

# Progress of modern agricultural chemistry and future prospects

Peter Jeschke\*

## Abstract

**Agriculture is facing an enormous challenge: it must ensure that enough high-quality food is available to meet the needs of a continually growing population. Current and future agronomic production of food, feed, fuel and fibre requires innovative solutions for existing and future challenges, such as climate change, resistance to pests, increased regulatory demands, renewable raw materials or requirements resulting from food chain partnerships. Modern agricultural chemistry has to support farmers to manage these tasks. Today, the so-called 'side effects' of agrochemicals regarding yield and quality are gaining more importance. Agrochemical companies with a strong research and development focus will have the opportunity to shape the future of agriculture by delivering innovative integrated solutions. This review gives a comprehensive overview of the innovative products launched over the past 10 years and describes the progress of modern agricultural chemistry and its future prospects.**

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**Keywords:** fungicides; herbicides; safeners; insecticides; nematicides; mode of action

## 1 INTRODUCTION

The modern agrochemical industry is currently confronted with elemental tasks and many challenges.<sup>1</sup> These challenges include consumer preferences, which are focusing more and more on quality, including ethical aspects and a healthier diet, high demand for the raw materials, tougher corporate competition, stringent regulations and the need for continual innovation.

In order to guarantee the food, feed, fibre and fuel production in high yield and quality, the best economical, ecological and environmental practices for sustainable agriculture are essential.<sup>2,3</sup>

For example, for several years scientific and technological advances have been opening up new possibilities for farmers in the global world. The networked digital farm of the future is already making agriculture more efficient and sustainable today (<http://www.cropscience.bayer.com/en/Magazine/Digital-Farming.aspx>).

Promising results of current high-throughput field phenotyping methods can be used as a basis for developing and improving techniques to achieve reliable time- and cost-efficient phenotyping platforms useful for precision agriculture, and to assist breeding programmes by monitoring important known traits or identifying novel traits.<sup>4</sup>

On the other hand, there is the strong impact of the biological system (soil, plant, climate or habitat), combined with current challenges such as climate change,<sup>5</sup> biotic or abiotic stress, soil erosion, the growing world population, energy and workforce. In addition, with limited arable land and a continually growing world population, the available farmland per capita is expected to decrease dramatically, e.g. from 0.25 ha in 2000 to 0.16 ha in 2050.<sup>6</sup>

Climate change is ongoing and presents the risk of weather extremes such as drought, flooding, storms and erosion, which can result in desertification and a lack of water.<sup>7</sup> Consequences could be changes in local cropping patterns and in the prevalence of

pests and disease, a higher risk of crop failure and increasing crop and food prices.<sup>8</sup> While there are opportunities for making use of regions that are not available for agriculture today, the overall reliability of agricultural output is threatened.

Within the coming years, enormous challenges will be presented by further energy demand and the increasing world population, with increased food, feed and water consumption, as well as global warming. Currently, an intensive search for the right answers is under way, involving politics and cooperation between nations and the public and private sectors, as well as science, research and technology.

But what will be the role of the modern agricultural chemistry in the future?

## 2 NEED FOR INNOVATION

Continual innovation in modern agricultural chemistry is vital, as reflected in the field of crop protection and stress relief. Based on analyses of major agricultural crops such as rice, wheat, barley, corn, etc., yields without crop protection would be reduced by around 50% of those currently attained with crop protection to control pests, weeds and diseases. However, given the losses due to pests, weeds and agricultural pathogens, as well as to storage and logistics failure, the theoretically attainable yield could be around 170% of current yields. This means that, through innovations in the field of crop protection and stress relief (e.g.

\* Correspondence to: Peter Jeschke, Bayer CropScience AG, Small Molecules Research, Pest Control Chemistry, Building 6550, Alfred-Nobel Str. 50, D-40789 Monheim am Rhein, Germany. E-mail: [peter.jeschke@bayer.com](mailto:peter.jeschke@bayer.com)

Bayer CropScience AG, Small Molecules Research, Pest Control Chemistry, Monheim am Rhein, Germany

without abiotic stress),<sup>9</sup> the total yield and quantity could be further increased significantly.

### 2.1 Crosslinked biological system research

An important aspect is (a) classical macroscopic understanding versus (b) enhanced microscopic understanding, including interdependences of the crosslinked biological system, which is mandatory to create the future of modern agriculture (Fig. 1).

In this context, the understanding of the correlation between (a) water supply, soil quality, agrochemicals, biologicals and biotic stress versus (b) agricultural crops and climate, symbionts, nutrients, habitat and abiotic stresses is important.

### 2.2 Market demands and innovative active ingredients

For new active ingredients, the market demands are rapidly changing because of emerging resistance in insects, weeds and agricultural pathogens, as well as resistance management, increased regulatory demands, requirements resulting from food chain partnerships, invasive species of insects, weeds and agricultural pathogens and shifts in existing pests.

Therefore, there is a strong need for innovative active ingredients with favourable properties such as novel modes of action (MoAs), for crop enhancement effects that could be used to improve plant health, for physicochemical properties such as systemicity that could be used for seed treatment applications or for the highly efficient drip irrigation method and for competitive economics.

Today, the agrochemical companies aim to supply integrated solutions to the market, but major research and development activities are still focused on innovation in agricultural chemistry.

To illustrate the progress of modern agricultural chemistry and the associated pros and cons, this article highlights selected agrochemicals that have been launched on the global crop protection market in the past 10 years, together with their target pests, pathogens or weed organisms defined by current farming practices.

## 3 TARGETS OF MARKET SEGMENTS FOR NEW AGROCHEMICALS

Since 2004, the various modern agrochemicals (total number 56) have been focused on around 20 economically important target segments of crop protection, covering fungicides, herbicides, insecticides and safeners, as well as nematocides (Fig. 2).

In a more detailed view, the 22 fungicides address around eight target sites associated with the respiratory chain, cell division, cell wall biosynthesis and host plant defence induction; the 20 herbicides and safeners address around eight target sites, which concern in most cases plant-specific pathways such as amino acid, fatty acid, cellulose and carotenoid biosynthesis or the photosystem II of plants; the 11 insecticides address around six target sites that are located in most cases in the nerves and muscles; the three nematocides are exemplified by neuronal or respiratory chain targets known from insecticide or fungicide classes.

During the past 25 years, the crop protection industry has undergone a significant consolidation process. In 1990 there were still 13 companies operating in this field, with global research and development activities.<sup>10</sup> Today, nearly 68% of the 56 new agrochemicals (number given in parentheses) since 2004 have been developed by only five of the global agro-companies: DuPont (4), Syngenta (5), BASF (7), Dow AgroSciences (7) and Bayer CropScience (15).

This article will describe a selection of the innovative agricultural chemicals launched between 2004 and 2014 as fungicides, herbicides and safeners, insecticides and nematocides, focusing on the most relevant biochemical targets or MoAs, with special reference to products from Bayer CropScience (see Table 1). These are:

1. Sterol biosynthesis (sterol-C<sub>14</sub>-demethylase) (DMIs), respiratory chain succinate dehydrogenase inhibitors (SDHIs) of complex II and so-called quinone outside (Q<sub>o</sub>-site) inhibitors of complex III, spectrin-like protein for fungicides and host plant defence induction and cellulose synthase (cell wall biosynthesis).
2. 4-Hydroxyphenylpyruvate dioxygenase (4-HPPD), acetolactate synthase (ALS), protoporphyrinogen-IX-oxidase (PPO), acetyl coenzyme A (CoA) carboxylase (ACCase) and cellulose biosynthesis (CBIs) inhibitors for herbicides as well as safeners for 4-HPPD and ALS inhibitor herbicides and transport inhibitor response 1 (TIR1)/auxin signaling F-box (AFB) proteins (auxin herbicides).
3. Nicotinic acetylcholine receptor (*nAChR*) competitive and allosteric modulators, ryanodin receptor (RyR) modulators and acetyl CoA carboxylase (ACCase) for insecticides.
4. Acetylcholinesterase (AChE), osmotic signal transduction (MAP/histidine kinases) and respiratory chain succinate dehydrogenase (SDH) inhibitors for nematocides.

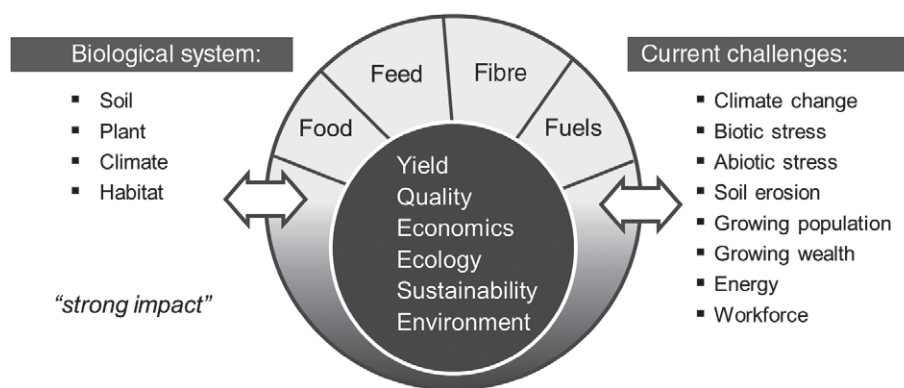
## 4 FUNGICIDES FOR DISEASE CONTROL

For many years, the basic cellular functions have been important targets in fungicide discovery research. Only six MoAs dominate around 80% of this market segment. These MoAs versus agricultural market products include around 30% DMIs such as triazole fungicides, 21% multisite/chemical reactives such as dithiocarbamates, 19% Q<sub>o</sub>-site inhibitors of complex III such as strobilurin derivatives and 6% SDHIs of complex II. All the other MoAs are much less important.

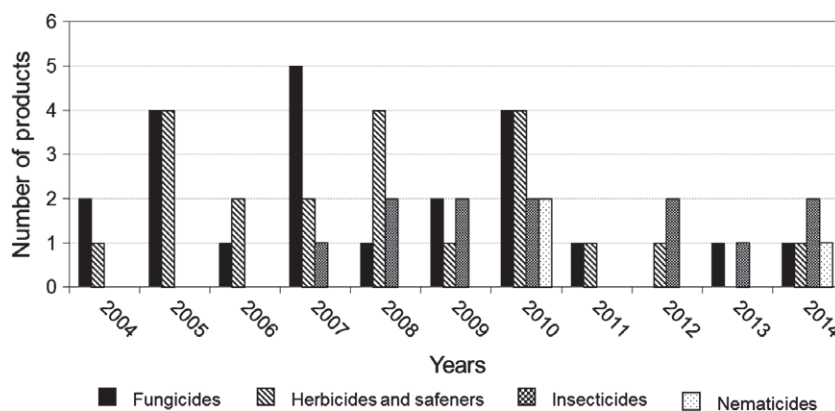
### 4.1 Sterol biosynthesis (sterol-C<sub>14</sub>-demethylase) inhibitors

The main MoA of the demethylation inhibitors (DMIs; SBI; class I) is the inhibition of the cytochrome-P450-dependent C<sub>14</sub>-demethylation of the intermediate C<sub>24</sub>-methylene-dihydrolanosterol in the sterol biosynthesis pathway of agricultural pathogens.<sup>11</sup> The 25 fungicides contained in the Fungicide Resistance Action Committee (FRAC; an expert committee of CropLife International; <http://www.frac.org>) MoA group G1 include piperazines, pyridines, pyrimidines, imidazoles and the triazoles. There are big differences in the activity spectra of DMI fungicides, and resistance is known in various fungal species, with several resistance mechanisms including target-site mutations (e.g. gene *cyp51* in *Aspergillus fumigatus* and *Fusarium graminearum*).<sup>12,13</sup> The triazolothione prothioconazole (2004; Bayer CropScience) (Fig. 3) is a novel candidate that was identified as a result of a stepwise optimisation programme that was focused on modification of the so far typically 1,2,4-triazole core of DMI fungicides and its lipophilic backbone.<sup>14</sup>

Besides the 1,2,4-triazolin-5-thione ring system, prothioconazole contains an *ortho*-chlorobenzyl substituent together with the innovative chlorinated cyclopropyl moiety as a new lipophilic residue, which produces outstanding fungicidal activity. The commercial product prothioconazole is a mixture of two active



**Figure 1.** Global trends and resulting current challenges: the agro-industry is confronted with elemental tasks (Klausener A, 12th IUPAC International Congress of Pesticide Chemistry, Melbourne, Australia, 2010).



**Figure 2.** Launch of commercial agrochemicals in the timeframe 2004–2014.

enantiomers, from which the (S)-(–)-enantiomer demonstrates higher activity than the racemate.<sup>14</sup> Based on its broad fungicidal spectrum, excellent bioavailability and long-lasting efficacy, prothioconazole represents a systemic fungicide with protective and curative properties. It has been developed to deliver a very high standard for control of agricultural pathogens in cereals and other arable crops.<sup>15,16</sup> Prothioconazole provides excellent control of all relevant cereal pathogens, including stem base and ear diseases and all important leaf spot diseases, as well as cereal rust (*Puccinia* spp.), powdery mildew (*Blumeria graminis*) and white mould (*Sclerotinia sclerotiorum*) in oilseed rape and canola.<sup>17,18</sup> Furthermore, it was shown that this novel DMI fungicide demonstrates plant-growth (PGR)-stimulating behaviour and represents a useful tool for resistance management.<sup>19</sup>

#### 4.2 Respiratory chain succinate dehydrogenase inhibitors (SDHIs)

During the past 10 years, halogen-substituted pyrazole-4-carboxamide SDHIs (FRAC MoA group G2) have been intensively developed as a promising class of modern, broad-spectrum fungicides, together with the new innovative subgroup of pyridinyl-ethyl benzamides.<sup>20</sup>

Since 2003, boscalid (BASF) has been known as a chlorine-substituted, systemic and broad active pyridine carboxamide fungicide in speciality crops.

Some years later, a new generation of novel fluorine-substituted (e.g. R<sup>1</sup> = F or R<sup>2</sup> = CHF<sub>2</sub>, CF<sub>3</sub>) pyrazol-4-yl-carboxamides has been established on the market, showing as SDHIs an evolution of

their biological profile and application rates in different crops (Table 2).<sup>21,22</sup>

The structures of the fluorinated SDHI fungicides can be explained in more detail. Whereas in penflufen the 5-position (R<sup>1</sup>) is fluorine substituted, the other pyrazol-4-yl-carboxamide structures are unsubstituted (R<sup>1</sup> = H). The 3-position (R<sup>2</sup>) is alkylated (e.g. penflufen; R<sup>2</sup> = CH<sub>3</sub>), but in most cases substituted with difluoromethyl (R<sup>2</sup> = CHF<sub>2</sub>) or trifluoromethyl (R<sup>2</sup> = CF<sub>3</sub>) residues. As has been demonstrated for boscalid, the substituent R<sup>3</sup> has to be a halogen-substituted bisphenyl moiety (cf. bixafen, fluoxapyroxad) or the second phenyl ring is replaced by a [1,1'-bicyclopropyl]-2-yl (cf. sedaxane) or branched 1,3-dimethylbutyl side chain (cf. penthiopyrad, penflufen). In penthiopyrad, the phenyl is replaced by a bioisosteric thiophene ring. Isopyrazam and the benzovindiflupyr are two members of the benzonorbornene amide subclass, containing a bulky 1-methylethyl [CH(CH<sub>3</sub>)<sub>2</sub>] or dichloromethylene (=CCl<sub>2</sub>)-substituted 1,2,3,4-tetrahydro-1,4-methano-naphthalene moiety in the 9-position.

Both isopyrazam and bixafen demonstrate excellent activity against leaf spot diseases in wheat and barley, and they can be used in cereal segments. In addition, they are very efficient against leaf spot diseases such as ear blight (*Alternaria solani*).

The mixture of bixafen with the triazolinthione SBI fungicide prothioconazole (see Section 4.1) is used as Xpro<sup>®</sup>, which has a broad spectrum of activity in the cereal segment and controls all major leaf spots, brown rust, as well as *Fusarium* species. Fluxapyroxad is a systemic, broad-spectrum SDHI that is efficient against leaf spot diseases in many crops and can be used for seed treatments. In order to obtain optimal curative activity against

**Table 1.** Selection of new agricultural chemicals launched between 2004 and 2014 as fungicides, herbicides and safeners, insecticides and nematocides

Common name	CAS chemical name	Trade name	Manufacturer	Year of launch	Use	Section <sup>a</sup>
Benzovindiflupyr	<i>N</i> -[9-(Dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	Solateno <sup>®</sup>	Syngenta	2014	Fungicide	4.2
Bixafen	<i>N</i> -(3',4'-Dichloro-5-fluoro[1,1'-biphenyl]-2-yl)-3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	Aviator <sup>®</sup>	Bayer CropScience	2007	Fungicide	4.2
Chlorantraniliprole	3-Bromo- <i>N</i> -[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1 <i>H</i> -pyrazole-5-carboxamide	Rynaxypyr <sup>®</sup>	DuPont	2007	Insecticide	7.3
Cyantraniliprole	3-Bromo-1-(3-chloro-2-pyridinyl)- <i>N</i> -[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1 <i>H</i> -pyrazole-5-carboxamide	Cyazypyr <sup>®</sup>	DuPont	2012	Insecticide	7.3
Cyprosulfamide	<i>N</i> -[[4-[(Cyclopropylamino)carbonyl]phenyl]sulfonyl]-2-methoxy-benzamide	<sup>c</sup>	Bayer CropScience	2008	Safener	6
Flubendiamide	<i>N</i> <sup>2</sup> -[1,1-Dimethyl-2-(methylsulfonyl)ethyl]-3-iodo- <i>N</i> <sup>1</sup> -[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide	Belt <sup>®</sup>	Nihon Nohyaku/ Bayer CropScience	2007	Insecticide	7.3
Flupyradifurone	4-[[6-Chloro-3-pyridinyl]methyl](2,2-difluoroethyl)amino]-2(5 <i>H</i> )-furanone	Sivanto <sup>®</sup>	Bayer CropScience	2014	Insecticide	7.1
Fluxapyroxad	3-(Difluoromethyl)-1-methyl- <i>N</i> -(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1 <i>H</i> -pyrazole-4-carboxamide	Xemium <sup>®</sup>	BASF	2010	Fungicide	4.2
Fluopicolide	2,6-Dichloro- <i>N</i> -[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl]-benzamide	Infito <sup>®</sup>	Bayer CropScience	2006	Fungicide	4.4.1
Fluopyram	<i>N</i> -[2-[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl)-benzamide	Luna <sup>®</sup>	Bayer CropScience	2007	Fungicide	4.2
		Velum <sup>®</sup>	Bayer CropScience	2014	Nematicide	8
Fluoxastrobin	(1 <i>E</i> )-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)-methanone- <i>O</i> -methylxime	Evito <sup>®</sup>	Bayer CropScience	2005	Fungicide	4.3
Halaxifen-methyl	4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-2-pyridinecarboxylic acid	Arylex <sup>®</sup>	Dow AgroSciences	2014	Herbicide	5.6
Imicyafos	<i>P</i> -[(2 <i>E</i> )-2-(Cyanoimino)-3-ethyl-1-imidazolidinyl]-phosphonothioic acid <i>O</i> -ethyl <i>S</i> -propyl ester	Nemakick <sup>®</sup>	Agro Kanesho	2010	Nematicide	8
Indaziflam	<i>N</i> <sup>2</sup> -[(1 <i>R</i> ,2 <i>S</i> )-2,3-Dihydro-2,6-dimethyl-1 <i>H</i> -inden-1-yl]-6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine	Alion <sup>®</sup>	Bayer CropScience	2011	Herbicide	5.4
Iprodione	3-(3,5-Dichlorophenyl)- <i>N</i> -(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide	Enclosure <sup>®</sup>	Devgen	2010	Nematicide	8
Isopyrazam	3-(Difluoromethyl)-1-methyl- <i>N</i> -[1,2,3,4-tetrahydro-9-(1-methyl-ethyl)-1,4-methanonaphthalen-5-yl]-1 <i>H</i> -pyrazole-4-carboxamide	Bontima <sup>®</sup>	Syngenta	2010	Fungicide	4.2

**Table 1.** Continued

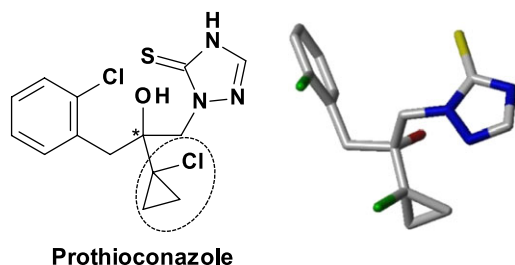
Common name	CAS chemical name	Trade name	Manufacturer	Year of launch	Use	Section <sup>a</sup>
Isotianil	3,4-Dichloro- <i>N</i> -(2-cyanophenyl)-5-isothiazolecarboxamide	Routine <sup>®</sup>	Sumitomo/Bayer CropScience	2011	HPD inductor <sup>b</sup>	4.3
Mandipropamid	4-Chloro- <i>N</i> -[2-[3-methoxy-4-(2-propyn-1-yloxy)phenyl]ethyl]- $\alpha$ -(2-propyn-1-yloxy)-benzeneacetamide	Revus <sup>®</sup>	Syngenta	2006	Fungicide	4.6
Orysastrobin	( $\alpha E$ )- $\alpha$ -(Methoxyimino)-2-[(3 <i>E</i> , 5 <i>E</i> ,6 <i>E</i> )-5-(methoxyimino)-4,6-dimethyl-2,8-dioxo-3,7-diazanona-3,6-dien-1-yl]- <i>N</i> -methyl-benzeneacetamide	Arashi <sup>®</sup>	BASF	2007	Fungicide	4.3
Penthiopyrad	<i>N</i> -[2-(1,3-Dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamide	Affet <sup>®</sup>	Mitsui Chemicals Agro	2010	Fungicide	4.2
Penflufen	<i>N</i> -[2-(1,3-Dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1 <i>H</i> -pyrazole-4-carboxamide	Ernesto <sup>®</sup>	Bayer CropScience	2009	Fungicide	4.2
Penoxsulam	2-(2,2-Difluoroethoxy)- <i>N</i> -(5,8-dimethoxy[1,2,4]triazolo[1,5- <i>c</i> ]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide	Granite <sup>®</sup>	Dow AgroSciences	2004	Herbicide	5.5
Pinoxaden	Propanoic acid, 2,2-dimethyl-8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7 <i>H</i> -pyrazolo[1,2- <i>d</i> ][1,4,5]oxadiazepin-9-yl-propanoic acid 2,2-dimethyl-ester	Arial <sup>®</sup>	Syngenta	2006	Herbicide	5.3
Prothioconazole	2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3 <i>H</i> -1,2,4-triazole-3-thione	Proline <sup>®</sup>	Bayer CropScience	2004	Fungicide	4.1
Pyrasulfotole	(5-Hydroxy-1,3-dimethyl-1 <i>H</i> -pyrazol-4-yl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-methanone	Precept <sup>®</sup>	Bayer CropScience	2008	Herbicide	5.1
Pyrimisulfan	<i>N</i> -[2-[(4,6-Dimethoxy-2-pyrimidinyl)hydroxymethyl]-6-(methoxymethyl)phenyl]-1,1-difluoromethanesulfonamide	Best-Partner <sup>™</sup>	Kumia	2010	Herbicide	5.5
Pyroxsulam	<i>N</i> -(5,7-Dimethoxy[1,2,4]triazolo[1,5- <i>a</i> ]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridine sulfonamide	Simplicity <sup>®</sup>	Dow AgroSciences	2008	Herbicide	5.5
Saflufenacil	2-Chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2 <i>H</i> )-pyrimidinyl]-4-fluoro- <i>N</i> -[[methyl(1-methylethyl)amino]sulfonyl]-benzamide	Kixor <sup>®</sup>	BASF	2010	Herbicide	5.2
Sedaxane	<i>N</i> -(2-[1,1'-Bicyclopropyl]-2-ylphenyl)-3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	Vibrance <sup>®</sup>	Syngenta	2011	Fungicide	4.2
Spinetoram		Delegate <sup>™</sup>	Dow AgroSciences	2008	Insecticide	7.2
Spirotetramate	<i>cis</i> -3-(2,5-Dimethylphenyl)-8-methoxy-2-oxo-1-azaspiro[4.5]dec-3-en-4-yl-carbonic acid ethyl ester	Movento <sup>®</sup>	Bayer CropScience	2009	Insecticide	7.4
Sulfoxaflor	<i>N</i> -[Methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]- $\lambda^4$ -sulfanylidene]-cyanamide	Close <sup>®</sup>	Dow AgroSciences	2012	Insecticide	7.1

**Table 1.** Continued

Common name	CAS chemical name	Trade name	Manufacturer	Year of launch	Use	Section <sup>a</sup>
Tembotrione	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	Laudis <sup>®</sup>	Bayer CropScience	2007	Herbicide	5.1
Thiencarbazone-methyl	4-[[[(4,5-Dihydro-3-methoxy-4-methyl-5-oxo-1 <i>H</i> -1,2,4-triazol-1-yl)carbonyl]amino]sulfonyl]-5-methyl-3-thiophene carboxylic acid methyl ester	Adengo <sup>®</sup>	Bayer CropScience	2008	Herbicide	5.5
Topramezone	[3-(4,5-Dihydro-3-isoxazolyl)-2-methyl-4-(methylsulfonyl)phenyl](5-hydroxy-1-methyl-1 <i>H</i> -pyrazol-4-yl)-methanone	Impact <sup>®</sup>	BASF	2005	Herbicide	5.1
Tritosulfurone	<i>N</i> -[[[4-Methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino]carbonyl]-2-(trifluoromethyl)-benzene sulfonamide	Biathlon <sup>®</sup>	BASF	2005	Herbicide	5.5
Valifenalate	<i>N</i> -[(1-Methylethoxy)carbonyl]- <i>L</i> -valyl-3-(4-chlorophenyl)- $\beta$ -alanine methyl ester	Java <sup>®</sup>	Isagro	2008	Fungicide	4.6

<sup>a</sup> Section number in the article.

<sup>b</sup> HPD = host plant defence.

<sup>c</sup> Combined with thiencarbazone-methyl.

**Prothioconazole**

**Figure 3.** Chemical structure of the triazolinthione SBI fungicide prothioconazole and its conformational view in molecular modelling.

early stages of pathogen infection, a mixture with the SBI fungicide epoxyconazole has been launched.

Penthiopyrad is active against foliar and key soil-borne pathogens such as white mould (*S. sclerotiorum*), brown patch (*Rhizoctonia solani*) and Southern blight (*Sclerotium rolfsii*), and also shows activity against other diseases.<sup>23</sup>

Penflufen is a systemic, xylem-mobile fungicide used as an in-furrow treatment on seed and as seed treatment fungicide on alfalfa, soybeans, cereal grains, vegetables, legume and seeds. It has a fungicidal activity against numerous phytopathogenic fungi such as the important *Rhizoctonia* spp. and *Fusarium* spp.

In EverGol<sup>®</sup> Xtend the product is mixed with the respiratory Qo-site/complex III inhibitor trifloxystrobin (see Section 4.3). This mixture can be combined, for example, with the new seed treatment product Poncho Plus<sup>®</sup> [240 g L<sup>-1</sup> of imidacloprid (IMD), 360 g L<sup>-1</sup> of clothianidin (CLT)] from the insecticide class of nAChR competitive modulators to control the establishment of insect pests and give stress shield benefits (see Section 7.1.1).

In comparison with isopyrazam, the foliar fungicide benzovindiflupyr (2014; Syngenta) has reduced stereocentres in the structure and demonstrates a broad spectrum with excellent crop tolerance. This compound was designed especially for the cereal segment (*Septoria tritici*, *Pyrenophora teres* and *Puccinia* sp.), but it is also

highly active on a wide range of destructive plant pathogens such as Asian soybean rust (*Phakopsora pachyrhizi*). In a mixture with the strobilurin azoxystrobin (1996; ICI/Zeneca, now Syngenta; see Section 4.3) the preventive SDHI fungicide benzovindiflupyr will be sold as Elatus<sup>™</sup> in major soy markets such as Brazil and Argentina.

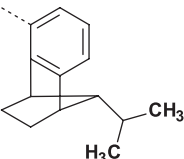
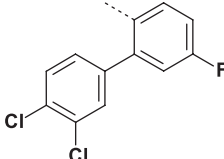
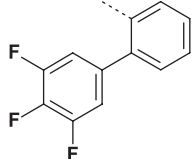
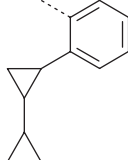
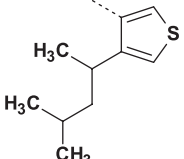
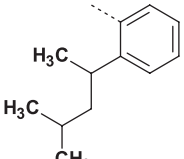
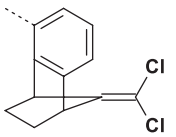
Cross-resistance patterns among SDHI fungicides is complex because many mutations in agricultural pathogen populations confer full cross-resistance, while others do not.<sup>24</sup> Therefore, FRAC has published resistance management recommendations for pathogens of different crop species in order to reduce the risk of resistance development to this important class.

Compared with boscalid and the new pyrazole-4-carboxamide SDHI inhibitors of complex II, the fungicide fluopyram (2007; Bayer CropScience) is different. Therefore, this fungicide was defined by FRAC as pyridinyl-ethyl benzamide. Initially, fluopyram was discovered by using an 'agrophore' chemical synthesis approach, which was considered to be the combination of fragments such as 3-chloro-5-trifluoromethyl-2-pyridinyl residue, known from other agrochemicals such as the fungicide fluopicolide (see Section 4.4.1), the herbicide haloxyfop-P-methyl or the insecticide fluzurone for animal health use.<sup>25</sup> The second 'agrophoric element', the *ortho*-CF<sub>3</sub> group, was taken, for example, from the classical SDHI flutolanil.

During the optimisation procedure it was found that the relatively minor variation of the linker between the substituted pyridine and carboxylic amide function (fluopicolide [–CH<sub>2</sub>–] versus fluopyram [–CH<sub>2</sub>–CH<sub>2</sub>–]) results in a remarkable shift in the fungicidal spectrum and MoA (Fig. 4).

Fluopicolide has excellent activity against oomycetes, whereas fluopyram very efficiently controls ascomycete pathogens such as *Botrytis* spp., *Monilinia* spp., *Sclerotinia* spp., powdery mildew and other diseases responsible for yield and quality losses in the food chain. It offers benefits for the food chain industry through better storability and a longer shelf life of harvested produce. Because of its systemic behaviour, fluopyram can also be used in seed treatment applications against *Pyrenophora* spp. in cereals.

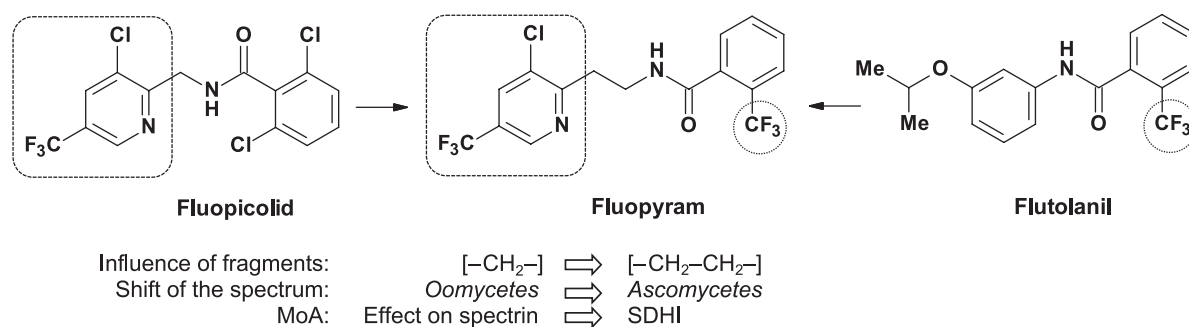
**Table 2.** From boscalid to pyrazol-4-yl-carboxamide structures of SDHI fungicides

Common name (trade name)	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Application rate (crop) (g AI ha <sup>-1</sup> )
Isopyrazam <sup>a</sup> (Bontima <sup>®</sup> )	H	CHF <sub>2</sub>		125 (cereals)
Bixafen (Aviator <sup>®</sup> )	H	CHF <sub>2</sub>		125 (cereals)
Fluxapyroxad (Xemium <sup>®</sup> )	H	CHF <sub>2</sub>		75 (curcubits, vines)
Sedaxane <sup>b</sup> (Vibrance <sup>®</sup> )	H	CHF <sub>2</sub>		20 (canola)
Penthiopyrad (Vertisan <sup>®</sup> )	H	CF <sub>3</sub>		100–250 (cereals)
Penflufen <sup>c</sup> (Emesto <sup>®</sup> )	F	CH <sub>3</sub>		50 (potatoes)
Benzovindiflupyr (Solatenol <sup>®</sup> )	H	CHF <sub>2</sub>		30 (soybeans)

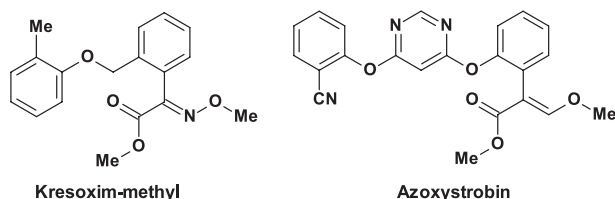
<sup>a</sup> Technical isopyrazam in a mixture of two *syn*-isomers and two *anti*-isomers: ratios 70:30 and 100:0.

<sup>b</sup> Vibrance<sup>®</sup>: 2.5–20 g AI 100 g<sup>-1</sup> seed.

<sup>c</sup> Emesto fusion<sup>®</sup>: mixture of 390 g AI h<sup>-1</sup> fluoxastrobin and 50 g AI h<sup>-1</sup> penflufen.



**Figure 4.** Agrophoric-element-based structure design of the SDHI fungicide fluopyram, influenced by fluopicolid and flutolanil.



**Figure 5.** Chemical structures of the strobilurin fungicides kresoxim-methyl and azoxystrobin.

Compared with the more rigid anilide moieties in boscalid, the [-CH<sub>2</sub>-CH<sub>2</sub>-] linker outlines a higher flexibility in fluopyram, which seems to allow a more flexible binding mode at the active site of the target species. Different genotype-specific cross-resistance relationships between the SDHIs boscalid and penthiopyrad and the lack of cross-resistance between these fungicides and fluopyram have been published.<sup>26</sup>

### 4.3 Respiratory chain (Qo-site/complex III) inhibitors

After introduction of the oximino-acetate kresoxim-methyl (1996; BASF) and the methoxy-acrylate azoxystrobin (1996; ICI/Zeneca, now Syngenta) (Fig. 5), strobilurins have been among the most commercially successful classes of agricultural fungicides over the past 19 years.<sup>27</sup> According to the naturally occurring lead structures strobilurin A and oudemansin A, all synthetic strobilurin analogues inhibit mitochondrial respiration by influencing the function of the so-called Q<sub>o</sub>-site of complex III (cytochrome bc<sub>1</sub> complex), which is located in the inner mitochondrial membrane of fungi and other eucaryotes.<sup>28</sup> The extremely broad activity spectrum of strobilurins, with potential to control all four major classes of phytopathogenic fungi (*Ascomycetes*, *Basidiomycetes*, *Deuteromycetes* and *Oomycetes*), is unique among commercial fungicides and triggered extensive research programmes within several research-based agrochemical companies.

At present, eleven different strobilurins have been introduced into the market, from which two new compounds have been launched in the past 10 years, having special structural characteristics as outlined by the two groups (a) and (b) in Fig. 6.

The leaf-systemic and broad-spectrum dihydro-acetamide fungicide fluoxastrobin (2005; Bayer CropScience) (Fig. 6) combines a novel (1*E*)-*O*-methoxylimine-5,6-dihydro-1,4,2-dioxazin-3-yl-methanone pharmacophore system with an optimally adjusted side chain containing a 2-chlorophenoxy-5-fluoropyrimidinyl moiety. Applied as foliar spray in cereals, fluoxastrobin provides excellent control of *Septoria* diseases (*S. tritici*) and glume blotch (*Leptosphaeria nodorum*), rust (*Puccinia recondita*, *P. striiformis*, *P. hordei*) and *Helminthosporium* diseases in wheat and barley

(*Pyrenophora tritici-repentis*), as well as scald (*Rhynchosporium secalis*) and powdery mildew (*B. graminis* spp.).<sup>29,30</sup> The SAR demonstrates that the fluorine atom has an important effect on the phytotoxicity (PTX) and leaf systemicity of this strobilurin fungicide.<sup>31</sup>

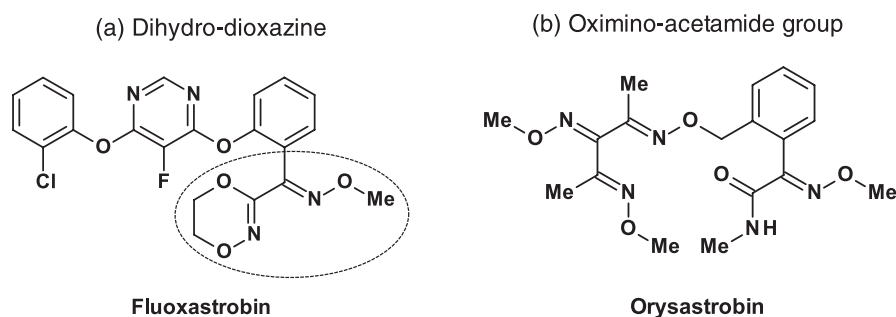
Oryastrobin (2007; BASF) (Fig. 6) with (2*E*)-*O*-methoximino acetamide structure and a (3*E*,5*E*,6*E*)-*tris*-(methoximino) side chain was specifically developed for application in a nursery box of rice seedlings for long-lasting control of leaf and panicle blast (*Magnaporthe grisea*) and sheath blight (*Thanatephorus cucumeris*) in rice with or without an insecticide partner.<sup>32</sup> The oximino-acetamide fungicide is systemic, with sufficient intrinsic activity, and its physicochemical properties demonstrate a low lipophilicity and high solubility in water.<sup>33</sup> Finally, the fungicide can be taken up by the roots and translocated acropetally into the rice leaves, with excellent plant selectivity under different environmental conditions.

During recent years, several strobilurin types have been announced as being developed or launched for the Chinese market by the Shenyang Research Institute of the Chemical Industry (SYRICI). Their pharmacophores demonstrate structural similarities to already known methoxy-acrylates such as pyraoxystrobin (SYP-3343),<sup>34</sup> coumoxystrobin (SYP-3375)<sup>35</sup> and flufenoxystrobin (SYP-3759)<sup>36</sup> or methoxy-carbamates such as pyrametostrobin (SYP-4155)<sup>37</sup> respectively.<sup>27</sup>

However, the unexpected, rapid development of resistance pathogens in wheat in Europe to these Qo-site/complex III inhibitors, like the shift to powdery mildew and *S. tritici* as major diseases, has limited their success in some key segments. Under practical conditions, the target-site mutation in the *cyt b* gene (G143A, F129L) has by far the greatest importance because it leads to disruptive resistance development (found, for example, in *B. graminis*, *Mycosphaerella graminicola* and *Plasmopara viticola*).<sup>38,39</sup> Therefore, as an important contribution to the resistance management strategy for application of strobilurins, mixtures with fungicides from other classes are important. In addition, the outstanding efficacy of strobilurins against soybean rust epidemic in South America has compensated the market losses. Recently, the methoxy-acrylate azoxystrobin has been coformulated in a mixture with the new SDHI fungicide benzovindiflupyr (see Section 4.2), trade name Elatus<sup>TM</sup>, which is a broad-spectrum, preventive fungicide for long-lasting soybean rust control.

Finally, the favourable effects of strobilurins on the physiology of treated crops, such as yield increase, stress tolerance and improved plant health, have resulted in further significant market opportunities (see similar effects shown by nAChR competitive modulators in Section 7.1.1).





**Figure 6.** Chemical structures of the strobilurin fungicides: (a) dihydro-dioxazine such as fluoxastrobin; (b) oximino-acetamide group such as orystrobin.

#### 4.4 Mitosis and cell division inhibitors

Inhibitors of  $\beta$ -microtubule assembly in mitosis that have been used as fungicides include the long-known group of methyl benzimidazole carbamates such as carbendazim and thiophanate fungicides such as thiophanate-methyl. However, there are several target-site mutations (mostly E198A/G/K and F200Y) in the  $\beta$ -tubulin gene described. The benzamide zoaxamide is the first inhibitor of  $\beta$ -microtubule assembly to be important for the control of oomycete pathogens such as *Phytophthora*, *Pythium* and *Plasmopara*.<sup>40</sup> At the cellular level, these fungicides arrest nuclear division and destroy the microtubule cytoskeleton by a highly specific covalent binding to cysteine (Cys239) on the  $\beta$ -subunit of tubulin.<sup>41</sup>

##### 4.4.1 Delocalisation of spectrin-like proteins

The benzamide fungicide fluopicolide (2006; Bayer CropScience) (Fig. 7) belongs to the new class of pyridinylmethyl-benzamides and exhibits a high level of activity against a broad spectrum of oomycetes, such as *Phytophthora infestans*, *P. viticola* and various *Pythium* species.<sup>42</sup> Because of the different MoAs, it does not show any cross-resistance to other commercial oomycete fungicides. Fluopicolide is effective against several stages of the fungal life cycle (e.g. the release and motility of zoospores, the germination of cysts, the growth of the mycelium and sporulation) within only a few minutes of application.<sup>43</sup> It was found that this fungicide induces a rapid reallocation of the cytoskeleton-associated spectrin-like proteins, considered to form a bridge between the cytoskeleton and the plasma membrane. The spectrin-like proteins could play a role in the tip extension of fungi and the polarity of hyphal elongation. Fluopicolide induces dramatic symptoms on *P. infestans* zoospores.<sup>44</sup> They stop swimming within a minute of contact with fluopicolide at a concentration as low as  $1 \mu\text{g mL}^{-1}$ , and their swelling up to total lysis has been observed (Fig. 7b).<sup>43,45</sup>

Immunological studies demonstrated that a cytoskeleton-associated spectrin-like protein was delocalised after fluopicolide treatment. This happens in both zoospores and hyphae of *P. infestans*.

As a modern fungicide, fluopicolide exhibits a high level of activity against a range of oomycete diseases in different crops such as potato, tomato, vines, brassicas, cucurbits, lettuce, onions, leeks, peppers, etc., and its spectrum can cover the most important genera of the orders Peronosporaceae and Pythiaceae.<sup>46</sup>

#### 4.5 Host plant defence inducers

The isothiadiazole carboxamide isotianil (2011; Sumitomo/Bayer Crop Science) (Fig. 8), a novel plant defence inducer with a low application rate, leads to a systemic induction of the plant's own

defence mechanism, which controls leaf blast (*M. grisea*), the most serious rice disease in Japan, and bacterial leaf blight in rice.<sup>47</sup>

In contrast to already existing plant defence inducers such as benzisothiazole (probenazole, 1981), benzothiodiazole (acibenzolar-*S*-methyl, 1996) and the thiadiazole carboxamide tiadinil (2003, Nihon Nohyaku), the new isotianil possesses an isothiazole moiety, which maintains a steady preventive effect of the molecule, influenced by its systemic properties and low water solubility.

Isotianil is flexible and can be used either at sowing or as a foliar treatment. It has a long-lasting and stable efficacy against rice blast and bacterial leaf blight. No cross-resistance to any other commercial products have been observed, and therefore it has a low risk of resistance development.

After its application to young plants, the plant is protected against infection. Gene expression profiling was used to support the MoA identification of the novel resistance inducer isotianil. Upon infection, isotianil-primed plants displayed a faster and stronger induction of plant-defence-related genes in comparison with the control (mock treated) (Fig. 8).<sup>47</sup>

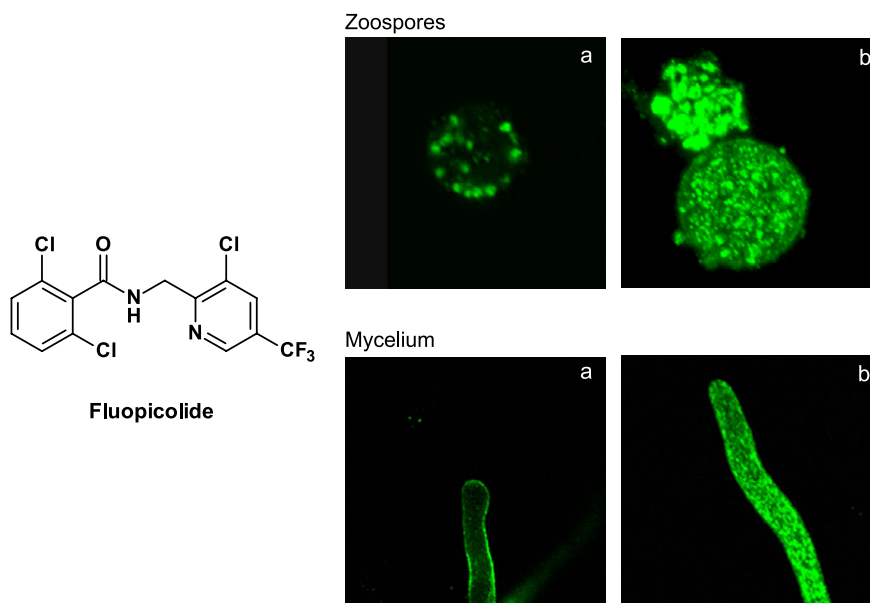
#### 4.6 Cellulose synthase inhibitors

During the past 10 years, two further new candidates of the chemical class of carboxylic acid amide (CAA) fungicides (FRAC: MoA group H) have been launched or under development.<sup>48</sup> They all belong to the cell wall biosynthesis inhibitors, interacting with cell wall deposition and cellulose biosynthesis.

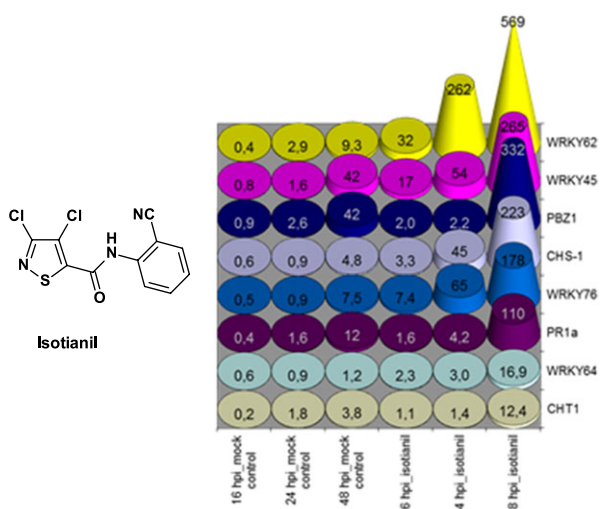
As the first member of the mandelic acid amide fungicides, mandipropamid (2006; Syngenta) (Fig. 9a) has been commercialised as a racemic mixture of both enantiomers. Because none of the enantiomers demonstrated a biological advantage over the mixture, the protective and curative fungicide was registered as racemate.<sup>49</sup> Mandipropamide can be used for oomycete disease control on potatoes, such as late blight (*Phytophthora infestans*), and on tomatoes, as well as for downy mildew control in vines. Valifenalate (2008; Isagro) (Fig. 9b), the third member of the valinamide carbamates (benthiavalicarb, iprovalicarb), is a fungicidal and racemic dipeptide with activity against *Phytophthora* sp., *Peronospora* sp. and *Plasmopara* sp.<sup>48</sup> It is suitable for application on crops such as grapevines, potatoes and vegetables. Finally, from the subclass of cinnamic acid amides (dimethomorph, flumorph), the candidate pyrimorph (ISO-proposed common name) (Fig. 9c) is still under development by China Agricultural University.<sup>50</sup>

## 5 HERBICIDES FOR WEED CONTROL

High-yield farming production systems are based on efficient herbicides as well as on integrated cultivation systems. In the



**Figure 7.** Structure of fluopicolide and immunofluorescence microscopic studies of (a) untreated and (b) treated zoospores and mycelium of oomycetes (data taken from Toquin *et al.*<sup>43</sup> and Jeschke<sup>45</sup>).



**Figure 8.** Differentially expressed genes during the time course of fungal infection in isotianil-primed and mock-treated rice seedlings. Upon infection, the isotianil-primed plant displayed a faster and stronger induction of plant-defence-related genes in comparison with the control (mock treated).

future, the global trend towards simplification of crop rotation will continue, as illustrated by corn and soy bean farming in the United States and wheat and oilseed rape production in the European Union. Conservation tillage will continue to increase, and the importance of herbicide resistance will grow significantly. It can be assumed that the number of available herbicides for the grower will further decline because of difficult regulatory requirements (e.g. Plant Protection Products Directive EU 91/414/EEC), because three herbicide classes represent approximately 50% of the world market and because the consolidation process in agricultural chemistry has resulted in only a few remaining companies with dedicated and broad herbicide research capability.

In order to avoid significant problems for agriculture, a new herbicide technology is urgently required.

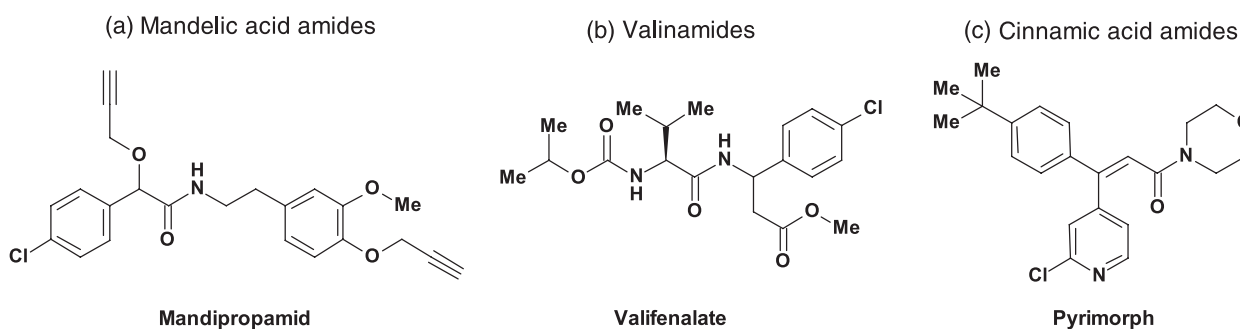
For herbicide market products, plant-specific pathways (except ACCase) are the most important. Unfortunately, no major MoA has been introduced into the marketplace for more than two decades.<sup>51</sup> Today, only six mechanisms of action dominate, and these account for around 80% of the herbicide market. These MoAs, as a percentage of agricultural market products, include around 24% 5-enolpyruvylshikimate-3-phosphate synthase inhibitor (glyphosate), 16% acetolactate synthase (sulfonyl ureas), 12% very-long-chain fatty acid elongase (chlorinated acetanilides) and 12% photosystem II (triazines).

The presence of herbicide-resistant weeds, particularly in major field crops, is a widespread problem, however, and a significant challenge for global food security.<sup>52</sup> Unfortunately, more than 60% of the global herbicide market is represented by products with MoAs that already today have serious resistance issues, such as ESPS, ALS, ACCase and auxins.

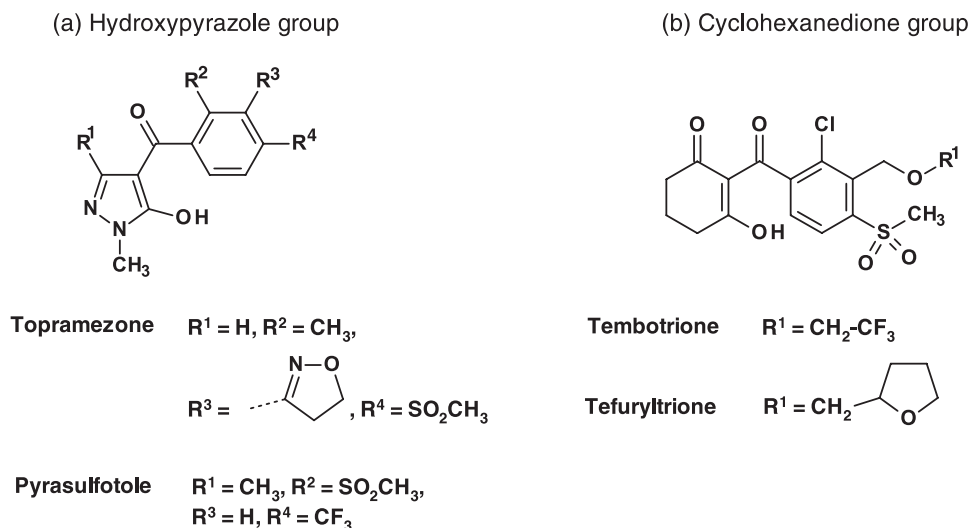
### 5.1 4-Hydroxyphenylpyruvate dioxygenase (4-HPPD) inhibitors

The enzyme 4-HPPD is responsible for catalysis of the oxidative decarboxylation and the rearrangement of *para*-hydroxyphenylpyruvate (HPP) to homogentisate (HGA). Inhibition of carotenoid biosynthesis by 4-HPPD inhibitors results in the bleaching and subsequent death of treated plants.<sup>53</sup> The 4-HPPD enzymes are homodimeric, non-haem-Fe<sup>II</sup>-containing dioxygenases.<sup>54–56</sup> The active site is located within an open twisted  $\beta$ -sheet. The main driving forces for inhibitor binding are the interaction of the chelating oxygen atoms with the cationic iron and the inhibitor atoms in the hydrophobic protein pocket. As described, 4-HPPD can exist in two different conformations ('open' versus 'closed'), and numerous inhibitors containing a 1,3-dione structure (e.g. cyclohexanediones, hydroxypyrazoles and diketone nitriles) as a chelating moiety bind to the open form of the active site of the 4-HPPD enzyme.

Since 2004, three new 4-HPPD inhibitors have been launched, two of the hydroxypyrazole and one of the cyclohexanedione type (Figs 10a and b).



**Figure 9.** Chemical structures of new carboxylic acid amide fungicides: (a) mandelic acid amides such as mandipropamid; (b) valinamides such as valifenalate; (c) cinnamic acid amides such as pyrimorph (ISO-proposed common name).



**Figure 10.** Chemical structures of 4-HPPD inhibitors: (a) hydroxypyrazole group such as pyrasulfotole and topramezone; (b) cyclohexanedione group such as tembotrione and tefuryltrione.

The first new 4-HPPD hydroxypyrazole inhibitor topramezone (2005; BASF) (Fig. 10a) is used predominantly in corn for post-emergence applications, with application rates of 12–75 g AI ha<sup>-1</sup>.<sup>57</sup> If applied in synergistic mixtures with PS II inhibitors such as atrazine or terbutylazine, most key grasses and broadleaf weeds in corn can be controlled.

With the second new 4-HPPD hydroxypyrazole inhibitor pyrasulfotole (2008; Bayer CropScience) (Fig. 10a), an active ingredient with a new MoA for broadleaf weed control in wheat and barley was brought onto the market. Pyrasulfotole is an innovative tool for resistance management, with excellent post-emergence use on wheat, barley and triticale.<sup>58</sup> It is active against a wide range of broadleaf weeds, such as chickweed (*Stellaria media*), lamb's quarters (*Chenopodium album*), nightshades (*Solanum* spp.), pigweeds (*Amaranthus* spp.) and velvetleaf (*Abutilon theophrasti*). The application rates of 25–50 g AI ha<sup>-1</sup> provide reliable weed control, especially in mixtures with the PS II inhibitor bromoxynil (Fig. 11).

The lipophilic 4-CF<sub>3</sub>-phenyl moiety in pyrasulfotole shows a binding preference for the hydrophobic niche of the open conformation of the 4-HPPD target enzyme, as outlined in Fig. 12.<sup>56,59</sup>

The crystal structure shows the active site of 4-HPPD, with its iron atom located within an open twisted  $\beta$ -sheet formed by seven  $\beta$ -strands. This iron is octahedrally coordinated by two histidines (His), one glutamic acid (Glu) residue, a well-defined water molecule and an inhibitor oxygen atom that is presumed to take the position of the substrate's oxygen in the transition state.<sup>60</sup>

Both the pyrazolone hydroxyl and the benzoyl oxygen interact directly with the catalytic iron ion.

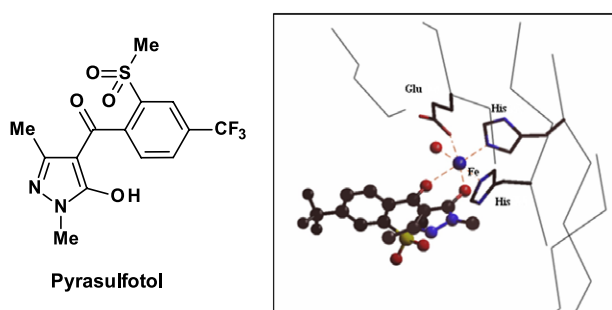
Tembotrione (2007; Bayer CropScience) (Fig. 10b) is the latest member of the 4-HPPD cyclohexanediones, and structurally similar to tefuryltrione (2002; Aventis;  $R^1 = CH_2CF_3$  versus tetrahydrofur-2-ylmethyl) (Fig. 10b), for selective control of broadleaf weeds and annual grasses in field corn, seed corn, sweet corn and popcorn.<sup>61</sup> Its application leads to a selective post-emergence control by rapid bleaching (depletion of carotenoids) and elimination of susceptible broadleaf weeds and annual grasses in corn. The introduction of the innovative 2,2,2-trifluoroethyl residue results in improved physicochemical properties (water solubility 28.3 g L<sup>-1</sup> at pH 7) that permit easy translocation of hydrophilic (aqueous) and lipophilic (waxy, fatty) barriers on the weed surface to the target sites in plant cells. By application with the safener (see Section 6) isoxadifen-ethyl (Laudis® OD: adjuvant system in an oil dispersion as a 'ready-for-use product'), corn can be protected from herbicide stress and demonstrates tolerance even under very challenging growing conditions.

## 5.2 Protoporphyrinogen-IX-oxidase (PPO) inhibitors

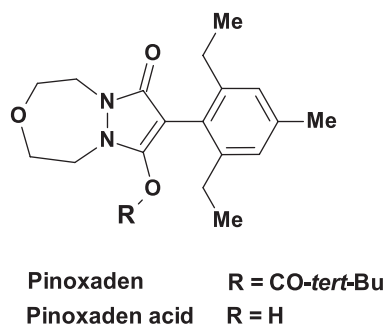
The inhibition of protoporphyrinogen-IX-oxidase leads to accumulation of the enzyme product protoporphyrin IX. Light induces protoporphyrin IX to generate large amounts of singlet oxygen, leading to the peroxidation of the unsaturated bond of the



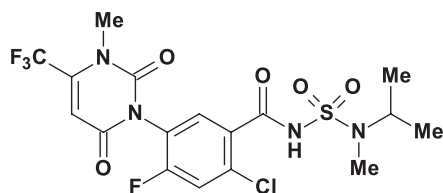
**Figure 11.** *Kochia scoparia* treated post-emergently with pyrasulfotole (A), bromoxynil (B) and a combination of pyrasulfotole and bromoxynil (C). The herbicides were applied with the recommended field dose. Pictures were taken 21 days after treatment.



**Figure 12.** Pyrasulfotole and its molecular interaction with the herbicide target 4-HPPD. Octahedral coordination of the iron at the active site of 4-HPPD (data taken from Freigang *et al.*<sup>56</sup>).



**Figure 14.** Structures of pinoxaden and pinoxaden acid.



**Figure 13.** Saflufenacil.

fatty acids found in cell membranes.<sup>62</sup> With the success of herbicide-resistant crops and the possibility of post-emergence applications combined with relatively low herbicide costs, combined with the perceived advantage of applying a herbicide only when weed growth was observed, the end of residual herbicides was prophesied to have arrived a while ago.<sup>63,64</sup> Today, the situation has changed with the appearance of glyphosate-resistant weeds such as *Amaranthus tuberculatus* and *Amaranthus palmeri*. The demonstrated advantage of using pre-emergence herbicides to reduce these highly resistant weeds led to the development of the new PPO inhibitor saflufenacil (2010; BASF) (Fig. 13), which can be used alone or in mixtures with glyphosate and applied preplanting for burndown applications in glyphosate- and ALS-tolerant crops.

Saflufenacil primarily controls dicotyledonous weeds. For example, it can be used as a pre-emergence treatment in corn and sorghum (*Sorghum bicolor*) to control major broadleaf weeds without triazine herbicides. If further weed shifts are observed in genetically modified crops, new market opportunities might open up for herbicides with other MoAs such as PPO inhibitors.

### 5.3 Acetyl CoA carboxylase (ACCCase) inhibitors

Acetyl CoA carboxylase (ACCCase; EC 6.4.1.2), crucial for the metabolism of fatty acids, is a biotin-dependent carboxylase that produces malonyl-CoA from bicarbonate as a source of carboxyl group, and ATP as a source of energy.<sup>65,66</sup> Besides the known ACCCase active herbicide classes cyclohexanediones (CHDs) and (*R*)-configured (het)aryloxyphenoxypropionates (AOPPs),<sup>67</sup> the phenylpyrazolinone (2006; Syngenta)<sup>68</sup> (Fig. 14) was developed as proherbicide (R = CO-*tert*-Bu)<sup>69</sup> for the selective post-emergence control of key annual grass weeds in cereals.

Pinoxaden also shows activity against several ACCCase-inhibitor-resistant biotypes but does not control all of them. It can be applied from the two-leaf stage up to the flag leaf stage of annual grasses and shows a weed spectrum that covers a wide range of important annual grass species such as blackgrass (*Alopecurus myosuroides*), silky bentgrass (*Apera spica-venti*), wild oats (*Avena* spp.), ryegrass (*Lolium* spp.), canary grass (*Phalaris* spp.), foxtails (*Setaria* spp.), meadowgrass (*Poa* spp.) and other monocotyledonous weed species in cereals.<sup>70</sup>

Pinoxaden is hydrolysed very rapidly in soil or plants, forming the vinylogous 'pinoxaden acid' (R = H) under aerobic, aerobic-anaerobic and sterile-aerobic conditions as a herbicidally active metabolite (see also Section 7.3).<sup>69</sup> Its tolerance in key cereal crops (wheat, barley) under adverse climatic conditions is obtained by incorporating the proprietary safener (see Section 6) cloquintocet-mexyl into an easy-to-use liquid formulation, which delivers maximum performance of pinoxaden when used with a specially optimised adjuvant.

### 5.4 Cellulose biosynthesis inhibitors (CBIs)

Indaziflam (2011; Bayer CropScience) (Fig. 15) belongs to the alkylazine class and inhibits the synthesis of crystalline cellulose fibres, which are necessary for plant cell wall stability.<sup>71</sup> The exact target

site is not yet known, but the phenomological MoA is disaggregation of 'rosettes', which are responsible for the ordered polymerisation of phosphorylated oligo-sugars [ $\beta$ -(1,4)-glucan chain] to cellulose fibres, the so-called microfibrils (Fig. 15).<sup>72</sup>

Because of two chirality centres in the (1*R*,2*S*)-2,3-dihydro-2,6-dimethyl-1*H*-inden-1-amine fragment of the molecule, its large-scale preparation needed a high degree of innovation in manufacturing. Indaziflam shows a broad-spectrum weed control for annual grasses and broadleaf weeds in established permanent crops such as tree plantations, perennial crops such as sugar cane and turf grasses.

Indaziflam manages weed populations resistant to other MoAs such as EPSPS, ALS and PS II, with application rates of 73–95 g AI ha<sup>-1</sup>, and provides a control of weeds for up to 90 days or longer after treatment. In order to expand the spectrum of weed control, it can be mixed with other herbicides such as metribuzin and isoxaflutole.

### 5.5 Acetolactate synthase (ALS) inhibitors

The four herbicide subclasses (a) triazolopyrimidine sulphonamides,<sup>73</sup> (b) sulfonyleureas,<sup>74</sup> (c) sulfonlaminocarbonyl-triazolinones and (d) imidazolinones<sup>75</sup> are efficient inhibitors of ALS, as the key enzyme in the biosynthesis of branched amino acids such as leucine (Leu), isoleucine (Ile) and valine (Val). Inhibition of amino acid production subsequently inhibits cell division and causes death in susceptible plants.

Penoxsulam (2004; Dow AgroScience) (Fig. 16a) was originally designed for use in rice fields and can be used for broad-spectrum control of broadleaf weeds such as barnyard grass (*Echinochloa crusgalli*), young water grass (*Paspalum dilatatum*) and wild buckwheat (*Polygonum convolvulus*) and important weeds in turf, retail market segments and cereal crops.<sup>76,77</sup> Penoxsulam is a systemic, phloem and xylem mobile herbicide that is absorbed via leaves, shoots and roots. The herbicide can be translocated in plants to meristematic tissue. A key attribute of penoxsulam is excellent post-emergent control with residual activity on white clover (*Trifolium repens*), ground ivy (*Glechoma hederacea*) and dollar weed (*Hydrocotyle* spp). It provides herbicidal efficacy at low use rates (6–70 g AI ha<sup>-1</sup>) compared with the higher rates of the most commonly used turf herbicides, such as 2,4-D, dicamba, MCPP and triclopyr.

Pyroxsulam (2008; Dow AgroSciences) (Fig. 16a), the latest innovation from the subclass of triazolopyrimidine sulfonamides, provides broad-spectrum control of annual grasses and broadleaf weeds, with some activity on certain perennial species.<sup>78</sup> For example, it is active against annual grasses and broadleaf weeds, with application rates of 9–15 g AI ha<sup>-1</sup>, and its crop selectivity in wheat, rye and triticale varieties (hybrids of wheat and rye) is possible in combination with the safener cloquintocet-mexyl (cf. ACCase inhibitor pinoxaden, Section 5.3).

As a new member of the subclass of sulfonlaminocarbonyl-triazolinones, the herbicide thienecarbazone-methyl (2008; Bayer CropScience) (Fig. 16c) demonstrates a selective activity against perennial grasses such as johnsongrass (*Sorghum halapense*) and *Elymus repens*, together with control of problem weeds such as *Polygonum convolvulus* and suppression of *Cirsium arvense* and *Convolvulus arvensis* primarily in corn.

It shows cross-spectrum activity against annual grasses and broadleaf weeds and can be applied at pre-emergence and post-emergence timings. To overcome inherent selectivity in corn,<sup>79</sup> thienecarbazone-methyl is always combined with safener technology (see Section 6), such as the novel safener

cyprosulfamide, and with other herbicidal active ingredients. In herbicides prepared for post-emergence use, thienecarbazone-methyl is coformulated, for example, with tembotrione (2007; Bayer CropScience) (see Section 5.1) (Fig. 10b).

Today, the large sulfonyleurea herbicide subclass contains more than 30 members, of which only two have been launched in the past 10 years.<sup>74</sup> The first sulfonyleurea tritosulfuron (2005; BASF) (Fig. 16b) was developed for broadleaf weed control in winter and spring wheat and maize. It is a broad-spectrum herbicide with some reported activity against cleavers (*Galium aparine*). Tritosulfuron (25%) is approved as a premix together with the growth-regulating auxin herbicide dicamba (50%) under the trade name Arrat<sup>®</sup> for the control in wheat and maize fields of broadleaf weed species such as wild bishop (*Bifora radians*), milk thistle (*Silybum marianum*), common cocklebur (*Xanthium strumarium*) and black nightshade (*Solanum nigrum*).

The second new sulfonyleurea orthosulfamuron (2006; Isagro) (Fig. 16b) is recommended for early post-emergence broadleaf, sedge and aquatic weed control (*Echinochloa* species, for example) in rice, with an excellent ecotoxicological profile. The compound is formulated as 50% wettable granules.

The novel sulfonlaniilide pyrimisulfan (2010; Kumiai) (Fig. 17) with divergent ALS inhibitor structure has been developed as herbicide for paddy fields.

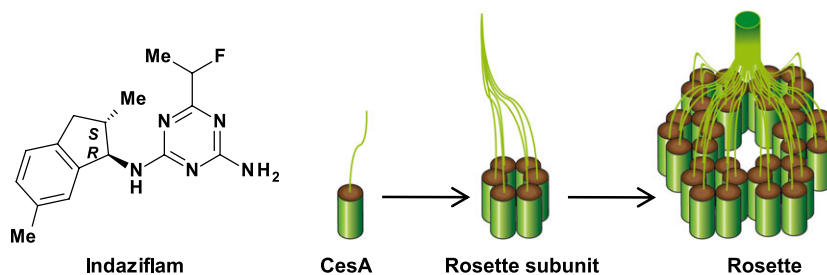
The herbicide shows good efficacy against a wide range of weeds such as *Echinochloa* spp., sedges, broadleaf weeds and sulfonyleurea-resistant weeds. Furthermore, pyrimisulfan also has good efficacy against troublesome perennial weeds, such as seaside bulrush (*Bolboschoenus maritimus*), spikerush (*Eleocharis kuroguwai*) and threeleaf arrowhead (*Sagittaria trifolia*). Because of its relatively low soil adsorption and high water solubility compared with other rice herbicides, a controlled-release formulation (6.7 g AI kg<sup>-1</sup> granules) was developed for use as a one-application herbicide and effective tool for rice cultivation in Japan.<sup>80</sup> The pyrimisulfan granule formulation can be applied at pre-emergence to the three-leaf stage of rice and exhibits consistent efficacy under simulated overflow conditions.

### 5.6 New auxin mimics and herbicides

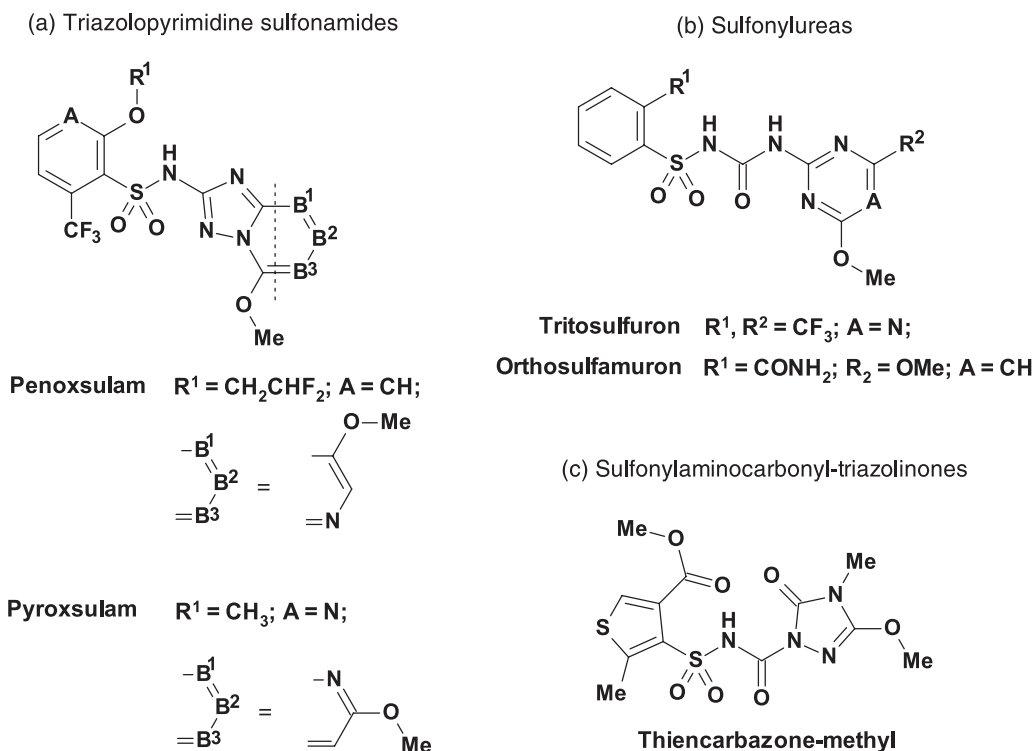
The plant hormone auxin regulates plant growth (PGR) and development.<sup>81</sup> Auxin acts by binding the F-box protein transport inhibitor response 1 (TIR1) and promotes the degradation of the auxin/indole-3-acetic acid (Aux/IAA) transcriptional repressors. In this context, efficient auxin binding requires assembly of an auxin coreceptor complex consisting of TIR1 and an Aux/IAA protein. As recently demonstrated, combinatorial interactions of auxin signalling F-box proteins (AFBs) and 29 Aux/IAA proteins in *Arabidopsis thaliana* may result in many coreceptors with distinct auxin-sensing properties, and the AFB5-Aux/IAA coreceptor selectively binds the auxinic herbicide picloram by interaction with the carboxylic functional group.<sup>82</sup>

Classified synthetic auxin mimics (HRAC: MoA group O) such as phenoxy-carboxylic acids (2,4-D), benzoic acid (dicamba), quinolinecarboxylic acid (quinclorac) and pyridine-carboxylic acids (e.g. picloram, clopyralid, aminopyralid) (see Fig. 19)<sup>83</sup> induce physiological and phenotypic effects similar to those induced by the natural plant hormone IAA.

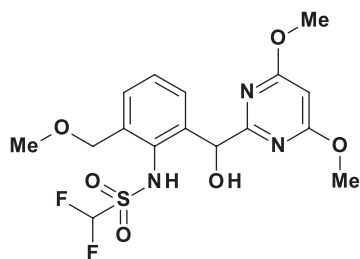
The auxin mimic halauxifen-methyl (ISO-proposed common name) (Fig. 18) was launched in 2014 by Dow AgroSciences as prodrug methyl pyridine-carboxylate for use in cereals and other crops, which can be metabolically converted in plants and soil into the pyridine-carboxylic acid halauxifen by enzymatic



**Figure 15.** MoA of indaziflam:  $\beta$ -(1,4)-glucan chain is transformed into cellulose microfibril (data taken from Cosgrove<sup>72</sup>).



**Figure 16.** Chemical structures of the ALS inhibitor subgroups: (a) triazolopyrimidines such as penoxsulam and pyroxsulam; (b) sulfonylureas such as tritosulfuron and orthosulfamuron; (c) sulfonylaminocarbonyl-triazolinones such as thien carbazole-methyl.



**Figure 17.** Pyrimisulfan.

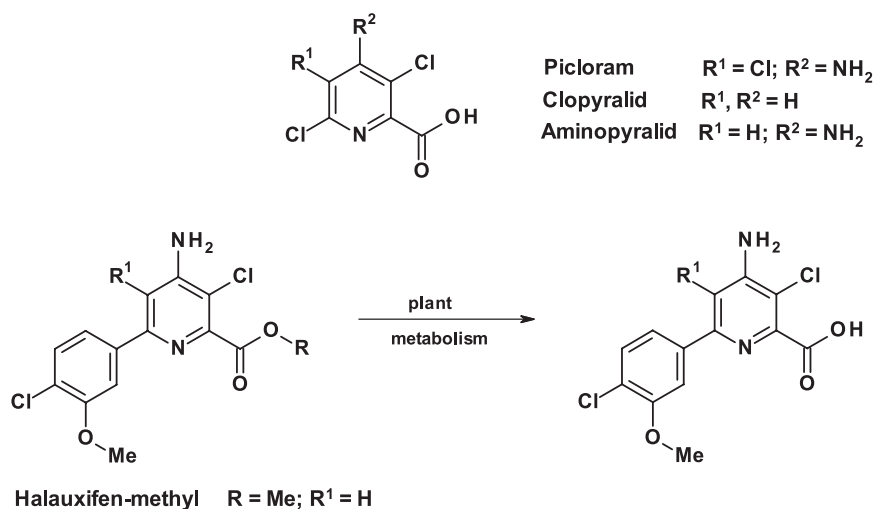
hydrolysis.<sup>69,84</sup> Initial registrations of the 5-fluoro analogue of halauxifen herbicide (brand name Rinskor<sup>TM</sup> active;  $R = \text{benzyl}$ ;  $R^1 = \text{F}$ ) (Fig. 18) for use in rice and other crops are anticipated in 2017–2018.<sup>84</sup>

## 6 SAFENERS FOR WEED CONTROL

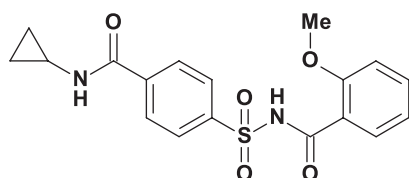
It has been known for some time that broad-spectrum herbicides can be combined with a safener for crop protection and

efficient weed management. The safener induces the degradation of the active ingredient only in the crop, but not in the weed. Full crop selectivity of some highly effective 4-HPPD, ACCase or post-emergence ALS-inhibiting herbicides can be obtained by using safeners, which increase the degradation or detoxification of the herbicide in the corresponding agricultural crop.<sup>85,86</sup> This effect is connected with the increased expression of genes coding for enzymes responsible for degradation in the crop, such as cytochrome-P450-dependent monooxygenases,<sup>87</sup> glutathione S-transferases (GST) and ABC transporters.

Since 2009, the new corn safener cyprosulfamide (Fig. 19) from Bayer CropScience has been combined with the ALS herbicide thien carbazole-methyl (see Section 5.5) (Fig. 16c) in the herbicidal product Adengo<sup>®</sup>. The high crop tolerance to two or three highly active ingredients in one commercial product is ensured by this novel safener cyprosulfamide, which can protect corn against herbicide damage via root uptake and via leaf uptake. In addition, it was found that cyprosulfamide, alone or with abscisic acid (ABA), protected plants (e.g. rice) from salinity stress and induced vigorous growth, including the formation of new tillers and early flowering.<sup>88</sup>



**Figure 18.** Chemical structures of the auxin mimic herbicides picloram, clopyralid and aminopyralid and the prodrug halauxifen-methyl. The latter can be converted in plants into halauxifen by enzymatic hydrolysis.



**Figure 19.** Cyprosulfamide.

In spite of enormous screening efforts by many research-oriented companies, safeners for dicotyledenous crops such as soybean, canola and sugar beet could not be identified. It was found that a broad-spectrum, one-application weed control was only efficient by using mixtures.<sup>63</sup>

## 7 INSECTICIDES FOR PEST CONTROL

For insecticide market products, neuronal and muscle targets are most important. Only three MoAs dominate, accounting for around 58% of this market segment. These MoAs versus agricultural market products include around 27% nicotinic acetylcholine receptor (*nAChR*) competitive modulators such as the neonicotinoids, 16% sodium channel modulators (SoCh) such as the pyrethroids and 15% acetylcholinesterase (AChE) inhibitors such as the organophosphates (OPs, 11%) and carbamates (4%).<sup>89</sup>

### 7.1 Nicotinic acetylcholine receptor (*nAChR*) competitive modulators

The agrochemical importance of synthetic competitive modulators selectively addressing the *nAChRs* located in the central nervous system of pest species is enormous and has been reviewed in numerous articles and book chapters over the past decade.<sup>90–92</sup>

In 2014, the neonicotinoid class (MoA group 4A) comprised seven compounds with a market share of more than 25% of total global insecticide sales, with the three members thiamethoxam (TMX), imidacloprid (IMD) and clothianidin (CLT) (Fig. 20) accounting for almost 85% of the total neonicotinoid sales in crop protection in 2012.<sup>93</sup> Although numerous insect species are still successfully controlled by these *nAChR* competitive modulators,

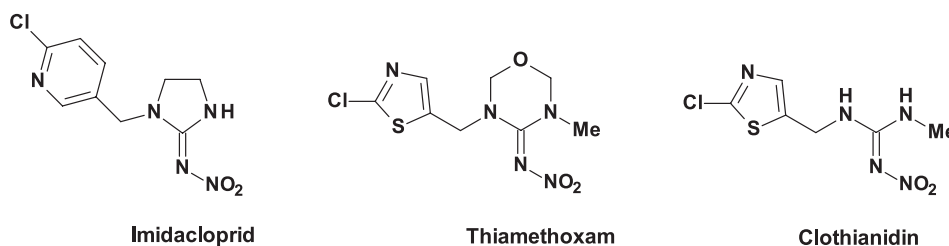
their popularity and widespread use has imposed a mounting selection pressure for resistance. In several important insect species, such as sweet potato whitefly (*Bemisia tabaci*), green peach aphid (*Myzus persicae*), cotton melon aphid (*Aphis gossypii*), brown planthopper (*Nilaparvata lugens*), Colorado potato beetle (*Leptenotarsa decemlineata*) and the glasshouse whitefly (*Trialeurodes vaporariorum*), resistance levels have been reached that compromise the efficacy of this insecticide class.<sup>89</sup>

Today, of the 26 IRAC MoA groups, only ten are commonly used for control of *B. tabaci*, one of the most damaging sucking pest species of numerous crops worldwide and responsible for the transmission of plant viruses. In spite of its structural difference to neonicotinoids, the neuroactive compound pymetrozine (MoA group 9B) is already showing cross-resistance to IMD in whiteflies.<sup>94,95</sup> Therefore, continuing research to discover and develop novel insecticidal *nAChR* competitive modulators overcoming metabolic resistance *in vivo* is essential.

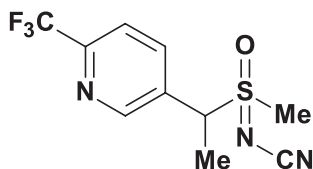
In this context, the value of privileged structures as new scaffolds for agrochemicals has been explored within the last 10 years. As a result, the identification of the sulfoximine core led to the diastereomeric sulfoxaflor (2012; Dow AgroSciences) (Fig. 21).<sup>96</sup> This is an insecticide acting against piercing-sucking insects such as cotton aphids (*A. gossypii*) and the green peach aphid (*M. persicae*), has been registered for use in apples, pears and red peppers and has been classified by IRAC as an *nAChR* competitive modulator in subgroup 4C.

On the other hand, inspired by the stemofoline lactone 'head group' as a topological pharmacophore pattern and molecular modelling investigations using structural features of relevant *nAChR* competitive modulators, the complex structure of the stemofoline alkaloid (isolated from Asian plants belonging to the Stemonaceae family) resulted in the discovery of flupyradifurone (2014; Bayer CropScience) (Fig. 22).<sup>97</sup>

As a modern insecticide, and based on results at recommended field rates, Sivanto<sup>®</sup> prime has an excellent safety profile with respect to (i) human safety (approved as a reduced-risk candidate by the US EPA), (ii) safety to honey bees and bumblebees and (iii) environmental safety, demonstrated by a perfect fit for IPM systems.<sup>98</sup> Flupyradifurone is active against major sucking pests, including neonicotinoid-resistant whiteflies and selected aphids, and is a resistance management tool for sustainable pest control.



**Figure 20.** Chemical structures of the neonicotinoids imidacloprid (IMD), thiamethoxam (TMX) and clothianidin (CLT).



**Figure 21.** Sulfoxaflor.

An explanation for the lack of metabolism of flupyradifurone in comparison with IMD was given by molecular docking studies. Based on a structural model of CYP6CM1vQ from whitefly (*B. tabaci*)<sup>99</sup> and molecular docking investigations with both IMD and flupyradifurone, it could be demonstrated that the rather non-reactive difluoromethyl moiety (cf. the circle in Fig. 22) of the *N*-2,2-difluoroethyl side chain in flupyradifurone increases the insecticidal efficacy and prevents its oxidative metabolism in *B. tabaci* at the active haem iron–oxygen centre of the CYP6CM1 cavity model, as outlined in Fig. 22.

Because it differs structurally from the neonicotinoid class and sulfoxaflor, in 2013 flupyradifurone was assigned to the IRAC MoA butenolide subgroup 4D.<sup>100</sup> Both sulfoxaflor (6-CF<sub>3</sub>-pyridyl moiety) and flupyradifurone (*N*-2,2-difluoroethyl side chain) are the first fluorine-containing *nAChR* competitive modulators marketed so far.

A novel class of mesoionic insecticides, as exemplified by triflumezopyrim and dichloromezotiaz (ISO-proposed common names) (Fig. 23), are currently under development by DuPont.<sup>101</sup> Triflumezopyrim, recently proposed for classification as an *nAChR* competitive modulator in the MoA subgroup 4E, provides excellent control of sucking insects such as brown planthoppers (*N. lugens*), which have developed strong resistance to neonicotinoids such as IMD, while dichloromezotiaz acts mainly against chewing pests.

### 7.1.1 Management of abiotic and biotic stress

Plant growth and productivity, as well as product quality, are strongly influenced by the environmental stress factors to which plants are continually exposed.<sup>102</sup> Stress impairs the energy balance of crops, resulting in higher energy consumption for cell repair and less energy generation for growth. In recent years it was found that the plant systemic neonicotinoid insecticide class, including IMD, CLT and TMX, has phytotonic or plant-growth-stimulating effects (cf. greening or vigour effects)<sup>103,104</sup> and increases stress tolerance. Field studies indicated that multiple foliar spray applications of IMD improved health and increased plant growth even in situations without insect infestation, as measured by barley leaf growth. After Confidor<sup>®</sup> treatment, results from the DNA microarray experiments show two different plant reactions: (i) the expression level of drought-stress marker genes in barley is delayed; (ii) photosynthesis-related

genes are simultaneously expressed at a higher level.<sup>102</sup> Compared with untreated plants, numerous pathogenesis-related proteins were found to be overexpressed, explaining field observations of synergistic fungicidal and bactericidal effects, the so-called biotic stress.

### 7.2 Nicotinic acetylcholine receptor (*nAChR*) allosteric modulators

Because the effects of spinosyns on target insects are consistent with the activation of the *nAChR*, albeit at a different site than nicotine or neonicotinoid insecticides, they have been classified as *nAChR* allosteric modulators and have been assigned to IRAC MoA group 5. Spinosyns also affect GABA ( $\gamma$ -aminobutyric acid) receptors, but the role of this effect in the overall activity is unclear. There is currently no known cross-resistance to other insecticide classes.<sup>105</sup>

After the successful introduction of the natural product spinosad in 1997, the second-generation spinosyn insecticide spinetoram (2008; Dow AgroSciences) (Fig. 24) was first marketed nearly one decade later.

The discovery of the semi-synthetic spinetoram, a mixture of 3'-*O*-ethyl-5,6-dihydro spinosyn J (major component) and 3'-*O*-ethyl spinosyn L (minor component), involved the novel application of an artificial neural network (ANN) to the molecular design of insecticides and the prediction of insecticidally more effective analogues against fruit-tree pests via multiple linear regression-based quantitative structure–activity relationships (QSARs) of spinosyns (base on calculated log *P* values, MOPAC dipole moment data) and closely related spinosoids.<sup>106</sup>

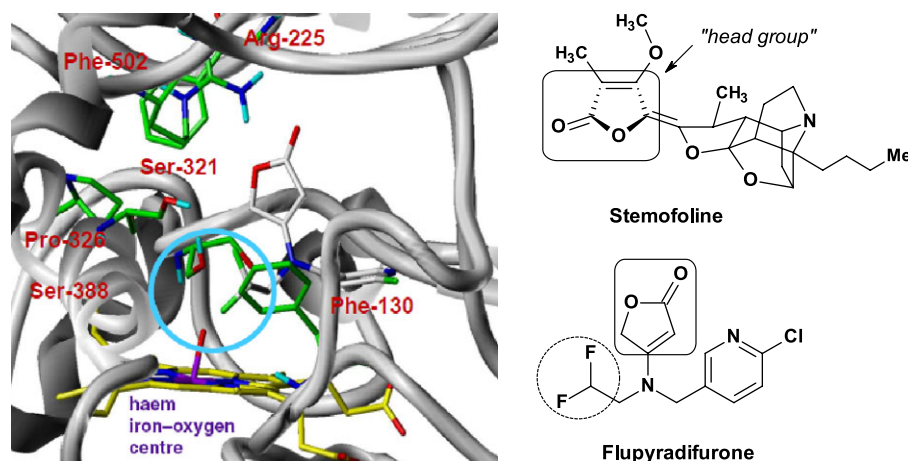
Spinetoram can be prepared from the naturally occurring fermentation products spinosyns J and L (produced by *Saccharopolyspora spinosa*) by hydrogenation of the C=C double bond in the 5,6-position and subsequent *O*-ethylation of the rhamnose sugar. It has been shown that implementation of the *O*-ethyl substituent leads to an increase in insecticidal activity and to a broader pest spectrum, whereas reduction of the C=C double bond is associated with better residual activity in the field.

The semi-synthetic spinetoram retains the favourable environmental benefits of spinosad and has replaced many OPs for use in tree fruits, tree nuts, small fruits and vegetables. Applications of spinetoram products (WG, SC) include control of crop-damaging pests such as codling moth (*Cydia pomonella*), leafminers, apple maggot (*Rhagoletis pomonella*), diamondback moth (*Plutella xylostella*), armyworm (*Spodoptera frugiperda*), thrips, cutworm (*Agrotis* sp.) and others. Crops likely to be treated with spinetoram include apples and pears, stone fruit, tree nuts, vegetables, citrus, corn, cotton, soybeans and berries.

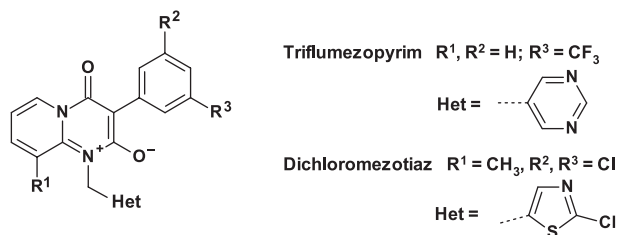
### 7.3 Ryanodin receptor (RyR) modulators

The insect ryanodine receptor (RyR) is a large tetrameric ryanodine-sensitive Ca<sup>2+</sup> release channel. It regulates the





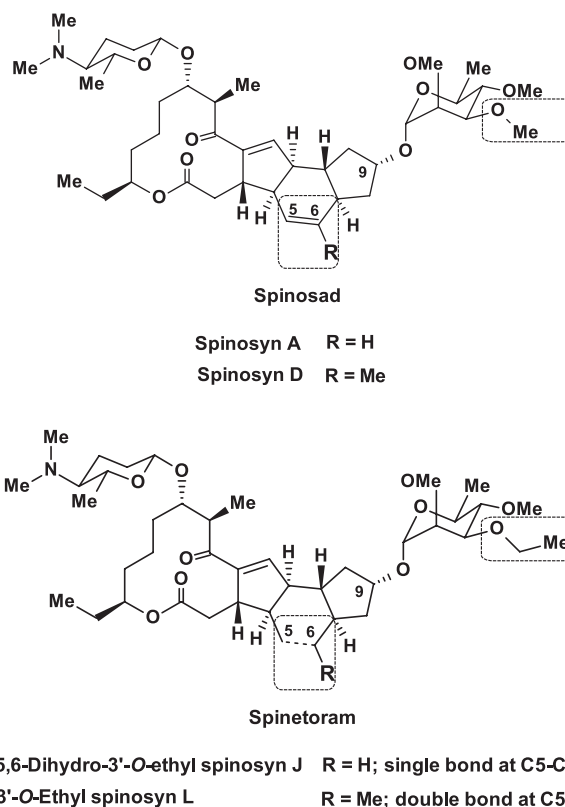
**Figure 22.** Molecular docking studies of flupyradifurone within the *CYP6CM1vQ* (*B. tabaci*) cavity model: representative flupyradifurone pose in surroundings of amino acids.



**Figure 23.** Structures of the two mesoionic insecticides triflumezopyrim and dichloromezotiaz (ISO-proposed common names).

intracellular release of stored  $\text{Ca}^{2+}$  ions as intracellular messengers (calcium homeostasis) from the sarcoplasmic/endoplasmic reticulum membrane into the cytosol, which is important for muscle contraction. The RyR has been described as a potential insecticide target; however, only natural product ryanodine (isolated from *Rynia speciosa*), which is highly toxic to mammals, was known as a ligand for several decades. This changed with the discovery of the new chemical class of insecticides based on diamide scaffolds that bind to insect RyRs at a site that is distinct from ryanodine.<sup>107</sup> The first representative was flubendiamide (2007; Nihon Nohyaku Co./Bayer CropScience)<sup>108</sup> (Fig. 25), with an until then unknown lipophilic heptafluoroisopropyl substitution pattern in the aniline part of the molecule, which belongs to a new insecticide chemical class called the phthalic acid diamides. The insecticide acts as a conformation-sensitive activator of the insect RyRs and is completely inactive on mammalian RyR subtypes, explaining its excellent toxicological profile.

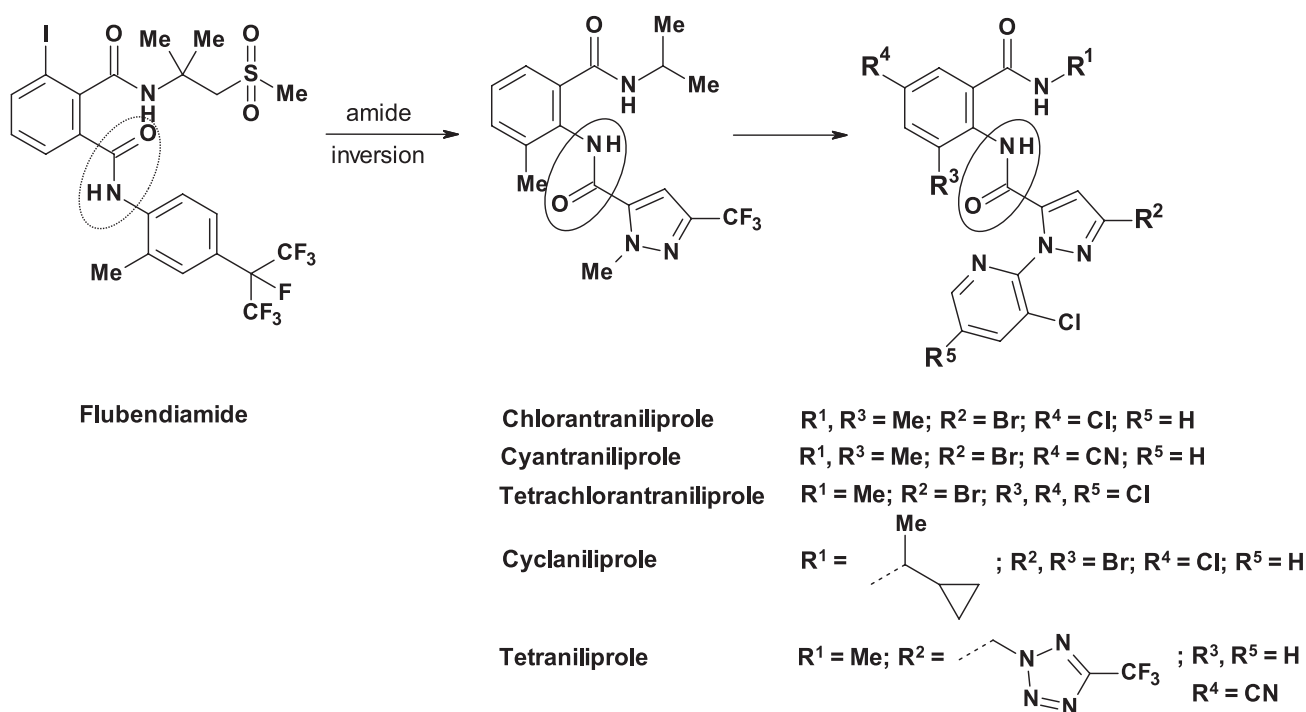
It was found that flubendiamide induced ryanodine-sensitive cytosolic  $\text{Ca}^{2+}$  transients that were independent of the extracellular  $\text{Ca}^{2+}$  concentration in isolated neurons from the pest species tobacco budworm (*Heliothis virescens*), as well as in transfected Chinese hamster ovary (CHO) cells expressing the RyR from fruit fly (*Drosophila melanogaster*). Binding studies on microsomal membranes from *H. virescens* flight muscle have revealed that flubendiamide interacts with a site distinct from the ryanodine binding site and disrupts  $\text{Ca}^{2+}$  regulation of ryanodine binding by an allosteric mechanism.<sup>109</sup> Flubendiamide controls a broad spectrum of lepidopteran insect pests. The insecticide has outstanding larvicidal activity, is safe to beneficial insects, has a broad crop utility because of its fast-acting and long-lasting effect and



**Figure 24.** Spinosad and spinetoram as mixture of 5,6-dihydro-3'-O-ethyl spinosyn J and 3'-O-ethyl spinosyn L.

shows no cross-resistance to other insecticide classes. Therefore, flubendiamide is an excellent tool for resistance management.

The structure of flubendiamide stimulated chemical research at DuPont to identify anthranilic acid diamides such as chlorantraniliprole (2007; DuPont) (Fig. 25) by a so-called amide inversion ( $\text{CO-NH}$  into  $\text{NH-CO}$ ) and following molecule optimisation mainly in the pyrazol-5-yl moiety.<sup>110,111</sup> In the search for analogues with an enhanced systemic profile, replacement of the chlorine in the  $\text{R}^4$ -position with a cyano moiety was successful. The resulting cyantraniliprole (2012; DuPont) (Fig. 25) has improved plant mobility and demonstrates broad activity against a wide range of insects,



**Figure 25.** Phthalic acid and anthranilic acid diamides as RyR modulators such as the lead structures flubendiamide, chlorantraniliprole and cyantraniliprole as well as the development candidates tetraclorantraniliprole, cyclaniliprole and tetraniliprole (ISO-proposed common names).

including chewing and sucking insects, as well as coleopteran pests.

In 2013, the three RyR modulators flubendiamide, chlorantraniliprole and cyantraniliprole demonstrated fast-rising sales, with a global turnover of over \$US 1.4 billion, representing approximately 8% of the insecticide market.<sup>89</sup>

Besides tetrachlorantraniliprole (Si Lv Chong Xian An, 2013; SYRICI) outlined in Fig. 25 with  $R^1 = \text{Me}$ ,  $R^2 = \text{Br}$  and  $R^3, R^4, R^5 = \text{Cl}$ , which was marketed only in China, further new compounds are currently under development by Ishihara and Bayer CropScience, exemplified by cyclaniliprole ( $R^1 = \text{CHMe-cyclopropyl}$ ;  $R^2, R^3 = \text{Br}$ ;  $R^4 = \text{Cl}$ ;  $R^5 = \text{H}$ ) and tetraniliprole ( $R^1, R^3 = \text{Me}$ ;  $R^2 = (5\text{-CF}_3\text{-2H-tetrazol-2-yl)methyl}$ ;  $R^4 = \text{CN}$ ,  $R^5 = \text{H}$ ) (ISO-proposed common names).

Recently conducted baseline studies and resistance monitoring campaigns confirmed the regional development of diamide insecticide resistance appearing in the field in a few pests such as diamondback moth (*P. xylostella*),<sup>112</sup> tea tortrix (*Adoxophyes honmai*)<sup>113</sup> and tomato leafminer (*Tuta absoluta*),<sup>114</sup> but resistance ratios vary between species.<sup>115</sup> Mutations in the C-terminal membrane-spanning domain of the *Plutella* RyR were described, influencing the binding of diamide insecticides, e.g. amino acid substitutions G4946E,<sup>116</sup> I4790M and Q4594L<sup>117</sup> respectively.

These investigations will provide an important tool for resistance management and deployment of suitable rotational applications.

### 7.4 Acetyl CoA carboxylase (ACCase) inhibitors

The acetyl CoA carboxylase (ACCase; EC 6.4.1.2), crucial for the metabolism of fatty acids, is a biotin-dependent carboxylase that produces malonyl-CoA from bicarbonate as a source of carboxyl group, and ATP as a source of energy.<sup>118,119</sup>

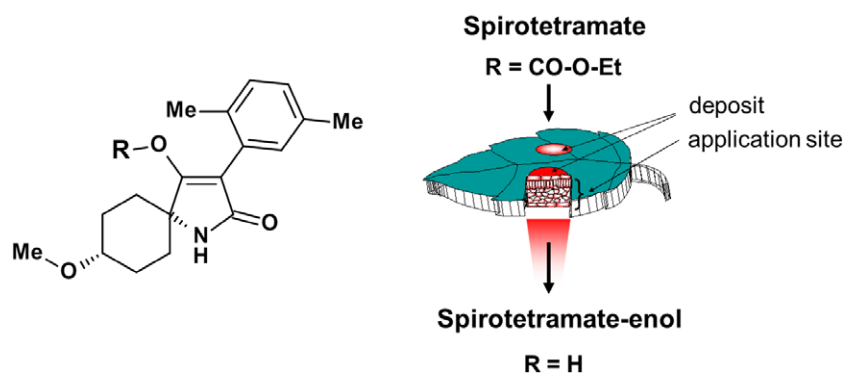
After the successful introduction of the two tetrionic acid derivatives spiroticlofen (2002) and spiromesifen (2004), 5 years later Bayer CropScience launched spirotetramate (2009; Bayer

CropScience) (Fig. 26). All so-called 'ketoenoles' (KTEs) are ACCase inhibitors and inhibit lipid (or fatty acid) synthesis, but they have completely different physicochemical properties and address different biological spectra. Whereas spiroticlofen is non-systemic with long-lasting activity against spider mites (only via contact activity), spiromesifen has translaminar activity against spider mites and is an important tool for whitefly insecticide resistance management (IRM).

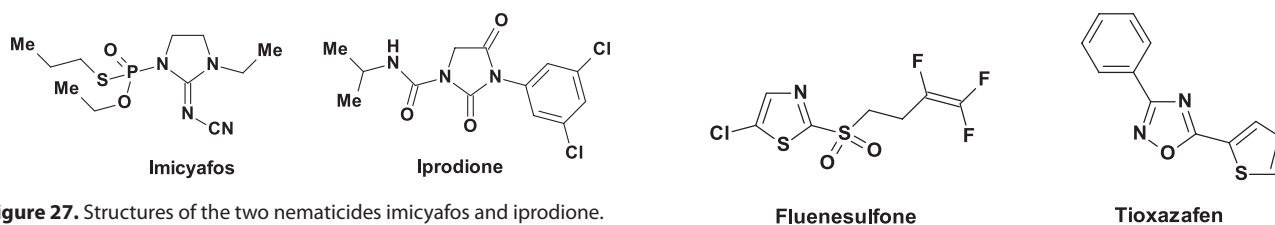
As a prodrug,<sup>69</sup> the insecticide spirotetramate ( $R = \text{CO-O-Et}$ ) demonstrates a broad activity against aphids and other sucking pests because of the ambimobile behaviour of the spirotetramate-enol ( $R = \text{H}$ ) (Fig. 26). In contrast to IMD, spirotetramate-enol ( $R = \text{H}$ ) is also translocated over a longer distance via the phloem stream, and thus shows basipetal and acropetal transport, also dubbed two-way systemicity. After application, the whole of the plant, including the roots, is protected. As a result, spirotetramate ( $R = \text{CO-O-Et}$ ) has excellent activity against difficult-to-control sucking pests such as the woolly apple aphid (*Eriosoma lanigerum*).

## 8 NEMATICIDES

Plant-parasitic nematodes (PPNs) such as the root-knot nematode (*Meloidogyne* spp.), cyst nematodes (*Globodera* spp. and *Heterodera* spp.) and migratory nematodes (*Radopholus* spp., *Pratylenchus* spp. and *Helicotylenchus* spp.) infest many important agricultural crops, such as soybean, coffee, potato, sugarbeet, corn, banana, etc., and they are responsible for approximately 12% of world crop production losses (<http://plpnemweb.ucdavis.edu/nemalex/Plntpara/damage.htm>; over \$US 100 billion per year). Besides damaging roots, they can also transmit viruses and make plants more vulnerable to attack by bacterial and fungal pathogens in the soil. PPNs have been controlled through extensive application of the fumigant nematicide methyl



**Figure 26.** The prodrug spirotetramate (R = CO-O-Et) forms spirotetramate-enol (R = H) by O-deacylation in the plant tissues.



**Figure 27.** Structures of the two nematicides imicyafos and iprodione.

**Figure 28.** Nematicides under development, fluenesulfone and tioxazafen (ISO-proposed common name).

bromide, which is now restricted owing to its ozone-depleting properties.<sup>120</sup> Currently available older active ingredients used as nematicides such as the acetylcholinesterase (AChE) inhibitor organophosphates (OPs) and carbamates have unfavourable toxicological and ecotoxicological profiles, are applied at high application rates and are being withdrawn from further use. Therefore, the search for innovative solutions useful for integrated nematode management has been started.<sup>121</sup>

In this context, the new contact OP nematicide and AChE inhibitor imicyafos (2010; Agro Kanesho)<sup>122</sup> (Fig. 27) was marketed, showing activity against root-knot, root-lesion as well as cyst nematodes, and can be used in fruits and vegetables, including potatoes, and further horticultural or glasshouse crops.

On the other hand, it was found that the old dicarboxamide fungicide iprodione (1976; BASF) (Fig. 27) has additional nematocidal activity. Around 35 years later, the MAP/histidine kinase inhibitor was found to act as a nematicide (2010; Devgen) and is used against nematodes in peanuts.

Recently, Bayer CropScience has launched a new nematicide that is based on the SDHI pyridinyl-ethyl benzamide fungicide fluopyram (2014) (see Section 4.2) (Fig. 4). In field trials, fluopyram has demonstrated a high level of efficacy against PPN, combined with a good safety profile, and has shown significant increases in yield and quality in a broad spectrum of crops, e.g. fruit, vegetables and tobacco, as well as cotton and peanuts. It is the first nematicide acting as a complex II inhibitor. Velum<sup>®</sup> prime (Verango<sup>®</sup> as a suspension concentrate formulation) selectively inhibits the mitochondrial respiratory chain and leads to severe depletion of cellular energy (ATP). Because of its high intrinsic activity, treated nematodes are very quickly immobilised. Depending on regulatory approval, both products can be used for drip irrigation, soil drench and in-furrow application and for soil incorporation. Additional benefits are their efficacy against fungal diseases such as *Alternaria* leaf spot (*Alternaria cucumerina*), powdery mildew (e.g. *Erysiphe* spp., *Sphaerotheca* spp.) and *Sclerotinia* rot (*Sclerotinia sclerotiorum*) (see Section 4.2).

In the coming years, further new nematicides will be introduced, such as the fluoralkylthioether fluensulfone (Adama)<sup>123</sup> and

the 3,5-disubstituted 1,2,4-oxadiazole thioxazafen (ISO-proposed common name)<sup>124</sup> from Monsanto (Fig. 28).

Fluensulfone affects the motility and body posture of PPNs, including *Meloidogyne* species, and has low toxicity to non-target insects and mammals. Fluensulfone has pleiotropic actions on nematodes and inhibits development, egg laying, egg hatching, feeding and locomotion.<sup>125</sup> In the case of feeding and locomotion, an early excitation precedes gross inhibition.

The new seed treatment nematicide tioxazafen provides consistent broad-spectrum control of nematodes in major field crops such as corn, soy and cotton. It exhibits excellent activity on cyst, root-knot and reniform nematodes in soy, on lesion, root-knot and needle nematodes in corn and on reniform and root-knot nematodes in cotton.

## 9 CONCLUDING REMARKS AND PROSPECTS

The agronomic production of food, feed, fuel and fibre requires innovative solutions for current and future challenges such as climate change, resistance issues and resistance management, increasing regulatory demands, renewable raw materials and requirements of food chain partnerships. Today, the modern agrochemical industry has to support farmers to manage these diversified tasks in accordance with further understanding of the crosslinked biological system and generation of innovation. Currently, several modern active ingredients are already matching these expectations, and further ones will need to follow in order to fulfil these ambitious criteria.

The innovative agricultural chemicals launched between 2004 and 2014 support these challenges, as reflected by novel fungicides, herbicides and safeners, insecticides and nematicides. Since 2007, a new generation of systemic, broad-spectrum fungicides (e.g. fluorine-substituted pyrazol-4-yl-carboxamide SDHIs) has been discovered, which can be used for seed treatment applications and as a perfect option for mixtures with complex III

inhibitors such as the strobilurins. With isotianil, a novel plant defence inducer could be developed to initiate systemic induction of the plant's own defence mechanism that controls rice diseases. Further optimised herbicide classes such as 4-HPPD and ALS inhibitors can be applied at much lower application rates. To overcome inherent selectivity of herbicides in special crops such as corn, safener technology has been further intensified (e.g. the combination of thien carbazole-methyl with cyprosulfamide). Research of highly specific ryanodine receptor modulators, demonstrating similar symptoms to those identified in insects treated with the toxic plant alkaloid ryanodine, resulted in the discovery of a new class of insecticides with novel MoAs (e.g. flubendiamide, chlorantraniliprole). The pyridinyl-ethyl benzamide fungicide fluopyram, combining a good safety profile with a significant increase in yield and quality in a broad spectrum of crops, will be a benefit for nematode control. In the past decade, the side effects of agrochemicals that affect crop yield (e.g. fluopicolide, fluopyram), virus vector control (e.g. flupyradifurone), plant health (e.g. novel aspects for imidacloprid and thiamethoxam), resistance-breaking potential (e.g. flupyradifurone, indaziflam), new physicochemical properties such as phloem mobility (e.g. spirotetramate) and quality have gained increasing importance. These beneficial effects are sometimes complemented by agricultural biologicals.

In spite of the significant consolidation of the agrochemical companies, modern agricultural chemistry is vital and will have the opportunity to shape the future of agriculture by continuing to deliver further innovative integrated solutions.

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