HETEROCYCLES, Vol. 102, No. 8, 2021, pp. 1449 - 1477.
Received, 2nd November, 2020, Accepted, 18th December, 2020,
DOI: 10.3987/REV-20-948

IMIDAZOLE CHEMISTRY IN CROP PROTECTION

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Abstract – An overview is given of the significance of the imidazole scaffold in crop protection chemistry. The main herbicidally, fungicidally and insecticidally active imidazole classes are presented, together with their synthesis routes, modes of action and biological efficacies. Also, partially and fully saturated imidazole derivatives, such as imidazolines and imidazolidines, oxygenated derivatives, such as imidazolinones and hydantoins as well as annulated derivatives, such as benzimidazoles, are covered. In addition, also the role of imidazoles as intermediates or reagents in the synthesis of other agrochemicals is reported.

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6. Conclusion

1. INTRODUCTION

During the last decades, intensive efforts have been undertaken to discover highly active agrochemicals for the control of weeds, insects and fungal diseases, which possess at the same time favourable toxicological properties and are safe for the environment. In several instances, imidazole derivatives have been found as promising active ingredients. The imidazoles are an important class of five-membered heterocyclic compounds, in which two ring nitrogen atoms are not directly next to each other. They are chemically related to the other azoles, such as pyrazole, oxazole and thiazole, but can be also seen as five-ring equivalent of the diazine pyrimidine, in which two ring nitrogens are separated by one ring carbon atom as well. The progress in preparative investigation on imidazoles,[1] benzimidazoles,[2] imidazolines[3] and imidazolones[4] has been summarized in review articles. Also, the antibacterial,[5] anticancer,[6] antifungal,[7] anti-inflammatory,[8] antitubercular[9] and antiviral[10] activity of imidazole derivatives has been reviewed recently. The only heterocyclic scaffolds, for which so far extensive reviews exist regarding their significance in crop protection chemistry, are pyrazole,[11] oxazole,[12] isoxazole,[12] thiazole,[13] isothiazole,[13] pyridine,[14] pyridazine[15] and pyrimidine.[16] This review deals with the agrochemical aspects of imidazole as well as its bicyclic derivatives, such as benzimidazoles, partially saturated derivatives, such as imidazolines, fully saturated derivatives, such imidazolidines, and oxygenated derivatives, such as imidazolones and hydantoins.

2. HERBICIDALLY ACTIVE IMIDAZOLE DERIVATIVES

2.1. ACETOHYDROXYACID SYNTHASE INHIBITORS

Acetohydroxyacid synthase (AHAS, also known as acetolactate synthase, ALS) is the first enzyme in the branched-chain amino acid biosynthesis pathway leading to valine, leucine and isoleucine. Since this enzyme is found only in bacteria, fungi and plants, inhibitors of this enzyme are usually characterized by low mammalian toxicity. A whole group of AHAS inhibitors has been found in the research labs of American Cyanamid and could be launched to the market, which all share the same 4-methyl-4-isopropylimidazolin-5-one substructure. The different members of this so-called herbicide class of imidazolinones show varying levels of herbicidal activity and crop selectivity. Imazamethabenz-methyl (**1**) is used as post-emergent herbicide for the grass control in cereals, whereas imazapyr (**2**) and imazapic (**3**) are primarily applied as non-selective herbicides in plantations, rangeland, ditch banks, fence rows, air fields, roadsides and railroads. Imazethapyr (**4**), imazamox (**5**) and imazaquin (**6**) are mainly used under pre- and postemergent conditions for the control of annual and perennial grasses and broadleaf weeds in soybeans and other crops (Figure 1).[17-20]

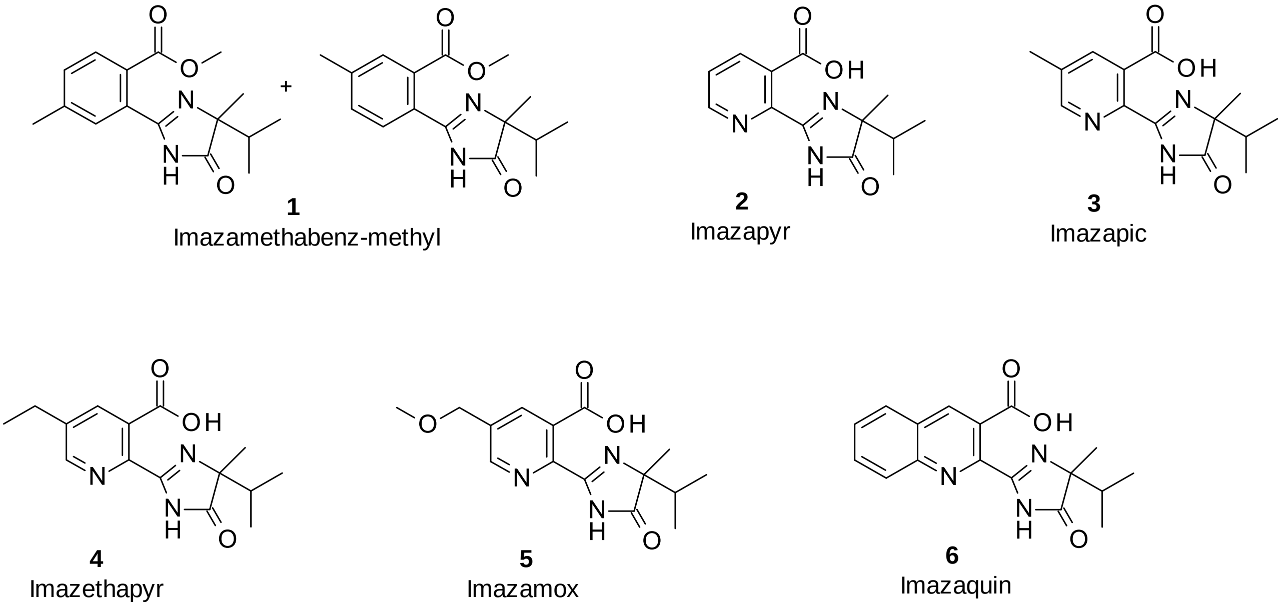
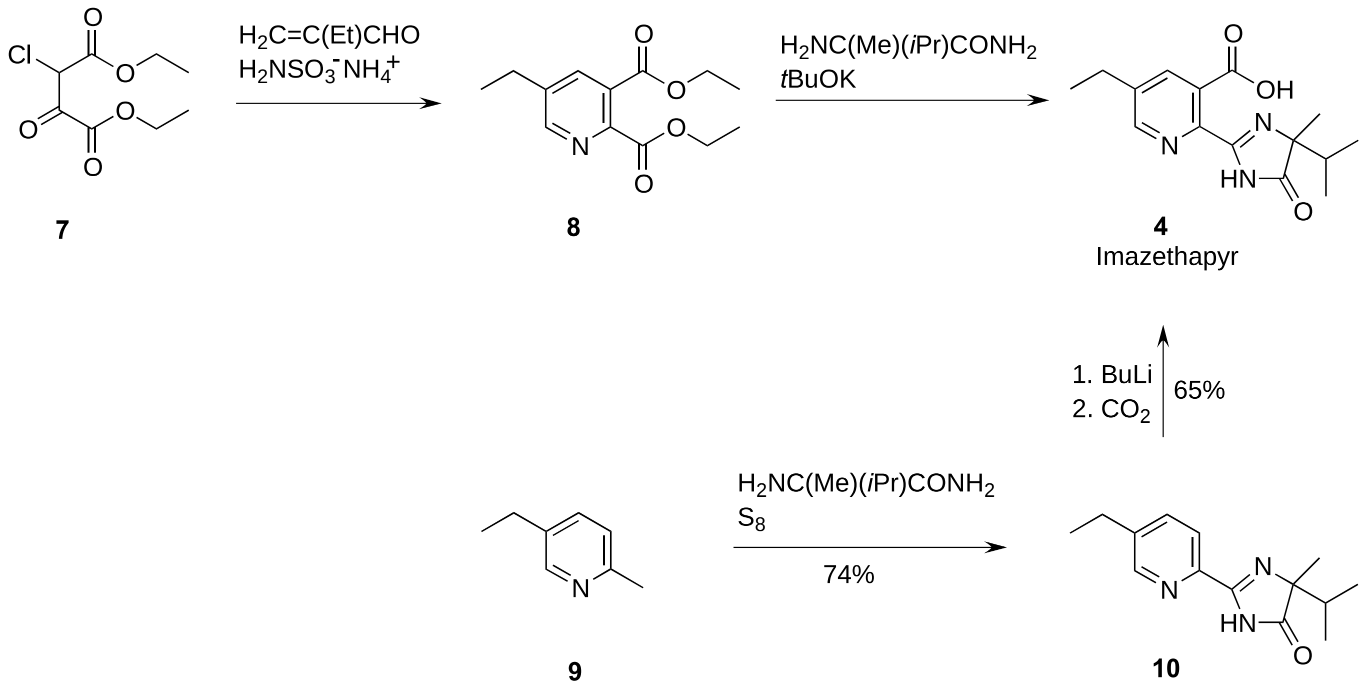


Figure 1. The imidazolinone herbicides imazamethabenz-methyl (**1**), imazapyr (**2**), imazapic (**3**), imazethapyr (**4**), imazamox (**5**) and imazaquin (**6**)

There are various routes available for the synthesis of the imidazolinone herbicides, as demonstrated in Scheme 1 for imazethapyr (**4**). It can be efficiently prepared in only two steps by condensation of diethyl chlorooxalacetate (**7**) and an enal, in the presence of a buffered ammonia source, to the pyridine diester **8** and its regioselective transformation into imazethapyr (**4**) with potassium *tert*-butoxide and α-methylvalinamide. The same amino acid amide is applied in an alternative two-step procedure, where it converts 5-ethyl-2-methylpyridine (**9**) together with an excess of sulfur in a Willgerodt-Kindler three-component condensation directly into the imidazolinone **10**. Due to the *ortho*-directing effect of this five-membered ring, a subsequent metalation/carboxylation sequence leads regioselectively to imazethapyr (**4**) (Scheme 1).[18,19,21,22]



Scheme 1. Synthesis of imazethapyr (**4**)

During the course of the optimization work on imidazolinone herbicides, also several compounds have been prepared, in which the imidazolinone pharmacophore is linked to a bicyclic scaffold, such as the dihydropyranopyridyl derivative **11**[23] and the *N*-methoxypyrrolopyridine derivative **12**,[24] which show both excellent postemergence weed control with good soybean selectivity. The thionoimidazoline derivative **13**, which is the thiono-analog of one of the two imazamethabenz-methyl regioisomers, displays good control of *Sinapis arvensis* (wild mustard) and *Avena fatua* (wild oats) under pre-emergent conditions.[25] The need of rotational planting with imidazolinone-sensitive crops started a search for imidazolinone herbicides with reduced soil persistence. In this context, the dimethylacetal derivative **14**[26] and the *N*-cyanoimidazolinone **15**[27] have been designed for faster metabolism, which indeed results in improved soil residual behavior (Figure 2).

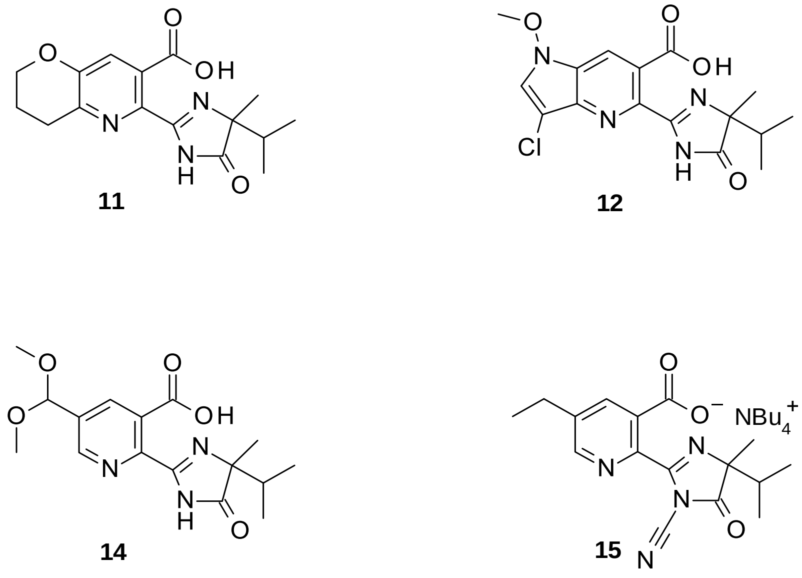


Figure 2. The experimental imidazolinone herbicides **11** – **15**

Also the well-known sulfonylurea herbicides inhibit AHAS. Three members of this chemistry class possess a bicyclic imidazole scaffold. The established commercialized products sulfosulfuron (**16**) and imazosulfuron (**17**) both bear an imidazopyridine unit, whereas the newer market entry propyrisulfuron (**18**) is based on an imidazopyridazine end group. Sulfosulfuron is specialized against grass and broadleaf weeds in cereals, whereas the strength of imazosulfuron and propyrisulfuron is the control of annual and perennial broadleaf weeds and sedges in paddy-field rice (Figure 3).[28-30]

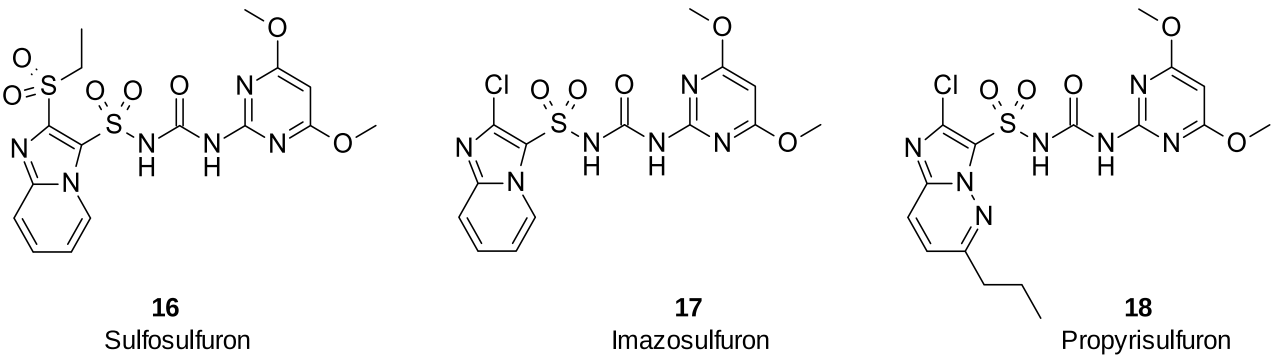


Figure 3. The sulfonylurea herbicides sulfosulfuron (**16**), imazosulfuron (**17**) and propyrisulfuron (**18**)

2.2. PROTOPORPHYRINOGEN-IX-OXIDASE INHIBITORS

Protoporphyrinogen-IX-oxidase (also called PPGO or protox) is the last enzyme in the porphyrin pathway that is common to both chlorophyll and heme synthesis. In treated tissues, PPGO inhibitors cause the accumulation of protoporphyrin IX. This tetrapyrrole is known to be a potent photosensitizer, generating in the presence of sunlight high levels of singlet oxygen. 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 PPGO inhibitors are also called peroxidizing herbicides. Although uracil, maleimide and triazolinone moieties seem to dominate the polar region of PPGO inhibitors, some oxygenated imidazole derivatives have been found to show excellent herbicidal activity. Most PPGO inhibitors have their strength in the control of broadleaf weeds under postemergent conditions. The commercialized product profluazol (**19**) possesses an unusal bicyclic imidazoledione unit with two chiral centers.[31] Also the other bicyclic imidazolidinedione **20**[32] and the imidazolidinetrione **21**[31] are good postemergence herbicides against dicotyledonous weeds. The two *N*-isopropylimidazolinedione derivatives **22**[33] and **23**[34] are both very active against *Ipomea hederacea* (morningglory). The benzimidazole derivative **24** displays excellent corn selectivity when applied preemergently, at the same time controlling several broadleaf weeds such as *Abutilon threophrasti* (velvetleaf), *Ipomea hederacea* (morningglory), *Solanum americanum* (nightshade) and *Stellaria media* (chickweed) (Figure 4).[35]

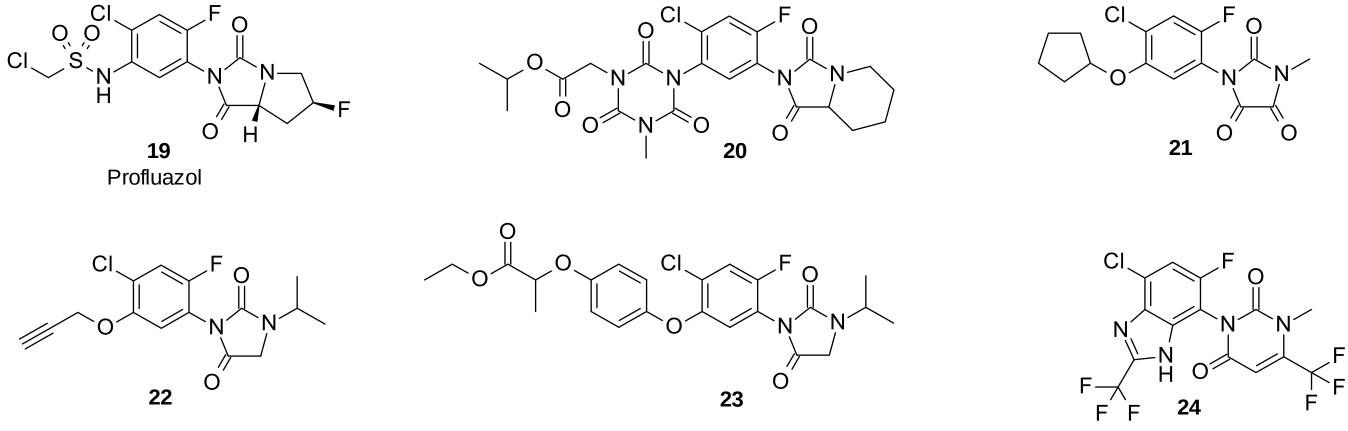

19
Profluazol
20
21
22
23
24

Figure 4. The PPGO inhibiting herbicides **19** - **24**

2.3. MISCELLANEOUS MODES OF ACTION

The older herbicides chlorflurazole (**25**)[36] and fluoromidine (**26**)[37] have been used some decades ago but have since being replaced by more effective and less toxic products. These 2-trifluoromethylbenzimidazoles act as uncouplers of the oxidative phosphorylation. The *N*-hydroxyimidazole derivative **27** displays high efficacy against *Echinochloa crus-galli* (barnyard grass), *Abutilon theophrasti* (velvetleaf) and *Chenopodium album* (lambsquarter) through inhibition of *p*-hydroxyphenylpyruvate dioxygenase (HPPD).[38] The phytoene desaturase inhibitor **28** possesses good preemergent herbicidal activity against different grass and broadleaf weeds.[39] The (*R*)-dimethylindanyl imidazole ester **29** is highly active against *Digitaria sanguinalis* (crabgrass) and other weeds by inhibition of obtusifoliol-14-α-methyl demethylase in the plant sterol biosynthesis.[40] The imidazolidinedione **30** efficiently controls broadleaf weeds such as *Ipomoea purpurea* (morningglory), *Abutilon theophrasti* (velvetleaf) and *Brassica kaber* (wild mustard), its mode of action is unknown (Figure 5).[41]

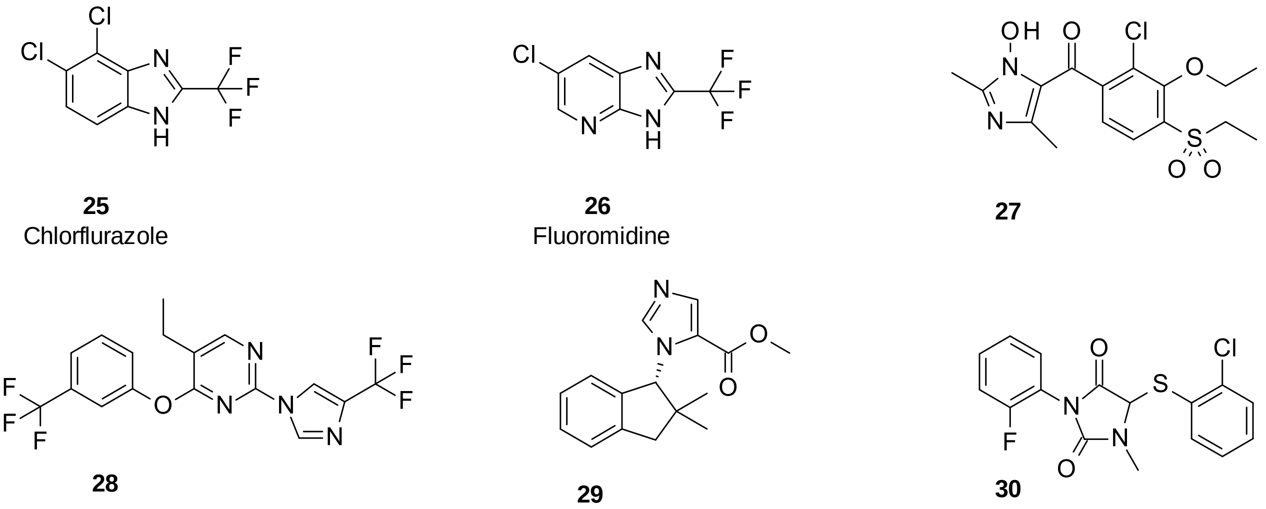
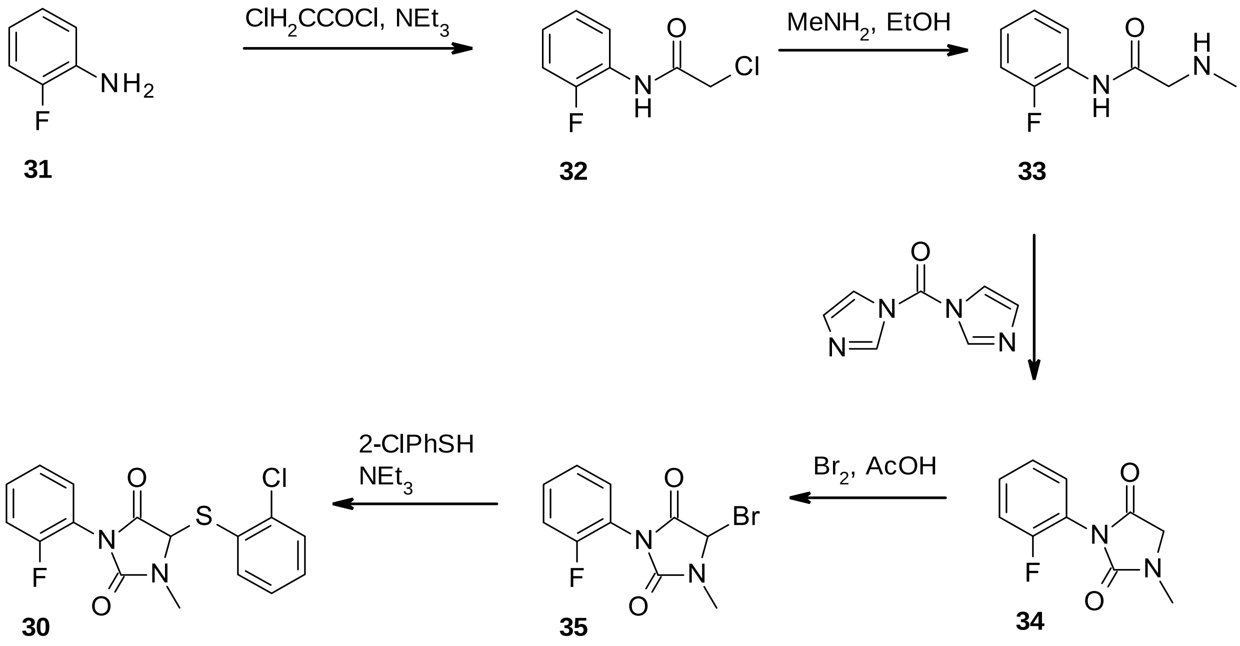


Figure 5. Further herbicidally active imidazole derivatives

2,4-Imidazolinediones such as **30** can be retrosynthetically viewed as reaction products of glycinamides with a carbonyl source such as phosgene or carbonyldiimidazole. Based on this consideration, its synthesis starts from 2-fluoroaniline (**31**), which is transformed via the chloroacetamide **32** into the glycinamide **33**. Transformation with 1,1'-carbonyldiimidazole affords the imidazolidinedione **34**, which is brominated in ring position 5 with bromine in glacial acetic acid to deliver **35**. Finally, the nucleophilic displacement of this leaving group by 2-chlorothiophenol yields the experimental herbicide **30** (Scheme 2).[41]



Scheme 2. Synthesis of the herbicidally active hydantoin derivative **30**

2.4. NATURAL PRODUCTS

The isolation of hydantocidin (**36**) from the fermentation broth of *Streptomyces hygroscopicus* (SANK 63584) provided the first example of a naturally occurring spironucleoside, in which two five-membered rings, a D-ribofuranose moiety and a hydantoin unit, are spiroannulated at the anomeric position.[42] It exhibits powerful non-selective postemergent herbicidal activity against a broad spectrum of annual and perennial grass and broadleaf weeds without being toxic to microorganisms and animals. After it has been converted into its active principle **37** by *in vivo* phosphorylation within the plant, it acts as an inhibitor of adenylosuccinate synthetase, an ubiquitous enzyme playing an important role in purine biosynthesis.[43] Ascamycin (**38**) has been isolated from a *Streptomyces* sp. fermentation broth and displays remarkable efficacy against different broadleaf weeds under postemergent conditions. It inhibits the protein biosynthesis of the plants by blocking amino acyl tRNA synthetase. This 5-sulfamoylnucleoside is a bioisostere of the corresponding nucleotide, the sulfamoyl function mimicking the natural phosphate group.[44] **39**, which is another 5-sulfamoylnucelsoide and which possesses the same 2-chloroadenine nucleobase as ascamycin, has been isolated from *Streptomyces albus* and efficiently controls *Xanthium spinosum* (cocklebur), *Stellaria media* (chickweed) and *Veronica persica* (speedwell).[45] Coformycin (**40**) was discovered in culture filtrates of *Nocardia interforma* and *Streptomyces kaniharaensis* and found to be active against different grass species such as *Sorghum halepense* (johnsongrass), *Echinochloa crus-galli* (barnyardgrass) and *Digitaria adscendens* (crabgrass).[46] It is a strong inhibitor of AMP deaminase, as well as nebularin (**41**), which is also herbicidally active.[47] The 2’-aminonucleoside herbiplanin (**42**)[48] and the carbocylic nucleoside coaristeromycin (**43**)[49] have both been isolated from *Streptomyces* strains. Herbiplanin (**42**) is effective against different *Lepidium* (pepperweed) and *Sinapis* (mustard) species,[48] whereas coaristeromycin (**43**) efficiently controls *Cyperus esculentus* (yellow nutsedge) and *Echinochloa crus-galli* (barnyardgrass) (Figure 6).[49]

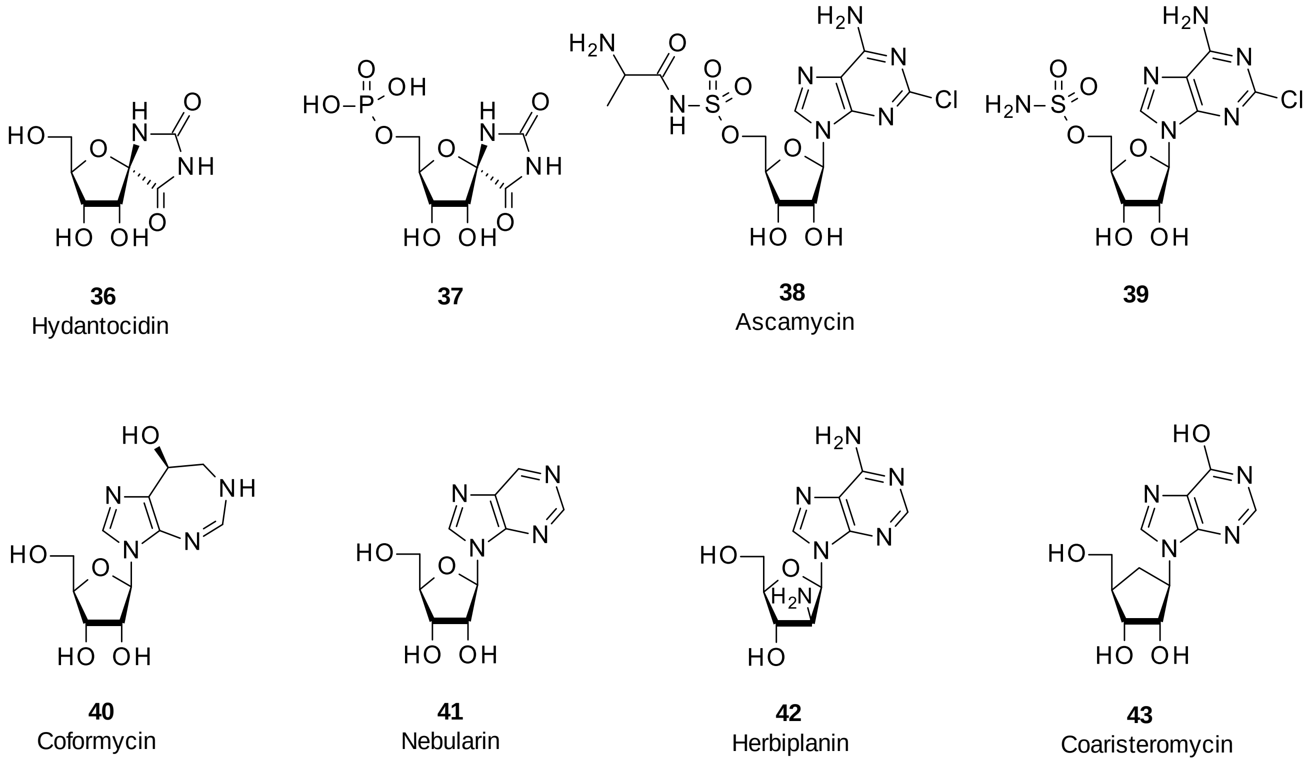
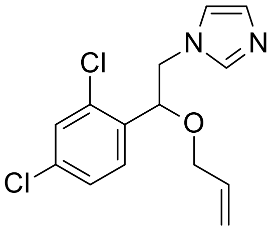

36
Hydantocidin
37
38
Ascamycin
39
40
Coformycin
41
Nebularin
42
Herbiplanin
43
Coaristeromycin

Figure 6. Naturally occurring imidazole derivatives with herbicidal activity

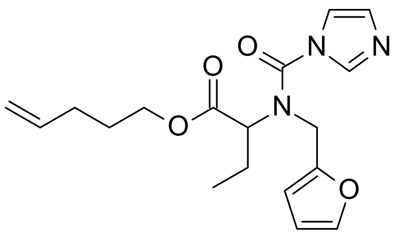
3. FUNGICIDALLY ACTIVE IMIDAZOLE DERIVATIVES

3.1. C14-DEMETHYLASE INHIBITORS

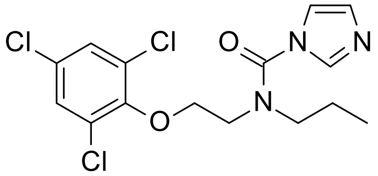
C14-Demethylase catalyzes one of the thirteen steps of the complex synthesis cascade, in which the acyclic terpenoid squalene is transformed into the tetracylic ergosterol, a major cell membrane component of all fungi belonging to the families of Ascomycetes and Basidiomycetes. C14-**Dem**ethylase **i**nhibitors (also called DMIs) constitute the mode of action class with the highest number of commercialized fungicides, in addition a similar high amount of DMIs are applied as pharmaceutical antimycotics. Most of the agrochemical DMIs bear a triazole ring, but also five imidazole derivatives have been launched to the crop protection market. Imazalil (**44**) was the first imidazole-based DMI and is mainly used today as a seed treatment in cereals. Pefurazoate (**45**) is a seed treatment agent as well, it effectively controls of all major seed-borne rice pathogens, such as *Fusarium moniliforme* (bakanae disease), *Cochliobolus miyabeanus* (brown spot) and *Magnaporthe grisea* (rice blast). Prochloraz (**46**) is a broad-spectrum fungicide with pronounced activity against all kind of Ascomycetes species and is primarily used in cereals against leaf and net blotch as well as eyespot diseases. Triflumizole (**47**) is mainly used in fruits and vegetables against pathogens such as *Venturia inaequalis* (apple scab) and *Monilinia fructicola* (brown rot of stone fruits). Also oxpoconazole (**48**), the latest market introduction amongst the imidazole DMIs, is applied in the fruit segment, but is also capable of protecting rice seedlings from infestations of *Magnaporthe grisea* (rice blast) and *Rhizoctonia solani* (sheath blight) (Figure 7).[50-52]



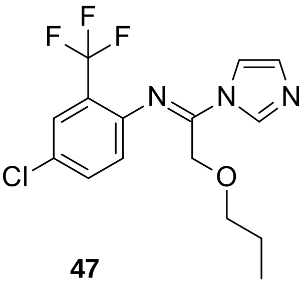
44
Imazalil



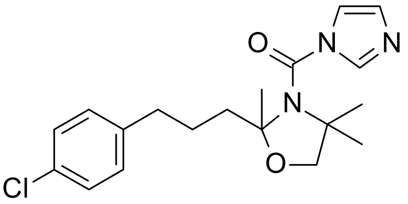
45
Pefurazoate



46
Prochloraz



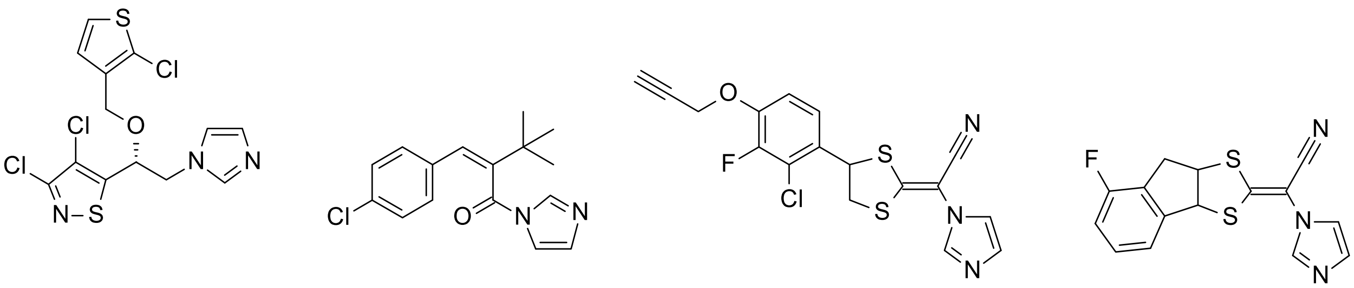
47
Triflumizole



48
Oxpoconazole

Figure 7. The DMI fungicides imazalil (**44**), pefurazoate (**45**), prochloraz (**46**), triflumizole (**47**) and oxpoconazole (**48**)

Also several other imidazole-based DMIs have been described to possess fungicidal activity. The unique compound **49** bearing with an imidazole, an isothiazole and a thiophene three different five-membered heterocycles, shows excellent control of *Botrytis cinerea* (grey mold) and *Rhizoctonia cerealis* (wheat sharp eyespot).[53] The 1-(α-*tert*-butylcinnamoyl)imidazole derivative **50** is very active against grey mold and wheat powdery mildew.[54] The imidazole-based ketene dithioacetal **51**[55] and its conformationally locked analog **52**[56] are both very effective against *Septoria tritici* (wheat leaf blotch) and different powdery mildew species (Figure 8).

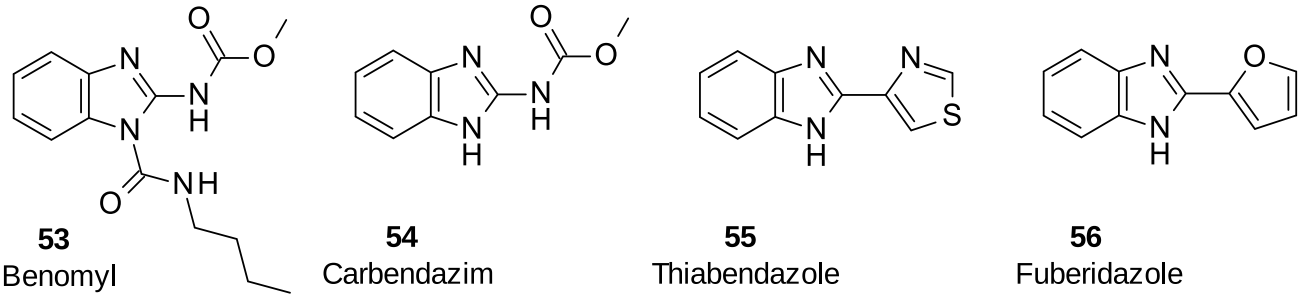


49 **50** **51** **52**

Figure 8. The experimental DMI fungicides **49** – **52**

3.2. TUBULIN POLYMERIZATION INHIBITORS AND PROMOTERS

A new era in the treatment of plant diseases began in end of the 1960's, when benomyl (**53**) was introduced to the crop protection market as very first broad-spectrum foliar systemic fungicide. This product, but also the closely related benzimidazole derivative carbendazim (**54**) have been applied for the control of a wide range of especially Ascomycetes species as well as some Fungi Imperfecti in cereals, grapes, pome and stone fruit, rice and vegetables. Thiabendazole (**55**), originally developed as an anthelmintic, was mainly used as post-harvest fungicide, fuberidazole (**56**) has been used primarily in Europe for cereal seed treatment. These benzimidazole fungicides inhibit the assembly of microtubules during cell division by binding to the β-subunit of tubulin (Figure 9).[57,58]



53 Benomyl

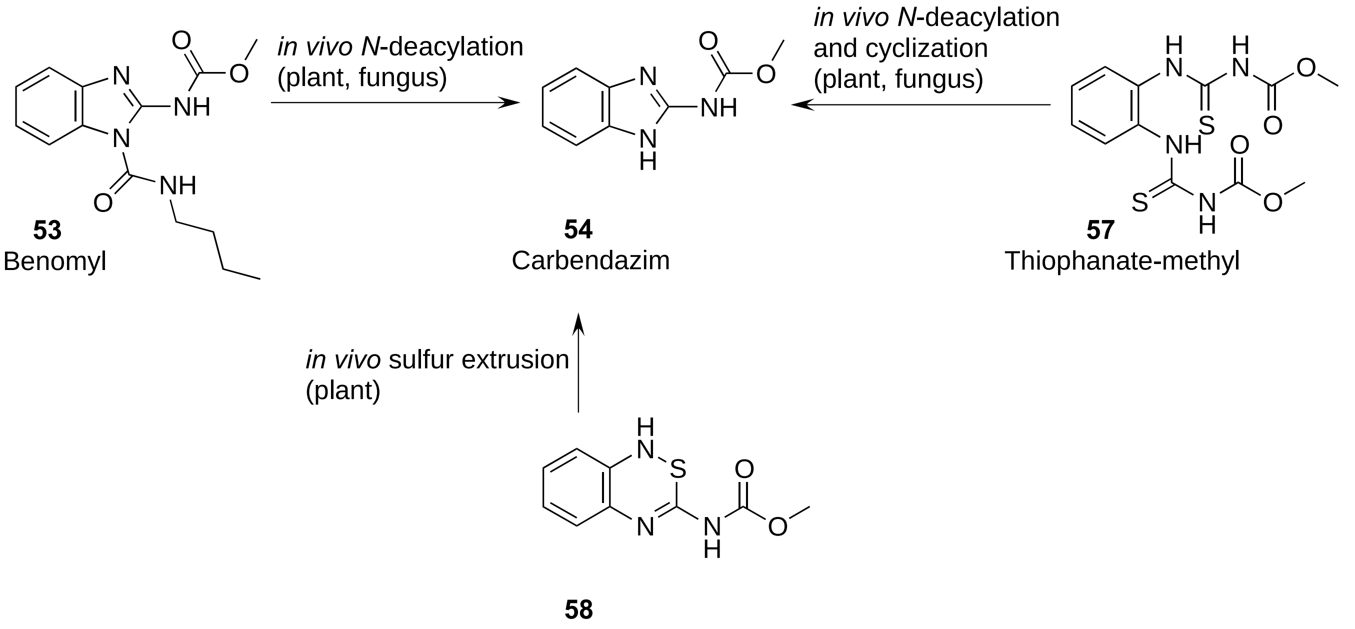
54 Carbendazim

55 Thiabendazole

56 Fuberidazole

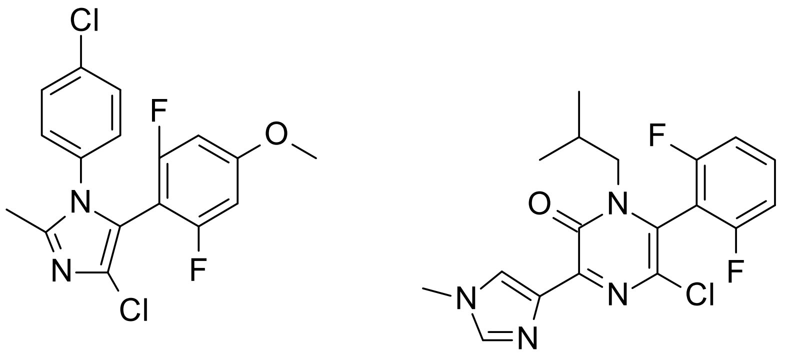
Figure 9. The benzimidazole fungicides benomyl (**53**), carbendazim (**54**), thiabendazole (**55**) and fuberidazole (**56**)

The fungicidal activity of several compounds originates from their ability to be converted *in vivo* into the benzimidazole fungicide carbendazim (**54**). The market product benomyl (**53**) loses in fungi and plants one equivalent of *n*-butylisocyanate, delivering carbendazim. Also, the commercialized fungicide thiophanate-methyl (**57**) is transformed by *in vivo*-deacylation and -cyclization into carbendazim. Finally, the efficacy of the benzothiadiazine derivative **58** is due to its *in planta*-desulfurization, leading to carbendazim (Scheme 3).[59,60]



Scheme 3. *In vivo* conversion of benomyl (**53**), thiophanate-methyl (**57**) and **58** into carbendazim (**54**)

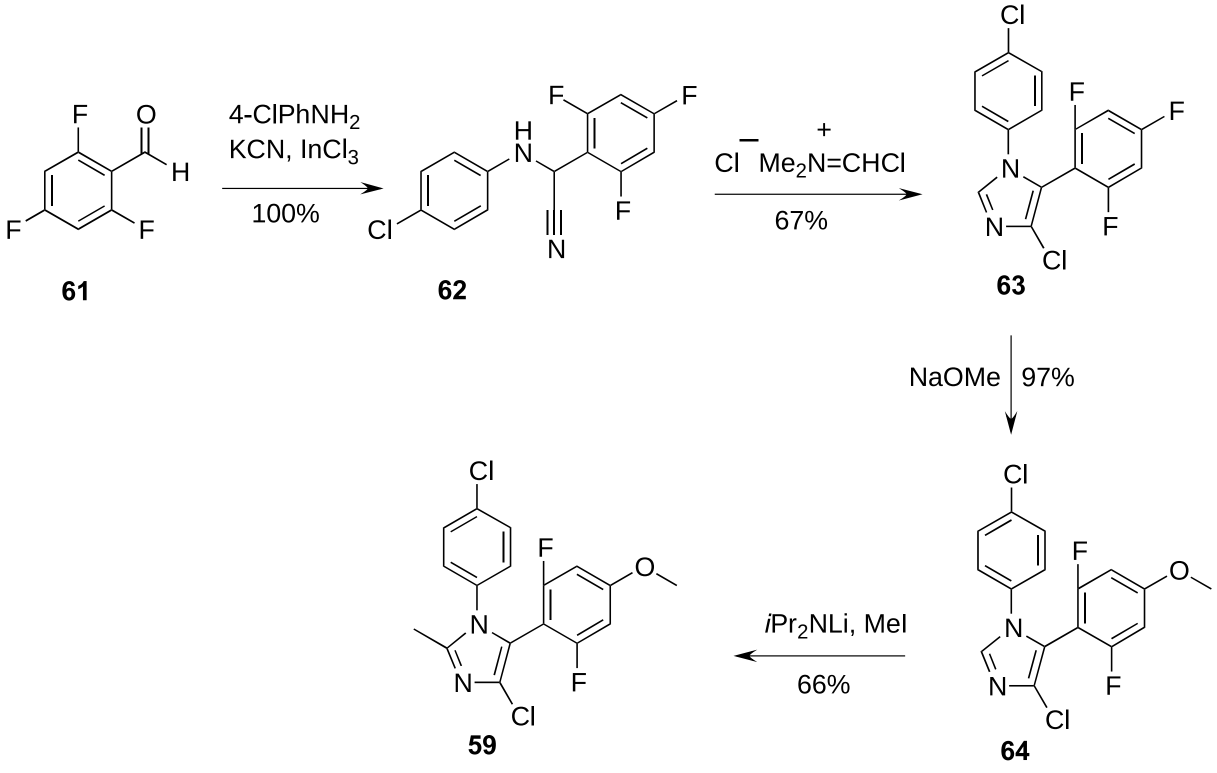
Microtubules are highly dynamic and switch constantly between growing and shrinking phases, delivering in the extremes by growing a rod-like microtubule, during shrinking α- and β-tubulin heterodimers. The above mentioned benzimidazoles disturb this equilibrium by inhibiting the tubulin polymerization, which destabilizes the microtubules. But also the opposite mode of action could be exploited for fungicidal activity, which is the promotion of tubulin polymerization, leading to a stabilization of microtubules. This is the mode of action, which is responsible for the excellent activity of the tetrasubstituted imidazole derivative **59**[61] and the imidazole-substituted pyrazinone **60**[62] against *Botrytis cinerea* (grey mold) and some other plant diseases (Figure 10).



59 **60**

Figure 10. The tubulin polymerization promoting fungicides **59** and **60**

The synthesis of the tubulin-active fungicide **59** starts with the three-component condensation of 2,4,6-trifluorobenzaldehyde (**61**) with 4-chloroaniline and potassium cyanide, delivering quantitatively the α-aminonitrile **62**. Catalytic amounts of indium(III) chloride enable the transformation of this Strecker reaction in organic solvents. **62** is then cyclized with Vilsmeier reagent and hydrochloric acid to the trisubstituted imidazole **63**, which has besides two aryl groups already the required chlorine atom in place. The replacement of the fluoro-substituent in the *para*-position of the phenyl ring by methoxy and the methylation of the free position in the imidazole by direct lithiation and methyl exchange leads to the fungicidally active persubstituted imidazole derivative **59** (Scheme 4).[61]



Scheme 4. Synthesis of the fungicidally active tubulin polymerization promoter **59**

3.3. MISCELLANEOUS MODES OF ACTION

Also, imidazole derivatives with other modes of action turned out be fungicidally active. The hydantoin iprodione (**65**) belongs to the dicarboximide fungicides and is very effective against *Botrytis cinerea* (grey mold) and *Sclerotinia* sp. in fruit, vines and vegetables by interfering with the fungal osmotic signal transduction pathway.[63] Fenamidone (**66**) is widely used for the control of Oomycete pathogens, such as *Plasmopara viticola* (grape downy mildew) and *Phytophthora infestans* (potato late blight). It has been developed as the *S*-enantiomer and specifically blocks the Qo site of cytochrome bc1 (complex III of the mitochondrial respiratory chain).[64] Also cyazofamid (**67**) and dimefluazole (**68**) are Complex III inhibitors and are specialized on Oomycete diseases as well, but they bind to the other target site within cytochrome bc1 which is the Qi site. Cyazofamid (**67**) found ample application especially against *Phytophthora infestans* (potato late blight),[64] whereas dimefluazole (**68**) did not achieve commercial status.[65] Besides cyazofamid and dimefluazole, also other *N*-sulfonylated 2-cyanoimidazoles were found to possess fungicidal activity.[66] The imidazole-substituted benzotriazine derivative triazoxide (**69**) is primarily used as a seed dressing for the control of *Pyrenophora graminea* (barley leaf stripe), its mode of action is still unknown.[67] The 1-benzoyl-3-isopropenylbenzimidazolone **70** showed impressive activity against *Botrytis cinerea* (grey mold).[68] The imidazole-4-carboxamide **71** is very effective against *Rhizoctonia solani* (rice sheath blight).[69] The imidazobenzothiazole derivative **72** displays good control of *Magnaporthe grisea* (rice blast) (Figure 11).[70]

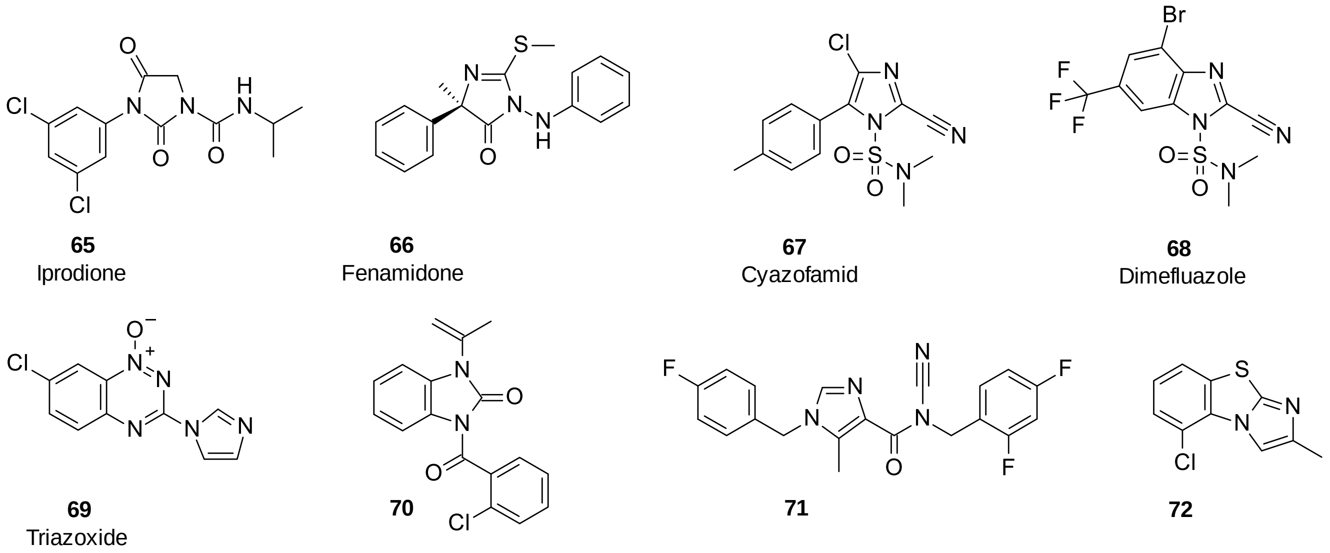
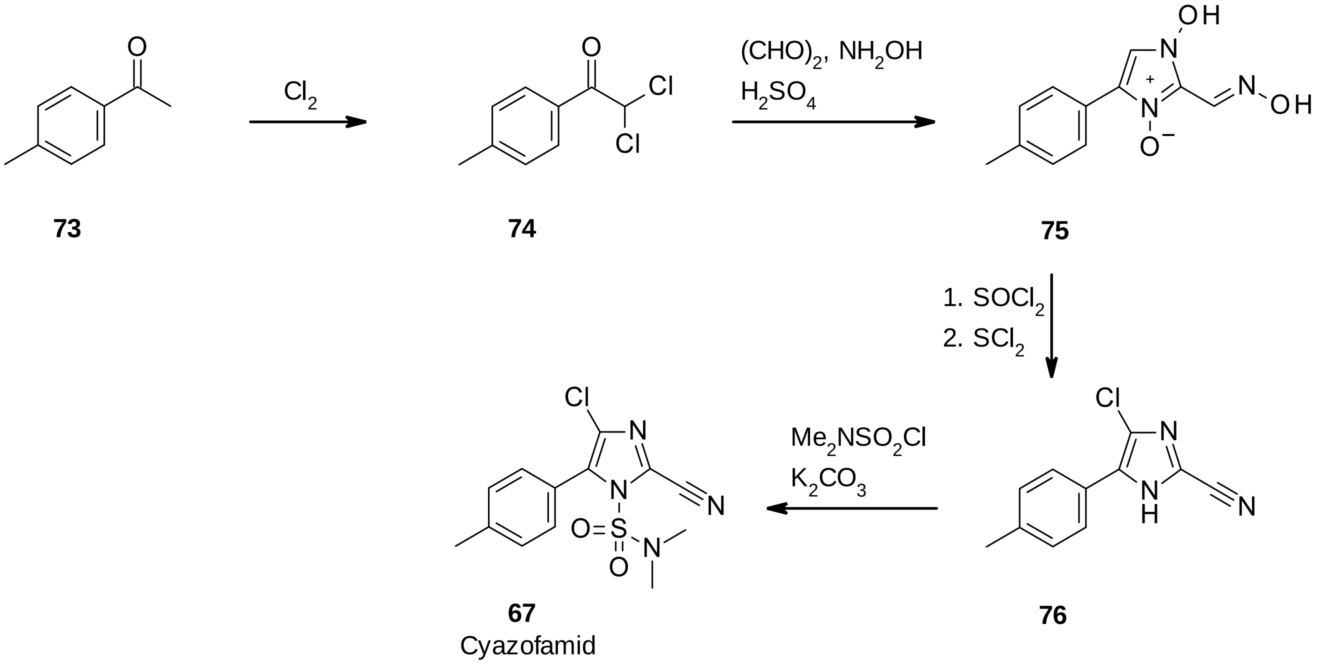


Figure 11. Further fungicidally active imidazole derivatives

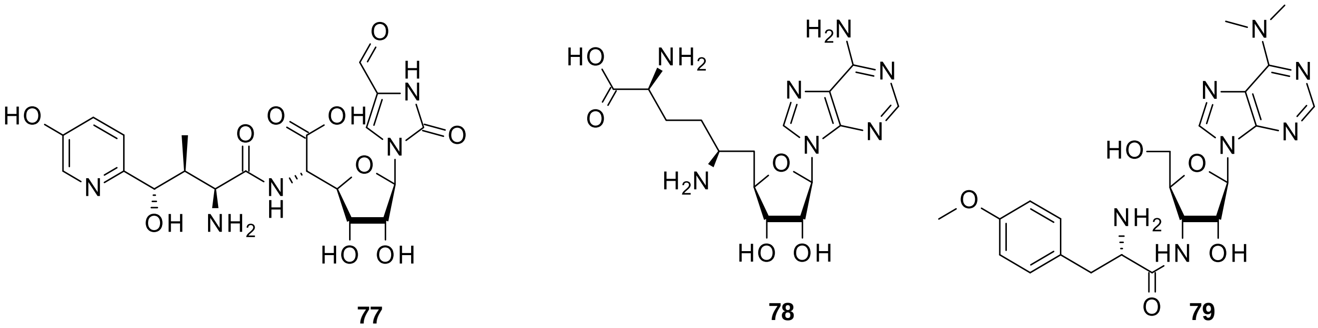
The synthesis of cyazofamid (**67**) is a text-book example for the easy accessibility of especially per-substituted heterocycles, as it can be assembled from 4-methylacetophenone (**73**) with only inexpensive reagents, such as chlorine, hydroxylamine, glyoxal, thionyl chloride and sulfur dichloride. In the first step the mentioned starting material is dichlorinated to **74**, which is transformed with glyoxal and hydroxylamine to the *N*-hydroxyimidazole *N*-oxide **75**. This unique imidazole derivative, in which both ring nitrogen atoms are oxygenated, reacts with thionyl chloride and sulfur dichloride to the trisubstituted imidazole **76**. Already the next step delivers cyazofamid (**67**) by *N*-sulfonylation with *N*,*N*-dimethylsulfamoyl chloride (Scheme 5).[64,71]



Scheme 5. Synthesis of cyazofamid (**67**)

3.4. NATURAL PRODUCTS

Several nucleosides with imidazole- or imidazolinone-based nucleobases display fungicidal activity. Neopolyoxin A (**77**) has been isolated from *Streptomyces cacaoi* and blocks chitin synthetase. It shows excellent control of *Magnaporthe grisea* (rice blast), *Botrytis cinerea* (grey mold) and *Cochliobolus miyabeanus* (brown spot).[72] The adenosine derivative sinefungin (**78**) was isolated from a strain of *Streptomyces griseolus* and is active against *Erysiphe polygoni* (pea powdery mildew) and *Uromyces phaseoli* (bean rust) by inhibition of different methyltransferases.[44] The protein biosynthesis inhibitor puromycin (**79**) has been isolated from *Streptomyces alboniger* and is effective against various growth stages of *Blumeria graminis hordei* (barley powdery mildew) (Figure 12).[73]



77 Neopolyoxin A (Nikkomycin X)

78 Sinefungin

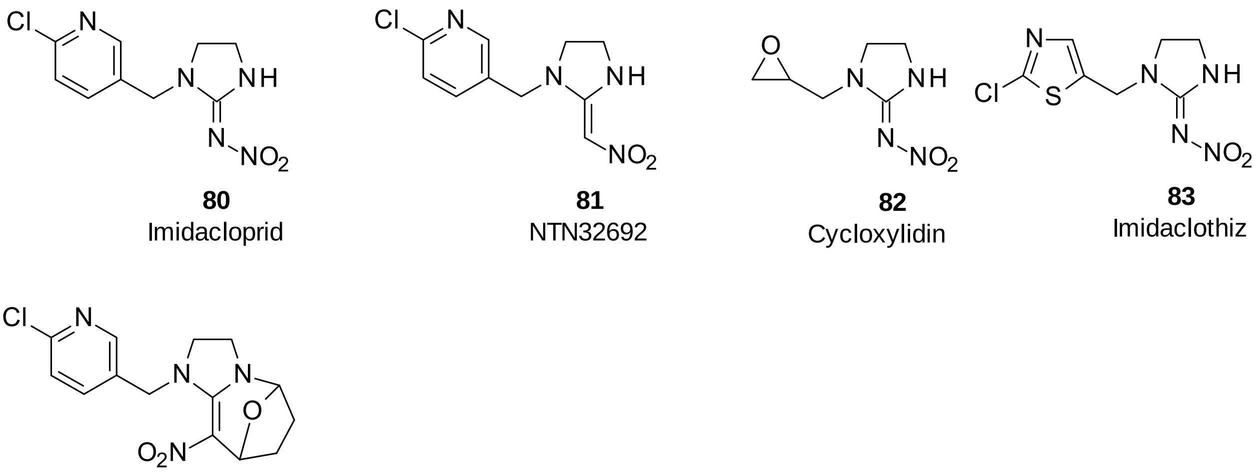
79 Puromycin

Figure 12. Naturally occuring imidazole derivatives with fungicidal activity

4. INSECTICIDALLY ACTIVE IMIDAZOLE DERIVATIVES

4.1. NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

The alkaloid nicotine has been used for a long time as a natural insecticide in form of aqueous tobacco extracts. It acts as an acetylcholine receptor agonist and is highly toxic, also to mammals. The synthetic active ingredient class of neonicotinoids combines the insecticidal mode of action of nicotine with a more specific efficacy against insects and therefore a much better toxicological profile.[74-77] Imidacloprid (**80**), the first commercialized neonicotinoid, was for several years the biggest selling insecticide worldwide. Its impressive target insect spectrum spans from sucking pests, such as aphids, thrips, scales, whiteflies, and psyllids to beetles, such as *Leptinotarsa decemlineata* (Colorado potato beetle) and *Lissorhoptrus oryzophilus* (rice water weevil), and also to other insects, such as leafhoppers and -miners, termites, locusts and fleas. Because of its high intrinsic potency and systemic properties, imidacloprid controls the mentioned species in low concentrations either in foliar spray, soil drench or seed treatment applications.[78,79] The nitromethylene derivative NTN32692 (**81**) was earlier discovered than imidacloprid and shows similar potency, however in sunlight it is much more labile than its nitroimine analog imidacloprid and therefore rapidly decomposes in field trials.[75,79,80] The oxirane derivative cycloxylidin (**82**) has been developed for the control of sucking pests in vegetables, rice and cotton, whereas imidaclothiz (**83**) is primarily used against *Jacobiasca formosana* (tea green leafhopper) and also against aphids in vegetable crops.[74] The oxa-bridged neonicotinoid cycloxaprid (**84**) displays excellent activity against *Aphis craccivora* (cowpea aphid) and *Pseudaletia separata* (armyworm) (Figure 13).[81]



80
Imidacloprid

81
NTN32692

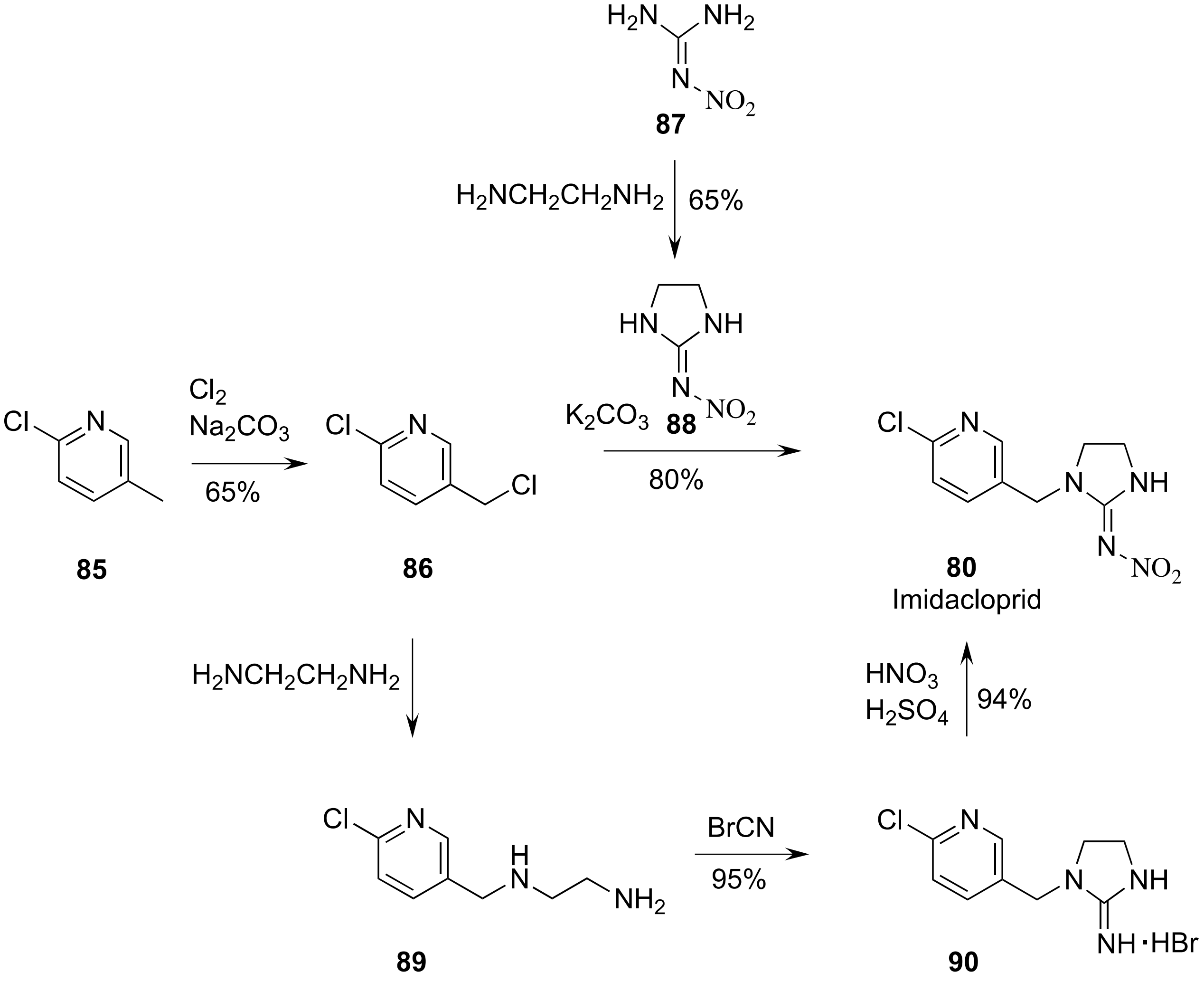
82
Cycloxylidin

83
Imidaclothiz

84
Cycloxaprid

Figure 13. The neonicotinoid insecticides imidacloprid (**80**), NTN32692 (**81**), cycloxylidin (**82**), imidaclothiz (**83**) and cycloxaprid (**84**)

The synthesis of imidacloprid starts with the chlorination of the picoline derivative **85** to 2-chloro-5-(chloromethyl)pyridine (**86**). It can be directly converted to imidacloprid (**80**) by alkylation of 2-*N*-nitroiminoimidazoline (**88**), which is usually prepared by cyclocondensation of *N*-nitroguanidine (**87**) and 1,2-ethylenediamine.[74,75,78,79] An alternative route to imidacloprid proceeds via the transformation of 2-chloro-5-(chloromethyl)pyridine (**86**) with 1,2-ethylenediamine to the primary amine derivative **89**, which is then ring-closed with the aid of cyanogen bromide to the cyclic guanidine **90**. Finally, the installation of the missing nitro function with fuming nitric acid and sulfuric acid delivers imidacloprid (**80**) (Scheme 6).[82]



Scheme 6. Synthesis of imidacloprid (**80**)

Paichongding (**91**), but also its synthetic precursor IPP-10 (**92**), the tetrahydroimidazopyrimidine derivative BAY T9992 (**93**) and the nitro olefin IPPA 152201 (**94**) are all structurally fixed *cis*-nitromethylene analogs of the important neonictinoid discovery milestone NTN32692 (**81**), from which all of them can also be obtained by only one or two synthetic steps.[74] Paichongding (**91**) is highly active against *Nilapavarta lugens* (brown planthopper), also those resistant to imidacloprid,[83] the closely related IPP-10 (**92**) shows both contact and systemic activity against *Rhopalosiphum padi* (cherry oat aphid).[84] BAY T9992 (**93**), prepared from NTN32692 (**81**) by Mannich reaction with formaldehyde and methylamine, can be considered as proneonicotinoid, because at different pH values its hydrolytic ring-opening back to NTN32692 (**81**) is observed.[85] IPPA 152201 (**94**) shows good activity against Lepidoptera species such as *Pseudaletia separata* (oriental armyworm) and *Cnaphalocrocis medinalis* (rice leafroller).[74] The imidazoline derivative **95** and the *N*-cyanoimidazolidine **96**, both closely related by structure to imidacloprid (**80**), possess strong efficacy against *Nephotettix cincticeps* (green rice leafhopper).[79] Compound **97**, in which imidacloprid's chloropyridine moiety has been replaced by a chlorofurane, is very active against *Aphis gossypii* (cotton aphid) (Figure 14).[86]

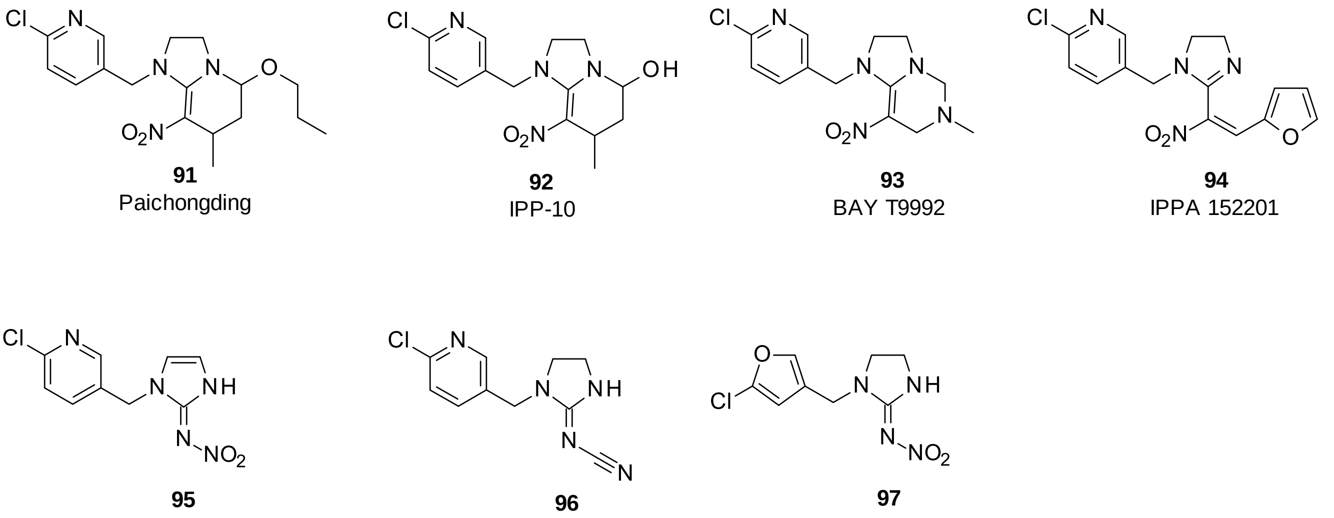
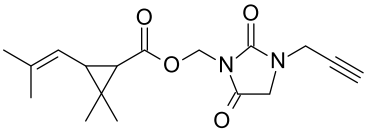


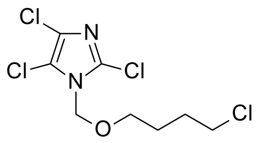
Figure 14. The experimental neonicotinoid insecticides **91** – **97**

4.2. MISCELLANEOUS MODES OF ACTION

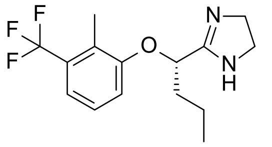
Imiprothrin (**98**) belongs to the huge family of sodium channel blocking pyrethroids and has a potent knockdown-effect against cockroaches and other crawling insects.[87] Also the trichlorinated imidazole S-377 (**99**) is a sodium channel blocker and highly active against *Blatella germanica* (German cockroach).[88] The imidazoline derivative **100** shows excellent efficacy against *Aphis craccivora* (cowpea aphid), *Bemisia tabaci* (silverleaf whitefly), *Aonidiella aurantii* (red scale), *Tetranychus urticae* (two-spotted spider mite) and *Myzus persicae* (green peach aphid) by acting on their octopamine receptors.[89,90] The ryanodine receptor modulator **101** strongly controls *Spodoptera littoralis* (cotton leafworm).[91] The *N*-aminoimidazole derivative **102** possesses good insecticidal activity as ecdysone receptor agonist.[92] The imidazothiadiazole derivative **103** displays potent larvicidal activity against *Mythimna separata* (oriental armyworm).[93] The imidazopyridine derivative fluazaindolizine (**104**) is highly potent against different plant-parasitic nematodes, such as *Meloidogyne* spp. (root-knot nematodes), *Helicotylenchus* spp. (spiral nematodes) and *Rotylenchulus reniformis* (reniform nematode) (Figure 15).[94,95]



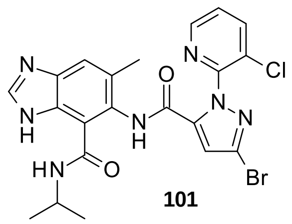
98
Imiprothrin



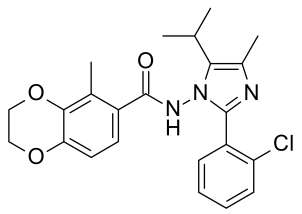
99
S-377



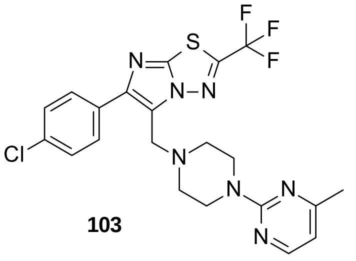
100



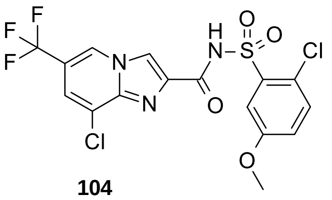
101



102



103

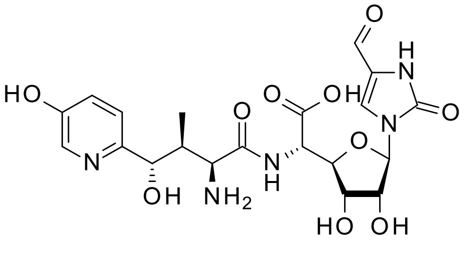


104
Fluazaindolizine

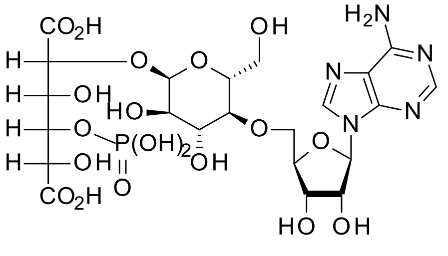
Figure 15. Further insecticidally, acaricidally and nematicidally active imidazole derivatives

4.3. NATURAL PRODUCTS

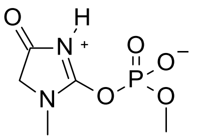
The chitin synthetase inhibitor nikkomycin X (**77**), which is identical to the naturally occurring fungicide neopolyoxin A and which has been isolated from *Streptomyces tendae*, has once been considered for commercial use against *Tetranychus urticae* (two-spotted spider mite).[21] The adenosine derivative thuringiensine (**105**), a metabolite isolated from *Bacillus thuringiensis*, possesses potent insecticidal and acaricidal activity, because at the low use rate of about 50 g/ha it is highly effective against *Leptinotarsa decemlineata* (Colorado potato beetle), *Lygus hesperus* (lygus bug), *Heliotis virescens* (tobacco budworm) and *Panonychus ulmi* (European red mite).[42] The phosphorylated zwitterionic hydantoin ulosantoin (**106**) has been isolated from the sponge *Ulosa ruetzleri* and found to exhibit marked insecticidal activity against *Manduca sexta* (tobacco hornworm) and *Periplaneta americana* (American cockroach) (Figure 16).[96]



77
Nikkomycin X
(Neopolyoxin A)



105
Thuringiensin

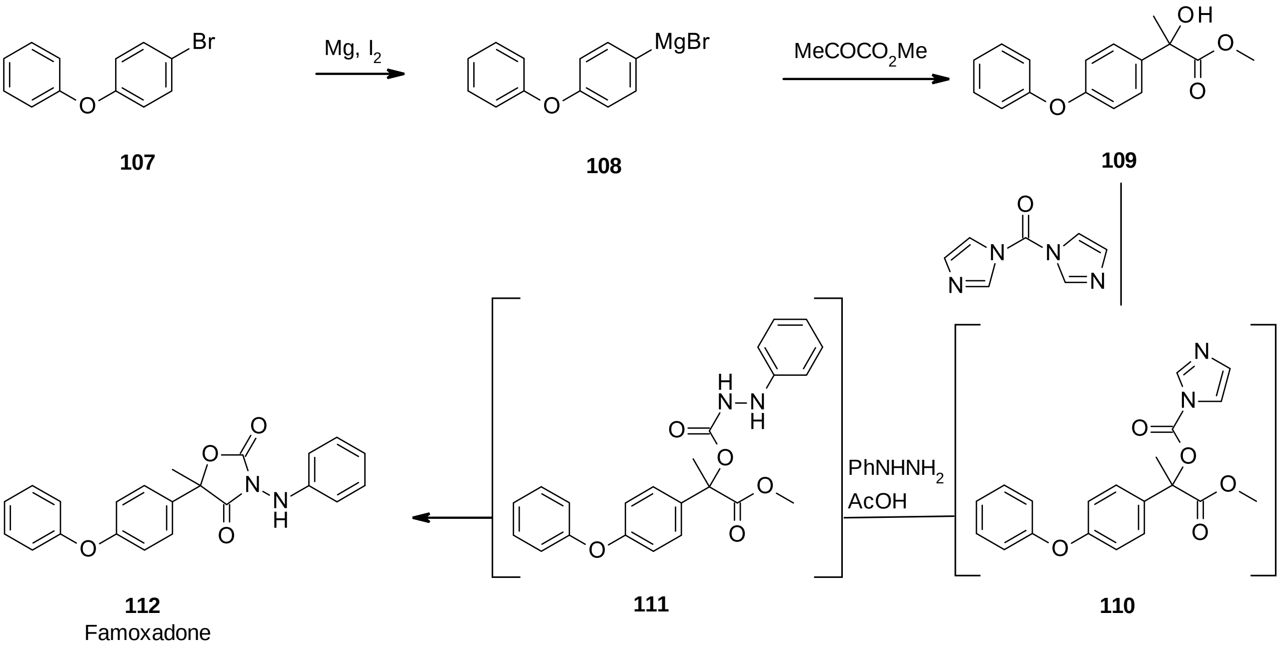


106
Ulosantoin

Figure 16. Naturally occurring imidazole derivatives with insecticidal and acaricidal activity

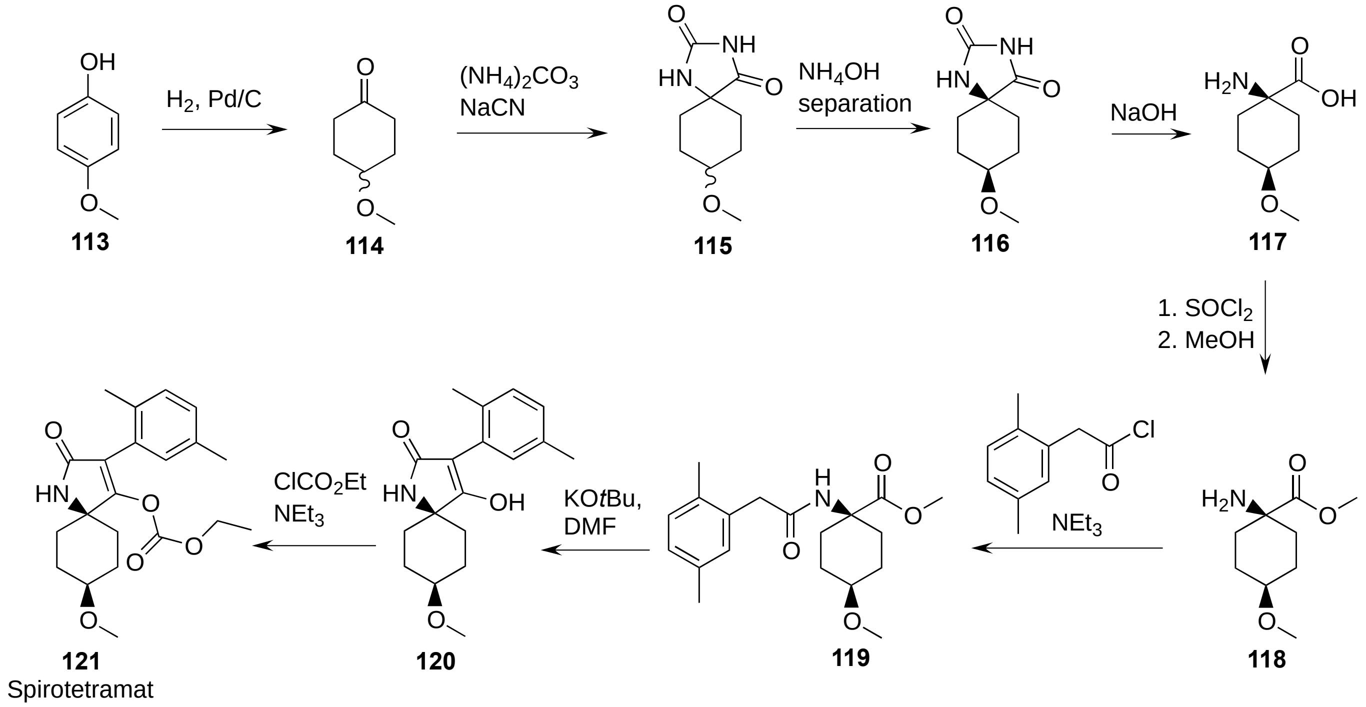
5. IMIDAZOLES AS REAGENTS AND INTERMEDIATES IN THE SYNTHESIS OF NON-IMIDAZOLE AGROCHEMICALS

The preparation of several agrochemicals, which don't bear any imidazole moiety, is made possible by imidazole-based reagents and intermediates. 1,1'-Carbonyldiimidazole (CDI) plays here an important role, as already seen in Scheme 2 in the synthesis of experimental herbicide **30**. Another example is the synthesis route to Oomycetes fungicide famoxadone (**112**), which starts with the transformation of 1-bromo-4-phenoxybenzene (**107**) into the corresponding Grignard reagent **108** and its further reaction with methyl pyruvate to the α-hydroxyester **109**. This α-methylated mandelic ester derivative reacts with 1,1'-carbonyldiimidazole to the labile carbamate **110**, which in turn is converted with phenylhydrazine to the hydrazinecarboxylate **111**. This reactive intermediate undergoes cyclization to an oxazolidine-2,4-dione, delivering the respiration inhibitor famoxadone (**112**) (Scheme 7).[97-99]



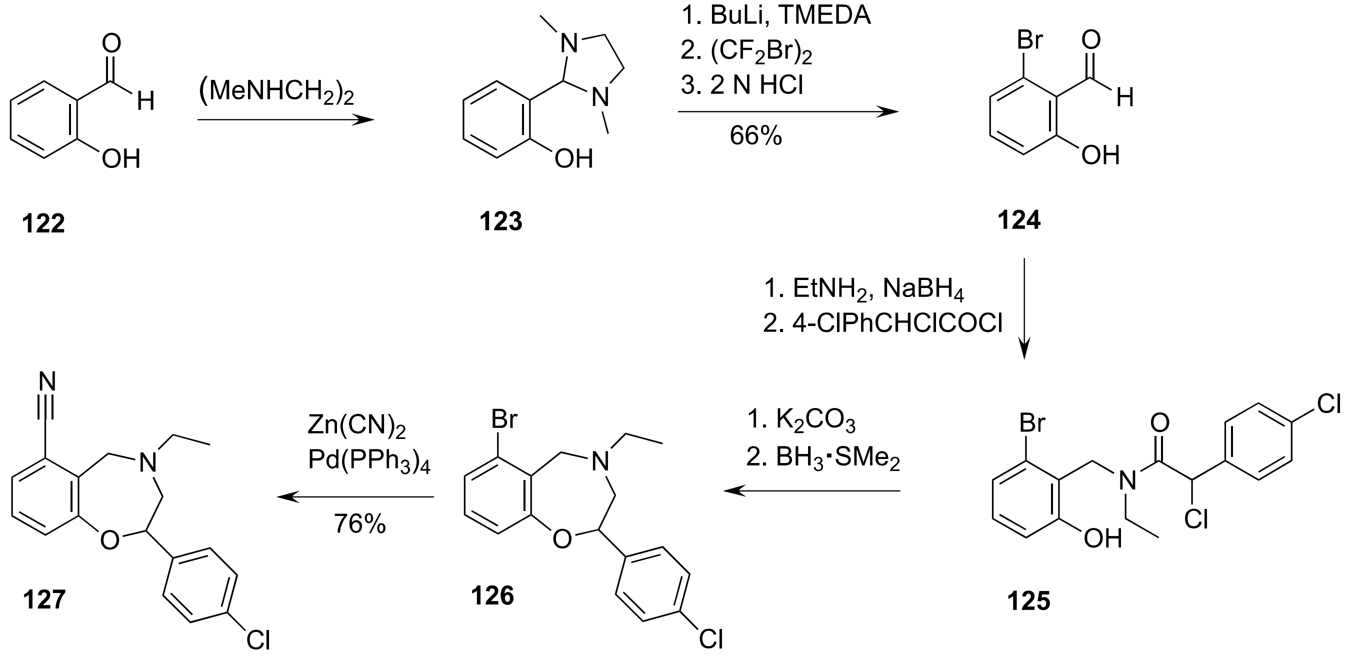
Scheme 7. Synthesis of famoxadone (**112**)

The efficient synthesis of the acetyl-CoA-carboxylase inhibiting insecticide spirotetramat (**121**) employs a Bucherer-Bergs reaction of 4-methoxycyclohexanone (**114**), which is available in one step by hydrogenation of *p*-hydroxyanisole (**113**), to deliver the hydantoin **115**. After separation of the *cis*-isomer **116**, the hydantoin ring is hydrolyzed to the amino acid **117**, which is then esterified with thionyl chloride and methanol. The acylation of the resulting ester **118** to the amidoester **119** is then followed by its Dieckmann cyclization to the tetramic acid **120**, from which spirotetramat (**121**) is obtained by acylation with ethyl chloroformate. Spirotetramat (**121**) controls efficiently silverleaf whitefly (*Bemisia tabaci*) and several different *Aphis* spp. (Scheme 8).[100,101]



Scheme 8. Synthesis of spirotetramat (**121**)

The synthesis of the insecticidally active benzoxazepine derivative **127** relies on an imidazolidine derivative as masked aldehyde. Salicylaldehyde (**122**) is transformed into the 1,3-dimethylimidazolidine derivative **123**. Using this aminal protection for the aldehyde function, a regioselective *ortho*-lithiation to the trisubstituted benzene derivative **124** is possible in the presence of the phenol group.[102] After reductive amination of the aldehyde function to a secondary amine, subsequent transformation with α,4-dichlorobenzeneacetyl chloride delivers the carboxamide **125**. Its base-catalyzed cyclization to a dihydrobenzoxazepine ring structure is followed by reduction of the lactame to an amine, delivering **126**. In the final step, the transition-metal catalyzed replacement of the bromine atom by a cyano group affords the experimental insecticide **127**, which is, as well as **126**, active against sucking pests, such as aphids and whiteflies (Scheme 9).[103]



Scheme 9. Synthesis of the experimental insecticide **127**

6. CONCLUSION

As seen in this review, many imidazole derivatives possess powerful activity 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 imidazole derivatives display interesting herbicidal, fungicidal and insecticidal activity, most of them are nucleosides with adenine- or guanine-type nucleobases. Furthermore, because of their easy accessibility, imidazole derivatives found application as reagents or intermediates in the synthesis route of different non-imidazole containing agrochemicals.

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