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Amino acid chemistry in crop protection☆

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Contents

1. Introduction

α-Amino carboxylic acids are one of five major classes of natural products and play a crucial role in diverse biological functions.[2] Historically, the amino acids have been subdivided into proteinogenic and non-proteinogenic respresentatives. The 20 proteinogenic amino acids are the monomeric constituents of proteins, naturally occurring polymeric amino acids. Mammals lack biosynthesis pathways to produce eight of these 20 proteinogenic amino acids and therefore must obtain them from their diet; they are therefore called essential amino acids. Peptides, oligomeric amino acids, as neurotransmitters or hormones influence a multitude of physiological processes by signal transduction. After binding to their membrane-bound receptors, these biologically active peptides influence cell–cell communication and control a series of vital functions, such as metabolism, immune defence, digestion, respiration, behaviour and reproduction.[3] In the meantime, more than 700 naturally occurring non-proteinogenic amino acids are known,[4] but, of course, many more unnatural amino acids, e.g., fluorinated,[5] boronated,[6] quaternary[7] and cyclic[8] amino acids, have been prepared. Another important biological function of amino acids is their metabolic transformation into physiologically

☆ See Ref. 1.

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important polyamines. Furthermore, amino acids are important constituents of biologically active compounds, such as drugs and agrochemicals. This review deals with the agrochemical aspects of α-amino acid chemistry. The fact that most amino acids are chiral compounds again emphasises the significance of chirality in modern crop protection chemistry.[9,10]

2. Herbicidally active amino acid derivatives

2.1. Phosphorus-containing amino acid herbicides

Even 36 years after its market launch in 1974, the broad-spectrum herbicide, glyphosate (**1**)[11], is still the world's largest-selling agrochemical and with annual sales of US $ 5,000 million under various brand names, it occupies more than 30% of the herbicide sales volume all around the globe! Glyphosate inhibits the plant-specific enzyme, 5-enolpyruvylshikimi-3-phosphate synthase, which is needed for the production of the essential aromatic amino acids, phenylalanine, tryptophan and tyrosine, on the shikimate pathway. It is used to control annual and perennial grasses and broad-leaved weeds, either non-selectively in fruit orchards, vineyards, rubber and oil palm plantations, ornamental trees and brushes, non-cropland and post-planting/pre-emergence in cereals, vegetables and other crops or selectively in genetically modified glyphosate-tolerant crops.[11] The naturally occurring tripeptide, bilanafos (**2**) and its N-terminal amino acid, L-phosphinothricin (**3**), are also non-selective total herbicides with a similar biological spectrum.[12–14] Bilanafos (**2**), which has been isolated from the fermentation broths of *Streptomyces viridochromogenes* and *Streptomyces hygroscopicus*, is a pro-herbicide and is only active after its metabolic hydrolysis in the plant to its active principle, L-phosphinothricin (**3**). Although only the (*S*)-enantiomer of phosphinothricin is herbicidally active, the ammonium salt of its racemate is widely applied as the total herbicide glufosinate. Bilanaphos and phosphinothricin both inhibit *glutamine synthetase*, an ammonia-fixing enzyme, which enables one of the rare known transformations in living systems, in which inorganic nitrogen is incorporated into organic forms, such as amino acids or pyrimidines.[15] The inhibition of this process results in the accumulation of ammonia in plant cells to toxic levels. The potent inhibition of *glutamine synthetase* by phosphinothricin is due to the fact, that it is a phosphinic acid mimic of (*S*)-glutamic acid, the natural substrate of this enzyme. Some synthetic analogues of phosphinothricin also efficiently block *glutamine synthetase*.[16] The tripeptide, phosalacine (**4**), also contains the amino acid L-phosphinothricin, and is therefore herbicidally active.[14,17] Phosalacine has been isolated from the culture filtrate of the soil isolate *Kitasatosporia phosalacinea*. The dehydroamino acid L-APPA (**5**), which is the C-terminal amino acid of the naturally occurring di- and tripeptide antibiotics, rhizocticin A–C, as well as plumbemycins A and B, is highly active against monocotyledonous weeds (Fig. 1).[18]

In the meantime, several stereoselective syntheses of L-phosphinothricin (**3**) have been reported,[19] e.g., through Michael addition of a chiral glycine Schiff base to a vinyl phosphorous compound,[20] asymmetric hydrogenation of prochiral α-acylamido acrylates[21] or enzyme-catalyzed racemate resolution.[22] An efficient asymmetric synthesis of L-phosphinothricin employs the enantiomerically pure Schöllkopf bis/lactime ether **6**, which is readily available from (*R*)-valine. Alkylation of **6** and subsequent hydrolysis of the intermediate **8** delivers L-phosphinothricin (**3**) with 93% ee[19,23] Another approach takes advantage of the accessibility of the chiral pool compound, (*S*)-glutamic acid, which can be converted into the protected (*S*)-vinylglycine derivative **7** in three steps. Regioselective addition of *O*-isobutyl methyl phosphonite to **7** gives, after deprotection of **9**, L-phosphinothricin (**3**) in high yields with 97% ee (Scheme 1).[19,24]

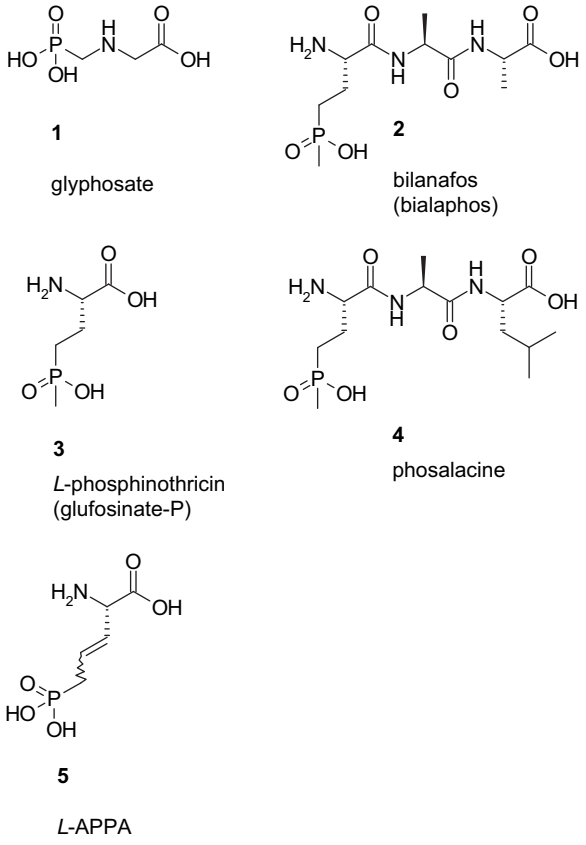
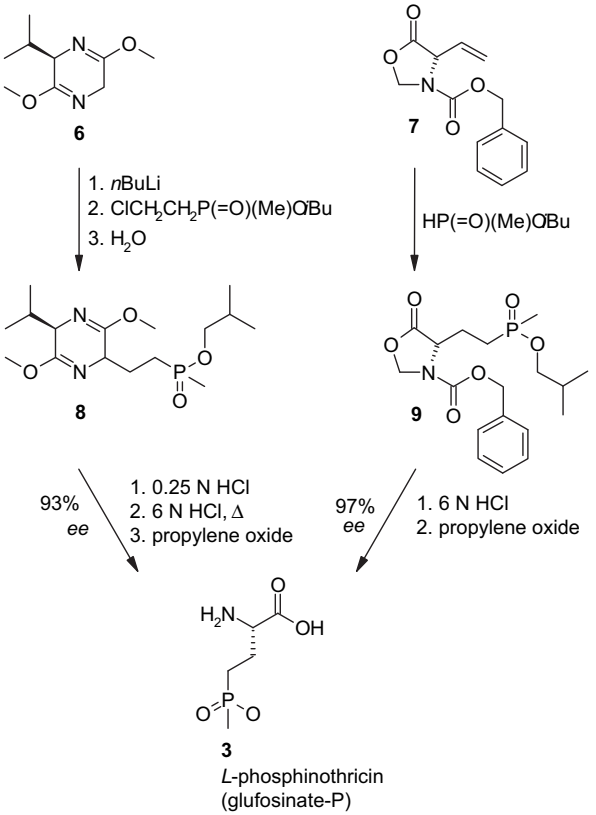


Figure 1. Phosphorus-containg amino acid herbicides.

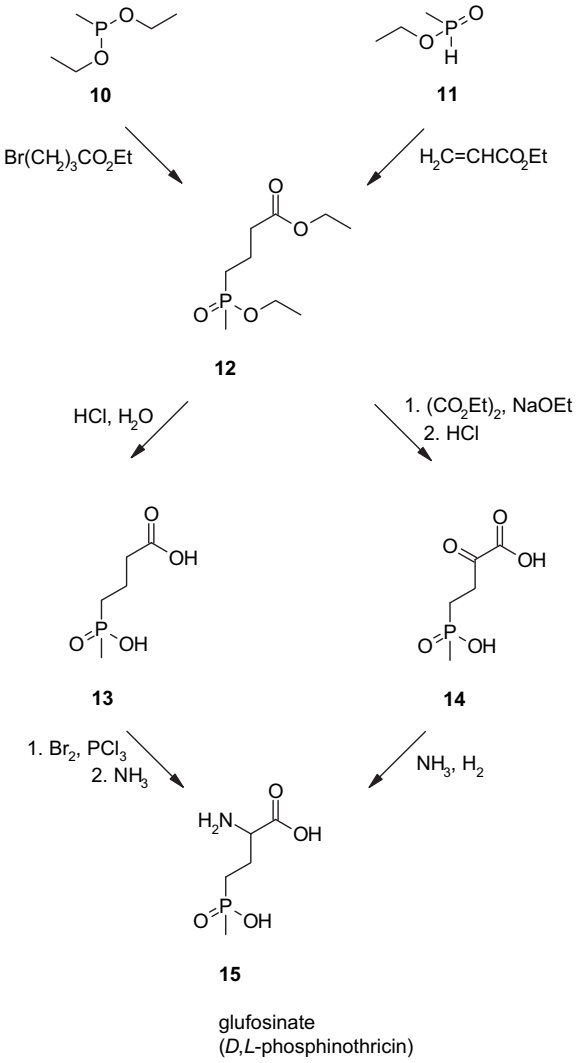


Scheme 1. Stereoselective syntheses of L-phosphinothricin (**3**).

There are several different synthetic routes to glufosinate (**15**), the racemate of L-phosphinothricin.[13,25] One possibility is the Arbuzov reaction of diethyl methylphosphonate (**10**) with ethyl 4-bromobutanoate to form the 4-[ethoxy(methyl)phosphinyl] butanoate **12**. Acidic saponification of both carboxylic and 'phosphonic' ester functions leads to **13**, which can be converted by bromination and amination into glufosinate (**15**).[13,26] An alternative pathway to the central intermediate **12** is the regioselective addition of ethyl methylphosphinate (**11**) to methyl acrylate. Claisen condensation of **12** with diethyl oxalate and subsequent hydrolysis and decarboxylation afford the α-keto acid **14**, which is transformed into glufosinate (**15**) by reductive amination (Scheme 2).[13,25]

2.2. Naturally occurring amino acid herbicides

Besides the tripeptides, bilanaphos and phosalacine, with their N-terminal amino acid, phosphinothricin, other naturally occurring amino acid derivatives also possess herbicidal activity. The dipeptide, L-alanyl-alanine (**16**), can be found in hydrolysed corn gluten meal, a byproduct of corn wetmilling. It shows activity against *Lolium perenne* (perennial ryegrass).[27] Pyridazocidin (**17**) was isolated from a *Streptomyces* sp. strain and is one of the very rare examples of naturally occurring pyridazines.[28] It shows significant post-emergence activity against *Setaria faberi* (giant foxtail). The cyclic tetrapeptide, tentoxin (**18**), is produced by the fungus *Alternaria alternata*.



Scheme 2. Syntheses of glufosinate (**15**).

It induces chlorosis on a variety of soybean and corn weeds, such as *Ipomoea hederacea* (morningglory), *Cassia obtusifolia* (sicklepod) and *Sorghum halepense* (Johnsongrass) without affecting the corresponding crops.[29] The simple glycine derivative, hadacidin (**19**), from *Penicillium purpurrescens*, inhibits purine biosynthesis by blocking the conversion of IMP into AMP at the site of *adenylosuccinate synthetase*. It demonstrates herbicidal activity against *Panicum crus-galli* (Japanese millet) and *Digitaria sanguinalis* (crabgrass).[30] The bis-amino acid *N*-glucoside, ascaulitoxin (**20**), was isolated from the culture filtrate of *Ascochyta caulina*. It causes leaf and stem necrosis of *Chenopodium album* (common lambsquarters) (Fig. 2).[31] Homoalanosine (**21**), isolated from the culture filtrate of *Streptomyces galilaeus*, is highly effective against *Xanthium strumarium* (common cocklebur) and *Polygonum persicaria* (ladysthumb).[32]

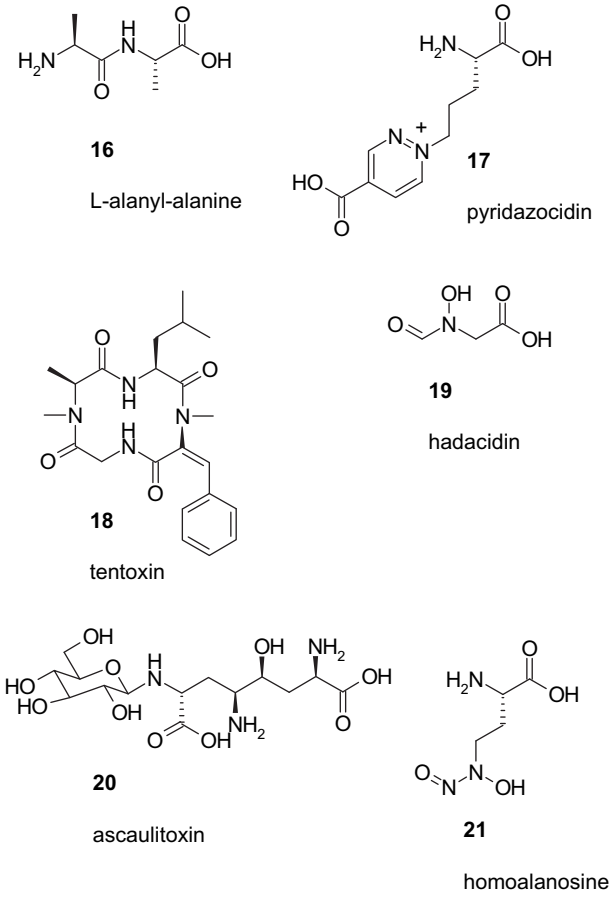


Figure 2. Naturally occurring amino acid herbicides.

2.3. Miscellaneous amino acid herbicides

The acetyl-CoA-carboxylase (ACCase) inhibitors flamprop-M-isopropyl (**22**)[33] and benzoylprop-ethyl (**23**),[34] are used as graminicides against *Avena fatua* (wild oat) in cereals. Their rate of herbicidal activity and selectivity is determined by the ester hydrolysis speed, because the corresponding free carboxylic acids are responsible for the herbicidal efficacy.[33,34] Only the (*R*)-enantiomers of flamprop-M-isopropyl and benzoylprop-ethyl are herbicidally active, and therefore both compounds are applied in the enantiomerically pure form. The auxin herbicide, benazolin (**24**), is used for the post-emergent control of *Galium aparine* (cleavers) and *Stellaria media* (common chickweed).[35] The glycine derivative, diethatyl (**25**), belongs to the herbicide class of chloracetanilides and is used for the pre-emergent control of mono- and dicotyledonous weeds in beet and spinach (Fig. 3).[36]

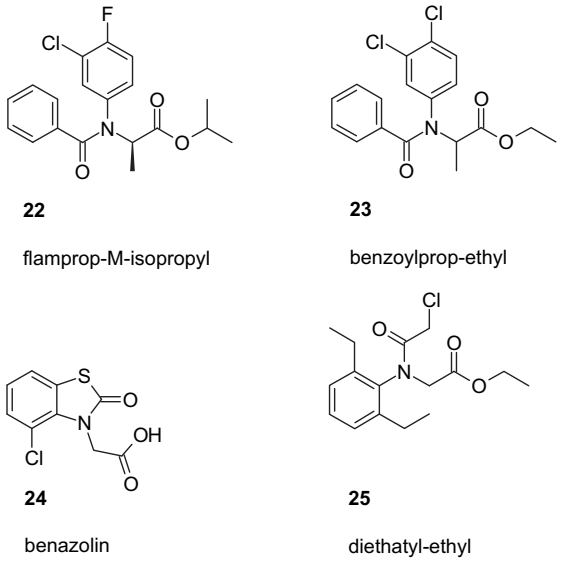


Figure 3. Commercialised amino acid herbicides.

The two glycine derivative **26**[37] and **27**,[38] as well as the two alanine derivatives **28**[39] and **29**,[40] are all potent inhibitors of protoporphyrinogen-IX oxidase (PPO, protox), which is the last enzyme in the porphyrin pathway, that is, common to both chlorophyll and heme synthesis. In treasted tissue, protox inhibitors cause the accumulation of protoporphyrin IX. This tetrapyrrole is known to be a potent photosensitiser, generating high levels of singlet oxygen in the presence of sunlight. This oxygen modification induces peroxidation of unsaturated fatty acids in cell membranes, resulting in membrane leakage, pigment breakdown and, finally, necrosis of the leaf. Therefore, PPO inhibitors are also called peroxidising herbicides.[41] The cyanurates **26** and **27**, as well as the benzotriazole **28**, which all have the nitrogen atom of the amino acid directly incorporated into their heterocycle, show full control of *Abutilon theophrasti* (velvetleaf), *Ambrosia artemisiifolia* (ragweed) and *I. hederacea* (morningglory) at a post-emergent application rate of less than 32 g/ha.[37–39] The isoxazole **29** possesses high pre- and post-emergent activity against *A. theophrasti* (velvetleaf) and *Echinochloa crus-galli* (barnyardgrass).[40] The tripeptide **30** exhibited strong root-growth inhibition in *E. crus-galli* (barnyardgrass).[42] The anomeric ribosyl α-ureidoamide **31** is an open-chain analogue of the herbicidal spironucleoside, hydantocidin. It is active against a broad range of weed species, such as *E. crus-galli* (barnyardgrass), *D. sanguinalis* (crabgrass), *S. halepense* (Johnsongrass), *Solanum nigrum* (black nightshade) and *A. artemisiifolia* (ragweed).[43] The herbicidal sulfonyl carboxamide **32** bears a quarternary amino acid and is a potent inhibitor of *acetolactate synthase* (ALS).[44] Finally, the glycine derivative **33**, a pyridine analogue of benazolin, possesses strong pre- and post-emergent auxin-like efficacy against *I. hederacea* (morningglory) and *S. media* (common chickweed) (Fig. 4).[45]

The auxin herbicide **33** can be prepared in three steps, starting from glycine methyl ester (**34**), which is treated with carbon disulfide and sodium hydroxide to produce the unstable dithiocarbamate **35**. Addition of chloroacetonitrile to the reaction mixture results, via an alkylation/cyclisation sequence, in the formation of the 4-imino-2-thioxo-3-thiazolidine acetate **36**. Subsequent condensation with a β-ethoxyenone delivers, in the presence of catalytic amounts of piperidine, regioselectively the thiazolo[4,5-*b*]pyridine derivative **37**, which is converted by desulfurisation with mercuric trifluoroacetate into the desired azabenazolin derivative **33** (Scheme 3).[45]

A comparison of the post-emergent efficacy of the free benzotriazole **38** and several of its N-substituted derivatives reveals that

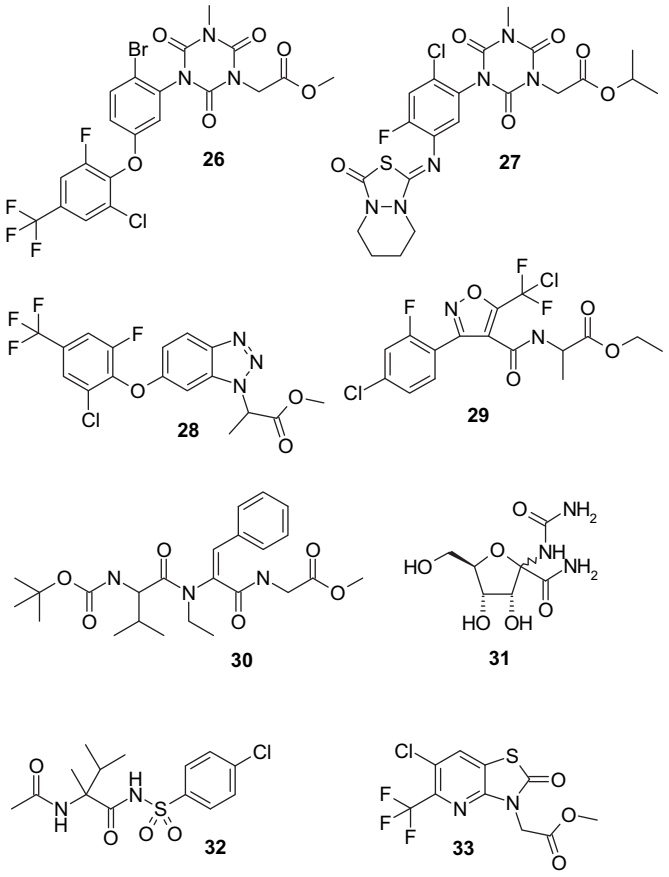
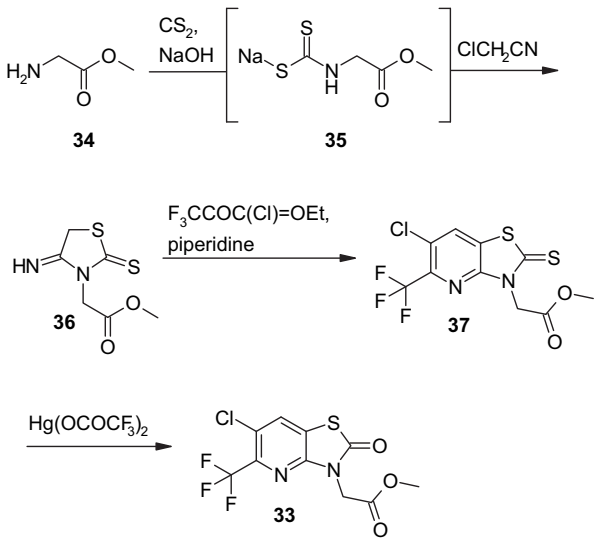


Figure 4. Miscellaneous herbicidally active amino acids.



Scheme 3. Synthesis of **33**.

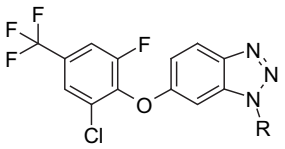
the glycine ester **41** and the alanine ester **28** deliver by far the best herbicidal results. These two PPO inhibitors display broad activity on different mono- and dicotyledonous weed species (Table 1).[39]

3. Fungicidally active amino acid derivatives

3.1. Phenylamide fungicides

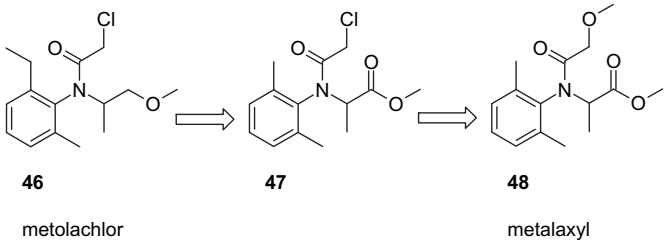
The origin of the phenylamide (also called acylanilide) fungicides is closely linked to the derivatisation of chloroacetanilide herbicides, such as metolachlor (**46**).[9,46] Replacing the alkoxyalkyl substituent in

Table 1
Post-emergent herbicidal activity of some *N*-substituted benzotriazole-based PPO inhibitors against five different mono- and dicotyledonous weed species



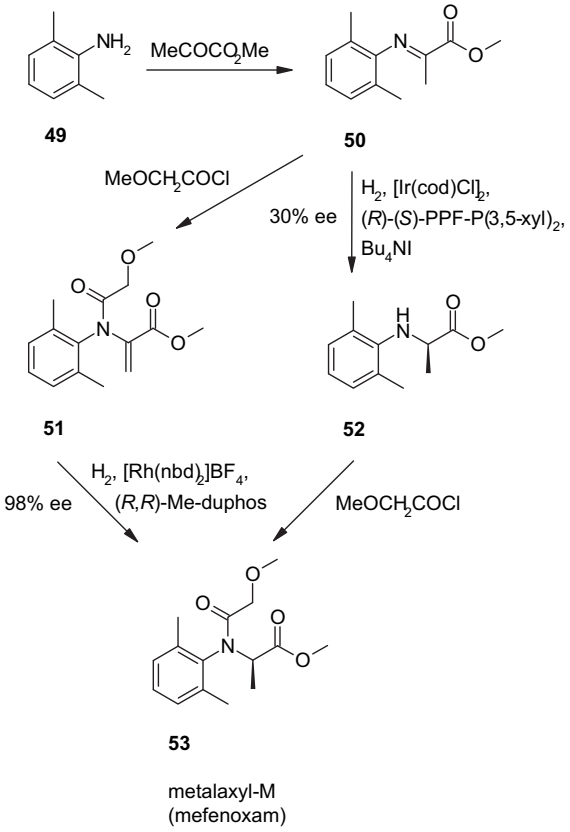
Compound	R	ED_{85} (g/ha)				
		A. theophrasti (velvetleaf)	*Ipomoea purpurea* (morningglory)	*Setaria viridis* (green foxtail)	*E. crus-galli* (barnyardgrass)	*D. sanguinalis* (crabgrass)
38	H	250	<32	>500	>500	250
39	Et	<32	<32	>500	>500	>500
40	$CH_2C{\equiv}CH$	250	<32	63	250	500
41	CH_2CO_2Me	>8	0.5	2	4	>8
42	$CH(Me)CO_2H$	<32	<32	125	63	125
28	$CH(Me)CO_2Me$	1	< 0.5	1	4	8
43	$CH(Me)CONH_2$	<32	<32	<32	125	<32
44	CH(Me)CN	<32	<32	63	125	63
45	$CH_2CH_2CO_2Me$	<32	<32	250	125	<32

metolachlor (**46**) by an ester function led to a prototype compound **47**, which exhibited curative and systemic activity against *Phytophthora infestans* (potato and tomato late blight).[9,46] Biological screening of its enantiomers revealed that the (*R*)-enantiomer is an excellent fungicide with low herbicidal activity, whereas its (*S*)-antipode showed high herbicidal, but no fungicidal, activity. Exchange of the chloro substituent of **47** by a methoxy group during an intensive optimisation program produced the fungicidally much more powerful, metalaxyl (**48**).[9,46] In this case, the (*R*)-enantiomer has up to 10-fold the fungicidal efficacy of (*S*)-metalaxyl, depending on the pathogens tested.[9] Because racemic metalaxyl (**48**) shows no phytotoxic effects, separation of the enantiomers was not necessary and the compound was developed first as a racemate.[9] Today, the fungicidally active, (*R*)-metalaxyl, has been also introduced into the market under the common names metalaxyl-M and mefenoxam.[47] Metalaxyl (**48**) and other related phenylamides are highly active against such devastating Oomycetes diseases, such as *P. infestans* (potato and tomato late blight), *Plasmopara viticola* (grape downy mildew) and *Pythium ultimum* (damping-off). The major mode of action of this important fungicidal class is the inhibition of fungal protein synthesis by interference with rRNA (ribosomal RNA) biosynthesis (Scheme 4).[47,48]



Scheme 4. Invention pathway to metalaxyl (**48**).

Two different stereoselective syntheses of metalaxyl-M (**53**) have been extensively studied, which both employ an enantioselective hydrogenation as the key step. They both start with the transformation of 2,6-dimethylaniline (**49**) with methyl pyruvate into the imine **50**. One possibility is now to convert this Schiff base with methoxyacetyl chloride into the enamide **51**. The enantioselective hydrogenation of the C–C double bond in **51** with a rhodium catalyst and a chiral phosphine ligand delivers metalaxyl-M (**53**) in high enantiomeric excess and excellent turnover number. On the other side, the asymmetric hydrogenation of the C–N double bond of the imine **50** to the (*R*)-alanine derivative **52** was not very successful. Only insufficient enantiomeric purities <30% could be achieved with an iridium catalyst as the best system (Scheme 5).[49]



Scheme 5. Synthesis of metalaxyl-M (mefenoxam, **53**) via enantioselective hydrogenation.

Besides metalaxyl (**48**) and its (*R*)-enatiomer, metalaxyl-M (**53**), some other phenylamide fungicides with amino-acid moieties have also reached the market. Benalaxyl (**54**),[50] furalaxyl (**55**)[51] and ofurace (**56**)[52] have a similar spectrum of activity as metalaxyl (**48**), furalaxyl being developed especially for the control of Oomycetes species on ornamentals. The replacement of the ester side chain, which is typical for phenylamide fungicides, by a lactone ring resulted in the experimental fungicide, clozylacon (**57**), having improved metabolic stability against microbial degradation and making it well suited for soil application against Oomycetes diseases.[53] The metalaxyl analogue **58**, in which one of the *ortho*-methyl groups has been exchanged by thiomethyl, exists as two

separable rotationally hindered isomers. These atropisomers behave completely different regarding their fungicidal activity against *P. infestans* (potato and tomato late blight) and *P. viticola* (grape downy mildew) (Fig. 5).[54]

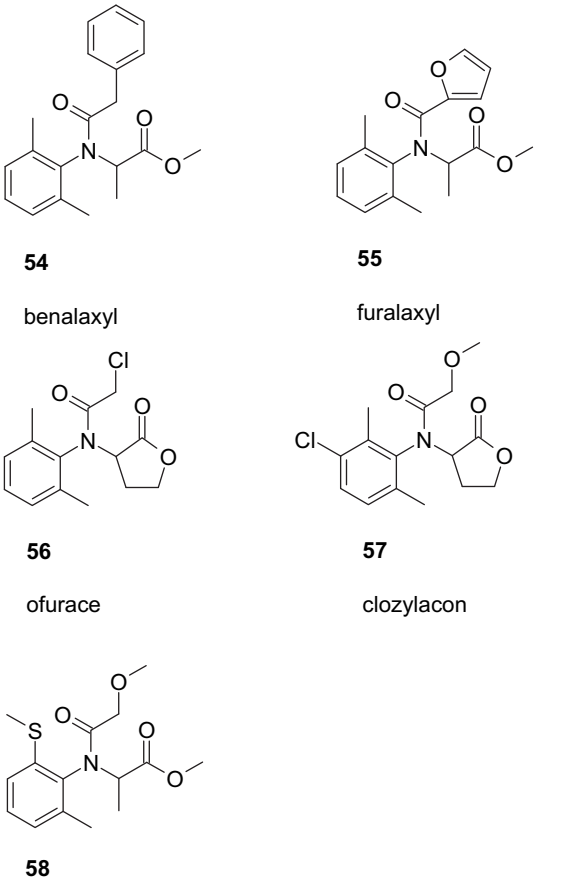


Figure 5. Phenylamide fungicides with amino-acid moieties.

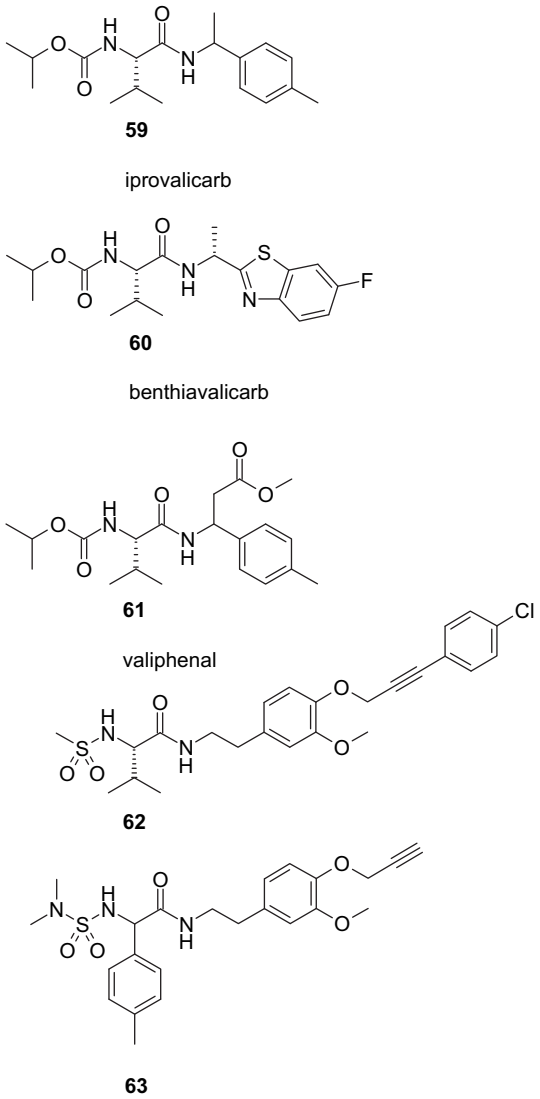


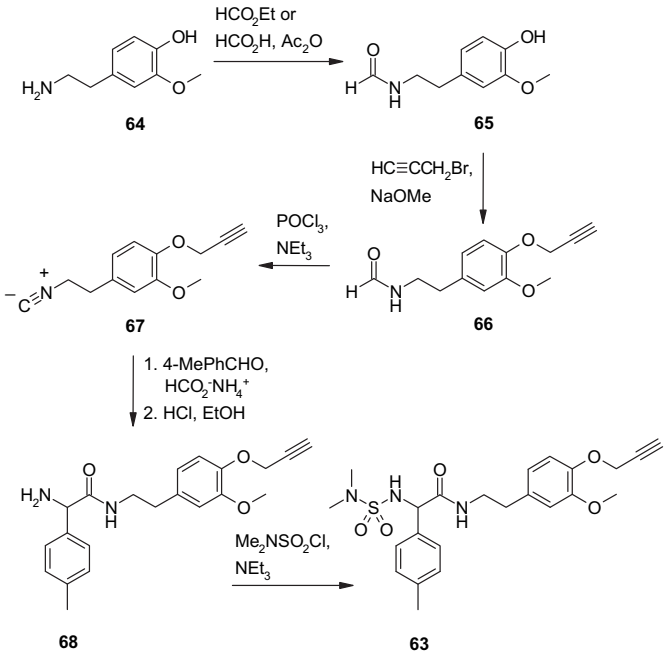
Figure 6. Valinamide and phenylglycinamide CAA fungicides.

3.2. Carboxylic acid amide (CAA) fungicides

The carboxylic acid amides (CAAs) are another class of fungicides, which are specialised on Oomycetes pathogens. They consist of special valinamides, mandelamides and cinnamic acid amides, which share the same, so far not completely elucidated, mode of action.[55] The valinamides, iprovalicarb (**59**)[55,56] and benthiavalicarb (**60**),[55,57] are already on the market, while valiphenal (**61**)[55] is currently in development. The carbamate moiety of these *N*-carbamoyl valinamides can be replaced by a sulfonamide function, with full preservation of their biological activity. However, in this case, the typical α-alkylbenzylamine moiety has to be replaced by a special dialkoxy-substituted phenethylamine. The resulting valinamide **62**,[55,58,59] as well as the related phenylglycinamide **63**,[55,58,59] are, like the three marketed fungicides **59**, **60** and **61**, highly active against *P. infestans* (potato and tomato late blight) and *P. viticola* (grape downy mildew) (Fig. 6).

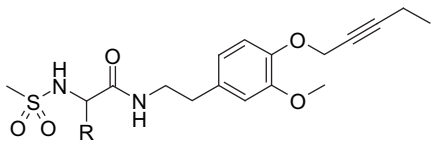
The Ugi four-component condensation offered a concise and flexible approach to phenylglycinamide fungicides such as **63**. 3-*O*-Methyldopamine (**64**), available in only two steps from vanilline,[55,59] is converted into the stable and odourless isocyanide **67** by standard N-formylation, O-propargylation and dehydration. Hereby, the formyl group serves as protecting group for the amine function during the alkylation of the phenol and also as precursor for the formation of the isocyanide function. The Ugi reaction of the isocyanide **67** with *p*-tolualdehyde and ammonium formate, which is both the acid and the amine component, leads to an *N*-formylphenylglycinamide, which can be transformed into the phenylglycinamide **68** with a free amino group by acidic hydrolysis. Finally, N-sulfonylation of **68** yielded the desired *N*-sulfonylphenylglycinamide **63** (Scheme 6).[58,59]

Table 2 shows the influence of the amino-acid chain on the fungicidal activity of such *N*-sulfonylated carboxylic acid amide fungicides. It seems that the amino acid needs a lipophilic backbone for the best fungicidal activity. The application of polar proteogenic amino acids such as threonine (**77**) and glutamic acid (**78**) does not lead to sufficient fungicidal activity. Several naturally occurring amino acids without polar groups, such as glycine (**69**), alanine (**70**) and methionine (**79**), did not achieve fungicidal efficacy either. Examples of suitable amino acids are valine (**73**) and isoleucine (**74**), but structurally related non-proteogenic amino acids like allylglycine (**71**) are also tolerated. The configuration of the chiral α-carbon atom is also important. The naturally occurring L-form (*S*-enantiomer) shows, in most cases, higher activities than the D-antipode.[59]



Scheme 6. Synthesis of **63** by Ugi four-component condensation.

Table 2
Fungicidal activity of different *N*-sulfonylated amino acid amides against *P. infestans* and *P. viticola*



Compound	R	Configuration	EC_{80} (mg/l)	
			P. infestans (tomato late blight)	*P. viticola* (grape downy mildew)
69	H	—	148	>200
70	Me	(*S*)	>200	>200
71	$CH_2CH{=}CH_2$	(*R,S*)	9	49
72	Pr	(*S*)	60	20
73	*i*-Pr	(*S*)	8	2
74	*s*-Bu	(*S*)	3	2
75	*i*-Bu	(*S*)	12	18
76	$CH(CH_2Me)_2$	(*R,S*)	16	16
77	CH(OH)Me	(*S*)	148	109
78	$CH_2CH_2CO_2H$	(*S*)	>200	>200
79	CH_2CH_2SMe	(*S*)	>200	>200
80	4-Cl–Ph	(*R,S*)	20	15

3.3. Strobilurin fungicides

The strobilurins are an important class of agrochemical fungicides, the discovery of which was inspired by a group of naturally occurring fungicidal derivatives of β-methoxyacrylic acid, e.g., strobilurin A (**81**) and oudemansin A (**82**).[60] The fungicidal efficacy of the strobilurins results from their ability to inhibit mitochondrial respiration by binding to the Qo site of cytochrome *b*. Cytochrome *b* is part of the cytochrome bc_1 complex (complex III), located in the inner mitochondrial membrane of fungi and other eukaryotes. When a strobilurin binds, it blocks the elctron transfer between cytochrome *b* and cytochrome c_1, which, in turn, disrupts the energy cycle within the fungus by stopping the production of ATP (Fig. 7).[60]

The amino acid derivatives **83** and **84**, simplified amide analogues of strobilurin A (**81**) and oudemansin A (**82**), showed good activity against a range of plant pathogenic fungi in greenhouse tests.[61] Pyrroles with an N-linked β-methoxyacrylate toxophore, such as the benzoate **85**, have also been very active in field trials against several different phytopathogens, especially against *Magnaporthe grisea* (rice blast).[62]

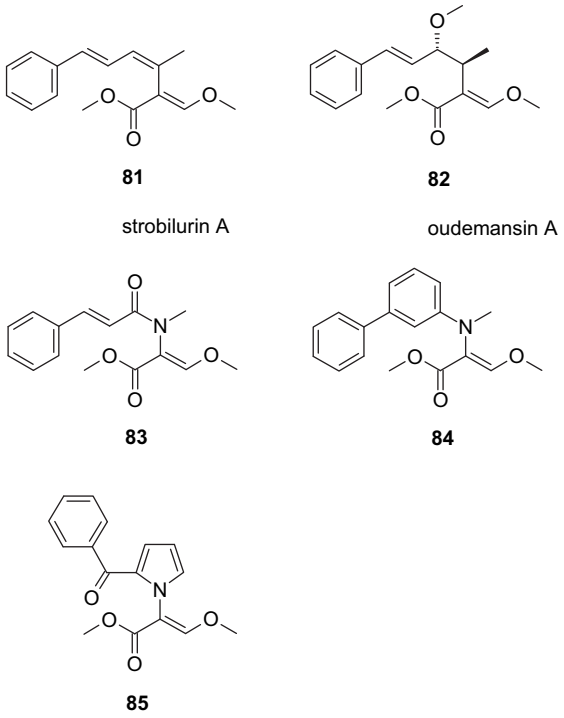


Figure 7. Strobilurin fungicides with amino-acid moieties.

3.4. Naturally occurring amino acid fungicides

Several naturally occurring amino acid derivatives possess fungicidal properties. Acivicin (**86**) and albizzin (**87**) both block *glutamine amidotransferases*.[63] Acivicin (**86**) was isolated from the fermentation broths of *Streptomyces sviceus* and is active against *P. infestans* (potato and tomato late blight), *Uncinula necator* (grape powdery mildew) and *Venturia inaequalis* (apple scab). Albizzin (**87**) is found in the seeds of Albizzia julibrissin and controls *P. infestans* (potato and tomato late blight) and *Mycosphaerella graminicola* (wheat leaf blotch).[63] Crocacin D (**88**)[64] and antimycin A_1 (**89**)[65] are both inhibitors of cytochrome bc_1 (mitochondrial complex III; see also Section 3.3). Crocacin D (**88**) is produced by the myxobacterium *Chondromyces crocatus* and is highly active against *P. viticola* (grape downy mildew), *P. infestans* (potato and tomato late blight), *Puccinia recondita* (wheat brown rust) and *M. graminicola* (wheat leaf blotch).[64] Antimycin A_1 (**89**) binds potently to the Q_i site of cytochrome bc_1 and has been efficiently used as an experimental fungicide against Magnaporthe grisea (rice blast).[65] Some dipeptide antibiotics also show fungicidal efficacy. Nitropeptin (**90**) is produced by *Streptomyces xanthochromogenus* and controls *M. grisea* (rice blast).[66] Rhizocticin A (**91**) has been isolated from *Bacillus subtilis ATCC 6633* and showed in field trials efficient control of *Botryotinia fuckeliana* (grape grey mould) (Fig. 8).[67]

Several nucleoside- or carbohydrate-based natural products with fungicidal efficacy are known.[68] The polyoxins are an important class of peptidyl nucleosides, which were isolated as metabolites of *Streptomyces cacaoi* var. *asoensis*.[69,70] They interfere with fungal cell wall synthesis by specifically blocking *chitin synthetase*, the enzyme, which facilitates the polymerisation of *N*-acetylglucosamine (GlcNAc) to chitin through the activated precursor, UDP-*N*-acetylglucosamine (UDP-GlcNAc), which is structurally related to the polyoxins.[71] The linear macromolecule, chitin, is an essential structural component for

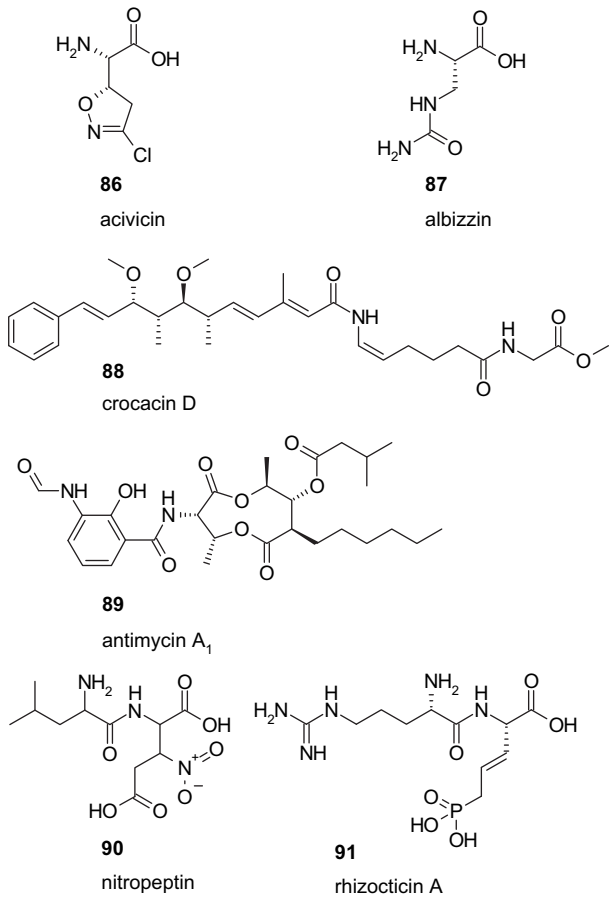


Figure 8. Naturally occurring amino acid fungicides.

growth in most fungi, being responsible for the shape and rigidity of the cell walls. Both polyoxin B (**92**) and polyoxin D (**93**) are commercially produced via fermentation. Polyoxin B (**92**) found ample application against a number of different fungal pathogens in ornamentals, vegetables and fruits, e.g., *Alternaria kikuchiana* (pear black spot), while polyoxin D (**93**) is marketed as the Zn salt mainly for the control of *Rhizoctonia solani* (rice sheath blight).[72,73] Polyoxin L (**94**) is also highly active against *Alternaria mali* (apple cork spot).[72] With neopolyoxin A (**95**; also called nikkomycin X) and neopolyoxin B (**96**), two members of the polyoxin family have also been isolated with five-membered imidazolinone nucelobases. Neopolyoxin A shows excellent fungicidal activity against *M. grisea* (rice blast), *B. fuckeliana* (grey mould) and *Cochliobolus miyabeanus* (brown spot).[74] Sinefungin (**97**) was isolated from a strain of *Streptomyces griseolus* (NRRL 3739) and is active against foliar diseases like *Erysiphe polygoni* (pea powdery mildew) and *Uromyces phaseoli* (bean rust).[75] This unusual *α*-amino acid is a competitive inhibitor of different methyltransferases, blocking for instance, transmethylation reactions of RNA and proteins.[76] The protein biosynthesis inhibitor, puromycin (**98**), is effective against various growth stages of *Blumeria graminis* (barley powdery mildew) (Fig. 9).[77]

In addition to all of these peptidyl furanoses, there are also fungicides known in which the amino acid chain is linked to a pyranose sugar. Mildiomycin (**99**) was isolated from *Streptoverticillium rimofaciens*[78] and inhibits—like puromycin (**98**)—fungal protein biosynthesis.[79] It combines a strong activity against powdery mildew diseases of several different crops with a remarkably low mammalian and fish toxicity.[80] Another protein biosynthesis inhibitor with a similar excellent safety profile is kasugamycin (**100**), which is produced by *Streptomyces kasugaensis*.[81] This interesting iminoacetic acid derivative is produced via a fermentation process and used as a potent systemic agent against *M. grisea* (rice blast).[72,82] Finally, prumycin (**101**), isolated from the culture broth of a *Streptomyces* species,[83] and, even more, its 3-deoxy derivative (**102**),[84] possess strong activity against *Botrytis cinerea* (grey mould), *Sclerotinia sclerotiorum* (bean white mould) and *Colletotrichum lagenarium* (cucumber anthracnose) (Fig. 10).

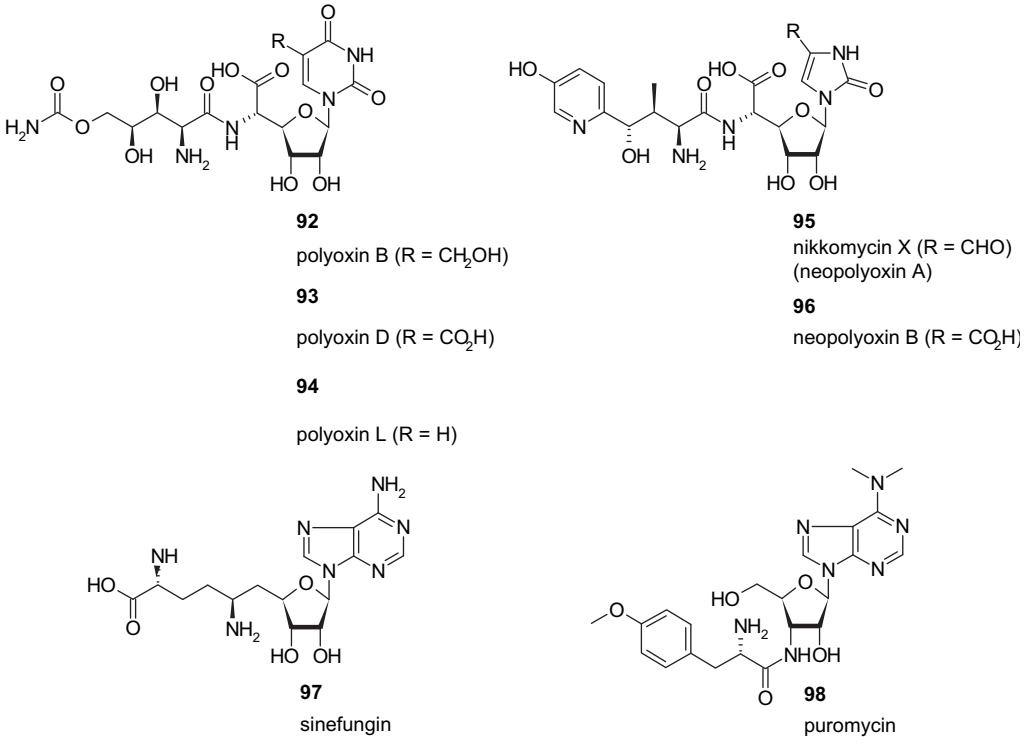


Figure 9. Naturally occurring amino acid fungicides.

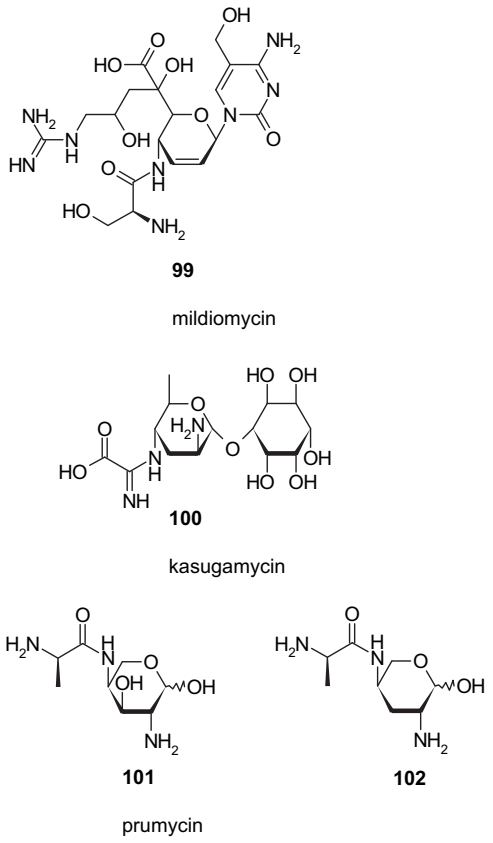


Figure 10. Naturally occurring amino acid fungicides.

3.5. Miscellaneous amino acid fungicides

The seed treatment fungicide, pefurazoate (**103**), an inhibitor of *C*14 *demethylase* in the fungal sterol biosynthesis pathway, exhibits effective control of all major seed-borne rice pathogens, including *Fusarium moniliforme* (bakanae disease) *C. miyabeanus* (brown spot) and *M. grisea* (rice blast).[85] Studies on the fungicidal activity of the two enantiomers of pefurazoate (**103**) revealed that the *S*-enantiomer exhibits a much higher activity against *F. moniliforme* (bakanae disease) than the *R*-enantiomer.[86] Eflornithine (**104**) controls a broad range of plant pathogens, such as *B. graminis* (wheat powdery mildew), *Neovossia indica* (karnal bunt of wheat) and *U. phaseoli* (bean rust).[87] It inhibits polyamine biosynthesis by blocking *ornithine decarboxylase* and is taken up and translocated by plants without any signs of phytotoxicity. The plant-growth regulator, aviglycine (**105**) efficiently inhibits fungal growth of *Fusarium oxysporum* (tomato foot and root rot) and *S. sclerotiorum* (bean white mould).[88] KC10017 (**106**) inhibits *Scytalone dehydratase* in the melanin biosynthesis pathway of *M. grisea* (rice blast) and therefore efficiently controls this phytopathogen.[89] The oxadiazole-based diglycine dipeptides **107**[90] and **108**[91] are both active against *F. oxysporum* (tomato foot and root rot) (Fig. 11).

A short synthesis of pefurazoate (**103**) (Scheme 7) starts with the transesterification of methyl 2-bromobutyrate (**109**) with 4-pentenyl alcohol to the unsaturated ester **110**. Its bromine atom is then substituted by furfurylamine. Finally, imidazoylcarbonylation of the resulting ethylglycine derivative **111** with imidazole and diphosgene delivers pefurazoate (**103**).[85]

The methionine sulfone **112** is highly active against Oomycetes diseases, *P. viticola* (grape downy mildew) and *Peronospora parasitica* (rape downy mildew).[92] The aspartic acid derivative **113**[93] and the *N*-cinnamoyl valine ester **114**[94] both efficiently prevent the

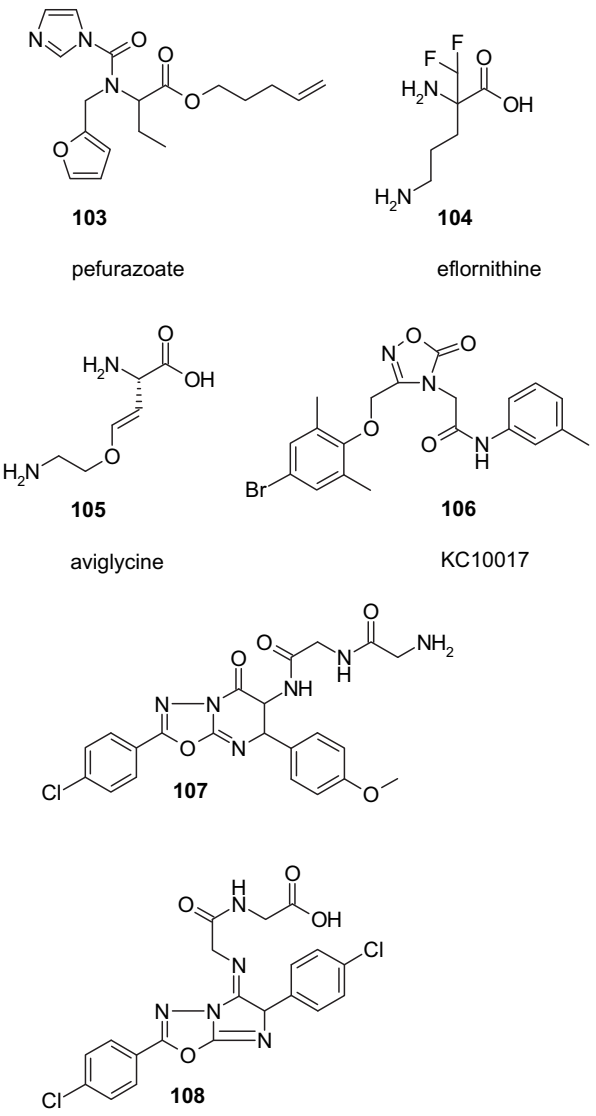
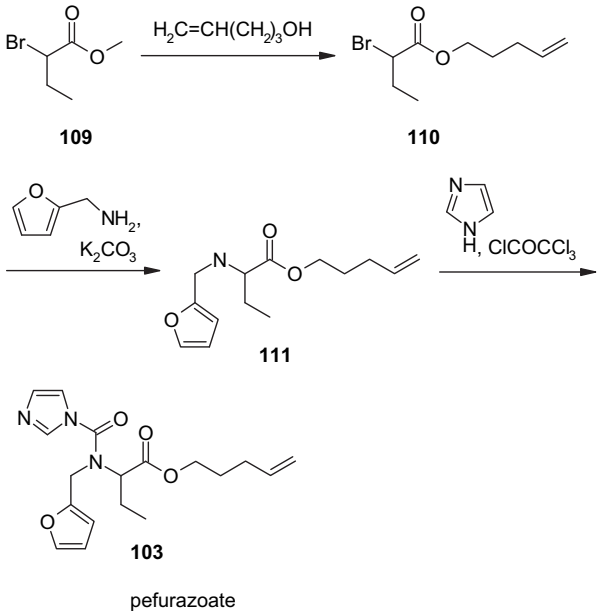


Figure 11. Miscellaneous fungicidally active amino acids.



Scheme 7. Synthesis of pefurazoate (**103**).

growth of different *Pythium* species (damping-off). Finally, the cyclic amino acid derivative **115** is highly active against *M. grisea* (rice blast),[95] whereas the *N*-triazolyl glycine ester **116** shows good control of *B. graminis* (wheat powdery mildew).[96] The valine ester **117** disrupts the dynamics of microtubuli by promoting tubulin polymerisation. It is very active against the wheat diseases *P. recondita* (brown rust) and *M. graminicola* (leaf blotch) (Fig. 12).[97]

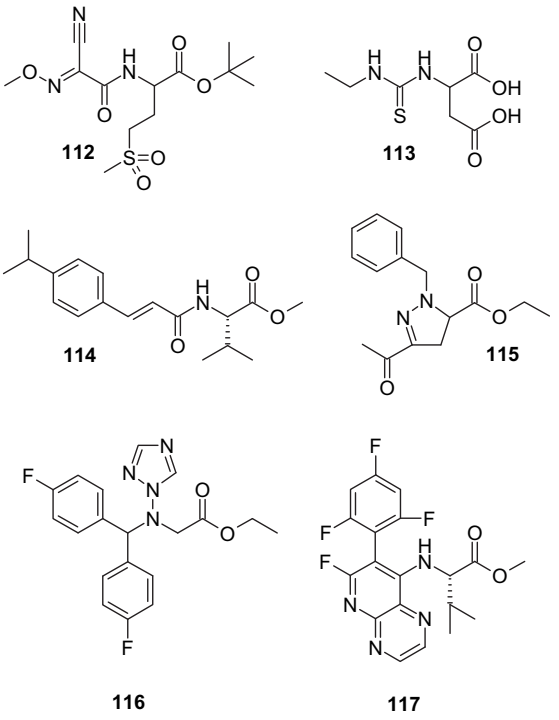


Figure 12. Miscellaneous fungicidally active amino acids.

4. Insecticidally and acaricidally active amino acid derivatives

4.1. Naturally occurring amino acid insecticides and acaricides

The fact, that chitin, which has been discussed already in Section 3.4 as a structural component of fungal cell walls, forms also the exoskeleton of invertebrates, but does not exist in green plants or vertebrates, makes *chitin synthetase*, the enzyme responsible for the chitin bioproduction, an ideal target for crop protection. As a result, inhibitors of this enzyme exhibit marked activity against phytopathogenic fungi and insects, but they are not toxic to bacteria, plants or animals. Structurally related to the already-mentioned polyoxins, the nikkomycins are another family of *chitin synthetase* inhibitors, which have been isolated as metabolites of *Streptomyces tendae*.[70a,98–100] Their mode of action was confirmed by studies on *chitin synthetase* isolated from insects.[101] In contrast to the related polyoxins (Section 3.4), almost all of which bear six-membered uracil-based nucleobases, in the field of nikkomycins a five-membered formyl-substituted imidazolinone nucleobase is also of importance, the biosynthetic source of which is L-histidine.[102] Most of the nikkomycins display, besides fungicidal activity, potent insecticidal and acaricidal efficacy. A mixture of nikkomycins X (**95**) and Z (**118**) was once considered for commercial use against *Tetranychus urticae* (two-spotted spider mite).[103] The two peptidyl nucleosides, aspiculamycin (**119**) and bagougeramine A (**120**), which bear both cytosine as nucleobase and a glucopyranosyl sugar moiety, display excellent acaricidal activity against *T. urticae* (two-spotted spider mite).[104,105] Aspiculamycin (**119**) was isolated from the fermentaion broth of *Streptomyces toyocaensis* var. *aspiculamyceticus*,[104] whereas bagougeramine A (**120**) is produced by *Bacillus circulans*.[105] Finally, rodaplutin (**121**) was isolated from *Nocardioides albus* strains and is active against a broad range of insects and mites, e.g., *Phaedon cochlearia* (mustard beetle), *Plutella maculipennis* (diamondback moth), *Myzus persicae* (peach-potato aphid), *Dysdercus intermedius* (cotton stainer) and *T. urticae* (two-spotted spider mite) (Fig. 13).[106]

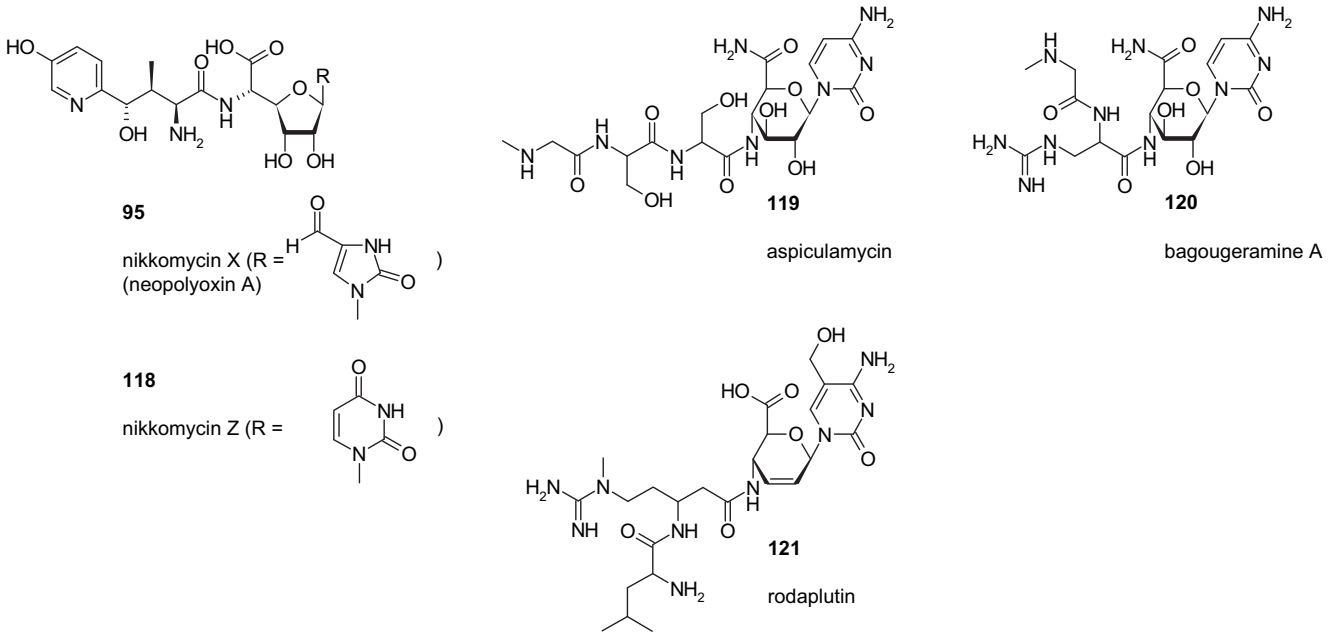
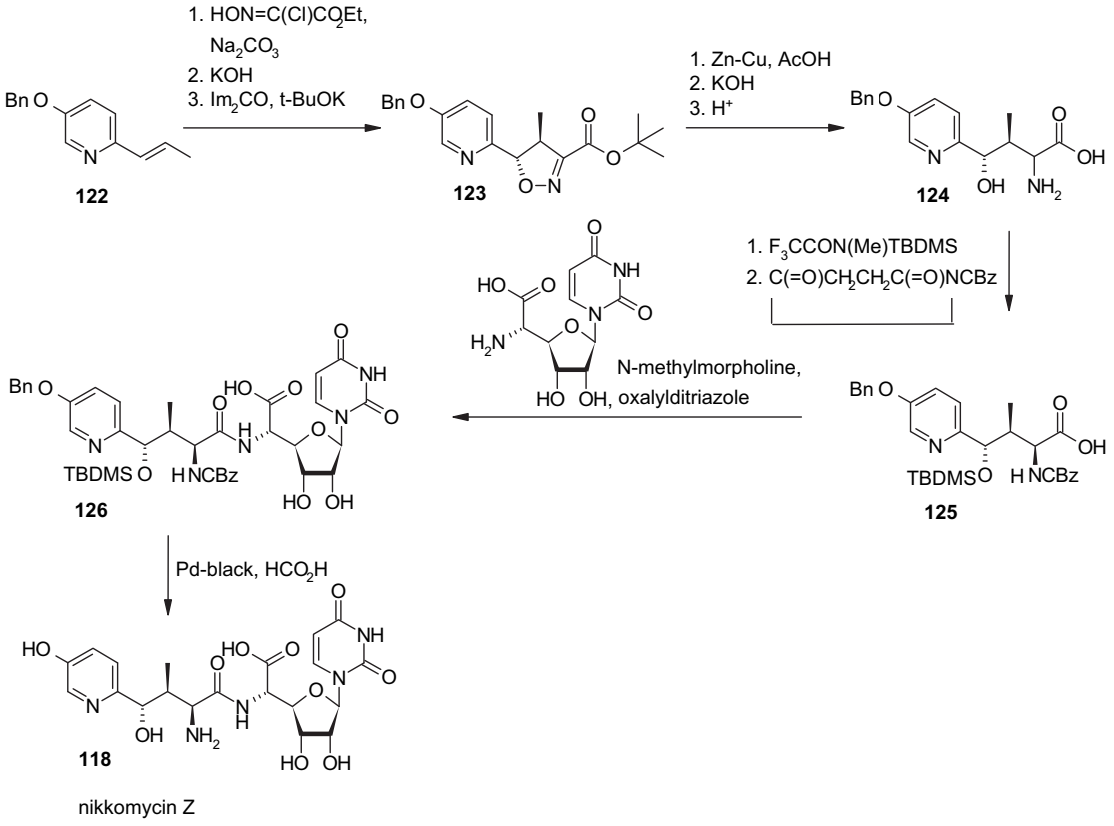


Figure 13. Naturally occurring amino acid insecticides.

The synthesis of nikkomycin Z (**118**) (Scheme 8) was accomplished, starting from 5-benzyloxy-2-propenylpyridine (**122**).[107] This simple *trans*-olefin gave in a 3+2-cycloaddition with in situ-prepared carbethoxy nitrile oxide and subsequent transesterification stereoselectively the isoxazoline **123**, which could be reduced and saponified to the α-amino-γ-hydroxy acid **124**. The subsequent protection of the amino and hydroxy functions is followed by amidation with polyoxin C, using oxalylditriazole as a unique activating reagent. Finally, the one-pot removal of the three different protecting groups of the resulting **126** leads to nikkomycin Z (**118**).[107]

Homoalanosine (**21**), which is produced by *S. galilaeus* and which was discussed already with its herbicidal properties in Section 2.2, efficiently inhibits the reproduction of *Musca domestica* (house fly).[108] The phenylalanine derivative, ochratoxin A (**127**), isolated from *Penicillium verrucosum*, is highly active against *Spodoptera frugiperda* (fall armyworm) and *Helicoverpa zea* (corn earworm).[109] Philanthotoxin 433 (**128**) is a neurotoxic constituent of the paralytic venom of *Philanthus triangulum* (digger wasp).[110] It inhibits the glutamate receptor of insect muscles, leading to muscle paralysis. The valine derivative, mellamide (**129**), from Aspergillus melleus, shows good insecticidal activity against larvae of *Lucilia*



Scheme 8. Synthesis of nikkomycin Z (**118**).

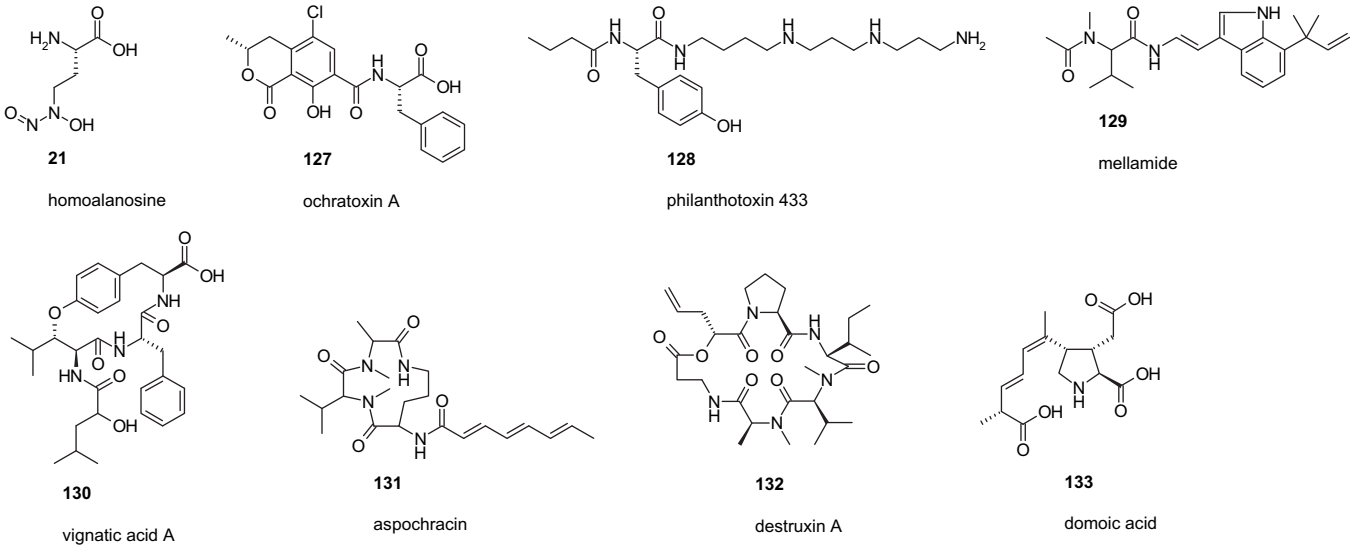
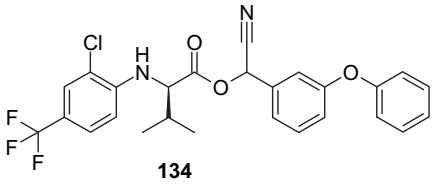


Figure 14. Naturally occurring amino acid insecticides.

sericata (sheep blowfly) and *Aedes aegypti* (yellow fever mosquito).[111] The cyclopeptide alkaloid, vignatic acid A (**130**), is found in *Vigna radiata* var. *sublobata* (wild mung bean) and protects it from *Callosobruchus chinensis* (azuki bean weevil).[112] The cyclotripeptide, aspochracin (**131**), isolated from the culture filtrate of Aspergillus ochraceus, displays strong activity against *Hyphantria cunea* (fall webworm),[113] whereas the cyclodepsipeptide, destruxin A (**132**) from the culture filtrate of *Metarhizium anisopliae*, controls *Heliothis virescens* (tobacco budworm) and *Spodoptera litura* (common cutworm).[114] Finally, domoic acid (**133**), a member of the kainoid amino acid family, which is produced by the red algae, *Chondria armata*, shows strong insecticidal efficacy when injected subcutaneously into the abdomens of *Periplaneta americana* (American cockroach) (Fig. 14).[115]

4.2. Miscellaneous amino acid insecticides and acaricides

The synthetic pyrethroid τ-fluvalinate (**134**), is a potent insecticide and acaricide used against a broad spectrum of different pests in fruits, vegetables and cotton.[116] It acts on the central nervous system of the insects and mites by blocking their voltage-dependent sodium channel. Since τ-fluvalinate (**134**) is virtually nontoxic to honeybees, it is one of the rare agents, which can be used to control the parasitic bee mite, *Varroa jacobsoni* (Varroa mite).[116] The isoleucyl-alanyl-*p*-aminobenzoic acid ethyl ester tripeptide **135** shows potent juvenile hormone activity against *Pyrrhocoris apterus* (red firebug) and *Dysdercus cingulatus* (red cotton bug).[117] Finally, the triglycine derivative **136** was found to possess insecticidal activity against *Heliothis virescens* (tobacco budworm) by injection (Fig. 15).[118]



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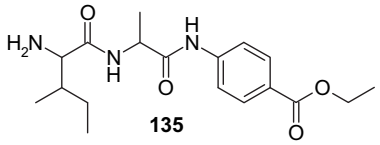
τ-fluvalinate



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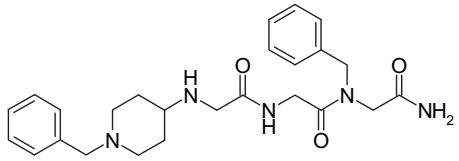

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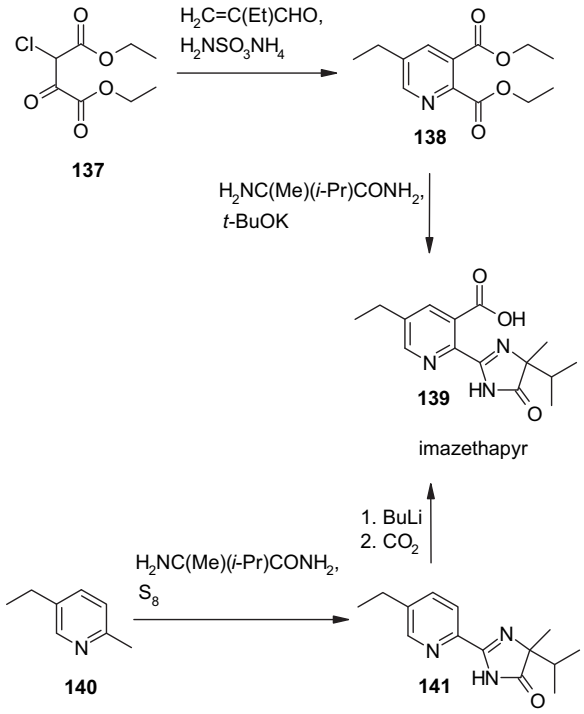
Figure 15. Miscellaneous insecticidally active amino acids.

5. Amino acids as starting materials or intermediates in the preparation of agrochemicals

5.1. Amino acid building blocks in herbicide synthesis

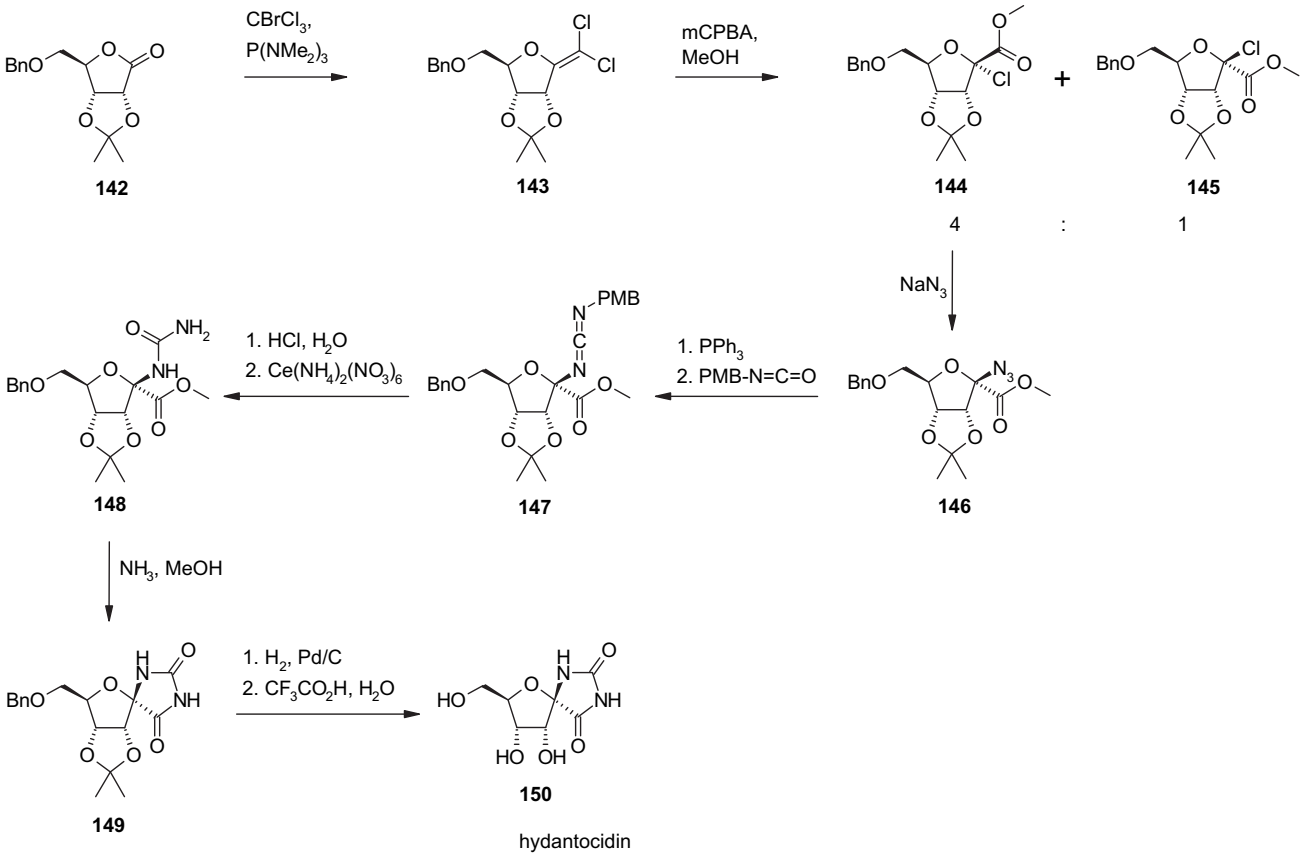
Imazethapyr (**139**) from the *acetohydroxyacid synthase* (AHAS/ALS)-inhibiting family of imidazolinones selectively controls a wide variety of broad-leaf weeds and grasses in soybeans and several other crops at low use rates. It can be efficiently prepared in only two steps by condensation of ethyl chlorooxalacetate (**137**) and an enal, in the presence of a buffered ammonia source, to the pyridine diester **138** and its subsequent regioselective transformation into imazethapyr (**139**) with potassium *tert*-butoxide and α-methylvalinamide (Scheme 9). The same amino acid amide is applied in an alternative two-step procedure, where it converts 5-ethyl-2-methylpyridine (**140**) together with an excess of sulfur in a Willgerodt–Kindler reaction directly into the imidazolinone **141**. Due to the *ortho*-directing effect of this five-membered ring, a subsequent metallation/carboxylation sequence leads regioselectively to imazethapyr (**139**).[119]



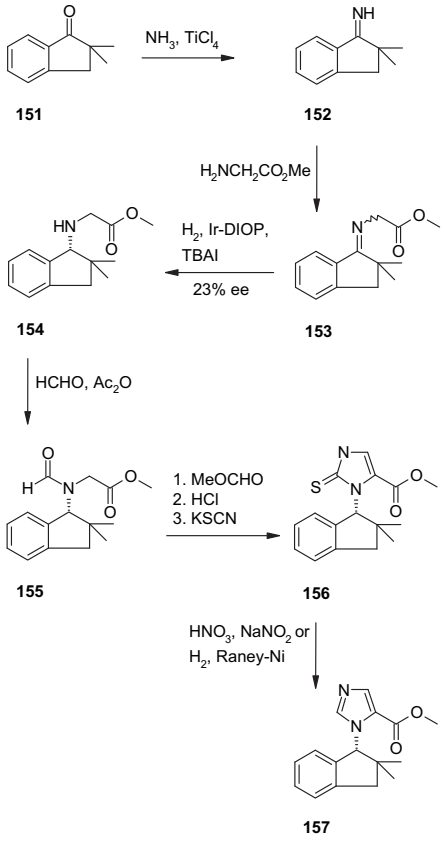
Scheme 9. Synthesis of imazethapyr (**139**).

An amino acid intermediate plays an important role in an elegant pathway to the spironucleoside, hydantocidin (**150**), which was isolated from *S. hygroscopicus* and which is a potent total herbicide against a broad range of annual and perennial weeds by blocking *adenylsuccinate synthetase*. Hereby, hydantocidin is prepared from the protected ribono-1,4-lactone **142**, which is converted into the dichlorovinyl sugar **143**. This *exo*-glycal is then further transformed into a separable 4:1 diastereomeric mixture of the methyl α-chlorourosonates **144** and **145** by treatment with 3-chloroperoxybenzoic acid via epoxide intermediates. Treatment of **144** with NaN_3 gives the azide **146** with inversion of configuration. Its aza-Wittig-type conversion with triphenylphosphine into an unstable phosphine imide and successive treatment with 4-methoxybenzyl isocyanate leads to the carbodiimide **147** as a single product, which is then transformed into the urea **148** by hydration with dilute hydrochloric acid and deprotection with ammonium cerium(IV) nitrate. The urea and carboxylic acid functions of **148** can be cyclised with methanolic ammonia into the hydantoin **149**, which delivers, after removal of the protecting group on the sugar moiety, the total herbicide, hydantocidin **150** (Scheme 10).[120]

The (*R*)-dimethylindanyl imidazole ester **157** is highly active against *D. sanguinalis* (crabgrass) and other weeds by inhibiting obtusifoliol-14-α-methyl demethylase in the plant sterol metabolism. The synthesis of **157** starts from 2,2-dimethylindan-1-one (**151**), which is converted in two steps into the imine **153**. The stereoselective reduction of this Schiff base by homogenous hydrogenation with a chiral iridium catalyst proceeds with modest



Scheme 10. Synthesis of hydantocidin (**150**).



Scheme 11. Synthesis of **157**.

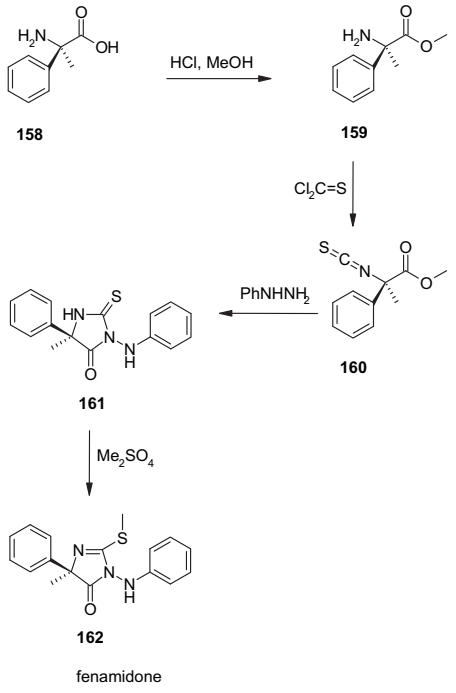
enantiomeric excess. The resulting glycine ester **154** is then formylated and further ringclosed by Jones cyclisation to the imidazole-2-thione **156**. Subsequent desulfurisation leads to the desired imidazole herbicide **157** (Scheme 11).[121]

5.2. Amino acid building blocks in fungicide synthesis

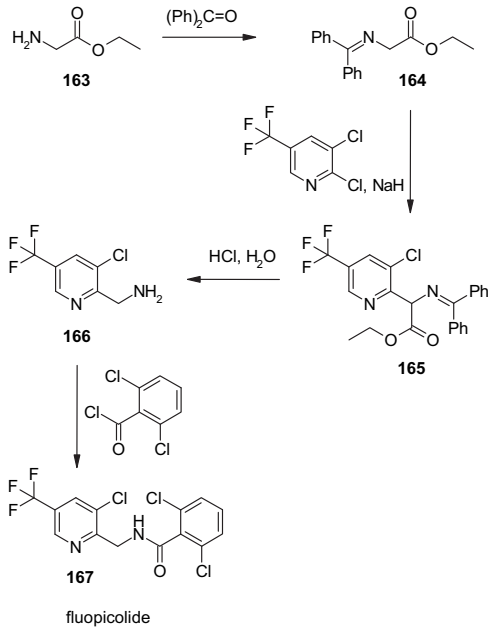
Fenamidone (**162**) is widely used for the control of Oomycetes, such as *P. viticola* (grape downy mildew) and *P. infestans* (potato and tomato late blight). It specifically blocks the Qo site of cytochrome bc_1 (complex III of the mitochondrial respiratory chain) and therefore is crossresistant to the strobilurin fungicides (Section 3.3). Fenamidone is prepared in four steps from (*S*)-methyl phenyl glycine (**158**), which is first converted into the methyl ester **159** and then further transformed with thiophosgene into the isothiocyanate **160**. The addition of phenylhydrazine to the isothiocyanate function of **160** leads to the thiohydantoin **161**, which is methylated to give the imidazolinone, fenamidone (**162**) (Scheme 12).[122]

Fluopicolide (**167**), another modern fungicide, which specialises, like fenamidone (**162**), in the control of Oomycete diseases, is also prepared via amino acid building blocks (Scheme 13). The glycine Schiff base **164**, prepared in one step from glycine ethyl ester (**163**) and benzophenone, can be transformed into the 2-pyridyl amino acid derivative **165** by treatment with 2,3-dichloro-5-trifluoromethylpyridine. Acidic hydrolysis of the imine and ester functionalities and subsequent decarboxylation of the resulting acid affords the 2-pyridylmethylamine **166**, which can be directly converted by amidation with 2,6-dichlorobenzoyl chloride into the fungicide, fluopicolide (**167**).[123]

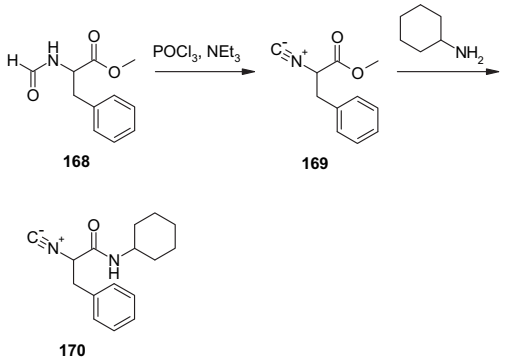
The α-isocyano-β-phenylpropionamide **170** proved to be highly efficient in field trials against *Sphaerotheca fuliginea* (cucumber powdery mildew). It is available in only two steps from *N*-formylphenylalanine methyl ester (**168**) (Scheme 14).[124]



Scheme 12. Synthesis of fenamidone (**162**).



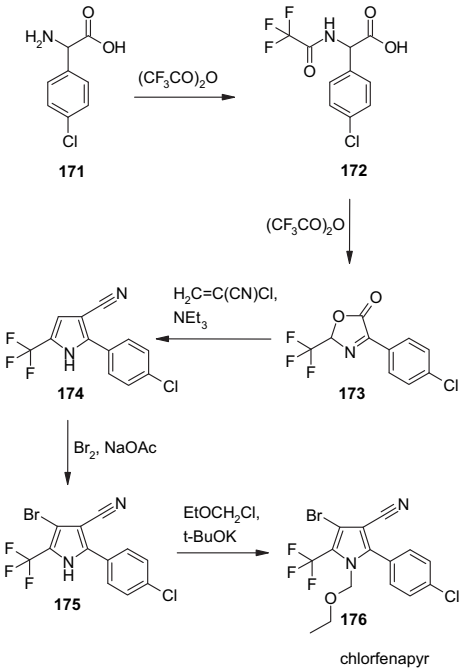
Scheme 13. Synthesis of fluopicolide (**167**).



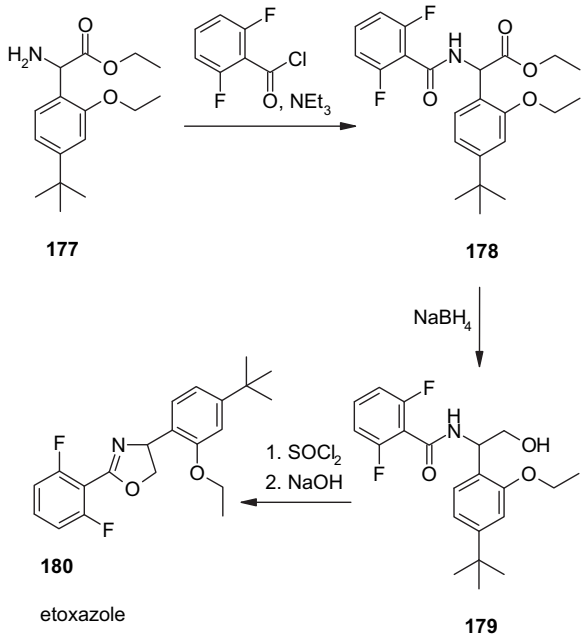
Scheme 14. Synthesis of **170**.

5.3. Amino acid building blocks in insecticide and acaricide synthesis

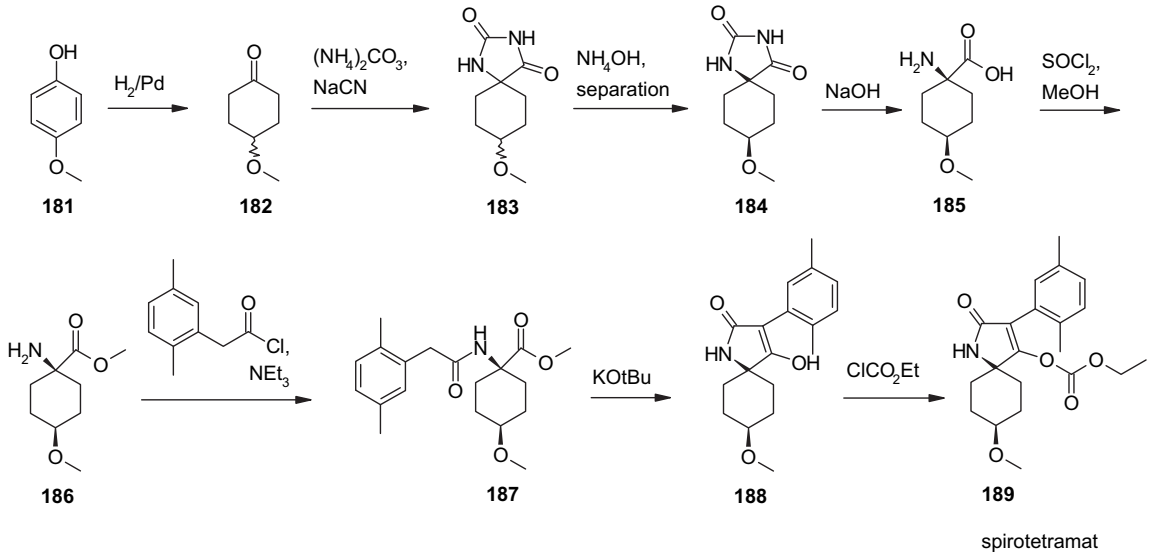
Chlorfenapyr (**176**) is a potent uncoupler of the oxidative phosphorylation and therefore highly active against a broad range of different insects and mites, such *Empoasca abrupta* (Western potato leafhopper) and *T. urticae* (two-spotted spider mite). An efficient synthesis of this persubstituted pyrrole with five different substituents starts from 4-chlorophenylglycine (**171**), which gives after treatment with trifluoroacetic anhydride first its trifluoroacetylated derivative **172** and, then, under dehydration the oxazolinone **173** (Scheme 15). This five-membered heterocycle adds to α-chloroacrylonitrile in a thermal cycloaddition reaction to the trisubstituted pyrrole **174**. Introduction of two further substituents by bromination and N-alkylation leads to the insecticide, chlorfenapyr (**176**).[125]



Scheme 15. Synthesis of chlorfenapyr (**176**).



Scheme 16. Synthesis of etoxazole (**180**).



Scheme 17. Synthesis of spirotetramat (**189**).

Not only chlorfenapyr (**176**), but also another structurally completely different acaricide/insecticide, etoxazole (**180**), can be efficiently prepared from a phenyl glycine derivative. Etoxazole is a chitin biosynthesis inhibitor and shows potent efficacy against juvenile stages of spider mites, such as *Panonychus ulmi* (European red mite) and *T. urticae* (two-spotted spider mite), and aphids, like *M. persicae* (green peach aphid) and *Aphis gossypii* (cotton aphid). An appropriate process for the synthesis of etoxazole (**180**) starts with the acylation of the already mentioned phenyl glycine ester (**177**) with 2,6-difluorobenzoyl chloride and the susbsequent reduction of the ester function of the intermediate amidoester **178**. The resulting amino alcohol **179** is then converted into the oxazoline, etoxazole (**180**), by chlorination and base-catalysed cyclisation (Scheme 16).[126]

The *acetyl-CoA-carboxylase* (ACCase) inhibitor, spirotetramat (**189**), is highly active against different sucking pests, such as aphids, scales, whiteflies and thrips. A key intermediate in the synthesis of spirotetramat (**189**) is *cis*-4-methoxy-1-amino-cyclohexanecarboxylic acid (**185**), which can be obtained in four steps from 4-hydroxyanisole (**181**) applying Bucherer–Bergs methodology. After sequential esterification and amidation of **185**, cyclisation of the resulting amidoester **187** leads to the tetramic acid **188**, from which spirotetramat (**189**) is delivered by acylation (Scheme 17).[127]

6. Conclusions

As seen in this review, many synthetic amino acid derivatives possess powerful efficacy against a broad variety of weeds, insects and fungal diseases. Their structural diversity is impressive as well as the wide range of different modes of action involved. In addition, several naturally occurring amino acid derivatives display interesting herbicidal, fungicidal and insecticidal activity. Furthermore, because of their ubiquitious availability, low complexity and low cost, amino acids are widely applied as starting materials and key intermediates in the synthesis of many agrochemicals.

References and notes

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