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PYRAZOLE CHEMISTRY IN CROP PROTECTION[1]

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Abstract – An overview is given of the significance of pyrazole derivatives in crop protection chemistry. The main herbicidally, fungicidally and insecticidally active pyrazole classes are presented, together with their synthetic routes, their modes-of-action and their biological efficacies. Indazoles and other bicyclic pyrazole derivatives are also covered.

CONTENTS

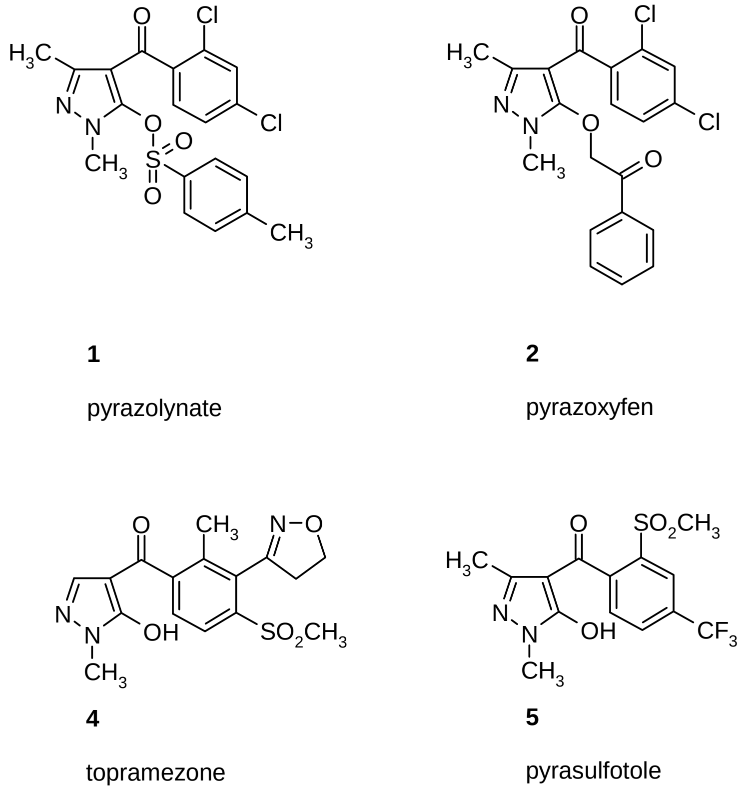
1 INTRODUCTION

During the last decades, intensive efforts have been undertaken to discover highly active chemicals with favorable environmental and safety features for the selective control of weeds, insects and fungal diseases. In several instances, pyrazole derivatives have been found as promising agrochemical products. The pyrazoles constitute a fascinating class of five-membered heterocyclic compounds with two adjacent ring nitrogens, chemically related to the other 1,2-azoles, isothiazoles and isoxazoles, as well as to the isomeric imidazoles, which belong to the 1,3-azoles. The progress in the extensive preparative and theoretical investigations on pyrazoles has been summarized periodically in exhaustive reviews.[2] Also the chemistry of condensed pyrazole derivatives, such as indazoles,[3] pyrazolopyridines,[4] pyrazolo- pyrimidines,[5] pyrazoloquinolines[6] and other biheterocyclic pyrazoles[7] is well documented. In addition, specific pyrazole derivatives, such as pyrazolones,[8] pyrazolines,[9] 5-aminopyrazoles[10] and *N*-acylpyrazoles[11] have been reviewed recently. This review deals with the agrochemical aspects of pyrazole chemistry as well as their bicyclic and saturated derivatives.

2 HERBICIDES

2.1 HPPD Inhibitors

The herbicidal activity of certain 5-hydroxypyrazole derivatives results from inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), the enzyme which catalyzes the formation of



1

pyrazolynate

2

pyrazoxyfen

3

benzofenap

4

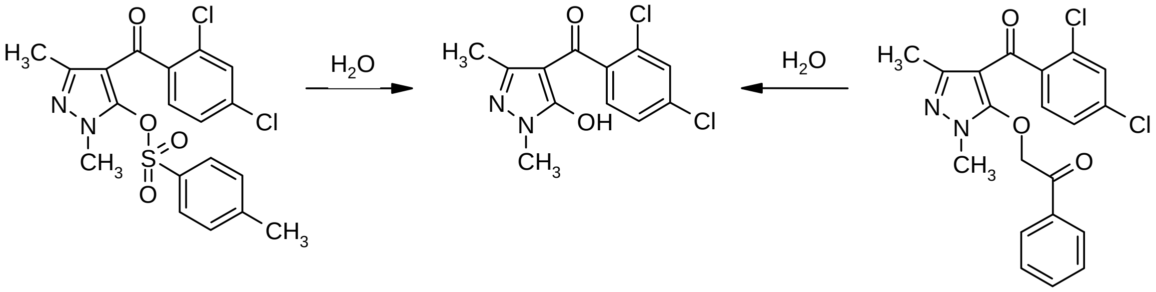
topramezone

5

pyrasulfotole

Figure 1

homogentisic acid. In plants, homogentisic acid is a precursor of plastoquinone, an important cofactor for phytoene desaturase. The enzyme phytoene desaturase plays an important role in the biosynthesis ofcarotenoids. These terpenoids are essential for the protection of the plant chloroplasts against light-induced radical degradation processes (photooxidation). Thus, inhibition of the carotenoid biosynthesis leads to the chlorosis of leafs, characterized by intense bleaching symptoms, and ultimately to plant death.[12]



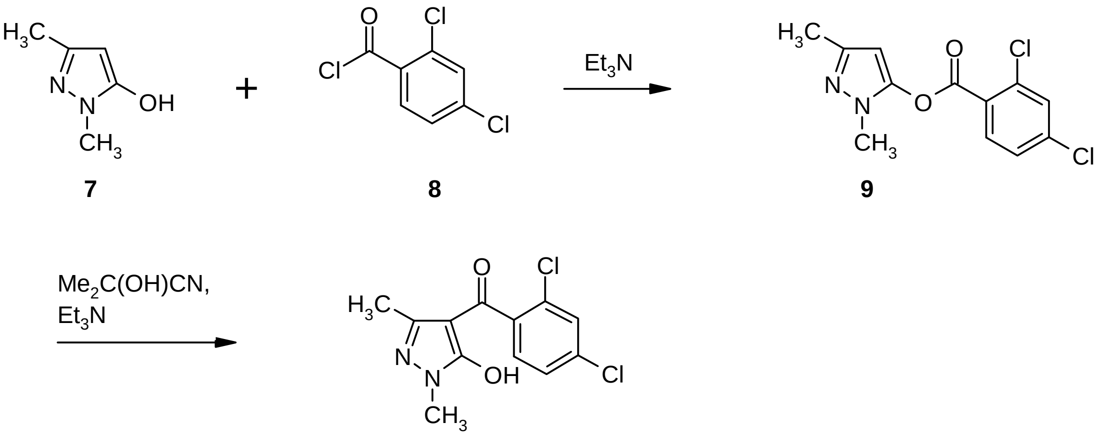
1 pyrazolynate

6 DTP

2 pyrazoxyfen

Scheme 1

Figure 1 shows the five so far commercialized compounds from the class of pyrazole HPPD inhibitors, which was initially discovered by Sankyo. They all have in common a 4-benzoyl-1-methylpyrazole scaffold and bear an oxy function in position 5. Hereby the pyrazole mimics the diketone moiety of the isocyclic HPPD inhibitors sulcotrione and mesotrione.[13] An important requirement for the herbicidal activity of HPPD inhibitors is the presence of an acidic enolic hydrogen atom in the α-position of the keto



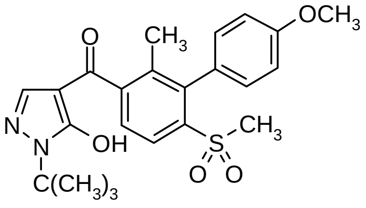
6

DTP

Scheme 2

function in the non-benzoid ring and an electron-deficient aromatic ring containing an *ortho*-substituent. This is the case for topramezone (**4**) and pyrasulfotole (**5**). Therefore the three other herbicides pyrazolynate (pyrazolate, **1**), pyrazoxyfen (**2**) and benzofenap (**3**) are pro-drugs, which are metabolically converted to the corresponding, herbicidally active 5-hydroxypyrazole. In this regard, the two rice herbicides pyrazolynate (**1**) and pyrazoxyfen (**2**) possess the same active principle: DTP (**6**) (Scheme 1).[14] DTP (**6**) is not only the first metabolite of pyrazolynate (**1**) and pyrazoxyfen (**2**), it is also the last intermediate of their synthesis. It is prepared by reaction of 1,3-dimethyl-5-pyrazolon (**7**) and 2,4-dichlorobenzoic acid (**8**) to the ester **9** and its subsequent rearrangement to the ketone DTP (**6**) (Scheme 2).[15]

The experimental 5-hydroxypyrazole HPPD inhibitor **10** combines impressive herbicidal activity against the important grass weeds *Avena fatua* (wild oat), *Setaria viridis* (green foxtail) and *Alopecurus myosuroides* (blackgrass) with excellent wheat selectivity (Figure 2).[16]

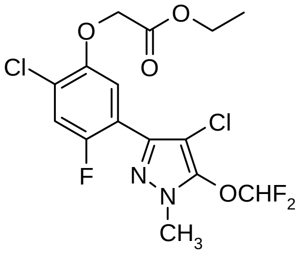


10

Figure 2

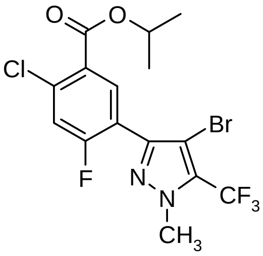
2.2 PPO (Protox) Inhibitors

Several herbicides are inhibiting protoporphyrinogen-IX oxidase (PPO, protox), which is the last enzyme in the porphyrin pathway that is common to both chlorophyll and heme synthesis. In treated tissues, protox inhibitors cause the accumulation of protoprophyrin 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



11

pyraflufen-ethyl



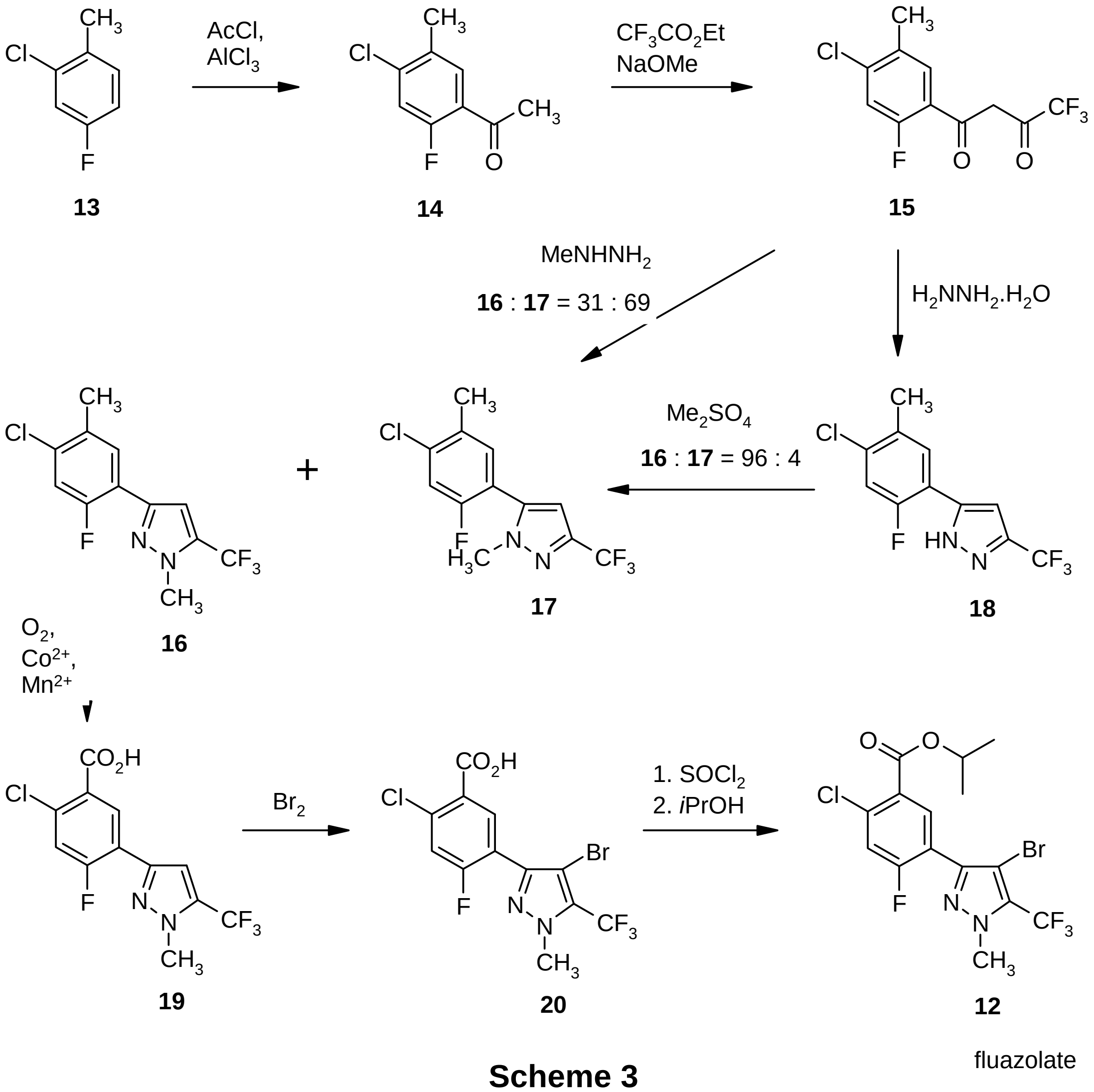
12

fluazolate

Figure 3

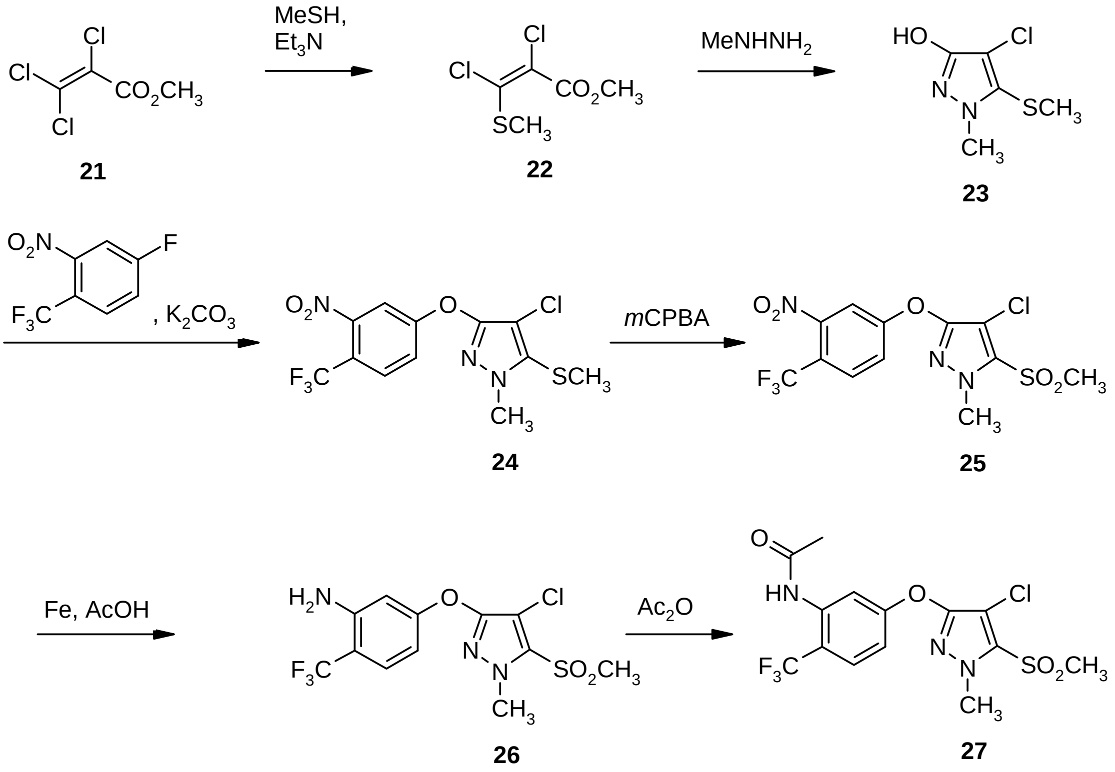
leakage, pigment breakdown and finally necrosis of the leaf.[17] Therefore PPO inhibitors are also called peroxidizing herbicides.

Specially substituted 3-phenylpyrazoles are highly active protox inhibitors. From this class, two structurally related cereal herbicides with completely different application timing have been commercialized. Pyraflufen-ethyl (**11**) is a post-emergent, fluazolate (**12**) a pre-emergent weed control agent (Figure 3). The straight-forward synthesis of fluazolate (**12**) starts from 2-chloro-4-fluorotoluene (**13**), which is converted by Friedel-Crafts acylation and subsequent aldol reaction into the diketone **15** (Scheme 3). Its regioselective transformation into the required 1-methyl-3-arylpyrazole **16** is acieved *via* a two step process by condensation with hydrazine hydrate and followed by alkylation with dimethyl sulfate. Direct cyclocondensation with methyl hydrazine leads predominantly to the undesired 1-methyl-5-arylpyrazole **17**. The methyl group in the phenyl ring of 16 is then oxidized to a carboxylic acid function and bromine is introduced into the pyrazole ring. Finally the transformation of the carboxy function of **20** through the acid chloride to the isopropyl ester delivers fluazolate (**12**) (Scheme 3).[18]



Scheme 3

Pyrazole phenyl ethers,[19,20] such as **27**,[19] are a further family of PPO inhibiting pyrazole derivatives. The synthesis route to **27** starts with the replacement of one of the chlorine atoms in position 3 of methyl trichloroacrylate (**21**) by a thiomethyl group (Scheme 4). The resulting methylthio acrylate **22**, upon reaction with methylhydrazine, gives regioselectively the desired pyrazole **23**, which reacts smoothly with 4-fluoro-2-nitrobenzotrifluoride to the pyrazole phenyl ether **24**. Oxidation of the methyl sulfide to the methyl sulfone is followed by Bechamp-type reduction of the nitro function. Finally, the acylation of the resulting aniline **26** leads to the desired photodynamic herbicide **27**.[19]



Scheme 4

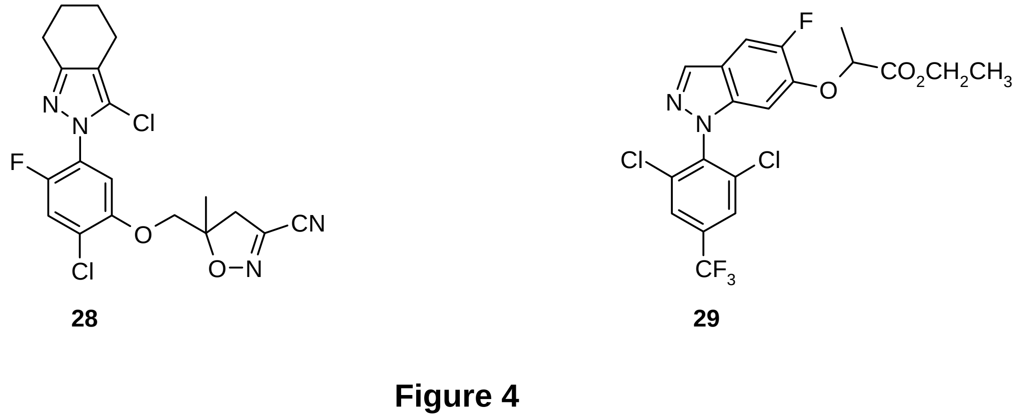
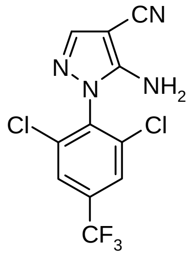


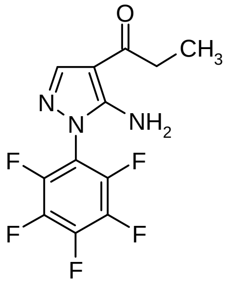
Figure 4

2-Aryl-4,5,6,7-tetrahydro-2*H*-indazoles,[21,22] such as **28**,[21] and 1-aryl-1*H*-indazoles,[23] such as **29**, are further examples for light-activated Protox inhibitors (Figure 4). **28** displays strong activity against *Echinochloa oryzicola* (barnyardgrass), *Monochoria vaginalis* (monochoria) and *Cyperus serotinus* (flatsedge).[21]
Also 5-amino-1-arylpyrazoles bearing either a cyano group in position 4,[24] such as M&B 39279 (**30**), or a keto function,[25] such as **31**, are inhibotors of PPO (Figure 5). **31** is very active against *Brassica napus* (canola, oilseed rape) and *Linum usitassimum* (linseed).[25]



30

M&B 39279

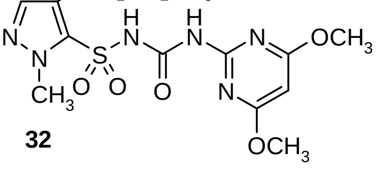


31

Figure 5

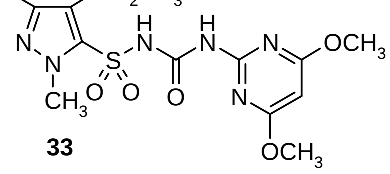
2.3 ALS Inhibitors

Another important herbicidal mode of action, which is also basis for the weed control ability of several pyrazole derivatives, is the inhibition of acetolactate synthase (ALS), an enzyme involved in the early stage of the biosynthesis of branched-chain amino acids, resulting in a rapid cessation of plant cell division and growth.[26] The three branched-chain amino acids valine, leucine and isoleucine are called "essential", because mammals lack biosynthesis pathways to produce them and therefore must obtain them from their diet. This selectivity towards plants undoubtedly contributes to the favourable environmental and toxicological profile of ALS inhibitors. The most important family of ALS inhibitors are the sulfonylureas, which have been discovered in the 1970's at Du Pont.[27] Figure 6 shows three commercialized sulfonylurea



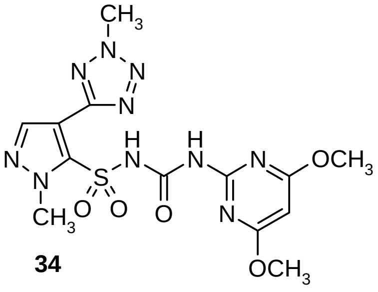
32

pyrazosulfuron-ethyl



33

halosulfuron-methyl



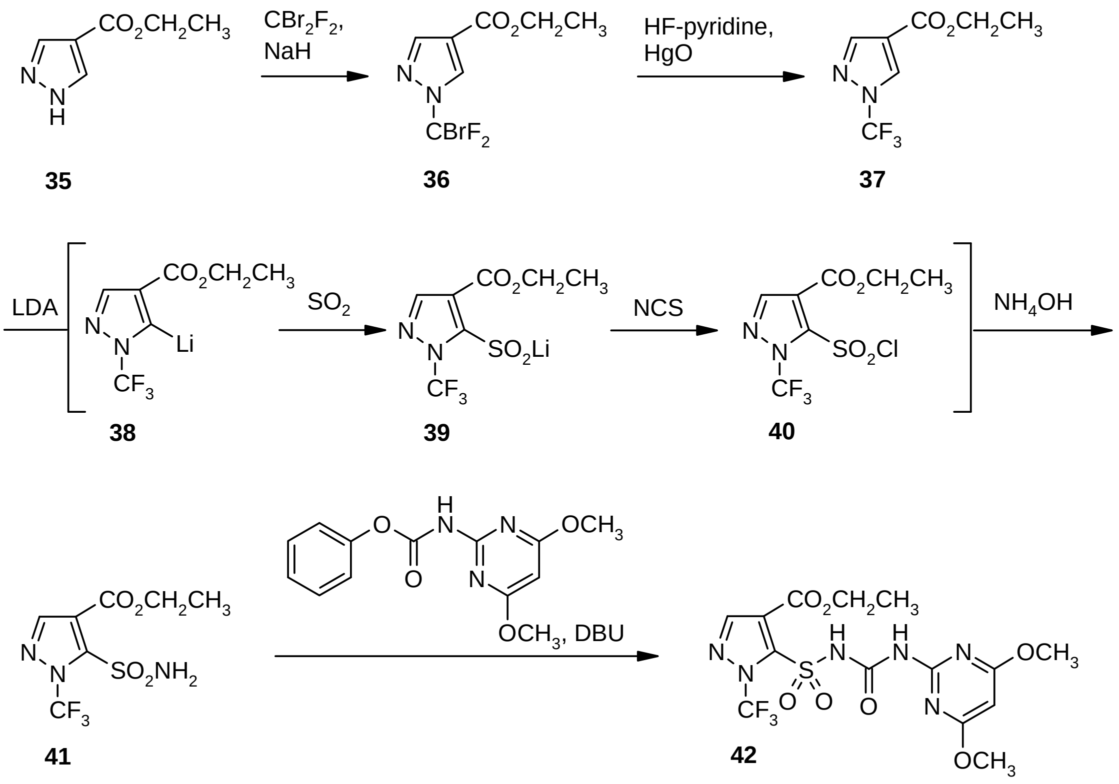
34

azimsulfuron

Figure 6

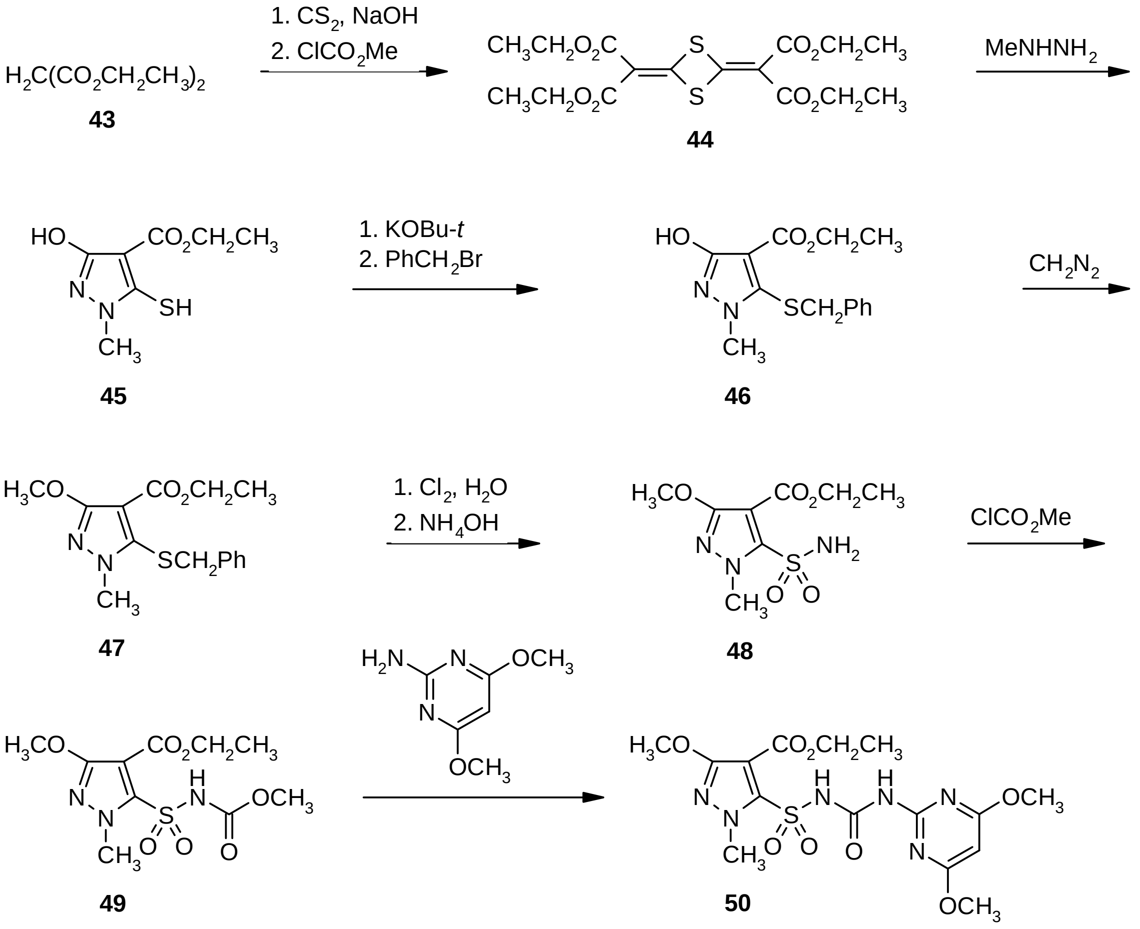
herbicides, in which the typical phenyl ring bearing the sulfonyl function is replaced by a pyrazole. The methyltetrazolyl ring present in azimsulfuron (**34**) serves as an isosteric replacement for the carboxylate function in pyrazosulfuron-ethyl (**32**), which is common for the α-position of the sulfonyl group.

Several syntheses of pyrazole sulfonylureas have been described in the literature.[28-31] Especially intriguing is the synthetic route to the CF_3-analog **42** of pyrazosulfuron-ethyl (**32**), which starts from ethyl pyrazol-4-yl carboxylate (**35**) (Scheme 5). The introduction of a trifluoromethyl group into position 1 of the pyrazole is achieved by *N*-alkylation with dibromodifluoromethane and subsequent halogen exchange reaction with poly(hydrogen fluoride)pyridine coupled with mercuric oxide.[28] This pyrazole can be selectively lithiated in position 5. The resulting organolithium species **38** is then tranformed via the lithium sulfinate **39** and the sulfonyl chloride **40** into the required sulfonamide **41**. This lithiation method was used quite often for the introduction of the sulfonyl function into the pyrazole moiety of sulfonylurea herbicides.[28-30] Finally, the sulfonamide **41** is converted with the phenylcarbamate of 2-amino-4,6-dimethoxypyrimidine to the CF_3-analog **42** of pyrazosulfuron-ethyl (**32**) (Scheme 5).[28]



Scheme 5

The synthesis of a pyrazosulfuron-ethyl derivative with an additional methoxy group in position 3 of the pyrazole moiety is also quite interesting (Scheme 6). The reaction of the 1,3-dithietane **44**, which is readily obtainable from diethyl malonate (**43**) and carbon disulfide, with methyl hydrazine affords regioselectively the 3-hydroxy-5-mercaptopyrazole **45**.[29] After benzylation of the thiol function, the hydroxy group is methylated to the methoxypyrazole **47**. Its oxidative chlorination and subsequent amination leads to the sulfonamide **48**, which is transformed *via* the sulfonylcarbamate **49** into the desired pyrazosulfuron-ethyl derivative **50**, which is highly active against *Abutilon theophrasti* (velvetleaf) and *Xanthium strumarium* (heartleaf cocklebur) (Scheme 6).[29]



Scheme 6

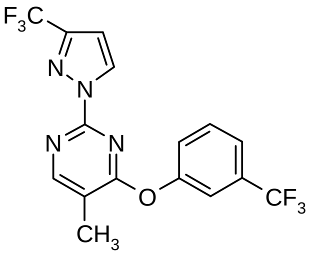
Also sulfonylurea derivatives are known, in which the typical ureapyrimidine or -triazine moiety is replaced by a carbamoylpyrazoline. Examples for this interesting class of ALS inhibitors are the phenyl derivative **51**[32] and the sultam derivative **52** (Figure 7).[33] The latter is a wheat-selective herbicide with powerful performance against *Solanum nigrum* (black nightshade), and *Galinsoga ciliata* (hairy galinsoga).[33]


51 **52**

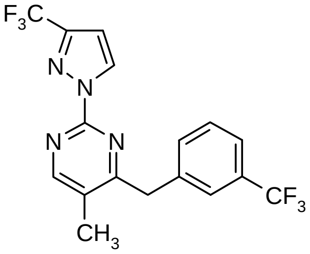
Figure 7

2.4 Miscellaneous Herbicidally Active Pyrazoles

The 2-(pyrazol-1-yl)-4-phenoxypyrimidine **53**[34] and its benzyl analog **54**[35] displayed strong broadleaf weed control at use rates of 5 – 10 g / ha in cereal field trials (Figure 8). Their herbicidal activity results from the inhibition of carotenoid biosynthesis.[34,35]



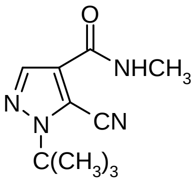
53



54

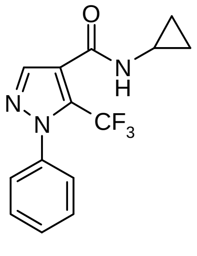
Figure 8

Several pyrazole-4-carboxamides have been reported to possess remarkable herbicidal activity. EL-177 (**55**) was investigated for use as pre-eemergent corn and post-emergent cereal herbicide.[36] **56** is highly effective against an impressive broad range of weeds, such as *Echinochloa crus-galli* (barnyard grass), *Chenopodium album* (lambsquarters), *Brassica kaber* (wild mustard), *Digitaria sanguinalis* (large



55

EL-177



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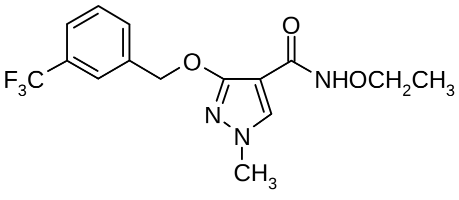
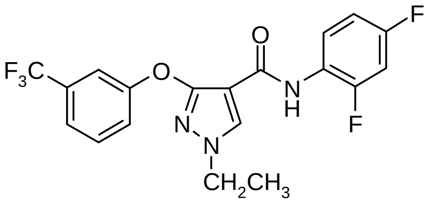


57

KPP-297



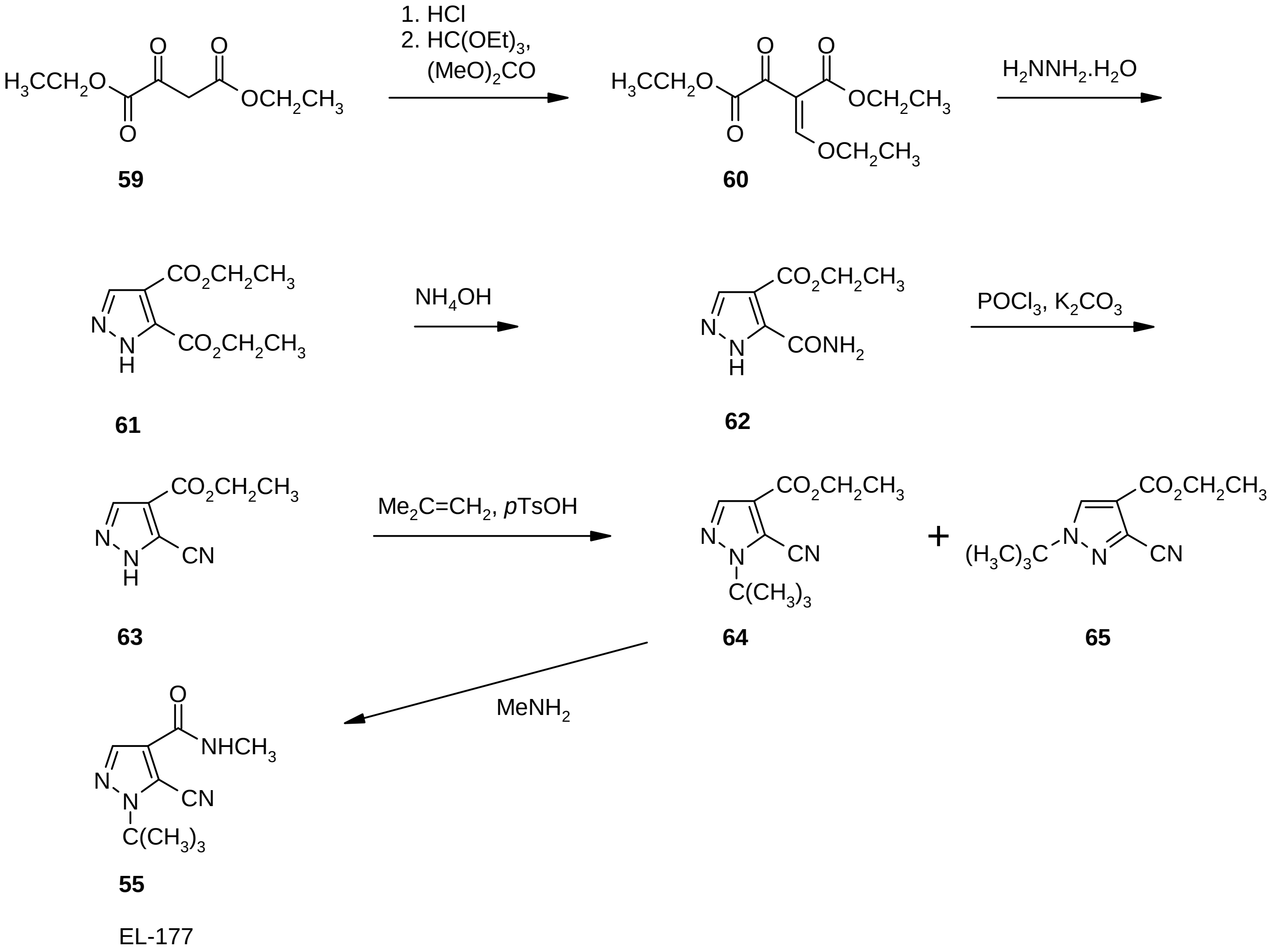
58

KPP-856

Figure 9

crabgrass), *Abuthilon threophrasti* (velvetleaf), *Setaria italica* (foxtail millet), *Ipomoea hederacea* (morningglory), *Amaranthus retroflexus* (redroot pigweed) and *Datura stramonium* (jimsonweed).[37] The two pyrazole-4-carboxamides KPP-297 (**57**)[38] and KPP-856 (**58**)[39] show excellent and selective activity against the rice weeds *Echinochloa oryzicola* (early watergrass), *Cyperus difformis* (smallflower umbrellaplant) and *Monochoria vaginalis* (monochoria) (Figure 9).[38,39]

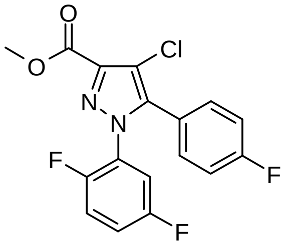
An economic synthesis of EL-177 (**55**) is possible from readily available precursors utilizing a novel regioselective *t*-butylation reaction (Scheme 7).[36,40] Condensation of the sodium salt of diethyl oxalacetate (**59**) with triethyl orthoformate gave **60**, which could be ring-closed with hydrazine hydrate to the pyrazole diester **61**. Treatment of **61** with ammonium hydroxide provided the amide ester **62**, which was dehydrated to the corresponding pyrazole cyano ester **63** with phosphorus oxychloride and potassium carbonate. The alkylation **63** with two equivalents of isobutylene and 0.3 equivalents of *p*-toluenesulfonic acid in acetonitrile at 80 °C for 24 hours affords the desired *N*-*t*-butyl pyrazole **64** in a regioselectivity greater than 90 : 1. Interestingly, the replacement of *p*-toluenesulfonic acid by strong Lewis acids such as aluminum trichloride leads to the exclusive formation of the undesired regioisomer **65**. Finally, transformation of the



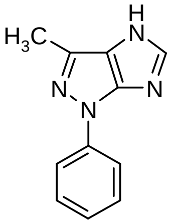
Scheme 7

ethyl ester function of **64** with methylamine delivers EL-177 (**55**) (Scheme 7).[36,40]

The 1,5-diarylpyrazole **66** possesses activity against a broad range of weeds, e.g. *Cyperus serotinus* (flatsedge), *Echinochloa oryzicola* (barnyard grass), *Eleocharis acicularis* (slender spikerush) and *Sagittaria pygmaea* (arrowhead).[41] The imidazo[4,5-c]pyrazole **67** displays good post-emergent efficacy against *Abutilon theophrasti* (velvetleaf), *Sesbania exaltata* (hemp sesbania), *Brassica kaber* (wild mustard) and *Echinochloa crus-galli* (barnyard grass) (Figure 10).[42]



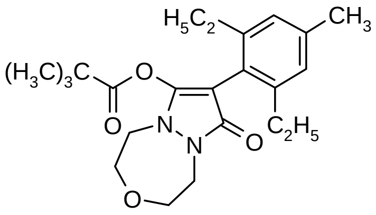
66



67

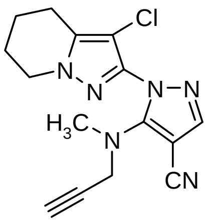
Figure 10

Two modern herbicides with bicyclic pyrazole systems have been recently introduced to the market. Pinoxaden (**68**) is inhibiting ACCase, whereas pyraclonil (**69**) is a PPO inhibitor (Figure 11). Pyroxasulfone (**70**) is currently under development.



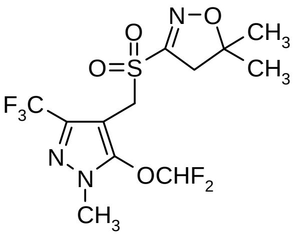
68

pinoxaden



69

pyraclonil



70

pyroxasulfone

Figure 11

3 FUNGICIDES

3.1 Complex 2 Respiration Inhibitors

The three 1-methyl-1*H*-pyrazole-4-carboxamides furametpyr (**71**), penthiopyrad (**72**) and bixafen (**73**) are respiration inhibitors, blocking the mitochondrial complex 2 (Figure 12).

These compounds possess the same mode of action as carboxin, the oldest fungicidal complex 2 inhibitor, which has a dihydrooxathiin ring system instead of the pyrazole moieties of furametpyr and penthiopyrad.

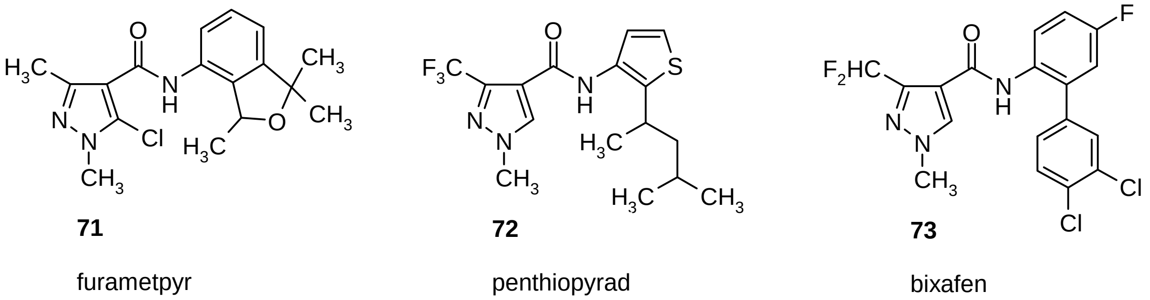
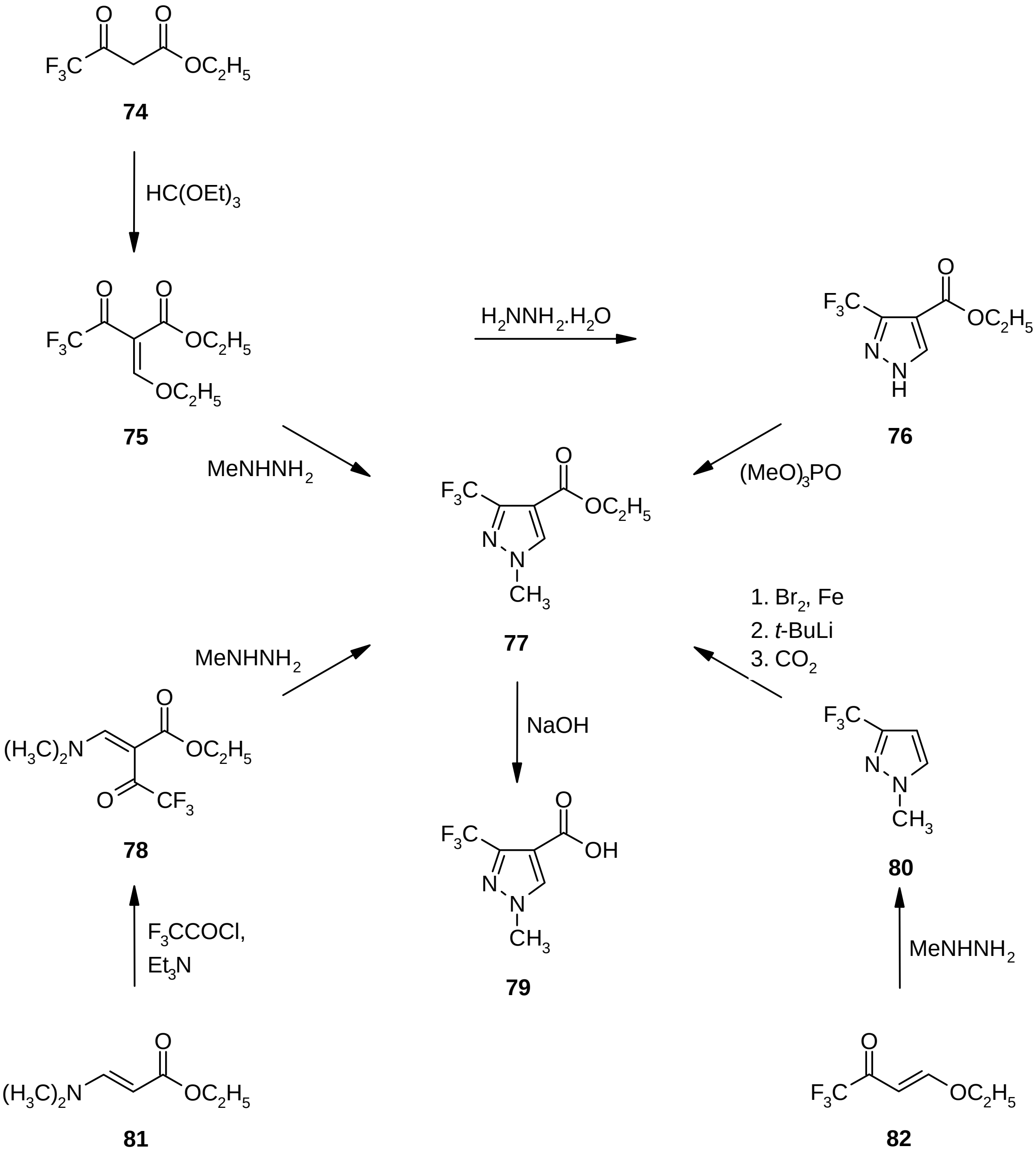


Figure 12

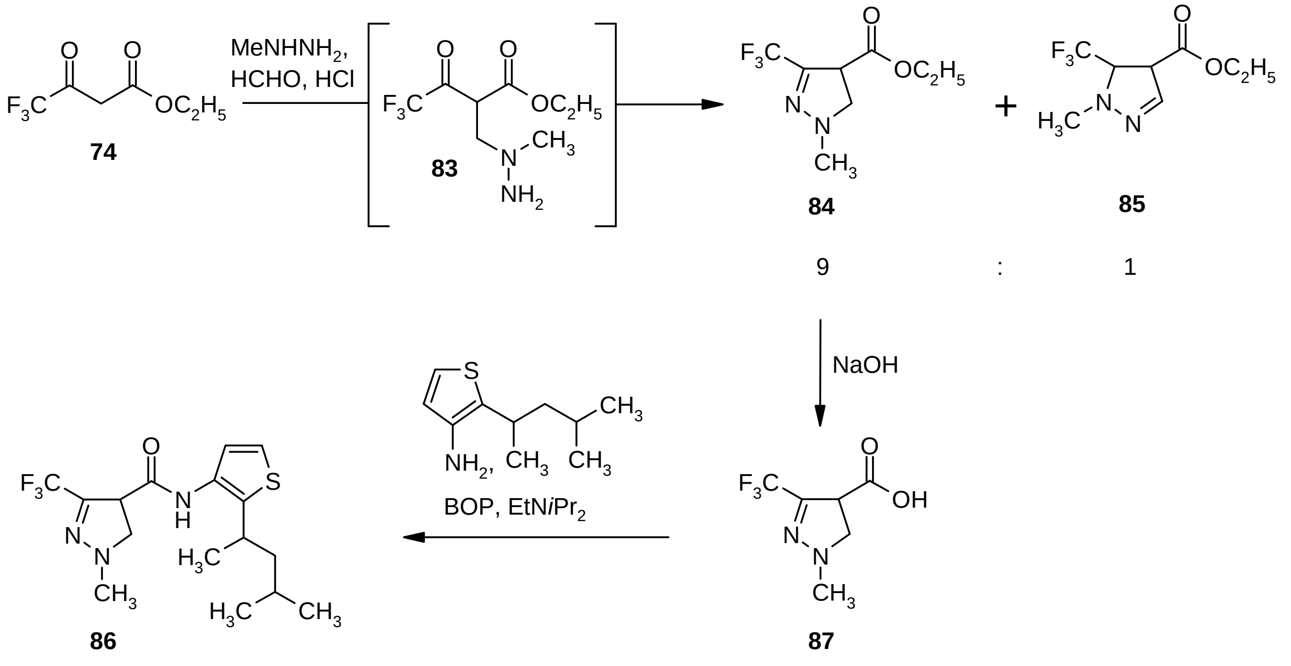
The earliest pyrazole analogs of carboxin have been reported already in 1976, bearing a methyl group in



Scheme 8

position 3.[43] Other fungicidally active 3-methyl-pyrazole-4-carboxanilides have also been described in the years thereafter,[44] leading finally to the discovery of furametpyr (**71**). In 1986, it was found, that the introduction of a trifluoromethyl group into position 3 of the pyrazole unit of complex 2 inhibitors results in increased fungicidal activity.[45] Since then, 1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid (**79**), the acid moiety of penthiopyrad (**72**), has gained importance as suitable building block in fungicide chemistry. Scheme 8 shows different synthetic pathways to this compound. The most straightforward procedure for the preparation of **79** is the condensation of methylhydrazine with the 2-ethoxymethylene substituted acetoacetate **75**, which is readily available from the convenient starting material ethyl 4,4,4-trifluoroacetoacetate (**74**).[46] Instead of this ring-closure reaction with methylhydrazine, **75** can also be condensed with hydrazine hydrate to the pyrazole **76**, which can be easily methylated with trimethyl phosphate.[47] The obtained pyrazole ethyl ester **77** can be hydrolysed to the free pyrazole acid **79** under standard saponification conditions.[46,48] Other possibilities for the synthesis of **77** include the reaction of ethyl dimethylaminoacrylate (**81**) with trifluoroacetyl chloride and methylhydrazine,[48] as well as the consecutive bromination, lithiation and carboxylation of 1-methyl-3-(trifluoromethyl)pyrazole (**80**) (Scheme 8).[49]

Just recently, an interesting synthesis of the pyrazoline analog **86** of penthiopyrad has been described by Mannich reaction of ethyl 4,4,4-trifluoroacetoacetate (**74**) with methyl hydrazine and formalin in the presence of catalytic amounts of hydrochloric acid in refluxing ethanol (Scheme 9).[50] The intermediate Mannich adduct **83** cyclizes spontanously to the desired 3-trifluoromethyl substituted 4,5-dihydro-1*H*-pyrazole **84**, accompanied by only minor amounts of the corresponding



Scheme 9

5-trifluoromethyl-4,5-dihydropyrazole **85**. The pyrazoline **84** can be converted via ester cleavage and amidation into dihydro-penthiopyrad **86** (Scheme 9).[50]

3.2 Complex 3 Respiration Inhibitors (Strobilurins)

The strobilurins are an important class of agricultural fungicides, the discovery of which was inspired by a group of naturally occuring fungicidally active derivatives of β-methoxyacrylic acid, e.g.strobilurin A, oudemansin A and myxothiazol A.[51,52] The fungicidal efficacy of the strobilurins results from their ability to inhibit mitochondrial respiration by binding to the Q_o 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 electron transfer between cytochrome b and cytochrome c_1, which, in turn, disrupts the energy cycle within the fungus by stopping the oxidative phosphorylation and therefore the production of ATP.[51,52]

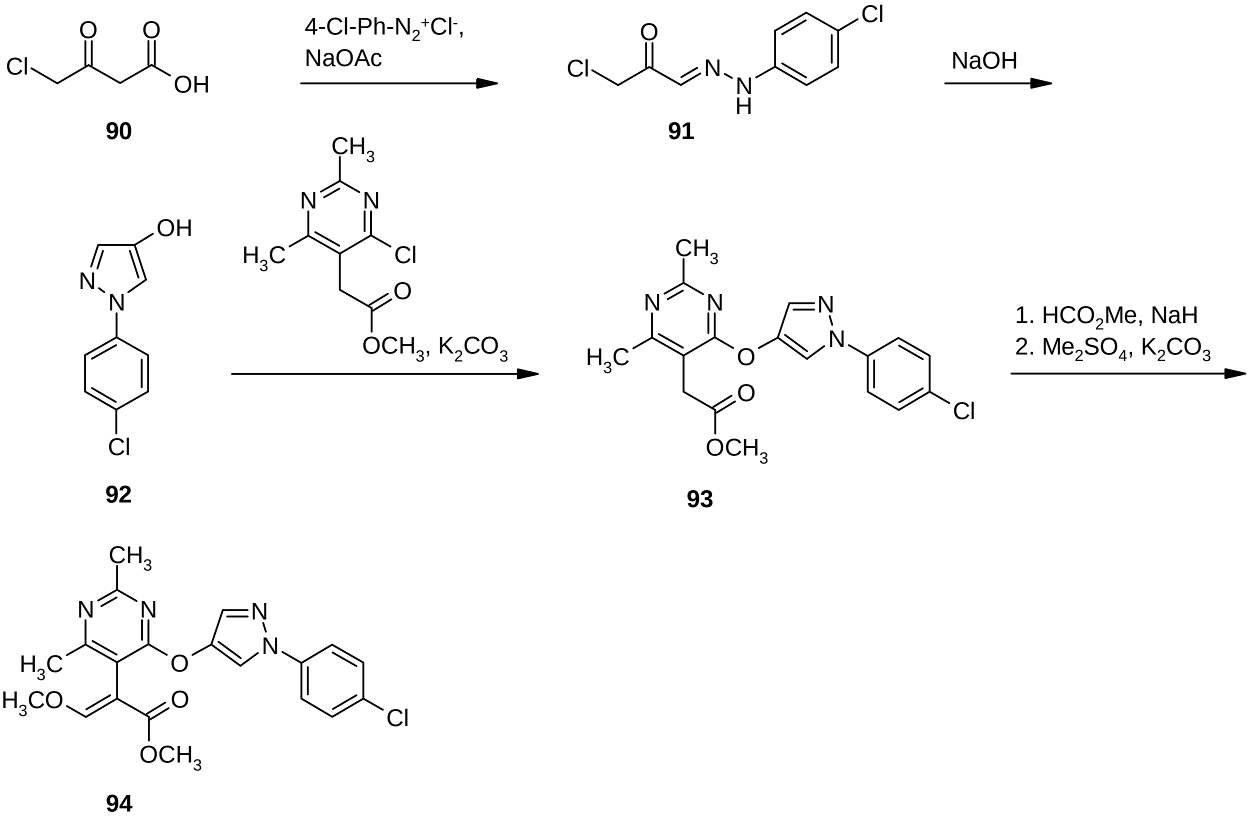
88

pyraclostrobin

89

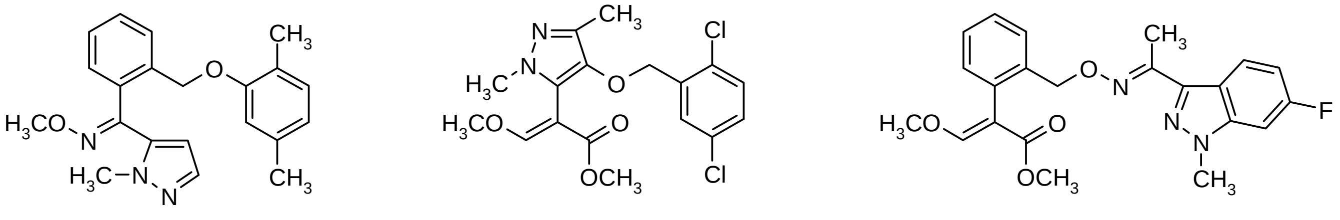
Figure 13

The introduction of a pyrazole ring into the sidechain of strobilurin fungicides results often in reduced lipophilicity (low log P values) and therefore enables the systemic movement of the compound through the plant. Examples for such quite polar strobilurins are pyraclostrobin (**88**), bearing a carbamate pharmacophor, and its oximeether-amide analog **89**, which both possess a 1-aryl-3-oxypyrazole sidechain (Figure 13).[52] Also strobilurin fungicides with a more rare 1-aryl-4-oxypyrazole moiety, such as **94**, are known (Scheme 10).[53] 1-(4-chlorophenyl)-4-hydroxypyrazole (**92**), the sidechain of the β-methoxyacrylate **94**, can be obtained from 4-chloroacetoacetic acid (**90**), which is decarboxylated in the presence of a freshly prepared aryldiazonium salt under the Japp-Klingemann conditions.[54] The resulting 3-chloropyruvic aldehyde hydrazone **91** is then cyclized under basic conditions to the 1-aryl-4-hydroxypyrazole **92**,[54] which can be linked to an appropriate methyl pyrimidin-5-yl-acetate.[55] Formylation and *O*-methylation of the resulting **93** finally leads to the desired fungicide **94**, which is very active against the cereal diseases *Erysiphe graminis* (powdery mildew), *Puccinia recondita* (brown rust) and *Pyrenophora graminea* (leaf stripe) (Scheme 10).



Scheme 10

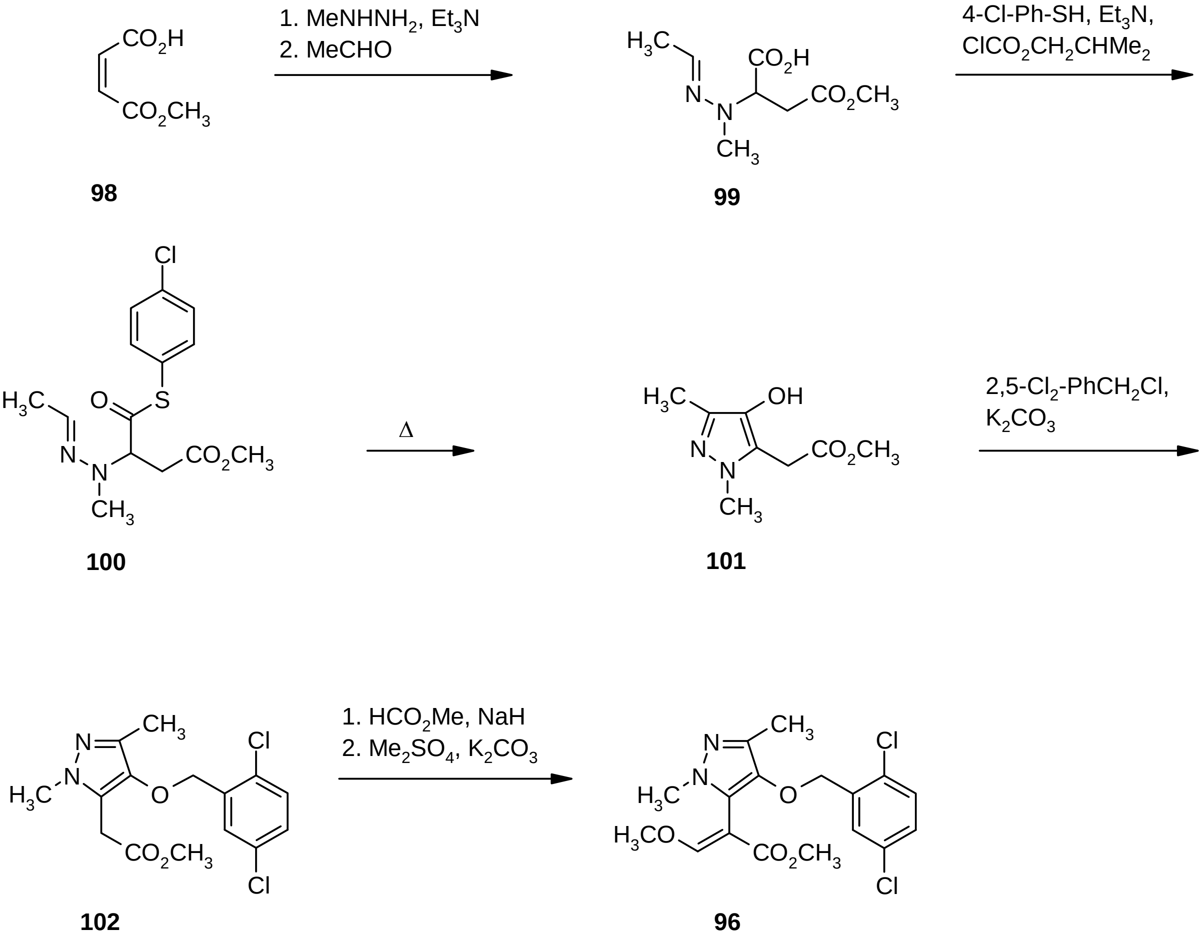
The introduction of a pyrazole heterocycle into the pharmacophore part of a strobilurin, as in **95**, does not seem to be successful, because **95** does not possess any fungicidal efficacy.[56] However, the highly active fungicide **96** demonstrates the suitability of pyrazole as isostere of the pharmacophore-bearing phenyl ring.[57] The indazole sidechain of **97** contributes to very favorable physico-chemical properties of this agrochemical, resulting in high fungicidal and insecticidal activities (Figure 14).[58]



95 **96** **97**

Figure 14

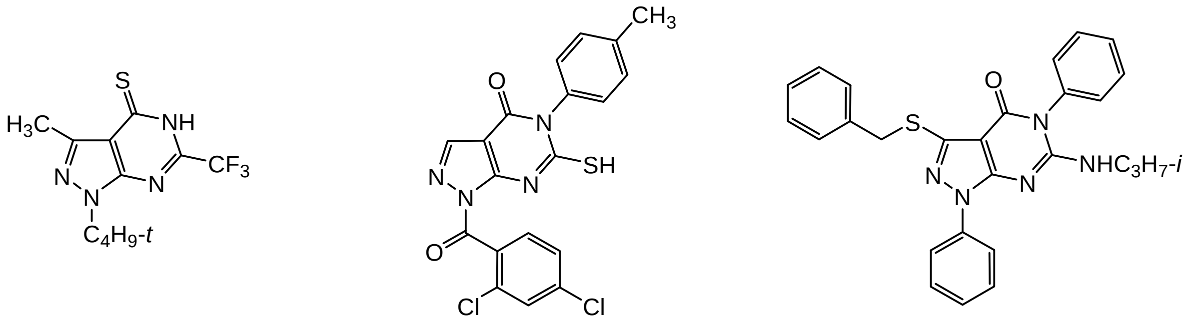
An interesting approach to the pyrazole strobilurin **96** has been described starting from maleic acid monomethyl ester (**98**) (Scheme 11).[59] This starting material is converted into the aspartic acid derivative **99**, which, via the thioester **100**, can be cyclized to the methyl pyrazol-5-yl-acetate **101**. The alkylation of its hydroxy function with 2,5-dichlorobenzyl chloride delivers the intermediate **102**, which is transformed into the final product **96** by formylation and *O*-methylation.[59]



Scheme 11

3.3 Miscellaneous Fungicidally Active Pyrazoles

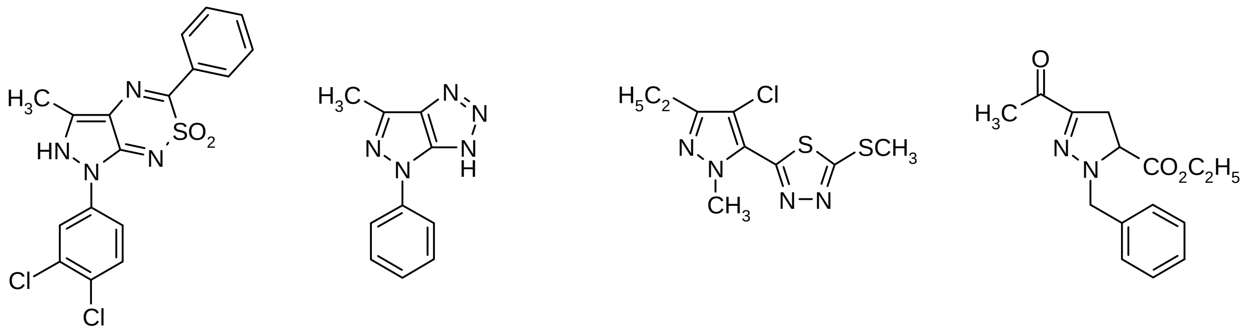
Several pyrazolo[3,4-*d*]pyrimidines have been reported to possess fungicidal activity (Figure 15). The pyrimidine-4-thione **103** is very active against *Pythium ultimum* (damping-off),[60] *Corticium solani* (black scurf)[60] and *Magnaporthe grisea* (rice blast),[61] whereas the pyrimdin-4-ones **104**[62] and **105**[63] are able to control *Helminthosporium oryzae* (brown spot of paddy)[62] or *Botrytis cinerea* (grey mould)[63] respectively. Also other [3,4-*d*]condensed pyrazole derivative show powerful fungicidal activities (Figure 16). The pyrazolothiadiazine-2,2,-dioxide **106** completely inhibits the growth of *Pythium ultimum* (damping-off), *Sclerotinia minor* (lettuce drop) and *Corticium solani* (black scurf).[64] The pyrazolotriazole **107** is especially active against *Fusarium culmorum* (head blight) and *Pythium ultimum* (damping-off).[65] The 5-thiadiazolyl



103 **104** **105**

Figure 15

substituted pyrazole **108**[66,67] and its oxadiazole analog[66] both possess strong fungicidal activity against *Rhizoctonia solani* (rice sheath blight). The pyrazoline derivative **109** is active against *Pyricularia oryzae* (rice blast) and *Erysiphe graminis* (cereal powdery mildew).[68]



106 **107** **108** **109**

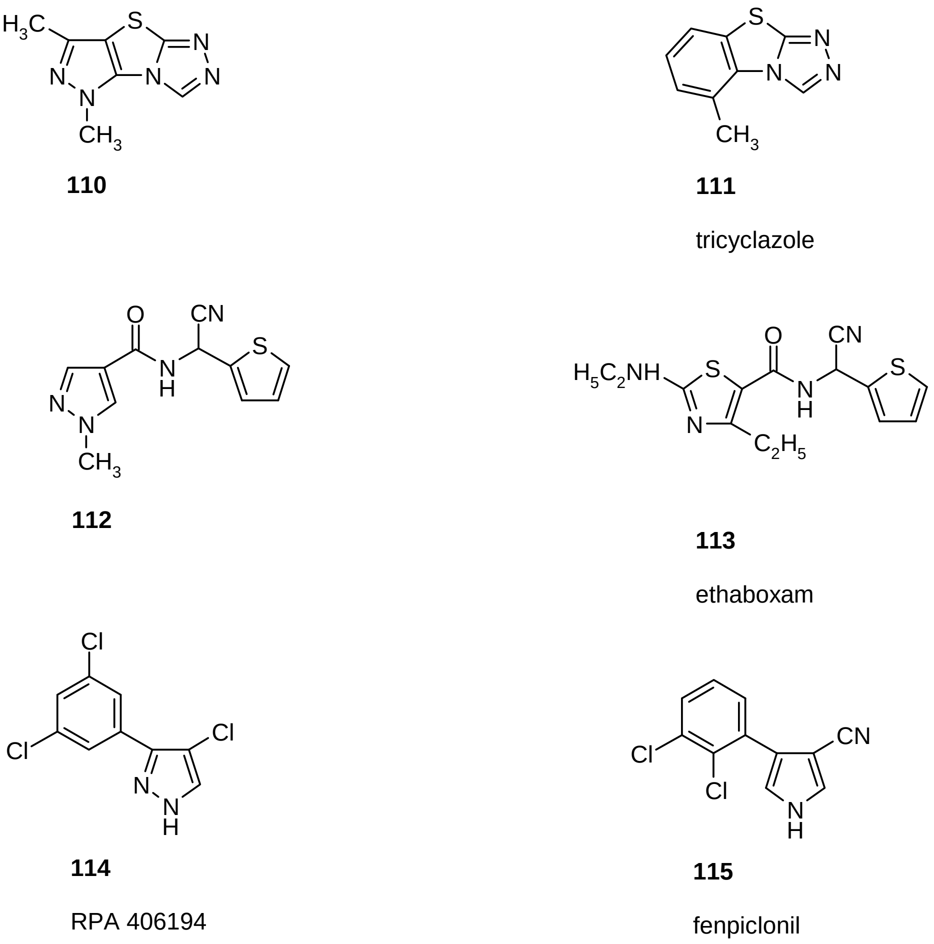
Figure 16

The pyrazole ring seems to be an appropriate isostere for several iso- or heterocyclic ring moieties in established fungicides (Figure 17). For instance **110**, in which the phenyl ring of tricyclozole (**111**) is exchanged by a dimethylpyrazole unit, possesses activity against *Magnaporthe grisea* (rice blast) and *Botrytis cinerea* (grey mould).[69] The amide **112**, in which pyrazole replaces the thiazole ring of ethaboxam (**113**),[70] is quite active against *Pseudoperonospara cubensis* (cucumber downy mildew).[71] The pyrazole analog RPA 406194 (**114**) of the phenylpyrrole fenpiclonil (**115**)[72] is effective against several fungal diseases.[73]

4 INSECTICIDES

4.1 Chloride Channel Blockers (Fiproles)

The fiproles are a very modern group of highly efficient broad-spectrum insecticides, which act as



110

111

tricyclazole

112

113

ethaboxam

114

RPA 406194

115

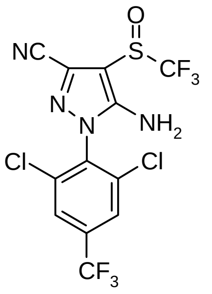
fenpiclonil

Figure 17

antagonistic inhibitors of the γ-aminobutyric acid (GABA)-gated chloride channnel in the membrane of insect nerve fibers, causing neuronal cell hyperexcitability.[74] Radioligand binding studies show, that they bind with higher affinity to insect than to vertebrate GABA receptors.[75] Several fiproles are either currently in development or already on the market with a broad range of uses for foliar, soil and seed treatment as well as for the control of ectoparasites (Figure 18). Fipronil (**116**), the first commercial insecticide from this class, was originally synthesized as herbicide, because related derivatives, which bear a nitro function instead of the trifluoromethylsulfinyl group are herbicidally active.[76]

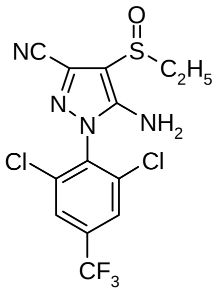
The fate of fipronil (**116**) in animals and in sunlight is completely different. The major metabolite in insects as well as in vertebrates is the sulfone **122**, which is definitely more toxic for mammals than fipronil itself.[75] In spray solutions and on plants, fipronil photolyzes to its desthio derivative **123** via a unique concerted SO extrusion mechanism (Scheme 12).[75,77]

The synthesis of fipronil (**116**) starts from 2,6-dichloro-4-trifluoromethylaniline (**124**), the diazonium salt of which is trapped with ethyl 2,3-dicyanopropionate to **125** (Scheme 13). This azo compound is ring closed in the presence of ammonia to the trisubstituted pyrazole **126**, which serves as central intermediate



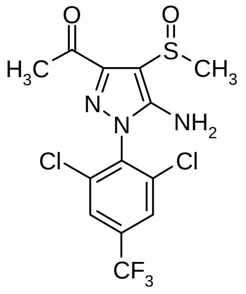
116

fipronil



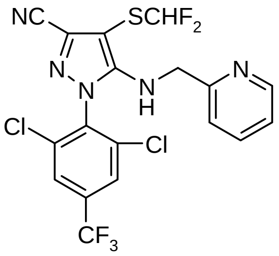
117

ethiprole



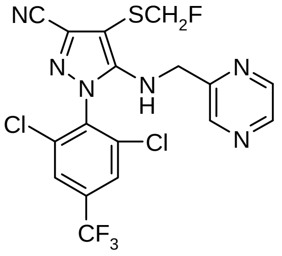
118

acetoprole



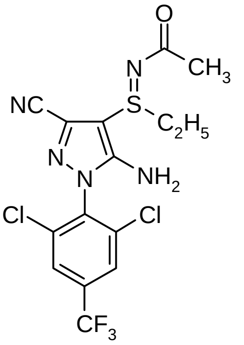
119

pyriprole



120

pyrafluprole

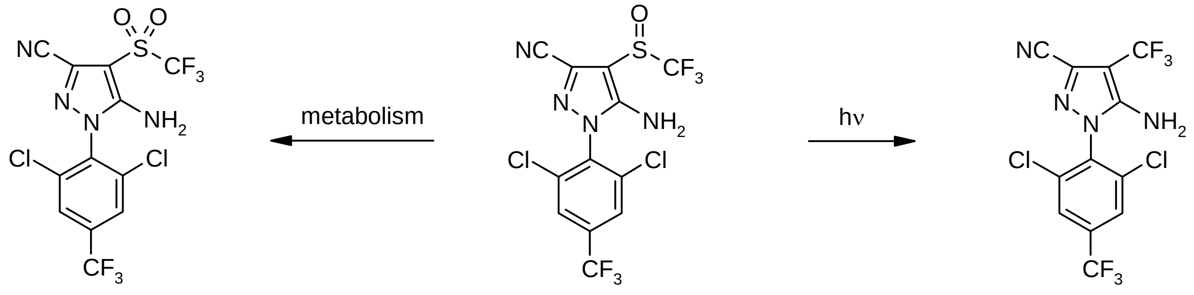


121

AVI-382

Figure 18

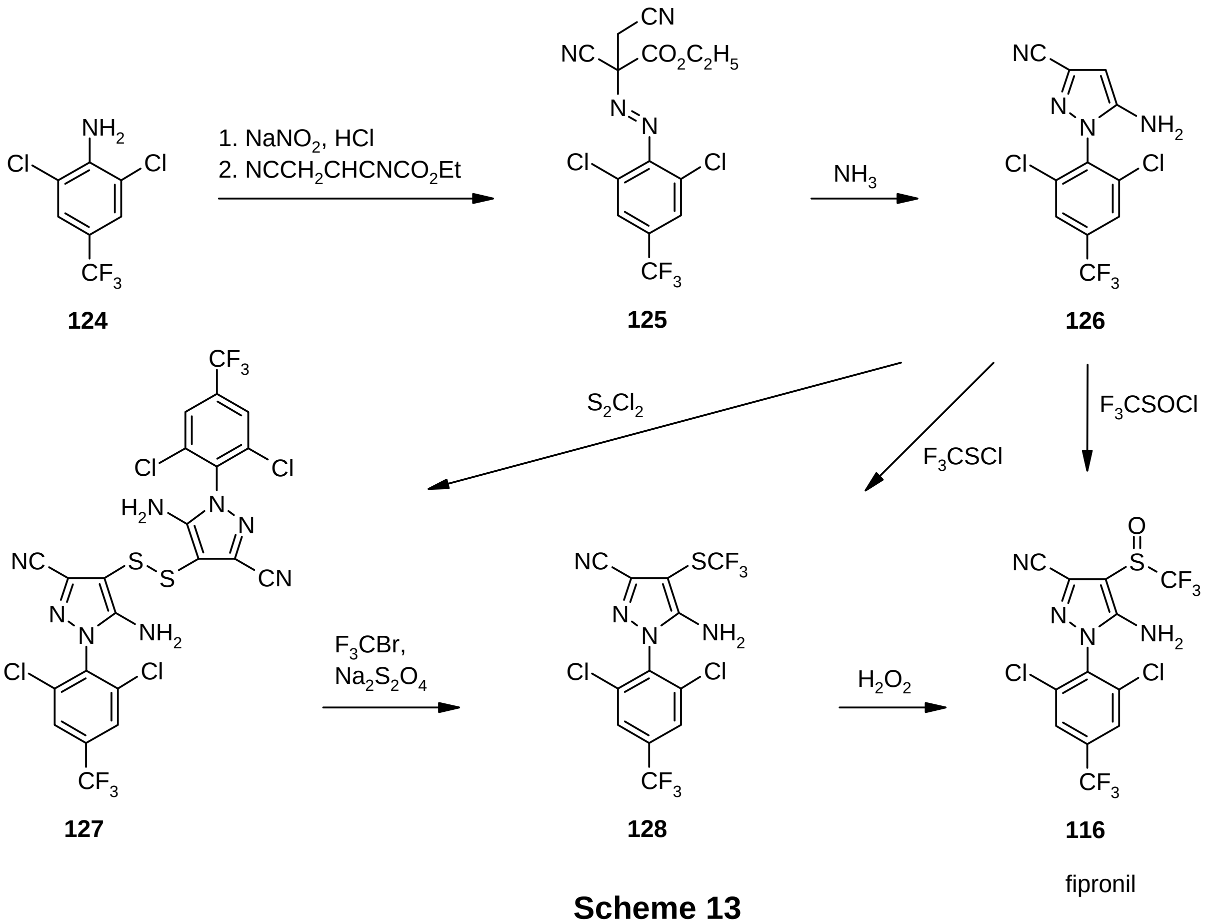
of the fipronil synthesis. It offers different possibilities for the introduction of the trifluoromethylsulfinyl group, the fourth substituent of fipronil. **126** can be transformed directly into fipronil (**116**) by reaction with trifluoromethylsulfinyl chloride, it also reacts with trifluoromethylsulfenyl chloride to the sulfide **128**, which can be oxididized to fipronil.[78] Alternatively, **126** can be reacted to the disulfide **127**, which can be cleaved with bromotrifluoromethane and sodium dithionite via a radical pathway to the trifluoromethyl sulfide **128** (Scheme 13).[78,79]



122 **116** **123**

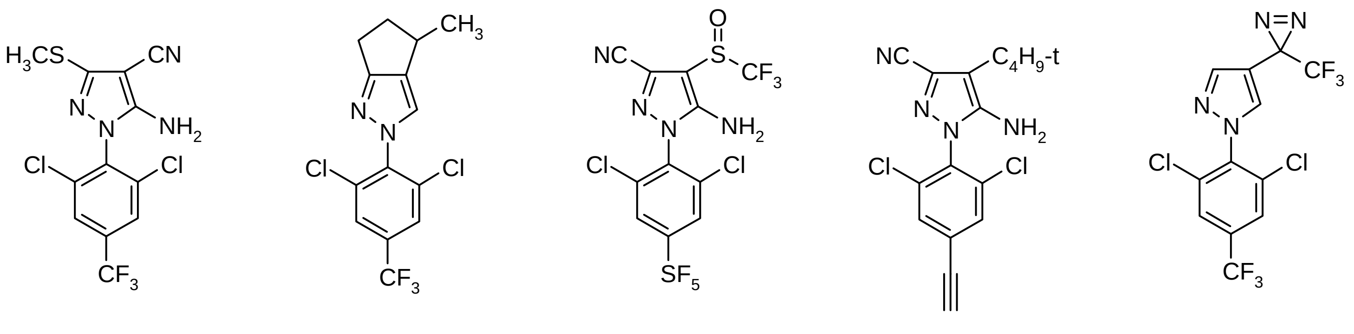
fipronil

Scheme 12



Scheme 13

Several analogs of fipronil (**116**) also possess potent insecticidal activities (Figure 19). For instance **129**, in which the thioalkyl function and the cyano group of fipronil have changed places,[80] and the tetrahydrocyclopentapyrazole **130**[81] possess high selectivities against the mammalian (mouse brain) GABA receptor. The trifluoromethyl group in the phenyl ring of fipronil can be replaced by a sulfur pentafluoride function, as in **131**,[82] or by acetylene, as in **132**,[83] under full preservation of the biological activity. The diazirine **133** is a structurally simplified, but highly potent fipronil mimick, which allows the photoaffinity labelling of the GABA receptor.[84]

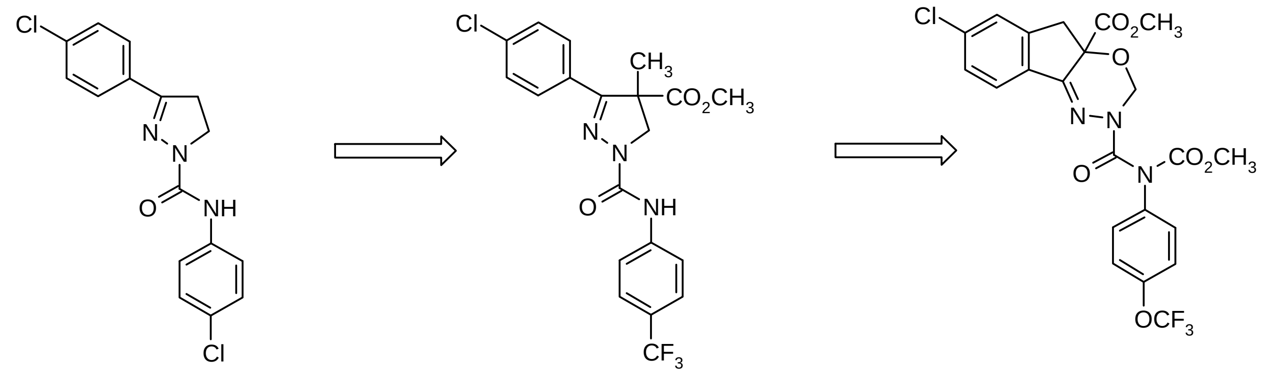


129 **130** **131** **132** **133**

Figure 19

4.2 Sodium Channel Blockers (Pyrazolines)

Several pyrazolines (dihydropyrazoles) are voltage-dependent inhibitors of the sodium channel. Hereby, the insects are paralyzed by suppressing activity in sensory nerves and in the centrol nervous system.[85] PH 60-41 (**134**), one of the first insecticidally active pyrazolines, has been discovered at Philips-Duphar in the early 1970's (Figure 20).[86] It is very active against *Leptinotarsa decemlineata* (Coloroda potato beetle) and *Aedes aegypti* (yellow fever mosquito).[86] Also derivatives of PH 60-41 with an additional phenyl ring in position 4[87] or 5[88] of the pyrazoline have been described. Further optimisation of PH 60-41 led via 4,4'-disubstitued pyrazolines such as RH 3421 (**135**), which has been described by Rohm and Haas in the mid 1980's to possess high insecticidal activity combined with low mammalian toxicity and a rapid rate of degradation in the environment,[89] finally to the discovery of indoxacarb (**136**) at DuPont in the mid 1990's.[90] Indoxacarb is highly efficient against a broad range of insect species such as *Spodoptera littoralis* (cotton leafworm), *Heliothis virescens* (tobacco budworm), *Plutella xylostella* (diamondback moth), *Trichoplusia ni* (cabbage looper) and *Cydia pomonella* (codling moth).[90]



134 PH 60-41

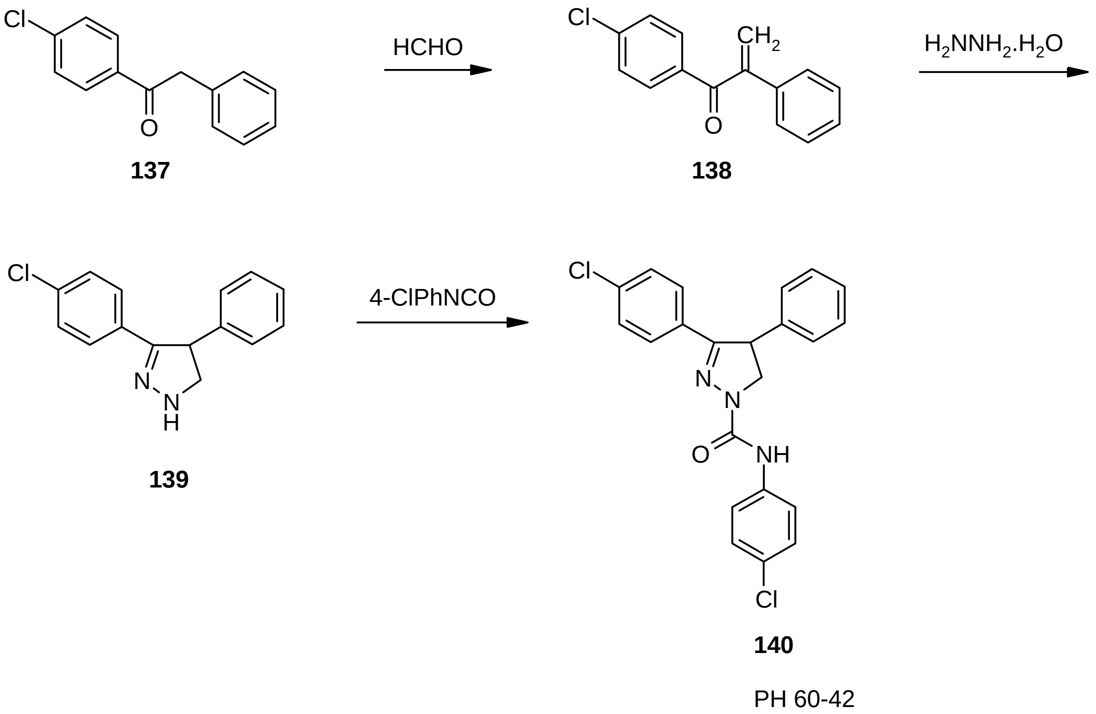
135 RH 3421

136 indoxacarb

Figure 20

The 3,4-diarylpyrazoline PH 60-42 (**140**) was found to have good activity against both lepidoptera and coleoptera species. It can be prepared from 4'-chloro-2-phenylacetophenone (**137**) by aldol condensation with formaldehyde and subsequent ring-closure with hydrazine hydrate to the pyrazoline derivative **139**. Finally, the construction of the semicarbazid function of PH 60-42 is performed by transformation of **139** with 4-chlorophenyl isocyanate (Scheme 14).[87]

Several interesting analogs of the highly active 3,4-diarylpyrazoline PH 60-42 (**140**) have been prepared (Figure 21). For example, the phenyl ring in position 4 of the pyrazoline can be replaced by a heterocycle, e.g. 1,2,4-triazole as in **141**, which is highly active against *Plutella xylostella* (diamondback moth) and *Spodoptera frugiperda* (fall armyworm).[91] Furthermore, the phenyl ring in position 3 of the pyrazoline can be tethered to the pyrazoline to form a tricyclic ring system, such as **142**,[92] or to the phenyl ring in position



Scheme 14

4 to obtain a tetracyclic ring system, e.g. **143**.[93] Quantitative structure-activity relationship studies in the pyrazoline area indicated the 4-substituent to be a key activity element in the structure.[94] X-ray studies have shown, that in the preferred conformers these substituents in position 4 typically adopt an axial orientation and therefore are out of the pyrazoline plane. In the tricyclic tetrahydrobenzoindazole **142** the conformation of the pyrazoline ring is locked and the angular phenyl group is forced in the desired axial orientation. Another example for a conformationally restrained pyrazoline is the tetracyclic dibenzooxocinopyrazoline **143**.[93] Both compounds **142** and **143** are highly active against *Heliothis virescens* (tobacco budworm) and *Spodoptera frugiperda* (fall armyworm).[92,93] The 1,5-diarylpyrazoline-3-carboxanilide **144** is the result of a

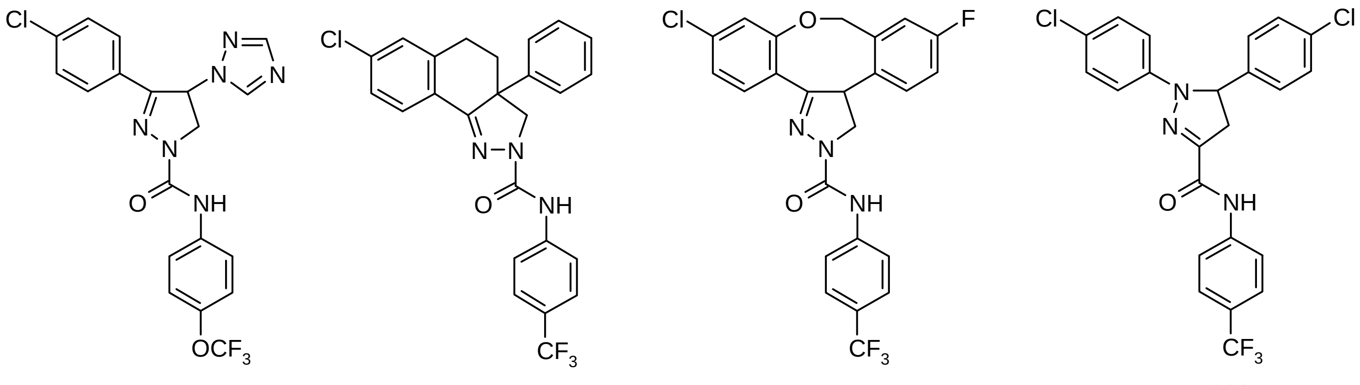
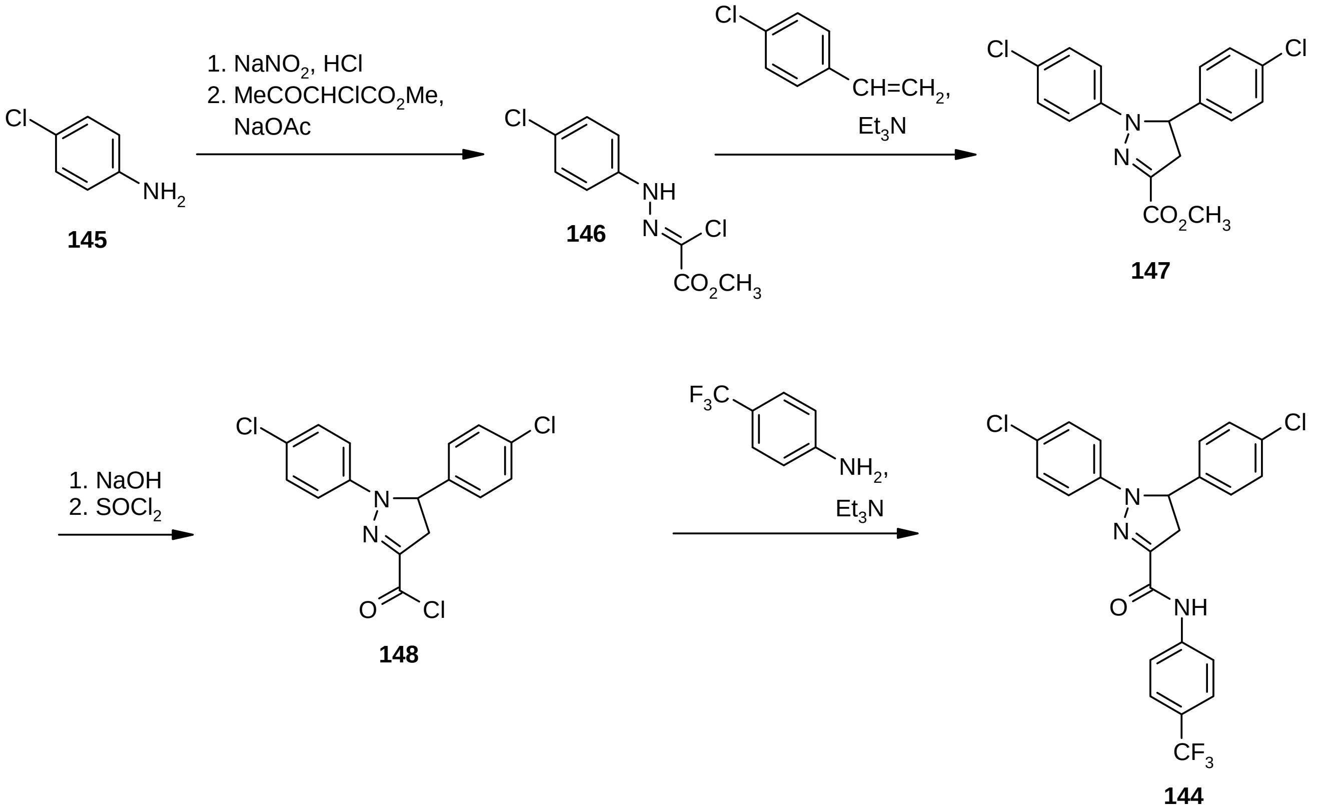

141 **142** **143** **144**

Figure 21

1,3 carbon-nitrogen atom inversion in the pyrazoline scaffold of lead structure **140**.[95] **144** does not only show a striking overlap with molecular models of its role model **140**, it also displays the same strong insecticidal efficacy.

The key intermediate in the straightforward synthesis of the pyrazoline **140** is the hydrazonyl chloride **146**, which is prepared from the diazonium salt of 4-chloroaniline **145** by Japp-Klingemann reaction with methyl 2-chloroacetoacetate and subsequently converted to the pyrazoline **147** via a nitrile-imine 3+2 cycloaddition with 4-chlorostyrene (Scheme 15).[95] The ester function of **147** can be transformed into the desired carboxamide **144** via the acid chloride **148**.[95]

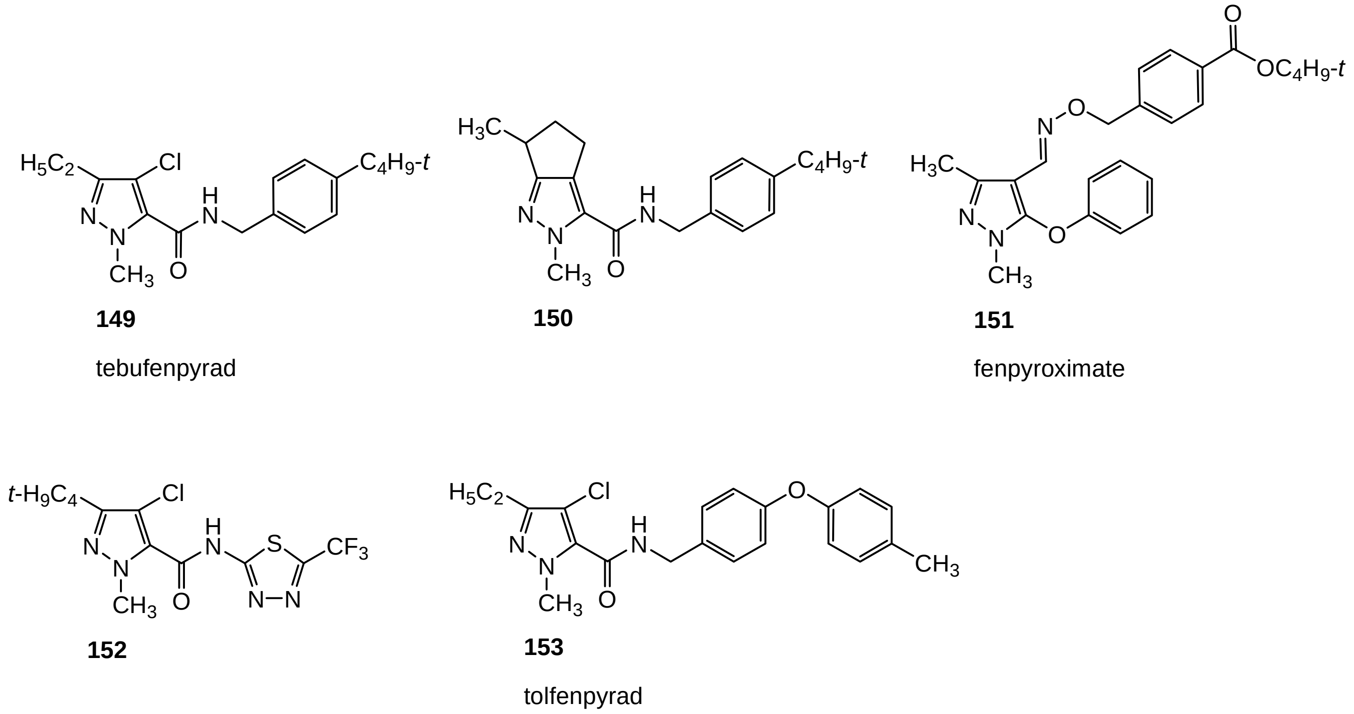


Scheme 15

Also many further variations of the standard pyrazoline lead structure, such as the diverse alkylation,[96,97] arylation[96], acylation[96,98] and amination[96] of the exocyclic urea nitrogen have been reported. Nevertheless, no commercial sodium channel blocker with a pyrazoline scaffold resulted from the tremendous synthetic effort in this field of chemistry, mainly due to unfavorouble toxicological and environmental properties.

4.3 Miscellaneous Insecticidally Active Pyrazoles

Several pyrazole compounds are very active acaricidal respiration inhibitors. In contrast to the fungicidal complex 2 inhibitors (Chapter 3.1) and complex 3 inhibitors (Chapter 3.2), they interrupt the mitochondrial electron transport by blocking NADH:ubiquinone oxidoreductase (complex 1).[99] Tebufenpyrad (**149**),[100] its bicyclic derivative **150**[101], fenpyroximate (**151**)[102] and the *N*-(1,3,4-thiadiazol-2-yl)pyrazolecarboxamide **152**[103] are pure acaricides with strong efficacy against both *Panonychus ulmi* (European red mite) and *Tetranychus urticae* (two-spotted spider mite) (Figure 22). These compounds not only lead to a rapid knockdown of mobil stages, but also suppress the moulting process in larval stages of mites. Notably, *N*-(4-aryloxybenzyl)-pyrazolecarboxamides, such as tolfenpyrad (**153**), show additional insecticidal activity against both chewing and sucking pests like for instance *Nephotettix cincticeps* (green rice leafhopper), *Plutella xylostella* (diamondback moth), *Bemisia tabaci* (whitefly), *Myzus persicae* (green peach aphid) and *Frankliniella occidentalis* (Western flower thrips).[104]



149
tebufenpyrad

150

151
fenpyroximate

152

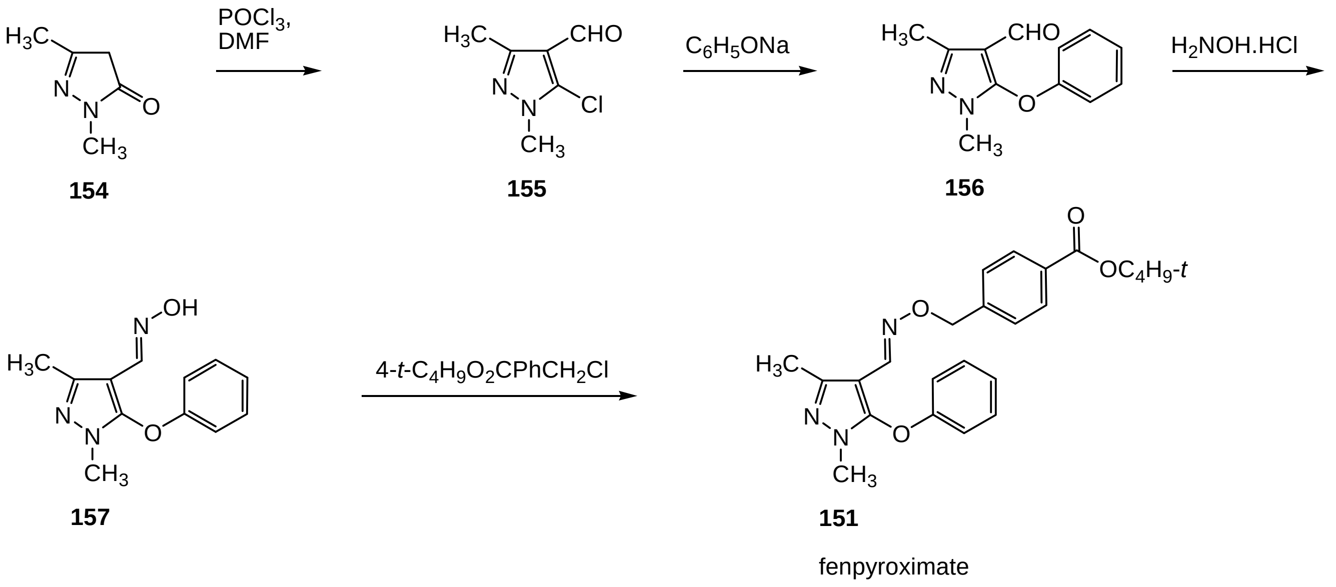
153
tolfenpyrad

Figure 22

The starting material for the synthesis of fenpyroximate (**151**) is 1,3-dimethylpyrazolin-5-one (**154**), which is in a Vilsmeier-Haack reaction simultaneously formylated and chlorinated (Scheme 16).[105] Successive treatment of the resulting pyrazole aldehyde **155** with sodium phenoxide, hydroxylamine and 4-(tert-butoxycarbonyl)benzyl chloride delivers fenpyroximate (**151**).

Also pyrethroids containing a pyrazole ring have been reported to possess high insecticidal activity. The *N*-allylpyrazole derivative **158** is very active against *Culex pipiens pallens* (Northern house mosquito) and *Blattella germanica* (German cockroach),[106] whereas the tetrasubstituted pyrazole **159** shows potency against *Spodoptera frugiperda* (fall armyworm), *Heliothis virescens* (tobacco budworm) and *Diabrotica undecimpunctata* (corn rootworm) (Figure 23).[107]

The pyrazole methanesulfonate **160** is highly active against *Diabrotica undecimpunctata* (corn rootworm),



Scheme 16

Nilaparvata lugens (brown planthopper) and *Nephotettix cincticeps* (green rice leafhopper) (Figure 24).[108] Also the corresponding pyrazoline methanesulfonates have been described to be insecticidally active.[109] The 5-pyridylpyrazole **161** was found to be active against *Aulacophora femoralis* (cucurbit leaf beetle),[110] whereas the 4,5-dihydropyrazole-5-thione **162** displays strong efficacy against *Tetranychus urticae* (two-spotted spider mite).[111] Last, but not least, chlorantraniliprole (**163**) was recently presented by DuPont as one of the first members of a new family of highly active insecticides.[112] These anthranilic diamides act as ryanodine receptor activators by causing the uncontrolled release of stored calcium from the sarcoendoplasmic reticulum, which results in impaired regulation of muscle contraction.[113]

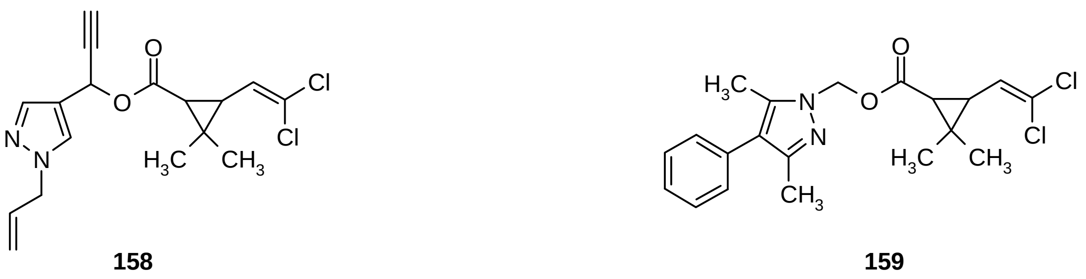
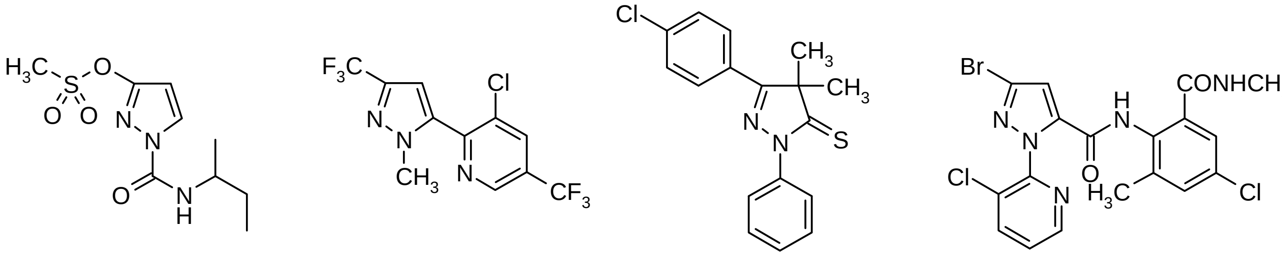


Figure 23

5 CONCLUSION

Natural products containing a pyrazole ring are quite rare. It seems that the evolution of organisms has produced few enzymes which cause the formation of nitrogen-nitrogen bonds. However, as we have seen, many synthetical pyrazoles possess powerful efficacy against weeds, insects and fungal plant diseases.



160 **161** **162** **163**

chlorantraniliprole

Figure 24

α-Keto or α-carboxyarylhydrazones, which are easily obtainable *via* the Japp-Klingemann reaction[114] seem to be versatile intermediates for the synthesis of biologically active pyrazole derivatives.

ACKNOWLEDGEMENTS

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