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Natural Products in Crop Protection

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Abstract. Nature is a rich source of products with interesting and useful biological activity. In the field of crop protection, natural products and analogues have successfully been introduced to the market to control insect pests, plant diseases, and weeds. The search for new natural products with promising activity continues in academia and in industry to initiate and to foster novel, ecologically and economically sound crop-protection solutions.

Introduction

The protection of crop plants from competing plants, insects, and diseases has been an issue ever since agriculture developed. Whereas in the early days manual labour was used to solve the weed problem, the manual control of insect infestations was in most cases an impossible task. Plant diseases were even more difficult to understand and to take measures against. The first generation of crop-protection products consisted of inorganic arsenic, sulfur, copper, and mercury compounds. In the first half of the 19th century, extracts from *Pyrethrum* flowers made their debut as household insecticides [2], and shortly after, the application of nicotine-containing insecticidal tabacco extracts marked the first use of an organic pesticide in crop protection [3]. After 1930, a broad search for new organic crop-protection agents began in industry by screening synthetic chemicals and to a lesser extent natural products. It was the start of an unprecedented success story, in which industry learned to understand more and more the delicate and complex interplay in ecology and to use this knowledge for the development of safe and ecologically sound products for the control of weeds, insects, and microbial plant pathogens.

Although the share of natural products in today's crop-protection market is small, their impact as lead structures spawning the synthesis of economically successful analogues is considerable. It is estimated that today the total market share of natural products including their analogues is *ca.* 10%, with a tendency to increase as new products will be entering the market. However, natural products should not be seen as an alternative to synthetic chemicals, but as a complement, as a source of chemical structures from nature's evolutionary playground, the secondary metabolism [4]. The structures of natural products generally show little overlap with those of synthetic chemicals, while often being more complex than the latter. With regard to toxicity, natural products have to be examined with the same scrutiny as synthetic chemicals [5]. However, mechanisms for biodegradation by soil microorganisms and reintegration into the environment already exist for natural products, so no long-term accumulation effects are to be expected.

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Screening for Biologically Active Natural Products

In contrast to a pharma primary screen which for obvious reasons cannot test on the actual target, but has to rely on mechanism-based assays, a primary screening in crop protection can start in the 'clinic'. Miniaturized agronomically relevant test arrangements indicate activity based on all possible modes of action, known or not yet known. To find potent lead structures at a reasonable rate, the search for new crop-protection agents has to tap all sources of chemicals, the ingenuity of the chemists, and that of nature. Mechanism-based assays used in parallel help to rank the leads.

The main goal of a natural product screen is to identify novel, biologically active metabolites which serve either as lead structures for the synthesis of optimized marketable analogues or as commercial products *per se*. Also valuable is the discovery of new natural products which operate with novel modes of action. These findings can be used to set up novel mechanism-based bioassays for the detection of novel lead structures.

Whereas synthetic chemicals are being tested as single compounds, natural products start out as crude extracts from organisms. These extracts represent large libraries of chemically diverse structures of unknown concentration. Very often, the biologically active natural products are minor or even trace components. To be able to run a natural products screening efficiently, it is important that the screening tests are sensitive, have a high throughput capacity, use small amounts of test sample, allow a simple test sample preparation, and give fast results.

Identification of Novel Leads

Fast detection and identification of novel active extract components is the primary goal of the natural products chemist. It is therefore of utmost importance that known natural products are recognized and eliminated in the deconvolution process as early as possible. This can be achieved with an efficient dereplication system. State-of-the-art systems consist of HPLC with UV diode array and mass detection coupled with on-line data analysis and databases. HPLC-NMR is emerging as a valuable additional tool. If the active components seem to be novel, a bioassay-guided extract deconvolution is carried out using efficient chromatographic techniques. The structures of the isolated pure natural products are then determined with spectroscopic methods, mainly with NMR and mass spectrometry.

Sources of Biologically Active Natural Products

Is there a best source for new biologically active natural products, and for crop-protection indications in particular? This question is difficult to answer, even when using available statistical data. At *Novartis Crop Protection*, we tend to include in our screening as many different types of organisms as possible, unicellular and filamentous bacteria, fungi, and also plants. The procaryotic actinomycetes with their active and highly variable secondary metabolism have been and still are an excellent source, and so are the myxobacteria. Anaerobic organisms, yeasts and organisms which do not allow a supply of gram quantities of active natural product for extended biological evaluation, have so

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far been excluded. The same applies to organisms which are exceedingly difficult to grow.

It is the task of the microbiologists to contribute to the screening by providing microbiologically diverse and highly talented strains. To comply with this requirement, a serious effort has to be made in the careful selection of the strain sources as well as in the development and application of strain isolation techniques, and of adequate cultivation methods. If microbiology has to feed a high-throughput screening, there is the latent danger, that number crunching will prevail over innovative strain isolation with the result, that only a fraction of the potential source will actually be tapped.

Development and Production

The relatively low market value of agricultural products sets a limit to the final price of a crop-protection agent. Treatment costs of 25–50 USD/ha are typical. If an application rate of 250 g ai/ha is assumed, this would amount to a price of 100–200 USD/kg active ingredient (= ai). Needless to say that the actual production costs will have to be lower [6]. An important criterion for commercialization is the ratio of biological activity to production costs. The task of natural product research is therefore twofold, to identify novel natural products which can be used as lead structures for an economical synthesis of highly active analogues, and to detect those natural products whose high intrinsic activity allows production *via* a more elaborate chemical or biological process.

Commercial Successes and Interesting Leads

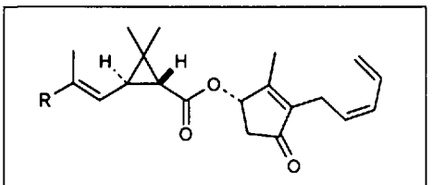
Insecticides

The worldwide efforts in the search for natural products and analogues for the crop-protection market have been remarkably successful, foremost in the field of insect control. It is interesting to note, that in this indication higher plants contributed significantly to this success as sources for highly active agents.

Pyrethroids

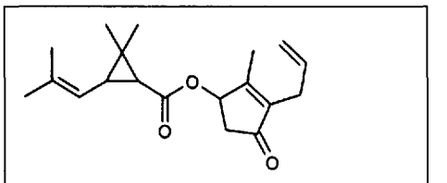
The pyrethroids are a prime example how a biologically active natural product served as a template for the creation of economically and ecologically sound hygiene and crop-protection insecticides by chemical synthesis. To adequately summarize this fascinating topic and to pay tribute to the enormous efforts put into synthesis and into studies of very complex structure-activity relationships would by far exceed the size of a general review. Three recent reviews, excellently written by firsthand authors, cover this field in detail [7–9]. In this summary, the practical results which emerged from the research programs in academia and in industry are highlighted. Powdered heads of the flowers of *Tanacetum cinerariifolium* (also known as *Chrysanthemum c.* or *Pyrethrum c.*) or an extract thereof have long been used and are still popular as household insecticides. Of the six insecticidal components of pyrethrum extract, **1** is mainly responsible for kill, whereas **2** exerts mainly knockdown activity. The insecticidal metabolites in pyrethrum are all unstable when exposed to light and air. Therefore, these natural products are not suited for agricultural application. The pioneering work by *Staudinger* and *Ruzicka*, carried out during 1910–16 [10], led to the correct structural assignment of the acid part of **1**, *trans*-(1*R*)-chrysanthemic acid and of **2**, *trans*-(1*R*)-pyrethric acid. The same authors also synthesized a number of analogues of the natural esters by varying both the acid and alcohol parts. They noticed, that both the acid and the alcohol part can be replaced by structural mimics with retention of some insecticidal activity [10], although none of the active analogues came close to the activity of the natural products. Nevertheless, this early work was a valuable source for future research which aimed at highly active, photostable pyrethroids. The topic was picked up at the US Department of Agriculture and at the Rothamstead Experimental Station in the UK. Then *Sumitomo* and *Roussel-Uclaf* joined in, while other companies followed later.

The first effort concentrated on replacing (*S*)-pyrethrolone, the photolabile alcohol part of **1** and **2**. Allethrin (**3**), which is structurally closely related to pyrethrin I (**1**), was the first synthetic pyrethroid to reach the market [11][12]. Its most active isomer, (*S*)-bioallethrin (**4**), was later commercialized by *Roussel-Uclaf*. In *Sumitomo*'s tetramethrin (**5**), the natural pyrethrolone is replaced by a much simpler isosteric substructure [13]. A major achievement was the synthesis of resmethrin (**6**) and bioresmethrin (**7**) which had a distinctly higher insecticidal activity than the natural pyrethrins [14]. Despite their high activity, bioresmethrin (**7**) and also phenothrin (**8**) are by an order of magnitude less toxic towards mammals than the natural product [15]. The introduction of the 3-phenoxybenzyl ester in **8**

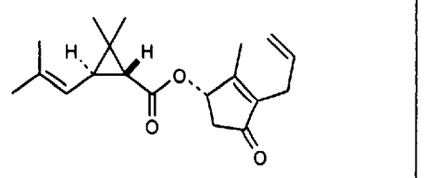


1 pyrethrin I R = CH_3

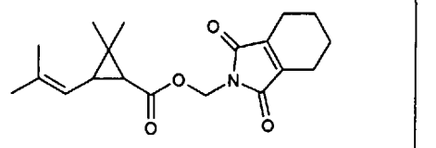
2 pyrethrin II R = $COOCH_3$



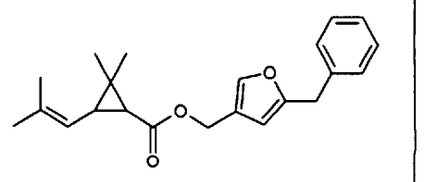
3 allethrin *USDA*



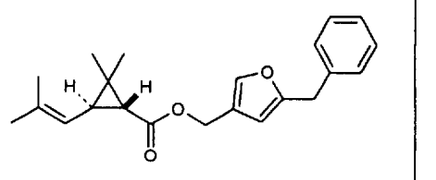
4 bioallethrin *USDA*



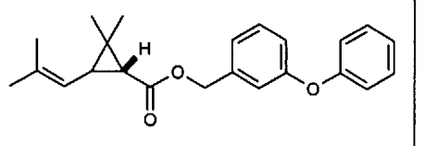
5 tetramethrin *Sumitomo*



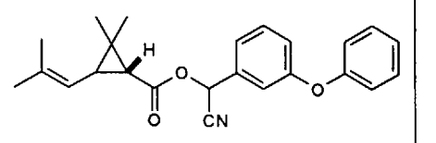
6 resmethrin *Rothamstead*



7 bioresmethrin *Rothamstead*



8 phenothrin *Sumitomo*



9 cyphenothrin *Sumitomo*

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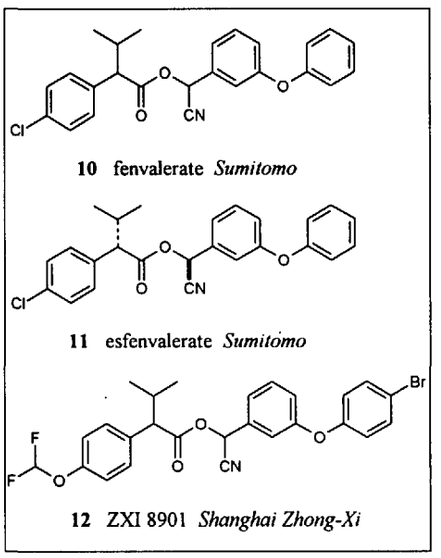
and of an additional α-cyano group in cyphenothrin (**9**) by chemists at *Sumitomo* [16][17] marked a very important step towards future development of photostable pyrethroids. Until that point, however, these synthetic pyrethroids **3–9** were still too photolabile to be used in crop protection, but they found use as hygiene and household insecticides.

Now that excellent replacements for the labile pyrethrolone were at hand, the focus in the search for photostable pyrethroids shifted towards improving the acid part. The *Sumitomo* research group made another breakthrough, when they found that chrysanthemic acid can be replaced by α-substituted phenylacetic acids. Following up on this finding, the *Sumitomo* group synthesized fenvalerate (**10**), the first truly photostable pyrethroid which appeared on the market [18]. The most active enantiomerically pure isomer is also marketed under the common name esfenvalerate (**11**) [19]. Recently, researchers from *Shanghai Zhong-Xi Pharmaceuticals* presented a new fenvalerate analogue, ZXI 8901 (**12**), a broad-spectrum insecticide/acaricide with much improved mammalian, fish, and bee toxicology [20].

Already in 1958, a Czech research group had found that replacement of the 3-(dimethylvinyl) side chain in the chrysanthemic-acid part of *trans*-allethrin by 3-(dichlorovinyl) did not cause loss of activity [21]. More than ten years later, this replacement was studied in more detail by *Elliot*'s Rothamstead group. This led to another breakthrough in the discovery of photostable pyrethroids [22], to permethrin (**13**), cypermethrin (**14**), and to deltamethrin (**15**) [23], one of the most active insecticides, which is applied in crop protection at rates of only 2.5–12.5 g/ha [24]. It is interesting to note, that the *cis*-(1*R*,'α'*S*)-isomers of the products **14–17** exert the highest activity of all possible isomers. Of this structural class, only **15** is being produced as a single enantiomer. Cyfluthrin (**16**) [25] and λ-cyhalothrin (**17**) [26] are two examples of developments based on the structure of cypermethrin (**14**). All these products are highly active broad-spectrum insecticides and acaricides which are used in many crops, with cotton being the largest market. Tefluthrin (**18**) is the first pyrethroid which was especially developed for the use in soil [27][28].

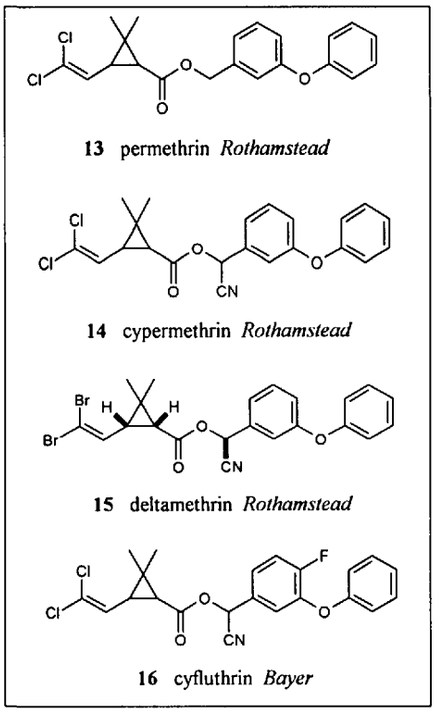
Two commercial pyrethroids which can be structurally placed in the vicinity of fenvalerate are cycloprothrin (**19**), with an extremly low toxicity to mammals and fish [29][30], and τ-fluvalinate (**20**), an excellent insecticide and acaricide, which fits well into integrated pest management programs. τ-Fluvalinate (**20**) is virtually nontoxic to honeybees, so that it is also used to control the bee parasite mite, *Varroa jacobsoni* [31][32].



10 fenvalerate *Sumitomo*

11 esfenvalerate *Sumitomo*

12 ZXI 8901 *Shanghai Zhong-Xi*

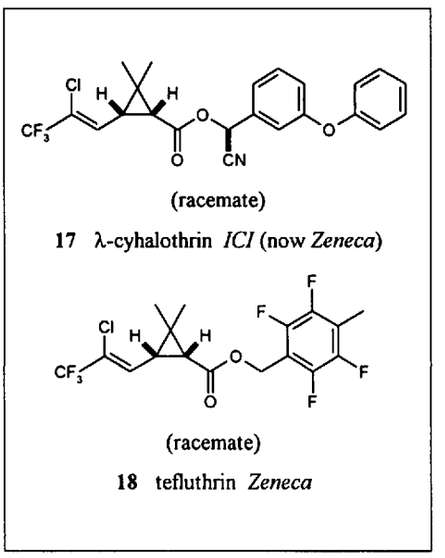


13 permethrin *Rothamstead*

14 cypermethrin *Rothamstead*

15 deltamethrin *Rothamstead*

16 cyfluthrin *Bayer*

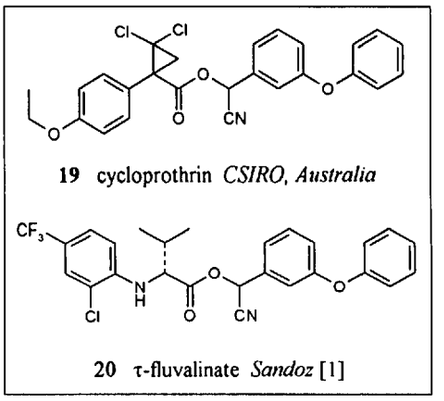


(racemate)

17 λ-cyhalothrin *ICI* (now *Zeneca*)

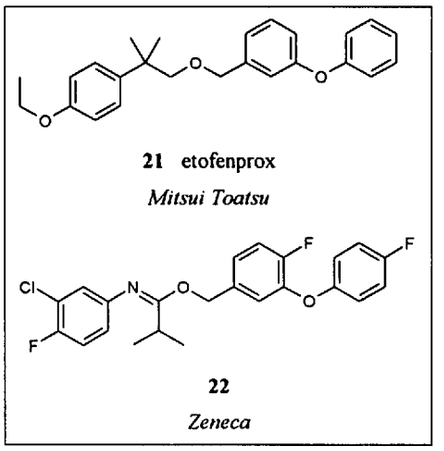
(racemate)

18 tefluthrin *Zeneca*



19 cycloprothrin *CSIRO, Australia*

20 τ-fluvalinate *Sandoz* [1]



21 etofenprox

Mitsui Toatsu

22

Zeneca

A major discovery in the field of pyrethroids was made by scientists of *Mitsui Toatsu*, when they found the non-ester pyrethroids [33]. Etofenprox (**21**), which has excellent safety features for mammals and fish [34], was the first representative of this class to be commercialized in 1987. The structure of **21** has little resemblance to that of the pyrethrins **1** and **2**, and yet it is the result of a consequent activity-guided abstraction of the structure of the natural products. The same applies to the imidate **22**, a member of a new class of pyrethroids recently described by *Zeneca* researchers [35].

The pyrethroids in general and the photostable representatives in particular were very well received by the market. In 1996, the total market volume of pyrethroids was 1.61 billion USD, with fenvalerate (**10**), esfenvalerate (**11**), cypermethrin (**14**), deltamethrin (**15**), cyfluthrin (**16**), and λ-cyhalothrin (**17**) being the best-sellers [28].

The mode of action of the pyrethroids has been intensively studied. Interference with some of the sodium-ion channels in nerve membranes leads to prolonged channel opening. This causes a blockage of the

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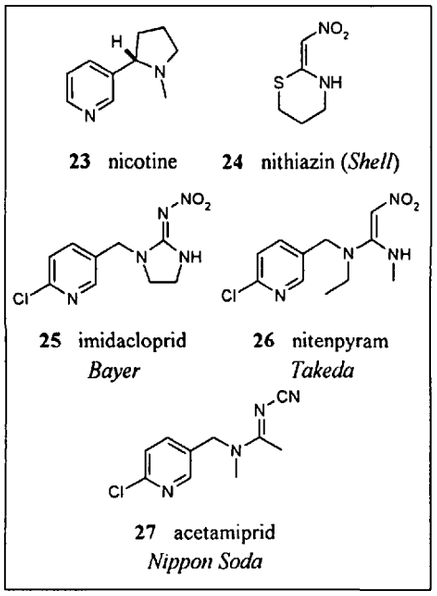
nerve signal which eventually results in the death of insects and mites [36–38].

Nicotine and Neonicotinoids

The alkaloid nicotine (**23**) has long been used in crop protection as a natural insecticide in the form of aqueous tabacco extracts [3]. Nicotine (**23**) acts as an acetylcholine receptor agonist and is highly toxic, also to mammals. Industry has struggled long to make use of this potent template and to create structurally related nicotinoids which have the same mode of action, but which are specifically active against insects. This task turned out to be not an easy one [39]. It was only after *Shell* researchers had published [40] the high insecticidal potential of nithiazin (**24**), that researchers of *Nihon Bayer*, building on this information, were able to create insecticidal analogues of **24** which can also be regarded as analogues of nicotine (**23**) [41]. Imidacloprid (**25**), the first commercial neonicotinoid [42], emerged from this program in 1984 [43–45]. This new systemic insecticide was developed by *Bayer* and put on the market in 1991 for the treatment against sucking insect pests. Aiming at the same target, *Takeda* followed in 1995 with the neonicotinoid nitenpyram (**26**) [46]. Acetamiprid (**27**) [47], which was developed by *Nippon Soda* against sucking insects, is also active against certain lepidoptera, like *Plutella xylostella*. Compounds **24–27** all act by binding to nicotinic acetylcholine receptors [48][49]. One can expect that the neonicotinoids will establish themselves as an important new class of safe insecticides, and it is very likely that more products of this class will appear on the market. Compounds **28**, **29** [50], and **30** [51] are promising lead structures, the latter of which shows an interesting biological spectrum of activity which includes lepidopteran pests.



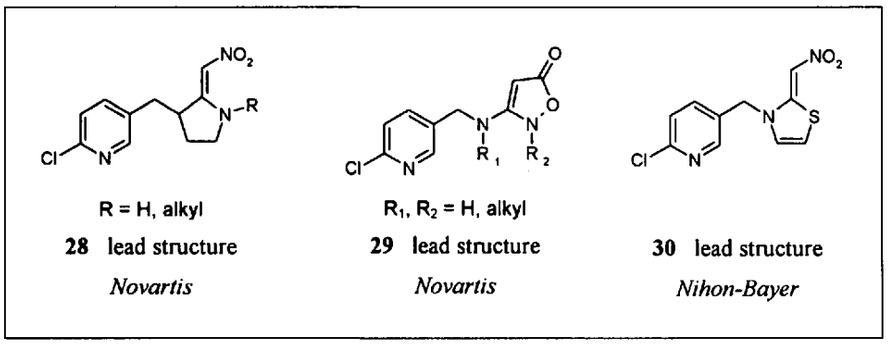
23 nicotine **24** nithiazin (*Shell*)

25 imidacloprid *Bayer* **26** nitenpyram *Takeda*

27 acetamiprid *Nippon Soda*

Juvenile-Hormone Mimics

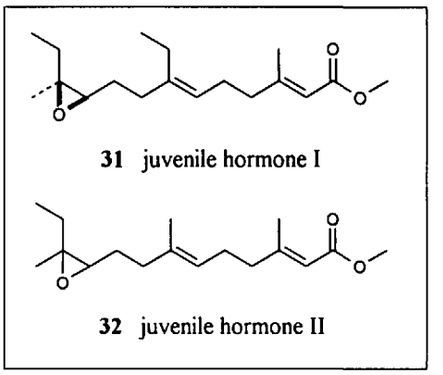
Due to observed effects on the development of insects, the existence of juvenile hormones was postulated by biologists [52] some time before they were isolated and their structures elucidated [53–55]. The juvenile hormones form a family of closely related compounds of which **31–33** are the main representatives. Whereas lepidoptera synthesize all three hormones **31–33**, other insects seem to rely just on **33** [56]. Juvenile hormones play a crucial role in the regulation of the molting and metamorphosis processes. Their presence or absence in the insect hemolymph during the molt determines, if a larger juvenile state is formed or if conversion to the fertile adult state is initiated. Fertile adults are produced only if the concentration of juvenile hormone drops to almost zero before the last molt [57]. Application of juvenile-hormone-active compounds to an insect population essentially prevents the formation of viable adults. When the structures of the juvenile hormones became known around 1970, *Zoecon*'s [1] research group pioneered the industrial search for insecticides with juvenile-hormone activity. Much of this work is described in an excellent review by *Henrick* [58]. *Zoecon* [1] developed hydroprene (**34**) for indoor cockroach control and methoprene (**35**) for the control of mosquitoes in still waters, horn flies, fleas, and pharaoh ants [59]. Due to their instability under field conditions, these two products are not suitable for crop protection. In the research laboratories of *Ciba-Geigy* [1] and of *Maag* [1], independent efforts were made to overcome the inherent instability of the juvenile hormones and their close analogues. Further abstraction of the juvenile-hormone structure through introduction of a 4-phenoxyphenoxy group as in **36** and **37** greatly contributed to the solution of the problem. Both



R = H, alkyl
28 lead structure
Novartis

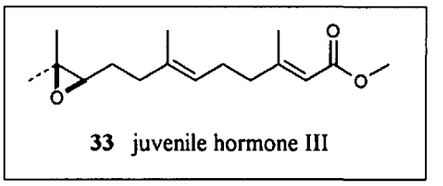
R_1, R_2 = H, alkyl
29 lead structure
Novartis

30 lead structure
Nihon-Bayer

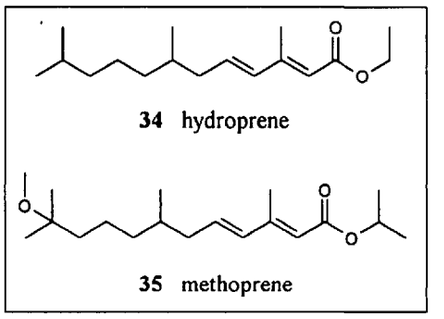


31 juvenile hormone I

32 juvenile hormone II

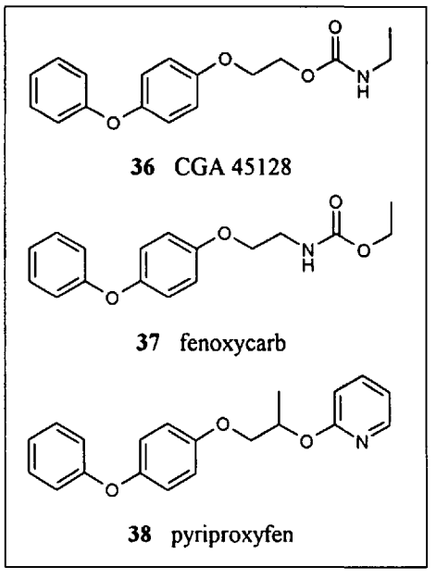


33 juvenile hormone III



34 hydroprene

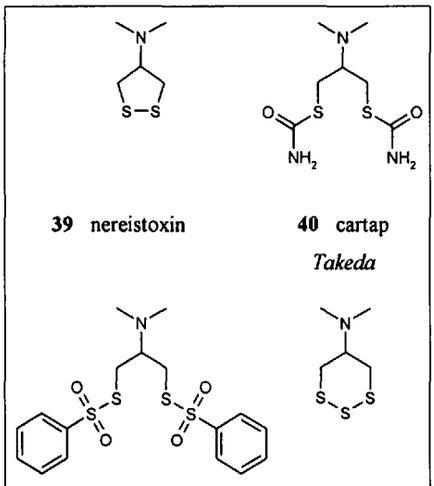
35 methoprene



36 CGA 45128

37 fenoxycarb

38 pyriproxyfen

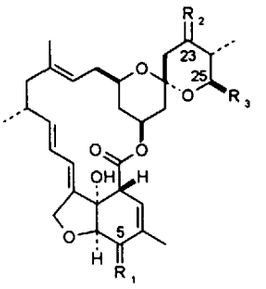


39 nereistoxin

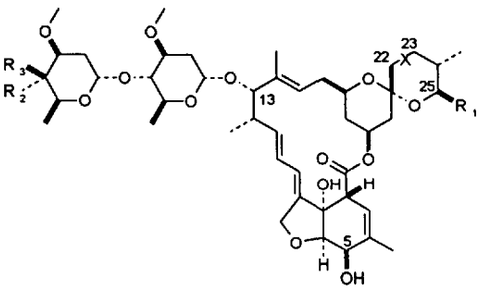
40 cartap
Takeda

41 bensultap
Takeda

42 thiocyclam
Sandoz [1]



	milbemycins	R_1	R_2	R_3	in development or marketed by
43	milbemectin	H, β-OH	H, H	CH_3:CH_2CH_3 = 7:3	*Sankyo*
44	LL-F 28249 = nemadectin	H, β-OH	H, α-OH	(Z)-$C(CH_3)$=CH-$CH(CH_3)_2$	*American Cyanamid*
	derivatives	R_1	R_2	R_3	**in development or marketed by**
45	milbemycin oxime	=NOH	H, H	CH_3:CH_2CH_3 = 7:3	*Sankyo, Novartis*
46	moxidectin	H, β-OH	$=NOCH_3$	(Z)-$C(CH_3)$=CH-$CH(CH_3)_2$	*American Cyanamid*



	avermectins	R_1	R_2	R_3	X	in development or marketed by
47	abamectin = avermectin B_{1a}	(R)-^{s}Bu	OH	H	CH=CH	*Merck, Novartis*
48	doramectin	Cyclohexyl	OH	H	CH=CH	*Pfizer*
	derivatives	R_1	R_2	R_3	X	**in development or marketed by**
49	ivermectin	(R)-^{s}Bu	OH	H	CH_2-CH_2	*Merck*
50	emamectin	(R)-^{s}Bu	H	$NHCH_3$	CH=CH	*Novartis*

36 [60] and **37** [61] are excellent juvenoid insecticides. The latter was developed by *Maag* [1] for the control of lepidopteran pests in orchards and vineyards as well as for a variety of other applications including the control of fire ants [61]. Pyriproxyfen (**38**), another stable juvenoid, was subsequently developed by *Sumitomo* [62] for the control of public health and agricultural insect pests. Due to their specific mode of action, all the juvenoid insecticides show extremely low toxicity to mammals and vertebrates in general [63].

Nereistoxin Analogues

The observation that feeding on diseased marine worms *Lumbriconereis heteropoda* is lethal to flies led to the isolation and identification of a new insecticidal natural product, nereistoxin (**39**) [64–66]. The natural product and a large number of analogues were synthesized and checked for insecticidal activity [67][68]. It was found, that only those compounds were active which could revert to the natural product **39** after uptake by insects. Two such products were developed for the market by *Takeda* against coleopteran and lepidopteran pests, namely cartap (**40**) [69], a broad-spectrum insecticide with good activity against the rice stem borer [70], and bensultap (**41**) [68] for the control of the Colorado beetle and other insect pests [71]. *Sandoz* [1] developed the nereistoxin analogue thiocyclam (**42**) [72] for the control of a broad spectrum of coleoptera and lepidoptera pests in several crops [73]. The mammalian toxicity of the prodrugs is lower than that of the natural product. Nereistoxin (**39**) acts on nicotinic acetylcholine receptors, as partial agonist at low concentration and as channel blocker at higher concentration [74].

Milbemycins/Avermectins

No other family of natural products has had a comparable impact in the field of animal health as agents against worms, ticks, and flies like the milbemycins **43–46** and the closely related avermectins **47–50** [75–78]. The family of milbemycins was detected in 1972 by researchers of *Sankyo* in the culture broth of a strain of *Streptomyces hygroscopicus* [79]. It was the broad acaricidal and insecticidal activity of this group of compounds which was recognized by the discoverers. The structures of the milbemycins were also determined at *Sankyo* [80], with X-ray diffraction analysis and other spectroscopic methods. In 1984, the LL-F 28249 group of milbemycins **44** with an unsaturated side chain at C(25) was isolated at *American Cyanamid* from a culture of *Streptomyces cyanogriseus* [81]. In the same year, researchers from *Glaxo* described the same compounds as metabolites of *Streptomyces thermoarchaensis* [82].

In an *in vivo* screening for natural products with anthelmintic activity, reseachers at *Merck* [83] found the avermectins in 1976 in the culture filtrate of a strain of *Streptomyces avermitilis* which had been supplied by the Kitasato Institute in Japan. The structures of the avermectins were elucidated by the *Merck* researchers using spectroscopic methods and *Sankyo*'s milbemycin X-ray data [84]. The first total

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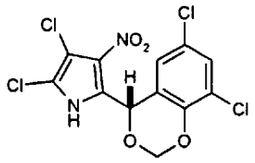
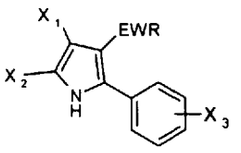
synthesis of avermectin B_{1a} (**47**) was reported in 1986 by *Hanessian* and coworkers [85–87]. The extensive literature on this topic has been reviewed in detail [75] [76].

Avermectins and milbemycins have the same mode of action, they potentiate glutamate- and GABA-gated chloride-channel opening [88][89]. A number of total syntheses of simpler analogues of the natural products were undertaken with the hope to get access to constructs containing the pharmacophore which would be biologically active, but more economical to prepare. None of these attempts led to a compound with high activity [77]. On the other hand, the search for derivatives of the natural products with improved biological properties such as **45**, **46**, **49**, and **50**, turned out to be very successful. The prime example is ivermectin (**49**), today a standard tool against animal parasites, with worldwide sales in 1995 of an estimated 665 million USD [77]. Researchers from *Pfizer* showed that directed biosynthesis is a very interesting way to get to new, highly active avermectins as, *e.g.*, doramectin (**48**) [90–92].

In crop protection, abamectin (**47**) and milbemectin (**43**) are being marketed as acaricides. Abamectin (**47**) also finds application against insects like leaf miners and certain lepidoptera. Its market volume in 1996 was 160 million USD [93]. Emamectin (**50**) [94], which was discovered by *Merck* chemists, will be introduced to the market by *Novartis* as an efficient insecticide against lepidoptera.



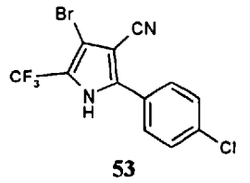
51 dioxapyrrolomycin



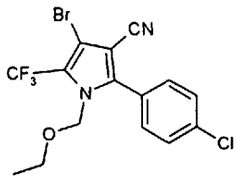
EWR : CN, NO_2, SO_2CF_3

X_1, X_2, X_3 : Cl, Br, CF_3

52

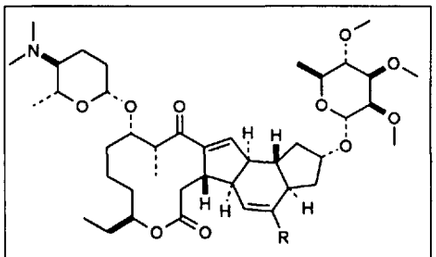


53



54 chlorfenapyr

American Cyanamid



	spinosyn	R
55	A	H
56	D	CH_3
57	spinosad	H:CH_3 = 85:15

Dioxapyrrolomycin Analogues

In 1987, researchers of *American Cyanamid* reported the isolation of dioxapyrrolomycin (**51**) from a strain of *Streptomyces fumanus* and described its insecticidal activity [95][96]. Independently and at about the same time, two other groups at *Meiji Seika* [97] and at *SS Pharmaceutical* [98] discovered the same *Streptomyces* metabolite due to its antimicrobial activity. Despite the relatively high toxicity of **51**, the *Cyanamid* researchers undertook the difficult task of creating less toxic analogues with improved insecticidal activity. By simplifying the structure of the lead compound, they found that members of the 2-aryl-pyrrole group **52** had excellent activity, with compound **53** having the highest potential [96][99]. However, **53** and others of this group showed intolerable phytotoxicity [100]. This problem was overcome by converting **53** into the prodrug **54** [101] which is metabolized by insects back to the active compound **53**. Chlorfenapyr (**54**) is a potent insecticide and less toxic than **51**. It has been developed by *American Cyanamid* for a variety of crops [100]. Dioxapyrrolomycin (**51**) and **53** are both uncouplers of the oxidative phosphorylation in mitochondria, whereas the prodrug **54** does not show any such activity [102], as long as it is not converted back to **53**.

Spinosyns

The spinosyns, a new class of highly active natural insecticides, were discovered in 1989 by researchers at *Eli Lilly* [103]. From a culture of the actinomycete *Saccharopolyspora spinosa*, they isolated spinosyn A (**55**) and D (**56**) as well as 21 minor analogues [104][105]. The structure elucidation of all these components was carried out by the same research group, mainly with NMR and X-ray diffraction analysis [104]. The mode of action of the spinosyns is reported to be novel [106], with no cross-resistance to known insecticides. Spinosyns cause excitation of motor neurons. A persistent activation of nicotinic acetylcholine receptors with a prolonged acetylcholine response by a yet unknown mechanism is observed. The total synthesis of **55** has been accomplished by *Evans* and *Black* [107]. Spinosad (**57**), a mixture of spinosyn A (**55**) (85%) and D (**56**) (15%), is being produced *via* fermentation and was introduced to the market by *DowElanco* in 1997 for the control of lepidoptera pests in cotton [106].

Bacillus thuringiensis

Bacillus thuringiensis has been known as an insect pathogen for almost a century [108][109]. The major insecticidal principle is the protein δ-endotoxin. During sporulation, *Bacillus thuringiensis* forms crystalline parasporal inclusion bodies which contain δ-endotoxin, either free or as part of a larger protein. After uptake by feeding, the parasporal bodies dissolve in the insect gut and δ-endotoxin is liberated. It then docks onto epithelial cells and causes them to swell and burst which leads to the death of the insect. Today, several different strain types are known with activity either against lepidoptera and diptera, against diptera alone, or against coleoptera. The size of the active δ-endotoxin is in the range of 60–70 kDa, depending on the bacterial strain and its spectrum of activity [110][111]. Due to its highly insect-specific mode of action, δ-endotoxin is not toxic to other living organisms [109]. Its first use as an insecticide was reported in 1938 [112], and commercialization started in 1957 [113]. Today insecticidal products based on BT δ-endotoxin are being produced and marketed by *Abbott*, *Caffaro*, *Ecogen*, *Mycogen*, and *Thermo Trilogy*. In 1996, the market volume of *Bacillus thuringiensis* products worldwide was 160 million USD [114]. Recently, the gene for *Bacillus thuringiensis* δ-endotoxin has been used to create transgenic crop plants which express δ-endotoxin and thus become insect-resistant. Such insect-resistant maize was introduced to the market by

Novartis [115], and *Monsanto* is commercializing insect-resistant transgenic cotton [116].

Azadirachtin/Neem

Seed kernels from the neem tree, *Azadirachta indica* (Meliaceae), contain a cocktail of insecticidal limonoids, of which azadirachtin (**58**) is the most active [117–119]. The elucidation of its structure proved to be difficult and was finally achieved by *Kraus* and coworkers in 1985 [120]. The total synthesis, an even more demanding task, is being tackled by *Ley* and coworkers [121]. Azadirachtin (**58**) has a complex mode of action. It is a strong feeding deterrent, but causes also metamorphosis disorders by interference with ecdysteroid synthesis and action [122] [123]. Furthermore, **58** seems to be specifically toxic to insect cells [124]. Insecticides prepared from neem kernels have long been used in India [125]. In the USA, two neem insecticides were developed, *Azatin*® by *Agri-Dyne* [126] and *Margosan O*® by *W.R. Grace & Co.* [127]. Both products are extracts enriched in azadirachtin (**58**) and contain several other limonoids [119] which add to the activity and reduce the risk that resistance develops.

Rotenone and Ryania

Preparations from several plant species of the genus *Derris*, *Lonchocarpus* (Leguminosae), and of a number of other closely related genera have long been used in Asia as fish poisons and insecticides [128]. The active principle was isolated around 1900 by *Geoffrey* [129] and by *Nagai* [130], who called it **59**. The elucidation of the structure was accomplished by USDA researchers, *LaForge et al.*, in 1933 [131]. The synthesis and biosynthesis of rotenone (**59**) has been reviewed by *Crombie* [132]. It acts as a mitochondrial complex-1 respiration inhibitor. Rotenone (**59**) is being commercially used as a broad-spectrum insecticide in the fruit and vegetable market as well as for the control of fire ants.

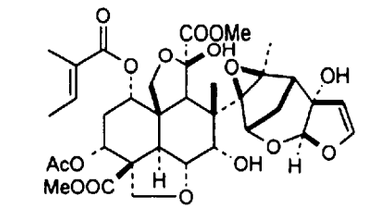
The insecticidal activity of powdered parts of the plant *Ryania speciosa* was first described in 1945 [133]. It could be shown that ryanodine (**60**) is the main active constituent [134][135]. The elucidation of the structure turned out to be a demanding problem which was solved by *Wiesner* and coworkers [136]. The synthesis of the hydrolysis product ryanodol (**61**) was achieved by *Deslongchamps* and coworkers [137]. Ryanodine (**60**) interferes with calcium channels in the sarcoplasmic reticulum, causing a lethal influx of calcium into the cells [138]. *Ryania* preparations were commercially available from *S.B. Penick & Co.* [139], but the product never found wide application.

Pheromones

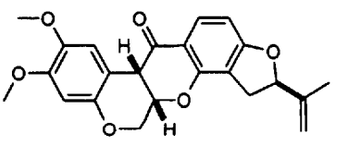
Insect sex pheromones are being used to control insect pests mainly in three ways. The mating disruption technique uses the pheromone to confuse the attracted partner such that it does not find its way to a mate. A disadvantage of this approach is that relatively large amounts of expensive pheromone are needed. The second method uses physical traps to which the insects are lured by the pheromone. Examples are the bark-beetle traps in European forests. In attract and kill, as the third method is called, small viscous droplets of a slow release formulation, which contains both a pheromone and a contact insecticide, are placed with a special application tool on cotton leafs for instance, or on non-vegetative parts of fruit trees. Attracted by the pheromone, the insects fly to a droplet. Upon touching it, they pick up a tiny but lethal amount of insecticide, and mating never happens. Commercial products based on this ecologically sound approach have been developed by *Novartis* [140][141]: *SIRENE*® *PBW* for the control of the pink bollworm *Pectinophora gossypiella* in cotton using the pheromone gossyplure (**62**), and *SIRENE*® *CM* for the control of the codling moth *Cydia pomonella* in apples with the pheromone codlemone (**63**). Permethrin (**13**) and cypermethrin (**14**) function as the contact insecticides.

Tetranactin

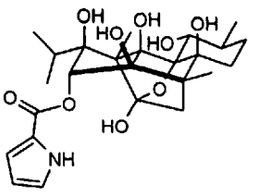
The macrotetrolide tetranactin (**64**) was discovered by scientists of *Chugai Pharmaceuticals* who isolated it as the main insecticidal component from a culture of *Streptomyces aureus* S-3466 [142][143]. The same research group reported the excellent acaricidal activity of **64** against *Tetranychus cinnabarinus* and other mites, and the low toxicity to mammals [144] [145]. Its total synthesis was achieved by *Schmidt* and *Werner* [146]. Tetranactin (**64**) had no major impact in the crop-protection market, possibly due to the fact, that it is predominantly an adulticide and has no effect on eggs.



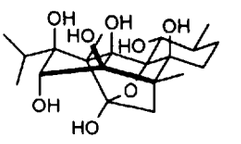
58 azadirachtin



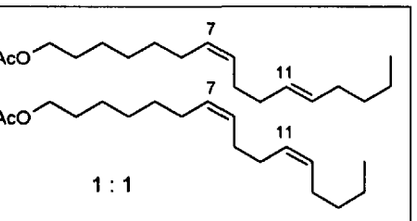
59 rotenone



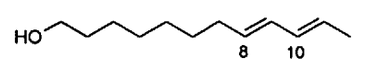
60 ryanodine



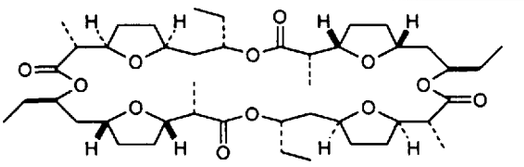
61 ryanodol



62 gossyplure



63 codlemone



64 tetranactin

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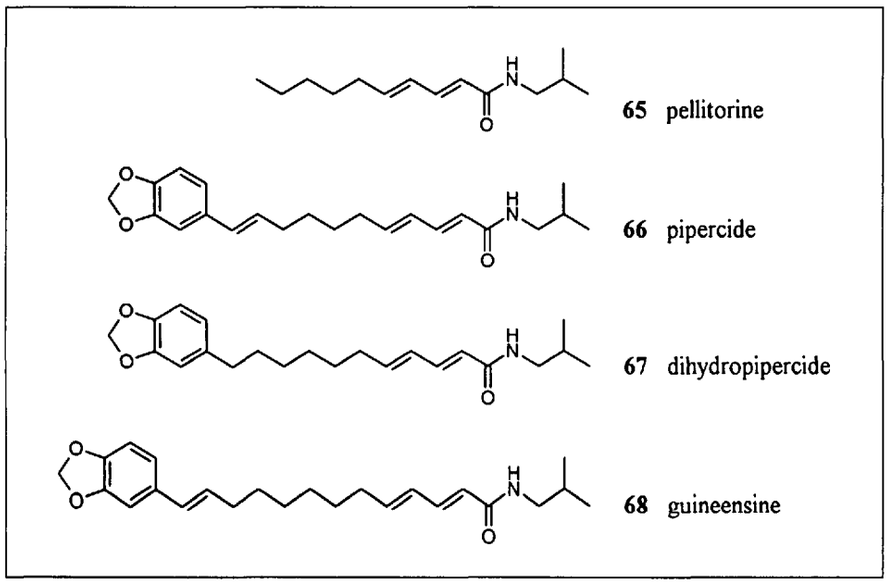
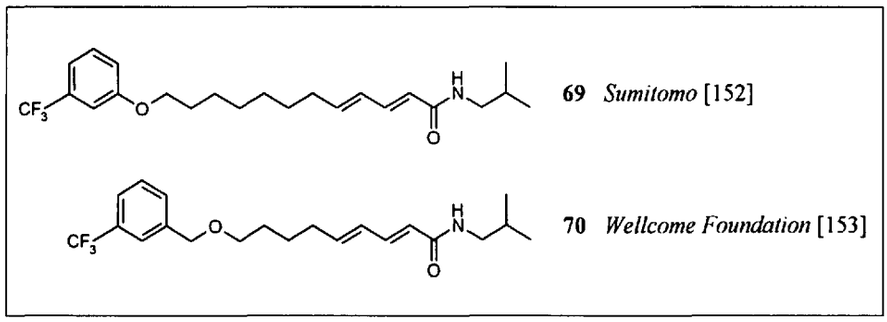


65 pellitorine

66 pipercide

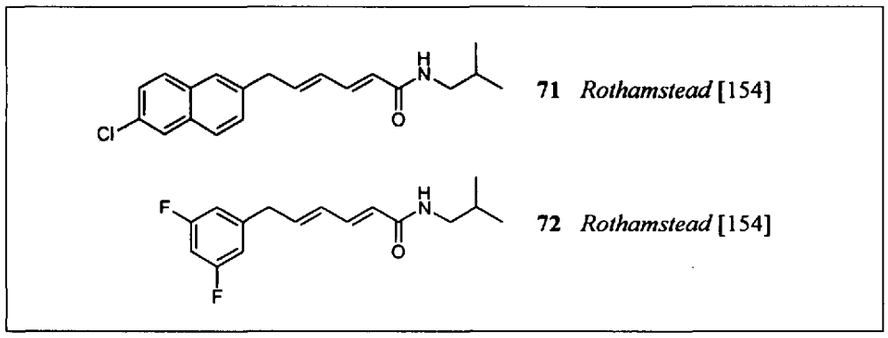
67 dihydropipercide

68 guineensine



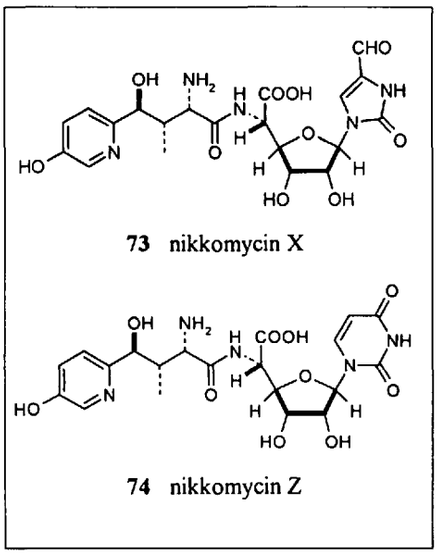
69 *Sumitomo* [152]

70 *Wellcome Foundation* [153]



71 *Rothamstead* [154]

72 *Rothamstead* [154]



73 nikkomycin X

74 nikkomycin Z

Dienamides

The unsaturated lipophilic amide pellitorine (**65**) was the first member of the large group of closely related natural products of the plant families Compositae, Piperaceae, and Rutaceae to be isolated [147], characterized, and synthesized [148][149]. *Jacobson*'s review [150] covers the history and the insecticidal properties of a number of these metabolites. He also reported on the early synthesis work and the structure-activity relationships of synthetic pellitorine analogues. Pellitorine (**65**) and close analogues are all too unstable for practical use as insecticides. Researchers from *Sumitomo* isolated from black pepper, *Piper nigrum*, the three isobutyl amides **66–68** which are more stable than pellitorine (**65**) and strongly insecticidal, especially when applied as a mixture [151]. Attempts to improve the insecticidal activity and to enhance the stability by synthesis of analogues were successful. It is interesting to note that the (2*E*,4*E*)-dienamide structural motif seems to be necessary for insecticidal activity, as all efforts to replace it led to inactive compounds [155]. The analogues **69–72** are all very active insecticides, comparable with the first generation pyrethroids, and thus much more active than the natural lead compounds. They exhibit activity against the adzuki-bean weevil, the rice stem borer, the mustard beetle, and the housefly. However, none was found suitable for commercial development. More research is necessary to improve the level and the spectrum of activity as well as the stability for the use under practical conditions [155]. The mode of action of the dienamides is particularly interesting. They are reported to interfere with some of the sodium-ion channels in nerve membranes in a similar manner to the pyrethroids, but when dienamides were tested on pyrethroid-resistant houseflies, no cross-resistance was observed [156].

Nikkomycins

The fungicidal and acaricidal nikkomycins were detected and isolated in 1972 by *Zähner* and coworkers as metabolites of *Streptomyces tendae* [157], with nikkomycin X (**73**) and Z (**74**) being the main members of this group. The elucidation of the structures was accomplished in collaboration with *Hagenmaier* and *König et al.* [158]. Researchers from *Schering-Plough* reported the synthesis of nikkomycin Z (**74**) [159]. Like the related polyoxins (see below), the nikkomycins inhibit chitin synthase. They are active against spider mites also under field conditions and were therefore investigated by *Bayer* as a possible acaricidal product [160]. Despite the good field performance of a mixture of **73** and **74**, the project was dropped by *Bayer*, reportedly for cost reasons [161].

Thiangazole

Due to its antiviral properties against HIV-1, thiangazole (**75**) was detected and isolated by *Höfle* and coworkers from a culture of the myxobacterium *Polyangium sp.* P13007 [162]. The same group also determined the structure and the abolute configuration of **75** [163]. The remarkable insecticidal activity of **75** against *Heliothis virescens* and *Lucilia sericata* was found at *Ciba-Geigy* [1][164]. To pave the way to possibly even more active thiangazole analogues, the total synthesis of **75** was carried out enantioselectively by *Ciba-*

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Geigy [1][165] chemists. The groups of *Pattenden* and *Heathcock* published their total syntheses of thiangazole almost simultaneously [166] [167].

Other Insecticidal Leads

Quassin (**76**) and a number of closely related compounds are insecticidal metabolites of medium activity, occuring quite frequently in extracts of plants from the Simaroubaceae family.

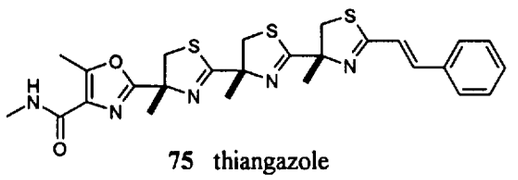
Annonin I (**77**) [168], a member of a large family of metabolites from the tree *Annona squamosa*, exhibited remarkable insecticidal activity in greenhouse tests at *Bayer* [169], but a commercial development was ruled out, the costly purification of **77** being one of the reasons [161]. The potential of annonaceous acetogenins as natural pesticides has been discussed in detail by *McLaughlin et al.* [170].

Haedoxan A (**78**), a sesquilignan isolated from the roots of the plant haedokusou, *Phryma leptostachya*, is highly insecticidal to houseflies and to lepidoptera, comparable with deltamethrin, when applied together with piperonyl butoxide [171].

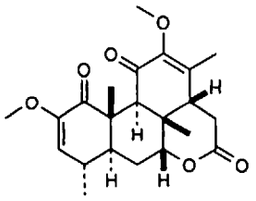
Rocaglamide (**79**), a metabolite of the plant genus *Aglaia* (Meliaceae), was reported to exert insecticidal activity against the variegated cutworm *Peridroma saucia*, the Asian armyworm *Spodoptera litura* [172], and against the Egyptian cotton leafworm *Spodoptera littoralis*, of a potency comparable with that of azadirachtin (**58**) [173].

An interesting approach to new insecticides was chosen by *FMC* chemists who used α-terthienyl (**80**), a nematocidal and insecticidal plant metabolite of the Compositae family as a template in the search for new insecticides. α-Terthienyl (**80**) acts as a light-driven sensitizer converting triplet oxygen into reactive singlet oxygen [174][175]. F-5183 (**81**), which evolved from this program, showed excellent antimite activity in the field against *Tetranychus urticae* in cotton and against *Phyllocoptruta oleivora* in orange orchards, at application rates of 30–225 g/ha [176].

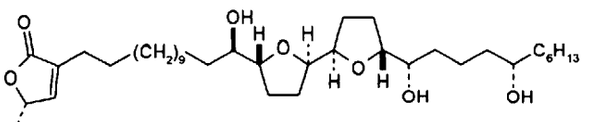
The cyclophosphates **82** from *Streptomyces antibioticus* Tü-1718 (=DSM 1951) [177][178] have been shown to be very efficient inhibitors of acetylcholine esterase, with compound Tü-1718-P (R = propyl) being as effective on the enzyme and on insects as the commercial insecticide carbofuran [179]. However, this discovery came at a time, when no more organic phosphates were developed for the insecticide market.



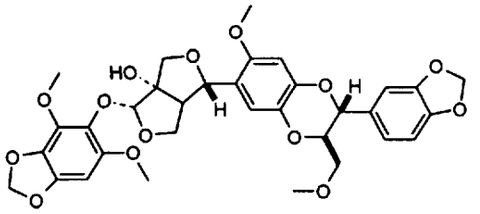
75 thiangazole



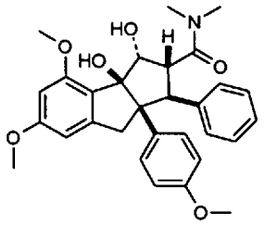
76 quassin



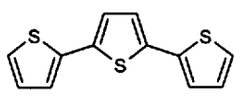
77 annonin I

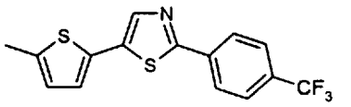


78 haedoxan A

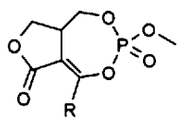


79 rocaglamide



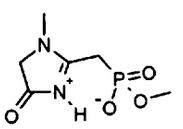


80 α-terthienyl **81** F-5183

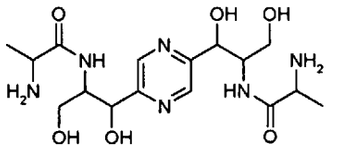


R = CH_3, propyl, i-propyl, butyl

82 cyclophosphates Tü-1718



83 ulosantoin



84 diabroticin A

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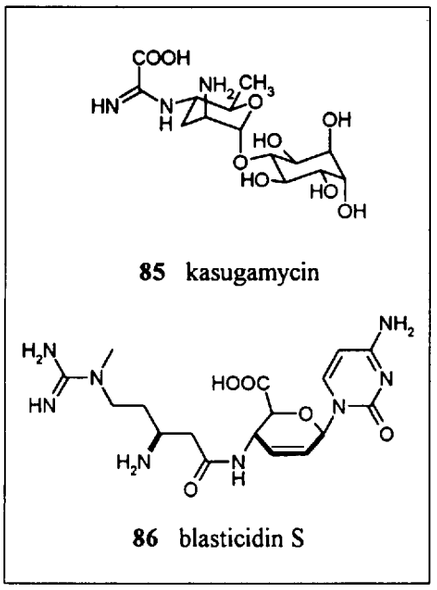
Another strong inhibitor of acetylcholine esterase with insecticidal activity on cockroaches is ulosantoin (**83**), isolated from the marine sponge *Ulosa ruetzleri* [180].

The polar insecticidal diabroticin A (**84**) is produced by *Bacillus subtilis* and *B. cereus*. It is highly active against the southern corn rootworm *Diabrotica undecimpunctata*, with an LD_{50} of 2–4 ppm when incorporated in the diet [181].

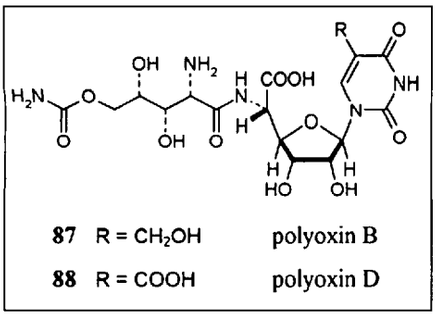
Fungicides and Bactericides

To prevent economically unacceptable losses of yield and quality of agricultural crops caused by microbial plant pathogens, protection of the crop plants with agrochemicals is necessary. With the exception of kasugamycin (**85**), which is mainly used as a fungicide (see below), the natural products and analogues which have so far been developed for controlling bacterial plant pathogens are based on the same modes of action as some of the antibiotics used in medicine. For the control of bacterial plant diseases, antibiotics like streptomycin and oxytetracyclin are being used in some countries. There is a concern, however, that their application in the environment might cause natural resistance, rendering these antibiotics useless for medical treatment. Compared with the economic losses entailed by bacterial plant diseases, those caused by fungi are much larger. The task to find novel bactericides suitable for crop protection turned out to be exceedingly difficult. In contrast, the search for useful antifungal natural products and analogues was very successful.



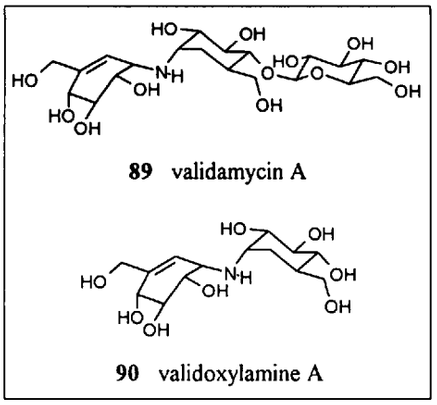
85 kasugamycin

86 blasticidin S



87 R = CH_2OH polyoxin B

88 R = COOH polyoxin D



89 validamycin A

90 validoxylamine A

Blasticidin S

Japanese research has greatly contributed to the discovery of new crop protection agents of natural origin. Blasticidin S (**86**), a metabolite of *Streptomyces griseochromogenes* [182][183], was discovered in Japan in 1958 and found use in the control of rice blast *Pyricularia oryzae*. This highly active fungicide is applied at 10–30 g ai/ha [184], but due to toxic and phytotoxic side effects, it has lost ground in the market to other better performing products like kasugamycin (**85**).

Kasugamycin

Umezawa and coworkers [185] discovered kasugamycin (**85**) as a bactericidal and fungicidal metabolite of *Streptomyces kasugaensis*. They also determined the structure of **85** [186] and accomplished the total synthesis [187]. Kasugamycin (**85**) acts as an inhibitor of protein biosynthesis in microorganisms but not in mammals [188], and its toxicological properties are excellent [189]. *Hokko Chem. Ind.* developed a fermentative production process to market the systemically active kasugamycin (**85**) for the control of rice blast *Pyricularia oryzae* and bacterial *Pseudomonas* diseases in several crops [189].

Polyoxins

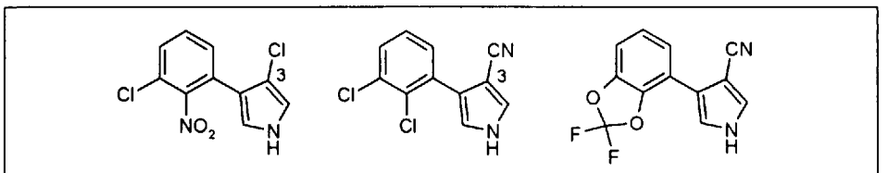
Polyoxin B (**87**) and D (**88**) were isolated as metabolites of *Streptomyces cacaoi var. asoensis* in 1965 by *Suzuki* and coworkers [190] as a new class of natural fungicides. The structures were determined by the same group [191][192]. The mode of action of the polyoxins makes them very acceptable with regard to environmental considerations. They interfere with the fungal cell-wall synthesis by specifically inhibiting chitin synthase [193]. Both **87** and **88** are commercially produced *via* fermentation. Polyoxin B (**87**) found application against a number of fungal pathogens in fruits, vegetables, and ornamentals, and polyoxin D (**88**) is marketed as Zn salt by several companies to control rice sheath blight *Rhizoctonia solani* [194].

Validamycin

The validamycin family was detected by *Takeda* researchers in 1968 in a greenhouse assay when screening streptomycete extracts for activity against rice sheath blight *Rhizoctonia solani* [195]. *Takeda* commercialized **89** by developing a fermentation process with *Streptomyces hygroscopicus var. limoneus*. The same group of antibiotics was discovered independently in China and given the name jinggangmycins [196]. The elucidation of the structure of validamycin A (**89**) [197] and the total synthesis [198] were both achieved by *Ogawa* and coworkers. Validamycin A (**89**) was found to be a prodrug which is converted within the fungal cell to validoxylamine A (**90**), an extremly strong inhibitor of trehalase [199]. This mode of action gives validamycin A (**89**) a favorable biological selectivity, because vertebrates do not depend on the hydrolysis of the disaccharide trehalose.

Pyrrolnitrin

The biological activity of pyrrolnitrin (**91**) was first decribed in 1964 by *Arima* and coworkers [200], who had isolated this antifungal antibiotic from *Pseudomonas pyrrocinia*. The same authors pub-



91 pyrrolnitrin **92** fenpiclonil *Novartis* **93** fludioxonil *Novartis*

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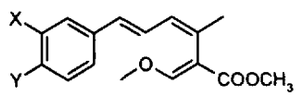
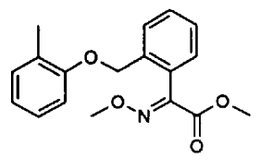
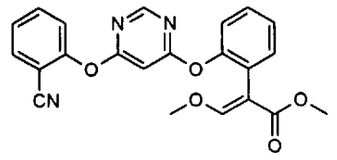


94 X = H, Y = H strobilurin A

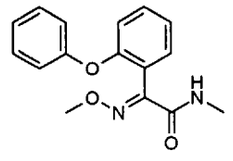
95 X = OCH_3, Y = Cl strobilurin B



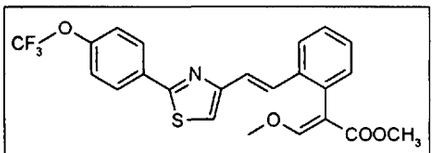
96 kresoxim methyl *BASF*



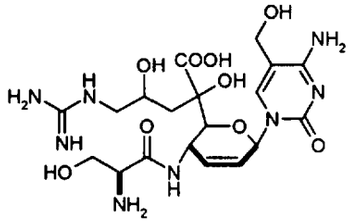
97 azoxystrobin *Zeneca*



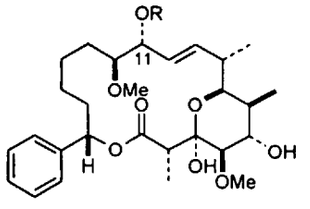
98 SSF 126 *Shionogi*



99



100 mildiomycin



101 R = CH_3 : soraphen A

102 R = $CH_2OCH_2CH_2OCH_3$

lished the structure in 1965 [201]. Pyrrolnitrin (**91**) was subsequently synthesized by chemists at *Fujisawa* [202] as well as at *Ciba-Geigy* [1][203]. Although **91** shows excellent activity *in vitro* and in the greenhouse against the fungal plant pathogens *Botrytis cinerea* and *Pyricularia oryzae*, its performance in the field was disappointing, because the natural product rapidly decomposed when exposed to sunlight. The cause of this photoinstability was investigated by chemists at *Ciba-Geigy* [1], with the aim of eliminating it while conserving the biological activity. It soon became apparent, that replacement of the chloro substituent at the 3-position of the pyrrole by a cyano group led to a remarkable enhancement in stability. Thus, the half-life of fenpiclonil (**92**) in simulated sunlight is 48 h as compared with $^1/_2$ h for its 3-chloro analogue [204]. Finally, the biological activity was optimized by appropriate substitution on the phenyl ring [204]. Two commercial products emerged from these efforts, fenpiclonil (**92**) [205] and fludioxonil (**93**) [206], both excellent seed treatment agents against fungal pathogens like *Fusarium graminearum* in maize and *Gerlachia nivalis* in wheat. Studies of the mode of action of these products and of pyrrolnitrin concluded, that they inhibit a protein kinase PK-III which is involved in the osmosensing signal transmission pathway. It is suggested, that this inhibition might lead to an increased concentration of a non-phosphorylated regulatory protein, causing a deregulation of a osmosensing mitogen-activated protein-kinase cascade [207][208].

Strobilurins

The antifungal antibiotic **94** was originally isolated in 1967 by *Musilek, Vondracek*, and coworkers from a culture of the basidiomycete *Oudemansiella mucida* and given the name mucidin [209][210]. Later, but independently, *Anke, Steglich*, and coworkers isolated **94** and **95** from the basidiomycete *Strobilurus tenacellus* [211] and called them strobilurin A (**94**) and B (**95**). On the basis of spectral data, it became apparent that mucidin and strobilurin A were identical. Both groups contributed to the elucidation of the structure of the strobilurins which finally could be proven by synthesis to be (*E,Z,E*)-configurated [212]. This class of antifungal compounds is reported to be produced by several basidiomycetes [213] [214]. At *Ciba-Geigy* [1], the strobilurins were also found as metabolites of an ascomycete, *Bolinia lutea* [215–217]. Several stereospecific syntheses of the strobilurins have been accomplished [212][218][219]. For detailed information consult the review by *Clough* [220]. The antifungal activity, especially of strobilurin B (**95**), *in vitro* and in the greenhouse against plant pathogens like *Venturia inaequalis, Cercospora arachidicola, Plasmopara viticola*, and *Phytophthora infestans* are excellent. *Becker et al.* [221] showed, that the strobilurins strongly inhibit mitochondrial respiration. The substructure responsible for the biological activity is the β-methoxy acrylic ester, in short β-MAE. This acronym is often used to describe compounds having this or a closely related toxophore. In field tests, the natural strobilurins were a failure, due to their inherent photoinstability. The half-life of strobilurin A (**94**) in simulated sunlight was determined to be only 12 s [222]. Several industrial research groups took up the challenge to design photostable analogues of the strobilurins with equal or even improved antifungal activity. Compounds **96–98** are successful strobilurin analogues which emerged from these efforts. Highly active, and with the same mode of action as the natural strobilurins, they all show a dramatically improved photostability. The analogue **96**, *e.g.*, has a half-life in simulated sunlight of more than 24 h [223]. *BASF* introduced kresoxim methyl (**96**) to the market in 1996 as a broad-spectrum fungicide in cereals, apples, and other crops. *Zeneca* recently launched sales of the broadly active azoxystrobin (**97**) in the cereal, fruit, and vegetable markets [224]. SSF 126 (**98**) from *Shionogi* is expected to appear on the market, soon. During the search for new fungicides, it was noted that certain strobilurin analogues also exhibit insecticidal activity, as, *e.g.*, **99** from *AgrEvo* [225].

Mildiomycin

The isolation of the antifungal mildiomycin (**100**) from a culture of *Streptoverticillium rimofaciens* was reported by *Takeda* scientists in 1978 [226–228]. Mildiomycin (**100**) is strongly active against several powdery mildews on various crops [227][229], acting as an inhibitor of the fungal protein biosynthesis [230]. Its low toxicity in vertebrates would make it an environmentally sound crop-protection agent [227], but mildiomycin (**100**) never appeared on the market. Recent publications indicate however, that *Takeda*'s efforts to develop mildiomycin (**100**) still continue [231].

Soraphen A

Soraphen A (**101**) was discovered by the research groups of *Reichenbach* and *Höfle* at GBF (= Gesellschaft für Biotech-

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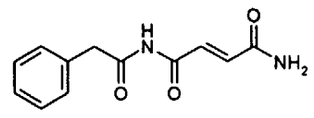
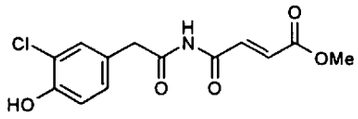
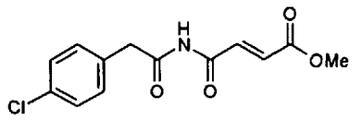
nologische Forschung mbH) [232][233]. In their screening of extracts from myxobacteria, a sample from *Sorangium cellulosum* strain So ce26 showed broad antifungal *in vitro* activity. The new metabolite soraphen A (**101**), which was mainly responsible for the activity, was isolated and fully characterized by NMR spectroscopy and X-ray crystallography [232]. The total synthesis of **101** was achieved by *Giese* and coworkers [234]. Greenhouse tests at *Ciba-Geigy* [1] soon revealed the high potential of **101** as a plant-protection agent against fungal pathogens [235]. Field tests met the high hopes generated by the greenhouse results, and economical application rates seemed feasible. A derivatization program was initiated both at GBF and at *Ciba-Geigy* [1] aiming at an improvement of the already excellent activity of **101**, and a number of derivatives and structural fragments were prepared and tested [236]. Natural analogues of **101** were isolated in small amounts at GBF [237] during the preparation of larger quantities of soraphen A (**101**) for field and toxicology testing. It soon became clear, that the excellent activity of **101** was difficult to improve on. None of the natural analogues was better. Most of the many derivatives were weaker, but some ether derivatives of the C(11)–OH group like **102** showed improved activity. However, this gain did not make up for the increased production costs, and further development was therefore focussed on the natural product soraphen A (**101**), both as a broad-spectrum seed dressing agent and a fungicide for foliar application. Mechanistic studies showed soraphen A (**101**) to be the first antifungal agent inhibiting acetyl-CoA carboxylase (ACC) [238]. The corresponding enzyme in plants is known to be the target of the aryloxyphenoxy-propionate and the cyclohexanedione herbicides [239]. Soraphen A (**101**), however, has no effect on the ACC of plants and did not show phytotoxic effects in the field. Its efficacy under practical conditions was outstanding. As a seed treatment agent at 0.3 g ai/kg seeds, it completely controlled mildew *Erysiphe graminis* in barley and snow mold *Gerlachia nivalis* in rye. Full control of apple scab *Venturia inaequalis* on apples and grey mold *Botrytis cinerea* on grapes was achieved with 10–25 g ai/hectoliter. Apart from fungal ACC, soraphen A (**101**) also inhibits the mammalian enzyme. Due to difficulty of production and a flaw in its toxicology profile, soraphen A (**101**) never reached the crop-protection market.



103 fumaramidmycin



104 fumarimid F-21223



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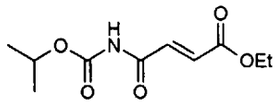

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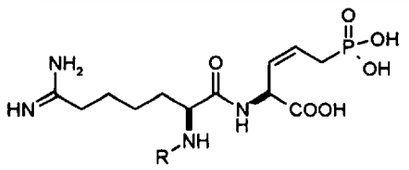
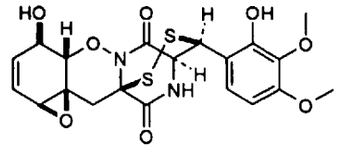
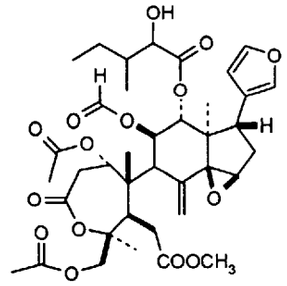


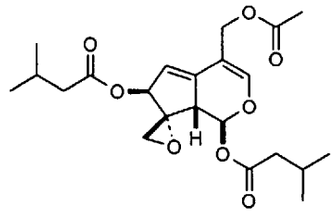
107 R = H rhizocticine A
108 R = L-val rhizocticine B
109 R = L-leu rhizocticine D



110 gliovirin



111 14,15β-epoxy-prieurianin



112 valtrate

Other Fungicidal Leads

Takeda researchers reported the isolation of the antibacterial fumaramidmycin (**103**) from *Streptomyces kurssanovii* [240]. At *Ciba-Geigy* [1], the structurally related compound **104** was detected in a culture of the fungus *Sordaria sp.* F-21223, due to its antifungal activity against *Pythium ultimum* [241]. From the fungus *Coniothyrium sp., Krohn* and coworkers also isolated **104** and called it coniothyriomycin [242]. A number of analogues were prepared and tested at *Ciba-Geigy* [1] for activity against oomycetes [243]. Although improvements in activity were achieved, as in the case of compound **105** with an EC_{80} of 60 ppm against *Phytophthora infestans* and *Plasmopara viticola* and of **106** with an EC_{80} of 6 ppm against *Pythium ultimum*, a competitive level of activity was not reached.

From *Bacillus subtilis* ATCC 6633, *Loeffler* and coworkers isolated the fungicidal metabolites, identified them as the peptides **107–109** and named them rhizocticins [244][245]. In greenhouse tests carried out at *Ciba-Geigy* [1], it became apparent that the rhizocticines control grey mold *Botrytis cinerea* on apples and vines. It could be shown after proteolytic digestion, that L-(*Z*)-2-amino-5-phosphonopent-3-enoic acid [246] was the actual active agent. The corresponding (3*E*)-compound did not show any activity. A mixture of rhizocticine A, B, and D (**107–109**) was tested in the field against grey mold *Botrytis cinerea* on grapes. The result looked promising, however, competing lead structures were given priority for further investigation.

Gliovirin (**110**), a natural fungicide active against *Pythium ultimum*, was isolated from *Gliocladium virens* [247]. At *Ciba-Geigy* [1], **110** was detected in a culture of *Aspergillus viridinutans* F-4464 [241] and tested in the greenhouse against oomycete pathogens. The good activity against *Pythium ultimum* reported earlier was confirmed under practical conditions, when **110** was incorporated into soil at 10 ppm. In other tests and especially against other oomycetes, the performance of gliovirin (**110**) was insufficient.

Many antifungal natural products have been isolated from higher plants. However, only very few were reported to be tested under practical conditions. The following two compounds are examples of

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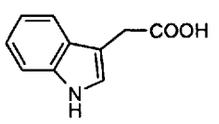
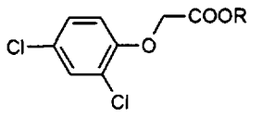
plant metabolites which were actually active in agronomically relevant greenhouse tests. 14,15β-Epoxy-prieurianin (**111**) was first isolated by *Lukacova* and coworkers from the bark of the South American tree *Guarea guidona* (Meliaceae) [248]. In the course of *Ciba-Geigy*'s [1] screening of plant extracts for biological activity relevant to crop protection, a bark extract from *Pseudocarapa championii* (Meliaceae) from Sri Lanka showed promising activity against the grey mold *Botrytis cinerea* on apples and beans [249]. Isolation of the active ingredient yielded **111**, which controlled grey mold at an EC_{80} of 60 ppm in the greenhouse. Under field conditions its performance did not reach that level.

Valtrate (**112**) isolated from the plant *Valeriana capense* (Valerianaceae) by *Hostettmann* and coworkers [250], showed anti-mildew activity in the greenhouse of *Ciba-Geigy* [1] at an EC_{80} of 60 ppm.

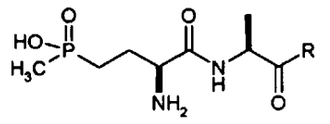


113 3-indolyl acetic acid

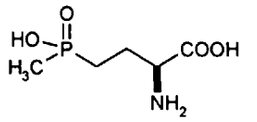


R = H, alkyl

114 2,4-D



115 R = L-ala bilanaphos



116 phosphinothricin

117 R = L-leu phosalacine
118 R = L-ala-L-ala trialaphos

Herbicides

Whereas natural products research has been very successful in providing lead structures and even marketable products for the control of insect pests and plant diseases, in the field of weed control, the ingenuity of the synthesis chemists has set the level of competion so high, that only a few natural products have actually contributed to marketable products.

Hormone Weed Killers

After *Kögl* had discovered the heteroauxin growth stimulator indol-3-yl acetic acid (**113**) in 1934 [251], programs were started in England, Germany, and in the USA for the search of new herbicides based on excessive growth stimulation. This approach proved to be successful. In 1942, researchers of the Boyce Thompson Institute in the USA synthesized 2,4-D (**114**) [252] which kills broad leafed weeds by the anticipated mode of action, and whose esters and salts are still useful herbicides today.

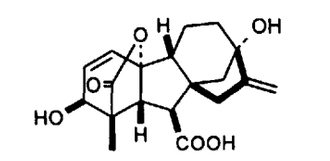
Phosphinothricin Peptides

Phosphinothricylalanylalanine (**115**, bilanaphos) was discovered independently by *Zähner* and coworkers [253] in a culture of *Streptomyces viridochromogenes* and by *Meiji Seika* researchers [254] as a metabolite of *Streptomyces hygroscopicus*. Both groups described the antimicrobial properties of **115** without recognizing its herbicidal potential. *Zähner* and coworkers identified phosphinothricin (**116**) as the biologically active agent and elucidated its mode of action as inhibition of the glutamine synthase [253]. Some time later, researchers from *Hoechst* (now *AgrEvo*) found the excellent herbicidal activity of phosphinothricin (**116**) [255].

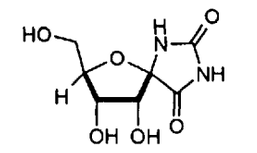
Independently, the herbicidal activity of **115** was detected in the *Meiji Seika* laboratories [256]. Following on from this, *Meiji Seika* developed a fermentation process for the production of bilanaphos (**115**) as a commercial herbicide. *Hoechst* went onto the market with glufosinate, the racemic form of **116** which is manufactured by synthesis. Glufosinate has excellent environmental properties. In 1996, its market share was estimated to be 140 million USD [257]. Two peptides closely related to **115**, phosalacine (**117**) [258] and trialaphos (**118**) [259], were described as metabolites from different species of actinomycetes.

Gibberellins

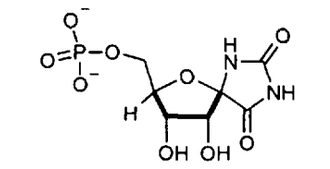
The metabolites of the fungus *Gibberella fujikuroi* gibberellin A_3 (**119**) and analogues are being used commercially as plant growth regulators for quality improvement and programmed harvesting in fruits, vegetables, and other crops [260], *e.g.*, in the production of seedless grapes, citrus fruits, and artichokes [261].



119 gibberellin A_3



120 hydantocidin



121 hydantocidin-5'-phosphate

Hydantocidin

Hydantocidin (**120**) was first discovered as a powerful herbicide by *Sankyo* researchers in 1985, who isolated it from *Streptomyces hygroscopicus* SANK 63584 [262][263]. Two independent discoveries of **120** from different *Streptomyces* strains were reported by *Ciba-Geigy* [1][264] and by *Mitsubishi* [265]. Hydantocidin (**120**) is a nonselective herbicide of at least the same potency as the commercial products glyphosate and bilanaphos (**115**) [266]. For a new product to be successful in this market segment, the production costs have to be low. Therefore, an effort was made by several groups to devise economical syntheses of **120** [267–274] and to search for herbicidal analogues of **120** which are more easily accessible. The independent studies of the mode of action of hydantocidin (**120**) by three groups showed that it is converted within the plant to hydantocidin-5'-phosphate (**121**), the actual herbicide which efficiently inhibits adenylosuccinate synthase [275–278]. Now that the crystal-structure data of adenylosuccinate synthase with the bound inhibitor **121** are at hand [277][278], the search for chemically more accessible inhibitors has gained a new dimension.

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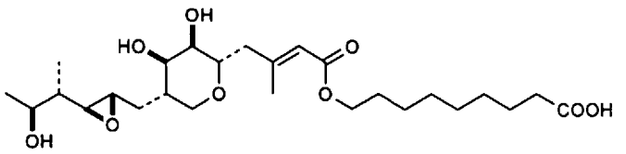
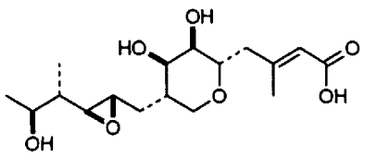
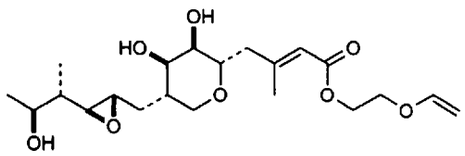


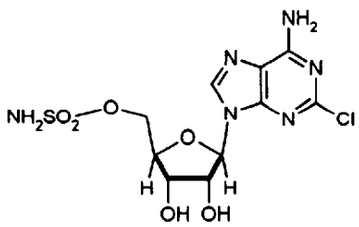
122 pseudomonic acid



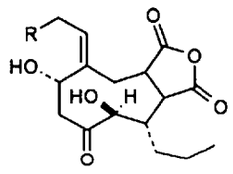
123 monic acid



124 *Zeneca*

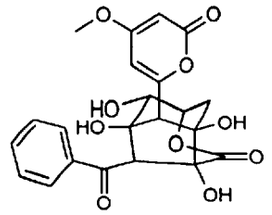


125 AT-265

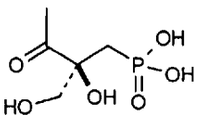


126 R = H cornexistine

127 R = OH hydroxycornexistine



128 vulgamycin



129 phosphonothrixin

Monic-Acid Derivatives

In 1993, researchers from *Zeneca* reported on the herbicidal activity of monic-acid derivatives [279]. Pseudomonic acid A (**122**), a bactericidal metabolite of *Pseudomonas fluorescens* [280], was hydrolyzed to monic acid (**123**) which subsequently was reesterified to the derivative **124**. In the greenhouse and in the field, **124** proved to be a very potent postemergent herbicide against broad-leafed weeds at application rates of 50–250 g/ha [281].

There is no information on the mode of action of **124**, but the parent compound **122** is reported to act as an inhibitor of isoleucyl-tRNA synthase [282].

AT-265

Several nucleoside-type metabolites have been reported to be phytotoxic [283]. From a strain of *Streptomyces albus*, the metabolite AT-265 (**125**) [284] was identified at *Ciba-Geigy* [1] as a potent postemergent herbicide. A number of weeds are controlled by **125** at less than 100 g/ha [285]. However, the mammalian cytotoxicity of **125** and of its herbicidal analogues precluded a commercial development.

Cornexistine

Cornexistine (**126**), a phytotoxic fungal metabolite, was first isolated in 1990 from a culture of *Paecilomyces variotii* SANK 21086 by *Sankyo* researchers, who also determined its structure and its herbicidal potential [286]. Although **126** controls both mono- and dicotyledonous weeds, it gives good protection for maize. From the identical strain, researchers at *DowElanco* isolated hydroxycornexistin (**127**). This analogue is even more potent than **126**, especially against broad-leafed weeds, giving good control at rates as low as 32 g/ha, with excellent selectivity for use in maize and sorghum [287]. The mode of action of cornexistine (**126**) has been studied [288] and seems to be novel.

Other Herbicidal Leads

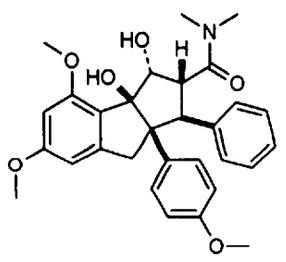
The herbicidal activity of the streptomycete metabolite vulgamycin (**128**) was detected by *Bayer* researchers [289]. Postemergent application of **128** at a rate of 250 g/ha gives excellent control of several weeds without damaging cotton, barley, or maize [289].

Phosphonothrixin (**129**), isolated at *Kureha* from a culture of *Saccharothrix sp.*, induces chlorosis in a nonselective way when applied to plant leaves [290–292], but the mode of action is not yet known. Several mono- and dicotyledonous weeds are controlled by **129** at an application rate of 500 g/ha.

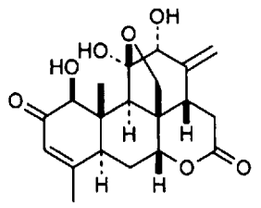
While screening extracts of higher plants for biological activity relevant for crop protection at *Ciba-Geigy* [1], we found that an extract from the bark of *Aglaia congylos* (Meliaceae) exhibited quite potent herbicidal activity. The metabolite responsible for the activity proved to be rocaglamide (**79**), which is also described as insecticidal [172][173]. Rocaglamide (**79**) showed postemergent and good preemergent activity at 0.5–1 kg/ha against a range of mono- and dicotyledonous weeds.

Another strongly herbicidal plant metabolite was recently reported. The quassinoid ailanthone (**130**) from *Ailanthus altissima* (Simaroubaceae) shows pronounced postemergent activity against several weeds when applied at *ca.* 1 kg/ha [293].

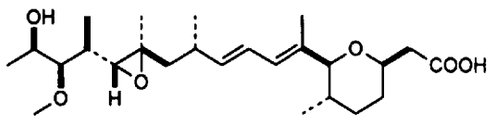
Herboxidiene (**131**) was isolated from a culture of *Streptomyces chromofuscus* A7847 by *Monsanto* researchers [294], who also reported on the remarkable herbicidal potency of this metabolite [295]. At 70 g/ha, **131** fully controlled several weed species, while having no effect on wheat and soybean. In the *Takeda* laboratories **131** was isolated from a yet uniden-



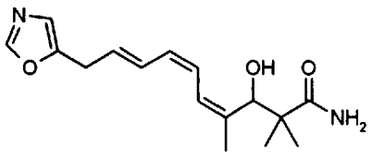
79 rocaglamide



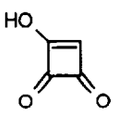
130 ailanthone



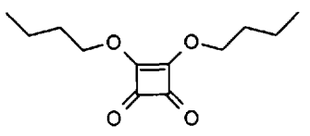
131 herboxidiene



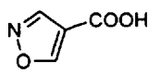
132 phthoxazolin A



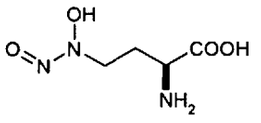
133 moniliformin



134 CGA 49445



135 isoxazole-4-carboxylic acid



136 homoalanosine

tified *Streptomyces* species. Mode-of-action studies showed that **131** induces apoptosis in the G2 phase of the cell cycle [296]. Independently, researchers at *Sandoz* [1] also discovered herboxidiene (**131**) and published the absolute configuration of this natural product [297].

Phthoxazolin A (**132**) was found by *Omura* and coworkers in a screening geared to yield inhibitors of the cellulose biosynthesis [298]. Independently, two other groups also discovered **132** [299] [300] which shows postemergent activity against broad-leafed plants [298][299].

Moniliformin (**133**), a phytotoxic metabolite of *Fusarium moniliforme* served as a lead structure in an optimization project at *Ciba-Geigy* [1]. The analogue **134** had much improved activity, yielding chlorosis and desiccation at 1–2 kg/ha [301]. However, it was not selected for further development.

Isoxazole-4-carboxylic acid (**135**), a metabolite of *Streptomyces sp.*, has been reported to exert herbicidal activity in pot tests [302].

Homoalanosine (**136**) had been known as a synthetic chemical with insecticidal and antimicrobial activity, when researchers at *Sumitomo* isolated it from a culture of *Streptomyces galilaeus* due to its phytotoxic properties. Homoalanosine (**136**) acts as an antimetabolite of L-aspartic acid and L-glutamic acid. In the paddy field, **136** was found to give full control of weeds at a rate of 4 kg/ha, without impairing the rice crop [303].

Outlook

In the future, many more new natural products useful for crop protection will be identified from diverse natural sources. It is foreseeable, that biotechnology will expand its influence on crop protection significantly. Techniques like directed biosynthesis and random gene shuffling will produce new 'natural' products with interesting biological activity. To render crop plants resistant to their pests or pathogens, transgenic varieties expressing the genes of insecticidal, fungicidal, or nematocidal natural products from other organisms will be constructed. *Novartis*' insect-resistant maize expressing the δ-endotoxin gene of *Bacillus thuringiensis* is a first-generation example [115]. This will certainly intensify the search for active natural products suitable for transgenic expression in plants. Such transgenic crop plants certainly represent excellent solutions to important crop-protection problems. However, in a dynamic field like crop protection, it can be expected that chemical crop protection will remain to be a strong pillar. Therefore, the search for conventional crop-protection agents will continue.

Received: December 4, 1997

[1] The company *Novartis International Inc.* was formed by the merger of *Ciba-Geigy Ltd.* and *Sandoz Ltd.* Prior to this merger, the company *Dr. R. Maag AG* had become part of *Ciba-Geigy Ltd.*, and *Zoecon Corp.* part of *Sandoz Ltd.*

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