

The unique role of halogen substituents in the design of modern agrochemicals[†]

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Abstract

The past 30 years have witnessed a period of significant expansion in the use of halogenated compounds in the field of agrochemical research and development. The introduction of halogens into active ingredients has become an important concept in the quest for a modern agrochemical with optimal efficacy, environmental safety, user friendliness and economic viability. Outstanding progress has been made, especially in synthetic methods for particular halogen-substituted key intermediates that were previously prohibitively expensive. Interestingly, there has been a rise in the number of commercial products containing 'mixed' halogens, e.g. one or more fluorine, chlorine, bromine or iodine atoms in addition to one or more further halogen atoms. Extrapolation of the current trend indicates that a definite growth is to be expected in fluorine-substituted agrochemicals throughout the twenty-first century. A number of these recently developed agrochemical candidates containing halogen substituents represent novel classes of chemical compounds with new modes of action. However, the complex structure–activity relationships associated with biologically active molecules mean that the introduction of halogens can lead to either an increase or a decrease in the efficacy of a compound, depending on its changed mode of action, physicochemical properties, target interaction or metabolic susceptibility and transformation. In spite of modern design concepts, it is still difficult to predict the sites in a molecule at which halogen substitution will result in optimal desired effects. This review describes comprehensively the successful utilisation of halogens and their unique role in the design of modern agrochemicals, exemplified by various commercial products from Bayer CropScience coming from different agrochemical areas.

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Keywords: halogenated agrochemicals; structure–activity relationship; insecticides; fungicides; herbicides; mode of action; physicochemistry; halogen effects; bioavailability; selectivity; resistance

1 INTRODUCTION

The task of inventing and developing active ingredients (AIs) with useful biological activities for modern crop protection requires a search for novel chemical substructures. This process may trigger the discovery of whole classes of chemicals of potential commercial interest. Similar biological effects can often be achieved by completely different molecules. However, compounds within a given structural family may exhibit quite different biological activities depending on their interactions with different intracellular proteins such as enzymes or receptors. By varying the functional groups and structural elements of a lead compound, its interaction with the active site of the target protein, as well as its physicochemical, pharmacokinetic and pharmacodynamic properties, can be modified and improved.¹

Since 1940, the number of launched agrochemicals containing halogens has increased. In this context, the past 30 years have witnessed a period of significant expansion in the use of halogenated compounds in the field of agrochemical research and development (Fig. 1).^{2–4} The introduction of halogens into AIs has become an important concept in the quest for a modern agrochemical with optimal efficacy, environmental safety, user friendliness and economic viability. Interestingly, there has been a rise in the number of commercial products containing 'mixed' halogens, e.g. one or more fluorine, chlorine, bromine or iodine atoms in addition to one or more further halogen atoms.

A differentiation of agrochemicals with regard to their level of fluorination, for example, shows a statistical pattern: fungicides often have about two fluorine atoms, insecticides/acaricides tend

to contain four or more fluorine atoms and herbicides often contain three or more fluorine atoms. Extrapolation of the current trend indicates that a definite growth is to be expected in fluorine-substituted agrochemicals throughout the twenty-first century.^{5,6}

A survey of new AIs (total number up to September 2008: 121) used as modern agrochemicals (insecticides/acaricides, fungicides and herbicides), provisionally approved by ISO in the last 10 years (1998–2008), shows that around 78.5% of them are halogen substituted (Br, I < Cl, Cl/F < F). For fungicides, a chlorine or fluorine (strong increase in 2008) substitution is often most important, whereas for insecticides/acaricides a 'mixed' halogen substitution such as chlorine and fluorine and for herbicides a fluorine substitution is favourable.

According to data from Phillips McDougall, in each crop protection area (insecticides, fungicides and herbicides), 11 halogen-containing products (around 60%) are among the 20 best-selling compounds. These are the insecticides imidacloprid (1991, Gaucho®), thiamethoxam (1997, Cruiser®), chlorpyrifos

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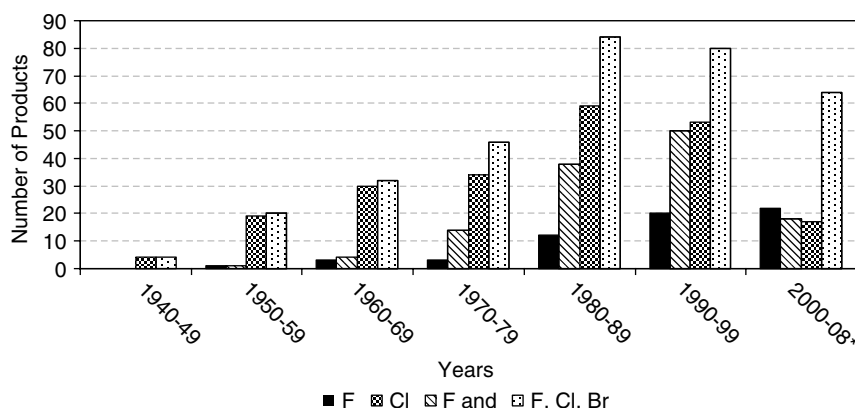


Figure 1. Launch of halogenated commercial products in the timeframe 1940–2008; inclusive compounds provisionally approved by ISO until September 2008 (www.alanwood.net).

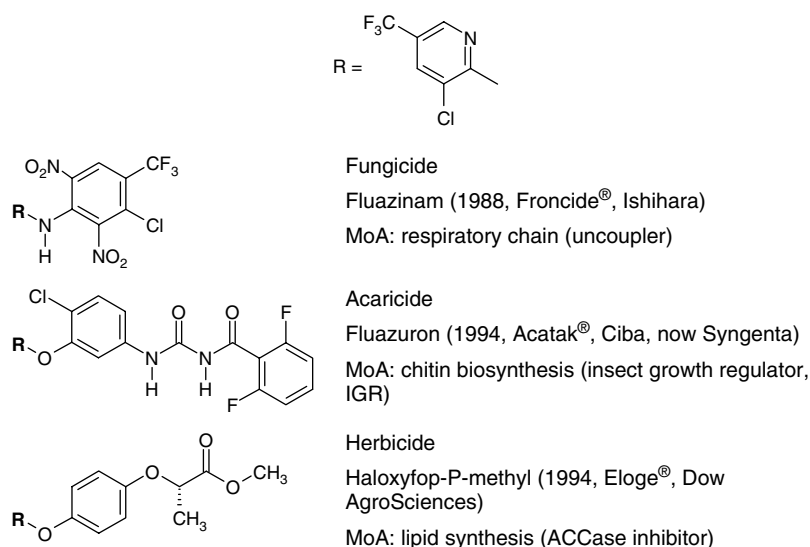


Figure 2. Active ingredients with different biological activities and MoAs containing the 3-chloro-5-trifluoromethyl-2-pyridinyl residue.

(1965, Dursban®) and fipronil (1993, Regent®), the fungicides tebuconazole (1988, Folicur®), pyraclostrobin (2001, Cabrio®) and epoxiconazole (1992, Opus®) and the herbicides acetochlor (1985, Harness®), S-metolachlor (1997, Dual Magnum®), 2,4-D (1945, Herbifen®), atrazine (1957, AtraneX®) and fenoxaprop-P-ethyl (1988, Puma S®), all of which achieved sales in 2006 of €270–830 million (total: €4384 million).

Today, around two-thirds of all known agrochemicals contain halogen-substituted aryl and hetaryl moieties. There are some halogenated pyridyl moieties used broadly in different crop protection areas, because they can strengthen the biological activity, as shown by the 3-chloro-5-trifluoromethyl-2-pyridinyl residue in fluazinam (1988, Froncide®; fungicide), in the benzoyl phenyl urea (BPU) fluazuron (1994, Acatak®; acaricide) and in haloxyfop-P-methyl (1994, Elogé®; herbicide) respectively (Fig. 2).

In addition, outstanding progress has been made in synthetic methods for particular halogen-substituted key intermediates that were previously prohibitively expensive (e.g. fluoroorganic chemistry – development of novel reagents/methodologies usable on a kilogram scale: deoxofluorination with SF₄, the modified Baltz–Schiemann reaction/fluorodediazotisation, electrophilic fluorination using F⁺-reagents including enantioselective variants,

Cl/F exchange reactions/HF chemistry including the Halex reaction, selective direct fluorination with F₂).^{7,8} The combination with other core technologies (e.g. chlorination, catalytic hydrogenation, Cl/N and Cl/O exchange, Sandmeyer reactions, Suzuki cross-coupling and others) allows the synthesis of a broad variety of new building blocks containing fluorine. These efforts also included the introduction of fluorinated aryl moieties, so-called ‘fluoroaromatics’, such as CHF₂O- or CF₃O-aryl fragments and other moieties, into modern agrochemicals.^{9,10} The basic raw material for such products, trifluoromethoxybenzene, is produced today on an industrial scale. Therefore, several agrochemicals from different crop protection areas produced from trifluoromethoxybenzene and its derivatives are known, such as indoxacarb (1998, Steward®; pro-insecticide), triflumuron (1979, Alsystin®; IGR), thifluzamide (1997, Greatam®; fungicide), flurprimidol [1989, Cutless®; plant growth regulator (PGR)] (Fig. 3) and flucarbazone-sodium (2000, Arysta®; herbicide) (see Section 5.3, Fig. 20).

2 THE HALOGEN SUBSTITUENT EFFECT

What is the rationale behind using halogen atoms and/or halogen containing substituents in the design of modern agrochemicals?

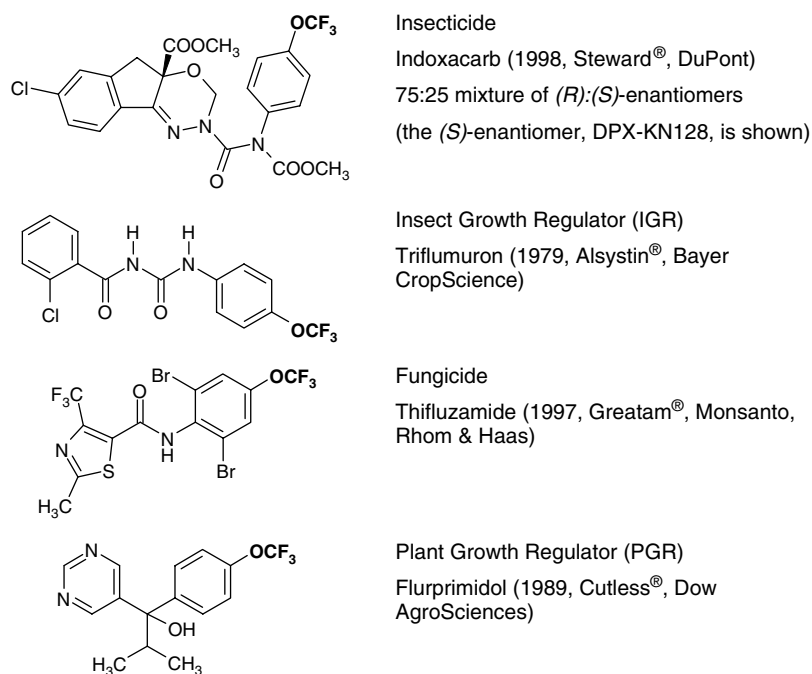


Figure 3. Active ingredients with different biological activities containing the 4-trifluorophenyl moiety.

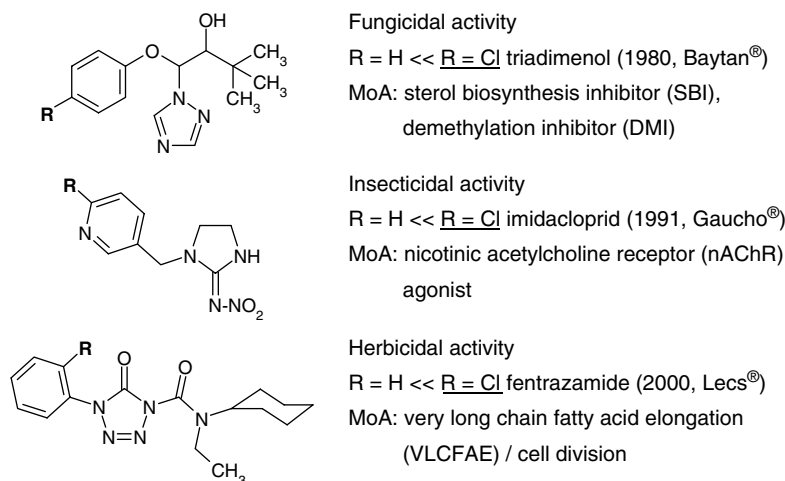


Figure 4. Commercial products triadimenol, imidacloprid and fentrazamide obtained by incorporation of chlorine (R) into the non-halogenated aryl(hetaryl) moiety.

The influence of halogens on the efficacy of a biological active molecule can be exciting and remarkable.¹¹ This can be demonstrated with examples from Bayer CropScience coming from different agrochemical areas (Fig. 4):

- Whereas the unsubstituted triazole (R = H) shows only low fungicidal activity, incorporation of chlorine in the *para*-position of the phenyl moiety leads to the highly active cereal fungicide triadimenol (R = Cl).¹²
- One of the most important structural requirements for active nAChR effectors such as imidacloprid is the incorporation of chlorine into the 6-position (R = Cl) of the 3-pyridinylmethyl substituent.¹³
- Starting with unsubstituted *N*-phenyl-tetrazolinone (R = H), the herbicidal activity is strongly increased by introduction of chlorine in the *ortho*-position, giving the selective paddy

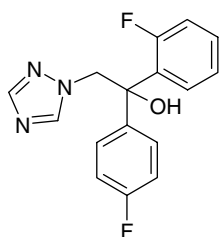
amide herbicide fentrazamide (R = Cl) with excellent crop compatibility, even on young seedlings.¹⁴

The minimal variation in the chemical structure by substitution with halogens such as chlorine into the aryl(hetaryl) moiety led to a commercial fungicide, insecticide and herbicide.

The significant and increasingly important role of halogen atoms and/or halogen-containing substituents can be attributed to the well-known physicochemical effects arising from the introduction of fluorine, chlorine, bromine or iodine and/or halogen-containing substituents into biologically active molecules such as commercial products. As expected for electronegative elements with accessible ion pairs, halogens can act as H-bond acceptors, but in the 1950s it became clear that halogens could also form complexes with H-bond acceptors.^{15,16} This behaviour

Table 1. Bond lengths, van der Waals radii and total size of carbon halogen bonds

Bond	Length (Å)	van der Waals radius (Å)	Total size (Å ³)
O–H	0.96	1.20	2.16
C–H	1.09	1.20	2.29
C=O	1.23	1.50	2.73
C–F	1.35	1.47	2.82
C–O–	1.43	1.52	2.95
C–Cl	1.77	1.80	3.57
C–Br	1.93	1.95	3.88
C–I	2.14	2.15	4.29

**Figure 5.** Fungicide flutriafol (1984, Impact®).

has been outlined on the basis of molecular electrostatic potential surfaces.¹⁷ Fluorine behaves like a ball of negative charge, and therefore it can only act as an H-bond acceptor. The other halogens display a more positive region on the surface opposite to the direction of the C–Hal bond (Hal = Cl, Br, I), as well as an equatorial belt of negative potential.¹⁸ As result, they can act as H-bond donors and acceptors, depending on the angle of approach. The magnitude and area of the zone of positive potential increases with the size of the appropriate halogen atom (F < Cl < Br < I). This means that iodine in particular makes relatively strong interactions with H-bond donors. On the other hand, the so-called ‘fluorine factor’ described in the literature several years ago stems from the unique combination of properties associated with the fluorine atom itself, namely its high electronegativity and moderately small size, its three tightly bound ion-pair electrons and the excellent match between its 2s and 2p orbitals and those of carbon.

In the present review, a few examples are selected to illustrate how halogen substitution is used successfully in contemporary agrochemistry.

2.1 The steric effect

The C–Hal bond lengths increase in the order C–F < C–Cl < C–Br < C–I (Table 1). Owing to the small total size of the C–F bond (2.82 Å) and a van der Waals radius similar to that of the C=O or C–O group (1.47 Å versus 1.50–1.52 Å), fluorine can mimic both in bioactive molecules with respect to steric requirements at the receptor sites or enzyme substrate recognition.^{19,20} Increasingly, these largely recognition aspects of fluorine substitution are used to enhance binding affinity to the target protein.

The fluorine atom was introduced, for example, as a chemical isostere of the essential tertiary hydroxy group (–OH versus –F, isoelectronic; bioisosterism) into the DMI triazole fungicide flutriafol (1984, Impact®; ICI/Zeneca, now Syngenta) (Fig. 5).

The trifluorinated analogue retains some biological activity, even though there is an overall reduction in spectrum.²¹ Unlike

the hydroxy group, organic fluorine is a very poor H-bond acceptor and is not an H-bond donor at all.^{22,23}

Substitution of a hydrogen atom by a fluorine atom (C–H versus C–F) is described as one of the most commonly applied bioisosteric replacements.²⁴ Fluorine can participate in hydrogen bonding interactions with H–C even if these bonds to C–F are definitely much weaker than those observed to oxygen or nitrogen.²⁵ Such C–F ↔ H–C interactions have been proposed as a design principle for crystal engineering.²⁶ Nevertheless, controversy remains over the existence of hydrogen bonds between the C–F group and HO or NH donors.²⁷ Notably, fluorine may also exert a substantial effect on the conformation of a molecule.²⁸

Beneficial steric halogen effects of fluorine atoms in the 2- and 6-position on environmental stability (e.g. soil degradation half-life), caused by the presence of these atoms, have been discussed for diflubenzuron (1975, Dimilin®; Philips Duphar) and its *N*-2,6-dichlorobenzoyl derivative.^{29,30} BPUs like diflubenzuron are stable at acidic pH values but are hydrolysed at pH 9–10 (DT₅₀ = 2–3 days) to give 2,6-difluorobenzoic acid and *N*-(4-chlorophenyl)urea. In contrast to the conformation of the less active *N*-2,6-dichlorobenzoyl analogue, which degrades between 6 and 12 months to form 2,6-dichlorobenzamide and 4-chloroaniline, the conformation of the 2,6-difluorobenzoyl moiety is in plane with the whole BPU structure. As a consequence, different metabolic pathways are observed for these two BPUs.

The CF₃ group has a relatively large van der Waals volume – larger than those of methyl and difluoromethyl and between those of the isopropyl and *tert*-butyl groups.³¹ The latter is comparable in size with the perfluoroisopropyl group.³² Rotational energy studies on *ortho*,*ortho*′-disubstituted biphenyl derivatives suggest that the CF₃ group supports a volume slightly larger than the volume of isopropyl,³³ whereas X-ray crystal data put its volume closer to that of an isobutyl group.³⁴

2.2 The electronic effect

2.2.1 Electronegativities of halogens and selected elements/groups on the Pauling scale

The replacement of hydrogen by the most electronegative element fluorine (P ~ H = 2.1 < C ~ S ~ I = 2.5 < C₆F₅ ~ Br = 2.8 < N ~ Cl = 3.0 < CF₃ = 3.3 < O = 3.5 < F = 4.0) affords bonds that possess a high ionic character and are strongly polarised $\delta^+ \text{C} - \text{F}^{\delta-}$; this alters the steric and electronic properties of the molecules, affecting their physicochemistry, such as the basicity or acidity of neighbouring functional groups, and strengthens all neighbouring bonds.³⁵ Furthermore, the fluorine substituent with three tightly bound non-bonding electron pairs is associated with a set of electronic effects that encompass both ‘push’ effects, such as +M or +I_π effects in aromatic systems and stabilisation of α -carbocations ($=\text{C}^+ - \text{F} \leftrightarrow =\text{C}=\text{F}^+$; relative stability: $^+ \text{CHF}_2 > ^+ \text{CH}_2\text{F} > ^+ \text{CF}_3 > ^+ \text{CH}_3$), and ‘pull’ effects, such as destabilisation of β -carbocations and possibly negative (or anionic) hyperconjugation. The influence of fluorine regarding stabilisation of tetrahedral transition states (e.g. the CF₃ group) and prevention of decomposition through proteolysis, by forming a vicinal positive charge, has also been described.³⁶

2.2.2 Effect of halogen polarity of the C–Hal bond

Halogens connected to a carbon atom, such as chlorine or fluorine, withdraw electrons from other parts of the molecule and can create a large dipole moment (μ) of the C–Hal bond [C–I (μ = 1.29 D) < C–Br (μ = 1.48 D) < C–F (μ = 1.51 D) < C–Cl (μ = 1.56 D)].³⁷

The C–Cl bond shows the strongest effect of halogen polarity of the C–Hal bonds.

2.2.3 Effect of halogens on pK_a value

Depending on the position of the fluorine substituent relative to the acidic or basic group in the molecule, a pK_a shift of several log units can be observed, which can again improve absorption properties.³⁸ Linear and cyclic amines become much less basic with both β - and γ -fluorine substitution [cf. $X-CH_2-NH_3^+$: $X = CH_3$ ($pK_a = 10.7$) > $X = CH_2F$ ($pK_a = 9.0$) > $X = CHF_2$ ($pK_a = 7.3$) > $X = CF_3$ ($pK_a = 5.7$)]. These inductive effects influence pK_a even with δ -substitution.³⁹ Quite often a change in pK_a can have a strong influence on a number of different parameters in lead optimisation, including physicochemical properties (solubility, log D), binding affinities (potency, selectivity) and pharmacokinetic properties (adsorption, distribution, metabolism, etc.), and safety issues as well. Halogen bonds in active ingredients of modern agrochemicals clearly demonstrate the potential significance of the interaction in ligand binding and recognition.

2.2.4 Improving metabolic, oxidative, and thermal stability with halogens

The stabilising potential of halogen bonds is estimated to range from about half to slightly greater than that of an average hydrogen bond in directing the self-assembly of organic crystals.⁴⁰ In comparison with C–H (416 kJ mol^{−1}), C–C (348 kJ mol^{−1}), C–N (305 kJ mol^{−1}) and other C–Hal bonds (C–Cl, 338 kJ mol^{−1}; C–Br, 276 kJ mol^{−1}; C–I, 238 kJ mol^{−1}), the high C–F bond energy of 485 kJ mol^{−1} significantly influences metabolic degradation and oxidative and thermal stability.⁴¹ In monohalogenalkanes, the C–F bond is around 100 kJ mol^{−1} stronger than the C–Cl bond, and the difference in heterolytic bond dissociation energies is even greater (~130 kJ mol^{−1}).

Oxidative metabolism of phenyl rings is a common problem, and fluorine substitution, usually at the *para*-position, has become a widespread practice to increase stability in various substance classes. A plot of Hammett δ coefficients against stability for various aromatic ring substituents shows that halogen atoms and halogen-containing substituents more strongly influence relative stability towards oxidation, hydrolysis and/or soil degradation than other residues. Electron-withdrawing, halogen-containing groups such as CCl₃, CF₃, CF₃O, CHF₂O, CF₃CO or CF₃SO₂ can stabilise an aromatic ring system to oxidative (or electrophilic) attacks, but too many withdrawing groups may bring susceptibility to nucleophilic attack. On the other hand, halogens and halogen-containing groups such as CCl₃, CF₃ or CF₃O are very stable to attack themselves. Therefore, an increasing degradative stability is observed for biologically active molecules or fragments having this special group of substituents.

Metabolic stability is one of the key factors in determining the bioavailability of agrochemicals. Rapid oxidative metabolism, e.g. by the P₄₅₀ cytochrome enzymes, can often lead to limited bioavailability. Therefore, a frequently employed strategy to overcome this problem is to block the reactive site by the introduction of halogen atoms. The replacement of hydrogen atoms at an oxidisable site by fluorine atoms protects against hydroxylation processes mediated by P₄₅₀ cytochrome enzymes. The metabolic stability of the C–F bond can be exploited to make a pro-insecticide, e.g. 29-fluorostigmasterol.⁴²

The different metabolic pathways of the triazolopyrimidine herbicide diclosulam (1997, Spider®; Dow AgroSciences) (Fig. 6)

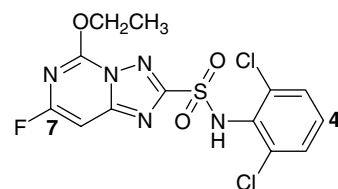


Figure 6. Herbicide diclosulam (1997, Spider®).

Table 2. Lipophilicity increments π as assessed for mono-substituted benzenes C₆H₅–X

Substituent X	π	Substituent X	π
OH	− 0.68	CF ₃	+ 0.88
COOH	− 0.32	Br	+ 0.89
H	0.00	CF ₃ O	+ 1.04
F	+ 0.14	I	+ 1.12
CF ₃ SO ₂	+ 0.55	SF ₅	+ 1.23
CH ₃	+ 0.56	CF ₃ S	+ 1.44
Cl	+ 0.71		

are guided by the fluorine substituent at the 7-position on the triazolopyrimidine ring system.⁴³

The predominance of one pathway is very crop specific, as shown for cotton (replacement of 7-F by 7-HO), soybeans (conjugation with homoglutathione) and wheat and maize (detoxification by aryl hydroxylation in the 4'-position).

2.3 Effect of halogens on physicochemical properties

2.3.1 Effect of halogens on molecular lipophilicity (π)

Lipophilicity is a key parameter that governs the pharmacokinetic behaviour of agrochemicals, such as absorption, uptake, etc., by enhancing their passive diffusion across membranes and their transport *in vivo*. The presence of halogen atoms and halogen-containing substituents in agrochemicals enhances their lipophilicities and finally their bioavailability. However, it seems that this effect is often relevant for fluorinated aryl(hetaryl) systems having interaction with π -electrons.

The incorporation of halogens, especially chlorine or fluorine, can be important for so-called 'fine-tuning' of the distribution of bioactive substances between aqueous and fatty media. In this context, the poor polarisability of fluorine-substituted groups plays a crucial role in phase behaviour. For example, numerous insecticides acting on the central nervous system (CNS) contain a fluorophenyl moiety or one of the most lipophilic functional groups such as CF₃ and CF₃–X (X = O, S), which contribute to the overall pharmacological activity by enhancing their CNS penetration. What makes the CF₃O-aryl moiety attractive is its ability to improve the membrane permeability of the compound in which it is embedded.

While halogens (Cl, Br, I) as well as CF₃ and CF₃O substituents invariably boost the lipophilicity, single fluorine atoms may alter this parameter in either direction (Table 2).⁴⁴ For example, the lipophilic 4-CF₃-phenyl moiety in pyrasulfotole (provisionally approved ISO name),⁴⁵ a new herbicidal 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor from Bayer CropScience, demonstrates a binding preference for the hydrophobic niche of the open conformation of the target enzyme (Fig. 7).⁴⁶

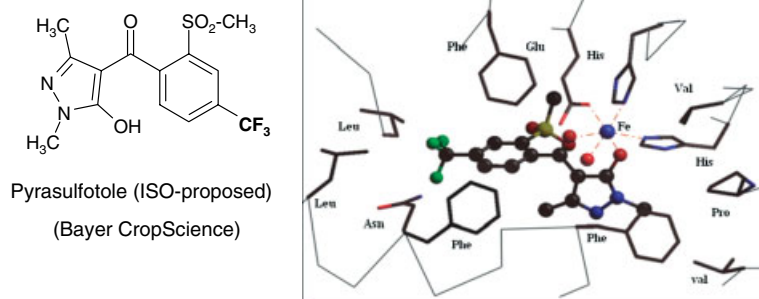


Figure 7. Pyrasulfotole (ISO-proposed) and its molecular interaction with the herbicide target HPPD. Data taken from Freigang *et al.*⁵⁰.

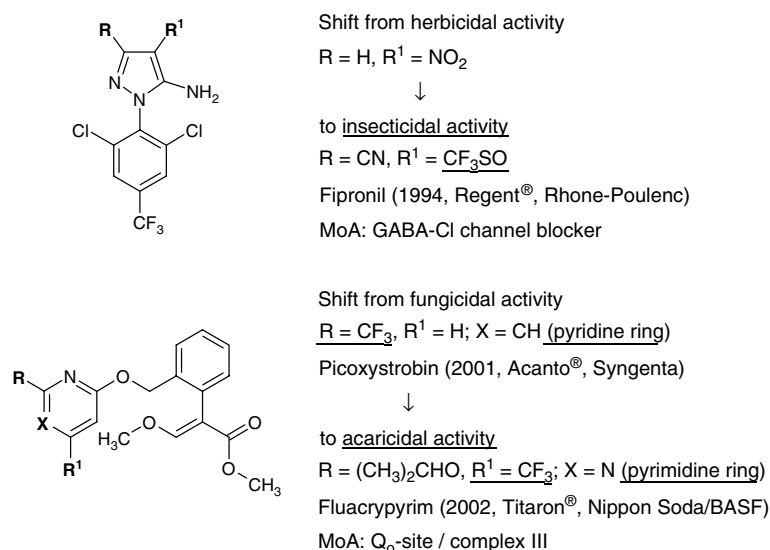


Figure 8. Examples from herbicidal *N*-aryl-pyrazoles and fungicidal methoxyacrylates for halogen-group-induced shift in biological activity.

According to the crystal structures, the active site of 4-HPPD with its iron atom is located within an open twisted β -sheet formed by seven β -strands.^{47,48} This iron is octahedrally coordinated by two histidines (His), one glutamic acid (Glu) residue, a well-defined water molecule and two inhibitor oxygen atoms which are presumed to replace the position of the substrate's oxygen atom in the transition state.⁴⁹ Both the pyrazolone hydroxyl and the benzoyl oxygen interact directly with the catalytic iron ion. It was found that the CF_3 group in the 4-position to the heteroaryl-carbonyl moiety is located within less than 4 Å of hydrophobic protein atoms and thus contributes towards the hydrophobic effect.⁵⁰

The increased lipophilicity and a superior metabolic stability compared with the methyl analogue often lead to an improved activity profile. Monofluorination and trifluorination of saturated aliphatic groups normally decrease lipophilicity, whereas higher fluoroalkyl groups (perfluoroalkyl groups) are introduced mainly to increase the lipophilicity,⁵¹ as recently shown for the 4-perfluoroisopropyl-2-methylphenylamine fragment in flubendiamide (2006, Belt®; Nihon Noyaku Co./Bayer CropScience) (for more details, see Section 3.3).

2.3.2 Classification in disjoint principle space

Systematic variation of substituents in a molecule has been the subject of various studies.⁵² Besides synthetic feasibility

and economic considerations, halogens and halogen-containing substituents are chosen on the basis of properties such as polarity, size and H-bonding capacity. The disjoint principle properties (DPPs), derived from a large set of property descriptors for substituents including halogen atoms and/or halogen-containing substituents, can be used to make rational and effective choices, e.g. from the following similarities:

- (i) $F \sim SH, C \equiv CH$;
- (ii) $Cl, Br, I \sim CF_3, NCS$;
- (iii) $CF_3SO_2 \sim CH_3SO_2, NH_2SO_2$;
- (iv) $CF_3O \sim CH_3OCO, CH_3CONH$;
- (v) $CF_3S \sim phenyl-O, phenyl-CO$.

Several excellent examples are known from the sulfonylurea and triazolone herbicides, such as the successful exchange of the 2- CH_3OCO group of propoxycarbazone-sodium (2001, Attribut®, Bayer CropScience) for the 2- CF_3O group of flucarbazone-sodium (2000, Everest®, Bayer CropScience) (for more details, see Section 5.3).

2.4 Effect of halogens on shift of biological activity

Sometimes, substitution with suitable halogen-containing residues can result in a so-called 'shift' of biological activity, as shown in two examples from herbicidal *N*-aryl-pyrazole and fungicidal methoxyacrylate chemistry (Fig. 8).

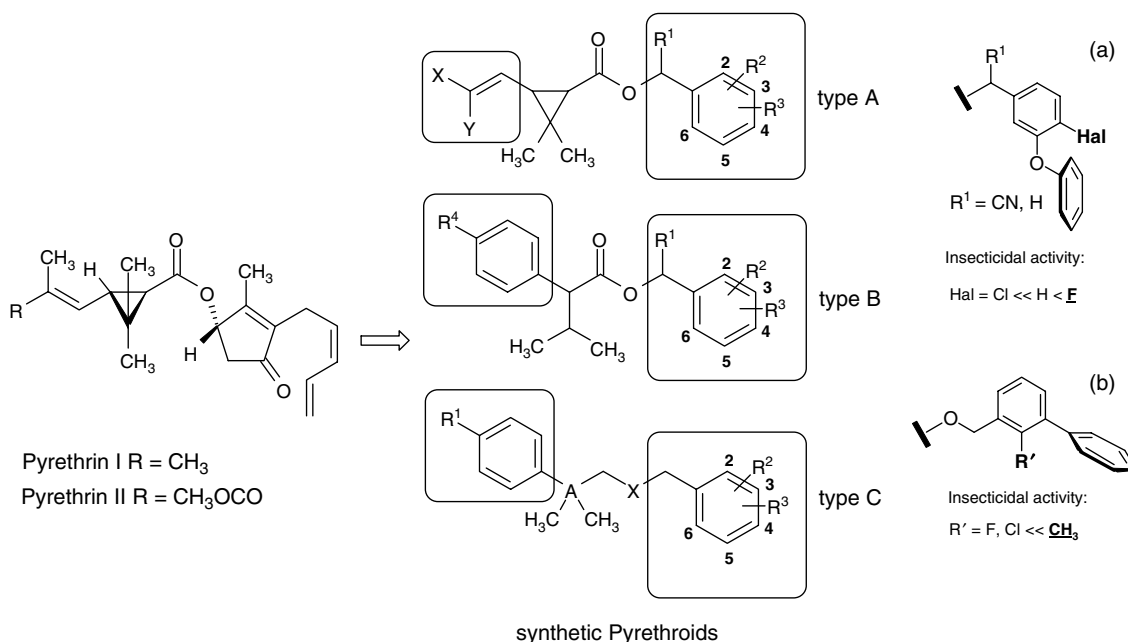


Figure 9. Structural evolution of synthetic pyrethroids (types A to C) from pyrethrins I and II as well as pyrethroid alcohol modification – SAR and conformation of preferred substitution pattern; cf. (a) cyfluthrin and (b) bifenthrin (modified after Jeschke⁵).

Starting with a herbicidally active *N*-(2,6-dichloro-4-trifluoromethylphenyl)-4-nitropyrazole, replacement of NO₂ by the CF₃S group leads to a highly active insecticidal derivative, which already shows structural similarity in the 4-position (R¹ = CF₃S versus CF₃SO) to the commercial insecticide fipronil (1994, Regent®; Rhone Poulenc, later BASF).

On the other hand, the formal replacement of the 6-trifluoro-2-pyridinyl moiety in the side chain of the methoxyacrylate (strobilurin) fungicide picoxystrobin (2002, Acanto®; Syngenta) by a 2-isopropoxy-4-trifluoro-6-pyrimidinyl moiety results in the acaricide flucycrypyrim (2002, Titaron®; Nippon Soda/BASF).

Therefore, the strong influence of halogen atoms and/or halogen-containing substituents can lead to biological superiority of halogenated AIs over their non-halogenated analogues. Various selected commercial products (the examples here are mainly from Bayer CropScience) testify to the successful utilisation of halogens in the design of agrochemicals, in particular insecticides, fungicides and herbicides.

Generally, the corresponding biochemical targets or modes of action have been described. These are:

- the voltage-gated sodium channel (vgSoCh), the nicotinic acetylcholine receptor (nAChR) and the ryanodine receptor (RyR) for insecticides;
- sterol biosynthesis (sterol-C₁₄-demethylase), the respiratory chain (the so-called Q_o-site of complex III) and the spectrine-like protein for fungicides;
- carotenoid biosynthesis – [phytoene desaturase (PDS)], cell growth and division and acetolactate synthase (ALS) for herbicides.

3 INSECTICIDES CONTAINING HALOGENS

Insecticides that act on targets of the insect CNS (cf. vgSoCh, nAChR) are the most effective compounds in preventing crop

damage. Generally, halogen substitution is a useful tool for improving pharmacological activity of AIs, e.g. by enhancing their CNS penetration. But also in the case of the calcium channel (RyR), which seems to be involved in muscle contraction, halogenated ligands are significant (see Section 3.3.).

3.1 Voltage-gated sodium channel (vgSoCh) modulators

The development of synthetic pyrethroids provides a significant historical illustration of agrochemicals regarding the introduction of halogen atoms (F, Cl, Br) and halogen-containing substituents (e.g. CF₃, CHF₂O, CF₂BrO, (CF₃)₂CHOCO and halogenated aryl). Shortening and simplifying the pentadienyl side chain of the natural insecticide pyrethrin I led in the 1950s to more stable synthetic pyrethroids. Pyrethroids block the nerve signal by prolonging the opening of the vgSoCh.^{53–55} With 43 members, the synthetic pyrethroid insecticides represent the largest single group within the chemical class. Besides natural pyrethrins, pyrethroid esters of general structure type A and B, as well as non-esters of type C, are currently registered worldwide (Fig. 9; for simplification, all chirality centres are deleted).

Today, around 40% of them contain no halogen substituents; the remaining 60% are halogen substituted – mainly by chlorine and 'mixed' halogens like fluorine and chlorine.

3.1.1 Pyrethroids of type A

More than 20 years later, replacement of the cyclopentenyl alcohol group, insertion of a α -cyano substituent R¹ at the phenoxybenzyl alcohol and introduction of the dichlorovinyl moiety resulted, for example, in permethrin and cypermethrin. Introduction of the dibromovinyl moiety resulted in deltamethrin, which shows a strong enhancement of insecticidal activity (Table 3A).

In 1980 the first fluorine-containing pyrethroid, cyfluthrin, was launched. This pyrethroid, containing the 4-fluoro-3-phenoxybenzyl substituent, was the remarkable result of a

Table 3A. Halogen-substituted pyrethroids of type A (see Figure 9 for basic structure)

Common name (trade name)	Manufacturer (year introduced)	X	Y	R ¹	R ²	R ³
Permethrin (Chinethrin [®])	ICI/Zeneca ^a (1977)	Cl	Cl	H	H	3-PhO
Deltamethrin (Decis [®])	Roussel Uclaf ^b (1977)	Br	Br	CN	H	3-PhO
Cypermethrin (Viper [®])	ICI/Zeneca ^a (1978)	Cl	Cl	CN	H	3-PhO
Cyfluthrin (Baythroid [®])	Bayer ^b (1980)	Cl	Cl	CN	F	3-PhO
λ -Cyhalothrin (Banish [®])	ICI/Zeneca ^a (1984)	CF ₃	Cl	CN	F	3-PhO
Bifenthrin (Brigade [®])	FMC Corporation (1986)	CF ₃	Cl	H	2-CH ₃	3-Ph
Tefluthrin (Attack [®])	ICI/Zeneca ^a (1988)	CF ₃	Cl	H	2,3,5,6-F ₄	4-CH ₃
Acrinathrin (Ardent [®])	Roussel Uclaf ^b (1991)	H	(CF ₃) ₂ CHOCO	CN	H	3-PhO

^a Now Syngenta.
^b Now Bayer CropScience.

Table 3B. Halogen-substituted pyrethroids of type B (see Figure 9 for basic structure)

Common name (trade name)	Manufacturer (year introduced)	R ¹	R ²	R ³	R ⁴
Fenvalerate (Belmark [®])	Sumitomo (1976)	CN	H	3-PhO	Cl
Flucythrinate (Pay off [®])	ACC/BASF (1981)	CN	H	3-PhO	CHF ₂ O
Esfenvalerate (Samurai [®])	Sumitomo (1986)	CN	H	3-PhO	Cl
Flubrocycythrinate (Lubrocycythrinate [®])	Shanghai Zhongxi (1992)	CN	H	3-(4-Br-Ph)O	Cl

programme directed at the synthesis of all possible isomers with fluorinated alcohol modifications.⁵⁶ Compared with cypermethrin, cyfluthrin needed less than one-third of the use rate for control of cotton pests. The more active form of cyfluthrin for interaction at the receptor sites involves a conformation in which the 3-phenoxy substituent is twisted because of the fluorine effect in the 4-position (Fig. 9a).

The commercialisation of CF₃-containing pyrethroids started in the 1980s with λ -cyhalothrin, which represents the optimum choice of fluorine-containing substituents for insecticidal activity ([CF₃(CF₃)C=] $\ll$ [F₂C=] = [Cl₂C=] = [CF₃(F)C=] < [CF₃(Cl)C=]). The presence of the CF₃ group in λ -cyhalothrin has effects on phytophagous mites. The biphenyl-type pyrethroid bifenthrin is available in a partially resolved (Z)-(1*RS*)-*cis*-isomer mixture and has become one of the most important termiticides. In bifenthrin the 3-phenyl substituent is twisted (Fig. 9b) because of the steric effect of the methyl group in the *ortho*-position (F, Cl $\ll$ CH₃). Replacement of the dihalogenvinyl moiety with a [(CF₃)₂CHOCOHC=] group led to acrinathrin, which controls the larval and adult stages of a broad range of phytophagous mites as well as various sucking insects. Finally, the extended exploitation of the acidic part of λ -cyhalothrin resulted in the (Z)-(1*RS*)-*cis*-isomer of tefluthrin, which is optimised in terms of stability, volatility, fast penetration and water solubility.

3.1.2 Pyrethroids of type B

The racemate fenvalerate, a non-systemic insecticide and acaricide with contact and stomach action, shows efficacy against chewing, sucking and boring insects such as lepidoptera (cotton: 30–150 g ha⁻¹), coleoptera (potatoes: 100–200 g ha⁻¹) and others (Table 3B).

Esfenvalerate, the (2*S*, α *S*)-fenvalerate isomer, has enhanced insecticidal activity against lepidopteran pests (cotton: 20–30 g ha⁻¹). Flucythrinate, the difluoromethyl derivate of fenvalerate (R⁴ = CHF₂O versus Cl), shows broad-spectrum activity with excellent residual efficacy. Introduction of a bromine atom into the 4-position of the phenoxy residue of flucythrinate leads to the less toxic flubrocycythrinate (acute oral LD₅₀ for rats: > 1000 mg kg⁻¹ versus 67–81 mg kg⁻¹), which shows additional activity against spider mites such as European red spider mite, *Panonychus ulmi* (Koch), two-spotted spider mite, *Tetranychus telarius* L., and hawthorn red spider mite, *T. veinnensis* Zach.

3.1.3 Pyrethroids of type C

The achiral etofenprox containing no halogen atom is a non-ester displaying pyrethroid-like activity and is highly advantageous in the rice insecticide market (Table 3C).

Incorporation of one fluorine and two bromine atoms in the ethoxy group R¹ leads to a shift in the spectrum of activity. The

Table 3C. Halogen-substituted pyrethroids of type C (see Figure 9 for basic structure)

Common name (trade name)	Manufacturer (year introduced)	X	A	R ¹	R ²	R ³
Etofenprox (Fogger®)	Mitsui (1986)	O	C	CH ₃ CH ₂ O	H	H
Eflusilanate (Silonen®)	Hoechst ^a (1991)	CH ₂	Si	CH ₃ CH ₂ O	4-F	3-PhO
Halfenprox (Prene EL®)	Mitsui (1993)	O	C	CF ₂ BrO	H	3-PhO

^a Now Bayer CropScience.

resulting halfenprox displays good acaricidal activity and has a similar short environmental persistence in soil (DT₅₀ = 10 days versus 6 days for etofenprox). Finally, organosilicon pyrethroids (X = CH₂, A = Si) such as eflusilanate have an extremely low fish and mammalian toxicity combined with insecticidal activity comparable with that of the parent compounds.

3.2 Nicotinic acetylcholine receptor (nAChR) agonists

The biology and agricultural uses of nAChR agonists are enormous, and numerous overviews, articles and book chapters have been published over the past decade.^{57–60}

The subclass of chloronicotinyl insecticides (CNIs) contains prominent members such as imidacloprid (IMI),^{61,62} recently also known for its additional stress shield mode of action (MoA) – IMI helps plants exposed to moderate abiotic and biotic stress,⁶³ and thiacloprid (THIACL),⁶⁴ which shows a favourable lack of toxicity towards beneficials such as bees. The excellent insecticidal activity was achieved by coupling the 6-chloro-3-pyridinylmethyl (CPM) residue to different types of pharmacophoric system such as *N*-nitroguanidine and *N*-cyanoamidine.

The additional introduction of fluorine into the CPM moiety of IMI resulted in a shift of insecticidal activity against sucking insects. Whereas the additional fluorine atom in the 5-position led

to strong activity (2-F < 6-F < 5-F; LC₉₅ = 8 mg L⁻¹) against peach potato aphid (*Myzus persicae*), Fluorine in the 2-position resulted in a strong activity (5-F < 2-F; LC₉₅ = 0.25 mg L⁻¹) against black bean aphid, *Aphis gossypii* (Glov.).

On the other hand, in most cases, replacement of chlorine in the 6-position of the 3-pyridinylmethyl residue by different halogen atoms (F, Br, I) leads to insecticidally active CNI structures as well.¹ A possible explanation could be given by the acetylcholine binding proteins (AChBPs) isolated from molluscs,^{65,66} which are suitable structural and functional surrogates of the nAChRs when combined with transmembrane spans of the nAChR.⁶⁷

As recently known from high-resolution crystallographic analysis of the atomic interaction of CNIs such as IMI or THIACL with the binding site of the saltwater mollusc, *Aplysia californica* Cooper, AChBP,⁶⁸ there is room for different halogen sizes at the 6-position of the 3-pyridinylmethyl moiety, indicated by the blue arrow in Fig. 10. In addition, a water or solvent molecule is observed near the pyridine nitrogen atom of the CPM moiety, forming a water-mediated H-bond to the backbone (loop B or loop E amino acids or both), indicated by the red arrow.

3.3 Ryanodine receptor (RyR) effectors

During a research programme at Nihon Nohyaku on pyrazine dicarboxamide herbicides, the benzodicarboxamides (BDCAs) having a nitro group at the 3-position were found to show insecticidal activity against lepidopteran pests. Replacement of the nitro group with halogen atoms (F < Cl < Br < I) gave good insecticidal activity, with iodine being the best. This ranking of halogen atoms shows a perfect correlation with the so-called Bondi volumes (cm³ mol⁻¹) for halogen atoms attached directly to phenyl rings [F (5.8 cm³ mol⁻¹) < Cl (12.0 cm³ mol⁻¹) < Br (15.12 cm³ mol⁻¹) < I (19.64 cm³ mol⁻¹)].⁶⁹

Furthermore, it was found that compounds having a lipophilic substituent in the *para*-position of the 2-methylanilide moiety were highly active. Besides fluorine, the CF₃ or CF₃O group and finally the (CF₃)₂CF group improve the insecticidal activity considerably. The latter is unusual in crop protection so far. Finally,

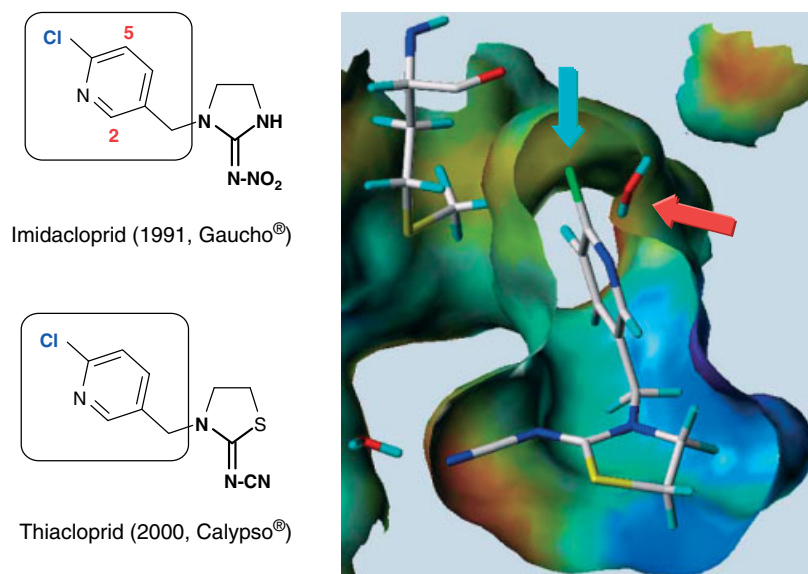


Figure 10. Structures of two members of the subclass CNIs IMI and THIACL; the latter is shown in the binding site of *Aplysia californica* AChBP. Blue arrow: room for different halogen sizes; red arrow: water-mediated H-bond (modified after Talley *et al.*,⁶⁸ alignment by Schindler M).

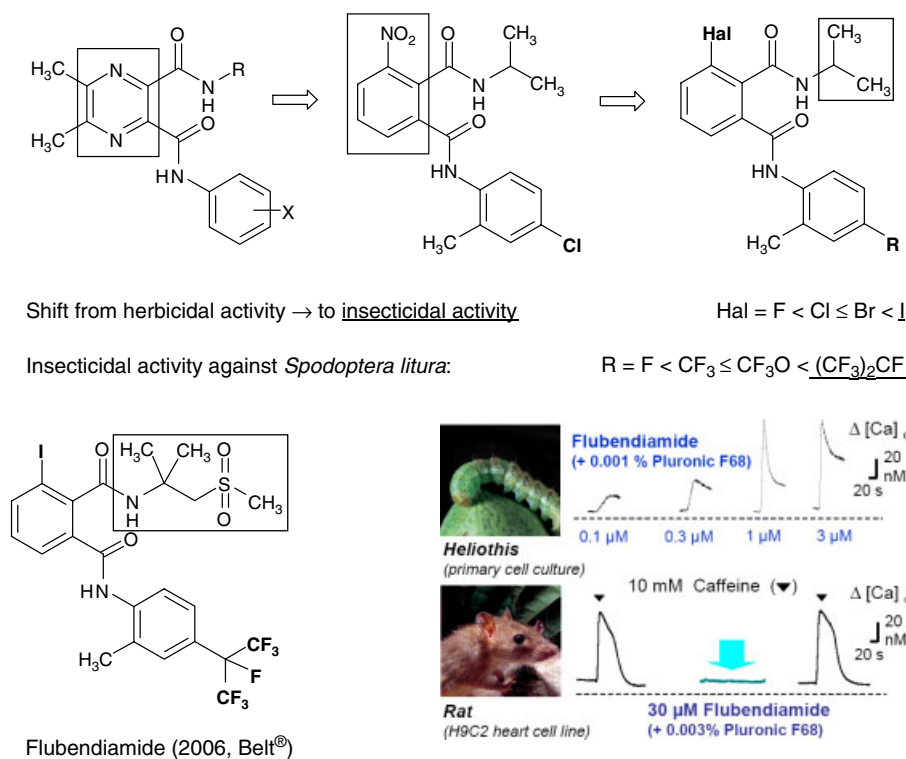


Figure 11. Identification of flubendiamide and binding studies on primary cell culture (*H. virescens*) and H9C2 heart cell line (rat). Data taken from Ebbinghaus-Kintscher et al.⁷².

introduction of a special methylsulfonyl-alkylamide group led to flubendiamide, which was launched in 2006 (Fig. 11).^{70,71}

Flubendiamide induces Ry-sensitive cytosolic Ca²⁺ transients that were found to be independent of extracellular Ca²⁺ concentration in isolated neurons from the insect *Heliothis virescens* F., as well as in transfected CHO cells expressing the RyR from *Drosophila melanogaster* Meig., but not on rat heart cell line H9C2, which expresses the RyR subtypes 2 and 3 endogenously. Binding studies on microsomal membranes from *H. virescens* flight muscle revealed that flubendiamide interacts with a site that is distinct from the Ry-binding site and disrupts Ca²⁺ regulation of Ry-binding by an allosteric mechanism. Flubendiamide activates selective Ry-sensitive intracellular Ca²⁺ release channels in insects as a novel MoA and is completely inactive on mammalian RyR subtypes, which explains its excellent toxicological profile (Fig. 11).^{72,73}

With flubendiamide, a broad-spectrum control of lepidopterous insect pests is possible.^{74,75} The insecticide has an outstanding larvicidal activity, is safe to beneficial insects, has a broad crop utility because of its fast-acting and long-lasting effect, shows no cross-resistance to other insecticide classes and is a unique tool in resistance management tactics for pest Lepidoptera difficult to control.⁷⁶

4 FUNGICIDES CONTAINING HALOGENS

Today, modern specific fungicides control fungal plant pathogens more effectively and at lower application rates than the older 'multisite' contact fungicides. Many of them have systemic properties and are therefore able to penetrate the plant tissue and to be further distributed via the xylem vessels into different plant parts not reached directly by the spray application.⁷⁷ In this

context, halogen substitution can have a remarkable effect on the physicochemical behaviour of fungicidally active compounds.

4.1 Sterol biosynthesis (sterol-C₁₄-demethylase) inhibitors

The main MoA of the important 1,2,4-triazole subclass is the inhibition of the cytochrome P₄₅₀-dependent C₁₄-demethylation of the intermediate C₂₄-methylene-dihydrolanosterol in the sterol biosynthesis pathway of fungi.⁷⁸ The majority of these so-called DMLs display systemic movement within plants, which is reflected in part by their log *P* values and is of relevance in the control of particular plant diseases. Among the 1,2,4-triazoles launched between the years 1976 and 2000, as well as prothioconazole, which was launched in 2004, the chlorophenyl moiety is strongly preferred, possibly because of the favourable physicochemical properties such as the advantageous log *P* value.

Nearly 92% of commercialised 1,2,4-triazoles are substituted with halogens, and around 68% of these commercialised so far possess chlorine substituents.

Prothioconazole is the result of a stepwise optimisation programme that was directed to modification of the 1,2,4-triazole nucleus and its lipophilic backbone (Fig. 12).⁷⁹

After 1,2,4-triazoline-5-thione formation and the incorporation of halogen-substituted benzyl residues, the halogenated cyclopropyl moiety was found to be favourable for outstanding fungicidal activity. Apart from the 1,2,4-triazoline-5-thione ring system, prothioconazole contains an *ortho*-chlorobenzyl residue and the innovative chlorocyclopropyl moiety as a new lipophilic substituent. The commercial AI is a mixture of two enantiomers (chirality of the quaternary carbon bearing the hydroxyl group).

Based on its broad spectrum of efficacy, excellent bioavailability and long-lasting activity, as well as curative and protective properties, prothioconazole represents a very high standard of

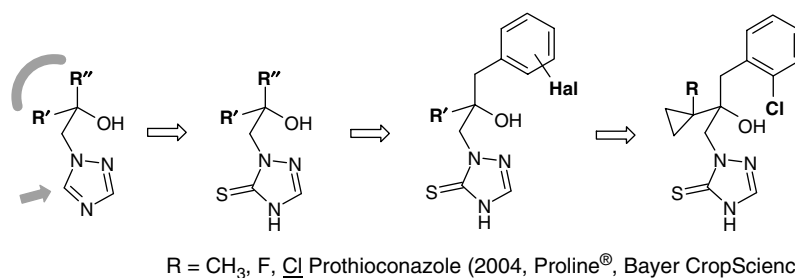


Figure 12. Stepwise optimisation according to the concept of lipophilic backbone and 1,2,4-triazole modification leading to the fungicide prothioconazole.

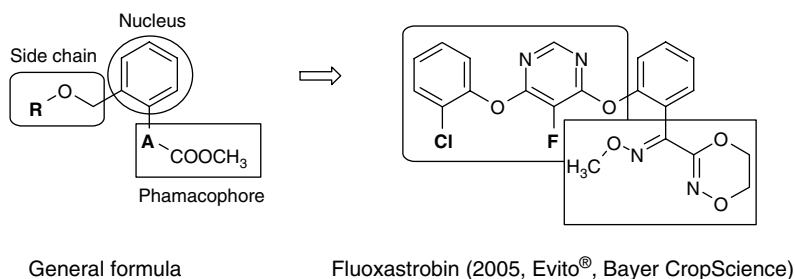


Figure 13. General formula of synthetic strobilurin fungicides and the chemical structure of fluoxastrobin.

control of fungal diseases in cereals and other arable crops.^{80,81} For example, it provides excellent control of all relevant cereal pathogens, including stem base and ear diseases [e.g. *Tapesia yallundae* Wallwork & Spooner, *T. acuformis* (Boerema, Pieters & Hamers) Crous, *Rhizoctonia* spp., *Microdochium nivale* (Fr.) Samuels & Hallett, and *Fusarium* spp.⁸²] and all important leaf spot diseases [e.g. *Septoria tritici* Rob., *Stagonospora nodorum* (Berk.) Cast. & Germ., and *Drechslera* spp.], as well as cereal rust (*Puccinia* spp.), powdery mildew, *Blumeria graminis* Speer and *Sclerotinia sclerotiorum* (Lib.) de Bary in oilseed rape and canola.^{83,84} In addition, this novel DMI fungicide shows plant-growth-stimulating properties and represents a useful tool for resistance management.⁸⁵

4.2 Respiratory chain (Q_o-site/complex III) inhibitors

Strobilurin fungicides have been among the most commercially successful classes of agricultural fungicides over the past 7 years.^{86,87} Like the major lead structure strobilurin A, all strobilurins inhibit mitochondrial respiration by influencing the function of the so-called Q_o site of complex III (cytochrome bc₁ complex),

which is located in the inner mitochondrial membrane of fungi and other eucaryotes.⁸⁸

The incorporation of halogen atoms into strobilurin fungicides began with trifloxystrobin in 1999, which contains a trifluoromethyl-phenyl moiety in its oxime ether side chain (Fig. 13, Table 4).

Crystallographic studies of the binding of trifloxystrobin have shown that this moiety interacts with a hydrophobic domain in the binding pocket.⁸⁹ Three years later, picoxystrobin with a 6-trifluoro-2-pyridinyl moiety and pyraclostrobin with an *N*-chlorophenyl-pyrazolyl moiety were developed. Fluoxastrobin, launched in 2005 by Bayer CropScience, combines a methoximino dihydro-dioxazinyl pharmacophore with an optimally adjusted side chain bearing a 2-chlorophenoxy-5-fluoropyrimidinyl moiety. The SAR indicates that the fluorine atom has an important influence on the phytotoxicity (PTX) and leaf systemicity of this fungicide. In comparison with chlorine and hydrogen, fluorine is strongly preferred (Cl << H < F).⁹⁰

Today, around 50% of all commercialised strobilurin fungicides are halogenated with chlorine or fluorine, or contain a 'mixed' halogen substitution pattern such as chlorine and fluorine.

Table 4. Commercialised halogen-substituted strobilurin fungicides

Common name (trade name)	Manufacturer (year introduced)	Chemical class	R	A
Trifloxystrobin (Flint®)	Novartis ^a (1999)	Oximinoacetamide		CH ₃ O-N=
Picoxystrobin (Acanto®)	Syngenta (2002)	Methoxyacrylate		CH ₃ O-HC=
Pyraclostrobin (Cabrio®)	BASF (2002)	Methoxycarbamate		CH ₃ O-N-

^a Now commercialized by Bayer CropScience.

Applied as a foliar spray in cereals, fluoxastrobin provides excellent control of, for example, *Septoria* diseases (*S. tritici*) and glume blotch (*Leptosphaeria nodorum* Muell.), rust (*Puccinia recondita* Rob. ex Desm., *P. striiformis* Westerd., *P. hordei* Otth.) and *Helminthosporium* diseases in wheat and barley [*Pyrenophora tritici-repentis* (Died.) Dreschler, *P. teres* Dreschler], as well as scald [*Rhynchosporium secalis* (Oudem.) Davis] and powdery mildew (*B. graminis* spp.).^{91,92}

As a contribution to a resistance management strategy for strobilurins, fluoxastrobin is developed as a coformulation or recommended as a tank mix with fungicides from other chemical classes (Fig. 14).

For example, the DMI fungicide prothioconazole (see Section 4.1.) is an ideal partner, providing at least additive effects and extending the spectrum of activity towards stem base and ear diseases such as *Pseudocercospora herpotrichoides* (Fron) Deighton and *Fusarium* ear blight. The mixture of the two, tradenamed Fandango[®], results in all-round improved control of these diseases.⁹³

4.3 Spectrin-like protein effectors

Fluopicolide was discovered by AgrEvo UK Ltd at Chesterford Park in the late 1990s by an innovative 'mix and match' or 'agrophore approach' and is structurally similar to the 2,6-dichlorobenzamide XRD-563 from Dow Elanco, which was stated to be effective for the control of powdery mildew diseases of wheat and barley (Fig. 15).⁹⁴

By using automated solution-phase parallel synthesis, small libraries were created containing 5-trifluoro-3-chloro-2-pyridinylmethylamine as the key building block. Finally, its *N*-acylation with numerous halogenated benzoic acids resulted in the discovery of fluopicolide, which belongs to a new chemical class of fungicides. Fluopicolide is a long-lasting disease control product and is highly effective on a broad spectrum of key oomycete pathogens of late blight [*Phytophthora infestans* (Mont.)

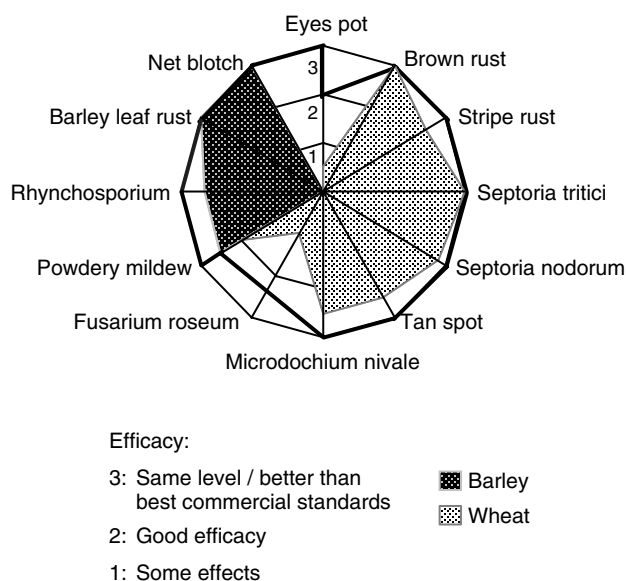


Figure 14. Fungicidal spectrum of activity and performance in field tests (barley and wheat) of both fluoxastrobin and prothioconazole (thick black line) used as mixture Fandango[®]. Data taken from Dutzmann and Suty-Heinze.⁸³

de Bary], downy mildews (*Plasmopora*, *Pseudoperonospora*, *Peronospora*, *Bremia*) and some *Phyrium* species.⁹⁵ It induces a redistribution of spectrin-like protein(s), which can be detected by immunofluorescence localisation of these protein(s) in hyphae of *P. infestans* 2 h post-treatment (Figs 15 and 16).⁹⁶

These proteins strengthen the membrane and link it to the cytoskeleton within the cytoplasm.^{97,98} Fluopicolide does not show any cross-resistance to other commercial oomycete fungicides such as metalaxyl (1977, Ridomil[®]), dimethomorph (1992, Acrobat[®]), fenamidone (2000, Fenomen[®]) or zoxamide (2001,

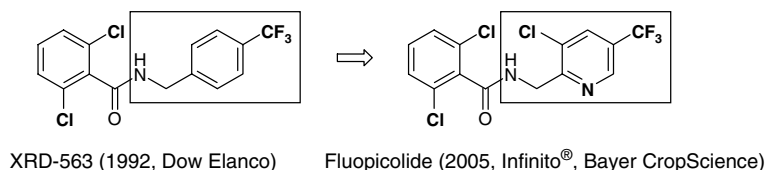


Figure 15. Structure of fluopicolide and its chemical precursor XRD-564. Data taken from Latorse *et al.*⁹⁵.

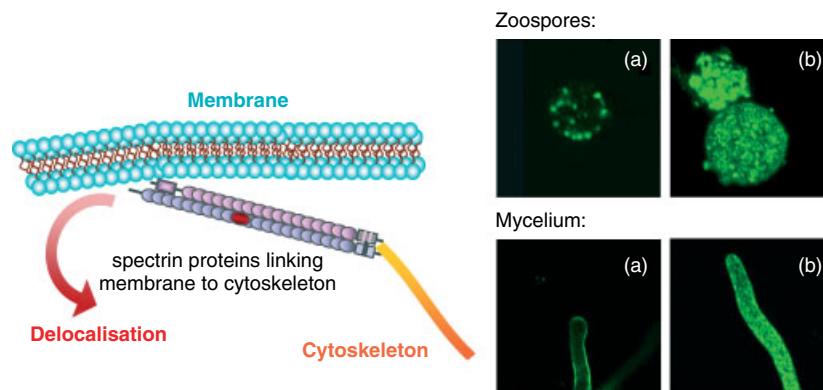


Figure 16. MoA of fluopicolide and immunofluorescence microscopical studies of (a) untreated and (b) treated zoospores and mycelium of oomycetes. Data taken from Toquin *et al.*⁹⁶.

Zoxium®). Zoospores swell and lyse rapidly on treatment with fluopicolide (cf. Figure 15b). Immunological studies showed that a cytoskeleton-associated spectrin-like protein was delocalised after fluopicolide treatment. This happens in both zoospores and hyphae of *P. infestans*.

5 HERBICIDES CONTAINING HALOGENS

Bayer CropScience and its predecessor companies have launched a series of new AIs since the early 1950s that have consistently offered farmers progressive solutions for weed management in cereals. Today, more than 70% of Bayer's proprietary cereal herbicides contain halogens: fluorine, chlorine, bromine or iodine. The excellent efficacy, selectivity and plant compatibility are the most prominent advantages for these halogen-containing commercial products.

5.1 Carotenoid biosynthesis – phytoene desaturase (PDS) inhibitors

Most of the so-called 'bleaching herbicides' inhibit the synthesis of carotenoids by interference with the biosynthesis of photosynthetic pigments, chlorophylls or carotenoids.⁹⁹ Owing to their low application rates, lack of resistance in the field and favourable mammalian toxicity, industrial research concentrated on this MoA, leading to seven potent halogenated herbicides for modern agriculture, such as the oldest representatives norflurazon, fluridone and flurochloridone.¹⁰⁰ Known products from Bayer CropScience are diflufenican and flurtamone, which can be applied in cereals as a mixture. More recent additions to the list are picolinafen and

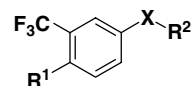


Figure 17. The 3-trifluoromethylphenyl moiety common to commercial PDS inhibitors.

beflubutamid, which contain an additional fluorine in the phenyl moiety (Fig. 17, Table 5).

They are generally used in cotton for pre-emergence control of weeds. An exception is flurochloridone, which is used in sunflowers, and diflufenican, which is used in cereal crops. However, it is still not known which structural elements are essential to make a PDS inhibitor potent at its target site. Nevertheless, the presence of the CF₃ group in the *meta*-position of the phenyl ring in different structures of inhibitors reflects the essential properties of the high lipophilicity and electron-withdrawing nature of this moiety. The structural requirements (phenyl ring, central heterocycle and additional substituents) for substitution at the five- or six-membered heterocycle of the PDS inhibitor have been discussed.¹⁰¹

5.2 Cell growth and division inhibitors

Starting with the selective paddy rice herbicide mefenacet (water solubility 4 mg L⁻¹ at 20 °C), the search for an oxyacetamide herbicide having efficacy even in the absence of irrigation water and that could be used as upland herbicide in maize, soybeans and other crops led to flufenacet (water solubility 56 mg L⁻¹ at 25 °C).¹⁰² Flufenacet is a selective pre- and early post-emergence herbicide. It is taken up mainly through the root system and transported in the xylem to the meristematic tissue of the roots

Table 5. Different classes of PDS inhibitors (see Figure 17 for the basic structure)

Common name (trade name)	Manufacturer (year introduced)	R ¹	X	-X-R ²
Norflurazon (Zorial®)	Syngenta (1971)	H	N	
Fluridone (Brake®)	Dow AgroSciences (1981)	H	C	
Flurochloridone (Racer®)	Makhteshim-Agan (1985)	H	N	
Diflufenican (Quartz®)	Bayer CropScience (1985)	H	O	
Flurtamone (Bleacher®)	Bayer CropScience (1997)	H	C	
Picolinafen (Sniper®)	BASF (2001)	H	O	
Beflubutamid (Herbaflex®)	Ube Industries (2003)	F	O	

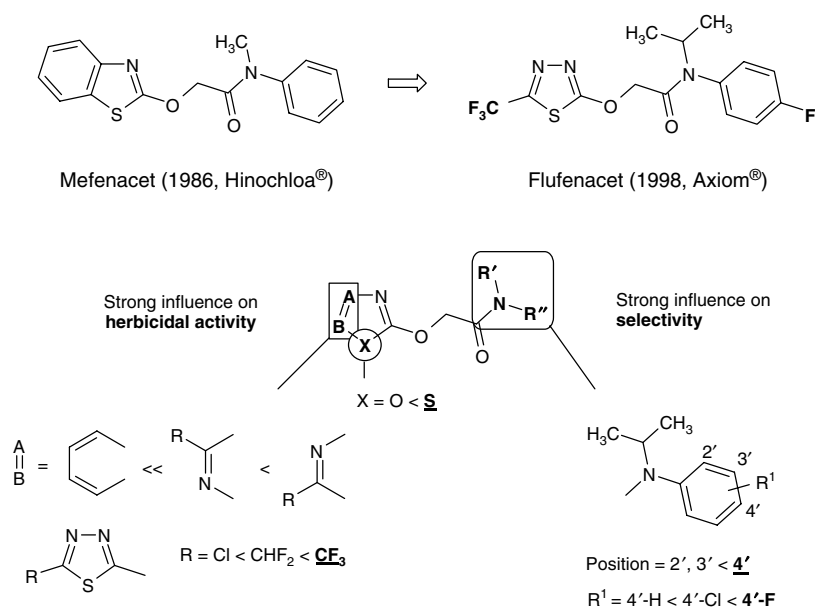


Figure 18. Structure of the oxyacetamides mefenacet and flufenacet. SAR in the chemical optimisation of the oxyacetamide class.

and young shoot to cause growth inhibition. It controls a wide range of annual grass weeds, sedges and some small-seeded broadleaf weeds.

The oxyacetamides inhibit early plant development by disturbing cellular and biochemical level function. The induced morphological and physiological symptoms are very similar to those of the well-known chloroacetamide herbicides.¹⁰³

Flufenacet is active against blackgrass species resistant to ACCase inhibitors and is also a good example to demonstrate the unique role of halogens in the design of modern agrochemicals (Fig. 18).

During optimisation of the herbicidal activity, it was found that the heterocyclic moiety has a strong influence on the herbicidal activity against grasses, in the order outlined in Fig. 18. The most potent heterocycles are 1,3,4-thiadiazoles having a substituent in the 5-position such as chlorine, CHF₂ or CF₃. In addition, the herbicidal selectivity and compatibility can be strongly influenced by the phenylamide part of the molecule in which the 4-fluorophenyl moiety shows the best results.

The crop tolerance of flufenacet is attributed to rapid detoxification by glutathione S-transferases.¹⁰⁴ Investigations on the metabolism of flufenacet showed that the covalent linkage to glutathione is the first step in the degradation pathway. The chemical structure of the flufenacet glutathione conjugate underlines that the reaction with glutathione S-transferase results in the expulsion of the 5-trifluoromethyl-1,3,4-thiadiazol-2-yloxy moiety.¹⁰⁵

5.3 Acetolactate synthase (ALS) inhibitors

Sulfonylureas are extremely potent inhibitors of ALS, the key enzyme within the biosynthesis of branched amino acids such as leucine (Leu), isoleucine (Ile) or valine (Val).^{106–109}

Up to now, approximately 62% of the 31 commercialised sulfonylureas are halogen free. Nearly 24% of the sulfonylureas launched so far contain fluorine, and only 14% have other halogens such as chlorine or iodine.

Sulfonylureas can be further divided into two subclasses: (i) triazinylsulfonylurea herbicides (Y = N) and (ii) pyrimidinylsulfonylurea herbicides (Y = CH) (Fig. 19):

- Halogen-containing triazinylsulfonylurea herbicides.* The first product of this type to be launched was a cereal-selective herbicide, chlorsulfuron, for weed control in wheat. Exchange of its *ortho*-chlorine substituent (ring A, X = CH, R¹) by the 3,3,3-trifluoropropyl residue leads to the maize-selective herbicide prosulfuron. In addition, such a change facilitates the filing of patent applications. Prosulfuron is metabolised in maize, for example, by an additional hydroxylation at the methyl group (ring B, R⁴) of the 1,3,5-triazine moiety (Fig. 19).
- Halogen-containing pyrimidinylsulfonylurea herbicides.* Comparison of rimsulfuron containing a 3-ethylsulfonyl-2-pyridinyl moiety (ring A, X = CH) with flazasulfuron shows that its 3-trifluoromethyl-2-pyridinyl moiety (ring A, X = CH) has a marked impact on metabolism (Fig. 19). The key transformation in tolerant turf grass is an unusual rearrangement and contraction of the sulfonylurea bridge, followed by hydrolysis and *O*-demethylation of a pyrimidinyl methoxy (R³) group. In 2003, Pang *et al.*¹¹⁰ published a crystal structure of yeast ALS as a complex with chlorimuron-ethyl (1985, Classic®, DuPont). It is obvious that a substitution in positions 3 and 4 of the aromatic ring A of the pyrimidinylsulfonylurea would have an adverse effect on the binding site and consequently on the herbicidal efficacy – the variation is restricted to the *ortho*-position.
- Sulfonylaminocarbonyl-triazolone herbicides (SACTs).*¹¹¹ Propoxycarbazone-sodium offers the farmer an opportunity to exert effective control aimed particularly at brome grass, *Bromus* spp., loose silky-bent, *Apera spica-venti* (L.) Beauv., common couchgrass, *Elymus repens* Gould, blackgrass, *Alopecurus myosuroides* Huds., jointed goatgrass, *Aegilops cylindrica* Host, and several broadleaf weeds from the mustard family.

During optimisation it was found that the sulfonylaryl moiety is more active than the corresponding sulfonylmethylaryl moiety. A

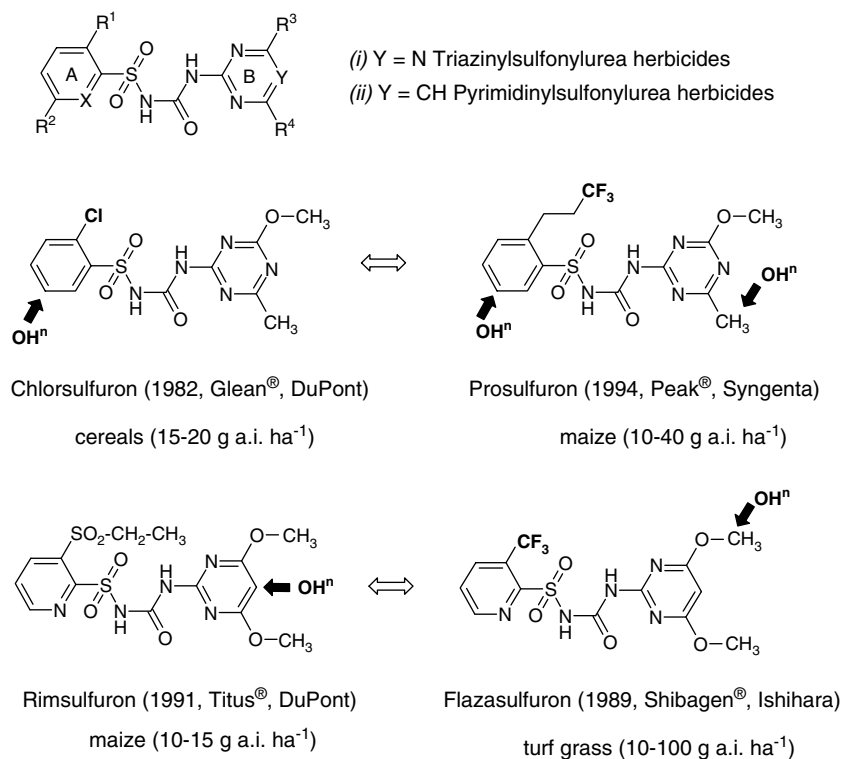


Figure 19. General formula of sulfonylurea herbicides and influence of fluorine-containing substituents on crop selectivity and metabolic pathway.

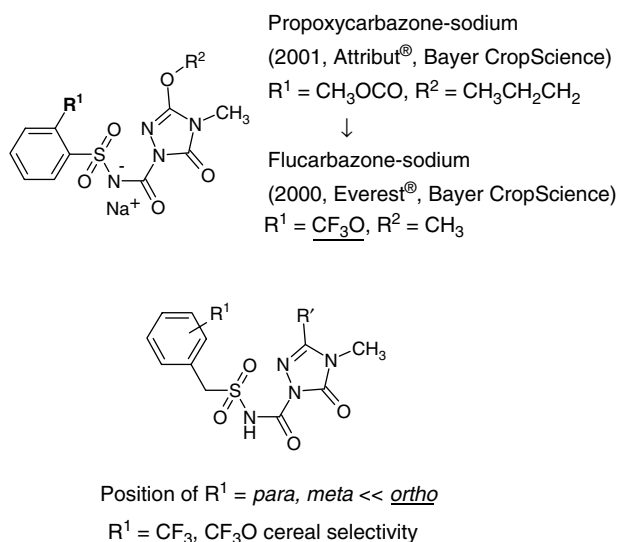


Figure 20. Sulfonylaminocarbonyl-triazolone herbicides and optimisation in their sulfonylmethylaryl moiety.

particularly good activity and cereal selectivity was identified for the CF₃ and CF₃O substitution (Fig. 20).

The exchange of the *ortho*-CH₃OCO for the CF₃O function in the sulfonylaryl moiety led to the systemic herbicide flucarbazone-sodium, which provides excellent activity against grass weeds and several important broadleaf weeds when applied post-emergence to wheat. The product has demonstrated strong and consistent activity against wild oat, *Avena fatua* L., and green foxtail, *Setaria viridis* (L.) Beauv., in spring wheat, *Triticum aestivum* L., and durum wheat, *T. durum* Desf.

6 CONCLUDING REMARKS AND PROSPECTS

In the search for a so-called 'optimal product' in modern crop protection in terms of efficacy, environmental safety, user friendliness and economic viability, the substitution of AIs with halogen atoms or halogen-containing substituents is an important tool. However, the introduction of halogen atoms or halogen-containing substituents into a molecule can lead to an increase or decrease in biological efficacy depending on the MoA, physicochemical properties or target interaction of the compound. The metabolism of the AI will be influenced by the substitution pattern in a given molecule and by the soil stability and/or water solubility. Finally, a shift into an other crop protection area can be observed by the introduction of halogen atoms or halogen-containing substituents into different biologically active molecules. Because of the complex SARs within AIs, it is difficult to predict sites where halogens or halogen-substituted substituents will increase biological efficacy. The technical availability of AIs containing halogens or halogen-substituted substituents has been improved by an increase in access to new intermediates also marketed for pharmaceuticals. In future, the influence of halogen substituents in biologically active molecules will have to be investigated in relation to the desired improvement of lead structures by modern technologies, and to better access to interesting intermediates, making them economically viable.

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