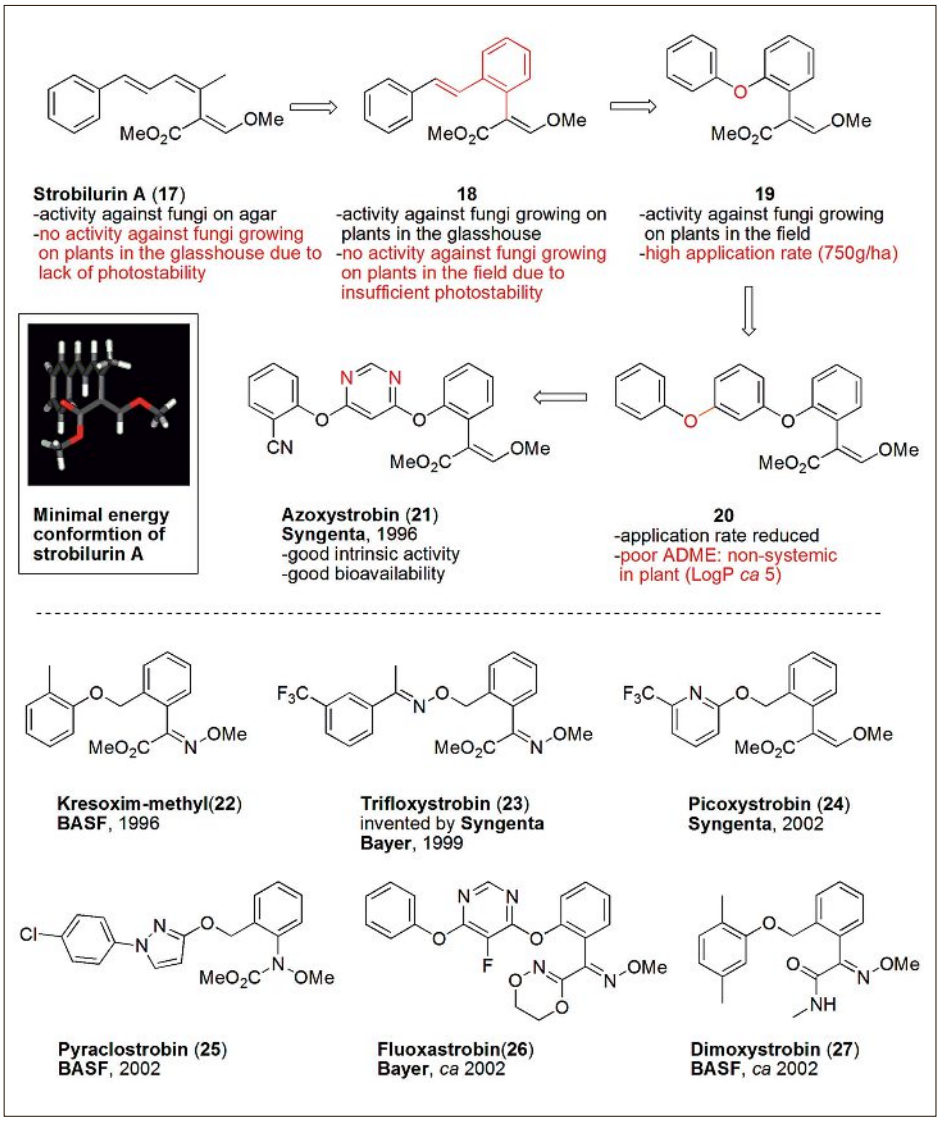
Higher Fungi and Plant Defense Metabolites as Source of Inspiration for Crop Protection: The Strobilurins and Stemofoline

Whereas one natural product-based approach includes assaying large collections of extracts obtained from taxonomically, geographically and environmentally biodiverse inputs and leads to unanticipated discovery of pesticidal natural products such as described above, study of chemical ecology offers a more targeted alternative. The evolutionary forces driving the survival of species include positive interactions such as mutualistic and symbiotic relationships and negative interactions such as competitive and parasitic relationships. Chemical defense is widespread in plants but also in fungi.[48] Chemical defense compounds are usually effective against animals, insects, plants or fungi, thus exhibiting toxic, pungent, bitter, herbicidal or fungicidal properties. To date at least three fundamentally different chemical defense mechanisms are known. While constitutive chemical defense relies on permanently present bioactive secondary metabolites, wound-activated chemical defense is based on the conversion of an inactive precursor into a bioactive defense compound that is only generated upon injury. In induced chemical defense, compounds are synthesized *de novo* on demand. The identification of a constitutive chemical defense metabolite is experimentally the simplest approach as it requires only a bioassay-guided screening against potential enemies or competitors without additional method development as would be the case for wound-activated and induced chemical defense. The very successful strobilurin class of fungicides originates from such an effort with the isolation in the 1970s of strobilurin A (**17**, Scheme 2) from the pinecone cap (*Strobilurus tenacellus*) in a research program targeted to grow mycelial cultures of *basidiomycetes* higher fungi.[49–51] Fungal mycelia have to compete with other fungi for nutrition and space and are potential victims of mycoparasitic fungi. Therefore, several fungi, including *S. tenacellus* contain fungicidal secondary metabolites, which suppress other competing organisms in the same environment, and by doing so give themselves an advantage. The strobilurins inhibit respiration in fungi selectively by binding at the so-called Q_o site of cytochrome b which is part of the bc_1 complex (complex III) located in the inner mitochondrial membrane of fungi and other eukaryotes, leading to intracellular deficiency in ATP.[52] With their rare combination of favorable molecular and biological properties, strobilurins were immediately seized upon as starting points for optimization as synthetic mimics. A clear attraction was the simplicity of their structures, which is a rarity in bioactive natural products. Independent programs of research aimed at optimizing strobilurin A started first within Syngenta (ICI at the time) and BASF which led after several years' work to the discovery and almost simultaneous launch of the first synthetic strobilurins: azoxystrobin (**21**, Scheme 2) and kresoxim-methyl (**22**). Many other compounds made it to the market despite similar structure and identical mode of action, demonstrating the creative power of chemical design and synthesis as tools to deliver multiple compounds in a successful class.

Milestones in the chemical optimization of azoxystrobin are shown in Scheme 2. The (*E*)-methyl-β-methoxyacrylate unit in strobilurin is the main enthalpic contributor for binding, important for activity and it was conserved in the design of analogues. The phenylpentadienyl unit of strobilurin A is to a great extent responsible for photoinstability and volatility and needed to be modified. Computer modelling shows that the β-methoxyacrylate and the phenylpentadienyl units of strobilurin A are cross-conjugated, being almost orthogonal with respect to each other in the lowest energy conformation.[53] This unusual and fortunate structural feature means that the interactions between the two parts of the molecule are minimized, so that structural changes to the phenylpentadienyl unit have little effect on the β-methoxyacrylate and *vice versa*. In the efforts to stabilize the dienyl system while retaining the same molecular shape, it was first discovered that the (*Z*)-olefinic bond could be replaced by an *ortho*-disubstituted benzene ring to give **18**, which is less volatile and much more stable in light. Compound **18** is active in the greenhouse but still degrades too quickly to express good activity in the field. The diphenyl ether which removed the extended stilbene conjugation **19** proved to be sufficiently stable. Furthermore, **19** was shown to be systemic in plants, an important property of many modern fungicides which improves field performance by redistribution of the compound within plant tissue after foliar application. However, the required high application rate in the field (750g/ha) was not economically viable and created some phytotoxicity issues (crop damage). Probing substitution around the aromatic rings of **19** to increase binding affinity led to analogues such as **20**. The tricyclic compound **20** had improved fungicidal potency but was too lipophilic to demonstrate systemic movement. Further extensive ex-

perimentation (*ca.* 1400 compounds made overall in the project) aimed at tailoring lipophilicity and other important physical properties by careful combinations of suitable rings and substituents on them led finally to the discovery of azoxystrobin, a compound with remarkable biological activity against plant pathogenic fungi and still the world's biggest-selling fungicide.

In the search for new chemical scaffolds leading to novel chemical classes of agrochemicals, constitutive defense systems in plants is another source of interesting leads. Amongst these, the alkaloids exert their effects on insects through antifeeding, repelling or neurotoxic mechanisms. The natural product stemofoline (**28**, Scheme 3), isolated from the stems and leaves of the oriental medicinal plant *Stemona japonica* and known as a potent agonist of insect nicotinic acetylcholine receptors (nAChRs),[54] was considered as a good starting point. Stemofoline shows fast-acting insecticidal, antifeedant and repellent activities, but its activity is significantly lower than that of commercial products acting on insect nAChRs. The natural material is not readily accessible and its complex structure is troublesome for the synthesis of analogues. Therefore, **28** was used as a lead structure in order to identify novel active ingredients, particularly for sucking pest control. Scientists at Syngenta designed smaller molecules focusing on the stemofoline 2,6-methanofuro[2,3,4-gh]pyrrolizine cage structure. Based on this structure, a first class of tropane ethers (Scheme 3) was identified. Although they had weaker insecticidal activity, their lower complexity made them synthetically more accessible. Optimization of this hit and implementation of a prodrug strategy eventually led to the class of pyridinyl-cyanotropanes and for example compound **31** (R = CH_2CF_2), highly active *in vivo* against aphids and whitefly, which is bioactivated to compound **30** in insects by cleavage of the *N*-(2,2-difluoroethyl) residue.[55,56]



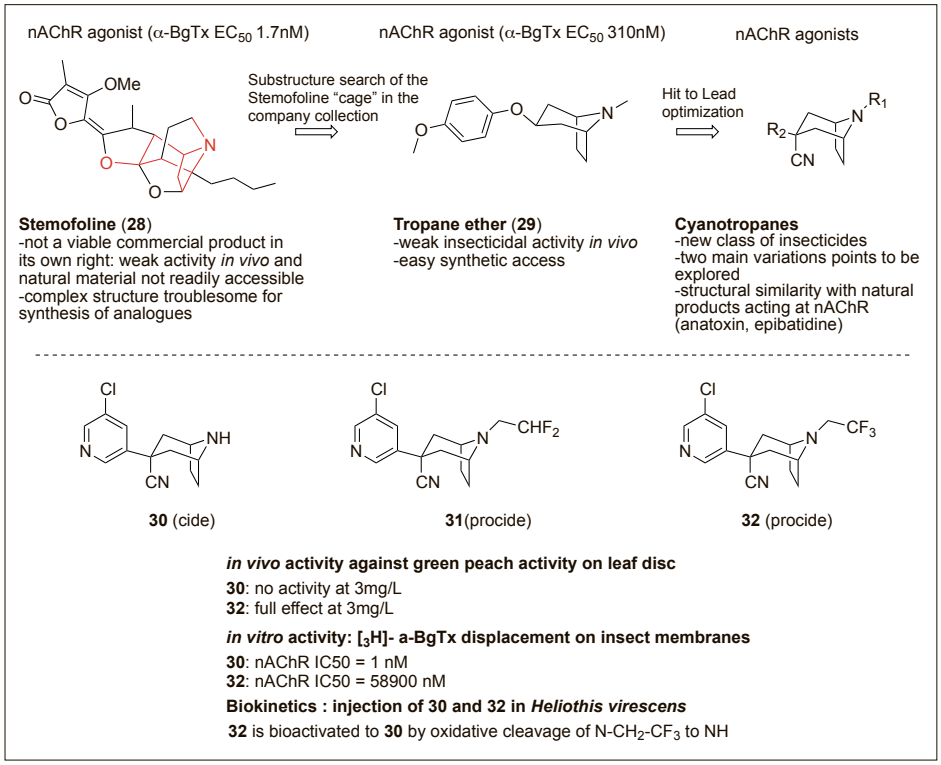
Scheme 2. Discovery of Azoxystrobin through chemical optimization of Strobilurin A and selected commercial strobilurins.

ADME for Agrochemicals: Tuning the Physicochemical Properties of Cyanotropanes

The optimization of agrochemicals is a multi-parameter endeavor (Fig. 4). Similar to drugs, agrochemicals are optimized to interact with their target receptors at low concentrations *via* the same molecular recognition processes. However, although ADME is vital to both pharmaceuticals and agrochemicals,[57] the compounds encounter different chemical environments from the site of application (foliar spray or application in soil for root uptake) to the biochemical target. After uptake of a sprayed agrochemical into the leaf, the LogP, molecular volume and pKa of agrochemicals dictate their distribution in the plant's compartment. When a compound is basic, an ion trap occurs that leads to its sequestration in vacuoles located inside the leaf owing to the low pH there (pH 5.5).[58] Trapping into vacuoles is not favorable for insect control, when sap-feeding pests such as a hemipteran are targeted. Vacuoles are not their preferred food source, nor do they participate in systemic transport. In the case of aphicides, the compounds should have low lipophilicity (LogP < 2.5) for good kinetics of transfer through the leaf tissue and be non-basic in order to allow optimal bioavailability. To tune the physical properties, a pro-form of the highly basic active cyanotropane was designed using the effect of fluorine substitution in β-position to reduce basicity and adjust lipophilicity (Fig. 5).[59,60] The optimum was reached by derivatization of the cyanotropane nitrogen with the metabolically labile 2,2-difluoroethyl group.

Natural Products Currently in Late Development: Afidopyropen and Fenpicoxamid

Mectins, spinosyns, the herbicide Bialaphos[61] and the fungicidal polyoxins are currently the only natural products and semi-synthetic derivatives introduced to the agromarket but two more microbial fermentation products are in late development and have received an international standardization organization (ISO) name.[62] Afidopyropen (**34**, Scheme 4) is a new natural product-derived insecticide active against piercing and sucking insect pests such as aphids.[44,63] The molecule is based on the natural product pyripyropene A (**33**) that was isolated by the group of Ōmura at the Kitasato Institute for Life Science in Japan, famous for its discovery not only of avermectin but also of many other experimental natural products with pesticidal activity.[64] The group of Gloer subsequently reported its insecticidal



Scheme 3. From Stemofoline to the cyanotropane procides.

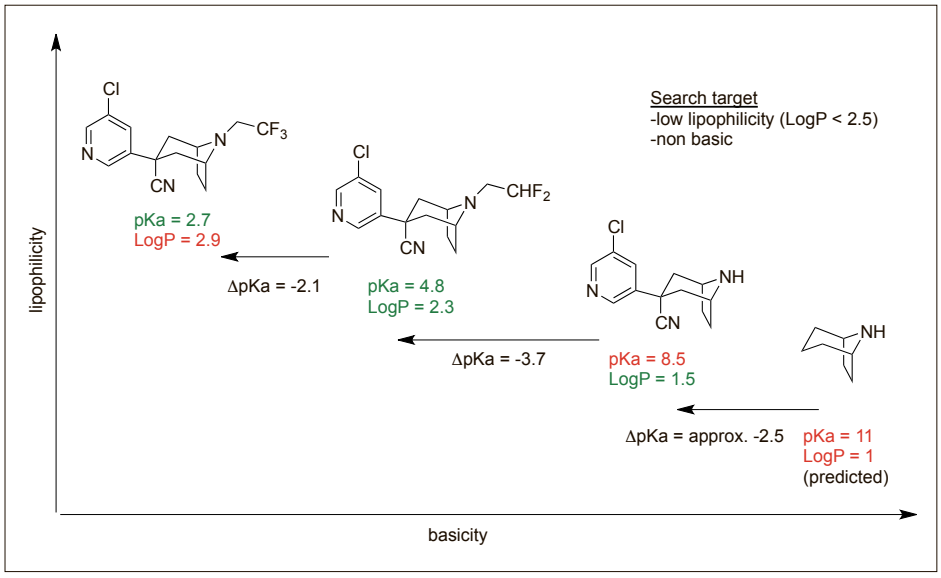
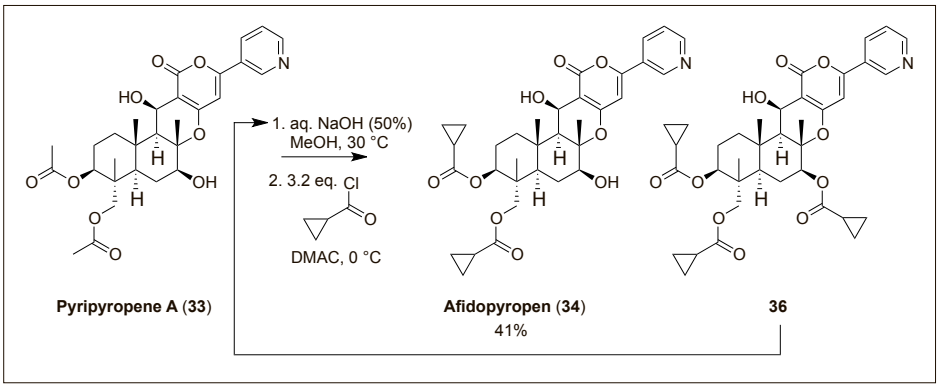


Fig. 5. Tuning of the physicochemical properties of cyanotropanes.

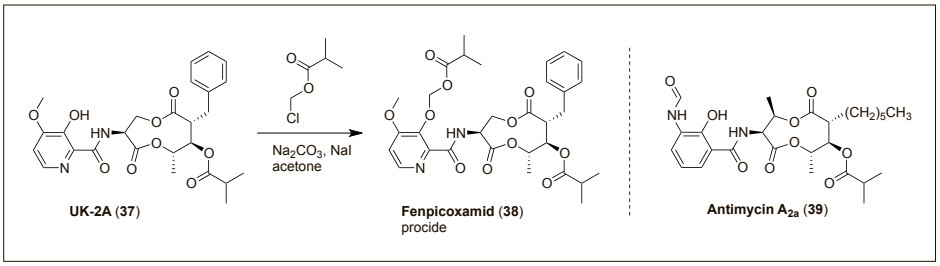
properties.[65] A collaboration between the Ōmura group and Meiji Seika Pharma, also confirmed pyripyropene A to be a potent insecticide,[66] which was the starting point for the discovery of afidopyropen. The molecule went under development through collaboration between Japan's Meiji Seika Pharma and BASF and the regulatory dossier was submitted in 2016.[67] The pyropyropenes are a rare example of a natural product family for which at least two unrelated target receptors are known. Ōmura reported that pyripyropene A is active on acylcoenzyme A cholesterol acyl transferase, (ACAT), a research target for the treatment or prevention of atherosclerosis and hypercholesterolemia with an IC_{50} value of 58 nM.[64] In 2017, scientists at BASF reported that afidopyropen activates the vanilloid-type transient receptor potential (TRPV) channels expressed exclusively in insect chordotonal stretch receptor neurons (EC_{50} = 2nM in pea aphid), hence controlling the insect plant pests by disturbing their motor coordination and ability to feed.[44] Interestingly the structurally unrelated synthetic pymetrozine and pyrifluquinazon commercial insecticides control insects *via* the same mechanism.[44]

Fenpicoxamid (**38**, Scheme 5) is a novel picolinamide fungicide currently developed by Dow AgroSciences in collaboration with Meiji Seika Pharma for use primarily in cereals.[45,68] Fenpicoxamid is an acyloxymethyl ether of the natural antifungal compound UK-2A (**37**) originally isolated from fermentation broths of a *Streptomyces sp*., extracts of which demonstrated strong antifungal activity against a broad spectrum of fungi in *in vitro* assays. UK-2A and its derivatives inhibit the respiration of fungi at the mitochondrial complex III site through binding to the Qi ubiquinone site rather than to the Qo site targeted by the strobilurin.

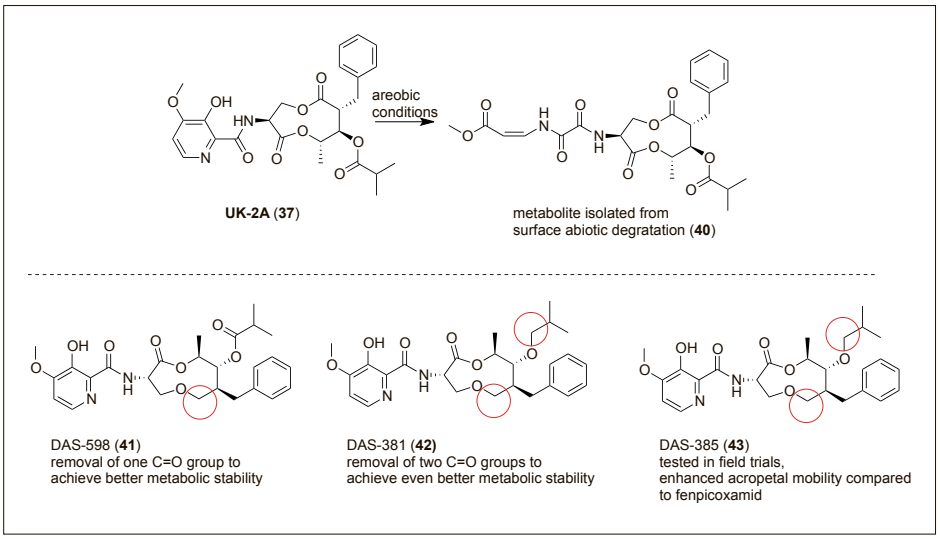
UK-2A is structurally related to the antimycin antibiotics[69] (**39**, Scheme 5) and differs mainly by the presence of a picolinamide moiety. Whereas both natural products exhibit their antifungal activity by specifically binding to the same Qi ubiquinone site, antimycin in contrast to UK-2A, is toxic to mammals.[70] Although the picolinic moiety in UK-2A may be responsible for selectivity compared to the antimycins, it bears electron-donating substituents including an ionizable OH group (pKa 8.5) and is prone to oxidative degradation, which is problematic for application in crop protection. These liabilities are apparent in the drop in activity observed when translating from *in vitro* studies of fungitoxicity to greenhouse tests in which the natural product is weaker than might be expected.[45] The abiotic degradation of UK-2A when exposed as thin films on surfaces (*e.g.* on leaves) to air and light (*e.g.* formation of **40**, Scheme 6)[71] is significant, and exposure to UV light for 24 h results in complete oxidative photodegradation. Scientists at Dow sought to stabilize the picolinamide and the protection of the OH group drove the synthetic effort that led to the identification of fenpicoxamid **38** as a development candidate. Clearly the picolinamide hydroxyl group plays a role in predisposing UK-2A to degradation phenomena, since its derivatization to the isobutyryloxymethyl ether addressed the issue very effectively. Fenpicoxamid was designed to act as a procide and short term metabolism studies show that fenpicoxamid **38** is almost completely converted to UK-2A **37** within a few hours of incubation in fungal isolate cultures and wheat cell suspensions. On the other hand the metabolically more stable OH-methylated ether of UK-2A is 1000 times less active than fenpicoxamid. Efforts at Dow have not ended with the development of fenpicoxamid. Subsequent structure–activity relationship investigations on the bislactone of the natural product led to the discovery of several macrocyclic compounds possessing chemical and biological properties unique to this class of chemistry (Scheme 6).[72]



Scheme 4. Afidopyropen, an insecticidal semi-synthetic natural product currently in late development.



Scheme 5. Fenpicoxamid, a fungicidal semi-synthetic natural product currently in late development.

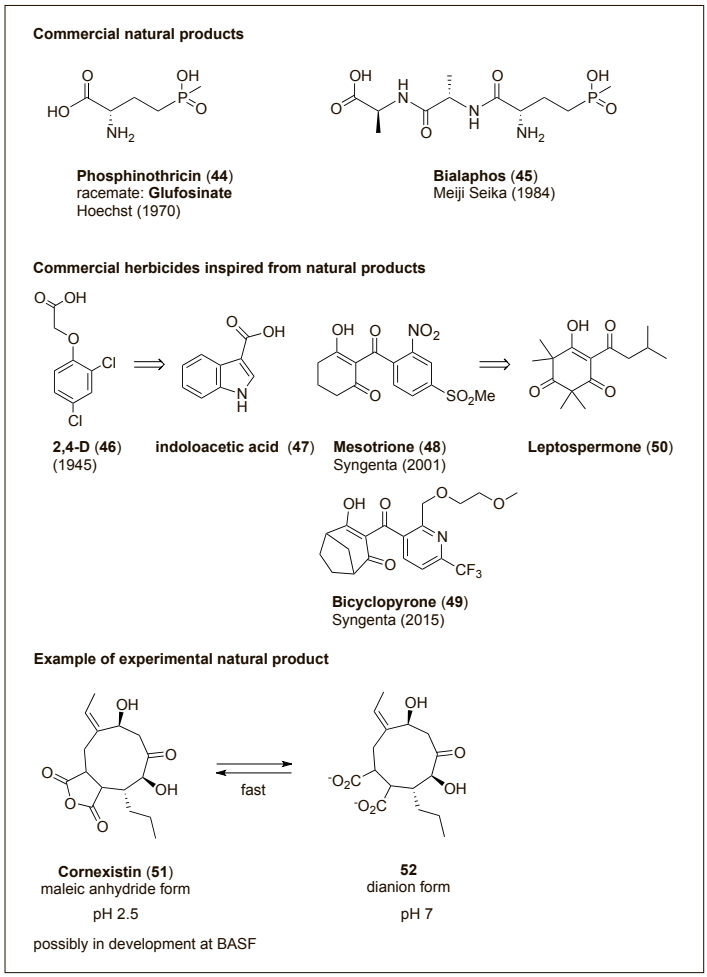


Scheme 6. Sensitivity of the picolinamide towards aerobic conditions and new synthetic UK-2A derivatives from Dow.

Natural Products as Herbicides

There are numerous reports of secondary compounds derived from plants and microorganisms that are phytotoxic[73,74] and the use of natural products as herbicides or as lead structures for herbicide discovery programs is an approach that has also been exploited. However, relatively few natural products or semi-synthetic analogues have made it to the market compared to insecticides and fungicides.[75] Phytotoxic natural products are in general structurally more complex than synthetic herbicides and many of them need to be applied at relatively high rates to be effective. For instance, the recommended rate for glufosinate (**45**, *vide infra*) is in the range of 500 g/ha, compared to 100 g/ha or less for many modern herbicides. This relatively low activity of the herbicidal natural products combined with their structural complexity is the reason for their smaller market presence. The topic of natural-product herbicides cannot be covered without featuring the success story of phosphinothricin (glufosinate) (**44**, Scheme 7). Phosphinothricin and the tripeptide analogue bialaphos (**45**) are broad spectrum herbicides that can be used to control a wide range of weeds after they have emerged from soil (post-emergence control).[76] Bialaphos is a proherbicide that is bioactivated into phosphinothricin by plants before exerting its herbicidal effect. It is obtained from fermentation cultures of a *Streptomyces*. Glufosinate, the racemic form of phosphinothricin, is synthetically produced and is the commercially relevant version of the chemical.[73] This class of natural products are unique inhibitors possessing a methylphosphinic acid unit. This unusual P-methylated amino acid is a structural analogue of glutamate and acts as an inhibitor of glutamine synthetase.[77] Glutamine synthetase is required for the production of glutamine and for ammonia detoxification. Inhibition of this enzyme results in a reduction of the cellular amount of glutamine and an increase in ammonia to toxic levels. This interrupts photosynthesis in the weed and leads to death within a few days.

For the herbicides in which natural products played a crucial role in the discovery and optimization process, two classes stand out; the auxin herbicides (*e.g.* 2,4-dichlorophenoxyacetic acid (2,4-D) (**46**)) and the triketones (*e.g.* **48** and **49**). 2,4-D, commercially available since 1945, provides effective post-emergence control of broadleaf weeds in a large variety of crops and was the first herbicide found to be capable of selectively killing weeds but not crops. It acts by mimicking the action of the auxin plant growth hormone, indoloacetic acid (**47**), which results in uncontrolled growth and eventually death in susceptible plants. The auxin herbicides have their origin in the study of the plant growth-regulating activity of **47**. As this compound was too unstable to work with, synthetic mimics were prepared and at some point in time, their herbicidal potential was realized. 2,4-D was one of the two first auxin herbicides to be developed.[78] The triketones[79,80] are a more recent class of herbicides with both pre-emergence and post-emergence weed-control which exert their herbicidal activity by inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD). Inhibition of this enzyme by chelation of the iron in the active site by the 1,3-dicarbonyl motif disrupts the biosynthesis of carotenoids and causes bleaching (loss of chlorophyll) of the foliage followed by necrosis and death of the treated weeds.[81,82] Among the several products which have been commercialized in this class, Syngenta's contribution was mesotrione (**48**), launched in 2001 and bicyclopyrone (**49**), belonging to the new class of nicotinoyl cyclohexane diones, launched in 2015.[83] Early in the course of the research which eventually would lead to mesotrione, scientists at Stauffer, a fore-runner company of Syngenta, realized that the bottlebrush plant (*Callistemon ci-*



Scheme 7. Herbicidal natural products having achieved commercial status or in development.

trinus) was repressing the growth of other plants in its surroundings, suggesting that it might produce a strong phytotoxic agent. Bioassay-guided isolation work led to the discovery of leptospermone (**50**), a previously characterized acyl syncarpic acid plant metabolite with no known biological activity. The natural product caused bleaching symptoms indicative of what would later become to be known as the HPPD mode of action. The syncarpic acid unit of leptospermone would then be incorporated in the triketones optimization program, combined with the benzoyl moiety and further evolved to obtain compounds with much higher overall herbicidal potencies and weed-controlling spectra.[80]

Cornexistin (**51**) is a maleidride isolated by Sankyo in the late 1980s from the fungus *Paecilomyces variotii*.[84] It is a potent wide-spectrum herbicide against weeds but with low activity against maize and thus shows promise as a commercial herbicide. The natural product is possibly in development at BASF.[85,86] The mode of action is the inhibition of transketolase and it is the only known inhibitor of this target with good herbicidal activity.[86] This feature may be explained by the molecular adaptability of the natural product. Indeed, cornexistin equilibrates between the maleic anhydride form and the dianion of the corresponding ring-opened diacid, as shown in Scheme 7. NMR experiments show that the anhydride form is preferred in organic solvents and in water at low pHs, while the ring-opened form is preferred in water at neutral pHs. Hence, these forms could be in rapid equilibrium at physiological pH allowing cornexistin to move easily in plants, being able to penetrate both aqueous and lipophilic phases.[87] Colton and Kazlauskas have studied a similar phenomenon in the use of dicarboxylic acids as proton transfer agents across membranes.[88] The ability of the acid to move through the membrane was found to depend upon a number of factors but at ambient temperature, the rate of anhydride formation was generally rate-limiting, varying with the structure of the diacid. Access to this natural product through synthesis is not practicable and fermentation remains the method of choice. To support bioprocess engineering, several studies have been reported on the elucidation of the biosynthesis of cornexistin and the characterization of the corresponding gene cluster.[86,89]

Natural Products as Biopesticides

Certain natural compounds used for pest management are recognized by state organizations such as the U.S. Environmental Protection Agency (EPA) as biopesticides.[90] They include insect repellants and attractants, biochemical insecticides, fungicides, herbicides, nematicides. Although there are many definitions throughout the world what a biopesticide is, their desirable properties are:

- Naturally occurring chemicals or their derivatives
- Reduced toxicity to non-target organisms
- Reduced persistence in the environment
- Low mammalian toxicity
- Safe for farmworkers and nearby residents
- Green technology

Amongst the various biopesticides in use nowadays, botanical pesticides are used for insect control in agriculture, mainly on fruits, vegetables and green house flowers. They consist of secondary metabolites from plants performing useful functions against insect herbivores as repellents, feeding inhibitors or toxins and they often are applied as semi-purified extracts rather than in their pure form.[91] Up to now there are only a handful of effective commercial botanical products: the pyrethrins, which represent economically the most important group, alkaloids such as nicotine or the sabadilla alkaloids, the isoflavone rotenone (**53**), the limonoid azadirachtin (**54**) and essential oils (Fig. 6).

Azadirachtin provides a good example of the advantages brought by botanicals but also the complexities they carry. The

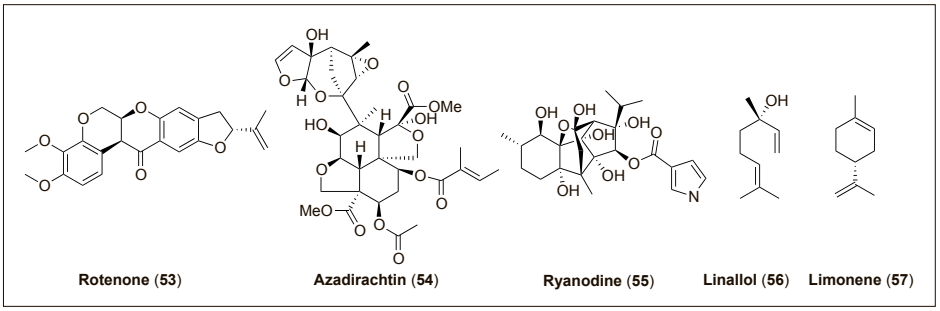


Fig. 6. Secondary metabolites responsible for activity in some botanical insecticides.

natural product, which is a complex tetranortriterpenoid, is the predominant insecticidal active ingredient derived from the neem tree and is considered to be environmentally friendly because it is relatively safe to mammals (LD_{50} rats > 3540 mg/Kg), fish and pollinators and has a short persistence on crops. It is derived from the seed kernels of the neem tree, which has been used for centuries in India as a potent antimicrobial and insecticide, either directly by cold-pressing or by hydroalcoholic extraction. Azadirachtin affects a broad spectrum of insect species including aphids, mealybugs, caterpillars, beetle and weevils, whiteflies, mites and thrips. Azadirachtin's potent biological action appears to come from a combination of behavioral and physiological effects leading to feeding deterrence.[92] Lepidopterians are very sensitive to azadirachtin which shows effective antifeedancies from < 1–50 ppm depending upon the species. The antifeedant effects observed in these species are correlated with the sensory response of chemoreceptors (taste receptors) in the insects,[93–95] resulting in starvation and death.[92,93] *Coleoptera*, *Hemiptera* and *Homoptera* are less sensitive to the antifeedant azadirachtin. For these other species, crop protection results from a combination of physiological effects after ingestion of azadirachtin.[96,97] An ED_{50} of around 1 mg/g body weight is consistently seen through these insect species.[97] The mode of action of azadirachtin is a complex research topic and recent reports have indicated that the action of azadirachtin at the cellular level is to block microtubule formation[98] and a possible binding protein has been identified in Drosophila Kc167 cells.[99]

The use of biopesticides has grown with increasing restrictions on persistent pesticides and the growth of the organic food and farming movement. Biopesticides, introduced in integrated pest management systems, are ideal for pre- or post-harvest treatments of fruits and vegetables as they do not leave residues on food. However, from a commercial point of view, many of these chemicals are not really used on large scale because of the lack of technology to produce them in sufficient quantities and the time consuming and laborious procedures to produce them. Currently, the demand for pyrethrins, for instance, is greater than world production. David Morgan reported in 2009[92] an average yield per hectare of 55 kg of dried flowers containing 1–2% of active ingredient. Thus, 0.55 Kg to 1.1 Kg of pyrethrins can be obtained per hectare for each harvest (every two weeks in the season). Sales forecast for Pyrethrins in 2017 is US$68 million.[100] Azadirachtin products from neem, by comparison, represent lower figures (US$29 million in 2017). For this perennial plant, harvesting is once per year. The yield is about 2000 kg seed kernels per hectare with a content in active ingredients of 0.45%, representing 9.0 Kg of product per year. Moreover, azadirachtin is hampered by the high cost of raw material due to the complex and expensive extraction processing of the seeds compared with pyrethrum, meaning that the cost for treating one hectare (20–60 g of the active ingredient are required) is relatively high, which can raise some profitability issues.[101] The main bottleneck in the conventional process of extraction of azadirachtin is the variability imposed by the heterozygosity in seeds resulting in fluctuating secondary metabolite content and uncontrollable seasonal and geography constraints. Despite being nontoxic to mammals, fish and pollinators, the influence of azadirachtin on beneficial insects is highly variable and requires special attention.

Lately, companies are relying on the commercial development of essential oils-based insecticides as a consequence of some facilities in registration procedure, easy access to raw material and relatively low cost.[102] Essential oils are obtained by hydrodistillation of aromatic plants (leaves, flowers, fruits) and are rather complex mixtures containing terpenoids, alcohols, ketone, aldehydes and phenolic compounds (given examples are **56** and **57**, Fig. 6). Essential oils are used as repellents or contact spray. They are generally lipophilic and hence can preferentially interact with membrane-bound receptors and enzymes in the insects and show effect through fumigation of insecticidal contact action. Because of variabilities in large scale production, agricultural practices and environmental conditions, their effects are relatively difficult to standardize but the interest in these solutions and the experiments on this efficacy has been increasing since the 1990s.

In the area of biopesticides in general, smaller, specialty companies such as Trécé, Marrone Bio Innovations or Vestaron are leading the technology, but larger companies such as Dow, DuPont, Monsanto, Syngenta, Merck, BASF, and Bayer are developing or marketing biopesticides along with the conventional chemicals that are their mainstays. State agencies have helped to catalyze the introduction of biopesticides by offering some regulatory relief for their registration.

Botanical insecticides have not only benefited biocontrol strategies; they also have provided mode of action knowledge in the discovery of commercially very successful synthetic compounds. The ryanodine alkaloid (**55**), which is the active principle of the extract from *Ryania* stems, is a prime example of this. Ryanodine and related alkaloids affect muscles by binding to calcium channels in the sarcoplasmic reticulum. This activates the uncontrolled release of calcium stores necessary for muscle cell function, leading to Ca^{2+} depletion, feeding cessation, muscle paralysis, and ultimately insect death.[103] *Ryania* extracts have found limited use as insecticides and ryanodine itself is not selective towards the corresponding mammalian receptors which leads to moderate toxicity. Recently a new class of insecticides, the diamides, has been discovered and provides exceptional control through selective action on the ryanodine receptors in insects.[104] Products on the market are flubendiamide (**58**)[105] jointly developed by Nihon Nohyaku and Bayer, chlorantraniliprole (**59**) and cyantraniliprole (**60**)[106] developed by Dupont (Fig. 7). In their works on the elucidation of the mode of action of flubendiamide, scientists at Nihon Nohyaku assayed several active substances with a known mode of action by injection into the larvae of lepidopterians.[105] The larvae injected with ryanodine showed sustained body contraction similar to the larvae treated with flubendiamide, which provided key information eventually leading to the elucidation of the target receptor for this important class of agrochemicals.[107]

Peptides with Insecticidal Properties Produced by Plants

Certain peptide compounds are environmentally more stable and persistent than secondary metabolites and may be strong candidates for the next generation of botanical pesticides.[91] This comprises for instance the cyclotides which constitute the largest class of ribosomally synthe-

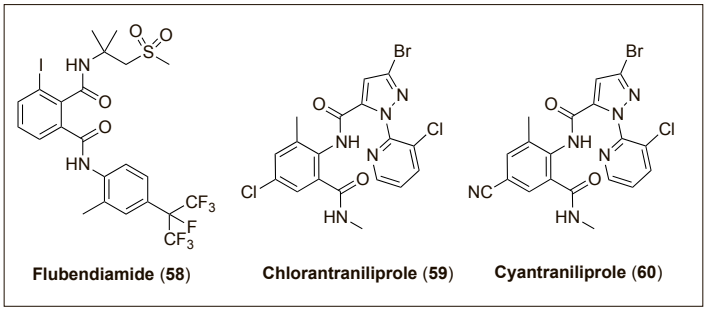


Fig. 7. The diamides insecticides binding to insects ryanodine receptors.

sized cyclic peptides produced by plants (Fig. 8). Cyclotides are typically constituted of 27–37 amino acid residues organized in a backbone stabilized by disulfide bonds which confers exceptional stability against enzymatic degradation, temperature variation and chemical stress.[108] Due to these properties, cyclotides have been evaluated for their biological functions, including antibacterial, nematicidal, and insecticidal activities.[109–111] The defensins represent another class of insecticidal proteinaceous compounds from plants. Defensins comprise a family of cysteine-rich, basic peptides with 45–54 amino acids in length forming an α-helix and a triple-stranded antiparallel β-sheet stabilized by four disulfide bonds.[112,113] Such biomolecules may find application in the field of transgenic crops rather than being applied as formulated biopesticides. All the peptides mentioned above exert their mechanism of action in the insect midgut mostly by interfering with the absorption of nutrients and affecting the integrity of insect's peritrophic membrane or the epithelial cells beneath.

Fig. 8. Cyclotides family members. Disulfide bonds are highlighted as yellow sticks.

Bacillus thuringiensis Toxins

Entomopathogenic bacteria and fungi have potential for insect control and have provided a wide variety of insecticidal proteins active against larvae of diverse insect orders.[114] By far, the most widely used and best-known of these proteins are the proteins from *Bacillus thuringiensis* (Bt), a Gram-positive, spore-forming bacterium which is the richest source of insecticidal genes.[115] Bt strains synthesize Crystal (Cry) (Fig. 9) and cytolytic (Cyt) toxins as parasporal crystalline inclusions during the pathogenic process at the time of sporulation. Once ingested by insects, these crystals are solubilized in the midgut. The toxins are then proteolytically activated by midgut proteases and bind to specific receptors located in the insect epithelial cell membrane, leading to pore formation followed by cell disruption and insect death.[116] Bt crystal and secreted soluble toxins are highly specific for their hosts and have gained worldwide importance as biocontrol agents. Several natural Bt strains have been incorporated in the production of sprayable Bt-based bioinsecticides wherein the active ingredient is a mixture of spores and protein crystals. Moreover, some cry toxin genes have been introduced into transgenic crops providing an effective way to control certain lepidopteran pests as well as some coleopteran.

Spider-venom Peptides

Disulfide-rich peptides are the dominant compounds in most spider venoms and they are the major contributors to the venom's insecticidal activity.[117] They have evolved to target a wide range of presynaptic ion channels or postsynaptic receptors either at peripheral neuromuscular junctions or at synapses in the insect central nervous system. These peptides can act individually or in combination, to rapidly immobilize the envenomated prey either by desensitizing its nervous system and causing flaccid paralysis or by over activating it and causing convulsive paralysis. The overall effect induced by these neurotoxins is complex and involves groups of peptides that act at different times and sites following envenomation. The natural prey of most spiders are invertebrates, mainly insects. Because most spiders are polyphagous, their venoms have evolved to contain an array of compounds that target a broad spectrum of insect prey. Moreover, although some large spiders consume small vertebrates, very few are toxic to humans.[118] Hence, the primary rationale for investigating spider venoms as a potential source of bioinsecticides is that their venoms are expected to contain a wide range of insecticidal peptides that mostly have little or no mammalian activity. The research on spider venoms has largely validated this hypothesis. Most of the insecticidal spider-venom peptides contain a unique arrangement of disulfide bonds that provides them with a strong level of protease resistance. As a result, these highly stable peptides are likely to have long residence times in the insect gut and in the hemolymph, and therefore even low rates of intestinal absorption will make them active through oral ingestion. Many of them have desirable properties, including high potency, rapid speed of kill, lack of vertebrate toxicity, and activity against a wide range of crop pests. Moreover, they should be stable in the field owing to their disulfide-rich molecular architecture, and their degradation is unlikely to produce toxic residues. Thus, spider-venom peptides may have potential for use as standalone bioinsecticides. Vestaron based in the United States is currently developing the first sprayable formulation containing a spider toxin (GS-omega/kappa-Hxtx-Hv1a) for use in controlling thrips

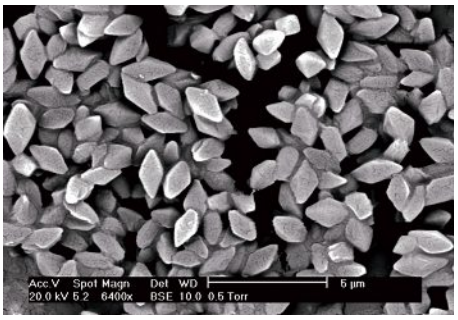


Fig. 9. Protein crystals (bipyramidal) mixed with spores from Bt strain.

in greenhouses.[119,120] The active ingredient claimed to have a dual mode of action has been registered by the United States Environmental Protection Agency in 2015 and commercial availability is expected in 2018 under the trademark Spear T. The company has three more products in pipeline: Spear P for potato beetle in combination with Bt, Spear C for lep control in combination with Bt and Spear O for ornamentals.

Conclusion and Outlook

Growing consumer demand, pest resistance pressure and an ever-changing regulatory environment necessitate the discovery of new crop protection agents for growers of today and tomorrow. Lead generation and optimization is the critical engine for any agrochemical chemical company wishing to maintain a robust pipeline of new high-value products. A wide variety of approaches exist for the generation of new leads, with many having demonstrated success. In that respect, natural products certainly had a broad influence over the past decades and will continue to do so in the 21st century. As noted, natural product-based discovery can be challenging in that finding new chemical classes with the activity and properties needed to be effective against agricultural pests is a rare event. Frontier technologies are increasingly gaining momentum in modern crop protection discovery and natural products accompany the movement.[121,122] However, the development of a scalable fermentation process

remains one of the greatest challenges for natural products in R&D and explains in part the long lead time between discovery and market launch.[123] Technological revolutions in genomic and synthetic biology certainly will benefit both to the discovery of new natural products[124] and to efficient bioprocess engineering, enabling complex molecules to be brought to market.[125–129] Finally, the brilliant lectures given by the speakers at the Swiss Chemical Society - Syngenta Symposium 2017 testify to what natural products can offer for our future.

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